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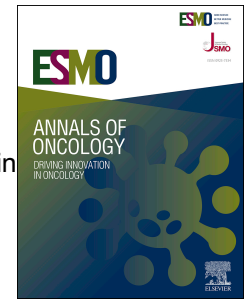

Pembrolizumab with or without platinum-based chemotherapy as first-line treatment in advanced NSCLC expressing PD-L1 ≥50%: The PERSEE randomized phase III trial (GFPC 01-2020)

Renaud Descourt, Alice Mogenet, Maelys Consigny, Marie Bernardi, Romain Corre, Olivier Bylicki, Jean-Bernard Auliac, Alain Vergnenègre, Charles Ricordel, Julian Pinsolle, Marie Wislez, Maud Pedrono, Rémi Veillon, Lionel Falchero, Florian Guisier, Pierre-Alexandre Hauss, Acya Bizieux-Thaminy, Stéphane Hominal, Anne Madroszyk, Hubert Curcio, Roland Schott, Eric Huchot, Benjamin Besse, Chrystèle Locher, Jacques Le Treut, Marie-Capucine Willemin, Géraldine François, Arnaud Uguen, Maurice Pérol, Christos Chouaïd, Laurent Greillier, Chantal Decroisette

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The addition of chemotherapy to pembrolizumab significantly prolonged PFS compared with pembrolizumab monotherapy in treatment-naïve patients with advanced NSCLC and high PD-L1 expression (≥50% of tumor cells)

PERSEE is an academic, prospective, multicenter, randomized, phase III trial conducted across 28 sites in France comparing pembrolizumab plus chemotherapy and pembrolizumab monotherapy as first-line in treatment-naïve patients with NSCLC.

Key eligibility criteria

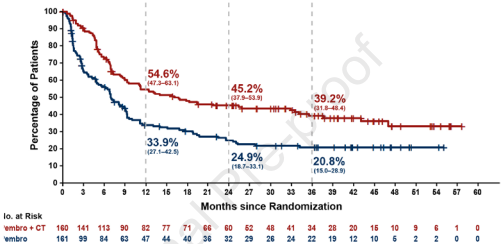
- Age ≥18 years
- Stage IV NSCLC OR Unresectable Stage III NSCLC not eligible for radiotherapy
- PD-L1 expression on ≥50% of tumor cells
- No known *EGFR* mutations, no *ALK* or *ROS1* rearrangements
- ECOG PS 0-1

	Pembro + CT	Pembro
Randomized ITT population	*N* = 160	*N* = 161
Received ≥1 dose Safety population	*n* = 158 Carbo + pacli (*n* = 32) Carbo + pemet (*n* = 111) Cispl + pemet (*n* = 15)	*n* = 159
Planned treatment completed	*n* = 45	*n* = 27

Conclusion: The addition of platinum-based chemotherapy to pembrolizumab significantly prolonged PFS compared with pembrolizumab monotherapy.

Primary endpoint: Progression-Free Survival*

Arm	Events *n* (%)	Median PFS (95% CI), months	HR (95% CI) Two-sided *P* value
Pembro + CT	93 (58.1)	16.1 (11–34.1)	0.56 (0.43–0.74)
Pembro	117 (72.7)	6.9 (5.5–9.3)	*P* < 0.001

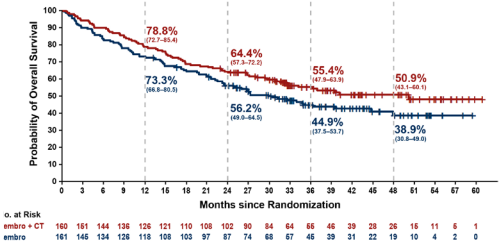


Median follow-up: 38.7 months

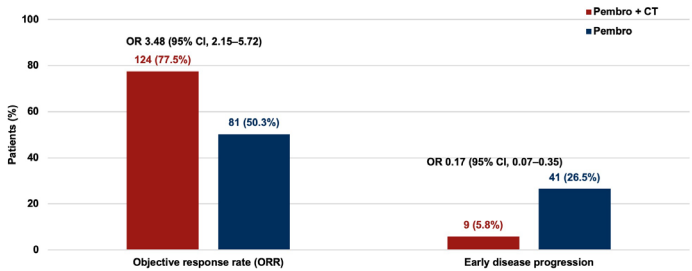
*PFS according to blinded central read

Overall Survival

Arm	Events *n* (%)	Median OS (95% CI), months	HR (95% CI) Two-sided *P* value
Pembro + CT	74 (46.3)	50.2 (32.6–NC)	0.77 (0.56–1.05)
Pembro	89 (55.3)	29.9 (23.4–47.9)	NC



Treatment response (ITT population)



Adverse Events (Safety population)

	Pembro + CT (*N* = 158)	Pembro (*N* = 159)
Treatment-related AE		
Any grade	149 (94)	119 (75)
Grade ≥3	86 (54)	31 (19)
Grade 5	3 (1.9)	3 (1.9)
Immune related AE		
Any grade	39 (25)	32 (20)
Grade ≥3	21 (13)	20 (13)
Grade 5	0 (0)	2 (1.3)
Treatment action (All AEs) leading to		
Pembro discontinuation	44 (28)	38 (24)
Pembro pause	78 (49)	39 (25)
CT discontinuation	76 (48)	NA
CT pause	72 (46)	NA
CT dose reduction	72 (46)	NA

Original article

Pembrolizumab with or without platinum-based chemotherapy as first-line treatment in advanced NSCLC expressing PD-L1 ≥50%: The PERSEE randomized phase III trial (GFPC 01-2020)

Short title: Pembrolizumab with or without chemotherapy in NSCLC

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Highlights

- PERSEE compared pembrolizumab plus platinum-based chemotherapy vs. pembrolizumab in PD-L1-high advanced NSCLC
- Adding chemotherapy to pembrolizumab prolonged PFS vs pembrolizumab monotherapy (16.1 vs 6.9 months; HR, 0.56; P<0.001)
- Duration of response was 30.0 months in the combination group and 15.6 months in the monotherapy group
- Grade ≥3 treatment-related adverse events were more frequent with combination therapy (54% vs 19%)
- Grade ≥3 immune-related adverse events occurred equally in both groups (13% each)

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Abstract

Background: Pembrolizumab, alone or combined with platinum-based chemotherapy, is a standard first-line treatment for patients with metastatic non-small-cell lung cancer (NSCLC) without actionable oncogenic alterations and with high programmed death-ligand 1 (PD-L1) expression. We conducted a head-to-head comparison of these two treatment strategies.

Methods: In this multicenter, phase III trial (PERSEE, NCT04547504), adult patients with treatment-naïve stage IV or unresectable stage III NSCLC not amenable to definitive radiotherapy and PD-L1 expression ≥50% were randomly (1:1) assigned to receive pembrolizumab (200 mg every 3 weeks, for up to 35 cycles) or pembrolizumab in combination with four cycles of induction chemotherapy, stratified according to the presence of brain metastases and histologic subtype. Patients with non-squamous histology received cisplatin or carboplatin (AUC 5) plus pemetrexed, followed by pembrolizumab–pemetrexed maintenance; patients with squamous histology received carboplatin (AUC 6) plus paclitaxel, followed by pembrolizumab maintenance. The primary endpoint was progression-free survival (PFS), assessed by blinded central review according to RECIST v1.1. Key secondary endpoints included overall survival (OS), objective response rate, duration of response, and safety.

Results: A total of 321 patients underwent randomization, with 160 assigned to pembrolizumab plus chemotherapy and 161 to pembrolizumab monotherapy. At a median follow-up of 38.7 months, median PFS was significantly longer with combination therapy than with monotherapy (16.1 months [95% CI, 11.0–34.1] vs. 6.9 months [95% CI, 5.5–9.3]; hazard ratio (HR), 0.56; 95% CI, 0.43–0.74; P<0.001). Median OS was 50.2 months versus 29.9 months, respectively (HR, 0.77; 95% CI, 0.56–1.05). Grade ≥3 treatment-related adverse events occurred in 54% and 19% of

patients, respectively; grade ≥3 immune-related adverse events occurred in 13% of patients in each group.

Conclusions: Among patients with treatment-naïve advanced NSCLC and high PD-L1 expression, the addition of platinum-based chemotherapy to pembrolizumab significantly prolonged PFS compared with pembrolizumab monotherapy.

Keywords: NSCLC; platinum-based chemotherapy; pembrolizumab; PD-L1 expression.

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Introduction

Immune checkpoint inhibitors (ICIs) targeting the programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) pathway has become a mainstay in the management of advanced non-small cell lung cancer (NSCLC).[1] Among ICIs, the PD-1 inhibitor pembrolizumab is recommended as a standard first-line monotherapy treatment for patients with metastatic NSCLC whose tumors express PD-L1 on at least 50% of tumor cells and who lack actionable oncogenic alterations, following the pivotal phase III KEYNOTE-024 trial.[2,3] In the second interim analysis of KEYNOTE-024, pembrolizumab significantly improved median progression-free survival (PFS) (10.3 versus 6.0 months; hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.37–0.68) and overall survival (OS) (HR, 0.60; 95% CI, 0.41–0.89) compared with platinum-doublet chemotherapy.[3] Long-term follow-up of KEYNOTE-024 confirmed the durability of benefit, with a 5-year OS rate of 31.9% in the pembrolizumab group compared with 16.3% in the chemotherapy group.[4]

Subsequently, the combination of pembrolizumab with platinum-based chemotherapy emerged as another standard first-line treatment option for metastatic NSCLC, irrespective of PD-L1 expression.[5,6] In the phase III KEYNOTE-189 trial that included patients with non-squamous NSCLC (nsqNSCLC), pembrolizumab combined with pemetrexed and platinum significantly improved survival outcomes compared with pemetrexed and chemotherapy plus placebo. At the final analysis with a median follow-up of 31 months (range, 26.5–38.8 months), median OS was 22.0 months in the pembrolizumab combination group versus 10.6 months in the chemotherapy alone group (HR, 0.56; 95% CI, 0.46–0.69), and the median PFS was 9.0 versus 4.9 months, respectively, (HR, 0.49; 95% CI, 0.41–0.59).[7] Similarly, in patients with squamous NSCLC (sqNSCLC), the phase III KEYNOTE-407 trial demonstrated significant improvements in median

OS (15.9 versus 11.3 months; HR, 0.64; 95% CI, 0.49–0.85) and median PFS (6.4 versus 4.8 months; HR, 0.56; 95% CI, 0.45–0.70) with pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel versus chemotherapy alone.[6] In both trials, the benefit of chemoimmunotherapy over chemotherapy alone was observed across PD-L1 expression subgroups, including patients with a PD-L1 tumor proportion score (TPS) ≥50%.[6,7] However, the survival benefit of the chemoimmunotherapy combination in PD-L1 ≥50% remains a matter of debate, according to certain pooled analysis and meta-analyses.[8, 9]

As a result, both pembrolizumab monotherapy and pembrolizumab combined with platinum-based chemotherapy are currently recommended by international guidelines as first-line treatment options for patients with advanced NSCLC, without actionable oncogenic alterations, and high PD-L1 expression.[2] However, the optimal therapeutic strategy for this population remains uncertain. While pembrolizumab monotherapy may avoid chemotherapy-related toxicities,[10] the addition of chemotherapy to pembrolizumab may increase response rates and reduce the risk of early progression.[11] Nevertheless, head-to-head data directly comparing chemotherapy plus pembrolizumab versus pembrolizumab monotherapy in PD-L1-high NSCLC remain limited.[11] Accordingly, we conducted PERSEE, an academic, multicenter, randomized, phase III trial (ClinicalTrials.gov identifier: NCT04547504), to evaluate whether the addition of platinum-based chemotherapy to pembrolizumab improves survival outcomes compared with pembrolizumab monotherapy in treatment-naïve patients with advanced NSCLC, PD-L1 TPS ≥50%, and no actionable oncogenic alterations.

Methods

Study design and patients

PERSEE is an academic, prospective, open-label trial conducted across 28 sites in France. The study methodology has been previously described,[12] and the study design is illustrated in **Supplementary Figure S1**. Patients 18 years of age or older were eligible for enrollment if they had histologically or cytologically confirmed stage IV or unresectable stage III (8th Tumor, Node, Metastasis [TNM] classification[10]) NSCLC not amenable to definitive radiotherapy. Additional inclusion criteria included PD-L1 TPS ≥50% tested locally; Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; measurable disease in at least one target lesion according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1); absence of known epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma kinase (*ALK*), or *ROS1* rearrangements; and asymptomatic or symptomatic but treated and stable brain metastases. Key exclusion criteria encompassed prior systemic treatment for metastatic disease (chemotherapy or targeted therapy), previous treatment with ICIs, interstitial lung disease, or other serious uncontrolled medical conditions.[11]

Informed consent was obtained from patients before their enrollment. The trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local regulations. The study protocol was approved by the competent French research ethics committee (*Comité de Protection des Personnes Est I; approval number: 20.06.15.56018, dated 30 July 2020*) and by the French National Agency for the Safety of Medicines and Health Products (*Agence Nationale de Sécurité du Médicament et des Produits de Santé*) in July 2020.

Treatment

Eligible patients were randomly assigned in a 1:1 ratio to receive either pembrolizumab plus chemotherapy or pembrolizumab monotherapy as first-line treatment, stratified according to

histology (squamous or non-squamous) and brain metastases (presence or absence). In the pembrolizumab plus chemotherapy group, patients with nsqNSCLC received pembrolizumab 200 mg, cisplatin 75 mg/m² or carboplatin (area under the curve [AUC] 5 mg/mL/min), and pemetrexed 500 mg/m² every 3 weeks for four cycles, followed by maintenance pembrolizumab plus pemetrexed (or either agent alone in case of toxicity). Patients with sqNSCLC received pembrolizumab 200 mg, carboplatin (AUC 6 mg/mL/min), and paclitaxel 200 mg/m² every 3 weeks for four cycles, followed by pembrolizumab monotherapy maintenance (**Supplementary Figure S1**). In the pembrolizumab monotherapy group, patients received pembrolizumab 200 mg every 3 weeks. Pembrolizumab could be continued for a maximum of 35 cycles or until disease progression, occurrence of unacceptable toxicity, withdrawal of consent, or discontinuation at the investigator's discretion. However, in certain protocol-defined situations (**Supplementary Figure S2**), pembrolizumab could be continued beyond disease progression. Pemetrexed maintenance could be continued until disease progression, occurrence of unacceptable toxicity, withdrawal of consent, or discontinuation at the investigator's discretion.

Assessments and outcomes

Tumor assessments were performed every 6 weeks during the first four treatment cycles, every 9 weeks during the first year, and every 12 weeks thereafter. Responses were assessed according to RECIST v1.1 in a blinded manner by a central committee of investigators (blinded central review, BCR).

The primary endpoint was PFS, defined as the time from randomization to disease progression or death from any cause, whichever occurred first, as assessed by BCR according to RECIST v1.1. Secondary endpoints included investigator-assessed PFS, PFS assessed according

to immunotherapy RECIST[12] (iRECIST, iPFS), OS, objective response rate (ORR), duration of response (DoR), duration of treatment (DoT), and safety.

OS was defined as the time from randomization to death from any cause. ORR was defined as the proportion of patients achieving a complete or partial response, per RECIST v1.1, and was assessed both by BCR and by the investigators. DoR was defined as the time from first documented response until disease progression or death. Safety was assessed throughout the study by monitoring all adverse events (AEs), grade ≥3 AEs, serious AEs (SAEs), as well as any AE of special interest (AESI), defined as immune-related AE (irAE). AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.

PFS analyses were also performed in several baseline subgroups, including PD-L1 expression level (50-74%, 75-100%, and 90-100%), brain metastasis (presence *versus* absence), and histology (squamous *versus* non-squamous). The early progression rate, defined as the proportion of patients with clinical and/or radiological tumor progression according to RECIST v1.1 before or at the first radiological evaluation at 6 weeks was an exploratory endpoint. PFS2, a prespecified exploratory endpoint, was defined as the time from randomization to objective disease progression on second-line therapy or death from any cause, whichever occurred first. The other exploratory endpoints, including quality of life, and novel biomarkers,[11] will be reported separately. Similarly, results of an ad-hoc central PD-L1 expression will be reported.

Statistical analysis

The study was designed to test the superiority of pembrolizumab plus chemotherapy over pembrolizumab monotherapy with respect to PFS. Assuming a HR of 0.70 in favor of pembrolizumab plus chemotherapy, with a two-sided α-level of 0.05 and 80% power, 249 PFS events were estimated to be required for the primary analysis. The planned sample size was 262 randomized patients (131 per group), recruited over three years, with two years of follow-up for the last enrolled patient, and was expected to yield 249 events. Because of a lower-than-expected event rate, 210 PFS events had occurred at the end of the prespecified follow-up period. Since reaching 249 events within a reasonable timeframe was unlikely, the final analysis was performed at the planned end of the study. This decision was made by the sponsor before database lock and without knowledge of the treatment effect, and the prespecified statistical methods were not modified. Because the timing of the analysis was independent of the observed results, the type I error rate was preserved; the reduced number of events decreased the statistical power from 80% to 73%.

Efficacy analyses were performed in the intention-to-treat (ITT) population, comprising all randomized patients. Time-to-event endpoints, including PFS, OS, and DoR, were estimated using a non-parametric Kaplan–Meier method. Time-to-event outcomes were analyzed using Cox proportional hazards models stratified by histology and presence at baseline of brain metastases. HRs and corresponding 95% CIs were calculated. In the event of non-proportionality, a post-hoc complementary restricted mean survival analysis (RMST) was performed for PFS and OS. PFS was descriptively analyzed in subgroups of patients according to three factors of interest: PD-L1 expression, brain metastasis, and histology. Safety analyses were descriptive and included all patients who received at least one dose of study treatment.

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The database was locked on 7 April 2026, which served as the data cutoff date for all efficacy and safety analyses. No interim analysis was planned or performed. Quantitative variables were summarized using descriptive statistics with number, mean, median, standard deviation (SD) and interquartile range (IQR), and qualitative variables using numbers and percentages with 95% CIs. All statistical tests were two-sided, and *P* values <0.05 were considered statistically significant. All statistical analyses were performed using R software version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics and treatment

From December 22, 2020, to December 21, 2023, a total of 321 patients (ITT population) at 28 centers in France underwent randomization, with 160 assigned to the pembrolizumab plus chemotherapy group and 161 assigned to the pembrolizumab monotherapy group. In the pembrolizumab plus chemotherapy group, 158 patients received the trial treatment with the most common chemotherapy regimen being carboplatin plus pemetrexed (in 111 patients); one patient was withdrawn by investigator decision and one because of a biological inflammatory syndrome observed before the start of the first treatment cycle. In the pembrolizumab monotherapy group, 159 patients received the trial treatment; one patient was withdrawn by investigator decision, and another one because of a SAE, that occurred before the start of the first treatment cycle (**Supplementary Figure S3**).

The demographic and baseline disease characteristics of the patients were generally well balanced between the treatment groups (**Table 1**). Median age was 64 years (IQR, 59-69) for the ITT population. For the overall ITT population, 32.4% of patients were female, 2.2% never

smoked, 23.4% had brain metastases, and 19.6% had squamous histology. The large majority of nsqNSCLC patients underwent molecular biology testing (245/258 patients; 95.0%), with Kirsten Rat Sarcoma Viral Oncogene Homolog (*KRAS*) being the most frequently identified (115/258 patients; 44.6%) (**Table 1 and Supplementary Table S1**). PD-L1 expression levels were similarly distributed between the pembrolizumab plus chemotherapy and pembrolizumab monotherapy groups, including the 90–100% category (52 [32.5%] and 57 [35.4%] patients, respectively) (**Table 1**).

As of April 7, 2026, the overall median duration of follow-up was 38.7 months (range, 35.3-41.6): 37.5 months (33.2-40.7) in the pembrolizumab plus chemotherapy group and 41.6 (36.4-44.9) in the pembrolizumab monotherapy group. Full planned treatment was completed by 45 patients in the pembrolizumab plus chemotherapy group and 27 patients in the pembrolizumab monotherapy group (**Supplementary Figure S3**). The median DoT was 10.5 months (range, 8.5-16.1) in the pembrolizumab plus chemotherapy group and 6.3 months (range, 4.7-8.4) in the pembrolizumab monotherapy group (HR for treatment discontinuation, 0.57; 95% CI, 0.45–0.71). The median number of pembrolizumab cycles was 7.5, 13, and 34 across the three subgroups of the pembrolizumab plus chemotherapy group and 10 in the pembrolizumab monotherapy (**Supplementary Table S2**). The median number of pemetrexed cycles was 8 and 10 for the carboplatin-pemetrexed and cisplatin-pemetrexed combinations, respectively.

Progression-free survival

In the ITT population, on the basis of 210 progression or death events, PFS as assessed by BCR was significantly longer in the pembrolizumab plus chemotherapy group than in the pembrolizumab monotherapy group (median, 16.1 months [95% CI, 11.0-34.1] vs. 6.9 months

183 [95% CI, 5.5-9.3]; HR for disease progression or death, 0.56; 95% CI, 0.43-0.74; P<0.001) (**Figure**
184 **1A**). The estimated percentage of patients who were alive and had no disease progression at 12
185 and 24 months was 54.6% (95% CI, 47.3–63.1) and 45.2% (95% CI, 37.9–53.9), respectively, in
186 the pembrolizumab plus chemotherapy group, and 33.9% (95% CI, 27.1–42.5) and 24.9% (95%
187 CI, 18.7–33.1), respectively, in the pembrolizumab monotherapy group. At 24 months, RMST for
188 PFS was 14.9 months with pembrolizumab plus chemotherapy versus 10.5 months with
189 pembrolizumab monotherapy, corresponding to an absolute difference of 4.42 months (95% CI,
190 2.42-6.42; P<0.001) (**Supplementary Table S3**).

191 The PFS assessed by investigators according to RECIST v1.1 followed the same trend as
192 that assessed by BCR (**Supplementary Figure S4**). PFS as assessed by BCR according to
193 iRECIST was similar to that assessed according to RECIST v1.1 (**Supplementary Figure S5**).
194 The PFS benefit of pembrolizumab plus chemotherapy, as assessed by BCR according to RECIST
195 v1.1, was consistent across all subgroups examined (**Figure 1B**). The subgroup analysis of PFS
196 by PD-L1 expression strata showed similar trends across subgroups, with no notable differences
197 according to PD-L1 expression level (**Figure 2**). The HR for disease progression or death for the
198 subgroup of patients with or without brain metastases and for those with squamous or non-
199 squamous carcinoma are presented in **Supplementary Figure S6 and S7**, respectively.

200 At the data cut-off, 180 PFS2 events had occurred as assessed by investigators: 79 in the
201 pembrolizumab plus chemotherapy group and 101 in the pembrolizumab monotherapy group.
202 Median PFS2 was 39.5 (26.2–not reached) months with pembrolizumab plus chemotherapy and
203 15.9 (13.2–29.9) months with pembrolizumab monotherapy (HR, 0.68; 95% CI, 0.5–0.91)
204 (**Supplementary Figure S8**).
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Overall survival

At the data cutoff date, 163 deaths had occurred: 74 in the pembrolizumab plus chemotherapy group and 89 in the pembrolizumab monotherapy group. The estimated percentages of patients who were alive at 24 and 48 months were 64.4% (95% CI, 57.3–72.2) and 50.9% (95% CI, 43.1–60.1), respectively, in the pembrolizumab plus chemotherapy group and 56.2% (95% CI, 49.0–64.5) and 38.9% (95% CI, 30.8–49.0), respectively, in the pembrolizumab monotherapy group (**Figure 3**). The median OS was 50.2 months (95% CI, 32.6–not calculated) in the pembrolizumab plus chemotherapy group and 29.9 months (95% CI, 23.4–47.9) in the pembrolizumab monotherapy group (HR for death, 0.77; 95% CI, 0.56–1.05). At 24 months, RMST was 19.3 months with pembrolizumab plus chemotherapy versus 18.0 months with pembrolizumab monotherapy (difference, 1.3 months; 95% CI, −0.39 to 3.0); at 48 months, RMST was 32.7 versus 29.2 months, respectively (difference, 3.34 months; 95% CI, −0.62 to 7.3) (**Supplementary Table S3**).

Response rate and disease progression

The ORR, as assessed by BCR according to RECIST v1.1, was 77.5% in the pembrolizumab plus chemotherapy group and 50.3% in the pembrolizumab monotherapy group (**Table 2**). A total of 101 patients (63.1%) in the pembrolizumab plus chemotherapy group and 66 (41.0%) in the pembrolizumab monotherapy group remained in objective response at 6 months post randomization. Median DoR was 30.0 months (95% CI, 13.1–not reached) in the pembrolizumab plus chemotherapy group and 15.6 months (95% CI, 9.8–32.8) in the pembrolizumab monotherapy group (HR for loss of response or death, 0.88; 95% CI, 0.60–1.29) (**Table 2**). Early progression

rates were 5.8% in the pembrolizumab plus chemotherapy group and 26.5% in the pembrolizumab monotherapy group (**Supplementary Table S4**).

After disease progression, the choice of the subsequent systemic therapy was left at the investigator's discretion according to standard clinical practice. Post-progression treatment types for each first-line treatment group are summarized in **Supplementary Figure S9 and Table S5**. A total of 212 patients had disease progression according to the investigator, of whom 40 died before receiving second-line therapies (15 in the pembrolizumab plus chemotherapy group and 25 in the pembrolizumab monotherapy group). Of the 212 patients, 41 (19.3%) continued to receive pembrolizumab beyond progression (18/93 patients [19.4%] in the pembrolizumab plus chemotherapy group and 23/119 [19.3%] in the pembrolizumab monotherapy group), and 139 (65.6%) received second-line treatment (62/93 [66.7%] and 77/119 [64.7%], respectively). Second-line treatment predominantly consisted of a chemotherapy doublet, administered after the first-line pembrolizumab monotherapy (n = 50) or after the first-line pembrolizumab plus chemotherapy (n = 18) (**Supplementary Table S5**). Of the 161 patients randomized to the pembrolizumab monotherapy group, 8 patients received second-line pembrolizumab combined with platinum-doublet chemotherapy and 70 (43.5%) received platinum-based chemotherapy. **Supplementary Table S6** presents the baseline characteristics of patients who received and those who did not receive second-line therapies after disease progression; it appears that no major differences exist between these two subgroups.

Safety

All patients in the ITT population, except for one in the pembrolizumab monotherapy group, experienced at least one AE of any grade. **Supplementary Table S7** summarizes the preferred

terms and their frequencies for the AEs with an incidence of 5% or greater in the Safety population of the pembrolizumab plus chemotherapy group. Most patients of the Safety population (n = 158 for the pembrolizumab plus chemotherapy group and n = 159 for the pembrolizumab monotherapy group) experienced at least one treatment-related AE (TRAE) of any-grade: 149 patients (94%) in the pembrolizumab plus chemotherapy group and 119 patients (75%) in the pembrolizumab monotherapy group (**Figure 4A** and **Supplementary Table S8**). Grade 3 or higher TRAEs were reported in 86 patients (54%) in the pembrolizumab plus chemotherapy group and in 31 patients (19%) in the pembrolizumab monotherapy group. Grade 5 TRAEs occurred in three patients in each study group (**Supplementary Table S8**). Immune-related AEs occurred at similar frequencies in both study groups. Grade 3 or higher irAEs were reported in 21 patients (13%) in the pembrolizumab plus chemotherapy group and in 20 patients (13%) in the pembrolizumab monotherapy group, of whom 2 patients had grade 5 irAE events; no grade 5 irAE events were reported in the pembrolizumab plus chemotherapy group (**Figure 4B** and **Supplementary Table S8**).

AEs leading to chemotherapy permanent discontinuation were reported in 76 patients (48%). AEs led to pembrolizumab discontinuation in 44 patients (28%) in the pembrolizumab plus chemotherapy group and in 38 patients (24%) in the pembrolizumab monotherapy group. (**Supplementary Table S8**).

Discussion

In this multicenter, randomized, phase III trial, with a median follow-up of 38.7 months, the addition of chemotherapy to pembrolizumab significantly prolonged PFS compared with pembrolizumab monotherapy in treatment-naïve patients with advanced NSCLC, PD-L1 TPS

≥50%, and no actionable *EGFR, ALK* or *ROS-1* alterations (HR, 0.56; 95% CI, 0.43–0.74). Median PFS assessed by BCR more than doubled from 6.9 months with pembrolizumab monotherapy to 16.1 months with the addition of chemotherapy, with a clinically meaningful benefit sustained over time.

The magnitude of PFS improvement observed in PERSEE is consistent with a patient-data level meta-analysis of 24 randomized controlled trials (RCTs), including 5,546 patients with advanced PD-L1 ≥50% NSCLC. The meta-analysis demonstrated that chemoimmunotherapy was associated with a significantly longer PFS compared with monoimmunotherapy, with a median PFS of 11.3 months versus 6.8 months (HR, 0.67; 95% CI, 0.60–0.75).[13] The PERSEE results exceed these pooled estimates, with a median PFS of 16.1 months in the combination group, highlighting that the addition of chemotherapy to pembrolizumab may provide superior early disease control in appropriately selected patients with high PD-L1 expression. Additionally, the median DoR achieved with chemoimmunotherapy in PERSEE was substantially long at 30.0 months, twice the DoR with pembrolizumab monotherapy (15.6 months). Of note, the reported median DoR was 12.6 months in KEYNOTE-189,[7] and 9.0 months in KEYNOTE-407.[6]

Importantly, outcomes in the pembrolizumab monotherapy group of PERSEE were consistent with those reported in pivotal trials of pembrolizumab monotherapy in patients with PD-L1 expression ≥ 50%, including KEYNOTE-024[4] (median PFS of 7.7 months at 5-year follow-up) and KEYNOTE-042[14] (median PFS of 7.1 months). This consistency suggests that the control arm of PERSEE did not underperform relative to historical benchmarks, supporting the robustness of the observed PFS benefit with the addition of chemotherapy. This benefit may, in part, reflect the ability of chemotherapy to enhance PD-1/PD-L1 blockade through rapid cytoreduction, increased tumor antigen release, and modulation of the tumor microenvironment.[15]

The improvement in PFS was accompanied by a numerically longer median OS of 50.2 months in the chemoimmunotherapy group compared with 29.9 months in the pembrolizumab monotherapy group (HR, 0.77; 95% CI, 0.57–1.05), consistent with the results of a target trial emulation addressing the same causal question using a nationwide real-world oncology data platform in France (HR, 0.81, 95% CI, 0.61–1.06).[16] A complementary RMST analysis of OS, which does not rely on the proportional hazards assumption, showed an absolute gain of 3.34 months (95% CI, -0.62–7.3) in favor of chemoimmunotherapy over the first 48 months of follow-up. These findings are also broadly consistent with previous indirect comparisons,[17,18] which support improved early disease control with the addition of chemotherapy, while the magnitude and durability of any OS benefit remains uncertain. PERSEE was powered to detect differences in PFS rather than OS, which limits its ability to detect statistically significant OS differences. In addition, according to the study protocol, post-progression treatments were left to the investigators' discretion, and platinum-based chemotherapy could be administered after progression on first-line pembrolizumab monotherapy. This treatment sequence was frequently used in PERSEE and may have partly attenuated the OS difference between the two treatment groups. The favorable PFS2 results are consistent with the PFS findings and provide additional exploratory information on outcomes beyond first disease progression, although they cannot be considered a validated surrogate for OS. The OS observed in the pembrolizumab monotherapy group of PERSEE was consistent with that reported in KEYNOTE-024 (4-year OS rate of 35.8%),[4] supporting the external validity of our findings for pembrolizumab monotherapy. By contrast, the 4-year OS rate was 50.9% in the chemoimmunotherapy group, while those reported in the PD-L1≥50% subgroups in KEYNOTE-189[19] and in KEYNOTE-407[20] were 34.3% and 24.7%, respectively. Although indirect comparisons between studies should be interpreted cautiously

because of differences in study design and patient characteristics, they suggest particularly favorable long-term outcomes with chemoimmunotherapy in the PERSEE trial.

When analyzed by PD-L1 expression level, the PFS benefit of chemoimmunotherapy appeared to be consistent across all PD-L1 expression categories above the 50% threshold (50–74%, 75–100%, and 90–100%). Interestingly, in patients with the highest PD-L1 expression (90–100%), the combination maintained a substantial PFS advantage, with a median PFS of 25.4 months compared with 7.1 months for monotherapy (HR, 0.6; 95% CI, 0.36–1.00). The observation that patients with PD-L1 expression ≥90% still achieved a median PFS exceeding 2 years with combination therapy suggests that even in this favorable biomarker-defined population, the addition of chemotherapy may provide additional disease control. Emerging biomarkers, including circulating tumor DNA dynamics, tumor mutational burden, and *STK11/KEAP1* mutations may further refine patient selection beyond PD-L1 expression alone.[21]

The favorable efficacy outcomes observed with chemoimmunotherapy should be weighed against its greater treatment-related toxicity, and treatment duration (median of 10.5 months in the pembrolizumab plus chemotherapy group and of 6.3 months in the pembrolizumab monotherapy). Treatment-related AEs of grade ≥3 were more frequent in the pembrolizumab plus chemotherapy group (54.0%) compared with pembrolizumab monotherapy (19.0%), reflecting the anticipated hematologic and gastrointestinal toxicities associated with platinum-based chemotherapy. Our safety findings are consistent with those reported in previous pembrolizumab-based chemoimmunotherapy trials.[19,20]

PERSEE possesses several strengths. It is, to our knowledge, among the largest randomized phase III trials specifically designed to compare head-to-head pembrolizumab plus platinum-based chemotherapy with pembrolizumab monotherapy exclusively in patients with PD-L1 TPS ≥50%.

Two similar RCTs were prematurely terminated, PAULIEN (EudraCT Number: 2019-002743-26; Dutch National Trial Register ID: NTR8896) because of futility, and LAPLACE-50 (Japan Registry of Clinical Trials: jRCTs031200078) owing to slow accrual. The PERSEE multicenter design involving 28 French centers enhances the robustness of the findings and reflects contemporary clinical practice. The use of a blinded central assessment for the primary endpoint minimizes potential assessment bias associated with the open-label design, while the inclusion of both squamous and non-squamous histology increases the generalizability of the results. Furthermore, the median follow-up of 38.7 months provides mature data for the primary endpoint and allows meaningful assessment of response durability and long-term disease control. The study also has some limitations. The trial was powered to detect differences in PFS rather than OS, limiting definitive conclusions regarding long-term survival. Moreover, the open-label design may introduce bias in investigator-assessed endpoints, although the blinded central assessment mitigates this concern. Furthermore, treatment was conducted exclusively in France, which may limit the generalizability of the results to healthcare systems with different patient populations, treatment practices, or access to subsequent therapies. Other limitations should be noted, notably local testing of PD-L1 expression for eligibility, absence of quality-of-life data in the present report, and the lack on specification of investigational agents in subsequent treatment, which may impact the assessment of the benefit-risk balance. Finally, OS results remain immature and continued follow-up is warranted to determine the long-term survival impact of the combination strategy. The ongoing INSIGNA study (NCT03793179), which specifically addresses the treatment-sequencing question in nsqNSCLC PD-L1 ≥1%, with OS as the primary endpoint, should provide insights on the overall benefit–risk balance of upfront versus sequential treatment strategies, which could not be fully assessed by design in previous studies, including PERSEE.

In conclusion, the PERSEE trial demonstrated that the addition of chemotherapy to pembrolizumab significantly prolonged PFS compared with pembrolizumab monotherapy, in treatment-naïve patients with advanced NSCLC and PD-L1 TPS ≥50%, reducing the risk of disease progression or death. The combination also achieved a higher ORR and a numerically longer OS compared with pembrolizumab monotherapy. While pembrolizumab monotherapy remains a first-line treatment option, these findings support pembrolizumab plus platinum-based chemotherapy as another first-line option, broadening therapeutic choices for patients with advanced NSCLC and high PD-L1 expression, particularly those who can tolerate the increased toxicity burden and those who may benefit from early disease control.

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Data sharing

De-identified individual participant data underlying the results reported in this article may be made available upon reasonable request. Requests should be submitted to the corresponding author and will be reviewed by the study sponsor (Brest University Hospital) and the French Lung Cancer Group (GFPC). Data will be made available following approval of a scientifically sound proposal and in accordance with applicable ethical, legal, and regulatory requirements.

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Table 1. Baseline demographic and disease characteristics (ITT population)

Characteristic	Pembrolizumab plus Chemotherapy (*N* = 160)	Pembrolizumab Monotherapy (*N* = 161)
Age, years		
Median (range)	63 (38-83)	64 (39-86)
<70 years	126 (78.8)	116 (72.0)
≥70 years	34 (21.3)	45 (28.0)
Sex		
Female	53 (33.1)	51 (31.7)
Male	107 (66.9)	110 (68.3)
ECOG performance status		
0	76 (47.5)	75 (46.6)
1	84 (52.5)	86 (53.4)
Disease stage		
III	11 (6.9)	10 (6.2)
IV	149 (93.2)	151 (93.7)
Smoking status[a]		
Current smoker	56 (35.2)	64 (39.8)
Former smoker	99 (62.3)	94 (58.4)
Non-smoker	4 (2.5)	3 (1.9)
Histologic features		
Non squamous	129 (80.6)	129 (80.1)
Squamous	31 (19.4)	32 (19.9)
Metastases		
Median metastasis sites (range)	2 (0-8)	2 (0-7)
>1 metastasis sites	122 (76.3)	120 (74.5)
>3 metastasis sites	34 (21.3)	32 (19.9)
Brain[b]	39 (24.4)	36 (22.4)
Liver	23 (14.4)	26 (16.1)
Bone	61 (38.1)	49 (30.4)
Sum of Longest Diameters, mm		
Median (range)	83 (13-206)	79 (14-346)
Ratio neutrophils/lymphocytes ≥4	90 (56.6)	66 (41.0)
PD-L1 tumor cell expression (≥50%)[c]		
50-74%	54 (33.8)	58 (36.0)
75-100%	91 (56.9)	95 (59.0)
90-100%	52 (32.5)	57 (35.4)
Not evaluated	15 (9.4)	8 (5.0)
Genetic alterations, *n/N* (%)[d]		
No	54 / 139 (38.8)	59 / 136 (43.4)
Yes	85 / 139 (61.2)	77 / 136 (56.6)
Missing[e]	21	25
Mutations identified, *n/N* (%)[f]		
KRAS	58 / 85 (68.2)	57 / 75 (76.0)
BRAF	8 / 84 (9.5)	6 / 69 (8.7)
HER2	0 / 80 (0.0)	2 / 68 (2.9)

Characteristic	Pembrolizumab plus Chemotherapy (*N* = 160)	Pembrolizumab Monotherapy (*N* = 161)
METEXON14	2 / 81 (2.5)	0 / 68 (0.0)

Data are *n* (%) unless otherwise specified.

ECOG, Eastern Cooperative Oncology Group; *n*, number of patients; *N*, total number of patients; PD-L1, Programmed Death-Ligand 1; ITT, intention-to-treat.

[a]Smoking status missing in one patient in the pembrolizumab plus chemotherapy group.

[b]Two patients in the pembrolizumab monotherapy group received brain radiotherapy prior to enrollment. In the pembrolizumab plus chemotherapy group, 5 patients received brain radiotherapy, of whom two also underwent brain surgery.

[c]PD-L1 expression level locally measured. "Not evaluated" indicates that the measurement was reported as ≥50% without an exact value.

[d]*N* is the total number of patients who underwent molecular testing and had available genetic data.

[e]The missing category corresponds to patients who did not undergo molecular testing and did not have available genetic data.

[f]*N* is the total number of patients who underwent genetic testing for the specific genetic alteration and had available genetic data.

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Table 2. Response to treatment[a] and duration of response (ITT population)

	Pembrolizumab plus Chemotherapy (*N* = 160)	Pembrolizumab Monotherapy (*N* = 161)
Objective response rate[b]	124 (77.5)	81 (50.3)
OR (95% CI)[c]	3.48 (2.15-5.72)	
Complete response	13 (8.1)	15 (9.3)
Partial response	111 (69.4)	66 (41)
Stable disease	23 (14.4)	41 (25.5)
Disease control rate	147 (91.9)	122 (75.8)
Progressive disease	8 (5.0)	31 (19.3)
Not evaluated[d]	5 (3.1)	8 (5.0)
Duration of response, months		
Median (95% CI)	30.0 (13.1-NC)	15.6 (9.8-32.8)
HR (95% CI)	0.88 (0.60-1.29)	
Early disease progression	9 (5.8)[e]	41 (26.5)[e]
OR (95% CI)	0.17 (0.07-0.35)	

Data are *n* (%) unless otherwise specified.
CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; *n*, number of patients; *N*, total number of patients; NC, not calculated; OR, odds ratio.
[a]Response and disease progression were assessed by a blinded review committee.
[b]Overall response was defined as a partial response or better.
[c]Shown are the stratified estimates of odds ratios. An odds ratio greater than 1 indicates an advantage for pembrolizumab plus chemotherapy. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.
[d]Patients who could not be evaluated were those without any postbaseline disease assessments.
[e]Percentages are based on non-missing values (pembrolizumab plus chemotherapy, *N* = 154; pembrolizumab monotherapy, *N* = 155)

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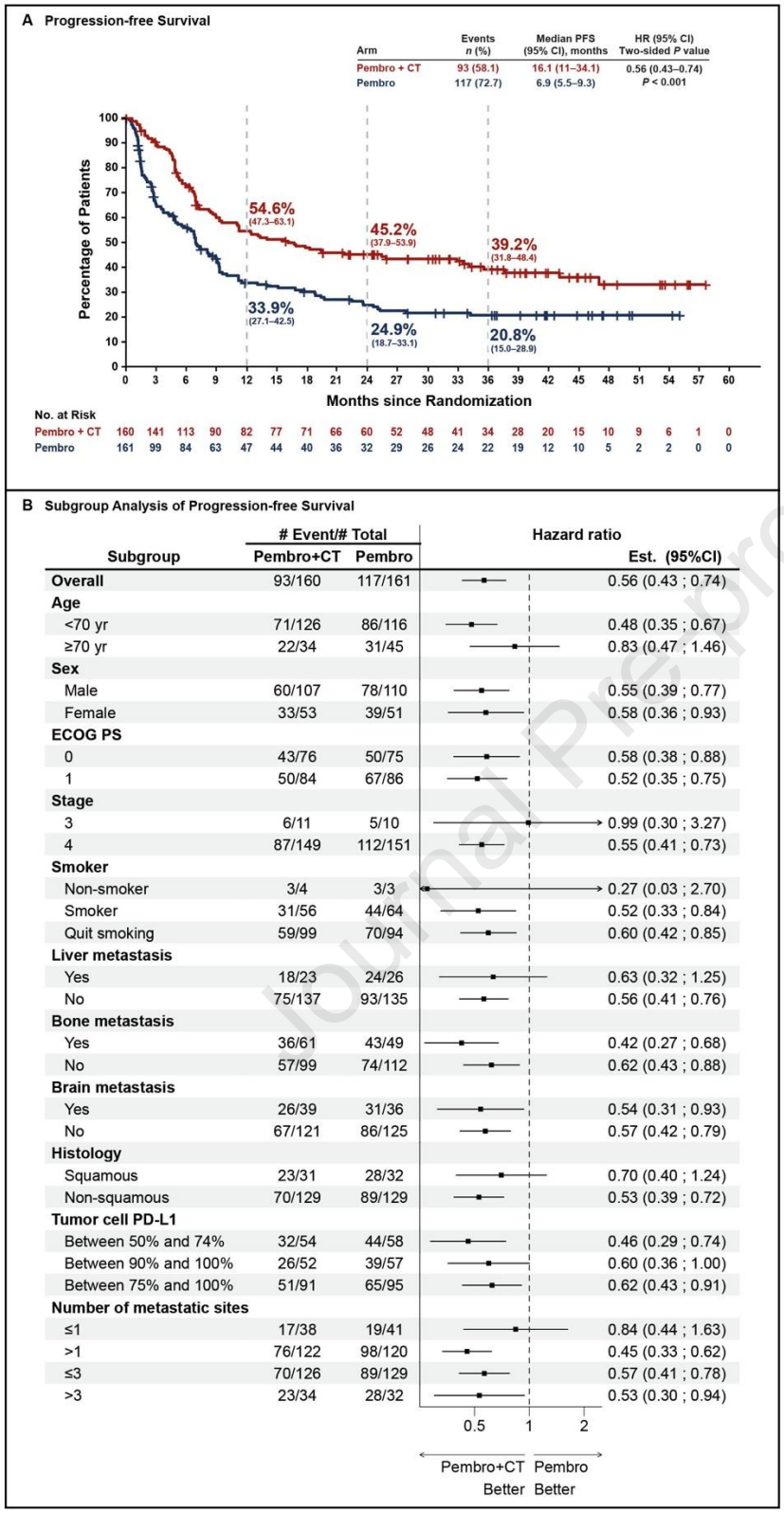

Figure 1. Progression-Free survival assessed by BCR (A) and subgroup analysis of progression-free survival (B).

Panel A shows Kaplan–Meier estimates of progression-free survival, stratified by histological type and presence of brain metastasis, among patients who had been randomly assigned to receive either pembrolizumab plus chemotherapy or pembrolizumab monotherapy (intention-to-treat population). Tick marks indicate censored data. Patients who have not progressed by BCR assessment or died at the time of analysis, and those who underwent radiotherapy or surgery on target lesion were censored at the time of their last evaluable RECIST assessment, and before any new treatment. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, PFS was censored at that date plus 1 day. At a median follow-up of 38.7 months, the median progression-free survival was 16.1 months in the pembrolizumab plus chemotherapy group and was 6.9 months in the pembrolizumab monotherapy, a result favoring the combination with chemotherapy. Dashed lines indicate the 12-month, 24-month, and 36-month landmark estimates with 95% confidence intervals in parenthesis.

Panel B shows the results of a prespecified subgroup analysis of progression-free survival in the intention-to-treat population. A hazard ratio of less than 1 indicates a lower risk of progression or death with pembrolizumab plus chemotherapy than with pembrolizumab monotherapy. ECOG PS scores range from 0 to 5, with higher scores indicating greater disability. CNS metastases status at baseline was based on investigator assessment of data in the electronic case-report form regarding the CNS lesion site at baseline, medical history, surgical history, or history of radiotherapy for CNS metastases. In the subgroup analysis, the widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

BCR, blinded central review; CI, confidence interval; CNS, central nervous system; CR, complete response; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Est, estimate; HR, hazard ratio; *n*, number of patients; PD-L1; Programmed Cell Death Ligand 1; Pembro, Pembrolizumab; PFS, Progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors, yr, year.

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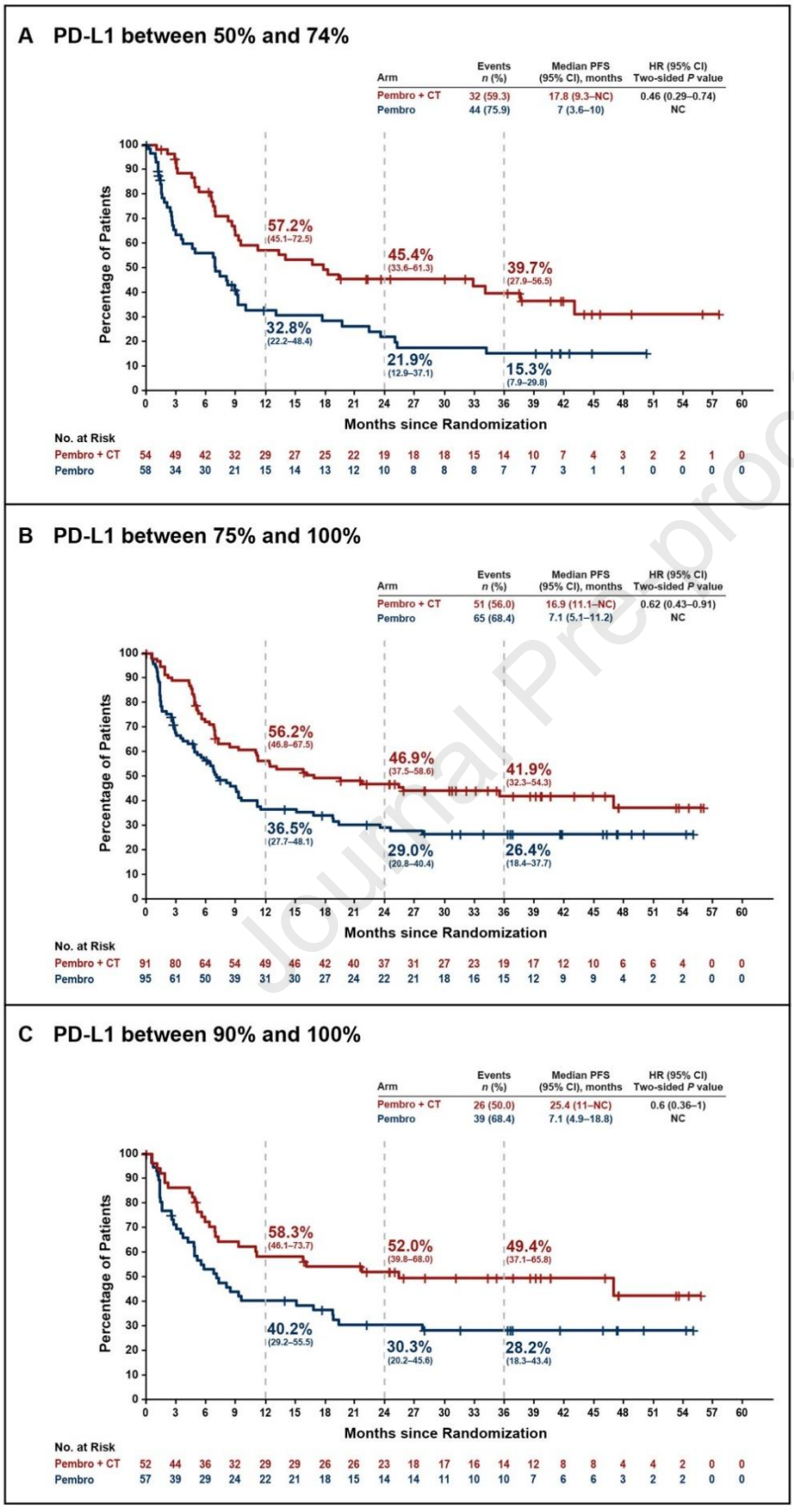

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Figure 2. Progression-free survival by PD-L1 expression status, as assessed by blinded central review according to RECIST v1.1.

Panel A presents the PFS for patients with PD-L1 expression status between 50% and 74%, Panel B for those with PD-L1 expression status between 75% and 100%, and Panel C for those with PD-L1 expression status between 90% and 100%. Dashed lines indicate the 12-month, 24-month, and 36-month landmark estimates with 95% confidence intervals in parenthesis.

CI, confidence interval; CT, chemotherapy; HR, hazard ratio; *n*, number of patients; NC, not calculable; PD-L1, Programmed Cell Death Ligand 1; Pembro, Pembrolizumab; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; v, version.

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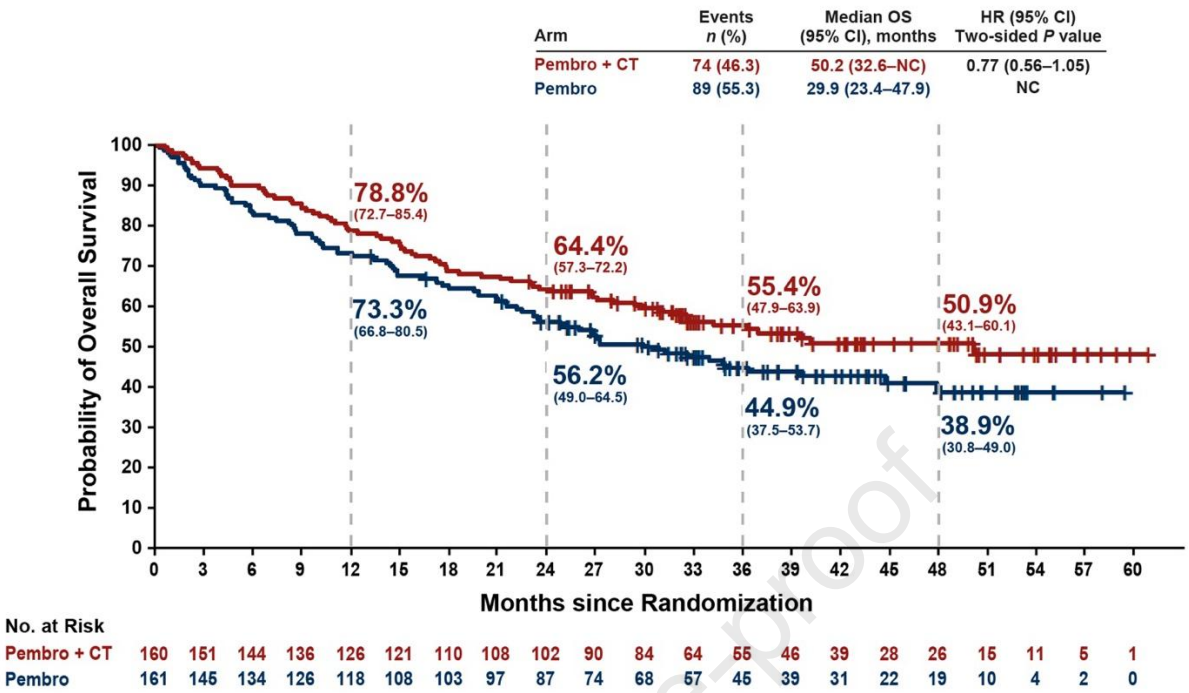

Figure 3. Overall survival.

Kaplan–Meier estimates of overall survival in the intention-to-treat population are shown. Tick marks indicate censored data; patients who had not died at the time of the analysis had their data censored at the last recorded known survival date. Dashed lines indicate the 12-month, 24-month, 36-month, and 48-month landmark estimates with 95% confidence intervals in parenthesis.

CI, confidence interval; CT, chemotherapy; HR, hazard ratio; *n*, number of patients; NC, not calculable; OS, overall survival; Pembro, pembrolizumab.

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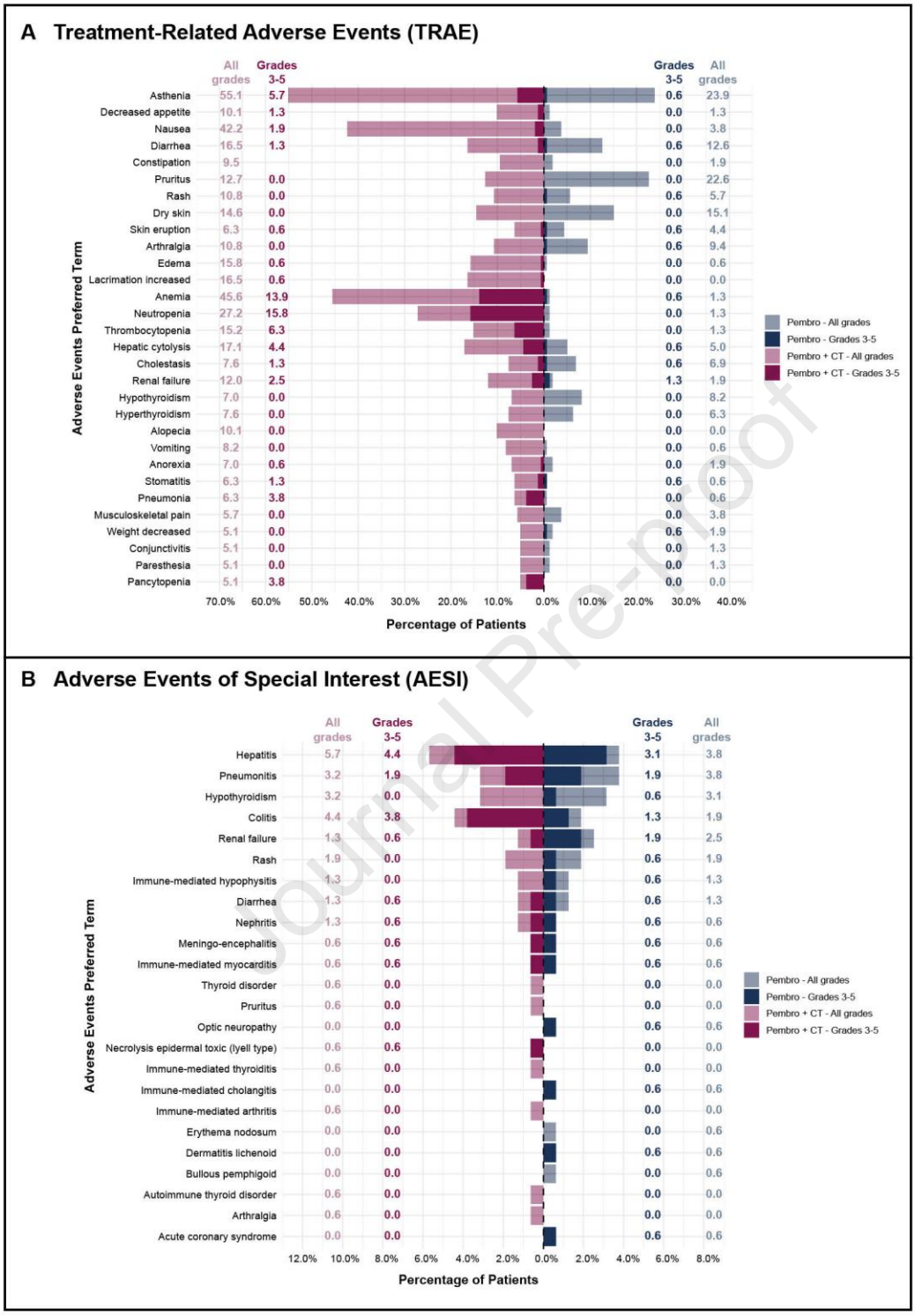

Figure 4. Treatment-Related adverse events (A) and immune-related adverse events (B) (Safety population).

Adverse events (AEs) of any cause that were reported in either group are listed according to the preferred term from the Medical Dictionary for Regulatory Activities, version 27.0. The safety analysis set included all the patients who had undergone randomization and received at least one

dose of trial treatment, according to the actual treatment received. AEs with an onset date occurring on or after the date of the first dose, up to and including 28 days after the discontinuation of treatment, and before the start of a subsequent anticancer therapy are reported. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. For each patient, only the maximum reported grade for each preferred term is listed. Adverse events of special interest (AESIs) were defined as immune-related AEs (irAEs). The light colors indicate the frequency for all grades AEs, and the dark colors for those of grade 3 to 5.
CT, chemotherapy; Pembro, pembrolizumab.

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Ethics declaration

Informed consent and patient details

Written informed consent to take part in the study and to publish the article has been obtained from all participants or their legal representatives. The privacy rights of participants have been observed.

Studies in Human

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place.

This study was approved by the Comité de Protection des Personnes Est I.

(Approval No. 20.06.15.56018)

Clinical Trials

The results of this clinical trial and any associated work have been posted in a registry.

This clinical trial was registered with number NCT04547504 (ClinicalTrials.gov).

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