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Original research

Efficacy of anti PD-1 therapy in children and adolescent melanoma patients (MELCAYA study)

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ABSTRACT

Background: Data on the efficacy and safety of anti PD-1 antibodies in children and adolescents (CA) with melanoma are lacking. The aim of this study was to determine outcomes of CA melanoma patients receiving anti PD-1 antibodies.
Methods: Melanoma patients ≤18 years treated with anti PD-1 were retrospectively retrieved from 15 academic centers. Information on histopathological diagnosis, surgical treatment, systemic therapy, objective response rate

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Outcome
Safety

(ORR), safety profile was collected. Progression-free survival (PFS) and overall survival (OS) were assessed by Kaplan-Meier method.
Results: Between April 2016 and March 2024, 99 patients treated with systemic therapy were retrieved, 81 treated with anti PD-1 therapy. Median age was 14 years (range 2–18 years), 37 pts were ≤12 yrs. Overall, 38 CA patients received anti PD-1 in adjuvant setting, and the 3-year PFS and OS were 70.6 % and 81.1 %, respectively. Two patients received anti-PD-1 based neoadjuvant treatment, both had a pathologic complete response and remain disease free. Fifty-six received a systemic therapy for advanced disease and among them, 43 received anti PD-1-based therapy for advanced disease in 1st line, while 12 and 5 pts received a 2nd and 3rd line, respectively. Among patients receiving a 1st line therapy with anti PD-1 monotherapy the ORR was 25 %, and the 3-year OS was 34 %. Toxicities were consistent with previous studies in adult melanoma patients.
Conclusions: Our study provides the first evidence of efficacy of anti PD-1 in CA melanoma patients and supports the use of anti PD-1 therapy in pts ≤18 years, included those <12 years.

Introduction

Melanoma in childhood and adolescence (CA) is underestimated and understudied, leading to inadequate diagnostic and therapeutic strategies. The incidence of melanoma is reported to be about 1.3–1.6 per million in children under 15 years of age and 15 per million in those aged 15–20 years, with an annual increase of 4.1 % in adolescents since 1997 [1–3]. Furthermore, melanoma is among the most frequent solid tumors diagnosed in young adults, with an incidence of 6.6 per 100.000 and a mortality of 4 per million in Europe [1–3].

The anti PD-1 antibodies represent one of the standard immunological therapies for the treatment of early-stage and advanced melanoma [4–10]. This kind of treatment has been highly developed during the past decade based on the comprehensive understanding of the role of tumor microenvironment and immune cells in melanoma, and has highly improved patient outcomes in advanced melanoma [4], and in the adjuvant setting for both stage III [5–7] and stage IIB/C disease [8–10].

Despite these advances, metastatic melanoma remains incurable in the majority of patients at any age and a major clinical challenge. Clinical trials are ongoing to develop novel and more effective targeted therapies and immunotherapies in order to overcome resistance and lead to a further improvement in long term survival. One challenge in developing this therapeutic trajectory is that, since melanoma in CA is rare, the management of pediatric melanoma patients has been extrapolated from adult treatment protocols, but specific clinical data are missing [11]. Furthermore, due to the limited understanding of the diagnosis and prognosis of childhood melanoma, these patients have been excluded from the vast majority of clinical trials available to adult patients. This strategy has hindered research efforts and access to treatment for this population. Overall, there are only minimal data on the efficacy of systemic therapy in CA with early-stage or advanced melanoma. Some explorative, phase I/II trials have been designed to evaluate therapies for pediatric cancer patients that included subsets of patients with advanced melanoma, and the approval of anti PD-1 and anti CTLA4 is based on few cases included in the adjuvant setting, without available data specifically focusing on pediatric cases [12–14]. Furthermore, no data are available in unselected, routinely treated CA melanoma patients. Due to the unmet medical need in CA melanoma patients, we report here, within the context of the MELCAYA project, the activity, efficacy and safety of anti PD-1 antibodies in CA melanoma patients, with radically resected or metastatic disease.

Methods

Melcaya is an independent, academic study funded by an EU Horizon Grant (ref. 101096667). This multicenter retrospective international study included CA melanoma patients, who received anti PD-1 therapy. Data was collected from 15 European, Australian, South American academic centers and 1 registry (The Netherlands). CA melanoma patients (≤ 18 years) with stage III and IV disease according to the American Joint Committee on Cancer (AJCC) staging (VIII Edition) have been included. The study data were entered into an electronic database (Athena, Barcelona) compliant with EU guidelines for data protection and management (General Data Protection Regulation – GDPR – 2016/679). Specifically, a certified academic center (Barcelona, University Hospital Clinic) created and maintained the study database, provided technical support for the study and long-term data storage. Patient data generated from this study are maintained in confidence and protected (through pseudonymization, key-code data creation), in accordance with regulatory requirements. Key-coded data are managed by study investigators, who get privileged access to the database. Data collected included: age, sex, previous diseases, tumor histotype, AJCC stage, previous treatments, concomitant diseases and medications, scheduled therapy, tumor genetics, complete blood count and chemistry, clinical response by RECIST, date of relapse/progression, date of death and cause.

Due to the rarity of this disease, a centralized pathology review, led by expert pathologists in the field was carried out in selected cases.

This clinical study was designed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki. The study is registered at Clinical Trial Gov (NCT06281912).

Outcomes

Progression and response were assessed using Response Evaluation Criteria in Solid Tumors, version 1.1. Adverse events were categorized and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

The primary study endpoint was overall survival (OS). Secondary endpoints included relapse free survival (RFS), progression free survival (PFS), objective response rate (ORR), and safety (incidence of immune-related adverse events, irAEs).

RFS was defined as the time from starting adjuvant treatment until the date of first recurrence or death as a result of any cause. For patients without any event, the follow-up was censored at the latest disease evaluation performed according to the routine activity. PFS was defined as the time from start of therapy until progression, symptomatic deterioration or death, whichever occurred first. PFS was based on the disease assessments provided by the site investigators. OS was defined as the time between therapy starting and death, whatever the cause. Complete response rate was defined as the percentage of patients who had a confirmed complete response that was achieved without a second-line treatment. ORR was defined as the percentage of patients who had a confirmed complete or partial response that was achieved without initiating a second-line treatment.

Statistical analysis

In the initial step, patient characteristics were categorized based on variable types. Categorical factors were presented as absolute frequencies and percentages while quantitative variables were represented

by their median, inter-quartile range and minimum and maximum values. Survival times were analysed using the Kaplan-Meier method and the median survival time was reported along with its corresponding 95 % confidence intervals. Survival rates at different time points were also derived from the Kaplan-Meier curve. Statistical analysis was conducted using the iBM-SPSS v.28.0 statistical software and R v.4.1.0.

Role of the funding source

The funding source had no role in study design, data collection, analysis, interpretation of data, writing of the report or the decision to submit the paper for publication.

Results

A cohort of 106 melanoma patients ≤ 18 years, who were diagnosed between June 1996 and March 2024, were retrieved from referral melanoma and pediatric oncology cancer centers from Europe, Australia, South America and considered for this study. Among them, 99 patients received systemic therapy either for resected stage III melanoma or for locally advanced/metastatic disease, and were included in this analysis. Median age at start of systemic therapy was 14 years (range 2–18 years), 37 patients were ≤12 years (Table 1).

Systemic therapy in the adjuvant/neo-adjuvant setting

Overall, 56 CA pts with stage III disease received adjuvant therapy. Specifically, 39 received immune checkpoint inhibitors (ICI) (29 nivolumab, 1 ipilimumab plus nivolumab, 1 ipilimumab, 8 pembrolizumab). In addition, 13 patients received BRAF and MEK inhibitors, and 4 interferon. With regards to the schedule of ICI, 15 patients received nivolumab or pembrolizumab as flat dose every 2 and 3 weeks, respectively; the remaining patients received a weight-adjusted dose of nivolumab or pembrolizumab (mg/Kg). Two patients, with palpable nodes, received anti-PD-1 based neoadjuvant treatment: one received a pembrolizumab-based treatment, while the other ipilimumab plus nivolumab followed by nivolumab as adjuvant therapy. The median follow-up was 33 months (IQR 19–53 months). The 3-year RFS and OS were 70.6 % and 81.1 %, respectively (Fig 1). Patients treated with targeted therapy (n=13) had a 3-year RFS of 82.1 % and a 3-year OS of 79.1 % (Fig 2). Two patients treated with neoadjuvant PD-1 based therapy achieved pathologic complete response and are still disease free after 36 and 18 months, respectively.

Table 1
Patient characteristics of 99 patients treated with a systemic therapy ≤ 18 years.

	Whole population	Age 0-12	Age 13-18
SEX			
Male	50 (50.5)	17 (45.9)	33 (53.2)
Female	49 (49.5)	20 (54.1)	29 (46.8)
Age in years (median, IQR)	14[11–16]	8[4–11]	16[14–14]
PRIMARY SITE			
Head and Neck	17 (17.2)	8 (21.6)	9 (14.5)
Trunk	31 (31.3)	11 (29.7)	20 (32.3)
Limbs	34 (34.3)	12 (32.4)	22 (35.5)
Unknown primary	15 (15.2)	6 (16.2)	9 (14.5)
Other	2 (2.0)	0	2 (3.2)
HISTOLOGY			
Superficial spreading	25 (25.2)	4 (10.8)	21 (33.9)
Spitzoid	16 (16.2)	8 (21.6)	8 (12.9)
Nodular	12 (12.1)	3 (8.1)	9 (14.5)
Melanoma in congenital nevi	10 (10.1)	8 (21.6)	2 (3.2)
NOS	11 (11.1)	5 (13.5)	6 (9.7)
Unknown	19 (19.2)	6 (16.2)	13 (21.0)
Acral	1 (1.0)	1 (2.7)	0
Nevoid	5 (5.1)	2 (5.4)	3 (4.8)
AJCC STAGE AT DIAGNOSIS			
I-II	13 (13.1)	4 (10.8)	9 (14.5)
III	65 (65.7)	26 (70.3)	39 (62.9)
IV	19 (19.2)	7 (18.9)	12 (19.4)
Unknown	2 (2.0)	0	2 (3.2)
BRAF			
Wild Type	48 (48.5)	23 (62.2)	25 (40.3)
Mutated	44 (44.4)	12 (32.4)	32 (51.6)
Unknown	7 (7.1)	2 (5.4)	5 (8.1)
SETTING ON TREATMENT			
Neo/Adjuvant	58 (58.6)	18 (48.6)	40 (64.5)
Metastatic	56 (56.6)	25 (67.6)	31 (50.0)

Systemic therapy in the advanced setting

Overall, 56 patients received a first line therapy for advanced melanoma. Among them, 8 had locally advanced disease, 8 M1a, 5 M1b, 24 M1c, 8 M1d, 3 stage IV not otherwise specified; LDH was elevated in 32 % of patients. Twenty-seven patients were BRAF mutated, 27 BRAF WT, in 2 patients the BRAF status was unknown.

Among patients with advanced disease, 37 received an ICI treatment (9 nivolumab, 19 ipilimumab plus nivolumab, 2 ipilimumab, 7 pembrolizumab), 11 BRAF and MEK inhibitors, 8 patients received nivolumab in combination with chemotherapy (7 patients received concomitant Temozolomide and 1 Irinotecan, respectively). Only 3 patients received nivolumab or pembrolizumab as flat dose, the remaining patients received a weight-adjusted dose of nivolumab or pembrolizumab.

Thirty-four patients received second line therapy, 14 received ICI (1 nivolumab, 6 ipilimumab plus nivolumab, 4 ipilimumab, 3 pembrolizumab), 10 BRAF and MEK inhibitors, 7 chemotherapy, 1 a toll-like receptor 9 agonist (tilsotolimod), 1 BRAF and MEK inhibitors plus nivolumab, and 1 anti PD-1 plus CAR-T.

Nineteen patients received third line therapy: 7 received ICI (2 nivolumab, 1 ipilimumab plus nivolumab, 2 ipilimumab, 2 pembrolizumab), 8 BRAF and MEK inhibitors, and 4 chemotherapy. Eight patients received a fourth line therapy, specifically 7 received ICI (2 nivolumab, 2 ipilimumab plus nivolumab, 1 ipilimumab, 2 pembrolizumab) and 1 nivo in combination with Dabrafenib and Trametinib. Median follow-up, from first line treatment, was 42 months (IQR 15–84 months). Among the 16 CA patients who received a 1st line therapy with anti PD-1 monotherapy the ORR was 25.0 % (4/16), while in those treated with ipilimumab and nivolumab the ORR was 31.6 % (6/19). The median PFS was 1.8 months (95 %CI: 1.5–2.2) and 3.7 months (95 % CI: 1.9–5.4), in patients receiving PD-1 alone and ipilimumab and nivolumab, respectively (Fig 3). Median OS was 6.3 months (95 %CI: 0.5–12.2) with anti PD-1 alone and 20.0 months (95 % CI: 0–41.3) with ipilimumab and nivolumab, the 3-year OS was 34 % and 30 %, respectively (Fig 4). Median PFS for patients treated with targeted therapy was 3.9 months (95 % CI: 1.0–6.7) and 3-year OS 22 % (Fig 5). Median age of responsive vs non responsive patients was 13 [3–3] vs 12 [2–2], respectively.

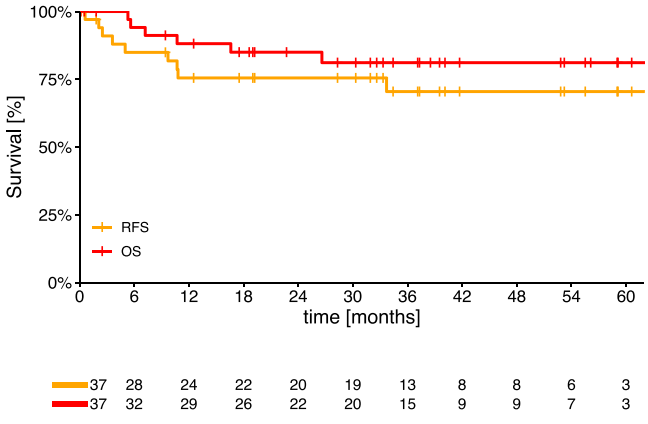

Fig. 1. RFS ed OS in patients ≤ 18 years receiving anti PD-1 in adjuvant setting.

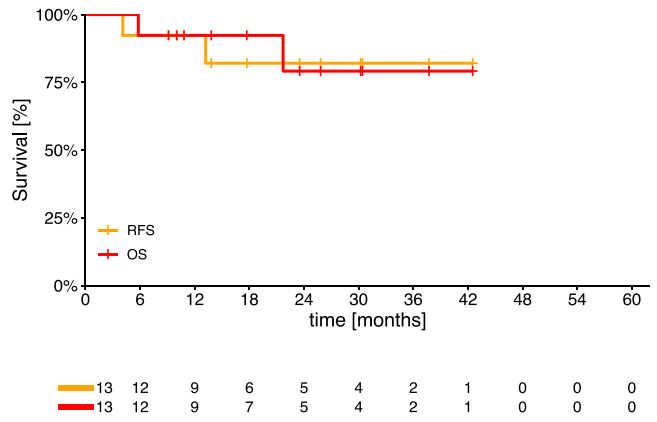

Fig. 2. RFS ed OS in patients ≤ 18 years receiving targeted therapy in adjuvant setting.

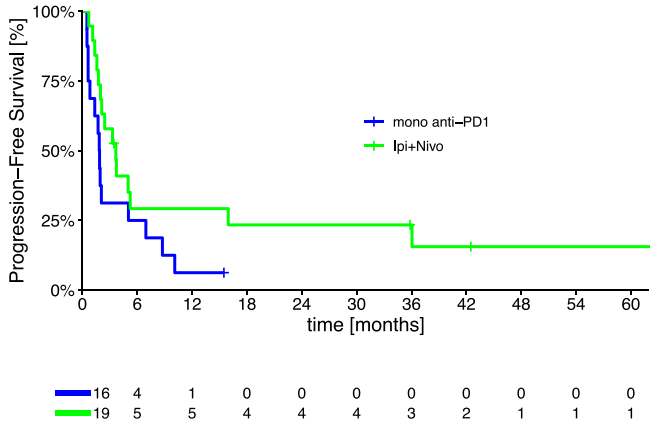

Fig. 3. PFS in patients ≤ 18 years receiving Nivolumab-Ipilimumab (green) or anti PD-1 (blue) in I line metastatic setting.

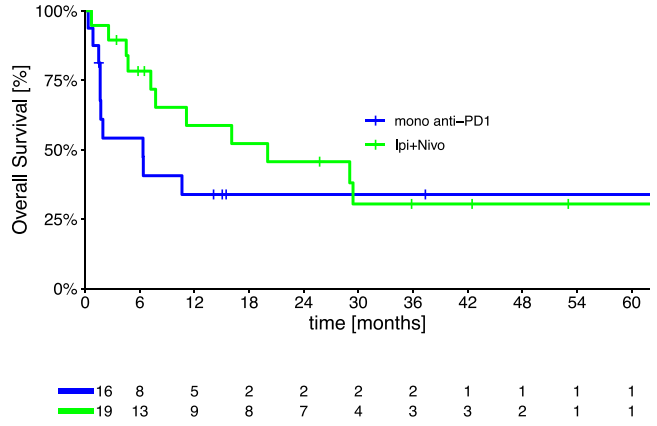

Fig. 4. OS in patients ≤ 18 years receiving Nivolumab-Ipilimumab (green) or anti PD-1 (blue) in I line metastatic setting.

In 2nd line, the ORR was lower, 25.0 % for anti PD-1 monotherapy, and 16.7 % for ipilimumab and nivolumab, while it was 0 % in 3rd line setting.

Safety

Toxicities were consistent with previous studies in adult melanoma pts.

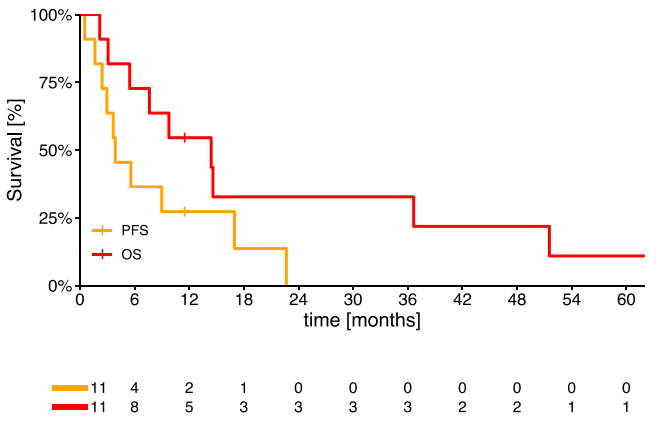

Fig. 5. PFS e OS in patients ≤ 18 years receiving targeted therapy in I line metastatic setting.

Specifically, in the adjuvant setting 13 (33 %) patients were reported to have at least one irAE of any grade. Among them 2/11 (18.2 %) occurred in patients < 12 years e 11/26 (42.3 %) in those ≥ 12 years.

Grade 3/4 irAEs (pancreatitis and liver toxicity) occurred in 2 (5 %) patients < 12 years treated with anti PD-1 monotherapy. Both adverse events were resolved at the time of the present analysis.

In patients with advanced disease, 2 patients (12 %) receiving anti PD-1 as monotherapy developed colitis G3, while 8 patients (42 %) who received ipilimumab and nivolumab developed G3 irAEs, specifically 5 patients had G3 liver toxicity, 1 meningitis, 1 type 1 diabetes and 1 fever. Among patients receiving ipilimumab and nivolumab as second line, 2 patients developed G3 irAEs. No treatment-related deaths occurred.

Discussion

Our study yields several clinically valuable findings in CA melanoma patients receiving anti PD-1-based immunotherapy: 1) 3-year RFS and OS outcomes in the adjuvant setting comparable to the adult high risk stage III patients; 2) safety outcomes were consistent with previous reports in adult patients, with no new irAEs observed; 3) outcomes and safety were similar in CA patients under and over 12 years; 4) one-third of patients with advanced disease were still alive at 3 years, which appears to be inferior to adult data.

We found no previous robust studies investigating the activity and efficacy of anti PD-1 therapy in CA melanoma patients outside case reports and very small patient cohorts in umbrella studies [12–14]. To the best of our knowledge, this is the first study investigating the activity and efficacy of anti PD-1 therapy in CA melanoma patients. To date, only the adjuvant trials Checkmate 76K and Keynote 716 included CA melanoma patients treated with anti PD-1 therapy (n=5), but no specific data have been reported in this subset of CA patients [8–10]. The phase I/II Keynote 051 trial included 8 CA patients with advanced melanoma [14]. Our study provides the first evidence of the efficacy of anti PD-1 in CA melanoma patients, both in the first-line metastatic setting and in the neoadjuvant/adjuvant setting. Our study has clinical implications in the context of a rare disease, since our results support the use of anti PD-1 therapy in melanoma patients ≤ 18 years, including those aged <12 years.

In this study, we collected data from academic centers. Although high quality evidence is generally conveyed through prospective single arm or randomized clinical trials, this kind of studies are highly unlikely to be carried out in rare diseases such as CA melanoma. Nevertheless, studies that produce real-world evidence provide some advantages over conventional clinical trials including the fact that patients are not selected with strict inclusion criteria.

The outcomes of patients in the adjuvant setting included in our

study were similar to adult cases enrolled in randomized clinical studies [5,6].

With regards to CA melanoma patients with advanced disease, the outcome was worse than that reported in previous studies focusing on adult melanoma cases [15,16]. In the checkmate 067 clinical study the ORR was 58 % in patients treated with combo immunotherapy (ipilimumab and nivolumab) and 45 % in those receiving nivolumab alone [16]. Furthermore, in the same trial 4-year overall survival was 53 % in the combination group, 46 % in the nivolumab alone group. In addition, in a recent real world cohort study including patients treated with anti PD-1 based therapy the 3-year OS rate was 44.0 % [15]. While it's hard to make indirect, cross trial comparisons, differences in patient populations as well as in the burden of the disease at the start of treatment may partially explain the different outcomes.

It is important to convey the message to clinicians and regulatory authorities that CA patients, included those under 12 years, can achieve long-term favorable outcomes with an anti PD-1 therapy even in advanced disease, particularly with first line treatment. Furthermore, it is worthy of consideration that our data reassure clinicians regarding the safety, without any new irAEs retrieved in medical charts compared to previous studies, and no death related to irAEs. Furthermore the severity and incidence of irAEs were similar to that already described in trials on adult melanomas [16].

Our study boasts several strengths, including I) the largest cohort of CA melanoma patients receiving anti PD-1 based therapy; ii) comprehensive data collection from specific databases including information on diagnosis, surgical and systemic therapies, and outcomes; iii) relatively long-term follow-up allowing for the examination of mature data on PFS and OS in both adjuvant and metastatic stages; iv) data collected from referral centers with expertize in melanoma management, providing a consistent approach; v) a centralized pathology review in 32 selected cases.

Nonetheless, we are also aware of some limitations, including the retrospective nature of our analysis with selection biases and no controls.

In conclusion, in the context of an independent, academic research, our study provides the first evidence of efficacy of anti PD-1 in CA melanoma patients, both in adjuvant and first line metastatic setting. Our study supports the use of anti PD-1 therapy in patients $\leq$18 years, including those $<$ 12 years.

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CRediT authorship contribution statement

Alice Indini: Resources. **Martina Ubaldi:** Data curation, Resources. **Giulia Pecci:** Data curation, Resources. **Pawel Teterycz:** Resources. **Piotr Rutkowski:** Resources. **Susana Puig:** Resources. **Gabriele Madonna:** Resources. **Rejin Kebudi:** Resources. **Shirly Grynberg:** Resources. **Lidia Rebolho:** Resources. **Malgorzata Krawczyk:** Resources. **Ewa Bien:** Resources. **Miranda P Dierselhuis:** Resources. **Daniela Massi:** Resources. **MARIO MANDALA':** Conceptualization, Funding acquisition, Resources, Supervision, Writing – original draft, Writing – review & editing. **Georgina V Long:** Resources. **Paolo A Ascierto:** Resources. **Alexander M.M. Eggermont:** Conceptualization, Writing – original draft. **Victoria Atkinson:** Resources. **Hildur Helgadottir:** Resources, Writing – review & editing. **Stefano Chiaravalli:** Resources. **Maria Debora Da Pasquale:** Resources. **Naima Benannoune:** Resources. **Caroline Robert:** Resources. **Andrea Ferrari:** Resources. **Ines B Brecht:** Resources. **Karijn PM Suijkerbuijk:** Resources. **Linda Maschke:** Resources. **Diana Giannarelli:** Data curation, Formal analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Contributors

MM, AMME conceived of and designed the study. DG conducted all statistical analyses and produced figures and tables, and MM and AMME co-wrote the initial draft. MU, GP, MM, DG helped to procure and clean the data. DM coordinated the centralized pathology review. All authors had access to the data, and MM, MU, DG, and SP have accessed and verified the data underlying the study. All authors edited the manuscript, provided feedback on the study, and approved the final manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114305.

References

1 Paulson KG, Gupta D, Kim TS, et al. Age-specific incidence of melanoma in the United States. JAMA Dermatol 2020;156(1):57–64.
2 Hawryluk EB, Moustafa D, Barry KK, Bahrani E, Reusch DB, Brahmbhatt M, et al. Risk factors and outcomes of melanoma in children and adolescents: a retrospective multicenter study. J Am Acad Dermatol 2024;90(4):716–26.
3 El Sharouni MA, Rawson RV, Potter AJ, Paver EC, Wilmott JS, Witkamp AJ, et al. Melanomas in children and adolescents: clinicopathologic features and survival outcomes. J Am Acad Dermatol 2023;88:609–16.
4 Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320–30.
5 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;377(19):1824–35.
6 Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson V, Dalle S, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med 2018;378(19):1789–801.
7 Eggermont AMM, Blank CU, Mandalà M, Long GV, Atkinson VG, Dalle S, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial (EORTC Melanoma Group) Lancet Oncol 2021;22(5):643–54.
8 Luke JJ, Rutkowski P, Queirolo P, Del Vecchio M, Mackiewicz J, Chiarion-Sileni V, 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(10336):1718–29.
9 Long GV, Luke JJ, Khattak MA, et al. Pembrolizumab versus placebo as adjuvant therapy in resected stage IIB or IIC melanoma (KEYNOTE-716): distant metastasis-free survival results of a multicentre, double-blind, randomised, phase 3 trial. Lancet Oncol 2022;23:1378–88.
10 Kirkwood JM, Del Vecchio M, Weber J, Hoeller C, Grob JJ, Mohr P, et al. Adjuvant nivolumab in resected stage IIB/C melanoma: primary results from the randomized, phase 3 CheckMate 76K trial. Nat Med 2023;29(11):2835–43.
11 Ferrari A, Lopez Almaraz R, Reguerre Y, et al. Cutaneous melanoma in children and adolescents: the EXPeRT/PARTNER diagnostic and therapeutic recommendations. Pediatr Blood Cancer 2021;68(4):e28992.
12 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.
13 Davis KL, Fox E, Merchant MS, et al. Nivolumab in children and young adults with relapsed or refractory solid tumours or lymphoma (ADVL1412): a multicentre, open-label, single-arm, phase 1–2 trial. Lancet Oncol 2020;21:541–50.
14 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.
15 van Not OJ, van den Eertwegh AJM, Jalving H, Bloem M, Haanen JB, van Rijn RS. Long-term survival in patients with advanced melanoma. JAMA Netw Open 2024;7: e2426641.
16 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;19:1480–92.