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Real-world external validation of the Society for Immunotherapy of Cancer (SITC) definitions of primary and secondary resistance to PD-1/PD-L1 inhibitors in patients with solid tumors

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Abstract

Purpose

The Society for Immunotherapy of Cancer (SITC) definitions of primary and secondary resistance to PD-1/PD-L1 inhibitors are widely used but were independently evaluated mainly in melanoma. We assessed their prognostic performance in a real-world pan-tumor cohort and explored alternative cutoffs.

Methods

This retrospective single-center study included adults with solid tumors treated with PD-1/PD-L1 inhibitors for at least 6 weeks, classified as having primary, secondary, or no resistance per the 2020 SITC definitions. Overall survival (OS) was analyzed using Kaplan–Meier methods and multivariable Cox regression, and the threshold separating primary from secondary resistance was varied from 3 to 24 months.

Results

Of 595 patients (49% non-small cell lung cancer), 294 (49.4%) had primary resistance, 125 (21.0%) secondary resistance, and 176 (29.6%) no resistance. At a median follow-up of 27.7 months, median OS was 28.5 months with primary resistance, 80.3 months with secondary resistance, and not reached without resistance (log-rank $p < 0.0001$). In multivariable analysis (n = 398), primary resistance (adjusted hazard ratio [aHR] 6.99, 95% CI 3.58–13.6) and secondary resistance (aHR 2.15, 95% CI 1.06–4.35) were associated with higher mortality; estimates were consistent without performance status (n = 568). A 3-month threshold yielded a concordance statistic of 0.777 versus 0.769 at 6 months; longer thresholds progressively reduced discrimination.

Conclusion

SITC-defined resistance categories stratified OS in this real-world pan-tumor cohort. A shorter threshold did not meaningfully improve discrimination, supporting retention of the 6-month cutoff. Because categories are assigned after treatment initiation, landmark-based and prospective validation is warranted.

Introduction

Immune checkpoint inhibitors (ICIs) have transformed the treatment of a wide range of solid tumors. Approved agents comprise antibodies against programmed cell death protein 1 (PD-1) and its ligand (PD-L1; collectively PD-(L)1), two antibodies against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), and one lymphocyte-activation gene 3 (LAG-3) inhibitor, used as monotherapy or in combination

(Alsaafeen et al. 2025; Huang et al. 2025). ICIs have transformed outcomes in advanced melanoma (Liang et al. 2025), and several agents are approved for non-small cell lung cancer (NSCLC) (Olivares-Hernández et al. 2023). Anti-PD-(L)1 agents have also become standard therapy in urothelial and renal cell carcinoma and, through tissue-agnostic approvals, in solid tumors with microsatellite instability-high (MSI-H) or mismatch repair-deficient status (Olivares-Hernández et al. 2023; Alsaafeen et al. 2025; Liang et al. 2025). Benefit, however, remains highly variable. Although median survival has doubled in patients with NSCLC (Olivares-Hernández et al. 2023), objective response rates range from 40% to 70% in immunologically responsive tumors such as melanoma, Hodgkin lymphoma, and MSI-H cancers, but are as low as 10% to 25% in most other solid tumors (Alsaafeen et al. 2025). Even among responders, a substantial proportion of patients eventually progress through tumor-intrinsic or tumor-extrinsic mechanisms. These patterns underlie two clinically distinct phenomena, primary and secondary resistance, which together represent a principal barrier to extending the benefit of immunotherapy to more patients (Alsaafeen et al. 2025; Cheng et al. 2026).

Progress in understanding and overcoming ICI resistance has been limited by a lack of agreement on how resistance should be defined. As Zhou et al. noted, definitions of acquired resistance to ICIs were historically heterogeneous across research groups, with no standard before the consensus effort of the Society for Immunotherapy of Cancer (SITC) (Zhou et al. 2021). This inconsistency hindered comparison of outcomes across trials, complicated biomarker research, because the identification of molecular or immunologic predictors of resistance depends on consistent definitions, and made it difficult to determine whether new combination strategies genuinely overcame resistance. In response, SITC developed consensus definitions of resistance (Kluger et al. 2020).

The SITC Immunotherapy Resistance Taskforce first published definitions of resistance to single-agent anti-PD-(L)1 therapy (Kluger et al. 2020). Primary resistance was defined as progressive disease as the best response after a minimum period of drug exposure, or stable disease lasting less than 6 months. Secondary resistance required a confirmed response or stable disease lasting at least 6 months before subsequent progression. The 6-month threshold reflects the difficulty of distinguishing shorter disease control from the indolent growth of tumors that never truly responded, whereas disease control sustained beyond 6 months more plausibly reflects a genuine, treatment-induced antitumor immune effect that subsequently failed (Kluger et al. 2020). Because this framework did not address ICI-based combinations, SITC subsequently issued definitions for combination regimens, including combinations with chemotherapy and with targeted therapies (Atkins et al. 2023; Kluger et al. 2023; Rizvi et al. 2023).

Despite growing adoption, independent validation of the SITC framework remains limited. SITC investigators have emphasized that validation of the definitions is critical and requires field-wide data sharing and collaboration (Kluger et al. 2023). The evidence supporting the framework rests predominantly on expert consensus and pathophysiologic reasoning rather than on large-scale empirical testing (Kluger et al. 2020, 2023). Published evaluations have been largely confined to melanoma, comprising an international observational cohort (Bai et al. 2021) and a systematic review (Shui et al. 2022). It therefore remains insufficiently established whether the SITC definitions stratify survival in a

large, real-world pan-tumor population, or whether alternative temporal cutoffs improve prognostic performance.

This gap has practical consequences. The SITC definitions are increasingly embedded in oncology research: they inform eligibility criteria for trials of resistance-directed therapies, shape the interpretation of novel immunotherapy combinations, and underpin translational and biomarker studies of resistance mechanisms (Kluger et al. 2023). If the framework does not reliably distinguish populations with meaningfully different survival trajectories, the trial designs, biomarker studies, and clinical decisions built upon it may rest on an unvalidated foundation.

We therefore evaluated the SITC consensus definitions of primary and secondary resistance in a large real-world pan-tumor cohort treated with PD-(L)1 inhibitors. We assessed their association with overall survival (OS) and duration of response (DOR), tested their robustness in a sensitivity analysis, and examined whether alternative temporal cutoffs improved prognostic discrimination.

Methods

Study design and setting

This retrospective cohort study was conducted at the American University of Beirut Medical Center (AUBMC), a tertiary academic hospital that serves as an oncology referral center for Lebanon and the wider Middle East and North Africa (MENA) region. Patients treated with PD-(L)1 inhibitors between January 2018 and August 2026 were identified from institutional medical records. The study was approved by the American University of Beirut Institutional Review Board (protocol BIO-2024-0295), which waived the requirement for informed consent given the retrospective design and the use of de-identified data.

Patient selection

We included adults aged 18 years or older with a solid tumor who received a PD-1 or PD-L1 inhibitor for active, measurable disease. All patients had a best overall response documented by the treating physicians on the basis of standard radiographic assessment (RECIST version 1.1). Patients who received less than 6 weeks of ICI therapy were considered not evaluable under the SITC framework and were excluded, as were patients whose records did not permit assignment of a resistance category.

Data collection

Data were retrieved from the electronic medical records. Collected variables included age at treatment initiation, sex, body mass index (BMI), Charlson Comorbidity Index (CCI), Eastern Cooperative Oncology Group (ECOG) performance status, history of autoimmune disease, primary tumor type, disease stage, ICI agent, number of administered cycles, treatment start and end dates, concurrent chemotherapy,

targeted therapy and radiotherapy, prior systemic therapy and corticosteroid exposure, best overall response, date of first documented response, date of progression or recurrence, date of last contact, and immune-related adverse events (irAEs) by organ system and Common Terminology Criteria for Adverse Events (CTCAE v5.0) grade.

SITC resistance classification

Patients were assigned to resistance categories using the 2020 SITC consensus definitions for PD-(L)1 blockade (Kluger et al. 2020). The date of ICI initiation served as the anchor for all time-to-event calculations. Patients with at least 6 weeks of ICI exposure whose disease progressed within 6 months of treatment initiation were classified as having primary resistance. Patients who achieved a complete response (CR), partial response (PR), or stable disease (SD) and whose disease progressed 6 months or later after treatment initiation were classified as having secondary resistance. Patients without documented progression at last contact were classified as non-resistant. Patients whose best overall response was progressive disease (PD) were assigned to the primary resistance category irrespective of the duration of subsequent follow-up, reflecting the intent of the SITC definition, in which primary resistance denotes failure to derive any objective benefit from checkpoint blockade rather than a purely temporal construct.

SITC has issued separate frameworks for monotherapy and for combination regimens (Kluger et al. 2020; Atkins et al. 2023; Rizvi et al. 2023). Because our cohort was heterogeneous and included patients receiving concurrent chemotherapy or targeted therapy, we applied the monotherapy criteria to the entire population, a limitation we acknowledge.

Endpoints

The primary endpoint was OS, measured from the date of ICI initiation to death from any cause; patients alive at last contact were censored at that date.

Prespecified secondary endpoints were (i) DOR, measured from the date of first documented response to progression, with censoring at last contact, among patients achieving CR or PR; and (ii) refinement of the resistance cutoff, in which the temporal threshold separating primary from secondary resistance was varied and model performance compared.

Statistical analysis

Continuous variables are reported as medians with interquartile ranges (IQRs) and categorical variables as counts with percentages. Comparisons across the three resistance categories used the Kruskal–Wallis test for continuous variables and Pearson’s chi-squared test for categorical variables.

Median follow-up was estimated using the reverse Kaplan–Meier method. Survival distributions were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards regression was used to estimate the independent association between resistance category and OS. Model building followed a two-stage approach. First, covariates selected a priori on clinical grounds were retained regardless of univariable significance: resistance category, age, ECOG performance status, primary tumor type, concurrent chemotherapy, and concurrent targeted therapy. Second, any additional variable reaching $p < 0.20$ on univariable screening was added. ICI agent met this screening threshold but was not carried forward, because one category contained too few patients for stable estimation and the variable violated the proportional hazards assumption. Estimates are presented as adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs). The proportional hazards assumption was assessed using scaled Schoenfeld residuals, and discrimination was quantified using the concordance (C) statistic.

Missing data were handled by complete-case analysis without imputation. Because ECOG performance status was unrecorded in a substantial minority of patients, a prespecified sensitivity analysis repeated the multivariable model with this covariate omitted, permitting inclusion of a larger number of patients than the primary model.

For cutpoint refinement, the threshold distinguishing primary from secondary resistance was set successively at 3, 6, 9, 12, 18, and 24 months; patients were reclassified, and the identical multivariable model was refitted at each threshold. Thresholds were compared on the magnitude of the aHR for primary resistance, the associated p value, and the C statistic.

Analyses were performed in R version 4.5.2 using the survival (version 3.8.6), survminer (version 0.5.2), and gtsummary (version 2.5.1) packages. Two-sided p values below 0.05 were considered statistically significant.

Results

Cohort and baseline characteristics

Of 676 patients who received PD-(L)1 inhibitor therapy during the study period, 68 had less than 6 weeks of exposure and 13 could not be assigned a resistance category, leaving 595 patients in the analytic cohort. The median age at treatment initiation was 67 years (IQR 59–74), and 376 patients (63%) were men. NSCLC was the predominant histology (289, 49%), followed by gastrointestinal (52, 8.7%) and bladder (48, 8.1%) cancers. Pembrolizumab was the most frequently used agent (348, 58%). Concurrent chemotherapy was received by 385 patients (65%) and concurrent targeted therapy by 61 (10%); ECOG performance status was not recorded for 180 patients (30%) (Table 1).

Overall, 294 patients (49.4%) met the criteria for primary resistance, 125 (21.0%) for secondary resistance, and 176 (29.6%) were non-resistant. A best overall response of PD accounted for 265 of the

294 patients with primary resistance (90%); the remainder had an initial PR (n = 24) or SD (n = 5) followed by progression within 6 months. No patient achieving a CR was classified as having primary resistance.

Patients with primary resistance had a greater comorbidity burden than non-resistant patients (median CCI 8 vs 7; p = 0.001 across the three categories) and were more often diagnosed with stage IV disease (83% vs 63%; p < 0.001). Concurrent chemotherapy use differed across categories (p = 0.002) and was most frequent in patients with secondary resistance (74%). Prior corticosteroid use also differed (p = 0.026) and was most frequent in patients with primary resistance (47%). irAEs of any grade were less frequent in patients with primary resistance (20%) than in non-resistant patients (53%) or patients with secondary resistance (51%) (p < 0.001), with the same pattern for grade ≥ 2 events (p < 0.001). Age, sex, and concurrent targeted therapy did not differ across categories.

Table 1
Baseline demographic, disease, and treatment characteristics by SITC resistance category

Characteristic	Overall N = 595[a]	Non-resistant N = 176[a]	Secondary resistance N = 125[a]	Primary resistance N = 294[a]	p value[b]
Age at ICI initiation, years	67.0 (59.0, 74.0)	65.0 (58.0, 74.0)	67.0 (60.0, 72.0)	67.0 (59.0, 76.0)	0.5
Sex					0.5
Male	376 (63%)	107 (61%)	76 (61%)	193 (66%)	
Female	219 (37%)	69 (39%)	49 (39%)	101 (34%)	
BMI, kg/m²[c]	25.7 (23.2, 28.8)	25.8 (22.9, 29.9)	25.5 (23.5, 29.1)	25.7 (23.2, 28.0)	0.4
Charlson Comorbidity Index[c]	8.0 (6.0, 10.0)	7.0 (6.0, 9.0)	8.0 (6.0, 9.0)	8.0 (7.0, 10.0)	**0.001**
ECOG performance status[c]					0.6
0	288 (69%)	88 (75%)	68 (69%)	132 (66%)	
1	104 (25%)	24 (20%)	26 (27%)	54 (27%)	
≥ 2	23 (5.5%)	6 (5.1%)	4 (4.1%)	13 (6.5%)	
Disease stage[c]					**< 0.001**
I–III	145 (25%)	62 (37%)	35 (29%)	48 (17%)	
IV	431 (75%)	106 (63%)	87 (71%)	238 (83%)	
History of autoimmune disease	43 (7.2%)	12 (6.8%)	9 (7.2%)	22 (7.5%)	> 0.9
Primary tumor type					**< 0.001**
NSCLC	289 (49%)	76 (43%)	83 (66%)	130 (44%)	
Bladder	48 (8.1%)	23 (13%)	4 (3.2%)	21 (7.1%)	
GI	52 (8.7%)	11 (6.3%)	9 (7.2%)	32 (11%)	
HPB	36 (6.1%)	9 (5.1%)	8 (6.4%)	19 (6.5%)	

[a] Median (Q1, Q3); n (%). [b] Kruskal–Wallis rank sum test; Pearson's chi-squared test. [c] Missing values: BMI, n = 8; Charlson Comorbidity Index, n = 5; ECOG performance status, n = 180; disease stage, n = 19; percentages are calculated among patients with available data. Bold p values indicate $p < 0.05$.BMI body mass index, ECOG Eastern Cooperative Oncology Group, GI gastrointestinal, HPB hepatopancreatobiliary ICI immune checkpoint inhibitor, irAE immune-related adverse event, NSCLC non-small cell lung cancer, RCC renal cell carcinoma, SITC Society for Immunotherapy of Cancer

Characteristic	Overall N = 595[a]	Non-resistant N = 176[a]	Secondary resistance N = 125[a]	Primary resistance N = 294[a]	p value[b]
Melanoma	31 (5.2%)	12 (6.8%)	1 (0.8%)	18 (6.1%)	
RCC	40 (6.7%)	19 (11%)	3 (2.4%)	18 (6.1%)	
Other[d]	99 (17%)	26 (15%)	17 (14%)	56 (19%)	
Concurrent chemotherapy	385 (65%)	96 (55%)	92 (74%)	197 (67%)	**0.002**
Concurrent targeted therapy	61 (10%)	20 (11%)	12 (9.6%)	29 (9.9%)	0.8
Concurrent radiotherapy	293 (49%)	79 (45%)	58 (46%)	156 (53%)	0.2
Prior chemotherapy	227 (38%)	61 (35%)	43 (34%)	123 (42%)	0.2
Prior targeted therapy	30 (5.0%)	6 (3.4%)	4 (3.2%)	20 (6.8%)	0.2
Prior immunotherapy	9 (1.5%)	3 (1.7%)	0 (0%)	6 (2.0%)	0.3
Prior corticosteroid use	249 (42%)	63 (36%)	47 (38%)	139 (47%)	**0.026**

[a] Median (Q1, Q3); n (%). [b] Kruskal–Wallis rank sum test; Pearson's chi-squared test. [c] Missing values: BMI, n = 8; Charlson Comorbidity Index, n = 5; ECOG performance status, n = 180; disease stage, n = 19; percentages are calculated among patients with available data. Bold p values indicate p < 0.05.BMI body mass index, ECOG Eastern Cooperative Oncology Group, GI gastrointestinal, HPB hepatopancreatobiliary ICI immune checkpoint inhibitor, irAE immune-related adverse event, NSCLC non-small cell lung cancer, RCC renal cell carcinoma, SITC Society for Immunotherapy of Cancer

Overall survival

Median follow-up was 27.7 months (95% CI 25.0–29.8). During follow-up, 156 deaths (26%) were recorded: 18 (10%) among non-resistant patients, 29 (23%) among patients with secondary resistance, and 109 (37%) among patients with primary resistance. Time-to-event data were unavailable for 6 patients despite known vital status; survival analyses were therefore conducted in the remaining 589 patients (175 non-resistant, 125 with secondary resistance, and 289 with primary resistance). Survival curves separated early and remained distinct throughout follow-up (log-rank p < 0.0001; Fig. 1). Median OS was not reached in the non-resistant group, and was 80.3 months (95% CI 62.9–not estimable) in the secondary resistance group and 28.5 months (95% CI 23.7–47.0) in the primary resistance group.

In univariable analysis (Online Resource Table S1), resistance category, CCI, ECOG performance status, disease stage, prior corticosteroid use, any-grade irAE, grade ≥ 2 irAE, concurrent chemotherapy, concurrent radiotherapy, and prior immunotherapy met the p < 0.20 screening threshold and were entered alongside the prespecified covariates. The multivariable model was fitted in 398 patients with

complete covariate data; 191 patients were excluded because of missing data, predominantly ECOG performance status.

In the multivariable model, primary resistance remained strongly associated with mortality relative to non-resistance (aHR 6.99, 95% CI 3.58–13.6; $p < 0.001$), as did secondary resistance (aHR 2.15, 95% CI 1.06–4.35; $p = 0.034$). An ECOG performance status of 2 or higher was also independently associated with mortality (aHR 3.62, 95% CI 1.78–7.33; $p < 0.001$). CCI, disease stage, primary tumor type, concurrent chemotherapy, concurrent radiotherapy, concurrent targeted therapy, prior immunotherapy, prior corticosteroid use, and irAEs were not independently associated with OS (Table 2). The C statistic of the model was 0.769.

Table 2
Multivariable Cox proportional hazards model for overall survival

Characteristic	aHR	95% CI	p value
SITC resistance category			
Non-resistant	Ref	–	
Secondary resistance	2.15	1.06–4.35	**0.034**
Primary resistance	6.99	3.58–13.6	**< 0.001**
Age, per year	1.00	0.98–1.02	0.869
Charlson Comorbidity Index, per point	1.03	0.91–1.17	0.594
ECOG performance status			
0	Ref	–	
1	1.15	0.70–1.87	0.586
≥ 2	3.62	1.78–7.33	**< 0.001**
Disease stage			
I–III	Ref	–	
IV	1.12	0.55–2.26	0.756
Primary tumor type			
NSCLC	Ref	–	
Bladder	0.49	0.16–1.44	0.194
GI	0.84	0.41–1.69	0.619
HPB	0.78	0.14–4.41	0.783
Melanoma	0.85	0.24–3.01	0.806
RCC	0.71	0.22–2.30	0.571
Other	1.43	0.83–2.45	0.196
Concurrent chemotherapy (yes vs no)	1.11	0.65–1.90	0.693
Concurrent targeted therapy (yes vs no)	1.41	0.57–3.51	0.454
Concurrent radiotherapy (yes vs no)	0.87	0.57–1.34	0.532
Prior immunotherapy (yes vs no)	2.98	0.77–11.5	0.113
Prior corticosteroid use (yes vs no)	1.29	0.83–2.02	0.262

Characteristic	aHR	95% CI	p value
SITC resistance category			
Any-grade irAE (yes vs no)	0.47	0.20–1.14	0.096
Grade ≥ 2 irAE, any system (yes vs no)	2.24	0.90–5.61	0.084

Model fitted in 398 patients with complete covariate data; C statistic, 0.769. Bold p values indicate p < 0.05.

aHR adjusted hazard ratio, CI confidence interval, ECOG Eastern Cooperative Oncology Group, GI gastrointestinal, HPB hepatopancreatobiliary, irAE immune-related adverse event, NSCLC non-small cell lung cancer, RCC renal cell carcinoma, Ref reference category, SITC Society for Immunotherapy of Cancer

Sensitivity analysis

Repeating the multivariable model without ECOG performance status permitted inclusion of 568 patients with 146 deaths (Online Resource Table S2). Effect estimates for both resistance categories were larger than in the primary model: aHR 8.91 (95% CI 5.06–15.7; p < 0.001) for primary resistance and 2.42 (95% CI 1.31–4.49; p = 0.005) for secondary resistance. CCI was independently associated with mortality in this analysis (aHR per 1-point increase 1.13, 95% CI 1.02–1.25; p = 0.016), as were grade ≥ 2 irAEs (aHR 2.30, 95% CI 1.11–4.73; p = 0.024), which had not reached significance in the primary model. The direction and relative ordering of the resistance categories were unchanged, suggesting that the primary findings were not materially dependent on restricting the analysis to patients with recorded ECOG performance status.

Duration of response

Of the 272 patients who achieved a CR or PR, 229 (84%) had a documented response date that was internally consistent with the recorded progression date and were included in this analysis; the remaining 43 were excluded because the response date was missing or postdated the progression date. Median DOR was 38.8 months (95% CI 27.0–52.4). Response was maintained at 6 months in 84.8% of patients (95% CI 80.3–89.7), at 12 months in 73.1% (95% CI 67.4–79.3), at 18 months in 66.5% (95% CI 60.3–73.3), and at 24 months in 58.7% (95% CI 52.1–66.1) (Table 3).

Table 3
Kaplan–Meier estimates of duration of response (N = 229)

Timepoint	No. at risk	Response maintained, % (95% CI)
6 months	180	84.8 (80.3–89.7)
12 months	135	73.1 (67.4–79.3)
18 months	116	66.5 (60.3–73.3)
24 months	91	58.7 (52.1–66.1)
Includes patients with a complete or partial response and a documented date of first response consistent with the recorded progression date. Median duration of response, 38.8 months (95% CI 27.0–52.4)		
CI confidence interval		

By construction, non-resistant responders had no progression events, so their median DOR was not reached; the median observed time from first response to last contact was 36.6 months among those achieving a CR (n = 38) and 23.0 months among those achieving a PR (n = 86). Among patients with secondary resistance, median DOR was 22.5 months after a CR (n = 4) and 13.7 months after a PR (n = 85). Among patients with primary resistance who had an initial PR (n = 16), median DOR was 3.2 months (Table 4).

Table 4
Duration of response by SITC resistance category and best response

SITC category	Best response	n	Progression events[a]	Median time from first response, months (range)[b]
Non-resistant	CR	38	0	36.6 (3.7–93.6)
Non-resistant	PR	86	0	23.0 (1.7–80.2)
Secondary resistance	CR	4	4	22.5 (16.6–34.9)
Secondary resistance	PR	85	85	13.7 (0.4–59.7)
Primary resistance	PR	16	16	3.2 (1.2–4.0)

[a] By definition, non-resistant patients had no documented progression and all patients with secondary or primary resistance progressed. [b] For non-resistant patients, all observations are censored; the values therefore describe follow-up after response, and median duration of response was not reached. For patients with secondary or primary resistance, the values are observed durations of response.

CR complete response, PR partial response, SITC Society for Immunotherapy of Cancer

Cutpoint refinement

The threshold separating primary from secondary resistance was varied across six timepoints, and the multivariable model was refitted at each (Table 5; Online Resource Fig. S1). The aHR for primary resistance declined monotonically as the threshold was extended, from 7.33 (95% CI 3.75–14.34) at 3 months to 4.93 (95% CI 2.62–9.28) at 24 months, and the C statistic followed the same pattern, falling from 0.777 to 0.741. The CIs for the 3-month and 6-month thresholds overlapped substantially (aHR 7.33, 95% CI 3.75–14.34 vs 6.99, 95% CI 3.58–13.65), and the C statistics were similar (0.777 vs 0.769).

Secondary resistance remained significantly associated with mortality at the 3-month (p = 0.020) and 6-month (p = 0.034) thresholds but not at 9 months (p = 0.061) or at any longer threshold.

Table 5
Adjusted hazard ratios and concordance statistics across alternative resistance thresholds

Threshold	NR / SR / PR, n	Primary resistance aHR (95% CI)	p value	Secondary resistance aHR (95% CI)	p value	C statistic
3 months	175 / 148 / 266	7.33 (3.75–14.34)	< 0.001	2.26 (1.14–4.49)	0.020	0.777
6 months (SITC)	**175 / 125 / 289**	**6.99 (3.58–13.65)**	**< 0.001**	**2.15 (1.06–4.35)**	**0.034**	**0.769**
9 months	175 / 97 / 317	6.12 (3.19–11.75)	< 0.001	2.03 (0.97–4.24)	0.061	0.763
12 months	175 / 79 / 335	6.02 (3.15–11.50)	< 0.001	1.69 (0.77–3.73)	0.190	0.759
18 months	175 / 57 / 357	5.30 (2.80–10.01)	< 0.001	1.71 (0.72–4.04)	0.224	0.749
24 months	175 / 40 / 374	4.93 (2.62–9.28)	< 0.001	1.72 (0.68–4.32)	0.251	0.741

Patient numbers refer to the 589 patients included in the survival analysis. At each threshold, the multivariable model shown in Table 2 was refitted with non-resistant patients as the reference category. The SITC 6-month threshold is shown in bold.

aHR adjusted hazard ratio, CI confidence interval, NR non-resistant, PR primary resistance, SITC Society for Immunotherapy of Cancer, SR secondary resistance

Discussion

In this retrospective real-world cohort of 595 patients with solid tumors treated with PD-(L)1 inhibitors, SITC-defined resistance categories were associated with distinct OS: outcomes were poorest with primary resistance, intermediate with secondary resistance, and most favorable in non-resistant patients. These associations persisted after adjustment for clinical and treatment-related characteristics and in a sensitivity analysis that omitted ECOG performance status. Together, these findings provide independent real-world evidence supporting the prognostic relevance of the SITC framework across a heterogeneous population of patients with solid tumors, subject to the time-related bias inherent in categories that are assigned after treatment initiation, which we discuss below.

Standardized definitions of immunotherapy resistance are essential for consistency in clinical research and therapeutic development. Historically, heterogeneous definitions of primary and acquired resistance complicated comparisons across studies and the evaluation of resistance-directed therapies (Zhou et al. 2021). The SITC Immunotherapy Resistance Taskforce therefore proposed consensus definitions incorporating best response, minimum treatment exposure, and duration of disease control (Kluger et al. 2020), and these recommendations were later extended to ICI-based combination regimens (Kluger et al. 2023; Rizvi et al. 2023). Our findings help to address the limited independent validation of these definitions by showing that SITC-defined resistance categories are associated with distinct survival trajectories in a large, heterogeneous cohort.

The prognostic separation between resistance categories was pronounced. Compared with non-resistant patients, those with primary resistance had substantially higher mortality (aHR 6.99, 95% CI 3.58–13.6), and those with secondary resistance had a more moderate but still significant increase (aHR 2.15, 95% CI 1.06–4.35). Median OS was 28.5 months with primary resistance and 80.3 months with secondary resistance, and was not reached in non-resistant patients. These findings highlight the difference in survival between patients whose cancer progresses early during immunotherapy and those who initially benefit but later progress. This distinction may reflect differences in the underlying mechanisms of resistance, including impaired antigen presentation, altered interferon signaling, T-cell dysfunction, and immunosuppressive changes within the tumor microenvironment (Sharma et al. 2017; Jenkins et al. 2018; Zhou et al. 2021; Alsaafeen et al. 2025). However, these mechanisms remain hypothetical in our cohort, as molecular and immunologic profiling was not performed.

Our findings are consistent with those of an international observational study that applied the SITC definitions to patients with advanced melanoma receiving anti-PD-1 monotherapy (Bai et al. 2021). In that study, secondary resistance was associated with lower tumor burden, slower disease progression, and longer post-progression survival than primary resistance (Bai et al. 2021). Similarly, a systematic review of advanced melanoma studies emphasized the importance of standardized resistance definitions while highlighting the challenges of applying these criteria across clinical datasets (Shui et al. 2022). Our study extends these observations beyond melanoma by demonstrating differences in OS

across multiple solid tumor types and treatment regimens, supporting the broader applicability of the SITC framework while underscoring the need for prospective validation.

DOR also differed across resistance categories. Among patients with secondary resistance, median DOR was 22.5 months after a CR and 13.7 months after a PR, whereas it was 3.2 months among patients with primary resistance who had an initial PR; non-resistant responders had not progressed by definition. These findings align with the SITC distinction between short-term disease control and more sustained benefit (Kluger et al. 2020). However, the timing of progression contributes directly to resistance classification, so these differences largely reflect the construction of the categories. They should therefore be interpreted as supporting the internal consistency of the framework rather than as independent validation. Moreover, the small number of responders in some subgroups, notably secondary resistance after a CR (n = 4), limits comparisons between individual response categories.

An important objective of our study was to evaluate whether alternative temporal thresholds could improve prognostic discrimination. Although the 3-month threshold yielded the highest C statistic (0.777), its advantage over the SITC 6-month threshold (0.769) was small, and the corresponding aHRs for primary resistance were similar, with substantially overlapping CIs. Extending the threshold beyond 6 months progressively reduced model discrimination and weakened the association between secondary resistance and mortality. An earlier threshold may therefore offer, at most, a marginal statistical advantage, which does not establish a clinically meaningful improvement sufficient to justify modifying the existing definition.

The SITC 6-month threshold was chosen to distinguish short-term disease stabilization from more sustained disease control, which is more likely to reflect a meaningful response to immunotherapy (Kluger et al. 2020). Although clinically relevant radiological changes can be detected early during anti-PD-1 therapy, such early changes do not necessarily indicate sustained clinical benefit (Bai et al. 2021). Our findings therefore support retaining the conventional 6-month threshold for consistency across studies, while recognizing that alternative thresholds may warrant evaluation in specific tumor types and treatment settings.

Differences in baseline characteristics across resistance categories also warrant consideration. Patients with primary resistance had a higher comorbidity burden and more frequently had stage IV disease than non-resistant patients, suggesting that resistance classification may partly reflect underlying differences in disease severity and patient characteristics. Nonetheless, resistance category remained strongly associated with mortality after multivariable adjustment. An ECOG performance status of 2 or higher was independently associated with poorer survival, emphasizing the prognostic importance of baseline functional status.

irAEs were substantially less frequent in patients with primary resistance than in those with secondary resistance or without resistance. Although this pattern could reflect differences in antitumor immune activation, it may also result from differences in treatment exposure and in opportunities for adverse-event detection. The association between any-grade irAEs and improved survival observed in univariable

analysis was not statistically significant in the primary adjusted model. Conversely, the association between grade ≥ 2 irAEs and higher mortality in the sensitivity analysis should be interpreted cautiously, because the model also included any-grade irAEs (so that this estimate effectively contrasts higher-grade with lower-grade events) and because irAEs occur after treatment initiation and are therefore subject to time-dependent bias.

From a clinical perspective, the observed survival differences support the use of standardized resistance definitions to characterize patient populations receiving ICIs. Distinguishing primary from secondary resistance may facilitate more consistent eligibility criteria for resistance-directed clinical trials, improve comparisons across therapeutic strategies, and support translational investigations of resistance mechanisms (Kluger et al. 2023; Rizvi et al. 2023). These distinctions may be particularly relevant as treatment strategies increasingly target the biological mechanisms underlying primary and acquired resistance (Sharma et al. 2017; Schoenfeld and Hellmann 2020; Alsaafeen et al. 2025). Nevertheless, because SITC resistance categories are based on treatment response and subsequent progression, they cannot predict the effectiveness of immunotherapy before treatment initiation, and whether they can guide subsequent treatment selection or predict benefit from specific therapies remains to be established.

This study has several strengths. The relatively large pan-tumor cohort provides an independent evaluation of the SITC resistance definitions beyond the predominantly melanoma-focused literature. Inclusion of patients treated at a tertiary academic center in the MENA region broadens the geographic representation of the available evidence, and the heterogeneous population reflects real-world immunotherapy use across multiple malignancies and treatment combinations. Evaluation of OS, DOR, alternative thresholds, and a sensitivity analysis provided complementary assessments of the framework's prognostic performance.

Several limitations should also be acknowledged. First, and most importantly, resistance categories were assigned using events that occurred after treatment initiation, whereas OS was measured from treatment initiation. Patients with secondary resistance must, by definition, have remained alive and progression-free for at least 6 months, as reflected by the absence of any loss from the at-risk population of this group during the first 6 months (Fig. 1). This guaranteed survival time (immortal-time bias) is likely to inflate the survival contrast between categories, and the comparison with non-resistant patients partly reflects the established prognostic value of disease progression itself. Landmark analyses, time-dependent classification, or analysis of post-progression survival would provide a less biased assessment. Second, the retrospective, single-center design introduces potential selection bias, residual confounding, and incomplete documentation. Third, heterogeneity in tumor types, disease stages, and treatment regimens may limit the applicability of aggregate findings to individual malignancies. Moreover, although many patients received concurrent chemotherapy or targeted therapy, the SITC monotherapy criteria were applied uniformly; this facilitated consistent classification but may not fully capture resistance patterns in patients receiving combinations, for whom separate consensus definitions exist (Atkins et al. 2023; Rizvi et al. 2023). Fourth, response assessments relied on

retrospective clinical documentation without centralized radiographic review, potentially introducing variability in resistance classification. Fifth, ECOG performance status was unavailable for approximately 30% of patients, reducing the size of the primary multivariable model; although the sensitivity analysis omitting ECOG yielded consistent findings, data may not be missing at random. Sixth, the multivariable models included post-baseline covariates (irAEs) and a relatively large number of parameters for the number of events, which may affect the stability of individual covariate estimates. Seventh, excluding patients who received less than 6 weeks of ICI therapy and responders with missing or inconsistent response dates may limit generalizability. Eighth, the absence of molecular and immunologic biomarker data limited our ability to investigate the biological mechanisms underlying resistance. Finally, cutpoint refinement was performed within the same cohort, and validation in independent populations is needed to confirm the observed differences in prognostic performance.

Future prospective, multicenter studies should evaluate the SITC definitions within individual malignancies and treatment regimens, particularly combination immunotherapy strategies, using landmark or time-dependent analytic approaches. Incorporating standardized imaging assessments, molecular profiling, circulating biomarkers, and tumor microenvironment characteristics may help determine whether clinically defined resistance categories correspond to biologically distinct phenotypes. Such studies should also investigate whether resistance classification provides prognostic information beyond established clinical and molecular markers, and whether it can guide subsequent treatment selection. Given the limited improvement observed with alternative temporal thresholds, integrating clinical definitions with biological parameters may ultimately be more informative than modifying the threshold alone.

Conclusions

This study provides independent real-world evidence supporting the prognostic relevance of SITC-defined primary and secondary resistance to PD-(L)1 inhibitors in patients with solid tumors. Primary resistance was associated with substantially worse survival than secondary resistance or non-resistance, with consistent findings in the multivariable and sensitivity analyses. Although a 3-month threshold yielded marginally higher discrimination, it did not offer a meaningful advantage over the conventional 6-month threshold. These findings support the continued use of the SITC definitions in clinical research, while highlighting the need for landmark-based and prospective validation and for integration of biological markers to refine resistance classification.

Declarations

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conceptualization and manuscript editing and provided supervision, project administration, and final approval of the manuscript. All authors read and approved the final manuscript.

Data availability: Patient-level data are not publicly available to protect patient confidentiality. Data may be made available upon qualified request, subject to institutional and ethics approval.

Ethics approval: This study was approved by the American University of Beirut Institutional Review Board (protocol BIO-2024-0295). All procedures were conducted in accordance with institutional guidelines and the ethical principles of the 1964 Declaration of Helsinki and its later amendments, and all patient information was anonymized to ensure confidentiality.

Consent to participate: Given the retrospective nature of the study and the use of de-identified data, the requirement for informed consent was waived by the American University of Beirut Institutional Review Board.

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Figures

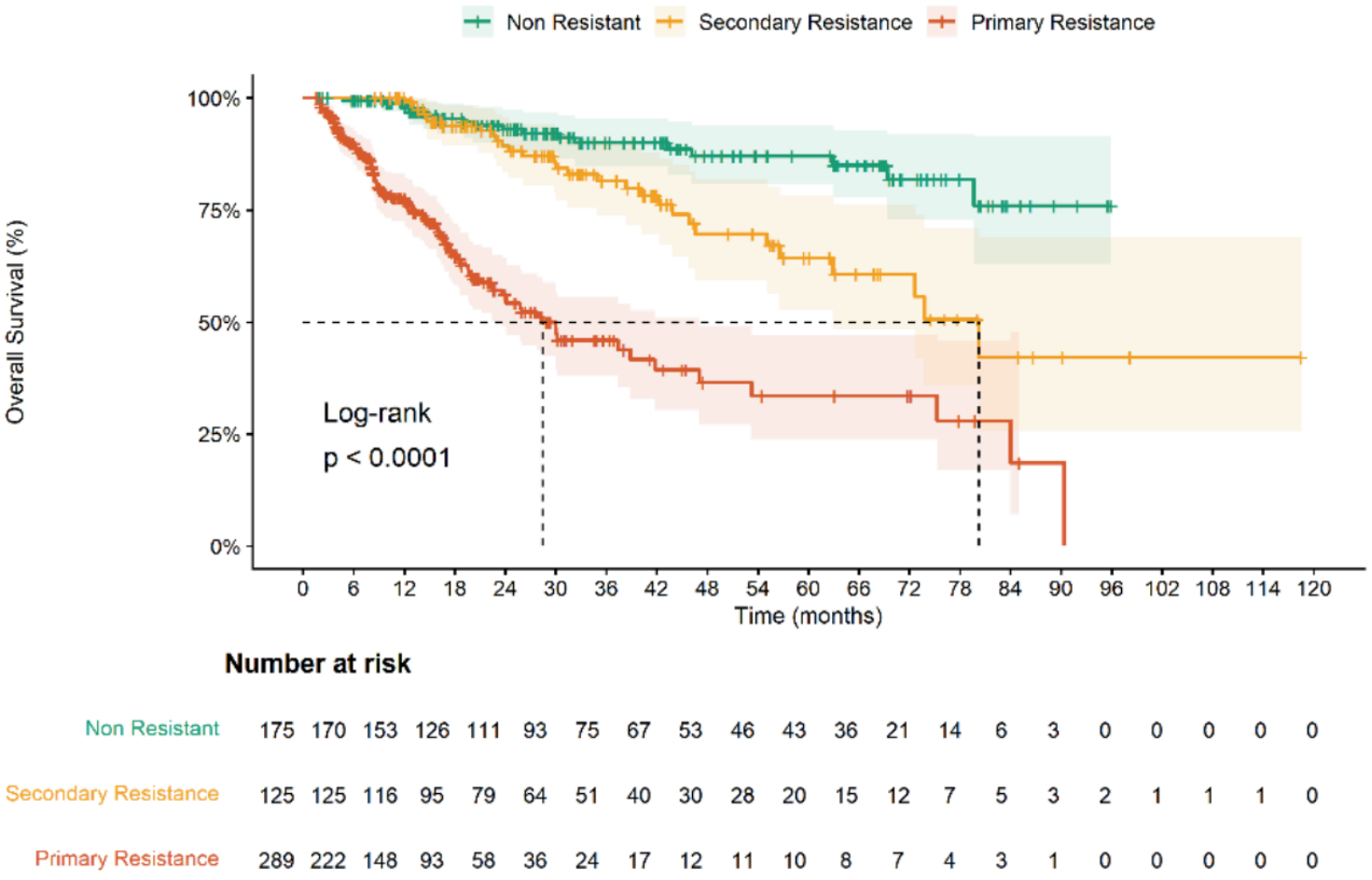


Figure 1

Kaplan–Meier estimates of overall survival by SITC resistance category (n = 589), with numbers at risk. Shaded bands indicate 95% confidence intervals, tick marks indicate censored observations, and dashed lines indicate median overall survival. SITC Society for Immunotherapy of Cancer

Supplementary Files

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- SITCOnlineResource1.docx