

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

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**Supplementary Materials**



## Supplementary Methods.

The selection and categorization of baseline clinicopathologic characteristics were guided by a principle of clinical prioritization based on the expert judgment of the authors. This process was further informed by prior literature and real-world evidence previously published in similar populations<sup>1-5</sup>. Baseline clinicopathologic characteristics of interest for the descriptive analysis were categorized as follows: age at pembrolizumab initiation (< 70 vs. ≥ 70 years old); biological sex (male vs. female); race (white vs. black/African-American vs. Asian vs. Hispanic vs. others); body mass index according to the World Health Organization (obese vs. overweight vs. normal-weight vs. underweight); 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 (squamous cell carcinoma vs. adenocarcinoma vs. other histologies/not otherwise specified); presence of central nervous system (CNS) metastases (yes vs. no); bone metastases (yes vs. no); liver metastases (yes vs. no); number of metastatic sites (> 3 vs. ≤ 3); corticosteroids administration at baseline within the 30 days before treatment commencement (doses ≥10 mg/day prednisone or equivalent vs. doses <10 mg/day prednisone or equivalent vs. none); epidermal growth factor receptor mutation status (positive vs. negative vs. not assessed); Kirsten rat sarcoma virus receptor mutation status (positive vs. negative vs. not assessed); BRAF mutation status (positive vs. negative vs. not assessed); anaplastic lymphoma kinase translocation status (positive vs. negative vs. not assessed); ROS-1 translocation status (positive vs. negative vs. not assessed). Although available for a minority of patients, tumor mutational burden (TMB) was classified as high and non-high as previously described (cut-off 19 mut/MB)<sup>6</sup>, following harmonization of the score provided by different platforms<sup>7</sup>. Distributions of other molecular findings such as RET translocations and MET exon14 skipping mutations were reported descriptively, given the different sequencing used with no pre-established standard reference. Patients with missing information for any of the variables were not excluded from the descriptive analysis and were categorized as unknown.

For the conditional inference tree analysis, baseline variables were chosen based on their clinical priority, excluding those with a high prevalence of data-missingness. Patients with EGFR mutation/ALK translocation were excluded *a priori*. The following variables were included: age at pembrolizumab initiation (< 70 vs. ≥ 70 years old); biological sex (male vs. female); race (white vs. any other race); 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 prednisone or equivalent vs. doses ≥10 mg/day prednisone or equivalent vs. none).

To create the KN024 look-alike cohort, we excluded patients with ECOG-PS ≥2 or unknown, those with EGFR/ALK positive tumors or unknown EGFR/ALK status, those with pre-existing autoimmune disease (excluding thyroid disorders) and those with pre-existing autoimmune disease status unknown.

1. Cortellini A, Friedlaender A, Banna GL, et al. Immune-related Adverse Events of Pembrolizumab in a Large Real-world Cohort of Patients With NSCLC With a PD-L1 Expression ≥50% and Their Relationship With Clinical Outcomes. *Clinical Lung Cancer*. 2020;21(6):498-508.e2. doi:10.1016/j.clcc.2020.06.010
2. Cortellini A, Cannita K, Tiseo M, et al. Post-progression outcomes of NSCLC patients with PD-L1 expression ≥50% receiving first-line single-agent pembrolizumab in a large multicentre real-world study. *European Journal of Cancer*. 2021;148:24-35. doi:10.1016/j.ejca.2021.02.005
3. Cortellini A, Ricciuti B, Tiseo M, et al. Baseline BMI and BMI variation during first line pembrolizumab in NSCLC patients with a PD-L1 expression ≥ 50%: a multicenter study with external validation. *Journal for ImmunoTherapy of Cancer*. 2020;8(2):e001403. doi:10.1136/jitc-2020-001403
4. Cortellini A, Tiseo M, Banna GL, et al. Clinicopathologic correlates of first-line pembrolizumab effectiveness in patients with advanced NSCLC and a PD-L1 expression of ≥ 50%. *Cancer Immunology, Immunotherapy*. 2020/11/01 2020;69(11):2209-2221. doi:10.1007/s00262-020-02613-9
5. Cortellini A, De Giglio A, Cannita K, et al. Smoking status during first-line immunotherapy and chemotherapy in NSCLC patients: A case-control matched analysis from a large multicenter study. *Thoracic Cancer*. 2021;12(6):880-889. doi:<https://doi.org/10.1111/1759-7714.13852>
6. Ricciuti B, Wang X, Alessi JV, et al. Association of High Tumor Mutation Burden in Non-Small Cell Lung Cancers With Increased Immune Infiltration and Improved Clinical Outcomes of PD-L1 Blockade Across PD-L1 Expression Levels. *JAMA Oncology*. 2022;8(8):1160-1168. doi:10.1001/jamaoncol.2022.1981
7. Vokes NI, Liu D, Ricciuti B, et al. Harmonization of Tumor Mutational Burden Quantification and Association With Response to Immune Checkpoint Blockade in Non-Small-Cell Lung Cancer. *JCO Precision Oncology*. 2019;(3):1-12. doi:10.1200/po.19.00171



Supplementary Table 1: Participating centers list.

Participating center	N	(%)
Papardo Hospital, Messina, Italy	2	0.2%
University of Naples Federico II, Naples, Italy	4	0.4%
Henry Dunant Hospital Center, Athens, Greece	28	2.6%
IRCCS Istituto Tumori "Giovanni Paolo II", 70124 Bari, Italy	16	1.5%
Beaumont Hospital, Beaumont RCSI Cancer Centre, Dublin, Ireland	9	0.8%
University of Brescia, ASST Spedali Civili, 25123 Brescia, Italy	4	0.4%
Chelsea and Westminster Hospital, London, United Kingdom	6	0.6%
Fondazione Policlinico Universitario Campus Bio-Medico, Roma, Italy	20	1.9%
University G. D'Annunzio of Chieti-Pescara, Chieti, Italy	9	0.8%
Centre Hospitalier Intercommunal, Creteil, France	14	1.3%
Dana-Farber Cancer Institute, Boston, Massachusetts, United States	132	12.4%
Careggi University Hospital, Florence, Italy	14	1.3%
University Hospital Frankfurt, Frankfurt, Germany	20	1.9%
Cantonal Hospital Fribourg, Fribourg, Switzerland	14	1.3%
Medical University of Gdańsk, Gdańsk, Poland	11	1.0%
Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy	22	2.1%
Guy's and St Thomas' Hospitals NHS Trust, London, United Kingdom	48	4.5%
Hospital Universitario 12 De Octubre, Madrid, Spain	6	0.6%
Hospital Clinic of Barcelona, Barcelona, Spain	16	1.5%
Hospital Sírio-Libanês, São Paulo, SP, Brazil	5	0.5%
Hospital Universitario Infanta Leonor, Madrid, Spain	3	0.3%
University Hospital, Geneva, Switzerland	19	1.8%
Catalan Institute of Oncology (ICO), L'Hospitalet, Barcelona, Spain	15	1.4%
IRCCS National Cancer Institute Regina Elena, Rome, Italy	21	2.0%
Hammersmith Hospital Campus, Imperial College London, London, United Kingdom	27	2.5%
Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy	26	2.4%
IRCCS Ospedale Policlinico San Martino, Genoa, Italy	16	1.5%
King Hussein Cancer Center, Amman, Jordan	10	0.9%
Santa Maria Goretti Hospital, Latina, Italy	6	0.6%
Azienda Ospedaliero-Universitaria di Perugia, Perugia, Italy	14	1.3%
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy	8	0.8%
AORN dei Colli Monaldi, Naples, Italy	7	0.7%
Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, United States	11	1.0%
IRCCS San Gerardo dei Tintori, Monza, Italy	12	1.1%
Department of Oncology, IRCCS Sacro Cuore "Don Calabria", Negrar, Italy	3	0.3%
Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Milan, Italy	5	0.5%
Northumbria Healthcare NHS Foundation Trust, Cramlington, United Kingdom	14	1.3%
University of Piemonte Orientale, Novara, Italy	14	1.3%
University of Turin, San Luigi Hospital, Orbassano, Italy	31	2.9%
The Ohio State University Comprehensive Cancer Center, Columbus, OH, United States	21	2.0%
University Hospital of Parma, Parma, Italy	20	1.9%
Istituto Nazionale Tumori, IRCCS "Fondazione G. Pascale" Naples, Italy	10	0.9%
Ospedale P. Pederzoli, Peschiera del Garda (VR), Italy	5	0.5%
Fondazione IRCCS Policlinico San Matteo, Pavia, Italy	13	1.2%
AUSL della Romagna, Ravenna, Italy	9	0.8%
Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands	36	3.4%
Rush University Medical Center Chicago IL, United States	9	0.8%
Azienda Ospedaliero Universitaria Sant'Andrea, Rome, Italy	22	2.1%
Hospital de la Santa Creu I Sant Pau, Barcelona, Spain	10	0.9%
Stanford Cancer Institute, Stanford University, Palo Alto, CA, United States	16	1.5%
"G. Mazzini" Hospital of Teramo, Teramo, Italy	8	0.8%
Azienda Ospedaliera Santa Maria of Terni, Terni, Italy	6	0.6%
The UCL Cancer Institute, University College London Hospitals NHS Trust, London, United Kingdom	18	1.7%
Cliniques Universitaires St-Luc, UCLouvain, Brussels, Belgium	33	3.1%
Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), Udine, Italy	17	1.6%
"Sapienza" University of Rome, Rome, Italy	4	0.4%
AUSL Latina (Aprilia) - University of Rome "Sapienza", Italy	3	0.3%
ASST Sette Laghi, Ospedale di Circolo e Fondazione Macchi, Varese, Italy	18	1.7%
Versilia Hospital, Azienda USL Toscana Nord Ovest, Lido di Camaiore, Italy	6	0.6%
Yale School of Medicine, New Haven, Connecticut, United States	84	7.9%
Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States	33	3.1%
Total	1063	100.0%



Supplementary Table 2: Patients’ comorbidities at baseline.

	1050 patients N (%)
<b>Hypertension</b>	
No	469 (44.7)
Yes	523 (49.8)
Not reported	58 (5.5)
<b>Myocardial infarction</b>	
No	858 (81.7)
Yes	128 (12.2)
Not reported	64 (6.1)
<b>Other cardio-vascular conditions</b>	
No	715 (68.1)
Yes	271 (25.8)
Not reported	64 (6.1)
<b>Type 2 diabetes</b>	
No	809 (77.0)
Yes	177 (16.9)
Not reported	64 (6.1)
<b>Pulmonary disease</b>	
No	711 (67.7)
Yes	275 (26.2)
Not reported	64 (6.1)
<b>Dyslipidemia</b>	
No	666 (63.4)
Yes	314 (29.9)
Not reported	70 (6.7)
<b>Other comorbidities</b>	
No	563 (53.6)
Yes	374 (35.6)
Not reported	113 (10.8)
<b>Pre-existent autoimmune disease</b>	
No	933 (88.9)
Not reported	64 (6.1)
Yes	53 (5.0)
Connective tissue disorders	11 (20.8)
Thyroid disorders	13 (24.5)
Inflammatory bowel disease	2 (3.8)
Psoriasis	11 (20.8)
Rheumatoid arthritis	7 (13.2)
Neurological disorders	4 (7.5)
Others	5 (9.4)



**Supplementary Table 3:** Additional details on baseline biomarkers assessment. FNAB: fine needle aspiration biopsy, EBUS-EUS TBNA: endobronchial/endoscopic ultrasound-guided trans bronchial needle aspiration; IHC: immunohistochemistry; TMB: tumor mutational burden; pts: patients.



	1050 patients N (%)
<b>Type of specimen used for PD-L1 assessment</b>	
Surgical specimen	127 (12.1)
Biopsy	510 (48.6)
FNAB/EBUS-EUS TBNA/cytology	360 (34.3)
Not reported	53 (5.0)
<b>Type of specimen used for PD-L1 assessment</b>	
Primary Tumor	510 (48.6)
Metastatic site	443 (42.2)
Not reported	97 (9.2)
<b>IHC antibody clone used for PD-L1 assessment</b>	
22C3	646 (61.5)
SP263	190 (18.1)
E1L3N	114 (10.9)
Others	48 (4.6)
Not reported	52 (5.0)
<b>EGFR mutations</b>	<b>19</b>
Ex20 Ins	4 (21.1)
Del_19	3 (15.8)
L858R	3 (15.8)
G719C	2 (10.5)
C781Y	1 (5.3)
L747P	1 (5.3)
L861G	1 (5.3)
T785T	1 (5.3)
V769M	1 (5.3)
Not reported	2 (10.5)
<b>KRAS mutations</b>	<b>224</b>
G12C	102 (45.5)
G12V	38 (17.0)
G12A	23 (10.3)
G12D	15 (6.7)
G12F	6 (2.7)
Q61H	5 (2.2)
G13C	5 (2.2)
G12S	4 (1.8)
Q61L	3 (1.3)
G12N	2 (0.9)
G13D	2 (0.9)
G61L	2 (0.9)
Q61R	1 (0.4)
G13R	1 (0.4)
L19F	1 (0.4)
G12I	1 (0.4)
G12R	1 (0.4)
NA	12 (5.4)
<b>BRAF mutations</b>	<b>26</b>
V600E	15 (57.7)
G469A	2 (7.7)
D594N	1 (3.8)
G466L	1 (3.8)
G469E	1 (3.8)
G469V	1 (3.8)
L485F	1 (3.8)
V471F	1 (3.8)
NA	3 (11.5)
<b>TMB details (Mut/Mb)</b>	<b>109 patients; median (range)</b>
FoundationOne CDx (10 pts)	10.0 (1.0-42.0)
OncoPanel DFCI (89 pts)	10.6 (1.5-41.8)
Whole exome sequencing (10 pts)	4.4 (2.0-22.0)

**Supplementary Table 4:** Cumulative incidence of real-world immune related adverse events of any grade and grade 3/4 occurred during the first 2 years of treatment (whole study population) and occurred after the first 2 years of treatment (population with minimum treatment exposure of 24 months).



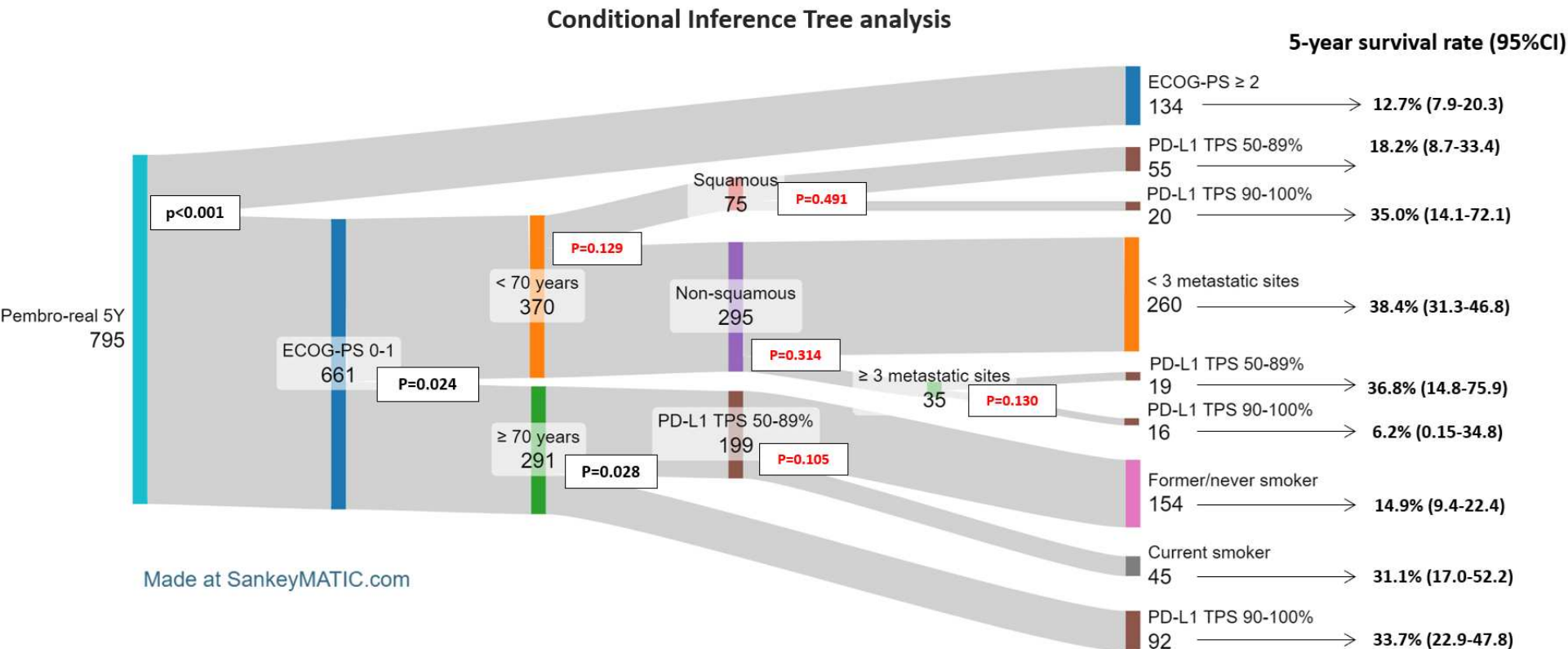
	First 2 years safety population (N=1031 pts)		Treatment beyond 2 years safety population (N=220 pts)	
	Any grade (%)	Grade 3-4 (%)	Any grade (%)	Grade 3-4 (%)
Overall	452 (43.8)	136 (13.2)	49 (22.3)	12 (5.5)
Skin	142 (13.8)	18 (1.7)	18 (8.2)	1 (0.5)
Thyroid	104 (10.1)	2 (0.2)	12 (5.5)	-
Gastro-intestinal	117 (11.3)	40 (3.9)	11 (5.0)	3 (1.4)
Liver	65 (6.4)	36 (3.5)	5 (2.3)	3 (1.4)
Pneumonitis	61 (5.9)	27 (2.6)	10 (4.5)	2 (0.9)
Rheumatologic	56 (5.4)	3 (0.3)	11 (5.0)	-
Neuromuscular	28 (2.7)	9 (0.9)	6 (2.7)	1 (0.5)
Renal	29 (2.8)	10 (1.0)	1 (0.5)	-
Other endocrine	30 (2.9)	5 (0.5)	2 (0.9)	2 (0.9)
Others	52 (5.0)	19 (1.8)	3 (1.4)	1 (0.5)

**Supplementary Table 5:** KN024 look alike cohort; cumulative incidence of real-world immune related adverse events of any grade and grade 3/4 occurred during the first 2 years of treatment and occurred after the first 2 years of treatment (population with minimum treatment exposure of 24 months).

	First 2 years safety population (N=703 pts)		Treatment beyond 2 years safety population (N=167 pts)	
	Any grade (%)	Grade 3-4 (%)	Any grade (%)	Grade 3-4 (%)
Overall	312 (44.4)	23 (3.3)	35 (21.0)	8 (4.8)
Skin	96 (13.7)	11 (1.6)	12 (7.2)	1 (0.6)
Thyroid	74 (10.5)	1 (0.1)	7 (4.2)	-
Gastro-intestinal	74 (10.5)	23 (3.3)	9 (5.4)	2 (1.2)
Liver	37 (5.3)	22 (3.1)	4 (2.4)	1 (0.6)
Pneumonitis	39 (5.5)	18 (2.6)	6 (3.6)	1 (0.6)
Rheumatologic	38 (5.4)	1 (0.1)	8 (4.8)	-
Neuromuscular	14 (2.0)	7 (1.0)	4 (2.4)	1 (0.6)
Renal	21 (3.0)	6 (0.9)	-	-
Other endocrine	19 (2.7)	5 (0.7)	1 (0.6)	1 (0.6)
Others	38 (5.4)	10 (1.4)	2 (1.2)	1 (0.6)

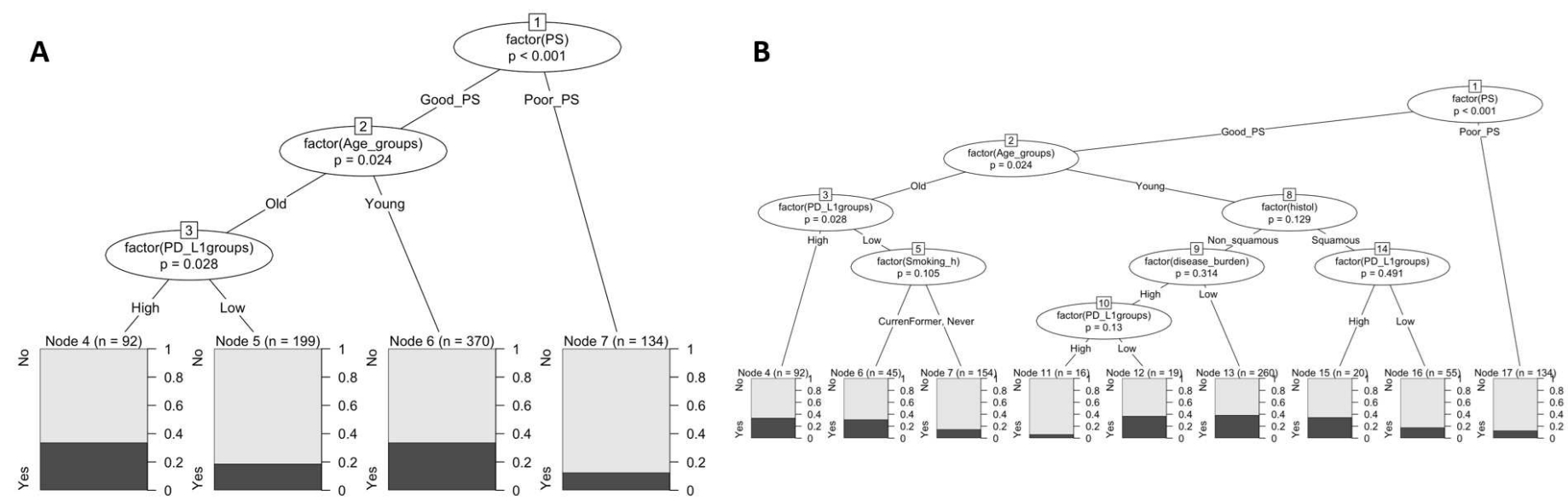


**Supplementary Figure 1:** Sankey diagram reporting the descriptive conditional inference tree (CIT) analysis performed using an alpha level of 0.5 to potentially include the highest number of variables. Patients with EGFR mutation/ALK translocation were excluded a priori, patients with missing variables were excluded. Included covariates were: age at pembrolizumab initiation (<70 vs. ≥70 years old); biological sex (male vs. female); race (white vs. any other race); 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). Non-significant split p-values were reported in red. 95%CI: 95% confidence intervals.



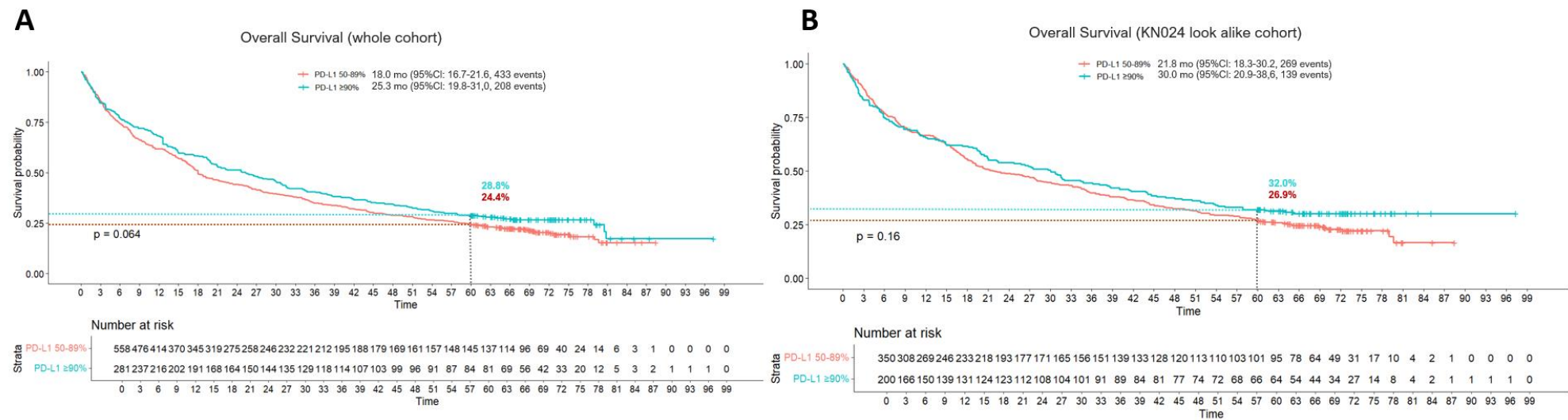


Supplementary Figure 2: Raw results of the conditional inference tree analysis. **A)** with alpha set at 0.1, **B)** with alpha set at 0.5.





**Supplementary Figure 3:** Kaplan-Meier survival estimates for overall survival according to the PD-L1 expression among the **A) Overall Population** and **B) KN024 look alike** population. 95%CI: 95% confidence intervals.



**Supplementary Figure 4:** Kaplan-Meier survival estimates for overall survival according to the Immunohistochemistry (IHC) antibody used to assess PD-L1 expression in the study population.

