Asco 2018 Highlights
LUNG CANCER

Dott. Paolo Allione

rete oncologica
PIEMONTE | VALLE D'AOSTA

BRA
ALBA
ASL CN2

Agenda

- ✓ Immunotherapy first line
- ✓ Combination immunotherapy
- ✓ Steroids
- ✓ Oncogene addicted
- ✓ Immunotherapy in Oncogene Addicted

Agenda

- ✓ **Immunotherapy first line**
- ✓ Combination immunotherapy
- ✓ Steroids
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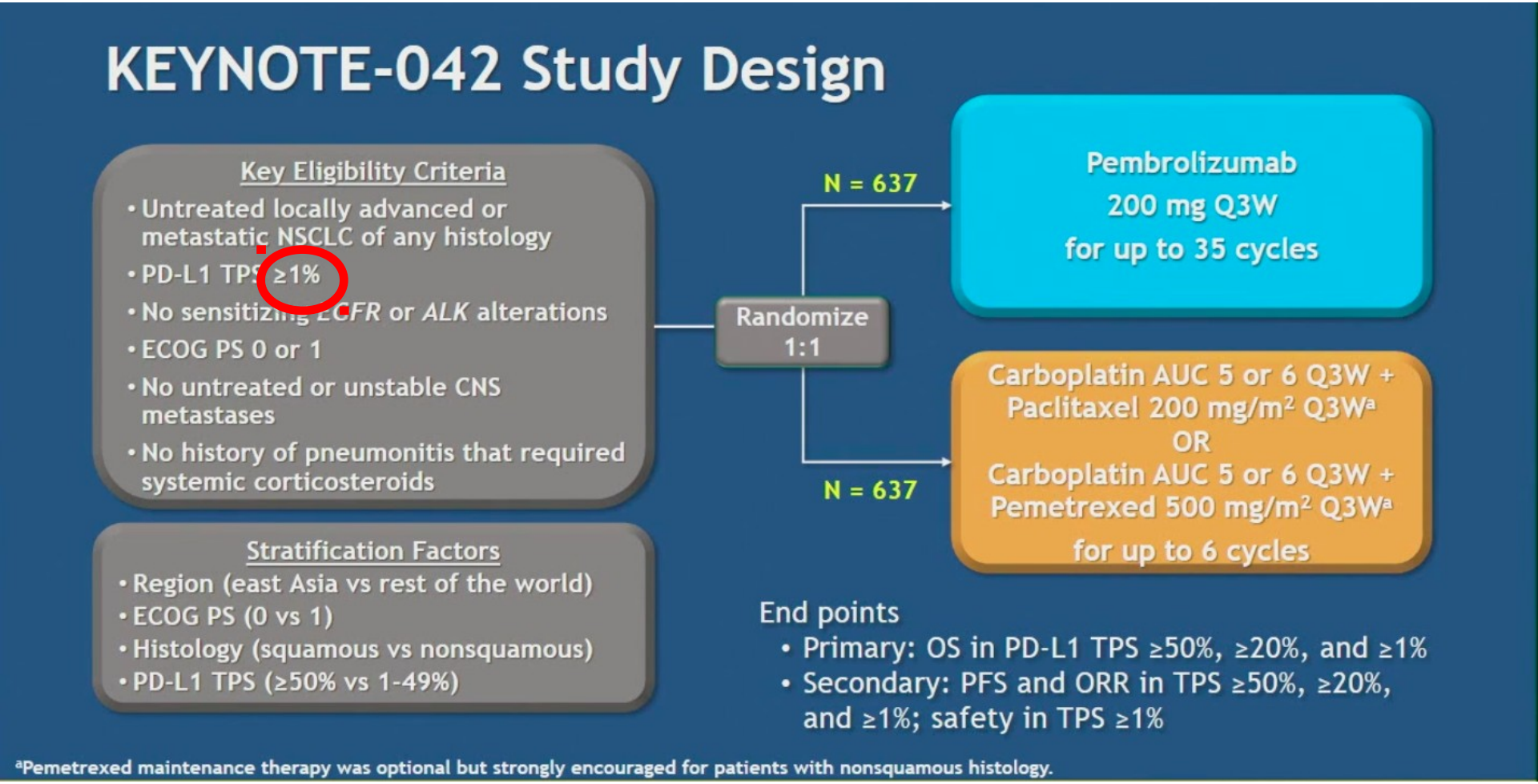
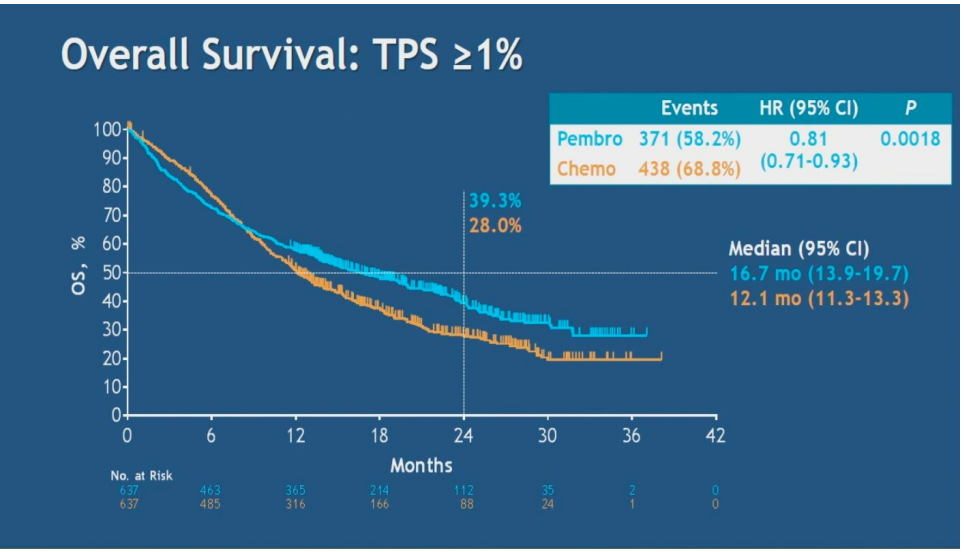
- ✓ Immunotherapy in Oncogene Addicted

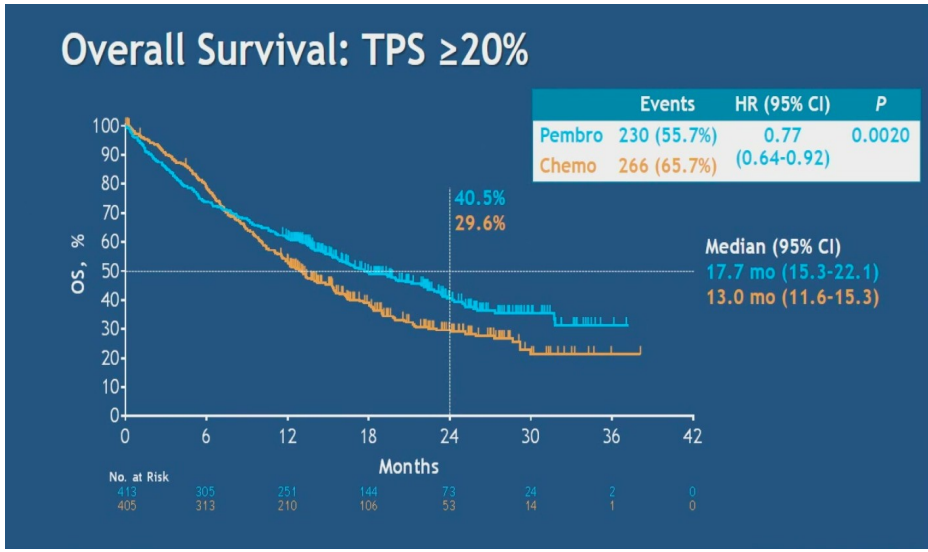
Pembrolizumab single agent first line

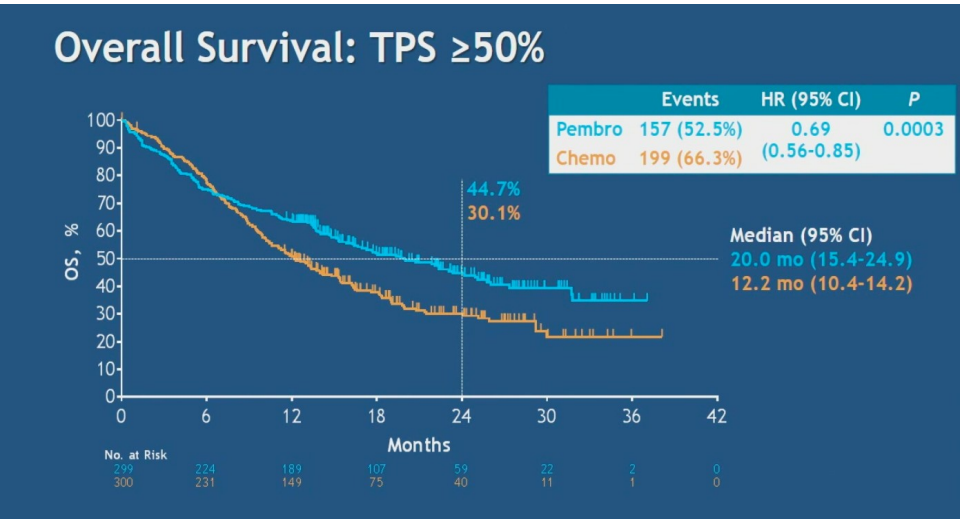


G.LOPES, ASCO 2018

Keynote 042: OS



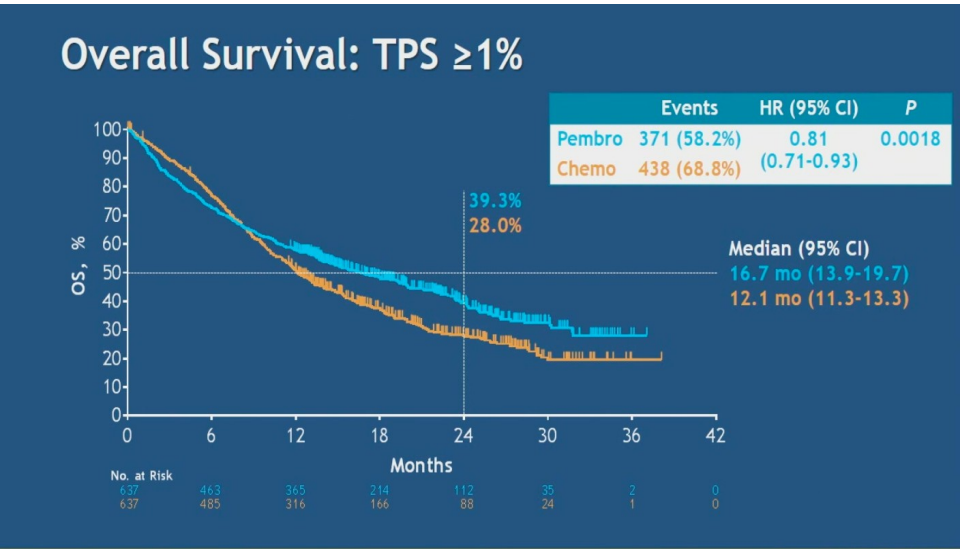


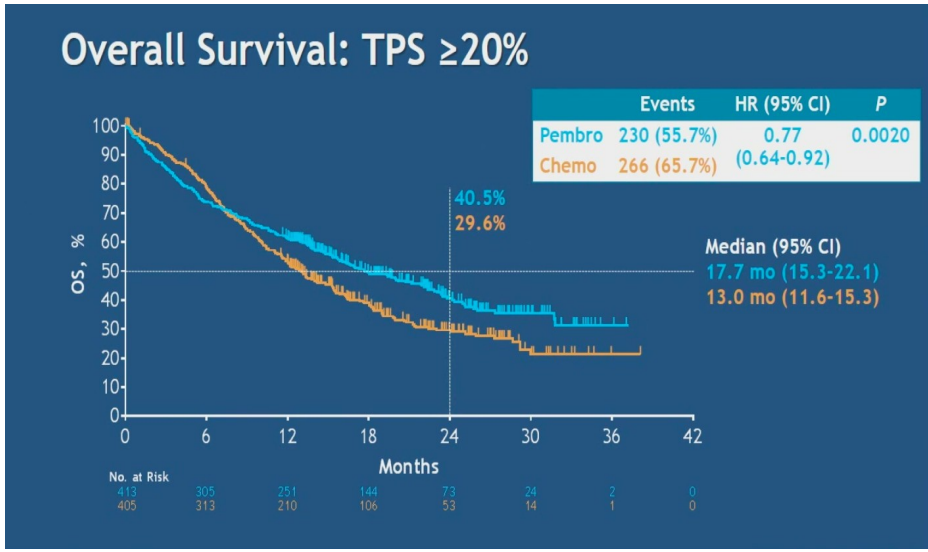


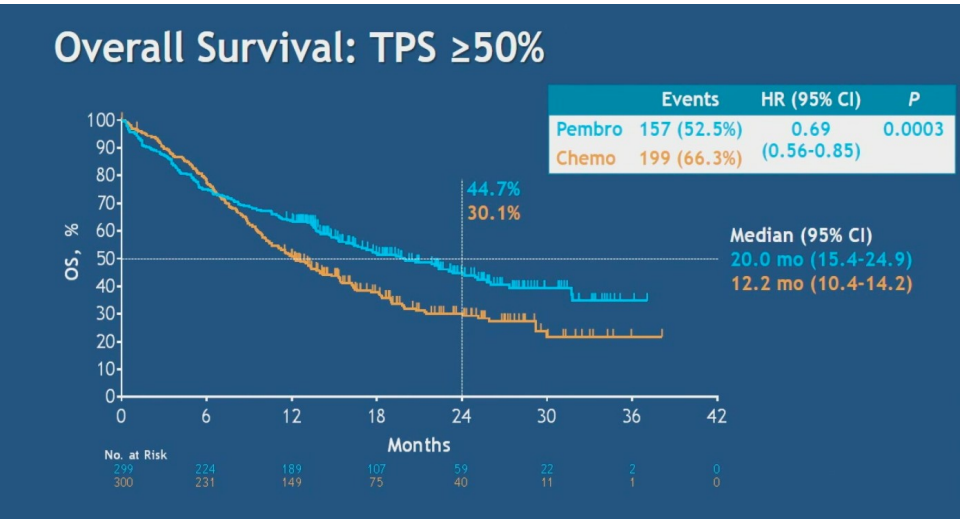
G.LOPES, ASCO 2018

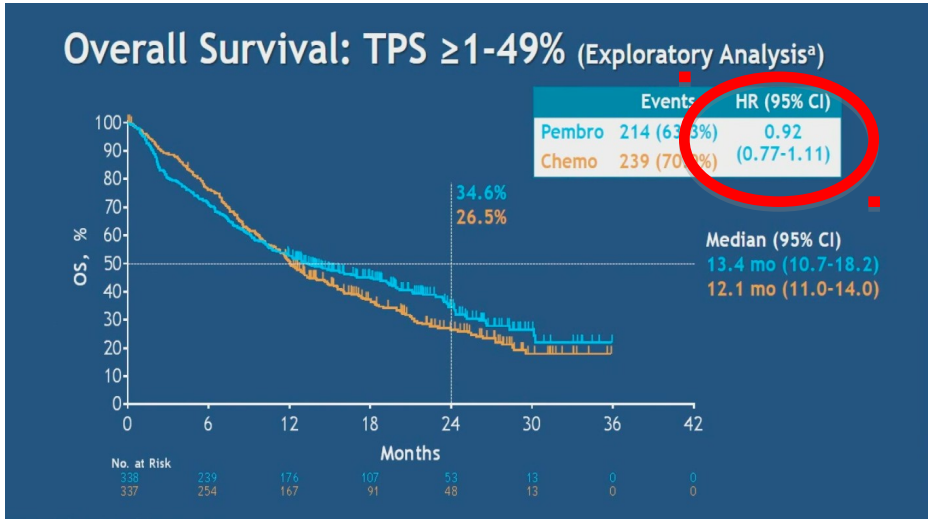
Data cutoff date: Feb 26, 2018

Keynote 042: OS

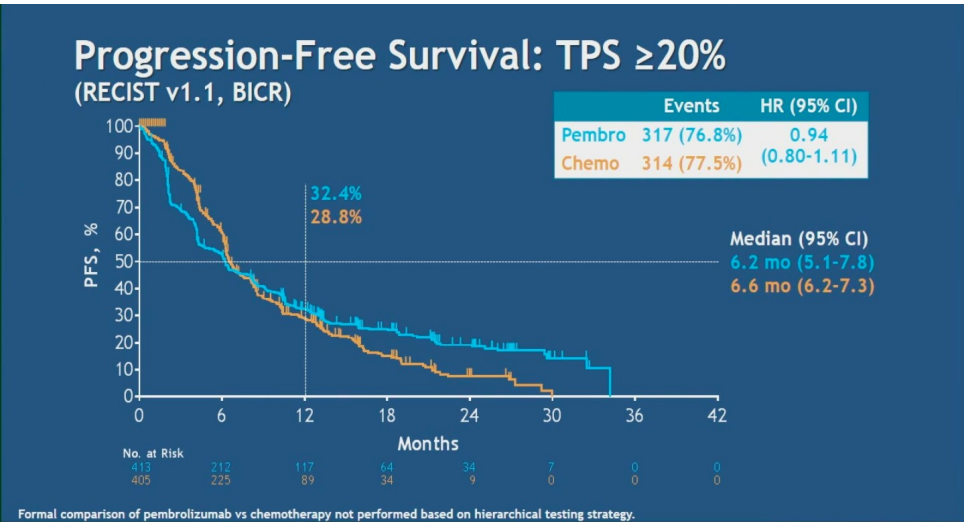


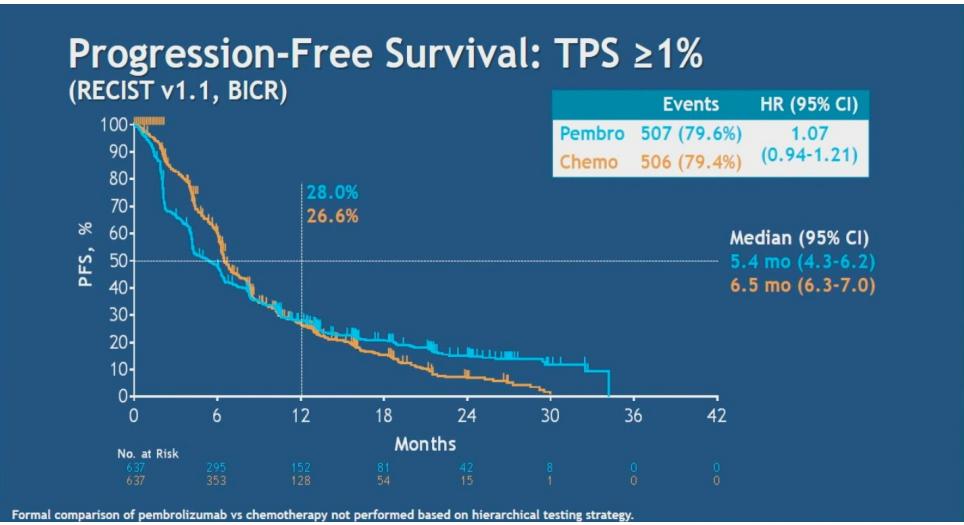


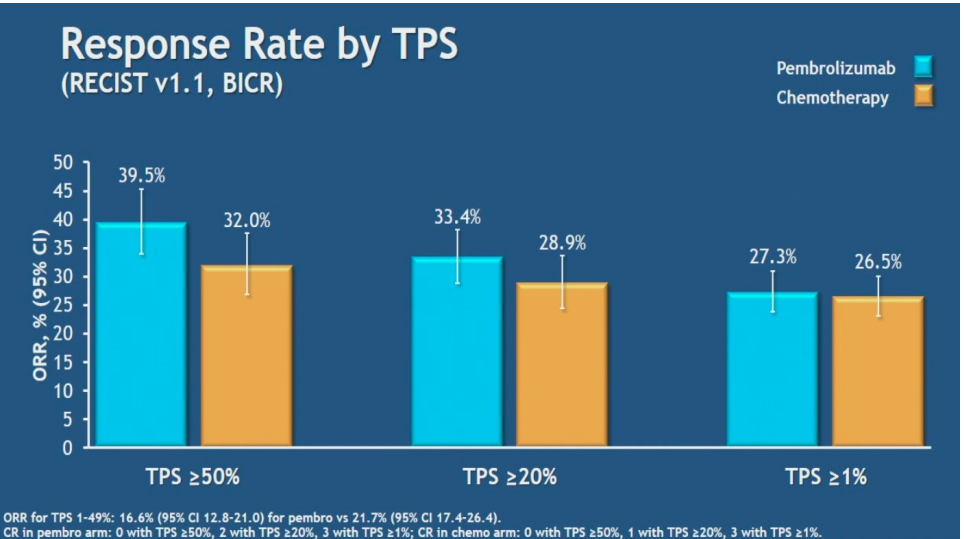




Keynote 042: PFS and ORR

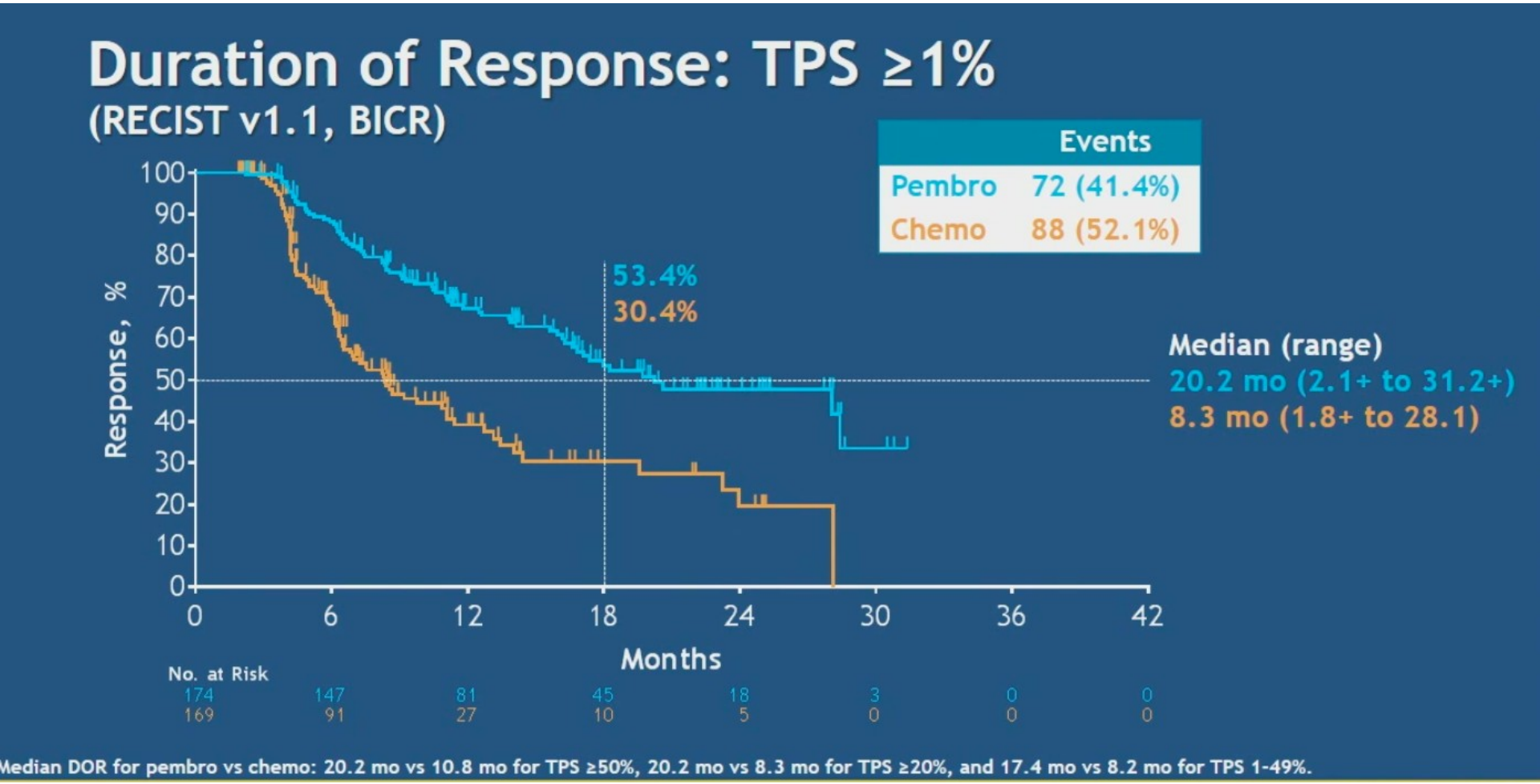






G.LOPES, ASCO 2018

Keynote 042: duration of response



G.LOPES, ASCO 2018

Keynote 042: Toxicity

	Pembrolizumab (N = 636)	Chemotherapy (N = 615)
No. of doses, median (range)	9 (1-36)	6 (1-42)
Treatment-related AEs	399 (62.7%)	553 (89.9%)
Grade 3-5	113 (17.8%)	252 (41.0%)
Led to death	13 (2.0%)	14 (2.3%)
Led to discontinuation	57 (9.0%)	58 (9.4%)
Immune mediated AEs and infusion reactions[a]	177 (27.8%)	44 (7.2%)
Grade 3-5	51 (8.0%)	9 (1.5%)
Led to death	1 (0.2%)[b]	0

G.LOPES, ASCO 2018

Keynote 042: Conclusion

- Despite longer exposure, frequency of treatment-related AEs was lower with pembrolizumab
  - Safety profile consistent with that previously observed for pembrolizumab
  - Better safety profile of pembrolizumab suggests it is an appropriate treatment option for any level of PD-L1 positivity
- KEYNOTE-042 is the first study with a primary end point of OS to demonstrate superiority of pembrolizumab over platinum-based chemotherapy in previously untreated, locally advanced or metastatic NSCLC without sensitizing *EGFR* mutations or *ALK* translocation and with a PD-L1 TPS ≥1%
- These data confirm and potentially extend the role of pembrolizumab monotherapy as a standard first-line treatment for patients with PD-L1-expressing tumors

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- ✓ Steroids
- ✓ Oncogene addicted
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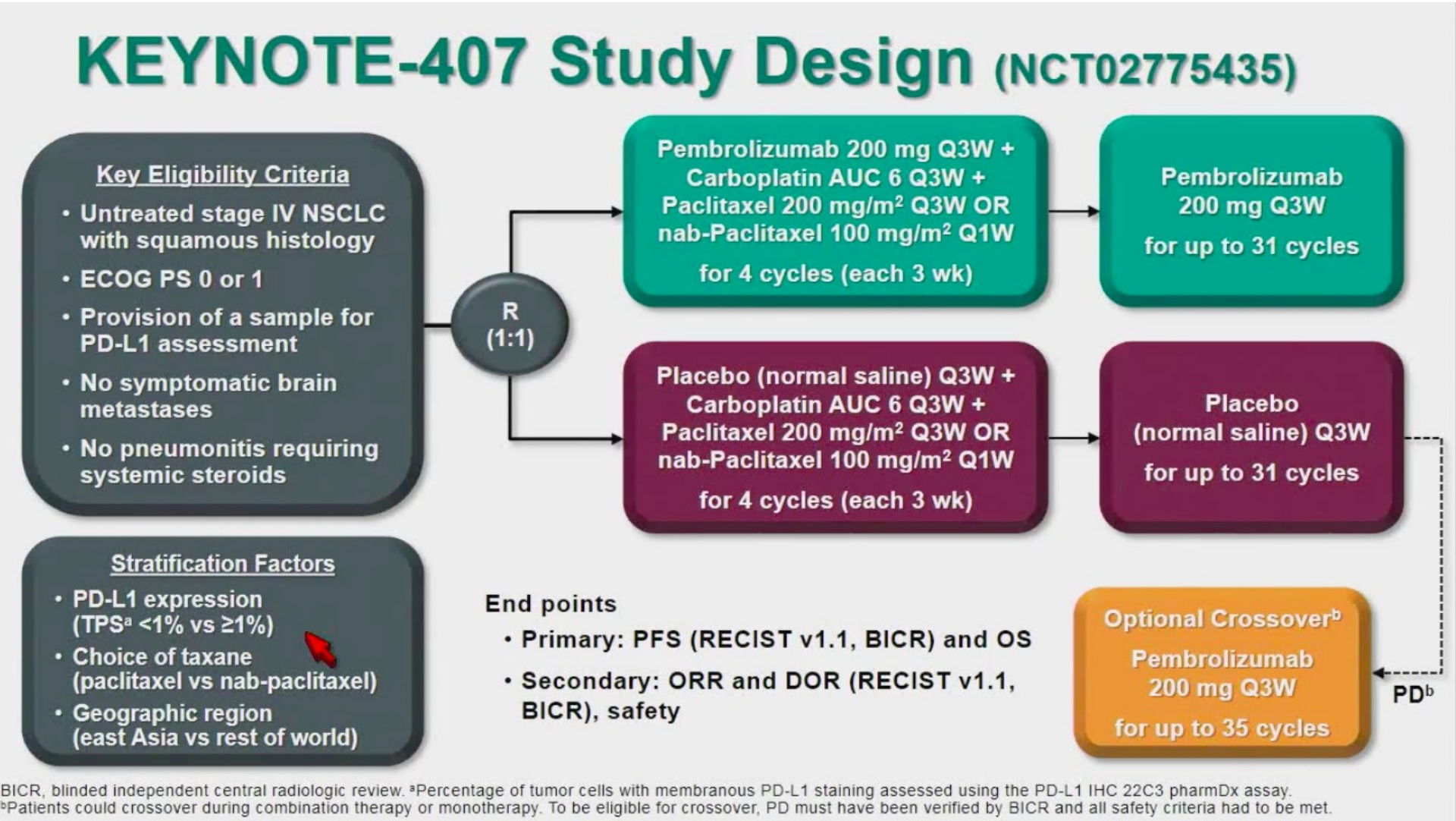
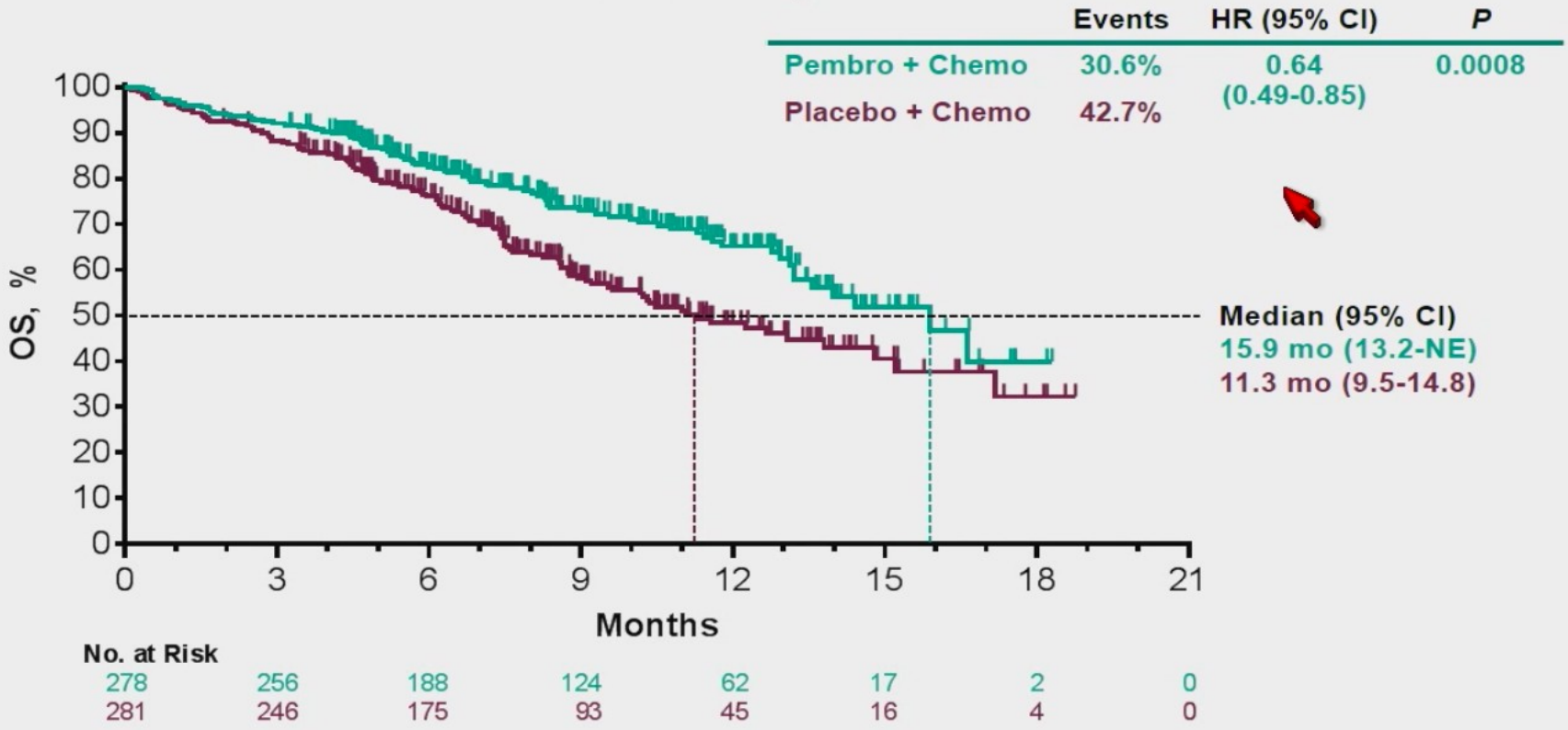
Keynote 407: chemotherapy plus pembrolizumab in SqNSCLC



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.

Keynote 407: OS

Overall Survival at IA2, ITT



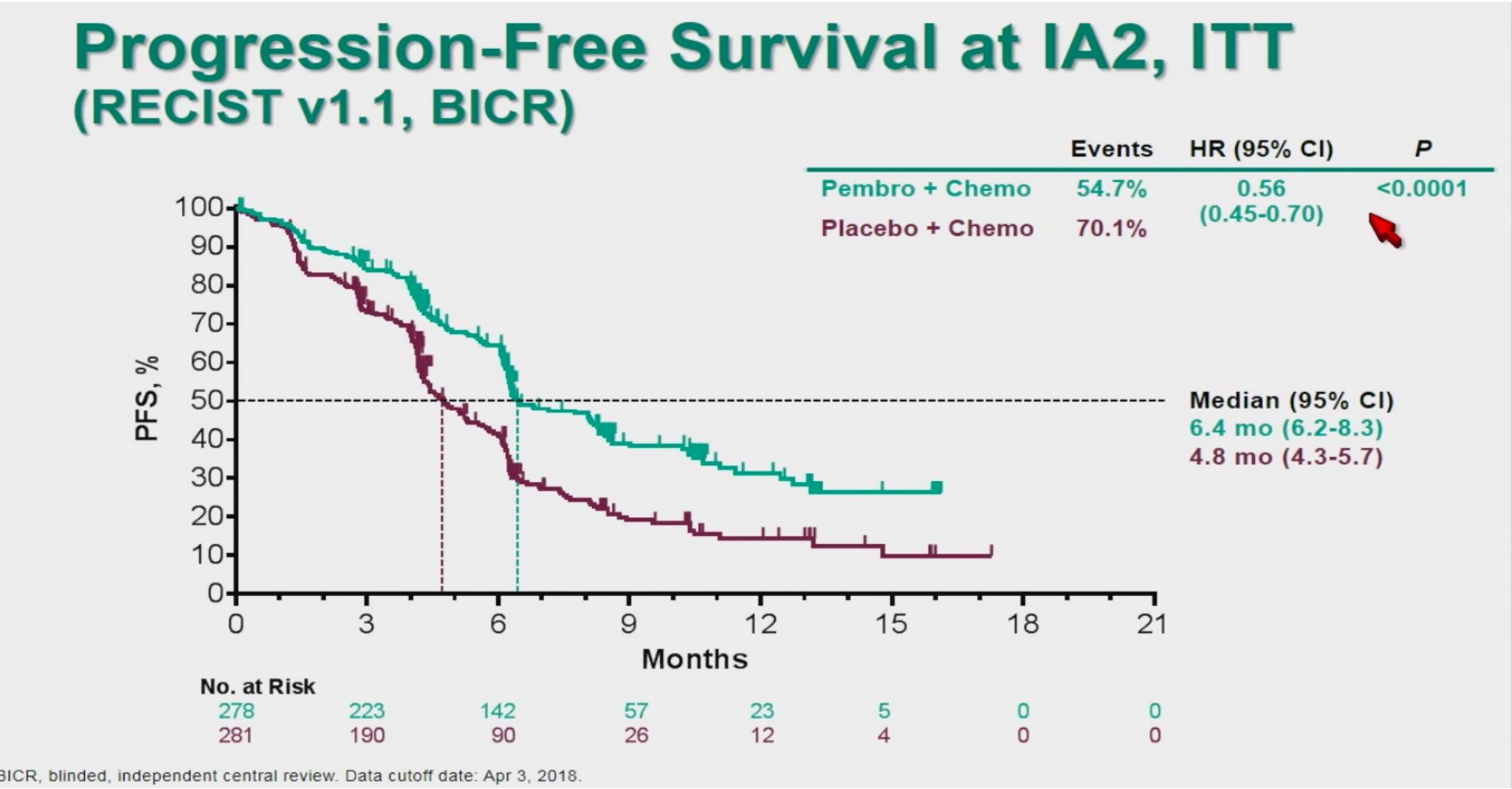
Data cutoff date: Apr 3, 2018.

L. Paz Ares, ASCO 2018

Keynote 407: OS by PDL-1 expression

L. Paz Ares, ASCO 2018

Keynote 407: PFS



L. Paz Ares, ASCO 2018

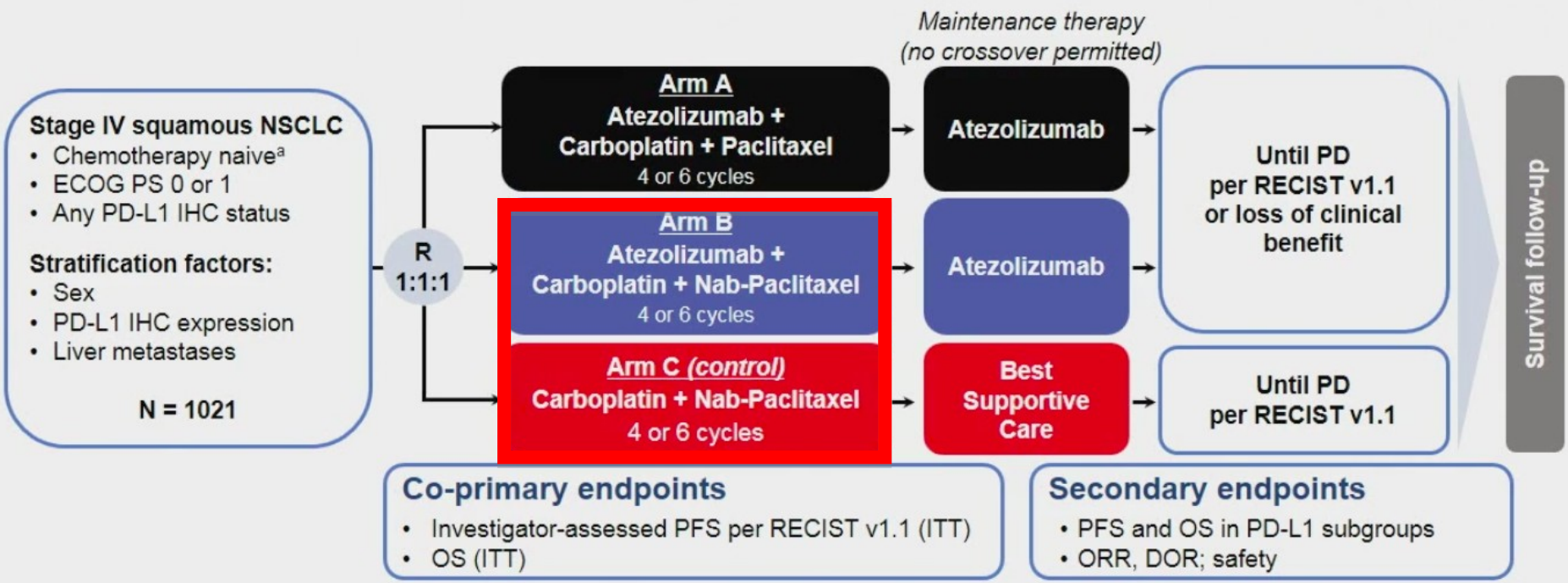
Keynote 407: Conclusions

Summary and Conclusions

- Pembrolizumab plus chemotherapy significantly improved OS (HR 0.64) over chemotherapy alone
  - Benefit was observed irrespective of PD-L1 TPS: HR 0.61 for TPS <1%, 0.57 for TPS 1-49%, and 0.64 for TPS ≥50%
- PFS (HR 0.56) and ORR (P = 0.0004) were also improved with pembrolizumab plus chemotherapy and responses were more durable
- AE frequency and severity were mostly similar between arms
  - Observed events consistent with known safety profiles of pembrolizumab and chemotherapy, with no new safety signals identified
  - Rates of discontinuation due to AEs were higher in the pembrolizumab plus chemotherapy arm, but generally low overall
  - Immune-mediated AEs were more frequent in the pembrolizumab arm, with frequency and severity consistent with those observed for pembrolizumab monotherapy
- Data suggest pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel should become a new standard-of-care for first-line treatment of metastatic squamous NSCLC, irrespective of PD-L1 expression

L. Paz Ares, ASCO 2018

ImPower131: chemotherapy plus atezolizumab in SqNSCLC

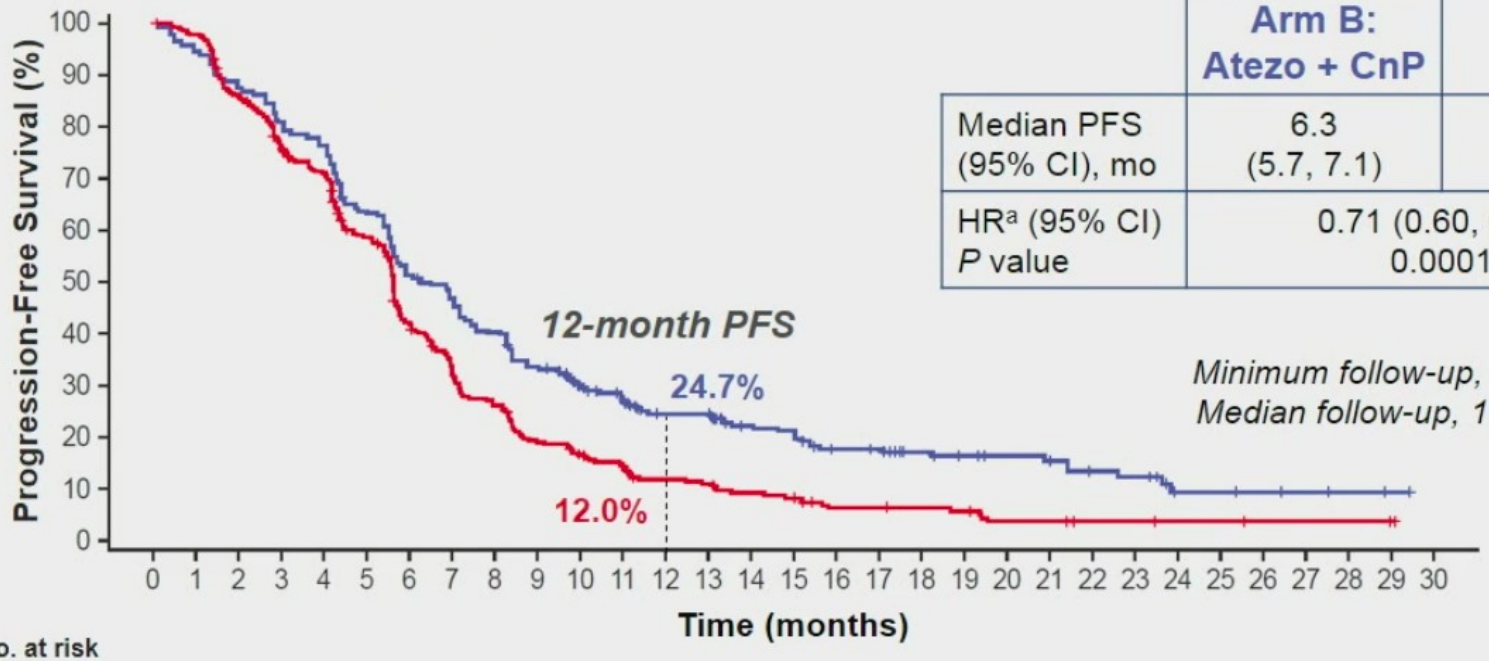


Atezolizumab 1200 mg IV q3w; carboplatin AUC 6 IV q3w; nab-paclitaxel 100 mg/m² IV qw; paclitaxel 200 mg/m² IV q3w.
[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance to treatment with ≥ 1 approved targeted therapies. Testing for *EGFR* mutation or *ALK* translocation was not mandatory.
[b] PD-L1 expression was evaluated using the VENTANA SP142 IHC assay.

Jotte R, ASCO 2018

ImPower131: PFS

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

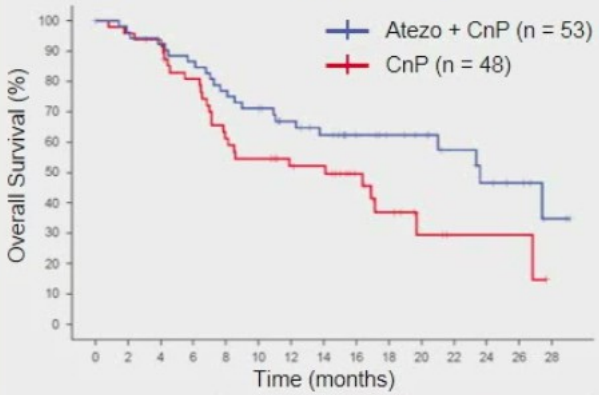
Data cutoff: January 22, 2018.

Jotte R, ASCO 2018

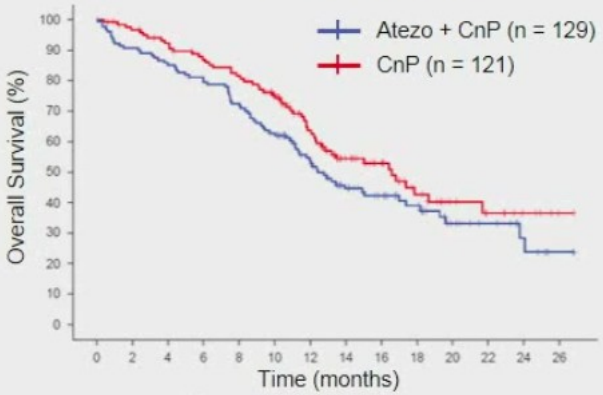
ImPower131: OS by PDL-1 expression

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

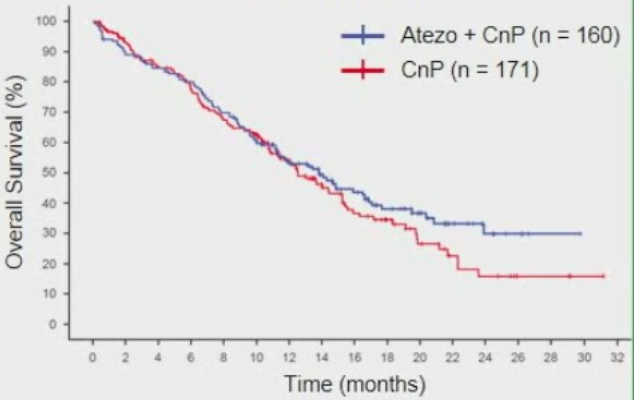
PD-L1 High
TC3 or IC3



PD-L1 Low
TC1/2 or IC1/2



PD-L1 Negative
TC0 and IC0

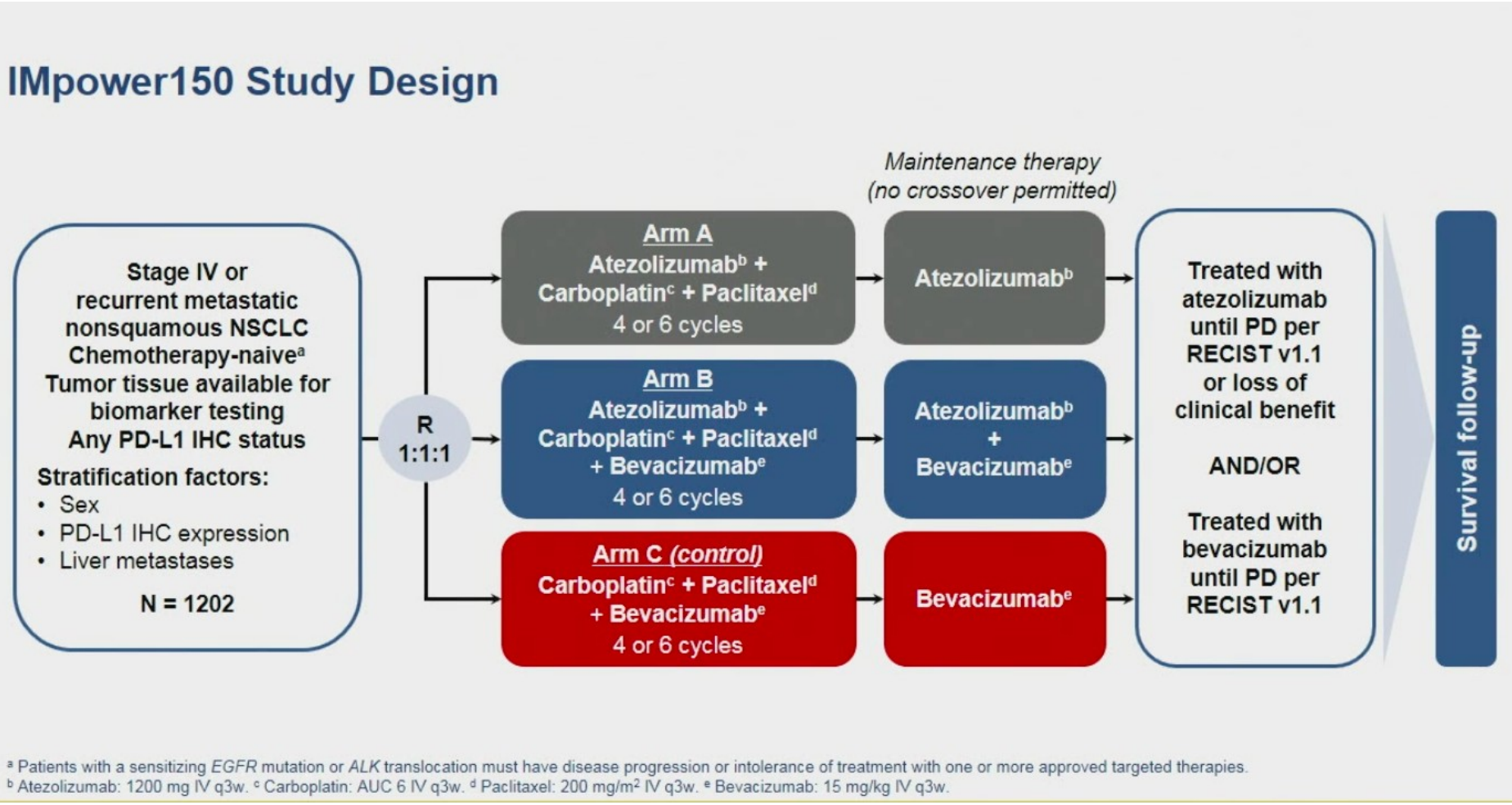


	Atezo + CnP	CnP	Atezo + CnP	CnP	Atezo + CnP	CnP
12-month OS	67%	52%	54%	64%	53%	53%
24-month OS	47%	30%	28%	37%	30%	16%
Median OS, mo	23.6	14.1	12.4	16.6	13.8	12.5
HR[a] (95% CI)	0.56 (0.32, 0.99)		1.34 (0.95, 1.90)		0.86 (0.65, 1.15)	

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

Jotte R, ASCO 2018

ImPower150: chemotherapy plus bevacizumab plus atezolizumab in nonSqNSCLC

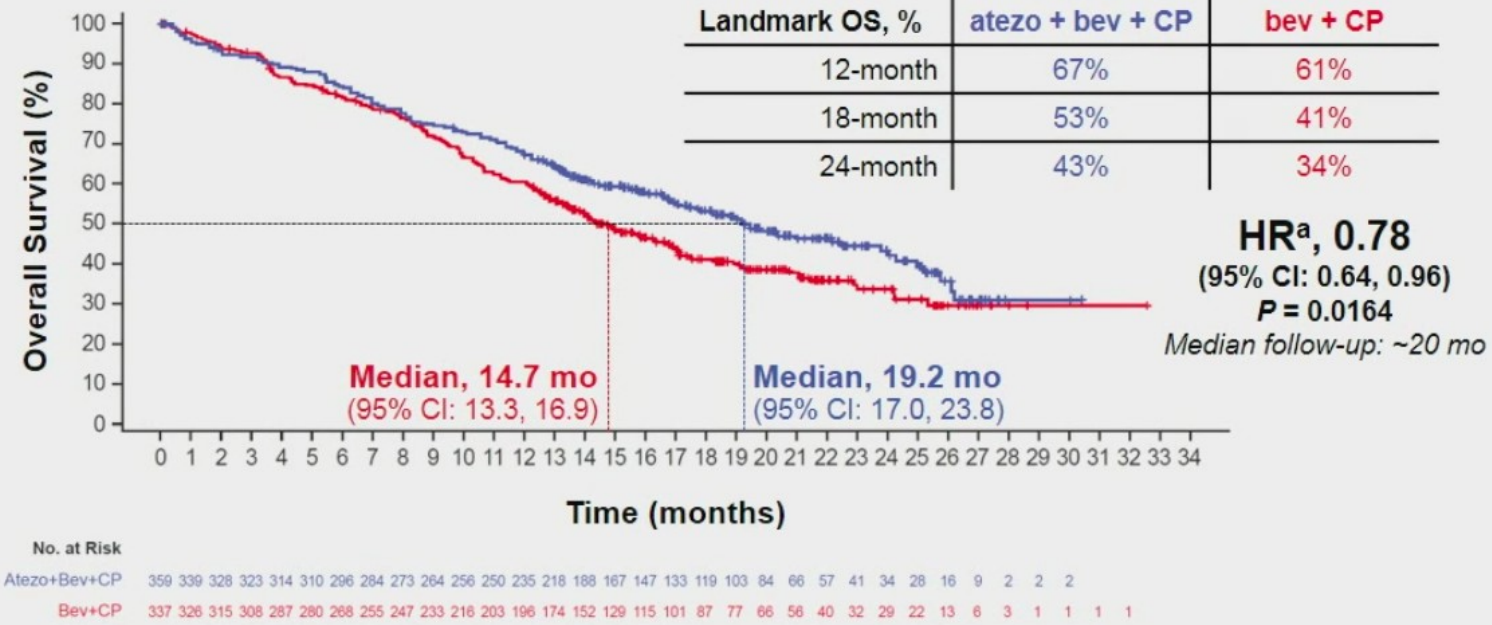


[a] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w. [d] Paclitaxel: 200 mg/m^2 IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.

Socinski M, ASCO 2018

ImPower150: Os

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



Landmark OS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
12-month	67%	61%
18-month	53%	41%
24-month	43%	34%

- Statistically significant and clinically meaningful OS benefit with atezolizumab + bevacizumab + chemotherapy vs bevacizumab + chemotherapy was observed

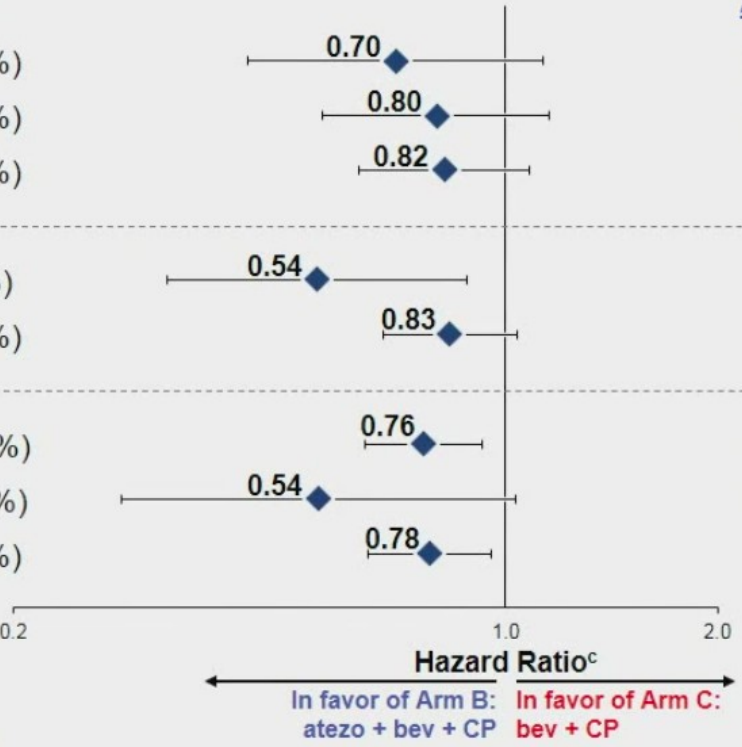
[a] Stratified HR.
Data cutoff: January 22, 2018

Socinski M, ASCO 2018

ImPowe150: Os (subgroups)

OS in Key Subgroups (Arm B vs Arm C)

Subgroup	n (%)[a]	Median OS, mo Arm B	Median OS, mo 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

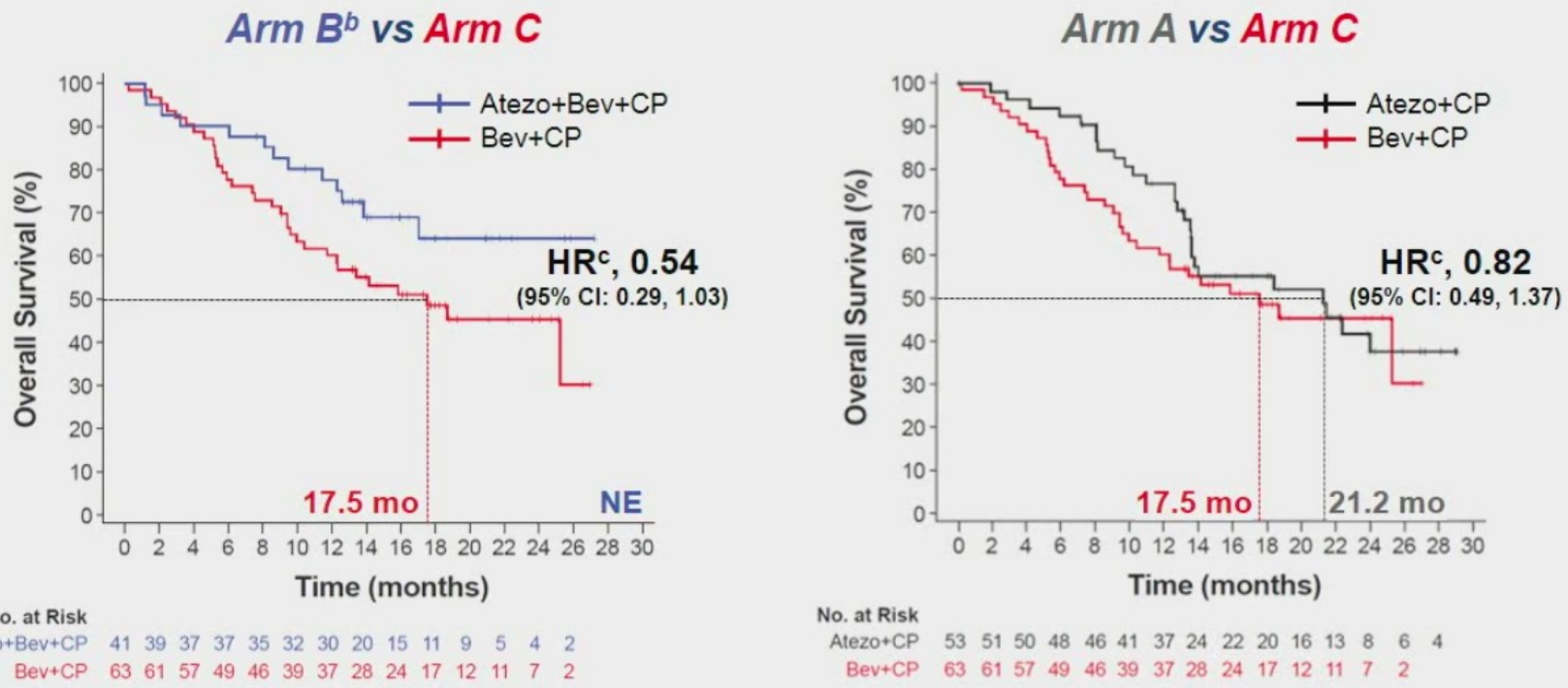


NE, not estimable.
[a] Prevalence % for PD-L1 IHC and liver metastases subgroups out of ITT-WT (n=696); prevalence of ITT, *EGFR/ALK*+, and ITT-WT out of ITT (n=800).
[b] One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab.
[c] Stratified HR for ITT and ITT-WT; unstratified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

Socinski M, ASCO 2018

Impower150: EGFR/ALK

Addition of Bevacizumab to Atezolizumab and Chemotherapy Prolongs Survival of *EGFR/ALK*+ Patients[a]

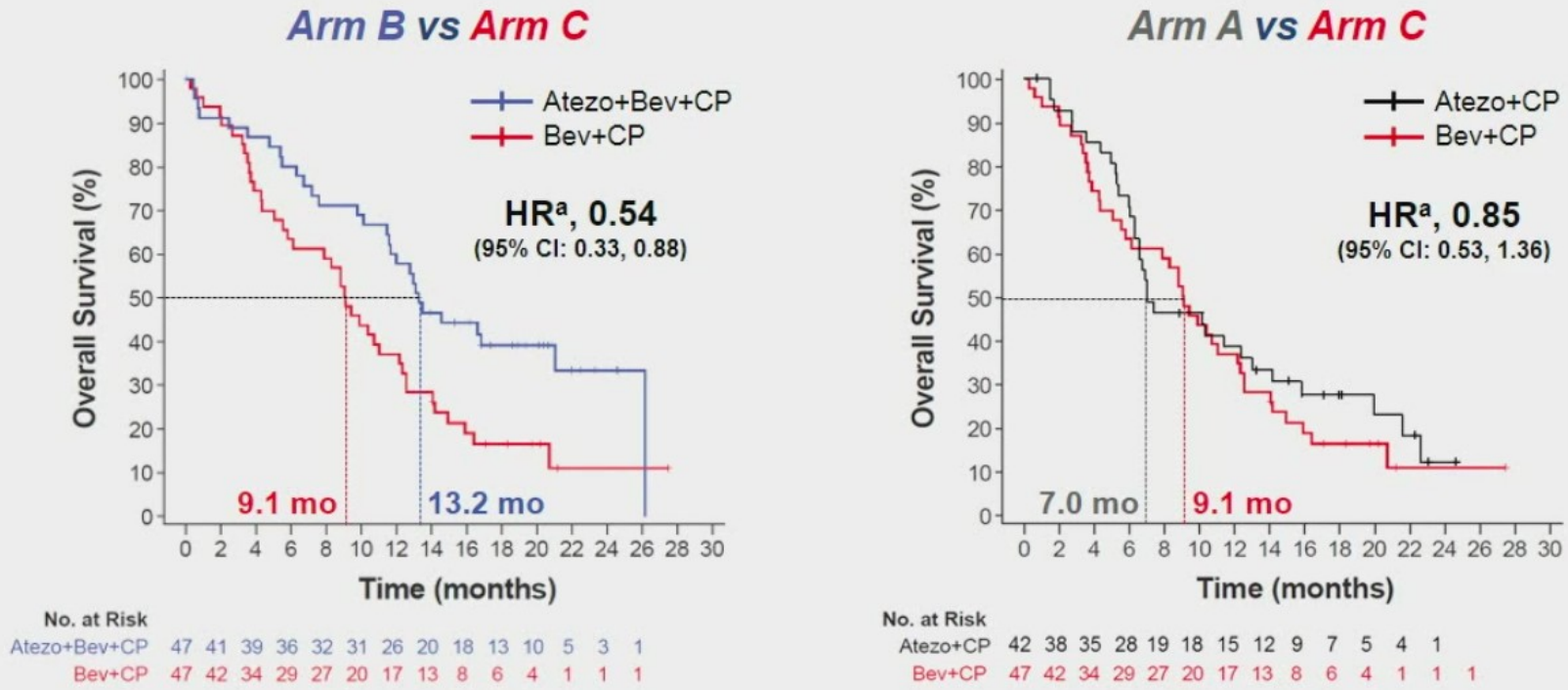


[a] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[b] One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab. [c] Unstratified HR.
Data cutoff: January 22, 2018

Socinski M, ASCO 2018

ImPower150: liver metastases

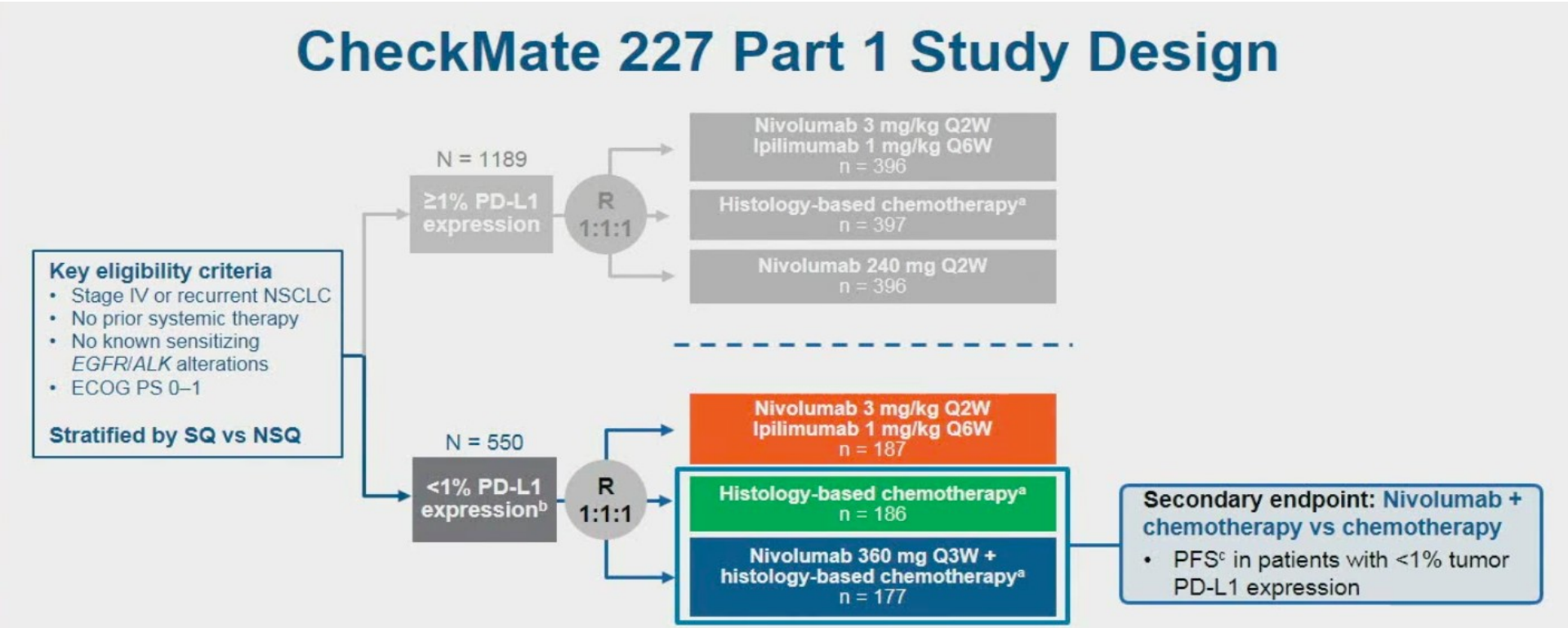
Addition of Bevacizumab to Atezolizumab and Chemotherapy Prolongs Survival of Patients With Liver Metastases in the ITT-WT



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

Socinski M, ASCO 2018

Checkmate 227: chemotherapy plus Nivolumab in NSCLC with PDL-1 <1%



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

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

[a]**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; [b]One patient was randomized with <1% tumor PD-L1 expression in IVRS, but was subsequently found to have ≥1% tumor PD-L1 expression; [c]Per BICR

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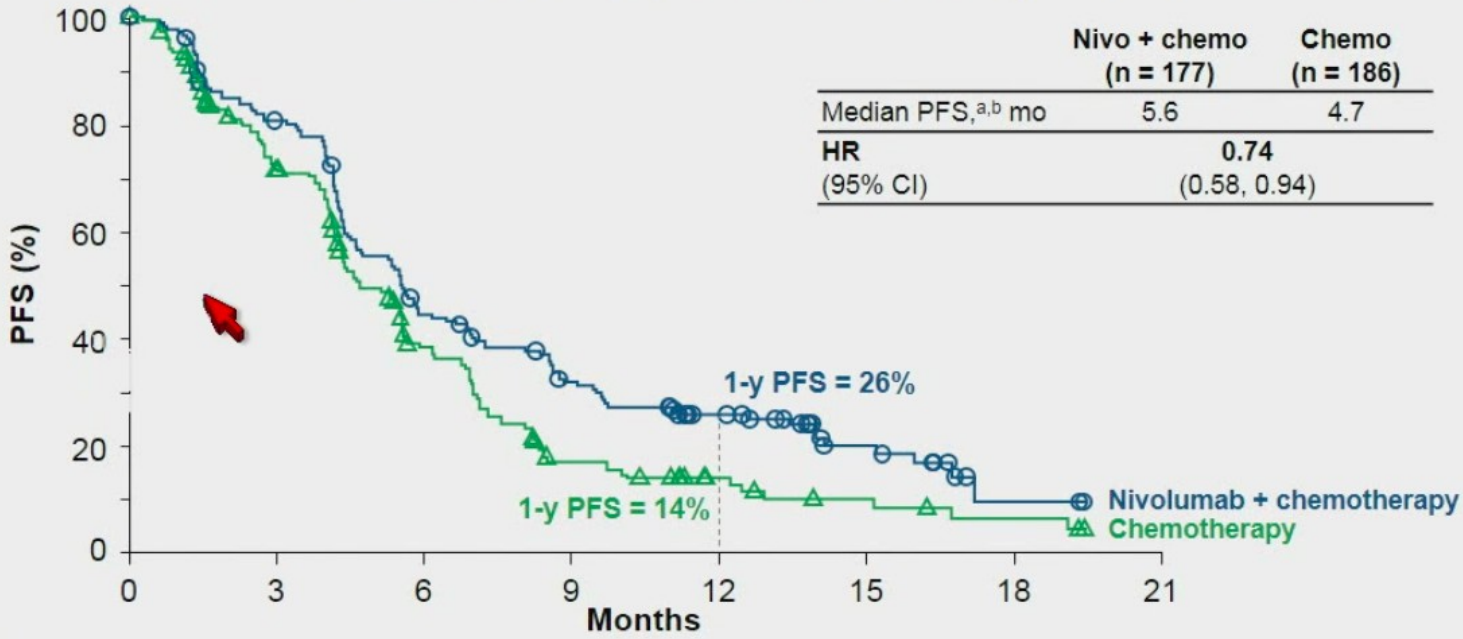
Borghaei H, ASCO 2018

Checkmate 227: PFS

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

All Randomized Patients (Squamous and Non-squamous)



	Nivo + chemo (n = 177)	Chemo (n = 186)
Median PFS,[a,b] mo	5.6	4.7
HR (95% CI)	**0.74** (0.58, 0.94)	

No. at risk								
Nivo + chemo	177	134	72	48	31	13	2	0
Chemo	186	121	56	22	11	6	3	0

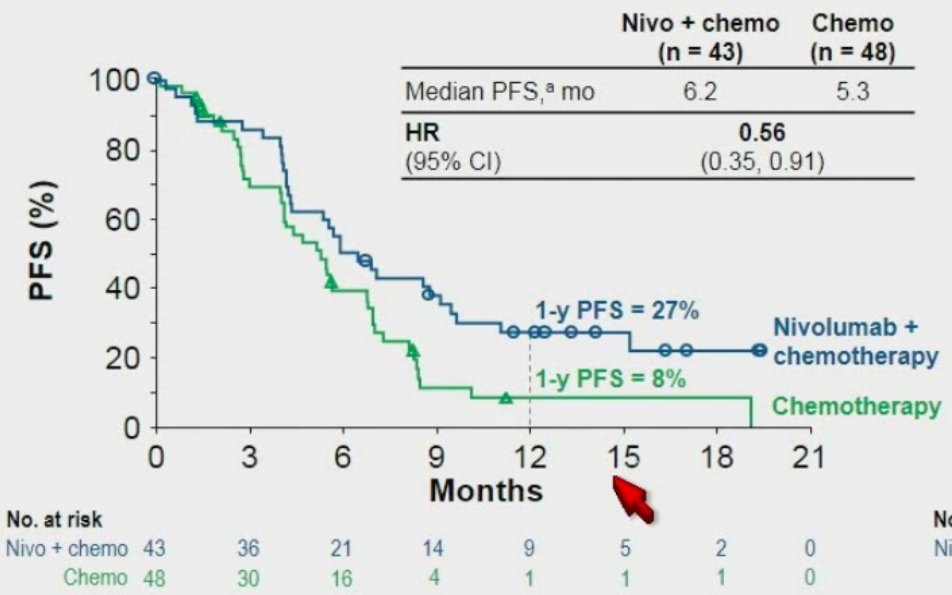
[a]95% CI: nivo + chemo (4.6, 6.7 mo), chemo (4.3, 5.6 mo); [b]In the nivo + ipi arm (n = 187), median (95% CI) PFS was 4.4 (3.1, 6.0), 1-y PFS was 29%, and HR vs chemo was 0.79 (0.62, 1.01)

Borghaei H, ASCO 2018

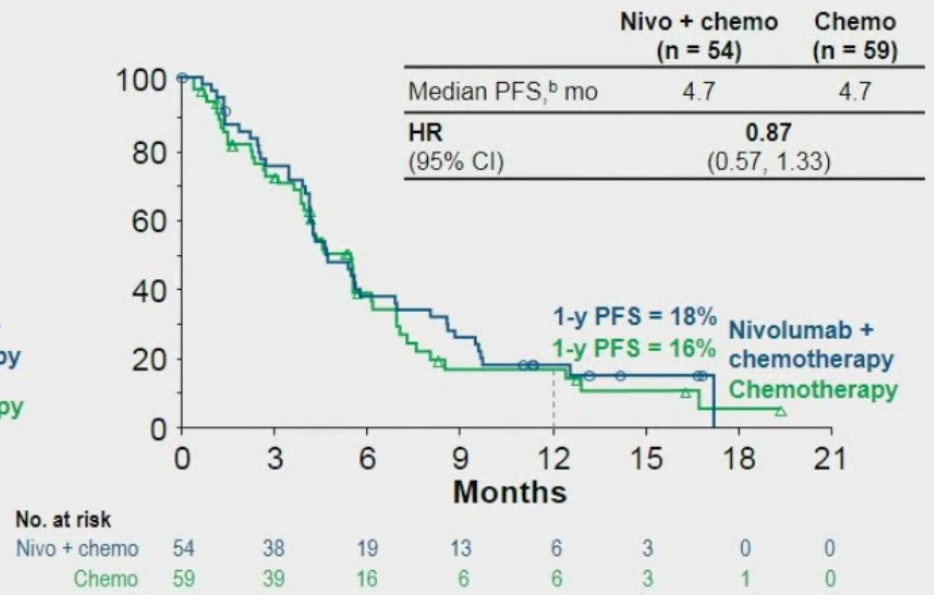
Checkmate 227: PFS by TMB

PFS: Nivolumab + Chemotherapy vs Chemotherapy By TMB

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



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



- 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

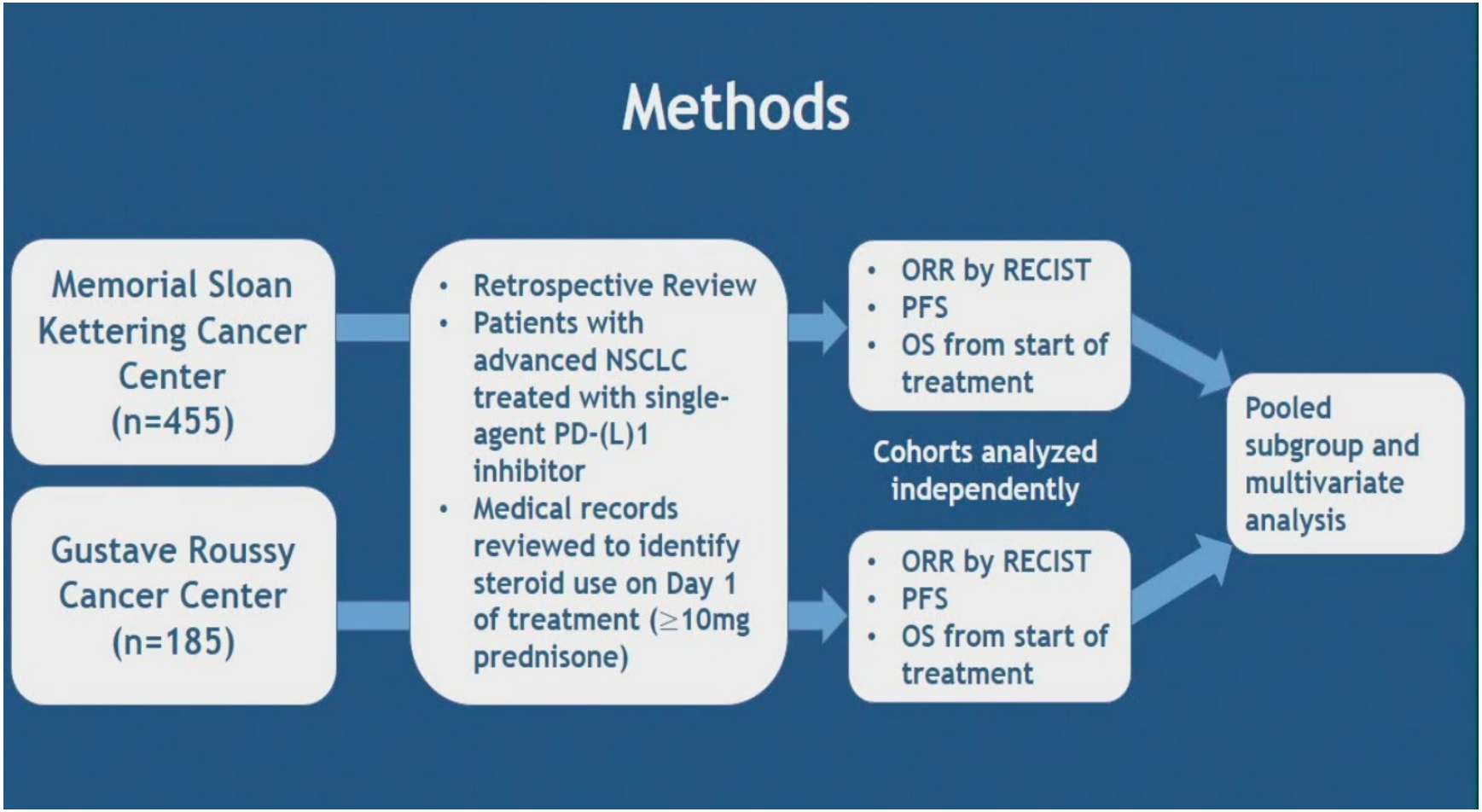
[a]95% CI: nivo + chemo (4.3, 9.1 mo), chemo (4.0, 6.8 mo); [b]95% CI: nivo + chemo (4.2, 6.9 mo), chemo (3.9, 6.2 mo)

Borghaei H, ASCO 2018

Agenda

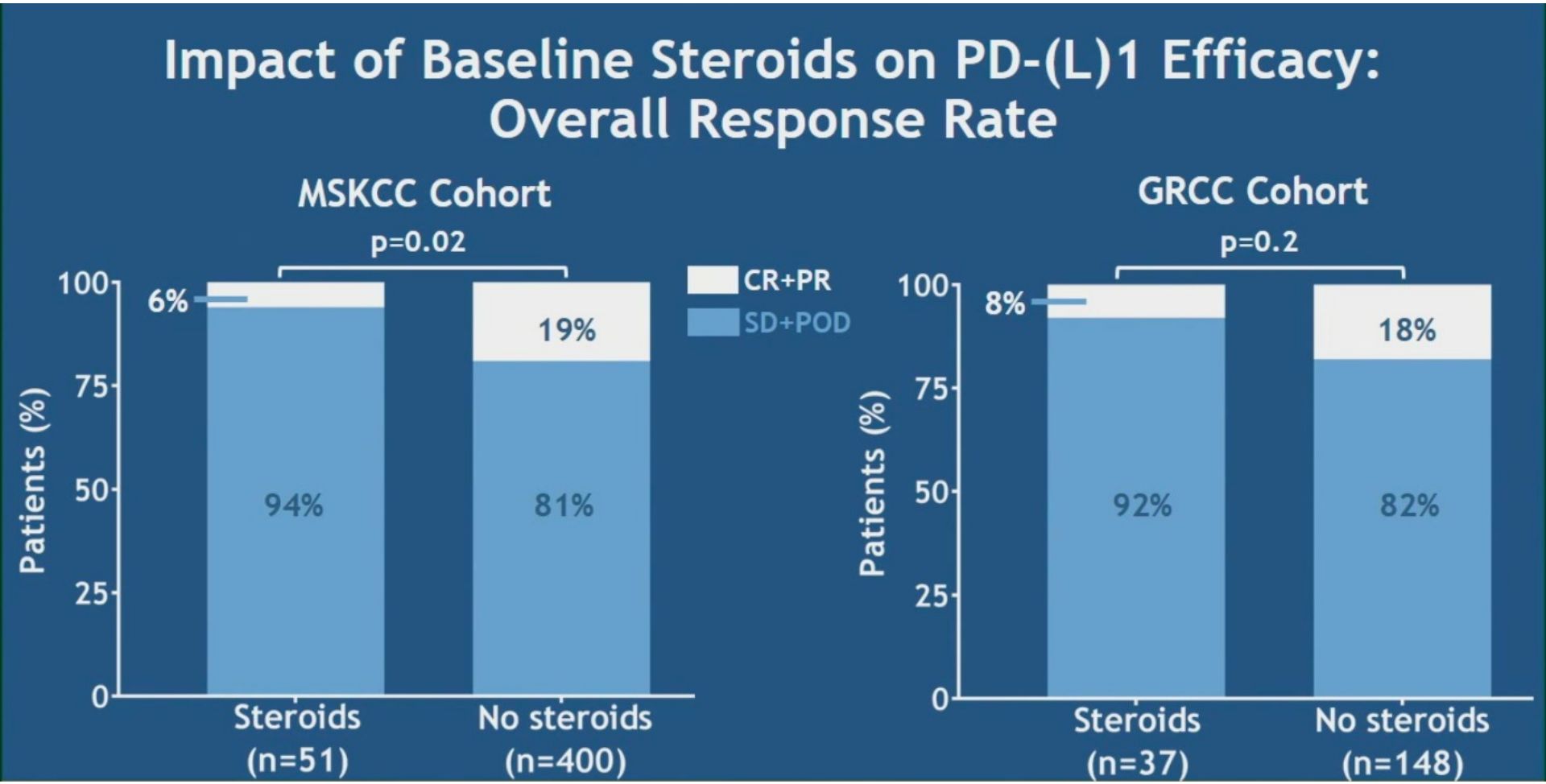
- ✓ Immunotherapy first line
- ✓ Combination immunotherapy
- ✓ **Steroids**
- ✓ Oncogene addicted
- ✓ Immunotherapy in Oncogene Addicted

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



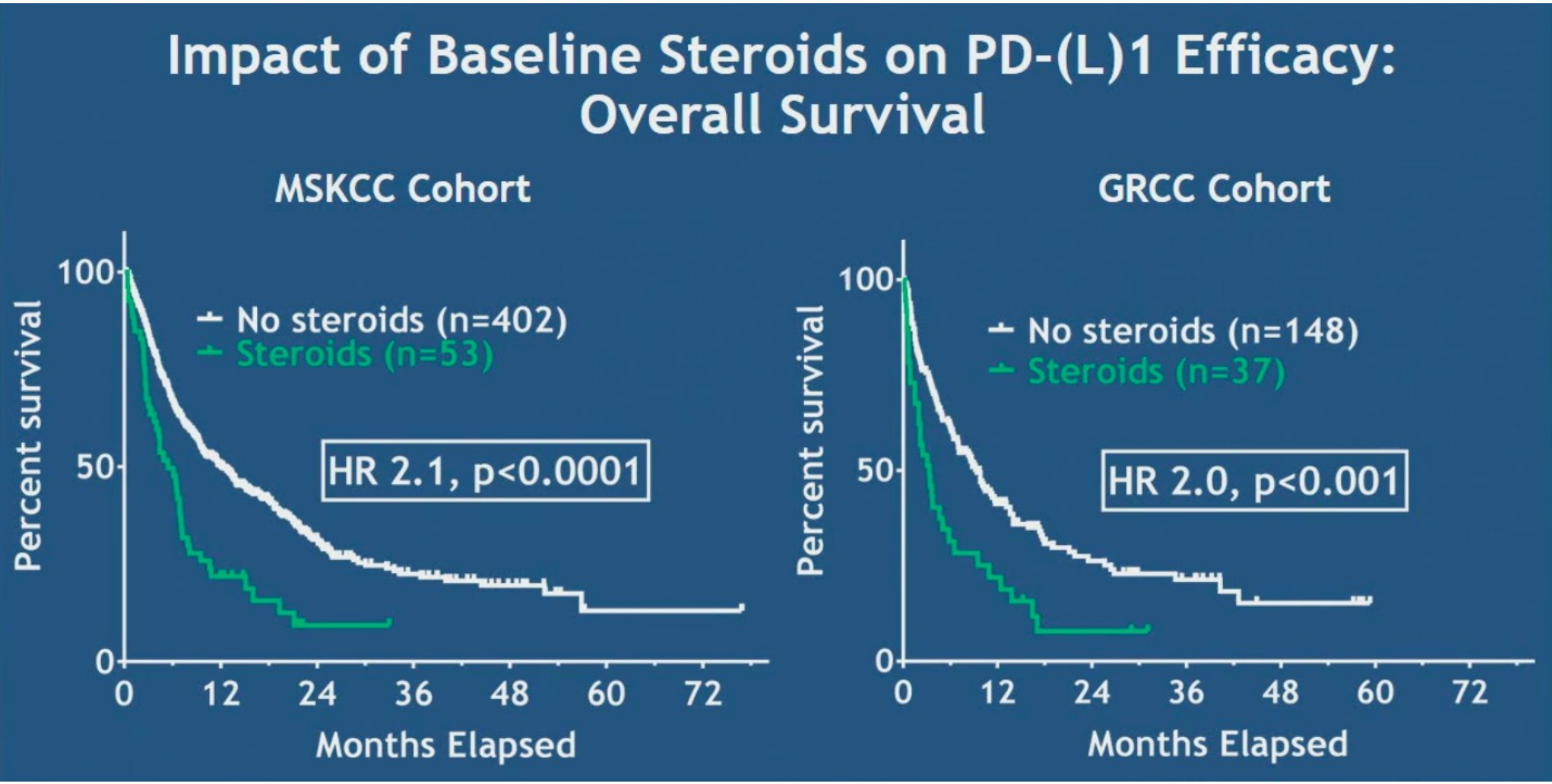
Arbour K, ASCO 2018

Effect of steroids: ORR



Arbour K, ASCO 2018

Effect of steroids: OS



Arbour K, ASCO 2018

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- ✓ Immunotherapy first line
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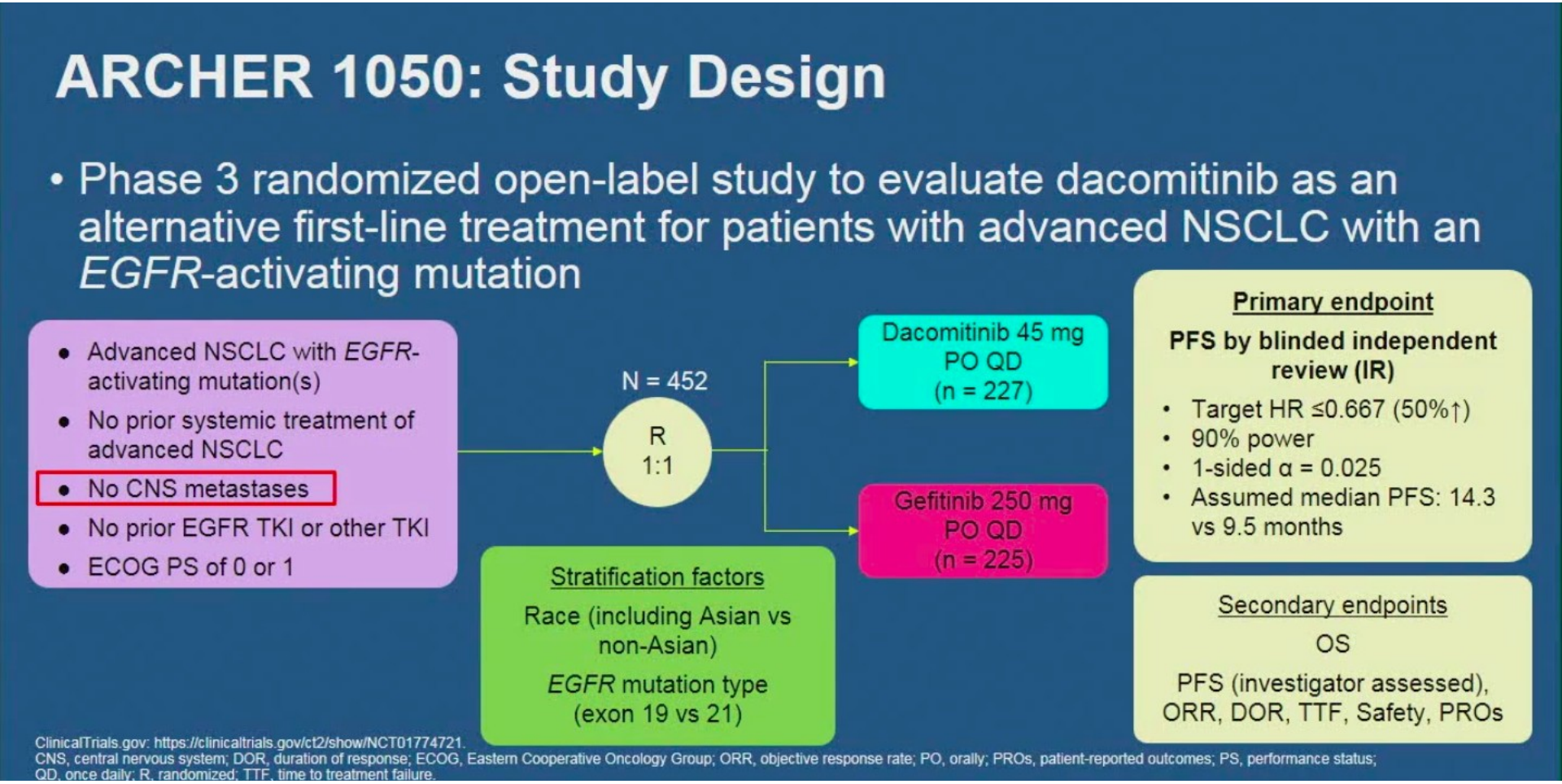
- ✓ **Oncogene addicted**
- ✓ Immunotherapy in Oncogene Addicted
- ✓ Small Cell

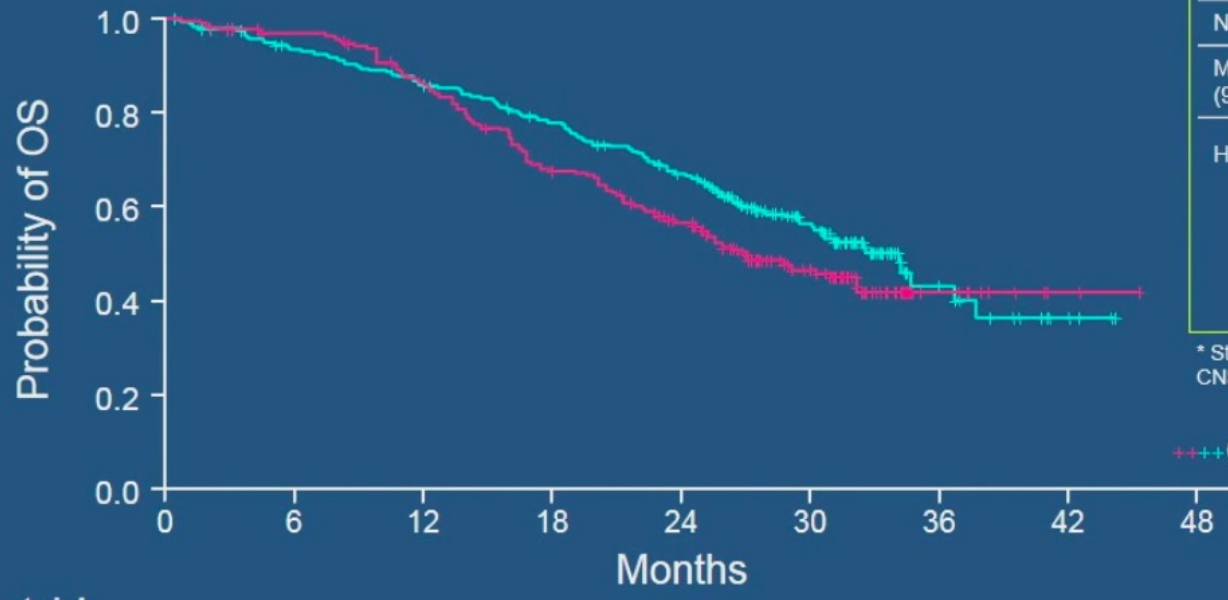
Archer 1050: dacomtinib vs gefitinib



Mok T, ASCO 2018

Archer 1050: OS

Final OS (Primary Analysis)



	Dacomitinib (n = 227)	Gefitinib (n = 225)
Number of deaths, n (%)	103 (45.4)	117 (52.0)
Median OS, months (95% CI)	34.1 (29.5, 37.7)	26.8 (23.7, 32.1)
HR* (95% CI)	0.760 (0.582, 0.993) 2-sided *P** = 0.0438	

* Stratified analysis.
CNS, central nervous system

No. at risk:

Dacomitinib	227	206	188	167	138	77	14	3	0
Gefitinib	225	213	186	144	113	63	12	3	0

Mok T, ASCO 2018

Archer 1050: AEs

Updated Long-Term Adverse Events

Adverse Event,[a] n (%)	Dacomitinib (n = 227)			Gefitinib (n = 224)		
	Grade 1	Grade 2	≥ Grade 3[b]	Grade 1	Grade 2	≥ Grade 3[b]
Diarrhea[c]	113 (49.8)	65 (28.6)	20 (8.8)	103 (46.0)	20 (8.9)	2 (0.9)
Paronychia	46 (20.3)	77 (33.9)	17 (7.5)	30 (13.4)	12 (5.4)	3 (1.3)
Dermatitis acneiform	37 (16.3)	43 (18.9)	31 (13.7)	43 (19.2)	21 (9.4)	0
Stomatitis	51 (22.5)	40 (17.6)	8 (3.5)	33 (14.7)	6 (2.7)	1 (0.4)
Decreased appetite	40 (17.6)	23 (10.1)	7 (3.1)	48 (21.4)	6 (2.7)	1 (0.4)
Dry skin	42 (18.5)	18 (7.9)	3 (1.3)	35 (15.6)	3 (1.3)	0
Weight decreased	31 (13.7)	22 (9.7)	5 (2.2)	22 (9.8)	14 (6.3)	1 (0.4)
Alopecia	41 (18.1)	11 (4.8)	1 (0.4)	26 (11.6)	2 (0.9)	0
Cough	39 (17.2)	9 (4.0)	0	36 (16.1)	5 (2.2)	1 (0.4)
Pruritus	27 (11.9)	17 (7.5)	1 (0.4)	24 (10.7)	4 (1.8)	3 (1.3)
ALT increased	37 (16.3)	5 (2.2)	2 (0.9)	45 (20.1)	24 (10.7)	19 (8.5)
Conjunctivitis	27 (11.9)	16 (7.0)	0	6 (2.7)	3 (1.3)	0
Nausea	32 (14.1)	8 (3.5)	3 (1.3)	46 (20.5)	2 (0.9)	1 (0.4)
AST increased	41 (18.1)	1 (0.4)	0	56 (25.0)	16 (7.1)	9 (4.0)
Rash	19 (8.4)	11 (4.8)	10 (4.4)	22 (9.8)	2 (0.9)	0
Back pain	15 (6.6)	3 (1.3)	0	28 (12.5)	6 (2.7)	1 (0.4)

[a]Adverse events occurring in at least 15% of patients in either study group in the safety population. [b]There were no grade 4 events in either arm and one grade 5 event in the dacomitinib arm. [c]One patient (0.4%) in the dacomitinib arm had grade 5 diarrhea.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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Archer 1050: dose modification

Dose Modification

Dacomitinib

- First dose reduction: 30 mg/day
- Second dose reduction: 15 mg/day

Gefitinib

- 250 mg every 2 days

	Dacomitinib (n = 227)	Gefitinib (n = 224)
Median time to dose reduction, months (range)	2.8 (0.3–20.3)	3.3 (1.2–25.7)
Median duration of dose reduction, months (range)	11.3 (0.1–33.6)	5.2 (0.3–17.8)
Reduction to 30 mg daily, n (%)	88 (38.8)	NA
Reduction to 15 mg daily, n (%)	63 (27.8)	NA
Total number of patients with dose modification, n (%)	151 (66.5)	18 (8.0)

NA, not applicable.

Mok T, ASCO 2018

Agenda

- ✓ Immunotherapy first line
- ✓ Combination immunotherapy
- ✓ Steroids
- ✓ Oncogene addicted
- ✓ **Immunotherapy in Oncogene Addicted**
- ✓ Small Cell

Efficacy of immune-checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC) patients harboring activating molecular alterations (ImmunoTarget).

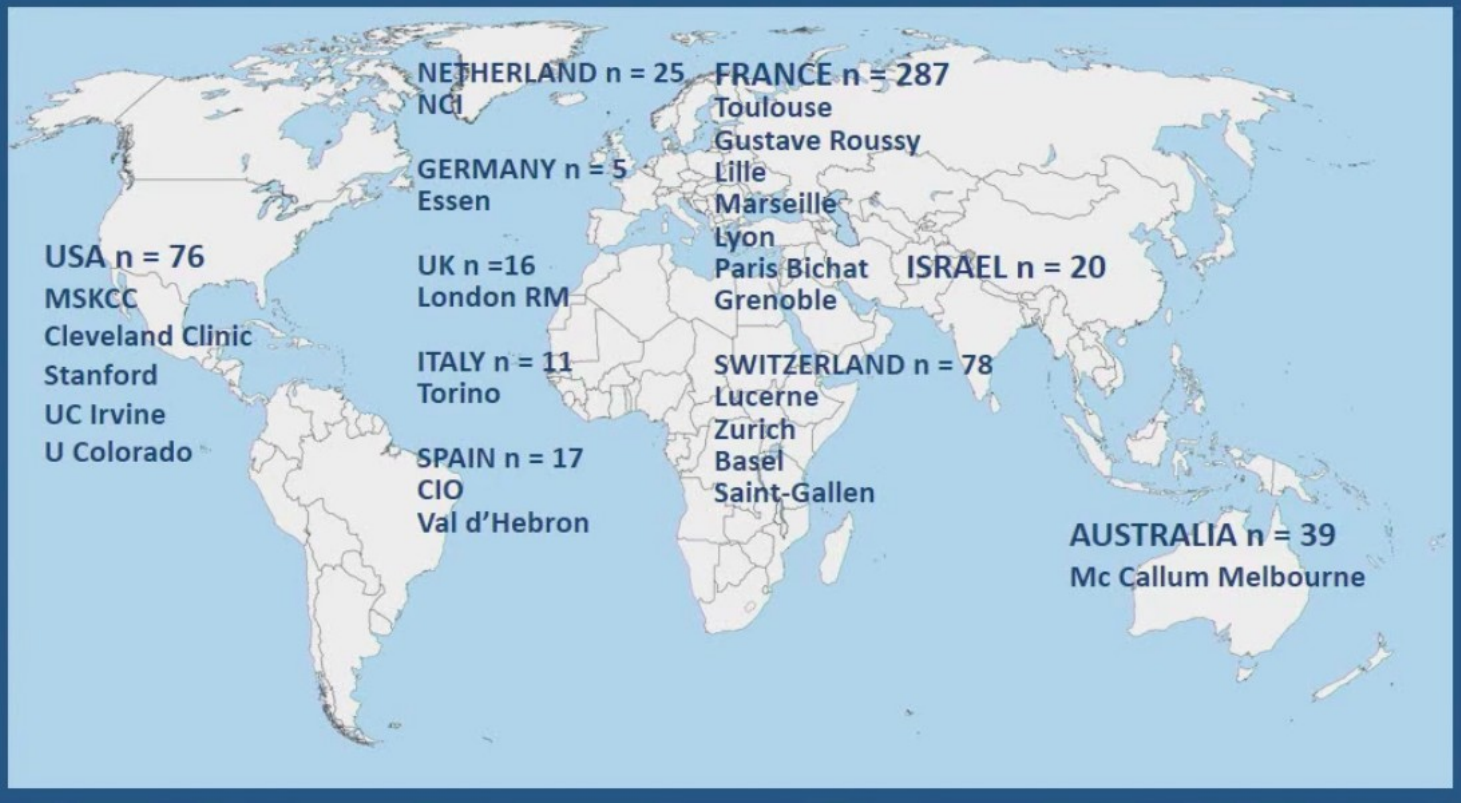
IMMUNOTARGET COHORT

Retrospective multicenter cohort

Inclusion:
- Patients with known activating mutation
- Treated with ICI monotherapy (any line)

Primary objective: PFS under ICI
Secondary objectives: RR, OS, PFS ratio
Exploratory objective: PDL1 expression

Local ethic committees



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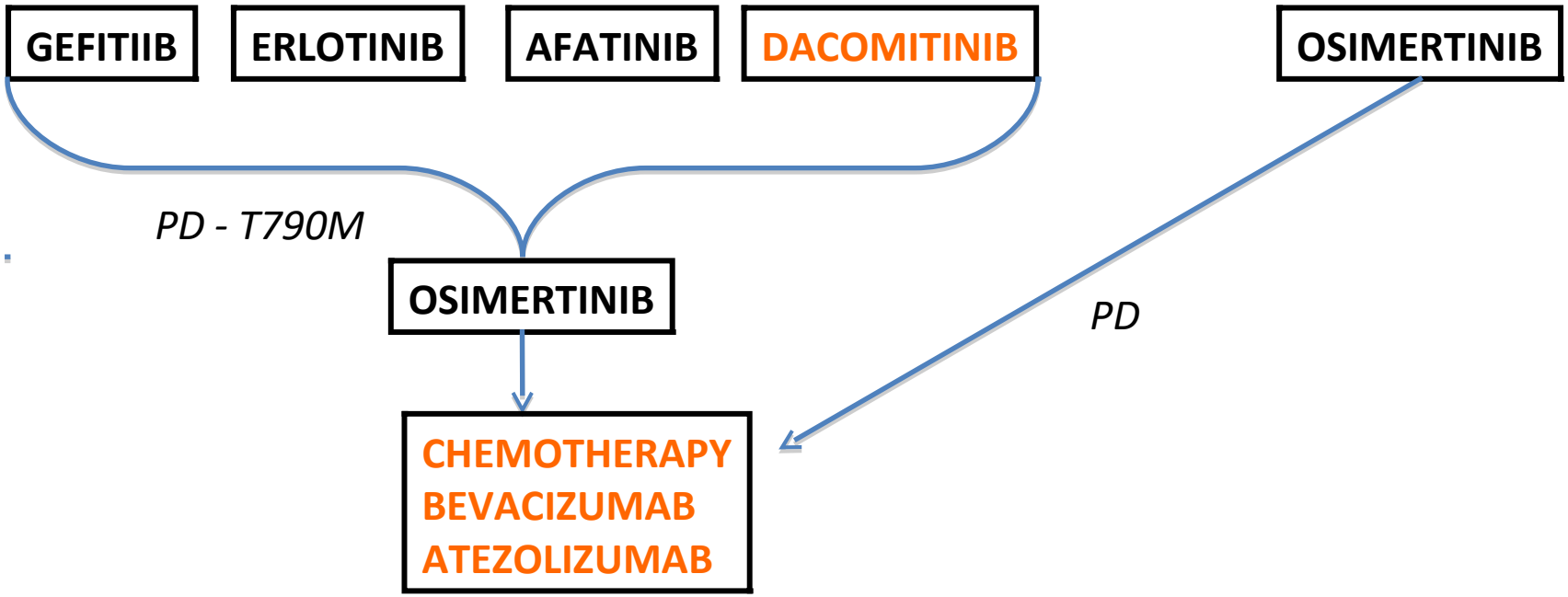
Immunotarget

Conclusion

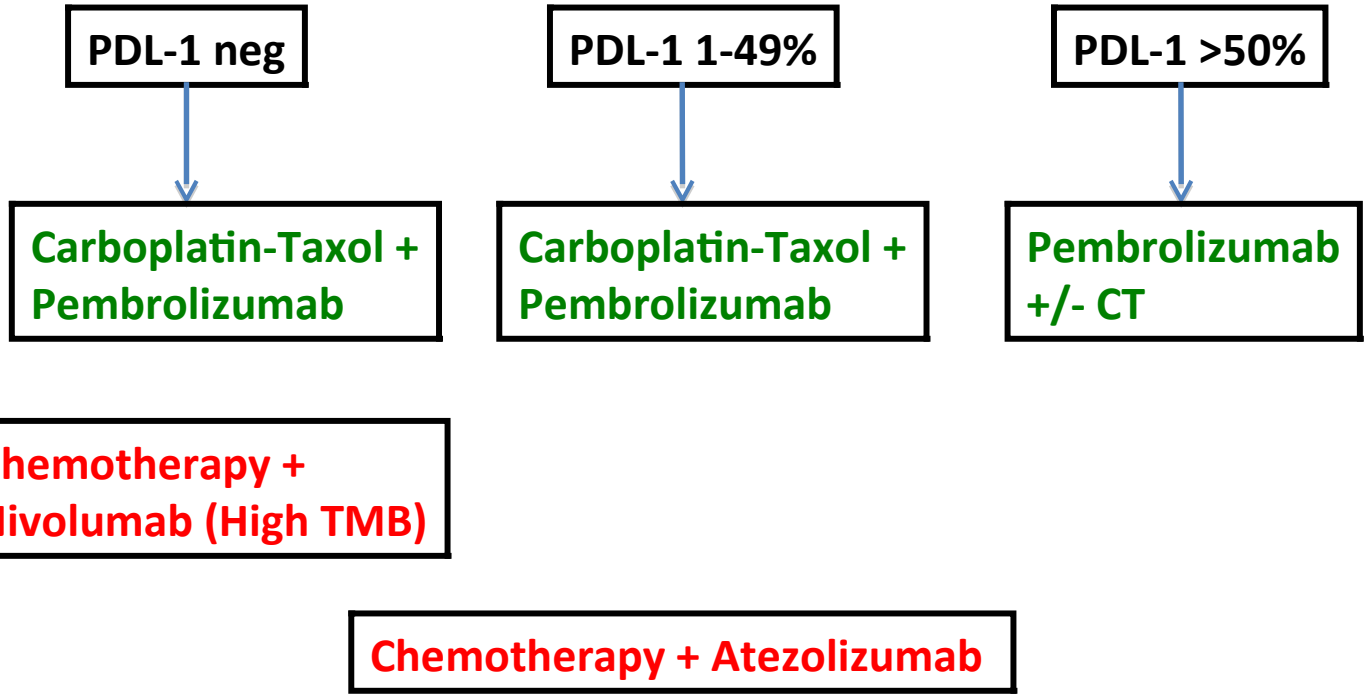
Driver	n	RR	PFS	OS	Impact (+/X) on PFS of				Comments
					PDL1	Smoking	Nb line	Subtype	
Total		19%	2.8	13.3					Outcome consistent with registration trials for ICI
KRAS	271	26%	3.2	13.5	+	X	X	X	Clear benefit across all subgroups
EGFR	125	12%	2.1	10	+	X	X	X	Could be considered in PDL1 + after TKIs exhaustion
BRAF	43	24%	3.1	13.6	X	+	X	NA	Could be considered in smokers
MET	36	16%	3.4	18.4	NA	X	NA	X	Could be considered after conventionnal treatment
HER2	29	7%	2.5	20.3	NA	+	X	NA	
ALK	23	0	2.5	17	X	X	X	NA	Poor outcome. New biomarker needed.
RET	16	6%	2.1	21.3					
ROS1	7	17%	-	-					

Mazieres J, ASCO 2018

Asco 2018: future scenarios
EGFR mut NSCLC



ASCO 2018: future scenarios
SQ NSCLC



ASCO 2018: future scenarios nonSQ NSCLC