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Adjuvant treatment of in-transit melanoma: Narrowing the knowledge gap left by clinical trials

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Abstract

Few clinical trials address efficacy of adjuvant systemic treatment in patients with in-transit melanoma (ITM). This study describes adjuvant systemic therapy of ITM patients beyond clinical trials. In this study, we included stage III adjuvant-treated melanoma patients registered in the nationwide Dutch Melanoma Treatment Registry between July 2018 and December 2020. Patients were divided into three groups: nodal disease only, ITM only and ITM and nodal disease. Recurrence patterns, recurrence-free survival (RFS) and overall survival (OS) at 12-months were analyzed. In our study population of 1037 patients, 66.8% had nodal disease only, 16.7% had ITM only and 16.2% had ITM with nodal disease. RFS at 12-months was comparable in the nodal only and ITM only group (72.2% vs70.1%, $P = .97$) but lower in ITM and nodal disease patients (57.8%; $P = .01$, $P < .01$). Locoregional metastases occurred as first recurrence in 38.9% nodal disease only, 71.9% of ITM-only and 44.0% of ITM and nodal disease patients. Distant recurrences occurred in 42.3%, 18.8% and 36.0%, respectively ($P = .02$). 12-months OS was not significantly different for nodal disease only patients compared with ITM-only (94.4% vs 97.6%, $P = .06$) but was significantly higher for ITM-only compared with ITM and nodal disease patients (97.6% vs 91.0%, $P < .01$). In conclusion, we showed that in the adjuvant setting, RFS rates in ITM-only patients are similar to non-ITM, though better than in ITM and nodal

Abbreviations: AJCC, American Joint Committee on Cancer; Anti-PD-1, anti-programmed cell death protein 1; DICA, Dutch Institute for Clinical Auditing; DMTR, Dutch Melanoma Treatment Registry; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC, European Organization for Research and Treatment of Cancer; ITM, in-transit melanoma; NR, not reached; OS, overall survival; RFS, recurrence-free survival; slnb, sentinel Lymph Node Biopsy; T-VEC, talimogene laherparepvec.

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disease patients. Adjuvant-treated ITM-only patients less often experience distant recurrences and have a superior OS compared with ITM and nodal disease patients.

KEYWORDS
adjuvant treatment, melanoma, checkpoint inhibition therapy, immunotherapy, in-transit melanoma, melanoma

What's new?

In some melanoma cases, metastases arise between the primary tumor site and the first draining regional lymph node, called in-transit melanoma (ITM). Here, the authors investigated the efficacy of adjuvant treatment for ITM. In patients with stage III, adjuvant-treated melanoma, recurrence-free survival after 12 months was comparable between patients with nodal disease only and those with ITM only, but shorter in patients with both. This is the first large cohort study on adjuvant-treated ITM, and the results suggest that nodal status could indicate different treatment strategies for ITM patients.

1 | INTRODUCTION

In-transit melanoma (ITM) is defined as cutaneous or subcutaneous metastases that occur between the primary tumor site and first draining regional lymph node and is almost unique to melanoma.[1] The pathophysiology of ITM has been the subject of debate for many years and is still not entirely understood.[2] It has been suggested that ITM results from tumor emboli trapped in congestive intradermal lymphatic vessels located between the primary melanoma and the first regional lymph node. To a lesser extent, implantation of tumor cells through hematogenous spread may play a role as well as migration of tumor cells through tissue fluid around the abluminal surface of lymphatics and blood vessels.[3] The hypothesis that emboli of melanoma may be more likely to become trapped in the lymphatic system after Sentinel Lymph Node Biopsy (SLNB) has been rejected by numerous studies.[3-6]

According to literature, 5% to 20 % of patients with high-risk melanoma will eventually develop satellite or ITM, and patients with ITM have a high risk of developing distant metastases (42.5%-56.5%).[2,3,6,7] We previously showed that up to 25% of adjuvant-treated melanoma patients in daily practice had ITM.[8] ITM treatment options are diverse and may exist of local, regional, or systemic therapies. Complete surgical resection of individual ITM lesions with clear margins is the treatment of choice when possible.

Unfortunately, not all adjuvant registration trials included ITM patients. In the COMBI-AD trial, adjuvant dabrafenib/trametinib was compared with placebo in resected stage III BRAF-mutated melanoma patients. In this trial, 12% of patients in the treatment group had ITM vs 8% in the placebo group.[9] However, endpoints were not stratified for ITM patients in this study. In the Checkmate-238 trial, a total of 164 adjuvant-treated ITM patients with or without nodal involvement were included,[10,11] demonstrating similar RFS benefit of adjuvant treatment in ITM patients. In the EORTC 1325/Keynote-054 trial, comparing pembrolizumab to placebo in stage III resected melanoma ITM patients were excluded.[12] All in all, the role of adjuvant treatment in ITM patients is not extensively addressed.

This study describes RFS and OS rates in ITM patients receiving adjuvant anti-PD-1 therapy in the Netherlands, including patient- and tumor characteristics, subsequent recurrence patterns and their management.

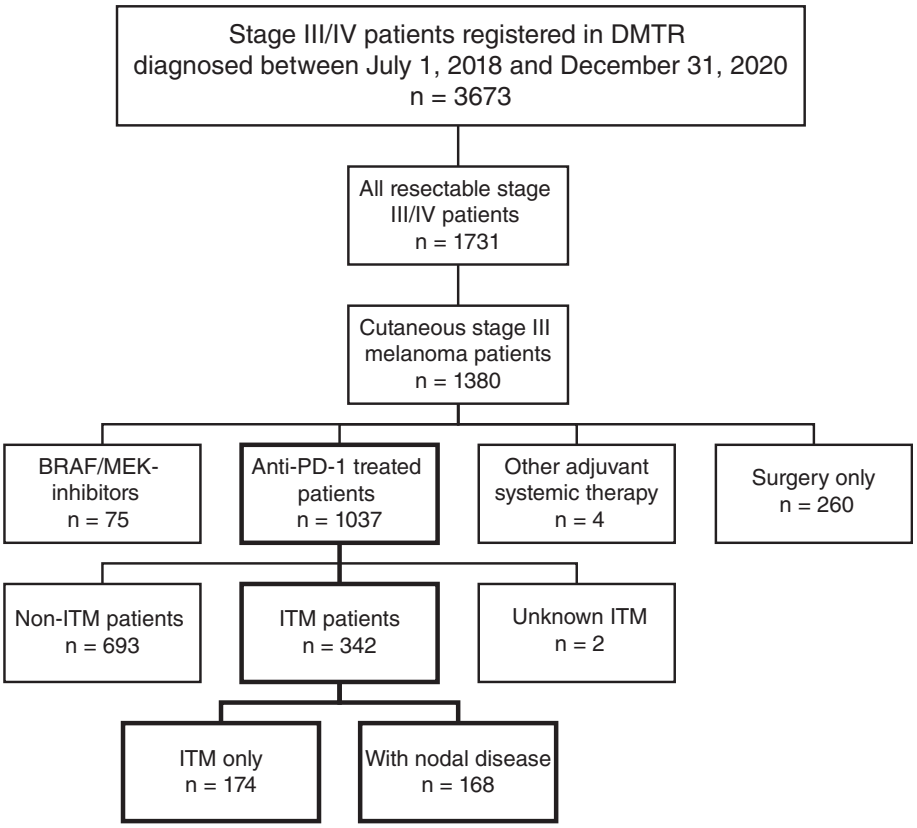
2 | METHODS

2.1 | Study population

Patients were identified using the Dutch Melanoma Treatment Registry (DMTR), a prospective nationwide registry containing data on all unresectable stage III/IV melanoma patients and resectable stage III/IV patients eligible for treatment with adjuvant systemic therapy since 2012 and 2018, respectively.[8,13] Data is registered by trained data managers and approved by medical oncologists representing the 14 melanoma centers in the Netherlands.

For this study, we selected resected stage III cutaneous melanoma patients diagnosed between January 7, 2018 and December 31, 2020 who were treated with adjuvant systemic anti-PD-1 therapy. The data cut-off date was January 3, 2022. Adjuvant systemic therapy was defined as "systemic therapy after complete resection of melanoma," and the stage of disease was classified using the American Joint Committee on Cancer (AJCC) eighth edition.[14] The adjuvant-treated patient population was divided into three subgroups receiving adjuvant therapy: patients with nodal disease only, patients with ITM only and patients with ITM and nodal disease. Patients with satellite lesions were also included as ITM patients due to similarities in prognosis and staging.[14] ITM at first diagnosis and ITM within 90 days of primary melanoma diagnosis were considered primary ITM. ITM registered after 90 days of primary melanoma diagnosis was deemed recurrent ITM.

FIGURE 1 Flowchart.



The adjuvant-treated patients described in this study were treated with anti-PD-1 therapy (nivolumab or pembrolizumab). Because BRAF/MEK inhibitors were approved and reimbursed in the Netherlands as an adjuvant systemic treatment for resected stage III/IV melanoma on November 1, 2020,[15] only a limited number of patients were treated with BRAF/MEK inhibitors during the inclusion period of this study. Due to these limited numbers, patients treated with BRAF/MEK inhibitors were not included in our analyses.

2.2 | Statistical analysis

Descriptive statistics were used to describe patient- and tumor characteristics, recurrence patterns and subsequent treatment regimens. Recurrence-free survival (RFS) rates at 12-months and overall survival (OS) rates at 12-months were estimated using the Kaplan-Meier method. The median follow-up duration was calculated using the reversed Kaplan-Meier method. RFS and OS were calculated from the start of systemic therapy until recurrence or death. Patients who did not meet the endpoints for RFS or OS were censored at the date of the last follow-up. RFS and OS were compared between adjuvant-treated ITM subgroups using a log-rank test at a two-sided alpha level. Fisher's exact test analyzed differences in the first recurrence site between ITM subgroups. First recurrences were categorized as locoregional recurrence, distant recurrence, or both locoregional and distant recurrence.

Data handling and statistical analyses were performed using the R software system for statistical computing (version 4.1.0; packages lubridate, plyr, dplyr, car, tidyverse, magrittr, tidyr, tableone, ggplot2, ggthemes, stringr, readxl, RColorBrewer, EnvStats, survminer, survival).[16,17,18-29]

3 | RESULTS

3.1 | Patient- and tumor characteristics

In total, 3673 resectable and irresectable stage III/IV patients were registered in the DMTR database between January 7, 2018 and December 31, 2020. We identified 1037 resectable stage III cutaneous melanoma patients 18 years or older at diagnosis who received adjuvant anti-PD-1 systemic therapy (Figure 1). Of these adjuvant anti-PD-1 treated patients, 342 (33.0%) patients had ITM. In 2 (0.19%) patients, data on the presence of ITM were missing. Of the patients with ITM, 50.9% (n = 174) had ITM only, and 49.1% (n = 168) had ITM with nodal disease. The patient and tumor characteristics of these patients are shown in Table 1. Furthermore, 260 cutaneous stage III melanoma patients waived adjuvant systemic therapy.

TABLE 1 Patient and tumor characteristics of cutaneous melanoma patients treated with adjuvant anti-PD-1 therapy

	Adjuvant anti-PD-1	Nodal disease only	ITM only	ITM with nodal disease
n	1037[a]	693	174	168
Sex (%)				
Male	604 (58.2)	413 (59.6)	80 (46.0)	109 (64.9)
Female	433 (41.8)	280 (40.4)	94 (54.0)	59 (35.1)
Age at diagnosis (median [range])	62 [19-90]	61 [19–90]	64 [25-85]	66.5 [26-90]
Stage of disease (AJCC tumor classification eighth edition; %)				
IIIA	72 (6.9)	72 (10.4)	0 (0.0)	0 (0.0)
IIIB	353 (34.0)	248 (35.8)	102 (58.6)	3 (1.8)
IIIC	477 (46.0)	278 (40.1)	46 (26.4)	153 (91.1)
IIID	10 (1.0)	10 (1.4)	0 (0.0)	0 (0.0)
Unknown	125 (12.1)	85 (12.3)	26 (14.9)	12 (7.1)
N category[b]				
N1a	261 (25.2)	261 (37.7)	0 (0.0)	0 (0.0)
N1b	144 (13.9)	144 (20.8)	0 (0.0)	0 (0.0)
N1c	162 (15.6)	0 (0.0)	159 (91.4)	3 (1.8)
N2a	88 (8.5)	88 (12.7)	0 (0.0)	0 (0.0)
N2b	79 (7.6)	79 (11.4)	0 (0.0)	0 (0.0)
N2c	159 (15.3)	0 (0.0)	0 (0.0)	159 (94.6)
N3a	4 (0.4)	4 (0.6)	0 (0.0)	0 (0.0)
N3b	56 (5.4)	56 (8.1)	0 (0.0)	0 (0.0)
Unknown	84 (8.1)	61 (8.8)	15 (8.6)	6 (3.6)
ECOG PS (%)				
0	751 (72.4)	506 (73.0)	506 (73.0)	131 (75.3)
1	225 (21.7)	147 (21.2)	147 (21.2)	32 (18.4)
2	16 (1.5)	9 (1.3)	9 (1.3)	4 (2.3)
Unknown	45 (4.3)	31 (4.5)	31 (4.5)	7 (4.0)
Melanoma type (%)				
Superficial spreading	579 (55.8)	399 (57.6)	97 (55.7)	83 (49.4)
Nodular	262 (25.3)	176 (25.4)	35 (20.1)	51 (30.4)
Acral lentiginous	29 (2.8)	20 (2.9)	3 (1.7)	6 (3.6)
Other	34 (3.3)	15 (2.2)	12 (6.9)	6 (3.6)
Unknown	133 (12.8)	83 (12.0)	27 (15.5)	22 (13.1)
Melanoma location (%)				
Head/neck	122 (11.8)	78 (11.3)	24 (13.8)	19 (11.3)
Trunk	476 (45.9)	343 (49.5)	55 (31.6)	78 (46.4)
Extremity/Acral	439 (42.3)	272 (39.2)	95 (54.6)	71 (42.3)
Breslow thickness (in mm; median [range])	2.7 [0.1-21.8]	2.6 [0.2-18.5]	2.3 [0.1-14.0]	3.2 [0.6-21.8]
Ulceration (%)				
No	567 (54.7)	383 (55.3)	104 (59.8)	80 (47.6)
Yes	369 (35.6)	255 (36.8)	43 (24.7)	71 (42.3)
Unknown	101 (9.7)	55 (7.9)	27 (15.5)	17 (10.1)
Satellite/ITM at first diagnosis (%)				
No satellite/ITM	827 (79.7)	637 (91.9)	124 (71.3)	66 (39.3)
Satellite only	104 (10.0)	0 (0.0)	30 (17.2)	74 (44.0)
ITM only	12 (1.2)	0 (0.0)	3 (1.7)	9 (5.4)

TABLE 1 (Continued)

	Adjuvant anti-PD-1	Nodal disease only	ITM only	ITM with nodal disease
Both	2 (0.2)	0 (0.0)	1 (0.6)	1 (0.6)
Unknown	92 (8.9)	56 (8.1)	16 (9.2)	18 (10.7)
ITM type				
No ITM	693 (66.8)	0 (0.0)	0 (0.0)	0 (0.0)
ITM at primary presentation	147 (14.2)	0 (0.0)	42 (24.1)	105 (62.5)
ITM during the course of the disease	195 (18.8)	0 (0.0)	132 (75.9)	63 (37.5)
Unknown	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
BRAF-V600 mutation (%)				
V600E	313 (30.2)	229 (33.0)	41 (23.6)	42 (25.0)
Non-V600E	443 (42.7)	279 (40.3)	82 (47.1)	81 (48.2)
Unknown	281 (27.1)	185 (26.7)	51 (29.3)	45 (26.8)
ITM removed during surgical resection prior to systemic treatment (%)				
1	0 (0.0)	0 (0.0)	135 (77.6)	67 (39.9)
>1	0 (0.0)	0 (0.0)	25 (14.4)	13 (7.7)
Unknown	0 (0.0)	0 (0.0)	14 (8.0)	88 (52.4)

Abbreviations: AJCC, American Joint Committee on Cancer; ECOGPS, Eastern Cooperative Oncology Group Performance score; ITM, in-transit melanoma.
[a]Two patients with missing data on the presence of ITM were excluded from rows 3 through 6.
[b]Nodal category of the AJCC tumor classification 8th edition.

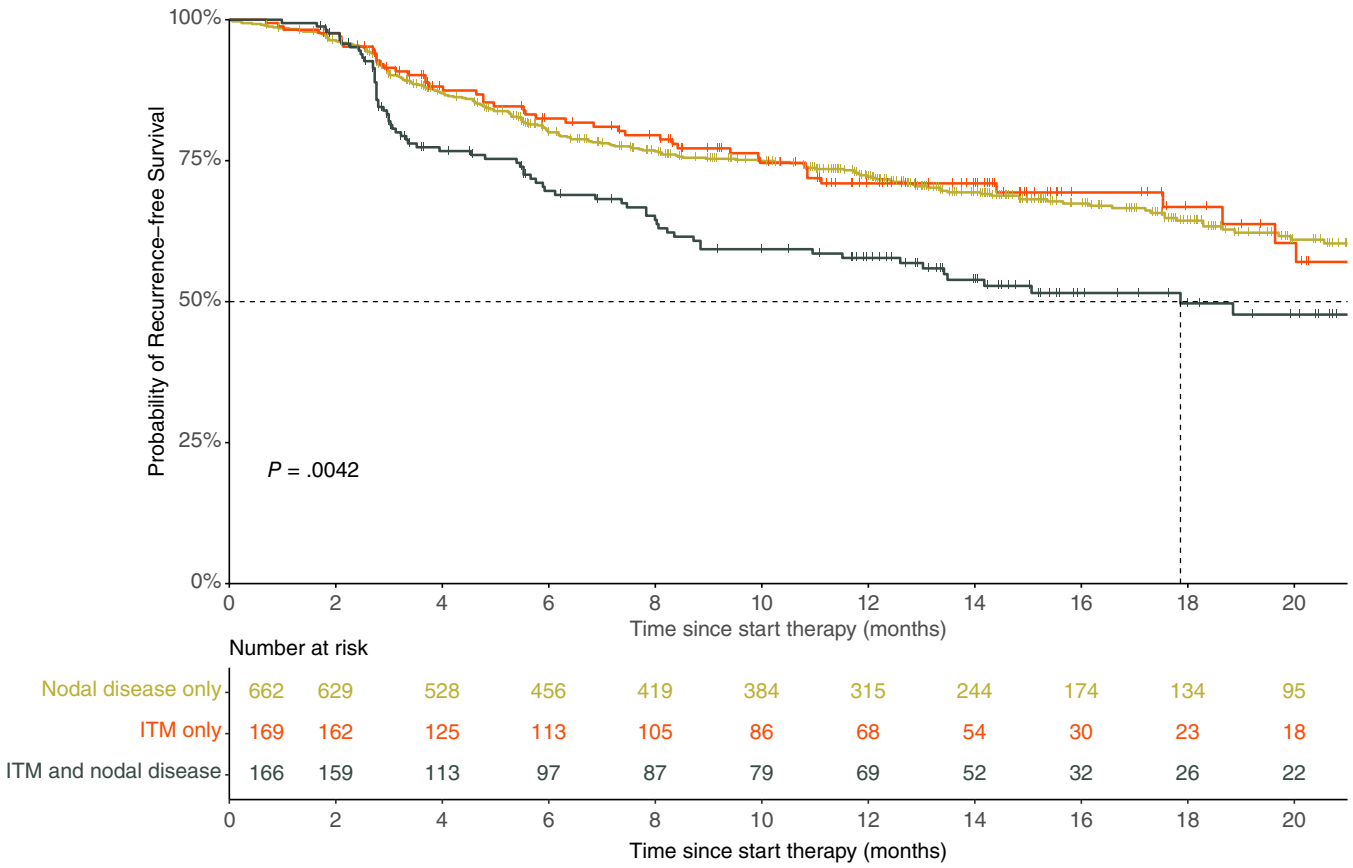


FIGURE 2 Kaplan-Meier for RFS in anti-PD-1 treated cutaneous melanoma patients per ITM subgroup. RFS at 18-months: Nodal disease only 64.4% (95% CI, 60.0-69.0), ITM only 66.8% (95% CI, 58.2-76.7), ITM and nodal disease 49.7% (95% CI, 41.4-59.6). Forty patients were excluded due to missing follow-up data.

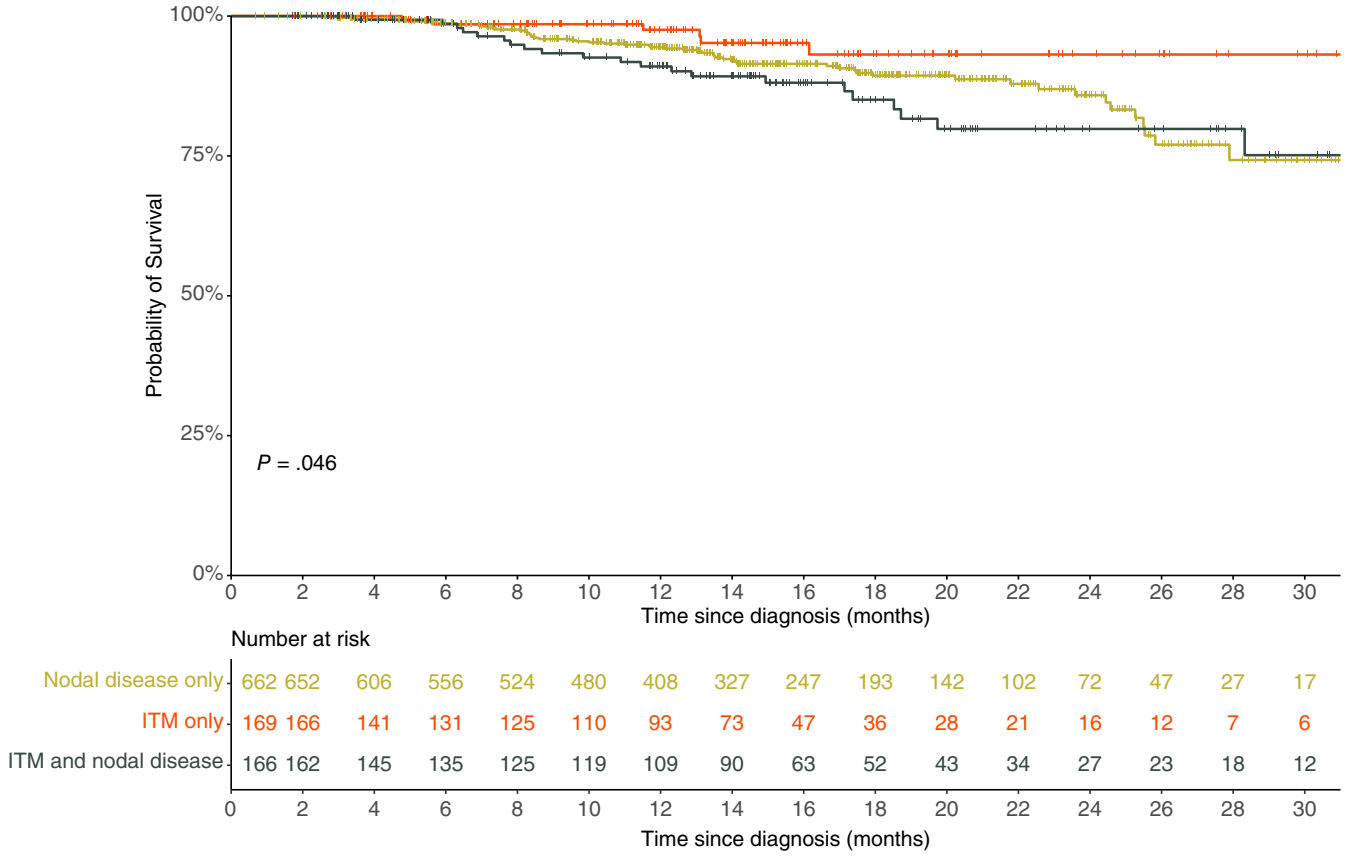


FIGURE 3 Kaplan-Meier for OS in anti-PD-1 treated cutaneous melanoma patients per ITM subgroup. OS at 18-months: Nodal disease only 89.4% (95% CI, 86.3-92.5), ITM only 93.1% (95% CI, 87.6-99.1), ITM and nodal disease 85.0% (95% CI, 78.4-92.2). Forty patients were excluded due to missing follow-up data.

TABLE 2 Location of the first recurrence in patients treated with anti-PD-1 with disease recurrence

	Nodal disease only	ITM only	ITM with nodal disease	*P* value
Location of recurrence; n	150	32	50	
Locoregional	58 (38.9)	23 (71.9)	22 (44.0)	.02
Distant	63 (42.3)	6 (18.8)	18 (36.0)	
Both	28 (18.8)	3 (9.4)	10 (20.0)	

Note: Nodal disease-only, ITM only, and ITM with nodal disease groups are based on ITM status at initial adjuvant treatment. *P* value based on Fisher's exact test. One patient was excluded due to missing ITM group. One nodal disease-only patient was excluded due to missing location of recurrence.
Abbreviation: ITM, in-transit melanoma.

3.2 | Recurrence-free survival in adjuvant-treated ITM subgroups

Recurrence-free survival rate (RFS) at 12-months was comparable between patients with nodal disease only and patients with ITM only (72.2% vs 70.1%, respectively, $P = .97$), but significantly lower for patients with ITM and nodal disease (57.8%; nodal disease only patients vs ITM with nodal disease $P < .01$, and ITM-only patients vs ITM with nodal disease $P = .01$; Figure 2). Predicted median RFS was 30.5 months (95% CI, 24.7-NR) in the nodal disease only patients, 29.8 months (95% CI, 19.6-NR) in the ITM-only subgroup, and 17.9 months (95% CI, 12.6-NR) in the ITM with nodal disease subgroup. The median follow-up time in the subgroup with nodal disease only, ITM only and ITM with nodal disease, were 14.5 (95% CI, 14.0-15.0), 13.1 (95% CI, 11.8-14.2) and 15.2 (95% CI, 14.5-16.2) months, respectively. There was no significant difference in RFS at 12-months between patients with a primary ITM and patients with a recurrent ITM at the start of adjuvant therapy ($P = .11$; Data S1).

3.3 | Overall survival in adjuvant-treated ITM subgroups

Overall survival (OS) at 12-months was not significantly different between nodal disease-only patients and patients with ITM only (94.4% vs 97.6%, $P = .06$). However, there was a significantly higher

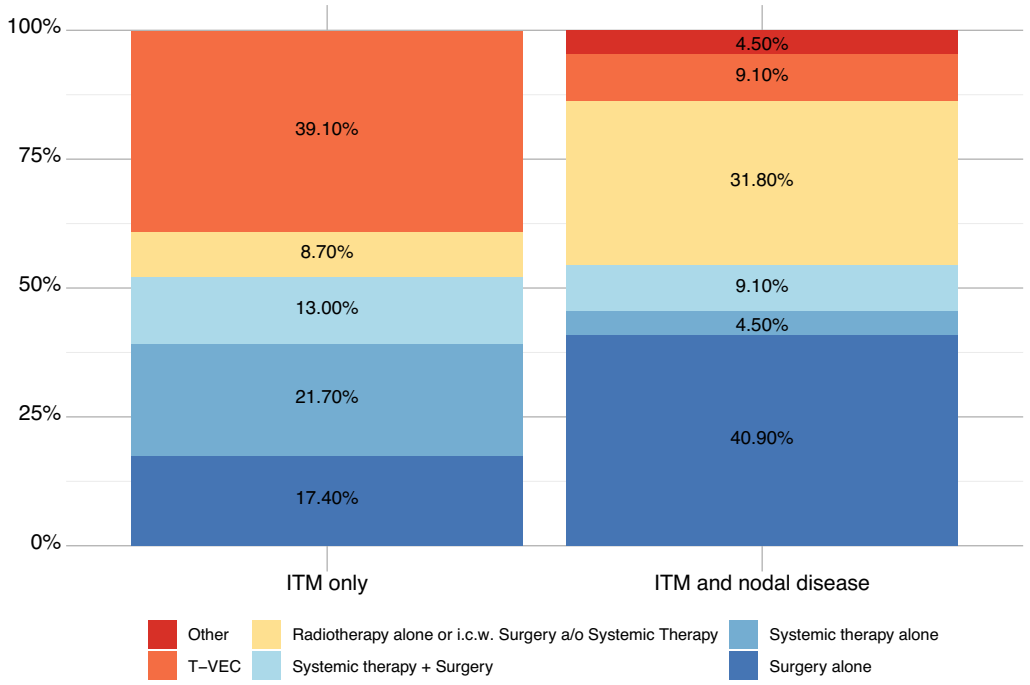


FIGURE 4 First subsequent (second-line) treatment of locoregional recurrences of ITM-only and ITM with nodal disease patients at initial presentation. (ITM only n = 23, ITM with nodal involvement n = 22).

OS in patients with ITM only compared with patients with ITM and nodal disease (97.6% vs 91.0%, $P < .01$). OS at 12-months was comparable for patients with nodal disease only and patients with ITM and nodal disease (94.4% vs 91.0%, $P = .23$; Figure 3). Predicted median OS rates could not yet be estimated for the ITM subgroups.

3.4 | First recurrence patterns in adjuvant-treated ITM subgroups and subsequent management

Of the 1037 stage III patients treated with anti-PD-1, 317 (30.7%) patients had a disease recurrence. Of the recurrent patients, 233 (73.5%) were subsequently registered and followed-up as unresectable stage III/IV patients.

Locoregional metastases occurred as the first recurrence site in 38.9% of patients with nodal disease only, 71.9% of ITM-only patients and 44.0% of ITM and nodal disease patients ($P = .02$). The location of the first recurrence per ITM subgroup is shown in Table 2. In comparison, distant recurrences occurred in 42.3% of patients with nodal disease only, 18.8% of adjuvant-treated patients with ITM only, and in 36.0% of patients with ITM and nodal disease ($P = .02$). Of the patients who had locoregional recurrence as the first recurrence, ITM-only patients more often had ITM only as the first recurrence site compared with nodal disease only and ITM with nodal disease patients (respectively, 95.7% vs 21.1% and 33.3%, $P < .01$; Data S2). The first subsequent treatment regimen (second-line treatment) for ITM-only and ITM with nodal disease patients with locoregional recurrence as the first recurrence site are illustrated in Figure 4.

4 | DISCUSSION

Our study of 342 ITM patients is, to our knowledge, the largest cohort of ITM patients treated with adjuvant systemic therapy. Our data show fewer distant recurrences in ITM-only patients compared with patients with nodal disease only and ITM with nodal disease patients. We also report better 12-month RFS rates in patients with ITM only compared with patients with ITM and nodal disease (70.1% vs 57.8%, $P = .01$). Furthermore, we show significantly better OS for ITM-only patients than ITM and nodal disease patients (97.6% in ITM-only patients vs 91.0% in patients with ITM and nodal disease $P < .01$). These real-world results offer valuable new insights into the outcome of adjuvant anti-PD-1 therapy in ITM patients in daily clinical practice, in addition to insights provided by the clinical trials.

Olofsson Bagge et al[30] described four out of seven randomized phase-III-trials that included unresectable stage III patients. However, upon examining the case report files of these trials, the authors were unable to properly identify patients with ITM due to a lack of information on the exact N disease stage. Updated results from the CheckMate-238 trial published in 2017 included 164 ITM patients in each treatment arm of the study (36% of the study population).[10,11] In this 4-year post hoc analysis from the Checkmate-238 trial, comparable RFS rates between ITM subgroups at 48-months were reported (48-months RFS of 54% in non-ITM patients treated with nivolumab compared with 49% and 53% in nivolumab-treated ITM-only and ITM with nodal disease patients, respectively).[11] Furthermore, Larkin et al[14] reported comparable OS rates between ITM subgroups (OS of 76% at 48-months for nivolumab-treated patients without ITM, 81% for ITM-only and 78% for ITM with nodal disease patients treated

with nivolumab). These data are in contrast with ours, and with results from the AJCC eighth edition analysis in which outcomes are better in ITM-only patients compared with patients with ITM and nodal disease. Moreover, in this post hoc analysis, similar metastasis patterns were observed in patients with ITM only and ITM with nodal disease and between ITM patients and patients with nodal disease only. However, in the CheckMate-238 analysis, only the organ-site at first (distant) recurrence was evaluated. No distinction between metastasis type (locoregional vs distant recurrence or the presence of ITM) was made.[11] In the COMBI-AD trial, 51 (12%) ITM patients were included in the dabrafenib/trametinib arm vs 36 (8%) ITM patients in the placebo arm of the study. Unfortunately, this study did not include the nodal status of the ITM patients.[9]

Read et al[2] previously described patterns of first recurrences in real-world ITM patients where 37.6% of first recurrences were reported as ITM-only, 10.7% as regional disease (with or without the concomitant presence of ITM) and 9.5% as distant metastases. We also show a high proportion of locoregional recurrences as first recurrence in ITM-only patients compared with nodal disease only patients and ITM with nodal disease patients. This particular finding of a different distribution of first recurrences between nodal disease-only patients, ITM-only patients and ITM with nodal disease patients, has not been reported previously. This difference in recurrence pattern likely explains the excellent OS in ITM-only patients. Pawlik et al[6] reported no distant metastasis at a median follow-up of 3.9 years in patients with ITM as the site of the first recurrence. Their data also support the hypothesis that a different pathophysiologic mechanism is responsible for the recurrence patterns observed in ITM-only patients.

Our previous study demonstrates that only 7% of adjuvant-treated patients registered in the DMTR would not have been eligible for trial participation.[8] We note no considerable difference between our ITM population and ITM patients included in the trials referred to in this paper. Forty-three percent of our ITM patients had ITM at primary presentation, while in 57%, the ITM occurred during the course of the disease. In the CheckMate-238 post hoc analysis, 55% of the adjuvant-treated ITM patients had an ITM at primary diagnosis compared with 45% with an ITM during the course of the disease.[11] Unfortunately, initial ITM tumor burdens are not well registered in the DMTR. Similarly, the ITM tumor burden was not reported in the Checkmate-238 trial. The actual difference and effect of ITM tumor burden thus remain unclear. However, as shown in this study, a substantial group of patients waived systemic therapy in the real world, of which 20% had ITM-only disease (data not reported). It is thus possible that ITM-only patients treated with adjuvant systemic therapy in the real world have better patient and tumor characteristics compared with trial patients. In return, patients with worse clinical characteristics renounce or might not be referred for adjuvant systemic treatment.

As illustrated by the subsequent treatment patterns for local recurrences described in this study, it is evident that clinical practices vary greatly. The NADINA trial (NCT04949113) comparing neoadjuvant ipilimumab and nivolumab to standard adjuvant nivolumab is being conducted in stage III melanoma patients, including patients with ITM. And in addition, results from the ongoing NIVEC trial (NCT04330430), in which resectable stage IIIB/C/D/IV M1a melanoma patients with injectable lesions are treated with neoadjuvant T-VEC and nivolumab combination therapy, might also propose a new treatment strategy for ITM-only patients. However, our data suggest a substantial proportion of localized recurrences with a good OS in ITM-only patients. This raises the question if systemic adjuvant immunotherapy is indicated at all in ITM-only patients.

4.1 | Strengths, limitations and implications for further research

The DMTR is a nationwide quality registry facilitated by the Dutch Institute for Clinical Auditing (DICA).[13] Data in the DMTR is well registered and has a high level of completeness.[8] Our comprehensive nationwide database includes more anti-PD-1 treated ITM patients than registered in any of the registrations trials for adjuvant systemic treatment and thus provides insight into this relatively underrepresented patient population. A limitation of this study is the lack of detailed information on ITM tumor burden and resections prior to adjuvant treatment. In addition, no distinction could be made between single and multiple ITM lesions, which hypothetically could influence the success of adjuvant therapy. Furthermore, we report a relatively short follow-up period. Recurrence rates may increase as the follow-up time lengthens. Also, patients who were not referred to a melanoma center to discuss adjuvant treatment were not included in this study. This leads to an underrepresentation of surgical resection-only patients in the Netherlands. To properly assess the effectiveness of adjuvant therapy in ITM patients, comparison with a (placebo) control group is necessary. Future investigation into optimum treatment methods for recurrences in ITM patients and the effects of subsequent treatment on recurrences and survival in these patients is necessary.

5 | CONCLUSION

For patients with stage III melanoma treated with adjuvant immunotherapy, the recurrence-free survival is similar for patients with nodal only disease and patients with ITM only, but worse for patients with both nodal disease and ITM. Adjuvant-treated patients with ITM only less often experience distant recurrences and have a superior OS compared with ITM and nodal disease patients.

AUTHOR CONTRIBUTIONS

de Meza: conceptualization, methodology, formal analysis, writing—original draft, writing—review & editing. Blokx: conceptualization, writing—review & editing, supervision. Bonenkamp: writing—review & editing. Blank: writing—review & editing. Aarts: writing—review & editing. van den Berkmortel: writing—review & editing. Boers-Sonderen: writing—review & editing. de Groot: writing—review & editing. Haanen: writing—review & editing.

Hospers: writing—review & editing. Kapiteijn: writing—review & editing. van Not: writing—review & editing. Piersma: writing—review & editing. van Rijn: writing—review & editing. Stevense-den Boer: writing—review & editing. van der Veldt: writing—review & editing. Vreugdenhil: writing—review & editing. van den Eertwegh: writing—review & editing. Suijkerbuijk: conceptualization, writing—review & editing, supervision. Wouters: conceptualization, writing—review & editing, supervision. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST

Alfons J. M. van den Eertwegh has advisory relationships with Amgen, Bristol Myers Squibb, Roche, Novartis, MSD, Pierre Fabre, Sanofi, Pfizer, Ipsen, Merck and has received research study grants not related to this paper from Sanofi, Roche, Bristol Myers Squibb, Idera and TEVA and has received travel expenses from MSD Oncology, Roche, Pfizer and Sanofi and has received speaker honoraria from BMS and Novartis. Marye J. Boers-Sonderen has consultancy/advisory relationships with Pierre Fabre, MSD and Novartis. Jan Willem B. de Groot has consultancy/advisory relationships with Bristol Myers Squibb, Pierre Fabre, Servier, MSD, Novartis. Geke A. P. Hospers has consultancy/advisory relationships with Amgen, Bristol Myers Squibb, Roche, MSD, Pfizer, Novartis, Pierre Fabre, Sanofi and has received research grants not related to this paper from Bristol Myers Squibb, Seerave. Ellen W. Kapiteijn has consultancy/advisory relationships with BristolMyers Squibb, Novartis, Merck, Pierre Fabre and received research grants not related to this paper from Bristol Myers Squibb. Karijn P. M. Suijkerbuijk has advisory relationships with Bristol Myers Squibb, Novartis, MSD, Pierre Fabre, Abbvie and received honoraria from Novartis, MSD and Roche. Astrid A. M. van der Veldt has consultancy relationships with Bristol Myers Squibb, MSD, Roche, Novartis, Pierre Fabre, Pfizer, Sanofi, Ipsen, Eisai, Merck, paid to the institute. John B. Haanen has advisory relationships with Aimm, Achilles Therapeutics, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb BioNTech, GSK, Immunocore, Ipsen, MSD, Merck Serono, Molecular Partners, Novartis, Neogene Therapeutics, Pfizer, Roche/Genentech, Sanofi, Seattle Genetics, Third Rock Ventures, Vaximm and has received research grants not related to this paper from Amgen, Bristol Myers Squibb, MSD, BioNTech, Neogene Therapeutics and Novartis. All grants were paid to the institutions. The funders had no role in the writing of this article or decision to submit it for publication. Maureen J. B. Aarts has advisory board/consultancy honoraria from Amgen, Bristol Myers Squibb, Novartis, MSD-Merck, Merck-Pfizer, Pierre Fabre, Sanofi, Astellas, Bayer. Research grants Merck-Pfizer. Not related to current work and paid to institute. CUB reports Advisory role: BMS, MSD, Roche, Novartis, GSK, AZ, Pfizer, Lilly, GenMab, Pierre Fabre, Third Rock Ventures, Research funding: BMS, Novartis, NanoString, 4SC, Stockownership: co-founder Immagene BV, Pending patent: WO 2021/177822 A1. Djura Piersma had consultancy/advisory relationships with Novartis and with Bristol Myers Squibb, Pierre Fabre paid to institution, none related to this paper. All remaining authors have declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available on request from the corresponding author.

ETHICS STATEMENT

The medical ethical committee has approved research using DMTR data, and this research was not deemed subject to the Medical Research Involving Human Subjects Act in compliance with Dutch regulations.

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REFERENCES

1. Riker AI. *Melanoma: A Modern Multidisciplinary Approach*, Switzerland: Springer; 2018:1-652.
2. Read RL, Haydu L, Saw RPM, et al. In-transit melanoma metastases: incidence, prognosis, and the role of lymphadenectomy. *Ann Surg Oncol*. 2015;22:475-481.
3. Read RL, Thompson JF. Managing in-transit melanoma metastases in the new era of effective systemic therapies for melanoma. *Expert Rev Clin Pharmacol*. 2019;12:1107-1119. doi:10.1080/17512433.2019.1689121
4. van Poll D, Thompson JF, Colman MH, et al. A sentinel node biopsy does not increase the incidence of in-transit metastasis in patients with primary cutaneous melanoma. *Ann Surg Oncol*. 2005;12:597-608.
5. Kretschmer L, Beckmann I, Thoms KM, Mitteldorf C, Bertsch HP, Neumann C. Factors predicting the risk of in-transit recurrence after sentinel lymphonodectomy in patients with cutaneous malignant melanoma. *Ann Surg Oncol*. 2006;13:1105-1112.
6. Pawlik TM, Ross MI, Johnson MM, et al. Predictors and natural history of in-transit melanoma after sentinel lymphadenectomy. *Ann Surg Oncol*. 2005;12:587-596.
7. Borgstein PJ, Meijer S, van Diest PJ. Are locoregional cutaneous metastases in melanoma predictable. *Ann Surg Oncol*. 1999;6:315-321.
8. de Meza MM, Ismail RK, Rauwerdink D, et al. Adjuvant treatment for melanoma in clinical practice: trial versus reality. *Eur J Cancer*. 2021;158:234-245. doi:10.1016/j.ejca.2021.08.044
9. Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in stage III BRAF-mutated melanoma. *N Engl J Med*. 2017;377:1813-1823.
10. Ascierto PA, del Vecchio M, Mandalá M, et al. Adjuvant nivolumab versus ipilimumab in resected stage IIIB-C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2020;21:1465-1477.
11. Larkin J, Gogas H, del Vecchio M, et al. Analysis of patients (pts) with in-transit metastases treated with nivolumab (NIVO) or ipilimumab (IPI) in CheckMate 238. *J Clin Oncol*. 2021;39:9569.
12. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med*. 2018;378:1789-1801.
13. Jochems A, Schouwenburg MG, Leeneman B, et al. Dutch melanoma treatment registry: quality assurance in the care of patients with metastatic melanoma in The Netherlands. *Eur J Cancer*. 2017;72:156-165. doi:10.1016/j.ejca.2016.11.021
14. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67:472-492.
15. Nederland Z. Farmaco-economisch herbeoordelingsrapport voor dabrafenib/trametinib (Tafinlar/Mekinist) bij de adjuvante behandeling van volwassen patiënten met melanoom in stadium III met een BRAF V600-mutatie, na complete resectie. 2020.
16. Garrett Grolemund HW. Dates and times made easy with {lubridate} [Internet]. 2011 https://www.jstatsoft.org/v40/i03/
17. Wickham H, François R, Henry L, Müller K, Vaughan D. dplyr: a grammar of data manipulation [Internet]. 2021 https://cran.r-project.org/package=dplyr
18. Wickham H, Averick M, Bryan J, et al. Welcome to the {tidyverse}. 2019.
19. Bache SM, Wickham SMB. magrittr: A forward-pipe operator for R [Internet]. 2014 https://cran.r-project.org/package=magrittr
20. Wickham H. tidyr: Tidy Messy Data. R Package Version 1.1.2. [Internet]. 2020 https://cran.r-project.org/package=tidyr
21. Yoshida K, Bartel A. tableone: Create "Table 1" to Describe Baseline Characteristics with or without Propensity Score Weights [Internet]. 2020 https://cran.r-project.org/package=tableone
22. Wickham H. ggplot2: Elegant Graphics for Data Analysis [Internet]. 2016 https://ggplot2.tidyverse.org
23. Arnold JB. ggthemes: Extra themes, scales and Geoms for "ggplot2" [Internet]. 2021 https://cran.r-project.org/package=ggthemes
24. Wickham H. stringr: Simple, consistent wrappers for common string operations [Internet]. 2019 https://cran.r-project.org/package=stringr
25. Wickham H, Bryan J. readxl: Read excel files [Internet]. 2019 https://cran.r-project.org/package=readxl
26. Neuwirth E. RColorBrewer: ColorBrewer Palettes [Internet]. 2014 https://cran.r-project.org/package=RColorBrewer
27. Millard SP. EnvStats: An R package for environmental statistics [Internet]. 2013 https://www.springer.com
28. Kassambara A, Kosinski M, Biecek P. survminer: drawing survival curves using "ggplot2" [Internet]. 2020 https://cran.r-project.org/package=survminer
29. Therneau T. A package for survival analysis in R. 2020.
30. Olofsson Bagge R, Ny L, Ascierto PA, et al. The efficacy of immunotherapy for in-transit metastases of melanoma: An analysis of randomized controlled trials. *Melanoma Res*. 2021;31:181-185.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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