Immunoterapia di 1° linea

Evidenze e Prospettive Future

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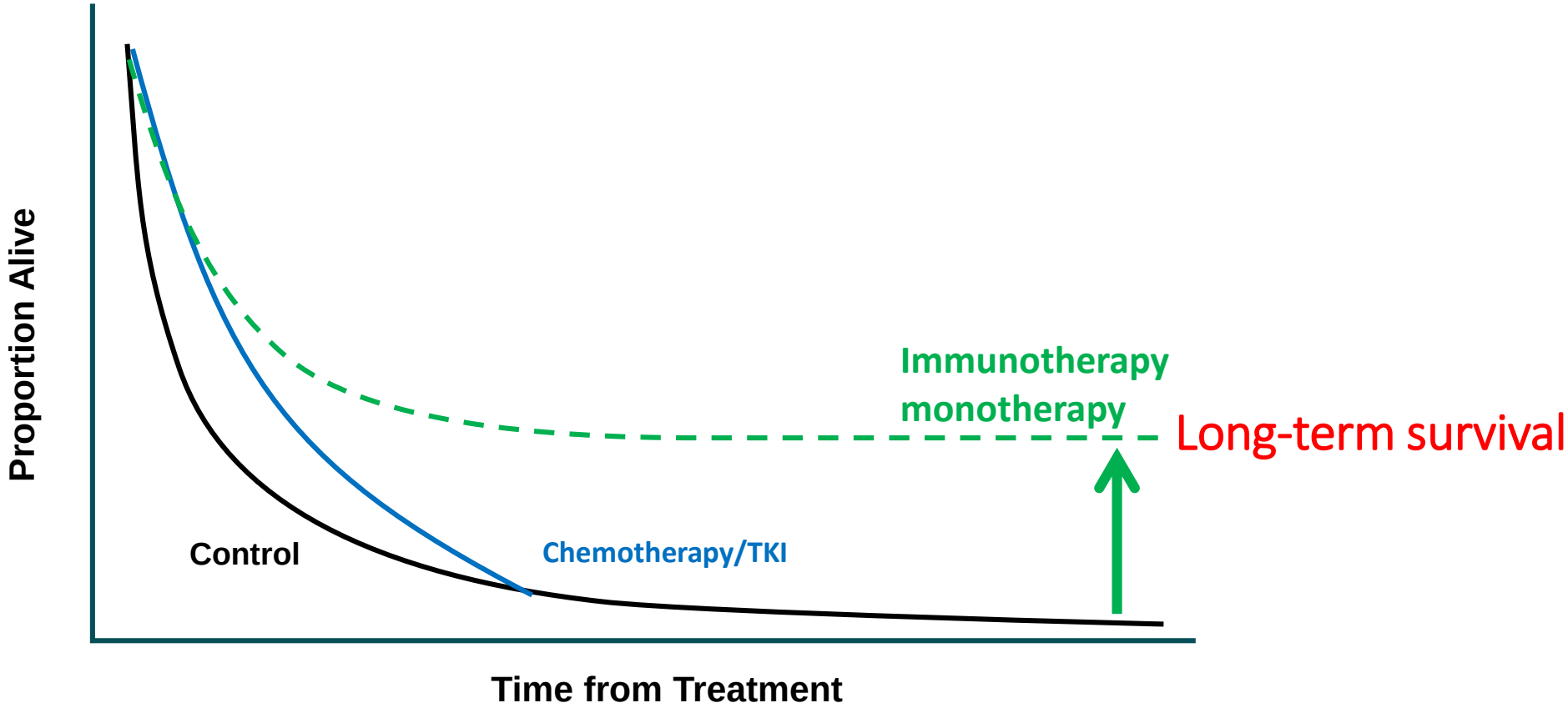
  - Fondazione *Cariverona*
  - Open Innovation
  - Astra-Zeneca

FONDAZIONE Cariverona

IASLC
International Association for the Study of Lung Cancer

AIRC

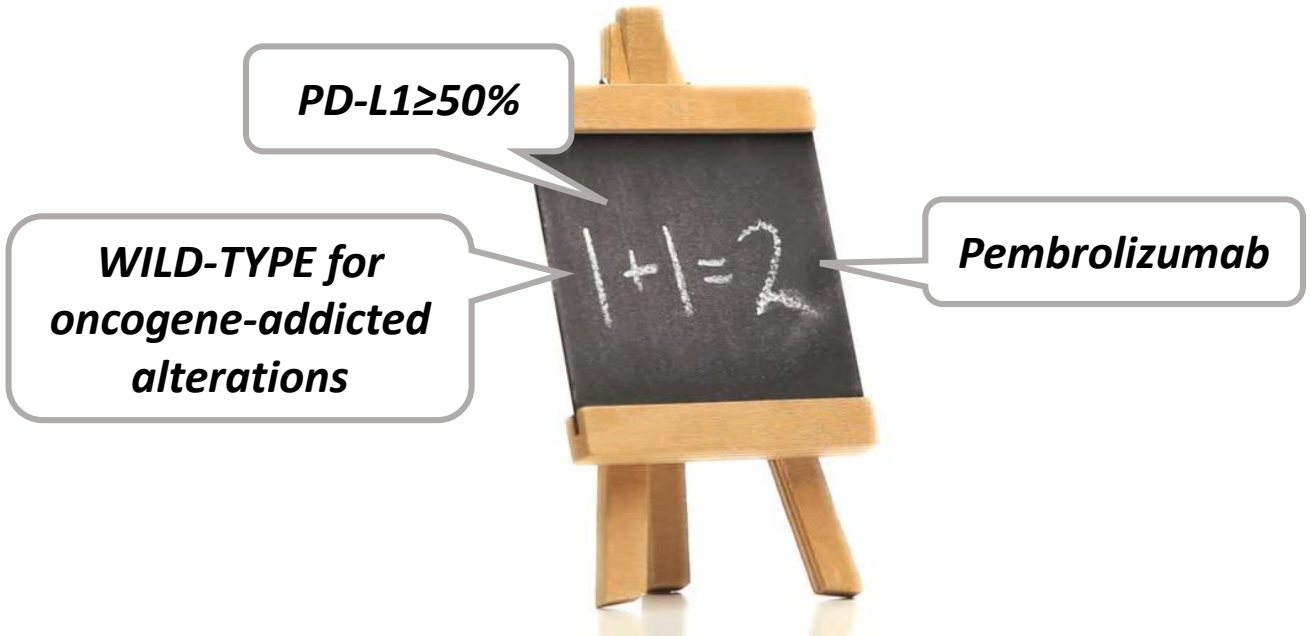
Hypothetical Goals of Immunotherapy



TKI = tyrosine kinase inhibitor.
Adapted from Sharma P, Allison JP. *Cell*. 2015;161(2):205-214.

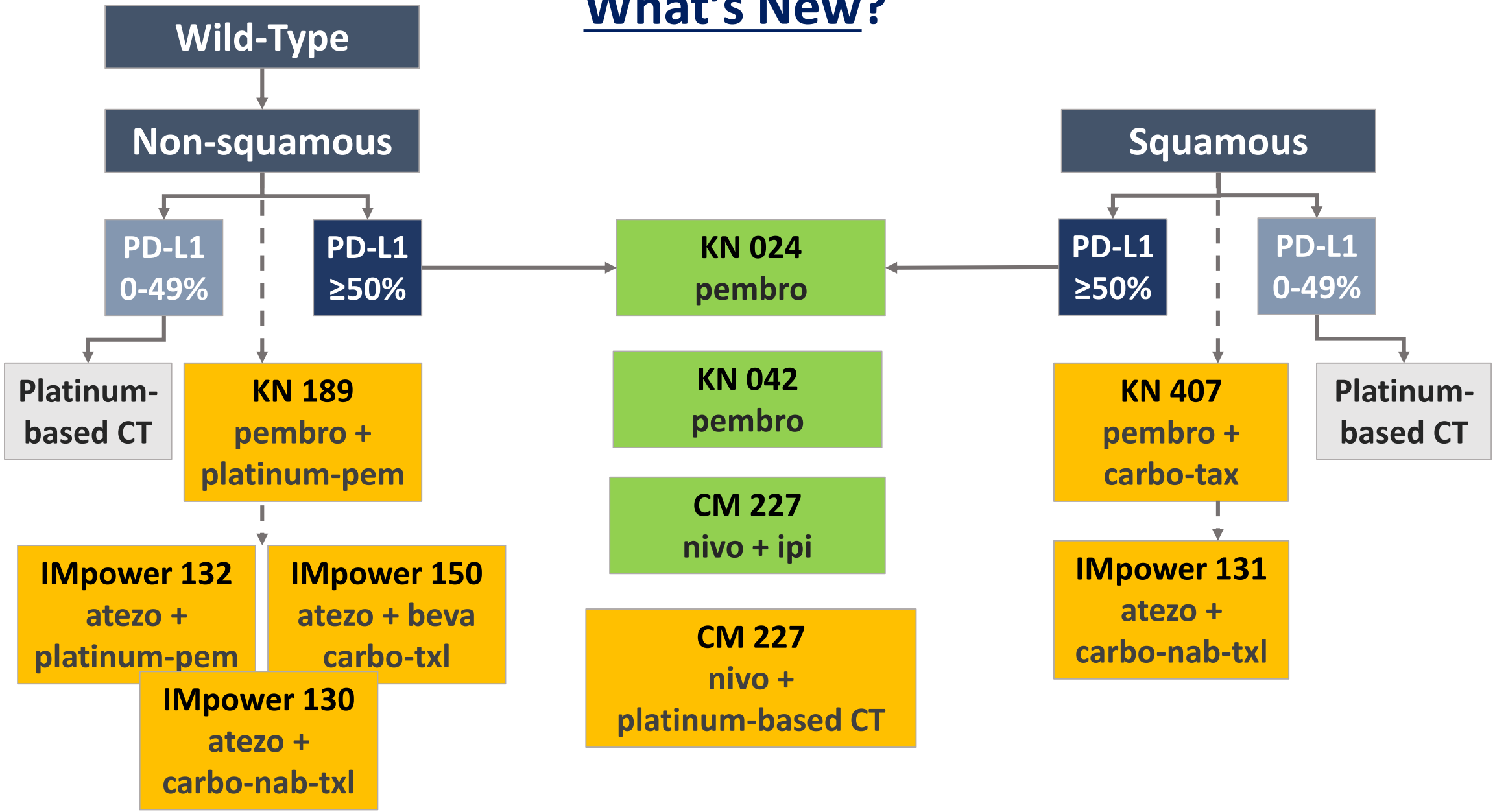
Horn, WCLC 2018

1st Line Treatment Landscape in NSCLC Today



1st Line Treatment Landscape in NSCLC

What's New?



Immuno alone?

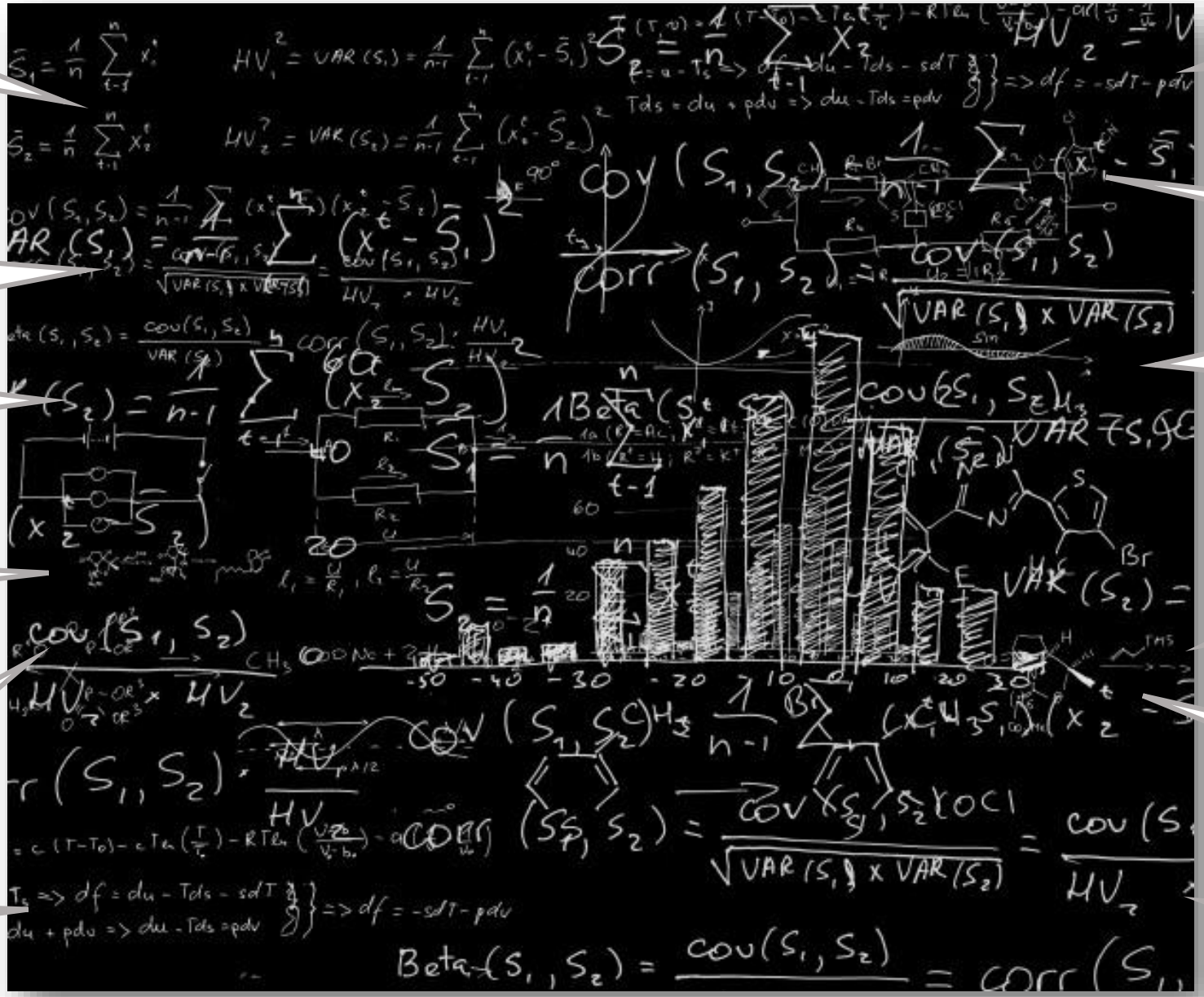
Immuno or chemo + immuno?

Antiangiogenic?

Sequence?

PD-L1 or TMB?

Toxicity?



Patients characteristics? Age-PS?

Histology?

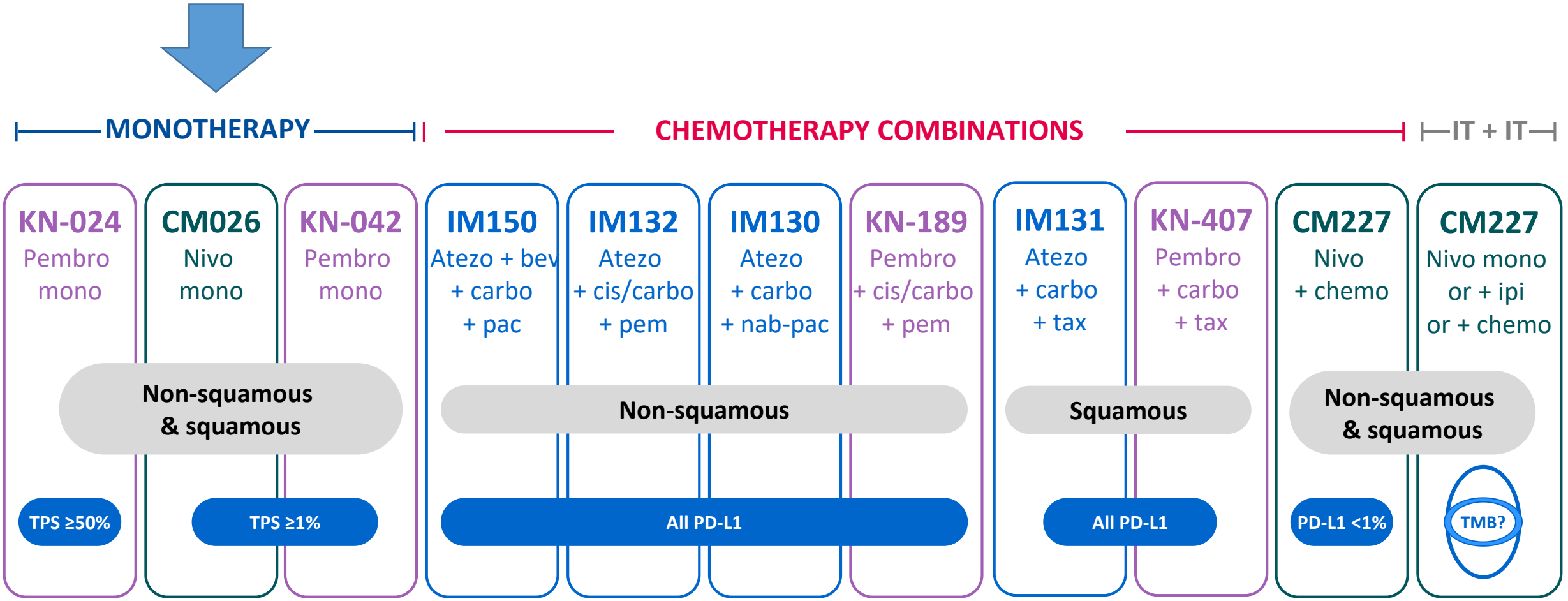
Oncogene-addicted?

Steroids? Antibiotics?

Immunological profile

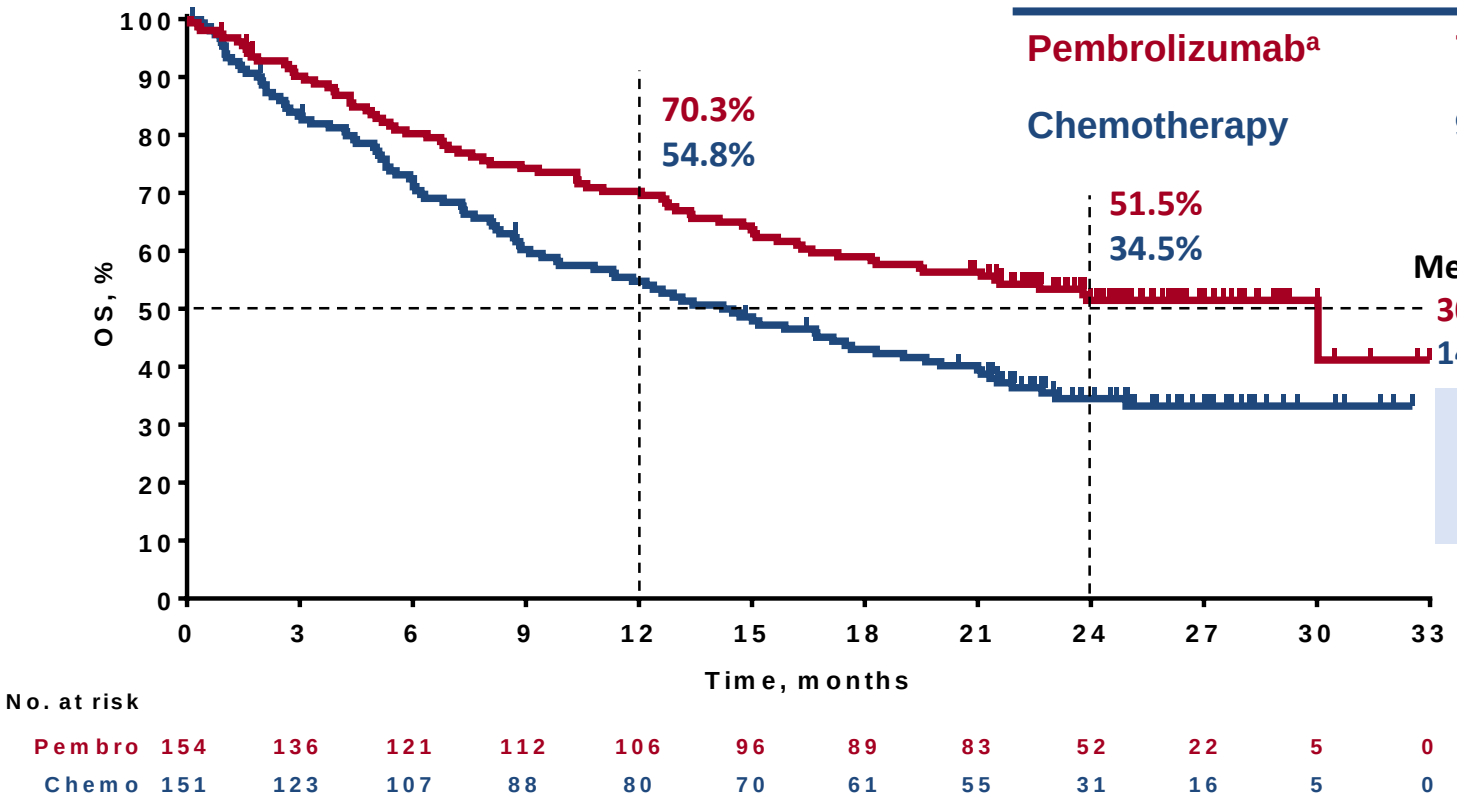
Molecular background

The invasion of clinical trials



Updated Analysis of KEYNOTE-024: Pembro in PD-L1 high (≥50%)

25.2 months follow-up



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

Median (95% CI)

30.0 mo (18.3 mo–NR)

14.2 mo (9.8 mo–19.0 mo)

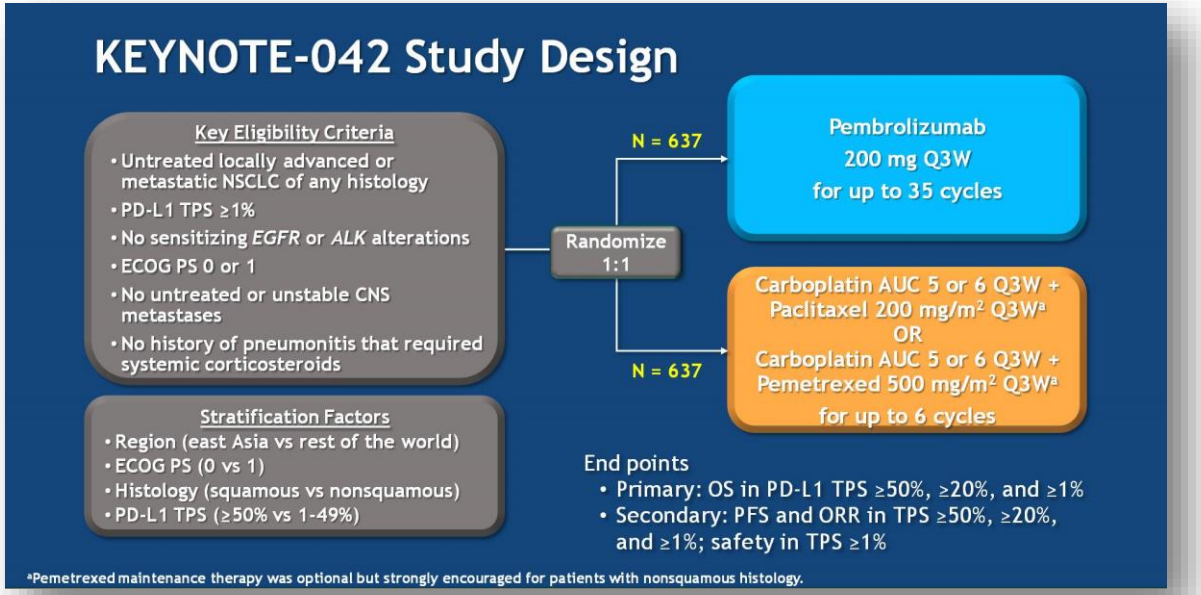
Control Arm: 63% of discontinued pts received IO

Censoring rate (55% of pts with event)

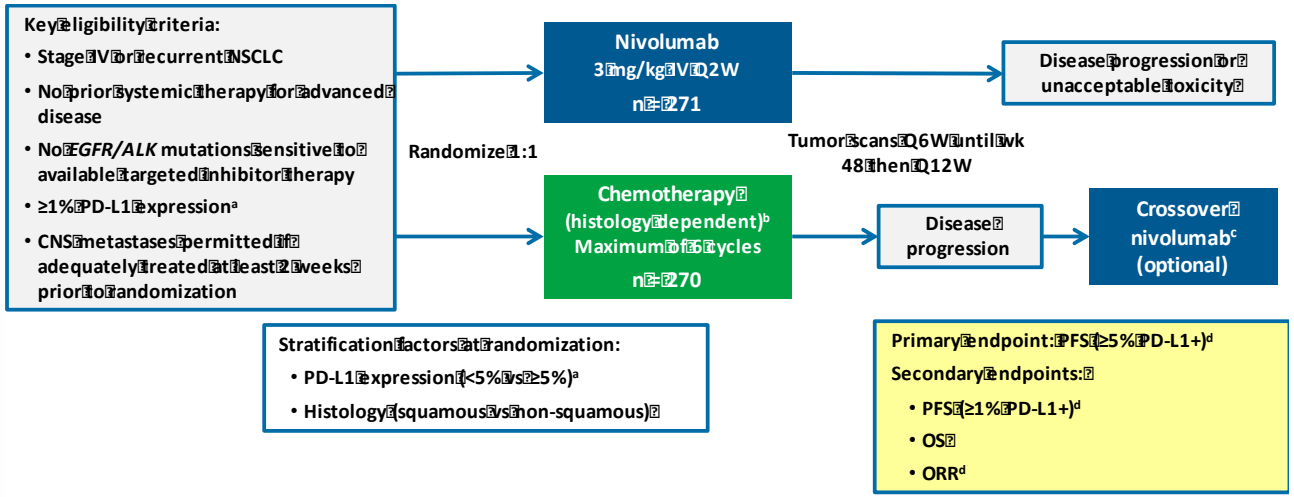
Brahmer J et al, WCLC 2017

IO single agent versus platinum-based CT: low PD-L1 expression

KEYNOTE 042: Study design



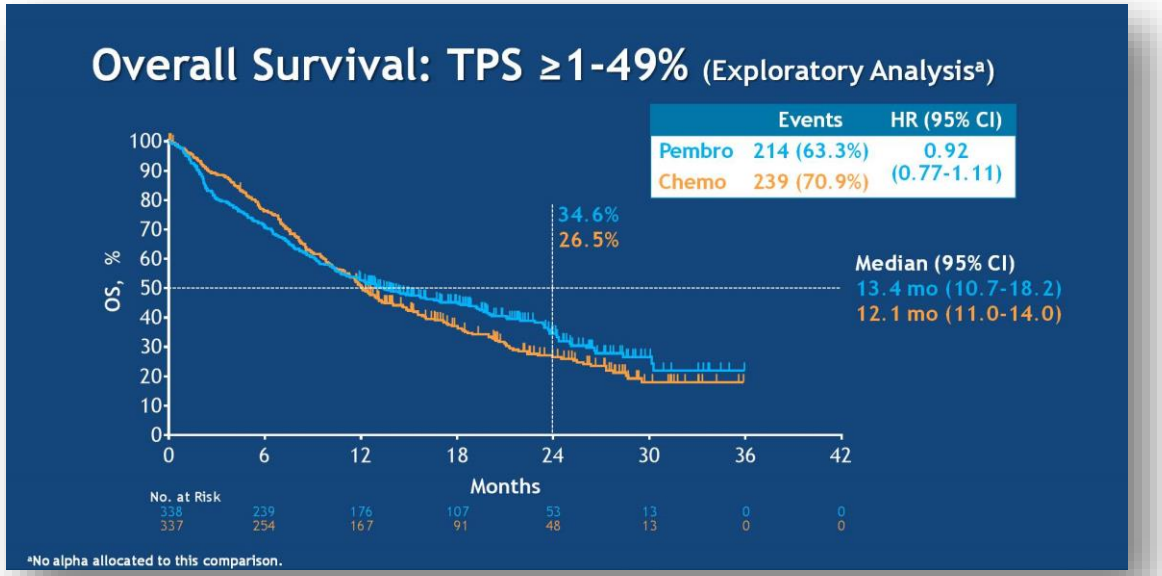
CheckMate 026: Study design



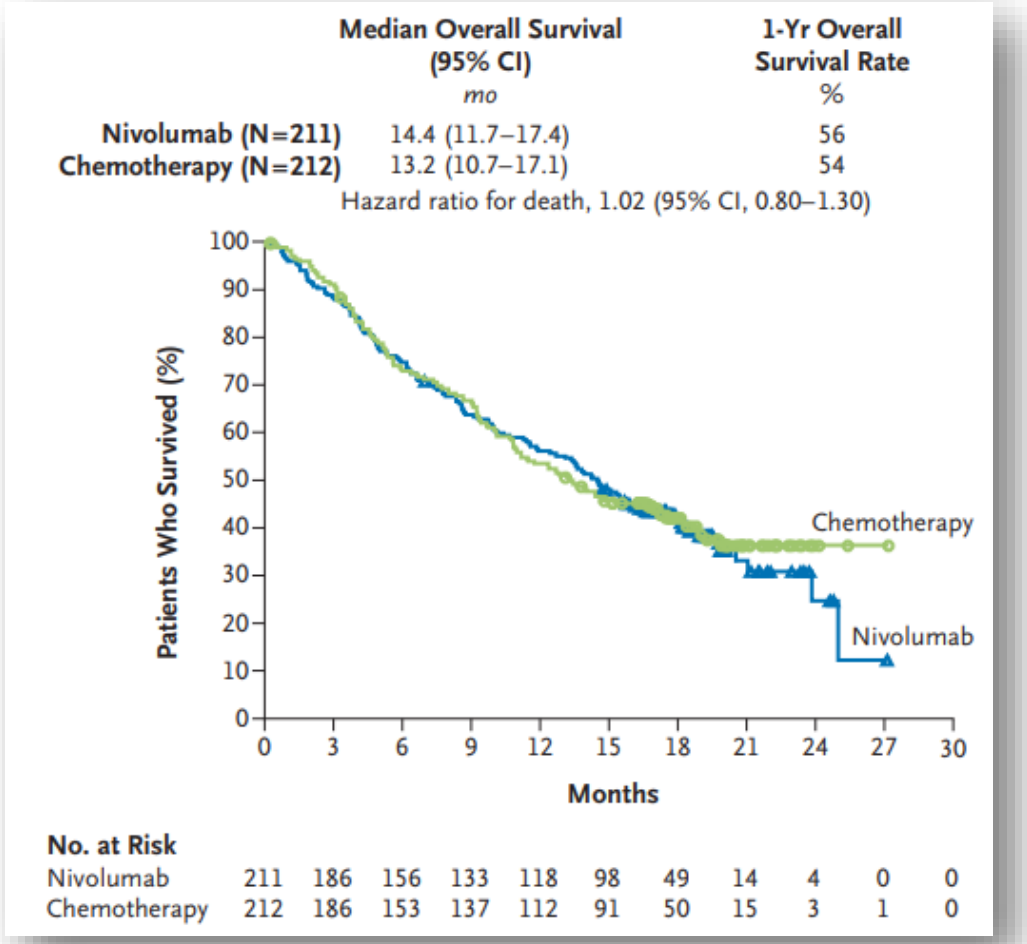
Lopes G, ASCO 2018; Carbone, NEJM 2017

IO single agent versus platinum-based CT: OS PD-L1 low expression

KEYNOTE 042

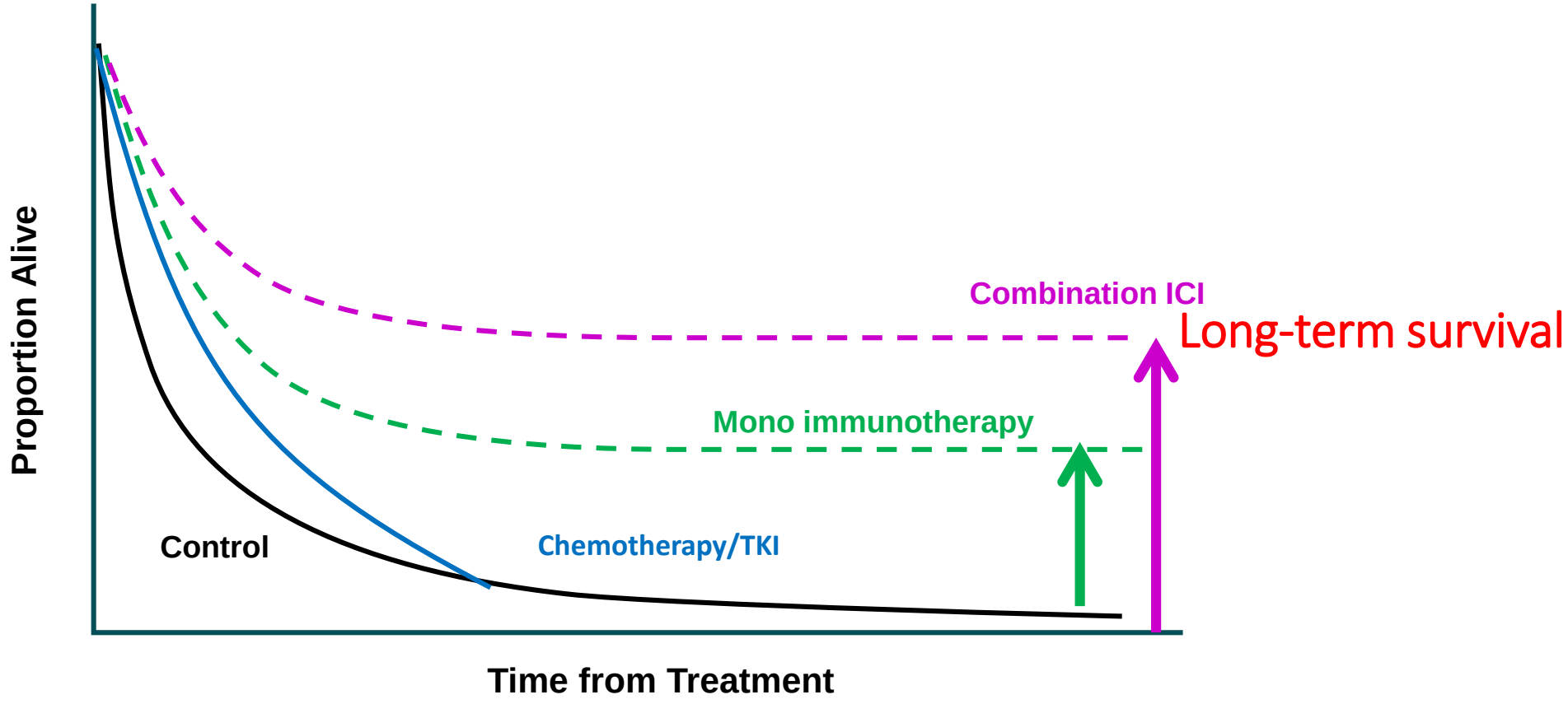


CheckMate 026



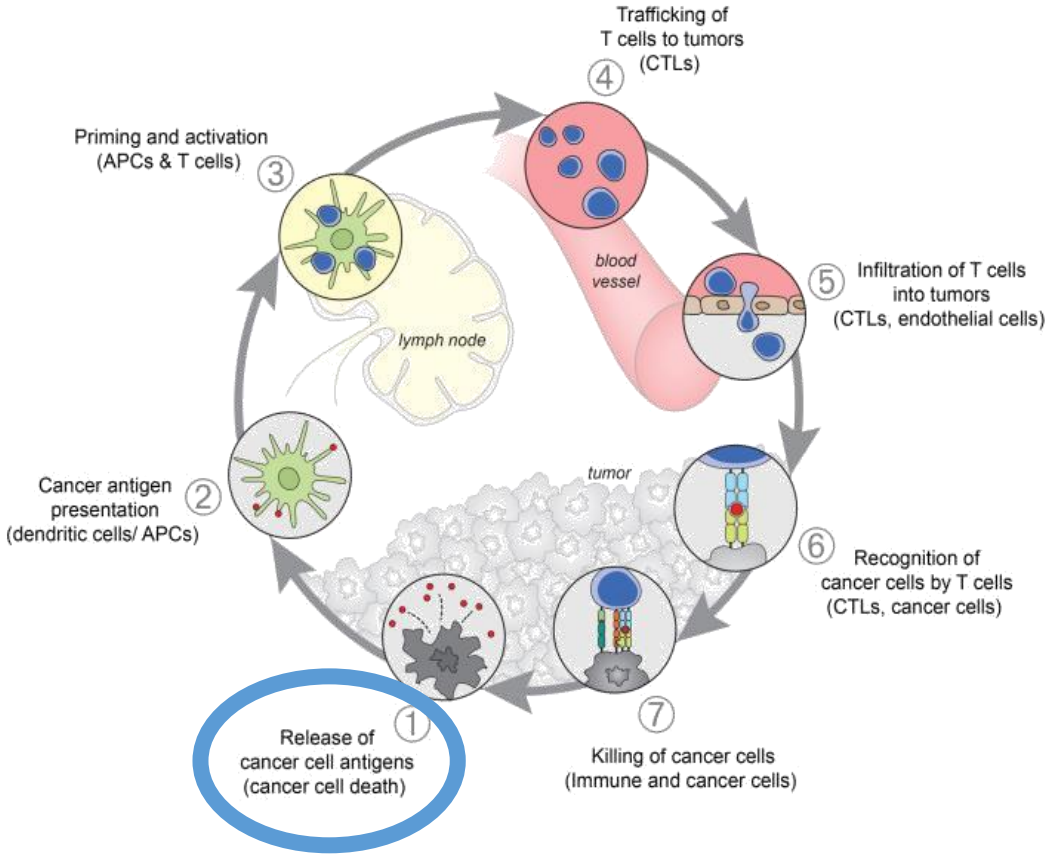
Lopes G, ASCO 2018; Carbone, NEJM 2017

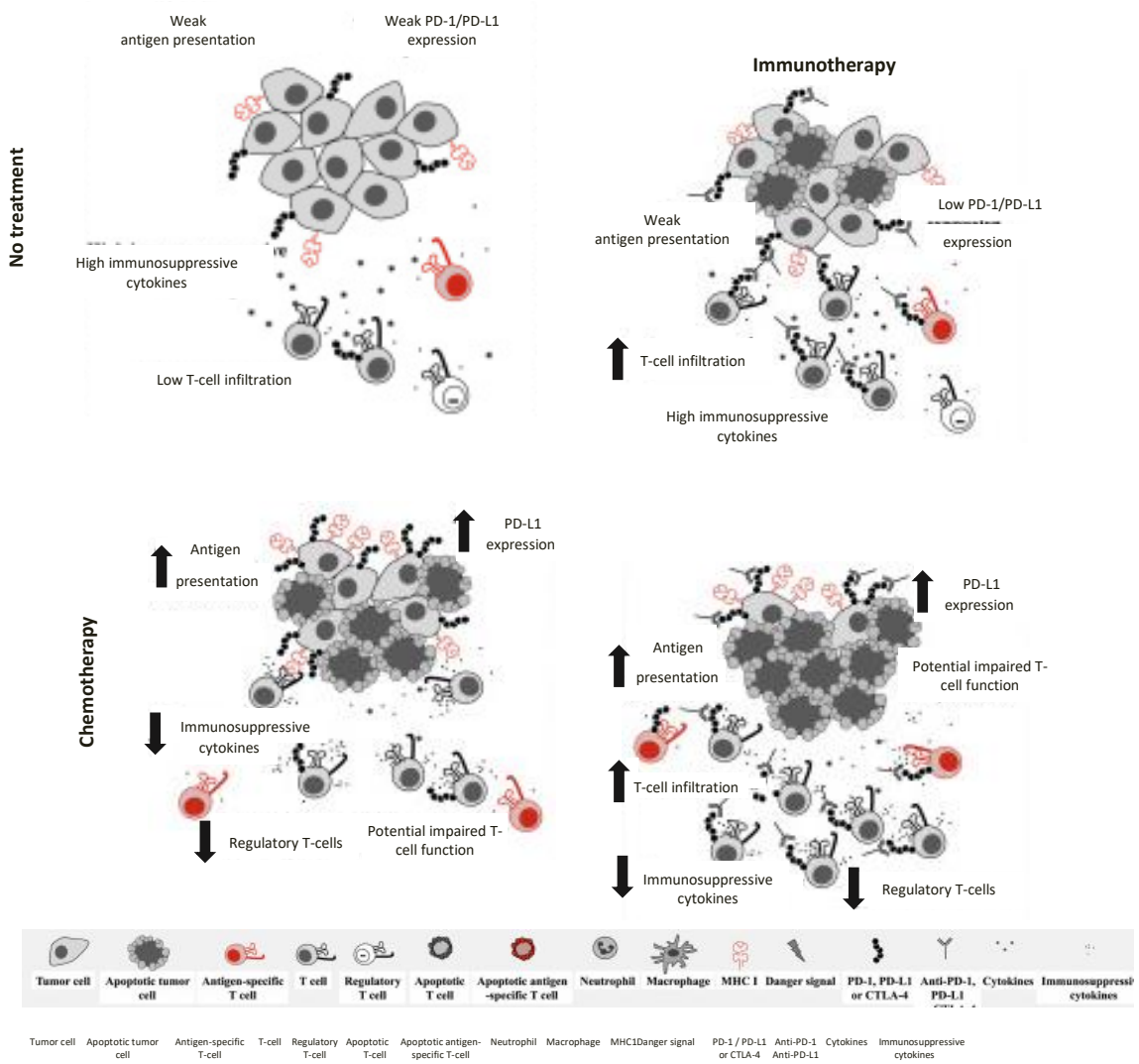
Hypothetical Goals of Immunotherapy in Combination



Horn, WCLC 2018

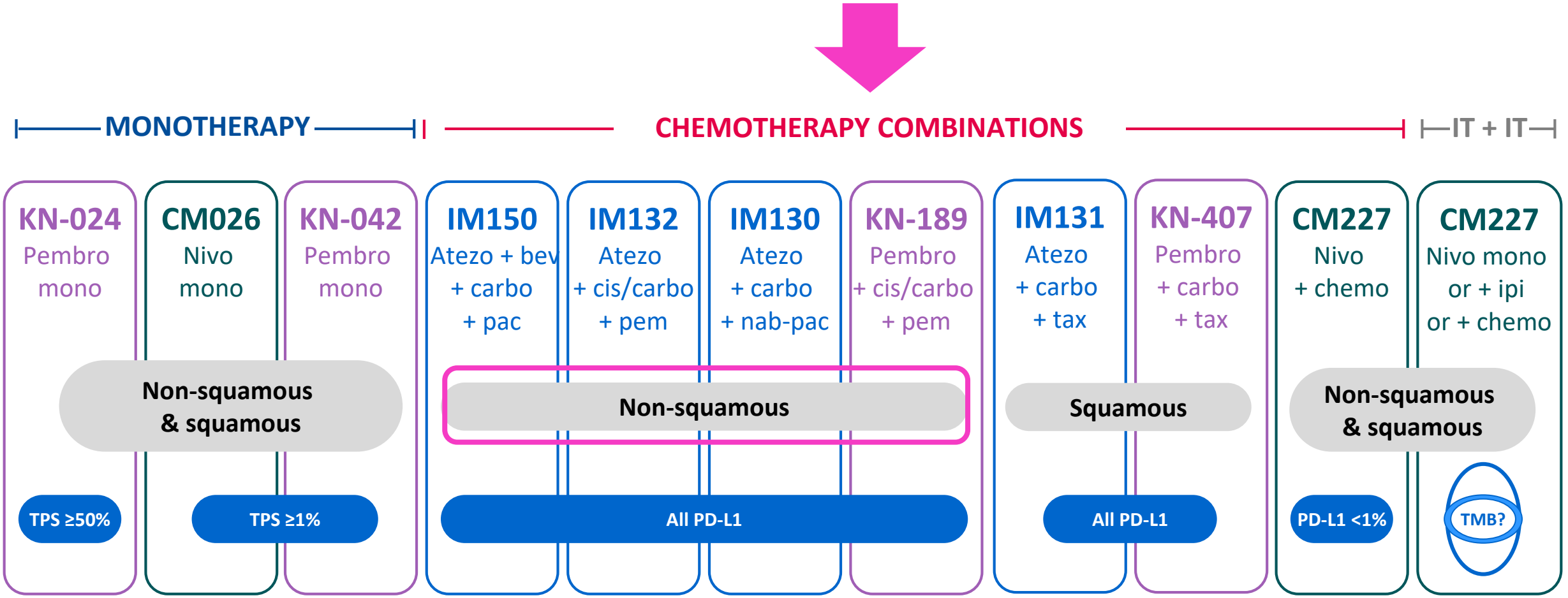
Does Tumor cell killing by cytotoxic chemotherapy expose immune system to high levels of tumor cell antigens?



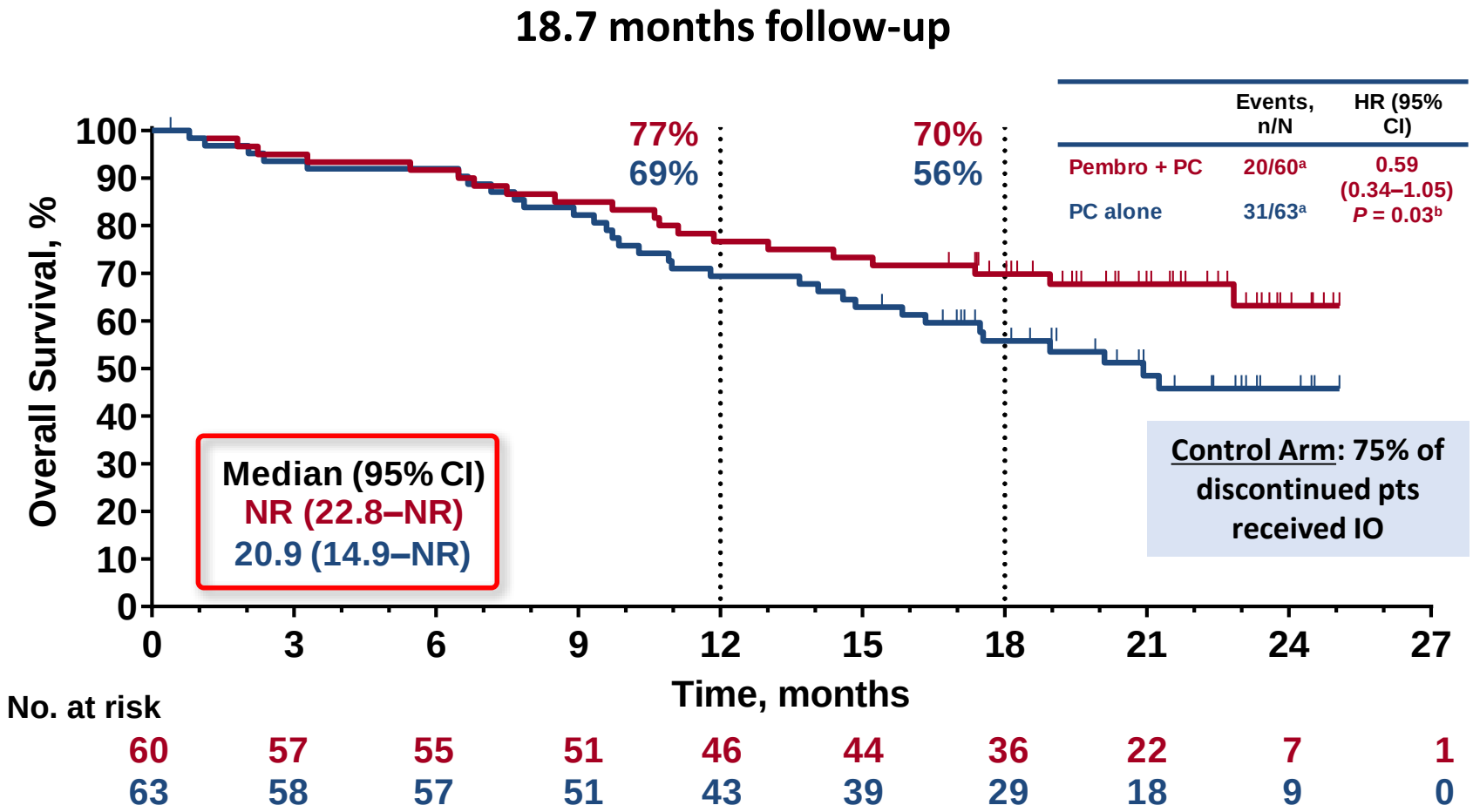


Horn, WCLC 2018

The invasion of clinical trials



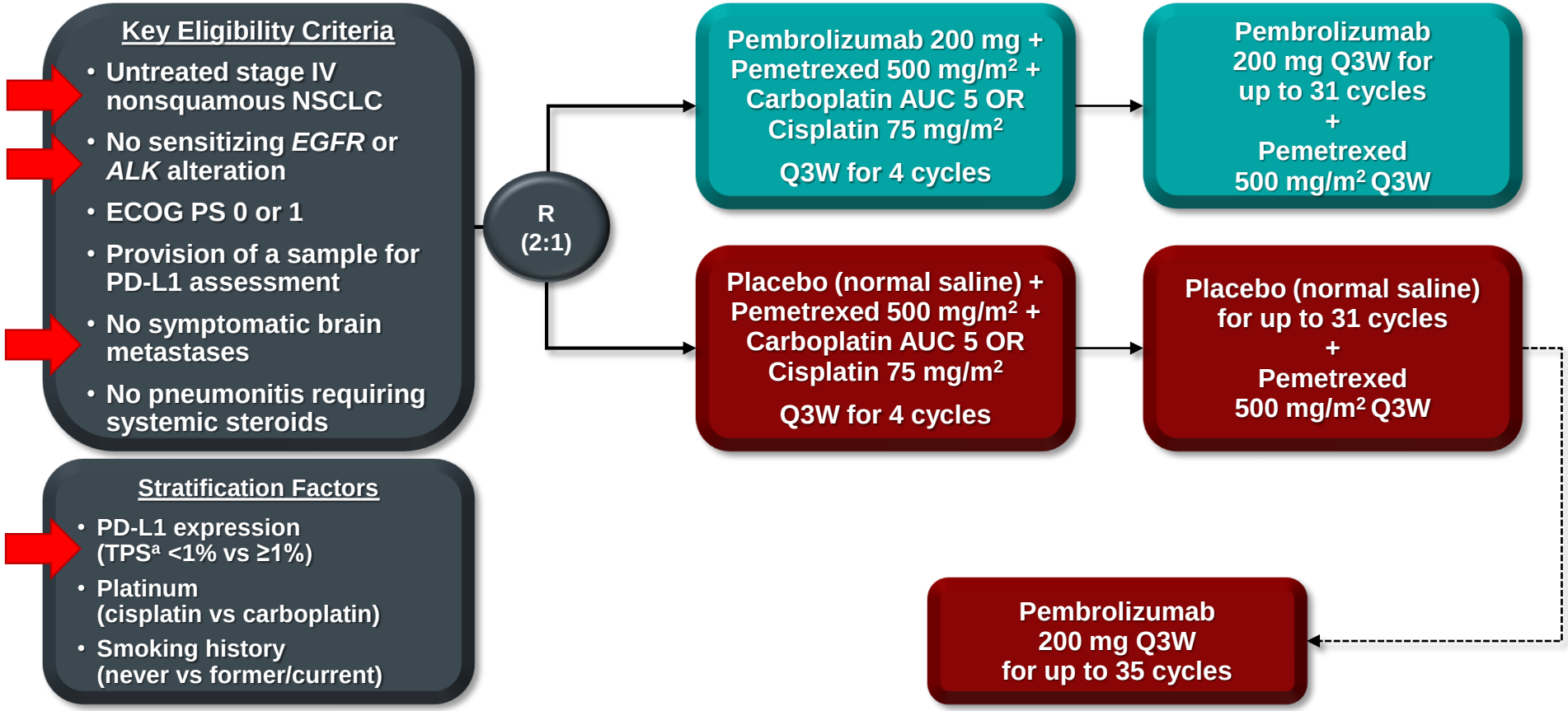
Non-Squamous NSCLC [KEYNOTE-021G]



Censoring rate (42% of pts with event)

Borghaei, WCLC 2017

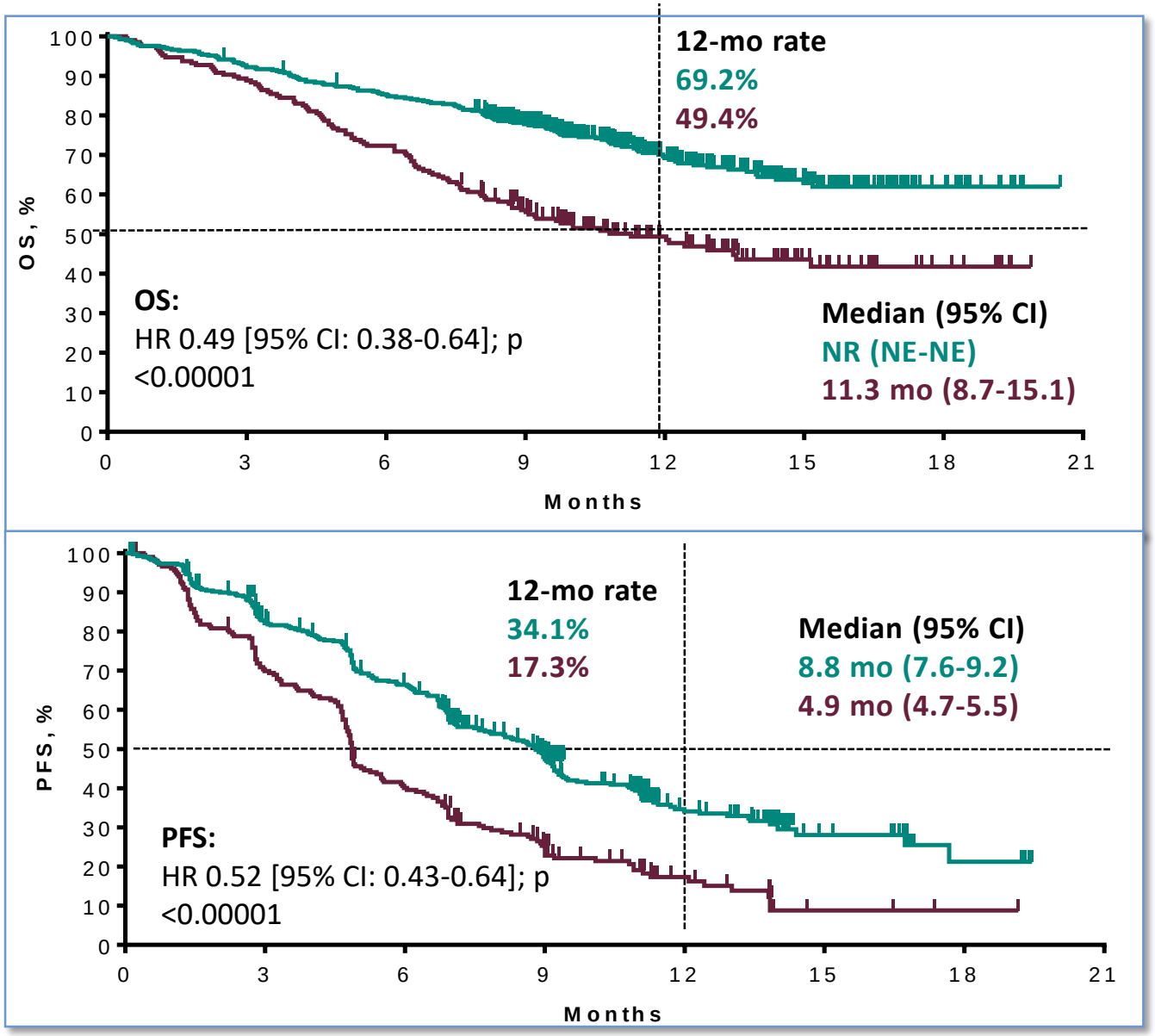
Non-Squamous NSCLC [KEYNOTE-189]

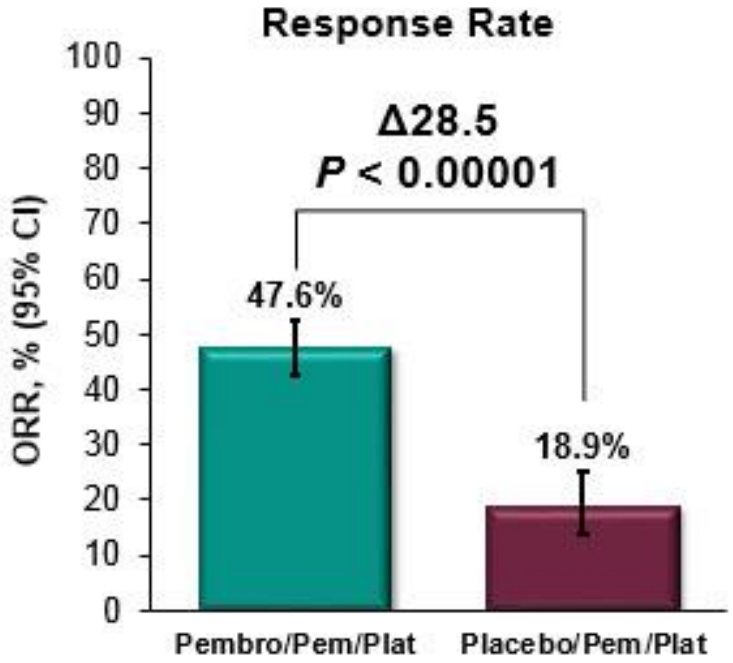


(616 patients)

Gandhi, NEJM 2018

Non-Squamous NSCLC [KEYNOTE-189]





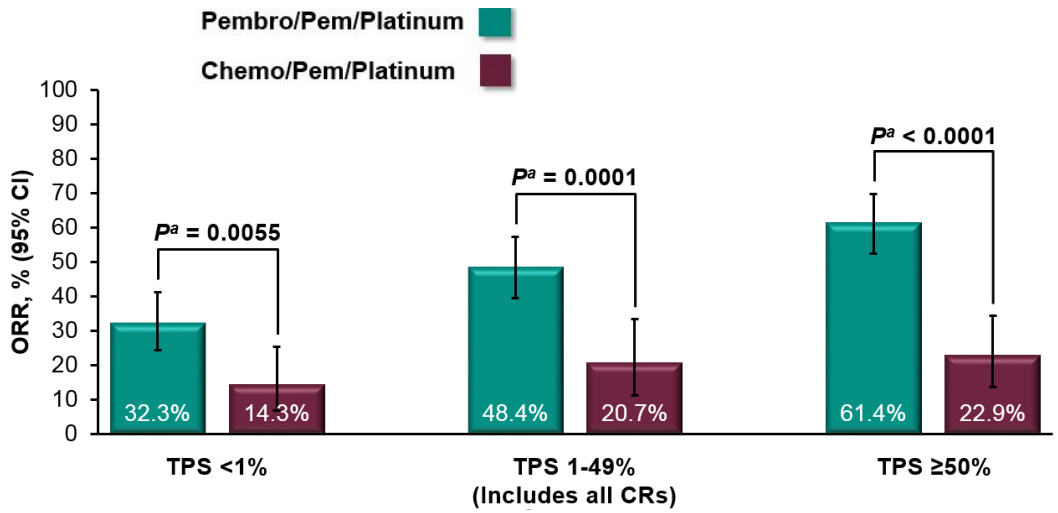
Subgroup Analyses

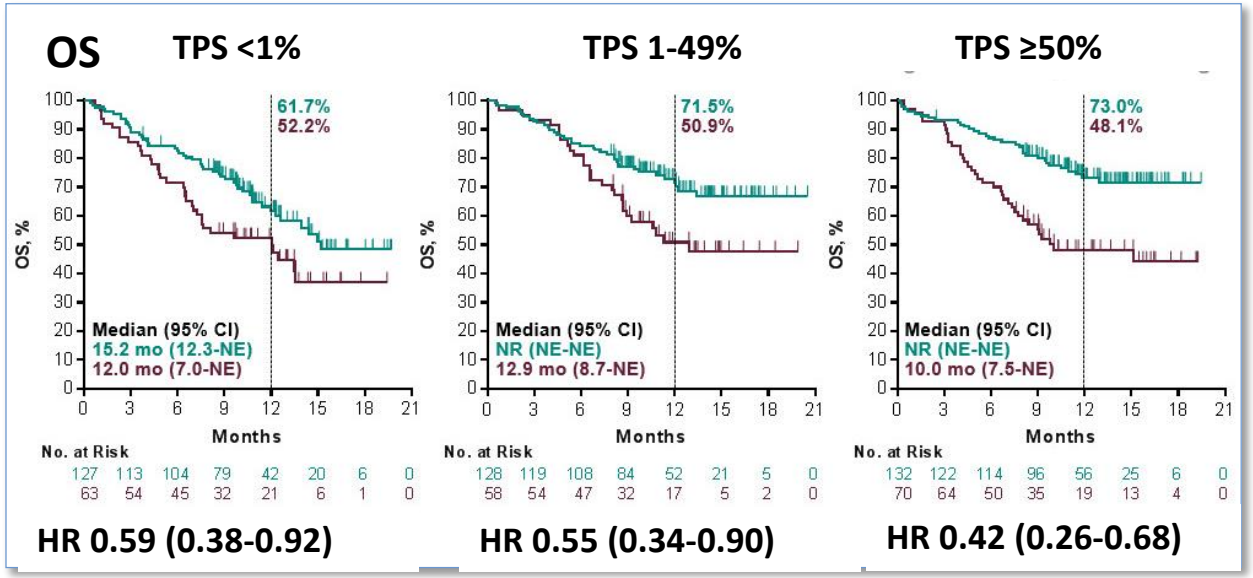
OS: Positive across all subgroups

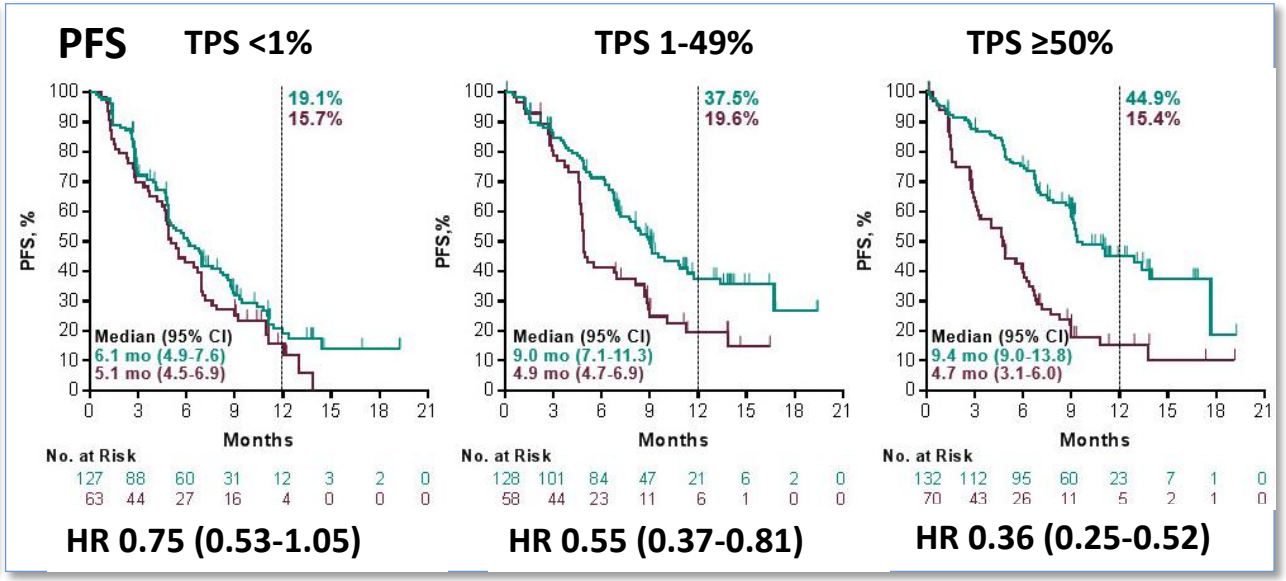
PFS: Positive across all subgroups except for PD-L1 TPS <1%

Gandhi, NEJM 2018

Non-Squamous NSCLC [KEYNOTE-189]

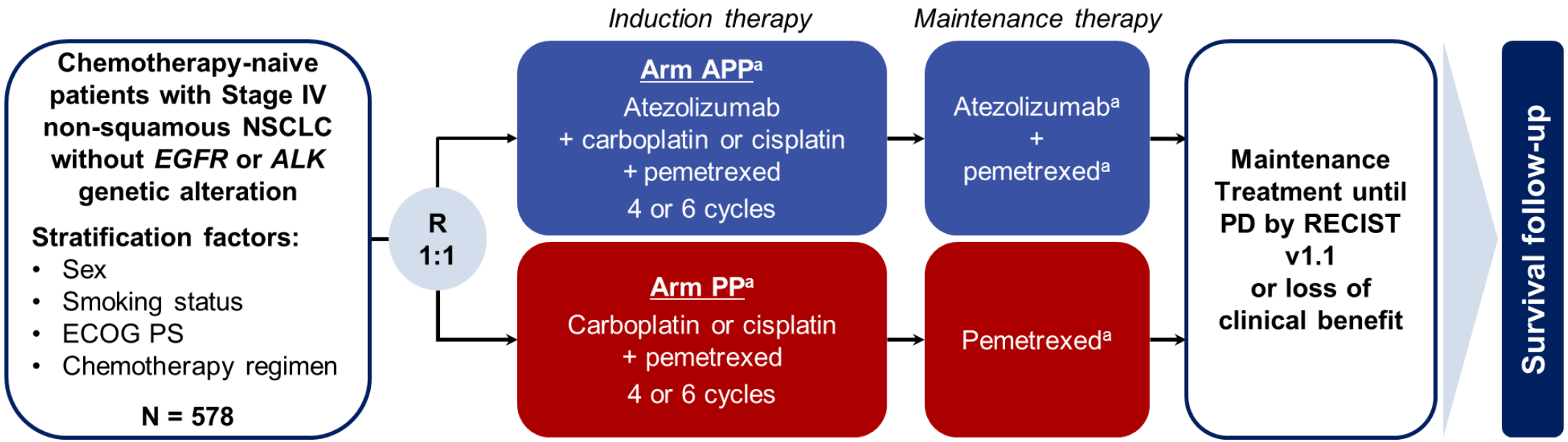






Gandhi, NEJM 2018

Non-Squamous NSCLC [IMpower132]

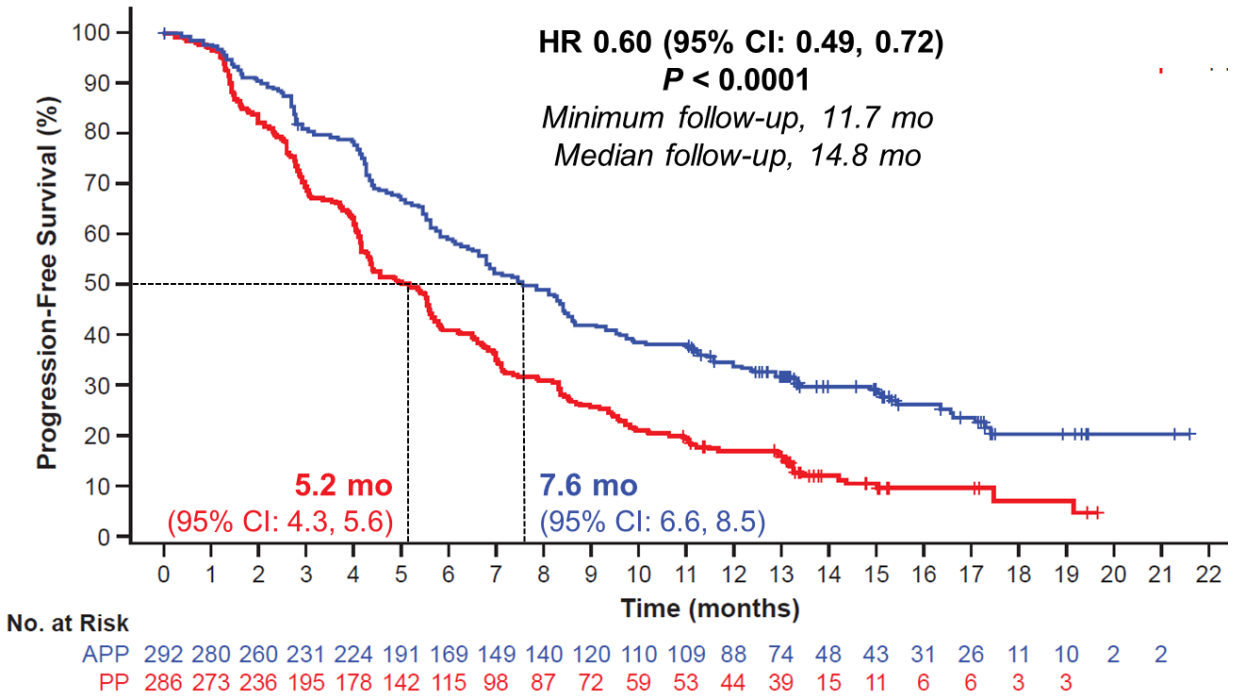


- Co-primary endpoints: INV-assessed PFS and OS
- Secondary endpoints: INV-assessed ORR and DOR, PRO and safety measures
- Exploratory analyses: clinical and biomarker subgroup analyses
  - Biomarker-evaluable tissue not mandatory for enrolment (was available from 60% of patients)

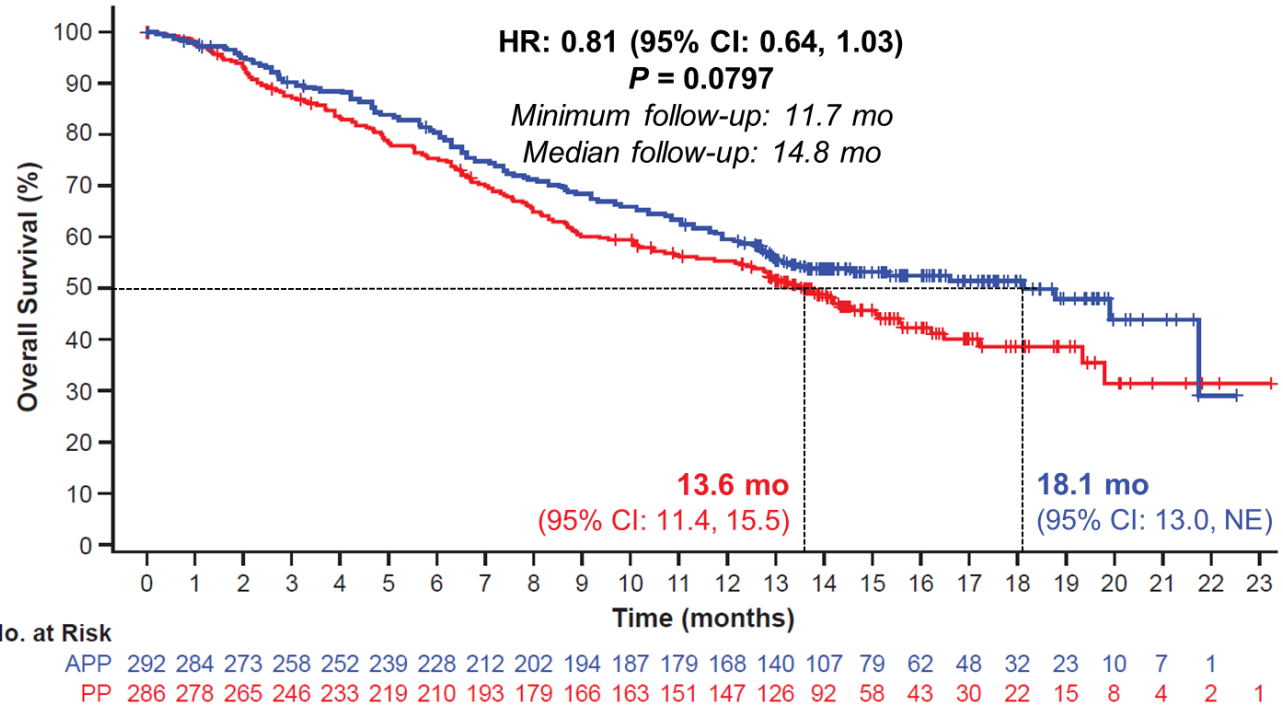
Papadimitrakopoulou, WCLC 2018

Non-Squamous NSCLC [IMpower132]

PFS



OS



Papadimitrakopoulou, WCLC 2018

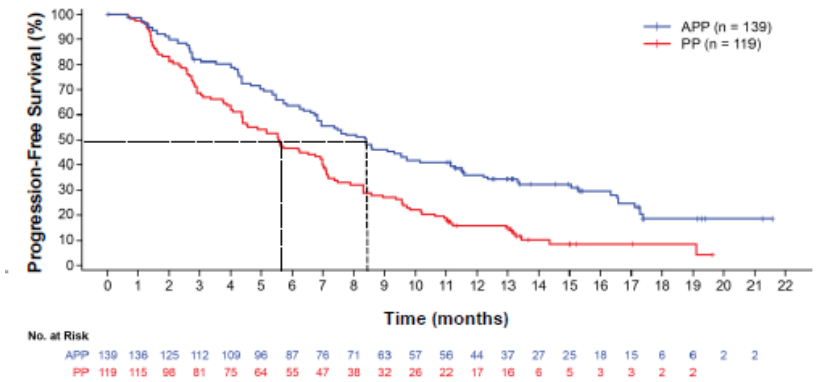
Non-Squamous NSCLC [IMpower132]
PFS benefit in key subgroups

75-84y HR 0.63

Patients aged ≥ 65 years

APP	PP
8.4 (6.8, 9.8)	5.6 (4.4, 7.0)

0.55 (0.42, 0.73)

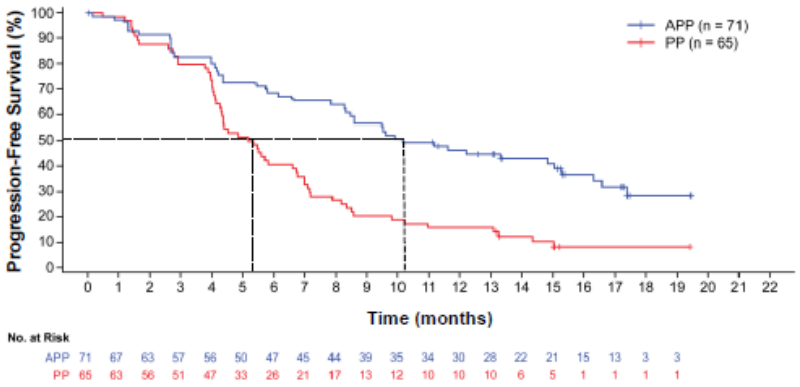


20% never smoker

Asian patients

APP	PP
10.2 (8.3, 15.3)	5.3 (4.3, 6.7)

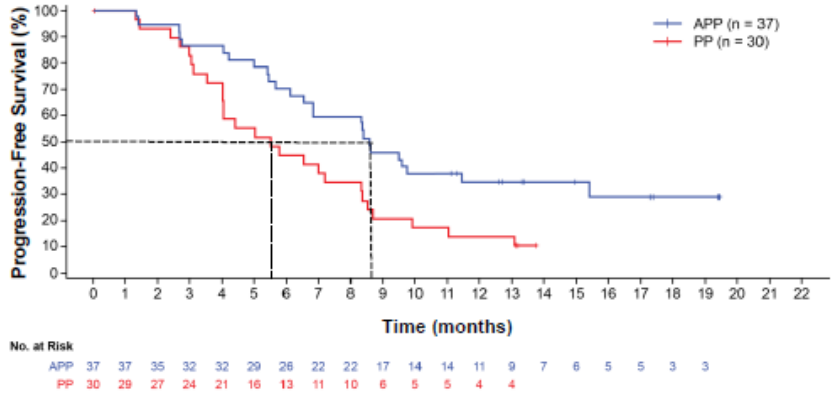
0.42 (0.28, 0.63)



Never smokers

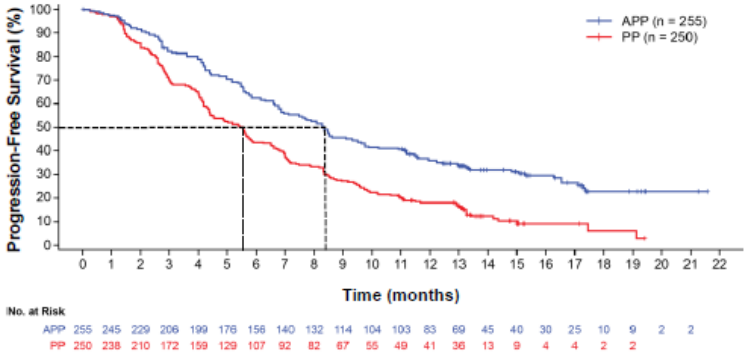
APP	PP
8.6 (6.5, 15.4)	5.5 (4.0, 8.3)

0.49 (0.28, 0.87)



Patients without liver metastases

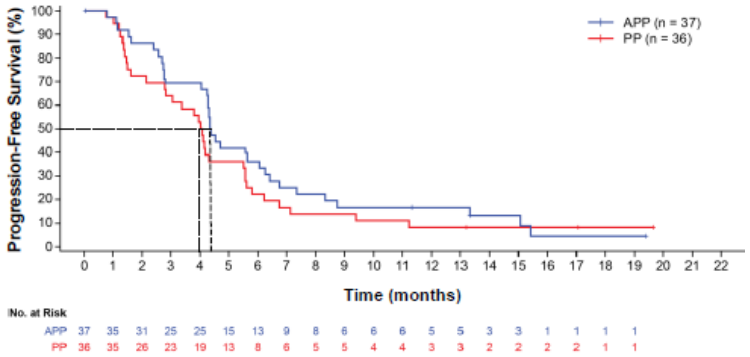
	APP	PP
Median PFS (95% CI), mo	8.4 (7.0, 9.5)	5.5 (4.4, 5.9)
HR (95% CI)	0.56 (0.46, 0.69)	



Patients with liver metastases

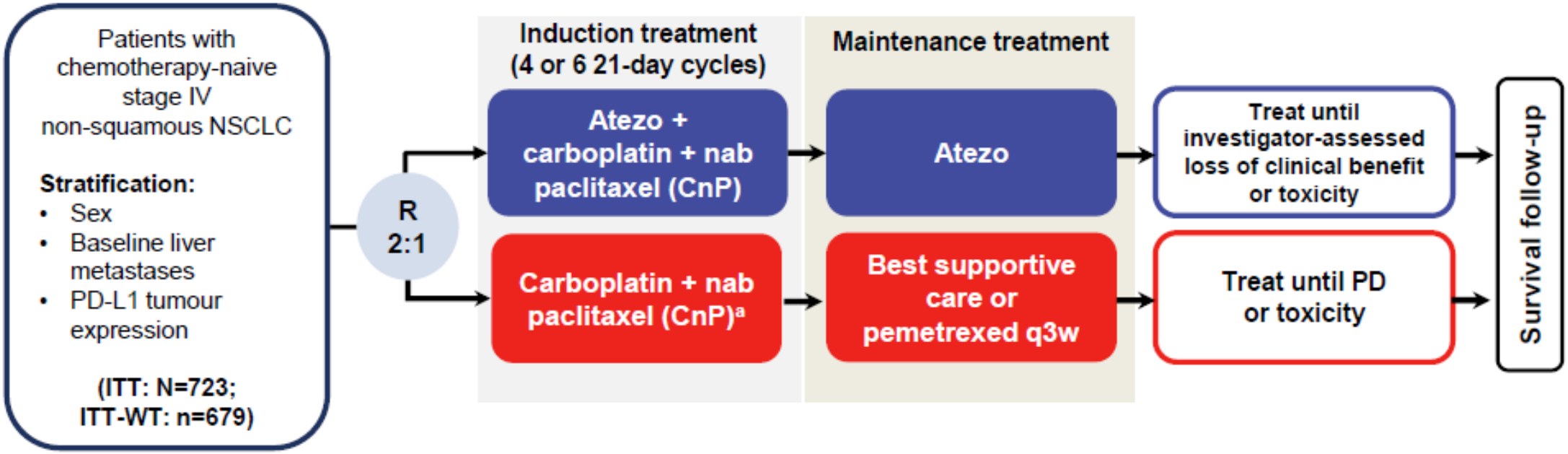
APP	PP
4.4 (4.2, 6.0)	4.0 (2.8, 5.5)

0.77 (0.47, 1.25)



Barlesi F, ESMO 2018

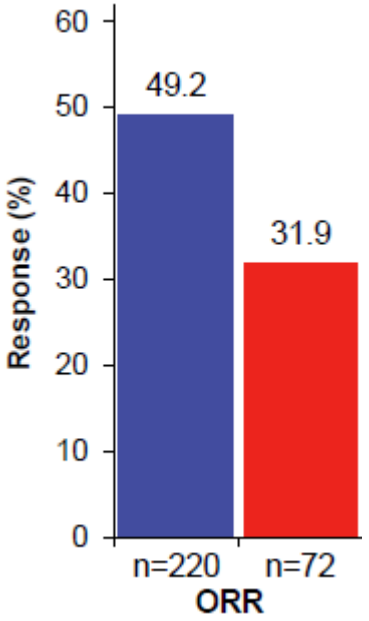
Non-Squamous NSCLC [IMpower130]



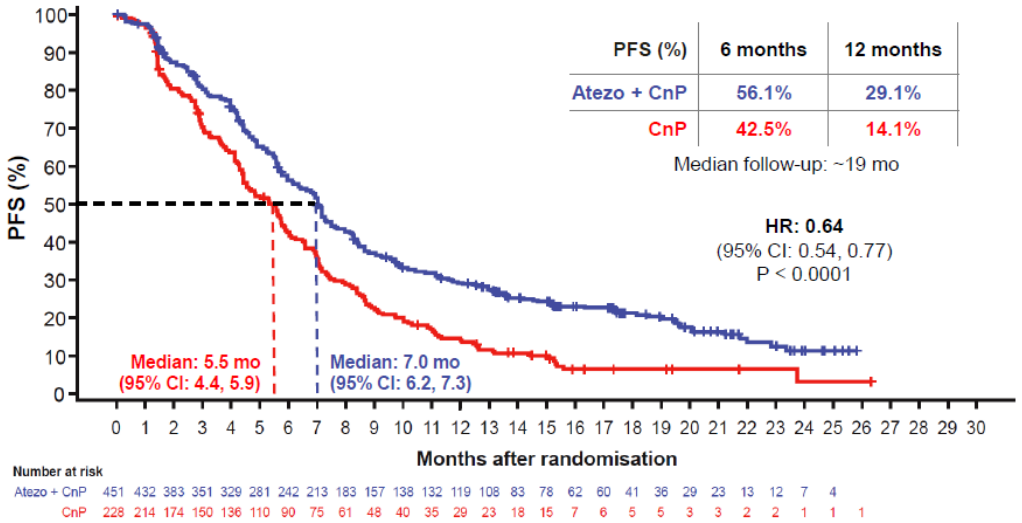
- **Co-primary endpoints:** investigator-assessed PFS and OS (ITT-WT population)
  - ITT-WT population: randomised patients excluding those with *EGFR* or *ALK* genomic alterations
- **Key secondary endpoints:** OS and PFS (ITT population and by PD-L1 expression), ORR and safety
  - ITT population could be formally tested for OS/PFS if ITT-WT OS was positive

Cappuzzo F, ESMO 2018

Non-Squamous NSCLC [IMpower130]
ITT



PFS

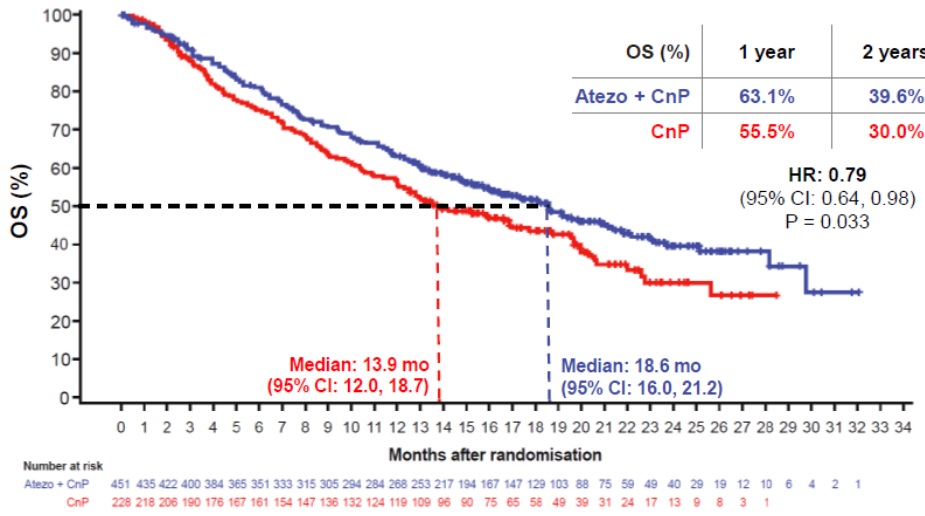


PFS (%)	6 months	12 months
Atezo + CnP	56.1%	29.1%
CnP	42.5%	14.1%

Median follow-up: ~19 mo

HR: 0.64
(95% CI: 0.54, 0.77)
P < 0.0001

OS



OS (%)	1 year	2 years
Atezo + CnP	63.1%	39.6%
CnP	55.5%	30.0%

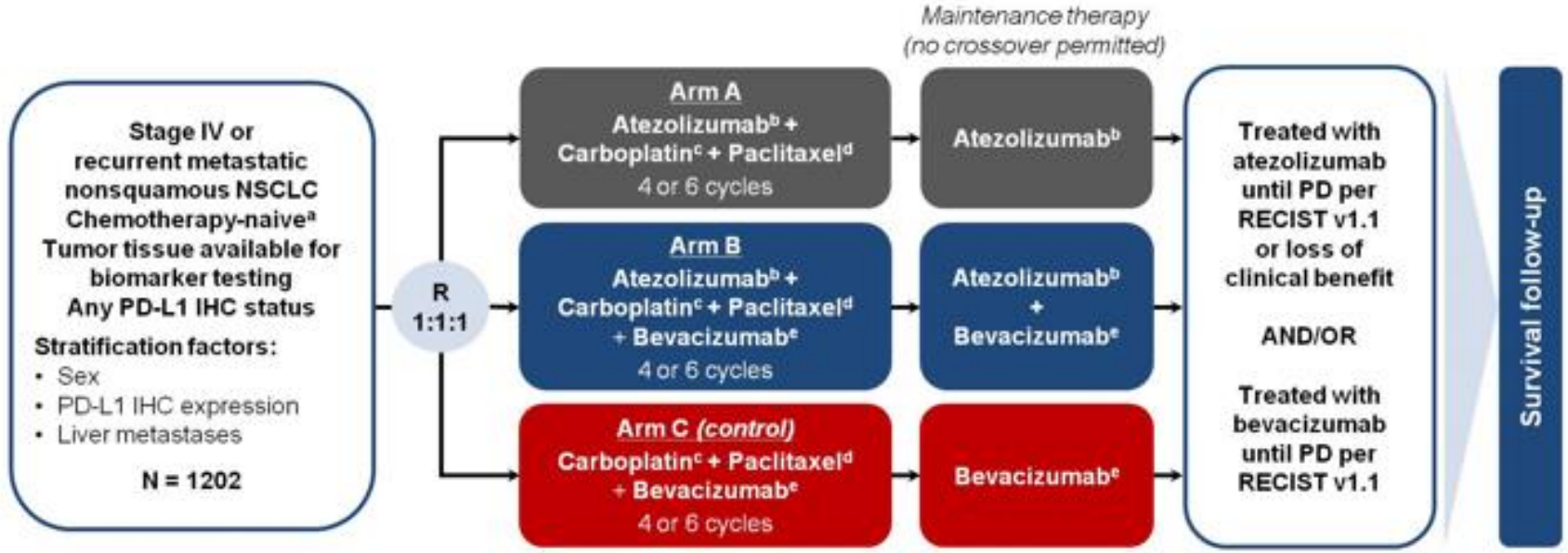
HR: 0.79
(95% CI: 0.64, 0.98)
P = 0.033

Control arm: 20% Pemetrexed switch maintenance

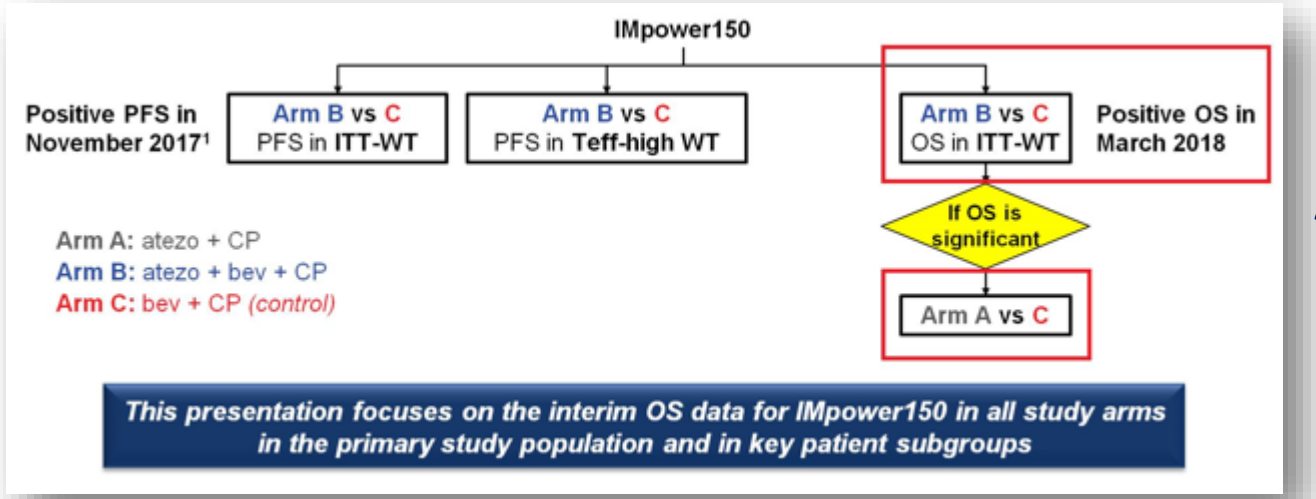
Cross over to immunotherapy 135 (59.2%)

Cappuzzo F, ESMO 2018

Non-Squamous NSCLC [IMpower150]



[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.

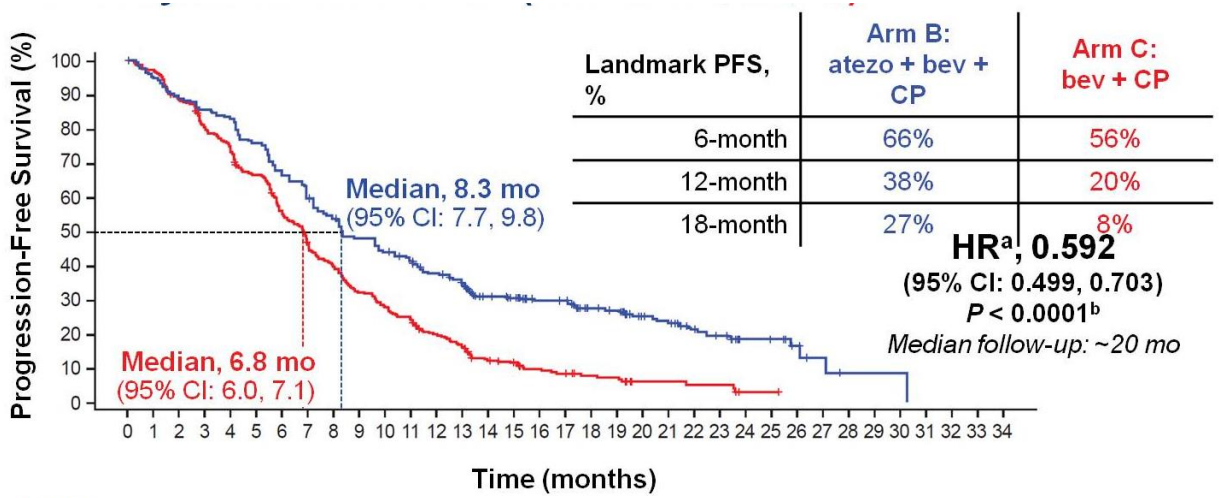


Co-Primary Endpoint Analysis

Socinski M, ASCO 2018

Non-Squamous NSCLC [IMpower150]

PFS (B vs C)



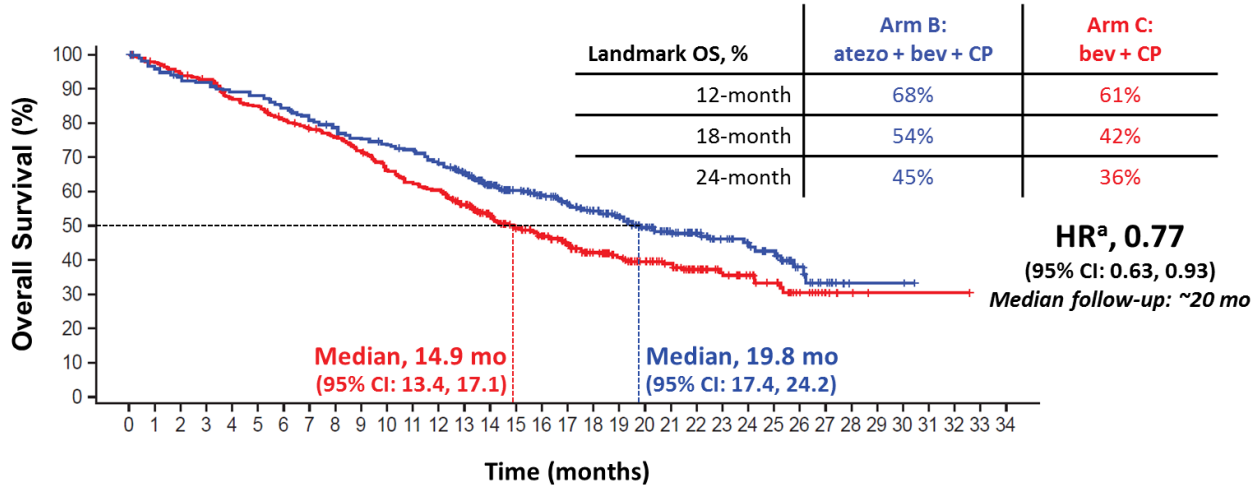
Landmark PFS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
6-month	66%	56%
12-month	38%	20%
18-month	27%	8%

HR[a], 0.592
(95% CI: 0.499, 0.703)
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					

OS (B vs C)

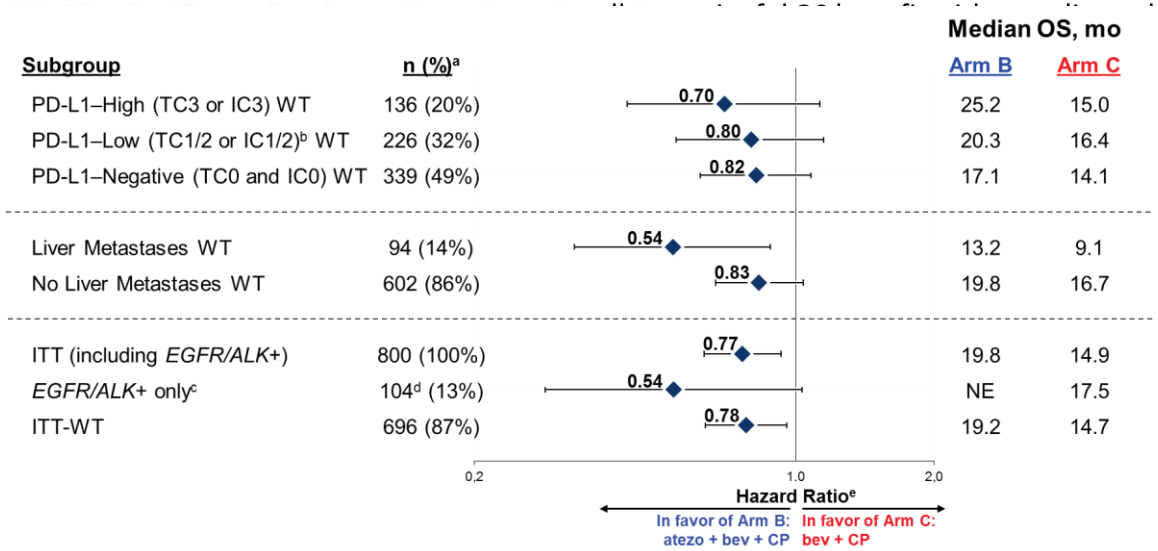


Landmark OS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
12-month	68%	61%
18-month	54%	42%
24-month	45%	36%

HR[a], 0.77
(95% CI: 0.63, 0.93)
Median follow-up: ~20 mo

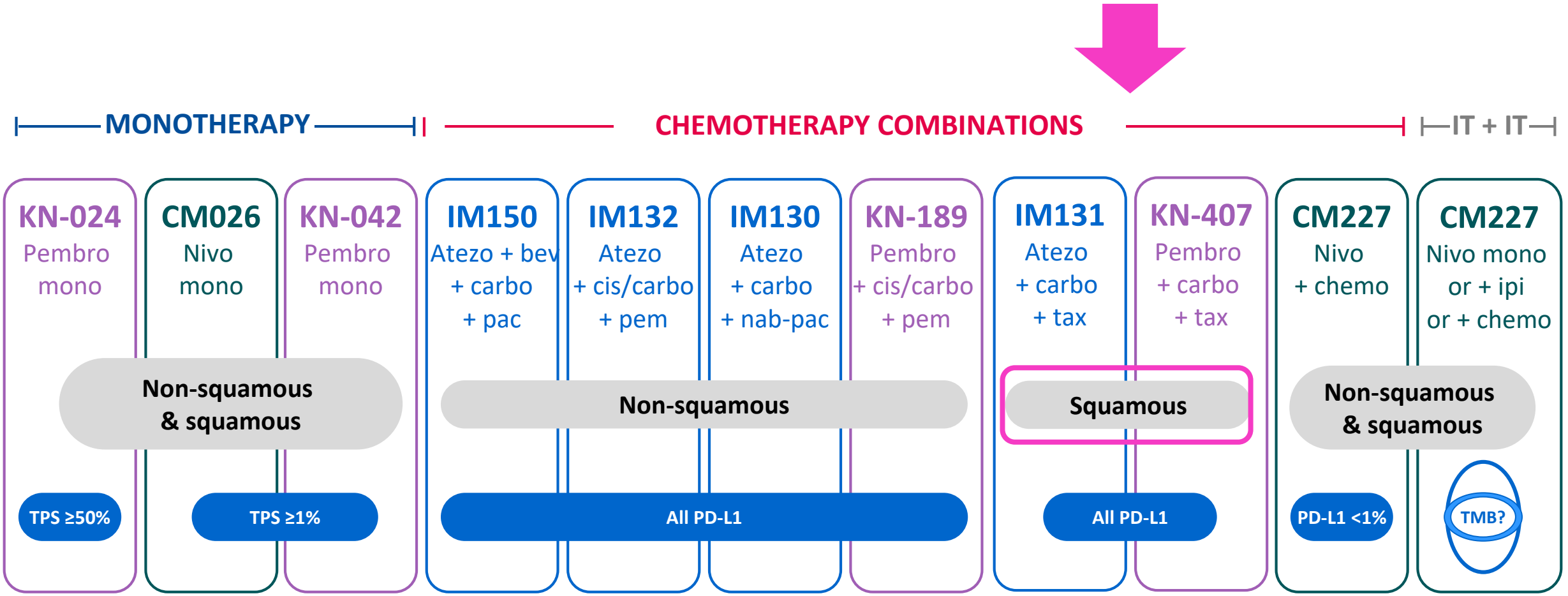
No. at Risk

Atezo+Bev+CP	400	380	367	361	351	347	333	320	308	297	288	281	265	244	208	185	162	147	130	112	93	73	62	45	38	32	18	10	2	2	2
Bev+CP	400	388	376	366	344	335	317	303	293	278	255	241	233	209	180	154	139	123	104	90	78	68	51	41	36	27	15	6	3	1	1	1	1

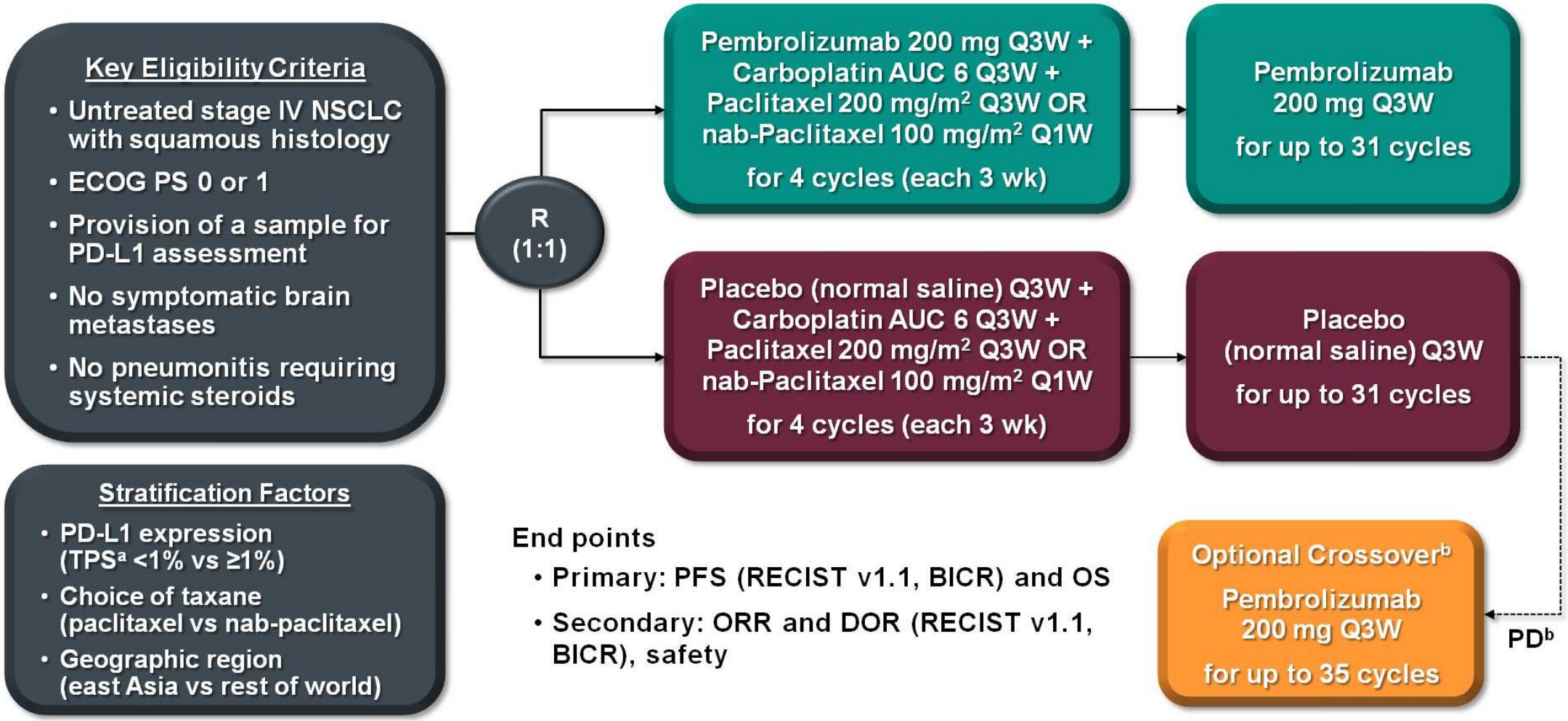


Socinski M, ASCO 2018

The invasion of clinical trials



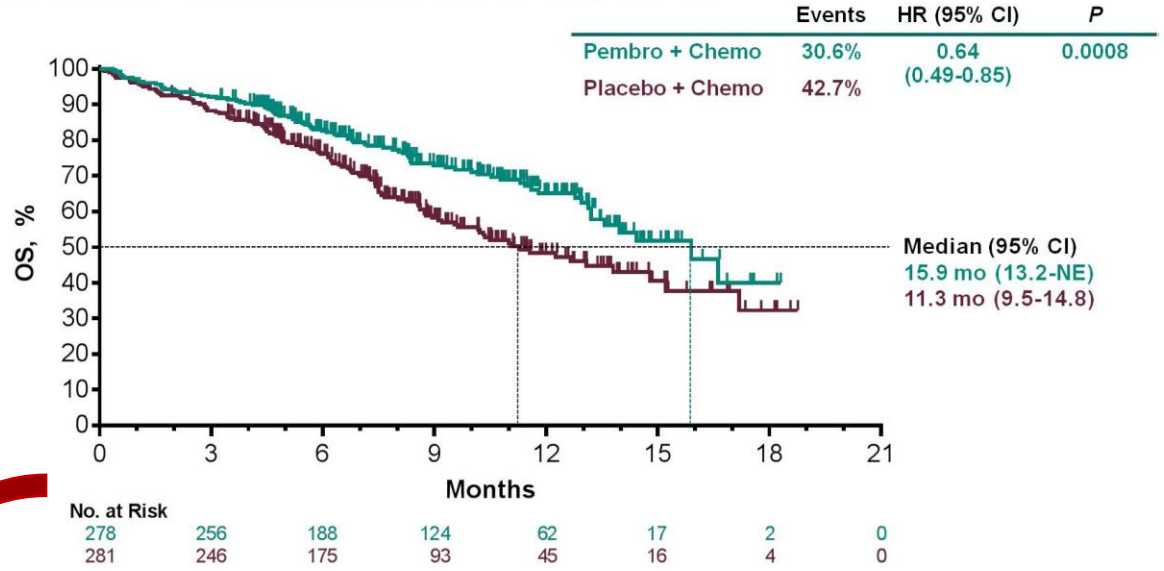
Squamous NSCLC [KEYNOTE-407]

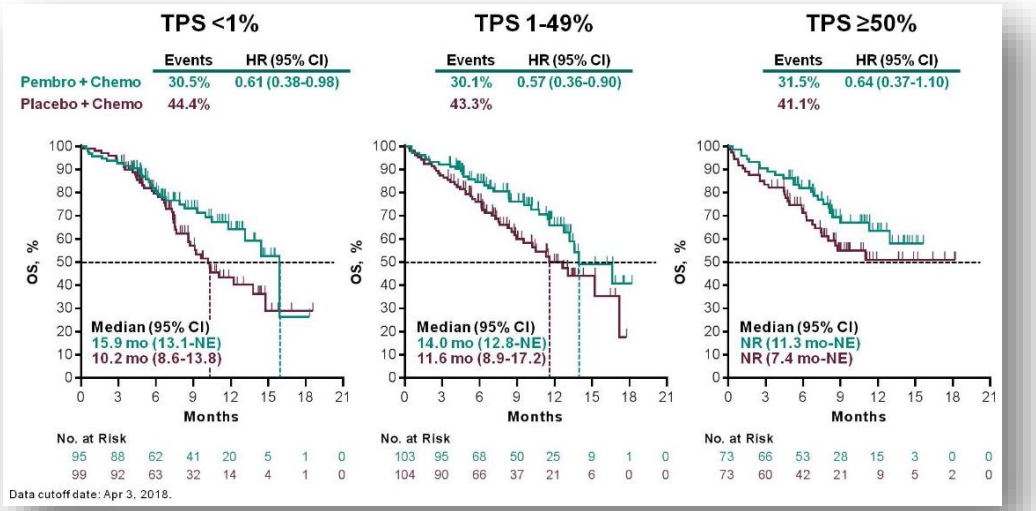


Paz-Ares L, ASCO 2018

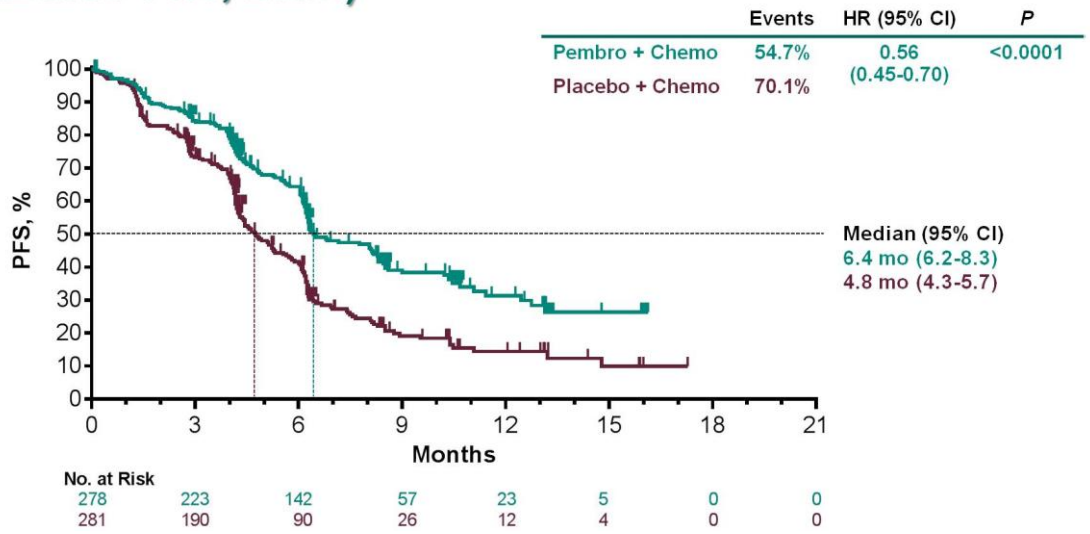
Squamous NSCLC [KEYNOTE-407]

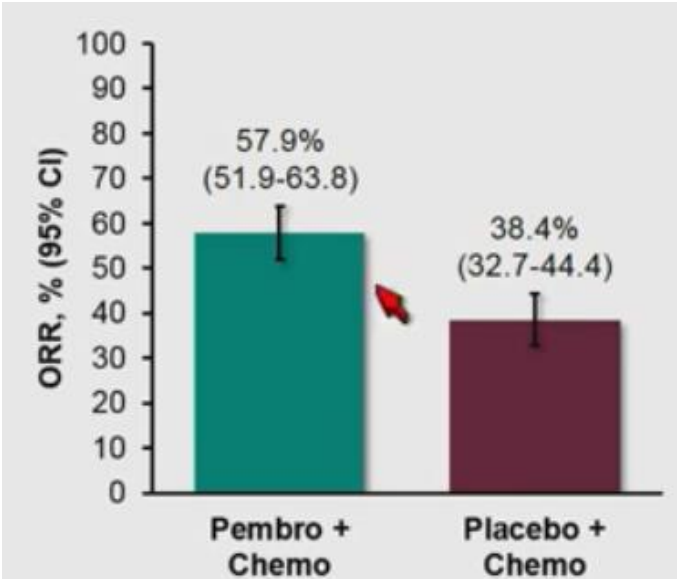
Overall Survival at IA2, ITT





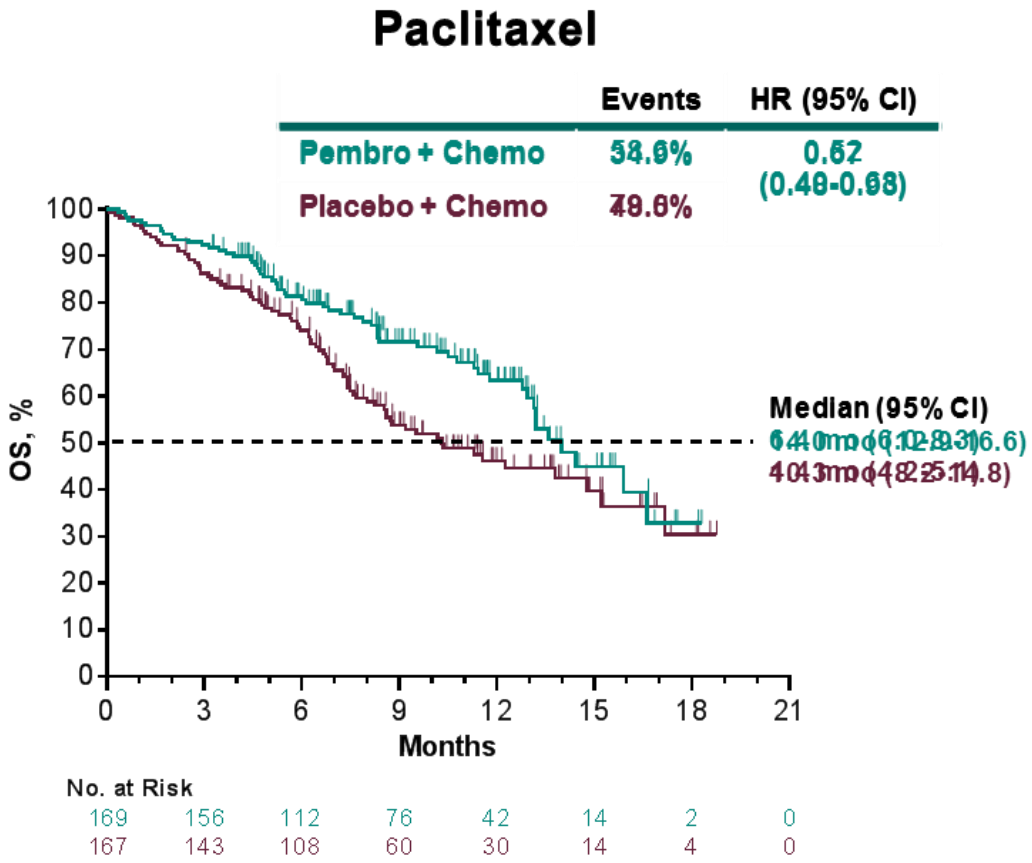
Progression-Free Survival at IA2, ITT (RECIST v1.1, BICR)

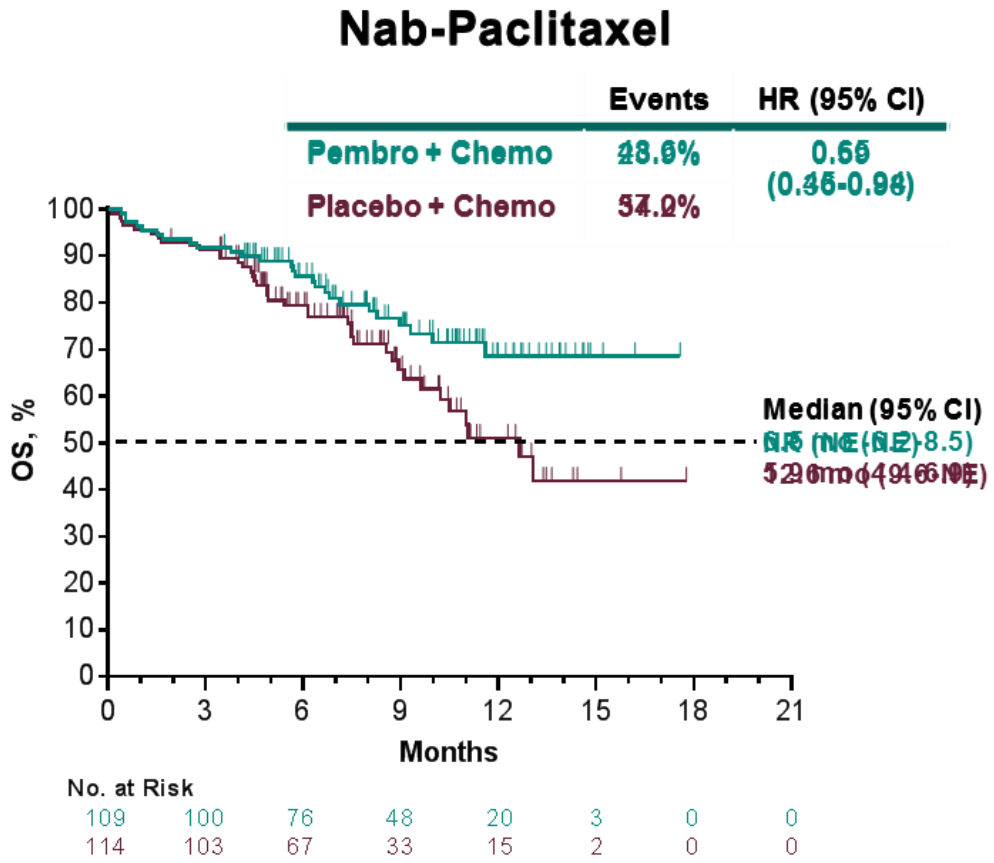




Paz-Ares L, ASCO 2018

Squamous NSCLC [KEYNOTE-407]

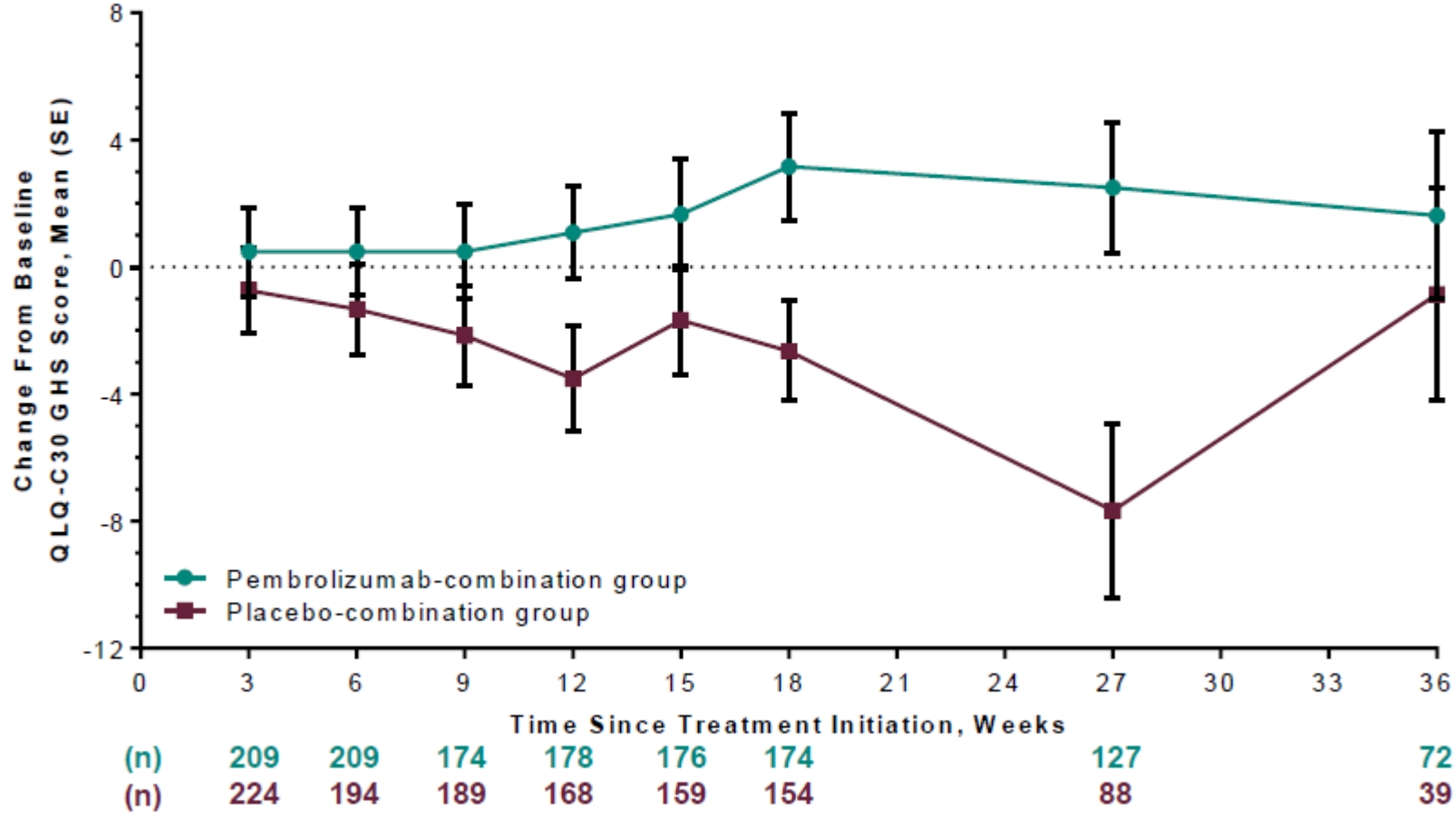




Halmos, WCLC 2018

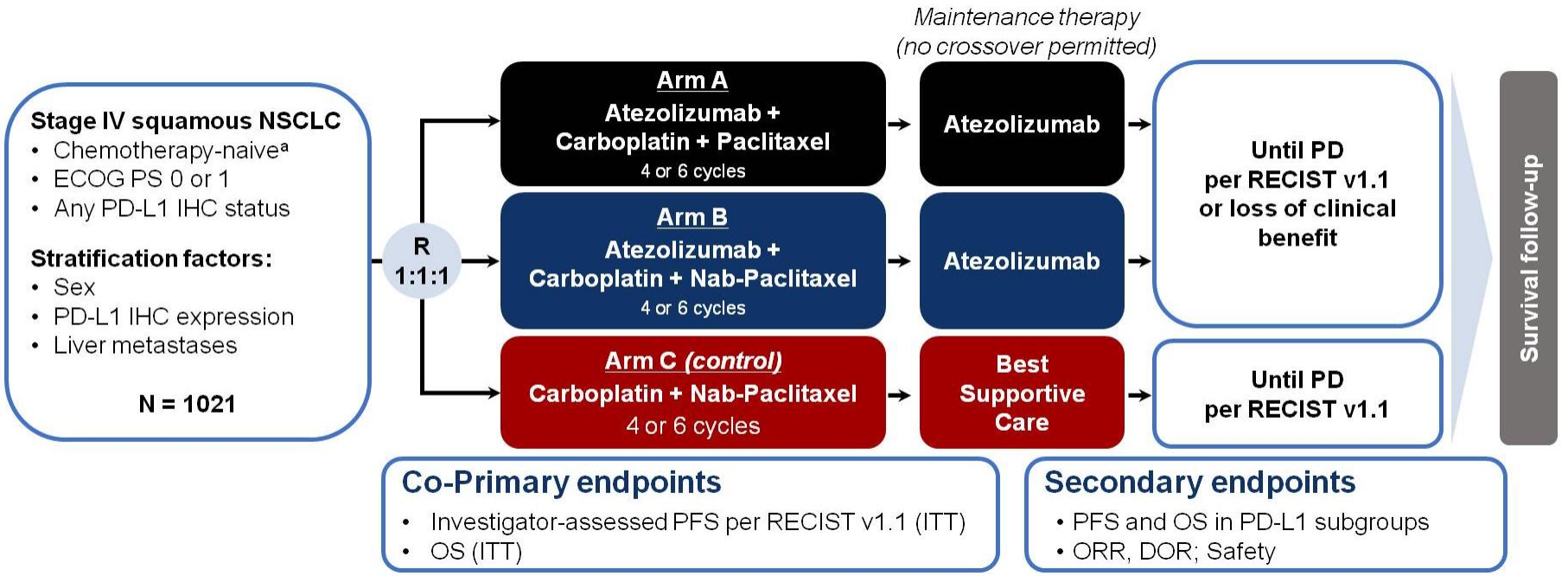
KN 407: PROs Results

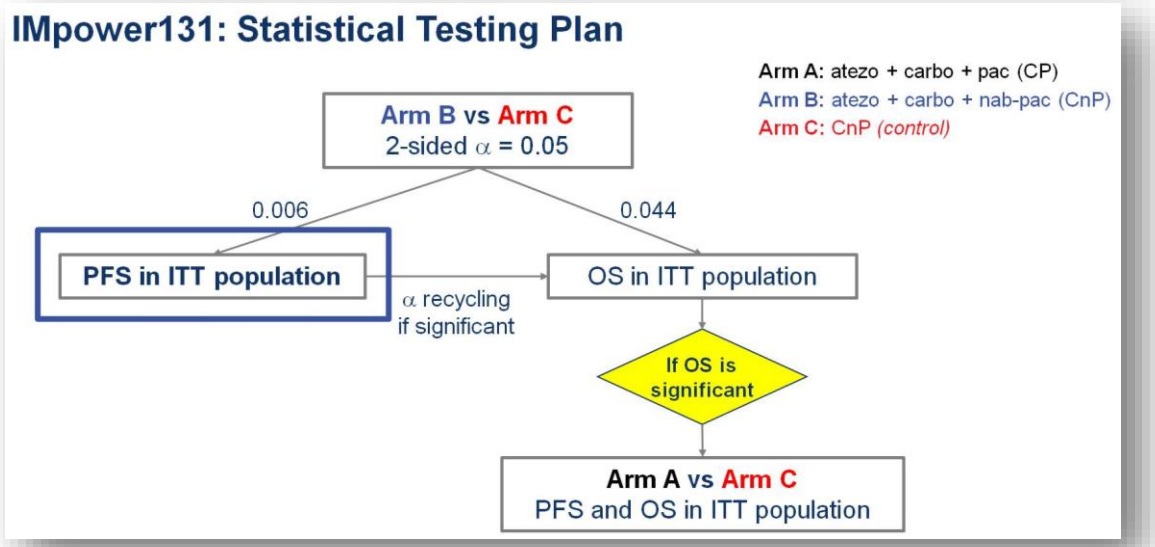
Mean Change From Baseline in QLQ-C30 GHS/QoL



Mazieres, ESMO 2018

Squamous NSCLC [IMpower131]

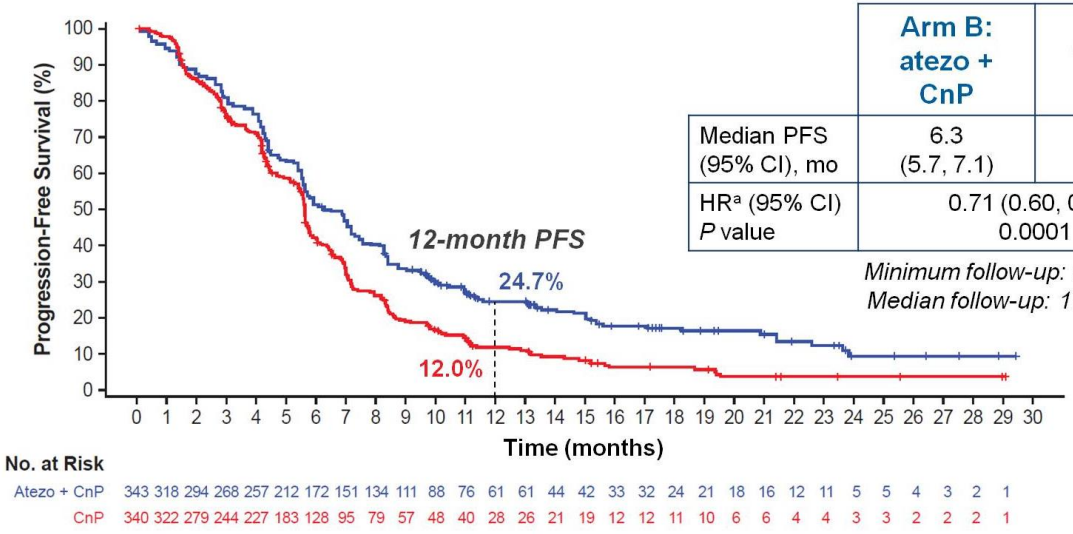




Jotte R, ASCO 2018

Squamous NSCLC [IMpower131]

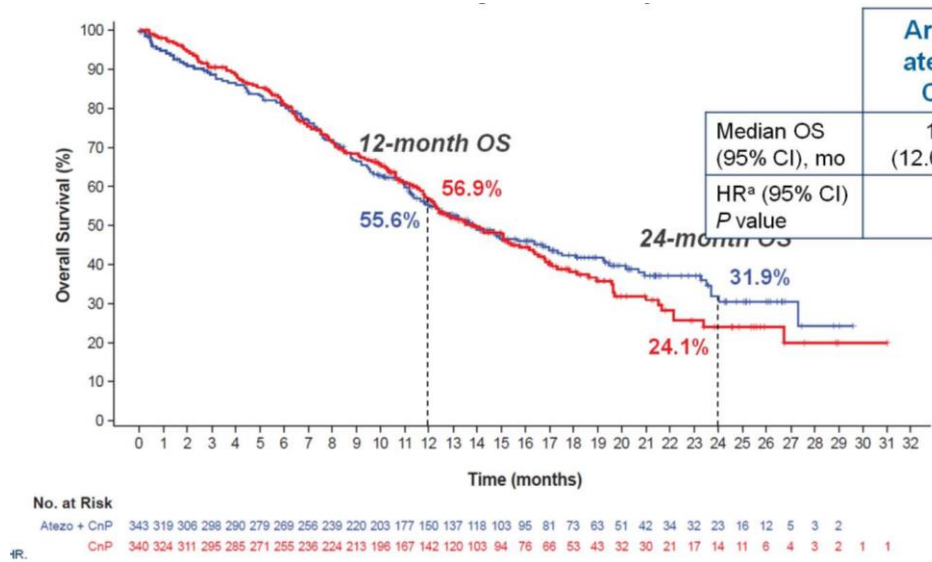
PFS (B vs C)



	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) *P* value	0.71 (0.60, 0.85) 0.0001	

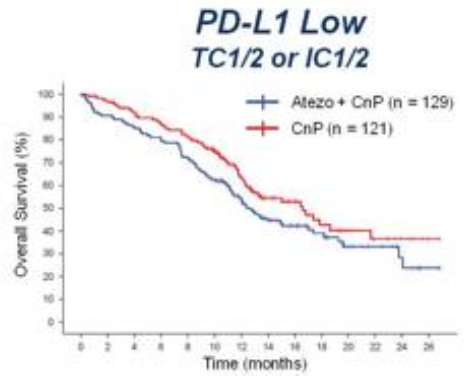
Minimum follow-up: 9.8 mo
Median follow-up: 17.1 mo

OS (B vs C)



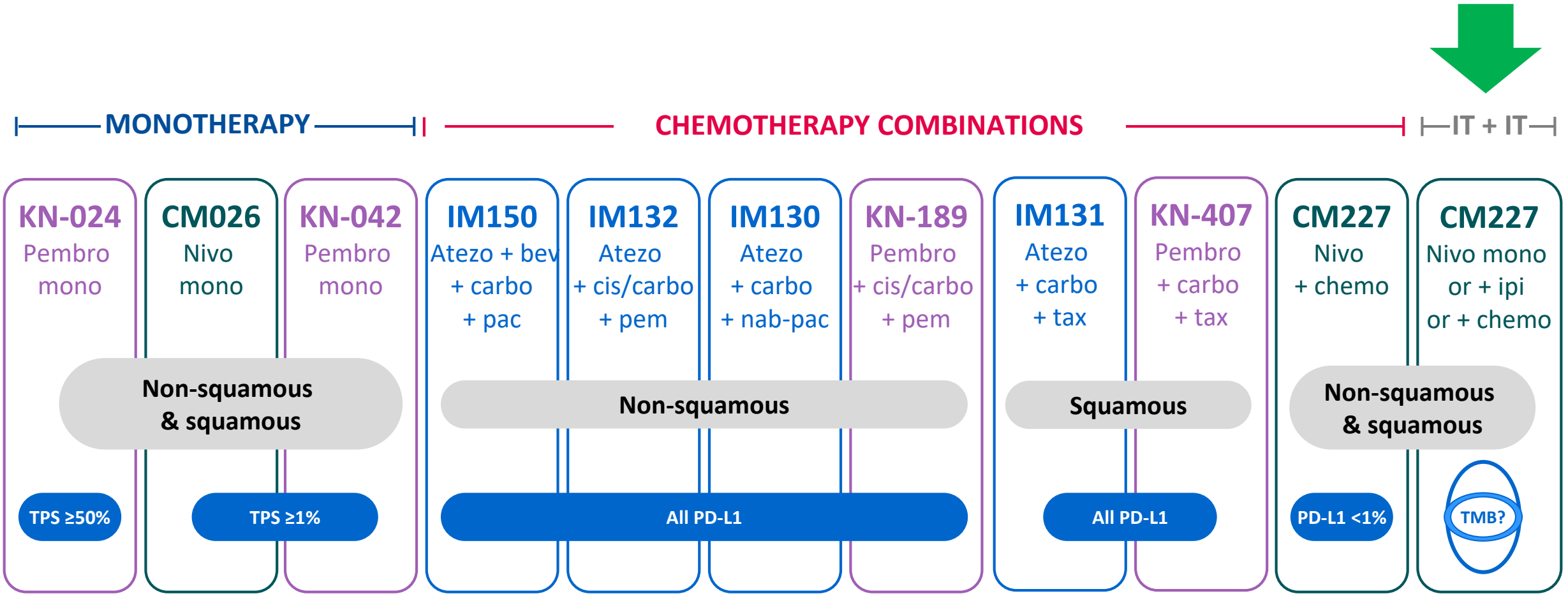
	Arm B: atezo + CnP	Arm C: CnP
Median OS (95% CI), mo	14.0 (12.0, 17.0)	13.9 (12.3, 16.4)
HR[a] (95% CI) *P* value	0.96 (0.78, 1.18) 0.6931	

*In **PD-L1 low (TC1/2 or IC1/2)** OS has an opposite trend*

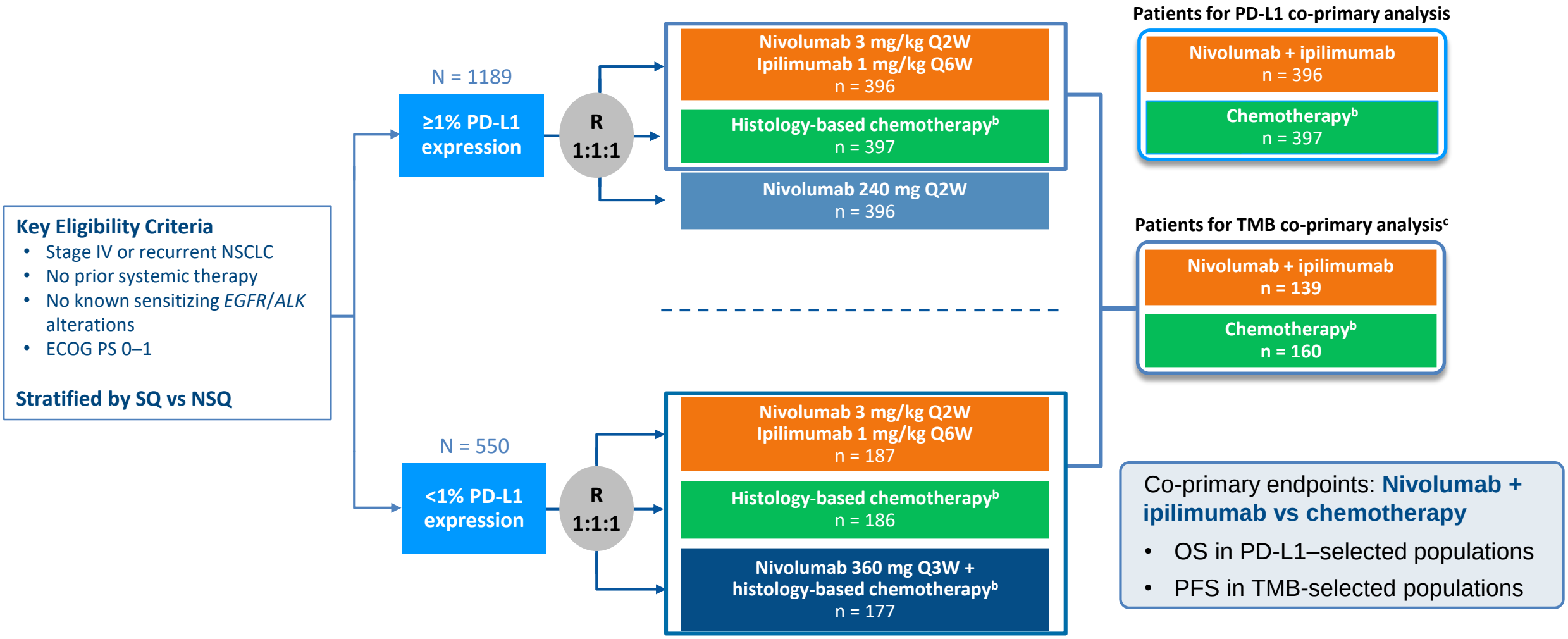


Jotte R, ASCO 2018

The invasion of clinical trials

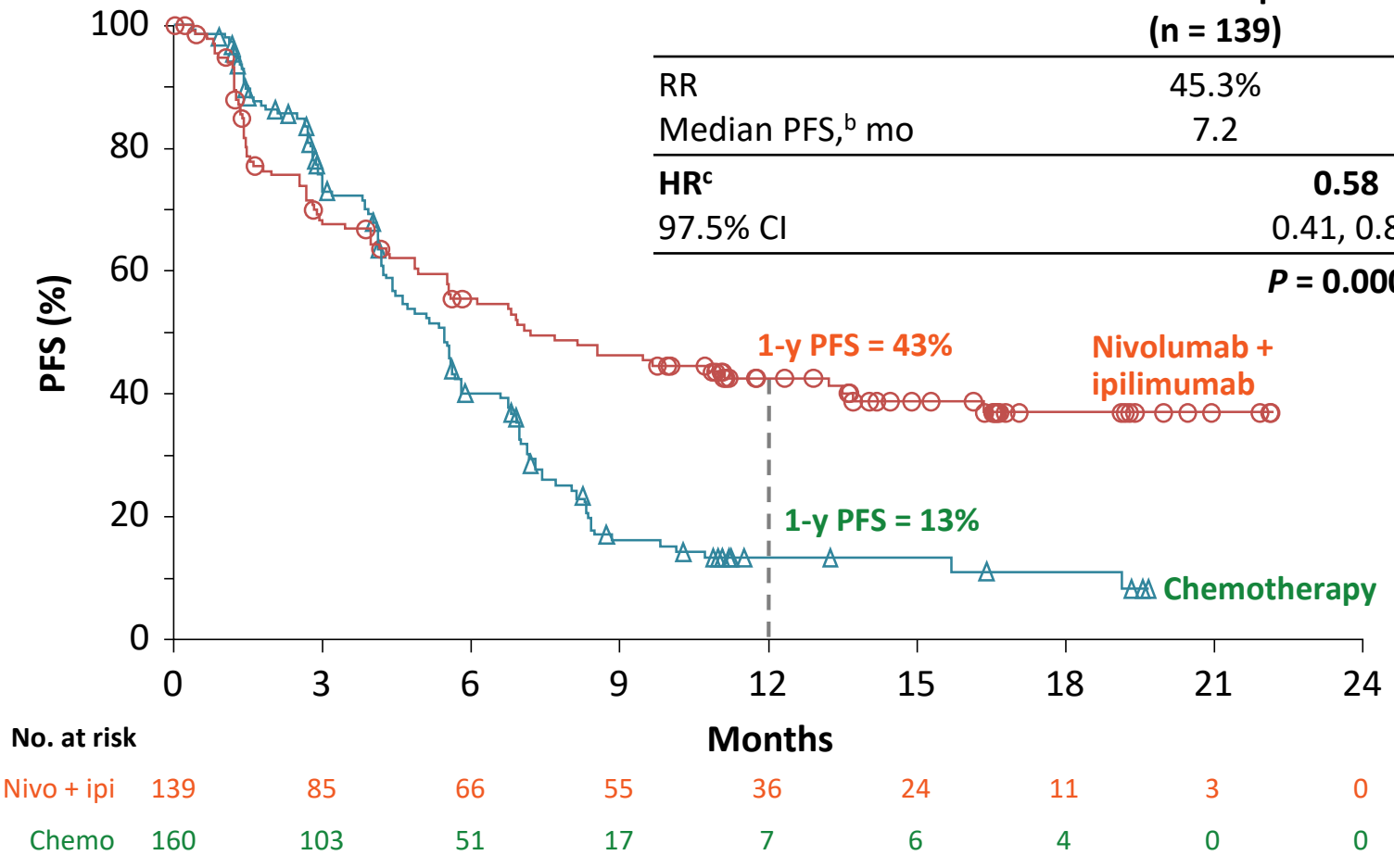


CheckMate-227



Hellman, AACR 2017

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



	Nivo + ipi (n = 139)	Chemo (n = 160)
RR	45.3%	26.9%
Median PFS,[b] mo	7.2	5.4
HR[c]	**0.58**	
97.5% CI	0.41, 0.81	
	***P* = 0.0002**	

Press release Oct 19th

Updated analysis, TMB ≥10 mut/Mb

HR for OS =0.77

(95% CI: 0.56 to 1.06).

Median OS 23.03 mo vs. 16.72 mo on the chemotherapy arm

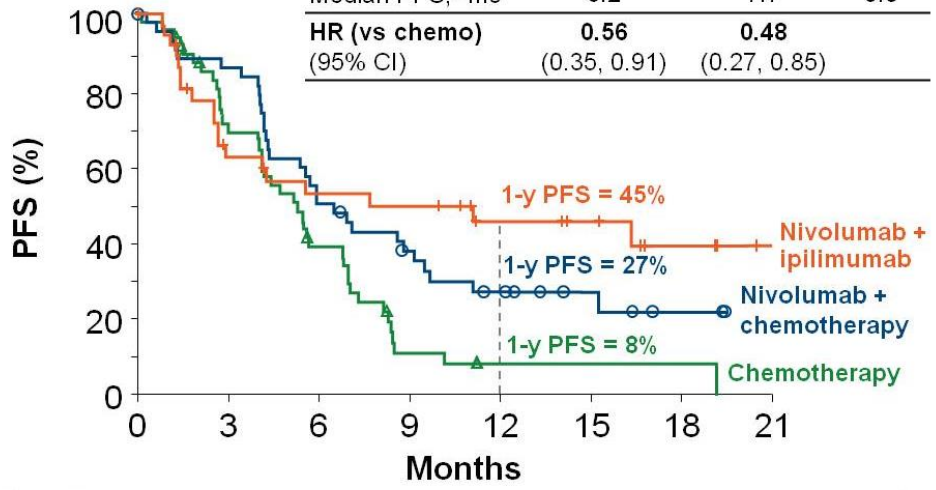
- PFS benefit was independent of PD-L1 and histology
- In patients with TMB <10 mut/Mb treated with nivo + ipi vs chemo, the HR was 1.07 (95% CI: 0.84, 1.35)[d]

Hellman, AACR 2017

PFS With Nivolumab + Chemotherapy and Nivolumab + Ipilimumab by TMB Status

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

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

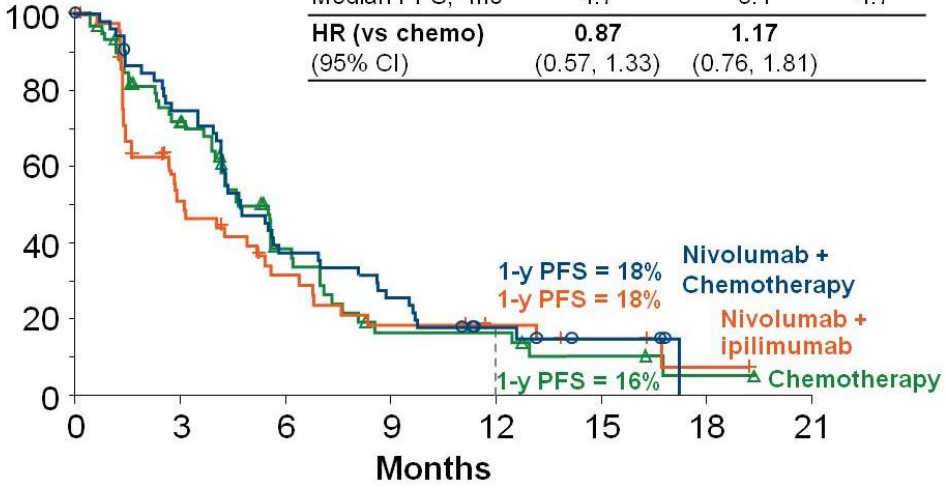


No. at risk

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

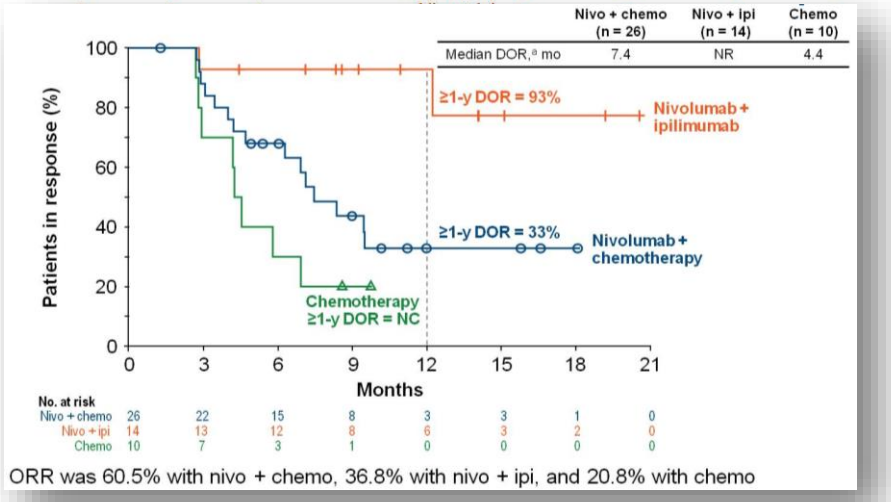
TMB <10 mut/Mb and <1% Tumor PD-L1 Expression

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



No. at risk

Nivo + chemo	54	38	19	13	6	3	0	0
Nivo + ipi					5	3	1	0
Chemo					6	3	1	0

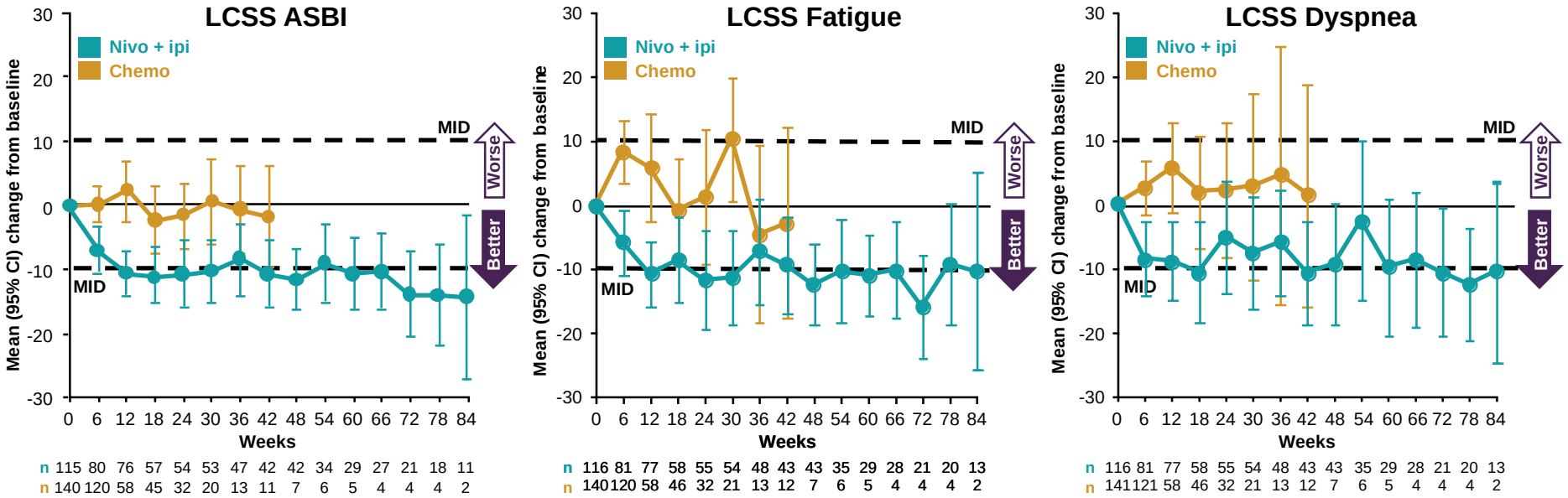


Borghaei H, ASCO 2018

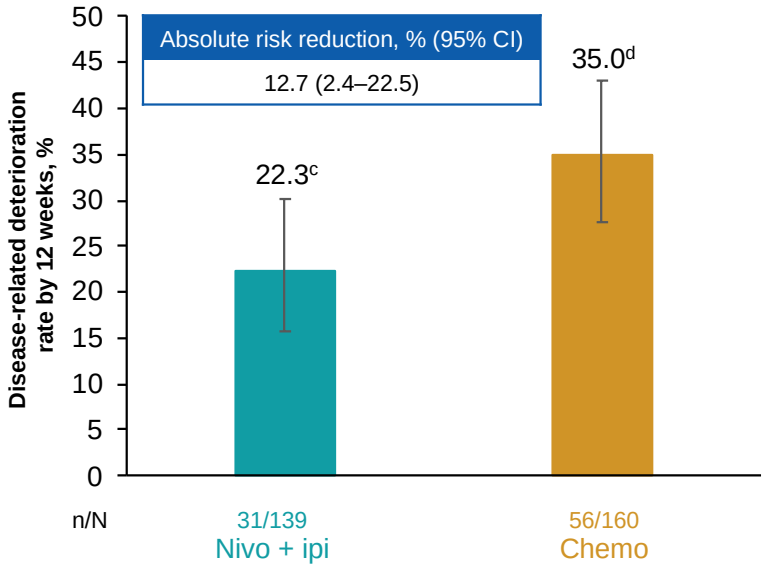
CM 227: PROs Results

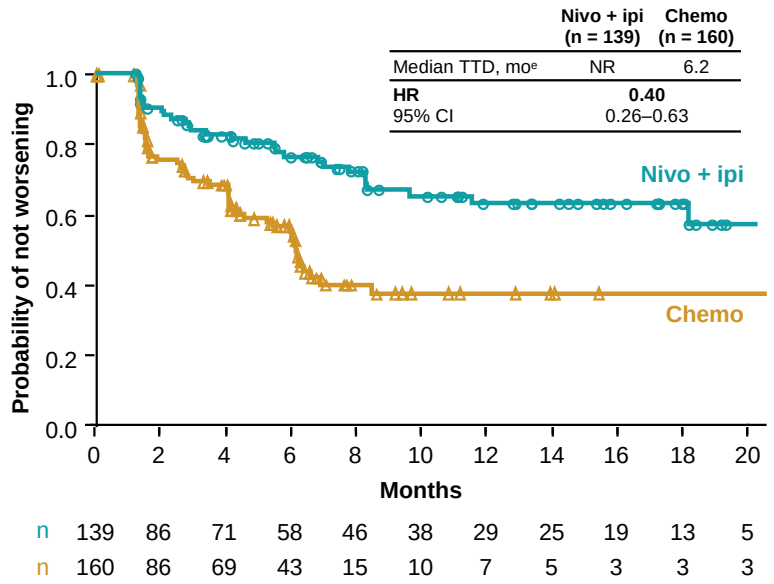
PRO measures assessed

- **LCSS: ASBI; 3-IGI**
- **EQ-5D (3-level): VAS; UI**



Proportion of patients with symptom deterioration on treatment or follow-up by week 12





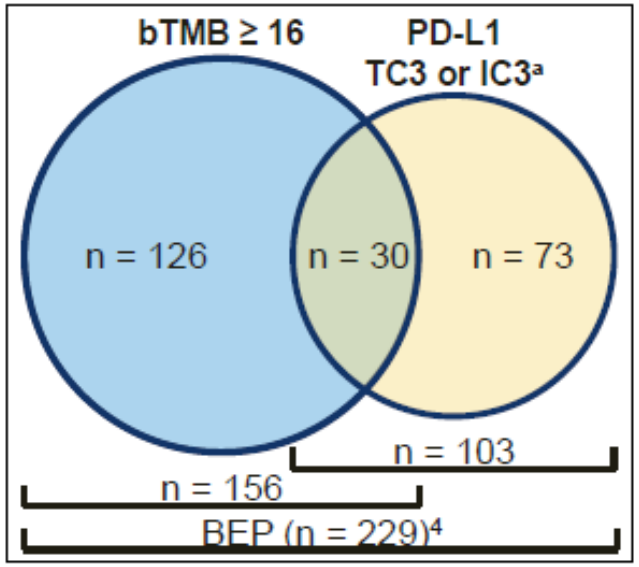
Time to first disease-related deterioration on treatment

Brahmer, WCLC 2018

B-F1RST

Patients with stage IIIb-IVa[a] locally advanced or metastatic NSCLC (any histology; N = 152[b]) → **Atezolizumab 1200 mg IV q3w** → **Until PD, unacceptable toxicity or loss of clinical benefit**

bTMB and PD-L1 are Orthogonal Biomarkers



Primary analysis

- All enrolled patients with at least 6 months of follow-up
- Prespecified bTMB biomarker cutoff of 16

Co-Primary Endpoints

- Efficacy endpoint: INV-assessed ORR per RECIST v1.1
- Biomarker endpoint: INV-assessed PFS per RECIST v1.1

Secondary Objectives

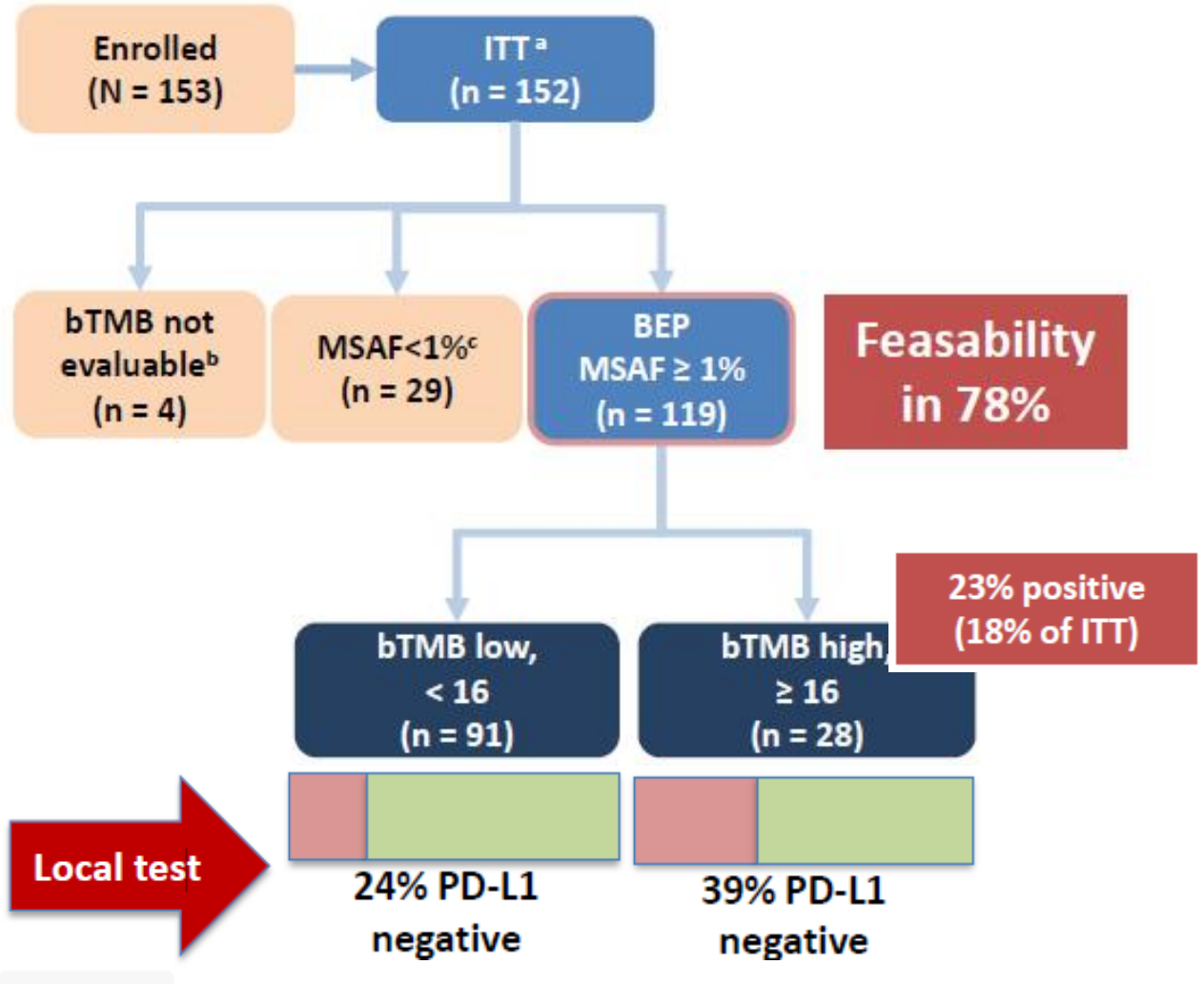
- Safety and assessment of efficacy by INV-assessed DOR, OS

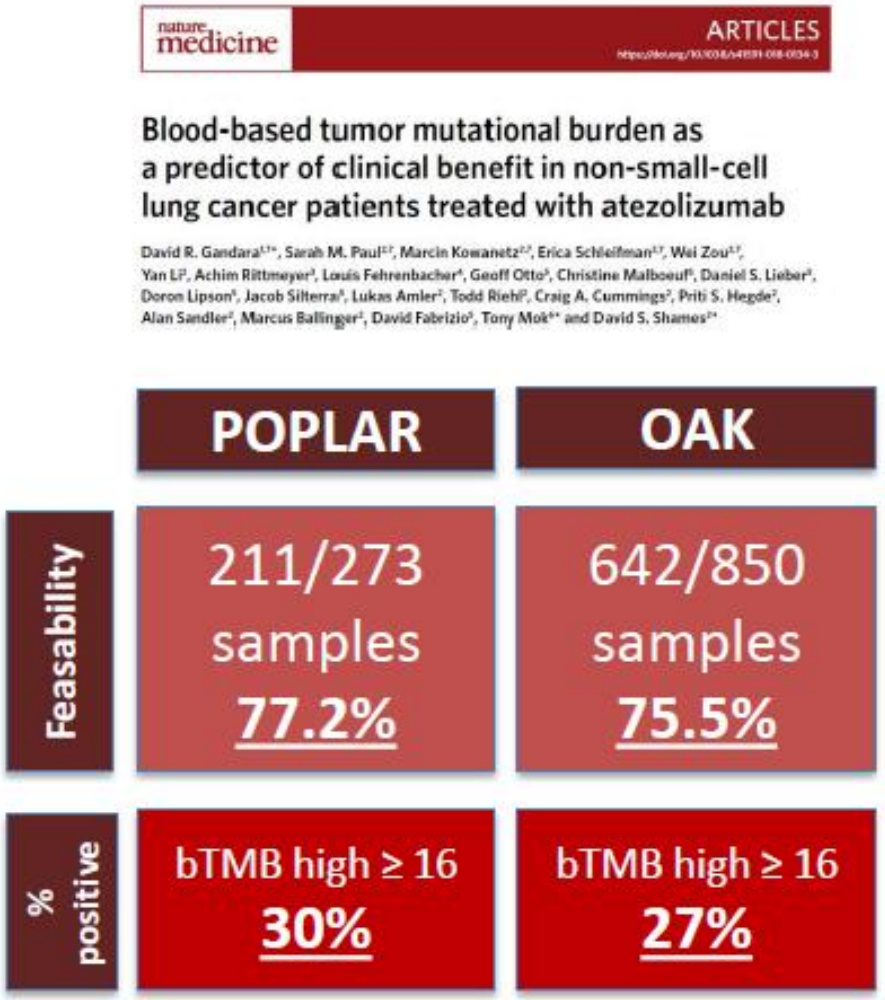
Major limitations
No tissue collection
No central PD-L1 testing
No tissue TMB

PD-L1 IHC Missing in 34.5%

Kim, ESMO 2018

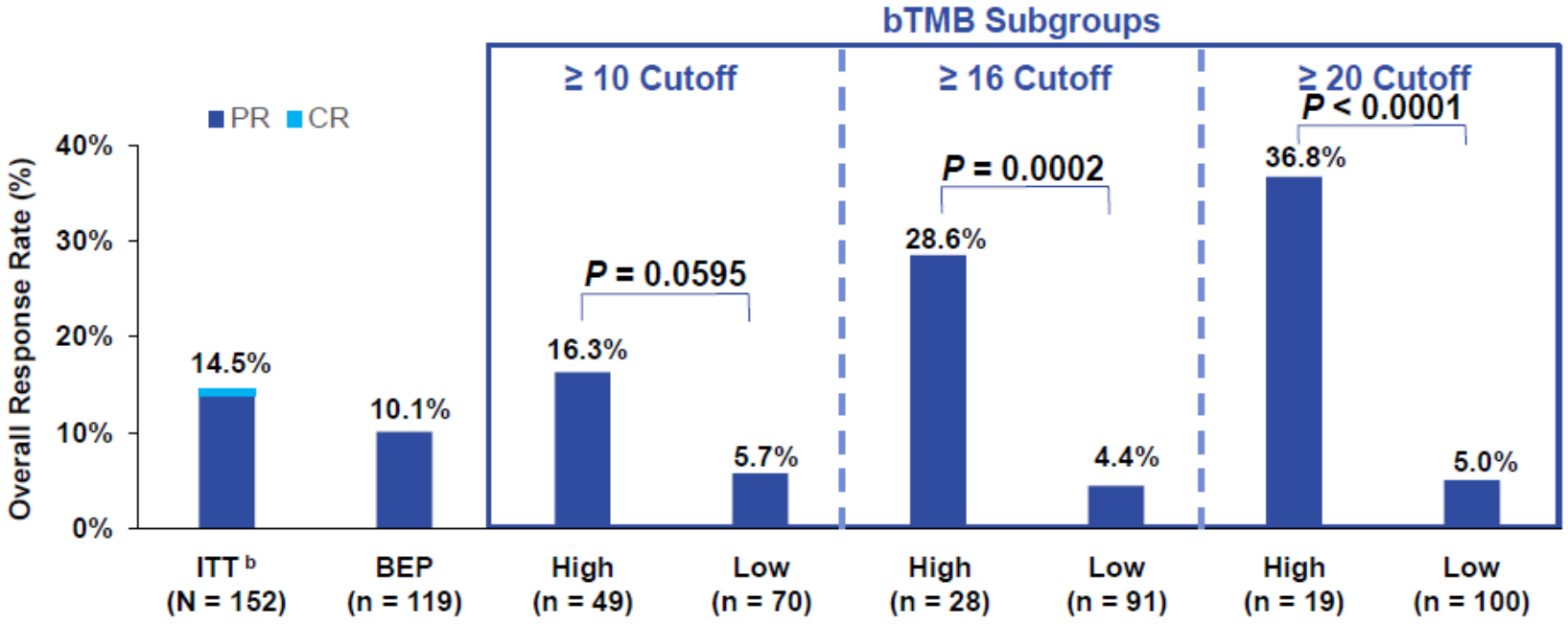
B-F1RST: Feasibility



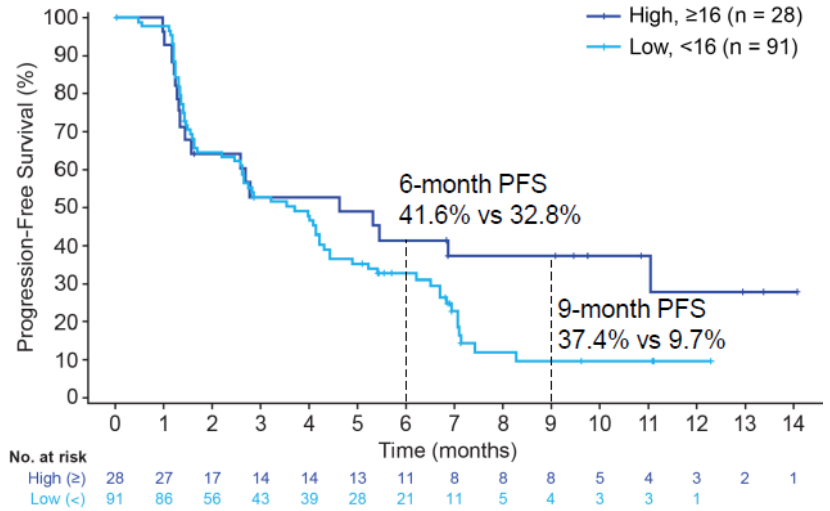


Kim, ESMO 2018

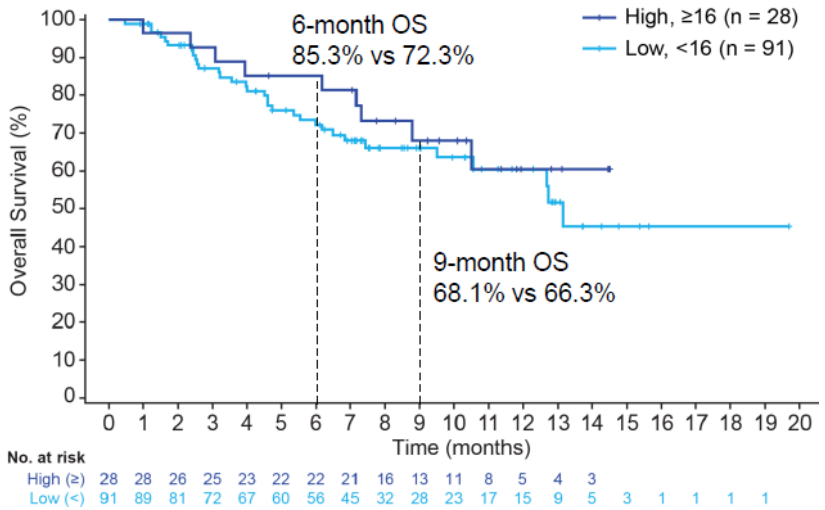
B-F1RST



PFS



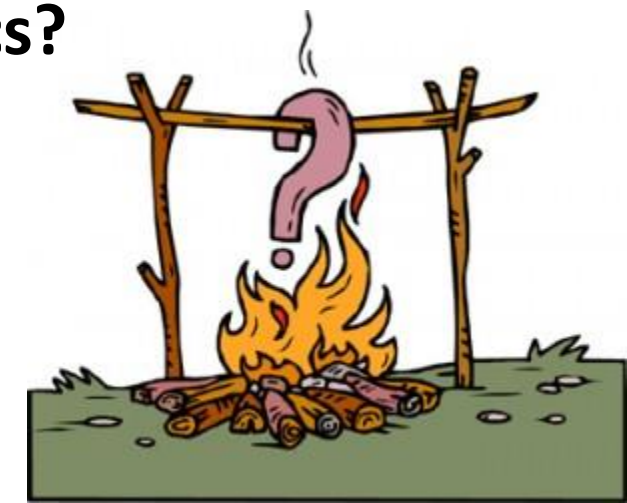
OS



Kim, ESMO 2018

Burning Questions for Tomorrow

1. What treatment according to PD-L1 expression level?
2. There is a role for the quadruplet with bevacizumab?
3. Patient characteristics: age and PS? Toxicity?
4. Concomitant treatment: steroids and antibiotics?



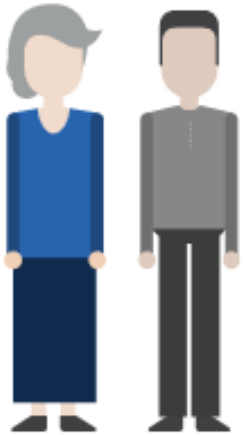
1. What treatment according to PD-L1 expression level?

High PD-L1 expression

This may indicate a pre-existing antitumour immune response that was arrested

Low PD-L1 expression

This may indicate a reduced immune response or impaired immune cell infiltration into the tumour

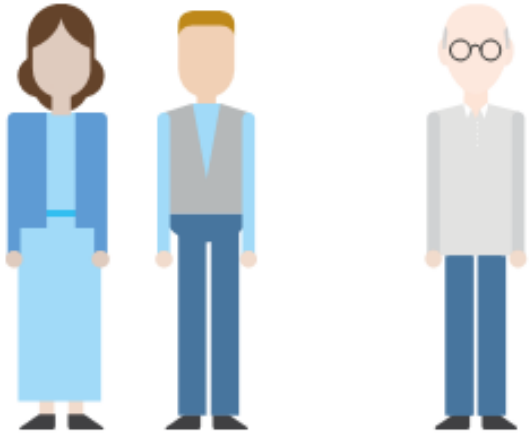


Negative or unknown PD-L1 expression

This may indicate a lack of antitumour immune response

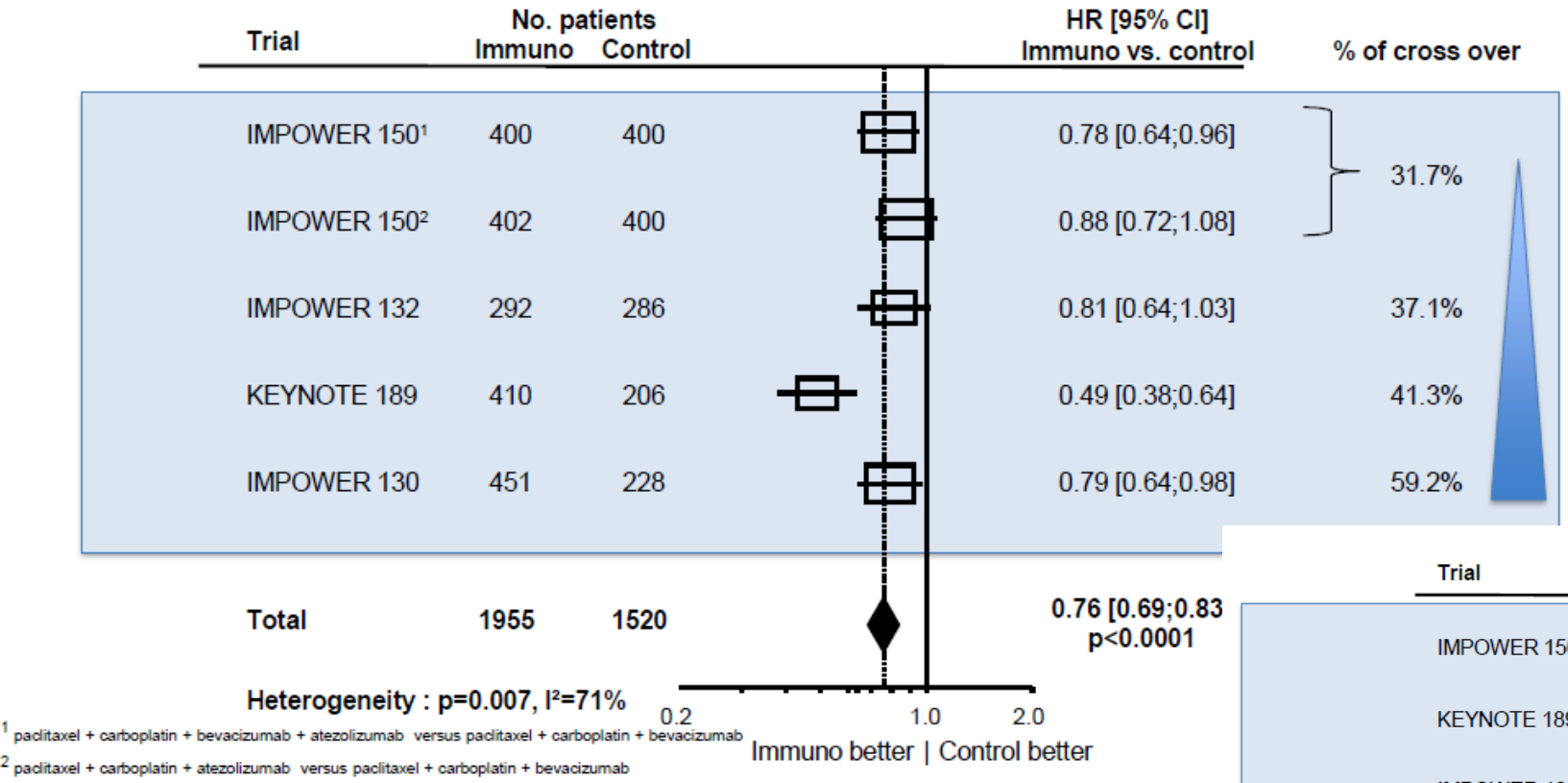
OR

lack of PD-L1 testing results



PD-L1 <50%: ICI + Chemo vs Chemo?

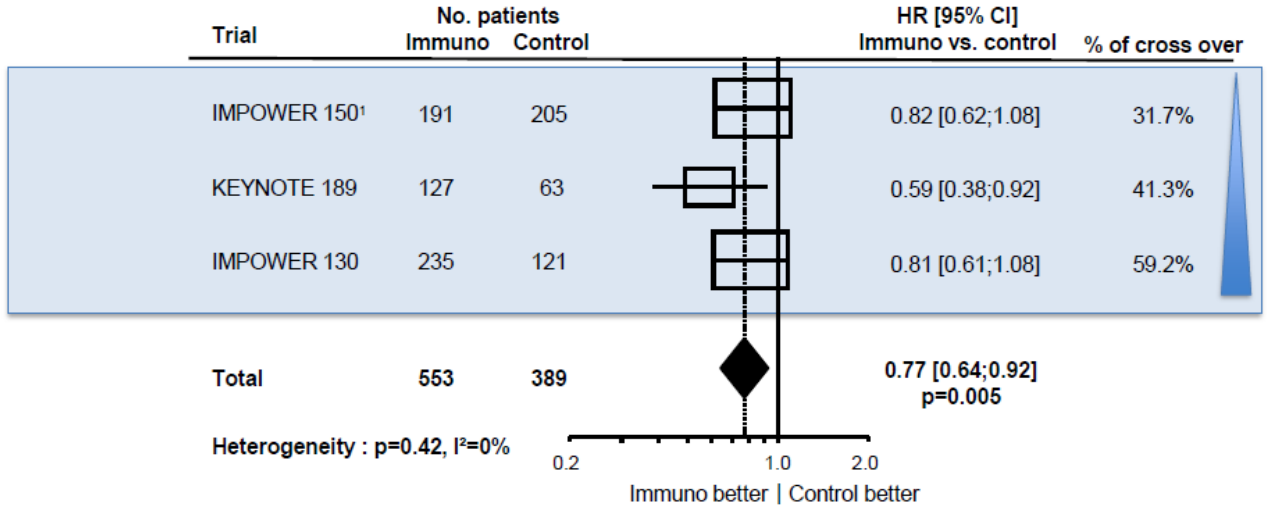
CT + immuno - OS



[1] paclitaxel + carboplatin + bevacizumab + atezolizumab versus paclitaxel + carboplatin + bevacizumab

[2] paclitaxel + carboplatin + atezolizumab versus paclitaxel + carboplatin + bevacizumab

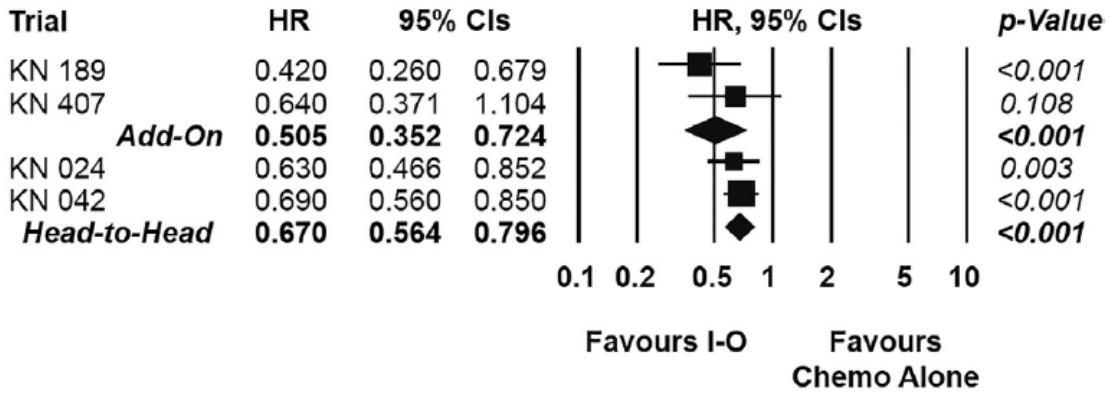
PDL1 negative - OS



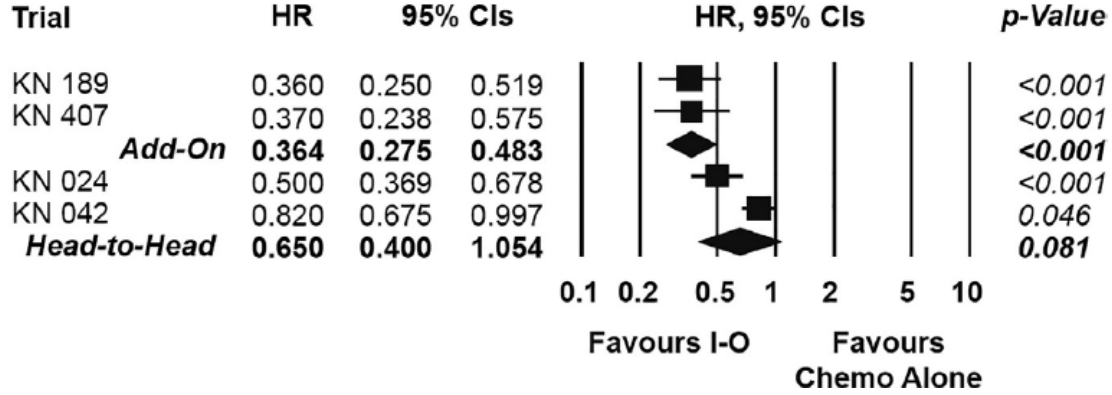
Besse, ESMO 2018

PD-L1 ≥50%: Pembro w/o Chemo?

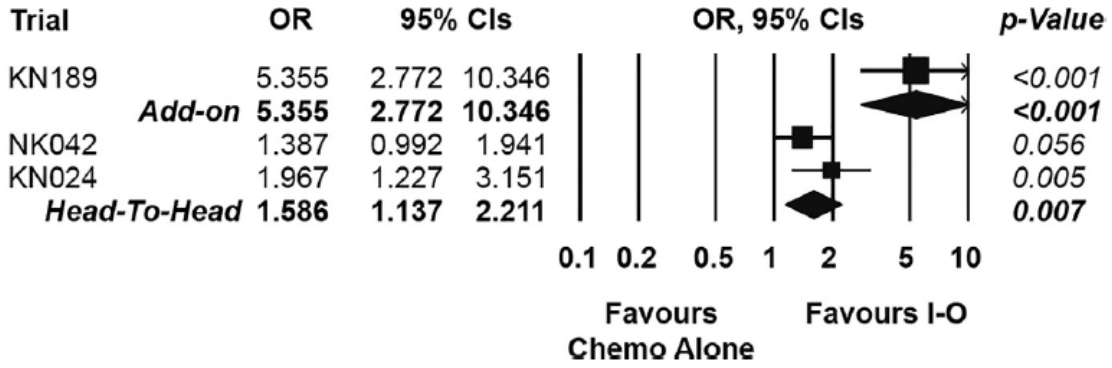
OS



PFS



ORR



Treatment Options (no comparative RCTs):

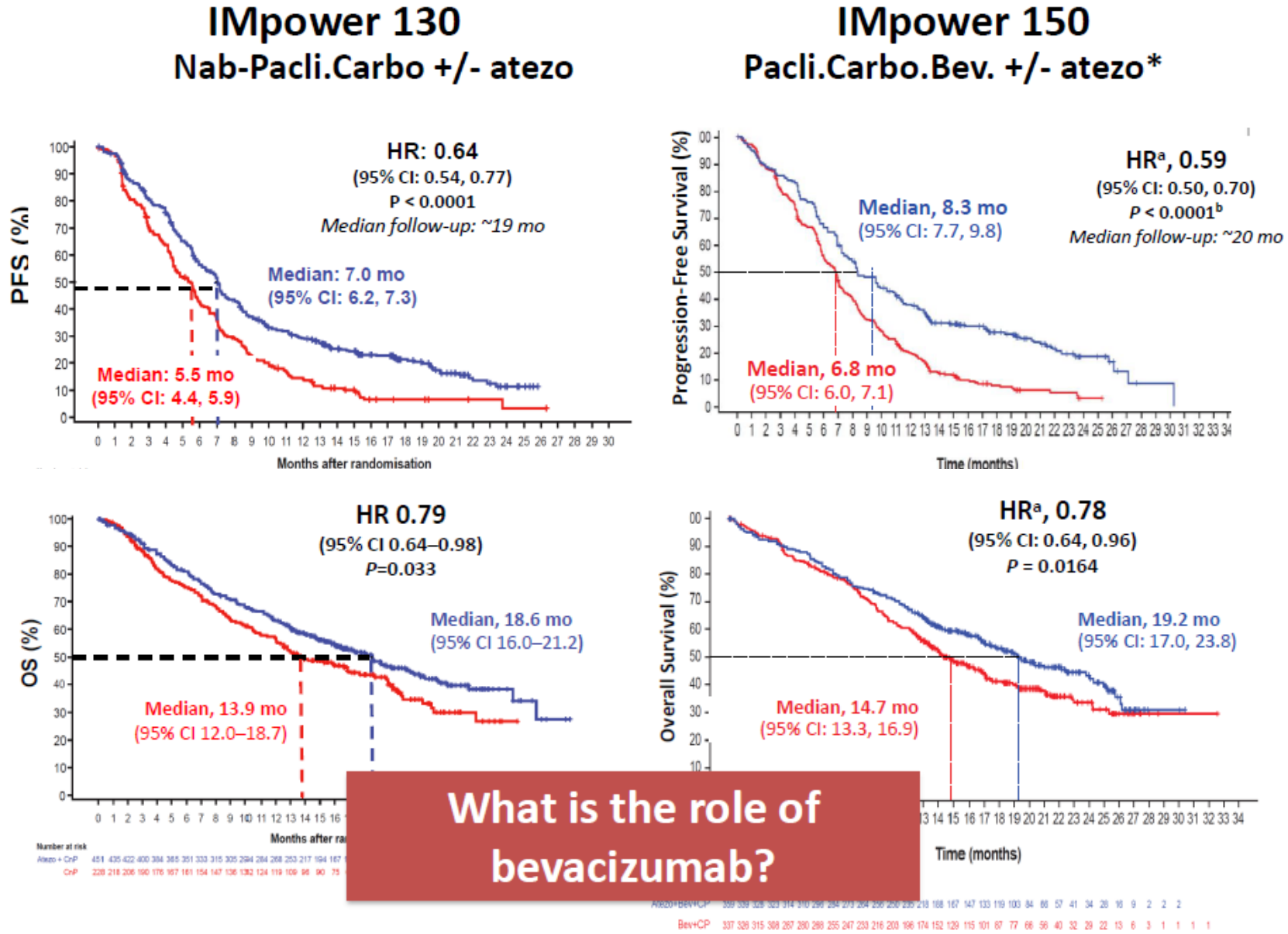
- **PEMBRO**
- **PEMBRO + Chemotherapy**

- **No significant Interaction in OS**
- **Significant Interaction in PFS and ORR in favour of the combo strategy**

- **Clinical decision should be individualized considering patients' overall health and comorbidities, disease characteristics (i.e. is rapid response required?), and safety concerns.**

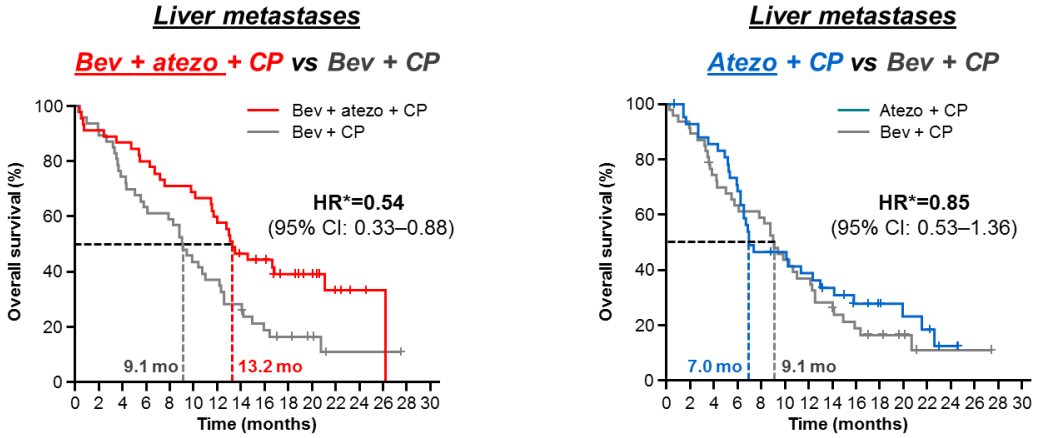
Pilotto S et al, Semin Oncol 2018 [in press]

2. There is a role for the quadruplet with bevacizumab?

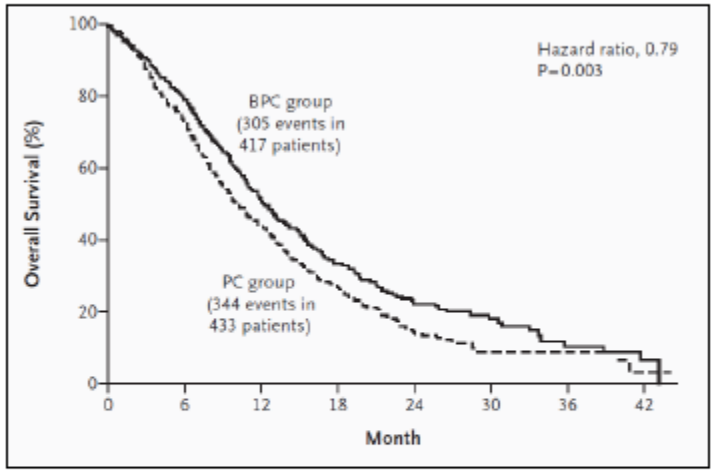


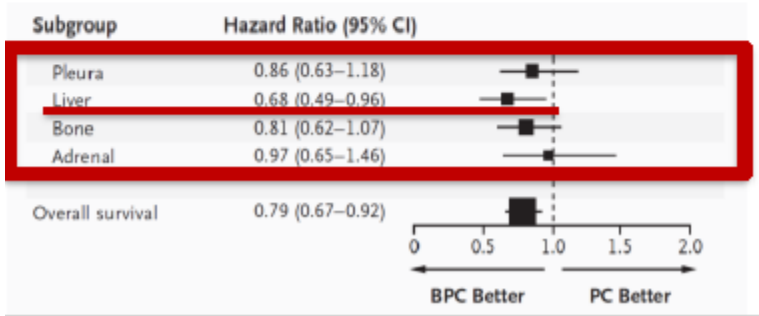
Besse, ESMO 2018

Liver Metastasis



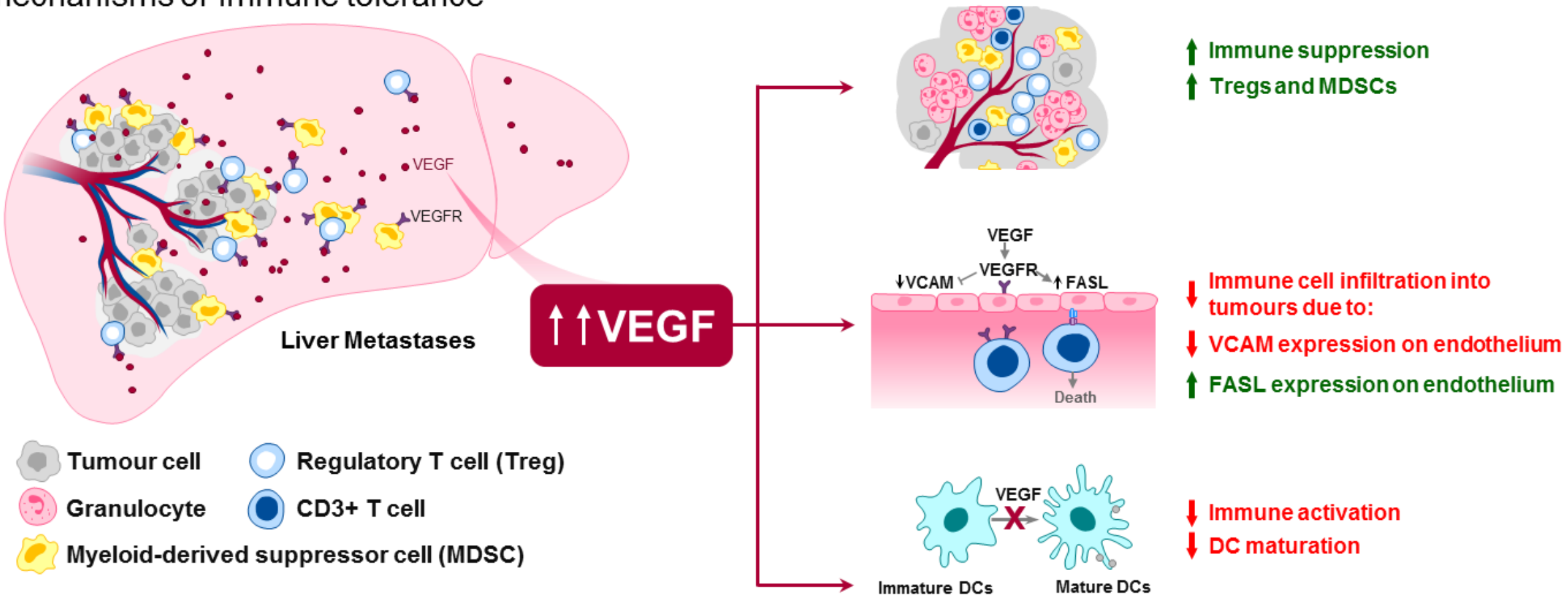
ECOG 4599
Paclitaxel-carboplatin +/- beva





Liver Metastasis

- High levels of VEGF in the liver support the hypothesis of VEGF-dependent modulation of liver-specific mechanisms of immune tolerance



Chen & Hurwitz. Cancer J 2018; Cao, et al. BMC Cancer 2009; Seo, et al. Cancer 2000; Joško, et al. Med Sci Monit 2004; Niu, et al. Oncogene 2002; Concha-Benavente, et al. Front Pharmacol. 2017; Stockhausen, et al. Neuro Oncol 2010; Semenza, et al. Nat Rev Cancer 2003; Bancroft, et al. Int J Cancer 2002; Chong, et al. Nat Med 2013

3. Patient characteristics: immunological age?

T-cell phenotype
CD28-CD57+KLRG1+
= iSenescence

iSenescence +

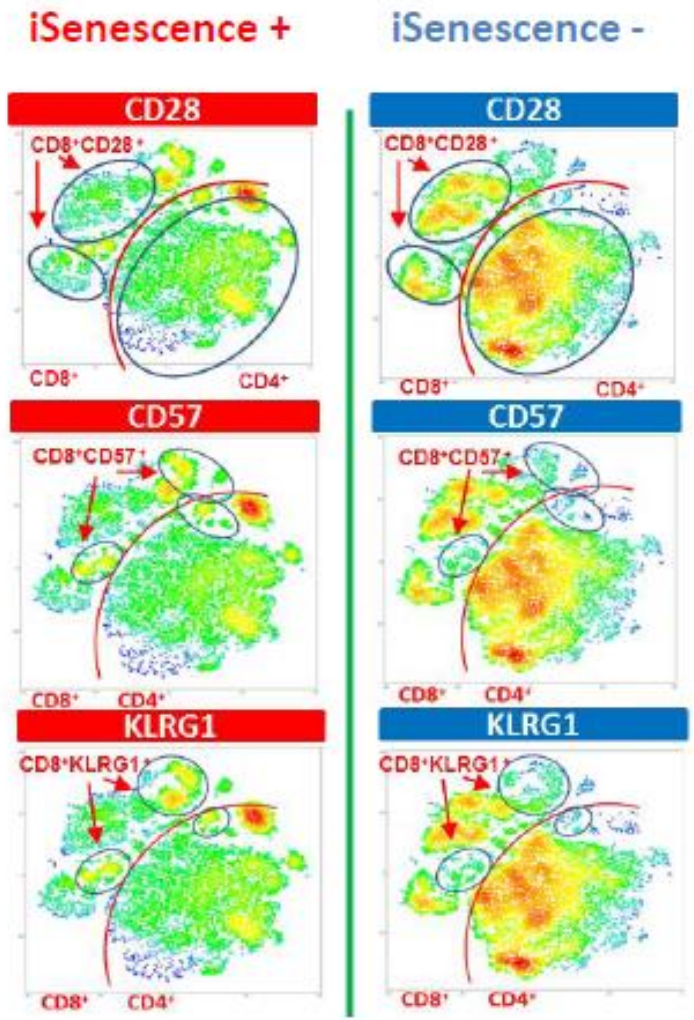
Patients PD (n=8)
Low CD28 density
High CD57 density
High KLRG1 density

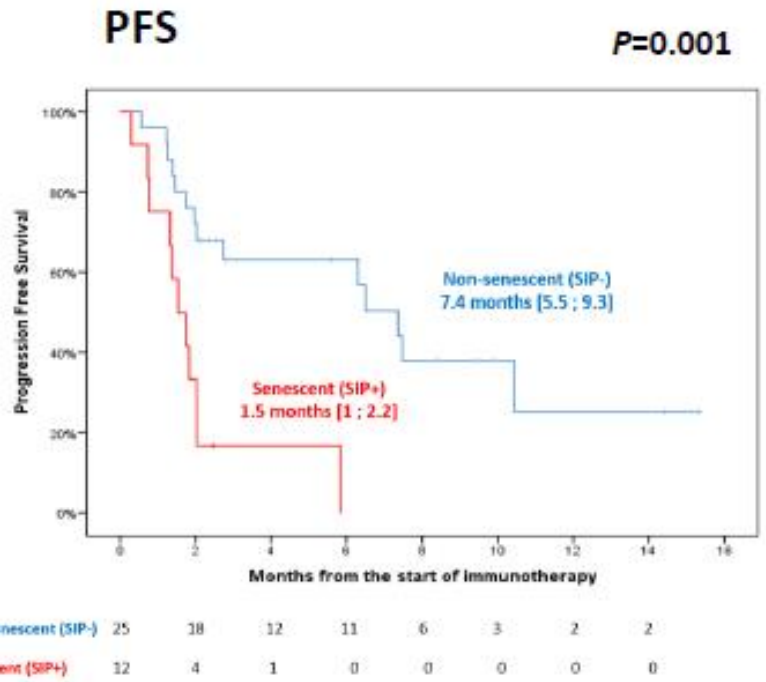
iSenescence -

Patients PR+SD (n=8)
High CD28 density
Low CD57 density
Low KLRG1 density

N=37 advanced NSCLC patients treated with IO

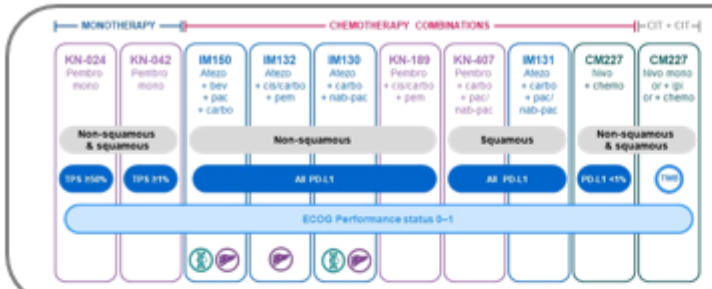
iSenescence (32%) independent of age





Ferrara et al. Poster 1416P ESMO 2018

3. Patient characteristics: PS?



The key phase III CIT studies in chemotherapy-naïve NSCLC have so far excluded patients with ECOG PS 2

Phase III

IPSOS

Atezolizumab monotherapy vs single-agent chemotherapy

Pts unsuitable for pt-chemo (incl. PS 2–3)

eNERGY

Nivolumab + ipilimumab vs carboplatin-based chemotherapy

PS 2 or elderly

Phase II

PePS2

Pembrolizumab monotherapy

PS 2

ESMO 2018 Abs 1384PD

NCT02581943

Pembrolizumab ± chemotherapy

PS 2

NCT03620669 & NCT02879617

Durvalumab monotherapy

PS 2

Line of therapy

	DCB (%)	Toxicity (%)	PR (%)	No RECIST	Median OS (95% CI)	Median PFS (95% CI)
All (*n* = 60)	20 (33.3)	13 (21.7)	17 (28.3)	16 (26.7)	11.7 (6.8 - NR)	5.4 (3.5 - 8.5)
Line of therapy						
First line (*n* = 9)	1 (11.1)	3 (33.3)	0 (0.0)	3 (33.3)	6.8 (2.4 - NR)	2.9 (1.9 - NR)
Subsequent line (*n* = 51)	19 (37.3)	10 (19.6)	17 (33.3)	13 (25.5)	12.1 (8.1 - NR)	6.0 (3.5 - 11.4)

- Limited clinical benefit in 1st line treatment, however only 9 patients – question remains about clinical efficacy in PS2 patients

Adverse events with IO single agent versus IO+CT combo

Trial	Grade 3-5 AE with IO (%)	Grade 3-5 AE with IO+CT (%)
Keynote 024	26.0*	-
Keynote 042	17.8*	-
Checkmate 026	17.6*	-
Keynote 189	-	67.2**
Keynote 407	-	69.8**
IMPOWER 150	-	57.0-62.0**
IMPOWER 131	-	73.0**
IMPOWER 130		73.2
IMPOWER 132		62

24% more g3+ irAEs with atezo

Patients with ≥ 1 AESI[a]	129 (32.8)	118 (37.8)	206 (52.4)	84 (21.3)	36 (13.3)	112 (28.4)
Grade 3-4	29 (7.4)	20 (6.4)	49 (12.5)	12 (3.0)	1 (0.4)	13 (3.3)

*Lower to platinum-based chemotherapy

** Similar to platinum-based chemotherapy

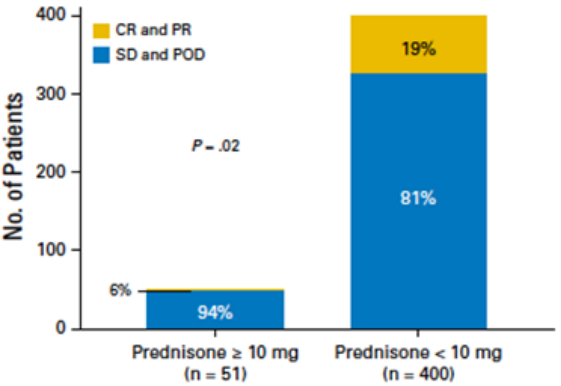
Safety Summary of Treatment-Related AEs: Nivo + Ipi could be less toxic than other combinations

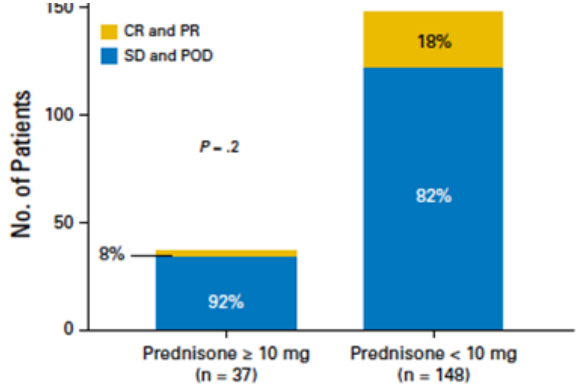
	Nivolumab + chemotherapy (n = 172)		Nivolumab + ipilimumab (n = 185)		Chemotherapy (n = 183)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE,[a] %	92	52	74	25	77	35
TRAE leading to discontinuation,[b] %	13	8	16	10	14	9
Median number of doses received, n	8.5 for nivolumab (Q3W) 4–7 for chemo (Q3W)		8.0 for nivolumab (Q2W) 3.0 for ipilimumab (Q6W)		4–7 for chemo (Q3W)	

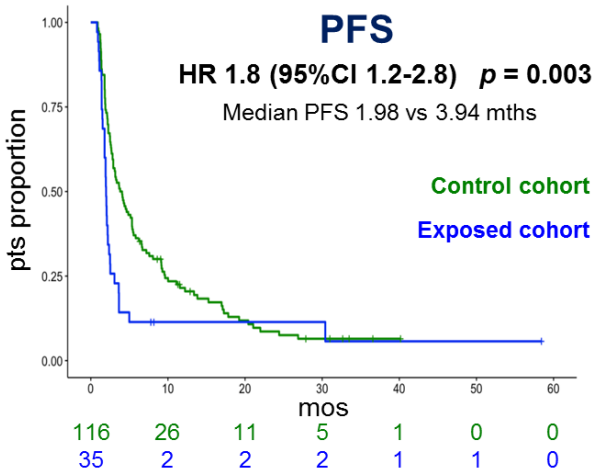
- There were 4 treatment-related deaths in the nivolumab + chemo arm, 7 in both nivolumab + ipilimumab arms in Part 1,[c] and 6 in both chemo arms in Part 1[d]

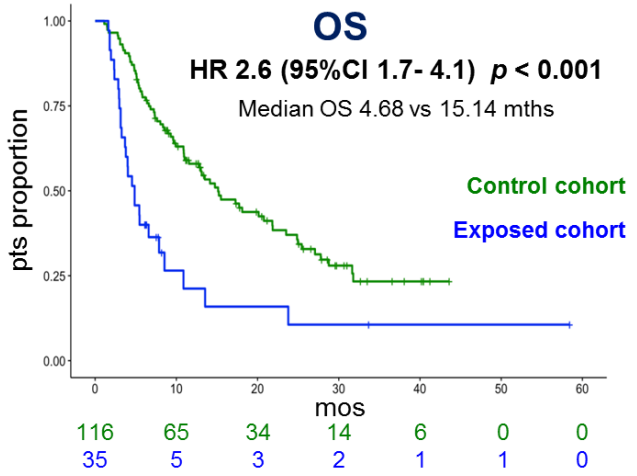
Borghaei H et al. ASCO 2018

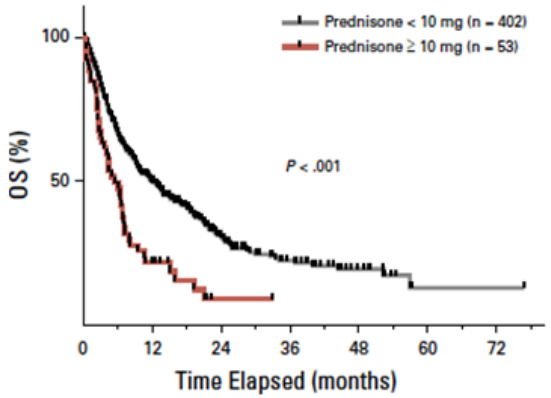
4. Concomitant treatment: steroids?

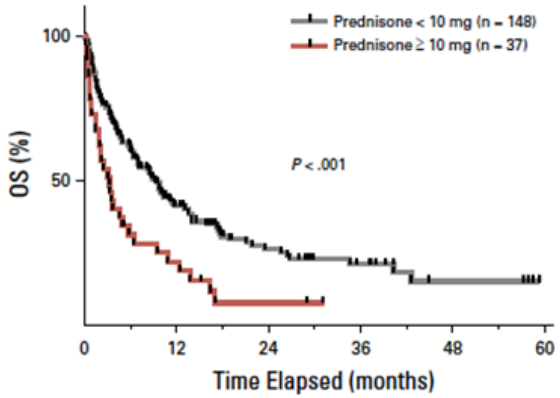


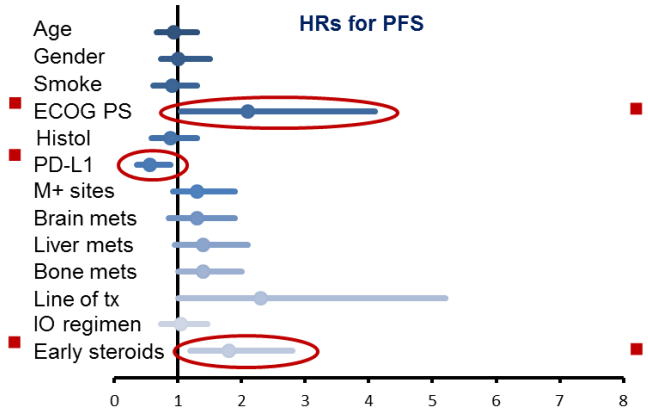


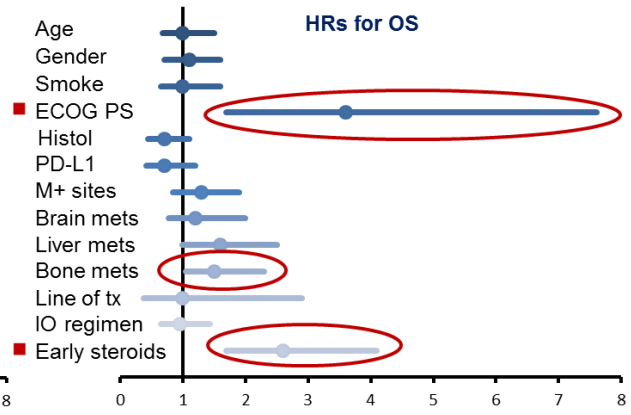








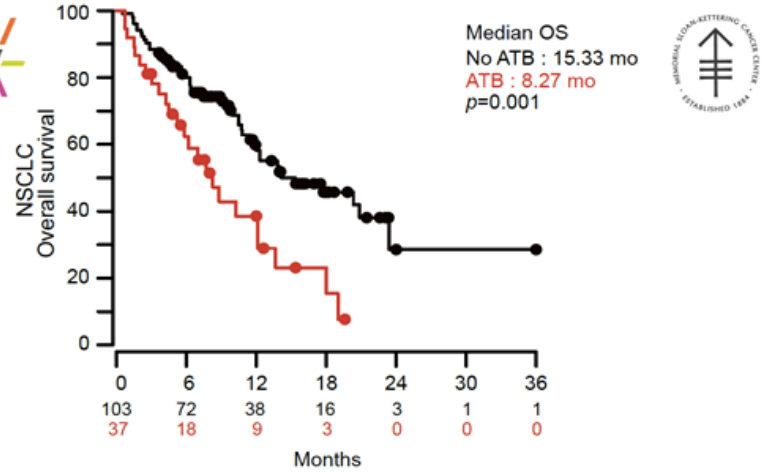




Arbour , JCO 2018

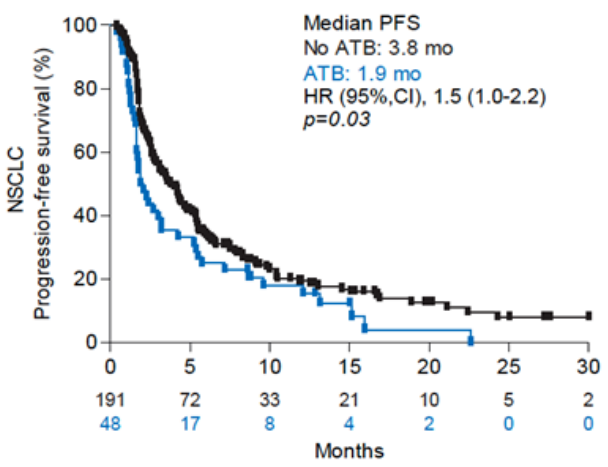
Fucà, WCLC 2018

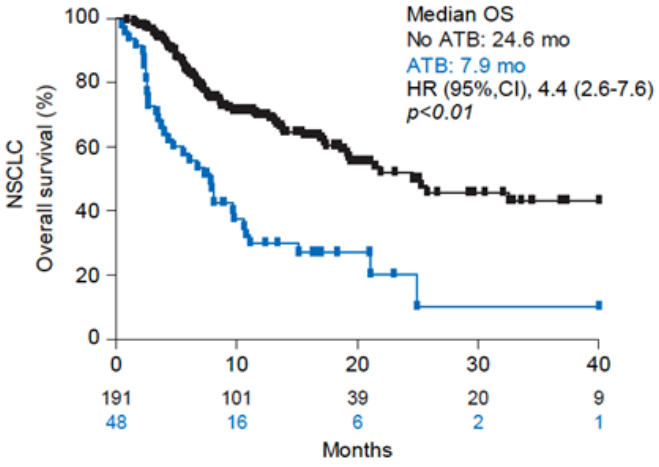
4. Concomitant treatment: antibiotics?



ATB use definition

2 months PRE or 1 month POST





ATB use definition

1 month PRE

Routy, Science 2018

Multiple reports on n=1744 demonstrate the negative influence of ATB on immune checkpoint inhibitors.

- Shorter course of ATB 6 days vs 9 days might be safer *[Gallio et al. WCLC 2018]*
- Patients hospitalized or receiving IV ATB should be considered separately *[Rubio et al. WCLC 2018]*
- Citrulline may represent a surrogate marker of GI health *[Leprieur et al. WCLC 2018]*

Immuno alone?

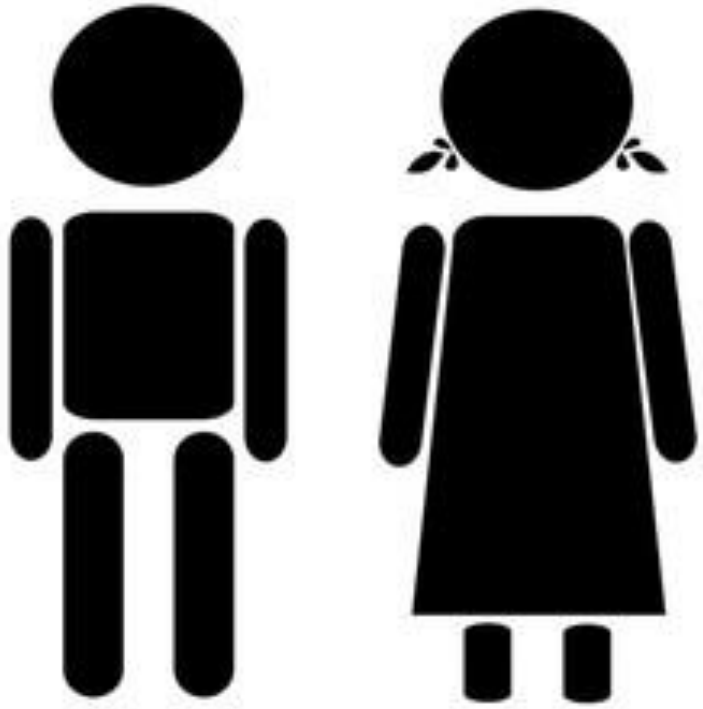
Immuno or chemo + immuno?

Antiangiogenic?

Sequence?

PD-L1 or TMB?

Toxicity?



Patients characteristics? Age-PS?

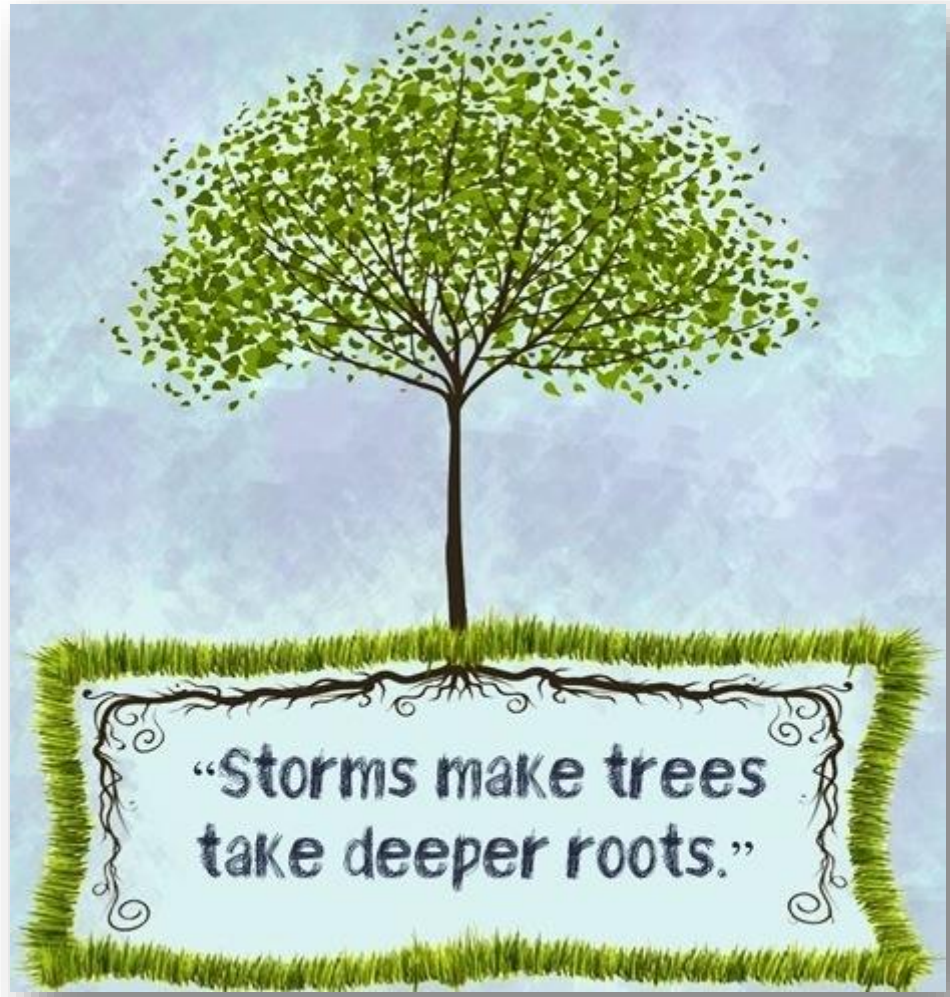
Histology?

Oncogene-addicted?

Steroids? Antibiotics?

Immunological profile

Molecular background


"Storms make trees
take deeper roots."