Review Article

The role of systemic therapy in paediatric cutaneous melanoma: a review

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Abstract: Paediatric cutaneous melanoma (<21 years) is rare and may differ from adult cutaneous melanoma in clinical features, melanoma subtype and molecular features. Data on treatment of conventional melanoma (CM) in children are largely derived from adult clinical trials extrapolated to the paediatric age group, taking into account the developmental and long-term health issues that are associated with treating young patients. Data on systemic therapy of other paediatric cutaneous melanoma subtypes are very limited and significant knowledge gaps exist. This review discusses the clinical and genetic features of paediatric cutaneous melanoma and summarises the current key data on the use of immunotherapies and targeted therapies, focussing on CM, for the benefit of clinicians responsible for the care of this rare but important patient group. Based on best current evidence, paediatric patients with cutaneous melanoma should largely follow adult guidance for treatment including guidelines on when to use systemic therapy. Children with BRAF mutant cutaneous melanoma requiring systemic therapy should be treated with dabrafenib and trametinib in the adjuvant setting and in patients with unresectable disease treatment should be with nivolumab and ipilimumab or monotherapy with nivolumab or pembrolizumab. Patients with high-risk paediatric melanoma should be examined for targeted gene fusions which may provide alternative treatment options. In this rare population, early phase trials should always be considered where relevant as these may provide further options. The review also highlights the pressing need to study cutaneous melanoma of paediatric age patients within adult systemic therapy trials and to find new approaches to metastatic or highest risk non-cutaneous melanoma in children.

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Introduction

Paediatric cutaneous malignant melanoma, whilst rare, is the commonest skin cancer in children. The definition of "paediatric" melanoma varies from upper age of 13–21 years. This article considers paediatric melanoma as including children and young people from birth to age 21 years, subdivided into prepubertal (congenital/childhood)

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melanoma in patients <12 years and post-pubertal (adolescent) melanoma, in 13–21-years old.

Melanoma is understudied amongst paediatric and adolescent patients, with a relative paucity of associated literature compared to the adult population. Evidence for the role of systemic therapy in paediatric patients with adult-type conventional melanoma (CM) is largely based on adult studies and there is very limited dedicated research into systemic management of other paediatric melanoma subtypes including relapsed/recurrent disease. Whilst outside the scope of this review, it highlights a now increasingly recognised need to have more inclusive lower age limits for clinical trials of CM to improve treatment options for young patients. It also highlights the need for ongoing close cooperation between international groups for young patients. Further, the ever-increasing number of paediatric early-phase precision medicine trials may provide further opportunities for the study of specific subgroups of paediatric melanoma patients.

Whilst there is significant overlap between CM in adult and paediatric patients, paediatric melanoma has unique features in relation to presentation, behaviour, biology, and subtypes. Absence of evidence specifically relating to paediatric patients means that adult CM principles are generally used to guide treatment in children and young people. The American Joint Committee on Cancer uses a TNM (tumour, node, metastasis) surgical staging system for CM in which the key clinical characteristics are tumour thickness (Breslow thickness), ulceration, spread to local lymph nodes and distant metastasis (1). Consensus European Society for Medical Oncology (ESMO) guidelines for adult CM recommend surgical management with wide local excision (WLE) +/– nodal sampling for stage I/II/IIIa melanoma (2,3). Additional adjuvant systemic therapy is indicated for some patients with stage III and stage IV fully-resected disease. However, since melanoma requiring systemic treatment is a rare sub-population of an already rare paediatric cohort, dedicated clinical practice guidelines are needed, particularly for younger patients. Within paediatric melanoma there is also significant variability in disease presentation, risk factors and expected disease course between neonatal, child and adolescent/young adult patients (4,5).

In this review, we first describe the clinical and biological features of the main subtypes of paediatric cutaneous melanoma, review the role of sentinel node biopsy in staging of children, and discuss indications for systemic therapy in these patient groups. We review the current data that inform the use of systemic therapy in melanoma, with a particular focus on paediatric CM.

Melanoma in children

Incidence

Paediatric melanoma is rare, comprising only 1–3% of all paediatric and adolescent cancers and 1–4% of all melanomas; the incidence differs around the world with Australia having one of the highest paediatric melanoma rates (0.2–0.5/100,000 0–14 years and 5.1/100,000 15–19 years) owing to high UV exposure combined with a predominantly Caucasian population. Rates of melanoma in the prepubertal population are significantly lower (1–2 cases per million person years) than in the post-pubertal group (4–8 cases per million person years) (6-12).

Results from the North American SEER (surveillance, epidemiology and end results cancer statistics review) database from 2008–2017 demonstrated an incidence of melanoma of 4.9/million patients aged 0–19 years (13). This incidence was stable compared to 1975, masking an apparent gradual rise in the number of paediatric melanoma cases until early the 2000's, followed by a fall over the past decade. It is thought that the recently reducing rate of paediatric melanoma, particularly in the post-pubertal population, is related to better public health awareness, with countries such as Australia and Sweden that have well-established education programs around the dangers of sun exposure reporting decreasing rates (14-16).

Paediatric melanoma subtypes

The World Health Organization (WHO) classifies paediatric cutaneous melanoma into four major subtypes—*de novo* melanoma, melanoma arising in congenital melanocytic nevi (CMN), Spitz melanoma and conventional (adult-type) melanoma (CM) (17). An additional subtype is paediatric melanoma arising in blue nevi. In the pre-pubertal group, Spitz melanoma is the most common form of melanoma, whereas in the post-pubertal group Spitz melanoma and CM are almost equally common. Pre-pubertal CM is usually nodular subtype, whereas post-pubertal CM is typically the superficial spreading subtype (4).

The major adult types of CM are superficial spreading melanoma (SSM) [low CSD (cumulative sun damage) melanoma], nodular melanoma (NM) (either low or high CSD; 2 separate subtypes), lentigo maligna melanoma (high CSD melanoma) and desmoplastic melanoma (high CSD).

Table 1 Somatic genetic aberrations in paediatric melanoma subtypes

Melanoma type	WHO pathway [2018]	Associated mutations	CSD
Spitz melanoma	IV	HRAS, ROS1, NTRK1, NTRK3, ALK, RET, MET, BRAF, CDKN2A, TERT	Low/not associated with UVR exposure
CM—SSM subtype	I	BRAF V600 E/K or NRAS, CDKN2A, TP53, SWI/SNF, TERT, PTEN	Low
CM—NM subtype	May occur in any pathway1919	BRAF, NRAS, PTEN, TERT	Low or high (2 subgroups)
Melanoma arising in CMN	VII	NRAS	Low/not associated with UVR exposure
Melanoma arising in blue naevus	VIII	GNAQ, GNA11, CYSLTR2, BAP1, SF3B1, EIF1AX	Low/not associated with UVR exposure
De novo melanoma	Unknown	Unknown	Low/not associated with UVR exposure

CM, conventional melanoma; SSM, superficial spreading melanoma; NM, nodular melanoma; CMN, congenital melanocytic naevus; UVR, ultraviolet radiation.

CM in children may be associated with both low and high CSD. By contrast, Spitz melanoma, melanoma arising in congenital nevi and melanoma arising in blue nevi are not consistently associated with CSD (17).

Spitz melanomas may occur at any age, but typically occur in the paediatric population (18). As they are not associated with CSD, their anatomical distribution is not limited to sun-exposed areas. Spitz melanomas fall within the family of Spitz tumours, a spectrum of melanocytic tumours ranging from Spitz nevi through the intermediate form of atypical Spitz tumour to the truly malignant Spitz melanoma (19). In addition, this group includes intermediate/high grade dysplasias known as STUMP (Spitzoid Tumour of Uncertain Malignant Potential) and MELTUMP (Melanocytic Tumour of Uncertain Malignant Potential). Spitz tumours have distinct genetic alterations, including HRAS, ALK, ROS1, RET, NTRK1, NRTK3, BRAF, MET, CDKN2A mutations and kinase fusions which may provide potential therapeutic targets, but unlike CM, typically have a normal karyotype (20). The characteristic somatic genetic aberrations seen in paediatric melanoma are depicted in *Table 1*. BRAF mutations, a useful therapeutic target in melanoma, are seen in 50% of adult CM, 90% of which are V600E mutations (21). Amongst the paediatric population there are less robust data, but a single study demonstrated 87% of paediatric CM harboured activating BRAF V600E mutations (22).

Melanoma arising in CMN is more aggressive and account for the highest rate of melanoma-related deaths in childhood. The risk of malignant transformation is 1–2%, varying with nevus size and number and increased if congenital neurological abnormalities are seen on magnetic resonance imaging (MRI) performed in the first six months of life (21). Infants born with giant (≥20 cm and typically unresectable) CMNs have a lifetime risk of 10–15% of malignant transformation (23,24) with the majority of CMN-associated melanoma occurring in patients with CMN >40 cm (8).

Children and adolescents with numerous melanocytic nevi, dysplastic nevus syndrome, numerous acquired melanocytic nevi (in adolescents, this is >100 nevi and >10 large nevi) and sporadic atypical nevi are at an increased risk of developing CM (8,24,25).

Neonatal melanoma may arise *de novo* or be associated with either giant-CMN (primary congenital melanoma) or transplacental transmission of melanoma. Transplacental transmission of melanoma has been described in a handful of case reports and is associated with a poor outlook (26).

Risk factors

There is significant overlap between the known risk factors for adult and paediatric CM; however, in paediatric melanoma, there is some variation depending on age of patient at diagnosis (neonatal, prepubertal (≤12 years) and post-pubertal (adolescent and young adult population).

Heritable factors such as fair skin (Fitzpatrick type I–II), blonde or red hair, freckles (ephelides), family history, a tendency to sunburn and blue eyes all increase the risk of developing CM, particularly in the post-pubertal group (6,27-30). Predisposition to melanoma changes with age, with a significant increase in incidence in Caucasian children >10 years of age (29).

Environmental factors linked to paediatric melanoma are more relevant in the adolescent population and include living close to the equator, high UV exposure, excessive sun exposure, recurrent and/or significant sunburn and use of indoor tanning equipment (8,9,11,14,29,31,32). Acquired immunosuppression including immunosuppressive medication, photosensitising medication, a previous history of malignancy and genetic immunodeficiency syndromes may all be a contributing factor to melanoma development (28,33-35).

There are several known syndromes associated with increased melanoma risk: cancer pre-disposition syndromes (such as Li Fraumeni syndrome), Werner syndrome, hereditary retinoblastoma, melanoma-pancreatic carcinoma syndrome, neurocutaneous melanosis and xeroderma pigmentosum (XP). XP carries a 5% risk of melanoma which usually develops in the second decade of life (28,36-38).

Germline *CDKN2A* and *BAP1* mutations are associated with development of melanoma; typically, the superficial spreading subtype (30,39-42). Germline inactivating *CDKN2A* mutations account for ~40% of familial melanoma cases (paediatric and adult) (43,44). In one study, 27% of paediatric melanoma patients had a first or second degree relative with melanoma (32). *MCR1* gene variants confer an increased risk of melanoma and are typically associated with a fair phenotype (45-47).

Children with melanoma should be referred for genetics opinion.

Molecular characteristics of melanoma

Somatic genetic alterations present in melanoma may be important in pathogenesis and can potentially be exploited using systemic targeted agents (precision medicine). Within paediatric melanoma, they can be broadly divided by melanoma subgroup (4,19).

Genetic alterations commonly seen in adult CM include activating mutations in *BRAF*, *CDKN2A*, *NRAS*, loss of function mutations in *TP53* genes as well as *TERT* promotor mutations (48). Lu and colleagues demonstrated the similarities in the 'mutational spectrum' between paediatric and adult CM with a high burden of single nucleotide variants (SNV) across the 15 studied CM cases although it is important to note the small numbers in this report (22). *BRAF* mutations were observed in 87% of CM and *TERT* promoter activation in 92% (4,49). The activating *TERT* promoter mutation is responsible for UV light contributing to melanoma risk in this young population as the increased transcriptional activity of *TERT* allows melanocytes to maintain telomere length and become immortalised (22,49,50). Inactivating mutations in the *PTEN* tumour suppressor gene, commonly seen in adult melanoma (51-53), were also seen in paediatric CM (22).

More than 50% of Spitzoid neoplasms, including Spitz melanoma, are associated with gene rearrangements involving the serine/threonine kinase genes, *BRAF* and *MAP3K8*, or the receptor tyrosine kinase genes, *ROS1*, *ALK*, *NTRK1*, *NTRK3*, *RET*, *MET* and *MERTK* (54-58). HRAS activating point mutations, often with copy number gain of mutant *HRAS*, are seen in ~15% of Spitz melanoma (20,54), although occur in less than 1% of melanoma overall (59). Mutations and rearrangements seen in Spitz neoplasms are mutually exclusive (60).

NRAS (up to 80%) and BRAF (5–15%) mutations or BRAF gene fusions are typically the initiating somatic mutations seen in CMN and malignant progression in these patients is thought to be related to amplification of mutated NRAS (4). CMN patients often have multiple segmental chromosomal abnormalities and UV mutational signatures have been reported (4).

Clinical features

Melanoma in children has an equal incidence between male and females, tends to present with primary lesions arising on the head, neck, and extremities and with thicker lesions at diagnosis. By contrast, adolescents have a higher incidence in females with the torso being the most common location (61,62).

Diagnosing melanoma in the paediatric population can be challenging as the lesions are often amelanotic, leading to missed or delayed diagnosis. Although the adolescent population tends to conform more to adult presentation with lesions fulfilling the ABCDE (asymmetry, border irregularity, colour variegation, diameter >6 mm, evolution) criteria, they may also present with the atypical features seen in the under 10 years age group (6,63). A modified version of the ABCDE criteria has been developed to improve timely diagnosis of paediatric melanoma, namely addition of amelanotic, bleeding, bump, colour uniformity, de novo, any diameter, and evolution of mole (32).

Paediatric melanoma typically presents with localised/stage I (77%) and regional/stage II (13%) disease (9).

Outcomes and prognostic factors

Overall survival rates between the adult and paediatric

melanoma population appear to be similar (5,64). Poor prognostic features in paediatric CM are similar to those in adult melanomas, specifically head and neck tumours, thicker primary lesions (Breslow thickness), ulceration, predisposing syndromes, advanced stage and darker skin colour (Fitzpatrick V and VI) (7,8,62).

Whilst paediatric patients are more likely to have SLN metastases at diagnosis (5), particularly the pre-pubertal group (up to 58% of patients aged <10 years present with nodal metastases), overall survival appears to be better than their adult counterparts with SLN metastases (7,61,65). Paradela *et al.* reported children with metastatic melanoma have a 30% 10-year survival, as compared to patients with localised disease (stage I/II) who have a 90% 10-year survival (66).

Staging and the role of sentinel lymph node biopsy (SLNB)

Whilst there has previously been controversy over the role of SLNB, lymphatic mapping and SLNB in patients with tumour thickness >0.8 mm, ulcerated tumours and clinically normal nodes (3,67) is now considered routine clinical practice in adults (3,68). The MSLT-I trial demonstrated that WLE plus SLNB with immediate lymphadenectomy for nodal metastasis detected on biopsy showed no difference in melanoma specific survival (MSS) compared to WLE plus observation (69). However, SLNB improved the accuracy of staging (up to 20% of clinically negative LNs harbour melanoma metastasis) and biopsy-based management improved the 10-year rate of distant disease-free survival (DFS) (3). Melanoma deposits with a diameter of ≥1 mm in SLN are now used as a criterion for stratification to receive adjuvant treatment (3,70).

The prognostic value of SNLB in the paediatric population has been more controversial. Kim *et al.* [2016] reviewed the SEER registry to assess the clinical impact of SLNB in the paediatric population (310 patients) and found positive SLNB is associated with poorer melanoma-specific survival (MSS) (89% if SLNB positive vs 100% for negative SLNB after 88 months) (71). Similarly, Mu *et al.* have previously reviewed SEER data to assess predictive factors of positive SNLB in children, with ulceration and Breslow thickness both associated with increased incidence of nodal involvement (72). Tumour thickness correlated with SNLB positivity in prepubertal patients (7). An analysis of data from the National Cancer Database showed a difference in overall survival (OS) between SLN positive and negative patients only for patients older than 11, while SLN positivity was not prognostic for prepubertal patients (61). These data remain challenging to interpret, given the inclusion of Spitz melanoma, which is known to have a more benign course. Mu *et al.* (72) recommended that SLNB should be performed in paediatric melanoma patients with a Breslow thickness >1 mm in line with the NCCN (National Comprehensive Cancer Network) guidelines on melanoma and this is our own local practice. Further staging requirements depend on clinical features (*Table 2*).

Treatment options

Treatment of primary tumour

Excision of the primary tumour is the cornerstone of treatment for localised melanoma. WLE with margins based on Breslow thickness is recommended by ESMO and the NCCN (3,73). Melanoma *in-situ* warrants a resection margin of 5 mm, for tumours up to a thickness of 2 mm a margin of 10 mm is recommended and a 20-mm margin for thicker tumours. However, patients younger than 18 years were excluded from trials establishing the recommended resection margins. In the past, data suggested more favourable outcomes for paediatric melanoma patients compared to adults with the same stage (74), however, data are inconsistent and overall numbers small (64). Consequently, a number of unanswered questions remain regarding the extrapolation of adult resection margins to the treatment of children, particularly given the potential functional and cosmetic implications which may have a more significant impact on younger patients. Overall, as the data on risk for recurrence are very challenging to interpret, we would recommend utilising resection margins established within adult cohorts whenever possible.

Complete lymph node dissection (CLND)

After results of the MSLT-I study were published, the MSLT-II study and the German DeCOG-SLT trial investigated the value of CLND for SN positive disease (69,75,76). While CLND improved the accuracy of staging with about 15-20% of patients having additional lymph node involvement outside the SN, CLND did not improve OS (75-77) and is therefore no longer recommended, especially considering the morbidity of the intervention (3). Whilst paediatric-specific studies regarding CLND in positive SLNB are scarce, given the data from the adult population, and treatment related morbidity, CLND is not recommended in the paediatric population.

However, CLND remains the approach for patients with

Table 2 Overview of staging and management of paediatric cutaneous melanoma

Stage	Disease sites	Sentinel node biopsy	Systemic therapy indicated	Staging imaging	Surveillance imaging
0	Melanoma *in situ*	Not required	No	None	None
I	≤1 mm Breslow thickness	'Consider and offer' SLNB for patients with T1b disease per AJCC guidelines	No	None	None
II	>1 mm Breslow thickness	Negative	No	Low risk (stage IIa): US regional LN; High risk (ulcerated or thick primary—stage IIb/c) stage II: LD CT chest; MRI brain, abdo., pelvis	Low risk: clinical follow up only; High risk: cross sectional imaging surveillance (LD CT chest, MRI brain, abdo., pelvis)—initially q. 3/12 (apart from brain q. 6/12) for first year and then 6–12 monthly
III	Involved LN or satellite lesions >2 cm distant	Positive (≥1 mm) or negative with transit/ satellite lesions	Yes, except stage IIIa <1 mm SLN deposit	Baseline US of regional LN and LD CT chest; MRI brain, abdo, pelvis	Stage IIIa (<1 mm SLN deposit): ultrasound surveillance only. Stage IIIa (>1 mm SLN deposit)-D: LD CT chest; MRI brain, abdo, pelvis at 3 months, then 6-monthly up to 3–4 years and annually after 4 years (MRI head q. 6/12 for first year and then annual)
IV	Distant spread beyond draining LN	N/A	Yes	LD CT chest; MRI brain, abdo., pelvis	CT chest; MRI brain, abdo., pelvis—frequency will depend on therapy employed and should mirror trial conduct

SLNB, sentinel lymph node biopsy; AJCC, American Joint Committee on Cancer; LD CT, low dose computerised tomography scan; MRI, magnetic resonance imaging; abdo., abdomen; US, ultrasound; LN, lymph node; SLN, sentinel lymph node.

clinically detectable (macroscopic) LN involvement without distant metastatic spread (3,73,78). Prior to any planned loco-regional intervention complete re-staging, including brain imaging, is recommended.

At present, for patients with localised melanoma without lymph node involvement who have undergone complete surgical excision with negative margins, active surveillance remains the standard of care. The care for these patients might change in the near future as the recently published Keynote-716 trial (79) showed a benefit for recurrence-free survival (RFS) for patients receiving one year of adjuvant treatment with pembrolizumab. After a median follow-up time of 21 months, 85% of patients were recurrence free in the pembrolizumab arm compared to 76% in the placebo arm (HR 0.61, 95% CI: 0.45–0.82). Whether this translates into standard of care awaits consideration of the missing data for overall survival and results from part two of the trial, which allowed cross-over after progression.

Systemic therapy

Systemic therapy in CM—evidence from adult patients

Unresectable stage III and stage IV disease

The treatment of unresectable stage III [without distant metastasis but technically or clinically unresectable disease (80)] or stage IV CM has been revolutionized within the last decade through immune checkpoint

inhibition and targeted therapies for those with BRAF mutant disease. Improved OS was first demonstrated amongst patients treated with the anti-CTLA-4 monoclonal antibody (mAb) ipilimumab (81) and subsequently for BRAF inhibitor monotherapy (82). The use of PD-1 inhibition as monotherapy or in combination with ipilimumab and treatment with combined BRAF and MEK inhibition is now an established as standard of care (83-86).

In 2010, Hodi *et al.* presented evidence for OS benefit for the treatment with ipilimumab monotherapy in metastatic melanoma after progression on 1st line treatment (81). The median OS was only 10 months, but longer follow-up revealed durable disease control with 20% of patients alive after 3 years (87). In 2015, results of the KEYNOTE-006 trial demonstrated superiority of anti-PD-1 monotherapy with pembrolizumab compared to ipilimumab (88). Pooled final data demonstrated 5-year overall survival rates of 39% in the pembrolizumab group and 31% in the ipilimumab group with HR 0.73 (95% CI: 0.61–0.88). In the same year, the CheckMate-066 trial demonstrated improved survival for nivolumab compared to chemotherapy with the alkylating agent dacarbazine (DTIC) (87). Follow-up data of this trial demonstrates 5-year survival rates of 39% for nivolumab compared to 17% for dacarbazine, HR 0.50 (95% CI: 0.40–0.63) (89). The CheckMate-067 study compared three different treatment regimens for metastatic melanoma: ipilimumab versus nivolumab versus four cycles of ipilimumab plus nivolumab followed by nivolumab maintenance therapy (84). The trial confirmed the superiority of PD-1 inhibition with nivolumab compared to treatment with ipilimumab. The addition of ipilimumab to nivolumab resulted in improved OS rates after 6.5 years (with 49% of patients in the nivolumab-ipilimumab arm alive compared to 42% in the nivolumab arm), although, a direct comparison of these two arms was not part of the study design (90,91). Results for the median treatment-free interval were also in favour of the combination with 18.1 months for nivolumab-ipilimumab compared to 1.8 months for nivolumab. Interestingly, 74% of patients treated with nivolumab and ipilimumab and 58% of patients treated with nivolumab and alive after 5 years did not require any further treatment, emphasising long-term disease control even after discontinuation of immunotherapy (90). The benefit of adding ipilimumab to nivolumab seems to be limited to an absolute survival benefit of less than 10% but comes with the cost of higher rates of grade 3 or 4 adverse events such as elevated lipase, transaminitis and diarrhoea (59% of patients receiving combination therapy, 24% nivolumab, 28% ipilimumab). Thirty patients in the combination group *vs.* 8 patients in the single agent nivolumab group needed to discontinue treatment for treatment-related adverse events. Therefore, clinical markers and biomarkers to predict which patients which benefit most from the combination treatment or for whom monotherapy is sufficient are urgently needed. Patients with asymptomatic brain metastasis (92) and patients with elevated LDH appear to derive greater benefit from the combination therapy compared to nivolumab alone (93). Tumour PD-L1 expression was not predictive for treatment efficacy in the Checkmate-067 trial (90).

Although PD-L1 antibodies, such as atezolizumab, have also been shown to have activity in the treatment of melanoma (94), they have not been approved for the treatment of melanoma and their use has not been incorporated into standard of care.

Amongst patients with BRAF mutant melanoma, combination BRAF and MEK inhibition represents an additional treatment option (2). Three different treatment regimens have been approved by the US Food and Drug Administration: dabrafenib plus trametinib (DT), vemurafenib plus cobimetinib (VC) and encorafenib plus binimetinib (EB). In the UK DT and EB have been approved for the treatment of patients with metastatic BRAF mutant melanoma, while vemurafenib is approved as monotherapy only. Treatment with DT was investigated in the COMBI-d trial against dabrafenib plus placebo and in the COMBI-v trial against vemurafenib (86). A combined analysis of both trials showed a median OS of 25.9 months, with 34% of patients receiving DT alive after 5 years compared to 27% in the dabrafenib-placebo group and 23% in the vemurafenib group (86). Similar trials investigated treatment with VC with 31% of patients alive after 5 years (95) and after treatment with EB, 57.6% patients were alive after 2 years (96). Compared to treatment with immune checkpoint inhibitors, long term survival is less often seen for patients treated with BRAF and MEK inhibitors, with about 28–34% of patients treated with DT alive after 5 years. The combination of dabrafenib and trametinib is generally well tolerated although most patients will experience a grade 1 or 2 toxicity, with gastrointestinal symptoms (nausea, diarrhoea, and vomiting) and fever being the most common AEs; only 3 patients in the combination group (n=350) experienced a grade 4 toxicity (83).

For BRAF wild-type (wt) patients, treatment either with anti-PD-1 monotherapy or combination of nivolumab

and ipilimumab represents the standard first-line systemic treatment. Current data suggest that the combination of ipilimumab and nivolumab will result in better OS rates after 6.5 years, longer treatment-free intervals and response rates and has the best chance to 'cure' melanoma even in the metastatic setting (91). However, this superior efficacy must be weighed against higher rates of toxicity. A small proportion of patients will suffer from long-term toxicity, including endocrinopathies, which might affect the growth and well-being of young patients. This may be a particular consideration in a paediatric treatment setting.

For patients with BRAF mutant melanoma, the optimal treatment sequence of immune check point inhibition and BRAF plus MEK inhibition has not been fully elucidated and is currently the subject of clinical trials (e.g., NCT02124772, NCT02631447). In patients with high tumour volume or symptomatic disease with urgent need for a response, combination targeted therapy may offer more rapid symptom control and higher response rates (2). Current data suggest better long-term disease control (97) with immunotherapy, with about 50% of patients being treated with ipilimumab and nivolumab being alive after 5 years, compared to about 30% for treatment with DT (97). Therefore, apart from situations of high tumour burden and the need for a rapid response, immunotherapy should be the first-line treatment for both adults and children with unresectable stage III or metastatic CM (2).

Stage III fully-resected and stage IV no evidence of disease (NED)

Since a first publication in 1995 (98), several studies have shown improved DFS and OS for adjuvant treatment with the immune modulating agent interferon-alfa for patients with localised melanoma, but with substantial toxicity (99,100). Twenty years later, Eggermont *et al.* published data providing evidence for improved RFS and OS for adjuvant treatment with ipilimumab (high dose/10 mg/kg) compared to placebo (100). As more effective and better tolerated immunotherapy treatments have since been established, alternatives to both interferon-alfa and ipilimumab are now recommended in the adjuvant setting (3).

After the introduction of ipilimumab as adjuvant treatment, the CheckMate 238 trial demonstrated improved RFS in patients with stage IIIB, IIIC and fully-resected stage IV melanoma following treatment with nivolumab compared to ipilimumab (93). An updated analysis showed a 4-year RFS of 51.7% in the nivolumab group, compared to 41.2% in the ipilimumab arm (HR 0.71; 95% CI: 0.60–0.86) (86). In the EORTC 1325 trial which included patients with stage IIIA [sentinel lymph node (SLN) involvement >1 mm] disease (101), adjuvant pembrolizumab was compared to placebo. The trial resulted in an improved RFS after 3 years for pembrolizumab (63.7%) compared to the placebo group (44.1%) (HR 0.56; 95% CI: 0.47–0.68); thus far, neither trial has shown statistically significant benefit for OS.

Parallel to the use of immune checkpoint inhibitors, adjuvant treatment with BRAF and MEK inhibitors has been investigated for patients with BRAF mutant disease. The COMBI-AD study compared dabrafenib and trametinib (DT) for patients with Stage IIIA (SLN involvement >1 mm), IIIB and IIIC melanoma to placebo and provided strong evidence for an improved RFS after five years, with 52% of patients treated with DT being alive without recurrence compared to 36% in the placebo group, HR 0.51, (95% CI: 0.42–0.61) (102).

The currently available data clearly support the use of systemic adjuvant therapy in stage IIIA–C (SLN involvement >1 mm for stage IIIA) and fully-resected stage IV melanoma. For BRAF wild type patients, treatment with an approved anti-PD-1 antibody is recommended. For the adjuvant treatment of BRAF mutated melanoma a head-to-head comparison of PD-1 inhibition versus targeted therapy is lacking, and between-trial comparisons should only be considered carefully. Thus far, activity in the adjuvant setting appears comparable, therefore, particularly in a paediatric population, treatment decisions should be guided by potential toxicity profiles. For the same reason, in the adult population adjuvant BRAF/MEK inhibition is typically favoured amongst those with BRAF mutant disease, especially those with stage IIIA disease (2). The potential long-term associated toxicity of checkpoint inhibition leads to preferential choice of BRAF plus MEK inhibition for adjuvant treatment of BRAF-mutated disease, except amongst those with stage IV fully-resected disease where there is only an evidence base to support use of adjuvant nivolumab.

Immune-related adverse events (IrAE)

Treatment with immune checkpoint antibodies directed against CTLA-4 and PD-(L)1 impacts immune tolerance, resulting in so-called IrAE. IrAE can occur in every organ and tissue with the skin, colon, endocrine organs and liver being most frequently affected (103). While both anti-CTLA-4 and -PD-(L)1 antibodies can cause IrAEs, they differ in pattern and frequency. In adults, the combination of ipilimumab (anti-CTLA4) and nivolumab

(anti-PD1) is associated with the highest rates of IrAEs with more than 50% of treated patients suffering from Grade III-IV IrAEs (90). IrAEs caused by ipilimumab are dose-dependent with about 20% of patients treated with 3 mg/kg ipilimumab monotherapy suffering from Grade 3–4 IrAEs (81,104). Ipilimumab more frequently causes colitis and hypophysitis compared to PD-(L)1 antibodies. Patients treated with anti-PD-(L)1 mAb will less often suffer from Grade III-IV IrAE (10–20%) compared to treatment with anti-CTLA-4 antibodies. Thyroiditis, fatigue and pneumonitis are the more common side effects seen with PD-(L)1 antibody treatment (105). While most IrAE resolve within a few weeks, some IrAE tend not to resolve, e.g., skin toxicity (vitiligo) and endocrine IrAEs, including insulin-dependent diabetes mellitus, which require long term hormone substitution.

Interestingly, there seems to be a correlation between the occurrence of IrAE and treatment efficacy (106). Amongst patients who stop treatment as a result of IrAE, there is no loss of efficacy compared to patients who continue. In a combined analyses of the CheckMate-067 and CheckMate-069 trials comparing patients who had to discontinue treatment due to IrAE (median number of cycles 3) versus those patients who did not discontinue due to IrAE (median number of cycles 14), the median PFS (8.4 *vs.* 10.8 months, HR 0.99; 95% CI: 0.72–1.37) did not differ (107). Within the Checkmate 067 study, at 5 years, median OS is comparable between those stopping therapy during the induction phase of combination immunotherapy (ipilimumab plus nivolumab) and those who continued onto maintenance nivolumab (90).

Toxicity of combination BRAF and MEK inhibition

Though treatment with BRAF plus MEK inhibitor combinations is often thought to be tolerated reasonably well, almost all patients will suffer from some side-effects with grade III–IV AEs reported in 46–56% of patients treated with DT, 69% of patients treated with VC and 58% of patients treated with EB (86,96,108). AE leading to discontinuation of treatment were reported for about 11.5–15.7% of patients. Many side-effects can be attributed to a class effect including gastrointestinal toxicity, transaminitis, arthralgia, skin and cardiovascular toxicities. In contrast, pyrexia is a typical and specific side effect of treatment with DT, with more than 50% patients suffering from at least one episode (86). Unlike treatment with immune checkpoint inhibitors, toxicity reliably settles on cessation or interruption of therapy; long-term toxicity is unusual (109).

Adjuvant systemic therapy—translation for paediatric patients

Overall, direct data for the use of adjuvant therapy in paediatric melanoma patients are scarce. Although it has been demonstrated that the use of interferon in children is safe (110), this therapeutic option is not recommended given the availability of more effective and less toxic drugs. The use of pembrolizumab in paediatric patients has been shown to be comparably safe to its use in adults (111), however data regarding the efficacy in paediatric CM are still lacking. The KEYNOTE-051 phase I/II trial (NCT02332668) of pembrolizumab in children with advanced melanoma or PD-L1 positive relapsed/refractory solid tumour is currently open and still recruiting and will hopefully provide more evidence for the use of pembrolizumab in patients with paediatric CM. The evidence for the use of BRAF and MEK inhibition in children in melanoma is even more limited although their safety has been demonstrated in trials in other malignancies (NCT02124772). One dose-finding study in children showed tolerability of vemurafenib, however it only included patients older than 12 years and overall, only 6 patients were treated due to the rarity of stage III/IV melanoma in children (112). A phase II study of ipilimumab in paediatric melanoma demonstrated activity in melanoma patients with no increased toxicity compared to the adult safety profile, however, the study only recruited 12 patients internationally over 3.5 years and was subsequently stopped. These findings highlight the need for inclusion of adolescent patients in adult melanoma trials (113). In view of the current limited evidence, we therefore recommend therapy for children analogous to guidelines for adults, taking into account potential side effects (NCT02124772). There are limited data available on the impact on fertility related to all approaches and consideration of fertility preservation should be made (114). Whenever possible, children should be treated within clinical trials and where possible, adolescents included on adult trials.

Second-line treatment

For patients with BRAF mutant melanoma, the choice of second-line treatment depends on whether targeted treatment was used in first line: both checkpoint inhibition and targeted treatment should be discussed as part of the treatment sequence. Second-line treatments for BRAF wild type melanoma following combination immunotherapy

are limited and no standard-of-care exists. Patients who relapsed on or after adjuvant anti-PD-1 monotherapy should be treated with either ipilimumab and nivolumab or ipilimumab monotherapy (115-117). After failure of 1st line anti-PD-1 monotherapy for metastatic melanoma, second line treatment should incorporate ipilimumab either as monotherapy or ipilimumab in combination with a PD-1 antibody (115,117). In a single arm trial of 70 melanoma patients with failure after anti-PD-(L)1 treatment, the combination of pembrolizumab plus low dose ipilimumab (1 mg/kg) achieved a median PFS of 5 months and median OS of 24 months (117). Major efforts continue in the refractory space and patients should be treated within clinical trials whenever possible.

Promising future options in (paediatric) melanoma

Although both immune- and targeted therapies have revolutionised melanoma management, approximately half of all patients with advanced disease either develop or have intrinsically resistant disease to first-line therapies. Major efforts are underway in the development of new therapies for melanoma, with a particular focus on overcoming resistance to immunotherapy, the discovery of new targets and targeted therapies, and exploring cellular therapy as an additional pillar of therapy (118).

Besides the role of PD-(L)1 and CTLA-4, several potential checkpoint inhibitors and immune modulators are of interest including anti-LAG-3, -TIM-3, -B7-H3, -TIGIT, -OX40, -TLR9 and -CD122. Treatments targeting these checkpoints/receptors are under investigation as monotherapy after the failure of treatment with PD-(L1) and CTLA-4 antibodies or in combination with checkpoint inhibitors.

Only about half of all melanoma harbour targetable BRAF mutations and almost all patients treated with BRAF/MEK inhibition will develop resistance. Therefore, the search for new targets and treatment remains an unmet need. Several potential targets including ERK1/2, PI3K, HDAC and KIT are under investigation, with the hope of expanding treatment options and providing a more personalised approach.

An important and emerging treatment option for patients with progression on checkpoint inhibition with or without BRAF/MEK inhibition is the use of adoptive cell therapy. Originally developed in the 1980s (119), the use of TILs has demonstrated promising activity for the treatment of refractory melanoma (120). The use of TILs can be complicated by toxicity due to treatment with lymphodepleting chemotherapy regimens or interleukin (IL-2) and the laborious manufacturing of the cellular products but comes with the advantage of being a 'once-only' treatment and toxicities occurring at the beginning of the treatment can be managed during hospitalisation. Timing of cellular therapies can sometimes be challenging, as the disease must be stable enough for patients to wait for the manufacturing time and there must be sufficient resectable tumour to allow the production of the TILs. Currently, research regarding TIL is focused on the optimisation of the manufacturing process, the reduction of toxicity, and the combination of TILs with checkpoint inhibitors. More advanced TIL products aim to identify tumour-specific antigens including neoantigens (NCT03997474). Latest studies have demonstrated promising, durable activity and in the first instance, polyclonal TIL therapy might become a standard treatment for some melanoma patients in the near future (120).

Given the small patient numbers in paediatric malignancies in general, there are increasing numbers of phase I/II basket trials which provide more opportunities to access targeted therapies for our young patients. The rarity of paediatric CM is a perfect example of the need for tumour agnostic treatments and trials. Molecular profiling platforms, for example through the NHS genomic medicine service for newly diagnosed solid tumours and the Stratified Medicine Paediatric study (ISRCTN 21731605) at relapse, are essential in facilitating these.

Conclusions

Whilst the majority of paediatric melanomas are early stage and do not require systemic therapy, paediatric patients with CM should largely follow adult guidance for treatment including guidelines on when to use systemic therapy. In the adjuvant setting (NED following resection), the combination of dabrafenib and trametinib is the preferred treatment option for children with BRAF mutant CM, owing to the risk of long-term side effects from immune checkpoint inhibition, and similar efficacy in this situation. Since immune checkpoint inhibition is the treatment with the best chance of cure in the situation of unresectable metastatic CM, treatment with nivolumab and ipilimumab or monotherapy with nivolumab or pembrolizumab is preferable to BRAF and MEK inhibition. The preference for immune checkpoint inhibition is justified in this situation despite the higher risk of long-term side effects due to its increased efficacy.

High risk paediatric melanomas should also be examined for targeted gene fusions such as ROS and NTRK which may provide alternative treatment options.

There is a pressing need to study CM of paediatric age patients within adult systemic therapy trials and to find new approaches to metastatic or highest risk non-CM melanoma in children.

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Footnote

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References

1. 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;18:775-84.
2. Keilholz U, Ascierto PA, Dummer R, et al. ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee. Ann Oncol 2020;31:1435-48.
3. Michielin O, van Akkooi ACJ, Ascierto PA, et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol 2019;30:1884-901.
4. Merkel EA, Mohan LS, Shi K, et al. Paediatric melanoma: clinical update, genetic basis, and advances in diagnosis. Lancet Child Adolesc Health 2019;3:646-54.
5. Han D, Zager JS, Han G, et al. The unique clinical characteristics of melanoma diagnosed in children. Ann Surg Oncol 2012;19:3888-95.
6. Pappo AS. Melanoma in children and adolescents. Eur J Cancer 2003;39:2651-61.
7. Moore-Olufemi S, Herzog C, Warneke C, et al. Outcomes in pediatric melanoma: comparing prepubertal to adolescent pediatric patients. Ann Surg 2011;253:1211-5.
8. Stefanaki C, Chardalias L, Soura E, et al. Paediatric melanoma. J Eur Acad Dermatol Venereol 2017;31:1604-15.
9. Wong JR, Harris JK, Rodriguez-Galindo C, et al. Incidence of childhood and adolescent melanoma in the United States: 1973-2009. Pediatrics 2013;131:846-54.
10. Alston RD, Geraci M, Eden TO, et al. Changes in cancer incidence in teenagers and young adults (ages 13 to 24 years) in England 1979-2003. Cancer 2008;113:2807-15.
11. Watts CG, Drummond M, Goumas C, et al. Sunscreen Use and Melanoma Risk Among Young Australian Adults. JAMA Dermatol 2018;154:1001-9.
12. Paulson KG, Gupta D, Kim TS, et al. Age-Specific Incidence of Melanoma in the United States. JAMA Dermatol 2020;156:57-64.
13. Cancer Statistics Review, 1975-2018 - SEER Statistics. [cited 2021 May 24]. Available online: https://seer.cancer.gov/csr/1975_2018/
14. Ghiasvand R, Weiderpass E, Green AC, et al. Sunscreen Use and Subsequent Melanoma Risk: A Population-Based Cohort Study. J Clin Oncol 2016;34:3976-83.
15. Baade PD, Youlden DR, Valery PC, et al. Trends in incidence of childhood cancer in Australia, 1983-2006. Br J Cancer 2010;102:620-6.
16. Karlsson PM, Fredrikson M. Cutaneous malignant melanoma in children and adolescents in Sweden, 1993-2002: the increasing trend is broken. Int J Cancer

2007;121:323-8.
17. Garbe C, Amaral T, Peris K, et al. European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics - Update 2019. Eur J Cancer 2020;126:141-58.
18. Spitz S. Melanomas of childhood. Am J Pathol 1948;24:591-609.
19. Elder DE, Bastian BC, Cree IA, et al. 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;144:500-22.
20. Bastian BC, LeBoit PE, Pinkel D. Mutations and copy number increase of HRAS in Spitz nevi with distinctive histopathological features. Am J Pathol 2000;157:967-72.
21. Ascierto PA, Kirkwood JM, Grob JJ, et al. The role of BRAF V600 mutation in melanoma. J Transl Med 2012;10:85.
22. Lu C, Zhang J, Nagahawatte P, et al. The genomic landscape of childhood and adolescent melanoma. J Invest Dermatol 2015;135:816-23.
23. Kinsler VA, O'Hare P, Bulstrode N, et al. Melanoma in congenital melanocytic naevi. Br J Dermatol 2017;176:1131-43.
24. Whiteman DC, Valery P, McWhirter W, et al. Risk factors for childhood melanoma in Queensland, Australia. Int J Cancer 1997;70:26-31.
25. Wood BA. Paediatric melanoma. Pathology 2016;48:155-65.
26. Fishman C, Mihm MC Jr, Sober AJ. Diagnosis and management of nevi and cutaneous melanoma in infants and children. Clin Dermatol 2002;20:44-50.
27. Ducharme EE, Silverberg NB. Pediatric malignant melanoma: an update on epidemiology, detection, and prevention. Cutis 2009;84:192-8.
28. Huynh PM, Grant-Kels JM, Grin CM. Childhood melanoma: update and treatment. Int J Dermatol 2005;44:715-23.
29. Strouse JJ, Fears TR, Tucker MA, et al. Pediatric melanoma: risk factor and survival analysis of the surveillance, epidemiology and end results database. J Clin Oncol 2005;23:4735-41.
30. Tucker MA, Fraser MC, Goldstein AM, et al. A natural history of melanomas and dysplastic nevi: an atlas of lesions in melanoma-prone families. Cancer 2002;94:3192-209.
31. Whiteman DC, Whiteman CA, Green AC. Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. Cancer Causes Control 2001;12:69-82.
32. Cordoro KM, Gupta D, Frieden IJ, et al. Pediatric melanoma: results of a large cohort study and proposal for modified ABCD detection criteria for children. J Am Acad Dermatol 2013;68:913-25.
33. Tucker MA, Misfeldt D, Coleman CN, et al. Cutaneous malignant melanoma after Hodgkin's disease. Ann Intern Med 1985;102:37-41.
34. Collins L, Quinn A, Stasko T. Skin Cancer and Immunosuppression. Dermatol Clin 2019;37:83-94.
35. Berg D, Otley CC. Skin cancer in organ transplant recipients: Epidemiology, pathogenesis, and management. J Am Acad Dermatol 2002;47:1-17; quiz 18-20.
36. van Steeg H, Kraemer KH. Xeroderma pigmentosum and the role of UV-induced DNA damage in skin cancer. Mol Med Today 1999;5:86-94.
37. Halkud R, Shenoy AM, Naik SM, et al. Xeroderma pigmentosum: clinicopathological review of the multiple oculocutaneous malignancies and complications. Indian J Surg Oncol 2014;5:120-4.
38. Kraemer KH, Lee MM, Scotto J. Xeroderma pigmentosum. Cutaneous, ocular, and neurologic abnormalities in 830 published cases. Arch Dermatol 1987;123:241-50.
39. Betti M, Aspesi A, Biasi A, et al. CDKN2A and BAP1 germline mutations predispose to melanoma and mesothelioma. Cancer Lett 2016;378:120-30.
40. Gabree M, Patel D, Rodgers L. Clinical applications of melanoma genetics. Curr Treat Options Oncol 2014;15:336-50.
41. Aitken J, Welch J, Duffy D, et al. CDKN2A variants in a population-based sample of Queensland families with melanoma. J Natl Cancer Inst 1999;91:446-52.
42. Walpole S, Pritchard AL, Cebulla CM, et al. Comprehensive Study of the Clinical Phenotype of Germline BAP1 Variant-Carrying Families Worldwide. J Natl Cancer Inst 2018;110:1328-41.
43. Berwick M, Orlow I, Hummer AJ, et al. The prevalence of CDKN2A germ-line mutations and relative risk for cutaneous malignant melanoma: an international population-based study. Cancer Epidemiol Biomarkers Prev 2006;15:1520-5.
44. Papakostas D, Stefanaki I, Stratigos A. Genetic epidemiology of malignant melanoma susceptibility. Melanoma Manag 2015;2:165-9.
45. Zocchi L, Lontano A, Merli M, et al. Familial Melanoma and Susceptibility Genes: A Review of the Most Common Clinical and Dermoscopic Phenotypic Aspect, Associated Malignancies and Practical Tips for Management. J Clin

Med 2021;10:3760.
46. Bastiaens MT, ter Huurne JA, Kielich C, et al. Melanocortin-1 receptor gene variants determine the risk of nonmelanoma skin cancer independently of fair skin and red hair. Am J Hum Genet 2001;68:884-94.
47. Box NF, Duffy DL, Chen W, et al. MC1R genotype modifies risk of melanoma in families segregating CDKN2A mutations. Am J Hum Genet 2001;69:765-73.
48. Hayward NK, Wilmott JS, Waddell N, et al. Whole-genome landscapes of major melanoma subtypes. Nature 2017;545:175-80.
49. Huang FW, Hodis E, Xu MJ, et al. Highly recurrent TERT promoter mutations in human melanoma. Science 2013;339:957-9.
50. Horn S, Figl A, Rachakonda PS, et al. TERT promoter mutations in familial and sporadic melanoma. Science 2013;339:959-61.
51. Hodis E, Watson IR, Kryukov GV, et al. A landscape of driver mutations in melanoma. Cell 2012;150:251-63.
52. Chin L, Garraway LA, Fisher DE. Malignant melanoma: genetics and therapeutics in the genomic era. Genes Dev 2006;20:2149-82.
53. Tsao H, Goel V, Wu H, et al. Genetic interaction between NRAS and BRAF mutations and PTEN/MMAC1 inactivation in melanoma. J Invest Dermatol 2004;122:337-41.
54. Wiesner T, Kutzner H, Cerroni L, et al. Genomic aberrations in spitzoid melanocytic tumours and their implications for diagnosis, prognosis and therapy. Pathology 2016;48:113-31.
55. Wiesner T, He J, Yelensky R, et al. Kinase fusions are frequent in Spitz tumours and spitzoid melanomas. Nat Commun 2014;5:3116.
56. Wang L, Busam KJ, Benayed R, et al. Identification of NTRK3 Fusions in Childhood Melanocytic Neoplasms. J Mol Diagn 2017;19:387-96.
57. Quan VL, Panah E, Zhang B, et al. The role of gene fusions in melanocytic neoplasms. J Cutan Pathol 2019;46:878-87.
58. Amin SM, Haugh AM, Lee CY, et al. A Comparison of Morphologic and Molecular Features of BRAF, ALK, and NTRK1 Fusion Spitzoid Neoplasms. Am J Surg Pathol 2017;41:491-8.
59. Cancer Genome Atlas Network. Genomic Classification of Cutaneous Melanoma. Cell 2015;161:1681-96.
60. Raghavan SS, Peternel S, Mully TW, et al. Spitz melanoma is a distinct subset of spitzoid melanoma. Mod Pathol 2020;33:1122-34.
61. Lorimer PD, White RL, Walsh K, et al. Pediatric and Adolescent Melanoma: A National Cancer Data Base Update. Ann Surg Oncol 2016;23:4058-66.
62. Averbook BJ, Lee SJ, Delman KA, et al. Pediatric melanoma: analysis of an international registry. Cancer 2013;119:4012-9.
63. Paradela S, Fonseca E, Prieto VG. Melanoma in children. Arch Pathol Lab Med 2011;135:307-16.
64. Livestro DP, Kaine EM, Michaelson JS, et al. Melanoma in the young: differences and similarities with adult melanoma: a case-matched controlled analysis. Cancer 2007;110:614-24.
65. Howman-Giles R, Shaw HM, Scolyer RA, et al. Sentinel lymph node biopsy in pediatric and adolescent cutaneous melanoma patients. Ann Surg Oncol 2010;17:138-43.
66. Paradela S, Fonseca E, Pita-Fernández S, et al. Prognostic factors for melanoma in children and adolescents: a clinicopathologic, single-center study of 137 Patients. Cancer 2010;116:4334-44.
67. Morton DL, Cochran AJ. The case for lymphatic mapping and sentinel lymphadenectomy in the management of primary melanoma. Br J Dermatol 2004;151:308-19.
68. Wong SL, Faries MB, Kennedy EB, et al. Sentinel Lymph Node Biopsy and Management of Regional Lymph Nodes in Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update. J Clin Oncol 2018;36:399-413.
69. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med 2014;370:599-609.
70. Dummer R, Hauschild A, Santinami M, et al. Five-Year Analysis of Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma. N Engl J Med 2020;383:1139-48.
71. Kim J, Sun Z, Gulack BC, et al. Sentinel lymph node biopsy is a prognostic measure in pediatric melanoma. J Pediatr Surg 2016;51:986-90.
72. Mu E, Lange JR, Strouse JJ. Comparison of the use and results of sentinel lymph node biopsy in children and young adults with melanoma. Cancer 2012;118:2700-7.
73. Coit DG, Thompson JA, Albertini MR, et al. Cutaneous Melanoma, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019;17:367-402.
74. Ferrari A, Bono A, Baldi M, et al. Does melanoma behave differently in younger children than in adults? A retrospective study of 33 cases of childhood melanoma from a single institution. Pediatrics 2005;115:649-54.
75. Leiter U, Stadler R, Mauch C, et al. Final Analysis of

DeCOG-SLT Trial: No Survival Benefit for Complete Lymph Node Dissection in Patients With Melanoma With Positive Sentinel Node. J Clin Oncol 2019;37:3000-8.
76. Leiter U, Stadler R, Mauch C, et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. Lancet Oncol 2016;17:757-67.
77. Wright FC, Souter LH, Kellett S, et al. Primary excision margins, sentinel lymph node biopsy, and completion lymph node dissection in cutaneous melanoma: a clinical practice guideline. Curr Oncol 2019;26:e541-e550.
78. Michielin O, van Akkooi A, Lorigan P, et al. ESMO consensus conference recommendations on the management of locoregional melanoma: under the auspices of the ESMO Guidelines Committee. Ann Oncol 2020;31:1449-61.
79. Luke JJ, Rutkowski P, Queirolo P, et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial. Lancet 2022;399:1718-29.
80. Nan Tie E, Lai-Kwon JE, Gyorki DE. Systemic therapies for unresectable locoregional melanoma: a significant area of need. Melanoma Manag 2019;6:MMT25.
81. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23. Erratum in: N Engl J Med 2010;363:1290.
82. Chapman PB, Robert C, Larkin J, et al. Vemurafenib in patients with BRAFV600 mutation-positive metastatic melanoma: final overall survival results of the randomized BRIM-3 study. Ann Oncol 2017;28:2581-7.
83. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015;372:30-9.
84. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015;373:23-34.
85. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320-30.
86. Robert C, Grob JJ, Stroyakovskiy D, et al. Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma. N Engl J Med 2019;381:626-36.
87. Schadendorf D, Hodi FS, Robert C, 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;33:1889-94.
88. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 2015;372:2521-32.
89. Robert C, Long GV, Brady B, et al. Five-Year Outcomes With Nivolumab in Patients With Wild-Type BRAF Advanced Melanoma. J Clin Oncol 2020;38:3937-46.
90. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med 2019;381:1535-46.
91. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. J Clin Oncol 2022;40:127-37.
92. Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol 2018;19:672-81.
93. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med 2017;377:1345-56. Erratum in: N Engl J Med 2018;379:2185.
94. de Azevedo SJ, de Melo AC, Roberts L, et al. First-line atezolizumab monotherapy in patients with advanced BRAFV600 wild-type melanoma. Pigment Cell Melanoma Res 2021;34:973-7.
95. Ascierto PA, Dréno B, Larkin J, et al. 5-Year Outcomes with Cobimetinib plus Vemurafenib in BRAFV600 Mutation-Positive Advanced Melanoma: Extended Follow-up of the coBRIM Study. Clin Cancer Res 2021;27:5225-35.
96. Dummer R, Ascierto PA, Gogas HJ, 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;19:1315-27.
97. Long GV, Eroglu Z, Infante J, et al. Long-Term Outcomes in Patients With BRAF V600-Mutant Metastatic Melanoma Who Received Dabrafenib Combined With Trametinib. J Clin Oncol 2018;36:667-73.
98. Creagan ET, Dalton RJ, Ahmann DL, et al. Randomized, surgical adjuvant clinical trial of recombinant interferon alfa-2a in selected patients with malignant melanoma. J Clin Oncol 1995;13:2776-83.
99. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. N Engl J Med 2016;375:1845-55. Erratum in: N Engl J Med 2018;379:2185.
100. Eggermont AMM, Blank CU, Mandala M, 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. J Clin Oncol 2020;38:3925-36.
101. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. N Engl J Med 2018;378:1789-801.
102. Dummer R, Brase JC, Garrett J, et al. Adjuvant dabrafenib plus trametinib versus placebo in patients with resected, BRAFV600-mutant, stage III melanoma (COMBI-AD): exploratory biomarker analyses from a randomised, phase 3 trial. Lancet Oncol 2020;21:358-72.
103. Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:iv119-iv142. Erratum in: Ann Oncol 2018;29:iv264-iv266.
104. Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol 2010;11:155-64.
105. Weber JS, Hodi FS, Wolchok JD, et al. Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma. J Clin Oncol 2017;35:785-92.
106. Eggermont AMM, Kicinski M, Blank CU, et al. Association Between Immune-Related Adverse Events and Recurrence-Free Survival Among Patients With Stage III Melanoma Randomized to Receive Pembrolizumab or Placebo: A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol 2020;6:519-27.
107. Schadendorf D, Wolchok JD, Hodi FS, et al. Efficacy and Safety Outcomes in Patients With Advanced Melanoma Who Discontinued Treatment With Nivolumab and Ipilimumab Because of Adverse Events: A Pooled Analysis of Randomized Phase II and III Trials. J Clin Oncol 2017;35:3807-14.
108. Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol 2016;17:1248-60.
109. Gogas HJ, Flaherty KT, Dummer R, et al. Adverse events associated with encorafenib plus binimetinib in the COLUMBUS study: incidence, course and management. Eur J Cancer 2019;119:97-106.
110. Navid F, Furman WL, Fleming M, et al. The feasibility of adjuvant interferon alpha-2b in children with high-risk melanoma. Cancer 2005;103:780-7.
111. Geoerger B, Kang HJ, Yalon-Oren M, et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1-2 trial. Lancet Oncol 2020;21:121-33.
112. Chisholm JC, Suvada J, Dunkel IJ, et al. BRIM-P: A phase I, open-label, multicenter, dose-escalation study of vemurafenib in pediatric patients with surgically incurable, BRAF mutation-positive melanoma. Pediatr Blood Cancer 2018;65:e26947.
113. Geoerger B, Bergeron C, Gore L, et al. Phase II study of ipilimumab in adolescents with unresectable stage III or IV malignant melanoma. Eur J Cancer 2017;86:358-63.
114. Hassel JC, Livingstone E, Allam JP, et al. Fertility preservation and management of pregnancy in melanoma patients requiring systemic therapy. ESMO Open 2021;6:100248.
115. Zimmer L, Apuri S, Eroglu Z, et al. Ipilimumab alone or in combination with nivolumab after progression on anti-PD-1 therapy in advanced melanoma. Eur J Cancer 2017;75:47-55.
116. Pires da Silva I, Ahmed T, Reijers ILM, et al. Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: a multicentre, retrospective, cohort study. Lancet Oncol 2021;22:836-47.
117. Olson DJ, Eroglu Z, Brockstein B, et al. Pembrolizumab Plus Ipilimumab Following Anti-PD-1/L1 Failure in Melanoma. J Clin Oncol 2021;39:2647-55.
118. Boos LA, Leslie I, Larkin J. Metastatic melanoma: therapeutic agents in preclinical and early clinical development. Expert Opin Investig Drugs 2020;29:739-53.
119. Rosenberg SA, Yannelli JR, Yang JC, et al. Treatment of patients with metastatic melanoma with autologous tumor-infiltrating lymphocytes and interleukin 2. J Natl Cancer Inst 1994;86:1159-66.
120. Sarnaik AA, Hamid O, Khushalani NI, et al. Lifileucel, a Tumor-Infiltrating Lymphocyte Therapy, in Metastatic Melanoma. J Clin Oncol 2021;39:2656-66. Erratum in: J Clin Oncol 2021;39:2972.

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