REVIEW ARTICLE

Advanced-Stage Non–Small Cell Lung Cancer: Advances in Thoracic Oncology 2018

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ABSTRACT

In 2018 research in the field of advanced NSCLCs led to an expanded reach and impact of immune checkpoint inhibitors (ICIs) as part of a frontline treatment strategy, regardless of histologic subtype, with ICI use extended to include stage III disease, shifting the prognosis of all these patients. This new standard first-line approach opens a gap in standard second-line treatment, and older combinations may again become standard of care after progression during treatment with an ICI. The characterization of predictive

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biomarkers, patient selection, the definition of strategies with ICI combinations upon progression during treatment with ICIs, as well as prospective evaluation of the efficacy of ICIs in subpopulations (such as patients with poor performance status or brain metastases) represent upcoming challenges in advanced thoracic malignancies. In oncogene-addicted NSCLC three major steps were taken during 2018: next-generation tyrosine kinase inhibitors have overtaken more established agents as the new standard of care in *EGFR* and *ALK* receptor tyrosine kinase gene (*ALK*)-positive tumors. Mechanisms of acquired resistance have been reported among patients treated with next-generation EGFR tyrosine kinase inhibitors, reflecting the diversity of the landscape. One major step forward was the approval of personalized treatment in very uncommon genomic alterations, mainly fusions. This raises a new question about the challenge of implementation of next-generation sequencing in daily clinical practice to detect new and uncommon genomic alterations and to capture the heterogeneity of the mechanisms of acquired resistance during treatment, as well as the need to extend research into new therapeutic strategies to overcome them.

Keywords: Advanced; Non–small cell lung cancer; Immune checkpoint inhibitors; Oncogenic drivers

Introduction

The year 2018 secured the role of immune checkpoint inhibitors (ICIs) in the frontline treatment strategy for advanced NSCLCs and extended ICI use to stage III disease, and it also set a new standard of care (SoC). In the field of oncogene-addicted tumors, next-generation tyrosine kinase inhibitors (TKIs) have replaced more established agents as the new SoC in *EGFR*- and *ALK* receptor tyrosine kinase inhibitor gene (*ALK*)-positive tumors based on improved progression-free survival (PFS) and intracranial activity; and new TKIs have been approved for uncommon genomic alterations such as ret proto-oncogene gene (*RET*) and neurotropic tropomyosin receptor kinase gene (*NTRK*) rearrangements. In this review we cover the main advances in all of these strategies for treatment of both treatment-naive and previously treated patients with advanced NSCLC.

Methods for Selection of the Studies

We reviewed MEDLINE/PubMed for citations from January 2018 up to January 2019; our search terms included *lung cancer*, *ICIs*, *programmed death 1* (*PD-1*)/*programmed death ligand 1* (*PD-L1*) *inhibitors*, *cytotoxic T-lymphocyte associated protein 4 inhibitors*, *targeted therapy*, and *chemotherapy*. The authors also checked and identified relevant abstracts presented during the year 2018 at the American Society of Clinical Oncology and European Society of Medical Oncology Congress, as well as at the World Conference on Lung Cancer and the European Society of Medical Oncology Immuno-Oncology Congress.

Immunotherapy in Advanced NSCLC

Immunotherapy in Stage III NSCLC

In approximately one-third of patients, NSCLC is diagnosed as unresectable stage III disease, and patients have a median 5-year overall survival (OS) rate of 15% with standard concurrent platinum-based doublet chemotherapy and radiotherapy (CTRT).[1]

In the phase III PACIFIC trial, for patients with stage III NSCLC without progression after concurrent CTRT, the addition of 1 year of durvalumab therapy compared with placebo as consolidation treatment significantly prolonged PFS time (16.8 versus 5.6 months [hazard ratio (HR) = 0.52, 95% confidence interval (CI): 0.42– 0.65, $p < 0.001$]) and OS time (not reached versus 28.7 months [HR = 0.68, 99.73% CI: 0.47–0.997, $p < 0.0025$]).[2] These PFS and OS benefits were observed across all prespecified subgroups, including those based on sex, histologic subtype, and response to previous treatment. Compared with placebo, durvalumab improved the response rate (RR) (30% versus 17.8% [$p < 0.001$]) and the median time to death or distant metastasis (28.3 and 16.2 months, respectively [HR = 0.53, 95% CI: 0.41–0.68]) and decreased the incidence of new brain metastases (BMs) (6.3% and 11.8%, respectively). The safety profiles were similar between arms, with rates of grade 3 or higher adverse events (AEs) of 29.9% versus 26.6%, including pneumonitis (3.6% versus 2.4%); 15.4% of patients treated with durvalumab and 9.8% of patients who received placebo discontinued the regimen on account of AEs.[2] On the basis of these compelling outcomes, the U.S. Food and Drug Administration (FDA) approved durvalumab in February 2018.

However, a subsequent unplanned post hoc analysis reported a lack of benefit in terms of outcome with durvalumab in tumors with PD-L1 expression less than 1% (for PFS, HR = 0.73 and 95% CI: 0.48–1.11; for OS, HR = 1.36 and 95% CI: 0.79–2.34),[3] and in September 2018 the European Medicines Agency (EMA) restricted approval of durvalumab to patients with tumors with a level of PD-L1 expression higher than 1%. It is noteworthy that PD-L1 expression was not an inclusion criterion in the PACIFIC trial, with baseline tissue samples available for only 64% of patients enrolled and only 148 patients having PD-L1 expression less than 1%. CTRT may induce changes in the tumor microenvironment; therefore, the predictive capacities of baseline PD-L1 expression cannot be accurately assessed. Therefore,

denying PD-L1–negative patients access to durvalumab would be more appropriate after prospective validation of their PD-L1 status.[4]

Data from phase II trial have shown that consolidation treatment with pembrolizumab for 1-year provides a median PFS of 15.0 months, median time to metastatic disease or death of 30.7 months, and 2-year OS rate of 62%,[5] endorsing the feasibility of a consolidation strategy with an anti–PD-1 drug. However, only consolidation treatment with durvalumab for 1 year should today be considered the new SoC and be used as the control arm in upcoming clinical trials. Table 1 summarizes some of the ongoing clinical trials, which may help to define the timing and duration of ICI in stage III NSCLC.

Immunotherapy in the First-Line Setting

Chemotherapy-Sparing Strategies. The KEYNOTE 024 trial randomized 305 patients whose tumors express PD-L1 of at least 50% or more to receive 200 mg of pembrolizumab every 3 weeks (for up to 2 years) or up to six cycles of standard platinum-doublet chemotherapy. Pembrolizumab achieved the PFS primary end point (10.3 versus 6.0 months [HR = 0.5, 95% CI: 0.37–0.68, $p < 0.001$]), and favored RR (45% versus 28%). The median OS time was 30.0 months with pembrolizumab and 14.2 months with chemotherapy (HR = 0.63, 95% CI: 0.47–0.86) despite the 54% of patients assigned to the control arm who crossed over on study to receive pembrolizumab. When adjusted for crossover, the HR for OS was 0.49 (95% CI: 0.34–0.69). The rate of treatment-related grade 3 or higher AEs (31.2% versus 53.3%)[6] and quality of life[7] also favored pembrolizumab.

In the KEYNOTE 042 trial[8], 1274 treatment-naive patients with advanced NSCLC and a level of PD-L1 expression of at least 1% were randomized 1:1 to pembrolizumab or chemotherapy. Randomization was per protocol stratified according to PD-L1 expression level (≥50% versus 1-49%) Pembrolizumab significantly improved OS compared with chemotherapy for the whole population (16.7 versus 12.1 months [HR = 0.81, 95% CI: 0.71–0.93, $p = 0.0018$]) (Table 2).[6,8–17] However, in the exploratory OS analysis according to PD-L1 expression, the OS benefit with pembrolizumab was driven largely by tumors with a level of PD-L1 expression of at least 50% (for almost half [47%] of the study population, the OS time was 20.0 versus 12.2 months [HR = 0.69; 95% CI: 0.56–0.85, $p = 0.003$]), whereas the OS benefit with pembrolizumab disappeared in tumors with a level of PD-L1 expression between 1% and 49%, 13.4 versus 12.1 months (HR = 0.92, 95% CI: 0.77–1.11). Grade 3 or higher drug-related AEs were less frequent with pembrolizumab (17.8% versus 41.0%).[8]

The survival benefit reported in KEYNOTE 024[6] and KEYNOTE 042[8] has established the role of pembrolizumab as first-line treatment restricted to patients with advanced NSCLC with a level of PD-L1 expression of at least 50% and without *EGFR/ALK* aberrations. In contrast, in the CheckMate 026 trial, nivolumab compared with chemotherapy did not improve the outcome in the whole population or in patients with high PD-L1[9] expression (see Table 2). Pembrolizumab may be an alternative to chemotherapy for patients with a level of PD-L1 expression between 1% and 49%, but as the results are seemingly even better with combination of chemotherapy and immunotherapy, the latter should be the preferred option for this population.

The phase III MYSTIC trial[10] assessed the efficacy of durvalumab with or without tremelimumab compared

Table 1. Ongoing Clinical Trials with Immune Checkpoint Inhibitors in Patients with Stage III NSCLC

NCT No.	Drug	ICI Strategy	Treatment Duration	Primary End Point
NCT03519971 (PACIFIC2)	Durvalumab	Concurrent	Until PD	PFS and OS
NCT03509012 (CLOVER)	Durvalumab	Concurrent		Dose-limiting toxicity
NCT03693300	Durvalumab	Consolidation	24 mo	Grade ≥3 TRAEs
NCT03285321 (LUN16-081)	Nivolumab Nivolumab + ipilimumab	Consolidation	6 mo	PFS
NCT03663166	Ipilimumab/nivolumab	Concurrent/consolidation	12 mo	Toxicity
NCT02768558 (RTOG-3505)	Nivolumab	Consolidation	12 mo	OS
NCT02434081 (NICOLAS)	Nivolumab	Concurrent + consolidation	12 mo	Grade ≥3 pneumonitis
NCT03631784 (KEYNOTE-799)	Pembrolizumab	Concurrent + consolidation	6 mo	Grade ≥3 pneumonitis
NCT02343952 (LUN14-179)	Pembrolizumab	Consolidation	12 mo	TTD or metastases
NCT03379441	Pembrolizumab	Consolidation	24 mo	OS
NCT02525757 (DETERRED)	Atezolizumab	Concurrent + consolidation Consolidation	12 mo	Time to toxicity
NCT00828009 (ECOG6508)	L-BLP25 + BVZ	Consolidation	Until PD	Safety

ICI, immune checkpoint inhibitor; PD, progressive disease; PFS, progression-free survival; OS, overall survival; TRAE, treatment-related adverse event; TTD, time to death; L-BLP25, recemotide; BVZ, bevacizumab.

Table 2. Clinical Trials Testing Immune Checkpoint Inhibitors in the First-Line Setting in Patients with Advanced NSCLC

Trial	n	Treatment arm	RR, %	Median PFS, mo HR (95% CI)	Median OS, mo HR (95% CI)
KEYNOTE 024[6] PD-L1 ≥50%	350	Pembrolizumab chemotherapy	45 vs. 28	10.3 vs. 6.0 HR = 0.5 (95% CI: 0.37-0.68)	30.0 vs. 14.2 HR = 0.63 (95% CI: 0.47-0.86)
KEYNOTE 042[8] PD-L1 ≥ 1%	1274	Pembrolizumab chemotherapy	27 vs. 27	5.4 vs. 6.5 HR = 1.07 (95% CI: 0.94-1.21)	16.7 vs. 12.1 HR = 0.81 (95% CI: 0.71-0.93)
CheckMate 026[9] PD-L1 ≥ 5%	423	Nivolumab chemotherapy	26 vs. 33	4.2 vs. 5.9 HR = 1.15 (95% CI: 0.91-1.45)	14.4 vs. 13.2 HR = 1.02 (95% CI: 0.80-1.30)
MYSTIC[10] PD-L1 ≥ 25%	488	Durvalumab Durvalumab + tremelimumab chemotherapy	36 vs. 34 vs. 38	4.7 HR = 0.87 (95% CI: 0.59-1.3) 3.9 HR = 1.05 (95% CI: 0.72-1.53) 5.4	16.3 HR = 0.76 (95% CI: 0.56-1.02) 11.9 HR = 0.85 (95% CI: 0.61-1.17-12.9)
CheckMate 227[11] TMB-high[a]	399	Nivolumab + ipilimumab chemotherapy	45 vs. 27	7.2 vs. 5.5 HR = 0.58 (95% CI: 0.41-0.81)	23.03 vs. 16.72 HR = 0.77 (95% CI: 0.56-1.06)
KEYNOTE189[12] All comers	616	Pembrolizumab + platinum + Pem Platinum + Pem	48 vs. 19	8.8 vs. 4.9 HR = 0.52 (95% CI: 0.43-0.64)	NR vs. 11.3 HR = 0.49 (95% CI: 0.38-0.64)
IMPOWER 150[13] All comers/WT[b]	696	BVZ + Atezolizumab + Carbo + P BVZ + Carbo + P	56 vs. 41	8.3 vs. 6.8 HR = 0.59 (95% CI: 0.50-0.70)	19.2 vs. 14.7 HR = 0.78 (95% CI: 0.69-0.96)
IMPOWER 130[14] All comers/WT	679	Atezolizumab + Carbo + nP Carbo + nP	49 vs. 32	7.0 vs. 5.5 HR = 0.64 (95% CI: 0.54-0.77)	18.6 vs. 13.9 HR = 0.79 (95% CI: 0.64-0.98)
IMPOWER 132[15] All comers	578	Atezolizumab + platinum + Pem Platinum + Pem	–	7.6 vs. 5.2 HR = 0.60 (95% CI: 0.49-0.72)	18.1 vs. 13.6 HR = 0.84 (95% CI: 0.64-1.03)
KEYNOTE 407[16] All comers	559	Pembrolizumab + Carbo + P/nP Carbo + P/nP	58 vs. 38	6.4 vs. 4.8 HR = 0.56 (95% CI: 0.45-0.70)	15.9 vs. 11.3 HR = 0.64 (95% CI: 0.49-0.85)
IMPOWER 131[17] All comers[c]	683	Atezolizumab + Carbo + nP Carbo + nP	49 vs. 41	6.5 vs. 5.6 HR = 0.74 (95% CI: 0.62-0.87)	14.6 vs. 14.3 HR = 0.92 (95% CI: 0.76-1.12)

[a]High-TMB means at least 10 mutations per megabase.
[b]Data reported for arm B (atezolizumab, bevacizumab, carboplatin, and paclitaxel) versus arm C (bevacizumab, carboplatin, and paclitaxel).
[c]Only arms B and C of the trial are reported in this table.
RR, response rate; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; PD-L1, programmed death ligand 1; Pem, pemetrexed; NR, not reached; WT, wild-type;. BVZ, bevacizumab; Carbo, carboplatin; P, Paclitaxel; nP, nab-paclitaxel; TMB, tumor mutation burden.

with that of platinum-based doublet chemotherapy in 1118 patients with metastatic NSCLC. The primary end points were OS for durvalumab versus chemotherapy and OS and PFS for the immunotherapy combination versus chemotherapy in patients with PD-L1 expression of at least 25% (by SP263 assay). The efficacy findings for the 488 patients with a level of PD-L1 expression by tumor cells of at least 25% showed median OS times of 16.3 versus 12.9 months for durvalumab versus chemotherapy (HR = 0.76, 97.54% CI: 0.76–1.019, p = 0.036) and 11.9 versus 12.9 months for the immunotherapy combination versus chemotherapy (HR = 0.85, 98.77% CI: 0.61–1.17, p = 0.202). The median PFS time was 3.9 versus 5.4 months for durvalumab plus tremelimumab versus chemotherapy (HR = 1.05, 99.5% CI: 0.72–1.53, p = 0.705 [see Table 2]). These results do not currently support the use of durvalumab as a single agent or in combination with tremelimumab in this patient population. The ongoing randomized phase III trial NEPTUNE (NCT02542293) is assessing durvalumab and tremelimumab versus chemotherapy in patients with advanced NSCLC (with either PD-L1–positive or PD-L1−negative tumors), and the primary end point is OS.

Tumor mutation burden (TMB) has recently emerged as an alternative biomarker independent of PD-L1 expression to identify patients who derive clinical benefit from PD-1 monotherapy or combination nivolumab and ipilimumab.[9,18] The CheckMate 227 phase III trial,[11] assessed multiple hypotheses including PFS, for nivolumab plus ipilimumab versus chemotherapy among patients with a high TMB (defined as ≥10 mutations per megabase [Mut/Mb], according to the results of the phase II CheckMate 568 trial[18]). Of the 1739 patients enrolled in the trial, only 1004 (58%) had valid results. Of those patients, 44% were classified as TMB high (24% of the intent-to-treat population), and just 299 were selected for evaluating the coprimary PFS end point. TMB-high status was associated with longer PFS time (7.2 versus 5.5

months [HR = 0.58, 97.5% CI: 0.41–0.81, $p < 0.001$]) and increased RR (45% versus 27%) with nivolumab and ipilimumab versus with chemotherapy. The PFS benefit was observed for all TMB-high subgroups regardless of PD-L1 expression (≥1% or < 1%). However, the percentatge of patients whose tumors express PD-L1 of 50% or more in the high TMB treated with the immunotherapy combination has not been reported. The rates of grade 3 or 4 treatment-related AEs were 31.2% and 36.1%, respectively. However, for patients with a TMB less than 10 Mut/Mb, exploratory analysis showed that the HR for OS with nivolumab and ipilimumab versus with chemotherapy was 0.78 (95% CI: 0.61–1.00 [medians of 16.2 months and 12.42 months, respectively]), which is similar to that observed in patients with a TMB of 10 or more (HR = 0.77, 95% CI: 0.56–1.06 [medians of 23.03 months and 16.72 months, respectively]) (see Table 2).[19] As such, TMB may be a prognostic rather than predictive biomarker, and further investigation is needed. On the basis of this lack of statistically significant benefit in terms of OS, the company has withdrawn its FDA application for lung cancer drug combinations. Other ongoing first-line clinical trials are assessing the role of nivolumab and ipilimumab with or without chemotherapy, such as the multicohort phase III/IV CheckMate 877 trial (NCT02869789),[20] and the CheckMate 9LA trial (NCT03215706).

Immunotherapy plus Chemotherapy Combinations. KEYNOTE 189 was an eagerly awaited phase IIII trial that solidified the role of first-line pembrolizumab plus chemotherapy for all patients with nonsquamous NSCLC.[12] Overall, 616 patients were randomized 2:1 to pembrolizumab plus platinum and pemetrexed (CPP) or platinum-pemetrexed and placebo, and after completing four cycles patients continued to receive pemetrexed and pembrolizumab or placebo as maintenance therapy. Individuals with *EGFR* or *ALK* alterations were excluded. The CPP triplet regimen demonstrated significant improvement of the two coprimary endpoints by an independent radiological review, with a longer PFS (8.8 versus 4.9 months [HR = 0.52, 95% CI: 0.43–0.64, $p < 0.001$]) and OS benefit (not reached versus 11.3 months [HR = 0.49, 95% CI: 0.38–0.64, $p < 0.001$]) over chemotherapy alone, despite a crossover rate of 41.3% (see Table 2). The benefit with the CPP triplet was reported regardless of platinum subtype and across all PD-L1 subgroups, including PD-L1–negative tumors, although it was most pronounced in those with higher PD-L1 expression.[12,21] The KEYNOTE 189 results confirmed earlier data from the phase II KEYNOTE 021G trial, which reported significantly better outcome in terms of RR, PFS, and OS with CPP than with chemotherapy.[22] Together, these results led to FDA and EMA approval of the CPP triplet.

Three phase III trials evaluated atezolizumab in combination with chemotherapy in patients with nonsquamous NSCLC: IMpower 150,[13,23] IMpower130,[14] and IMpower132.[15] The coprimary end points for all three trials were investigator-assessed PFS and OS in the wild-type population (intention to treat). The three-arm IMpower150 study compared the efficacy of atezolizumab, bevacizumab, carboplatin, and paclitaxel (ABCP) and atezolizumab, carboplatin, and paclitaxel (ACP) to bevacizumab, carboplatin, and paclitaxel (BCP). After four or six cycles of chemotherapy, bevacizumab, and/or atezolizumab were given as maintenance treatment. Crossover was not allowed, but subsequent nonprotocol ICI treatment was administered in 31.7% of patients in the BCP arm.[23] IMpower130 randomized (2:1) patients to atezolizumab, carboplatin, and nab-paclitaxel (ACnP) followed by maintenance atezolizumab or carboplatin and nab-paclitaxel (CnP), followed by switch maintenance to pemetrexed or best supportive care. Crossover was allowed, and 59.2% of patients in the control arm received subsequent ICI treatment at progression. In both clinical trials, patients with *EGFR and ALK* alterations were included if they had exhausted their TKI therapy options (N = 164 in IMpower 150, with 124 *EGFR*-mutant, and N = 44 in IMpower 130). The magnitude of benefit in both trials was similar in terms of PFS (in IMpower 150[13] for ABCP versus BCP, HR = 0.59, 95% CI: 0.50–0.70, $p < 0.001$; in IMpower130[14] for ACnP versus CnP, HR = 0.64, 95% CI: 0.54–0.77, $p < 0.001$ [see Table 2]) and OS (in IMpower 150[13,23] for ABCP versus BCP HR = 0.78, 95% CI: 0.69–0.96, $p < 0.0164$; in IMpower130[14] for ACnP versus CnP, HR = 0.79, 95% CI: 0.64–0.98, $p < 0.033$ [see Table 2]). Indeed, in both trials, the PFS benefit with atezolizumab was positively correlated with PD-L1 expression,[14,23] although this correlation was not significant for OS for any PD-L1 subgroup.[13,14] As a result, in December 2018 the FDA approved ABCP for use in first-line treatment of metastatic nonsquamous wild-type NSCLC, and in January 2019 the EMA extended the approval to *EGFR*- or *ALK*-positive tumors after failure of appropriate targeted therapy.

In IMpower 150, the ACP arm did not improve OS compared with BCP (19.4 versus 17.4 months [HR = 0.88, 95% CI: 0.78–1.08, $p = 0.2041$]); however, a direct comparison between ABCP and ACP was not included in the IMpower150 study, although the median OS values seem similar.[13] Similarly, IMpower150 (ABCP arm) and IMpower 130 obtained similar survival outcomes, and these results raise a new question about the added benefit of bevacizumab. Subgroup analysis from IMpower150 demonstrated favorable OS with ABCP in patients with *EGFR/ALK* alterations (HR = 0.54, 95% CI: 0.29–1.03), as well as in patients with liver metastases (HR = 0.54, 95% CI: 0.33–0.88)[24]; however, benefit in

these subgroups was not reported in the ACP arm from IMpower150 (with *EGFR/ALK* alterations, HR = 0.82, 95% CI: 0.49–1.37; with liver metastases, HR = 0.85, 95% CI: 0.53–1.36)[24] or with ACnP from IMpower 130 (with *EGFR/ALK* alterations, HR = 0.98, 95% CI: 0.41–2.31; with liver metastases, HR = 1.04, 95% CI: 0.63–1.72). Thus additional prospective data are necessary to understand whether the hypothesized synergy between immunotherapy and antiangiogenic agents is clinically apparent.

Contrary to KEYNOTE 189,[12] IMpower132[15] demonstrated that the addition of atezolizumab to platinum-pemetrexed followed by pemetrexed and atezolizumab as maintenance treatment, improved PFS (HR = 0.60, 95% CI: 0.49–0.72, $p < 0.0001$) but not OS (HR = 0.81, 95% CI: 0.64–1.03, $p = 0.0797$) compared with chemotherapy alone (see Table 2). In the control arm, 37.1% of patients received subsequent ICIs.

The KEYNOTE 407 randomized squamous patients to pembrolizumab or placebo with carboplatin and either paclitaxel or nab-paclitaxel. Crossover was allowed, and 32% of patients in the control arm received an ICI.[7] OS time was improved by 4.9 months with pembrolizumab plus chemotherapy (HR = 0.64, 95% CI: 0.49–0.85, $p = 0.0008$), with a 44% reduction in risk of disease progression (HR = 0.56, 95% CI: 0.45–0.70 [see Table 2]).[16] The OS benefit was consistent regardless of PD-L1 expression and subtype of taxane chosen.[16,25] The FDA rapidly approved this pembrolizumab-chemotherapy combination for squamous disease (in October 2018), thus moving immunotherapy into the first-line setting for all patients with NSCLC and creating a new gap in the SoC for patients in the second line. Also for the squamous histologic subtype in the IMpower131,[17] atezolizumab plus carboplatin and nab-paclitaxel provided PFS benefit compared with chemotherapy alone across all PD-L1 tumor proportion score subgroups (6.5 versus 5.6 months [HR = 0.74, 95% CI: 0.62–0.87]), with a greater PFS advantage among those with high PD-L1 expression (10.1 versus 5.5 months [HR = 0.44, 95% CI: 0.27–0.71]). The second interim OS analyses did not show a significant difference in OS (14.6 versus 14.3 months [HR = 0.92, 95% CI: 0.76–1.12]) ($p = 0.41$) (see Table 2).[17]

In the Supplementary Data, we provide a forest plot of the outcome of the combination of ICIs and chemotherapy (with or without bevacizumab) compared with chemotherapy as first-line therapy in the overall population of patients with advanced NSCLC (Supplementary Fig. 1), in PD-L1–negative tumors (Supplementary Fig. 2), and in tumors with a level of PD-L1 expression of at least 50% (Supplementary Fig. 3). Whether this strategy is better than monotherapy in patients with tumors with PD-L1 expression of at least 50% remains unknown (see Supplementary Fig. 3), and only a clinical trial would definitely answer this question.

Immunotherapy in the Second- and Later-Line Settings

The updated efficacies of ICIs from phase I trials have provided evidence of them overcoming the prognosis of patients with advanced NSCLC, leading to 4-year OS rates of 16.4% and 27.2% among previously treated and treatment-naive patients with advanced NSCLC, respectively.[26] However, not all clinical trials with ICIs have obtained positive results in second-line setting. In contrast to other PD-1 and PD-L1 inhibitors in patients with NSCLC who have failed platinum-based chemotherapy, in the JAVELIN-Lung 200 phase III trial, avelumab in tumors with a level of PD-L1 expression of at least 1% did not improve the OS compared with docetaxel (11.4 versus 10.3 months [HR = 0.90, 96% CI: 0.72–1.12, one-sided $p = 0.16$]). This lack of survival benefit could be explained by the 26% rate of poststudy ICI therapy in the control arm.[27] Current approved anti–PD-1/PD-L1 drugs in the second-line setting remain the SoC for those patients who have not received upfront ICI.

The ARCTIC trial assessed the efficacy of ICIs in the third-line setting or beyond. Durvalumab monotherapy provided a clinically meaningful improvement in OS versus SoC (erlotinib, gemcitabine, or vinorelbine) in patients with a level of PD-L1 expression of at least 25%. A combination of durvalumab plus tremelimumab did not significantly improve OS or PFS versus the SoC in patients with a level of PD-L1 expression less than 25%.[28] However, as treatment with ICIs is already approved in earlier settings, the potential use of ICI in third-line is very limited.

Future Research Directions in Immunotherapy

Recently, hyperprogressive disease has been reported as a new pattern of progression in patientsw with NSCLC who are when taking an ICI. The tumor growth rates (TGRs) before and during treatment and variation per month (ΔTGRs) were calculated. Hyperprogressive disease was defined as disease progression at the first evaluation with ΔTGR exceeding 50%. Hyperprogressive disease was reported in almost 14% of patients with NSCLC versus in 5% who are underoing chemotherapy, and correlate with high metastatic burden and poor prognosis,[29] Future challenge is identifying which patients have increased risk of hyperprogressive disease during treatment and a consensus in the definition of this pattern of progression. Retrospective analyses of the OAK trial explored the risk-benefit of atezolizumab treatment beyond progression. The RR with treatment beyond progression

was 16% (7% in target lesions), and median PFS and OS times were 1.7 and 12.7 months, respectively, without increased toxicity.[30] However, on the basis of the limited efficacy of this strategy and no reliable available biomarkers of efficacy or progression, careful evaluation of patients' disease-related symptoms and performance status (PS) should always be put in perspective along with the results of radiological evaluation to guide physicians' decisions case by case.[31] Prospective trials should evaluate both this strategy and how local therapies may modulate its benefit. Other challenges are the efficacy of ICI in specific populations, such as pateints with BM or poor PS. Approximately 15% of patients enrolled in the OAK trial had asymptomatic treated BM. Atezolizumab provided better outcomes than did docetaxel in this population (OS times of 16.0 versus 11.9 months [HR = 0.74; 95% CI: 0.49–1.13]) and a lower probability of development of new symptomatic BM, suggesting that this population (even patients with active BM) should not be excluded from future trials with ICIs.[32] The PeP2 study assessed the efficacy of pembrolizumab in patients with previously treated advanced NSCLC and PS 2. Pembrolizumab gave an RR of 25.5% and median PFS and OS times of 6.0 and 12.1 months, respectively, with a 12% rate of grade 3 or higher AEs. Efficacy was higher in patients whose tumors had high PD-L1 expression.[33] These outcomes are at least comparable with those obtained with second-line pembrolizumab in patients with PS 0/1, suggesting pembrolizumab as a potential strategy in this population regardless of PD-L1 expression.

Finally, some concomitant treatments may affect outcome of ICI therapy. Baseline steroid use (10 mg/d of prednisone or the equivalent) are associated with shorter PFS and OS in patients with advanced NSCLC treated with ICIs[34]; however, outcomes in NSCLC are not apparently hampered by the use of steroids for the treatment of immune-related AEs.[35] Similarly, primary resistance to ICIs can be attributed to abnormal gut microbiome composition caused by antibiotic use or proton-pump inhibitors in patients with advanced solid tumors. Transplantation of fecal microbiota from patients with cancer who responded to ICIs into germ-free or antibiotic-treated mice ameliorated the antitumor effects of PD-1 blockade, whereas transplantation of fecal microbiota from nonresponding patients failed to do so.[36] In NSCLC, baseline antibiotic use within 30 days before initiation treatment with an ICI correlated with reduced survival benefit.[37] Prospective validation in large cohorts merits evaluation as well as investigation of how to modulate microbiome and the potential correlation between microbiome and risk of onset of immune-related AEs.

Liquid Biopsy and Immunotherapy

Despite the fact that blood-based assays are not theSoC, their predictive value to measure blood TMB (bTMB) has been assessed in the first- and second-line settings. In the second-line setting, retrospective bTMB (determined by using a 394 gene-based next-generation sequencing [NGS] assay) was assessed in approximately 75% of patients from two large randomized trials (the POPLAR trial as a discovery set and the OAK trial as validation set). The prevalence of high bTMB, defined as at least 16 Mut/Mb, was 30%. High bTMB significantly correlated with better PFS with atezolizumab, and PFS outcomes improved in patients whose tumors had high PD-L1 expression and a high bTMB, suggesting that a combination of biomarkers may be better at predicting outcomes than a single biomarker.[38] However, bTMB is not yet considered an SoC for assessing TMB.

An exploratory analysis of the MYSTIC trial[10] examined OS according to high bTMB (≥16 Mut/Mb, as determined by using a 500 gene-based panel). More than 70% of patients underwent bTMB evaluation, 40% of whom had a high bTMB; for these patients, the OS time was 16.5 months with the durvalumab and tremelimumab combination (versus 11.0 and 10.5 months with durvalumab and chemotherapy, respectively). The 2-year OS rates in patients with a high bTMB were 39% with the combination, 30% with durvalumab, and 18% with chemotherapy. For patients with a low bTMB, the OS was 8.5 months with durvalumab and tremelimumab, 12.2 months with durvalumab alone, and 11.6 months with chemotherapy. Contrary to the results of CheckMate 227, these results show a potential role for TMB as a predictive biomarker for OS benefit from combination immunotherapy; however, it was an exploratory analysis and these results require prospective validation. The phase II B-F1RST trial prospectively assessed bTMB as a predictive biomarker for atezolizumab efficacy in the first-line setting. Of 152 patients, 119 (77%) had adequate circulating tumor DNA (ctDNA) and 23% (n = 28) had a high bTMB (≥16 Mut/Mb). Atezolizumab was reported to improve outcome in patients with tumors with a high bTMB compared with in patients with tumors with a low bTMB in terms of RR (28.6% versus 4.4% [$p < 0.0002$]) and PFS (4.6 versus 3.7 months [HR = 0.66, 90% CI: 0.42–1.02, $p = 0.12$]), both of which were assessed by the investigator, as well as improved OS (not estimated versus 13.1 months [HR = 0.77; 90% CI: 0.41–1.03, $p = 0.48$]).[39] However, compared with other immunotherapy strategies using less expensive biomarkers such as PD-L1 in first-line setting, the results from B-F1RST do not seem very impressive, raising the question of whether monotherapy is the best strategy in tumors with high bTMB. Before bTMB may be

considered the SoC, the role of TMB in NSCLC needs validation; the most appropriate assays to measure bTMB must be identified and standardized cutoff points for high bTMB must be defined. Prospective validation of the bTMB assay in the first-line is ongoing in the randomized phase III BFAST trial (NCT03178552). In cohort C of the trial defined by high bTMB, patients will be randomized to atezolizumab or platinum chemotherapy with investigator-assessed PFS as the primary end point.

Targeted Therapies in Advanced NSCLC

Advances in EGFR-Mutant NSCLC

First-Line EGFR Therapies. EGFR TKIs, such as gefitinib, erlotinib, and afatinib, are the standard first-line therapy for patients with *EGFR*-mutant NSCLC.[40–42] However, resistance develops in most patients after 1 year of treatment, and new treatment strategies have been tested to improve the efficacy of first-line treatment. One approach is using novel EGFR TKIs in the first-line setting. The phase III ARCHER 1050 study compared the second-generation irreversible EGFR TKI dacomitinib with gefitinib in 452 patients with *EGFR*-mutant NSCLC without baseline BM. Dacomitinib compared with gefitinib improved PFS (HR = 0.59, 95% CI: 0.47–0.74, $p < 0.0001$),[43] as well as OS (median 34.1 versus 26.8 months [HR = 0.76, 95% CI: 0.582–0.993, $p = 0.0438$]),[44] without differences in RR. Skin AEs and diarrhea were reported more frequently in the dacomitinib arm, leading to frequent dose reductions in 66% of patients and treatment discontinuations,[43] which can limit acceptance of dacomitinib as the SoC. Nonetheless the FDA and EMA approved dacomitinib in the first-line setting in September 2018 and January 2019, respectively.

Similarly, after the randomized phase III FLAURA trial (N = 556), osimertinib, which is an oral central nervous system (CNS)-active, irreversible third-generation EGFR TKI selective for sensitizing both *EGFR* and T790M mutations, is also recommended as first-line treatment for patients with *EGFR*-mutant NSCLC on the basis of significant improvement in PFS (median 18.9 versus 10.0 months [HR = 0.46, 95% CI: 0.37–0.57, $p < 0.001$]) compared with the SoC first-generation EGFR TKIs (erlotinib or gefitinib), with similar RRs (80% versus 76% [$p = 0.242$]).[45] Postprogression end points also favored osimertinib, with the median second PFS with osimertinib not reached compared with 20 months in SoC arm.[46] However, the OS results are immature and the crossover rate in SoC is limited. One unique aspect of the FLAURA trial in comparison with the ARCHER 1050 study is that it included patients with CNS metastases, although for asymptomatic patients, brain scans were not mandated. However, in a preplanned subgroup analysis, osimertinib gave significant benefit in terms of CNS efficacy end points in patients with BM compared with the SoC, including response and time to CNS progression.[47] The FDA and the EMA both approved osimertinib for first-line treatment (in April and June 2018, respectively).

Other potential approaches in the first-line setting are adding chemotherapy, antiangiogenic monoclonal antibody, or anti-EGFR monoclonal antibody to EGFR TKIs. The phase III NEJ009 trial (N = 342) compared gefitinib plus carboplatin-pemetrexed combination treatment with gefitinib alone. The combination showed dramatic improvement in PFS (20.9 versus 11.2 months [HR = 0.494, 95% CI: 0.391–0.625, $p < 0.001$]) as well as OS (52.2 versus 38.8 months [HR = 0.695, 95% CI: 0.52–0.93, $p = 0.013$]) compared with gefitinib monotherapy. Grade 3 to 5 hematologic toxicities were more common in the combination arm.[48] The randomized phase II JO25567 study (N = 154) compared the combination of erlotinib plus bevacizumab with erlotinib monotherapy. The combination gave significantly longer PFS (16.0 versus 9.7 months [HR = 0.54, 95% CI: 0.36–0.79, $p = 0.0015$]),[49] and the EMA approved this combination in the first-line setting in June 2016. However, survival analyses did not demonstrate differences between arms (47.0 versus 47.4 months [HR = 0.81 95% CI: 0.53–1.23, $p = 0.326$]), although the sample size was not sufficiently powered to assess the OS benefit with the combination.[50] In contrast, another recent phase II trial (N = 88) did not report significant improvement in PFS with erlotinib plus bevacizumab versus with erlotinib monotherapy (17.9 months and 13.5 months, respectively [HR = 0.87, 95 CI: 0.54–1.43, $p = 0.59$]) in patients with *EGFR*-mutant NSCLC, with the survival data still immature.[51] Limited number of patients and treatment postprogression may influence the final results of this study. Results of the ongoing phase III NEJ026 trial (N = 224) comparing erlotinib plus bevacizumab with erlotinib alone endorse the PFS benefit of this combination (16.9 versus 13.3 months [HR = 0.605, 95% CI: 0.417–0.877, $p = 0.0157$]), with OS data not yet available.[52] The final results of this study may provide the real evidence about the efficacy of this strategy. Contrary to the other combinations, in the phase II SWOG1403 trial (N = 170) the addition of cetuximab to afatinib compared with afatinib alone did not improve PFS or OS, and it resulted in more frequent grade 3 or higher treatment-related AEs.[53]

One of the major challenges in the first-line setting is defining the optimal treatment approach, upfront third-generation versus sequential strategies, based on the lack of survival data, not second-generation EGFR TKI as a control arm in the FLAURA trial, and chemotherapy remains the SoC upon osimertinib progression. The ongoing APPLE trial (NCT02856893) assesses the best

strategy for delivering osimertinib in the first-line setting, upfront versus sequential according to biological or RECIST progression.[54] Another challenge is defining the role of combination strategies. Despite some combination strategies having overcome the 30-month OS reported in historical data with EGFR TKI monotherapy, potential overselection of patients, limitation in terms of generalizability (bevacizumab trials were performed only in the Japanese population), increased toxicity with combination therapy, and lack of data about the efficacy of some of these combinations in specific populations (such as patients with baseline BM) are limitations for broadly adopting combinations as current strategies in the first-line worldwide. Key results from the recent first-line EGFR TKIs studies are summarized in Table 3.[43–45,48–53]

Mechanisms of Acquired Resistance. The development of resistance to first-line treatment with gefitinib, erlotinib, or afatinib is inevitable, and the T790M mutation accounts for more than 50% of resistance followed by MNNG HOS Transforming gene (*MET*) amplification, activation of other bypass pathways, and histologic transformation to SCLC.[55] SCLC transformation occurs in 3% to 10% of cases within an average of 17.8 months after diagnosis, and it is usually characterized by retinoblastoma 1 gene (*RB1*), tumor protein p53 gene (*TP53*), and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alph gene (*PIK3CA*) mutations, with all cases retaining the *EGFR* mutation.[56] Both *RB1* and *TP53* may be present at baseline, suggesting that close and more frequent monitoring could be implemented in such patients on the basis of increased risk of SCLC transformation.[57] The phase III AURA 3 trial established osimertinib as the SoC in patients with NSCLC with acquired EGFR *T790M* mutation after failure during treatment with a first-line EGFR TKI, based on improved RR and PFS versus with platinum-pemetrexed, with survival data not yet reported.[58] Recently, mature clinical trial data from a pooled analysis of phase II trials gave a median OS of 26.8 months with osimertinib in patients with pretreated, acquired *T790M*-positive NSCLC.[59] However, tumors acquired resistance to osimertinib after 10 months of treatment. The resistance mechanism against osimertinib in 41 repeated tissue biopsy samples demonstrated that 28 patients (68%) showed loss of T790M and those patients had shorter PFS than did patients who retained *T790M* (6.1 versus 15.2 months [$p = 0.01$]). The resistance mechanisms in patients with loss of *T790M* include SCLC transformation (6), *MET* amplification (2), *BRAF* mutation (2), *PIK3CA* mutation (2), *KRAS* mutation (1), and fusion of *RET,* fibroblast growth factor receptor 3 gene (*FGFR3*), and *BRAF*. On the other hand, among 13 patients who retained *T790M* at

Table 3. Recent First-Line EGFR TKI Studies in *EGFR* Mutant-Positive NSCLC

Study	n	Treatment	ORR, %	Median PFS, mo	Median OS, mo	Gr3 AE (any cause), %
ARCHER1050[43,44]	452[a]	Dacomitinib vs. gefitinib	75 vs. 72	14.7 vs. 9.2 (HR = 0.59, $p < 0.0001$)	34.1 vs. 26.8 (HR = 0.76, $p = 0.044$)	63 vs. 41
FLAURA[45]	556	Osimertinib vs. gefitinib or erlotinib	80 vs. 76	18.9 vs. 10.2 (HR = 0.46, $p < 0.001$)	Not reported	34 vs. 45
NEJ009[48]	342	Gefinitb/carbo/pemetrexed vs. gefitinib	84 vs. 67	20.9 vs. 11.2 (HR = 0.49, $p < 0.001$)	52.2 vs. 38.8 (HR = 0.70, $p = 0.013$)	65 vs. 31
JO25567[49,50]	154	Erlotinib/bevacizumab vs. erlotinib	69 vs. 63	16.0 vs. 9.7 (HR = 0.54, $p = 0.0015$)	47.0 vs. 47.4 (HR = 0.81, $p = .3267$)	91 vs. 53
Stinchcombe[51]	88	Erlotinib/bevacizumab vs. erlotinib	83 vs. 81	17.9 vs. 13.5 (HR = 0.87, $p = 0.59$)	29.9 vs. not evaluable (HR = 1.54, $p = 0.25$)[b]	
NEJ026[52]	224	Erlotinib/bevacizumab vs. erlotinib	72 vs. 66	16.9 vs. 13.3 (HR = 0.61, $p = 0.0157$)	Not reported	56 vs. 38
SWOG S1403[53]	170	Afatinib/cetuximab vs. afatinib	Not reported	10.6 vs. 13.1 (HR = 1.17, $p = 0.42$)	26.9 vs. not reached (HR = 1.23, $p = 0.55$)	62 vs. 39 (treatment related)

[a]No baseline central nervous system metastasis.
[b]Immature data.
ORR, objective response rate; PFS, progression-free survival; OS, overall survival; Gr3, grade 3; AE, adverse event; HR, hazard ratio; Carbo, carboplatin.

the time of resistance, nine showed *C797S* (22%) and two had *PIK3CA* mutation, suggesting heterogeneity.[60] Besides *C797S* mutations, other tertiary *EGFR* mutations such as *L718* and *L792* confer osimertinib resistance with potential clinical implications.[61]

Recently, exploratory analysis of resistance mechanisms to osimertinib in the AURA3 trial from 73 plasma samples using the Guardant NGS method (Guardant Health, Inc.) with ctDNA demonstrated loss of *T790M* in approximately half the patients: 21% with acquired *EGFR* mutations, 19% with *MET* amplification, 5% with erb-b2 receptor tyrosine kinase 2 (*HER2*) amplification, 5% with *PIK3CA* mutation and/or amplification, 4% with oncogenic fusion (*RET, NTRK,* and *FGFR*), 4% with cell cycle mutation, and 3% with *BRAF V600E* mutation (Fig. 1).[62] Among the 21% of patients with acquired *EGFR* mutation, *C797X* was the most common mutation (usually in *cis* position when co-occurring with *T790M* mutation) followed by *L792H/F, L792H*, *G796S*, *L718Q*, and exon 20 insertion (Fig. 2). Of note, more than one mechanism of acquired resistance was reported in up to 20% of patients.[62] Similarly, plasma samples from 91 patients who experienced development of resistance to upfront osimertinib in the FLAURA trial were analyzed by using Guardant NGS; no evidence of *EGFR T790M* was identified. The most common resistance mechanisms were *MET* amplification (15%) and *EGFR C797S* mutation (7%). Other mechanisms include *HER2* amplification and *PIK3CA* and *RAS* mutation (Fig. 3).[63] Given the limitation of ctDNA analysis, which can result in underdiagnosis of some mechanisms of acquired resistance such as amplifications, the ELIOS trial (NCT03239340) is a single-arm tissue and plasma acquisition study assessing the tumor genetic and proteomic markers at the point of disease progression in patients with *EGFR*-mutant NSCLC who receive first-line osimertinib. Furthermore, after the upcoming clinical intervention ORCHARD phase II platform trial, different treatment strategies will be allocated on the basis of resistance mechanism against osimertinib.

This heterogeneity in the mechanisms of acquired resistance suggests that biomarkers other than T790M are important and reflect the challenge of NGS implementation in daily clinical practice for detecting them, as well as the need to research therapeutic strategies to address them. In *EGFR*-positive and *MET*-positive NSCLC, the combination of EGFR and mesenchymal-epithelial transition (MET) TKIs was reported to provide promising results. The phase Ib TATTON trial, the combination of osimertinib and savolitinib in 46 *EGFR*-mutant NSCLC patients *T790M*-negative and acquired *MET* amplification after first- or second genration EGFR TKI, reported a RR of 52% and median duration of response (DoR) of 7.1 months. Likewise, the same combination in 48 *T790M*-negative and acquired *MET*-amplified tumors after osimertinib reportd a RR of 25% and DoR of 9.7 months. In TATTON trial centrally confirmed *MET* positivity was defined by fluorescence in situ hybridization, with copy gene number [CGN] $\geq$5, or with MET-to–centromere chromosome 7 ratio $\geq$2[64,65] Similarly, gefitinib and capmatinib (INC280) were reported to provide an RR of 47% in patients with *MET* amplification (copy gene number $\geq$6) who experienced disease progression while receiving EGFR TKI treatment (not osimertinib).[66] Finally, in 21 patients with *EGFR*-mutant, T790M-

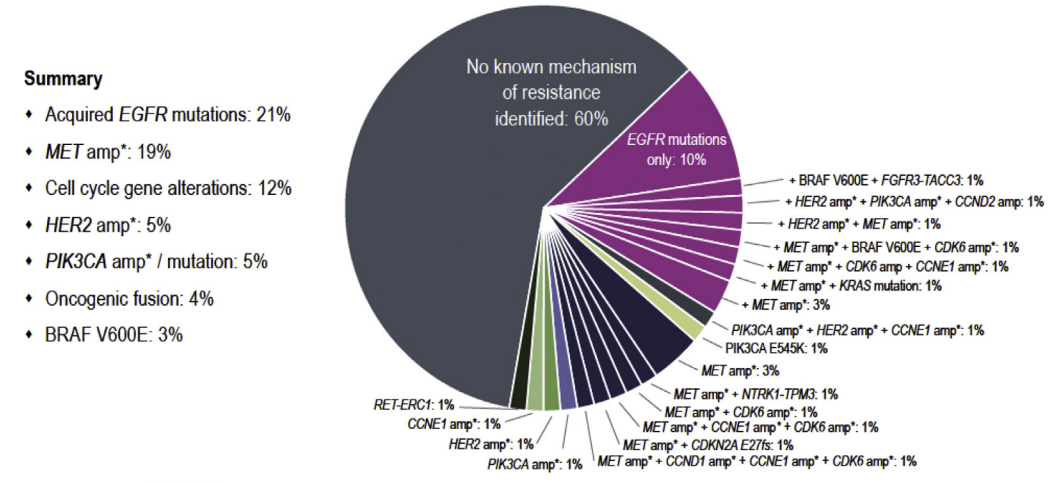

Figure 1. Acquired resistance mechanism after osimertinib treatment (n = 73). *Amplification events may be underrepresented in plasma analyses. Abbreviations: *MET*, MNNG HOS Transforming gene; amp, amplification; *HER2*, erb-b2 receptor tyrosine kinase gene; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alph gene; *RET*, ret proto-oncogene gene; *ERC1*, ELKS/RAB6-interacting/CAST family member 1 gene; *CCNE1*, cyclin E1 gene; *FGFR3*, fibroblast growth factor receptor 3 gene; *TACC3*, transforming acidic coiled-coil containing protein 3 gene; *CCND2*, cyclin D2 gene; *CDK6*, cyclin D6 gene. Reprinted from Papadimitrakopoulou et al.[62] with permission from *Annals of Oncology*.

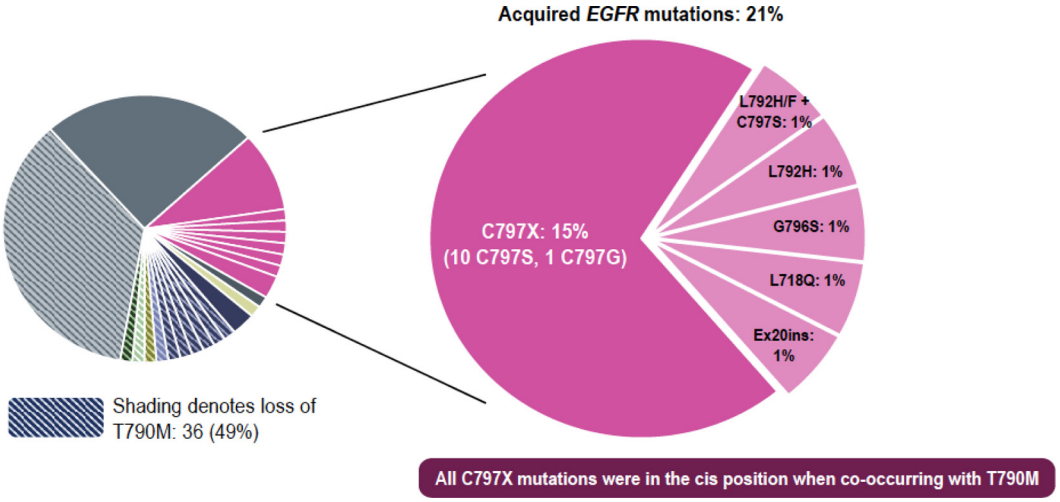

Figure 2. Acquired *EGFR* mutations after osimertinib treatment. Abbreviation: Ex20ins, exon 20 insertion. Reprinted from Papadimitrakopoulou et al.[62] with permission from *Annals of Oncology*.

negative NSCLC with *MET* amplification (GCN≥5 or MET-to–centromere chromosome 7 ratio ≥2) after progression while taking an EGFR TKI (not osimertinib), personalized treatment with gefitinib and tepotinib dramatically improved PFS (21.2 versus 4.2 months [HR = 0.17, 90% CI: 0.05–0.57]) versus that with platinum-pemetrexed, as well as RR (67% versus 43%).[67]

Diverse mechanisms can lead to MET pathway activation, but MET expression is not sufficiently selective for oncogenic target activation in most patients with NSCLC[67]; thus, standardization of the cutoff point for defining *MET*-amplification is a challenge. The combination of osimertinib and a selective ret proto-oncogene TKI (BLU-667) has also shown clinical activity for acquired *RET* fusion–resistant tumors.[68]

Immunotherapy in *EGFR*-Mutant NSCLC. Contrary to preclinical evidence according to which PD-L1 expression is higher in *EGFR*-mutant cell lines than in their wild-type counterpart,[69] in the FLAURA trial, PD-L1 expression (evaluated by SP263) was less common in *EGFR*-mutant samples than in *EGFR* wild type samples (51% versus 68%), particularly for higher thresholds (for PD-L1 expression ≥25%, 8% versus 35%; for PD-L1 expression of 50%, 5% versus 28%). The PFS benefit with osimertinib versus with the SoC occurred regardless of PD-L1 status (HR = 0.30, 95% CI: 0.15–0.60 in tumors with PD-L1 expression ≥1% and HR = 0.37, 95% CI: 0.17–0.74 in tumors with PD-L1 expression ≤1%, respectively).[70] Despite potential overlap of *EGFR* mutations with high PD-L1 expression, an ICI is not an

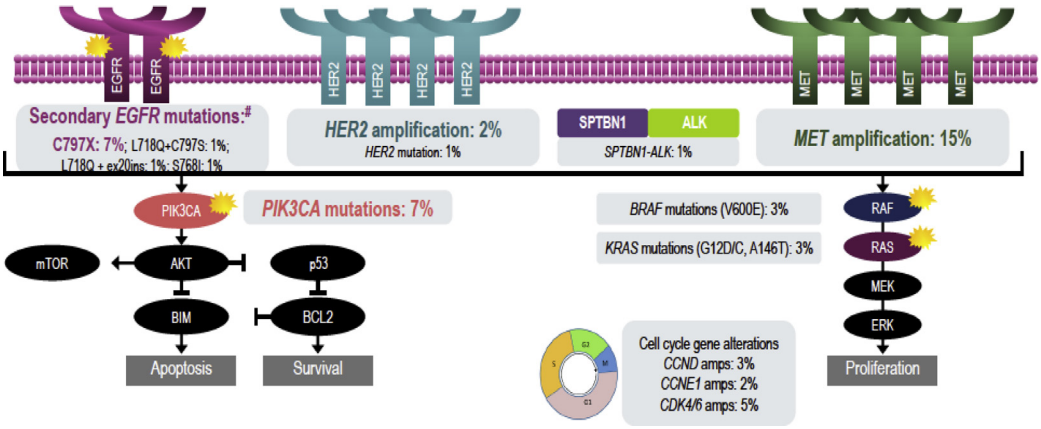

Figure 3. Acquired resistance mechanism to first-line osimertinib treatment (n = 91). *Resistance mechanism reported may overlap with another. #Two patients had *de novo* T790 mutations at baseline, with one of the patients acquiring C797S at progression. Abbreviations: *HER2*, erb-b2 receptor tyrosine kinase gene; *SPTBN1*, gene; *ALK*, gene; *MET*, MNNG HOS Transforming gene; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alph gene; mTOR, mechanistic target of rapamycin; BIM, synonym of BCL2L11 (i.e., BCL2 like 11); BCL2, BCL2, apoptosis regulato; *CCND*, cyclin D gene; *CCNE1*, cyclin E1 gene; *CDK4*, cyclin-dependent kinase 4 gene; *CDK6*, cyclin-dependent kinase 6 gene. Reprinted with permission from Ramalingam et al.[63] with permission from *Annals of Oncology*.

appropriate therapeutic choice in the first-line setting because of lack of efficacy in TKI-naive patients, and EGFR TKI remains the SoC regardless of PD-L1 expression in this setting.[71] In a phase Ib trial, the combination of erlotinib and atezolizumab in 28 TKI-naive *EGFR*-mutant patients was reported to provide an RR of 75%, and the median PFS time was 15 months. However, these results are not a marked improvement over those reported with EGFR TKI monotherapy.[72] A recent retrospective analysis has demonstrated that TKI-naive patients with *EGFR*-mutated tumors generally have a low TMB (assessed by NGS) compared with patients with wild-type tumors, and higher TMB predicts worse response to EGFR TKI, with shorter time to discontinuation and OS. Mutations in TP*53* have been more common in patients with *EGFR* mutation with a high TMB. TMB increase during treatment with an EGFR TKI, and TMB is higher at the time of progression compared to their pretreatment samples.[73] It is suggested that the increased TMB may be linked to the emergence of subclonal mutations, but it remains unknown whether the upfront treatment strategy should be more intensive in patients with *EGFR*-mutant tumors and a high TMB or TP*53* mutation (combination strategies) or whether high TMB confers effective immunogenicity.[73,74]

In patients with *EGFR*-mutant NSCLC previously treated with an EGFR TKI, different cohorts such as the ImmunoTarget cohort[75] and the Italian cohort[76] have reported limited efficacy with ICIs (RR 9%–12%, median PFS 22.1–3.0 months, and OS 8.3–10 months),[75,76] and the outcome did not seem to be influenced by *EGFR* mutation subtype.[75] These results mirror those previously reported in the ATLANTIC trial.[77] Activity of the ABCP combination (IMPOWER 150) in the *EGFR*-mutant population has been reported in the section of this review on immunotherapy and chemotherapy.[13,24] In several ongoing phase III trials, such as CheckMate722 (NCT02864251) and KEYNOTE789 (NCT03515837), which are testing different ICI strategies in patients with *EGFR*-mutant, T790M-negative NSCLC who failed treatment with a previous EGFR TKI may help to elucidate the efficacy and role of ICIs in the therapeutic strategy of these patients. Furthermore, to avoid the potential increased risk of interstitial lung disease with sequential or concurrent treatment with ICIs and third-generation EGFR TKIs, an appropriate washout period of at least five half-lives and careful monitoring is recommended.[78]

Uncommon *EGFR* mutations. Uncommon *EGFR* mutations (point mutations or duplications in exons 18–21, excluding *Del19, L858R,* and *T790M* mutations) represent 10% of all *EGFR* mutations and are characterized by variable sensitivity to EGFR TKIs, and upfront chemotherapy may achieve a better outcome (OS time 27.7 versus 16.9 months [95% CI: 13.6–25.9, $p = 0.075$]).[79] However, in the phase II KCSG-LU15-09 study trial,[80] which enrolled 35 patients with uncommon *EGFR* mutations (exon 20 insertions excluded), osimertinib gave an RR of 50% and a median PFS of 8.2 months. *EGFR* exon20 insertions represent approximately 2% of all NSCLC[81,82]; they comprise the third most common *EGFR* mutation subtype,[81] and the RR to EGFR TKIs is very poor. They represent a heterogeneous group of *EGFR* mutations, and chemotherapy is, for instance, the SoC first-line treatment. New TKIs that are selective for *EGFR* and *HER2* exon 20 mutations have been reported to have clinical activity in this population. In a phase II trial, poziotinib was reported to have a confirmed RR of 43% and a median PFS of 5.5 months, with grade 3 or higher AEs in 57% of patients (mainly skin rash and diarrhea).[83] TAK788 has also been reported to show antitumor activity and safety in this population.[84] Developing new treatment strategies for exon 20 insertion *EGFR* mutants with better toxicity profiles and improving knowledge about the mechanisms of resistance are new challenges in this population.

Advances in Targeting ALK- and ROS1-Rearranged NSCLC

ALK Therapies. *ALK* gene rearrangements are observed in 5% to 7% of patients with advanced nonsquamous NSCLC. Crizotinib and ceritinib are first- and second-generation *ALK*-directed TKIs, respectively. They are now considered SoC first-line treatment options over platinum-based chemotherapy from landmark phase III randomized trials.[85,86] Mechanisms of acquired resistance to these agents include the emergence of *ALK* secondary mutations that may be covered by next-generation TKIs, including alectinib, brigatinib, and lorlatinib.[87] The OS of *ALK*-positive patients may be remarkably long, up to 7 years,[88] highlighting the need for adequate decision making for the treatment sequences. CNS failure during crizotinib therapy is a common event,[89] and four trials have compared second-generation TKIs with crizotinib as first-line treatment for *ALK*-positive NSCLC: J-ALEX, ALEX, and ALESIA with alectinib[90–93] and ALTA-1L with brigatinib,[94] establishing the second-generation ALK TKI alectinib as an optimal SoC treatment in this population in the first-line setting.

The updated outcome data from the ALEX trial were reported in 2018: after a median 28 months of follow-up, the investigator-assessed PFS time was 34.8 months with alectinib versus 10.9 months with crizotinib (HR = 0.43, 95% CI: 0.32–0.58)[92]; this is the highest reported figure for median PFS in *ALK*-positive NSCLC to date. The survival data are not yet mature, but crossover was not

allowed in the ALEX trial. The ALESIA trial confirmed those results with the 600-mg twice-daily dose of alectinib in Asian patients[93] (whereas J-ALEX was conducted with a 300-mg twice-daily dose[90]). Globally, compared with crizotinib, alectinib demonstrated a significant benefit in terms of CNS efficacy end points, including response and time to CNS progression, and in the ALEX trial this benefit was irrespective of prior CNS disease or radiotherapy.[95] Results are summarized in Table 4.[90–94] Alectinib therefore became a preferred first-line treatment option in *ALK*-positive NSCLC patients.[96]

ALTA-1L is a phase III study that compared brigatinib with crizotinib in 275 patients with *ALK*-positive NSCLC. Almost 25% of patients enrolled in the trial had previously reated with chemotherapy. The results indicate a 12-month PFS rate of 67% with brigatinib versus 43% with crizotinib (HR = 0.49; 95% CI: 0.33–0.74 [see Table 4])[94] regardless of previous chemotherapy or not; and intracranial PFS was also significantly higher with brigatinib (HR = 0.27, 95% CI: 0.13–0.54). Crossover was allowed; however, the survival data are not yet mature.[94] Two additional first-line trials in patients with ALK TKI–naive NSCLC are ongoing, comparing crizotinib with ensartinib in the eXalt3 trial (NCT02767804) and with lorlatinib in the CROWN trial (NCT03052608). Both drugs have shown promising activity in phase II trials in this population (RR 90% and 80%, with median PFS times of 21 and 26.2 months with lorlatinib[97] and ensartinib,[98] respectively).

Taken together, these data demonstrate better efficacy for the next-generation ALK TKIs alectinib and brigatinib in first-line treatment of *ALK*-positive NSCLC. The availability of these agents in the clinic raises the challenge of redefining the subsequent therapeutic strategy: first, by taking into account the new resistance mechanisms resulting from initial therapy, and in particular, the emergence of the *G1202R* mutation that is targeted only by lorlatinib,[99] achieving an RR of 33% and a median PFS time of 5.5 months[97]; second, by the development of new ALK TKIs, including entrectinib and repotrectinib; and third, by discussing the optimal momentum and strategy for sequential or combined chemotherapy and immunotherapies, given that combinations of ALK TKIs and ICIs are associated with AEs, mainly increased risk of hepatotoxicity, without significant efficacy signals.[100–103] For instance, both the FDA

Table 4. Randomized Trials Showing the Superiority of Next-Generation ALK-Directed TKIs vs. Crizotinib as First-Line Treatment

	J-ALEX[90]	ALEX[91]	ALESIA[93]	ALTA[94]
Experimental ALK TKI	Alectinib, 300 mg twice daily	Alectinib, 600 mg twice daily	Alectinib, 600 mg twice daily	Brigatinib. 180 mg with 7-d lead-in at 90 mg
Randomization vs. crizotinib	1:1	1:1	2:1	1:1
Primary end point	PFS by BIRC	PFS by investigator	PFS by investigator	PFS by BIRC
Stratification on CNS metastasis	No	Yes	Yes	Yes
N	207	303	187	275
Median age, y	60	55	50	59
Stage IV	74%	96%	91%	93%
Never-smokers	56%	63%	69%	58%
Previous chemotherapy	36%	0%	9%	27%
CNS metastasis	16%	40%	36%	29%
Previous radiotherapy on CNS metastasis	N/A	16%	7%	13%
Objective response rate with experimental ALK TKI	92%	83%	91%	71%
HR for PFS of the experimental TKI	HR = 0.34 (99.7% CI: 0.17-0.71)	HR = 0.47 (95% CI: 0.34-0.65)	HR = 0.22 (95% CI: 0.13-0.38)	HR = 0.49 (95% CI: 0.3-0.74)
Intracranial objective response rate with experimental ALK TKI[a]		81%	73%	67%
Intracranial PFS/time to CNS progression of the experimental TKI	HR = 0.16 (95% CI: 0.02-1.28) (baseline CNS metastases) HR = 0.41 (95% CI: 0.17-1.01) (no baseline CNS metastases)	HR = 0.18 (95% CI: 0.09-0.36) (baseline CNS metastases) HR = 0.14 (95% CI: 0.06-0.33) (no baseline CNS metastases)	Not reported	HR = 0.27 (95% CI: 0.13-0.54) (baseline CNS metastases)

[a]Measurable and nonmeasurable CNS disease.

ALK, ALK receptor tyrosine kinase; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; BIRC, blinded-independent review committee; CNS, central nervous system; N/A, not available; HR, hazard ratio; CI, confidence interval.

and EMA (conditional marketing authorization) have approved second-line treatment with lorlatinib in patients with *ALK*-positive NSCLC previously treated with upfront second-generation ALK TKIs (alectinib or ceritinib), as well as third-line treatment after crizotinib and at least one other ALK TKI.

ROS1 therapies. *ROS1* gene rearrangements represent an actionable genomic target found in 1% to 2% of patients with NSCLC. Although like *ALK* rearrangements *ROS1* rearrangements are enriched in never-smokers or light smokers, the recent International Association for the Study of Lung Cancer/College of American Pathologists/Association for Molecular Pathology guidelines mandate testing of all patients with newly diagnosed adenocarcinoma for *ROS1* rearrangements regardless of clinical characteristics. Testing may involve immunohistochemistry with confirmatory fluorescence in situ hybridization or NGS. Crizotinib was the first and remains the only currently approved TKI for *ROS1*-rearranged NSCLC. In the phase I PROFILE1001 study, an objective RR of 72% with crizotinib was seen in 53 patients with *ROS1*-rearranged NSCLC, with a median PFS time of 19.3 months and a median OS of 51.4 months with a 4-year OS rate of 51%., which was independent of the *ROS* fusion partner.[104] Confirmatory data were provided in a prospective Asian study.[105] Similar to *ALK*-positive NSCLC, disease progression after crizotinib can occur in the setting of CNS failure[106] and acquired resistance to crizotinib with *ROS1* TKI domain mutations, including *G2032R* (41%) and *D2033N* (6%),[107] as well as with other mechanisms of resistance such as KIT proto-oncogene receptor tyrosine kinase gene (*KIT*) or B-catenin gene mutations.[108]

Activity of new TKIs targeting *ROS1* has been demonstrated in recent clinical trials typically showing more CNS activity than crizotinib but with a variable spectrum of *ROS1* mutation coverage. In a Korean phase II study with the *ALK/ROS1* inhibitor ceritinib, although no responses were seen in two crizotinib-refractory patients, in crizotinib-naive patients (n = 30) the response rate was 66% and the median PFS time was 19.3 months.[109] Entrectinib is an oral inhibitor of *ALK, ROS1*, and tropomyosin receptor kinase (*TRK*) kinases with CNS activity superior to that of crizotinib. In a pooled analysis of phase I and II trials with entrectinib in 53 *ROS1*-positive NSCLC, the RR in crizotinib-naive patients was 77.4%, with a median PFS time of 19 months (reaching 26.3 months among those patients without baseline BM [13.6 months for patients with baseline BM]). Among 23 patients (43.4%) enrolled in the trial with evaluable BM, the intracranial RR was 55%.[110] In the *ROS1* cohort of a phase I/II study with the *ALK* and *ROS1* inhibitor lorlatinib, responses were seen in eight of 13 crizotinib-naive patients (61.5%) and nine of 34 patients (26.5%) who had prior crizotinib therapy, with median PFS times of 21 months and 8.5 months, respectively. Lorlatinib showed 67% and 52.3% intracranial RRs in the crizotinib-naive (n = 6) and crizotinib-pretreated (n = 19) populations, respectively.[111] However, no objective responses with lorlatinib were seen in patients with the *G2032R* mutation.[112] In a report of the ongoing TRIDENT-1 phase I study with repotrectinib (TPX-0005), a ROS1/TRK/ALK inhibitor designed to overcome TKI resistance such as G2032R, a response was seen in eight of 10 crizotinib-naive patients and in three of 17 crizotinib-pretreated patients (two of six responses at a 160-mg daily dose, including a response in a patient with the G2032R mutation). Three of three TKI-naive patients and one of four TKI-pretreated patients with measurable intracranial disease had objective intracranial responses (Table 5).[104,105,109–111,113]

The forthcoming availability of new ROS TKIs in the clinic challenges the optimal treatment sequence according to the pattern of progression and mechanisms of resistance, which are not yet completely elucidated for these new agents, as well as the risk-benefit ratio with ICIs, which remains unknown in *ROS1*-positive NSCLC.

Advances in Other Genomic Alterations

***BRAF* Mutations.** Targetable *BRAF V600E* mutations occur in approximately 2% of lung adenocarcinomas, including in patients with a smoking history. The

Table 5. Treatment Efficacy of ROS1 in TKI-Naive Patients with *ROS1*-Rearranged NSCLC

Drug	n	RR, %	PFS, mo	OS, mo/1-y OS, %	Patients with BM	icRR (%)
Crizotinib[104]	53	72	19.3	51.4/79	Not reported	
Crizotinib[105]	127	72	15.9	32.5/83.1	23	Not reported
Ceritinib[109]	32	66	19.3	24/not reported	8	25
Entrectinib[110]	53	77.4	19	NR/85	23	55
Lorlatinib[111]	13	62	21	Not reported	6	67
Repotrectinib[113]	10	80	Not reported	Not reported	3	100

TKI, tyrosine kinase inhibitor; RR, response rate; PFS, progression-free survival; OS, overall survival; BM, brain metastasis; icRR, intracranial response rate; NR, not reached.

combination of dabrafenib (a BRAF TKI) and trametinib (a MEK TKI) is the SoC treatment according to the FDA and EMA in patients with *BRAF* V600E–mutant NSCLC regardless of prior treatment,[114,115] as BRAF TKI monotherapy has been reported to have limited efficacy, such as in AcSé trial (RR = 45%, PFS = 5.2 months, and OS = 9.3 months [Table 6]).[114–132] The recent functional classification of *BRAF* mutations (class I, V600 mutations; class II, non-V600 mutations; and class III, ERK-signaling amplification) demonstrated that class II and III tumors have unfavorable prognosis and suggested that class-specific therapies are necessary.[133]

BRAF-mutant NSCLC overlaps with PD-L1 expression in 60% of cases (45% with PD-L1 expression ≥50%), low or intermediate TMB, and microsatellite-stable status,[134] but ICI efficacy is similar to that in patients with wild-type *BRAF*. In the IMMUNOTARGET cohort, ICIs in 43 patients with *BRAF*-mutant NSCLC gave an RR of 24% and median PFS and OS times of 3.1 and OS 13.6 months, respectively, with a trend toward benefit in patients with non-V600E mutations ($p = 0.20$) as well as in smoking patients ($p = 0.03$). However, data on the correlation with PD-L1 expression were not provided.[75] The potential synergism of combining ICIs and double BRAF-MEK inhibition in patients with NSCLC remains unknown, but the toxicity-to-benefit ratio should be carefully weighed.

***MET* Deregulation.** *MET* amplification and exon 14 mutation are reported in 3.3% of NSCLC cases, and both correlate with poorer survival.[135] Crizotinib (the PROFILE 1001 phase I trial[117] and the AcSé phase II trial[118]), tepotinib (the VISION phase II trial[119]), and capmatinib (the GEOMETRY phase II trial[120]) have been reported as having clinical activity in patients with the *MET* exon14 mutation (see Table 6). Crizotinib has been reported to provide an RR of 32% and median PFS and OS times of 7.2 and 20.5 months, respectively, with the benefit occurring regardless of the mutation type and the presence of concurrent *MET* amplification,[117] leading to its obtaining breakthrough designation from the FDA in May 2018. Intracranial activity and mechanism of acquired resistance are the current challenges in patients with *MET* exon 14 mutation. For high–*MET*-amplified NSCLC tumors, crizotinib has also been reported to have clinical activity[118,121] (see Table 6); however, compared with in patients with other druggable genomic alterations, upfront treatment with personalized strategies in this population seems less attractive.

Despite the fact that 40% of *MET* exon14–mutant NSCLCs express PD-L1 at a level of at least 50%, the median TMB in this population is lower than in the population with unselected NSCLCs. This may explain the modest clinical efficacy seen with ICIs (RR of 17%

Table 6. Clinical Trials with Targeted Therapies in Oncogenic Alterations Other than *EGFR*, *ALK*, and *ROS1*

Genetic Driver	Drug	Phase	Treatment Line	n	RR, %	PFS, mo	OS, mo
BRAF V600E	Dabrafenib + trametinib[114]	II	Second and beyond	59	63	10.2	18.2
	Dabrafenib + trametinib[115]	II	First	36	64	10.9[a]	24.6
MET exon 14 mutation	Crizotinib (PROFILE 1001)[117]	I	Any (38% had no previous lines)	69	32	7.3	20.5
	Crizotinib (AcSé)[118]	II	≥1	25	40	3.6	9.5
	Tepotinib (VISION)[119]	II	0-2 (35% had no previous lines)	46	43	NR	NR
	Capmatinib (GEOMETRY)[120]	II	Second and third	69	38	NR	NR
			First	28	72	NR	NR
MET amplification	Crizotinib (PROFILE 1001)[121]	I	≥1	20	40	6.7	NR
	Crizotinib (AcSé)[118]	II	≥1	20	32	3.4	7.7
HER2 mutant	Afatinib[122]	Expanded	≥1	28	19	NR	NR
	Afatinib[123]	Retrospective	≥1	27	13	NR	20.3[b]
	Poziotinib[83]	II	Any (15% had on previous lines)	13	50	5.1	NR
	Pyrotinib[124]	II	≥1	15	53.3	6.4	12.9
	DS-8201a[125]	I	≥1	11	73	14.1	NR
	T-DM1[126]	II	Any (16% had no previous lines)	18	44	5	NR
HER2 expression	T-DM1 in HER2 score 3+[127]	II	≥1	20	20	2.7	15.3
RET fusion	Vandetanib[128]	II	≥1	19	53	6.5	13.5
	BLU667 (ARROW)[129]	I	≥1	19	50	NR	NR
	LOXO-292 (LIBRETTO-001)[130]	I	≥1	38	68	NR	NR
NTRK fusion	Larotrectinib[131]	I/II (pooled)	Any (54% had 0-1 previous lines)	122	81	NR	NR
	Entrectinib[132]	I/II (pooled)	Any (57% had 0-1 previous lines)	54	57.4[c]	11.2[c]	20.9

[a]PFS by independent review: 14.6 months.
[b]Median OS from the date of diagnostic of metastatic or recurrent disease
[c]Eleven patients with baseline brain metastases; the intracranial RR and intracranial PFS were 55% and 14.3 months, respectively.
ALK, receptor tyrosine kinase; RR, response rate; PFS, progression-free survival; OS, overall survival; *MET*, MNNG HOS Transforming gene; NR, not reported; *HER2*, erb-b2 receptor tyrosine kinase 2; *RET*, ret proto-oncogene gene; *NTRK*, neurotropic tropomyosin receptor kinase gene.

and median PFS 1.9 months, with no enriched efficacy in tumors with high PD-L1 or high TMB[136]).

***HER2* Deregulation.** *HER2* mutations (mainly insertions in exon 20) and *HER2* amplifications are found in approximately 2% to 5% of lung adenocarcinomas. *HER2* mutations and amplifications are not associated.[137] Afatinib is modestly active in *HER2*-mutant NSCLC (RR 13%–19%, with increased activity in *HER2* insertion mutations).[122,123] The activity of new erb-b2 receptor tyrosine kinase 2 (HER2) TKIs has recently been reported. In a phase II study with poziotinib in 13 *HER2* exon 20 insertion patients, the RR was 50% and the median PFS was 5.1 months, with a 58% rate of grade 3 or higher AEs[83]; a confirmatory trial is ongoing (NCT03318939). In another phase II cohort of 15 patients with *HER2*-mutant NSCLC, pyrotinib was reported to provide an RR of 53.3% and a median PFS of 6.4 months.[124] Recently, in preclinical models with *HER2*-mutant cell lines, poziotinib was the most sensitive drug. The major mechanism of acquired resistance during poziotinib therapy was the secondary C805S mutation (31%) homologous to C797S in *EGFR* gene, and heat shock protein 90 inhibitors have been reported to have potent activity against poziotinib-resistant cells.[138] DS-8201a is a new HER2-targeting antibody-drug conjugate incorporating a novel topoisomerase I inhibitor. In *HER2*-mutant patients, it gave a clinically significant RR of 73% and a median PFS of 14.2 months[125]; and a phase II trial (NCT03505710) is ongoing (see Table 6).

In tumors overexpressing HER2 (immunohistochemistry score 2+ and 3+), the efficacy of trastuzumab emtansine (TDM-1) was limited in terms of RR (0% and 20%, respectively), PFS (2.6 and 2.7 months, respectively) and OS (12.2 and 15.3 months, respectively).[127] However, in a phase II trial enrolling 18 patients with pretreated *HER2*-mutant NSCLC,[126] TDM1 achieved an RR of 44% with a median PFS of 5 months, suggesting *HER2* mutations as the optimal potential predictive biomarker for TDM1. In *HER2*-mutant or *HER2*-amplified tumors, the RR to trastuzumab plus pertuzumab was limited (21% and 13%, respectively [see Table 6]).[139]

Most *HER2*-mutant lung cancers have a level of PD-L1 expression less than 1%, and TMB is similar to that in unselected lung cancers,[140] having limited efficacy with ICIs (RR <10%, and a PFS of 2 months).[75,140]

***RET* Rearrangement.** *RET* rearrangements occur in 1% to 2% of lung adenocarcinomas and at a rate of up to 14% in enriched wild-type patients. In NSCLC, at least 12 fusion *RET* partner genes have been identified, with the most common, kinesin family member 5B gene (*KIF5B*)-*RET,* found in 75% of cases.[141] Multi-TKIs with anti-RET activity, such as vandetanib, have been reported to have limited efficacy and high toxicity leading to treatment discontinuations.[142] In the updated Japanese phase II LURET trial in 19 patients with *RET*-positive NSCLC, vandetanib gave an RR of 53%, PFS of 6.5 months, and OS of 13.5 months, with better outcomes in non–*KIF5B-RET* fusions.[128] In a phase Ib cohort of 31 RET inhibitor-naïve patients with *RET* fusion-positive NSCLCs, RXDX-105 (a VEGFR-sparing multikinase RET inhibitor) reported a RR of 19% with a not reached median treatment duration. However, as contrary to selective RET TKI, RXDX-105 reported responses only in non-*KIF5B-RET*-containing cancers (67% *vs.* 0%).The value of RET-fusion partner for making treatment decisions in RET-positive tumors merits further evaluation, at least for multikinase RET inhibitors.[143] The selective RET TKIs, BLU667 and LOXO292 have been reported to have better activity, safety, and intracranial activity in this population (see Table 6). In the phase I ARROW trial,[129] BLU667 was tested in *RET*-altered solid tumors, including in 19 patients with NSCLC with *RET* fusion. The RR in patients with NSCLC was 50%, with a rate of grade 3 or higher AEs of 16%. In the phase I LIBRETTO-001 trial[130] enrolling 38 patients with NSCLC with *RET* fusion, LOXO292 demonstrated a confirmed RR of 68%, independent of the *RET* fusion subtype, with a rate of grade 3 or higher AEs of 1% leading to breakthrough designation from the FDA in September 2018 for those patients with *RET* fusion–positive NSCLC. Similar to in NSCLC with other oncogenic alterations, ICI efficacy in *RET*-positive NSCLC is modest.[75]

***NTRK* Rearrangements.** The incidence of *NTRK* fusion in NSCLC is 0.23%; it occurs across sexes, ages, smoking histories, and histologic subtypes.[144] NGS and targeted RNA testing for *NTRK* fusions are de rigueur at the moment. However, immunohistochemistry is a useful surrogate for NTRK fusions. NTRK positivity by immunohistochemistry requires that more than 50% of tumor cells show cytoplasmic decoration or any nuclear staining.[145]

At 100 mg twice daily, the pan-TRK TKI larotrectinib[146] has shown activity in adult and pediatric patients with *NTRK* fusion cancer,[147] leading the FDA to grant orphan drug designation to larotrectinib for *NTRK*-positive solid tumors. In the updated results of the trial with 122 *NTRK*-positive tumors (n=11 NSCLC), larotrectinib gave an RR of 81% regardless of tumor type and age, with grade 3 or higher AEs in 5% of patients.[131] In a pooled analysis of phase I and II trials with entrectinib in 54 adult *NTRK*-positive tumors (n=10 NSCLC), entrectinib gave an RR of 57.4% and median PFS and OS times of 11.2 and 20.9 months, respectively. In 11 patients with baseline brain metastases, the intracranial RR and PFS time were 54.5% and 14.2 months, respectively[132] (see Table 6).

Conclusions

Collectively, these advances have led to major improvements in the outcome of patients with advanced NSCLC; however, new challenges have now opened on the horizon. Moving immunotherapy into the first-line setting for all patients with NSCLC creates a new gap in the SoC for patients requiring second-line therapy other than chemotherapy with or without an antiangiogenic. In oncogene-addicted tumors, the optimal treatment sequence, as well as the development of new drugs for personalizing treatment upon progression according to the mechanisms of resistance are eagerly awaited to improve survival.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.03.022.

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