Journal for ImmunoTherapy of Cancer

Determinants of 5-year survival in patients with advanced NSCLC with PD-L1≥50% treated with first-line pembrolizumab outside of clinical trials: results from the Pembro-real 5Y global registry

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To cite: Cortellini A, Brunetti L, Di Fazio GR, *et al*. Determinants of 5-year survival in patients with advanced NSCLC with PD-L1≥50% treated with first-line pembrolizumab outside of clinical trials: results from the Pembro-real 5Y global registry. *Journal for ImmunoTherapy of Cancer* 2025;**13**:e010674. doi:10.1136/jitc-2024-010674

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/jitc-2024-010674).

Accepted 29 December 2024

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ABSTRACT

Background Pembrolizumab monotherapy is an established front-line treatment for advanced non-small cell lung cancer (NSCLC) with programmed cell death-ligand 1 (PD-L1) tumor proportion score (TPS)≥50%. However, real-world data on its long-term efficacy remains sparse.

Methods This study assessed 5-year outcomes of first-line pembrolizumab monotherapy in a large, multicenter, real-world cohort of patients with advanced NSCLC and PD-L1 TPS≥50%, referred to as Pembro-real 5Y. Individual patient-level data (IPD) from the experimental arm of the KEYNOTE-024 trial were extracted (KN024 IPD cohort) to compare the long-term outcomes between the two

cohorts. To further assess the reproducibility of clinical trial results, we reconstructed the "KN024 look-alike" cohort by excluding patients with an Eastern Cooperative Oncology Group-performance status (ECOG-PS)≥2, those requiring corticosteroids with doses ≥10 mg of prednisolone/equivalent, patients with positive/unknown epidermal growth factor receptor/anaplastic lymphoma kinase genotype, and those with pre-existing autoimmune disease. We additionally provided a hierarchical organization of determinants of long-term benefit through a conditional inference tree analysis.

Results The study included 1050 patients from 61 institutions across 14 countries, with a median follow-up of 70.3 months. The 5-year survival rate was 26.9% (95% CI: 23.8% to 30.2%), and median OS was 21.8 months (95% CI: 19.1 to 25.7), while 32 (3.0%) patients who achieved a complete response remained progression-free at the data cut-off. The KN024 look-alike cohort had a 5-year survival rate of 29.3% (95% CI: 25.5% to 33.6%) and a median OS of 27.5 months (95% CI: 22.8 to 31.3). Neither the overall study population nor the KN024 look-alike cohort exhibited significantly different OS compared with the KN024 IPD cohort. By the data cut-off, 1015 patients (96.7%) had permanently discontinued treatment: 659 (64.9%) due to progressive disease, 156 (15.4%) due to toxicity, 77 (7.6%) due to treatment completion, and 106 (10.4%) due to other reasons. Overall, 222 participants (21.1%) were treated for a minimum period of 24 months, among them the 5-year survival rates were: 31.7%, 72.7%, 78.6%, 84.2% for patients who discontinued treatment due to progressive disease, toxicity, treatment completion, and other reasons, respectively.

Conclusion This study provides valuable real-world evidence that confirms the long-term efficacy of pembrolizumab outside of clinical trials. Hierarchical organization indicates ECOG-PS, age and PD-L1-TPS as the most important predictors of 5-year survival, potentially informing clinical practice.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pembrolizumab monotherapy improves survival in advanced non-small cell lung cancer (NSCLC) with programmed cell death-ligand 1 (PD-L1)≥50% in trials, but real-world long-term outcomes in broader patient populations remain unclear.

WHAT THIS STUDY ADDS

⇒ This global real-world study demonstrates that pembrolizumab achieves a 5-year survival rate of 26.9% in an unselected population, comparable to clinical trial outcomes in a KN024 look-alike cohort. Conditional inference tree analysis identified Eastern Cooperative Oncology Group-performance status, age, and PD-L1 tumor proportion score as key determinants of long-term survival, and safety analysis confirms manageable toxicity beyond 2 years.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ By providing granular real-world evidence, this study bridges the gap between trial data and clinical practice, emphasizing the importance of patient selection and real-world granularity for managing advanced NSCLC.

INTRODUCTION

The KEYNOTE-024 trial demonstrated that pembrolizumab monotherapy is an effective first-line, chemotherapy-free treatment for patients with advanced non-small cell lung cancer (NSCLC) and a programmed cell death-ligand 1 (PD-L1) tumor proportion score (TPS) of ≥50%.[1] In the long-term follow-up update of this study, the overall survival (OS) for the pembrolizumab arm was 26.3 months, with a 5-year survival rate of 31.9%, establishing an unprecedented survival landmark for patients with advanced lung cancer.[2]

Although real-world case series have validated the clinical efficacy of pembrolizumab beyond the trial setting, the inclusion of patients with adverse prognostic factors—typically excluded from prospective randomized studies—resulted in less favorable outcomes compared with clinical trials.[3 4] A recently published long-term follow-up study from a real-world repository reported a 5-year survival rate of 25.1% and a median OS of 19.2 months among patients selected for performance status and epidermal growth factor receptor (EGFR)/anaplastic lymphoma kinase (ALK) genotype.[5] These outcomes compare unfavorably with the KEYNOTE-024 trial population,[2] highlighting the attrition between the trial setting and the real-world scenario in the context of chemo-free immunotherapy in NSCLC.

On the other hand, the range of first-line treatment options for patients with advanced NSCLC, including those with a PD-L1 TPS of ≥50%, has expanded to include chemoimmunotherapy combinations.[6–13] Because of the absence of head-to-head comparisons and evidence suggesting that the addition of the chemotherapy backbone may improve response rate and progression-free survival in this subgroup,[14–16] a debate exists about the best first-line treatment option (between monotherapy vs combinational approaches) for patients with PD-L1 high NSCLC in clinical practice.[17]

In the context of the rapid expansion of immunotherapy-based options for the first-line treatment of patients with NSCLC, there is a gap in knowledge about the real-world evidence of the long-term efficacy of first-line programmed death-1 (PD-1)/PD-L1 inhibitor monotherapy in patients with advanced NSCLC with high PD-L1 expression. This gap dictates an urgent assessment of large real-world evidence to inform clinical practice and identify clinicopathologic correlates of long-term benefit.

The Pembro-real 5 years study capitalizes on the clinical experience with first-line pembrolizumab monotherapy of the participating centers to assess the 5-year outcomes from a large, multicenter, real-world cohort and to identify clinicopathologic correlates of long-term benefit.

METHODS

Study design

The overarching aim of this retrospective study was to describe the 5-year outcomes of patients with advanced-stage NSCLC with PD-L1 TPS≥50% treated with first-line pembrolizumab monotherapy outside of clinical trials. To this end, we gathered a large, global, real-world cohort by pooling data from an existing registry, identified as Pembro-real IT,[3 4 18–20] and additional data collected through an ad hoc international registry, forming a single registry, henceforth referred to as Pembro-real 5Y.

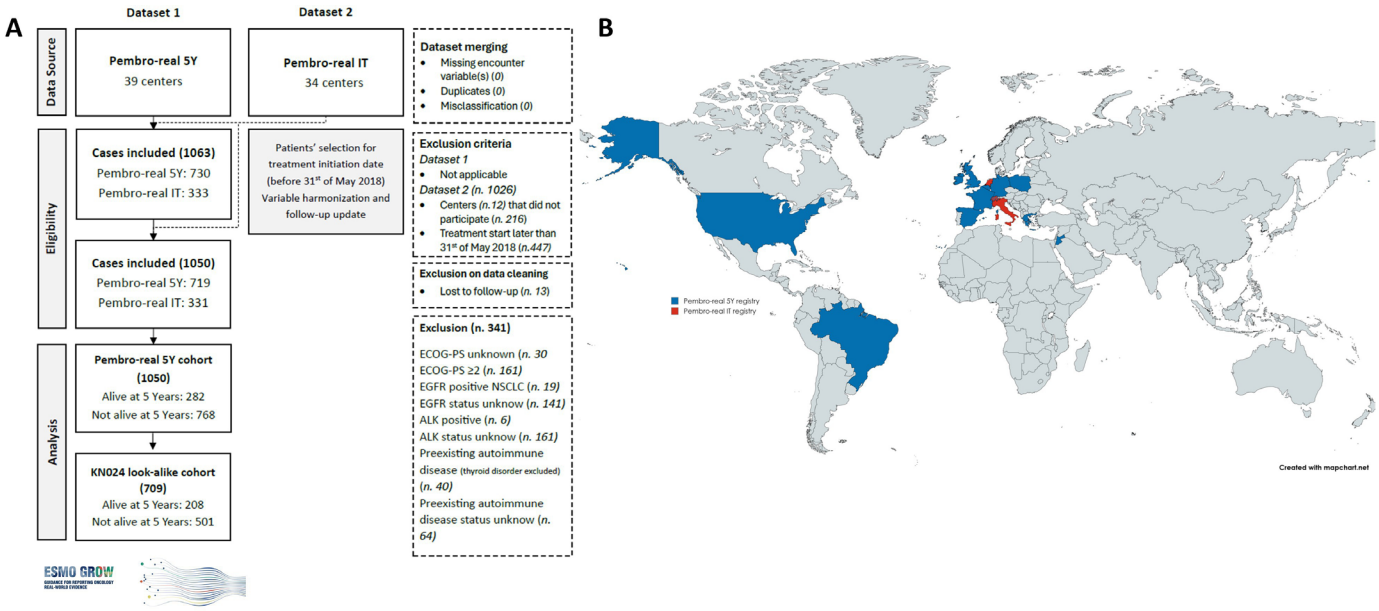

Figure 1 (A) ESMO Guidance for Reporting Oncology real-World Evidence (ESMO-GROW) flow chart for the study population. (B) Geographical distribution of participating centers. ALK, anaplastic lymphoma kinase; ECOG-PS, Eastern Cooperative Oncology Group-performance status; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

The primary eligibility criteria included receiving first-line pembrolizumab monotherapy outside of clinical trials, having a PD-L1 TPS of ≥50%, and starting treatment by May 31, 2018. To ensure at least 5 years of follow-up for long-term responders, the minimum data cut-off for patients still alive was set on May 1, 2023. Patients from centers that did not participate in the updated Pembro-real IT study were excluded from the analysis as follow-up data were not available for these individuals, precluding their inclusion in the long-term outcome assessments. After variable harmonization between the two registries, consecutive patients were screened for eligibility through medical record reviews by their treating teams at each participating center; patients lost to follow-up were subsequently excluded from the analysis. Figure 1A summarizes the patient selection process using the European Society of Medical Oncology (ESMO) Guidance for Reporting Oncology real-World Evidence (ESMO-GROW) flow chart[21] (ESMO-GROW informative score is available as online supplemental file 3). The final study population consisted of patients treated from November 2015 to May 2018 at 61 institutions across 14 countries worldwide (figure 1B).

We established the 5-year survival rate and OS as the clinical endpoints of interest. The 5-year survival rate was defined as the crude rate of patients alive at the 5-year mark from the treatment initiation date, while OS was defined as the time from treatment initiation to death or loss to follow-up. We also assessed real-world progression-free survival (rw-PFS), defined as the time from treatment initiation to disease progression or death, whichever occurred first, and the objective response rate (ORR), defined as the proportion of patients experiencing an objective response (complete or partial response) as the best response to treatment. Patients were assessed with radiological imaging in clinical practice as indicated by their physicians; investigators were asked to provide disease assessments following the Response Evaluation Criteria in Solid Tumors (RECIST) criteria V.1.1, although no formal imaging review was performed. Patients alive beyond the 5-year mark were censored at the date of their last clinical follow-up for OS, while patients who did not experience disease progression by the data collection date were censored at the date of their last radiological assessment for rw-PFS. As an additional clinical endpoint, we described the cumulative incidence of immune-related adverse events (irAEs) according to the Common Terminology Criteria for Adverse Events (CTCAE; V.5.0).

We first reported the distribution of clinicopathologic characteristics of interest across the overall population and according to the 5-year survival status to describe the potential associations between baseline features and long-term benefit from pembrolizumab treatment. A detailed description of the variables of interest is provided in the online supplemental methods. Subsequently, after reporting the clinical outcomes across the overall population using univariable analysis, we presented the rate of patients who achieved a complete response to the treatment, their progression rate at the data cut-off, along with the median time to and duration of complete response, providing a potential description of the long-term "eradication rate" in this setting. We then assessed the risk of death through a fixed multivariable model that included all pre-established variables of interest. To provide a hierarchical understanding of the determinants of long-term benefit, we conducted a conditional inference trees (CIT) analysis using the 5-year survival state as the endpoint, with variables chosen for the CIT procedure based on

their clinical priority and data completeness (see online supplemental methods).

We then compared the outcomes of the overall population with those reported for the experimental arm of the KEYNOTE-024 trial at the 5-year follow-up update. To this aim, we extracted individual patient-level data (IPD) from the published Kaplan-Meier OS curve[2] to reconstruct it following the method outlined by Guyot *et al*[22] (in the following text, abbreviated as KN024 IPD cohort). Considering that patients with Eastern Cooperative Oncology Group-performance status (ECOG-PS)≥2, positive EGFR/ALK genotype, requiring systemic corticosteroid treatments with doses ≥10 mg of prednisolone or equivalent, and with active pre-existing autoimmune diseases were not eligible for the KEYNOTE-024 trial, we additionally assessed clinical outcomes after excluding patients with these characteristics or missing information about them (hereafter referred to as the "KN024 look alike" cohort). Variables excluded from the KN024 look alike cohort are reported in online supplemental methods. In addition, considering the debate about the best first-line treatment option (between single-agent immunotherapy and combinational approaches) for patients with PD-L1 high NSCLC,[15] we analyzed the KN024 look-alike cohort, stratifying patients by non-squamous (NS) and squamous (Sq) histology to provide clinically relevant results comparable to the KEYNOTE-189 and KEYNOTE-407 studies.[23 24]

To explore the potential differential outcomes in patients with very high PD-L1 TPS (≥90%), an additional analysis stratified by PD-L1 expression levels (≥90% vs 50–89%) was performed in the overall cohort and the KN024 look-alike subgroup among patients with detailed TPS information[3 25] along with an exploratory analysis to evaluate whether differences in outcomes could be attributed to the type of immunohistochemistry (IHC) antibody used for PD-L1 testing.

Next, we reported the 5-year survival rate according to the reason for treatment interruption categorized as progressive disease, discontinuation due to limiting toxicity, treatment completion (defined as 2 years of treatment), others (including patient's preference, clinical decision, and treatment interruption following the 2-year mark), and unknown/not reported. Acknowledging the increasing attention on the outcomes of long-term responders depending on treatment duration,[26] we conducted an additional exploratory analysis among patients with a minimum treatment duration of 24 months, reporting their 5-year survival rates and OS according to the reason for discontinuation.

Lastly, we used the large sample size and extended clinical follow-up to confirm the safety profile of pembrolizumab monotherapy in the whole study population and among the KN024 look alike cohort. We reported the cumulative incidence of irAEs among the study population. Patients were monitored for safety evaluation in clinical practice as clinically indicated by their treating teams. To reflect the real-world nature of this study, irAEs were adjudicated and graded retrospectively by site investigators based on treating physician documentation in medical records, following CTCAE criteria. These events are defined as "real-world irAEs" (rw-irAEs) to acknowledge the potential variability in reporting and grading across centers. Rw-irAEs were defined as adverse events with a putative immunological basis as a direct result of pembrolizumab treatment and grouped into all grade rw-irAEs and grade 3/4 (G3/4) irAEs. The rw-irAEs were further categorized based on the organ/system involved as follows: skin rw-irAEs, thyroid rw-irAEs, gastrointestinal rw-irAEs, liver rw-irAEs, pulmonary rw-irAEs, rheumatologic rw-irAEs, neuromuscular rw-irAEs, renal rw-irAEs, other endocrine rw-irAEs, and other rw-irAEs. Patients were monitored for safety evaluation in clinical practice as clinically indicated by their treating teams. We first reported the incidence of all grade rw-irAEs and G3/G4 during the first 2 years of treatment among the whole study population, and subsequently, we reported the incidence of rw-irAEs occurring beyond the first 2 years of treatment among patients with a minimum treatment duration of 24 months.

Statistical analysis

We estimated the minimum sample size for this analysis based on previously published data, which reported a 2-year survival rate of~39% with pembrolizumab monotherapy in a large multicenter cohort of patients treated outside clinical trials,[3 4] compared with the~51% reported in the KEYNOTE-024 trial.[3 27] Assuming a 24% reduction in the 5-year survival rate compared with the experimental arm of the KEYNOTE-024 trial, we hypothesized a 5-year survival rate of 24.4% in our study population. Therefore, the minimum sample size for a descriptive study of a dichotomous variable with a 95% confidence level (interval width of 0.1) was set at 301.[28]

We used descriptive statistics to report baseline clinicopathologic features of interest, assessing differential distribution through the χ^2 test. The 5-year survival rate was reported as a crude rate with 95% CIs. Median follow-up was estimated using the reverse Kaplan-Meier method, while median OS, rw-PFS and duration of response estimates were computed using the Kaplan-Meier method and compared with the log-rank test. Cox regression was used to compute HRs for the risk of death with 95% CI and for the fixed multivariable analysis of OS.

Log-rank tests and Cox regression models were additionally applied to compare time-to-event endpoints across clinicopathologic features and distinct cohorts, including the KN024 IPD cohort and the KN024 look-alike cohort.

To create a comprehensive model for OS, we included all variables of interest, categorizing missing values as "unknown" for the multivariable model. Considering that data-source consisted of 61 different institutions, which could represent a source of bias, we applied a center-specific conditional interpretation using frailty models to correct all 95% CIs from the multivariable Cox regression.

Considering our descriptive aim, we set the alpha level for the CIT analysis at 0.1. Additionally, we performed an exploratory CIT procedure with an alpha level of 0.5 to potentially include the highest number of variables in the final model. Patients with missing information for any of the included covariates were excluded from the CIT analysis, with results reported through Sankey diagrams. In the safety analysis, the incidence of irAEs was reported as a crude rate. All p values were two-sided, with significance predefined at <0.05. Analyses were performed using RStudio software, R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, and MedCalc Statistical Software V.20 (MedCalc Software, Ostend, Belgium; https://www.medcalc.org; 2021).

RESULTS

Cohort characteristics

After the exclusion of patients from centers that did not participate in the Pembro-real IT update (n=216) and those with a treatment starting date after May 31, 2018 (n=447), 1063 consecutive patients were entered in the registry (figure 1A). Online supplemental table 1 reports the number of patients entered by each participating institution. Given the exclusion of 13 patients lost to follow-up, the final study population consisted of 1050 patients, with a median follow-up period of 70.3 months (95% CI: 69.0 to 70.9) and a total of 805 death events. Overall, 282 patients were alive at the 5-year landmark, resulting in a 5-year survival rate of 26.9% (95% CI: 23.8% to 30.2%).

Table 1 reports a detailed distribution of the clinicopathologic characteristics of interest in the overall population and according to the 5-year survival status. The median age was 69 years (range 31–92), with 45.1% of patients aged ≥70 years. The majority of patients were men (59.8%), white (82.9%), normal weight (39.8%), with adenocarcinoma histology (73.5%) and reported to be former (62.9%) or current (26.7%) smokers. Importantly, the study population included 15.3% of patients with ECOG-PS≥2, with 10.9% and 8.7% requiring corticosteroid treatments with doses <10 mg and ≥10 mg of prednisolone or equivalent at baseline, respectively. The exact PD-L1 TPS value was not available for 20% of the patients. Similarly, EGFR mutation status and ALK translocation status were not assessed in 13.4% and 15.3% of patients, respectively, while 1.8% and 0.6% of patients had EGFR and ALK positive tumors. Kirsten rat sarcoma virus (KRAS) mutational status and the tumor mutational burden (TMB) were not available for 43.7% and 89.6% of patients, respectively. At least one comorbidity at baseline was reported for a significant proportion of patients, including hypertension (49.8%), myocardial infarction (12.2%), other cardiovascular comorbidities (25.8%), type 2 diabetes (16.9%), pulmonary disease (26.2%), dyslipidemia (29.9%), pre-existing autoimmune disease (5.0%), and others (35.6%) (detailed description available in online supplemental table 2). Online supplemental table 3 summarizes additional details on biomarker status and assessment, including PD-L1 TPS, EGFR, KRAS, and B-Raf (BRAF) mutational status and TMB.

As described in table 1, patients alive at 5 years were more likely to be younger than 70 years (65.2% vs 51.0%, p<0.0001), have an ECOG-PS of 0–1 (92.4% vs 81.2%, p<0.0001), and have adenocarcinoma histology (76.8% vs 72.3%, p=0.0259). Patients without a history of smoking (7.1% vs 9.9%, p=0.0188), patients with bone metastases (28.0% vs 37.1%, p=0.0061), liver metastases (11.3% vs 17.3%, p=0.0185), as well as those with >3 metastatic sites (6.4% vs 11.2%, p=0.0207) at baseline were less likely to be alive at 5 years. Despite the high degree of missingness, a non-significant trend of increased proportions of patients with KRAS-positive tumors (43.6% vs 35.4%, p=0.0560) and with high TMB[29] (25.0% vs 11.0%, p=0.0586) was reported for patients alive at 5 years.

Clinical outcomes

The median overall survival for the study population was 21.8 months (95% CI: 19.1 to 25.7, 805 events), while the rw-PFS and the ORR were 10.4 months (95% CI: 8.5 to 11.8, 862 events) and 49.6% (95% CI: 45.2% to 54.2%, 477 tumor responses out of 962 evaluable patients), respectively.

Out of 962 evaluable patients, 59 achieved a complete response to treatment (6.1%, 95% CI: 4.6% to 7.9%). Among these, data on time to response were available for 38 patients, with a median time to achieve a complete response of 4.6 months (range: 0.42–9.5). At the data cut-off 32 of them (54.2%) were progression free and the median duration of complete response was 47.5 months (95% CI: 23.1 to 47.5, 19 events, assessed in 38 patients only).

In the fixed multivariable analysis including all baseline covariates of interest, age ≥70 years (HR 1.25, 95% CI: 1.08 to 1.46), baseline ECOG-PS≥2 (HR 2.12, 95% CI: 1.73 to 2.59), presence of liver (HR 1.37, 95% CI: 1.12 to 1.67) and bone (HR 1.35, 95% CI: 1.16 to 1.58) metastases, use of <10 mg of prednisolone or equivalent (HR 1.52, 95% CI: 1.21 to 1.93) or ≥10 mg of prednisolone or equivalent (HR 1.48, 95% CI: 1.13 to 1.95) at baseline were confirmed as independent predictors of increased risk of death (table 2).

After excluding patients with EGFR/ALK positive tumors and those with missing information for any of the baseline covariates of interest (online supplemental methods), 795 patients were included in the CIT analysis. This corresponds to a dropout rate of 24.3% (255 patients excluded out of 1,050 total). This analysis provided a hierarchical disposition of determinants of the 5-year survival rate among age, biological sex, ethnicity, ECOG-PS, PD-L1 TPS value, smoking status, primary tumor histology, number of metastatic sites, and corticosteroid exposure at baseline (figure 2). As a result, ECOG-PS was the strongest determinant (p<0.001), with a 5-year survival rate of only 12.7% (95% CI: 7.9% to 20.3%) among those

Table 1 Patients' characteristics of the overall cohort and according to the survival status at 5 years of follow-up

	Overall N° 1050 (%)	Not alive at 5 years N° 768 (%)	Alive at 5 years N° 282 (%)	P value
Age, (years)				
Median (range)	69 (31–92)	70 (31–92)	65 (34–90)	p<0.0001
<70 years old	576 (54.9)	392 (51.0)	184 (65.2)	
≥70 years old	474 (45.1)	376 (49.0)	98 (34.8)	
Sex				
Female	422 (40.2)	303 (39.5)	119 (42.2)	p=0.4215
Male	628 (59.8)	465 (60.5)	163 (57.8)	
Ethnicity*				
White	870 (82.9)	633 (89.9)	237 (90.8)	p=0.0559
Black/African-American	31 (3.0)	20 (2.8)	11 (4.3)	
Asian	29 (2.7)	25 (3.6)	4 (1.5)	
Hispanic	9 (0.8)	4 (0.6)	5 (1.9)	
Others	26 (2.5)	22 (3.1)	4 (1.5)	
Unknown	85 (8.1)	64	21	
WHO BMI category*				
Obese	162 (15.4)	110 (16.5)	52 (21.5)	p=0.3784
Overweight	286 (27.2)	215 (32.3)	71 (29.3)	
Normal weight	418 (39.8)	310 (46.7)	108 (44.5)	
Underweight	41 (3.9)	30 (4.5)	11 (4.5)	
Unknown	143 (13.7)	103	40	
ECOG-PS*				
0–1	859 (81.8)	604 (81.2)	255 (92.4)	p<0.0001
≥2	161 (15.3)	140 (18.8)	21 (7.6)	
Unknown	30 (2.9)	24	6	
Histology				
Squamous	238 (22.8)	188 (24.5)	50 (17.9)	p=0.0259
Adenocarcinoma	768 (73.5)	554 (72.4)	215 (76.8)	
Others/NOS	39 (3.7)	24 (3.1)	15 (5.3)	
Smoking status*				
Current smokers	280 (26.7)	187 (24.8)	93 (33.1)	p=0.0188
Former smokers	660 (62.9)	492 (65.3)	168 (59.8)	
Never smokers	95 (9.0)	75 (9.9)	20 (7.1)	
Unknown	15 (1.4)	14	1	
PD-L1 TPS*				
≥90%	559 (53.2)	422 (67.8)	136 (62.7)	p=0.1647
50–89%	281 (26.8)	200 (32.2)	81 (37.3)	
Not specified	210 (20.0)	146	65	
CNS metastases				
No	841 (80.1)	619 (80.6)	222 (78.7)	p=0.5001
Yes	209 (19.9)	149 (19.4)	60 (21.3)	
Bone metastases				
No	686 (65.3)	483 (62.9)	203 (72.0)	p=0.0061
Yes	364 (34.7)	285 (37.1)	79 (28.0)	
Liver metastases				
No	885 (84.3)	635 (82.7)	250 (88.7)	p=0.0185
Yes	165 (15.7)	133 (17.3)	32 (11.3)	

Continued

Table 1 Continued

	Overall N° 1050 (%)	Not alive at 5 years N° 768 (%)	Alive at 5 years N° 282 (%)	P value
Number of metastatic sites				
≤3	946 (90.1)	682 (88.8)	264 (93.6)	p=0.0207
>3	104 (9.9)	86 (11.2)	18 (6.4)	
Baseline corticosteroids				
None	845 (80.5)	608 (79.2)	237 (84.0)	p=0.1992
<10 mg pred or eq.	114 (10.8)	90 (11.7)	24 (8.6)	
≥10 mg pred or eq.	91 (8.7)	70 (9.1)	21 (7.4)	
EGFR mutation status*				
No	890 (84.8)	635 (97.7)	255 (98.5)	p=0.4680
Yes	19 (1.8)	15 (2.3)	4 (1.5)	
Not-tested	141 (13.4)	118	23	
ALK translocation status*				
No	883 (84.1)	631 (99.2)	252 (99.6)	p=0.5209
Yes	6 (0.6)	5 (0.8)	1 (0.4)	
Not-tested	161 (15.3)	132	29	
ROS-1 translocation status*				
No	710 (67.6)	502 (98.8)	208 (98.6)	p=0.7917
Yes	9 (0.9)	6 (1.2)	3 (1.4)	
Not-tested	331 (31.5)	260	71	
KRAS mutation status*				
No	367 (35.0)	265 (64.6)	102 (56.4)	p=0.0560
Yes	224 (21.3)	145 (35.4)	79 (43.6)	
Not-tested	459 (43.7)	358	101	
BRAF mutation status*				
No	491 (46.8)	337 (94.4)	154 (96.3)	p=0.3735
Yes	26 (2.5)	20 (5.6)	6 (3.7)	
Not-tested	533 (50.7)	411	122	
Tumor mutational burden*				
Non-high	92 (8.8)	65 (89.0)	27 (75.0)	p=0.0586
High	17 (1.6)	8 (11.0)	9 (25.0)	
Not-tested	941 (89.6)	695	246	
Other molecular findings				
No	237 (22.6)	171 (22.3)	66 (23.4)	–
Yes	127 (12.1)	82 (10.7)		
Not-tested	685 (65.3)	514 (67.0)	171 (60.6)	
Tp53	42 (4)	26 (3.4)	16 (5.7)	
cMET amplification	16 (1.5)	11 (1.4)	5 (1.8)	
cMET exon14	14 (1.3)	11 (1.4)	3 (1.1)	
RET fusions	4 (0,4)	4 (0.5)	0	

*Patients with missing information were excluded from the denominator for the χ^2 test.
ALK, anaplastic lymphoma kinase; BMI, body mass index; BRAF, B-Raf; CNS, central nervous system; ECOG-PS, Eastern Cooperative Oncology Group-performance status; EGFR, epidermal growth factor receptor; eq, equivalent; KRAS, Kirsten rat sarcoma virus; NOS, not otherwise specified; PD-L1, programmed death-ligand 1; pred, prednisone/prednisolone; ROS-1, proto-oncogene tyrosine-protein kinase ROS; TPS, tumor proportion score.

with a poor PS. Among patients with an ECOG-PS 0–1, the second determinant was age (p=0.024), with a 5-year survival rate of 33.8% (95% CI: 28.1% to 40.2%) among those younger than 70 years. Among patients with an ECOG-PS 0–1 and ≥70 years, those with a PD-L1 TPS between 50% and 89% achieved a 5-year survival rate

Table 2 Fixed multivariable analysis for the risk of death (overall survival). Considering that the data source consisted of 61 institutions, a conditional interpretation for participating center was applied to correct all the 95% CI

	Overall survival - risk of death HR (95% CI)
Age	
≥70 vs <70 years	1.25 (1.08 to 1.46)
Ethnicity	
White	1
Black/African-American	0.72 (0.45 to 1.15)
Asian	1.12 (0.73 to 1.72)
Hispanic	0.53 (0.20 to 1.37)
Others	1.04 (0.64 to 1.69)
Unknown	1.09 (0.78 to 1.54)
Smoking status	
Current smoker	1
Former smoker	1.06 (0.89 to 1.27)
Never smoker	1.28 (0.95 to 1.71)
Unknow	1.61 (0.86 to 3.01)
ECOG-PS	
0–1	1
≥2	2.12 (1.73 to 2.59)
Unknow	1.47 (0.87 to 2.47)
WHO BMI	
Normal weight	1
Underweight	1.19 (0.81 to 1.76)
Overweight	1.03 (0.86 to 1.23)
Obese	0.89 (0.71 to 1.11)
Unknow	0.89 (0.67 to 1.17)
Sex	
Male vs female	1.01 (0.86 to 1.17)
CNS metastases	
Yes vs no	1.04 (0.86 to 1.26)
Liver metastases	
Yes vs no	1.37 (1.12 to 1.67)
Bone metastases	
Yes vs no	1.35 (1.16 to 1.58)
Corticosteroids at baseline	
No	1
<10 mg pred or eq.	1.52 (1.21 to 1.93)
≥10 mg pred or eq.	1.48 (1.13 to 1.95)
PD-L1 tumor proportion score	
50–89	1
≥90	0.91 (0.77 to 1.08)
Not reported	0.89 (0.72 to 1.11)
EGFR mutational status	
Wild type	1
Mutant	1.16 (0.66 to 2.02)
Not tested	0.89 (0.71 to 1.11)
KRAS mutational status	
Wild type	1
Mutant	0.79 (0.65 to 0.98)
Not tested	1.18 (0.97 to 1.43)
ALK translocation status	
Wild type	1
Translocated	1.32 (0.53 to 3.26)
Not tested	0.99 (0.68 to 1.45)

ALK, anaplastic lymphoma kinase; BMI, body mass index; CNS, central nervous system; ECOG-PS, Eastern Cooperative Oncology Group-performance status; EGFR, epidermal growth factor receptor; eq, equivalent; KRAS, Kirsten rat sarcoma virus; NOS, not otherwise specified; PD-L1, programmed death-ligand 1; pred, prednisone/prednisolone; TPS, tumor proportion score.

of 18.6% (95% CI: 13.1% to 25.6%), while those with a PD-L1 TPS≥90% had a 5-year survival rate of 33.7% (95% CI: 22.9% to 47.8%) (p=0.028). The additional descriptive CIT analysis performed using an alpha level of 0.5 is reported in online supplemental figure 1. Raw results of the CIT analysis are reported in online supplemental figure 2.

As reported in figure 1A, 341 patients were excluded to create the KN024 look-alike cohort, which consisted of 709 patients with ECOG-PS 0–1, EGFR/ALK wild-type tumors, and no pre-existing autoimmune disease. With 208 patients alive, the 5-year survival rate for the KN024 look-alike cohort was 29.3% (95% CI: 25.5% to 33.6%), with an OS of 27.5 months (95% CI: 22.8 to 31.3, 523 events) that was similar to the OS reported for the overall study population (figure 3A, log-rank p value 0.098). Similarly, the rw-PFS for the KN024 look-alike cohort (11.4 months, 95% CI: 9.7 to 13.3, 560 events) was similar to the overall study population (log-rank p value 0.12), while its ORR was 51.7% (95% CI: 46.4% to 57.5%, 343 tumor responses out of 663 evaluable patients).

Using the methods outlined by Guyot *et al*,[22] we reconstructed the Kaplan-Meier survival curve for the KN024 IPD cohort, which resulted in an OS of 26.4 months (95% CI: 19.5 to 41.4, 154 patients and 103 events). Figure 3B reports the log-rank comparison between the Pembro-real 5Y overall study population and the KN024 IPD cohort, highlighting similar overall survival (log-rank p value 0.19), although with numerically lower estimates for the Pembro-real 5Y cohort. Figure 3C compares the KN024 look-alike and the KN024 IPD cohorts, reporting a

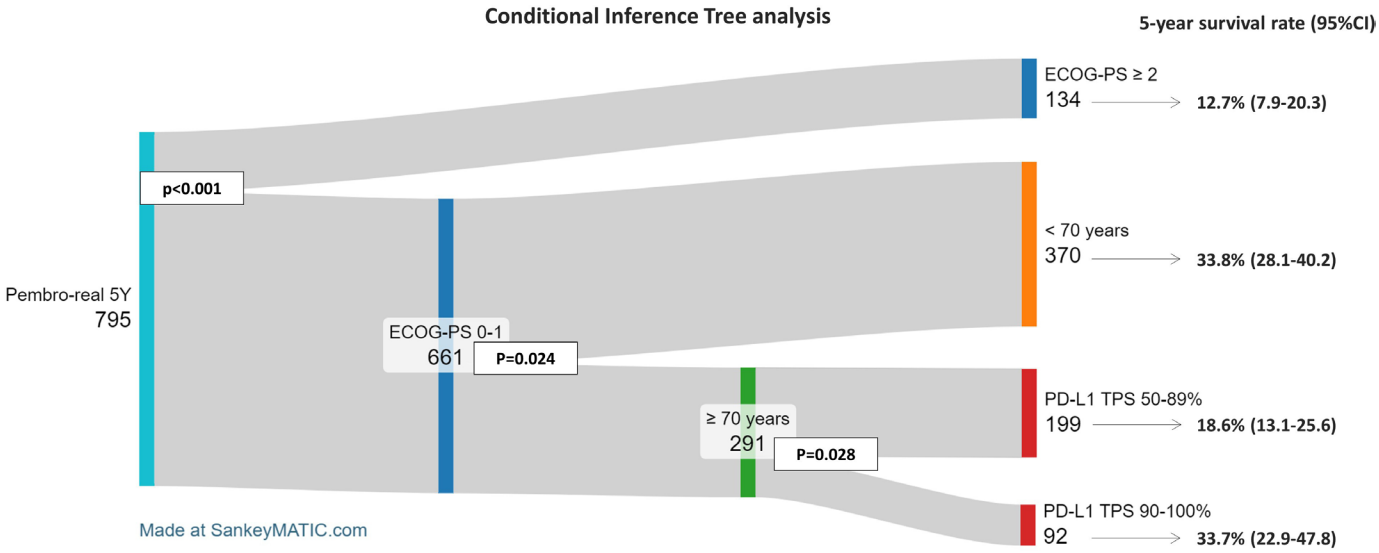

Figure 2 Sankey diagram reporting the descriptive conditional inference tree analysis performed using an alpha level of 0.1. Patients with EGFR mutation/ALK translocation were excluded a priori, patients with missing variables were excluded. Included covariates were: age at pembrolizumab initiation (<70 vs ≥70 years old); biological sex (male vs female); ethnicity (white vs any other ethnicity); Eastern Cooperative Oncology Group-performance status (ECOG-PS) (0–1 vs ≥2); PD-L1 TPS value (≥90% vs <90%); smoking status (never smokers vs former smokers (≥1 year) vs current smokers); primary tumor histology (non-squamous cell carcinoma vs squamous cell carcinoma); number of metastatic sites (>3 vs ≤3); corticosteroids administration at baseline within the 30 days before treatment commencement (none/doses <10 mg/day prednisolone or equivalent vs doses ≥10 mg/day prednisolone or equivalent vs none). Variables not included in the final model were those that did not produce significant splits in 5-year survival within the population. PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

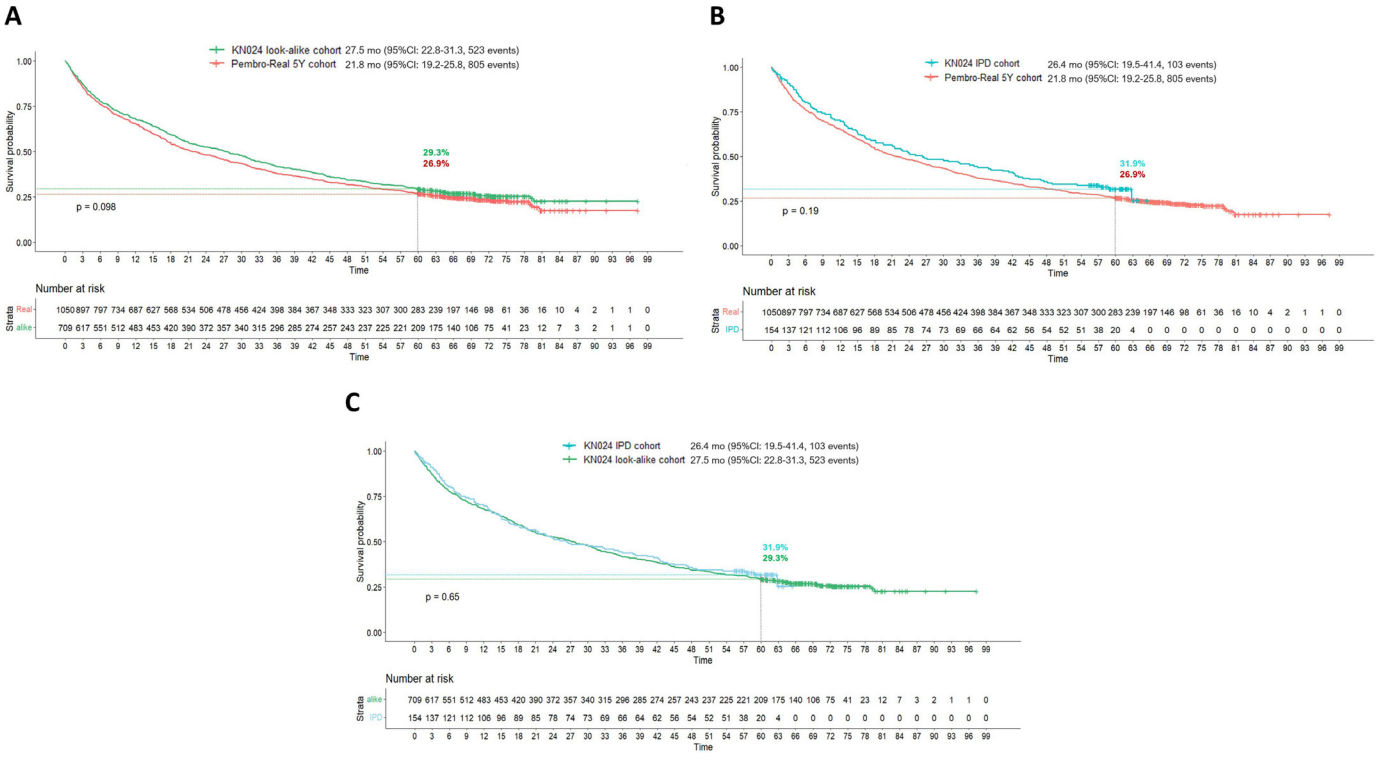

Figure 3 Kaplan-Meier survival estimates. (A) Overall survival and 5-year survival rates for the Pembro-real 5Y cohort and the KN024 look alike cohort; (B) overall survival and 5-year survival rates for the Pembro-real 5Y cohort and the KN024 IPD cohort; (C) overall survival and 5-year survival rates for the KN024 look alike cohort and the KN024 IPD cohort. IPD, individual patient-level data.

nearly perfect alignment of the overall survival (log-rank p value 0.65).

In the KN024 look-alike cohort, the 5-year survival rate for patients with NS histology was 29.7% (95% CI: 25.5% to 34.4%) with a median OS of 26.8 months (95% CI: 21.5 to 31.4), while for patients with Sq histology the 5-year survival rate was 26.5% (95% CI: 17.9% to 37.9%) with a median OS of 27.9 months (95% CI: 19.6 to 36.6).

In the overall cohort, patients with PD-L1 TPS≥90% had a median OS of 25.3 months (95% CI: 19.8 to 31.0) and a 5-year survival rate of 24.4% (136/558, 95% CI: 20.4% to 28.8%), compared with a median OS of 18.0 months (95% CI: 16.7 to 21.6) and a 5-year survival rate of 28.8% (81/281, 95% CI: 20.4% to 28.9%) in those with PD-L1 TPS 50–89% (online supplemental figure 3A). In the KN024 look-alike subgroup, the 5-year survival rate was 26.9% (94/350, 95% CI: 21.8% to 32.9%) for patients with PD-L1 TPS≥90% and 32.0% (64/200, 95% CI: 24.6 to 40.8) for those with TPS 50–89% (online supplemental figure 3B). The exploratory analysis of outcomes based on the IHC antibody used for PD-L1 testing did not reveal any significant differences in 5-year survival rates or median OS across the various antibodies used (online supplemental figure 4).

Treatment duration analysis

By the data cut-off, 1015 patients (96.7%) had permanently discontinued treatment: 659 (64.9%) due to progressive disease, 156 (15.4%) due to toxicity, 77 (7.6%) due to treatment completion, and 106 (10.4%) due to other reasons. The reason for discontinuation was not available for 17 patients (1.7%). Median treatment durations were: 4.4 months (range: 0.1–76.9) for patients who discontinued due to progressive disease, 7.5 months (range: 0.3–63.2) for those who discontinued due to toxicity, 24.2 months (range: 20–32.9) for patients who discontinued due to treatment completion, 27.7 months (range: 0.6–72.2) for those who discontinued due to other reasons, and 9.8 months (range: 0.4–72.7) for patients whose discontinuation reason was not reported.

Figure 4A reports the 5-year survival rates according to the reason for discontinuation, which were 7.9% (52/659 patients) for those who discontinued treatment due to progressive disease, 39.7% (62/156 patients) for those who discontinued due to toxicity, 75.3% (58/77 patients) for those who discontinued due to treatment completion, 67.9% (72/106 patients) for those who discontinued due to other reasons, and 17.6% (3/17 patients) for those whose reason for discontinuation was not provided (p<0.0001).

A total of 222 participants (21.1%) had a minimum treatment duration of 24 months. Among them, 63 (28.4%) patients discontinued treatment due to progressive disease, 22 (9.9%) patients discontinued due to toxicity, 42 (18.9%) patients discontinued due to treatment completion, 57 patients (25.7%) discontinued treatment due to other reasons, and for 3 patients (1.4%) the underlying reason for discontinuation was not reported. At the data cut-off, treatment was still ongoing in 35 patients (15.8%), with a median duration of 69.7 months (range: 60.1–85.3). Figure 4A summarizes the 5-year survival rates according to the underlying discontinuation reason among patients with a minimum treatment duration of 24 months, which were 31.7% (20/63 patients) for those who discontinued treatment due to progressive disease, 72.7% (16/22 patients) for those who discontinued due to toxicity, 78.6% (33/42 patients) for those

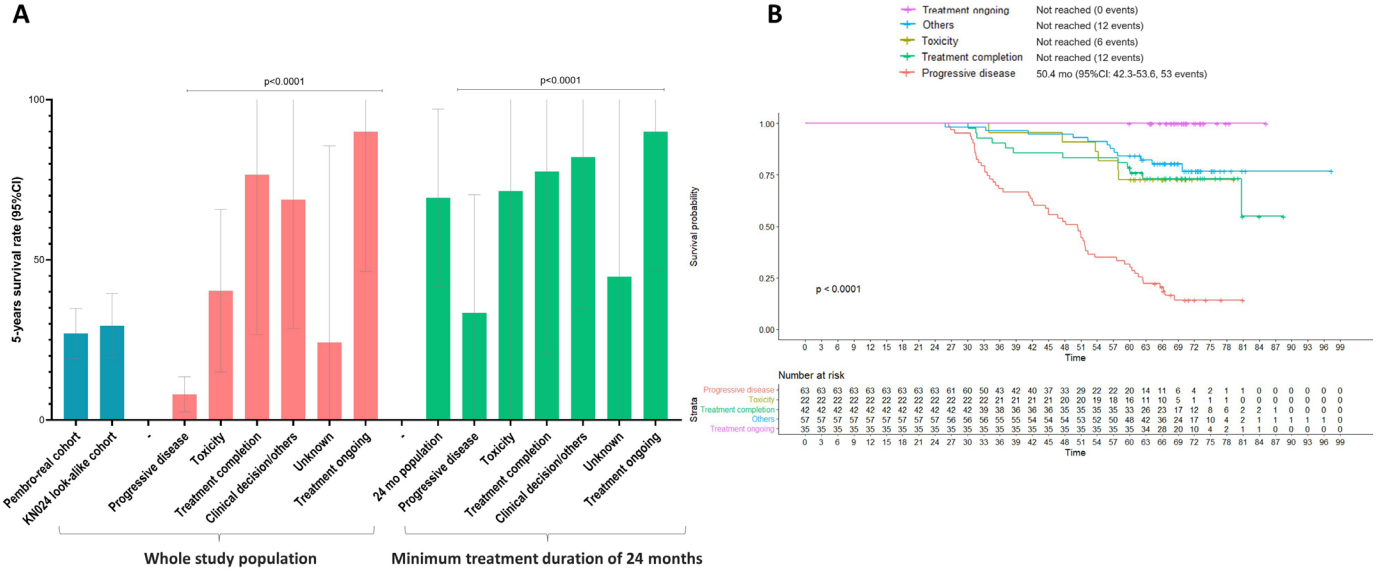

Figure 4 (A) Histogram plot reporting the 5-year survival rate with 95% CI for the whole population and the KN024 look alike cohort (light blue), for the overall study population according to the reason for treatment discontinuation (light red) and for patients with a minimum treatment duration of 24 months according to the reason for treatment discontinuation (red), p value computed with the χ^2 test. (B) Kaplan-Meier survival estimates for overall survival according to the reason for discontinuation among patients with a minimum treatment duration of 24 months. P value computed with the log-rank test.

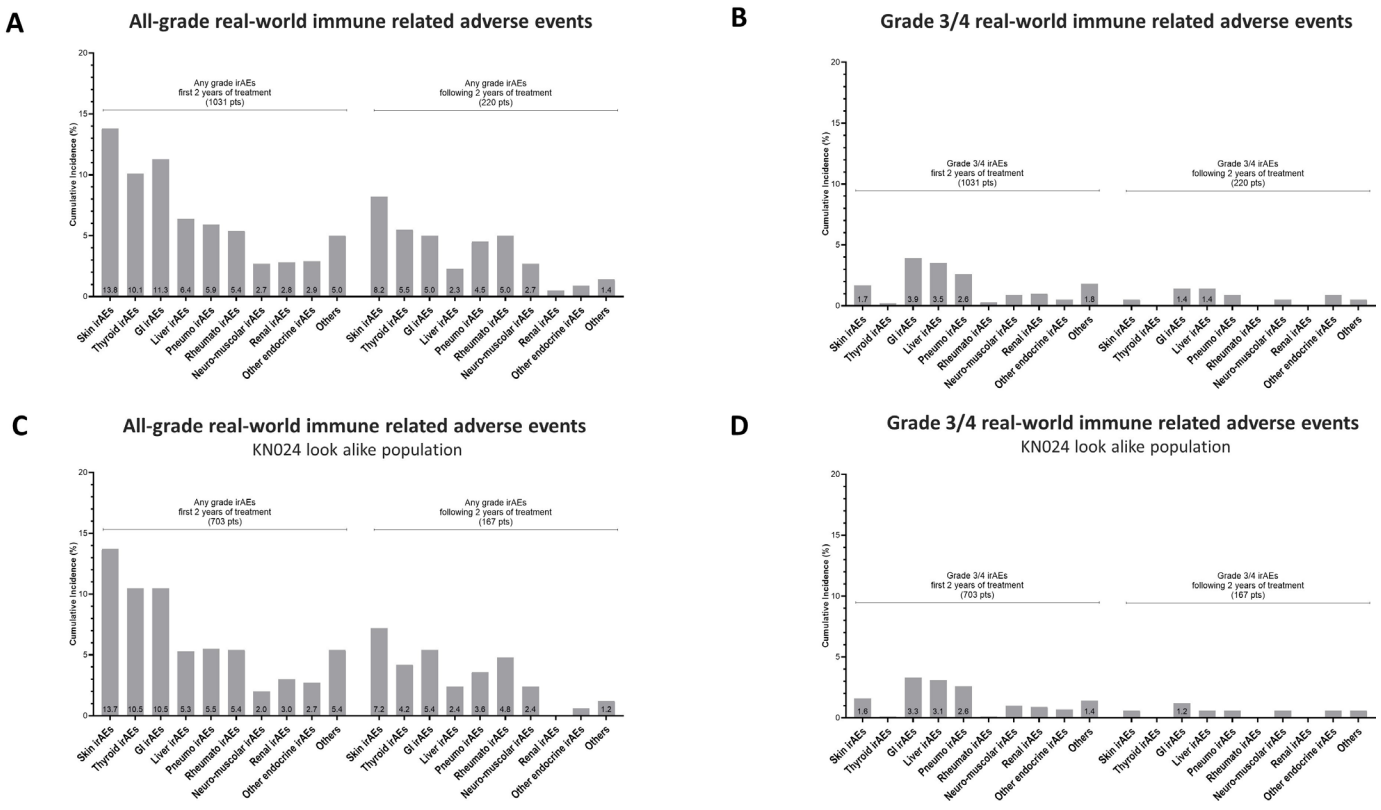

Figure 5 (A) Histogram plot reporting the cumulative incidence of real-world immune-related adverse events (rw-irAEs) of any grade occurred during the first 2 years of treatment among the whole study population and those occurred after the first 2 years of treatment among patients with a minimum treatment duration of 24 months. (B) Histogram plot reporting the cumulative incidence of grade 3/4 rw-irAEs occurred during the first 2 years of treatment among the whole study population and those occurred after the first 2 years of treatment among patients with a minimum treatment duration of 24 months. (C) Histogram plot reporting the cumulative incidence of rw-irAEs of any grade occurred during the first 2 years of treatment among the KN 024 look alike population and those occurred after the first 2 years of treatment among patients with a minimum treatment duration of 24 months. (D) Histogram plot reporting the cumulative incidence of grade 3/4 rw-irAEs occurred during the first 2 years of treatment among the KN 024 look alike population and those occurred after the first 2 years of treatment among patients with a minimum treatment duration of 24 months. Details reported in online supplemental table 4 and 5. irAEs, immune related adverse events; GI, gastrointestinal.

who discontinued due to treatment completion, 84.2% (48/57 patients) for those who discontinued due to other reasons, 33.3% (1/3 patients) for those whose reason for discontinuation was not provided (p<0.0001). Figure 4B reports the Kaplan-Meier survival estimates according to the reason for discontinuation among patients with a minimum treatment duration of 24 months, indicating a significant difference in OS (log-rank p value<0.0001), mostly driven by those who discontinued treatment due to progressive disease, while patients who discontinued due to toxicity, treatment completion, and other reasons achieved similar survival estimates.

Safety analysis

Overall, 1031 patients were included in the safety population, with a 43.8% incidence of rw-irAEs of any grade and a 13.2% incidence of G3/4 rw-irAEs occurring during the first 2 years of treatment (online supplemental table 4 and figure 5A/B). Specifically, skin rw-irAEs of any grade occurred in 13.8% of the patients, followed by gastrointestinal rw-irAEs in 11.3% and thyroid rw-irAEs in 10.1%. The most frequent G3/4 toxicities within the first 2 years were gastrointestinal rw-irAEs in 3.9% of the patients, liver rw-irAEs in 3.5%, and pneumonitis in 2.6%. Among the 220 patients with a minimum treatment duration of 24 months included in the safety analysis for rw-irAEs occurring after the first 2 years of treatment, the incidence was 22.3% for rw-irAEs of any grade and 5.5% for G3/4 rw-irAEs (online supplemental table 4 and figure 5A/B). Similar incidence of any grade and G3/4 rw-irAEs was reported among the KN024 look alike cohort (online supplemental table 5 and figure 5C/D).

DISCUSSION

Pembrolizumab monotherapy represents the most used first-line treatment option for patients with advanced NSCLC with PD-L1≥50% globally. Nonetheless, there is limited data on the long-term efficacy and safety of this treatment outside of clinical trials. Whether there are specific subsets of patients that are more likely to benefit

long-term from pembrolizumab monotherapy was also in need of further investigation.

Our study offers a comprehensive real-world analysis of long-term outcomes with commercial pembrolizumab, providing valuable comparisons to the KEYNOTE-024 trial.[1 2] By including a broader and more heterogeneous population, our study reflects the practical applications and outcomes of pembrolizumab in routine clinical practice. While we observed a slightly lower 5-year survival rate of 26.9% and a median OS of 21.8 months in the overall population, these outcomes remain consistent with the variability anticipated in real-world settings. The KEYNOTE-024 trial reported a 5-year survival rate of 31.9% and a median OS of 26.3 months, achieved under stricter patient selection criteria. Despite these differences, the effectiveness of pembrolizumab observed in our study underscores its clinical relevance outside the trial setting.

To further strengthen our findings, we analyzed a KN024 look-alike cohort, in which we noted a 5-year survival rate of 29.3% and a median OS of 27.5 months. These results closely align with the survival outcomes reported in the original 5-year update of the KEYNOTE-024 trial.[2] This comparison underscores that real-world outcomes can approximate those observed in clinical trials when similar patient selection criteria are applied, as demonstrated in the KN024 look-alike cohort. Furthermore, the broader patient population included in this study reflects the efficacy of pembrolizumab in a more heterogeneous real-world setting, beyond the strict eligibility of clinical trials.

In addition to the long-term follow-up of our study population, we aimed to offer a hierarchical breakdown of the baseline clinicopathologic factors influencing 5-year survival outcomes through CIT analysis, although with a descriptive approach. ECOG-PS emerged as the first hierarchical driver of long-term benefit among all variables, followed by age among those with a good PS, and by PD-L1 TPS among patients aged ≥70 years. While ECOG-PS and PD-L1 TPS with the ≥90% cut-off were already known to significantly impact clinical outcomes in this setting,[3 25 30] increasing age had not been established as a strong prognostic factor in the context of single-agent PD-1 checkpoint inhibitor treatment in previous literature. This observation is the likely result of the extended 5-year observation period, which amplifies the prognostic influence of age as a variable.

Our analysis of treatment duration confirmed that the most prevalent reason for discontinuation was progressive disease. Notably, patients who discontinued due to toxicity had a high 5-year survival rate of 39.7%, consistent with prior evidence suggesting that irAEs may indicate an activated antitumor immunity.[19 31 32] The exceptionally high 5-year survival rates for patients who discontinued due to treatment completion or other reasons are likely influenced by immortal time bias, which is associated with prolonged treatment exposure and better prognosis.

For the first time, our study describes a potential "eradication rate" in the context of the advanced stage disease, represented by the 32 (3.0%) patients who achieved a complete response and remained progression-free at the data cut-off, with a median duration of complete response of 47.5 months. While these patients could be considered potentially cured of their stage IV disease, we acknowledge the complexity of defining cure in this context. Achieving a sustained complete response for 5 years or more might represent a reasonable benchmark, as this aligns with survival landmarks traditionally associated with cure in oncology. However, further research is needed to elucidate the mechanisms and long-term outcomes of this subset, and to refine definitions and criteria for cure in stage IV NSCLC. Similarly, the findings in the KN024 look-alike cohort are comparable to those reported in the KEYNOTE-189 and KEYNOTE-407 trials,[23 24] with similar 5-year survival rates and median OS for NS patients, and better outcomes for Sq patients compared with KEYNOTE-407, highlighting the potential real-world effectiveness of pembrolizumab monotherapy in this population.

In the KEYNOTE-24 trial, 25.8% of patients in the pembrolizumab completed the 35 cycles of treatment,[2] a rate comparable to the 21.1% of patients in our cohort who had a minimum treatment duration of 24 months. The immortal time bias also appears to affect the outcome results in this group. Specifically, 5-year survival rates ranged from 31.7% for those who discontinued due to progressive disease to 100% for those whose treatment was ongoing at the data cut-off, similar to the 81.4% 5-year survival rate reported for this subgroup in the KEYNOTE-24 trial.[2] While these data speak to the tremendous improvements in survival we have seen in this patient population, it is also true that more than 75% of patients are not alive at the 5 years landmark. Therefore, continued efforts to understand the mechanism and correlates of benefits from single-agent PD-1 inhibition remain a critical need.

In this study, we also explored the long-term safety of pembrolizumab monotherapy. In this analysis we showed a 43.8% incidence of rw-irAEs of any grade and a 13.2% incidence of grade 3/4 rw-irAEs within the first 2 years, consistent with the safety profile previously reported for pembrolizumab monotherapy in both clinical trials and real-world studies.[1 19 33] Notably, our study extended the analysis of rw-irAEs to those occurring beyond 2 years of treatment, finding an incidence of 22.3% for any grade and 5.5% for grade 3/4 rw-irAEs. This long-term safety data is relatively scarce in the literature, providing new insights into the management of irAEs over extended treatment periods. Importantly, the incidence of irAEs does not appear to be cumulative, indicating no linear increase over time with prolonged exposure to pembrolizumab. These results align with the 5-year follow-up of the KEYNOTE-001 trial, where pembrolizumab monotherapy was administered continuously until disease progression.[34]

This study acknowledges several limitations, including the retrospective design, which introduces relevant associative bias, and the lack of centralized data review.

We did not use a centralized adjudication of RECIST-based disease assessments, reflecting the inherent variability of real-world clinical practice. While this limitation could have introduced bias in RECIST-dependent endpoints such as response rate and rwPFS, we addressed this through a cluster correction by participating center in the multivariate analyses and prioritized OS and 5-year survival rates as the key endpoints, which are less influenced by center-specific differences. Similarly, the collection of treatment-related adverse events was based on retrospective review of medical records, with adjudication and grading performed by individual site investigators according to CTCAE criteria, with potential implication for reliability and comparability of the reported adverse events across centers.

The limited representation of certain racial groups in our study reflects the demographics of the participating centers but reduces the generalizability of our findings to under-represented populations. This limitation highlights the need for more inclusive research to better understand the impact of pembrolizumab monotherapy in diverse racial and ethnic groups.

The high prevalence of missing data for key variables such as TMB, KRAS mutations, and co-mutational status (eg, TP53) prevented us from conducting a powered analysis that includes these established biomarkers for cancer immunotherapy in NSCLC.[29 35] Additionally, the absence of detailed time points following treatment interruption limited our ability to perform a time-adjusted analysis among patients with a minimum treatment exposure of 24 months, resulting in a primarily descriptive analysis.

This study did not collect specific data on intracranial response in patients with brain metastases. As a result, the potential impact of pembrolizumab on intracranial disease control could not be evaluated, limiting our ability to assess outcomes in this subgroup.

Lastly, this study predominantly included data from elite cancer centers, which may limit the generalizability of the findings to less specialized or community-based clinical settings. These centers often have access to advanced diagnostic and therapeutic resources, potentially influencing patient outcomes and treatment practices.

Despite these limitations, we applied a rigorous methodology to report our data and present outcomes from the study cohort, adhering closely to recently published guidelines on reporting real-world evidence.[21]

In conclusion, our real-world study supports the long-term benefits of pembrolizumab observed in clinical trials like KEYNOTE-024, while also highlighting the additional challenges and broader patient demographics encountered in routine practice. The CIT analysis offers valuable clinical insights into the potentially hierarchical role of baseline clinicopathologic factors, establishing ECOG-PS as the most significant predictor of long-term benefit from treatment, followed by age and PD-L1 expression. This study provides valuable real-world evidence that guides clinical decisions and enhances the understanding of single-agent immunotherapy impact on diverse patient populations with NSCLC.

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Acknowledgements AC acknowledges the support of the International Association for the Study of Lung Cancer (IASLC) young investigators grant 2024. EB acknowledges the support by the Associazione Italiana per la Ricerca sul Cancro (AIRC, Investigator Grant No. IG20583), by Institutional funds of Università Cattolica del Sacro Cuore (UCSC-project D1), and funds of Ministero della Salute (Ricerca Corrente 2024).

Contributors All authors contributed to the publication according to the ICMJE guidelines for the authorship (study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision). All authors read and approved the submitted version of the manuscript (and any substantially modified version that involves the author's contribution to the study). Each author has agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. AC serves as the guarantor for data integrity.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests AC received grants for consultancies/advisory boards from MSD, BMS, OncoC4, IQVIA, AstraZeneca, REGENERON, Access Infinity, Ardelis Health, Alpha Sight, Guidepoint, Roche; speaker fees from AstraZeneca, Pierre-Fabre, MSD, Sanofi/REGENERON; payment for writing/editorial activity from BMS, MSD; travel support from Sanofi/REGENERON, MSD. JB declares honoraria/consulting or advisory role from AstraZeneca, BMS, Roche, Access Oncology, travel support from MSD, Roche, Janssen Oncology. GPS has received payment or honoraria for advisory boards from Novartis, Roche, Bayer, unrelated to this project. DO'R has received conference attendance support from Takeda, Janssen, Servier, MSD. EB has received grants or contracts from AstraZeneca, Roche and honoraria for lectures from Merck-Sharp & Dome, AstraZeneca, Pfizer, Eli-Lilly, Bristol Myers Squibb, Novartis, Takeda and Roche; EB has been member of Data Safety Monitoring Board or Advisory Board of Merck-Sharp & Dome, Pfizer, Novartis, Bristol Myers Squibb, AstraZeneca, Celltrion and Roche. AA declares consulting or advisory role for Bristol Myers Squibb, AstraZeneca, Boehringer Ingelheim, Roche, MSD, Pfizer, Eli Lilly, Astellas, Takeda, and Amgen; speaker's bureau for Eli Lilly, and AstraZeneca. AR has received advisory board or speaker bureau honoraria from AstraZeneca, MSD, Novartis, Pfizer, BMS, Takeda, and Amgen; compensated activity for editorial projects from AstraZeneca, MSD, Novartis, Roche, and Regeneron. AL has received speakers' fee for AstraZeneca, MSD, Sanofi and Takeda; he also received travel support from MSD and Novartis, has been on advisory board for AstraZeneca, BeiGene, Novartis and Sanofi, and has attended editorial activities sponsored by Eli Lilly and Roche. FM received honorary for advisory board roles with MDS, BMS, Takeda, Roche, AstraZeneca, Novartis. Paolo Bironzo served as consultant/advisory board for Regeneron, Pierre-Fabre, Janssen, Seagen. DO declares research funding/grants (to institution) from BMS, Merck, Palobiofarma, Pfizer, Genentech, AstraZeneca, Nuvalent, AbbVie, Onc.AI. TN-D received support to attend educational conferences from AbbVie, AstraZeneca, BMS, Boehringer Ingelheim, Lilly, MSD, Otsuka, Roche, Takeda; advisory roles for AbbVie, Amgen, Bayer, AstraZeneca, BMS, Boehringer Ingelheim, Chugai, Daiichi Sankyo, Eli-Lilly, EQRx, Gilead, GSK, Janssen, Merck, MSD, Novartis, Novocure, Otsuka, Pfizer, Roche, Sanofi, Takeda; speaker bureau from Amgen, AstraZeneca, Chugai, Gilead, Janssen, Lilly, Medscape, Guardant, Merck, MSD, Roche, Takeda; trial steering committees' member for AstraZeneca, Roche. BT received lecture fees from Pfizer. LC is an employee of Fortrea. BT declares honoraria from Roche. IM declares travel support from Takada, MSD, Pfizer, Oxyvie and speaker fees from Regeneron. A-MD declares research grants from Amgen, the Dutch Cancer Society and HANART, consulting fees from Amgen, Bayer, Boehringer Inglheim, Sanofy, Roche, Janssen and AstraZeneca, speaker fees from Janssen, Pfizer, AstraZeneca, Lilly and Takeda,

advisory board role for Takeda and Roche. GLR declares fees for advisory boards, travel support, consultancies from MSD, BMS, Roche, Sanofi, Regeneron, Lilly, AstraZeneca, Janssen, Pfizer, Novartis, Bayer, Takeda, Amgen, GSK, Daichii. TAH declares stock interests for GlaxoSmithKline and honoraria from Novartis. BR served as consultant/advisory board for AMGEN, Regeneron, AstraZeneca, Capvision. Speaker fee: AstraZeneca. Received honoraria from Targeted Oncology, SITC. All other authors declare no conflicts of interest associated with the present study.

Patient consent for publication Not applicable.

Ethics approval The procedures followed were in accordance with the precepts of Good Clinical Practice and the declaration of Helsinki. The Pembro-real IT cohort Institutional Review Board (IRB) approval reference is "Comitato Etico per le province di L'Aquila e Teramo, verbale N.15 del 28 Novembre 2019)". For Italian institutions participating to the Pembro-real 5 years cohort the IRB reference is "Comitato Etico Fondazione Policlinico Universitario Campus Bio-Medico, IRB ID approval N.PAR 70.23 OSS, 17 May 2023, registry number: SC 2023.0682" (written informed consent was obtained for patients alive at the time of data collection). For the non-Italian institutions participating to the Pembro-real 5 years cohort the IRB reference is "Health Research Authority approval of the 22nd of November 2023, REC reference 23/HRA/4467" (written informed consent was waived due to the retrospective and observational nature of the study). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The dataset used for this study contains patient-level data that cannot be made available to third parties, although anonymized. Third party research proposals will be assessed by the study investigators and performed by the study team if accepted. Requests can be made to AC (a.cortellini@policlinicocampus.it).

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