



Asco 2018 Highlights

LUNG CANCER

Dott. Paolo Allione



Agenda

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



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Pembrolizumab single agent first line

KEYNOTE-042 Study Design

Key Eligibility Criteria

- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 TPS $\geq 1\%$
- No sensitizing EGFR or ALK alterations
- ECOG PS 0 or 1
- No untreated or unstable CNS metastases
- No history of pneumonitis that required systemic corticosteroids

Stratification Factors

- Region (east Asia vs rest of the world)
- ECOG PS (0 vs 1)
- Histology (squamous vs nonsquamous)
- PD-L1 TPS ($\geq 50\%$ vs 1-49%)

Randomize
1:1

N = 637

Pembrolizumab
200 mg Q3W
for up to 35 cycles

N = 637

Carboplatin AUC 5 or 6 Q3W +
Paclitaxel 200 mg/m² Q3W^a
OR
Carboplatin AUC 5 or 6 Q3W +
Pemetrexed 500 mg/m² Q3W^a
for up to 6 cycles

End points

- Primary: OS in PD-L1 TPS $\geq 50\%$, $\geq 20\%$, and $\geq 1\%$
- Secondary: PFS and ORR in TPS $\geq 50\%$, $\geq 20\%$, and $\geq 1\%$; safety in TPS $\geq 1\%$

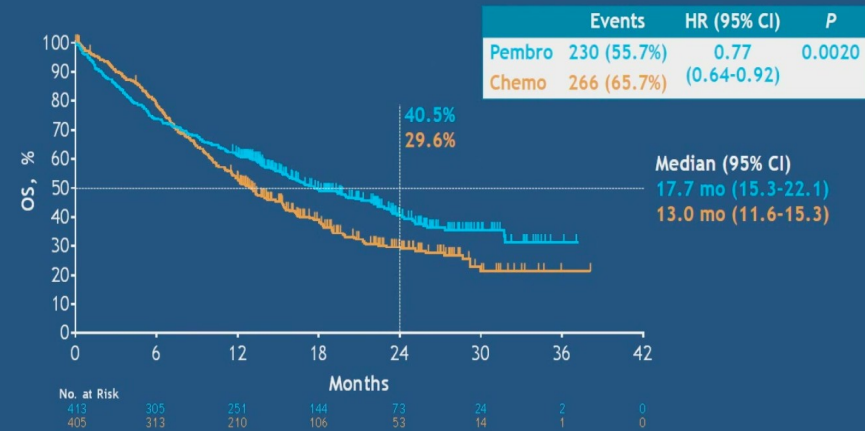
^aPemetrexed maintenance therapy was optional but strongly encouraged for patients with nonsquamous histology.

Keynote 042: OS

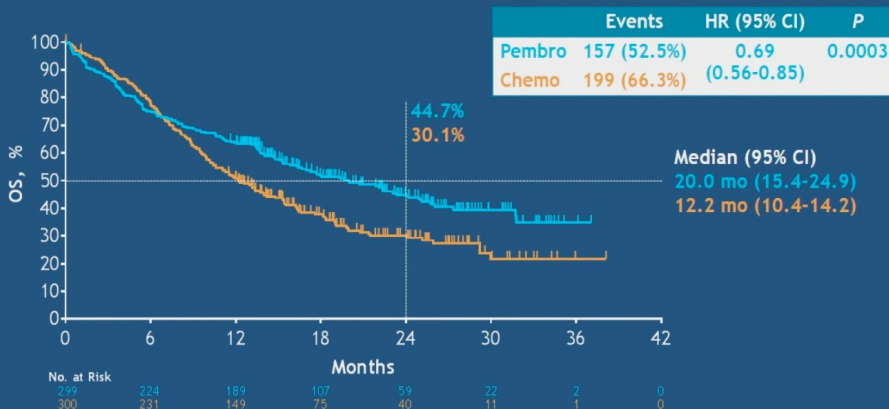
Overall Survival: TPS $\geq 1\%$



Overall Survival: TPS $\geq 20\%$



Overall Survival: TPS $\geq 50\%$

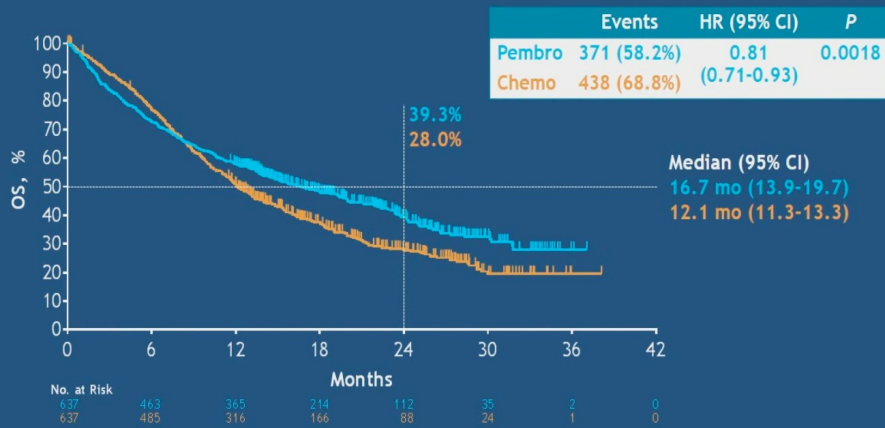


G.LOPES, ASCO 2018

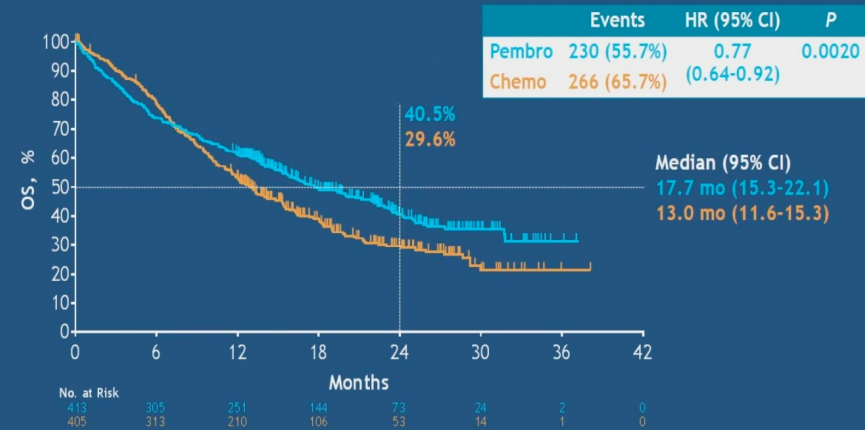
Data cutoff date: Feb 26, 2018

Keynote 042: OS

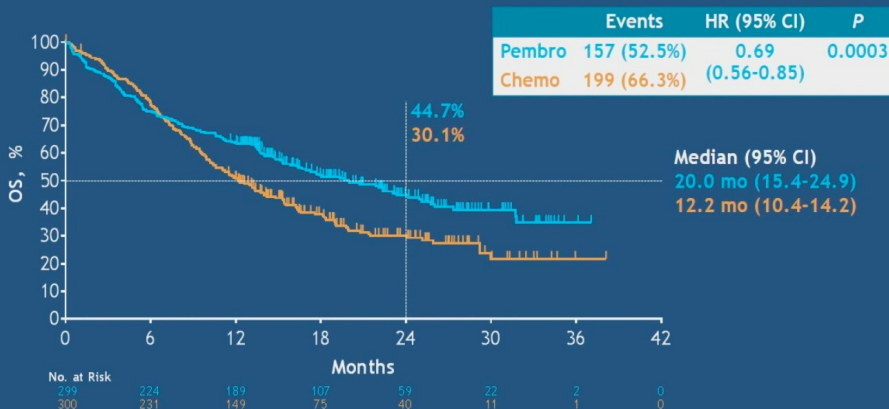
Overall Survival: TPS $\geq 1\%$



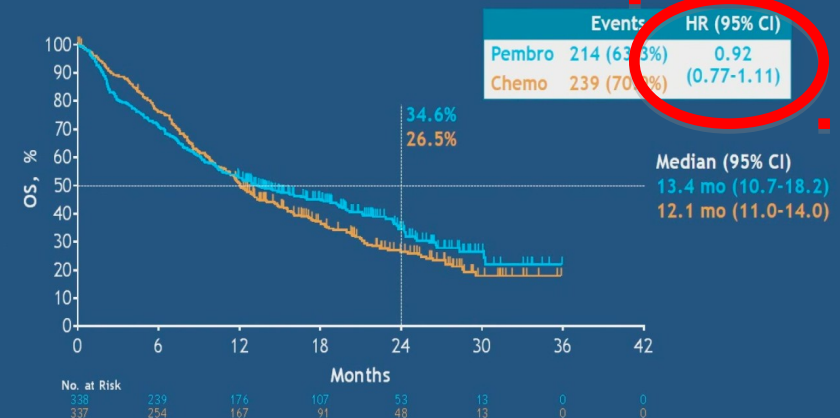
Overall Survival: TPS $\geq 20\%$



Overall Survival: TPS $\geq 50\%$

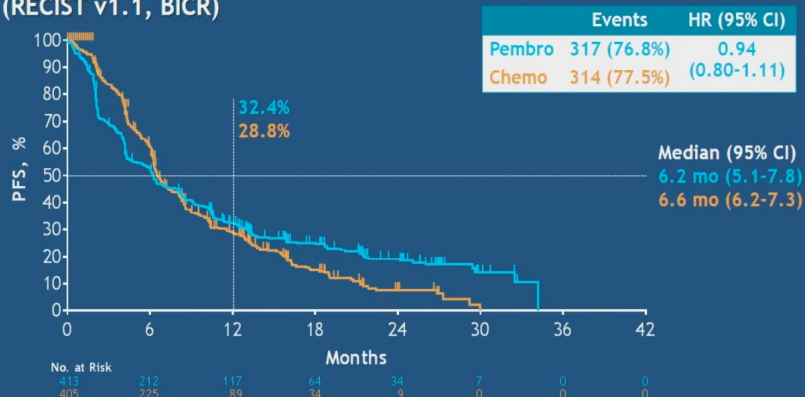


Overall Survival: TPS $\geq 1-49\%$ (Exploratory Analysis^a)



Keynote 042: PFS and ORR

Progression-Free Survival: TPS ≥20% (RECIST v1.1, BICR)



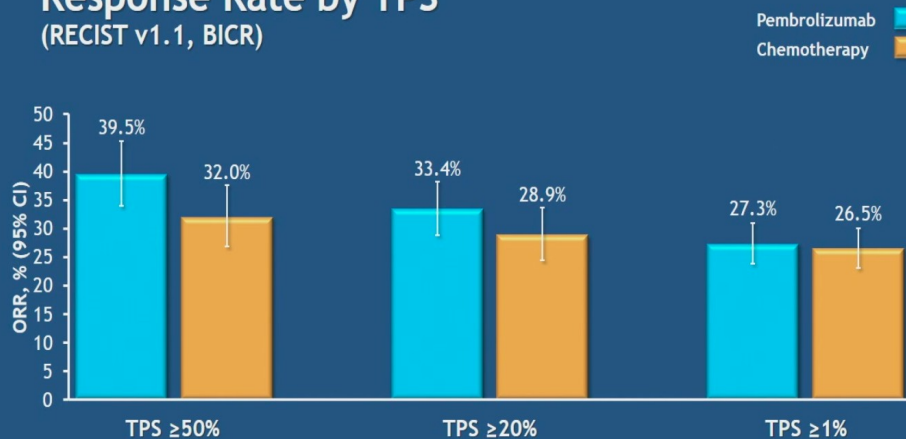
Progression-Free Survival: TPS ≥1% (RECIST v1.1, BICR)



Formal comparison of pembrolizumab vs chemotherapy not performed based on hierarchical testing strategy.

Formal comparison of pembrolizumab vs chemotherapy not performed based on hierarchical testing strategy.

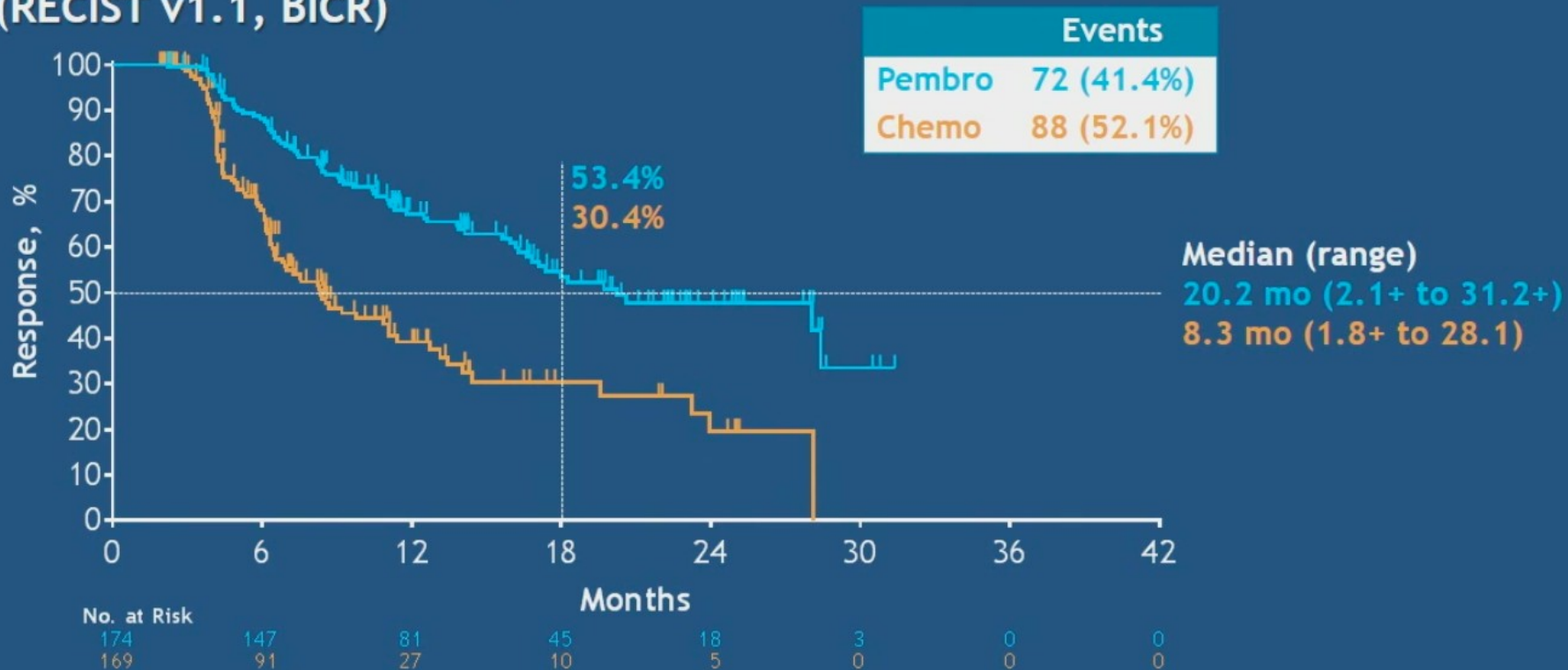
Response Rate by TPS (RECIST v1.1, BICR)



ORR for TPS 1-49%: 16.6% (95% CI 12.8-21.0) for pembro vs 21.7% (95% CI 17.4-26.4).
 CR in pembro arm: 0 with TPS ≥50%, 2 with TPS ≥20%, 3 with TPS ≥1%; CR in chemo arm: 0 with TPS ≥50%, 1 with TPS ≥20%, 3 with TPS ≥1%.

Keynote 042: duration of response

Duration of Response: TPS $\geq 1\%$ (RECIST v1.1, BICR)



Median DOR for pembro vs chemo: 20.2 mo vs 10.8 mo for TPS $\geq 50\%$, 20.2 mo vs 8.3 mo for TPS $\geq 20\%$, and 17.4 mo vs 8.2 mo for TPS 1-49%.

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

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 $\geq 1\%$
- 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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- ✓ **Combination immunotherapy**
- ✓ Steroids
- ✓ Oncogene addicted
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Keynote 407: chemotherapy plus pembrolizumab in SqNSCLC

KEYNOTE-407 Study Design (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

Stratification Factors

- PD-L1 expression (TPS^a <1% vs ≥1%)
- Choice of taxane (paclitaxel vs nab-paclitaxel)
- Geographic region (east Asia vs rest of world)

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

End points

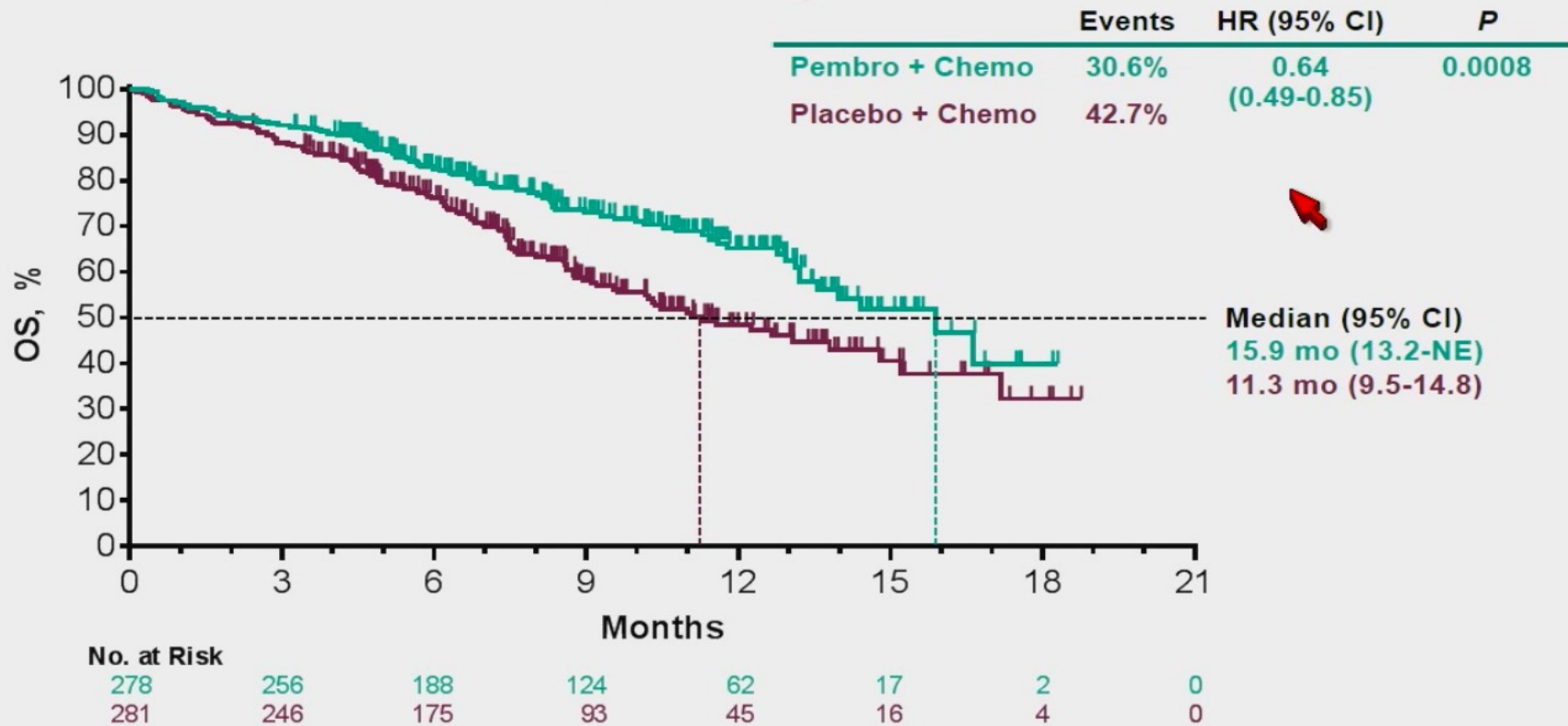
- Primary: PFS (RECIST v1.1, BICR) and OS
- Secondary: ORR and DOR (RECIST v1.1, BICR), safety

Optional Crossover^b
Pembrolizumab
200 mg Q3W
for up to 35 cycles

PD^b

Keynote 407: OS

Overall Survival at IA2, ITT

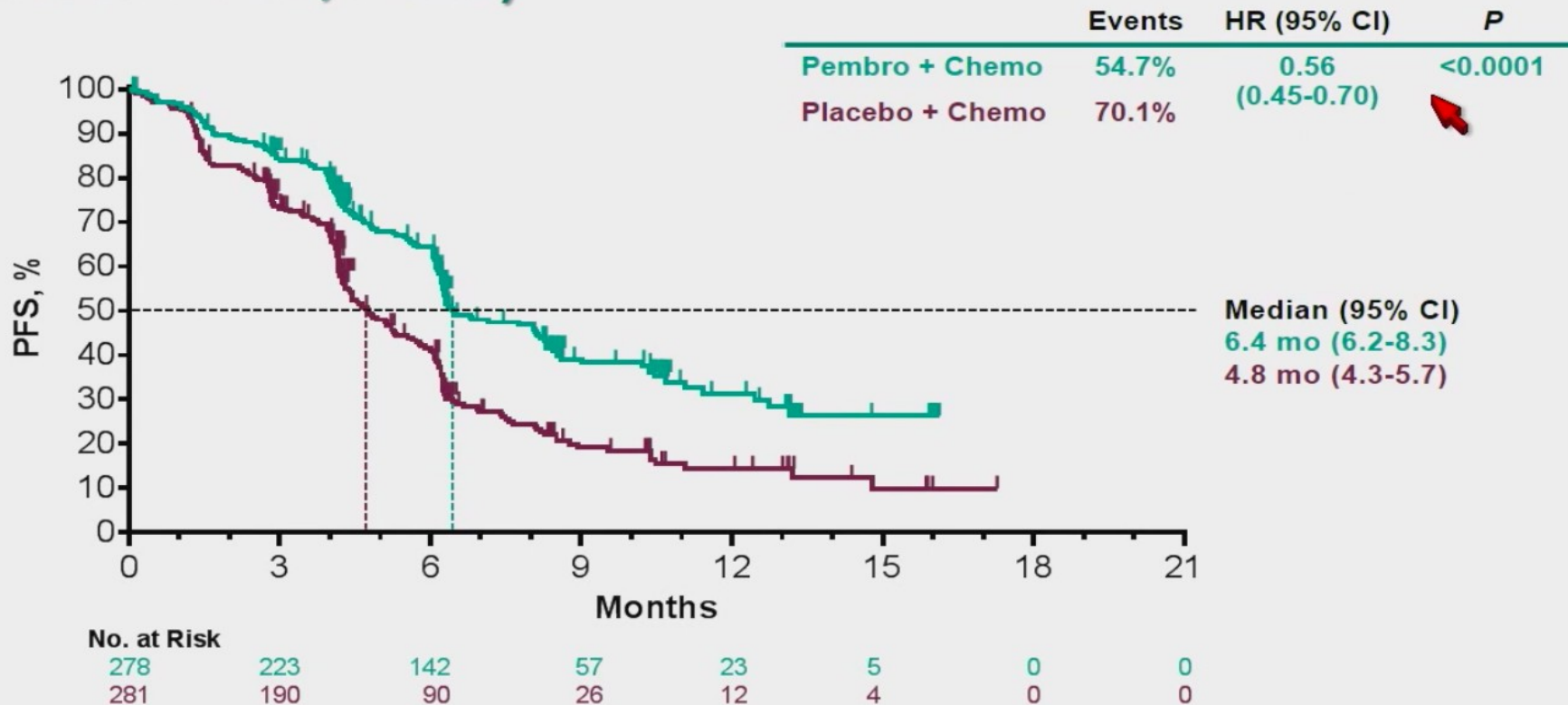


Data cutoff date: Apr 3, 2018.

Keynote 407: OS by PDL-1 expression

Keynote 407: PFS


Progression-Free Survival at IA2, ITT (RECIST v1.1, BICR)



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

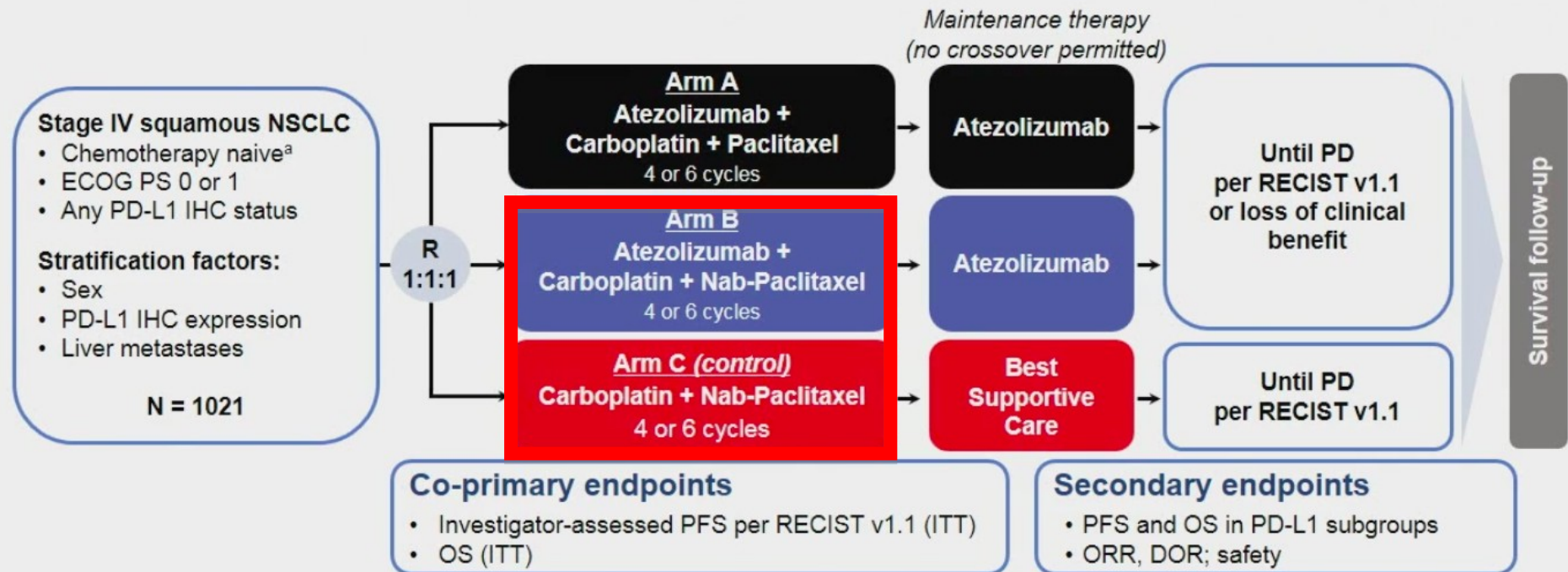
Keynote 407: Conclusions

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 

ImPower131: chemotherapy plus atezolizumab in SqNSCLC

IMpower131: Study Design



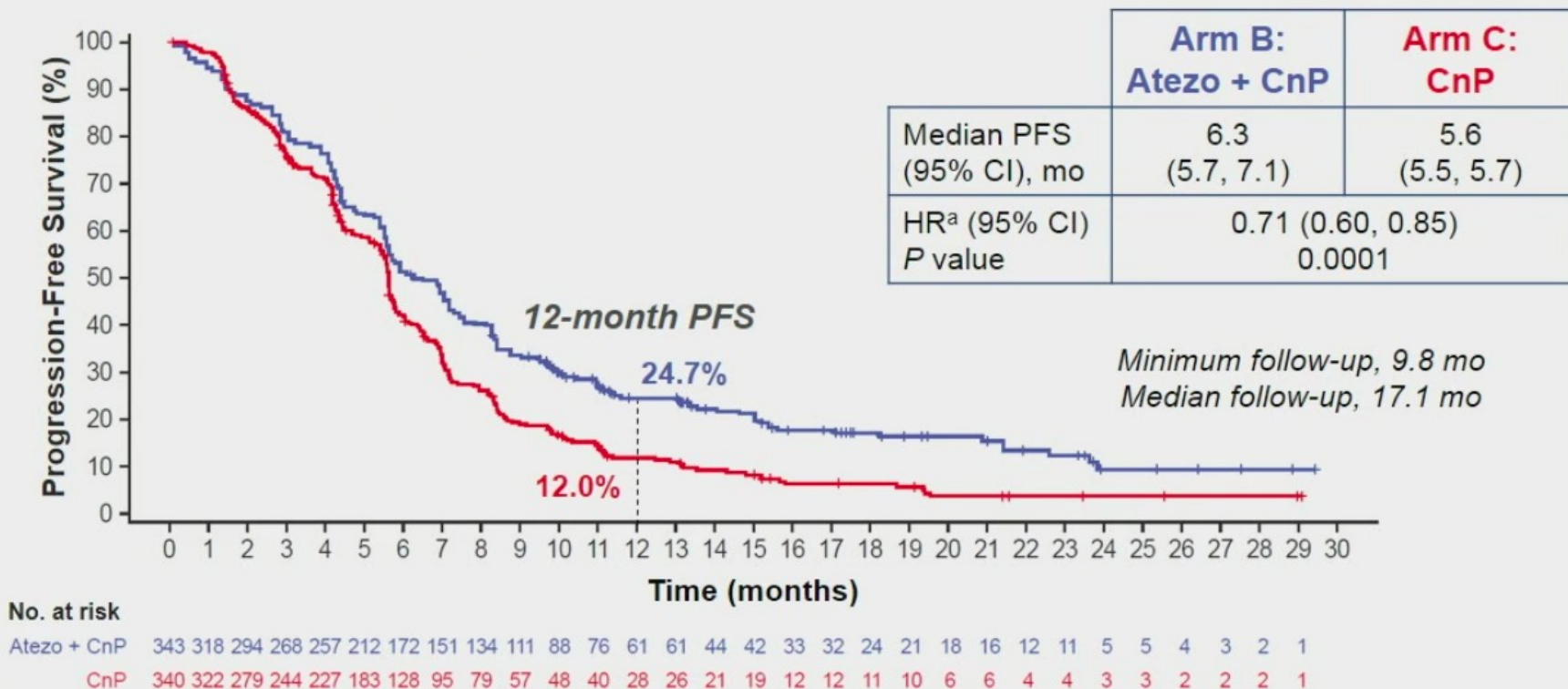
Atezolizumab 1200 mg IV q3w; carboplatin AUC 6 IV q3w; nab-paclitaxel 100 mg/m² IV qw; paclitaxel 200 mg/m² IV q3w.

^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.

ImPower131: PFS

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



Data cutoff: January 22, 2018.

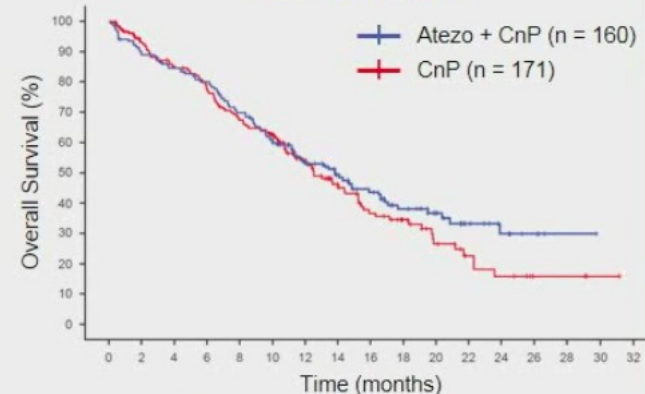
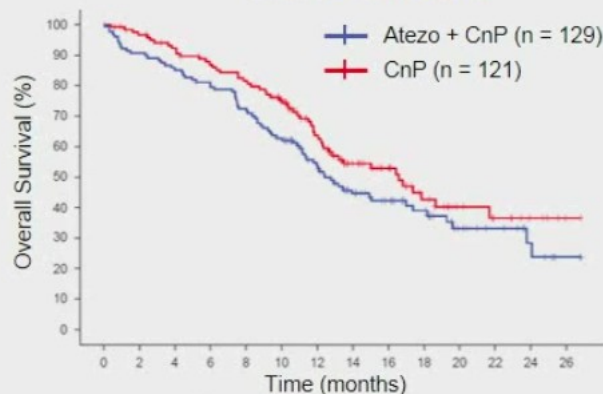
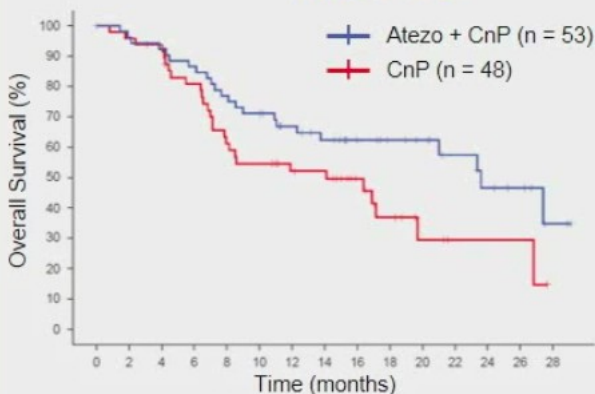
ImPower131: OS by PDL-1 expression

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



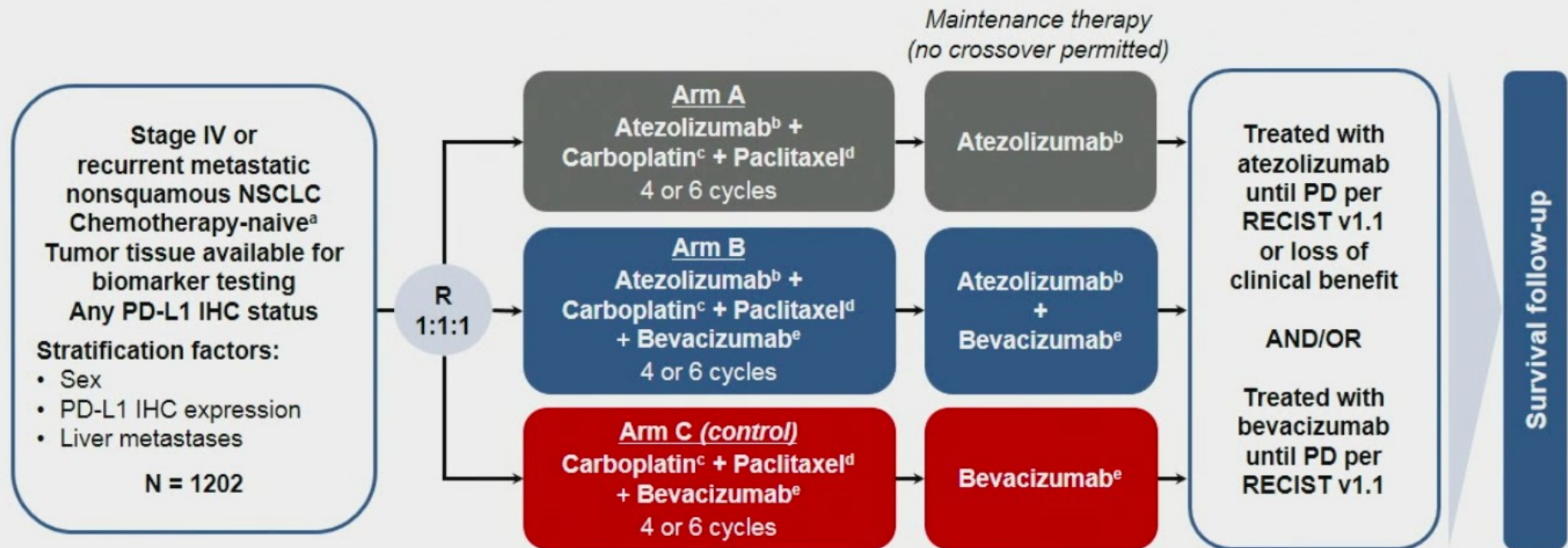
	Atezo + CnP	CnP	Atezo + CnP	CnP	Atezo + CnP	CnP
12-month OS	67%	52%	54%	64%	53%	53%
24-month OS	47%	30%	28%	37%	30%	16%
Median OS, mo	23.6	14.1	12.4	16.6	13.8	12.5
HR^a (95% CI)	0.56 (0.32, 0.99)		1.34 (0.95, 1.90)		0.86 (0.65, 1.15)	

Data cutoff: January 22, 2018.

^a Unstratified HR.

ImPower150: chemotherapy plus bevacizumab plus atezolizumab in nonSqNSCLC

IMpower150 Study Design

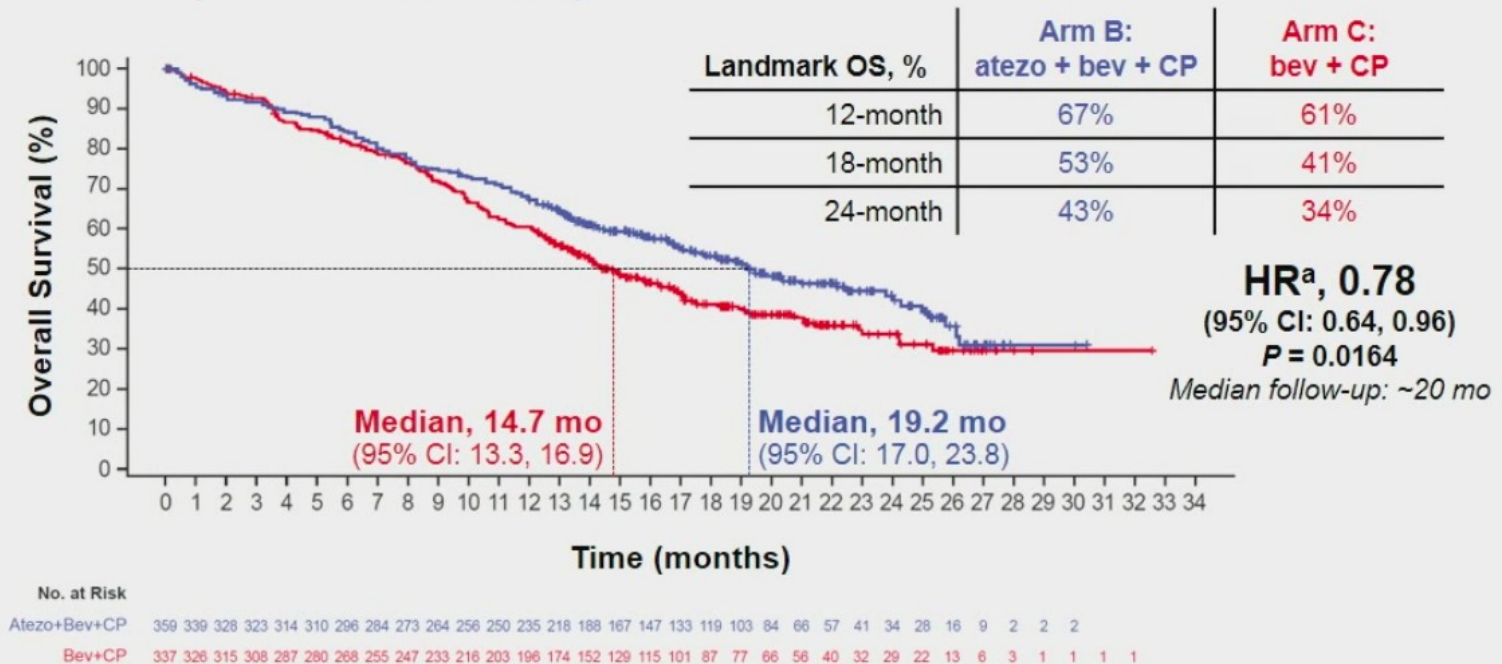


^a Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.

^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.

ImPower150: Os

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

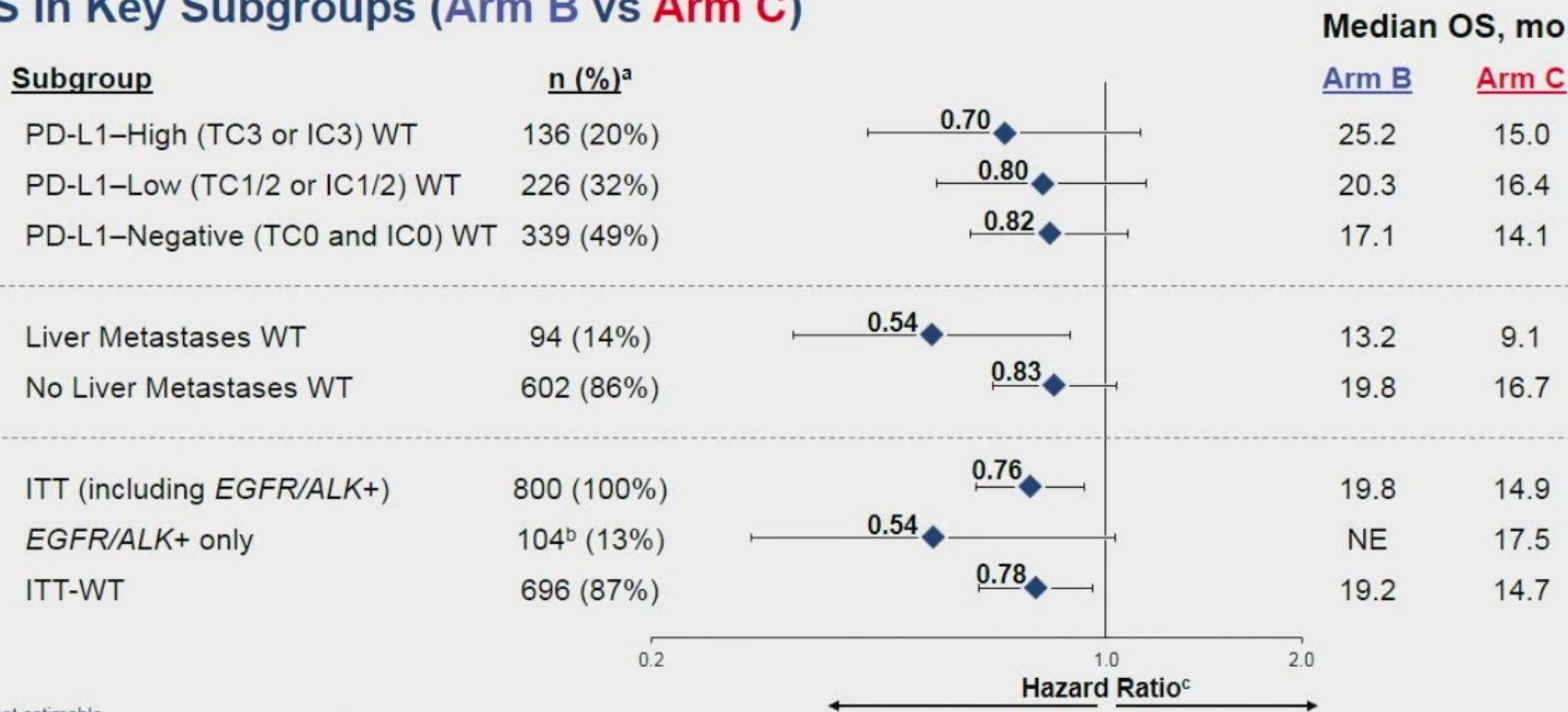


- Statistically significant and clinically meaningful OS benefit with atezolizumab + bevacizumab + chemotherapy vs bevacizumab + chemotherapy was observed

^a Stratified HR.
Data cutoff: January 22, 2018

ImPowe150: Os (subgroups)

OS in Key Subgroups (Arm B vs Arm C)



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).

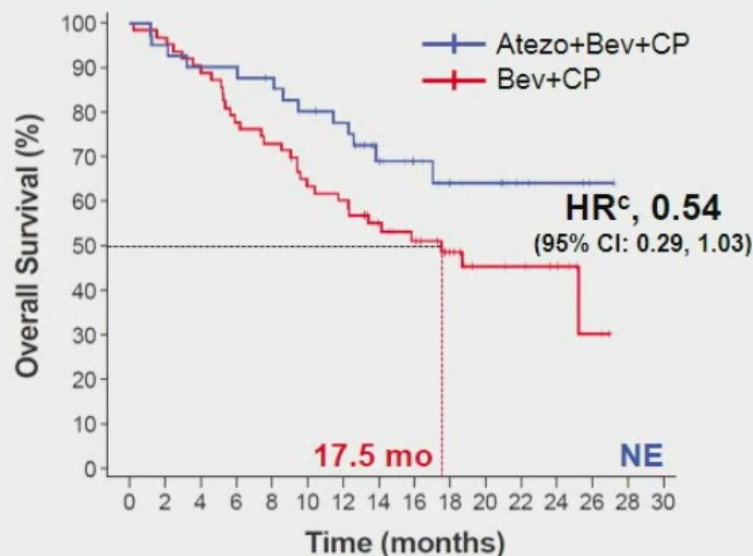
^b One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab.

^c Stratified HR for ITT and ITT-WT; unstratified HR for all other subgroups. Data cutoff: January 22, 2018

Impower150: EGFR/ALK

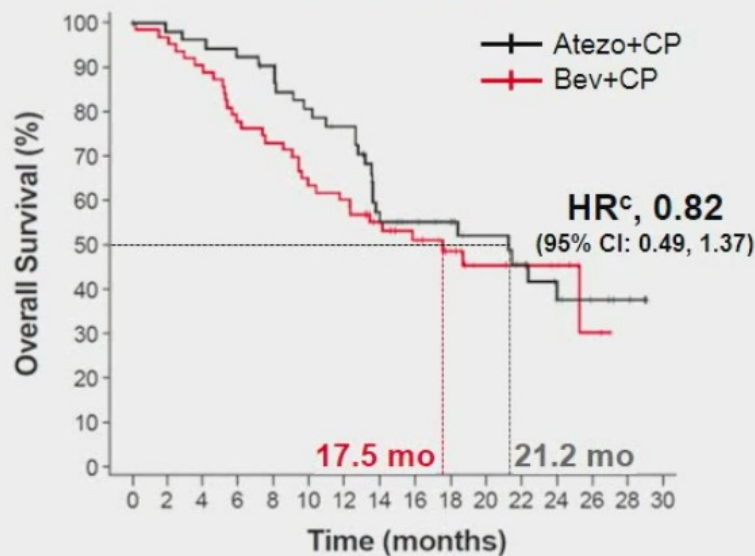
Addition of Bevacizumab to Atezolizumab and Chemotherapy Prolongs Survival of *EGFR/ALK*+ Patients^a

Arm B^b vs Arm C



No. at Risk	
Atezo+Bev+CP	41 39 37 37 35 32 30 20 15 11 9 5 4 2
Bev+CP	63 61 57 49 46 39 37 28 24 17 12 11 7 2

Arm A vs Arm C



No. at Risk	
Atezo+CP	53 51 50 48 46 41 37 24 22 20 16 13 8 6 4
Bev+CP	63 61 57 49 46 39 37 28 24 17 12 11 7 2

^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.

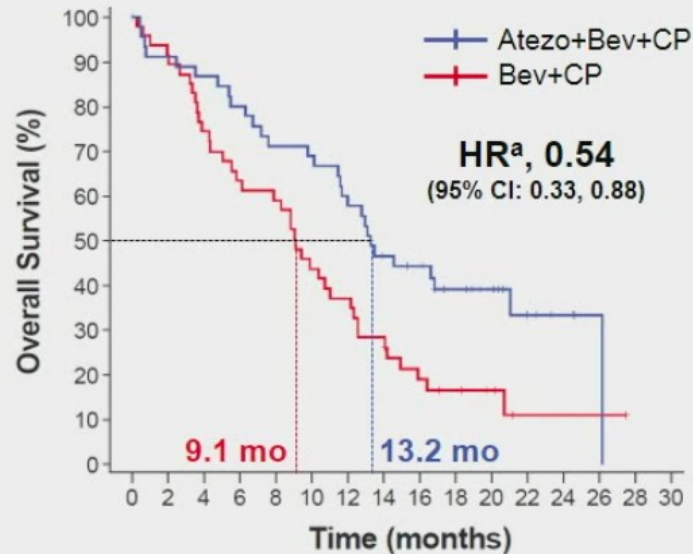
^b One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab. ^c Unstratified HR.

Data cutoff: January 22, 2018

ImPower150: liver metastases

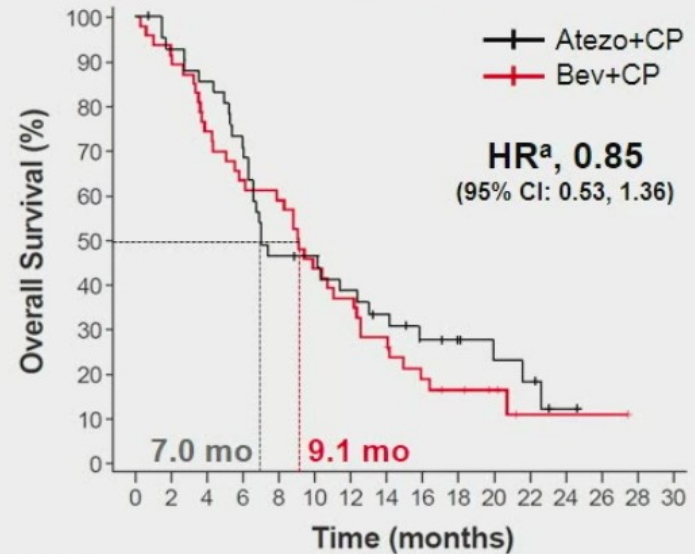
Addition of Bevacizumab to Atezolizumab and Chemotherapy Prolongs Survival of Patients With Liver Metastases in the ITT-WT

Arm B vs Arm C



No. at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Atezo+Bev+CP	47	41	39	36	32	31	26	20	18	13	10	5	3	1		
Bev+CP	47	42	34	29	27	20	17	13	8	6	4	1	1	1		

Arm A vs Arm C

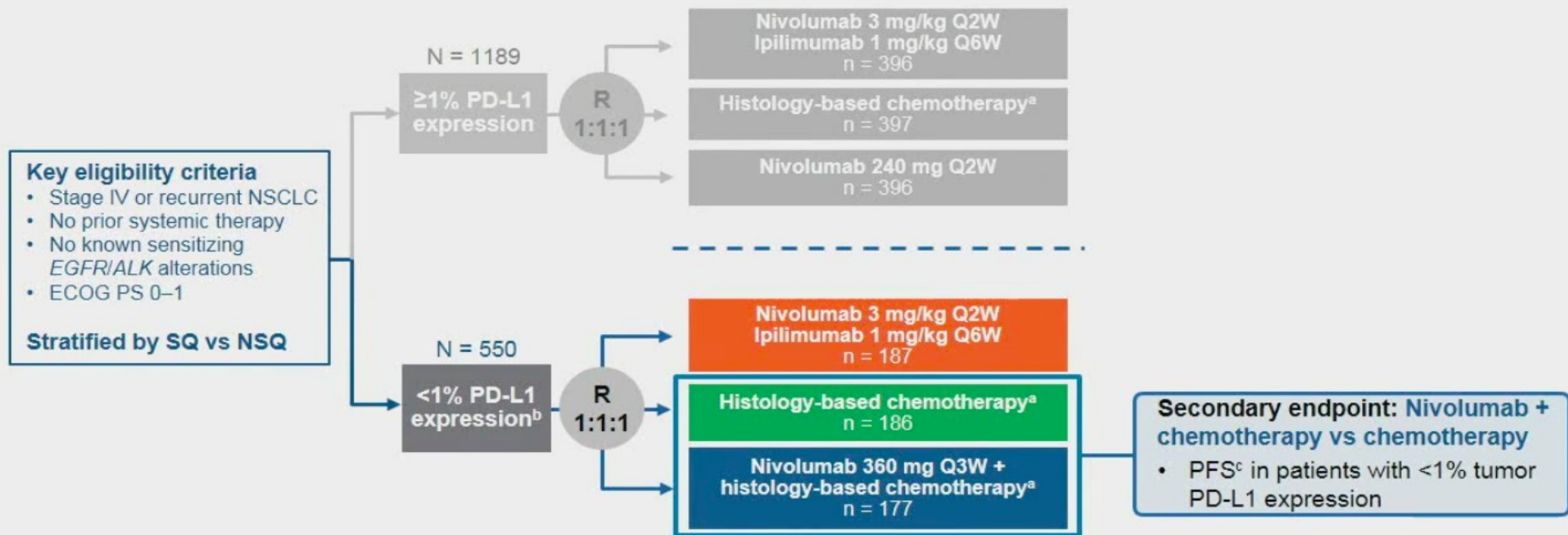


No. at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Atezo+CP	42	38	35	28	19	18	15	12	9	7	5	4	1			
Bev+CP	47	42	34	29	27	20	17	13	8	6	4	1	1	1		

^a Unstratified HR.
Data cutoff: January 22, 2018

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

CheckMate 227 Part 1 Study Design



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

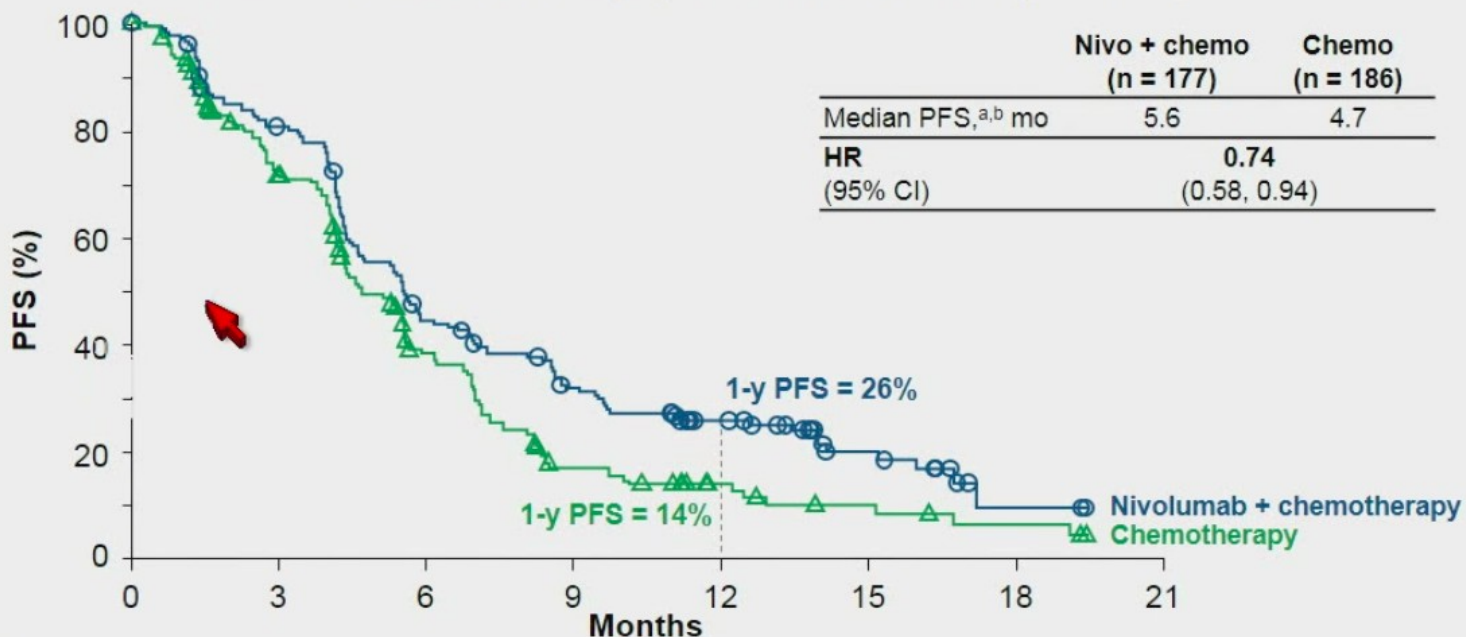
Database lock: January 24, 2018; minimum follow-up: 11.2 months

^aNSQ: pemetrexed + cisplatin or carboplatin, Q3W for ≤4 cycles, with optional pemetrexed maintenance following chemotherapy or nivolumab + pemetrexed maintenance following nivolumab + chemotherapy; ^bSQ: gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤4 cycles; ^cOne patient was randomized with <1% tumor PD-L1 expression in IVRS, but was subsequently found to have ≥1% tumor PD-L1 expression; ^dPer BICR

Checkmate 227: PFS

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

All Randomized Patients (Squamous and Non-squamous)



No. at risk

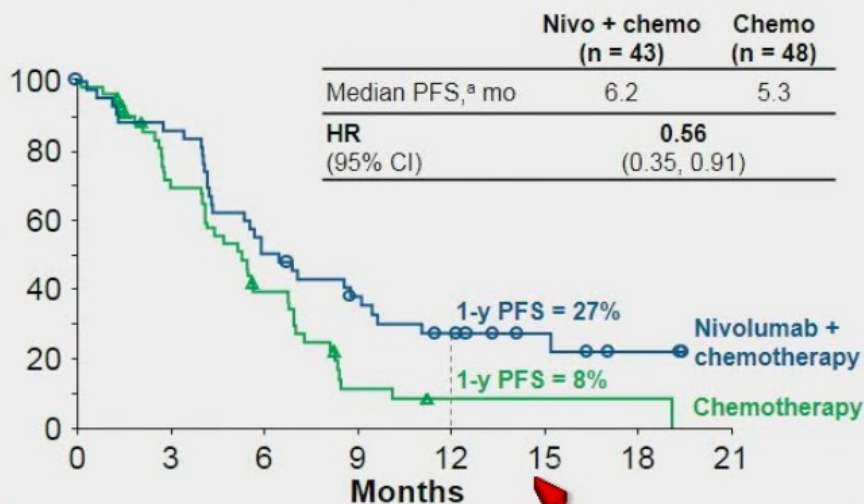
Nivo + chemo	177	134	72	48	31	13	2	0
Chemo	186	121	56	22	11	6	3	0

^a95% CI: nivo + chemo (4.6, 6.7 mo), chemo (4.3, 5.6 mo); ^bIn 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)

Checkmate 227: PFS by TMB

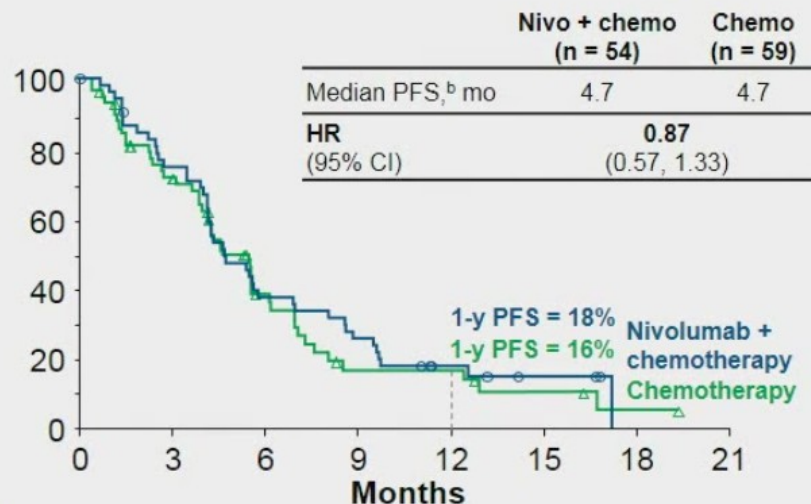
PFS: Nivolumab + Chemotherapy vs Chemotherapy By TMB

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



No. at risk	0	3	6	9	12	15	18	21
Nivo + chemo	43	36	21	14	9	5	2	0
Chemo	48	30	16	4	1	1	1	0

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



No. at risk	0	3	6	9	12	15	18	21
Nivo + chemo	54	38	19	13	6	3	0	0
Chemo	59	39	16	6	6	3	1	0

- 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

^a95% CI: nivo + chemo (4.3, 9.1 mo), chemo (4.0, 6.8 mo); ^b95% CI: nivo + chemo (4.2, 6.9 mo), chemo (3.9, 6.2 mo)

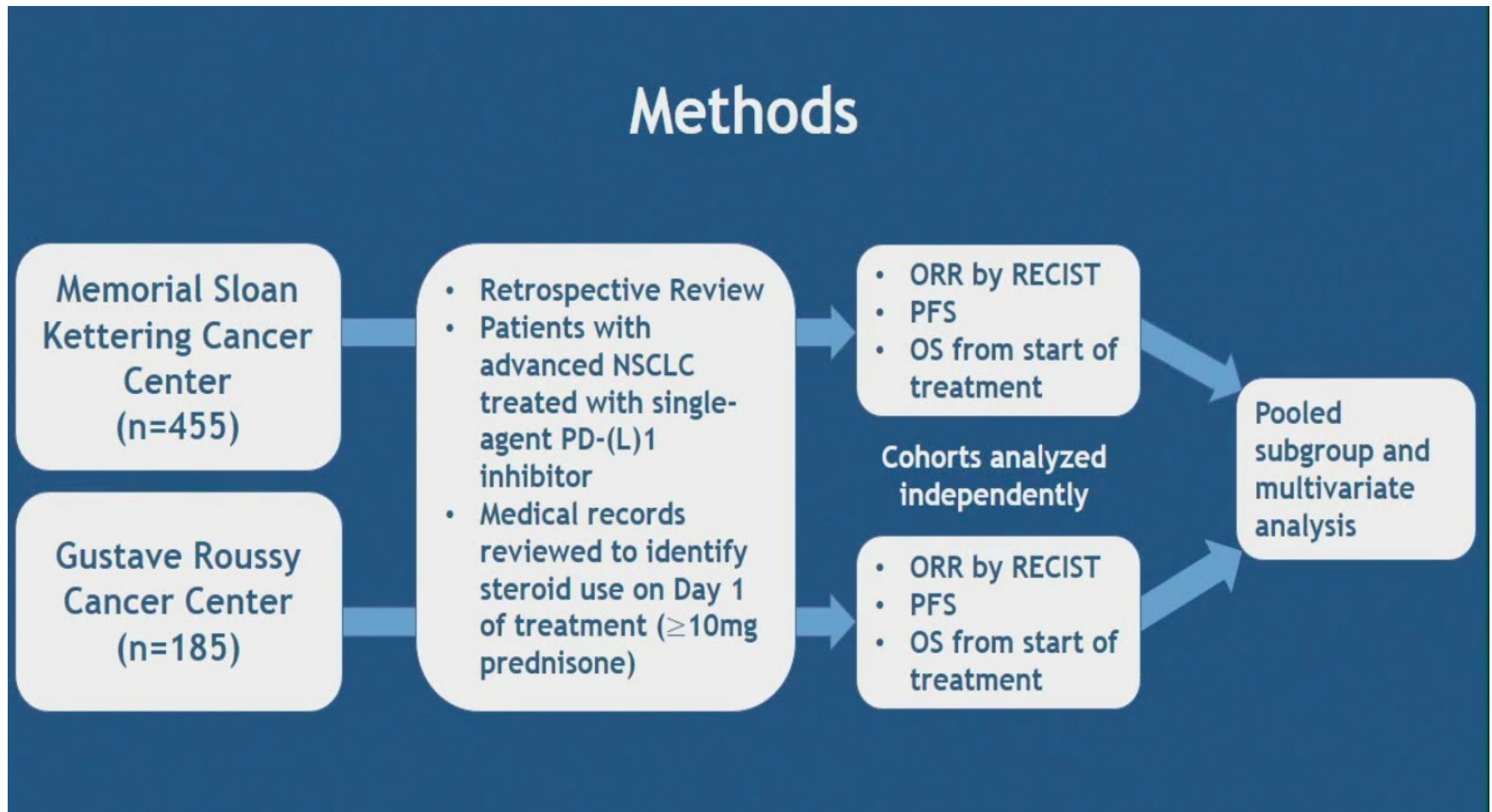
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- ✓ **Steroids**
- ✓ Oncogene addicted
- ✓ Immunotherapy in Oncogene Addicted



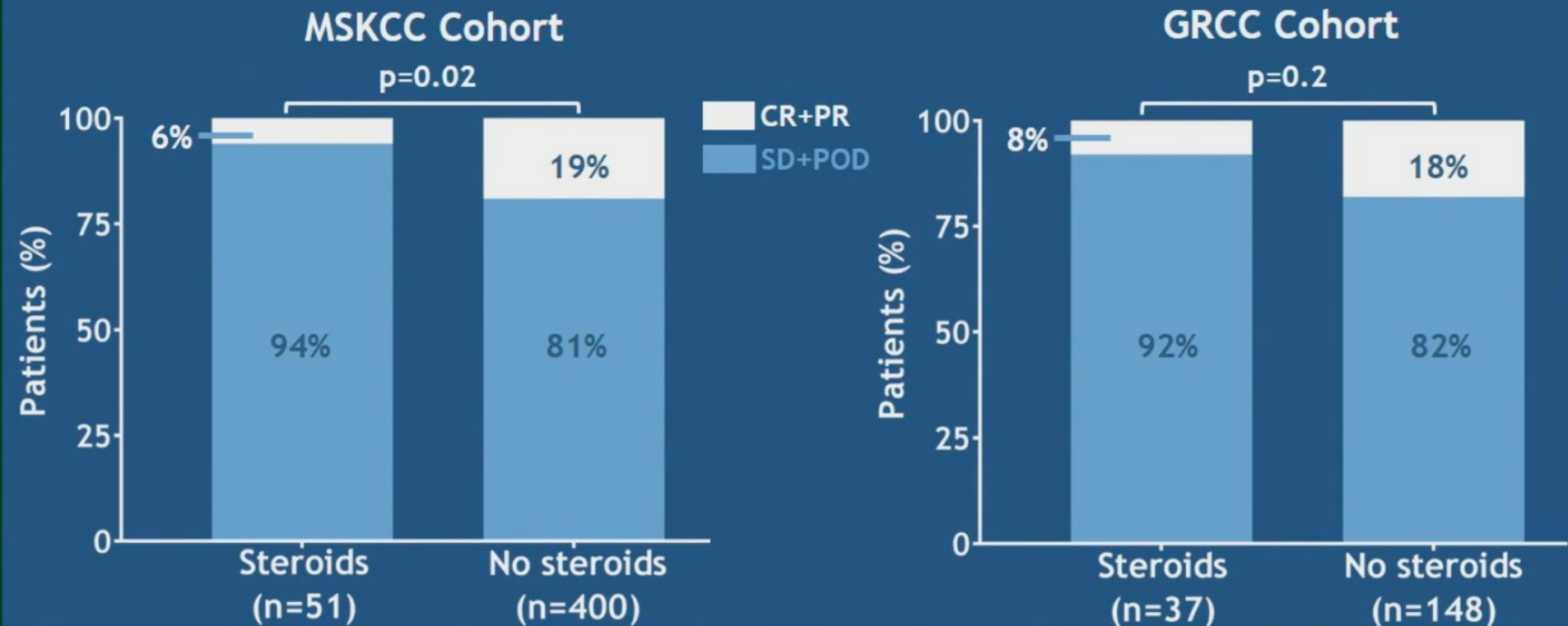
Deleterious effect of baseline steroids on efficacy of PD-(L)1 blockade in patients with NSCLC

Methods



Effect of steroids: ORR

Impact of Baseline Steroids on PD-(L)1 Efficacy: Overall Response Rate



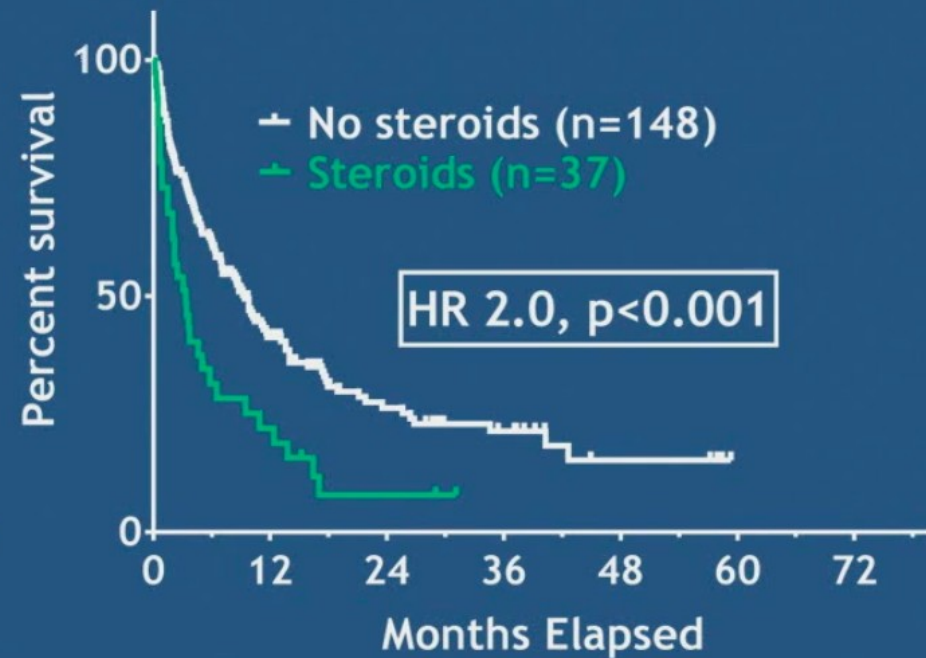
Effect of steroids: OS

Impact of Baseline Steroids on PD-(L)1 Efficacy: Overall Survival

MSKCC Cohort



GRCC Cohort



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- ✓ Small Cell



Archer 1050: dacomitinib vs gefitinib

ARCHER 1050: Study Design

- Phase 3 randomized open-label study to evaluate dacomitinib as an alternative first-line treatment for patients with advanced NSCLC with an *EGFR*-activating mutation

- Advanced NSCLC with *EGFR*-activating mutation(s)
- No prior systemic treatment of advanced NSCLC
- No CNS metastases
- No prior *EGFR* TKI or other TKI
- ECOG PS of 0 or 1

N = 452

R
1:1

Dacomitinib 45 mg
PO QD
(n = 227)

Gefitinib 250 mg
PO QD
(n = 225)

Stratification factors

Race (including Asian vs non-Asian)

EGFR mutation type (exon 19 vs 21)

Primary endpoint

PFS by blinded independent review (IR)

- Target HR ≤ 0.667 (50% \uparrow)
- 90% power
- 1-sided $\alpha = 0.025$
- Assumed median PFS: 14.3 vs 9.5 months

Secondary endpoints

OS

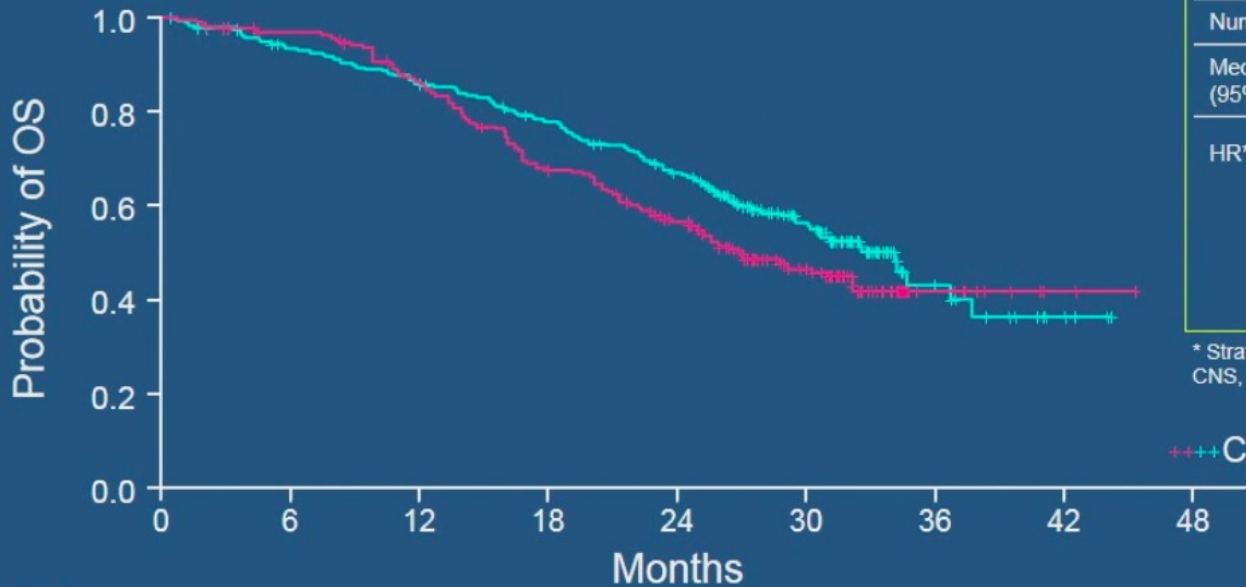
PFS (investigator assessed),
ORR, DOR, TTF, Safety, PROs

ClinicalTrials.gov: <https://clinicaltrials.gov/ct2/show/NCT01774721>.

CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; PO, orally; PROs, patient-reported outcomes; PS, performance status; QD, once daily; R, randomized; TTF, time to treatment failure.

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

+++ Censored

No. at risk:

	0	6	12	18	24	30	36	42	48
Dacomitinib	227	206	188	167	138	77	14	3	0
Gefitinib	225	213	186	144	113	63	12	3	0

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)

^aAdverse events occurring in at least 15% of patients in either study group in the safety population. ^bThere were no grade 4 events in either arm and one grade 5 event in the dacomitinib arm. ^cOne patient (0.4%) in the dacomitinib arm had grade 5 diarrhea. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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.

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:

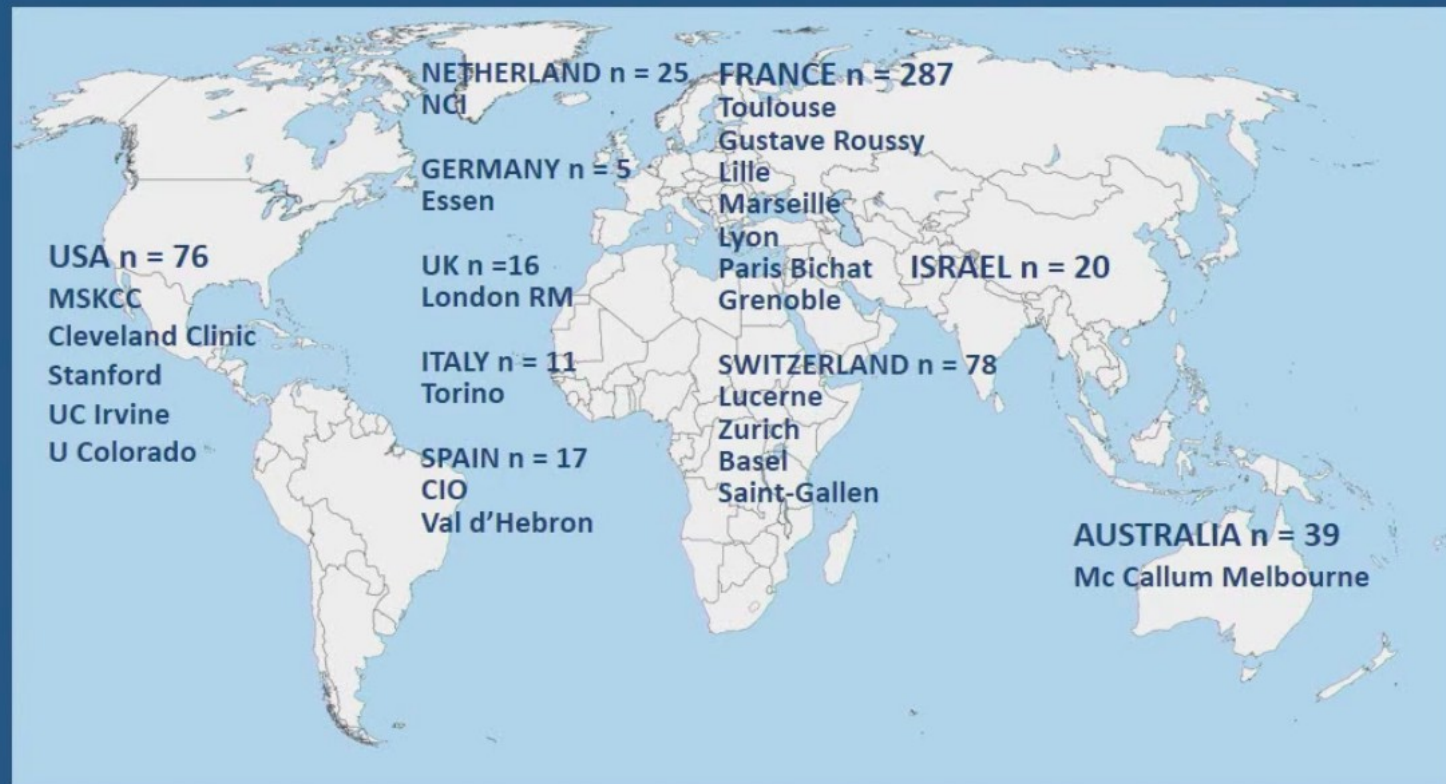
- Patients with known activating mutation
- Treated with ICI monotherapy (any line)

Primary objective: PFS under ICI

Secondary objectives: RR, OS, PFS ratio

Exploratory objective: PDL1 expression

Local ethic committees

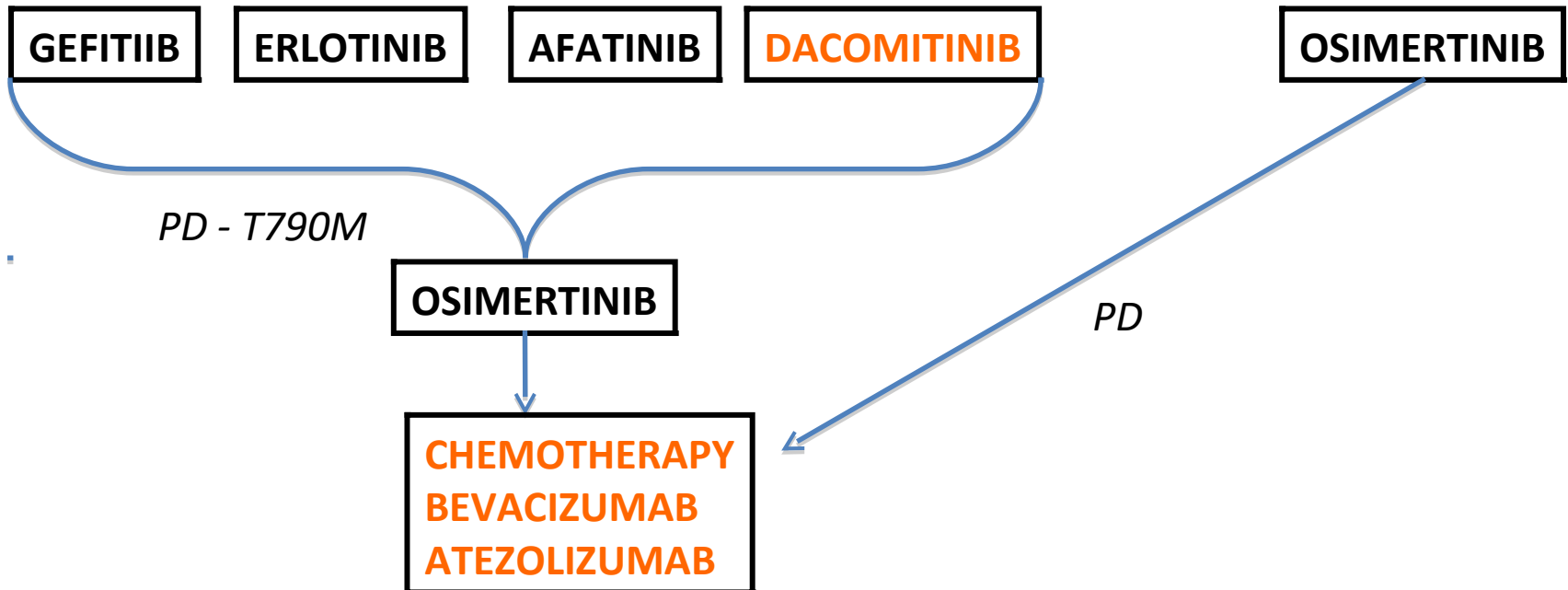


Immunotarget

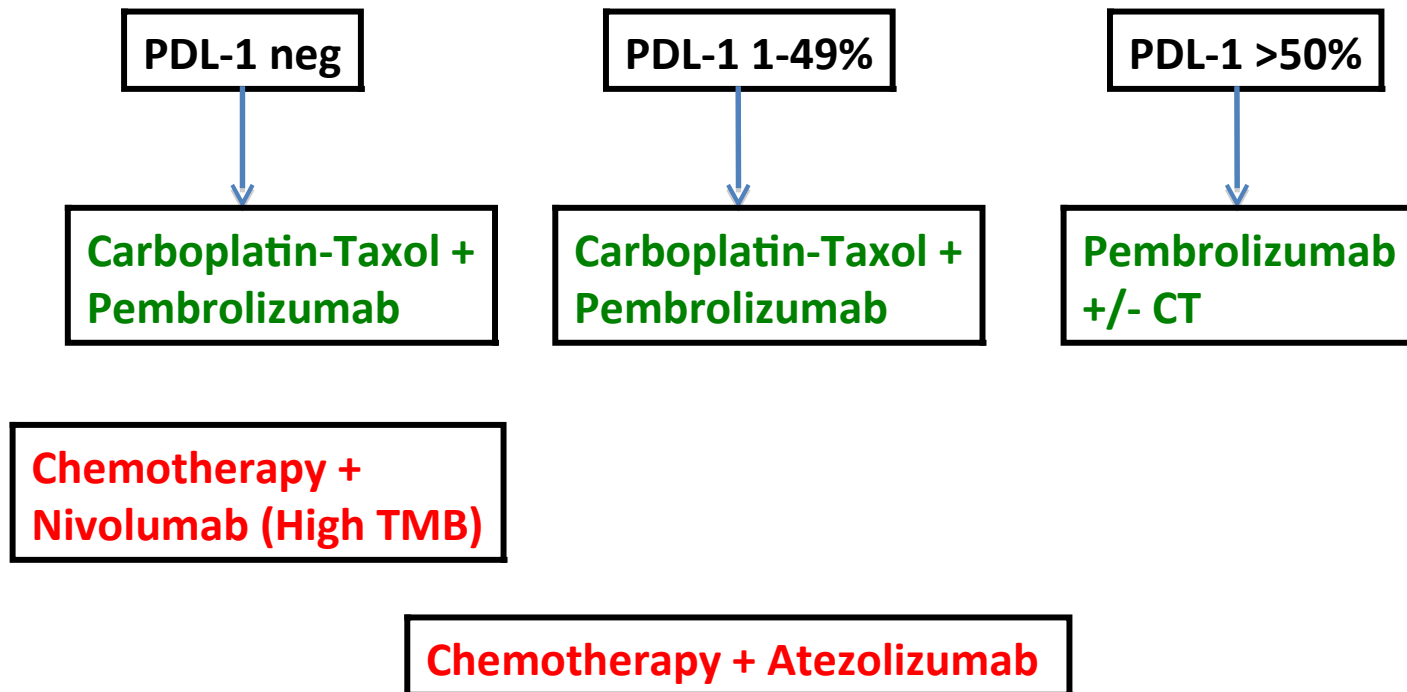
Conclusion

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					Poor outcome. New biomarker needed.
RET	16	6%	2.1	21.3	X	X	X	NA	
ROS1	7	17%	-	-					

Asco 2018: future scenarios EGFR mut NSCLC



ASCO 2018: future scenarios SQ NSCLC



ASCO 2018: future scenarios nonSQ NSCLC

