VIII Simpósio Internacional Câncer de PULMÃO

13 e 14 de março de 2020

Hotel Intercontinental

First Line Immunotherapy When and How

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Professor

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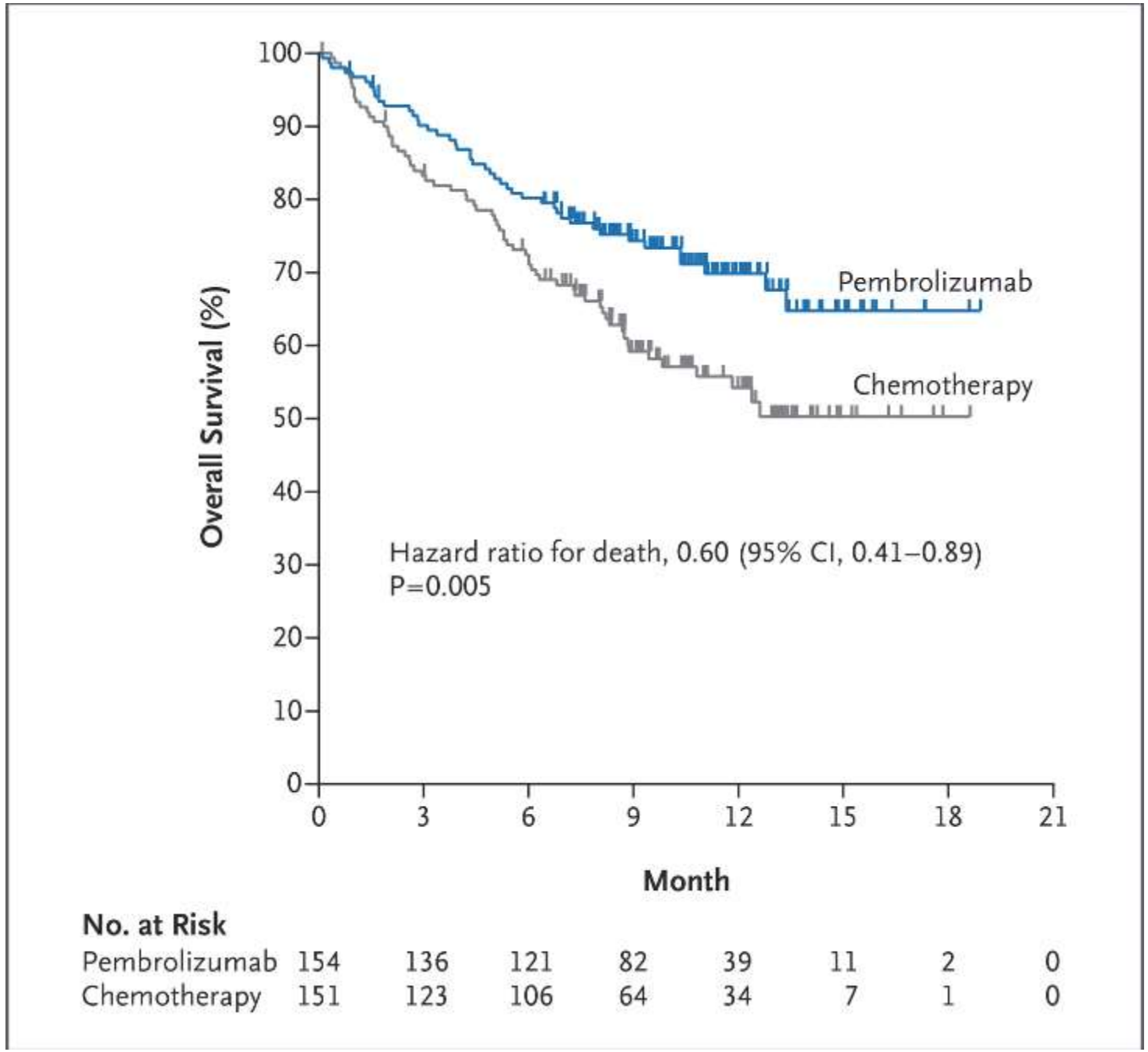
Agenda

- Immunotherapy alone
- Chemo+immunotherapy
- Combination immunotherapy

KEYNOTE-024

- Randomized trial of first line pembrolizumab vs platinum doublet chemotherapy in tumors expressing PD-L1 ≥ 50% (30% of all patients evaluated)
- 305 patients randomized
- Primary objective was progression-free survival and patients randomized to chemotherapy had the option of crossing over to pembrolizumab
- High cross-over rate: of the 106 patients who discontinued therapy 66 crossed over to pembrolizumab

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



No. at Risk

Pembrolizumab	154	136	121	82	39	11	2	0
Chemotherapy	151	123	106	64	34	7	1	0

IMPOWER 110

- 554 patients randomized to atezolizumab vs histology based chemotherapy
- Patients randomized to atezo received maintenance therapy as well as those with non-squamous histology (pemetrexed)
- Survival analysis for TC3 (PD-L1 expression ≥50%) and IC3 (tumor infiltrating immune cells ≥ 10%)
- Median follow-up 15.7 months
- Overall Survival: Atezolizumab 20.2 months and chemotherapy 13.1 months

ESMO 2019- Barcelona

Pembrolizumab vs Platinum-Based Chemotherapy as First-Line Therapy for Advanced/Metastatic NSCLC With a PD-L1 TPS ≥1%: Open-Label, Phase 3 KEYNOTE-042 Study

Gilberto Lopes,[1] Yi-Long Wu,[2] Iveta Kudaba,[3] Dariusz M Kowalski,[4] Byoung Chul Cho,[5] Hande Z Turna,[6] Gilberto Castro, Jr,[7] Vichien Srimuninnimit,[8] Konstantin K. Laktionov,[9] Igor Bondarenko,[10] Karou Kubota,[11] Gregory M Lubiniecki,[12] Jin Zhang,[12] Debra Kush,[12] Tony Mok[13]

[1]Sylvester Comprehensive Cancer Center at the University of Miami, Miami, FL, USA; [2]Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guandong, China; [3]Riga East Clinical University - Latvian Oncology Center, Riga, Latvia; [4]The Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; [5]Yonsei Cancer Center, Seoul, South Korea; [6]Instanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey; [7]Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil; [8]Siriraj Hospital, Bangkok, Thailand; [9]NN Blokhin Russian Cancer Research Center, Moscow, Russia; [10]Dnipropetrovsk Medical Academy, Dnipro, Ukraine; [11]Nippon Medical School Hospital, Tokyo, Japan; [12]Merck & Co., Inc., Kenilworth, NJ, USA; [13]The Chinese University of Hong Kong, Shatin, Hong Kong PRC

KEYNOTE-042 Study Design

Key Eligibility Criteria

- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 TPS ≥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 (≥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 ≥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%

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

Median (95% CI)
20.0 mo (15.4-24.9)
12.2 mo (10.4-14.2)

Overall Survival: TPS ≥20%

	Events	HR (95% CI)	P
Pembro	230 (55.7%)	0.77 (0.64-0.92)	0.0020
Chemo	266 (65.7%)		

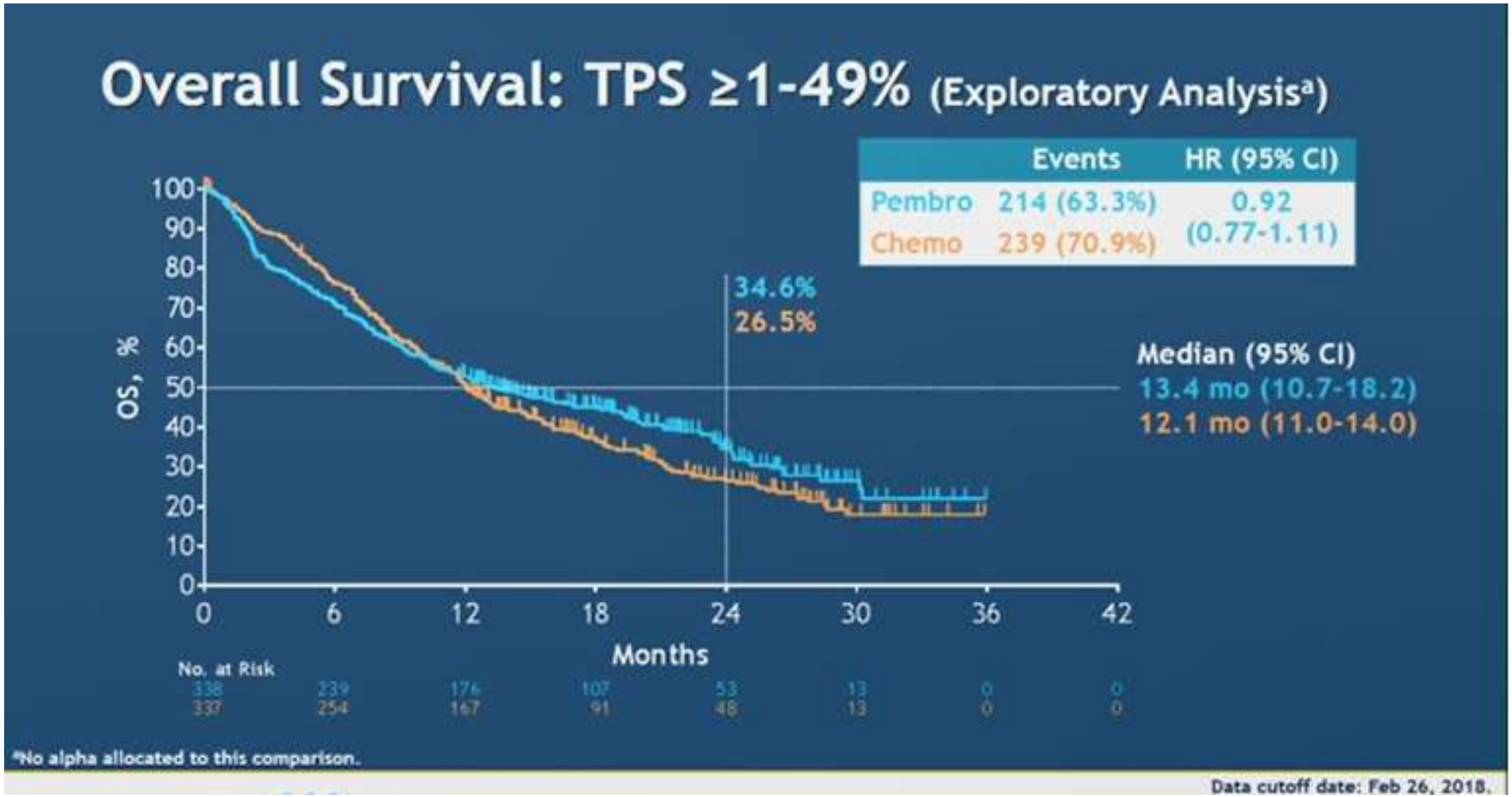
Median (95% CI)
17.7 mo (15.3-22.1)
13.0 mo (11.6-15.3)

Overall Survival: TPS ≥1%

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

Median (95% CI)
16.7 mo (13.9-19.7)
12.1 mo (11.3-13.3)

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



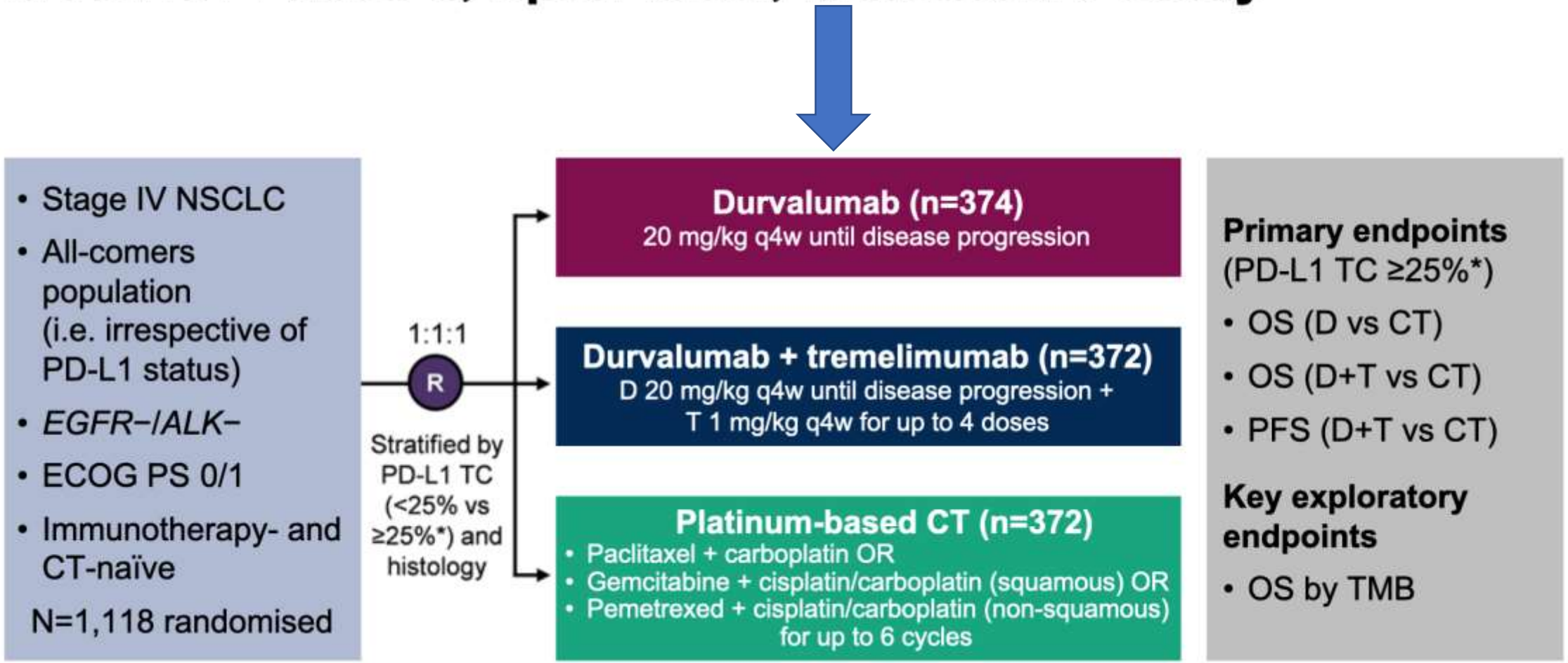
[a]No alpha allocated to this comparison.

Data cutoff date: Feb 26, 2018.

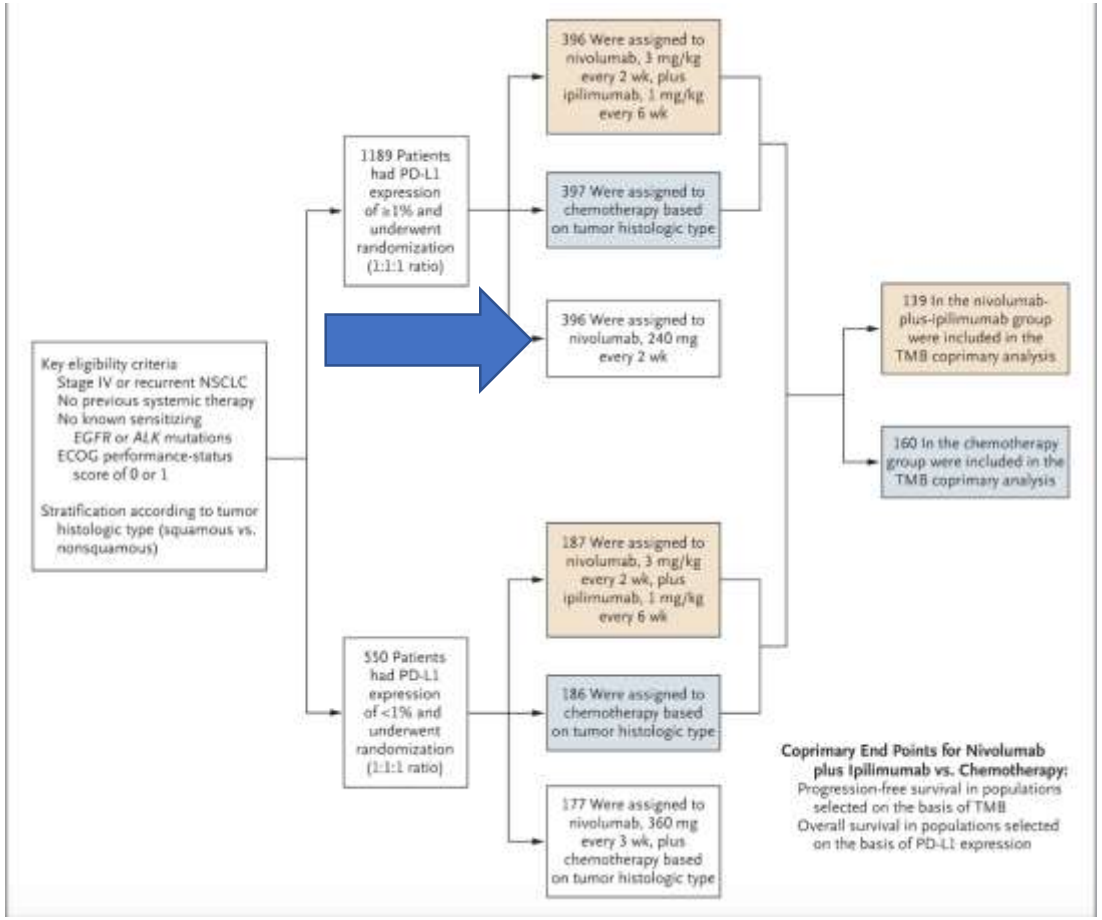
Failed trials

- Durvalumab as first line therapy: MYSTIC trial
- Nivolumab as first line therapy: CHECKMATE 227
- Pembrolizumab in 1-49%: KEYNOTE 042

MYSTIC: Phase 3, open-label, multicentre study



CHECKMATE 227



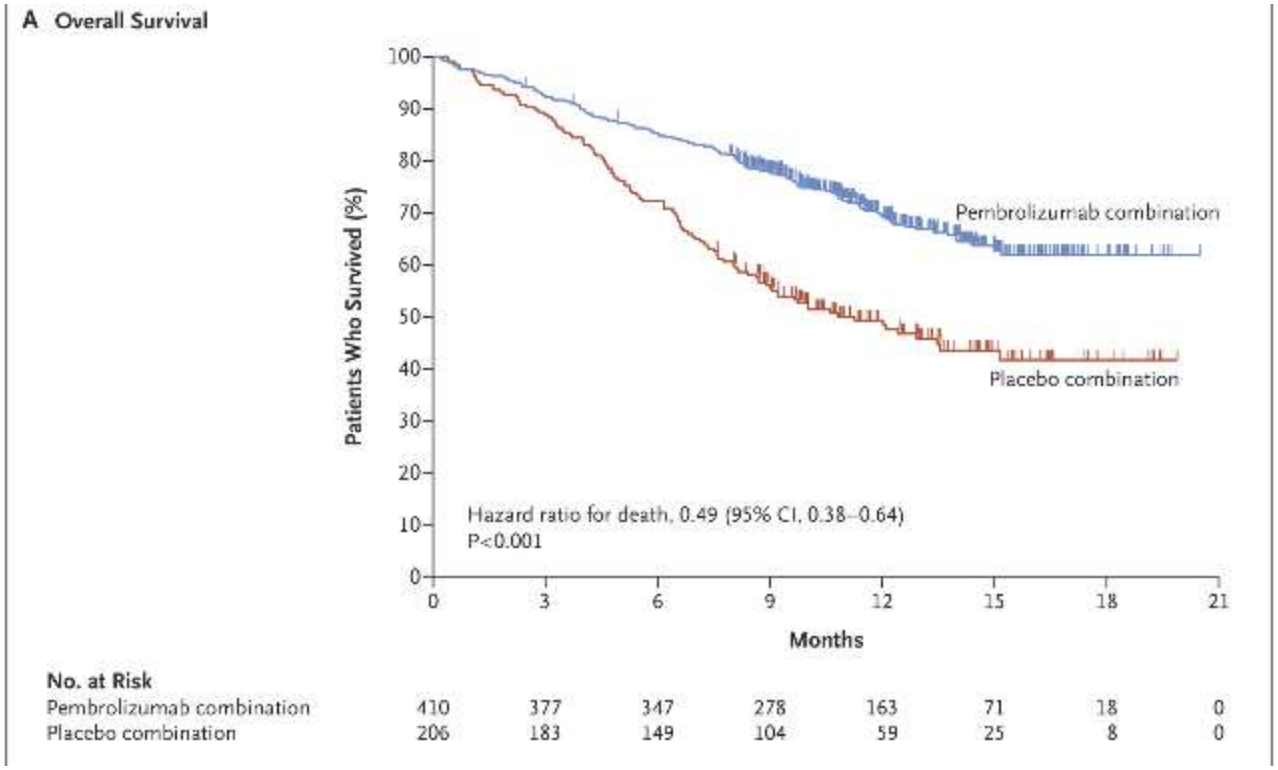
Chemo+Immunotherapy

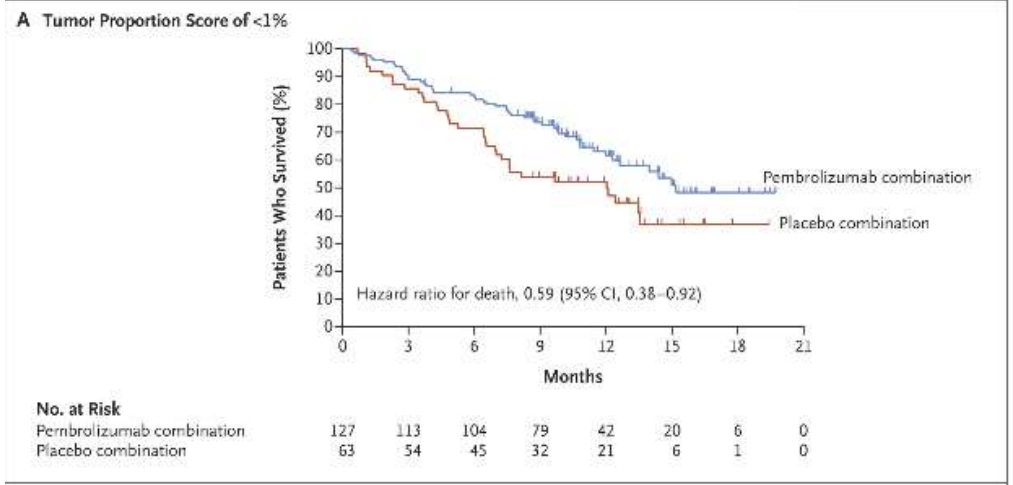
Keynote-189

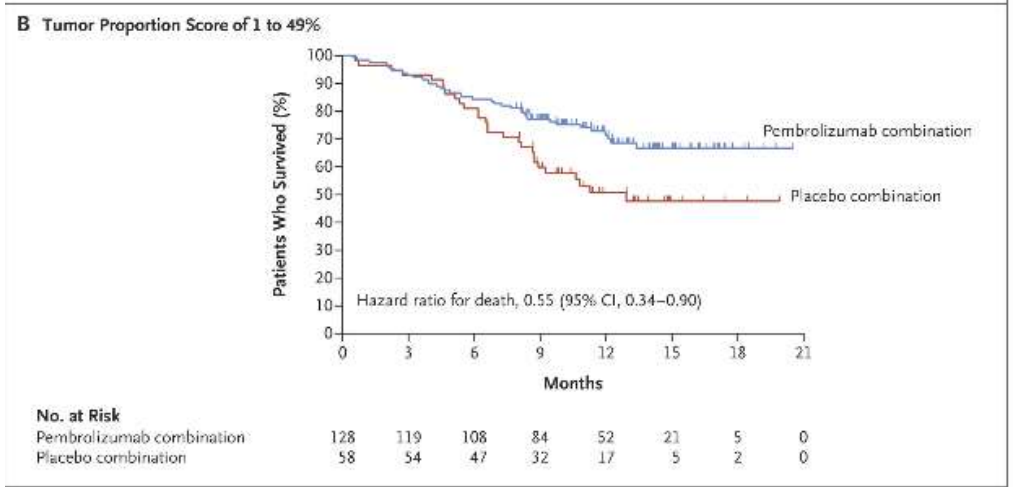
- Carboplatin or cisplatin+pemetrexed and randomized to pembrolizumab or placebo (2:1)
- 4 cycles of chemo followed by maintenance pemetrexed with pembrolizumab or placebo
- Placebo patients were eligible to cross over
- 616 patients randomized
- PD-L1 used for stratification but not as inclusion criteria

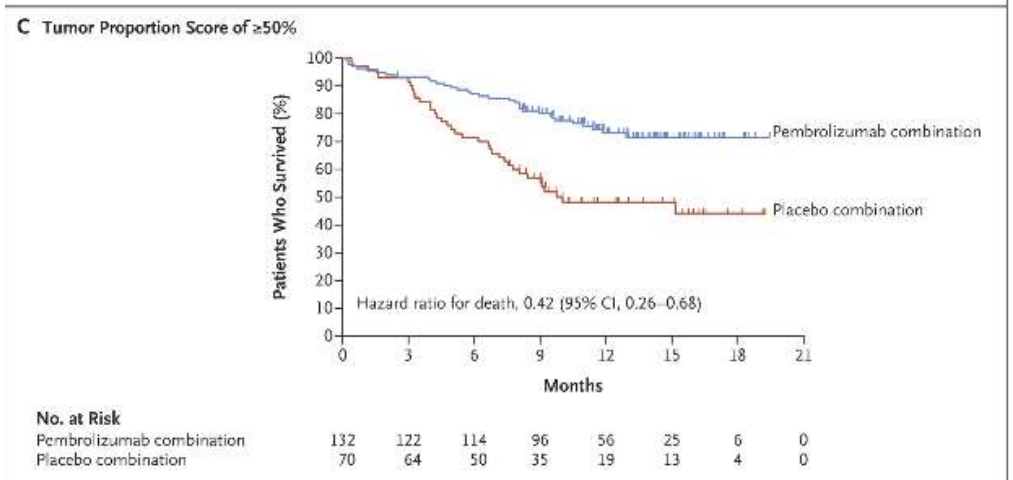
PD-L1 tumor proportion score — no. (%)¶		
<1%	127 (31.0)	63 (30.6)
≥1%	260 (63.4)	128 (62.1)
1–49%	128 (31.2)	58 (28.2)
≥50%	132 (32.2)	70 (34.0)
Could not be evaluated	23 (5.6)	15 (7.3)

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







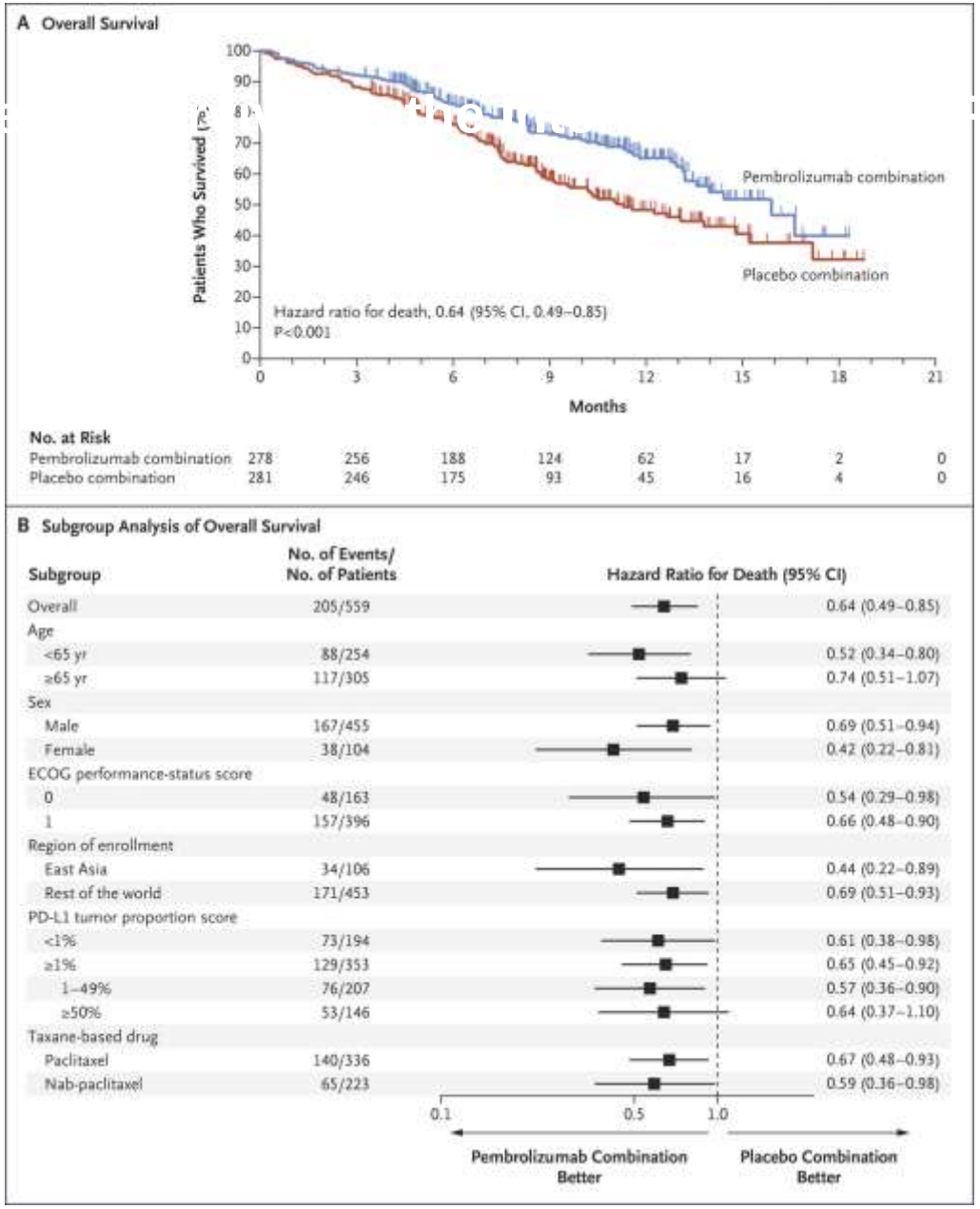


Ganghi L et al N Engl J Med 2018;378:2078-2092

Squamous cell carcinoma Keynote-407

- Squamous cell restricted trial
- Carboplatin+paclitaxel/nab-paclitaxel for 4 cycles
- Randomized to receive pembrolizumab or placebo
- Pembrolizumab or placebo maintenance
- Cross-over as part of design
- Primary objectives PFS and OS
- 559 patients randomized
- PD-L1 expression was present in 63% of tumors
- 43% of those who discontinued therapy on the control arm received PD-1 or PD-L1 agent as part of the trial (cross over) or off-study

ASCO 2018 Abstract 105

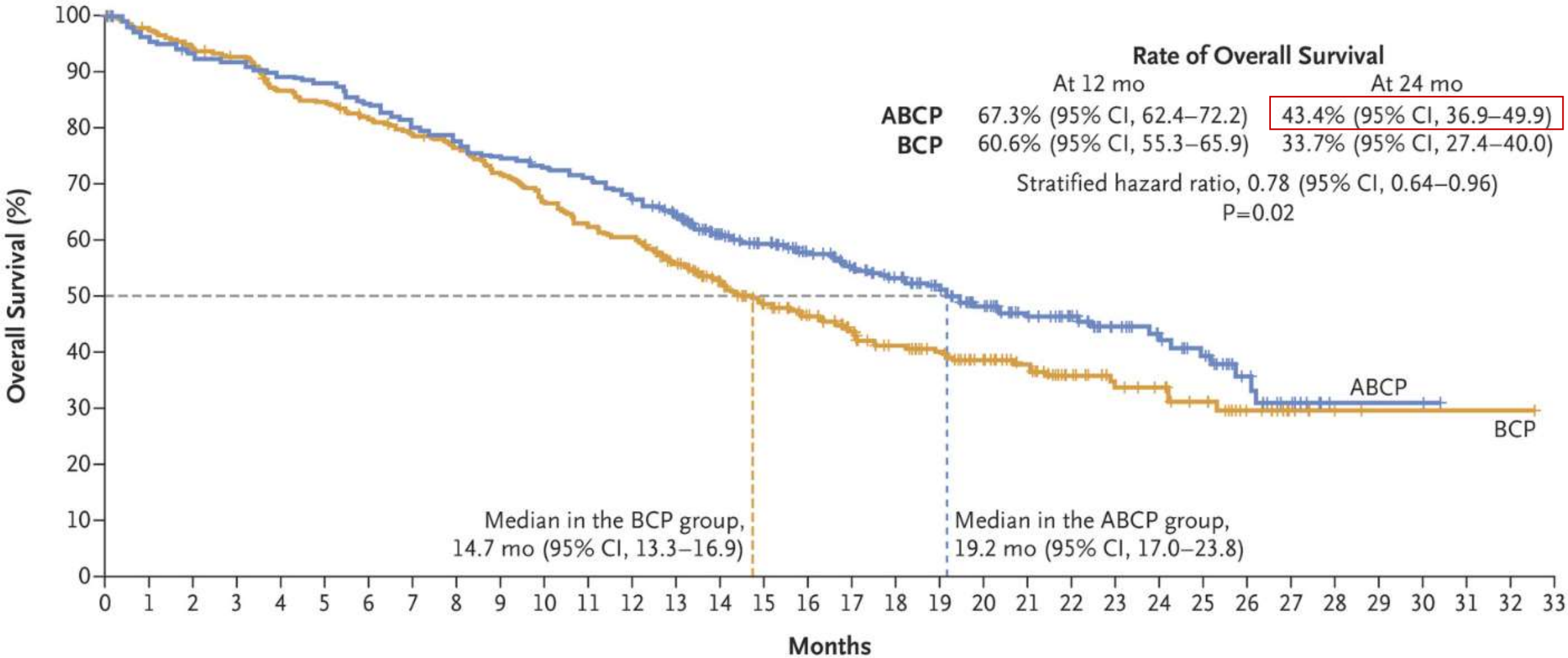


L Paz-Ares et al. N Engl J Med 2018;379:2040-2051.

IMPOWER 150

- 1202 patients with non-squamous NSCLC randomized between, carboplatin+paclitaxel+atezolizumab (A), carboplatin+paclitaxel+bevacizumab+atezolizumab (B) or CP+Bev (C)
- Maintenance with atezo (A), bev+atezo (B), or bev (C) depending on the arm
- OS HR of B vs C was 0.78 (p=0.016)
- HR of A vs C was 0.88 (p= 0.2)
- Grade 3/4 in B: 57%
- Grade 3/4 in C: 49%

J Clin Oncol 36, 2018 (suppl; abstr 9002)/NEJM online June 4th



No. at Risk

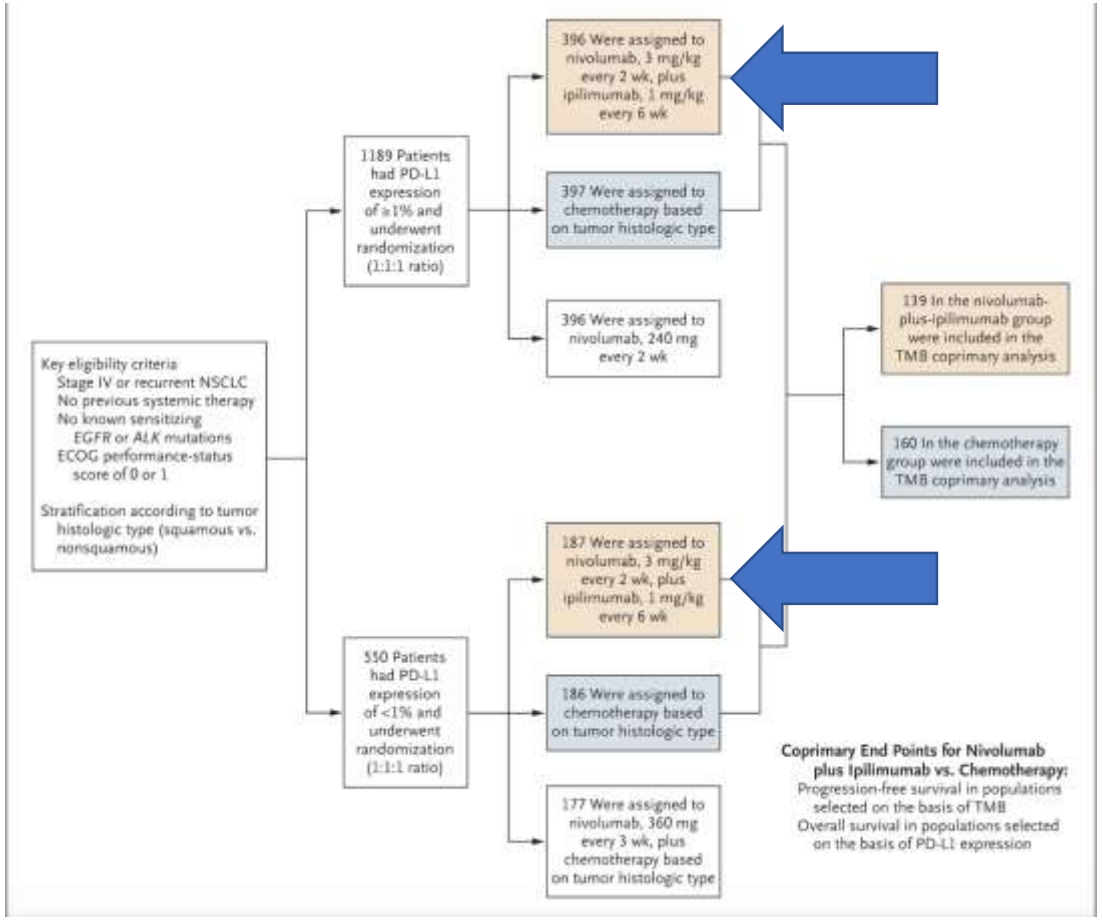
ABCP	359	339	328	323	314	310	296	284	273	264	256	250	235	218	188	167	147	133	119	103	84	66	57	41	34	28	16	9	2	2	2
BCP	337	326	315	308	287	280	268	255	247	233	216	203	196	174	152	129	115	101	87	77	66	56	40	32	29	22	13	6	3	1	1	1	1

Failed Trial

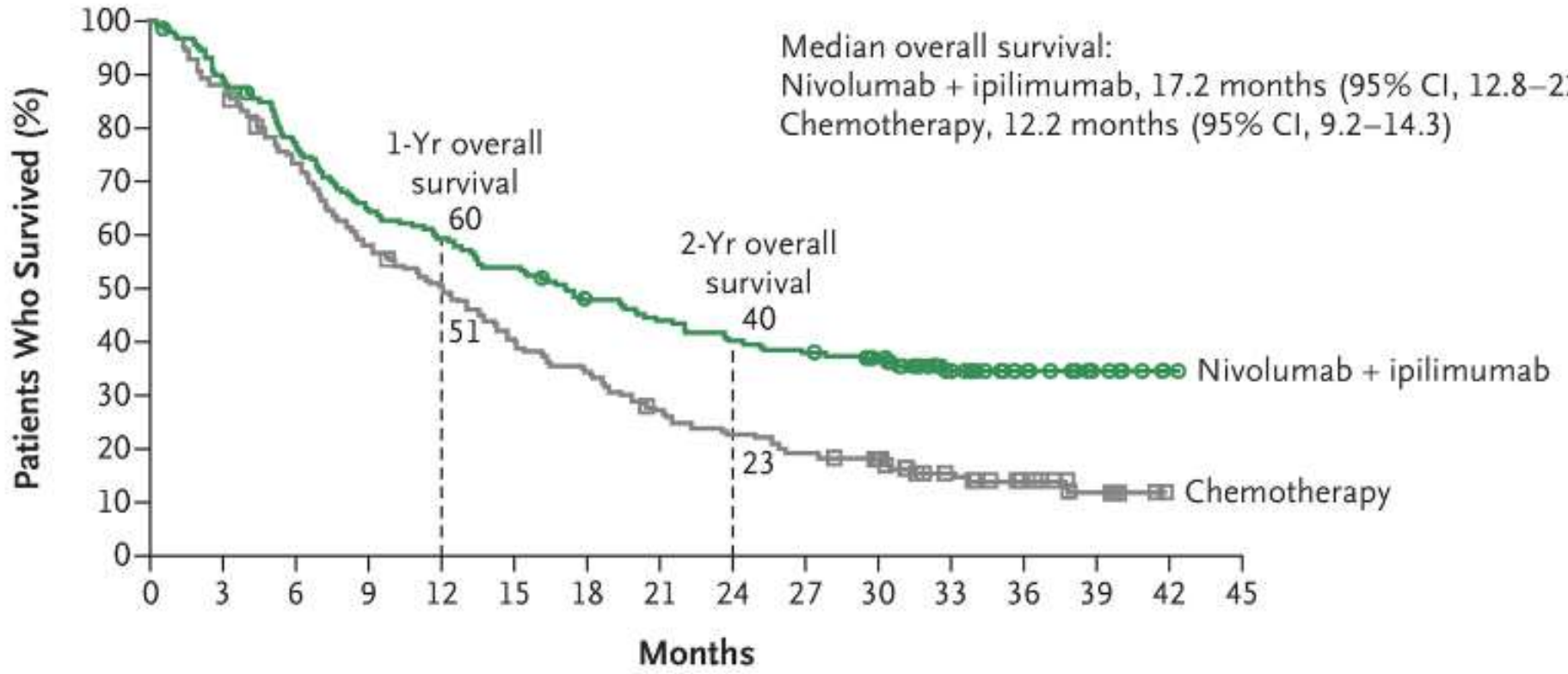
- CHECKMATE 227

Combination Immunotherapy

CHECKMATE 227



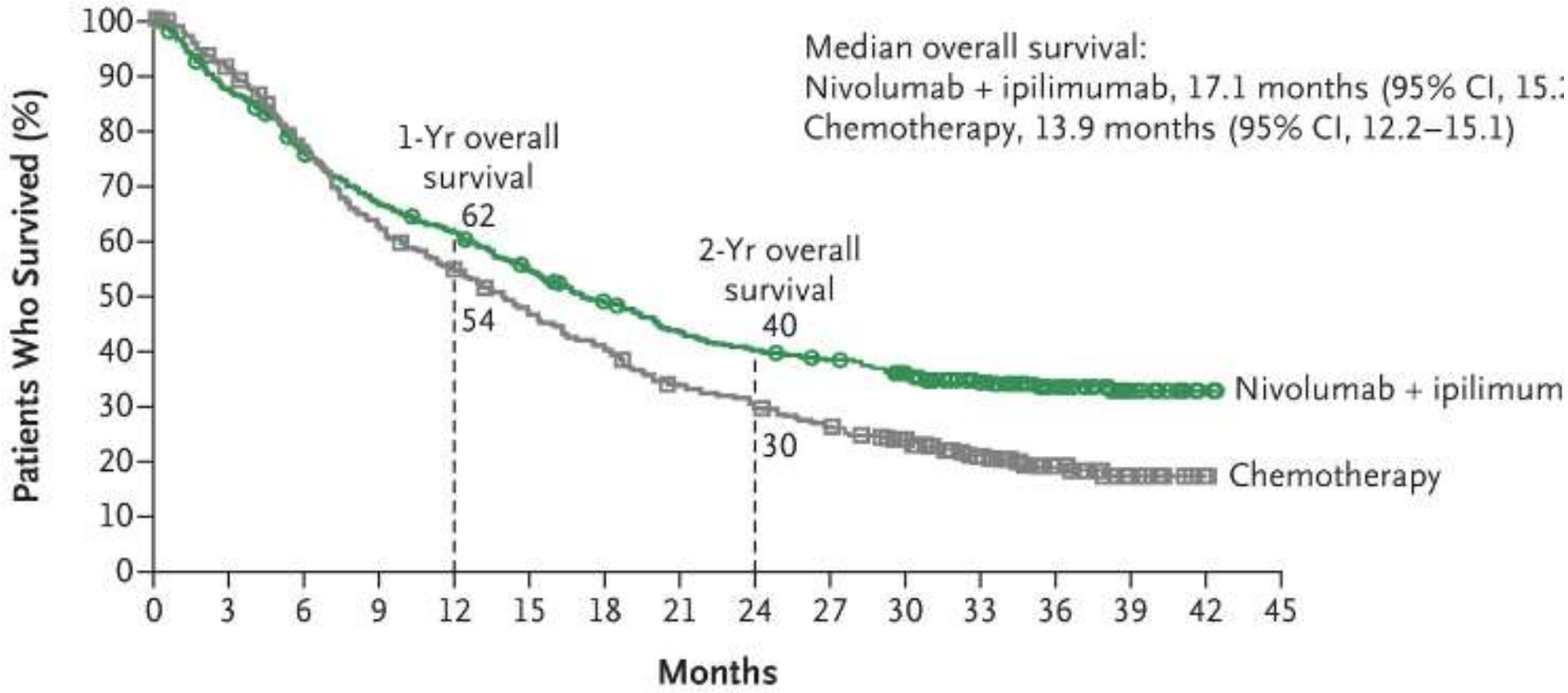
A **Overall Survival in Patients with a PD-L1 Expression Level of <1%**



No. at Risk

Nivolumab + ipilimumab	187	165	142	120	110	100	87	80	73	69	59	34	19	8	2	0
Chemotherapy	186	164	135	107	92	74	62	49	41	35	29	19	12	5	0	0

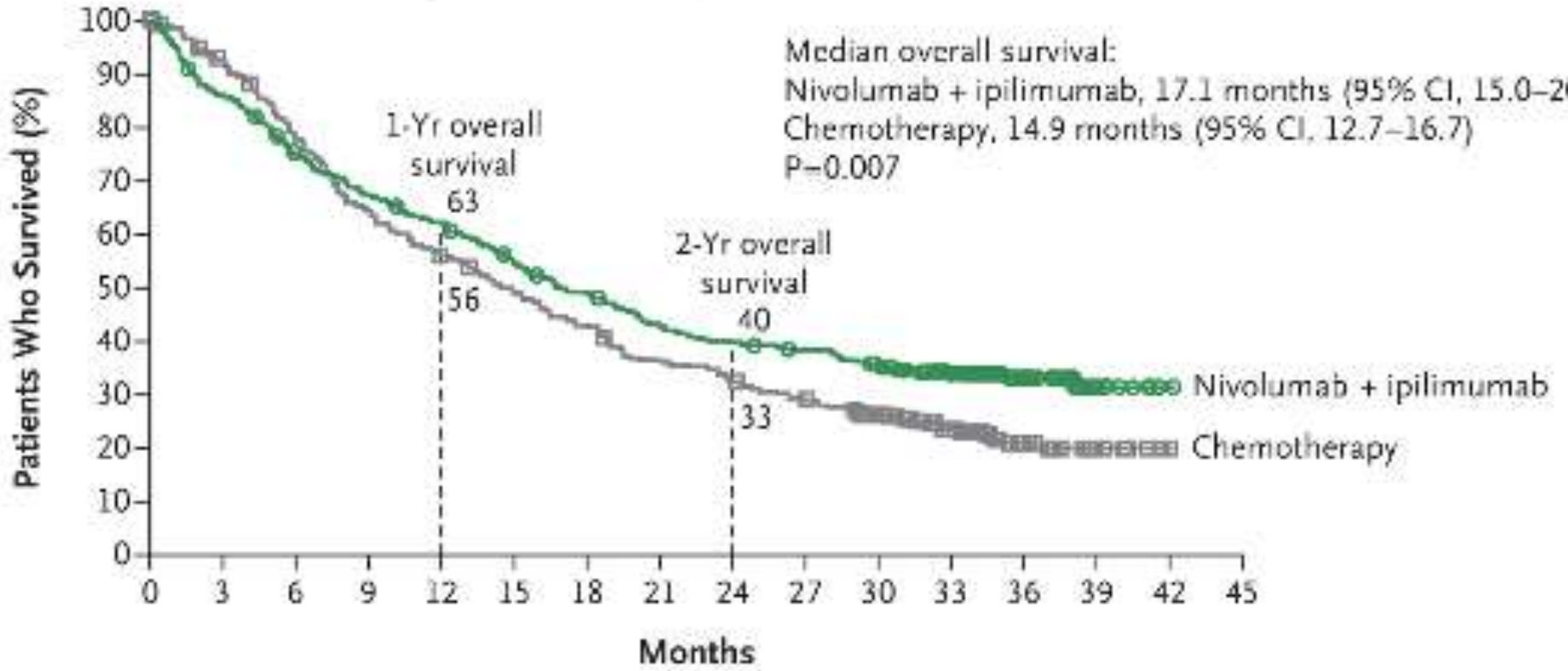
B **Overall Survival in All the Patients**



No. at Risk

Nivolumab + ipilimumab	583	506	437	384	354	312	277	245	226	214	188	125	60	17	3	0
Chemotherapy	583	522	441	357	310	264	228	190	167	147	122	76	34	11	1	0

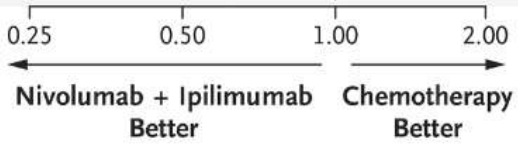
A Overall Survival in Patients with a PD-L1 Expression Level of 1% or More



No. at Risk

Nivolumab + ipilimumab	396	341	295	264	244	212	190	165	153	145	129	91	41	9	1	0
Chemotherapy	397	358	306	250	218	190	166	141	126	112	93	57	22	6	1	0

Subgroup	No. of Patients	Median Overall Survival (months)		Unstratified Hazard Ratio for Death (95% CI)
		Nivolumab + ipilimumab (N=583)	Chemotherapy (N=583)	
Randomized Groups				
PD-L1				
All randomized	1166	17.1	13.9	0.73 (0.64–0.84)
<1%	373	17.2	12.2	0.62 (0.49–0.79)
≥1%	793	17.1	14.9	0.79 (0.65–0.96)
Additional Exploratory Subgroup Analyses				
PD-L1				
1–49%	396	15.1	15.1	0.94 (0.75–1.18)
≥50%	397	21.2	14.0	0.70 (0.55–0.90)
Tumor mutational burden				
Low, <10 mut/Mb	380	16.2	12.6	0.75 (0.59–0.94)
High, ≥10 mut/Mb	299	23.0	16.4	0.68 (0.51–0.91)
PD-L1 and tumor mutational burden (mut/Mb) combined				
PD-L1 <1%				
Tumor mutational burden <10	111	15.5	13.0	0.69 (0.46–1.05)
Tumor mutational burden ≥10	86	20.4	11.2	0.51 (0.30–0.87)
PD-L1 ≥1%				
Tumor mutational burden <10	269	16.2	12.1	0.78 (0.59–1.02)
Tumor mutational burden ≥10	213	24.4	18.1	0.77 (0.54–1.09)
PD-L1 ≥50%				
Tumor mutational burden <10	125	18.1	8.1	0.67 (0.44–1.03)
Tumor mutational burden ≥10	111	NR	17.2	0.63 (0.37–1.07)



Tumor Tissue Specimens

Archival (or fresh) formalin-fixed, paraffin-embedded tumor tissue collected within 6 months prior to enrollment was sent to a third-party laboratory for determination of programmed death ligand 1 (PD-L1) status using the analytically and clinically validated approved immunohistochemical 28-8 pharmDx assay (Agilent Dako[1]), to assess PD-L1 expression on viable tumor cells.

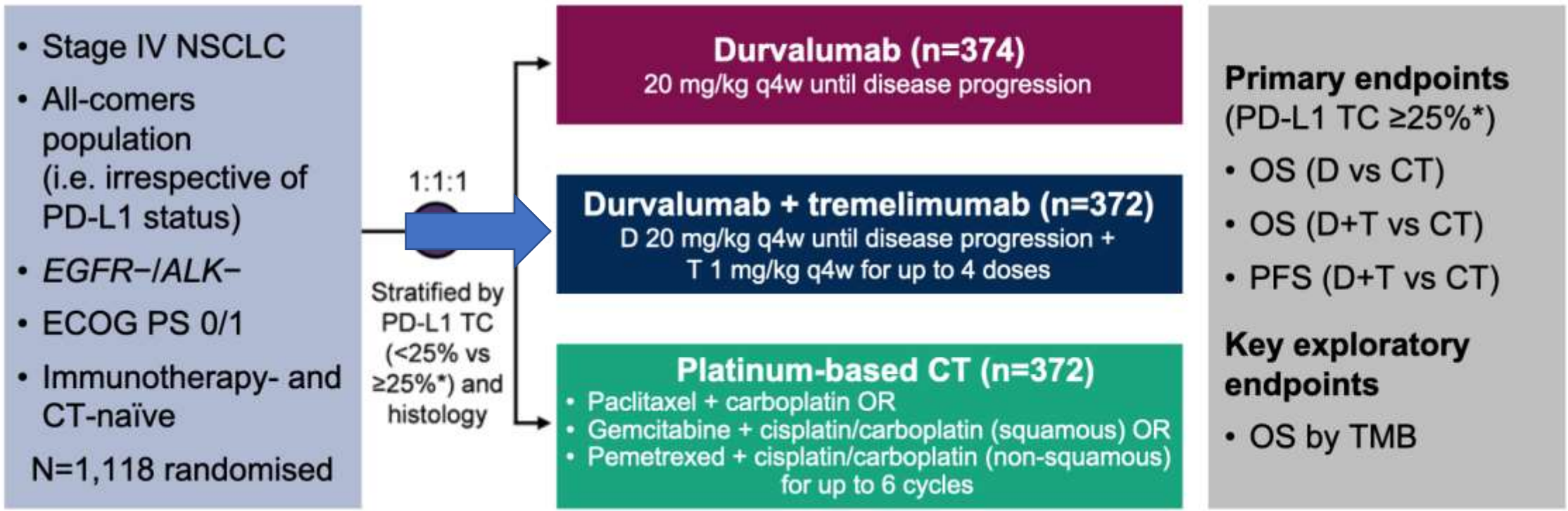
Tumor mutational burden (TMB) was assessed using the validated FoundationOne CDx™

Hellmann MD et al N Engl J Med on line Sept 28th 2019

Failed Trial

- MYSTIC

MYSTIC: Phase 3, open-label, multicentre study



Thank You

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Immunotherapy in Tumors with a Driver Mutation

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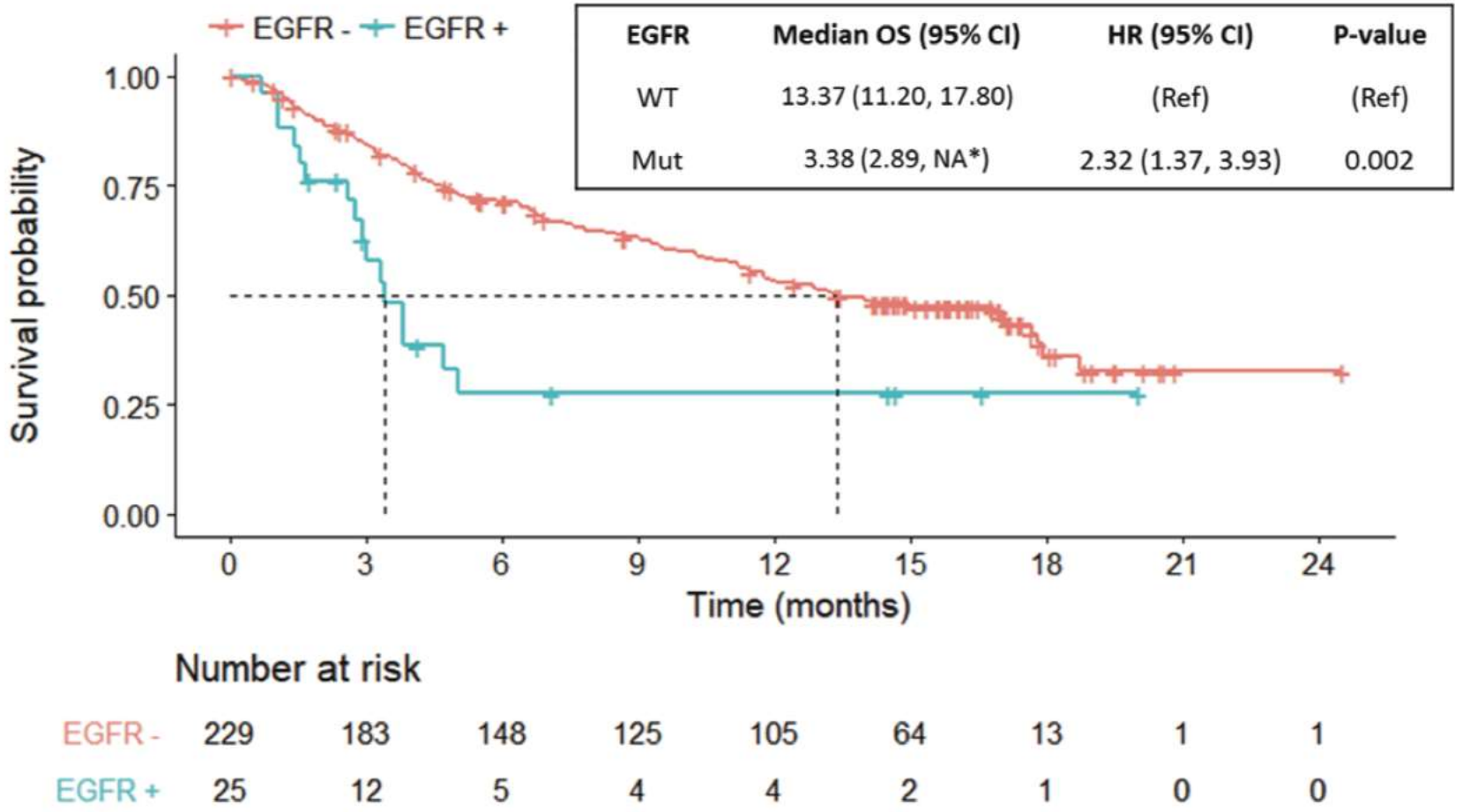
Agenda

- “Real life” outcomes of single agent immunotherapy in tumors with a driver mutation
- Risk of pneumonitis
- Immunotherapy and chemotherapy combination in EGFR mutated tumors
- Future directions

Immunotherapy in “Real Life”

- Canadian Data of 472 patients treated in the expanded access program for nivolumab
- Median age 66
- >50% receiving therapy on 4th line and beyond
- 73% nonsquamous histology
- 5% had EGFR mutated tumors while 1% had ALK translocation
- Median overall survival 12 months
- Randomized data CheckMate 017 (squamous) and 057 (nonsquamous) both second line vs docetaxel: 9.2 months and 12.2 months, respectively

JUERGENS, R. A. et al. Real-world benefit of nivolumab in a Canadian non-small-cell lung cancer cohort.**Current Oncology**, [S.l.], v. 25, n. 6, dec. 2018. ISSN 1718-7729

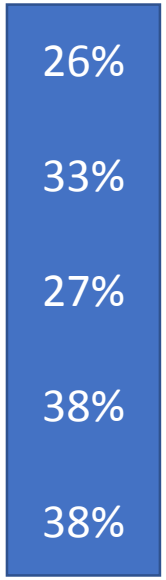


EGFR	Median OS (95% CI)	HR (95% CI)	P-value
WT	13.37 (11.20, 17.80)	(Ref)	(Ref)
Mut	3.38 (2.89, NA*)	2.32 (1.37, 3.93)	0.002

JUERGENS, R. A. et al. Real-world benefit of nivolumab in a Canadian non-small-cell lung cancer cohort.**Current Oncology**, [S.l.], v. 25, n. 6, dec. 2018. ISSN 1718-7729

Other Driver Mutations

- 107 patients with :
- BRAF V600 (n=26)
- BRAF non-V600 (n=18)
- HER-2 (n=23)
- MET (n=30)
- RET (n=9)
- Different immunotherapies
- Median lines of prior therapy: 1
- Median Survival: 16.2 months



Guisier F et al. in press JTO

Immunotherapy in Tumors with Driver Mutation: European Experience

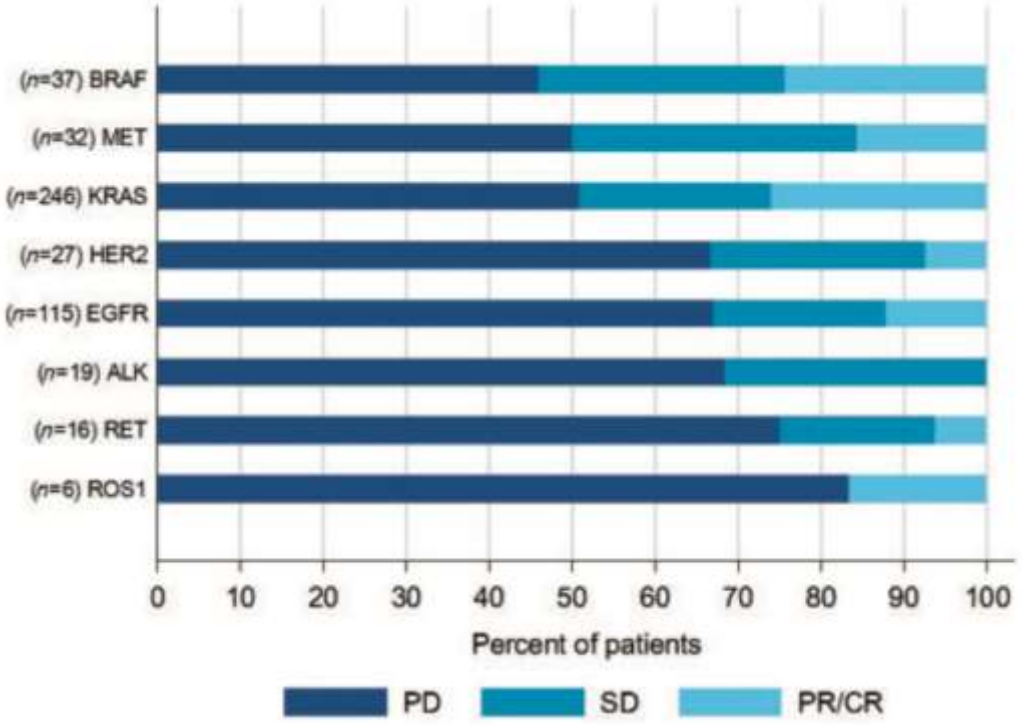
- 551 patients from 24 centers in 10 countries treated with single agent PD-1/PD-L1 antibody

Table 1. Clinical and biological description according to mutation type

	EGFR *N* = 125		KRAS *N* = 271		ALK *N* = 23		BRAF *N* = 43		ROS1 *N* = 7		HER2 *N* = 29		RET *N* = 16		MET *N* = 36	
Gender (*n*=551)																
Male	48	38.4%	141	52%	12	52.2%	24	55.8%	5	71.4%	15	51.7%	7	43.8%	21	58.3%
Female	77	61.6%	130	48%	11	47.8%	19	44.2%	2	28.6%	14	48.3%	9	56.3%	15	41.7%
Smoking (*n*=551)																
Never smoker	78	63.4%	12	4.6%	10	47.6%	11	26.2%	5	71.4%	14	51.9%	10	66.7%	8	23.5%
Former smoker	38	30.9%	168	64.6%	8	38.1%	22	52.4%	2	28.6%	12	44.4%	4	26.7%	15	44.1%
Current smoker	7	5.7%	80	30.8%	3	14.3%	9	21.4%	0	0%	1	3.7%	1	6.7%	11	32.4%
Missing	2		11		2		1				2		1		2	
Histological type (*n*=551)																
Adenocarcinoma	121	96.8%	262	96.7%	21	91.3%	40	93%	6	85.7%	28	96.6%	14	87.5%	34	94.4%
Squamous	1	0.8%	0	0%	0	0%	1	2.3%	0	0%	0	0%	0	0%	0	0%
Sarcomatoid	0	0%	1	0.4%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2.8%
Large cell carcinoma	0	0%	6	2.2%	1	4.3%	1	2.3%	0	0%	1	3.4%	1	6.3%	0	0%
Not specified/other/missing	3	2.4%	2	0.7%	1	4.3%	1	2.3%	1	14.3%	0	0%	1	6.3%	1	2.8%
Age at diagnosis (*n*=551)																
Median (year)	60		59		55		61		45		62		54.5		63	
Range (year)	33–80		30–83		30–73		42–75		42–67		31–77		29–73		4–82	

Mazieres et al Annals Oncol 30:1321-1328

Efficacy



Progression-Free Survival at 12 months

- KRAS: 25.6%
- EGFR: 6.4%
- ALK: 5.9%
- MET: 23.4%
- BRAF: 13.6%
- RET: 7%
- Excluding KRAS median PFS was 2.4 months

Mazieres et al Annals Oncol 30:1321-1328

Is there a role for single agent immunotherapy in tumors with EGFR and ALK mutations ?

YES

If patients are motivated and cost considerations are not an issue

Is there a role for single agent immunotherapy in tumors with KRAS mutations ?

YES

Not as clear in non-smoker KRAS mutations

Is there a role for single agent immunotherapy in tumors with other driver mutations ?

YES

Risk of pneumonitis with Osimertinib rechalenge

- After a break of > 6 months of no TKI, retreatment with TKIs may have a RR 20-30%
- However there an increased risk of pneumonitis if osimertinib is used after immunotherapy and that risk is time dependent
- < 3 months: 24%
- 3-12 months: 13%
- >12 months: 0%
- Small dataset of 41 patients

Schoenfeld et al Annals of Oncol 30:839-844

Can combination therapy improve the efficacy of immunotherapy in tumors with a driver mutation?

IMPOWER 150

- 1202 patients with non-squamous NSCLC randomized between, carboplatin+paclitaxel+atezolizumab (A), carboplatin+paclitaxel+bevacizumab+atezolizumab (B) or CP+Bev (C)
- Maintenance with atezo (A), bev+atezo (B), or bev (C) depending on the arm
- OS HR of B vs C was 0.78 (p=0.016)
- HR of A vs C was 0.88 (p= 0.2)
- Grade 3/4 in B: 57%
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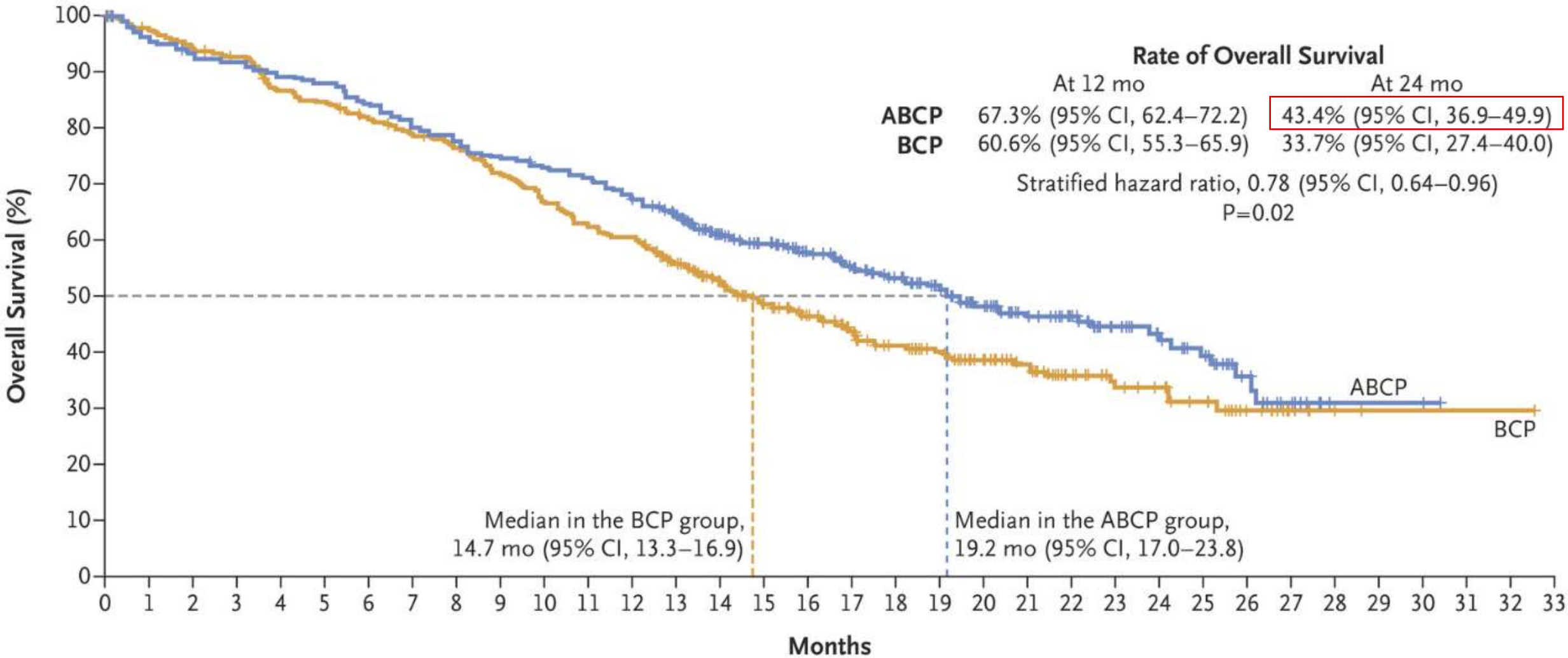
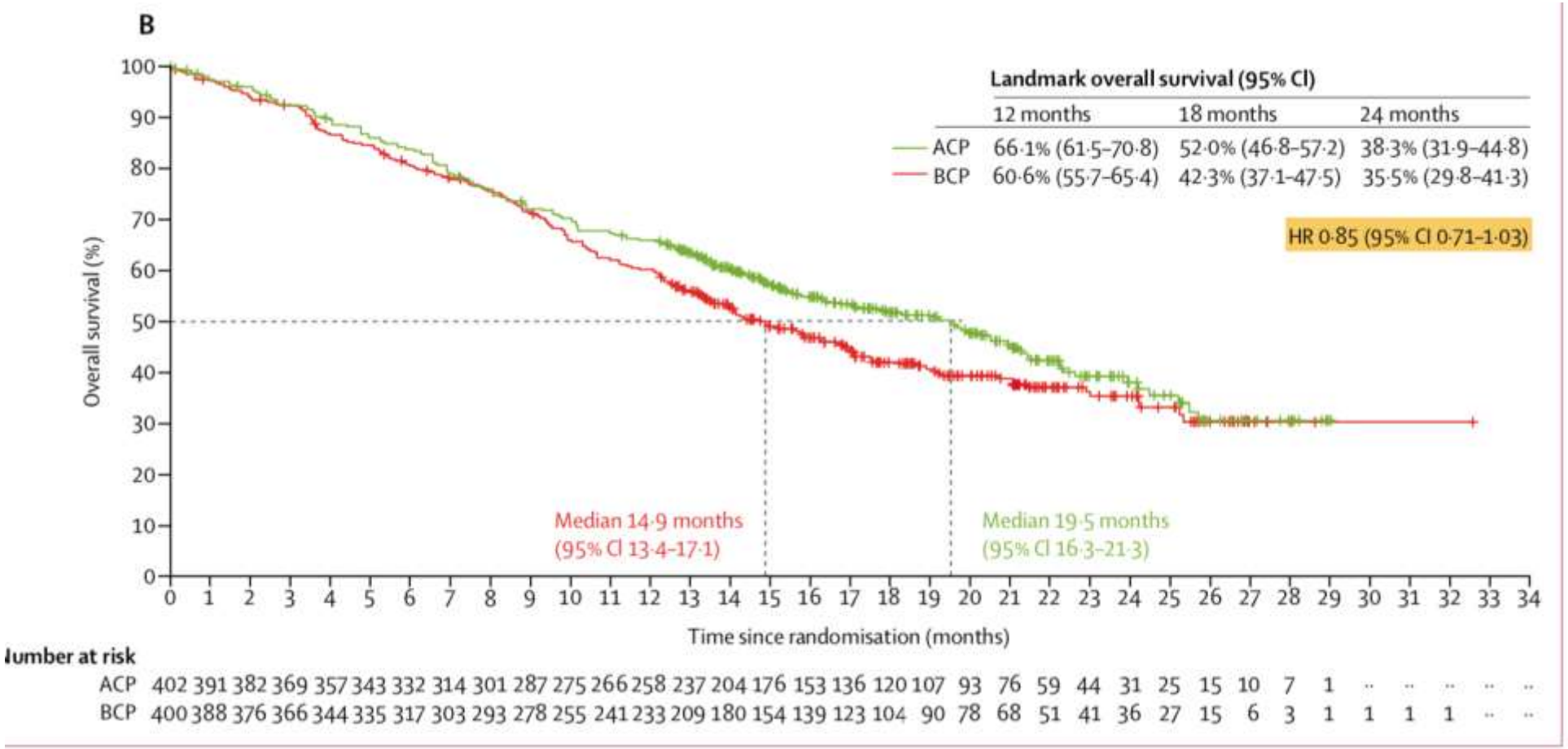


No. at Risk

ABCP	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
BCP	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



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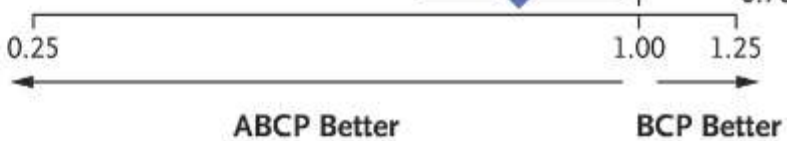
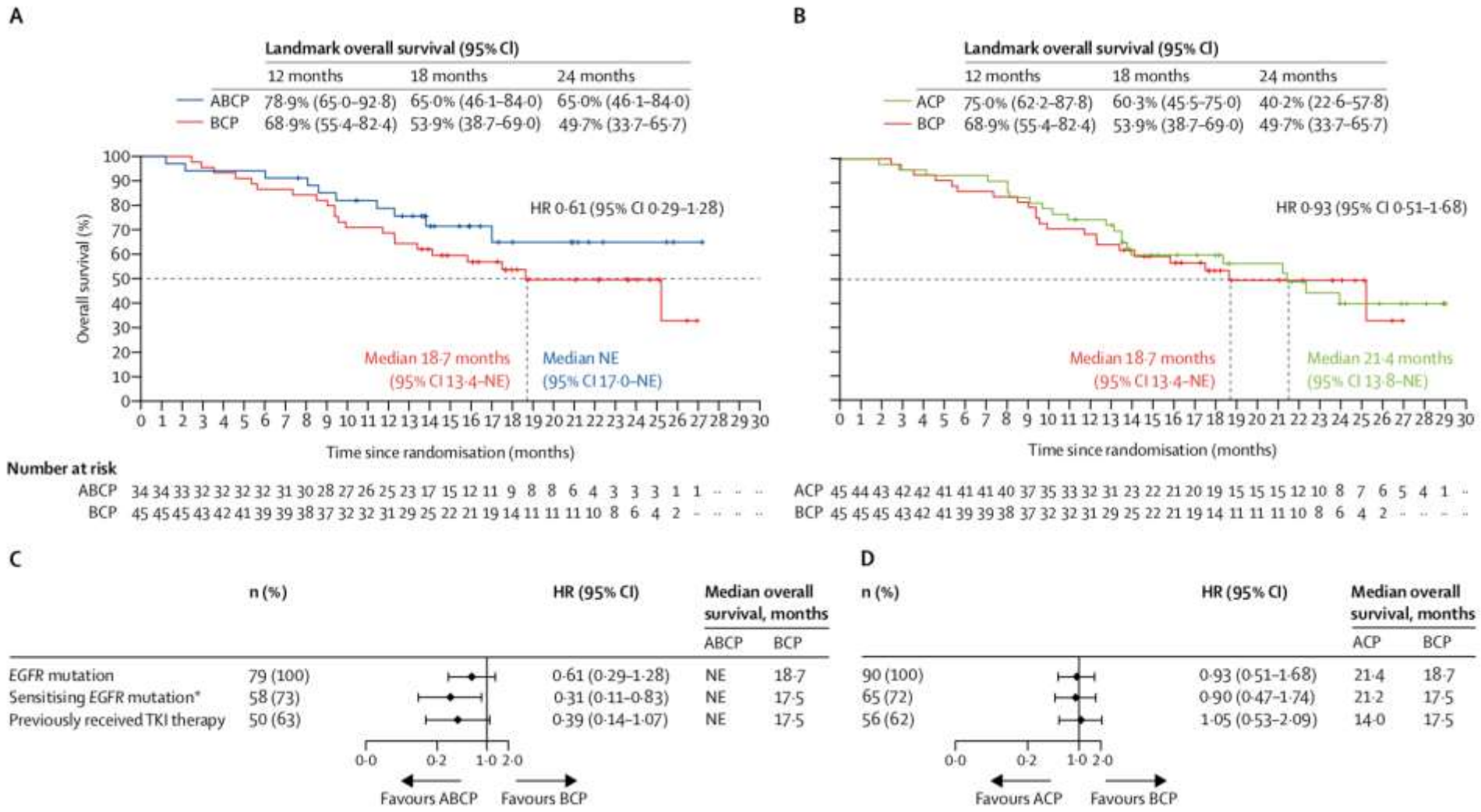
B Hazard Ratios for Disease Progression or Death in Biomarker Subgroups

Population	No. of Patients (%)	Median Progression-free Survival (mo)		Hazard Ratio (95% CI)
		ABCP	BCP	
ITT population	800 (100)	8.3	6.8	0.61 (0.52–0.72)
Patients with *EGFR* or *ALK* genetic alternations	108 (14)	9.7	6.1	0.59 (0.37–0.94)
WT population	692 (87)	8.3	6.8	0.62 (0.52–0.74)
PD-L1 subgroups (in the WT population)				
TC3 or IC3	135 (20)	12.6	6.8	0.39 (0.25–0.60)
TC1/2/3 or IC1/2/3	354 (51)	11.0	6.8	0.50 (0.39–0.64)
TC1/2 or IC1/2	224 (32)	8.3	6.6	0.56 (0.41–0.77)
TC0/1/2 and IC0/1/2	557 (80)	8.0	6.8	0.68 (0.56–0.82)
TC0 and IC0	338 (49)	7.1	6.9	0.77 (0.61–0.99)
Teff subgroups (in the WT population)				
High gene-signature expression	284 (43)	11.3	6.8	0.51 (0.38–0.68)
Low gene-signature expression	374 (57)	7.3	7.0	0.76 (0.60–0.96)





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Future

- Combination immunotherapy
- Cellular immunotherapy
- Vaccines in combination with immunotherapy
- Cellular vaccination

Thank You e-mail: rgmart@uw.edu