INSTITUT JULES BORDET

11th BELGIAN SYMPOSIUM ON THE INTEGRATION OF MOLECULAR BIOLOGY ADVANCES INTO ONCOLOGY CLINICAL PRACTICE

BSMO

Thoracic oncology 2018

Update of new therapies

23/1172018

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Centre Hospitalier de Luxembourg

Outline

- Small cell, progress at last
- ALK-EML, a new player
- NSCLC immunotherapy in locally advanced
- Stage IV first line, what are the options

SCLC – Progress at Last?

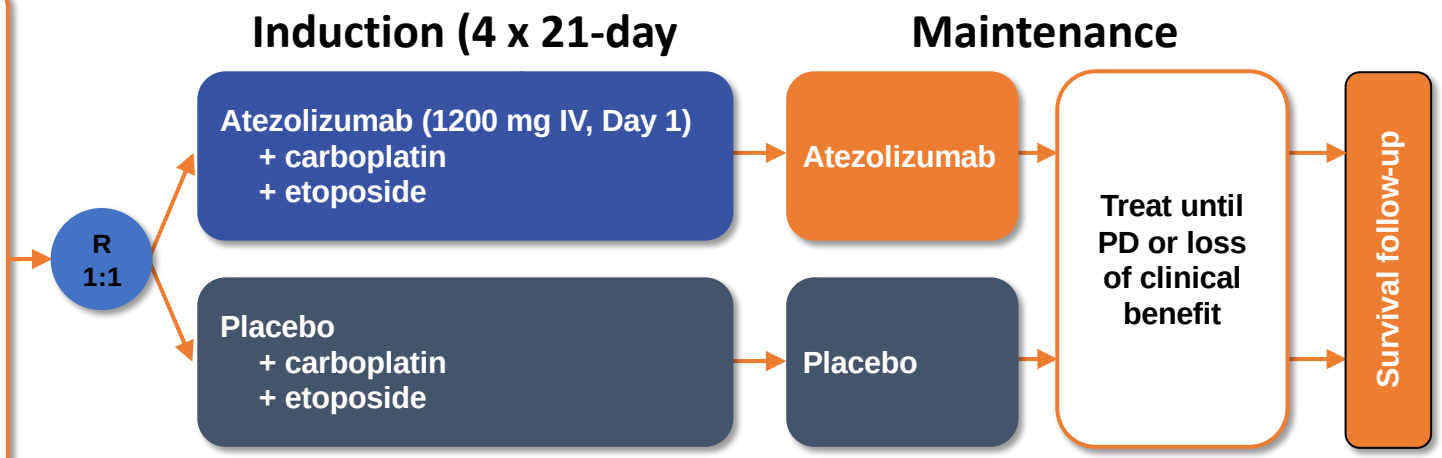
IMpower133: Phase 1/3, of carboplatin + etoposide +/- atezolizumab in first line extensive stage SCLC

Patients with (N = 403):

- Measurable ES-SCLC (RECIST v1.1)
- ECOG PS 0 or 1
- No prior systemic treatment for ES-SCLC
- Patients with treated asymptomatic brain metastases were eligible

Stratification:

- Sex (male vs. female)
- ECOG PS (0 vs. 1)
- Brain metastases (yes vs. no)[a]



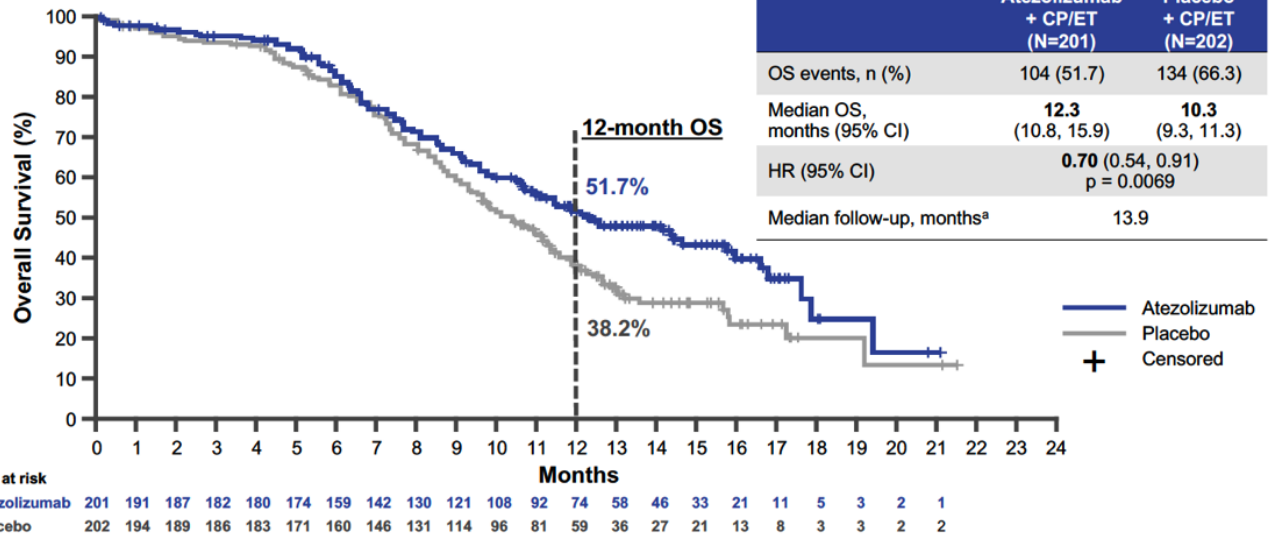
Co-primary end points:

- Overall survival
- Investigator-assessed PFS

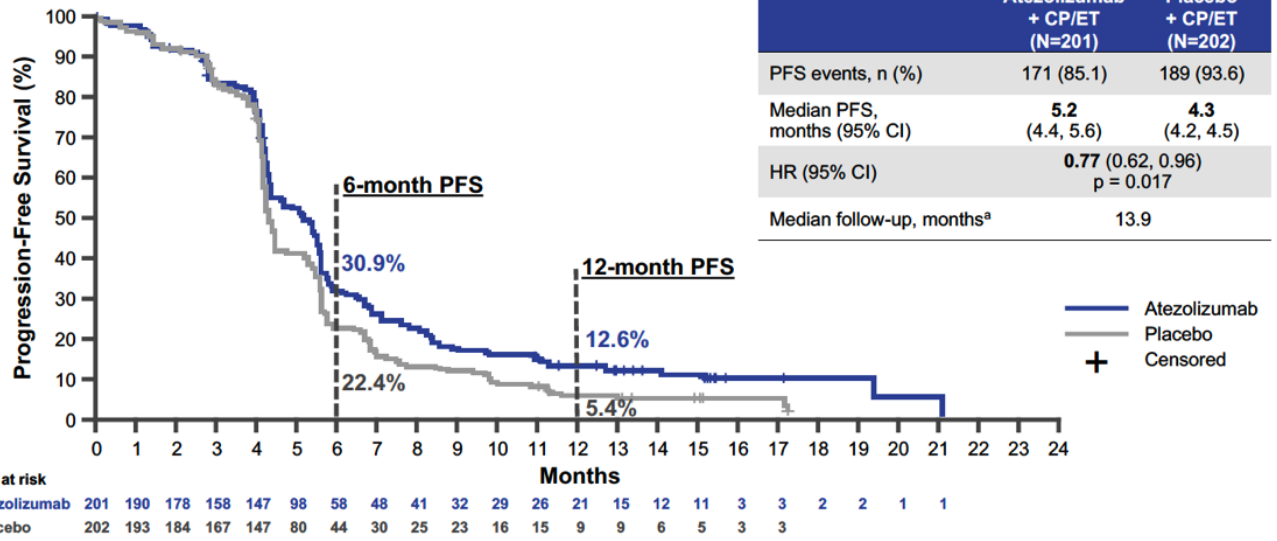
Key secondary end points:

- Objective response rate
- Duration of response
- Safety

Survival



	Atezolizumab + CP/ET (N=201)	Placebo + CP/ET (N=202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	**12.3** (10.8, 15.9)	**10.3** (9.3, 11.3)
HR (95% CI)	**0.70** (0.54, 0.91) p = 0.0069	
Median follow-up, months[a]	13.9	



	Atezolizumab + CP/ET (N=201)	Placebo + CP/ET (N=202)
PFS events, n (%)	171 (85.1)	189 (93.6)
Median PFS, months (95% CI)	**5.2** (4.4, 5.6)	**4.3** (4.2, 4.5)
HR (95% CI)	**0.77** (0.62, 0.96) p = 0.017	
Median follow-up, months[a]	13.9	

Safety

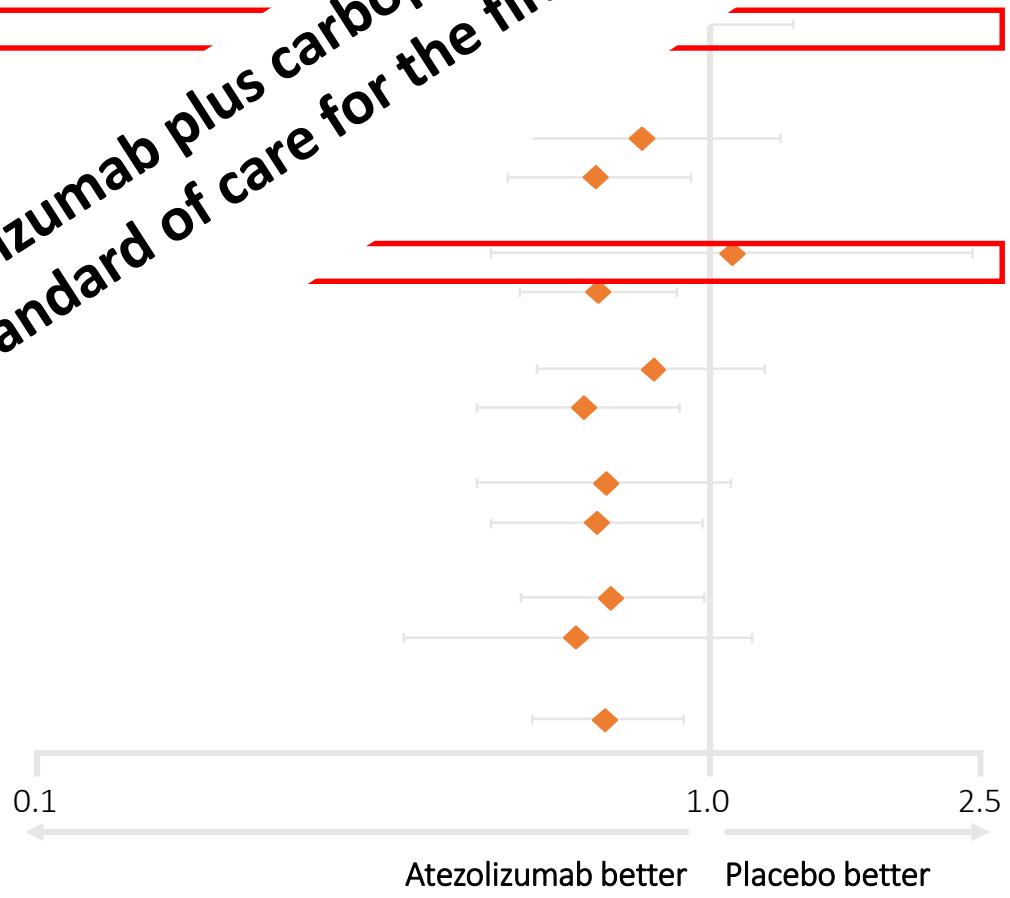
Immune-related AEs — no. (%) > 1% Grade 3–4 AEs in either treatment group	Atezolizumab + CP/ET (N=198)			Placebo + CP/ET (N=196)		
	Grade 1–2	Grade 3–4	Grade 5	Grade 1–2	Grade 3–4	Grade 5
Rash	33 (16.7)	4 (2.0)	0	20 (10.2)	0	0
Hepatitis	11 (5.6)	3 (1.5)	0	9 (4.6)	0	0
Infusion-related reaction	7 (3.5)	4 (2.0)	0	9 (4.6)	1 (0.5)	0
Pneumonitis	3 (1.5)	1 (0.5)	0	3 (1.5)	2 (1.0)	0
Colitis	1 (0.5)	2 (1.0)	0	0	0	0
Pancreatitis	0	1 (0.5)	0	0	2 (1.0)	0

No new safety signals

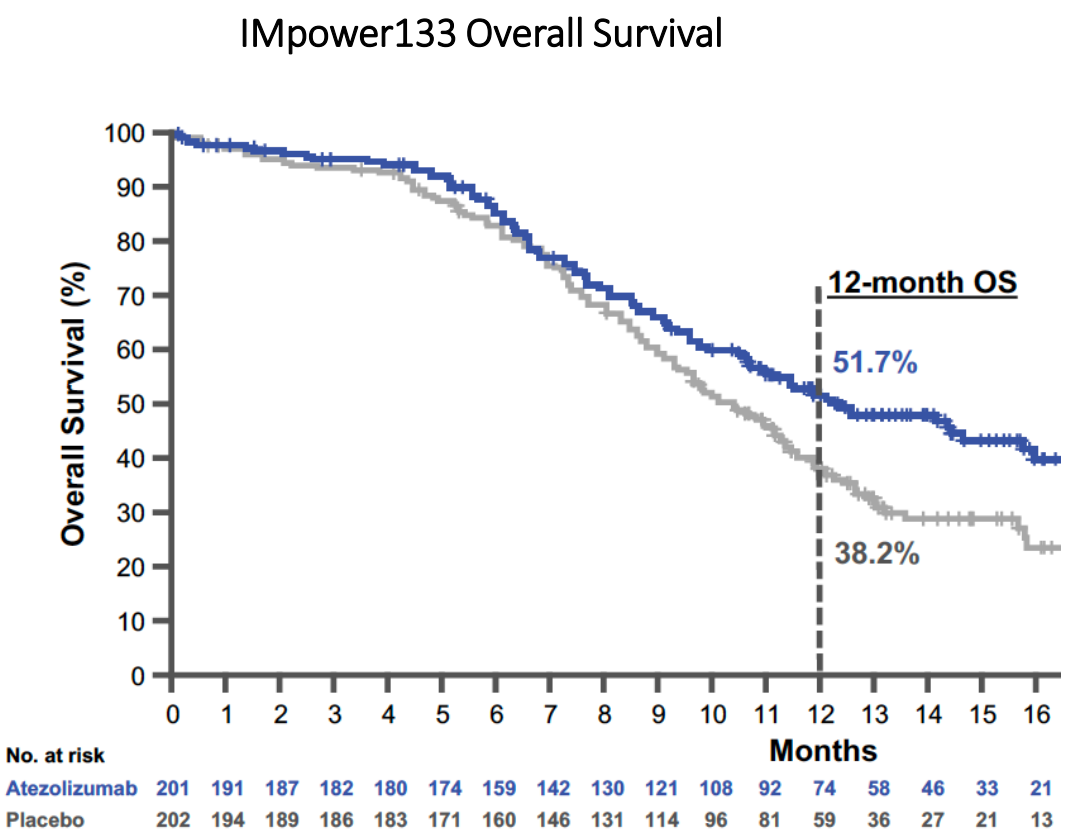
Overall survival in key subgroups

Population	Median overall survival (months) Atezolizumab + CP/ET	Placebo + CP/ET	OS hazard ratio[a] (95% CI)
Male (n = 261)	12.3	10.9	0.74 (0.54, 1.02)
Female (n = 142)	12.5	9.5	0.65 (0.42, 1.00)
< 65 years (n = 217)	12.1	11.5	0.92 (0.64, 1.32)
≥ 65 years (n = 186)	12.5	9.6	0.53 (0.36, 0.77)
ECOG PS 0 (n = 140)	16.6	12.4	0.79 (0.49, 1.27)
ECOG PS 1 (n = 263)	11.4	9.3	0.68 (0.50, 0.93)
Brain metastases (n = 35)	8.5		1.07 (0.47, 2.43)
No brain metastases (n = 368)	12.6		0.68 (0.52, 0.89)
Liver metastases (n = 149)	9.3		0.81 (0.55, 1.20)
No liver metastases (n = 254)	16.8		0.64 (0.45, 0.90)
bTMB < 10 mut/mb (n = 139)			0.70 (0.45, 1.07)
bTMB ≥ 10 mut/mb (n = 212)		1.2	0.68 (0.47, 0.97)
bTMB < 16 mut/mb (n = 271)		9.9	0.71 (0.52, 0.98)
bTMB ≥ 16 mut/mb (n = 8[illegible])		11.9	0.63 (0.35, 1.15)
ITT (N = 403)		10.3	0.70 (0.54, 0.91)

These data suggest that atezolizumab plus carboplatin and etoposide might be a new standard of care for the first-line treatment of ES-SCLC.



Some questions remain…



- **Is the benefit of atezolizumab during concurrent chemotherapy or maintenance?**
- **Is the benefit additive, synergistic or neither?**
- **Who benefits? Biomarker analysis?**
- **Do the chemotherapy agents used matter?**
- **How does SCLC evade immune surveillance + chemotherapy?**
- **Is this clinically significant?**

NSCLC – from rare to frequent

Cellular ALK phosphorylation mean IC_{50} (nmol/L)

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4–ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4–ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4–ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4–ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4–ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4–ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4–ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4–ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4–ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4–ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

$IC_{50} \leq 50$ nmol/L

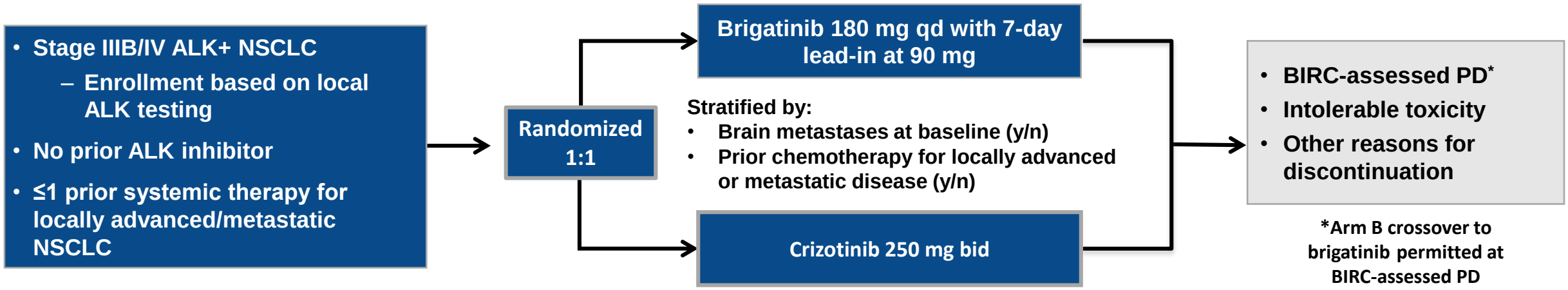
$IC_{50} > 50 < 200$ nmol/L

$IC_{50} \geq 200$ nmol/L

b

ALTA-1L Camidge et al. WCLC 2018

ALTA-1L: Phase 3, Open-label, Randomized, Multicenter, Study (NCT02737501)



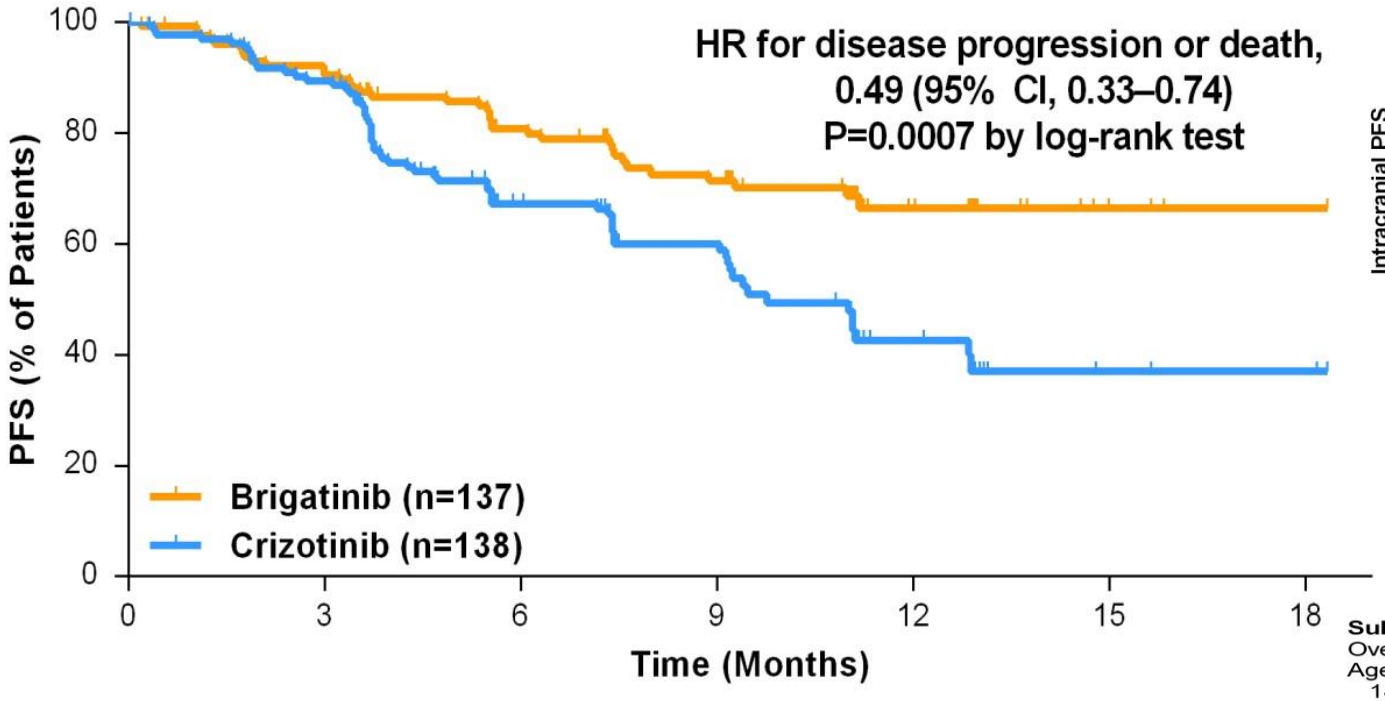
Disease assessment every 8 weeks, including brain MRI for all patients

- **<u>Primary endpoint</u>: PFS**
- **<u>Key secondary endpoints</u>: ORR, confirmed intracranial ORR, intracranial PFS, OS, safety, and tolerability**

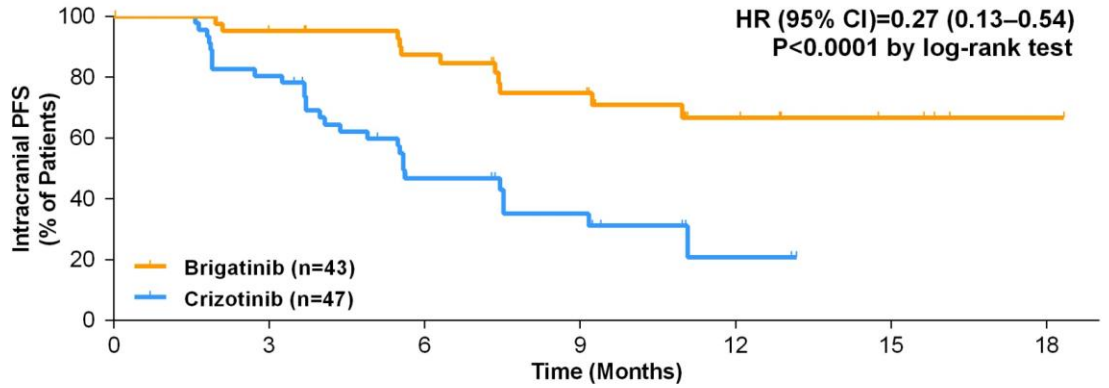
First Interim Analysis:
- **A total of 99 PFS events are included**

Primary Endpoint: PFS

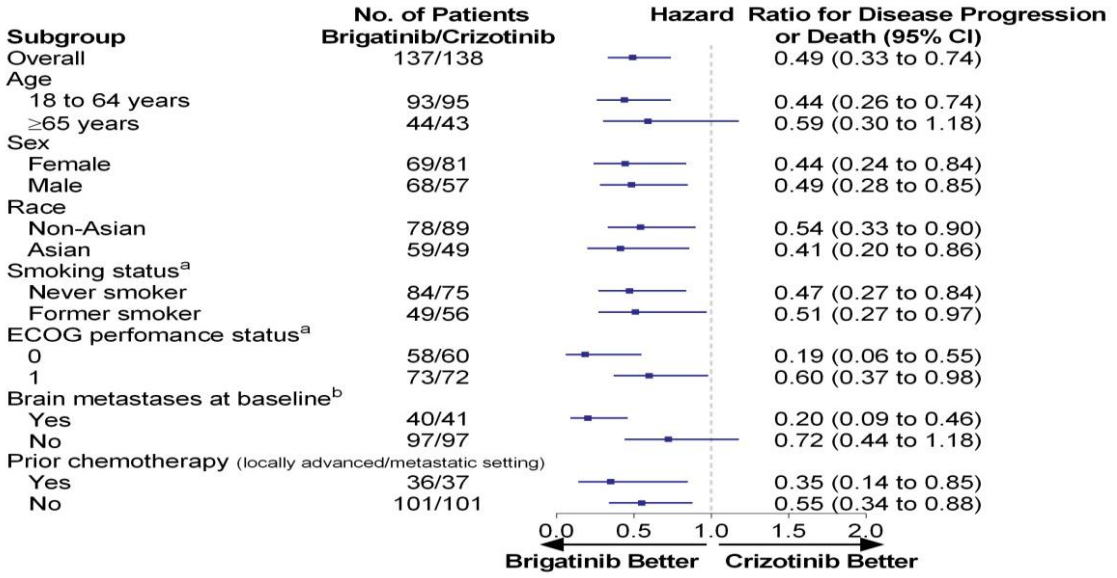
- **Brigatinib met the prespecified threshold for statistical superiority vs crizotinib**



Treatment	No. (%) of Patients With Events	Median PFS (95% CI)	1-Year PFS, % (95% CI)
Brigatinib (n=137)	36 (26)	NR (NR–NR)	67 (56–75)
Crizotinib (n=138)	63 (46)	9.8 months (9.0–12.9)	43 (32–53)

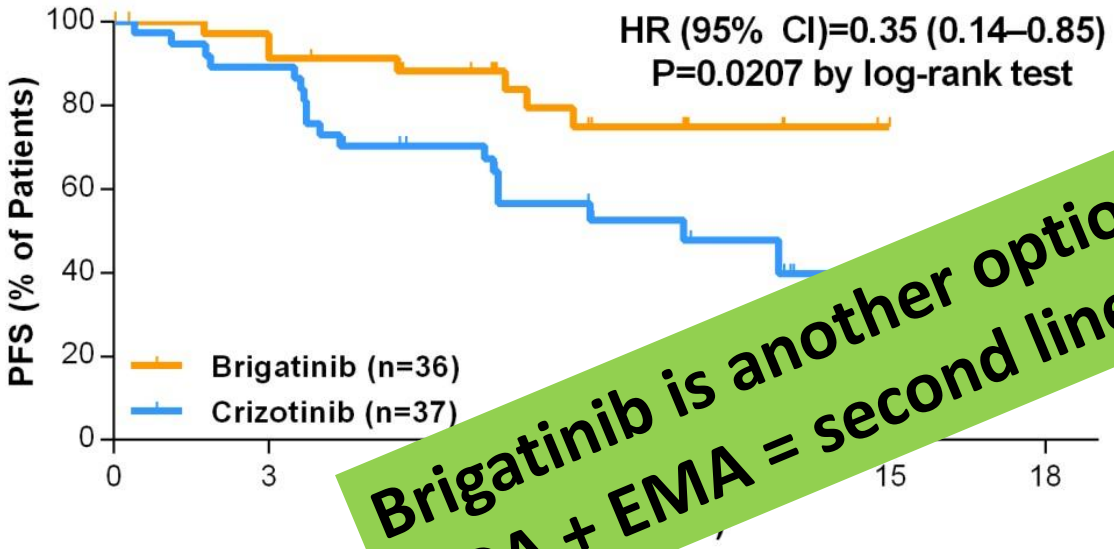


Treatment	Median Intracranial PFS (95% CI)	1-Year PFS Probability, % (95% CI)
Brigatinib (n=43)	NR (11.0–NR)	67 (47–80)
Crizotinib (n=47)	5.6 months (4.1–9.2)	21 (6–42)



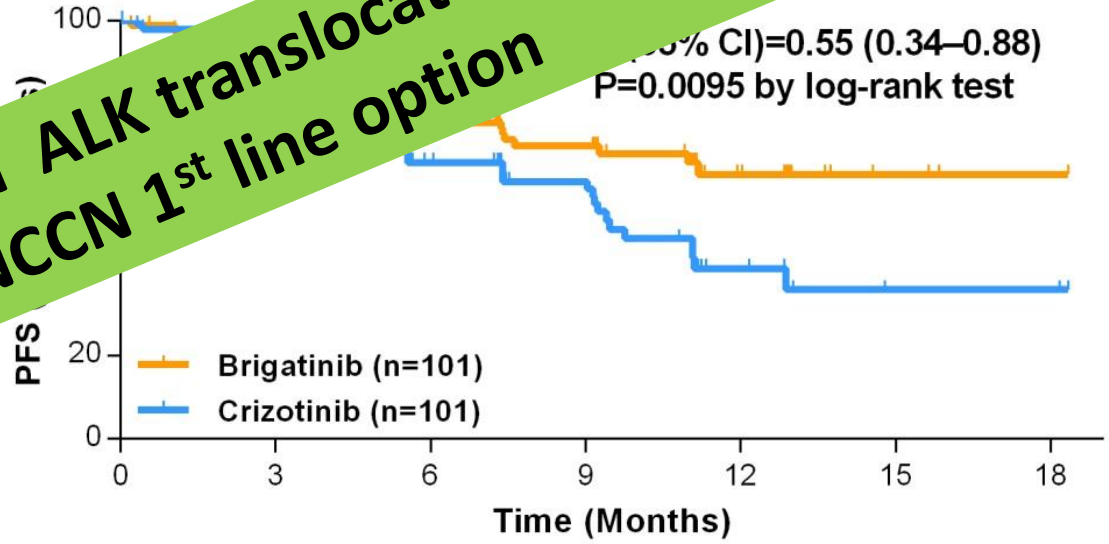
PFS Based on Prior Chemotherapy in the Locally Advanced or Metastatic Setting

Patients With Prior Chemotherapy



Treatment	PFS (95% CI)	1-Year PFS, % (95% CI)
Brigatinib (n=36)	NR (NR–NR)	75 (54–87)
Crizotinib (n=37)	11.0 months (7.2–NR)	48 (29–64)

Patients Without Prior Chemo



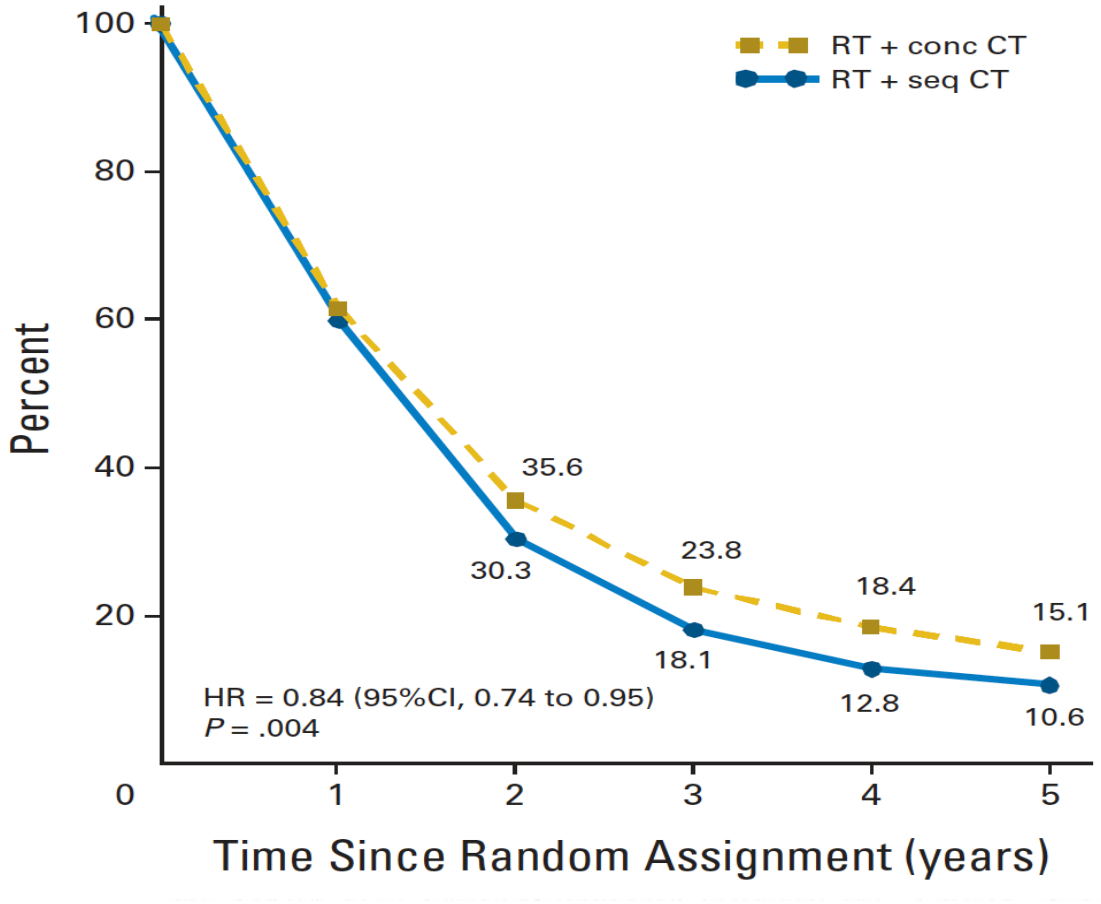
Treatment	Median PFS (95% CI)	1-Year PFS, % (95% CI)
Brigatinib (n=101)	NR (NR–NR)	63 (50–74)
Crizotinib (n=101)	9.8 months (9.0–12.9)	41 (28–53)

Brigatinib is another option in ALK translocated NSCLC (FDA + EMA = second line), NCCN 1st line option

Stage III inoperable

NSCLC – from rare to frequent

Last 20 Years: Standard for CRT for Unresectable Stage III NSCLC has changed minimally (1995 meta-analysis, mostly sequencial)



NSCLC Collaborative Group. *BMJ.* 1995;311:899-909, Auperin A, et al. *J Clin Oncol*. 2010;28:2181-2190

PACIFIC Study Design

Phase III, randomized, double-blind, placebo-controlled, multicenter, global study[1,2]

Treatment of patients with stage III unresectable NSCLC who have not progressed following platinum-based concurrent chemoradiation
Patients randomized = 713[a]

Randomization 2:1
1-42 days post-cCRT

Durvalumab IV 10 mg/kg Q2W up to 12 months (n = 476)

Placebo IV Q2W (n = 237)

Stratification factors

1. Age at randomization (<65 vs ≥65 years of age)
2. Sex (male vs female)
3. Smoking history (smoker vs nonsmoker)

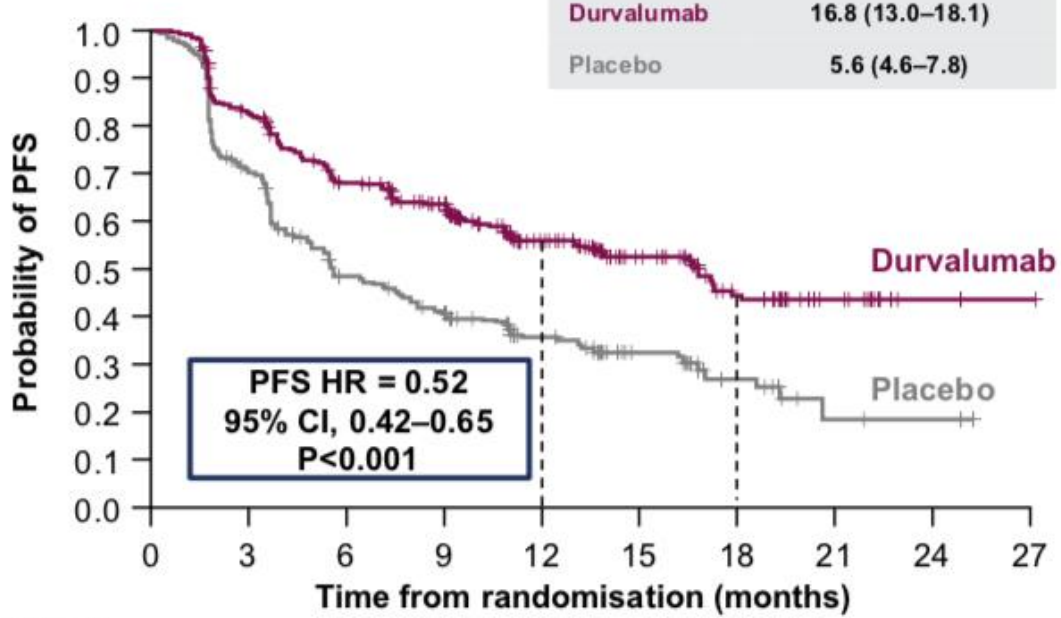
Coprimary Endpoints	Secondary Endpoints	
• OS • PFS[b]	• OS24 • DOR (per BICR) • ORR (per BICR) • APF12 and APF18	• TTDM • Safety and tolerability • PFS2 • PROs[3] • PK and immunogenicity

[a]A total of 713 patients were randomized, out of which 709 received consolidation therapy; [b]Response Evaluation Criteria In Solid Tumors v1.1.
APF12, proportion of patients alive and progression-free at 12 months; BICR, blinded independent central review; cCRT, concurrent chemoradiation therapy; DOR, duration of response; IV, intravenously; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; OS24, number (%) of patients who are alive at 24 months; PFS, progression-free survival; PK, pharmacokinetics; PROs, patient-reported outcomes; Q2W, every 2 weeks; SOC, standard of care; TTDM, time to death or distant metastasis.
1. US National Institutes of Health. https://www.clinicaltrials.gov/ct2/show/NCT02125461; 2. Antonia SJ, et al. *N Engl J Med*. 2017;377(20):1919-1929; 3. Hui R et al. COSA 2017. Abstract 218.

PACIFIC: PFS and OS in the ITT population

PFS (BICR)[1]

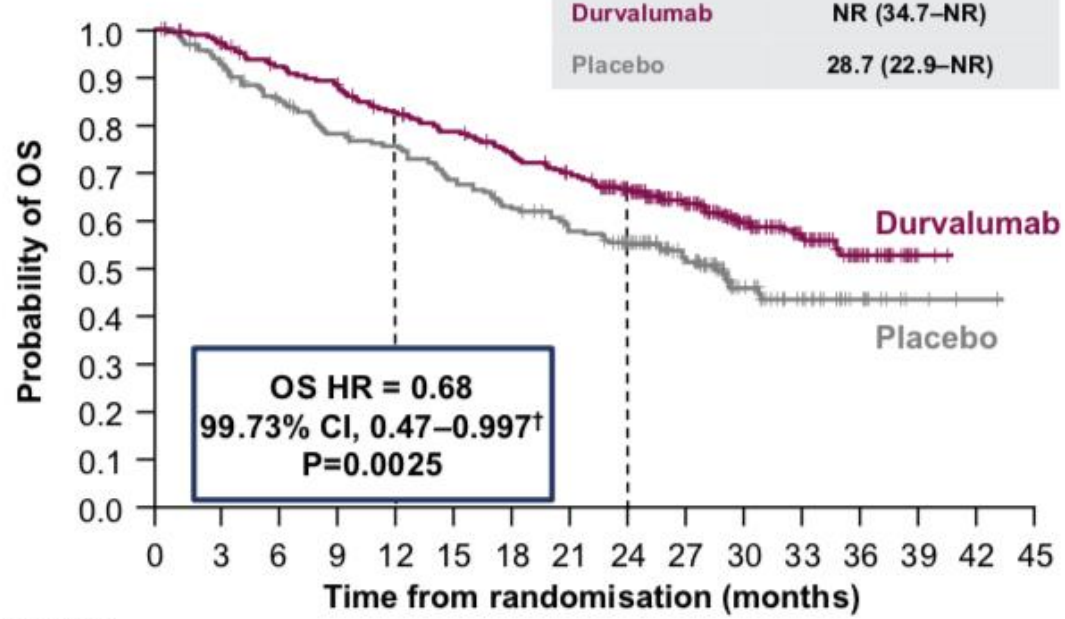
	Median PFS (95% CI) months
Durvalumab	16.8 (13.0–18.1)
Placebo	5.6 (4.6–7.8)



No. at risk										
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0

OS[2,*]

	Median OS (95% CI) months
Durvalumab	NR (34.7–NR)
Placebo	28.7 (22.9–NR)



No. at risk																
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

*Median duration of follow-up was 25.2 months (range 0.2–43.1); †adjusted for interim analysis

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NR, not reached

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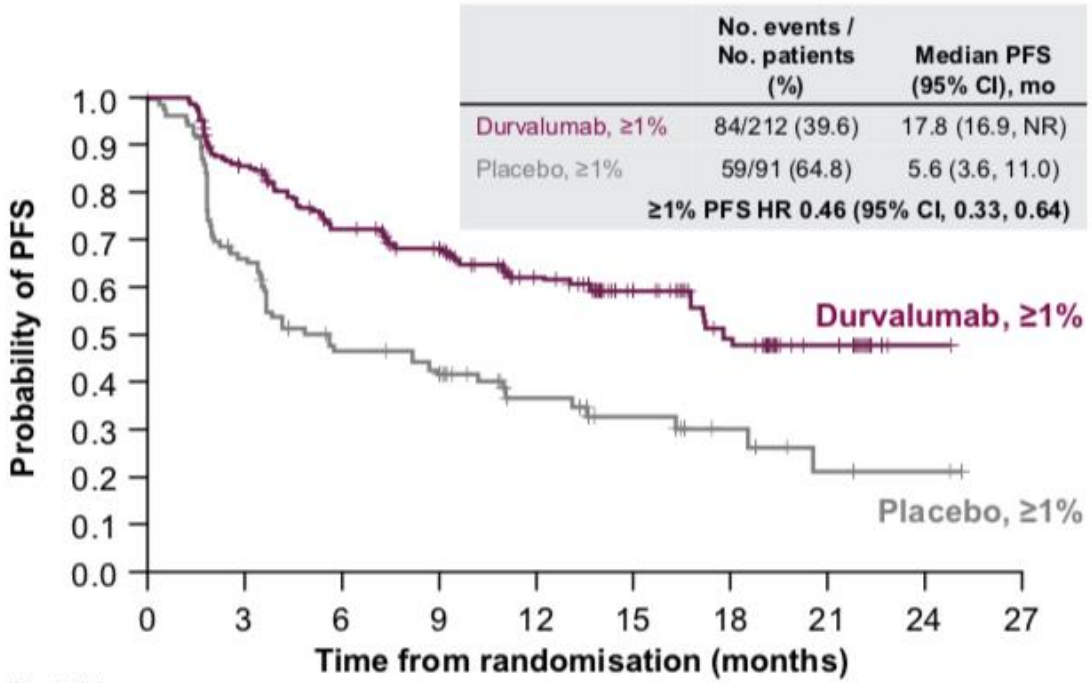
1. Antonia SJ, et al. N Engl J Med 2017;377:1919–29;
2. Antonia SJ, et al. N Engl J Med 2018; Epub Sep 25

PFS DCO: 13 February 2017; OS DCO: 22 March 2018

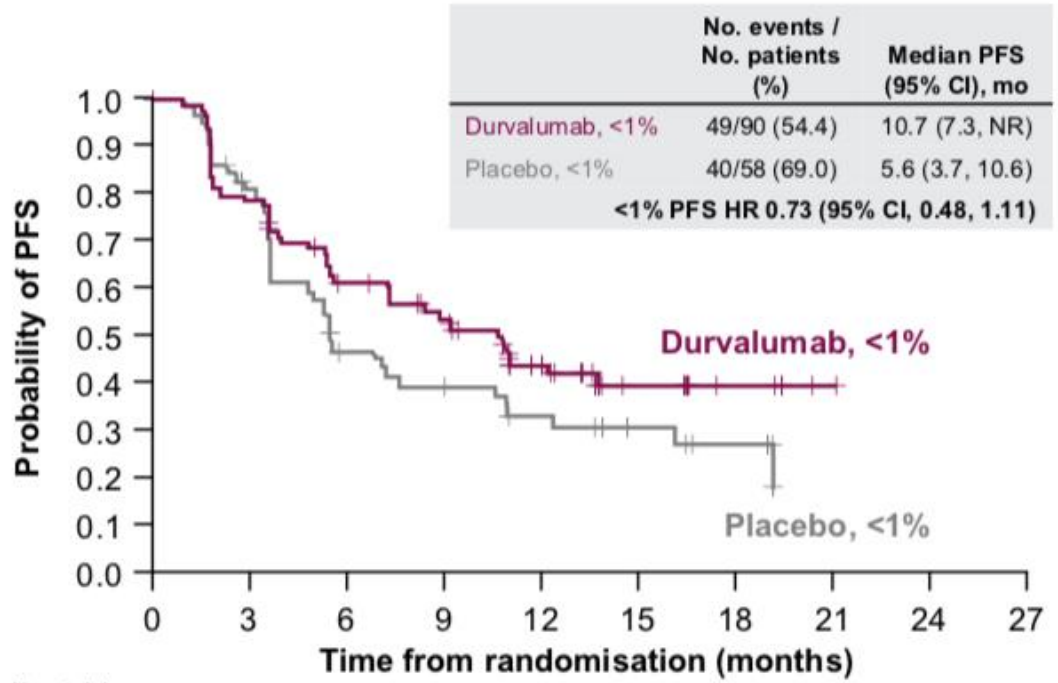
Improvement in PFS by PD-L1 TC ≥1% and <1%

PFS (BICR) by PD-L1 TC ≥1%



No. at risk										
Durvalumab, ≥1%	212	174	143	127	82	52	30	14	1	0
Placebo, ≥1%	91	59	39	34	20	13	8	4	3	0

PFS (BICR) by PD-L1 TC <1%



No. at risk										
Durvalumab, <1%	90	70	51	42	23	9	4	1	0	0
Placebo, <1%	58	45	25	21	14	8	5	0	0	0

mo, months; NR, not reached; TC, tumour cell

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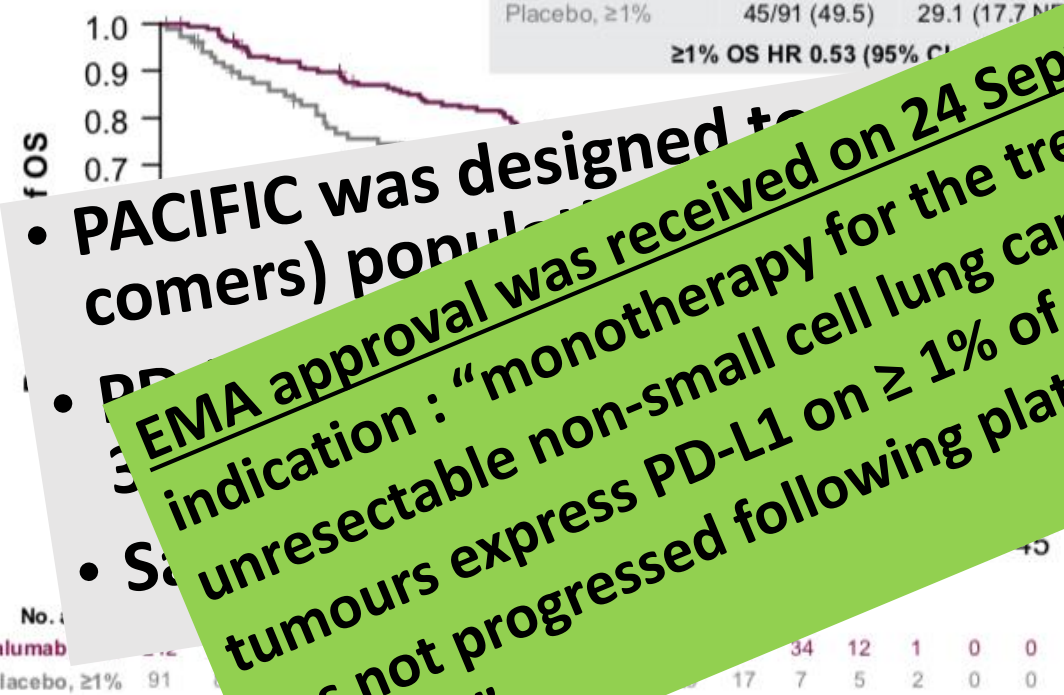
PFS DCO: 13 February 2017; OS DCO: 22 March 2018

OS by PD-L1 TC ≥1% and <1%

OS by PD-L1 TC ≥1%

	No. events / No. patients (%)	Median OS (95% CI), mo
Durvalumab, ≥1%	70/212 (33.0)	NR (NR, NR)
Placebo, ≥1%	45/91 (49.5)	29.1 (17.7 NR

≥1% OS HR 0.53 (95% CI



No. at risk

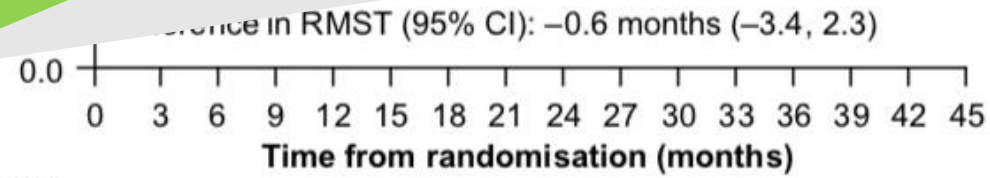
Durvalumab							34	12	1	0	0						
Placebo, ≥1%	91					17	7	5	2	0	0						

- PACIFIC was designed to
- PD
- Su

EMA approval was received on 24 September with the following indication : "monotherapy for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum based chemoradiation therapy"

<1%

	vents /	an OS CI), mo
		.8, NR)
		3, NR)
		2.34)



No. at risk

Durvalumab, <1%	90	88	84	81	72	65	56	50	45	35	20	7	3	0	0	0	
Placebo, <1%	58	56	47	45	44	43	40	36	35	21	11	8	3	1	1	0	

- In the PD-L1 TC <1% subgroup, the number of events are low and overall the subgroup is small
- Imbalances in baseline characteristics

RMST, restricted mean su me

PFS DCO: 13 February 2017; OS DCO: 22 March 2018

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Stage IV first line immunotherapy

NSCLC – what is the best 1st line

Comparison	Selection	ORR	PFS	OS
Nivo vs Platinum doublet	PD-L1 > 1% (anal <5%)	26% vs 33%	HR = 1.15, p=0.25	HR = 1.02
Nivo, Ipi vs Platinum doublet	High TMB ≥ 10 mut/Mb	45.3% vs 26%	HR=0.58, p<0.01	Immature
Pembro vs Platinum doublet	PD-L1 ≥ 50%	44.8% vs 27.8%	HR = 0.50, p<0.01	HR=0.60, p<0.01
Carbo Pemetrexate +/- Pembro	ALL PD-L1 / Nonsquam.	47.6% vs 18.9%	HR = 0.52, p<0.01	HR=0.49, p<0.01
Carbo pacli/Nab-Pacli +/- Pembro	ALL PD-L1 / Squamous	58.4% vs 35%	HR=0.56, p<0.01	HR=0.64, p<0.01
Carbo, Pacli, beva +/- Atezo	ALL PD-L1, Nonsquam.	64% vs 48%	HR=0.62, p<0.01	Positive
Carbo, nab-pacli +/- Atezo	ALL PD-L1, Nonsquam.	49.2% vs 31.9%	HR=0.64, p<0.0001	HR=79, P<0.033
Carbo, Nab-Pacli +/- Atezo	ALL PD-L1, Squamous	49% vs 41%	HR=0.74, p<0.0004	Immature
Carbo/cis + pemetrexed +/- Atezo	ALL PD-L1, Nonsquam.	47% vs 32%	HR, 0.60, p<0.0001	HR=0.81,p=.0797

Reck et al NEJM 2016, Gandhi et al NEJM 2018, Lopes et al ASCO 2018, Reck et al ESMO immuno 2017, Kowanetz et al AACR 2018, Paz-Ares et al ASCO 2018, Socinski et al ASCO 2018, Hellman et al NEJM 2018, Carbone et al NEJM 2017

Nivolumab 1st line

Phase 3 CheckMate 026 Study Design: Nivolumab vs Chemotherapy in First-line NSCLC

Key eligibility criteria:
- Stage IV or recurrent NSCLC
- No prior systemic therapy for advanced disease
- No *EGFR/ALK* mutations sensitive to available targeted inhibitor therapy
- ≥1% PD-L1 expression[a]
- CNS metastases permitted if adequately treated at least 2 weeks prior to randomization

Randomize 1:1

Nivolumab 3 mg/kg IV Q2W n = 271 → Disease progression or unacceptable toxicity

Chemotherapy (histology dependent)[b] Maximum of 6 cycles n = 270 → Disease progression → Crossover nivolumab[c] (optional)

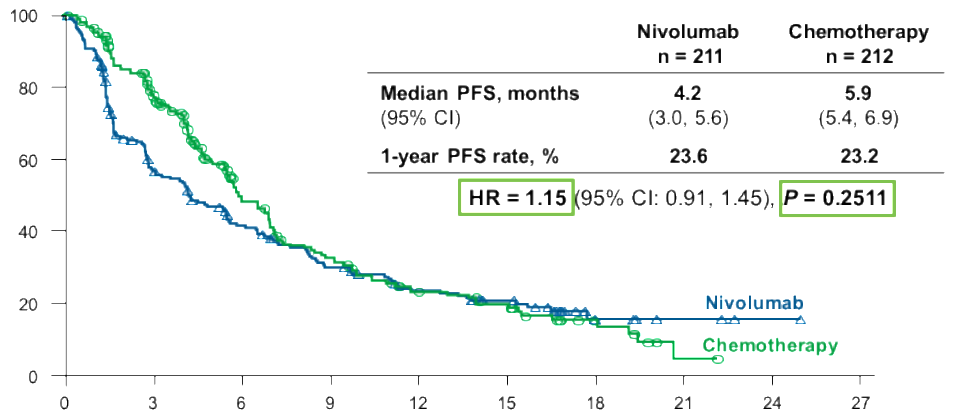
Tumor scans Q6W until wk 48 then Q12W

Stratification factors at randomization:
- PD-L1 expression (<5% vs ≥5%)[a]
- Histology (squamous vs non-squamous)

Primary endpoint: PFS (≥5% PD-L1+)[d]

Secondary endpoints:
- PFS (≥1% PD-L1+)[d]
- OS
- ORR[d]

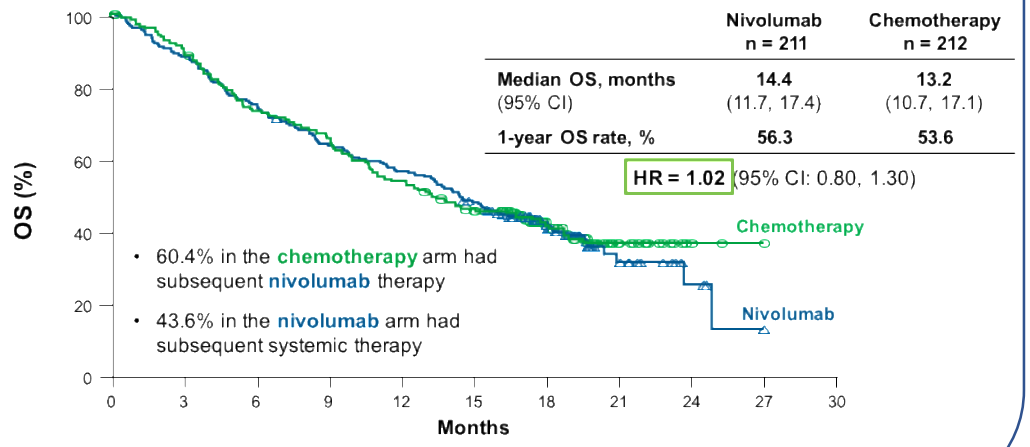
PFS ≥5% PD-L1+



	Nivolumab n = 211	Chemotherapy n = 212
Median PFS, months (95% CI)	4.2 (3.0, 5.6)	5.9 (5.4, 6.9)
1-year PFS rate, %	23.6	23.2

HR = 1.15 (95% CI: 0.91, 1.45), *P* = 0.2511

OS (≥5% PD-L1+)



	Nivolumab n = 211	Chemotherapy n = 212
Median OS, months (95% CI)	14.4 (11.7, 17.4)	13.2 (10.7, 17.1)
1-year OS rate, %	56.3	53.6

HR = 1.02 (95% CI: 0.80, 1.30)

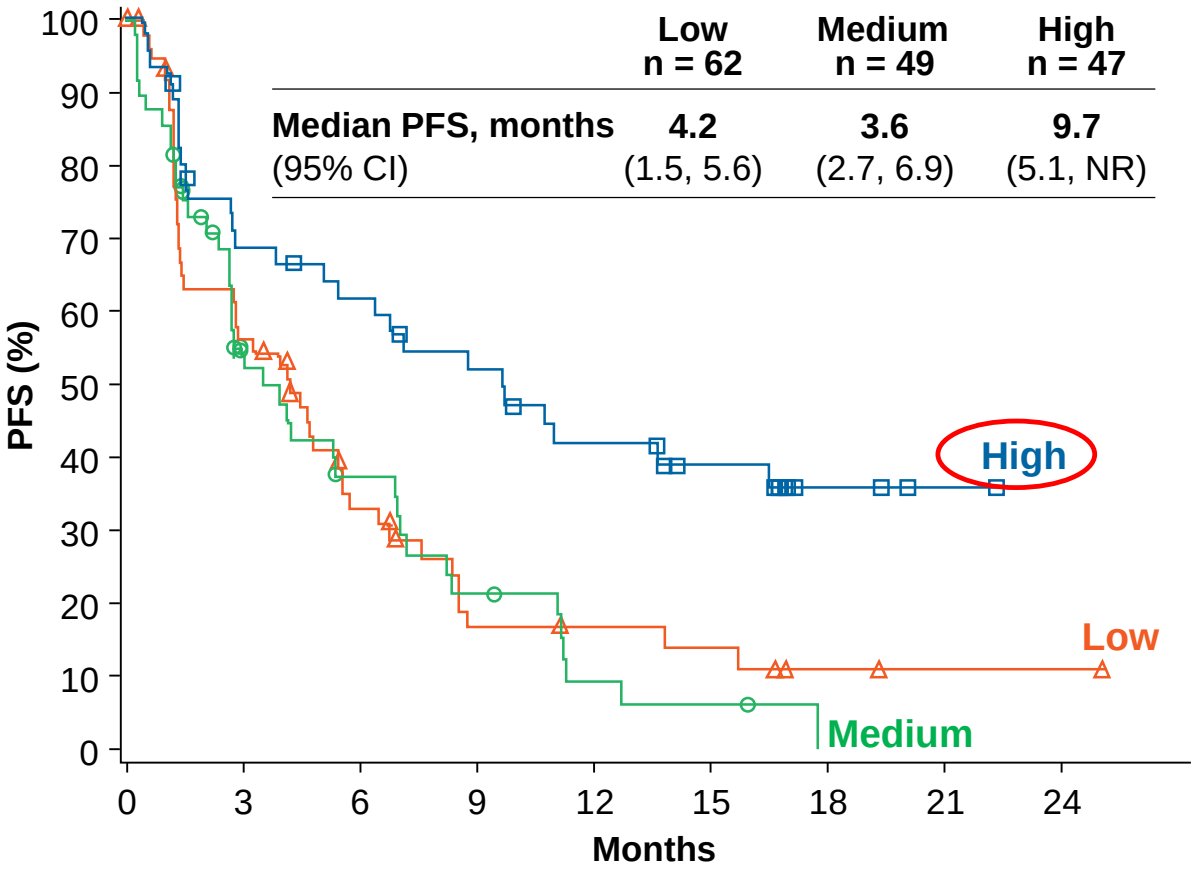
Problems with this study:

- **40% RxT pretreated (palliative + curative)**
- **Imbalances:**
  - proportion of women,
  - patients with liver mets,
  - No stratification >5% PD-L1
- **Chemo arms better than historic controls**
- **Only 60,4% in control arm received nivolumab afterwards…**

PFS by Tumor Mutation Burden

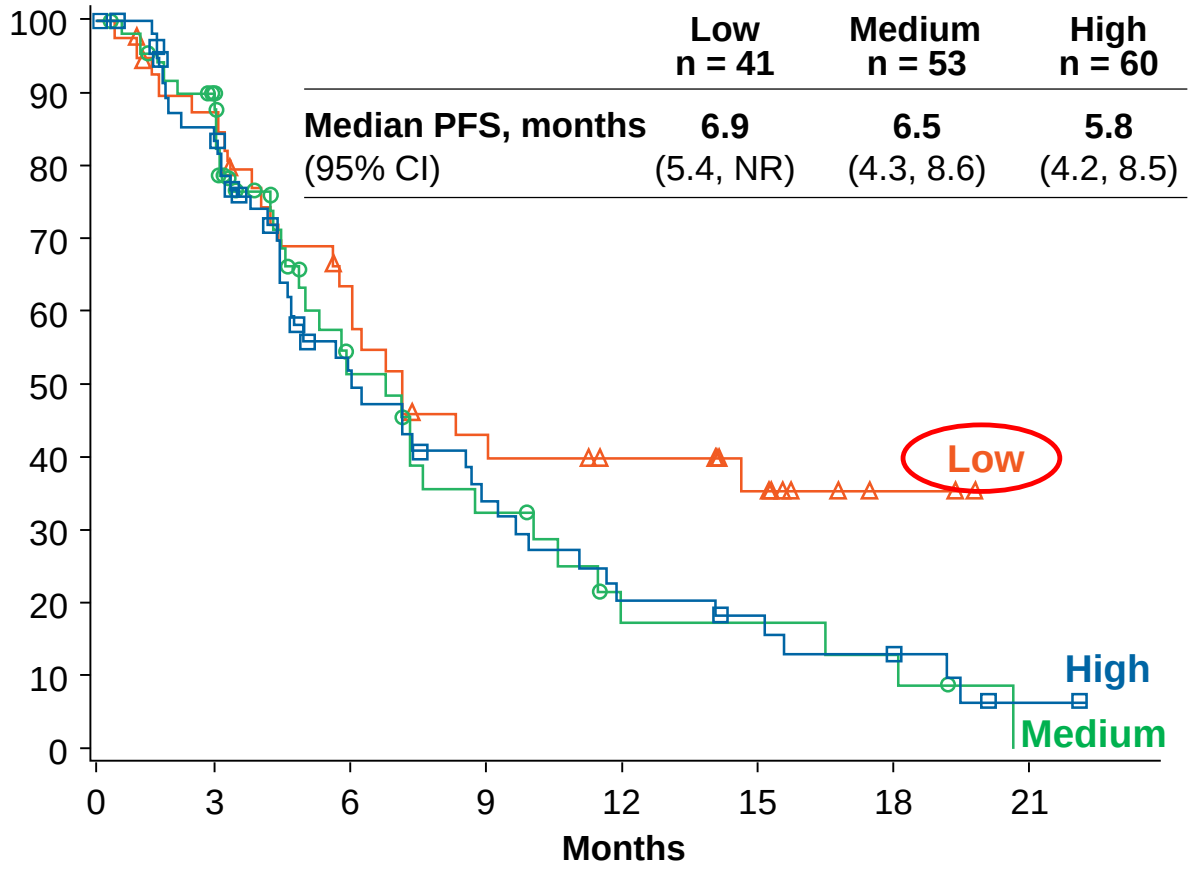
CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

Nivolumab Arm



	Low n = 62	Medium n = 49	High n = 47
Median PFS, months	**4.2**	**3.6**	**9.7**
(95% CI)	(1.5, 5.6)	(2.7, 6.9)	(5.1, NR)

Chemotherapy Arm



	Low n = 41	Medium n = 53	High n = 60
Median PFS, months	**6.9**	**6.5**	**5.8**
(95% CI)	(5.4, NR)	(4.3, 8.6)	(4.2, 8.5)

- Data for patients with low and medium TMB were pooled in subsequent analyses

Stage IV first line immunotherapy

NSCLC – what is the best 1st line

Comparison	Selection	ORR	PFS	OS
Nivo vs Platinum doublet	PD-L1 > 1% (anal <5%)	26% vs 33%	HR = 1.15, p=0.25	HR = 1.02
Nivo, Ipi vs Platinum doublet	High TMB ≥ 10 mut/Mb	45.3% vs 26%	HR=0.58, p<0.01	Immature
Pembro vs Platinum doublet	PD-L1 ≥ 50%	44.8% vs 27.8%	HR = 0.50, p<0.01	HR=0.60, p<0.01
Carbo Pemetrexate +/- Pembro	ALL PD-L1 / Nonsquam.	47.6% vs 18.9%	HR = 0.52, p<0.01	HR=0.49, p<0.01
Carbo pacli/Nab-Pacli +/- Pembro	ALL PD-L1 / Squamous	58.4% vs 35%	HR=0.56, p<0.01	HR=0.64, p<0.01
Carbo, Pacli, beva +/- Atezo	ALL PD-L1, Nonsquam.	64% vs 48%	HR=0.62, p<0.01	Positive
Carbo, nab-pacli +/- Atezo	ALL PD-L1, Nonsquam.	49.2% vs 31.9%	HR=0.64, p<0.0001	HR=79, P<0.033
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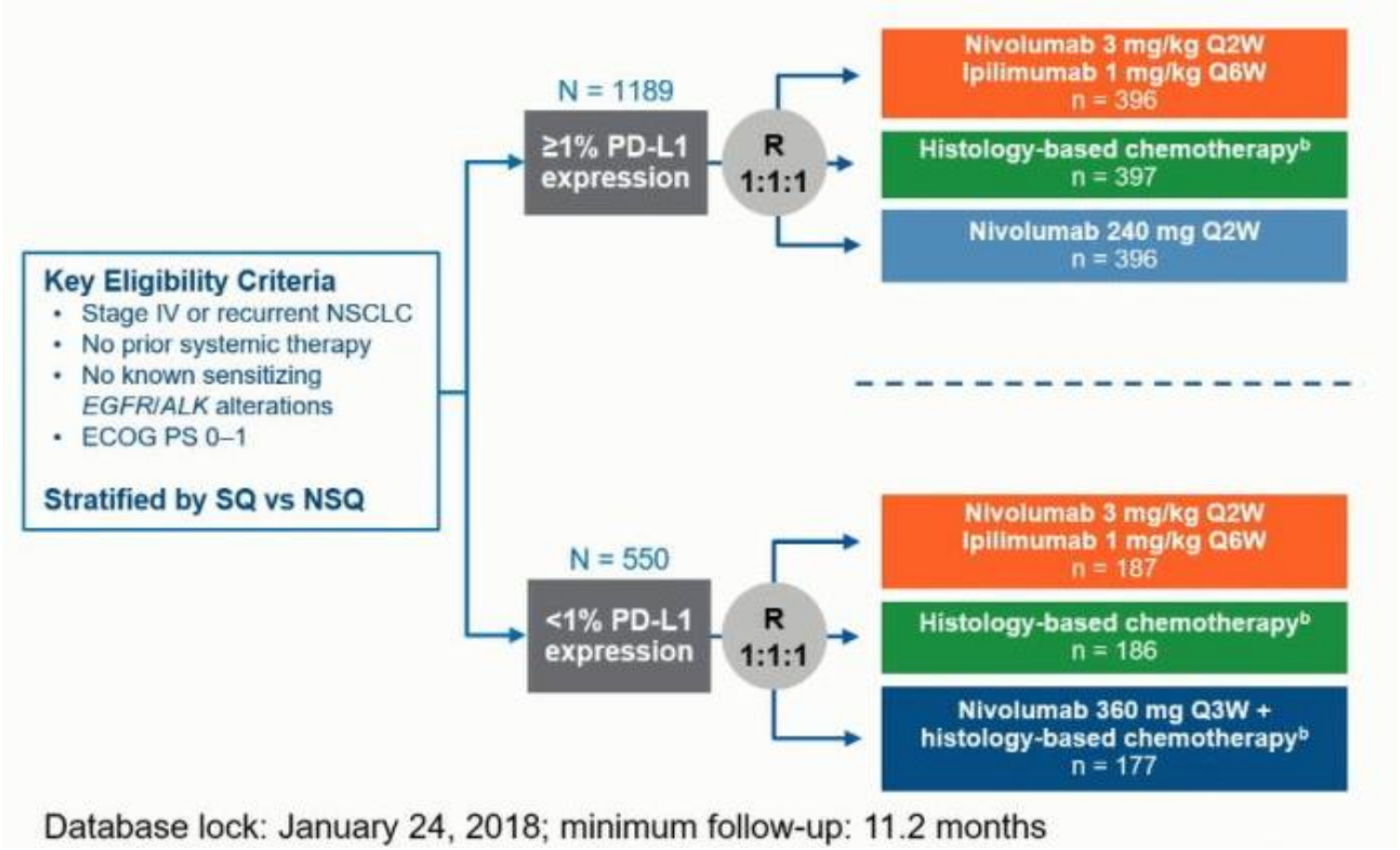
Reck et al NEJM 2016, Gandhi et al NEJM 2018, Lopes et al ASCO 2018, Reck et al ESMO immuno 2017, Kowanetz et al AACR 2018, Paz-Ares et al ASCO 2018, Socinski et al ASCO 2018, Hellman et al NEJM 2018, Carbone et al NEJM 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden

M.D. Hellmann, T.-E. Ciuleanu, A. Pluzanski, J.S. Lee, G.A. Otterson,



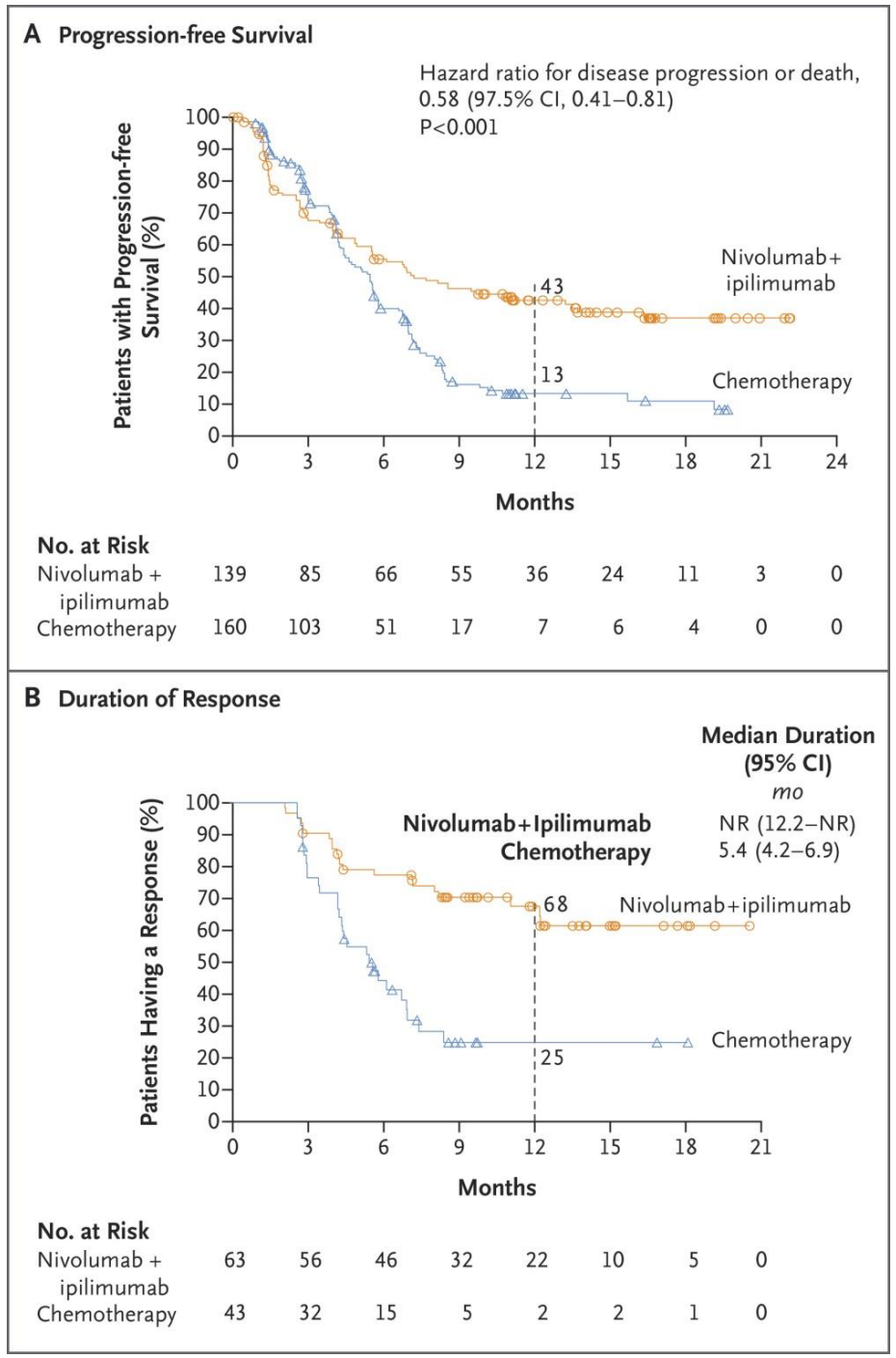
phase 3 trial,
progression-free survival was analyzed with nivolumab plus ipilimumab versus chemotherapy among patients with a high tumor mutational burden (≥10 mutations per megabase).

Hellmann MD et al. N Engl J Med 16 April 2018

Efficacy

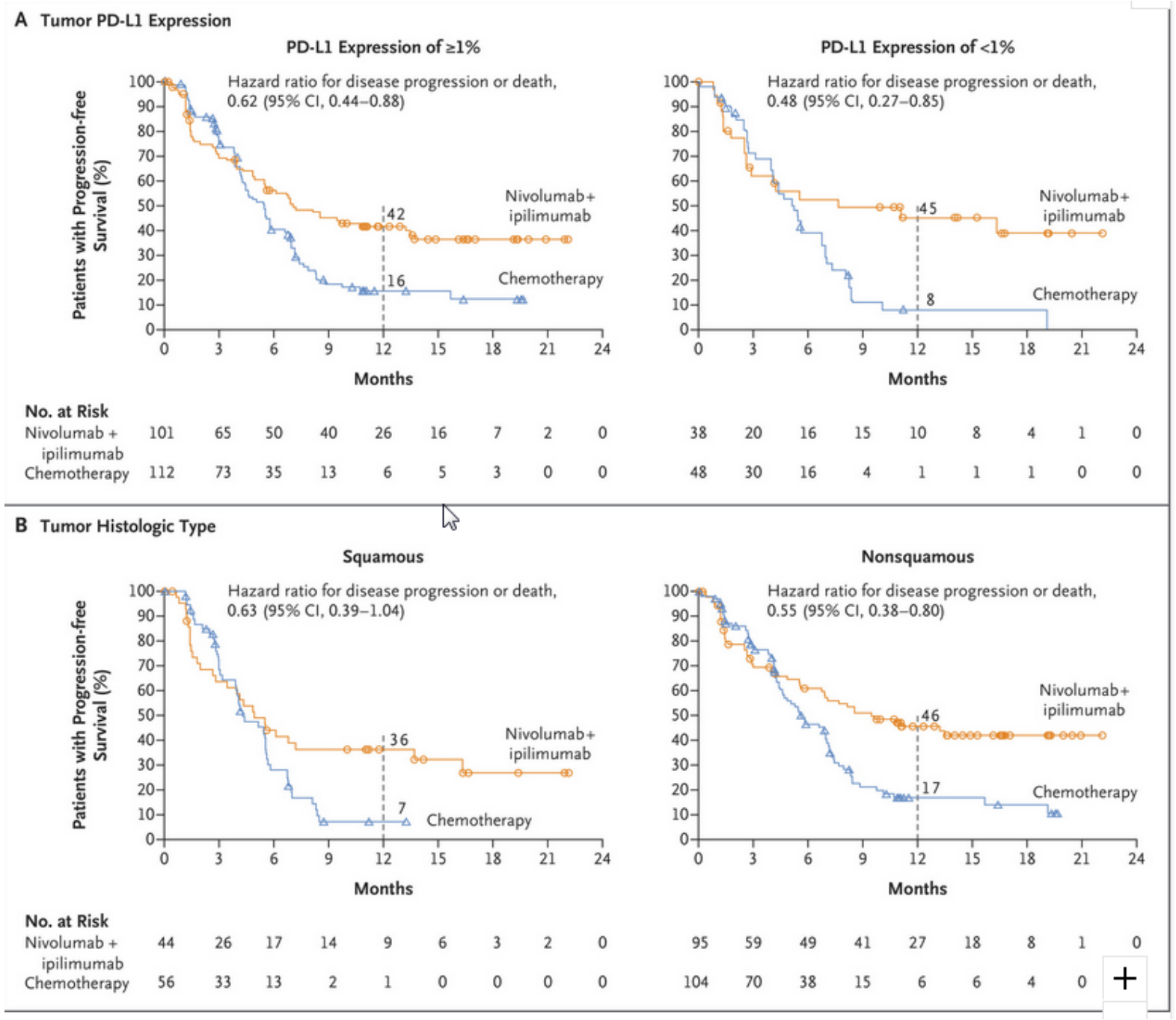
Efficacy of Nivolumab plus Ipilimumab versus Chemotherapy in Patients with a High Tumor Mutational Burden is undeniable

But !!! As expected , high toxixity



- PD-L1
- Histology

No influence…



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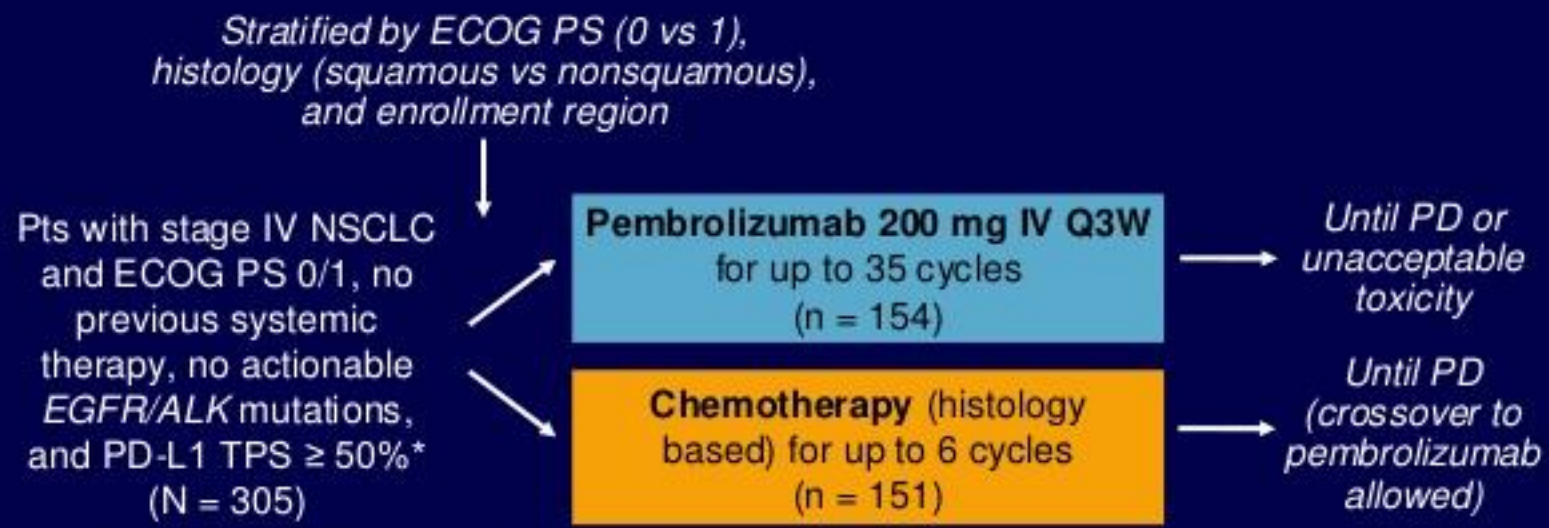
Pembrolizumab vs CT as First-line Therapy for Adv NSCLC (KEYNOTE-024)

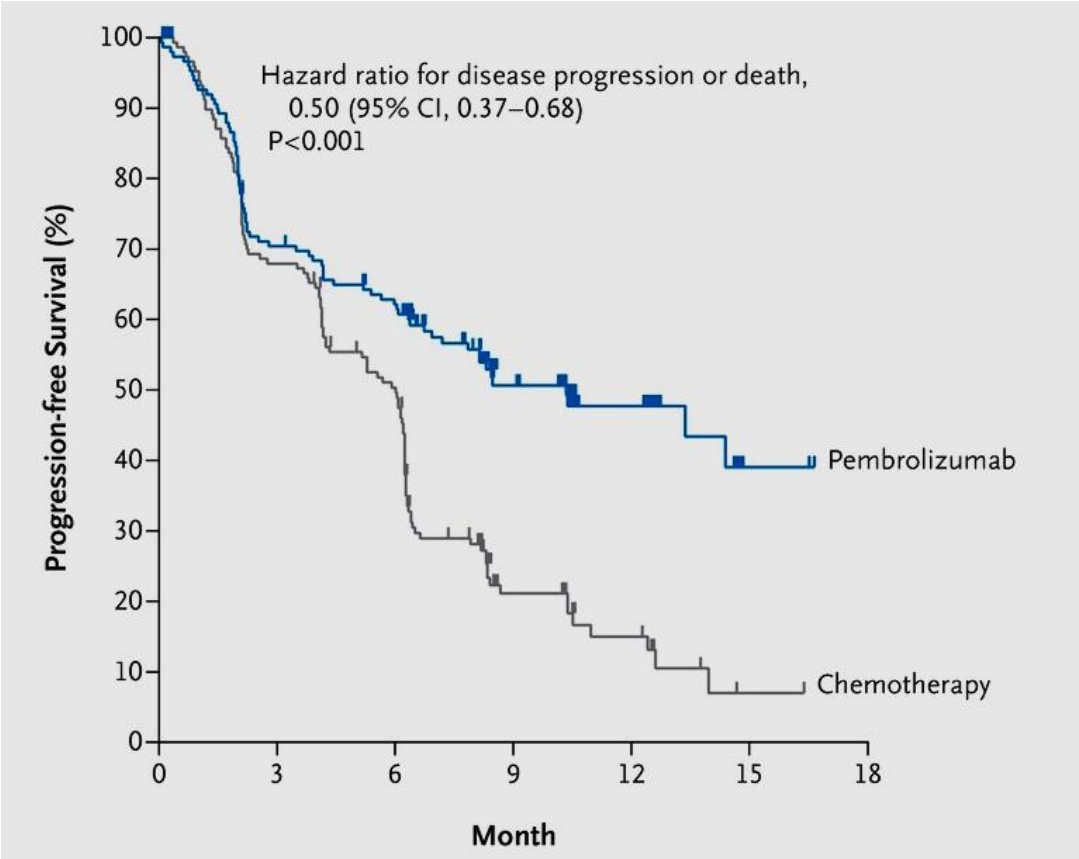


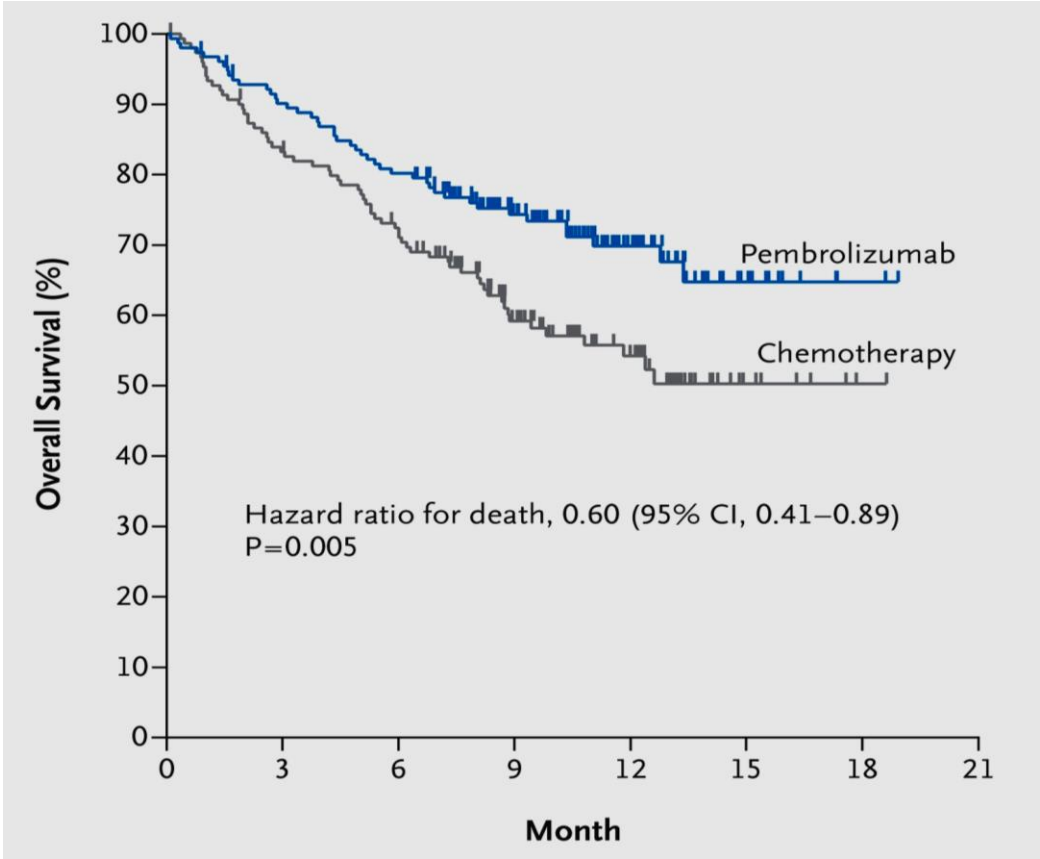
*≥ 50% tumor cell staining using 22C3 companion diagnostic IHC assay.

- Primary endpoint: PFS
- Secondary endpoints: ORR, OS, and safety

Reck M, et al. N Engl J Med. 2016;[Epub ahead of print].

Pembro vs Platinum doublet in PD-L1 ≥ 50%

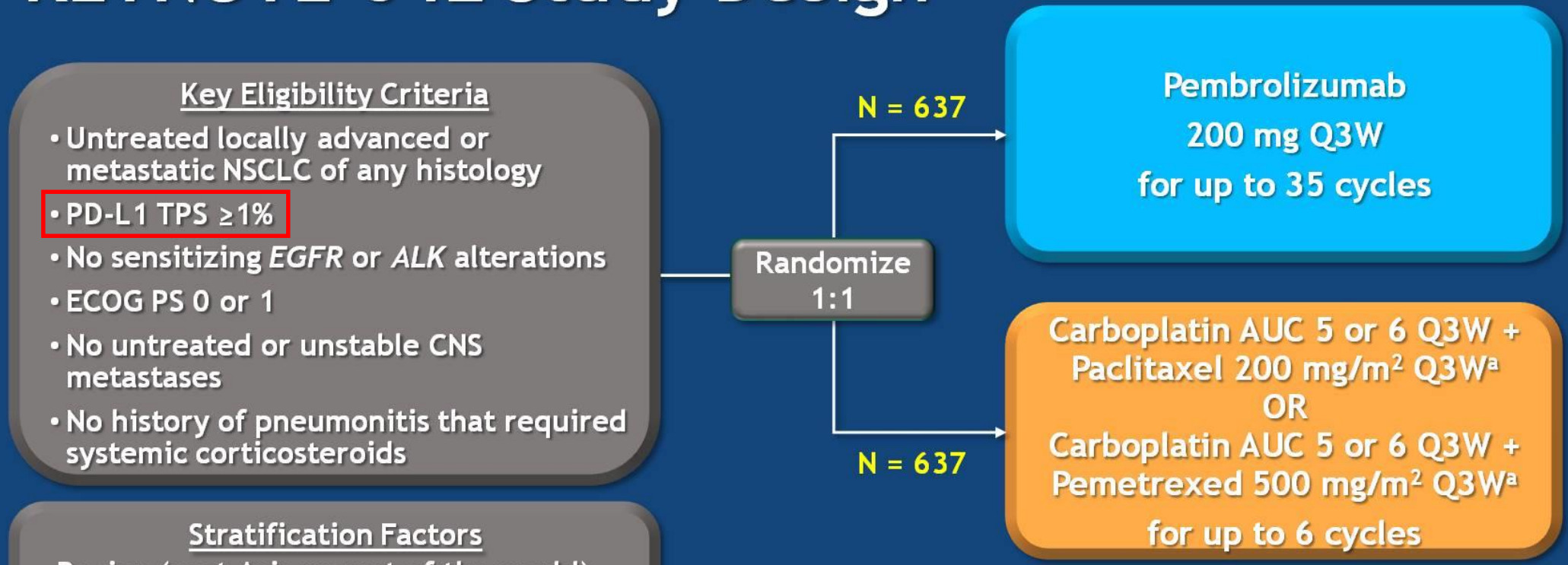




ORR: 44.8 vs 27.8
Efficacy squamous vs nonsquamous was similar
Safety in favor of pembrolizumab

Reck M et al. N Engl J Med 2016;375:1823-1833

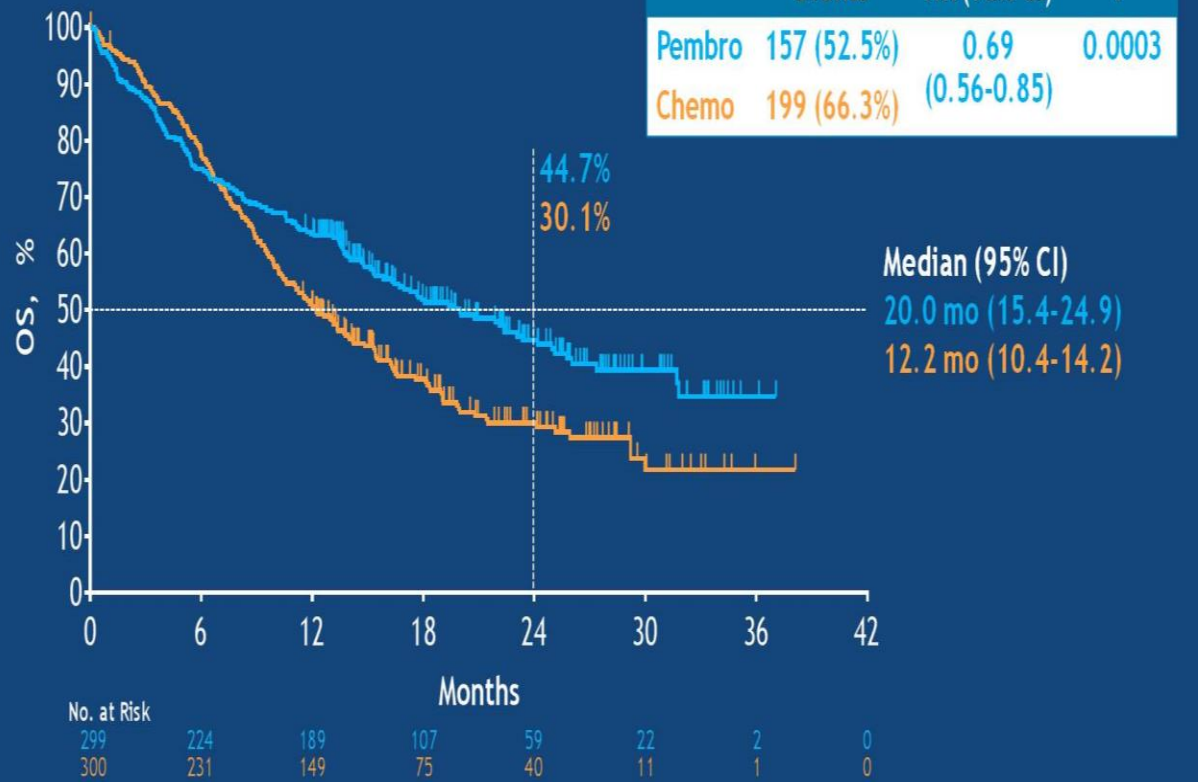
KEYNOTE-042 Study Design



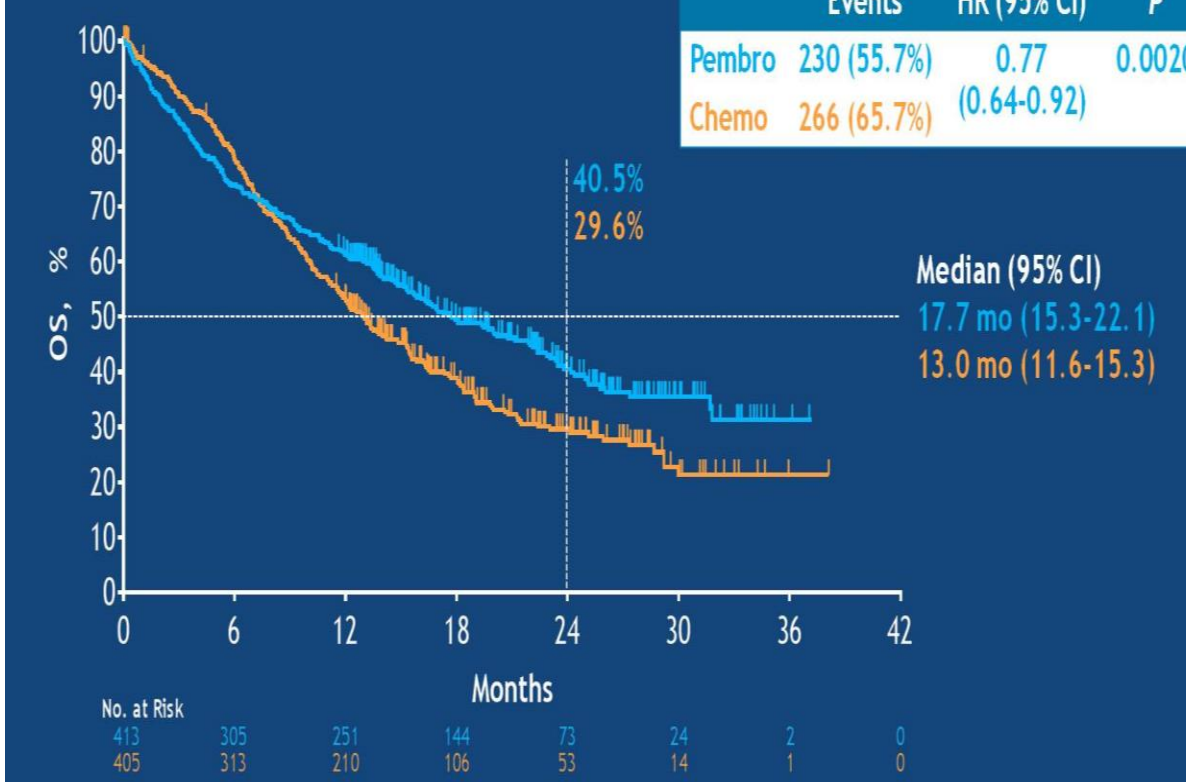
End points
- Primary: OS in PD-L1 TPS ≥50%, ≥20%, and ≥1%
- Secondary: PFS and ORR in TPS ≥50%, ≥20%, and ≥1%; safety in TPS ≥1%

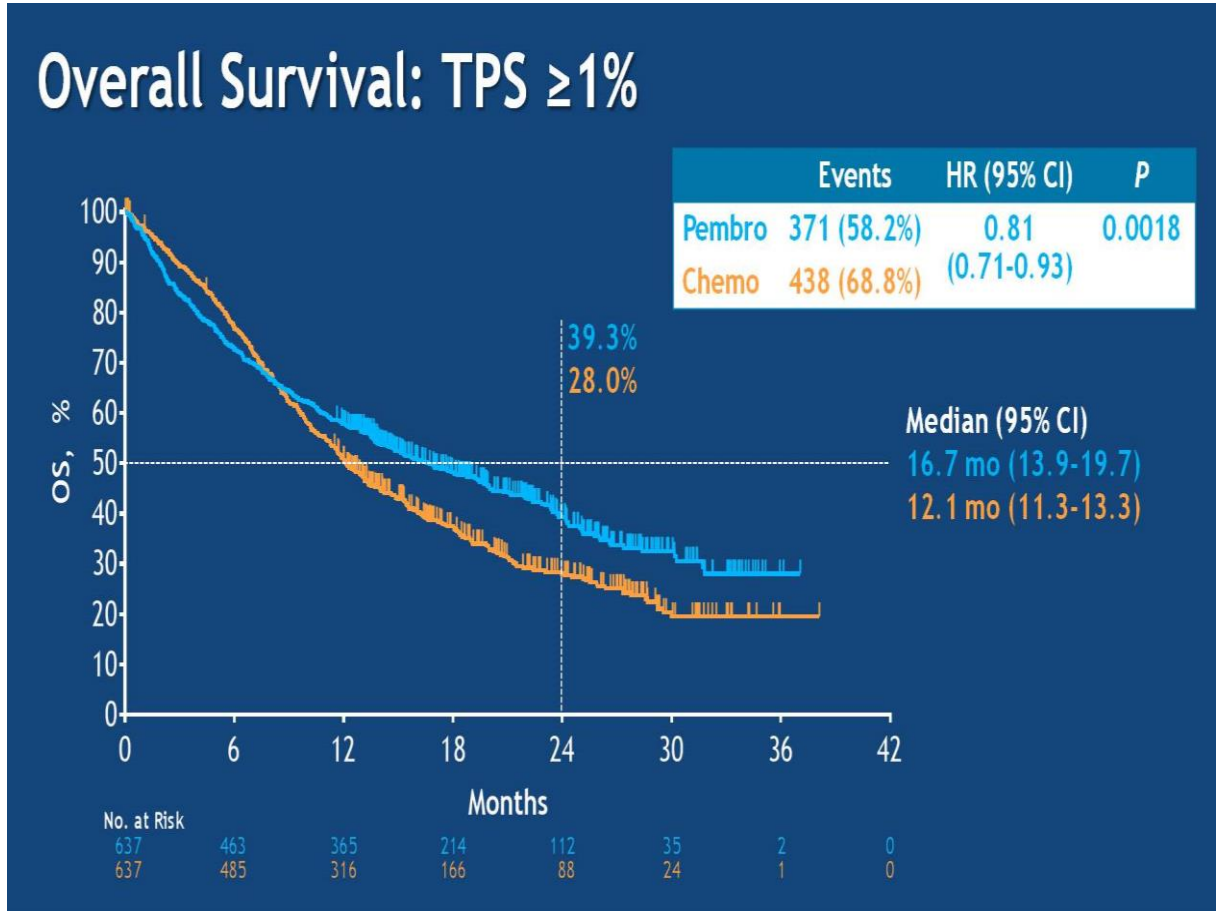
[a]Pemetrexed maintenance therapy was optional but strongly encouraged for patients with nonsquamous histology.

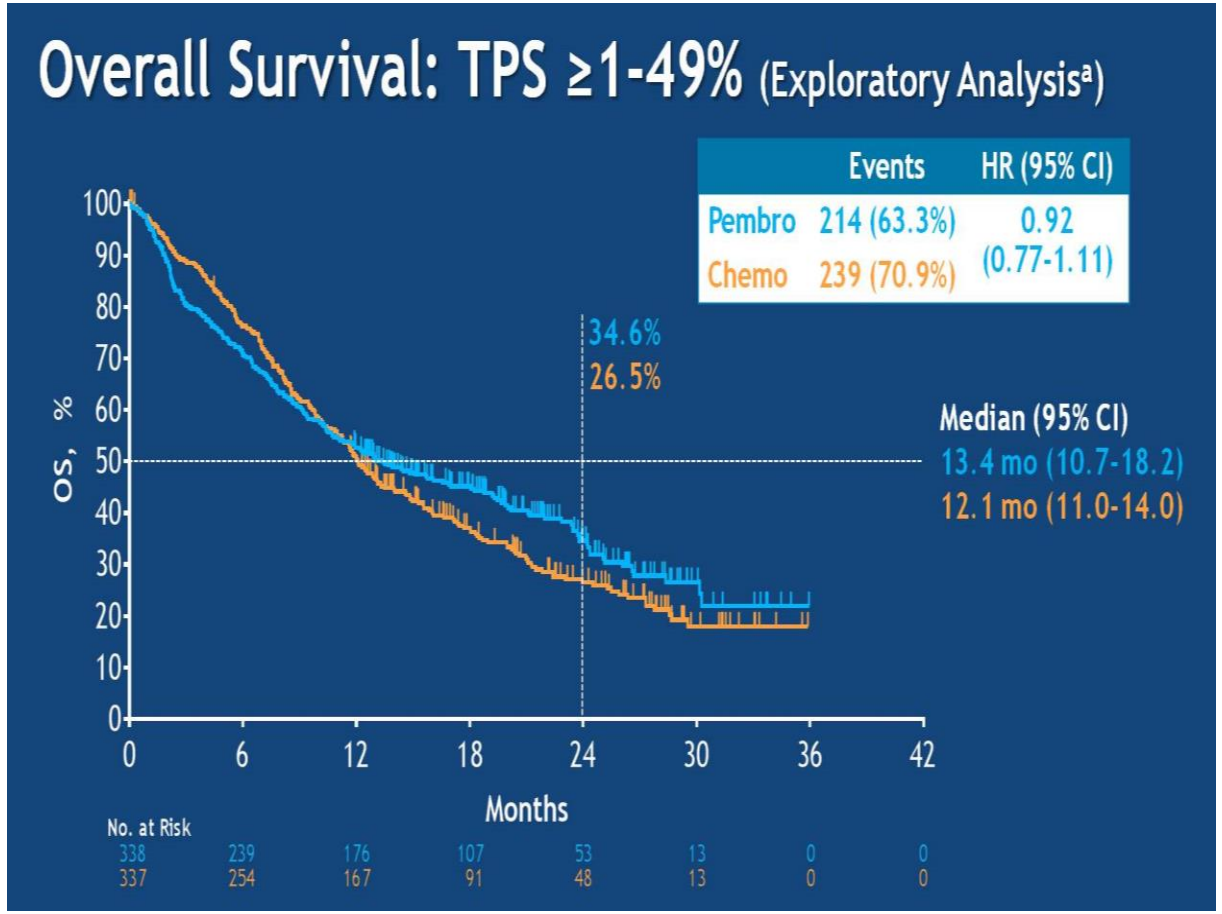
Overall Survival: TPS ≥50%



Overall Survival: TPS ≥20%







Effect is clearly driven by high PD-L1 expressors

Stage IV first line immunotherapy

NSCLC – what is the best 1st line

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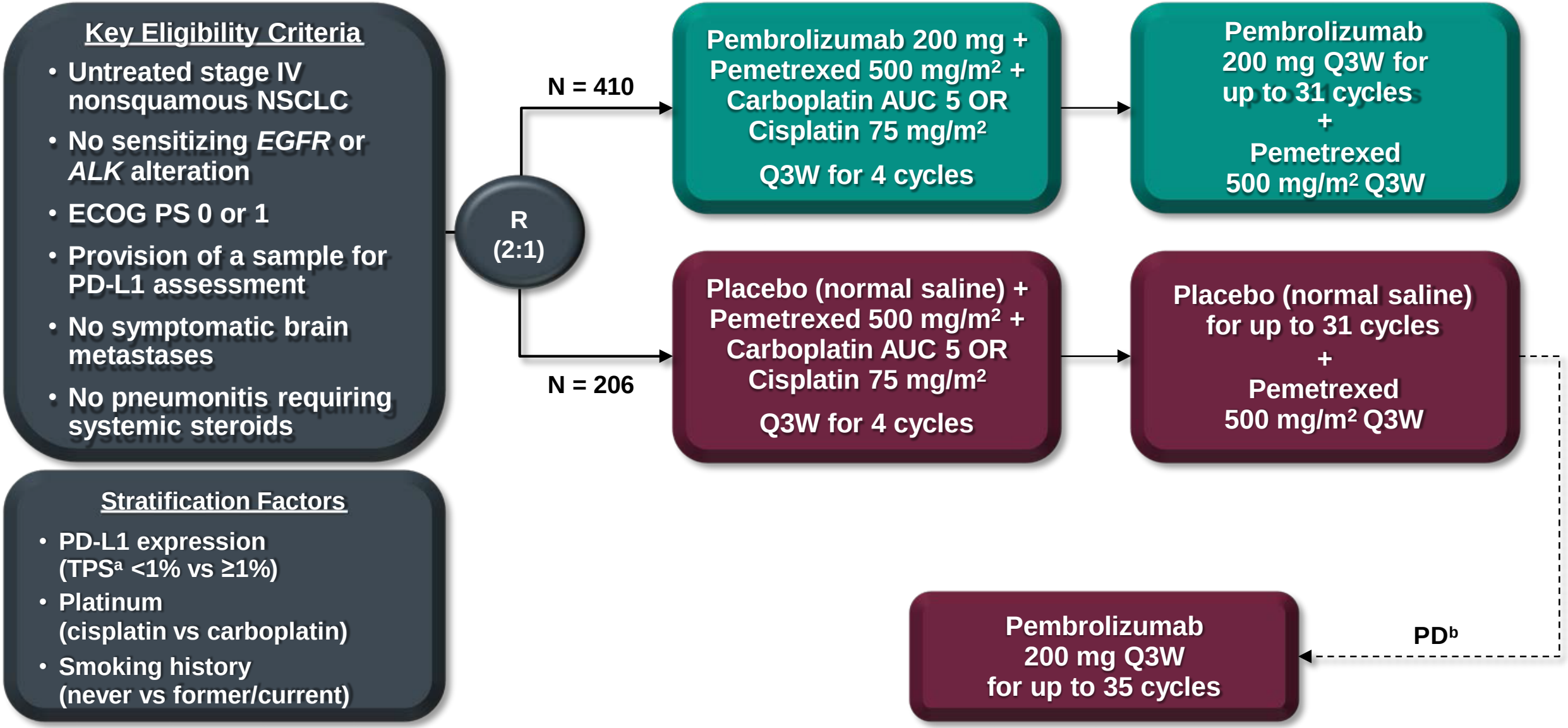
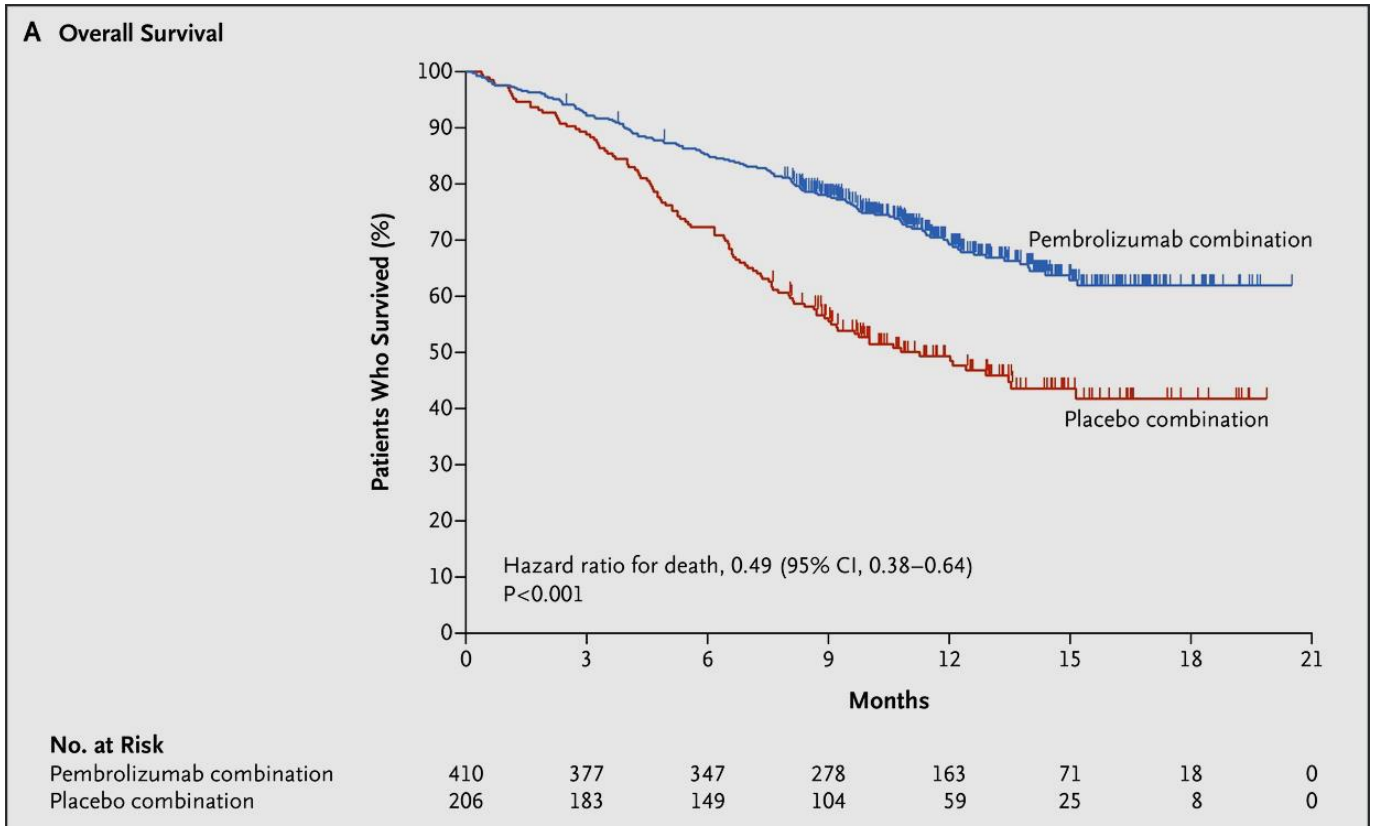
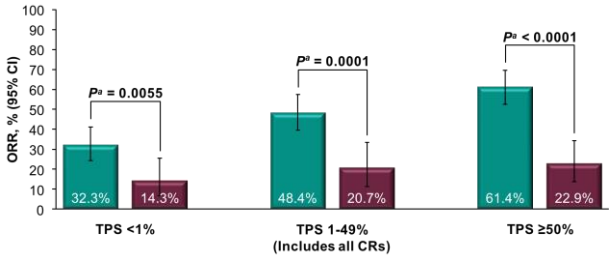
KEYNOTE-189 Study Design ALL PD-L1 / Nonsquamous

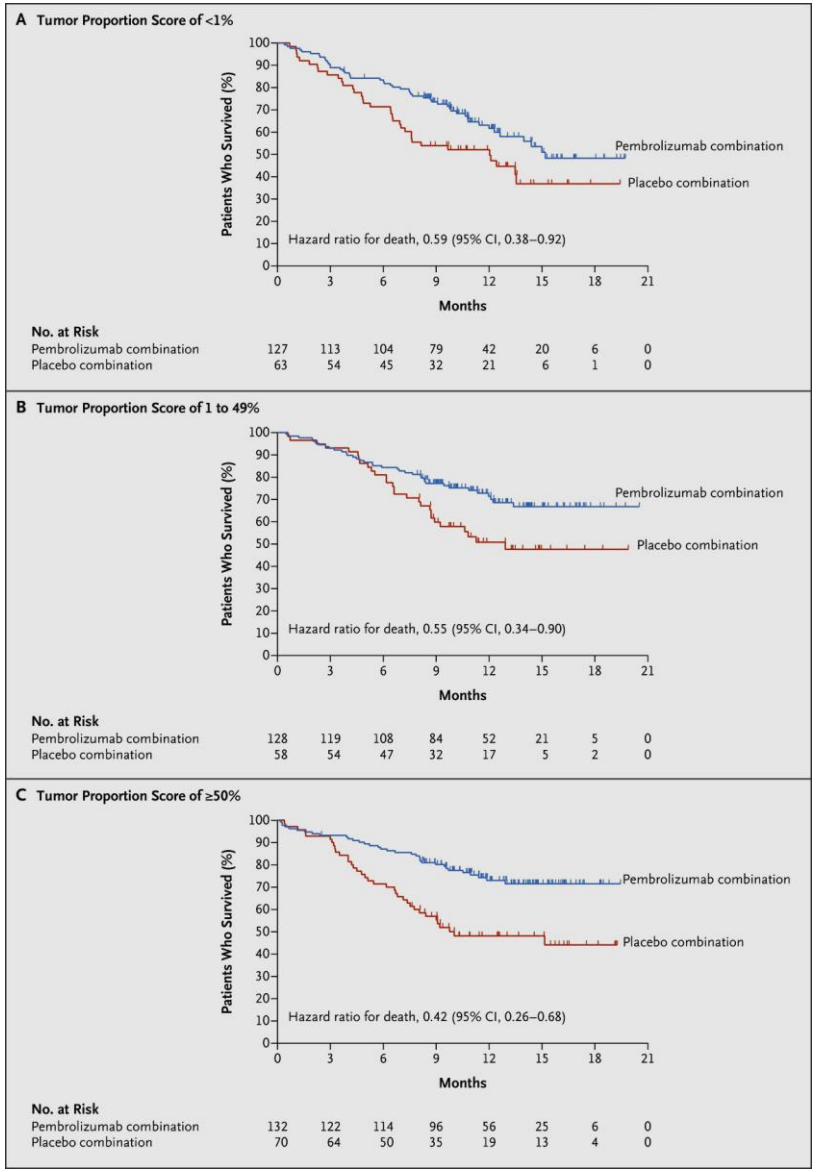


Survival in Carbo Pemetrexate +/- Pembro in Nonsquamous NSCLC





Tolerance as expected



Gandhi L et al. N Engl J Med 2018;378:2078-2092

Stage IV first line immunotherapy

NSCLC – what is the best 1st line

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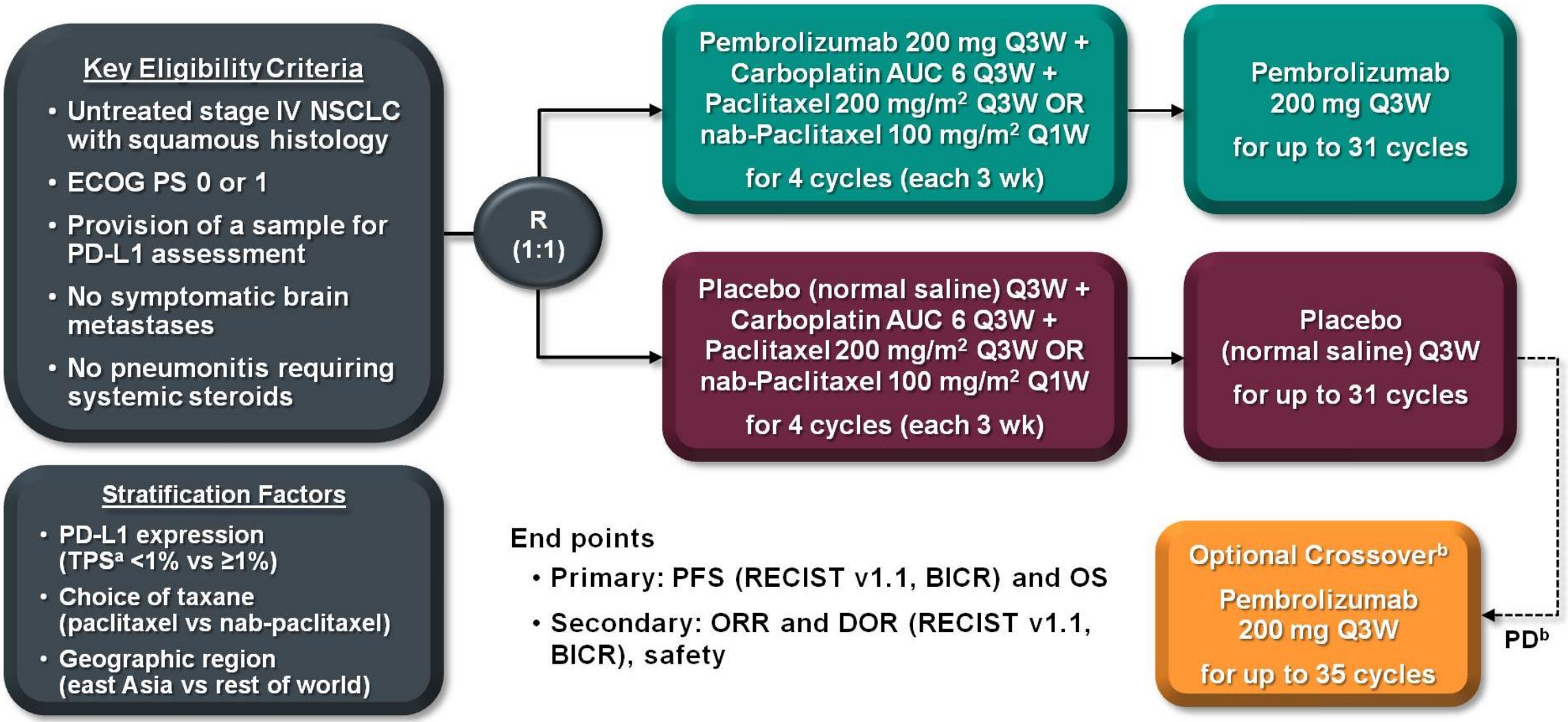
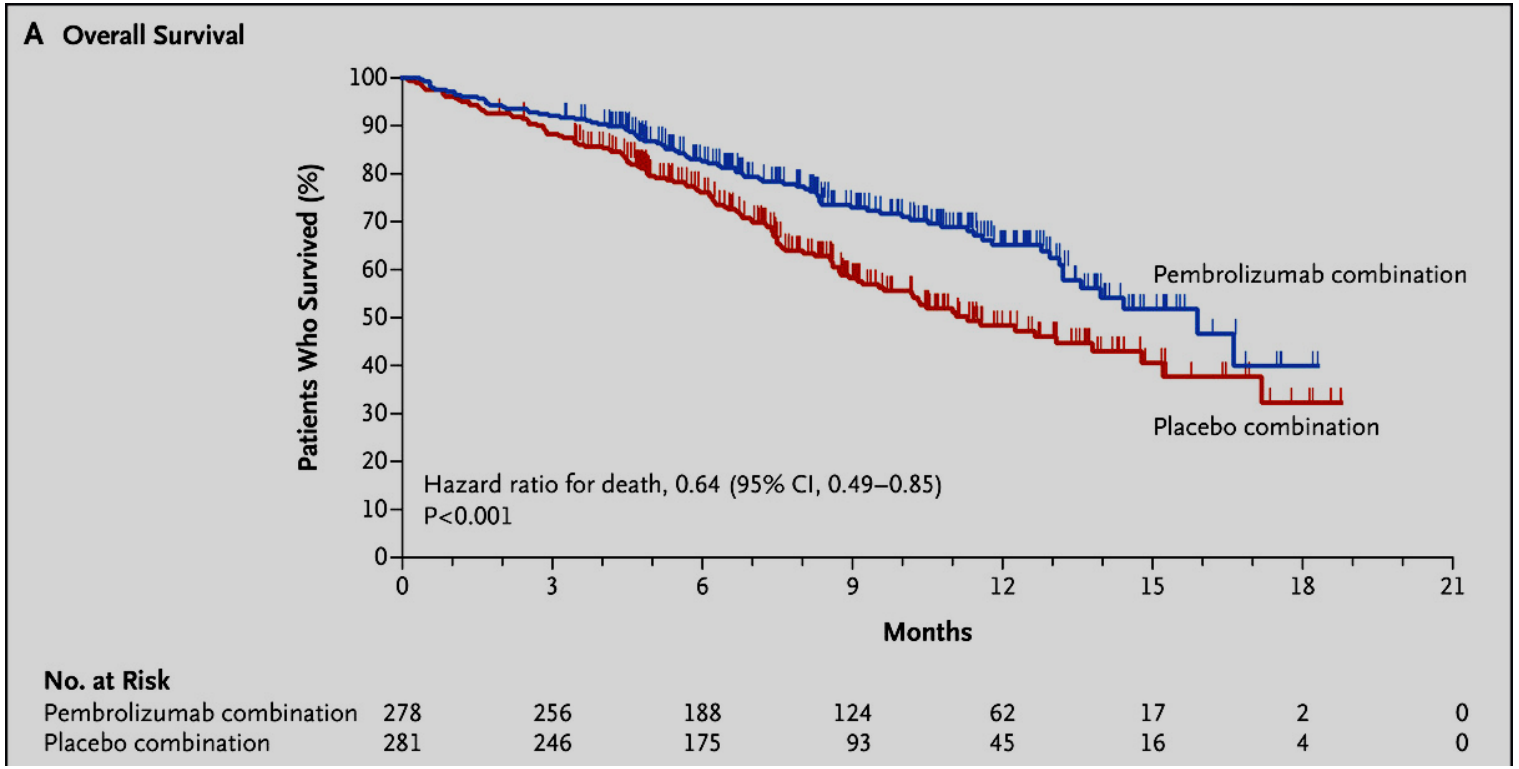
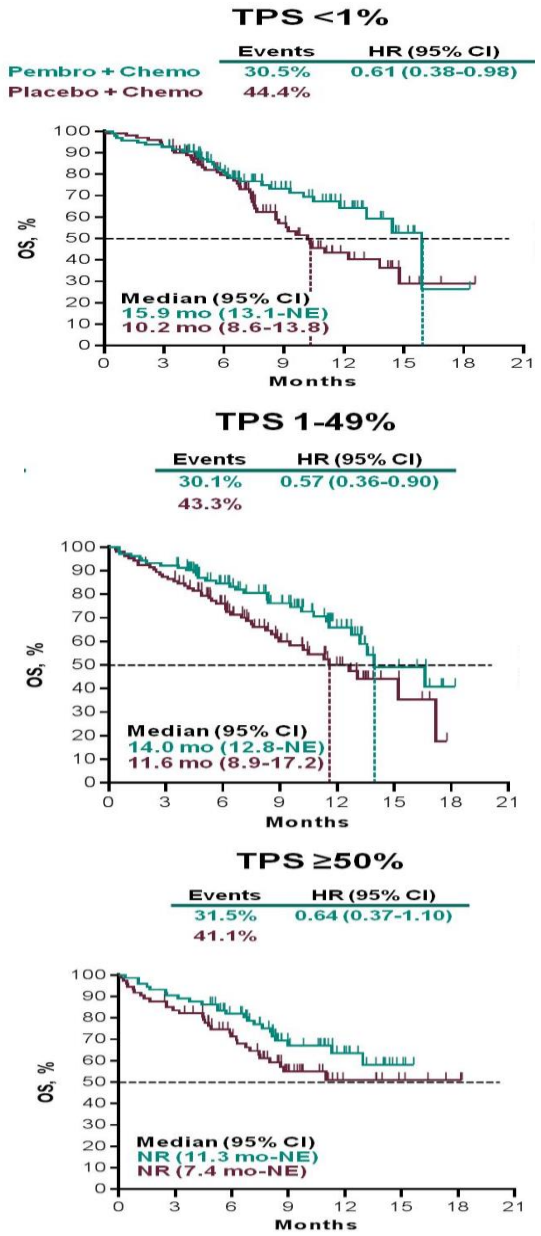
KEYNOTE-407 Study Design ALL PD-L1 / Squamous



Survival Carbo pacli/Nab-Pacli +/- Pembro in ALL PD-L1 / Squamous





Tolerance as expected

L Paz-Ares et al. N Engl J Med 2018.

Stage IV first line immunotherapy

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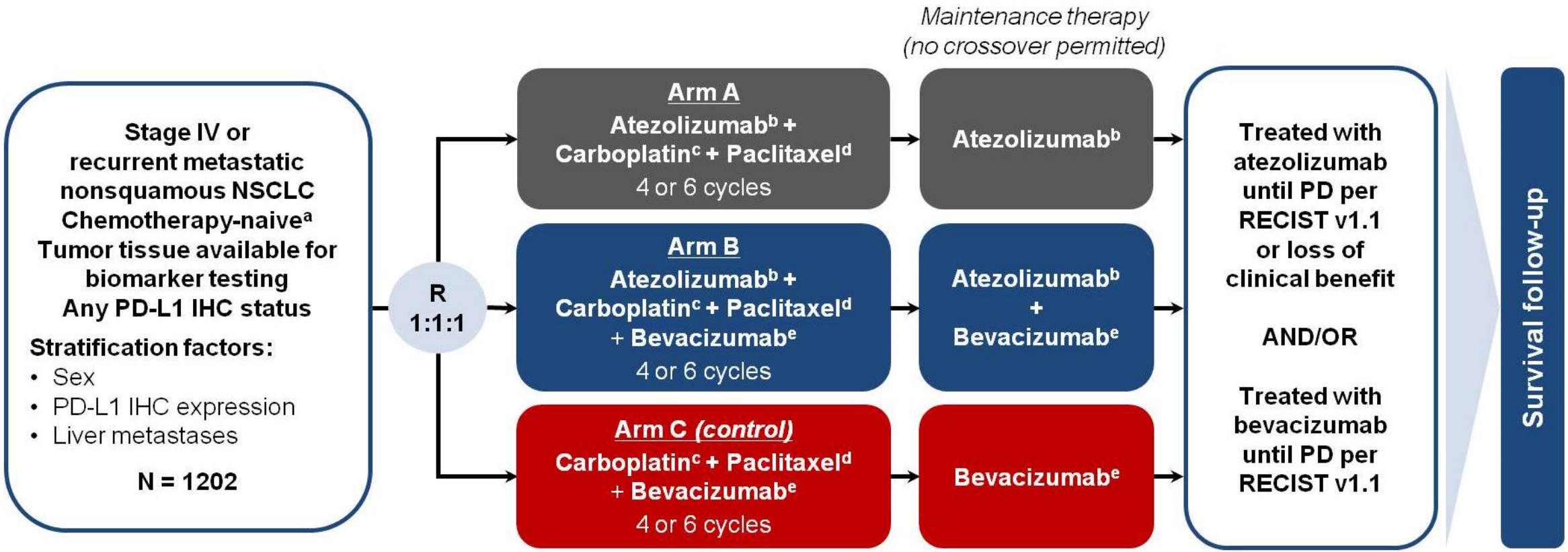
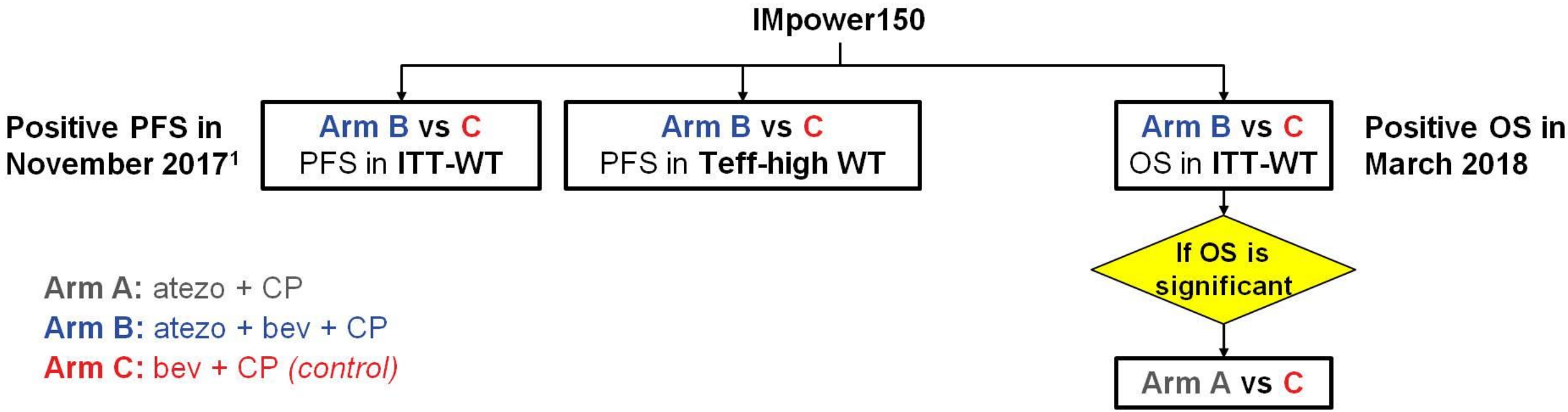
IMpower150 Study Design



Statistical Testing Plan for the Co-primary Endpoints in IMpower150



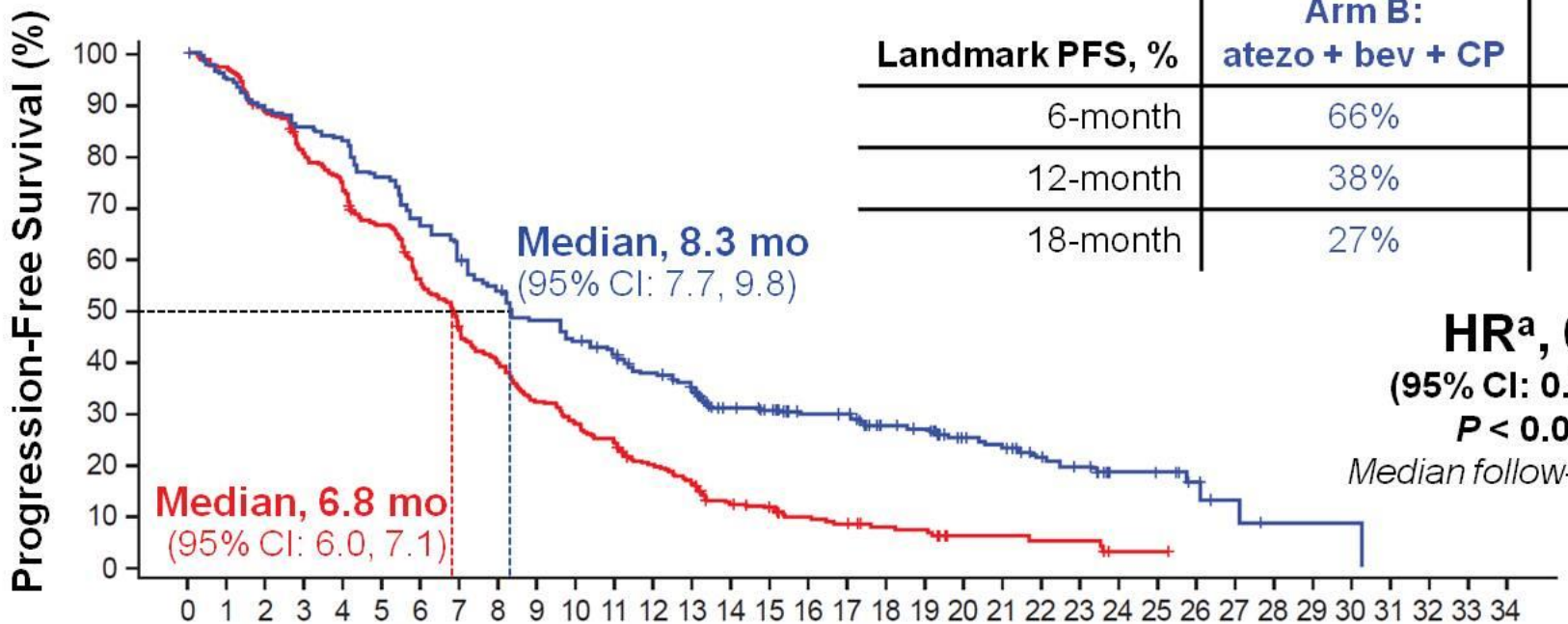
Arm A: atezo + CP
Arm B: atezo + bev + CP
Arm C: bev + CP *(control)*

Baseline Characteristics

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%)

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

Addition of atezo to the 3



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

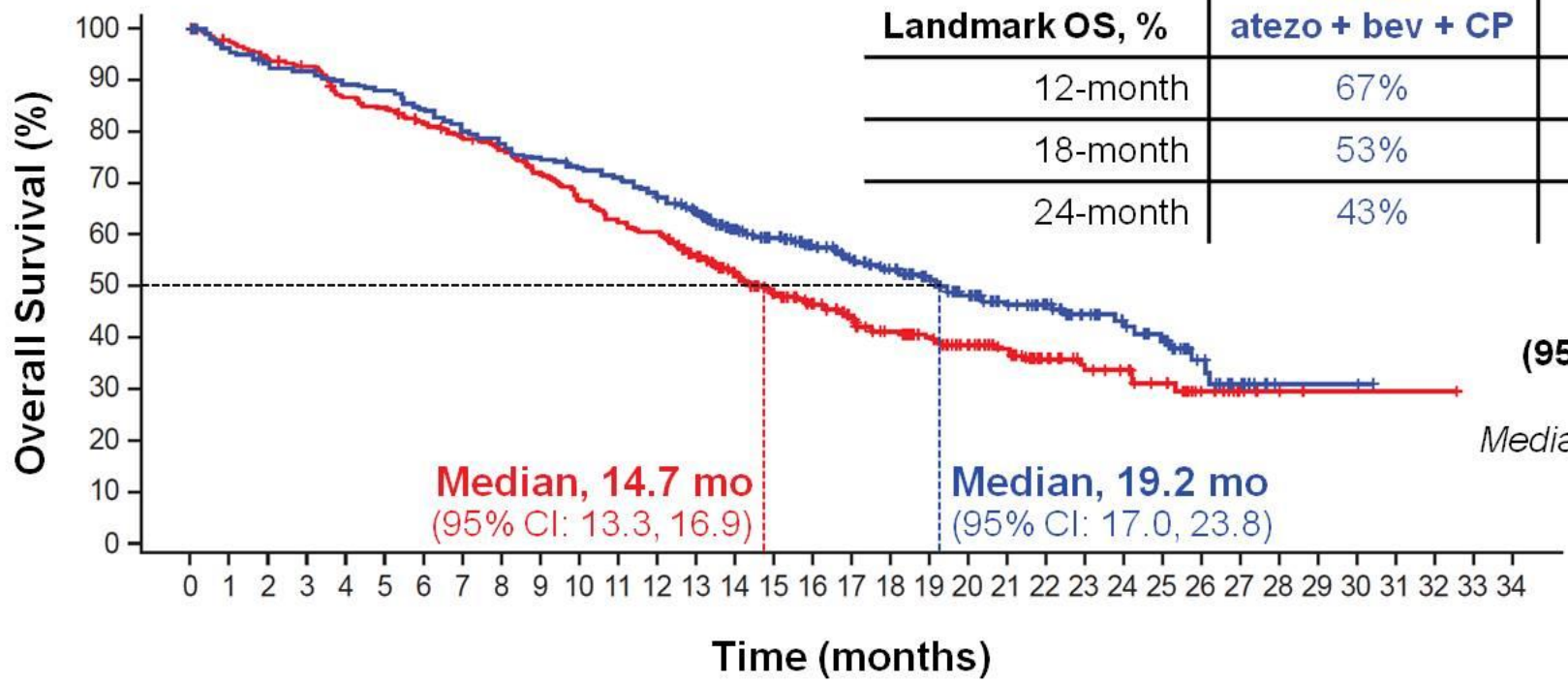
No. at Risk

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

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%



HR[a], 0.78
(95% CI: 0.64, 0.96)
***P* = 0.0164**
Median follow-up: ~20 mo

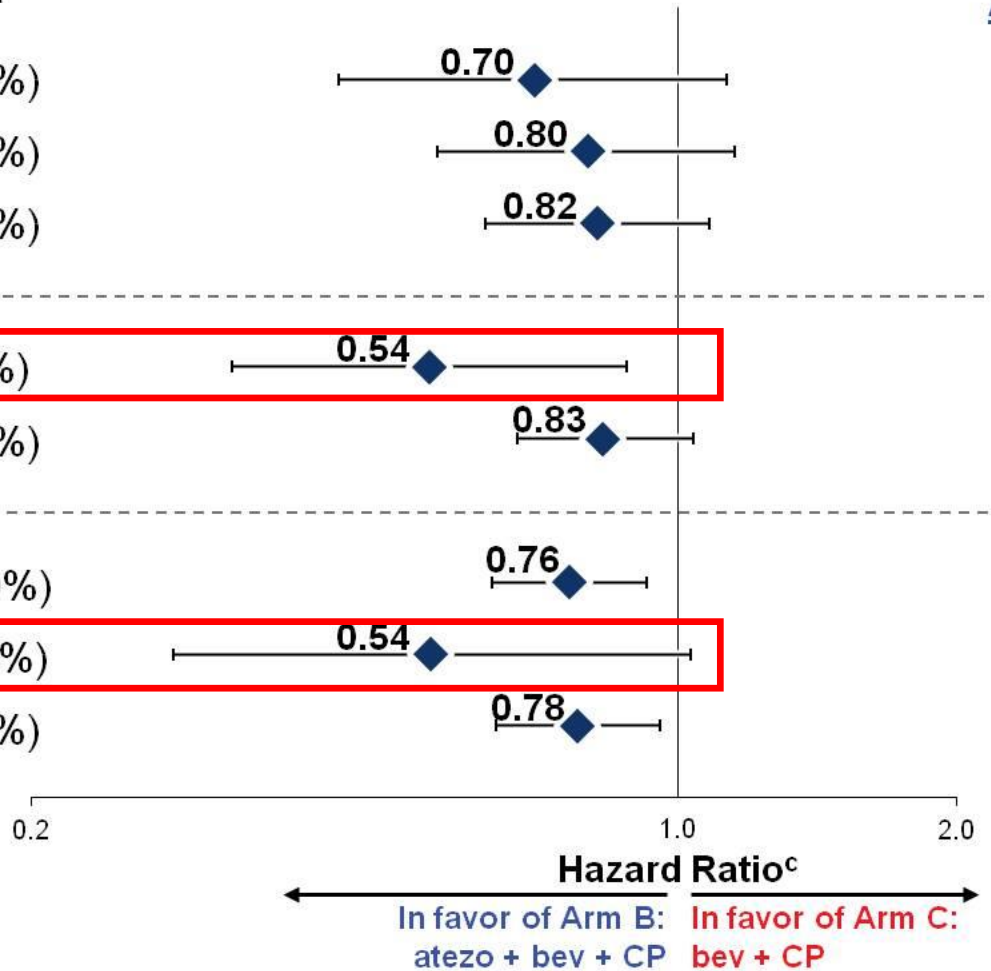
No. at Risk

Atezo+Bev+CP	359	339	328	323	314	310	296	284	273	264	256	250	235	218	188	167	147	133	119	103	84	66	57	41	34	28	16	9	2	2	2
Bev+CP	337	326	315	308	287	280	268	255	247	233	216	203	196	174	152	129	115	101	87	77	66	56	40	32	29	22	13	6	3	1	1	1	1

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

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

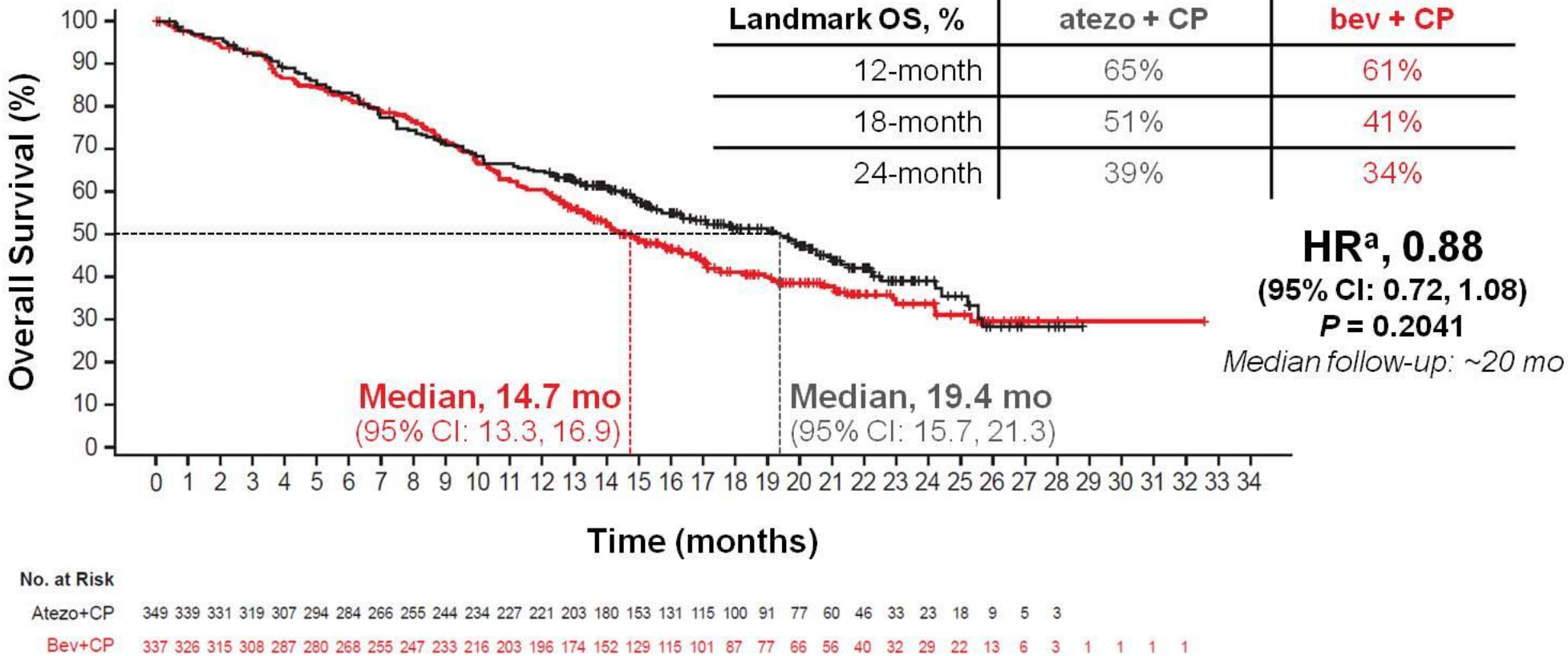


NE, not estimable.
[a] Prevalence % for PD-L1 IHC and liver metastases subgroups out of ITT-WT (n=696); prevalence of ITT, *EGFR/ALK*+, and ITT-WT out of ITT (n=800).
[b] One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab.
[c] Stratified HR for ITT and ITT-WT; unstratified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

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

Beva vs atezo

Landmark OS, %	Arm A: atezo + CP	Arm C: bev + CP
12-month	65%	61%
18-month	51%	41%
24-month	39%	34%



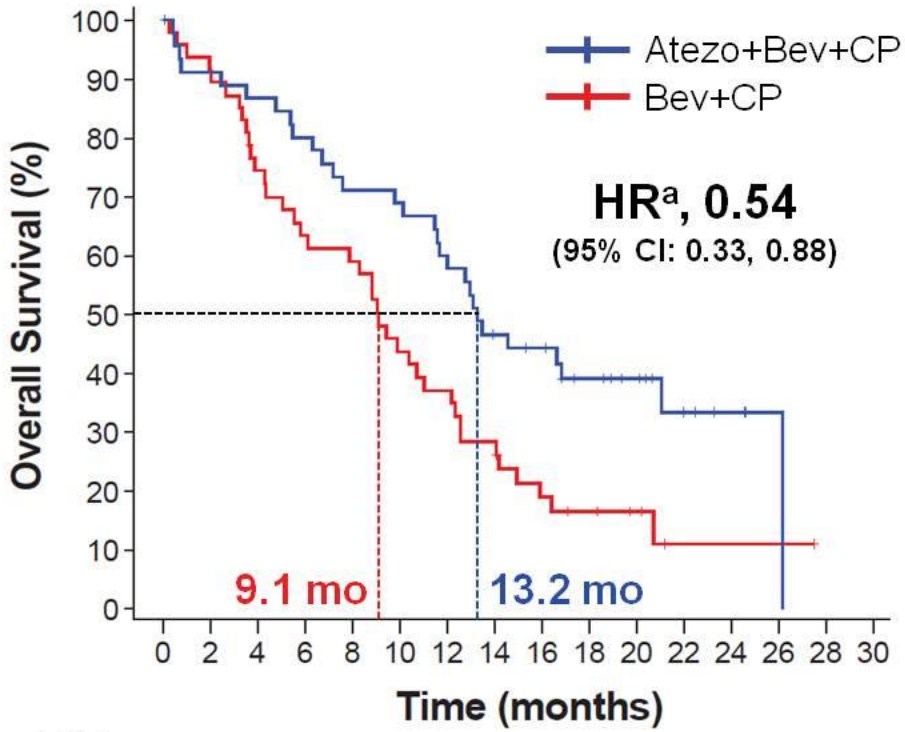
HR[a], 0.88
(95% CI: 0.72, 1.08)
***P* = 0.2041**
Median follow-up: ~20 mo

- A trend toward OS benefit was observed with atezolizumab + chemotherapy vs bevacizumab + chemotherapy, but the efficacy boundary has not yet been crossed and will be tested again at the time of the final analysis

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

Arm B vs Arm C

Addition of atezo to the 3

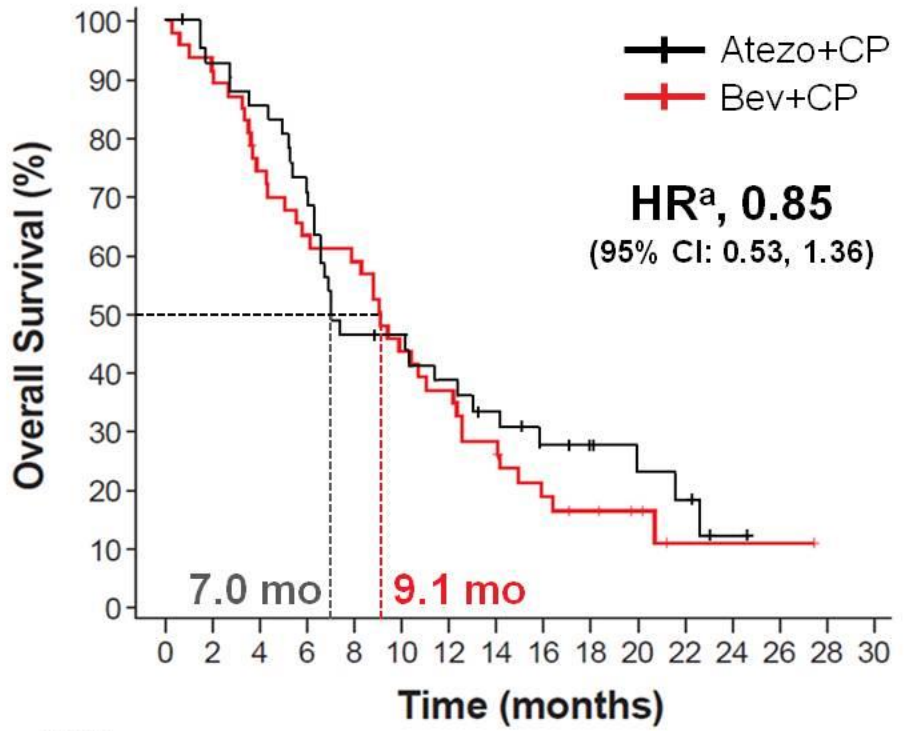


No. at Risk

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

Beva vs atezo

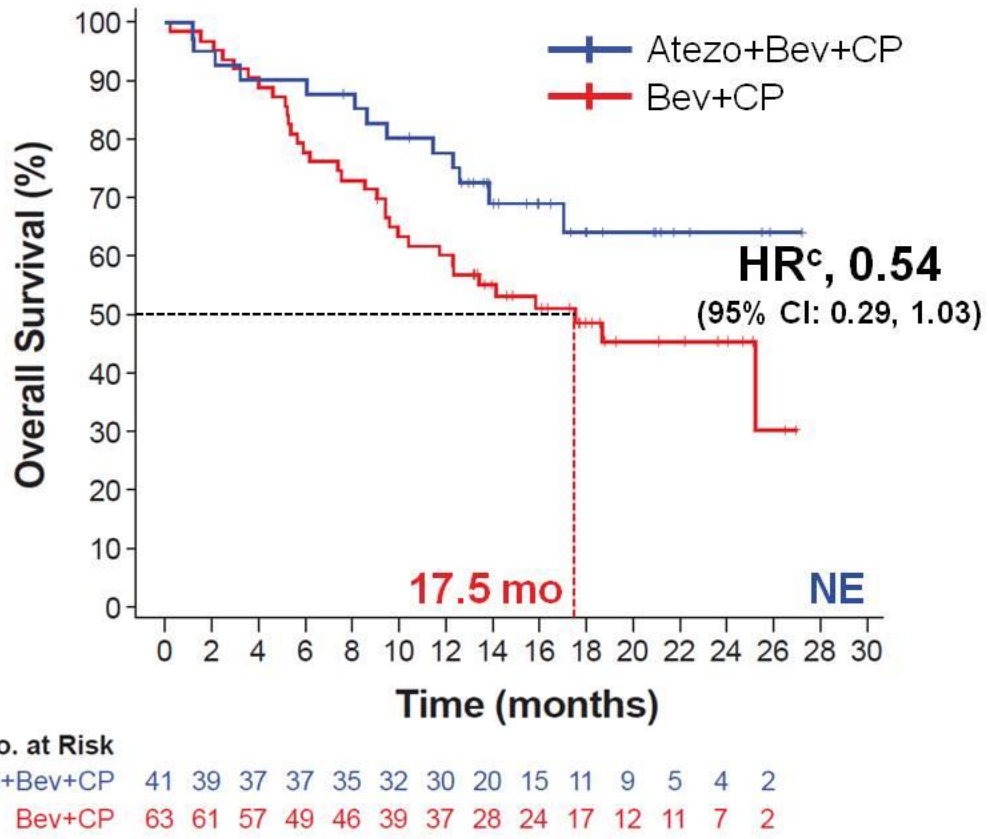


No. at Risk

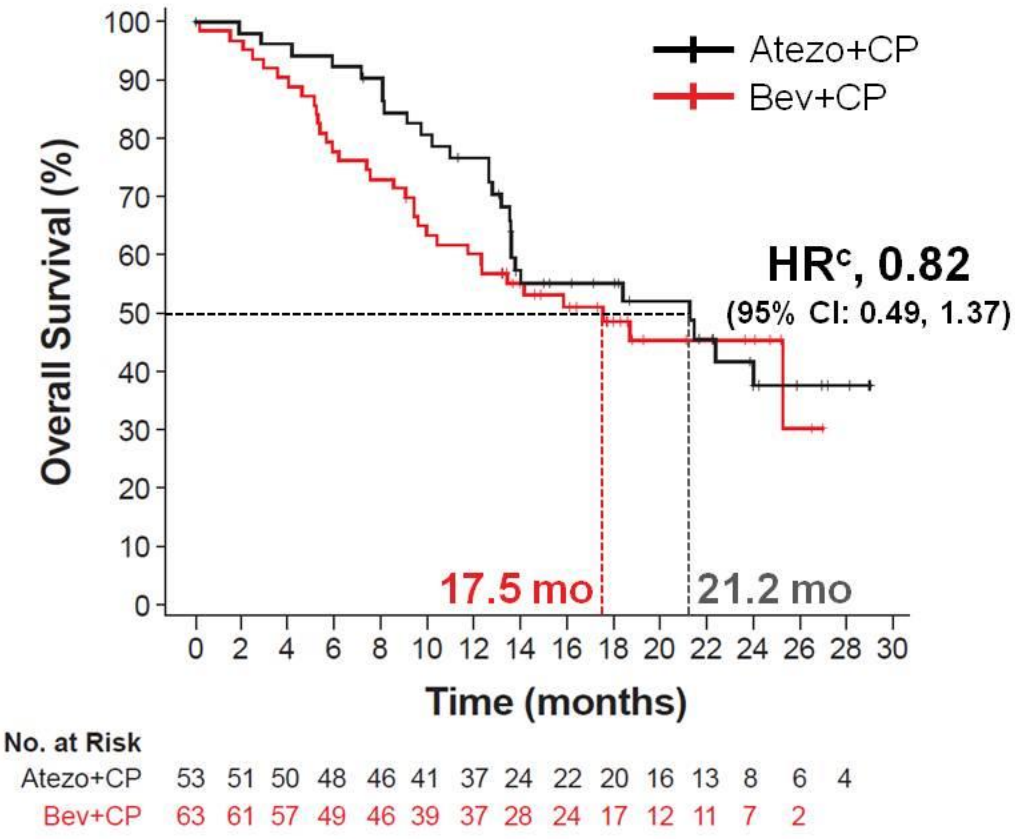
Atezo+CP	42	38	35	28	19	18	15	12	9	7	5	4	1	
Bev+CP	47	42	34	29	27	20	17	13	8	6	4	1	1	1

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

Arm B[b] vs Arm C Addition of atezo to the 3



Arm A vs Arm C Beva vs atezo



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

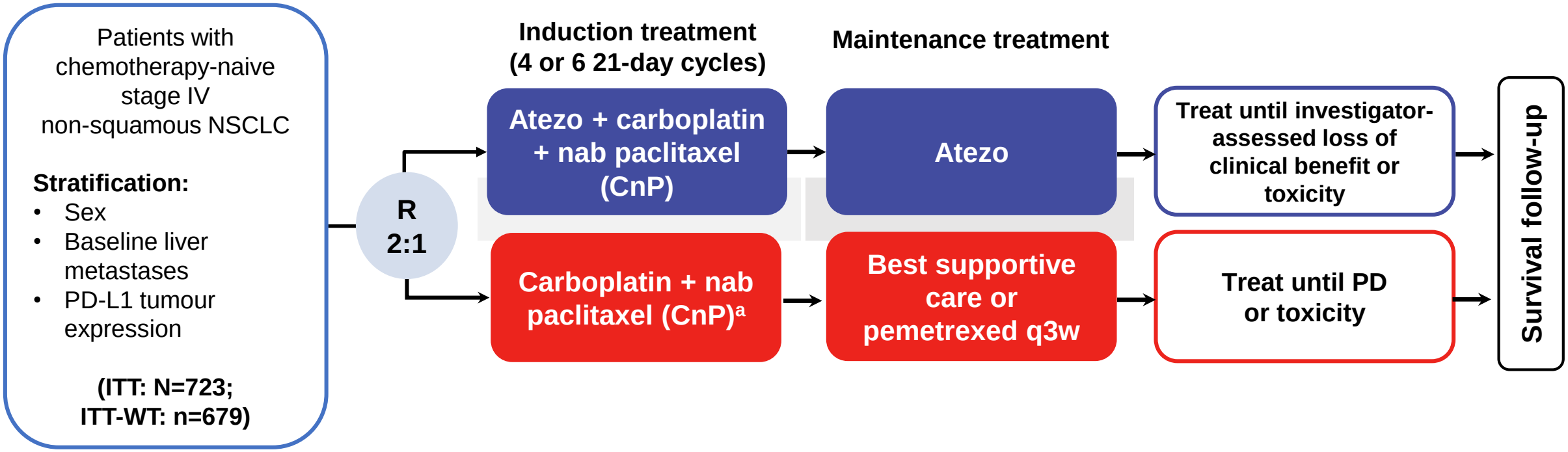
Stage IV first line immunotherapy

NSCLC – what is the best 1st line

Comparison	Selection	ORR	PFS	OS
Nivo vs Platinum doublet	PD-L1 > 1% (anal <5%)	26% vs 33%	HR = 1.15, p=0.25	HR = 1.02
Nivo, Ipi vs Platinum doublet	High TMB ≥ 10 mut/Mb	45.3% vs 26%	HR=0.58, p<0.01	Immature
Pembro vs Platinum doublet (2 stud)	PD-L1 ≥ 50% or ≥ 1%	44.8% vs 27.8% (≥ 50%)	HR = 0.50, p<0.01	HR=0.60, p<0.01
Carbo Pemetrexate +/- Pembro	ALL PD-L1 / Nonsquam.	47.6% vs 18.9%	HR = 0.52, p<0.01	HR=0.49, p<0.01
Carbo pacli/Nab-Pacli +/- Pembro	ALL PD-L1 / Squamous	58.4% vs 35%	HR=0.56, p<0.01	HR=0.64, p<0.01
Carbo, Pacli, beva +/- Atezo	ALL PD-L1, Nonsquam.	64% vs 48%	HR=0.62, p<0.01	Positive
Carbo, nab-pacli +/- Atezo	ALL PD-L1, Nonsquam.	49.2% vs 31.9%	HR=0.64, p<0.0001	HR=79, P<0.033
Carbo, Nab-Pacli +/- Atezo	ALL PD-L1, Squamous	49% vs 41%	HR=0.74, p<0.0004	Immature
Carbo/cis + pemetrexed +/- Atezo	ALL PD-L1, Nonsquam.	47% vs 32%	HR, 0.60, p<0.0001	HR=0.81,p=.0797

Reck et al NEJM 2016, Gandhi et al NEJM 2018, Lopes et al ASCO 2018, Reck et al ESMO immuno 2017, Kowanetz et al AACR 2018, Paz-Ares et al ASCO 2018, Socinski et al ASCO 2018, Hellman et al NEJM 2018, Carbone et al NEJM 2017

IMpower130 study design

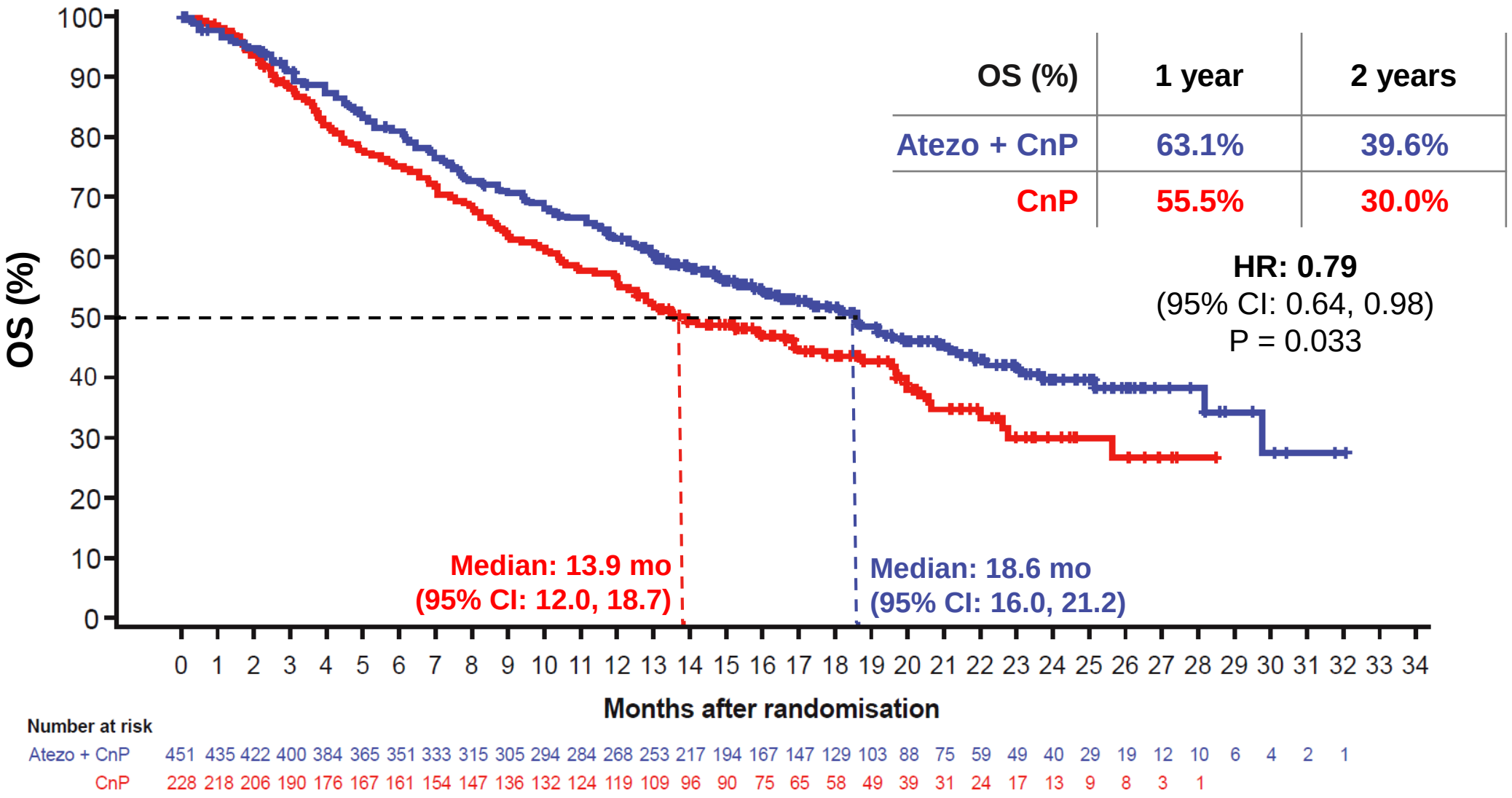


- **Co-primary endpoints:** investigator-assessed PFS and OS (ITT-WT population)
  - ITT-WT population: randomised patients excluding those with *EGFR* or *ALK* genomic alterations
- **Key secondary endpoints:** OS and PFS (ITT population and by PD-L1 expression), ORR and safety
  - ITT population could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

Atezo 1200 mg IV q3w; carboplatin area under the curve 6 mg/mL/min q3w; nab-paclitaxel 100 mg/m^2 IV q3w. PD-L1 status tested with VENTANA SP142 IHC assay. Data cut-off: 15 March 2018.

[a] Crossover to receive atezo at PD was permitted only for patients enrolled to protocol versions 1–4.

OS (ITT-WT)



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

Stage IV first line immunotherapy

NSCLC – what is the best 1st line

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Carbo pacli/Nab-Pacli +/- Pembro	ALL PD-L1 / Squamous	58.4% vs 35%	HR=0.56, p<0.01	HR=0.64, p<0.01
Carbo, Pacli, beva +/- Atezo	ALL PD-L1, Nonsquam.	64% vs 48%	HR=0.62, p<0.01	Positive
Carbo, nab-pacli +/- Atezo	ALL PD-L1, Nonsquam.	49.2% vs 31.9%	HR=0.64, p<0.0001	HR=79, P<0.033
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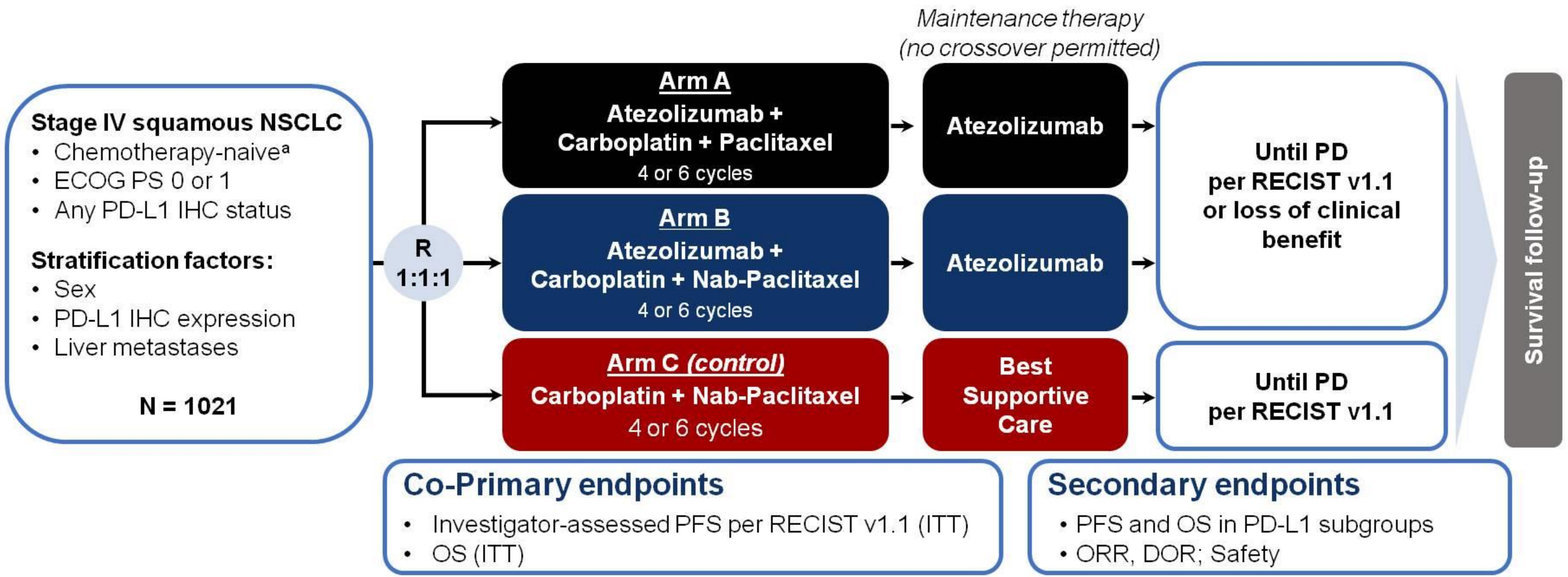
Reck et al NEJM 2016, Gandhi et al NEJM 2018, Lopes et al ASCO 2018, Reck et al ESMO immuno 2017, Kowanetz et al AACR 2018, Paz-Ares et al ASCO 2018, Socinski et al ASCO 2018, Hellman et al NEJM 2018, Carbone et al NEJM 2017

IMpower131: Study Design

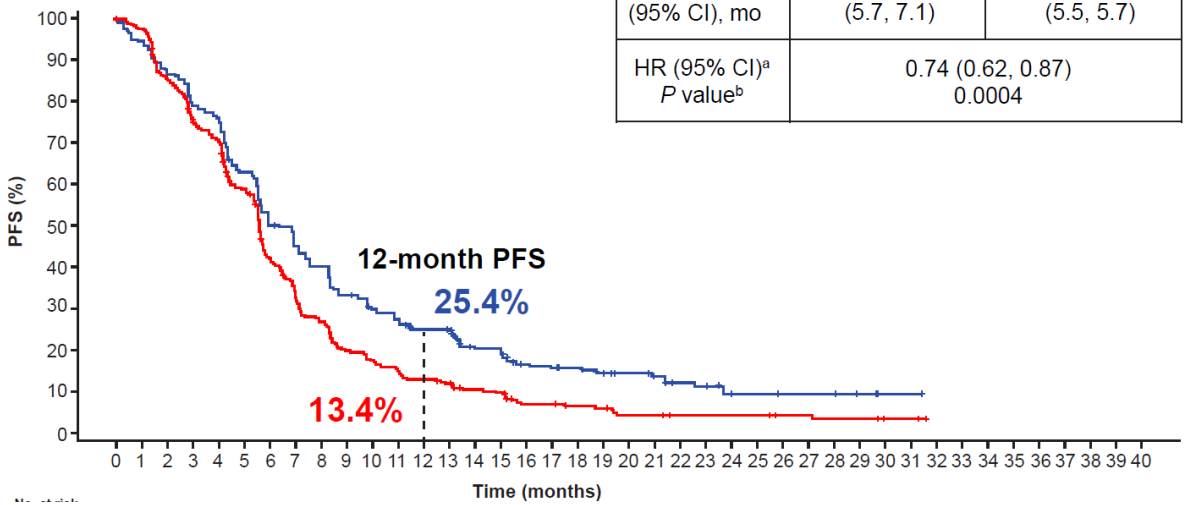


[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance to treatment with ≥1 approved targeted therapies. Testing for *EGFR* mutation or *ALK* translocation was not mandatory. Atezolizumab: 1200 mg IV q3w; carboplatin: AUC 6 IV q3w; nab-paclitaxel 100 mg/m^2 IV qw; paclitaxel: 200 mg/m^2 IV q3w.

PFS + OS at the Second Interim OS Analysis

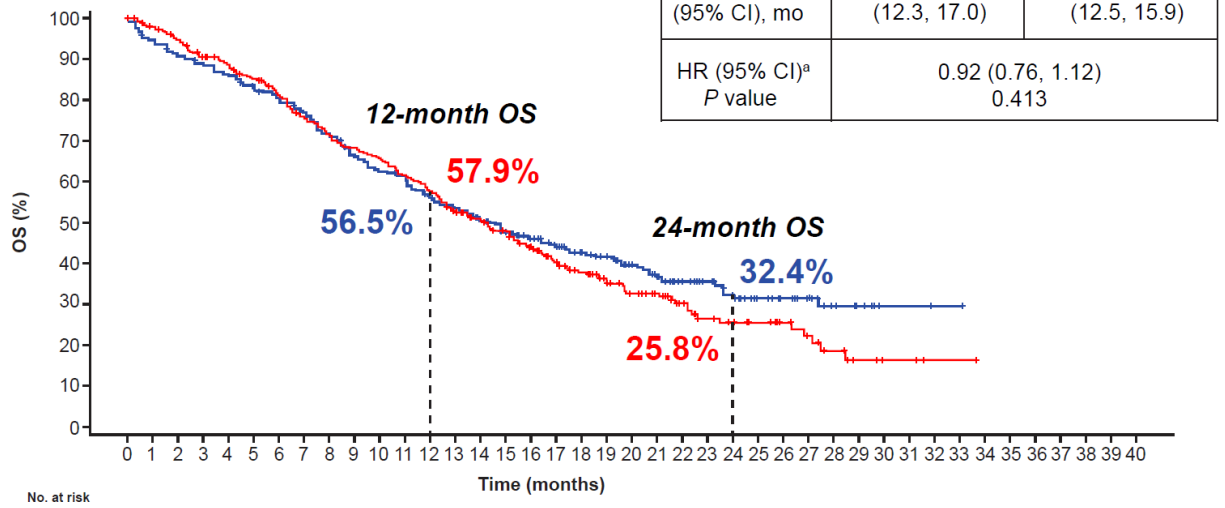
PFS in the ITT Population

	Arm B: Atezo + CnP (n = 343)	Arm C: CnP (n = 340)
Median PFS (95% CI), mo	6.5 (5.7, 7.1)	5.6 (5.5, 5.7)
HR (95% CI)[a] *P* value[b]	0.74 (0.62, 0.87) 0.0004	

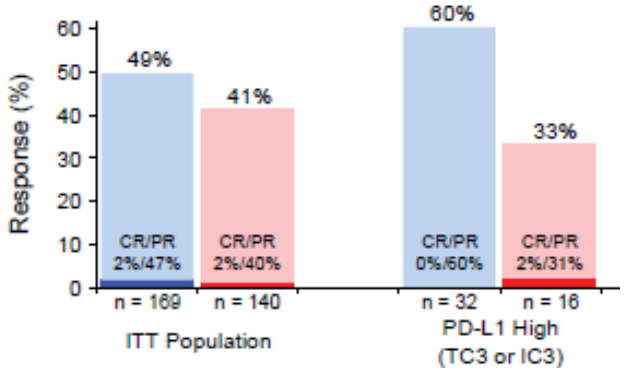


OS in the ITT Population

	Arm B: Atezo + CnP (n = 343)	Arm C: CnP (n = 340)
Median OS (95% CI), mo	14.6 (12.3, 17.0)	14.3 (12.5, 15.9)
HR (95% CI)[a] *P* value	0.92 (0.76, 1.12) 0.413	



- ORR: 49% vs 41%
- OS = immature



Socinski M. IMpower131 Second Interim OS Analysis
http://bit.ly/2yaFYe7

Stage IV first line immunotherapy

NSCLC – what is the best 1st line

Comparison	Selection	ORR	PFS	OS
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Nivo, Ipi vs Platinum doublet	High TMB ≥ 10 mut/Mb	45.3% vs 26%	HR=0.58, p<0.01	Immature
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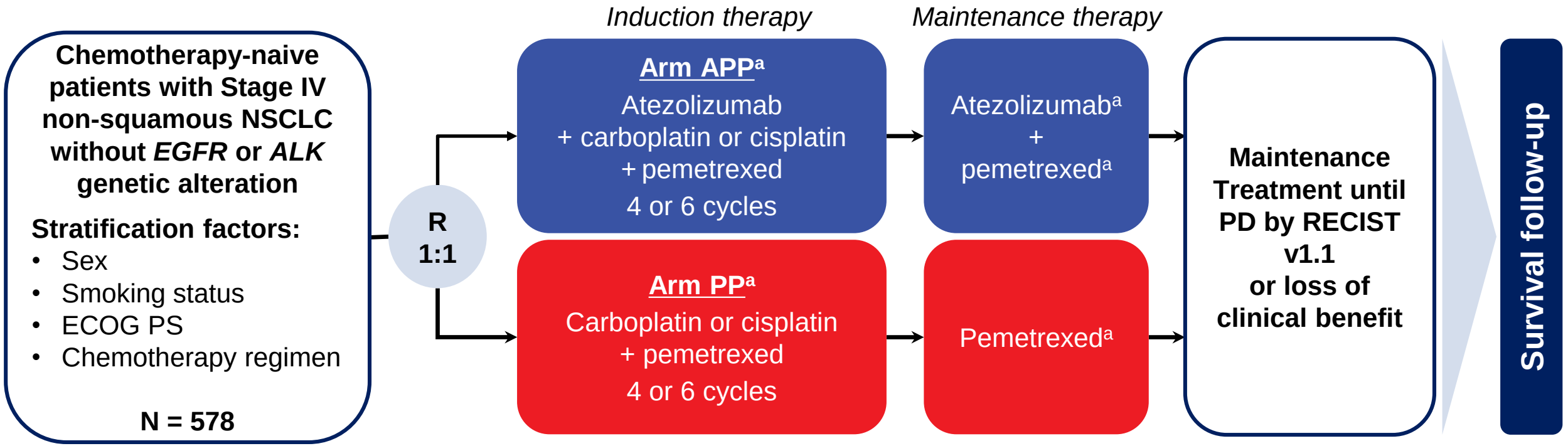
Carbo Pemetrexate +/- Pembro	ALL PD-L1 / Nonsquam.	47.6% vs 18.9%	HR = 0.52, p<0.01	HR=0.49, p<0.01
Carbo pacli/Nab-Pacli +/- Pembro	ALL PD-L1 / Squamous	58.4% vs 35%	HR=0.56, p<0.01	HR=0.64, p<0.01
Carbo, Pacli, beva +/- Atezo	ALL PD-L1, Nonsquam.	64% vs 48%	HR=0.62, p<0.01	Positive
Carbo, nab-pacli +/- Atezo	ALL PD-L1, Nonsquam.	49.2% vs 31.9%	HR=0.64, p<0.0001	HR=79, P<0.033
Carbo, Nab-Pacli +/- Atezo	ALL PD-L1, Squamous	49% vs 41%	HR=0.74, p<0.0004	Immature
Carbo/cis + pemetrexed +/- Atezo	ALL PD-L1, Nonsquam.	47% vs 32%	HR, 0.60, p<0.0001	HR=0.81,p=.0797

Reck et al NEJM 2016, Gandhi et al NEJM 2018, Lopes et al ASCO 2018, Reck et al ESMO immuno 2017, Kowanetz et al AACR 2018, Paz-Ares et al ASCO 2018, Socinski et al ASCO 2018, Hellman et al NEJM 2018, Carbone et al NEJM 2017

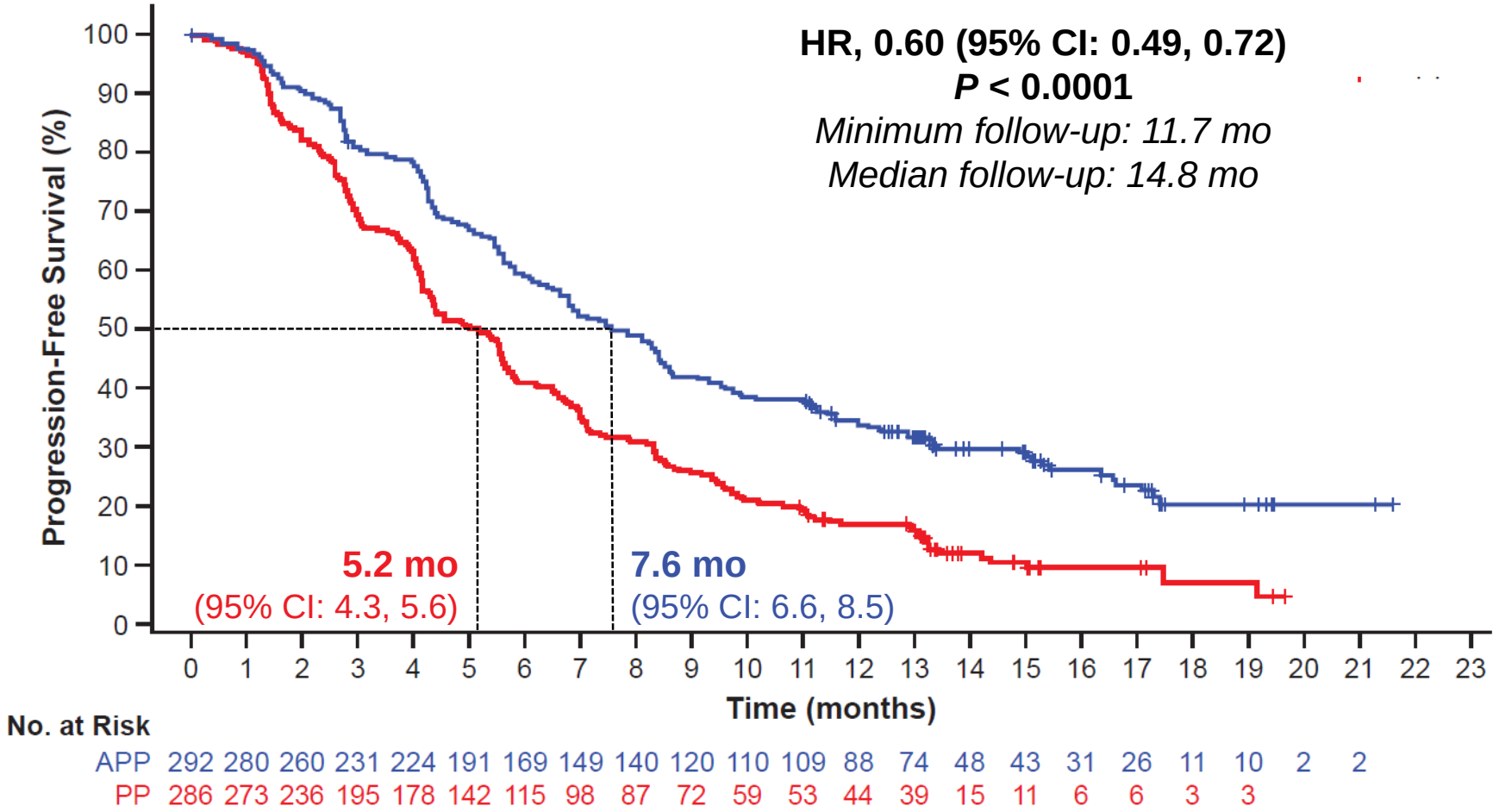
IMpower132 study design



APP, atezolizumab + carboplatin/cisplatin + pemetrexed; PP, carboplatin/cisplatin + pemetrexed.
[a] Atezolizumab: 1200 mg IV q3w; carboplatin: AUC 6 mg/mL/min IV q3w; cisplatin: 75 mg/m^2 IV q3w; pemetrexed: 500 mg/m^2 IV q3w.
[b] Biomarker-evaluable tissue not mandatory for enrolment and was available from 60% of patients. NCT02657434.
Data cutoff: May 22, 2018.

- Co-primary endpoints: INV-assessed PFS and OS
- Secondary endpoints: INV-assessed ORR and DOR, PRO and safety measures
- Exploratory analyses: clinical and biomarker[b] subgroup analyses

PFS in the ITT population[1]

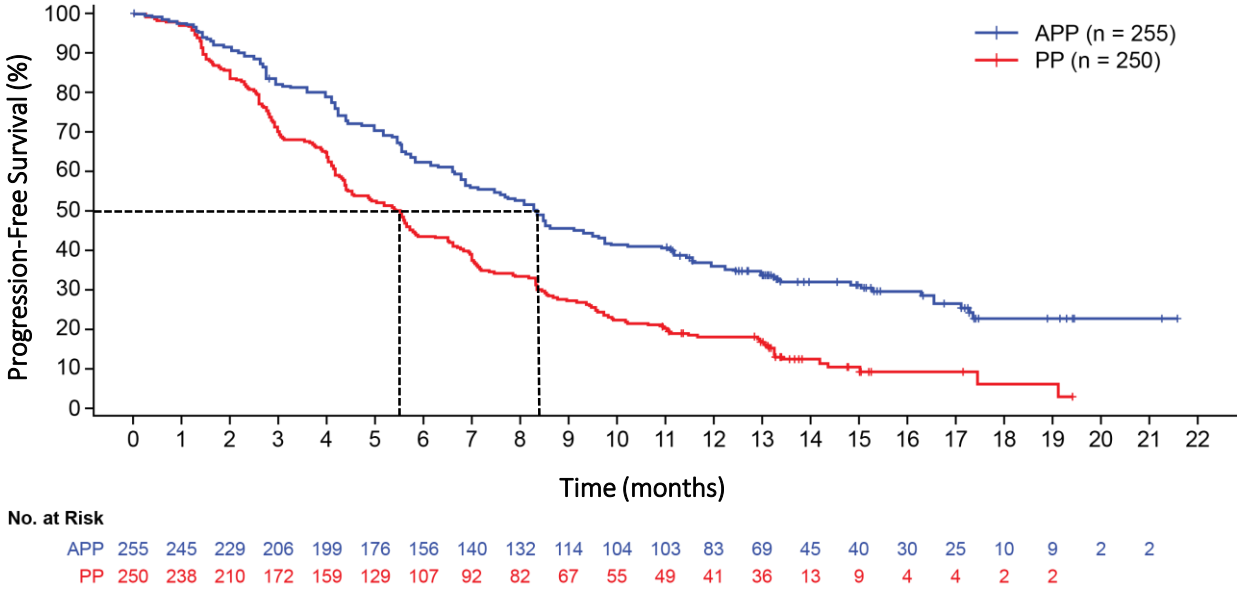


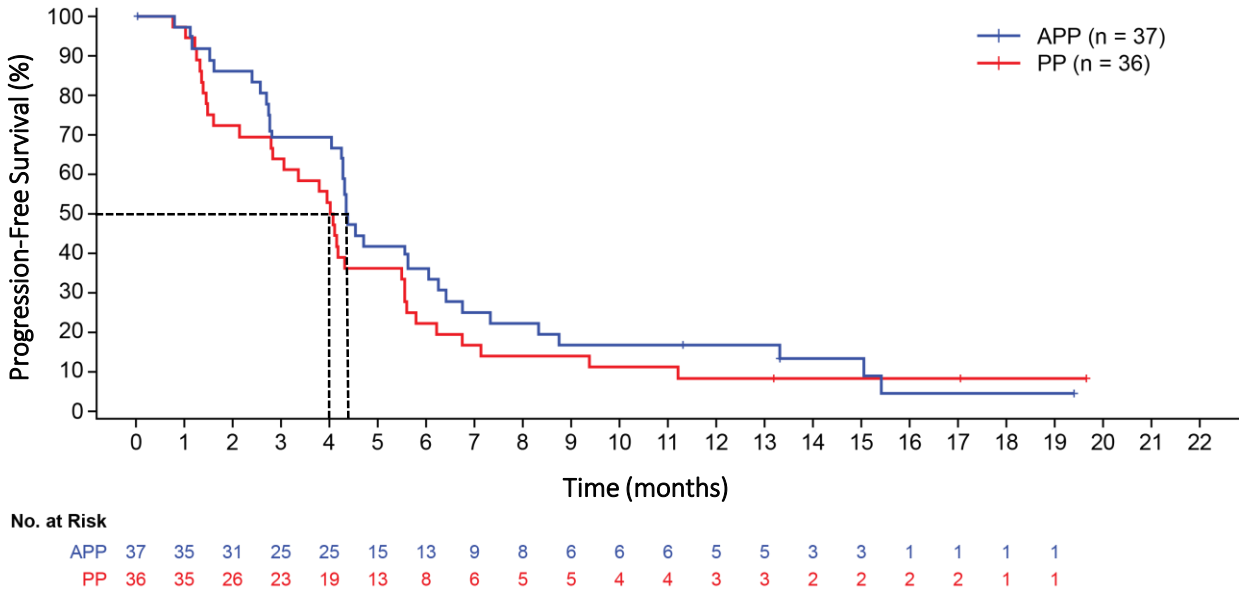
	APP	PP
6-mo PFS, %	59%	41%
12-mo PFS, %	34%	17%
ORR, %	47%	32%
CR	2%	1%
PR	45%	32%
Median DOR, mo	10.1	7.2
Ongoing response, %	42%	30%

APP, atezolizumab + carboplatin/cisplatin + pemetrexed; PP, carboplatin/cisplatin + pemetrexed.
Data cutoff: May 22, 2018.
1. Papadimitrakopoulou VA, et al. WCLC, 2018.

PFS in patients without/with liver metastases

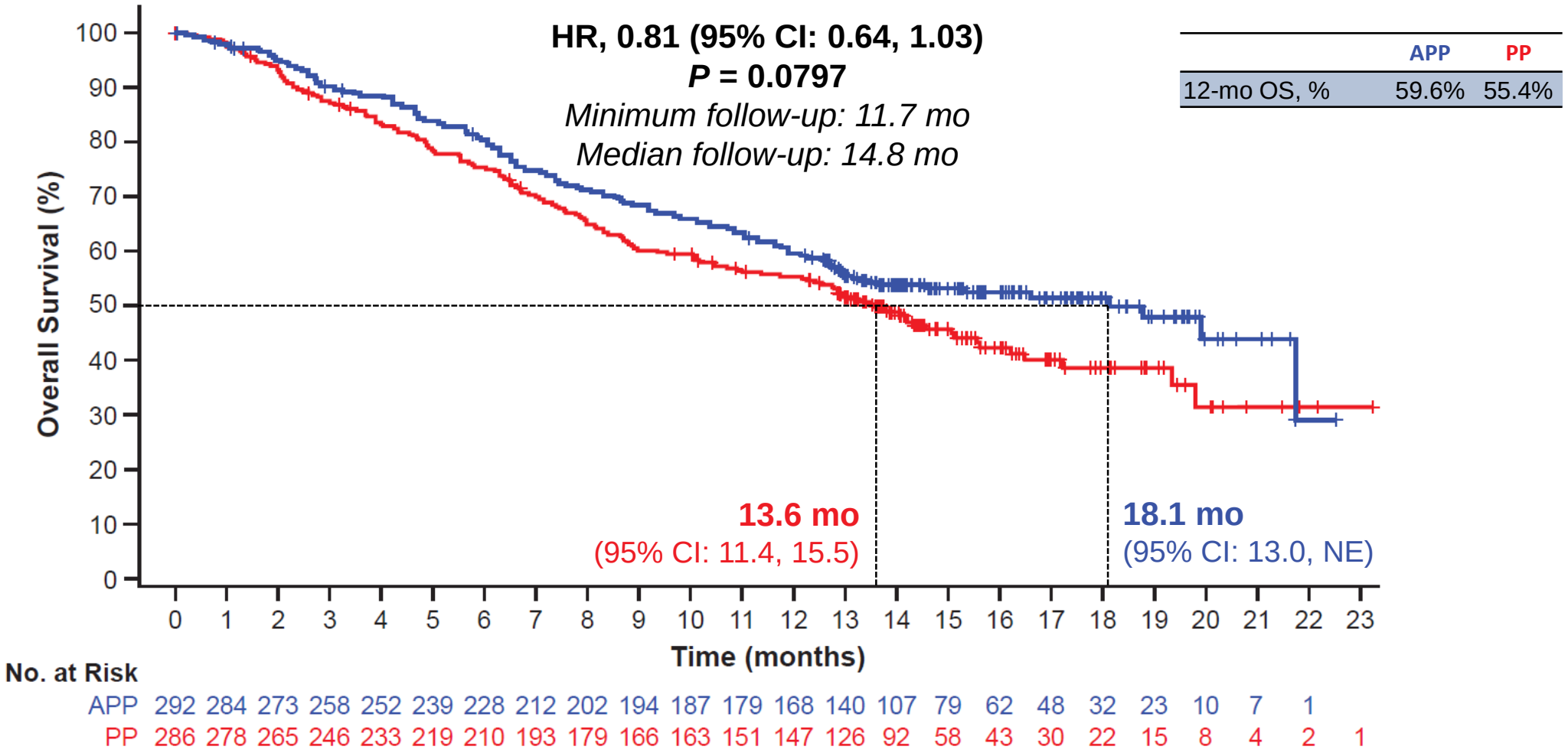
	Patients without liver metastases		Patients with liver metastases	
	APP	PP	APP	PP
Median PFS (95% CI), mo	8.4 (7.0, 9.5)	5.5 (4.4, 5.9)	4.4 (4.2, 6.0)	4.0 (2.8, 5.5)
HR (95% CI)	0.56 (0.46, 0.69)		0.77 (0.47, 1.25)	





APP, atezolizumab + carboplatin/cisplatin + pemetrexed; PP, carboplatin/cisplatin + pemetrexed.
Data cutoff: May 22, 2018.

Interim OS analysis in the ITT population[1]



Papadimitrakopoulou VA. WCLC, 2018.

Discussion… (no conclusion)

- **Paul Valéry : « Le simple est toujours faux. Ce qui ne l'est pas est inutilisable. »** (*Œuvres II*, 1942)

- **What is simple?**

  - PD-L1 ≥ 50% (all NSCLC) => Pembrolizumab monothérapie (for 1-49% mono insufficient)
  - High TMB (all NSCLC) => Nivolumab + Ipilimumab (if test available and standardized)

- **What is a little less simple**

  - PD-L1: 1-49% => Carbo - pacli/Nab-pacli - Pembro in Squamous

    Carbo - Pemetrexed - Pembro in Non-squamous

    or ?

    Carbo – Pacli - Beva – Atezo in Non Squamous (EGFR/ALK, liver mets)

    Carbo – Nab-pacli - Atezo in Non-squamous (pos. study)

    Carbo/cis - pemetrexed – Atezo Non-squamous (OS = NS)

    Carbo – Nab-pacli - Atezo in Squamous (OS immature)

- **What is a little less simple**

  - PD-L1: < 1% => Carbo - pacli/Nab-pacli - Pembro in Squamous (HR 61, high RR)

    Carbo - Pemetrexed - Pembro in Non-squamous (HR 59, high RR)
    Chemo alone Non-squamous

    or ?

    Carbo – Pacli - Beva – Atezo in Non Squamous
    (EGFR/ALK, liver mets)

    Carbo – Nab-pacli - Atezo in Non-squamous (pos. study)

    Carbo/cis - pemetrexed – Atezo Non-squamous (OS = NS)

    Carbo – Nab-pacli - Atezo in Squamous (OS immature)