Therapeutic Landscape in Advanced Non-small Cell Lung Cancer (NSCLC):

Langer's Perspective on the New Immunotherapy Paradigm

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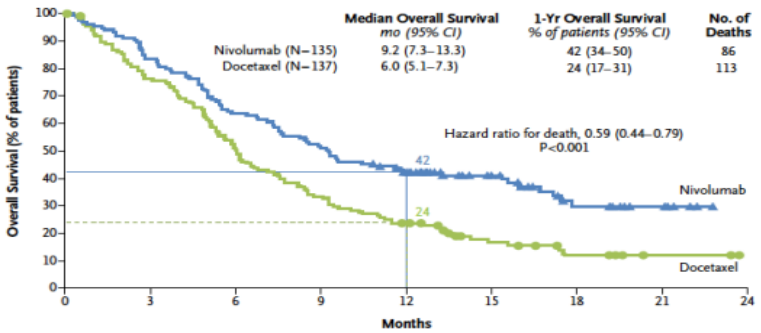
Langer Disclosures: Past 12 months

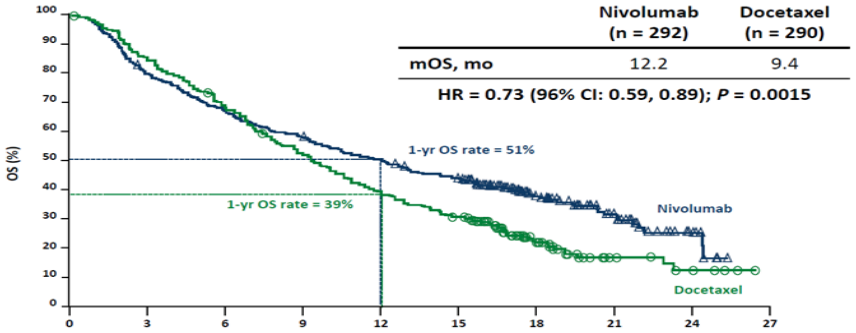
- Grant/Research Support:
  - Genentech, OSI (Astellas), Merck, GlaxoSmithKline, Nektar, Advantagene, Clovix; Ariad; Inovio, Threshold, AZ, Celgene, MGA
- DSMC:
  - Lilly, Amgen, Synta, Agennix, SWOG, Peregrine, Incyte, AbbVie
- Scientific Advisor:
  - Bristol Myers Squibb, Pfizer, Lilly, Astra Zeneca, Novartis, Genentech, Abbott, Celgene, Boehringer-Ingelheim, Hospira, Clovis, Merck

PD1/PD-L1 Inhibitors increase Overall Survival in Platinum-Refractory NSCLC

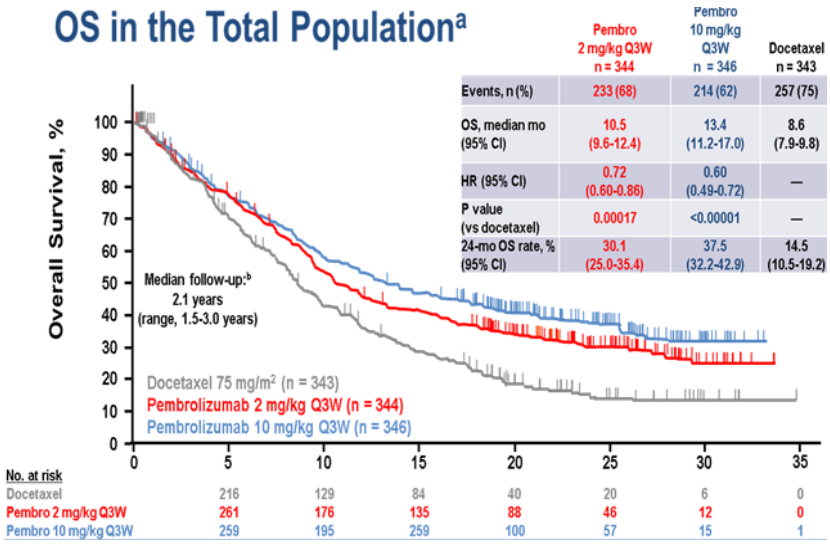
CHECKMATE 017



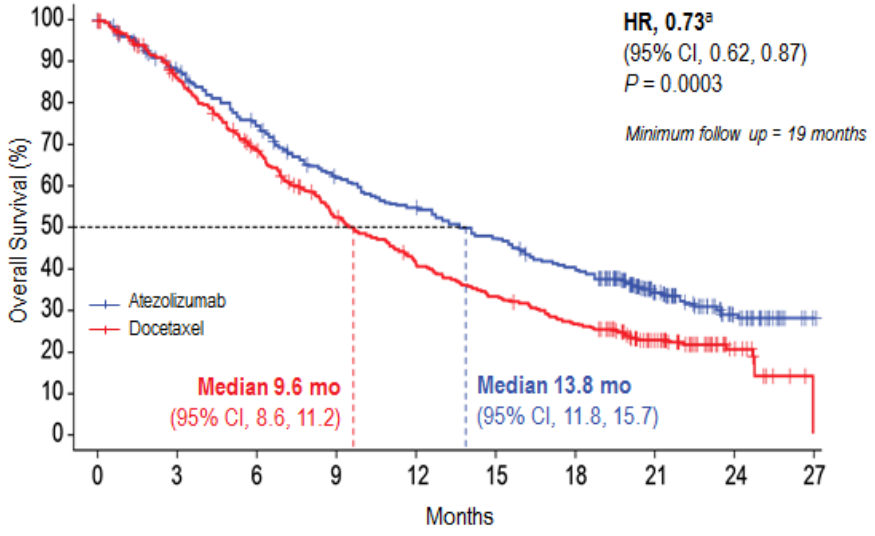
CHECKMATE 057



KEYNOTE 010 (TPS ≥ 1%)

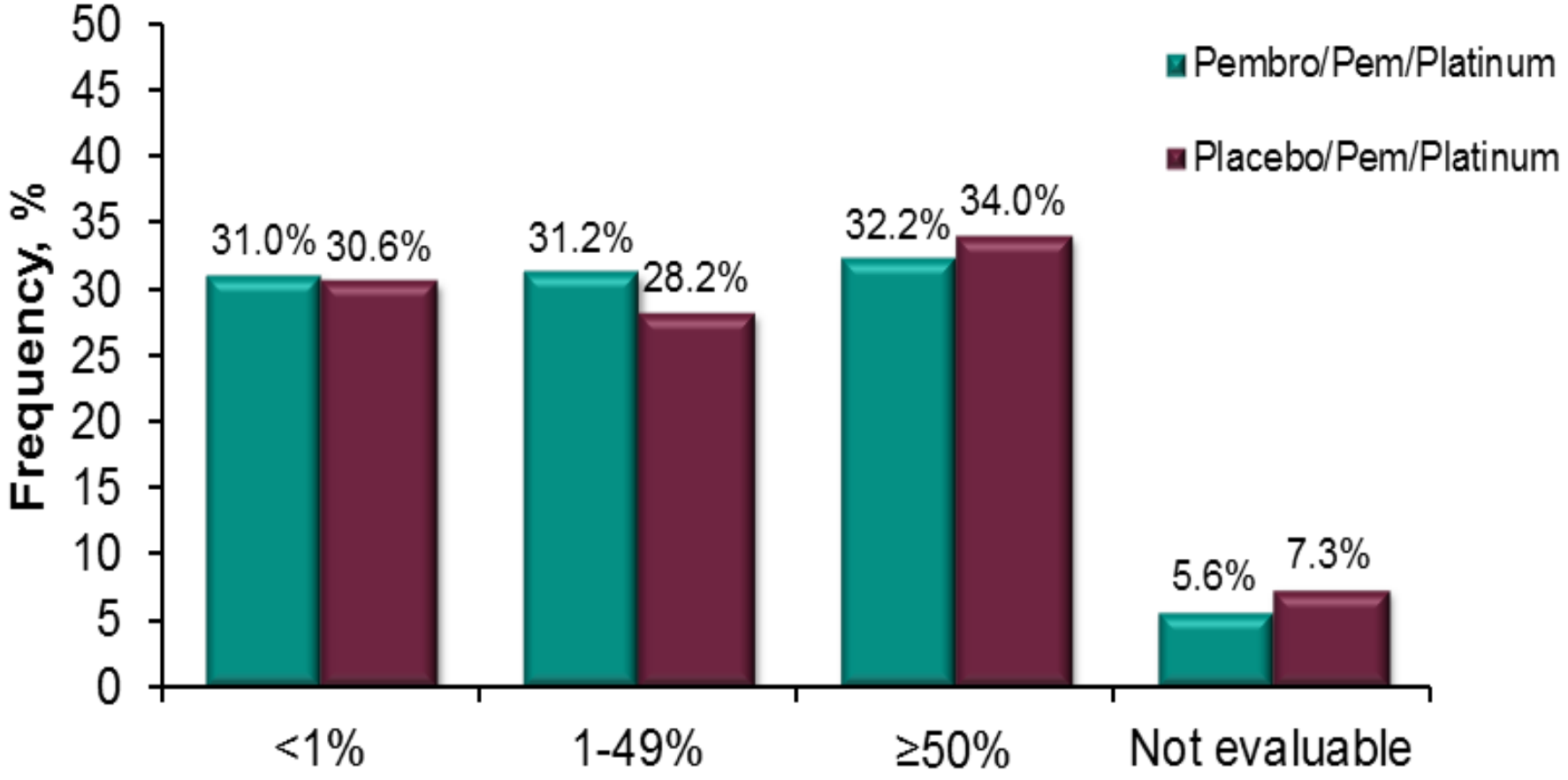


OAK



Brahmer NEJM 2015 Borghaei, NEJM 2015
Herbst Lancet 2016. Rittmeyer Lancet 2017

Frequency of PD-L1 TPS Categories



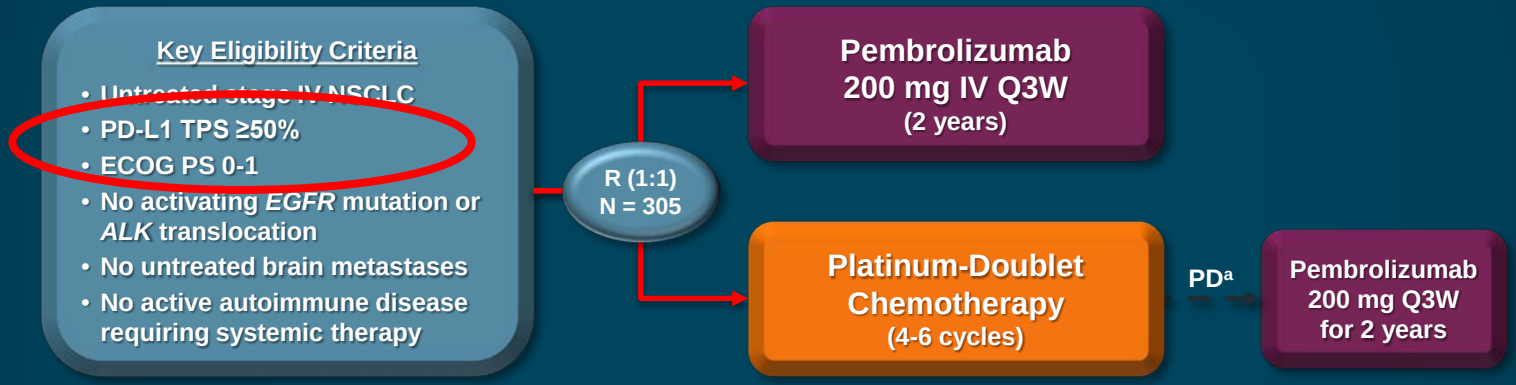
Not evaluable refers to specimens with an inadequate number of tumor cells or no tumor cells seen; these patients were included in the PD-L1 TPS <1% group for randomization stratification but excluded from analyses of efficacy by TPS. Data cutoff date: Nov 8, 2017.

Langer's Current Paradigm: 2019 (could change at any moment)

Tx Cohort	Non-Squamous	Squamous
PDL1 $\geq$ 50%	Pembro > Pem/Carbo/Pembro	Pembro > Taxane/Carbo/Pembro
PDL1 1-50%	Pem/Carbo/Pembro > Pembro	Taxane/Carbo/Pembro > Pembro
PDL1 < 1%	Pem/Carbo/Pembro	Taxane/Carbo/Pembro
PDL1 < 1%, TMB > 10	Pem/Carbo/Pembro vs Ipi/Nivo	Taxane/Carbo/Pembro vs Ipi/Nivo
TKI-Refractory	Pac/Carbo/Bev/Atezo or Pem/Carbo/Bev	
Tissue QNS	Pem/Carbo/Pembro	Taxane/Carbo/Pembro

Non-Squamous; PDL1 > 50% Advanced NSCLC?

KEYNOTE-024 Study Design (NCT02142738)



Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

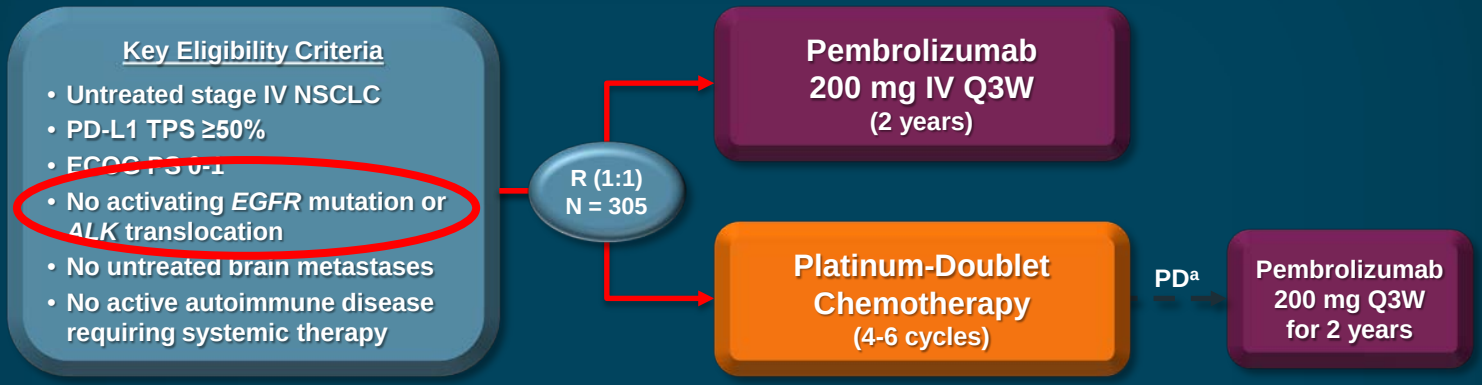
Secondary: OS, ORR, safety

Exploratory: DOR

[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

Reck M et al, KN 024, ESMO 2016, NEJM 2016

KEYNOTE-024 Study Design (NCT02142738)



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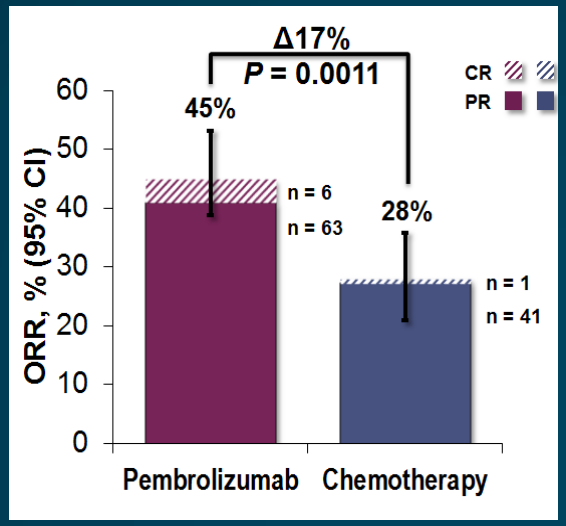
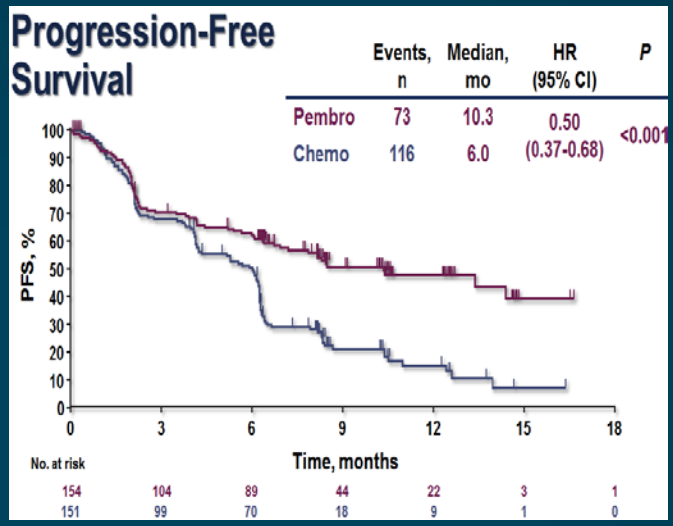
Reck M et al, KN 024, ESMO 2016, NEJM 2016

Efficacy Data: KEYNOTE-024



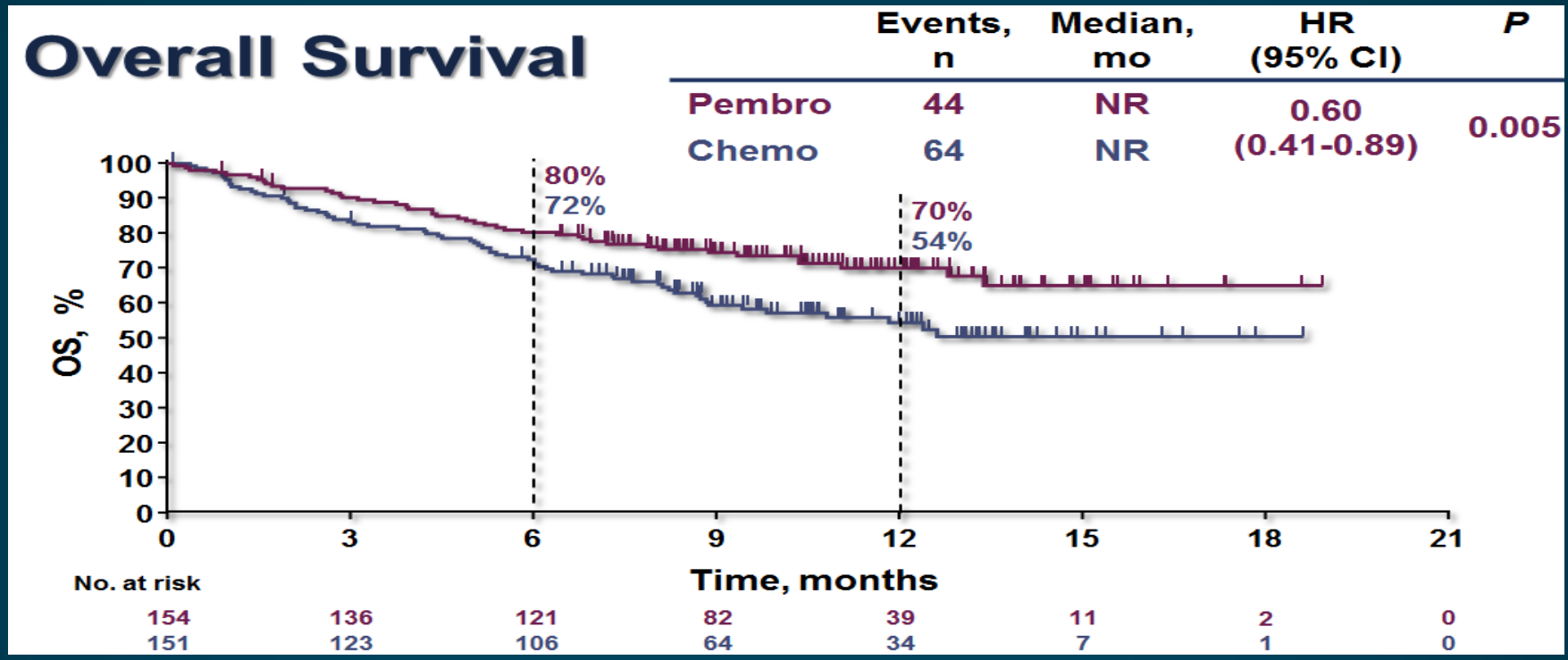


imaging was every 9 weeks

- **Clear and strong signal of activity**
  - → **ORR improved vs control arm that performed as expected (based on other phase III trials)**
  - → **45% ORR: one of best RRs ever reported in 1st line setting (and with monotherapy!)**
  - → **Time to Response identical between Pembro and Chemo**
  - → **PFS improved by 4.3 months (HR of 0.50)**
  - → **Improvement of PFS in all subgroups (except female/never smokers => lower mutational load ?)**
  - → **Strongest signal of PFS benefit observed in SqCC (HR of 0.35)**

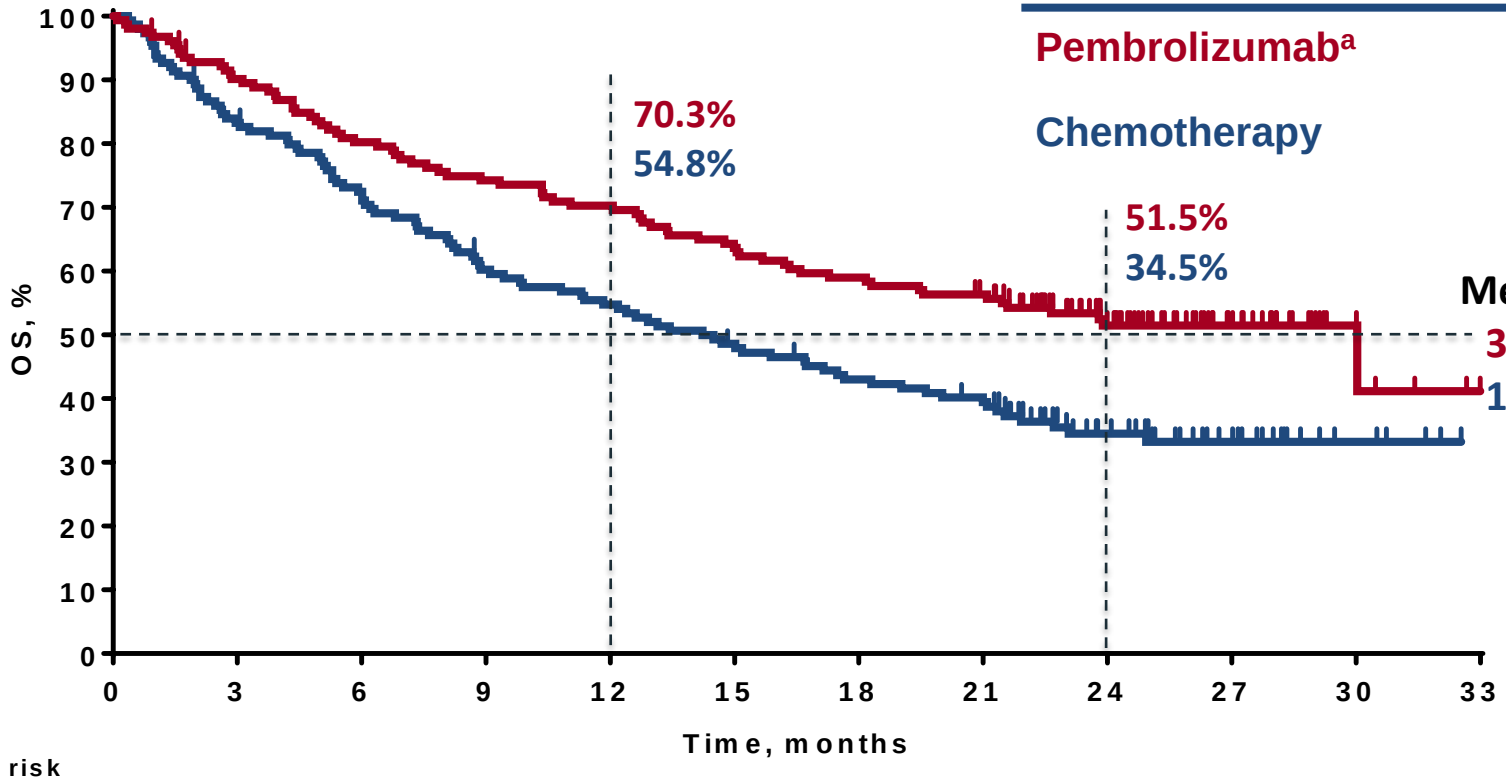
Reck M et al, KN 024, ESMO 2016, NEJM 2016

KEYNOTE-024: Survival Data



- **Clear-cut survival benefit for NSCLC pts with PDL1 ≥ 50%**
  - **Estimated rate of OS @ 12 months: 70% (Pembro) vs 54% (CT)**
  - **HR for death: 0.60**
  - **Despite cross-over in 50% of patients on the control arm**

Overall Survival: KN24



	Events, n	HR (95% CI)
Pembrolizumab[a]	73	0.63 (0.47–0.86)
Chemotherapy	96	*P* = 0.002[b]

Median (95% CI)

30.0 mo (18.3 mo–NR)

14.2 mo (9.8 mo–19.0 mo)

No. at risk

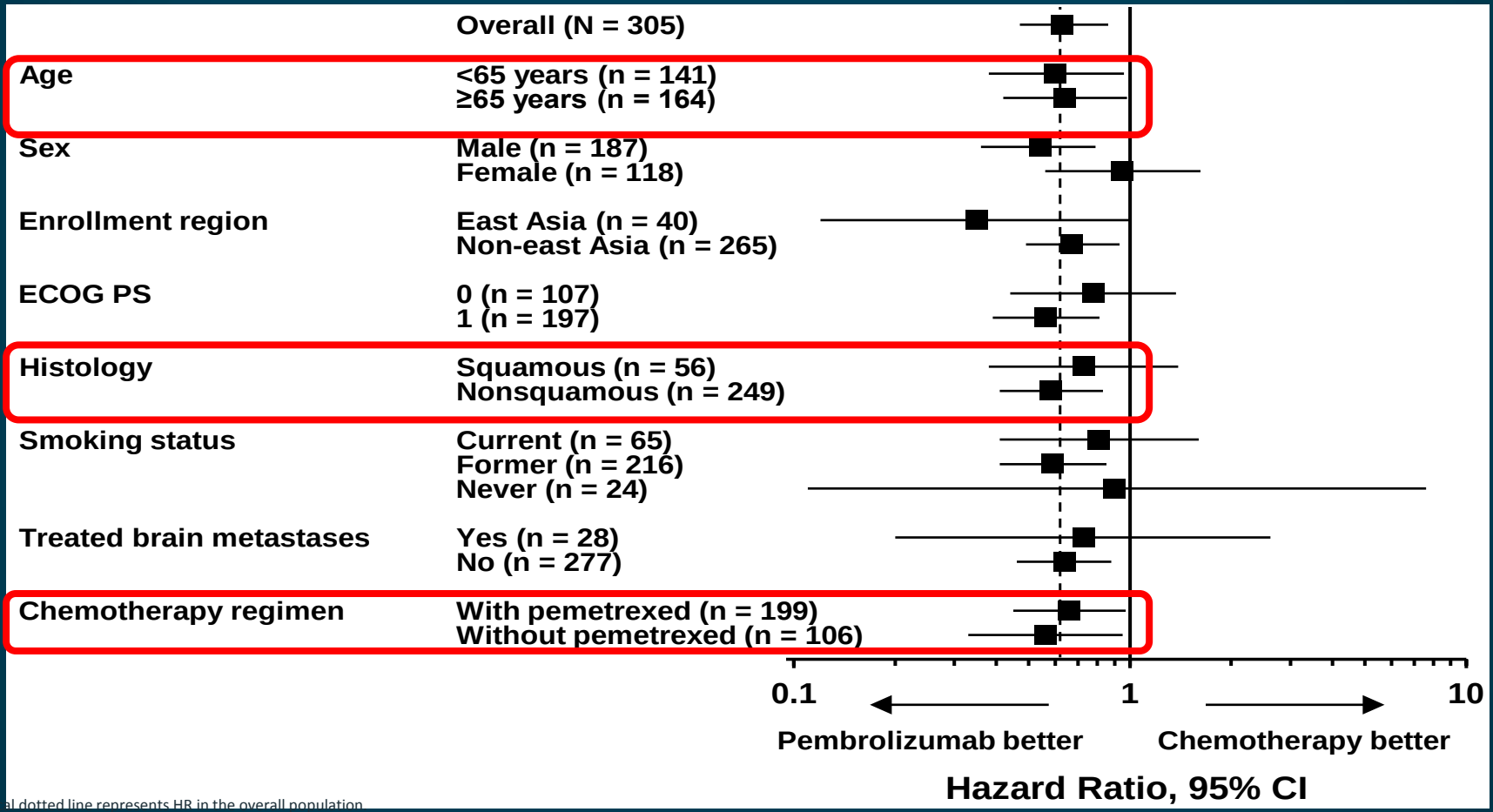
Pembro	154	136	121	112	106	96	89	83	52	22	5	0
Chemo	151	123	107	88	80	70	61	55	31	16	5	0

Median FU- 25.2 months

[a]Effective crossover rate from chemotherapy to anti-PD-L1 therapy, 62.3% (82 patients crossed over to pembrolizumab during the study and 12 received anti-PD-L1 therapy outside of crossover). [b]Nominal *P* value. NR, not reached.
Data cutoff: July 10, 2017.

Brahmer, WCLC 2017

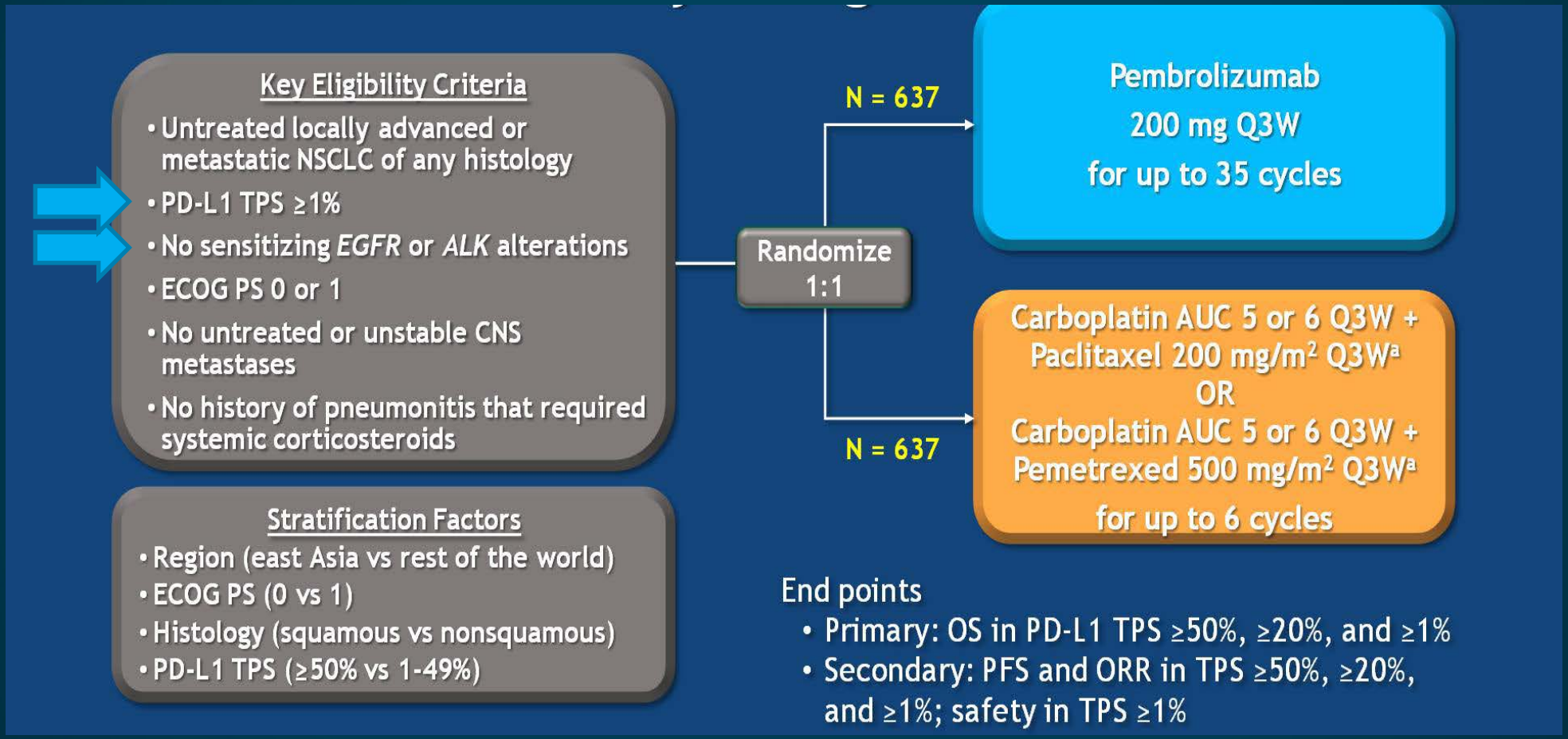
Overall Survival in Subgroups: KN 024



Vertical dotted line represents HR in the overall population
Data cutoff: July 10, 2017

Brahmer, WCLC 2017

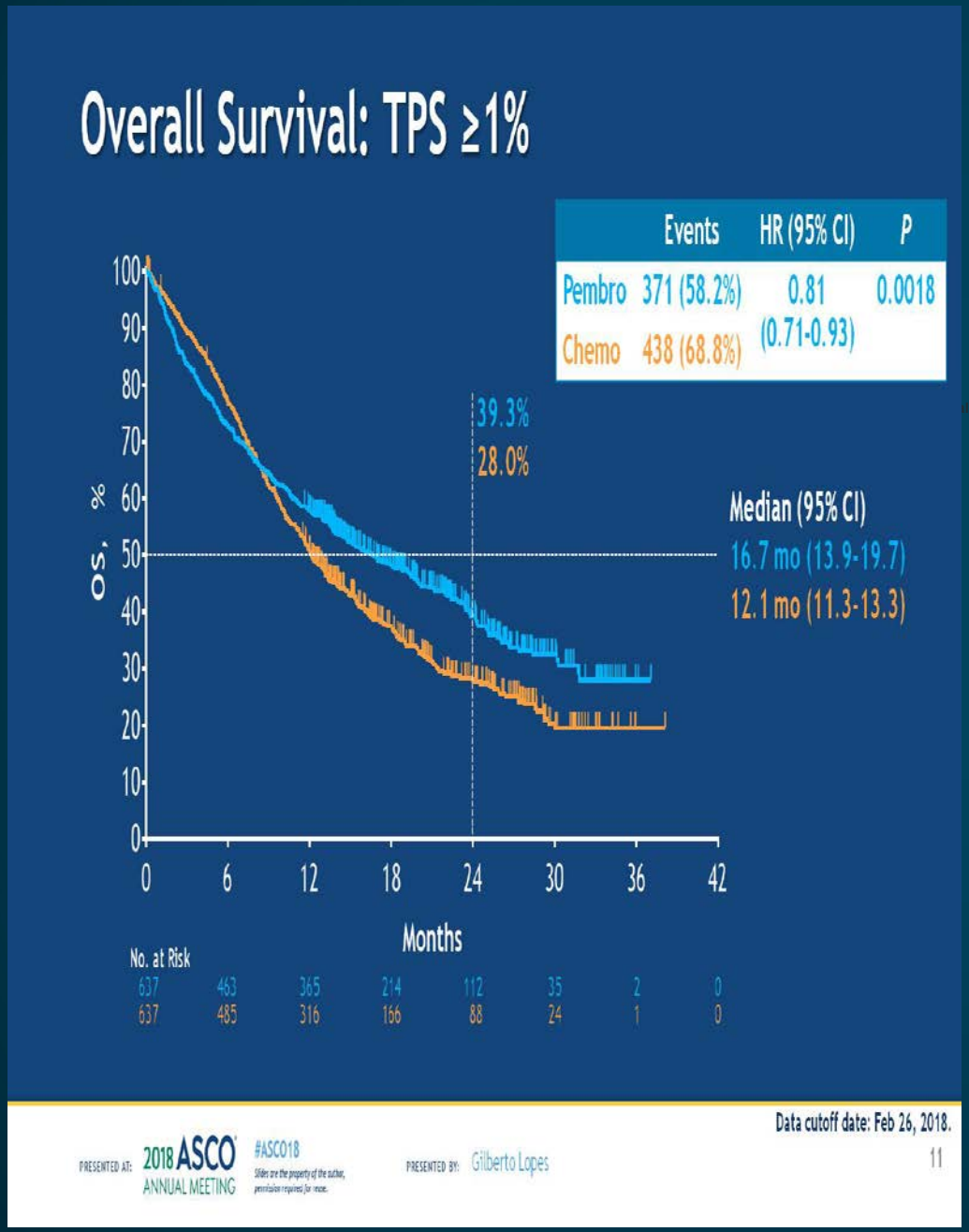
KEYNOTE-042: Pembro vs. Chemotherapy



All histologies
Squamous ALLOWED

Lopes et al, ASCO 2018

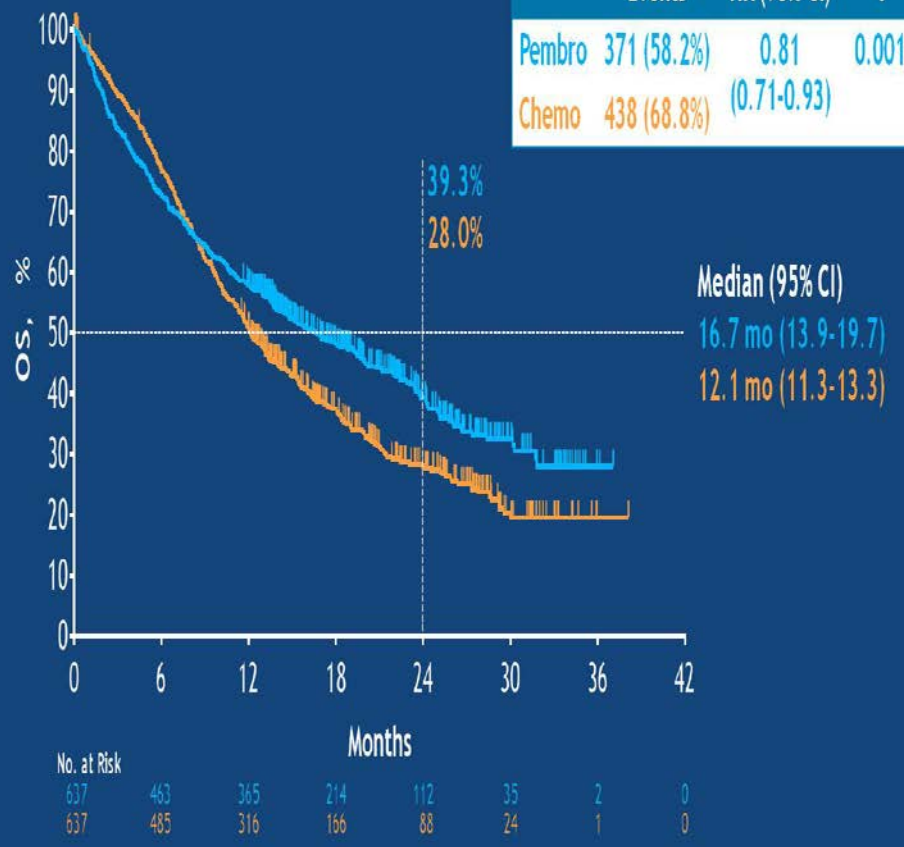
KEYNOTE-042: Pembro vs. Chemotherapy



KEYNOTE-042: Pembro vs. Chemotherapy

Overall Survival: TPS ≥1%

	Events	HR (95% CI)	P
Pembro	371 (58.2%)	0.81 (0.71-0.93)	0.0018
Chemo	438 (68.8%)		



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Data cutoff date: Feb 26, 2018.

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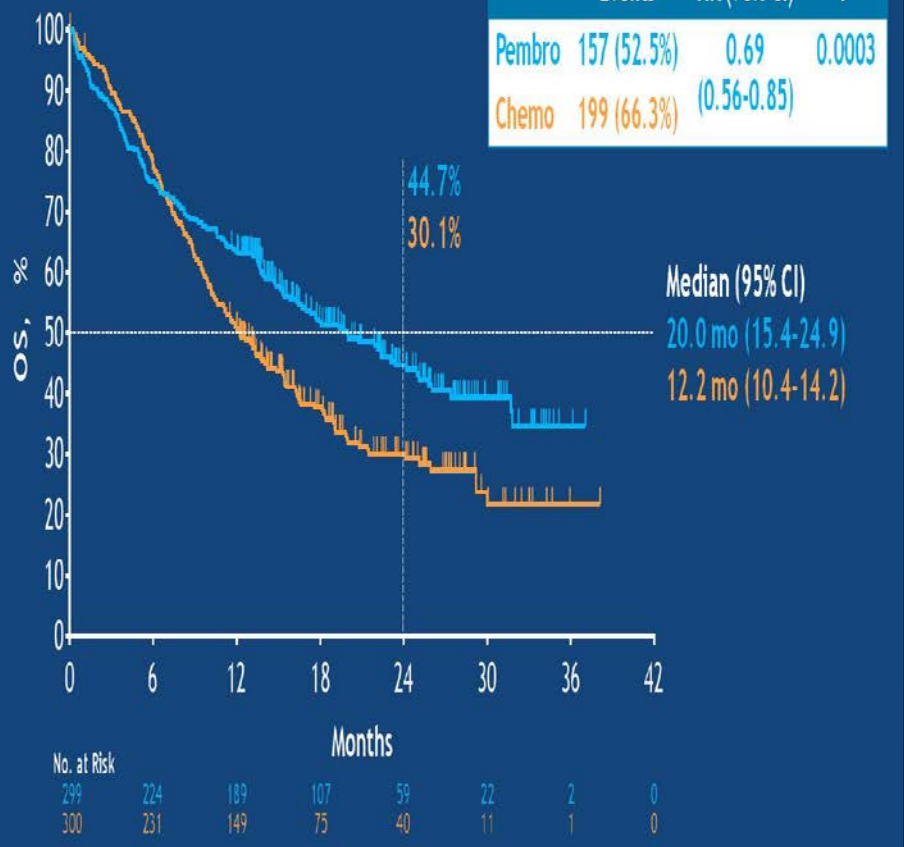
Overall Survival: TPS ≥50%

	Events	HR (95% CI)	P
Pembro	157 (52.5%)	0.69 (0.56-0.85)	0.0003
Chemo	199 (66.3%)		



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Data cutoff date: Feb 26, 2018.

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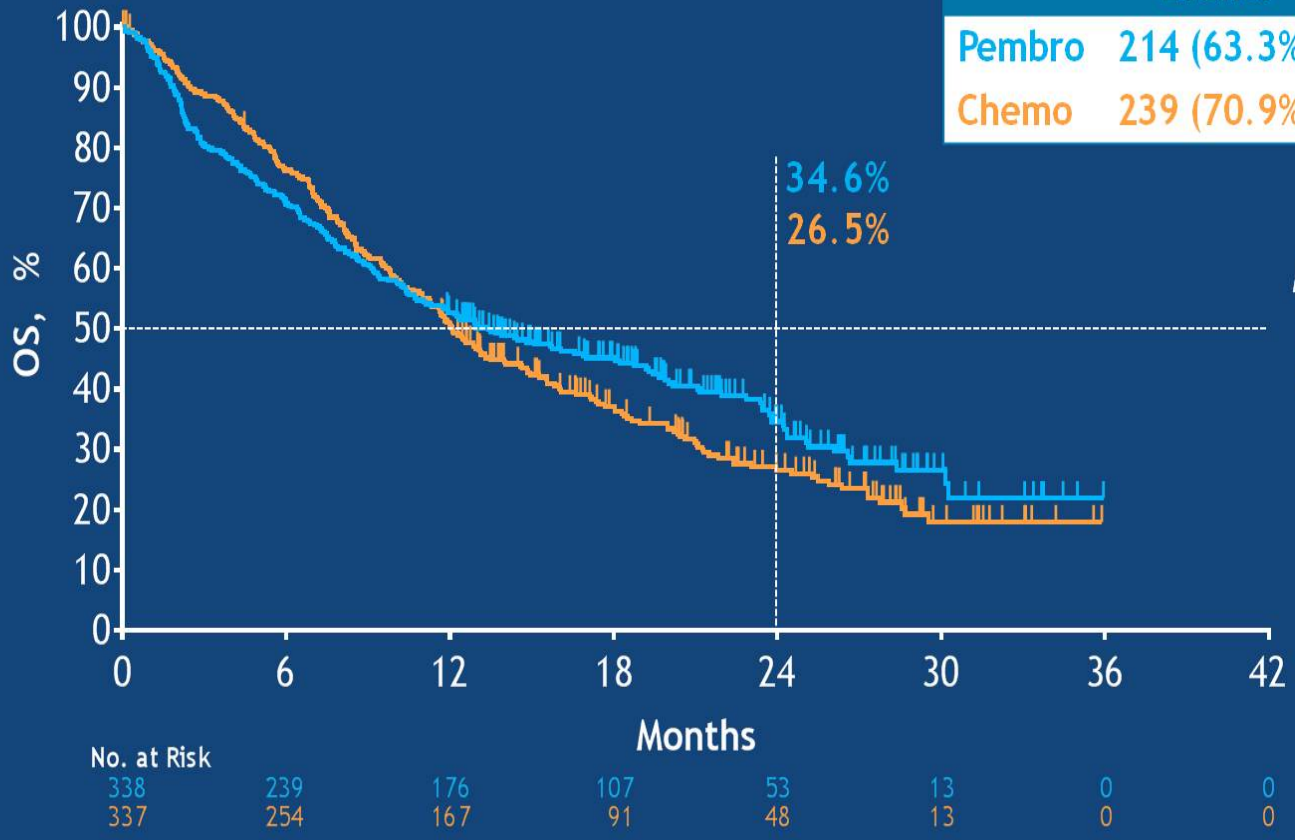
Overall Survival: TPS ≥1-49% (Exploratory Analysis[a])

	Events	HR (95% CI)
Pembro	214 (63.3%)	0.92 (0.77-1.11)
Chemo	239 (70.9%)	



Median (95% CI)
13.4 mo (10.7-18.2)
12.1 mo (11.0-14.0)

[a]No alpha allocated to this comparison.

Overall Survival: TPS ≥1-49% (Exploratory Analysis[a])

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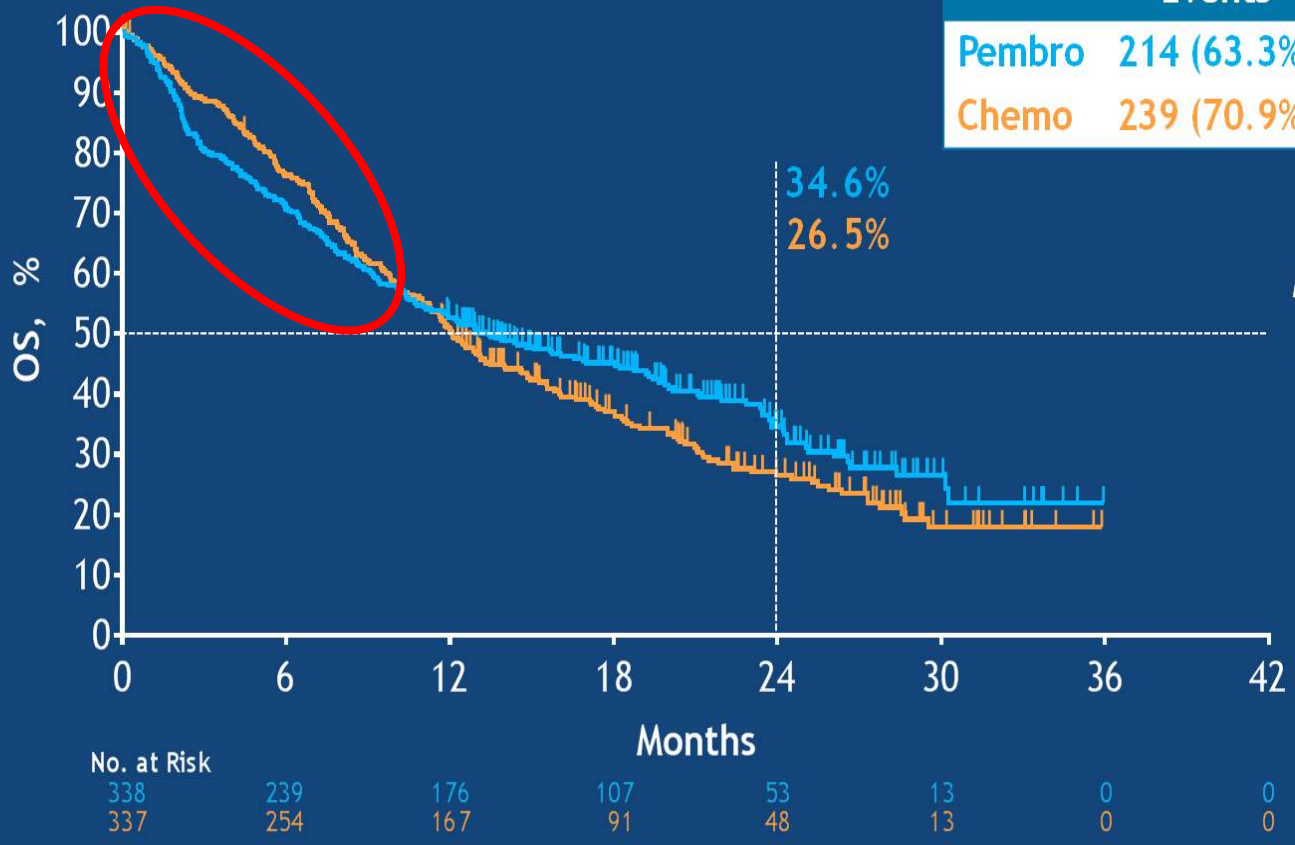


Median (95% CI)
13.4 mo (10.7-18.2)
12.1 mo (11.0-14.0)

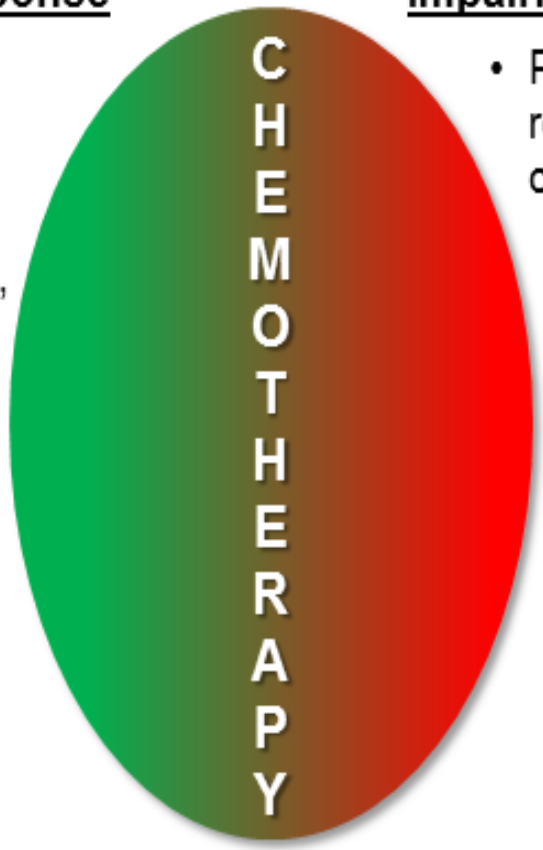
[a]No alpha allocated to this comparison.

Chemotherapy Has Complex and Pleiotropic Effects on Antitumor Immune Responses

Gandhi KN189
AACR 2018

Promotion of Antitumor Immune Response

- Antigen shedding and presentation
  - Release of cancer antigens
  - Upregulation of MHC I
  - Enhanced DC activation
- Altered immune regulatory receptors, ligands, and cytokines
  - Increased T_{eff} function, proliferations, and recruitment
- Activation of innate immunity
  - e.g., STING, RIG-1, TLR9
- Favorable effect on immune regulatory cells
  - Suppression of T_{regs}, MDSCs, etc



Impairment of Antitumor Immune Response

- Post chemotherapy Induction of immune regulatory receptors, ligands, and cytokines
  - e.g., negative feedback from IFNγ
  - Decreased T_{eff} function
- Unfavorable effect on immune regulatory cells
  - Reduced number of circulating lymphocytes
  - Increased number of circulating monocytes, MDSCs, etc

Enhances positive immune effects of chemotherapy

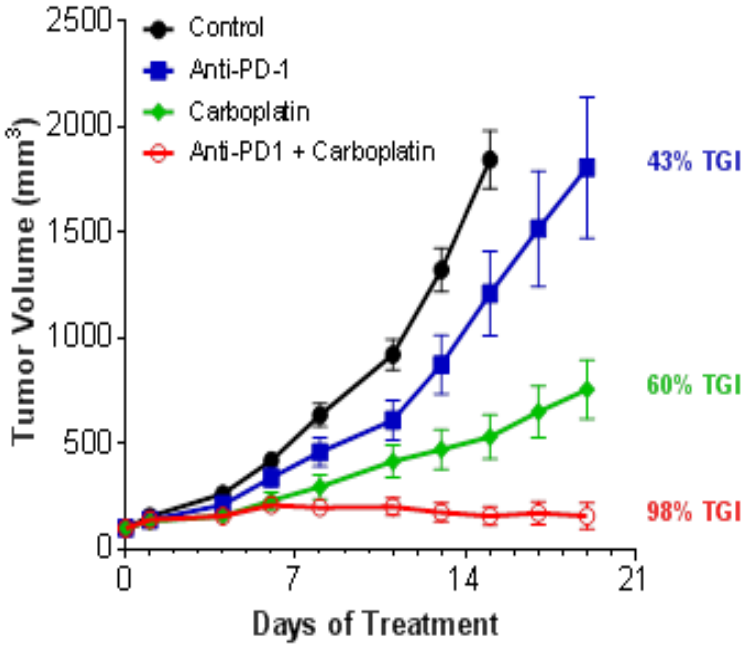
Anti–PD-1

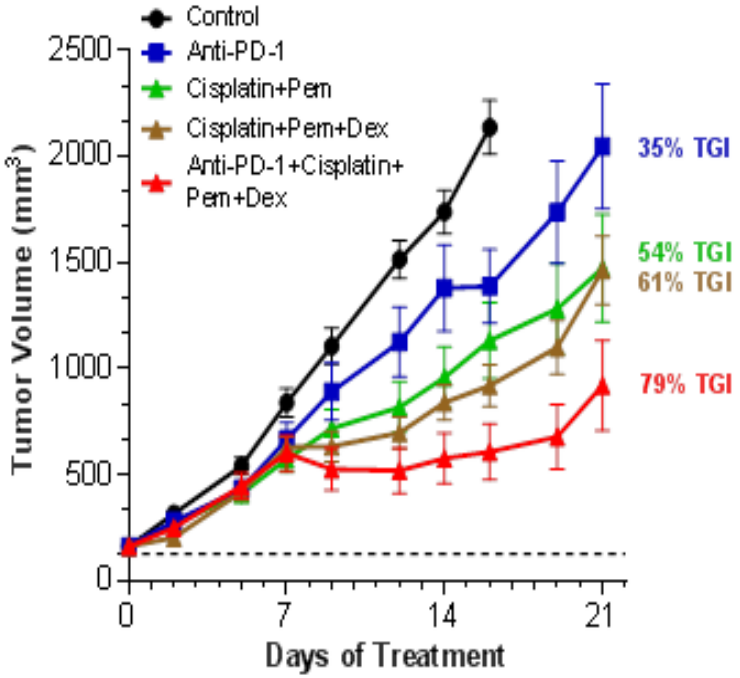
Reduces negative immune effects of chemotherapy

Bracci L et al. *Cell Death Differ* 2014;21:15-25. Roselli M et al. *Oncoimmunology* 2013;2:e27025. Galluzzi L et al. *Cancer Cell* 2015;28:690-714. Medler TR et al. *Trends Cancer* 2015;1:66-75. van Meir H et al. *Oncoimmunology* 2017;6:e1267095. Peng J et al. *Cancer Res* 2015;75:5034-5045. Zhang P et al. *Cancer Sci* 2016;107:1563-1571. Novosiadly RD et al. 18th IASLC World Conference on Lung Cancer; Oct 15-18, 2017; abstract P3.07-006.

Gandhi KN189
AACR 2018

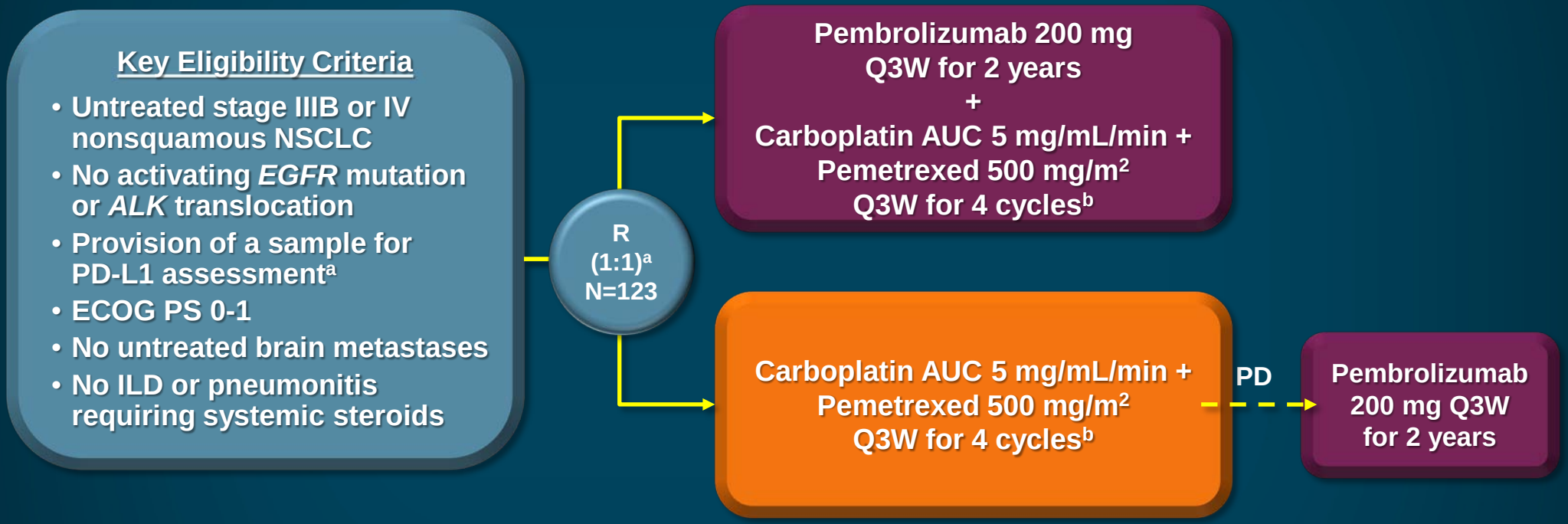
RENCA Tumor-Bearing Mouse Models Suggest a Benefit for Anti–PD-1 Combined With Platinum-Based Chemotherapy





Dex, dexamethasone; Pem, pemetrexed; TGI, tumor growth inhibition.
Merck & Co., Inc., data on file.

KEYNOTE-021 Cohort G:
Pem/Carbo +/- Pembrolizumab



End Points

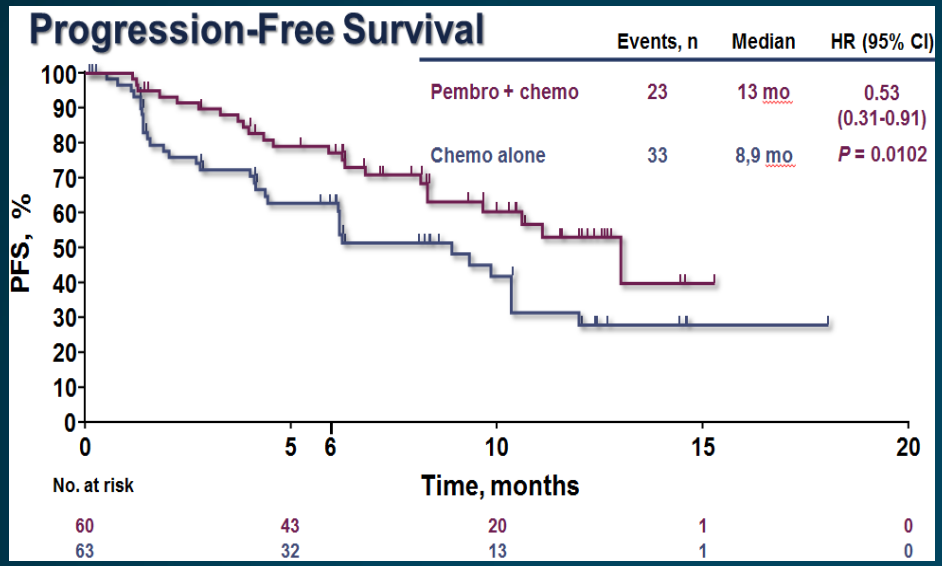
Primary: ORR (RECIST v1.1 per blinded, independent central review)

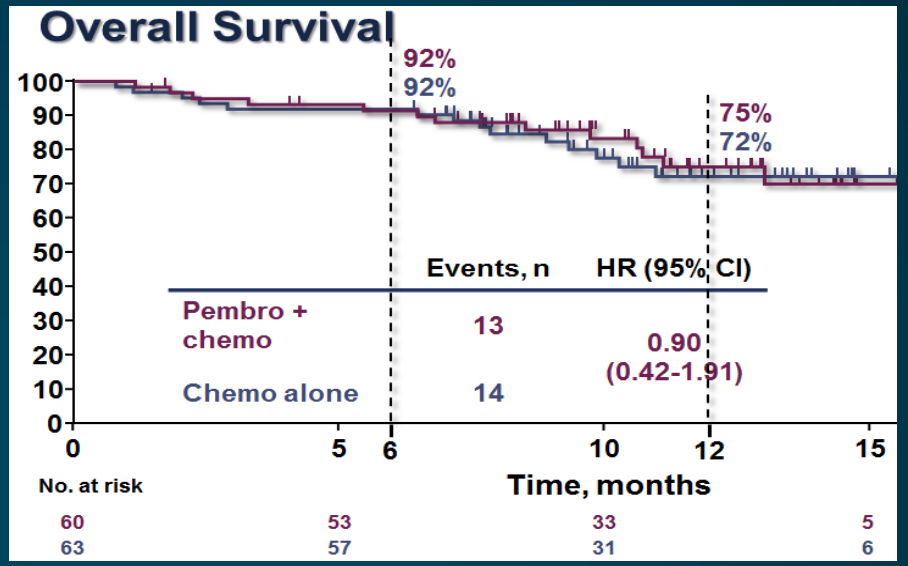
Key secondary: PFS

Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS

Langer et al, Lancet Oncology, 2016

PFS and OS Survival data





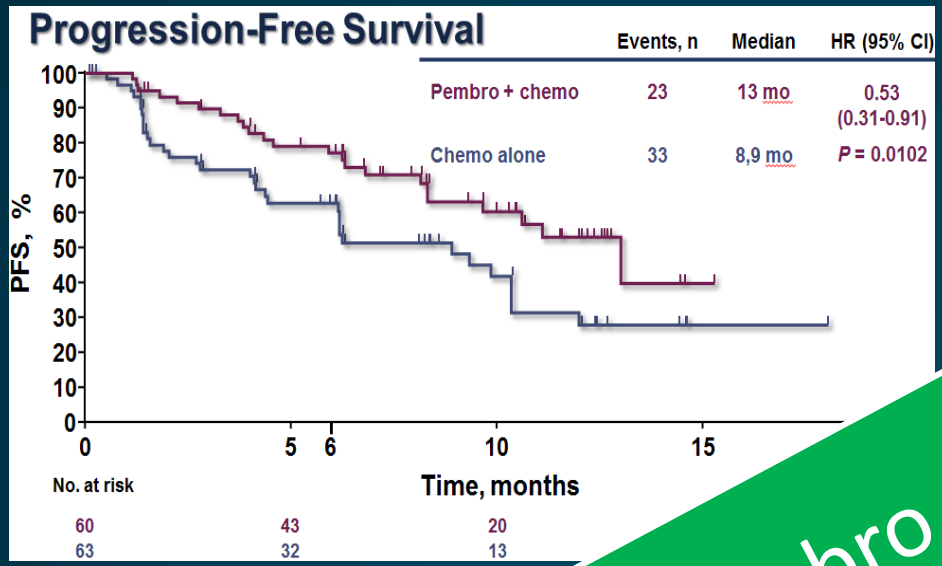
Clear RR% PFS benefit and no OS advantage

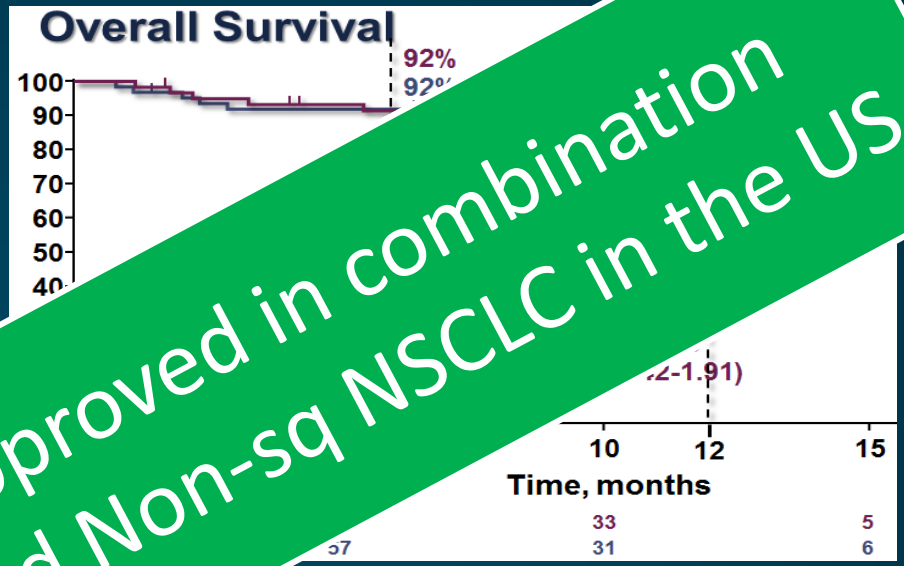
- RR: 55% vs 28%
- Median PFS improved by 4.1 months
- PFS HR is 0.53
- No difference for OS
- Estimated rate of OS @ 12 months: 75% (Combo) vs 72% (CT)
- In CT arm cross-over is 51% to PD-(L)1 therapies (pembro & others), but > 70% in those eligible

COPENHAGEN 2016 ESMO congress

Langer et al, Lancet Oncology, 2016

PFS and OS Survival data





As of 05/09/17 , Pembro approved in combination with Pem/Carbo in Advanced Non-sq NSCLC in the US

Clear RR% PFS benefit a

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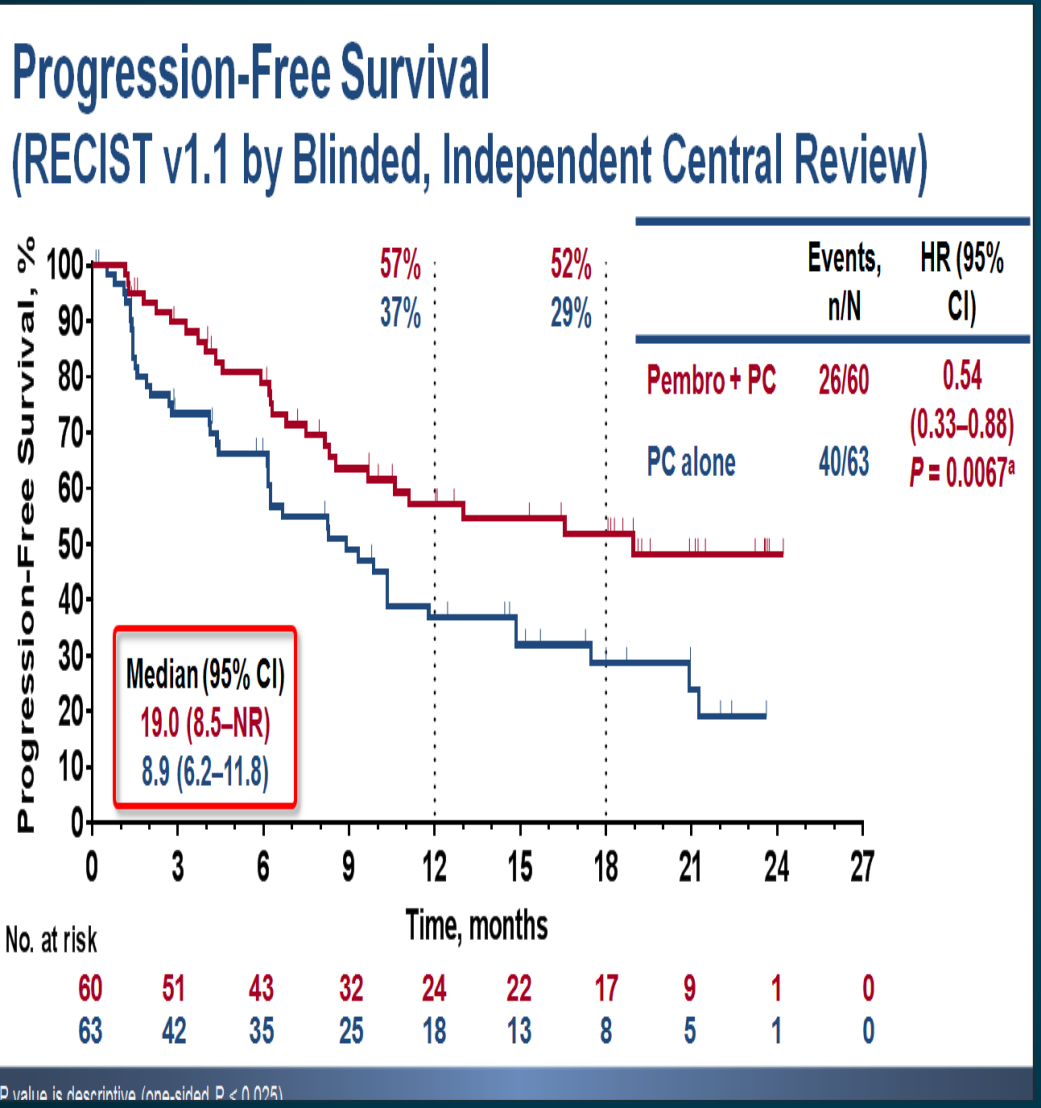
- Median P
- PFS
-
- months: 75% (Combo) vs 72% (CT)
- s 51% to PD-(L)1 therapies (pembro & others), but >
- gible

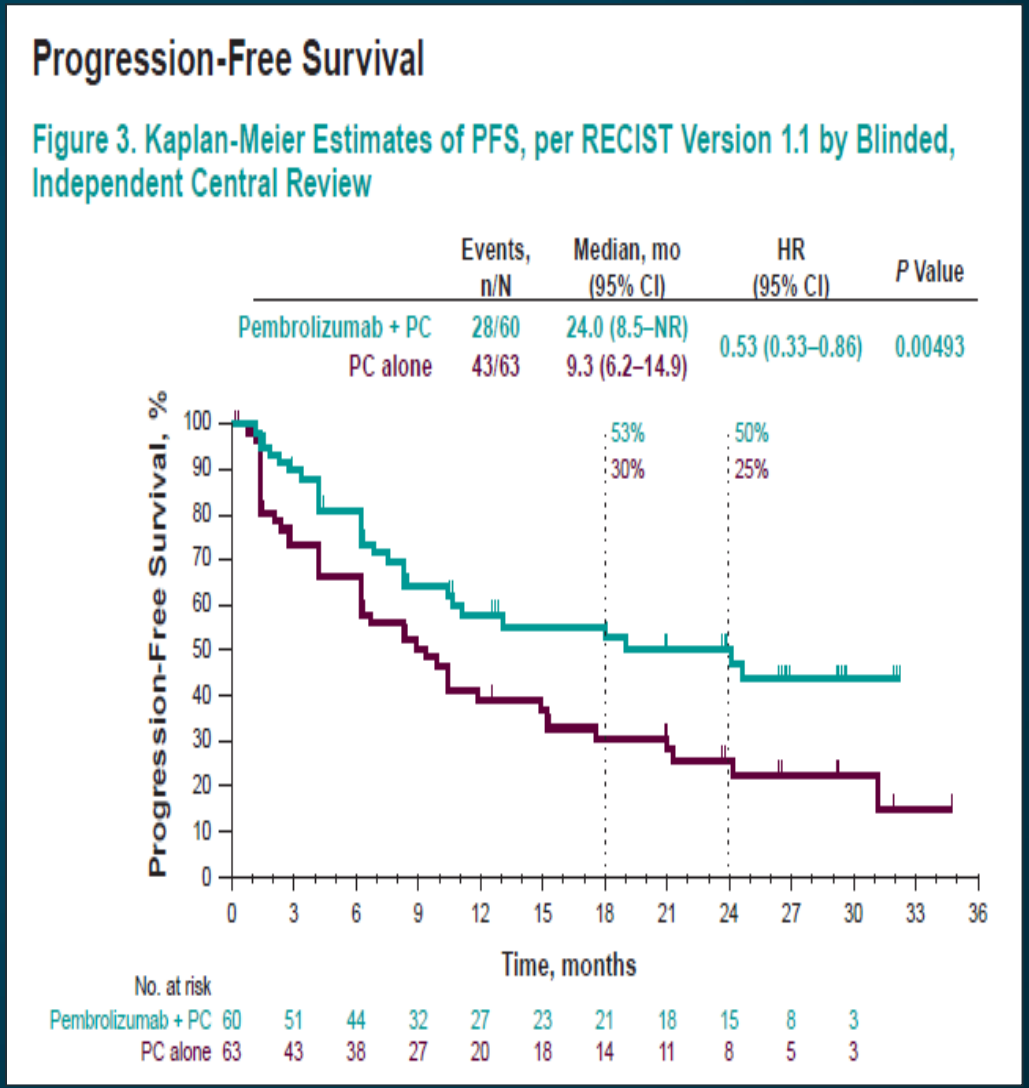
COPENHAGEN 2016 ESMO congress

Langer et al, Lancet Oncology, 2016

KN 021G Updated PFS Data – WCLC 2017 → ASCO 2018

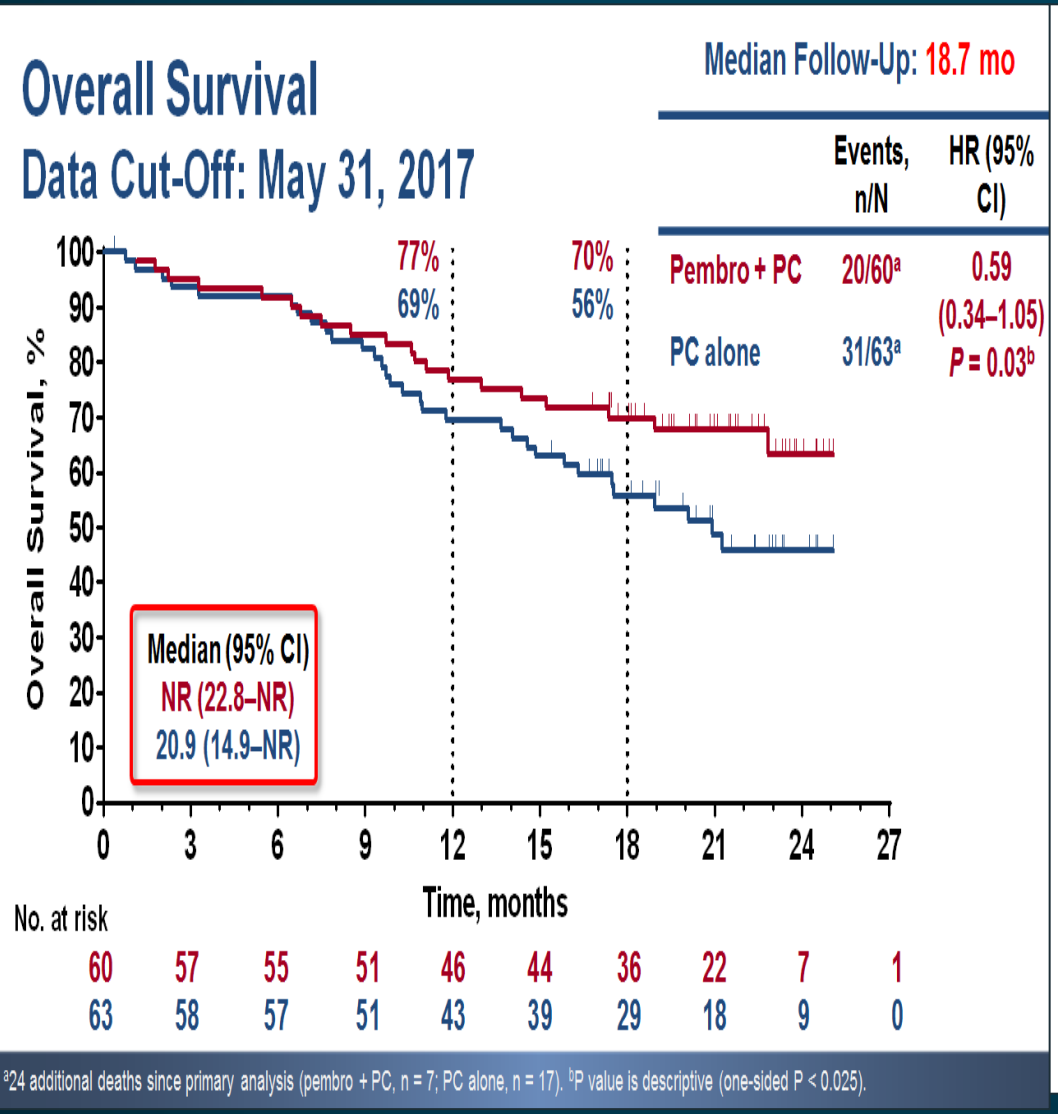


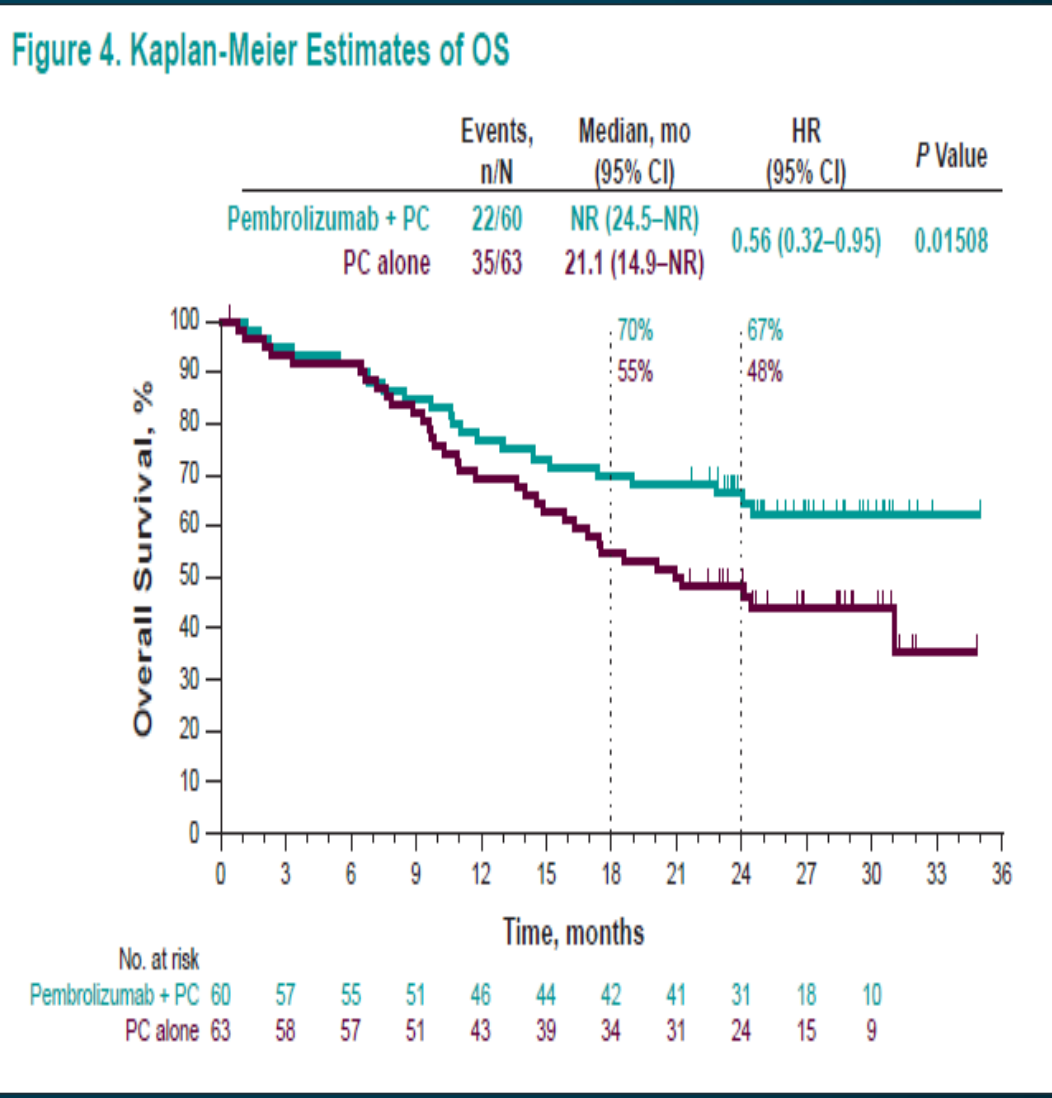
Langer, Borghaei WCLC 2017



Gentzler et al, ASCO 2018

KN 021G Updated OS Data: WCLC 2017 → ASCO 2018

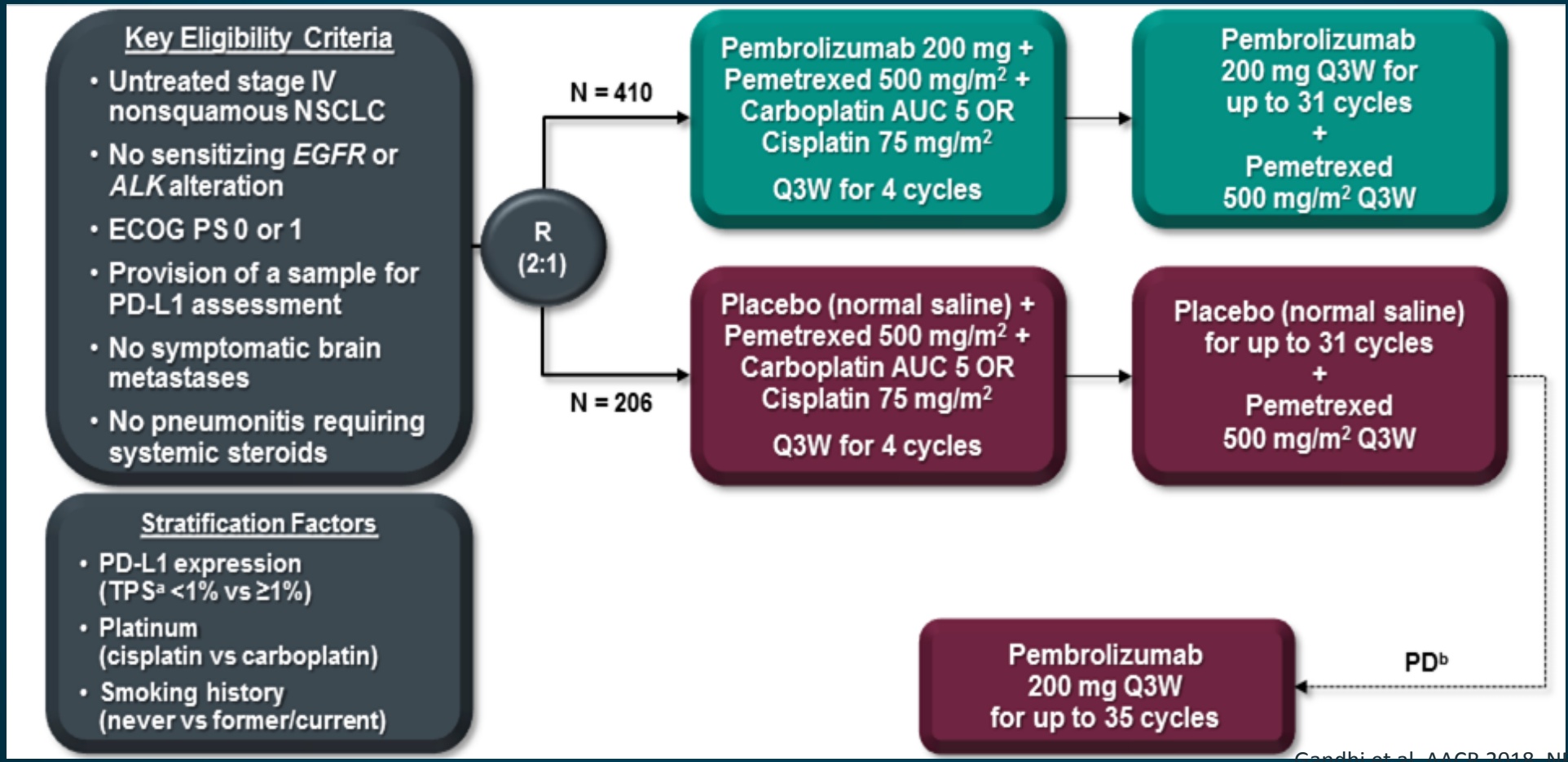




Langer, Borghaei WCLC 2017

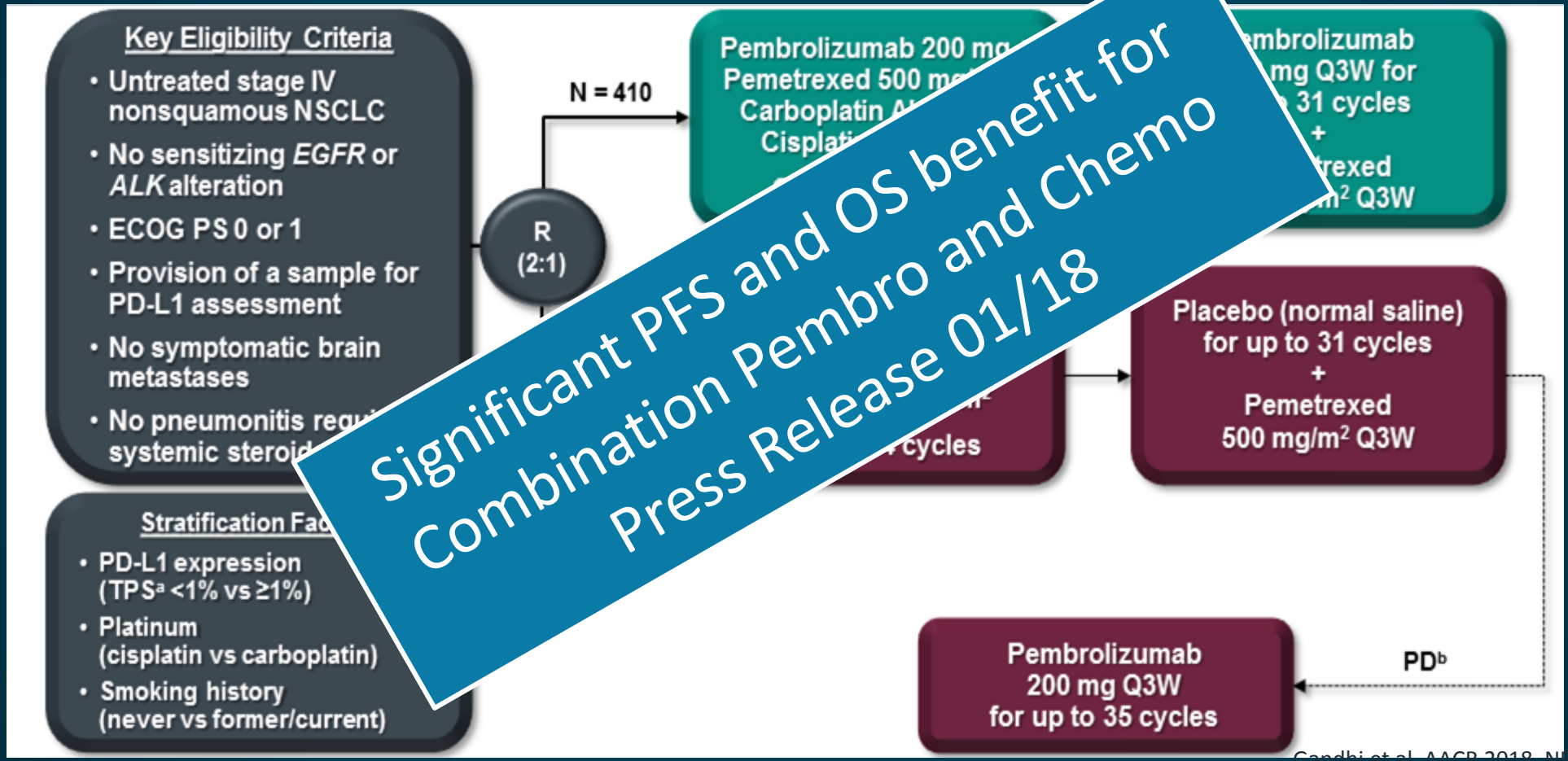
Gentzler et al, ASCO 2018

KEYNOTE-189: ChemoIO vs. Chemotherapy



Gandhi et al, AACR 2018, NEJM 2018,

KEYNOTE-189: ChemoIO vs. Chemotherapy

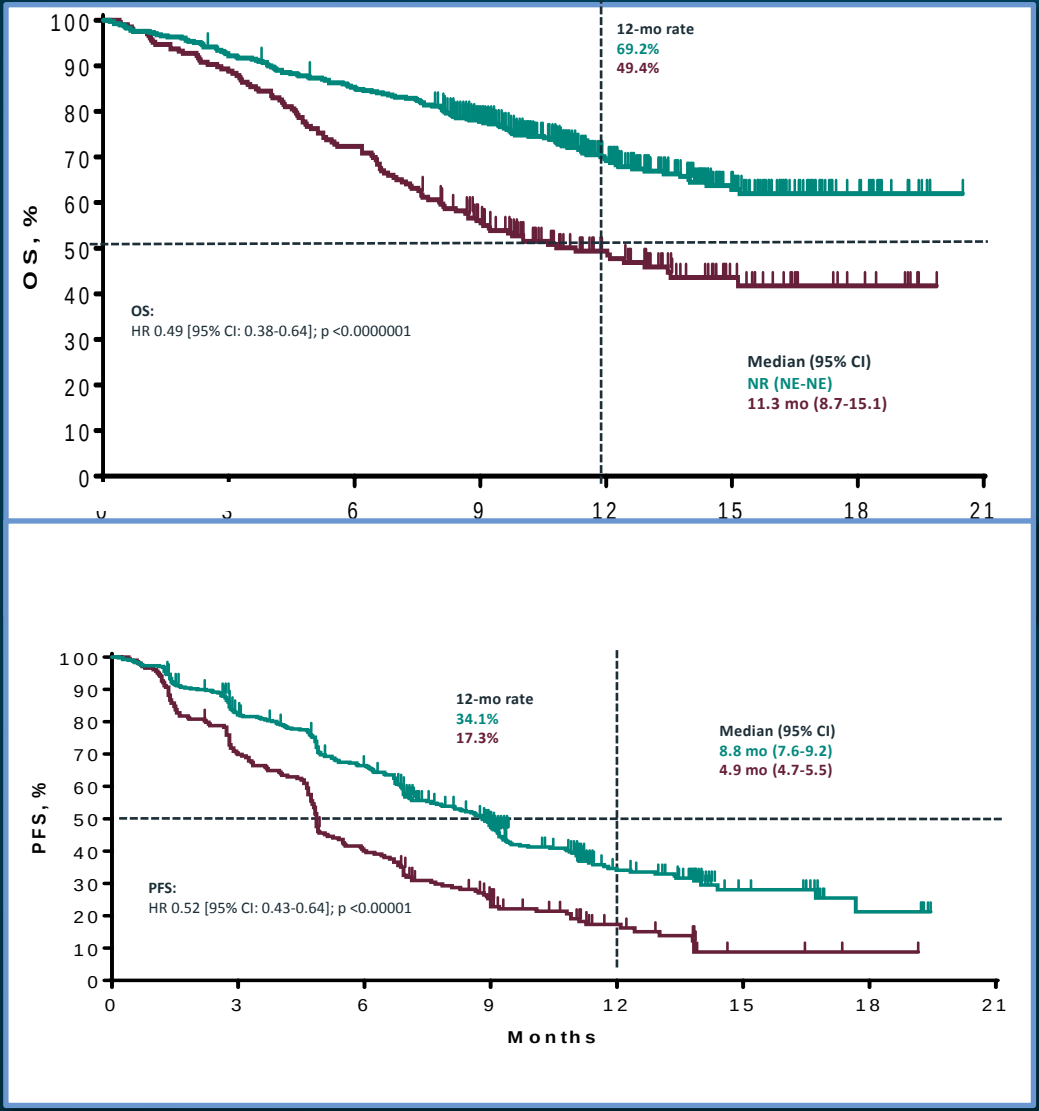


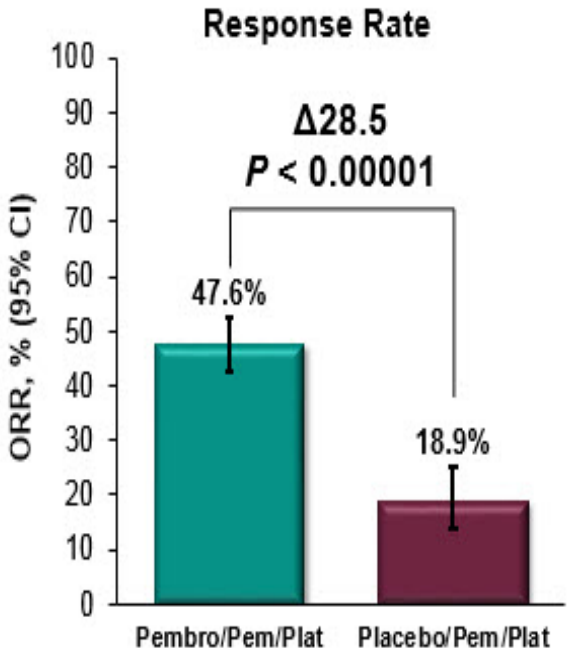
Significant PFS and OS benefit for Combination Pembro and Chemo Press Release 01/18

Gandhi et al, AACR 2018, NEJM 2018,

KEYNOTE-189: Results

Pem/Carbo +/- Pembro

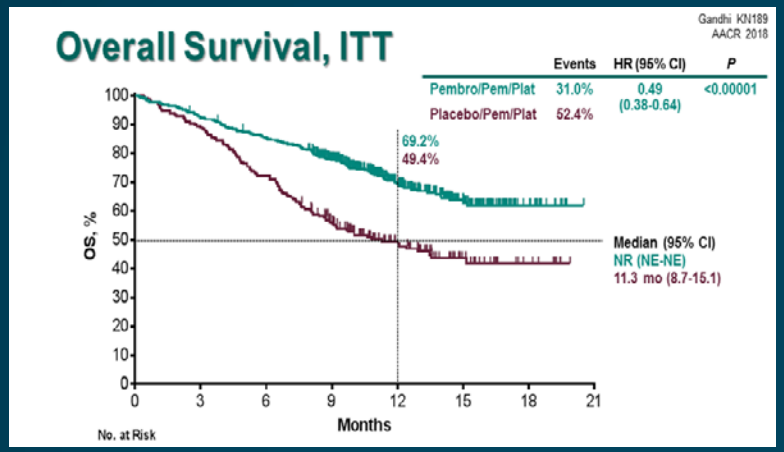




Subgroup Analyses
OS: Positive across all subgroups
PFS: Positive across all subgroups except for PD-L1 TPS <1%

Gandhi et al, AACR 2018, NEJM 2018,

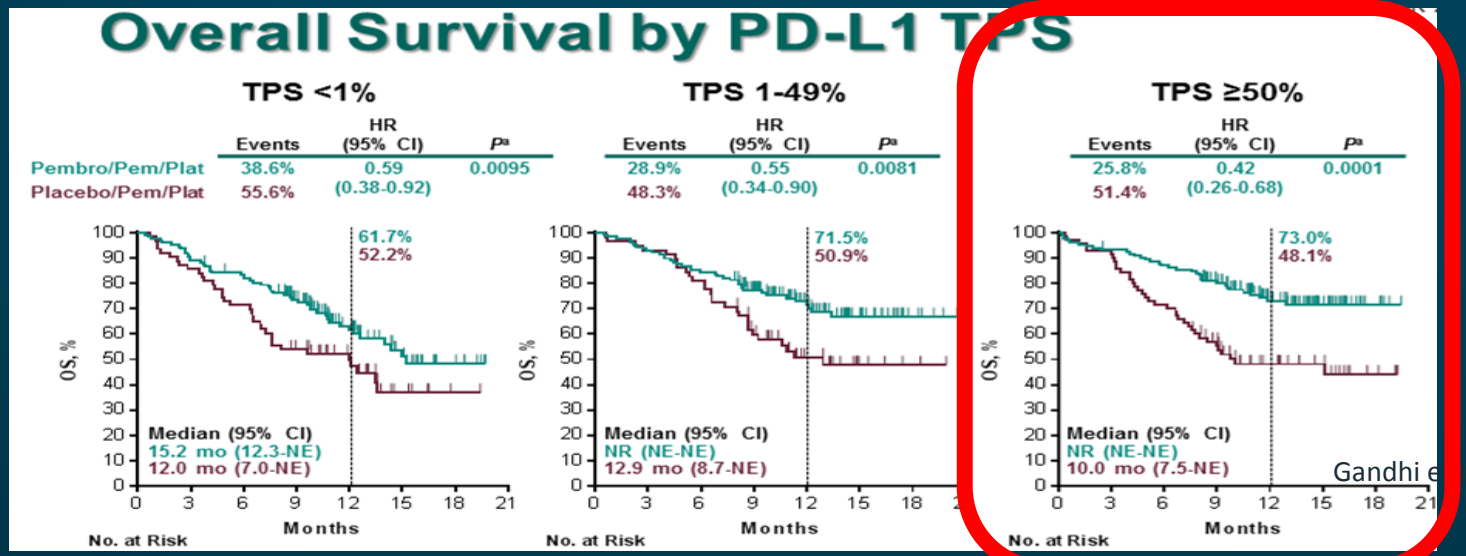
KEYNOTE-189: Results



N= 410 vs. 206
PDL1 expression categories balanced - mirroring the prevalence of 33-34%

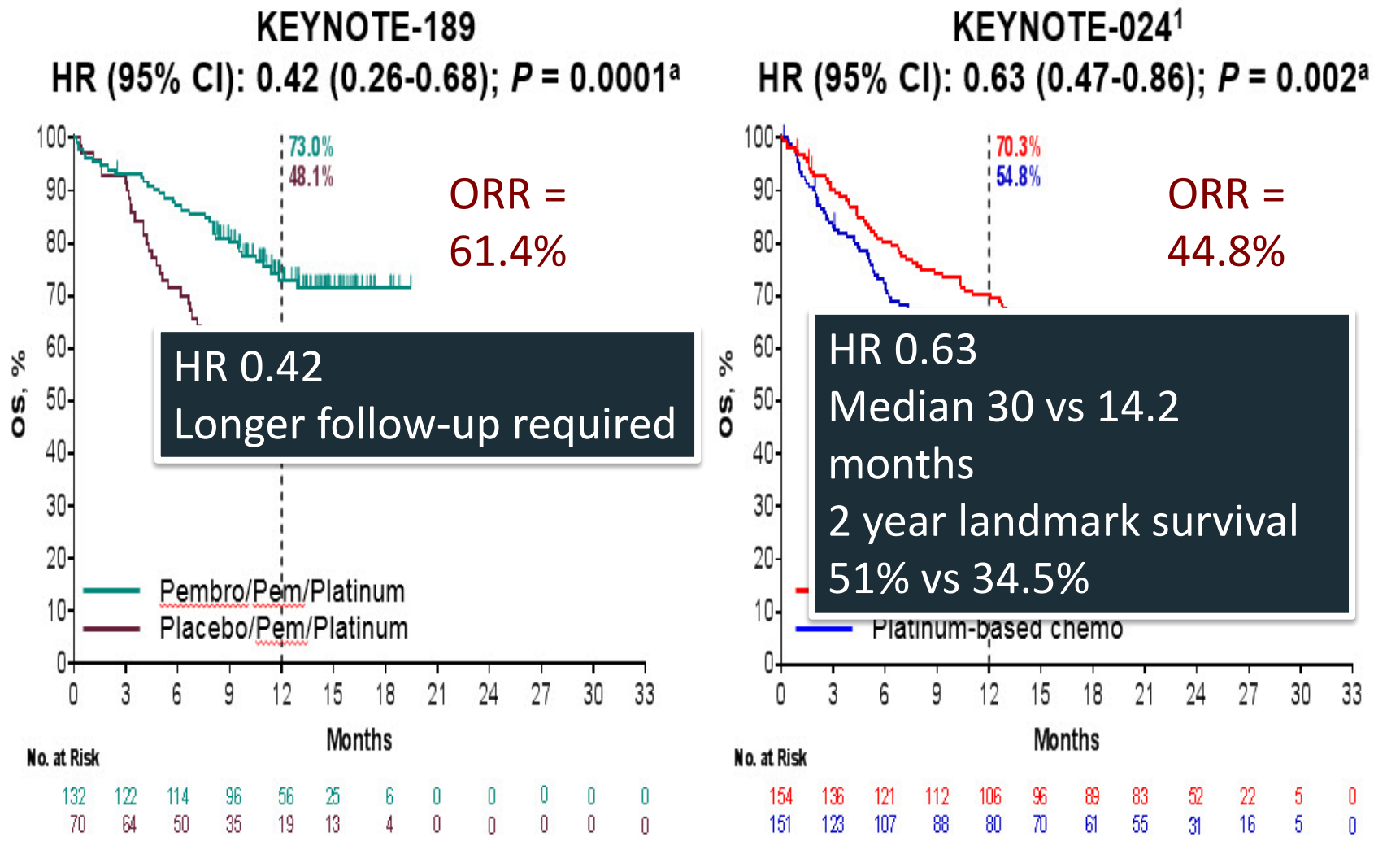
HR 0.49!!

Benefit seen across all subgroups
RR highest in PDL1 high (61.4%)



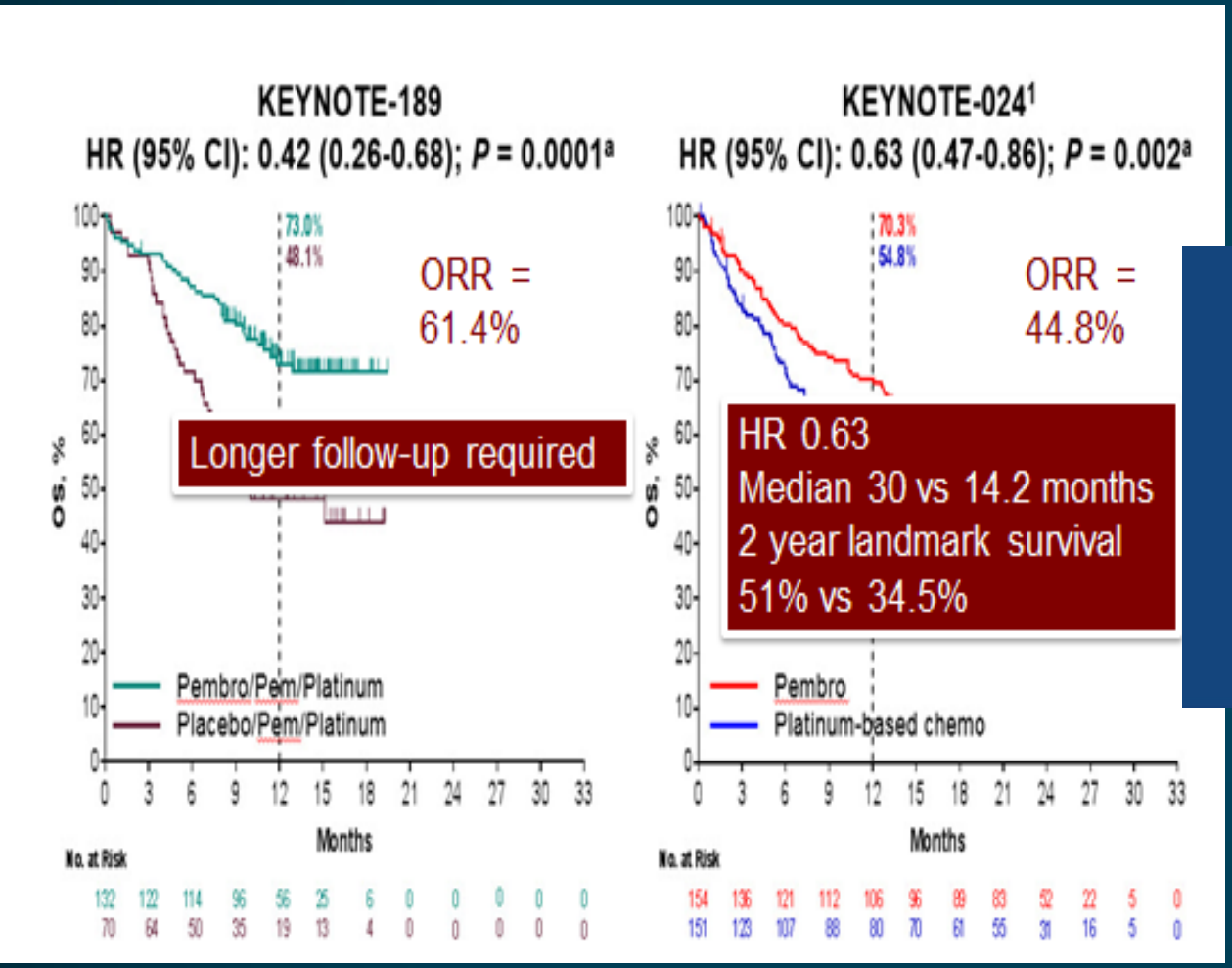
Gandhi et al, AACR 2018, NEJM 2018,

Cross Trial Comparison for PDL1 > 50%

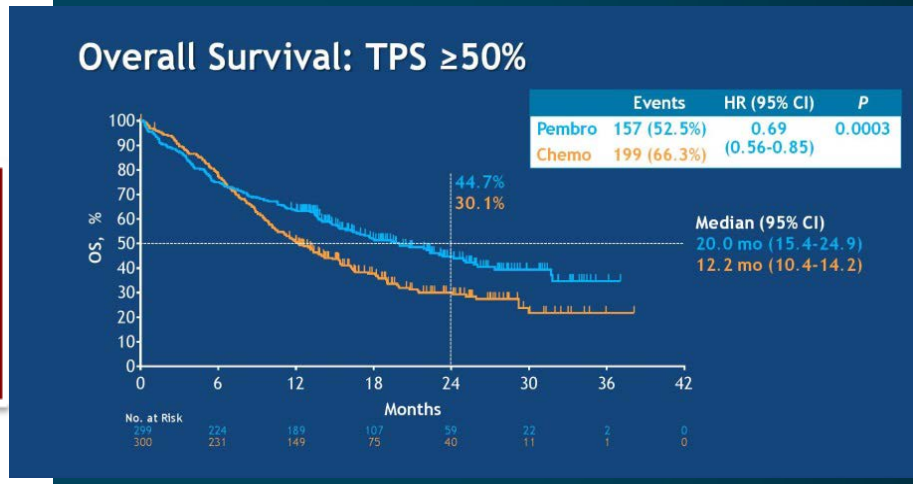


Gandhi et al, AACR 2018, NEJM 2018, Brahmer et al, WCLC 2017

Cross Trial Comparison for PDL1 > 50%



KEYNOTE-042, TPS>50%



HR = 0.69
Median 20 vs. 12.2 months
2 year landmark survival 44.7% vs 30.1%
ORR 39.5%

Gandhi et al, AACR 2018, NEJM 2018; Brahmer et al, WCLC 2017; Lopes et al ASCO 2018

Pembro vs. Combination Pem/Carbo/Pembro In Non-Sq NSCLC with PDL1 ≥ 50%, ?

- **Rationale for Pembro Single agent**
  - We've no HTH comparisons of Pembro vs Pem/Pem/Carbo (yet)
  - Less toxicity and lower cost for single agent Pembro
  - Does not preclude option of Pem/Carbo +/- bevacizumab at time of PD
- **Rationale for Pem/Pem/Carbo**
  - High RR% of 80% in 021G and 61% in KN 189 c/w 45% in KN 024 and 39.5% in KN042; very low rates of primary PD (~ 3 - 8%)
  - PFS ~ 2 yrs in 021G: 13 mos (ESMO '16) → 19 (WCLC '17) → 24 mos (ASCO '18); this strategy delays the "turmoil of progression"
  - OS continues to trend in 021G with drop in HR from 0.90 (ESMO'17) to 0.69 (ASCO '17) to 0.59 (WCLC '17), then 0.56 (ASCO '18): drop in p value from 0.369 to 0.13 to 0.03 to 0.015 with 2yr OS 67 vs 48%
  - Confirmatory Data in KN 189 for the ≥ 50% cohort
    - Superior RR: 61% vs 23%; p <0.0001 (KN 024: 46% vs 30%; p = 0.0031)
    - Better PFS: 1 yr 45% vs 15% Med 9.4 vs 4.7; HR 0.36; p <0.00001 (KN 024: 1yr 48 v 15%; Med 10.3 vs 6.0, HR 0.50, p <0.0001)
    - Improved OS: 1 yr 73% vs 48%; HR 0.42, p 0.0001 (KN 024: 1 yr 70% vs 55%; HR 0.63; p 0.002)

Langer's Practical Strategy for PDL1 > 50% in advanced Non-squamous NSCLC

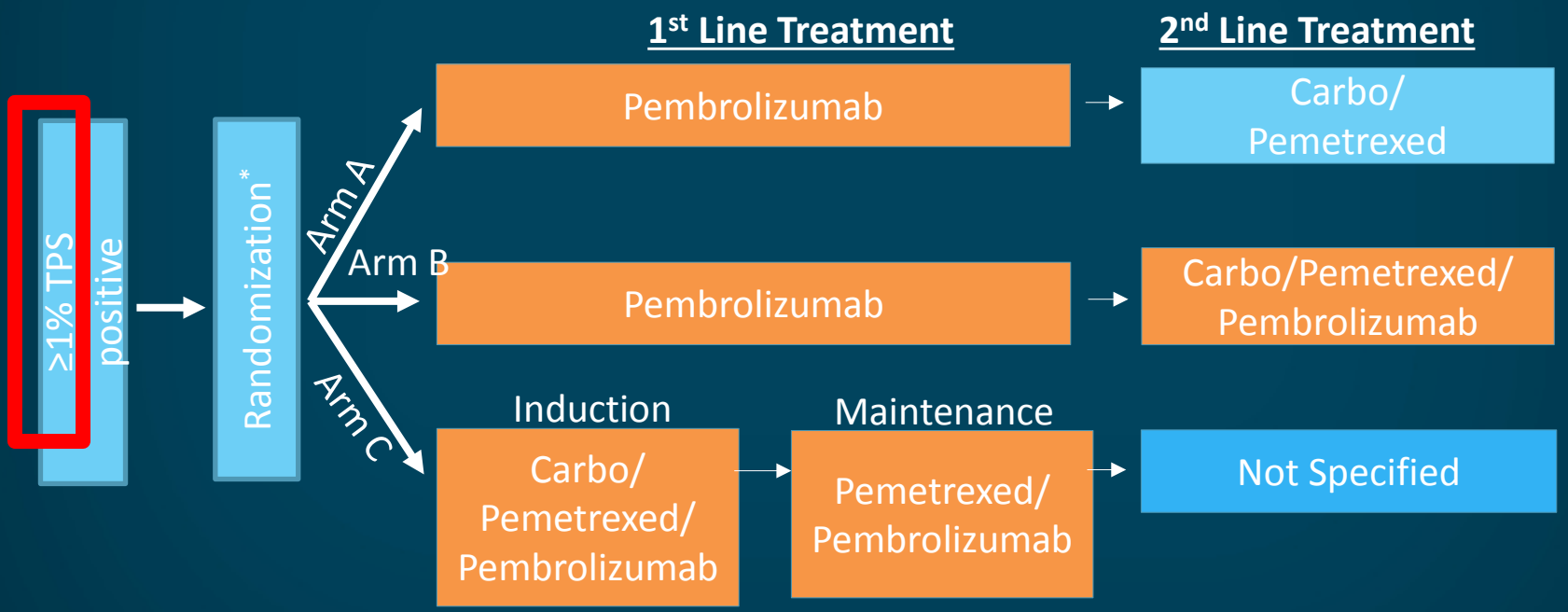
- **Pembro alone**
  - Older, frailer patients
  - Lower metastatic burden
  - Significant co-morbidity
- **Combination Pembro and Pem/Carbo**
  - Younger, heartier patients
  - Higher metastatic burden
  - Greater symptomatology
  - More aggressive tumors
  - Limited co-morbidity

VIEW ALL PRESS RELEASES

And The Landscape is Changing

KEYTRUDA® (pembrolizumab) Monotherapy Met Primary Endpoint in Phase 3 KEYNOTE-042 Study, Significantly Improving OS as First-Line Therapy in Locally Advanced or Metastatic NSCLC Patients Expressing PD-L1 in at Least 1 Percent of Tumor Cells

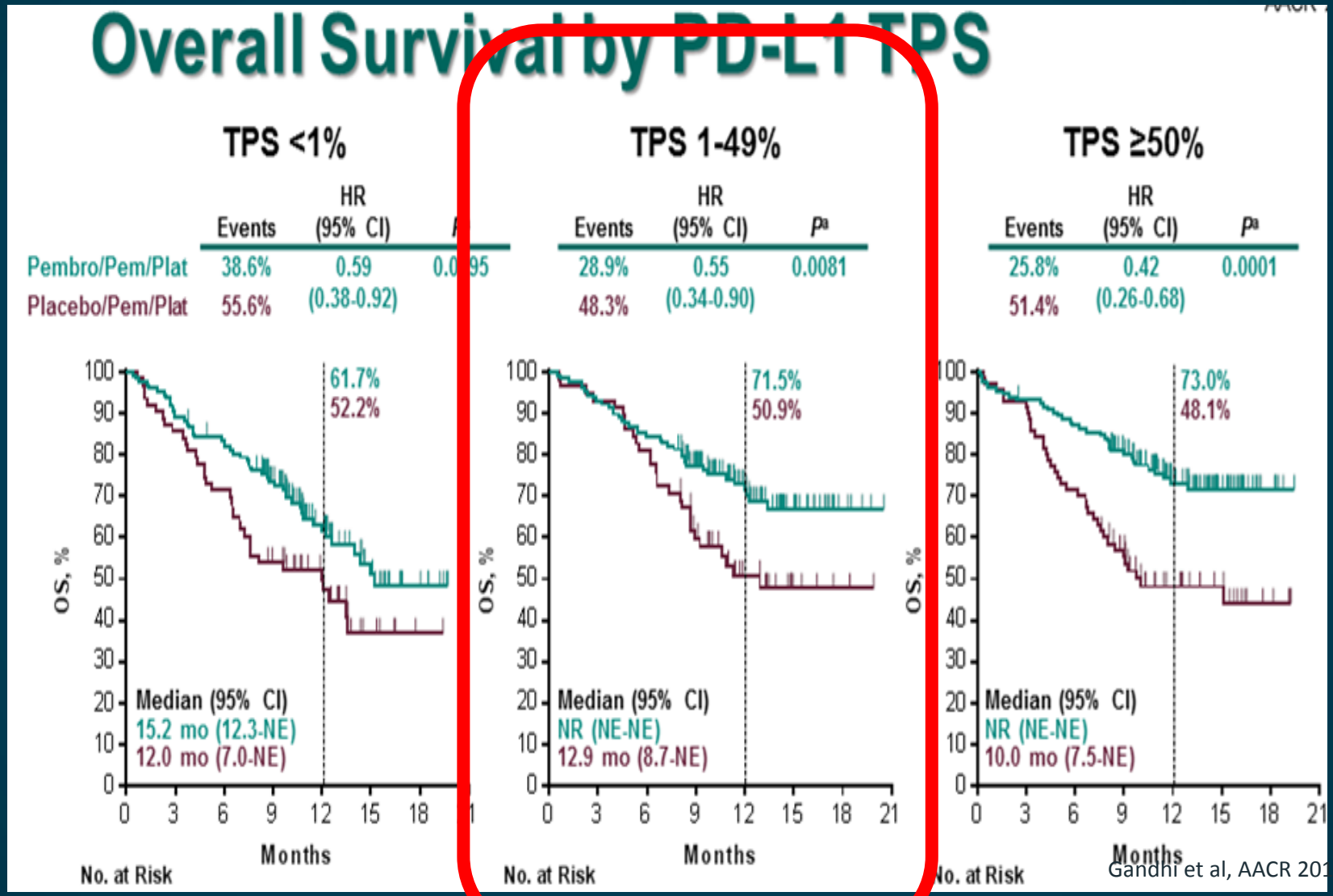
APRIL 09, 2018



SWOG-ECOG collaboration NCTN NCI network (A. Chiang, H. Borghaei)

Non-Squamous; PDL1 1-49% Advanced NSCLC

KEYNOTE-189: Results

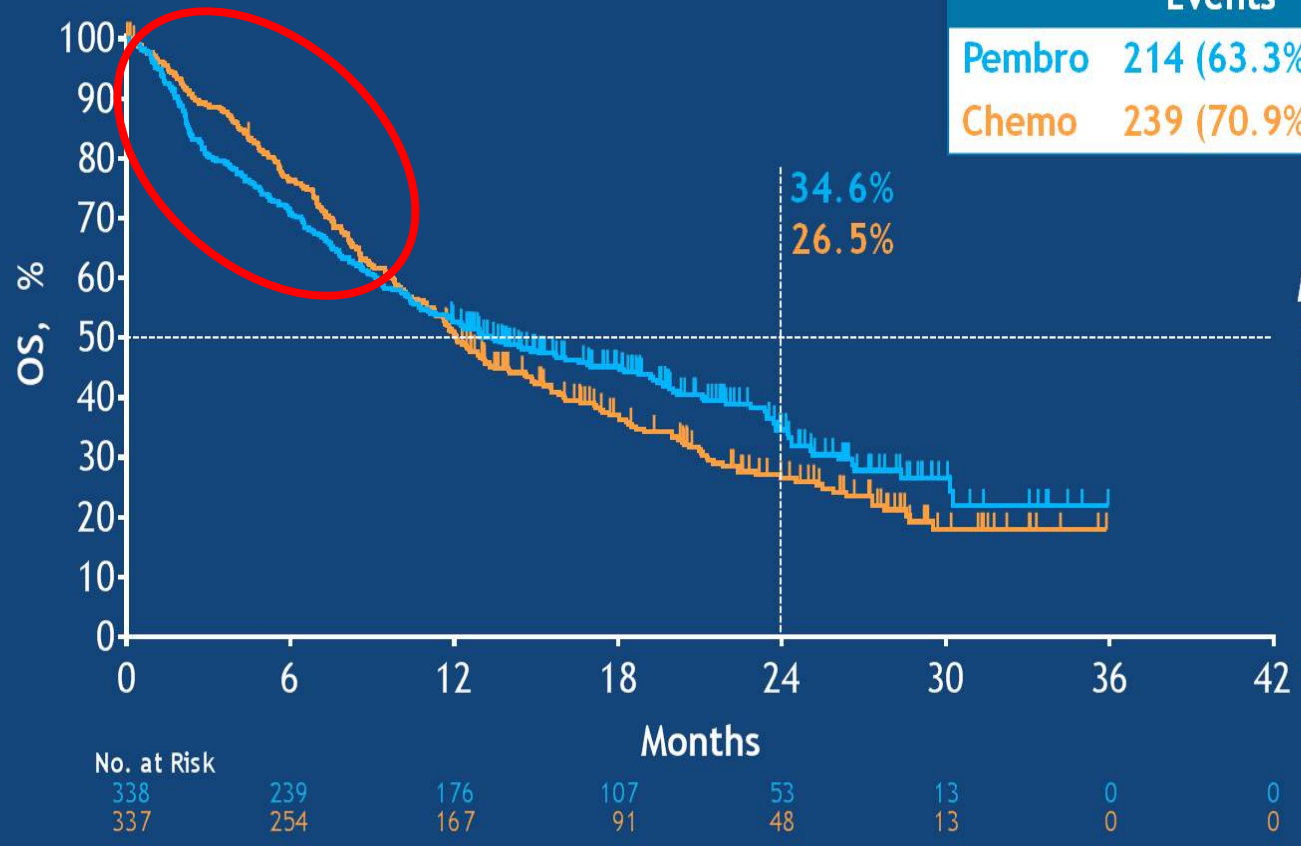


Gandhi et al, AACR 2018, NEJM 2018

KEYNOTE-042: Results

Overall Survival: TPS ≥1-49% (Exploratory Analysis[a])

	Events	HR (95% CI)
Pembro	214 (63.3%)	0.92 (0.77-1.11)
Chemo	239 (70.9%)	



Median (95% CI)
13.4 mo (10.7-18.2)
12.1 mo (11.0-14.0)

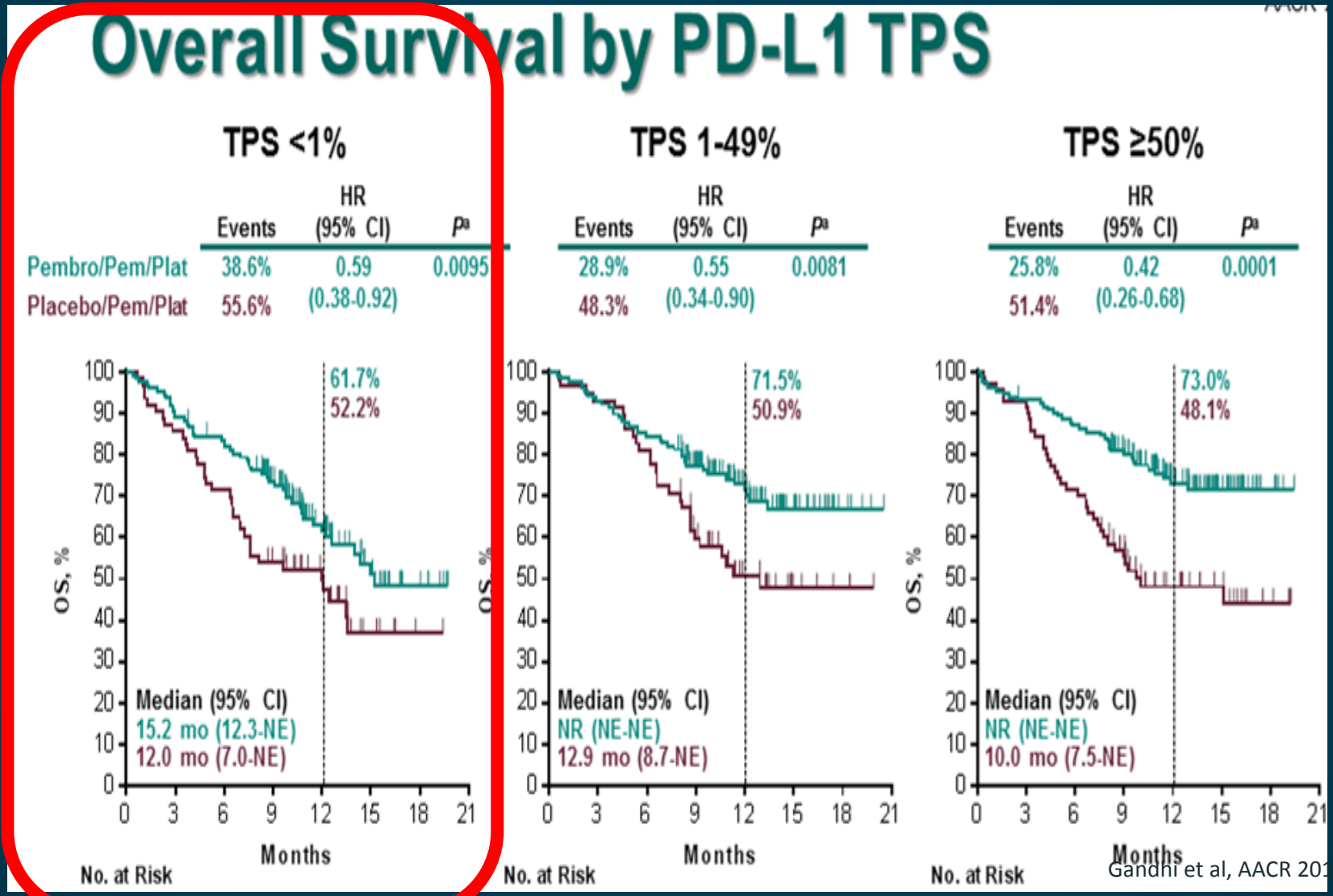
[a]No alpha allocated to this comparison.

Langer's Practical Strategy for PDL1 1-49 % In Non-Squamous NSCLC

- **Pembro alone**
  - Even Older, frailer patients
  - Significant co-morbidity
  - Chemo-averse or Chemo-ineligible
- **Combination Pembro and Pem/Carbo**
  - SOC in PS 0-1
  - All ages
  - Any metastatic burden
  - Limited to moderate co-morbidity

Advanced Non-Squamous NSCLC
PDL1 < 1%

KEYNOTE-189: Results in TPS < 1%

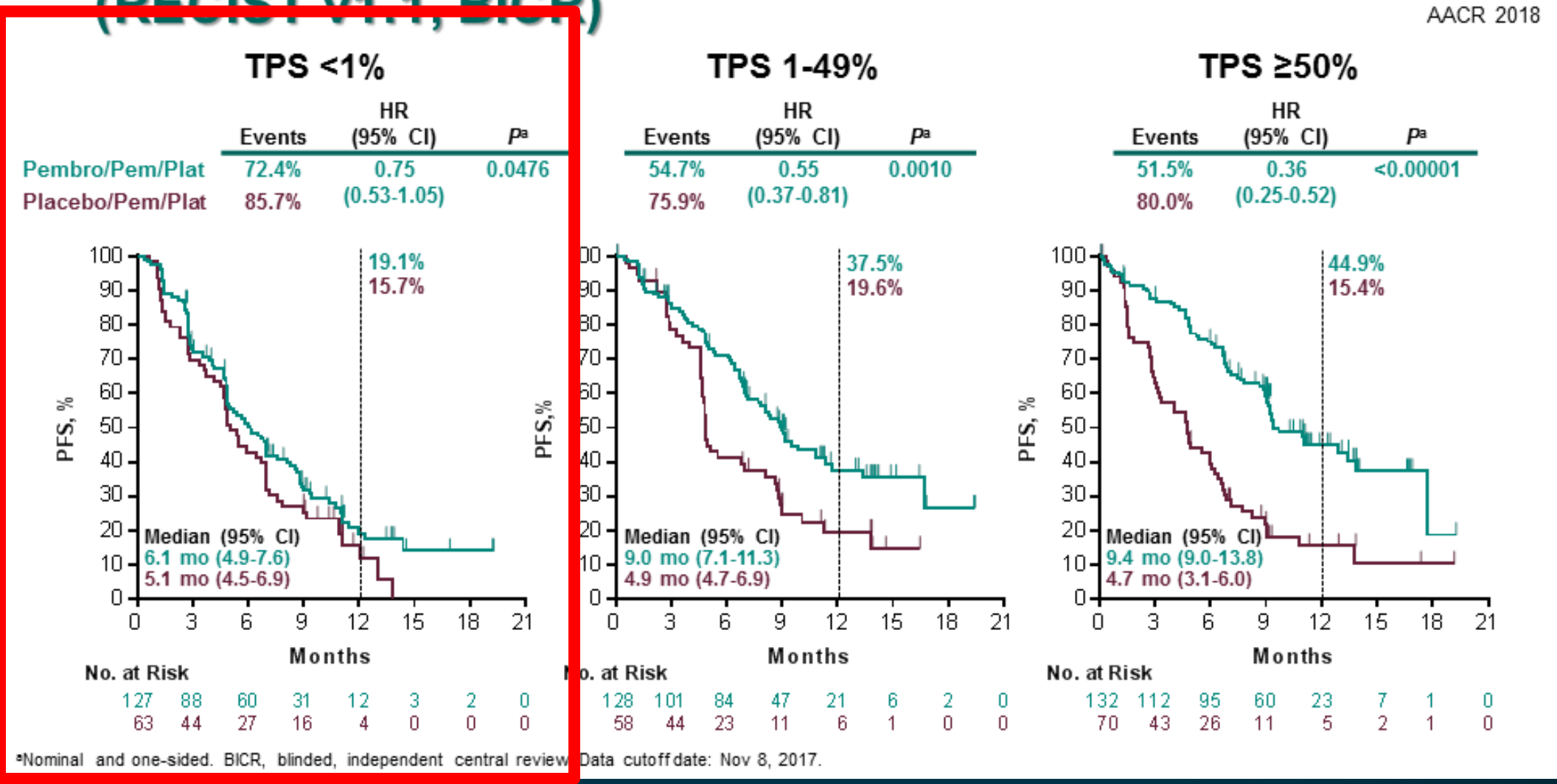


Gandhi et al, AACR 2018, NEJM 2018

KEYNOTE-189: Results in TPS < 1%

Progression-Free Survival by PD-L1 TPS (RECIST v1.1, BICR)

Gandhi KN189
AACR 2018



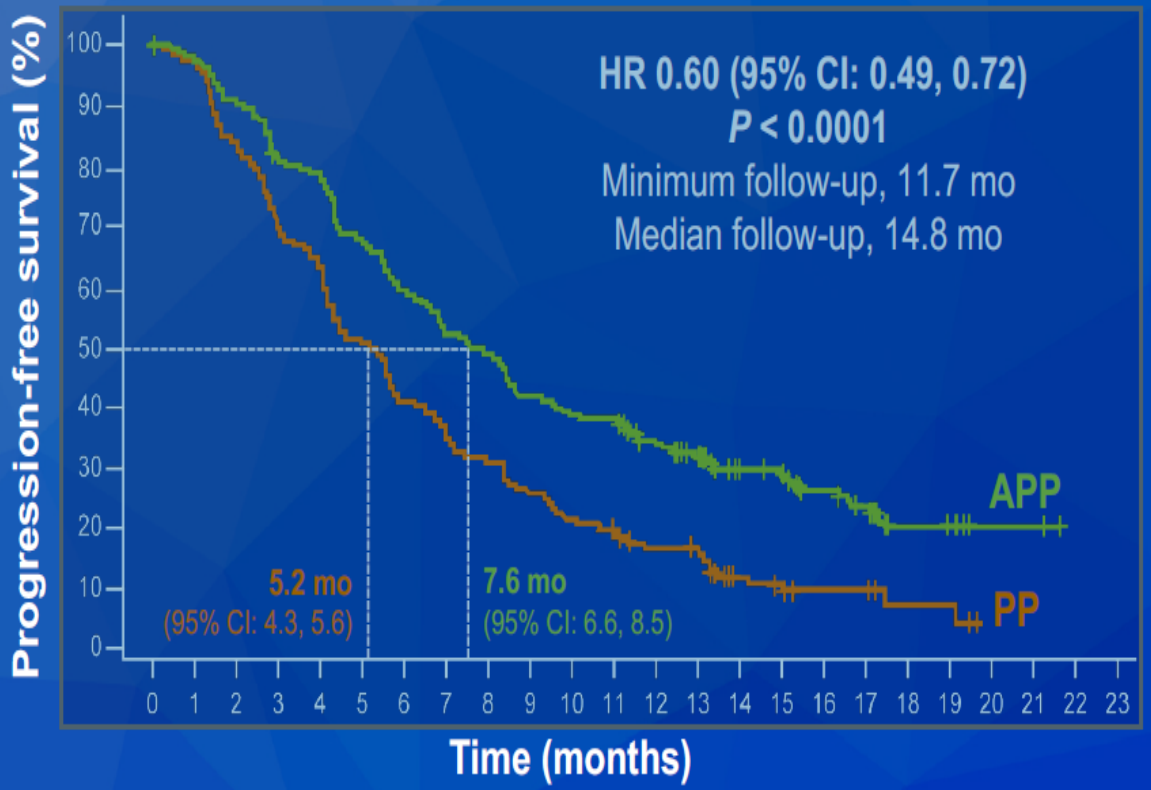
[a]Nominal and one-sided. BICR, blinded, independent central review. Data cutoff date: Nov 8, 2017.

Is Atezo in Combination an Option in Non-squamous NSCLC?

Impower 132

Impower 130

IMpower132: Efficacy and Safety Results with First-Line Atezolizumab and Chemotherapy in Metastatic Nonsquamous NSCLC



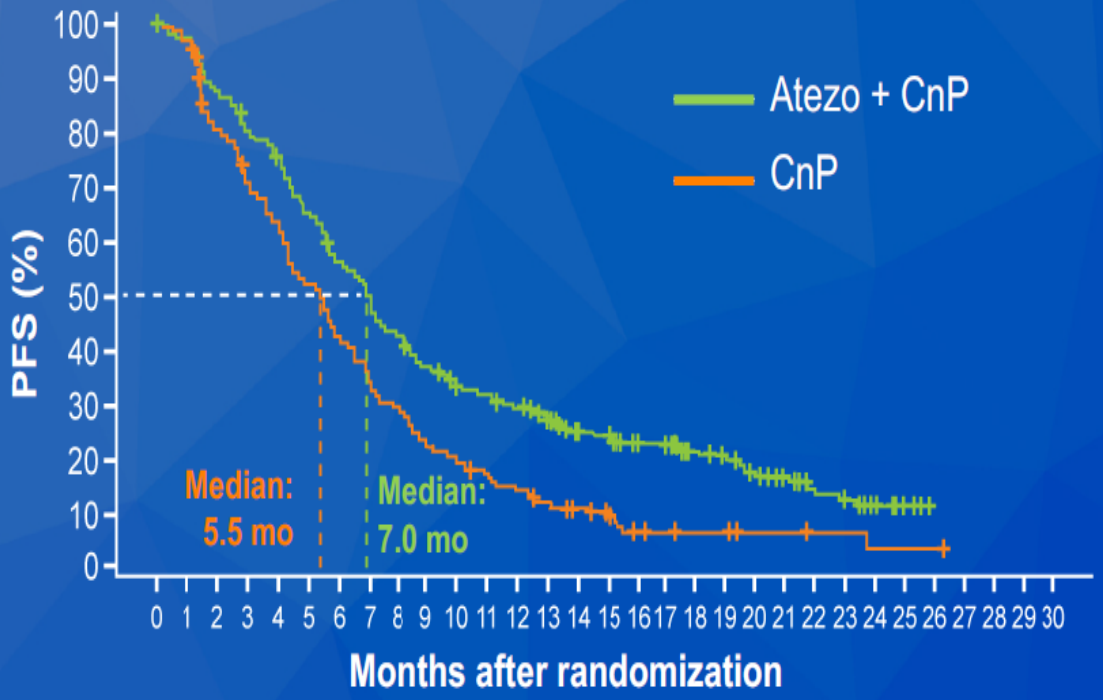
	APP	PP
6-mo PFS	59.1%	40.9%
12-mo PFS	33.7%	17.0%
	APP	**PP**
ORR	47%	32%
CR	2%	1%
PR	45%	32%
Median DOR, mo	10.1	7.2
Ongoing response, %	42%	30%

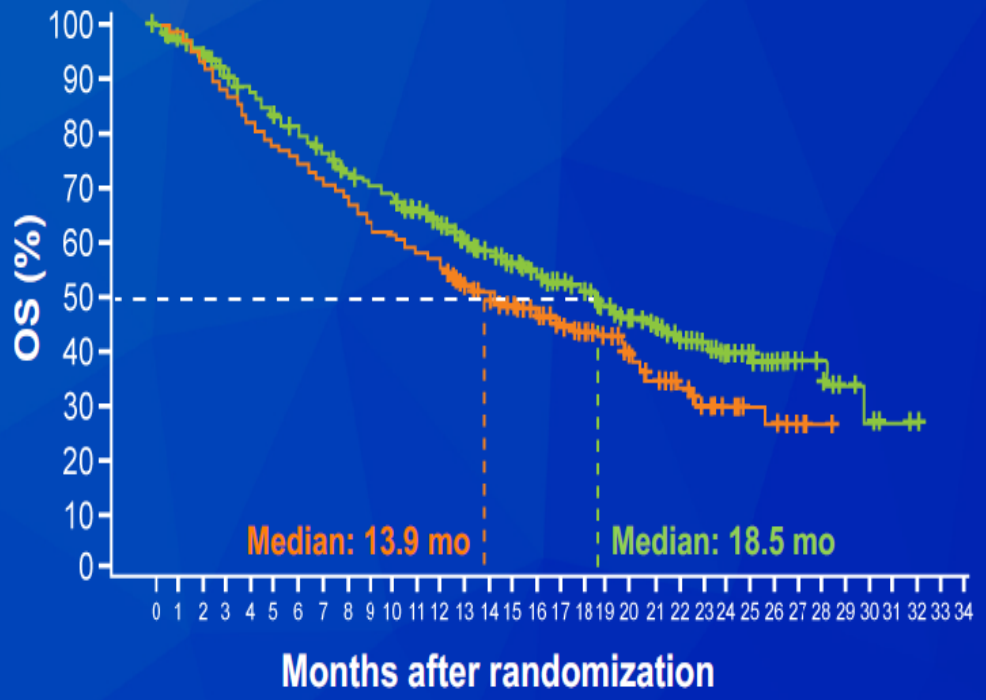
APP = atezolizumab + PP; PP = pemetrexed + cisplatin or carboplatin

- At interim analysis, median OS was 18.1 mo with APP and 13.6 mo with PP (HR 0.81; $p = 0.0797$).
- No new safety signals were identified with the APP combination; the safety profile is consistent with known safety risks of the individual therapies.

Papadimitrakopoulou VA et al. *Proc WCLC* 2018;Abstract OA05.07.

IMpower130: PFS and OS of CnP with or without Atezo in the Intention-to-Treat Wild-Type (ITT-WT) Population





PFS (ITT-WT)	6 mo	1-year	HR	*p-value*
Atezo + CnP	56.1%	29.1%	0.64	*P* < 0.0001
CnP	42.5%	14.1%		

OS (ITT-WT)	1-year	2-year	HR	*p-value*
Atezo + CnP	63.1%	39.6%	0.79	*P* = 0.033
CnP	55.5%	30.0%		

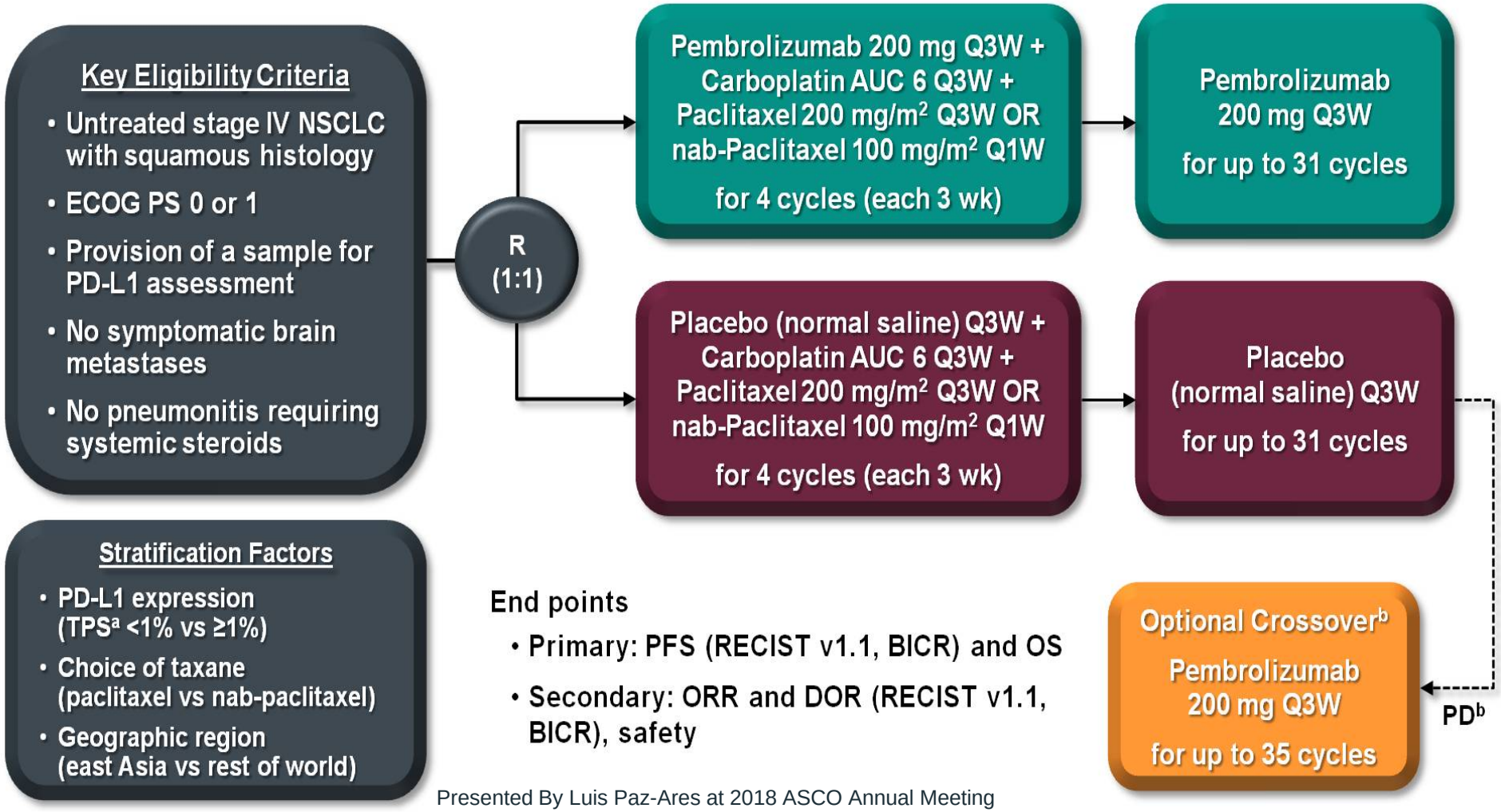
- Outcomes in patients with EGFR or ALK genomic alterations suggest treatment benefit was mostly driven by the ITT-WT population
- Atezo with chemotherapy had a safety profile consistent with the AEs associated with single-agent therapy; no new safety signals were identified

Cappuzzo F et al. *Proc ESMO* 2018;Abstract LBA53.

Advanced Squamous NSCLC

KN 407 >> IMPower 131

KEYNOTE-407 Study Design (NCT02775435)



Presented By Luis Paz-Ares at 2018 ASCO Annual Meeting

BICR, blinded independent central radiologic review. [a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay.
[b]Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and all safety criteria had to be met.

Paz-Ares L et al. *J Clin Oncol* 2018;36(15_suppl): abstr 105.

KEYNOTE-407 (NCT02775435)

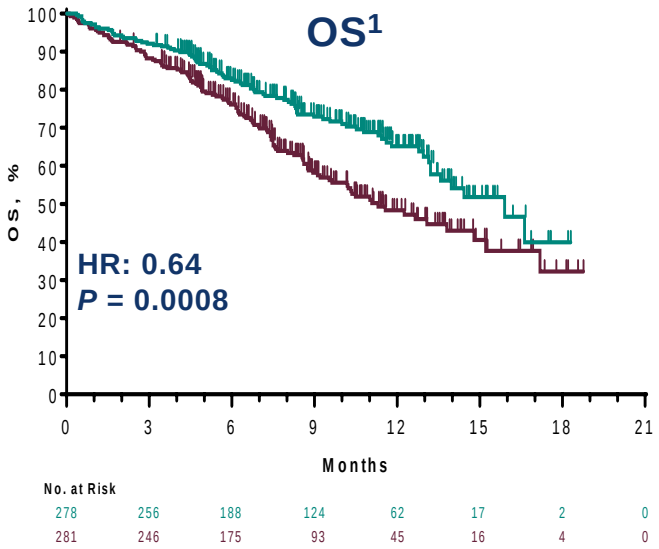
Key Eligibility Criteria

- Untreated stage IV NSCLC with squamous histology
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

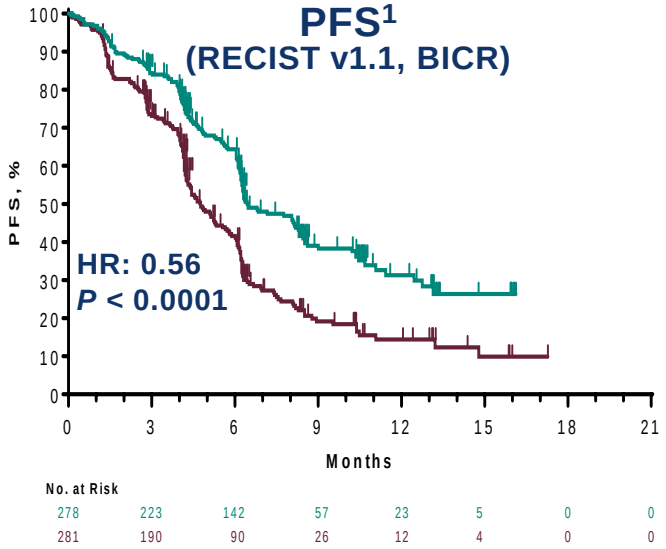
R (1:1)

Pembrolizumab 200 mg Q3W + Carboplatin AUC 6 Q3W + Paclitaxel 200 mg/m² Q3W OR nab-Paclitaxel 100 mg/m² Q1W for 4 cycles (each 3 wk) → Pembrolizumab 200 mg Q3W for up to 31 cycles

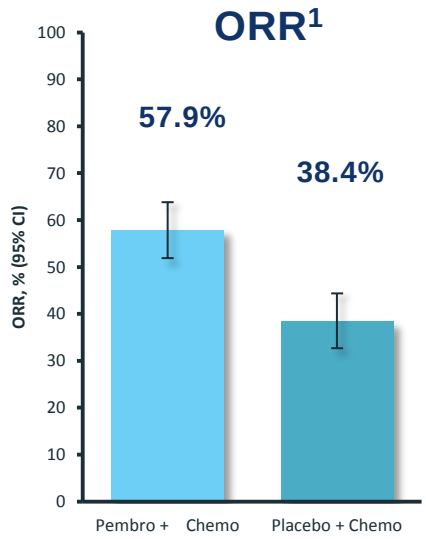
Placebo (normal saline) Q3W + Carboplatin AUC 6 Q3W + Paclitaxel 200 mg/m² Q3W OR nab-Paclitaxel 100 mg/m² Q1W for 4 cycles (each 3 wk) → Placebo (normal saline) Q3W for up to 31 cycles → PD → Optional Crossover[b] Pembrolizumab 200 mg Q3W for up to 35 cycles



Median (95% CI)
15.9 mo (13.2-NE)
11.3 mo (9.5-14.8)

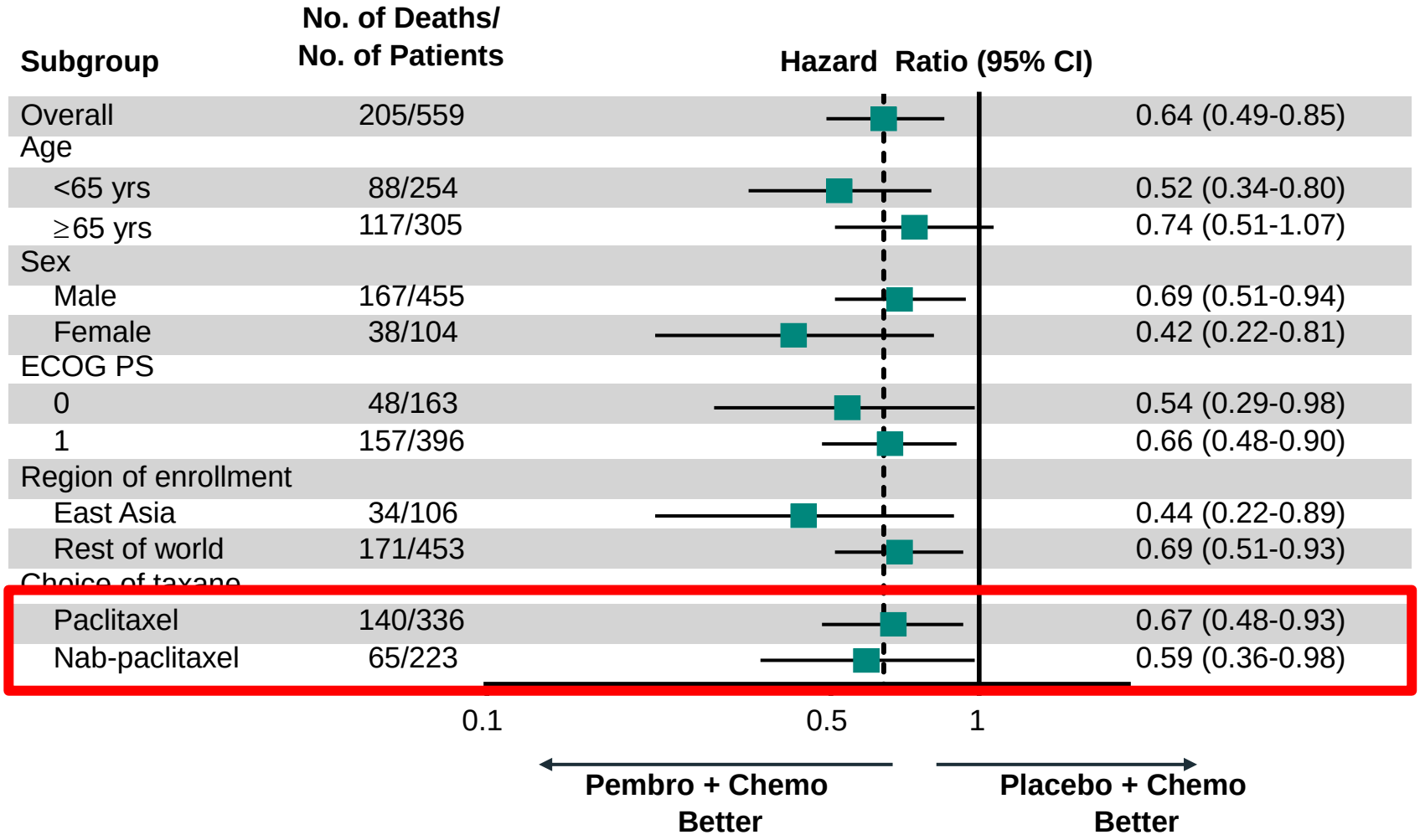


Median (95% CI)
6.4 mo (6.2-8.3)
4.8 mo (4.3-5.7)



Paz-Ares L et al. *J Clin Oncol* 2018;36(15_suppl): abstr 105.

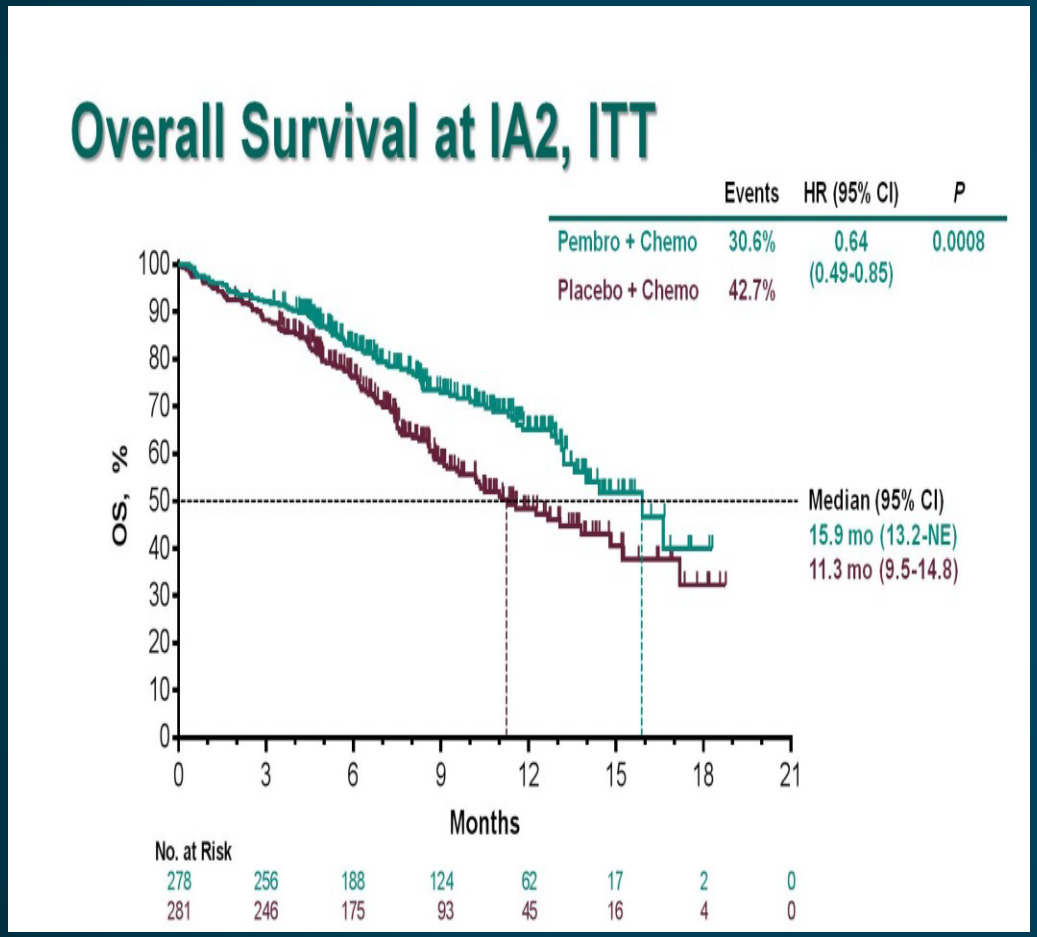
Overall Survival at IA2 in Key Subgroups: KN 407



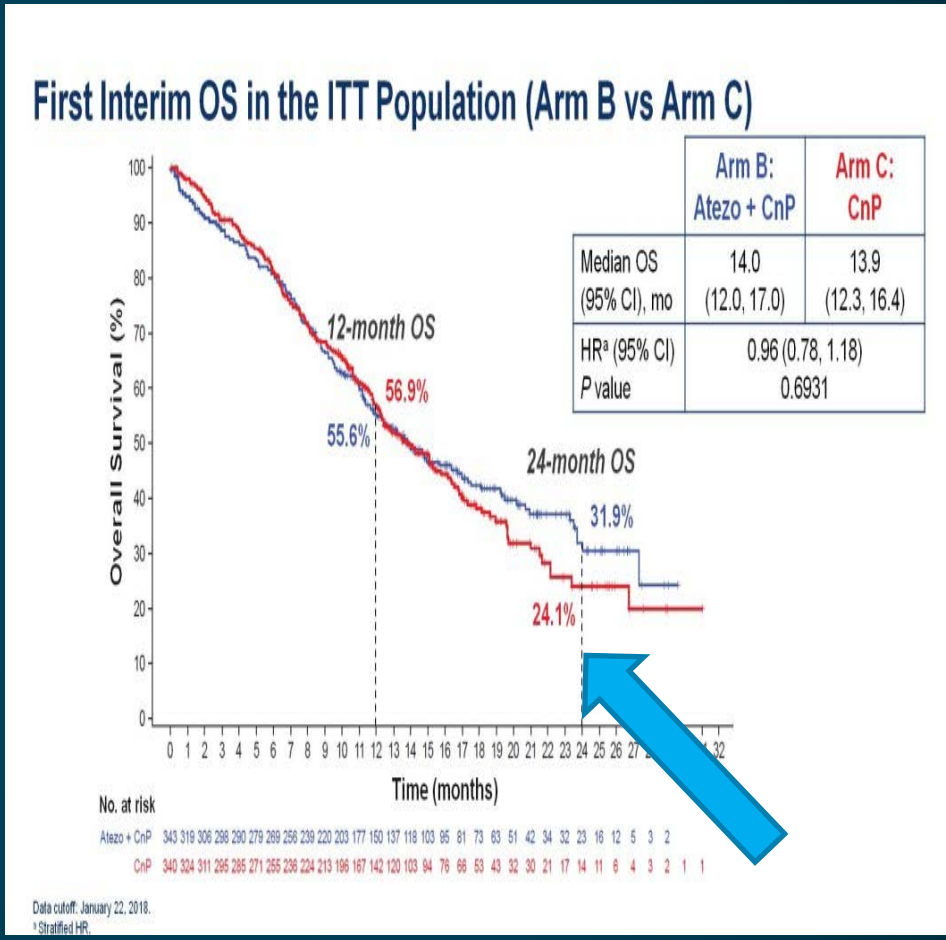
- Data cutoff date: Apr 3, 2018.

Cross Trial Comparison

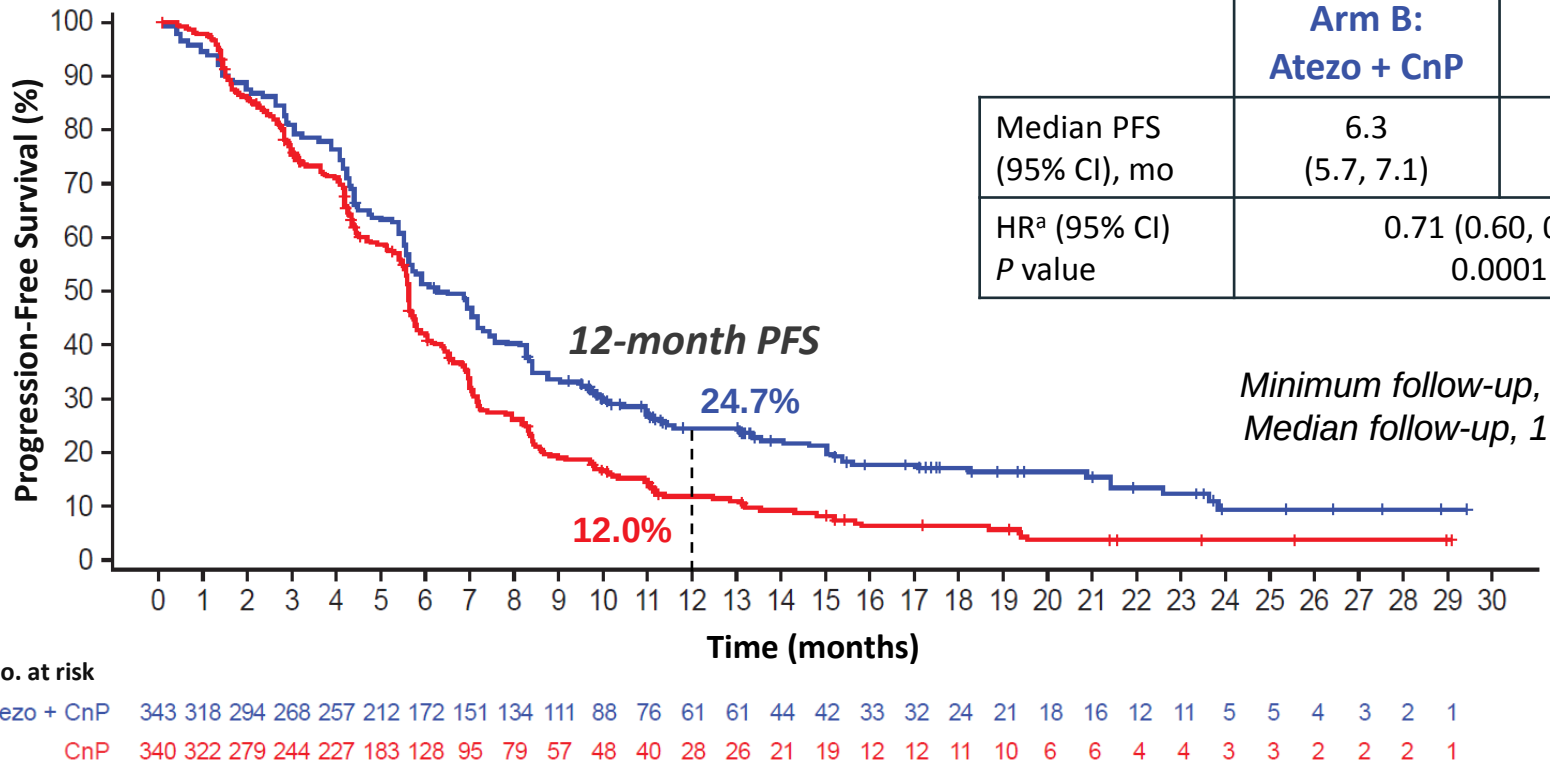
KEYNOTE-407 SQUAMOUS



IMPOWER-131 SQUAMOUS



IMPower 131:
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

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

Advanced Squamous NSCLC
PDL1 > 50%

Overall Survival in Subgroups: KN 024

Vertical dotted line represents HR in the overall population
Data cutoff: July 10, 2017

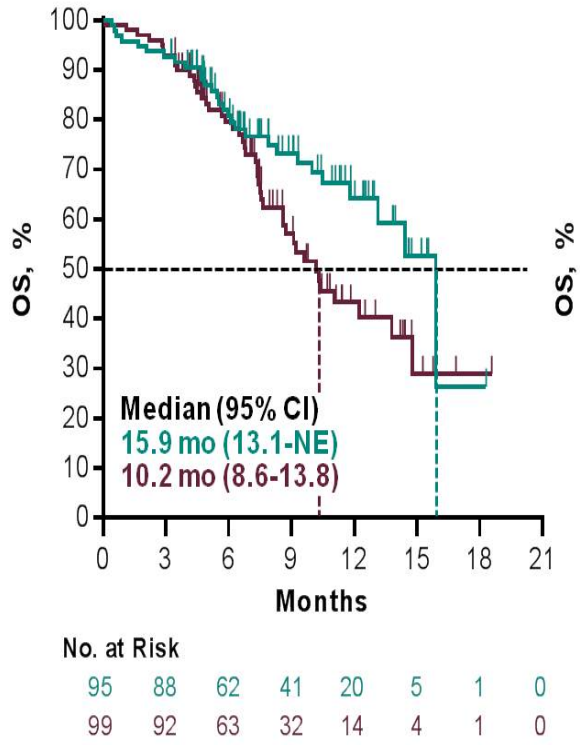
Brahmer, WCLC 2017

KEYNOTE 407

Overall Survival at IA2 by PD-L1 TPS

TPS <1%

	Events	HR (95% CI)
Pembro + Chemo	30.5%	0.61 (0.38-0.98)
Placebo + Chemo	44.4%	

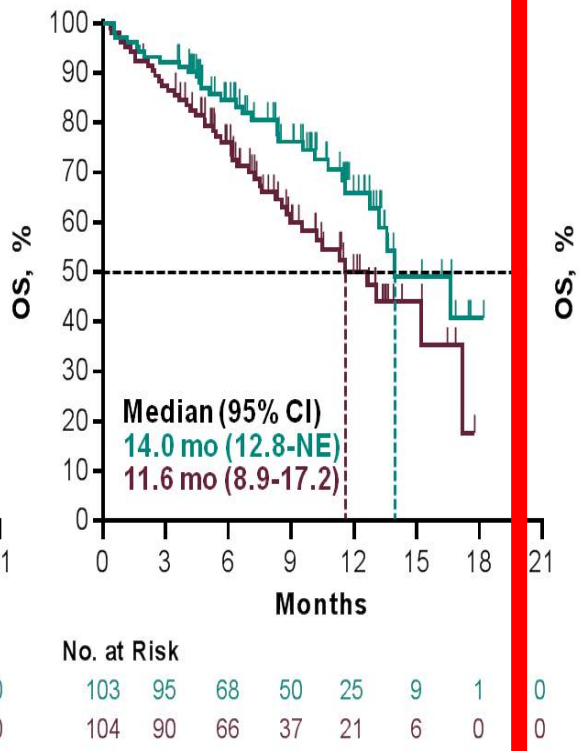


No. at Risk

95	88	62	41	20	5	1	0
99	92	63	32	14	4	1	0

TPS 1-49%

	Events	HR (95% CI)
Pembro + Chemo	30.1%	0.57 (0.36-0.90)
Placebo + Chemo	43.3%	

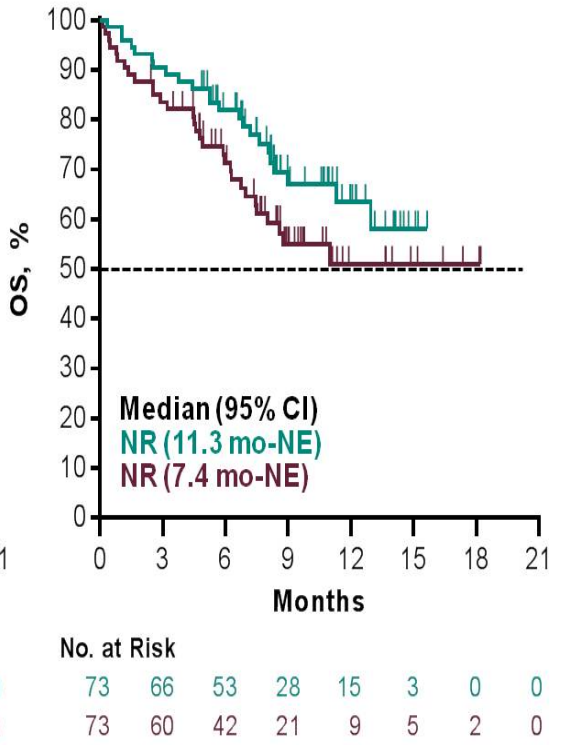


No. at Risk

103	95	68	50	25	9	1	0
104	90	66	37	21	6	0	0

TPS ≥50%

	Events	HR (95% CI)
Pembro + Chemo	31.5%	0.64 (0.37-1.10)
Placebo + Chemo	41.1%	



No. at Risk

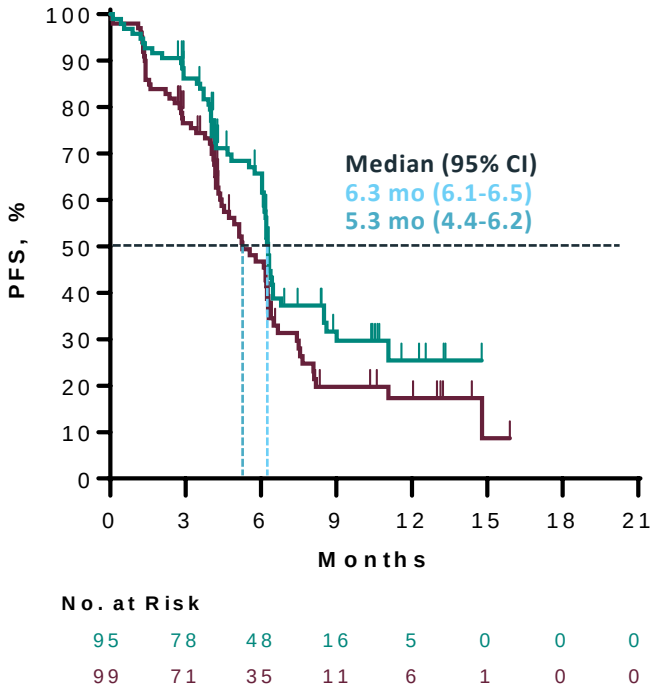
73	66	53	28	15	3	0	0
73	60	42	21	9	5	2	0

Data cutoff date: Apr 3, 2018.

KN 407: Progression-Free Survival by PD-L1 TPS (RECIST v1.1, BICR)

TPS <1%

	Events	HR (95% CI)
Pembro + Chemo	57.9%	0.68 (0.47-0.98)
Placebo + Chemo	67.7%	

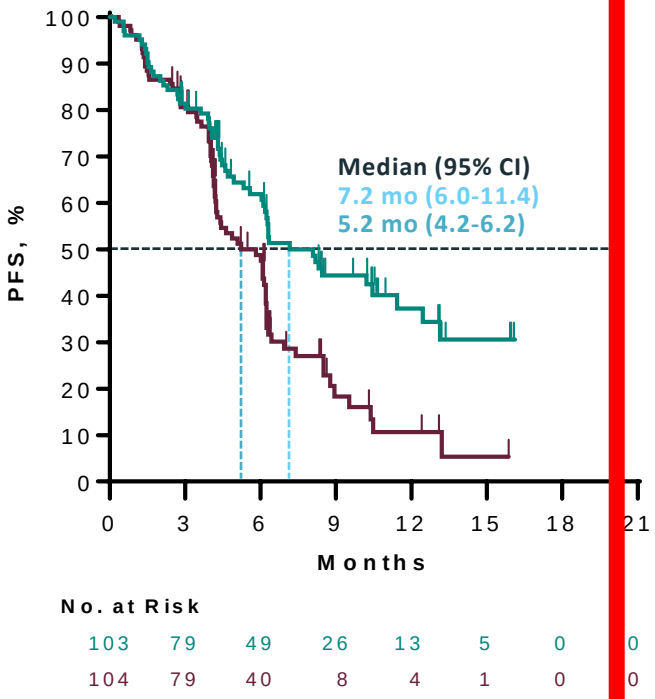


No. at Risk

95	78	48	16	5	0	0	0
99	71	35	11	6	1	0	0

TPS 1-49%

	Events	HR (95% CI)
Pembro + Chemo	52.4%	0.56 (0.39-0.80)
Placebo + Chemo	70.2%	

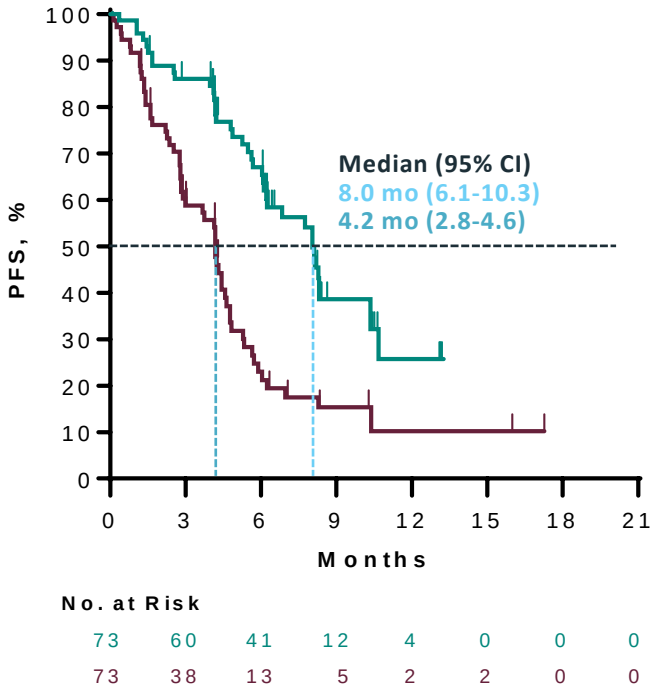


No. at Risk

103	79	49	26	13	5	0	0
104	79	40	8	4	1	0	0

TPS ≥50%

	Events	HR (95% CI)
Pembro + Chemo	53.4%	0.37 (0.24-0.58)
Placebo + Chemo	75.3%	



No. at Risk

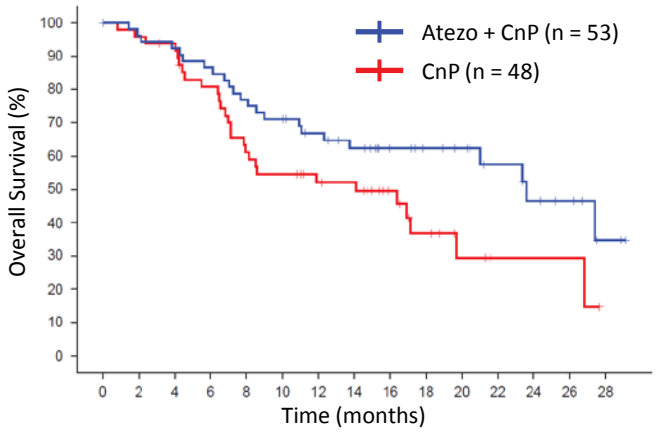
73	60	41	12	4	0	0	0
73	38	13	5	2	2	0	0

- BICR, blinded, independent central review. Data cutoff date: Apr 3, 2018.

IMPOWER 131

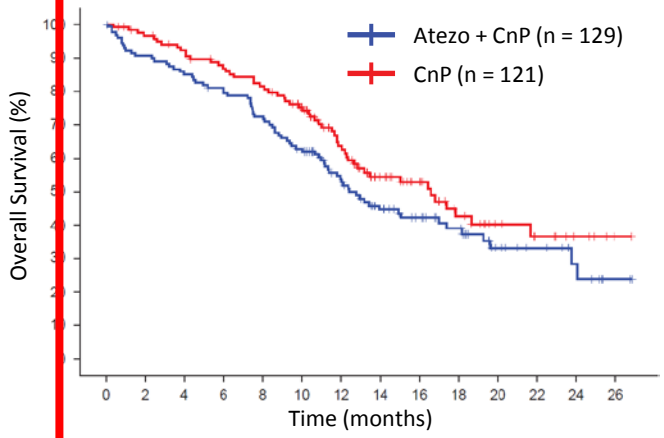
First Interim OS in PD-L1 Subgroups (Arm B vs Arm C)

PD-L1 High TC3 or IC3



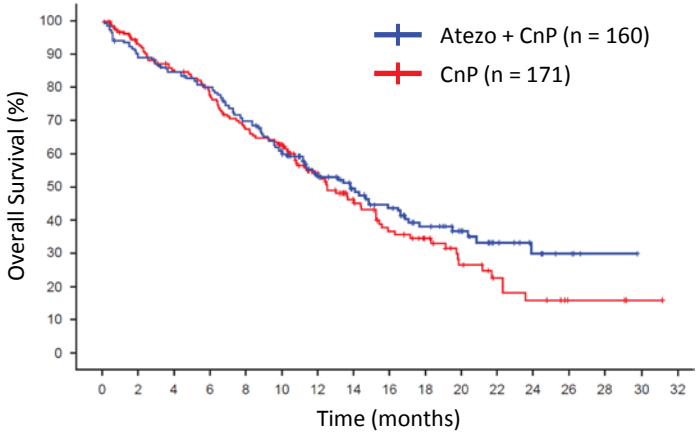
	Atezo + CnP	CnP
12-month OS	67%	52%
24-month OS	47%	30%
Median OS, mo	23.6	14.1
HR[a] (95% CI)	0.56 (0.32, 0.99)	

PD-L1 Low TC1/2 or IC1/2



	Atezo + CnP	CnP
12-month OS	54%	64%
24-month OS	28%	37%
Median OS, mo	12.4	16.6
HR[a] (95% CI)	1.34 (0.95, 1.90)	

PD-L1 Negative TC0 and IC0

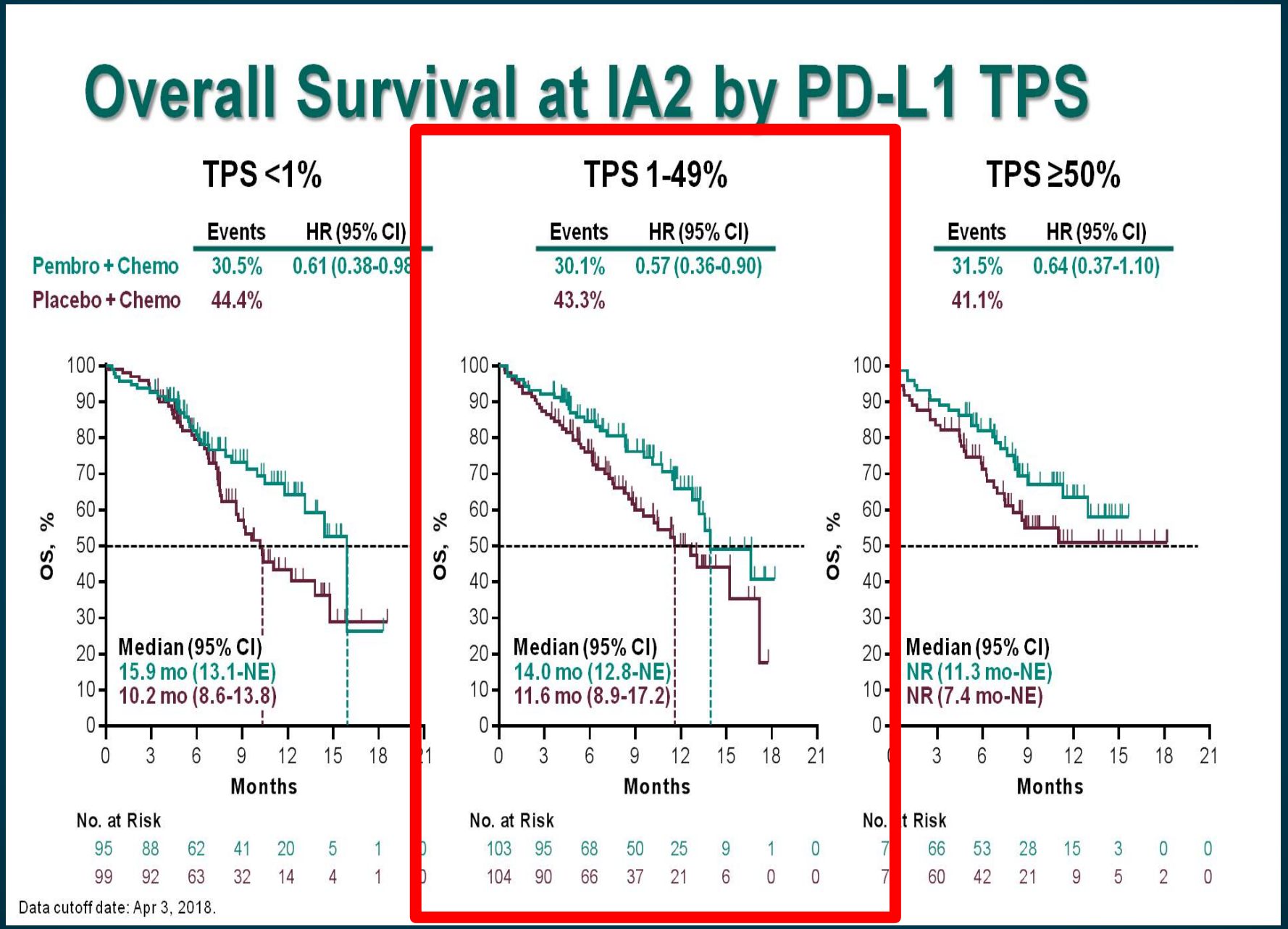


	Atezo + CnP	CnP
12-month OS	53%	53%
24-month OS	30%	16%
Median OS, mo	13.8	12.5
HR[a] (95% CI)	0.86 (0.65, 1.15)	

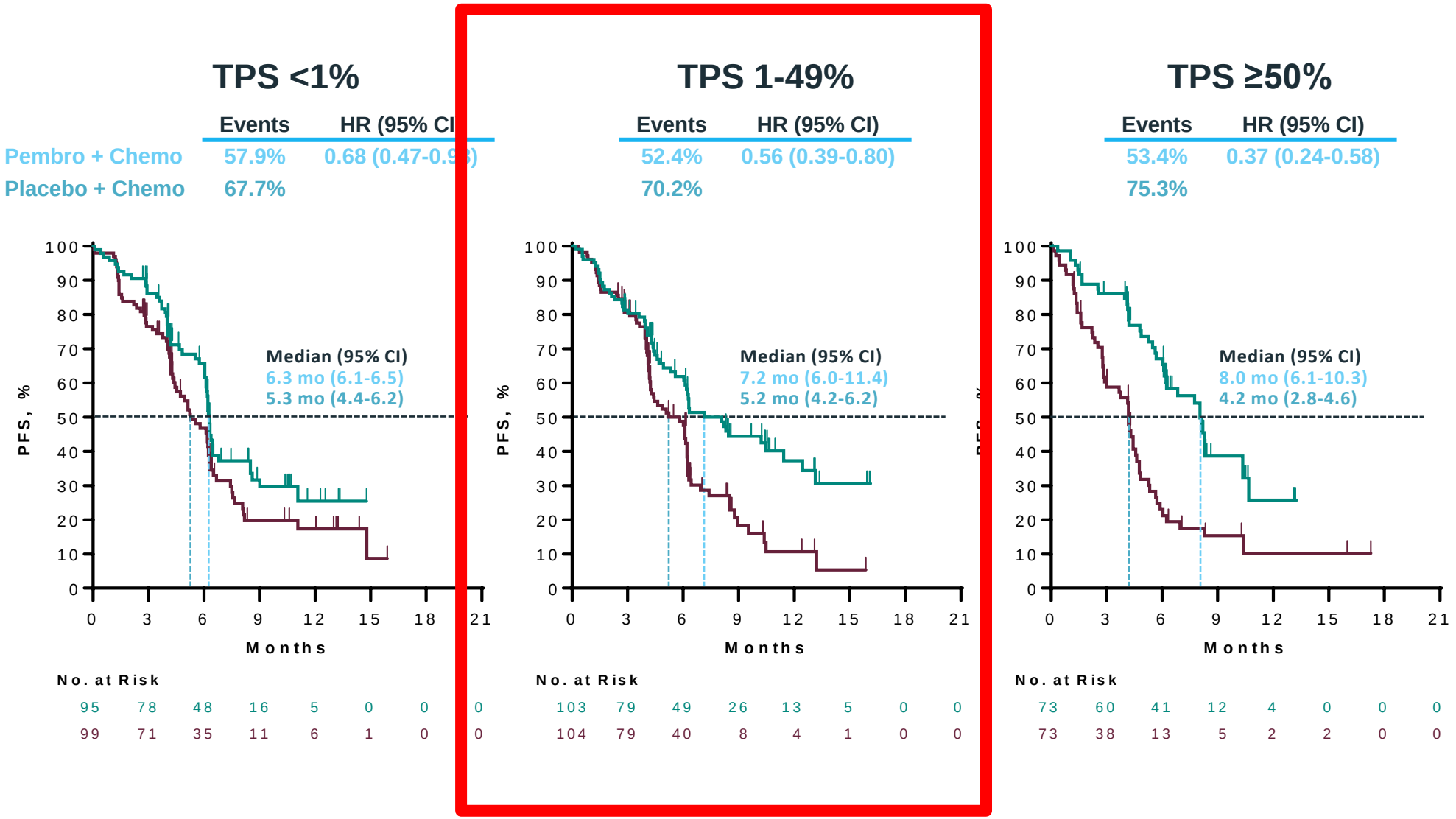
Data cutoff: January 22, 2018.
[a] Unstratified HR.

Advanced Squamous NSCLC
PDL1 1-49%

KEYNOTE 407


Overall Survival at IA2 by PD-L1 TPS
TPS <1%
Events
HR (95% CI)
Pembro + Chemo
30.5%
0.61 (0.38-0.98
Placebo + Chemo
44.4%
OS, %
Median (95% CI)
15.9 mo (13.1-NE)
10.2 mo (8.6-13.8)
Months
No. at Risk
95 88 62 41 20 5 1 0
99 92 63 32 14 4 1 0
TPS 1-49%
Events
HR (95% CI)
30.1%
0.57 (0.36-0.90)
43.3%
OS, %
Median (95% CI)
14.0 mo (12.8-NE)
11.6 mo (8.9-17.2)
Months
No. at Risk
103 95 68 50 25 9 1 0
104 90 66 37 21 6 0 0
TPS ≥50%
Events
HR (95% CI)
31.5%
0.64 (0.37-1.10)
41.1%
OS, %
Median (95% CI)
NR (11.3 mo-NE)
NR (7.4 mo-NE)
Months
No. at Risk
66 53 28 15 3 0 0
60 42 21 9 5 2 0
Data cutoff date: Apr 3, 2018.

KN 407: Progression-Free Survival by PD-L1 TPS (RECIST v1.1, BICR)



- BICR, blinded, independent central review. Data cutoff date: Apr 3, 2018.

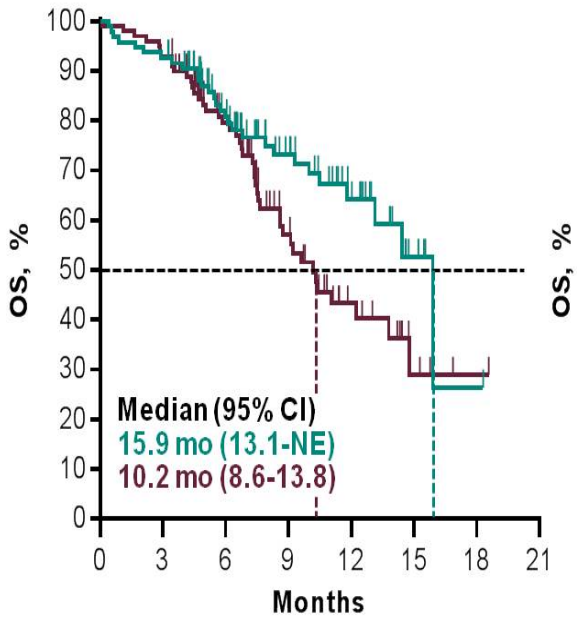
Advanced Squamous NSCLC
PDL1 <1%

KEYNOTE 407

Overall Survival at IA2 by PD-L1 TPS

TPS <1%

	Events	HR (95% CI)
Pembro + Chemo	30.5%	0.61 (0.38-0.98)
Placebo + Chemo	44.4%	



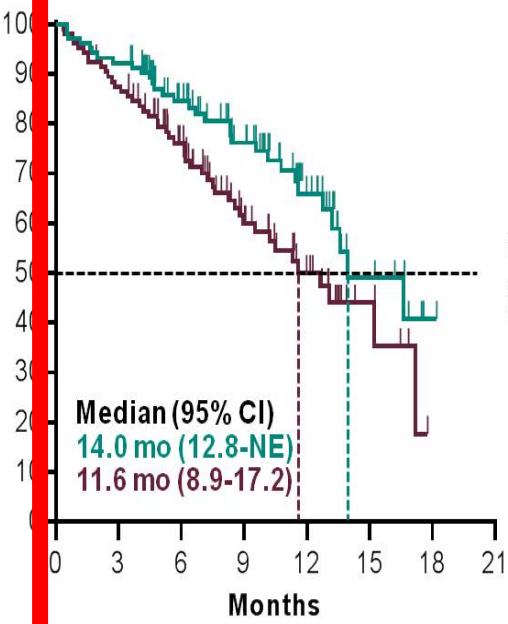
No. at Risk

95	88	62	41	20	5	1	0
99	92	63	32	14	4	1	0

Data cutoff date: Apr 3, 2018

TPS 1-49%

	Events	HR (95% CI)
Pembro + Chemo	30.1%	0.57 (0.36-0.90)
Placebo + Chemo	43.3%	

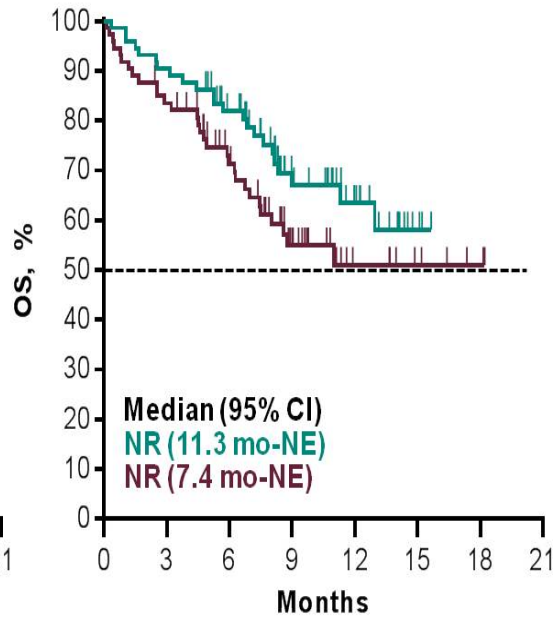


No. at Risk

03	95	68	50	25	9	1	0
04	90	66	37	21	6	0	0

TPS ≥50%

	Events	HR (95% CI)
Pembro + Chemo	31.5%	0.64 (0.37-1.10)
Placebo + Chemo	41.1%	



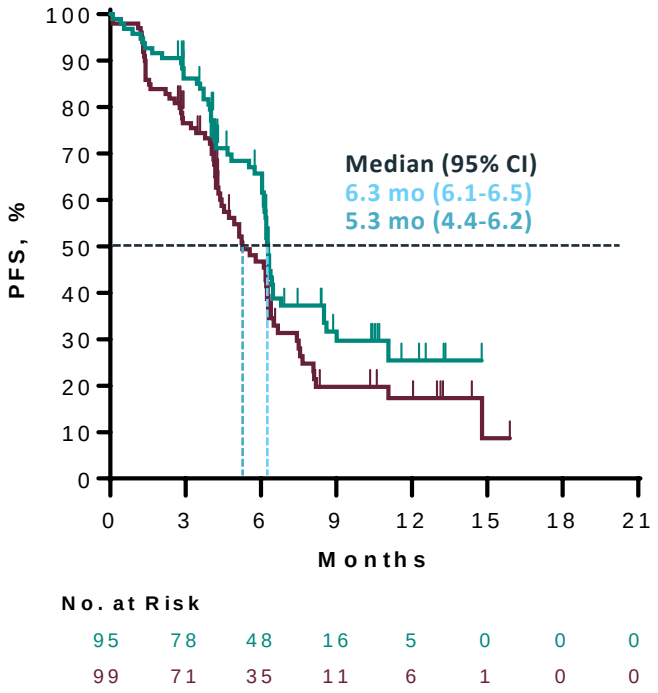
No. at Risk

73	66	53	28	15	3	0	0
73	60	42	21	9	5	2	0

KN 407: Progression-Free Survival by PD-L1 TPS (RECIST v1.1, BICR)

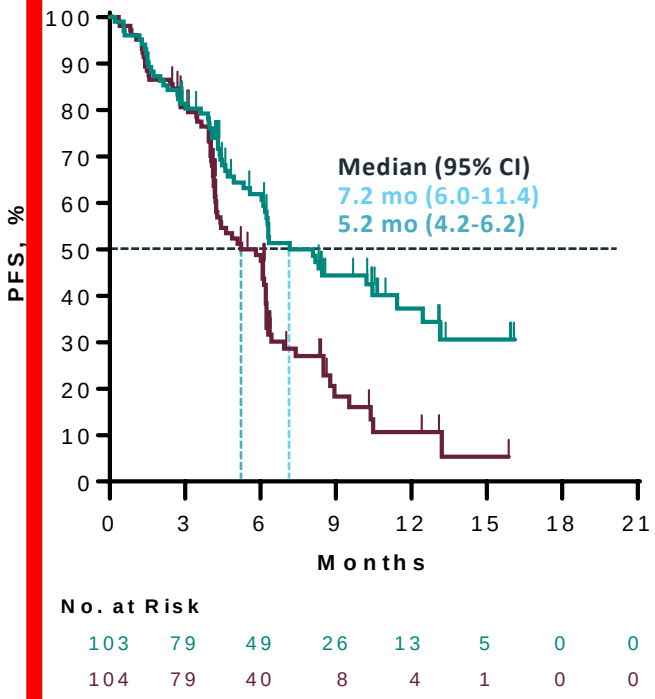
TPS <1%

	Events	HR (95% CI)
Pembro + Chemo	57.9%	0.68 (0.47-0.98)
Placebo + Chemo	67.7%	



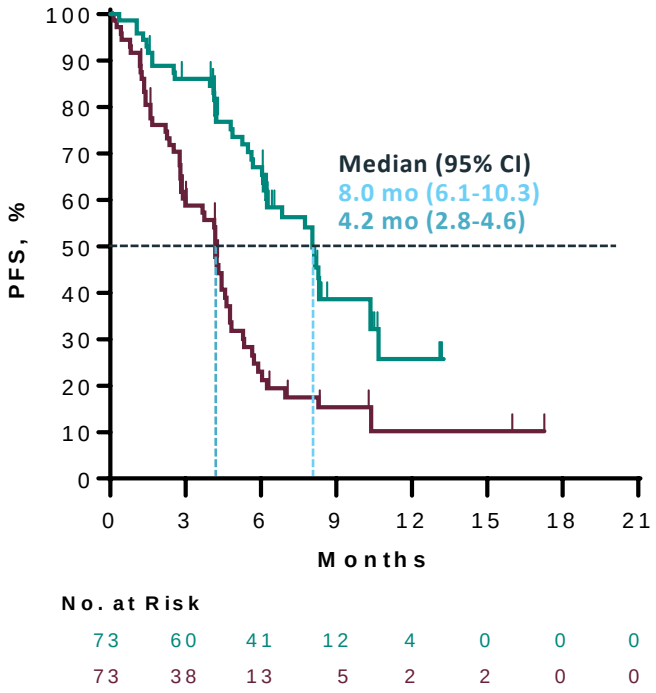
TPS 1-49%

	Events	HR (95% CI)
Pembro + Chemo	52.4%	0.56 (0.39-0.80)
Placebo + Chemo	70.2%	



TPS ≥50%

	Events	HR (95% CI)
Pembro + Chemo	53.4%	0.37 (0.24-0.58)
Placebo + Chemo	75.3%	



- BICR, blinded, independent central review. Data cutoff date: Apr 3, 2018.

Advanced NCLC PDL1 Agnostic TKI-Refractory

EGFR mt

ALK translocation

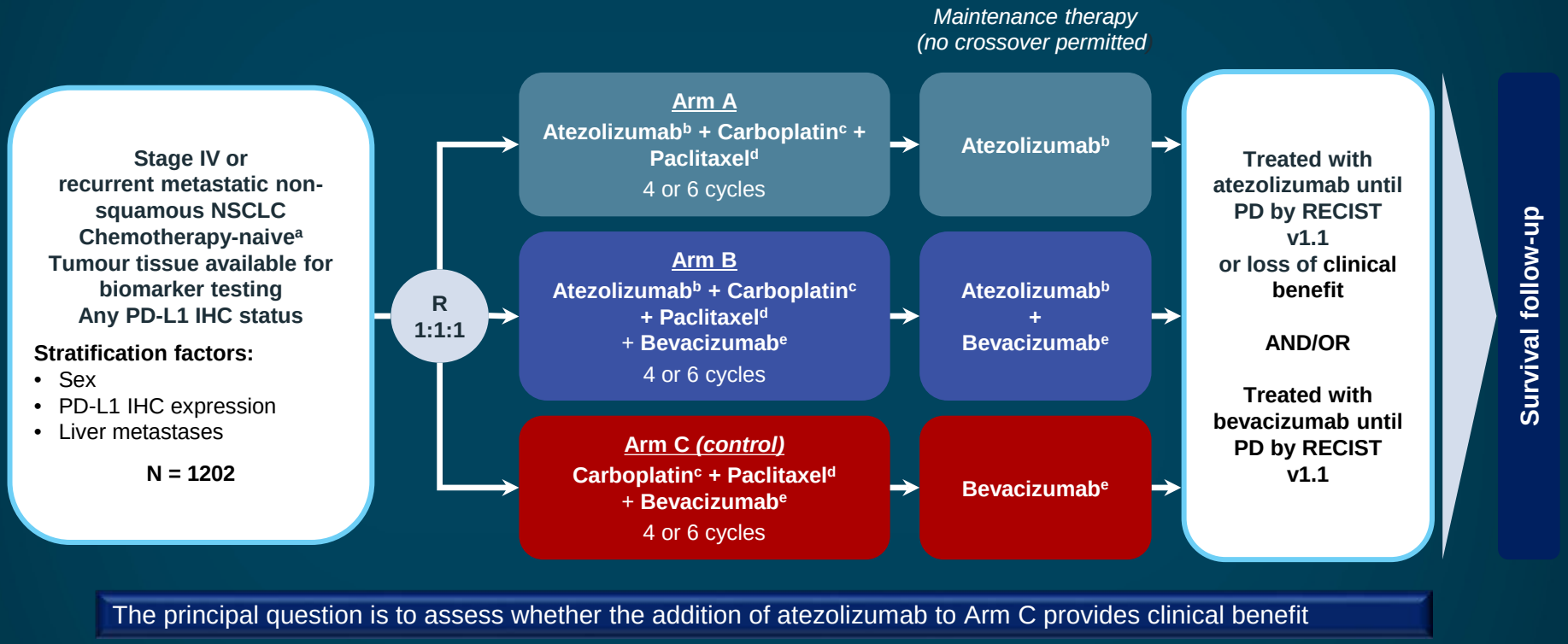
?? ROS1, RET, etc

Expanding the Role of Checkpoint Inhibitors in Non-Squamous NSCLC

Angiogenesis Inhibition

ALK and EGFR (+) Pts

IMpower150 study design



[a] Patients with a sensitising *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/m^2 IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.

- Unique trial in that It allowed pirior TKI for oncogenic drivers
- Only recent study in front-line Tx-naïve, advanced NSCLC to test IO in combination with Mab targeting angioenesis

Reck M et al ESMO 2017

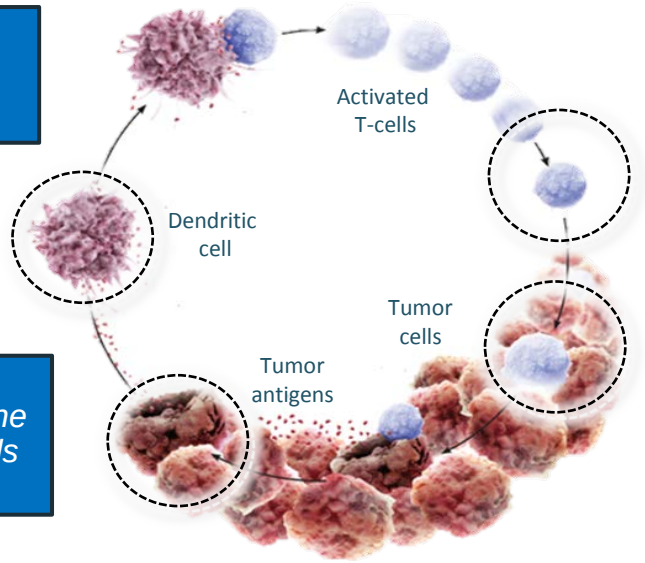
Reck M, et al. IMpower150 PFS analysis.

Rationale for the Combination of Atezolizumab + Bevacizumab + Chemotherapyr the Combination of Atezolizumab + Bevacizumab + Chemotherapy

- In addition to its known anti-angiogenic effects[1], bevacizumab's inhibition of VEGF has immune modulatory effects[2]

Inhibition of VEGF can promote T-cell priming and activation via dendritic cell maturation[2-4]

Normalization of the tumor vasculature through VEGF inhibition increases T-cell tumor infiltration[2,5-8]



Tumor cell killing by chemotherapy may expose the immune system to high levels of cancer cell antigens[9]

VEGF blockade can establish an immune-permissive tumor microenvironment by decreasing myeloid-derived suppressor cell and regulatory T cell populations[2,8,10-13]

- Atezolizumab's T-cell mediated cancer cell killing may be enhanced through bevacizumab's reversal of VEGF-mediated immunosuppression

1. Ferrara N, et al. *Nat Rev Drug Discov*, 2004. 2. Hegde PS, et al. *Semin Cancer Biol*. 2017 . 3. Gabrilovich DI, et al. *Nat Med*, 1996. 4. Oyama T, et al. *J Immunol*, 1998. 5. Goel S, et al. *Physiol Rev*, 2011. 6. Motz GT, et al. *Nat Med*, 2014. 7. Hodi FS, et al. *Cancer Immunol Res*, 2014. 8. Wallin JJ, et al. *Nat Commun*, 2016. 9. Zitvogel L, et al. *Immunity*, 2013. 10. Gabrilovich DI, Nagaraj S. *Nat Rev Immunol*, 2009. 11. Roland CL, et al. *PLoS One*, 2009. 12. Facciabene A, et al. *Nature*, 2011. 13. Voron T, et al. *J Exp Med*, 2015. Figure adapted from Chen DS, Mellman I. *Immunity*, 2013.

IMPower 150: Baseline Demographics

Baseline characteristics	Arm A: atezo + CP (N = 402)	Arm B: atezo + bev + CP (N = 400)	Arm C (*control*): bev + CP (N = 400)
Median age (range), years	63 (32-85)	63 (31-89)	63 (31-90)
Sex, male, n (%)	241 (60%)	240 (60%)	239 (60%)
ECOG PS, 0, n (%)	180 (45%)	159 (40%)	179 (45%)
Tobacco use history, n (%)			
Current smoker | Previous smoker	98 (24%) | 227 (57%)	90 (23%) | 228 (57%)	92 (23%) | 231 (58%)
Never smoker	77 (19%)	82 (21%)	77 (19%)
Liver metastases, yes, n (%)	53 (13%)	52 (13%)	57 (14%)
EGFR mutation, positive, n (%)	45 (11%)	34[a] (9%)	45 (11%)
EML4-ALK rearrangement, positive, n (%)	9 (2%)	11 (3%)	20 (5%)
Teff gene signature expression, high, n (%)[b]	177 (44%)	166 (42%)	148 (37%)
PD-L1 expression, n (%)[c]			
TC3 or IC3	68 (17%)	75 (19%)	73 (18%)
TC2/3 or IC2/3	137 (34%)	140 (35%)	133 (33%)
TC1/2/3 or IC1/2/3	213 (53%)	209 (52%)	195 (49%)
TC0 and IC0	188 (47%)	191 (48%)	205 (51%)

- Patients baseline characteristics were balanced across all arms

IC, tumour-infiltrating immune cells; TC, tumour cells.
[a] One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab. [b] The Teff gene signature high cut-off ≥ –1.91 was used. [c] 1 patient in Arm A had unknown PD-L1 IHC expression. TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1+; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1+; TC1/2/3 or IC1/2/3 = TC or IC ≥ 1% PD-L1+; TC0 and IC0 = TC and IC < 1% PD-L1+.
Data cutoff: January 22, 2018

Reck M et al ESMO 2017 → Socinski ASCO, NEJM 2018

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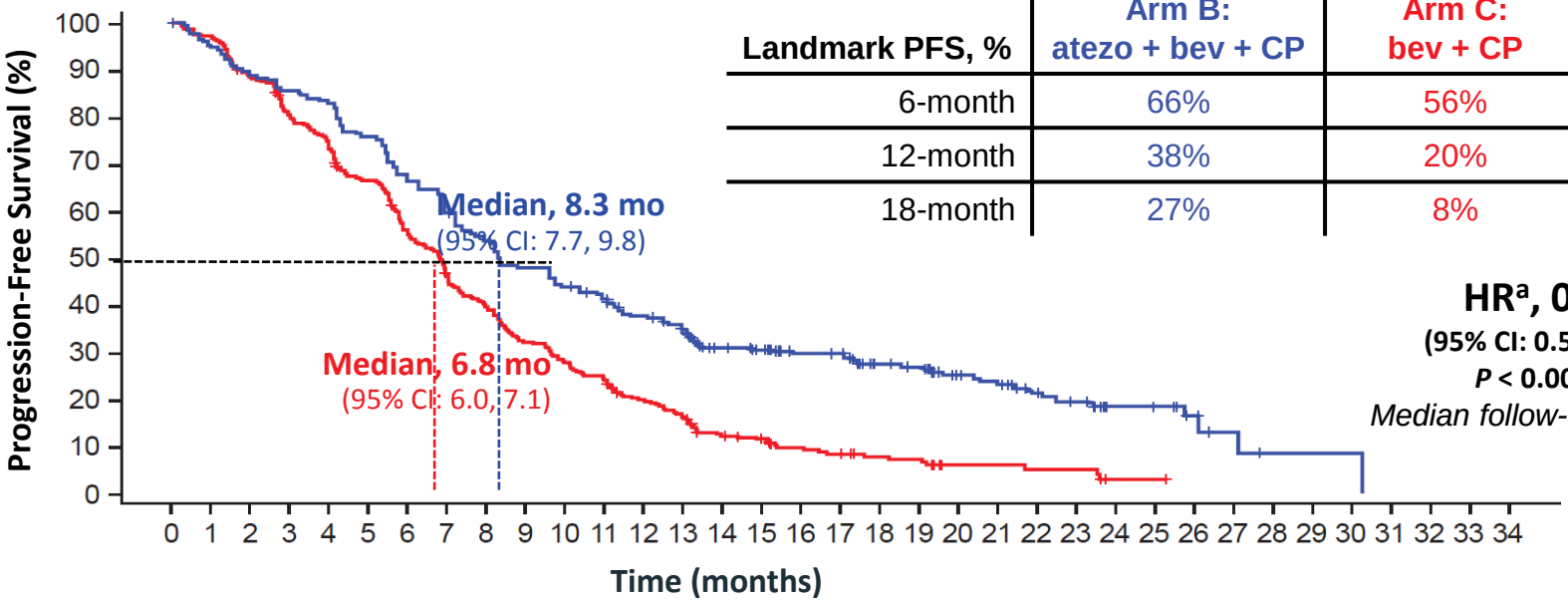
Data cutoff: January 22, 2018

Reck M et al ESMO 2017 → Socinski ASCO, NEJM 2018

Updated PFS Analysis in the ITT-WT (Arm B vs Arm C)



Landmark PFS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
6-month	66%	56%
12-month	38%	20%
18-month	27%	8%

HR[a], 0.59
(95% CI: 0.50, 0.70)
***P* < 0.0001[b]**
Median follow-up: ~20 mo

No. at Risk

Atezo+Bev+CP	359	336	315	301	293	267	234	213	190	168	154	146	125	112	85	80	69	68	53	50	37	33	24	20	12	11	6	3	1	1	1
Bev+CP	337	323	294	263	244	215	180	148	127	103	89	78	61	50	35	29	21	18	14	13	6	6	5	5	1	1					

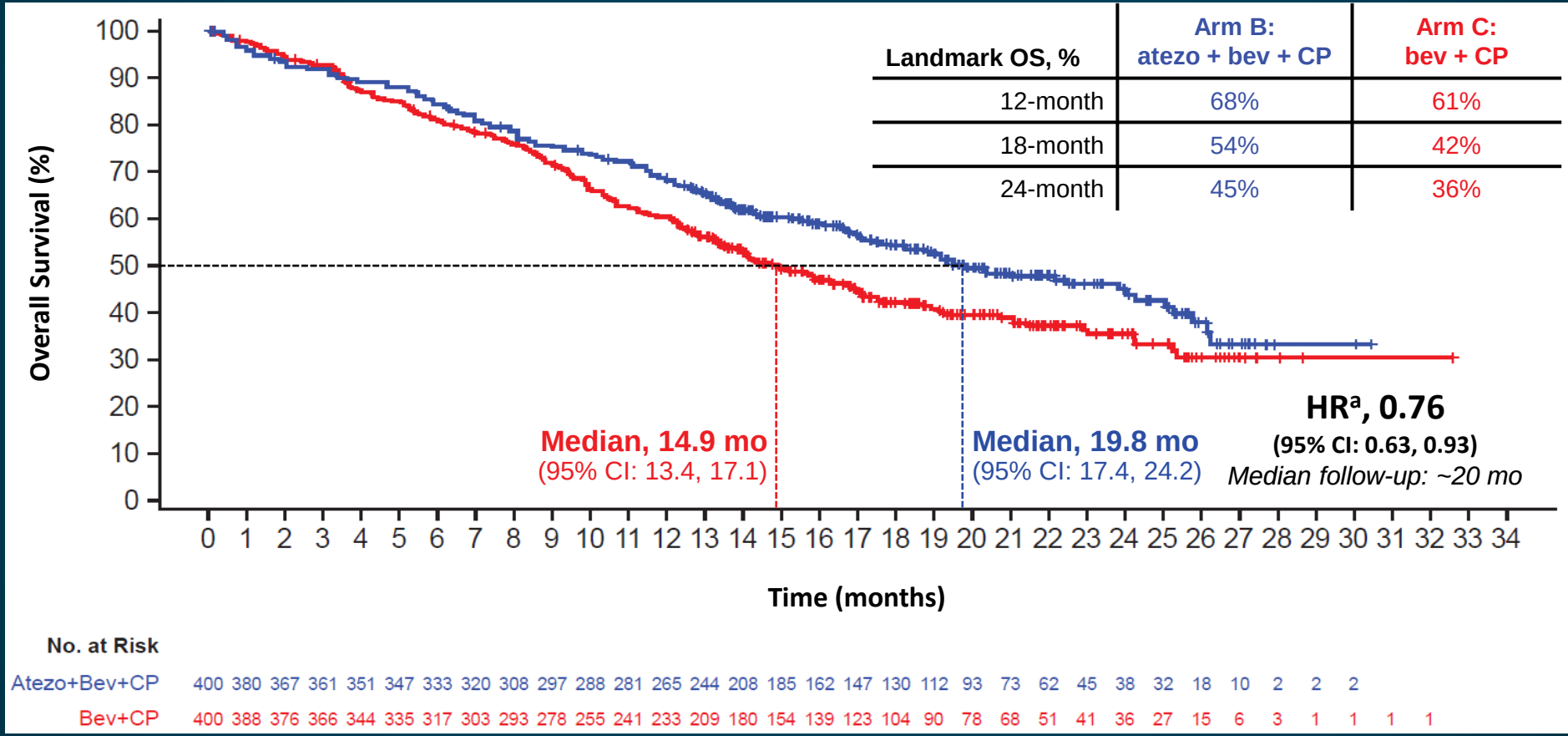
- Statistically significant and clinically meaningful PFS benefit with atezolizumab + bevacizumab + chemotherapy vs bevacizumab + chemotherapy was previously observed[1] and continued to improve with additional follow-up

[a] Stratified HR. [b] For descriptive purposes only. Data cutoff: January 22, 2018
1. Reck M, et al. ESMO IO 2017 [abstract LBA1_PR].

Reck M et al ESMO 2017 → Socinski ASCO, NEJM 2018

OS in ITT-WT (Arm B vs Arm C)

OS in the ITT (Arm B vs Arm C)



Landmark OS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
12-month	68%	61%
18-month	54%	42%
24-month	45%	36%

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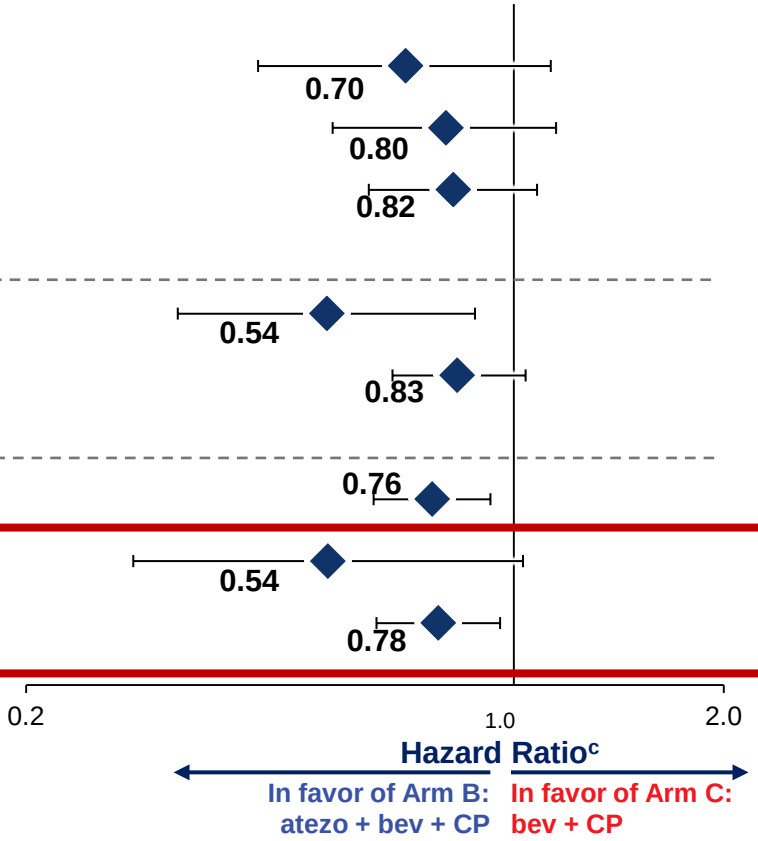
- Clinically meaningful OS benefit with atezolizumab + bevacizumab + chemotherapy vs bevacizumab + chemotherapy was observed in all patients

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

Reck M, et al. IMpower150 PFS analysis.

IMPower 150: OS in Key Subgroups

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) WT	226 (32%)	20.3	16.4
PD-L1–Negative (TC0 and IC0) WT	339 (49%)	17.1	14.1
Liver Metastases WT	94 (14%)	13.2	9.1
No Liver Metastases WT	602 (86%)	19.8	16.7
ITT (including *EGFR/ALK*+)	800 (100%)	19.8	14.9
EGFR/ALK+ only	104[b] (13%)	NE	17.5
ITT-WT	696 (87%)	19.2	14.7



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] One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab.
[c] Stratified HR for ITT and ITT-WT; unstratified HR for all other subgroups. Data cutoff: January 22, 2018

Reck M et al ESMO 2017 → Socinski ASCO, NEJM 2018

IMPower 150: OS in Key Subgroups

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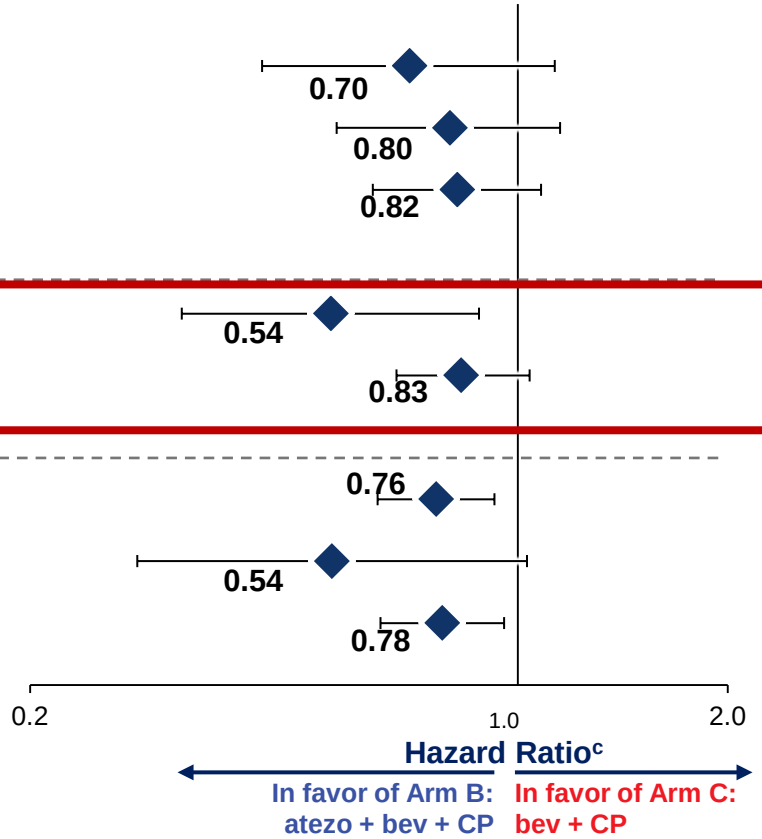

NE, not estimable.
[a] Prevalence % for PD-L1 IHC and liver metastases subgroups out of ITT-WT (n=696); prevalence of ITT, *EGFR/ALK*+, and ITT-WT out of ITT (n=800).
[b] One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab.
[c] Stratified HR for ITT and ITT-WT; unstratified HR for all other subgroups. Data cutoff: January 22, 2018

Reck M et al ESMO 2017 → Socinski ASCO, NEJM 2018

IMPower 150: Safety

Incidence, n (%)	Arm A: atezo + CP (n = 400)		Arm B: atezo + bev + CP (n = 393)		Arm C (*control*): bev + CP (n = 394)	
Median doses received (range), n						
Atezolizumab	10 (1-43)		12 (1-44)		NA	
Bevacizumab	NA		10 (1-44)		8 (1-38)	
Treatment-related AE[a]	377 (94%)		370 (94%)		377 (96%)	
Grade 3-4	172 (43%)		223 (57%)		191 (49%)	
Grade 5[b]	4 (1%)		11 (3%)		9 (2%)	
Serious AE	157 (39%)		174 (44%)		135 (34%)	
AE leading to withdrawal from any treatment	53 (13%)		133 (34%)		98 (25%)	
Immune-related AEs[c] in > 5 patients in any arm	**All grade**	**Grade 3-4**	**All grade**	**Grade 3-4**	**All grade**	**Grade 3-4**
Rash	119 (30%)	14 (4%)	117 (30%)	9 (2%)	53 (14%)	2 (1%)
Hepatitis[d]	42 (11%)	12 (3%)	54 (14%)	20 (5%)	29 (7%)	3 (1%)
Laboratory abnormalities	36 (9%)	10 (3%)	48 (12%)	18 (5%)	29 (7%)	3 (1%)
Hypothyroidism	34 (9%)	1 (<1%)	56 (14%)	1 (<1%)	18 (5%)	0
Pneumonitis[d]	23 (6%)	8 (2%)	13 (3%)	6 (2%)	5 (1%)	2 (1%)
Hyperthyroidism	11 (3%)	0	16 (4%)	1 (<1%)	5 (1%)	0
Colitis	3 (1%)	2 (1%)	11 (3%)	7 (2%)	2 (1%)	2 (1%)

- The safety profiles of ABCP and ACP were similar to A, B and C+P individually; no new safety signals were identified with the combinations

[a] Related to any study treatment. [b] Including fatal hemorrhagic AEs: Arm A: 2; Arm B: 6; Arm C: 3. [c] Immune-related AEs were defined using MedDRA Preferred Terms that included both diagnosed immune conditions and signs and symptoms potentially representative of immune-related events, regardless of investigator-assessed causality. [d] In Arm A, 1 patient had grade 5 acute hepatitis and 1 patient had grade 5 interstitial lung disease. Data cutoff: January 22, 2018

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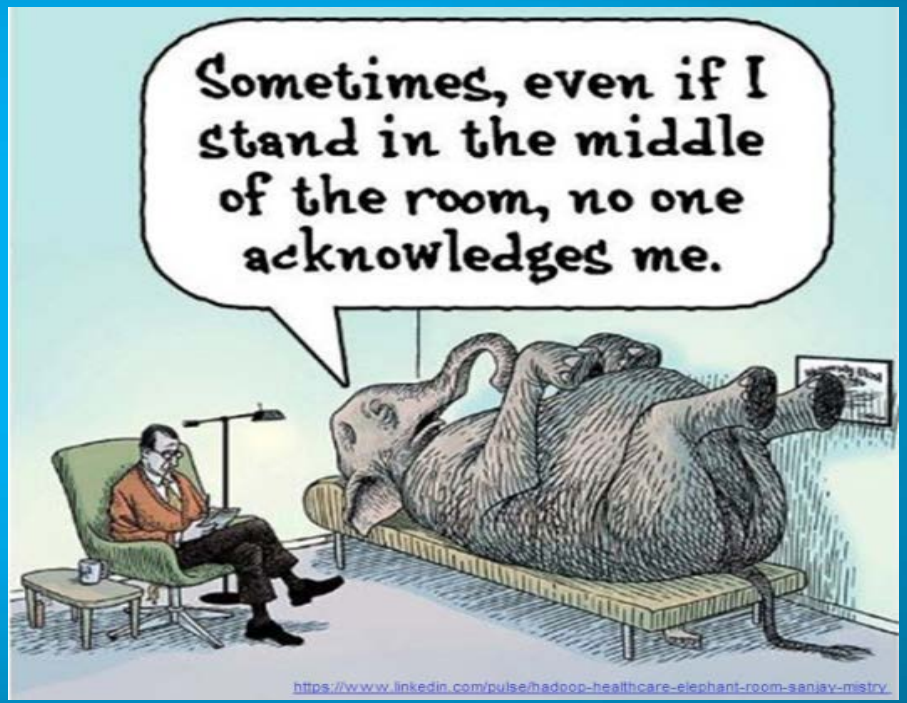
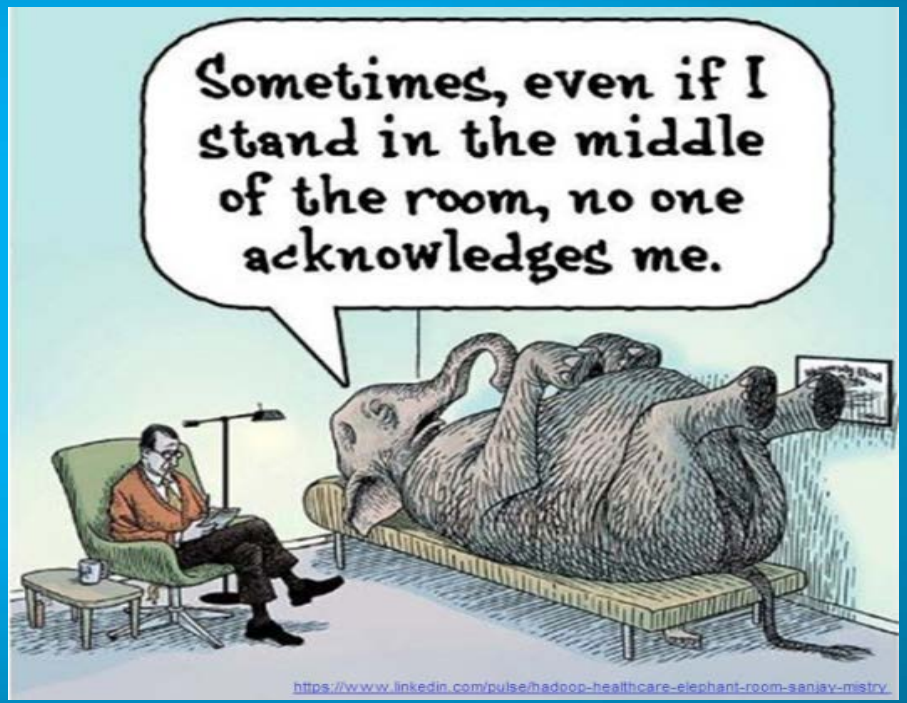
We cannot Ignore the "Elephant in the Room"



We cannot Ignore the "Elephant in the Room"

TMB



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

Matthew D. Hellmann,[1] Tudor-Eliade Ciuleanu,[2] Adam Pluzanski,[3] Jong Seok Lee,[4] Gregory A. Otterson,[5] Clarisse Audigier-Valette,[6] Elisa Minenza,[7] Helena Linardou,[8] Sjaak Burgers,[9] Pamela Salman,[10] Hossein Borghaei,[11] Suresh S. Ramalingam,[12] Julie Brahmer,[13] Martin Reck,[14] Kenneth J. O'Byrne,[15] William J. Geese,[16] George Green,[16] Han Chang,[16] Joseph Szustakowski,[16] Prabhu Bhagavatheeswaran,[16] Diane Healey,[16] Yali Fu,[16] Faith Nathan,[16] Luis Paz-Ares[17]

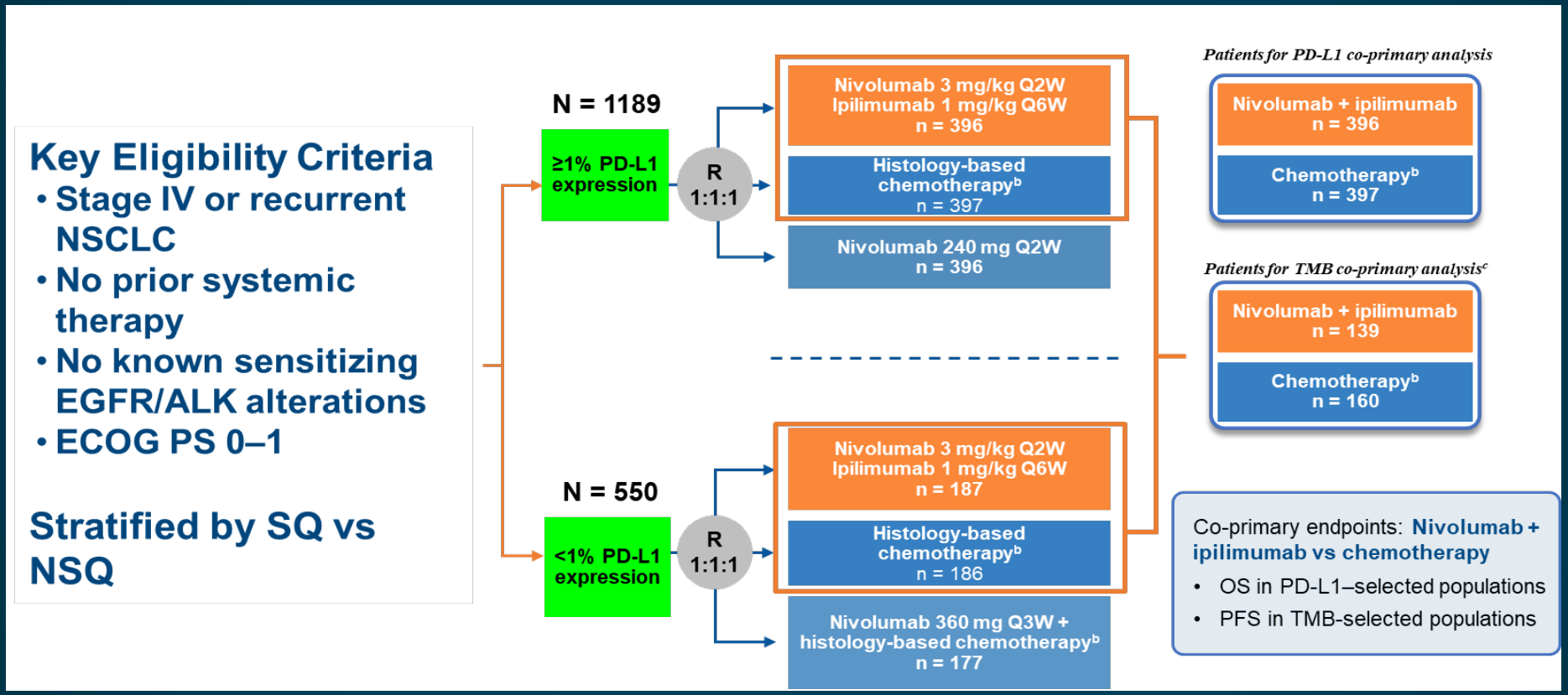
[1]Memorial Sloan Kettering Cancer Center Hospital, New York, NY, USA; [2]Prof. Dr. Ion Chiricuta Institute of Oncology and Universitatea de Medicina si Farmacie Iuliu Hatieganu, Cluj-napoca, Romania; [3]Centrum Onkologii–Instytut im. Marii Sklodowskiej-Curie, Warsaw, Poland; [4]Seoul National University Bundang Hospital, Seoul, South Korea; [5]The Ohio State University, Columbus, OH, USA; [6]Hôpital Sainte Musse, Toulon, France; [7]Ospedale Santa Maria della Misericordia, Perugia, Italy; [8]First Department of Oncology, Metropolitan Hospital, Athens, Greece; [9]Antoni Van Leeuwenhoek Ziekenhuis, Amsterdam, the Netherlands; [10]Fundación Arturo López Pérez, Santiago, Chile; [11]Fox Chase Cancer Center, Philadelphia, PA, USA; [12]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [13]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [14]LungenClinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; [15]Princess Alexandra Hospital, Brisbane, QLD, Australia; [16]Bristol-Myers Squibb, Princeton, NJ, USA; [17]Hospital Universitario 12 de Octubre, Centro Nacional de Investigaciones Oncológicas, Universidad Complutense, & CiberOnc, Madrid, Spain

Hellmann et al AACR, NEJM 2018

https://bit.ly/2Ld0jng

CheckMate 227 Part 1 Study Design[a]

CheckMate 227: Nivo + Ipi in 1L NSCLC With High TMB (≥10 mut/Mb)

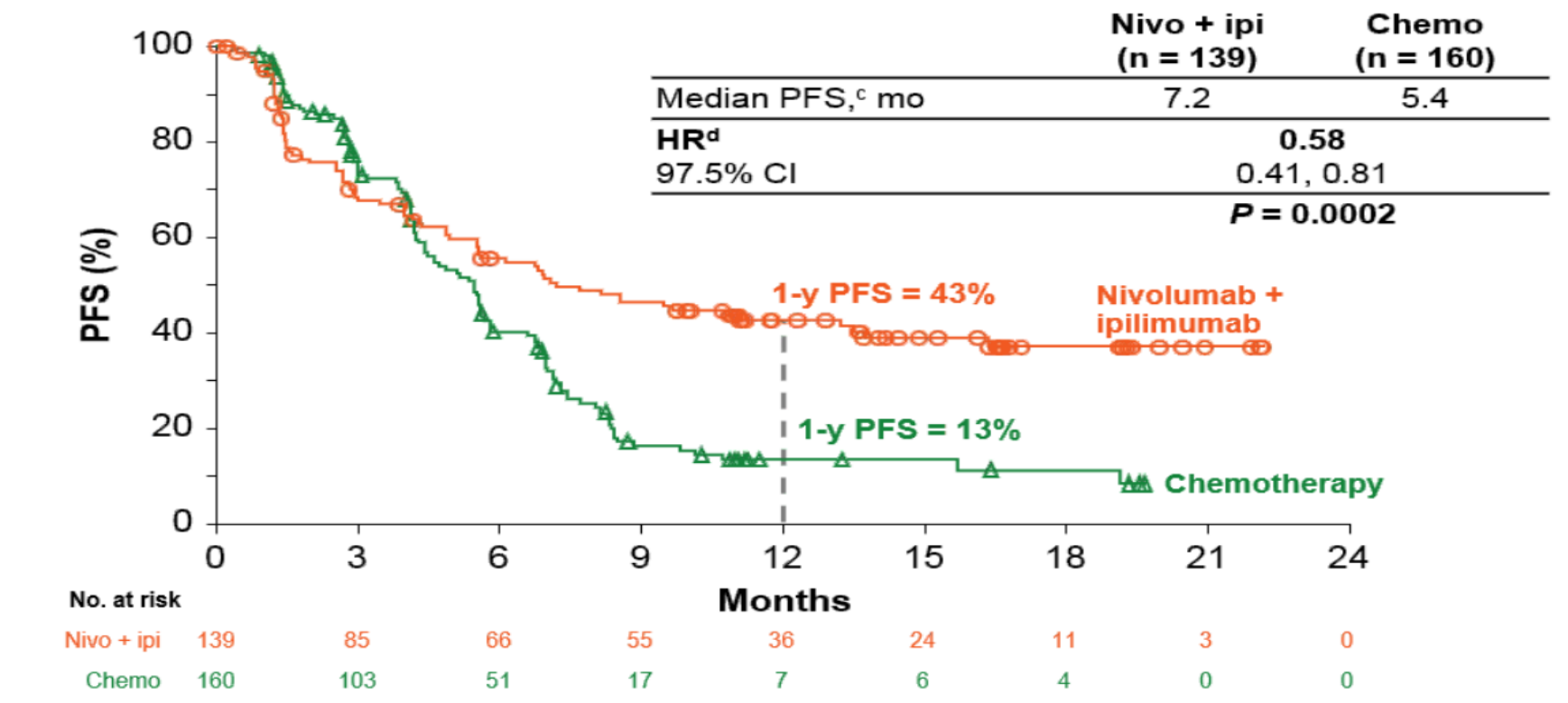


Database lock: January 24, 2018; minimum follow-up: 11.2 months

[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.

Hellmann MD, et al. AACR 2018. Abstract 350; Hellmann MD, et al. *N Engl J Med*. April 16, 2018.

Co-Primary Endpoint: PFS With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)[a,b]

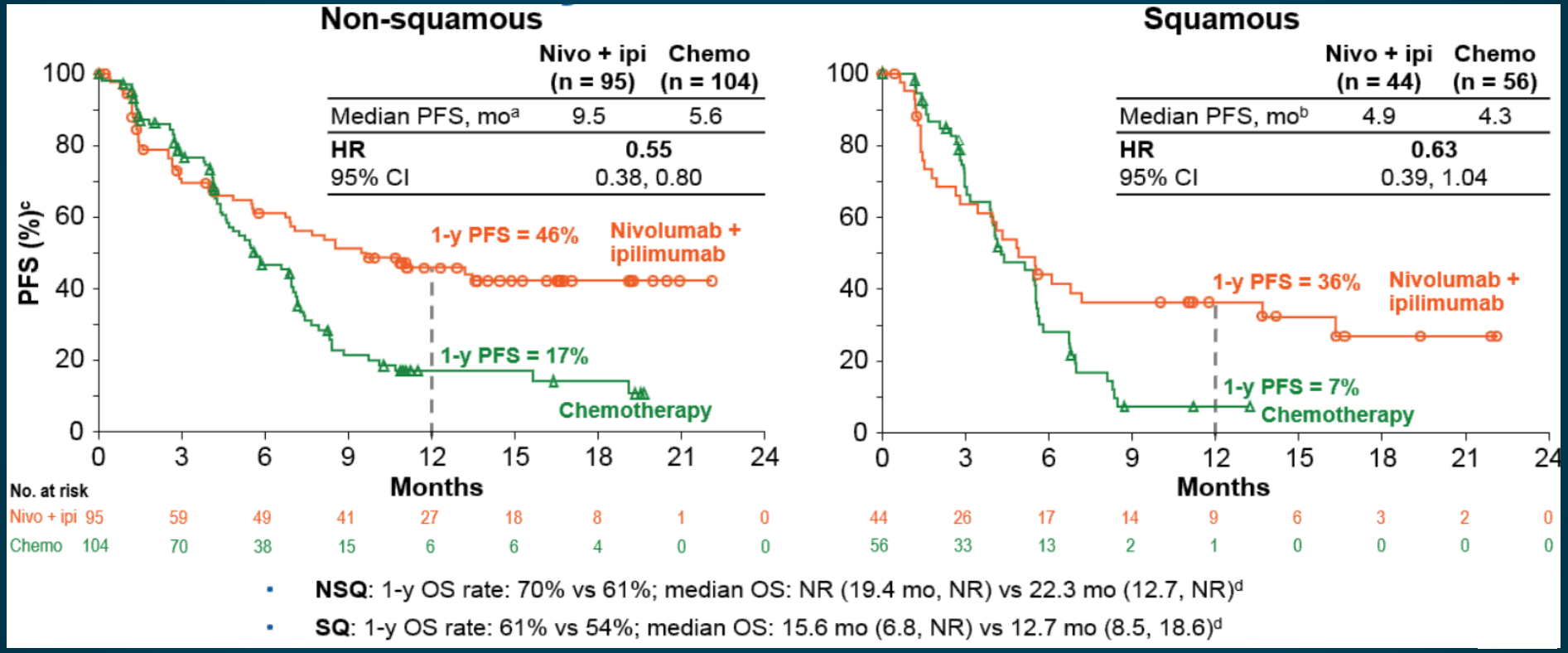


In patients with TMB <10 mut/Mb treated with nivo-ipi vs chemo, HR was 1.07 (95% CI, 0.84-1.35).

a Per blinded independent central review: median follow-up in coprimary analysis population was 13.6 mo for nivo-ipi and 13.2 mo for chemo. b *P* value for treatment interaction was 0.0018. c 95% CI: nivo-ipi (5.5, 13.2 mo), chemo (4.4, 5.8 mo). d95% CI: 0.43, 0.77 mo.

Hellmann MD, et al. AACR 2018. Abstract 350; Hellmann MD, et al. *N Engl J Med*. April 16, 2018.

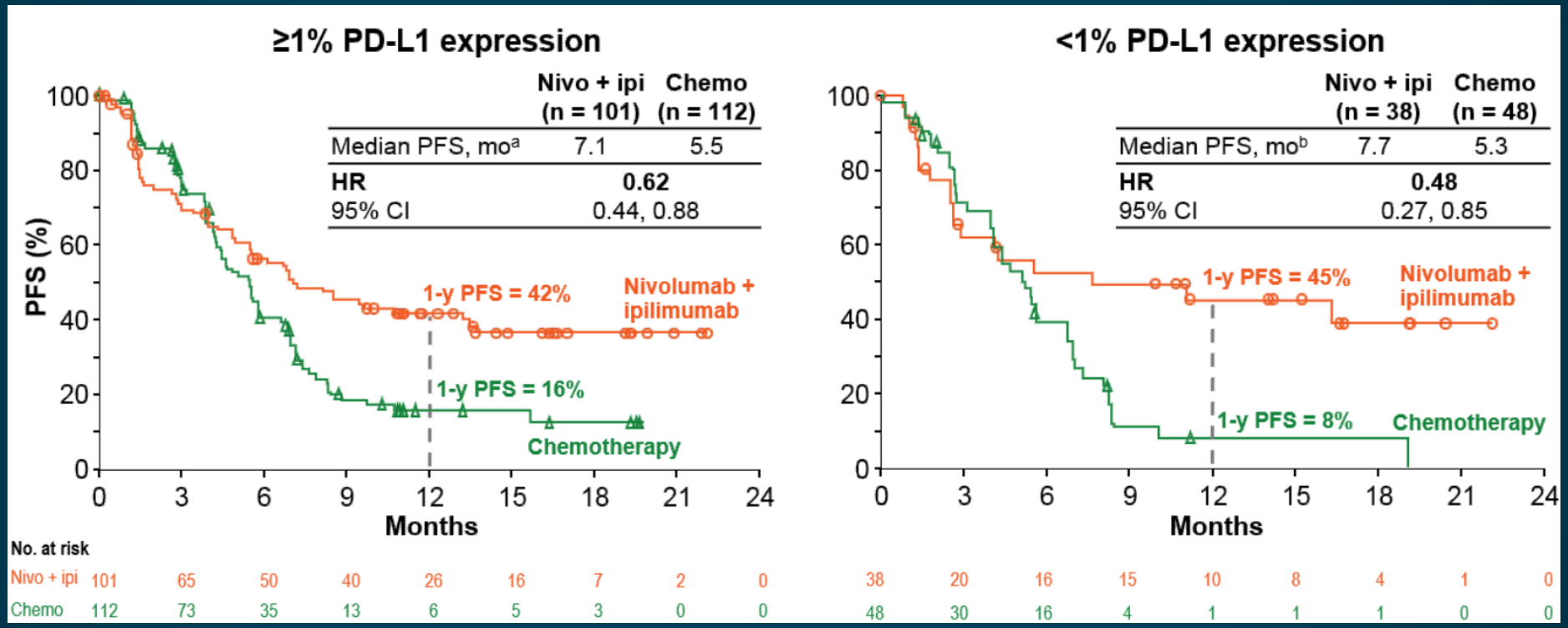
PFS in Patients With High TMB (≥10 mut/Mb) by Tumor Histology



a 95% CI: nivo-ipi (5.6 mo, NR), chemo (4.5, 7.0 mo). b 95% CI: nivo-ipi (2.7, 13.7 mo), chemo (3.2, 5.6 mo). c PFS: January 24, 2018 database lock for PFS. d OS: March 15, 2018 database lock for OS.

Hellmann MD, et al. AACR 2018. Abstract 350; Hellmann MD, et al. *N Engl J Med*. April 16, 2018.

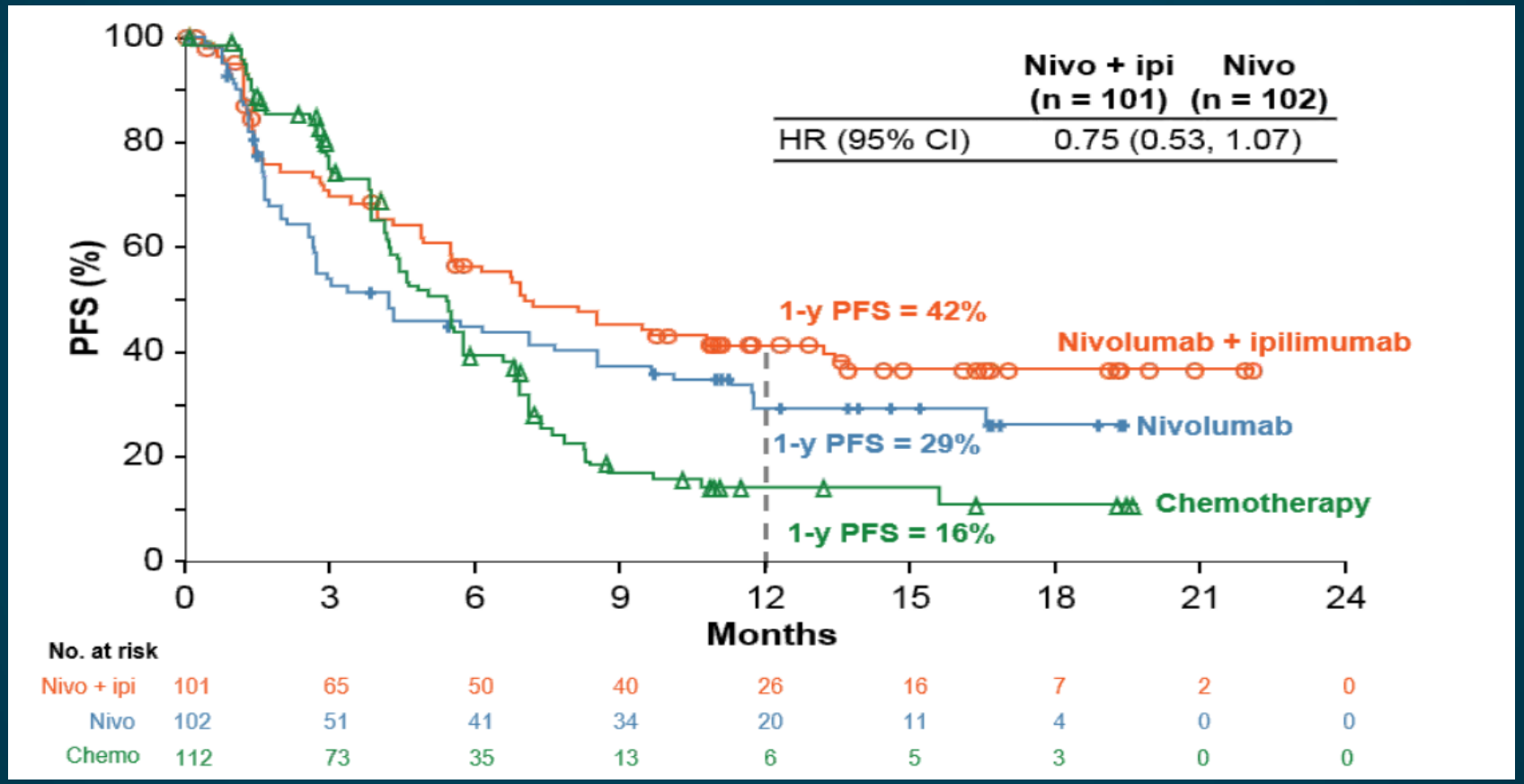
PFS in Patients With High TMB (≥10 mut/Mb) by Tumor PD-L1 Expression



a 95% CI: nivo-ipi (5.5, 13.5 mo), chemo (4.3, 6.6 mo). b 95% CI: nivo-ipi (2.7 mo, NR), chemo (4.0, 6.8 mo).

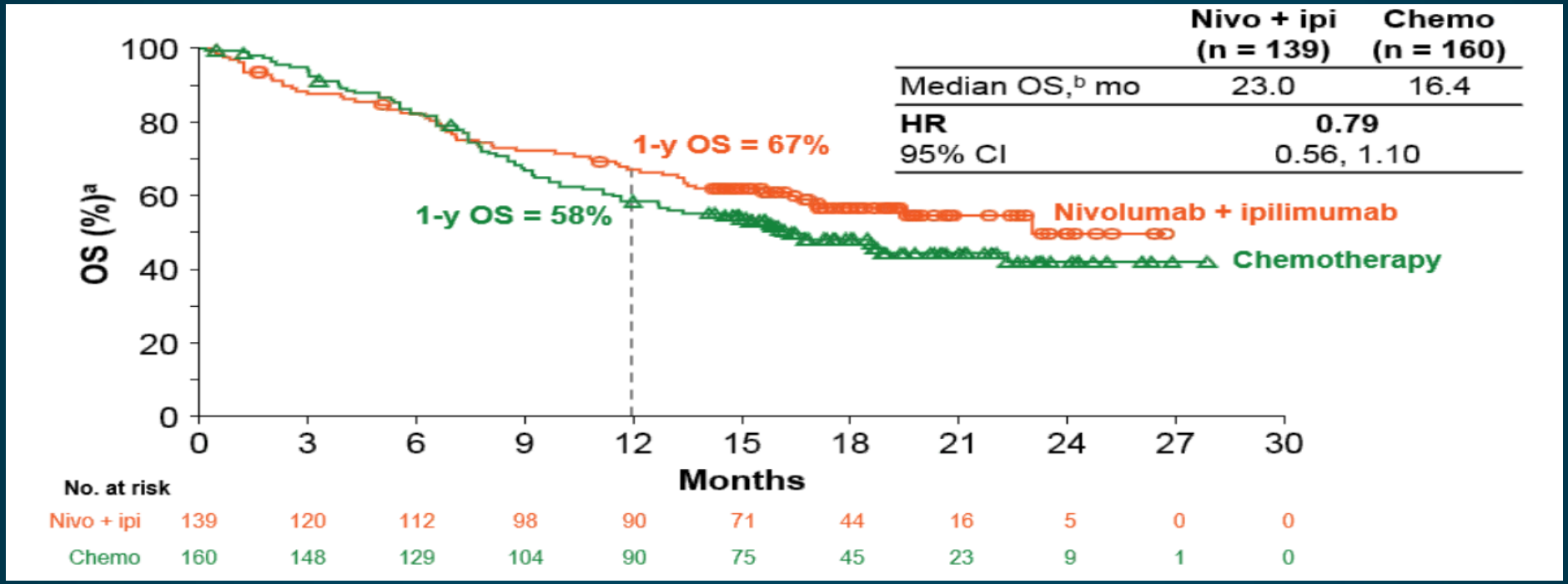
Hellmann MD, et al. AACR 2018. Abstract 350; Hellmann MD, et al. *N Engl J Med*. April 16, 2018.

PFS: Nivolumab + Ipilimumab vs Nivolumab in Patients With High TMB (≥10 mut/Mb) and ≥1% PD-L1 Expression



Hellmann MD, et al. AACR 2018. Abstract 350; Hellmann MD, et al. *N Engl J Med*. April 16, 2018.

Preliminary OS With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)



- **Database lock: March 15, 2018; minimum follow-up: 14.2 months; 53% of patients were censored.**
- **In the chemotherapy arm, 31.3% received subsequent immunotherapy (38.3% among those with PD[c]).**

a In the first 1.5 mos, 8 deaths occurred in nivo-ipi arm (4 due to PD; 1 patient never treated [respiratory sepsis]; 2 due to AEs unrelated to study drug per investigator; 1 due to myocarditis related to study drug); 2 deaths occurred in the chemo arm (1 due to PD; 1 due to multiple brain infarctions related to carboplatin). b 95% CI: nivo-ipi (16.5 mo, NR), chemo (12.6 mo, NR); c Per investigator.

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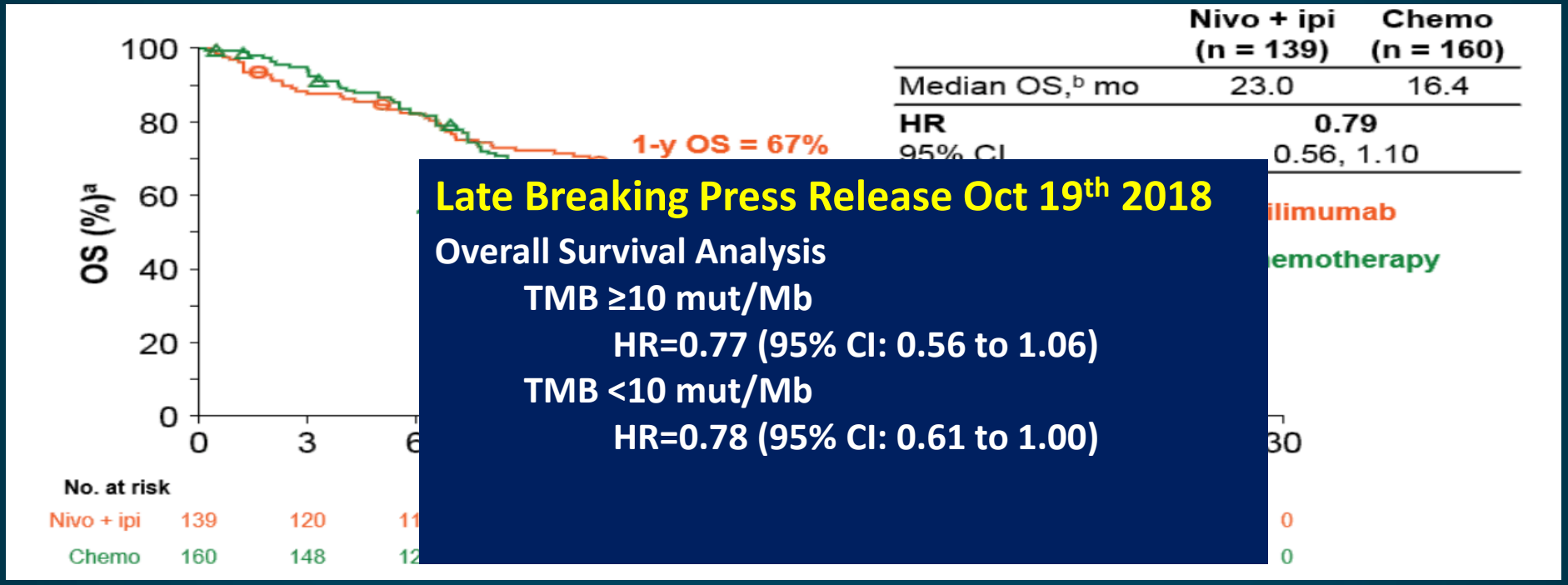

Late Breaking Press Release Oct 19th 2018

Overall Survival Analysis

TMB ≥10 mut/Mb

HR=0.77 (95% CI: 0.56 to 1.06)

TMB <10 mut/Mb

HR=0.78 (95% CI: 0.61 to 1.00)

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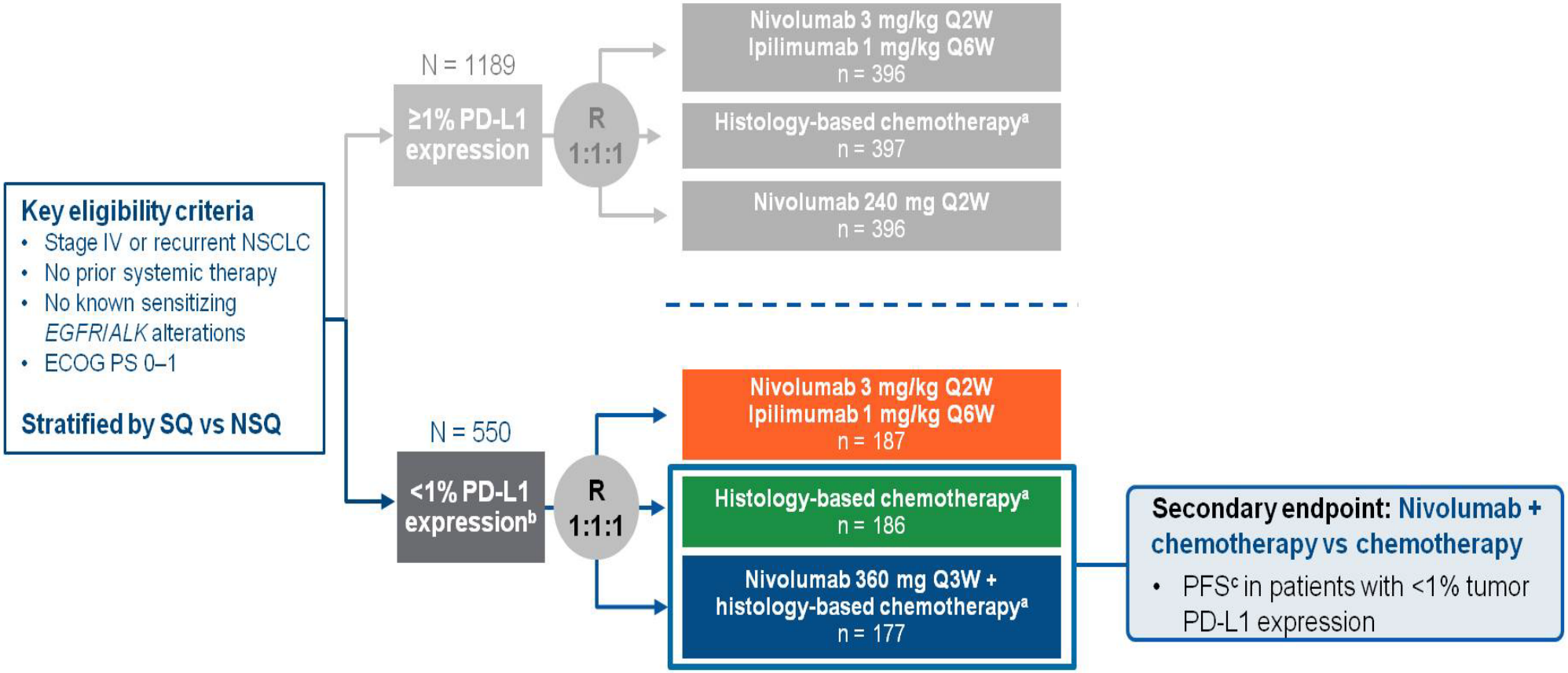
CheckMate 227: Ipi/Nivo vs. ChemoIO vs. Chemo

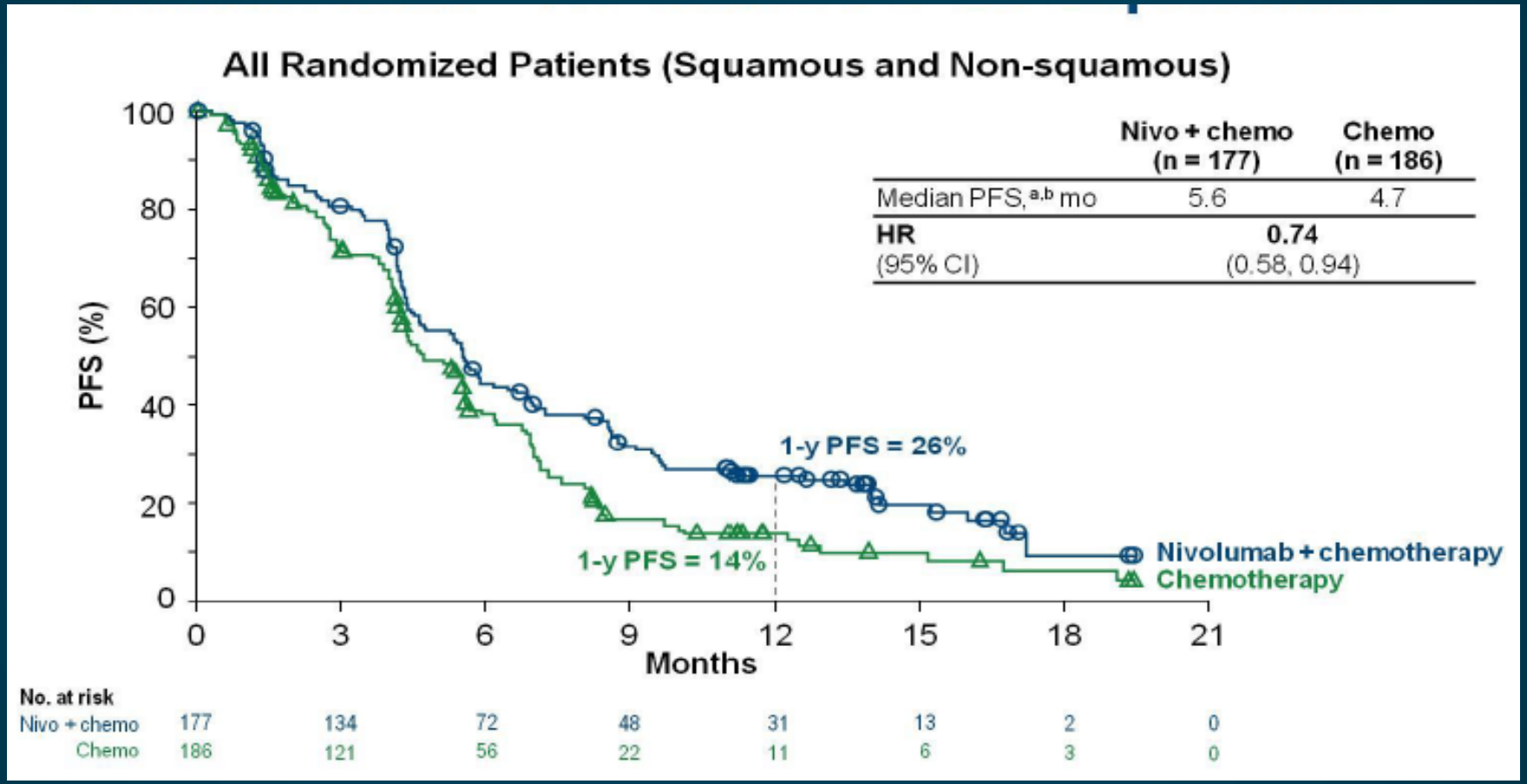


- Co-primary endpoints: OS in PD-L1–selected populations and PFS[c] in TMB-selected populations treated with nivolumab + ipilimumab vs chemotherapy

Borghaei et al, ASCO 2018

PFS: Nivo/Chemo vs Chemo in PD-L1 <1%

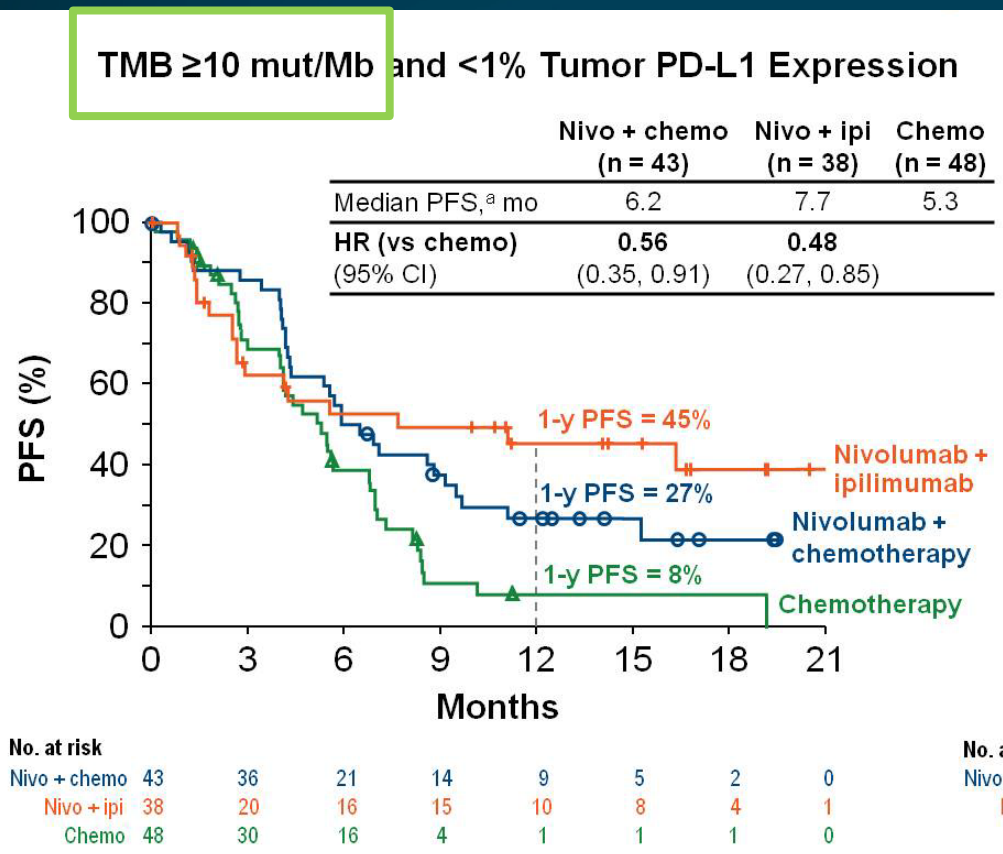
CheckMate 227: Nivo + Ipi, Nivo + Chemo, and Chemo in 1L NSCLC With <1% Tumor PD-L1

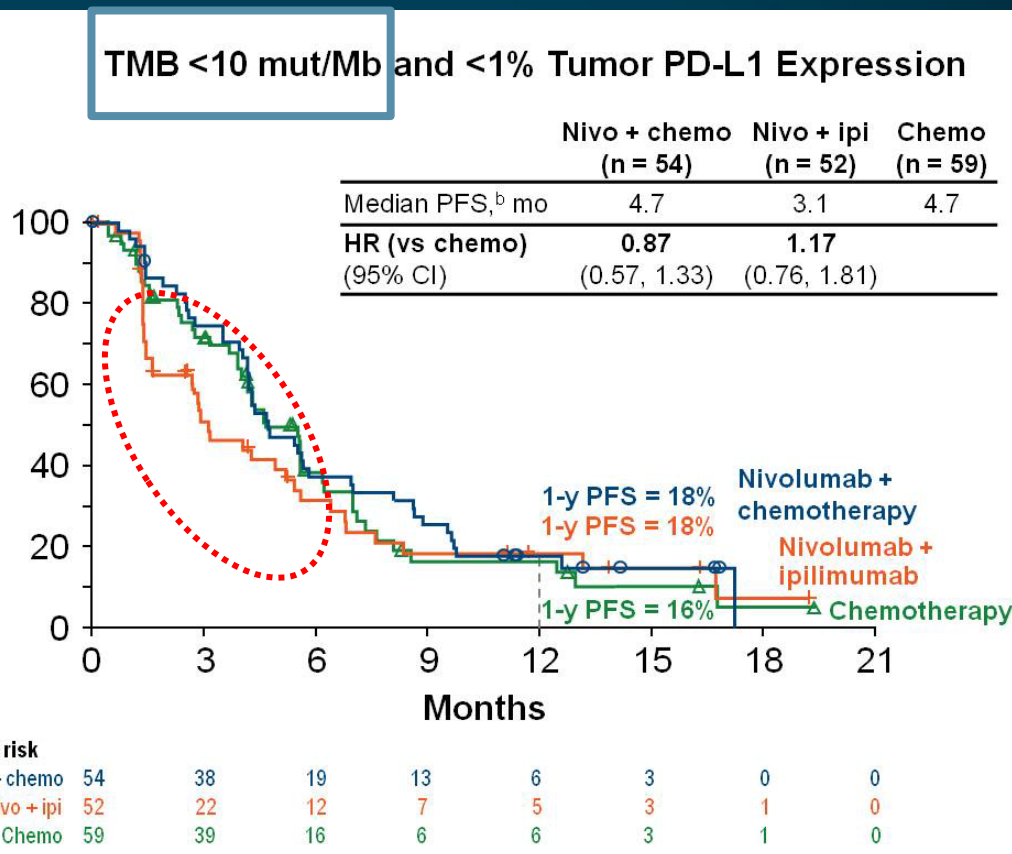


a 95% CI: nivo-ipi (4.6, 6.7 mo), chemo (4.3, 5.6 mo). b In the nivo-ipi arm (n = 187), median PFS: 4.4 (3.1, 6.0), 1-y PFS: 29%; HR vs chemo: 0.79 (0.62-1.01).

Borghaei H, et al. ASCO 2018. Abstract 9001.

CheckMate 227: Ipi/Nivo vs. ChemoIO vs. Chemo





Remember this is all PDL1 NEGATIVE patients

Borghaei et al, ASCO 2018

TMB: Langer's Perspective

- Not ready for prime time (yet) despite its promise (hype).
  - Need an OS benefit (not yet realized), though RR and PFS advantage is substantial for IPI/Nivo vs Chemo in pts with TMB > 10 mut/Mb
  - Toxicity is substantial – NEJM paper soft-pedaled side effects
  - Testing is expensive and requires NGS – 2-3 wk TAT
- Foundation now routinely includes TMB in its reports, which is very helpful, but standardization is a challenge
  - no "real" consensus on which assay to use or ideal cut offs
- May become an appealing option in fit pts with low PDL1 expression and high TMB

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I would have equipoise comparing Ipi/Nivo to Pembro and Histology-appropriate Chemo in pts with PDL1 <1% and TMB > 10 mt/MB

Conclusions: Checkpoint Inhibitors in Advanced NSCLC

- Checkpoints inhibitors are active, with often durable responses in platinum-refractory setting in NSCLC
  - Higher responses seen in settings with increased "mutation burden," eg. KRAS mt, former/heavy smokers, etc
  - RR ~ 20% independent of line of Tx
  - Based on RP3 data, Nivolumab and Atezolizumab are approved in 2nd line Squamous and Non-Sq NSCLC, independent of PD-L1 status
  - Pembrolizumab approved in PD-L1 (+) NSCLC (initially ≥ 50%, now > 1%)
- PD-L1 IHC, though imperfect, is the best available biomarker currently in 2017
- Pseudo-progression can be observed, but is rare (<3-7%)
- Unique side effects consistent with the immune mechanism of action
  - Toxicities of CTLA4 inhibitors >> PD-1/PD-L1 inhibitors
- **Pembro has shown OS/PFS/RR advantage c/w platinum-based combination chemo in Tx-naïve NSCLC with > 50% PD-L1 (+) expression (and now ≥ 1%) independent of histology (KN 024 and 042)**
- **Combination Pembro and Pem/Carbo in Tx-naive Non-Sq NSCLC** has yielded significant improvement in RR (>55%) and PFS (≥ 19 mos), conditionally approved in the US as of 05/17, **now (01/18) confirmed in phase III, with "stunning" OS benefit as well (KN 189)**
- **Combination Atezo with Pac/Carbo/Bev: superior PFS and OS vs Pac/Carbo/Bev in phase III (IP 150)**
- **Combination Atezo with Nab-Pac/Carbo: superior PFS and OS vs Nab-Pac/Carbo in phase III (IP 130)**
- **Combination Atezo with Nab-Pac/Carbo in Sq NSCLC yields superior PFS vs Chemo alone (IP 131)**
- **Combination Pembro with sb or Nab-Pac/Carbo in Sq NSCLC yields superior OS and PFS vs Chemo alone (KN 407)**
- **High TMB identifies a cohort of patients who benefit from Ipi/Nivo vs Chemo wrt ORR% and PFS, but OS data so far are not "positive" (CM 227)**
- **In LA-NSCLC, Durvalumab leads to increased PFS and OS vs placebo after definitive chemoradiation**
- Ongoing studies are exploring front-line Tx with chemo, I/O combinations and their role in LA-NSCLC

Conclusions: Checkpoint Inhibitors in Tx-Naïve Advanced NSCLC - 2019

- Pembro has shown OS/PFS/RR advantage c/w platinum-based combination chemo in Tx-naïve NSCLC with > 50% PD-L1 (+) expression (and now ≥ 1%) independent of histology (KN 024 and 042)
- Combination Pembro and Pem/Carbo in Tx-naive Non-Sq NSCLC has yielded significant improvement in RR (>55%) and PFS (~ 24 mos), conditionally approved in the US as of 05/17, now (01/18) confirmed in phase III, with "stunning" OS benefit as well (KN 189)
- Combination Pembro with sb or Nab-Pac/Carbo in Sq NSCLC yields superior OS and PFS vs Chemo alone (KN 407)
- Multiple (+) Phase III Atezo Studies
- Combination Atezo/Pac/Carbo/Bev: superior PFS and OS vs Pac/Carbo/Bev (IP 150)
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- High TMB identifies a cohort of patients who benefit from Ipi/Nivo vs Chemo wrt ORR% and PFS, but OS data so far are not "positive" (CM 227)
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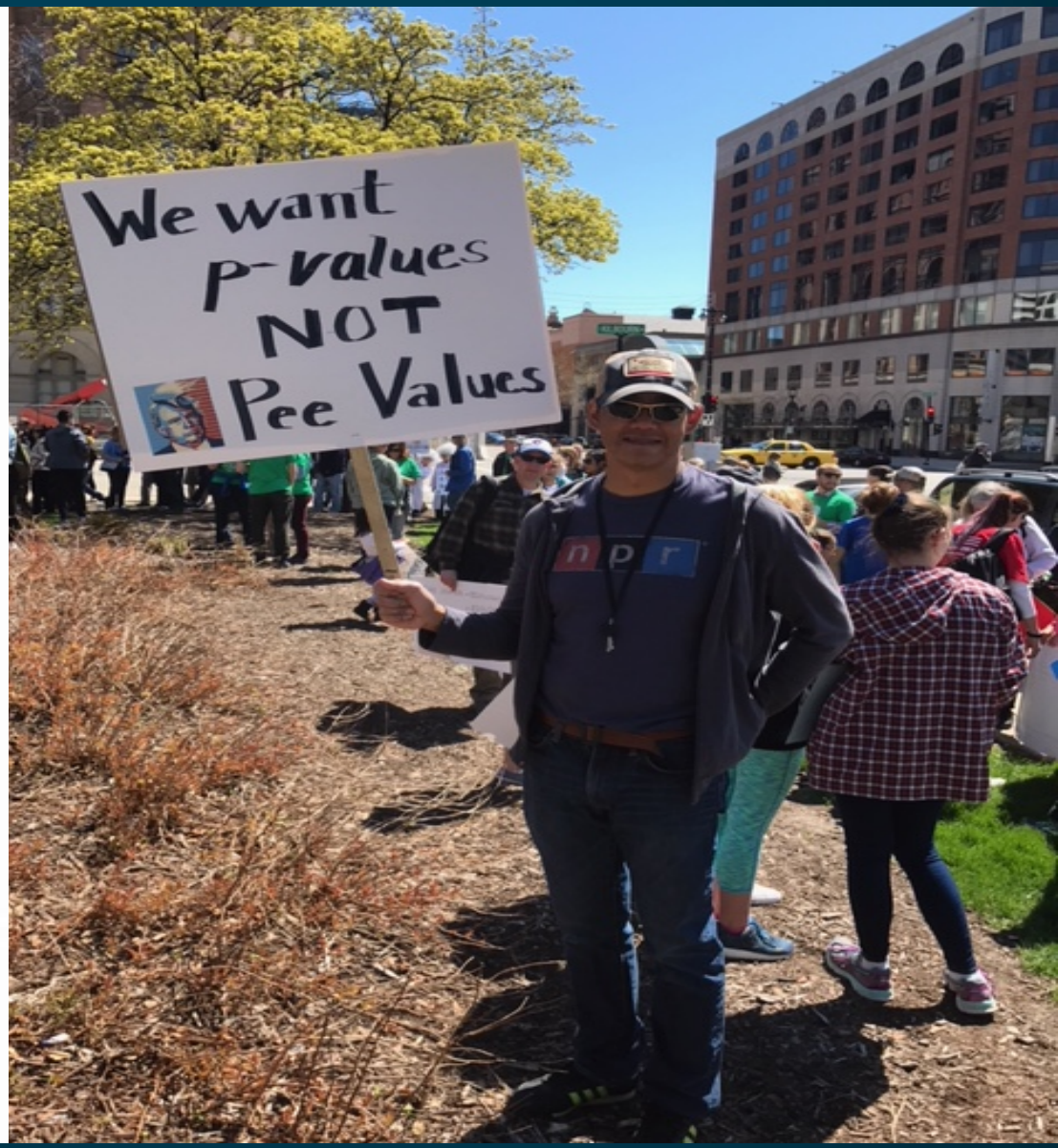
Langer's Current Paradigm: 2018 (could change at any moment)

Tx Cohort	Non-Squamous	Squamous
PDL1 $\geq$ 50%	Pembro > Pem/Carbo/Pembro	Pembro > Taxane/Carbo/Pembro
PDL1 1-50%	Pem/Carbo/Pembro > Pembro	Taxane/Carbo/Pembro > Pembro
PDL1 < 1%	Pem/Carbo/Pembro	Taxane/Carbo/Pembro
PDL1 < 1%, TMB > 10	Pem/Carbo/Pembro vs Ipi/Nivo	Taxane/Carbo/Pembro vs Ipi/Nivo
TKI-Refractory	Pac/Carbo/Bev/Atezo or Pem/Carbo/Bev	
Tissue QNS	Pem/Carbo/Pembro	Taxane/Carbo/Pembro

Open Questions

- Why was KN 407 positive while IMP 131 proved negative wrt OS?
- Can IO/IO combinations match or exceed results seen with Chemo/IO combinations?
- Will composite markers (PDL1, TMB, gene signature, etc) help select or exclude pts more or less likely to benefit from Chemo/IO or IO/IO combinations?
- What should we do for PDL1 < 1% pts with Low TMB?
- How long should Tx continue?
- Should we treat beyond progression? What is the role of XRT in “Oligo-PD?”
- Can Tx with IOs increase OS in the curative setting?

As Dedicated Clinical Trialists, we Worship at the Altar of the p Value



Thank You

Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA