Management of advanced melanoma

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Management of Advanced Melanoma

GRADUATE THESIS

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Abbreviations

WHO – World Health Organization
CSD – Cumulative Solar Damage
RGP – Radial Growth Phase
VGP – Vertical Growth Phase
AJCC – American Joint Committee on Cancer
RCT – Randomized Controlled Trial
SLN – Sentinel Lymph Node
SLNB – Sentinel Lymph Node Biopsy
CLND – Complete Lymph Node Dissection
RFS – Relapse-Free Survival
OS – Overall Survival
UV – Ultraviolet

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2 Summary

Title: Management of Advanced Melanoma

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The management of advanced melanoma is complex and differs according to the stage of the tumor. The stage is defined by the 2018 American Joint Committee on Cancer (AJCC) melanoma staging system and utilizes the TNM classification. Complete excision of the primary tumor with one to two-centimeter margins is the gold standard. According to tumor thickness and ulceration, a sentinel lymph node biopsy may be performed. The result from this procedure has the greatest overall prognostic value compared with other prognostic factors. If a sentinel lymph node biopsy exhibits micrometastases, a complete lymph node dissection, nodal observation, or adjuvant therapy may be indicated. Metastatic melanoma requires most often systemic therapy. With a number of immune and targeted therapy medications receiving FDA approval during the last ten years, the prognosis of patients with advanced melanoma has significantly improved from an overall survival rate of less than 10 % to values ranging between 34 and 60 %. Immune therapy agents such as the PD-1 blocking antibodies Pembrolizumab and Nivolumab, and the CTLA-4 blocking antibody Ipilimumab and their specific combination have shown great results in phase III randomized clinical trials. Targeted therapy aims at melanomas with BRAF V600 mutations. The MEK inhibitors Trametinib, Cobimetinib, and Binimetinib and the BRAF inhibitors Vemurafenib, Dabrafenib, and Encorafenib are preferably administered in combination as this has shown to increase response duration compared with monotherapy. Patients with advanced melanoma may undergo follow-up examinations every three to twelve months depending on the stage of the tumor and the time that passed from their initial diagnosis. Adoptive cell transfer and a melanoma vaccine are therapies in development. They have not shown clinical outcomes that prompted their adaption to clinical routine practice. The European Society for Medical Oncology (ESMO) has formulated clear recommendations for the management of melanoma patients during the COVID-19 pandemic. Generally, as many visits as possible should be conducted via telemedicine, and patients are categorized as low, medium, and high priority.

Key words: advanced melanoma, melanoma, sentinel lymph node biopsy, surgical management, adjuvant therapy, immunotherapy, targeted therapy

3 Sažetak

Naslov: Liječenje Uznapredovalog Melanoma

Autor: Carmen Roeper

Liječenje uznapredovalog melanoma je složeno i razlikuje se ovisno o stadiju tumora. Stadij je definiran prema sustavu za određivanje stadija melanoma Američkog zajedničkog odbora za rak (engl. *American Joint Committee on Cancer*, AJCC) iz 2018.godine i koristi TNM klasifikaciju. Potpuna ekscizija primarnog tumora s rubom od jednog do dva centimetra zlatni je standard. S obzirom na debljinu i ulceraciju tumora, možda će biti potrebno napraviti biopsiju sentinel limfnog čvora. Rezultat ovog postupka ima najveću ukupnu prognostičku vrijednost u usporedbi s ostalim prognostičkim čimbenicima. Ako biopsija sentinel limfnog čvora pokaže mikrometastaze, može biti indicirana disekcija cijelog limfnog čvora, opservacija čvora ili adjuvantna terapija. Metastatski melanom zahtijeva najčešće sistemsku terapiju. Uz niz imunoloških i lijekova za ciljanu terapiju koje je odobrila FDA tijekom posljednjih deset godina, prognoza pacijenata s uznapredovalim melanomom značajno se poboljšala u odnosu na ukupnu stopu preživljavanja manju od 10% do vrijednosti u rasponu od 34 do 60%. Agensi imunoterapije kao što su antitijela koja blokiraju PD-1 pembrolizumab i nivolumab, i CTLA-4 blokirajuće antitijelo ipilimumab i njihova specifična kombinacija pokazali su odlične rezultate u randomiziranim kliničkim ispitivanjima faze III. Ciljana terapija usmjerena je na melanome s BRAF V600 mutacijama. MEK inhibitore trametinib, kobimetinib i binimetinib i BRAF inhibitore vemurafenib dabrafenib i encorafenib poželjno je koristiti u kombinaciji jer je ta praksa pokazala povećanje trajanja odgovora u usporedbi s monoterapijom. Pacijenti s uznapredovalim melanomom mogu se podvrgnuti kontrolnim pregledima svaka tri do dvanaest mjeseci ovisno o stadiju tumora i vremenu koje je prošlo od postavljanja njihove dijagnoze. Adoptivni prijenos stanica i cjepivo protiv melanoma su terapije u razvoju. Nisu pokazali kliničke rezultate koji bi potaknuli njihovu prilagodbu kliničkoj rutinskoj praksi. Europsko društvo za medicinsku onkologiju (engl. *European Society for Medical Oncology*, ESMO) je formuliralo jasne preporuke za liječenje oboljelih od melanoma tijekom pandemije COVID-19. Općenito, posjeti bi se trebali provoditi putem telemedicine što je više moguće, a pacijenti su kategorizirani po prioritetu kao niski, srednji i visoki prioriteti.

Ključne riječi: uznapredovali melanom, melanom, biopsija sentinel limfnog čvora, kirurško liječenje, adjuvantna terapija, imunoterapija, ciljana terapija

4 Types of Melanomas

In the updated WHO Classification of Skin Cancers in 2018, nine subtypes of melanoma were distinguished based on epidemiology, clinical and histologic morphology, and genomic characteristics. Considering these features, melanomas with and without sun exposure were broadly grouped into two main categories being “Melanomas typically associated with cumulative solar damage (CSD)” and “Melanomas not consistently associated with CSD”. Nodular melanomas formed a third main category as they display unique characteristics. For instance, nodular melanomas do not display the classical “ABCDE” signs. Any or most of the nine subtypes can present as this type of melanoma.(1)

By the degree of solar elastosis, melanomas associated with CSD were further divided into tumors arising from low and high CSD. Solar elastosis is caused by the damaging effects of ultraviolet radiation on elastic fibers in the dermis and commonly presents as “yellow, thickened, coarsely wrinkled skin”.(2) Superficial spreading melanoma is categorized as a low CSD tumor and lentigo maligna and desmoplastic melanoma as high CSD tumors. Spitz melanomas, acral melanomas, mucosal melanomas, melanomas arising in congenital nevi, melanomas arising in blue nevi, and uveal melanomas (not further considered in this review) belong to the group of melanomas not associated with CSD.

Cutaneous melanomas mostly arise from melanocytes in the epidermis and usually advance through two stages of development. The initial radial growth phase (RGP) is characterized by a horizontal growth pattern and has the appearance of an irregular patch or plaque. In the vertical growth phase (VGP), the tumor extends into the dermis or forms a nodule in the epidermis, raising the level of the skin. VGP lesions have a high potential for metastasis and its associated complications. Nodular melanomas represent an exception to this phasic growth pattern as vertical growth can be identified in the earliest stage of the lesion. Therefore, these tumors exhibit a high risk of already existing metastasis at diagnosis.(1)

5 Melanoma Staging

The latest American Joint Committee on Cancer (AJCC) melanoma staging system had been implemented in 2018. Melanomas are staged according to the TNM classification. T stands for the direct extent of the primary tumor and is further specified according to tumor thickness and the presence or absence of ulceration. The N stage informs about the regional lymph node involvement and the M stage indicates the presence of distant metastasis. Metastatic melanoma commonly spreads to lymph nodes, liver, lung, brain, and bone.(3) The staging is specified in tables 1-4.

Table 1 (3)

Primary Tumor (T)

Primary Tumor (T)	Thickness (mm)	Ulceration Status
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
Tis	Melanoma in situ	
T1	≤1.0	a: Breslow <0.8mm w/o ulceration b: Breslow 0.8-1.0mm w/o ulceration or ≤1.0mm w/ ulceration
T2	1.1-2.0	a: w/o ulceration b: w/ ulceration
T3	2.1-4.0	a: w/o ulceration b: w/ ulceration
T4	>4.0	a: w/o ulceration b: w/ ulceration

Table 2 (3)

Regional Lymph Nodes (N)

Lymph Node (N)	Number of Nodes	Clinical detectability	Presence of in-transit, satellite, and/or microsatellite metastasis
Nx	Regional nodes not assessed		No
N0	No regional metastasis detected		No
N1	0-1		
N1a		1 clinically occult (ie, detected by SLN biopsy)	No
N1b		1 clinically detected	No
N1c		No regional lymph node disease	Yes
N2	1-3		
N2a		2 or 3 nodes clinically occult	No
N2b		2 or 3 nodes, at least 1 was clinically detected	No
N2c		1 clinically occult or clinically detected	Yes
N3	>1		
N3a		≥4 clinically occult nodes	No
N3b		≥4 nodes, at least one was clinically detected, or presence of any number of matted nodes	No
N3c		≥2 clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

Table 3 (3)

Distant Metastasis

Distant Metastasis (M)	Anatomic Site	Classification	Serum LDH
M0	No evidence of distant metastasis	M1a-d	Not assessed
M1a	Skin, soft tissue, distant lymph nodes	M1a-d(0)	Normal
M1b	Lung	M1a-d(1)	Elevated
M1c	Non-CNS visceral sites		
M1d	CNS		

Table 4 (3)

Pathological Staging of Melanoma

Pathological Staging (pTNM)	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
	T1b		
IB	T2b		
IIA	T2b	M0	M0
	T2a		
IIB	T3b		
	T4a		
IIC	T4b		
IIIA	T1-2a	N1a	M0
	T1-2a	N2a	
IIIB	T0	N1b-c	M0
	T1-2a	N1b-c	
	T1-2a	N2b	
	T2b-3a	N1a-2b	
IIIC	T0	N2b-c	M0
	T0	N3b-c	
	T1a-3a	N2c-3c	
	T3b-4a	Any N	
	T4b	N1a-2c	
IIID	T4b	N3a-c	M0
IV	Any T	Any N	M1

Staging of melanoma is fundamental to the initial assessment of the patient. Furthermore, it allows treatment planning, surveillance, the design of clinical trials, and reporting in data registries.(4)

6 Overview of Management of Advanced Melanoma

While most primary cutaneous melanomas are cured after excision, advanced melanoma requires a more complex approach thereafter. A sentinel lymph node biopsy (SLNB) informs about tumor burden and is potentially curative if metastases were limited to the removed node(s). A positive SLNB may warrant complete lymph node dissection (CLND), close observation, or adjuvant therapy depending on the characteristics of the tumor. Adjuvant therapy and treatment of metastatic melanoma largely consist of immunotherapy, targeted therapy, or a combination thereof. The advent of these new treatment options significantly improved the prognosis of advanced melanoma in recent years and ongoing research promises further advances in this field.

7 Melanoma Treatment up to date

First attempts at treating advanced melanoma included chemotherapy. However, it did not prevail due to its relatively low clinical response and its high toxicity. In 1998, the approval of IL-2 for metastatic melanoma revolutionized melanoma treatment as it successfully treated a small percentage of patients. Nevertheless, its high toxicity limited its use and more effective treatment options exist today. Immunotherapy and targeted therapy have been extensively studied in recent years and greatly improved the prognosis for patients with advanced melanoma.

Generally, the primary tumor is surgically excised. If a patient has one or very few metastases, it may be beneficial to excise these as well. Different treatment options are discussed in detail in the respective paragraphs and the choice and sequence of therapy will be discussed here. Adjuvant therapy is offered to patients with high-risk melanoma. In patients with stage IIB/C melanoma, one year of treatment with Pembrolizumab is recommended. This proved a prolonged recurrence-free survival; however, surveillance is a legitimate alternative if treatment adverse events are a concern.(5)

Resected stage IIIA low-risk node-positive melanoma is treated depending on the characteristics of the primary tumor. If the primary tumor is non-ulcerated and sentinel lymph node metastasis is <1mm, surveillance is preferred. The recurrence-free survival is very high in this patient group, increased morbidity from adverse events is avoided, and systemic therapy is available in the case of recurrence or metastasis. Patients with BRAF V600 positive melanomas who desire treatment may be treated with Dabrafenib plus Trametinib for one year. It is favored over immunotherapy due to its milder side effect profile. An ulcerated primary tumor or lymph

node metastasis ≥1mm is treated according to BRAF mutation. BRAF wild-type tumors are treated with a PD-1 inhibitor. Nivolumab or Pembrolizumab is possible in this context. The same treatment is an option for BRAF mutant tumors, with the additional possibility of targeted therapy with Dabrafenib plus Trametinib.

Patients with a resected stage IIIB/C/D tumor are at high risk for disease recurrence. Depending on BRAF mutation status, these patients should be treated with adjuvant therapy. BRAF wild-type tumors are preferentially treated for one year with a PD-1 inhibitor being Nivolumab or Pembrolizumab. For patients with BRAF-mutated melanoma, the best possible treatment option has not been established. Immunotherapy with Nivolumab or Pembrolizumab is one option and targeted therapy with Dabrafenib plus Trametinib represents the alternative.

For patients with metastatic melanoma stage IV whose metastasis had been definitely removed via surgery or radiation, adjuvant therapy is applicable. Regardless of BRAF status, Nivolumab plus Ipilimumab for one year is the recommended combination therapy.(6)

Systemic treatment of metastatic melanoma is complex and initial genetic sequencing is indicated to identify common mutations that can be treated with targeted therapy. BRAF mutations are most common and TRK gene fusions, KIT, and NRAS mutations are rarer. When deciding on a treatment regimen, mutational status, prior drug therapy, and contraindications to certain treatments need to be considered.(7) Previously untreated metastatic melanoma with BRAF mutation is recommended to be treated with Nivolumab plus Ipilimumab. It is preferred over initial targeted therapy with a combination of BRAF and MEK inhibitor due to its superior OS rate. Additionally, immunotherapy seems to be less potent after targeted therapy which does not apply the other way around.(8,9) Alternative immunotherapies are Pembrolizumab or Nivolumab monotherapy. If there are contraindications or the patient does not wish to undergo immunotherapy, BRAF plus MEK inhibitor is the alternative. Possible combinations are Dabrafenib plus Trametinib, Encorafenib plus Binimetinib, or Vemurafenib plus Cobimetinib. Despite Atezolizumab plus Vemurafenib plus Cobimetinib being FDA-approved and having achieved improved progression-free survival, it is not routinely used in clinical practice. It has only been compared to targeted therapy alone, and not to the current standard of immunotherapy followed by targeted therapy. Its toxicity profile was also less favorable.

The treatment of metastatic melanoma with BRAF-positive mutation, which has been previously treated adjuvantly, will generally depend on the original therapy received. If a PD-1 inhibitor such as Nivolumab or Pembrolizumab had been previously administered, treatment with Nivolumab plus Ipilimumab is recommended. However, the combination therapy of a

BRAF and MEK inhibitor also seems plausible. If a patient with BRAF-positive metastatic melanoma previously received adjuvant therapy consisting of BRAF and MEK inhibitors, immunotherapy with checkpoint inhibitors is commonly used thereafter.

Subsequent therapy may be necessary if a patient relapses after initial systemic therapy. Generally, patients who received immunotherapy will receive targeted therapy in the next step and vice versa.(7)

The systemic treatment of metastatic melanoma without BRAF mutation will be discussed in this paragraph. Immunotherapy with Nivolumab plus Ipilimumab is the first-line treatment for aggressive metastatic melanoma that has not been treated before. Features considered aggressive include elevated lactate dehydrogenase (LDH), acral melanoma, brain or liver metastasis, and metastases with systemic symptoms. Monotherapy with Pembrolizumab or Nivolumab is recommended in the absence of these features. The treatment duration ranges from six months to two years depending on the responsiveness of the tumor. If treatment progression occurs after combination therapy, enrolment in clinical trials is advised. Alternatively, high-dose IL-2 or chemotherapy may be considered. Patients with BRAF wild-type metastatic melanoma previously treated with a PD-1-inhibitor as adjuvant therapy or for metastatic melanoma may be treated with Nivolumab plus Ipilimumab.(10)

Several targeted therapies have been developed for non-BRAF melanoma. First-line therapy for patients with NRAS mutation is immunotherapy, followed by the MEK inhibitor Binimetinib.(11,12) Metastatic melanoma with TRK gene fusion is treated with checkpoint inhibitor immunotherapy. Second-line treatment is a TRK-gene fusion inhibitor such as Larotrectinib or Entrectinib.(13–15) KIT mutations most commonly occur in acral or mucous melanoma. It is treated with Imatinib should immunotherapy fail.[7,13] Treatment of rare mutations will not be further elaborated on in this paper.

7.1 Surgical Management

7.1.1 Excision

An excisional biopsy with the intention of cure is the gold standard for the treatment of primary cutaneous melanoma. Despite an overall 5-year survival of 92 % of localized, invasive melanoma, there is an ongoing debate regarding the appropriate margin size.(16)

Table 5 (17)

Surgical Margin Recommendation by Country

Country	Surgical margin recommendation (cm) according to Breslow Thickness (mm)			
	<1 mm	1.01 - 2 mm	2.01- 4 mm	>4 mm
UK 2021	1 cm	1-2 cm	≥2 cm	≥2 cm
USA 2014	1 cm	1-2 cm	2 cm	2 cm
Australia 2018	1 cm	1-2 cm	1-2 cm	2 cm
Germany 2014	1 cm	1 cm	2 cm	2 cm
Switzerland 2016	1 cm	1 cm	2 cm	2 cm
The Netherlands 2013	1 cm	1 cm	2 cm	2 cm

As seen in table 5, the national guidelines recommendations for surgical margin width are very similar in countries such as the UK, USA, Australia, Germany, Switzerland, and the Netherlands. A maximum margin of 2 cm is generally accepted as larger margins have not been shown to reduce recurrence or improve survival.(17) Past RCTs and meta-analyses had presented evidence in favor of these margins. However, a meta-analysis from 2016 argues that narrow margins (1-2 cm) may lead to a worse outcome than wide margins (3-5 cm). Overall survival probability may be 94 % worse than with wide margin excisions. On the other hand, wider margins related to an increased amount of non-melanoma deaths. The authors argued that non-significant p-values have been "misinterpreted" as being indifferent. Overall, it is not possible to conclude from current available RCTs whether narrow margins are definitely safe.(18) An updated meta-analysis will be expected including the ongoing MelMarT trial which is estimated to be completed in 2026. This RCT compares 1 cm versus 2 cm margins of invasive cutaneous melanomas with a thickness of ≥1 mm with regards to local recurrence and melanoma-specific survival.(19) As the biggest dispute currently exists whether a 1 cm or 2 cm margin is reasonable, this trial could potentially be the basis for new evidence-based guidelines. A systematic review and meta-analysis from 2021 did not show a significant difference in local recurrence, metastasis, melanoma, and non-melanoma-related deaths between narrow and wide margins. Nevertheless, when studies at high RoB (a tool for assessing the risk of bias) were excluded, the results shifted to favor wide margins for melanoma-specific survival. More research may be required to reliably weigh the benefits of wide margins against the disadvantages of potential morbidity caused by prolonged hospital stays, complications, and the need for reconstructive surgery.(16)

Margins positive for invasive disease after excision require re-excision. If satellite lesions are discovered at the margin, no re-excision is required as it is not possible to know the location of further satellite lesions. These lesions should be closely monitored in follow-ups.(20) If melanoma in-situ is present in the margin, a re-excision is advised. However, the chance of finding another positive margin is approximately 10 %. Such patients may benefit from topical imiquimod treatment.(21)

Mucosal melanoma is considered rare with 0.8 to 3.7 % of melanomas being mucosal. However, this type of melanoma is particularly aggressive and has a less favorable prognosis. It is therefore treated with wide excision margins.(22)

Management of auricular melanoma was historically associated with a poorer prognosis. This has not proven to be the case and total ear amputations, total parotidectomies, and radical neck dissections are usually not necessary today. Cartilage-sparing excision with narrow margins (1 cm) and reconstruction using skin grafts or local flaps have shown excellent results regarding local control rate.(23) Furthermore, the perichondrium may serve as a local barrier against melanoma invasion. Only gross local invasion into cartilage may necessitate excision of cartilage and amputation.(24)

Subungual melanoma is frequently misdiagnosed and therefore often discovered at a later stage. Historically, it was classified as a more aggressive form of melanoma, however, the literature did not confirm this. Therefore, aggressive amputations became rare but may be indicated after local recurrence. No national guidelines on the treatment of subungual melanoma exist and RCTs are necessary to establish such guidelines.(25)

7.1.2 Sentinel Lymph Node Biopsy

A sentinel lymph node (SLN) is the “First lymph node to receive drainage from the primary tumor”(26)

The American Society of Clinical Oncology and the Society of Surgical Oncology Clinical Practice Guideline have formulated the following recommendations. A Sentinel Lymph Node Biopsy (SLNB) is not routinely recommended for thin melanomas staged as T1a with nonulcerated lesions < 0.8 mm in Breslow thickness. T1b patients with 0.8 to 1.0 mm in Breslow thickness or < 0.8 mm in Breslow thickness with ulceration may be contemplated to receive SLNB on an individual basis. Patients with intermediate-thickness melanomas with a Breslow thickness of 1.0 to 4.0 mm (T2 or T3) are recommended to undergo SLNB. Thick melanomas with a Breslow thickness of > 4.0 mm staged at T4 may be considered for SLNB. Regardless of stage, the risks and benefits always need to be discussed with the patient.(27)

The value of SLNB has shifted in recent years from a therapeutic approach to one that is crucial in providing prognostic information.(28) Results from the RCT Multicenter Selective Lymphadenectomy Trial 1 (MLST-1) showed that the findings from an SLNB are the strongest predictive factor regarding disease recurrence and death from melanoma.(29) Possible complications of an SLNB occur at a frequency of approximately ten percent and include seroma, hematoma, infection, dysesthesia, and lymphedema.(30) Several studies and RCTs have investigated SLNB versus nodal observation. The results were not unanimous, however, most studies and trials found that patients with intermediate-thickness and thick melanomas had a significant increase in disease-free survival after SLNB. SLNB and nodal observation did not show a difference in melanoma-specific survival.(27) Nevertheless, the literature largely agrees that the benefits of SLNB outweigh the potential harm in selected patient groups.

In many institutions, the sentinel lymph node is traced in a dual manner. The primary tumor is injected with Technetium and can be preoperatively traced with lymphoscintigraphy and during surgery with gamma probes. Injection of the tumor with isosulfan blue dye allows for visual recognition of the node. The identification rate of 97 to 99 percent is very high with the combined method.(31) However, blue dye can cause anaphylactic shock, and some studies argue that it may be unnecessary. Trained surgeons may achieve similarly high identification rates using only radiotracers.(32) The “10 % rule” suggests that all nodes with radioactivity of at least ten percent of the hottest node ex vivo and with blue dye should be removed to reduce the number of false-negative results.(33,34) Patients with a negative SLNB that later develop metastasis in a draining lymph node, are considered false-negative cases. A meta-analysis conducted by Valsecchi et al. concluded that nodal recurrence after negative SLNB was less than five percent.(35) A negative SLNB warrants no further surgery, less follow-up visits, and is associated with prolonged survival.

7.1.3 Lymph Node Dissection

After a positive SLNB, a complete lymph node dissection (CLND) or nodal observation are possible treatment directions. 15-20 percent of patients with metastases in SLNs additionally show metastases in non-SLNs.(36) The meta-analysis by Moody et al. reported a total complication rate of 37.3 percent after CLND. Among those were infections, delayed wound healing, lymphedema, seroma, and hematoma.(37) Additionally, reduced quality of life after CLND compared with SLNB only was observed.(38) There is considerable controversy in the literature on whether a CLND is necessary for patients with positive SLNB as approximately 80 percent do not have metastasis in non-SLNs and would still suffer from the morbidity of the

procedure. Two RCTs investigated this issue. The DeCOG (German Dermatologic Cooperative Oncology Group Selective Lymphadenectomy Trial) and MSLT-2 (Multicenter Selective Lymphadenectomy Trial) came to the general conclusion that CLND increased disease control rate, but not the melanoma-specific survival. Therefore, CLND will most likely be performed less frequently in the future.(39) Nevertheless, some limitations to both studies have been reported. The DeCOG encountered problems recruiting patients and ended early. Both trials could be biased by short follow-up periods of up to 140 days and a high number of participants with a small tumor burden.(40) The possibility of adjuvant therapy can be explored in patients with a positive SLNB and will be further discussed in the next paragraphs.

7.2 Adjuvant Therapy

Adjuvant therapy is usually offered to high-risk patients who already received primary treatment typically consisting of excisional surgery. High-risk melanoma is deeper than 4 mm with or without ulcerations, 2 to 4 mm with ulceration, or involves spread to nearby lymph nodes. With CLND performed less frequently, adjuvant therapy becomes more important and potentially offers a good alternative to surgical solutions beyond the primary resection.(41)

7.2.1 Interferon

Interferons belong to the group of cytokines and are antiviral, antiproliferative, and immunomodulatory agents. They act through multiple signaling cascades such as the JAK (Janus activated kinase) and the STAT (signal transducer and activator of transcription) pathway.(42) For the treatment of melanoma, IFN-α is most relevant. IFN-αa, IFN-αb, and IFN-αc are commercially available as drugs. IFN-α enhances tumor immunogenicity and increases dendritic cell (DC) response to melanomas.(43) Anti-tumor effects are exerted by tumor necrosis factor-alpha, interferon-gamma, interleukin-1 (IL-1), IL-2, and IL-12 which are produced by Th2 cells. On the other hand, Th2 cells produce IL-4 and IL-10 and facilitate tumor growth by suppressing the host immune system.(44) IFN-α promotes a shift from a Th2- to a Th1-dominant response. This strengthens cell-mediated cytotoxicity. IFN-α was approved by the FDA for the treatment of stage III melanoma in 2011. During that time, several RCTs acknowledged IFN-α as one of the main adjuvant treatment options in resected IIB/III melanoma. High-dose treatment was necessary to increase relapse-free survival (RFS) and overall survival (OS).(43,45) The Eastern Cooperative Oncology Group Trial EST 1684 found that IFNα-2b significantly increased median RFS. The treatment group showed a median RFS of 1.72 years, while the observation-only patient group was relapse-free for a median of 0.98

years. The OS was 3.82 years in the group treated with IFNα-2b and 2.78 years in the observation group. IFN2α-2b was administered IV daily for five days a week for four weeks at 20 MU/m2/d and thereafter three times a week for 48 weeks at 10 MU/m2/d. The control group underwent close observation. IFNα combination treatment is shortly described in the following paragraph. Possible toxicity of the treatment can be substantial and includes constitutional and neuropsychiatric symptoms, laboratory evidence of myelosuppression, and hepatotoxicity. (46,47) With the development of checkpoint inhibitors, and interferon's unfavorable toxicity profile, the relevance of IFN-α in the treatment of melanoma ceased.(48)

7.2.2 Ipilimumab

Ipilimumab is an FDA and European Medicines Agency-approved human IgG1 monoclonal antibody that alters the adaptive immune system. One important factor in the activation of T-cells is the binding of the B7 ligand on the antigen-presenting cell (APC) to the CD28 receptor on the T-cell. Following T-cell activation, the expression of cytotoxic T-lymphocyte antigen 4 (CTLA-4) on the T-cells is upregulated. CTLA-4 competes with CD28 for the B7 ligand on APCs and does so with a higher affinity. The binding of CTLA-4 to the APC leads to downregulation of the T-cells. Ipilimumab binds to the CTLA-4 receptor and reinstates the proliferation of naturally developed melanoma-specific T-cells.(49) Adjuvant therapy with Ipilimumab was approved for fully resected stage III melanoma in 2015. A randomized, double-blind, phase 3 trial including 951 patients found that the 5-year rate of recurrence-free survival was 40.8 % in the group receiving Ipilimumab and 30.3 % in the placebo group. The overall survival proved to be 65.4 % in the treatment group and 54.4 % in the placebo group. The absence of distant metastasis could be confirmed in 48.3 % in the Ipilimumab group and in 38.9 % in the placebo group. 10 mg per kilogram was administered every 3 weeks. This was repeated four times and thereafter every three months for 3 years or until the disease recurred, intolerable toxicity developed, or other complications arose. More than 50 % of the patients in the treatment group had grade 3 or 4 adverse effects. However, 26.2 % in the placebo group proved adverse effects at those levels. Immune-related adverse effects are common with Ipilimumab and occurred in 41.6 % (grade 3 or 4). These included with decreasing frequency gastrointestinal, hepatic, and endocrine disturbances. Other adverse effects included dermatologic events such as rashes, and neurologic events. 1.1 % of the patients died because of adverse effects from Ipilimumab. The most common cause was colitis with intestinal perforation, followed by myocarditis, and multiorgan failure associated with Guillain-Barré syndrome.(50) Depending

on the characteristics of the tumor, Pembrolizumab and Nivolumab have shown higher clinical efficiency and are the preferred agents in patients with resected stage III melanoma.(51,52)

7.2.3 Nivolumab

Nivolumab is an IgG4 monoclonal antibody with a high affinity for the PD-1 receptor. PD-1 receptors are expressed on activated T- and B-cells and generally reduce the immune response. Tumor cells and infiltrating immune cells express the ligands PD-L1 and PD-L2 that bind to the PD-1 receptor and downregulate the host immune response. Nivolumab interferes with this binding and therefore increases anti-tumor reactions, slows tumor growth, and assists in tumor rejection.(53,54) Patients in a randomized, double-blind, phase III clinical trial who received complete resection of stage IIIB, IIIC, or IV melanoma received Nivolumab 3 mg /kg every two weeks. Based on the results from this trial, Nivolumab received FDA approval as adjuvant therapy for stage III melanoma and completely resected metastatic melanoma in 2017. 70.5% of patients were recurrence-free after 12 months. Adverse effects of grades three or four were noted in 14.4%.[55,56] Adverse effects of any grade were fatigue (32%), rash (23%), and diarrhea (18%). Immune-related adverse events included skin disorders (36%), gastrointestinal disorders (18%), and endocrine disturbances (13%). Drug-related deaths were not reported.(54) Nivolumab and Ipilimumab are both immune checkpoint inhibitors and their efficiency and safety profiles have been compared in the abovementioned clinical trial. The 18-months recurrence-free survival amounted to 66.4% in the Nivolumab group and 52.7% in the Ipilimumab group. Recurrence or death within 27 months was reported in 34.0% of patients treated with Nivolumab and 45.5% of patients treated with Ipilimumab. The Nivolumab group also reported longer distant metastasis-free survival. Adverse effects of any grade were experienced in nearly all patients of either drug regimen. However, the number of grade three or four adverse events differed significantly. The Nivolumab group experienced such in 14.4% of cases compared to 45.9% in the Ipilimumab group. The discontinuation rate due to drug-related adverse effects of any grade was 9.7% in the Nivolumab group and 42.6% in the Ipilimumab group. All things considered, Nivolumab seems to be superior to Ipilimumab regarding recurrence-free survival, metastatic-free survival, and safety profile.(55) A four-year follow-up of this study reinforced these results and indicated that combination therapy of Ipilimumab and Nivolumab may have the greatest overall benefit.[57]

7.2.4 Vemurafenib

Vemurafenib selectively inhibits mutated BRAF V600E kinase. The mitogen-activated protein kinase (MAPK) signaling pathway is vital in promoting the growth of melanoma cells. Extracellular signals such as growth factors and hormones activate this pathway. These ligands bind to a tyrosine kinase receptor on the plasma membrane and activate RAS. Signals are further transduced through the proteins BRAF, MEK, and ERK, activate transcription factors and finally lead to cell proliferation. If any gene coding for these proteins mutates, it can lead to constitutive activation of the pathway. Approximately 40 to 60 percent of patients with melanoma showed point mutations in BRAF. 90 percent of these mutations led to a substitution of glutamic acid for valine at codon 600, hence the name BRAF V600E. This mutation is 10.7-fold more active than the wild type. Consequentially, the pathway is activated independently of RAS and uncontrollable cell proliferation follows. Other mutations are V600R, V600M, V600D, and V600G. Their clinical response to targeted therapy is usually lower than that of BRAF V600E mutations as Vemurafenib selectively inhibits the activity of BRAF V600E. BRAF mutations are commonly noted in sun-exposed areas often affected by melanoma development such as the trunk and the extremities. [58–61] The application of adjuvant therapy with Vemurafenib was investigated in the BRIM8 phase III, double-blind, randomized, placebo-controlled trial. Patients with BRAF V600 positive mutations were divided into two cohorts. In cohort 1, patients with stage IIC to IIIB, and in cohort 2, patients with stage IIIC were included. The patients received 960 mg tablets or the matched placebo twice per day for 52 weeks. Cohort 2 showed a one-year disease-free survival of 78.9% in the Vemurafenib group and 58.0% in the placebo group. However, the two-year disease-free survival was very similar in the two groups with 46.3% in the Vemurafenib group and 47.5% in the placebo group. It seems that single-agent targeted therapy rapidly leads to treatment resistance. The primary endpoint of disease-free survival was not met in cohort 2 and the testing of cohort 2 before cohort 1 rendered results from cohort 1 as not significant. Median disease-free survival was not reached in the Vemurafenib group of cohort 1. In cohort 1, the two-year disease-free survival in the Vemurafenib group was 72.3% and 56.5% in the placebo group. However, the relevance of this favorable disease-free survival rate remains to be established in future trials as it is not statistically significant. Adverse effects were consistent with those of patients treated for advanced melanoma and will be discussed in the paragraph about Vemurafenib under targeted therapy.[62] Vemurafenib monotherapy is not recommended in the adjuvant therapy of melanoma. Immunotherapy or Dabrafenib + Trametinib are commonly used in this setting.(6)

7.2.5 Dabrafenib + Trametinib

Dabrafenib is a BRAF inhibitor, and its mechanism of action is similar to that of Vemurafenib. Trametinib is a MEK inhibitor, like Cobimetinib. As the principles of BRAF and MEK inhibitors are outlined in the paragraphs about Vemurafenib and Cobimetinib, respectively, it will not be further discussed here.[63] In a double-blind, placebo-controlled, phase III trial, patients with completely resected stage III melanoma with BRAF V600 mutation were either assigned to receive a placebo or 150mg of Dabrafenib plus 2mg of Trametinib. The relapse-free survival in the combination-therapy group was 88%, 67%, 58%, and 52%, and 56%, 44%, 39%, and 36% in the placebo group after one, two, three, and five years, respectively. The combination-therapy arm showed a three-year OS rate of 86% compared to 77% in the placebo arm. 65% of patients in the combination therapy group and 54% in the placebo group were alive and free of distant metastasis at five years. In conclusion, the combination regimen portrayed a significantly lower risk of recurrence. An adverse event of any grade occurred in 97% of the patients treated with the combination regimen and in 88% in the placebo group. The most common adverse events in the combination therapy group were pyrexia (63%), fatigue (47%), and nausea (47%). Grade three or worst adverse events occurred in 36% of patients treated with the combination therapy and 10% treated with the placebo.(63,64) In 2018, the FDA approved Dabrafenib + Trametinib for the adjuvant treatment of completely resected BRAF V600E/K positive melanoma with involvement of lymph nodes.(65)

7.2.6 Pembrolizumab

Like Nivolumab, Pembrolizumab is an FDA-approved PD-1 blocking antibody. The two drugs show notable differences in how they bind to the PD-1 receptor. However, molecular, preclinical, and early clinical data suggest that the drugs may be used interchangeably. Differences in trial results may be attributed to the patient population and trial design. Nevertheless, an incomplete understanding of mechanisms and insufficient clinical data warrant further research on their interchangeability.(66) A phase III double-blind clinical trial evaluated Pembrolizumab versus placebo in high-risk stage III melanoma. The treatment group received 200 mg every three weeks for the period of one year, until the disease recurred, or until intolerable adverse effects occurred. The three-year RFS was 63.7% in the Pembrolizumab group and 44.1% in the placebo group. At three-year follow-up, 37% and 56% in the Pembrolizumab and placebo group, respectively, had a recurrence or died. The rate of distant metastasis at three years was 22.3% and 37.3%, respectively.(67) 77.8% of patients experienced adverse events of any grade in the treatment group. 66.1% in the placebo group were affected. Grade three, four, or five adverse events occurred in 14.7% in the Pembrolizumab group and

3.4% in the placebo group. The general adverse effects listed in decreasing frequency were fatigue, skin reactions including rash and pruritus, diarrhea, arthralgia, nausea, and dyspnea. Immune-related disorders were endocrine abnormalities, the most frequent ones being hypothyroidism and hyperthyroidism, respiratory, thoracic, and mediastinal disorders, such as pneumonitis, interstitial lung disease, or sarcoidosis, vitiligo, or other severe skin reactions and occurred at an overall rate of 37.3% in the Pembrolizumab group compared with 9.0% in the placebo group.(68) A phase III randomized controlled trial, compared high-dose interferon or Ipilimumab to Pembrolizumab in patients with resected melanoma stage IIIA to IV. In the Pembrolizumab group, RFS was improved, however, OS did not differ significantly.(51) In 2019, the FDA approved Pembrolizumab for the adjuvant treatment of resected melanoma with involvement of lymph nodes.(69) KEYNOTE-716 is a phase III double-blind, multi-center, placebo-controlled randomized clinical trial that investigated Pembrolizumab versus placebo in resected stage IIB/C melanoma patients. The RFS after 14.4 months was 16.8% in the Pembrolizumab group and 11.1% in the placebo group. The one-year recurrence-free survival amounted to 90.5% in the Pembrolizumab group and 83.1% in the placebo group.(51) Due to the high efficiency indicated in this trial, the FDA approved Pembrolizumab for the treatment of resected stage IIB/C melanoma in 2021.(70) Therefore, one year of treatment with Pembrolizumab is preferred over surveillance in this patient group.(6)

7.3 Immunotherapy

Historically, patients diagnosed with advanced melanoma had a median OS of 8 to 10 months and a five-year survival rate of approximately ten percent.(71) Immunotherapy, as well as targeted therapy, changed the grim prognosis of these patients and have the potential to improve it further as clinical trials are still ongoing. A slow response to treatment with immunotherapy is common and an initial worsening of the disease has been described. If a long-lasting response to immunotherapy is achieved, patients may be reevaluated for surgical removal of metastases.(72)

7.3.1 Ipilimumab

Ipilimumab is discussed in detail in the paragraph “Ipilimumab” under “Adjuvant Therapy”. A pooled analysis of phase II and III trials in patients with unresectable or metastatic melanoma analyzed the long-term survival in patients treated with Ipilimumab. The median OS was 11.4 months. The three-year survival rate was 22 % for all patients, 26% for patients who did not receive past systemic treatment for melanoma, and 20 % for previously treated patients. Doses

were administered at 3 and 10 mg/kg. A phase III clinical trial compared these two dosing regimens and showed a significant OS benefit in the patient group treated with 10 mg/kg. The median OS prevailed at 15.7 months for 10 mg/kg dosing compared to 11.5 months for 3 mg/kg. A survival plateau at five years showed promising results for a subgroup of patients. As already suggested in earlier studies, the higher dosing regimen related to more adverse effects overall, and, especially in grades three and four. (73) Ipilimumab nowadays is mainly administered in combination with a PD-1 inhibitor due to superior clinical efficiency. This will be elaborated on in other paragraphs.(74)
36 percent of patients treated with 10 mg/kg experienced grade three and four adverse effects compared with 20 % at 3 mg/kg. Diarrhea (11%), colitis (6%), and elevated alanine aminotransferase (4%) were the most common grade three and four adverse effects for the 10 mg/kg. The 3 mg/kg group showed a distribution of diarrhea (6%), colitis (3%), and hypophysitis (2%). Adverse effects resulting from treatment-related immune mechanism in the 3 and 10 mg/kg group lied at 55% and 74%, respectively. This study may offer a basis for the development of new anti-CTLA-4 agents. Several agents are already under investigation.(73)

7.3.2 Pembrolizumab

Pembrolizumab is discussed in detail earlier in this paper in the paragraph “Pembrolizumab” under “Adjuvant Therapy”. The KEYNOTE-001 trial investigated five-year survival outcomes in patients with advanced/metastatic melanoma in a phase Ib clinical trial. The median OS was 38.6 months in patients who did not receive previous treatment and 23.8 months in all patients.(75) Following the results from this trial, Pembrolizumab was the first PD-1 inhibitor to receive FDA approval for the treatment of unresectable or advanced melanoma after progression on other therapies in 2014.(76) The KEYNOTE-006 was a multicenter, randomized, controlled phase III trial for patients with unresectable or advanced melanoma. The patients were randomly assigned to 10mg/kg Pembrolizumab every two weeks, every three weeks, or 3mg of Ipilimumab every three weeks for four doses. The two-year OS rate was 55% in both Pembrolizumab groups and 43% in the Ipilimumab group. The two-year progression-free survival rate was 31%, 28%, and 14% in the two-week, three-week Pembrolizumab, and Ipilimumab group, respectively. Most adverse events were of grade one or two. Adverse events of any grade occurred in 82% of patients in the two-week group, 77% of patients in the three-week group, and 74% of patients in the Ipilimumab group. Overall, frequent adverse events were fatigue, pruritus, diarrhea, and rash. Both Pembrolizumab groups experienced grade three, four, or five adverse events in 17% and in 20% of patients treated with Ipilimumab. Generally,

the different dosing regimens of Pembrolizumab did not have distinguishable safety outcomes and Pembrolizumab displayed favorable OS and progression-free survival in comparison to Ipilimumab with less grade three or four adverse events. The authors support the implication of Pembrolizumab as a standard of care for patients with advanced/metastatic melanoma.(77) Even though the study was not designed to determine optimal treatment duration, complete responders showed a durable response regardless of at what point in a period of six months to two years the discontinuation occurred.(78) Today, Pembrolizumab is frequently used as first-line therapy for BRAF wild-type treatment-naïve melanoma with less aggressive features (no elevated LDH level, acral melanoma, brain/liver metastasis, or symptomatic systemic metastasis). However, in many instances, combined immunotherapy is preferred. Nivolumab plus Ipilimumab is a standard of care.(10) Pembrolizumab plus Nivolumab in the treatment of patients with advanced melanoma is currently being investigated in a phase I trial (KEYNOTE-029). Adverse events were manageable and clinical efficiency seems encouraging. Future RCTs will show if Pembrolizumab plus Ipilimumab is a good or superior alternative to Nivolumab plus Ipilimumab.(79)

7.3.3 Nivolumab

Nivolumab is discussed in detail earlier in the paragraph “Nivolumab” under “Adjuvant therapy”. In addition to its use in the adjuvant setting, it was originally FDA-approved for second-line treatment of unresectable or metastatic melanoma in patients who previously received Ipilimumab, and for patients with BRAF V600 mutations who progressed after treatment with Ipilimumab and a BRAF inhibitor in 2014. Today, it is recommended for less aggressive metastatic BRAF wild-type melanoma instead of Ipilimumab or high-dose IL-2.(10,80) The CheckMate037 trial was a randomized, controlled, open-label, phase III trial that compared chemotherapy (dacarbazine, carboplatin, or paclitaxel) with Nivolumab in the above-mentioned patient group. The patients in the Nivolumab group received 3 mg/kg every two weeks until the diseases progressed, or intolerable toxicity occurred. In the Nivolumab group, 31.7% of patients showed a treatment response, in the chemotherapy group it was 10.6%. Six-month progression-free survival was 48% for patients treated with Nivolumab and 34% for patients treated with chemotherapy. The authors concluded that Nivolumab is a good treatment option for patients in this advanced disease stage and acknowledge that such a second-line treatment option had been overdue.(81,82)

7.3.4 T-VEC

T-VEC (Talimogene laherparepvec) is a 2015 FDA-approved oncolytic viral immunotherapy for the treatment of local unresectable and nodal melanoma that recurred after initial surgery.(83) Herpes simplex virus type 1 (HSV-1) is genetically modified. ICP34.5 and ICP47 are functionally deleted, and GM-CSF is inserted at the place of ICP34.5. ICP34.5 is a neurovirulence factor and its inactivation prevents neuronal involvement and promotes tumor-selective replication. The local production of GM-CSF leads to increased dendritic cell activity and fosters cytotoxic T-cell responses to tumor cells. ICP47 normally inhibits antigen presentation in cells infected with HSV. If deleted, expression of surface antigens on tumor cells would be expected to increase and antigen-presenting cells should not be inhibited. Furthermore, enhanced viral replication and greater oncolysis were observed.(84–87) A randomized open-label phase III trial (OPTiM) was conducted in patients with unresectable stage IIIB to IVM1c melanoma. Patients either received intra-tumoral T-VEC or subcutaneous recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF). The T-VEC group showed a median OS of 23.3 months and the GM-CSF group of 18.9 months. The overall response rate was 31.5% and 6.4%, and the CR rate was 16.9%, and 0.7% in the T-VEC and GM-CSF arms, respectively. T-VEC showed greater efficiency than GM-CSF, however, it may be criticized that T-VEC was not compared to a placebo or a standard of care treatment regimen.(88) A phase Ib clinical trial suggests the effective combination of T-VEC with the anti-PD-1 antibody Pembrolizumab in previously untreated patients with IIIB to IV melanoma. The confirmed objective response rate amounted to 61.9%, and the complete response rate was 33.3%. Ongoing trials are further exploring this combination.(84,89) In the largest real-world review, 121 patients were treated with T-VEC for three years. Regarding OR, 57% of patients had a locoregional response, 39% a complete response, and 18% a partial response. 58% of patients did not notice any adverse events, which confirms its low toxicity profile noted in previous studies. Therefore, T-VEC appears to be a well-tolerated treatment option with durable results.(90) The typical dosing regimen consists of up to 4 ml of 10^6 to 10^8 pfu/ml in phosphate-buffered saline and is administered in the central portion of the lesion. If the lesion is easily visualized or palpated, the injection is done under visual guidance. Otherwise, ultrasound-guided localization may be utilized.(87) In terms of adverse events, patients enrolled in the OPTiM trial most commonly reported fatigue, chills, pyrexia, nausea, and flu-like illness. Grade three or four adverse events only occurred in 11.3% of patients. Cellulitis was the only grade three or four adverse event that occurred in more than 2% of patients. Immune-related adverse events manifested in 8.1% of patients and 6.2% of those reported vitiligo (grade one or two).

Many of the patients who experienced grade three adverse events had a previous medical condition that potentially exacerbated. Grade four immune-related adverse events were not noted.(88)

7.3.5 Nivolumab + Ipilimumab

A phase III, randomized, double-blind study compared Nivolumab monotherapy, Ipilimumab monotherapy, and combined Nivolumab and Ipilimumab therapy in patients with untreated unresectable or metastatic melanoma (Checkmate 067). Based on the results from this trial, the FDA approved this combination therapy for the treatment of unresectable or metastatic melanoma regardless of BRAF mutational status in 2016.(91,92) Regarding the combination therapy, Nivolumab was administered at a dose of 1 mg/kg and Ipilimumab at a dose of 3 mg/kg every 3 weeks for four doses. Thereafter, 3 mg/kg of Nivolumab every two weeks, or 3 mg/kg of Ipilimumab every three weeks were administered. The median OS varied greatly, being more than 60 months for the Nivolumab-Ipilimumab combination therapy, 36.9 months in the Nivolumab treatment group, and 19.9 months in the Ipilimumab treatment group. The median progression-free survival for the Nivolumab-Ipilimumab combination therapy, Nivolumab, and Ipilimumab were 11.5 months, 6.9 months, and 2.9 months, respectively. The grade three and four adverse events in the Nivolumab-Ipilimumab combination group were 59%, compared to 23% in the Nivolumab, and 28% in the Ipilimumab group.(93) Nivolumab-Ipilimumab combination therapy being the only treatment without determined five-year survival for metastatic melanoma seems promising and clinical trials investigating alternative dosing are currently ongoing. Nivolumab plus Ipilimumab is currently the first-line therapy for metastatic melanoma. (92)

7.3.6 Aldesleukin (IL-2)

Interleukin-2 (IL-2) is a cytokine that stimulates the proliferation and maturation of T-cells. Aldesleukin is its recombinant form. As part of the adaptive immune system, the T-cells respond to foreign proteins, microorganisms, and tumor cells.(94) The T cell growth factor received FDA approval in 1998 for the treatment of stage IV melanoma. Today, it is only rarely used due to its unfavorable toxicity profile and more effective alternatives.(95,96) Typical dosing consisted of 600,000 to 720,000 IU/kg IV every eight hours. The maximum of 14 doses shall not be exceeded. Based on tolerance, the therapy can be repeated after six to nine days of rest. A new course may be started after six to twelve weeks. According to a trial with 270 patients with metastatic melanoma, the overall response rate was 16 %. Six percent of patients acquired a complete response and ten percent a partial response. The overall duration of

response was 8.9 months. Partial responders averaged 5.9 months and more than half of the patients with complete responses were still responsive to treatment after 24 to 106 months. The most frequent side effects comprise fatigue, fever, chills, nausea, diarrhea, and capillary leak syndrome. The latter may result in consequential peripheral edema, hypotension, renal insufficiency, and pulmonary edema. Anaphylaxis, shock, severe infections, autoimmune disorders, and neurologic conditions such as stupor, somnolence, and coma are more serious complications.(94,97,98)

7.4 Targeted Therapy

Targeted therapy aims at specific mutations that a tumor may inherit. Patients with metastatic melanoma are assessed for mutations and the results further guide treatment.(7)

7.4.1 Vemurafenib

Vemurafenib is discussed in detail earlier in the paragraph “Vemurafenib” under “Adjuvant Therapy”. A randomized phase III study (COLUMBUS) conducted in 162 hospitals in 28 countries investigated among others the drug Vemurafenib in patients with locally advanced, unresectable, or metastatic melanoma. Patients in the Vemurafenib group received 960 mg twice daily, until disease progression, death, intolerable adverse effects, or withdrawal of consent was reached. The primary endpoint was defined as progression-free survival. One-year overall survival was 63.1% and two-year survival was 43.3% in the Vemurafenib group. These were the lowest values in the study, with Encorafenib alone and in combination with Binimetinib achieving better results. These treatments will be discussed further in the next paragraph. Duration of response was also lowest in the Vemurafenib group and amounted to 12.3 months.(99) In earlier clinical trials, Vemurafenib displayed a clinical benefit over dacarbazine.(100) A major problem in the monotherapy with Vemurafenib is the rapid development of resistance within six to eight months. Due to this reason, combination of Vemurafenib with other agents such as Cobimetinib may evade this problem.(101,102) In the COLUMBUS trial, 66% of patients in the Vemurafenib group experienced grade three or four adverse events. 17% of adverse events lead to the discontinuation of the treatment. The most common grade three or four adverse events were arthralgia (5.9%), asthenia (4.3%), rash (3.2%), and diarrhea (2.2%). Less common adverse effects in these groups were for instance photosensitivity, palmoplantar keratoderma, constipation, headache, myalgia, and decreased appetite. Among all grades, the most common adverse events proved to be arthralgia (46.2%),

alopecia (37.6%), nausea (34.9%), diarrhea (34.4%), rash (30.1%), hyperkeratosis (29.0%), pyrexia (28.5%), dry skin (23.1%), keratosis pilaris (23.1%), decreased appetite (19.4%), headache (19.9%), asthenia (18.8%), myalgia (18.3%), vomiting (16.1%), pruritus (10.8%), pain in the extremities (14.5%), and decreased appetite (19.4%).(103) In comparison to the COLUMBUS study, the extended follow-up of the BRIM-3 study, a randomized phase III open-label study, conducted prior to the COLUMBUS study, found cutaneous squamous cell carcinoma (19%), keratoacanthomas (10%), rash (9%), and abnormal liver function tests (11%) to be the most frequent grade three or four adverse events. If a keratoacanthoma or cutaneous squamous cell carcinoma were discovered, it was excised without altering or discontinuing treatment with Vemurafenib.(104,105) Due to the rapid development of resistance and the existence of drug regimens with more favorable clinical outcomes, Vemurafenib monotherapy is currently not recommended.(7)

7.4.2 Dabrafenib + Trametinib

Dabrafenib and Trametinib were discussed in detail earlier in the paragraph "Dabrafenib + Trametinib" under "Adjuvant Therapy". In a double-blind, phase III study, patients with unresectable stage IIIC or IV melanoma with BRAF V600 mutation were treated with 150mg Dabrafenib daily plus 2mg Trametinib once daily or Dabrafenib only. Three-year progression-free survival in the combination therapy group was 22% and in the monotherapy group 32%. The median OS accounted for 25.1 months in the combination therapy group and 18.7 months in the monotherapy group. According to the authors, these results support long-term first-line use of this combination regimen in advanced melanoma. Adverse events of any grade occurred in 97% of patients in either group. 48% of patients receiving combination therapy and 50% of patients receiving monotherapy had grade three or four adverse events. Common side effects in both groups were pyrexia, vomiting, chills, and peripheral edema. The incidence of hyperkeratosis, alopecia, skin papilloma, palmoplantar cutaneous squamous cell carcinoma, keratoacanthoma, and basal cell carcinoma was more frequent in the monotherapy group.(106) DREAMseq is a randomized phase III clinical trial that investigated whether immunotherapy should be followed by targeted therapy or the other way around. Patients with BRAF V600-positive metastatic melanoma were admitted to the study. In the first step, patients received either Nivolumab + Ipilimumab or Dabrafenib + Trametinib. When disease progression occurred, step two was initiated, and patients were switched to the drug regimen they did not receive previously. The two-year OS rate was significantly higher in the group treated with immunotherapy followed by targeted therapy (72% versus 52%). Due to clear beneficial results,

the trial was stopped prematurely.(9) The FDA granted approval to Dabrafenib + Trametinib for the treatment of unresectable or metastatic melanoma with BRAF V600E/K mutation in 2014.(107) Compared with other BRAF and MEK inhibitors, Dabrafenib + Trametinib may be the therapy of choice for patients with CNS metastasis.(7)

7.4.3 Vemurafenib + Cobimetinib

Vemurafenib was discussed in detail earlier in the paragraph "Vemurafenib" under "Adjuvant Therapy" and "Targeted Therapy". Cobimetinib is a MEK inhibitor that is FDA approved in combination with Vemurafenib for unresectable stage IIIC or IV melanoma with BRAF V600 mutation. The MAPK signaling pathway is outlined in the paragraph about adjuvant treatment with Vemurafenib. As Vemurafenib inhibits BRAF, Cobimetinib inhibits another protein in the MAPK signaling pathway, namely MEK which is located downstream of BRAF. 80% of tumors developed resistance to BRAF inhibitors alone within six to seven months. Combining a BRAF and MEK inhibitor showed a longer lasting and improved response with less toxicity compared to monotherapy with Vemurafenib.[60,99,100] The international, multicenter, randomized phase III CoBRIM trial evaluated efficiency and safety in patients treated with Vemurafenib only and in combination with Cobimetinib in the abovementioned patient group. Median progression-free survival was 9.9 months for the combination treatment and 6.2 months for patients treated with Vemurafenib only. The overall response rate accounted for 68% in the combination group and 45% in the monotherapy group.(109) The median duration of response was 13.0 months in the combination arm and 9.2 months in the monotherapy arm. The combination group showed a median overall survival of 22.3 months compared with 17.4 months in the monotherapy group. In the Vemurafenib versus the Vemurafenib plus Cobimetinib group, one-year overall survival was 63.8% versus 74.5%, and two-year overall survival was 38.0% versus 48.3%, respectively. 98% of patients experienced adverse events in the combination group and 95% in the monotherapy group. Grade three or worse adverse events occurred in 60% in the combination arm and 52% in the monotherapy arm. The known adverse event of cutaneous squamous cell carcinoma, keratoacanthoma, and Bowen's disease occurred in fewer patients in the Vemurafenib and Cobimetinib group. Six % in the combination group were affected versus 20% in the Vemurafenib-only group. Photosensitivity was more common with 34% in the combination group and 20% in the monotherapy group. These were mostly adverse events of grade one or two. Other adverse events more common with Cobimetinib were serous retinopathy, decreased left ventricular ejection fraction, and increased phosphokinase level. Discontinuation of the treatment occurred in 14% in the Cobimetinib and Vemurafenib

group and in 17% in the Vemurafenib group.(110) An indirect comparison utilized results from the coBRIM and COMBI-v trial to compare the efficiency and safety profile of Dabrafenib + Trametinib with Vemurafenib + Cobimetinib. No statistical difference had been found in terms of efficacy; however, it was suggested that Dabrafenib + Trametinib was associated with fewer adverse events. Adverse events of any grade, adverse events of grade three or higher, and dose interruption or modification were significantly lower in patients treated with Dabrefinib + Trametinib.(111)

7.4.4 Encorafenib + Binimetinib

Encorafenib is a BRAF inhibitor and functions in a similar fashion to Vemurafenib and Dabrafenib. Binimietinib is a MEK inhibitor like Trametinib and Cobimetinib.(112) Combination of a BRAF and MEK inhibitor is standard of care in advanced or metastatic melanoma with BRAF V600 mutations. However, the development of resistance and adverse events limit the long-term use in many cases. The pharmacological properties of Encorafenib were modified in a way to enhance efficacy while decreasing toxicity. A shorter serum half-life may contribute to delayed resistance and better tolerability. (113) The COLUMBUS study was a multicenter, randomized, open-label, phase III study that randomly distributed patients into three groups. The first group was administered 450mg of Encorafenib + 45mg of Binimetinib (COMBO450), the second group received 960mg of Vemurafenib(VEM), and the third group was given 300mg of Encorafenib (ENCO300). The median OS was highest in the COMBO450 arm with 33.6 months compared to 23.5 months in the ENCO300 arms, and 16.9 months in the VEM arm. Median progression-free survival was 14.9 months for the COMBO450 group, 9.6 months for the ENCO300 group, and 7.3 months for the VEM group. The incidences of grade three or four adverse events were very similar among all groups (68%,68%, and 66%), and the adverse events that led to discontinuation did not differ considerably either (16%, 15%, 17% in the COMBO450, ENCO300, and VEM groups, respectively).(103) The adverse events were overall similar to those observed in other BRAF and MEK inhibitors with certain differences. For instance, a lower incidence of pyrexia and photosensitivity in patients treated with Encorafenib + Binimetinib was observed compared to previous BRAF and MEK inhibitors. Moreover, these adverse events were commonly a single event and not recurrent and long-lasting as with Vemurafenib + Cobimetinib or Dabrafenib + Trametinib.(114) This study served as a basis for the FDA approval of this combination drug regimen for patients with unresectable or metastatic melanoma with a BRAF V600E/K mutation in 2018.(115) Encorafenib +

Binimetinib may be preferred over other BRAF and MEK inhibitors due to their convenience. It can be stored at room temperature and intake is independent of the last meal.(7)

7.4.5 Vemurafenib + Cobimetinib + Atezolizumab

Atezolizumab is a programmed death-ligand 1 (PD-L1) inhibitor. The receptor PD-1 is expressed on activated T and B cells, dendritic cells, and macrophages. When activated, an inhibitory sign is delivered, and the production of cytokines and the proliferation of T cells is dampened. If tumor cells express PD-L1, they evade the host immune response by binding to the PD-1 receptor. Atezolizumab being a PD-L1 inhibitor potentially prevents tumor cells from escaping the immune system in this way.(116) The ongoing IMspire150 randomized, double-blind, placebo-controlled phase III trial compared Vemurafenib plus Cobimetinib plus Atezolizumab placebo with Vemurafenib plus Cobimetinib plus Atezolizumab. The progression-free survival in the Atezolizumab group was 15.1 months versus 10.6 months in the control group. Patients with BRAF V600 mutation-positive advanced melanoma can potentially benefit from this combination therapy in the future. 99% of both groups showed adverse events related to the treatment. Adverse events more common in the Atezolizumab group were increased blood creatine phosphokinase, pyrexia, arthralgia, myalgia, liver enzymes and bilirubin, hyper- and hypothyroidism, pneumonitis, pruritus, and peripheral edema. Adverse events of grade three or four occurred at a similar incidence, with 79% in the Atezolizumab arm and 73% in the control arm.(117) Due to the significant increase in progression-free survival, the triple combination was FDA-approved in 2020 for unresectable or metastatic melanoma with BRAF V600 mutation.(118) It has been criticized that Vemurafenib + Cobimetinib + Atezolizumab in the IMspire150 trial were not compared to monotherapy with a PD-1 inhibitor such as Pembrolizumab or Nivolumab or Nivolumab + Ipilimumab. Therefore, it is not possible to conclude whether combining immunotherapy with targeted therapy is superior to the current approach of immunotherapy followed by targeted therapy. This is the reason why triple therapy is currently not widely used in clinical practice despite FDA approval.(7)

7.5 Radiotherapy

Generally, radiation therapy has a limited role in the treatment of melanoma. Adjuvant radiotherapy may be applicable for patients with positive margins after surgical removal of the primary tumor where re-excision would cause significant morbidity.(119) Desmoplastic melanoma has a high local recurrence rate of up to 48% after resection of the primary tumor and adjuvant radiotherapy is indicated in this patient group rather than surgery alone.(120)

Based on a phase III randomized clinical trial, patients with a high risk of nodal recurrence may be considered for local radiation therapy. High-risk factors are multiple positive nodes, especially in the parotid gland, two or more nodes in the axilla, three or more nodes in the groin, extranodal spread, size of three or more centimeters in the neck, four or more centimeters in the axilla or groin, positive margins, and recurrent disease after previous surgery. In the palliative setting, radiotherapy can provide symptomatic relief for cerebral metastases, bone pain, spinal cord compression, and symptomatic soft tissue metastases.(121)

7.6 Therapies in Development

7.6.1 Adoptive Cell Transfer

There are several types of adoptive cell transfer (ACT) and the one most extensively studied in clinical trials is TIL (tumor-infiltrating lymphocytes). Other types such as endogenous T-cell therapy, CAR T, and TCR transduced T-cells will not be further discussed here.(122) Before the adoptive cell transfer with TIL, the patients must be preconditioned. This is commonly done with nonmyeloablative chemotherapy (NMA) with cyclophosphamide and fludarabine. Another option is total body irradiation (TBI) or a combination thereof. This lymphodepletion is thought to lay a basis for TIL to work more efficiently. One potential mechanism is the depletion of regulatory T cells normally suppressing immune reactions. IL-7 and IL-15 increase survival and proliferation of T cells. After lymphodepletion, the transferred T cells need to compete with less endogenous lymphocytes for these cytokines. Additionally, lymphodepletion may create “physical space” for the treatment.(123,124) It has not been shown yet whether NMA, TBI, or a combination thereof is the most effective preconditioning. Conflicting results regarding efficacy and toxicity have been noted so far. A phase II clinical trial in the Sheba center in Israel investigating this issue is still ongoing.(124,125) TIL are gained from resected melanoma metastasis of the patient and these lymphocytes are multiplied ex vivo. TIL are administered to the patient in the form of an infusion together with IL-2. IL-2 seems necessary to allow proliferation and maintenance of the infused T cells.(122,126) The infused T cells shall recognize and eradicate the tumor cells. There are currently more than 20 clinical trials investigating TIL therapy as monotherapy and in combination with other drugs.(124) In a phase II clinical trial, 22% of patients reached complete tumor regression. The overall three- and five-year survival rates were 36% and 29%, respectively. However, it was 100%, and 93% for the complete responders. Prior treatment did not seem to influence response to TIL.(127) Most adverse events were related to the lymphodepletion or the application of IL-2. Toxicity related to TIL was mostly transient and mild. Dyspnea, chills, and fever may develop. Autoimmune

toxicity such as vitiligo, uveitis, or hearing loss rarely occurred. Despite promising results, TIL therapy has several constraints. As every infusion is produced for the individual patient, costs are relatively high, and production takes more than one month. Additionally, equipping facilities appropriately is expensive and staff needs to be trained properly. Nevertheless, TIL shows great potential and ongoing phase III RCTs will clarify its clinical effectiveness and safety.(124)

7.6.2 Melanoma Vaccine

The goal of the vaccine is to elicit an immune response against the tumor. The vaccine carries incorporated tumor-associated antigens, possibly in combination with vaccine adjuvants to further increase the immune response. The tumor-associated antigens are presented on MHC complexes by antigen-presenting cells (APCs). MHC class I stimulate CD8 T cells (TCD8), and MHC class II stimulate CD4 helper T cells (TCD4). A combination of CD8 and CD4 T cells is likely necessary to trigger a sufficient response. Antigens used in the vaccine may be neoantigens that are specifically identified from a particular patient or antigens commonly shared in patients with melanoma. Several types of shared melanoma antigens have been identified.

Melanocytic differentiation antigens include proteins such as Tyrosinase, TRP-2, Melan-A/MART-1, and gp-100. They are expressed on many melanomas, but also on normal melanocytes. Therefore, central tolerance may decrease the desired T cell response.(128) Nevertheless, a phase I/II clinical trial testing melanoma vaccine containing proteins such as MAGE, MART-1/MelanA, gp-100, and tyrosinase on stage IIIB to IV melanoma patients showed preliminary moderate clinical success. 12% of patients underwent objective clinical tumor regression and 12% noted lasting stable disease. Clinical outcomes were measured on 17 patients, and a larger study group is necessary to draw statistically significant conclusions. Toxicity was evaluated for 39 patients who initially participated in the study. No grade four adverse events, deaths, or dose-limiting toxicities were encountered. Flu-like symptoms after the administration of the vaccine were common. Other frequently encountered adverse events were fatigue, headache, myalgias, rigors/chills, arthralgias, nausea, dizziness, hyperkalemia, and a decrease in hemoglobin. Autoimmune adverse events such as vitiligo or asymptomatic elevation of rheumatoid factor occurred in 21% of patients.(129) Shared mutated antigens can arise from somatic mutations or single-nucleotide polymorphisms in melanoma cells. BRAF; KIT, and NRAS are antigens that are often mutated in melanoma. BRAF V600 peptide vaccine induced an immune response in mice and inhibited tumor growth.

In how far this translates to humans would be a subject of further studies.(128,130) Cancer germline antigens have immune privilege at sites such as the placenta, and testes. Some malignant tumors also express these antigens. The selective expression of these antigens in melanoma and the inaccessibility of the immune cells to healthy cells at immune privileged sites offer a good possibility to target melanoma cells with a vaccine. Examples of cancer germline antigens include MAGE-A1, MAGE-A3, BAGE, GAGE, and NY-ESO-1. In a pilot trial, ACT with T cells expressing a T cell receptor (TCR) transduced with NY-ESO-1 showed promising results which could potentially be translated into the vaccine setting. 55% of patients with melanoma proved an objective clinical response.(128,131) However, a phase III, double-blind, randomized, placebo-controlled, multicenter trial failed to prove clinical benefits in stage IIIB/C melanoma patients treated with MAGE-A3 vaccine in the adjuvant setting. Based on these results, further exploration of this treatment option has been halted.(132) Malignant transformation is promoted by the phosphorylation of oncogenic proteins. Phosphorylated peptides, the product of these proteins, may be used as tumor-specific phosphopeptide antigens that are potentially presented by MHC class I and II molecules and elicit an immune response against tumor cells. A study with 15 stage IIA to IV melanoma patients assessed vaccines containing cancer-associated phosphopeptides pBCAR3 and pIRS2 regarding safety and immunogenicity. No grade three or four adverse events or deaths were reported, and other adverse events included for instance fatigue, chills, headaches, autoimmune disorders, and diarrhea. Altogether, 40% of patients had a T cell immune response. The authors state that these results merit further exploration, but the sample size is too small to draw conclusions about clinical outcomes.(133)

Mutated neoantigens are mutations found in tumor cells, but not in normal cells. These DNA, RNA, or translated peptides may be used as tumor-associated antigens. Data suggests that central tolerance may be avoided while strong reactions toward these antigens can be achieved. This is an example of personalized medicine where individual mutations are targeted. This comes with the drawback of requiring more advanced facilities and longer periods of time until the administration of treatment compared to conventional drug or vaccine therapy. In a phase I study including five patients with melanoma, an RNA vaccine was utilized. All patients developed a T cell response and 40% of patients with metastatic disease showed an objective response. Further trials shall be awaited to understand the clinical impact of such vaccines.(128,134)

Whole-cell vaccines integrate complete cancer cells into vaccines. With this strategy, multiple mutated neoantigens from the tumor are introduced in the vaccine. However, mutations may

not be identified preceding vaccine development. A placebo-controlled, phase III clinical trial using a whole-cell vaccine in patients with completely resected stage IV melanoma did not show beneficial clinical outcomes in the treatment group compared to the placebo group.(135) A different multicenter, double-blind, placebo-controlled phase III trial that is still ongoing showed potentially favorable results. Patients with stage IIB to III melanoma received the polyvalent vaccine seviprotimut-L consisting of three human melanoma cell lines. The three cell lines were taken from a metastatic melanoma, a BRAF V600-positive amelanotic metastatic melanoma, and a BRAF V600-positive and NRAS wild-type axillary lymph node. As not all parts of the study have been concluded, final results cannot be reported yet. However, current results suggest that patients with stage IIB/C melanoma, patients under the age of 60, and patients with ulcerated melanoma should be further evaluated in the next part of the trial.(136) A relatively new approach to melanoma vaccines is the use of induced pluripotent stem cells (iPSCs). Tumor-associated antigens were discovered in human and murine iPSCs. Tumor models showed decreased tumor growth and based on these positive preclinical outcomes, future studies are to be expected.(137)

8 Follow-up Care

The main objective of follow-up care is early recognition of recurrent disease. With new treatment options having emerged, patients with advanced disease have better outcomes nowadays compared to ten years ago. Additionally, patients with malignant disease are more likely to develop a second primary tumor which can be recognized at follow-up visits. Another advantage of follow-up care is the psychological support of the patient and the possibility to track therapeutical outcomes.(138)

Follow-up is guided by recommendations varying by country and no universal guidelines have been established till now. The following table compares the recommendations in the US and Germany.

Table 6 (138)

Comparison of follow-up recommendations for patients with melanoma from the NCCN guidelines (United States) and the clinical practice guidelines from the German Cancer Society

Follow-up Category	NCCN (US)	Germany
Self-examination recommended?	Yes	Not stated
Follow-up Interval		
Stage I	3-12 mo x 5 years (a)	6 mo x 5 years (b)
Stage II and III	3-6 mo x 2 years (a) 3-12 mo x 3 years (a)	3 mo x 5 years (c)
Routine Imaging		
Stage I	No	No
Stage II and III	Consider (d)	Yes (e)
Routine Blood Work?	No	Yes (f)

(a) Annual follow-up after 5 years as clinically indicated.
(b) 6-12 months follow-up in years 6-10.
(c) 6-months follow-up in years 6-10.
(d) Consder CXR, CT, and/or PET-CT scans to screen for recurrent/metastatic disease. Consider brain MRI annually. Routine imaging is not recommended after 5 years.
(e) Reginal lymph node US for stage II (every 6 months) and III (every 3 months) melanomas for 5 years. Andominal US and CXR or CT, MRI, or PET scan at each visit for 5 years.
(f) Serum S-100B protein levels every 3-6 months for stage II and III melanomas.

Depending on the stage, follow-up visits every 3 to 12 months are recommended for the first five years. Routine imaging is considered or recommended for stage II melanoma and higher. There is a consensus that most melanoma recurrences are discovered by the patient. A study conducted to detect differences in survival based on physician or patient-detected recurrence did not find a statistically significant survival difference. 72% of recurrences in this study were detected by patients.(139) As no randomized clinical trials have investigated the effect of detection methods on the survival of patients with melanoma, it remains questionable whether regular follow-ups are always reasonable. A retrospective analysis of patients with stage III melanoma showed that first recurrences were detected in 47% by the patient or his family, in 21% by the physician, and in 32% by imaging. Regarding stage IIIA to IIIC melanoma, the authors recommended follow-up visits including physical examination and radiologic imaging for a period of one to three years depending on the exact stage. Beyond this time frame, little evidence supports further check-ups.(140) Compared to physical examination, laboratory testing could identify recurrences earlier. The

S-100B protein is utilized as a routine immunohistochemical maker for melanoma and melanoma metastasis in stage II and III melanoma patients in Germany. With a sensitivity of 32% and a specificity of 96%, this marker may be suboptimal and not reliable. Therefore, only a few countries adopted this marker into routine follow-ups.(141)
The lungs are the most common target site of metastatic melanoma. Therefore, the question arose whether chest X-rays or CTs would increase survival. This has not been assessed in any RCTs and the literature contains conflicting information. However, it seems that patients with advanced melanoma seem most likely to benefit from screening in the form of imaging.(141)
It was suggested that subclinical stage IV melanoma may be identified with regular lymph node US. Metastasis in lymph nodes may be fully resected, while a spread to visceral organs may render a complete resection more difficult. Therefore, this patient group may particularly benefit from lymph node US. Several studies investigated the use of US for nodal recurrences and reported sensitivities between 86.6% and 98%, and specificities between 94.6% and 99.7%. However, these studies must be considered with caution as they were conducted prior to routine use of sentinel lymph node biopsy which removes the most common site of affected lymph nodes. The MSLT-II trial investigated complete dissection versus observation with lymph node US for sentinel-node metastasis in melanoma. No significant difference in melanoma-specific survival was proven. Considering complications such as lymphedema from complete dissection, US as a means of observation may be of great value in this patient group.(142)
Germany, for instance, recommends US lymph node screening every six months for stage II melanoma and every three months for stage III melanoma. Germany additionally recommends abdominal US and X-ray, or CT, MRI, or PET in stage II or III melanoma for five years every three months. In the US, the physician decides on an individual basis to which extent a patient with stage II or III melanoma requires imaging.(138)

9 Management of Advanced Melanoma in Patients with COVID-19

COVID-19 is caused by the novel coronavirus-CoV2, and the pandemic has challenged the health care system in many ways. Apart from those patients directly affected by the virus, many patients suffer indirect consequences through postponed surgeries, treatments, follow-ups, or screening appointments. The future will show the extent of “invisible collateral damage” caused by COVID-19.(143)
The European Society for Medical Oncology (ESMO) has formulated clear recommendations for the management of melanoma patients during the COVID-19 pandemic according to low, medium, and high priority. This paragraph will only review those recommendation applicable

to advanced melanoma. Regarding outpatient visits, a high priority is given to newly diagnosed invasive primary melanoma, patients with post-operative complications, patients on immune-oncology therapy with shortness of breath, grade two or higher diarrhea, or new disease affecting the nervous system. Patients on BRAF/MEK inhibitors with unremitting fever should undergo COVID-19 testing. Generally, as many visits as possible should be conducted via telemedicine. This includes visits between treatments, post-operative patients reporting no complications, and follow-ups for recovered patients and patients off treatment. The dosing regimen for patients receiving PD-1 inhibitors has been adapted to reduce the number of visits necessary. Pembrolizumab shall be administered every 6 weeks at a dose of 400 mg and Nivolumab at a dose of 480 mg every 4 weeks with a telemedicine visit in between. If possible, blood work-up shall be performed in a local laboratory. Similarly, follow-up visits via telemedicine and blood work-up in local laboratories are recommended for patients treated with tyrosine kinase inhibitors. High priority surgeries are resection of stage III melanoma with curative intent, wide excision, and sentinel lymph node biopsy for T3 or T4 melanoma, management of complications from prior surgical interventions, and patients enrolled in neo-adjuvant trials. Medium priority is granted to T1 or T2 melanoma scheduled for wide excision and sentinel lymph node biopsy. In the setting of adjuvant systemic therapy, high priority is given to patients participating in a clinical trial. Patients receiving immune or targeted therapy with melanoma stage IIIB or higher receive a medium priority. Melanoma with stage IIIA or lower is categorized as low priority. Systemic non-operable stage III/IV melanoma patients are always high priority.(144) The American National Comprehensive Cancer Network (NCCN) recommends vaccination in cancer patients, including those receiving targeted or immune therapy, as well as major surgery. Patients with a weakened immune system should receive a third dose approximately four weeks after their second shot, which is followed by a booster shot after three months. Cancer patients with an intact immune system receive two doses and a booster after at least five months. The committee believes that mRNA vaccines such as Pfizer-BioNTech and Moderna should be first-line vaccinations.(145)

10 Melanoma Prognosis

The incidence of melanoma continuously increased during the last decades. However, between 2005 and 2018, it decreased by one percent in the age group below 50. The incidence rate between 2014 and 2018 in patients older than 50 years stabilized. In the US, deaths from melanoma decreased every year between 2015 and 2019 by four percent. This decrease may be attributed to advances in treatment of melanoma.(146)

Five-year survival in T1a to T4b melanoma (stage IA to IIC) reaches from 99% to 82%. Stage IIIA, B, C, and D melanoma has a five-year survival rate of 93%, 83%, 69%, and 32% respectively.(147) The five-year survival rate for stage IV metastatic melanoma is approximately 30%.(148) Combining the results of multiple studies, the five-year OS rates for patients with metastatic melanoma treated with immunotherapy or targeted therapy range between 34 and 60 percent. Historically, the survival rate was less than ten percent.(149–151)

11 Melanoma Prevention

The development of melanoma is influenced by genetic and environmental factors. Primary prevention aims at reducing exposure to environmental factors that increase the risk of developing melanoma. It is estimated that two-thirds of malignant melanomas develop because of exposure to ultraviolet (UV) radiation.(152) National public health campaigns such as the "SunSmart" campaign in Australia have contributed to a decreased incidence of melanoma.(153) UV radiation is a carcinogen that is strongly associated with the development of melanoma.(154) UV radiation is distinguished by wavelength. UVC radiation (200-280 nm) in Europe is fully filtered by the ozone layer while UVB radiation (280-320 nm) reaches the stratum basale of the epidermis and can cause sunburns and tanning. UVA radiation (320-400 nm) can penetrate window glass and contributes to the aging of the skin.(155) Fair-skinned people are at a higher risk of developing melanoma.(156) A systemic review suggests that UV exposure may not be a significant risk factor for the development of melanoma in darker skin types.(157) Children's skin is especially sensitive to UV radiation and an increased risk for the development of melanoma has been described in the context of sunburns and cumulative exposure.(158) Atypical nevi or an increased number of common naevi are associated with an increased risk of melanoma. However, controversy exists about whether protection from UV radiation lowers the risk of developing melanoma in this subgroup.(159–161) It is especially important to protect vulnerable groups from UV radiation. Evidence suggests broad-spectrum UVA and UVB sunscreen with a minimum SPF of 30 as a protective measure against melanoma.(162) Sun-protective clothes and special window glass, films, and cosmetics containing broad-spectrum sunscreen offer further protection from UV radiation.(163–165) The use of indoor tanning beds significantly increases the risk of developing melanoma later in life and should not be practiced.(166) Chemoprevention aims at delaying or preventing the development of cancer via using certain agents. Agents such as Vitamin E, Vitamin D, Nicotinamide, Selenium, and nonsteroidal anti-inflammatory drugs have been investigated. To date, none have proved to be efficient in clinical trials.(167)

The goal of secondary prevention is the detection of disease in its earliest stage. There are no universal guidelines stating which population should undergo screening. The literature suggests that it would be out of proportion to screen an entire population and the focus should lie on high-risk groups.(168) This includes white adults above the age of 50, a total naevus count above 50, and/or the presence of atypical/dysplastic naevi, personal history of skin cancer, immunosuppression, very fair-skinned individuals, and a family history of melanoma. A clinician (usually a dermatologist or general practitioner) performs a total body skin examination and closer examines suspicious lesions with a dermatoscope. It is suggested that every person may benefit from self-examination carried out at home. A potential downside of screening is overdiagnosis. Some lesions may only be identified because of screening and would potentially never evolve into a malignancy. This would cause increased morbidity without a decrease in mortality.(169)

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13 References

1. Elder DE, Bastian BC, Cree IA, Massi D, Scolyer RA. The 2018 World Health Organization classification of cutaneous, mucosal, and uveal melanoma detailed analysis of 9 distinct subtypes defined by their evolutionary pathway. Arch Pathol Lab Med. 2020;144(4):500–22.

2. Heng JK, Aw DCW, Tan KB. Solar elastosis in its papular form: Uncommon, mistakable. Case Rep Dermatol. 2014;6(1):124–8.

3. Keung EZ, Gershenwald JE. The eighth edition American Joint Committee on Cancer (AJCC) melanoma staging system: implications for melanoma treatment and care. Expert Rev Anticancer Ther. 2018 Aug 3;18(8):775–84.

4. Gershenwald JE, Scolyer RA. Melanoma Staging: American Joint Committee on Cancer (AJCC) 8th Edition and Beyond. Ann Surg Oncol. 2018 Aug 1;25(8):2105–10.

5. Luke J, Luke JJ, Rutkowski P, Queirolo P, del Vecchio M, Mackiewicz J, et al. Pembrolizumab versus placebo after complete resection of high-risk stage II melanoma: Efficacy and safety results from the KEYNOTE-716 double-blind phase III trial. Oncol Pro [Internet]. 2021; Available from: https://oncologypro.esmo.org/meeting-resources/esmo-congress/pem…ma-efficacy-and-safety-results-from-the-keynote-716-double-blind

6. Sosman JA. Adjuvant and neoadjuvant therapy for cutaneous melanoma [Internet]. 2022 [cited 2022 Apr 24]. Available from: http://www.uptodate.com

7. Sosman JA. Systemic treatment of metastatic melanoma with BRAF and other molecular alterations [Internet]. 2022 [cited 2022 Apr 24]. Available from: http://www.uptodate.com

8. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation. N Engl J Med. 2011 Jun 30;364(26):2507–16.

9. Atkins MB, Lee SJ, Chmielowski B, Ribas A, Tarhini AA, Truong TG. DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing): A phase III trial—ECOG-ACRIN EA6134. J Clin Oncol. 2021;39(36).

10. Sosman JA. Systemic treatment of metastatic melanoma lacking a BRAF mutation [Internet]. 2022 [cited 2022 Apr 24]. Available from: http://www.uptodate.com

11. Ascierto PA, Schadendorf D, Berking C, Agarwala SS, van Herpen CML, Queirolo P, et al. MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: A non-randomised, open-label phase 2 study. Lancet Oncol. 2013 Mar;14(3):249–56.

12. Postow MA, Chapman PB. A step forward for patients with NRAS-mutant melanoma. Vol. 18, Lancet Oncol. Lancet Publishing Group; 2017. p. 414–5.

13. Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1–2 trials. Lancet Oncol. 2020 Feb 1;21(2):271–82.

14. Drilon A, Siena S, Ou SHI, Patel M, Ahn MJ, Lee J, et al. Safety and antitumor activity of the multitargeted pan-TRK, ROS1, and ALK inhibitor entrectinib: Combined results from two phase I trials (ALKA-372-001 and STARTRK-1). Cancer Discov. 2017 Apr 1;7(4):400–9.

15. Hong DS, DuBois SG, Kummar S, Farago AF, Albert CM, Rohrberg KS, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol. 2020 Apr 1;21(4):531–40.

16. Joyce KM. Surgical Management of Melanoma. In: Cutaneous Melanoma: Etiology and Therapy. Codon Publications; 2017. p. 91–100.

17. Hanna S, Lo SN, Saw RP. Surgical excision margins in primary cutaneous melanoma: A systematic review and meta-analysis. Eur J Surg Oncol. 2021 Jul 1;47(7):1558–74.

18. Wheatley K, Wilson JS, Gaunt P, Marsden JR. Surgical excision margins in primary cutaneous melanoma: A meta-analysis and Bayesian probability evaluation. Cancer Treat Rev. 2016 Jan 1;42:73–81.

19. MelmarT Melanoma Margins Trial Investigating 1cm v 2cm Wide Excision Margins for Primary Cutaneous Melanoma Information provided by Melanoma and Skin Cancer Trials Limited (Responsible Party) [Internet]. 2022. Available from: https://beta.clinicaltrials.gov/study/NCT02385214?patient=Melm…Primary%20Cutaneous%20Melanoma%20

20. Pavri SN, Clune J, Ariyan S, Narayan D. Malignant melanoma: Beyond the basics. Plast Reconstr Surg. 2016 Aug 1;138(2):330e–40e.

21. Pandit AS, Geiger EJ, Ariyan S, Narayan D, Choi JN. Using topical imiquimod for the management of positive in situ margins after melanoma resection. Cancer Med. 2015 Apr 1;4(4):507–12.

22. Yde SS, Sjoegren P, Heje M, Stolle LB. Mucosal Melanoma: a Literature Review. Vol. 20, Current Oncology Reports. Current Medicine Group LLC 1; 2018.

23. McCarty MA, Lentsch EJ, Cerrati EW, Stadelmann WK. Melanoma of the ear: Results of a cartilage-sparing approach to resection. Eur Arch Oto-Rhino-Laryngology. 2013 Nov;270(11):2963–7.

24. Craig ES, Nagarajan P, Lee ES, Lazova R, Terner J, Narayan D. The perichondrium in auricular melanomas: Implications for surgical management. Otolaryngol - Head Neck Surg (United States). 2013 Mar;148(3):431–5.

25. Cochran AM, Buchanan PJ, Bueno RA, Neumeister MW. Subungual melanoma: A review of current treatment. Plast Reconstr Surg. 2014;134(2):259–73.

26. Sentinel Lymph Node - MeSH - NCBI.

27. Wong SL, Faries MB, Kennedy EB, Agarwala SS, Akhurst TJ, Charlotte C, et al. Sentinel Lymph Node Biopsy Sentinel Lymph Node Biopsy and Management of Regional and Management of Regional Lymph Nodes in Melanoma: ". Available from:

https://ascopubs.org/doi/10.1200/JCO.2017.75.7724?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

28. Bello DM, Faries MB. The Landmark Series: MSLT-1, MSLT-2 and DeCOG (Management of Lymph Nodes). Ann Surg Oncol. 2020 Jan 1;27(1):15–21.

29. Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, et al. Final Trial Report of Sentinel-Node Biopsy versus Nodal Observation in Melanoma. N Engl J Med. 2014 Feb 13;370(7):599–609.

30. Morton DL, Cochran AJ, Thompson JF, Elashoff R, Essner R, Glass EC, et al. Sentinel node biopsy for early-stage melanoma: Accuracy and morbidity in MSLT-I, an international multicenter trial. In: Annals of Surgery. 2005. p. 302–13.

31. Morrison S, Han D. Re-evaluation of Sentinel Lymph Node Biopsy for Melanoma. Curr Treat Options Oncol. 2021 Mar 1;22(3).

32. Hu Y, Melmer PD, Slingluff CL. Localization of the sentinel lymph node in melanoma without blue dye. Ann Surg. 2016;263(3):588–92.

33. Kroon HM, Lowe L, Wong S, Fullen D, Su L, Cimmino V, et al. What is a sentinel node? Re-evaluating the 10% rule for sentinel lymph node biopsy in melanoma. J Surg Oncol. 2007 Jun 15;95(8):623–8.

34. McMasters KM, Reintgen DS, Ross MI, Wong SL, Gershenwald JE, Krag DN, et al. Sentinel Lymph Node Biopsy for Melanoma: How Many Radioactive Nodes Should be Removed? Ann Surg Oncol. 2001 Apr;8(3):192–7.

35. Valsecchi ME, Silbermins D, de Rosa N, Wong SL, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in patients with melanoma: A meta-analysis. J Clin Oncol. 2011 Apr 10;29(11):1479–87.

36. Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Elasho R, Essner R, et al. Sentinel-Node Biopsy or Nodal Observation in Melanoma. N Engl J Med. 2006 Sep 28;355(13):1307–17.

37. Moody JA, Botham SJ, Dahill KE, Wallace DL, Hardwicke JT. Complications following completion lymphadenectomy versus therapeutic lymphadenectomy for melanoma – A systematic review of the literature. Vol. 43, Eur. J. Surg. Oncol. W.B. Saunders Ltd; 2017. p. 1760–7.

38. de Vries M, Hoekstra HJ, Hoekstra-Weebers JEHM. Quality of life after axillary or groin sentinel lymph node biopsy, with or without completion lymph node dissection, in patients with cutaneous melanoma. Ann Surg Oncol. 2009 Oct;16(10):2840–7.

39. Bello DM, Faries MB. The Landmark Series: MSLT-1, MSLT-2 and DeCOG (Management of Lymph Nodes). Ann Surg Oncol. 2020 Jan 1;27(1):15–21.

40. Falk Delgado A, Zommorodi S, Falk Delgado A. Sentinel Lymph Node Biopsy and Complete Lymph Node Dissection for Melanoma. Curr Oncol Rep. 2019 Jun 1;21(6).

41. Adjuvant Therapy [Internet]. https://guides.library.uq.edu.au/referencing/vancouver/webpages#s-lg-box-17165996. [cited 2022 Apr 24]. Available from: http://www.uptodate.com

42. Platanias LC. Mechanisms of type-I- and type-II-interferon-mediated signalling. Nat Rev Immunol. 2005 May;5(5):375–86.

43. Rafique I, Kirkwood JM, Tarhini AA. Immune checkpoint blockade and interferon-α in melanoma. Semin Oncol. 2015 Jun 1;42(3):436–47.

44. Zhao X, Liu J, Ge S, Chen C, Li S, Wu X, et al. Saikosaponin A Inhibits Breast Cancer by Regulating Th1/Th2 Balance. Front Pharmacol [Internet]. 2019;10. Available from: https://www.frontiersin.org/article/10.3389/fphar.2019.00624

45. Tarhini AA, Gogas H, Kirkwood JM. IFN-α in the Treatment of Melanoma. J Immunol. 2012 Oct 15;189(8):3789–93.

46. Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: The Eastern Cooperative Oncology Group trial EST 1684. J Clin Oncol. 1996;14(1):7–17.

47. Mocellin S, Lens MB, Pasquali S, Pilati P, Chiarion Sileni V. Interferon alpha for the adjuvant treatment of cutaneous melanoma. Cochrane Database Syst Rev. 2013 Jun 18;2013(6).

48. Najjar YG, Puligandla M, Lee SJ, Kirkwood JM. An updated analysis of 4 randomized ECOG trials of high-dose interferon in the adjuvant treatment of melanoma. Cancer. 2019 Sep 1;125(17):3013–24.

49. Tarhini A, Lo E, Minor DR. Releasing the brake on the immune system: Ipilimumab in melanoma and other tumors. Cancer Biother Radiopharm. 2010 Dec 1;25(6):601–13.

50. Eggermont AMM, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, Schmidt H, et al. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. N Engl J Med. 2016 Nov 10;375(19):1845–55.

51. Grossmann KF, Othus M, Pradyuman Patel S, Tarhini AA, Sondak VK, Petrella TM, et al. Final analysis of overall survival (OS) and relapse-free-survival (RFS) in the intergroup S1404 phase III randomized trial comparing either high-dose interferon (HDI) or ipilimumab to pembrolizumab in patients with high-risk resected melanoma. J Clin Oncol. 2021 Feb;

52. Ascierto PA, del Vecchio M, Mandalá M, Gogas H, Arance AM, Dalle S, et al. Adjuvant nivolumab versus ipilimumab in resected stage IIIB–C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial. Lancet Oncol. 2020 Nov 1;21(11):1465–77.

53. Belum VR, Benhuri B, Postow MA, Hellmann MD, Lesokhin AM, Segal NH, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. Eur J Cancer. 2016 Jun 1;60:12–25.

54. Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol. 2014 Apr 1;32(10):1020–30.

55. Weber J, Mandala M, del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med. 2017 Nov 9;377(19):1824–35.

56. Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Cowey CL, 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 Nov 1;19(11):1480–92.

57. Yang H, Higgins B, Kolinsky K, Packman K, Go Z, Iyer R, et al. RG7204 (PLX4032), a selective BRAFV600E inhibitor, displays potent antitumor activity in preclinical melanoma models. Cancer Res. 2010 Jul 1;70(13):5518–27.

58. Sharma A, Shah SR, Illum H, Dowell J. Vemurafenib: Targeted inhibition of mutated BRAF for treatment of advanced melanoma and its potential in other malignancies. Vol. 72, Drugs. 2012. p. 2207–22.

59. Tanda ET, Vanni I, Boutros A, Andreotti V, Bruno W, Ghiorzo P, et al. Current State of Target Treatment in BRAF Mutated Melanoma. Vol. 7, Front. Mol. Biosci. Frontiers Media S.A.; 2020.

60. Menzer C, Menzies AM, Carlino MS, Reijers I, Groen EJ, Eigentler T, et al. Targeted therapy in advanced melanoma with rare BRAF mutations. In: J Clin Oncol. American Society of Clinical Oncology; 2019. p. 3142–51.

61. Maio M, Lewis K, Demidov L, Mandalà M, Bondarenko I, Ascierto PA, et al. Adjuvant vemurafenib in resected, BRAFV600 mutation-positive melanoma (BRIM8): a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. Lancet Oncol. 2018 Apr 1;19(4):510–20.

62. Bowyer S, Lee R, Fusi A, Lorigan P. Dabrafenib and its use in the treatment of metastatic melanoma. Melanoma Manag. 2015;2(3):199–208.

63. Long G v, Hauschild A, Santinami M, Atkinson V, Mandalà M, Chiarion-Sileni V, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med. 2017 Nov 9;377(19):1813–23.

64. Dummer R, Hauschild A, Santinami M, Atkinson V, Mandalà M, Kirkwood JM, et al. Five-Year Analysis of Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma. N Engl J Med. 2020;383:1139–48.

65. FDA approves dabrafenib plus trametinib for adjuvant treatment of melanoma with BRAF V600E or V600K mutations [Internet]. 2018 [cited 2022 Mar 5]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-dabrafenib-plus-trametinib-adjuvant-treatment-melanoma-braf-v600e-or-v600k-mutations

66. Fessas P, Lee H, Ikemizu S, Janowitz T. A molecular and preclinical comparison of the PD-1–targeted T-cell checkpoint inhibitors nivolumab and pembrolizumab. Vol. 44, Semin. Oncol. W.B. Saunders; 2017. p. 136–40.

67. Eggermont AMM, Blank CU, Mandala M, Long G v., Atkinson VG, Dalle S, et al. Longer follow-up confirms recurrence-free survival benefit of adjuvant pembrolizumab in high-risk stage III melanoma: Updated results from the EORTC 1325-MG/KEYNOTE-054 trial. In: J Clin Oncol. American Society of Clinical Oncology; 2020. p. 3925–36.

68. Eggermont AMM, Blank CU, Mandala M, Long G v., Atkinson V, Dalle S, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. N Engl J Med. 2018 May 10;378(19):1789–801.

69. FDA approves pembrolizumab for adjuvant treatment of melanoma [Internet]. 2019 [cited 2022 Mar 5]. Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-adjuvant-treatment-melanoma

70. FDA approves Pembrolizumab for Adjuvant Treatment of Stage IIB or IIC Melanoma [Internet]. 2021 [cited 2022 Mar 5]. Available from: https://www.esmo.org/oncology-news/fda-approves-pembrolizumab-for-adjuvant-treatment-of-stage-iib-or-iic-melanoma

71. Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. J Clin Oncol. 2015 Jun 10;33(17):1889–94.

72. Sosman JA. Overview of the management of advanced cutaneous melanoma [Internet]. 2022 [cited 2022 Apr 24]. Available from: http://www.uptodate.com

73. Ascierto PA, del Vecchio M, Mackiewicz A, Robert C, Chiarion-Sileni V, Arance A, et al. Overall survival at 5 years of follow-up in a phase III trial comparing ipilimumab 10 mg/kg with 3 mg/kg in patients with advanced melanoma. J Immunother Cancer. 2020 Jun 4;8(1).

74. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2019 Oct 17;381(16):1535–46.

75. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. Ann Oncol. 2019 Apr 1;30(4):582–8.

76. Inman S. FDA Approves Pembrolizumab for Advanced Melanoma [Internet]. [cited 2022 Mar 6]. Available from: https://www.onclive.com/view/fda-approves-pembrolizumab-for-advanced-melanoma

77. Schachter J, Ribas A, Long G v., Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet. 2017 Oct 21;390(10105):1853–62.

78. Robert C, Ribas A, Schachter J, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol. 2019 Sep 1;20(9):1187–9.

79. Long G v., Atkinson V, Cebon JS, Jameson MB, Fitzharris BM, McNeil CM, et al. Standard-dose pembrolizumab in combination with reduced-dose ipilimumab for patients with advanced melanoma (KEYNOTE-029): an open-label, phase 1b trial. Lancet Oncol. 2017 Sep 1;18(9):1202–10.

80. Lawrence L. FDA Approves Second PD-1 Inhibitor, Nivolumab, for Melanoma [Internet]. cancerNETWORK. 2014 [cited 2022 Mar 5]. Available from: https://www.cancernetwork.com/view/fda-approves-second-pd-1-inhibitor-nivolumab-melanoma

81. Koppolu V, Rekha Vasigala V. Checkpoint immunotherapy by nivolumab for treatment of metastatic melanoma. Vol. 14, J. Cancer Res. Ther. Wolters Kluwer Medknow Publications; 2018. p. 1167–75.

82. Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): A randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015;16(4):375–84.

83. Broderick JM. FDA Approves T-VEC for Advanced Melanoma [Internet]. [cited 2022 Mar 6]. Available from: https://www.onclive.com/view/fda-approves-t-vec-for-advanced-melanoma

84. Ferrucci PF, Pala L, Conforti F, Cocorocchio E. Talimogene laherparepvec (T-vec): An intralesional cancer immunotherapy for advanced melanoma. Vol. 13, Cancers. MDPI AG; 2021. p. 1–14.

85. Hersey P, Gallagher S. Intralesional immunotherapy for melanoma. Vol. 109, J. Surg. Oncol. 2014. p. 320–6.

86. Liu BL, Robinson M, Han ZQ, Branston RH, English C, Reay P, et al. ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumour properties. Vol. 10, Gene Ther. 2003. p. 292–303.

87. Johnson DB, Puzanov I, Kelley MC. Talimogene laherparepvec (T-VEC) for the treatment of advanced melanoma. Immunotherapy. 2015 Jul 1;7(6):611–9.

88. Andtbacka RHI, Collichio F, Harrington KJ, Middleton MR, Downey G, Öhrling K, 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 Jun 6;7(1).

89. Ribas A, Dummer R, Puzanov I, VanderWalde A, Andtbacka RHI, Michielin O, et al. Oncolytic Virotherapy Promotes Intratumoral T Cell Infiltration and Improves Anti-PD-1 Immunotherapy. Cell. 2017 Sep 7;170(6):1109-1119.e10.

90. Louie RJ, Perez MC, Jajja MR, Sun J, Collichio F, Delman KA, et al. Real-World Outcomes of Talimogene Laherparepvec Therapy: A Multi-Institutional Experience. J Am Coll Surg. 2019 Apr 1;228(4):644–9.

91. Nivolumab plus Ipilimumab Regimen Receives Expanded FDA Approval in Unresectable or Metastatic Melanoma Across BRAF Status | ESMO [Internet]. European Society for Medical Oncology. 2016 [cited 2022 Mar 5]. Available from: https://www.esmo.org/oncology-news/archive/nivolumab-plus-ipilimumab-regimen-receives-expanded-fda-approval-in-unresectable-or-metastatic-melanoma-across-braf-status

92. Lebbé C, Meyer N, Mortier L, Marquez-Rodas I, Robert C, Rutkowski P, et al. Evaluation of two dosing regimens for nivolumab in combination with ipilimumab in patients with advanced melanoma: Results from the phase IIIb/IV CheckMate 511 trial. In: J Clin Oncol. American Society of Clinical Oncology; 2019. p. 867–75.

93. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2019 Oct 17;381(16):1535–46.

94. Bethesda. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases [Internet]. 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548091/

95. Sosman JA. Interleukin 2 and experimental immunotherapy approaches for advanced melanoma [Internet]. [cited 2022 Mar 6]. Available from: http://www.uptodate.com

96. Interleukin-2 (IL-2, Aldesleukin, PROLEUKIN®) [Internet]. [cited 2022 Mar 6]. Available from: https://www.curemelanoma.org/patient-eng/melanoma-treatment/immunotherapy/interleukin-2-il-2-proleukin/

97. Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, Margolin K, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: Analysis of 270 patients treated between 1985 and 1993. J Clin Oncol. 1999;17(7):2105–16.

98. Wargo JA, Reuben A, Cooper Z, Amaria R. Update on use of aldesleukin for treatment of high-risk metastatic melanoma. ImmunoTargets Ther. 2015 Apr;79.

99. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018 Oct 1;19(10):1315–27.

100. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation. N Engl J Med. 2011 Jun 30;364(26):2507–16.

101. Garbe C, Eigentler TK. Vemurafenib. In: Recent Results in Cancer Research. Springer New York LLC; 2018. p. 77–89.

102. Kim A, Cohen MS. The discovery of vemurafenib for the treatment of BRAF-mutated metastatic melanoma. Expert Opin Drug Discov. 2016 Sep 1;11(9):907–16.

103. Ascierto PA, Dummer R, Gogas HJ, Flaherty KT, Arance A, Mandala M, et al. Update on tolerability and overall survival in COLUMBUS: landmark analysis of a randomised phase 3 trial of encorafenib plus binimetinib vs vemurafenib or encorafenib in patients with BRAF V600–mutant melanoma. Eur J Cancer. 2020 Feb 1;126:33–44.

104. McArthur GA, Chapman PB, Robert C, Larkin J, Haanen JB, Dummer R, et al. Safety and efficacy of vemurafenib in BRAFV600E and BRAFV600K mutation-positive melanoma (BRIM-3): Extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol. 2014;15(3):323–32.

105. Hagen B, Anh Trinh V. Managing Side Effects of Vemurafenib Therapy for Advanced Melanoma [Internet]. Vol. 5, J Adv Pract Oncol. 2014. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4530112/

106. Long G v., Flaherty KT, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/ K-mutant melanoma: Long-term survival and safety analysis of a phase 3 study. Ann Oncol. 2017 Jul 1;28(7):1631–9.

107. Inman S. Dabrafenib/Trametinib Combination Approved for Advanced Melanoma [Internet]. 2014 [cited 2022 Mar 5]. Available from: https://www.onclive.com/view/fda-approves-first-ever-combination-for-metastatic-melanoma

108. Signorelli J, Shah Gandhi A. Cobimetinib: A Novel MEK Inhibitor for Metastatic Melanoma. Ann Pharmacother. 2017 Feb 1;51(2):146–53.

109. Grimaldi AM, Simeone E, Ascierto PA. Vemurafenib plus cobimetinib in the treatment of mutated metastatic melanoma: The CoBRIM trial. Vol. 2, Melanoma Manag. Future Medicine Ltd.; 2015. p. 209–15.

110. Ascierto PA, McArthur GA, Dréno B, Atkinson V, Liszkay G, di Giacomo AM, et al. Cobimetinib combined with vemurafenib in advanced BRAFV600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol. 2016 Sep 1;17(9):1248–60.

111. Daud A, Gill J, Kamra S, Chen L, Ahuja A. Indirect treatment comparison of dabrafenib plus trametinib versus vemurafenib plus cobimetinib in previously untreated metastatic melanoma patients. J Hematol Oncol. 2017 Jan 4;10(1):1–9.

112. Rose AAN. Encorafenib and binimetinib for the treatment of BRAF V600E/K-mutated melanoma. Drugs of Today. 2019 Apr 1;55(4):247–64.

113. Koelblinger P, Thuerigen O, Dummer R. Development of encorafenib for BRAF-mutated advanced melanoma. Curr Opin Oncol. 2018 Mar 1;30(2):125–33.

114. Gogas HJ, Flaherty KT, Dummer R, Ascierto PA, Arance A, Mandala M, et al. Adverse events associated with encorafenib plus binimetinib in the COLUMBUS study: incidence, course and management. Eur J Cancer. 2019 Sep 1;119:97–106.

115. FDA approves encorafenib and binimetinib in combination for unresectable or metastatic melanoma with BRAF mutations [Internet]. [cited 2022 Mar 6]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-encorafenib-and-binimetinib-combination-unresectable-or-metastatic-melanoma-braf

116. Aleem A, Shah H. Atezolizumab Continuing Education Activity [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK567758/

117. Gutzmer R, Stroyakovskiy D, Gogas H, Robert C, Lewis K, Protsenko S, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAFV600 mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020 Jun 13;395(10240):1835–44.

118. FDA approves atezolizumab for BRAF V600 unresectable or metastatic melanoma [Internet]. 2020 [cited 2022 Mar 5]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-braf-v600-unresectable-or-metastatic-melanoma

119. Mendenhall WM, Shaw C, Amdur RJ, Kirwan J, Morris CG, Werning JW. Surgery and adjuvant radiotherapy for cutaneous melanoma considered high-risk for local-regional recurrence. American Journal of Otolaryngology - Head and Neck Medicine and Surgery. 2013 Jul;34(4):320–2.

120. Ballo MT, Ang K kian. Radiotherapy for cutaneous malignant melanoma: rationale and indications. Oncology. 2004;18(1).

121. Hong AM. Radiation therapy in the management of melanoma [Internet]. [cited 2022 Mar 6]. Available from: https://www.uptodate.com

122. Itzhaki O, Levy D, Zikich D, Treves AJ, Markel G, Schachter J, et al. Adoptive T-cell transfer in melanoma. Vol. 5, Immunotherapy. 2013. p. 79–90.

123. Gattinoni L, Finkelstein SE, Klebanoff CA, Antony PA, Palmer DC, Spiess PJ, et al. Removal of homeostatic cytokine sinks by lymphodepletion enhances the efficacy of adoptively transferred tumor-specific CD8+ T cells. J Exp Med. 2005 Oct 3;202(7):907–12.

124. Rohaan MW, van den Berg JH, Kvistborg P, Haanen JBAG. Adoptive transfer of tumor-infiltrating lymphocytes in melanoma. Vol. 6, J. Immunother. Cancer. BioMed Central Ltd.; 2018.

125. Goff SL, Dudley ME, Citrin DE, Somerville RP, Wunderlich JR, Danforth DN, et al. Randomized, prospective evaluation comparing intensity of lymphodepletion before adoptive transfer of tumor-infiltrating lymphocytes for patients with metastatic melanoma. J Clin Oncol. 2016 Jul 10;34(20):2389–97.

126. Dudley ME, Wunderlich JR, Yang JC, Hwu P, Schwartzentruber DJ, Topalian SL, et al. A phase I study of nonmyeloablative chemotherapy and adoptive transfer of autologous tumor antigen-

specific T lymphocytes in patients with metastatic melanoma. Clin Trial [Internet]. 25(3):243–51. Available from: https://pubmed.ncbi.nlm.nih.gov/12000866/

127. Rosenberg SA, Yang JC, Sherry RM, Kammula US, Hughes MS, Phan GQ, et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Clin Cancer Res. 2011 Jul 1;17(13):4550–7.

128. Kwak M, Leick KM, Melssen MM, Slingluff CL. Vaccine Strategy in Melanoma. Surg Oncol Clin N Am. 2019 Jul 1;28(3):337–51.

129. Slingluff CL, Petroni GR, Olson W, Czarkowski A, Grosh WW, Smolkin M, et al. Helper T-cell responses and clinical activity of a melanoma vaccine with multiple peptides from MAGE and melanocytic differentiation antigens. J Clin Oncol. 2008 Oct 20;26(30):4973–80.

130. Liu Q, Zhu H, Liu Y, Musetti S, Huang L. BRAF peptide vaccine facilitates therapy of murine BRAF-mutant melanoma. Cancer Immunol Immunother. 2018 Feb 1;67(2):299–310.

131. Robbins PF, Kassim SH, Tran TLN, Crystal JS, Morgan RA, Feldman SA, et al. A pilot trial using lymphocytes genetically engineered with an NY-ESO-1-reactive T-cell receptor: Long-term follow-up and correlates with response. Clinical Cancer Research. 2015 Mar 1;21(5):1019–27.

132. Dreno B, Thompson JF, Smithers BM, Santinami M, Jouary T, Gutzmer R, et al. MAGE-A3 immunotherapeutic as adjuvant therapy for patients with resected, MAGE-A3-positive, stage III melanoma (DERMA): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2018 Jul 1;19(7):916–29.

133. Engelhard VH, Obeng RC, Cummings KL, Petroni GR, Ambakhutwala AL, Chianese-Bullock KA, et al. MHC-restricted phosphopeptide antigens: Preclinical validation and first-in-humans clinical trial in participants with high-risk melanoma. J Immunother Cancer. 2020 May 7;8(1).

134. Sahin U, Derhovanessian E, Miller M, Kloke BP, Simon P, Löwer M, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature. 2017 Jul 13;547(7662):222–6.

135. Faries MB, Mozzillo N, Kashani-Sabet M, Thompson JF, Kelley MC, DeConti RC, et al. Long-Term Survival after Complete Surgical Resection and Adjuvant Immunotherapy for Distant Melanoma Metastases. Ann Surg Oncol. 2017 Dec 1;24(13):3991–4000.

136. Slingluff CL, Lewis KD, Andtbacka R, Hyngstrom J, Milhem M, Markovic SN, et al. Multicenter, double-blind, placebo-controlled trial of seviprotimut-L polyvalent melanoma vaccine in patients with post-resection melanoma at high risk of recurrence. J Immunother Cancer. 2021 Oct 1;9(10).

137. Kooreman NG, Kim Y, de Almeida PE, Termglinchan V, Diecke S, Shao NY, et al. Autologous iPSC-Based Vaccines Elicit Anti-tumor Responses In Vivo. Cell Stem Cell. 2018 Apr 5;22(4):501-513.e7.

138. Fields RC, Coit DG. Evidence-based follow-up for the patient with melanoma. Vol. 20, Surg. Oncol. Clin. N. Am. 2011. p. 181–200.

139. Mooney MM, Kulas M, McKinley B, Michalek AM, Kraybill WG. Impact on survival by method of recurrence detection in stage I and II cutaneous melanoma. Ann Surg Oncol. 1998 Jan;5(1):54–63.

140. Romano E, Scordo M, Dusza SW, Coit DG, Chapman PB. Site and timing of first relapse in stage III melanoma patients: Implications for follow-up guidelines. J Clin Oncol. 2010 Jun 20;28(18):3042–7.

141. Garbe C, Leiter U, Ellwanger U, Blaheta HJ, Meier F, Rassner G, et al. Diagnostic value and prognostic significance of protein S-100β, melanoma-inhibitory activity, and tyrosinase/MART-1 reverse transcription-polymerase chain reaction in the follow-up of high-risk melanoma patients. Cancer. 2003 Apr 1;97(7):1737–45.

142. Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, Zager JS, et al. Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. N Engl J Med. 2017 Jun 8;376(23):2211–22.

143. Moraliyage H, de Silva D, Ranasinghe W, Adikari A, Alahakoon D, Prasad R, et al. Cancer in Lockdown: Impact of the COVID-19 Pandemic on Patients with Cancer. Oncologist. 2021 Feb 1;26(2):e342–4.

144. ESMO Management and Treatment Adapted Recommendations in the COVID-19 Era: Melanoma [Internet]. 2022 [cited 2022 Mar 1]. Available from: https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/melanoma-in-the-covid-19-era

145. Recommendations of the National Comprehensive Cancer Network® (NCCN®) Advisory Committee on COVID-19 Vaccination and Pre-exposure Prophylaxis* Vaccination Recommendations for Patients with Cancer [Internet]. 2022 [cited 2022 Mar 1]. Available from: https://www.nccn.org/docs/default-source/covid-19/2021_covid-19_vaccination_guidance_v5-0.pdf?sfvrsn=b483da2b_80

146. Statistics adapted from the American Cancer Society's (ACS) publications, Cancer Facts & Figures 2022 and Cancer Facts & Figures 2020 [Internet]. 2022 [cited 2022 Mar 1]. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2022/2022-cancer-facts-and-figures.pdf

147. Tumor, node, metastasis (TNM) staging system and other prognostic factors in cutaneous melanoma. [cited 2022 Apr 24]; Available from: http://www.uptodate.com

148. Cancer Research UK Survival [Internet]. 2020. Available from: https://www.cancerresearchuk.org/about-cancer/melanoma/survival

149. Ribas A, Daud A, Pavlick AC, Gonzalez R, Lewis KD, Hamid O, et al. Extended 5-year follow-up results of a phase Ib study (BRIM7) of vemurafenib and cobimetinib in BRAF-mutant melanoma A C. Clin Cancer Res. 2020 Jan 1;26(1):46–53.

150. Robert C, Grob JJ, Stroyakovskiy D, Karaszewska B, Hauschild A, Levchenko E, et al. Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma. N Engl J Med. 2019 Aug 15;381(7):626–36.

151. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2019 Oct 17;381(16):1535–46.

152. Armstrong B, Kricker A. How much melanoma is caused by sun exposure? Melanoma Res. 1993;3(6):395–402.

153. Tabbakh T, Volkov A, Wakefield M, Dobbinson S. Implementation of the SunSmart program and population sun protection behaviour in Melbourne, Australia: Results from crosssectional summer surveys from 1987 to 2017. PLoS Med. 2019;16(10).

154. Maclennan R, Green AC, Mcleod GRC, Martin NG. Increasing incidence of cutaneous melanoma in Queensland, Australia. J Natl Cancer Inst. 1992 Sep 16;84(18):1427–32.

155. Sterry W, Czaika VA, Drecoll U, Hadshiew I, Kiecker F. Kurzlehrbuch Dermatologie. 2. Auflage. Thieme; 2018. 35 p.

156. Gilchrest BA, Eller MS, Geller AC, Yaar M. The Pathogenesis of Melanoma Induced by Ultraviolet Radiation. N Engl J Med. 1999 Apr 29;340(17):1341–8.

157. Lopes FCPS, Sleiman MG, Sebastian K, Bogucka R, Jacobs EA, Adamson AS. UV Exposure and the Risk of Cutaneous Melanoma in Skin of Color: A Systematic Review. Vol. 157, JAMA Dermatology. American Medical Association; 2021. p. 213–9.

158. Volkmer B, Greinert R. UV and Children's skin. Prog Biophys Mol Biol. 2011 Dec;107(3):386–8.

159. de Maleissye MF, Beauchet A, Saiag P, Corrêa M, Godin-Beeckmann S, Haeffelin M, et al. Sunscreen use and melanocytic nevi in children: A systematic review. Pediatr Dermatol. 2013 Jan;30(1):51–9.

160. Gallagher RP, Rivers JK, Lee TK, Bajdik CD, McLean DI, Coldman AJ. Broad-spectrum sunscreen use and the development of new nevi in white children. A randomized controlled trial. J Am Med Assoc. 2000 Jun 14;283(22):2955–60.

161. Harrison SL, Buettner PG, Maclennan R. The North Queensland "Sun-Safe Clothing" study: design and baseline results of a randomized trial to determine the effectiveness of sun-protective clothing in preventing melanocytic nevi. Am J Epidemiol. 2005;

162. Li H, Colantonio S, Dawson A, Lin X, Beecker J. Sunscreen Application, Safety, and Sun Protection: The Evidence. J Cutan Med Surg. 2019 Jul 1;23(4):357–69.

163. Draelos ZD, Lett ST. The multifunctional value of sunscreen-containing cosmetics [Internet]. Vol. 16. 2011 [cited 2022 Apr 24]. Available from: https://www.skintherapyletter.com/sunscreen/value-cosmetics/

164. Tuchinda C, Srivannaboon S, Lim HW. Photoprotection by window glass, automobile glass, and sunglasses. Vol. 54, J. Am. Acad. Dermatol. Mosby Inc.; 2006. p. 845–54.

165. Patel SP, Chien AL. Sun Protective Clothing and Sun Avoidance: The Most Critical Components of Photoprotection in Patients With Melanoma. Dermatol Surg. 2021 Mar 1;47(3):333–7.

166. Green A, Autier P, Boniol M, Boyle P, Doré JF, Gandini S, et al. The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: A systematic review. Int J Cancer. 2007 Mar 1;120(5):1116–22.

167. Jeter JM, Bowles TL, Curiel-Lewandrowski C, Swetter SM, Filipp F v., Abdel-Malek ZA, et al. Chemoprevention agents for melanoma: A path forward into phase 3 clinical trials. Vol. 125, Cancer. John Wiley and Sons Inc.; 2019. p. 18–44.

168. Finding skin cancer early [Internet]. [cited 2022 Apr 24]. Available from: https://actcancer.org/information-and-support/publications/information-sheets/finding-skin-cancer-early/

169. Geller AC, Swetter S. Screening for melanoma in adults and adolescents [Internet]. 2022 [cited 2022 Apr 24]. Available from: https://www.uptodate.com

14 Biography

Carmen Roeper was born on the 20th of August 1994 in Pinneberg, Germany. She lived in the US, the Netherlands, and Croatia. While she went to school in Germany, she participated in an international study abroad program and attended high school for a year in Carrolton, Texas, USA. After graduation, she enrolled in psychology at the University of Groningen in the Netherlands. After a semester, she decided to go into medicine and pursued her medical studies 2016 in Zagreb, Croatia.

During her studies, she worked as a private tutor for children and taught German at a language school for children. Later, she worked as an online German trainer in a language school for corporate companies.

During the summer of 2020 and 2021 she completed clerkships at the department of dermatology and venerology at the university hospital Hamburg-Eppendorf (UKE) and the department for plastic-aesthetic, reconstructive and hand surgery at Asklepios Klinik St. Georg in Hamburg, Germany, respectively. As part of her clinical rotations, the author attended additional clerkships in 2022 at the Elbe Kliniken Buxtehude in Germany and the UKE at the department for dermatology and venerology. She enjoyed furthering her knowledge in dermatology and seeing her theoretical acquired knowledge through this thesis be applied in every day clinical practice.

In her spare time, she likes to stay active dancing, going to the gym, and going on hikes.