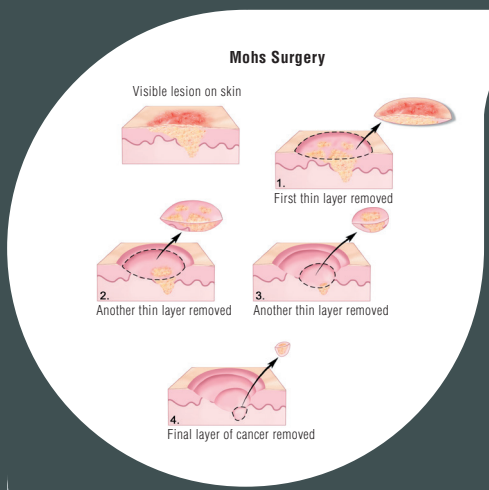
ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

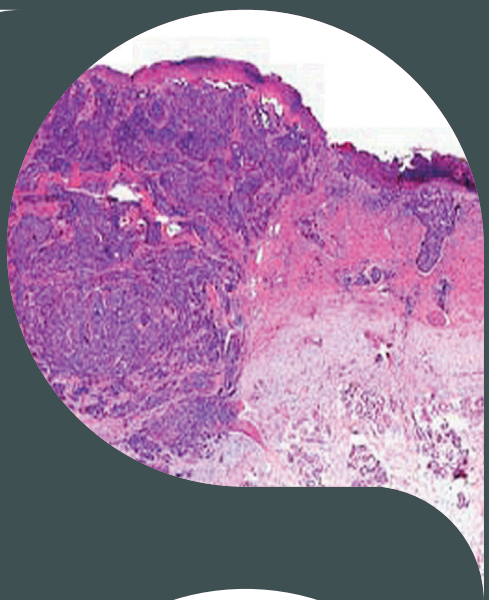
www.esmo.org

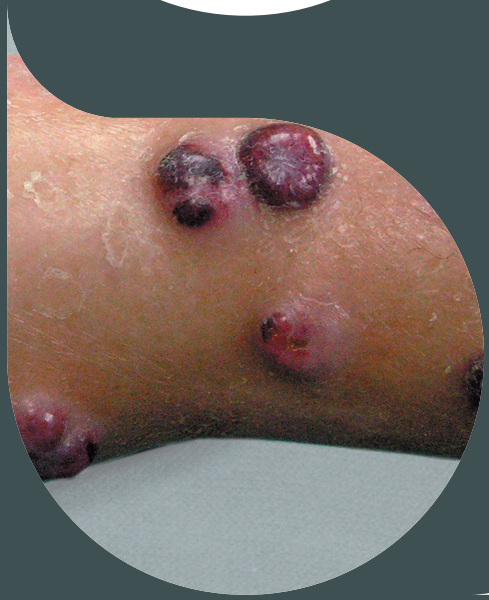
edited by
Paolo A. Ascierto
Iwona Lugowska
Ruth Plummer

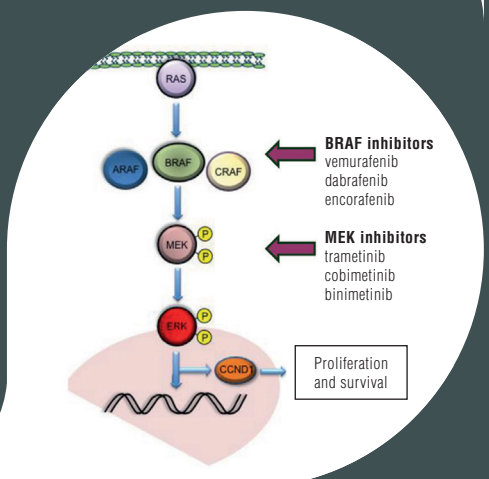
MELANOMA & OTHER SKIN CANCERS

ESSENTIALS *for* CLINICIANS









ESMO Press

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Melanoma & Other Skin Cancers
Essentials for Clinicians

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Melanoma & Other Skin Cancers
Essentials for Clinicians

Edited by

Paolo A. Ascierto

Istituto Nazionale Tumori IRCCS 'Fondazione G. Pascale', Naples, Italy

Iwona Lugowska

Maria Skłodowska-Curie National Research Institute of Oncology (MSCI) Warsaw, Poland

Ruth Plummer

Northern Centre for Cancer Care, Newcastle Hospitals NHS Trust; Newcastle University, Newcastle upon Tyne, UK

Series editor

Michele Ghielmini

Oncology Institute of Southern Switzerland, Ospedale San Giovanni Bellinzona, Switzerland

ESMO Press

First published in 2021 by ESMO Press

A CIP record for this book is available from the British Library.

ISBN: 978-88-944465-3-1

For orders, corporate sales, foreign rights, and reprint permissions, please contact:

ESMO Head Office

Guidelines and Publishing Department

Via Ginevra 4

6900 Lugano

Switzerland

Tel: +41 (0) 91 973 1900

Email: publication_support@esmo.org

www.esmo.org

Contents

Preface

Melanoma is the most aggressive form of skin cancer and its incidence has been rising over the last decade. Fortunately, advances in disease knowledge through research and innovation, as well as a multidisciplinary treatment strategy, has placed clinicians in a position to better manage melanoma patients and changed how we evaluate and treat them. Nonetheless, there is much more that needs to be discovered to improve outcomes and increase awareness.

In this scenario, this first edition of *Melanoma & Other Skin Cancers: Essentials for Clinicians* has been designed to provide an up-to-date and multidisciplinary overview of the epidemiology, pathology and current and innovative evidence-based treatment options for patients with all stages of melanoma and other skin cancers.

This extensive book brings together leading skin cancer researchers and clinicians from across the world; the content is organised in two sections. Part A, *'What every oncologist should know'*, seven chapters, provides a comprehensive overview of the epidemiology, prevention, screening and surveillance as well as staging, prognostic factors and current treatment of melanoma. Part B, *'More advanced knowledge'*, six chapters, discusses the advances in melanoma and skin cancer research and treatment, exploring the pathology and molecular profile, predictive biomarkers and, finally, emerging targets and personalised medicine.

We greatly appreciate the efforts of our internationally recognised contributing authors for their time, experience and knowledge. We hope to provide helpful, relevant information for all physicians and researchers who may treat patients with melanoma, in the hope of enhancing knowledge and improving the overall care of these patients.

Professor Paolo A. Ascierto
Naples, Italy

Professor Iwona Lugowska
Warsaw, Poland

Professor Ruth Plummer
Newcastle upon Tyne, UK

Editors

Paolo A. Ascierto, MD, PhD

Istituto Nazionale Tumori IRCCS 'Fondazione G. Pascale', Naples, Italy

Professor Paolo A. Ascierto obtained his medical degree from the University of Naples, Italy, where he subsequently earned his Board Certification in Oncology. He went on to serve consecutive positions at the National Tumour Institute 'Fondazione G. Pascale' in Naples, as a postdoctoral fellow and then as Vice Director of the Department of Clinical Immunology. Professor Ascierto is currently Director of the Department of Skin Cancers, Cancer Immunotherapy and Development Therapeutics at that same institution. He is Associate Editor for Onco-Immunology of *Annals of Oncology*, Associate Editor of the *Journal for ImmunoTherapy of Cancer,* Chief Section Editor for the Combination Strategies section of the *Journal of Translational Medicine* and a member of the Editorial Board for *ESMO Open*.

He has been a valued invited speaker at more than 450 national and international meetings and is an active member of several cancer societies. Professor Ascierto has presided as Principal Investigator on over 150 clinical trials and authored more than 500 publications in peer-reviewed journals. His interests are skin cancer molecular biology, molecular markers for tumour progression, targeted therapies, vaccination treatments and immunotherapy, and combination treatment approaches.

Iwona Lugowska, MD, PhD

Maria Skłodowska-Curie National Research Institute of Oncology (MSCI), Warsaw, Poland

Professor Iwona Lugowska is Plenipotentiary Director for International Affairs, Head of the Early Phase Clinical Trials Unit, Leader of the Centre of Excellence for Precision Oncology, Coordinator of the Centre for Research and Development and Consultant in Oncology in the Department of Soft Tissue/Bone Sarcoma and Melanoma at the Maria Skłodowska-Curie National Research Institute of Oncology (MSCI), Warsaw, Poland.

Professor Lugowska is Chair of the European Society for Medical Oncology (ESMO) Educational Publications Working Group, a board member of the European Organisation for Research and Treatment of Cancer (EORTC), a Horizon Europe, Mission: Cancer representative for Poland and a member of the Ethics Committee at MSCI. She received an award from the American Society of Clinical Oncology (ASCO) IDEA Program 2010, visited the Memorial Sloan Kettering Cancer Center, New York (mentor, Robert Maki), and undertook a fellowship at the Sir Bobby Robson Cancer Trials Research Centre, Newcastle, UK (mentor, Ruth Plummer).

Her main fields of interest are sarcoma, melanoma research, immunotherapy, precision oncology and early phase clinical trials. She also developed a Clinical Support System for the management of gastrointestinal stromal tumours (GISTs).

Ruth Plummer, MD, PhD

Northern Centre for Cancer Care, Newcastle Hospitals NHS Trust; Newcastle University, Newcastle upon Tyne, UK

Ruth Plummer is Professor of Experimental Cancer Medicine, Newcastle University and an honorary consultant medical oncologist in Newcastle Hospitals NHS Foundation Trust, UK. She directs the Sir Bobby Robson Cancer Trials Research Centre and leads the Newcastle Experimental Cancer Medicine Centre and Cancer Research UK (CRUK) Newcastle Cancer Centre. She has taken multiple agents targeting DNA damage response (DDR) into the clinic, including the first-in-human PARP and ATR inhibitors. In addition, she has an active clinical practice treating skin cancer, in both the advanced and adjuvant settings, and with an associated clinical trials portfolio including both early and later phase trials.

Nationally she sits on grant funding committees for CRUK, the Medical Research Council (MRC) and the National Institute for Health Research (NIHR) and was elected a Fellow of the Academy of Medical Sciences in 2018 for her work developing PARP inhibitors as novel cancer treatments for patients.

Contributors

PA Ascierto
Department of Skin Cancers, Cancer Immunotherapy and Development Therapeutics, Istituto Nazionale Tumori IRCCS 'Fondazione G. Pascale', Naples, Italy

M Battistella
Pathology, AP-HP, Saint-Louis Hospital, Paris, France

R Dummer
Faculty of Medicine, University of Zurich, Zurich, Switzerland

AMM Eggermont
Department of Surgical Oncology, Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands

F Herms
Dermatology, AP-HP, Saint-Louis Hospital, Paris, France

AM Grimaldi
Department of Skin Cancers, Cancer Immunotherapy and Development Therapeutics, Istituto Nazionale Tumori IRCCS 'Fondazione G. Pascale', Naples, Italy

K Homicsko
Department of Oncology, CHUV, Lausanne, Switzerland

C Kelly
Northern Centre for Cancer Care, Newcastle Hospitals NHS Trust; Newcastle University, Newcastle upon Tyne, UK

C Lebbé
Université de Paris, INSERM U976, Paris, France

I Lugowska
Early Phase Clinical Trials Unit, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

D Massi
Division of Pathological Anatomy, Department of Surgery and Translational Medicine, University of Florence, Florence, Italy

GA McArthur
Division of Research, Peter MacCallum Cancer Centre, Melbourne; Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Victoria, Australia

O Michielin
Department of Oncology, CHUV, Lausanne, Switzerland

P Nathan
Mount Vernon Cancer Centre, Northwood, UK

G Palmieri
Unit of Cancer Genetics, Institute of Genetic and Biomedical Research (IRGB), National Research Council (CNR), Sassari, Italy

R Plummer
Northern Centre for Cancer Care, Newcastle Hospitals NHS Trust; Newcastle University, Newcastle upon Tyne, UK

E Ramelyte
Department of Dermatology, University Hospital Zurich and University of Zurich, Zurich, Switzerland

P Rutkowski
Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

JJ Sacco
Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool; The Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, UK

D Schadendorf
Department of Dermatology, University Hospital Essen, Essen, Germany

M Slowinska
Dermatological Clinic, Military Institute of Medicine, Central Clinical Hospital of the Ministry of Defence in Warsaw, Warsaw, Poland

ACJ van Akkooi
Department of Surgical Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, Netherlands

A Zaremba
Department of Dermatology, University Hospital Essen, Essen, Germany

M Zdzienicki
Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Abbreviations

5-FU	5-fluorouracil
ABC	Anti-PD1 Brain Collaboration study
AE	Adverse event
AJCC	American Joint Committee on Cancer
AK	Actinic keratosis
AM	Acral melanoma
APC	Antigen-presenting cell
AUC	Area under the curve
BCC	Basal cell carcinoma
BD	Bowen's disease
CBCL	Cutaneous B-cell lymphoma
ccfDNA	Circulating cell-free DNA
ChT	Chemotherapy
CLND	Completion lymph node dissection
CM	Cutaneous melanoma
CNS	Central nervous system
CR	Complete response
cSCC	Cutaneous squamous cell carcinoma
CSD	Chronic sun damage
CT	Computed tomography
CTC	Circulating tumour cell
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-cell lymphoma
CTLA-4	Cytotoxic T-lymphocyte antigen-4
cuMM	Cutaneous malignant melanoma
DC	Dendritic cell
DCR	Disease control rate
DFS	Disease-free survival
DFSP	Dermatofibrosarcoma protuberans
DM	Desmoplastic melanoma
DMFS	Distant metastasis-free survival
DoR	Duration of response
ECT	Electrochemotherapy
ERK	Extracellular signal-regulated kinase
FAMMM	Familial atypical multiple mole melanoma
FDA	Food & Drug Administration
GM-CSF	Granulocyte-macrophage colony-stimulating factor
gp100	Glycoprotein 100
HDAC	Histone deacetylase
HDACi	Histone deacetylase inhibitor
HGF	Hepatocyte growth factor
Hh	Hedgehog pathway
HHV8	Human herpes virus 8
HILP	Hyperthermic isolated limb perfusion
HIV	Human immunodeficiency virus
HSV-1	Herpes simplex virus 1
ICI	Immune checkpoint inhibitor
IFN	Interferon
IFN-α	Interferon alpha
IL	Interleukin
ILI	Isolated limb infusion
IO	Immunotherapy
irAE	Immune-related adverse event
iRECIST	Immune RECIST
ITM	In-transit metastases
i.v.	Intravenous
KA	Keratoacanthoma
KS	Kaposi's sarcoma
LA-BCC	Locally advanced BCC
LAG-3	Lymphocyte activation gene 3
LDH	Lactate dehydrogenase
LMM	Lentigo-maligna melanoma
LN	Lymph node
M	Metastasis
MAPK	Mitogen-activated protein kinase
MBM	Melanoma brain metastases
MCC	Merkel cell carcinoma
MCPyV	Merkel cell polyomavirus
MHC	Major histocompatibility complex
MM	Malignant melanoma
mMCC	Metastatic MCC
moBCC	Morphoeic basal cell carcinoma
mOS	Median overall survival
mPFS	Median progression-free survival
MRI	Magnetic resonance imaging
mTTR	Median time to relapse
MUP	Melanoma of unknown primary
N	Lymph node
NAST	Neoadjuvant systemic therapy
nBCC	Nodular basal cell carcinoma
NF1	Neurofibromin 1
NF-κB	Nuclear factor kappa B
NK	Natural killer
NMSC	Non-melanoma skin cancer
NTRK	Neurotrophic tyrosine receptor kinase
ORR	Overall response rate
OS	Overall survival
PD-1	Programmed cell death protein 1
PDGFB	Platelet-derived growth factor B
PDGFR	Platelet-derived growth factor receptor
PD-L1/2	Programmed death-ligand 1/2
PET	Positron emission tomography
PFS	Progression-free survival
PHP	Percutaneous hepatic perfusion
p.o.	Orally
PR	Partial response
PS	Performance status
RCM	Reflectance confocal microscopy
RECIST	Response Evaluation Criteria in Solid Tumours
RFS	Relapse-free survival
ROC	Receiver operating characteristic
RR	Response rate
RT	Radiotherapy
rTNM	Recurrent TNM classification
sBCC	Superficial basal cell carcinoma
SCC	Squamous cell carcinoma
SD	Stable disease
SLNB	Sentinel lymph node biopsy
SM	Spitz melanoma
SN	Sentinel node
SN+	Sentinel node positive
SRS	Stereotactic radiosurgery
SSM	Superficial spreading melanoma
T	Tumour
TCR	T-cell receptor
TERT	Telomerase reverse transcriptase
TIL	Tumour-infiltrating lymphocyte
TIM-3	T-cell immunoglobulin and mucin domain 3
TKI	Tyrosine kinase inhibitor
TLR9	Toll-like receptor 9
TMB	Tumour mutation burden
TNFα	Tumour necrosis factor-alpha
TNM	Tumour, Node, Metastasis
TP53	Tumour protein 53
TT	Targeted therapy
T-VEC	Talimogene laherparepvec
UM	Uveal melanoma
UV	Ultraviolet
WBRT	Whole brain radiotherapy
WHO	World Health Organization
WLE	Wide local excision

Acknowledgements

The editors would like to thank the members of the Educational Publications Working Group and the Educational Committee for their support in this initiative. The editors also wish to acknowledge and thank Claire Bramley, Nicki Peters and Aude Galli for their support in the preparation of this publication.

Paolo A. Ascierto, Iwona Lugowska and Ruth Plummer

A

What every oncologist should know

1 Epidemiology, prevention, screening and surveillance of skin cancer

Epidemiology of malignant melanoma

Malignant melanoma (MM) arises from melanocytes responsible for pigmentation, which are located in the skin, mucosa, central nervous system or uveal tract of the eye.

Worldwide, cutaneous MM (cuMM) comprises 1.7% cases of all newly diagnosed primary malignant cancers (excluding non-melanoma skin cancer [NMSC]).

Incidence and mortality vary substantially between continents with low incidences in Asia and the highest incidences in Australia.

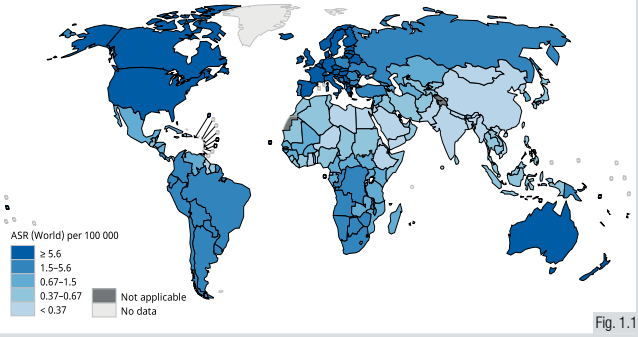


Fig. 1.1

ASR, age-standardised rate; cuMM, cutaneous malignant melanoma.

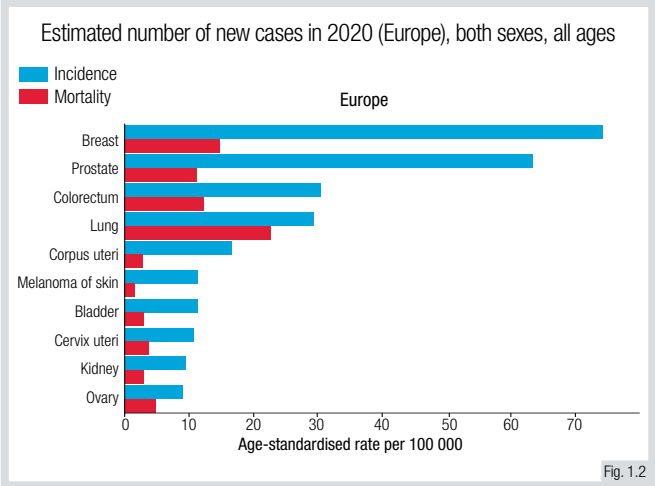


Fig. 1.2

In Europe, the overall incidence of cuMM is rising rapidly with highest rates in northern and north-western countries such as the UK, Ireland and the Netherlands, and lowest rates in Portugal and Spain.

Currently, cuMM is the sixth most common tumour in men and women in Europe across all malignancies (NMSC included in 'other cancers').

Although cuMM represents only 4% of all skin cancers (including NMSC), it is responsible for 80% of all skin cancer deaths.

During the last 20 years, multiple approaches have resulted in a better understanding of tumour immunology and the genomic characteristics of melanoma.

Survival for melanoma patients with metastases is significantly prolonged by new therapeutic options compared with chemotherapy.

Melanoma-specific survival of MM depends on the stage at initial diagnosis, comprising primary tumour characteristics, and local and distant metastasis status.

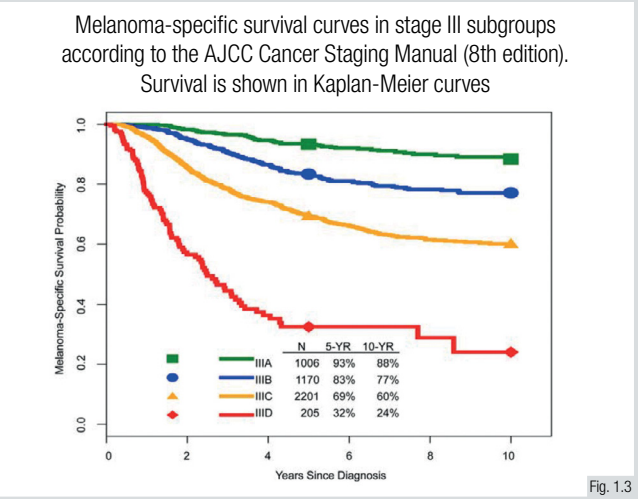


Fig. 1.3

AJCC, American Joint Committee on Cancer.

REVISION QUESTIONS

1. Where are melanocytes located?
2. Which countries have the highest incidences of melanoma?
3. What led to an increased survival of advanced melanoma patients?

Prevention of malignant melanoma

Persons with Fitzpatrick scale skin type I (fair hair, fair eyes, fair skin colour and freckles) have a higher risk of developing melanoma.

Well-known risk factors comprise ultraviolet (UV) radiation (sun exposure, tanning beds), sunburn, multiple or dysplastic naevi, and medical history of melanoma.

Inherited genetic mutations are possible, but rare, and should be considered if one person has multiple cuMMs, or several family members suffer from cuMM and/or associated tumour entities: FAMMM (familial atypical multiple mole melanoma) syndrome.

The Fitzpatrick scale of skin types is a numeric classification schema for human skin colour

Skin type	I	II	III	IV	V
					
Description	**Skin:** noticeably fair-skinned, pale **Freckles:** large number **Hair:** reddish **Eyes:** green, blue, seldom brown	**Skin:** somewhat darker than type I **Freckles:** seldom **Hair:** blonde to brown **Eyes:** blue, green, grey	**Skin:** light brown **Freckles:** none **Hair:** dark blonde, brown **Eyes:** grey, brown	**Skin:** brown **Freckles:** none **Hair:** dark brown, black **Eyes:** brown	**Skin:** dark brown, black **Freckles:** none **Hair:** black **Eyes:** brown

Fig. 1.4

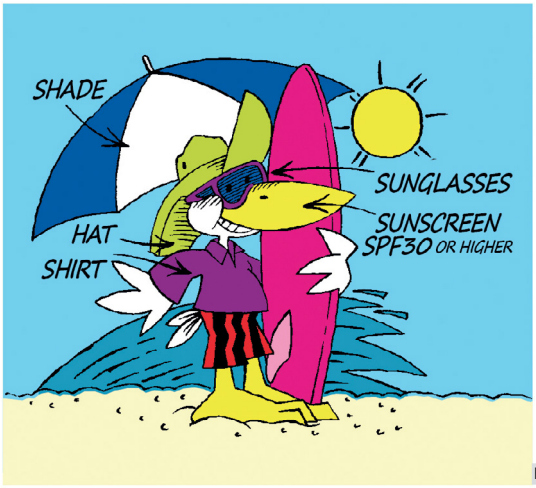


Fig. 1.5

Australia is one of the few countries where incidence has been decreasing since 2005, possibly reflecting an increased awareness due to primary preventive approaches.

National campaigns promoting physical and chemical sun protection support education from early childhood about acute and chronic sun damage and skin cancer.

In Europe, larger primary prevention campaigns were started in the 1990s, aiming to increase knowledge and awareness. Nowadays, broad campaigns and international, collaborative research projects to understand melanoma genetics and survival are funded by European institutions.

More common subtypes are superficial spreading melanoma and nodular melanoma, while rarer melanoma subtypes include melanoma of unknown primary (MUP), acrolentigious melanoma, mucosal melanoma and blue naevus-like melanoma.

Rare subtypes harbour a distinct mutation pattern and are assumed to be less UV-associated, which makes primary prevention in general more difficult.

Two to three percent of melanomas appear without a primary tumour, but with metastases. Possibly, the primary tumour has vanished by regression after recognition by the immune system or never existed in the first place.

Fig. 1.6

REVISION QUESTIONS

1. Which skin type has the highest risk for developing melanoma and why?
2. Name one measure which is used as primary prevention in melanoma.
3. What does MUP stand for?

Screening and surveillance of malignant melanoma

Awareness for self-examination of pigmented naevi using easily recognisable rules is underlined. One example is the ABCD rule for pigmented lesions: A-Asymmetry, B-Border, C-Colour, D-Diameter, helping to differentiate between benign and malignant lesions.

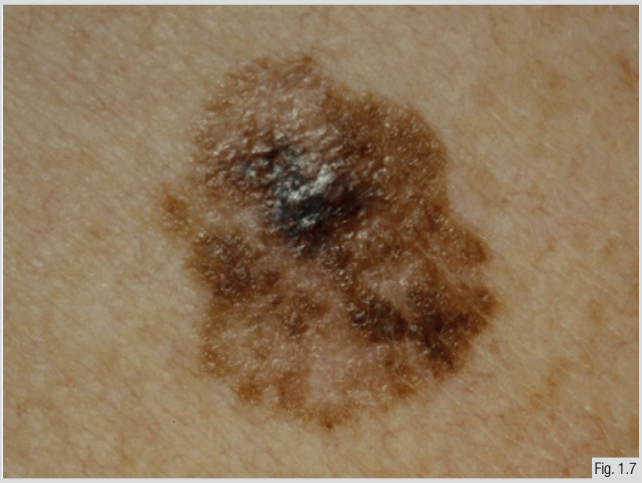


Fig. 1.7

Patients at risk should be screened by total body skin examinations with a dermatoscope or comparable imaging technique (see Chapter 9).

Screenings should be performed by experienced physicians including mucous membranes and examination and palpation of lymph node stations.

Histopathology of a malignant melanoma

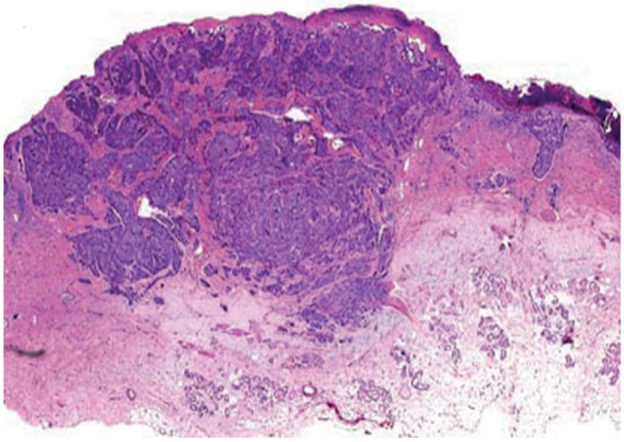


Fig. 1.8

Suspicious lesions should be excised completely and examined histopathologically. If a melanoma is confirmed, further diagnostics and therapeutic options should be initiated.

Secondary prevention is established by a regular follow-up schedule including clinical examination and ultrasound.

For higher tumour stages, imaging techniques should be used to detect disease progression early and thus increase disease-specific survival.

Regular screening can lead to early detection of skin cancer with lower invasion and depth of the tumour, which is known to be a risk factor for worse prognosis.

Skin cancer screening programmes vary between countries, with regular investigations every 2 years from the age of 35 in Germany to no general regular screenings in the USA.

So far, a decrease in mortality attributed to skin cancer screening has not been detected. Still, potential benefits might be relative to quality of life or aggressiveness of treatment.

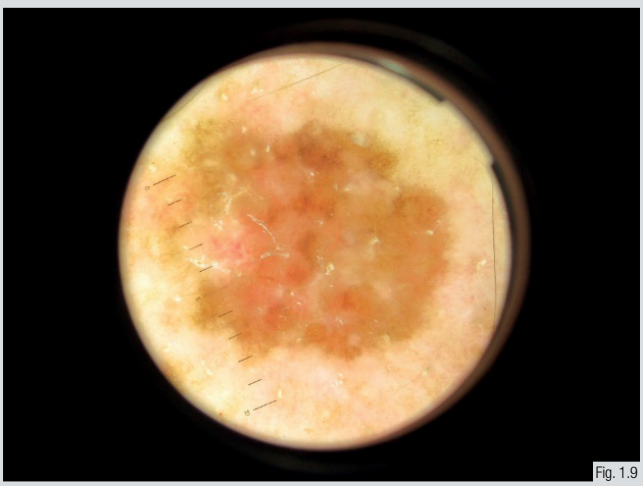


Fig. 1.9

REVISION QUESTIONS

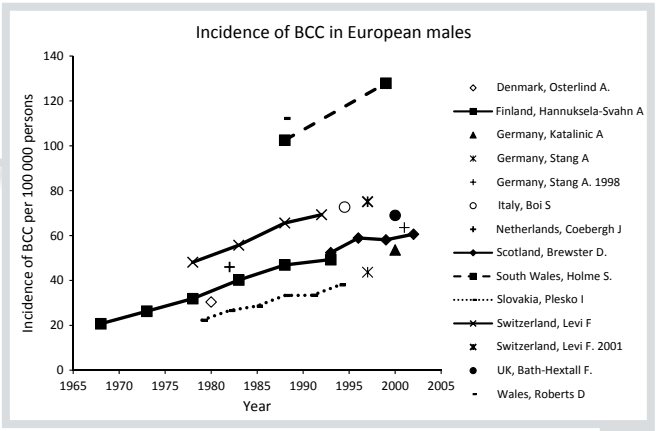
1. What does ‘C’ in the ABCD rule stand for?
2. What does regular screening consist of?
3. How is the diagnosis of melanoma confirmed and by whom?

Epidemiology, prevention, screening and surveillance of NMSC

NMSCs make up the greatest proportion of all human cancers, with an incidence of 8% worldwide.

Common NMSCs comprise basal cell carcinoma (BCC) arising from basal cells: 57%-80% of all NMSCs, and cutaneous squamous cell carcinoma (cSCC) arising from epidermal keratinocytes: 20%-25% of all NMSCs.

Rare NMSCs comprise Merkel cell carcinoma (MCC), cutaneous lymphomas, cutaneous adnexal tumours, Kaposi's sarcoma and others.



BCC, basal cell carcinoma. Fig. 1.10

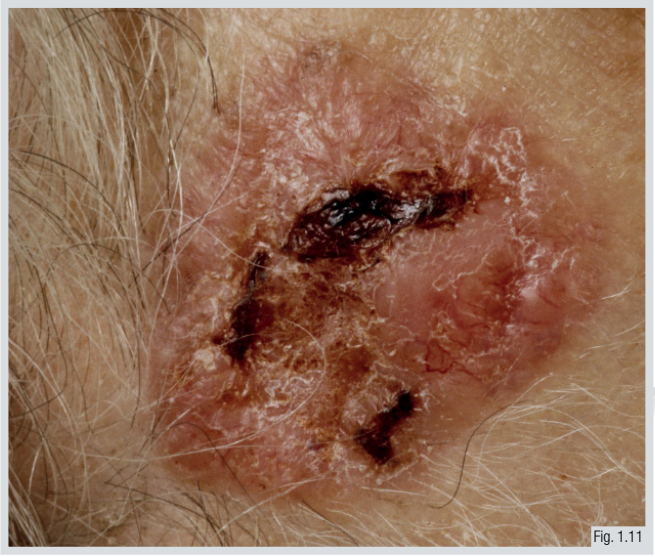


Fig. 1.11

BCC and cSCC show a low rate for distant metastases, but a higher risk for local recurrence. Major risk factors are chronic sun-damaged skin and immunosuppression.

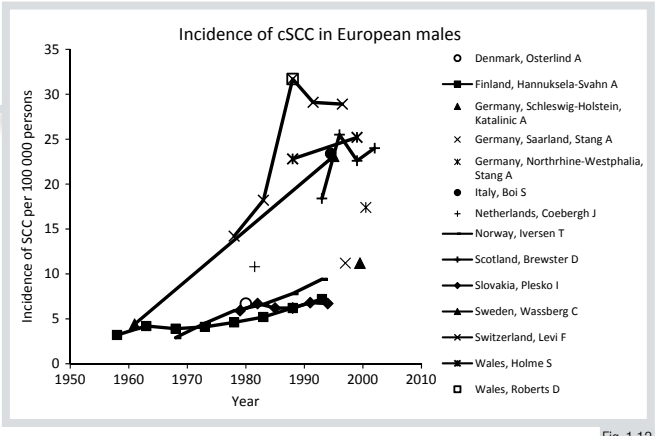
Risk factors for aggressive courses of cSCCs are immunosuppression (e.g. after solid-organ transplantation), high tumour thickness (>6 mm), poor differentiation and localisation (e.g. lips, ears).

BCCs more often arise in males (ratio 2.1:1) and elderly patients; the median age at diagnosis is 67 years. Around 80% of all BCCs are located in the head and neck region, followed, more rarely, by the hands.

cSCCs usually originate from precancerous lesions such as actinic keratosis, but they can also develop *de novo*.

Histology should always confirm the diagnosis of precancerous lesions before using any therapeutic modality other than surgery.

High-risk patients should be screened regularly with a whole-body examination, e.g. at 3-month intervals after organ transplantation or after previous high-risk NMSC.



cSCC, cutaneous squamous cell carcinoma. Fig. 1.12

REVISION QUESTIONS

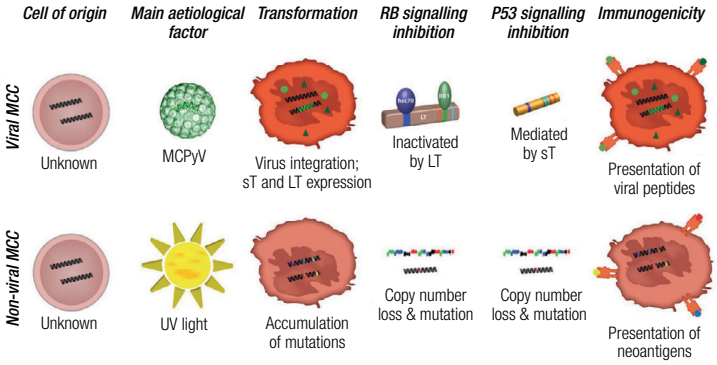
1. Which malignancies belong to common and which to rare NMSC?
2. From which cells does squamous cell cancer arise?
3. Name three risk factors for the emergence of cSCCs.

Epidemiology, prevention, screening and surveillance of NMSC (continued)

Risk factors for MCC are immunosuppression, older age and UV damage. The majority of tumours are associated with the Merkel cell polyomavirus.

Incidence is rising with approximately 2500 new cases per year in Europe (very rare), but its highly aggressive growth and disseminated spreading leads to a disease-specific mortality rate in the range of 25%-50%.

Screening is unwarranted due to the low incidence. Selection of immunosuppressive medication in dependant patients may be a crucial factor for prevention.



LT, large T antigen; MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; RB, retinoblastoma protein; sT, small T antigen; UV, ultraviolet. Fig. 1.13

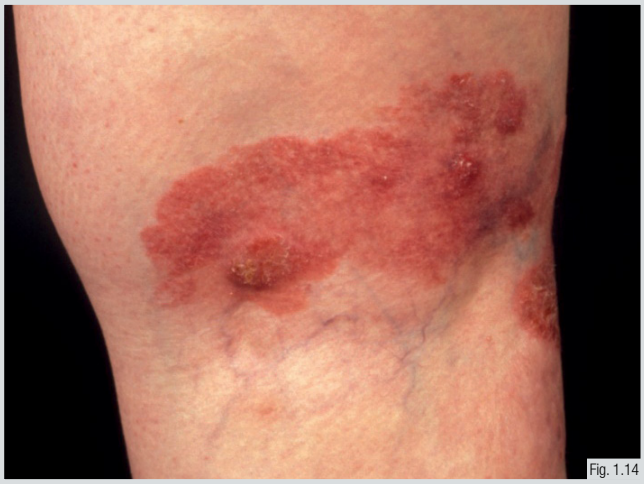


Fig. 1.14

Primary cutaneous T- (CTCL) and B- (CBCL) cell lymphomas are incurable, primary extra-nodal lymphomas of major T or B cells, respectively.

The most frequent CTCL is mycosis fungoides, which is a slowly progressing, low-grade lymphoma, clinically presenting with patches, plaques, nodules, ulcerations, but also potentially organ involvement and fatal outcome.

CBCLs are a rather rare entity with an overall incidence of 3.9/1 000 000 between 2006 and 2010. They present a heterogeneous group of malignancies, varying from slowly recurring courses to those with rapid courses.

Although rare in Europe, Kaposi's sarcoma is one of the most common neoplasms of people living with human immunodeficiency virus (HIV), with high incidences in some regions of Africa.

Overall, many patients show an immunosuppressed baseline status when developing skin cancer; this is also a risk factor for invasiveness and prognosis.

Increased awareness and regular screening of patients at risk may help to increase early diagnosis and improve outcomes in young and elderly patients.

Fig. 1.15

REVISION QUESTIONS

1. Name three risk factors for MCC.
2. From which cells do cutaneous lymphomas arise?
3. What different kinds of immunosuppression are known risk factors for skin cancer development?

Summary: Epidemiology, prevention, screening and surveillance of skin cancer

- There are great differences in incidence and mortality between countries internationally and also in Europe
- Survival for advanced melanoma patients has been significantly prolonged by new therapeutic options
- Risk factors for development of melanoma comprise UV radiation (sun exposure, tanning beds), sunburn, multiple or dysplastic naevi and medical history of melanoma
- Rising melanoma awareness among the population and protection from UV light has potentially led to a decrease in incidence in some countries (e.g. Australia)
- NMSCs make up the greatest proportion of all human cancers and include BCC, cSCC and further, rarer entities
- Major risk factors for NMSC are chronic sun-damaged skin and immunosuppression
- MCC is a very rare NMSC with a highly aggressive growth and a high disease-specific mortality rate
- Primary CTCLs and CBCLs are incurable primary extra-nodal lymphomas, which frequently show a rather chronic course of disease, but can also involve organs and show aggressive courses

Further Reading

Arnold M, Holterhues C, Hollestein LM, et al. Trends in incidence and predictions of cutaneous melanoma across Europe up to 2015. J Eur Acad Dermatol Venereol 2014; 28:1170–1178.

Ascierto PA, Schadendorf D. Immunotherapy in non-melanoma skin cancer: updates and new perspectives. Drugs Context 2019; 8:212583.

Bastian BC. The molecular pathology of melanoma: an integrated taxonomy of melanocytic neoplasia. Annu Rev Pathol 2014; 9:239–271.

Becker JC, Stang A, DeCaprio JA, et al. Merkel cell carcinoma. Nat Rev Dis Primers 2017; 3:17077.

Komatsubara KM, Jeter J, Carvajal RD, et al. Advances in the treatment of advanced extracutaneous melanomas and nonmelanoma skin cancers. Am Soc Clin Oncol Educ Book 2017; 37:641–650.

Korgavkar K, Weinstock MA. Changing incidence trends of cutaneous B-cell lymphoma. J Invest Dermatol 2014; 134:840–842.

Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol 2012; 166:1069–1080.

Schadendorf D, van Akkooi ACJ, Berking C, et al. Melanoma. Lancet 2018; 392:971–984.

Stang A, Garbe C, Autier P, Jöckel KH. The many unanswered questions related to the German skin cancer screening programme. Eur J Cancer 2016; 64:83–88.

Ugurel S, Röhmel J, Ascierto PA, et al. Survival of patients with advanced metastatic melanoma: the impact of MAP kinase pathway inhibition and immune checkpoint inhibition - Update 2019. Eur J Cancer 2020; 130:126–138.

2 Staging and prognostic factors

Staging introduction

The current staging used for cutaneous melanoma is based on the AJCC (American Joint Committee on Cancer) Cancer Staging Manual, 8th edition, published in 2017.

Melanoma has four clinical stages, determined by characteristics of the primary tumour (T) and involvement of the lymph nodes (N) and distant organs (M [metastases]).

Five-year overall survival (OS) in stage I-II disease is 65%-100%, dropping to 41%-71% in patients with local metastases (stage III) and 9%-28% in patients with distant metastases (stage IV).

AJCC melanoma of the skin: staging

Clinical staging (cTNM)				Pathological staging (pTNM)			
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b				T1b		
	T2a			IB	T2a		
Stage IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a				T3a		
Stage IIB	T3b			IIB	T3b		
	T4a				T4a		
Stage IIC	T4b			IIC	T4b		
Stage III	Any T, Tis	≥N1	M0	IIIA	T1a/b-T2a	N1a or N2a	M0
				IIIB	T0	N1b, N1c	M0
					T1a/b-T2a	N1b/c or N2b	
					T2b/T3a	N1a-2b	
				IIIC	T0	N2b/c or N3b/c	M0
					T1a-3a	N2c or N3a/b/c	
					T3b/4a	Any N ≥N1	
					T4b	N1a-2c	
				IIID	T4b	N3a/b/c	M0
Stage IV	Any T	Any N	M1	IV	Any T, Tis	Any N	M1

AJCC, American Joint Committee on Cancer; M, metastases; N, node; T, tumour; Tis, tumour *in situ*.

Fig. 2.1

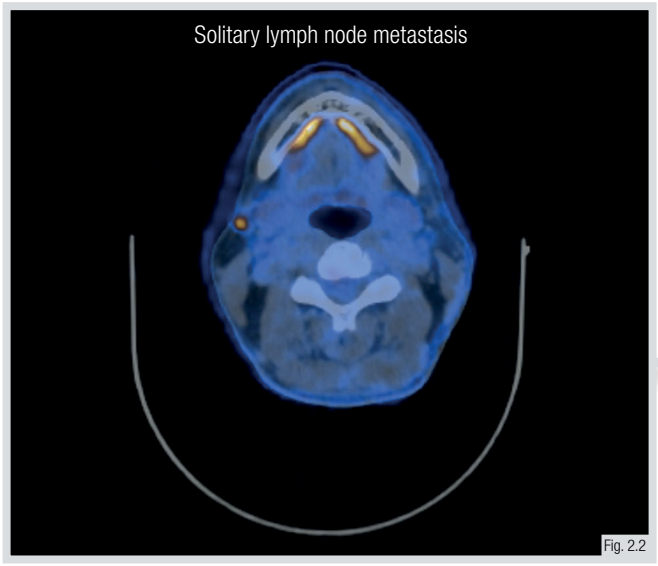


Fig. 2.2

The risk of metastatic disease increases with the thickness of the primary tumour; therefore, any further work-up is done accordingly.

In low-risk melanomas (pT1a), after complete excision, no additional investigations are necessary and patients enter follow-up.

In other melanomas (pT1b-pT4b), imaging techniques (ultrasound, computed tomography [CT], magnetic resonance imaging [MRI], positron emission tomography [PET]-CT) are used to assess tumour extension before sentinel lymph node biopsy (SLNB).

PET-CT has limitations in tissues with high metabolic activity such as brain; thus if cerebral metastases are suspected, a brain MRI should be performed.

SLNB should be offered to patients with ≥pT1b melanoma, considering the imaging results and patient's performance status.

There is no consensus on the follow-up, but regular clinical and, in high-risk cases, imaging examination is crucial to capture disease recurrence.

Multiple in-transit metastases on the right popliteal area

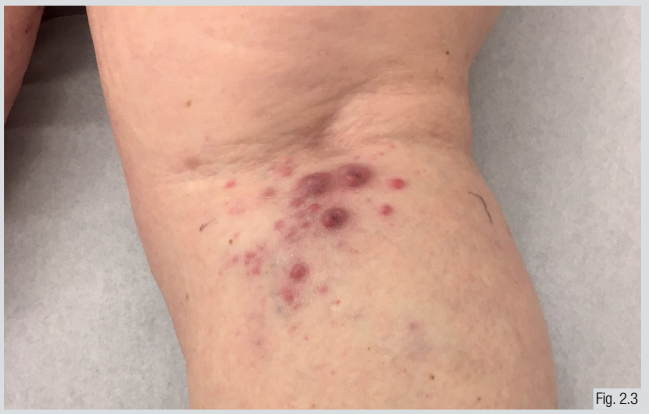


Fig. 2.3

REVISION QUESTIONS

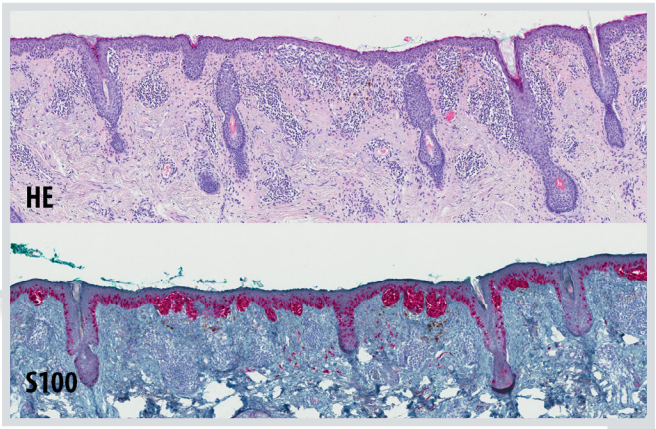
1. In which cases is it rational to perform imaging examinations?
2. What is the approximate 5-year OS in stage I-IV melanoma patients?
3. Which imaging techniques are used for detection of brain metastases?

Staging of primary tumour (T)

Primary melanoma can be staged after complete excision, where the thickest part of the primary tumour can be assessed.

The primary melanoma is measured by Breslow thickness: from the granular layer up to deepest sitting melanocytes. It is recorded to the nearest 0.1 mm.

Immunohistochemical staining with melanocytic markers, such as S100, is usually used for more accurate measurement.



HE, haematoxylin and eosin. Fig. 2.4

Fig. 2.5

Along with the tumour thickness, ulceration is a T-category criterion. It is designated as T-'a' or 'b', according to its presence or absence.

Ulceration is defined as a complete absence of the epidermis above the primary melanoma, accompanied by adjacent tissue reaction.

In lack of adjacent tissue reaction, the loss of epidermis above the primary tumour is likely artificial and should not be reported as ulceration.

Mitoses (marked with arrows) in deep parts of primary cutaneous melanoma

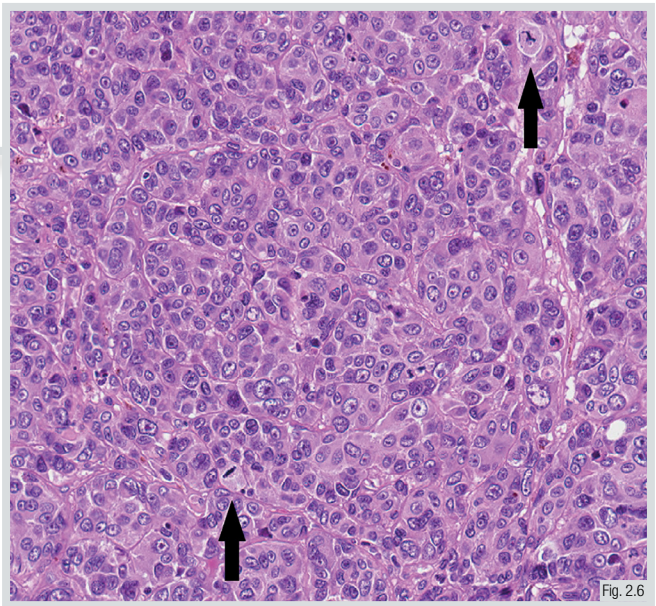


Fig. 2.6

Mitotic rate is defined as the number of mitoses per square millimetre in the invasive part of the primary tumour and was previously used in the TNM staging.

Even though not included in the 8th edition AJCC staging of cutaneous melanoma, it is recommended to report the mitotic rate of the primary melanoma.

Other factors, recommended to be assessed, are (Clark's) level of invasion, tumour-infiltrating lymphocytes (TILs) and lymphovascular and neural invasion.

REVISION QUESTIONS

1. What are the factors used in the staging of primary melanoma?
2. What should be reflected in the pathology report of primary melanoma?
3. How do you define an ulceration of primary melanoma?

Staging of lymph nodes and in-transit metastases (N)

The N category reflects metastatic disease in the regional lymph nodes and non-nodal regional sites (i.e. microsatellite, satellite and in-transit metastases).

First assessment is made clinically, using imaging (ultrasound, CT or PET-CT) and SLNB.

Depending on clinical properties and number of involved lymph nodes or non-nodal sites, N 1-3 stages with a-c subcategories are defined.

Lymph node scintigraphy marking radionuclide uptake in the sentinel lymph node

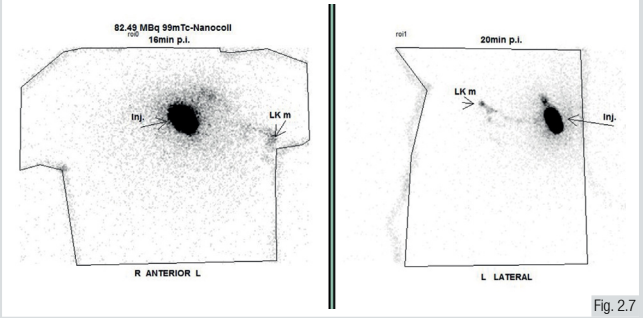
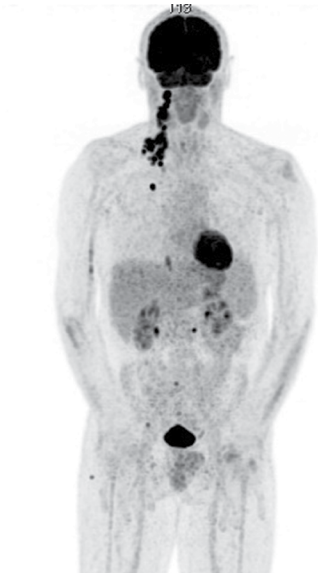


Fig. 2.7

PET-CT scan showing multiple lymph node metastases in the right neck region



CT, computed tomography; PET, positron emission tomography.

Fig. 2.8

'Clinically occult' metastases are only identified microscopically, while 'clinically detected' metastases are evident before microscopic examination.

Clinically occult lymph node metastases are designated as N1-3a, while clinically detected metastases are designated as N1-3b.

>2 nodes adherent through metastatic disease and identified in the same specimen are defined as matted nodes and are staged as N3.

A microsatellite is a metastasis, adjacent or deep to, but not connected to, the primary tumour. A satellite occurs within 2 cm from the primary melanoma.

Microsatellite, satellite or in-transit metastases are designated as 'c' subcategory, whether clinically occult or detected.

In melanoma of unknown primary, the N staging does not differ from cases where the primary tumour is known.

Clinical and histological image of a satellite metastasis

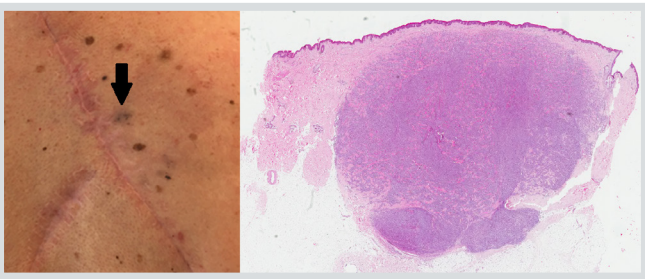


Fig. 2.9

REVISION QUESTIONS

1. Explain the basics of N staging (what characteristics are taken into consideration).
2. What is the difference between a clinically occult and clinically detected lymph node metastasis?
3. How different is N staging in melanoma of unknown primary tumour?

Staging of distant metastases (M) and clinical stages

The M subcategories reflect the distant organ involvement. It is defined as M0 in patients without distant metastases and M1a-M1d in those with distant metastases.

Distant lymph node or soft tissue metastases are staged as M1a, lung metastases as M1b, other visceral metastases as M1c and central nervous system (CNS) metastases as M1d.

Even though lactate dehydrogenase (LDH) level remains an important prognostic factor, it is not considered a category criterion in the most recent staging manual.

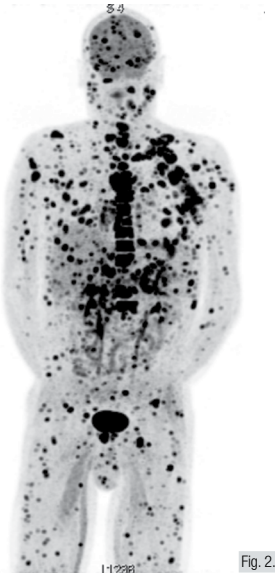


Fig. 2.10

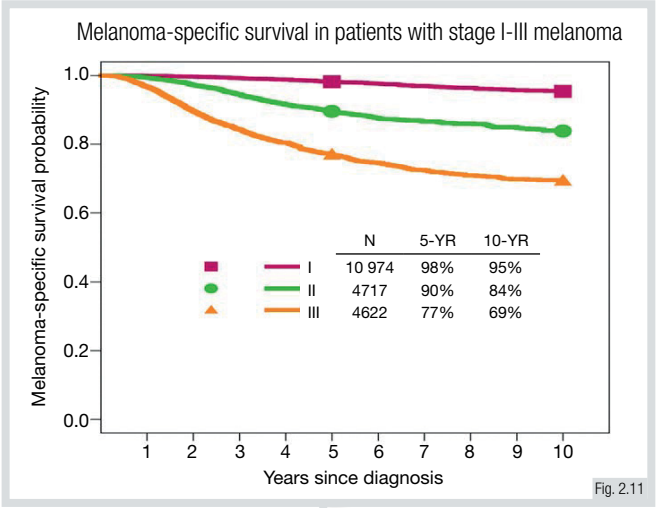


Fig. 2.11

Clinical staging includes microstaging of the primary melanoma and clinical/radiological or histological assessment for regional and distant metastases.

At initial staging, various imaging techniques can be used. However, brain MRI and PET-CT/CT should be applied only for very high-risk (>pT3b) patients.

Pathological staging includes all the clinical staging information and additional information from the surgical treatment or diagnostic procedures.

Melanoma-specific survival differs for clinical and pathological stages because of histological exclusion of suspected lesions.

The number of organs affected by metastatic disease is reported to be prognostic. However, it is not an M-category criterion.

Clinical and pathological staging occur at the initial diagnosis. In the case of recurrent melanoma, it is suggested that recurrent TNM (rTNM) classification is used.

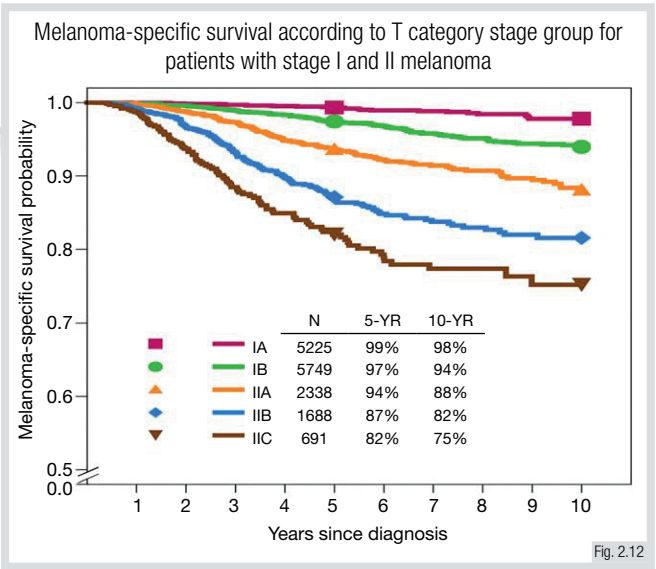


Fig. 2.12

REVISION QUESTIONS

1. Explain M staging.
2. Define the difference between clinical and pathological staging systems.
3. Why is melanoma-specific survival different between the same clinical and pathological stages?

Prognostic factors

Primary tumour thickness is an independent prognostic factor, which directly correlates with melanoma-specific survival.

Increased mitotic rate (>1 mitosis/mm^2) and tumour ulceration are associated with poor disease-free survival (DFS) and OS.

TILs have been reported to be associated with negative sentinel lymph node and better prognosis. A positive effect of TILs is also seen in metastases.

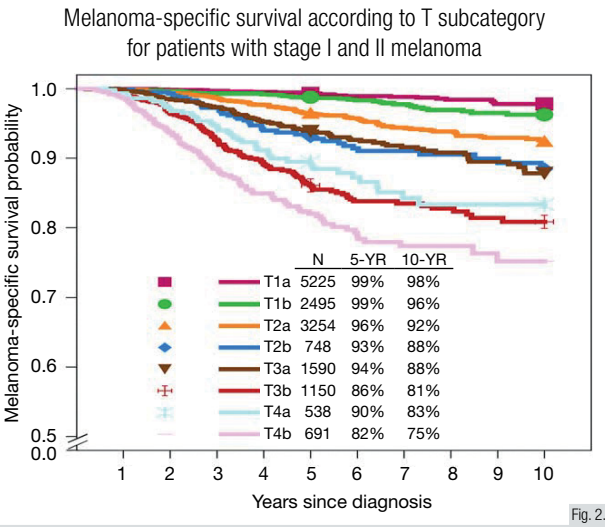


Fig. 2.13

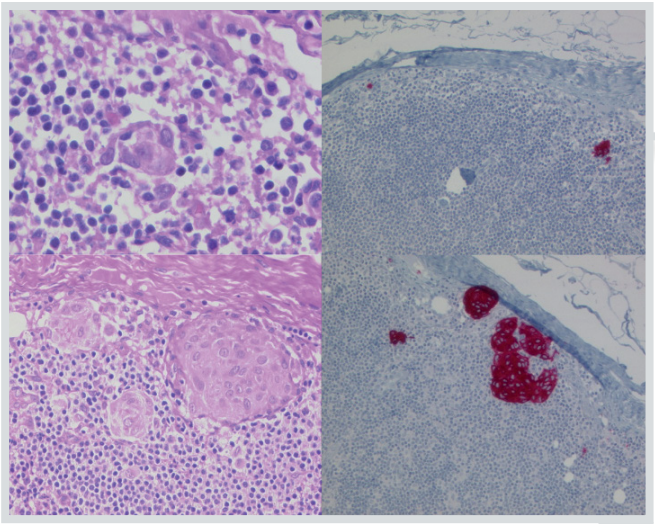


Fig. 2.14

Presence of melanoma cells in a sentinel lymph node reduces 5-year OS from 80%-95% to 35%-75%. Detection of macrometastases reduces it even more.

Extracapsular extension of tumour tissue and involvement of multiple lymph nodes also correlate with poor DFS.

In patients with stage IV disease, patients with soft tissue metastases show longer OS, compared with those with lung and other visceral organ metastases.

Elevated serological markers, such as serum LDH and S100, are associated with poor prognosis.

Patients with both markers elevated show worse prognosis than those with one marker being within normal ranges.

Low LDH and S100 levels at the baseline are predictive for better response to targeted and immune therapies.

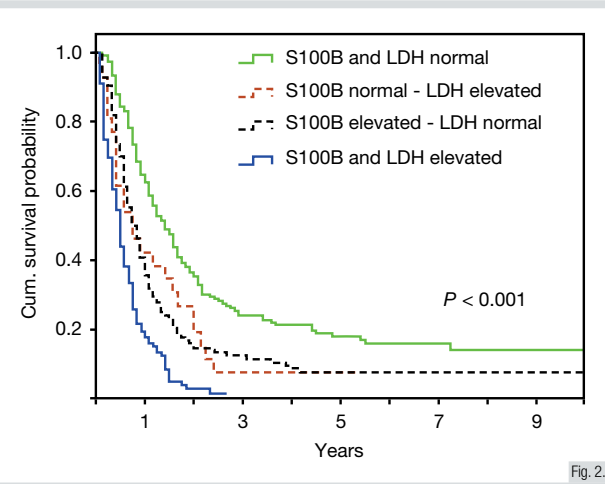


Fig. 2.15

Cum, cumulative; LDH, lactate dehydrogenase.

REVISION QUESTIONS

1. What characteristics of the primary lesion are associated with poor prognosis?
2. What characteristics of lymph node involvement are associated with better outcome?
3. Which blood tests are necessary for M-stage patients?

Summary: Staging and prognostic factors

- Cutaneous melanoma is staged according to the TNM classification, which reflects characteristics of the primary tumour, lymph node status and distant metastases
- Five-year OS in stage I-II disease is 65%-100% and is 9%-28% in patients with metastatic stage IV disease
- PET-CT is suitable for detection of distant metastases. If brain involvement is suspected, MRI must be done
- Primary tumour thickness and tumour burden in lymph nodes directly correlate with melanoma-specific survival
- For patients with thin primary tumour (pT1a), no further investigation is needed. For patients with higher risk primary melanoma (T1b-T4b), staging using imaging techniques and SLNB is recommended
- In pathological T-staging, the thickness and ulceration of the primary tumour is assessed; in pathological N-staging – the extent of lymph node and satellite/in-transit metastases, and in pathological M-staging – the presence of distant organ metastases
- For clinical staging, only the primary tumour has to be assessed histologically, while for the N and M stages, clinical/radiological assessment is sufficient. In pathological staging, along with all the clinical staging information, additional information from the surgical treatment or diagnostic procedures is required
- Elevated LDH and S100 values are associated with poor prognosis, while low LDH and S100 levels at the baseline are predictive for better response to targeted and immune therapy

Further Reading

Egger ME, Bower MR, Czyszczon IA, et al. Comparison of sentinel lymph node micrometastatic tumor burden measurements in melanoma. J Am Coll Surg 2014; 218:519–528.

Frauchiger AL, Dummer RR, Mangana J. Serum S100B levels in melanoma. In: Heizmann CW (Ed.). Calcium-Binding Proteins of the EF-Hand Superfamily. Methods in Molecular Biology, Vol 1929. New York, NY: Humana Press, 2019; pp. 691–700.

Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al (Eds). AJCC Cancer Staging Manual, 8th edition. New York: Springer International Publishing, 2017; pp. 563–585.

Gershenwald JE, Scloyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017; 67:472–492.

Weide B, Elsässer M, Büttner P, et al. Serum markers lactate dehydrogenase and S100B predict independently disease outcome in melanoma patients with distant metastasis. Br J Cancer 2012; 107:422–428.

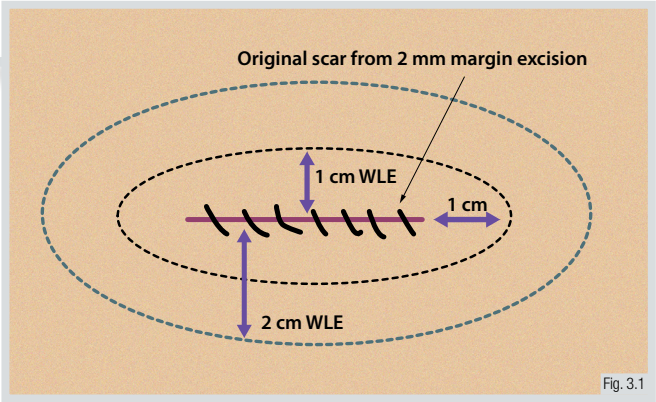
3 Local treatment of melanoma

Primary melanoma

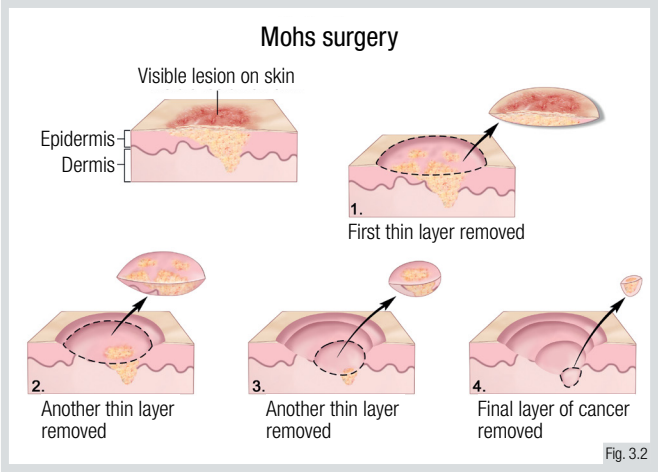
Wide local excision (WLE) with clinical safety margins is recommended after the diagnosis of a primary melanoma.

The width of the WLE clinical safety margins depends on the Breslow thickness of the melanoma: 0.5 cm for *in situ*, 1 cm for Breslow thickness ≤2 mm, and 2 cm for >2 mm Breslow-thickness melanomas.

WLE improves relapse-free survival (RFS), but does not improve overall survival (OS).



WLE, wide local excision.



Modifications with lesser safety margins are allowed for functional or cosmetic areas (e.g. face/joints). Mohs micrographic surgery can also be considered in these cases.

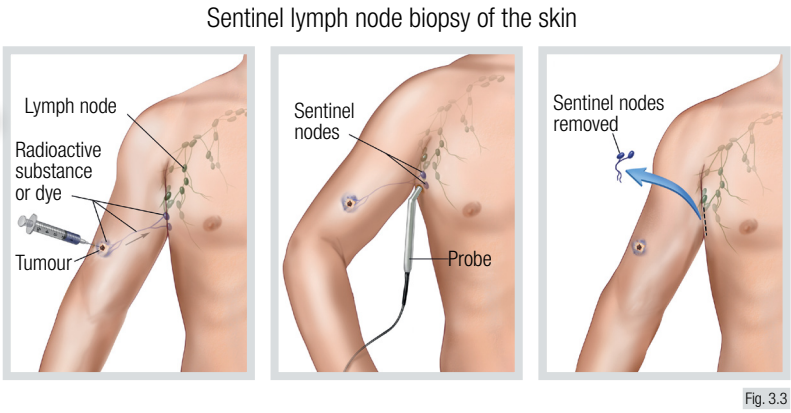
Definitive radiotherapy (RT) can be considered for lentigo maligna or for rare palliative cases, when excision is not possible due to comorbidity of the patient, or when the morbidity of the excision is considered too great.

Immediate WLE of a suspected lesion is NOT indicated, because some cases turn out to have another diagnosis that does not require WLE and an immediate WLE compromises the reliability of a potential sentinel node (SN) biopsy.

Elective lymph node (LN) dissection or elective RT of LNs is NOT indicated for primary melanoma.

SN staging is recommended for melanomas with a Breslow thickness >1.0 mm and NOT recommended for Breslow <0.8 mm, without ulceration.

SN staging can be discussed for melanomas with a Breslow thickness 0.8–1.0 mm or <0.8 mm, but with ulceration.



REVISION QUESTIONS

1. Does WLE improve OS?
2. Can definitive RT be given as a curative alternative to WLE?
3. Is SN staging recommended for melanomas with a Breslow thickness >1.0 mm?

Primary melanoma (continued)

If SN staging is indicated, this should be performed at the same time as the WLE to avoid lymph drainage modifications.

SN staging in itself does not improve the OS of melanoma patients.

Completion lymph node dissection (CLND) for patients with a metastasis in the SN does not improve OS over sequential nodal observation with ultrasound.

Melanoma-specific survival, intermediate thickness melanomas

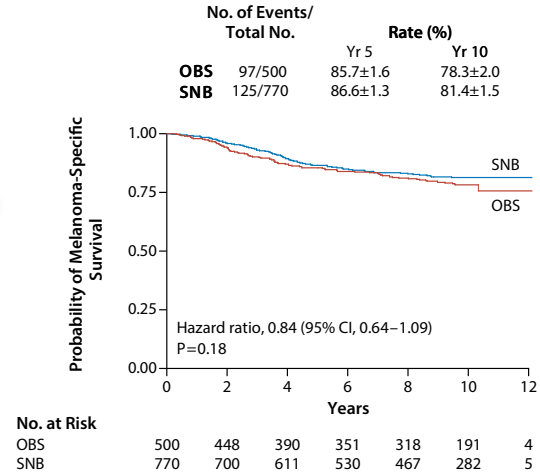


Fig. 3.4

CI, confidence interval; OBS, observation; SNB, sentinel node biopsy.

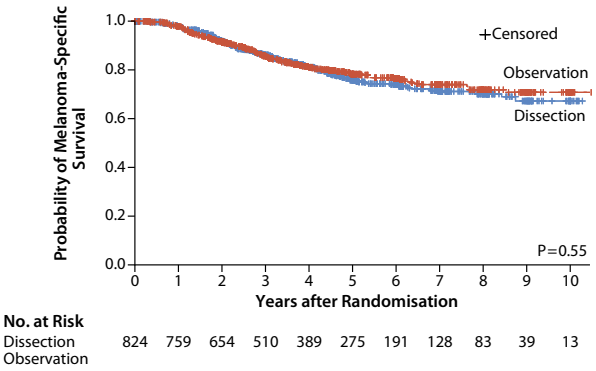


Fig. 3.5

CLND induces significantly more morbidity in SN-positive (SN+) patients.

The morbidity of a CLND includes wound dehiscence, infections, seroma, lymphoceles (short term), nerve damage (rare) and chronic lymphoedema (long term).

CLND improves the staging of SN+ patients, but only in 6% of patients and therefore is not warranted.

SN+ patients should be considered for adjuvant systemic therapy either with an anti-programmed cell death protein 1 (PD-1) (nivolumab or pembrolizumab) or BRAF/MEK inhibitors (dabrafenib/trametinib).

A formal LN dissection is indicated for patients with a clinical (macroscopic) node recurrence (either palpable node or image detected).

Adjuvant RT reduces the frequency of in-field recurrences after LN dissection for high-risk stage III melanoma, but does not improve survival.

Cumulative incidence curves of lymph-node field relapse as a site of first relapse (competing risks: other relapse and death)

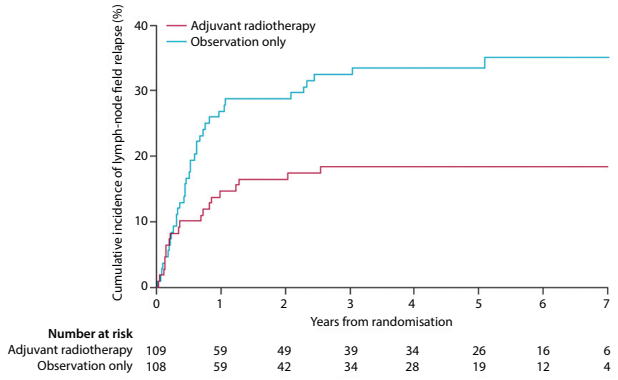


Fig. 3.6

REVISION QUESTIONS

1. Does a SN procedure improve survival in melanoma?
2. Should a CLND be considered for SN+ melanoma?
3. Does adjuvant RT improve survival after LN dissection for a clinical recurrence?

Lymph node metastases

Patients who have undergone a formal LN dissection for a clinical recurrence should be considered for adjuvant systemic therapy.

Patients undergoing a LN dissection should be adequately staged by computed tomography (CT) of the thorax/pelvis/abdomen or whole-body positron emission tomography (PET)-CT plus brain imaging, prior to surgery.

Patients should be restaged by thorax/pelvis/abdomen CT, or whole-body PET-CT plus brain imaging, before starting on adjuvant systemic therapy.

Fig. 3.7

CI, confidence interval.

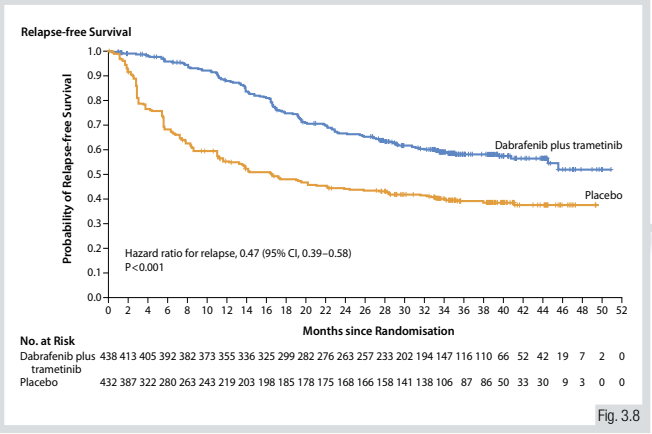


Fig. 3.8

CI, confidence interval.

For *BRAF* wild-type patients, the current standard-of-care adjuvant therapy is 1 year of anti-PD-1 (nivolumab or pembrolizumab).

For *BRAF* V600E/K-mutated patients, both 1 year of BRAF/MEK inhibitors (dabrafenib/trametinib) and 1 year of anti-PD-1 (nivolumab or pembrolizumab) are options. It is unclear if one is superior to the other.

Adjuvant systemic therapy (both targeted and immunotherapy) improves RFS, but it is unclear if this translates into an OS benefit.

Severe (grade 3/4) toxicity from adjuvant BRAF/MEK inhibitors is higher (31%) than from adjuvant anti-PD-1 (15%). However, toxicity due to BRAF/MEK inhibitors resolves, but immunotherapy-related toxicity can be permanent.

When proposing adjuvant systemic therapy, an in-depth discussion is required with patients on the risks, the relative and absolute benefits, and the potential toxicities.

It is currently unclear what the best treatment option is for patients developing recurrence during adjuvant systemic therapy. These patients have poor prognosis and should be offered trial participation where appropriate.

Comparison of AEs: EORTC 18071, CheckMate 067 and CA184-169

Toxicity	Ipilimumab 10 mg/kg[1,2]		Nivolumab 3 mg/kg[2]		Pembrolizumab 200 mg[3,4]		Dabrafenib + trametinib[5,6]	
All values in %	All	G 3-4	All	G 3-4	All	G 3-4	All	G 3-4
Any AE	99	55	97	25	93	32	97	41
Any drug-related AE	96	46	85	14	78	15	91[6]	31[6]
Fatigue	33	1	35	<1	37	1	47	4
Rash	29	3	20	1	16	<1	24	0
Diarrhoea / colitis	46/10	10/8	24/2	2/1	19/4	1/2	33/NR	1/NR
Increased AST/ALT	13/15	4/6	6/6	<1/1	NR/NR	NR/NR	14/15	4/4
Pneumonitis	2	1	1	0	3	1	-	-
Hypophysitis	11	3	2	<1	2	1	-	-
Adrenal disorder	3	1	1	<1	1	<1	-	-
Thyroid disorder	13	1	20	1	21	<1	-	-
Type I diabetes	<1	<1	<1	0	1	1	-	-

Fig. 3.9

1 Eggermont, NEJM 2016; 2 Weber, NEJM 2017; 3 Eggermont, NEJM 2018; 4 Eggermont, AACR 2018; 5 Long, NEJM 2017; 6 Long, SMR 2017.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EORTC, European Organisation for Research and Treatment of Cancer; G, grade; NR, not reported.

REVISION QUESTIONS

1. Is dabrafenib/trametinib always the first-choice adjuvant systemic therapy for *BRAF* V600E/K-mutated melanoma patients?
2. Is adjuvant immunotherapy preferable to BRAF/MEK inhibition due to the lower risk of severe (grade 3/4) toxicity?
3. Should patients developing a recurrence during adjuvant systemic therapy always switch to second-line systemic therapy?

Summary: Local treatment of melanoma

- WLE with clinical safety margins, depending on the primary Breslow thickness, is indicated for the treatment of a primary melanoma
- SN staging should always be considered for melanomas with a Breslow thickness >1 mm
- If a SN biopsy is performed, it should be done at the same time as the WLE
- Sequential nodal observation by ultrasound is indicated for SN+ disease rather than CLND
- Adjuvant systemic therapy should be considered for SN+ disease
- Formal LN dissection is indicated to treat clinical/macroscopic nodal disease (either palpable or image-detected)
- Patients should be adequately staged prior to undergoing a LN dissection and restaged prior to starting adjuvant systemic therapy
- Adjuvant RT after node dissection should only be considered in cases where local control is an issue; it does not improve survival
- For *BRAF* wild-type patients, 1 year of adjuvant anti-PD-1 (nivolumab or pembrolizumab) is the standard choice when using adjuvant systemic therapy
- For *BRAF* V600E/K-mutated patients, both 1 year of BRAF/MEK inhibitors (dabrafenib/trametinib) and 1 year of adjuvant anti-PD-1 (nivolumab or pembrolizumab) are currently equally good options when using adjuvant systemic therapy

Further Reading

Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med 2018; 378:1789–1801.

Faries MB, Thompson JF, Cochran AJ, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. N Engl J Med 2017; 376:2211–2222.

Hauschild A, Dummer R, Schadendorf D, et al. Longer follow-up confirms relapse-free survival benefit with adjuvant dabrafenib plus trametinib in patients with resected *BRAF* V600-mutant stage III melanoma. J Clin Oncol 2018; 36:3441–3449.

Henderson MA, Burmeister BH, Ainslie J, et al. Adjuvant lymph-node field radiotherapy versus observation only in patients with melanoma at high risk of further lymph-node field relapse after lymphadenectomy (ANZMTG 01.02/TROG 02.01): 6-year follow-up of a phase 3, randomised controlled trial. Lancet Oncol 2015; 16:1049–1060.

Leiter U, Stadler R, Mauch C, et al; German Dermatologic Cooperative Oncology Group. Final analysis of DeCOG-SLT trial: No survival benefit for complete lymph node dissection in patients with melanoma with positive sentinel node. J Clin Oncol 2019; 37:3000–3008.

Morton DL, Thompson JF, Cochran AJ, et al; MSLT Group. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med 2014; 370:599–609.

Thomas JM, Newton-Bishop J, A'Hern R, et al; United Kingdom Melanoma Study Group; British Association of Plastic Surgeons; Scottish Cancer Therapy Network. Excision margins in high-risk malignant melanoma. N Engl J Med 2004; 350:757–766.

Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 2017; 377:1824–1835.

4 Adjuvant treatment of melanoma

Developments in adjuvant treatment

Adjuvant radiotherapy (RT) can be considered after resection of high-risk stage III melanoma to improve in-field control, but it does not improve survival.

High-risk stage III melanoma has been defined as ≥1 parotid, ≥2 cervical/axillary or ≥3 inguinal lymph nodes, ≥3 cm cervical, ≥4 cm axillary/inguinal nodes or extracapsular extension.

Neither adjuvant RT nor adjuvant systemic therapy are recommended for stage I/II melanoma after complete resection.

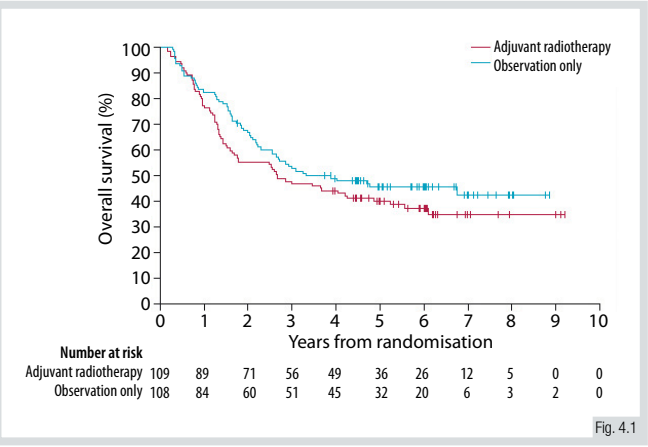
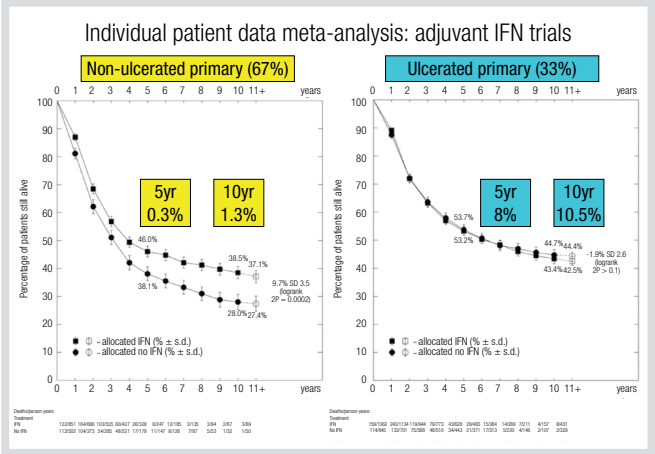


Fig. 4.1



IFN, interferon.

Fig. 4.2

Adjuvant systemic therapy with interferon (IFN) regimens was a historical option, which improved relapse-free survival (RFS) but did not improve overall survival (OS) much.

IFN should only be considered if there is no access to modern adjuvant systemic therapy and then only for ulcerated and/or sentinel node-positive (SN+) patients. Not for macroscopic disease.

Adjuvant Iscador (mistletoe extract) is not beneficial for melanoma patients and potentially promotes brain metastases; it should not be used.

Adjuvant high-dose (10 mg/kg) ipilimumab (anti-cytotoxic T-lymphocyte antigen-4 [CTLA-4]) is highly toxic with nearly half of patients developing grade 3-5 toxicity in the first four courses.

Adjuvant high-dose (10 mg/kg) ipilimumab improves RFS, distant metastasis-free survival (DMFS) and OS.

Adjuvant ipilimumab (3 mg/kg) is superior to IFN treatment efficacy in terms of RFS/OS and not worse than high-dose (10 mg/kg) ipilimumab, but less toxic.

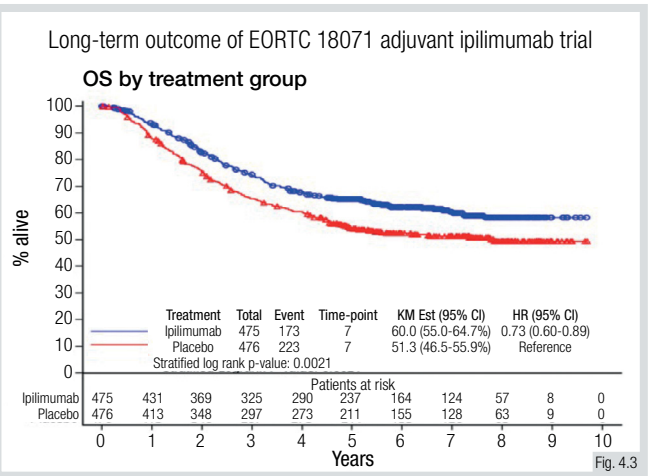


Fig. 4.3

CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; KM, Kaplan Meier; OS, overall survival.

REVISION QUESTIONS

1. Does adjuvant RT improve OS in melanoma?
2. Does high-dose (10 mg/kg) ipilimumab improve OS?
3. Can you recommend Iscador (mistletoe extract) in melanoma patients?

Developments in adjuvant treatment (continued)

Adjuvant nivolumab (3 mg/kg) is superior to adjuvant high-dose ipilimumab (10 mg/kg) in terms of both toxicity and efficacy for RFS.

Adjuvant fixed-dose pembrolizumab (200 mg every 3 weeks) showed an RFS benefit over placebo with a hazard ratio of 0.57.

For *BRAF* wild-type patients, anti-programmed cell death protein 1 (PD-1) (either nivolumab 3 mg/kg every 2 weeks or fixed-dose pembrolizumab 200 mg every 3 weeks) is the current standard-of-care adjuvant therapy.

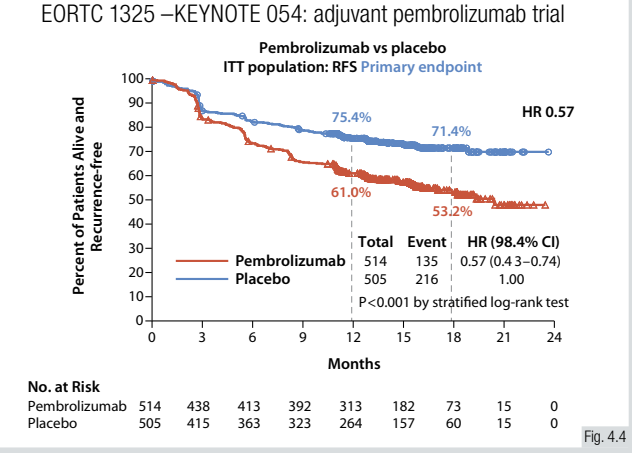


Fig. 4.4

CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; ITT, intention-to-treat; RFS, relapse-free survival.

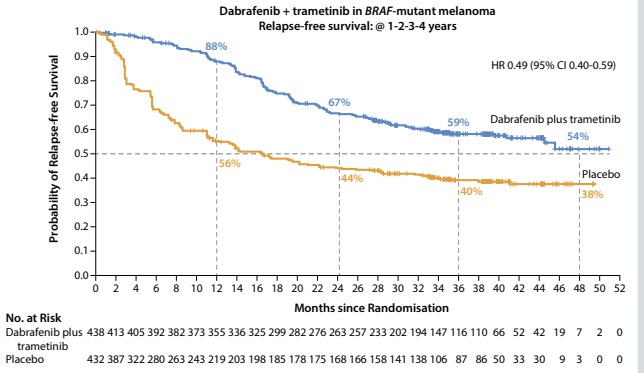


Fig. 4.5

CI, confidence interval; HR, hazard ratio.

For *BRAF* V600E/K-mutant completely resected melanoma, BRAF inhibition with vemurafenib did not show a significant benefit over placebo.

For *BRAF* V600E/K-mutant completely resected melanoma, combination dabrafenib (150 mg twice daily) plus trametinib (2 mg once daily) showed an RFS benefit over placebo.

For *BRAF*-mutant melanoma, both 1 year of dabrafenib/trametinib and anti-PD-1 (nivolumab or pembrolizumab) are adjuvant therapy options.

Neoadjuvant systemic therapy (NAST) is currently only given in clinical trials.

Neoadjuvant BRAF-directed therapy for *BRAF*-mutant melanoma can potentially improve resectability.

Neoadjuvant combination therapy with ipilimumab (1 mg/kg) and nivolumab (3 mg/kg) seems to have a very high and durable response rate in early trials.

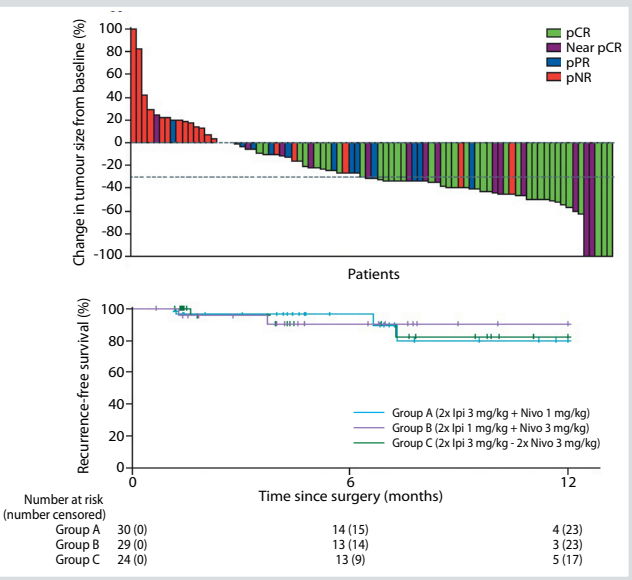


Fig. 4.6

Ipi, ipilimumab; Nivo, nivolumab; pCR, pathological complete response; pNR, no pathological response; pPR, partial pathological response.

REVISION QUESTIONS

1. What is the current standard-of-care adjuvant therapy for *BRAF* wild-type melanoma patients?
2. Can you use vemurafenib adjuvant therapy in melanoma?
3. Did dabrafenib/trametinib improve RFS in melanoma?

Summary: Adjuvant treatment of melanoma

- Adjuvant RT after resection of high-risk stage III melanoma provides RFS benefit but no OS benefit (trial: ANZMTG 01.02/TROG 02.01)
- Adjuvant ipilimumab 10 mg/kg provides long-term OS benefit at the cost of significant toxicity
- Adjuvant ipilimumab 3 mg/kg is superior to high-dose IFN therapy and is less toxic than ipilimumab 10 mg/kg
- Adjuvant nivolumab or pembrolizumab are standard options for all stage III melanoma patients. Nivolumab is also approved for resected stage IV disease
- Adjuvant dabrafenib/trametinib is a standard option only for *BRAF*-mutant stage III melanoma patients
- The combination of nivolumab and ipilimumab is currently being investigated as adjuvant therapy
- Adjuvant IFN therapy remains an option in countries without access to the new drugs and should be restricted to patients with an ulcerated primary

Further Reading

Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med 2018; 378:1789–1801.

Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of stage III melanoma: long-term follow-up results of the European Organisation for Research and Treatment of Cancer 18071 double-blind phase 3 randomised trial. Eur J Cancer 2019; 119:1–10.

Henderson MA, Burmeister BH, Ainslie J, et al. Adjuvant lymph-node field radiotherapy versus observation only in patients with melanoma at high risk of further lymph-node field relapse after lymphadenectomy (ANZMTG 01.02/TROG 02.01): 6-year follow-up of a phase 3, randomised controlled trial. Lancet Oncol 2015; 18:1049–1060.

Ives NJ, Suciu S, Eggermont AMM, et al; International Melanoma Meta-Analysis Collaborative Group (IMMCG). Adjuvant interferon-α for the treatment of high-risk melanoma: an individual patient data meta-analysis. Eur J Cancer 2017; 82:171–183.

Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med 2017; 377:1813–1823.

Weber J, Mandala M, Del Vecchio M, et al; CheckMate 238 Collaborators. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 2017; 377:1824–1835.

Treatment of metastatic melanoma in transit

5

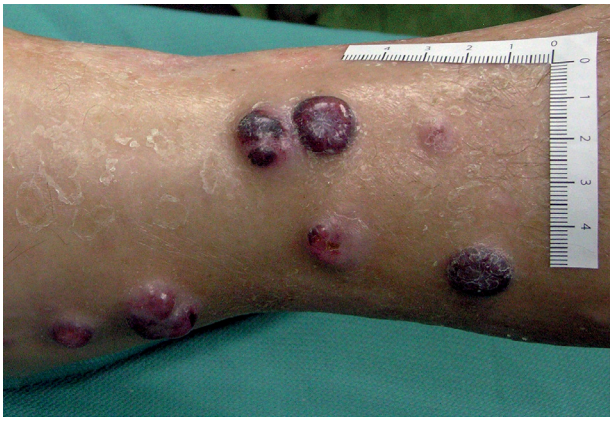
Epidemiology and clinical features

The term 'in-transit metastases' (ITM) refers to locoregional (dermal or subdermal) recurrences of melanoma, located between the primary tumour and the regional lymphatic basin.

It is widely believed that they arise from melanoma cells, which, for some reason, have been trapped in regional lymph vessels. The terms satellitosis (micro- or macroscopic), local recurrence and ITM form a kind of continuity and represent different forms of one pathological phenomenon.

The clinical picture of ITM can vary – from single, small nodules to neoplastic infiltration covering large areas of the skin. The latter can be combined with serious complications such as bleeding, infections and necrosis with loss of a significant mass of tissue. This can be a life-threatening situation and is usually connected with a significant decrease in quality of life.

ITM of lower leg, medial ankle area



ITM, in-transit metastases. Fig. 5.1

AJCC melanoma of the skin: staging			
Pathological staging (pTNM)	T	N	M
IIIB	T0	N1b, N1c	M0
	T1a/b-T2a	N1b/c or N2b	
	T2b/T3a	N1a-2b	
IIIC	T0	N2b/c or N3b/c	M0
	T1a-3a	N2c or N3a/b/c	
	T3b/4a	Any N ≥N1	
	T4b	N1a-2c	
IIID	T4b	N3a/b/c	M0

AJCC, American Joint Committee on Cancer; M, metastasis; N, node; T, tumour. Fig. 5.2

The risk of ITM is 3%-6% in all melanoma patients. ITM correspond to ~10%-20% of melanoma relapses.

The median time to ITM occurrence is 13-18 months after treatment of the primary tumour.

In the AJCC (American Joint Committee on Cancer) TNM (Tumour, Node, Metastasis) classification, ITM are within pathological stage IIIB, IIIC or IIID, depending on their number and the status of regional lymph nodes. This is a heterogeneous population of patients with very different prognoses (5-year overall survival [OS] rates range from 30% to about 80%).

Diagnosis of ITM is usually simple and can be based on clinical features.

In doubtful situations, diagnosis can be confirmed by cytopathological examination of material obtained by fine-needle biopsy.

In the case of single isolated nodules, excisional biopsy with histopathological verification may be performed. Appropriate staging studies should be obtained.

Cutaneous metastases of malignant melanoma patterns: a. blue naevus-like pattern; b. naevus-like globular pattern; c. naevus-like nonglobular pattern; d. angioma-like pattern; e. vascular pattern; f. unspecific pattern

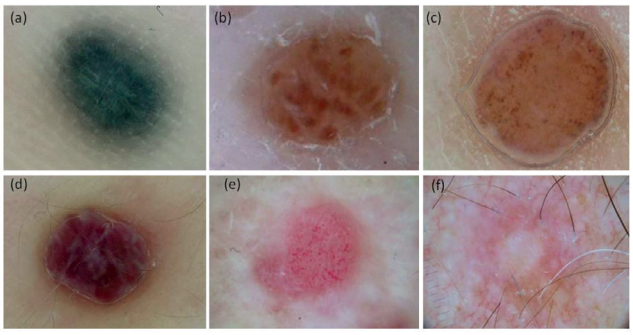


Fig. 5.3

REVISION QUESTIONS

1. What is the definition of ITM in melanoma?
2. What is the epidemiology of ITM?
3. What is the prognosis of patients with ITM relapse?

Local treatment of ITM

In the case of single/oligometastatic lesions, surgical resection of the nodules with clear margins may be the treatment of choice.

The procedure can usually be performed under local anaesthesia, in the outpatient setting. In case of a single lesion with late occurrence after primary tumour treatment, another sentinel lymph node biopsy (SLNB) may be considered. Systemic adjuvant therapy (immunotherapy or targeted therapy) should be implemented as recommended for stage III disease.

The selection of patients for surgical treatment should be cautious, taking into account the number of lesions, their growth rate and the biological behaviour of the tumours. The risk of rapid progression after surgery may negatively affect the effectiveness of subsequent systemic treatment.

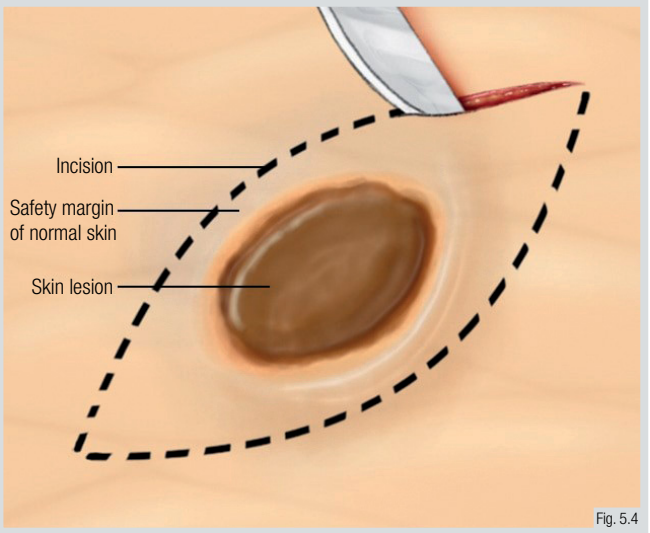
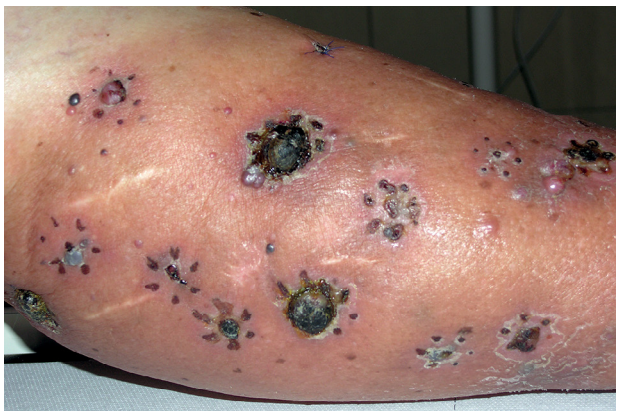


Fig. 5.4

Clinical presentation of massive ITM on the lower extremity 4 weeks after ECT procedure



ECT, electrochemotherapy; ITM, in-transit metastases.

Fig. 5.5

Electrochemotherapy (ECT) may be another option for patients with measurable ITM. This method uses the effect of electroporation to increase the effective concentration of chemotherapy (ChT) agent in cancer cells.

In melanoma patients, bleomycin is the most commonly used ChT and is administered intravenously. With few nodules, it can also be administered intratumourally. In some centres, intratumourally administered cisplatin is used. It can be used for the trunk and extremities.

The response rate (RR) to ECT is high and reaches 90%. However, relapses are frequent. Only in ~20% of patients can long-term benefit be expected, but quality of life can be improved.

In case of a recurring in-transit lesion, re-excision may be considered if technically feasible.

With multiple lesions, carbon dioxide laser ablation can be used, but the recurrence rate is very high and this technique is limited to lesions <1 cm in diameter.

Other local/locoregional modalities including radiotherapy (RT), cryotherapy, intralesional injections, hyperthermic isolated limb perfusion (HILP) or topical therapy (such as imiquimod) may be used in specific situations.

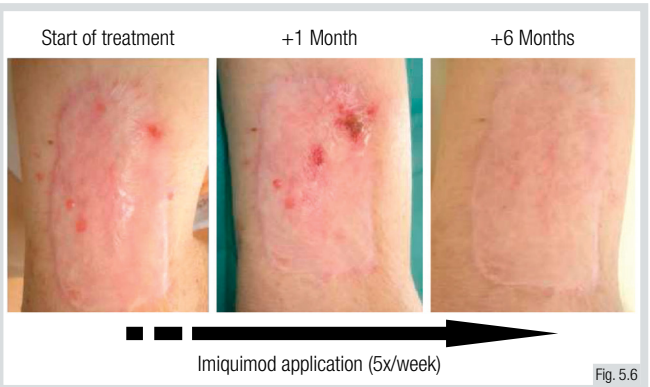


Fig. 5.6

REVISION QUESTIONS

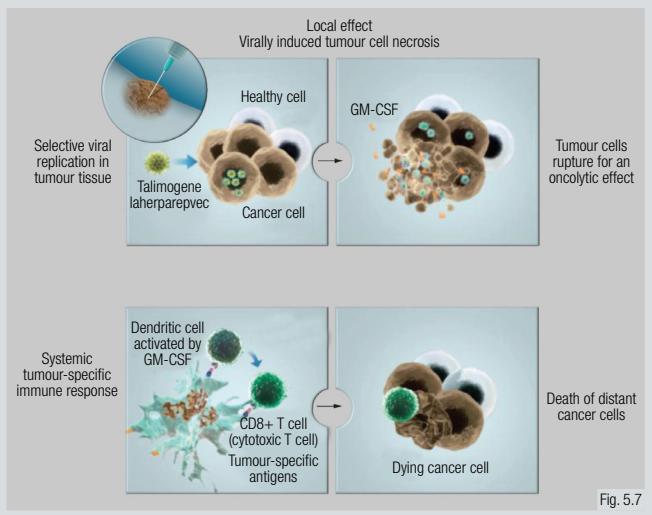
1. What is the treatment of choice for a single ITM?
2. Describe the mechanism of action of ECT for ITM treatment.
3. Which locoregional techniques are used in the therapy of ITM?

Intratumoural treatment of ITM

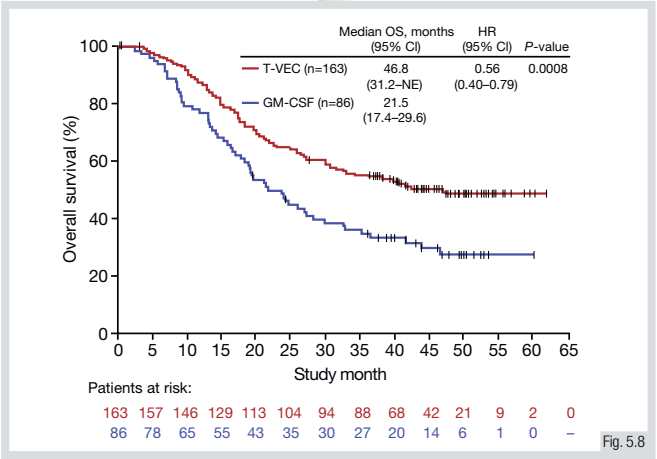
T-VEC (talimogene laherparepvec) represents a newly registered approach to ITM treatment. The drug contains a modified herpes simplex virus 1 (HSV-1) that, when given intratumourally, multiplies in melanoma cells, leading to their death.

In addition, a cytokine (granulocyte-macrophage colony-stimulating factor [GM-CSF]) coding sequence has been incorporated into the genome of the virus.

GM-CSF is released after the death of melanoma cells and is responsible for the systemic immune response directed against cancer cells. T-VEC activity has been proven in a phase III trial (OPTiM) associated with durable complete responses that were linked to prolonged survival.



GM-CSF, granulocyte-macrophage colony-stimulating factor.



CI, confidence interval; GM-CSF, granulocyte-macrophage colony-stimulating factor; HR, hazard ratio; NE, not evaluable; OS, overall survival; T-VEC, talimogene laherparepvec.

The RR is high and, in some reports, exceeds 50%. If complete remission is achieved, the response may be durable.

Treatment is usually well tolerated by patients. Adverse effects are mild but occur relatively frequently (>85%). Most side effects are injection-site inflammation or flu-like symptoms.

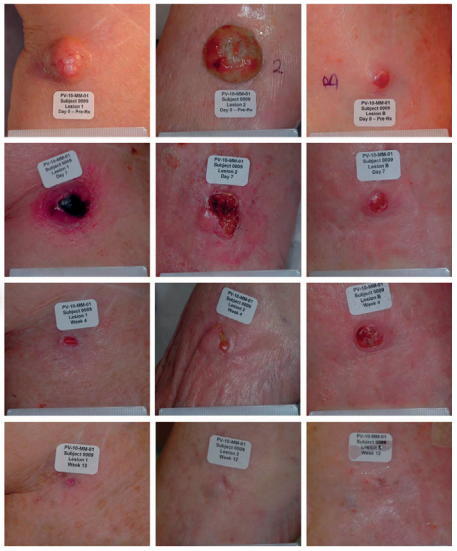
Based on a phase II trial, neoadjuvant T-VEC may be an option before surgery in resectable ITM, improving relapse-free survival (RFS) and OS.

Other agents can also be used for intratumoural injections in patients with ITM (e.g. interleukin-2 [IL-2]).

One such drug currently being studied is PV-10 (rose bengal). After intratumoural administration, the RR can reach up to 80%.

Currently, however, data on the effectiveness of this treatment are limited and come from the observations of a small number of patients.

Activity of rose bengal after intratumoural administration to ITM



ITM, in-transit metastases.

REVISION QUESTIONS

1. Does intratumoural injection with T-VEC improve survival in patients with unresectable ITM?
2. What is the tolerability of T-VEC?
3. What are other studied locoregional agents for therapy for ITM?

Locoregional treatment options of ITM

For multiple lesions limited to the limb, HILP is an option.

The method involves perfusing the limb with high concentrations of ChT, using an extracorporeal circulation system. This requires access to vessels by surgery.

The advantage of this method is the possibility of obtaining this high concentration of ChT in the affected limb, which can act not only on visible ITM, but also on undetected tumour cells, and can avoid systemic toxicity.

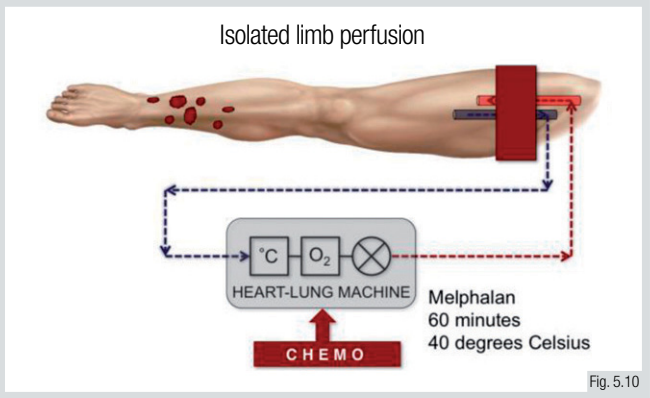


Fig. 5.10

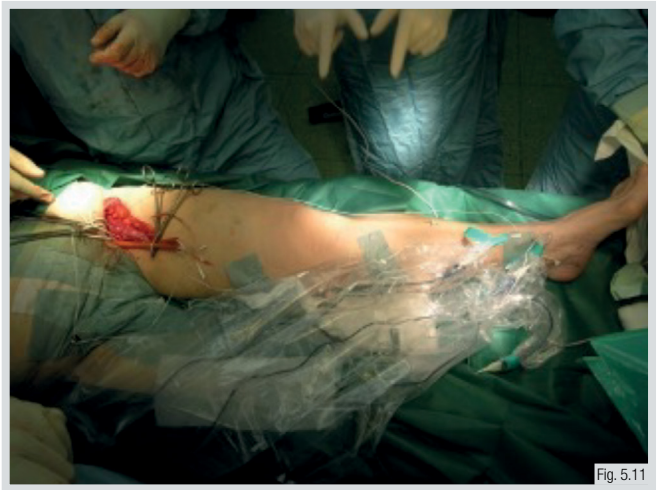


Fig. 5.11

The most commonly used ChT in this procedure is melphalan.

For more massive ITM (bulky disease), in some centres melphalan is combined with tumour necrosis factor-alpha (TNFα).

The RR is high and reaches 85%. However, >65% of patients responding to treatment experience final progression. So far, no impact of HILP on OS has been demonstrated.

HILP can be performed in patients with normal vascular flow within the operated limb and without significant comorbidities.

The procedure is associated with an approximately 10%-12% risk of complications, including vascular complications (vein thrombosis, embolism, limb ischaemia, etc.). In ~0.7%-1% of patients, severe complications may lead to the need for major amputation.

A technical variation of this procedure is isolated limb infusion (ILI), as originally proposed by Australian investigators.

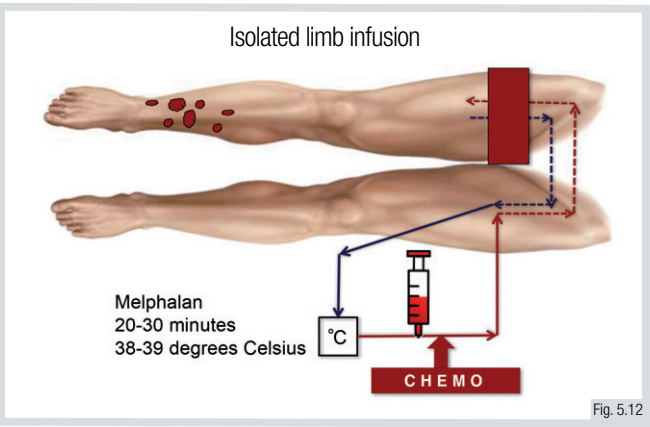


Fig. 5.12

REVISION QUESTIONS

1. What kind of chemotherapeutic agent is used in HILP?
2. What are the most common complications of HILP?
3. What are the outcomes of HILP for treatment of melanoma ITM?

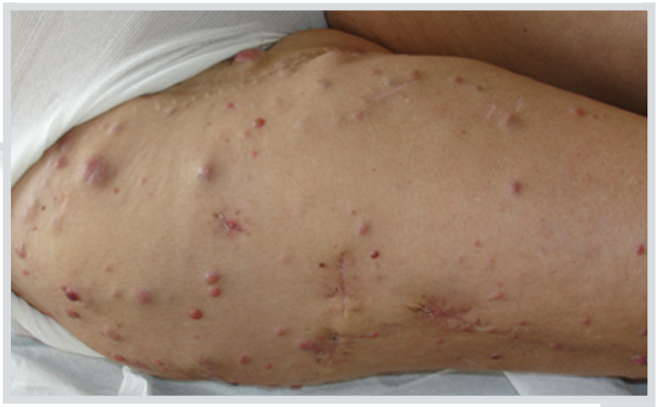
Systemic treatment

Recent progress in the treatment of advanced melanoma has led to the introduction of effective systemic therapy into clinical practice.

This treatment may be based on immunotherapy (checkpoint inhibitors – anti-cytotoxic T-lymphocyte antigen-4 [CTLA-4] or anti-programmed cell death protein 1 [PD-1] – alone, or in combination).

In addition, BRAF and MEK inhibitors may be used in patients with a known *BRAF* mutation.

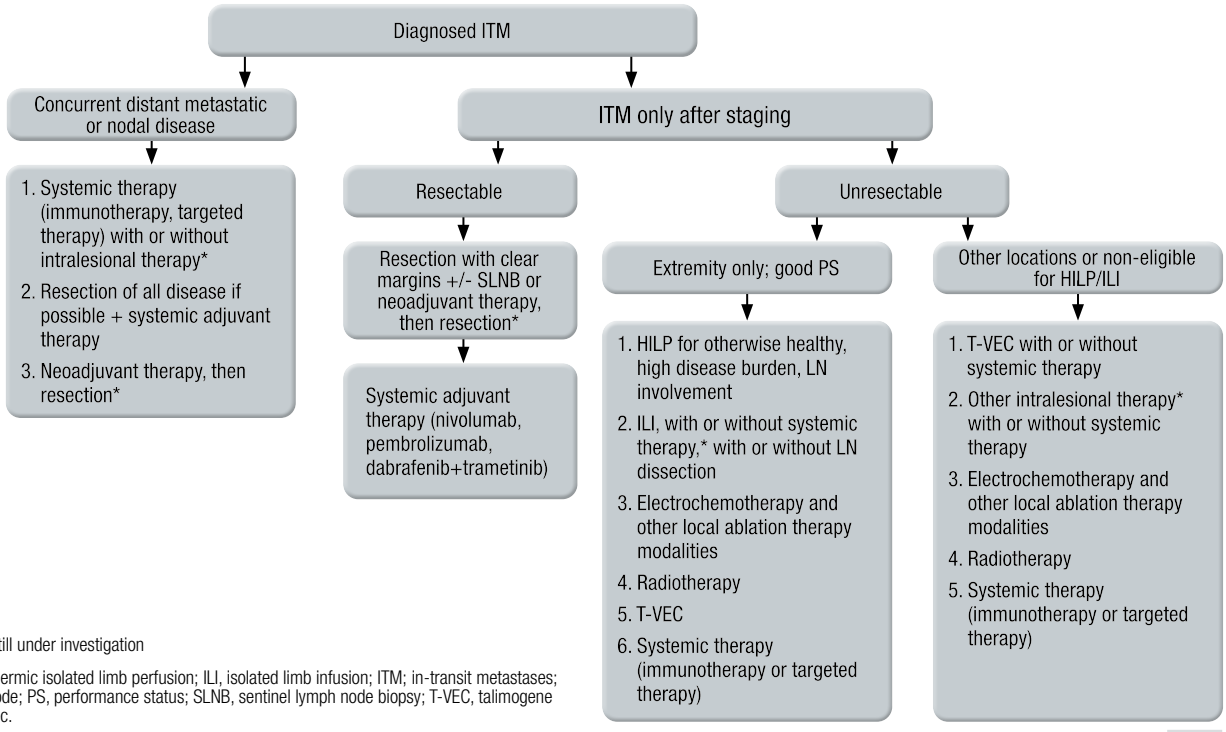
ITM during treatment (at 3 weeks) with ipilimumab 3 mg/kg



ITM, in-transit metastases. Fig. 5.13

Systemic treatment can be successfully used in patients with ITM, especially when other locoregional therapies are not applicable. The results achieved with systemic treatment seem to be better than with the locoregional methods described previously. Although there are no studies that directly compare different methods, it appears that the progression-free survival (PFS) obtained with systemic treatment is similar to, or longer than with, locoregional methods.

Nevertheless, there remains a population of patients who do not respond to systemic treatment. Therefore, the use of locoregional methods still seems justified, because it is an additional line of treatment. However, cautious patient selection for regional therapy is necessary. It seems that, in many cases, the combination of locoregional methods with systemic treatment would lead to an improvement in the outcomes of ITM treatment. The studies on neoadjuvant therapy in resectable or borderline-resectable ITM show promising results.



*Therapies still under investigation

HILP, hyperthermic isolated limb perfusion; ILI, isolated limb infusion; ITM; in-transit metastases; LN, lymph node; PS, performance status; SLNB, sentinel lymph node biopsy; T-VEC, talimogene laherparepvec.

Fig. 5.14

REVISION QUESTIONS

1. What types of systemic therapy may be used in melanoma ITM?
2. Which systemic therapy may be indicated for therapy of melanoma ITM?
3. What kind of molecular testing is indicated for choosing therapy for melanoma ITM?

Summary: Treatment of metastatic melanoma in transit

- Melanoma patients with ITM represent a heterogeneous population and present a therapeutic challenge
- Surgery is an essential method to treat oligometastatic ITM, with a microscopic melanoma infiltration-free margin (it may be macroscopically narrow)
- Systemic adjuvant therapy should be considered after resection of ITM
- Therapy should be individualised and should consider the number of metastases, their size, localisation and clinical course
- Other local/locoregional modalities including ECT, RT, carbon dioxide laser ablation, cryotherapy, intralesional injections and HILP may be used in specific situations
- Oncolytic viral immunotherapy with T-VEC appears to be an effective, approved treatment option, especially in patients with multiple and/or recurrent ITM
- No studies have been conducted to compare the different traditional locoregional therapies with intralesional therapy or systemic therapy
- Promising approaches comprise neoadjuvant therapies of ITM
- It is unknown what the best locoregional or systemic treatment option is for melanoma patients with ITM in terms of RR and long-term survival

Further Reading

Andtbacka RHI, Collichio F, Harrington KJ, et al. Final analyses of OPTiM: a randomized phase III trial of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor in unresectable stage III-IV melanoma. J Immunother Cancer 2019; 7:145.

Grob JJ, Garbe C, Ascierto P, et al. Adjuvant melanoma therapy with new drugs: should physicians continue to focus on metastatic disease or use it earlier in primary melanoma? Lancet Oncol 2018; 19:e720–e725.

Johnson DB, Puzanov I, Kelley MC. Talimogene laherparepvec (T-VEC) for the treatment of advanced melanoma. Immunotherapy 2015; 7:611–619.

Mali B, Jarm T, Snoj M, et al. Antitumor effectiveness of electrochemotherapy: a systematic review and meta-analysis. Eur J Surg Oncol 2013; 39:4–16.

Nan Tie E, Henderson MA, Gyorki DE. Management of in-transit melanoma metastases: a review. ANZ J Surg 2019; 89:647–652.

Read T, Lonne M, Sparks DS, et al. A systematic review and meta-analysis of locoregional treatments for in-transit melanoma. J Surg Oncol 2019; 119:887–896.

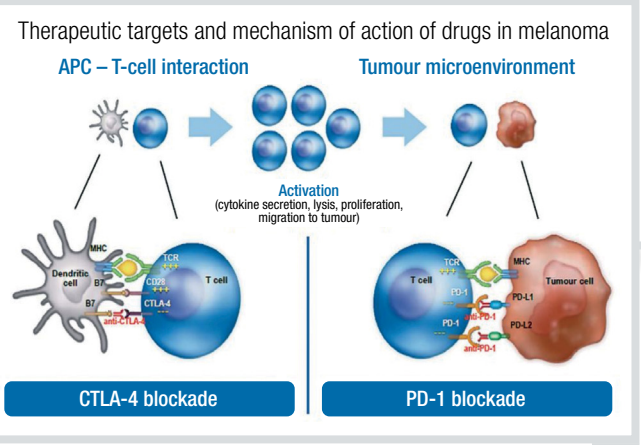
Treatment of advanced/metastatic melanoma

Overview

Patients with metastatic melanoma have a poor prognosis which relates to the following factors: performance status (PS), the site and number of metastases (M), serum lactate dehydrogenase (LDH), and duration of remission.

In stage IV of the American Joint Committee on Cancer (AJCC) classification, the M1 category is described as: M1a – non-visceral distant metastasis to nodes, subcutaneous tissue, M1b – metastasis to lung, M1c – non-central nervous system (CNS) visceral metastasis, and M1d – CNS visceral metastasis with or without any other distant sites of disease.

Selected patients with stage IV resectable, oligometastatic melanoma should be considered for local therapy with complete surgery/ablative radiotherapy (RT) combined with adjuvant therapies.



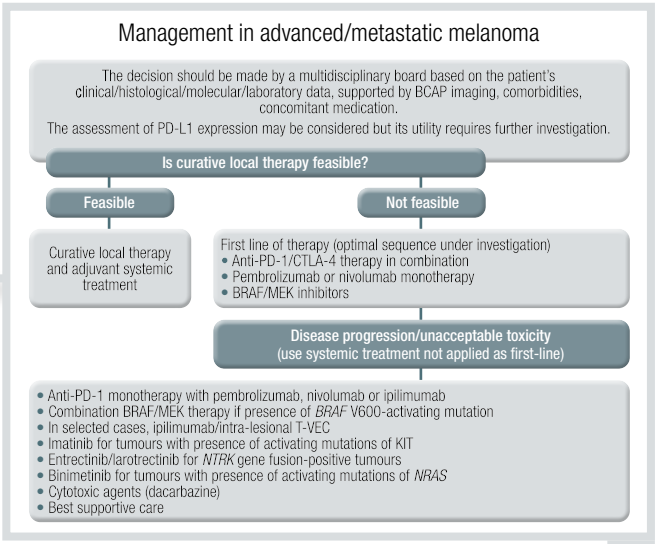
APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1/L2, programmed death-ligand 1/2; TCR, T-cell receptor.

Fig. 6.2

Approved drugs targeting cellular pathways are dabrafenib, vemurafenib and encorafenib (inhibition of *BRAF*), and trametinib, cobimetinib and binimetinib (inhibition of *MEK*).

BRAF together with *ARAF* and *CRAF* activates *MEK*, which in turn activates extracellular signal-regulated kinase (ERK). This results in proliferation and prolonged cancer cell survival.

BRAF inhibition is associated with increased CD8 T-cell infiltration in tumours, increased expression of melanoma antigens, and decreased levels of immunosuppressive cytokines such as interleukin 6 (IL-6) and interleukin 8 (IL-8).



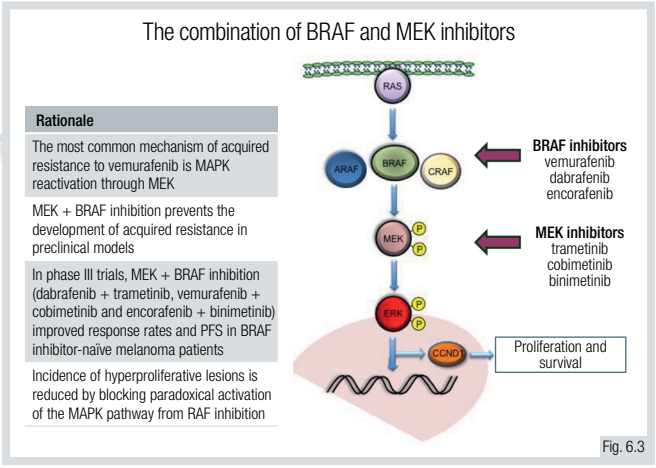
BCAP, brain, chest, abdomen, pelvis; CTLA-4, cytotoxic T-lymphocyte antigen-4; NTRK, neurotrophic tyrosine receptor kinase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; T-VEC, talimogene laherparepvec.

Fig. 6.1

The main therapeutic options are immunotherapy (IO) and in *BRAF*-mutant melanomas also targeted therapies (TTs). The optimal sequence of therapy (IO vs TT) has not yet been established.

For IO, anti-programmed cell death protein 1 (PD-1) is used as monotherapy or in combination with anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4).

The interaction between PD-1 and its ligands is involved in the suppression of the immune system, similar to the CD28/CTLA-4 receptor interactions with their two natural ligands CD80 (B7-1) and CD86 (B7-2).



ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; PFS, progression-free survival.

Fig. 6.3

REVISION QUESTIONS

1. What is the concept behind IO in melanoma?
2. What is the concept behind TT in melanoma?
3. What kind of drugs are recommended in the first and further lines of systemic therapy?

Immunotherapy

Nowadays IO is a standard of care; it is recommended for no longer than 2 years, until disease progression or unacceptable toxicity.

The main relative contraindications for IO are autoimmune diseases and therapy with steroids: >10 mg or equivalent of prednisolone.

Nivolumab as monotherapy can be dosed at either 240 mg or 480 mg Q4W, and pembrolizumab: 200 mg Q3W or 400 mg Q6W, both i.v. (intravenous) infusion.

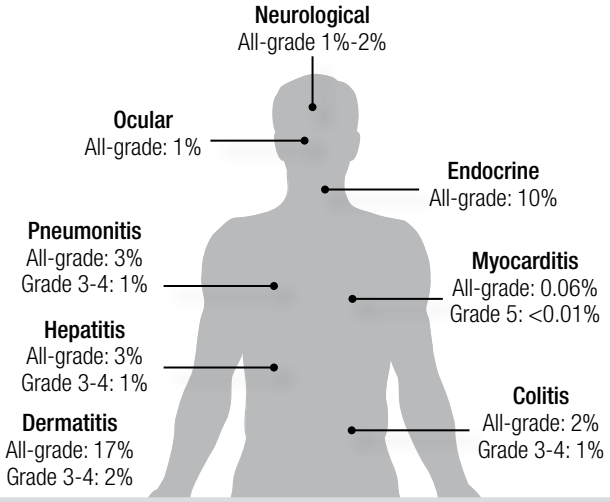
Results of immunotherapy clinical trials in melanoma

	KEYNOTE-002	CheckMate 037	KEYNOTE-006	CheckMate 066
Phase	II	III	III	III
Design	P2 Q3W vs P10 Q3W vs ChT	N3 Q2W vs ChT	P10 Q2W vs P10 Q3W vs Ipi	N3 Q2W vs Ipi
PFS (months)	2.9 vs 2.9 vs 2.7	4.7 vs 4.2 (HR 0.82)	5 vs 4 vs 3 (HR 0.58)	5.1 vs 2.2 (HR 0.43)
OS (months)	21 vs 25 vs 4	31 vs 11	34 vs 33 vs 12	40 vs 14
BRAF	WT 23%	WT 32%	WT 35%	WT only
With P/N toxicity was less severe than during ChT or Ipi				

ChT, chemotherapy; HR, hazard ratio; Ipi, ipilimumab; m, months; N, nivolumab (N3 – 3 mg/kg); P, pembrolizumab (P2 – 2 mg/kg, P10 – 10 mg/kg); OS, overall survival; PFS, progression-free survival; WT, wild-type.

Fig. 6.4

The incidence of toxicity related to anti-PD-1 immunotherapy



PD-1, programmed cell death protein 1.

Fig. 6.5

Severe immune-related adverse events (irAEs) occur in 10% of patients receiving anti-PD-1 agents and may be present at any time during therapy. They occur in 38% of patients on ipilimumab and ~50% of patients on ipilimumab/nivolumab.

The general guidelines for the treatment of low grade irAEs are: mild symptoms – only monitoring; moderate – start low-dose corticosteroids, withhold IO temporarily (exception: pneumonitis, myocarditis).

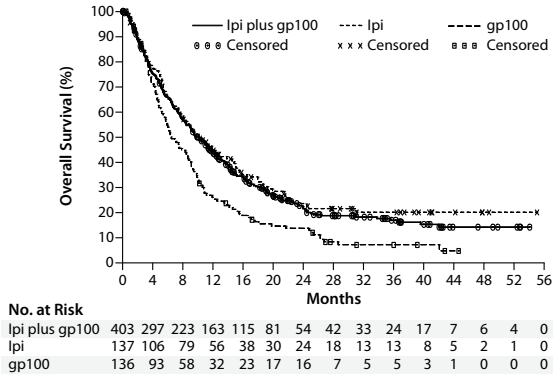
Severe symptoms need a permanent stop of IO. High-dose corticosteroids should be commenced rapidly. The occurrence of irAEs is often associated with favourable outcomes.

3-year overall survival (OS) due to ipilimumab was 22%. Responses appear to be durable. In progression after long term follow-up, re-induction is possible with a 21% response rate. The predictive factors are unknown.

Ipilimumab toxicity occurs in 38% of cases as grade 3-4 (diarrhoea/colitis, hepatitis, pituitary endocrinopathies are potentially life-threatening).

Ipilimumab dosing is 3 mg/kg i.v. over 90 minutes Q3W, for a maximum of four doses. In the event of toxicity, dosing may be delayed, but all treatment must be administered within 16 weeks of the first dose.

The results of a phase III trial (MDX010-20) in melanoma patients treated with ipilimumab



No. at Risk															
Ipi plus gp100	403	297	223	163	115	81	54	42	33	24	17	7	6	4	0
Ipi	137	106	79	56	38	30	24	18	13	13	8	5	2	1	0
gp100	136	93	58	32	23	17	16	7	5	5	3	1	0	0	0

Fig. 6.6

gp100, glycoprotein 100; Ipi, ipilimumab.

REVISION QUESTIONS

1. Compare the different anti-PD-1 antibodies used in melanoma in terms of schema, efficacy and toxicity.
2. When and how is ipilimumab used?
3. What are the contraindications and toxicities related to anti-PD-1 and anti-CTLA-4 agents?

Immunotherapy (continued)

The combination of nivolumab/ipilimumab improves antitumour response and progression-free survival (PFS) but with a higher frequency of adverse events (AEs).

The approved dose is nivolumab 1 mg/kg Q3W over 30 minutes with ipilimumab 3 mg/kg over 90 minutes (both drugs are given as 4 doses), then nivolumab as maintenance (dosing as monotherapy).

In the CheckMate 511 phase IIIb/IV trial, nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) led to a more optimal safety profile without any obvious compromise in efficacy.

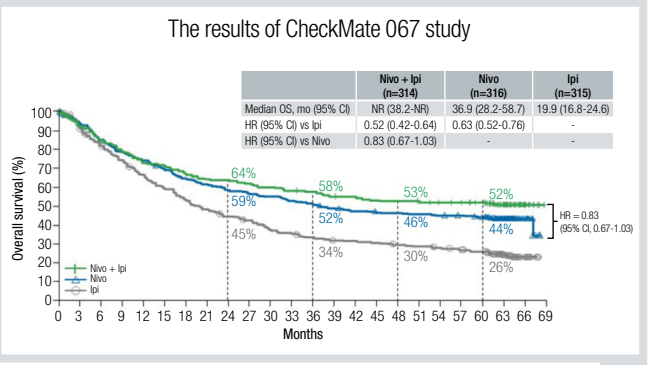


Fig. 6.7

CI, confidence interval; HR, hazard ratio; Ipi, ipilimumab; Nivo, nivolumab; NR, not reported; ORR, objective response rate; OS, overall survival.

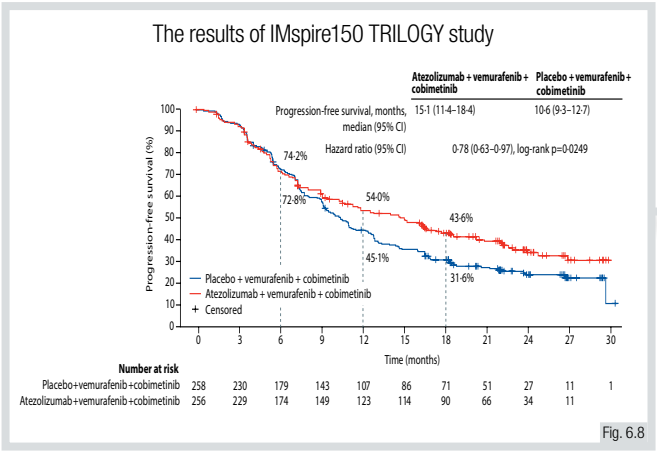


Fig. 6.8

CI, confidence interval.

Preclinical data have shown that BRAF/MEK inhibitors affect the tumour microenvironment and immunogenicity, providing support for the investigation of combinations with IO.

In a randomised phase III trial, the addition of atezolizumab to vemurafenib/cobimetinib was associated with longer median PFS and longer duration of response than vemurafenib/cobimetinib alone; however, the triplet induced more toxicity.

The triplet of pembrolizumab and dabrafenib/trametinib was associated with longer median PFS compared with the doublet of dabrafenib/trametinib, but serious AEs occurred: 58% in the triplet arm and 25% in the doublet.

The improved durable responses with triplet combinations come at a cost, with higher frequencies of serious AEs and a temporary decrease in quality of life over the first two cycles of therapy.

Talimogene laherparepvec (T-VEC) is an injectable modified oncolytic herpes virus for the treatment of advanced melanoma (especially metastatic in transit).

In selected cases with metastatic melanoma, the combination of T-VEC and ipilimumab led to a higher overall response rate (ORR) than ipilimumab alone, which was without additional safety concerns.

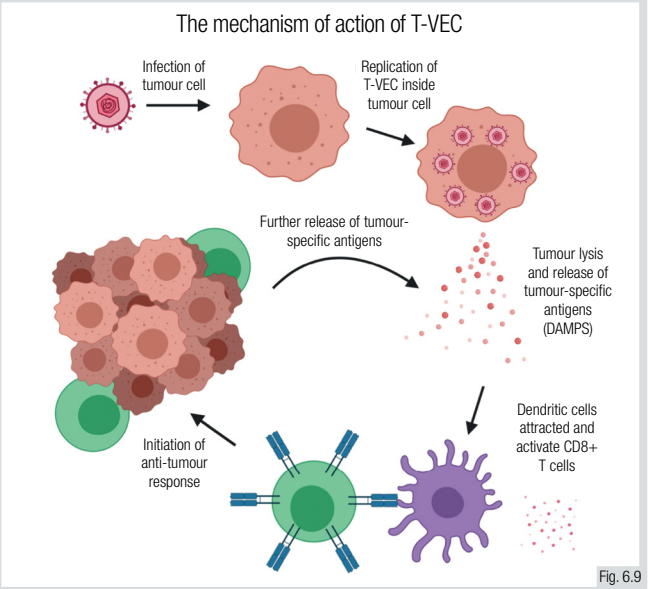


Fig. 6.9

DAMPS, damage-associated molecular patterns; T-VEC, talimogene laherparepvec.

REVISION QUESTIONS

1. What is the concept behind combination IO in melanoma?
2. What kinds of trials are ongoing with IO and TT as a combination in melanoma?
3. What is the mechanism of action of T-VEC?

Targeted therapy

BRAF inhibitors as monotherapy are no longer recommended; the BRAF/MEK combination therapy is more effective with an acceptable toxicity profile.

Vemurafenib is dosed at 2 x 480 mg p.o. (orally) daily and cobimetinib, 1 x 60 mg daily p.o., 3 weeks on/1 week off, until progression or unacceptable toxicity.

Toxicity of vemurafenib/cobimetinib is as follows: rash, diarrhoea, other skin cancers, phototoxicity, stomatitis, elevation of liver enzymes, rhabdomyolysis, cardiotoxicity and retinal detachment; but with dose adjustment, toxicity is manageable.

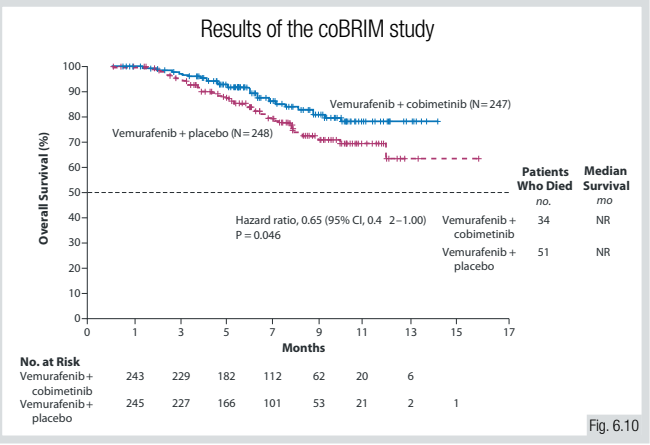


Fig. 6.10

CI, confidence interval; NR, not reached.

The results of clinical trials with BRAF/MEK inhibitors in melanoma

	BRIM-3	METRIC	BREAK-3	coBRIM	COMBI-d	COMBI-v	COLUMBUS
Study design	V vs DTIC	T vs DTIC	D vs DTIC	V+C vs V	D+T vs D	D+T vs V	E+B vs E vs V
ORR (%)	59 vs 11	22 vs 8	50 vs 6	70 vs 50	68 vs 55	64 vs 51	63 vs 51 vs 40
mPFS (months)	6.9 vs 1.6	4.8 vs 1.5	6.7 vs 2.9	12.3 vs 7.3	11 vs 8.8	11.4 vs 7.3	14.9 vs 9.6 vs 7.3
HR (PFS)	0.38	0.45	0.35	0.58	0.56	0.56	0.54
mOS (months)	13.5 vs 9.7	81% vs 67% (*)	31% vs 28% (**)	22.3 vs 17.4	43% vs 31% (**)	44% vs 31% (**)	33.6 vs 23.5 vs 16.9
HR (OS)	0.70	0.54	0.61	0.70	0.75	0.66	0.61

*at 6 months; **at 3 years

Fig. 6.11

B, binimetinib; C, cobimetinib; D, dabrafenib; DTIC, dacarbazine; E, encorafenib; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; T, trametinib; V, vemurafenib.

The recommended dose for dabrafenib is 150 mg p.o. twice a day, with trametinib 2 mg p.o., daily. The efficacy of dabrafenib/trametinib combination was proven in phase III clinical trials comparing it with vemurafenib or dabrafenib alone.

The most common dabrafenib/trametinib AE is pyrexia (≥38.0° C), which occurs in 71% of patients, leading to dose delay or reduction in 59% of patients and permanent discontinuation in 4% of patients.

Other dabrafenib-related toxicities are headache, arthralgia and squamous cell carcinoma (SCC); for trametinib alone: rash, diarrhoea and peripheral oedema. With dabrafenib/trametinib, rash is rare.

The recommended dose for encorafenib is 450 mg daily, and for binimetinib, 45 mg twice per day p.o. In the encorafenib/binimetinib combination, OS is 33.6 months and PFS, 14.9 months.

Grade 3-4 AEs include increased transaminases, increased blood creatine phosphokinase and hypertension. Only 5% of patients discontinue treatment due to side effects.

In selected cases with disease progression on subsequent IO/chemotherapy, it is possible to rechallenge with BRAF/MEK inhibitors.

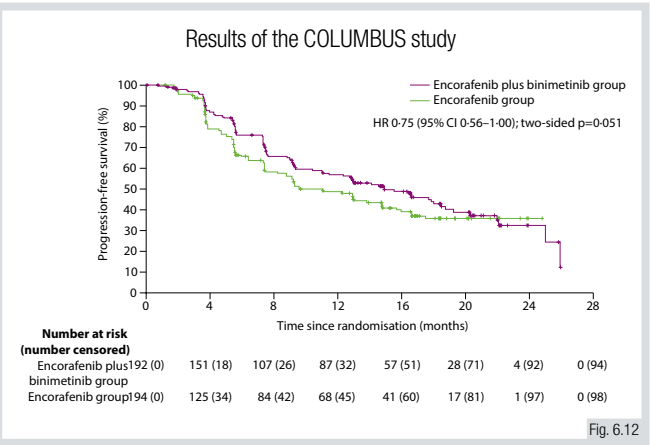


Fig. 6.12

CI, confidence interval; HR, hazard ratio.

REVISION QUESTIONS

1. What is the concept behind combination TT in melanoma?
2. When is there an indication to rechallenge with BRAF/MEK inhibitors?
3. What are the most common side effects related to BRAF/MEK inhibitors?

Systemic therapy in other melanoma subtypes and imaging

In the NEMO study for *NRAS*-mutant melanoma, median PFS (mPFS) was 2.8 months in the binimetinib group and 1.5 months in the dacarbazine group (hazard ratio 0.62 [95% confidence interval 0.47-0.80]; p <0.001).

KIT inhibitors are effective in acral or mucosal melanomas: 10%-25% of them harbour *KIT* mutation. Response rate (RR) is 15%-30%, with the best responses in *KIT* mutation exons 11 and 13.

The presence of a neurotrophic tyrosine receptor kinase (*NTRK*) family fusion in melanoma may provide a therapeutic opportunity for entrectinib or larotrectinib (78% ORR in *NTRK* fusion-positive tumours, regardless of histology.)

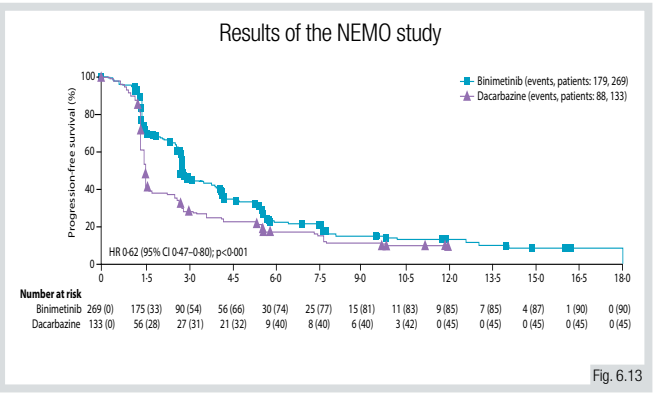


Fig. 6.13

CI, confidence interval; HR, hazard ratio.

Due to atypical response patterns in IO, a new version of RECIST (Response Evaluation Criteria in Solid Tumours) was developed to monitor immune response: immune RECIST (iRECIST).

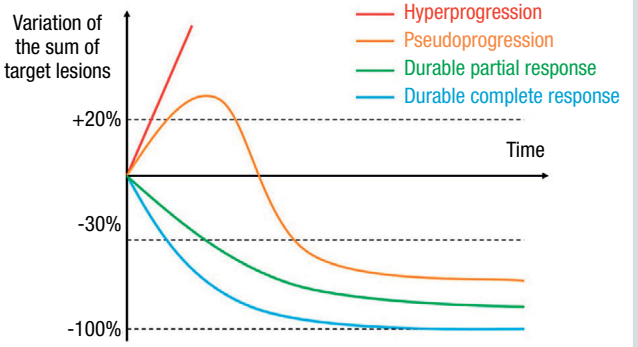


Fig. 6.14

Pseudoprogression occurs in 7%–10% of patients during treatment with immune checkpoint inhibitors (ICIs), particularly monotherapy with ipilimumab, which stems from their mechanism of action. Initially, lesions increase in size compared with the pre-treatment scan, but further continuation of therapy may lead to response.

Hyperprogression is the rapid increase in tumour growth rate after IO. The molecular mechanism remains unknown.

The abscopal effect refers to the rare phenomenon of tumour regression at a site distant from the primary site of RT.

The underlying biological characteristics of the abscopal effect may be mediated by immunological mechanisms. The combination of ICIs and RT can be more potent than either treatment alone.

Patients with mixed response, either on IO or TTs, may benefit from stereotactic radiosurgery directed to the solitary progressing metastasis.

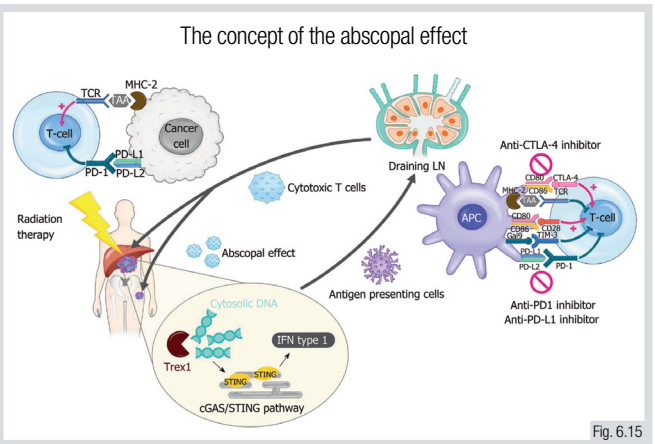


Fig. 6.15

APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; IFN, interferon; LN, lymph node; MHC-2, microsatellite histocompatibility complex 2; PD-1, programmed cell death protein 1; PD-L1/2, programmed death-ligand 1/2; TCR, T-cell receptor.

REVISION QUESTIONS

1. What is a treatment option for *NRAS*-, *NTRK*- or *KIT*-mutant melanoma?
2. How is the response to TTs and IOs monitored?
3. What is the abscopal effect and how can it be enhanced in melanoma?

Summary: Treatment of advanced/metastatic melanoma

- All patients should be screened for the presence of mutations (*BRAF*, *NRAS*, and in mucosal/acral melanoma – *KIT*), with the treatment options depending on the kinetics of progression. It is mandatory to evaluate mutational status before starting systemic treatment
- First-line treatment in patients with good PS is often the combination of nivolumab/ipilimumab, which leads to a higher chance of being alive and treatment-free compared with monotherapy
- irAEs occur in 10% of patients receiving anti-PD-1 therapy, in 38% of patients on ipilimumab, and about 50% of patients on ipilimumab/nivolumab; irAEs may be present at any time during therapy or after discontinuation
- In *BRAF*-mutated melanomas, the combination of BRAF/MEK inhibitors is recommended (available combinations: vemurafenib/cobimetinib; dabrafenib/trametinib; encorafenib/binimetinib). It remains uncertain whether BRAF/MEK inhibitors or ICIs are preferable in the first line for *BRAF*-mutant patients
- Patients should be informed about side effects related to BRAF/MEK inhibitors with emphases on phototoxicity related to vemurafenib, pyrexia related to dabrafenib, and ocular and cardiac toxicity related to MEK inhibitors
- In case of limited progression on IO, RT may also be beneficial because of the abscopal effect
- Treatment response should be based on clinical features and radiological response (iRECIST for IO and RECIST for TTs)

Further Reading

Dummer R, Schadendorf D, Ascierto PA, et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2017; 18:435–445.

Gellrich FF, Schmitz M, Beissert S, Meier F. Anti-PD-1 and novel combinations in the treatment of melanoma – an update. J Clin Med 2020; 9:223.

Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol 2018; 19:1480–1492.

Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med 2012; 366:925–931.

Robert C, Grob JJ, Stroyakovskiy D, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. N Engl J Med 2019; 381:626–636.

Wang DY, Johnson DB, Davis EJ. Toxicities associated with PD-1/PD-L1 blockade. Cancer J 2018; 24:36–40.

Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2017; 377:1345–1356.

Management of brain metastases in melanoma

Incidence, prognosis and presentation

Metastatic spread of disease to the brain can occur with any cancer type.

Melanoma is one of the solid tumours where brain metastases are relatively common, being reported in 40%-50% of patients with advanced disease.

The blood-brain barrier means the brain is regarded as a 'sanctuary site' and standard cytotoxic treatments have limited penetration and efficacy in any cancer. Melanoma brain metastases are vascular and more prone to haemorrhage than other metastases.

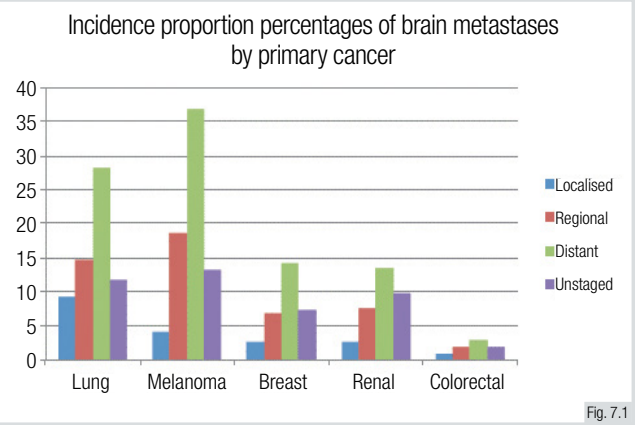


Fig. 7.1

M Stage	
M0	No evidence of metastatic disease
M1a	Distant metastases to skin/soft tissue/non-regional LNs
M1b	Distant metastases to lung +/- M1a disease
M1c	Distant metastases to non-CNS visceral organ +/- M1a or b disease
M1d	Distant metastases to CNS +/- M1a, b, or c disease

CNS, central nervous system; LN, lymph node; M, metastasis.

Fig. 7.2

Patients with brain metastases have stage IV disease (as per the American Joint Committee on Cancer [AJCC] classification), defined as M1d under the 8th edition.

Patients can present with isolated brain disease or in the context of multiple sites of extracranial disease.

Before recent treatment advances in both radiotherapy (RT) techniques and systemic therapies, prognosis was very poor with a median survival <4 months.

Brain metastases often present late in the disease with fits, headache, nausea or neurological deficits.

Increased use of both computed tomography (CT) and magnetic resonance imaging (MRI) monitoring for high-risk disease (resected stage 3) has led to more frequent early diagnosis of small asymptomatic lesions.

The diagnosis of any brain lesion has significant implications for patients, even if asymptomatic, with limitations on the ability to drive.

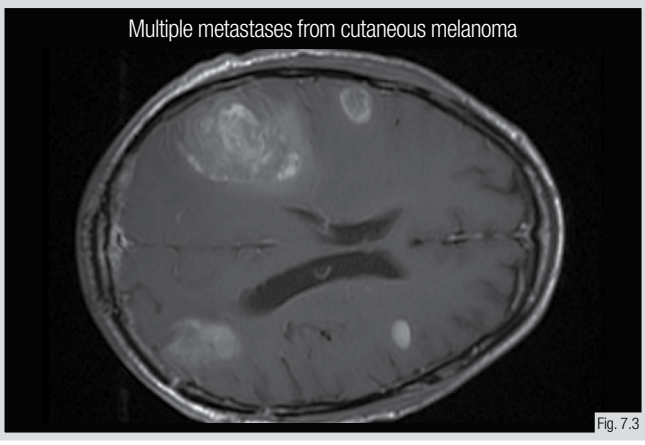


Fig. 7.3

REVISION QUESTIONS

1. What is the stage and prognosis of melanoma with brain metastases?
2. What are the major implications for patients?
3. Which cancer types most commonly develop intracranial spread?

Treatment options: Whole brain radiotherapy

Whole brain radiotherapy (WBRT) is a palliative treatment. Without any treatment, median survival for melanoma brain metastases (MBM) is about 1 month, with corticosteroids 2 months.

WBRT median survival is approximately 3–4 months. Response to corticosteroids may be a surrogate marker for WBRT response.

WBRT is associated with reduced neurocognitive function and decreased quality of life. Morbidity may be reduced by blocking RT to the hippocampus. Neurocognitive morbidity is more likely in patients aged over 65 years.

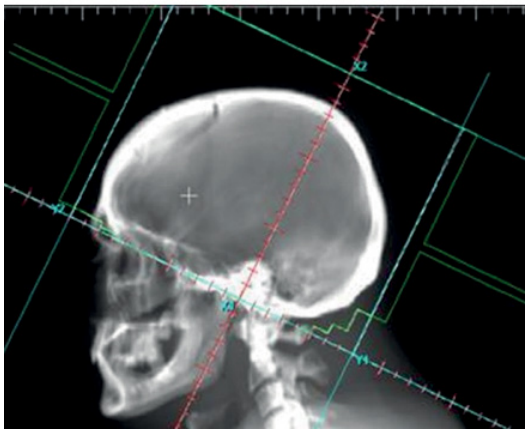


Fig. 7.4

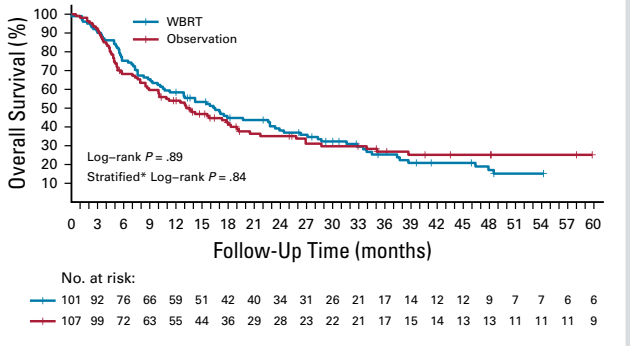


Fig. 7.5

WBRT, whole brain radiotherapy.

WBRT after local treatment, neurosurgery or stereotactic radiosurgery (SRS) for one to three metastases does not improve survival, intracranial control or preservation of performance status (PS) compared with observation.

Positive results from trials such as the COMBI-MB and CheckMate 204 studies may reduce the use of WBRT even further in the future.

The role of WBRT and SRS in improving immune stimulation before the use of immunotherapy is still being investigated. For larger metastases, surgery followed by cavity SRS has a control rate of 80% at 1 year compared with 40% with surgery alone.

The role of WBRT in patients who have multiple MBM or leptomeningeal disease, where SRS or neurosurgery is not appropriate, is less clear.

But there is probably still a role for palliative WBRT for these patients, provided they have reasonable PS and controllable extracranial disease.

Future studies may look at adding an integrated RT boost to the brain metastasis, in addition to WBRT.

Integrated boost cranial radiotherapy

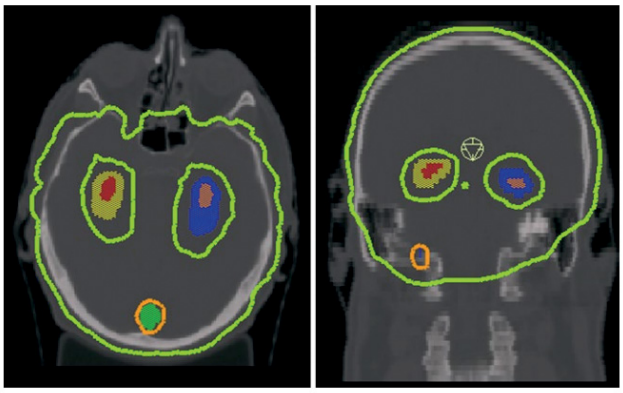


Fig. 7.6

REVISION QUESTIONS

1. Is the use of WBRT increasing or decreasing?
2. What are the potential side effects of WBRT?
3. WBRT may still be appropriate for which patient groups?

Treatment options: Stereotactic radiosurgery

SRS can treat deep-seated metastases not accessible by neurosurgery and is equally effective.

There is some evidence that adding immunotherapy to RT for MBM can improve survival, but combined treatment carries a higher risk of brain necrosis.

Initially SRS was used for patients with three or fewer small brain metastases, but as experience has developed five lesions or more are now treated.

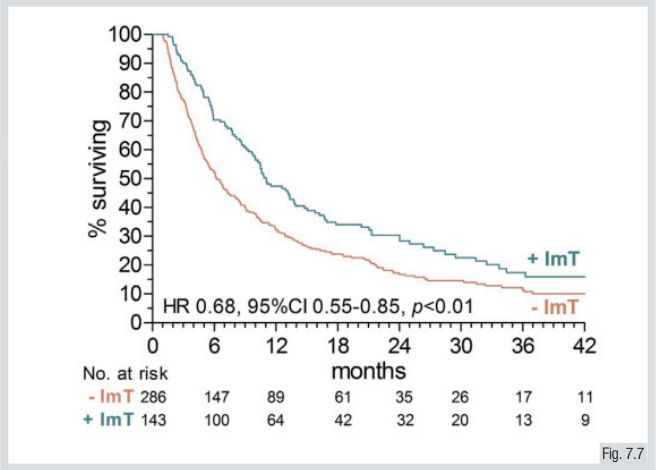


Fig. 7.7

CI, confidence interval; HR, hazard ratio; ImT, immunotherapy.

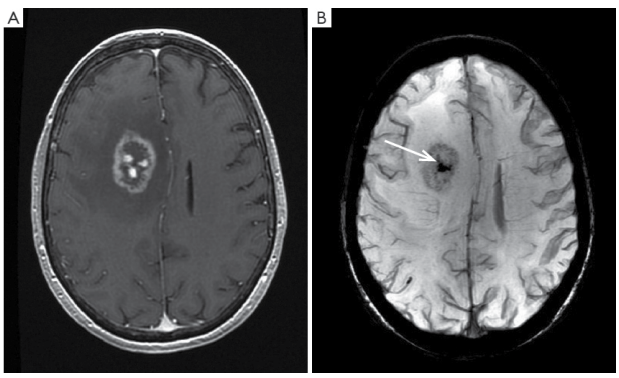


Fig. 7.8

The total brain volume treated, usually below 20 cc, is now considered to be the more important limit. Individual metastases are not usually larger than 3 cm.

The total volume treated is more prognostic of outcome and overall survival than the number of lesions treated.

Even with very accurately focused SRS, there is still a risk of brain necrosis, especially if re-treating, with a 12%-15% risk of necrosis at 1 year. More SRS fractionation is now being used, allowing larger volumes to be treated. Fractionated SRS is usually delivered in 6 fractions or fewer.

The sequencing of RT and immunotherapy may be important, with a benefit if RT is given first.

SRS is being more widely used as secondary management after neurosurgery, previous SRS or WBRT.

After SRS, 'pseudoprogression' can occur with increased oedema around the treated area, which reduces with time and is not disease progression.

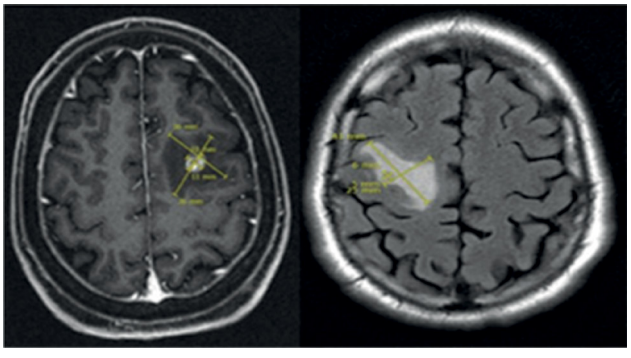


Fig. 7.9

REVISION QUESTIONS

1. Which patients is SRS more suitable for?
2. What are the contraindications to SRS for MBM?
3. Can SRS be used in second-line management of MBM?

Treatment options: Targeted therapy for *BRAF*-mutant disease

For patients with *BRAF*-mutant melanoma, targeted therapies can give rapid and durable responses.

Patients with known brain metastases were excluded from the major clinical trials with these agents.

In routine clinical use, single-agent BRAF inhibitors and the combination of BRAF and MEK inhibitors have shown responses in patients with brain metastases.

Overall survival in *BRAF*-mutant metastatic melanoma treated with dabrafenib plus trametinib stratified by LDH level

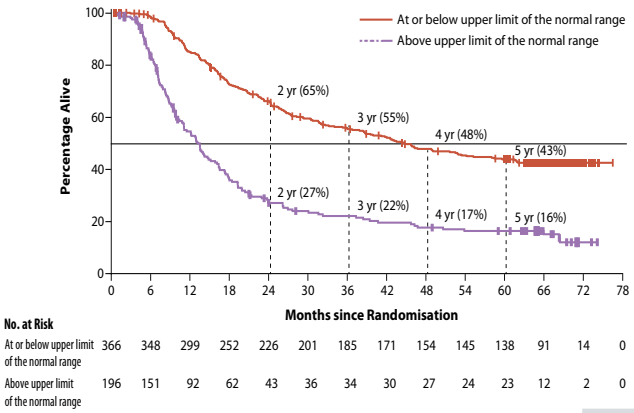


Fig. 7.10

LDH, lactate dehydrogenase.

Median progression-free survival in patients with *BRAF*-mutant melanoma brain metastases

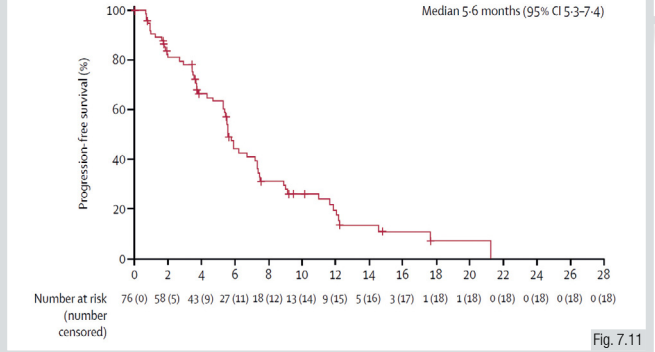


Fig. 7.11

CI, confidence interval.

The COMBI-MB study explored the response rate to dabrafenib and trametinib in patients with brain metastases from *BRAF*-mutant melanoma.

125 asymptomatic patients were treated, stratified by previous local treatment and *BRAF* V600E versus other *BRAF* V600 mutations.

Responses were seen in all groups, ranging from 44% to 59%. However, the median duration of response was short.

Responses to targeted therapy are rapid and these treatments are very useful in patients with symptomatic and rapidly progressing disease.

Care needs to be taken about potential drug-drug interactions in patients requiring antiepileptic medications, which can increase exposure and toxicity.

Adverse events were not increased in patients with brain metastases, with drug-related fever, asthenia, diarrhoea and arthralgia being the most common.

Most common adverse events (any cause) from COMBI-MB study, all cohorts

	Grade 1/2	Grade 3
Pyrexia	50.4%	3%
Asthenia	31.2%	<1%
Headache	34.4%	2%
Nausea	32.0%	0%
Diarrhoea	32.0%	0%
Arthralgia	20.8%	0%

Fig. 7.12

REVISION QUESTIONS

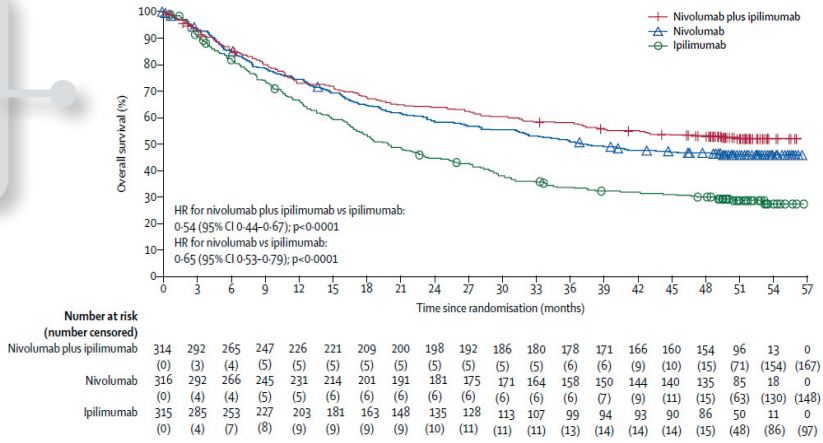
1. What is the most common toxicity of the targeted agents used to treat metastatic melanoma?
2. Why do you need to be careful about drug-drug interactions?
3. Which group of patients should be treated with targeted agents?

Treatment options: Immunotherapy

Immunotherapy with either combination anti-programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) or single-agent anti-PD-1 inhibitors is now standard of care for many patients with melanoma.

Immunotherapy has brought significant improvements in overall survival for patients on these agents for both *BRAF*-mutant and wild-type disease.

However, patients with untreated brain metastases were specifically excluded from many of the clinical trials with immune checkpoint inhibitors.



CI, confidence interval; HR, hazard ratio. Fig. 7.13

Response to treatment			
Variable	**Intracranial (N=94)**	**Extracranial (N=94)**	**Global (N=94)**
Best overall response – no. (%)			
Complete response	24 (26)	7 (7)	8 (9)
Partial response	28 (30)	40 (43)	40 (43)
Stable disease for ≥6 months	2 (2)	6 (6)	5 (5)
Progressive disease	31 (33)	28 (30)	33 (35)
Could not be evaluated	9 (10)	13 (14)	8 (9)
Objective response			
No. of patients	52	47	48
Percent of patients (95% CI)	55 (45-66)	50 (40-60)	51 (40-62)
Clinical benefit			
No. of patients	54	53	53
Percent of patients (95% CI)	57 (47-68)	56 (46-67)	56 (46-67)

CI, confidence interval. Fig. 7.14

CheckMate 204 explored the use of ipilimumab and nivolumab in patients with asymptomatic, but measurable, brain metastases.

Combination immunotherapy was active with a 57% response rate (RR) (26% complete response [CR] and 30% partial response [PR]). Other trials have shown the RR to single agent anti-PD-1 is in the order of 15%-22%.

Fifty-five percent of patients developed CTCAE (Common Terminology Criteria for Adverse Events) grade 3 or 4 toxicity, including 7% of patients who developed neurological toxicity.

Evidence of activity of immunotherapy was also seen in a phase II investigator-led study – the ABC (Anti-PD1 Brain Collaboration) study.

In the CheckMate 204 and ABC trials, a cohort of patients with symptomatic disease was treated, and lower RRs were observed (16% and 6%, respectively).

In patients who are fit enough, combination immunotherapy is a potential treatment option, following careful discussion of the risk of side effects.

Cohort A combination immunotherapy with ipilimumab and nivolumab, cohort B nivolumab alone, cohort C previously treated or symptomatic disease

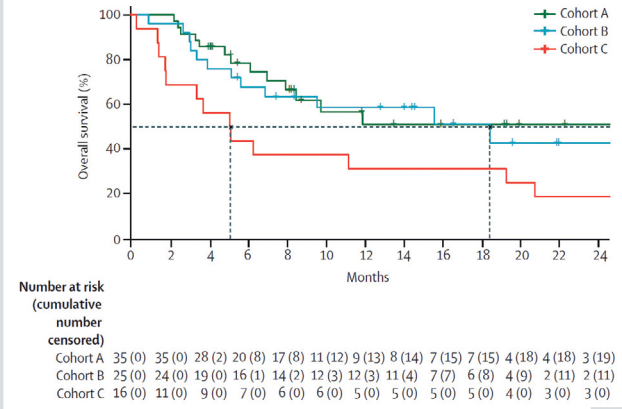


Fig. 7.15

REVISION QUESTIONS

1. Is treatment with combination immunotherapy more effective than single-agent anti-PD-1?
2. Is immunotherapy treatment safe to give to patients with MBM?
3. Are neurological immune-related side effects more common in this group of patients?

Summary: Management of brain metastases in melanoma

- Brain metastases in melanoma are common and have a very poor prognosis in untreated patients
- Treatment options now include both RT and systemic therapies
- SRS should be offered to patients with up to 10-12 low-volume metastases
- Combination immunotherapy is becoming the standard of care for asymptomatic patients who do not require steroid use
- Combination immunotherapy has significant toxicities and the risks of this need to be fully discussed in this poor-prognosis group of patients
- For symptomatic patients with *BRAF*-mutant melanoma, targeted therapy with BRAF and MEK inhibitors can give durable palliation
- WBRT is now rarely used in the setting of MBM
- SRS is being used more, especially for melanoma metastasis in areas of the brain inaccessible to neurosurgery
- The total number of small metastatic brain lesions that can be treated is increasing as experience with SRS accumulates, and the total brain volume treated is now thought to be the more important metric
- SRS is also being used in re-treatment after primary management with previous SRS, WBRT or neurosurgery
- It is important to realise that pseudoprogression, where post-SRS oedema occurs, is not disease progression
- Even with very accurate, focused SRS, there is still a risk of necrosis

Further Reading

Chukwueke U, Batchelor T, Brastianos P. Management of brain metastases in patients with melanoma. J Oncol Pract 2016; 12:536–542.

Davies MA, Saiag P, Robert C, et al. Dabrafenib plus trametinib in patients with $BRAF^{V600}$-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol 2017; 18:863–873.

Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre randomised, phase 3 trial. Lancet Oncol 2018; 19:1480–1492.

Hong AM, Fogarty GB, Dolven-Jacobsen K, et al. Adjuvant whole-brain radiation therapy compared with observation after local treatment of melanoma brain metastases: a multicenter, randomized phase III trial. J Clin Oncol 2019, 37:3132–3141.

Jardim A, Scott J, Drew Z. Extent of surrounding edema does not correlate with acute complications after radiosurgery for melanoma brain metastases. J Neurooncol 2019; 145:581–585.

Keilholz U, Ascierto PA, Dummer R, et al. ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee. Ann Oncol 2020; 31:1435–1448.

Le Rhun E, Guckenberger M, Smits M, et al. EANO–ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol 2021. In Press. DOI: https://doi.org/10.1016/j.annonc.2021.07.016

Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol 2018; 19:672–681.

Nowak-Sadzikowska J, Walasek T, Jakubowicz J, et al. Current treatment options of brain metastases and outcomes in patients with malignant melanoma. Rep Pract Oncol Radiother 2016; 21:271–277.

Oskan F, Ganswindt U, Schwarz SB, et al. Hippocampus sparing in whole-brain radiotherapy. A review. Strahlenther Onkol 2014; 190:337–341.

Schmidberger H, Rapp M, Ebersberger A, et al. Long-term survival of patients after ipilimumab and hypofractionated brain radiotherapy for brain metastases of malignant melanoma: sequence matters. Strahlenther Onkol 2018; 194:1144–1151.

Stokes WA, Binder DC, Jones BL, et al. Impact of immunotherapy among patients with melanoma brain metastases managed with radiotherapy. J Neuroimmunol 2017; 313:118–122.

Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med 2018; 379:722–730.

Vosoughi E, Lee JM, Miller JR, et al. Survival and clinical outcomes of patients with melanoma brain metastasis in the era of checkpoint inhibitors and targeted therapies. BMC Cancer 2018; 18:490.

Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of immunotherapy for the practitioner. J Clin Oncol 2015; 33:2092–2099.

B

More advanced knowledge

8 Pathology and molecular profile of melanomas

Pathway I. Low chronic sun damage melanoma/superficial spreading melanoma

The pagetoid pattern of *in situ* low chronic sun damage (CSD) melanoma/superficial spreading melanoma (SSM) is characterised by an intraepidermal proliferation of variably sized nests (red arrow) and single atypical melanocytes (blue arrow) at all levels of the epidermis.

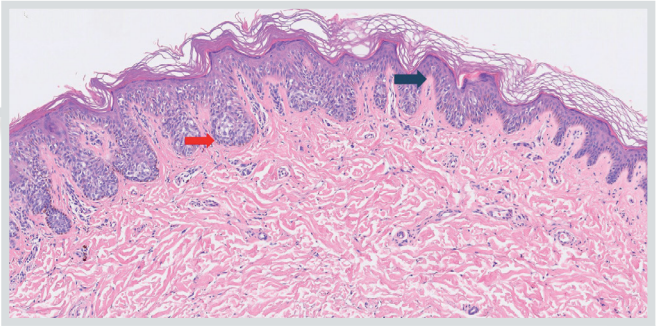


Fig. 8.1

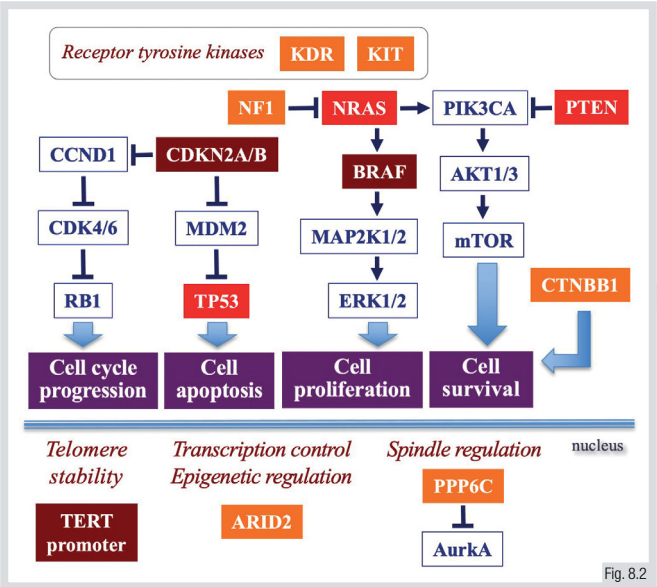


Fig. 8.2

ARID2; AT-rich interaction domain 2; AurkA, aurora kinase A; CCND1, cyclin D1; CDK4/6, cyclin-dependent kinase 4/6; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; KDR, kinase insert domain receptor; MAP2K1/2, mitogen-activated protein kinase kinase 1/2; mTOR, mammalian target of rapamycin; NF1, neurofibromin 1; PPP6C, protein phosphatase 6 catalytic subunit; PTEN, phosphatase and tensin homologue; TERT, telomerase reverse transcriptase; TP53, tumour protein 53.

Genes recurrently altered in low CSD melanoma/SSM:

In dark red, genes mutated in ≥30% of cases; in red, ≥20% to <30%; in orange, ≥10% to <20%. Arrows (↓), activating signals; interrupted lines (⊥), inhibiting signals.

(see Appendix 4, page 71)

The most common mutations are the valine substitution at codon 600 (V600) for *BRAF*, the glutamine substitution at codon 61 (Q61) for *NRAF* and, for *KIT*, the pathogenic variants at exon 11 (L576P) and at exon 13 (K642E).

All these mutations have been reported as mutually exclusive.

Main molecular features	Frequency
BRAF mutation	50%-55%
NRAS mutation	15%-20%
KIT mutation	1%-3%
Gain chromosome 7	10%-15%
Loss chromosome 10	15%-20%

Fig. 8.3

REVISION QUESTIONS

1. Which genes are mostly altered in low CSD/SSM?
2. Which signalling pathways are involved?
3. Which histological characteristics are present?

Pathway II. High CSD melanoma/lentigo-maligna melanoma

In lentigo-maligna melanoma (LMM), histology shows epidermal thinning, loss of web ridges and lentiginous (basal) proliferation of atypical melanocytes, and irregularly distributed nests (red arrow) in the epidermis.

There are signs of prominent solar elastosis (blue arrow) in the dermis.

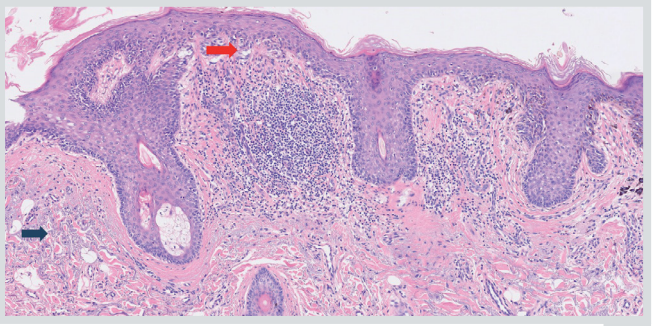


Fig. 8.4

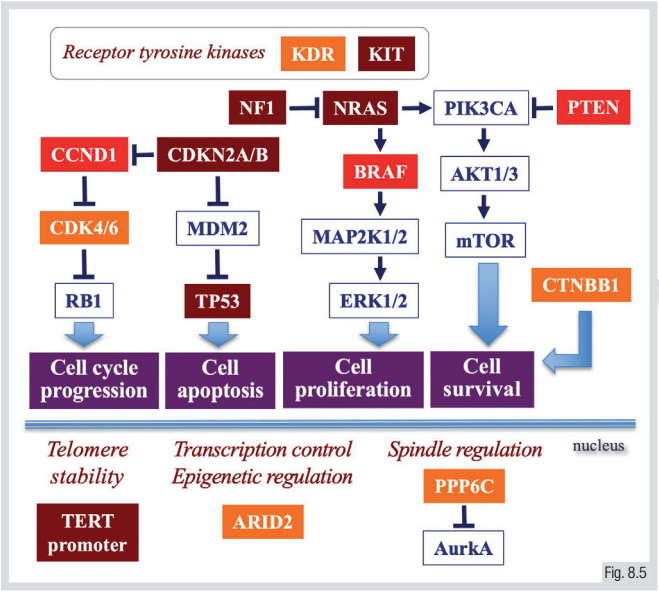


Fig. 8.5

ARID2; AT-rich interaction domain 2; AurkA, aurora kinase A; CCND1, cyclin D1; CDK4/6, cyclin-dependent kinase 4/6; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; KDR, kinase insert domain receptor; MAP2K1/2, mitogen-activated protein kinase kinase 1/2; mTOR, mammalian target of rapamycin; NF1, neurofibromin 1; PPP6C, protein phosphatase 6 catalytic subunit; PTEN, phosphatase and tensin homologue; TERT, telomerase reverse transcriptase; TP53, tumour protein 53.

Genes recurrently altered in high CSD melanoma/LMM):

In dark red, genes mutated in ≥30% of cases; in red, ≥20% to <30%; in orange, ≥10% to <20%. Arrows (⇓), activating signals; interrupted lines (⊥), inhibiting signals.

(see Appendix 4, page 72)

The *BRAF*-V600E mutation is more common in younger age at diagnosis (primary melanoma is mostly on the trunk), whereas *BRAF*-V600K and *NRAS* mutations are more common in older age (primary melanoma is on anatomical areas with increased cumulative sun damage).

Main molecular features	Frequency
BRAF	15%-20%
NRAS	25%-35%
KIT	2%-8%
NF1	25%-30%
Gain *CCND1*	20%-25%
ARID2	15%-20%
TP53	20%-25%

NF1, neurofibromin 1; *TP53*, tumour protein 53.

Fig. 8.6

REVISION QUESTIONS

1. Where is anatomical location of LMM?
2. What are the molecular differences between low and high CSD?
3. Are *BRAF* mutation variants dependent on age at melanoma onset?

Pathway III. Desmoplastic melanoma

Desmoplastic melanoma (DM) is a variant of spindle cell melanoma ('neurotropic' melanoma) typically found on chronically sun-damaged skin of older individuals.

There is dermal proliferation of non-pigmented spindle cells (red arrow) showing an undulating or wavy fibre pattern reminiscent of Schwannian differentiation. In the pure form of DM, tumour cells are separated by delicate collagen fibres. There are intratumoural nodular clusters of lymphocytes (blue arrow) and signs of grade III dermal solar elastosis.

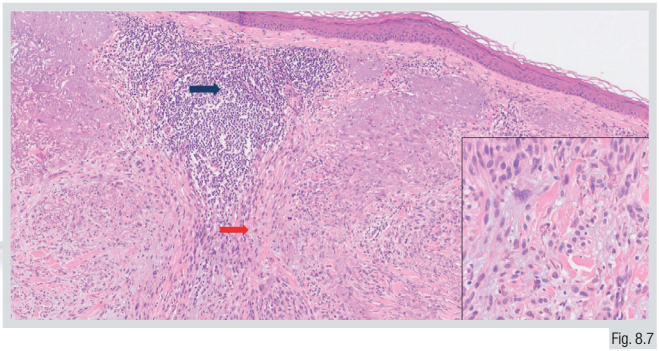


Fig. 8.7

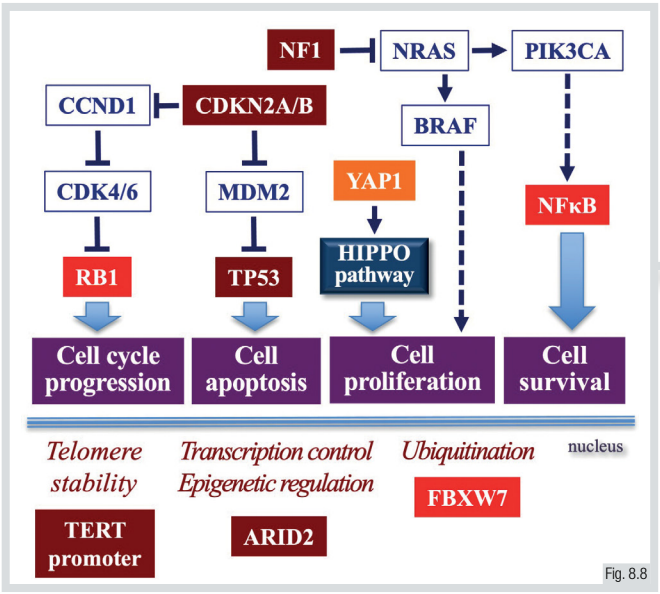


Fig. 8.8

ARID2; AT-rich interaction domain 2; CCND1, cyclin D1; CDK4/6, cyclin-dependent kinase 4/6; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; NF-κB, nuclear factor kappa B; NF1, neurofibromin 1; TERT, telomerase reverse transcriptase; TP53, tumour protein 53; YAP1, yes associated protein 1.

Genes recurrently altered in DM:

In dark red, genes mutated in ≥30% of cases; in red, ≥20% to <30%; in orange, ≥10% to <20%. Arrows (↓), activating signals; interrupted lines (⊥), inhibiting signals.

(see Appendix 4, page 73)

Regulation of nuclear factor kappa B (NF-κB) activity is a fundamental event in activating target genes involved in the control of cell cycle, cell growth and survival, and inflammation.

For this reason, NF-κB is persistently activated in many types of human tumours, protecting the tumour cell from death and thereby contributing to tumourigenesis and cancer therapy resistance.

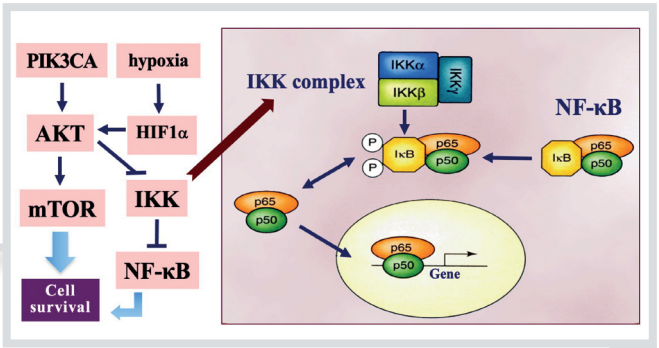


Fig. 8.9

HIF1α, hypoxia-inducible factor 1alpha; IKK, inhibitor of kappa B kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa B.

REVISION QUESTIONS

1. Where is the most frequent anatomical location of DM?
2. Which is the main histological characteristic of DM?
3. Which additional molecular pathway is involved in DM?

Pathway IV. Spitz melanoma/malignant Spitz tumour

An ulcerated Spitz melanoma (SM) is characterised by the presence of large spindle and/or epithelioid melanocytes, whose cells have abundant amphophilic hyaline cytoplasm and large nuclei with regular nuclear membranes, pale chromatin and prominent nucleoli (insert).

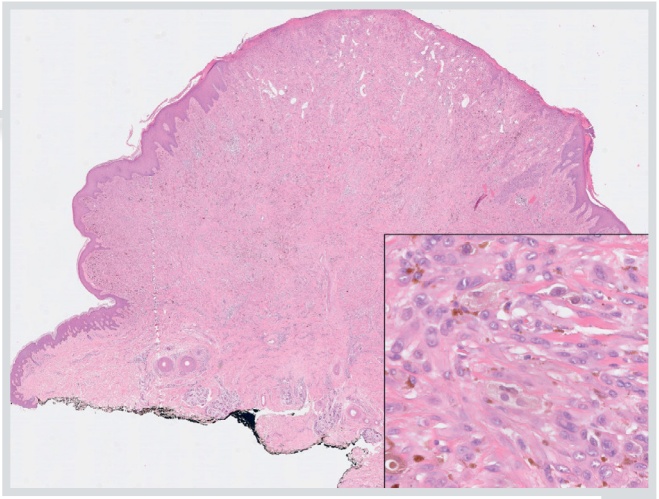


Fig. 8.10

SM is considered the malignant form of Spitz naevus, defined by clinical, histopathological and genetic characteristics, while the term 'spitzoid' melanoma is used for melanoma with some morphological resemblance to Spitz naevus.

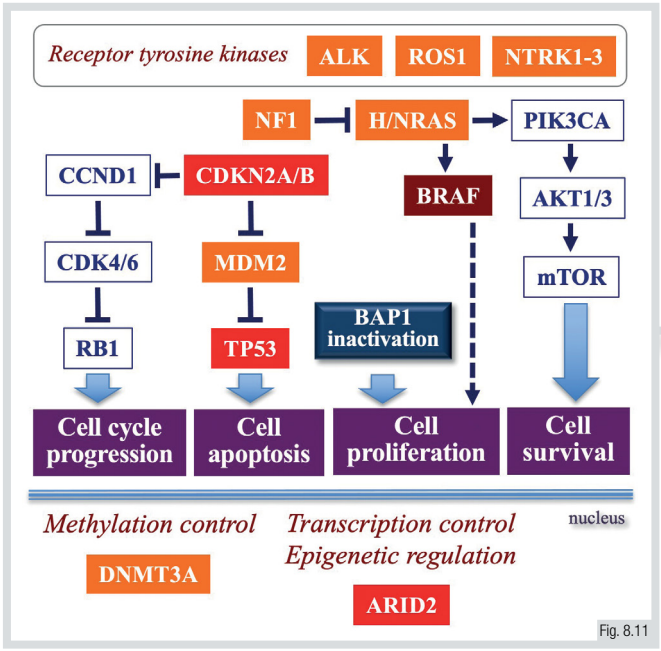


Fig. 8.11

ALK, anaplastic lymphoma kinase; ARID2; AT-rich interaction domain 2; CCND1, cyclin D1; CDK4/6, cyclin-dependent kinase 4/6; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; mTOR, mammalian target of rapamycin; NF1, neurofibromin 1; NTRK1-3, neurotrophic tyrosine receptor kinase 1-3; TP53, tumour protein 53.

Genes recurrently altered in SM:

In dark red, genes mutated in ≥30% of cases; in red, ≥20% to <30%; in orange, ≥10% to <20%. Arrows (↓), activating signals; interrupted lines (⊥), inhibiting signals.

(see Appendix 4, page 74)

SMs may be reasonably classified according to their distinctive molecular alterations; they carry several copy number changes as well as genomic rearrangements involving some kinases.

Inactivation of *BAP1* (sometime combined with *BRAF* mutations) has also been reported in SM.

Main molecular features
11p amplification ± *HRAS* mutation
6q23 homozygous deletion
9p21 homozygous deletion
BAP1 loss ± *BRAF* V600E mutation
Kinase driver *(ROS1, ALK, NTRK1-3, MET, BRAF* and *RET)* translocations

ALK, anaplastic lymphoma kinase; NTRK1-3, neurotrophic tyrosine receptor kinase 1-3. Fig. 8.12

REVISION QUESTIONS

1. What is the histological difference between Spitz and 'spitzoid' melanomas?
2. What is the main histological characteristic of SM?
3. What are the underlying molecular features of SM?

Pathway V. Acral melanoma

Acral melanoma (AM) is a distinct subtype of melanoma on acral skin. Patient presentation at later stages and delayed diagnosis contribute to a worse associated prognosis and survival rate.

In situ AM shows a poorly circumscribed proliferation of intraepidermal atypical melanocytes (red arrow) in a lentiginous pattern.

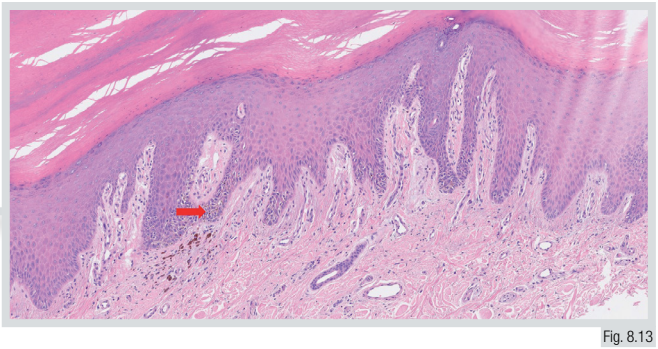


Fig. 8.13

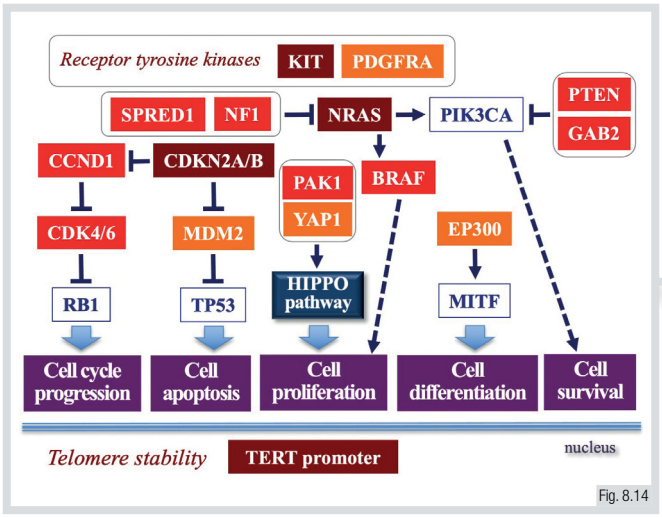


Fig. 8.14

CCND1, cyclin D1; CDK4/6, cyclin-dependent kinase 4/6; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; MITF, melanocyte-inducing transcription factor; NF1, neurofibromin 1; PDGFRA, platelet-derived growth factor receptor alpha; PTEN, phosphatase and tensin homologue; TERT, telomerase reverse transcriptase; TP53, tumour protein 53; YAP1, yes associated protein 1.

Genes recurrently altered in AM:

In dark red, genes mutated in ≥30% of cases; in red, ≥20% to <30%; in orange, ≥10% to <20%. Arrows (⇩), activating signals; interrupted lines (⊥), inhibiting signals.

(see Appendix 4, page 75)

Activating telomerase reverse transcriptase (*TERT*) promoter mutations have been associated with increased cell proliferation and survival, favouring downstream telomerase activity and maintenance of the telomere length.

In addition, *TERT* may be activated by gene amplification as well as by the constitutive induction of the mitogen-activated protein kinase (MAPK) pathway through the hyperphosphorylation of the downstream extracellular signal-regulated kinase (ERK) effector and the transduction of the activated signal to the nucleus.

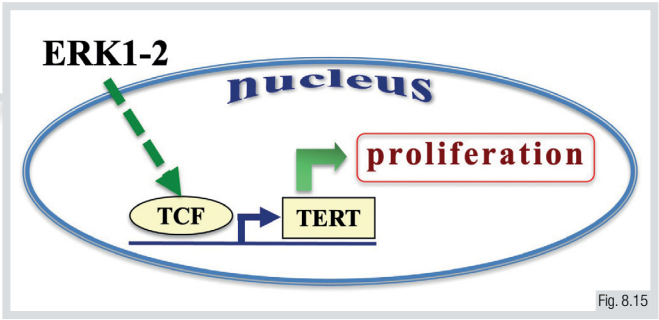


Fig. 8.15

ERK 1-2, extracellular signal-regulated kinase 1-2; TCF, transcription factor; TERT, telomerase reverse transcriptase.

REVISION QUESTIONS

1. What is the histological pattern in AM?
2. Which is the most mutated gene in AM?
3. What is the clinical presentation of AM?

Pathway VI. Mucosal melanoma

The most frequent site of mucosal melanoma is the head and neck area (up to 60% in the nasal cavity and paranasal sinuses), followed by the anorectal region (25%) and the vulvo-vaginal region (20%); about 5% of mucosal melanoma is in the distal urethra (both male and female).

The radial growth phase of a vulvar mucosal melanoma shows atypical cells with tendency to nesting (red arrow) and pagetoid scatter in the epithelium. There is no evidence of solar elastosis.

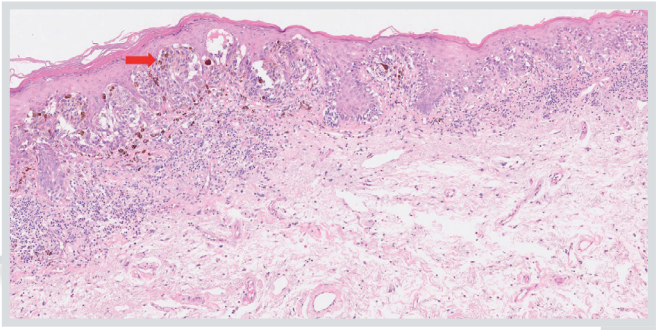


Fig. 8.16

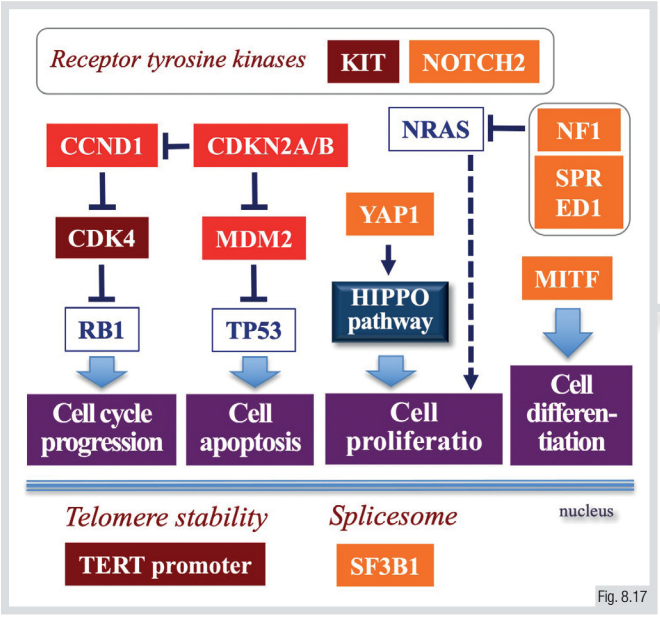


Fig. 8.17

CCND1, cyclin D1; CDK4, cyclin-dependent kinase 4; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; MITF, melanocyte-inducing transcription factor; NF1, neurofibromin 1; NOTCH2, notch receptor 2; TERT, telomerase reverse transcriptase; TP53, tumour protein 53; YAP1, yes associated protein 1.

Genes recurrently altered in mucosal melanoma:

In dark red, genes mutated in ≥30% of cases; in red, ≥20% to <30%; in orange, ≥10% to <20%. Arrows (↓), activating signals; interrupted lines (⊥), inhibiting signals.

(see Appendix 4, page 76)

In mucosal melanoma, the mutational profiles are slightly different between the 'upper' and 'lower' part of the body.

Unlike cutaneous melanoma, exposure to ultraviolet (UV) light is not a risk factor. Mucosal melanomas generally present at a later stage, are more aggressive and carry a worse prognosis, regardless of the stage at diagnosis.

Main molecular features	Frequency
BRAF	1%-5%
NRAS (up to 43% in vaginal)	10%-15%
KIT (up to 35% in anorectal)	15%-30%

Fig. 8.18

REVISION QUESTIONS

1. Is there any difference in mucosal melanoma prevalence according to the anatomical site of onset?
2. Which are the most frequent molecular alterations?
3. What is the most evident histological feature of mucosal melanoma?

Summary: Pathology and molecular profile of melanomas

- Melanomas have histological and molecular characteristics according to the different anatomical sites of onset
- For the histopathological classification of melanoma, categories are those reported in Classification of Skin Tumours of the World Health Organization (WHO); however, histotype is not considered as an independent prognostic factor
- Cutaneous melanoma has a high prevalence of somatic mutations; the vast majority of them are represented by C>T substitutions, which are strictly dependent on a mutagenic effect of UV rays (so-called 'UV signature')
- For all histotypes, the RAS-RAF-MEK-ERK (MAPK) pathway is the most important signal transduction cascade, regulating cell proliferation, invasion and survival
- Distinct molecular subtypes are recognised in:
  a) cases with mutations activating the *BRAF* gene
  b) cases with mutations activating the *RAS* genes (including the three isoforms: *NRAS* and, to a much lesser extent, *KRAS* and *HRAS*)
  c) cases with mutations activating the *KIT* gene
  d) cases without mutations in these genes, with prevalence of mutations inactivating the neurofibromin 1 (*NF1*) gene (though *NF1* mutations are present – at lower frequency – also in the other subtypes)
- Mutations in the *BRAF*, *RAS* and *KIT* genes are generally mutually exclusive (<3% of cases with coexistence of mutations in *BRAF* and *NRAS*)
- The *BRAF*-V600 mutation has a predictive significance since its occurrence identifies a potential sensitivity to treatment with the combination of *BRAF* and *MEK* inhibitors, for patients with either advanced melanoma (unresectable stage III or stage IV) or resected stage III melanoma
- Several fusion gene (*ALK, MET, NTRK1-3, ROS1*) mutations are becoming targets for specific kinase inhibitors and, thus, should be searched for in clinical practice

Further Reading

Bastian BC. The molecular pathology of melanoma: an integrated taxonomy of melanocytic neoplasia. Annu Rev Pathol 2014; 9:239–271.

Cancer Genome Atlas Network. Genomic classification of cutaneous melanoma. Cell 2015 161:1681–1696.

Colombino M, Capone M, Lissia A, et al. BRAF/NRAS mutation frequencies among primary tumors and metastases in patients with melanoma. J Clin Oncol 2012; 30:2522–2529.

Elder DE, Barnhill RL, Bastian BC, et al. Melanocytic tumour classification and the pathway concept of melanoma pathogenesis. In: Elder DE, Massi D, Scolyer RA, Willemze R (Eds). WHO Classification of Skin Tumours, 4th edition. Lyon: IARC, 2018; 66–71.

Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017; 67:472–492.

Palmieri G, Colombino M, Casula M, et al; Italian Melanoma Intergroup (IMI). Molecular pathways in melanomagenesis: what we learned from next-generation sequencing approaches. Curr Oncol Rep 2018; 20:86.

Pollock PM, Harper UL, Hansen KS, et al. High frequency of BRAF mutations in nevi. Nat Genet 2003; 33:19–20.

Shain AH, Bastian BC. From melanocytes to melanomas. Nat Rev Cancer 2016; 16:345–358.

Shain AH, Yeh I, Kovalyshyn I, et al. The genetic evolution of melanoma from precursor lesions. N Engl J Med 2015; 373:1926–1936.

Sullivan RJ (Ed). BRAF targets in melanoma: biological mechanisms, resistance, and drug discovery. New York, NY: Springer New York; 2015.

Wiesner T, Kutzner H, Cerroni L, et al. Genomic aberrations in spitzoid melanocytic tumours and their implications for diagnosis, prognosis and therapy. Pathology 2016; 48:113–131.

Dermoscopy in melanoma and other skin cancers

9

Principles and applications

Dermoscopy (also known as epiluminescence microscopy) is a simple diagnostic method to evaluate pigmented and non-pigmented structures of the epidermis, dermal-epidermal junction and papillary dermis.

Critical components are illumination (polarised or non-polarised light) and magnification (10x in handheld devices or 20-200x in video dermatoscopes). With non-polarised light, an immersion fluid needs to be used to avoid the reflection of the corneum stratum of the skin.

It significantly improves the diagnostic accuracy of early melanomas and non-melanoma skin cancers (NMSCs) and reveals the most difficult and featureless ones.

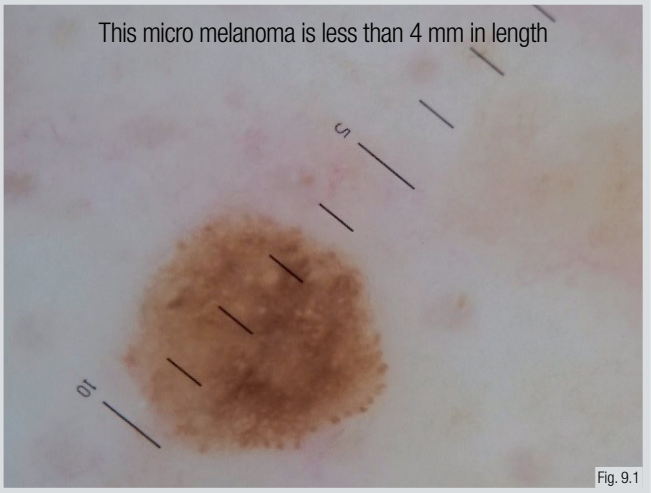


Fig. 9.1

Multiple SCC detected within field of actinic keratosis

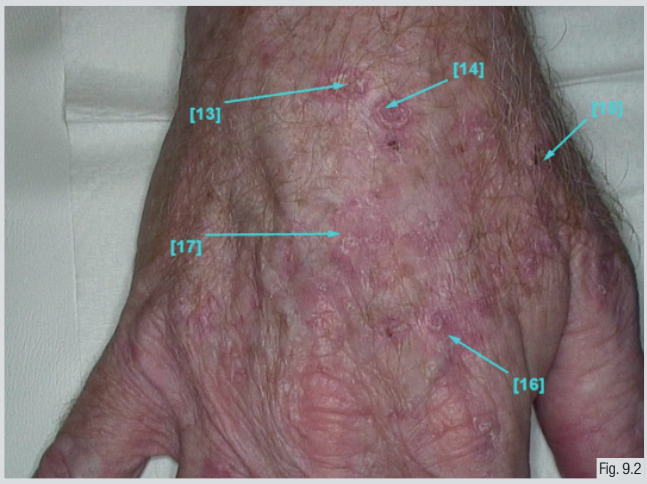


Fig. 9.2

SCC, squamous cell carcinoma.

It reduces the number of unnecessary excisions and helps to precisely define the neoplasm's borders in presurgical margin-mapping.

It is irreplaceable in the surveillance of patients with many naevi and high-risk patients (with field cancerisation or organ transplant recipients) as well as in the assessment of treatment results.

Dermoscopy reveals the characteristic structures and specific patterns found in different types of lesions. Application of algorithms helps to distinguish the malignant from the benign.

Each dermoscopic structure has a counterpart in histopathology; therefore the patterns of melanocytic lesions are characteristic for some anatomical areas.

Generally, dermoscopic structures are divided into melanocytic and non-melanocytic, which can be accompanied by vascular structures; all compose specific or non-specific patterns.

The colours of the skin lesion give additional information about its components and the melanin's location in the skin (black: corneum layer; brown: epidermis; grey: upper dermis; blue: mid-dermis).

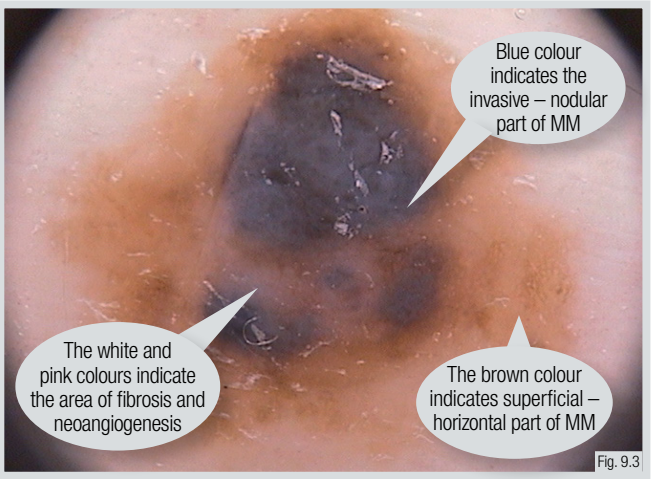


Fig. 9.3

MM, malignant melanoma.

REVISION QUESTIONS

1. Why is it that dermoscopy can be applied in clinical oncology?
2. Where does dermoscopy show its superiority over the naked eye?
3. What features are detected with dermoscopy?

Dermoscopy of melanoma

Dermoscopic structures vary among the different types of melanomas. Those with the broadest range of structures and colours are the superficial spreading ones.

The pigment network is one of the most important structures that we can see with dermoscopy; alteration of such a structure can indicate atypical lesions or melanoma.

Benign junctional naevi are composed of a brown, regular, thinning to the periphery, pigment network. In the case of malignant melanomas (MMs), islands of atypical (dense, thickened) dark brown or black pigment network, sharply demarcated, are usually detected (see below).

Colour in dermoscopy	Description
Black	Melanin in the corneum layer or a blood clot
Dark brown	Melanin in the epidermis (dense)
Light brown	Melanin in the epidermis (delicate)
Grey	Melanin in the papillary dermis or melanophages
Blue	Melanin in the reticular dermis
Orange	Combination of melanin and keratin or serous crust
Yellow	Keratin
White	Keratin or fibrosis in dermis; lack of melanin
Red	Blood
Purple	Blood (poorly oxygenated)

Fig. 9.4

Reed naevus-like melanoma

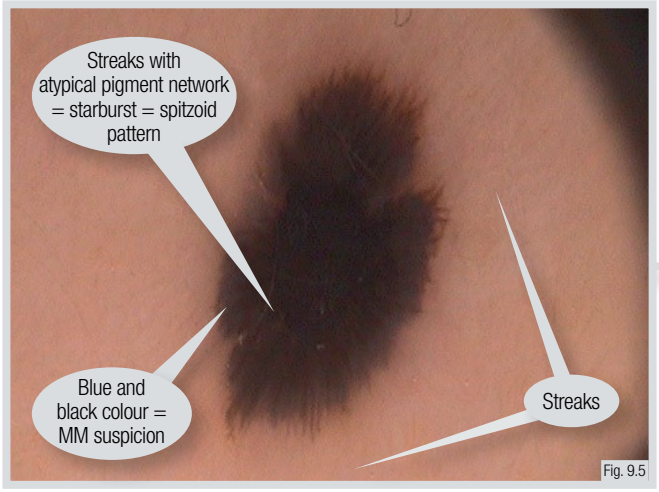


Fig. 9.5

MM, malignant melanoma.

Dermoscopy-based studies resulted in the formulation of diagnostic algorithms and rules, which changed the approach to patient examination and decision-making in clinically suspicious lesions.

Spitzoid lesions are the best example of dermoscopy's influence on patient stratification into observation or excision groups, based on the patient's age (>/< 12 years old) and the revealed morphological structures.

The diagnosis of amelanotic melanomas (some with classical spitzoid pattern) is usually performed by exclusion of NMSCs.

Dermoscopy has a lower specificity in the diagnosis of lesions found in so-called 'specific locations': the face, mucous membranes and nail apparatus.

In the non-invasive diagnosis of facial lesions, combined examination with dermoscopy and reflectance confocal microscopy (RCM) is the most helpful.

Vascular structures (type and arrangement) are crucial for the diagnosis of hypomelanotic or amelanotic melanomas. The type of vessels depends on the tumour volume and differs between flat (dotted) and nodular (linear, polymorphic) lesions.

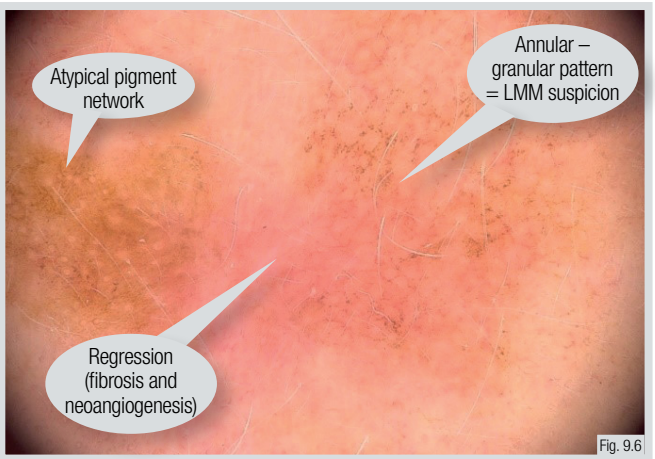


Fig. 9.6

LMM, lentigo-maligna melanoma.

REVISION QUESTIONS

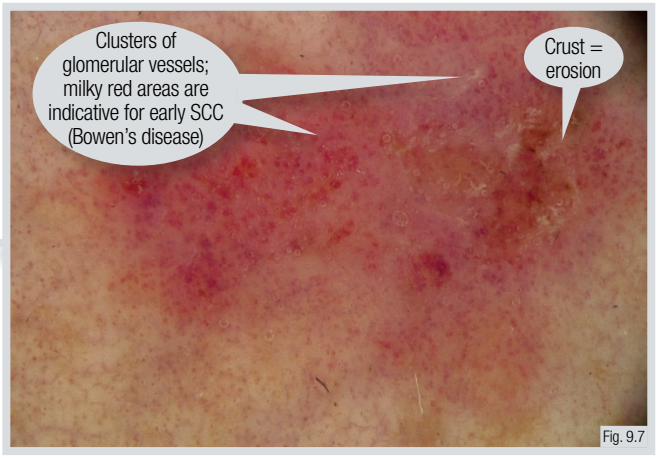
1. Which features may cause difficulties in the diagnosis of melanoma?
2. Describe the impact of dermoscopy on the examination of the patient and lesion decision-making.
3. What is the alternative to dermoscopy in the non-invasive diagnosis of facial lesions?

Dermoscopy of basal cell carcinoma and squamous cell carcinoma

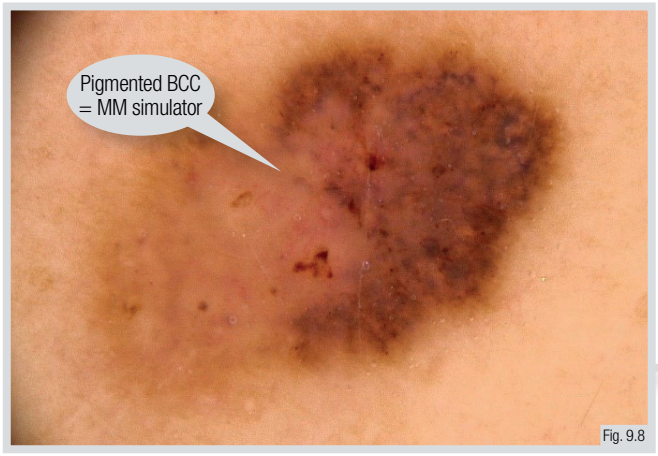
Dermoscopy of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) is easy to learn and very helpful in daily practice, especially in patients with multiple lesions, photo-damaged skin and in high-risk groups.

Specific structures are described for the superficial and invasive stages of BCC and SCC; this gives the opportunity to choose the most representative area for biopsy, or the best treatment option in each individual case.

The description of the excisional margins for NMSC, monitoring of treatment results and secondary prevention are other examples of the impact of dermoscopy on clinical practice.



SCC, squamous cell carcinoma.



BCC, basal cell carcinoma; MM, malignant melanoma.

Most NMSCs are non-pigmented, so in dermoscopy the predominant structures are the vascular ones, where the morphology is specific for BCC and SCC.

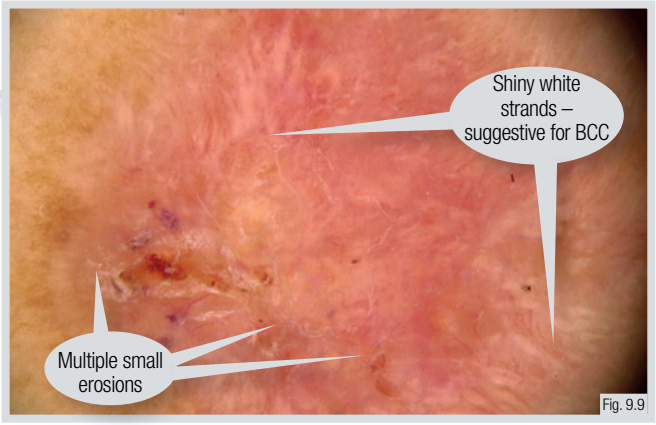
Some histopathological types of BCC can be distinguished by dermoscopy. Nodular SCC can mimic keratoacanthoma (KA) as the dermoscopic and clinical structures overlap.

The pigmented type of actinic keratosis or NMSC can be very difficult to distinguish from melanoma, both clinically and dermoscopically.

Despite the high specificity of dermoscopic structures in the diagnosis of NMSC, the so-called 'shiny white' structures can be observed in BCC, SCC, Spitz naevi, melanomas and dermatofibromas.

The metastases of adenocarcinomas may greatly mimic nodular BCC, while BCC in unspecific locations may resemble melanomas or SCC.

The greatest clinical and dermoscopic mimickers of melanomas and BCC are the adnexal tumours – especially trichoblastomas and pilomatricomas.



BCC, basal cell carcinoma.

REVISION QUESTIONS

1. Describe the impact of dermoscopy on the diagnosis and treatment of NMSC.
2. What are the most important dermoscopic structures in the diagnosis of non-pigmented NMSC?
3. What is the differential diagnosis of BCC and SCC examined with dermoscopy?

Summary: Dermoscopy in melanoma and other skin cancers

- Dermoscopy is a non-invasive diagnostic method revealing *in vivo* morphology of a skin lesion, leading to its classification as benign or malignant, and melanocytic or non-melanocytic
- Dermoscopy enables description of a tumour's borders in the preoperative setting, assessment of treatment results, early detection of cancer recurrence, and is useful in secondary prevention
- Each dermoscopic structure has a counterpart in histopathology. This is why diagnostic algorithms could be established
- Each type of melanoma (superficial spreading, amelanocytic/hypomelanocytic, nodular, on sun-damaged skin) presents a particular dermoscopic pattern
- Melanomas in special locations (face, acral, mucosal, nail) present unique dermoscopic structures and patterns according to the histological architecture of those areas. Some may require additional examination with RCM
- Dermoscopy of BCC and SCC helps to distinguish the early and invasive stages that may indicate the accurate diagnostic or therapeutic approach
- Knowledge of vascular types and their patterns is helpful in the differential diagnosis of non-pigmented (pink) skin lesions
- Pigmented BCCs (rarely) and pigmented KA/Bowen's disease/SCC (frequently) can be difficult to distinguish from melanoma as they can present equivocal dermoscopic structures
- To detect all melanocytic and non-melanocytic skin neoplasms of the patient, all lesions must be examined dermoscopically

Further Reading

www.dermoscopedia.org

Argenziano G, Catricalà C, Ardigo M, et al. Seven-point checklist of dermoscopy revisited. Br J Dermatol 2011; 164:785–790.

Argenziano G, Zalaudek I, Ferrara G, et al. Dermoscopy features of melanoma incognito: indications for biopsy. J Am Acad Dermatol 2007; 56:508–513.

Ascierto PA, Palmieri G, Botti G, et al; Melanoma Cooperative Group. Early diagnosis of malignant melanoma: proposal of a working formulation for the management of cutaneous pigmented lesions from the Melanoma Cooperative Group. Int J Oncol 2003; 22:1209–1215.

Cameron A, Rosendahl C, Tschandl P, et al. Dermatoscopy of pigmented Bowen's disease. J Am Acad Dermatol 2010; 62:597–604.

Lallas A, Apalla Z, Argenziano G, et al. The dermatoscopic universe of basal cell carcinoma. Dermatol Pract Concept 2014; 4:11–24.

Lallas A, Pyne J, Kyrgidis A, et al. The clinical and dermoscopic features of invasive cutaneous squamous cell carcinoma depend on the histopathological grade of differentiation. Br J Dermatol 2015; 172:1308–1315.

Lallas A, Tzellos T, Kyrgidis A, et al. Accuracy of dermoscopic criteria for discriminating superficial from other subtypes of basal cell carcinoma. J Am Acad Dermatol 2014; 70:303–311.

Lallas A, Zalaudek I, Apalla Z, et al. Management rules to detect melanoma. Dermatology 2013; 226:52–60.

Marghoob AA, Malvehy J, Braun RP. An Atlas of Dermoscopy, second edition. Boca Raton, FL, USA: Informa Healthcare, 2012.

Menzies SW, Moloney FJ, Byth K, et al. Dermoscopic evaluation of nodular melanoma. JAMA Dermatol 2013; 149:699–709.

Navarrete-Dechent C, Bajaj S, Marchetti MA, et al. Association of shiny white blotches and strands with nonpigmented basal cell carcinoma: evaluation of an additional dermoscopic diagnostic criterion. JAMA Dermatol 2016; 152:546–552.

Sinz C, Tschandl P, Rosendahl C, et al. Accuracy of dermatoscopy for the diagnosis of nonpigmented cancers of the skin. J Am Acad Dermatol 2017; 77:1100–1109.

Zalaudek I, Giacomel J, Schmid K, et al. Dermatoscopy of facial actinic keratosis, intraepidermal carcinoma, and invasive squamous cell carcinoma: a progression model. J Am Acad Dermatol 2012; 66:589–597.

Basal cell carcinoma, squamous cell and other rare skin cancers

10

Basal cell carcinoma

Basal cell carcinoma (BCC) is the most frequent cancer worldwide (estimated 5.9 million new cases in 2017, increasing around 5% annually in Europe) with an average lifetime risk in white-skinned individuals of 30%.

The most significant risk factors for developing BCC include male gender, older age, ultraviolet (UV) light exposure, fair skin and immunosuppression. BCCs metastasise very rarely (estimated incidence of 0.0028%-0.55%) but can be locally destructive (0.8% of all BCCs).

Activation of the Hedgehog (Hh) pathway, with inactivating mutations of *PTCH1* or activating mutations of *SMO*, is the main driver of pathogenesis.

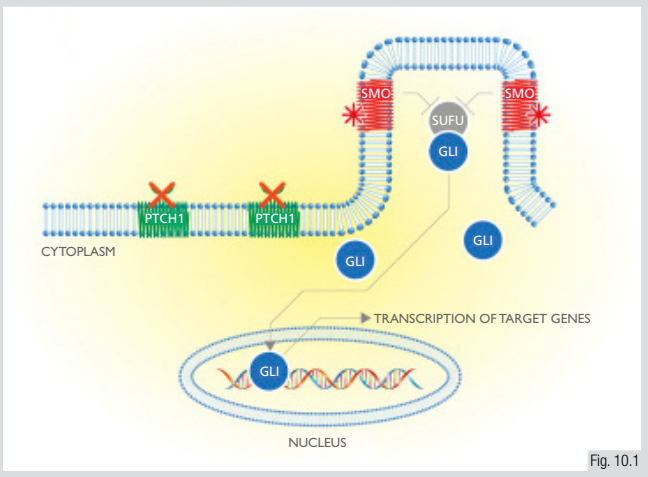


Fig. 10.1

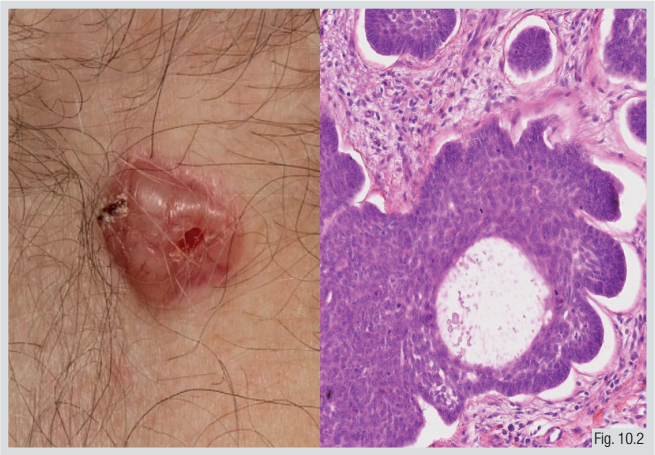


Fig. 10.2

Nodular BCC (nBCC) is the most common clinical form, presenting mostly in sun-exposed areas as an erythematous or translucent papule, sometimes ulcerated, with branching vessels.

Other clinical presentations are: superficial BCC (sBCC), presenting as a squamous erythematous plaque, and morphoeic BCC (moBCC), presenting as a light pink to white induration with ill-defined borders.

Dermoscopy and reflectance confocal microscopy can be helpful. Histological features include proliferation of basaloid keratinocytes in nodules or strands, peripheral palisading and clefts between tumour and stroma.

Low-risk BCC (small nBCC and sBCC) can be treated with surgery with safety margins or topical treatments (imiquimod, photodynamic therapy, cryotherapy).

Surgical excision of high-risk BCC is the first-line treatment. Safety margins of 10 mm or micrographic surgery are mandatory for moBCC.

Locally advanced BCC (LA-BCC), defined as inoperable BCC, can be treated with Hh pathway inhibitors (vismodegib or sonidegib) or curative radiotherapy (RT).

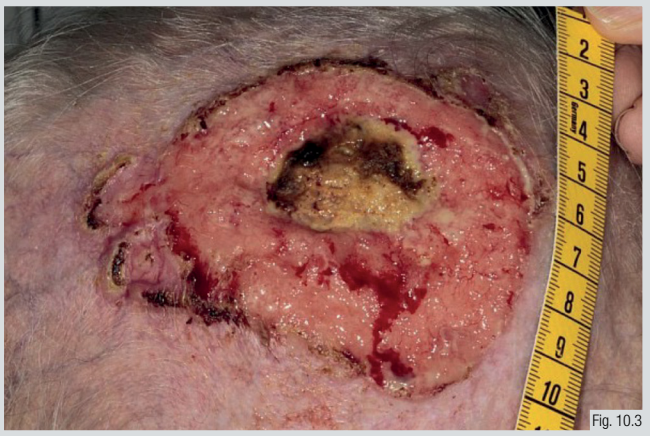


Fig. 10.3

REVISION QUESTIONS

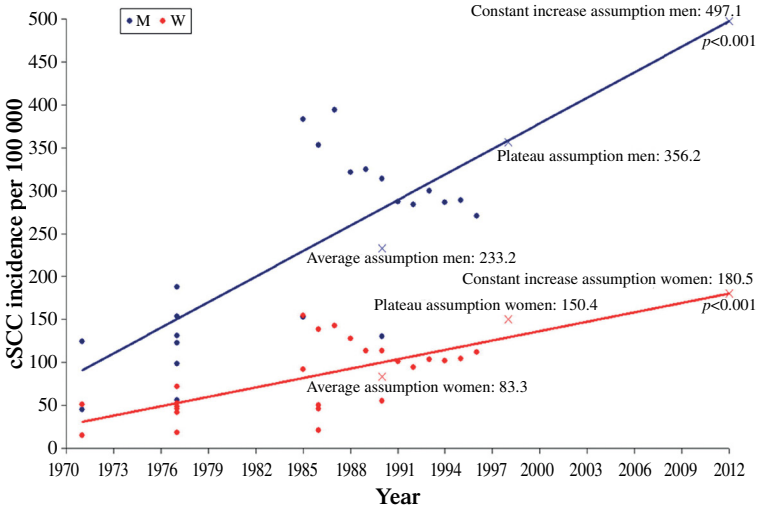
1. Which signalling pathway is involved in BCC physiopathology?
2. What is the most frequent clinical form of BCC?
3. What treatment can be used in LA-BCC?

Squamous cell carcinoma

Cutaneous squamous cell carcinoma (cSCC) is the second most frequent skin cancer among fair-skinned people, with incidence increasing worldwide.

Risk factors for developing cSCC are the same as for BCC, although patients tend to be older.

The tumour mutation burden (TMB) is one of the highest of all cancers. The most common genes involved are tumour protein 53 (*TP53*), *CDKN2A, RAS* and *NOTCH1*.



cSCC, cutaneous squamous cell carcinoma; M, men; W, women. Fig. 10.4

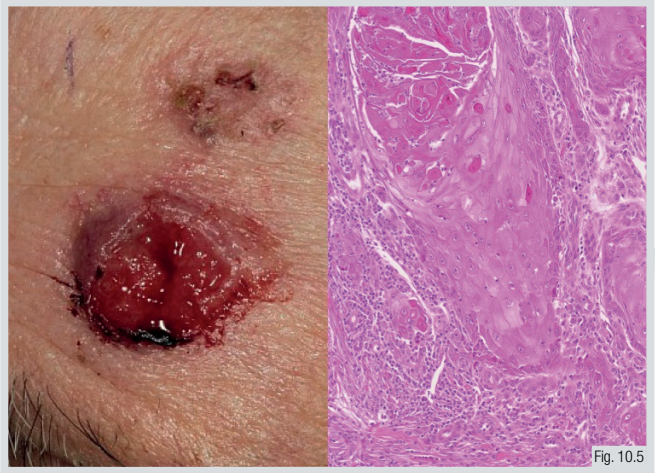


Fig. 10.5

cSCC arises *de novo* or in the context of pre-cancerous lesions such as actinic keratosis (AK) or Bowen's disease (BD).

cSCC mostly appears in sun-exposed areas and can present as an asymptomatic erythematous plaque or nodule, enlarging over time. It can become ulcerated, necrotic, crateriform or exophytic.

Dermoscopy can help with diagnosis, showing glomerular vessels in BD or hairpin vessels in invasive cSCC. Histological confirmation is mandatory, showing a malpighian carcinoma with variable keratinisation.

Factors associated with recurrence and metastases include tumour diameter (>20 mm), histological depth (>6 mm), perineural involvement, invasion beyond fat, poor differentiation, recurrent cSCC, site (temple, ear and lip) and immunosuppression.

Surgical excision with safety margins is the first-line treatment. Topical treatments (cryotherapy, 5-fluorouracil [5-FU], imiquimod, photodynamic therapy) can be used in AK or BD.

Locally advanced or inoperable cSCC and metastatic cSCC (representing around 5% of cSCCs) should be treated with RT if feasible. Otherwise, patients should receive first-line treatment with an anti-programmed cell death protein 1 (PD-1) antibody.

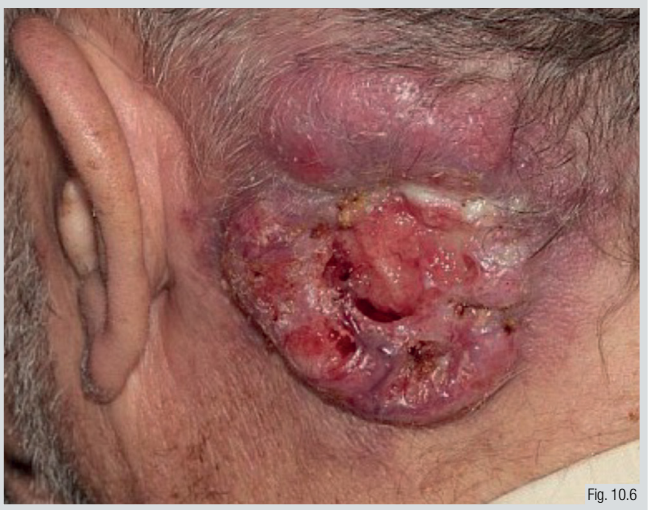


Fig. 10.6

REVISION QUESTIONS

1. What are the most common risk factors for developing cSCC?
2. What tool can be used for diagnosis of cSCC?
3. What is the first-line treatment of cSCC?

Merkel cell carcinoma

Merkel cell carcinoma (MCC) is a rare primary cutaneous cancer, with an incidence rate ranging from 0.2 to 0.4/100 000 in Europe, increasing from 1980 to 2000.

The main factors involved in MCC pathogenesis are older age, UV radiation, immunosuppression and Merkel cell polyomavirus (MCPyV) infection.

MCC shares epithelial and neuroendocrine features; its origin is debated, but most probably derives from epithelial precursors located in the hair follicle and in the interfollicular epidermis. MCPyV is found in 80% of MCCs.

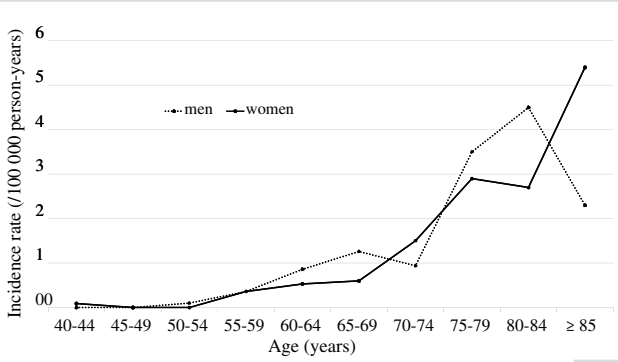


Fig. 10.7

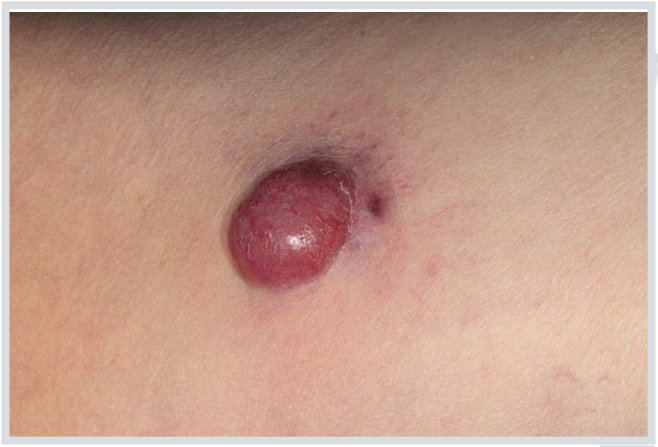


Fig. 10.8

MCC most frequently presents as a rapidly growing red to violet nodule on a sun-exposed area. Regional and distant metastases are frequent, with 5-year survival rates of 52% and 17%, respectively.

Imaging at the time of diagnosis includes ultrasound of the regional nodal basin, whole-body computed tomography (CT) or positron emission tomography (PET)-CT with brain magnetic resonance imaging (MRI).

Histopathological features include cells with characteristic nuclei (salt-and-pepper chromatin) in nodules or trabeculae in the dermis/subcutis; frequent lymphatic invasion; expression of CK20 in a perinuclear dot-like pattern and of neuroendocrine markers (chromogranin, synaptophysin and CD56).

Non-metastatic MCC (non-mMCC) must undergo surgery with a 1-2 cm safety margin, associated with sentinel lymph node biopsy (SLNB). Lymph node dissection is proposed if SLNB shows micrometastasis.

Adjuvant RT of the tumour region (50 Gy) should be proposed. Adjuvant RT of the lymphatic drainage area if affected (50 Gy) should be discussed by a tumour board.

mMCC should be treated with an anti-programmed death-ligand 1 (PD-L1) antibody (avelumab) first-line. Enrolment in clinical trials, palliative chemotherapy or supportive care can be discussed in patients resistant to immunotherapy.

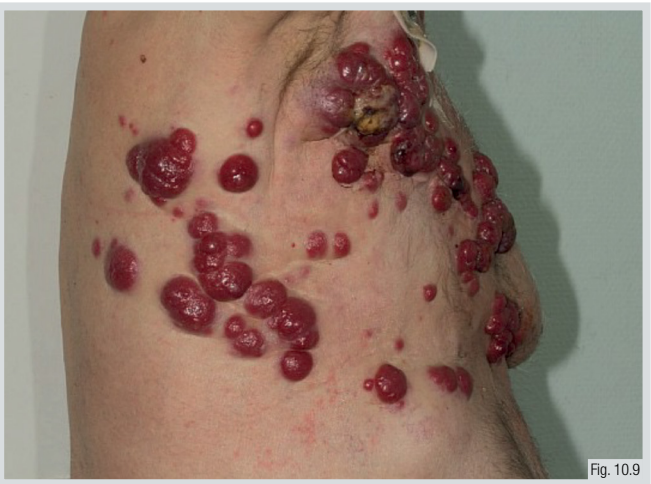


Fig. 10.9

REVISION QUESTIONS

1. Which virus is associated with MCC pathogenesis?
2. Which immunohistochemistry markers can be found in MCC histopathology?
3. What is the first-line treatment of non-mMCC?

Other rare skin cancers: Kaposi's sarcoma, dermatofibrosarcoma protuberans and adnexal carcinomas

Kaposi's sarcoma (KS) is a neoplasm of lymphatic endothelium-derived cells infected with human herpes virus 8 (HHV8). Clinical subtypes are classic, endemic, epidemic (human immunodeficiency virus [HIV]-infected patients) and iatrogenic (immunosuppressive therapy).

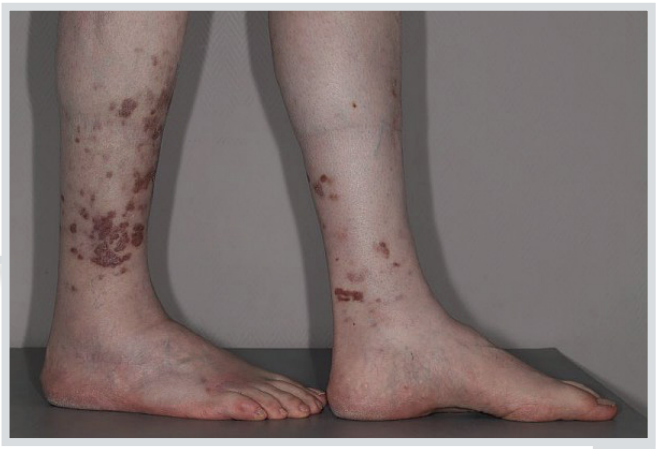


Fig. 10.10

Typical clinical presentation consists of brown, purple macules, plaques or nodules, with frequent lymphoedema. Mucosal and visceral involvement is more frequent in epidemic and iatrogenic KS.

Multiple local therapies such as RT, surgery, imiquimod or retinoids can be used for localised lesions. Pegylated liposomal doxorubicin, paclitaxel and interferon are commonly used for extensive or symptomatic KS. Anti-PD-1 immunotherapy appears promising and is currently under investigation.

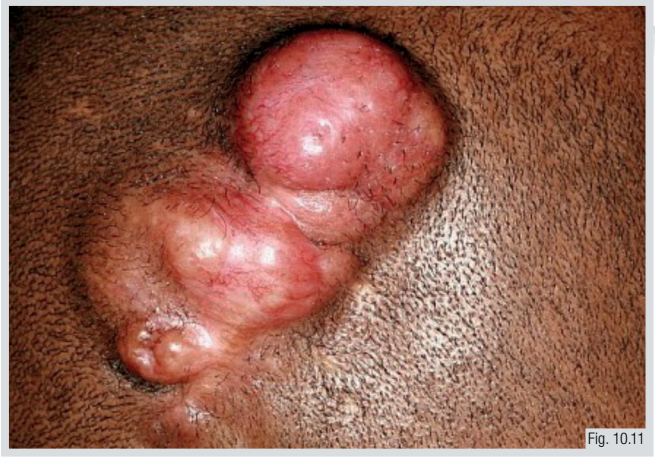


Fig. 10.11

Dermatofibrosarcoma protuberans (DFSP) is a rare cutaneous malignancy (1/100 000 persons) presenting as a slow-growing flesh-coloured, sometimes reddish, tumour.

DFSP is a locally aggressive tumour. Metastases are rare. Histology shows an infiltration of the dermis and subcutaneous fat by spindle-shaped CD34-positive cells. *COL1A1-PDGFB* (platelet-derived growth factor B) fusion gene detection can be used to confirm diagnosis.

Micrographic surgery or wide-margin excision (2-3 cm) are the main treatments. Imatinib (a platelet-derived growth factor receptor [PDGFR]-selective oral tyrosine kinase inhibitor) is approved for inoperable or metastatic DFSP.

Adnexal carcinomas are rare (incidence: 5/1 000 000 and increasing) and diverse (22 subtypes in the 2018 WHO [World Health Organization] classification), derived from eccrine, apocrine, sebaceous glands and hair follicles.

The most frequent adnexal carcinomas include porocarcinoma, sebaceous carcinoma, extramammary Paget's disease, hidradenocarcinoma and microcystic adnexal carcinoma.

They are typically ulcerated nodules or plaques that may metastasise to lymph nodes or distant sites according to the subtype. Surgical excision with safety margins is the first-line treatment. No consensus exists regarding RT or systemic treatment of advanced cases.

Age-standardised incidence rate per million (standardisation using the European standard population) of skin adnexal carcinoma in the Netherlands, 1989-2010

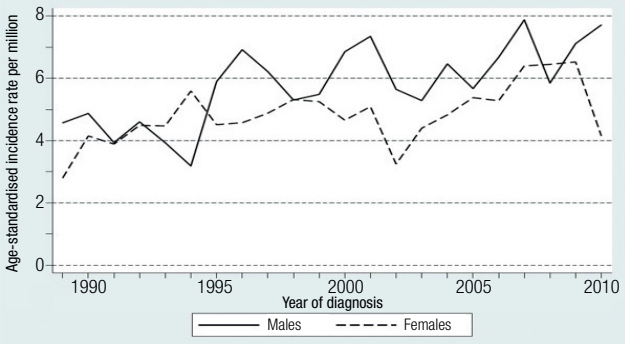


Fig. 10.12

REVISION QUESTIONS

1. Which virus is associated with KS?
2. Which fusion gene can be detected to confirm diagnosis of DFSP?
3. In most cases, what is the first-line treatment of adnexal carcinoma?

Summary: Basal cell carcinoma, squamous cell and other rare skin cancers

- Incidence of BCC and cSCC is increasing worldwide
- UV exposure, age and immunosuppression are the most common risk factors for BCC and cSCC
- Surgical excision with safety margins is the first-line treatment of cutaneous carcinomas
- Metastatic or locally advanced BCC can be treated with RT or Hh pathway inhibitors
- Metastatic or locally advanced cSCC can be treated with chemotherapy, RT or immune-checkpoint inhibitors (anti-PD-1)
- MCC is a highly aggressive primary cutaneous carcinoma with epithelial and neuroendocrine features
- Treatment of KS depends on the subtype, the extension and the patient's symptoms
- HIV serology is mandatory in patients diagnosed with KS
- Micrographic or wide-margin surgery is the first-choice treatment for dermatofibrosarcoma
- Adnexal carcinomas include 22 WHO subtypes, derived from sweat glands, sebaceous glands or hair follicles
- Metastatic risk and prognosis of adnexal carcinomas varies greatly among subtypes. First-line treatment of adnexal carcinomas is surgical excision with safety margins

Further Reading

Basset-Séguin N, Hauschild A, Kunstfeld R, et al. Vismodegib in patients with advanced basal cell carcinoma: primary analysis of STEVIE, an international, open-label trial. Eur J Cancer 2017; 86:334–348.

Lear JT, Migden MR, Lewis KD, et al. Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study. J Eur Acad Dermatol Venereol 2018; 32:372–381.

Lebbe C, Becker JC, Grob JJ, et al. Diagnosis and treatment of Merkel cell carcinoma. European consensus-based interdisciplinary guideline. Eur J Cancer 2015; 51:2396–2403.

Lebbe C, Garbe C, Stratigos AJ, et al. Diagnosis and treatment of Kaposi's sarcoma: European consensus-based interdisciplinary guideline (EDF/EADO/EORTC). Eur J Cancer 2019; 114:117–127.

Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med 2018; 379:341–351.

Peris K, Fargnoli MC, Garbe C, et al. Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines. Eur J Cancer 2019; 118:10–34.

Saiag P, Grob JJ, Lebbe C, et al. Diagnosis and treatment of dermatofibrosarcoma protuberans. European consensus-based interdisciplinary guideline. Eur J Cancer 2015; 51:2604–2608.

Stam H, Lohuis PJ, Zupan-Kajcovski B, et al. Increasing incidence and survival of a rare skin cancer in the Netherlands. A population-based study of 2,220 cases of skin adnexal carcinoma. J Surg Oncol 2013; 107:822–827.

Stratigos AJ, Garbe C, Dessinioti C, et al. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: Part 1. epidemiology, diagnostics and prevention. Eur J Cancer 2020; 128:60–82.

Stratigos AJ, Garbe C, Dessinioti C, et al. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: Part 2. Treatment. Eur J Cancer 2020; 128:83–102.

Work Group; Invited Reviewers; Kim JYS, Kozlow JH, Mittal B, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. J Am Acad Dermatol 2018; 78:560–578.

11 Uveal and mucosal melanoma

Introduction

Although the skin is by far the most common site of origin, melanoma can also develop in other sites including the eye and the mucosa of several organs.

These forms have a distinct biology and natural history, which underpin major differences in response to treatment compared with cutaneous melanoma (CM).

The rarity of these forms of melanoma has limited large scale clinical trials. The outcome from treatment for metastatic disease remains poor for most patients.

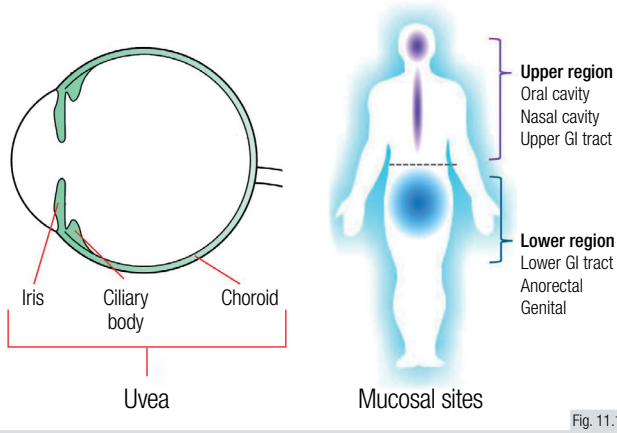


Fig. 11.1

GI, gastrointestinal.

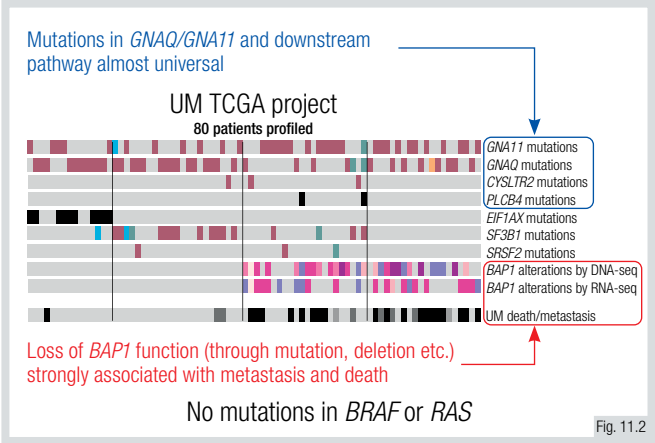


Fig. 11.2

TGCA, The Cancer Genome Atlas; UM, uveal melanoma.

Uveal melanoma (UM) is the most common non-CM, with an incidence of ~6/1 000 000 in the USA and Europe (5% of all melanomas).

UM is associated with light skin but not, however, with an ultraviolet (UV)-mutational signature. The pattern of driver mutations is very different from CM. Presenting symptoms include blurred vision, photopsia, floaters or visual field loss; however, UM is often asymptomatic, and detected on routine fundoscopy.

Treatment (usually surgery or radiotherapy) almost always controls the primary tumour, often sparing sight, but ~50% relapse with metastases.

Metastatic UM is hepatotropic. It is unusual to see metastatic disease that does not involve the liver, although other organs may also be involved.

Active liver surveillance of patients at risk is associated with earlier detection of metastatic disease and potentially more treatment options.

Several prognostic factors have been identified, most notably monosomy 3 (or loss of *BAP1* expression), and polysomy 8q, which combined with clinicopathological features can enable detailed prognostication (Liverpool Uveal Melanoma Online). Alternatively, a gene expression signature (DecisionDx-UM) has been shown to identify patients at high risk of metastasis.

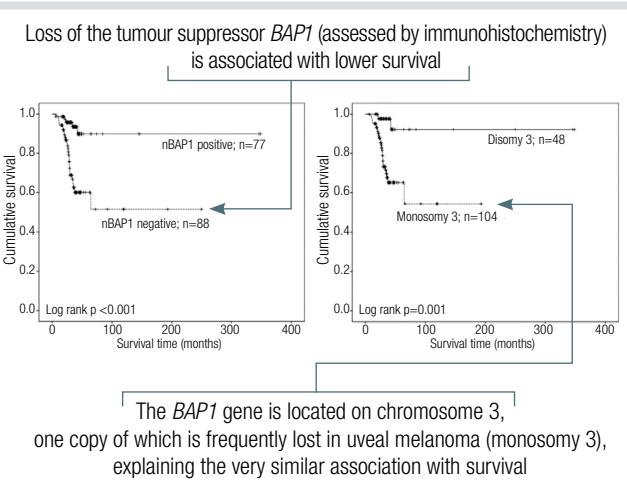


Fig. 11.3

REVISION QUESTIONS

1. What is the most likely pattern of clinical progression for UM?
2. What are the strongest prognostic factors for the development of metastases in UM?
3. What are the common driver mutations in UM?

Treatment of metastatic UM – locoregional and systemic

UM metastases often remain confined to the liver for some time. Locoregional liver treatments are therefore frequently used.

This includes liver resection and/or ablation of individual metastases as well as use of locoregional therapies such as chemoembolisation and percutaneous hepatic perfusion (PHP).

To date, there are no studies demonstrating an improvement in survival with these techniques, although PHP has been shown to improve progression-free survival (PFS).

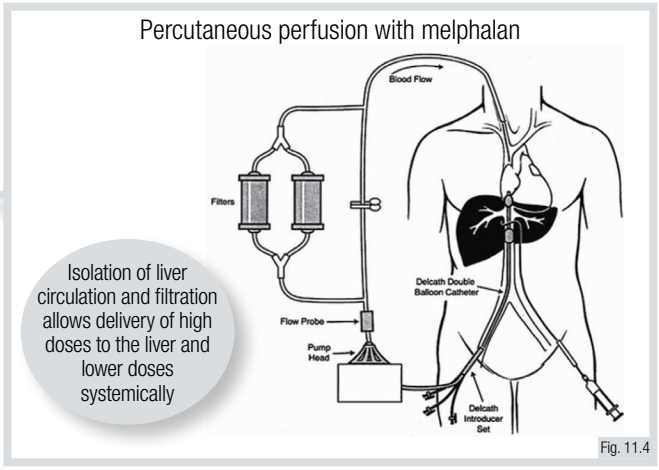


Fig. 11.4

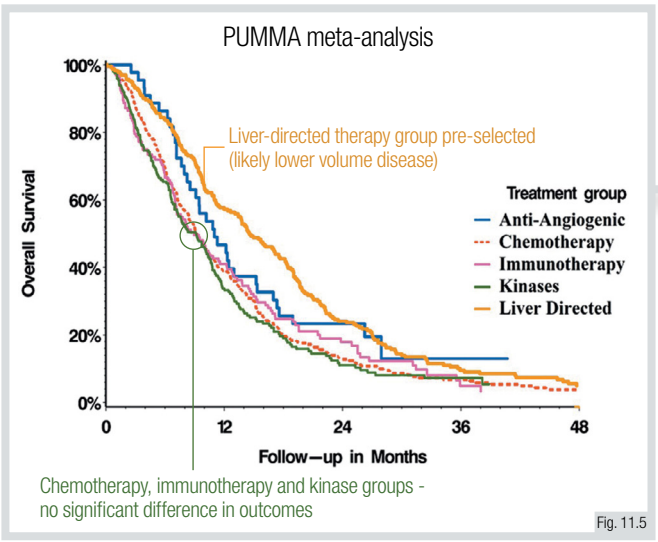


Fig. 11.5

Chemotherapy (ChT) agents lead to response infrequently (<8% in most trials) and generally provide very little benefit in terms of PFS or overall survival.

Immune checkpoint inhibitors (ICIs) have very limited activity in UM, with response rates of ~3%-8% reported for single agents, and ~10%-18% for combination treatment.

There are no directly druggable mutations in UM (*BRAF* is not mutated), and key mutations lead to activation of multiple downstream pathways.

Tumour-infiltrating lymphocyte adoptive transfer has shown some efficacy, with a response rate of 35% and durable benefit in some; however, it is not widely available.

Tebentafusp (IMCgp100) is a novel bispecific agent that redirects T cells against a glycoprotein 100 (gp100) peptide presented in the context of HLA-A*0201. It confers an improvement in overall survival compared with investigator's choice in a recent randomised phase III study (NCT03070392), and which is likely to become the new standard of care in patients with the appropriate HLA genotype.

The mitogen-activated protein kinase (MAPK) pathway is generally activated and MEK inhibitors have shown some clinical activity. However, as single agents, these appear relatively ineffective.

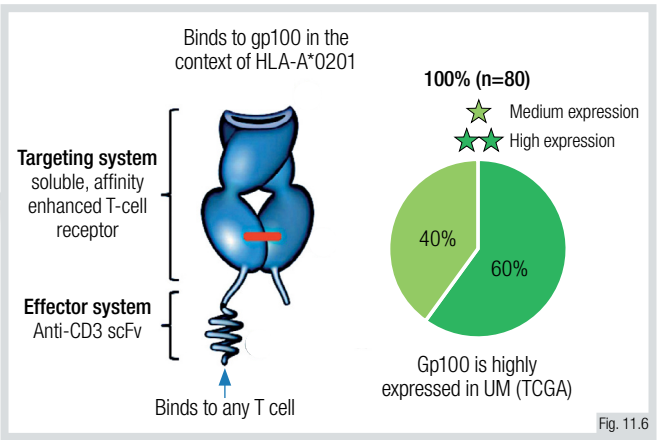


Fig. 11.6

gp100, glycoprotein 100; scFv, single-chain variable fragment; TCGA, The Cancer Genome Atlas; UM, uveal melanoma.

REVISION QUESTIONS

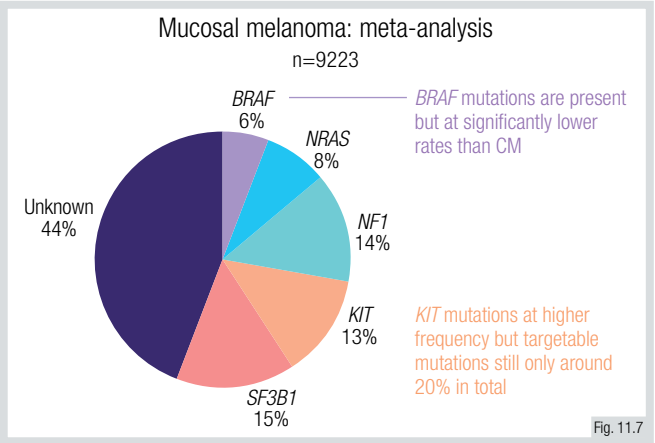
1. What is the clinical utility of ChT or ICIs?
2. When would one consider using locoregional therapy?
3. What other agents are under investigation?

Mucosal melanoma

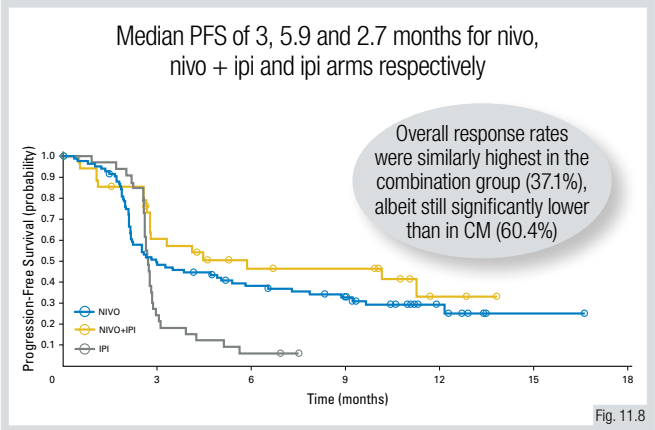
Mucosal melanoma constitutes <2% of all melanoma cases. Each individual anatomical subsite has different characteristics/treatment options.

A meta-analysis has shown that *BRAF* and *NRAS* mutations occur less frequently than in CM. Activating mutations in *c-KIT* are sometimes seen.

Conjunctival melanoma (even more rare than UM) arises from the conjunctiva and is more akin to CM in mutational patterns/response to therapy.



CM, cutaneous melanoma; NF1, neurofibromin 1.



CM, cutaneous melanoma; ipi, ipilimumab, nivo, nivolumab; PFS, progression-free survival.

Treatment of most mucosal melanoma is primarily surgical, although radiotherapy may also be used for local control. Recurrence and metastasis are frequent.

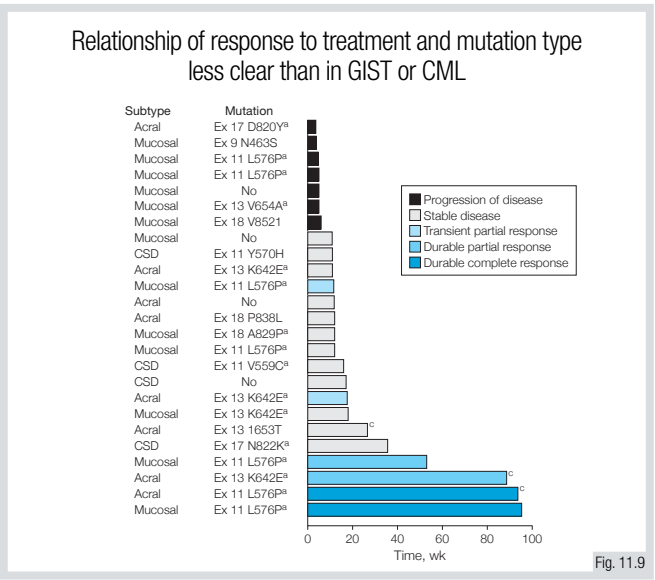
A pooled analysis of patients with metastatic mucosal melanoma treated with ICIs in clinical trials has shown that these agents are effective in a proportion.

Response rates of 23% and 41% were observed with single-agent nivolumab (anti-programmed cell death protein 1 [PD-1]) and in combination with ipilimumab (anti-cytotoxic T-lymphocyte antigen-4 [CTLA-4]), lower than in CM.

BRAF inhibitors have shown activity in metastatic disease where mutations are present; however, due to the rarity of the disease, the magnitude of benefit is less defined.

***KIT* mutations (in contrast to overexpression) are associated with clinical response to imatinib and potentially other *KIT* inhibitors.**

In mucosal melanoma, as in UM, there is thus a clear need for further investigation to identify new treatments and, wherever possible, trials should be considered.



CML, chronic myeloid leukaemia; CSD, chronic sun damage; GIST, gastrointestinal stromal tumour.

REVISION QUESTIONS

1. Which driver mutations are found in mucosal melanoma?
2. What treatment options are available for metastatic mucosal melanoma?
3. What are the treatment options for conjunctival melanoma?

Summary: Uveal and mucosal melanoma

- Rare melanoma subtypes are particularly challenging to manage, with outcomes that are significantly worse than in CM
- Insights from fundamental biology are informing clinical investigation and as yet there is no standard of care for UM
- Local and regional therapy may be considered in UM where disease is confined to the liver
- Checkpoint inhibitor immunotherapy has modest benefits at best so far in UM; alternative approaches may yet prove to have much greater benefit. This significant clinical need underpins the need for assessment of new investigational agents
- Tebentafusp is a novel T-cell receptor (TCR) therapeutic that has shown improved survival in HLA-A*0201 patients with metastatic UM; however, this is less than 50% of the population with UM
- The ability to prognosticate effectively provides a rare opportunity for adjuvant approaches in UM; however, these are dependent on having treatments with proven clinical benefit and other treatment options are urgently needed
- At present, targeted therapy has no place in standard of care for UM, however, both BRAF- and KIT-targeted agents have shown benefit in mucosal melanoma
- Immunotherapy with checkpoint inhibitors is the standard of care for mucosal melanoma, and combination nivolumab/ipilimumab appears to have higher activity (albeit with increased side effects)
- At present (and particularly for UM), trials should be considered first and foremost

Further Reading

Carvajal RD, Piperno-Neumann S, Kapiteijn E, et al. Selumetinib in combination with dacarbazine in patients with metastatic uveal melanoma: a phase III, multicenter, randomized trial (SUMIT). J Clin Oncol 2018; 36:1232–1239.

Chandran SS, Somerville RPT, Yang JC, et al. Treatment of metastatic uveal melanoma with adoptive transfer of tumour-infiltrating lymphocytes: a single-centre, two-stage, single-arm, phase 2 study. Lancet Oncol 2017; 18:792–802.

D'Angelo SP, Larkin J, Sosman JA, et al. Efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with mucosal melanoma: a pooled analysis. J Clin Oncol 2017; 35:226–235.

Farquhar N, Thornton S, Coupland SE, et al. Patterns of BAP1 protein expression provide insights into prognostic significance and the biology of uveal melanoma. J Pathol Clin Res 2017; 4:26–38.

Hofmann UB, Kauczok-Vetter CS, Houben R, Becker JC. Overexpression of the KIT/SCF in uveal melanoma does not translate into clinical efficacy of imatinib mesylate. Clin Cancer Res 2009; 15:324–329.

Hughes MS, Zager J, Faries M, et al. Results of a randomized controlled multicenter phase III trial of percutaneous hepatic perfusion compared with best available care for patients with melanoma liver metastases. Ann Surg Oncol 2016; 23:1309–1319.

Khoja L, Atenafu EG, Suciu S, et al. Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an international rare cancers initiative (IRCI) ocular melanoma study. Ann Oncol 2019; 30:1370–1380.

Nassar KW, Tan AC. The mutational landscape of mucosal melanoma. Semin Cancer Biol 2020; 61:139–148.

Piperno-Neumann S, Hassel JC, Rutkowski P, et al. Phase 3 randomized trial compared tebentafusp with investigator's choice in first line metastatic uveal melanoma. Presented at: AACR Annual Meeting 2021; April 10-15, 2021; Virtual. CT002.

Robertson AG, Shih J, Yau C, et al. Integrative analysis identifies four molecular and clinical subsets in uveal melanoma. Cancer Cell 2017; 32:204–220.

12 Predictive biomarkers for immunotherapy and targeted therapies in melanoma

Clinical correlates of innate and adaptive resistance in melanoma

Predictive biomarkers indicate sensitivity or resistance to a particular therapy. In contrast, prognostic biomarkers indicate the natural evolution of an untreated population. Some biomarkers can be both predictive and prognostic.

For example, the programmed cell death protein 1 (PD-1)/cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitor combination fails in ~30% of patients after 3 months. A predictive biomarker of resistance could identify these patients and propose an alternative treatment option.

In contrast, 36% of patients will never progress on PD-1/CTLA-4 combination and a predictive biomarker of sensitivity would flag these patients for this therapy.

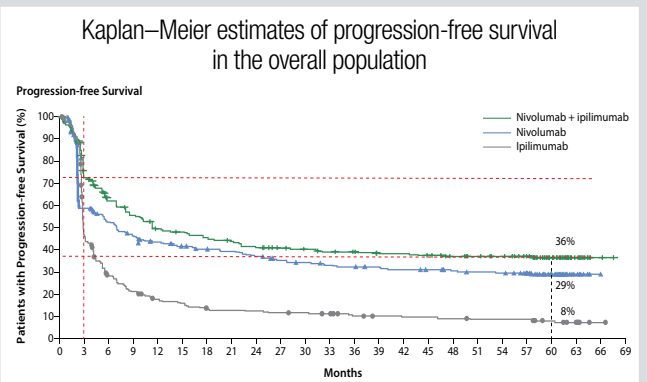


Fig. 12.1

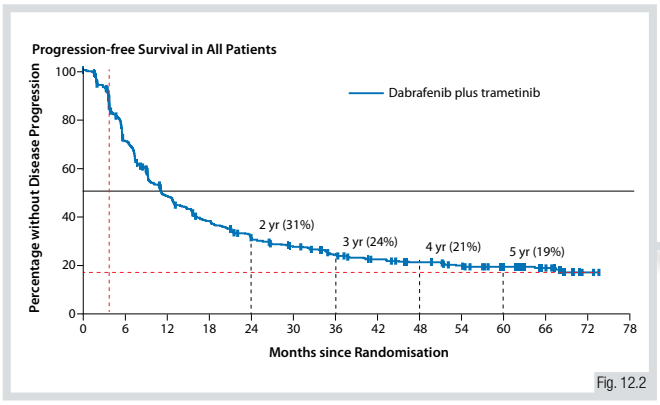


Fig. 12.2

Similar to immunotherapy, although to a smaller extent, 10% of patients will progress rapidly within the first 3 months on combined BRAF and MEK inhibitors. These patients likely harbour innate resistance mechanisms and would need to be identified.

Although a fraction of patients (20%) will not progress even after 5 years of dual BRAF/MEK inhibition, 70% of patients will develop adaptive resistance mechanisms.

Predictive biomarkers would be needed to identify the mechanisms leading to adaptive resistance in individual patients, and to provide actionable targets.

An idealised biomarker would predict treatment benefit with high sensitivity and specificity. Receiver operating characteristic (ROC) curves are the best way to assess the value of a biomarker.

A value of 0.5 AUC (area under the curve) would mean that a biomarker is not better than random chance. An AUC of 1 would imply that the marker has 100% accuracy in predicting the outcome (no false positives).

Tumour cell PD-L1 (programmed death-ligand 1) status is a well-studied marker for immunotherapy. The AUC for PD-L1 is very low, hence limiting its clinical relevance.

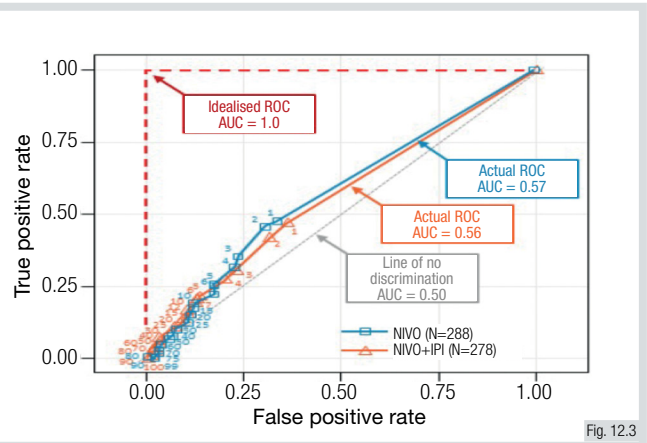


Fig. 12.3

AUC, area under the curve; IPI, ipilimumab; NIVO, nivolumab; ROC, receiver operating characteristic.

REVISION QUESTIONS

1. What is the percentage of adaptive resistance occurring with dual immunotherapy?
2. What percentage of patients are alive with combination TKIs (tyrosine kinase inhibitors) after 5 years?
3. Can you describe the concept of an ROC curve analysis?

Predictive markers of response and resistance mechanisms to immunotherapy in melanoma

Multiple steps are necessary to mount an immune response against melanoma cells, as conceptualised by the cancer immunity cycle.

The steps are performed by multiple cell types and are regulated positively or negatively by a multitude of proteins. Dysfunction within the immune cycle can lead to absence of anticancer immune response.

However, none of the factors of the immune cycle alone is predictive of an immune response or the lack of it (low negative and positive predictive values and AUC).

Cycle step	Main cellular participants	Main protein regulator
1. Release of antigens	Cancer cells	DAMPs, calretinin, HMGBP1, ATP
2. Cancer antigen presentation	Dendritic cells/APCs	TNFα, IL10, TLRs
3. Priming and activation	APCs and T cells	CTLA-4, PD-1, CD28, OX40/L, CD137/L, IL2
4. Trafficking of T cells to tumours	T cells and blood	CXCL1, CXCL9, CXCL10, CCL5
5. Infiltration of T cells into tumours	T cells/endothelial cells, pericytes	VEGF, ANG2, LFA1, ICAM1
6. Recognition by T cells	T cells and cancer cells	TCR, MHC
7. Killing of cancer	T cells	PD-1/PD-L1, BTLA, LAG-3

ANG2, angiopoietin-2; APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; DAMP, damage-associated molecular pattern; HMGPB1, high mobility group protein B1; ICAM1, intercellular adhesion molecule 1; IL2/10, interleukin 2/10; LAG-3, lymphocyte-activation gene 3; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor; TLR, toll-like receptor; TNFα, tumour necrosis factor alpha; VEGF, vascular endothelial growth factor. Fig. 12.4

Innate resistance	Adaptive resistance
Loss of HLA expression	*B2M* mutations
Decreased antigen processing	*JAK1/2* mutations
Dedifferentiation	Loss of neoantigen expression
Lack of neoantigens	Loss of IFN-γ signalling
High Wnt signalling	
High MAPK pathway activity	
High PI3K/PTEN pathway activity	
High CDK4/6 checkpoint activity	

CDK4/6, cyclin-dependent kinase 4/6; HLA, human leukocyte antigen; IFN-γ, interferon gamma; MAPK, mitogen-activated protein kinase. Fig. 12.5

Both adaptive and innate resistance mechanisms are in place to evade response to PD-1 or CTLA-4 therapies. It is also possible that tumours present with a combination of these mechanisms.

Innate resistance is mainly linked to pre-existing suppression within the steps of the cancer immunity cycle.

Adaptive resistance mechanisms also influence the cancer immunity cycle, mainly by limiting the activated and ongoing cancer-cell killing by T cells.

No molecular biomarker exists that would be clinically applicable for the prediction of response to immunotherapies with a high enough confidence/accuracy.

Current clinical parameters are only correlative biomarkers of benefit but with limited predictive values.

An emerging biomarker of response to immunotherapy is the gut microbiome, which is still difficult to study routinely.

Marker	Predictive value for immunotherapy
BRAF	Mutant = better with CTLA-4 or CTLA-4/PD-1 combination
LDH	Low = better outcome with all ICB
Tumour mutation burden (TMB)	High = better outcome with all ICB
Sex	Male = better outcome with PD-1 inhibitors
CD8 TILs	More CD8 = better outcome
PD-L1 status	Higher = better outcome with PD-1 inhibitors
Immune evasion signature (CDK4/6)	Lower = better outcome with PD-1 inhibitors
IMPRES/IPRES signatures	Lower = better outcome with PD-1 inhibitors
Classical monocytes in blood	Higher = better outcome with PD-1 inhibitors
Gut microbiome	High diversity = better IO response
Brain metastases	PD-1/CTLA-4 better than PD-1 alone
IFN-γ signature	Higher = better outcome
Pathological complete response (PCR)	In adjuvant therapy PCR is a sign of better survival

CDK4/6, cyclin-dependent kinase 4/6; CTLA-4, cytotoxic T-lymphocyte antigen-4; ICB, immune checkpoint blockade; IFN-γ, interferon gamma; IMPRES, immuno-predictive score; IO, immuno-oncology; IPRES, innate anti-PD-1 resistance; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TIL, tumour-infiltrating lymphocyte. Fig. 12.6

REVISION QUESTIONS

1. What are the main steps of the cancer immunity cycle?
2. Which innate and adaptive resistance mechanisms are in action for immune therapy?
3. Which are the main correlative biomarkers, linked to better outcomes?

Predictive markers of resistance mechanisms and response to BRAF/MEK inhibitors

The majority of patients treated with BRAF/MEK inhibitors will eventually fail therapy, except the 20% long-term survivors.

Innate and adaptive resistance to BRAF/MEK inhibitor mechanisms are multiple, and even the same tumour or different tumours in the same patient can develop multiple alterations.

The rational combination of BRAF inhibitors with MEK inhibition delays a part of the innate/adaptive resistance mechanisms to BRAF inhibitors but cannot completely prevent it.

Innate mechanism	Adaptive mechanism	Innate/adaptive mechanism
RAC1 mutations	BRAF splice variants	MITF
HGF expression by fibroblasts	BRAF amplification	PI3K pathway activation
CDK4/6 upregulation	Upregulation of tyrosine kinases	Loss of PTEN (for BRAF monotherapy)
HOXD8 mutations	Increased ERK feedback	COT expression
Cyclin D upregulation	TORC1 upregulation	Loss of NF1
PRKD3 upregulation		*NRAS* mutations

CDK4/6, cyclin-dependent kinase 4/6; HGF, hepatocyte growth factor; MITF, melanocyte-inducing transcription factor; NF1, neurofibromin 1.

Fig. 12.7

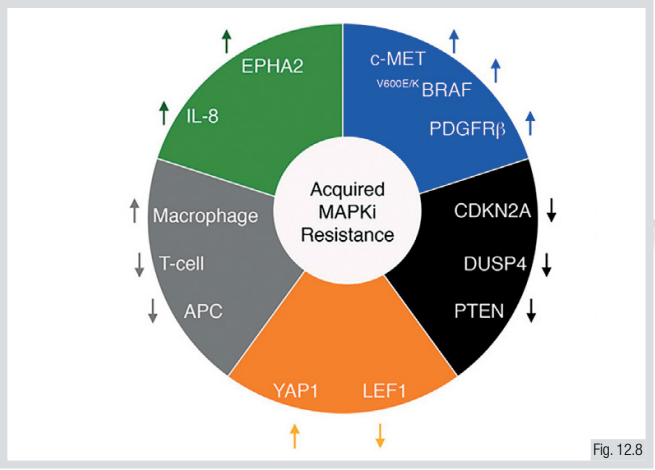


Fig. 12.8

APC, antigen-presenting cell; IL-8, interleukin 8; MAPKi, mitogen-activated protein kinase inhibitor; PDGFRβ, platelet-derived growth factor receptor beta.

Beyond cancer cell-intrinsic resistance to BRAF inhibitors, non-genomic mechanisms including the tumour microenvironment play an important part in the resistance.

For example, hepatocyte growth factor (HGF) produced by cancer-associated fibroblasts can rescue melanoma cells from BRAF inhibition by induction of MET signalling in melanoma cells.

During adaptation to BRAF inhibitors, increased angiogenesis, increased macrophage infiltration (M2), reduced T cells and antigen-presenting cells (APCs) can lead to resistance.

Clinical parameters can also influence the outcome of patients on BRAF/MEK inhibition. These markers are shared with immunotherapies.

Lactate dehydrogenase (LDH) levels, number of metastatic sites and performance status are linked to survival.

Tumour mutation burden (TMB), PD-L1, ccfDNA (circulating cell-free DNA) and CTCs (circulating tumour cells) are emerging markers of BRAF/MEK-inhibitor therapies.

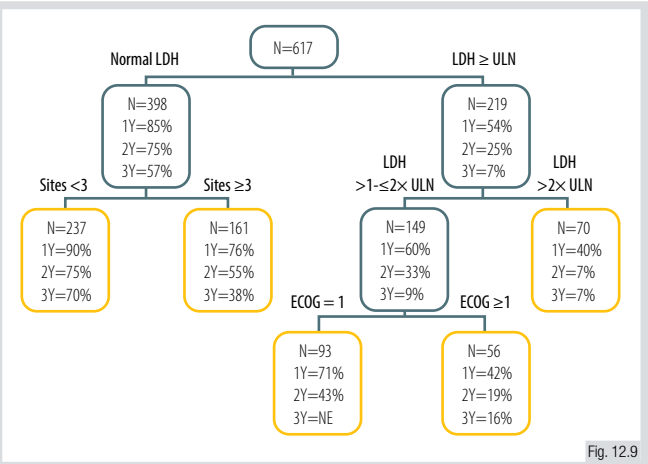


Fig. 12.9

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NE, not evaluated; ULN, upper limit of normal.

REVISION QUESTIONS

1. What is the only approved therapy to limit resistance to BRAF-inhibitor therapy?
2. Name the shared mechanisms of adaptive and innate resistance to BRAF inhibition?
3. Which marker can be used to exclude patients from BRAF inhibitors?

Summary: Predictive biomarkers for immunotherapy and targeted therapies in melanoma

- To date, melanoma is the tumour with one of the highest response rates to PD-1-based immunotherapy
- Similarly, *BRAF*-mutant melanoma patients significantly benefit from dual BRAF/MEK inhibition
- In both cases, a minority of patients (20%-30%) will present with innate resistance mechanisms
- Both kinase inhibitors and immunotherapy will induce adaptive resistance in the majority of patients, which will predict loss of benefit from therapy
- No single biomarker has a sufficiently high positive and negative predictive value to select patients for one or other therapy
- Due to the high number of mechanisms of resistance, a personalised approach is needed either upfront (innate resistance) or during therapy (adaptive resistance) to combat treatment failure
- Novel predictors from the gut microbiome, peripheral blood and the tumour microenvironment of melanoma cells are expected to further improve prediction
- Complex biomarkers will be required to efficiently describe the complex biology and the heterogeneity of the human melanoma population

Further Reading

Auslander N, Zhang G, Lee JS, et al. Robust prediction of response to immune checkpoint blockade therapy in metastatic melanoma. Nat Med 2018; 24:1545–1549.

Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. Nature 2017; 541:321–330.

Gopalakrishnan V, Helmink BA, Spencer CN, et al. The influence of the gut microbiome on cancer, immunity, and cancer immunotherapy. Cancer Cell 2018; 33:570–580.

Hugo W, Shi H, Sun L, et al. Non-genomic and immune evolution of melanoma acquiring MAPKi resistance. Cell 2015; 162:1271–1285.

Hugo W, Zaretsky JM, Sun L, et al. Genomic and transcriptomic features of response to anti-PD-1 therapy in metastatic melanoma. Cell 2016; 165:35–44.

Jerby-Arnon L, Shah P, Cuoco MS, et al. A cancer cell program promotes T cell exclusion and resistance to checkpoint blockade. Cell 2018; 175:984–997.e24.

Luebker SA, Koepsell SA. Diverse mechanisms of BRAF inhibitor resistance in melanoma identified in clinical and preclinical studies. Front Oncol 2019; 9:268.

Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. Cell 2017; 168:707–723.

Shin DS, Zaretsky JM, Escuin-Ordinas H, et al. Primary resistance to PD-1 blockade mediated by JAK1/2 mutations. Cancer Discov 2017; 7:188–201.

Straussman R, Morikawa T, Shee K, et al. Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. Nature 2012; 487:500–504.

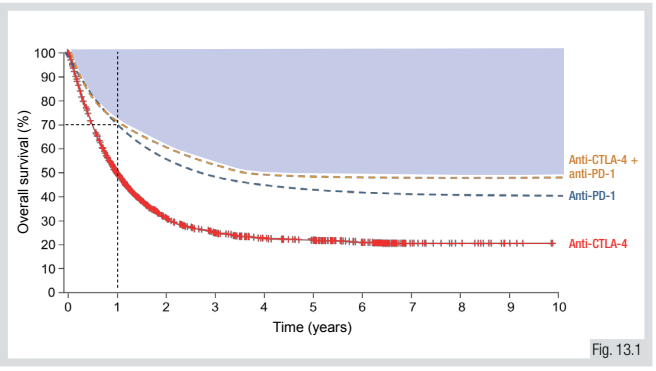
13 The most emerging targets and personalised medicine

Achievements and unmet needs in metastatic melanoma – combine to move forward

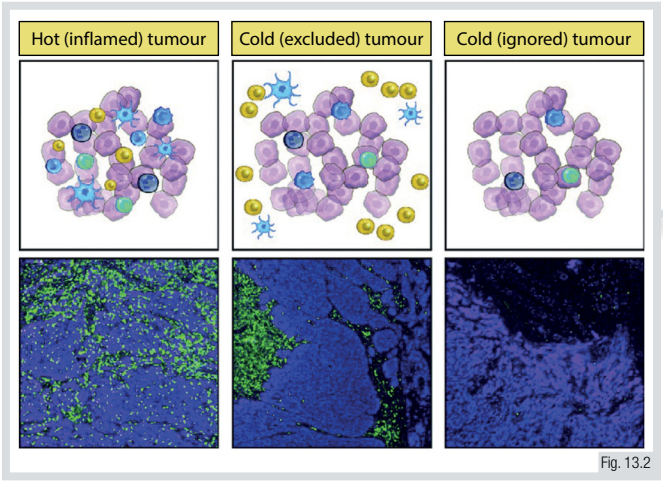
Until 2011, the prognosis for metastatic melanoma was very poor. Since the advent of immune checkpoint inhibitors (ICIs) and BRAF inhibitors, prognosis has dramatically improved.

In the CheckMate 067 trial, ~20% of patients achieved long-term benefit (still alive at 10 years) with anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibodies; ~45% with anti-programmed cell death protein 1 (PD-1) antibodies; and 50% when combined.

With the combination ICIs, more than 50% of the patients were alive at 5 years, but for the same reason ~50% had no, or very limited, benefit.



CTLA-4, cytotoxic T-lymphocyte antigen-4; PD-1, programmed cell death protein 1.



In order to achieve long-term benefit in a higher number of patients, we need to overcome primary and acquired resistance.

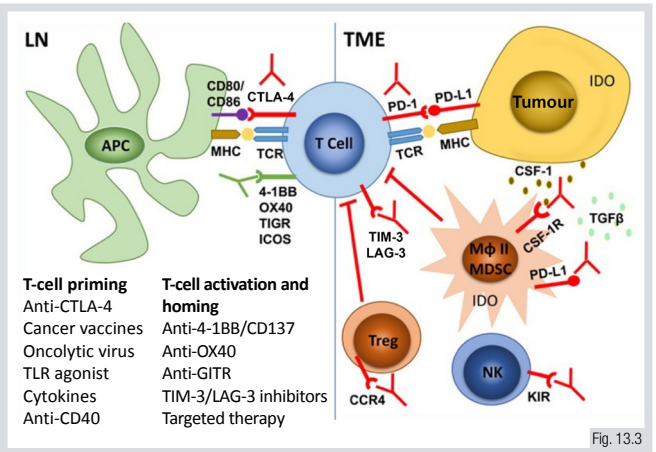
For this we distinguish inflamed tumours, with intratumoural T-cell infiltration; immune-excluded tumours, with T cells solely in the periphery, excluded from contact with tumoural cells by stroma; and immune-desert tumours, without T-cell infiltration.

Only inflamed tumours respond to ICIs. For this reason, there is an unmet need to make 'cold' (uninflamed) tumours 'hot', and therefore sensitive to immunotherapy.

So far, new targets have been detected that might improve the efficacy of the anti-melanoma immune response. Consequently, new agents to combine with ICIs have been identified.

The most interesting agents in development are toll-like receptor 9 (TLR9) agonists, anti-lymphocyte activation gene 3 (LAG-3) antibodies, histone deacetylase inhibitors (HDACis) and bempegaldesleukin.

New combinations of immunotherapies with other treatments are now in development, so the potential of anti-PD-1s in combination with other novel agents is being explored.



APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; KIR, killer-immunoglobulin-like receptor; LAG-3, lymphocyte activation gene 3; LN, lymph node; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; NK, natural killer; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand-1; TCR, T-cell receptor; TGFβ, transforming growth factor beta; TIM-3, T-cell immunoglobulin and mucin domain 3; TLR, toll-like receptor; TME, tumour microenvironment; Treg, regulatory T cell.

REVISION QUESTIONS

1. What are the rates of long-term survivorship with ICIs (monotherapy and combination)?
2. How many cancer immune phenotypes can be distinguished and why?
3. How can we overcome melanoma resistance to ICIs? Which pathways are the most interesting for overcoming resistance at the moment?

TLR9 agonists – from injected to distant lesions

TLR9 is a receptor expressed on immune system cells including dendritic cells (DCs), macrophages, natural killer (NK) cells and other antigen-presenting cells (APCs).

TLR9 agonists alter the tumour microenvironment by improving the antigen presentation of APCs with a proliferation of antigen-specific CD8+ T cells.

The combination of TLR9 agonists with ICIs demonstrated a synergistic effect in patients, both naïve and those progressing after anti-PD-1.

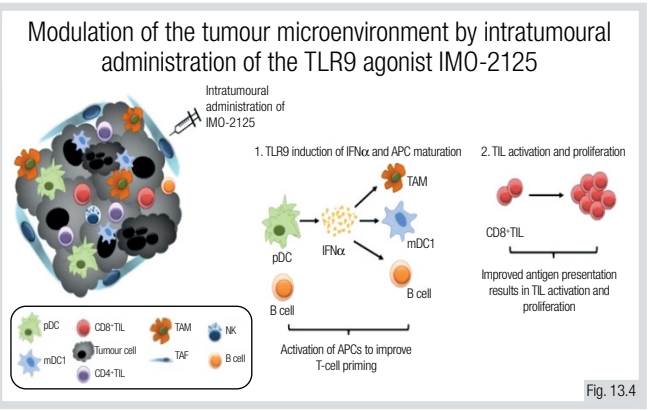


Fig. 13.4

APC, antigen-presenting cell; IFNα, interferon alpha; NK, natural killer; pDC, plasmacytoid dendritic cell; TIL, tumour-infiltrating lymphocyte; TLR9, toll-like receptor 9.

TLR9 agonists induce changes in immune checkpoint gene expression in injected tumours and increase DC activation, upregulation of major histocompatibility complex (MHC) class II and interferon alpha (IFN-α) signalling, suggesting improved antigen presentation.

In responding patients, expanding clones of lymphocytes in distant metastases are shared with the injected lesions, demonstrating an 'abscopal effect'.

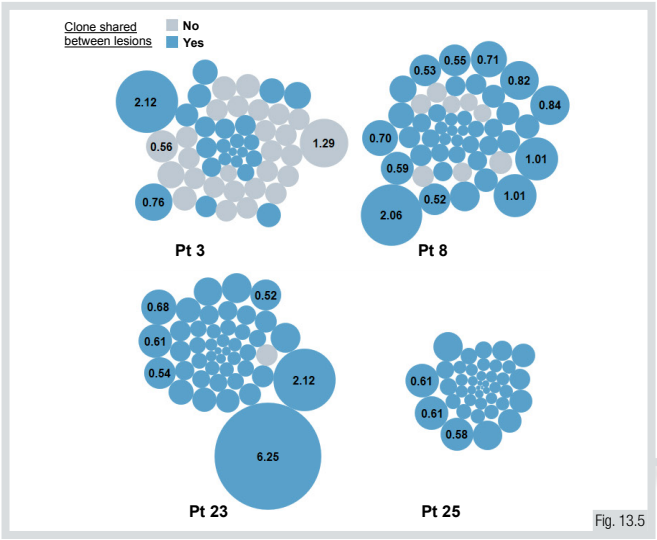


Fig. 13.5

Pictured opposite, the top 50 clones in the distant lesions in responding patients. The number indicates clonal-specific change in frequency. The circle size reflects the frequency of the clone relative to the other clones present.

Tilsotolimod (IMO-2125) is an oligonucleotide with potent immunostimulating activity that binds to TLR9. It increases the antigen-presenting phase with consequent proliferation of antigen-specific CD8+ T cells.

In patients progressing after anti-PD-1, tilsotolimod 8 mg intralesionally was combined with ipilimumab 3 mg/kg intravenously in a phase I/II study (NCT02644967). The overall response rate (ORR) was 22.4%, and disease control rate (DCR) 72%. Median overall survival (mOS) was 21 months, much better than ipilimumab alone. A phase III trial is ongoing.

Other TLR9 agonists are now in phase I/II clinical trials. CMP-001 with pembrolizumab in patients resistant to anti-PD-1 had 22.5% ORR; and SD-101 with pembrolizumab in naïve patients had a 71% ORR (2 CR [complete response] and 28 PR [partial response]). Progression-free survival (PFS) was not reached.

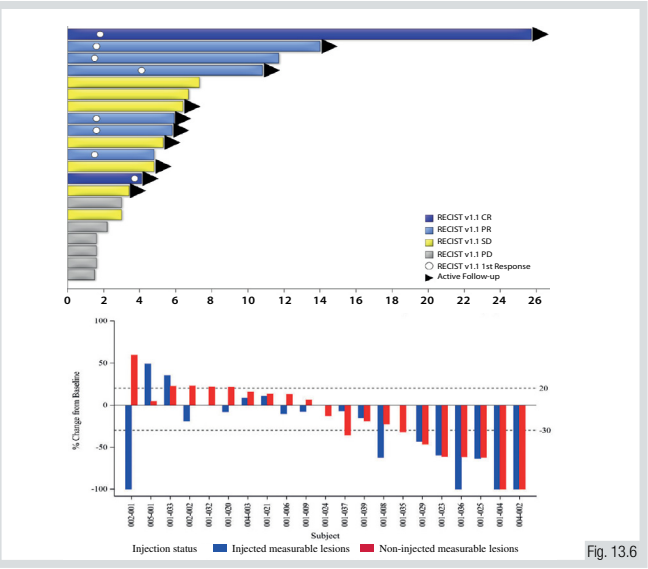


Fig. 13.6

CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.

REVISION QUESTIONS

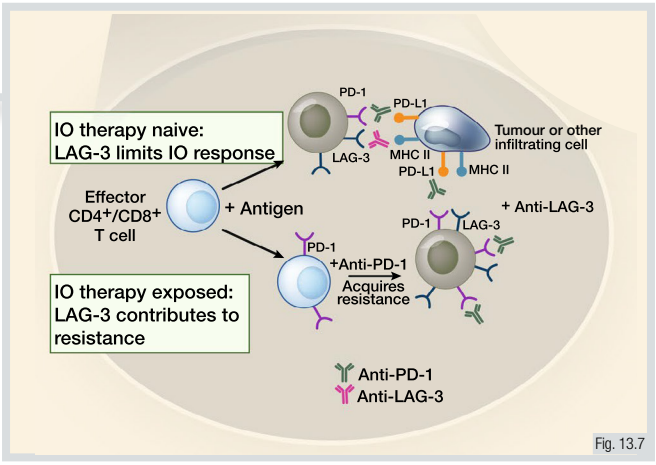
1. The combination of tilsotolimod plus ipilimumab is involved in which phase of the anti-melanoma immune response?
2. How is tilsotolimod administered?
3. What is the difference in response rate between the combination tilsotolimod plus ipilimumab compared with data from the literature on ipilimumab alone?

New anticancer agents for combinations – strength in unity

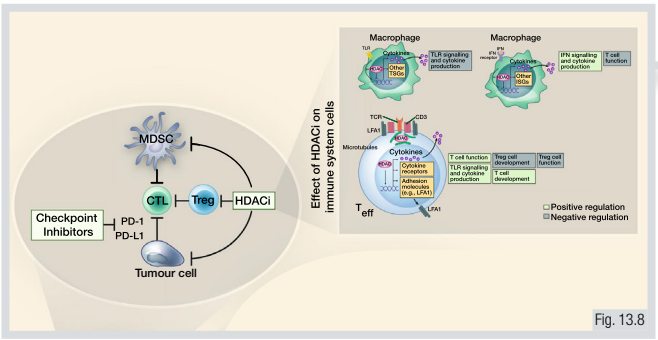
LAG-3 is an inhibitory receptor that, like PD-1 and T-cell immunoglobulin and mucin domain 3 (TIM-3), is expressed on the surface of CD8+ cells. LAG-3 binds to MHC class II of APCs, avoiding the link with T-cell receptor (TCR) and leading to T-cell dysfunction.

By blocking PD-1 and LAG-3 together it is possible to obtain a synergistic anticancer immune response and restore T-cell antitumour activity in melanoma resistant to anti PD-1 therapy.

Relatlimab (anti-LAG-3) combined with nivolumab in patients refractory to anti-PD-1 obtained ~20% response rate (RR) in melanoma positive for LAG-3. A phase III trial comparing the combination vs nivolumab alone, as first-line therapy, is ongoing.



IO, immuno-oncology; LAG-3, lymphocyte activation gene 3; MHC II, major histocompatibility complex class II; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.



HDAC, histone deacetylase; HDACi, histone deacetylase inhibitor; IFN, interferon; MDSC, myeloid-derived suppressor cell; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor; T_{eff}, effector T cell; TLR, toll-like receptor; Treg, T regulatory cell; TSG, tumour suppressor gene.

DNA is wrapped around histones. DNA expression is regulated by acetylation and deacetylation. Histone deacetylases (HDACs) are a class of enzymes that allow the histones to wrap the DNA more tightly.

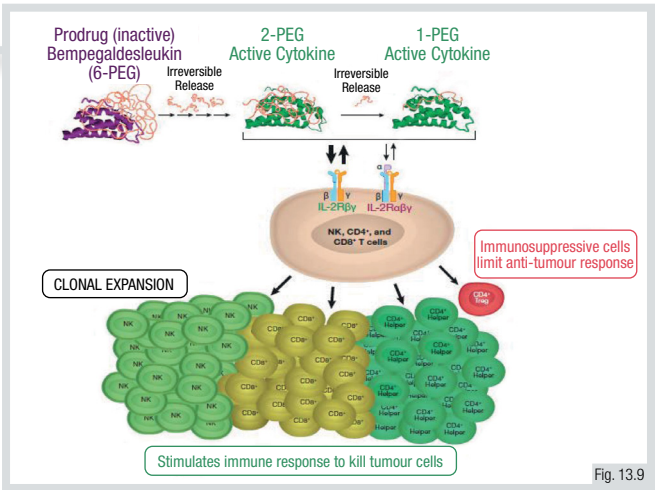
HDACis are a class of cytostatic agents that inhibit tumour growth by inducing cell-cycle arrest through modulating the acetylation/deacetylation of histones.

Entinostat (a HDACi) combined with pembrolizumab, in 53 patients refractory to anti-PD-1, had 19% ORR (1 CR, 9 PR) and 9 stable disease (SD) >6 months. Median duration of response (DoR) was 13 months. Other HDACis (e.g. domatinostat) to combine with ICIs are under development.

Bempegaldesleukin (NKTR-214) is a CD122-preferential interleukin (IL)-2 pathway agonist, which stimulates CD8+ and NK cells. CD122, the IL-2 receptor beta subunit, increases proliferation and expansion of effector T cells.

Bempegaldesleukin creates a favourable tumour microenvironment for combination with ICIs, increasing tumour-infiltrating lymphocytes (TILs), CD8+ and PD-1 expression, and converting programmed death-ligand 1 (PD-L1)-negative tumours to PD-L1-positive.

Bempegaldesleukin combined with nivolumab, as a first-line therapy in 38 melanoma patients, had 53% ORR with 34% CR. DCR was 74%. The combination was effective in M1C and elevated lactate dehydrogenase (LDH) patients. Median time to relapse (mTTR) was 2 months. A phase III trial is ongoing.



IL, interleukin; NK, natural killer; Treg, PEG, polyethylene glycol; T regulatory cell.

REVISION QUESTIONS

1. What is the mechanism of action of an anti-LAG-3?
2. How do HDACis work as anticancer drugs?
3. How do nivolumab and bempegaldesleukin synergise as an anti-melanoma treatment?

Summary: The most emerging targets and personalised medicine

- About 50% of MM patients treated with ICIs are alive at 10 years, but half of the patients have no benefit from the treatment
- Inflamed tumours, rich in intratumoural T cells, respond to immunotherapy, while immune-excluded and immune-desert tumours do not
- New combinatorial approaches try to make tumours that are not sensitive to immunotherapy, sensitive (making 'cold' tumours 'hot')
- TLR9 is located on APCs and regulates the 'presenting phase' of immune response
- TLR9 agonists stimulate a local response that becomes a systemic immune response
- Tilsotolimod plus ipilimumab demonstrated a good synergy and antitumour activity in patients refractory to anti-PD-1. Other TLR9 agonists, such as SD-101 and CMP-001, demonstrated good clinical activity with ICIs
- LAG-3 is an inhibitory receptor, located on T-lymphocytes, that binds to MHC II on APCs
- Relatlimab plus nivolumab obtained good responses in heavily pretreated patients
- HDACis are a class of cytostatic agents that inhibit tumour growth by inducing cell-cycle arrest, improving the antitumour immune response
- Entinostat plus pembrolizumab obtained good responses in patients refractory to anti-PD-1
- Bempegaldesleukin plus nivolumab improves the efficacy of anti-PD-1 therapy as first-line treatment of metastatic melanoma

Further Reading

Ascierto PA, Bono P, Bhatia S, et al. Efficacy of BMS-986016, a monoclonal antibody that targets lymphocyte activation gene-3 (LAG-3), in combination with nivolumab in pts with melanoma who progressed during prior anti–PD-1/PD-L1 therapy (mel prior IO) in all-comer and biomarker-enriched populations. Ann Oncol 2017; 28(suppl_5):V611-V612.

Ascierto PA, McArthur GA. Checkpoint inhibitors in melanoma and early phase development in solid tumors: what's the future? J Transl Med 2017; 15:173.

Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. Nature 2017; 541:321–330.

Diab A, Haymaker C, Bernatchez C, et al. Intratumoral (IT) injection of the TLR9 agonist tilsotolimod (IMO-2125) in combination with ipilimumab (ipi) triggers durable responses in PD-1 inhibitor refractory metastatic melanoma (rMM): results from a multicenter, phase I/II study. Ann Oncol 2018; 29(suppl_8):VIII442.

Diab A, Puzanov I, Maio M, et al. Clinical activity of BEMPEG plus NIVO in previously untreated patients with metastatic melanoma: updated results from the phase 1/2 PIVOT-02 study. J Immunother Cancer 2019; 7(Suppl 1):283.

Haymaker C, Uemura M, Hwu W-J, et al. TLR9 agonist harnesses innate immunity to drive tumor-infiltrating T-cell expansion in distant lesions in a phase 1/2 study of intratumoral IMO-2125+ipilimumab in anti-PD1 refractory melanoma patients. J Immunother Cancer 2017; 5(Suppl 2):86.

Marks PA, Rifkind RA, Richon VM, Breslow R. Inhibitors of histone deacetylase are potentially effective anticancer agents. Clin Cancer Res 2001; 7:759–760.

Sullivan RJ, Moschos SJ, Johnson ML. Efficacy and safety of entinostat (ENT) and pembrolizumab (PEMBRO) in patients with melanoma previously treated with anti-PD1 therapy. Cancer Res 2019; 79(13 Suppl):Abstract CT072-CT072.

Wang D, Jiang W, Zhu F, et al. Modulation of the tumor microenvironment by intratumoral administration of IMO-2125, a novel TLR9 agonist, for cancer immunotherapy. Int J Oncol 2018; 53:1193–1203.

Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2017; 377:1345–1356.

Appendix 1: AJCC TNM eighth edition staging system of melanoma of the skin

T—primary tumour			
T category		**Thickness**	**Ulceration status**
TX	Primary tumour thickness cannot be assessed (e.g. diagnosis by curettage)	Not applicable	Not applicable
T0	No evidence of primary tumour (e.g. unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma *in situ*)		Not applicable	Not applicable
T1		≤1.0 mm	Unknown or unspecified
T1a		<0.8 mm	Without ulceration
T1b		<0.8 mm	With ulceration
		0.8-1.0 mm	With or without ulceration
T2		>1.0-2.0 mm	Unknown or unspecified
T2a		>1.0-2.0 mm	Without ulceration
T2b		>1.0-2.0 mm	With ulceration
T3		>2.0-4.0 mm	Unknown or unspecified
T3a		>2.0-4.0 mm	Without ulceration
T3b		>2.0-4.0 mm	With ulceration
T4		>4.0 mm	Unknown or unspecified
T4a		>4.0 mm	Without ulceration
T4b		>4.0 mm	With ulceration

N—node		
N category	**Number of tumour-involved regional lymph nodes**	**Presence of in-transit, satellite, and/or microsatellite metastases**
NX	Regional nodes not assessed (e.g. sentinel lymph node biopsy [SLNB] not performed, regional nodes previously removed for another reason); Exception: pathological N category is not required for T1 melanomas, use clinical N information	No
N0	No regional metastases detected	No
N1	One tumour-involved node or any number of in-transit, satellite, and/or microsatellite metastases with no tumour-involved nodes	
N1a	One clinically occult (i.e.detected by SLNB)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumour-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with one tumour-involved node	
N2a	Two or three clinically occult (i.e. detected by SLNB)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumour-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with two or more tumour-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (i.e. detected by SLNB)	No
N3b	Four or more, at least one of which was clinically detected, or the presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

M—metastasis			
M category[a]		**Anatomical site**	**LDH level**
M0		No evidence of distant metastasis	Not applicable
M1		Evidence of distant metastasis	See below
M1a		Distant metastasis to skin, soft tissue including muscle and/or nonregional lymph node	Not recorded or unspecified
	M1a(0)		Not elevated
	M1a(1)		Elevated
M1b		Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
	M1b(0)		Not elevated
	M1b(1)		Elevated
M1c		Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
	M1c(0)		Not elevated
	M1c(1)		Elevated
M1d		Distant metastasis to CNS with or without M1a, M1b or M1c sites of disease	Not recorded or unspecified
	M1d(0)		Not elevated
	M1d(1)		Elevated

T	N	M	Pathological stage group
Tis	N0[b]	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b or N3c	M0	IIIC
T1a/b-T2a	N1a or N2a	M0	IIIA
T1a/b-T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a-T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV

[a]Suffixes for M category: (0) LDH not elevated, (1) LDH elevated. No suffix is used if LDH is not recorded or is unspecified.
[b]Pathological stage 0 (melanoma *in situ*) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging; use clinical N information to assign their pathological stage.
AJCC, American Joint Committee on Cancer; CNS, central nervous system; LDH, lactate dehydrogenase; SLNB, sentinel lymph node biopsy; TNM, tumour, node, metastasis; Tis, tumour *in situ*.

Appendix 2: AJCC TNM eighth edition staging system of Merkel cell carcinoma of skin

Classification system for Merkel cell carcinoma of skin		
T category		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Tis	Carcinoma *in situ*	
T1	Greatest tumour dimension ≤2 cm	
T2	Greatest tumour dimension >2 cm but ≤5 cm	
T3	Greatest tumour dimension >5 cm	
T4	Primary tumour invades deep extradermal structures, i.e., cartilage, skeletal muscle, fascia or bone	
N category		
NX		Regional lymph nodes cannot be assessed
N0		No involvement of nearby lymph nodes as determined clinically/radiologically
	pN0	Absence of lymph node involvement on biopsy
N1		Metastasis to regional lymph nodes
	pN1	Confirmed in biopsy
	pN1a	Clinically occult, detected by lymph node dissection
	pN1a(sn)	Clinically occult, detected by SLNB
	pN1b	Detected clinically or radiologically and confirmed in biopsy
N2		In-transit metastasis without lymph node metastasis
	pN2	In-transit metastasis confirmed in biopsy without lymph node metastasis
N3		In-transit metastasis with regional lymph node metastasis
	pN3	In-transit metastasis with regional lymph node metastasis confirmed in biopsy
M category		
M0		No clinical/radiological evidence of distant metastasis
M1		
	M1a	Cutaneous or subcutaneous distant metastasis or distant but not regional lymph node metastasis
	M1b	Pulmonary metastasis
	M1c	Metastasis in other viscera

Staging system for Merkel cell carcinoma of skin			
T	**N**	**M**	**Pathological stage group**
Tis	N0	M0	0
T1	N0	M0	I
T2-T3	N0	M0	IIA
T4	N0	M0	IIB
T1-T4	N1a(sn) or N1a	M0	IIIA
T0	N1b	M0	IIIB
T1-T4	N1b-N3	M0	IIIC
T0-T4	N0-N3	M1	IV

AJCC, American Joint Committee on Cancer; SLNB, sentinel lymph node biopsy; TNM, tumour, node, metastasis; Tis, tumour *in situ*.

Appendix 3: AJCC TNM eighth edition staging system of skin carcinoma of the head and neck

The classification applies only to cutaneous carcinomas of the head and neck region excluding the eyelid and excluding Merkel cell carcinoma and malignant melanoma.

Classification system for skin carcinoma of the head and neck		
T category		
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
Tis		Carcinoma *in situ*
T1		Greatest dimension <2 cm
T2		Greatest tumour dimension >2 cm but <4 cm
T3		Greatest tumour dimension ≥4 cm or minimal erosion of the bone or perineural invasion or deep invasion[a]
T4	T4a	Tumour with extensive cortical or medullary bone involvement
	T4b	Invasion of the base of the cranium or invasion through the foramen of the base of the cranium
N category		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in an isolated ipsilateral lymph node ≤3 cm in greatest dimension, ENE (-)
N2	N2a	Metastasis in an isolated ipsilateral lymph node 3-6 cm in greatest dimension, ENE (-)
	N2b	Metastasis in multiple ipsilateral lymph nodes <6 cm, ENE (-)
	N2c	Metastasis in bilateral or contralateral lymph nodes, <6 cm, ENE (-)
N3	N3a	Metastasis in a lymph node >6 cm, ENE (-)
	N3b	Metastasis in any lymph node(s) and ENE (+)
M category		
M0		Absence of distant metastasis
M1		Distant metastasis

AJCC TNM staging system for skin carcinoma of the head and neck			
T	**N**	**M**	**Pathological stage group**
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1-T3	N1	M0	III
T1-T3	N2, N3	M0	IVA
T4	Any N	M0	IVA
Any T	Any N	M1	IVB

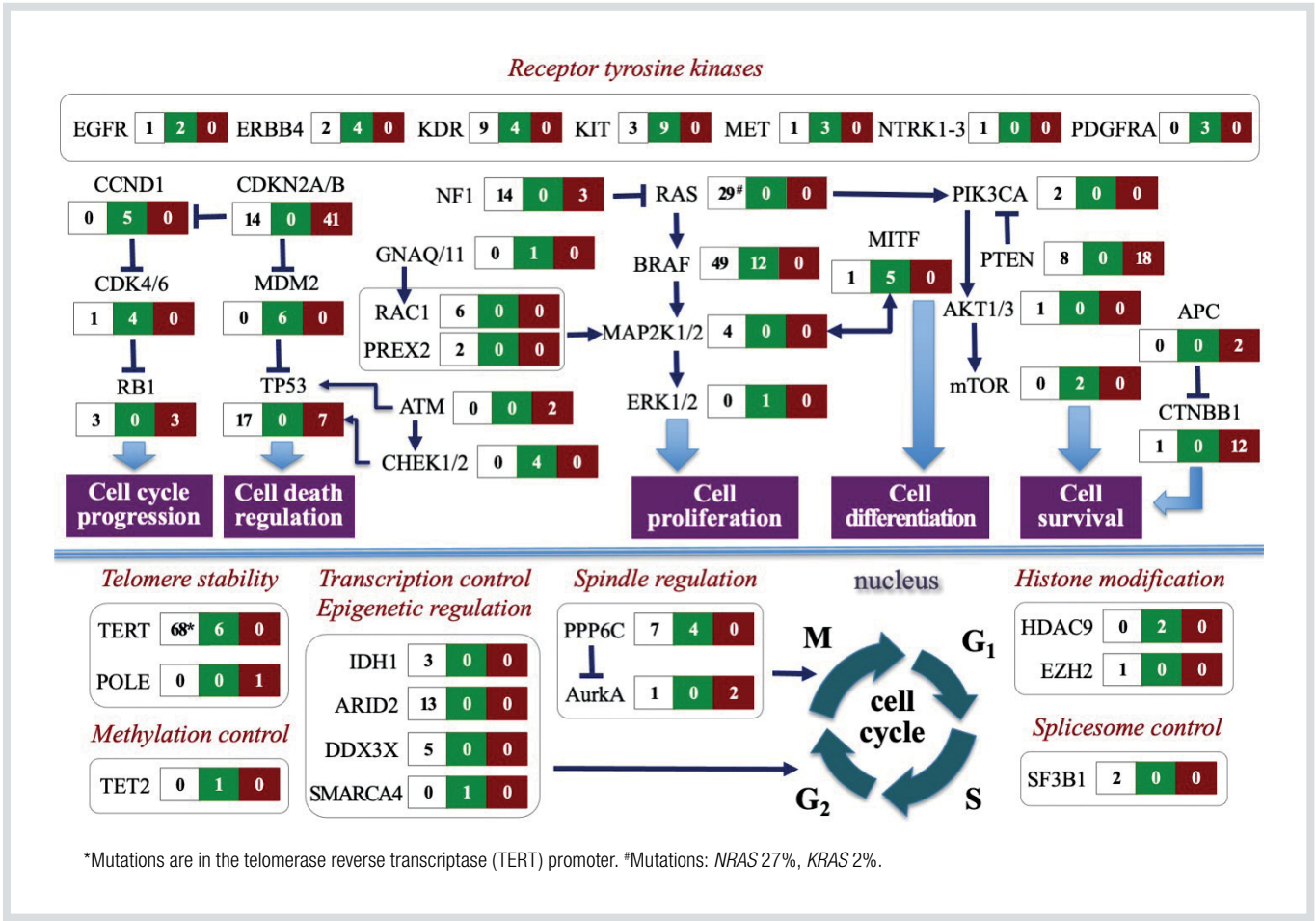
[a]Deep invasion defined as thickness greater than 6 mm or invasion deeper than subcutaneous fat. For a tumour to be T3, perineural invasion should be present in nerves greater than 0.1 mm, deeper than the dermis, or clinical and radiological involvement of affected nerves without involvement or invasion of the base of the cranium.
AJCC, American Joint Committee on Cancer; ENE, extranodal or extracapsular extension defined as extension through the lymph node capsule in the surrounding connective tissue with or without stromal reaction; Tis, tumour *in situ*; TNM, tumour, node, metastasis.

Appendix 4: Melanoma pathways

Pathway I. Genes recurrently altered in low chronic sun damage melanoma/superficial spreading melanoma

Pathways associated with intracellular mitogen-activated protein kinase (MAPK): RAS-BRAF-MAPK kinase (MAP2K)-extracellular signal-regulated kinase (ERK), cyclin-dependent kinase inhibitor 2A (CDKN2A), melanocyte-inducing transcription factor (MITF) and PIK3CA-phosphatase and tensin homologue (PTEN)-AKT are represented.

Arrows (↓), activating signals; interrupted lines (⊥), inhibiting signals. Percentage of samples with pathogenic mutations or protein-affecting alterations (white box), copy number amplifications (green box) and copy number deletions (red box) are reported.



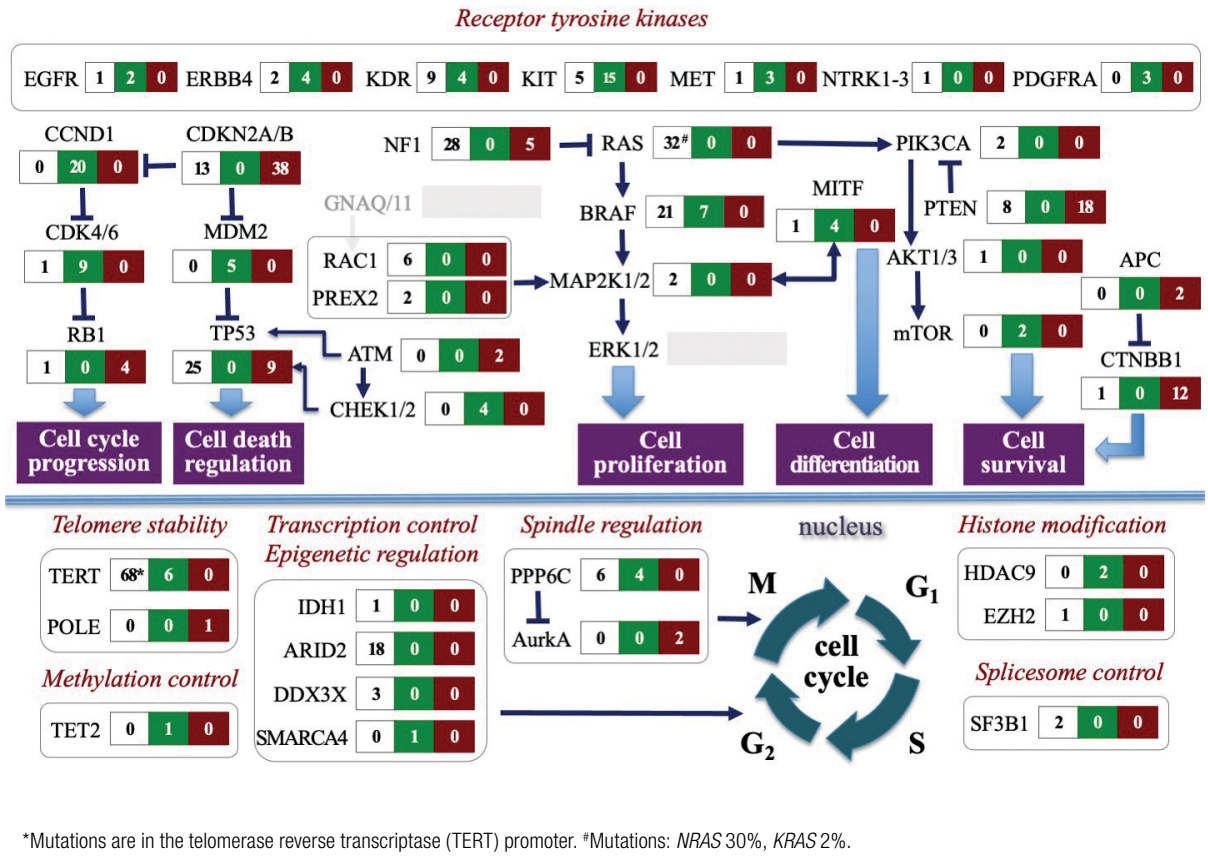
*Mutations are in the telomerase reverse transcriptase (TERT) promoter. #Mutations: *NRAS* 27%, *KRAS* 2%.

APC, adenomatous polyposis coli; ARID2; AT-rich interaction domain 2; AurkA, aurora kinase A; CCND1, cyclin D1; CDK4/6, cyclin-dependent kinase 4/6; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; CHEK1/2, checkpoint kinase 1/2; DDX3X, DEAD-box helicase 3 X-linked; EGFR, epidermal growth factor receptor; ERK1/2, extracellular signal-regulated kinase 1/2; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; HDAC9, histone deacetylase 9; IDH1, isocitrate dehydrogenase 1; KDR, kinase insert domain receptor; MAP2K1/2, mitogen-activated protein kinase kinase 1/2; MITF, melanocyte-inducing transcription factor; mTOR, mammalian target of rapamycin; NF1, neurofibromin 1; NTRK1-3, neurotrophic tyrosine receptor kinase 1-3; PDGFRA, platelet-derived growth factor receptor alpha; PPP6C, protein phosphatase 6 catalytic subunit; PREX2, phosphatidylinositol-3,4,5-trisphosphate dependent Rac exchange factor 2; PTEN, phosphatase and tensin homologue; SF3B1, splicing factor 3b subunit 1; TTP53, tumour protein 53; TET2, Tet methylcytosine dioxygenase 2.

Pathway II. Genes recurrently altered in high chronic sun damage melanoma/lentigo-maligna melanoma

The pathways involved are the same as for low chronic sun damage (CSD) melanoma: MAPK, CDKN2A, MITF and PTEN-AKT; the differences are the mutation frequencies for some main driver cancer genes.

Arrows (⇩), activating signals; interrupted lines (⊥), inhibiting signals. Percentage of samples with pathogenic mutations or protein-affecting alterations (white box), copy number amplifications (green box) and copy number deletions (red box) are reported.



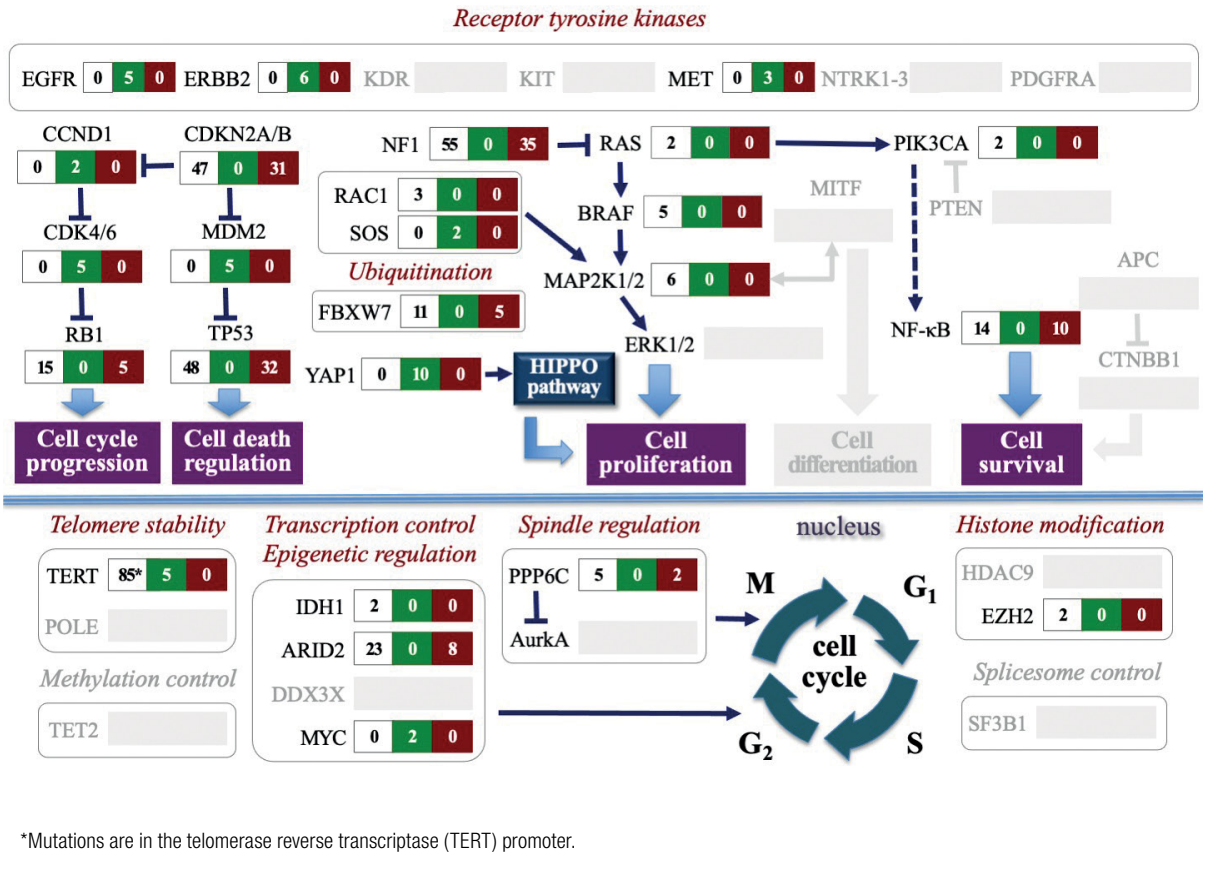
*Mutations are in the telomerase reverse transcriptase (TERT) promoter. #Mutations: *NRAS* 30%, *KRAS* 2%.

APC, adenomatous polyposis coli; ARID2; AT-rich interaction domain 2; AurkA, aurora kinase A; CCND1, cyclin D1; CDK4/6, cyclin-dependent kinase 4/6; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; CHEK1/2, checkpoint kinase 1/2; DDX3X, DEAD-box helicase 3 X-linked; EGFR, epidermal growth factor receptor; ERK1/2, extracellular signal-regulated kinase 1/2; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; HDAC9, histone deacetylase 9; IDH1, isocitrate dehydrogenase 1; KDR, kinase insert domain receptor; MAP2K1/2, mitogen-activated protein kinase kinase 1/2; MITF, melanocyte-inducing transcription factor; mTOR, mammalian target of rapamycin; NF1, neurofibromin 1; NTRK1-3, neurotrophic tyrosine receptor kinase 1-3; PDGFRA, platelet-derived growth factor receptor alpha; PPP6C, protein phosphatase 6 catalytic subunit; PREX2, phosphatidylinositol-3,4,5-trisphosphate dependent Rac exchange factor 2; PTEN, phosphatase and tensin homologue; SF3B1, splicing factor 3b subunit 1; TP53, tumour protein 53; TET2, Tet methylcytosine dioxygenase 2

Pathway III. Genes recurrently altered in desmoplastic melanoma

The pathways involved are mostly CDKN2A (with high incidence of copy number aberrations) and to a lesser extent MAPK (low mutation rates in *BRAF* and *RAS* genes) and the PIK3CA (with high involvement of the downstream nuclear factor kappa B [*NF-κB]* gene).

Arrows (⇩), activating signals; interrupted lines (⊥), inhibiting signals. Percentage of samples with pathogenic mutations or protein-affecting alterations (white box), copy number amplifications (green box) and copy number deletions (red box) are reported.



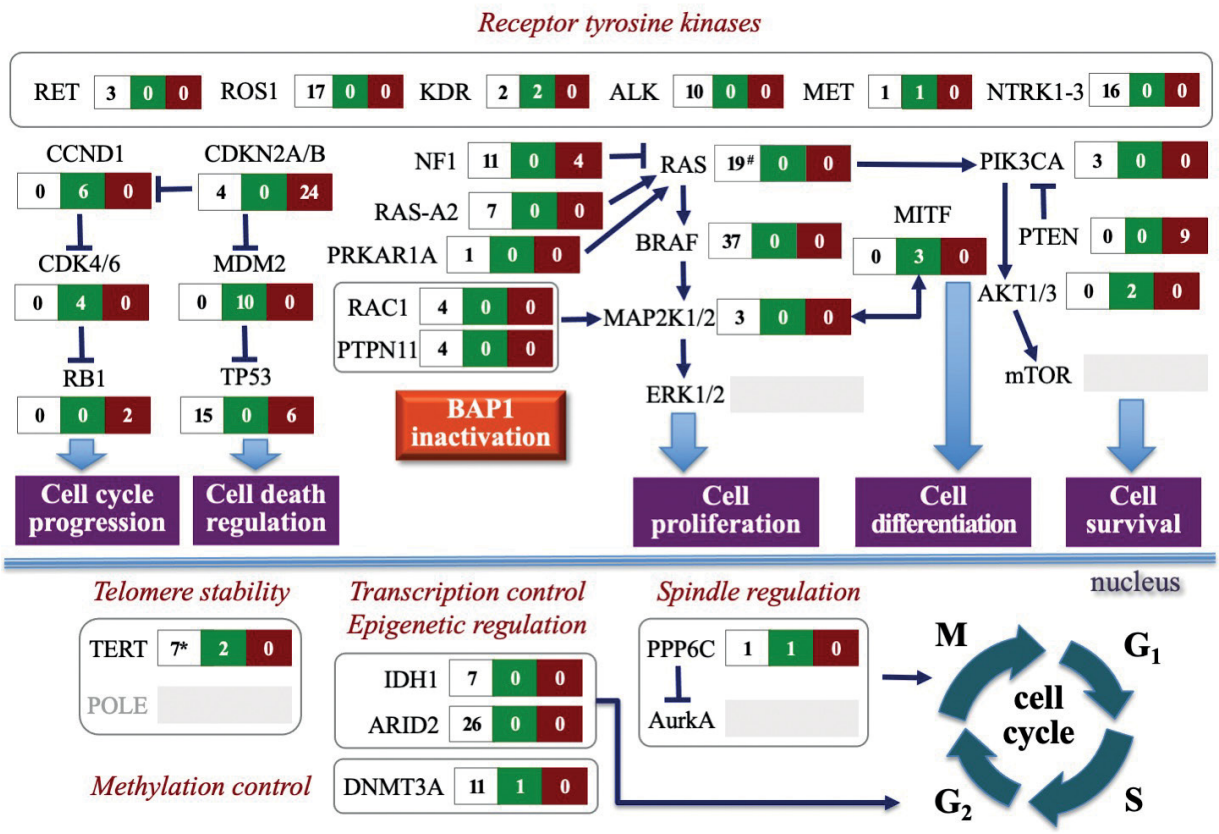
*Mutations are in the telomerase reverse transcriptase (TERT) promoter.

APC, adenomatous polyposis coli; ARID2; AT-rich interaction domain 2; AurkA, aurora kinase A; CCND1, cyclin D1; CDK4/6, cyclin-dependent kinase 4/6; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; DDX3X, DEAD-box helicase 3 X-linked; EGFR, epidermal growth factor receptor; ERK1/2, extracellular signal-regulated kinase 1/2; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; HDAC9, histone deacetylase 9; IDH1, isocitrate dehydrogenase 1; KDR, kinase insert domain receptor; MAP2K1/2, mitogen-activated protein kinase kinase 1/2; MITF, melanocyte-inducing transcription factor; NF1, neurofibromin 1; NF-κB, nuclear factor kappa B; NTRK1-3, neurotrophic tyrosine receptor kinase 1-3; PDGFRA, platelet-derived growth factor receptor alpha; PPP6C, protein phosphatase 6 catalytic subunit; PTEN, phosphatase and tensin homologue; SF3B1, splicing factor 3b subunit 1; TP53, tumour protein 53; TET2, Tet methylcytosine dioxygenase 2; YAP1, yes associated protein 1.

Pathway IV. Genes recurrently altered in Spitz melanoma/malignant Spitz tumour

The main pathway involved is MAPK (higher prevalence of activating *HRAS* mutations as compared with other melanoma types); a large percentage of Spitz melanomas (SMs) carry fusion mutations in tyrosine kinase receptor genes (with the highest rates in neurotrophic tyrosine receptor kinase 1-3 [*NTRK1-3*]).

Arrows (↓), activating signals; interrupted lines (⊥), inhibiting signals. Percentage of samples with pathogenic mutations or protein-affecting alterations (white box), copy number amplifications (green box) and copy number deletions (red box) are reported.



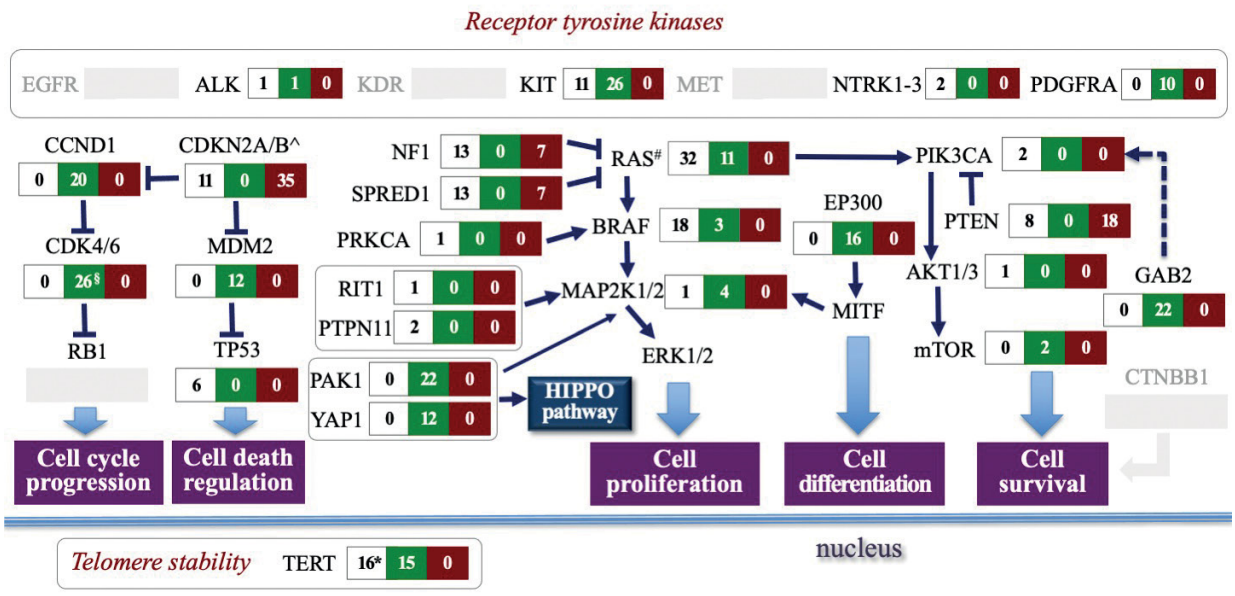
*Mutations are in the telomerase reverse transcriptase (TERT) promoter. #Mutations: *NRAS* 13%, *HRAS* 6%.

ALK, anaplastic lymphoma kinase; ARID2; AT-rich interaction domain 2; AurkA, aurora kinase A; BAP1, BRCA1 associated protein 1; CCND1, cyclin D1; CDK4/6, cyclin-dependent kinase 4/6; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; ERK1/2, extracellular signal-regulated kinase 1/2; IDH1, isocitrate dehydrogenase 1; KDR, kinase insert domain receptor; MAP2K1/2, mitogen-activated protein kinase kinase 1/2; MITF, melanocyte-inducing transcription factor; mTOR, mammalian target of rapamycin; NF1, neurofibromin 1; NTRK1-3, neurotrophic tyrosine receptor kinase 1-3; PPP6C, protein phosphatase 6 catalytic subunit; PTEN, phosphatase and tensin homologue; PTPN11, protein tyrosine phosphatase non-receptor type 11; TP53, tumour protein 53.

Pathway V. Genes recurrently altered in acral melanoma

The main pathway involved remains MAPK, directly with the highest frequency of *RAS* mutations, or indirectly through genes activating the pathway.

Arrows (⇩), activating signals; interrupted lines (⊥), inhibiting signals. Percentage of samples with pathogenic mutations or protein-affecting alterations (white box), copy number amplifications (green box) and copy number deletions (red box) are reported.



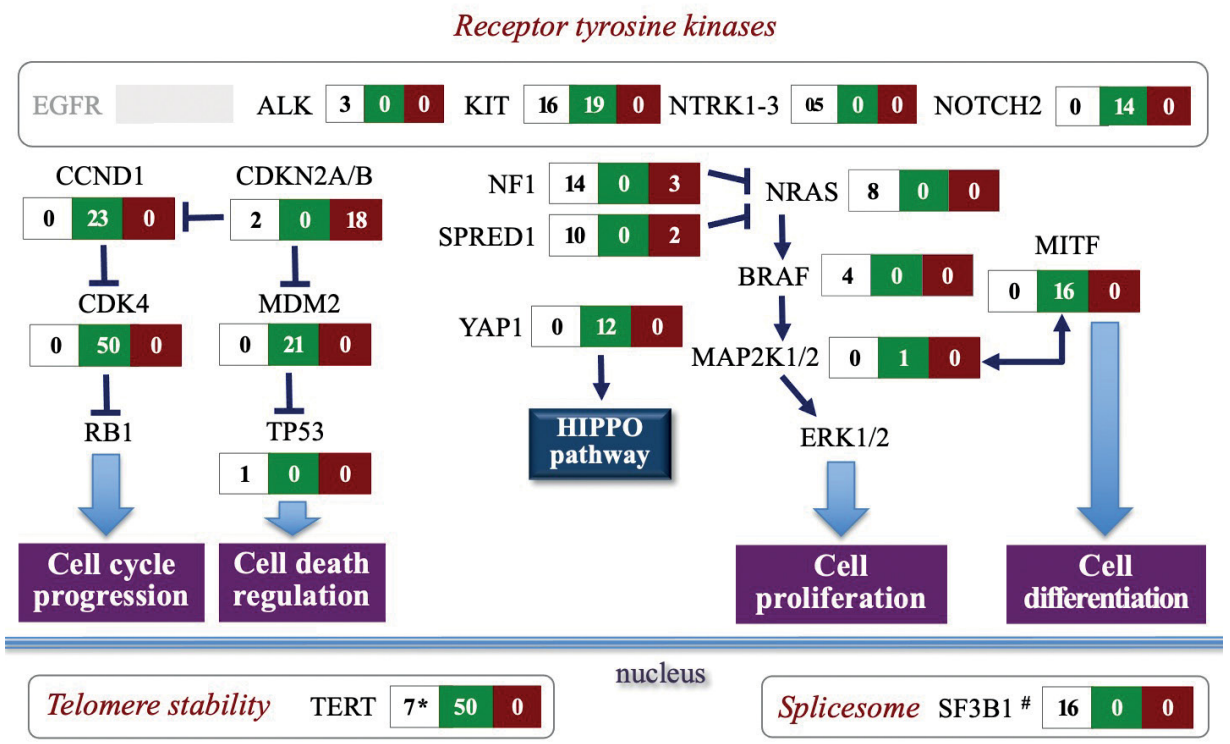
*>50% mutations are in the telomerase reverse transcriptase (TERT) promoter (the remaining ones are structural alterations)
§*CDK4*, 22%; *CDK6* 4%
^46% cases presented cyclin-dependent kinase inhibitor 2A (*CDKN2A*) inactivation (also by epigenetic mechanisms)
#Mutated: *NRAS* 20%, *KRAS* 10%, and *HRAS* 2%; Amplified: *NRAS* 3%, *KRAS* 7%, *HRAS* 1%.

ALK, anaplastic lymphoma kinase; CCND1, cyclin D1; CDK4/6, cyclin-dependent kinase 4/6; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; EGFR, epidermal growth factor receptor; IDH1, isocitrate dehydrogenase 1; ERK1/2, extracellular signal-regulated kinase 1/2; KDR, kinase insert domain receptor; MAP2K1/2, mitogen-activated protein kinase kinase 1/2; MITF, melanocyte-inducing transcription factor; mTOR, mammalian target of rapamycin; NF1, neurofibromin 1; NTRK1-3, neurotrophic tyrosine receptor kinase 1-3; PDGFRA, platelet-derived growth factor receptor alpha; PTEN, phosphatase and tensin homologue; TP53, tumour protein 53; YAP1, yes associated protein 1.

Pathway VI. Genes recurrently altered in mucosal melanoma

The common drivers (*BRAF* and *NRAS*) found in cutaneous melanoma have lower mutation rates; *KIT* and splicing factor 3b subunit 1 (*SF3B1*) are the most frequently mutated genes. Overall, the main molecular characteristics are the gene copy number alterations.

Arrows (↓), activating signals; interrupted lines (⊥), inhibiting signals. Percentage of samples with pathogenic mutations or protein-affecting alterations (white box), copy number amplifications (green box) and copy number deletions (red box) are reported.



*Mutations are in the telomerase reverse transcriptase (TERT) promoter. #27% in lower gastrointestinal (GI), anorectal, and genital; 7% in head and neck, and upper GI.

ALK, anaplastic lymphoma kinase; CCND1, cyclin D1; CDK4, cyclin-dependent kinase 4; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; EGFR, epidermal growth factor receptor; ERK1/2, extracellular signal-regulated kinase 1/2; MAP2K1/2, mitogen-activated protein kinase kinase 1/2; MITF, melanocyte-inducing transcription factor; NF1, neurofibromin 1; NTRK1-3, neurotrophic tyrosine receptor kinase 1-3; NOTCH2, notch receptor 2; SF3B1, splicing factor 3b subunit 1; TP53, tumour protein 53; YAP1, yes associated protein 1.

Image sources

The authors acknowledge with gratitude the following sources of the images used in this publication.

Chapter 1
Figure 1. Schadendorf D, et al. Lancet 2018;392:971-984; **2.** Ferlay J, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today (date last accessed, 3 August 2021); **3.** Gershenwald JE, et al. CA Cancer J Clin 2017;67:472-492; **4, 6-9, 11, 14.** courtesy Department of Dermatology, University Hospital Essen; **5.** courtesy Cancer Council Australia; **10, 12.** Lomas A, et al. Br J Dermatol 2012;166:1069-108013; **13.** Becker JC, et al. Cancer Immunol Immunother 2018;67:341-351; **15.** courtesy Euromelanoma.

Chapter 2
Figure 1. used with the permission of the American College of Surgeons. Amin MB, Edge SB, Greene FL, et al. (Eds.) AJCC Cancer Staging Manual, 8th Ed. Springer New York, 2017; **2, 7.** courtesy Department of Nuclear Medicine, University Hospital Zurich; **3-6, 8-10, 14.** courtesy University Hospital Zurich; **11-13.** Gershenwald JE, et al. CA Cancer J Clin 2017;67:472-492; **15.** Weide B, et al. Br J Cancer 2012;107:422-428.

Chapter 3
Figure 2. © 2010 Terese Winslow LLC, U.S. Govt. has certain rights; **3.** © 2008 Terese Winslow LLC, U.S. Govt. has certain rights; **4.** Morton DL, et al. N Engl J Med 2014;370:599-609; **5.** Faries MB, et al. N Engl J Med 2017;376:2211-2222; **6.** Henderson MA, et al. Lancet Oncol 2015;16:1049-1060; **7.** Weber J, et al. N Engl J Med 2017;377:1824-1835; **8.** Long GV, et al. N Engl J Med 2017;377:1813-1823; **9.** courtesy O Michielin, presented at ASCO 2018 Annual Meeting.

Chapter 4
Figure 1. Henderson MA, et al. Lancet Oncol 2015;16:1049-1060; **2.** Ives NJ, et al. Eur J Cancer 2017;82:171-183; **3.** Eggermont AMM, et al. Eur J Cancer 2019;119:1-10; **4.** Eggermont AMM, et al. N Engl J Med 2018;378:1789-1801; **5.** Long GV, et al. N Engl J Med 2017;377:1813-1823; **6.** Rozeman EA, et al. Lancet Oncol 2019;20:948-960.

Chapter 5
Figures 1 and 5. courtesy M Zdzienicki; **2.** used with the permission of the American College of Surgeons. Amin MB, Edge SB, Greene FL, et al. (Eds.) AJCC Cancer Staging Manual, 8th Ed. Springer New York, 2017; **3.** Costa J, et al. Br J Dermatol 2013;169:91-99; **4.** used with permission of Mayo Foundation for Medical Education and Research, all rights reserved; **6.** Aspord C, et al. J Invest Dermatol 2014;134:2551-2561; **7.** Johnson DB, et al. Immunotherapy 2015;7:611-619; **8.** Andtbacka RHI, et al. J Immunother Cancer 2019;7:145; **9.** Thompson JF, et al. Melanoma Res 2008;18:405-411; **10, 12.** Olofsson Bagge R, et al. Int J Hyperthermia 2018;35:667-673; **11.** courtesy Piotr Rutkowski; **13.** Wilgenhof S, et al. Cancer Invest 2012;30:712-720.

Chapter 6
Figure 2. Cancer World, no 76, January/February 2017; **3.** Gowrishankar K, et al. Acquired resistance to targeted MAPK inhibition in melanoma. In: Duc GHT (ed.) Melanoma - From Early Detection to Treatment; InTech 2013, https://www.intechopen.com/books/melanoma-from-early-detection-to-treatment (date last accessed, 3 August 2021); **5.** Wang DY, et al. Cancer J 2018;24:36-40; **6.** Hodi FS, et al. N Engl J Med 2010;363:711-723; **7.** courtesy J Larkin, LBA68_PR presented at ESMO 2019, Ann Oncol 2019;30(Suppl 5):v904-v905; **8.** Gutzmer R, et al. Lancet 2020;395:1835-1844; **9.** Haitz K, et al. J Am Acad Dermatol 2020;83:189-196; **10.** Larkin J, et al. N Engl J Med 2014;371:1867-1876; **12.** Dummer R, et al. Lancet Oncol 2018;19:603-615; **13.** Dummer R, et al. Lancet Oncol 2017;18:435-445; **14.** Frelaut M, et al. Int J Mol Sci 2019;20:2674; **15.** Choi C, et al. World J Gastroenterol 2019;25:2416-2429.

Chapter 7
Figure 1. adapted from Barnholtz-Sloan JS, et al. J Clin Oncol 2004;22:2865-2872; **2.** used with the permission of the American College of Surgeons. Amin MB, Edge SB, Greene FL, et al. (Eds.) AJCC Cancer Staging Manual, 8th Ed. Springer New York, 2017; **5.** Hong A, et al. J Clin Oncol 2019;37:3132-3141; **6.** Oskan F, et al. Strahlenther Onkol 2014;190:337-341; **7.** Stokes WA, et al. J Neuroimmunol 2017;313:118-122; **8.** Patel U, et al. Transl Cancer Res 2014;3:373-382; **9.** Jardim A, et al. J Neurooncol 2019;145:581-585; **10.** Robert C, et al. N Engl J Med 2019;381:626-636; **11.** Davies MA, et al. Lancet Oncol 2017;18:863-873; **12.** adapted from Davies MA, et al. Lancet Oncol 2017;18:863-873; **13.** Hodi FS, et al. Lancet Oncol 2018;19:1480-1492; **14.** Tawbi HA, et al. N Engl J Med 2018;379:722-730; **15.** Long GV, et al. Lancet Oncol 2018;19:672-681.

Chapter 8 and Appendix 4
All figures courtesy of D Massi & G Palmieri.

Chapter 9
All figures courtesy of M Słowińska.

Chapter 10
Figure 1. Peris K, et al. Eur J Cancer 2019;118:10-34; **2, 3, 5, 6, 8-11.** courtesy Dermatology and Pathology units, Saint-Louis Hospital, Paris; **4.** Karia PS, et al. J Am Acad Dermatol 2013;68:957-966; **7.** Kieny A, et al. Int J Cancer 2019;144:741-745; **12.** Stam H, et al. J Surg Oncol 2013;107:822-827.

Chapter 11
Figure 1. left: Millodot M. Dictionary of Optometry and Visual Science, 7th edition, 2009. Butterworth-Heinemann; **right:** Nassar KW & Tan AC. Semin Cancer Biol 2020;61:139-148; **2.** Robertson AG, et al. Cancer Cell 2017;32:204-220.e15; **3.** Farquhar N, et al. J Pathol Clin Res 2017;4:26-38; **4.** Alexander HR Jr & Butler CC. Cancer J 2010;16:132-141; **5.** Khoja L, et al. Ann Oncol 2019;30:1370-1380; **6.** courtesy Immunocore; **7.** Nassar KW & Tan AC. Semin Cancer Biol 2020;61:139-148; **8.** D'Angelo SP, et al. J Clin Oncol 2017;35:226-235; **9.** Carvajal RD, et al. JAMA 2011;305:2327-2334.

Chapter 12
Figure 1. Larkin J, et al. N Engl J Med 2019;381:1535-1546; **2.** Robert C, et al. N Engl J Med 2019;381:626-636; **3.** Wolchok JD, et al. N Engl J Med 2017;377:1345-1356; **8.** Hugo W, et al. Cell 2015;162:1271-1285; **9.** Long GV, et al. Lancet Oncol 2016;17:1743-1754.

Chapter 13
Figure 1. courtesy PA Ascierto; **2.** van der Woude LL, et al. Trends Cancer 2017;3:797-808; **3.** Hu-Lieskovan S & Ribas A. Cancer J 2017;23:10-22; **4.** courtesy Idera Pharma; **5, 6.** courtesy A Diab, poster 1245PD presented at ESMO 2018, Ann Oncol 2018;29(Suppl 8):viii442; **7, 8.** Ascierto PA & McArthur GA. J Transl Med 2017;15:173; **9.** courtesy A Diab, from: Diab A, et al. J Immunother Cancer 2020;8(Suppl 3):SITC2020.0420.

While every effort has been made to contact the copyright holders of all images, the publisher would be grateful for any additional information about any images where they have been unable to trace or obtain permissions and will be glad to make amendments in future editions.

Declarations of interest

PA Ascierto: Consultant/advisory role: Bristol-Myers Squibb, Roche-Genentech, Merck Sharp & Dohme, Novartis, Array, Merck Serono, Pierre Fabre, Incyte, NewLink Genetics, Genmab, Medimmune, AstraZeneca, Syndax, Sun Pharma, Sanofi, Idera, Ultimovacs, Sandoz, Immunocore, 4SC Alkermes; stock ownership: Primevax; research funding: Bristol-Myers Squibb, Roche-Genentech, Array; travel support: Merck Sharp & Dohme.

M Battistella: Consulting: Innate-Pharma, Leo Pharma, Bristol-Myers Squibb, Takeda, Kyowa Kyrin; congress expenses: Roche.

R Dummer: Research funding: Novartis, Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, GlaxoSmithKline; consultant or advisory-board relationships: Novartis, Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, GlaxoSmithKline, Amgen.

AMM Eggermont: Personal fees as consultant advisor: Biocad, BioInvent, Bristol-Myers Squibb, CatalYm, Ellipses, GlaxoSmithKline, HalioDX, Incyte, IO Biotech, ISA Pharmaceuticals, Merck Sharp & Dohme, Novartis, Pfizer, Polynoma, Regeneron, Sanofi, Sellas, SkylineDx.

F Herms: Consulting: Sanofi-Aventis; congress expenses: Sun Pharma.

AM Grimaldi: Consultant/advisory role: Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis; travel support: Bristol-Myers Squibb, Novartis, Merck Serono, Pierre Fabre, Roche.

K Homicsko: No conflict of interest.

C Kelly: No conflict of interest.

C Lebbé: Consulting: Bristol-Myers Squibb, Merck Sharp & Dohme, Sanofi-Aventis, Merck, Roche, Novartis, Pierre Fabre; congress expenses: Roche, Bristol-Myers Squibb.

I Lugowska: Honoraria: Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Janssen, AstraZeneca, Amgen, Pfizer, Boehringer Ingelheim, Novartis, Checkpoint, Agenus, Macrogenics, Incyte, Celon, Takeda, Genmab, Loxo, Menarini, Blueprint, Odonate, Debio; research grants for IST: Agenus, Roche.

D Massi: No conflict of interest.

GA McArthur: Coordinating PI (costs for activities on clinical trials reimbursed to institute): Genentech Roche, Pfizer; advisory board: Novartis, Bristol-Myers Squibb, Canthera; director: Melanoma World Society.

O Michielin: No conflict of interest.

P Nathan: Honoraria for advisory board membership, speaker's fees and/or support for meeting attendance: AstraZeneca, Bristol-Myers Squibb, Delcath, Immunocore, Ipsen, Merck, Merck Sharp & Dohme, Novartis, Pfizer, Roche, 4SC.

G Palmieri: No conflict of interest.

R Plummer: No conflict of interest.

E Ramelyte: Consultant relationships: Amgen.

P Rutkowski: Honoraria for lectures and advisory board: Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Pierre Fabre, Roche, Amgen, Blueprint Medicines.

JJ Sacco: Honoraria: Bristol-Myers Squibb, Immunocore, Pierre Fabre, Novartis; travel and conference expenses: Bristol-Myers Squibb, Merck Sharp & Dohme, Immunocore; advisory boards: Immunocore, Delcath, Merck Sharp & Dohme, Amgen; research funding (through institution): AstraZeneca, Bristol-Myers Squibb, Immunocore.

D Schadendorf: Personal fees, advisory boards and patient's fees: Pierre Fabre, Merck-EMD, Amgen, Roche, Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Regeneron, 4SC, Incyte, Philogen; personal fees: Boehringer Ingelheim, Leo Pharma, Sanofi, Neracare, InflaRX, Pfizer, Array.

M Slowinska: No conflict of interest.

ACJ van Akkooi: Advisory board/consultancy: Amgen, Bristol-Myers Squibb, Novartis, Merck Sharp & Dohme-Merck, Merck-Pfizer, Pierre Fabre, Sanofi, Sirius Medical, 4SC; research grant: Amgen, Merck-Pfizer.

A Zaremba: Travel support: Novartis, Bristol-Myers Squibb.

M Zdzienicki: Speaker fees: Novartis, Merck Sharp & Dohme; local PI: Amgen (personal and institute fees).

Index

Note: Abbreviations used in the index are listed on page x

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

www.esmo.org

MELANOMA & OTHER SKIN CANCERS

ESSENTIALS *for* CLINICIANS

edited by
Paolo A. Ascierto
Iwona Lugowska
Ruth Plummer

Melanoma is the most aggressive form of skin cancer and its incidence has been rising over the last decade. Fortunately, advances in disease knowledge and a multidisciplinary treatment strategy have changed how we evaluate and treat patients. *Melanoma & Other Skin Cancers: Essentials for Clinicians* has been designed to provide an overview of the epidemiology, pathology and current and innovative evidence-based treatment options for patients with all stages of melanoma and other skin cancers. The content is organised in two sections. Part A, *'What every oncologist should know'* discusses epidemiology, prevention, screening and surveillance as well as staging, prognostic factors and treatment. Part B, *'More advanced knowledge'* explores advances in research and treatment, pathology and molecular profiles, predictive biomarkers and, finally, emerging targets and personalised medicine.

Series Editor
Michele Ghielmini

ESMO Press

ESMO Press · ISBN 978-88-944465-3-1

9 788894 446531