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European Society for Medical Oncology (ESMO)

European Society for Medical Oncology

The European Society for Medical Oncology (ESMO) is the leading professional organization for medical oncology. With more than 25,000 members representing oncology professionals from over 150 countries worldwide, ESMO was founded in 1975.

Annals of Oncology

Founded in 1990, ESMO's flagship scientific journal, Annals of Oncology, publishes articles addressing medical oncology, surgery, radiotherapy, pediatric oncology, basic research and the comprehensive management of patients with malignant diseases. Annals of Oncology is the official journal of ESMO and from 2008 of the Japanese Society for Medical Oncology (JSMO)

ESMO Clinical Practice Guidelines

The ESMO Clinical Practice Guidelines (CPG) are intended to provide oncology professionals with a set of recommendations for the best standards of cancer care, based on the findings of evidence-based medicine. Each Clinical Practice Guideline includes information on the incidence of the malignancy, diagnostic criteria, staging of disease and risk assessment, treatment plans and follow-up designed to help oncologists deliver an appropriate quality of care to their patients.

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European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)

In 2015, ESMO published the first version of its Magnitude of Clinical Benefit Scale to grade the magnitude of clinical benefit of cancer therapies incorporating efficacy, long-term survival and side-effects of any anticancer agent into a single score. ESMO-MCBS was updated with the publication of the version 1.1 in 2017. Forms are available from the official website of ESMO.

Provide your patients with the best care options.

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Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC)

Phase II study of berzosertib (M6620) + topotecan in patients with relapsed platinum-resistant SCLC: DDRiver SCLC 250

Background:

Small cell lung cancer (SCLC) displays high genomic instability. Therefore, targeting key proteins involved in maintaining genomic stability, such as ataxia telangiectasia and Rad3-related (ATR) protein kinase and topoisomerase I (TOP1), is a rational treatment strategy for SCLC. Berzosertib (M6620), an intravenous, highly potent and selective, first-in-class ATR inhibitor, is well tolerated and synergizes with topotecan (TOP1 inhibitor) in patients with advanced solid tumors, particularly those with platinum (plt)-resistant SCLC. This study (NCT04768296) includes a global primary cohort and a Japan safety run-in with two dose levels (DL1 and DL2). The study will evaluate efficacy, safety, tolerability and pharmacokinetics of berzosertib + topotecan in patients with relapsed, plt-resistant SCLC. The primary endpoints are objective response (primary cohort) and establishing the recommended phase II dose in Japanese patients (safety run-in).

Trial design:

Patients with advanced solid tumors with no effective standard therapy are eligible for DL1. Patients with histologically confirmed SCLC, disease progression on/after first-line of chemoradiation plt-based treatment with a plt-free interval <90 days, and measurable disease per Response Evaluation Criteria in Solid Tumors 1.1, are eligible for the primary cohort and DL2. Patients previously treated with an ATR or TOP1 inhibitor, or those with unstable brain metastases, are excluded. Berzosertib (Days 2, 5) + topotecan (Days 1-5) will be administered intravenously in 21day cycles until disease progression. The safety run-in will follow a Bayesian Optimal Interval Design. Japanese patients in the DL1 arm (n=3-9) will receive berzosertib 105 mg/ m^2 + topotecan 1.25 mg/m^2; if tolerated, patients will be enrolled to the DL2 arm (same dose as primary cohort; n=3-9). If DL2 is tolerated, Japanese patients will be enrolled to the primary cohort. In the primary cohort, w80 patients will receive berzosertib 210 mg/m^2 + topotecan 1.25 mg/m^2. Interim analysis is planned after 40 patients. The treatment effect assumption is an objective response rate of 30%.

Clinical trial identification:

NCT04768296

Anlotinib plus irinotecan or docetaxel in small-cell lung cancer (SCLC) relapsed within six months: Updated results from a single-arm phase II study

Background:

There is still no unsatisfactory treatment strategy for patients (pts) with advanced SCLC relapsed within six months after first-line treatment, although chemotherapy alone is the standard treatment. Anlotinib, an oral multitarget tyrosine kinase inhibitor, effectively inhibits angiogenesis and enhances tumor cell response to chemotherapy. In the ALTER 1202 trial, anlotinib had significantly improved progression-free survival (PFS) and overall survival (OS) of advanced SCLC pts who received at least two lines chemotherapy. Therefore, we presented the updated efficacy and safety of anlotinib plus irinotecan or docetaxel in SCLC relapsed within six months after first-line treatment.

Methods:

Eligible pts with advanced SCLC who have relapsed within six months after first-line platinum-based treatment received anlotinib (12mg, QD from day 1 to 14 of a 21-day cycle) and irinotecan (65mg/m^2, day 1,8, q3w, up to 4 cycles) or docetaxel (60mg/m^2, q3w, up to 4 cycles) until progression or intolerable toxicity. The primary endpoint was the objective response rate (ORR). Secondary endpoints included PFS, the disease control rate (DCR), OS and safety.

Results:

As of April 28, 2021, we recruited 26 pts, among which 24 pts (median age: 61.9 years, male: 79.2%, ECOG PS 1: 75.0%, brain metastasis: 50%, liver metastasis: 41.7%) were eligible for efficacy analysis. Median follow-up time was 9.2 months (95% Cl, 1.63-16.77). Median PFS was 4.0 months (95%Cl: 3.16-4.84). The median OS was 7.5 months (95%Cl: 3.01-11.99). Of 21 evaluable pts, 1 pts had complete response (CR) and 9 pts reached partial response (PR). The ORR was 47.6% (10/21) and the DCR was 90.5% (19/21), respectively. Most common grade 1-2 treatment related adverse events (TRAEs) included weakness (37.5%), anorexia (33.3%), anemia (33.3%) and hypertension (20.8%). 3 pts (12.5%) suffered from grade 3 AEs, which were leukopenia, thrombocytopenia, and anemia.

Conclusions:

Anlotinib plus irinotecan or docetaxel continued to show promising efficacy and manageable toxicities in SCLC relapsed within six months after first-line treatment. It may become a novel therapeutic strategy for the population.

Clinical trial identification:

NCT04757779

Anlotinib plus oral fluoropyrimidine S1 in treating patients with refractory or relapsed small cell lung cancer (SALTER TRIAL): An open-label, multicenter, single-arm, phase II trial

Background:

Patients with relapsed small cell lung cancer (SCLC) have limited treatment options and dismal survival. Phase II study shows the moderate activity of anlotinib monotherapy (a novel multitarget tyrosine kinase angiogenesis inhibitor) in previously treated SCLC. The purpose of this study is to assess the efficacy and safety of anlotinib combination with oral fluoropyrimidine S1 in patients with Refractory or Relapsed SCLC.

Methods:

This open-label, multicentre, single-arm, phase II trial was done at three hospitals in China. Eligible patients were age 18 to 75 years. Patients with relapsed/ refractory SCLC whose disease progressed or recurred after at least one prior platinum-based chemotherapy regimen. Pts received six cycles of anlotinib (12mg once daily [QD]) plus S-1 (60mg twice daily [BID]) for 14 consecutive days every 21 days followed by maintenance S-1 until disease progression. The primary outcome was objective response rate (ORR) or progression-free survival (PFS) as assessed by the investigators according to RECIST 1.1. Secondary endpoints included overall survival (OS) and safety.

Results:

Between March 2019 to June 2020, 71 patients were assessed for eligibility, of 52 pts enrolled, 48 were received at least two doses of the study drug. Median follow-up was months was 755 days. The overall response was seen in 21 patients (43.8%). Median PFS was 134 days (95% CI, 104-164 days). Median OS was 178 days (95% CI,137-219 days). The most common grade 3-4 adverse events were fatigue, hand-foot syndrome, hypertension, anorexia, and blurred vision. No treatment related deaths were reported.

Conclusions:

Anlotinib combination with oral fluoropyrimidine S1 was active for relapsed/refractory SCLC in terms of overall response and had an acceptable and manageable safety profile.

Clinical trial identification:

NCT03823118

Induction osimertinib in EGFR-mutant stage IIIA/B NSCLC

Background:

Definitive chemoradiation (CRT) followed by durvalumab is the standard of care in stage III NSCLC. Osimertinib showed high efficacy in metastatic and resectable settings and is currently assessed in unresectable IIIA/B. This study aimed at testing the efficacy of osimertinib as induction therapy before definitive radiotherapy (RT) in EGFRm stage III patients to induce tumor shrinkage and reduction of the radiation field.

Methods:

This phase 2 open-label study enrolled EGFRm NSCLC stage IIIA/B patients. Osimertinib (80 mg) was given daily for a maximum of 12 weeks followed by definitive RT and/or surgery. Response to therapy was assessed by PET-CT at weeks 3, 6, and 12. In case of response, patients were referred to sequential definitive RT at week 12 while in case of progression, patients were referred to CRT. After RT+/- surgery or CRT, patients were followed (no adjuvant therapy). ORR is the primary endpoint, secondary endpoints are: mPFS, gross tumor volume (GTV) and planned target volume (PTV) before and after treatment. All the patients will be followed for 2 years.

Results:

This preliminary analysis includes 13 patients (11 female; age 73.0 5.4 years) with a median follow-up of 13.5 months. All non-smokers with adenocarcinoma. 9 patients harbored exon 19 del, 3 L858R, and 1 had a rare mutation. T status was T1, T2, T3, and T4 in 2, 9, 1, and 1 and N status was N2 and N3 in 10 & 3 patients respectively. Thus, stage IIIA, B, and C were in 5, 5, and 3 patients. Among 9 patients who have completed 12 weeks of osimertinib therapy, ORR was 100%, (2 CR, 7 PR, 0 SD or PD), 3 are still on osimertinib, and 1 withdrew (unrelated adverse events). Following osimertinib induction, 6 patients completed RT & 1 underwent surgery (pT1aN0) without RT. The other 2 pts are still under RT. Pre-osimertinib GTV & PTV were 20.2 ±42.9 cm^3 and 196.4 ± 241.5 cm^3 respectively. Both were reduced to 12.8±21.8 cm^3 (-36.7%) and 181.9±113.0 cm^3 (-7.4%), respectively. Data are immature for PFS. No safety issues reported.

Conclusions:

Osimertinib induction in stage III EGFRm NSCLC is feasible and led to tumor shrinkage in 92% of the cases, resulting in a significant reduction of the radiation field and enabling preservation of the lung tissue radiation-induced toxicity. This chemotherapy-free novel approach should be further investigated as an alternative to CRT in this setting for EGFRm patients.

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Background:

The standard treatment for patients with good performance status with unresectable LANSCLC is concurrent chemoradiotherapy (CRT), The new treatment strategies of patients who could not tolerate CRT or refused chemotherapy are necessary. Anlotinib is a novel multi-target anti-angiogenesis agent that inhibits VEGFR, FGFR, PDGFR, c-kit, which showed encouraging efficacy and good tolerability for advanced NSCLC in ALTER-0303 trial. Emerging clinical data suggested that antiangiogenic drugs could enhance the efficacy of radiotherapy by alleviating tumor hypoxia and improving perfusion. In this trial, we assessed the efficacy and safety of anlotinib combined with radiotherapy in unresectable LANSCLC.

Methods:

In the phase II trial, patients with driver gene negative unresectable LANSCLC who could not tolerate CRT or refused chemotherapy were enrolled. Eligible patients were previously untreated with immune checkpoint inhibitors. All included patients received anlotinib (12mg, QD, day 1 to 14 of a 21-day cycle) and radiotherapy (60-66Gy/30-33F, 5F/W, 6-7W) until disease progression or treatment intolerance. The primary endpoints were objective response rate (ORR) and disease control rate (DCR). PFS, OS and safety were secondary endpoints.

Results:

At data cut-off (Dec 20, 2020), we recruited 18 patients in this trial, of which 16 patients were evaluable. Complete response was observed in 1 patient, partial responses in 8, and stable disease in 7. The ORR was 56.25% (9/16), and the DCR was 100% (16/16). The median PFS and OS were not reached. The PFS rates at 6 and 12 months were 100% and 80.81% (95CI, 42.35%-94.85%), respectively. The OS rates at 6 and 12 months were 100% and 90% (95CI, 47.28%-98.53%), respectively. The most common grade 1-2 adverse events (AEs) were hand and foot skin reaction (4/16, 25%). Grade 3 or higher AEs included hypertension (1/16, 6.25%), oral mucositis (1/16, 6.25%) and hemoptysis (1/16, 6.25%).

Conclusions:

Anlotinib combined with radiotherapy showed the promising ORR and DCR in patients with unresectable LANSCLC, and the combination was well-tolerated. The phase II trial is ongoing to furtherly evaluate the PFS and OS outcomes.

Clinical trial identification:

ChiCTR2100043364

EGFR mutation p.747_749del enhances anlotinib sensitivity by upregulating EGR1 and DUSP6 in NSCLC cells

Background:

Lung cancer is very common and one of the leading causes of cancer mortality worldwide. Anlotinib has been widely applied to treat many types of cancers in the clinic, including NSCLC. In clinic, we found the effect of treatment with anlotinib was more significant in NSCLC with EGFR mutation p.747_749del. In this study, we have verified the hypothesis and further study its specific path which is mainly achieved by increasing the expression of the EGR1 and UBE2C genes.

Methods:

This experiment selected A549, SPC-A-1 two NSCLC cell strains. First using MTT assays to detect the IC50 value of four drugs. The inhibition and apoptosis rates of the two cell strains were compared and analyzed by MTT assays and Annexin VAPC single-dye methods. The Affymetrix gene chip was then used to screen out all the differential genes, and then a real-time quantitative PCR detecting system was used to detect the expression level of the differential genes. We then applied RNA interference technology, trans-dyeing, PCR technology, DNA sequencing, western blotting and other technologies to build, package, detect EGR1, DUSP6 interference romvirus vector and over-expression adenovirus vector, and then transinfect A549 with the built romvirus, and finally with MTT assays detection EPR1, DUSP6 reduction rate.

Results:

In this study, we verified that both the EGFR mutation p.747_749del and A750p increased the inhibition and apoptosis rates of two non-small cell lung cancer cells, A549 and SPC-A-1, indicating that the mutations themselves have lethality to NSCLC cells. The whole gene sequencing found that the expression of the EGR1 and DUSP6 genes significantly increased anlotinib to the cells of the gene of interest, and after the two genes knockdown, the inhibition rate decreased significantly. Mechanism studies showed that the EGFR p.747_749del mutation works mainly by increasing the expression of EGR1 and DUSP6 to make non-small cell lung cancer cells more sensitive to anlotinib.

Conclusions:

EGFR mutation p.747_749del enhances anlotinib sensitivity by upregulating EGR1 and DUSP6 in NSCLC cells, EGR1 and DUSP6 may be a novel target for NSCLC for sensitizing cells to the chemotherapeutic agent anlotinib.

Anlotinib combined with radiotherapy in locally advanced non-small cell lung cancer (LANSCLC): A prospective, singlearm, phase II study

Background:

The standard treatment for patients with good performance status with unresectable LANSCLC is concurrent chemoradiotherapy (CRT), The new treatment strategies of patients who could not tolerate CRT or refused chemotherapy are necessary. Anlotinib is a novel multi-target antiangiogenesis agent that inhibits VEGFR, FGFR, PDGFR, c-kit, which showed encouraging efficacy and good tolerability for advanced NSCLC in ALTER-0303 trial. Emerging clinical data suggested that antiangiogenic drugs could enhance the efficacy of radiotherapy by alleviating tumor hypoxia and improving perfusion. In this trial, we assessed the efficacy and safety of anlotinib combined with radiotherapy in unresectable LANSCLC.

Methods:

In the phase II trial, patients with driver gene negative unresectable LANSCLC who could not tolerate CRT or refused chemotherapy were enrolled. Eligible patients were previously untreated with immune checkpoint inhibitors. All included patients received anlotinib (12mg, QD, day 1 to 14 of a 21-day cycle) and radiotherapy (60-66Gy/30-33F, 5F/W, 6-7W) until disease progression or treatment intolerance. The primary endpoints were objective response rate (ORR) and disease control rate (DCR). PFS, OS and safety were secondary endpoints.

Results:

At data cut-off (Dec 20, 2020), we recruited 18 patients in this trial, of which 16 patients were evaluable. Complete response was observed in 1 patient, partial responses in 8, and stable disease in 7. The ORR was 56.25% (9/16), and the DCR was 100% (16/16). The median PFS and OS were not reached. The PFS rates at 6 and 12 months were 100% and 80.81% (95CI, 42.35%-94.85%), respectively. The OS rates at 6 and 12 months were 100% and 90% (95CI, 47.28%-98.53%), respectively. The most common grade 1-2 adverse events (AEs) were hand and foot skin reaction (4/16, 25%). Grade 3 or higher AEs included hypertension (1/16, 6.25%), oral mucositis (1/16, 6.25%) and hemoptysis (1/16, 6.25%).

Conclusions:

Anlotinib combined with radiotherapy showed the promising ORR and DCR in patients with unresectable LANSCLC, and the combination was well-tolerated. The phase II trial is ongoing to furtherly evaluate the PFS and OS outcomes.

Clinical trial identification:

ChiCTR2100043364

MRTX-500: Phase II trial of sitravatinib (sitra) + nivolumab (nivo) in patients (pts) with non-squamous (NSQ) non-small cell lung cancer (NSCLC) progressing on or after prior checkpoint inhibitor (CPI) therapy

Background:

Therapy with CPI has improved OS across many tumor types, including in a subset of pts with NSCLC. Mechanisms of CPI resistance, however, have been described, including an immunosuppressive TME, which may include recruitment of immunosuppressive myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and M2-polarized macrophages within the TME. Sitra, a spectrum-selective TKI targeting TAM (Tyro3/Axl/MerTK) receptors and VEGFR2, reduces the number of MDSCs and Tregs while increasing the ratio of M1/M2-polarized macrophages, and thus is hypothesized to overcome an immunosuppressive TME and augment antitumor immune responses.

Methods:

MRTX-500 (NCT02954991) is a phase II study evaluating sitra (120 mg QD) + nivo (Q2W or Q4W) in pts with NSQ NSCLC who have progressed on or after treatment, with a CPI-based regimen (anti-PD1/PD-L1) and/or platinum doublet chemotherapy. The primary endpoint is ORR per RECIST 1.1. Secondary endpoints include OS, PFS, and safety. We report updated efficacy data for pts with NSCLC with PCB (prior clinical benefit; CR, PR, or SD ≥12 weeks) from a CPI who were treated with sitra + nivo as either 2L or 3L therapy.

Results:

As of 17 October 2020, 68 pts with PCB (57% female; median age, 66 years; ECOG PS 0/1/2, 27%/66%/7%) were treated. Median follow-up was 28 months, median OS was 15 months (95% CI 9.3, 21.1),1- and 2-year OS rates were 56% and 32%, respectively. Median PFS was 6 months, and ORR was 16% (11/68), including 2 CRs. Median duration of response was 13 months. In all CPI-experienced pts evaluable for safety (n=124), treatment related adverse events (TRAEs) occurred in 91% of pts, with Gr 3/4 TRAEs occurring in 60% of pts. The most common (≥10%) Gr 3/4 TRAEs were hypertension and diarrhea. There were no Gr 5 TRAEs. Discontinuation rates for sitra and nivo due to any AE were 30% and 27%, respectively.

Conclusions:

Sitra + nivo demonstrated antitumor activity and encouraging OS compared to historical controls and no new safety signals were observed in pts with NSQ NSCLC who progressed on prior CPI. This combination is being evaluated in the phase III SAPPHIRE study.

Clinical trial identification:

NCT02954991

Amivantamab monotherapy and in combination with lazertinib in post-osimertinib EGFR-mutant NSCLC: Analysis from the CHRYSALIS study

Background:

Amivantamab (ami), an epidermal growth factor receptor (EGFR)-MET bispecific antibody, has demonstrated efficacy in EGFR mutant non-small cell lung cancer (NSCLC) that progressed on osimertinib (osi), both as monotherapy and in combination with lazertinib (laz), a 3rd-generation tyrosine kinase inhibitor. Clinical outcomes of patients (pts) treated with ami monotherapy (mono) and ami in combination with laz (combo) are presented here.

Methods:

CHRYSALIS is an ongoing study of ami in pts with advanced EGFR mutant NSCLC (NCT02609776). Pts who progressed on osi were pooled to form the mono group, a majority of whom were preselected for C797S/other resistance mutations or MET amplification. The combo group comprised unselected pts who had progressed on osi but were chemotherapy-naïve. Response was assessed by the investigator per RECIST v1.1.

Results:

As of 19 Apr 2021, 121 pts in the mono group (85% with EGFR/MET-based resistance) and 45 in the combo group (38% with EGFR/MET-based resistance) were efficacy-evaluable, with median follow-up of 6.9 and 11.1 months, respectively. Antitumor activity was observed in the mono group, with 33 achieving partial response (PR) as best response, of which 23 were confirmed, for an overall response rate (ORR) of 19% (95% CI, 12-27). In the combo group, 1 complete response and 15 PRs were observed, all of which confirmed, for an ORR of 36% (95% CI, 22-51). Median duration of response was 5.9 months with mono, 9.6 months with combo (Table). The safety profile for both mono and combo was consistent with previouslyreported safety. No new safety signals were identified.

Table: 1192MO Efficacy of amivantamab monotherapy and in combination with lazertinib among efficacy-evaluable[a] patients

	Efficacy	
	Monotherapy (n=121)	Combination (n=45)
ORR (95% CI)	19% (12–27)	36% (22–51)
CBR (95% CI)	48% (39–57)	64% (49–78)
mDOR, month (95% CI)	5.9 (4.2–12.6)	9.6 (5.3–NR)

[a]Patients who had at least 2 post-baseline disease assessment or discontinued before the second assessment. CBR, clinical benefit rate (complete response, partial response, or stable disease of at least 11 weeks); mDOR, median duration of response; ORR, overall response rate; NR, not reached

Conclusions:

Antitumor activity of ami + laz in the post-osi setting appears favorable even without molecular selection post osimertinib failure, supporting that simultaneous targeting of the extracellular and catalytic domains of EGFR provides additive benefits.

Clinical trial identification:

NCT02609776

Amivantamab plus lazertinib in post-osimertinib, postplatinum chemotherapy EGFR-mutant non-small cell lung cancer (NSCLC): Preliminary results from CHRYSALIS-2

Background:

The combination of amivantamab (ami), an epidermal growth factor receptor (EGFR)-MET bispecific antibody, with the 3rd-generation tyrosine kinase inhibitor lazertinib (laz), yielded a 36% overall response rate (ORR) in the post-osimertinib (osi), chemotherapy-naïve setting (Cho Ann Oncol 2020;31:S813, Oral 1258). The activity of ami + laz after progression on both osi and platinum doublet chemotherapy is unknown.

Methods:

CHRYSALIS-2 (NCT04077463) is an ongoing open-label study that includes a single-arm cohort (Cohort A) examining ami + laz in patients (pts) with EGFR Exon19del or L858R NSCLC whose disease progressed after standard of care osi and platinum chemotherapy (3rd /4th line; “target” population) and in more heavily pretreated (5th line +) pts. Pts received the established recommended combination dose of 1050 mg IV ami (1400 mg, ≥80 kg) + 240 mg oral laz. Investigator-assessed response per RECIST v1.1 is reported for pts with ≥2 post-baseline disease assessments.

Results:

As of 19 Apr 2021, 116 pts were enrolled in Cohort A (median 63 y, 68% women, 60% Asian, median of 3 [range, 2-14] prior lines), with 59 in the target and 57 in the heavily-pretreated populations. Of 28 response-evaluable pts in the target population, 12 (43% [95% CI, 24-63]) reported partial response (PR) as best response; of the 12 responses, 9 were confirmed (3 pending), for an overall response rate (ORR) of 32% (95% CI, 16e52). Of 45 pts in the heavily-pretreated population, 7 reported best response of PR, of which 6 were confirmed (1 pending), for an ORR of 13% (95% CI, 5-27). At 3.7-mo median follow-up, 17 pts in the target population remain on treatment: 10 with PR (3 pending confirmation) and 7 with stable disease. The safety profile for Cohort A was consistent with previously reported experience with ami + laz at the recommended combination dose, and no new safety signals were identified.

Conclusions:

Ami + laz is showing encouraging early activity in a population that progressed on both standard of care osi and platinum chemotherapy. Activity is consistent with the post-osi population, suggesting intervening chemotherapy does not impact ami + laz activity.

Clinical trial identification:

NCT04077463

Brigatinib (BRG) vs crizotinib (CRZ) in ALK TKI-naive ALK+ NSCLC: Final results from ALTA-1L

Background:

In 2 planned interim analyses of ALTA-1L (NCT02737501), BRG BIRC assessed PFS was superior to CRZ. We report final ALTA-1L results.

Methods:

Patients (pts) with ALK TKI - naive advanced ALK+ NSCLC were enrolled and stratified by baseline (BL) brain metastases (BM) and prior chemotherapy (CT). One prior CT for advanced NSCLC and asymptomatic BM was allowed. Pts were randomized 1:1 to BRG 180 mg QD (7-day lead-in at 90 mg) or CRZ 250 mg BID. Pts in the CRZ arm were offered BRG at progression. Primary endpoint: BIRC-assessed PFS (RECIST v1.1). Secondary endpoints included confirmed iORR, iPFS by BIRC, OS, safety, and QoL.

Results:

275 pts randomized (BRG/CRZ, n=137/138); median age 58/60 y; prior CT 26%/27%; BL BM 29%/30%. As of 29 Jan 2021 (last patient contact), median follow-up was (BRG/CRZ): 40.4/15.2 mo, with 166 (73/93) PFS events. BIRC-assessed PFS HR was 0.48 (95% CI: 0.35-0.66, log-rank P<0.0001); BRG mPFS was 24.0 mo (95% CI: 18.4-43.2) vs CRZ 11.1 mo (95% CI: 9.1-13.0); 3-yr PFS rate was (BRG/CRZ) 43%/ 19%. Investigator-assessed PFS HR was 0.43 (95% CI: 0.31e0.58, mPFS 30.8 vs 9.2 mo). mDoR (BIRC) was 33/14 mo. Median OS was not reached in either group (events BRG/CRZ: 41/51; HR: 0.81 [95% CI: 0.53-1.22]; log rank P=0.3311); 3-yr OS was 71%/ 68%. In pts with BL BM, OS HR was 0.43 (95% CI: 0.21-0.89; Table); in pts with no BL BM, 1.16 (0.69-1.93). Most common grade ≥3 TEAEs: BRG: increased CPK (26%) and lipase (15%), hypertension (14%); CRZ: increased ALT (10%), lipase, (8%), AST (7%). Any grade ILD/pneumonitis (BRG/CRZ): 4.4%/2.2%; discontinuation due to AE: 13.2%/ 8.8%. Median time to worsening in pt-reported global health status/QoL was (BRG/ CRZ) 26.7/8.3 mo; HR: 0.69 (95% CI: 0.49-0.98).

Conclusions:

BRG demonstrated durable overall and intracranial efficacy, and the tolerability profile remained consistent and manageable despite extended treatment duration, confirming BRG as an effective standard-of-care treatment in pts with treatment-naive ALK+ NSCLC.

Clinical trial identification:

NCT02737501

Pre-existing and acquired mechanisms of resistance to lorlatinib in previously treated patients (pts) with ALK+ advanced non-small cell lung cancer (NSCLC)

Background:

Lorlatinib, a potent, brain-penetrant, 3rd-generation (gen) ALK/ROS1 tyrosine kinase inhibitor (TKI) active against most known resistance mutations, showed robust clinical activity in ALK+ or ROS1+ NSCLC in a Ph 1/2 study that enrolled mostly heavily pretreated pts with CNS metastases. We evaluated potential resistance mechanisms, pre-existing or acquired, and efficacy in these settings.

Methods:

Pts with ALK+ NSCLC previously treated with ≥1 2nd-gen ALK TKI (N=139) were treated with lorlatinib 100 mg QD in the ongoing Ph 1/2 study (NCT01970865). Plasma samples were collected at baseline (BL) and at end of treatment (EoT) for circulating tumor (ct)DNA. Objective response rate (ORR), duration of response (DOR), and median progression-free survival (mPFS) by independent central review were evaluated according to mutation status.

Results:

TP53 mutations were found in 44 of 103 (42.7%) samples with detectable ctDNA at BL. ORR was 38.6% (95% CI: 24.4-54.5) and 45.8% (95% CI: 32.7-59.2) in pts with or without TP53 mutations, respectively; median DOR was 15.1 and 12.5 mo; and mPFS was 4.1 and 6.9 mo (hazard ratio [HR] = 0.83; 95% CI: 0.52-1.31). Restricting analysis to pts' samples harboring ALK fusion (n=58) led to similar results. Pre-existing aberrations in potential bypass mechanisms (eg, BRAF, KRAS known mutations, or EGFR, CDK4/6 or MET amplification) resulted in weaker efficacy, with mPFS of 3.2 and 6.9 mo (HR= 0.49; 95% CI: 0.29-0.84) in pts with (n=21; 20.4%) or without (n=82; 79.6%) aberrations, respectively. Confirmation of these results in tumor tissue is ongoing. In pts with matched paired samples (N=53), 7.5% had ALK compound mutations, while 20.8% had potential bypass mechanism aberrations at progression. The remaining pts did not show specific patterns of resistance.

Conclusions:

imitations apply to ctDNA analyses, but in this heavily pretreated group of pts with ALK+ NSCLC, presence of TP53 mutations at BL was potentially associated with decreased lorlatinib efficacy, while presence of bypass mechanism aberrations with reduced activity. Upon progression, ALK compound mutations and bypass mechanism aberrations emerged in ~28% of pts.

Clinical trial identification:

NCT01970865

First-line lorlatinib versus crizotinib in ALK-positive nonsmall cell lung cancer: Asian subgroup analysis of CROWN

Background:

Lorlatinib, a 3rd-generation ALK inhibitor, significantly prolonged progression-free survival (PFS) vs crizotinib in the CROWN trial in patients with untreated ALKpositive non-small cell lung cancer (NSCLC). We report data from the Asian subgroup of CROWN.

Methods:

In this ongoing phase III trial (NCT03052608), untreated patients (n = 296) with ALK-positive advanced NSCLC were randomized to lorlatinib or crizotinib, stratified by presence of brain metastases and ethnicity (Asian/non-Asian). The primary endpoint was PFS by blinded independent central review. Primary and key secondary endpoints were analyzed in the Asian subgroup (unstratified analyses).

Results:

In the Asian subgroup, 120 patients were randomized (59 to lorlatinib, 61 to crizotinib [1 not treated]): 48 in Japan, 21 South Korea, 20 mainland China, 16 Taiwan, 8 Singapore and 7 Hong Kong. Baseline characteristics (median age: 61 and 55 years; female: 46% and 61% for lorlatinib and crizotinib, respectively) were similar to the overall population except for a slightly greater gender imbalance between treatments. Lorlatinib prolonged PFS and increased overall and intracranial response vs crizotinib (Table). The most common any-grade adverse events (AEs) with lorlatinib were hypertriglyceridaemia (68%), hypercholesterolaemia (68%), oedema (44%) and weight increased (42%), and with crizotinib were nausea (58%), diarrhea (58%), vomiting (45%), vision disorder (43%) and constipation (42%). Grade 3/4 AEs were reported by 78% (lorlatinib) vs 60% (crizotinib). Fewer patients had AEs leading to permanent treatment discontinuation in the lorlatinib arm (6.8%) than the crizotinib arm (11.7%).

Table: 1197P

	Asian subgroup		Overall population[a]	
	Lorlatinib (n = 59)	Crizotinib (n = 61)	Lorlatinib (n = 149)	Crizotinib (n = 147)
PFS (BICR)				
HR (95% CI)	0.44 (0.24–0.78)		0.28 (0.19–0.41)	
P-value	0.002[b]		<0.001	
Event-free at 12 months, % (95% CI)	72 (59–82)	48 (32–62)	78 (70–84)	39 (30–48)
ORR (BICR)				
n (%)	45 (76.3)	35 (57.4)	113 (75.8)	85 (57.8)
95% CI	63.4–86.4	44.1–70.0	68.2–82.5	49.4–65.9
Intracranial ORR (BICR)[c]	(n = 11)	(n = 16)	(n = 38)	(n = 40)
n (%)	8 (72.7)	4 (25.0)	25 (65.8)	8 (20.0)
95% CI	39.0–94.0	7.3–52.4	48.6–80.4	9.1–35.6

[a]Shaw et al. *N Engl J Med.* 2020; 383:2018-2029. [b]No adjustment for multiplicity. [c]Patients with brain metastases at baseline by neuroradiologist. BICR, blinded independent central review.

Conclusions:

In the Asian subgroup, a consistent and clinically meaningful improvement in PFS was observed for lorlatinib vs crizotinib. The efficacy and safety of lorlatinib vs crizotinib in the Asian subgroup of CROWN was consistent with the overall population.

Clinical trial identification:

NCT03052608

Dose modification for the management of CNS adverse events in the phase III CROWN study of lorlatinib in nonsmall cell lung cancer (NSCLC)

Background:

In the ongoing phase III CROWN study (NCT03052608), lorlatinib, a 3rdgeneration inhibitor of anaplastic lymphoma kinase (ALK), improved progression-free survival (PFS) and intracranial response rates vs crizotinib in patients with previously untreated ALK-positive NSCLC. Here we present data on lorlatinib dose modification for the management of CNS adverse events (AEs).

Methods:

296 patients were randomized 1:1 to oral lorlatinib (100 mg QD) or crizotinib (250 mg BID). Guidelines for AEs management included medication, dose interruption, dose reduction to 75 or 50 mg QD, or a combination of the above. PFS landmark analysis was used to assess the effect of lorlatinib dose modifications (as relative dose intensity [RDI]) on efficacy.

Results:

In total, 86 CNS AEs (all-causality) were reported in 52/149 (35%) patients who received lorlatinib: most were cognitive (38/86, 44%) or mood effects (34/86, 40%). Maximum CNS AE severity was Grade 1 in 32/52 (62%) and Grade 2 in 15/52 (29%) patients. In 53/86 (62%) CNS AEs, lorlatinib dose was not modified and no medication was initiated; of 53 CNS AEs, 28 resolved spontaneously (53%), 1 improved (2%), and 24 did not resolve (45%). The majority (23/24) of the not resolved events were Grade 1. 20/86 (23%) CNS AEs were managed with lorlatinib dose modifications, with or without concomitant medication. A total of 15/20 (75%) of CNS AEs resolved, 2/20 (10%) improved, and 3/20 (15%) did not resolve (Table). Landmark analysis showed no difference in PFS between patients categorized by mean RDI within the first 16 weeks of treatment. The percentage of patient's event-free at 12 months was 90% (95% CI, 82 to 94) in the subgroup whose RDI was ≥mean and 93% (95% CI, 59 to 99) in those whose RDI was < mean.

Conclusions:

CNS AEs spontaneously resolved in 53% of cases, and lorlatinib dose modification was effective in managing CNS AEs without compromising efficacy.

Clinical trial identification:

NCT03052608

Amivantamab monotherapy and in combination with lazertinib in post-osimertinib EGFR-mutant NSCLC: Analysis from the CHRYSALIS study

Background:

Amivantamab (ami), an epidermal growth factor receptor (EGFR)-MET bispecific antibody, has demonstrated efficacy in EGFR mutant non-small cell lung cancer (NSCLC) that progressed on osimertinib (osi), both as monotherapy and in combination with lazertinib (laz), a 3rd-generation tyrosine kinase inhibitor. Clinical outcomes of patients (pts) treated with ami monotherapy (mono) and ami in combination with laz (combo) are presented here.

Methods:

CHRYSALIS is an ongoing study of ami in pts with advanced EGFR mutant NSCLC (NCT02609776). Pts who progressed on osi were pooled to form the mono group, a majority of whom were preselected for C797S/other resistance mutations or MET amplification. The combo group comprised unselected pts who had progressed on osi but were chemotherapy-naïve. Response was assessed by the investigator per RECIST v1.1.

Results:

As of 19 Apr 2021, 121 pts in the mono group (85% with EGFR/MET-based resistance) and 45 in the combo group (38% with EGFR/MET-based resistance) were efficacy-evaluable, with median follow-up of 6.9 and 11.1 months, respectively. Antitumor activity was observed in the mono group, with 33 achieving partial response (PR) as best response, of which 23 were confirmed, for an overall response rate (ORR) of 19% (95% CI, 12-27). In the combo group, 1 complete response and 15 PRs were observed, all of which confirmed, for an ORR of 36% (95% CI, 22-51). Median duration of response was 5.9 months with mono, 9.6 months with combo (Table). The safety profile for both mono and combo was consistent with previously reported safety. No new safety signals were identified.

Table: 1192MO Efficacy of amivantamab monotherapy and in combination with lazertinib among efficacy-evaluable[a] patients

	Efficacy	
	Monotherapy (n=121)	Combination (n=45)
ORR (95% CI)	19% (12–27)	36% (22–51)
CBR (95% CI)	48% (39–57)	64% (49–78)
mDOR, month (95% CI)	5.9 (4.2–12.6)	9.6 (5.3–NR)

[a]Patients who had at least 2 post-baseline disease assessment or discontinued before the second assessment. CBR, clinical benefit rate (complete response, partial response, or stable disease of at least 11 weeks); mDOR, median duration of response; ORR, overall response rate; NR, not reached

Conclusions:

Antitumor activity of ami + laz in the post-osi setting appears favorable even without molecular selection post osimertinib failure, supporting that simultaneous targeting of the extracellular and catalytic domains of EGFR provides additive benefits.

Clinical trial identification:

NCT02609776

Amivantamab plus lazertinib in post-osimertinib, postplatinum chemotherapy EGFR-mutant non-small cell lung cancer (NSCLC): Preliminary results from CHRYSALIS-2

Background:

The combination of amivantamab (ami), an epidermal growth factor receptor (EGFR)-MET bispecific antibody, with the 3rd-generation tyrosine kinase inhibitor lazertinib (laz), yielded a 36% overall response rate (ORR) in the post-osimertinib (osi), chemotherapy-naïve setting (Cho Ann Oncol 2020;31:S813, Oral 1258). The activity of ami + laz after progression on both osi and platinum doublet chemotherapy is unknown.

Methods:

CHRYSALIS-2 (NCT04077463) is an ongoing open-label study that includes a single-arm cohort (Cohort A) examining ami + laz in patients (pts) with EGFR Exon19del or L858R NSCLC whose disease progressed after standard of care osi and platinum chemotherapy (3^{rd} /4^{th} line; "target" population) and in more heavily pretreated (5^{th} line +) pts. Pts received the established recommended combination dose of 1050 mg IV ami (1400 mg, ≥80 kg) + 240 mg oral laz. Investigator-assessed response per RECIST v1.1 is reported for pts with≥2 post-baseline disease assessments.

Results:

As of 19 Apr 2021, 116 pts were enrolled in Cohort A (median 63 y, 68% women, 60% Asian, median of 3 [range, 2-14] prior lines), with 59 in the target and 57 in the heavily-pretreated populations. Of 28 response-evaluable pts in the target population, 12 (43% [95% CI, 24-63]) reported partial response (PR) as best response; of the 12 responses, 9 were confirmed (3 pending), for an overall response rate (ORR) of 32% (95% CI, 16-52). Of 45 pts in the heavily-pretreated population, 7 reported best response of PR, of which 6 were confirmed (1 pending), for an ORR of 13% (95% CI, 5-27). At 3.7-mo median follow-up, 17 pts in the target population remain on treatment: 10 with PR (3 pending confirmation) and 7 with stable disease. The safety profile for Cohort A was consistent with previously reported experience with ami + laz at the recommended combination dose, and no new safety signals were identified.

Conclusions:

Ami + laz is showing encouraging early activity in a population that progressed on both standard of care osi and platinum chemotherapy. Activity is consistent with the post-osi population, suggesting intervening chemotherapy does not impact ami + laz activity.

Clinical trial identification:

NCT04077463

Treatment sequencing and duration of subsequent tyrosine kinase inhibitors in ALK+ non-small cell lung cancer patients treated with brigatinib in the US

Background:

Next-generation targeted therapies for anaplastic lymphoma kinase positive (ALK+) non-small cell lung cancer is associated with improved clinical outcomes, however, tumors develop resistance thus requiring subsequent therapies. Limited data are available on ALK TKI sequencing. The aim of our study was to understand duration of post-brigatinib ALK TKI therapy in the real-world setting.

Methods:

Adults with ≥ 1 claim for brigatinib (index date; ID) between 01-Apr-2017 and 30-Sep-2020 were identified in IQVIA's Pharmacy Claims Database. Patients had ≥ 12 months of data pre-ID and were followed until the end of available data. KaplanMeier methods estimated time to treatment discontinuation (TTD) for brigatinib and the subsequent ALK TKI.

Results:

413 brigatinib patients were included (median age: 57.9 years; 58.4% female; median follow-up 8.4 months). Prior to initiating brigatinib, 195 patients had front line crizotinib with or without subsequent ALK TKIs, 133 had crizotinib followed by alectinib and/or ceritinib, 62 had only crizotinib, 99 had only alectinib, and 80 had no observed ALK TKI. 167 (40.4%) brigatinib patients discontinued or switched to another ALK TKI. Median (95% confidence interval [CI]) brigatinib TTD was 10.3 (8.215.0) months. Among patients who discontinued brigatinib, 100 (59.9%) received subsequent ALK-TKIs. Lorlatinib was the most common next ALK TKI (57.0%), followed by brigatinib retreatment (16.0%), alectinib (13.0%), ceritinib (10.0%), and crizotinib (4.0%). The median (95% CI) TTD of the post-brigatinib ALK TKI was 7.2 (3.9-13.8) months. In patients who received crizotinib then brigatinib, the median (95% CI) TTD of the post-brigatinib ALK TKI was 6.7 (3.7-22.2) months. In patients who received lorlatinib after brigatinib was discontinued, median (95% CI) lorlartinib TTD was 8.0 (3.9-not reached) months.

Conclusions:

These results indicate that brigatinib has real-world durable clinical effects for patients. Treatment with subsequent TKIs, can still bring benefit to patients after discontinuing brigatinib. More formalized prospective data are needed to establish sequencing recommendations.

These results indicate that brigatinib has real-world durable clinical effects for patients. Treatment with subsequent TKIs, can still bring benefit to patients after discontinuing brigatinib. More formalized prospective data are needed to establish sequencing recommendations.

Background:

About 10% of EGFR mutations (EGFRmut) are 'uncommon mutations' (ucEGFRmut), correlating with lower response to 1st &2nd generation EGFR inhibitors (EGFRi) compared to common mutations. Osimertinib is a 3rd generation EGFRi, active against common EGFRmut. Efficacy data of osimertinib in ucEGFRmut are scarce. We aimed to collect real-world data of the usage of osimertinib as the 1st EGFRi for ucEGFRmut.

Methods:

This is a multi-center, international, academic-initiated retrospective study of mNSCLC with ucEGFRmut treated with osimertinib prior to any other EGFRi. RECIST response was evaluated by investigators. PFS and OS were calculated by Kaplan-Meier method from initiation of Osimertinib, duration of response (DOR) was calculated for responders.

Results:

46 patients were identified in 18 centers from 8 countries (Austria, Belgium, France, Germany, Italy, Israel, Spain, Switzerland). Median age was 64 (range 37-91) years, 72% females, 89% Caucasian, never/former/current smokers were 50%/33%/ 15% respectively, ECOG PS was 0-1/2/3-4 in 78%/13%/6.5%. G719X was the most frequent mutation (16 pts, 34.8%), followed by de novo T790M (9 pts, 22%, 5 of them compound with common mutations) and L861Q (7 pts, 15.2%). Compound EGFR mutations were found in 16 pts (34.8%), TP53 mutations in 13 pts (28.3%). Most frequent metastatic sites were brain/bone/lung in 47%/47%/36% respectively. For 37 pts (80.4%), osimertinib was the 1st treatment given for advanced disease. Most frequent toxicities were gastrointestinal (24 pts, 52%) and skin (16 pts, 35%); 5 patients had grade 3-4 AEs. RECIST response (RR) was available for 44 pts, CR for 2 (4.5%), PR for 20 (45.5%), SD for 17 (38.6%), and PD for 5 (11.4%). Median DOR was 17.4 months (95% CI 9.1-NA). RR for G719X was 43.8%, 33.3% for T790M, and 71.4% for L861Q. Median PFS was 9.1 months (95% CI 8.1-19.2). Median OS was 18.4 months (95% CI 13.5-NR).

Conclusions:

Osimertinib showed activity in ucEGFRmut with 85% disease control rate and encouraging PFS and DOR. This report comprises, to the best of our knowledge, the largest dataset of osimertinib as the first EGFRi for ucEGFRmut. UNICORN continues to recruit patients, to expand our knowledge on efficacy of osimertinib for these patients.

Bevacizumab + erlotinib vs erlotinib alone as first-line treatment of pts with EGFR mutated advanced non squamous NSCLC: Final analysis of the multicenter, randomized, phase III BEVERLY trial

Background:

Adding bevacizumab to erlotinib prolonged PFS in NEJ026 and CTONG 1509 trials, but limited data are available in non-Asian patients (pts). BEVERLY is an Italian no-profit, randomized, open-label, multicenter phase III trial of bevacizumab (BEV) plus erlotinib (E) vs E alone as first-line treatment for EGFR-mutated advanced NSCLC.

Methods:

Eligible pts was randomized 1:1 to E (150mg daily) alone or combined with BEV (15mg/kg iv q3w) until disease progression or unacceptable toxicity. Center, ECOG PS and type of mutation (ex19 deletion vs ex21 L858R vs others) were stratification variables. Co-primary endpoints were investigator-assessed PFS (IA-PFS) and blinded-independent centrally-reviewed PFS (BICR-PFS). Secondary endpoints were OS, QoL, IA- and BICR- objective response rate (ORR) and safety; biomarker analyses are also planned. 126 events out of 160 randomized pts were required to detect a PFS prolongation with BEV from 10 to 16.7 mos (HR 0.60), with 2-sided a¼0.05, 80% power

Results:

From Apr 11, 2016 to Feb 27, 2019, 160 pts were randomized to BEV+E (80) or E alone (80). Pts were mainly female (63.8%), never smokers (51.9%), ECOG PS 0-1 (98.1%), median age 66 (IQR 59-73); 55% of pts had ex19Del and 41% L858R mutation. At a median follow-up of 31 mos, 130/160 (81.3%) pts had a PFS event (progression or death) and 84/160 (52.5%) died. BEV+E significantly prolonged IA-PFS over E alone with a median of 15.4 vs 9.7 mos (HR 0.60; 95%CI 0.42-0.85, log-rank P=0.0039). Median OS was 28.4 vs 23.0 mos in BEV+E and E arms, respectively (HR 0.70; 95%CI 0.46-1.10, log-rank P¼0.12). One toxic death was reported, due to intracranial hemorrhage with BEV+E. Hypertension (any grade: 49% vs 18%; grade≥3: 24% vs 5%), skin rash (grade≥3: 31% vs 14%), thromboembolic events (any grade: 11% vs 4%), and proteinuria (any grade: 23% vs 6%) were more frequent with the experimental combination treatment.

Conclusions:

The addition of BEV to E significantly prolonged IA-PFS compared with E alone as first-line treatment in Italian EGFR-mutated NSCLC patients, with no unexpected safety issues. Blinded radiologic revision of PFS and ORR is ongoing and will be presented at the meeting.

Clinical trial identification:

NCT02633189; EudraCT 2015-002235-17

High dose osimertinib in patients with advanced stage EGFR exon 20 mutation-positive NSCLC: Results from a phase II multicenter study, POSITION20

Background:

Clinical benefit to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI's) is lacking for non-small cell lung cancer (NSCLC) patients with an EGFR exon 20 mutation (EGFRex20+), with known response rate (RR) from 0-28%, and median progression free survival (PFS) of w3 months to 1st and 2nd generation EGFR TKI's (Remon, Cancer Treatment Reviews 2020). A high dose of the 3rd generation TKI osimertinib shows promising antitumor activity to EGFRex20+ in vitro. The safety and efficacy results from a multicenter single arm phase II study investigating osimertinib in EGFRex20+ NSCLC patients are reported here.

Methods:

EGFRex20+ (mutation, deletion and/or insertion), T790M negative, advanced NSCLC patients with WHO PS 0-2 were treated with osimertinib 160mg QD till progression or unacceptable toxicity. We allowed patients to be pre-treated (chemo- or immunotherapy) or/and have asymptomatic brain metastases. Primary endpoint: investigator assessed RECIST 1.1 objective response rate (ORR). Secondary outcomes: duration of response (DoR), PFS, overall survival (OS) and treatment related adverse events (TRAEs).

Results:

From June 2018 to April 2021, 24 patients were enrolled at 4 centers in the Netherlands. The exon 20 mutations were clustered between A763 and D777. The most common mutation was N771_H773duplication (n=3). 6 patients had a response (ORR 27%, 1 complete, 5 partial), 12 had stable disease and 4 progressive disease (PD) as best response. Median DoR was 8.2 months. The median PFS was 5.5 (95% CI 2.09.0) months and the median OS was 15.8 (95% CI 13.8-17.8) months. Primary reasons for discontinuation were PD in 12/24 patients (50%) or due to grade 3 TRAE (2/24 [8%], including pneumonitis [n=1] and left ventricular systolic dysfunction [n=1]). A dose reduction to 80mg was required in 5 patients (21%), of which 2 were due to grade 3 TRAE's (diarrhea and hepatotoxicity) and 3 were due to grade 2 TRAE's(QTc prolongation, nausea and increased CPK in combination with myalgia).

Conclusions:

The POSITION20 study shows antitumor activity in EGFRex20+ NSCLC patients treated with 160mg osimertinib, with an ORR of 27%. The TRAEs are consistent with other reports.

Clinical trial identification:

NTR6875

Impact of radiotherapy pattern on the prognosis of stage IV lung adenocarcinomas harboring EGFR mutations

Background:

The aim of this study was to investigate the role of local radiotherapy in the management of epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancers (NSCLCs) treated with EGFR tyrosine kinase inhibitors (TKIs).

Methods:

Patients with stage IV EGFR-mutant NSCLC treated with radiotherapy concomitant to EGFR TKIs from May 2010 to December 2017 were retrospectively identified. Overall survival (OS) was the primary endpoint of the study.

Results:

A total of 205 patients were enrolled in the study. One hundred eleven patients received one-time single-site radiotherapy (SSR), and 94 patients received multiple-site radiotherapy (MSR). Patients who received MSR had longer OS (median OS, 40.0 months; 95% confidence interval [CI], 29.6 to 50.4) than those who received SSR (median OS, 28.9 months; 95% CI, 24.3 to 33.5; P=0.031). Thoracic radiotherapy was associated with prolonged median OS (41.7 months, 95% CI, 29.0 to 54.4 vs 27.1 months, 95% CI 22.7 to 31.5; log-rank P<0.001). Multivariate analysis confirmed that thoracic radiotherapy was independently associated with improved OS (adjusted hazard ratio [HR], 0.514; 95% CI 32.3% to 81.8%; P=0.005).

Conclusions:

MSR improves survival outcomes in patients with advanced-stage, EGFR mutant, lung adenocarcinoma, with thoracic radiotherapy having the most significant effect on prognosis.

ORCHARD osimertinib + savolitinib interim analysis: A biomarker-directed phase II platform study in patients (pts) with advanced non-small cell lung cancer (NSCLC) whose disease has progressed on first-line (1L) Osimertinib

Background:

Most pts with epidermal growth factor receptor mutation-positive (EGFRm) NSCLC treated with osimertinib, a third-generation, irreversible, CNS-active EGFR-tyrosine kinase inhibitor (TKI), eventually develop resistance. MET alterations are common resistance mechanisms to osimertinib. The phase II ORCHARD platform study (NCT03944772) aims to characterize 1L osimertinib resistance mechanisms and identify optimal post-progression therapies. This interim analysis reports use of osimertinib + savolitinib, an oral, potent and highly selective MET-TKI, in adults with EGFRm advanced NSCLC and MET alterations (MET amplification / MET exon 14 skipping).

Methods:

Pts were allocated to treatment cohorts after disease progression on 1L osimertinib, based on molecular profiling of a tumor biopsy with NGS. Pts whose tumors harbor MET alterations were allocated to osimertinib 80 mg QD + savolitinib 300 or 600 mg QD. Primary endpoint: investigator assessed objective response rate (ORR; RECIST v1.1). Other endpoints include duration of response and safety / tolerability. Interim data cut-off (DCO): Jan 2021.

Results:

Of 20 pts that received osimertinib + savolitinib, median duration on prior 1L osimertinib was 414 (197-1722) days. At DCO, 17 pts were evaluable for confirmed response. ORR was 41% (n=7; 80% CI: 25, 59); 7 pts (41%) had partial response, 7 (41%) had stable disease and 1 (6%) had disease progression as their best response; 2 pts (12%) were not evaluable. Overall, 6 / 20 pts (30%) reported a grade ≥3 adverse event (AE), most commonly pneumonia and decreased neutrophil count (each n=2; 10%); 6 / 20 pts (30%) reported a serious AE. Three pts (15%) discontinued combination treatment due to AEs. No deaths due to AEs were reported.

Conclusions:

Osimertinib + savolitinib showed preliminary activity in pts with MET alterations after 1L osimertinib. Based on interim efficacy, enrolment will continue to 30 pts as pre-specified per protocol. The safety profile was acceptable and consistent with known profiles of osimertinib / savolitinib. Further exploration of this combination is underway in the SAVANNAH study.

Clinical trial identification:

NCT03944772

Afatinib for the treatment of NSCLC with uncommon EGFR mutations: An updated database of 1023 cases

Background:

Optimal treatment (tx) of patients (pts) with NSCLC and uncommon EGFR mutations (non Del19/L858R) remains unclear due to limited clinical data. We previously developed a database of 693 pts with NSCLC and uncommon EGFR mutations treated with afatinib (afa) in RCTs and real-world practice. Here, we provide an update of >1000 pts, with more data on specific mutations.

Methods:

Pts were identified from a prospective database developed by Boehringer Ingelheim and published cases. Pts were categorized as T790M+, ex20ins, major uncommon (G719X, L861Q, S768I) and 'other' mutations. Pts with compound mutations (≥2 any/≥1 uncommon EGFR mutations) were also analyzed. Key endpoints were time to tx failure (TTF) and ORR (mostly based on investigator review).

Results:

1023 pts were identified: EGFR TKI naïve/pretreated/unknown n = 587/425/ 11. Most pts were treated in clinical studies/compassionate use programs. Demographics (TKI naïve/pretreated): Asian 63/46%; ≥75 yrs 20/11%; female 53/64%, confirmed brain mets 12/6%. Mutation categories (TKI naïve/pretreated): T790M+ 10/35%; ex20ins 23/20%; major 52/28%; other 15/18% (including E709X 3/3%, L747X 3/<1%); compound 31/49%. Overall, median TTF (TKI naïve/pretreated): 10.7/4.5 mos. Median TTF (TKI naïve) in Asians/non-Asians and pts with brain mets: 11.5/10.3 and 8.2 mos. ORR (TKI naïve) in major uncommon, compound and other mutations was 59/64/64%. The table shows TTF and ORR (TKI naïve) by mutation category. Few ex20ins were fully described, but notable activity was seen against some subtypes such as A763, M766, N771, V769. 15 pts with known acquired EGFR resistance mutations to osimertinib (osi; G724S, L718X, C797S) were given afa post osi: ORR: 36%.

Conclusions:

Afa showed activity against major uncommon, compound, other (including E709X and L747X) and some specific ex20ins mutations. The data support the use of afa in these settings. Moderate activity was seen post-osi.

Table: 1212P

Mutation category, pts (n)	Median TTF, mos (95% CI)	ORR, %
T790M, (59)	4.7 (2.8–6.5)	26.2
Exon20ins, (135)	5.7 (4.8–8.3)	27.2
Fully described, (23)	9.1 (5.2–14.2)	47.4
Major uncommon, (305)	12.6 (11.5–15.9)	59.0
Others, (88)	10.7 (7.0–12.0)	63.9
E709X, (15)	11.4 (3.8–19.3)	84.6
L747X, (18)	14.7 (9.0–19.8)	80.0
Compound, (182)	11.5 (9.5–13.8)	63.9
With major, (90)	16.0 (14.2–20.5)	73.5
With exon20ins, (11)	12.5 (3.8–13.1)	55.6
With T790M, (48)	4.7 (3.0–6.5)	31.4
With others, (33)	11.5 (9.5–13.8)	78.6

Characterization and management of mobocertinib (TAK788) induced skin toxicity in patients with EGFR exon 20 insertion+ (ex20ins+) non-small cell lung cancer (NSCLC) who previously received platinum chemotherapy

Background:

Mobocertinib, an oral EGFR tyrosine kinase inhibitor (TKI) designed to target EGFRex20ins mutations, demonstrated clinical efficacy in 114 platinum-pretreated EGFRex20ins+ NSCLC patients (PPP) in a phase I/II study. Confirmed objective responses by independent assessment were reported in 28% of patients with median duration of response of 17.5 months. Skin toxicities are commonly reported with irreversible EGFR TKIs, including skin rash, dry skin, and paronychia.

Methods:

All patients received 160 mg QD mobocertinib. We report type and incidence of any-grade (gr) and gr ≥3 skin toxicity treatment-emergent adverse events (TEAEs), frequency of dose modifications (reduction, discontinuation), and management of these events.

Results:

Among 114 patients in the PPP cohort, skin toxicity events were observed in 105 (92%), with gr ≥3 events in 5 patients (4%). No patients had serious events, 5 (4%) doses reduced, and 1 patient (<1%) required dose discontinuation. Median time to onset was 9 days and median time to resolution of gr 2 and gr 3 events were 9 and 5 weeks, respectively. Rash, paronychia, dry skin, and pruritus were the most commonly reported skin toxicities (>20% of patients) (Table). Proactive management included skin care and use of topical corticosteroids (43%) including hydrocortisone (12%) and antibiotics (28%), such as clindamycin (21%) and mupirocin (18%).

Conclusions:

The majority of skin toxicity events were low grade, started within the first 2 weeks of treatment, and were largely managed with skin care and proactive use of topical steroids and/or antibiotics. Types of skin toxicities observed with mobocertinib are consistent with those reported with the class of EGFR TKIs, with low frequency of high-grade toxicity.

Clinical trial identification:

NCT02716116

Table: 1231P Skin toxicity TEAEs in >10% of patients

Data cut-off: 01 November 2020	Platinum-pretreated patients N = 114 n (%)
Patients with ≥1 skin event	**105 (92)**
Rash*	97 (85)
Rash	52 (46)
Pruritus	29 (25)
Dermatitis acneiform	22 (19)
Rash maculopapular	16 (14)
Paronychia	44 (39)
Dry skin	41 (36)
Alopecia	23 (20)

*TEAEs grouped under Rash

Tepotinib + osimertinib for EGFR-mutant NSCLC with resistance to first-line osimertinib due to MET amplification (METamp): INSIGHT 2

Background:

METamp is a mechanism of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs), occurring in 7e15% of patients (pts) who progress on first-line osimertinib. Tepotinib is an oral, once daily (QD), highly selective, potent MET TKI. Tepotinib + gefitinib improved outcomes vs chemotherapy in pts with EGFR-mutant METamp NSCLC and EGFR TKI resistance (INSIGHT; NCT01982955). Median progression-free survival (PFS) was 16.6 vs 4.2 months (HR=0.13; 90% CI: 0.04, 0.43) and median overall survival (OS) was 37.3 vs 13.1 months (HR¼0.08; 90% CI: 0.01, 0.51). The objective response (OR) rate was 67% vs 43% (odds ratio=2.67; 90% CI: 0.37, 19.56), and duration of response (DOR) was 19.9 (90% CI: 7.0, NE) vs 2.8 months (90% CI: 2.8, 9.7). Tepotinib + osimertinib may overcome MET-related osimertinib resistance.

Trial design:

INSIGHT 2 (NCT03940703) is a global, open-label, phase II trial of tepotinib + osimertinib in pts with advanced EGFR-mutant NSCLC. Pts with acquired resistance to first-line osimertinib and METamp are enrolling (protocol amendment, April 2020). Pts must be ≥18 years old, ECOG PS 0/1 and have normal organ function. METamp in tissue and liquid biopsies, obtained at osimertinib progression, will be centrally confirmed by fluorescence in situ hybridization (FISH) and blood-based next generation sequencing, respectively. For pts with METamp detected by local FISH, central confirmation is not mandated prior to treatment initiation. Pts will receive tepotinib 500 mg (450 mg active moiety) QD + osimertinib 80 mg QD until progressive disease (PD) or withdrawal. The estimated enrollment is 120 pts. The primary endpoint is OR by independent review committee (IRC) (RECIST v1.1) in pts with METamp, centrally confirmed by FISH. Secondary endpoints: OR by investigator assessment, DOR, disease control, PFS, OS, pharmacokinetics, health-related quality of life, tolerability, and safety. An exploratory tepotinib monotherapy arm will enroll 12 pts. At PD (by IRC), pts can switch to combination treatment. These pts will be analyzed separately. Recruitment is ongoing; approximately 125 sites in 17 countries are expected to participate. As of April 2021, 95 sites are active.

Clinical trial identification:

NCT03940703

AUTOMAN: A phase Ib/IIa study of osimertinib combined with anlotinib in EGFRm, treatment-naive advanced NSCLC patients

Background:

Osimertinib has been demonstrated superior PFS and OS compared to 1st-generation EGFR-TKIs. There is little information on efficacy and safety of combined therapy with Anlotinib which is an oral multiple-target TKI (inhibit VEGFR2/3, FGFR1-4, PDGFR α/β, c-Kit, and Ret) in advanced EGFRm NSCLC patients.

Methods:

This open-label, single arm, phase Ib/IIa study is expected to enroll 25 treatment-naïve patients of locally advanced or metastatic non-squamous EGFRm NSCLC. The phase Ib adopted the rolling six design to assess the tolerability and safety of Osimertinib combined with Anlotinib. The dosing of Osimertinib was 80mg p.o. daily in combination with Anlotinib which administrated 8mg, 10mg and 12mg p.o. daily from day 1 to day 14 (21 days per cycle) in each cohort respectively. Phase IIa is an expansion cohort at the recommended phase II dose (RP2D). The primary endpoint of this study is objective response rate (ORR). Secondary endpoints include disease control rate (DCR), depth of response, progression free survival, overall survival rate at 12 months and safety profile.

Results:

As of the 25th, Apr 2021 (DCO), 12 patients were allocated in dose escalation part and 7 patients in dose expansion part. Osimertinib in combination with Anlotinib was well tolerated, and the RP2D was Osimertinib 80 mg p.o. daily in combination with Anlotinib 12mg p.o. daily from day 1 to day 14 (21 days per cycle). Overall, 8 patients completed first assessment. The ORR was 87.5% (95% CI 52.9, 97.8), DCR was 100% (95% CI 67.6, 100.0) and median depth of response was 35.0% (range 26%71%). At the DCO, 18 patients remained on treatment and 1 patient discontinued treatment due to AE. Treatment-emergent AEs (TEAEs) occurred in 6 patients (50%) and 1 patient experienced 1 grade 3 SAE (pneumothorax). The common (≥10%) TEAEs was stomatitis (n=4, 33.3%). No Osimertinib-related discontinuations or interruption and no treatment related deaths were observed.

Conclusions:

Osimertinib in combination with Anlotinib is well tolerated and has demonstrated encouraging antitumor activity in treatment naïve EGFRm advanced NSCLC patients. The phase IIa part enrollment is currently ongoing and results will be updated later in the meeting.

Clinical trial identification:

NCT04770688

Pharmacokinetic and dose finding study of osimertinib in patients with impaired renal function and low body weight

Background:

his dose-finding study of osimertinib aimed to investigate the safety, pharmacokinetics (PK), and recommended dose (RD) for EGFR-mutated non-small cell lung carcinoma (NSCLC) patients with impaired renal function and low body weight.

Methods:

NSCLC patients with activated EGFR mutations, regardless of T790M mutation, were allocated into the following four cohorts according to renal function and body weight: cohort A, normal renal function (eGFR ≥50 mL/min/1.73 m2) and normal body weight (≥ 45 kg); cohort B, moderate renal dysfunction (eGFR = 30-50 mL/min/1.73 m2); cohort C, low body weight (< 45 kg); and cohort D, severe renal dysfunction (eGFR < 30 mL/min/1.73 m2 or undergoing dialysis). We evaluated the PK and safety in cohort A as the control group. Cohorts B, C, and D consisted of two parts, dose-escalation using a standard 3 + 3 design and expansion. The starting dose of osimertinib in cohorts A, B, and C was 80 mg once daily, while for cohort D, it was 40 mg once daily. For PK analysis, serial blood samples were collected on days 1 and 15, and pre-dose blood samples were collected on days 29 and 56.

Results:

Thirty eligible patients with EGFR-mutated NSCLC were enrolled in eight institutions in Japan. In cohort A, one patient discontinued osimertinib therapy on day six due to an exacerbation of chronic obstructive pulmonary disease. Twenty-nine patients were evaluated for PK and safety (N=12 for A, N=8 for B, N=8 for C, and N=1 for D). In the dose-escalation part, no DLT was observed, and the RD was determined to be 80 mg once in cohorts B and C. Due to the poor accrual, only one patient was included in cohort D. Four serious adverse events occurred in this study, and two considered to be related to osimertinib (heart failure grade 3 in cohort B and ILD grade 3 in cohort C). The PK parameters of osimertinib in cohorts A, B, and C were similar. However, the toxicity of any grade occurred more frequently in cohorts B and C than in cohort A.

Conclusions:

The RD of osimertinib was determined to be 80 mg once for patients with moderate renal function (cohort B) and low body weight (cohort C). Although the PK parameters of osimertinib were similar across all cohorts, toxicity occurred more frequently in cohorts B and C than in cohort A.

Clinical trial identification:

UMIN000033301

Anlotinib with gefitinib as first-line therapy in advanced non-small cell lung cancer harboring EGFR mutations: A phase II study

Background:

Anti-angiogenic monoclonal antibodies combined with EGFR-TKI has shown excellent efficacy and prolong PFS in patients(pts) with EGFR mutations. Anlotinib, an oral and multi-target tyrosine kinase inhibitor, has significantly improved OS and PFS in advanced NSCLC pts in the ALTER0303 study. This is the first trial evaluating anlotinib plus gefitinib in treatment-naive advanced NSCLC pts.

Methods:

This is a prospective, single-arm clinical trial. Pts with previously untreated, EGFR mutationepositive (exon 19 deletion or L858R) advanced NSCLC were enrolled. Eligible pts received anlotinib (12 mg QD from day 1 to 14 of a 21-day cycle) and gefitinib (at a dose of 250 mg once daily) until disease progression or treatment intolerance. The primary endpoint is PFS. Secondary endpoints are ORR, DCR and OS and safety.

Results:

rom May 2019 to Feb 2021, a total of 21 pts were enrolled. As of March 18, 2021, median follow-up was 7.6 months. Among all pts, 13 pts achieved PR, 8 pts achieved SD. ORR was 61.9%, DCR was 100%. Median PFS was not reached. 16 pts are still receiving treatment and the longest exposure was 22.9 months. 10 (77%) of 13 pts with exon 19 deletions and 3 (38%) of 8 pts with L858R mutations achieved an objective response. The most common Grade 3 TRAE were hypertension (14.3 %), rash (9.5%) and hand and foot skin reaction (9.5%), and no grade 4/5 observation.

Conclusions:

The combination of anlotinib and gefitinib showed a promising efficacy for previously untreated, EGFR mutation-positive advanced NSCLC pts, and with a manageable safety profile. The PFS and OS outcomes need further evaluation.

Osimertinib and crizotinib cardiotoxicity: Are real-world studies the way forward?

Background:

Whilst tyrosine-kinase inhibitors (TKIs) have revolutionized the treatment of non-small cell lung cancer (NSCLC), some are associated with cardiotoxicity. With eligibility criteria not as restrictive as clinical trials, real-world data is needed for establishing safety. This study aims to compare the development of cardiotoxicity in the real-world setting to those reported in clinical trials. We investigated whether patients who developed cardiotoxicity induced by osimertinib and crizotinib would have met respective clinical trials inclusion criteria.

Methods:

Retrospective data with inclusion criteria of having received at least one dose of a UK approved TKI at the Royal Marsden. This was over a two-year timeframe (2017-2019), providing a meaningful sample size. Cardiotoxicity was defined as per CTCAE V.5. A literature review was conducted on PubMed, Science Direct and ClinicalTrials.gov to identify published trials on osimertinib and crizotinib. Patients who developed cardiotoxicity associated with osimertinib and crizotinib in our real-world study were compared to trials eligibility criteria. Variations of cardiotoxicity incidence among the real-world study and clinical trials were investigated. FLAURA, AURA3, PROFILE1007 and PROFILE1014 were the trials included for analysis.

Results:

18% (n=37/206) of patients developed cardiotoxicity. Osimertinib and crizotinib were responsible for n=7/33, 21.2%, and n=7/22, 31.8% of cardiotoxicities, respectively. None of the patients would have been eligible to participate in FLAURA and PROFILE1014 trials whereas n=4/7 and n=5/7 patients would have been eligible to enroll in AURA3 and PROFILE1007. Exclusion reasons were prior treatment with other anti-cancer agents and the presence of other diseases. Cardiotoxicity incidence in the real-world study is consistent with FLAURA (20%) (OR=1.04, P=0.09), but higher than AURA3 (9.8%) (OR=2.5, P=0.07), PROFILE1007 (4.1%) (OR=11, P<0.001) and PROFILE1014 (2.3%) (OR=19.5, P<0.001).

Conclusions:

Although clinical trials give the drug a license, real-world studies are needed to show the true safety profile and the real risk of cardiotoxicity. Further investigation is required into risk factors contributing to the development of cardiotoxicity.

Final results of APOLLO study: Overall survival (OS) of aumolertinib in patients with pretreated EGFR T790M-positive locally advanced or metastatic non-small cell lung cancer (NSCLC)

Background:

Aumolertinib is a novel, irreversible third generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI). APOLLO, a pivotal phase II single arm study (NCT02981108), has demonstrated progression-free survival (PFS) benefit with a favorable safety profile in pretreated EGFR T790M positive NSCLC patients.

Methods:

Adult pts received aumolertinib 110 mg once daily until disease progression. Treatment beyond progression was allowed if clinical benefit was expected. The primary endpoint was objective response rate by independent central review. Secondary endpoints included PFS, OS and safety. Explore endpoints included the drug resistance mechanism.

Results:

At data cutoff (Jul 20, 2021), 126 (51.6%) pts had died among 244 pts. The median follow-up time was 34.5 mo (95%CI 34.0-35.4). The median OS was 30.2 mo (95% CI, 24.2-36.4), and the OS rate at 24 mo was 57.5% (95% CI, 50.8-63.6). OS analyses across pts subgroups was summarized in the table. A total of 82 (33.6%) pts continued aumolertinib treatment beyond disease progression. Forty-two pts had molecular profiling using tumor tissue or blood samples upon first progression on aumolertinib. Seven pts had acquired EGFR C797S in cis with T790M. EGFR L718Q mutation was found in 1 pt. Aberrations in bypass tracks including PIK3CA, JAK2, BRAF and KRAS mutation, HER2 amplification and FGFR3-TACC3 fusion were found in 8 pts. The safety profile of aumolertinib remained consistent with previous data.

Conclusions:

Clinical benefit in OS was observed in pts with pretreated EGFR T790Mpositive advanced NSCLC receiving aumolertinib. The common mechanisms of resistance to aumolertinib were EGFR C797S mutation and aberrations in bypass tracks.

Clinical trial identification:

NCT02981108

Table: 1208P

	mOS (95% CI), mo
EGFR mutation	
Ex19del	30.2 (23.8, NA)
L858R	28.5 (22.7, NA)
Brain metastases at baseline	
Yes	19.1 (16.0, 23.7)
No	36.4 (31.5, NA)
Sex	
Male	25.2 (20.4, 32.5)
Female	34.7 (25.9, NA)
Age	
<65yr	34.1 (23.9, NA)
≥65yr	28.4 (22.9, 34.7)
Smoking history	
Yes	23.9 (18.2, 34.1)
No	32.5 (25.6, NA)
WHO PS	
0	34.1 (27.9, NA)
1	27.0 (20.2, 36.4)

RELAY, ramucirumab plus erlotinib (RAMDERL) in untreated metastatic EGFR-mutant NSCLC (EGFRDNSCLC): Association between TP53 status and clinical outcome

Background:

Tumour Protein 53 (TP53) plays a role in angiogenesis by regulating vascular endothelial growth factor A (VEGFA) and VEGF receptor 2 (VEGFR2). In patients (pts) with EGFR+ NSCLC, TP53 mutations, notably on exon 8, are associated with poorer outcomes of EGFR tyrosine kinase inhibitor treatment and may be involved in primary resistance. We evaluated the relationship between TP53 status and outcomes in RELAY.

Methods:

Pts with untreated metastatic EGFR+ NSCLC received oral ERL (150 mg/day) with either intravenous RAM (10 mg/kg) or placebo (P+ERL) every 2 weeks. This exploratory analysis consisted of 386 pts with any mutation detected at baseline by Guardant 360 next-generation sequencing. The primary endpoint was PFS. Secondary and exploratory endpoints included overall response rate (ORR), disease control rate (DCR), DoR, overall survival (OS), safety, and biomarker analysis. TP53 status was assessed in relation to outcomes and treatment-emergent gene alterations at progression.

Results:

TP53 mutations were detected in 46% of White and 42% of Asian pts and was similar for EGFR exon 19 and exon 21 mutations (w43%). Other pt and disease characteristics and concurrent gene alterations were comparable between TP53 mutant (mt) and wildtype (wt) tumors. Irrespective of treatment, pts with TP53 mutations, notably on exon 8, had worse outcomes than pts with TP53wt. In all pts, RAM+ERL improved PFS and DoR, while ORR (78% to 82%) and DCR (95% to 97%) were similar. OS data were immature. Safety was comparable between TP53mt and wt subgroups. Treatment-emergent T790M mutation rates at progression were higher in TP53mt (33% to 39%) than TP53wt tumors (19% to 21%) regardless of treatment.

Conclusions:

The addition of RAM to ERL showed consistent benefit in both TP53wt and TP53mt EGFR+ NSCLC, suggesting that the RELAY regimen is a suitable first-line treatment option for pts with EGFR+ NSCLC irrespective of TP53 status.

Clinical trial identification:

NCT02411448

Indirect comparison of mobocertinib and standard of care in platinum-pretreated patients with NSCLC with EGFR exon 20 insertion

Background:

Mobocertinib, a novel EGFR tyrosine kinase inhibitor (TKI), demonstrated clinically meaningful benefit in platinum-pretreated patients with EGFR exon 20 insertion mutant (EGFRex20ins+) non-small cell lung cancer (NSCLC) in an open label, multicenter clinical trial. This study describes an indirect comparison of clinical outcomes for platinum-pretreated patients with EGFRex20ins+ NSCLC treated with mobocertinib in a clinical trial vs. standard of care (SoC) from real-world data (RWD).

Methods:

Clinical outcomes were compared for platinum-pretreated patients with EGFRex20ins+ NSCLC treated with mobocertinib 160 mg QD in a phase I/II trial (NCT02716116; cutoff 1 Nov 2020) vs. SoC in the post-platinum second or later line (≥2L) setting from the Flatiron electronic health record database (RWD; cutoff 29 Feb 2020). The analysis was conducted in an unadjusted data set and using propensity score modeling with inverse probability of treatment weighting (IPTW) to adjust for group differences in key baseline characteristics. Confirmed overall response rate (cORR), progression-free survival (PFS), and overall survival (OS) were compared between groups.

Results:

This study included 164 platinum-pretreated patients (n¼114 mobocertinib/ n¼50 RWD; mean age 60/64 years; female, 66%/68%; smoking history 29%/42%; with baseline brain metastasis, 35%/34%). In the RWD, ≥2L SoC treatment consisted of 20% EGFR TKI, 40% immunotherapy alone, and 40% chemotherapy ± immunotherapy or monoclonal antibody. Baseline characteristics were balanced after weighting. In the weighted cohort, cORR for mobocertinib vs. RWD was 35 % vs. 12%, median PFS was 7.3 vs. 3.3 mo, and median OS was 24.0 vs. 12.4 mo, respectively (Table).

Conclusions:

Mobocertinib was associated with significant improvements in cORR, PFS, and OS compared to SoC used in the in platinum-pretreated patients with EGFRex20ins+ NSCLC.

Table: 1211P

	Mobocertinib (n=114)[a]	RWD Post-platinum ≥2L [b]	
		Unweighted (n=50)	Weighted (n=109)
cORR % (95% CI)	35 (26, 45)	14 (6, 27)	12 (6, 18)
Rate difference % (95% CI)		21 (8, 34)	23 (12, 34)
Odds ratio (95% CI)[c]		3.32 (1.68, 6.58)	3.75 (2.05, 6.89)
P-value		0.0006	<0.001
Median PFS, mo (95% CI)	7.3 (5.6, 8.8)	3.3 (2.3, 5.9)	3.3 (2.2, 7.3)
HR (95% CI)[d]		0.57 (0.36, 0.89)	0.57 (0.36, 0.90)
P-value		0.0149	0.0153
Median OS, mo (95% CI)	24.0 (14.6, 28.8)	11.5 (7.9, 16.6)	12.4 (7.1, 16.6)
HR (95% CI)[d]		0.54 (0.34, 0.84)	0.53 (0.33, 0.83)
P-value		0.0068	0.0056

[a]cORR and PFS: per investigator using RECIST 1.1 [b]cORR: confirmed real-world response by radiologic imaging [c]Logistic model [d]Cox model CI, confidence interval; HR, hazard ratio

Sequential afatinib (afa) and osimertinib (osi) in patients (pts) with advanced EGFR mutation-positive (EGFRm+) NSCLC who acquire the T790M resistance mutation: A noninterventional cohort study (UpSwinG)

Background:

While 2nd- and 3rd-gen EGFR TKIs have shown clinical benefit vs 1st-gen EGFR TKIs in pts with EGFRm+ NSCLC, optimal sequence of treatment (tx) has yet to be defined. Overall survival (OS) is influenced by the availability/use of subsequent therapy after 1st-line tx. Emergence of T790M is the main mechanism of resistance to 2nd-gen EGFR TKIs and 2nd-line osi could be a tx option in this instance. A previous study (GioTag) showed median OS of >3 yrs in T790M+ pts treated with sequential afa/osi.

Methods:

In this non-interventional, global study (NCT04179890), existing medical/ electronic records were identified for consecutive EGFR TKI-naïve pts with EGFRm+ NSCLC (Del19 or L858R) treated with 1st-line afa/2nd-line osi in regular clinical practice (n ¼ 191; all T790M+). Primary objective: time to tx failure (TTF). Key secondary objectives: OS and ORR.

Results:

At the start of afa: median age (range) 62 yrs (34e88); female 55%; Asian 67%; ECOG PS (0/1/≥2) 31%/57%/12%; brain mets 14%; Del19/L858R 71%/29%. At the start of osi: ECOG PS (0/1/≥2) 25%/61%/14%; brain mets 14% (end of osi: 29%). Source of biopsy material (solid/liquid) 86%/3% at the start of afa; 54%/33% at the start of osi. Mutations were mainly detected with PCR methods (81%/86% at start of afa/osi). Overall, median TTF was 27.7 mos (afa 15.1 mos; osi 9.5 mos) and median OS was 36.5 mos. Median time from end of osi to death was 5.0 mos. ORR with afa and osi was 74% and 45%. TTF, OS and ORR were generally consistent across subgroups (Table).

Conclusions:

These data support the previous GioTag study and show encouraging activity of sequential afa/osi in pts with EGFRm+ NSCLC and acquired T790M. Activity was highest in Asian pts with Del19 mutations but was observed across all subgroups including pts with poor ECOG PS or brain mets. ECOG PS and incidence of brain mets remained stable prior to, and after, afa tx.

Clinical trial identification:

NCT04179890

Poziotinib in NSCLC harbouring EGFR or HER2 exon 20 insertion mutation

Background:

Patients (pts) with advanced Non-Small Cell Lung Cancer (aNSCLC) harbouring an EGFR and HER2 exon 20 insertion mutation (ex20-ins) display a poor prognosis compare to wild type aNSCLC and their treatments remain unsatisfied. Poziotinib (POZ) a new generation tyrosine kinase inhibitor (ngTKI) demonstrated activity in EGFR and HER2 ex20-ins. The aim of this study is to compare overall survival (OS) of the expanded access program (EAP) pts cohort treated with POZ (POZ-c) with historical cohort of aNSCLC pts not treated with POZ (NPOZ-c) to assess the adding value of POZ.

Methods:

We collected data from 30 pts in the POZ-c form May 2018 to April 2021 treated with POZ 16mg once daily or less and from 28 pts in the NPOZ-c from April 2010 until May 2020. None of NPOZ-c were treated with ngTKI. A propensity score approach (PCA) was used in order assess differences variable distribution (sex, age, ECOG, type of mutation, first-line (1L) therapy, baseline bone, brain, pleural-pericardial metastases (mts) among cohorts and to estimate the effect of POZ on survival. Hazard ratio (HR) was calculated under proportional hazards model.

Results:

Among 58 pts included in the study at IV-stage diagnosis time median age were 58 years (y) (24 e 80 y). Most pts were female (70%), young < 70 y (76%) and had ECOG 0-1 (88%), an EGFR ex20-ins (77%), presented with bone mts (65%) and used platinum based as 1L (76%). Brain mts were present in 36%. Overall median OS (mOS) for both cohorts was 19.5 months (m) (95%CI, 16.6 -22.3 m). No differences were seen among mOS in POZ-c and NPOZ-c: 19.2 m (95% CI 16.2 -23.8) vs 18.2 m (95% CI 8.3 - 27.0), respectively, with a hazard ratio (HR) of 0.82 (95%CI, 0.47 e 1.44). The PCA showed that POZ-c had a worse clinical characteristics presentation at baseline (AUC¼0.80) than NPOZ-c. Thus, adjusting the Cox hazard model for the PCA the risk mortality of POZ-c was reduced from 18to34% (HR0.66 95% CI, 0.35 e 1.24, p value=0.207).

Conclusions:

POZ showed a clinical activity in aNSCLC EGFR/HER2 ex20-ins aNSCLC pts. Despite the not significant differences between mOS among cohorts, in the adjusted model we can observe a reduction in risk mortality in the POZ-c compare to NPOZ-c, this to demonstrate the POZ adding value in improving prognosis. Due to the small sample size these data have to be validated in larger cohorts.

Effectiveness of osimertinib plus chemotherapy and avastin for EGFR-mutated advanced non-small cell lung cancer with brain metastases

Background:

Previous studies suggested that the addition of bevacizumab (7. 5/15 mg/kg) tends to have PFS benefit for patients with asymptomatic CNS metastases. Therefore, whether osimertinib plus bevacizumab (15 mg/kg) could benefit those patients with multiple BMs remains undetermined, especially for those with edema.

Methods:

The study was expected to enroll 26 patients diagnosed with EGFR-mutant NSCLC and brain metastases who received osimertinib (80mg QD) plus pemetrexed (500mg/m^2), cisplatin (75mg/m^2) and bevacizumab (15mg/kg) for 6 cycles, then maintained with osimertinib/bevacizumab (15mg/kg), and not received radiotherapy. The primary endpoint was intracranial objective response rate (iORR), the secondary endpoint was the reduction of edema index (EI). Treatment was continued until disease progression and the tumor response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. EI was calculated according to Chinese Consensus Guidelines for Brain Edema Therapy. The toxicity was determined according to CTCAE 4.0.

Results:

From February 2018 to January 2021, 26 patients enrolled showed in the table. All the patients were evaluable and showed partial response (PR) when make efficacy evaluation at the first time. The average reduction of the intracranial target lesions is 48.8%, ranged from 33% of Pt12 to 72% of Pt24. The average edema index (EI) reduction is of 3.49, 6 patients had no edema after therapy evaluated at the first time, Pt2 reduced from severe edema to moderate edema, and Pt20 reduced from moderate edema to mild edema. The toxicities associated with these protocols were manageable. Only 1 patient was 3/4-grade diarrhea and 3 patients was 3/4-grade lymphopenia.

Conclusions:

Osimertinib in combination with chemotherapy and Bevacizumab exhibits superior activity and generally manageable toxicities for the EGFR-mutated advanced NSCLC patients with brain metastases, and also for the patients with concurrent edema. It may provide a new and effective therapy strategy for them, but large sample and additional clinical trials are also needed.

Table: 1216P

Baseline patient characteristic	Patients (N=26)
Age (years old)	
Average age	45
Range	23-67
Gender, n (%)	
Men	10 (38%)
Women	16 (62%)
ECOG PS, n (%)	
0	1 (4%)
1	21 (81%)
2	4 (15%)
History of tobacco use, n (%)	
Never	17 (65%)
Current	2 (9%)
Previous	7 (26%)
Brain metastasis with edema, n (%)	
Yes	8 (31%)
No	18 (69%)
No. of therapy lines	
1 lines	7 (27%)
≥2 lines	19 (73%)
Mutation type, n (%)	
L858R	15 (57%)
19del	11 (43%)

The progression-free survival of the first-line EGFR-TKI is a strong prognosticator of the second-line osimertinib in nonsmall cell lung cancer (NSCLC) patients with EGFR-T790M mutation: A real-world study

Background:

As a third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), osimertinib is recommended as standardized treatment for advanced or metastatic non-small cell lung cancer (NSCLC) patients with EGFR-T790M mutation after progressed on first-line EGFR-TKI. Our study aims to investigate the prognostic value of first-line EGFR-TKI on the second-line osimertinib in the real-world practice.

Methods:

A total of 198 NSCLC patients with EGFR-T790M between 2016 and 2020 were included in this study. All patients were resistant to first-line EGFR-TKI and received osimertinib as second-line therapy. The endpoint was the occurrence of progression on osimertinib. Univariate and multivariate COX regression analysis were used to identify the prognostic value of clinical factors. Log-rank test was conducted to compare survival outcomes of different groups.

Results:

At the end of follow-up, disease progression occurred in 132 (66.7%) patients. The median PFS of the second-line osimertinib was 12.2-Mo (95%CI: 10.8-14.7 Mo). In the first-line EGFR-TKI treatment, the median PFS of the total cohort was 13.0 Mo. A longer PFS of the first-line EGFR-TKI was associated with a delayed disease progress of the second-line osimertinib (HR, 95%: 0.969, 0.948-0.990, P=0.004) in univariate analysis. Other factors that could predict the survival outcomes of the second-line osimertinib therapy included pretreatment T stage, M stage and performance status. In the multivariate analysis, the PFS of the first-line EGFR-TKI was still a predictor of the second-line osimertinib (HR, 95%: 0.970, 0.948-0.993, P=0.011). Patients with PFS of the first-line EGFR-TKI over 13.0 Mo had much favorable prognosis in the second-line osimertinib than those with PFS of the first-line EGFR-TKI less than 13.0 Mo (median PFS: 17.0 Mo vs. 10.2 Mo, P=0.009).

Conclusions:

Our study identified that the PFS of the first-line EGFR-TKI was a strong prognosticator of the second-line osimertinib for NSCLC patients with EGFR-T790M. This finding would be helpful for clinical decision-making and patients' consultation.

Efficacy and safety of apatinib plus EGFR-TKI in advanced non-small cell lung cancer with EGFR-TKI resistance

Background:

Dual blockade of both EGFR and VEGFR pathways in EGFR-mutant NSCLC has shown enhanced antitumor efficacy versus EGFR-TKIs alone. Apatinib is an orally effective VEGFR-2 tyrosine kinase inhibitor (TKI). Previous studies have shown that apatinib (a TKI against VEGFR-2) combined with EGFR-TKI might prevent progression of the disease. This study aims to evaluate the efficacy and safety of apatinib plus EGFR-TKIs compared with chemotherapy for EGFR-TKI resistant NSCLC patients.

Methods:

From Mar 2017 to Nov 2019, this study enrolled 42 advanced NSCLC patients who acquired resistance to the EGFR-TKI therapy. 27 patients received apatinib plus EGFR-TKI (apatinib in start dose of 250 mg plus original EGFR-TKI dose); 15 patients received chemotherapy (pemetrexed or vinorelbine with platinum).

Results:

In the apatinib group, 24/27 patients were available to be evaluated. The objective response rate (ORR, % (95%CI)) was 20.83% (7.13%-42.15%) and the disease control rate [DCR, % (95%CI)] was 95.83% (78.88%-99.89%). The most common adverse events in the apatinib group were gastrointestinal reaction (70.37%, 19/27), diarrhea (62.92%, 17/27), hypertension (62.97%, 17/27) and palmar-plantar erythrodysesthesia (40.74%, 11/27). The most common grade 3 or 4 toxicity was proteinuria (11.11%, 3/27). Most adverse events were grade 1 or 2, as well as controllable and tolerable. Six patients with brain metastases in the apatinib group got long median progression-free survival (PFS) of 15.66 months. In the chemotherapy group, 12/15 patients were available to be evaluated. The ORR was 25.00% (5.49%-57.19%) and the DCR was 91.67% (61.52%-99.79%). The most common adverse events were gastrointestinal reaction (80.00%, 12/15) and vomiting (46.67%, 7/15). The median PFS of the apatinib group was 12.55 months, and the chemotherapy group was 3.78 months. The longest PFS in the apatinib group was 35.93 months.

Conclusions:

Apatinib plus EGFR-TKI shown a good clinical efficacy in patients with acquired EGFR-TKI resistance. Patient's quality of life and the compliance with therapy had been increased by oral drugs. In addition, we found that patients' PFS tended to be prolonged in those with EGFR 21 mutation (15.70 months), or were male (17.13 months).

Clinical trial identification:

ChiCTR-OIN-17012051

MET exon14 skipping in non-small cell lung cancer: Clinicopathological characteristics, treatments, and efficacy of crizotinib according to functional analysis: AFonMET GFPC study

Background:

MET targeted tyrosine kinase inhibitors (TKI) demonstrated efficacy in advanced non-small cell lung cancer (aNSCLC) with METexon 14 skipping mutation (METexon14). Different variants of this mutation exist. Some do not affect the splice sites and may result in incomplete exon 14 skipping. This could explain a different anti-tumor activity of TKI.Functional analysis could specify if the exon skipping is effective.

Methods:

AFonMET was a real-life, retrospective study of the management of METexon14 aNSCLC. Primary endpoint was the median overall survival (mOS) of patients treated with crizotinib and no other TKI (CRIZO-cohort). We also assessed mOS of patients treated with at least one anti-MET TKI (TKI-cohort) and the antitumor activity of crizotinib according to functional analyses results.

Results:

106 treated patients were included between December 2015 and June 2019 in 13 centers: median age 72 years, female: 63%, adenocarcinoma: 86%, stage IV: 92%, more than 3 metastatic sites: 24%. 73% received at least one anti-MET TKI: crizotinib: 70%, tepotinib: 28%, capmatinib: 14%; 10% received two anti-MET TKIs in their treatment sequences. With a median follow-up of 16 months, mOS of the CRIZO cohort was 19.7 (CI95%, 13.6-29.7) months. mOS of patients never treated with crizotinib was 28 (CI95%, 16.4-NR) months. There was no significant difference between these two cohorts (p=0.16). mOS of the TKI-cohort and of the TKI-naïve patient cohort were 27.1 (CI95%, 18-29.7) months and 35.6 (CI95%, 8.6-NR) months respectively, with no significative difference (p=0.7). 39 (73.6%) patients treated with crizotinib had a complete exon 14 skipping variant (group 1) and 8 (15.1%) a partial exon skipping variant (group 2). Duration of treatment and overall response rate with crizotinib were not statistically different between groups: 5.2 (CI95% 2.58.2) vs 5.6 (CI95% 0.9-22.3) months (p=0.6), and 53.8% vs 50% respectively.

Conclusions:

In this real-life study, there was no evidence of benefit in OS with antiMET TKIs. Functional analyses of MET exon 14 variants do not predict better efficacy of crizotinib. An update of the data will be presented at the congress.

Elderly patients treated with afatinib in clinical practice: Final results of the GIDEON study in EGFR mutated NSCLC in Germany

Background:

Despite the high prevalence of lung cancer among older adults, these are often under-represented in clinical trials, leading to uncertainties in the treatment of these patients in the clinical routine. With 43%, the German prospective non-interventional study (NIS) GIDEON enrolled a high proportion of patients aged ≥70 years, providing an opportunity to study the efficacy and safety of afatinib in this subcohort in routine clinical practice.

Methods:

161 EGFR-mutated NSCLC patients were enrolled from 41 sites in Germany. 152 received at least one dose of afatinib, 146 patients were treated according to label. Efficacy (12-months progression-free survival (PFS) rate; objective response rate, ORR; disease control rate, DCR; progression-free survival, PFS and overall survival, OS) was prospectively assessed by investigators. Data about tolerability were collected during routine treatment. Exploratory post hoc analyses according to age group (<70 years, ≥70 years) were undertaken. All analyses were descriptive. Therefore, testing for statistical significance between patient groups was not performed.

Results:

The most important results are summarized in the table.

Table: 1230P

	<70 years (n=86)	≥70 years (n=66)
Del19 / L858R / others ex 18-21	65% / 26% / 9%	64% / 18% / 18%
ECOG PS 0 / 1 / 2 / higher /	53% / 41% / 0 / 1%	41% / 45% / 6% / 3%
missing	5%	5%
Comorbidity index		
0	74%	38%
≥ 1	26%	62%
Starting dose		
40mg	84%	62%
< 40mg	16%	38%
efficacy		
mPFS	10.6 mo	17.2 mo
12-mo PFS rate	44%	59%
mOS	27.4 mo	30.4 mo
12-mo OS rate / 24-mo OS rate	79% / 62%	79% / 52%
ORR / DCR	76% / 88%	72% / 96%
safety		
ADRs (all grades)	97%	95%
ADRs (≥ grade 3)*	41%	35%
Dose reduction	62%	58%

Conclusions:

Elderly patients (!70 years) were well represented in GIDEON. Although these patients tended to have a worse ECOG PS and a higher proportion had a comorbidity index of ≥1, this seemed not to compromise efficacy. Furthermore, the safety profile of afatinib in elderly patients was similar to that seen in the younger subgroup with no new safety signals.

Clinical trial identification:

NCT02047903

ALK-2016-CPHG: French cohort of advanced non-small cell lung cancer (aNSCLC) with ALK (ALK+) or ROS1 (ROS1+) gene rearrangement treated by crizotinib

Background:

Crizotinib is the first tyrosine kinase inhibitor authorized for the treatment of aNSCLC ALK+ or ROS1+, regardless of lines. Real-world (RW) data is scarce for these populations.

Methods:

We conducted a non-interventional ambispective multicentric study on aNSCLC ALK+ or ROS1+ treated by crizotinib in collaboration with the CPHG (French College of General Hospital Respiratory Physician). The aim was first to describe patient's characteristics, and second to evaluate effectiveness and safety of crizotinib in a RW setting in General Hospital in France.

Results:

73 patients were included: 51 patients ALK+, 22 patients ROS1+. Median age was 65 -year-old [Q1-Q3: 52.0; 73.0], 45 (63.4%) female, 52 (82.5%) patients with ECOG < 2, 40 (56.3%) non-smokers. 70 (98.6%) adenocarcinoma, 62 (87.3%) stage IV. Bone and cerebral metastasis presented respectively in 46% and 12.7%. Diagnostic was usually histologic (90.1%) on primitive tumor (73.2%). The median delay between biopsy and positive result for ALK+ or ROS1+ was respectively 10 and 8 days. 26 (36.6%) patients had prior treatment before crizotinib, respectively 20 (28.2%) and 9 (13.6%) chemotherapy and radiotherapy. 70 (98.6%) patients initiated crizotinib at the recommended dose 250 mg bid and 47 (64.4 %) started crizotinib before inclusion (≤ 3 months). 24 (33.8%) patients had at least one dose reduction and 14 (19.7%) a treatment interruption. Objective Response Rate for ALK+ and ROS 1+ was 62.7% and 55% respectively. Median progression-free survival (IC95) was ALKþ 9.4 months (7-16.1) and ROS1+ 6.6 months (4.3-14.3) median Overall Survival (IC95), not reach (NE-NE) and 13.7 months (5.0 e NE). According to the most recent safety analysis, 74 % and 37% had presented at least one adverse event (AE) and serious AE respectively. The most common AEs of any cause were diarrhea (24.7 %), nausea and oedema (16.4 % both) or vision disorders (12.3 %).

Conclusions:

Our results are consistent with other RW in terms of effectiveness and safety. Crizotinib was effective in both ALK+ and ROS1+ aNSCLC in a real-life setting with no new safety concerns.

Clinical trial identification:

NCT03718117

ALK-2016-CPHG: French cohort of advanced non-small cell lung cancer (aNSCLC) with ALK (ALK+) or ROS1 (ROS1+) gene rearrangement treated by crizotinib

Background:

Crizotinib is the first tyrosine kinase inhibitor authorized for the treatment of aNSCLC ALK+ or ROS1+, regardless of lines. Real-world (RW) data is scarce for these populations.

Methods:

We conducted a non-interventional ambispective multicentric study on aNSCLC ALK+ or ROS1+ treated by crizotinib in collaboration with the CPHG (French College of General Hospital Respiratory Physician). The aim was first to describe patient's characteristics, and second to evaluate effectiveness and safety of crizotinib in a RW setting in General Hospital in France.

Results:

73 patients were included: 51 patients ALK+, 22 patients ROS1+. Median age was 65 -year-old [Q1-Q3: 52.0; 73.0], 45 (63.4%) female, 52 (82.5%) patients with ECOG < 2, 40 (56.3%) non-smokers. 70 (98.6%) adenocarcinoma, 62 (87.3%) stage IV. Bone and cerebral metastasis presented respectively in 46% and 12.7%. Diagnostic was usually histologic (90.1%) on primitive tumor (73.2%). The median delay between biopsy and positive result for ALK+ or ROS1+ was respectively 10 and 8 days. 26 (36.6%) patients had prior treatment before crizotinib, respectively 20 (28.2%) and 9 (13.6%) chemotherapy and radiotherapy. 70 (98.6%) patients initiated crizotinib at the recommended dose 250 mg bid and 47 (64.4 %) started crizotinib before inclusion (≤3 months). 24 (33.8%) patients had at least one dose reduction and 14 (19.7%) a treatment interruption. Objective Response Rate for ALK+ and ROS1þ was 62.7% and 55% respectively. Median progression-free survival (IC95) was ALK+ 9.4 months (7-16.1) and ROS1þ 6.6 months (4.3-14.3) median Overall Survival (IC95), not reach (NE-NE) and 13.7 months (5.0 e NE). According to the most recent safety analysis, 74 % and 37% had presented at least one adverse event (AE) and serious AE respectively. The most common AEs of any cause were diarrhea (24.7 %), nausea and oedema (16.4 % both) or vision disorders (12.3 %).

Conclusions:

Our results are consistent with other RW in terms of effectiveness and safety. Crizotinib was effective in both ALK+ and ROS1+ aNSCLC in a real-life setting with no new safety concerns.

Clinical trial identification:

NCT03718117

BrigALK2 study: A multicentric real-world study evaluating brigatinib in ALK positive advanced pre-treated non-small cell lung cancers: Long-term follow-up with focus on lorlatinib efficacy after brigatinib

Background:

Brigatinib is a next-generation ALK inhibitor (ALKi) approved in ALK+ advanced NSCLC (aNSCLC) pretreated with crizotinib and in first-line setting. The objective of BrigALK study was to assess efficacy of brigatinib during the French early access program (FEAP).

Methods:

BrigALK study retrospectively included ALK+ aNSCLC pretreated with at least one ALKi during brigatinib FEAP. Primary endpoint was investigator-assessed progression-free survival (invPFS). BrigALK2 covered the entire EAP period and was an update of abstract 1392P presented at ESMO 2020 with a longer follow-up and a focus on lorlatinib efficacy after brigatinib.

Results:

183 patients were included by 66 centers in France: median age: 60 ±12.7 years; never smokers: 78.3%; median number of previous lines: 3 ±1.3 and of ALKi: 2 ±0.5. 68.1% of patients had performance status 0-1 and 55.6 % more than 3 metastatic sites. With a median follow up of 40.5 (95%CI 38.4-42.4) months, median invPFS was 7.4 (95% CI: 5.9-9.6) months. Median duration of brigatinib treatment was 7.4 (95% CI 5.3-8.3) months. Median OS from brigatinib initiation was 20.3 months (95%CI: 15.6-27.6). For patients who received 1 (n=23), 2 (n=146) or 3 (n= 14) ALKi before brigatinib, median duration of treatment was 13.8 (95%CI 3.8-26.4), 7.4 (95%CI 5.6-9.9) and 4.9 (95%CI 1.7-9.3) months, respectively and median OS from brigatinib initiation was 24.3 (95%CI 9.7-NR), 20.3 (95%CI 16.2-28.7) and 18.1 (95%CI 3.3-34.5) months, respectively. 92 (50%) patients received at least 1 post-brigatinib treatment. 68 (73.9%) were treated with lorlatinib: 51 (75%) immediately after brigatinib, 12 (17.6%) after 1 subsequent treatment, 5 (7.4%) after at least 2 subsequent treatments. With a median follow-up of 29.9 (25.7-33.1) months, median duration of lorlatinib treatment was 5.3 (95% CI 3.6-7.6) months and median OS from lorlatinib initiation was 14.1 (95%CI 10.3-19.2) months.

Conclusions:

The analysis of the EAP confirms the effectiveness of brigatinib in a cohort of heavily pretreated ALK-positive aNSCLC patients and the activity of subsequent ALKi after brigatinib.

Efficacy and safety of anlotinib plus docetaxel in non-small cell lung cancer (NSCLC) after failure of previous immune checkpoint inhibitors (ICIs) therapy: Results from a phase I/II trial

Background:

ICIs are widely used in 1st -line or 2nd -line treatment of advanced NSCLC, but effective treatment after resistance to ICIs is still controversial. We previously reported that anlotinib plus docetaxel as 2nd-line treatment in advanced NSCLC showed better clinical efficacy than docetaxel alone in a phase I/II trial. Here, we provided the efficacy and safety of the combination in advanced NSCLC patients (pts) who had been pre-treated with ICIs in the phase II study.

Methods:

Pts with driver-negative advanced NSCLC who had progressed after 1st-line platinum-based chemotherapy were randomized 2:1 to receive anlotinib (10mg, QD, d1 to 14 of a 21-day cycle) plus docetaxel (60mg/m^2, q3w, 4-6 cycles) (A+D arm) or docetaxel (60mg/m^2, q3w, 4-6 cycles) (D arm) until progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints were the objective response rate (ORR), the disease control rate (DCR), overall survival (OS) and safety. This data analysis was based on pts with progression after prior treatment with ICIs in A+D arm.

Results:

As of 1 May, 2021, 51 pts were enrolled, 34 pts with a median age of 62.7, squamous cell carcinoma (47.1%), ECOG PS 1 (85.3%) in A+D arm and 17 pts with a median age of 60.6, squamous cell carcinoma (47.1%), ECOG PS 1 (70.6%) in D arm. Median PFS was 6.5 months (95% Cl: 3.20-9.80) in A+D arm and 2.7 months (95% Cl: 0.05-5.35) in D arm (HR: 0.30; 95% Cl: 0.12-0.74, p=0.004). Of 46 evaluable pts, the ORR was 21.9% (7/32) in A+D arm and 14.3% (2/14) in D arm (p¼0.70), and significant DCR benefit was observed for the combination treatment (A+D arm vs. D arm =100.0% vs. 57.1%, p< 0.001). The median OS was not reached. Most common grade 1-2 treatment-related adverse events (TRAEs) in A+D arm were hypertension (17.6%), neutropenia (14.7%), leukopenia (14.7%), and proteinuria (14.7%). Grade 3/4 TRAEs mainly included neutropenia (5.9%), leukopenia (5.9%), oral mucositis (5.9%) and hypertension (5.9%) in A+D arm and were not observed in D arm.

Conclusions:

Anlotinib plus docetaxel continued to show better clinical benefit with manageable toxicity for advanced NSCLC pts with progression after 1st-line platinumbased chemotherapy. The combination regimen may become a new option for the 2nd-line treatment.

Clinical trial identification:

NCT03726736

Updated results from a phase I/II study of anlotinib plus docetaxel vs docetaxel as second-line treatment of advanced non-small cell lung cancer (NSCLC)

Background:

Chemotherapy or Immunotherapy alone as 2nd-line treatment in driver negative advanced NSCLC has unsatisfactory efficacy. We previously reported some results of the phase I/II trial, which demonstrated that anlotinib (10mg) plus docetaxel (60mg/m^2) had encouraging efficacy and manageable toxicity as 2nd-line treatment in advanced NSCLC. Here, we continued to update the efficacy and safety of the combination for advanced NSCLC in the phase II trial.

Methods:

Pts with advanced NSCLC who had progressed after 1st-line platinum-based chemotherapy and without sensitizing EGFR/ALK/ROS1 alterations were randomized in a 2:1 ratio to receive anlotinib (10mg, QD, d1 to 14 of a 21-day cycle) plus docetaxel (60mg/m^2, q3w, 4-6 cycles) (A+D arm) or docetaxel (60mg/m^2, q3w, 4-6 cycles) (D arm) until progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints included the objective response rate (ORR), the disease control rate (DCR), overall survival (OS) and safety.

Results:

As of 1 May, 2021, 51 pts were enrolled, 34 pts with a median age of 62.7, squamous cell carcinoma (47.1%), ECOG PS 1 (85.3%) in A+D arm and 17 pts with a median age of 60.6, squamous cell carcinoma (47.1%), ECOG PS 1 (70.6%) in D arm. Median PFS was 6.5 months (95% Cl: 3.20-9.80) in A+D arm and 2.7 months (95% Cl: 0.05-5.35) in D arm (HR: 0.30; 95% Cl: 0.12-0.74, p=0.004). Of 46 evaluable pts, the ORR was 21.9% (7/32) in A+D arm and 14.3% (2/14) in D arm (p=0.70), and significant DCR benefit was observed for the combination treatment (A+D arm vs. D arm = 100.0% vs. 57.1%, p< 0.001). The median OS was not reached. Most common grade 1-2 treatment-related adverse events (TRAEs) in A+D arm were hypertension (17.6%), neutropenia (14.7%), leukopenia (14.7%), and proteinuria (14.7%). Grade 3/4 TRAEs mainly included neutropenia (5.9%), leukopenia (5.9%), oral mucositis (5.9%) and hypertension (5.9%) in A+D arm and were not observed in D arm.

Conclusions:

Anlotinib plus docetaxel continued to show better clinical benefit with manageable toxicity for advanced NSCLC pts with progression after 1st-line platinumbased chemotherapy. The combination regimen may become a new option for the 2nd-line treatment.

Clinical trial identification:

NCT03726736

Sitravatinib + tislelizumab in patients with anti-PD-(L)1 refractory/resistant metastatic NSCLC

Background:

Patients with metastatic non-small cell lung cancer (NSCLC) who are refractory/resistant (R/R) to anti-PD-(L)1 therapies have limited treatment options. Sitravatinib is a spectrum-selective tyrosine kinase inhibitor targeting TAM and VEGFR2 receptors, which can reduce the number of myeloid-derived suppressor cells, regulatory T cells, and increase the ratio of M1/M2 polarized macrophages, potentially augmenting antitumor immune responses. Tislelizumab, is an anti-PD-1 antibody engineered to minimize binding to FcgR on macrophages to abrogate antibodydependent phagocytosis, a potential mechanism of resistance. This phase Ib study assessed safety/tolerability and antitumor activity of sitravatinib + tislelizumab in solid tumors (NCT03666143). We report results from NSCLC cohorts.

Methods:

Eligible patients had metastatic non-squamous (NSQ) or squamous (SQ) NSCLC with radiographic disease progression on/after anti-PD-(L)1 therapy as their most recent treatment. Patients with EGFR/BRAF mutations or ALK/ROS1 rearrangements were ineligible. Treatment included sitravatinib 120 mg orally QD and tislelizumab 200 mg IV Q3W. The primary endpoint was safety and tolerability. Key secondary endpoints included investigator-assessed objective response rate (ORR), duration of response (DoR), disease control rate (DCR) and progression-free survival (PFS).

Results:

As of 13 Oct 2020, 47 patients with NSQ (n=24) and SQ (n=23) NSCLC were enrolled with a median study follow-up of 7.8 months (range: 0.4-18.1). Median age was 60 years (range: 25-79) and 72% of patients had ≥2 lines of prior therapies. All patients had a treatment-emergent adverse event (TEAE); 68% had a grade ≥3 TEAE (most common: hypertension, 19%). Confirmed ORR was 14% (95% CI: 5.2-27.4) and DCR was 86% (95% CI: 72.7-94.8). Median DoR was 6.9 months (95% CI: 3.1-NE). Median PFS was 5.2 months (95% CI: 4.1-5.9). There was no association between PDL1 expression and clinical response.

Conclusions:

Sitravatinib plus tislelizumab demonstrated a manageable safety profile and promising antitumor activity in patients with PD-(L)1 antibody-pretreated NSCLC. Further investigation of this combination in these pts is warranted.

Clinical trial identification:

NCT03666143

Efficacy and safety of tepotinib in patients (pts) with advanced age: VISION subgroup analysis of pts with MET exon 14 (METex14) skipping NSCLC

Background:

The pt population defined by METex14 skipping is typically elderly, and may be challenging to treat due to comorbidities. In the VISION study (median age 73.1 years [yr; range 41-94]), the selective MET inhibitor tepotinib had an objective response rate of 44.7%, and median duration of response of 11.1 months. We investigated outcomes according to age.

Methods:

Pts with advanced METex14 skipping NSCLC received 500 mg (450 mg active moiety) tepotinib orally once daily. All pts who received tepotinib in Cohorts A (primary analysis) and C (confirmatory) were assessed for safety; pts in Cohort A were assessed for efficacy. Primary endpoint was objective response by independent review committee. Secondary endpoints included duration of response, and safety. Subgroup analysis according to age was predefined.

Results:

A total of 152 pts were enrolled in Cohort A. Baseline characteristics were similar in pts <75/≥75 yr (n=84/68): 52.4/51.5% were male, 60.7/41.2% had a history of smoking, 70.2/76.5% had ECOG PS 1, 89.3/82.4% had adenocarcinoma histology, and 44.0/47.1% were treatment-naïve. Efficacy in pts <75 or ≥75 yr is shown (Table). Of 124 patients who discontinued tepotinib, 47 received subsequent treatments; the majority were <75 yr (n=36; 76.6%). A total of 255 pts were assessed for safety. In pts <75/≥75 yr (n=146/109), treatment-related adverse events (TRAEs) occurred in 87.7/84.4%, Grade ≥3 TRAEs occurred in 18.5/33.9%, and TRAEs led to discontinuation in 7.5/14.7%. The most common TRAE, peripheral edema, occurred in 56.2% of pts <75, and 51.4% of pts ≥75 yr.

Conclusions:

Tepotinib demonstrated robust and durable efficacy in elderly pts, with a manageable safety profile, and a low proportion of TRAEs leading to discontinuation. Given the vulnerability of pts of advanced age, prioritization of effective and convenient targeted therapies in this population is warranted.

Clinical trial identification:

NCT02864992

Table: 1254P

Efficacy (IRC)	Patients <75 years (n=84)	Patients ≥75 years (n=68)
Best objective response, n (%)		
Complete response	0	0
Partial response	41 (48.8)	27 (39.7)
Stable disease	19 (22.6)	20 (29.4)
Progressive disease	17 (20.2)	9 (13.2)
Not evaluable	7 (8.3)	12 (17.6)
Objective response rate,	**48.8**	**39.7**
% (95% CI)	(37.7, 60.0)	(28.0, 52.3)
Disease control rate,	**71.4**	**69.1**
% (95% CI)	(60.5, 80.8)	(56.7, 79.8)
Median duration of response,	**12.4**	**10.1**
months (95% CI)	(8.4, not estimable)	(5.8, 18.5)
Median progression-free survival,	**10.3**	**8.6**
months (95% CI)	(8.2, 12.1)	(6.9, 12.4)

Data cut-off: July 1, 2020.

CI, confidence interval; IRC, independent review committee.

Second-line nintedanib + docetaxel for patients with lung adenocarcinoma after first-line chemo-immunotherapy treatment: Updated efficacy and safety results from VARGADO Cohort C

Background:

Treatment strategies for patients with advanced non-small cell lung cancer (NSCLC) without targetable driver mutations have changed significantly during the last decade. Immune checkpoint inhibitors (ICIs), with or without chemotherapy, have become the first-line (1L) standard of care. Limited clinical data is available to help guide treatment decisions for treatment post-progression. Nintedanib (Vargatef®) is an oral triple angiokinase inhibitor targeting the vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR) pathways. It is approved in the EU and other countries in combination with docetaxel for the treatment of advanced adenocarcinoma NSCLC after progression on 1L chemotherapy.

Methods:

This updated analysis is part of the ongoing, prospective, non-interventional VARGADO study of nintedanib plus docetaxel. The current analysis includes efficacy and safety results from 137 patients (pts) with adenocarcinoma NSCLC who received second-line (2L) nintedanib plus docetaxel after prior 1L chemo-ICI treatment (Cohort C).

Results:

In this cohort, the median age was 63 years (range: 37e84); 80 pts (58.4%) were men, and 98 pts (71.5%) had an ECOG PS 0/1. 127 pts (92.7%) had received prior 1L pembrolizumab-based combination therapy. Objective response rate with 2L nintedanib plus docetaxel was 37.5% (30/80 pts), disease control rate was 72.5% (58/80 pts), and median progression-free survival was 4.8 months (95% confidence interval: 3.7e6.6). Grade ≥3 treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs leading to treatment discontinuation were observed in 62 pts (45.3%), 50 pts (36.5%) and 40 pts (29.2%), respectively.

Conclusions:

These results suggest that 2L nintedanib plus docetaxel represents an effective treatment option with a manageable safety profile in pts with advanced adenocarcinoma NSCLC following progression on 1L chemo-immunotherapy.

Clinical trial identification:

NCT02392455

Preclinical and preliminary clinical investigations of furmonertinib in NSCLC with EGFR exon 20 insertions (20ins)

Background:

Currently neither chemotherapy nor approved EGFR TKIs have satisfactory efficacy in most EGFR 20ins mutations. Activity of furmonertinib, a novel 3rd generation EGFR TKI, against EGFR 20ins was assessed in preclinical models and a phase Ib study.

Methods:

The preclinical activity of furmonertinib were evaluated in vitro and in vivo. Then the clinical efficacy and safety were investigated in a phase Ib study in which 30 advanced NSCLC patients (pts) with EGFR 20ins were planned to be enrolled: Cohort 1 (10 pts): treatment-naïve, furmonertinib 240mg QD; cohort 2 and 3: previously treated, 240mg QD and 160mg QD respectively. Previously treated pts would be randomized into cohort 2 or 3. The primary endpoint was ORR.

Results:

In preclinical studies, furmonertinib effectively inhibited BaF3 cells expressing EGFR 20ins with mean IC50 of 11w20 nM. Good efficacy and well tolerance were also observed in patient-derived xenograft models harboring EGFR 20ins (LU0387) with furmonertinib at 45mg/kg/day. As of 30 Apr 2021, 10 EGFR 20ins advanced NSCLC pts were enrolled in cohort 1 and received furmonertinib 240mg QD. In these pts: median age, 67.5y (range 47–69); women, 70%; ECOG 0/1, 30%/70%. Median time on treatment was 3.5 months and all pts remain on treatment. At data cutoff, all pts had ≥1 disease assessment. The best response was PR in 7 pts and SD in 3 pts. 5/7 objective responses (all PR) were confirmed, with 2 awaiting confirmation. All pts showed tumor shrinkage in target lesions (median best percent change, -43.0% [-72.3%, -3.0%]). The most common treatment emergent adverse events (TEAE, ≥20%) were diarrhea, paronychia, skin fissures (each 30%), anorexia, upper respiratory tract infection, creatinine renal clearance decreased, pain in extremity, rash, face oedema and stomatitis (each 20%). No grade ≥3 TEAE was observed. Dose interruption was reported once due to diarrhea. No dose reduction or discontinuation were observed.

Conclusions:

Furmonertinib has shown encouraging anti-tumor activity in EGFR 20ins NSCLC based on the preclinical data and the preliminary results of the phase Ib study without new safety signals. Further exploration of this phase Ib study is ongoing.

Clinical trial identification:

NCT04858958

Capmatinib safety update in MET dysregulated NSCLC from the GEOMETRY mono-1 trial

Background:

apmatinib showed clinically meaningful efficacy in patients (pts) with advanced non-small cell lung cancer (NSCLC) harboring MET exon 14 skipping mutations (METex14) in GEOMETRY mono-1, a phase II, multi-cohort, multicenter trial evaluating capmatinib 400 mg BID in MET dysregulated stage IIIB/IV NSCLC. Here, we present updated safety from this study (data cut-off: 18-Sep- 2020), including all pts with MET dysregulated NSCLC.

Methods:

The median time to first occurrence is reported using descriptive statistics; median time to resolution is calculated using the Kaplan-Meier method. At the data cut-off date.

Results:

373 pts with MET dysregulation were enrolled; this included 29 pts with METex14 mutation who had brain metastasis (BM) at baseline and neurological BIRC review. Treatment-related (TR) AEs were reported in 86.9% of pts in the safety population and 89.7% of those with BM at baseline. The most common TRAEs for the safety population and pts with BM at baseline are reported in the table. Similar AEs were observed in pts with BM and the safety population; no nervous system disorders were reported in pts with BM. For the most frequent TRAEs in the safety population, peripheral edema and nausea, the median (min-max) time to first occurrence of any grade of symptoms was 2.04 (0.03–24.84; n=178) and 0.39 (0.03–21.42, n=128) months, respectively; the median (min–max) time to first occurrence of grade 3 or 4 symptoms was 5.04 (0.03–31.80; n=34) and 0.54 (0.20–1.48; n=6) months, respectively. The median (95% CI) time to resolution of first grade 3 or 4 symptoms (recovered/resolved or return to grade ≤ 2) of TR peripheral edema and nausea was 0.49 (0.33, 0.92) and 0.18 (0.10, NE) months, respectively. TR peripheral edema and nausea led to a dose adjustment in 9.7% and 1.9% pts, dose interruption in 10.5% and 5.4% pts and to permanent discontinuation in 2.1% and 0.5% of pts, respectively.

Conclusions:

Overall, capmatinib demonstrated a manageable safety profile, with no new safety signals in pts with MET dysregulated NSCLC.

Clinical trial identification:

NCT02414139

A phase I dose-escalation study of mobocertinib (TAK-788), an oral tyrosine kinase inhibitor (TKI), in Japanese NSCLC patients

Background:

Mobocertinib is an orally administered TKI that potently inhibits activating epidermal growth factor receptor (EGFR) mutations, including in-frame insertions in exon 20, which are associated with poor survival. We present results from the phase I open-label, dose-escalation of a phase I/II study (NCT03807778), aimed to confirm the recommended phase II dose (RP2D)/maximum tolerated dose (MTD) identified in global studies (160 mg once daily [QD]) in Japanese patients with NSCLC.

Methods:

Patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC refractory to standard available therapies were included. Dose escalation cohorts started with 40 mg QD followed by higher doses according to a Bayesian logistic regression model [MC1] until an MTD was found or 160 mg QD was shown to be safe and tolerable. MTD was reached when ≥9 patients at all doses were dose-limiting toxicity (DLT)-evaluable, ≥6 patients at the current dose level were DLT evaluable, and the next recommended dose was equal to the current dose

Results:

In total, 20 patients (40 mg QD, n¼4; 120 mg QD, n¼4; 160 mg QD, n¼12) were enrolled at 4 sites: 18 (90%) had tumors harboring EGFR exon 20 insertion mutation; all patients had ≥1 prior anticancer therapy, and 55% had received ≥3 regimens. No DLT was observed at 40 mg QD. One patient receiving 120 mg QD reported a DLT of diarrhea (Grade 3), and 2 patients receiving 160 mg QD reported DLT: one had interstitial lung disease (Grade 3), the other had aspartate aminotransferase increased (Grade 2), alanine aminotransferase increased (Grade 3) and diarrhea (Grade 2). All patients in the 160 mg QD cohort reported a treatment emergent adverse event (TEAE). The most common TEAEs were diarrhea (reported in all but 1 patient receiving 40 mg QD) and nausea (50% of each dose cohort). MTD/ RP2D of mobocertinib was confirmed as 160 mg QD. Pharmacokinetic parameters were also assessed and will be presented.

Conclusions:

Mobocertinib showed a manageable safety profile in Japanese NSCLC patients. Based on the totality of pharmacokinetics and safety data from various mobocertinib doses, 160 mg QD was selected as the RP2D for further clinical studies in Japanese patients.

Clinical trial identification:

TAK-788-1003

Study of anlotinib combined with icotinib as the first-line treatment in NSCLC patients harboring activating EGFR mutations: Updated results of ALTER-L004

Background:

In ALTER-L004 (NCT03736837), anlotinib plus icotinib showed encouraging efficacy and good tolerability. Here, we reported the updated results.

Methods:

Patients with EGFR-mutated locally advanced and/or metastatic stage IIIbIV non-squamous NSCLC were enrolled. The regimen consists of anlotinib (12 mg QD, day 1 to 14 every 21-day cycle) and icotinib (125mg, TID). The primary endpoint is PFS. Secondary endpoints are OS, ORR, DCR and safety.

Results:

Between Jul 2018 and Dec 2020, 60 patients were enrolled and 56 had received at least one tumor assessment. By Apr 30, 2021 data cutoff, patients were followed up for a median of 18.2 months. The mPFS was 15.100 months (95%CI: 11.309-18.891). The ORR was 67.9% and DCR was 98.2%. 58.9% of patients experienced ≥30% reduction by the first evaluation, which defined ETS. The mPFS was 15.600 months (95%CI: 10.407-20.793) and 14.900 months (95%CI: 9.089-20.711) of patients with concomitant mutation and pathogenic concomitant mutation, respectively. Patients with concomitant mutation or pathogenic concomitant mutation achieved ORR more than 80%, DCR 100% and ETS greater than 70%. 23 patients are still receiving treatment and the longest exposure was 30 cycles. Upon analyses, adverse events (AEs) occurred in 100% of the patients and the incidence of grade 3/4 AEs was 40%. The most common AEs were hypertriglyceridemia, diarrhea, hypercholesteremia, hypertension, rash, proteinuria, hand and foot skin reaction, increased ALT, hypothyroidism, increased thyroid-stimulating hormone, increased AST, urine occult blood. The most common grade 3/4 AEs were hypertension and diarrhea. There was 1 drug-related serious AE due to acute coronary syndrome. 26.7% of patients had to adjust treatment dosage.

Conclusions:

This updated analysis has confirmed that anlotinib plus icotinib showed encouraging efficacy for untreated, EGFR-mutated advanced NSCLC patients and may represent a new treatment option for patients with concomitant mutations. The combination was well tolerated and the AEs were manageable.

Clinical trial identification:

NCT03736837

Real-world comparative effectiveness of 1L alectinib (ALC) vs crizotinib (CRZ) in patients (pts) with ALK+ advanced NSCLC with or without baseline CNS metastases (mets)

Background:

The phase III ALEX study (NCT02075840) demonstrated superiority of ALC vs CRZ for treatment of advanced ALK+ NSCLC. In this study, real-world comparative effectiveness of 1L ALC vs CRZ was retrospectively analyzed.

Methods:

Adult pts with advanced ALK+ NSCLC who received 1L ALC (from 11 Dec 2015) or CRZ (from 1 Jan 2014) were included from the nationwide Flatiron Health electronic health record-derived de-identified database. Propensity scores were applied to balance baseline characteristics. Weighted hazard ratios (wHR) of ALC vs CRZ were calculated for real-world outcomes, including progression-free survival (rwPFS), overall survival (rwOS) and time to first/new CNS met (rwTTNCM; death was included as an event). In pts with baseline brain scans, outcomes in pts with or without baseline CNS mets were analyzed. Sensitivity analyses were performed in pts with known ECOG PS or treated after 11 Dec 2015. To compare real-world comparative effectiveness with the ALEX study, a population filtered by ALEX laboratory inclusion/exclusion criteria (ALEX-like RWD cohort) was analyzed, and wHRs compared with corresponding HRs from ALEX.

Results:

The RWD cohort comprised 364 pts (141 ALC; 223 CRZ); differences in baseline characteristics were: CNS mets (38 vs 26%), Asian race (15 vs 5%), known PDL1 status (72 vs 15%) and known ECOG PS (65 vs 48%). In the RWD cohort, rwPFS and rwOS were significantly improved with ALC vs CRZ (Table). In 243 pts with baseline brain scans (102 ALC; 141 CRZ), a significant rwPFS benefit was seen regardless of baseline CNS mets. In pts without baseline CNS mets, development of first CNS met was delayed with ALC vs CRZ (rwTTNCM: adjusted HR¼0.42, 95% CI 0.24e0.77). The ALEX-like RWD cohort comprised 325 pts (120 ALC; 205 CRZ); wHRs of ALC vs CRZ for rwPFS showed similar benefit to ALEX (Table).

Conclusions:

Outcomes were significantly improved with 1L ALC vs CRZ in pts with advanced ALK+ NSCLC in the real-world setting.

Clinical trial identification:

NCT02075840

Table: 1201P

N ALC, N CRZ ALC vs CRZ HR 95% CI		PFS*			OS		
		RWD†	ALEX-like RWD†	ALEX	RWD†	ALEX-like RWD†	ALEX
All patients		*141, 221* 0.46 0.33 −0.65	*120, 203* 0.46 0.32 −0.66	*152, 151* 0.43 0.32 −0.58	*141, 223* 0.46 0.31 −0.69	*120, 205* 0.47 0.32 −0.73	*152, 151* 0.70 0.48 −1.02
Patients with baseline brain scans	Baseline CNS mets	*50, 50* 0.27 0.14 −0.53	*44, 45* 0.30 0.16 −0.57	*64, 58* 0.37 0.23 −0.58	*50, 51* 0.44 0.21 −0.92	*44, 46* 0.41 0.20 −0.83	*64, 58* 0.58 0.34 −1.00
	No baseline CNS mets	*52, 90* 0.35 0.20 −0.62	*45, 87* 0.34 0.22 −0.52	*88, 93* 0.46 0.31 −0.68	*52, 90* 0.57 0.29 −1.12	*45, 87* 0.53 0.25 −1.14	*88, 93* 0.76 0.45 −1.26

*Progression was not assessed in all patients in the electronic health record database †wHR

MRTX-500: Phase II trial of sitravatinib (sitra) + nivolumab (nivo) in patients (pts) with non-squamous (NSQ) non-small cell lung cancer (NSCLC) progressing on or after prior checkpoint inhibitor (CPI) therapy

Background:

Therapy with CPI has improved OS across many tumor types, including in a subset of pts with NSCLC. Mechanisms of CPI resistance, however, have been described, including an immunosuppressive TME, which may include recruitment of immunosuppressive myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and M2-polarized macrophages within the TME. Sitra, a spectrum-selective TKI targeting TAM (Tyro3/Axl/MerTK) receptors and VEGFR2, reduces the number of MDSCs and Tregs while increasing the ratio of M1/M2-polarized macrophages, and thus is hypothesized to overcome an immunosuppressive TME and augment antitumor immune responses.

Methods:

MRTX-500 (NCT02954991) is a phase II study evaluating sitra (120 mg QD) + nivo (Q2W or Q4W) in pts with NSQ NSCLC who have progressed on or after treatment, with a CPI-based regimen (anti-PD1/PD-L1) and/or platinum doublet chemotherapy. The primary endpoint is ORR per RECIST 1.1. Secondary endpoints include OS, PFS, and safety. We report updated efficacy data for pts with NSCLC with PCB (prior clinical benefit; CR, PR, or SD ≥12 weeks) from a CPI who were treated with sitra + nivo as either 2L or 3L therapy.

Results:

As of 17 October 2020, 68 pts with PCB (57% female; median age, 66 years; ECOG PS 0/1/2, 27%/66%/7%) were treated. Median follow-up was 28 months, median OS was 15 months (95% CI 9.3, 21.1),1- and 2-year OS rates were 56% and 32%, respectively. Median PFS was 6 months, and ORR was 16% (11/68), including 2 CRs. Median duration of response was 13 months. In all CPI-experienced pts evaluable for safety (n=124), treatment related adverse events (TRAEs) occurred in 91% of pts, with Gr 3/4 TRAEs occurring in 60% of pts. The most common (≥10%) Gr 3/4 TRAEs were hypertension and diarrhea. There were no Gr 5 TRAEs. Discontinuation rates for sitra and nivo due to any AE were 30% and 27%, respectively.

Conclusions:

Sitra + nivo demonstrated antitumor activity and encouraging OS compared to historical controls and no new safety signals were observed in pts with NSQ NSCLC who progressed on prior CPI. This combination is being evaluated in the phase III SAPPHIRE study.

Clinical trial identification:

NCT02954991

Radiotherapy combined with apatinib and PD-1 inhibitors in patients with brain metastases from non-small cell lung cancer: A single-arm exploratory clinical study

Background:

Brain is one of the most common sites of distant metastasis from lung cancer. Patients with brain metastasis (BM) from lung cancer have a poor prognosis, with a natural mean survival time of only 1-2 months. Radiotherapy is the cornerstone of the treatment of brain metastases in patients with non-small cell lung cancer (NSCLC), which can improve the survival rate and reduce the local recurrence rate. At present, the vast majority of prospective clinical studies on lung cancer immunotherapy have excluded patients with BM. Some retrospective studies have shown the efficacy of programmed cell death protein 1 (PD-1) inhibitors in the treatment of lung cancer brain metastasis. The efficacy of immunotherapy in lung cancer brain metastasis remains to be explored and confirmed. Several studies have shown the efficacy of antiangiogenic therapy in lung cancer with brain metastasis. However, the safety and efficacy of radiotherapy combined with immunotherapy and antiangiogenic therapy of BMs remains unclear. Therefore, this study was conducted to explore its efficacy.

Trial design:

This study is a single-arm exploratory clinical study, which is expected to enroll 42 patients with wild type NSCLC with BM from April 2021 to April 2023, and will be treated with brain radiotherapy combined with apatinib (antiangiogenic drugs against vascular endothelial growth factor receptor-2) and PD-1 inhibitors. The primary end points were intracranial progression-free time (refer to the immunotherapy Response Assessment in Neuro-Oncology (iRANO) standard). The secondary endpoints were: intracranial objective response rate (IORR), objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), quality of life score (QOL), and safety. The exploratory endpoints were neurocognitive function status (Mini-mental State Examination and Neurologic Assessment in Neuro-Oncology scale) and edema index. Expectation: This study is expected to provide new treatment options for patients with brain metastases from advanced non-small cell lung cancer and bring new hope.

Befotertinib versus icotinib as first-line treatment in patients with advanced or metastatic EGFR-mutated non-small cell lung cancer: A multicenter, randomized, open-label, controlled phase III study

Background:

EGFR-TKI provide superior efficacy to chemotherapy in the treatment of EGFE-mutant advanced NSCLC. However, most patients will develop variable degrees of resistance after receiving first/second-generation EGFR-TKI treatment, highlighting the urgent need for novel agents. Befotertinib (D-0316) is a third-generation EGFR-TKI that is selective to EGFR-sensitizing mutations (exon 21 L858R mutation and exon 19 deletion) or T790M mutation. Its efficacy has been confirmed in a phase II study (NCT03861156), which reported an objective response rate (ORR) of 64.8% and a disease control rate (DCR) of 95.2% in NSCLC patients with EGFR T790M who progressed on previous treatment with first-line EGFR-TKIs. Based on the above findings, we conducted a multicenter, randomized, open-label, controlled phase III study to evaluate the efficacy, safety, and tolerability of befotertinib versus icotonib as firstline treatment for advanced or metastatic EGFR-mutations NSCLC.

Trial design:

Treatment-naive patients with locally advanced or metastatic NSCLC harboring positive EGFR mutation were eligible. The sample size was specified assuming a hazard ratio (HR) of 0.625, corresponding with an increase in progression free survival (PFS) from an expected 10 months for icotinib to 16 months for befotertinib. To provide an 86% power at a two-sided 5% significance level, and an estimated 20% dropout rate, a total of 360 patients are required. Eligible patients will be randomized 1:1 ratio assigned to receive icotinib (125 mg TID orally) or befotertinib (100 mg once daily with a 21-day lead-in at 75 mg once daily), until disease progression or death. The primary endpoint was PFS assessed by an independent review committee. Secondary endpoints included ORR, DCR, intracranial objective response rate (iORR), intracranial progression-free survival (iPFS), overall survival (OS), duration of response (DOR) and safety. Progression: The study was conducted in 40 centers in China. As of 18 December, 2020, the recruitment was completed.

Clinical trial identification:

NCT04206072

Efficacy and safety of anti-PD-1 therapy plus anlotinib in previously treated advanced NSCLC

Background:

Nivolumab or pembrolizumab is the standard second-line treatment for patients (pts)with advanced NSCLC. Anlotinib is an oral VEGFR, FGFR, PDGFR and c-Kit tyrosine kinase inhibitor. The interaction between tumor immune microenvironment and angiogenesis has been well established. This study was designed to assess the benefit and optimal time of nivolumab or pembrolizumab plus anlotinib in previously treated advanced NSCLC.

Methods:

This is a prospective observational study. Pts with advanced NSCLC who had previous progression after platinum-based chemotherapy were eligible. For NSCLC with EGFR variations pts who had disease progression with prior EGFR TKI therapies and chemotherapy were also eligible. Nivolumab on day 1 (3 mg/kg) every 2 weeks or pembrolizumab on day 1 (200 mg) every 3 weeks for up to 8 weeks, for pts who have no symptomatic deterioration and can benefit from the treatment, then followed by the former therapy plus anlotinib maintenance until progression or unacceptable toxic effects. Anlotinib was given orally 12mg for 2 weeks of a 21-day cycle (days 1-14). The primary outcome was ORR. The secondary outcomes were DCR, PFS, OS and safety.

Results:

From Mar-2019 to Apr-2021, a total of 19 pts were enrolled. Most were male (84.2%), adenocarcinoma histology (68.4%) and most were treated as second-line treatment (57.9%). 4 had baseline brain metastases. For 8 weeks' treatment of nivolumab or pembrolizumab monotherapy, 5 pts achieved PR, 8 pts achieved SD and 6 pts had PD; ORR was 26.3%, DCR was 73.7%. During the anti-PD-1 therapy plus anlotinib, 1 pt achieved CR, 12 pts achieved PR (4 of them were PD during monotherapy), 4 pts achieved SD. ORR was 68.4%, DCR was 89.5%. Median PFS was 13.1 months (95% CI 8.6 to14.9). Grade !3 TRAE occurred in 26% pts. 2 pts with squamous cell carcinoma died due to pulmonary embolism and respiratory tract hemorrhage. The most common TRAE were fatigue, hypothyroidism and rash.

Conclusions:

Anti-PD-1 therapy plus anlotinib has shown promising anti-tumor efficacy compared to the previous anti-PD-1 monotherapy studies for pts with previously treated advanced NSCLC, and with a tolerable safety profile. We may focus on exploring the optimal time and advantage group of this combination in future studies.

Brigatinib (BRG) vs crizotinib (CRZ) in ALK TKIenaive ALK+ NSCLC: Final results from ALTA-1L

Background:

In 2 planned interim analyses of ALTA-1L (NCT02737501), BRG BIRC assessed PFS was superior to CRZ. We report final ALTA-1L results.

Methods:

Patients (pts) with ALK TKI-naive advanced ALK+ NSCLC were enrolled and stratified by baseline (BL) brain metastases (BM) and prior chemotherapy (CT). One prior CT for advanced NSCLC and asymptomatic BM was allowed. Pts were randomized 1:1 to BRG 180 mg QD (7-day lead-in at 90 mg) or CRZ 250 mg BID. Pts in the CRZ arm were offered BRG at progression. Primary endpoint: BIRC-assessed PFS (RECIST v1.1). Secondary endpoints included confirmed iORR, iPFS by BIRC, OS, safety, and QoL.

Results:

275 pts randomized (BRG/CRZ, n=137/138); median age 58/60 y; prior CT 26%/27%; BL BM 29%/30%. As of 29 Jan 2021 (last patient contact), median follow-up was (BRG/CRZ): 40.4/15.2 mo, with 166 (73/93) PFS events. BIRC-assessed PFS HR was 0.48 (95% CI: 0.35-0.66, log-rank P<0.0001); BRG mPFS was 24.0 mo (95% CI: 18.4-43.2) vs CRZ 11.1 mo (95% CI: 9.1-13.0); 3-yr PFS rate was (BRG/CRZ) 43%/ 19%. Investigator-assessed PFS HR was 0.43 (95% CI: 0.31-0.58, mPFS 30.8 vs 9.2 mo). mDoR (BIRC) was 33/14 mo. Median OS was not reached in either group (events BRG/CRZ: 41/51; HR: 0.81 [95% CI: 0.53-1.22]; log rank P=0.3311); 3-yr OS was 71%/ 68%. In pts with BL BM, OS HR was 0.43 (95% CI: 0.21-0.89; Table); in pts with no BL BM, 1.16 (0.69-1.93). Most common grade ≥3 TEAEs: BRG: increased CPK (26%) and lipase (15%), hypertension (14%); CRZ: increased ALT (10%), lipase, (8%), AST (7%). Any grade ILD/pneumonitis (BRG/CRZ): 4.4%/2.2%; discontinuation due to AE: 13.2%/ 8.8%. Median time to worsening in pt-reported global health status/QoL was (BRG/ CRZ) 26.7/8.3 mo; HR: 0.69 (95% CI: 0.49-0.98).

Conclusions:

BRG demonstrated durable overall and intracranial efficacy, and the tolerability profile remained consistent and manageable despite extended treatment duration, confirming BRG as an effective standard-of-care treatment in pts with treatment-naive ALK+ NSCLC.

Clinical trial identification:

NCT02737501

Table: 1195P

Efficacy per BIRC	BRG	CRZ	P
BL brain metastases			
any, n	40[a]	41[a]	
PFS events, n (%)	24 (60)	31 (76)	
HR	0.25 (0.14–0.46[b])		<0.0001[c]
OS events, n (%)	11 (28)	22 (54)	
3-yr OS, %	74 (57–85[b])	55 (38–69[b])	
HR	0.43 (0.21–0.89[b])		0.0199[c]
	47[d]	49[d]	
None, n	97[a]	97[a]	
PFS events, n (%)	49 (51)	62 (64)	
HR	0.62 (0.43–0.91[b])		0.0131[c]
	90[d]	89[d]	
iPFS events, n (%)	25 (28)	23 (26)	
HR	0.70 (0.39–1.26[b])		0.2410[c]
Measurable, n	18	23	
iORR[e], %	78 (52–94[b])	30 (13–53[b])	0.0036[f]
Confirmed iORR, %	78 (52–94[b])	26 (10–48[b])	0.0014[f]
Median iDoR[g], mo	28 (6–NE[b])	9 (4–NE[b])	

[a]Per investigator; [b]95% CI; [c]Log-rank; [d]Per BIRC; [e]Response,≥1 assessment; [f]Cochran-Mantel-Haenszel test; [g]Confirmed responders

Health utility with tepotinib in patients (pts) with MET exon 14 (METex14) skipping non-small cell lung cancer (NSCLC)

Background:

The phase II VISION trial showed durable clinical activity of tepotinib in pts with advanced METex14 skipping NSCLC. To complement the clinical findings, utilities were analyzed based on pt-reported outcomes (PROs) from VISION (Cohort A; data cut: July 1, 2020). Utilities are preference-based, health-related quality of life (HRQL) metrics expressed on a scale including 0 (dead) and 1 (full health).

Methods:

EORTC QLQ-C30 and EQ-5D-5L questionnaires were completed at Day 1, then every 6 weeks for 9 months, and then every 12 weeks, for up to 30 days after the last tepotinib dose. EORTC QLE-C10D and EQ-5D utilities were derived using UK value sets. Linear mixed models analyzed utilities according to baseline observation and progression status, assessed by independent review committee (IRC) or investigators (INV).

Results:

Utilities were estimated for 150 of 151 pts, with 983 observations for EORTC and 907 for EQ-5D. Mean EORTC utilities increased after tepotinib initiation, from 0.657 at baseline to 0.688 in the IRC-assessed progression-free period, and decreased after progression (0.638). Consistent trends were seen when progression was based on INV assessment. Analyses of EQ-5D utilities yielded similar findings and utilities from the two questionnaires were generally highly correlated (Table). Progression status significantly predicted utility in all progression-based models ($p \leq 0.002$). In exploratory analyses based on IRC progression, EQ-5D utility was not significantly predicted by prior treatment (yes/no; $p=0.580$), adenocarcinoma ($p=0.830$) or squamous histology ($p=0.930$).

Conclusions:

VISION is the first trial of a MET inhibitor to provide data on PROs and utilities in METex14 skipping NSCLC. EORTC and EQ-5D utilities show an increase in HRQL from baseline during tepotinib therapy until progression, which exceeds the previously reported minimally important difference of 0.08 for EQ-5D. Utility with tepotinib did not vary by prior treatment or histology.

Clinical trial identification:

NCT02864992

Pre-existing and acquired mechanisms of resistance to lorlatinib in previously treated patients (pts) with ALK+ advanced non-small cell lung cancer (NSCLC)

Background:

Lorlatinib, a potent, brain-penetrant, 3rd-generation (gen) ALK/ROS1 tyrosine kinase inhibitor (TKI) active against most known resistance mutations, showed robust clinical activity in ALK+or ROS1+ NSCLC in a Ph 1/2 study that enrolled mostly heavily pretreated pts with CNS metastases. We evaluated potential resistance mechanisms, pre-existing or acquired, and efficacy in these settings.

Methods:

Pts with ALK+ NSCLC previously treated with ≥1 2nd-gen ALK TKI (N¼139) were treated with lorlatinib 100 mg QD in the ongoing Ph 1/2 study (NCT01970865). Plasma samples were collected at baseline (BL) and at end of treatment (EoT) for circulating tumor (ct)DNA. Objective response rate (ORR), duration of response (DOR), and median progression-free survival (mPFS) by independent central review were evaluated according to mutation status.

Results:

TP53 mutations were found in 44 of 103 (42.7%) samples with detectable ctDNA at BL. ORR was 38.6% (95% CI: 24.4e54.5) and 45.8% (95% CI: 32.7e59.2) in pts with or without TP53 mutations, respectively; median DOR was 15.1 and 12.5 mo; and mPFS was 4.1 and 6.9 mo (hazard ratio [HR] = 0.83; 95% CI: 0.52e1.31). Restricting analysis to pts' samples harboring ALK fusion (n=58) led to similar results. Pre-existing aberrations in potential bypass mechanisms (eg, BRAF, KRAS known mutations, or EGFR, CDK4/6 or MET amplification) resulted in weaker efficacy, with mPFS of 3.2 and 6.9 mo (HR = 0.49; 95% CI: 0.29-0.84) in pts with (n=21; 20.4%) or without (n=82; 79.6%) aberrations, respectively. Confirmation of these results in tumor tissue is ongoing. In pts with matched paired samples (N=53), 7.5% had ALK compound mutations, while 20.8% had potential bypass mechanism aberrations at progression. The remaining pts did not show specific patterns of resistance.

Conclusions:

Limitations apply to ctDNA analyses, but in this heavily pretreated group of pts with ALK+ NSCLC, presence of TP53 mutations at BL was potentially associated with decreased lorlatinib efficacy, while presence of bypass mechanism aberrations with reduced activity. Upon progression, ALK compound mutations and bypass mechanism aberrations emerged in w28% of pts.

Clinical trial identification:

NCT01970865

Dose modification for the management of CNS adverse events in the phase III CROWN study of lorlatinib in nonsmall cell lung cancer (NSCLC)

Background:

In the ongoing phase III CROWN study (NCT03052608), lorlatinib, a 3rdgeneration inhibitor of anaplastic lymphoma kinase (ALK), improved progression-free survival (PFS) and intracranial response rates vs crizotinib in patients with previously untreated ALK-positive NSCLC. Here we present data on lorlatinib dose modification for the management of CNS adverse events (AEs).

Methods:

296 patients were randomized 1:1 to oral lorlatinib (100 mg QD) or crizotinib (250 mg BID). Guidelines for AEs management included medication, dose interruption, dose reduction to 75 or 50 mg QD, or a combination of the above. PFS landmark analysis was used to assess the effect of lorlatinib dose modifications (as relative dose intensity [RDI]) on efficacy.

Results:

In total, 86 CNS AEs (all-causality) were reported in 52/149 (35%) patients who received lorlatinib: most were cognitive (38/86, 44%) or mood effects (34/86, 40%). Maximum CNS AE severity was Grade 1 in 32/52 (62%) and Grade 2 in 15/52 (29%) patients. In 53/86 (62%) CNS AEs, lorlatinib dose was not modified and no medication was initiated; of 53 CNS AEs, 28 resolved spontaneously (53%), 1 improved (2%), and 24 did not resolve (45%). The majority (23/24) of the not resolved events were Grade 1. 20/86 (23%) CNS AEs were managed with lorlatinib dose modifications, with or without concomitant medication. A total of 15/20 (75%) of CNS AEs resolved, 2/20 (10%) improved, and 3/20 (15%) did not resolve (Table). Landmark analysis showed no difference in PFS between patients categorized by mean RDI within the first 16 weeks of treatment. The percentage of patient's event-free at 12 months was 90% (95% CI, 82 to 94) in the subgroup whose RDI was ≥ mean and 93% (95% CI, 59 to 99) in those whose RDI was < mean.

Conclusions:

CNS AEs spontaneously resolved in 53% of cases, and lorlatinib dose modification was effective in managing CNS AEs without compromising efficacy.

Clinical trial identification:

NCT03052608

Table: 1199P

Interventions	Total number of CNS AEs	Outcome			
		Resolved, n (%)	Partially resolved, n (%)	Not resolved, n (%)	Not applicable, n (%)
Total	86	48 (56)	3 (3)	33 (38)	2 (2.3)
No intervention	53	28 (33)	1 (1.2)	24 (28)	0
CM only	11	5 (5.8)	0	6 (7.0)	0
Lorlatinib dose modification +/- CM					
DR only	3	2 (2.3)	0	1 (1.2)	0
DI only	10	9 (10.5)	1 (1.2)	0	0
DR + DI	2	2 (2.3)	0	0	0
DR + CM	2	2 (2.3)	0	0	0
DI + CM	2	0	0	2 (2.3)	0
DR + DI + CM	1	0	1 (1.2)	0	0
Permanent treatment discontinuation	2	0	0	0	2 (2.3)

CM, concomitant medication; DI, dose interruption; DR, dose reduction.

Capmatinib versus docetaxel in pretreated patients with MET exon 14 skipping-mutated locally advanced or metastatic NSCLC: The GeoMETry-III phase III study

Background:

In previously treated patients (1 or 2 lines) with MET exon 14 skipping mutated (METex14) advanced non-small cell lung cancer (NSCLC), the evidence of the efficacy of standard therapies (chemotherapy or immunotherapy) is limited. Capmatinib, a MET inhibitor, is approved in the USA, Japan, Hong Kong, and Switzerland for the treatment of adult patients with metastatic METex14 NSCLC, based on the results from the phase II GEOMETRY mono-1 study. Results of this trial demonstrated an overall response rate (ORR) and median overall survival (OS) of 67.9% and 20.8 months in treatment-naive (N=28) and 40.6% and 13.6 months in pretreated (N=69) patients with METex14 NSCLC treated with capmatinib. GeoMETry-III (NCT04427072) is a multicenter, open-label, randomized, global, phase III trial evaluating the efficacy and safety of capmatinib versus docetaxel as second- or third-line therapy in patients with METex14 NSCLC.

Trial design:

This study began enrollment in September 2020 and is recruiting adult patients with EGFR wild-type, ALK-rearrangement negative, stage IIIB/IIIC or IV METex14 NSCLC, who have progressed on 1 or 2 prior lines of systemic therapy and are candidates for single-agent docetaxel. Patients with neurologically unstable, symptomatic central nervous system (CNS) metastases or those requiring increasing doses of steroids ≤2 weeks prior to study entry to manage CNS symptoms are excluded. The study aims to enroll around 90 patients, in 2:1 randomization, stratified by number of prior lines (1 or 2) of systemic therapy, to receive oral capmatinib 400 mg twice daily or intravenous docetaxel 75 mg/m^2 every 21 days. Patients meeting protocol-specified eligibility criteria can cross over from the docetaxel to the capmatinib arm after blinded independent review committee (BIRC)-confirmed progressive disease as per the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Study endpoints:

Table: 1362TiP

Category	Endpoint
Primary	Progression-free survival (PFS) by BIRC per RECIST 1.1
Key secondary	ORR by BIRC per RECIST 1.1
Secondary	PFS, ORR by investigator Duration of response, time to response, disease control rate by BIRC and investigator OS Safety Pharmacokinetics Patient-reported outcomes Intracranial antitumor activity by BIRC per the Response Assessment in Neuro-Oncology Brain Metastases criteria in patients with baseline CNS lesions

Clinical trial identification:

NCT04427072

A dose exploration study of almonertinib for epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) patients with newly diagnosed or recurrent brain/leptomeningeal metastasis (ARTISTRY)

Background:

Approximately 25 to 40% of patients with NSCLC have brain metastases (BM) and 3% to 4% develop leptomeningeal metastases (LM). Prognosis for patients with NSCLC and BM or LM is dismal, which seriously affects the quality of life and survival of patients. Several therapeutic options have been applied to manage BM or LM. However, the efficacy is limited. More recently, EGFR-TKIs have shown potential as a treatment option for BM or LM NSCLC patients. Almonertinib (HS-10296), a thirdgeneration EGFR tyrosine kinase inhibitor (TKI), efficiently penetrates the blood brain barrier. This study aims to explore the efficacy and safety of different doses of almonertinib in the first-line and second-line treatment of BM or LM NSCLC patients.

Trial design:

The ARTISTRY study (NCT04778800) was a single-arm, three cohort study. NSCLC patients with EGFR mutations who developed CNS progression are eligible for this study. This trial prepared to enroll approximately 60 patients. For cohort 1, the patients had to have measurable brain lesions and undergone no previous treatment with EGFR-TKI or radiotherapy for brain metastases(n=30). And they will receive oral almonertinib 110 mg/d first and receive 160 mg/d with disease progression in the central nervous system for this group. For cohort 2, the patients had to have LMs confirmed by either CSF cytology or brain MRI and have undergone no previous treatment with EGFR-TKI or radiotherapy for brain metastases(n=10). For cohort 3, the patients have measurable brain lesions whose disease had progressed on first or second-generation EGFR-TKI therapy. For cohort 2 and 3, patients will receive almonertinib 110/160/220 mg/d once daily with a dose-escalation phase if no disease progression was observed in twice consecutive assessments. The primary endpoint is intracranial progression-free survival. Secondary endpoints are progression-free survival, overall survival, intracranial objective response rate, disease control rate, intracranial disease control rate, safety and tolerability.

Clinical trial identification:

NCT04778800

Central Nervous System Tumor (CNS tumor)

A phase 0 'Trigger' trial of CDK4/6 plus ERK1/2 inhibitors in recurrent glioblastoma

Background:

This dual-drug phase 0 study (NCT04391595) evaluates the tumor pharmacokinetics (PK) and tumor pharmacodynamics (PD) of abemaciclib, a selective CDK4/6-inhibitor, plus LY3214996, a selective ERK1/2 inhibitor, in recurrent GBM patients.

Methods:

Adult recurrent GBM patients (n¼10) with intact RB expression, >30% pERK expression, and CDKN2A/B deletion or CDK4/6 amplification received six days of abemaciclib (150mg BID) plus LY3214996 (200mg QD) prior to a planned resection at 3-5 or 7-9 hour time interval after the final drug dose in a Time-Escalation Arm. Tumor tissue (gadolinium [Gd]-enhancing and nonenhancing regions), cerebrospinal fluid (CSF), and plasma were collected. Total and unbound drug concentrations were measured using validated LC-MS/MS methods. Tumor PD effects, including RB and RSK phosphorylation, were compared to matched archival or pre-treatment biopsied tissue. A PK 'trigger' (i.e., unbound concentration > 5x biochemical IC50) was set for each drug. Gd-nonenhancing tumor tissue exhibiting abemaciclib and LY3214996 concentrations in excess of their trigger threshold qualified patients for postoperative dual-drug therapy.

Results:

No dose-limiting toxicities were observed. In Gd-nonenhancing tumor regions, median unbound concentrations of abemaciclib were 31.2 nM (3-5 hour cohort) and 25.1 nM (7-9 hour cohort) while median unbound concentrations of LY3214996 were 52.0 nM (3-5 hour cohort) and 10.2 nM (7-9 hour cohort). Tumor RB and RSK phosphorylation decreased in 6/10 and 2/10 patients, respectively. Tumor proliferation (MIB-1) was decreased in 8/10 patients. 5/10 patients exceeded PK thresholds for both abemaciclib (12 nM) and LY3214996 (25 nM), thereby entering the study's therapeutic expansion phase.

Conclusions:

Abemaciclib and LY3214996 achieve pharmacologically-relevant concentrations in Gd-non-enhancing GBM tissue and are associated with suppression of the RB pathway and tumor proliferation. The Optimal Time Interval (OTI) for tissue sampling was 3-5 hours after the final drug dose. Based on this interim analysis, the trial will accrue an additional 25 patients at this OTI.

Intracranial administration of CTLA-4 and PD-1 immune checkpoint blocking monoclonal antibodies in recurrent glioblastoma (rGB): A multi-cohort adaptive phase I clinical trial

Background:

Intracerebral (iCE) administration (admin) of ipilimumab (IPI) and nivolumab (NIVO) plus IV admin of NIVO following resection of rGB was well tolerated and resulted in encouraging overall survival (OS)(Schwarze et al, JITC 2021). In 4 subsequent cohorts (A to D), the safety of intratumoral (iTU) admin of NIVO and IPI, followed by repeated intracavitary (iCA), or intrathecal (iTH) admin of NIVO +/increasing doses of IPI was investigated.

Methods:

Within 24h prior to surgery, NIVO (10mg) was administered IV in all patients (pts), followed by a maximal safe resection (B+C), or biopsy (A+D), followed by iCE (B+C) or iTU (A+D) admin of IPI (5 mg) plus NIVO (10 mg). At the end of surgery, 10 mg NIVO plus 1, 5 or 10 mg of IPI was administered iCA or iTH (: Ommaya reservoir) in C and D respectively. iCA and iTH admin of NIVO with/-out IPI, as well as IV admin of NIVO (10 mg) were repeated Q2w (max 24w). On-treatment CSF samples were used for cytology, chemical analysis and measurements of NIVO/IPI concentrations.

Results:

39 pts (27 male) were enrolled (A: n¼16, B: n¼16, C: n¼4, D: n¼3; enrolment ongoing in C+D). At database lock, all pts in A+B were off study treatment. All pts received the predefined dose of iCE/iTU IPI/NIVO. The median of iCE/IV NIVO admin was 5 (1-12) in A and 4(1-12) in B. Most frequent AEs were fatigue (n¼30), headache (n¼19), confusion (n¼14), dysphasia (n¼13), fever (n¼10), and bacterial colonization of the Ommaya reservoir (n¼5). On-treatment neurological deterioration due to subacute symptomatic cerebral edema requiring corticosteroids occurred in 6 pts. There were no G5 AEs. irAEs were infrequent. In A+B, PD was diagnosed in all pts, and 27 pts have died. Median PFS and OS were numerically inferior for pts treated in A vs. B (median PFS 5w (95% CI 1-8) vs. 13w (95% CI 7-19); median OS 23w (95% CI 053) vs. 42w (95% CI 30-54); 6m-OS-rate 50% (95% CI 26-75) vs. 68.8% (95% CI 46-91)). An elevated protein level and lymphocytic pleocytosis were observed in >90% of CSF samples. There was no evidence for accumulation of NIVO/IPI in the CSF.

Conclusions:

Intracranial admin of NIVO +/- IPI in pts with rGB was found to be feasible, safe, and associated with encouraging OS in pts amenable to resection.

Clinical trial identification:

NCT03233152.

Clinical features and DNA methylation patterns in long- and short-term survivors of WHO grade II-III glioma

Background:

WHO grade II-III gliomas affect rather young individuals and are characterized by a heterogenous survival prognosis ranging from months to years. Postoperative treatment prolongs survival but potentially impacts long-term quality of life and cognitive functioning. Therefore, refined prognostic stratification models are needed to guide future treatment studies.

Methods:

Patients with histological diagnosis of WHO grade II/III glioma (lower-grade glioma, LGG) and treated in 2000 e 2018 at the Medical University of Vienna were identified. Short-term survivors (STS) were defined by OS < 12 months, while longterm survivors (LTS) were defined by OS > 10 years after diagnosis. Histological diagnosis according to the current WHO classification was done by a board-certified neuropathologist. DNA methylation profiling was performed using the Illumina EPIC 850k platform and methylation-based tumor classification was obtained using the Heidelberg Methylation Classifier.

Results:

Among 599 LGG patients, 123 LTS (20.5%; 40/123 astrocytic, 44/123 oligodendroglial, 39/123 not otherwise specified or pre-WHO 2016 diagnosis = NOS) and 36 STS (6.0%, 24/36 astrocytic, 1/36 oligodendroglial, 11/36 NOS) were identified. At LGG diagnosis, Karnofsky Performance Scale (KPS) was lower ($p < 0.001$) and age was higher in STS as compared to LTS ($p < 0.001$). Epileptic seizures were more frequent in LTS, while motor deficits ($p < 0.001$), aphasia ($p = 0.025$) and visual disturbances ($p = 0.031$) were more common in STS at diagnosis. WHO grade II, IDH mutations, 1p19q codeletions and MGMTpromoter methylation were each more frequent in LTS than in STS ($p < 0.001$). Unsupervised clustering of patient samples based on their methylome revealed 3 clusters. Cluster A included LTS with IDH-mutated tumors (n = 42, 68.9%). Cluster B was defined by STS with IDH-wildtype gliomas (n = 16, 26.2%). Cluster C comprised STS with IDH-mutated tumors (n = 3, 4.9%). Age, KPS and symptomatic burden did not differ between IDH-mutated tumors of clusters A and C ($p > 0.05$).

Conclusions:

Our data indicate that DNA methylation profiling identifies IDH-mutated LGG with unfavorable prognosis. Further studies are needed to elucidate the pathobiology and optimal treatment of these high-risk LGG.

Experience of GEINO (Spanish cooperative group for research in neuro-oncology) oncologists in the management of adult medulloblastoma

Background:

Medulloblastoma (MB) is extremely rare in adults (1% of CNS tumors). Comparative studies show important biological differences between adult and pediatric patients with implications in clinical behaviour and patient outcomes. Although MB is potentially curable with a multidisciplinary approach comprising a combination of maximal safe resection, craniospinal irradiation (CSI), and chemotherapy (CT), the lack of specific studies in the adult subpopulation forces oncologist to adapt treatment regimens.

Methods:

GEINO Neuro-oncologists were asked to register MB patients in the GEINOGETHI National CNS tumor register (pts alive at the time of inclusion gave informed consent).

Results:

Between 1996 and 2021, 71pts either diagnosed as adults (median age 32y range 18-71) or referred to adult units (7pts), were identified. 42% were female, common symptoms included headache (69%) and ataxia (31%). Of 14 pts with molecular classification, 10 were SHH+(1 pt p53 mutated) and the others non-WNT nonSHH+ and of 23 patients with histological subtype 19 were desmoplasic-nodular. 70,6% underwent complete resection, 23,5 partial and 5,9 biopsy. 95% received radiotherapy, most commonly to the tumor (61%) with a median dose of 55Gy and to the neuroaxis (48%) with a median dose of 36 Gy. Diverse treatment strategies were used: sequential chemotherapy 42.9% (of wich 29% Vincristine-lomustine-platin), 19% concomitant and sequential (80%concomitant vincristine followed in 50% by Vincristine-lomustine-platin), 14% only concomitant CT (66% with vincristine) 7.9% only neoadjuvant(80% carboplatin-VP16, followed in 40% by the same schema) and 7.9% only CT(66% with a platin-VP16 triplet). Median survival was 14,37y and 70.1% remain relapse free.

Conclusions:

Significant heterogeneity is present in the management of adult MB in Spain. Although treatment in MB should be individualized and treatment outcomes are in line with published series, differences in treatment schemas and availability of molecular diagnostic tools highlight the importance of collaborative groups to standardize management.

Treatment associated changes in the inflammatory microenvironment composition of brain metastases

Background:

Radio- and immunotherapy were postulated to have synergistic efficacy in brain metastasis (BM) treatment due to the immune modulating properties of radiation. Therefore, we aimed to investigate changes in the inflammatory microenvironment after local radiation treatments in BM specimens.

Methods:

Formalin fixed and paraffin embedded BM samples from treatment naïve patients (group 1) and from patients treated whole brain radiotherapy (WBRT) (group 2) or stereotactic radiosurgery (SRS) (group 3) or combined WBRT and SRS (group 4) or prophylactic cranial irradiation (group 5) before BM resection were identified from the Vienna Brain Metastasis Registry. T cell subsets (CD3+, CD8+, CD45RO+, FOXP3+ and LAG3) as well as expression of PD-L1 were investigated.

Results:

Specimens from 81 patients (55 lung cancer, 15 breast cancer, 4 renal cell cancer, 1 melanoma, 1 colorectal cancer & 5 other tumor types) were available for analysis. Group 1 presented with statistically significantly higher CD3+ (median: 492.6 cells/mm2), CD8+ (median: 116.3 cells/mm2) and LAG3+ (median: 17.6 cells/mm2) TIL densities than group 2 (CD3+ median:55.5 cells/mm2; LAG3+ median: 4.6 cells/mm2), group 3 (CD3+ median: 67.7 cells/mm2; CD8+ median: 40.6 cells/mm2) and group 4 (CD3+ median: 38.28 cells/mm2; p-value <0.05; Kruskal Wallis test). No significant changes of the inflammatory microenvironment in group 5 compared to the other groups, and in PD-L1 expressions between the groups were observed (pvalue >0.05; Kruskal Wallis test). Of 24/81 (29.6%) patients matched samples of initial resected BM and recurrent BM were available. All investigated T cell subsets were numerically lower in recurrent BM from patients treated with radiation therapy between resections than in recurrent BM from patients without radiation treatment between BM resections ($p > 0.05$; Mann-Whitney U-test).

Conclusions:

Our data indicate an immunosuppressive effect of radiotherapy on BM, as evidenced by decreased T cell infiltration in radiated versus non-radiated BM specimens. Future clinical studies should focus on the optimal timely sequencing of immune modulating therapies and radiotherapy.

Safety of idroxioleic acid in combination with standard of care (temozolomide and/or radiation therapy) in newly diagnosed glioblastoma patients: A phase Ib trial

Background:

Glioblastoma multiforme (GBM) is the most frequent primary malignant brain tumour in adults (>60%), with very poor prognosis. First-line standard of care (SoC) treatment for patients involves surgery/surgical resection along with radiation therapy (RT) and concomitant adjuvant temozolomide (TMZ). Idroxioleic acid (2hydroxyoleic acid sodium salt; 2-OHOA), a new class of orally bioavailable fatty acid that modulates the lipid composition and structure of the membranes, has shown specific effects against cancer due to a dual-mode molecular mechanism of action (cell cycle arrest and programmed cell death by non-protective autophagy in glioma). The aim of this study was to determine the safety, tolerability and maximum tolerated dose of 2-OHOA added to first-line SoC for newly diagnosed GBM patients.

Methods:

A phase 1B, open-label, dose-finding study, 3+3 de-escalating design (starting at 12 g/day). The trial (NCT03867123) recruited newly diagnosed GBM patients with a partial or complete surgical resection of the grade 4 astrocytic tumour in two independent arms: arm 1 (6-week concurrent phase of RT + TMZ + 2-OHOA) and arm 2 (8-week maintenance phase of TMZ + 2-OHOA). Both arms were to be followed by a 4-week safety follow-up.

Results:

Nineteen patients were recruited, 10 patients in Arm 1 and 9 in Arm 2. As no DLTs were found, all received 12 g/day of 2-OHOA. All patients from both arms presented at least one AE. The AEs presented in >40% of the patients were diarrhoea (8/10), headache (5/10), nausea (5/10), asthenia (4/10), constipation (4/10) and vomiting (4/10) in Arm 1, and nausea (6/8), diarrhoea (5/8) and vomiting (5/8) in Arm 2. None of the patients suffered any grade 4 or 5 AEs by CTCAE grade in any arm. The only attributed SAE in the study eembolism CTAE 3 in one patient in Cohort 1 (1/10)e was not related to 2-OHOA.

Conclusions:

Addition of 12 g daily of 2-OHOA to standard of care (RT/TMZ) in newly diagnosed GBM patients was generally well tolerated, offered a favourable safety profile (no 2-OHOA-related serious or high-grade AEs), and it is the recommended dose of 2-OHOA for phase III trials.

Clinical trial identification:

NCT03867123.

5-Aminolevulinic acid sonodynamic therapy in recurrent glioblastoma: A first-in-human phase 0/1 clinical trial

Background:

5-aminoleveulinic acid sonodynamic therapy (5-ALA SDT) is a drug-device strategy that exploits the metabolic liabilities of cancer. Following systemic administration of 5-ALA, incomplete tumor metabolism leads to accumulation of a photosensitive intermediary, protoporphyrin-IX (PpIX). Activation of PpIX by noninvasive, non-ablative magnetic resonance-guided focused ultrasound (MRgFUS) induces cytotoxic reactive oxygen species and tumor cell death. This first-in-human phase 0/1 study investigates the feasibility, safety, and biological effects of 5-ALA SDT in recurrent glioblastoma patients (GBM).

Methods:

Ascending energy doses of 5-ALA SDT are tested in adult patients with recurrent GBM undergoing planned re-resection. In a Dose-Escalation Arm, 9-18 patients are assigned to one of three dose levels of MRgFUS (200J, 400J, and 800J), followed by a four-day interval to tumor resection. In each patient, half the tumor volume, including Gadolinium-enhancing and nonenhancing tumor, is targeted with MRgFUS and the other half is an internal control. Using tumor pharmacodynamic endpoints, the Minimum Biological Dose (MBD) associated with 5-ALA SDT response is identified. In a subsequent Time-Escalation Arm, 12 patients are treated at the MBD and assigned to one of two time-intervals (two-days vs. six-day) between SDT and resection.

Results:

As of May 1, accrual to the 200J dose level was completed (n¼3) without significant drug- or device-related adverse events. No cellular or radiographic changes to non-targeted tissue were observed. Following 5-ALA infusion, the median Cmax for 5-ALA and PpIX were 307 mM and 319 nM, respectively. For all patients, the oxidative stress biomarkers 4-hydroxynonenal , glutathione, cysteine, and thiol were elevated in treated tissue vs. internal control. Similarly, the apoptosis biomarker cleaved caspase3 was increased in treated tumor vs. control (median, 48.6% vs. 29.6%, p=0.05).

Conclusions:

This initial, first-in-human experience with a new therapeutic modality for recurrent glioblastoma indicates that 5-ALA SDT is well-tolerated and safe at 200J.
Sonodynamic therapy leads to targeted oxidative stress and accompanying cell death in human glioblastoma tissue.

Clinical trial identification:

NCT04559685.

Up-regulation of sorcin promotes glioblastoma progression via activating the PI3K/AKT/mTOR pathway

Background:

Glioblastoma (GBM) is one of the most common malignant intracranial tumors exhibiting highly aggressive and invasive features. Sorcin (SRI) is a soluble calcium (Ca2+)-binding protein, one prominent member of penta-EF-hand (PEF) protein family, and was involved in the tumorigenesis. In this study, the expression of SRI and the functional role in the progression of GBM were investigated.

Methods:

The expression of SRI in GBM was examined in Oncomine and TCGA database and was further measured in clinical tissues and cell lines by immunohistochemical staining, western blot, and RT-PCR. The biological functions of SRI in GBM were performed in vitro models and the underlying molecular mechanisms were further investigated.

Results:

We found that SRI expression was up-regulated in GBM tissues and cells compared to nontumorous samples. The results in vitro demonstrated that tumor proliferation is facilitated by the upregulation of SRI. Concurrently, the migration and invasion of GBM cells were significantly enhanced. Reversely, knocking down of SRI expression attenuated the pro-GBM activities. We further indicated that the overexpression of SRI promoted the epithelial-mesenchymal transformation (EMT) and significantly triggered the PI3K/AKT/mTOR pathway in GBM cells, which was hindered by depletion of SRI. Moreover, the key variant of SRI with a mutation at the number of 159 amino acid was identified and played a crucial role in promoting the oncogenic behaviors induced by SRI overexpression.

Conclusions:

Collectively, these findings suggest that SRI was up-regulated in GBM and functions as an oncogenic role in the progression of GBM via triggering the PI3K/ AKT/mTOR pathway. Then it highlights that SRI may represent a valuable therapeutic target for the clinical intervention of GBM.

The amount of cancer stem cells and the sensitivity to anticancer drugs in glioblastoma primary cell culture

Background:

It is assumed that aggressiveness and therapy resistance of glioblastoma multiforme (GBM) is determined by its high heterogeneity and presence of cancer stem cells (CSC). The primary glioblastoma cell lines (pGBM lines) could better than the cultured cell lines reflect the tumor heterogeneity and, thus, provide the additional opportunities for personalized medicine. In our study, we compared the response of the pGBM lines and cell glioblastoma lines to chemotherapy drugs with the CSC content in cell cultures.

Methods:

Four pGBM lines obtained from patients and standart glioblastoma line U251 were used. The amount of CSCs in cell culture was evaluated with flow cytometry by expression of CD133/CD44 and CD90/CD95. Further, the cultures were characterized by immunostaining with Nestin and Oct4.Chemotherapeutic agents included both drugs, commonly used in clinical practice for glioblastoma treatment and drugs used for therapy of other types of cancer. Cytotoxicity was tested via MTT assay. Proliferation rate was measured through cell counting within 3 following days.

Results:

The correlations between CD133/ CD44 and CD90/CD95 expression, proliferation rate, and drug resistance of cell cultures were evaluated. The U251 cell line demonstrated significantly increased sensitivity towards cytostatic agents such as gemcitabinum, cisplatin, irinotecan, doxorubicin as compared to pGBM-lines, although its proliferation rate was not the highest. For all studied GBM-lines, the amount of CD90+/CD95+ cells negatively correlated with rozustin sensitivity. The Gbl24n line was the only cell culture with CD133+ cells (about 10%) and it was 20-25% less sensitive to lomustine. Carfilzomib sensitivity positively correlates with the amount of CD133-/CD44- cells, whereas irinotecan sensitivity has a negative correlation with this parameter.

Conclusions:

In total, the pGBM lines are less sensitive to anti-cancer drugs, than the U251 cell line. That might result from heterogeneity of primary culture and the presence of CSC in primary tumor cultures. For several drugs (lomustine), the correlation between the amount of CSC in cell culture and drug sensitivity was found.

Molecular profiling of tumor tissue and tumor-derived cell lines in patients with glioblastoma

Background:

Glioma grade IV (glioblastoma, GBM) is an aggressive central nervous system tumor, which demonstrates high heterogeneity and resistance to treatment. Patient-derived cell cultures (GBM-lines) were shown to be representative models for analyzing the drug sensitivity of tumor cells for a better choice of appropriate treatment. Our aim was to compare molecular profiles of the tumor and the established patient's cell line to find out if the cell line preserved important biomarkers of the tumor.

Methods:

The study included 22 patients with GBM (19 primary and 3 secondary tumors). The status of IDH1/2, BRAF genes and MGMT promoter were analyzed using real-time PCR and Sanger sequencing. The primary cell lines were obtained from GBM surgical specimens and characterized after 5-6 passages of growing. For five patients, matched samples of tumor tissue, periphery blood and GBM lines were analyzed using 415-gene panel targeted sequencing. Somatic and germline mutations and copy number variations were identified.

Results:

The IDH1 mutation was found in two secondary GBM. MGMT promoter was methylated in 13 of 22 tumors. The neuronal origin of cell lines was confirmed by immunofluorescent staining for nestin and b3-tubulin, and proliferation rate was measured. Somatic mutations in PTEN, TP53, RB1, mTOR, PIK3CG, GNAS genes were found in 4/5 tumor samples analyzed by NGS. The CNV changes were detected in chromosomes 10, 13, 15, 17 and 22. One cell line derived from secondary GBM was characterized by a high proliferative rate and had a very similar molecular profile to the initial tumor with additional loss of heterozygosity for mutations in PTEN and TP53 genes. Two cell lines with a slow rate of proliferation had mutation profiles completely different from the initial tumor without specific mutations and CNV changes. Two other lines had the partial coincidence of mutations compared with matched tumors.

Conclusions:

Molecular profiling of patient-derived cell lines revealed initial tumor heterogeneity, providing hints for further translational research to better understand the effects of genetic alterations on treatment and prognosis. Thus, the genetic testing of patient-derived cell cultures may be important before using them as a model of glioblastoma tumor cells.

Impact of time to initiation post-operative adjuvant chemo-radiation in glioblastoma multiform: A systematic review

Background:

Glioblastoma multiform is the most common malignancy and very aggressive tumor found in the central nervous system. The current standard treatment for glioblastoma includes maximal safe resection followed by adjuvant concurrent chemo-radiation and adjuvant chemotherapy. With its aggressive behavior, delayed adjuvant therapies may lead to worse survival outcome that is showed by data from other tumors such as breast cancer and lung cancer. However, the relationship between timing to initiation post-operative adjuvant chemo-radiotherapy in glioblastoma remains unclear.

Methods:

A literature search was conducted on 5 databases by 2 persons. Bias assessment for individual studies was evaluated using the Newcastle-Ottawa Quality Assessment Scale by 2 independent reviewers.

Results:

Total of 2,804 studies were found from initial database search. Twenty studies met eligibility criteria and were reviewed. Nine studies found no statistically significant effects of time to initiation post-operative adjuvant chemo-radiotherapy on overall survival. On the other hand, eleven studies found statistically significant effects of time to initiation post-operative adjuvant chemo-radiotherapy on overall survival.

Conclusions:

Time to initiation adjuvant chemo-radiotherapy is a challenging issue. Most of the studies reported that slight delayed (4-6 weeks) timing to initiation of chemo-radiation seems to have a better survival outcome.

The impact of carmustine implants and concurrent chemoradiation on outcomes in primary treatment of glioblastoma: A single centre experience over a 10-year period

Background:

Standard primary surgical management of glioblastoma is maximal safe de-bulking. In the United Kingdom, for those patients' where more than 90% of debulking is possible, carmustine wafers (Gliadel) have been approved for insertion along the operative bed. (NICE TA121 2007). Although a meta-analysis of 513 patients demonstrated a survival advantage of gliadel wafer insertion. (Xing et al 2015), the usage varies within different neuro surgical centres. In this retrospective analysis we look at our tertiary neuro surgical centre experience in this clinical scenario.

Methods:

We collected data from 110 patients who completed standard treatment of adjuvant chemoradiotherapy following neurosurgery from 2007 to 2016. Data were reviewed from surgical entry and oncology records. Patients who did not receive adjuvant chemoradiotherapy within 3 months due to post op complications from Gliadel wafers were excluded in the final analysis.

Results:

The median age was 60 years and median overall survival was 16 months for the entire cohort. Maximal debulking was achieved in 39%, partial de-bulking in 50% and 11% had biopsy only. For patients who had gliadel wafer insertion, median overall survival was 19.5 months (95% confidence interval 14-30) for those without wafers median overall survival was 16 months (95% confidence interval 14 e 21), P=0.06. On Cox regression analysis Gliadel wafer insertion was a statistically significant predictor of overall survival, P-Value, 0.008. Progression-free survival was not significantly significant with the insertion of Gliadel wafers. It was 12.2 (10.43-19.7) months with wafer insertion and 11.8 (8.93-15) without.

Conclusions:

Within our select cohort of glioblastoma patients, carmustine wafer insertion at the time of primary de-bulking surgery showed improved overall survival without impacting the progression free survival.

Treatment outcome of temozolomide in elderly patients with glioblastoma: A systematic review

Background:

Glioblastoma has a poor survival rate around 40% after one year since diagnosis and 17% in the second year. However, studies about treatment of Temozolomide to improve outcome in patients with glioblastoma remains unclear. The aim of the study is to know the overall survival of Temozolomide treatment of glioblastoma, specifically in elderly patients.

Methods:

Two reviewers independently extracted studies from online databases PubMed, PMC and Scopus using combinations of keywords related to Temozolomide, glioblastoma, elderly, and survival. Studies that were extracted will be analyzed and selected according to inclusion criteria such as cohort and randomized clinical trial studies in the last 10 years. We excluded systematic reviews, meta-analysis, case series, case report, and animal study. We included studies that investigate the combination of radiotherapy and Temozolomide. Quality of each included study is assessed using the Newcastle-Ottawa Scale (NOS) and Cochrane review for Randomized controlled trial (RCT).

Results:

Five studies were extracted from 32 initial eligible one. All five studies included were in good quality. Four of 5 studies showed that Temozolomide's overall survival rate increased significantly. In one of the cohort studies, Temozolomide with radiotherapy compared to radiotherapy alone, 2-year survival rate were increased from 14% to 41%. However, one of 5 studies reported negative result.

Conclusions:

In conclusion temozolomide may increase overall survival rate in elderly patients with glioblastoma. However, further RCT studies are needed confirm this finding.

Extended dosing (12 cycles) vs. conventional dosing (6 cycles) of adjuvant temozolomide in adults with newly diagnosed high grade gliomas: A randomized, single-blind, two-arm, parallel-group controlled trial

Background:

Maximum safe surgical resection followed by adjuvant chemoradiation and temozolomide chemotherapy is the current standard of care in the management of newly diagnosed high-grade glioma. However, there are controversies about the optimal number of adjuvant temozolomide cycles. This study aimed to compare the survival benefits of 12 cycles against 6 cycles of adjuvant temozolomide adults with newly diagnosed high grade gliomas.

Methods:

Adult patients with newly diagnosed high-grade gliomas, and a Karnofsky performance status >60%, were randomized to receive either 6 cycles or 12 cycles of adjuvant temozolomide. Patients were followed-up for assessment of overall survival (OS) and disease-free survival (DFS) by brain MRI every 3 months within the first year after treatment and thereafter every six months.

Results:

A total of 100 patients (6 cycles, 50; 12 cycles, 50) were entered (Table). The rate of treatment completion in 6 cycles and 12 cycles group were 91.3% and 55.1%, respectively. With a median follow-up of 16.5 months, the 12-, 24-, and 36month OS rates in 6 cycles and 12 cycles groups were 82.6% vs 78.8%, 55.5% vs 63.5%, and 44.4% vs 54.4%, respectively (p=.976). The 12-, 24-, and 36-month DFS rates in 6 cycles and 12 cycles groups were 72.1% vs 57.7%, 42.6% and 34.3, and 39.6% vs 30.8%, respectively (p=.276).

Table: 354P **The demographic characteristics of the patients at baseline**

Variable	6-cycle group n (%)	12-cycle group n (%)	p-value
Headache	35 (76.1)	33 (67.3)	.345
Seizure	16 (34.8)	14 (28.6)	.515
Paresthesia	10 (21.7)	18 (36.7)	.213
Focal neurologic deficit	16 (34.8)	18 (36.7)	.834
Midline shift	29 (63)	31 (63.3)	.982
Type of surgery			
Gross total resection	8 (17.4)	9 (18.4)	.436
Subtotal resection	28 (60.9)	24 (49)	
Biopsy only	10 (21.7)	16 (32.7)	
Histology			
Glioblastoma multiform	37 (80.4)	40 (81.6)	.882
Anaplastic astrocytoma	9 (19.6)	9 (18.4)	
CTV (cc, median)	244.7	263	.461

Conclusions:

Patients with newly diagnosed high-grade gliomas treated with the adjuvant temozolomide after maximum safe surgical resection and adjuvant chemoradiation do not benefit from increasing the number of cycles of adjuvant temozolomide beyond 6 cycles.

Clinical trial identification:

IRCT20160706028815N3

Butterfly glioblastoma: Treatment strategies and clinical outcome

Background:

Butterfly glioblastoma (bGBM) is a rare and sparsely described subgroup of glioblastoma with a bihemispheric tumour crossing the corpus callosum. bGBM is associated with a dismal prognosis, and optimal treatment remains unclear.We aimed to evaluate overall survival and survival stratified by treatment strategies in a realworld setting.

Methods:

This was a retrospective population-based study on patients diagnosed with bGBM in Western Norway from 2007 to 2014. Clinical data and treatment strategy were collected from medical records. Treatment modalities included resection, radiation therapy and Temozolomide. Survival analyses were caluclated by Kaplan Meier method and Cox regression.

Results:

Among 381 diagnosed with glioblastoma in the study period, we identified 36 patients (9.4%) with bGBM. Sixteen (44.4%) were histologically confirmed and 20 (55.6 %) were diagnosed solely by MRI. Median age was 65.9 years. Median overall survival was 5.9 months (95% CI 2.7-9.2). One-, two, and three-year survival rates were 19.4%, 16.7%, and 8.3%. Median survival in patients receiving best supportive care, one, two, and three treatment modalities was 1.6 months (95% CI 0.5-2.6), 4.5 months (95% CI 3.5-5.5), 7.4 months (95% CI 5.5-9.3), and 7.8 months (95% CI 6.7-8.9) ($p<0.001$). Further survival analysis in the table. Median survival in patients aged under 70 years was 7.8 months (95% CI 6.3-9.3), compared to 2.1 months (95% CI 0.0-5.0) in patients aged over 70 years ($p<0.001$). In these two groups, 21 of 23 patients (91.3%) vs two of 13 patients (15.4%) were treated with at least two modalities ($p<0.0001$).

Table: 355P Multivariate Cox regression analysis for overall survival in 36 patients diagnosed with butterfly glioblastoma between 2001 and 2014

	n	(%)	Adjusted hazard ratio (HR)	95%CI	P value
Female	21	(58.3%)	0.53	0.24-1.18	0.12
Age ≥ 70 years	13	(36.1%)	2.35	0.64-8.61	0.20
Primary treatment (including resection, radiation therapy and Temozolomide)					
Best supportive care	6	(16.7%)	Ref		
One modality	7	(19.4%)	0.24	0.07-0.80	0.02
Two modalities	17	(47.2%)	0.13	0.03-0.63	0.01
Three modalities	6	(16.7%)	0.15	0.03-0.86	0.03

Conclusions:

Median overall survival was poor, however with a three-year survival rate comparable to that observed in non-butterfly glioblastoma cohorts. Increased treatment intensity was associated with improved survival. Patients with bGBM may benefit from a more aggressive treatment approach despite a dismal prognosis. Few patients aged over 70 years received multimodal treatment and had a significantly inferior outcome.

Redo surgery in relapsed glioblastoma multiforme: A comparative cohort analysis of a single institution experience

Background:

Glioblastoma multiforme (GBM) is the most common intracranial primary malignant brain tumor. Concurrent chemo-radiation as definitive treatment after maximal debulking is established as first-line treatment standard but recurrences are treated based on institutional experiences with or without surgery before second and subsequent line of chemotherapy. In this study we look at our tertiary centre institution experience of recurrent Glioblastoma who underwent redo surgery for first recurrence.

Methods:

We retrospectively reviewed the surgical and oncological data for patients at the Royal Stoke university Hospitals who underwent redo surgery for recurrent GBM between 2006 and 2015. These patients (G1) were then compared with a randomly selected control group (G2), who did not have redo surgery but matched the reviewed group by age, primary treatment, PFS. Data on overall survival, progression free survival, extent of surgical resection, postoperative complications was collected.

Results:

total of 30 patients in G1 and 32 patients in G2 were matched. Progression free survival was 25 weeks in G1, overall survival was 109 weeks (range, 45-180) versus 57 weeks (range 28-127) in G1 vs G2 respectively from time of first diagnosis. There was an incidence of 57% complication rate after second surgery (this included haemorrhage, infarction, worsening neurology due to oedema, CSF leak, and wound infection). More than half of the Redo patients went on to have second and subsequent lines of chemotherapy.

Conclusions:

In spite of redo surgery in recurrent GBM is variable, our conclusion is that it is a valid option in select group of patients with good performance status and patients who have a longer progression-free survival from primary treatment. It can also help alleviate compressive symptoms. A well-designed randomized control trial in this population would help set the standard of surgical care.

A phase II study of anlotinib in the treatment of recurrent high-grade glioma

Background:

Recurrent high-grade glioma is associated with limited survival and there is no standard treatment option currently. We assessed if anlotinib, a multitarget tyrosine kinase inhibitor, is safe and effective for the treatment of these patients.

Methods:

This is an open-label, single-arm, single-center, phase II clinical trial (NCT04822805). Eligible patients were aged more than 18 years old, histologically confirmed high grade glioma with progression after surgery followed by radiotherapy and temozolomide chemotherapy. Additional inclusion criteria included KPS≥60, disease progression on MRI as defined by Response Assessment in Neuro-Oncology (RANO) criteria at least 12 weeks after completion of postoperative adjuvant radiotherapy. Patients were received 12mg anlotinib once daily for 14 days every 3 weeks until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Safety assessment was done in patients who received at least one dose of anlotinib. Here we report the results of a planned interim analysis.

Results:

From April 2020 to February 2021, 12 of 27 patients (9 males and 3 females) were enrolled, and the median age is 57 (range 23-69). Pathological types included glioblastoma (n=9), anaplastic astrocytoma (n=2), anaplastic oligodendroglioma (n=1). At the data cutoff date on April 22, 2021, the median duration of treatment was 8.1 months, and the median PFS was not reached. 11 patients were eligible for the evaluation of tumor response. 2 achieved complete response (CR), 3 achieved partial response (PR) and the objective response rate (ORR) was 45.4% (5/11). 6 had stale disease (SD) and the disease control rate (DCR) was 100% (11/11). The clinical benefit rate (CBR), defined as the proportion of patients who achieved durable disease control (CR/PR/SD) more than 6 months, was 72.7% (8/11). Most adverse events were grade 1 or 2. Grade 3 adverse events occurred in 3 (25%) of 12 patients, included seizures, neutropenia, leukopenia, respectively. And there was a death due to intracranial hemorrhage during the treatment.

Conclusions:

This interim analysis showed anlotinib is effective and well toleranced for recurrent high-grade glioma patients.

Anlotinib plus temozolomide for recurrent glioma: A singlecenter, retrospective study of 30 cases

Background:

The prognosis of patients with recurrent malignant glioma (rMG) is quite poor. According to the NCCN guidelines, bevacizumab is recommended drug for rMG. Anlotinib is a multitarget tyrosine kinase inhibitor that can inhibit tumor angiogenesis and tumor cell growth. We report results from this retrospective study to determine the efficacy and tolerability of Anlotinib plus temozolomide (TMZ) as a first-line treatment for rMG.

Methods:

A total of 30 eligible patients who relapsed from the standard chemoradiotherapy regimen (TMZ and radiotherapy) or had macroscopic residual tumor after surgery because of tumor located in the eloquent brain areas were enrolled in this study between March 2018 and January 2021. Patients were subjected to a concurrent treatment of Anlotinib (12mg qd) and TMZ (200mg/m2, 5 days on with 23 days off) until disease progression or intolerable toxicity. Efficacy was evaluated using Response Assessment in Neuro-Oncology criteria for high-grade glioma. Safety was assessed using NCI-CTCAE 4.0. Survival was estimated with the Kaplan-Meier curve and log-rank test.

Results:

All patients were eligible for efficacy analysis. The objective response rate (ORR) was 76.7%. The disease control rate (DCR) was 90%. The median progress-free survival time was 8.3 months. The median overall survival was 10.8 months. The most common treatment-related adverse events were hand-foot syndrome (43.3%), leukopenia (40%), transaminase elevation (40%), hypertension (30%), thrombocytopenia (30%), albuminuria (26.7%), hyperbilirubin (36.7%), anemia (23.3%), neutropenia (16.7%) and gastrointestinal reaction (13.3%). The rate of grade 3/4 AE was relatively low, including hand-foot syndrome 6.7% (2/30), thrombocytopenia 6.7% (2/ 30), and hyperbilirubin 3.3% (1/30).

Conclusions:

Anlotinib combined with TMZ was effective in terms of PFS, ORR, and DCR, and was well tolerated. Further randomized controlled clinical studies are needed to confirm the efficacy of Anlotinib combined with TMZ for the treatment of rMG.

Regorafenib in recurrent glioblastoma patients: A large real-life experience

Background:

Regorafenib (REG), showed encouraging benefit in recurrent GBM patients in REGOMA trial. We investigated the clinical outcome and safety of REG in a real-life population of recurrent GBM patients treated at Veneto Institute of Oncology as off-label use.

Methods:

Patients receiving REG were entered prospectively on a clinical database. Data were retrospectively analyzed. The primary endpoints were overall survival (OS) and safety. The major inclusion criteria were: histologically confirmed diagnosis of GBM, disease progression by RANO criteria after surgery and chemoradiotherapy, ECOG PS ≤2; PTS with ≥2 prior lines of therapy were excluded. Patients received REG 160 mg once daily for the first 3 weeks of each 4-week cycle until disease progression, death, unacceptable toxicity, or consent withdrawal. Kaplan-Meier method was used to estimate the survival curves, CTCAE v5.0 for drug related adverse events.

Results:

From February2018 to September2020, 54 consecutive patients were treated with REG: median age was 56, ECOG PS 0-1 in 91%, MGMTmet in 53%, second surgery at relapse were performed in 30%, 41% underwent steroids at baseline. Median follow-up was 11.1 ms, 30 PTS (56%) had died and 50 PTS (93%) had progressed. Median OS was 10.2 ms (95%CI, 6.4-13.9), 12m-OS was 43%; median PFS was 2.3ms (95%CI, 1.3-3.3) and 6m-PFS was 18%. All patients were evaluable for response: disease control rate (DCR) was 46.3%; stable disease was reported in 38.8% and partial response in 7.4%. Age, MGMT and corticosteroid use at baseline were not statistically significant on multivariate analysis for OS. Grade 3 drug-related adverse events (AEs) occurred in 10 patients (18%) and the most frequent were hand-foot skin reaction, asthenia and increased lipase and transaminases; 1 PT (2%) reported a grade 4 AE (maculo-papular rash). AEs led to REG dose reductions in 37% of patients and, it was permanently discontinued in 5%. No death was considered to be drug-related.

Conclusions:

We reported a large, mono-institutional “real-world” experience of REG in recurrent GBM patients. Overall, results are close to those reported in REGOMA trial although, we showed a longer OS. Toxicity was moderate and manageable. Encouraging clinical benefits of REG in recurrent GBM population were confirmed.

Metronomic temozolomide therapy in heavily pretreated patients with recurrent glioblastoma: A large mono-institutional retrospective study

Background:

Glioblastoma (GBM) is the most common and aggressive primary brain cancer. Despite advances in surgical and first-line treatment, all pts relapse. The aim of this study is to evaluate the benefit of metronomic Temozolomide (mTMZ) for recurrent GBM.

Methods:

All pts treated at Veneto Institute of Oncology from September 2013 to March 2021 were retrospectively reviewed. Major inclusion criteria were: first-line therapy with Stupp protocol, relapse after first or subsequent line of therapy, treatment with mTMZ schedule (50mg/m2 continuously), hystologically confirmed diagnosis of GBM. RANO criteria and CTCAE v 5.0 were used for response and toxicity assessment.

Results:

120 pts were enrolled. Median follow-up was 15.6ms. Median age was 59ys (range 18-81), ECOG PS was 0-2 in 107 patients (89%) and 3 in 11 (9%). MGMT was methylated and IDH mutated in 66 of 105 (62%) and in 9 of 106 (8%) evaluable pts, respectively. Median number of prior lines of treatment was 2 (range 1-7) and 41% of pts received the therapy beyond the third line. Median time between the last standard maintenance TMZ (sTMZ) cycle and the mTMZ administration was 6ms (range 150) and 40% of pts started mTMZ after 3ms from sTMZ. All pts were evaluable for response: 3 (2%) and 48 (40%) showed PR and SD. mOS from the start of mTMZ was 5.4ms (95% CI 4.3-6.4), mPFS was 2.6ms (95% CI 2.3-2.8). On univariate analysis, MGMTmet and MGMTunmet pts had a mOS of 5.6 and 4.4ms (p=0.03); mOS for patients with ECOG PS > or ≤2 was 2.3 and 6.0 ms (p<0.001); number of prior lines of therapies, time between sTMZ and mTMZ and age were not significant. On multivariate analysis, MGMT methylated status (HR=2.3, 95% CI, p=0.004) and ECOG PS (HR=0.5, 95% CI, p=0.017) remained statistically significant for PFS, while ECOG PS (HR=0.4, 95% CI, p=0.001) was the only factor significantly associated with OS. The most common grade 3 and 4 hematologic toxicities were lymphopenia (10%) and thrombocytopenia (3%). Grade 3 and 4 nonhematologic toxicities were uncommon.

Conclusions:

Rechallenge with mTMZ can be a well tolerated treatment option for recurrent GBM, even in heavily pretreated pts. Pts with MGMTmet and good ECOG PS might report the major benefit.

Efficacy of chemotherapy plus bevacizumab in recurrent multiforme glioblastoma: A real-life study

Background:

Bevacizumab and chemotherapy are frequently used to treat recurrence of glioblastoma (GBM). However, the selection of the concomitant chemotherapeutic agent remains an open question.

Methods:

All patients treated with at least one cycle of chemotherapy plus bevacizumab for recurrent GBM at the Georges-François Leclerc Cancer Centre in Dijon, France between June 2005 and August 2019 were included in this retrospective study. The primary and secondary objectives were progression-free survival (PFS) and overall survival (OS), respectively. As fotemustine is preponderant in the treatment of GBM, as recommended by the survival criteria, we compared this with other chemotherapy agent groups.

Results:

A total of 160 patient files were analysed. One hundred patients received fotemustine (62.5%), 18 temozolomide (11.2%), seven lomustine (4.4%), and 35 irinotecan (21.9%). The majority were male (63.7%), and the mean age was 59.8 years. Further, 81% of patients had a Karnofsky performance status ≥90, and 43% had undergone initial surgical resection. All patients received the first-line Stupp regimen. In the whole cohort, the median PFS was 4.5 months [2.7-8.5] and median OS was 9 months [4.5-23]. Only MGMT (methyl guanine methyltransferase) unmethylated status was associated with poor PFS upon univariate analysis. For OS, fotemustine treatment was associated with poor survival: 7.3 mo vs 19.9 mo (HR=2.13[1.23-3.7], p=0.006). In the fotemustine group, steroid usage at baseline was associated with poor survival: median OS of 6.7 mo vs not reached (HR=2.9 [1.1-7.3], p=0.03). Similarly, in the low Karnofsky performance status subgroup, fotemustine treatment was associated with poor OS: median OS of 4.3 mo vs not reached, (HR=4.5 [1.316.7], p=0.02).

Conclusions:

Using real-life data, this study shows the worst efficacy of the addition of fotemustine to bevacizumab compared with other added chemotherapeutic agents. We find that in patients with low-performance status, a concomitant steroid treatment other than an alkylating agent or irinotecan is a better choice for combotherapy.

Influence of the expression of ABCG2 transporters on the results of photodynamic therapy in malignant gliomas

Background:

The analysis of the effect of ABCG2 transporters on the effects of photodynamic therapy in malignant gliomas was carried out.

Methods:

A total of 98 patients with a glial tumor of supratentorial localization, a high degree of tumor anaplasia according to Grade (III-IV), were treated at the RNSI prof. A.L. Polenov. The analysis of the expression level of ABCG2 transporters and the effect on median survival during PDT was carried out. Chlorin e6 was used for PDT; the source of laser radiation was Latus 2.5 with a wavelength of 662 nm and a maximum power of 2.5 W.

Results:

Data are presented that glioma malignant cells are characterized by high expression of several ABCG2 transporters. It is also presented that gene expression of these transporters can correlate with the effects of ongoing photodynamic therapy and chemotherapy and affect the survival rate in patients with gliomas, and can be used as a prognostic biomarker. Median survival of patients with Grade III gliomas up to 42.1 ± 4.1 months with low expression of ABCG2 transporter (with high expression of ABCG2 - 18.3 ± 3.9 months), for patients with Grade IV gliomas up to 22.7 ± 3.5 months with low expression of ABCG2 carrier (with high expression of ABCG2 - 11.6 ± 1.9 months) (P = 0.0001).

Conclusions:

Malignant gliomas are characterized by various genetic and epigenetic aberrations, the influence of the microenvironment on the tumor, and the presence of cancer stem cells (CSCs), which make the tumor more aggressive, invasive, and resistant to treatment methods. A significant role in this complex process is played by ABCG2 transporters localized in tumor cells.

Clinical significance of telomerase reverse transcriptase (TERT) promoter mutations, telomere length and MGMT promoter methylation status in newly diagnosed and recurrent IDH wildtype glioblastoma (GBM) patients (PTS): A large mono-institutional study

Background:

The clinical significance of TERT promoter mutations, telomere length and their interactions with MGMT status in patients with IDHwt GBM PTS is unclear. We performed a large study to investigate their impact on clinical outcomes.

Methods:

TERT promoter mutations (C228T, C250T), relative telomere length (RTL) and MGMT status were assessed in 278 newly diagnosed (ND) and in 65 recurrent (REC) IDHwt GBM PTS which were treated from Dec 2016 to Jan 2020. We retrospectively explored association between gene characteristics and radiological response, progression free survival (PFS), overall survival (OS). Telomere length was measured by monochrome multiplex PCR and RTL values were calculated as a telomere/single-copy gene ratio.

Results:

Characteristics of ND GBM PTS were median age 63, ECOG PS 0-1 in 71%, radical surgery in 38%, 78% received radiotherapy plus TMZ, MGMTmet in 53%, TERT promoter was mutated in 80% (75% C228T, 25% C250T), median RTL was 1.57 (range 0.4-11.37). ORR was reported in 15% of PTS, mOS was 15ms (95%CI 13-18), mPFS was 8ms (95%CI 7-9). At multivariable analysis TERT mutations and RTL were not associated with clinical outcomes and about OS, reported a HR of 1.05 (95% CI 0.64-1.64) and 0.99 (95% CI 0.89-1.10), respectively; MGMTmet tumors showed significant improved PFS and OS with a HR of 0.54 (95% CI 0.40-0.71) and 0.47 (95% CI 0.340.64), respectively. All interactions among MGMT, TERT mutation and RTL were not significant. Characteristics of REC GBM PTS were median age 55, ECOG PS 0-1 in 60%, MGMTmet in 37%, TERT mutations in 75% (75% C228T, 25% C250T), RTL was 1.67 (0.68-8.87). At multivariable analysis only MGMTmet tumors resulted significantly associated to prolonged OS (HR 0.16 95% CI 0.07-0.40). No gene interaction was significant.

Conclusions:

We analyzed the impact of TERT mutations, RTL and MGMT status in both nd and rec IDHwt GBM PTS. TERT status and RTL were not associated with clinical outcomes at both diagnosis and relapse. MGMT status was the only prognostic factor in both cases. No significant interaction was demonstrated between TERT mutations, RTL and MGMT status.

Implementation of a comprehensive streamlined next generation sequencing (NGS) test for glioma including detection of the 1p/19q codeletion

Background:

In 2016 the World Health Organization updated the classification of central nervous system tumours to incorporate molecular analysis alongside histopathological evaluation. Under the revised system, diagnosis of oligodendroglioma requires presence of both an IDH mutation and codeletion of chromosomal regions 1p and 19q. In 2019, the All Wales Medical Genomics Service (AWMGS) introduced a bespoke multi-gene NGS panel for a range of tumour types, which included 10 genes/ regions implicated in the diagnosis, prognosis and treatment of gliomas. The NGS panel was designed to detect 1p/19q codeletion to streamline glioma testing, also demonstrating the ability to successfully identify different driver mutations in tumours efficiently using a single test.

Methods:

Validation involved evaluation of the panel for determining 1p/19q codeletion status in FFPE-extracted DNA from samples previously tested by FISH. The workflow consisted of SeqCap EZ HyperCap (Roche) protocol and sequencing on the Nextseq 550 (Illumina). Copy number variants (CNVs) were identified using the CNVkit software that calculates copy number ratio based on average read depths for ontarget and off-target reads from NGS. Additionally, the NGS panel was designed with probes to target polymorphic SNPs along the full length of chromosome arms 1p and 19q used to assess loss of heterozygosity (LOH).

Results:

The NGS panel showed a high degree of specificity (>99.9%), sensitivity (97.5%) and reproducibility, and could reliably detect 1p/19q codeletion in samples with >50% neoplastic cell content. Of the 46 glioma samples tested (amounting to 66 results), 98.5% of results were concordant with the expected result generated by FISH.

Conclusions:

Validation demonstrated the utility of a custom-built, hybridisationcapture based NGS panel in identifying the 1p/19q codeletion. Using the NGS panel for concurrent detection of SNVs, indels and 1p/19q codeletion provides a more costeffective, streamlined approach for glioma molecular characterisation, with the added benefit of reduced tissue requirement. Addition of 1p/19q analysis to the glioma service contributes to the comprehensive glioma service provided by AWMGS.

The analysis of FGFR-gene family alterations in glioma

Background:

Fibroblast growth factor (FGFR) alterations are implicated across a range of solid tumors, promoting oncogenesis as a result of amplification, mutations, and structural variations. The FGFR gene family consists of four highly conserved transmembrane tyrosine kinase receptors (FGFR1e4). FGFR signaling influences angiogenesis and tumor cell migration, differentiation, proliferation, and survival. Recently, the cIMPACT-NOW released update 4 and update research, which considered FGFR alterations as a marker in brain tumor classification and prognosis. FGFR inhibitors have presented good clinical trial data in CNS tumors. Therefore, the features of FGFRgene family alterations in Chinese gliomas are of great interest.

Methods:

Tumor specimens from 993 glioma patients were analyzed using the 131gene profiling. FGFR variants including mutations, amplification, and fusion were detected by following the standard operating procedure (SOP). The molecular characteristics, FGFR mutation types, and frequency were also evaluated.

Results:

A total of 116 FGFR variants, including mutations, fusions, and gene amplification were identified. The majority of the FGFR variants were mutations (62.1%), amplification and fusion being observed in similar frequencies (17.2%, 20.7%). FGFR1 alterations were slightly more than in FGFR2-4. Interestingly, we observed more amplification events in FGFR1 (66.7%, 13/20), more fusion in FGFR3 (75%, 18/24), no amplification in FGFR2, only mutations in FGFR4. In addition to FGFR-TACC fusion, 4 novel FGFR fusions retaining the intact kinase domain were detected, including FGFR3-KCNB1, FGFR3-POC1A, FGFR2-CEACAM1 (Intergenic), FGFR3-WASF2 (Intergenic). FGFR variants were more common in IDH wild-type and H3 mutant than in IDH-mutant gliomas (P¼0.003461, P¼0.002304). Pathway enrichment (GO, KEGG) analysis was performed, revealed no significant differences between FGFR mutation and wild type.

Conclusions:

We report the prevalence of FGFR variants was 9.1% in in Chinese glioma patients, including mutations, gene amplifications, and novel FGFR fusions. Moreover, targeting FGFR pathway in gliomas with FGFR alterations may be a therapeutic strategy.

The genetic landscape of tumor predisposition syndromes in Chinese patients with glioma

Background:

Tumorigenesis is generally driven by a combination of inherited genetic alterations and acquired somatic cell mutations. Glioma usually manifests sporadically, while certain tumors are now known to be associated with tumor predisposition syndromes. The spectrum of syndromes that have glioma manifestations includes neurofibromatosis types 1 and 2, tuberous sclerosis complex, Li-Fraumeni syndrome, Cowden syndrome, Turcot syndrome. A comprehensive understanding of the genetics and molecular pathogenesis of glioma is critical in improving clinical care and promoting the development of molecularly targeted therapeutics. Herein, germline mutations were analyzed through NGS to investigate the molecular profiling and mutation frequency in Chinese glioma patients.

Methods:

Germline mutations including SNV, small INDEL, and the corresponding somatic mutations from 805 glioma patients were analyzed with a 131-gene next generation sequencing (NGS) panel. The pathogenicity of germline mutations was categorized based on American College of Medical Genetics and Genomics (ACMG) guidelines.

Results:

In total 805 patients with glioma, 27(3.35%) patients were identified harboring 28 pathogenic (P)/likely pathogenic (LP) germline mutations, and the remaining 778 patients were carried non-pathogenic (Non-P) mutations. The P/LP mutation genes mainly involved DNA repair (BRCA1 and BRCA2, MLH1, MSH2, MSH6, PMS2, POLE), cell cycle regulation (ATM, CHEK2), and tumor suppressor (NF1, TSC2). Most P/LP mutations were loss of function (LOF) variants. No significant differences were found between P/LP and Non-P groups with gender ($p=0.167$), age ($p=0.734$), IDH status (22/546 IDH wild-type vs. 5/259 IDH mutation, $p=0.145$). There was a significant statistical difference in MSI-H that the P/LP group was higher than the Non-P group (5/27 vs. 2/778, $p<0.001$), and all patients with MSI-H in the P/LP group carried MMR gene mutations.

Conclusions:

A proportion of germline variants of tumor syndromes was 3.35% in patients with glioma, which may be potentially linked to tumorigenesis, treatment, and prognosis. Integrative analysis in gliomas based on tumor syndromes and somatic variants needs to be further studied.

The analysis of STAG2 variants in Chinese adult patients with glioma

Background:

Gliomas are the most frequently occurring primary tumor of the central nervous system, of which HGG is an aggressive form with no effective therapy. So far, standard therapy in the adult setting includes maximal safe surgical resection followed by adjuvant temozolomide and radiation therapy (RT). Stromal Antigen-2 (STAG2) is a component of the cohesion complex that is required for DNA replication, the cohesion of the sister chromatids, and transcriptional regulation. Inactivating mutations in STAG2 can lead to aneuploidy and chromosomal instability in cancer. Within glioblastoma, approximately 4-6% of tumors harbor STAG2 mutations, according to large-scale genomic databases. At present, cell line trials have reported that glioblastomas carrying STAG2 mutations are sensitive to PARP inhibitors. To explore the possibility of more targeted drugs in glioma, herein, we explore STAG2 mutation profiles in Chinese adult gliomas.

Methods:

Tumor specimens from 915 Chinese clinical glioma patients were analyzed using the 131-gene profiling, including all the exons of the STAG2 gene, flanking intronic regions. STAG2 mutations were detected by following the standard operating procedure (SOP).

Results:

Atotal of 67 STAG2 aberrations, including mutations, amplification, and deletion were detected in 50/915 adult glioma patients. Loss of function (LOF) mutations, including frameshift, nonsense, splicing was more (43/67, 71.6%) observed, and 26.9% are missense mutations. STAG2 mutations were more frequently observed in IDH wild-type glioma (7.3%, 43/590) than IDH mutation glioma (2.15%, 7/325). There was a significant difference in the frequency of IDH wild-type and IDH-mutant gliomas with STAG2 mutations (7.3% vs. 2.15%, P=0.001217). 36/43 cases of clinical staging are grade IV and others are unknown. Pathway enrichment analysis was performed, and both GO and KEGG enrichment revealed no significant differences in the functions or biological processes between STAG2 mutation and wild type.

Conclusions:

In our Chinese patients, STAG2 gene mutations mostly occur in IDH wildtype gliomas and may be a molecular marker of IDH wild-type glioma. PARP inhibitors may be a potential treatment option for IDH wild-type gliomas accompanying STAG2 mutation.

Characteristics of deleterious germline mutations in glioma patients

Background:

Glioma is the most common primary central nervous system (CNS) tumor with the highest incidence rate and mortality. The genetic basis of glioma has been found in somatic genomics research, but the characteristics of germline mutations have not been fully elucidated. Here, we reported an analysis of genomic features in 35 glioma patients (pts) with autosomal-dominant inheritance of germline mutations.

Methods:

We retrospectively analyzed the next-generation sequencing data of 9,287 pts in a Chinese CNS tumor cohort. The germline mutation features and correlation with somatic IDH1/2 mutations (sIDH1/2m) were analyzed.

Results:

A total of 35 (0.37%) cases with germline mutations were detected, of which 9 pts carried TP53 mutations, 11 pts had NF1/2 mutations, 12 pts had BRCA1/2 mutations and the other three cases harbored mutation in RET, MSH6 and PMS2 respectively. We observed that 65.71% (23/35) of pts' germline mutations occurred in DNA damage response (DDR) genes (TP53, BRCA1, BRCA2, MSH6 and PMS2), while the other 12 pts (34.29%) carried non-DDR gene (NF1, NF2 and RET) mutations. There was no gender and age difference between germline DDR mutation (gDDRm) positive and negative groups. Besides, gDDRm can occur in both high-grade and low-grade gliomas pts (P¼0.7). In addition, 56.5% (13/23) of pts with gDDRm have coexistent sIDH1/2m, which is a marker of good prognosis for glioma, while only 8.3% (1/12) of pts with non-gDDRm carried sIDH1/2m (P¼0.006). We further found that low-grade gliomas pts with gDDRm are more likely to carry sIDH1/2m than high-grade gliomas pts (P<0.001), indicating that this population may have a better prognosis.

Conclusions:

In summary, we comprehensively analyzed the characteristics of deleterious germline mutations in pts with glioma, which may be helpful to elucidate the mechanism of glioma, and prompt the prognosis of the disease.

Characterization of the inflammatory tumor microenvironment composition in brain metastases after failure of immune checkpoint inhibitor therapy

Background:

Immunotherapy (IO) is an important pillar in the treatment of various advanced solid cancers, but resistance is frequent. We aimed to characterize the inflammatory tumor microenvironment of patients with brain metastasis (BM) progression after IO to gain insight on potential inflammatory resistance mechanisms.

Methods:

Patients with BM resection after failure of IO were identified (IO cohort). Tumor-infiltrating lymphocytes (TILs; CD3, CD8, FOXP3) as well as immune checkpoint molecules (PD-L1) were investigated. A control group of BM patients without prior IO was included for comparison (no immunotherapy cohort, NIO).

Results:

Twenty-three IO patients (9/23 (39.1%) females, 14/23 (60.9%) males; 11/23 (47.8%) lung cancer patients; 1/23 (4.3%) breast cancer patient; 5/23 (21.7%) melanoma patients; 6/23 (26.1%) patients with other cancer entities) and 79 NIO patients were included in the analyses. Thirteen/23 (56.5%) IO patients showed tumor PD-L1 expression (TPS range 0-100) in BM. FOXP3+ TIL density was statistically significantly higher in IO compared to NIO patients (Mann-Whitney U test; p=0.001, 83.5 cells/ mm2 vs. 28.1 cells/mm2). Median CD8+ TIL density was numerically higher in IO (327.0 cells/mm2) compared to NIO (129.8 cells/mm2, p=0.05) whereas median CD3+ TIL density was lower in IO (226.4 cells/mm2) vs. NIO (459.0 cells/mm2, p=0.08) patients, respectively. There was no correlation of time from last IO application to BM resection with TIL density (Spearman correlation coefficient <±0.3).

Conclusions:

Higher infiltration with regulatory immunosuppressive FOXP3+ T cells could be an immunological escape mechanism in BM from solid cancers. New immunological targets are warranted to increase the likelihood of response to IO in BM patients.

Prospective study of apatinib combined with whole brain radiation therapy and simultaneous integrated boost for brain metastases from lung cancer

Background:

Brain metastases (BM) develop during the disease course in 20-65% of lung cancer patients. As neo-angiogenesis is crucial to BM growth, the combination of angiogenesis inhibitors and brain radiotherapy is an active focus of research. Apatinib, a tyrosine kinase inhibitor that selectively inhibits the vascular endothelial growth factor receptor-2, is safe and significantly prolongs survival in chemotherapy-refractory gastric cancer. This prospective study evaluated the safety and efficacy of apatinib combined with concurrent whole brain radiation therapy (WBRT) in lung cancer patients with BM.

Methods:

Apatinib (500 or 250 mg/day) was administered orally for one week before radiotherapy, and continued in the same manner concurrently with WBRT (15 fractions; 37.5Gy to the whole brain plus a simultaneous integrated boost (SIB) to gross disease of 49.5-52.5Gy) and another week after WBRT completion. The intracranial progression free survival (iPFS), overall survival (OS), brain edema index, intracranial overall response rate (iORR), and intracranial disease control rate (iDCR) were analyzed, and the adverse reactions of the patients were also observed.

Results:

From July 2016 to January 2020, 17 patients were treated. At three months after WBRT, the iORR was 70.6%, the iDCR was 88.2%, and brain edema index was significantly reduced compared to before brain radiation therapy (4.2 vs 1.9, P=0.02). The median iPFS time was 9 months (95% CI, 7.1-18.1 months) and the median OS time was 17 months (95% CI, 15.5-37.9 months). The iPFS rates at 6 months, 1 year, and 2 years were 64.7%, 41.2%, and 17.6%, respectively; corresponding OS rates were 76.5%, 70.6%, and 47.1%, respectively. Most patients tolerated apatinib well; 7 patients had side effects, most commonly grade 1 or 2. Only two patients experienced grade 3 adverse events (hypertension and oral mucositis); no grade 4 or 5 toxicities were observed.

Conclusions:

Apatinib combined with SIB WBRT appears to be safe and effective in treating BM from lung cancer.

Low-dose bevacizumab for the treatment of focal post radiation necrosis of the brain

Background:

Focal radiation necrosis of the brain (fRNB) is an adverse event (AE) following the treatment of benign or malignant brain lesions with stereotactic radiation therapy (SRT) or stereotactic radiosurgery (SRS). An increased incidence of fRNB has been reported in cancer patients (pts) treated with immune checkpoint inhibitors. Bevacizumab (BEV), a vascular endothelial growth factor-neutralizing monocolonal antibody, has shown to be an effective treatment for fRNB at a dose of 5-7.5 mg/kg Q2W x4. Based on pharmacokinetic/-dynamic data, a “low-dose regimen” of BEV (400 mg loading dose followed by 100 mg Q4W) was investigated in pts diagnosed with fRNB.

Methods:

Clinical outcome data on all pts who received low-dose BEV for the treatment of fRNB at our center were retrospectively collected.

Results:

Between March 2016 and December 2020, 10 pts (6 male, 4 female; median age 50 (range 31-68)) started treatment with low-dose BEV for fRNB. SRS/SRT had been administered for brain metastases from melanoma (5 pts), non-small cell lung cancer (2 pts), renal cell carcinoma (1 pt), medulloblastoma (1 pt), or arteriovenous malformation (1 pt). Three pts had previously been treated with and responded well to the BEV standard dosing regimen, but suffered a recurrence of fRNB after stopping BEV administrations. One pt did not receive a loading dose. All 10 pts had a marked improvement in clinical symptoms and magnetic resonance imaging (MRI) abnormalities. In the 3 pts who had previously been treated with the standard dose regimen of BEV, the response to the low-dose BEV regimen was identical. One pt with therapy-resistant partial epilepsy experienced a complete resolution of seizure activity after initiating treatment. There were no severe AE related to the BEV treatment. In 3 pts BEV was stopped after obtaining a maximal clinical and radiological response, but had to be resumed at the time of relapse of symptoms and MRI abnormalities. At the time of this report, 3 pts are on treatment with low-dose BEV and 7 pts are offtherapy with a remission of their fRNB. All pts treated with the low-dose regimen were alive at latest follow-up.

Conclusions:

Treatment of fRNB with a low-dose regimen of BEV is an effective and cost-lowering alternative for standard-dose BEV.

The prognostic value of liver metastases and how affects the applicability of the lung-molGPA in non-small cell lung cancer patients with brain metastases

Background:

Brain metastases (BM) from lung cancer is a common clinical scenario in which, prognostic assessment is vital for clinical decision-making. The updated diagnostic-specific graded prognostic assessment (Lung-molGPA) is one of the most useful indices for prognosis in this scenario. Even though there is growing evidence that liver metastases (LM) confer worst survival, this is not considered in any prognostic score for BM.

Methods:

From a single-center retrospective database of 782 patients treated for NSCLC between 2011-2016, patients with newly diagnosed BM were identified. We examined the effect of LM in the survival of our cohort of patients with BM and according to stratification using Lung-molGPA.

Results:

A total of 134 patients presented BM during the period specified. The median age at BM diagnosis was 62.2 years. According to histologic classification, 68.7% were classified as adenocarcinoma, and 26.9% as non-adenocarcinoma. BM were present at diagnosis in 42.5%. LM were present in 20.9% at the moment of which BM were diagnosed. Gene alterations were detected in 18.6%. The overall survival (OS) from the time of the initial diagnosis of the disease was 19.7 months (95% confidence interval (CI): 15.5-24). We found that the free interval of BM (6 months) had prognostic significance (HR 0.46; P<0.00001). From the time of diagnosis of BM, the OS was 11.8 months (95% CI: 7.1-16.4). A better KPS (>70), younger age (<60), and number of BM (1) were significantly related to decreased risk of death. We also found that the patients with LM had a median OS of 4.1 vs 14.3 months in the group without LM (HR 1.92; P<0.001). Finally, we validate the Lung-molGPA in our cohort of patients showing a significant separation between groups (P<0.00001). We found that for patients without LM the Lung-molGPA scores kept the good stratification power (P<0.00001), but no differences were observed in the group of patients with LM (P¼0.532).

Conclusions:

When using BM prognosis indices in NSCLC patients, the individual presence of LM or the free interval of BM should be considered for an accurate stratification, to individualize treatment options and better select patients for clinical trials.

Brain metastases: Extracranial disease status as a prognostic factor after whole brain radiotherapy. Results from a prospective, population-based study

Background:

Deciding the optimal treatment for patients with brain metastases (BM) remains challenging. For patients not candidates for surgery (S) or stereotactic radiosurgery (SRS), prognostic factors to identify those with a survival benefit after whole brain radiotherapy (WBRT) are needed. Prognostic scoring systems based on clinical trial data exist, but extracranial disease status is not part of most of these systems. Clinical trials typically include selected patients (i.e ≤4 BM, good performance status [PS]). Real-life data from unselected BM patients may supply such trial results in treatment decision making.

Methods:

A population-based prospective observational study at four hospitals in Norway (up-take ~3.5 million inhabitants). Consecutive patients with newly diagnosed BM from solid cancers were included. Clinical data were collected every 3 months (mo).

Results:

930 patients (pt) were included Nov 2017-March 2021. In preliminary analyses of 771 pt with ≥ 6 mo follow-up (46% male, median age 68 [21-96]), most frequent primary cancers were lung (non-small cell, 44%), melanoma (16%), breast (15%) and colorectal (9%). 35% had ≥5 BMs, 45% had ECOG PS≥2, 79% had extracranial metastases. Median OS (mOS) after BM diagnosis for all patients was 6 mo, longest for breast (13 mo), shortest for colorectal (4 mo). 34% of pt died within 3 months, 8% lived >2 years. Age>75, male sex, PS≥2, ≥ 5 BM and presence of extracranial disease were associated with worse mOS in multivariable analyses. Primary BM treatments were: S 17%; SRS 34%; systemic 2%; no tumor-directed therapy 5%; 329 (43%) pt received WBRT, 157/329 (48%) died within 3 months after BM diagnosis. PS 0-1, age <65 and non-progressive extracranial disease were associated with longer survival in WBRT-treated patients.

Conclusions:

Although some patients live >2 years after BM diagnosis, many still die within 3 mo. WBRT should be considered reserved to younger patients not suitable for other intracranial treatments with PS 0-1 and non-progressive extracranial disease, as many are unlikely to benefit in terms of OS. Extracranial disease status should be assessed before treatment decision making.

Clinical trial identification:

NCT03346655

A real-world application of aqueous humor and vitreous fluid for the diagnosis of vitreoretinal lymphoma and treatment monitoring

Background:

The diagnosis of vitreoretinal lymphoma (VRL), a rare subtype of primary central nervous system lymphoma (PCNSL), currently relies on the histopathology of vitreous biopsy. Misdiagnoses occasionally happen due to the extremely low number of cancerous cells in vitreous fluid, and the examination of visual acuity and fundus can be subjective and inaccurate during VRL treatment monitoring.

Methods:

This study enrolled 16 VRL patients whose baseline aqueous humor (AH) and/or vitreoretinal fluid (VF) specimen subject to comprehensive genomic profiling using targeted next generation sequencing. Serial post-treatment AH or VF samples were also available for five patients. Cerebrospinal fluid (CSF) sampling and MRI examination were performed for patients showing symptoms of CNS metastasis.

Results:

Mutational profiles of baseline samples revealed that MYD88 (L265P) and/or CD79B activating mutations were present in 62.5% (10/16) of the cohort, whereas about 56% (9/16) of the patients carried IRF4 mutations and half (8/16) had CDKN2B copy-number loss, both of which the frequency was much higher in VRL than PCNSL. Mutations identified in baseline AH or VF specimens were highly concordant with comparable allele frequencies (AFs). Moreover, partial response was observed in 1 out of 7 patients (objective response rate [ORR], 14%) treated with ibrutinib, a BTK inhibitor that has demonstrated anti-tumor efficacy in PCNSL (ORR: 65%). Changes of variant AFs observed in post-ibrutinib samples were closely associated with changes in interleukin 10 (IL-10) levels indicative of treatment response. In addition, both AH and VF biopsies appeared to have more mutations detected at higher AFs when compared to CSF samples in patients who had signs of CNS metastasis (N = 5).

Conclusions:

AH represents a substitute for vitreous fluid as a rich source of eye specific tumoral genomic information, and we demonstrated that molecular profiling of the AH has clinical utility for VRL diagnosis and treatment monitoring. While different genomic traits may underlie variability in response to ibrutinib between VRL and PCNSL, further research of larger sample size is warranted.

Clinical outcomes of targeting therapy with BRAF/MEK inhibitors in patients with BRAF V600-mutated brain tumors

Background:

Off-label use of BRAF/MEK inhibitors (i-BRAF/MEK) for the treatment of brain tumors with BRAF-V600 mutation (BRAF-V600m) has only been evaluated in a few studies, mainly case reports, which modest efficacy results. The aim is to describe the clinical outcomes of the treatment with i-BRAF/MEK in patients with BRAF V600m brain tumors.

Methods:

All patients diagnosed with brain tumor who have been treated with an iBRAF/MEK were included. Variables collected: gender, age, performance status (PS), diagnosis, line and duration of treatment. Effectiveness: response to treatment (RT), progression-free survival (PFS) and overall survival (OS). Safety: adverse reactions (AR) and dose reductions or temporary interruptions required due to toxicity.

Results:

7 patients included (6 men), median age 25.0 years (IR:17.8-27.6) diagnosed with low-grade astrocytoma (n=1), pleomorphic xanthoastrocytoma (n=1), low-grade (n=2) and high-grade (n=1) glioma, glioblastoma (n=1) and ganglioglioma (n=1). PS: 1(n=5) or 2 (n=2). Line of treatment of i-BRAF/MEK: 1st (n=1), 2nd (n=3), 3rd and subsequent lines (n¼4). 3 received dabrafenib in monotherapy, 1 trametinib in monotherapy and 3 dabrafenib/trametinib (1 of them previously received vemurafenib+cobimetinib). Median duration of treatment: 16.08 months (IR:9.00-24.88). After a median follow-up of 20 months, RT was: - Dabrafenib in monotherapy: partial response (n=3). 2 continue at the end of the study and the other, progressed at 21.8 months. -Trametinib: stable disease (n=1). -Dabrafenib/trametinib: disease progression (n=1, died 4 months later) and partial response (n=2). 1 subsequent progression disease (PFS 18.7 months). Median PFS 21.8 months CI95% (15.4-28.2) and OS 40.4 months CI95% (22.3 -58.5). Safety: main AR were dermatological (n=6), gastrointestinal (n=4), hepatic (n=2), other (metallic taste, fever, edema) (n=4). Due to toxicity, 4 patients required dose reductions, 4 temporary interruptions and 1 definitive suspension due to grade IV toxicity.

Conclusions:

In our experience, i-BRAF/MEK therapy has been a good option in brain tumors with BRAF-V600m, with somewhat superior results in terms of efficacy but with a safety profile similar to those reported in previous studies.

Nucleolin and its prognostic value in pediatric patients with intracranial ependymoma: A systematic review and meta-analysis

Background:

Nucleolin (NCL) is one of several potential molecular biomarkers that have been suggested as predictors for pediatric intracranial ependymomas. However, few studies have assessed whether NCL is an optimal prognostic marker to predict outcome in pediatric intracranial ependymoma. Thus, this systematic review and meta-analysis aimed to examine the prognostic role of NCL in predicting the outcome of patients with intracranial ependymoma.

Methods:

An independent search was conducted by each reviewer (JH and RS) on 4th May 2021 from ScienceDirect, PubMed, Europe PMC, and Cochrane Central Database. The terms nucleolin, NCL, outcome, prognosis, ependymoma, and ependymomas were used as keywords. Publications of English language, children population less than 18 years of age, WHO-graded ependymoma, and report the critical exposure were included. Publications of case reports, letters to the editor, animal studies, and preprints were not included. NCL as a predictor for ependymoma outcome, which provides for relapse-free survival (RFS) and overall survival (OS), was the critical exposure. The OS referred to a period of 5 years. In this study, two groups of NCL expression were used: high and low, with a cutoff of 50% considered common expression. Hazard ratio (HR) was used as a pooled measure. Quality of each studies was assessed using the Newcastle-Ottawa Scale (NOS) and GRADE.

Results:

A total of 5 retrospective observational studies consisting of 443 ependymoma patients were included. All 5 included studies are good in quality and showed that NCL expression can predict the outcome for pediatric intracranial ependymoma patients. Our meta-analysis showed that high expression of NCL had a hazard ratio (HR) of 3.11 [1.8, 5.4], P = 0.009; I2 = 70% for RFS and 240.19 [21.48, 2686.12], P = 0.04; I2 = 63% for OS within 5 years. Based on GRADE, the result of this systematic review and meta-analysis proved to be moderate in quality as there is no inconsistency and variability in results with minimal publication biases.

Conclusions:

Current studies showed that overexpression of NCL was related to a poor prognosis in patients with intracranial ependymoma. Further studies with prospective design and larger samples are required.

Comparison of current guidelines and real-world evidence data for the treatment of glioblastoma across Europe

Background:

Glioblastoma (GBM) is the most frequent primary malignant brain tumor in adults. The standard of care in Europe is temozolomide (TMZ) ± lomustin and radiotherapy. In other countries (USA, Canada, and Switzerland) bevacizumab is approved for GBM, since it showed improved progression-free survival, however no overall survival increase was proven. Furthermore, no standard of care is established in recurrent or progressive cases due to the complex heterogeneity of the disease. Due to the limited treatment options in Europe and considering that bevacizumab is approved for GBM in other countries, treatment patterns based on real-world data will be analyzed to detect potential off-label use of bevacizumab in the UK and EU4 countries.

Methods:

Anonymized patients-level data collected through a large web-based survey between January 2017 and December 2020 was used. The study reported patient case history information across all cancer types in EU4 (France, Germany, Italy, Spain) & UK. Treatment information on 3.657 glioblastoma drug treated patients was analyzed.

Results:

The analysis of the treatment landscape of glioblastoma in Europe showed a share of 99% of (neo-)adjuvant and 89% of 1st line patients treated with TMZ. However, when analyzing the 2nd line only 17% of patients were treated with TMZ. On the other hand, bevacizumab treated patients represented a 0,1% in the (neo-) adjuvant setting, 6% in 1st line which raised to 59% in the 2nd line. More specifically a significant increase of bevacizumab treated patients from the 1st to the 2nd line was observed in Spain (1st Line: 5%, 2nd Line: 73%) and France (1st Line: 12%, 2nd Line: 90%). Furthermore, 73% of patients in Spain and 75% of patients in France changed therapy from TMZ to bevacizumab due to local/distant progression.

Conclusions:

Conforming to the European guidelines, the majority of patients in (neo)adjuvant and 1st line setting are treated with TMZ. However, in France and Spain a high off-label use of bevacizumab has been identified in the 2nd line. Most of those patients arise from an unsuccessful TMZ treatment due to progression of the disease.

A phase I/II/IIb study to evaluate the safety and efficacy of the tumor-targeting human antibody-cytokine fusion protein L19TNF plus standard temozolomide chemoradiotherapy in patients with newly diagnosed glioblastoma

Background:

Glioblastoma is a poorly immunogenic cancer and is inevitably lethal despite a multimodal standard of care treatment comprising surgery followed by radio-chemotherapy with temozolomide. Different immunotherapies including peptide vaccination and immune checkpoint inhibition have so far failed to improve survival.
The administration of pro-inflammatory cytokines may convert the immunologically "cold" glioblastoma microenvironment into a "hot" one and may trigger potent antitumor immunity. Tumor necrosis factor (TNF) is one of the most potent pro-inflammatory cytokines. However, its systemic administration at therapeutically active doses is hampered by toxic side effects. L19TNF is a fully human antibody-cytokine fusion protein, comprising TNF fused to the antibody L19 that binds a tumor-specific epitope of the extracellular matrix protein fibronectin. This allows targeted delivery of therapeutic doses of TNF to the tumor while sparing healthy organs. In fully immunocompetent preclinical glioma mouse models, L19TNF demonstrated promising antiglioma activity and had encouraging synergistic activity in combination with local irradiation and temozolomide chemotherapy, providing a strong rationale to translate this treatment combination to patients with newly diagnosed glioblastoma.

Trial desgin:

This multi-step trial has three consecutive parts: (1) a dose-finding part to determine the recommended dose of L19TNF in combination with standard temozolomide-based chemoradiotherapy for newly diagnosed glioblastoma (phase I), (2) a signal-seeking part to determine the preliminary activity for 32 patients (phase II) and (3) a 1:1 randomized activity-evaluation part that investigates the efficacy of L19TNF + chemoradiotherapy versus chemoradiotherapy alone in up to 164 patients (phase IIb). The primary endpoint of the activity-evaluation part is overall survival (OS). Eligibility criteria include histologically confirmed newly diagnosed glioblastoma with no prior therapy except surgery, a Karnofsky Performance Status (KPS) ≥70%, and adequate organ function.

Clinical trial identification:

NCT4443010

TEM-GBM: A phase I-IIa clinical study of genetically modified Tie-2-expressing monocytes in patients with glioblastoma multiforme

Background:

We developed a cell-based treatment, Temferon, relying on ex-vivo transduction of autologous HSPCs to express IFNa within the tumor microenvironment by Tie-2-expressing macrophages (TEMs). As of 8th April 2021, 18 patients have been enrolled; 12 received Temferon (D+0) with follow-up of 42-640 days. There was rapid engraftment and hematological recovery after the conditioning regimen. Median neutrophil & platelet engraftment occurred at D+13 and D+12, respectively. Temferon-derived differentiated cells, as determined by the presence of vector genomes in the DNA of peripheral blood and bone marrow cells, were found within 14 days post treatment and persisted albeit at lower levels up to 18 months. We also detected very low concentrations of IFNa in the plasma & in the CSF, suggesting tight regulation of transgene expression. 3 deaths occurred: 2 at D+340 & +402 after Temferon administration due to disease progression, 1 at D+60 due to complications following the conditioning regimen. Eight patients had progressive disease (PD; range D-11 to +239) as expected for this tumor type. SAEs include infections, venous thromboembolism, brain abscess, hemiparesis, GGT elevation & poor performance status compatible with ASCT, concomitant medications & PD. Four patients underwent second surgery. These recurrent tumors had gene-marked cells present and increased expression of IFN-responsive gene signatures compared to diagnosis, indicative of local IFNa release by TEMs. In one patient, a stable lesion (as defined by MRI) had a higher proportion of T cells and TEMs within the myeloid infiltrate and an increased ISG than in a progressing lesion. The T-cell immune repertoire changed with evidence for expansion of tumor-associated clones. Our interim results show that Temferon is well tolerated by patients, with no dose limiting toxicities identified to date. The results provide initial evidence of Temferon potential to activate the immune TME of GBM patients, as predicted by preclinical studies.

Trial design:

TEM-GBM is an open-label, phase I/IIa dose-escalation study evaluating safety and efficacy of Temferon in up to 21 newly diagnosed patients with glioblastoma and unmethylated MGMT promoter.

Clinical trial identification:

NCT03866109

A phase I/II dose-escalation and expansion cohort study of intracerebroventricular radioimmunotherapy using ^{177}Lu-DTPA-omburtamab in pediatric and adolescent patients with recurrent or refractory medulloblastoma

Background:

Medulloblastoma represents 20% of all pediatric brain tumors. Recurrent/refractory medulloblastoma is particularly challenging, with no standard of care and poor treatment outcomes. The B7-H3 receptor is an attractive target for radioimmunotherapy as it is overexpressed on the cell surface of >96% of medulloblastomas. Omburtamab is a monoclonal antibody that specifically binds to B7-H3 and can be radiolabeled allowing targeted delivery of therapeutic radiation to tumor cells. Intracerebroventricular administration of ^{131}I-omburtamab is currently under study in patients (pts) with neuroblastoma and CNS/leptomeningeal metastases and has received breakthrough designation by the FDA. The trial described here (Study 301) is a first-in-human study to evaluate the tolerability and safety of ^{177}Lu-DTPA-omburtamab in pts with recurrent/refractory medulloblastoma.

Trial design:

Study 301 is an open-label phase I/II study. Part 1 is a dose-escalation phase to be conducted at ~8 sites (US/Europe) with a primary objective of identifying the maximum tolerated dose and/or recommended phase II dose for Part 2 (RP2D). It will follow a 3+3 design (except 1st dose, which is limited to 1+2 pts) with pts receiving up to two 5-week cycles of ^{177}Lu-DTPA-omburtamab. Part 2 is a cohort expansion phase at ~11 sites (US/Europe) with pts receiving up to five 5-week cycles of treatment at the RP2D from Part 1. The primary objective of Part 2 is to establish the safety of repeat doses of ^{177}Lu-DTPA-omburtamab. Additional objectives of Parts 1/2 include the evaluation of absorbed radiation doses, PK profile, investigator assessed response, duration of response, progression-free survival, and overall survival. Up to 25 pts are expected to participate in Part 1 and 24 in Part 2. Key inclusion criteria include age 3-19 years; histologically confirmed medulloblastoma; available molecular classification; recurrent/refractory to frontline therapy; Lansky or Karnofsky score of 50-100, acceptable hematological status and liver and kidney function, and a life expectancy of >3 months.

Clinical trial identification:

NCT04167618

Vaccination with autologous dendritic cells loaded with autologous tumour homogenate in resected glioblastoma: A phase II study (CombiGVax)

Background:

Glioblastoma (GBM) is a poor prognosis malignant glioma. After surgical resection, standard therapy consists of concomitant radiotherapy (RT) and temozolomide (TMZ) followed by TMZ alone. Dendritic cells (DCs) are the most potent professional antigen-presenting cells capable of generating a specific immune response against various cancers. Multiple phase I/II trials and at least three meta-analysis showed improved survival (OS) and progression-free survival (PFS) with DC vaccination in High-grade gliomas (HGGs) patients. Since 2001, we have treated over 80 advanced melanoma patients with a tumor lysate-loaded autologous DC vaccine, obtaining a clinical benefit of 54.1% with a favorable toxicity profile. In patients developing antitumor immunity, DC vaccination increased the amount of intra-tumoral activated cytotoxic T lymphocytes and decreases the number of FoxP3 positive regulatory T cells. Based on these data we have developed a phase II protocol with DC vaccine concomitant to standard RT-CT in patients undergone radical surgery for GBM.

Trial design:

This is a single-arm phase II trial evaluating progression free-survival (PFS) and safety of a DC vaccination integrated to standard therapy in resected GBM patients. All Patients will receive a dendritic cell vaccine loaded with autologous tumor homogenate for up to one year. The vaccine administration will start at the end of the RT-CT (Induction Phase) and then will be alternated to TMZ cycles (Maintenance Phase). Treatment schedule: DC Vaccine: 10x106 cells administered intradermally on weeks 1, 2, 3, 4, 7, 11, 15, ...and every 28 days TMZ: 150-200mg/m2/day administered orally from day 1 to 5 on weeks: 5,9,13,...and every 28 days Primary end points are PFS and safety, among secondary end points there are the in vitro (Elispot, Plasma Cytokines, Tumor tissue analysis) and in vivo (DTH skin test) Immune response evaluations. A Simon's two-stage design has been used for the sample size calculation. In the first stage, 9 patients will be accrued and a total of 28 patients will be enrolled Time to events (PFS and OS) will be calculated with the Kaplan-Meier method and the analysis will be performed on the eligible population.

Clinical trial identification:

EudraCT 2020-003755-15

Breast Cancer

Real-world outcomes and safety of pyrotinib in HER2positive metastatic breast cancer (MBC) patients: A prospective cohort study

Background:

Pyrotinib, a novel irreversible EGFR/HER2 dual tyrosine kinase inhibitor, shows promising antitumor activity and acceptable tolerability in phase II and phase III randomized clinical trials. However, the real-world data of pyrotinib have been rarely reported. Here, we assessed the treatment outcomes of pyrotinib in real-world practice in patients with HER2-positive MBC patients.

Methods:

This was a China-based, prospective, real-world, observational cohort study. HER-2 Positive MBC Patients treated with pyrobitinib were indentified from the Breast Cancer Information Management System between 2017/06 and 2020/09. Treatment outcomes assessment included provider-reported objective response rate (ORR), progression-free survival (PFS) and overall survival (OS). The responses were determined by RECIST 1.1, and adverse events were assessed using patients and clinical records.

Results:

113 pyrotinib-treated patients with an average age of 51 years enrolled in the study. 64 (56.6%) patients had 2 or more sites of metastasis. Distant metastases were in lungs, livers, brains and bones (45.1%, 38.9%, 26.6% and 8.0%, respectively). Pyritinib was used as first-line therapy in 20 (17.7%) patients, second-line in 61 (54.0%) patients, and as third-line and beyond in 30 (28.3%) patients. 102 (90.3%) patients had used anti-HER2 therapy before. By the cut-off day therapy was continued in 47 (41.2%). Complete response, partial response and stable disease were observed in 9 (8.0%), 66 (58.4%), and 17 (15.0%) patients, respectively; progressive disease was recorded in 20 (17.7%) patients. The median PFS was 14.1 months. The median OS was 34.1 months after a median follow up of 17.2 months. Among the patients with brain metastases, the median PFS and OS was 15.2 and 19.8 months, respectively. The most common adverse events of any grade were diarrhea (87.6%), vomiting (31.9%), palmar-plantar erythrodysesthesia syndrome (26.6%).

Conclusions:

Compared with phase II and phase III clinical trials of pyrotinib, our real-world data showed similar clinical effectiveness in HER-2 positive MBC patients and, in particular, improved outcomes in patients with brain metastasis.

Survival after neoadjuvant therapy with trastuzumab lapatinib and chemotherapy in patients with HER2-positive early breast cancer: A meta-analysis of randomized trials

Background:

Studies testing addition of lapatinib (L) to neoadjuvant trastuzumab (T) plus chemotherapy reported an increase in pathologic complete response (pCR) rates but were discordant on the effect of treatment on survival, mainly due to suboptimal power. We here leverage the meta-analytic approach to resolve these inconsistencies

Methods:

We conducted a meta-analysis to combine findings from published or unpublished randomised phase 2 and 3 studies testing L in combination with neoadjuvant T plus chemotherapy for HER2+ early breast cancer. Pooled hazard ratios (HRs) were obtained for the effect of L plus T compared to T only, pCR compared to no pCR in the whole study populations, and pCR compared to no pCR in the hormone receptor-negative or positive cohorts.

Results:

The meta-analysis included four studies (CALGB40601, CHER-LOB, NSABPB41, NeoALTTO) for an overall population of 1410 patients. Patients received either T and L or T alone, in combination with paclitaxel or anthracyclines. Relapse-free survival (RFS) was higher with the combination of L plus T than with T only (HR 0.62, 95% CI 0.46-0.85). Dual blockade also led to improved overall survival (OS) (HR 0.65, 95% CI 0.43-0.98). For all treatments combined, patients achieving a pCR had better RFS and OS than those with residual disease at surgery (HR 0.45, 95% CI 0.34-0.60, and HR 0.34, 95% CI 0.23-0.51, for RFS and OS, respectively). In patients with hormone receptor-negative tumors, pCR was associated with a 65% reduction of risk of relapse (HR 0.35, 95% CI 0.23-0.53) and a 73% reduction of risk of death (HR 0.27, 95% CI 0.15-0.47). Patients with hormone receptor-positive tumors also had improved RFS if they achieved pCR (HR 0.60, 95% CI 0.37-0.97), but the benefit was smaller than in hormone receptor-negative disease.

Conclusions:

These findings further validate the role of pCR as a strong predictor of outcome in patients with HER2+, especially in hormone receptor-negative disease. Moreover, we here provide robust evidence that dual blockade with L in combination with T and chemotherapy prolongs overall survival, suggesting that L could be repurposed in early settings.

Event-free survival (EFS), overall survival (OS), and safety of adding veliparib (V) plus carboplatin (Cb) or carboplatin alone to neoadjuvant chemotherapy in triple-negative breast cancer (TNBC) after ‡4 years of follow-up: BrighTNess, a randomized phase III trial

Background:

In BrighTNess, adding Cb with or without V to neoadjuvant chemotherapy significantly improved pathological complete response (pCR) with an acceptable safety profile in operable TNBC. We report EFS, OS, and second malignancies ≥4 years postsurgery.

Methods:

Women with untreated stage II/III TNBC were randomized (2:1:1) to A) paclitaxel (P) 80 mg/m^2 (weekly, 12 doses) + Cb area under the curve 6 mg/mL (every 3 weeks, 4 cycles) + V 50 mg orally twice a day (PCbV); B) P + Cb + V placebo (PCb); or C) P + Cb/V placebo (P). All patients (pts) then received 4 cycles of doxorubicin + cyclophosphamide every 2-3 weeks. The primary (pCR) and secondary (EFS and OS) endpoints used a fixed testing procedure that ordered PCbV vs P, then PCbV vs PCb. Efficacy was assessed in all randomized pts and safety in all who received ≥1 dose. In primary pCR analyses, PCbV was superior to P but not PCb, so subsequent secondary analyses are descriptive with nominal P values.

Results:

Overall, 634 pts were randomized to PCbV (n=316), PCb (n=160), and P (n=158). Median follow-up time was 4.5 years. Hazard ratio (HR) for EFS with PCbV vs P was 0.63 (95% confidence interval [CI] 0.43–0.92, P=0.016) and 1.12 (95% CI 0.72– 1.72, P=0.620) for PCbV vs PCb. In post hoc analysis, HR for EFS with PCb vs P was 0.57 (95% CI 0.36–0.91, P=0.018). Deaths occurred in 38/316 (12%) with PCbV, 16/ 160 (10%) with PCb, and 22/158 (14%) with P. HR for OS was 0.82 (95% CI 0.48–1.38, P=0.452) for PCbV vs P, 1.25 (95% CI 0.70-2.24, P=0.455) for PCbV vs PCb, and 0.63 (95% CI 0.33-1.21, P=0.166) for PCb vs P. See table for myelodysplastic syndromes (MDS) and second malignancies.

Conclusions:

Adding Cb to P improved pCR and EFS without increasing MDS or acute myeloid leukemia. Addition of V did not impact pCR or EFS. Mortality rate was low, but numerically higher with P than PCbV and PCb.

Clinical trial identification:

NCT02032277

Table: 119O Myelodysplastic syndromes and selected second cancers

n (%)	PCbV N = 313[a]	PCb N = 158[a]	P N = 157[a]
Myelodysplastic syndrome[b]	5 (1.6)	3 (1.9)	1 (0.6)
Pancytopenia	4 (1.3)	3 (1.9)	0
Myelodysplastic syndrome	1 (0.3)	0	1 (0.6)
Second malignancy[b]	6 (1.9)	6 (3.8)	4 (2.5)
Acute leukemia	1 (0.3)	0	0
Acute myeloid leukemia	2 (0.6)	3 (1.9)	1 (0.6)
Chronic myeloid leukemia	1 (0.3)	0	0
Colon cancer	0	1 (0.6)	0
Lung cancer	1 (0.3)	0	0
Malignant melanoma	1 (0.3)	0	0
Pancreatic cancer	0	0	2 (1.3)

[a]Patients who received ≥1 dose.
[b]*Standardized Medical Dictionary for Regulatory Activities* (MedDRA) query.
Cb, carboplatin; P, paclitaxel; V, veliparib.

BARBICAN: A randomized, phase II study to determine the contribution of ipatasertib to neoadjuvant chemotherapy plus atezolizumab in women with triple-negative breast cancer

Background:

Pathological complete response (pCR) to neoadjuvant treatment in TNBC is strongly correlated with improved EFS and OS. Randomised trials have demonstrated increased pCR rates with the addition of checkpoint inhibitors to NACT in TNBC. Preclinical evidence suggests that AKT inhibition can enhance checkpoint inhibitor efficacy. The AKT inhibitor ipatasertib (IPAT) has shown promising activity in combination with paclitaxel as 1L therapy for metastatic TNBC. BARBICAN was designed to evaluate the clinical and biological effects of adding IPAT to NACT plus atezolizumab (atezo).

Methods:

International phase II, randomized trial in 146 patients (pts) with newly diagnosed, non-metastatic, high risk (node+ and/or tumor size ≥2 cm) TNBC. Patients were randomized (1:1) to receive one cycle of atezo (1200mg Q3W) ± IPAT (400mg D1-14), followed by 3 cycles of atezo (840mg Q2W) + weekly paclitaxel (80mg/m2) ± IPAT (400mg D1-21), followed by 4 cycles of atezo (840mg Q2W) + dose-dense doxorubicin (60mg/m^2)/cyclophosphamide (600 mg/m^2). Tumor biopsies were obtained at baseline, after each treatment phase and surgery. The primary clinical endpoint was pCR rate (ypT0/is ypN0). PD-L1 expression was assessed using the SP142 assay (1% cut-off).

Results:

144 pts received treatment, IPAT (n = 72) vs no ipatasertib (no-IPAT) (n = 72). There was no difference in pCR rates between treatment groups (chemo/atezo + IPAT, 49.3%, 95%CI, 36.8%-61.8%; chemo/atezo alone, 48.5%, 95%CI, 36.2%-61.0%). For IPAT vs no-IPAT, pCR was 66.7% vs 75.0% in the PD-L1-positive population (65 pts) and 32.4% vs 25.0% in the PD-L1-negative population (70 pts). pCR in node-positive pts was 55.6% (IPAT, 51.6%, no-IPAT 59.4%) compared to 43.1% (IPAT, 47.2%, no-IPAT 38.9%) in node-negative pts. Grade 3 or higher AE rates were 73.6% in the chemo/ atezo + IPAT group and 40.3% in the chemo/atezo alone group, with rash, neutropenia, ALT increase, diarrhoea and mucosits being the most common. The majority of patients required IPAT dose modifications and the dose intensity was low.

Conclusions:

Addition of IPAT to neoadjuvant atezo plus chemotherapy did not improve pCR rates. IPAT dose intensity was low due to increased toxicity.

Clinical trial identification:

NCT03800836

Health economic properties of palbociclib in breast cancer patients with high risk of relapse following neoadjuvant therapy: Results from the Penelope-B trial

Background:

Patients with hormone receptor-positive, HER2enegative breast cancer who have residual invasive disease after neoadjuvant chemotherapy (NACT), are at high risk of relapse. PENELOPE-B was a double-blind, placebo-controlled, phase III study that investigated adding palbociclib (PAL) to adjuvant endocrine therapy (ET) in these high-risk patients. Clinical results showed no improvement in invasive disease-free survival with PAL compared to ET alone (Loibl S et al. JCO 2021). Here we evaluated the cost-effectiveness of PAL in PENELOPE-B.

Methods:

A total of 1250 patients from 10 countries and 221 centers were randomly assigned to receive 125 mg of PAL or placebo over 13 28-day cycles. Health status and medical resource use were assessed before, during, and after treatment for up to 72 months. The EQ-5D instrument was used to score the health-related quality of life. Direct medical costs were assessed from the German health system perspective. Costs and effects were discounted at 3%. The incremental impacts of PAL on costs and Quality-Adjusted Life Years (QALYs) were estimated with generalized linear models adjusting for randomization, between-country heterogeneity, and censoring. Scenario and sensitivity analyses explored uncertainty in patient pathways and costs. Subgroup analyses were performed for key prognostic risk factors.

Results:

In the analysis based on all patients, PAL led to a marginal increase in QALYs per patient of 0.005 (bootstrap 95% confidence interval (CI) -0.049; 0.040) at an incremental cost of EUR 9262 (CI -14572; 33096) and a cost-effectiveness ratio above EUR 2000000 per QALY gained. Analysis restricted to patients enrolled in Germany differed in the direction and the magnitude of the effects. Neither outcome was statistically significant. Costs varied greatly among patients; scenario analysis indicated the therapy might be cost-saving in Germany. Findings from subgroup analyses by risk factor were consistent with main results.

Conclusions:

One year of PAL added to ET is unlikely to be cost-effective in women with residual invasive disease after NACT but could be cost-saving in some settings.

Clinical trial identification:

NCT01864746

HER2+/HR+ breast cancer patients at high risk of relapse derive benefit from extended adjuvant treatment with neratinib: An exploratory analysis from ExteNET study

Background:

Randomized clinical trials investigate general and representative patient populations, yet clinical decisions increasingly depend on the characteristics of individual patients. In this exploratory analysis of the ExteNET trial, we tested the efficacy of continuing with 1 year of neratinib after completing adjuvant trastuzumab therapy in breast cancer patients at high risk of relapse.

Methods:

For the purpose of our analysis, we tested invasive disease-free survival (iDFS) at 2 and 5 years in hormone receptor-positive BC patients included in ExteNET population after Amendment 3, which ruled out patients with stage I/ node negative disease, and those with pCR after neoadjuvant therapy, in order to enrich the population with patients at higher risk of recurrence.

Results:

Out of 1334 HER2+/HR+ BC patients initially recruited by ExteNET, 1056 (79%) qualified as at high-risk according to baseline disease characteristics. Neratinib reduced the relative risk for 2-year iDFS by 48% compared with placebo (HR 0.52, 95% CI 0.32-0.84). This advantage was confirmed with the 5-year iDFS analysis which was reduced by 39% (HR 0.61, 95%CI 0.42-0.88) (Table). Notably, no significant interaction between risk categories, hormone receptor status, and use of neratinib was observed for both endpoints, suggesting that the benefit derived by high-risk patients resembled that derived by the whole ExteNET study population.

Table: 139P

	Number of events		Absolute difference (%)	Hazard Ratio (95% CI)
	Neratinib (n=531)	Placebo (n=525)		
2-year iDFS	25	49	4.7	0.52 (0.32-0.84)
5-year iDFS	47	76	5.6	0.61 (0.42-0.88)

Conclusions:

Although descriptive in nature, our results show that patients with HER2+/ HR+ breast cancer with large primary tumors, lymph node involvement, and lack of response to neoadjuvant therapy are likely to derive meaningful and sustained benefit over time when treated with neratinib after standard trastuzumab-based therapy.

Clinical trial identification:

NCT00878709

Long-term follow-up of neoadjuvant dual anti-HER2 therapy with trastuzumab and lapatinib plus paclitaxel, with or without endocrine therapy for HER2-positive primary breast cancer: Neo-LaTH (JBCRG-16) study

Background:

Dual blockade of HER2 promises increased pathological complete response (pCR) rates compared with single blockade in the presence of chemotherapy for HER2-positive (+) primary breast cancer. We have reported that CpCRypN0 was confirmed in 46% (98/212); in 62% and 34% of ER-negative and ER-positive patients, respectively, from the neoadjuvant JBCRG-16 study (Breast Cancer 25:407-15, 2018). Long-term 5-year follow-up after surgery has been successful.

Methods:

This was a randomized phase II, five-arm study (trial no: UMIN000007576) to evaluate the efficacy and safety of lapatinib and trastuzumab (6 weeks) followed by lapatinib and trastuzumab plus weekly paclitaxel (12 weeks) with/without prolonged anti-HER2 therapy prior to chemotherapy (18 vs. 6 weeks), and with/without endocrine therapy in HER2+ primary breast cancer patients. After surgery, patients received an anthracycline-based regimen according to the physician's choice mainly depending on the efficacy of neoadjuvant treatment, followed by trastuzumab and endocrine therapy (in ER+). We evaluated the 5-year disease-free survival (DFS), distant-DFS (DDFS), and overall survival by the Kaplan-Meier method.

Results:

The 5-year DFS was 87.8% (95%CI, 82.5-91.6); it was higher in patients with CpCRypN0 than in those without CpCRypN0 (91.7% vs 85.1%; p¼0.0387). Among nonpCR patients, G2b (defined as only focal invasive tumor residues confirmed in the removed breast tissue; near pCR) was confirmed in 9 of 35 ER- patients and in 11 of 78 ER+ patients; no survival event was observed in the 20 patients with G2b. Adjuvant anthracycline therapy was performed in 48%; 5-year DDFS was similar between patients with and without adjuvant anthracycline. Four (T3N1 in 3) patients had brain metastasis; 2 of them had achieved CpCRypN0 and omitted adjuvant anthracycline.

Conclusions:

A good prognosis was observed in patients who had CpCRypN0 after neoadjuvant treatment, including those with near pCR. The omission of adjuvant anthracycline may be considered for patients with CpCRypN0, however, the risk of brain metastasis should be taken into consideration.

Clinical trial identification:

UMIN000007576

Genomic profile and response prediction of eribulin mesylate-based neoadjuvant chemotherapy in triple negative breast cancer patients

Background:

Little is known about predictive factors for eribulin mesylate (eribulin)based chemotherapy. In this translational research of a randomized neoadjuvant phase II study, we aimed to explore predictive factors for eribulin-based neoadjuvant chemotherapy in triple-negative breast cancer (TNBC) using tumor genomic profiling.

Methods:

Tumour tissues were collected from the Japan Breast Cancer Research Group-22 trial, examined either 4 cycles of paclitaxel plus carboplatin (arm A1) or eribulin plus carboplatin (arm A2), followed by anthracycline-based therapy in patients with aged <65y and homologous recombination deficiency (HRD) score ≥42, and any age carrying pathogenic germline variant (PGV) of BRCA1/2, and also examined non-carboplatin regimens, either started with eribulin plus cyclophosphamide (arm B1) or eribulin plus capecitabine (arm B2) in patients with aged <65y with HRD score <42 or aged ≥65y without PGV of BRCA1/2. Tumor BRCA1/2 mutation (tBRCA1/2m) and HRD were analyzed in 86 cases. Fifty tumor samples were also analyzed by target sequencing capturing 189 breast cancer driver genes.

Results:

608 women were included, of which 304 women had HER2-0 and 304 had HER2-low disease. Lobular subtype was more common in HER-0 compared to HER2low disease (17% vs. 8%, p=0.005). All other characteristics did not differ between the two groups. At a median follow up of 10.3 years, OS, DFS and DDFS were similar for the whole population. Analyses by genomic risk showed comparable outcomes for women with low genomic risk (RS≤25), but for women with high genomic risk (RS>25), HER2-low was associated with significantly favorable OS (HR=0.31, 95% CI 0.11-0.78, p=0.01), DFS (HR= 0.40, 95% CI 0.20-0.82; p=0.01) and DDFS (HR=0.26, 95% CI 0.11-0.63, P=0.002).

Conclusions:

The prognostic impact of HER2-low expression in early-stage luminal disease varies across the genomic risk, with significant favorable outcomes of HER2low compared to HER2-0 in women with high genomic risk. As other prognostic characteristics were comparable between HER2-low and HER2-0, our findings may be consistent with a novel prognostic feature for this population.

Adjuvant endocrine therapy combined with abemaciclib in monarchE patients with high-risk early breast cancer: Disease characteristics and endocrine therapy choice by menopausal status

Background:

MonarchE demonstrated that adjuvant abemaciclib, oral CDK4 & 6 inhibitor + endocrine therapy (ET) significantly improved invasive disease-free survival in HR+, HER2- high-risk early breast cancer (EBC) compared to ET alone. As prescribing practices for ET vary in younger patients (pts), we present here disease characteristics and ET choice in premenopausal pts (preM) enrolled in monarchE.

Methods:

Patients with, invasive, resected, HR+, HER2- node positive, high risk, EBC were randomly assigned 1:1 to adjuvant ET +/- abemaciclib in monarchE. Disease characteristics, prior chemotherapy, and ET patterns were examined by menopausal status at initial diagnosis: preM and postmenopausal pts (postM). ET choices for preM are further described by age.

Results:

Of the 5637 pts, 43.5% and 56.5% were preM and postM, respectively, with an even distribution between both arms. Median age for preM and postM was 44 and 59 years (y), respectively; 31.5% of preM were ≤40y. PreM had larger tumor size and higher rates of neoadjuvant chemotherapy administration compared to postM (Table). Aromatase inhibitor (AI) use was higher in postM, while tamoxifen use was higher in preM. Among preM, AI use was highest in preM ≤40y in both arms (49.9% abemaciclib + ET, 49.4% ET) and tamoxifen use was highest in preM >40y to ≤50y in both abemaciclib + ET and ET arms, 60.1% and 65.0%, respectively.

Table: 153P Summary of baseline characteristics and first endocrine therapy for premenopausal and postmenopausal patients

	PreM		PostM	
	Abemaciclib + ET N=1227, %	ET Alone N=1224, %	Abemaciclib + ET N=1576, %	ET Alone N=1605, %
Age (years)				
≤40	31	32	1	2
>40 to ≤50	58	57	15	14
>50	12	10	84	84
Tumor size at diagnosis				
<5cm	75	76	81	82
≥5cm	21	21	15	14
Prior chemotherapy				
Neoadjuvant	42	42	32	32
Adjuvant	56	55	60	60
None	2	3	8	8
Region				
Asia	28	28	15	15
NA/EU	49	49	55	55
Other	24	23	30	30
1st ET				
AI	43	40	90	89
Tamoxifen	57	59	10	11

Conclusions:

PreM had larger tumors at baseline and were more likely to have received neoadjuvant chemotherapy, suggesting they may have a higher risk of recurrence than PostM.

Clinical trial identification:

NCT03155997

The addition of pyrotinib in early or locally advanced HER2positive breast cancer patients with no response to two cycles of neoadjuvant therapy: A prospective, multicenter study

Background:

Early assessment of clinical response to treatment would facilitate individualized therapy, with ineffective therapy changed. Pyrotinib is a new oral, irreversible pan-ErbB receptor tyrosine kinase inhibitor that targets human epidermal growth factor receptor (HER) 1, HER2, and HER4. Whether the addition of pyrotinib to TCH (trastuzumab, docetaxel, carboplatin) regimen can bring benefit to non-responder after 2 neoadjuvant cycles of TCH is unclear. This prospective, open-label, multicenter study (NCT03847818) explored the efficacy and safety of neoadjuvant pyrotinib + TCH in patients with early or locally advanced HER2-positive breast cancer who did not respond after 2 neoadjuvant cycles of TCH.

Methods:

Eligible patients were aged 18e70 years, with stage II-III HER2-positive invasive breast cancer. Patients received 2 cycles of TCH (docetaxel: 75 mg/m2 every 3 weeks; carboplatin: area under the curve 5; and trastuzumab: 8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) first, and those with complete/partial response continued 4 cycles of TCH (cohort A). Non-responder after 2 cycles of TCH received 4 cycles of TCH (cohort B) or pyrotinib (400 mg orally once per day) + TCH (cohort C). The primary endpoint was the proportion of patients who achieved total pathological complete response (tpCR, ypT0/is, ypN0).

Results:

From December 2018 to December 2020, a total of 66 patients were enrolled and completed the neoadjuvant therapy and surgery, including 30 patients in cohort A, 10 in cohort B, and 26 in cohort C. The tpCR rate was the highest in cohort C (34.6%), followed by 30.0% in cohort A and 10.0% in cohort B. The most common grade 3-4 adverse events were diarrhea (40.3%), vomiting (25.2%), and neutropenia (7.5%) in cohort C. No treatment-related death was observed.

Conclusions:

This exploratory analysis demonstrated the efficacy and tolerable toxicity of pyrotinib + TCH in patients with early or locally advanced HER2-positive breast cancer who did not respond after 2 cycles of TCH in the neoadjuvant setting, and also confirmed the importance of early efficacy assessment during neoadjuvant therapy.

Anlotinib plus chemotherapy as neoadjuvant treatment of high-risk, early-stage triple-negative breast cancer: A prospective, single-arm, single-center, phase II clinical study

Background:

Anlotinib is an oral multi-targeted tyrosine kinase inhibitor (TKI) that strongly inhibits VEGFR, PDGFR, FGFR, and c-kit. Combining anti-angiogenesis with chemotherapy yielded increased response rates in patients with early-stage triple negative breast cancer (TNBC). This phase II study aims to evaluate the efficacy and safety of adding anlotinib to standard neoadjuvant chemotherapy in primary TNBC.

Methods:

Patients aged 18 years or older with previously untreated stage IIB-IIIA histologically documented TNBC were assigned to receive chemotherapy plus oral anlotinib (12 mg qd, d1-14; 21 days per cycle; total 8 cycles). Chemotherapy comprised epirubicin at 90 mg/m2 and cyclophosphamide at 600 mg/m2 followed by docetaxel at 100 mg/m2, (21 days per cycle; both total 4 cycles), which was then followed by surgery. The primary endpoint was pathologic complete response (pCR; no invasive carcinoma in breast or axilla). Stratification was based on the clinical breast cancer stage.

Results:

Between July 2019 and September 2020, 20 patients (female) with pathological stage IIB (85%), and IIIA (15%) were enrolled with a median age of 48.5 years (range: 32-72). Overall pCR rate was 50.0% (10/20, CI 95% : 29.9%-70.1%). The pCR rate of pathological stage IIB patients was 52.9% (CI 95% : 31.0%-73.8%), which tends to be better than the pCR rate of 33.3% (CI 95%: 6.2%-79.2%) for patients with pathological stage IIIA. There were 21 kind of AEs observed, all including 76 grade 1 AEs and 21 grade 2 AEs; no grade 3 or higher AE was observed. The most common AEs included hand-foot syndrome (60% in total with 35% grade 2 and 25% grade 1), oral mucositis (55.0% in total with 35% grade 2 and 20.0% grade 1), fatigue (60.0%, all grade 1), hoarse voice (33.5%, all grade 1), nasal bleeding (25.0%, all grade 1), hypertension (25% with 5.0% grade 2) and diarrhea (25% with 5.0% grade 2). Neither unexpected safety signals nor treatment-related death occurred.

Conclusions:

The addition of anlotinib to neoadjuvant chemotherapy showed manageable toxicity and promising antitumor activity for patients with high-risk, early-stage TNBC.

Clinical trial identification:

ChiCTR2000038174

ELEANOR: A multi-national, prospective, non-interventional study (NIS) in patients with human epidermal growth factor receptor (HER2) positive, early breast cancer (eBC) observing real-life extended adjuvant treatment with neratinib and concurrent use of the eHealth solution CANKADO

Background:

The aim of (post-)/(neo)adjuvant chemotherapy and HER2-targeted therapy in HER2+ eBC is to prevent locoregional recurrences and development of distant metastases. Despite significant improvements of long-term clinical outcomes, (late) recurrences are still frequently observed with longer follow-up. Neratinib is an irreversible pan-HER tyrosine kinase inhibitor registered in Europe as extended adjuvant treatment for patients with HR-positive (HR+), HER2+ eBC who completed adjuvant trastuzumab-based therapy 1 year before starting neratinib (EMA-/ Swissmedic-label" population). In the ExteNET study, neratinib improved the 5-year iDFS-rate by 5.1% versus placebo (90.8% vs. 85.7%; HR 0.58 [95% CI 0.41-0.82]) in this population, mainly by prolonging the time to development of distant metastases. Diarrhea, the most common grade 3 adverse event (neratinib: 39% without primary diarrhea prophylaxis, median cumulative duration 5 days; placebo: 1%; no grade 4 events) can generally be managed through adequate diarrhea prophylaxis and treatment management. ELEANOR is the first NIS to investigate real-world use of neratinib in the modern treatment landscape in the registered population in Germany, Austria and Switzerland. 200 female patients are planned to be documented in accordance with the SmPC.

Trial design:

The primary objective is patients' adherence to neratinib treatment. Secondary objectives include patient and disease characteristics, details on prior trastuzumab-based therapies (including pertuzumab and T-DM1), neratinib doses and concurrent medication, relapses, safety, and quality of life (QoL). CANKADO, an application developed to support patient/physician communication, is an integral part of the NIS. Different CANKADO modules can be used optionally, including QoL documentation (EQ-5D-5L- and diarrhea-specific questionnaires) and continuous documentation of health status and symptoms. As of 2021-05-03, 116 patients had been enrolled at 42 sites, including hospitals and practices.

ALOMA-4: Primary results from a phase III trial of palbociclib (PAL) + letrozole (LET) vs placebo (PBO) + LET in Asian postmenopausal women with estrogen receptore positive/human epidermal growth factor receptor 2e negative (ER+/HER2e) advanced breast cancer (ABC)

Background:

The incidence of breast cancer in Asian women has increased rapidly over the past 40 years. A previous subgroup analysis from PALOMA-2 indicated that PAL + LET may be effective as first-line therapy in postmenopausal Asian women with ER+/HER2e ABC. The PALOMA-4 study assessed the efficacy and safety of PAL + LET in Asian patients (pts).

Methods:

PALOMA-4, an international, double-blind, phase 3 trial, randomized postmenopausal Asian women who had not received prior systemic therapy for ER+/ HER2e ABC 1:1 to receive PAL (125 mg/d orally; 3 weeks on, 1 week off) + LET (2.5 mg/d orally; continuously) or PBO + LET. The primary endpoint was Kaplan-Meier analysis of investigator-assessed progression-free survival (PFS); between-arms comparisons used a stratified log-rank test. Secondary endpoints included objective response rate (ORR) and safety; between-arms comparisons used the Cochran Mantel-Haenszel test. Safety was summarized descriptively.

Results:

Pts (N=340) were randomized (PAL + LET, 169; PBO + LET, 171). The median duration of follow-up for overall survival was 52.8 mo. Baseline characteristics were generally similar between the 2 groups. At the data cutoff (Aug 31, 2020), the median PFS based on investigator assessment was 21.5 mo for PAL + LET and 13.9 mo for PBO + LET (hazard ratio, 0.68 [95% CI, 0.53-0.87]; P=0.0012). The ORR based on investigator assessment was 37.3% vs 31.6%, respectively, among all pts (P=0.154) and 43.4% vs 38.0% in pts with measurable disease (P=0.206). The most common grade 3/4 adverse events (AEs) with PAL + LET vs PBO + LET were neutropenia (84.5% vs 1.2%), leukopenia (36.3% vs 0.6%), thrombocytopenia (6.5% vs 0.6%), and anemia (4.8% vs 1.8%). Febrile neutropenia was reported only with PAL + LET (2.4 %). The discontinuation rate due to AEs was 7.7% with PAL + LET and 2.9% with PBO + LE

Conclusions:

PALOMA-4, the largest study to date of a cyclin-dependent kinase 4/6 inhibitor in Asian pts with ABC, confirmed the efficacy and safety of PAL + LET as first line therapy in postmenopausal Asian women with ER+/HER2e ABC.

Clinical trial identification:

NCT02297438

Overall survival (OS) of palbociclib (P) plus endocrine therapy (ET) versus capecitabine (CAP) in hormone receptor+/HER2- metastatic breast cancer (MBC) that progressed on aromatase inhibitors (AIs): Final results of the PEARL study

Background:

PEARL study did not show superiority in progression-free survival (PFS) with P+ET versus (vs) CAP in patients (pts) with AI-resistant MBC, but P+ET was better tolerated and showed a significant delay in quality-of-life deterioration. Final OS data

Methods:

PEARL had two consecutive cohorts: cohort 1 (C1) with 296 pts randomized to P+exemestane vs CAP, and cohort 2 (C2) with 305 pts randomized to P+fulvestrant (F) vs CAP. Secondary endpoints included OS in C2 and in wild-type (wt) ESR1 (measured in ctDNA at baseline) pts (C1+C2). OS analysis was planned when 152 deaths occurred in C2, in order to have an 80% power to detect an increase of 50% in OS from 22 months (m) with CAP to 33 m with P+F or P+ET in wtESR1 pts. Adjusted hazard ratio (aHR) was calculated using a stratified Cox proportional hazard model with treatment arm, stratification factors and number of involved sites as covariates.

Results:

At data cut-off (11Jan2021), the median follow-up of C2 and wtESR1 pts were 28.0 m and 30.3 m, respectively. Median OS in C2 was 31.1 m with P+F vs 32.8 m with CAP (aHR 1.10, 95% CI, 0.81e1.50; p=0.550). Median OS in wtESR1 pts was 37.2 m with P+ET vs 34.8 m with CAP (aHR 1.06, 95% CI, 0.81-1.37; p=0.683). None of the subgroup analyses showed superiority in OS for P+ET vs CAP. Subsequent therapy was given to 79.8% and 82.9% of pts with P+ET and CAP, respectively. The median number of subsequent lines was 3 (1-10) in the P+ET arm and 3 (1-9) in the CAP arm. First subsequent therapy was CDK4/6 inhibitor+ET in 26.1% of pts in the CAP arm and CAP in 36.1% of pts in the P+ET arm. The median PFS2 defined as time from randomization to the end of first subsequent therapy or death, was similar in both arms either in C2, 18.3 m with P+F vs 17.7 m with CAP (aHR 0.95, 95% CI, 0.73-1.25; p=0.728), and in wtESR1 pts, 18.3 m with P+ET vs 18.2 m with CAP (aHR 1.04, 95% CI, 0.83-1.31; p=0.717). PFS and response did not change in this final analysis. No new safety findings were observed with longer follow-up.

Conclusions:

Palbociclib + endocrine therapy did not show a statistically superior OS compared to CAP in MBC pts progressing to AIs.

Clinical trial identification:

NCT02028507

First in human, modular study of samuraciclib (CT7001), a first-in-class, oral, selective inhibitor of CDK7, in patients with advanced solid malignancies

Background:

CDK7 inhibition is a promising therapeutic strategy in cancer. CDK7 is a key kinase, regulating cell division, transcription and nuclear receptor function, particularly the estrogen receptor.

Methods:

Tolerability, pharmacokinetics and efficacy of samuraciclib were assessed; including evaluation of ascending doses (M1A), paired tumor biopsy (PB) samples (M1A), effect of food on bioavailability (M4) and a triple-negative breast cancer (TNBC) expansion cohort (M1B).

Results:

M1A recruited 33 patients in 5 cohorts: 120, 240, 360mg and 480 mg once daily (OD), and 180 mg twice daily (BID). 11 further patients were dosed in PB cohorts for pharmacodynamic assessment. M4 recruited 15 patients. M1B recruited 23 patients. At 120 mg, 240 mg and 360mg, most common adverse drug reactions (AE) were: G1-2 nausea, vomiting and diarrhea. At 480 mg, 3/6 patients experienced a DLT (G3 diarrhea, G3 oral mucositis, G3 vomiting). At 180mg BD, 1/7 patients experienced a DLT (G4 thrombocytopenia). 240mg OD and 360 mg OD were determined clinically relevant doses, with 360mg OD as the preliminary recommended phase 2 dose. In fasted patients, median Tmax ¼ 1.5 - 4 hrs. and geomean T1/2 w 75 hrs. Steady-state was achieved within 8 - 15 days. Plasma exposure increased dose proportionally; pharmacologically active exposures were achieved throughout the entire dosing period. Food had no clinically significant effect on exposure. 57% (25/44) of RECIST evaluable patients had evidence of disease control at first post baseline scan (FPBS) observed across the ‘all comer’ cohorts in M1A and M4, including a partial response (PR) in a patient with HR+ breast cancer; PSA reductions were observed in the 4 castrate-resistant prostate cancer patients recruited. Preliminary tumor biopsy data supports tumor target engagement. 20 patients with TNBC were evaluable for RECIST assessment: 12/ 20 had stable disease at FPBS; 3 have been on treatment > 1year.

Conclusions:

Samuraciclib has demonstrated an acceptable safety profile with evidence of anti-tumor activity.

Clinical trial identification:

2017-002026-20

Longitudinal circulating tumor DNA (ctDNA) analysis in the phase 1b MONALEESASIA study of ribociclib (RIB) + endocrine therapy (ET) in Asian patients (pts) with hormone receptor positive (HR+)/human epidermal growth factor receptor 2enegative (HER2e) advanced breast cancer (ABC)

Background:

MONALEESASIA included dose-escalation and -expansion phases and enrolled premenopausal and postmenopausal Japanese pts and postmenopausal Asian non-Japanese pts. In the dose-escalation phase, all pts received RIB + letrozole (LET). In the dose-expansion phase, all Asian non-Japanese pts received RIB + LET, whereas Japanese pts received RIB + LET or fulvestrant (for postmenopausal pts) or RIB + TAM + goserelin (for premenopausal pts). Cell-free DNA (cfDNA) samples were collected from pts at baseline (BL), during treatment, and at end of treatment (EOT). ctDNA was evaluated with a targeted NGS panel comprising z 600 cancer-related genes. ctDNA levels were evaluated throughout treatment by best overall response (BOR).

Methods:

86 pts were included in this analysis, and 574 cfDNA samples were tested. Some of the most frequently altered genes were PIK3CA, TP53, and ESR1.The alteration frequency for PIK3CA and TP53 was similar from BL to EOT but was numerically higher at EOT for ESR1. There was a consistent trend of lower BL ctDNA levels in pts with partial response (PR) or stable disease (SD) vs pts with progressive disease; however, there was no difference in ctDNA levels at on-treatment time points and EOT by BOR. In all treatment arms, pts with PR and SD had a decrease in ctDNA levels at the first collected on-treatment time point vs BL. Three categories of case studies will be presented: (1) ctDNA was detectable at BL and became undetectable on treatment; (2) ctDNA increased before tumor progression; (3) ctDNA was not detectable throughout treatment.

Conclusions:

ctDNA levels were dynamic throughout treatment in Asian pts with HR+/ HER2e ABC in MONALEESASIA. These findings suggest that on-treatment ctDNA levels may help identify pts at risk of progression.

Clinical trial identification:

NCT02333370

Association of quality of life (QOL) with overall survival (OS) in patients (pts) with HR+/HER2L advanced breast cancer (ABC) treated with ribociclib (RIB) + endocrine therapy (ET) in the MONALEESA-3 (ML-3) and ML-7 trials

Background:

ML-3 and -7 demonstrated a significant OS benefit and maintenance/ improvement of QOL with RIB + ET vs ET in pts with HR+/HER2 ABC. We evaluated the association of QOL with OS in ML-3 and -7.

Methods:

In ML-3, postmenopausal pts were treated with RIB + fulvestrant (FUL) or FUL alone. This analysis included the NSAI cohort of ML-7, in which peri/premenopausal pts were treated with RIB + NSAI or NSAI alone. QOL was assessed with EORTC QLQ-C30. A responder analysis was performed based on published minimal clinically important differences in change from baseline to group pts as improvers/maintainers (responder) or non-improvers/non-maintainers (non-responder). The percentage of responders was summarized for each visit by treatment arm for pts who lived longer and pts who lived shorter (OS cutoffs: 39.2 mo for ML-3; 33.1 mo for ML-7).

Results:

In ML-3 and -7, pts living longer vs living shorter had more improved/ maintained QOL over the course of tx. In both trials, RIB was generally associated with a greater percentage of pts with improvement/maintenance of GHS compared with ET alone, with greater tx benefit in pts living longer.

Table: 233P

Pt population, %	Mean % of pts with improved/maintained GHS
ML-3	
All pts (n=631)	
RIB (n=422)	32
PBO (n=209)	26
Pts living longer (n=316)	
RIB (n=219)	45
PBO (n=97)	38
Pts living shorter (n=315)	
RIB (n=203)	21
PBO (n=112)	20
ML-7 (NSAI cohort)	
All pts (n=478)	
RIB (n=242)	35
PBO (n=236)	26
Pts living longer (n=241)	
RIB (n=135)	45
PBO (n=106)	34
Pts living shorter (n=237)	
RIB (n=107)	32
PBO (n=130)	26

Conclusions:

In ML-3 and -7, pts living longer vs living shorter had more improved/ maintained QOL over the course of tx. In both trials, RIB was generally associated with a greater percentage of pts with improvement/maintenance of GHS compared with ET alone, with greater tx benefit in pts living longer.

Clinical trial identification:

MONALEESA-3; NCT02422615; MONALEESA-7; NCT02278120

ffect of palbociclib (PAL) + endocrine therapy (ET) on time to chemotherapy (TTC) across subgroups of patients (pts) with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced breast cancer (ABC): Post hoc analyses from PALOMA-2 (P2) and PALOMA-3 (P3)

Background:

Previous analyses from P2 and P3 studies showed that PAL + ET prolongs TTC vs placebo (PBO) + ET in the overall population of pts with HR+/HER2e ABC. Here, we evaluated TTC in relevant pt subgroups.

Methods:

These post hoc analyses evaluated TTC by subgroup using data from 2 randomized phase 3 studies of women with HR+/HER2e ABC. In P2, postmenopausal pts previously untreated for ABC were randomized 2:1 to receive PAL (125 mg/d, 3/1 schedule) + letrozole (LET; 2.5 mg/d) (n=444) or PBO + LET (n=222). In P3, pre/postmenopausal pts whose disease had progressed after prior ET were randomized 2:1 to receive PAL (125mg/d, 3/1 schedule) + fulvestrant (FUL; 500 mg) (n=347) or PBO + FUL (n=174).

Results:

More patients in the PBO + ET vs PAL + ET group received first subsequent chemotherapy (CT) after discontinuation of study treatment (46.8% vs 33.6% and 74.7% vs 69.7% in P2 and P3, respectively). Across all subgroups analyzed, TTC was longer with PAL + ET vs PBO + ET (Table). Regardless of treatment arm, a higher percentage of pts who received vs who did not receive first subsequent CT were aged <65 years (PAL arm: 71% vs 53% in P2, 80% vs 64% in P3; ET arm: 70% vs 58% in P2, 77% vs 71% in P3) or had a disease-free interval (DFI) of ≤12 months (P2: PAL arm: 32% vs 17%; ET arm: 27% vs 17%). A higher percentage of pts with visceral metastases in the PBO arm received first subsequent CT vs those who did not (60% vs 41% in P2, 65% vs 46% in P3); in contrast, in the PAL arm, similar percentages of pts received vs did not receive first subsequent CT (50% vs 47% in P2, 57% vs 59% in P3).

Table: 234P Median time (mo) to first subsequent chemotherapy

	PALOMA-2			PALOMA-3		
	TTC		HR (95% CI)	TTC		HR (95% CI)
	PAL + LET	PBO + LET		PAL + FUL	PBO + FUL	
ITT	40	30	0.7 (0.6–0.9)	18	9	0.6 (0.5–0.7)
Visceral	34	25	0.6 (0.5–0.9)	15	6	0.6 (0.4–0.8)
Nonvisceral	46	35	0.9 (0.6–1.2)	23	17	0.6 (0.4–0.9)
Bone only	40	30	0.7 (0.4–1.2)	23	20	0.8 (0.5–1.2)
Liver involvement	20	14	0.7 (0.5–1.1)	13	6	0.6 (0.4–0.8)
Lung involvement	47	30	0.6 (0.4–0.8)	17	8	0.6 (0.4–0.8)
DFI ≤12 mo	24	17	0.8 (0.5–1.2)	–	–	–
DFI >12 mo	46	31	0.6 (0.5–0.9)	–	–	–
Pts without prior CT in ABC	–	–	–	18	12	0.6 (0.5–0.8)
Pts with prior CT in ABC	–	–	–	14	7	0.6 (0.4–0.8)

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat population.

Conclusions:

Across all subgroups, PAL + ET vs PBO + ET prolonged TTC. As expected, pts in P2 who received PAL + ET in the first-line setting had a longer time to subsequent CT than pts in P3 who received PAL + ET after progressing on prior ET.

Clinical trial identification:

NCT01740247; NCT01942135

Real-world comparative effectiveness of palbociclib plus letrozole vs letrozole in older patients with metastatic breast cancer

Background:

Palbociclib, the first clinically available oral CDK4/6 inhibitor, in combination with endocrine therapy has become standard of care for HR+/HER2- advanced/ metastatic breast cancer (MBC). Little is known about effectiveness of palbociclib plus endocrine compared with endocrine therapy alone in older MBC patients. This study compared real-world progression free survival (rwPFS) and overall survival (OS) of palbociclib plus letrozole (PB+LE) vs letrozole alone (LE) in older MBC patients in US clinical practices.

Methods:

We conducted a retrospective analysis of MBC patients from the Flatiron Health longitudinal database, which contains electronic health records from over 280 cancer clinics representing more than 2.2 million actively treated cancer patients in the US. Between February 2015 and February 2019, 796 HR+/HER2e MBC women aged ≥ 65 years started PB+LE or LE as first-line therapy. Patients were evaluated from start of PB+LE or LE to May 2019, death, or last visit, whichever came first. rwPFS was defined as months from start of PB+LE or LE to death or disease progression based on clinical assessment or radiographic scan/tissue biopsy. Stabilized inverse probability treatment weighting (sIPTW) was used to balance patient characteristics.

Results:

After sIPTW, 450 patients in PB+LE and 335 in LE were included. Median age was 74.0 years. Median rwPFS was 22.2 months (95%CI = 20.0-30.4) in PB+LE cohort and 15.8 months (95%CI=12.9-18.9) in LE cohort (HR=0.59, 95%CI=0.47-0.74, p <.0001). Median OS was not reached (NR) in PB+LE cohort vs 43.4 months (95% CI=30.0dNR) in LE cohort (HR=0.55, 95%CI=0.42-0.72, p <.0001). The table presents key patient characteristics and rwPFS and OS rates.

Conclusions:

This comparative analysis of PB+LE vs LE alone provides evidence of effectiveness for the palbociclib combination, supporting this treatment as a standard of care for older HR+/HER2- MBC patients in the first line setting.

Clinical trial identification:

NCT04176354

Abemaciclib plus fulvestrant in participants with HR+/HER2advanced breast cancer: A pooled analysis of the endocrine therapy naïve (EN) participants in MONARCH 2

Background:

MONARCH 2 (M2) demonstrated that the addition of continuously dosed abemaciclib to fulvestrant significantly improved progression-free survival (PFS) and overall survival (OS) compared to placebo plus fulvestrant in women with HR+, HER2- advanced breast cancer (ABC) who had progressed on endocrine therapy (ET). Here we present the Objective Response Rate (ORR) from endocrine-naïve (EN) participants enrolled in MONARCH 2.

Methods:

A small cohort of EN participants, with measurable disease at baseline, were initially enrolled in the M2 main study [excluded from the intent-to-treat (ITT) population] (N¼20). Subsequently, 90 additional participants were enrolled under the EN addendum. The analysis population consist of a pooled EN cohort (N ¼ 110). All participants were scheduled to receive abemaciclib (150mg or 200 mg Q12H) plus fulvestrant (500 mg, per label). Participants were not allowed to have had prior ET in any setting or prior chemotherapy in the metastatic setting. The primary endpoint was investigator-assessed confirmed ORR. The secondary endpoints were investigator-assessed PFS, duration of response (DoR), disease control rate (DCR), clinical benefit rate (CBR), and safety and tolerability.

Results:

In the pooled EN cohort, confirmed ORR was 59.1% (95% CI 49.9-68.3). Median follow-up was 9.8 (0.03-73.05) months. PFS and DoR data are not mature at this time. No new safety signals were reported in the pooled EN cohort, and the safety profile was consistent with the previously reported MONARCH 2 population.

Conclusions:

The primary analysis of confirmed ORR compares favorably with previously reported ORR for fulvestrant monotherapy in participants with a similar disease state. PFS and DoR data are not yet mature. The safety profile is similar to that previously reported in the primary MONARCH 2 main study.

Clinical trial identification:

NCT02107703

Palbociclib combined with aromatase inhibitors (AIs) in women ‡75 years with estrogen receptor positive (ER+ve), human epidermal growth factor receptor 2 negative (HER2ve) advanced breast cancer: A real-world multi center UK study

Background:

Breast cancer accounts for 21% of all cancer diagnoses in women aged !75 years. The older population is under-represented in clinical trials; thus, real-world data in this patient group is critical to guide management. In this large-scale UK-wide real-world study, we evaluated the tolerability and efficacy of palbociclib combined with an AI for first-line treatment of advanced ER+ve/HER2-ve breast cancer in elderly women.

Methods:

14 cancer centers participated in this national retrospective study. Patients aged !75 years who received at least one cycle of palbociclib combined with an AI for first-line treatment of advanced ER+ve/HER2-ve breast cancer were eligible. Data included baseline demographics, co-morbidities, metastatic disease burden, toxicities, dose reductions and delays, response to treatment and in-patient secondary care burden. Multivariable Cox regression was used to assess independent predictors of progression-free survival (PFS).

Results:

276 patients met the eligibility criteria. The median age of patients was 78 (range 75-92) years. The PFS rates at 12 and 24 months were 75.9% and 64.9%, respectively. The best radiological response was complete response (2%), partial response (32.9%) and stable disease (54.9%) with a clinical benefit rate at 24 weeks of 87%. The most common toxicities were neutropenia, fatigue, anemia and thrombocytopenia. 50.7% of patients required a dose reduction and 59.2% required at least one dose delay. 22 patients (9.6%) required hospital admission due to toxicity and 6 patients (2.2%) had febrile neutropenia. Multivariable analysis identified fewer dose delays, increasing ECOG performance status and age-adjusted Charlson co-morbidity index, and increasing number of metastatic sites to be independent adverse predictors of PFS.

Conclusions:

This largest known dataset of Palbociclib tolerability and efficacy in women aged ≥75 years shows that this is an effective therapy that is well tolerated and appropriately managed with dose delays/reductions resulting in very low levels of clinically significant toxicity requiring hospital admission.

Palbociclib dose patterns in Swedish patients with metastatic breast cancer: Evidence from the SIRI study

Background:

Palbociclib is a cyclin-dependent kinase (CDK) 4/6 inhibitor indicated for use in combination with aromatase inhibitors or fulvestrant for patients with hormone receptor-positive (HR+) human epidermal growth factor receptor 2 (HER2) negative metastatic breast cancer (MBC). The Swedish Ibrance Registries Insights (SIRI) study investigated real-world dose patterns using a nationwide Swedish cohort of palbociclib-treated MBC patients.

Methods:

This was a retrospective study utilizing population-based Swedish Health Data Registers. The cohort included all patients ≥ 18 years with ≥ 1 filled prescription of palbociclib from January 2017 e June 2020. Minimum follow-up was 3 months. Starting dose and dose changes for the full population, for subgroups, in total and over time, was investigated.

Results:

1226 patients with palbociclib prescription were identified, 10 were men. Mean (SD) age at treatment initiation was 65 (11) years. 11% of patients had de novo MBC. Most patients were initiated on 125 mg (86.8%), with a lower share for older patients (80%), and a falling share over time (Table). 43.5% of patients had !1 dose reduction, with a falling share over time (47.1% in 2017; 35.2% in 2020). The share of patients starting on 125 mg reduced to 100 mg and 75 mg (final doses) was 26.6% and 19.4%, respectively, whereas 28% of patients starting on 100 mg reduced to 75 mg. Endocrine therapy backbone did not affect dose patterns. Younger patients (<50 years) starting on 125 mg were more frequently down dosed to a final dose of 100 mg (34% vs 25.7% for age 50-69 and 26.1% for age ≥70), whereas dose reduction from 125 to 75 mg increased with age (<50: 12%; 50-69: 18%; ≥70: 23.6%).

Table: 237P HR+ HER2- hTMB mBC pts who received ICI in Mayo/Duke and CGDB cohorts

	Mayo/Duke (n = 8)	CGDB (n = 20)
APOBEC	6 (75%)	13 (65%)
Median TMB (IQR)	32.5 (23.2, 47.5)	20.9 (13.8, 33.8)
ICI Monotherapy	2 (25%)	14 (70%)
ICI Line		
1-2	3 (37.5%)	1 (5.0%)
3+	5 (62.5%)	19 (95%)
ICI > 6 mo	4 (50.0%)	5 (25.0%)
Median TTD (mo, 95%CI)	5.8 (2-NA)	2.8 (1.4-NA)

Conclusions:

Most Swedish palbociclib-treated patients were initiated on the recommended starting dose, but a trend towards a reduced starting dose was observed over time. In total, dose reductions appear to be slightly more common in clinical practice, but with a falling trend approaching clinical trial findings over time.

Efficacy and safety of ribociclib (RIB) in combination with letrozole (LET) in patients with estrogen receptor positive advanced breast cancer (ABC): Secondary and exploratory results of phase 3b RIBECCA study

Background:

RIBECCA was a phase 3b, multicentre, open-label study of RIB + LET in patients (pts) of any menopausal status with HR+, HER2eABC, who were not amenable to curative treatment (tx). The study investigated RIB + LET in pt settings broader than those considered in MONALEESA (ML) studies. Data on primary endpoint, clinical benefit rate (CBR) at week 24 in cohorts A (tx naive postmenopausal pts) and B (comprising cohort B1 [tx naive pre- and perimenopausal pts] and B2 [pre-, peri- and postmenopausal pts pretreated with ≤1 prior chemotherapy and ≤2 lines of endocrine therapy]) were reported previously. Here, we report secondary efficacy and safety on prespecified cohorts B1 and B2, together with multivariate analysis on the overall study population.

Methods:

Secondary endpoints of the study include CBR, and overall response rate (ORR) at week 24, progression-free survival (PFS), overall survival (OS), changes in quality of life and safety in both cohorts B1 and B2, respectively. The impact of various demographic and anamnestic factors on PFS in the overall population was evaluated using Cox regression model.

Results:

In cohort B1 (n=26), confirmed CBR was (57.7% [95% CI, 36.9-76.6], ORR at week 24 was 23.1% (95% CI, 9.0-43.6) and median PFS was 16.5 months (mo; 95% CI, 3.2-not calculable). In cohort B2 (n=154), confirmed CBR was 56.5% (95% CI, 48.364.5), ORR at week 24 was 11.7% (95% CI, 7.1-17.8) and median PFS was 8.8 mo (95% CI, 8.1-16.3). Median OS was not reached in this study. The most common tx-emergent adverse events (grade 3/4) in cohort B1 were neutropenia (34.6%) and leucopenia (19.2%), and that in cohort B2 were neutropenia (40.8%) and neutrophil count decreased (14.0%). Baseline ECOG, histological grade, therapy situation and progesterone receptor (PR) status tended to impact PFS in multivariate analysis.

Conclusions:

The data confirmed the clinical and PFS benefit of RIB + LET in both cohorts B1 and B2. Baseline ECOG, histological grade, therapy situation and PR status might impact PFS outcome. No new safety signals were observed. These results confirm findings of ML studies in broader population.

Clinical trial identification:

CLEE011XDE01; NCT03096847

Palbociclib: Early treatment-related neutropenia as a potential pharmacodynamic marker?

Background:

Early palbociclib-related neutropenia has been associated with prolonged PFS (progression-free survival). However, there is limited real-world information. The aim of the study was to determine whether early neutropenia in our cohort of patients is associated with disease response to palbociclib combined with fulvestrant or aromatase inhibitor.

Methods:

Retrospective study including all patients who started treatment with palbociclib between December 2016 and January 2021. Demographic and clinical data were obtained from the electronic clinical records. Primary endpoints included both PFS and OS (overall survival). Early neutropenia was defined as the nadir absolute neutrophil count (ANC) during the first 2 cycles of treatment. PFS and OS were analyzed through Kaplan-Meier survival curves comparing neutropenia grades using log-rank test to check differences between survival curves. Multivariate Cox proportional hazard regression model was also used to predict OS.

Results:

A total of 78 patients were included. Demographic and clinical characteristics are shown in the table.

Table: 250P

	Total patients (n=78)
Age in years, mean±SD	62±12.7
Female, N(%)	77(98.7%)
Weight in kg, mean±SD	67.2±14.8
Baseline ECOG PS 0-1, N(%)	71(91.0%)
Line of therapy, N(%)	
1	55(70.5%)
2	16(20.5%)
≥3	7(9.0%)
Concomitant drug, N(%)	
Fulvestrant	29(37.2%)
Aromatase inhibitor	49(62.8%)
Baseline ANC, mean±SD	4.7±2.4

Thirty-six patients (46.2%) stopped the treatment and 31 (86.1%) discontinued due to progression. Thirty-four patients (43.6%) required ≥ 1 dose reduction. In the first two cycles, 69 patients (88.5%) experienced grade 1e4 neutropenia. Patients who experience grade 2-4 neutropenia in the first two cycles were associated with significantly prolonged median OS (log-rank p=0.020). However, there was no significantly association with prolonged median PFS (log-rank p=0.228). After adjusting for potential cofounders (baseline ACN, age and weight), grade 2-4 neutropenia remained significantly and independently associated with prolonged OS (HR 0.30, 95% CI 0.11e0.81, p=0.018).

Conclusions:

Early treatment-related neutropenia was significantly associated with a prolonged OS, supporting the suggestion that neutropenia could be a pharmacodynamic marker for palbociclib dosing.

Risk factor (RF) identification (ID) and hyperglycemia (HG) prevention with alpelisib (ALP) + fulvestrant (FLV) in PIK3CA-mutated, hormone-receptor positive (HR+), human epidermal growth factor-2 negative (HER2-) advanced breast cancer (ABC)

Background:

SOLAR-1 investigated use of ALP+FLV in patients (pts) with HR+/HER2-, PIK3CA-mutated ABC after progression on endocrine-based therapy. SOLAR-1 demonstrated a clinically significant increase in all-grade (G) and G3-4 HG compared to placebo+FLV. Current guidance recommends an insulin sensitizer (metformin, thiazolidinedione, DPP-4 inhibitor) at HG onset. Given high rates of HG, a preventative protocol and ID of associated RFs was implemented to minimize HG, dose reductions and discontinuation.

Methods:

This single-center, retrospective study included pts receiving at least one 28-day cycle of ALP+FLV between June 2019 and April 2021. One week prior to ALP initiation, pts initiatedan insulin-sensitizer. Pts had fasting plasma glucose (FPG) levels drawnonday8, 15, 28, and monthly while on ALP. G2-4 HG was the primary outcome. Descriptive statistics summarized demographics, clinical characteristics, and outcomes. Number of RFs for HG (age $\geq$ 65 years, BMI $\geq$ 25 kg/m^2, baseline FPG $\geq$100 mg/dL, and A1c $\geq$ 5.7%) were compared between pts with and without HG using Wilcoxon rank-sum test.

Results:

16 women were included with a median age of 59 years. The cohort was 69% White and 25% Black, 75% overweight/obese, and 50% had a history of type 2 diabetes mellitus (T2DM), gestational diabetes, or pre-diabetes. 15 pts received a CDK4/ 6 inhibitor prior to starting ALP. By day 28, 9 pts (56%) had G2-4 HG, with only 3 (19%) having G3 HG and zero having grade 4. Pts with G2-4 HG had a median of 2 RFs compared to only 1 RF if no HG (p=0.03). 5 pts (31%) required a temporary hold of ALP and 3 pts (19%) required a dose reduction in ALP due to HG. 13 pts permanently discontinued ALP - 9 due to disease progression and 4 due to an adverse event with only 1 due to HG. Median duration of ALP was 86 days (range 24-442), with 3 pts continuing to receive ALP at time of analysis.

Conclusions:

Implementation of a HG prevention protocol with ALP in the real-world setting demonstrated fewer G3-4 HG events compared to that seen in SOLAR-1 (19% vs 36.6%). An increase in HG-associated RFs correlated with a higher incidence of G2-4 HG.

Impact of palbociclib-dose reduction on survival: A retrospective cohort study

Background:

Palbociclib dose reductions do not affect efficacy in the clinical trial setting, as previous data have shown. No significant differences in progression-free survival were observed across the various palbociclib doses in the real world, but more dose reductions have been reported. Our aim was to evaluate if dose reductions in Palbociclib affect the duration of treatment (DoT) and overall survival (OS) of metastatic breast cancer (mBC) patients in the first and second-line setting in the real world.

Methods:

We identified HR+/HER2- mBC female patients (pts) treated with first and second-line Palbociclib between January 2016 and June 2020 using the institutional computerized prescriber order entry system and performed a retrospective review of the electronic medical records. Our primary outcome was to compare DoT and OS among the groups treated with three different doses of Palbociclib, (125 mg, 100 mg and 75 mg) with the Kaplan Meier method. Secondary outcomes were to evaluate the impact of age and Body Mass Index (BMI) among the dose groups on DoT and OS.

Results:

100 pts were included, with 65 and 35 pts receiving palbociclib as first and second line, respectively. 28% of the pts tolerated Palbociclib at a dose of 125 mg, 29% were dose-reduced to 100 mg, and 43% to 75 mg. The number of pts requiring dose reductions here was higher than that reported in PALOMA-2 (72% vs 36%). After a median follow-up of 28.9 mos, 33% remained on Palbociclib, 59% progressed or died, and 6% discontinued due to toxicity. Median DoT was 21.2 mos for all pts, 10.9 mos for pts receiving 150mg, 23 mos for pts receiving 100 mg and 26.7 mos for pts receiving 75 mg. Differences between groups were not statistically significant. Mean OS was 48.9 mos for all pts; 37.4 mos for pts receiving 150mg dose, 45.3 mos for pts receiving 100 mg and 54.9 mos for pts receiving 75 mg (p .02) which was statistically significant. There was no statistically significant difference in DoT or OS among the groups when considering age and BMI factors.

Conclusions:

In this retrospective cohort of mBC patients treated with Palbociclib in either first or second-line, more dose reductions were observed than that reported in PALOMA-2, but there was no negative impact on median DoT or mean OS when compared with the group receiving the standard dose of 125mg.

Study of samuraciclib (CT7001), a first-in-class, oral, selective inhibitor of CDK7, in combination with fulvestrant in patients with advanced hormone receptor positive HER2 negative breast cancer (HR+BC)

Background:

CDK7 inhibition is a promising therapeutic strategy in cancer; acting as a regulator of transcription, the cell cycle and endocrine receptor signalling. Patients with HR+BC post CDK4/6 inhibitor treatment have a poor prognosis; median progression free survival (mPFS) of w 8 weeks for fulvestrant post CDK4/6i in HR+BC. Pre-clinical HR+BC models indicate the potential for synergy when the CDK7 inhibitor samuraciclib is combined with fulvestrant.

Methods:

This single arm cohort assessed the tolerability and efficacy of samuraciclib in combination with fulvestrant in patients with advanced HR+BC; all patients had previously received an aromatase inhibitor and a CDK4/6 inhibitor for advanced disease.

Results:

31 patients with HR+BC received the combination of standard dose with fulvestrant and samuraciclib. 6 patients received samuraciclib dose of 240mg once daily (OD) and 25 patients a dose of 360mg (OD). The combination treatment was generally well tolerated, with adverse drug reactions (AE) of note being G1-2 nausea, vomiting and diarrhea; the majority of patients staying on treatment until disease progression. RECIST evaluation indicates evidence of reduction in tumor disease burden, including a partial response in one patient who has been on treatment for ~1 year. Graphic illustrations of data, including ‘waterfall’ and ‘swimmer’ plots, will be presented.

Conclusions:

Samuraciclib has demonstrated an acceptable safety profile with evidence of anti-tumor activity in combination with fulvestrant for patients with advanced HR+BC who have progressed on their prior CDK4/6.

Clinical trial identification:

2017-00202620

Patient-reported outcomes (PRO) with talazoparib (TALA) vs physician's choice chemotherapy (PCT) in patients (pts) with HER2- advanced breast cancer (ABC) and a germline BRCA1/ 2 mutation (gBRCAm): Subgroup analysis of pts with and without TALA dose reductions vs PCT in the EMBRACA trial

Background:

In EMBRACA, TALA vs PCT demonstrated significant improvement in progression-free survival, a manageable adverse event (AE) profile, and quality of life (QoL) improvement. AEs were managed with supportive care and dose modifications. This post hoc analysis evaluated PROs in TALA pts without/with dose reductions vs PCT.

Methods:

431 pts were randomized 2:1 to TALA (1 mg/d; n=287) or PCT (n=144); 52% of pts in the TALA arm had dose reductions (0.75 mg, 0.5 mg, or 0.25 mg). PROs were assessed at baseline, Day 1 of each 3-wk. cycle, and end of treatment using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30) and BC module (BR23). Higher scores indicate better functioning or global health status (GHS)/QoL, or worse symptoms. PRO analyses included overall (longitudinal mixed effects model) mean change from baseline and time to definitive (TTD) clinically meaningful deterioration for TALA pts without/with dose reductions vs PCT. TTD was compared using a stratified log-rank test and Cox proportional hazards model.

Results:

Between arm overall change from baseline significantly favored TALA without/with dose reduction vs PCT in GHS/QoL, functional (physical, role, emotional, social), and symptom (fatigue, pain, insomnia, appetite loss) scales (Table). A delay in TTD was observed in GHS/QoL with TALA vs PCT in pts without (not reached vs 6.3 mo; hazard ratio [HR]=0.42 [95% CI: 0.26, 0.66]; P=0.0001) and with (16.9 vs 6.3 mo; HR¼0.35 [0.22, 0.54]; P<0.001) dose reductions. Additional PRO results from the BR23 module will be presented.

Table: 269P Model estimated between arm overall change from baseline (EORTC QLQ-C30)

	TALA without Dose reduction vs PCT	P-Value	TALA with Dose reduction vs PCT	P-Value
GHS/QoL, & Function				
GHS/QoL	9.4	<0.001	7.5	<0.001
Physical	10.5	<0.001	9.1	<0.001
Role	12.5	<0.001	11.7	<0.001
Emotional	8.3	0.001	5.9	0.028
Cognitive	2.8	0.247	6.9	0.006
Social	8.3	0.004	9.6	0.004
Symptom				
Fatigue	-13.1	<0.001	-11.0	<0.001
Pain	-11.0	<0.001	-13.6	<0.001
Nausea/ vomiting	-4.5	0.099	-3.2	0.121
Dyspnea	-6.4	0.015	-2.5	0.398
Insomnia	-8.4	0.006	-7.6	0.005
Appetite loss	-13.4	<0.001	-10.5	<0.001
Diarrhea	-2.9	0.037	-2.1	0.192
Constipation	-5.7	0.034	-3.9	0.211

Conclusions:

In these subgroup analyses evaluating PROs in pts without/with TALA dose reductions vs PCT, improvement in GHS/QoL, and several functional and symptom scales were observed regardless of dose reductions.

Clinical trial identification:

NCT01945775

Phase Ib study of venadaparib, a potent and selective PARP inhibitor, in homologous recombination repair (HRR) mutated breast cancer

Background:

Poly ADP-ribose polymerase (PARP) is an enzyme that is central to the repair of DNA replication errors and are currently approved for ovary, breast, pancreas and prostate cancers. VASTUS study is a basket trial investigating the safety and efficacy of venadaparib in 6 cohorts of different tumors, including breast cancer.

Methods:

VASTUS is a phase 1b/2a seamless trial. Objectives of 1b part of the trial is to assess the safety and tolerability of venadaparib and determine recommended phase 2a dose, and to assess the anticancer activity of venadaparib based on the objective response rate (ORR) and the disease control rate (DCR). Metastatic breast cancer (mBC) patients with pathogenic germline BRCA 1/2 (gBRCA1/2) mutation, somatic BRCA 1/2 (sBRCA 1/2), ATM, PALB2, or RAD51C were enrolled. 10 patients' response evaluation is reviewed by data safety monitoring board (DSMB) to determine go/no-go decision into phase 2a.

Results:

Between Feb 2020 to Apr 2021, 14 patients were enrolled into HER2 negative mBC cohort, of which 10 patients were evaluated for DSMB review. Patients were administered with venadaparib doses ranging from 120mg to 240mg, based on emerging data from ongoing phase 1a dose finding study. Frequently observed all grade treatment related adverse event (TRAE) were as follows e anemia 8/14 (57%), nausea 7/14 (50%), neutropenia 7/14 (50%) and thrombocytopenia 4/14 (29%). Based on these results, phase 2a part of the breast cancer cohort has been opened with RP2D of 160mg. Of the 10 evaluable patients (8 gBRCAmt and 2 sBRCAmt), 1 patient had complete response (CR), 7 patients had partial responses (PR) and 2 patients had stable disease (SD), leading to 80% ORR and 100% DCR. Remaining 4 patients are under evaluation.

Conclusions:

Venadaparib showed efficacy in gBRCAmt or sBRCAmt mBC patients. Preliminary efficacy findings suggest strong potency of venadaparib in g/sBRCAmt mBC, while preliminary safety findings are comparable to commercially available PARP inhibitors. These findings warrant further investigation of venadaparib in breast cancer beyond gBRCAmt.

Clinical trial identification:

NCT04174716

Outcomes of patients (pts) who had received prior platinum (PP) therapy in the phase III EMBRACA trial of talazoparib (TALA) vs physician's choice of chemotherapy (PCT) in patients with germline BRCA1/2 mutated (gBRCA1/2mut) advanced breast cancer (ABC)

Background:

TALA is a poly (ADP-ribose) polymerase inhibitor approved in the US, EU, and other countries for the treatment of deleterious/suspected deleterious gBRCA1/ 2mut HER2-negative ABC. While TALA treatment in the phase 3 EMBRACA trial (NCT01945775) benefited pts regardless of PP, greater improvements in clinical outcomes for TALA vs PCT (capecitabine, eribulin, gemcitabine, or vinorelbine) were seen for pts not treated with PP (PFS hazard ratio [95% CI] 0.76 [0.40-1.45], P=0.41 for PP vs 0.52 [0.39-0.71], P < 0.0001 for no-PP subgroups). Exploratory analysis revealed that pts with a longer platinum-free interval were more likely to have a longer duration of survival, particularly in the TALA arm. This finding aligns with results from the ABRAZO trial, which showed greater clinical activity associated with longer platinum-free interval.

Methods:

In this post hoc analysis, outcomes were further explored in the PP subgroup of the EMBRACA trial population (data cut-off dates: PFS/ORR 15 Sept 2017; OS/exposure 30 Sept 2019). Previous neoadjuvant/adjuvant (neoadj/adj) platinum therapy was permitted if the pt had a disease-free interval of ≥6 months after the last dose.

Results:

Of 431 pts randomized, 76 had PP (46 TALA [22 as neoadj/adj treatment, 22 for advanced disease, 2 for both] and 30 PCT [14 neoadj/adj, 15 advanced, 1 both). Outcomes according to PP setting are shown (Table). Median (range) exposure in the PP subgroup was 6.4 (0.7-38.2) months for TALA (n=46) and 2.1 (0.2-9.2) months for PCT (n=29). Eleven pts (24%) received TALA for ≥12 months, while no pts received PCT for ≥12 months.

Table: 272P Efficacy outcomes by PP setting

	PP in neoadj/adj setting		PP in adv setting	
	TALA (n=24)	PCT (n=15)	TALA (n=24)	PCT (n=16)
PFS				
Events, n	14	9	13	10
Median (95% CI), mo	8.9 (4.2–23.2)	2.9 (1.4–11.3)	5.6 (1.6–NR)	4.3 (1.2–27.3)
ORR[a]				
% (95% CI)	71.4 (47.8–88.7)	21.4 (4.7–50.8)	22.2 (6.4–47.6)	25.0 (5.5–57.2)
OS				
Events, n	16	10	21	14
Median (95% CI), mo	20.9 (9.2–27.9)	16.8 (3.7–39.9)	9.6 (6.8–13.6)	9.4 (4.5–15.6)

Hazard ratios and odds ratios are not presented due to the small size subgroups, and as these were not prespecified analyses. [a]In pts with measurable disease (n=21/18 for TALA; n=14/12 PCT).

Conclusions:

Efficacy outcomes generally favored TALA over PCT in the PP subgroup in both early- and late-stage settings but were particularly favorable for pts who received PP as neoadj/adj treatment.

Clinical trial identification:

NCT01945775

Dalpiciclib, a novel CDK4/6 inhibitor, combined with pyrotinib for HER2+ advanced breast cancer: Interim results of a phase II trial

Background:

Given nearly all patients (pts) with human epidermal growth factor receptor 2-positive (HER2+) breast cancer (BC) developed resistance to trastuzumab eventually, novel approaches were urgently needed. This study aimed to evaluate the efficacy and safety of a novel CDK4/6 inhibitor dalpiciclib combined with pyrotinib, a HER2-targeted tyrosine kinase inhibitor (TKI), in HER2+ advanced BC.

Methods:

In the single-arm, phase II study, HER2+ advanced BC pts who had received no more than 1 line of systemic therapy in advanced setting were recruited. Prior CDK4/6 inhibitors and HER2 targeted TKI were not allowed. Eligible pts received dalpiciclib 125 mg daily for 3 weeks and 1 week off, and pyrotinib 400 mg daily in 28day cycles. The primary endpoint was objective response rate (ORR) as per RECIST 1.1. Using a 2-stage design, response in at least 13 of the first 23 pts allowed continued enrollment to a planned 41.

Results:

24 pts were enrolled in the first stage: HR+ disease, 54.2% (13/24); trastuzumab (tras)-treated, 66.7% (16/24); visceral metastasis, 91.6% (22/24). As of April 13th, 2021, of 23 evaluable pts 65.2% (15/23) had achieved confirmed ORR (15PR, 6SD, 2PD). Descriptive subgroup analyses of ORR were performed based on HR status (100% in HR- pts vs 38.5% in HR+ pts), previous lines of systemic therapy in advanced setting (69.2% in 0 line pts vs 60.0% in 1st-line pts) and resistance to trastuzumab (66.7% in tras-sensitive pts vs 63.6% in tras-resistant pts). 62.5% (15/24) of pts experienced grade 3/4 adverse events (AEs), and the common grade 3/4 AEs were neutropenia (13, 54.2%), leukopenia (12, 50%) and diarrhea (2, 8.3%). Most AEs were tolerable, only 1 patient needed dose reduction.

Conclusions:

Dalpiciclib combined with pyrotinib was associated with promising efficacy and manageable toxicity, and could be considered as a completely oral, chemo-free regimen for patients with HER2-positive advanced breast cancer. The enrollment of the second stage is ongoing.

Clinical trial identification:

NCT04293276

Phase II randomized study of trimebutine maleate and probiotics for abemaciclib-induced diarrhea in patients with HR-positive and HER2-negative advanced breast cancer (MERMAID) WJOG11318B

Background:
Abemaciclib-induced diarrhea (AID) occurs about 80-90% of patients, resulting in the impairment of QOL and compliance. Previous reports showed that over 40% patients had constipation due to prophylactic use of loperamide. We hypothesized that bifidobacterial and trimebutine maleate decrease the frequency of AID without increasing constipation.

Methods:
Women with estrogen receptor-positive, HER2-negative inoperable and/or recurrent breast cancers were enrolled and randomized into bifidobacterial (arm A) or bifidobacterial and trimebutine maleate (TM; arm B). Both arms received hormone therapies and abemaciclib over 28 days, and simultaneously were given at least more than 60mg/day bifidobacterial. Once patients experienced type-6 or -7 diarrhea on the Bristol scale, salvage use of loperamide was required. In addition to loperamide, patients in arm B were administered TM. Information on diarrhea and other side effects were reported by each patient with a medication diary and confirmed by the physician every two weeks. The primary endpoint is percentage of patients who experienced onset of grade 2 or higher diarrhea, and the statistical threshold was set at 40% based on historical data. The secondary endpoints are safety, frequency and duration of all-grade diarrhea, frequency of emesis and constipation, use of loperamide, and QOL/PRO in the 28-day study duration.

Results:
Fifty-three patients were enrolled and 51 patients completed the study treatments. Two patients terminated due to grade 4 hepatic dysfunction and exacerbation of comorbidities. Grade 2 diarrhea occurred in 54.2 and 50.0% of arm A and B. Only one patient occurred grade 3 diarrhea in each arm. The median duration of grade 2 or higher diarrhea was one day. Constipation of grade 2 or higher was observed in 4 and 3.6% in arm A and B.

Conclusions:
Although the incidence of diarrhea did not improve in both arms compared to historical data, bifidobacterial with or without TM shortened the duration of AID and prevented grade 3 or higher diarrhea, while the rate of constipation unchanged. As a result, the incidences of drug suspension/reduction were decreased.

Clinical trial identification:
WJOG11318B

Real-world outcomes associated with pyrotinib-based therapy for HER2-positive metastatic breast cancer

Background:

Pyrotinib, a novel irreversible pan-ErbB receptor tyrosine kinase inhibitor, has shown promising antitumor activity and manageable toxicity in HER2-positive metastatic breast cancer. However, the efficacy and safety of pyrotinib-based treatment in the real-world setting in China is limited. The aim of this study was to evaluate actual clinical outcomes in HER2-positive metastatic breast cancer treated with pyrotinib.

Methods:

In this retrospective study, 275 patients who received pyrotinib-based therapy for HER2-positive metastatic breast cancer from 12 institutions between March 2019 to August 2020 were initially included. Progression-free survival (PFS), objective response rate (ORR), and treatment-related adverse events (TRAEs) were analyzed.

Results:

Eight out of 275 patients were lost to follow up and the clinical outcomes of 267 patients were reported in this study. Of them, 213 (79.8%) patients had visceral metastatic lesions, 141 (52.9%) had more than 3 metastatic sites, 240 (89.9%) had received trastuzumab-based therapy, 54 (20.2%) had received lapatinib-based therapy, and 226 (84.7%) received pyrotinib-based therapy as a second or further line of treatment. The treatment regimens of 267 patients included pyrotinib alone (11.2%), pyrotinib in combination with capecitabine (58.4%), vinorelbine (6.0%), or nab-paclitaxel (5.2%). The median age and follow-up time were 51 years and 8.0 months, respectively. The median PFS of 267 patients was 11.0 months. Lapatinib-naïve patients had significantly longer PFS than lapatinib-treated patients (12.0 months vs. 5.0 months, P<0.0001). Of 254 patients who were available for ORR evaluation, 5 (2.0%) achieved complete response, and 84 (33.1%) had partial response. ORR for lapatinib-naive and lapatinib-treated patients was 38.0% and 24.5%, respectively. The most common grade 3 or 4 adverse events were diarrhea (18.0%), hand-foot syndrome (6.7%) and mucositis (2.6%).

Conclusions:

Among patients with HER2-positive metastatic breast cancer, pyrotinibbased therapy demonstrated encouraging effects and acceptable tolerability in the real-world setting. More data would be further analyzed and reported.

Genitourinary Tumor

Randomized, open-label, 3-arm phase III study comparing MK-1308A + lenvatinib and pembrolizumab (pembro) + belzutifan + lenvatinib versus pembro + lenvatinib as first line (1L) treatment for advanced clear cell renal cell carcinoma (ccRCC)

Background:

Combination therapy with the PD-1 inhibitor pembro and the VEGF inhibitor lenvatinib showed activity in patients (pts) with advanced ccRCC in the phase III KEYNOTE-581/CLEAR trial. The HIF-2a inhibitor belzutifan (MK-6482) and MK-1308A, a coformulation of pembro and the CTLA-4 inhibitor quavonlimab, have each shown antitumor activity in phase I/II trials. HIF-2a or CTLA-4 inhibition with PD1 and VEGF inhibition backbone combination may provide additional benefit as 1L treatment in ccRCC.

Trial design:

This open-label, phase III study (NCT04736706) is currently enrolling patients and will compare 2 new combination therapies with pembro + lenvatinib (control): pembro + belzutifan + lenvatinib (HIF arm) or MK-1308A + lenvatinib (CTLA arm). Eligible pts are adults with metastatic ccRCC, measurable disease per RECIST v1.1, KPS ≥70%, and no prior systemic therapy for advanced ccRCC. Pts will be stratified by IMDC score (0, 1/2, or 3-6) and region (North America, Western Europe, or rest of the world). The study will enroll w1431 pts, randomly assigned 1:1:1 to the HIF arm (belzutifan 120 mg + lenvatinib 20 mg oral QD + pembro 400 mg IV Q6W), CTLA-4 arm (MK-1308A [quavonlimab 25 mg + pembro 400 mg] IV Q6W and lenvatinib 20 mg oral QD), or control (pembro 400 mg IV Q6W + lenvatinib 20 mg oral QD). Treatment will be given until documented disease progression, withdrawal of consent, or other discontinuation event; pembro and MK-1308A will be limited to 18 infusions (~2 years). Response will be evaluated per RECIST v1.1 by BICR with CT/MRI imaging at week 12 from randomization through week 78, and Q12W thereafter. Adverse events (AEs) and serious AEs will be monitored throughout the study and for 90 days after treatment. Dual primary end points are progression-free survival per RECIST v1.1 and overall survival. Primary end points will be assessed in the HIF arm vs control and in the CTLA arm vs control for pts with IMDC intermediate/poor status and in all pts regardless of IMDC status. Secondary end points are objective response rate, duration of response, patient-reported outcomes, and safety.

Clinical trial identification:

NCT04736706

KEYNOTE-676 cohort B: Randomized comparator-controlled cohort to evaluate efficacy and safety of pembrolizumab (pembro) plus bacillus Calmette-Guérin (BCG) in patients with high-risk BCG treatment-naive non-muscle invasive bladder cancer (HR NMIBC)

Background:

The phase II KEYNOTE-057 study showed that pembro monotherapy provided effective antitumor activity and acceptable safety in BCG-unresponsive HR NMIBC pts. Combining pembro and BCG earlier in the disease course might provide anticancer activity superior to that of BCG monotherapy. KEYNOTE-676 (NCT03711032) is an open-label, comparator-controlled, phase III study of pembro + BCG vs BCG monotherapy in pts with HR NMIBC. The initial study (cohort A) is enrolling pts with persistent/recurrent HR NMIBC after BCG induction. Cohort B is a new, randomized cohort that will be used to evaluate BCG treatmentenaive or treatment-remote (> 2 years prior) pts.

Trial design:

Approximately 975 pts with blinded independent central reviewe confirmed histologic diagnosis of HR NMIBC (T1, high-grade Ta or carcinoma in situ [CIS]) will be included in cohort B. Pts must have undergone cystoscopy/TURBT ≤12 wk before random allocation, have provided tissue for biomarker analysis, and have an ECOG PS 0-2. Pts must not have been treated with BCG ≤2 y before randomization. Pts will be randomly assigned 1:1:1 to receive pembro 400 mg IV Q6W + BCG reduced maintenance (BCG induction then 1 maintenance cycle); pembro 400 mg IV Q6W + BCG full maintenance (BCG induction then maintenance cycles up to 18 mo); or BCG monotherapy (BCG induction then BCG maintenance up to 18 mo). Randomization will be stratified by NMIBC stage (CIS ± papillary disease or papillary disease alone) and PD-L1 expression (combined positive score [CPS] ≥10 or CPS <10). Disease status will be assessed by use of cystoscopy, urine cytology, and biopsy (as appropriate per protocol) Q12W from randomization through year 2, then Q24W through year 5; imaging with CTU will occur Q72W. The primary end point is event free survival (EFS) in all pts. Secondary end points are complete response rate, duration of response (DOR), and 12-mo DOR rate for pts with CIS and recurrence-free survival, overall survival, disease-specific survival, time to cystectomy, 24-mo EFS rate, time to deterioration in health-related quality of life, safety, and tolerability.

Clinical trial identification:

NCT03711032

SunRISe-1: Phase IIb study of TAR-200 in combination with cetrelimab (CET), TAR-200 alone, or CET alone in participants with high-risk non-muscle invasive bladder cancer unresponsive to intravesical bacillus Calmette-Guérin who are ineligible for or elected not to undergo radical cystectomy

Background:

Treatment options are limited for patients (pts) with high-risk non-muscle-invasive bladder cancer (HR-NMIBC) unresponsive to intravesical bacillus CalmetteeGuérin (BCG). TAR-200 is an intravesical drug-delivery system which provides local continuous release of gemcitabine within the bladder. This study will assess rate of complete response (CR) upon treatment with TAR-200 + systemic CET (antie PD-1 antibody), TAR-200, and CET in BCG-unresponsive pts with HR-NMIBC ineligible for or who decline radical cystectomy.

Trial design:

SunRISe-1 (NCT04640623) is an open-label, parallel-group, multicenter phase IIb study designed to assess efficacy and safety of TAR-200 + CET, TAR-200 alone, and CET alone in participants with BCG-unresponsive HR-NMIBC. Eligible participants are aged >/=18 y with ECOG PS 0-2 and histologically confirmed carcinoma-in-situ, with or w/o papillary disease (T1, high-grade Ta), and within 12 mo of completing BCG. Participants (N=200) are randomized 2:1:1 to TAR-200 + CET (cohort 1, n = 100), TAR-200 (cohort 2, n = 50), or CET (cohort 3, n = 50). In cohorts 1 and 2, TAR-200 is dosed every 3 wks (Q3W) through wk 24, and Q12W thereafter until wk 96. Cystoscopy, urine cytology, and MRI/CT are performed at baseline. Subsequent cystoscopy and centrally read urine cytology occur Q12W through y 2, then Q24W until end of y 3, with additional disease assessments in y 4 and y 5 in accordance with institutional standards of care. Primary endpoint for the 3 cohorts is overall CR rate at any time point. Secondary endpoints include duration of response (time of first CR achieved to first evidence of recurrence, progression, or death for participants who achieve a CR), overall survival, PK, safety/tolerability, and patient reported outcomes. Participants are being enrolled at w165 study sites in 16 countries. Enrollment initiated January 2021.

Clinical trial identification:

NCT04640623

Systematic literature review (SLR) and network meta-analysis (NMA) of first-line (1L) therapies for locally advanced/metastatic urothelial carcinoma (la/mUC)

Background:

Gemcitabine+ cisplatin (GC) or carboplatin (GCa) are the global 1L standard of care (SOC) therapies for la/mUC; however, prognosis is poor and <50% of patients receive 1L chemotherapy. Several alternative 1L regimens are recognized by guidelines/used in practice, and new therapies are emerging. This SLR and NMA of randomized controlled trials (RCTs) compared outcomes of alternative 1L regimens with SOC to better understand the unmet need.

Methods:

An SLR of phase II/III RCTs was conducted in accordance with PRISMA and NICE guidelines to identify 1L la/mUC therapies (01/2000-05/2020). Two networks were created: cisplatin (cis)-eligible/mixed eligibility and cis-ineligible. Comparative efficacy and safety were assessed via NMA under a Bayesian framework. Survival outcomes with 1L regimens vs SOC (GC/GCa) are reported.

Results:

Among 1765 publications identified in the SLR, 96 representing 39 unique RCTs were selected for data extraction. Of these, 11 were included in the cis-eligible/ mixed network and 6 in the cis-ineligible network. The NMA excluded therapies that were not effective or adopted in clinical practice; 3 maintenance trials were identified but excluded due to differences in study design precluding comparisons. Based on a fixed effects meta-analysis of SOC arms in each network, median overall survival (OS) was 13.2 mo (95% CI 12.4-14.0) for the cis-eligible/mixed and 9.7 mo (95% CI 6.712.8) for the cis-ineligible network; progression-free survival (PFS) was 6.9 (95% CI 6.3-7.4) and 5.6 mo (95% CI 4.9-6.3), respectively. OS and PFS were similar to SOC across all interventions included in the NMA (all credible intervals [CrI] crossed or were close to 1; Table).

Table: 705P HR for OS and PFS compared with SOC (GC/GCa for cis-eligible, GCa for cis-ineligible)

Comparator	OS	PFS
Cis-eligible, HR (95% CrI)		
ddMVAC	0.7 (0.5, 1.0)	0.7 (0.5, 0.9)
ddGC	0.7 (0.4, 1.1)	0.5 (0.3, 0.9)
Atezo+GC/GCa	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)
Durva+tremelimumab	0.9 (0.7, 1.0)	–
Paclitaxel+GC/GCa	0.9 (0.7, 1.0)	0.9 (0.7, 1.0)
Pembro+GC/GCa	0.9 (0.7, 1.0)	0.8 (0.7, 0.9)
MVAC	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)
Pembro	0.9 (0.8, 1.1)	–
Durva	1.0 (0.8, 1.2)	–
Atezo	1.0 (0.8, 1.2)	–
Docataxel+cis	1.4 (1.0, 2.0)	1.6 (1.1, 2.3)
Cis-ineligible, HR (95% CrI)		
Durva+tremelimumab	0.9 (0.7, 1.1)	–
Viniflunine+gem	1.1 (0.6, 1.9)	0.8 (0.4, 1.3)
Oxaliplatin+gem	1.4 (0.8, 2.3)	1.1 (0.7, 1.8)
M-CAVI	–	1.0 (0.7, 1.3)

Conclusions:

Survival outcomes are similar and remain poor among existing 1L therapies for la/mUC, highlighting the continued unmet need in this largely incurable population. The impact of maintenance could not be evaluated within the framework of this 1L NMA.

Efficacy and safety of relugolix vs leuprolide (LEU) in men with advanced prostate cancer (APC): Clinical subgroup analysis from the phase III HERO study

Background:

Relugolix, the once-daily oral GnRH receptor antagonist, demonstrated suppression of testosterone to castrate levels in 96.7% of patients, and a 54% lower risk of major adverse cardiovascular events relative to LEU in the HERO study (Shore N, 2020 NEJM 382;23). A subgroup analysis was undertaken to further evaluate relugolix treatment for various clinical subgroups included in the HERO study.

Methods:

The phase III HERO study was designed to evaluate relugolix in men with APC. Assessments included sustained testosterone suppression to castrate levels (<50 ng/dL) from day 29 through 48 weeks, early and profound castration rates, and safety parameters. Subgroups analyzed included men with 1 of 3 clinical disease presentations: biochemical (PSA) or clinical relapse following local primary intervention (RELAPSE), newly diagnosed androgen-sensitive metastatic disease (METASTATIC), or advanced localized disease (ALD).

Results:

Of the 930 men (relugolix: 622; LEU: 308) who received study drug, 467 (50.2%), 211 (22.7%), and 252 (27.1%) men were enrolled with RELAPSE, METASTATIC, and ALD, respectively. Across all clinical subgroups, point estimates for sustained castration rates for men receiving relugolix were consistent with the overall sustained castration rate. Differences in sustained castrations rates at week 48 between relugolix and LEU groups were 9.4% (95% CI:3.6%, 15.2%) in men with RELAPSE, 11.3% (95% CI: 2.7%, 19.9%) in METASTATIC, and 2.1% (95% CI: -3.4%, 7.6%) in ALD disease. The incidence of grade !3 adverse events were higher in ALD for the LEU group vs relugolix group (relugolix: 13.4%; LEU: 22.5%). The incidence of grade !3 adverse events was higher overall in METASTATIC men (relugolix: 26.2%; LEU: 28.6%) vs the overall population (relugolix: 18.0%; LEU: 20.5%), as expected.

Conclusions:

Treatment with relugolix was associated with improved castrations rates vs LEU in men with a broad range of clinical presentations for APC. Treatments were well-tolerated across the subgroups analyzed, with higher rates of grade !3 adverse events in men in the METASTATIC group.

Clinical trial identification:

NCT03085095

Dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (dd-MVAC) or gemcitabine and cisplatin (GC) as perioperative chemotherapy for patients with muscle invasive bladder cancer (MIBC): Results of the GETUG/AFU VESPER V05 phase III trial

Background:

The optimal perioperative chemotherapy regimen for patients (pts) with MIBC is not defined.

Methods:

Between February 2013 and February 2018, 500 pts were randomized in 28 French centers and received either 4 cycles of GC every 3 weeks or 6 cycles of dd-MVAC every 2 weeks before surgery (neoadjuvant group) or after surgery (adjuvant group). The primary endpoint of the VESPER trial was the progression-free survival (PFS) at 3 years.

Results:

437 patients (88%) received neoadjuvant chemotherapy, 60% of pts received the planned 6 cycles in the dd-MVAC arm and 84% received 4 cycles in the GC arm. Thereafter, 91% and 90% of pts underwent surgery, respectively. Organ-confined response (< ypT3N0) was observed more frequently in the dd-MVAC arm (77% vs 63%, p=0.001). In the adjuvant group, 40% of pts received 6 cycles in the dd-MVAC arm, 81% received 4 cycles in the GC arm. In the perioperative setting of the VESPER trial, PFS at 3 years was improved in the dd-MVAC arm (64% vs 56%, HR=0.77 (95% CI, 0.57-1.02), p¼0.066), as was also time to progression (TTP) (3-year rate: 69% vs 58%, HR=0.68 (95% CI, 0.50-0.93), p=0.014). In the neoadjuvant group, the PFS at 3 years was significantly higher for the dd-MVAC arm (66% vs 56%, HR=0.70 (95% CI, 0.51-0.96), p=0.025). In the adjuvant group, the results were not conclusive due to the limited sample size (n¼56).

Conclusions:

n the VESPER phase III trial, we reported a benefit on PFS at 3 years for the dd-MVAC arm. In the neoadjuvant group, a better bladder tumor local control with a significant improvement on PFS at 3 years were observed in the dd-MVAC arm.

Clinical trial identification:

NCT 018 12369

A phase II prospective trial of frontline cabozantinib in metastatic collecting ducts renal cell carcinoma: The BONSAI trial (Meeturo 2)

Background:

Metastatic collecting ducts carcinoma (mCDC) is biologically poorly characterized and under-represented in prospective randomized trials.

Methods:

This prospective, monocentric, phase II trial tested cabozantinib (cabo) 60 mg in treatment-naïve mCDC patients (pts). Primary endpoint was objective response rate (ORR) per RECIST 1.1. Secondary endpoints were progression-free survival (PFS), overall survival and safety profile. Exploratory objectives were: to identify somatic mutations by targeted DNA sequencing; to define molecular subtypes, signatures and transcript fusions genes by RNA sequencing. A central pathological review was mandatory. The study was based on a Simon's two-stage optimal design.

Results:

From January 2018 to November 2020, 25 pts were enrolled, of whom 23 started treatments. Median age was 66 years, 19 pts were male. The most common metastatic sites were lymph nodes and bone (15 and 13 pts), followed by lung and liver (10 and 4 pts). Median follow up was 8 months. ORR was 35% (1 CR and 7 PR). Median PFS was 6 months. All pts reported at least one grade (G) 1-2 adverse event (AE): the most common were fatigue (43%), hypothyroidism (28%), stomatitis (28%), anorexia (26%), hand-foot syndrome (13%), hypertension (17%), and diarrhea (13%). Five pts reported G3 AEs (2 thromboembolic events, 2 arterial hypertensions, 1 fatigue), while no G4-5 AEs were reported. 17% of pts required dose reduction. DNA sequencing was successful in 21 (91%) patients. All tumors were microsatellite stable. No association between tumor mutational burden and response to cabo was observed. The most affected pathways were chromatin-modifying enzymes (46%) and adaptive immune system (23%). Responsive pts (PFS > 6 months) showed high frequency of mutations affecting deubiquitination, cell-cell communication, and TGF-b signaling. Non-responders were frequently mutated in chromatin remodeling, transcriptional regulation and WNT pathways.

Conclusions:

The study met its primary endpoint showing promising efficacy and acceptable tolerability of cabo in mCDC pts. Mature results according to mutational profiles and gene signatures will be presented.

Clinical trial identification:

NCT03354884

Conditional survival and 5-year follow-up in Check Mate 214: First-line nivolumab + ipilimumab (N+I) versus sunitinib (S) in advanced renal cell carcinoma (aRCC)

Background:

Conditional survival, used to predict sustained treatment benefit, accounts for time since treatment initiation and provides improved prognostic information at landmark time points. Conditional survival in aRCC patients (pts) was estimated in Check Mate 214 with a minimum 5-y follow-up (median follow-up, 67.7 mo).

Methods:

Pts with clear cell aRCC were randomized to N 3 mg/kg + I 1 mg/kg Q3W4 then N 3 mg/kg Q2W vs S 50 mg QD for 4 wk on, 2 wk off. Trial endpoints included overall survival (OS), progression-free survival (PFS) and objective response rate (ORR; both per independent radiology review using RECIST v1.1) in IMDC intermediate/poor risk (IP; primary), intent-to-treat (ITT; secondary), and favorable risk (FAV; exploratory) pts. Conditional survival-the probability of remaining alive (cOS), progression-free (cPFS), or in response (cDOR) 2 y beyond landmark time points of 2 y and 3 y-was analyzed.

Results:

Superior OS, PFS, ORR and complete response (CR) benefits with N+I vs S were maintained in ITT and IP pts and are summarized together with outcomes in FAV pts (Table). Consistently higher cOS, cPFS, and cDOR rates were observed with N+I vs S in ITT and IP pts at all time points (Table). In the N+I arm, the probability of remaining alive 2 y beyond the 3-y landmark (cOS) was 81% (ITT), 79% (IP), and 85% (FAV). The probability of remaining progression-free (cPFS) for an additional 2 y beyond the 3-y landmark was 89% (ITT), 90% (IP), and 85% (FAV). For N+I pts who were in response at 3 y, the probability of remaining in response (cDOR) for an additional 2 y was 89% (ITT), 90% (IP), and 85% (FAV). No new safety signals emerged with longer follow-up.

Table: 661P

	ITT N+I n = 550	S n = 546	IP N+I n = 425	S n = 422	FAV N+I n = 125	S n = 124
OS HR (95% CI)	0.72 (0.62-0.85)		0.68 (0.58-0.81)		0.94 (0.65-1.37)	
mOS, mo	56	38	47	27	74	68
PFS HR (95% CI)	0.86 (0.73-1.01)		0.73 (0.61-0.87)		1.60 (1.1-2.3)	
mPFS, mo	12	12	12	8	12	29
ORR (95% CI), % CR, %	39 12	32 3	42 11	27 2	30 13	52 6
DOR HR (95% CI)	0.49 (0.35-0.68)		0.46 (0.31-0.66)		0.62 (0.32-1.21)	
mDOR, mo	NR	25	NR	20	61	33
2-y conditional OS from landmark, %[a] 2 y 3 y	76 81	72 72	75 79	68 72	77 85	78 72
2-y conditional PFS from landmark, %[a] 2 y 3 y	87 89	53 57	91 90	50 62	73 85	56 50
2-y conditional DOR from landmark, %[a] 2 y 3 y	91 89	57 63	92 90	64 88	89 85	53 45

[a]n = pts alive, progression free, or in response at each time point (data not shown). DOR, duration of response; NR, not reached.

Conclusions:

Long-term follow-up in this 5-y analysis demonstrated durable efficacy benefits with N+I vs S. Conditional survival results predict increased probability of durable OS, PFS, and response with N+I at 2-y and 3-y landmarks, and highlight the long-term clinical benefit with N+I in pts with aRCC.

Clinical trial identification:

NCT02231749

First-line nivolumab + cabozantinib vs sunitinib in patients (pts) with advanced renal cell carcinoma (aRCC) in subgroups based on prior nephrectomy in the Check Mate 9ER trial

Background:

First-line (1L) nivolumab + cabozantinib (N+C) significantly improved progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) vs sunitinib (S) in aRCC pts in the phase III Check Mate 9ER trial. Pts without upfront nephrectomy have poor prognoses and clinical trial data in this population remain limited. Assessment of how different baseline characteristics may impact outcomes with N+C vs S in aRCC pts is of clinical interest.

Methods:

Pts with any IMDC risk and clear cell aRCC were randomized to N 240 mg IV Q2W + C 40 mg PO QD vs S 50 mg PO QD (4 weeks of 6-week cycles). In this post hoc exploratory analysis, efficacy was evaluated in subgroups with and without prior nephrectomy. PFS and ORR were assessed per RECIST v1.1 by blinded independent central review.

Results:

Of 651 intent-to-treat (ITT) pts, 455 had prior nephrectomy (N+C, n ¼ 222; S, n = 233) and 196 had no prior nephrectomy (N+C, n= 101; SUN, n= 95). Of pts with prior nephrectomy, 24.3% (N+C) and 30.9% (S) underwent nephrectomy within 3 months of enrollment. Baseline characteristics were generally balanced between arms within subgroups. Versus pts without prior nephrectomy, a higher proportion of pts with prior nephrectomy had a lower tumor burden, more favorable IMDC risk scores, and derived greater efficacy benefits with either N+C or S. Notably, N+C improved PFS, ORR, complete response, and response durability outcomes vs S regardless of nephrectomy status (Table). Of evaluable pts without prior nephrectomy, median reduction in target kidney lesions was 30% (N+C; n = 53) vs 16% (S; n = 51). OS benefits were observed with N+C vs S in pts with prior nephrectomy; longer follow-up is needed to characterize OS outcomes between arms in pts without prior nephrectomy.

Table: 663P

Outcome[a]	Prior nephrectomy		No prior nephrectomy	
	N+C n = 222	S n = 233	N+C n = 101	S n = 95
PFS HR (95% CI)	0.50 (0.39–0.64)		0.62 (0.43–0.89)	
Median PFS (95% CI), mo	19.4 (15.6–22.9)	8.9 (7.0–10.4)	11.3 (8.8–16.0)	7.0 (5.5–9.4)
18-mo PFS probability, %	54	27	33	18
OS HR (95% CI)	0.54 (0.37–0.78)		0.87 (0.57–1.35)	
Median OS (95% CI), mo	NR (NE)	NR (28.4–NE)	23.8 (21.4–NE)	29.5 (19.4–29.5)
18-mo OS probability, %	84	72	68	61
ORR (95% CI), %	61 (54–67)	30 (25–37)	42 (32–52)	23 (15–33)
CR, %	11	6	5	0
Ongoing response probability at 18 mo, %	59	47	41	25

[a]Data based on minimum follow-up of 16 mo (median 23.5 mo) for OS in ITT pts, acknowledging censoring at later timepoints. CR, complete response; NE, not estimable; NR, not reached.

Conclusions:

N+C provided improved efficacy benefits vs S in pts with and without prior nephrectomy. These results continue to support N+C as a 1L treatment option for pts with aRCC.

Clinical trial identification:

NCT03141177

Final results from phase I trial of cabozantinib/nivolumab (CaboNivo) alone or with ipilimumab (CaboNivoIpi) and peripheral immunity in metastatic genitourinary (mGU) tumors

Background:

Cabozantinib (Cabo) exhibits innate and adaptive immunomodulation providing a rationale for a phase I trial of CaboNivo or CaboNivoIpi in mGU tumors. We present the final results of the phase I with correlative peripheral blood immune subsets.

Methods:

This phase I dose escalation and expansion study in pts with advanced mGU tumors refractory to front-line therapy. The objectives were to determine the clinical activity, safety/tolerability of both combinations CaboNivo (n=60) and CaboNivoIpi (n=56) and correlate activity with immunosuppressive peripheral blood immune subsets.

Results:

120 pts (median age 59 yrs; range 20-82 yrs) were enrolled including urothelial carcinoma; renal cell carcinoma; bladder adenocarcinoma; penile carcinoma, and other mGU tumors: 64 pts received CaboNivo and 56 CaboNivoIpi. Median follow-up was 40.4 months (range 2.2-62.2). The ORR for 108 evaluable pts was 38% (95% CI: 28.8-47.8%) with 12 complete responses (11.1%) and 29 partial responses (26.9%). The progression free survival (PFS) was 5.5 months (95% CI: 4.5-10.1), with overall survival (OS) of 15.9 months (95% CI: 11.6 -23.9). CaboNivo and CaboNivoIpi decreased immunosuppressive monocytic MDSCs (M-MDSCs) and classical monocytes ($p = 0.027$, $p<0.0001$), and increased the CD8+/CD4+ T cell ratio ($p = 0.0001$). Dendritic cell (DC) subsets (CD1c+ mDC, CD141+ mDC, CD303+ pDC) decreased with treatment ($p < 0.001$, $p = 0.0026$, $p<0.0001$). CTLA-4 and Tim-3 on T cells increased ($p<0.0001$, $p<0.0001$) and higher CTLA-4 on CD4+ T cells was associated with higher PFS/OS (CaboNivoIpi OS: $p = 0.046$; CaboNivo PFS: $p = 0.0347$; CaboNivo OS $p = 0.0335$). CaboNivo treatment increased proliferative activated T cells (Ki67+HLA-DR+, Ki67+ICOS+, Ki67+GITR+) at C2 but not C3, and this increase correlated with better PFS ($p=0.0097$) and OS ($p=0.004$). CaboNivoIpi strongly increased these subsets at both C2D1 ($p <0.0001$) and C3D1 ($p ¼ 0.0004$) without association with OS/ORR.

Conclusions:

CaboNivo and CaboNivoIpi showed promising clinical activity and manageable safety in mGU tumors. These therapies modulated innate and adaptive peripheral blood immune subsets with response distinctive patterns.

Clinical trial identification:

NCT02496208

Matching-adjusted indirect comparison (MAIC) of health-related quality of life (HRQoL) of nivolumab plus cabozantinib (N+C) vs pembrolizumab plus axitinib (P+A) in previously untreated advanced renal cell carcinoma (aRCC)

Background:

The landscape for first-line (1L) aRCC is rapidly evolving, with P+A and N+C recommended as standard of care irrespective of risk group by the European Association of Urology and the European Society for Medical Oncology. P+A and N+C have similar modes of action and demonstrated a significant efficacy benefit versus sunitinib (S), although no head-to-head data exist. As aRCC significantly impacts HRQoL, understanding HRQoL benefits of these 2 treatments is of interest to inform clinical decision making.

Methods:

An anchored MAIC was conducted using patient-level data from the CheckMate 9ER trial (NCT03141177; N+C vs S) and aggregate published data from the KEYNOTE-426 trial (NCT02853331; P+A vs S). Outcomes included Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index e Disease Related Symptoms (FKSI-DRS) and EQ-5D visual analog scale (EQ VAS) due to limited published HRQoL data from KEYNOTE-426. Hazard ratios for time to first and confirmed deteriorations (TTFD and TTCD, respectively) and baseline to week 30 least squares mean differences in these outcomes were re-estimated for CheckMate 9ER using a weighted population and indirectly compared with those in KEYNOTE-426 via a Bayesian framework.

Results:

A total of 651 CheckMate 9ER patients (pts) were matched to 861 KEYNOTE426 pts using age, region, risk group, sites of metastatic disease, and prior nephrectomy. Results from the MAIC favored N+C versus P+A in all outcomes with statistically significant differences for FKSI-DRS and TTFD in EQ VAS score (Table).

Table: 668P

Outcome	MAIC results, N+C vs P+A
TTFD, HR (95% CrI)	
EQ-5D VAS	0.73 (0.55–0.96)[a]
TTCD, HR (95% CrI)	
EQ-5D VAS	0.72 (0.52–1.01)
FKSI-DRS	0.48 (0.33–0.69)[a]
Change from baseline at week 30, LSMD (95% CrI)	
EQ-5D VAS	2.55 (−0.88 to 5.98)
FKSI-DRS	1.85 (0.96–2.74)[b]

[a]The 95% CrI does not contain 1. HR < 1 favors N+C over P+A. [b]The 95% CrI does not contain 0. LSMD > 0 favors N+C over P+A. CrI, credible interval; HR, hazard ratio; LSMD, least squares mean difference.

Conclusions:

In pts with 1L aRCC, MAIC analyses indicate that compared with P+A, N+C demonstrated a significant improvement in DRS and significantly delayed deterioration in HRQoL. These results, combined with the efficacy and favorable safety profile of N+C, may further inform treatment decisions of clinicians and pts with 1L aRCC.

Clinical trial identification:

NCT03141177; NCT02853331

Subsequent therapy following pembrolizumab + axitinib or sunitinib treatment for advanced renal cell carcinoma (RCC) in the phase III KEYNOTE-426 study

Background:

In the phase III KEYNOTE-426 study, pembrolizumab + axitinib showed significant improvement in OS, PFS, and ORR vs sunitinib in patients with RCC. This analysis assessed subsequent treatment in patients enrolled in KEYNOTE-426.

Methods:

Treatment-naive patients with clear cell RCC, KPS score !70%, and measurable disease (RECIST v1.1) were randomly assigned 1:1 to receive pembrolizumab 200 mg IV every 3 weeks for up to 35 doses + axitinib 5 mg orally twice daily or sunitinib 50 mg once daily (4 weeks on/2 weeks off) until progression, toxicity, or withdrawal. Type of and time to subsequent therapy were assessed.

Results:

Of patients in the pembrolizumab + axitinib arm and in the sunitinib arm, 81.4% (349/432) and 90.6% of patients (385/429), respectively, discontinued treatment; radiologic or clinical PD was the most common reason for discontinuation in both (pembrolizumab + axitinib: 65.0% [227/349]; sunitinib: 68.1% [262/385]). Of patients who discontinued, 58.5% of patients (204/349) in the pembrolizumab + axitinib arm and 73.0% (281/385) in the sunitinib arm received subsequent therapy (Table). Although a similar proportion of patients in both arms received subsequent therapy with a VEGF/VEGFR inhibitor (pembrolizumab + axitinib: 88.2% [180/204]; sunitinib: 68.7% [193/281]), a greater proportion of patients in the sunitinib arm (74.4% [209/281]) received subsequent PD-1/PD-L1 inhibitor therapy than in the pembrolizumab + axitinib arm (21.6% [44/204]). Of patients in the pembrolizumab + axitinib arm and the sunitinib arm, 32.4% (66/204) and 22.8% (64/281), respectively, received other therapies.

Conclusions:

The superior efficacy of pembrolizumab + axitinib compared with sunitinib is observed despite the increased use of subsequent therapy in the sunitinib arm. These data continue to support the use of first-line pembrolizumab + axitinib in patients with RCC.

Table: 669P

n/N (%)	Pembrolizumab + Axitinib N = 432	Sunitinib N = 429
Discontinued treatment	349/432 (80.8)	385/429 (89.7)
Owing to radiographic PD	214/349 (61.3)	243/385 (63.1)
Owing to clinical PD	13/349 (3.7)	19/385 (4.9)
Other[a]	122/349 (35.0)	123/385 (31.9)
Received subsequent therapy	204/349 (58.5)	281/385 (73.0)
Any PD-1/PD-L1 inhibitor	44/204 (21.6)	209/281 (74.4)
Any VEGF/VEGFR inhibitor	180/204 (88.2)	193/281 (68.7)
Other	66/204 (32.4)	64/281 (22.8)

[a]Adverse event, excluded medication, CR, nonadherence, nonstudy anticancer therapy, physician decision, patient withdrawal.

Clinical trial identification:

NCT02853331

Cabozantinib associated with concomitant radiotherapy or a bone targeted agent (multimodal approach, results from the CABOREAL study post-hoc analysis)

Background:

Cabozantinib (Cabo) is approved in Europe for the treatment of patients (pts) with metastatic renal cell carcinoma (mRCC) in treatment-naïve adults with intermediate or poor risk or following prior VEGF-targeted therapy. CABOREAL describes the use of Cabo in a real-world setting (RWS) in the largest unselected population to date of pts with mRCC who received at least one dose of Cabo. We report here, the use and the activity of Cabo in subgroup of pts who received concomitant radiotherapy (cRT) or concomitant bone targeted agents (cBTA).

Methods:

Data were retrospectively collected from 26 centers (NCT03744585). Pts were treated with Cabo via the French Early Access Program from Sep 12, 2016 to Feb 19, 2018. Descriptive analyses were conducted. Median overall survival since Cabo initiation (mOS) was assessed but safety was not.

Results:

Overall, 410 pts were included. 85 pts received cRT, 24.7% of them received Cabo as 2nd line therapy. 35 pts received cBTA (denosumab or bisphosphonates). Cabo patterns of use are summarized in the table. In the subgroup of pts treated with Cabo and cRT vs no cRT, the median duration of treatment (mDOT) (range) was 10.9 months (m) (0.6;29.1) vs 6.5 m (0.1;28.0) ($p<0.001$), the mOS was 16.6 m vs 14.2 m and the overall survival rate at 24 m (OS24) was 31.7% vs 29.5%. In the subgroup of pts with bone metastasis (met) treated by Cabo and cBTA vs no cBTA the mDOT (range) was 8.2 m (1.1;22.7) vs 6.9 m (0.1;29.0) (not significant), the mOS 14.8 m vs 12.4 m and the OS24 was 25.3% vs 26.2%.

Table: 670P

Pts subgroup	N	Initiation dose at 60 mg %	Average daily dose median mg	Dose modification %
Overall population				
- Cabo and cRT - Cabo and no cRT	85 325	75.3 69.8	37.9 40.0	61.2 58.0
Population with bone met				
- Cabo and cRT for bone met - Cabo and no cRT for bone met	62 171	75.8 69.0	40.2 40.1	56.5 53.8
- Cabo and cBTA - Cabo and no cBTA	35 194	68.6 71.0	36.7 40.5	68.6 51.8

Conclusions:

In a RWS of Cabo use in 2nd/3rd line or beyond for mRCC, the use of cRT was associated with longer DOT suggestive of increase benefit of therapy management strategy. A similar trend was noted in pts treated with cBTA in pts with bone met. A multimodal approach with cRT and cBTA was associated with longer time on treatment with Cabo.

Clinical trial identification:

NCT03744585

Real-world study of cabozantinib in patients with advanced renal cell carcinoma (aRCC) after VEGF-targeted therapy (CASSIOPE): Interim data for patients who had received prior nivolumab

Background:

Cabozantinib is a tyrosine kinase inhibitor approved in Europe for use in adults with aRCC who have received prior VEGF-targeted therapy, or are treatment naive with intermediate or poor risk. We report interim data on the real-world use of cabozantinib in patients with aRCC who have received prior VEGF-targeted therapy and nivolumab.

Methods:

CASSIOPE (NCT03419572) is an ongoing, non-interventional study of cabozantinib in patients with aRCC who have received prior VEGF-targeted therapy; a pre-planned interim analysis was conducted when 50% of patients had completed ≥ 3 months of follow-up. This post-hoc analysis assessed patient characteristics, best overall response (BOR) based on RECIST 1.1, dose modifications and tolerability at 3 months in the patient subgroup who had received prior nivolumab.

Results:

CASSIOPE included 337 patients treated with cabozantinib following prior VEGF-therapy. Of all first-line therapies, sunitinib (56.7%) and pazopanib (32.3%) were most common; nivolumab was the most common second-line therapy. In total, 154 (45.7%) patients had received prior nivolumab in any line (median age, 67.5 years; 70.8% male, 87.7% clear-cell histology, 96.1% metastatic disease; 80.8% ECOG PS 0e 1). Within this subgroup, 58.4% of patients initiated cabozantinib at 60 mg/day; median daily dose during the study was 40 mg. Dose modifications and safety data are summarized in the table. During the first 3 months, 58 patients in the prior nivolumab subgroup had an evaluable BOR: 39.7% had a partial response, 44.8% stable disease and 12.1% progressive disease (not evaluable for 3.4% of the patients).

Table: 672P

Dose modification, n (%)	Prior nivolumab CASSIOPE subgroup (n = 154)	
	Any	Due to adverse events
Any	121 (78.6)	103 (66.9)
Reduction	72 (46.8)	67 (43.5)
Interruption	84 (54.5)	72 (46.8)
Discontinuation	40 (26.0)	22 (14.3)
Most common treatment-emergent adverse events of any grade, n (%)		
Any	146 (94.8)	
Diarrhea	56 (36.4)	
Palmar-plantar erythrodysaesthesia syndrome	39 (25.3)	
Asthenia	35 (22.7)	
Nausea	34 (22.1)	
Fatigue	33 (21.4)	
Hypertension	32 (20.8)	
Decreased appetite	26 (16.9)	
Mucosal inflammation	25 (16.2)	
Stomatitis	23 (14.9)	
Deaths, n (%)		
All cause	17 (11.0)	

Conclusions:

This post-hoc analysis of interim CASSIOPE data suggests that cabozantinib, used in routine care, is broadly tolerable and may offer tumor response in patients previously treated with VEGF-targeted therapy and nivolumab.

Clinical trial identification:

NCT03419572

Cabozantinib-nivolumab (CN) vs. nivolumab-cabozantinib (NC) in patients (pts) with metastatic clear cell renal cell carcinoma (mRCC) following one prior VEGFR tyrosine kinase inhibitor (TKI): The CABIR multicentric matching adjusted study

Background:

N and C are two approved agents after a prior TKI in mRCC pts. However, the optimal sequence, CN or NC, is still unknown. The superiority of C over everolimus in pts with prior anti-PD-1 (HR 0.22) in the METEOR trial suggests a sensitizing role of N. We conducted the CABIR study to identify the optimal sequence between CN and NC after one prior TKI.

Methods:

In this multicenter retrospective study, we collected data from pts receiving CN or NC, after 1st line TKI. A propensity score (PS) was calculated to handle bias selection, and sequence comparisons were carried out with a cox model on a matched sample 1:1. A weighted 1:2 matching and a cox model with PS as adjusting covariate were also performed as sensibility analysis. Primary endpoint was progression-free survival (PFS) from the start of 2nd line to progression in 3rd line (PFS2/ 3), secondary endpoint was overall survival from 2nd line (OS2).

Results:

Among the 135 pts included, 38 (28%) and 97 (72%) received CN and NC, respectively. Overlap in PS allowed 1:1 matching of all CN pts, with pts' characteristics being well balanced. For both PFS2/3 and OS2, NC was superior to CN (PFS2/3: HR ¼ 0.58 [0.34-0.98], p¼0.043; OS2: 0.66 [0.42-1.05], p¼0.080). Considering PFS2 and PFS3 separately, the only significant difference was in PFS3 in favor of C over N (p¼0.0012). This difference was solely driven by pts previously treated with 6 to 18 months of 1st line TKI. Interaction between sequence and 1st line duration was significant in the matched cohort.

Table: 673P

Results of cox model

Population	Number of patients (CN vs NC)	Outcome	HR (95%CI)	P-value
All with PS as covariate	135 (38 vs 97)	PFS2/3 OS2	0.62 [0.39-0.98] 0.64 [0.43-0.95]	0.039 0.028
Matched 1:1	76 (38 vs 38)	PFS2/3 OS2	0.58 [0.34-0.98] 0.66 [0.42-1.05]	0.043 0.080
Matched 1:2	152 (76 vs 76)	PFS2/3 OS2	0.63 [0.43-0.92] 0.65 [0.46-0.90]	0.016 0.009

Conclusions:

We report here in a matching-adjusted comparison a prolonged OS and PFS with NC sequence compared to CN in mRCC pts treated with 6 to 18 months of prior TKI. Cabozantinib efficacy after N in 3rd line seems to drive this NC superiority strengthening the hypothesis of a sensitizing role of anti-PD-1 on TKI efficacy.

CABOPRE: A phase II study of cabozantinib (cabo) prior cytoreductive nephrectomy (CN) in metastatic renal cell carcinoma (mRCC)

Background:

Favorable response to systemic therapy has been suggested as a suitable approach to select ideal candidates for CN in mRCC. Cabo demonstrated clinical benefit as first-line therapy in mRCC patients with intermediate- or poor-risk International Metastatic Renal Cell Carcinoma Database Consortium criteria (IMDC). CABOPRE trial is a single arm prospective multi-center phase II trial to assess the efficacy and safety of neoadjuvant cabo in patients with clear cell mRCC and potential candidates to CN.

Methods:

mRCC patients received three cycles of cabo 60mg/daily followed by CN. Patients continued cabo therapy after surgery. The primary endpoint was objective response rate (ORR) at 12 weeks (prior to CN). Progression-free survival (PFS), overall survival (OS), safety and exploratory biomarker analyses in paired tissue and blood samples were secondary endpoints.

Results:

From Dec 2018 to Dec 2020, 18 patients were enrolled. The table summarizes baseline characteristics. At a median follow-up of 9.0 months, the 12 weeks ORR in the evaluable population (N=16) was 26.7% PR; 66.7% SD; 6.7% PD. Median PFS was 12.7 months. Median OS has not been reached. No new or unexpected safety findings were observed with cabo. No severe complications were reported postoperatively. Sequential microRNA profiling from plasma as well as tumor-derived exosomes is being analyzed.

Table: 676P Baseline characteristics

Median age/range [years]	**56.5 (49.0, 63.0)**
Male/Female	66.6%/33.3%
ECOG 0/1:	33.6%/66.6%
IMDC intermediate/poor risk	77.7%/22.3%
≥ 2 measurable metastatic sites	77.7%
Mean primary tumor size (mm)	96
Progression at week 12* (*before CN)	N=1 (6,7%)
CN performed	N=11/16 (68.8%)*2 not evaluable

Conclusions:

Cabozantinib at 60 mg/day is feasible and active as a perioperative treatment in intermediate/poor-risk mRCC patients. Dynamic biomarkers might inform and help patient selection.

Clinical trial identification:

EudraCT 2018-001201-93

Immunotherapy vs sunitinib as first-line treatment for advanced renal cell carcinoma in favorable risk patients: A meta-analysis of randomized clinical trials

Background:

Renal cell carcinoma accounts for 90% of all kidney cancers. Five-year survival rates are 80% to 90% among stage I or II patients, only 12% in metastatic disease. Treatment of advanced renal cell carcinoma (aRCC) is challenging. Recent evidence shows immunotherapy improve the prognosis of these patients. We aim to evaluate the efficacy and safety of immunotherapy versus sunitinib as first line treatment in patients with favorable risk aRCC.

Methods:

We conducted a systematic search in PubMed, Ovid MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. The GRADE approach was used to assess the quality of evidence. Survival hazard ratios were extracted for analysis in the entire population and the favorable risk subgroup (IMDC).

Results:

A total of six randomized controlled trials with a total of 5121 patients were included in quantitative synthesis. The studies included different immunotherapy regimens. All clinical trials reported OS and PFS data showing an overall advantage of the immunotherapy regimen vs sunitinib for these outcomes (OS: HR = 0.71, 95% CI = 0.61 – 0.84; PFS: HR =0.64, 95% CI = 0.51 – 0.82). There was no difference for survival between treatment arms in the favorable risk subgroup analysis (OS: HR = 1.07, 95% CI = 0.81 – 1.41; PFS: HR = 0074, 95% CI = 0.46 – 1.19) (see the table). The safety profile reported is consistent with previous reports.

Table: 676P Baseline characteristics

Median age/range [years]	**56.5 (49.0, 63.0)**
Male/Female	66.6%/33.3%
ECOG 0/1:	33.6%/66.6%
IMDC intermediate/poor risk	77.7%/22.3%
≥ 2 measurable metastatic sites	77.7%
Mean primary tumor size (mm)	96
Progression at week 12* (*before CN)	N=1 (6,7%)
CN performed	N =11/16 (68.8%)*2 not evaluable

Conclusions:

Immunotherapy as first-line treatment improves overall survival and progression-free survival for patients with advanced renal cell carcinoma. In the favorable risk subgroup, this advantage is not confirmed yet. More prospective trials with a larger sample size and longer-term follow-up are needed to identify an advantage in OS and PFS.

Cabozantinib and axitinib after VEGF therapy in patients with aRCC: A retrospective cohort study

Background:
Second-line (2L) treatment options for advanced renal cell carcinoma (aRCC) include the tyrosine kinase inhibitors (TKI) cabozantinib and axitinib. We characterized real-world (RW) use of cabozantinib (most recently approved TKI) and axitinib (most commonly used 2L TKI) for aRCC in England.

Methods:
This was a retrospective cohort study using the Cancer Analysis System (CAS). Patients were ≥18 yrs, had renal cell carcinoma (RCC; ICD-10 code C64 or C65), initiated 2L cabozantinib or axitinib following prior VEGF therapy, had aRCC at diagnosis, or initiated aRCC therapy during the study (Jan 1, 2011-Jan 31, 2020). We described treatment patterns and sequences in patients who received ≥ 2L cabozantinib (prior axitinib excluded) or axitinib (prior cabozantinib excluded). Duration of therapy (DoT) and overall survival (OS) were also assessed. Inverse probability weighting (IPW) was used to reduce between-cohort differences and compare OS.

Results:
At study initiation, 77 305 patients in CAS had an RCC diagnosis; 440 were eligible for the cabozantinib cohort, 1045 for the axitinib cohort (median age, 62.5 vs 63.0 yrs; 76.4% vs 70.2% male; 58.6% vs 53.2% aRCC at diagnosis; 18.2% vs 20.4% ECOG PS 0e1). In the cabozantinib cohort, the most common treatment sequences were 1L sunitinib (n = 186) or pazopanib (n = 178) →2L cabozantinib (n = 377) →3L nivolumab (n = 68); 7 patients received 3L axitinib. For the axitinib cohort they were 1L pazopanib (n = 500) or sunitinib (n = 422) →2L axitinib (n = 919) → 3L nivolumab (n = 171) or cabozantinib (n = 49). In the cabozantinib cohort, 27.7% of patients received ≥ 3L therapy vs 34.4% in the axitinib cohort. DoT, OS and the IPW OS comparison are shown in the table.

Conclusions:
This study demonstrates the potential of CAS to generate RW data to complement (and compare vs) randomized controlled trials. There was a signal for prolonged RW OS with 2L cabozantinib (vs axitinib) in patients with aRCC in England who had received prior VEGF therapy.

Clinical trial identification:
CLIN-60000-450 | IPN60000

Genome-wide association meta-analysis identifies novel variants that correlate with efficacy outcomes in sunitinib treated patients with metastatic renal cell carcinoma

Background:

Sunitinib is successfully used in the treatment of metastatic renal cell carcinoma (mRCC), although the individual response is highly variable. In candidate gene studies, sunitinib efficacy or toxicity was related to germline single nucleotide polymorphisms (SNPs) in CYP3A5 and ABCB1. The aim of this meta-analysis of genome-wide association studies (meta-GWAS) is to provide novel leads into biological mechanisms underlying sunitinib mechanism of action.

Methods:

We included 550 mRCC patients that participated in the European EuroTARGET consortium and 219 mRCC patients from the RIKEN cohort in Japan. After SNP imputation using the 1000Genomes reference panel, SNPs were tested for association with progression-free survival (PFS) and overall survival (OS) using Cox regression. Summary statistics of both cohorts were combined using a fixed effect meta-analysis.

Results:

In the EuroTARGET cohort, we identified novel genetic variants in PDLIM3 and DSCAM with genome wide significance ($p<5\times10^{-8}$) for association with PFS and OS. SNPs rs28520013 (PDLIM3) and the highly correlated variants rs2205096 and rs111356738 (DSCAM) remained significant ($p<4.8\times10^{-8}$) in the meta-analysis that includes the RIKEN cohort. The variant T-allele of rs28520013 associated with an inferior PFS of 5.1 months (CI95%: 1.5-6.2) compared with 12.5 months (95%CI: 10.914.9) in non-carriers ($p=4.02\times10^{-10}$,HR=7.26). T-allele carriers also showed an inferior OS of 6.9 months (95%CI: 5.5-27.6) compared with 30.2 months (95%CI: 27.433.4) for non-variant carriers ($p=1.62\times10^{-8}$,HR=5.96).

Conclusions:

This meta-GWAS demonstrates that SNPs in PDLIM3 and DSCAM have a negative impact on PFS and OS in sunitinib-treated mRCC patients. The SNP rs28520013 is hypothesized to change PDLIM3 protein activity that regulates the NFkB p65 subunit and thereby cytokine production. The DSCAM protein influences the function of p21-associated kinase (PAK) that also effects NF-kB. Genetic polymorphisms in genes encoding PDLIM3 and DSCAM may be involved in the PI3K/AKT signaling pathway by intervention with PAK or NF-kB, and possibly influence sunitinib efficacy.

Characterization of the tumor immune microenvironment in early-stage clear cell renal cell carcinoma (ccRCC): Prognostic value of an M0-macrophage enriched subtype

Background:

The treatment paradigm for clear cell renal cell carcinoma (ccRCC) has been transformed by the advent of immunotherapies. However, the composition and role of cells making up the ccRCC tumor immune microenvironment (TIME) has yet to be comprehensively described. Here, we leveraged a genomic data driven approach to characterize TIME subtypes in ccRCC.

Methods:

Whole transcriptome data from patients with localized disease in the Cancer Genome Atlas KIRC (TCGA-KIRC) project was utilized (n¼382). CIBERSORT was used for immune cell deconvolution, and unsupervised hierarchical clustering divided the cohort based on similar immune profiles. Survival of each cluster was analyzed, and gene set enrichment analysis was performed among clusters. The tumor immune dysfunction and exclusion (TIDE) tool, which uses a genomic signature validated on immunotherapy-treated melanoma patients to model tumor immune evasion, was then used to predict response to immune checkpoint blockade (ICB) in the clusters.

Results:

A distinct M0hi cluster demonstrated decreased survival, more aggressive disease, and enrichment of epithelial to mesenchymal transition (EMT) hallmark genes [Enrichment Score = 0.69, p=0.001]. This cluster also showed an increase in myeloid derived suppressor cell (MDSC) and cancer associated fibroblast (CAF) gene signatures and a lower predicted response to ICB using the TIDE tool (Table).

Table: 692P

	CL1 ($M2^{mod}$)	CL2 (CD4 $Memory^{hi}$)	CL3 ($M2^{hi}$)	CL4 ($M0^{hi}$)	CL5 ($CD8^{hi}$)
Median OS (mo., 95% CI)	NR (77.0 – NR)	NR (90.5 – NR)	NR (84.3 – NR)	45.3 (31.3 – NR)	118.8 (93.0 – NR)
Median PFS (mo., 95% CI)	NR (89.9 – NR)	123.8 (106.8 – NR)	NR (NR – NR)	40.4 (20.1 – NR)	NR (NR – NR)
Stage III/IV (%)	28	35	20	48	35
PD-L1*	0.01	-0.01	-0.07	-0.93 p = 0.0001**	0.30
T-Cell Exclusion*	0.19	0.21	0.32	0.69 p= $6.3x10^{-10}$**	-0.10
Predicted ICB Response (%)	27	23	20	4	34
CAF*	0.03	0.04	0.06	0.09 p= $2.2x10^{-16}$**	-0.03
MDSC*	0.02	0.02	0.02	0.05 p=$6.3x10^{-5}$**	0.02

NR: not reached CAF: Cancer Associated Fibroblast MDSC: Myeloid Derived Suppressor Cells *Signatures from TIDE tool, Z scores **Global p-value, Kruskal-Wallis

Conclusions:

Comprehensive characterization of the TCGA-KIRC cohort led to the identification of a distinct cluster of ccRCC defined molecularly by decreased PD-L1 and increased EMT gene expression and cellularly by enrichment of M0 macrophages, CAFs, MDSCs, and an exclusion of T Cells. Future work will translate immune cells defining this cluster more broadly into a scoring paradigm that can be applied prospectively to better identify and treat early-stage patients with this aggressive TIME subtype.

Drug-drug interactions between pazopanib and proton pump inhibitors may significantly affect clinical outcome of patients affected by metastatic renal cell carcinoma

Background:

Proton pump inhibitors (PPIs) are widely used in cancer patients to mitigate polypharmacy-associated adverse gastroesophageal events. However, pharmacokinetic data showed that concomitant administration of pazopanib and PPIs leads to decreased plasma concentrations and exposure of pazopanib by 40% (Cancer Chemother Pharmacol 2013; 71: 1635-1643). The current study aimed at investigating the effect of concomitant PPIs on pazopanib progression-free survival (PFS) in patients affected by metastatic renal cell carcinoma (mRCC).

Methods:

mRCC patient's candidate to pazopanib as first line treatment were enrolled in this retrospective observational study. Patients were defined as "no concomitant PPIs" if no PPIs were administered during pazopanib, and as "concomitant PPIs" if the administration of PPIs covered the entire or not less than 2/3 of treatment with pazopanib. All clinical interventions were made according to clinical practice.

Results:

A total of 126 patients were enrolled; median PFS to pazopanib was 12 months. Fifty-nine patients belonged to "no concomitant PPIs" during pazopanib treatment and 67 to the "concomitant PPIs" group. Most prescribed PPIs were lansoprazole and pantoprazole. The overall population was stratified according to PFS, showing no difference in the two groups (PFS 8.9 vs 13.7 months, p=0.95). Patients were stratified based on median PFS as "short" (n=70) and "long" (n=56) responders. In the long-responders group, there was a significant difference in terms of PFS in patients assuming vs not assuming PPIs, being 24.7 vs 45.5 months, respectively (n=35 vs 21, p=0.03). Multivariate analysis included gender, age, ECOG, nephrectomy, radiotherapy, number of metastatic sites, and IMDC score and confirmed the use of concomitant PPIs as the only independent predictive factor for shorter PFS (p=0.04).

Conclusions:

This study demonstrates that concomitant use of PPIs in mRCC patients treated with pazopanib for long time has a detrimental effect on PFS. Therefore, it is recommended to prescribe PPIs with strict compliance with the registered indications and for short periods (usually not more than 2 weeks) or use alternative gastroprotective procedures.

Colorectal Cancer

XELOX/XELIRI alternative regimen as first-line treatment of metastatic colorectal cancer (CCRCTO-2: TROT): A phase II study

Background:

Since 2000, the combination of three drugs and targeted drugs has further improved the survival of metastatic colorectal carcinoma(mCRC), while the incidence of side effects of triple regimens over grade 3 are much higher than double regimens. Since adjusting the dosage of drugs can't avoid serious toxicity, here we present a new method of optimizing the scheme by adjusting the time and mode of administration.

Methods:

TROT is a prospective, open-label, multicentric phase II randomized trial in which unresectable and previously untreated mCRC patients are randomized to receive first-line XELOX followed by XELIRI after disease progression ± bevacizumab(arm A) or these two schemes alternatively use ± bevacizumab of every 2 cycles until disease progression(arm B). The primary endpoint is to compare the efficacy of these two treatment strategies in terms of time to failure of strategy (TFS) and secondary objectives were ORR、DCR、OS and safety. The curative effect will evaluate in every 2 cycles.

Results:

66 patients were enrolled.6 patients were lost to follow or fall off. The analysis of curative effect has been evaluated in 31 patients in the arm A and 29 patients in the arm B.ORR was 27.6% in the first-line and 11.5% in the second-line in the arm A vs 67.7% in the arm B ($P < 0.001$). The DCR was 89.7% in the first-line and 57.7% in the second-line in the arm A vs 100% in the in the arm B ($P < 0.001$). ETS was 64.5% and DpR was 46% in the arm B. Median TFS was 12.9 months in arm A vs 12.0 months in arm B ($P = 0.735$, HR 1.103). Median OS was 20.4 months in arm A vs 18.8 months in arm B ($P=0.712$, HR 0.887). Grade ≥3 AEs occurred in 10 patients (32%) in arm B vs 21 patients (72.4%) in arm A($P<0.001$). No treatment-related death was reported. There were significantly lower AEs than current triplet regimens.

Conclusions:

XELOX/XELIRI alternate regimen ± bevacizumab, compared with first-line XELOX followed by XELIRI after disease progression ± bevacizumab, can improve the effect of tumor shrinkage and significantly reduce treatment-related side effects in mCRC patients with widespread metastasis, and this alternate regimen may become an alternative for patients who can't tolerate the three-drug combination regimen.

Clinical trial identification:

NCT03511170

A single-arm, multicenter, phase II study of anlotinib combined with CAPEOX as first-line treatment in RAS/BRAF wild-type unresectable metastatic colorectal cancer (ALTERC002)

Background:

Anlotinib is an oral multi-target tyrosine kinase inhibitor, mainly targets VEGFR1-3, FGFR 1-4, PDGFR a/b and c-kit. Previous trial has demonstrated that anlotinib monotherapy was effective and safe in advanced colorectal cancer following the failure of standard treatment. ALTER-C002 trial was designed to evaluate the efficacy and safety of anlotinib plus CAPEOX as first-line therapy in patients with RAS/ BRAF wild-type unresectable metastatic colorectal cancer (mCRC). Preliminary results demonstrated significant antitumor activity and manageable toxicity. Here we updated the results at the data cutoff of Apr 30, 2021.

Methods:

Patients with RAS/BRAF wild-type unresectable mCRC and no prior systemic treatment received anlotinib (12 mg p.o. qd, on day1-14 every 3 weeks), capecitabine (850 mg/m2 p.o., bid, on day 1-14 every 3 weeks) and oxaliplatin (130 mg/m2 i.v., on day 1 every 3 weeks) for 6 cycles followed by anlotinib and capecitabine maintenance until disease progression. Tumor response was assessed every 6 weeks according to RECIST v1.1 by investigator. The primary endpoint was ORR, and secondary endpoints included safety, DCR, DOR and PFS.

Results:

rom Nov 2019 to Feb 2021, 30 eligible patients were enrolled, of whom, median age was 60y (range, 32-72y), 26 (86.7%) had left colon or rectal cancer, and 24 (80.0%) had liver metastases. The ORR was 73.3% (95% CI, 54.1-87.7%) with 1 patient achieved a complete response (CR); DCR was 100% (95% CI, 88.4-100.0%). 2 patients received radical surgery after treatment; 12 patients had ongoing responses at data cutoff. Grade 3-4 treatment-emergent adverse events (TEAEs) occurred in 22 (73.3%) patients; the most common (≥10%) TEAEs were hypertension (46.7%, 14/30 pts), neutropenia (26.7%, 8/30 pts) and diarrhea (13.3%, 4/30 pts). No grade 5 treatment related events occurred.

Conclusions:

Anlotinib combined with CAPEOX achieved higher ORR in the first-line treatment of mCRC compared to those of previous treatment. Longer follow-up is needed for more complete assessment, and we’re launching a phase III, multicenter, double-blind trial to further assess the efficacy of this regimen.

Clinical trial identification:

NCT04080843

FOLFIRINOX with or without targeted therapy as first line for metastatic colorectal cancer: An AGEO multicenter real-world study

Background:

Triplet-chemotherapy (TC) with or without (w/o) bevacizumab (TC-B) or anti-EGFR (TC-E) is highly effective as first line treatment (1L) for metastatic colorectal cancer (mCRC). However, it remains unclear if adding targeted therapy (TT) to TC improves clinical outcomes and metastasis resection rates compared to TC alone.

Methods:

In this retrospective multicenter study, all consecutive patients (pts) with mCRC who started TC w/o TT as 1L treatment between January 2014 and 2019 in 14 centers in France were enrolled. We aimed to describe efficacy and safety of TC w/o TT and to identify potential predictive factors.

Results:

A total of 332 pts (46% TC, 44% TC-B and 10% TC-E) were enrolled (186 male, median age 59.6 yo [21-86], 305 synchronous metastases, 163 RAS-mutated and 54 BRAF-mutated). Primitive tumor resection rate was significantly different between the 3 groups (p¼0.004). Primitive tumor localization was also significantly different with more rectal cancer in TC (40%), right colon in TC-B (41%) and left colon in TC-E (61%); p<0.001. BRAF mutations were more frequent in the TC-B group (29%) compared to TC (9%) and TC-E (3%); p<0.001. Median OS were 34.8, 26.7 and 34.0 months in the TC, TC-B and TC-E group, respectively (NS). Median PFS were 14.9, 12.1 and 12.8 months in the TC, TC-B and TC-E group, respectively (p=0.017). Metastasis resection rates were 47%, 36% and 49% in the TC, TC-B and TC-E groups, respectively. After adjusting for age, primitive tumor localization, number of metastasis and primitive tumor resection, OS and PFS did not differ in the 3 groups. In the sub-group analysis of BRAF-mutated pts, median OS were 17.9 and 13.6 months in the TC and TCeB group, respectively (NS). In a predictive multivariate analysis, RAS and BRAF mutations were associated with reduced OS while no association was observed on PFS. Grade 3-4 adverse events were experienced in 31% of pts.

Conclusions:

Efficacy and safety results in this real-world study were in line with published trials. All treatment regimens seemed similarly effective when well adapted to the RAS status. In BRAF-mutated pts, the adjunction of anti-VEGF to TC does not show significant effect on this small population but needs to be evaluated in further prospective trials.

From clinical trial to bedside: Triplet chemotherapy (FOLFOXIRI-B) in metastatic colorectal cancer

Background:

Triplet chemotherapy (fluorouracil, oxaliplatin, irinotecan) plus bevacizumab (FOLFOXIRI-B) is a first-line treatment option for patients with metastatic colorectal cancer (mCRC). Its benefit on overall survival compared to doublet chemotherapy plus bevacizumab has been shown in several phase III randomized controlled trials and a recent meta-analysis. However, the implementation of this regimen by medical oncologists in daily practice is unknown. We evaluated the current prescription rate of FOLFOXIRI-B in mCRC and investigated the perspectives of medical oncologists towards this treatment option.

Methods:

This was a nationwide, one-week, multicenter, cross-sectional flash mob study. During a single week in March 2021, we retrieved clinical data of 282 currently diagnosed mCRC patients, while simultaneously interviewing 101 medical oncologists from 52 different hospitals in the Netherlands. Patient eligibility for treatment with FOLFOXIRI-B was estimated. We compared current practice to retrospective FOLFOXIRI-B prescription rates as documented by the Netherlands Cancer Registry.

Results:

Since 2015-2018, the FOLFOXIRI-B prescription rate has increased from 2.4% to 8.9% in 2021. This means one in seven eligible patients is currently treated with FOLFOXIRI-B. Eighty-six percent of medical oncologists discuss FOLFOXIRI-B as a treatment option in daily practice, of which 56% generally communicate a preference for a chemotherapy doublet over FOLFOXIRI-B to patients. These oncologists reported a significantly lower awareness of literature regarding FOLFOXIRI-B compared to oncologists that claimed not to communicate a preference regularly. Toxicity was the most reported reason to prefer an alternative regimen.

Conclusions:

FOLFOXIRI-B prescription rates have marginally increased in the last 5 years. Considering most medical oncologists report to discuss this treatment option, the prescription rate is below what would be expected considering the 4.9-month survival benefit with FOLFOXIRI-B treatment. We show that awareness of guidelines and trial data contributes to the discussion of available treatment options by medical oncologists, emphasizing the need for repeated and continuing medical education.

Update results from ALTER-C-001 study: Efficacy and safety of anlotinib plus XELOX regimen as first-line treatment followed by maintenance monotherapy of anlotinib for patients with mCRC: A single arm, multi-center, phase II clinical trial

Background:

The standard therapy followed by maintenance treatment is an optional approach to balance the efficacy and toxicity for metastatic colorectal cancer (mCRC). But clinical trials have largely remained inconclusive regarding the maintenance strategy. Anlotinib, a novel multi-target TKI, significantly prolonged the PFS of refractory mCRC in a phase III clinical trial. The preliminary results of anlotinib plus XELOX regimen followed by anlotinib as first-line treatment (ALTER-C-001) exhibited antitumor efficacy and manageable toxicity for mCRC. Here we updated the results with more patients enrolled.

Methods:

53 patients with unresectable mCRC, aged 18-75, without prior systemic treatment and ECOG performance status 0-1 will be prospectively recruited. Anlotinib 10mg and capecitabine 1000mg/m2 was given for 14 days, q3w; oxaliplatin 130mg/m2 was given by intravenous infusion on day 1, q3w. After 6 cycles of inducing therapy, patients would receive anlotinib (12mg, po, d1~14, q3w) until disease progression or intolerable adverse events. The primary endpoint was PFS; Secondary endpoints included ORR, DCR, DOR and safety.

Results:

At the data cut-off date of April, 2021, a total of 21 patients were enrolled, the median (range) age was 58 (48-66) years, 15 (71%) were males, ECOG PS 0/1 was 10 (48%)/11 (52%), 18 (86%) had more than one metastatic tumor. Among 17 efficacy-available patients, the ORR (CR/PR) was 53% (9/17) and the DCR (CR/PR/SD) was 88% (15/17) in best overall response assessment, of which the longest duration of treatment was 12.1 months and the response was still ongoing. The median PFS was not reached. The Grade 3/4 treatment related adverse events (TRAE, >10%) were hypertension (19%), hypertriglyceridemia (14%), neutropenia (14%), lipase elevated (10%). One grade 5 TRAE was pancytopenia that occurred at 2.7 mths.

Conclusions:

The update results suggested that anlotinib combined with XELOX as first line regimen followed by anlotinib monotherapy showed a promising clinical benefit and favorable safety profile for mCRC. And the results needed to be confirmed in trials continued subsequently.

Clinical trial identification:

ChiCTR1900028417

Spotlight on refractory metastatic colorectal cancer (refMCRC): Role of prognostic characteristics in the continuum of care

Background:

Changes in prevalence and therapeutic landscapes of mCRC have translated into a progressive increase of refMCRC population. The efficacy of the available therapies in this setting is limited. Prognostic groups have been evaluated to determine better which patients (pts) could benefit from late-line treatments. We aim to explore the numeric representation of these groups in a real population that would support this strategy as a tool in daily care.

Methods:

A cohort of mCRC pts treated at our hospital was retrospectively reviewed using medical charts from 2010 to 2020. Clinical, laboratory and molecular data were evaluated. We divided pts into 3 clinical groups according to previously reported prognostic characteristics: Good Prognostic Characteristics (GPC) defined as 18 m since metastatic disease debut, <3 metastatic sites and presence of liver metastasis, Best Prognostic Characteristics (BPC) defined as 18 m, since metastatic disease debut, < 3 metastatic sites and absence of liver metastases and Poor Prognostic Characteristics (PPC) defined as < 18m since metastatic disease debut and/or 3 metastatic sites. Statistical analysis was done using R version 4.

Results:

A total of 735 out of 2365 mCRC pts (35%) were identified as refMCRC. Median age at diagnosis was 59 years, 130 pts (18%) were < 50y. Molecular profiles were: KRAS mutant (mt): 339 (46%), BRAF mt: 87 (12%) and MSI-H 29 (4%). In our cohort, 408/735 (55.51%) pts received > 3 lines of therapy (median lines 4, IQR 3-8) and 50.98% of these pts were included in clinical trials. The prognostic subgroup classification was: 266 pts (36%) GPC, 136 (19%) BPC and 333 (45%) PPC. The mOS of the cohort was 12.6m (11.4-13.9) and OS according to Prognostic Characteristics was: GPC 14.1m (11.8-16.4), BPC 16m (14.6-19.4) and PPC 10m (8.3-11.5).

Conclusions:

According to data previously reported, prognostic characteristic subgroups are well represented in this cohort with a similar distribution and survival outcomes. We should further explore the potential utility of this tool in routine clinical practice or clinical trials. Of note, 35% of the pts in our series received a third line therapy and more than a half were included in clinical trials with longer mOS compared to previous data.

Retrospective cohort study of low-dose apatinib plus S-1 versus regorafenib and fruquintinib for refractory metastatic colorectal cancer

Background:

Colorectal cancer (CRC) is the fifth most common cancer and one of the leading causes of cancer-related death in China. Although apatinib and S-1, respectively, are used in the treatment of advanced colorectal cancer, the efficacy and safety of the combination of the two drugs are unclear. The aim of this study was to investigate the efficacy and safety of low-dose apatinib plus S-1 compared with regorafenib and fruquintinib in patients with metastatic colorectal cancer (mCRC) refractory to standard therapies.

Methods:

Records of 114 patients with refractory mCRC in our center from April 2016 to 17 September 2020 were retrospectively reviewed. Among these patients, 43 received apatinib 250mg/day combined with S-1, 36 received regorafenib starting at 80mg/day with weekly escalation, and 35 received fruquintinib.

Results:

The median progression-free survival was 3.9 months [95% confidence interval (CI),2.5-5.3 months] in the apatinib plus S-1 group, 3.1 months (95% CI 1.9-4.2 months) in the fruquintinib group, and 2.4 months (95% CI 2.1-2.7 months) in the regorafenib group, the mPFS of apatinib plus S-1 was significantly longer than that of regorafenib. The median overall survival was 8.2 months (95%CI, 5.4-11.0 months) in the apatinib plus S-1 group, 7.8 months (95%CI, 5.3-10.3 months) in the fruquintinib group, and 7.5 months (95%CI, 4.2-10.7 months) in the regorafenib group, which was comparable among the three groups. Disease control rate (DCR) was 83.7% in the apatinib plus S-1 group, 71.4% in the fruquintinib group, and 66.7% in the regorafenib group, and no significant difference was shown among the three groups. Patients in the apatinib plus S-1 group had a higher incidence of hematological toxicity including anemia, leukopenia, and thrombocytopenia, and the hand-foot skin reaction was more prevalent in the regorafenib group, while the adverse reaction of hypertension in the fruquintinib group was very significant.

Conclusions:

Low-dose apatinib plus S-1 prolonged PFS compared with regorafenib, and is a promising clinical regimen for the treatment of refractory mCRC with tolerable and controlled toxicity that is worth studying in the future.

First line treatment patterns in BRAFV600E-mutant metastatic colorectal cancer patients (mCRC): The CAPSTAN European retrospective study

Background:

8-12% of mCRC patients harbor a BRAFV600E mutation ($BRAF^{MT}$), which confers a poor prognosis. In the first-line setting, there is no specific treatment for $BRAF^{MT}$-mCRC, although a doublet or triplet chemotherapy (CT) plus bevacizumab is recommended by European guidelines. CAPSTAN is a retrospective, multi center, observational study to describe effectiveness and safety of first-line regimens in $BRAF^{MT}$ mCRC patients in Europe.

Methods:

$BRAF^{MT}$, unresectable mCRC patients who initiated first-line treatment between 2016 and 2018 were included. The primary endpoint was the description of first-line treatment patterns. Secondary endpoints included effectiveness (ORR, PFS, OS) and description of BRAF mutation testing procedures.

Results:

259 patients were eligible for analysis. The median age was 66 years and the majority were female (58.3%). 52.9% of patients had right sided tumor and $BRAF^{MT}$ was confirmed using mostly PCR (46.1%) or NGS (38.3%). 59.5% had an assessment of microsatellite instability (MSI) status of which 23.4% were MSI. Majority of patients (73.8%) received doublet CT in first line (28.2% doublet CT alone, 38.2% doublet CT + anti-VEGF, 7.3% doublet CT + anti-EGFR). Only 18.5% of patients received a triplet CT (3.1% triplet CT alone, 14.7% triplet CT + anti-VEGF and 0.8% triplet CT + anti-EGFR). Main first-line treatments received were FOLFOX + Bevacizumab, FOLFOX alone and FOLFOXIRI + Bevacizumab (26.6%, 18.9% and 13.1% respectively). The median duration of first-line treatment was 4.86 months and disease progression was the main reason for treatment discontinuation (62.6%). 52.5% of patients received a second line of treatment. Further efficacy and safety data will be presented at the meeting.

Conclusions:

Results showed that the majority of $BRAF^{MT}$ mCRC patients were treated with a doublet CT (with or without TT) as first line. Treatment duration for these patients was short and highlights the aggressive nature of $BRAF^{MT}$ mCRC. The incidence of MSI patients identified is in line with recent data suggesting approximately 20% of $BRAF^{MT}$ patients have a high level of MSI.

Response to BRAF inhibitors combined with anti-EGFR after previous anti-EGFR exposure for BRAF V600E mutant metastatic colorectal cancer patients

Background:

Encorafenib and cetuximab is efficient in anti-EGFR-naïve patients (pts) with $BRAF^{V600E}$ mutated (BRAFm) metastatic colorectal cancer (mCRC) after failure of one or two prior lines of treatment (BEACON trial). However, to date, the efficacy of BRAF inhibitors in combination with anti-EGFRs (B+E) in patients (pts) previously treated with an anti-EGFR agent has never been reported.

Methods:

We collected retrospectively a series of pts with BRAFm mCRC treated with an anti-EGFR and anti-BRAF combination therapy after previous anti-EGFR treatment, in 11 French and Italian centers. PFS and OS were calculated since the start of the anti-BRAF therapies. Response and disease control rates (ORR, DCR) were also reported as treatment tolerability.

Results:

A total of 19 BRAFm pts were enrolled (male: 8, median age: 61 [38-74], right-sided: 5, synchronous metastases: 10, >1 metastatic sites: 15, pMMR: 19). Prior to B+E treatment, 2/8/9 pts were treated with 1/2/>2 previous lines of therapy. 9 pts received previous panitumumab and 10 previous cetuximab. Immediate progression with previous anti-EGFR was reported for 6 pts. B+E treatment was encorafenib+ cetuximab for 16 pts and dabrafenib+ trametinib+ panitumumab for 3 pts. Median B+E treatment duration was 4.7 months [1.8-10.1]. ORR (RECIST) was observed in 7 pts (37%), stable disease in 9 pts (47%) leading to a DCR of 84%. Median PFS was 4.6 months and median OS was 7.2 months. No difference was noted between pts previously treated with cetuximab or with panitumumab (DCR of 100% and 66%, p¼0.09). Median PFS amongst pts with previous primary resistance to anti-EGFR agent was 5,4 months. Grade 3+ adverse events were experimented in 7 pts, but only 1 discontinued B+E due to drug-related AEs.

Conclusions:

These results show, to our knowledge for the first time, the efficacy of the combination of anti-BRAF and anti-EGFRs in BRAFm mCRC pts previously treated with an anti-EGFR. The oncological outcomes observed here are very close to those reported in the BEACON pivotal trial. The use of an anti-BRAF and an anti-EGFR combination should not be ruled out in this population with limited therapeutic options and poor prognosis.

A study of vemurafenib and cetuximab in combination with FOLFIRI for patients with BRAF V600E-mutated advanced colorectal cancer (NCT03727763): Preliminary results

Background:

The prevalence of BRAF V600E in colorectal cancer （CRC） was about 10%. Despite recent therapeutic advances, BRAF V600E mutant CRC is still a challenge with a low response rate and suboptimal survival. Here we reported the safety and preliminary anti-tumor activity of vemurafenib and cetuximab in combination with FOLFIRI for BRAF V600E-mutated advanced CRC patients.

Methods:

In this single-arm, single-center trial, we are currently in enrollment of patients with BRAF V600E-mutated, RAS-wild type advanced CRC. Patients received vemurafenib 960mg orally every 12 hours, cetuximab 500mg/m^2 in combination with FOLFIRI, consisting of irinotecan 180mg/m^2 2 hour-intravenous infusion, leucovorin 400mg/m^2,5-fluorouracil (5-FU) 400mg/m^2 intravenous injection on day 1, followed by a 46-h continuous infusion of 5-FU (2400 mg/m^2). The primary objective was to measure the objective response rate (ORR). And the secondary objective included safety, progression-free survival and overall survival.

Results:

18 patients were enrolled in this study and 16 patients completed at least 3 sessions of treatment for efficacy assessment. The ORR was 81.3% with 2 complete response (CR) and 11 partial responses (PR). The disease control rate (CR+PR+SD) was 100%. Out of 7 patients receiving the treatment at second or third line, 5 patients (1 CR, 4 PR) had an objective response (71.4%). 81.8% of the adverse events (AEs) were grade 1 or 2. Grade 3/4 AEs (!2 patients) included neutropenia (8 pts, 44.4%), rash (3 pts, 16.7%), anemia (3 pts, 16.7%), fatigue (2 pts, 11.11%), diarrhea (2 pts, 11.11%), and leukopenia (2 pts, 11.11%),. 12 out of 18 patients (66.7%) reduced vemurafenib dose due to AEs, in which 4 patients reduced once from 960mg to 720mg and the remaining 8 patients reduced twice from 720mg to 480mg. Only one patient dropped out due to the intestinal obstruction.

Conclusions:

A combination of vemurafenib, cetuximab and FOLFIRI was generally well-tolerated and the preliminary result indicated considerably increased response rate for advanced colorectal cancer patients with BRAF V600E mutation. The enrollment for the trial is still under way.

Clinical trial identification:

NCT03727763

Bayesian monitoring of lapatinib (L) plus trastuzumab (T) treatment of HER2 positive metastatic colorectal cancer (mCRC): An observational cohort study

Background:

HER2 positivity is found in 3-5% of mCRC. The phase II HERACLES-A trial showed that dual anti-HER2 therapy with T + L has 30% response rate (RR) in HER2+ RAS wt mCRC after failure of standard care (Sartore-Bianchi 2016). These data led to inclusion of T+ L among recommended treatments by NCCN and other guidelines, but still lack confirmation by large trials comparing treatments. The latter, especially for this uncommon subset of mCRC, would require efforts unbearable in the setting of independent clinical research. We designed this study to confirm HERACLES-A data of efficacy through a Bayesian approach allowing to monitor longitudinally efficacy of T + L in the practice setting.

Methods:

We adopted a Bayesian design for an observational cohort study in order to report the RR of T + L in HER2+ mCRC by updating the prior probability of response observed in the HERACLES-A trial with the likelihood of the RR in all consecutive patients with the same characteristics treated at Niguarda Cancer Center after the HERACLES-A closure. We simultaneously monitored efficacy and toxicity using the Bayesian optimal phase II (BOP2) design (Zhou, Lee, e Yuan 2017), with futility boundaries for efficacy and safety and a total sample size of 40 patients. We planned 3 interim analyses at 10, 20 and 30 patients evaluable for RR. Type I = II error was ~10%, calculated after 10000 simulations under H0 and H1 scenario.

Results:

From May 2019 to Jan 2021, we collected data of HER2+ mCRC patients treated with T + L according to HERACLES-A inclusion criteria (Sartore-Bianchi et al. 2016). Patients were followed for RR and adverse events (AE). On May 1st 2021, at the first interim analysis, 2/10 evaluable patients had PR according to RECIST criteria, with an updated likelihood of response of 26.2% and a 95% credible interval of 13.7-39.2%. No AE G3 drug-related were reported.

Conclusions:

At the first planned interim analysis, treatment with T + L for HER2+ mCRC patients was confirmed to be safe and effective. A Bayesian approach, allowing to monitor results accounting for previously available data, can support the process of approval by regulatory authorities for treatments targeted to uncommon subsets such as HER2+ mCRC.

Efficacy of combinations of BRAF inhibitors and anti-EGFR antibodies in metastatic colorectal carcinoma (mCRC) patients with mBRAF in the real clinical practice

Background:

Combination of BRAF inhibitors and anti-EGFR antibodies is a standard of 2nd and subsequent line of treatment in pts with mBRAF mCRC. We performed analysis of prospective multicentric database of pts with mBRAF metastatic CRC to evaluate the efficacy of such approach in the real clinical practice.

Methods:

We analyzed a database of pts with mCRC in 7 cancer clinics in Russia and chose pts with 2nd and subsequent lines. The primary endpoints were progression free survival (PFS) and overall survival (OS), which were calculated from the time of starting systemic treatment. Analysis was performed with the SPSS v.20 software package.

Results:

The study included 73 pts with mBRAF. All pts had V600 mutations; female 70%, average age - 69 years (20-79), MSI-H -10%; the right-sided primary tumor e 53%; the primary tumor was removed in 81%, adjuvant chemotherapy was administered in 32%; lung metastases e in 29%, liver - 53%, peritoneal metastases e in 44%; metastasectomy was performed in 22% pts. The first line was FOLFOXIRI in 19%. BRAF inhibitors and anti-EGFR were administered in 30 pts (42%): in the 2nd line e 18 (60%), 3rd line e 7 (23%), 4-5th lines e 5 (17%). Chemotherapy was administered in the 2nd line in 43 (58%) pts: with bevacizumab or aflibercept in 52%. In pts with BRAF inhibitors and anti-EGFR treatment ORR was 27%, with 7% CR, disease control rate was 60%, median PFS was 4 months (95% CI 1,2-6,8), and OS e 11 months (95% CI 8,5-13,4). There were no statistical differences between chemotherapy group and combinations of BRAF inhibitors and anti-EGFR treatment in 2nd line neither in PFS (HR 1,3, 95% CI 0,7-2,5, p=0,4) or OS (R 1,4, 95% CI 0,52-4,0, p=0,5)

Conclusions:

treatment with BRAF inhibitors and anti-EGFR antibodies shows the same efficacy as in BEACON study in pts with mutant BRAF mCRC in real clinical practice. However, there were no survival benefit in comparison with another systemic treatment in the 2nd line, this suggests we need a prospective randomized study to compare BRAF inhibitors combinations and chemotherapy with anti-VEGF agents in the 2nd line of treatment.

Efficacy and safety of pyrotinib-based therapy in HER2positive metastatic colorectal and gastric cancer: A retrospective study

Background:

Pyrotinib, an irreversible pan-Human epidermal growth factor receptor (HER） tyrosine kinase inhibitor, has shown its antineoplastic activity in HER2-positive metastatic breast cancer and HER2 mutation lung cancer. This retrospective study was designed to analyze the efficacy of pyrotinib-based therapy in HER2-positive metastatic colorectal and gastric cancer.

Methods:

Patients with HER2 positive advanced colorectal and gastric cancer received pyrotinib-based therapy were collected from December 2018 to January 2021 in Fudan University Zhongshan Hospital. The primary endpoint was objective response rate (ORR). Secondary endpoints were disease control rate (DCR), duration of treatment (DOT), progression-free survival (PFS) and adverse events (AE).

Results:

15 patients with colorectal cancer (CRC) and 11 gastric cancer (GC) were enrolled. In patients with CRC, 12 (80%) showed HER2 overexpression and 3 (20%) were HER2 mutation with or without HER2 overexpression. In GC, 10 (90.9%) patients showed HER2 overexpression, and 1 (9.1%) showed HER2 mutation. 20% CRC patients and 90.9% GC patients had undergone anti-HER2 therapy, previously. The ORR and DCR were 26.9% (7/26) and 61.5% (16/26) in all enrolled patients with a median DOT of 6.1 months (range 0.8-13.2 months) and a median PFS of 5.7 months (95% CI 3.67.8 months). In the subgroup analysis, ORR and DCR were 33.3% (5/15) and 66.7% (10/15) in CRC, 18.2% (2/11) and 54.5% (6/11) in GC, respectively. The median DOT was similar in CRC (6.3 months) and GC (5.8 months). While median PFS was 5.7 months in CRC and 4.3 months in GC. Grouped by different previous therapies, patients receiving ≤ 2 lines had a numerically longer median PFS than those receiving >2 lines: 7.3 vs 4.3 months (HR 0.740, 95% CI 0.294-1.847, P = 0.519). The most frequent AE were diarrhea (14, 53.8%) and rash (5, 19.2%). Pyrotinib reduction was observed in 2 patients, no treatment-related deaths and administration delay were recorded.

Conclusions:

Pyrotinib-based therapy demonstrates promising effects in HER2-positive metastatic colorectal and gastric cancer and prospective clinical trial is warranted to confirm its activity in patients failed to first-line therapy.

A phase Ib study of cetuximab combined with fruquintinib in the previously treated RAS/BRAF wild-type metastatic colorectal cancer: The preliminary result of CEFRU study

Background:

The standard third-line treatment of metastatic colorectal cancer (mCRC) is regorafenib, fruquintinib, or TAS-102. However, the efficacy was not satisfied. We conducted a phase Ib /IIa clinical study to evaluate the safety and efficacy of fruquintinib plus cetuximab in mCRC（TPS151, 2021 ASCO GI） This time we reported the phase Ib dose-escalation study results.

Methods:

This is a single-center, non-random, prospective, dose-escalation (3 + 3 design), exploratory study. Eligible patients were diagnosed with advanced RAS/BRAF wild-type colorectal cancer and had received at least two prior regimens. The starting dose of fruquintinib was 4 mg once daily (QD) in a 28-day cycle (3 weeks on/1 week off) plus cetuximab. If tolerable, fruquintinib was escalated to 5 mg. If not tolerable, the fruquintinib dose was reduced to 3 mg. The dose of cetuximab is 500mg/m2 every two weeks. 6-9 patients were involved in this study. Adverse events（AEs） were graded according to NCI-CTCAE v4.0. Drug limiting toxicities (DLTs) were evaluated in cycle 1. The response was assessed using RECIST v1.1 q8 wks. The purpose is to confirm the safety and recommended phase II dose (RP2D).

Results:

As of Feb 2021, 7 patients were involved. 3 patients received fruquintinib 4mg and 4 received fruquintinib 5 mg. One DLTs of grade 3 acneiform rash was observed in 1/ 3 patients at the 4 mg dose. Two DLTs with grade 3 hypertension and two DLTs with grade 3 proteinuria were confirmed at the 5 mg dose level in 3/4 patients. The RP2D is fruquintinib 4 mg QD (3 weeks on/1 week off) plus cetuximab 500mg/m2 every two weeks. The most common treatment-related AEs were hypertension (3/7), proteinuria (3/7), acneiform rash (3/7), creatinine elevation（2/7）, hypoproteinemia (2/7), hemorrhinia (2/7), fatigue (2/7), anemia (2/7), elevated alkaline phosphatase (2/7), elevated aspartic transaminase (1/7) and dry skin (1/7). Evaluation in 7 treated patients showed 4 cases were stable disease (SD) and 3 cases were progressive disease (PD).

Conclusions:

Cetuximab combined with fruquintinib showed acceptable anti-tumor activity in CRC with resistance to at least two prior regimens. No unexpected toxicities were observed.

Clinical trial identification:

ChiCTR2000038227

REGINA: A phase II trial of neoadjuvant regorafenib (rego) in combination with nivolumab (nivo) and short-course radiotherapy (SCRT) in intermediate-risk, stage II-III rectal cancer (RC)

Background:

Despite recent improvements, management of locally advanced rectal cancer (LARC) remains challenging, and many patients (pts) still experience recurrence. In preclinical models, combining Rego with an anti-PD-1 inhibitor led to superior tumor growth suppression as compared with either treatment alone. In a phase I clinical trial, remarkable results were reported for the combination of Rego and Nivo in advanced MSS colorectal cancer. This synergistic effect is thought to be secondary to the anti-angiogenic effects of Rego and its potential to reduce TAMs, promote M1 macrophage conversion, and downregulate expression of immunosuppressive factors. Building on these data, we designed a trial of Rego-Nivo with standard SCRT in the neoadjuvant setting of RC.

Trial design:

REGINA is an academic, multicentre, single-arm, phase II trial sponsored by Institut Jules Bordet. Eligible patients are treated according to the following plan: induction phase (Nivo 240 mg IV D1&15, and Rego 80 mg PO D1-14), SCRT (D22-26), consolidation phase (Nivo 240 mg IV D29,43&57, and Rego 80 mg PO D29-49), and surgery (7-8 weeks after SCRT). Key eligibility criteria include age ≥18 years, ECOG PS ≤1, adenocarcinomas below the peritoneal reflection, intermediate-risk, stage II-III tumor (ie, cT3/T4aNany or cT1-2N+, no involvement/threatening of the mesorectal fascia, no involvement of lateral pelvic lymph nodes). The primary endpoint is pathological complete response (pCR). Secondary endpoints include, among others, toxicity, compliance to treatment, pTRG, event-free survival, and overall survival. The study follows a Simon's two-stage design (null hypothesis pCR=12%, alternative hypothesis pCR=24%;α=5%, β=20%) with a maximum of 60 pts to be enrolled. A safety interim analysis is planned after the first 6 pts have completed treatment. Serial collection of tumor, blood, and stool samples is mandatory at pre-specified time points for exploratory correlative biomarker analyses. The trial is planned to be run at 8-10 centers across Belgium. Study recruitment started in Q1 2021 and is anticipated to complete in Q3 2023.

Clinical trial identification:

EudraCT 2020-000876-40

Pembrolizumab plus lenvatinib versus standard of care for previously treated metastatic colorectal cancer (mCRC): Phase III LEAP-017 study

Background:

Pembrolizumab, a PD-1 inhibitor, is now recommended as a 1L treatment for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) unresectable or mCRC. However, treatment options are needed for patients with non-MSI-H or MMR proficient (pMMR) mCRC. Pembrolizumab + lenvatinib, a multikinase inhibitor, showed antitumor activity and had manageable safety in patients with previously treated non-MSI-H/pMMR CRC in the phase II LEAP-005 (NCT03797326) study. LEAP-017 (NCT04776148) is designed to compare the efficacy and safety of pembrolizumab + lenvatinib vs standard of care in patients with nonMSI-H/dMMR mCRC that has progressed on or after prior treatment or disease that has become intolerant to prior treatment.

Trial design:

Eligibility criteria include age ≥18 y, histologically/cytologically confirmed non-MSI-H/dMMR, unresectable or metastatic Stage IV (AJCC 8th edition) mCRC, ECOG performance status 0 or 1, and provision of a baseline tumor sample. Patients will be randomly assigned 1:1 to pembrolizumab 400 mg IV Q6W + lenvatinib 20 mg PO QD or investigator's choice (selected before randomization) of regorafenib 160 mg QD (d 1-21, no dose on d 22-28) Q4W or TAS-102 (trifluridine + tipiracil hydrochloride) 35 mg/m2 Q4W (BID on d 1-5 and d 8-12, no doses on d 6-7 or d 1328). Randomization will be stratified by absence/presence of liver metastases. Pembrolizumab will continue for up to ~2 y; lenvatinib may continue beyond 2 y in cases of clinical benefit, until progression, unacceptable toxicity, or investigator/patient decision. The primary end point is OS. Secondary end points are PFS, ORR, and DOR per RECIST v1.1 by blinded independent central review, safety and tolerability (AEs per NCI CTCAE v5.0), and change from baseline scores and time to deterioration in global health status/quality of life, physical functioning, appetite loss, and bloating (EORTC QLQ-C30 and EORTC QLQ-CR29). Exploratory end points include health utilities (EQ-5D-5L). Approximately 434 patients will be enrolled.

Clinical trial identification:

NCT04776148; EudraCT, 2020-004289-20

PRESERVE 1: A phase III, randomized, double-blind trial of trilaciclib versus placebo in patients receiving FOLFOXIRI/ bevacizumab for metastatic colorectal cancer

Background:

Trilaciclib, an intravenous (IV) kinase inhibitor that protects hematopoeitic stem and progenitor cells during chemotherapy exposure, is FDA approved to decrease the incidence of chemotherapy-induced myelosuppression in patients (pts) with extensive-stage small cell lung cancer based on data from three randomized, placebo-controlled phase II trials. In another randomized phase II trial in pts with triple-negative breast cancer, administering trilaciclib prior to chemotherapy had limited myeloprotective effects, but improved overall survival (OS).

Trial design:

PRESERVE 1 (NCT04607668) is a randomized, double-blind, phase III trial to evaluate the myeloprotective and antitumor effects of trilaciclib administered prior to fluorouracil (5FU), leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI)/bevacizumab in adult pts with previously untreated metastatic colorectal cancer. Eligible pts must have confirmed unresectable and evaluable disease, an ECOG PS of 0/1, and adequate organ function. Tumors must be mismatch repair proficient/microsatellite stable and can be of any known BRAF mutation status. Pts should have no symptomatic peripheral neuropathy, uncontrolled hypertension, or other contraindications to FOLFOXIRI/bevacizumab. Approximately 296 pts will be stratified by country, prior therapy, and BRAF V600E mutation status, and randomly assigned 1:1 to receive IV trilaciclib 240 mg/m^2 or placebo on days 1 and 2 prior to FOLFOXIRI/bevacizumab in 14-day cycles for up to 12 cycles (Induction). Following Induction, pts will receive trilaciclib or placebo prior to 5FU/leucovorin/bevacizumab. Treatment will continue until disease progression, unacceptable toxicity, withdrawal, or the end of the trial. Primary endpoints are duration of severe neutropenia (SN) in cycle 1 and occurrence of SN during Induction. Key secondary endpoints are progression-free survival, OS, and time to confirmed deterioration in chemotherapy-induced fatigue during Induction. The effects of trilaciclib on red blood cell and platelet lineages will also be investigated. Recruitment began in the US in October 2020, and globally in early 2021.

Clinical trial identification:

NCT04607668

PRODIGE 68 - UCGI 38 - SOREGATT: A randomized phase II study comparing the sequences of regorafenib (reg) and trifluridine/tipiracil (t/t) after failure of standard therapies in patients (pts) with metastatic colorectal cancer (mCRC)

Background:

First-line treatment for mCRC pts consists of a fluoropyrimidine-based chemotherapy (5-FU or capecitabine combined with oxaliplatin and/or irinotecan) with VEGF or EGFR inhibitors. Once these treatment options have been used, or are no longer appropriate, pts are eligible for either reg or t/t treatment. Although both treatments are approved in mCRC, no randomized trial has investigated the sequence of reg and t/t. The optimal strategy to extend survival while maintaining quality of life still needs to be determined. We have designed this trial to evaluate both treatment sequences and determine the best one in this setting.

Trial design:

This international, randomized phase II, open-label trial is designed to compare the feasibility of the treatment sequences: reg followed by t/t vs t/t followed by reg. Pts 18 years, with mCRC, ECOG PS 0-1, after failure of fluoropyrimidine based chemotherapy combined with oxaliplatin and/or irinotecan as well as EGFR (if RAS wild-type) and/or VEGF inhibitors are enrolled. Reg will be given according to ReDOS dose-escalation scheme at 1st cycle (increasing from 80 mg to 160 mg daily over 3 weeks) to determine the highest dose tolerated that will be then used for the next cycles (3 weeks followed by 1 week off). T/t 35 mg/m2 will be taken orally twice daily on D1-D5 and D8-D12 of each 4-week cycle. The primary endpoint is the treatment feasibility of the 2 sequences, assessed as the percentage of pts able to receive at least 2 cycles of both treatments, which corresponds to the first tumor evaluation at each line. If a pt does not receive the second treatment, he will be considered a failure. Secondary endpoints are overall survival, progression-free survival, disease control rate, objective response rate, time to treatment failure, time to ECOG PS ≥2 deterioration, quality of life and safety. We assume that 50% of the pts receiving t/t will be able to receive further treatment as compared to 65% with reg. With a Chi-square test between the 2 arms, a bilateral a-risk of 5% and a power of 80%, 170 pts are required in each arm. Since November 2020, 42 pts are enrolled in 14 sites.

Clinical trial identification:

NCT04450836

Camrelizumab combined with fruquintinib or regorafenib as second or later line therapy for BRAF positive-mutation advanced colorectal cancer (CRC) with microsatellite stability (MSS): A single-arm, phase II study

Background:

CRC is an aggressive disease which accounts for a third of cancer-related death. Compared with the microsatellite instability-high phenotype, the effect of the BRAF mutation in the MSS-CRC on the prognosis seems to be more obvious. Regorafenib and furquintinib are small-molecule multikinase inhibitors that target signaling pathways implicated in tumor angiogenesis, oncogenesis and the tumor microenvironment. Camrelizumab, an anti-PD-1 monoclonal antibody, has shown preliminary results in advanced CRC. Thus, this trial was designed to investigate the efficacy and safety of camrelizumab plus fruquintinib or regorafenib in BRAF positivemutation advanced MSS-CRC.

Trial design:

This is a phase II, single-arm, prospective trial. Eligible patients are histologically or cytologically confirmed advanced CRC with metastatic disease. Patients have to be adults (18-75 years) with ECOG PS ————————————1 and BRAF V600E mutated CRC that is resistant/refractory/intolerant to 1 prior lines of therapy. Patients could not participate if they have bone metastases with spinal cord compression. Patients are treated with camrelizumab (200mg, iv, q2w) combined with fruquintinib (4 mg/d) or regorafenib (80 mg/d) medication for 3 weeks, 1 week apart, until disease progression or intolerance toxicity occurs. For patients, blood samples at baseline, at the time of best response and after disease progression, will undergo NGS testing, which detects a panel of gene mutations, including single nucleotide variants, insertions/ deletions, copy number amplifications, and gene rearrangements. The NGS testing is needed to identify better biomarkers of response to immunotherapy in CRC. The primary endpoint is progress-free survival (PFS) assessed by researcher according to RECIST v1.1. Secondary endpoints are objective response rate, disease control rate, overall survival and safety. On the basis of a threshold PFS of 3 months, targeting an expected PFS of 5 months and assuming 12 months follow-up, 80% power and a one sided a¼0.05, this design requires 37 evaluable patients to be accrued over 2 years.

Clinical trial identification:

ChiCTR2100043066

Biliary Tract Cancer and Cholangiosarcoma

(BREGO) Regorafenib combined with modified m-GEMOX in patients with advanced biliary tract cancer (BTC): A phase II randomized trial

Background:

We have already evaluated the feasibility (Phase Ib) and the potential benefits of regorafenib (Reg) in combination with chemotherapy in BTC (BREGONCT02386397).

Methods:

BREGO is a multicenter phase II randomized trial. This trial will assess the safety and efficacy of m-GEMOX and Reg versus m-GEMOX alone. The stratification (2:1) of the 63 planned patients will be made according to the center and tumor localization (intra- versus extra-hepatic). Reg starting dose was 160mg daily from day 1 to day 14, with fixed doses of Gem (900 mg/m2) and Ox (80 mg/m2) on day 1 and 8 followed by 2 weeks' rest.

Results:

Sixty-three patients were randomised. Median age was 62.5 [31-75], male 56%, PS 0 (59%), 62% patients had intra hepatic CCK, 21% extra hepatic CCK and 17% gallbladder carcinoma. Median duration of Reg treatment was 5.1 months [0.4619.32]; median number of mGEMOX cycles was 7 [2-17]. The median PFS was 7.82 months (95% CI: 5.78-8.15) in Reg-mGEMOX arm, and 7.23 months (95%CI: 7.58-11.2) in mGEMOX arm (p¼0.825). The ORR/DCR were 33.3%/78% and 21.7%/82.6% in the Reg-mGEMOX and mGEMOX arms, respectively. The median OS was 13.5 months (95% CI: 9.69-16.76) in Reg-mGEMOX arm, and 15.08 months (95%CI: 8.8-NA) in mGEMOX arm (p¼0.356). In subgroup analysis no differences were seen between intrahepatic or extrahepatic primary tumour location, but in experimental arm 25/42 patients continued Reg alone beyond 4 cycles (up to 28 cycles) experienced a strong improvement in term of DCR, PFS and OS. Main toxicities were (Reg-mGEMOX/ mGEMOX) G3-4 neutropenia (16.7%/26.1%), G3-4 thrombocytopenia (23.8%/17.3%), G3 diarrhoea (4.8%/8.7%), G3 peripheral neuropathy (2.4%/4.3%), G3 HTA (7.1%/0%), and G2-3 hand-foot syndrome (16.7%/0%). Ancillary studies (PK, early metabolic response on PET scanner analysis and biomarkers (FGF19, SCT1) are ongoing to identify subpopulations of interest.

Conclusions:

Even if the primary endpoint on PFS is not met in BREGO phase IIR trial, it proposes an alternative and probably a highly active regimen in a subgroup of metastatic or locally advanced biliary tract cancer patients. This new regimen is feasible and warrants biomarkers of response to further target patient who benefit of Reg combination.

Clinical trial identification:

BREGO-NCT02386397

A phase II trial of nivolumab and gemcitabine and S-1 as the first-line treatment in patients with advanced biliary tract cancer

Background:

The regimen of modified gemcitabine and S-1 (GS) is active and safe for patients with advanced biliary tract cancer (ABTC) in our previous study. Herein, we report the results of a single arm phase II of Nivolumab plus modified GS as the firstline treatment in ABTC patients.

Methods:

Patients with chemonaïve ABTC receive nivolumab 240 mg and 800 mg/m2 gemcitabine on day 1 plus daily 80/100/120 mg of S-1 (based on body surface area) for days 1-10, in a 2-week cycle. With Optimal Simon's two-stage design and (p0¼0.15, p1¼0.35) for objective response rate (ORR, complete or partial response [CR/PR]) and given error probabilities (alpha¼0.05, beta¼0.1), the null hypothesis (p0) would be rejected if 10 or more patients had CR/PR among 44 evaluable cases. Tumor response was assessed by CT/MRI every 6 weeks according to RECIST v1.1. The PR should be confirmed by two consecutive image examinations.

Results:

Between December 2019 and December 2020, a total of 48 patients were enrolled. After a median of 6.4 months (95% CI, 4.8-8.0) follow-up, 1 patient showed pathological CR and 19 patients achieved confirmed PR. The ORR was 41.7% with additional 22 patients (45.8%) of stable disease and a long-term disease control rate of 77.1% (CR+PR+SD >12weeks). The median progression-free survival and overall survival was 8.0 (95% CI, 5.8-not reached) and not reached (95% CI, 10.7-not reached) months, respectively. All grade 3/4 chemotherapy-related adverse events (AEs) were less than 7%. Fourteen patients (35.4%) experienced immune-related AEs with skin toxicity (14.6%), hypothyroidism, hypophysitis and pneumonitis (all 6.3%). Two patients with grade 3 pneumonitis recovered well without any treatment-related death. Conclusions: By the observation of 20 patients with CR/PR, the null hypothesis was rejected. Nivolumab in combination with modified GS is a promising regimen with good safety profiles, which deserves further investigation for the management of Asian ABTC patients.

Clinical trial identification:

Trial registration number NCT04172402.

Efficacy and safety of pemigatinib in Chinese patients with unresectable, advanced/ recurrent or metastatic intrahepatic cholangiocarcinoma with FGFR2 fusion or rearrangement that failed to prior systemic therapy

Background:

Pemigatinib is a selective FGFR inhibitor that showed highly effectiveness and tolerability in patients with cholangiocarcinoma, which has been demonstrated in Fight 202 study with an ORR of 35.5%. However, pemigatinib has not been investigated in Chinese population with cholangiocarcinoma(CCA).

Methods:

Patients aged 18 years or older with recurrent or metastatic CCA that failed to at least 1 line prior systemic therapy were enrolled. In stage 1, 3 subjects were enrolled regardless of the FGFR2 status and were treated at 9mg pemigatinib. The other 31 subjects with documented FGFR2 fusion or rearrangement were enrolled in stage 2 and received 13.5 mg pemigatinib. From 2/26/2020 to 1/29/2021, all the subjects in both stages were orally given pemigatinib QD on a 2 weeks on/1 week off schedule until disease progression, unacceptable toxicity, withdrawal of consent, or physician decision. The primary end point was ORR assessed by independent radiological review committee (IRRC) per RECIST V1.1 in 31 patients enrolled in stage 2.

Results:

As of Jan 29, 2021, 30 subjects in stage 2 were included in the efficacy evaluable population with 1 participant excluded due to inadequate FGFR2 aberrant frequency. Among 30 efficacy evaluable subjects, 15 of them had confirmed response assessed by IRRC, with an ORR of 50% (95% CI: 31.3%, 68.7%). With a median follow up of 5.13 months, 13 patients were still in response, the median DOR was not reached (95% CI: 3.4, NR), and the median PFS was 6.3 (95% CI: 4.9, NR) months. The DCR was 100% (95% CI: 88.4%, 100%). All 34 subjects in both stages were included for safety analysis. As of data cutoff date, each subject experienced at least 1 treatmentrelated adverse event (TRAE), the most common TRAEs were hyperphosphatemia (73.5%), xerostomia (55.9%) and alopecia (50.0%), and 14.7% had grade 3 or higher TRAEs. Three participants had SAEs, which were rectal polyps, abnormal liver function and bile duct infection. There was no treatment discontinuation and deaths due to TRAE.

Conclusions:

Pemigatinib was highly effective and tolerable in Chinese patients with recurrent or metastatic CCA with FGFR2 fusion or rearrangement.

Clinical trial identification:

NCT04256980.

Pooled analysis safety profile of futibatinib in patients with advanced solid tumors, including intrahepatic cholangiocarcinoma (iCCA)

Background:

Futibatinib, an irreversible FGFR1e4 inhibitor, has shown efficacy in iCCA with FGFR2 fusions/rearrangements and antitumor activity in advanced solid tumors, along with a manageable safety profile. This integrated safety analysis evaluated the safety profile of futibatinib 20 mg QD (the recommended phase II dose) in an expanded patient (pt) population across tumor types.

Methods:

Pts who received ≥1 futibatinib dose at 20 mg QD in a global phase I/II (NCT02052778) and a Japanese phase I study (JapicCTI-142552) were included in this retrospective analysis. AEs, treatment (tx)-related AEs (TRAEs), AEs of special interest (AESIs), and time to onset/resolution (TTO/TTR) of AESIs were analyzed.

Results:

As of October 1, 2020, 318 pts had received futibatinib 20 mg QD across trials (median [m] duration, 111 d). The most common tumor types were CCA (60%), primary CNS tumors (11%), and gastric cancer (9%); 98% had received ≥1 prior tx. Overall, 43% of pts experienced grade (gr) 3 TRAEs, and 1% gr 4 TRAEs; no gr 5 TRAEs were reported. The most frequent gr ≥3 TRAE was hyperphosphatemia (in 23%; defined as ≥7 mg/dL serum phosphate), followed by increased alanine aminotransferase (6%) and increased aspartate aminotransferase (5%). Gr ≥3 diarrhea (<1%), nausea (1%), stomatitis (3%), and fatigue (3%) were rare. Nearly all cases of gr 3 hyperphosphatemia resolved (73/75; mTTR, 7 d) with phosphate binders and dose adjustments. Other AESIs were mostly mild to moderate in severity (nail toxicities [gr ≥3: 1%], hepatotoxicity [gr ≥3: 12%], and palmar-plantar erythrodysesthesia [gr ≥3: 3%]); most gr ≥3 events resolved. Retinal toxicities occurred in 8% of pts (all gr 1e2), and 2% had a TRAE of cataract (gr ≥3: 1%). Management of TRAEs included dose adjustments (54% of pts). Overall, 3% of pts discontinued tx due to TRAEs (only diarrhea and stomatitis in >1pt[n¼2 each]; none due to hyperphosphatemia). No obvious differences in safety were noted between tumor types.

Conclusions:

Futibatinib was safe and tolerable in this pooled analysis of pts with advanced solid tumors. In the majority of pts, TRAEs were gr 1e2 in severity, and most gr ≥3 events resolved with adequate management. Tx-related discontinuations were rare.

Clinical trial identification:

NCT02052778 JapicCTI-142552.

Assessment of futibatinib exposureeresponse (EeR) relationships in patients with advanced solid tumors, including cholangiocarcinoma (CCA)

Background:

The irreversible FGFR1e4 inhibitor futibatinib has demonstrated efficacy in patients (pts) with intrahepatic CCA (iCCA) with FGFR2 fusions/rearrangements along with a manageable safety profile in a pivotal phase II study. Here, we report an integrated EeR analysis of futibatinib safety and efficacy.

Methods:

Pts with advanced solid tumors receiving futibatinib once daily (QD; 4e24mg) or thrice weekly (TIW, 8e200 mg) in a global phase I/II study (NCT02052778) or a Japanese phase I study (JapicCTI-142552) and for whom individual-predicted exposure metrics were generated with a nonlinear mixed-effects population pharmacokinetic (PopPK) model were included in the safety analysis. The efficacy EeR analysis comprised pts with iCCA from the phase II study who received futibatinib 20 mg QD. EeR relationships between efficacy endpoints (including objective response rate [ORR] and duration of response) or safety endpoints (including adverse events of special interest [AESIs]) and PopPK model-based estimated exposure metrics were determined.

Results:

As of October 1, 2020, 318 pts were included in the analysis. Exposureesafety analyses showed a significant relationship between hyperphosphatemia and futibatinib exposure; for grade 3 hyperphosphatemia, there was a significant correlation with QD dosing (N¼247), with a steep increase at 24 mg QD. In multivariate analyses, higher baseline serum phosphate was an independent predictor for hyperphosphatemia, and increase from baseline correlated with futibatinib exposure. The only other AESIs with statistically significant E-R relationships were any-grade nail toxicities (QD only) and retinal toxicities (TIW only). Baseline body weight, age, and race showed no influence on exposureesafety relationships. No statistically significant relationships were observed between any efficacy parameter and futibatinib exposure metrics (N¼98), although a trend toward higher ORR was observed with increasing steady-state futibatinib trough concentrations.

Conclusions:

The EeR results support 20 mg QD as the starting dose for futibatinib, with dose adjustments as needed for the management of hyperphosphatemia.

Clinical trial identification:

NCT02052778 JapicCTI-142552.

FGFR2 fusion and/or rearrangement profiling in Chinese patients with intrahepatic cholangiocarcinoma

Background:

FGFR2 fusions and rearrangements occurring in 10e16% of patients with intrahepatic cholangiocarcinoma (ICC) reported in published scientific literature. Pemigatinib, a selective FGFR inhibitor, has demonstrated the high therapeutic potentials for ICC patients with FGFR2 fusions or rearrangements, according to the results of FIGHT 202 study. Whereas in Chinese population, the epidemiological data of FGFR2 fusions and rearrangements is still insufficient with limited sample sizes, and partner genes in FGFR2 fusion are still unknown.

Methods:

A total of 728 pathologically confirmed ICC samples (including surgical and biopsy samples from 728 patients aged over 18 years) were collected and tested FGFR2 fusion or rearrangement using fluorescence in situ hybridization (FISH) with break-apart probes. Thirty samples with known FGFR2 fusion or rearrangement were tested with next generation sequence (NGS) to identify the partner genes of FGFR2.

Results:

As of October 31, 2020, 728 patients were included and their samples were tested for FGFR2 gene fusion or rearrangement, 717 samples had readout. Forty-four samples (44/717, 6.14%) were tested FGFR2 gene fusion or rearrangement positive. Regionally, the highest positive rate (10.5%) was found in Southwest China (Sichuan and Yunnan province), and the lowest positive rate (5%) was in South China (Guangdong and Guangxi province). Twenty-six different FGFR2 fusion partner genes were identified in 30 samples, 22 (84.6%) of which were unique to individual patients. The most common partner was FGFR2-WAC (3/30, 10%).

Conclusions:

Based on a large sample size, the rate of FGFR2 gene fusion or rearrangement in Chinese ICC patients was 6.14%, and the FGFR2 partner genes were highly heterogeneous.

Clinical trial identification:

NCT04256980.

Assessment of EU4 laboratory readiness for FGFR2 fusion testing of cholangiocarcinoma by NGS

Background:

ESMO recently published Next Generation Sequencing (NGS) testing recommendations for solid tumors, which includes cholangiocarcinoma (CCA), for use of small or large multigene target NGS panels to identify actionable variants. The European Medicines Agency has approved an FGFR2 inhibitor for advanced, metastatic CCA FGFR2 fusion positive patients. With more FGFR2 therapies anticipated, it will be important to identify all CCA patients with any FGFR2 fusion.

Methods:

Using our Diagnostic Network for Precision Medicine (DXRX), 102 EU4 labs across France, Germany, Italy, and Spain were assessed for their capability to provide full coverage of FGFR2 fusions using NGS, in a clinical setting. Data was collected from between January-June 2020 and included NGS testing capabilities, sample type, FGFR2 fusion testing availability & turnaround time (TAT) to reporting results.

Results:

Our analysis revealed Spain has the highest number of labs (86%) capable of detecting a full range of FGFR2 fusions. In contrast, fewer French NGS labs (36%) are prepared for routine clinical FGFR2 testing, however, they provide faster TAT (10 days versus median of 11.5 days and max of 14 days in Italy). 59% and 41% of German and Italian labs, respectively, provide full FGFR2 fusion detection. All labs test using solid tissue biopsies. Uptake of liquid biopsy use varies from 77% in France to 5% in Spain.

Conclusions:

Gene fusion testing clinical utility is well established, and the breadth of possible actionable gene fusions (e.g., ALK, NTRK, FGFR2) in solid tumors continues to grow. NGS provides a means to identify any fusion present using a single test and is the recommended method of choice to provide simultaneous, full coverage of FGFR2 fusions where the paucity of tissue for tumors (e.g., CCA) limits PCR or FISH. Results reveal the proportion of labs ready to provide full FGFR2 fusion detection via NGS in CCA varies across the EU4. This may reflect a possible centralized approach to NGS testing in some countries. It may also highlight a need for more labs to prepare NGS use beyond common diseases (e.g., lung cancer) to rarer conditions like CCA.

Integrative genomic analysis identified primary ciliumassociated genes by as novel key genes in biliary tract cancer (BTC)

Background:

Biliary tract cancer (BTC) is an aggressive and highly lethal cancer arising from the epithelium lining the biliary tree. The mechanisms underlying cholangiocyte malignant transformation and BTC progression are largely unknown. Genomic and transcriptomic profiling can offer a deeper understanding of disease biology in BTC. We performed large-scale integrative analyses on a clinically-annotated cohort of BTC patients to identify novel key-genes driving BTC initiation and progression as well as drug-resistance.

Methods:

We analyzed 100 resected specimens from a well-annotated cohort of BTC patients from the University of Modena. Overall, whole-exome sequencing (WES) was performed on 40 samples, RNA sequencing (RNAseq) on 80 samples, and small RNA sequencing on 30 samples. Somatic alterations, transcriptomic and epigenetic profiles of tumours and stromal area were identified for each sample, and searched for driver genes. By using a bio-informatic pipeline, we integrated somatic mutation patterns and epigenetic features defined at the spatial level to identify novel target genes in the tumour microenvironment. Functional studies in 2D and 3D culturing models were conducted to investigate candidate genes linked to BTC progression.

Results:

A total of 3392 and 6315 DEGs (Differentially expressed genes) were respectively observed in BDC comparing tumour (T), normal (N) and stromal (ST) areas with the criterion of false discovery rate <0.05. In top-ranked differentially regulated gene sets, we identified primary cilium-associated genes (PC). OFD1, CNGB1, AURKA, CENPF, STIL, STK39, RAB23 and OSR1 were found based on the criteria of fold change >2.5 and P<0.01. We started also to clarify at molecular level the role of PC in BDC pathogenesis and progression. A therapeutic approach targeting OFD1 in BDC cells was also investigated.

Conclusions:

We investigated the molecular mechanisms underlying the cilia loss and test whether may be potential therapeutic target. These findings could be useful to establish treatment and diagnostic strategies for BTCs based on genetic information.

Serum protein signatures as potential novel diagnostic biomarkers for biliary tract cancer

Background:

Biliary tract cancer (BTC) has a very poor prognosis. The only potentially curative treatment is surgery, but most patients are ineligible for this treatment due to advanced disease. Thus, biomarkers that can identify BTC at an early stage are needed. We aimed to identify protein signatures that could discriminate patients with BTC from non-cancer participants.

Methods:

The study included 191 patients with all stages of BTC (gall bladder cancer (n¼37), intrahepatic cholangiocarcinoma (CC) (n¼92), and extrahepatic CC (n¼62), and 250 controls (healthy (n¼90), benign biliary tract disease (n¼25), and other benign diseases (n¼135)). We analyzed serum levels of immuno-oncology (I-O) related proteins using the Olink I-O assay (Olink Proteomics, Sweden) as well as CA199. To identify protein signatures and test their performance, the cohort was split randomly in a training (2/3) and replication set (1/3). Signatures were identified in the training set using logistic elastic-net (Lasso and Ridge) regressions. We generated signatures with decreasing number of proteins based on the proteins' stability as predictors in Lasso regression. Signature performance was evaluated in both datasets using receiver operating characteristics (ROC) and area under the ROC curve (AUC). Sensitivity and specificity were calculated using best point.

Results:

Sixteen unique protein signatures including 2 to 84 proteins were generated. All signatures included CA19-9 and chemokine (C-C motif) ligand 20 (CCL20). Overall, all signatures showed promising performance in both the training and replication set with AUC ranging from 0.95 e 0.99 for BTC vs. all controls. The lowest AUC was observed for signatures with less than 6 proteins. The best point sensitivity ranged from 91% -100% and specificity from 85% - 96% in the replication set. The best performing signatures achieved an AUC of 0.99 with a sensitivity of 96% and a specificity of 96%. All signatures identified patients with BTC independent of primary tumor location and stage (AUC $\geq$ 0.95).

Conclusions:

We identified several protein signatures that could discriminate BTC patients from non-cancer participants with high sensitivity and specificity. A validation study in an independent cohort is ongoing.

The characteristics of IDH mutations in Chinese bile duct carcinoma patients

Background:

The isocitrate dehydrogenase (IDH) is an important enzyme in the tricarboxylic acid cycle and IDH mutations play an important role in tumor treatment and prognosis evaluation. IDH mutations have been reported in approximately 15% of cholangiocarcinoma (CCA) patients, while these aberrations are considered to be less frequent in other bile duct carcinoma (BDC) patients. IDH inhibitors have been approved for targeted therapy, which holds great promise for improving the management of BDCs. Here we provide an overview of IDH mutations in a large cohort of Chinese BDCs.

Methods:

BDC tissue specimens and/or circulating cell-free DNA from patients who had undergone molecular profiling were retrospectively reviewed. IDH1, IDH2 and other BDC related genes were detected using hybridization-based targeted next generation sequencing.

Results:

A total of 874 Chinese BDC cases had undergone molecular profiling from January 2017 to March 2021. We identified 60 IDH mutations in 59 of the 874 patients. Of these patients, Active-site mutations in IDH1 and IDH2 (IDH1_R132, IDH2_R140 and IDH2_R172) were detected in 50 patients (5.72%, 50/874), including 28 (56%) males and 22 (44%) females. The median age of patients with IDH active-site mutations was 57.5 years old (age range 32e79 years). Among the 60 IDH mutations, missense variation was the most frequent mutation category (98.3%, 59/60), and the other one was frameshift. Out of the 36 IDH1 active-site mutated specimens, 27 (75%) carried IDH1 R132C mutations, followed by IDH1-R132L (11.1%), IDH1-R132S (8.3%) and IDH1-R132G (5.6%). 14 patients harbored IDH2 active-site mutations, including IDH2-R172W (78.6%), IDH2-R172K (7.14%), IDH2-R172M (7.14%) and IDH2R140Q (7.14%). Among the 50 activating IDH mutations patients, co-variations in TP53 (7, 14%), KRAS (7, 14%), ARID1A (7, 14%), KMT2C (3, 6%) and BAP1 (3, 6%) were observed. Compared to other patients, the activating IDH mutations group had a relatively lower TMB (Median 3.97 vs 2.86, p¼0.09).

Conclusions:

We elucidate the molecular and clinicopathological characteristics of IDH mutant BDCs from a large number of Chinese patients to provide foundational knowledge on personalized clinical management for IDH-directed therapy.

Intrahepatic cholangiocarcinoma (iCCA) hidden amongst the unknown: A retrospective analysis of cancer of unknown primary (CUP) cases from a tertiary cancer centre

Background:

Many patients (pts) with CUP present with presumed metastatic disease to the liver. Due to lack of definitive histological markers, iCCA may be an overlooked diagnosis. With the emergence of efficacious molecularly targeted therapies in iCCA, this study assessed the potential frequency of iCCA (previously not identified) within a CUP cohort.

Methods:

A single-centre retrospective study of sequential pts referred to a regional CUP multi-disciplinary team (MDT) (Jan 2017 - Apr 2020) was performed. Demographic data, histopathology, MDT history, treatment/survival outcomes were collected. For pts presenting with liver involvement, baseline diagnostic imaging was reviewed independently by a hepatobiliary radiologist and/or oncologist. Pts with radiological features of iCCA (dominant liver lesion, capsular retraction) were identified. For a subset of pts molecular characterisation of tumour tissue was performed.

Results:

Of 233 pts referred to the CUP MDT, 74 pts had malignancy involving the liver. For 13 of these pts, a primary tumour diagnosis (different primaries) was subsequently established. Of the remaining liver-involved CUP cohort (n¼61), 56 pts had evaluable radiology reviewed and 25 (43%) had radiological features consistent with iCCA. These 25 pts were predominantly female (n¼19; 77%) with a median age of 65 years (range 31-79). 64% had an ECOG PS 2 and 50% received first line platinumbased chemotherapy. Molecular alterations (IDH mutations/FGFR fusions) supporting an iCCA diagnosis were detected in a subset of pts where testing was performed. Median overall survival (OS) of the potential iCCA group (n¼25) and remaining liverinvolved CUP group (not iCCA) were similar (OS 3.8 vs 3.9 months, logrank p-value ¼ 0.805); comparatively, patients with subsequent primary diagnosis (and liverinvolvement, n¼13) had significantly better OS (10.2 months, logrank p-value ¼ 0.0227).

Conclusions:

In this study 41% of patients referred with liver-involved CUP, matched the radiological criteria for an iCCA diagnosis, highlighting the importance of identifying these pts within CUP cohorts, ensuring correct diagnosis, molecular characterisation and treatment.

Phase III study of NUC-1031 + cisplatin vs gemcitabine + cisplatin for first-line treatment of patients with advanced biliary tract cancer (NuTide:121)

Background:

Biliary tract cancer (BTC) is an aggressive disease with a poor prognosis. Gemcitabine + cisplatin (GemCis) is the accepted global standard of care; however, key cancer resistance mechanisms associated with the transport, activation and breakdown of gemcitabine are known to limit its clinical activity. NUC-1031 is a phosphoramidate transformation of gemcitabine designed to overcome these key resistance mechanisms and generate much higher levels of the active anti-cancer metabolite, dFdCTP, in cells. Promising efficacy has been observed in the phase Ib ABC-08 study of NUC-1031 + cisplatin for first-line treatment of advanced BTC. Of 21 patients (pts) enrolled in 2 dose cohorts (NUC-1031 625 mg/m2 or 725 mg/m2 + cisplatin 25 mg/m2 on Days 1 and 8 of 21-day cycles), 16 were considered to be efficacy evaluable. In this population, 1 pt had a CR and 6 pts had PRs, resulting in an ORR of 44% (7/16). This compares favorably to the 26% ORR reported for GemCis. In addition, 6 pts had SD, resulting in a DCR of 81% (13/16). The combination was well tolerated with no unexpected AEs or DLTs. The recommended dose of NUC-1031 with cisplatin was 725 mg/m2. The encouraging efficacy and tolerability profile led to initiation of a global registrational study.

Trial design:

NuTide:121 is a phase III, open-label, randomised study of NUC-1031 + cisplatin vs GemCis for first-line treatment of advanced BTC. Pts !18 years with histologically- or cytologically-confirmed BTC (including cholangiocarcinoma, gallbladder, or ampullary cancer), who have had no prior systemic chemotherapy for locally advanced/metastatic disease, are eligible. A total of 828 pts are being randomised (1:1) to either 725 mg/m2 NUC-1031 or 1000 mg/m2 gemcitabine, both with 25 mg/m2 cisplatin, administered on Days 1 and 8 of 21-day cycles. Primary endpoints are OS and ORR. Secondary endpoints include PFS, safety, PK and pt-reported QoL. In addition to the final analysis, three interim analyses are planned. NuTide:121 is being conducted at approximately 125 sites across North America, Europe and Asia Pacific.

Clinical trial identification:

NCT04163900.

Derazantinib for patients with intrahepatic cholangiocarcinoma harboring FGFR2 fusions/ rearrangements: Primary results from the phase II study FIDES-01

Background:

FGFR2 fusions/rearrangements ($FGFR2^{fus}$) occur in w15% of patients (pts) with intrahepatic cholangiocarcinoma (iCCA), a disease with poor outcomes upon progression after 1L standard treatment. Derazantinib is a potent FGFR1-3 kinase inhibitor that has shown broad clinical activity in iCCA pts with FGFR2 fusions, mutations and amplifications. Here, we present efficacy and safety data for the completed $FGFR2^{fus+}$ cohort from study FIDES-01.

Methods:

Eligible pts with advanced iCCA, ≥1L of prior treatment and a confirmed $FGFR2^{fus}$ received derazantinib 300 mg QD. Primary endpoint was objective response rate (ORR) by independent central review per RECIST v1.1; secondary endpoints included duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety.

Results:

103 $FGFR2^{fus+}$ pts were enrolled; 65% were female, 50% were ≥56 years, and 47% had ≥2 prior treatment lines. At data cutoff (April 25, 2021), 91% of pts had discontinued treatment. The study met its primary endpoint with a centrally confirmed ORR of 21.4% (95% CI 13.9, 30.5) 74.8%; median (m) DOR was 6.4 mo (95% CI 3.9, 9.2) with a probability of 68% of retaining a response for ≥6 mo; mPFS was 7.8 mo (95% CI 5.5, 8.2); mOS was 15.5 mo (95% CI 11.8, 21.9). Efficacy outcomes were consistent in 2L and 3+L treatment (ORR: 21.8% in 2L / 20.8% in 3+L; mPFS 6.0 / 8.2 mo in 2L / 3+L). Most common adverse drug reactions (ADRs) were hyperphosphatemia (37% ADRs; 70% laboratory values), asthenia/fatigue (31%), transaminase elevations (31%), nausea (30%), dry eye (26%), and dry mouth (21%); most common grade ≥3 ADRs were transaminase elevations (12%), fatigue/asthenia (5%), hyperphosphatemia (4%), and abdominal pain (3%). Drug-related retinal events (1%; grade 1), nail toxicities (6%, grade ≤2), stomatitis (2%, grade 1) and hand-foot syndrome (1%, grade 1) were rare.

Conclusions:

Derazantinib showed clinically meaningful efficacy with durable objective responses, and a manageable safety profile with a particularly low incidence of drug-related hand-foot syndrome, stomatitis, retinal or nail toxicity in pts with iCCA harboring $FGFR2^{fus}$.

Clinical trial identification:

NCT03230318.

Endocrine Tumor

Clinical impact of the GAPP score and SDHB negativity in patients with pheochromocytoma/paraganglioma

Background:

Pheochromocytoma (PCC) and paraganglioma (PGL) are rare tumors occurring in the adrenal medulla and extra-adrenal tissues, respectively. The clinicopathological features have not been fully elucidated, especially in Asian cohorts.

Methods:

We retrospectively reviewed 65 patients with PCC/PGL between 1983 and 2020. Patient characteristics and clinical outcomes (overall survival [OS] and relapse free survival [RFS]) were analyzed based on the medical records. Morphological assessment and immunostaining of Ki-67 and succinate dehydrogenase complex subunit B (SDHB) were performed in the available specimens. Subsequently, the influence of the grading system for pheochromocytoma and paraganglioma (GAPP) score and SDHB negativity on the clinical outcomes was evaluated.

Results:

The median age of the patients was 51 years, and PGL accounted for 69% of the cases. Initial stage was localized disease in 83% of the patients, and the major primary lesions were in the adrenal gland (31%), retroperitoneum (24%), and bladder (15%). Fifty-three patients with localized disease underwent curative resection, and six and two patients with metastatic disease underwent surgery and chemotherapy, respectively. Morphologically, the GAPP score was 0-2 (low-risk) in nine, 3-6 (intermediate-risk) in 33, and 7-10 (high-risk) in three specimens. SDHB immunostaining was performed in 41 specimens, and the negativity rate was 19%. The 3-year OS rate in all 65 patients was 95%, and was significantly better in patients with localized than metastatic disease (3-year OS 98% vs. 80%, P=0.008). The 3-year RFS rate in the 53 patients with localized disease was 87%. The rate was significantly different among patients in the low-risk, intermediate-risk, and high-risk groups (3-year rate 100% vs. 96% vs. 33%, P < 0.0001), and between those in the SDHB-positive and SDHB negative groups (3-year rate 100% vs. 57%, P= 0.03).

Conclusions:

While the general outcome of PCC/PGL was favorable, our analysis suggested that high-risk GAPP score and SDHB negativity were predictors of subsequent relapse in patients with localized disease who underwent resection. The correlation between lack of SDHB expression and SDH-related mutations should be assessed in future studies.

Cabozantinib plus atezolizumab in advanced and progressive neoplasms of the endocrine system: A multicohort phase II trial (CABATEN trial / GETNE-T1914)

Background:

Antiangiogenic agents have demonstrated antitumor properties in endocrine malignancies regardless of their primary origin. Experience with immune checkpoint inhibitors is limited in this area and early results when used as single agents are discouraging. The aim of this trial is to assess the efficacy and safety of the combination of cabozantinib and atezolizumab, which may overcome the resistance in previously treated metastatic endocrine tumors.

Trial design:

CABATEN is a prospective, multi-center, open-label, phase II study of cabozantinib plus atezolizumab in advanced and refractory tumors of the endocrine system stratified into 6 cohorts: (1) well differentiated neuroendocrine tumors (NETs) of the lung, (2) anaplastic thyroid cancer, (3) adrenocortical carcinoma, (4) pheochromocytoma/ paraganglioma, (5) well differentiated gastroenteropancreatic NETs, (6) grade 3 neuroendocrine neoplasms. Patients (pts) included in the trial must have progressed on standard therapies in each setting, with no limit to the number of previous lines. For pts included in cohort 2, inclusion in the first-line is allowed if pts are not eligible for chemotherapy. All pts will receive atezolizumab 1200 mg every 3 weeks and cabozantinib 40 mg daily continuously until progression, unacceptable toxicity or consent withdrawal. Cabozantinib dose reduction to 20 mg daily is allowed. The primary endpoint is overall response rate (ORR) assessed by investigators according to RECIST v1.1. Secondary endpoints include progression-free survival, overall survival, quality of life, safety and a wide panel of biomarkers in blood and tumor samples. Using a Simon II stage design with a null hypothesis of 5% ORR from previous studies and an alternate hypothesis of 20% ORR, 24 pts per cohort (9 in a first stage and 15 in a second stage) are needed. Accrual started in October 2020. To date, 55 out of 144 expected pts have been enrolled.

Clinical trial identification:

EudraCT 2019-002279-32; NCT04400474

Real-life monocentric, retrospective study on efficacy and tolerability of lenvatinib (Len) in patients (pts) with advanced radioactive iodineerefractory differentiated thyroid cancer (rDTC)

Background:

Lenvatinib (Len) was approved by the FDA and EMA as 1st-line treatment for rDTC pts. This study aims to describe the efficacy and toxicity of Len treatment in a monocentric real-life multidisciplinary-based management of rDTC pts.

Methods:

Medical records of 49 consecutive pts with histologically/cytologically diagnosis of DTC and progressive disease, treated with Len between July 2015 and December 2020, were collected. Treatment was validated by multidisciplinary local board (oncologist, endocrinologist, radiotherapist, endocrine surgeon, nuclear medicine physician); all pts were managed by an oncologist and/or by an endocrinologist at Unità Tumori Ereditari-IOV-IRCCS, Padova, Italy.

Results:

All 49 pts (24M/25F) were considered; median age at Len initiation was 72 ys (51-87). All pts were metastatic (lung 87%, bones 38%, lymphnodes 59%, liver 14%, brain 4%, kidney 2%); for 44 pts (90%) Len was the 1st systemic treatment and 14 pts (28%) had cancer-related symptoms at treatment initiation. With median duration of treatment of 14.2 months (1.7-60.9), median Progressione Free Survival (PFS) was 31.2 months (95% CI, 19-N.D.) and 24 months Overall Survival (OS) was 75.3%. Best response was partial response in 30 pts (61.2%) and stable disease in 14 pts (28.6%); no complete responses were observed. Almost all pts (98%) experienced Adverse Events (AEs) and 53% developed grade 3 AEs. The most frequent AEs were hypertension (84% all grade, 45% grade 3), fatigue 57%, weight loss 43%, diarrhea 33%, mucositis 43%, skin 43%. No grade 4 AEs or treatment-related deaths were observed. Dose reduction for AEs was needed for 22 pts (44%); 39 pts (79%) interrupted Len with a median dose interruption of 3.3% compared with total treatment duration.

Conclusions:

Higher PFS (and OS) observed in this study, compared with other Clinical trials, is probably due to fewer pts needing dose reductions, shorter time of treatment interruption and fewer pts with cancer-related symptoms at Len initiation. Hence, a multidisciplinary approach could lead to establish appropriate timing for Len initiation and may allow the early detection and better management of AE.

Retrospective analysis of PDL-1, LAG3, TIM3, OX40L and MSI status in gastroenteropancreatic neuroendocrine tumors (GEP-NETs)

Background:
The current study aimed to evaluate the expression status of immune checkpoints (PDL-1, LAG3, TIM3, OX40L) and determine MSI status in patients with GEP-NETs.

Methods:
Immunohistochemistry staining of 61 GEP-NET patients were carried out to detect PDL-1 (IC or TC), LAG3, TIM3, OX40L and MSI (MLH1, MSH2, MSH6, PMS2) retrospectively.

Results:
A total of 61 patients were analyzed, and 32.8% (n¼20) of patients had metastatic disease. The median age at diagnosis was 55.4 (IQR:43.6-63.8). Thirty three (52.4%) patients were male, and 29 (47.6%) patients were female. Pancreas (n¼22) is the most common primary tumor localization, and there were 4 patients with unknown primary tumor. It was observed that 17 patients had G1, 27 patients had G2, and 17 patients had G3 GEP-NET. It was found that 12 patients were PDL-1 positive, 5 patients were MSI-H, 3 patients were TIM3 positive, 10 patients were OX40L positive, and none of the patients were LAG3 positive. At all, PDL-1 positivity was the most common in G3 tumors, and MSI-H was in G1 tumors (table). Of Note, 67.3% of PDL-1 positivity and 80% of MSI-H status were observed in locoreginoal diseases.

Conclusions:
While PDL-1 positivity is higher in higher grade tumor, MSI-H status is higher in lower grade tumors. Both PDL-1 positivity and MSI-H status were prominent in locoregional diseases.

First International Randomized Study in Malignant Progressive Pheochromocytoma and Paragangliomas (FIRSTMAPPP): An academic double-blind trial investigating sunitinib

Background:

Malignant pheochromocytoma and paraganglioma (MPP) is a very rare cancer (annual incidence < 1 per million). Here, we report the first academic randomized double-blind phase II study results assessing Sunitinib efficacy compared to placebo.

Methods:

Patients with progressive MPP with 1.5year according to (RECIST) were randomized 1/1 for Sunitinib therapy 37.5 mg/d or Placebo and stratified for SDHB status and line of treatment. Primary endpoint: progression-free survival (PFS) at 12 months according to real-time central review (RECIST 1.1), analyzed every 3 months (ITT). Key secondary endpoints: ORR, response (delay, duration), overall PFS, overall survival, safety (NCI CTCAE v.4). On the basis of a two-step Simon model (alpha 10%, power 90%), we aimed for 74 patients, assuming a PFS improvement at 12 months from 20 to 40%. 11 or more patients out of 37 with no progression at 12 months were expected to conclude that Sunitinib is effective. The placebo group served as an internal control to validate the hypothesis of the Simon design with a 12-m PFS equal to 20%. An IDMC was set up to review the accrual, toxicity, and interim analysis.

Results:

78 patients were enrolled (median age, 53 yrs; 59% men). Main characteristics: adrenal/PGL primaries, each 50%; 32% SDHx inherited, 71% secreting, distant lymph node/bone/lung/liver mets, 73%/65%/51%/49%; 60% prior therapy. 39 patients were randomized in each arm. The primary endpoint was met: PFS at 12 months was 35.9% (Sunitinib) vs. 18.9% (Placebo; within the 90%CI confirming the Simon design conclusion). Median PFS was 8.9 (95CI: 5.5-12.7) vs. 3.6 months (3.1-6.1). Reasons for drug discontinuation were AE/tumor progression in 14%/64% (Sunitinib) and 0%/86% (Placebo). 54% patients with Sunitinib vs. 49% with Placebo experienced SAE; most frequent grade 3-4 were asthenia/fatigue (18% vs. 3%) and hypertension (10% vs. 6%).One death occurred in each arm.

Conclusions:

After 8 years of enrolment, this first randomized study in the field of MPP provides the highest level of evidence ever reached in this very rare cancer. Sunitinib becomes the first-line option in patients with progressive MPP.

Clinical trial identification:

NCT01371201

FOLFOX-bevacizumab chemotherapy in patients with progressive metastatic neuroendocrine tumors

Background:

Well-differentiated neuroendocrine tumors (NETs) are relatively rare, highly vascularized neoplasms. Antiangiogenic drugs have shown efficacy in patients with advanced NETs, although the efficacy of FOLFOX-bevacizumab has been scarcely described in this setting. Hence, we aimed to report its efficacy and tolerance in patients with metastatic NETs.

Methods:

We retrospectively studied the records of all consecutive patients with metastatic well-differentiated digestive or lung NETs, treated by FOLFOX-bevacizumab, in two expert centers, from 2013 to 2020. We analyzed time to treatment failure (TTF), objective response (OR) rate and toxicity. We assessed factors associated with TTF and OR using multivariate Cox proportional hazard or logistic regression models, respectively.

Results:

We included 57 patients (65% male, median age 62 years), with mostly pancreatic (67%), small-intestine (14%) or lung (7%) NETs. Most patients (58%) had extra-hepatic metastases, including bone metastases in 35% of cases, and median Ki67 index was 18% (G3 NETs, 40%). Patients had either progressive disease (82%) or were treated on first line (18%). Patients received a median of 17 cycles of FOLFOX bevacizumab (interquartile range, 9-31), including a median 10 cycles of bevacizumab and/or LV5FU2 maintenance. The median TTF was 15.5 months (95% CI [9.8-21.2]). At multivariate analysis, age >60 years (HR 2.09, 95% CI (1.01-4.33), p=0.048) and >1 previous systemic treatment line (HR 3.55, 95% CI (1.60-7.09), p=0.002) increased the risk of treatment failure. The OR and disease control rates were 43% and 95%, respectively. The OR rate was 53% among pancreatic NETs and was higher in G3 NETs (57%) compared to G2 NETs (33%) and G1 NETs (0%). Performance status at 0 (OR 5.85, 95% CI (1.29-26.53), p=0.022) and G3 NET (OR 5.47, 95% CI (1.26-23.65), p=0.023) independently increased the probability of OR.

Conclusions:

The FOLFOX-bevacizumab combination has promising efficacy in patients with progressive metastatic NETs, notably in those with G3 NETs, for which optimal treatment is ill-defined yet. Hence, it could be a relevant alternative to alkylating-based chemotherapy in this setting and should be further explored prospectively.

Causes of death in patients with metastatic digestive neuroendocrine tumors

Background:
Survival of patients with metastatic digestive neuroendocrine tumors (NETs) is often prolonged and has improved over the last decades. The causes of death (COD) in this setting have been poorly described.

Methods:
We identified all deceased patients from the prospectively collected cohort of all patients (n=1250) treated in one expert center from January 2000 to December 2019. All consecutive dead patients with metastatic, histologically proven well differentiated NET from pancreatic (p) or small-intestine (si) origin were included. We centrally determined the main/secondary CODs and related mechanisms and explored their associations with disease characteristics using logistic regression analyses.

Results:
We included 196 patients (female gender 46%, median age 59 years) with metastatic pNET (55%) or siNET (45%), functioning in 49% and classified as G1, G2 or G3 NETs in 25%, 64% and 12% of cases, respectively. Tumor invasion was responsible for 69% of CODs, which were mainly hepatobiliary (liver failure, biliary obstruction; 24% of all patients) or digestive (occlusion, ischemia, bleeding; 13%). Hormone hypersecretion was responsible for 13% of CODs, mainly cardio-respiratory (carcinoid heart disease; 10%). Iatrogenic mechanism was related to 13% of CODs, mainly cardio-respiratory and sepsis (5% and 4%, respectively). On multivariate analysis (mechanisms related to primary or secondary CODs), death by tumor invasion was associated with pNET ($p=0.03$), sporadic setting ($p<0.01$) and higher number of systemic treatments ($p<0.01$). Death by hormone secretion was associated with carcinoid heart disease ($p<0.01$), more metastatic sites ($p=0.02$) and higher number of systemic treatments ($p<0.01$). Death by iatrogenic mechanism was associated with liver-directed therapies ($p=0.02$), older age ($p=0.11$) and the absence of targeted therapies ($p=0.037$).

Conclusions:
This is the first study with precise description of CODs and related mechanisms in a large real-life cohort. It provides meaningful insights on of the natural history of these neoplasms and its evolution over the past two decades.

Hepatocellular Carcinoma

Predicting the efficacy of lenvatinib plus anti-PD-1 antibodies in unresectable hepatocellular carcinoma (uHCC) using radiomics features of tumors extracted from baseline MRI

Background:
Development of a method to predict the response of HCC to combination therapy with lenvatinib plus anti-PD-1 antibodies before treatment initiation would have great clinical benefit.

Methods:
Consecutive patients with uHCC receiving first-line lenvatinib plus an antiPD-1 antibody between Sep 2018 and Feb 2021, and who had at least one radiological response evaluation, were eligible for this study. Intrahepatic tumor response was assessed every 2 months (± 2 weeks) using modified RECIST; patients with a best intrahepatic tumor response of complete or partial response were defined as radiological responders and those with stable or progressive disease were defined as radiological non-responders. Radiomic features of intrahepatic tumors were extracted from the enhanced arterial and delayed phase of baseline MRI images. A Least Absolute Shrinkage and Selection Operator (LASSO) model was employed for feature selection. A Neural Network was used to develop the prediction model. The optimal cutoff value was determined using a receiver operating characteristic (ROC) curve by maximizing the Youden index.

Results:
Of 96 eligible patients, 50% (n = 48) were radiological responders and 50% (n = 48) were non-responders. All patients were randomly divided into training (n = 72) and validation (n = 24) sets. A total of 2,420 radiomic features were extracted and normalized with min-max normalization. Features in the training set with intraclass correlation coefficients ≥ 0.80 were introduced into the LASSO model. Five features in the arterial phase and five in the delayed phase were identified as significant and used to build a neural network. The optimal cutoff value was 0.504. The area under the ROC curve, accuracy, specificity, and sensitivity for predicting objective response were 0.971 ($P < 0.001$), 97.2%, 97.2% and 97.2% in the training set, respectively; and were 0.778 ($P = 0.010$), 75.0%, 91.7% and 58.3% in the validation set, respectively.

Conclusions:
Radiomics features from baseline MRI may serve as predictors for objective response to lenvatinib plus anti-PD-1 antibodies in uHCC patients before treatment initiation.

Clinical trial identification:
NCT04639284

An exploratory subgroup analysis of a phase II/III trial of donafenib versus sorafenib in the first-line treatment of advanced hepatocellular carcinoma

Background:

An open-label, randomized, multicenter phase II/III trial (ZGDH3) has demonstrated that compared with sorafenib, donafenib significantly prolonged the overall survival (OS) of patients with advanced hepatocellular carcinoma (HCC). It also showed a better survival benefit than sorafenib in the prespecified subgroup analysis. This article aimed to further explore whether the baseline characteristics of patients other than the predefined subgroups were related to the better OS benefit of donafenib.

Methods:

This analysis was based on the ITT population of ZGDH3 study. The median OS of donafenib and sorafenib was assessed by the Kaplan-Meier method and was compared for each baseline characteristic subgroup. The stratified Cox proportional hazard model was used to calculate the hazard ratio and its 95% confidence interval.

Results:

668 patients were included in the analysis (334 in each group). Donafenib was associated with a trend of improved OS benefit when compared with sorafenib in most subgroups (HR < 1), with significant differences in the following subgroups: ECOG PS score of 1 (p = 0.0462), normal AST (p = 0.0439), no prior interventional therapy (p = 0.0433), lung target lesion absent (p = 0.0062), lymph node target lesion present (p = 0.0277), age ≥ 65 years (p = 0.0089), and BMI < 25 (p = 0.0054). Among patients ≥ 65 years of age, the median OS of the donafenib group and the sorafenib group was 12.1 and 8.9 months, respectively, representing the most significant benefit in the donafenib group (HR 0.516, 95% CI 0.315e0.847).

Table: 935P Exploratory subgroup comparison of donafenib *vs* sorafenib in OS

Subgroup	Median (months)	HR (95% CI)
ECOG PS 1	11.7 *vs* 9.6	0.804 (0.649, 0.996)
AST Normal	15.7 *vs* 13.5	0.776 (0.606, 0.993)
No prior interventional therapy	11.5 *vs* 8.8	0.741 (0.554, 0.991)
Lung target lesion absent	13.0 *vs* 10.1	0.758 (0.622, 0.925)
Lymph node target lesion present	7.9 *vs* 7.2	0.599 (0.380, 0.945)
Age ≥ 65	12.1 *vs* 8.9	0.516 (0.315, 0.847)
BMI <25	11.2 vs 9.1	0.757 (0.622, 0.921)

Conclusions:

Donafenib exhibited a better survival benefit than sorafenib in most of the baseline characteristic subgroups, which further confirmed the excellent efficacy of donafenib in the first-line treatment of advanced HCC.

Multicenter phase II trial of lenvatinib plus hepatic intraarterial infusion chemotherapy with cisplatin for advanced hepatocellular carcinoma: LEOPARD

Background:

The aim of this trial was to evaluate the efficacy and safety of lenvatinib (LEN) in combination with HAIC using cisplatin (CDDP) in patients (pts) with advanced hepatocellular carcinoma (HCC).

Methods:

In this multicenter, open-labeled, single-arm, phase II trial, advanced HCC pts categorized as Child-Pugh class A with no prior history of systemic therapy were enrolled to receive Len+CDDP (lenvatinib: 12 mg once daily for patients weighing ≥60 kg, 8 mg once daily for patients weighing <60 kg; HAIC with CDDP: 65 mg/m2, day 1, every 4 to 6 weeks, up to a maximum of 6 cycles). The primary endpoint was the objective response rate (ORR) as assessed with modified RECIST by an independent review committee (IRC). The secondary endpoints were the ORR as assessed with RECIST v1.1 by IRC, the progression-free survival, the overall survival, and frequency of adverse events associated with the treatment. The threshold and expected ORRs were 20% and 40%, respectively at a one-sided significance level of 0.05, and statistical power of 80%. Based on these data, the number of pts required was estimated to be 35.

Results:

A total of 36 pts was enrolled between September 2018 and March 2020, but two pts were judged as having no measurable lesions by the IRC. Among the remaining 34 evaluable pts, the ORR by the IRC according to modified RECIST and RECISTv1.1 were 64.7% (95% confidence interval (CI): 46.5%-80.3%), and 45.7% (95% CI: 28.8%-63.4%), respectively. The study treatment was discontinued in all the 36 pts for the following reasons: disease progression (24 pts, 67%), adverse events (9 pts, 25%), others (3 pts, 8%). The median progression-free survival and overall survival were 6.3 months (95% CI: 5.1-7.9 months) and 17.2 months (95% CI: 10.9-NA, months), respectively. The main grade 3-4 adverse events were increased AST (34%), hyponatremia (25%), leukopenia (22%), increased ALT (19%), and hypertension (11%). There were no treatment-related deaths in this series.

Conclusions:

Len+CDDP yielded very favorable ORR and overall survival, and was well tolerated in pts with advanced HCC. Further evaluation of this regimen in a phase III trial is warranted.

Clinical trial identification:

jRCTs031180019

KN046 (an anti-PD-L1/CTLA-4 bispecific antibody) in combination with lenvatinib in the treatment for advanced unresectable or metastatic hepatocellular carcinoma (HCC): Preliminary efficacy and safety results of a prospective phase II trial

Background:

In IMbrave 150 study combo treatment of PD-L1 inhibitor (Atezolizumab) with VEGFR inhibitor（Bevacizumab) prolonged the overall survival dramatically in HCC. However, the objective response rate (ORR) of 27% by RECIST v1.1 was still low. There is unmet clinical need to further improve ORR in conversion treatment for unresectable HCC. Here we assessed the safety and efficacy of KN046 in combination with Lenvatinib in 1st line HCC treatment.

Methods:

Enrolled patients (pts) with Barcelona Clinic Liver Cancer (BCLC) stage B or C had received Lenvatinib 12 mg/day (bodyweight [BW] ≥60 kg) or 8 mg/day (BW<60 kg) orally and KN046 5 mg IV on Day 1 of a 21-day cycle until disease progression or intolerable toxicity or 2 years. Primary endpoints were safety and ORR by RECISTv1.1 per investigators.

Results:

As of April 8th, 2021, 25 enrolled pts received combination treatment with median duration of 10 weeks. Only two pts discontinued treatments, one for disease progression and one for pneumonitis. For 21 evaluable pts, ORR was 57% (95% CI 34.0%-78.2%) and DCR was 95% (95% CI 76.2%-99.9%) by RECIST v1.1 and imRECIST. When evaluated by mRECIST, ORR and DCR improved to 76.2% (95% CI 52.8%-91.8%) and 95% (95% CI 76.2%-99.9%), respectively. Treatment-emergent adverse events (TEAEs) occurred in 64% (16 out of 25) of pts, 20% (n=5) of which was ≥grade 3. The incidence of TEAE related KN046 was 60% (n=15), 8% of which was ≥grade 3. The ≥grade 3 TRAE related KN046 were pneumonitis (n=1, 4.0%) and platelet count decreased (n=1, 4.0%).

Conclusions:

KN046+Lenvatinib showed promising antitumor activity with relatively high ORR and a tolerable safety profile in 1st line HCC treatment.

Clinical trial identification:

NCT04542837 Unique Protocol ID: 20200825

Adjuvant camrelizumab combined with apatinib treatment after resection of hepatocellular carcinoma in CNLC II and III stage: A single-center prospective phase II trial

Background:
Hepatocellular carcinoma (HCC) is a common tumor worldwide and a leading cause of tumor-related death. Surgical resection is one of the most effective treatments with curative potential. However, high recurrence rate (up to 50-70% in 5 years) after curative resection severely reduces the long-term survival of HCC patients. Especially, survival after resection of HCC in China liver cancer (CNLC) stage II-III remains poor. Anti-PD-1 antibody Camrelizumab combined with apatinib has been shown to be safe and effective in patients with advanced HCC. In the present study its efficacy and safety in CNLC stage II-III HCC patients after resection was explored.

Methods:
In this single-center, open-label, prospective, phase II trial, the patients received Camrelizumab (fixed dose 200 mg) every 3 weeks, total one year, and apatinib (250 mg/day), total one year, until they experienced disease recurrence or intolerable toxicity. The primary endpoint was relapse-free survival (RFS); the secondary endpoints was safety and overall survival (OS).

Results:
From a total of 76 patients who were screened between October 2018 and June 2019, 45 study participants received Camrelizumab and apatinib. Of the 45 patients, there were 25 CNLC stage II patients and 20 CNLC stage III patients. The median follow-up was 21.5 months [interquartile range (IQR): 19.6-24.0 months]. The median RFS was 11.7 months [95% confidence interval (CI): 5.8-17.6 months]. The 1year OS rate and 1-year RFS rate was 97.8% and 48.9% after surgery, respectively. The 2-year OS rate and 2-year RFS rate was 75.7% and 41.0%, respectively. A total of 12 (26.7%) patients experienced adverse events, and one (2.2%) patient had grade 3 or 4 adverse events (grade 3 thrombocytopenia and grade 4 leukopenia). The most frequent adverse event is liver dysfunction (n=11/45, 24.4%). No treatment-related deaths occurred.

Conclusions:
Camrelizumab combined with apatinib showed promising efficacy, and was well tolerated in patients with CNLC stage II-III HCC after resection. Further studies are warranted.

Clinical trial identification:
NCT03722875

Hepatic artery infusion chemotherapy (HAIC) combined with apatinib and camrelizumab for hepatocellular carcinoma (HCC) in BCLC stage C: A prospective, single-arm, phase II trial (TRIPLET study)

Background:

The combination of anti-angiogenesis and immune checkpoint blockade has been proved to improve clinical outcomes of advanced HCC. We assessed the efficacy and safety of HAIC combined with apatinib and camrelizumab for BCLC stage C HCC.

Methods:

Consecutive treatment-naïve patients with BCLC stage C HCC were enrolled in this phase II trial (NCT04191889). Eligible patients were administrated with HAIC (oxaliplatin 85 mg/m2, leucovorin 400 mg/m2 and fluorouracil 2500 mg/m2; q3w; 6 cycles), combined with apatinib (250 mg qd) and camrelizumab (200 mg q3w) until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR). Following an optimal Simon 2-stage design, 26 eligible patients needed to be included in the first stage, of whom at least 11 patients had to achieve objective responses to warrant further investigation in the second stage.

Results:

From April 13th, 2020 to March 19th, 2021, 26 eligible patients were enrolled. As of April 30th, 2021, the median follow-up was 8.87 months and all patients had at least one post-baseline tumor assessment. The confirmed ORR was 61.54% (95% CI, 42.54%e77.57%) with 16 partial responses (PR) per RECIST v1.1, which met the threshold for expanding enrollment, while 76.92% (95% CI, 57.95%e 88.96%) with 2 (7.69%) complete responses (CR) and 18 (69.23%) PR per mRECIST. The disease control rate (DCR) was 92.31% (95% CI, 75.86%-97.87%) whether per RECIST v1.1 or mRECIST. The median time to response (mTTR) was 2.37 months (interquartile range (IQR), 1.39-2.76) per RECIST v1.1 or 1.67 months (IQR, 1.37-2.72) per mRECIST. The estimated 6-month progression-free survival (PFS) rate was 73.7% per RECIST v1.1, while the 12-month overall survival rate was 90.7%. Grade ≥3 adverse events (AEs) occurred in 69.23% of the patients, of which the most common were decreased neutrophils (38.46%), decreased lymphocytes (34.62%), and increased ALT and AST (26.92% for each).

Conclusions:

The triplet treatment of HAIC, apatinib and camrelizumab showed promising clinical benefits and acceptable safety for BCLC Stage C HCC.

Clinical trial identification:

NCT04191889