Research Article

For reprint orders, please contact: reprints@futuremedicine.com

Immunotherapy



Real-world effectiveness of pembrolizumab in advanced melanoma: analysis of a French national clinicobiological database

Emilie Casarotto[1,11], Sheenu Chandwani[2], Laurent Mortier[3], Olivier Dereure[4], Caroline Dutriaux[5], Sophie Dalac[6], Emilie Scherrer[7], Laurie Lévy-Bachelot[1], Laetitia Verdoni[1], Gaëlle Farge[1], Clara Allayous[8], Bastien Oriano[8], Stéphane Dalle[9] & Céleste Lebbé*[,10]

[1]MSD France, Puteaux, France
[2]Merck & Co., Inc., Kenilworth, NJ 07033, USA
[3]Department of Dermatology, CHRU de Lille, University of Lille, ONCO-THAI INSERM, Lille, U1189, France
[4]Department of Dermatology, University Hospital of Montpellier, Montpellier, France
[5]Department of Dermatology, Bordeaux Saint-André Hospital, Bordeaux, France
[6]Department of Dermatology, University Hospital of Dijon, Dijon, France
[7]MSD, London, UK
[8]Department of Dermatology, AP-HP Hôpital Saint Louis, F-75010 Paris, France
[9]Department of Dermatology, Hospices Civils de Lyon, Cancer Research Center of Lyon, Pierre-Bénite, France
[10]Université de Paris, Department of Dermatology, AP-HP Hôpital Saint Louis, F-75010 Paris, France; INSERM U976
[11]Current affiliation: Ividata Life Sciences, Levallois Perret, France
*Author for correspondence: Tel.: +33 142 499 392; celeste.lebbe@aphp.fr

Aim: To describe real-world pembrolizumab administration and outcomes for advanced melanoma in France. **Materials & methods:** Using the MelBase longitudinal database, this multicenter historical-prospective study examined treatment and outcomes of patients with nonuveal, unresectable stage III/IV melanoma initiating pembrolizumab from April 2016 to September 2017, with follow-up to September 2019. Kaplan–Meier time-to-event analyses were conducted. **Results:** Of 223 patients (median age 67; 51% men), 134 (60%), 36 (16%) and 53 (24%) initiated pembrolizumab in first, second and thirdline, respectively. Median overall survival (months) was 32.6 (95% CI: 20.3–not reached [NR]), 14.4 (8.6–NR) and 9.3 (6.4–NR), respectively. Best real-world tumor response of complete or partial response was recorded for 49, 39 and 26% of patients, respectively. **Conclusion:** Study results support benefits of pembrolizumab therapy for advanced melanoma.

First draft submitted: 5 April 2021; Accepted for publication: 5 May 2021; Published online: 2 June 2021

Keywords: cohort study • immunotherapy • melanoma • oncology • pembrolizumab • survival

Guidelines for the treatment of advanced melanoma in Europe are based on the results of randomized controlled trials (RCTs) [1]. Currently, immunotherapies such as the anti-PD-1 agents pembrolizumab and nivolumab form the cornerstone of systemic therapy for advanced melanoma together with BRAF/MEK targeted therapies (the latter for *BRAF*-mutant melanoma) [1]. However, many patients are treated outside of the RCT setting, and the results of observational studies provide important information for understanding the effectiveness of therapies outside of RCTs [2–4]. Moreover, the findings of RCTs may not be generalizable to real-life clinical practice because of close monitoring of the trial environment and strict eligibility criteria that exclude many patients, such as those with poor performance status or active/untreated brain metastases [5].

In France, pembrolizumab was first made available for advanced melanoma under temporary use authorization (ATU), the early access program starting in September 2015 in a restricted population relative to its full marketing authorization indication. The early access indication included use of pembrolizumab therapy for *BRAF* wild-type tumors from first line, and for *BRAF*V600-mutated tumors that had progressed after treatment with a BRAF inhibitor or with contraindications to targeted therapies. Subsequently, on 10 January 2017, the official gazette publication was released, and pembrolizumab became available with reimbursement within its full marketing authorization indication, including in the first line setting irrespective of tumor *BRAF* mutation status.

Future Medicine

The French National Authority for Health (Haute Autorité de Santé) recommends generation of complementary survival data in real-world clinical practice to reduce uncertainty around trial results in French settings. In the efficiency opinion from 16 March 2016, a real-world study of pembrolizumab therapy for advanced melanoma was requested by the Economic and Public Health Assessment Committee (CEESP), a dedicated committee within the Haute Autorité de Santé in charge of assessing the cost–effectiveness of treatments. While real-world observational studies of anti-PD-1 therapy for melanoma in the USA and European countries have been published recently [6–9], there remains a need for studies following large patient cohorts in the French healthcare setting since anti-PD-1 approvals [10,11].

The aim of this study was to describe the real-world use of pembrolizumab therapy for treating advanced melanoma in France during the early access program and after full authorization. The primary objectives were to describe demographic and clinical characteristics of patients with advanced melanoma treated with pembrolizumab, pembrolizumab utilization patterns and pembrolizumab discontinuation. Secondary and exploratory objectives were to describe the real-world clinical outcomes of pembrolizumab therapy.

Materials & methods

Patients & study design

This multicenter, historical, prospective cohort study employed data from MelBase, a longitudinal clinical database linked with a virtual biobank, established in 2013 as the first French national clinicobiological database for advanced melanoma [12,13]. Overseen by a team bringing together medical, bioinformatic, health economic and scientific expertise, MelBase is sponsored by the French National Cancer Institute and industrial partners and administered by the Public Hospitals of Paris (AP-HP) Department of Clinical Research and Innovation [12–14]. The 26 participating centers from the GCC group (skin cancer group of the French Dermatology Society) recruit approximately 300 patients per year and use an electronic case report form (eCRF) for prospective collection of clinical and radiological information, with on-site training for data entry by the MelBase coordination team. Each center has a biobank, supported by a central Biological Resource Center.

Information collected in the Melbase eCRF for each patient includes demographics, clinical features of initial melanoma diagnosis, medical background, advanced tumor characteristics, treatment history before initiating pembrolizumab, details regarding pembrolizumab administrations, response assessments, discontinuation status and reasons, rechallenge and vital status. Data are updated every 3 months, and then at each change in line of therapy. A regular monitoring of all data is performed remotely based on a list of requests (data missing, consistency issues, etc.) with special care regarding key data, such as efficacy and safety data. In cases of unknown vital status, the MelBase monitoring team follows up with the treating center to determine whether there was notification of a patient's death.

Enrolment in MelBase requires availability of a tumor sample for histologic confirmation of advanced primary melanoma (unresectable stage III or stage IV), diagnosed at age 18 years or older, without prior systemic treatment other than adjuvant treatment. Patients with uveal melanoma and earlier stages of melanoma are not included in MelBase.

The study population included patients enrolled in MelBase with advanced melanoma who initiated pembrolizumab treatment from 1 April 2016 to 30 September 2017 (index period), outside of a clinical trial setting. The study period ended on 1 September 2019, providing almost 2 years of potential minimum follow-up. This resulted in inclusion of patients prescribed pembrolizumab in both the ATU period (early access, restricted indication) and the post-ATU time period (full indication; Figure 1).

The MelBase protocol was approved by the French Ethics Committee (CPP Ile-de-France XI, number 12027, 2012), and patients provided written informed consent to be included in MelBase (clinicaltrials.gov number NCT02828202).

Assessments

The primary study objectives were to describe patient characteristics and pembrolizumab treatment patterns, including rate and reasons for discontinuing pembrolizumab therapy. Secondary objectives were to estimate overall survival (OS), defined as the time from pembrolizumab initiation to death, and real-world progression-free survival (rwPFS), defined as the time from pembrolizumab initiation to the first documented disease progression or death due to any cause, whichever occurred first, with censoring on date of the last recorded activity in the eCRF. Patients

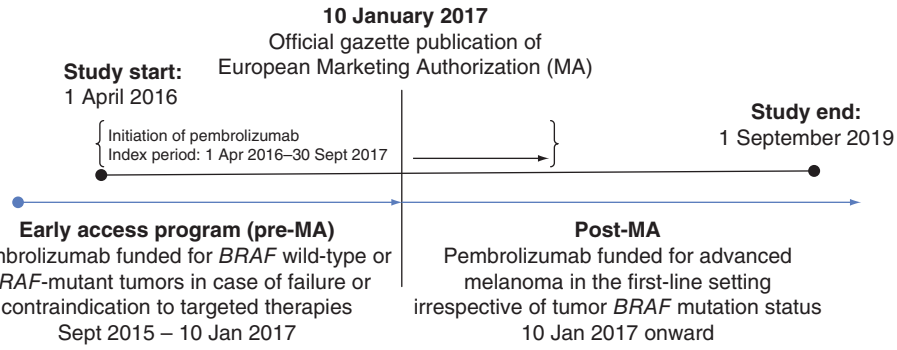


Figure 1. Study timeline for enrolment of patients with advanced melanoma initiating pembrolizumab therapy from 1 April 2016 to 30 September 2017 (index period).
MA: Marketing authorization.

lost to follow-up were censored at the date of their last recorded activity, and patients who were still alive, as reported in their eCRF, were censored at the end of follow-up.

Exploratory objectives included estimating real-world tumor response (rwTR) with pembrolizumab therapy, rechallenge with anti-PD-1 therapy and time to rechallenge. Clinical or radiological progression was determined by the presence of new lesions or progression of existing lesions on clinical and radiological evaluation during the prospective follow-up according to RECIST 1.1 [15], based on local investigator interpretation. The rwTR was determined from physician's notes in the eCRF as complete response, partial response, stable disease or progressive disease, with the best real-world response used for patients with multiple assessments within a line of pembrolizumab therapy. In addition, we investigated the real-world time to next treatment (rwTTNT) for patients who initiated pembrolizumab as first line systemic therapy, defining rwTTNT as the time from first pembrolizumab dose to first dose of the subsequent treatment or death, as previously described [8]; patients with no subsequent treatment were censored at their last recorded activity in the eCRF.

Pembrolizumab discontinuation was defined as a treatment gap of >12 weeks (four-times the treatment interval) or an eCRF notation indicating the 'stop of treatment'. Rechallenge was defined as anti-PD-1 therapy (pembrolizumab or nivolumab) administration ≥12 weeks after the previous dose or administration after an eCRF record of treatment discontinuation [16]. The time to rechallenge was defined as the interval between last dose of pembrolizumab in the first course and first dose of pembrolizumab in the second course.

Statistical analyses

A formal calculation of sample size and power was not performed because of the descriptive nature of the study. All analyses were stratified by pembrolizumab line of therapy. Baseline demographic and disease characteristics were summarized as numbers and percentages for categorical variables and as mean, standard deviation, median, interquartile range and range for continuous variables, as appropriate. Missing data were also computed for each variable.

Real-world time-to-event outcomes including OS, rwPFS and rwTTNT were estimated using the Kaplan–Meier method with associated 95% CI. In addition, the numbers and proportions of patients were calculated for the real-world response categories (complete response, partial response, stable disease or progressive disease), those who discontinued pembrolizumab therapy, reasons for discontinuation and rechallenge. Patients censored before 12 months were patients actually lost to follow-up (most commonly patients who had finished their follow-up). The log-rank test was used to compare differences in survival and rwPFS for the first line of therapy by *BRAF* mutation status, applying multiple imputation methods to account for missing baseline data [17]. The follow-up period was calculated from the first dose of pembrolizumab to the recorded activity for each patient.

Data analyses were conducted using R statistical software version 3.3.1 and the R Multivariate Imputation by Chained Equations package [17] to address missing data (The R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Baseline patient demographic and clinical characteristics by pembrolizumab line of therapy.

Characteristics	Pembrolizumab line of therapy			Ref.
	First line (n = 134)	Second line (n = 36)	Third line/later (n = 53)	
Male sex	65 (49)	21 (58)	28 (53)	
Age, median (range), years	72 (24–90)	59 (20–88)	56 (30–88)	
Age ≥70 years	71 (53)	9 (25)	14 (26)	
Height, mean (SD), m	1.7 (9.6)	1.7 (8.6)	1.7 (7.8)	
Weight, mean (SD), kg	76 (17)	75 (16)	75 (15)	
ECOG PS[†]				
0–1	126 (94)	35 (97)	45 (85)	
≥2	8 (6)	1 (3)	8 (15)	
BRAF mutation	21 (16)	28 (78)	44 (83)	
Lactate dehydrogenase level[‡]				
Elevated: >ULN	44 (33)	12 (33)	16 (30)	
Missing	0	7 (19)	9 (17)	
Brain metastasis	21 (16)	11 (31)	18 (34)	
AJCC 7 stage				[18]
Stage III, unresectable	26 (19)	1 (3)	3 (6)	
Stage IV	108 (81)	35 (97)	50 (94)	
Prior history of melanoma	7 (5)	2 (6)	0	
Pre-existing autoimmune disease	15 (12)	2 (6)	4 (8)	
Prior systemic therapy				
Targeted therapy	NA	20 (56)	39 (72)	
Immunotherapy	NA	3 (8)	12 (23)	
Anti-PD1 + anti-CTLA-4	NA	1 (3)	4 (8)	
Clinical trial therapy	NA	10 (28)	3 (6)	
Chemotherapy	NA	3 (8)	0	

Data are n (%) unless otherwise indicated. Percentages may not total 100% because of rounding.
[†]ECOG PS was captured on the date of first pembrolizumab administration or, if not available, the nearest value within 2 weeks before or after the first dose.
[‡]LDH captured on the date of first pembrolizumab administration.
AJCC: American Joint Committee on Cancer; ECOG PS: Eastern Cooperative Oncology Group performance status; SD: Standard deviation; ULN: Upper limit of normal.

Results

Patients

Of 1940 patients included in MelBase in September 2019, 734 (38%) received at least one pembrolizumab dose, including 234/734 patients (32%) who initiated pembrolizumab from 1 April 2016 to 30 September 2017. 11 patients were excluded from the study for withdrawal of consent or loss to follow-up. The final study population included 223 eligible patients with advanced melanoma initiating pembrolizumab at 26 centers across France during this period. 93 patients (42%) initiated pembrolizumab from 1 April 2016 to 9 January 2017 under the early access program, and 130 (58%) initiated pembrolizumab from 10 January 2017 to 30 September 2017.

Overall median age was 67 years (range 20–90 years); 43 patients (19%) were younger than 50 years of age and 94 patients (42%) were 70 years of age or older. One-half of patients were men (114; 51%). The majority of patients initiated pembrolizumab as first line therapy (134; 60%), while 36 initiated as second line (16%) and 53 as third line or later therapy (24%). Patient characteristics by line of therapy at pembrolizumab initiation are summarized in Table 1. Median ages were 72, 59 and 56 years for patients initiating pembrolizumab in first, second and third line/later. Most patients had good performance status, with Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; only 17 patients (8%) had ECOG PS ≥2. Overall, one-fifth of patients had one or more brain metastases (50; 22%, including both active and inactive brain metastases) and a third (72; 32%) had an elevated LDH level at the time of pembrolizumab initiation, including 11 (5%) with LDH > two-times the upper limit of normal (Table 1).

Melanoma was first diagnosed at stage IV (American Joint Committee on Cancer 7 staging [18]), for 25, 14 and 26% of patients initiating pembrolizumab in first, second and third line/later, respectively (Table 2). The most common histological type overall was superficial spreading melanoma (42%), followed by nodular melanoma

Table 2. Characteristics of initial melanoma by pembrolizumab line of therapy.

Characteristics	Pembrolizumab line of therapy		
	First line (n = 134)	Second line (n = 36)	Third line/later (n = 53)
Primary melanoma known, n (%)	114 (85)	33 (92)	41 (77)
Location, n (%)			
Torso	35 (26)	17 (47)	21 (40)
Lower limbs	37 (28)	9 (25)	13 (25)
Cervicofacial (head and neck)	17 (13)	4 (11)	3 (6)
Upper limbs	13 (10)	1 (3)	5 (9)
Nasal-sinus mucosa	3 (2)	1 (3)	0
Vaginal or vulvar mucosa	2 (2)	0	0
Anal canal mucosa	0	0	1 (2)
Buttocks	1 (1)	0	0
Unknown primary melanoma	17 (13)	3 (8)	12 (23)
Other	9 (7)	1 (3)	2 (4)
Histologic type of melanoma, n (%)			
Superficial spreading	53 (40)	18 (50)	23 (43)
Nodular	25 (19)	5 (14)	5 (9)
Acral lentiginous	7 (5)	1 (3)	4 (8)
Lentigo maligna	0	2 (6)	1 (2)
Mucosal lentiginous	4 (3)	1 (3)	0
Unclassifiable	16 (12)	3 (8)	4 (8)
Unknown primary melanoma	17 (13)	3 (8)	12 (23)
Missing	12 (8)	3 (8)	4 (8)
Initial melanoma stage, n (%)			
0	7 (5)	2 (6)	2 (4)
I	28 (21)	11 (31)	7 (13)
II	46 (34)	9 (25)	13 (25)
III	20 (15)	9 (25)	17 (32)
IV†	33 (25)	5 (14)	14 (26)
Known time from initial to advanced melanoma, n (%)	31 (51)	61 (60)	32 (50)
Median (range), months	17 (0–331)	15 (0–231)	14 (0–236)

Percentages may not total 100% because of rounding.
†Stage IV includes 17 patients with unknown stage at diagnosis.

(16%) and acral lentiginous melanoma (5%); seven patients (3%) had mucosal melanoma. Overall, the median number of metastatic sites was 2 (interquartile range: 1–3); and 86 patients (39%) had three or more metastatic sites.

The median age of the 93 patients (42%) with *BRAF*-mutant tumors was 56 years, while the median age of the 130 patients (58%) with *BRAF* wild-type tumors was 73 years; the age ranges were similar (20–88 and 24–90 years, respectively). The *BRAF*-mutant cohort included a slightly higher percentage of men than women (54 vs 46%), while percentages of men and women were similar in the *BRAF* wild-type cohort (49 vs 51%).

Among the 93 patients with *BRAF*-mutant tumors, 72 (81%) had received prior systemic therapies. The percentages of patients with *BRAF*-mutant tumors in first, second and third line/later cohorts were 16, 78 and 83%, respectively, and the most common prior systemic therapy was targeted therapy (Table 1). Overall, 21 patients with *BRAF*-mutant melanoma received BRAF/MEK inhibitors as first line therapy.

OS & rwPFS

The median duration of follow-up at data cut-off ranged from 25.3 months in the first line cohort to 28.9 months in the second line cohort (Table 3). Overall, 107 patients (48%) were alive at data cut-off.

For patients treated with pembrolizumab in first line, median OS was 32.6 months (95% CI: 20.3–not reached [NR]), and the 24-month survival rate was 54.2% (95% CI: 46.1–64.2; Table 3 & Figure 2A). The median

Table 3. Follow-up time, overall survival and real-world progression-free survival by pembrolizumab line of therapy.

Variable	Pembrolizumab line of therapy		
	First line (n = 134)	Second line (n = 36)	Third line/later (n = 53)
Follow-up time, median (range), months	25.3 (2.3–30.9)	28.9 (9.2–32.2)	27.8 (8.7–32.9)
OS, median (95% CI)	32.6 (20.3–NR)	14.4 (8.6–NR)	9.3 (6.4–NR)
6-month survival, % (95% CI)	84.2 (78.2–90.6)	75.0 (62.1–90.6)	64.2 (52.5–78.5)
12-month survival, % (95% CI)	70.3 (62.9–78.6)	55.2 (41.0–74.2)	45.1 (33.4–60.7)
18-month survival, % (95% CI)	61.5 (53.5–70.7)	49.4 (35.3–69)	41.5 (29.8–56.9)
24-month survival, % (95% CI)	54.2 (46.1–64.2)	46.3 (32.4–66.2)	35.2 (24.3–50.9)
30-month survival, % (95% CI)	51.7 (43.1–61.9)	33.9 (20.5–56.1)	35.2 (24.3–50.9)
36-month survival, % (95% CI)	47.0 (36.2–60.9)	25.5 (11.9–54.3)	35.2 (24.3–50.97)
rwPFS, median (95% CI)	4.7 (3.2–7.0)	2.7 (2.5–3.3)	2.6 (2.1–3.1)
6-month rwPFS, % (95% CI)	44.8 (37.1–54)	22.2 (12.1–40.9)	22.6 (13.8–37.2)
12-month rwPFS, % (95% CI)	34.3 (27.1–43.3)	19.0 (9.6–37.7)	22.6 (13.8–37.2)
18-month rwPFS, % (95% CI)	27.3 (20.5–36.2)	15.9 (7.3–34.3)	20.6 (12.1–35)
24-month rwPFS, % (95% CI)	24.1 (17.6–33.1)	15.9 (7.3–34.3)	18.5 (10.5–32.8)

NR: Not reached; OS: Overall survival; rwPFS: Real-world progression-free survival.

Table 4. Best recorded real-world tumor response during pembrolizumab therapy.

rwTR	Pembrolizumab line of therapy		
	First line (n = 134)	Second line (n = 36)	Third line/later (n = 53)
Best response, n (%)			
Complete response	28 (21)	5 (14)	5 (9)
Partial response	38 (28)	9 (25)	9 (17)
Stable disease	19 (14)	2 (6)	13 (25)
Progressive disease	49 (37)	20 (56)	26 (49)
Objective response†	66 (49)	14 (39)	14 (26)
Disease control†	85 (63)	16 (44)	27 (51)

Percentages are column percentages and may not total 100% because of rounding.
†Objective response was defined as complete response or partial response, and disease control was defined as complete response, partial response or stable disease.
rwTR: Real-world tumor response.

OS for patients with *BRAF*-mutant versus *BRAF* wild-type tumors who received pembrolizumab in first line was 32.6 months (95% CI: 25.2–NR) versus NR (95% CI: 18.8–NR), respectively (log-rank p = 0.30; Figure 2B).

For the 50 patients with brain metastases, median OS was 9.1 months (95% CI: 5.9–25.8), and survival was 45.3% (95% CI: 33.3–61.6%) at 12 months and 37.9% (95% CI: 26.3–54.8%) at 24 months. The 129 patients with the two most common histological types of melanoma (superficial spreading and nodular melanoma) experienced median OS of 24.8 months (95% CI: 15.8–NR). Survival in this group of patients was 59.9% (95% CI: 51.9–69.1%) at 12 months and 51.1% (95% CI: 42.9–60.8%) at 24 months.

For patients treated in first line, the median rwPFS was 4.7 months (95% CI: 3.2–7.0); Table 3 & Figure 3A. In the first line setting, patients with *BRAF*-mutant tumors experienced median rwPFS of 7 months (95% CI: 3.0–NR), and patients with *BRAF* wild-type tumors experienced median rwPFS of 4.7 months (95% CI: 2.9–6.9; log-rank p = 0.20; Figure 3B).

Real-world tumor response

The best recorded rwTR during pembrolizumab therapy was complete response for 38 patients overall (17%; Table 4), of whom 11 remained on pembrolizumab treatment at data cut-off. Of the other 27 patients who discontinued pembrolizumab after complete response, two were rechallenged with anti-PD-1 therapy and remained on treatment at data cut-off.

In the first line setting, 66 patients (49%) had a complete or partial response to pembrolizumab therapy, and 14 (39%) and 14 (26%) in second and third line/later, respectively, had a complete or partial response (Table 4). Disease progression was recorded as best rwTR for 37, 56 and 49% in first, second and third line/later, respectively.

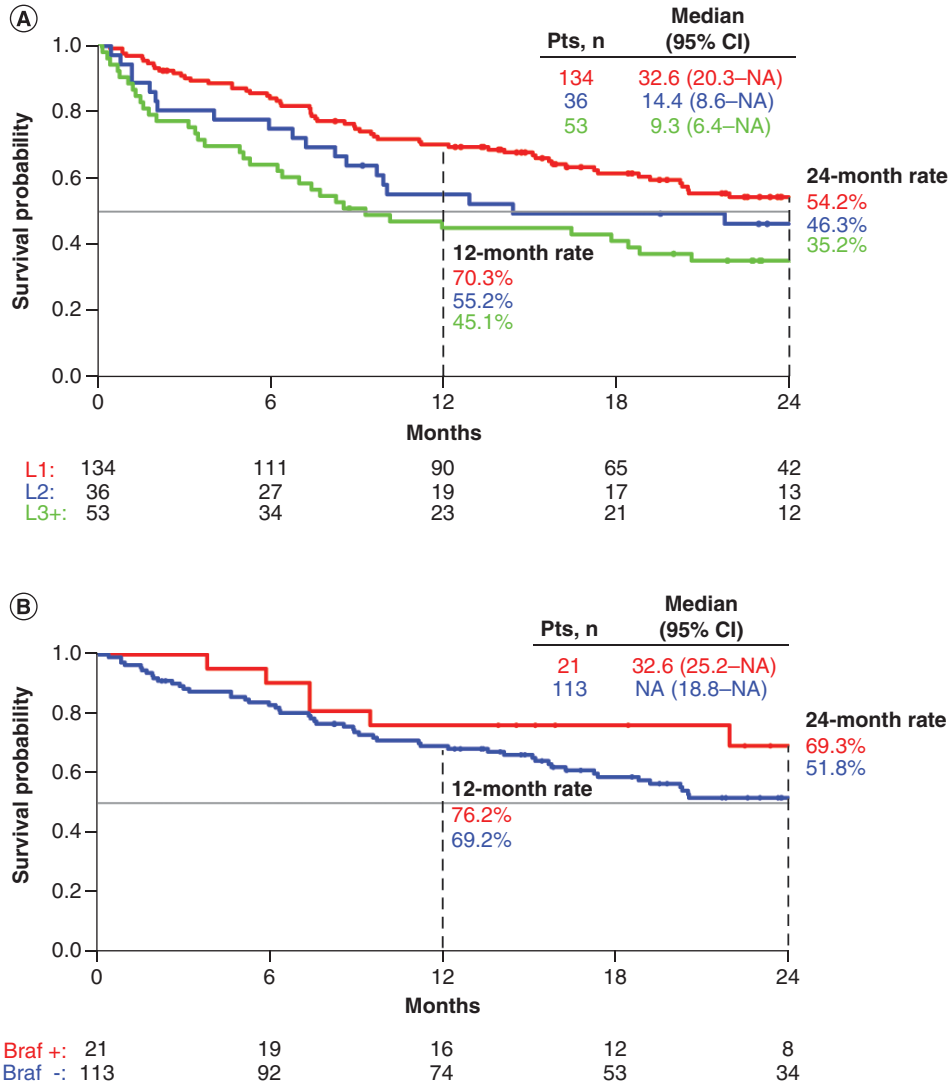


Figure 2. Kaplan-Meier estimates of overall survival. (A) By pembrolizumab line of therapy and **(B)** by *BRAF* mutation status for patients treated with pembrolizumab in first line.
NR: Not reached.

Treatment summary

A total of 13 patients were rechallenged with pembrolizumab or nivolumab (Table 5). The median rwTTNT for patients initiating pembrolizumab in first line (n = 134) was 13.1 months (95% CI: 9.2–NR).

Discussion

The findings of this multicenter historical-prospective cohort study describe pembrolizumab utilization patterns for 223 patients with advanced melanoma treated in French clinical practice during a period spanning the initial funding of pembrolizumab therapy under the early access program (ATU) and for almost 3 years after pembrolizumab funding publication per the marketing authorization (January 2017). The use of the MelBase data enabled us to capture and describe key details of patients' clinical characteristics, including ECOG PS and LDH levels, as well as survival according to line of treatment, *BRAF* mutation status and presence of brain metastases. We observed long-term effectiveness of pembrolizumab therapy for patients with advanced melanoma, particularly for those treated in the first line setting.

The survival results in the first line setting are in agreement with results of clinical trials (KEYNOTE-006, KEYNOTE-001 [19,20]), as well as of prior observational studies of pembrolizumab therapy for advanced melanoma

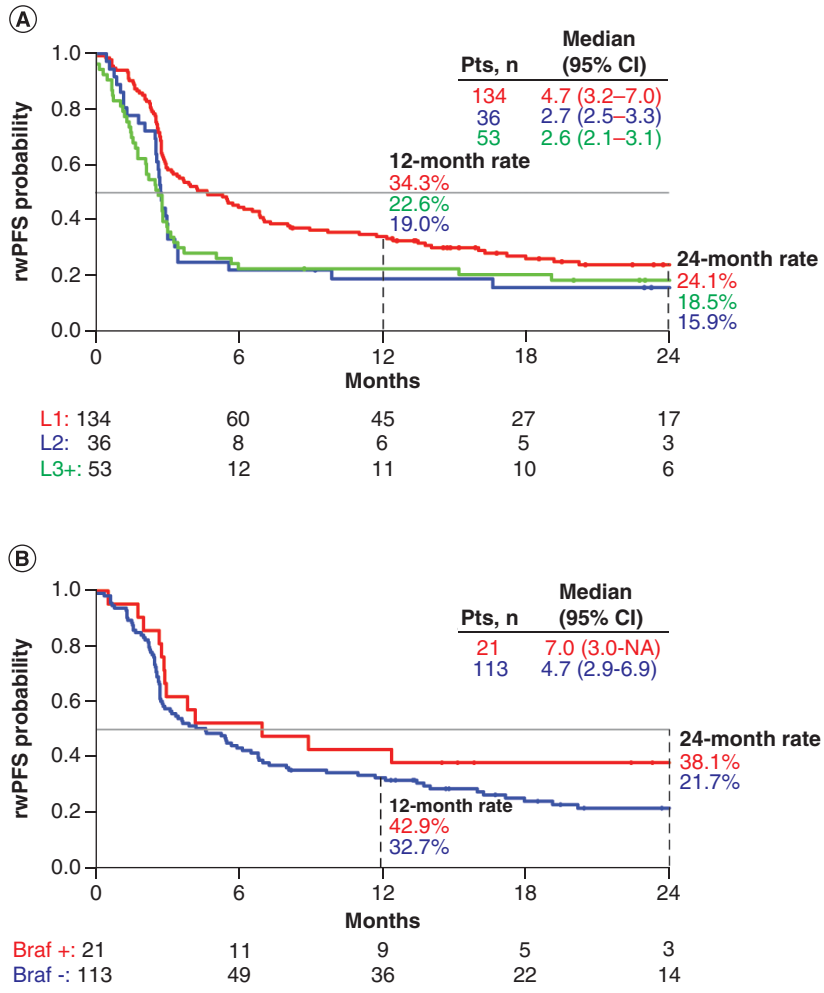


Figure 3. Kaplan-Meier estimates of real-world progression-free survival. (A) By pembrolizumab line of therapy and **(B)** by *BRAF* mutation status for patients treated with pembrolizumab in first line.
NR: Not reached.

Table 5. Pembrolizumab treatment history at data cut-off, by line of therapy.

Characteristics	Pembrolizumab line of therapy		
	First line (n = 134)	Second line (n = 36)	Third line/later (n = 53)
Rechallenge, n (%)	8 (6)	4 (11)	1 (2)
rwTTNT, median (95% CI), mo	13.1 (9.2–NR)	–	–
Discontinued pembrolizumab, n (%)	106 (79)	34 (94)	50 (94)
Reason for discontinuation			
Progression	62 (58)	21 (62)	26 (52)
Death	10 (9)	4 (12)	11 (22)
Toxicity	13 (12)	2 (6)	3 (6)
Medical decision	5 (5)	5 (15)	4 (8)
Not stated	9 (8)	1 (3)	2 (4)
Expected end of treatment[†]	5 (5)	1 (3)	4 (8)
Patient decision	2 (2)	0	0

[†]The 'expected end of treatment' corresponded to long responders (≥2 years) with complete response.
NR: Not reached; rwTTNT: Real-world time to next treatment line.

at community oncology practices in the USA [21,22]. At 5 years of follow-up in KEYNOTE-006, the median OS was 38.7 months (95% CI: 27.3–50.7) and estimated survival rates were 58 and 51% at 2 and 3 years, respectively, with first line pembrolizumab therapy [19]. In the present study, median OS was 32.6 months (95% CI: 20.3–NR), and estimated survival rates were 54 and 47% at 2 and 3 years, respectively, in the first line cohort. We note that our patient population included some patients who would not have been eligible for KEYNOTE-006 or other clinical trials, such as the 8% with poor performance status (ECOG PS ≥2) and those with active brain metastases.

Prior studies, both KEYNOTE trials and observational [19–22], recorded similar outcomes irrespective of *BRAF* mutation status in line with our findings in the first line setting. We observed 12-month survival rates of 76 and 69% for patients treated in first line with pembrolizumab for *BRAF*-mutant and *BRAF* wild-type tumors, respectively, and 24-month survival rates of 69 and 52%, respectively. Current European Society for Medical Oncology guidelines consider anti-PD-1 therapy as the standard of care for first line therapy of unresectable stage III/IV melanoma, regardless of *BRAF* mutation status [1]. However, the majority of patients with *BRAF*-mutant tumors in this study received pembrolizumab as second or third line/later therapy, soon after the launch of pembrolizumab for the indication.

With regard to the real-world end points, such as rwPFS and rwTR, while these were similar to end points used in clinical trials, the estimation methods differed and some were determined retrospectively, so these end points should be distinguished from, and not compared with, similar end points from clinical trial data [23]. Overall, we found that 21% of patients who received pembrolizumab in the first line setting had a recorded best rwTR of complete response. In their retrospective study of anti-PD-1 therapy for advanced melanoma, Betof Warner *et al.* [7] reported a complete response rate of 26% among the 396 patients, 40% of whom had previously received ipilimumab and 17% of whom had CNS metastasis at the start of anti-PD-1 therapy.

Databases such as MelBase serve as important sources of information about the outcomes of therapy for heterogeneous patient populations treated in oncology practice, outside of RCTs [12,24]. The strengths of this study include the large patient population with advanced melanoma treated in French clinical practice and the median follow-up of over 2 years. The 26 centers participating in MelBase include 24 academic and research hospitals, one public hospital and one nonprofit center dedicated to cancer treatment, thus some of the best-regarded facilities for advanced melanoma treatment in France. The detailed, longitudinal clinical information in MelBase, with standardized data collection, enabled us to examine and describe patient characteristics overall and by treatment line, including individual treatment courses. Patients are followed prospectively after inclusion in MelBase at the time of advanced melanoma diagnosis. The few data that were missing included tumor histology for a third of patients overall and LDH level for approximately one-fifth of patients treated with pembrolizumab in second and third line/later.

As for any database study, a limitation is the possibility of missing data or recording errors. Moreover, we did not examine adverse events (AEs) in this study. A recent single-center French study (August 2014–April 2018) reported that the most common type of AEs were cutaneous AEs, occurring among 39 of 189 patients (21%) with metastatic melanoma treated with pembrolizumab or nivolumab [25]. These cutaneous AEs were generally manageable and associated with significantly better survival. Overall, in that study, 16 patients (8%) discontinued anti-PD-1 therapy because of a severe AE, two of them cutaneous AEs [25].

Further work is needed to study larger numbers of patients with long-term follow-up in clinical practice. Moreover, in light of the benefits recorded in clinical trials and recent approvals of anti-PD-1 agents as adjuvant therapy for high-risk stage III melanoma [26–28], future analyses in early treatment settings are needed, as well as studies following patients treated with adjuvant therapy in stage III who progress to stage IV. Our findings suggest that pembrolizumab may be less effective in second and third line/later settings; however, larger patient numbers are needed to analyze the effectiveness of pembrolizumab for previously treated melanoma, including for patients who received prior BRAF/MEK inhibitors. Other areas of interest for future research include outcomes by number of metastatic sites and outcomes for different patient subpopulations, including those with mucosal melanoma and those ≥70 years of age. Ongoing research in clinical practice, as well as in clinical trials, will help to address current and future questions about optimizing treatment for advanced melanoma.

MelBase enables longitudinal studies to describe patients' care paths over long time periods, with the goals of improving epidemiologic and scientific knowledge as well as medical management of advanced melanoma. The results of this study demonstrate the real-world value of pembrolizumab therapy in a large cohort of French patients with advanced melanoma. In addition, our findings highlight the fact that not all patients respond to treatment;

thus, there remains a continuing need for novel therapies for patients with advanced melanoma who had prior exposure to anti-PD-1 agents.

Summary points

- In France, pembrolizumab was first available for treating advanced melanoma under temporary use (early access) authorization starting in September 2015, and reimbursement conditions for pembrolizumab were first published on 10 January 2017.
- We used MelBase, the French national clinicobiological database for advanced melanoma, to study the real-world use of pembrolizumab therapy for treating advanced melanoma in France.
- Patients with advanced melanoma (nonuveal, unresectable stage III or stage IV) initiating pembrolizumab, outside of a clinical trial, from 1 April 2016 to 30 September 2017, were followed until 1 September 2019.
- The 223 eligible patients, of median age 67 years (range 20–90 years), included 114 men (51%) and the majority initiated pembrolizumab as first line therapy (134; 60%), while 36 initiated as second line (16%), and 53 as third line or later therapy (24%).
- Overall, most patients had European Cooperative Oncology Group (ECOG) performance status of 0 or 1 (17 [8%] had ECOG performance status $\geq$2); 50 (22%) had active or inactive brain metastases; 72 (32%) had an elevated lactate dehydrogenase level at the time of pembrolizumab initiation and the percentages with *BRAF*-mutant tumors in first, second and third line/later were 16, 78 and 83%, respectively.
- The median duration of follow-up at data cut-off was 25.3, 28.9 and 27.8 months in first, second and third line, respectively.
- Patients treated with pembrolizumab in first line experienced median OS of 32.6 months (95% CI: 20.3–NR) and 24-month survival rate of 54.2% (95% CI: 46.1–64.2), while those treated in second and third line/later experienced median overall survival of 14.4 months (8.6–NR) and 9.3 months (6.4–NR), respectively.
- The median real-world progression free survival rate for patients treated in first line was 4.7 months (95% CI: 3.2–7.0), in second line, 2.7 months (95% CI: 2.5–3.3), and in third line/later, 2.6 months (95% CI: 2.1–3.1).
- Best real-world tumor response of complete or partial response was recorded for pembrolizumab therapy in the first line setting for 66 patients (49%) and in second and third line/later for 14 (39%) and 14 (26%), respectively. Disease progression was recorded as best real-world tumor response for 37, 56 and 49% in first, second and third line/later, respectively.
- The results of this study demonstrate the real-world value of pembrolizumab therapy in a large cohort of French patients with advanced melanoma and a continuing need for novel therapies for patients with advanced melanoma who had prior exposure to anti-PD-1 agents.

Author contributions

E Casarotto, S Chandwani, B Oriano, E Scherrer, L Lévy-Bachelot and C Lebbé contributed toward conception and design of the study. B Oriano contributed toward data analysis. All authors contributed toward interpretation of findings, critical review and revision of the manuscript. They read and approved the final manuscript and agree to be accountable for all aspects of the work.

Financial & competing interests disclosure

This work was supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., NJ, USA. The funder of the study participated in development of the study design and funded the analysis of the data. All authors, including those employed by Merck, participated in the data interpretation and writing of the manuscript. Industrial partners supporting MelBase include Bristol-Myers Squibb, Roche, MSD, Amgen, and Novartis. E Casarotto was an employee of MSD France, Puteaux, France, at the time of this study. S Chandwani is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., NJ, USA and stockholder of Merck & Co., Inc., NJ, USA. L Mortier reports medical board membership and travel support from MSD, Roche, Bristol-Myers Squibb (BMS) and Novartis. C Dutriaux is clinical investigator, speaker or board participant for Novartis, BMS, MSD and Pierre Fabre. S Dalac reports honoraria from BMS, Novartis, MSD and Pierre Fabre; consultancy for BMS, Novartis and MSD; research funding support from BMS, Novartis and MSD; being on a speakers bureau for BMS; and travel and accommodations support from BMS. E Scherrer is an employee of MSD and stockholder of Merck & Co., Inc., NJ, USA; L Lévy-Bachelot, L Verdoni and G Farge are employees of MSD France, and L Lévy-Bachelot and L Verdoni are stockholders of Merck & Co., Inc., NJ, USA. C Allayous reports travel and accommodations support from Amgen, BMS and Roche. S Dalle reports institutional research grants from MSD, BMS and Roche; travel support from BMS, Pierre Fabre and MSD; and S Dalle spouse is an employee of Sanofi. C Lebbe reports honoraria from BMS, MSD, Novartis, Amgen, Roche, Pierre Fabre, Pfizer and Incyte; consultancy or advisory board membership for BMS, MSD, Novartis, Amgen, Roche and Avantis; being on a speakers bureau for BMS, Novartis, Amgen and Roche; research support received from Roche; travel and accommodations support from BMS, MSD. O Dereure and B Oriano report no relevant

conflicts of interest. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Editorial assistance was provided by EV Hillyer, DVM (freelance). This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., NJ, USA.

Ethical conduct of research

The de-identified dataset supporting the conclusions of this article was provided by MelBase. The MelBase protocol was approved by the French Ethics Committee (CPP Ile-de-france XI, number 12027, 2012), and patients provided written informed consent to be included in MelBase (clinicaltrials.gov number NCT02828202). The data remained de-identified throughout the analyses to protect patient confidentiality.

Open access

This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit http://creativecommons.org/licenses/by-nc-nd/4.0/

References

Papers of special note have been highlighted as: • of interest

1. Michielin O, van Akkooi ACJ, Ascierto PA, Dummer R, Keilholz U. Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 30(12), 1884–1901 (2019).

• **Most recent European consensus guidelines for treating cutaneous melanoma.**

2. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA* 291(22), 2720–2726 (2004).

3. Miller RS, Wong JL. Using oncology real-world evidence for quality improvement and discovery: the case for ASCO's CancerLinQ. *Future Oncol.* 14(1), 5–8 (2018).

4. Berger ML, Curtis MD, Smith G, Harnett J, Abernethy AP. Opportunities and challenges in leveraging electronic health record data in oncology. *Future Oncol.* 12(10), 1261–1274 (2016).

5. Donia M, Kimper-Karl ML, Hoyer KL, Bastholt L, Schmidt H, Svane IM. The majority of patients with metastatic melanoma are not represented in pivotal Phase III immunotherapy trials. *Eur. J. Cancer* 74, 89–95 (2017).

• **Danish study comparing eligibility criteria of melanoma clinical trials with characteristics of real-world patients with melanoma.**

6. Jansen YJL, Rozeman EA, Mason R *et al.* Discontinuation of anti-PD-1 antibody therapy in the absence of disease progression or treatment limiting toxicity: clinical outcomes in advanced melanoma. *Ann. Oncol.* 30(7), 1154–1161 (2019).

• **Observational study of outcomes for patients with advanced melanoma after discontinuation of pembrolizumab or nivolumab therapy.**

7. Betof Warner A, Palmer JS, Shoushtari AN *et al.* Long-term outcomes and responses to retreatment in patients with melanoma treated with PD-1 blockade. *J. Clin. Oncol.* 38(15), 1655–1663 (2020).

8. Whitman ED, Scherrer E, Ou W, Krepler C. Outcomes of retreatment with anti-PD-1 monotherapy after response to first course in patients with cutaneous melanoma. *Future Oncol.* 16(20), 1441–1453 (2020).

9. Moser JC, Chen D, Hu-Lieskovan S *et al.* Real-world survival of patients with advanced BRAF V600 mutated melanoma treated with front-line BRAF/MEK inhibitors, anti-PD-1 antibodies, or nivolumab/ipilimumab. *Cancer Med.* 8(18), 7637–7643 (2019).

10. Kandel M, Dalle S, Bardet A *et al.* Quality-of-life assessment in French patients with metastatic melanoma in real life. *Cancer* 126(3), 611–618 (2020).

11. Vallet A, Oriano B, Mortier L *et al.* Association of time from primary diagnosis to first distant relapse of metastatic melanoma with progression of disease and survival. *JAMA Dermatol.* 155(6), 673–678 (2019).

12. Follow-up of a national cohort of melanoma stage IV and unresectable stage III patients (MelBase; ClinicalTrials.gov Identifier NCT02828202). https://clinicaltrials.gov/ct2/show/NCT02828202

13. Kandel M, Allayous C, Dalle S *et al.* Update of survival and cost of metastatic melanoma with new drugs: estimations from the MelBase cohort. *Eur. J. Cancer* 105, 33–40 (2018).

• **Prior study using the MelBase database to examine survival data and costs for patients with advanced melanoma.**

14. Institut National du Cancer. Suivi d'une cohorte de patients atteints de mélanome stade IV ou stade III inopérable, MELBASE. http://lesdonnees.e-cancer.fr/Projets-de-Recherche/Suivi-d-une-cohorte-de-patients-atteints-de-melanome-stade-IV-ou-stade-III-inoperable-MELBASE

15. Schwartz LH, Litiere S, de Vries E *et al.* RECIST 1.1-update and clarification: From the RECIST committee. *Eur. J. Cancer* 62, 132–137 (2016).

16. Gebhardt C, Ascierto P, Atkinson V, Corrie P, Dummer R, Schadendorf D. The concepts of rechallenge and retreatment in melanoma: a proposal for consensus definitions. *Eur. J. Cancer* 138, 68–76 (2020).

17. The R Foundation for Statistical Computing. Multivariate imputation by chained equations (MICE), v3.13.0. https://cran.r-project.org/web/packages/mice/mice.pdf

18. American Joint Committee on Cancer. *AJCC Cancer Staging Manual* (*7th Edition*). Springer, NY, USA (2010).

19. Robert C, Ribas A, Schachter J *et al.* 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.* 20(9), 1239–1251 (2019).

20. Hamid O, Robert C, Daud A *et al.* Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. *Ann. Oncol.* 30(4), 582–588 (2019).

- **Long-term follow-up reported for 655 patients with advanced melanoma who received pembrolizumab as first line or later line of therapy in the KEYNOTE-001 clinical trial.**

21. Liu FX, Ou W, Diede SJ, Whitman ED. Real-world experience with pembrolizumab in patients with advanced melanoma: a large retrospective observational study. *Medicine (Baltimore)* 98(30), e16542 (2019).

- **Large real-world study in the USA of outcomes for 532 patients prescribed pembrolizumab as first line or later line of therapy.**

22. Cowey CL, Liu FX, Black-Shinn J *et al.* Pembrolizumab utilization and outcomes for advanced melanoma in US community oncology practices. *J. Immunother.* 41(2), 86–95 (2018).

23. Robert C, Ribas A, Hamid O *et al.* Durable complete response after discontinuation of pembrolizumab in patients with metastatic melanoma. *J. Clin. Oncol.* 36(17), 1668–1674 (2018).

24. Casarotto E, Noize P, Gouverneur A *et al.* Overview of French databases available for studying anticancer drugs in real-life setting. *Fundam. Clin. Pharmacol.* 35(1), 76–85 (2021).

25. Bottlaender L, Amini-Adle M, Maucort-Boulch D, Robinson P, Thomas L, Dalle S. Cutaneous adverse events: a predictor of tumour response under anti-PD-1 therapy for metastatic melanoma, a cohort analysis of 189 patients. *J. Eur. Acad. Dermatol. Venereol.* 34(9), 2096–2105 (2020).

26. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). EMA/CHMP/706955/2018 chmp-post-authorisation-summary-positive-opinion-keytruda-ii-47_en.pdf

27. Eggermont AMM, Blank CU, Mandala M *et al.* Longer follow-up confirms recurrence-free survival benefit of adjuvant pembrolizumab in high-risk Stage III melanoma: updated results from the EORTC 1325-MG/KEYNOTE-054 trial. *J. Clin. Oncol.* 38(33), 3925–3936 (2020).

28. Weber J, Mandala M, Del Vecchio M *et al.* Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N. Engl. J. Med.* 377(19), 1824–1835 (2017).