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Pembrolizumab plus chemotherapy (PEM + CT) versus pembrolizumab (PEM) as first-line therapy for advanced NSCLC with PD-L1 tumor proportion score (TPS) ≥50%: Open-label, phase III, randomized trial (PAULIEN)

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Background

PEM is the standard first-line therapy for advanced NSCLC without targetable alterations and PD-L1 TPS ≥50%. When a rapid tumor response is needed, CT is often added to PEM, though its benefit is unclear. The PAULIEN trial compared PEM + CT with PEM to assess tumor responses at 6 weeks.

Methods

This multicenter trial randomized patients (pts) 1:1 to receive PEM (every 3 or 6 weeks) or PEM + platinum-based CT with either pemetrexed or paclitaxel. PEM and pemetrexed were continued as maintenance therapy. Randomization was stratified by age, performance status, T-stage, histology, and center. Co-primary endpoints were investigator-assessed objective response rate (ORR), tested for superiority using a chi-squared test, and disease control rate (DCR) at week 6 (w6) per RECIST v1.1 in the intention-to-treat (ITT) population. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety (data cutoff: April 17, 2025). ORR and DCR at week 12 (w12) were also collected. A sample size of 84 pts would yield 80% power to detect a 30% increase in ORR (from 40% to 70% by adding CT) at a 2-sided $\alpha = 5\%$.

Results

Enrollment was halted for futility following an interim analysis. A total of 72 pts were included in the ITT analysis, of whom 42 received PEM + CT and 30 PEM. The ORR at week 6 was comparable between PEM + CT and PEM (ORR w6, 33% vs. 23%, respectively; relative risk, 1.43 [95% CI, 0.66–3.11]; *P*=0.36). The DCR at week 6 (DCR w6, 69% vs. 63%, respectively) and the ORR and DCR at week 12 were also comparable (ORR w12, 48% vs. 47%, respectively; DCR w12, 64% vs. 60%, respectively). After a median follow-up of 29.1 months with 46 events for PFS and 31.1 months with 37 events for OS, both PFS and OS were comparable between the two arms (PFS HR, 0.91 [0.51–1.64]; OS HR, 0.89 [0.47–1.70]). Grades 3-4 treatment-related adverse events occurred more frequently in the PEM + CT arm (54% vs. 35%). No treatment-related deaths were observed.

Conclusions

The addition of chemotherapy to pembrolizumab did not lead to a significant increase in tumor responses at week 6 in patients with advanced and high (TPS ≥50%) PD-L1 expressing NSCLC.

Clinical trial identification

EudraCT 2024-516581-11-00 (Transition trial, original EudraCT 2019-002743-26; National Trial Registry 8896 [not available anymore]).

Legal entity responsible for the study

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Disclosure

All authors have declared no conflicts of interest.