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Resistance to anti-PD-1 immunotherapy for stage III and IV melanoma: a global chart review study

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ABSTRACT

Background Anti-programmed cell death protein 1 (PD-1) immunotherapy has revolutionized the treatment of stage III and IV melanoma. Real-world data on its resistance is needed to facilitate the development of combinatorial approaches to overcome anti-PD-1 resistance.

Objectives To characterize anti-PD-1 resistance and assess whether progressive disease assigned by clinicians is concordant with scan data assessed by independent central reviewers (ICR).

Methods A retrospective chart review was conducted in adult patients with stage III/IV melanoma who initiated anti-PD-1 therapy from January 2018 until 12 months before the start of data collection at 22 sites across six countries. Primary resistance and late relapse in the adjuvant setting, and primary, secondary resistance, and late progression in the advanced setting were assigned using *Society for Immunotherapy of Cancer* definitions. Demographic and clinical characteristics by type of resistance were compared with appropriate univariate tests. Time to resistance (TTR) and overall survival were analyzed using Kaplan-Meier. To compare the concordance of progression assigned by clinicians and ICR, the positive predictive value (PPV) was calculated in a subset of patients.

Results Of 981 eligible patients, 738 were included. In the adjuvant setting (n=240), 53 (22.1%) patients developed primary resistance and 60 (25.0%) experienced late relapse. In the advanced setting (n=498), 222 (44.6%), 50 (10.0%), and 64 (12.9%) patients developed primary, secondary resistance, and late progression. Type of resistance significantly differed by country, race, type of *BRAF* mutation, and PD-L1 expression in both settings; and by sex, disease stage and tumor thickness in the adjuvant setting only ($p<0.05$). Mean (SD) TTR was 47.7 (1.3) and 24.2 (1.0) months in the adjuvant and advanced setting, respectively. Patients with primary resistance had the poorest overall survival. The PPV of progression assigned by clinicians was 87.2% (95% CI 72.6% to 95.7%).

Conclusions This study showed that a substantial proportion of patients with melanoma receiving anti-PD-1 therapy in the adjuvant (47.1%) and advanced (67.5%) settings developed resistance or late relapse/progression, highlighting an unmet medical need. Real-world clinical practice provided a reliable assessment of progression. Factors associated with different types of resistance were identified. Further study is warranted to evaluate their impact on patient risk stratification. (Graphical abstract)

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Many patients with melanoma fail to respond to anti-programmed cell death protein 1 (PD-1) treatment or relapse after initial clinical benefit, and there is limited real-world data on the distribution and characteristics of such patients.

WHAT THIS STUDY ADDS

⇒ This real-world study applied harmonized *Society for Immunotherapy of Cancer* definitions of PD-1 resistance in adjuvant and advanced stage III/IV melanoma and identified-associated clinical and molecular factors. Resistance or late relapse/progression was common, with patterns varying by country, race, *BRAF* mutation type, PD-L1 expression and, in the adjuvant setting, by sex, stage, and tumor thickness. There was a high concordance between clinician and independent central review assessments of progression.

HOW THIS MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights a global unmet need in PD-1-resistant melanoma and potential factors for patient stratification and supports the use of clinician-assessed evaluation of progression in future studies.

BACKGROUND

Although immune checkpoint inhibitors (ICIs) such as anti-programmed cell death protein 1 (PD-1) have revolutionized the treatment of melanoma, a significant proportion of patients fail to respond initially (primary resistance) or relapse after an initial clinical benefit.[1 2] Data from clinical trials suggest that in the advanced setting, primary resistance occurs in approximately 30% of melanomas treated with anti-PD-1 monotherapy and 25% of melanomas treated with ipilimumab and nivolumab combination therapy.[2] Secondary resistance is reported to occur in 17% of patients with complete response and 54% of patients with partial response to anti-PD-1 monotherapy, and 20% of those treated with ICI combination therapy.[2] Data from phase II-III trials of anti-PD-1 therapy in the adjuvant setting suggest recurrence rates of 69% (stage IV at 4 years), 45% (stage III at 5 years), and 19% (stage II at 2 years).[2] For combined immune checkpoint blockade with a PD-1 and a cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor, recurrence rates were 36% after 4 years in stage IV melanoma.[2]

Although the percentage of patients with primary resistance was broadly consistent across clinical trials, high variability was found for observational studies, likely due to the different study populations and lines of therapy (LOT) assessed. Only four studies provided real-world data on secondary resistance. Observational resistance data from the adjuvant setting are even more sparse, particularly for earlier recurrence (primary resistance) versus late relapse.[3] A recent study (data up to 2022) characterized recurrence in 711 patients from 17 international sites and determined that 48% of patients treated with anti-PD-1 in the adjuvant setting had recurrence within 6 months of starting therapy.[3]

However, prior published studies have used their own definitions of resistance, resulting in a lack of cohesion and difficulty comparing and interpreting resistance results. In 2020, the *Society for Immunotherapy of Cancer* (*SITC*) published consensus definitions for resistance to anti-PD-1 single-agent therapy, comprising primary resistance and late relapse (adjuvant setting), and primary, secondary resistance, and late progression (advanced setting).[4] In 2023, this was followed by *SITC* consensus definitions for resistance to combination therapy.[5] In a recent systematic review exploring resistance in advanced melanoma, whereby most of the 55 identified studies did not specify a resistance definition, *SITC* definitions were applied by the reviewers based on additional variables/information.[1]

To our knowledge, this chart review study has, for the first time, used harmonized *SITC* definitions to evaluate and characterize anti-PD-1 resistance in both adjuvant and advanced settings by pooling data from multiple sites and countries in a retrospective chart review. Patient clinical and demographic characteristics and survival were described and compared by type of resistance. Concordance of melanoma progression defined by site clinicians versus independent central reviewers (ICR) was also assessed (online supplemental graphical abstract).

METHODS

Study design and participants

This was a multicountry, descriptive, retrospective chart review cohort study conducted in dermatology and medical oncology departments from 22 sites in the USA, France, Germany, the UK, Australia and South Korea. Data collection was from March 17, 2023, to May 31, 2024.

Patients who initiated anti-PD-1 therapy either as monotherapy or in combination for histologically confirmed cutaneous stage III or IV melanoma from January 1, 2018, until 12 months before site-specific start of data collection were included. Patients were aged ≥18 years, had at least 12 months of follow-up (unless due to death), and had received at least two cycles of anti-PD-1 therapy as part of routine clinical practice in the adjuvant (fully resected stage III or IV) or advanced (unresected stage III or IV) settings.

A subset of patients with advanced melanoma was derived from the main cohort to assess concordance of disease progression defined clinically or by Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1 as assigned by the site clinicians, as compared with the assessment by ICR using only RECIST V.1.1 criteria from scans. All participating sites in this subset routinely used RECIST V.1.1 in clinical practice. However, the use of RECIST V.1.1 was not a requirement for patient inclusion, as the assessment of progression could also be based on clinical criteria. Patients in this subset were eligible if they participated in the main cohort and had a baseline/nadir scan, a scan documenting progression, and a follow-up scan at least 4 weeks after the scan documenting progression. A 4-week follow-up scan was not required for inclusion of patients with rapid progression (as defined by the study sites).

Study outcomes

The primary outcomes for this study were the percentage and clinical/demographic characteristics of melanoma patients developing anti-PD-1 resistance. Type of resistance (primary resistance and late relapse in the adjuvant setting, and primary, secondary resistance and late progression in the advanced setting) was defined following the published *SITC* guidelines for the adjuvant and advanced settings[4] (online supplemental figures 1 and 2). Clinical and demographic characteristics included country, age, sex, race, body mass index (BMI), primary tumor characteristics (eg, tumor stage, Breslow thickness, ulceration), Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance status, lymphedema, comorbidities, biomarkers (eg, V-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) mutations, programmed cell death protein 1 ligand (PD-L1) status), and index LOT (anti-PD-1 monotherapy or combination therapy). Time to resistance (TTR) and overall survival (OS) were defined

as time from the index date (initiation of anti-PD-1) to date of first relapse/progression and the date of death/end of follow-up, respectively. TTR by diagnosis stage and OS by type of resistance and diagnosis stage were reported.

In a subset of study patients with advanced melanoma, the positive predictive value (PPV) was applied to compare progressive disease assigned by site clinicians (as per local criteria/RECIST V.1.1 guidelines) to ICR assessment of radiological scans using RECIST V.1.1. PPV was defined as the probability that patients identified as having progressive disease by the site clinicians did indeed have progressive disease as confirmed by independent central review.

Statistical analysis

The data were analyzed using SAS V.9.4 (2025; SAS Institute, Cary, North Carolina, USA). A target sample size of 750 patients was set to allow for the estimation of a proportion of 10% with a precision of ±2.15% at a 95% confidence level. This calculation was based on binomial distribution, to ensure sufficient statistical precision for the overall study population and subgroup analyses. Of this sample, a maximum of 25–35% could be from the adjuvant setting.

The percentages of patients with melanoma with primary resistance and late relapse in the adjuvant setting, and primary, secondary resistance, and late progression in the advanced setting were calculated. TTR and OS were analyzed using Kaplan-Meier, and the log-rank test was used to compare differences in TTR by diagnosis stage and OS by type of resistance. Clinical and demographic characteristics were described by type of resistance. Univariate analyses were intended to explore and identify potential differences in patient and treatment characteristics by type of resistance. χ^2 or Fisher's exact tests were used to compare categorical variables by type of resistance; t-test and analysis of variance or Mann-Whitney U and Kruskal-Wallis tests were used for continuous variables (tests not conducted for index LOT). A two-sided p value of <0.05 was used as a threshold for statistical significance.

PPV was calculated using the formula: PPV=TP/(TP+FP)×100, where TP represents true positives defined as patients with progressive disease allocated by both clinicians and ICR, and FP represents false positives as patients with progressive disease assigned only by the site clinicians.

RESULTS

Study population

A total of 981 patients comprised the eligible population (figure 1). The study protocol specified a target sample size of 750 patients, with a maximum of 25–35% from the adjuvant setting. Screening and enrollment of patients were conducted consecutively at each site, and adjuvant and advanced patients were screened independently. Consecutive eligible adjuvant patients were enrolled starting from January 01, 2018, until the site-specific quota was reached, and consecutive eligible patients with advanced melanoma were enrolled starting from January 01, 2018, until the site-level target was met. Enrollment was thus concluded on reaching the global target, despite additional eligible patients. Of the 751 enrolled patients, 13 were excluded due to invalid primary analysis data (progression could not be determined/treatment sequence could not be constructed), resulting in a full analysis set (FAS) of 738 patients. The FAS comprised two groups: patients treated in the adjuvant setting (n=240, median follow-up 48.6 months) and the advanced setting (n=498, median follow-up 32.3 months). Of the included patients, most were male (60.8% and 64.5% in the adjuvant and advanced settings, respectively), white (82.3% and 73.7%), and aged ≥50 at index date (78.8% and 86.5%). In the adjuvant setting, 81 (33.8%) of patients were contributed from the USA, 46 (19.2%) from Germany, 42 (17.5%) from France, 33 (13.8%) from the UK, 25 (10.4%) from Australia, and 13 (5.4%) from South Korea. In the advanced setting, 188 (37.8%) of patients were contributed from sites in the USA, 83 (16.7%) from France, 74 (14.9%) from Germany, 66 (13.3%) from the UK, 50 (10.0%) from Australia, and 37 (7.4%) from South Korea. Except in South Korea, where all patients were of Asian race, >65% of patients from each country, in each setting, were white. All Asian patients in the FAS (n=13 in the adjuvant setting, n=37 in the advanced setting) were from South Korea.

To assess concordance of progression, 45 patients were included in a subset derived from the 118 advanced setting patients enrolled at sites using RECIST V.1.1 criteria.

Clinical and demographic characteristics by resistance

Among 240 patients in the adjuvant setting, 127 (52.9%) patients had no progression, while primary resistance was observed in 53 (22.1%) patients, and late relapse occurred in 60 (25.0%) patients. Statistically significant differences in resistance were observed by sex, race, and country (table 1). 45 (30.8%) males developed late relapse compared with 15 (16.0%) females, and 35 (24.0%) males developed primary resistance compared with 18 (19.1%) females (p=0.007). A greater proportion of primary resistance was observed among Asian patients as compared with white patients (n=8; 61.5% vs n=30; 18.4%) but experienced less late relapse (n=0; 0.0% vs n=46; 28.2%) (p<0.001). Eight (61.5%) patients in South Korea developed primary resistance, in comparison to five (6.2%) in the USA, and between 21.4% and 32.0% for Australia and European countries. The proportion of patients who experienced late relapse varied from 0 (0.0%) patients in South Korea to 15 (32.6%) patients in Germany. No significant differences in rates of resistance were shown for other demographic or clinical factors (age, BMI, ECOG performance status, Karnofsky performance status, lymphedema, and comorbidities) (online supplemental table 1).

Among 498 patients in the advanced setting, primary resistance was observed in 222 (44.6%) of patients, while

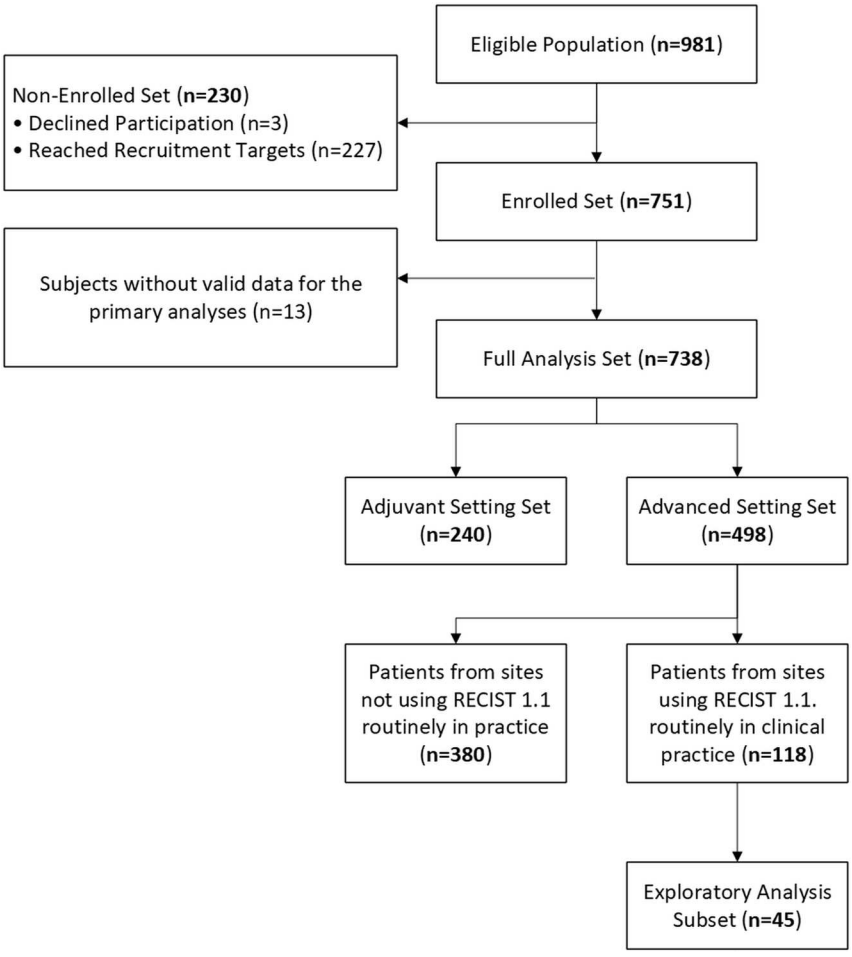

Figure 1 Flowchart of included patients. RECIST, Response Evaluation Criteria in Solid Tumors.

secondary resistance was found in 50 (10.0%), and late progression in 64 (12.9%). Resistance varied significantly by race and country only (table 1). 18 (48.6%) Asian patients developed primary resistance, 14 (37.8%) secondary resistance, 2 (5.4%) late progression versus 125 (40.8%), 27 (8.8%), 39 (12.7%) of white patients (p<0.001). 14 (37.8%) patients from South Korea developed secondary resistance, in comparison to between 4.0% and 15.2% for other countries (p<0.001). The proportion of patients that experienced primary resistance ranged from 73 (38.8%) patients in the USA to 42 (56.8%) patients in Germany, and late relapse varied from 2 (5.4%) patients in South Korea to 17 (20.5%) patients in Germany. No significant differences in rates of resistance were shown for other demographic or clinical factors (online supplemental table 2).

Tumor characteristics by resistance

In the adjuvant setting, type of resistance varied significantly by tumor stage (IIIA vs IIIB vs IIIC vs IIID vs unknown vs IV, p=0.021) and tumor Breslow thickness (mean thickness of 4.3, 4.5, and 3.7 mm for patients with primary resistance, late relapse or no relapse, respectively (p=0.040) (table 2). However, these significant differences by stage and Breslow thickness were not observed in the advanced setting. Additionally, no significant differences were found for resistance regarding the primary tumor site, mitotic index, ulceration, or presence of lymphedema in both settings (online supplemental table 3).

Biomarker results by resistance

In the adjuvant setting, 86.3% (207/240) had available information on biomarker testing. *BRAF* mutation testing (yes/no) and the type of *BRAF* mutation varied significantly by type of resistance (table 3). All patients with primary resistance were tested for the *BRAF* mutation (n=51), compared with 96 (94.1%) patients with no relapse and 47 (87.0%) patients with late relapse (p=0.019). Regarding types of *BRAF* mutation, no mutation was reported in 58 (60.4%), 20 (39.2%), and 25 (53.2%) of patients with no progression, primary resistance, and late progression, respectively. Interestingly, a greater proportion of patients with primary resistance (n=10; 19.6%) or late relapse (n=13; 27.7%) had non-V600 *BRAF* mutations versus those with no relapse (n=6; 6.3%) (p<0.001). Only 21 (20.6%) patients with no relapse had been tested for PD-L1 expression, compared with 5 (9.8%) patients with primary resistance and 7 (13.0%) patients with late relapse (p=0.014). Among patients who had been tested for PD-L1 expression, 17 (81.0%) patients with no relapse had positive PD-L1 expression, in comparison to 3 (60.0%) patients who developed primary

Table 1 Patient characteristics and disease history at index date by type of resistance to anti-PD-1 in the adjuvant (N=240) and advanced setting (N=498)

Characteristics, N (%)	Adjuvant setting			Advanced setting			
	No relapse (N=127)	Primary resistance (N=53)	Late relapse (N=60)	No progression (N=162)	Primary resistance (N=222)	Secondary resistance (n=50)	Late progression (n=64)
Country	**P value*<0.001**			**P value*<0.001**			
Australia	9 (36.0)	8 (32.0)	8 (32.0)	19 (38.0)	20 (40.0)	2 (4.0)	9 (18.0)
France	21 (50.0)	9 (21.4)	12 (28.6)	23 (27.7)	37 (44.6)	6 (7.2)	17 (20.5)
Germany	17 (37.0)	14 (30.4)	15 (32.6)	19 (25.7)	42 (56.8)	5 (6.8)	8 (10.8)
South Korea	5 (38.5)	8 (61.5)	0 (0.0)	3 (8.1)	18 (48.6)	14 (37.8)	2 (5.4)
UK	19 (57.6)	9 (27.3)	5 (15.2)	19 (28.8)	32 (48.5)	10 (15.2)	5 (7.6)
USA	56 (69.1)	5 (6.2)	20 (24.7)	79 (42.0)	73 (38.8)	13 (6.9)	23 (12.2)
Sex	**P value*=0.007**			**P value*=0.164**			
Male	66 (45.2)	35 (24.0)	45 (30.8)	109 (34.0)	135 (42.1)	38 (11.8)	39 (12.1)
Female	61 (64.9)	18 (19.1)	15 (16.0)	53 (29.9)	87 (49.2)	12 (6.8)	25 (14.1)
Race	**P value*<0.001**			**P value*<0.001**			
White/Caucasian	87 (53.4)	30 (18.4)	46 (28.2)	115 (37.6)	125 (40.8)	27 (8.8)	39 (12.7)
Asian	5 (38.5)	8 (61.5)	0 (0.0)	3 (8.1)	18 (48.6)	14 (37.8)	2 (5.4)
Other	0 (0.0)	0 (0.0)	1 (100.0)	1 (12.5)	7 (87.5)	0 (0.0)	0 (0.0)
Unknown	14 (66.7)	6 (28.6)	1 (4.8)	20 (31.3)	35 (54.7)	3 (4.7)	6 (9.4)
Missing†	21	9	12	23	37	6	

*χ^2 or Fisher's exact tests used for comparison of categorical variables depending on the appropriateness. Continuous variables compared with t-test and ANOVA, or Mann-Whitney U and Kruskal-Wallis tests as non-parametric approaches if normality of the distributions is not verified with the Shapiro-Wilk test.
†Percentages for missing values are not applicable and therefore not reported.
ANOVA, analysis of variance; PD-1, programmed cell death protein 1.

resistance and 2 (28.6%) of those with late progression (p=0.020).

In the advanced setting, 87.8% (437/498) of patients had available information on biomarker testing. The type of *BRAF* mutation varied significantly by type of resistance (p=0.026) (table 3). The most common reported *BRAF* mutation was the V600E mutation. No mutation was reported in 62 (49.6%), 108 (60.3%), 21 (53.8%), and 27 (56.3%) of patients with no progression, primary resistance, secondary resistance, and late progression, respectively (p=0.026). All tested patients with late progression had positive PD-L1 expression (n=9; 100%) in comparison to 15 (50.0%) patients that developed primary resistance and 18 (78.3%) with no progression (p=0.009).

However, the association of resistance with PD-L1 expression should be interpreted with caution since only 13.8% (33/240) and 14.3% (71/498) of patients were tested for PD-L1 expression in the adjuvant and advanced settings, respectively. In addition, biomarker results for defective DNA mismatch repair, tumor mutation burden, gene expression profile, and interferon-γ signature were available for <5 patients for some stratifications when described by type of resistance. Therefore, their associations with resistance were not evaluated, and these results are not presented.

Index LOT by resistance

In the adjuvant setting, 234 (97.5%) patients received anti-PD-1 as monotherapy as the index LOT, while only 6 (2.5%) received anti-PD-1 in combination with anti-CTLA-4 (all stage IV). Due to the small sample size in anti-PD-1-based combination therapy, the association of index LOT components with resistance should be interpreted with caution (online supplemental table 4).

In the advanced setting, 314 (63.1%) received anti-PD-1 monotherapy as the index LOT, 179 (35.9%) received anti-PD-1 in combination with anti-CTLA-4, and 5 (1.0%) received anti-PD-1 in other combinations. No significant differences in type of resistance were found between anti-PD-1 monotherapy and anti-PD-1-based combination therapy in the advanced setting (online supplemental table 4).

TTR by stage

No significant differences in TTR were observed by stage in both settings (figure 2). In the adjuvant setting, 35 (31.0%) patients developed resistance within 6 months, 30 (26.5%) between 6 and 12 months, and 48 (42.5%) more than 12 months after the index date. The TTR (mean±SD) was 48.1±1.4 months for stage III patients, compared with 20.9±1.4 months for stage IV patients

Table 2 Tumor characteristics before or at index date by type of resistance and setting

Tumor characteristics	Adjuvant setting			Advanced setting			
	No relapse (N=127)	Primary resistance (N=53)	Late relapse (N=60)	No progression (N=162)	Primary resistance (N=222)	Secondary resistance (N=50)	Late progression (N=64)
Disease stage, N (%)	P value*=0.021			P value*=0.926			
Stage III	111 (52.6)	45 (21.3)	55 (26.1)	25 (36.8)	30 (44.1)	3 (4.4)	10 (14.7)
Stage IIIA	11 (61.1)	5 (27.8)	2 (11.1)	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)
Stage IIIB	47 (64.4)	12 (16.4)	14 (19.2)	6 (40.0)	6 (40.0)	1 (6.7)	2 (13.3)
Stage IIIC	52 (45.6)	27 (23.7)	35 (30.7)	16 (35.6)	20 (44.4)	2 (4.4)	7 (15.6)
Stage IIID	0 (0.0)	1 (20.0)	4 (80.0)	1 (20.0)	3 (60.0)	0 (0.0)	1 (20.0)
Unknown	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage IV	16 (55.2)	8 (27.6)	5 (17.2)	137 (31.9)	192 (44.7)	47 (10.9)	54 (12.6)
Breslow thickness	P value*=0.040			P value*=0.578			
n, missing	98, 29	34, 19	53, 7	85, 77	123, 99	19, 31	34, 30
Mean (SD)	3.7 (3.2)	4.3 (2.7)	4.5 (3.2)	4.2 (5.0)	5.1 (6.5)	3.2 (2.7)	4.6 (4.5)
Median (Q_1, Q_3)	2.7 (1.5, 4.5)	3.9 (2.3, 6.0)	3.5 (2.3, 6.0)	2.8 (1.7, 4.5)	3.0 (1.7, 6.0)	2.3 (1.6, 3.3)	3.0 (1.5, 7.0)

*χ^2 or Fisher's exact tests used for comparison of categorical variables depending on the appropriateness. Continuous variables compared with t-test and ANOVA, or Mann-Whitney U and Kruskal-Wallis tests as non-parametric approaches if normality of the distributions is not verified with the Shapiro-Wilk test. p values are for the differences for each of the substages of stage III and IV.
ANOVA, analysis of variance; Q1, percentile 25; Q3, percentile 75.

(p=0.43) (figure 2C). In the advanced setting, 217 (64.6%) patients developed resistance within 6 months, 54 (16.1%) between 6 and 12 months, and 65 (19.3%) more than 12 months after the index date. The TTR (mean±SD) was 13.6±1.2 months for stage III patients, compared with 23.9±1.0 months for stage IV patients (p=0.37) (figure 2D).

OS by type of resistance

In the adjuvant setting, no significant difference in OS was observed for stage III (96.2% alive at 12 months; mean±SD of OS, 52.5±1.2 months, compared with stage IV (96.4% alive at 12 months; mean±SD of OS, 38.4±1.8 months) (p=0.514). Patients without relapse showed the most favorable survival outcomes (98.4% alive at 12 months; mean±SD of OS, 56.1±0.8 months), while those with primary resistance exhibited the poorest survival outcomes (88.7% alive at 12 months, mean±SD of OS, 42.4±3.1 months) (p<0.001) (figure 3A).

In the advanced setting, no significant difference in OS was observed for stage III (82.4% alive at 12 months; mean±SD of OS, 33.1±1.8 months), compared with stage IV (82.4% alive at 12 months; mean±SD of OS, 40.3±1.1 months) (p=0.320). Patients without progression demonstrated the most favorable survival outcomes (92.0% alive at 12 months; mean±SD of OS, 31.6±0.7 months) compared with those with primary resistance (67.4% alive at 12 months; mean±SD of OS, 30.6±1.5 months) and secondary resistance (96.0% alive at 12 months; mean±SD of OS 38.5±2.9 months) (p<0.001) (figure 3B).

Concordance of progression in advanced melanoma

Among 45 patients (100.0%) classified as having progressive disease by site investigators/clinicians, ICR confirmed progression in 34 (75.6%) patients. ICR were unable to determine progression/non-progression for six patients and these patients were therefore excluded from the denominator of the PPV calculation, leading to an estimated PPV of 87.2% (95% CI 72.6% to 95.7%).

DISCUSSION

In this large, global real-world evidence study, approximately half of patients in the adjuvant setting developed primary resistance (22.1%) or late relapse (25.0%), and almost three quarters of patients in the advanced setting developed primary resistance (44.6%), secondary resistance (10.0%) or late progression (12.9%), during a median of 48.6 and 32.3 months of follow-up, respectively.

Comparing resistance rates and time to resistance across studies is challenging due to differences in patient characteristics and duration of follow-up, as well as variations in the definitions of resistance. However, our findings are broadly consistent with those in the literature. In a recent systematic review, resistance in advanced melanoma ranged from 25.04% to 81.25% for patients treated with anti-PD-1 monotherapy and from 15.79% to 73.33% for those on combination therapies.[1] In a real-world US study involving patients with unresectable or metastatic disease (advanced setting) treated with monotherapy only without definitions of primary and secondary resistance (median follow-up of 33 months), 34% of patients

Table 3 Patient biomarker results before or at index date by type of resistance and setting*

Biomarkers, N (%)	Adjuvant setting			Advanced setting			
	No relapse (N=102)	Primary resistance (N=51)	Late relapse (N=54)	No progression (N=137)	Primary resistance (N=200)	Secondary resistance (N=45)	Late progression (N=55)
BRAF mutation testing	**P value*=0.019**			**P value†=0.717**			
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
No	6 (5.9)	0 (0.0)	7 (13.0)	12 (8.8)	20 (10.0)	6 (13.3)	7 (12.7)
Yes	96 (94.1)	51 (100.0)	47 (87.0)	125 (91.2)	179 (89.5)	39 (86.7)	48 (87.3)
Type of BRAF mutation	**P value*<0.001**			**P value†=0.026**			
V600E	26 (27.1)	20 (39.2)	5 (10.6)	31 (24.8)	42 (23.5)	15 (38.5)	13 (27.1)
V600K	1 (1.0)	0 (0.0)	2 (4.3)	11 (8.8)	6 (3.4)	0 (0.0)	0 (0.0)
V600D	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-V600 mutation	6 (6.3)	10 (19.6)	13 (27.7)	21 (16.8)	19 (10.6)	3 (7.7)	5 (10.4)
Other mutation	4 (4.2)	1 (2.0)	2 (4.3)	0 (0.0)	4 (2.2)	0 (0.0)	3 (6.3)
No mutation reported‡	58 (60.4)	20 (39.2)	25 (53.2)	62 (49.6)	108 (60.3)	21 (53.8)	27 (56.3)
PD-L1 expression testing	**P value*=0.014**			**P value†=0.829**			
Unknown	11 (10.8)	10 (19.6)	4 (7.4)	21 (15.3)	39 (19.5)	5 (11.1)	8 (14.5)
No	70 (68.6)	36 (70.6)	43 (79.6)	93 (67.9)	131 (65.5)	31 (68.9)	38 (69.1)
Yes	21 (20.6)	5 (9.8)	7 (13.0)	23 (16.8)	30 (15.0)	9 (20.0)	9 (16.4)
PD-L1 expression	**P value*=0.020**			**P value†=0.009**			
Unknown	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)
Negative	4 (19.0)	1 (20.0)	5 (71.4)	5 (21.7)	14 (46.7)	5 (55.6)	0 (0.0)
Positive	17 (81.0)	3 (60.0)	2 (28.6)	18 (78.3)	15 (50.0)	4 (44.4)	9 (100.0)

*This table presents data only for patients with valid data on biomarker testing.
†χ^2 or Fisher's exact tests used for comparison of categorical variables depending on the appropriateness. Continuous variables compared with t-test and ANOVA, or Mann-Whitney U and Kruskal-Wallis tests as non-parametric approaches if normality of the distributions is not verified with the Shapiro-Wilk test.
‡This category includes patients in whom BRAF testing was performed and no mutation was detected/reported in the medical record.
ANOVA, analysis of variance; PD-L1, programmed cell death protein 1 ligand.

responded initially to anti-PD-1 therapy.[6] While the methods differed with respect to the current study, the overall absence of progression in 32.5% of patients in the advanced setting in the current study (median follow-up of 2.7 years) is similar, lending support to the generalizability of the present study results. A recent study in the adjuvant setting (data up to 2022) characterized recurrence in 711 patients from 17 international sites and determined that 48% of patients treated with anti-PD-1 in the adjuvant setting recurred within 6 months of starting therapy, 23% between 6 and 12 months, 20% between 12 and 24 months and 8% after 24 months; that is, 99% of patients recurred during the follow-up period.[3] This is significantly higher than rates of primary resistance and late relapse estimated in the present study, likely due to differences in the study populations and endpoint definitions (ie, recurrence vs resistance/relapse). Future studies should consider using *SITC* definitions of resistance to facilitate the comparison of results in the literature.[1 4 5]

In this study, we observed a higher proportion of males who developed primary resistance or late relapse in the adjuvant setting. Some studies contradict this finding, supporting a better response to immunotherapy by men,[7 8] while others are inconclusive.[9 10] Differences in responses to immunotherapy between the sexes may be attributable to the modulatory action of estrogen over the immune response,[11 12] or the difference in expression of X-linked immune-related genes, which has been reported to drive the difference in response to ICI between the sexes.[13] However, additional clinical research is needed to understand these differences.

In addition, most Asian patients developed primary or secondary resistance in both the adjuvant (primary resistance only) and advanced settings, and a few developed late relapse or progression. This observation is consistent with documented differences in melanoma subtypes and genomic alterations across different races.[14] In Asian populations, acral and mucosal melanomas are the most common subtypes, whereas cutaneous melanoma predominates in white patients.[15 16] Importantly, acral and mucosal melanomas have shown lower responsiveness to ICIs such as toripalimab, ipilimumab, and pembrolizumab compared with cutaneous melanomas.[17–19] This may help

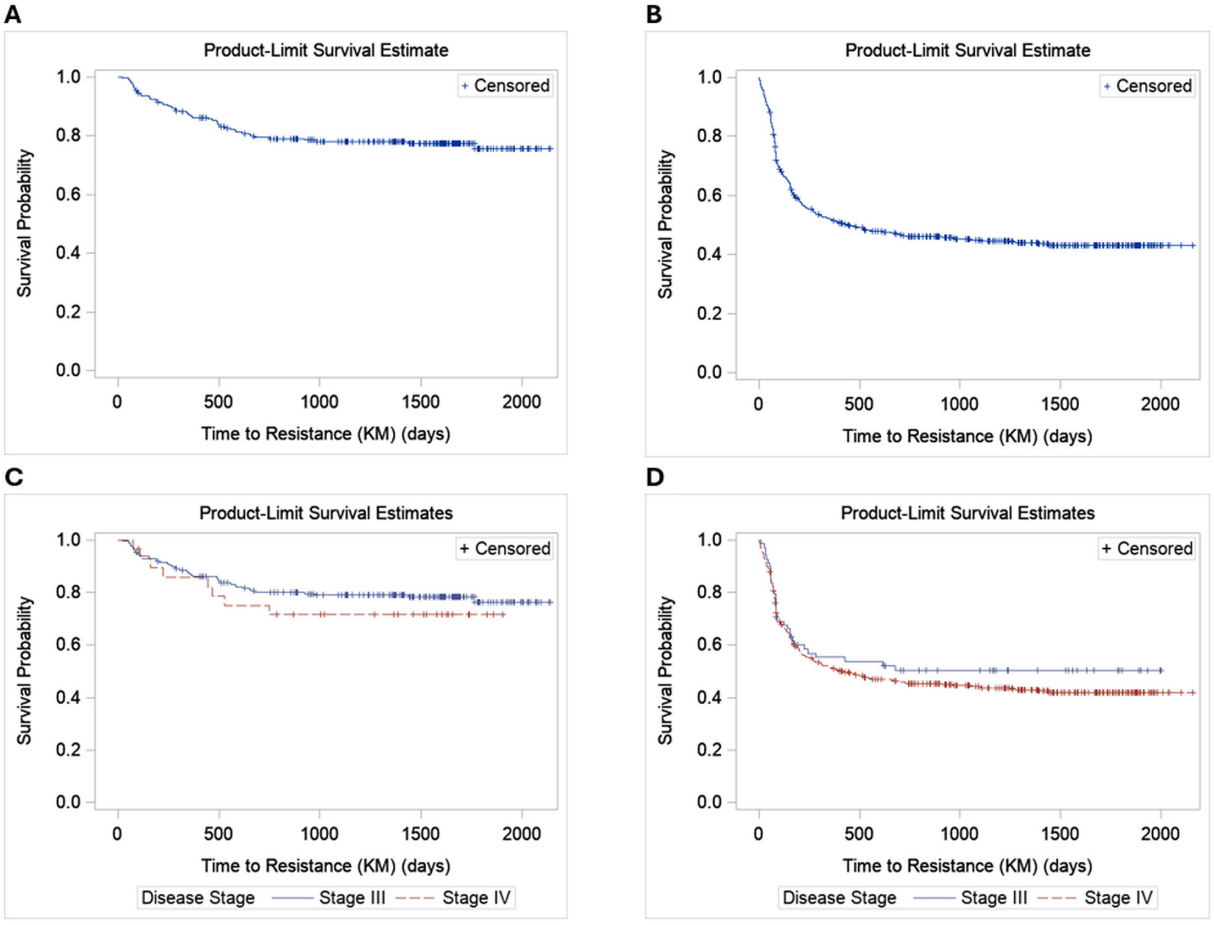

Figure 2 Time to resistance overall (A) in the adjuvant setting and (B) in the advanced setting; time to resistance by diagnosis stage (C) in the adjuvant setting and (D) in the advanced setting. KM, Kaplan-Meier.

to explain the higher proportion of Asian patients developing resistance in the present study. While the results of the present study should be interpreted considering the smaller sample size of Asian patients (n=13 in the adjuvant setting, n=37 in the advanced setting), the poorer prognosis highlights the need for further study to improve the management and treatment of melanoma in this population.[15] Of note, all Asian patients were from South Korea; therefore, these findings may be confounded by country-specific differences in melanoma diagnosis and management. Indeed, significant differences in resistance were observed by country in both settings. This was most pronounced for the adjuvant setting, whereby 61.5% of patients in South Korea developed primary resistance, in comparison to just 6.2% in the USA, and between 21.4% and 32.0% for Australia and European countries; likely reflecting different approaches to melanoma diagnosis and management, as well as differences in race by country.

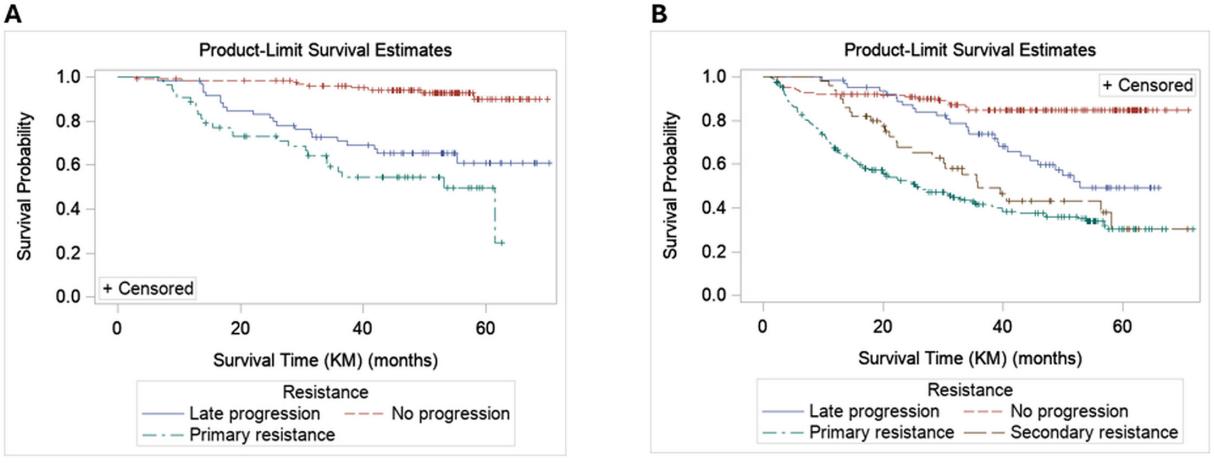

Figure 3 Overall survival by resistance in (A) the adjuvant setting and (B) the advanced setting. KM, Kaplan-Meier.

Data on melanoma subtype were not analyzed by country and, as a result, could not be directly linked to geographic differences in resistance in this study. References to acral and mucosal versus cutaneous melanoma are provided to offer epidemiological and biological context based on prior literature rather than to present findings derived from our analysis. Future real-world studies with melanoma subtype capture and broader geographic representation (eg, including Latin America, Africa) would help to further elucidate such differences.

In the adjuvant setting, patients receiving anti-PD-1 combination therapy (n=6) as index LOT had higher primary resistance rates as compared with those treated with anti-PD-1 monotherapy (66.7% vs 20.9%, respectively). Anti-PD-1-based combination therapy is not approved for use in the adjuvant setting. These patients received off-label treatment, as all were stage IV, and physicians may have opted to apply advanced-stage protocols for high-risk patients. However, these results should be considered with caution due to the small sample size of patients receiving combination anti-PD-1 therapy (n=6).

Patients with primary resistance exhibited the poorest OS, with an average of 42.3 months in the adjuvant setting, and 31.6 months in the advanced setting, as compared with those with secondary resistance, late relapse/progression, and no relapse/progression. However, these results should be interpreted with caution because the definition of resistance influences the findings. For example, in the advanced setting, patients with secondary resistance appear to have better OS than those with no progression, but this is because a key condition for being classified as having secondary resistance is having survived at least 6 months. This occurs to a lesser degree for late relapse (adjuvant setting) and late progression (advanced setting), as a key condition is having survived more than 12 weeks after the last dose of anti-PD-1 therapy. The interpretation of median survival time and the Kaplan-Meier figures provides a more accurate picture of survival, ultimately concluding that patients with primary and secondary resistance have a worse OS. Moreover, no differences were found in OS by stage, which highlights the efficacy of modern therapies like anti-PD-1.

The resistance phenotypes described herein may aid clinicians in stratifying risk among patients receiving anti-PD-1 therapy, for whom earlier clinical trial enrollment or treatment escalation may be considered. Although this study did not evaluate treatment selection and rechallenge outcomes after resistance, published evidence supports the use of ipilimumab plus nivolumab over ipilimumab alone in patients with primary resistance.[20] While some reports indicate that retreatment with ICIs is common in clinical practice after progression on anti-PD-1 therapy,[21] the supporting literature is heterogeneous and largely retrospective; prospective studies are needed to define optimal treatment sequencing by resistance type.

The substudy indicated a strong level of agreement on assessment of progressive disease between site clinicians and ICR, suggesting that progression assessed in routine clinical practice, without the need for ICR, and recorded in the medical notes, is a reliable method to document progression. It should be acknowledged that this study was not designed to systematically assess pseudo-progression. Disease progression was determined based on treating clinician's assessment and documentation in the clinical record, and standardized immune-specific response criteria (eg, immune Response Evaluation Criteria in Solid Tumors (iRECIST)) were not uniformly applied across study sites. Consequently, the available data do not allow reliable identification or differentiation of pseudo-progression from true disease progression. While the RECIST V.1.1 criteria provide the most widely used definitions for disease progression, other response assessment methods are also employed, including iRECIST, modified RECIST V.1.1, and modified WHO criteria.[1] It is important to establish clearer, standardized definitions of resistance in real-world settings to ensure reliability and consistency of progression data in observational studies. This will help minimize potential bias and variability in interpreting results.

The strengths of this study include the use of a multisite chart review across a wide spectrum of geographically diverse countries with a varied patient population, allowing the collection of data reflecting real-world clinical practice and outcomes and enhancing the applicability and generalizability of the findings. Further, the relatively large sample size (N=738) contributes to the robustness and generalizability of the results. Finally, standardized definitions from the *SITC* were used to define resistance in this study, enhancing the consistency and reproducibility of the study results.[4] However, it is important to note that at the time of this study, the *SITC* had only published consensus definitions of resistance in the context of response to single-agent ICIs. Therefore, in this study, *SITC* definitions of resistance to single-agent ICIs were also applied to assess resistance to combination therapy. In 2023, the *SITC* published new consensus definitions for resistance to various combinations of ICIs.[5] These definitions remain broadly consistent with those used in the present study.

Our study has several limitations. All study sites are academic centers, which may not be representative of all centers that treat stage III and IV melanoma, although treatment of melanoma is largely guideline-driven, so it would be anticipated that treatment patterns in academic and non-academic centers would be similar, barring differences in patient demographics, tumor types, and the use of RECIST V.1.1. Enrollment was stopped once prespecified sample size targets were met, introducing potential selection bias if patient characteristics varied over calendar time. In addition, multiple univariate comparisons were conducted across a range of variables, increasing the risk of type I error. These analyses were exploratory and intended to identify potential differences by resistance type rather than to provide confirmatory evidence; therefore, individual statistically significant findings should be interpreted cautiously and considered

as hypothesis-gathering. Treatment patterns may also have been affected by anomalous events such as the introduction of stage IIID into the American Joint Committee on Cancer (AJCC) melanoma staging system in 2018, the approval of pembrolizumab in the adjuvant setting in 2018/2019, and the COVID-19 pandemic during the study. Finally, pseudo-progression could not be systematically assessed, as progression was determined based on real-world documentation rather than standardized response criteria (eg, iRECIST). Further, different sites or countries may have used slightly different criteria to assess study endpoints, such as response to treatment (especially for some sites involved in the primary outcomes, which did not use RECIST V.1.1 criteria). To examine this, outcomes were tabulated by country and site use of RECIST V.1.1 criteria (online supplemental table 5) to assess any systematic differences.

CONCLUSIONS

In this large, global real-world evidence study, a substantial proportion of patients with melanoma in the adjuvant (47.1%) and advanced (67.5%) setting developed resistance or late relapse/progression after treatment with anti-PD-1. These findings highlight the unmet need for alternative therapeutic strategies for patients who progress on anti-PD-1 therapy, particularly for those with advanced disease. Significant differences in anti-PD-1 resistance were observed by country, race, type of *BRAF* mutation, and PD-L1 status in both settings; and by sex, disease stage and tumor thickness in the adjuvant setting only. Future research may explore the effectiveness of these risk factors for patient risk stratification and management. The high agreement between clinicians and ICR in the evaluation of progression supports the reliability of clinician-assessed evaluation in the classification of resistance for future observational studies.

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