LUNG CANCER UPDATES

ASCO HIGHLIGHTS

1-5 JUNIO 2018, CHICAGO

NSCLC estage IV. inmunoterapia

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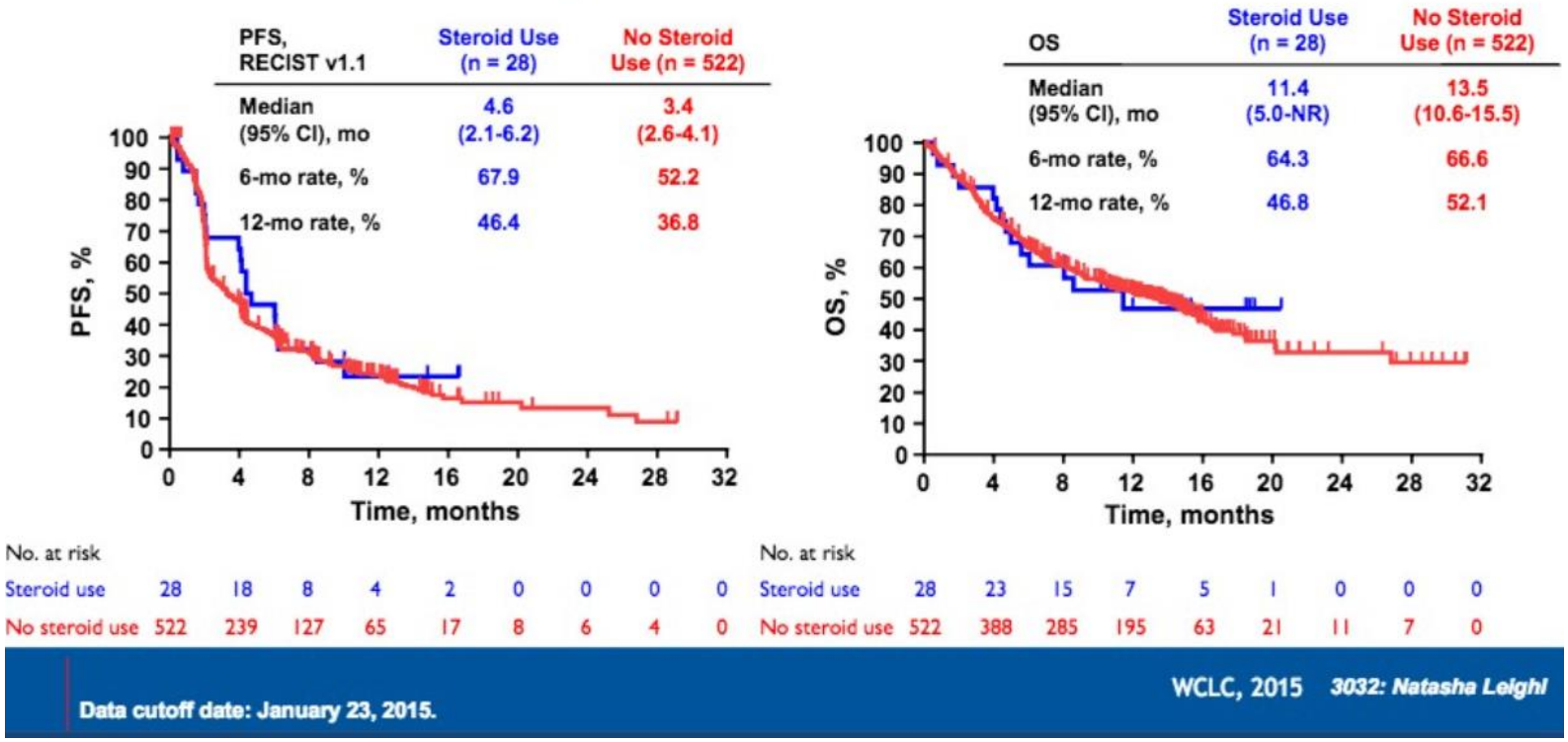
2º /1º lin stage IV NSCLC. Treatment with inmunotherapy. Factors related to decrease benefit

Deleterious effect of baseline steroids on efficacy of PD-(L)1 blockade in patients with NSCLC

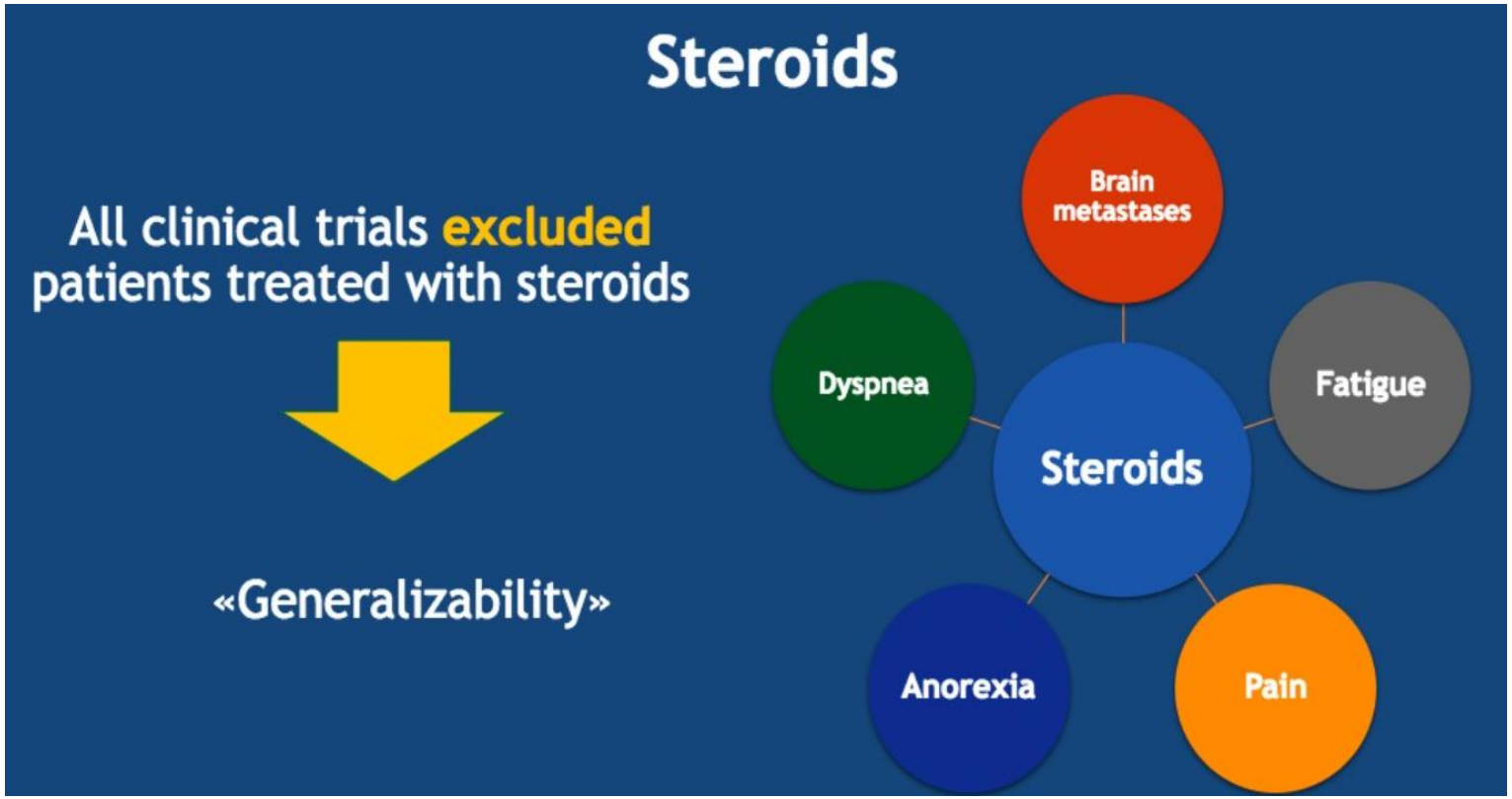
Survival and Corticosteroid Use To Manage Immune-Mediated AEs



On-treatment steroids for treatment of irAEs do not appear to affect efficacy,

Kathryn Cecilia Arbour. ASCO 2018. ORAL

Deleterious effect of baseline steroids on efficacy of PD-(L)1 blockade in patients with NSCLC



But the potential impact of baseline steroids at time of treatment initiation is unknown.

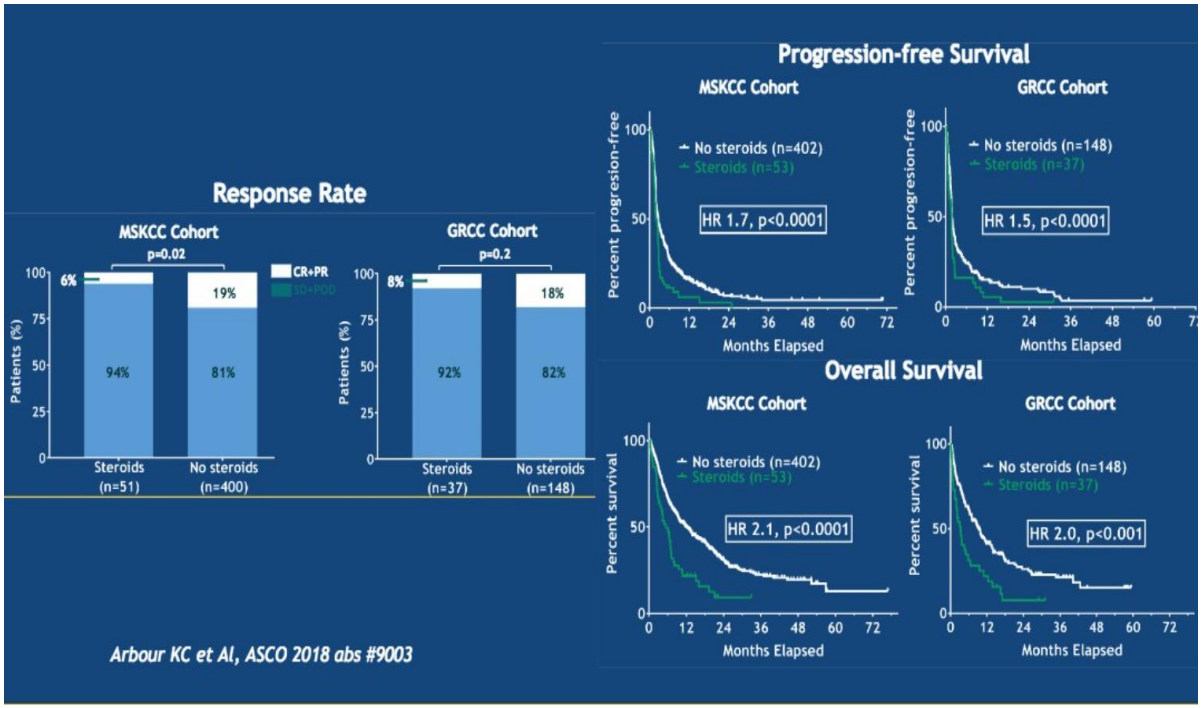
640 patients form two institution swith advanced NSCLC treated with single agent PD-(L)1 blockade.

PTS were reviewed restrospectively to identify IV or PO steroid use at the time of beginning PD-(L)1

stratified into two groups: ≥10mg qd prednisone equivalents vs < 10mg/no steroids on Day 1 of PD-(L)1 therapy

Kathryn Cecilia Arbour. ASCO 2018. ORAL

Deleterious effect of baseline steroids on efficacy of PD-(L)1 blockade in patients with NSCLC



- **Results:** **14% (90/640) received ≥10mg/qd steroids** at the start of PD-(L)1 blockade. (dyspnea, fatigue , and brain metastases
- Baseline steroids were associated with decreased ORR, PFS, and OS with PD-(L)1 blockade In the pooled population
- After adjusting for smoking history, performance status, and history of brain metastases, baseline **steroids** remained **significantly associated with decreased** **ORR** ($p = 0.05$), **PFS** ($p = 0.03$), and **OS** ($p < 0.001$)

Kathryn Cecilia Arbour. ASCO 2018. ORAL

1º line stage IV NSCLC. Treatment with inmunotherapy

Afianzamos datos combinación quimioterapia + inmunoterapia en primera línea

Afianzamos datos combinación quimioterapia + inmunoterapia en primera línea

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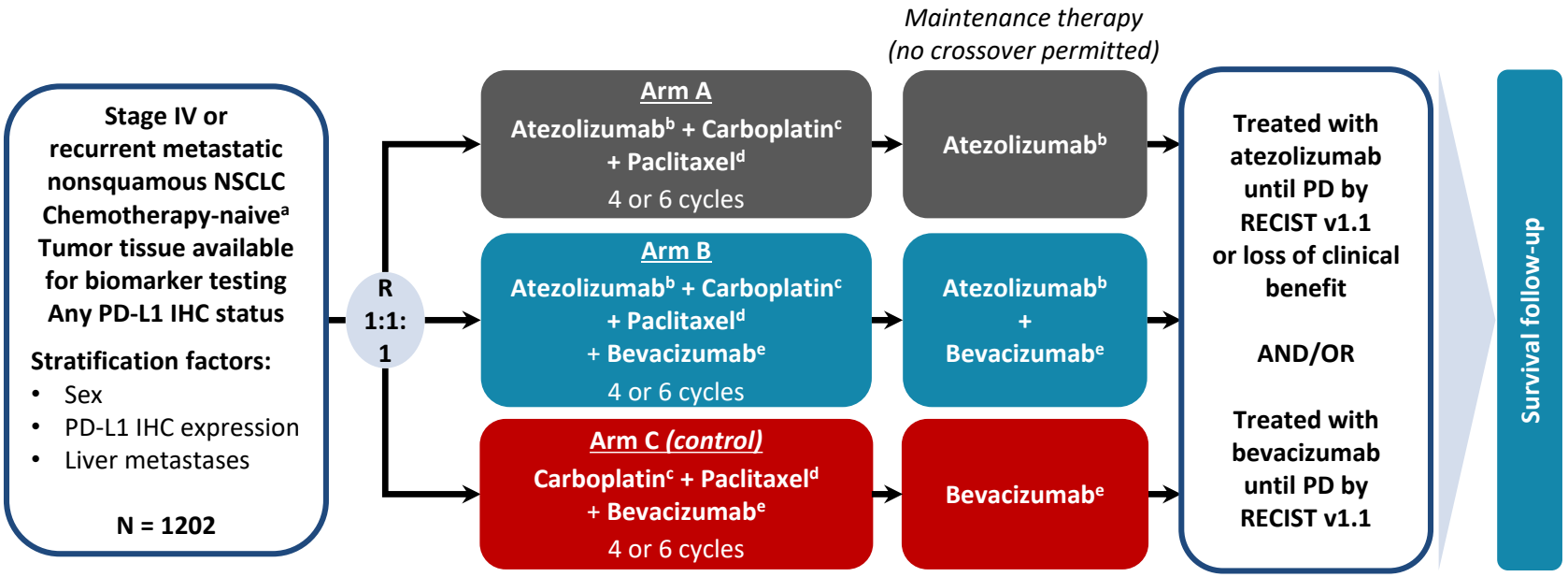
IMpower150 . Overall survival (OS) analysis of IMpower150, a randomized Ph 3 study of atezolizumab (atezo) + chemotherapy (chemo) ± bevacizumab (bev) vs chemo + bev in 1L nonsquamous (NSQ) NSCLC50 study design



1 Co-primary objectives

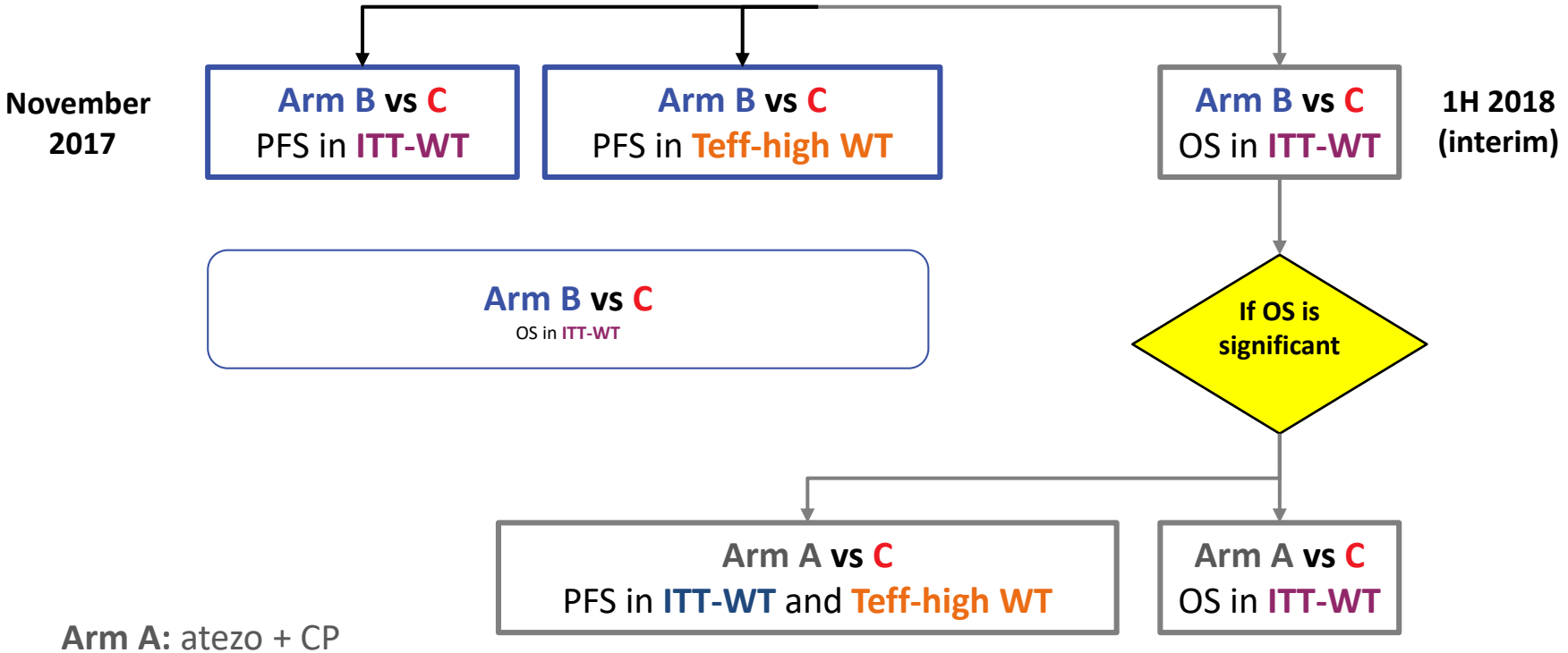
- Investigator-assessed **PFS** in **ITT-WT**[f]
- Investigator-assessed **PFS** in **Teff-high WT**[f,g]
- **OS** in **ITT-WT**[f]

2 Key secondary objectives

- Investigator-assessed **PFS** and **OS** in **ITT**
- Investigator-assessed **PFS** in PD-L1 IHC subgroups
- Independent review facility (IRF)-assessed **PFS**
- **ORR** and **DOR** per RECIST v1.1
- **Safety** in **ITT**

a Patients with a sensitizing EGFR mutation or ALK translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies. b Atezolizumab: 1200 mg IV q3w. c Carboplatin: AUC 6 IV q3w. d Paclitaxel: 200 mg/m2 IV q3w. e Bevacizumab: 15 mg/kg IV q3w. f WT refers to patients without EGFR or ALK genetic alterations. g The T-effector (Teff) gene signature is defined by expression of PD-L1, CXCL9 and IFNγ and is a surrogate of both PD-L1 IHC expression and pre-existing immunity (Kowanetz M, et al. WCLC 2017).

- atezo, atezolizumab; bev, bevacizumab; CP, carboplatin + paclitaxel.

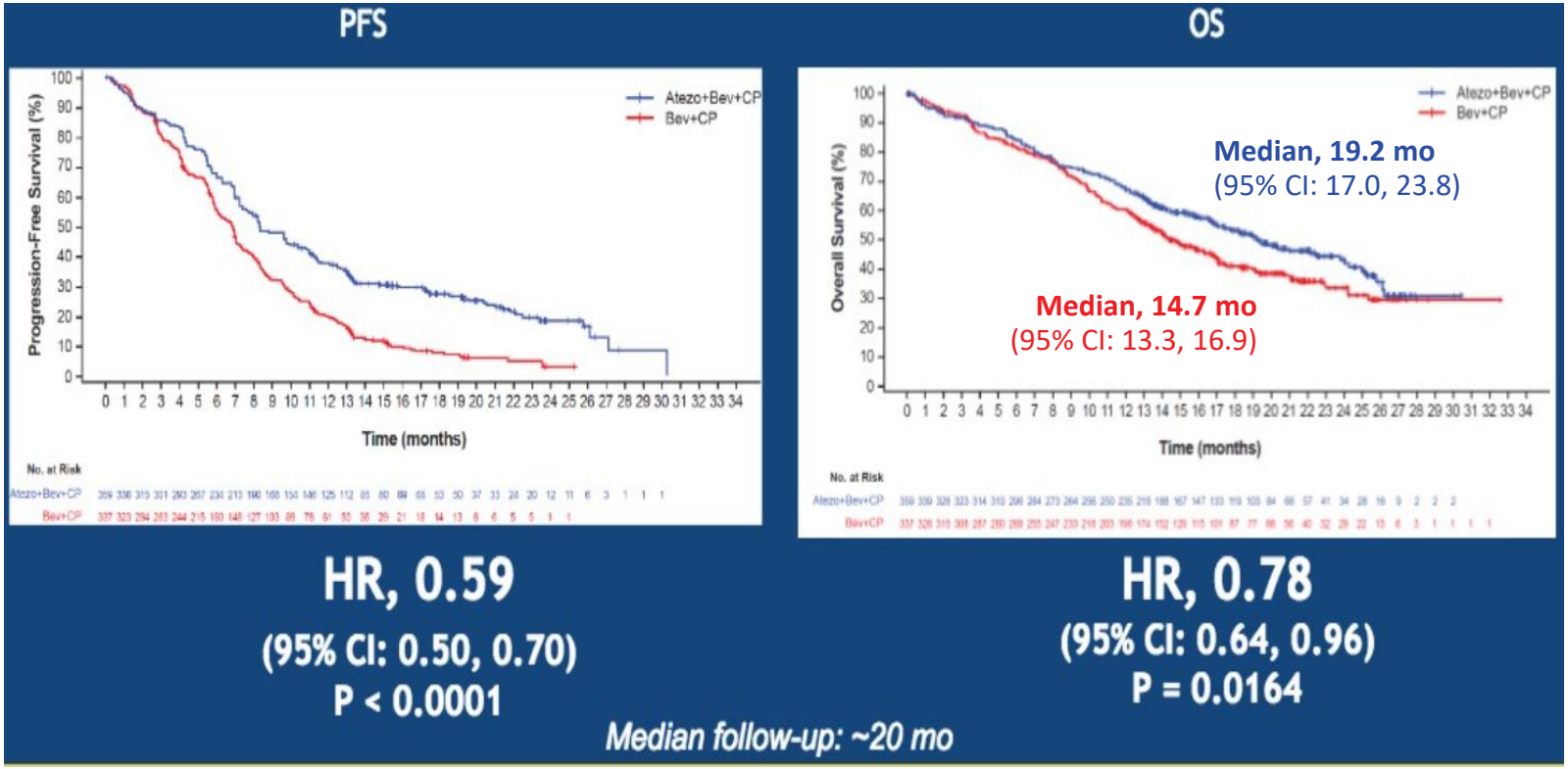


Arm A: atezo + CP

Arm B: atezo + bev + CP

Arm C: bev + CP *(control)*

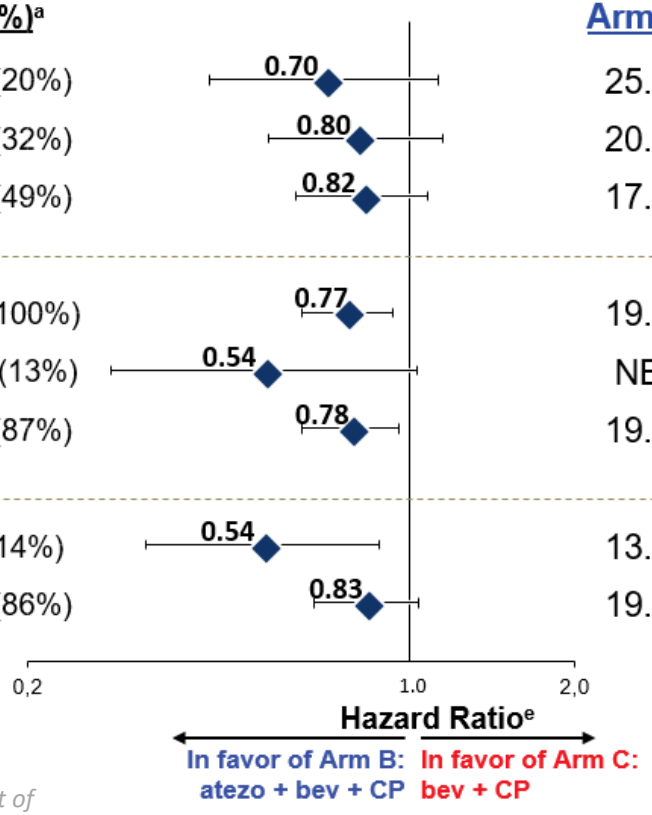
IMpower1Overall survival (OS) analysis of IMpower150, a randomized Ph 3 study of atezolizumab (atezo) + chemotherapy (chemo) ± bevacizumab (bev) vs chemo + bev in 1L nonsquamous (NSQ) NSCLC50 study design



Mark A. Socinski. ASCO 2018 .ORAL

OS in Key Subgroups (Arm B vs Arm C)

Subgroup	n (%)[a]	Median OS, mo Arm B	Arm C
PD-L1–High (TC3 or IC3) WT	136 (20%)	25.2	15.0
PD-L1–Low (TC1/2 or IC1/2)[b] WT	226 (32%)	20.3	16.4
PD-L1–Negative (TC0 and IC0) WT	339 (49%)	17.1	14.1
ITT (including *EGFR/ALK*+)	800 (100%)	19.8	14.9
EGFR/ALK+ only[c]	104[d] (13%)	NE	17.5
ITT-WT	696 (87%)	19.2	14.7
Liver Metastases WT	94 (14%)	13.2	9.1
No Liver Metastases WT	602 (86%)	19.8	16.7



NE, not estimable.

[a] Prevalence % for PD-L1 IHC and liver metastases subgroups out of ITT-WT (n=696); prevalence of ITT, EGFR/ALK+, and ITT-WT out of ITT (n=800).

[b] Mutually exclusive subgroup that excludes TC3 or IC3 patients from the TC1/2/3 or IC1/2/3 subgroup.

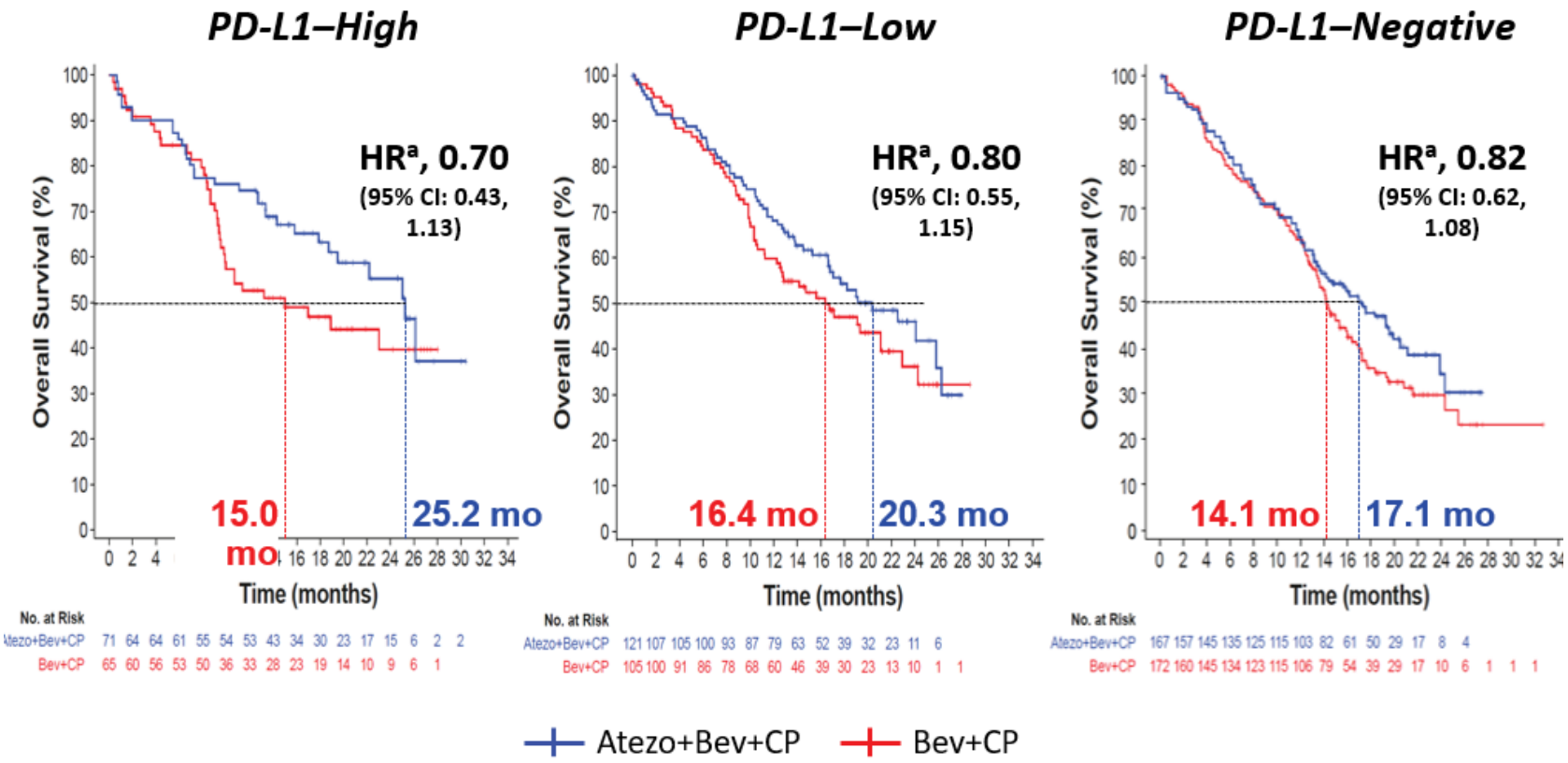
[c] Patients with a sensitizing EGFR mutation or ALK translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.

[d] One patient had EGFR exon 19 deletion and also tested ALK positive per central lab.

[e] Stratified HR for ITT-WT; unstratified HR for all other subgroups. Data cutoff: January 22, 2018

Mark A. Socinski.

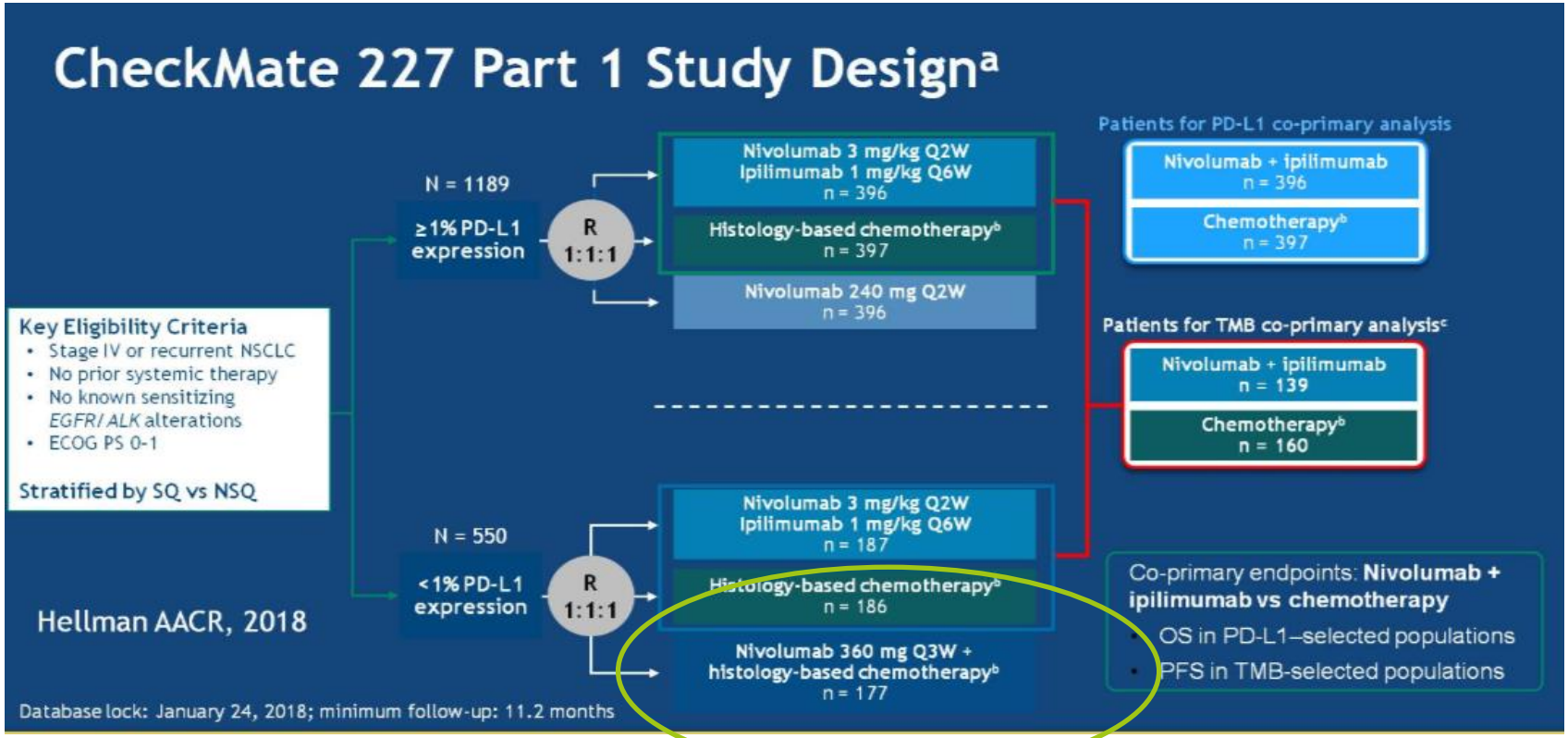
Survival Benefit Was Observed Across All PD-L1 Subgroups in the ITT-WT (Arm B vs Arm C)



PD-L1–high = TC3 or IC3; PD-L1–low = TC1/2 or IC1/2; PD-L1–negative = TC0 and IC0.

[a] Unstratified HR. Data cutoff: January 22, 2018

Nivolumab (Nivo) + Ipilimumab (Ipi) vs Platinum-Doublet Chemotherapy (Chemo) as First-line (1L) Treatment (Tx) for Advanced Non-Small Cell Lung Cancer (NSCLC): Safety Analysis and Patient-Reported Outcomes (PROs) From CheckMate 227



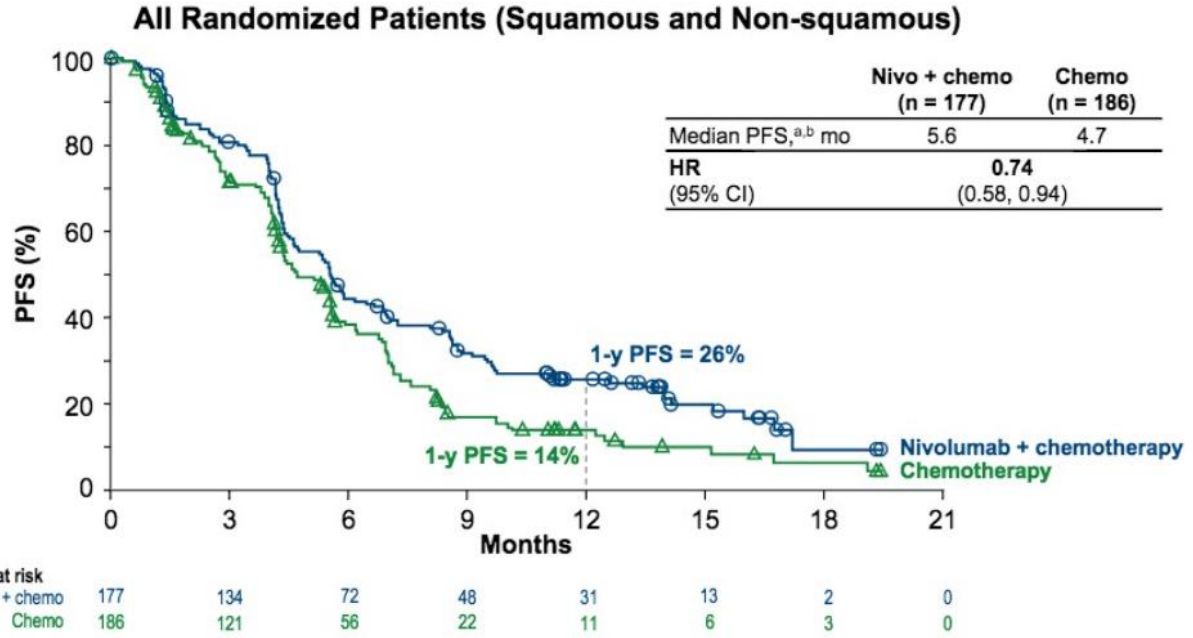
Results for nivo + chemo vs chemo in pts with < 1% tumor PD-L1 expression

CheckMate 227 (NCT02477826) is a phase 3 study of 1L nivo + ipi, nivo, or nivo + chemo vs chemo in advanced NSCLC with different levels PD-L1 expresion. randomized 1:1:1 to nivo (3 mg/kg Q2W) + ipi (1 mg/kg Q6W), nivo monotherapy (240 mg Q2W), or chemo for pts with ≥1% tumor PD-L1 expression and to nivo + ipi, nivo (360 mg Q3W) + chemo, or chemo for pts with < 1% tumor PD-L1.

Hossein Borghaei,. ASCO 2018. ORAL

CheckMate 227: Nivo + Ipi, Nivo + Chemo, and Chemo in 1L NSCLC With <1% Tumor PD-L1 Expression

PFS: Nivolumab + Chemotherapy vs Chemotherapy in Patients With <1% Tumor PD-L1 Expression

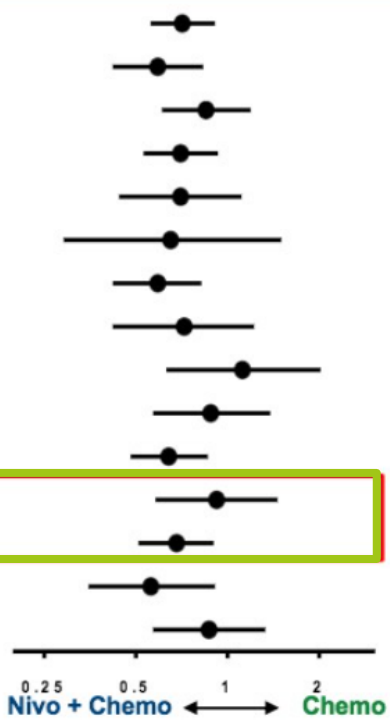


[a]95% CI: nivo + chemo (4.6, 6.7 mo), chemo (4.3, 5.6 mo); [b]In the nivo + ipi arm (n = 187), median (95% CI) PFS was 4.4 (3.1, 6.0), 1-y PFS was 29%, and HR vs chemo was 0.79 (0.62, 1.01)

PFS was **improved with nivo + chemo** vs chemo (**HR = 0.74** [95% CI: 0.58, 0.94]; minimum follow-up 11.2 mo

PFS Subgroup Analyses in Patients With <1% Tumor PD-L1 Expression

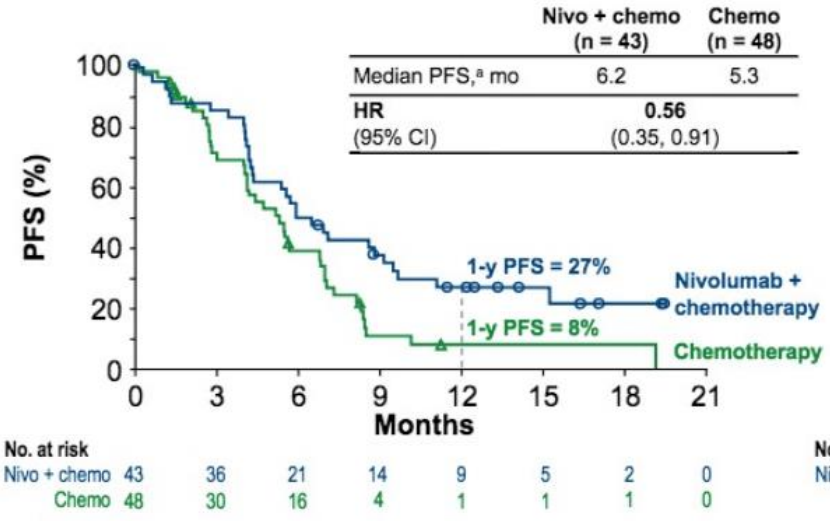
Subgroup	Nivo + chemo n	Chemo n	Unstratified HR
Overall	177	186	0.71
<65 years	91	98	0.59
≥65 years	86	88	0.85
Male	130	125	0.70
Female	47	61	0.70
North America	25	15	0.65
Europe	90	92	0.59
Asia	36	43	0.72
Rest of world	26	36	1.12
ECOG PS 0	59	57	0.88
ECOG PS 1	117	127	0.64
Squamous	43	46	0.92
Non-squamous	134	140	0.68
TMB high (≥10 mut/Mb)	43	48	0.56
TMB low (<10 mut/Mb)	54	59	0.87



CheckMate 227: Nivo + Ipi, Nivo + Chemo, and Chemo in 1L NSCLC With <1% Tumor PD-L1 Expression

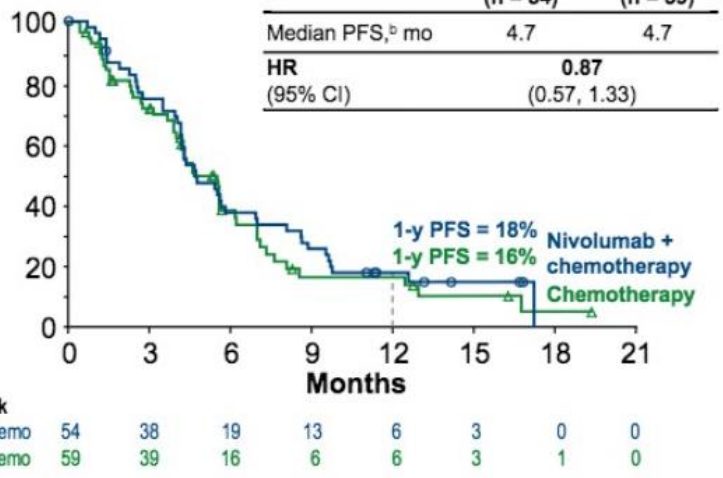
PFS: Nivolumab + Chemotherapy vs Chemotherapy By TMB

TMB ≥10 mut/Mb and <1% Tumor PD-L1 Expression



	Nivo + chemo (n = 43)	Chemo (n = 48)
Median PFS,[a] mo	6.2	5.3
HR (95% CI)	0.56 (0.35, 0.91)	

TMB <10 mut/Mb and <1% Tumor PD-L1 Expression



	Nivo + chemo (n = 54)	Chemo (n = 59)
Median PFS,[b] mo	4.7	4.7
HR (95% CI)	0.87 (0.57, 1.33)	

- TMB ≥10 mut/Mb: ORR was 60.5% with nivo + chemo and 20.8% with chemo
- TMB <10 mut/Mb: ORR was 27.8% with nivo + chemo and 22.0% with chemo

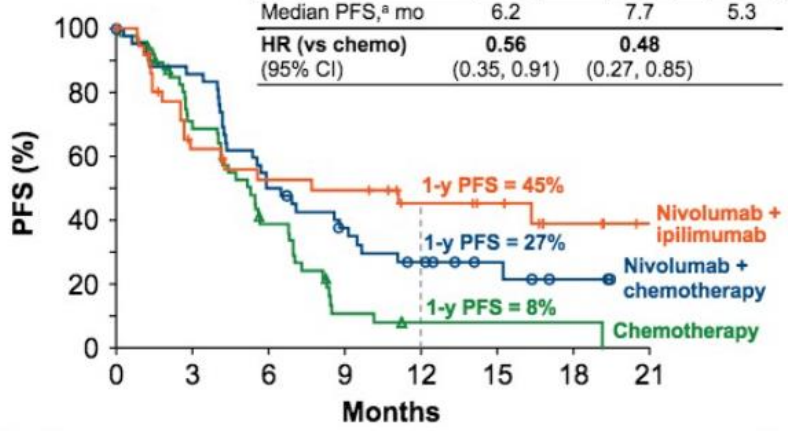
[a]95% CI: nivo + chemo (4.3, 9.1 mo), chemo (4.0, 6.8 mo); [b]95% CI: nivo + chemo (4.2, 6.9 mo), chemo (3.9, 6.2 mo)

CheckMate 227: Nivo + Ipi, Nivo + Chemo, and Chemo in 1L NSCLC With <1% Tumor PD-L1 Expression

PFS: Nivolumab + Chemotherapy and Nivolumab + Ipilimumab By TMB

TMB ≥10 mut/Mb and <1% Tumor PD-L1 Expression

	Nivo + chemo (n = 43)	Nivo + ipi (n = 38)	Chemo (n = 48)
Median PFS,[a] mo	6.2	7.7	5.3
HR (vs chemo) (95% CI)	**0.56** (0.35, 0.91)	**0.48** (0.27, 0.85)	

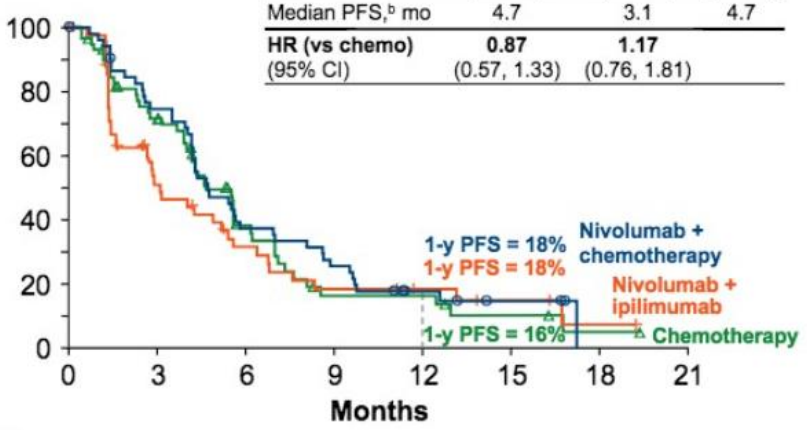


No. at risk

Nivo + chemo	43	36	21	14	9	5	2	0
Nivo + ipi	38	20	16	15	10	8	4	1
Chemo	48	30	16	4	1	1	1	0

TMB <10 mut/Mb and <1% Tumor PD-L1 Expression

	Nivo + chemo (n = 54)	Nivo + ipi (n = 52)	Chemo (n = 59)
Median PFS,[b] mo	4.7	3.1	4.7
HR (vs chemo) (95% CI)	**0.87** (0.57, 1.33)	**1.17** (0.76, 1.81)	



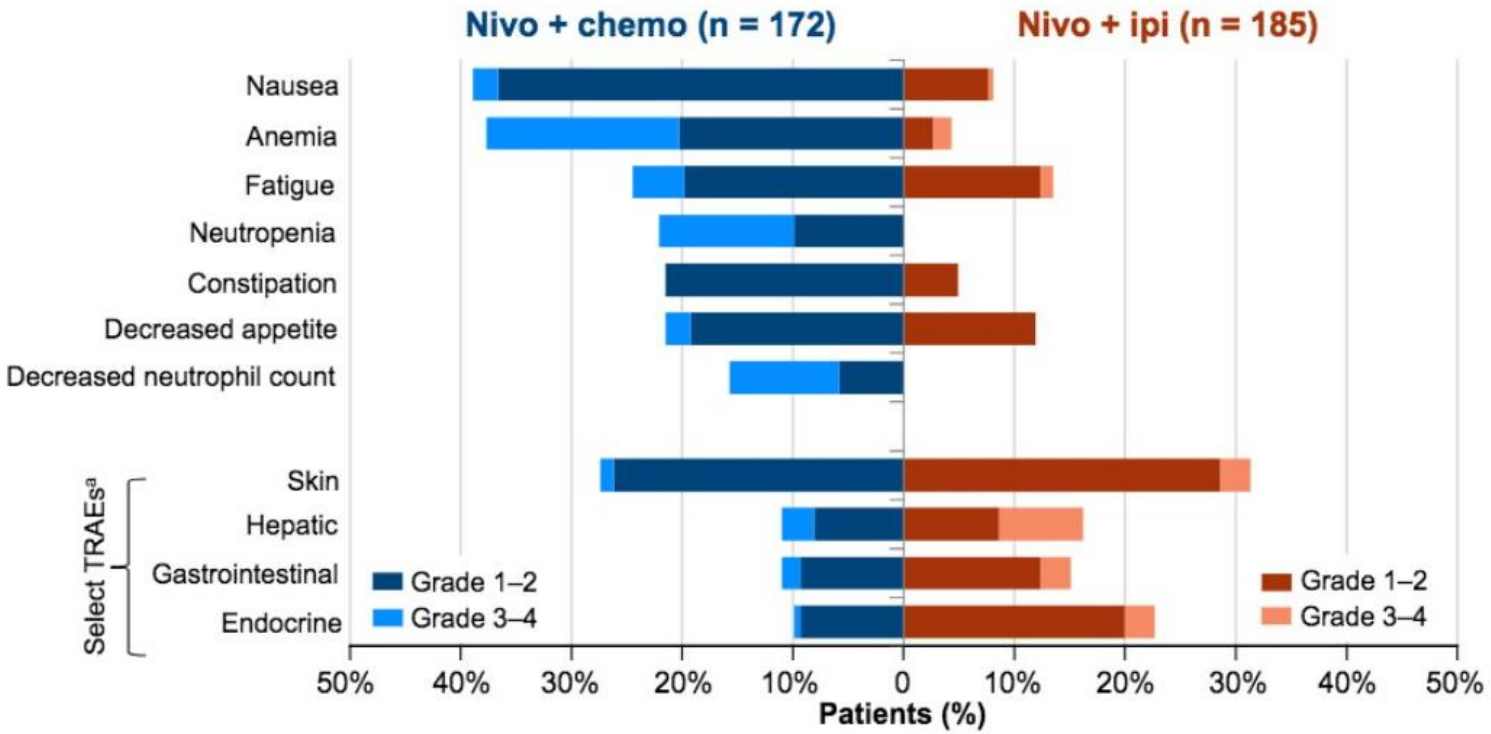
No. at risk

Nivo + chemo	54	38	19	13	6	3	0	0
Nivo + ipi	52	22	12	7	5	3	1	0
Chemo	59	39	16	6	6	3	1	0

Exploratory analysis
[a]95% CI: nivo + chemo (4.3, 9.1 mo), nivo + ipi (2.7, NR mo), chemo (4.0, 6.8 mo); [b]95% CI: nivo + chemo (4.2, 6.9 mo), nivo + ipi (1.6, 5.4 mo), chemo (3.9, 6.2 mo)

CheckMate 227: Nivo + Ipi, Nivo + Chemo, and Chemo in 1L NSCLC With <1% Tumor PD-L1 Expression

Most Frequent TRAEs (≥15%)



- TRAEs in the chemo arm were consistent with prior reports[1,2]

[a]Select AEs are those with potential immunologic etiology that require frequent monitoring/intervention

1. Langer C, et al. *Lancet Oncol* 2016;17:1497–508. 2. Hellmann MD, et al. *N Engl J Med* 2018;378:2093–104.

Resumen Ensayos con resultados maduros

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Trial		PFS / OS (months)	PFS HR in PD-L1 neg.	Toxicities Grade 3-5
KEYNOTE-024 PD-L1≥50%	Pembro Plat/Pem or Gem or Pacli	10.3 / 30 6 / 14.2	NA	27 vs 53%
KEYNOTE-042 PD-L1≥1%	Pembro Plat/Pem or Pacli	5.4 / 16.7 6.5 / 12.1	NA (in 1-49%: 0.92, NS)	18 vs 41%
IMPower150 Non-squamous	Atezo + Beva + Plat/Pacli Plat/Pacli	8.3 / 19.2 6.8 / 14.4	0.72	59 vs 50%
KEYNOTE-189 Non-squamous	Pembro + Plat/Pem Plat/Pem	8.8 / 21.5 4.9 / 11.3	0.59	67 vs 65%
KEYNOTE-407 Squamous	Pembro + Plat/Pacli or NabPacli Plat/Pacli or NabPacli	6.4 / 15.9 4.8 / 11.3	0.68	70 vs 68%
CheckMate 227 TMB≥10mut/Mb	Nivo + Ipi Plat/Pem or Gem	7.2 / 23 5.4 / 16.4	0.48	31 vs 36%

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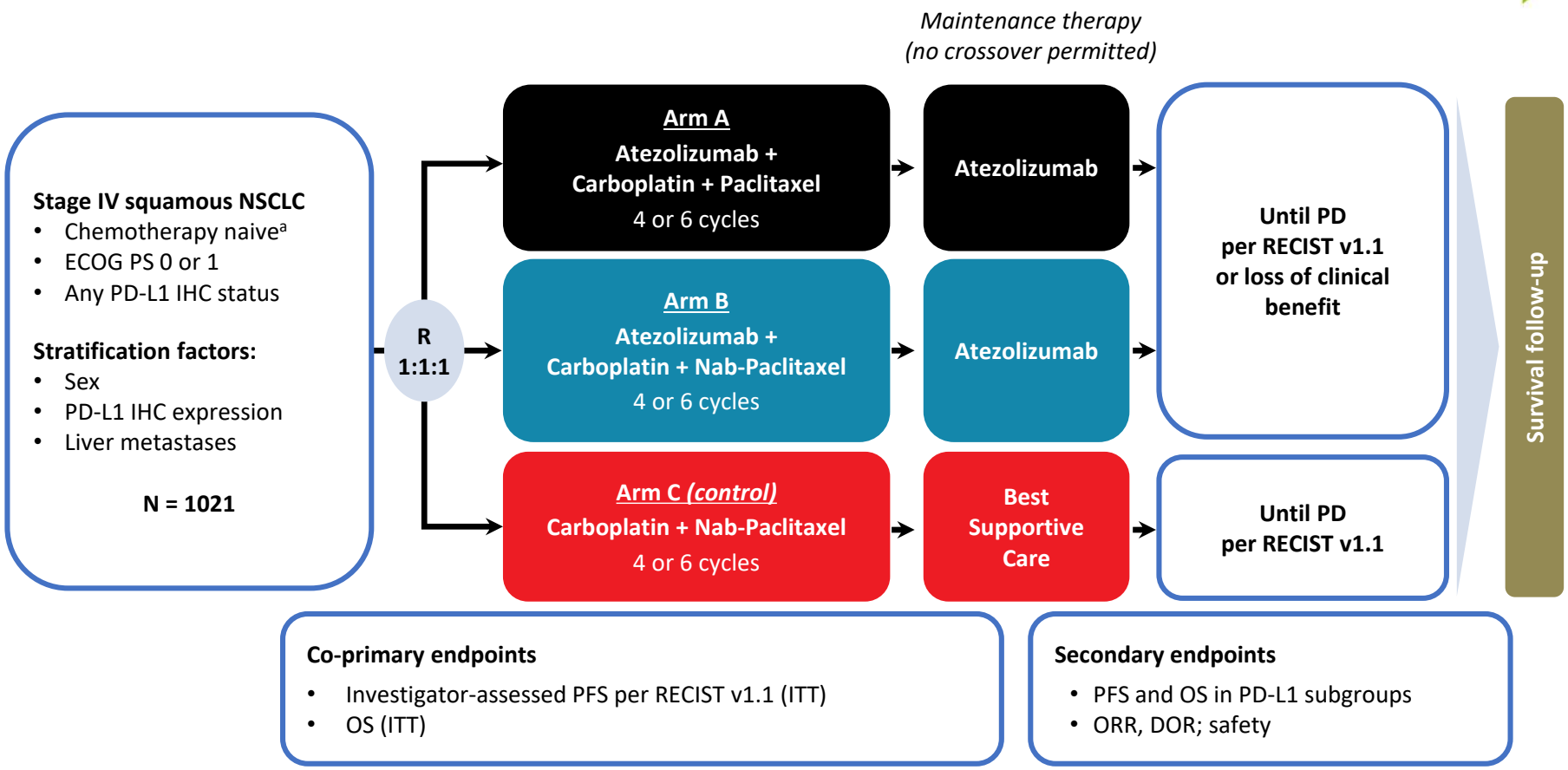
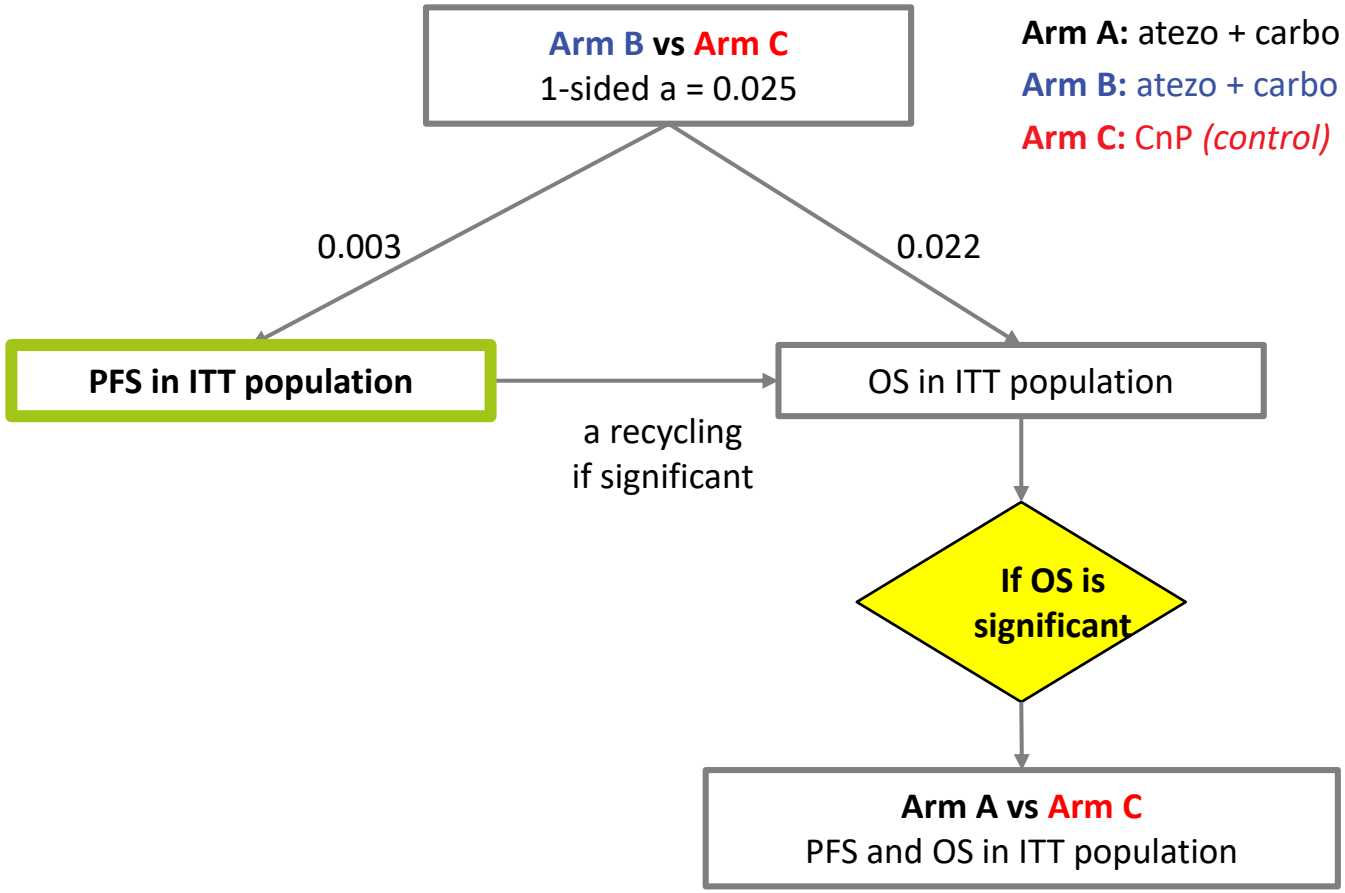
IMpower131: Primary PFS and safety analysis of a randomized phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC.



Atezolizumab 1200 mg IV q3w; carboplatin AUC 6 IV q3w; nab-paclitaxel 100 mg/m2 IV qw; paclitaxel 200 mg/m2 IV q3w.
a Patients with a sensitising EGFR mutation or ALK translocation must have disease progression or intolerance to treatment with ≥ 1 approved targeted therapies. Testing for EGFR mutation or ALK translocation was not mandatory.

IMpower131: Statistical Testing Plan



Arm A: atezo + carbo + pac (CP)

Arm B: atezo + carbo + nab-pac (CnP)

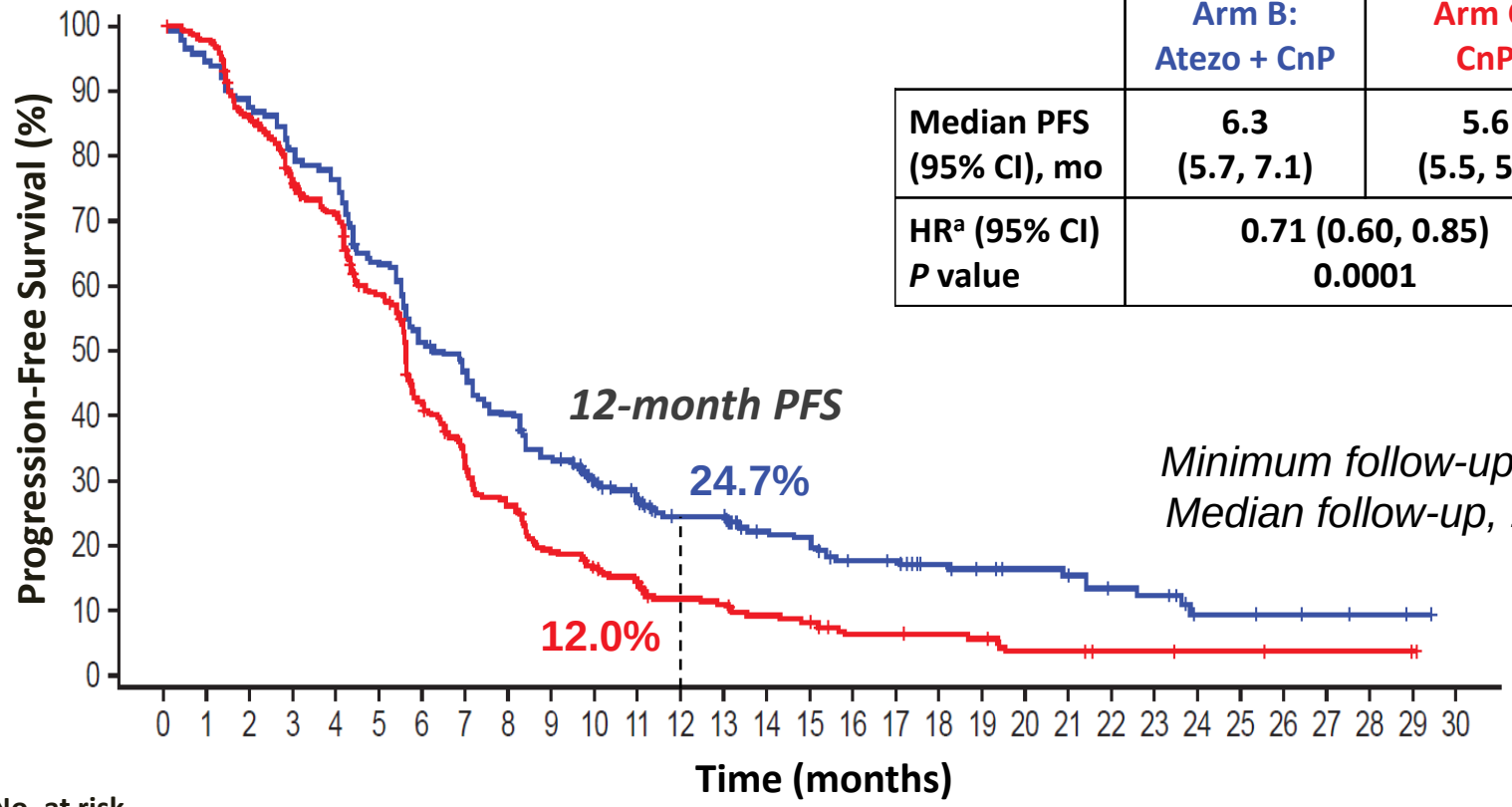
Arm C: CnP *(control)*

Data cutoff: January 22, 2018.

atezo, atezolizumab; carbo, carboplatin; nab-pac, nab-paclitaxel; pac, paclitaxel.

INV-Assessed PFS in the ITT Population (Arm B vs Arm C)

	Arm B: Atezo + CnP	Arm C: CnP
Median PFS (95% CI), mo	6.3 (5.7, 7.1)	5.6 (5.5, 5.7)
HR[a] (95% CI)	0.71 (0.60, 0.85)	
P value	0.0001	



Minimum follow-up, 9.8 mo
Median follow-up, 17.1 mo

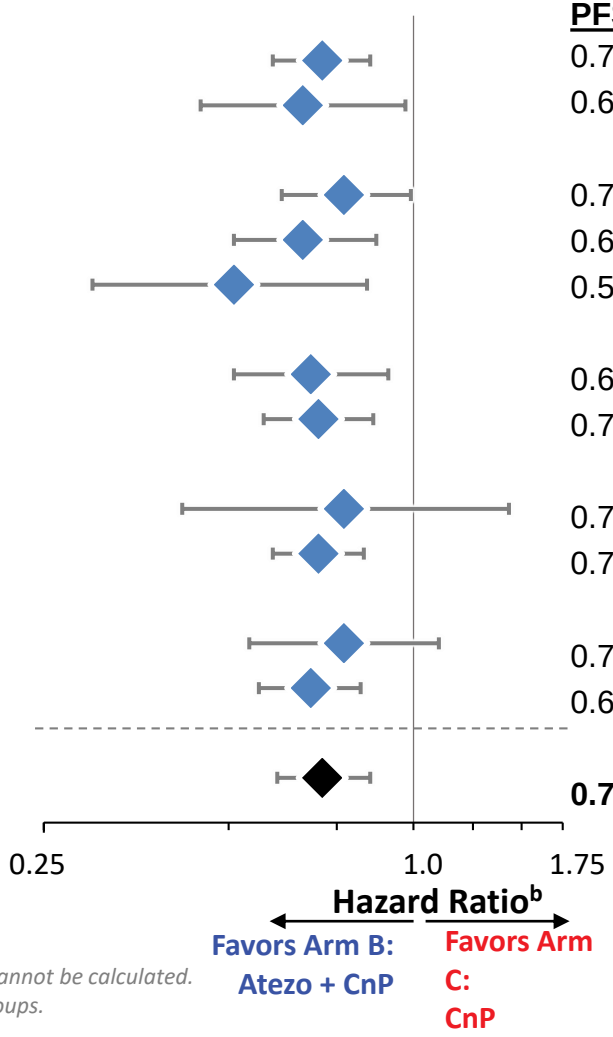
No. at risk

Atezo + CnP	343	318	294	268	257	212	172	151	134	111	88	76	61	61	44	42	33	32	24	21	18	16	12	11	5	5	4	3	2	1
CnP	340	322	279	244	227	183	128	95	79	57	48	40	28	26	21	19	12	12	11	10	6	6	4	4	3	3	2	2	2	1

Data cutoff: January 22, 2018.
INV, investigator. [a] Stratified HR.

INV-Assessed PFS in Clinical Subgroups

Subgroup	n (%)	PFS HR (95% CI)	Median PFS, mo: Arm B	Median PFS, mo: Arm C
Male	557 (82)	0.71 (0.59, 0.85)	6.3	5.6
Female	126 (18)	0.66 (0.45, 0.97)	6.5	5.6
< 65 years	326 (48)	0.77 (0.61, 0.99)	6.0	5.6
65-74 years	279 (41)	0.66 (0.51, 0.87)	6.0	5.6
75-84 years[a]	77 (11)	0.51 (0.30, 0.84)	7.0	5.6
ECOG PS 0	225 (33)	0.68 (0.51, 0.91)	7.2	5.7
ECOG PS 1	456 (67)	0.70 (0.57, 0.86)	5.8	5.5
Never smoker	55 (8)	0.77 (0.42, 1.43)	8.3	5.3
Current or former smoker	627 (92)	0.70 (0.59, 0.83)	6.2	5.6
Liver metastases	139 (20)	0.77 (0.54, 1.10)	5.5	4.2
No liver metastases	544 (80)	0.68 (0.56, 0.82)	7.0	5.6
ITT population	**683 (100)**	**0.71 (0.60, 0.85)**	**6.3**	**5.6**



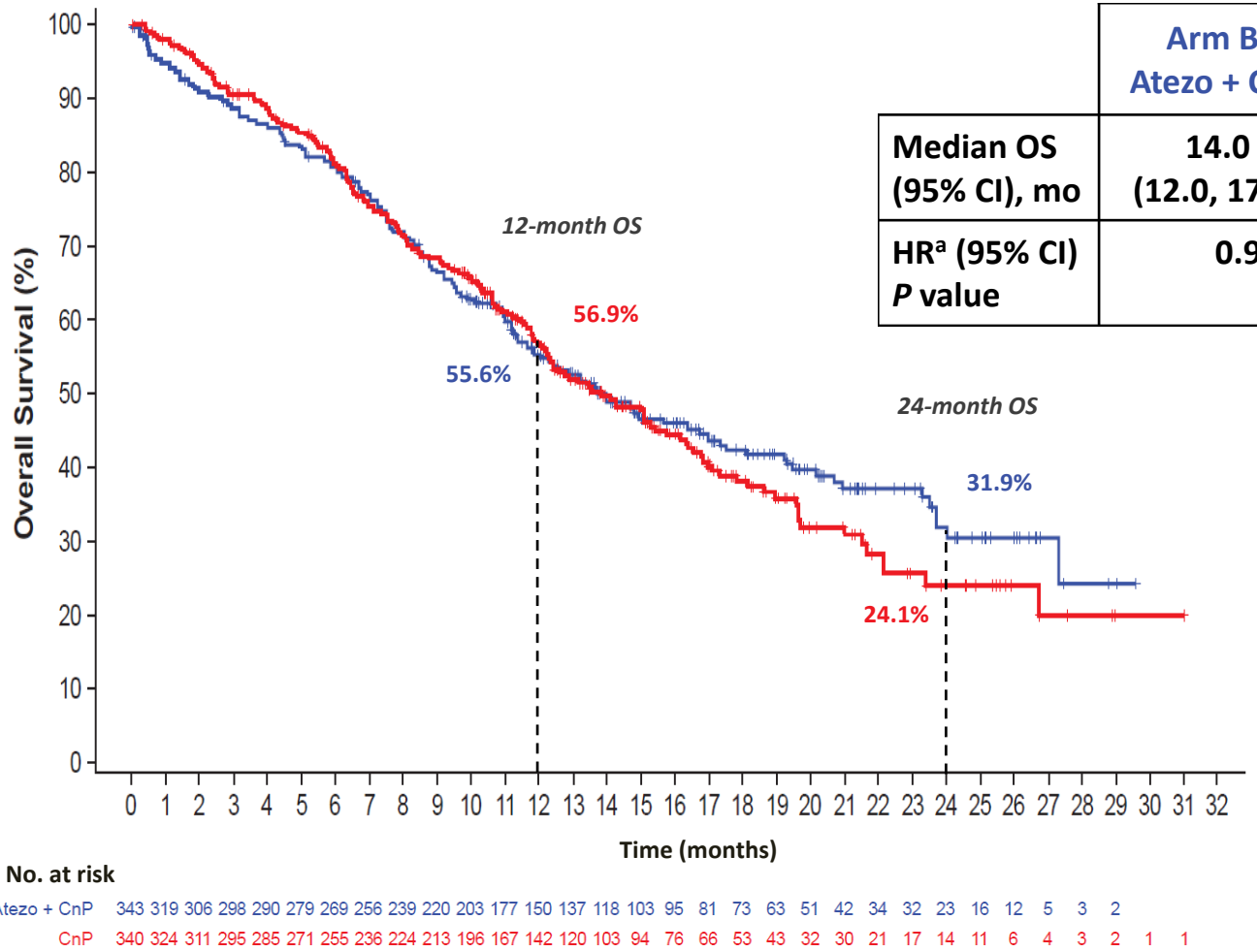
Data cutoff: January 22, 2018.

[a] One patient in Arm C was aged ≥ 85 years; thus, an HR cannot be calculated.

[b] Stratified HR for ITT; unstratified HRs for all other subgroups.

Dr. Mark. A. Socinski

First Interim OS in the ITT Population (Arm B vs Arm C)



	Arm B: Atezo + CnP	Arm C: CnP
Median OS (95% CI), mo	14.0 (12.0, 17.0)	13.9 (12.3, 16.4)
HR[a] (95% CI)	0.96 (0.78, 1.18)	
P value	0.6931	

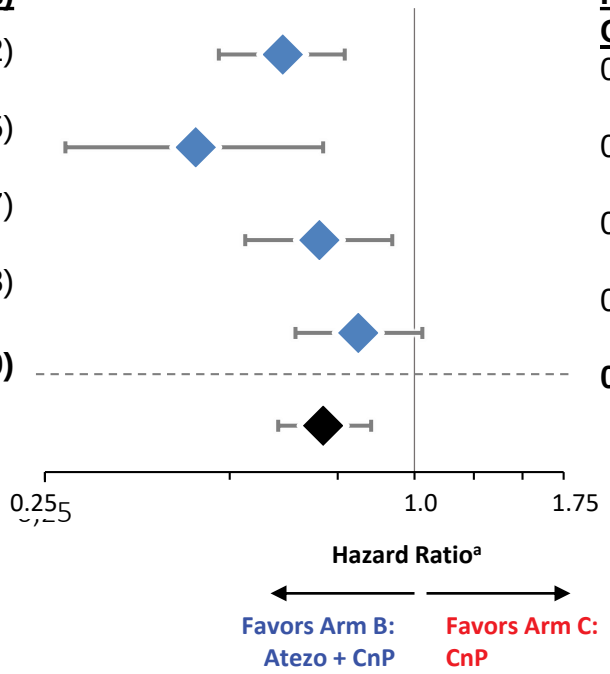
Data cutoff: January 22, 2018.

[a] *Stratified HR.*

Dr. Mark. A. Socinski

INV-Assessed PFS in PD-L1 Subgroups

Subgroup	n (%)	PFS HR (95% CI)	Median PFS, mo: Arm B	Median PFS, mo: Arm C
PD-L1 positive (TC1/2/3 or IC1/2/3)	351 (52)	0.61 (0.48, 0.77)	7.0	5.6
PD-L1 high (TC3 or IC3)	101 (15)	0.44 (0.27, 0.71)	10.1	5.5
PD-L1 low (TC1/2 or IC1/2)	250 (37)	0.70 (0.53, 0.92)	6.0	5.6
PD-L1 negative (TC0 and IC0)	331 (48)	0.81 (0.64, 1.03)	5.7	5.6
ITT population	**683 (100)**	**0.71 (0.60, 0.85)**	**6.3**	**5.6**

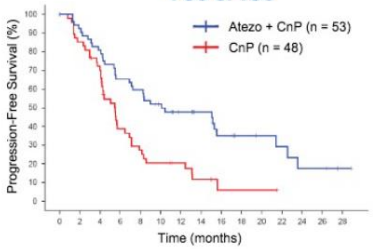


- PFS benefit with atezolizumab + CnP (Arm B) vs CnP (Arm C) was observed across all PD-L1 subgroups

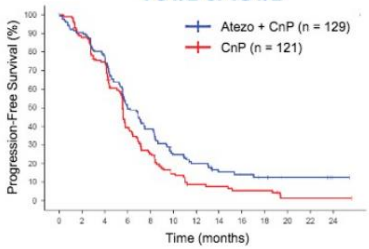
Data cutoff: January 22, 2018.
[a] Stratified HR.

INV-Assessed PFS in PD-L1 Subgroups (Arm B vs Arm C)

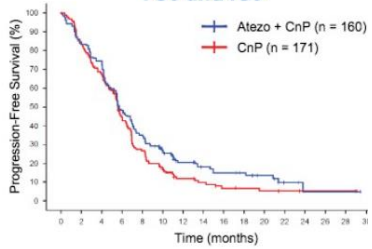
PD-L1 High
TC3 or IC3



PD-L1 Low
TC1/2 or IC1/2



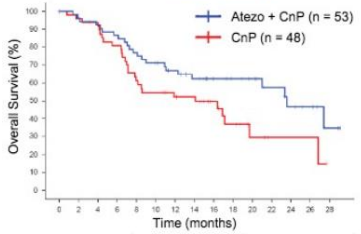
PD-L1 Negative
TC0 and IC0



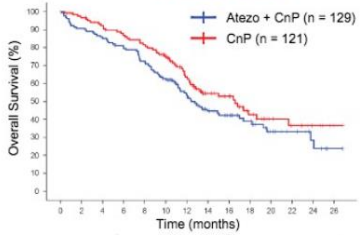
	Atezo + CnP	CnP	Atezo + CnP	CnP	Atezo + CnP	CnP
12-month PFS	48%	20%	20%	9%	20%	12%
Median PFS, mo	10.1	5.5	6.0	5.6	5.7	5.6
HR[a] (95% CI)	0.44 (0.27, 0.71)		0.70 (0.53, 0.92)		0.81 (0.64, 1.03)	

First Interim OS in PD-L1 Subgroups (Arm B vs Arm C)

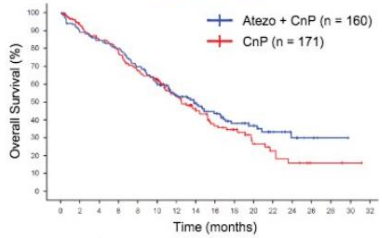
PD-L1 High
TC3 or IC3



PD-L1 Low
TC1/2 or IC1/2



PD-L1 Negative
TC0 and IC0



	Atezo + CnP	CnP	Atezo + CnP	CnP	Atezo + CnP	CnP
12-month OS	67%	52%	54%	64%	53%	53%
24-month OS	47%	30%	28%	37%	30%	16%
Median OS, mo	23.6	14.1	12.4	16.6	13.8	12.5
HR[a] (95% CI)	0.56 (0.32, 0.99)		1.34 (0.95, 1.90)		0.86 (0.65, 1.15)	

Safety Summary

	Arm B: Atezo + CnP (N = 334)	Arm C (control): CnP (N = 334)
Treatment duration, median (range), mo		
Atezolizumab	6.7 (0-30)	NA
Carboplatin	2.6 (0-7)	2.4 (0-7)
Paclitaxel/nab-paclitaxel	3.0 (0-7)	2.8 (0-7)
All-cause AE, n (%)	332 (99)	324 (97)
Grade 3-4	243 (73)	220 (66)
Grade 5	31 (9)	14 (4)
Treatment-related AE, n (%)	316 (95)	303 (91)
Grade 3-4	227 (68)	190 (57)
Grade 5	4 (1)	3 (1)
Serious AE, n (%)	152 (46)	96 (29)
Treatment-related serious AE	68 (20)	35 (10)
AEs of special interest, n (%)	162 (49)	71 (21)
Grade 3-4	39 (12)	8 (2)
Grade 5	1 (< 1)	0
AE leading to any treatment withdrawal, n (%)	97 (29)	58 (17)
AE leading to any dose interruption or modification, n (%)	258 (77)	219 (66)

Data cutoff: January 22, 2018.
Dr. Mark. A. Socinski