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Outcome of adjuvant immunotherapy in a real-world nation-wide cohort of patients with melanoma

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ABSTRACT

Background: Clinical trials have demonstrated promising outcomes for adjuvant immunotherapy in patients with resected melanoma. Real-life data provide valuable insights to support patient guidance and treatment decisions.
Methods: Observational population-based study examining a national cohort of patients with resected stage III-IV melanoma referred for adjuvant therapy. Data were extracted from the Danish Metastatic Melanoma Database (DAMMED).
Results: Between November 2018 and January 2022, 785 patients received adjuvant anti-PD-1. The majority had stage III resected melanoma (87%), normal LDH levels (80%), and performance score 0 (87%). Patients were followed for a median of 25.6 months (95%CI 24–28). The median recurrence-free survival (RFS) and melanoma-specific survival (MSS) were not reached. The RFS was 78% (95%CI 75–81), 66% (63–70), and 59% (55–63); MSS was 97% (95–98), 93% (91–95), and 87% (84–90) at 1-, 2-, and 3-year; respectively. Less than half (42%) of the patients finalized planned therapy, 32% discontinued due to toxicity, and 19% due to melanoma recurrence. Patients discontinuing adjuvant treatment prematurely, without recurrence, had similar outcomes as patients finalizing therapy. In a multivariable analysis, ipilimumab plus nivolumab did not improve outcomes compared to ipilimumab monotherapy as a first-line metastatic treatment after adjuvant anti-PD-1.
Conclusion: Survival outcomes in real-world patients with melanoma treated with adjuvant anti-PD-1 align with results from the randomized controlled trials. Patients discontinuing therapy prematurely, for other reasons than recurrence, had similar outcomes as patients finalizing planned treatment. First-line metastatic treatment with ipilimumab and nivolumab post-adjuvant anti-PD-1 did not show improved outcomes compared to ipilimumab/anti-PD-1 monotherapy.

1. Background

Treatment with immune checkpoint inhibitors (ICIs) has led to durable responses with exceptional prolongation of progression-free survival (PFS) and overall survival (OS) in several advanced cancers, particularly in melanoma [1]. Due to these impressive outcomes, the use of ICIs has extended to the adjuvant setting [2–4].

Anti-programmed death protein-1 (anti-PD-1) antibodies are approved as first choice of adjuvant therapy for resected melanoma in Denmark since 2018. The B-Raf proto-oncogene (BRAF) and mitogen-activated protein kinase (MEK) inhibitors, dabrafenib plus trametinib, also approved for adjuvant therapy [5], were allowed only to patients unsuitable for immunotherapy.

While adjuvant treatment with ICIs has improved recurrence-free survival (RFS), the data on overall survival (OS) remain immature, and real-life data are scarce. The long-term consequences of immune-

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related adverse events (irAEs) and their potential impact on quality of life (QoL) are still unknown [6–10]. Previous studies have reported real-world data on the efficacy of adjuvant anti-PD-1 agents [11–15]. In this study, we present treatment outcomes from a large and complete national cohort of patients with resected melanoma, including outcomes for patients discontinuing therapy prematurely. Limited knowledge exists on how adjuvant ICIs influence the choice and efficacy of further systemic therapies in case of recurrence and metastatic disease. Therefore, we provide data on outcomes of systemic therapy after melanoma recurrence in this real-world patient cohort. Finally, we include information on the reasons why patients referred for adjuvant anti-PD-1 decline therapy.

2. Methods

2.1. Patient selection and data acquisition

This study is a retrospective population-based study. All Danish patients diagnosed with melanoma and candidates for receiving adjuvant anti-PD-1 therapy since its approval in Denmark on November 14, 2018, have been registered in the national Danish Metastatic Melanoma Database (DAMMED) [16]. Oncological melanoma treatment is centralized at four sites, covering a complete national cohort. This study includes all patients with stage III-IV resected cutaneous melanoma or melanoma of unknown primary starting adjuvant anti-PD-1 from November 2018 to January 2022. All patients were followed until January 1, 2023, or until the last observation of being alive or deceased, with a minimum 12-month follow-up. Data on patient characteristics (detailed in Supplementary Materials), adjuvant treatment (and reason for discontinuation), outcomes, and reasons for not receiving adjuvant therapy were collected.

Referred patients not receiving systemic adjuvant treatment were systematically recorded in two of four centers, representing 70% of the national population. Reasons for not receiving therapy were registered in the patient files as either the patient's or physician's choice based on various subcategories. For further details see Supplementary Methods. Patients treated with first-line adjuvant dabrafenib and trametinib and patients with resected mucosal melanoma were excluded due to insufficient data for meaningful conclusions.

2.2. Procedures

All patients were staged according to AJCC classification 8th edition [17]. Candidates for adjuvant therapy included patients with resected melanoma stage IIIA-IV; however, patients with stage IIIA, non-ulcerated melanoma, and/or a sentinel node (SN) metastasis <1 mm were generally advised against therapy. Patients received nivolumab 6 mg/kg intravenously (maximum: 480 mg) every four weeks up to one year of treatment (13 cycles). Clinical examinations were done every three months in the first two years of therapy and every six months in years 3–5. Patients with a positive SN were offered additional ultrasound of the resected region. Positron-emission tomography-computed tomography (PET-CT) scans were performed every three months during therapy and 12-, 24-, and 36-months post-surgery. Patients with prior or suspected intracranial metastases underwent magnetic resonance imaging (MRI) of the brain.

2.3. Outcome measures and statistical analysis

RFS and melanoma-specific survival (MSS) were defined as the date of first treatment until melanoma recurrence or melanoma-related death. The Kaplan-Meier method was used for survival analyses with recurrence or melanoma-related death as the event. Pembrolizumab and nivolumab were considered to have the same outcome. Patients not reaching the endpoint were censored at their last date of follow-up, whereas patients switching to dabrafenib plus trametinib were censored at the date of initiation of this treatment. Group comparisons were done by the Log-rank test. For three or more categories, an overall Log-rank test was conducted, and if significant, pairwise Log-rank tests were adjusted for multiple comparisons using the Holm-Bonferroni method. Median follow-up was calculated using a reversed Kaplan-Meier.

Two-sided 95% confidence intervals (95%CI) were calculated for survival analyses, with medians reported as range or interquartile range (IQR). Cox proportional hazard models were used for hazard ratios (HR) and multivariable analysis of RFS and MSS. Statistical analyses were executed using R (version 4.2.0).

3. Results

3.1. Anti-PD-1 in the adjuvant setting; Patient characteristics and outcome

Out of 1080 patients with resected grade III-IV melanoma referred for adjuvant therapy, 785 patients received adjuvant nivolumab for resected cutaneous or unknown primary melanoma (Supplementary Fig. S1). Eleven patients initially treated with nivolumab switched to adjuvant pembrolizumab due to severe nivolumab-related infusion reactions (n = 10), or toxicity (n = 1). Additionally, seven patients switched to adjuvant dabrafenib and trametinib, either due to irAEs (n = 4) or as second-line adjuvant therapy following surgical resection of recurrence (n = 3).

Patients' median age was 62 years (range 16–88). The majority had cutaneous melanoma (92%), a performance status (PS) of 0 (87%), were male (56%), had stage IIIB-IIIC melanoma (74%), and had no severe comorbidities (65%). Baseline characteristics are provided in Table 1. Patients were followed for a median of 25.6 months (95%CI 23.8–27.7). Median RFS and MSS were not reached. RFS at 1, 2, and 3 years were 78.2% (95%CI 75.1–81.0), 66.3% (62.6–69.8), and 59.1% (54.6–63.3), respectively. The MSS at 1, 2, and 3 years were 96.5% (95.0–97.6), 92.8% (90.6–94.5), and 87.4% (84.2–90.0), respectively (Fig. 1A+B). Melanoma recurrence occurred in 267 out of 785 patients (34.0%) during or following adjuvant anti-PD-1; 168 patients (62.9%) had recurrence ≤12 months of the first treatment, and 91 patients (34.1%) >6 months after the last treatment. During the study period, 109 patients (13.9%) died; 88 patients (11.2%) due to melanoma, and five patients (0.6%) due to irAEs during adjuvant anti-PD-1.

RFS and MSS decreased with advancing disease stage (stage IIIA to IV) with patients resected for stage M1d disease having the poorest MSS (Fig. 1C-H). Patients initiating adjuvant anti-PD-1 immediately after the primary melanoma diagnosis had a significantly longer RFS and MSS compared to those receiving adjuvant anti-PD-1 after resection of a recurrence ($p < 0.001$). Additionally, males in contrast to females, had a shorter RFS, although no differences were observed in MSS. Severe comorbidities, age ≥70 years, and high PS significantly influenced both RFS and MSS. BRAF mutational status did not impact RFS or MSS (Supplementary Fig. S2).

Multivariable analysis revealed significant differences in RFS based on sex (female vs. men, $p = 0.015$) and ACJJ stages (IIIA vs. IIIC [$p < 0.001$]; IIIA vs. IV [$p = 0.014$]). A comparable trend was observed in MSS, although statistical significance was only reached in stages IIIA vs. IIIC (Fig. 2).

3.2. Adjuvant treatment decision

Of the 812 referred patients, 265 (32.6%) patients did not receive medical adjuvant treatment, despite fulfilling the criteria, following consultation with a melanoma oncologist. These non-treated patients tended to be older, had a higher PS, more severe comorbidities, and a lower disease stage compared to patients receiving therapy (Table 1). No differences were observed in RFS and MSS between patients receiving adjuvant anti-PD-1 or not, although a trend ($p = 0.092$) was observed in

Table 1
Patient characteristics.

Adjuvant anti-PD-1	Treatment	No treatment	P-value
Patients, n (%)	785 (74.8)	265 (25.2)	
Age, years – median (range)	62 (16–88)	73 (28–92)	< 0.001
Sex, n (%)			
Female	348 (44.3)	114 (43.0)	0.76
Male	437 (55.7)	151 (57.0)	
Melanoma diagnosis, n (%)			
Cutaneous melanoma	723 (92.1)	252 (95.1)	0.13
Melanoma - unknown primary	62 (7.9)	13 (4.9)	
Performance Status, n (%)			
0	682 (86.9)	174 (65.7)	
1	95 (12.1)	58 (21.9)	< 0.001
≥2	8 (1)	33 (12.5)	
Comorbidities			
No	506 (64.5)	104 (39.2)	< 0.001
Yes	279 (35.5)	161 (60.8)	
BRAF-status, n (%)			
Mutation	234 (29.8)	61 (23.0)	
Wildtype	220 (28)	79 (29.8)	0.1
Not tested	331 (42.2)	125 (47.2)	
Stage, n (%)			
IIIA	92 (11.7)	92 (34.7)	
IIIB	303 (38.6)	73 (27.5)	
IIIC	278 (35.4)	73 (27.5)	< 0.001
IIID	7 (0.9)	2 (0.8)	
IV	105 (13.4)	25 (9.4)	
M-stage, n (%)			
M1a	66 (62.9)	15 (60.0)	
M1b	16 (15.2)	4 (16.0)	0.66
M1c	9 (8.6)	4 (16.0)	
M1d	14 (13.3)	2 (8.0)	
PD-L1 status, n (%)			
PD-L1 < 1%	182 (23.2)	50 (18.9)	
PD-L1 ≥ 1%	113 (14.4)	26 (9.8)	0.03
Not tested	490 (62.4)	189 (71.3)	
Lactate dehydrogenase, n (%)			
Normal	628 (80)	7 (2.6)	
Elevated >ULN	151 (19.2)	4 (1.5)	< 0.001
Unknown	6 (0.8)	254 (95.8)	

Baseline characteristics for patients treated with adjuvant anti-PD-1 and for patients who were referred for adjuvant therapy but did not receive therapy. BRAF, B-Raf proto-oncogene; ULN, upper level of normal.

the adjusted HR for age, PS, and stage (Supplementary Fig. S3). Subanalysis according to baseline characteristics showed significant differences in RFS and MSS according to substages, age, and PS, and significant differences in RFS according to comorbidities (Supplementary Fig. S4).

The primary reasons for not receiving adjuvant anti-PD-1 were fear of toxicity (37%); high age, comorbidities, or poor PS (25%); low risk of recurrence (17%), and other reasons (21%) (Fig. 3A). Of the 265 non-treated patients, 106 (40%) patients experienced recurrence; six of these patients initiated adjuvant treatment post-surgery, and 57 received therapy for metastatic melanoma.

3.3. Outcomes for patients discontinuing adjuvant therapy prematurely due to toxicity

Patients received a median of eight cycles (range 1–13) of anti-PD-1, and less than half completed the planned 1-year treatment (331/785, 42%). Among these, 249 patients discontinued due to toxicity (32%), and 150 patients discontinued therapy due to melanoma recurrence (19%). A smaller subgroup of patients discontinued for various other reasons (n = 55, 7%), primarily comorbidities (Fig. 3B). Ir-colitis (12%), ir-hepatitis (12%), skin toxicity (11%), and arthritis (10%) were the four most common single irAEs leading to discontinuation. Furthermore, 21% of the patients discontinuing therapy due to toxicity experienced multiple toxicities (≥3 ir-toxicities, including one irAE of grade 2–5; 21%).

A 12-month landmark analysis was performed to compare outcomes for patients discontinuing therapy prematurely (patients discontinuing due to recurrence were excluded) to patients finalizing the planned 1-year therapy. The results indicated similar survival outcomes for both groups (Fig. 4). A 12-month landmark was chosen to mitigate immortal time bias for patients finalizing planned treatment.

When analyzing outcomes for patients discontinuing adjuvant anti-PD-1 due to toxicity we observed, as expected, fewer patients treated with combination immunotherapy in first-line metastatic setting. However, these patients tended to exhibit longer PFS (HR 0.65, 95%CI 0.39–1.06, p = 0.081) and MSS (HR 0.52, 95%CI 0.25–1.08, p = 0.075) on first-line metastatic therapy compared to patients discontinuing adjuvant anti-PD-1 due to other reasons or patients who finalized planned adjuvant treatment (Table 2; Supplementary Fig. S5A+B). This trend was particularly notable for patients treated with first-line BRAF+MEK inhibitors (PFS: HR 0.32, 95%CI 0.12–0.83, p = 0.013; OS: HR 0.21, 95%CI 0.05–0.89, p = 0.019) (Supplementary Fig. S5C+D).

3.4. Outcome after systemic recurrence therapy

Of the 267 patients with a recurrence, 185 (69%) underwent first-line systemic metastatic therapy, with 131 patients (71%) initiating treatment ≤6 months, and 53 patients (29%) initiating treatment >6 months after the last dose of anti-PD-1.

Patients receiving first-line BRAF+MEK inhibitors had the highest overall response rate (ORR) at 81.4%. Notably, ipilimumab plus nivolumab resulted in a lower ORR, PFS, and MSS than ipilimumab or anti-PD-1 monotherapy. The number of patients discontinuing due to toxicity was comparable between treatment groups, although slightly higher with combination therapy (34.5% vs 32.3% and 28.6% for ipilimumab and anti-PD-1 monotherapy, respectively). Importantly, baseline characteristics, such as the presence of brain metastases, significantly differed between treatment groups (Table 2). In a multivariable analysis, the time of melanoma recurrence (during or within the first six months after adjuvant therapy or more than six months after) did not affect PFS or MSS following metastatic treatment (Fig. 5). As anticipated, patients with elevated lactate dehydrogenase (LDH) and brain metastasis at baseline had a poorer survival outcome. In multivariable analysis, patients treated with first-line BRAF+MEK inhibitors had a favorable PFS (HR 0.42, 95%CI 0.36–0.68, [p < 0.001]) compared to patients receiving ipilimumab plus nivolumab, however; no advantages in MSS. Patients receiving anti-PD-1 or ipilimumab monotherapy as first-line metastatic therapy achieved at least comparable survival outcomes to those receiving ipilimumab plus nivolumab, as revealed in the multivariable analysis (Fig. 5).

4. Discussion

In this complete national cohort of 785 patients with resected stage III-VI melanoma receiving adjuvant anti-PD-1, we report extended follow-up data with 3-year RFS and MSS. Notably, our findings reveal comparable survival outcomes between patients discontinuing therapy prematurely due to toxicity and those finalizing the intended 1-year adjuvant anti-PD-1 therapy. Interestingly, exploration of the survival outcomes to subsequent systemic therapies in case of progression to metastatic disease shows no clear benefits associated with combination immunotherapy.

We found a 1-, 2-, and 3-year RFS and MSS of 78%, 66%, and 59%, and 97%, 93%, and 87%, respectively. In the CheckMate-283, patients with stage III-IV resected melanoma treated with nivolumab, had a 1, 2, 3, 4, and 5-year RFS of 70%, 62%, 58%, 52%, and 50% respectively [2,8,18], which were similar to the CheckMate-915 (stage IIIB-IV) nivolumab arm, 2-year RFS of 63% [4], and the EORTC-1325 pembrolizumab arm (stage IIIA-C) with 1-, 2-, 3, 3.5, and 5-year RFS of 75%, 68%, 64%, 60%, and 55% [3,19,20]. Comparable outcomes data were found in

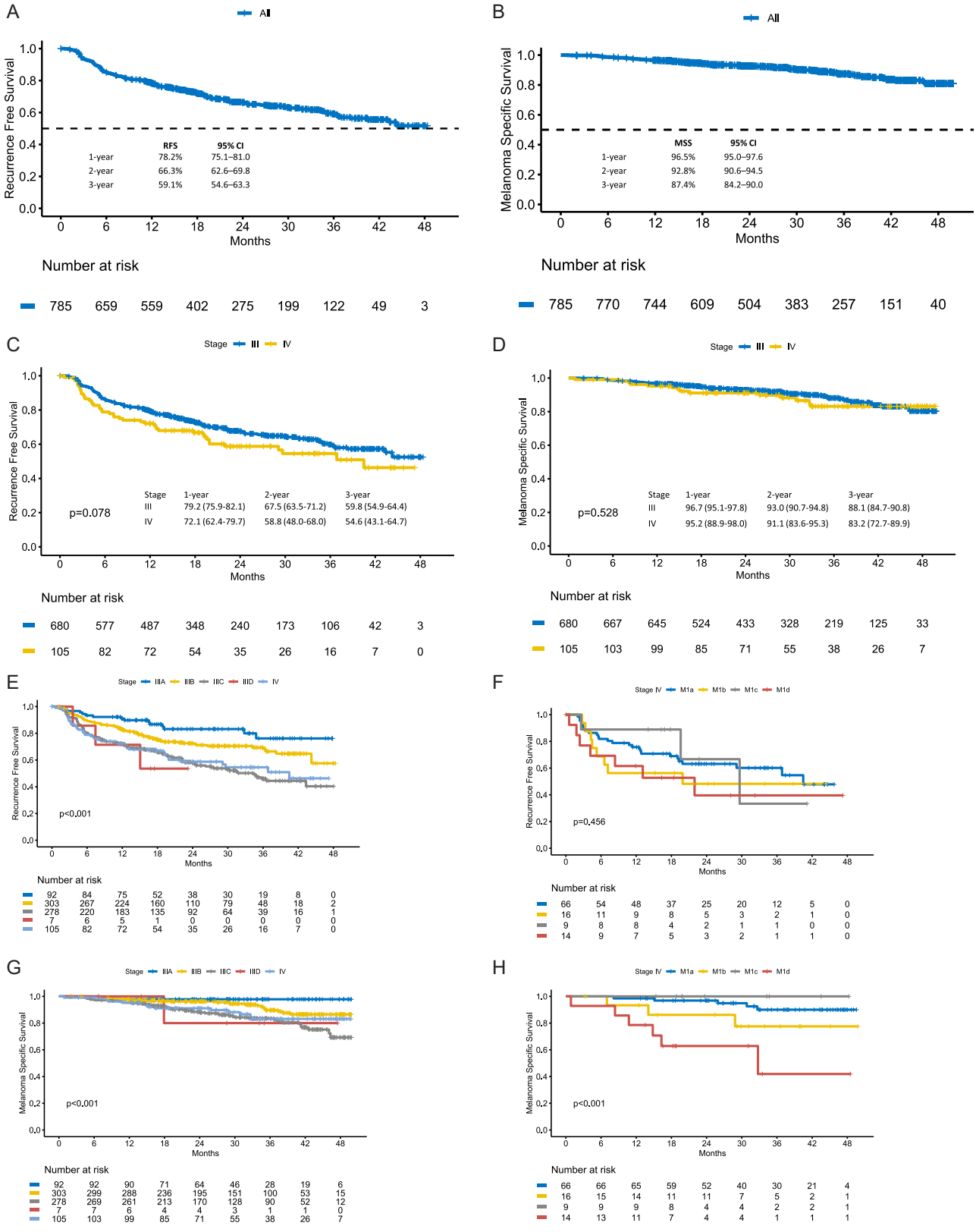


Fig. 1. Recurrence-free survival (RFS) and melanoma-specific survival (MSS) after adjuvant anti-PD-1 in the complete Danish cohort (A+B) and according to stages III-IV (C-H). Fig. 1A) RFS and 1B) MSS after adjuvant anti-PD-1 in the complete Danish cohort. Fig. 1C) RFS and 1D) MSS according to stage III vs. stage IV, Fig. 1E) RFS and 1F) MSS according to stage IV and subgroups of stages III, pairwise comparisons showed p-values <0.05 in RFS between stage IIIA vs. IIIC and IV, IIIB vs. IIIC and IV; and in MSS between stage IIIA vs. IIIC and IIIB vs. IIIC. Fig. 1G) RFS and 1H) MSS according to subgroups of stage IV, pairwise comparisons showed p-value <0.05 in MSS between stage M1a vs. M1d. Further details of RFS and MSS for the different substages in Fig. 1E-H are available in Supplementary Table S1.

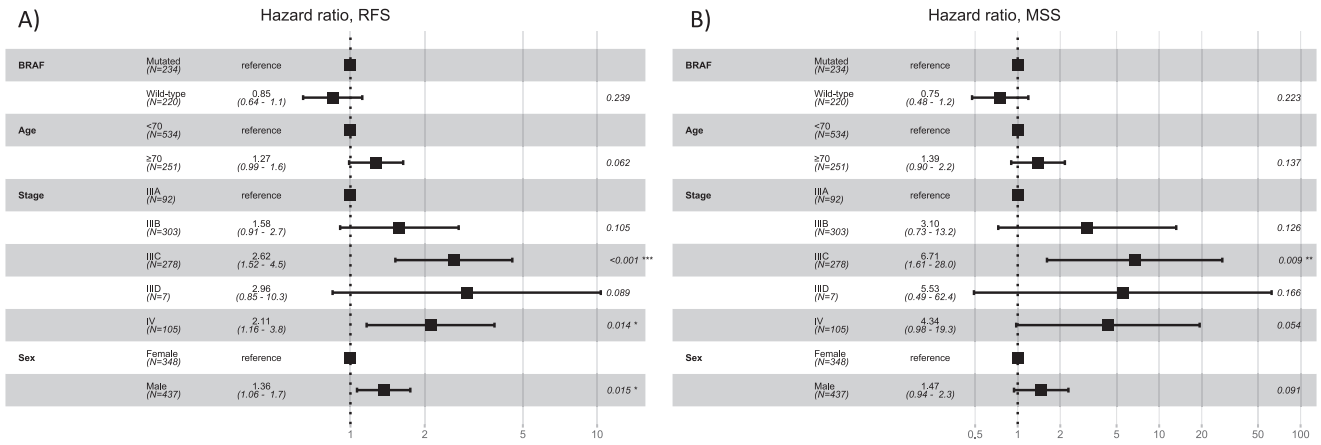


Fig. 2. Multivariable analysis of A) recurrence-free survival (RFS) and B) melanoma-specific survival (MSS) for all patients following adjuvant anti-PD-1, n = 785. Patients with unknown BRAF status were not included in the subanalysis of RFS and MSS according to BRAF.

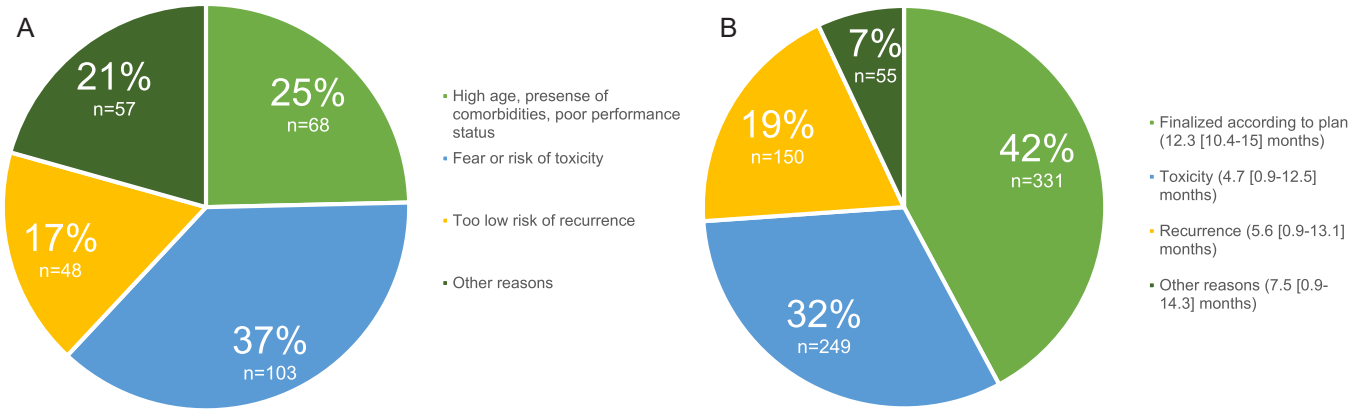
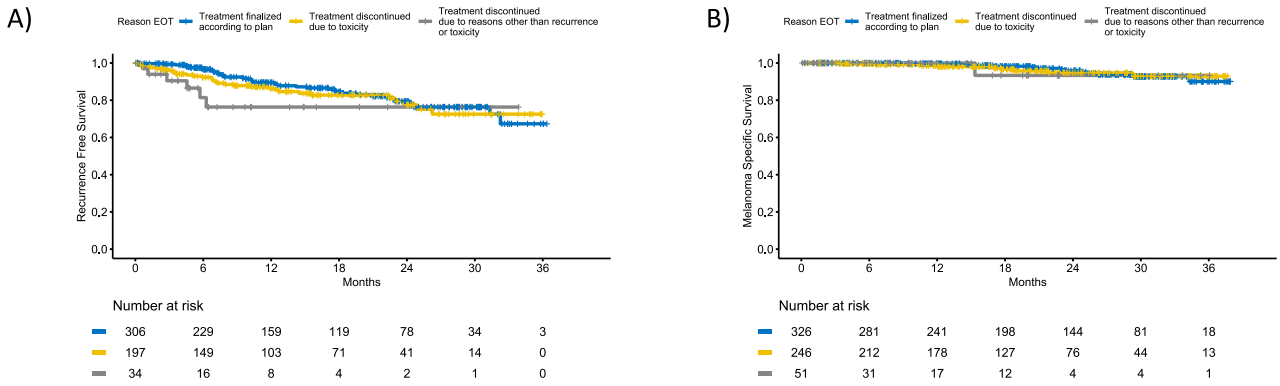


Fig. 3. Reasons for discontinuing or not receiving adjuvant treatment with anti-PD-1. Fig. 3A) Reasons for not receiving adjuvant anti-PD-1, multiple reasons per patient are possible. In 2/4 centers, covering around 70% of the total national cohort, patients not receiving therapy were registered systematically. One-third of referred patients to the Departments of Oncology will not receive adjuvant anti-PD-1 mainly due to fear or risk of toxicity. Patients with stage IIIA with sentinel node metastasis <1 mm who did not receive anti-PD-1 were included in the "too low risk of recurrence", as were patients who found the risk of recurrence too low compared to possible toxicities. Other reasons include pregnancy, lack of compliance, rescue therapy, and unknown reasons. Fig. 3B) Reasons for discontinuing adjuvant treatment with anti-PD-1 in an entire national cohort followed for more than 12 months (n = 785). Half of the patients discontinued treatment prematurely due to either toxicity or recurrence. Other reasons include secondary cancer, additional comorbidities, and non-melanoma-related death. Numbers in brackets are the median treatment duration in months and ranges.

previously published real-world studies. The Dutch Melanoma Treatment Registry (DMTR) reported a 1-year RFS of 70% [11], while other real-world studies have reported a 1-year and 2-year RFS of 74–77% and 60–68%, and OS of 94–97% and 86–93%, respectively [13–15]. Furthermore, the American National Cancer Database recently reported a 5-year OS of 87% in resected stage III melanoma post-adjuvant immunotherapy [21]. Surprisingly, patients with stage IV disease did not have a worse RFS or MSS compared to patients with stages IIIC/IIID (Supplementary Table S1A, and Figure 2). In the CheckMate-238 trial, patients with stage IV diseases who were treated with nivolumab showed comparable RFS rates with 1-year RFS of 72.1 (95%CI 62.4–79.7) in our study versus 63.0% (95%CI, 51.6–72.5) in CheckMate-238 [2], and 3-year RFS rates of 54.6% (43.1–64.7) versus 52.8% [8], respectively.

Subanalyses of survival among patients treated with anti-PD-1 compared to those not receiving therapy will be biased due to the various reasons for not receiving therapy with one part of the group having an excellent prognosis (stage IIIA with small tumor burden in SN) and another part of the patients having a poor prognosis with i.e., poor PS or severe comorbidities). However, after adjustments for age, PS, and stage (IIIA-D and IV) a trend toward improved RFS was observed in patients receiving adjuvant anti-PD-1. No changes were observed in MSS. Again, these results must be interpreted with caution due to the many possible biases. Interestingly, a nationwide Swedish study comparing outcomes in patients with stage III melanoma before and after the introduction of adjuvant therapy was not able to show any differences between groups despite comprehensive subanalyses. Notably, patients exposed to adjuvant therapy had a higher T-stage melanoma and a shorter follow-up time [12].

Like in the DMTR, over half of all Danish patients discontinued adjuvant anti-PD-1 treatment prematurely: 32% due to toxicity and 19% due to melanoma recurrence, whereas only 42% of the patients finalized full treatment. Patients discontinuing therapy due to toxicity received a median of 4.7 months of therapy compared to 5.6 and 7.5 months of therapy for patients discontinuing due to recurrence, or other reasons, respectively [11]. This contrasts with the large, randomized trials, where only 9–13% discontinued due to toxicity (mainly colitis/diarrhea and hepatitis) and 21–27% discontinued due to recurrence [2–4]. However, our data do not reveal differences in RFS or MSS in patients discontinuing prematurely due to toxicity and other reasons. Real-world patients receiving adjuvant anti-PD-1 show only a slightly elevated risk of irAEs compared to clinical trial patients [10,11,22], and QoL is



12-months landmark-analysis	Overall	Finalized planned treatment	Premature EOT due to toxicity	Premature EOT due to other reasons than recurrence or toxicity
Recurence rate, % (95% CI)	15.1 (12.2–18.4)	14.1 (10.4–18.5)	16.2 (11.4-22.2)	17.6 (6.8-34.5)
RFS, % (95% CI)				
6 months	94.2 (91.7–96.0)	96.6 (93.6–98.2)	92.3 (87.4-95.4)	81.4 (60.1-92.0)
12 months	87.5 (84–90.4)	89.5 (84.7–92.9)	86.3 (80.0-90.7)	76.3 (53.7-88.9)
24 months	78.3 (73.1–82.7)	79.5 (72.5–84.9)	77.5 (68.2-84.5)	76.3 (53.7-88.9)
Log-rank test		P=0.146		
MSS, % (95% CI)				
6 months	99.8 (98.8–100)	100	99.6 (97.0-99.9)	100
12 months	99.2 (97.9–99.7)	99.6 (97.4–99.9)	98.6 (95.6-99.5)	100
24 months	95.3 (92.4–97.1)	95.9 (91.9–97.9)	94.7 (89.4-97.4)	93.3 (61.3-99.0)
36 months	91.2 (85.8–94.6)	90.1 (81.2–94.9)	92.9 (85.8-96.6)	93.3 (61.3-99.0)
Log-rank test		P=0.951		

Fig. 4. Landmark analysis of (A) recurrence-free survival (RFS) and (B) melanoma-specific survival (MSS) according to the reason for the end of treatment (EOT). Patients who had a melanoma recurrence during the first 12 months were not included in the analyses. The 12-month landmark analysis was done to avoid immortal time bias for the patients fulfilling the planned treatment. The table included in the figure shows the recurrence rate, and 6-, 12-, and 24-months RFS and 6-, 12-, 24-, and 36-months MSS.

minimally affected, with only a small or temporary influence [14,23]. However, outside clinical trials, physicians may be more prone to discontinue adjuvant therapy in case of mild toxicities, and patients may be less tolerant of toxicities.

First-line metastatic treatment using BRAF+MEK inhibitors showed the highest ORR following adjuvant anti-PD-1, although this did not translate into superiority in MSS. Unexpectedly, patients treated with anti-PD-1 or ipilimumab monotherapy exhibited an improved ORR, RFS, and MSS compared to patients receiving ipilimumab plus nivolumab. The observed variations in treatment outcomes may stem from selection bias, given substantial differences in baseline characteristics among treatment regimens, as expected in a real-world dataset. To address some of these differences, a multivariable analysis (Figure 5) including the presence of brain metastases and elevated LDH, was conducted. Results reaffirmed at least comparable outcomes for patients treated with monotherapy (ipilimumab or anti-PD-1) as to patients receiving combination immunotherapy. In the ipilimumab and anti-PD-1 groups, only one or two patients, respectively, had brain metastases compared to 13 patients (23%) in the ipilimumab plus nivolumab group. However, it is important to note that almost all patients with brain metastases in the combination group (12/13) were asymptomatic. Previous studies indicate that these patients have almost identical ORR to combination immunotherapy as patients with only extracranial disease [24].

Previous studies on post-anti-PD-1 therapy indicated higher response rates with anti-PD-1 plus ipilimumab [25,26], but with a cost of increased toxicity [26]. Rechallenge with pembrolizumab in the EORTC-1325 demonstrated lower efficacy (ORR 11%) compared to patients from the placebo arm (ORR 39%) [27], though patients off anti-PD-1 for >1 month showed some benefit from re-induction. In our dataset, anti-PD-1 therapies yielded an ORR of 43%, but caution is warranted due to limited cases (11%). While ipilimumab and BRAF+MEK inhibitors show promise in early recurrence [28], comprehensive data on optimal treatment for patients progressing on or post-adjuvant anti-PD-1 requires further investigation.

Real-world patients often differ from randomized clinical trial criteria [29]. However, in the adjuvant setting, patients closely align with trial cohorts, excluding those with i.e., high comorbidities or poor PS [11,29]. Our study, consistent with previous research, mirrors these patterns, with nearly one-third of patients not receiving adjuvant anti-PD-1 [30].

Study limitations include its retrospective nature with real-world data affected by upfront bias during treatment decision-making. Despite a fair number of patients, subgroup analyses may have limited patient counts, hindering definitive conclusions. This is particularly relevant when assessing treatment efficacy and survival outcomes in patients with metastatic melanoma, where specific prognostic factors may influence treatment choices. Despite multivariable analyses addressing some confounding factors, numerous unknown biases will not be possible to include in a non-randomized setting and cannot be fully accounted for. Therefore, interpretations of the recurrence treatment results should be approached with the utmost caution.

In this real-world study, we analyzed a complete national cohort of patients with resected melanoma treated with adjuvant anti-PD-1. Our findings demonstrate comparable outcomes to the pivotal phase III clinical trials that led to the approval of anti-PD-1 antibodies in the adjuvant setting. Moreover, our study reveals no significant impact on outcomes for patients who discontinue adjuvant therapy prematurely due to toxicity. Interestingly, our data suggest that ipilimumab plus nivolumab may not confer improved outcomes compared to ipilimumab monotherapy as a first-line metastatic treatment post-adjuvant anti-PD-1 therapy, however, important bias might be found in variations of baseline characteristics. Additional data on managing patients with metastatic melanoma after adjuvant therapy is crucial, and further research will contribute to refining optimal treatment strategies.

Table 2
Outcome to first-line metastatic treatment for irresectable melanoma after previous therapy with adjuvant anti-PD-1.

	First-line metastatic treatment					
	Total	BRAF+MEK	Ipilimumab + nivolumab*	Ipilimumab	Anti-PD-1	Experimental treatment§
Patients, n (%)	184† (100)	70 (37.8)	55 (29.7)	31 (16.8)	21 (11.3)	7 (3.8)
Age, median (range)	68 (19–87)	64 (31–81)	64 (27–78)	71 (35–84)	76 (19–87)	60 (34–74)
Performance state, n (%)						
0	126 (68.5)	48 (68.6)	39 (70.9)	21 (67.7)	12 (57.1)	6 (85.7)
≥1	58 (31.5)	22 (31.4)	16 (29.1)	10 (32.3)	9 (42.9)	1 (14.3)
LDH U/L, median (range)	197 (115–1618)	200 (118–1618)	190 (139–1350)	215 (140–183)	196 (115–525)	187 (159–223)
BRAF-status, n (%)						
Mutation	80 (43.5)	70 (100)	17 (30.9)	8 (25.8)	3 (14.3)	3 (42.9)
Wildtype	100 (54.3)	-	35 (63.6)	23 (74.2)	17 (80.9)	4 (57.1)
Not tested	4 (2.2)	-	3 (5.5)	-	1 (4.8)	-
M-stage, n (%)						
M1a	47 (25.5)	22 (31.4)	10 (18.2)	8 (25.8)	6 (28.6)	1 (14.3)
M1b	28 (15.2)	10 (14.3)	8 (14.5)	4 (12.9)	5 (23.8)	1 (14.3)
M1c	78 (42.4)	23 (32.9)	24 (43.6)	18 (58.1)	8 (38.1)	5 (71.4)
M1d	31 (16.8)	15 (21.4)	13 (23.6)	1 (3.2)	2 (9.5)	-
Brain metastasis, n (%)	31 (16.8)	15 (21.4)	13 (23.6)	1 (3.2)	2 (9.5)	-
Asymptomatic	21 (67.7)	6	12	1	2	-
Symptomatic	10 (32.3)	9	1	-	-	-
Discontinued adjuvant anti-PD-1 due to toxicity						
Yes, n (%)	**39 (21.2)**	**16 (22.9)**	**9 (16.7)**	**4 (12.9)**	**10 (47.6)**	**0 (0)**
1-years PFS, % (95%CI)	58.6 (40.8–72.2)	86.2 (55.0–96.4)	-	50.0 (5.8–84.5)	46.7 (15.0–82.1)	-
1-years MSS, % (95%CI)	89.3 (74.0–95.9)	93.3 (61.3–99.0)	77.8 (36.5–93.9)	100	90.0 (47.3–98.5)	-
2-years MSS, % (95%CI)	60.0 (28.8–81.0)	74.7 (24.6–94.1)	-	50.0 (0.6–91.0)	90.0 (47.3–98.5)	-
No, n (%)	**145 (78.8)**	**54 (77.1)**	**46 (83.3)**	**27 (87.1)**	**11 (52.4)**	**7 (100)**
1-years PFS, % (95%CI)	36.1 (27.6–44.7)	41.5 (27.0–55.4)	26.5 (13.0–42.0)	39.4 (20.4–57.9)	36.4 (11.2–62.7)	38.1 (6.1–71.6)
1-years MSS, % (95%CI)	71.4 (62.6–78.6)	64.8 (49.4–76.5)	73.7 (56.0–85.1)	75.9 (53.8–88.5)	72.7 (37.1–90.3)	100
2-years MSS, % (95%CI)	47.2 (36.6–57.0)	34.1 (19.1–49.7)	33.6 (11.9–57.2)	66.4 (43.5–81.8)	48.5 (8.8–80.6)	100
Time from adjuvant anti-PD-1 to PD ≤ 6 months#, n (%)	**131 (71.2)**	**55 (78.6)**	**33 (60)**	**27 (87.1)**	**10 (47.6)**	**6 (85.7)**
ORR	70 (53.4)	44 (80)	8 (24.2)	11 (40.7)	4 (40)	3 (50)
1-years PFS, % (95%CI)	42.0 (32.9–50.8)	53.2 (37.9–66.3)	28.8 (14.1–45.4)	39.6 (20.6–58.1)	30.0 (7.1–57.8)	50.0 (11.1–80.4)
1-years MSS, % (95%CI)	73.7 (64.6–80.8)	72.8 (57.7–83.3)	70.2 (50.3–83.3)	75.9 (53.8–88.5)	70 (32.9–89.2)	100
2-years MSS, % (95%CI)	48.0 (36.9–58.2)	35.3 (19.1–52.2)	33.7 (11.7–57.6)	66.1 (43.0–81.6)	52.5 (15.0–80.4)	100
> 6 months, n (%)	**53 (28.8)**	**15 (21.4)**	**22 (40)**	**4 (12.9)**	**11 (52.4)**	**1 (14.3)**
ORR	28 (52.8)	13 (86.7)	8 (36.4)	2 (50)	5 (45.5)	-
1-years PFS, % (95%CI)	36.9 (21.2–52.6)	42.2 (13.2–69.2)	18.5 (1.5–51.1)	50.0 (5.8–84.5)	53.0 (20.9–77.3)	100
1-years MSS, % (95%CI)	79.5 (64.1–88.9)	66.0 (36.5–84.3)	83.7 (57.4–94.5)	100	90.9 (50.8–98.7)	-
2-years MSS, % (95%CI)	57.7 (34.1–75.5)	66.0 (36.5–84.3)	-	66.7 (5.4–94.5)	90.9 (50.8–98.7)	-
Total ORR, n (%)	98 (53.3)	57 (81.4)	16 (29.1)	13 (41.9)	9 (42.9)	3 (42.3)
mPFS, median (95%CI)	8.2 (6.2–10.7)	12.7 (8.3–17.9)	3.9 (2.7–6.2)	8.7 (3.5–17.7)	5.8 (3.0–NR)	7.1 (2.4–NR)
mMSS, median (95%CI)	22.3 (16.8–33.2)	18.1 (14.2–33.2)	17.4 (13.7–NR)	NR (15.5–NR)	24.2 (16.2–NR)	NR (26.1–NR)

Missing values are due to no patients at risk at the given time points.
BRAF, B-Raf proto-oncogene; MSS, melanoma-specific survival; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; ULN, upper level of normal.
*All patients received treatment of ipilimumab 3 mg/kg and nivolumab 1 mg/kg.
†One patient with BRAF wildtype metastatic melanoma receiving temozolomide as first-line metastatic therapy due to contraindications for further therapy with ICIs has not been included in the analysis.
§Experimental treatment: Five patients were treated with anti-PD-1 + peptide vaccine, and two patients received tumor-infiltrating lymphocytes.
#Time from adjuvant anti-PD-1 to progressive disease includes patients' progression to metastatic disease during adjuvant therapy.

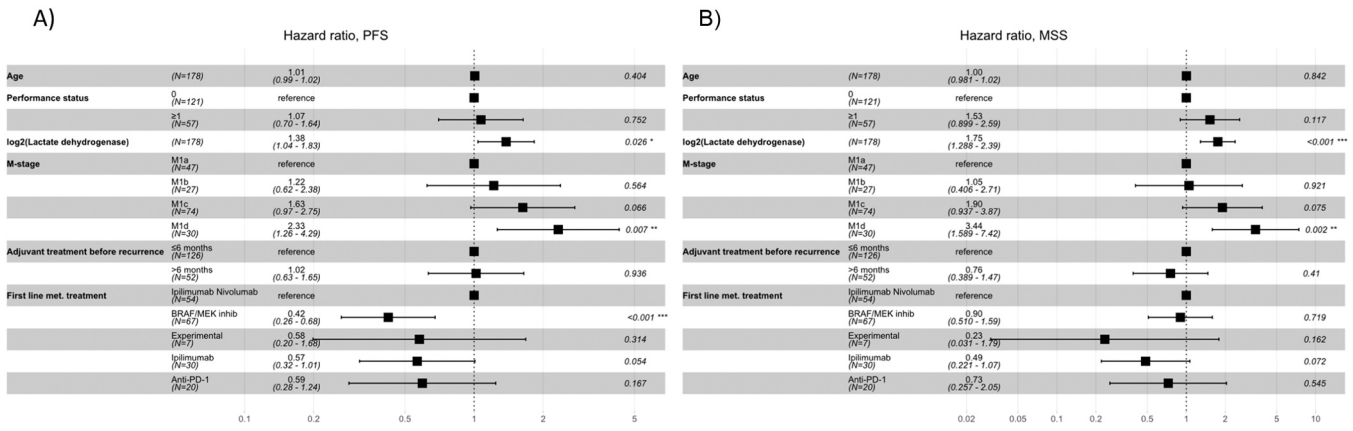


Fig. 5. Multivariable analysis of (A) progression-free survival (PFS) and B) melanoma-specific survival (MSS) for patients who had a recurrence post-adjuvant anti-PD-1 and who started first-line systemic metastatic treatment, n = 178. Patients in experimental treatment are not included in the analysis of patients' characteristics. Lactate dehydrogenase levels from six patients were missing.

Declaration of interest statement

Within the last two years: RJ has received travel/conference expenses from Pierre Fabre. MD has received proprietary data access from Bristol Myers Squibb and Genentech and is an advisor of Achilles Therapeutics. CR reports grants from Novo Nordisk Foundation and Helsinn Healthcare SA, and personal fees from Bristol-Myers Squibb, Helsinn Healthcare SA, and Pharmanovia, outside the submitted work. CAH has received honoraria for lectures from BMS and GSK. IMS has received honoraria for consultancies and lectures from IO Biotech, Novartis, MSD, Pierre Fabre, BMS, Novo Nordisk, TILT Bio; research grants from IO Biotech, BMS, Lytix, Adaptimmune, and TILT Bio. EE received honoraria from BMS, Pierre Fabre, and Novartis for consultancies, lectures, and travel/conference expenses from Pierre Fabre and MSD. No potential conflict of interest was reported by the other author (s).

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CRediT authorship contribution statement

Eva Ellebaek: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rikke B Holmstroem:** Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Lars Bastholt:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Data curation, Conceptualization. **Inge Marie Svane:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Henrik Schmidt:** Writing – review & editing, Resources, Project administration. **Charlotte A. Haslund:** Writing – review & editing, Resources, Project administration. **Christina H. Ruhlmann:** Writing – review & editing, Resources, Project administration. **Kasper Madsen:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation. **Marco Donia:** Writing – review & editing, Resources. **Sidsel Pedersen:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Rebecca Jurlander:** Writing – review & editing, Investigation, Data curation, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this paper, the authors used Chat GPT to improve readability and language. After using this tool, the authors have reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of Competing Interest

Within the last two years: RJ has received travel/conference expenses from Pierre Fabre. MD has received proprietary data access from Bristol Myers Squibb and Genentech and is an advisor of Achilles Therapeutics. CR reports grants from Novo Nordisk Foundation and Helsinn Healthcare SA, and personal fees from Bristol-Myers Squibb, Helsinn Healthcare SA, and Pharmanovia, outside the submitted work. CAH has received honoraria for lectures from BMS and GSK. IMS has received honoraria for consultancies and lectures from IO Biotech, Novartis, MSD, Pierre Fabre, BMS, Novo Nordisk, TILT Bio; research grants from IO Biotech, BMS, Lytix, Adaptimmune, and TILT Bio. EE received honoraria from BMS, Pierre Fabre, and Novartis for consultancies, lectures, and travel/conference expenses from Pierre Fabre and MSD. No potential conflict of interest was reported by the other author (s).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114023.

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