PRESIDENTIAL SYMPOSIUM
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PS1
Phase 3 KEYNOTE-042 Study: Pembrolizumab vs Platinum-Based Chemotherapy as 1l Therapy for Advanced NSCLC with a PD-L1 TPS ≥1%

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Background: First-line (1L) therapy with pembrolizumab in patients with metastatic NSCLC without targetable aberrations and programmed death ligand 1 (PD-L1) tumor proportion score (TPS) ≥50% significantly improved the primary endpoint of PFS, and OS (secondary endpoint) compared to chemotherapy in the KEYNOTE-024 study. In KEYNOTE-042 (NCT02220894), we evaluated pembrolizumab vs chemotherapy at the lower PD-L1 TPS of ≥1%. **Method:** Eligible patients were randomized 1:1 to ≤35 cycles of pembrolizumab 200 mg Q3W or investigator's choice of ≤6 cycles of paclitaxel + carboplatin or pemetrexed + carboplatin with optional pemetrexed maintenance (nonsquamous only). Randomization was stratified by region (east Asia vs non-east Asia), ECOG PS (0 vs 1), histology (squamous vs nonsquamous), and TPS (≥50% vs 1-49%). Primary endpoints were OS in patients with TPS ≥50%, ≥20%, and ≥1%. OS differences were assessed sequentially using the stratified log-rank test. Efficacy boundaries at the prespecified second interim analysis were one-sided $P = 0.0122$, 0.01198, and 0.01238, respectively. **Results:** Overall, 1274 patients were randomized: 637 to each arm. 599 patients (47.0%) had TPS ≥50%, 818 (64.2%) had TPS ≥20%. After a median follow-up of 12.8-months, 13.7% were still on pembrolizumab and 4.9% were receiving pemetrexed maintenance. Pembrolizumab significantly improved OS in patients with TPS ≥50% (HR 0.69), TPS ≥20% (HR 0.77), and TPS ≥1% (HR 0.81) (Table). Grade 3-5 drug-related AEs were less frequent with pembrolizumab (17.8% vs 41.0%). The external DMC recommended continuing the trial to evaluate PFS (secondary endpoint). **Conclusion:** KEYNOTE-042 is the first study with a primary endpoint of OS to demonstrate superiority of pembrolizumab over platinum-based chemotherapy in patients with previously untreated locally advanced or metastatic NSCLC without sensitizing *EGFR* or *ALK* abberations and a PD-L1 TPS ≥1%. These data confirm and potentially extend the role of pembrolizumab monotherapy as a standard 1L treatment for PD-L1-expressing locally advanced or metastatic NSCLC. **Keywords:** chemotherapy, KEYNOTE-042, programmed death ligand 1 (PD-L1), pembrolizumab

Table: Overall Survival by PD–L1 TPS

	PD-L1 TPS					
	≥50%		≥20%		≥1%	
	Pembrolizumab n = 299	Chemotherapy n = 300	Pembrolizumab n = 413	Chemotherapy n = 405	Pembrolizumab n = 637	Chemotherapy n = 637
HR (95% CI); *P*-value	0.69 (0.56–0.85)		0.77 (0.64–0.92)		0.81 (0.71–0.93)	
	$P = 0.0003$		$P = 0.0020$		$P = 0.0018$	
Median (95% CI), months	20.0 (15.4–24.9)	12.2 (10.4–14.2)	17.7 (15.3–22.1)	13.0 (11.6–15.3)	16.7 (13.9–19.7)	12.1 (11.3–13.3)

PS2
CheckMate 227: Nivolumab + Ipilimumab vs Chemotherapy as 1L Treatment for Advanced NSCLC With High Tumor Mutational Burden

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Background: CheckMate 227 (NCT02477826) is a large phase 3 study of first-line nivolumab-based regimens vs platinum-doublet chemotherapy in advanced non-small cell lung cancer (NSCLC). We report results from Part 1, including a preplanned co-primary endpoint evaluating progression-free survival (PFS) of nivolumab + ipilimumab vs chemotherapy in patients with high tumor mutational burden (TMB ≥10 mut/Mb), safety of nivolumab + low-dose ipilimumab, and patient-reported outcomes (PROs). **Method:** Patients (N = 1739) with chemotherapy-naive, stage IV/recurrent NSCLC without known sensitizing *EGFR*/*ALK* alterations were randomized 1:1:1 to nivolumab (3 mg/kg Q2W) + ipilimumab (1 mg/kg Q6W), nivolumab monotherapy (240 mg Q2W), or chemotherapy for patients with ≥1% tumor programmed death-ligand 1 (PD-L1) expression and to nivolumab + ipilimumab, nivolumab (360 mg Q3W) + chemotherapy, or chemotherapy for patients with <1% tumor PD-L1 expression. Co-primary endpoints were overall survival for nivolumab + ipilimumab vs chemotherapy in patients with PD-L1—selected tumors and PFS (blinded independent central review) for nivolumab + ipilimumab vs chemotherapy in patients with high TMB ≥10 mut/Mb. TMB was determined from tumor tissue using the FoundationOne CDx™ assay. Safety analyses included time to onset and time to resolution of select treatment-related adverse events (select TRAEs; those with a potential immunologic cause) and corticosteroid use. PROs were assessed using the Lung Cancer Symptom Scale and EQ-5D instruments. **Results:** Minimum follow-up was 11.2 months. PFS was significantly longer with nivolumab + ipilimumab vs chemotherapy in patients with high TMB ≥10 mut/Mb (HR = 0.58 [97.5% CI: 0.41, 0.81]; $P = 0.0002$); results were consistent across subgroups, including PD-L1 expression and tumor histology. Rates of TRAEs leading to discontinuation were 17% with nivolumab + ipilimumab and 9% with chemotherapy. Grade 3—4 TRAEs occurred in 31% and 36% of patients treated with