European Journal of Cancer 169 (2022) 210–222

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

The efficacy of immune checkpoint blockade for melanoma in-transit with or without nodal metastases – A multicenter cohort study

Carl-Jacob Holmberg [a,b,c], Lars Ny [a,d], Tina J. Hieken [e,f], Matthew S. Block [f,g], Michael J. Carr [h], Vernon K. Sondak [h], Christoffer Örtenwall [a,c], Dimitrios Katsarelias [a,c], Florentia Dimitriou [i,j], Alexander M. Menzies [i,k,l], Robyn PM. Saw [i,k,m], Aljosja Rogiers [i], Richard J. Straker III [n], Giorgos Karakousis [n], Rona Applewaite [o], Lalit Pallan [o], Dale Han [p], John T. Vetto [p], David E. Gyorki [q], Emilia Nan Tie [q], Maria Grazia Vitale [r], Paulo A. Ascierto [r], Reinhard Dummer [j], Jade Cohen [s], Jane YC. Hui [s], Jacob Schachter [t], Nethanel Asher [t], H. Helgadottir [u,v], Harvey Chai [w,x], Hidde Kroon [w,x], Brendon Coventry [w,x], Luke D. Rothermel [y,z], James Sun [y,z], Matteo S. Carlino [i,aa], Zoey Duncan [ab], Kristy Broman [ab], Jeffrey Weber [ac], Ann Y. Lee [ac,ad], Russell S. Berman [ac,ad], Jüri Teras [ae], David W. Ollila [af], Georgina V. Long [i,k,l], Jonathan S. Zager [h,ag], Alexander van Akkooi [ah], Roger Olofsson Bagge [a,b,c,*]

[a] *Sahlgrenska Center for Cancer Research, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden*
[b] *Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, Sweden*
[c] *Department of Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden*
[d] *Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden*
[e] *Department of Surgery, Mayo Clinic, Rochester, USA*
[f] *Mayo Clinic Cancer Center, Rochester, USA*
[g] *Department of Oncology, Mayo Clinic, Rochester, USA*
[h] *Department of Cutaneous Oncology Moffitt Cancer Center, Tampa, USA*
[i] *Melanoma Institute Australia, The University of Sydney, Sydney Australia*
[j] *Department of Dermatology, University Hospital of Zürich, Zürich, Switzerland*
[k] *Faculty of Medicine and Health, The University of Sydney, Sydney, Australia*
[l] *Royal North Shore and Mater Hospitals, Sydney, Australia*
[m] *Department of Melanoma and Surgical Oncology, Royal Prince Alfred Hospital, Camperdown, Australia*
[n] *Department of Surgery, University of Pennsylvania, Perelman School of Medicine, Philadelphia, USA*

* *Corresponding author:* Department of Surgery, Sahlgrenska University Hospital 413 45 Gothenburg, Sweden.
E-mail address: rob@gu.se (R. Olofsson Bagge).

https://doi.org/10.1016/j.ejca.2022.03.041

[o] University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[p] Division of Surgical Oncology, Department of Surgery, Oregon Health & Science University, Portland, USA
[q] Division of Cancer Surgery, Peter MacCallum Cancer Centre and Sir Peter MacCallum Department, University of Melbourne, Melbourne, Australia
[r] Department of Skin Cancers, Cancer Immunotherapy and Development Therapeutics, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Napoli, Italy
[s] Department of Surgery, University of Minnesota, Minneapolis, USA
[t] The Ella Lemelbaum Institite for Immuno-oncology, Sheba Medical Center, Tel Aviv, Israel
[u] Theme Cancer, Karolinska University Hospital, Stockholm, Sweden
[v] Department of Oncology and Pathology, Karolinska Institute, Stockholm, Sweden
[w] Department of Surgery, Royal Adelaide Hospital, Adelaide, Australia
[x] Adelaide Medical School, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, Australia
[y] Department of Surgery, University Hospitals Cleveland Medical Center, Cleveland, USA
[z] Case Western Reserve University, Cleveland, USA
[aa] Department of Medical Oncology, Westmead and Blacktown Hospitals, The Crown Princess Mary Cancer Centre, Sydney, Australia
[ab] University of Alabama at Birmingham, Birmingham, USA
[ac] Laura and Isaac Perlmutter Cancer Center at NYU Langone Health, New York, USA
[ad] NYU Grossman School of Medicine, Department of Surgery, New York, USA
[ae] North Estonian Medical Centre Foundation, Tallinn, Estonia
[af] Division of Surgical Oncology and Endocrine Surgery, University of North Carolina at Chapel Hill, Chapel Hill, USA
[ag] Department of Oncologic Sciences, University of South Florida Morsani College of Medicine, Tampa, USA
[ah] Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands

Received 18 January 2022; received in revised form 16 March 2022; accepted 31 March 2022
Available online 26 May 2022

KEYWORDS
Melanoma;
In-transit metastasis;
Immune checkpoint inhibitor;
PD-1;
Nivolumab;
Pembrolizumab;
Ipilimumab

Abstract ***Purpose:*** Guidelines addressing melanoma in-transit metastasis (ITM) recommend immune checkpoint inhibitors (ICI) as a first-line treatment option, despite the fact that there are no efficacy data available from prospective trials for exclusively ITM disease. The study aims to analyze the outcome of patients with ITM treated with ICI based on data from a large cohort of patients treated at international referral clinics.
Methods: A multicenter retrospective cohort study of patients treated between January 2015 and December 2020 from Australia, Europe, and the USA, evaluating treatment with ICI for ITM with or without nodal involvement (AJCC8 N1c, N2c, and N3c) and without distant disease (M0). Treatment was with PD-1 inhibitor (nivolumab or pembrolizumab) and/or CTLA-4 inhibitor (ipilimumab). The response was evaluated according to the RECIST criteria modified for cutaneous lesions.
Results: A total of 287 patients from 21 institutions in eight countries were included. Immunotherapy was first-line treatment in 64 (22%) patients. PD-1 or CTLA-4 inhibitor monotherapy was given in 233 (81%) and 23 (8%) patients, respectively, while 31 (11%) received both in combination. The overall response rate was 56%, complete response (CR) rate was 36%, and progressive disease (PD) rate was 32%. Median PFS was ten months (95% CI 7.4–12.6 months) with a one-, two-, and five-year PFS rate of 48%, 33%, and 18%, respectively. Median MSS was not reached, and the one-, two-, and five-year MSS rates were 95%, 83%, and 71%, respectively.
Conclusion: Systemic immunotherapy is an effective treatment for melanoma ITM. Future studies should evaluate the role of systemic immunotherapy in the context of multimodality therapy, including locoregional treatments such as surgery, intralesional therapy, and regional therapies.

1. Introduction

Approximately, 5–10% of patients with high-risk cutaneous melanoma will develop in-transit metastases (ITM) [1], a form of tumor spread within the lymphatic channels between the primary tumor site and regional lymph nodes [2]. According to the American Joint Committee on Cancer (AJCC) staging system, patients with ITM are considered to have stage III disease with a corresponding high risk of both locoregional and systemic recurrence [3]. When there are few lesions and all can be removed with an excision, surgical resection is recommended, but for patients with unresectable ITM (e.g., multiple, bulky, or quickly recurrent), there are numerous locoregional treatment options available. These include isolated limb perfusion (ILP) [4], isolated limb infusion (ILI) [5], intralesional injections with talimogene laherparepvec (TVEC) [6] and electrochemotherapy [7]. These locoregional therapies offer very high overall response rates (ORR) (70–90%) and complete response (CR) rates (50–70%). The majority of the literature on locoregional treatments are retrospective series, with few prospective clinical trials, and there are no studies directly comparing these locoregional treatments with each other or to systemic immunotherapy [8].

There have been major advances recently in the treatment of advanced melanoma with the introduction of effective systemic treatments, including targeted therapies with BRAF-MEK inhibitors [9–11] and immune checkpoint inhibitors (ICI) [12–14]. These agents have proven to be effective in unresectable disease as well as in the adjuvant and neoadjuvant settings. Many guidelines addressing ITM recommend ICI as an option for first-line treatment, despite the fact that there are no data available from prospective trials on the efficacy of these agents for ITM. When the pivotal registration trials of PD-1 inhibitors for patients with advanced melanoma were analyzed, no patients with exclusively ITM were identified [15]. Two small retrospective analyses of patients with ITM treated with systemic immunotherapy, showed an ORR of 31–54% with a CR rate of 13–26% [16,17].

The aim of this study was to analyze the outcome of patients with ITM treated with immune checkpoint blockade using PD-1 inhibitors and/or a CTLA-4 inhibitor based on real-world data from a large international cohort of patients from melanoma centers in Australia, Europe, and the USA.

2. Material and Methods

2.1. Study design

A multicenter retrospective cohort study that included patients treated between January 2015 and December 2020. All participating study sites are national or regional referral clinics for the treatment of melanoma. The study was conducted in adherence to the ethical principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and ICH Guidelines with the approval of the Swedish Ethical Review Authority (477–18 and 2021–02315). Sahlgrenska University Hospital served as the coordinating center and participating institutions obtained appropriate ethical approval and performed independent data extraction and provided data to the coordinating center in compliance with individual institutional requirements and negotiated data use agreements.

2.2. Study cohort

This study included cutaneous melanoma patients treated with ICIs for in-transit melanoma metastases (AJCC8 stages IIIB-D), with or without concurrent nodal involvement (AJCC8 N1c, N2c, and N3c). Patients were included if they were treated with a PD-1 inhibitor (nivolumab or pembrolizumab) and/or CTLA-4 inhibitor (ipilimumab); with or without previous treatment for in-transit metastases, e.g., surgery, locoregional, and systemic treatments. Patients having received concomitant therapies parallel to ICI treatment were excluded. All in-transit lesions were required to be evaluable by RECIST criteria, but modified so that lesions not visible by radiology were measured by calipers instead. Patients with previous or synchronous distant metastases (stage IV disease) were excluded.

2.3. Outcomes

The primary endpoint was CR rate, with best overall response, time to local progression (TTLP), time to nodal progression (TTNP), time to systemic progression (TTSP), progression-free survival (PFS), melanoma-specific survival (MSS), and overall survival (OS) as secondary endpoints. MSS and OS were calculated from the start of immunotherapy to death or end of follow-up, and PFS was calculated from the start of immunotherapy to progression or death. The response was evaluated as the best response during follow-up according to the RECIST criteria modified for cutaneous lesions (allowing for caliper measurement if lesions were not visible on radiology). To be considered a CR, all lesions had to disappear. Partial response (PR) was defined as a decrease of more than 30% of the total tumor burden, measured as a number of lesions or shrinkage in the largest tumor diameter. Progressive disease (PD) was defined as an increase of more than 25% in existing lesions or the appearance of new lesions. Stable disease (SD) was defined as when criteria for CR, PR, or PD were not met.

2.4. Statistical analysis

Survival was estimated using the Kaplan-Meier method and analyzed using the log-rank test. Adjusted analyses were performed using binary logistic regression for CR and Cox regression for TTLP, PFS, and MSS, with results reported as hazard ratios (HR) with 95% confidence intervals (CIs) and p-values. Statistical significance was set at $p < 0.05$. Covariates for adjustment were selected a priori (age, gender, performance status, geographic region, T-status, mutational status, having received adjuvant therapy, anatomical site of ITM, number of ITM, size of largest ITM>=30 mm, lymph node status, and having received previous treatment for ITM). Statistical analysis was performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 287 patients with melanoma ITM from 21 institutions in eight different countries treated with immunotherapy were included in the analysis (Supplementary Table 1). Overall, 161 patients (56%) were male, and the median age at the start of ICI was 69 years (IQR 59–78). The median time from melanoma diagnosis to the first in-transit recurrence was 13 months (IQR 5–30). The most common site for in-transit metastasis was the lower limb, both for females (95/124, 77%) and males (74/157, 47%), and 127 (44%) had concomitant lymph node metastasis. A BRAF mutation was present in 84 (29%) and an NRAS mutation in 57 (20%) of the tumors. The most common histological subtypes of the primary melanomas were nodular (35%) and superficial spreading (32%), while acral lentiginous was present in only 8% of the patients. Ulceration was present in 122 (42.5%) of primary tumors (Table 1). Data on disease stage at diagnosis of the primary melanoma were available for 88% (n = 253) of patients, with 1% (n = 2) stage 0, 9% (n = 25) stage I, 24% (n = 60) stage II, and 66% (n = 166) stage III.

Immunotherapy was first-line treatment in 22% (n = 64) of the patients, or 60% (n = 173) if excluding previous surgical excisions. The remaining 40% of patients received previous treatments, either one or a combination of multiple therapies, with ILP (12%, n = 34), TVEC (10%, n = 28), radiotherapy (9%, n = 27), or ILI (3%, n = 9) being the most common (Table 1). Regional differences in treatment regimens were found when comparing geographical location, and treatments given prior to immunotherapy were in Europe previous surgical excision 66% (n = 69), ILP 14% (n = 15), ILI 2% (n = 2), and TVEC 11% (n = 12), in North America, the treatments were previous surgical excision 60% (n = 78), ILP 14% (n = 18), ILI 4% (n = 5), and TVEC 11% (n = 14), and in Australia, the treatments were previous surgical excision 80% (n = 41), ILP 2% (n = 1), ILI 4% (n = 2), and TVEC 4% (n = 2).

Single-agent treatment with a PD-1 or CTLA-4 inhibitor was given in 81% (n = 233) and 8% (n = 23) of the patients, respectively, while 11% (n = 31) received combination therapy with both a PD-1 and a CTLA-4 inhibitor. The median treatment time was five months (IQR 2–12), and the median follow-up time was 20 months (IQR 12–37). The ORR was 56%. The best response rate was CR in 36% (n = 104), PR in 20% (n = 58), SD in 11% (n = 32), and PD in 32% (n = 93) of the patients, respectively. The CR rate was 37% (86/233) for single-agent PD-1 inhibitor, 30% (7/23) for single-agent CTLA-4 inhibitor, and 35% (11/31) for the combination treatment of PD-1 and CTLA-4 inhibitor, with ORR of 56%, 43%, and 68%, respectively (Table 2). In both univariate and multivariate analysis, no predictive factors for CR were identified (Table 3).

The median time to local progression was 12 months (95% CI 6.0–18.0) and occurred in 160 patients (56%). There was a significant difference in time to local progression depending on response, where the median time was not met for CR, and for patients with a PR or SD, 23 and 21 months, respectively ($p < 0.001$) (Fig. 1). A total of 72 patients (25%) developed regional nodal progression after a median time of five months (95% CI 2.9–7.1). A total of 89 patients (31%) progressed with distant metastases after a median time of nine months (95% CI 6.7–11.3).

Out of the 104 patients that experienced an initial CR, 24 patients (23%) later progressed with further ITM after a median time of ten months, ten patients (10%) progressed with lymph node metastases after a median time of seven months, and 16 patients (15%) progressed with distant metastases after a median time of ten months (Table 2).

The median PFS from the start of ICI was ten months (95% CI 7.5–12.5 months) with a one-, two-, and five-year PFS rate of 47%, 33%, and 19%, respectively. When dividing PFS based on the type of immunotherapy received, there was no significant difference with a median PFS of ten months for single-agent PD-1 inhibitor, nine months for single-agent CTLA-4 inhibitor, and nine months for the combination treatment of PD-1 and CTLA-4 inhibitor ($p = 0.77$) (Fig. 2). In multivariate analysis, only ECOG performance status ≥2 (HR 2.16, 95% CI 1.04–4.50, $p = 0.04$) was found to be predictive for PFS (Supplementary Table 2).

One-, two-, and five-year MSS rate from the start of ICI was 95%, 83%, and 72%, respectively, with median MSS not reached (Supplementary Fig. 1). In multivariate analysis, female sex (HR 0.40, 95% CI 0.17–0.92, $p = 0.03$), ECOG performance status ≥2 (HR 7.52, 95% CI 2.14–26.46, $p = 0.01$), and positive lymph node status at the start of immunotherapy (HR 2.84, 95% CI

Table 1
Baseline patient characteristics at start of ICI for ITM.

	Overall (n = 287)	PD-1 (n = 233)	CTLA4 (n = 23)	PD1+CTLA4 (n = 31)
Age, median	69 years	71 years	66 years	65 years
Gender, n (%)				
Male	161 (56.1)	132 (56.7)	13 (56.5)	16 (51.6)
Female	126 (43.9)	101 (43.3)	10 (43.5)	15 (48.4)
Performance status, n (%)				
0	182 (63.4)	145 (62.2)	17 (73.9)	20 (64.5)
1	86 (30.0)	70 (30.0)	6 (26.1)	10 (32.3)
2	15 (5.2)	15 (6.4)	0 (0.0)	0 (0.0)
3	2 (0.7)	1 (0.4)	0 (0.0)	1 (3.2)
Missing	2 (0.7)	2 (0.9)	0 (0.0)	0 (0.0)
Geographic region, n (%)				
Europe[a]	105 (36.6)	91 (39.1)	4 (17.4)	10 (32.3)
Australia	51 (17.8)	42 (18.0)	5 (21.7)	4 (12.9)
North America	131 (45.6)	100 (42.9)	14 (60.9)	17 (54.8)
Histological subtype, n (%)				
Superficial spreading	91 (31.7)	78 (33.5)	5 (21.7)	8 (25.8)
Nodular	99 (34.5)	76 (32.6)	9 (39.1)	14 (45.2)
Acral lentiginous	23 (8.0)	17 (7.3)	4 (17.4)	2 (6.5)
Lentigo maligna	4 (1.4)	4 (1.7)	0 (0.0)	0 (0.0)
Other[b]	70 (24.4)	58 (24.9)	5 (21.6)	7 (22.6)
Ulcerated primary tumor, n (%)	122 (42.5)	98 (42.1)	12 (52.2)	12 (38.7)
T-status, n (%)				
T1	20 (7.0)	16 (6.9)	3 (13.0)	1 (3.2)
T2	55 (19.2)	45 (19.3)	3 (13.0)	7 (22.6)
T3	90 (31.4)	74 (31.8)	8 (34.8)	8 (25.8)
T4	101 (35.2)	80 (34.3)	7 (30.4)	14 (45.2)
Missing	21 (7.3)	18 (7.7)	2 (8.7)	1 (3.2)
Mutational status, n (%)				
BRAF/NRAS wt	125 (43.6)	106 (45.5)	8 (34.8)	11 (35.5)
BRAF mut	84 (29.3)	68 (29.2)	7 (30.4)	9 (29.0)
NRAS mut	57 (19.9)	40 (17.2)	6 (26.1)	11 (35.5)
Other, incl. unknown	21 (7.3)	19 (8.2)	2 (8.7)	0 (0.0)
Adjuvant treatment, n (%)				
None	227 (79.1)	192 (82.4)	17 (73.9)	18 (58.1)
Immunotherapy	51 (17.8)	35 (15.0)	5 (21.7)	11 (35.5)
Targeted therapy	6 (2.1)	4 (1.7)	1 (4.3)	1 (3.2)
Missing	3 (1.0)	2 (0.9)	0 (0.0)	1 (3.2)
Site of ITM, n (%)				
Head and neck	28 (9.8)	26 (11.2)	0 (0.0)	2 (6.5)
Upper limb	33 (11.5)	26 (11.2)	3 (13.0)	4 (12.9)
Trunk	51 (17.8)	41 (17.6)	3 (13.0)	7 (22.6)
Lower limb	169 (58.9)	135 (57.9)	17 (73.9)	17 (54.8)
Missing	6 (2.1)	5 (2.1)	0 (0.0)	1 (3.2)
Number of ITMs, n (%)				
1	63 (22.0)	52 (22.3)	3 (13.0)	8 (25.8)
2–3	75 (26.1)	63 (27.0)	4 (17.4)	8 (25.8)
4–10	75 (26.1)	61 (26.2)	9 (39.1)	5 (16.1)
>10	65 (22.6)	52 (22.3)	4 (17.4)	9 (29.0)
Missing	9 (3.1)	5 (2.1)	3 (13.0)	1 (3.2)
Size of largest ITM, n (%)				
<30 mm	201 (70.0)	160 (68.7)	14 (60.9)	27 (87.1)
>=30 mm	45 (15.7)	39 (16.7)	3 (13.0)	3 (9.7)
Missing	41 (14.3)	34 (14.6)	6 (26.1)	1 (3.2)
Lymph node status[c], n (%)				
N0	144 (50.2)	118 (50.6)	11 (47.8)	15 (48.4)
N+	127 (44.3)	102 (43.8)	12 (52.2)	13 (41.9)
Missing	16 (5.6)	13 (5.6)	0 (0.0)	3 (9.7)
Previous treatment for ITM, n (%)				
None	64 (22.3)	49 (21.0)	3 (13.0)	12 (38.7)
Surgical excision[d]	188 (65.5)	156 (67.0)	17 (73.9)	15 (48.4)
TVEC	28 (9.8)	24 (10.3)	3 (13.0)	1 (3.2)
Radiotherapy	27 (9.4)	17 (7.3)	4 (17.4)	6 (19.4)
ILP	34 (11.8)	26 (11.2)	4 (17.4)	4 (12.9)
ILI	9 (3.1)	5 (2.1)	1 (4.3)	3 (9.7)

Table 1 (*continued*)

	Overall (n = 287)	PD-1 (n = 233)	CTLA4 (n = 23)	PD1+CTLA4 (n = 31)
Other[e]	38 (13.2)	32 (13.7)	4 (17.4)	2 (6.4)
Number of previous treatments (excluding surgical excision), n (%)				
0	173 (60.3)	143 (61.4)	12 (52.2)	18 (58.1)
1	92 (32.1)	74 (31.8)	7 (30.4)	11 (35.5)
2	17 (5.9)	12 (5.2)	3 (13.0)	2 (6.5)
≥3	5 (1.7)	4 (1.8)	1 (4.3)	0 (0.0)

[a] Includes Israel.
[b] Includes unknown primary, other subtypes, and missing information.
[c] At time of diagnosis of the primary melanoma.
[d] Includes amputation (n = 1).
[e] PV-10, laser therapy, electrochemotherapy, imiquimod, diphencyprone, IL2 and TLR agonist, either alone or in combination.

Table 2
Response rate based on the type of treatment and subsequent disease progression.

Best response	Treatment				Subsequent disease progression		
	Overall n (%)	PD-1 n (%)	CTLA-4 n (%)	PD1+CTLA-4 n (%)	Local n (%)	Nodal n (%)	Distant n (%)
CR	104 (36.2)	86 (36.9)	7 (30.4)	11 (35.5)	24 (23.1)	10 (9.6)	16 (15.4)
PR	58 (20.2)	45 (19.3)	3 (13.0)	10 (32.3)	28 (48.3)	14 (24.1)	18 (31.0)
SD	32 (11.1)	24 (10.3)	5 (21.7)	3 (9.7%)	15 (46.9)	12 (37.5)	7 (21.9)
PD	93 (32.4)	78 (33.5)	8 (34.8)	7 (22.6)	93 (100)	36 (38.7)	48 (51.6)
ORR	162 (56.4)	131 (56.2)	10 (43.4)	21 (67.7)	52 (32.11)	24 (14.8)	34 (21.0)

1.15–7.06, p = 0.02) were found to be the prognostic for MSS (Supplementary Table 3). The one-, two-, and five-year OS was 92%, 77%, and 63%, respectively, with median OS not reached at the time of analysis. Melanoma-specific survival analyzed by best response from the start of ICI showed that response was a significant factor for survival (log-rank p < 0.001) (Fig. 3).

4. Discussion

This is the largest pooled multi-institutional analysis to date presenting real-world (outside of clinical trials) outcomes for patients with in-transit metastasis treated with systemic immunotherapy. The topic is clinically challenging and a pooled analysis is timely, particularly as patients with ITM only were not included as a subgroup for analysis in the previous registration trials for unresectable stage III or stage IV melanoma [15]. We report a CR rate of 36%, which is higher than the 26% and 13% recently reported by Nan Tie *et al.* and Zaremba *et al* respectively [16,17]. Nan Tie *et al.* presented a retrospective analysis of 54 patients with in-transit metastasis treated with PD-1 inhibitor (nivolumab or pembrolizumab) ± CTLA-4 inhibitor (ipilimumab) at three tertiary hospitals in Australia. Their cohort (partly included in this study) is comparable to ours in patient characteristics and treatment regimes, except that our study includes more patients with ulcerated primary tumors and more patients with concurrent nodal metastasis at the start of immunotherapy. We report a higher one- and two-year OS, while ORR and PFS are comparable.

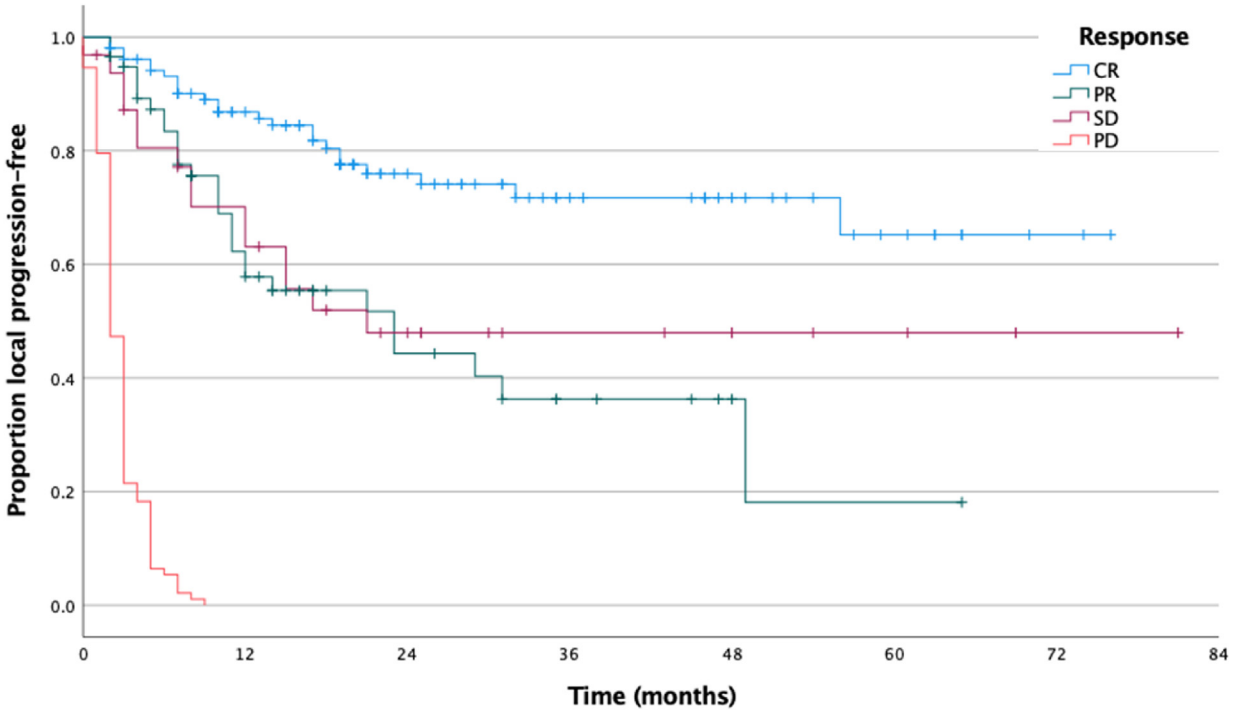
More recently, Zaremba *et al.* retrospectively reported on 191 patients with unresectable stage IIIB-D in-transit and satellite metastases from 16 centers in Germany. Notably, they excluded patients who had received prior treatments followed by adjuvant immunotherapy and only included patients receiving PD-1±CTLA4-inhibitor as first-line treatment. Patient characteristics were, again, roughly comparable to this cohort, but the overall CR rate for patients receiving PD-1 inhibitor was only 13% [17].

Our CR rate is also higher than the response data from the registration trials investigating immunotherapy for unresectable stage III and stage IV patients. The CR rates in these registration trials range from a CR rate of 2% for CTLA4-inhibitor monotherapy, up to 22% for combination PD-1 and CTLA4-inhibitors [12,14,18–23]. Though the direct comparison is difficult, we also see a significantly higher MSS in our CR patient group. We also see an unexpectedly high CR rate of 30% for single-agent CTLA4 in this study. This is significantly higher than reported from other cohorts and is possibly an overestimate due to the small sample size of only twenty-three patients in this subgroup. However, it should be noted that direct comparisons of response rates are complicated by the lack of a standardized method of judging response in cutaneous lesions. We used RECIST criteria for the definition of response, with the modification that the lesions did not have to be visible on

Table 3
Logistic regression analysis for complete response.

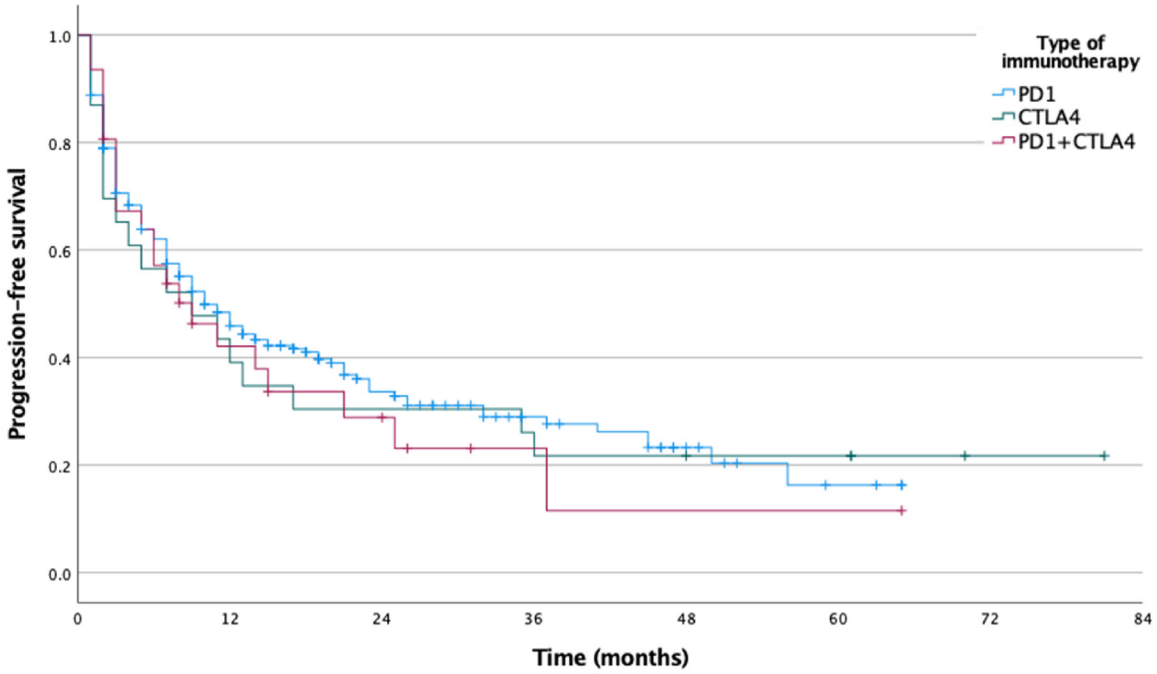
	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age, years	1.00	0.98–1.02	0.97	1.00	0.97–1.02	0.83
Gender						
Male	*ref*			*ref*		
Female	1.02	0.63–1.66	0.93	1.01	0.57–2.15	0.77
Performance status						
0–1	*ref*			*ref*		
≥2	1.62	0.61–4.33	0.34	1.52	0.40–5.67	0.54
Geographic region						
Europe[a]	*ref*			*ref*		
North America	1.38	0.80–2.35	0.25	1.24	0.60–2.57	0.56
Australia	1.14	0.56–2.31	0.72	1.12	0.43–2.92	0.82
Histological subtype						
Superficial spreading	*ref*			*ref*		
Nodular	1.16	0.64–2.09	0.64	1.46	0.69–3.21	0.31
Acral lentiginous	0.68	0.25–1.91	0.47	0.90	0.22–3.62	0.88
Lentigo maligna	1.94	0.26–14.41	0.52	2.45	0.13–47.90	0.55
Other	1.29	0.68–2.46	0.44	1.13	0.51–2.50	0.77
Mutational status						
BRAF/NRAS wt	*ref*			*ref*		
BRAF	0.77	0.43–1.39	0.38	0.98	0.45–2.12	0.96
NRAS	1.25	0.66–2.37	0.50	1.39	0.56–3.47	0.48
Adjuvant treatment						
No	*ref*			*ref*		
Immunotherapy	0.91	0.48–1.72	0.77	0.73	0.30–1.81	0.50
Targeted therapy	0.33	0.04–2.91	0.32	0.67	0.05–8.26	0.76
Site of ITM						
Lower limb	*ref*			*ref*		
Upper limb	0.83	0.30–2.29	0.72	1.18	0.30–4.58	0.82
Trunk	0.46	0.18–1.18	0.11	0.76	0.20–2.94	0.70
Head and neck	0.50	0.22–1.11	0.09	0.71	0.21–2.41	0.58
Number of ITMs						
1	*ref*			*ref*		
2–3	1.37	0.69–2.71	0.37	2.34	0.90–6.08	0.08
4–10	0.92	0.46–1.86	0.82	1.45	0.56–3.76	0.45
>10	0.77	0.37–1.61	0.49	1.07	0.36–3.15	0.91
Size of largest ITM						
<30 mm	*ref*			*ref*		
>=30 mm	0.84	0.42–1.66	0.62	0.67	0.29–1.58	0.36
Lymph node status						
N0	*ref*			*ref*		
N+	0.75	0.45–1.24	0.26	0.56	0.29–1.06	0.07
Previous surgical excision						
No	*ref*			*ref*		
Yes	1.21	0.73–2.02	0.46	1.28	0.64–2.56	0.48
Previous local treatment						
No	*ref*			*ref*		
Yes	0.71	0.3 –1.29	0.26	1.16	0.52–2.37	0.78
Previous radiotherapy						
No	*ref*			*ref*		
Yes	0.87	0.38– 2.01	0.74	0.65	0.20– 2.16	0.48
Previous locoregional treatment						
No	*ref*			*ref*		
Yes	0.83	0.42–1.65	0.59	0.70	0.27–1.83	0.46
Type of immunotherapy						
PD1-inhibitor	*ref*			*ref*		
CTLA4-inhibitor	0.75	0.30–1.89	0.54	1.30	0.38–4.50	0.68
PD1+CTLA4	0.94	0.43–2.06	0.88	1.08	0.41–2.88	0.88

[a] Including Israel.



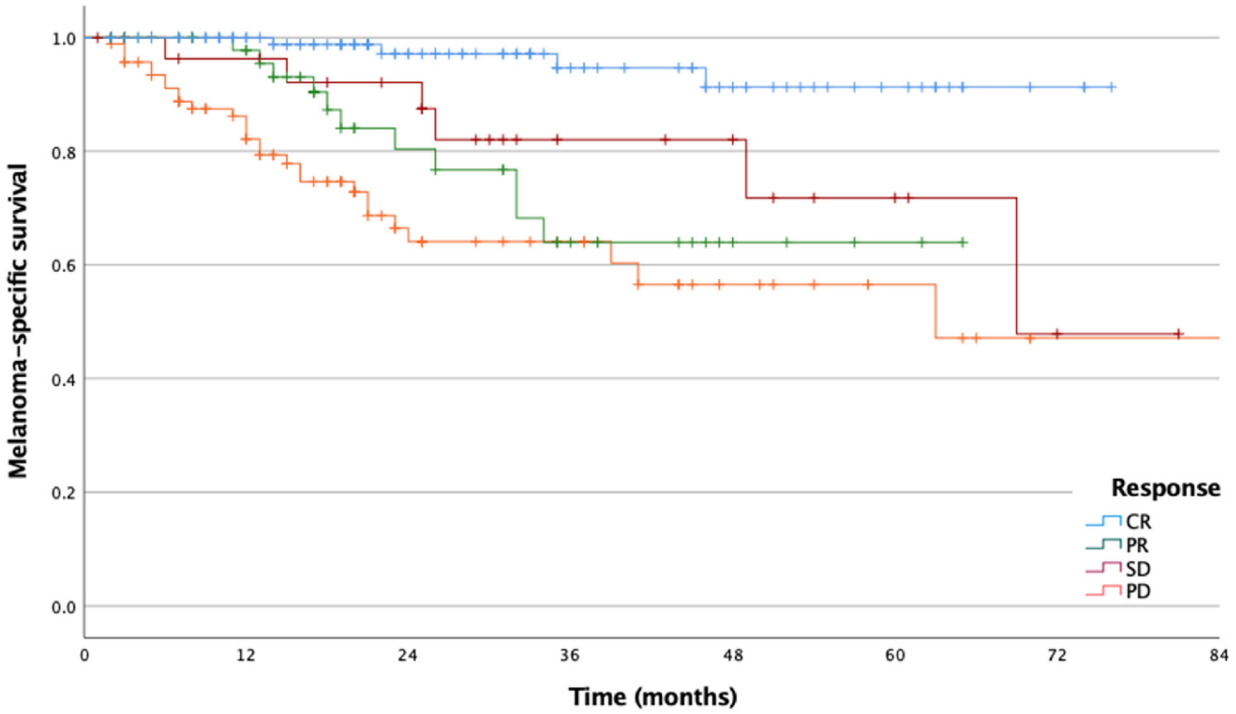
No at risk:								
CR	104	74	41	23	15	7	1	0
PR	58	27	11	5	2	1	0	0
SD	32	19	10	5	4	2	1	0
PD	93	0	0	0	0	0	0	0

Fig. 1. Local progression-free survival (in-transit metastasis) based on response of treatment from start of immunotherapy.



No at risk:								
PD1	233	95	42	22	9	3	0	0
CTLA4	23	9	7	5	4	3	1	0
PD1+CTLA4	31	10	5	2	1	1	0	0

Fig. 2. Progression-free survival from start of immunotherapy by treatment.



No at risk:								
CR	104	86	55	34	21	11	3	0
PR	58	43	22	11	4	2	0	0
SD	32	25	20	10	8	4	1	0
PD	93	63	27	20	10	6	1	1

Fig. 3. Melanoma-specific survival by best response from the start of ICI.

radiology, but could be measured by calipers. This is a strength, since the response rates can be compared to other publications, and using calipers is the most common way in-transit lesions are measured. Of note, how the response was evaluated was not stated at all in the Zaremba manuscript [17], and the Nan Tie manuscript [16] used the WHO criteria for PR (50% cut-off). In addition, any biological particularities of in-transit metastases underlying response and progression patterns are currently unknown.

Other treatment options for patients with ITM include, e.g., TVEC, ILI, or ILP, with reported CR rates of up to 62%, 38%, and 65%, respectively [4,24–27]. Owing to the heterogeneous follow-up between these different studies, any comparison of response duration is not possible. In the current cohort, there was no benefit of having received locoregional treatments prior to immunotherapy. This finding can be the result of a selection bias due to our study design, where only patients progressing after a previous locoregional treatment were included. Patients with limited and resectable in-transit metastases may undergo a resection of the metastases followed by adjuvant systemic therapy, supported by data from the CheckMate-238 study showing a benefit in four-year RFS favoring nivolumab over ipilimumab with a HR of 0.63.

Another important finding was the rate of patients with no response and primary resistance; the rate of PD as the best response in this real-world cohort was 32% compared to 30% in Nan Tie *et al.* [16] and 43% in Zaremba *et al.* [17]. These are all higher PD rates than reported for locoregional therapies, e.g., 3% for ILP [4], 7% for ILI [5], 18% for TVEC [28] and 3% for electrochemotherapy [29]. We, therefore, hypothesize that for patients with multiple, bulky, or quickly recurrent ITM, a combination of locoregional with systemic treatment might be appealing. This strategy might combine the very high ORR and low PD rates of T-VEC, ILP, or ILI, together with a systemic treatment that would also treat undetected micrometastatic disease outside of the area treated with locoregional therapy.

Hypothetically, the combination of locoregional and systemic treatment might not just have effects independent of each other but might also act in synergy. It has, for example, been shown that ILP leads to an activation of tumor-specific T-cells, which potentially can be enhanced by the addition of a PD-1 inhibitor [30,31]. A phase I study of TVEC together with pembrolizumab

showed a potential synergistic effect [32], and the following placebo-controlled Masterkey-265 phase III trial showed an increased response rate (18% vs. 12%), however, without any benefit in PFS or OS after a median of 31 months of follow-up [33]. On the other hand, TVEC has been shown to be an effective salvage therapy with ORR of 51% and CR rates of 37% after the failure of systemic immunotherapy for ITM [34]. Another phase III trial (ILLUMINATE-301), examined the synergistic effect of intratumoral injections of the Toll-like receptor 9 agonist tilsotolimod together with ipilimumab, however, there was no difference in ORR compared to ipilimumab alone, 8.8% vs 8.6% (data not published). In summary, the optimal combination and sequence of these different treatment modalities for patients with ITM needs further clarification through prospective trials. Two examples of ongoing studies are the Nivo-ILP (ClinicalTrials.gov: NCT03685890) and NIVEC (ClinicalTrials.gov: NCT04330430) studies, which are examining the combination of ILP and nivolumab and T-VEC and nivolumab for patients with ITM, respectively.

We demonstrate a five-year OS of 63%, and in comparison, 44% for patients treated with ILI as shown by Kroon *et al.*; 26% for patients treated with ILP as shown by Olofsson Bagge *et al.*; and 49% for patients treated with TVEC (stage IIIB-IV M1a patients) as reported by Andtbacka *et al.* [4–6,14]. However, any direct comparisons are not possible as some of these studies were undertaken before effective systemic therapies were available, and the patient selection criteria/baseline characteristics, patient prognosis, methodologies, and follow-up times are also very different.

The relatively low rate of BRAF positive patients in the current cohort, 32% (84/266) when excluding missing values, can be compared to 42% (71/170) in the material by Zaremba *et al.*, and 19% (10/52) in the material by Nan Tie *et al.* Hypothetically, patients developing in-transit metastasis might have a different proportion of BRAF mutations, or there may be a selection bias where patients with a BRAF-mutation to a larger extent have received targeted therapies rather than immunotherapy. Unfortunately, based on the current data, we cannot draw any conclusions concerning this, but it is indeed a question that warrants further investigation.

A strength of this study is the large, international, and multi-center cohort. This results in what we believe to be an accurate overview of current practice and outcomes internationally. There were regional differences in treatment regimens when comparing centers by geographical location, and it is very possible that these differences reflect dissimilarities in either treatment availability or management approach between countries. Further, the study is limited by the retrospective design, inherent selection bias, and relatively small subgroups. Also, as has been noted previously, measurement of treatment response in this patient group is difficult as the disease in this stage may not be accurately evaluable by RECIST [35] or WHO [36] criteria. Many institutions report using RECIST criteria modified for cutaneous lesions, but do not specify the modifications further. In our view, there is currently a lack of objective and standardized criteria by which to assess in-transit lesions sufficiently accurately, and future research should be focused on this aspect.

5. Conclusions

In summary, systemic immunotherapy with checkpoint inhibition is an effective treatment for melanoma in-transit metastases. Future studies should be conducted to establish not only the optimal sequencing, timing, and role of surgery and/or other locoregional therapies in combination with systemic immunotherapy but also the mechanisms of clinical immune responses making such treatments effective.

Author contributions

Carl-Jacob Holmberg: conceptualization, methodology, formal analysis, investigation, data curation, writing - original draft, writing - review & editing, visualization. **Lars Ny**: conceptualization, methodology, investigation, writing - review & editing. **Tina Hieken:** investigation, writing - review & editing. **Matthew Block:** investigation, writing - review & editing. **Michael Carr:** investigation, writing - review & editing. **Vernon Sondak:** investigation, writing - review & editing**. Christoffer Örtenwall:** investigation, writing - review & editing. **Dimitrios Katsarelias:** investigation, writing - review & editing. **Florentia Dimitriou:** investigation, writing - review & editing. **Alexander M Menzies:** investigation, writing - review & editing. **Robyn PM Saw:** investigation, writing - review & editing. **Richard J Straker III:** investigation, writing - review & editing. **Giorgos Karakousis:** investigation, writing - review & editing. **Rona Applewaithe:** investigation, writing - review & editing. **Lalit Pallan:** investigation, writing - review & editing. **Dale Han:** investigation, writing - review & editing. **John T Vetto:** investigation, writing - review & editing. **David Gyorki:** investigation, writing - review & editing. **Emilia Nan Tie:** investigation, writing - review & editing. **Maria Grazia Vitale:** investigation, writing - review & editing. **Paulo A Ascierto:** investigation, writing - review & editing. **Reinhard Dummer:** investigation, writing - review & editing. **Jade Cohen:** investigation, writing - review & editing. **Jane YC Hui:** investigation, writing - review & editing. **Jacob Schachter:** investigation, writing - review & editing. **Nethanel Asher:** investigation, writing - review & editing. **Hildur Helgadottir:** investigation, writing - review & editing. **Harvey Chai:** investigation, writing - review & editing. **Hidde Kroon:** investigation, writing - review & editing. **Brandon Coventry:** investigation, writing - review & editing. **Luke D Rothermel:** investigation, writing - review & editing.

James Sun: investigation, writing - review & editing. **Matteo S Carlino:** investigation, writing - review & editing. **Zoey Duncan:** investigation, writing - review & editing. **Kristy Broman:** investigation, writing - review & editing. **Jeffrey Weber:** investigation, writing - review & editing. **Ann Lee:** investigation, writing - review & editing. **Russel S Berman:** investigation, writing - review & editing. **Jüri Teras:** investigation, writing - review & editing. **David W Ollila:** investigation, writing - review & editing. **Georgina V Long:** conceptualization, methodology, investigation, writing - review & editing, visualization. **Jonathan S Zager:** conceptualization, methodology, investigation, writing - review & editing, visualization. **Alexander van Akkooi:** conceptualization, methodology, investigation, writing - review & editing, visualization. **Roger Olofsson Bagge:** conceptualization, methodology, formal analysis, investigation, resources, data curation, writing - original draft, writing - review & editing, visualization, supervision, project administration.

Funding

The Swedish Cancer Society (Dnr 19 0040 Pj). Knut and Alice Wallenberg Foundation, Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, Sweden

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

R Olofsson Bagge: Advisory boards for Amgen, Bristol-Myers Squibb, Merck Sharp & Dhome, Novartis, Roche, and Sanofi Genzyme. Speaker honorarium from Roche and Pfizer. Institutional research grant from Astra Zeneca and SkylineDx.

L Ny: Consultant/advisory role for Bristol-Myers Squibb, Merck Sharp & Dhome, Novartis, Pierre Fabre, Sanofi Genzyme and Zealth. Speaker honorarium from Bristol-Myers Squibb, Leo Pharma, Merck Sharp & Dhome, Novartis, and Pfizer. Institutional research support from Merck Sharp & Dhome and Syndax Pharmaceuticals.

T Hieken: Institutional research funding from Genentech and SkylineDx.

M Block: Advisory Boards TILT Biotherapeutics, Viewpoint Molecular Targeting and Sorrento Therapeutics. Grant/Research support from: Genentech, Marker Therapeutics, Immune Design, Pharmacyclics, Merck, Bristol-Myers Squibb, Transgene, Viewpoint Molecular Targeting and Sorrento Therapeutics.

F Dimitriou: Honoraria and travel support from Merck Sharp & Dohme and Sun Pharma.

AM Menzies: Advisory boards for Bristol-Myers Squibb, Merck Sharp & Dhome, Novartis, Roche, Pierre-Fabre and Qbiotics.

RPM Saw: Honoraria for advisory board participation from Merck Sharp & Dhome, Novartis and Qbiotics, and speaking honoraria from Bristol-Myers Squibb and Novartis.

A Rogiers: Speaker fee from Merck Sharpe and Dohme.

G Karakousis: Investigator intitated research trial institutional support from Merck.

L Pallan: Speakers fees and travel support from Bristol-Myers Squibb. Conference attendance support from Eli-Lilly.

JT Vetto: Speakers fee from CastleBiosciences.

D Gyorki: Advisory board Amgen, Provectus and Bayer. Speaker fees Bristol-Myers Squibb and Merck Sharp & Dhome.

PA Ascierto: Consultant/advisory role for Bristol Myers Squibb, Roche-Genentech, Merck Sharp & Dohme, Novartis, Merck Serono, Pierre-Fabre, AstraZeneca, Sun Pharma, Sanofi, Idera, Sandoz, Immunocore, 4SC, Italfarmaco, Nektar, Boehringer-Ingelheim, Eisai, Regeneron, Daiichi Sankyo, Pfizer, Oncosec, Nouscom, Lunaphore, Seagen and iTeos. Research funding from Bristol Myers Squibb, Roche-Genentech, Pfizer and Sanofi.

R Dummer: intermittent, project focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome, Bristol-Myers Squibb, Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Regeneron, Alligator, T3 Pharma, MaxiVAX SA and touchIME outside the submitted work.

J Schachter: Advisory board Merck Sharp & Dhome. Speaker honoraria Bristol-Myers Squibb, Merck Sharp & Dhome, Novartis and Medison.

N Asher: Advisory boards for Medison, Bristol-Myers Squibb, Merck Sharp & Dhome, Novartis, Roche, and Sanofi. Speaker honoraria from Medison, Bristol-Myers Squibb, Merck Sharp & Dhome, Novartis, and Sanofi. Institutional research grants from Medison and Novartis.

H Helgadottir: Advisory boards for Merck Sharp & Dhome and Novartis. Speaker honorarium from Bristol-Myers Squibb.

MS Carlino: Advisory board member for Amgen, Bristol-Myers Squibb, Eisai, Ideaya, Merck Sharp & Dhome, Nektar, Novartis, Oncosec, Pierre-Fabre, Qbiotics, Regeneron, Roche, Merck and Sanofi, and honoraria from Bristol-Myers Squibb, Merck Sharp & Dhome, and Novartis.

J Weber: Consult for Merck, Genentech, Astra Zeneca, GlaxoSmithKline, Novartis, Nektar, Celldex, Incyte, Biond, ImCheck, Sellas, Evaxion and EMD Serono. Advisory board member Bristol-Myers Squibb.

Equity in Biond, Evaxion, Instil Bio and Neximmune. Scientific advisory boards for CytoMx, Incyte, ImCheck, Biond, Sellas, Instil Bio OncoC4 and Neximmune. Institutional research support from Bristol-Myers Squibb, Merck, GlaxoSmithKline, Moderna, Pfizer, Novartis and Astra Zeneca. Named on patents from Moffitt Cancer Center and Biodesix.

D Ollila: Advisory boards and/or Consulting for Philogen, Merck, Novartis and Castle Biosciences. Medical Advisory Bopard - Delcath Systems. Speaker honorarium from Sun Pharma and Pfizer. Institutional research funding from Neracare, Castle Biosciences, Delcath Systems, Philogen and Provectus, GV Long: Consultant advisor for Aduro Biotech Inc, Amgen Inc, Array Biopharma inc, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb, Evaxion Biotech A/S, Hexel AG, Highlight Therapeutics S.L., Merck Sharpe & Dohme, Novartis Pharma AG, OncoSec, Pierre Fabre, QBiotics Group Limited, Regeneron Pharmaceuticals Inc, SkylineDX B.V. and Specialised Therapeutics Australia Pty Ltd.

J Zager: Advisory boards and/or Consulting for Philogen, Merck, Novartis and Castle Biosciences. Medical Advisory Board Delcath Systems. Speaker honorarium from Sun Pharma and Pfizer. Institutional research funding from Neracare, Castle Biosciences, Delcath Systems, Philogen and Provectus.

A van Akkooi: Advisory Board and Consultancy Honoraria from Amgen, Bristol-Myers Squibb, Novartis, Merck Sharp & Dhome, Merck, Pfizer, Pierre Fabre, Sanofi, Sirius Medical and 4SC. Research grants from Amgen, Merck and Pfizer. All unrelated to current work and paid to institute.

The funding bodies had no part in the design of the study, the collection of data, in the analysis of data or in writing the manuscript.

Acknowledgements

This publication is dedicated to the memory of our colleague and friend Dr Dale Han.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.03.041.

References

[1] Pawlik TM. Predictors and natural history of in-transit melanoma after sentinel lymphadenectomy. Ann Surg Oncol 2005;12(8):587–96.
[2] Karakousis CP, Choe KJ, Holyoke ED. Biologic behavior and treatment of intransit metastasis of melanoma. Surg Gynecol Obstet 1980;150(1):29–32.
[3] Gershenwald JE. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67(6):472–92.
[4] Olofsson R, Mattsson J, Lindnér P. Long-term follow-up of 163 consecutive patients treated with isolated limb perfusion for in-transit metastases of malignant melanoma. Int J Hyperther 2013;29(6):551–7.
[5] Kroon HM. Australian multicenter study of isolated limb infusion for melanoma. Ann Surg Oncol 2016;23(4):1096–103.
[6] Andtbacka RHI. Final analyses of OPTiM: a randomized phase III trial of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor in unresectable stage III-IV melanoma. J Immunother Cancer 2019;7(1):145.
[7] Goggins CA, Khachemoune A. The use of electrochemotherapy in combination with immunotherapy in the treatment of metastatic melanoma: a focused review. Int J Dermatol 2019;58(8):865–70.
[8] Read T. A systematic review and meta-analysis of locoregional treatments for in-transit melanoma. J Surg Oncol 2019;119(7):887–96.
[9] Chapman PB. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364(26):2507–16.
[10] Hauschild A. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380(9839):358–65.
[11] Long GV. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet 2015;386(9992):444–51.
[12] Hodi FS. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363(8):711–23.
[13] Hamid O. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. Ann Oncol 2019;30(4):582–8.
[14] Larkin J. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2019;381(16):1535–46.
[15] Olofsson Bagge R. The efficacy of immunotherapy for in-transit metastases of melanoma: an analysis of randomized controlled trials. Melanoma Res 2021;31(2):181–5.
[16] Nan Tie E. Efficacy of immune checkpoint inhibitors for in-transit melanoma. J Immunother Cancer 2020;8(1).
[17] Zaremba A. Clinical characteristics and therapy response in unresectable melanoma patients stage IIIB-IIID with in-transit and satellite metastases. Eur J Cancer 2021;152:139–54.
[18] Robert C. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol 2019;20(9):1239–51.
[19] Ascierto PA. Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 2017;18(5):611–22.
[20] Weber JS. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015;16(4):375–84.
[21] Robert C. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015;372(26):2521–32.
[22] Schachter J. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet 2017;390(10105):1853–62.
[23] Long GV. Epacadostat plus pembrolizumab versus placebo plus pembrolizumab in patients with unresectable or metastatic melanoma (ECHO-301/KEYNOTE-252): a phase 3, randomised, double-blind study. Lancet Oncol 2019;20(8):1083–97.

[24] Andtbacka RH. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol 2015;33(25):2780–8.
[25] Kroon HM. Outcomes following isolated limb infusion for melanoma. A 14-year experience. Ann Surg Oncol 2008;15(11):3003–13.
[26] Stahlie EHA. T-VEC for stage IIIB-IVM1a melanoma achieves high rates of complete and durable responses and is associated with tumor load: a clinical prediction model. Cancer Immunol Immunother 2021;70(8):2291–300.
[27] Miura JT. Long-Term oncologic outcomes after isolated limb infusion for locoregionally metastatic melanoma: an international multicenter analysis. Ann Surg Oncol 2019;26(8):2486–94.
[28] Louie RJ. Real-world outcomes of talimogene laherparepvec therapy: a multi-institutional experience. J Am Coll Surg 2019; 228(4):644–9.
[29] Kunte C. Electrochemotherapy in the treatment of metastatic malignant melanoma: a prospective cohort study by InspECT. Br J Dermatol 2017;176(6):1475–85.
[30] Olofsson R. Melan-A specific CD8+ T lymphocytes after hyperthermic isolated limb perfusion: a pilot study in patients with in-transit metastases of malignant melanoma. Int J Hyperther 2013; 29(3):234–8.
[31] Kiffin R. Anti-PD-1 checkpoint blockade improves the efficacy of a melphalan-based therapy in experimental melanoma. Eur J Surg Oncol 2021;47(9):2460–4.
[32] Ribas A. Oncolytic virotherapy promotes intratumoral T cell infiltration and improves anti-PD-1 immunotherapy. Cell 2017; 170(6):1109–1119 e10.
[33] Ribas A. 1037O MASTERKEY-265: a phase III, randomized, placebo (Pbo)-controlled study of talimogene laherparepvec (T) plus pembrolizumab (P) for unresectable stage IIIB–IVM1c melanoma (MEL). Ann Oncol 2021;32:S868–9.
[34] Carr MJ. Talimogene laherparepvec (T-VEC) for the treatment of advanced locoregional melanoma after failure of immunotherapy: an international multi-institutional experience. Ann Surg Oncol; 2021.
[35] Eisenhauer EA. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–47.
[36] Miller AB. Reporting results of cancer treatment. Cancer 1981; 47(1):207–14.