In the immunotherapy possibilities, pembrolizumab appeared as a leader, along with nivolumab and atezolizumab, in the second-line setting (1). In the last years, the results of phase III KEYNOTE trials (2-6) confirmed the Pembrolizumab as ahead of other checkpoint inhibitors in the first-line setting. Firstly, KEYNOTE-10 (7) showed that the PD-1 inhibitor represented a standard second-line treatment option in NSCLC as it significantly improved OS in comparison with docetaxel following prior platinum-based chemotherapy. Secondly, KEYNOTE-024 (8), which only included patients with PD-L1 Tumor Proportion Score (TPS) ≥50%, found that pembrolizumab monotherapy presented a better OS and progression-free survival (PFS) over standard chemotherapy with platinum. Thus, Food and Drug Administration (FDA) and European Medicine Agency (EMA) approved pembrolizumab as first line therapy for advanced NSCLC with TPS ≥1%. Pembrolizumab monotherapy presented better results over chemotherapy in all TPS subgroups, despite greater benefits were associated with higher PD-L1 expression. In the TPS ≥1% population (overall population), pembrolizumab presented a median OS of 16.7 months while chemotherapy a median OS of 12.1 months (HR: 0.81; 95% CI: 0.71–0.93; P=0.0036). For the TPS ≥20% subgroup, the median OS was 17.7 months for the pembrolizumab group and 13.0 months for the chemotherapy group (HR:0.77; 95% CI: 0.64–0.92; P=0.004). For the TPS ≥50% subgroup, the estimated median OS was 17.7 months for the pembrolizumab group and 13.0 months for the chemotherapy group (HR:0.77; 95% CI: 0.64–0.92; P=0.004). The comparison of PFS (secondary end-point) or overall response rate between arms in any population showed no significant difference. Median PFS duration among the 3 TPS populations were 7.1 vs. 6.4 months, 6.2 vs. 6.6 months, and 5.4 vs. 6.5 months (significance not formally tested in ≥20% or ≥1% population, since the superiority boundary was not met in ≥50% population). At least 1 subsequent anticancer therapy was received by 38% of the
pembrolizumab group and 44% of the chemotherapy group, including immunotherapy in 3% and 20%, respectively. Pembrolizumab group compared to chemotherapy group presented lower rate of treatment-related adverse events of any grade (63% vs. 90%) and of grade 3 or worse (18% vs. 41%), while death considered related to treatment was similar (2% vs. 2%). Based on the results of KEYNOTE 042, the FDA (10) approved pembrolizumab for first-line treatment for stage III NSCLC patients without EGFR or ALK genomic aberrations and not suitable for surgery and for definitive chemoradiation, and of stage IV NSCLC.

However, as highlighted by other authors (11,12), the KEYNOTE-042 presents several limitations that should be strictly analyzed before drawing definitive conclusions on the real efficacy of pembrolizumab monotherapy in advanced NSCLC patients with low PDL TPS. In the KEYNOTE 042 study population, 599 patients (47%) had a TPS of ≥50%, and 818 (64%) had a TPS of ≥20%, with 35% vs. 36% having a TPS of 1% to 19%, 18% vs. 16% having a TPS of 20% to 49%, and 47% vs. 47% having a TPS ≥50%. Thus, the number of patients with a PD-L1 TPS of 50% or greater was close to 50%, which is more than 30% higher than usually seen in the general population. Since the main benefit of treatment was associated with increasing PD-L1 TPS, in theory the results obtained in all three TPS subgroups of the KEYNOTE-042 study population were driven by high PD-L1 expression. An exploratory analysis of the results of KEYNOTE-042 revealed that little survival advantage emerged with pembrolizumab versus chemotherapy in patients with a TPS of 1% to 49% (median OS: 13.4 vs. 12.1 months; HR 0.92, 95% CI: 0.77–1.11). The OS benefit associated with pembrolizumab in KEYNOTE-042 is driven by the high PD-L1 subgroup (TPS ≥50%) while the benefits are not as clear-cut for those with PD-L1 TPS of 1% to 49%. Therefore, patients with low PD-L1 expression may benefit from an association between pembrolizumab with standard chemotherapy. This seems to be confirmed by results of the KEYNOTE-189 (13) and KEYNOTE-407 (14) trials showing that pembrolizumab combined with standard first-line platinum chemotherapy presented better OS and PFS than chemotherapy alone independent of PD-L1 tumor expression. Thus, patients with PD-L1 TPS ≥50% and without driver mutations should receive first-line pembrolizumab monotherapy, while in patients with lower PD-L1 TPS a pembrolizumab-chemotherapy combination may be likely indicated. The lack of prospective direct comparison does not allow to draw definitive conclusions, thus, the gold-standard treatment should be choice based on patient's clinical condition that may support the decision to add or eliminate chemotherapy.

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**Footnote**

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