LUNG CANCER UPDATES

AACR HIGHLIGHTS

14-18 ABRIL 2018, CHICAGO

Combinación de inmunoterapia en primera línea de enfermedad avanzada

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Con el patrocinio de

Bristol-Myers Squibb

Iniciativa científica de:

GECP

Grupo Español de Cáncer de Pulmón

Spanish Lung Cancer Group

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Nivolumab + Ipilimumab vs Platinum-Doublet Chemotherapy as First-line Treatment for Advanced Non-Small Cell Lung Cancer: Initial Results From CheckMate 227

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ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden

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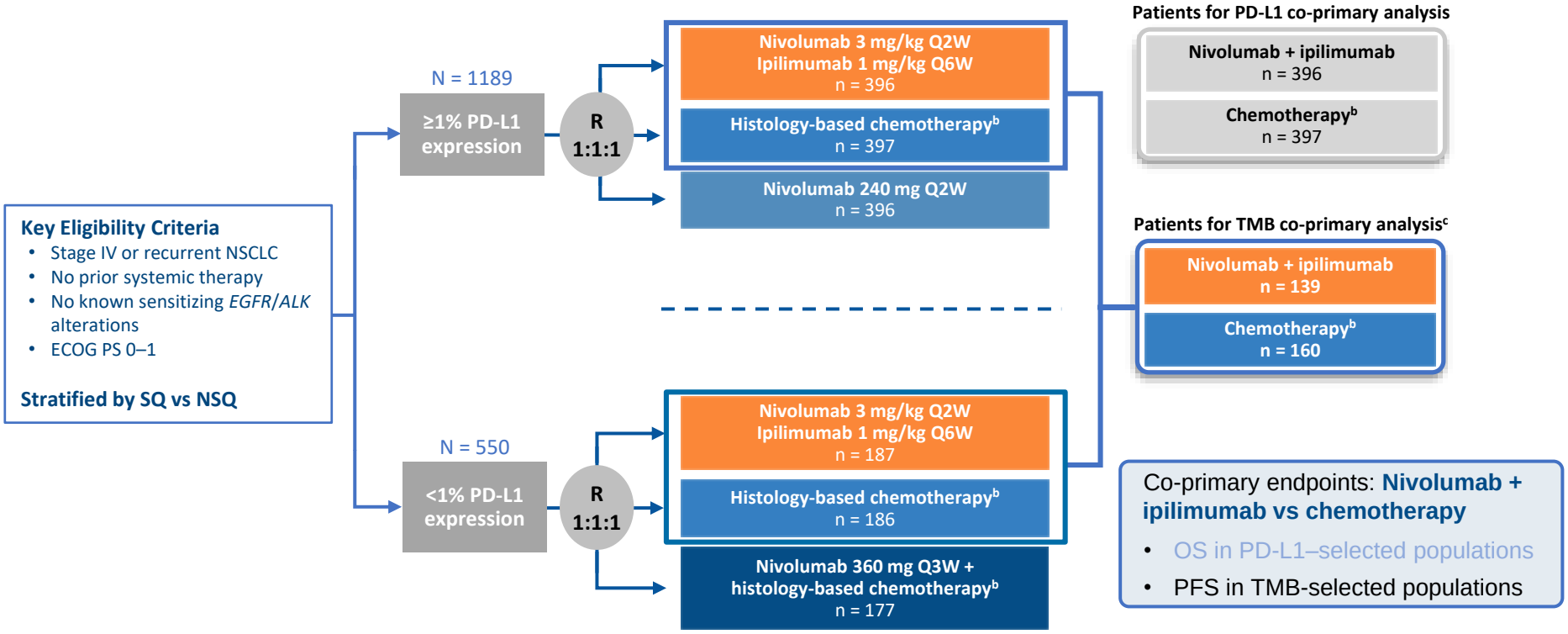
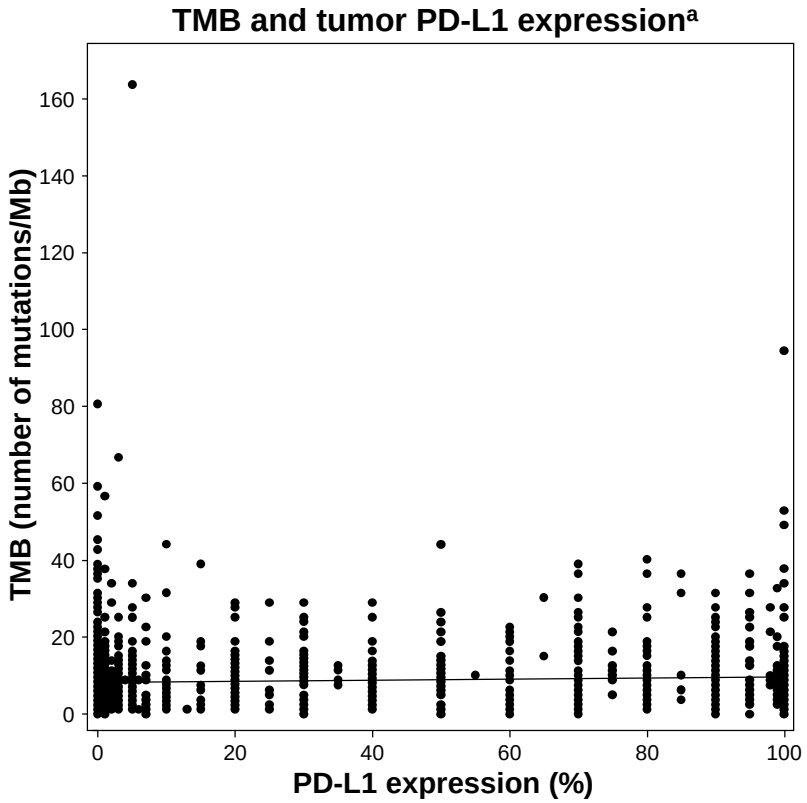
CheckMate 227 Part 1 Study Design[a]

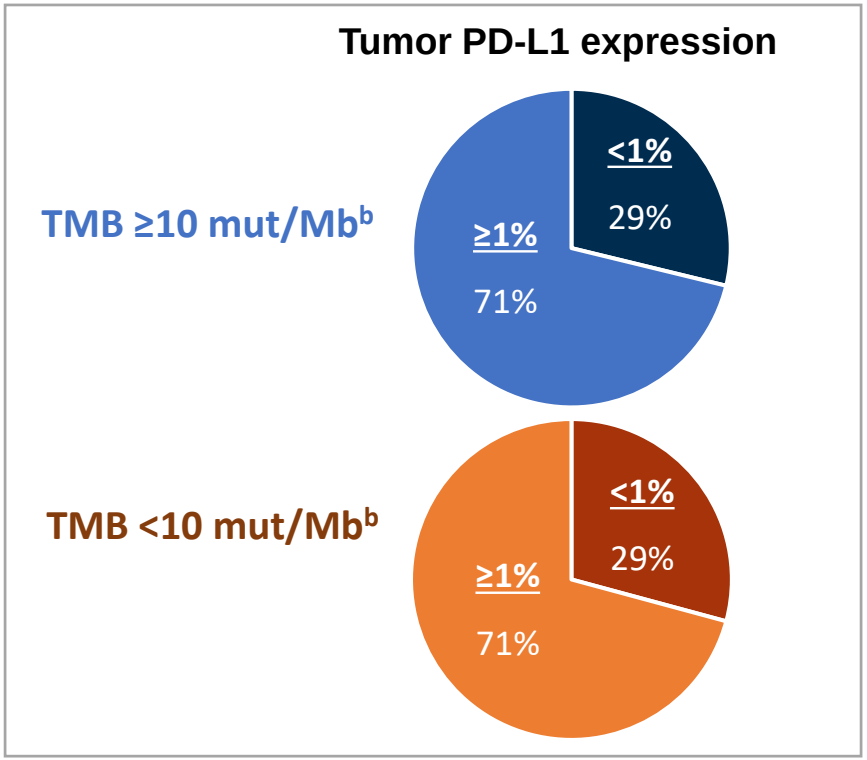


Database lock: January 24, 2018; minimum follow-up: 11.2 months

[a]NCT02477826 [b]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤4 cycles, with optional pemetrexed maintenance following chemotherapy or nivolumab + pemetrexed maintenance following nivolumab + chemotherapy; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤4 cycles; [c]The TMB co-primary analysis was conducted in the subset of patients randomized to nivolumab + ipilimumab or chemotherapy who had evaluable TMB ≥10 mut/Mb

TMB and Tumor PD-L1 Expression Identify Distinct and Independent Populations of NSCLC



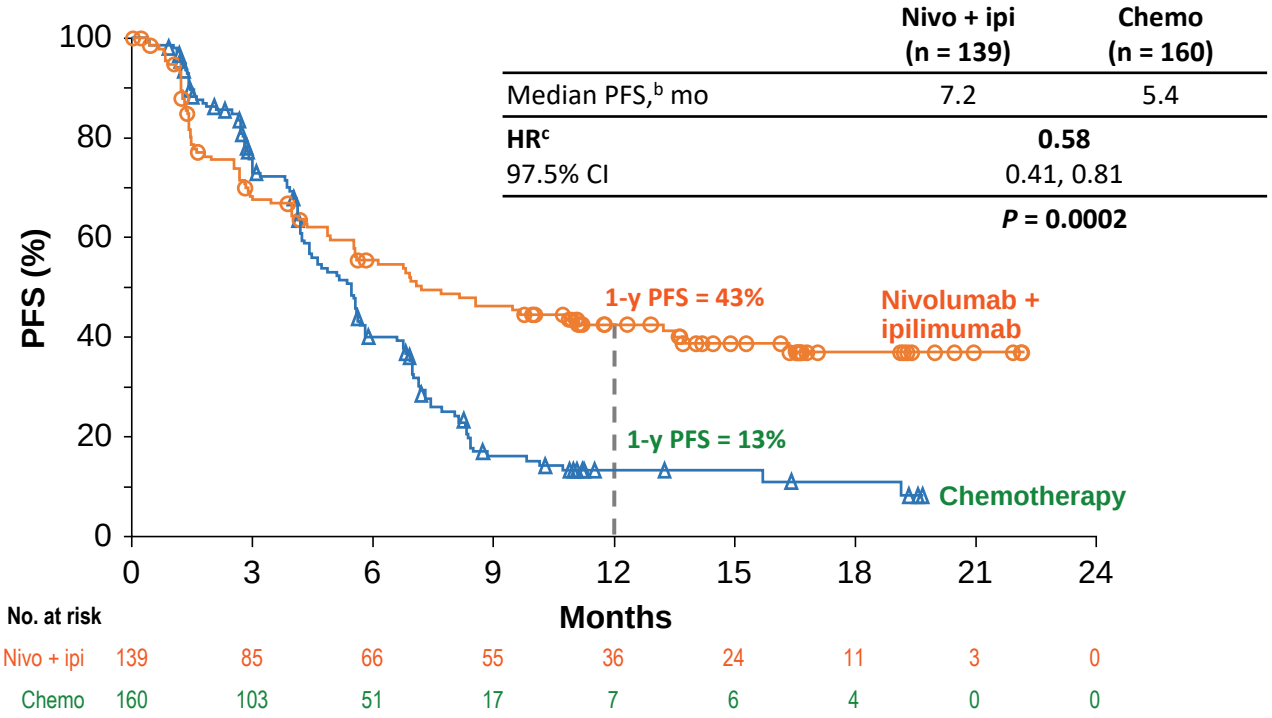


[a]Symbols (dots) in the scatterplot may represent multiple data points, especially for patients with <1% tumor PD-L1 expression. The black line shows the relationship between TMB and PD-L1 expression as described by a linear regression model; [b]Among patients in the nivolumab +ipilimumab and chemotherapy arms; TMB ≥10 mut/Mb, n = 299; TMB <10 mut/Mb, n = 380

Baseline Characteristics in Patients With High TMB (≥10 mut/Mb)

	Nivolumab + ipilimumab (n = 139)	Chemotherapy (n = 160)
Age, median (range), y	64 (41-87)	64 (29-80)
Female, %	29	34
ECOG PS, %		
0	40	31
1	59	69
≥2	1	1
Smoking status, %		
Current/former smoker	94	91
Never smoker	5	7
Unknown	1	2
Histology, %		
Squamous	32	34
Non-squamous	68	66
Tumor PD-L1 expression, %		
<1%	27	30
≥1%	73	70

Co-primary Endpoint: PFS With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)a



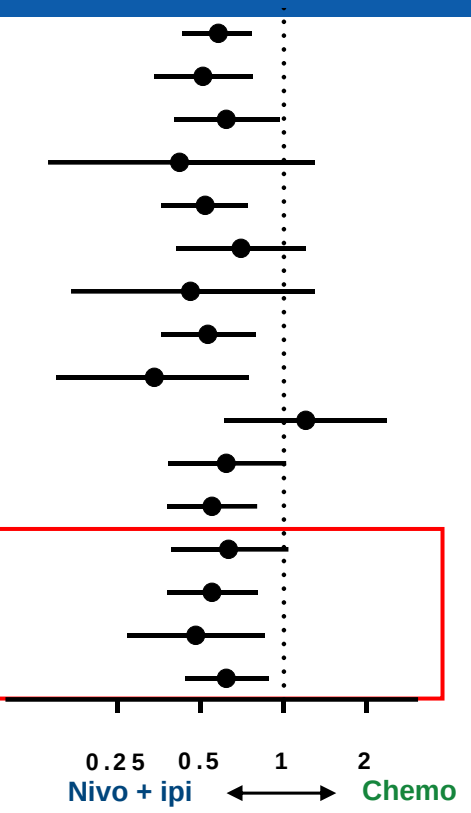
	Nivo + ipi (n = 139)	Chemo (n = 160)
Median PFS,[b] mo	7.2	5.4
HR[c]	**0.58**	
97.5% CI	0.41, 0.81	
	***P* = 0.0002**	

- In patients with TMB <10 mut/Mb treated with nivo + ipi vs chemo, the HR was 1.07 (95% CI: 0.84, 1.35)[d]

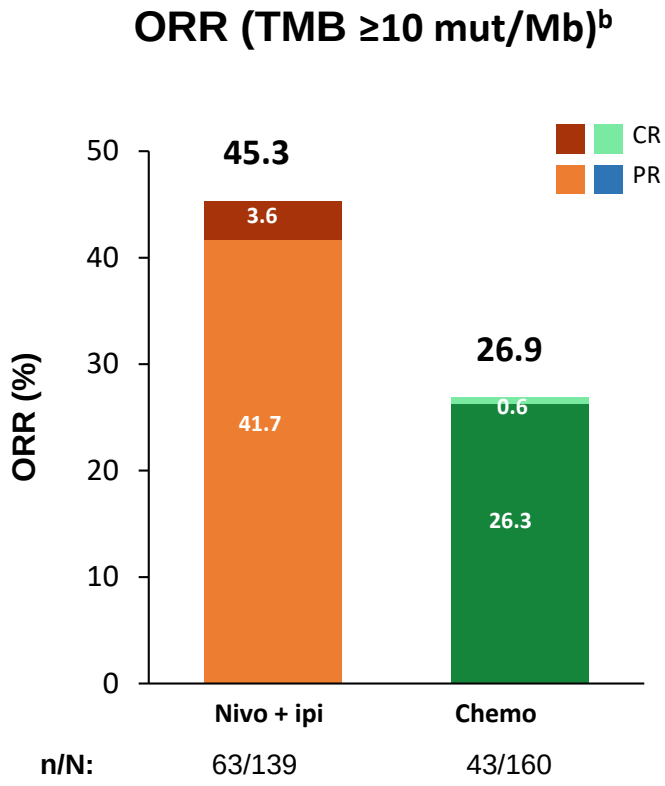
[a]Per blinded independent central review (BICR); median (range) of follow-up in the co-primary analysis population was 13.6 mo (0.4, 25.1) for nivo + ipi and 13.2 mo (0.2, 26.0) for chemo; [b]95% CI: nivo + ipi (5.5, 13.2 mo), chemo (4.4, 5.8 mo); [c]95% CI: 0.43, 0.77 mo; [d]The *P*-value for the treatment interaction was 0.0018

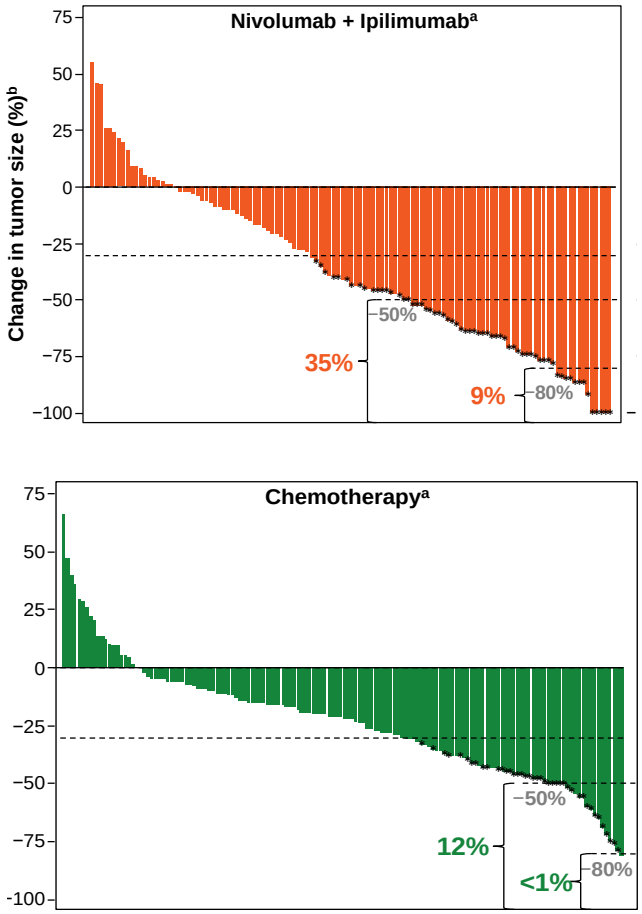
PFS Subgroup Analyses in Patients With High TMB (≥10 mut/Mb)

Subgroup	Nivo + ipi n	Chemo n	Unstratified HR (95% CI)
Overall	139	160	0.58 (0.43, 0.77)
<65 years	73	83	0.51 (0.34, 0.77)
≥65 years	66	77	0.62 (0.40, 0.97)
≥75 years	13	14	0.42 (0.14, 1.30)
Male	98	106	0.52 (0.36, 0.74)
Female	41	54	0.70 (0.41, 1.20)
North America	14	16	0.46 (0.17, 1.30)
Europe	77	87	0.53 (0.36, 0.79)
Asia	21	32	0.34 (0.15, 0.75)
Rest of world	27	25	1.20 (0.61, 2.36)
ECOG PS 0	56	49	0.62 (0.38, 1.02)
ECOG PS 1	82	110	0.55 (0.38, 0.80)
Squamous	44	56	0.63 (0.39, 1.04)
Non-squamous	95	104	0.55 (0.38, 0.80)
PD-L1 <1%	38	48	0.48 (0.27, 0.85)
PD-L1 ≥1%	101	112	0.62 (0.44, 0.88)



ORR and Best Change in Target Lesion in Patients With High TMB (≥10 mut/Mb)[a]





[a] Per BICR; [b]ORR in patients with TMB <10 mut/Mb was 24.6% in nivo + ipi arm and 25.9% in chemo arm

Safety Summary of Treatment-Related AEs

TRAE,[a] %	Nivolumab + ipilimumab (n = 576)		Chemotherapy (n = 570)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE	75	31	81	36
TRAE leading to discontinuation[b]	17	12	9	5
Most frequent TRAEs (≥15%)				
Rash	17	2	5	0
Diarrhea	16	2	10	1
Fatigue	13	1	18	1
Decreased appetite	13	<1	19	1
Nausea	10	<1	36	2
Constipation	4	0	15	<1
Anemia	4	2	32	11
Neutropenia	<1	0	17	9
Treatment-related deaths[c]	1		1	

- Median duration (range) of therapy was 4.2 mo (0.03–24.0+) with nivolumab + ipilimumab and 2.6 mo (0.03–22.1+) with chemotherapy
- Median number of doses of nivolumab (Q2W) and ipilimumab (Q6W) received were 9 and 3, respectively

[a]Includes events reported between first dose and 30 days after last dose of study drug; [b]For nivo + ipi, these events include TRAEs leading to discontinuation of ipi or both study drugs; patients could not discontinue nivo without discontinuing ipi; [c]Treatment-related deaths in the nivo + ipi arm included pneumonitis (n = 3), myocarditis, acute tubular necrosis, circulatory collapse, and cardiac tamponade; deaths in the chemo arm included sepsis (n = 2), multiple brain infarctions, interstitial lung disease, thrombocytopenia, and febrile neutropenia with sepsis

Summary: Nivolumab + Ipilimumab in First-line NSCLC With High TMB (≥10 mut/Mb)

In first-line TMB high (>10) metastatic NSCLC, nivolumab + ipilimumab prolonged PFS vs chemotherapy

- PFS HR = 0.58 (97.5% CI: 0.41, 0.81); P = 0.0002
- Benefit independent of PD-L1, histology, and observed across nearly all subgroups

Results from CheckMate 227 may introduce 2 new standards of care for first-line NSCLC

- Introduces nivolumab + ipilimumab as a new option for first-line NSCLC with TMB ≥10 mut/Mb
  - Durable benefit while sparing first-line chemotherapy and preserving effective second-line options
- Validates TMB as an important and independent biomarker to be routinely tested in treatment-naive, advanced NSCLC (TRIALS 568, 227)

[a]In patients with ≥1% tumor PD-L1 expression and high TMB (≥10 mut/Mb)