16th CONGRESS Lung ON CANCER

BARCELONA 27 / 28 NOVEMBER 2025

GECP lung cancer research

How to choose immunotherapy agent/s in first line

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Disclosures

- Consultant or Advisory Role: BMS, MSD, Takeda, Roche, Pfizer, Roche, Ipsen, Astra-Zéneca, Boehringer, Bayer, Janssen
- Speaking: GSK, Roche, Ipsen, Lilly, Astellas, Janssen, Novartis, Boehringer, Eisai, Sanofi, Amgen, MSD
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- Participation in clinical trials: Merck, Astellas, Pfizer, Ipsen, Roche, AZ, Mirati, PharmaMar, Gilead

Fundación Biomédica Galicia Sur

Instituto de Investigación Sanitaria Galicia Sur

GECP lung cancer research

Outline

GECP lung cancer research

concl
molecular
clinical
intro

1 INTRO

2 CLINICAL

3 MOLECULAR

Outline

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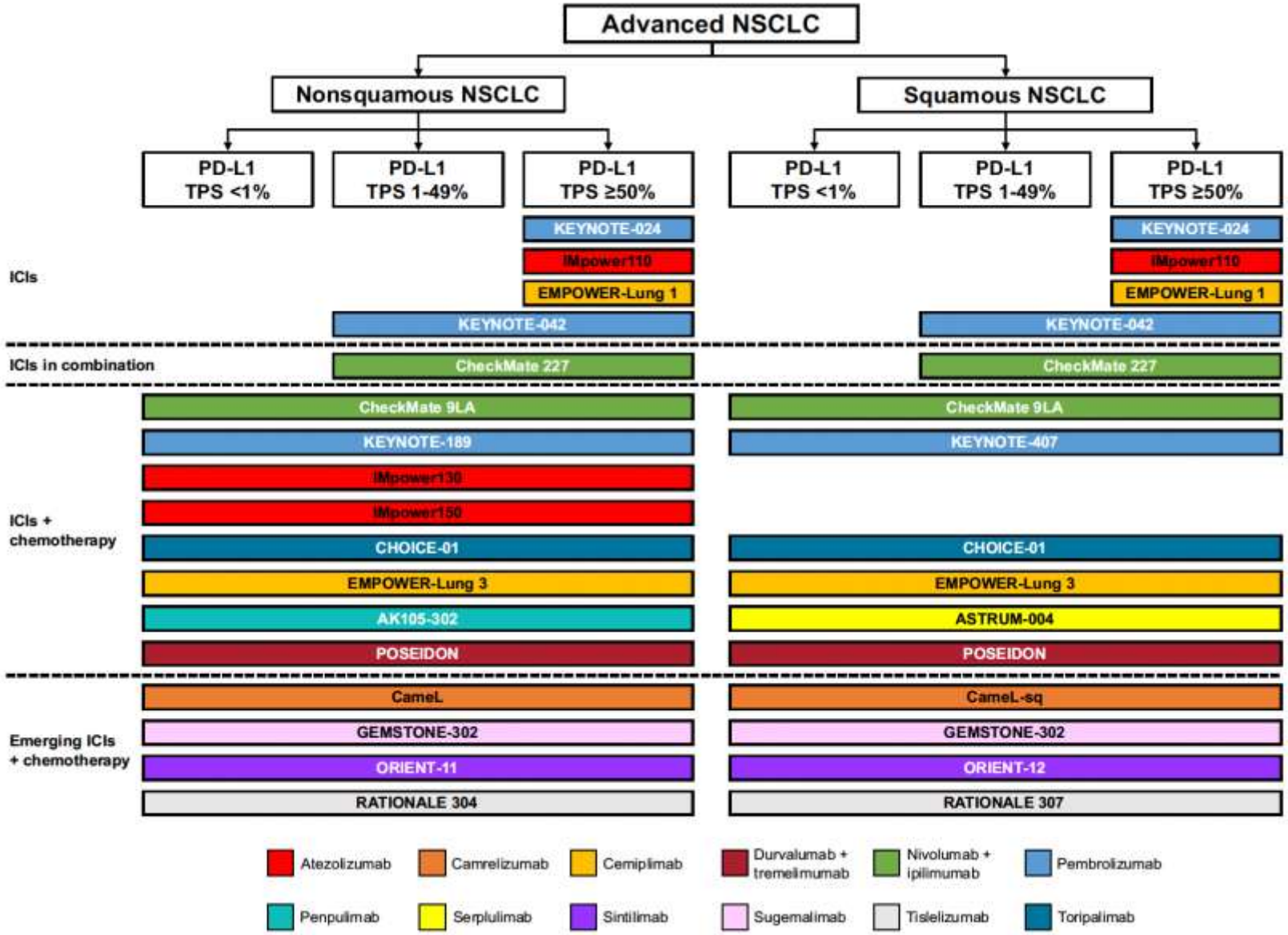
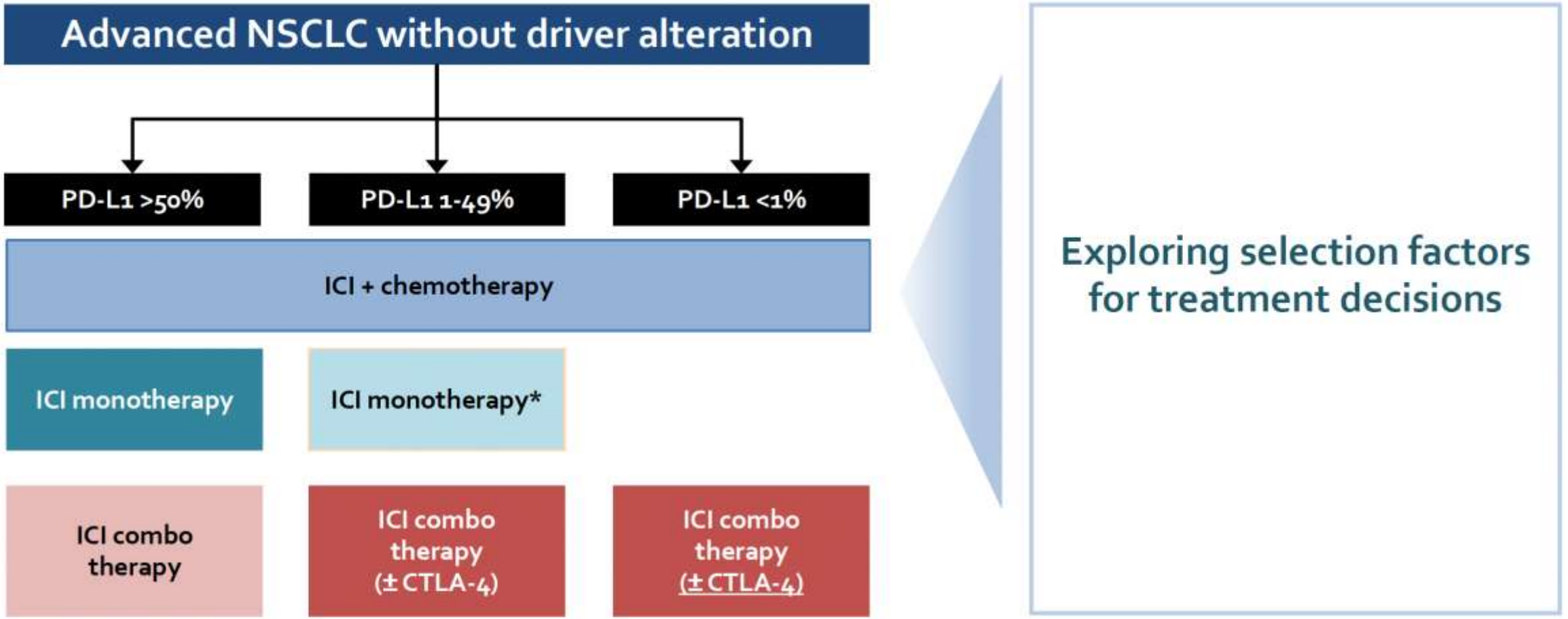
First-line ICI-based treatment landscape for patients with advanced NSCLC



Pu. Thoracic Cancer, 2025; 16:e70113

Like an octopus in a garage

First-line ICI-based treatment landscape for patients with advanced NSCLC



S Peters, ESMO 2025

Biological Framework for Correlates of ICB Response

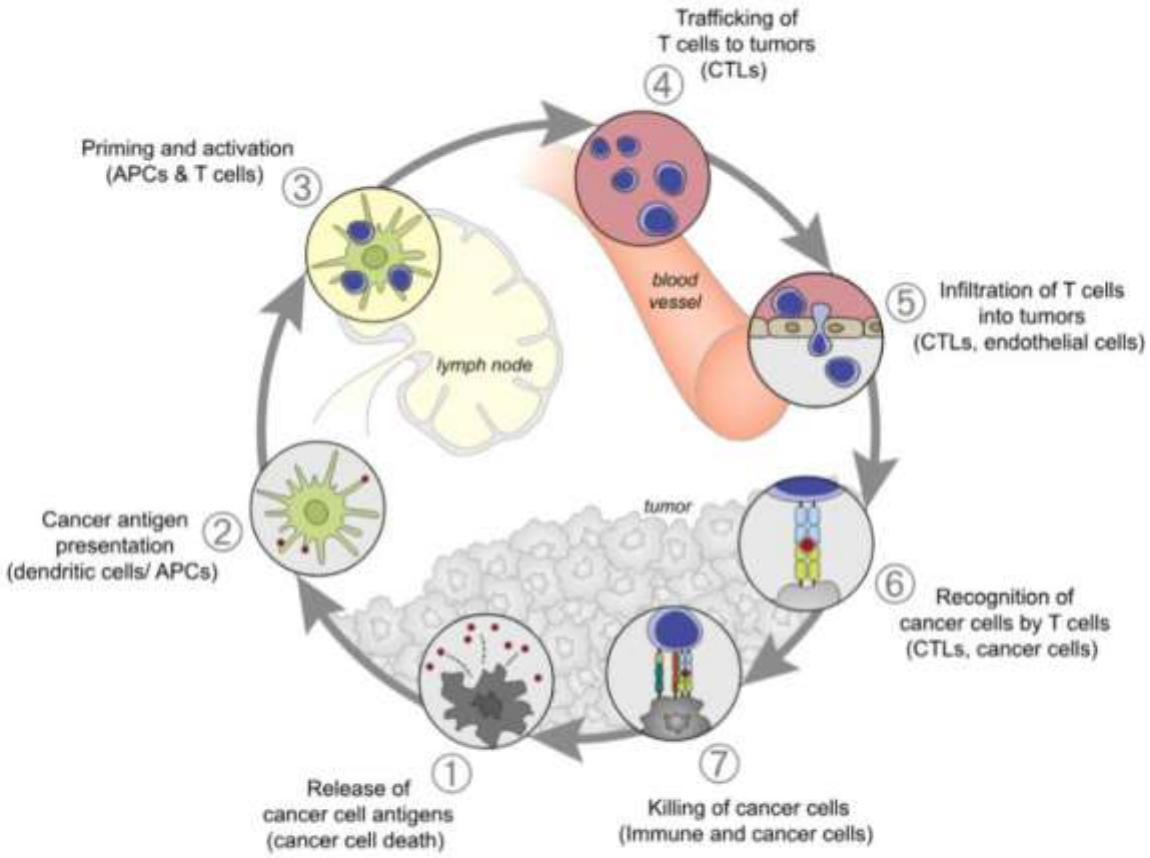
Tumor Intrinsic Predictors

Mutation burden/neoantigen load
- Clonality/heterogeneity
- Indel load
- Mutation signatures (smoking, APOBEC)

Genomic loss of neoantigens

Loss of antigen presentation
- B2M loss
- HLA loss/phenotypes

Single gene associations/ Oncogenic immune exclusion
- Oncogenic drivers (*EGFR, ALK*)
- *STK11/KEAP1*
- Cell cycle
- *JAK1/2* mutations
- Impaired STING activation



Chen, Mellman, Immunity, 2013

Associated with benefit
Associated with resistance

Tumor Extrinsic Predictors

T cell activation
- IFN-gamma/T cell inflamed signatures
- PD-L1 expression

T cell infiltrate/inflamed tumor

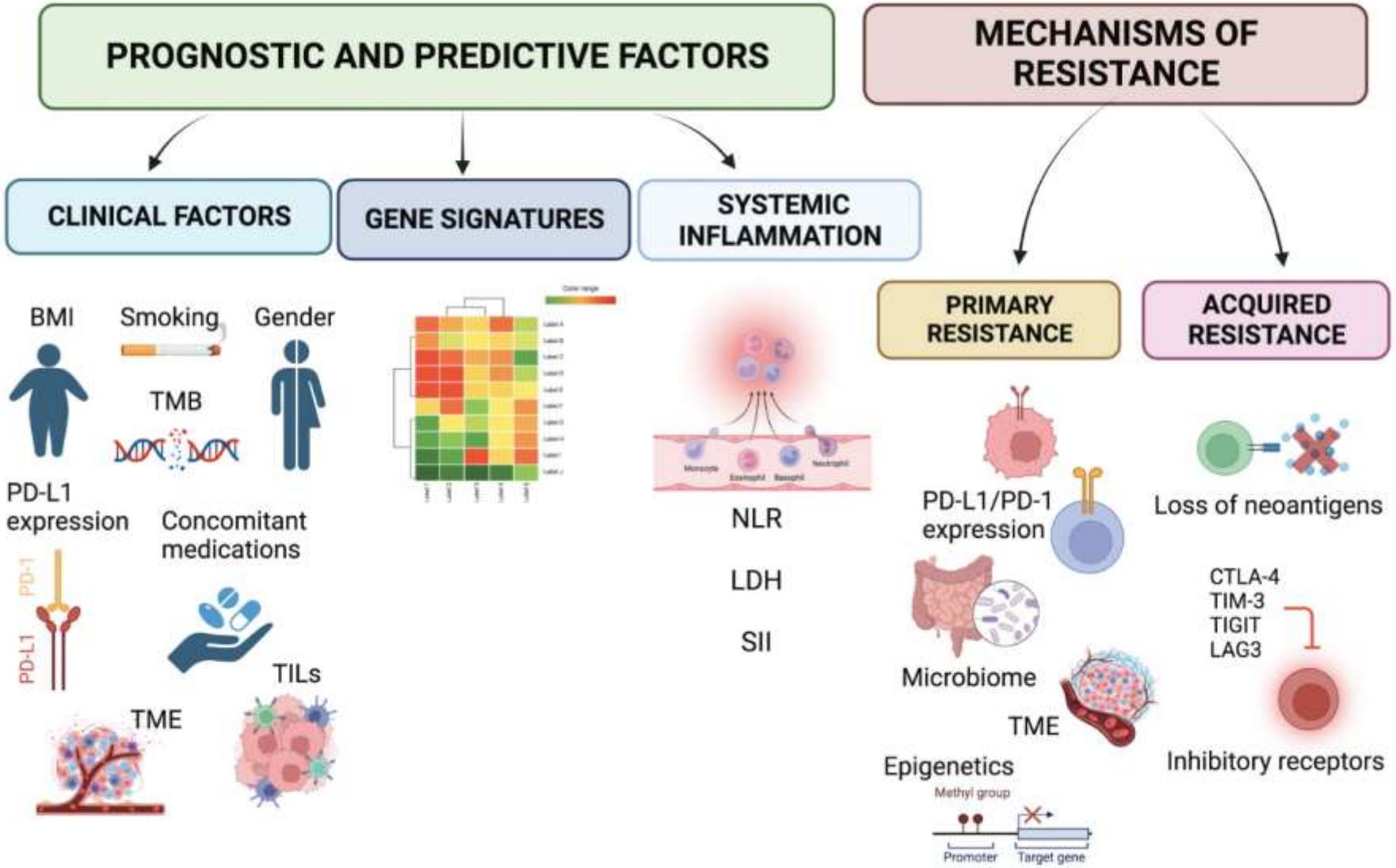
TCR diversity

Immune excluded/cold tumors

Immune suppressive populations
- Suppressive myeloid cells
- Fibroblasts/TGF-beta

Modified from Vokes, MDACC

IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER



Mogavero. Expert Rev Resp Med 2023;17:1191

Outline

concl
molecular
clinical
intro

1 INTRO

2 CLINICAL

3 MOLECULAR

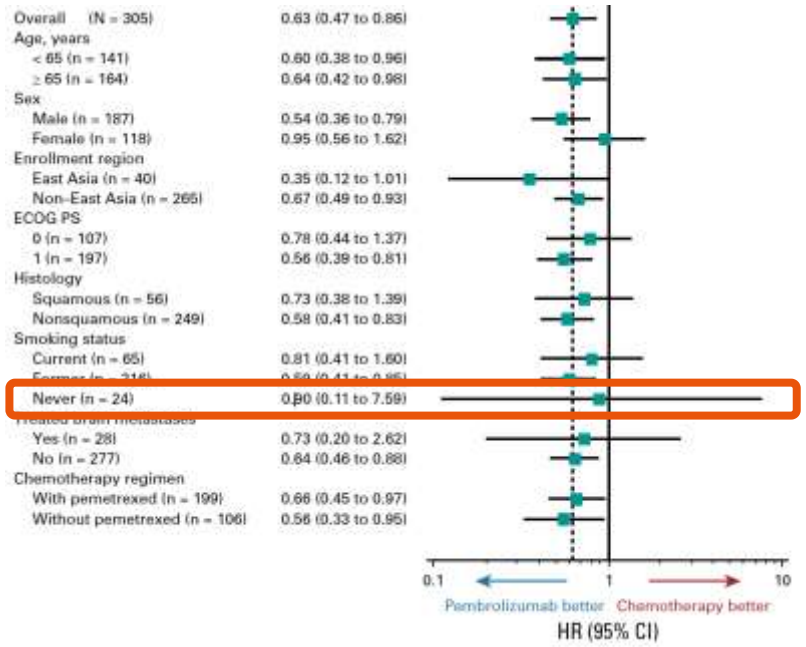
Clinical features

Smoking

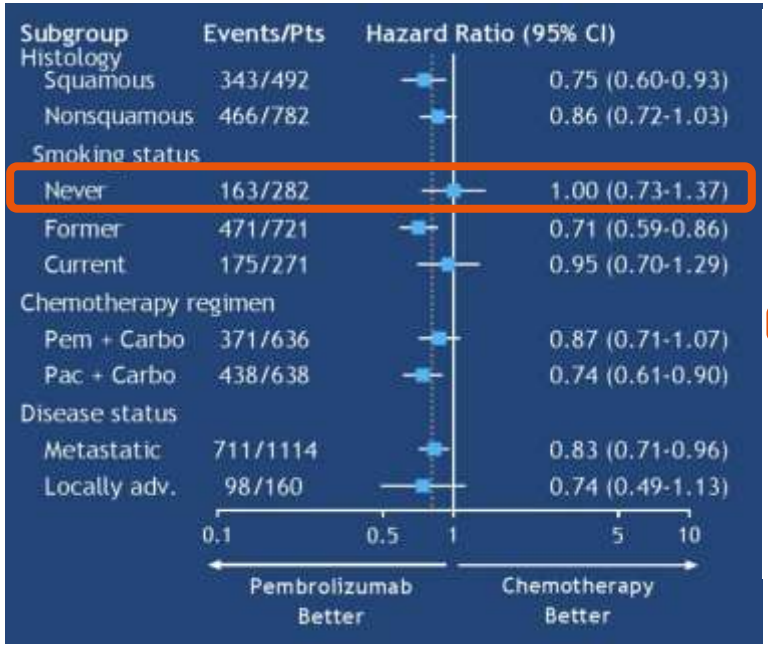
Never smokers

Monotherapy

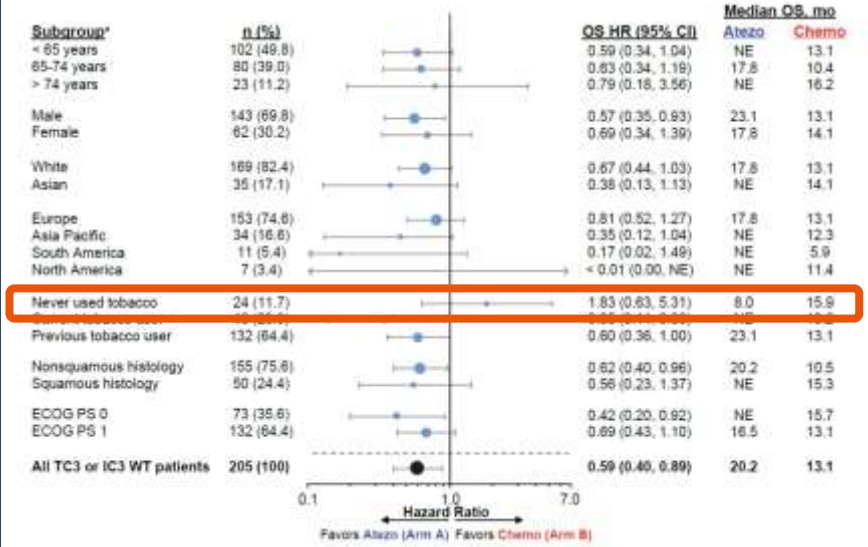
KN-024 (TPS≥50%)



KN-042 (TPS≥1%)



Impower 110 (TC3/IC3(TPS≥50%))

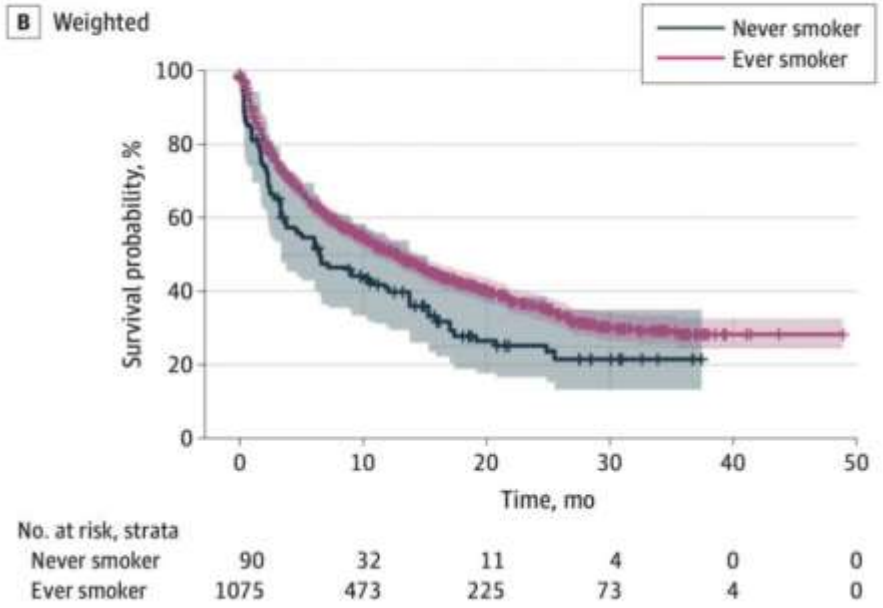


1. Reck M et al, *J Clin Oncol.* 2019;37:537–46. 2. Lopes G et al, ASCO 2018, abstract LBA4; Herbst R et al, N *Engl*J Med. 2020;383:1328–39

Clinical features

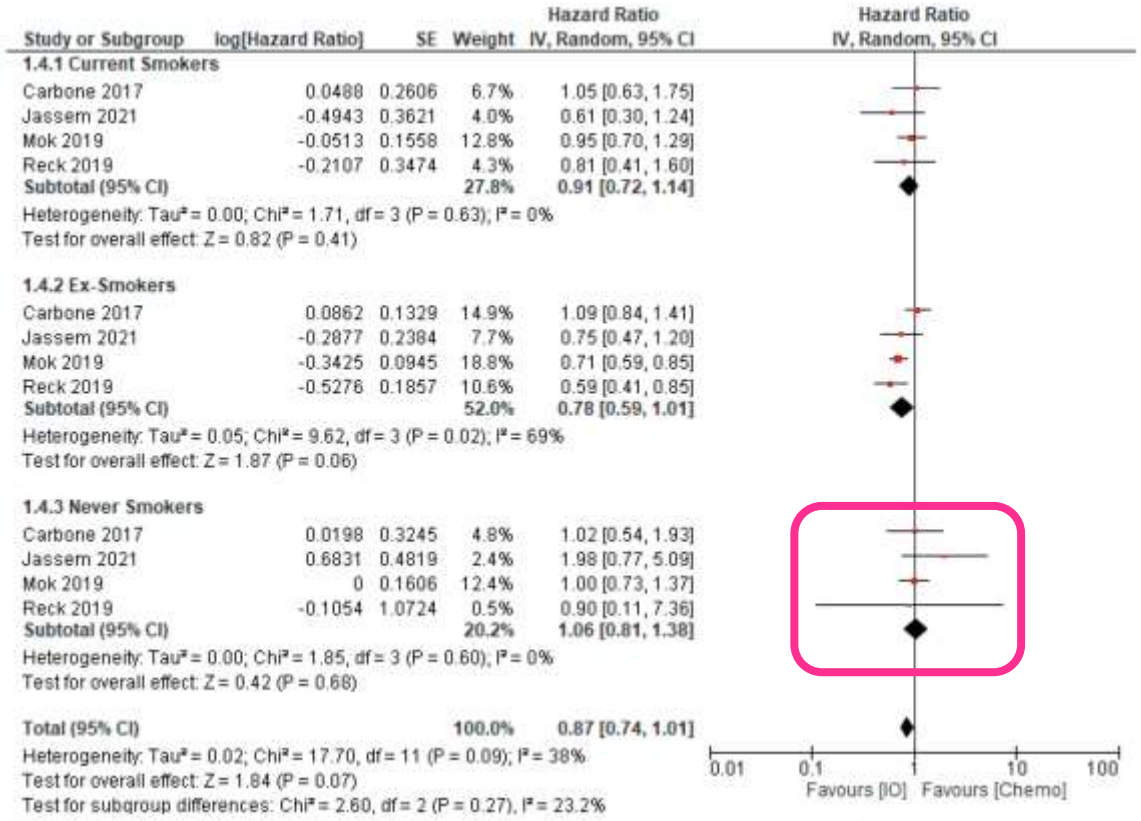
Smoking

Never smokers



1196 p, retrospective; monotherapy (pembrolizumab)

Pooled analysis of **overall survival** in **treatment naïve patients with advanced NSCLC** treated with first-line **immunotherapy** or chemotherapy, compared by smoking status at study entry



Popat, JAMA network2022; Corke, Curr Oncology 2022; 29:6260

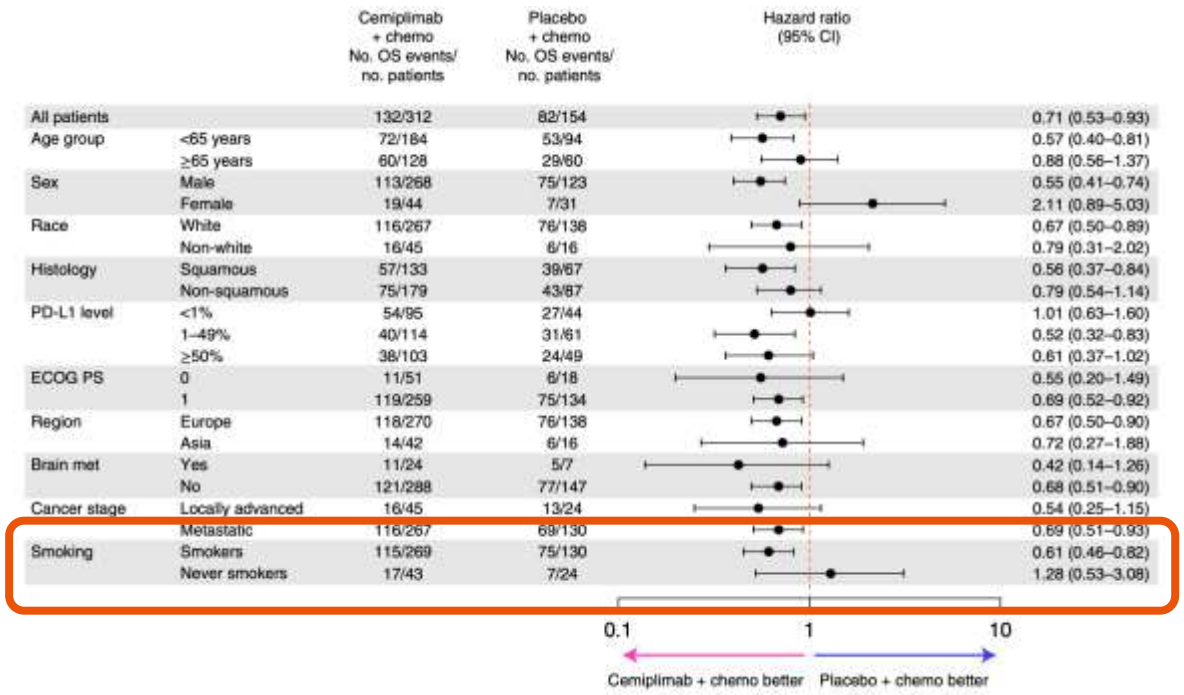
Clinical features

Smoking

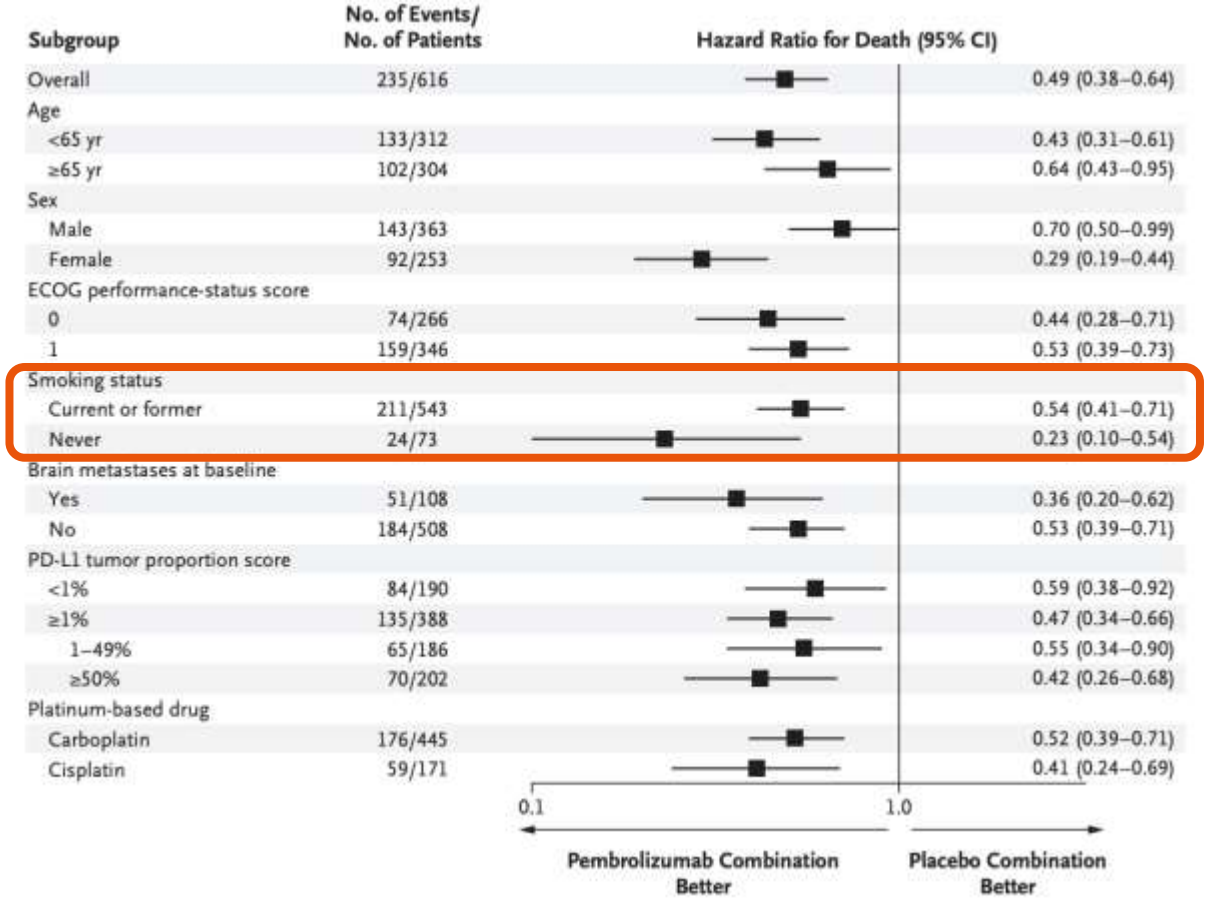
Never smokers

Chemo-immuno

Overall survival



		Cemiplimab + chemo No. OS events/ no. patients	Placebo + chemo No. OS events/ no. patients	Hazard ratio (95% CI)
All patients		132/312	82/154	0.71 (0.53–0.93)
Age group	<65 years	72/184	53/94	0.57 (0.40–0.81)
	≥65 years	60/128	29/60	0.88 (0.56–1.37)
Sex	Male	113/268	75/123	0.55 (0.41–0.74)
	Female	19/44	7/31	2.11 (0.89–5.03)
Race	White	116/267	76/138	0.67 (0.50–0.89)
	Non-white	16/45	6/16	0.79 (0.31–2.02)
Histology	Squamous	57/133	39/67	0.56 (0.37–0.84)
	Non-squamous	75/179	43/87	0.79 (0.54–1.14)
PD-L1 level	<1%	54/95	27/44	1.01 (0.63–1.60)
	1–49%	40/114	31/61	0.52 (0.32–0.83)
	≥50%	38/103	24/49	0.61 (0.37–1.02)
ECOG PS	0	11/51	6/18	0.55 (0.20–1.49)
	1	119/259	75/134	0.69 (0.52–0.92)
Region	Europe	118/270	76/138	0.67 (0.50–0.90)
	Asia	14/42	6/16	0.72 (0.27–1.88)
Brain met	Yes	11/24	5/7	0.42 (0.14–1.26)
	No	121/288	77/147	0.68 (0.51–0.90)
Cancer stage	Locally advanced	16/45	13/24	0.54 (0.25–1.15)
	Metastatic	116/267	69/130	0.69 (0.51–0.93)
Smoking	Smokers	115/269	75/130	0.61 (0.46–0.82)
	Never smokers	17/43	7/24	1.28 (0.53–3.08)



Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Death (95% CI)
Overall	235/616	0.49 (0.38–0.64)
Age		
<65 yr	133/312	0.43 (0.31–0.61)
≥65 yr	102/304	0.64 (0.43–0.95)
Sex		
Male	143/363	0.70 (0.50–0.99)
Female	92/253	0.29 (0.19–0.44)
ECOG performance-status score		
0	74/266	0.44 (0.28–0.71)
1	159/346	0.53 (0.39–0.73)
Smoking status		
Current or former	211/543	0.54 (0.41–0.71)
Never	24/73	0.23 (0.10–0.54)
Brain metastases at baseline		
Yes	51/108	0.36 (0.20–0.62)
No	184/508	0.53 (0.39–0.71)
PD-L1 tumor proportion score		
<1%	84/190	0.59 (0.38–0.92)
≥1%	135/388	0.47 (0.34–0.66)
1–49%	65/186	0.55 (0.34–0.90)
≥50%	70/202	0.42 (0.26–0.68)
Platinum-based drug		
Carboplatin	176/445	0.52 (0.39–0.71)
Cisplatin	59/171	0.41 (0.24–0.69)

Gogishvili. Nat Med 2022;;28:2374
Gandhi. N Engl J Med 378:2078-2092

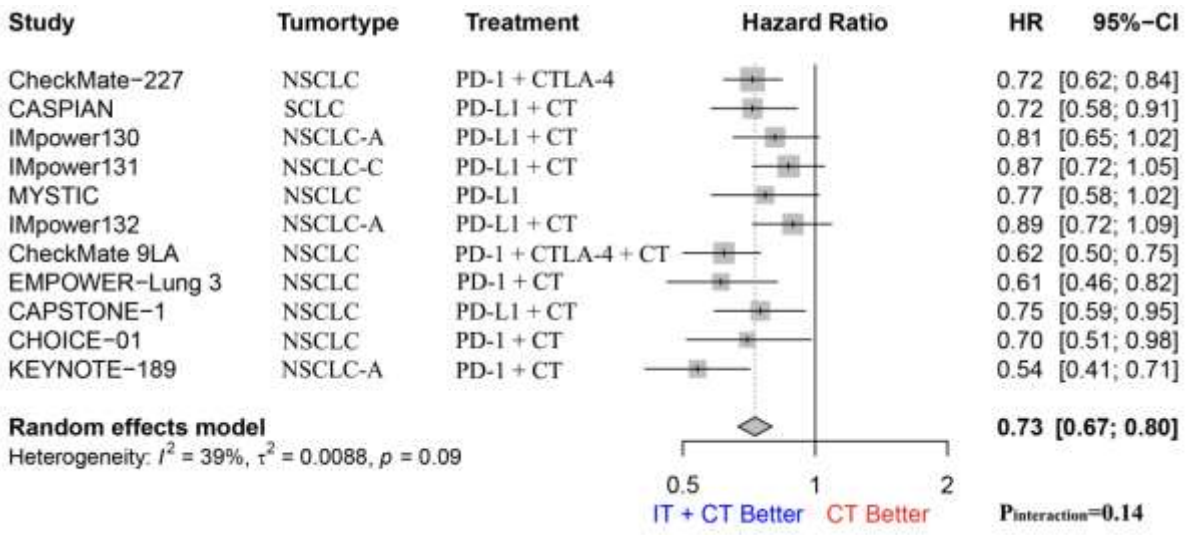
Clinical features

Smoking

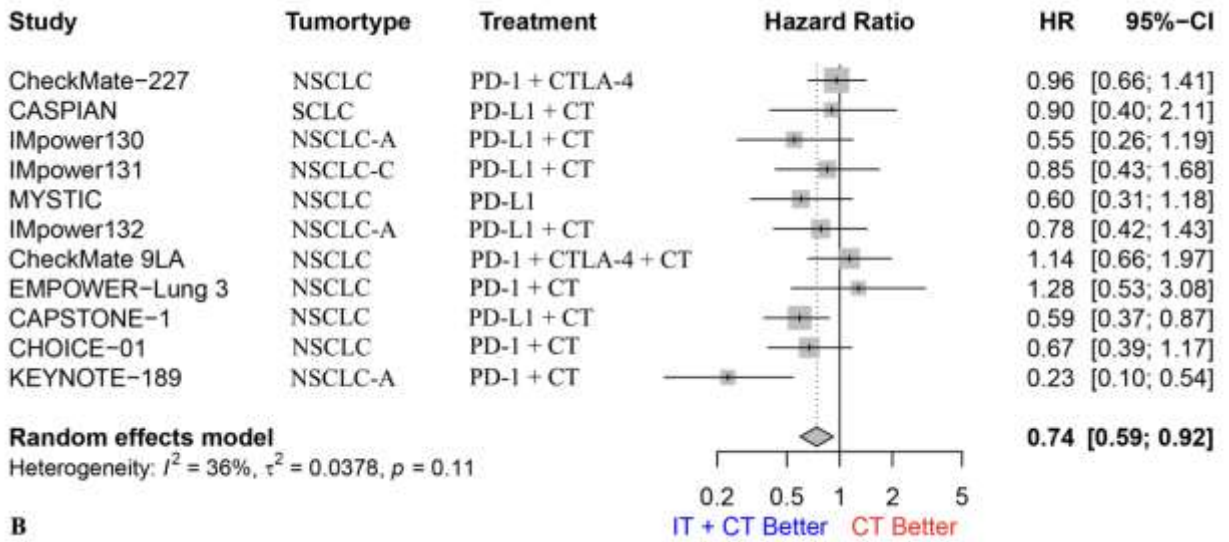
Never smokers

Meta-analysis

Smoking patients



Non-smoking patients



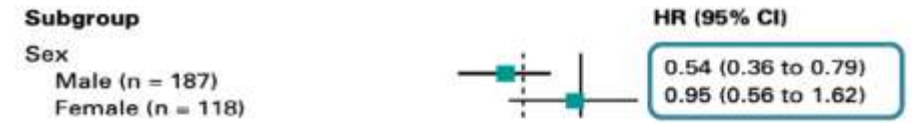
Luo. Front Oncol. 2024 Oct 8;14:1422160

Clinical features

Gender

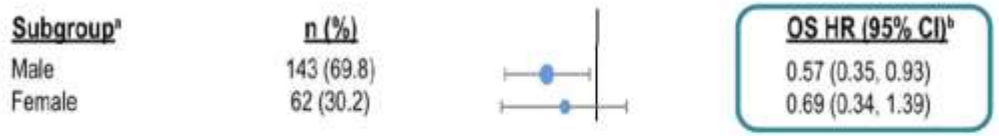
Monotherapy

KN-024



IMpower110

High PDL1
(SP142 TC3/IC3 WT)



KN-042

PD-L1≥1%

Javelin100

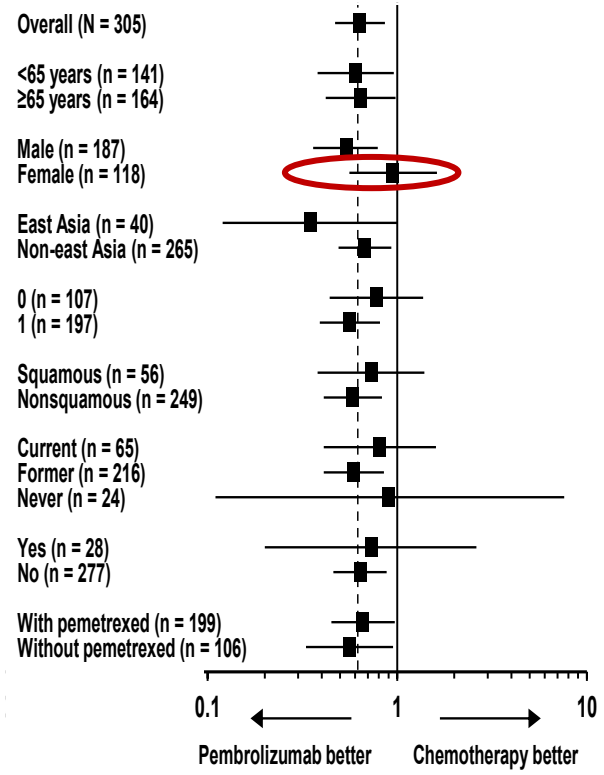
PD-L1≥80%

Reck et al, JCO 2019; 37(7):537-546. 2Sezer et al, Lancet 2021;397:592-604. Spigel et al, EMSO 2019. Mok et al, ELCC 2019. Reck et al, WCLC 2023;O
Mod from S Peters ESMO 2025

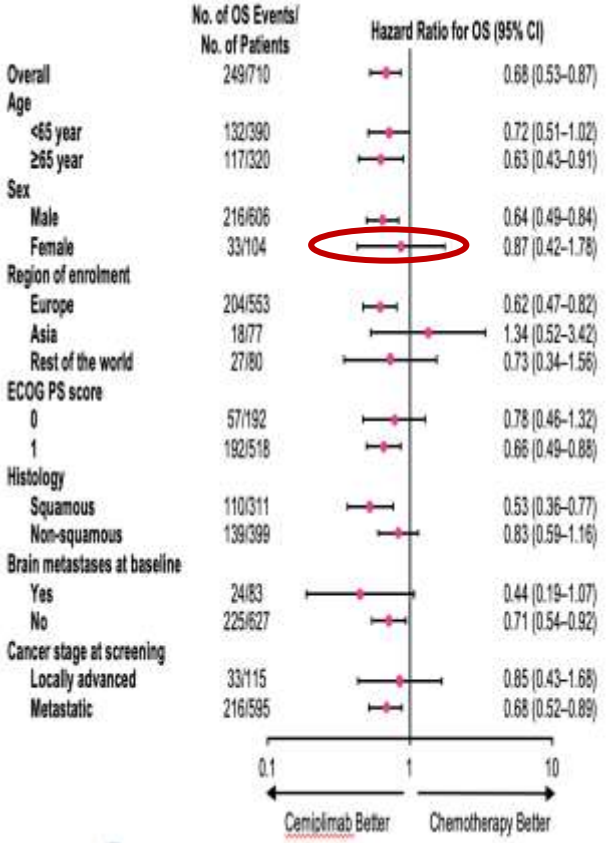
Clinical factors

Gender

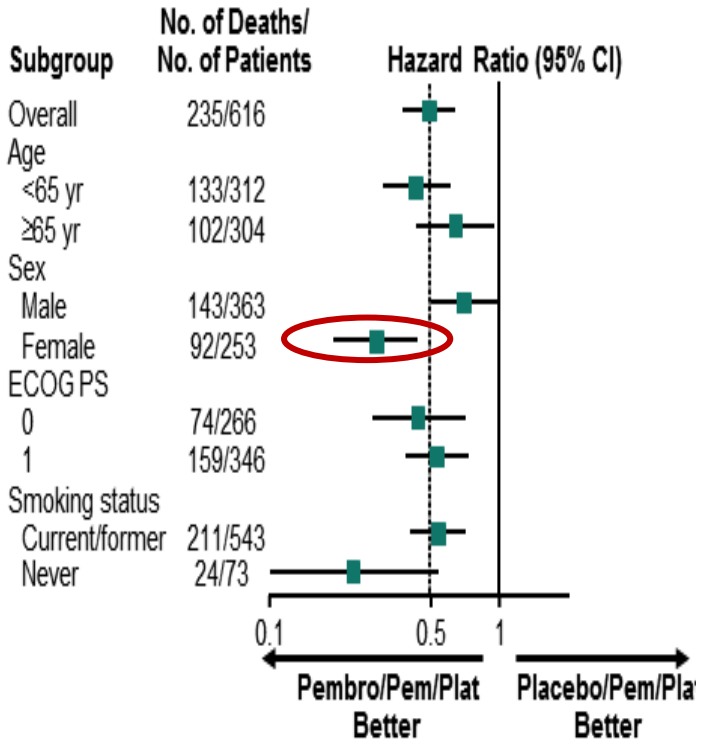
KEYNOTE-024



EMPOWER LUNG 1



KEYNOTE-189

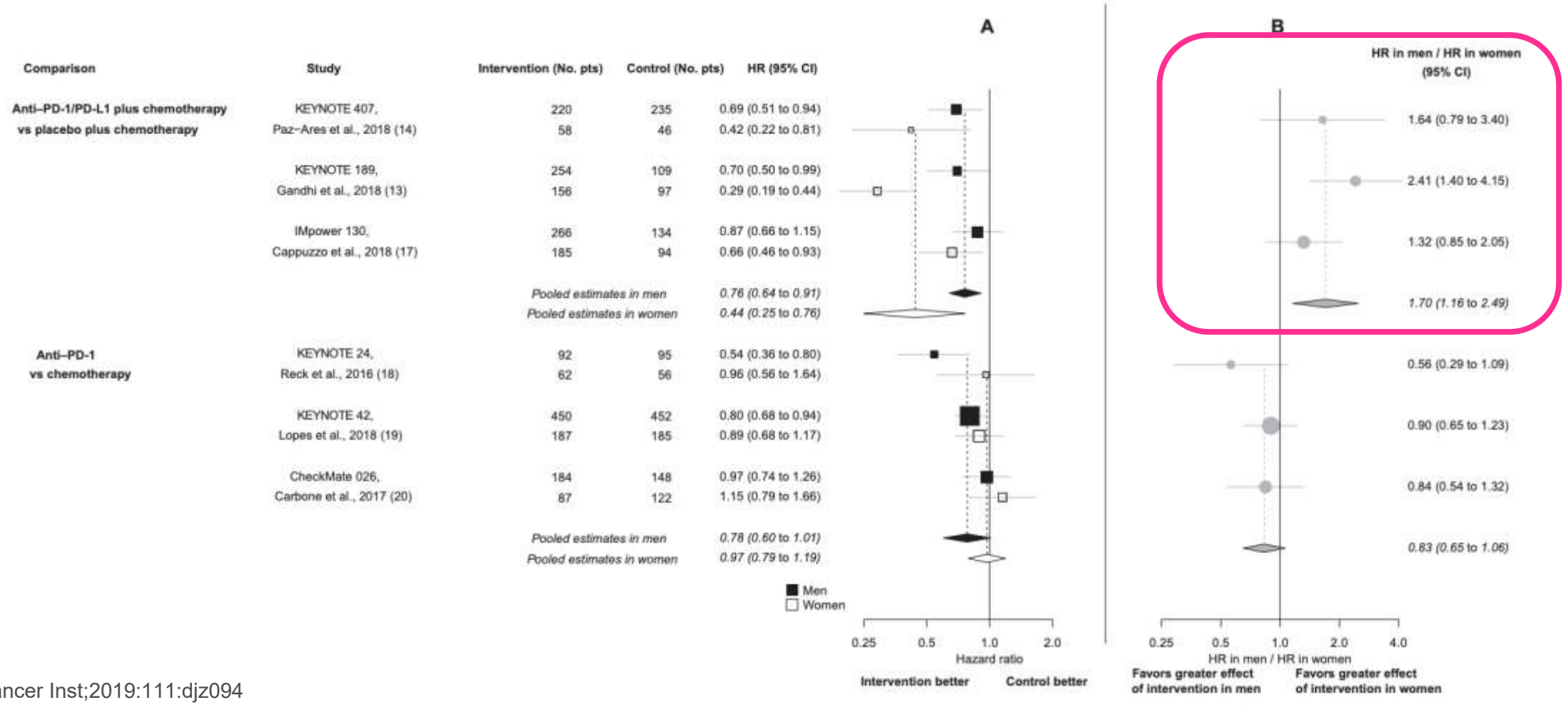


Reck M, et al. N Engl J Med 2016; Sezar et al. Lancet 2021
Gandhi L et al. N Engl J Med. 2018.

Clinical factors

Gender

Women with advanced lung cancer derived a **statistically significantly larger benefit from the addition of chemotherapy to anti–PD-1/PD-L1** as compared with men



Conforti. J Ntl Cancer Inst;2019:111:djz094

Clinical factors

Brain metastases

Post-hoc exploratory analysis

ICI monotherapy (PD-L1 ≥ 50%)	KEYNOTE-001, 010, 024 & 042 (pooled analysis); EMPOWER-Lung 1
Dual ICI ± chemo (any PD-L1)	CheckMate-227 & CheckMate-9LA
Chemo + ICI (any PD-L1)	KEYNOTE-021, 407 & 189 (pooled analysis)

Previoulsy treated and controlled BrM (attrition)

Corticosteroids ≤10mg PDN

Specific BrM trials

ICI monotherapy (PD-L1 ≥ 1%)	NCT02085070
Dual ICI ± chemo (any PD-L1)	CheckMate-817; NIVIPI-Brain
Chemo + ICI (any PD-L1)	ATEZO-Brain (*)

Untreated BrM

Measurable disease in the CNS

(*) Corticosteroids ≤ 4mg DXM

Cortesía del Dr E. Nadal

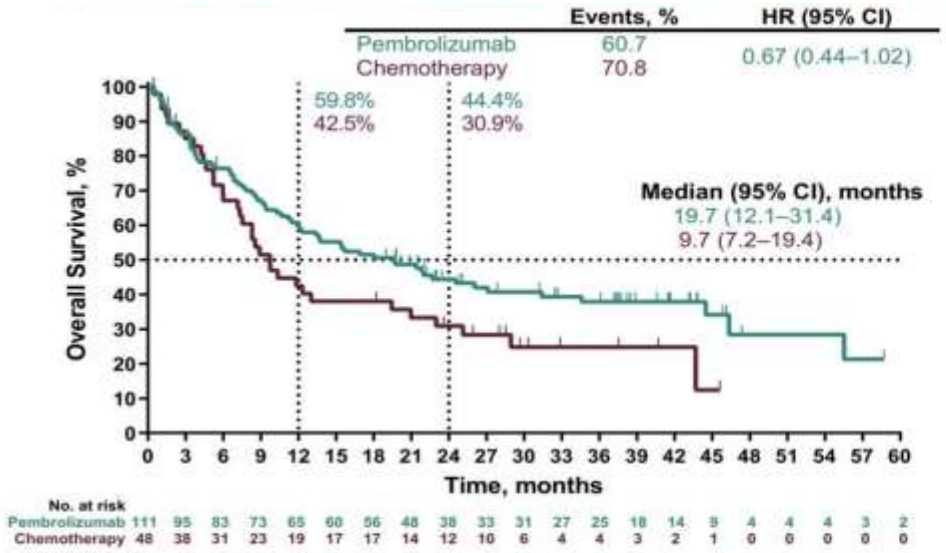
Clinical factors

Brain metastases

Monotherapy with ICI in patients with **treated** CNS metastases and PD-L1 ≥ 50% improved OS compared to chemotherapy.

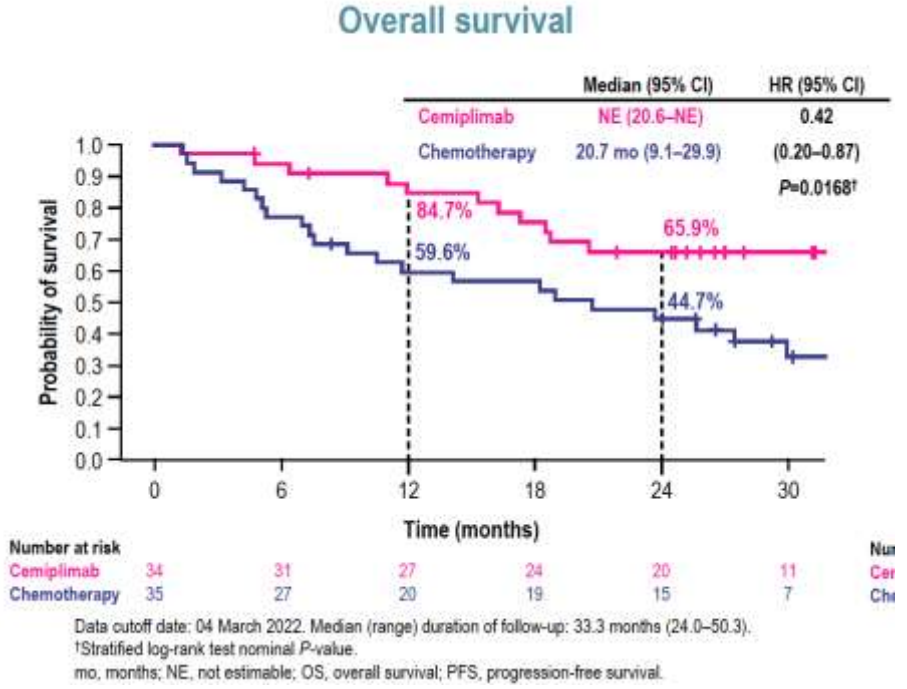
Pooled analysis KEYNOTE 001-010-024-042[1] 1L

Pembrolizumab in PD-L1≥50%



EMPOWER Lung 1[2]

1L Cemiplimab in PD-L1≥50%



(1) Mansfield et al. JTO CRR 2021; (2) Kilickap et al. ELCC 2023

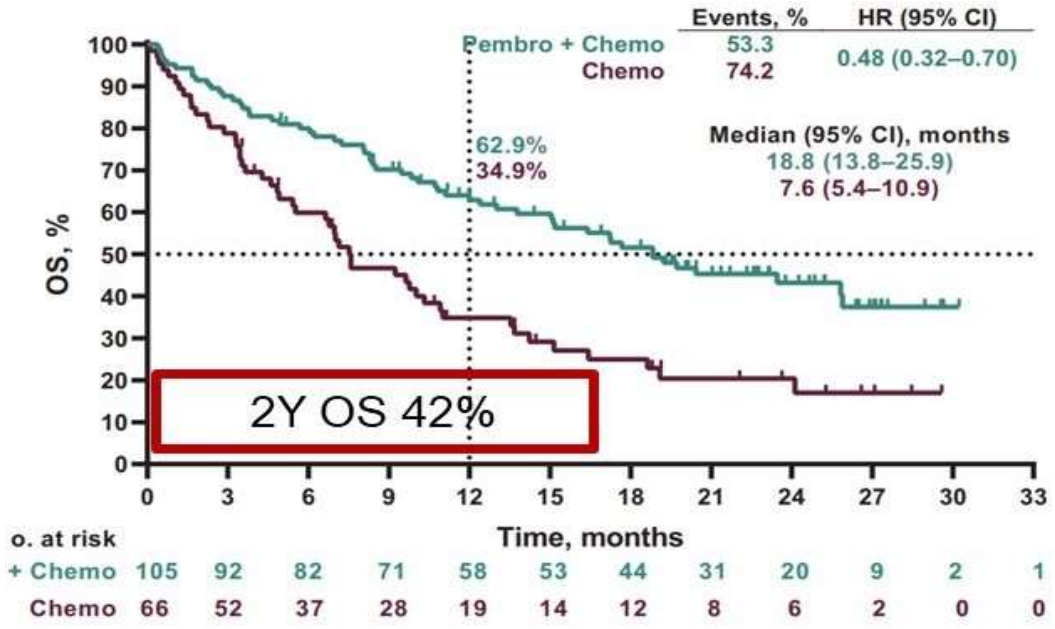
Clinical factors

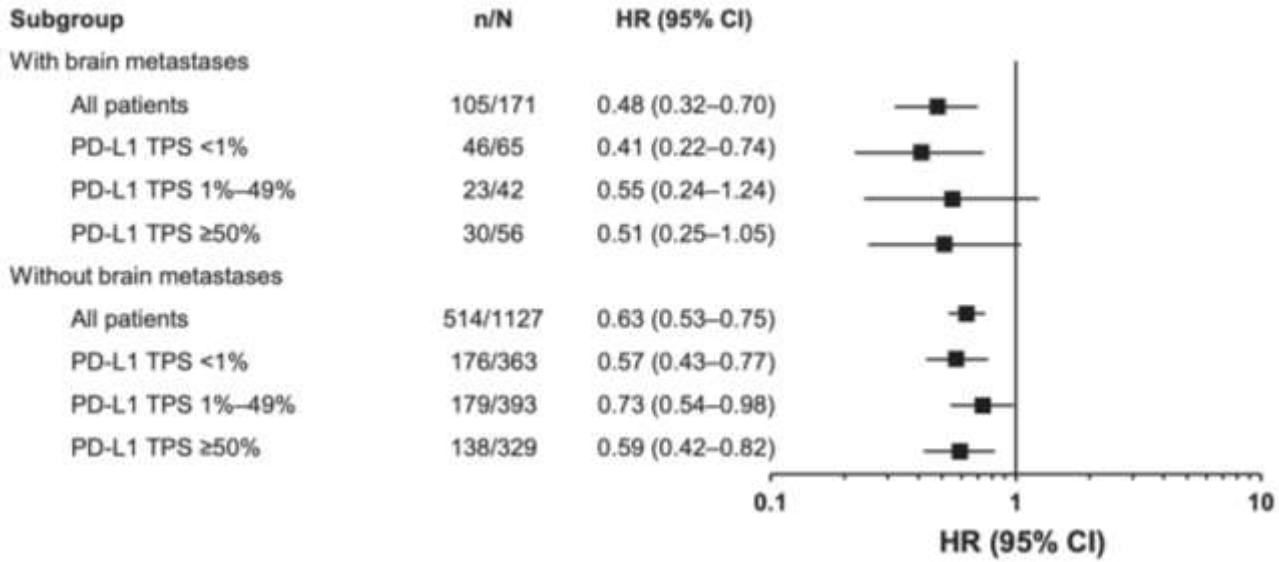
Brain metastases

The combination of **QMT + IO** in treated and **untreated** mCNS patients improved OS compared to QMT regardless of PD-L1 expression.

Pooled analysis KEYNOTE 021-189-407
1L Pembro + chemo vs chemo

171 / 1298 (13%) had BrM
20 /171 received prior brain RT (12%)
Asymptomatic, no steroids





Higher benefit in terms of OS in patients with brain mets (HR=0.48) compared to those without brain mets (HR=0.63)

Powell et al. J Thorac Oncol 2021

Clinical factors

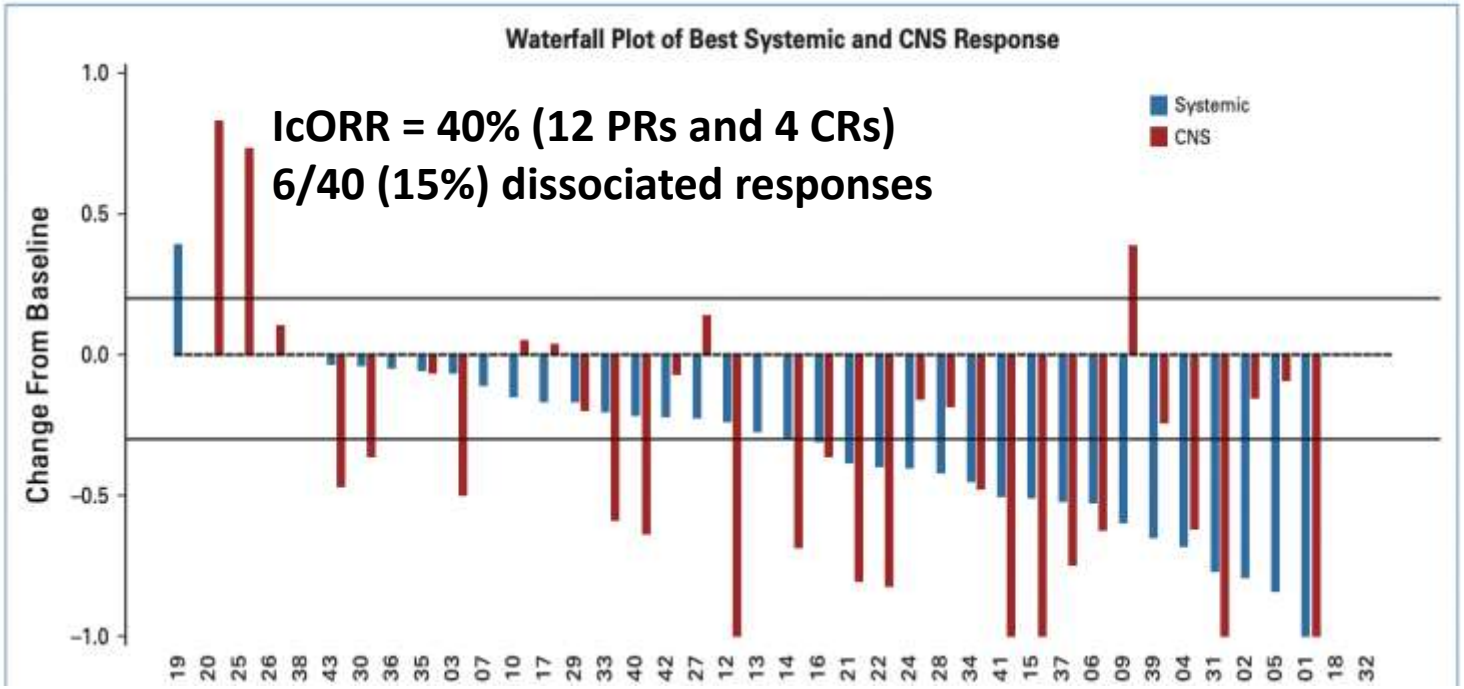
Brain metastases

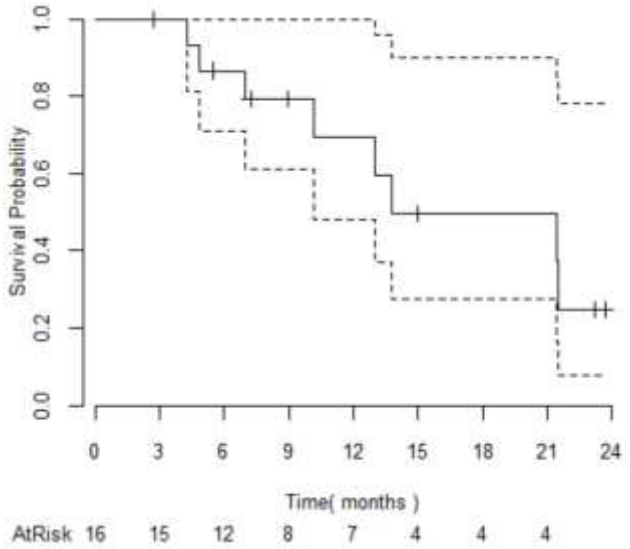
IO + QMT en pacientes con mSNC no tratadas: SG a los 2 años del 31%

ATEZO-BRAIN
CBDCA + Pem + atezo
(n=40, 20 PD-L1+)

Asymptomatic and olygosymptomatic BrM
BrM 10mm (RANO-BM)
Corticosteroids ≤4mg DXM

Median DoR in the CNS = 14 m (95% CI, 10 to NR)





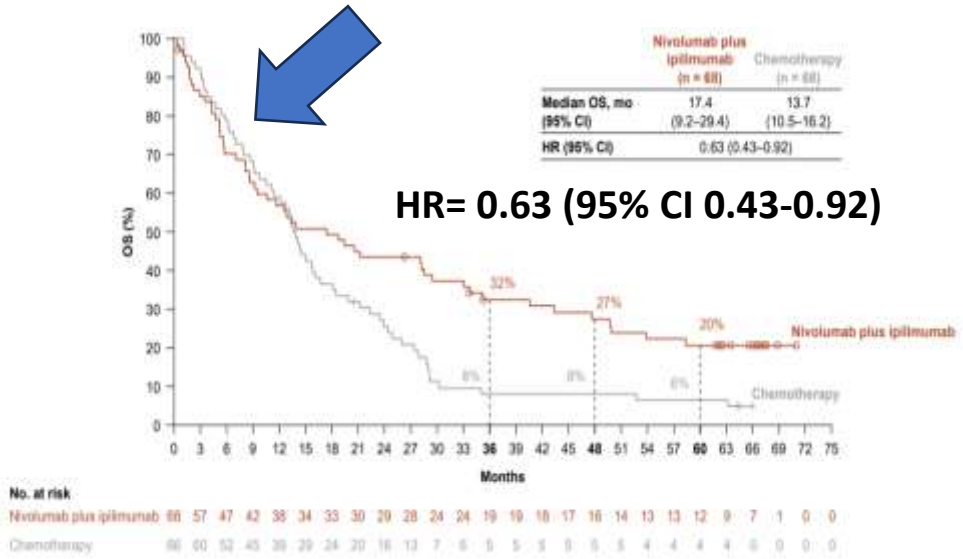
Nadal et al. J Clin Oncol 2023

Clinical factors

Brain metastases

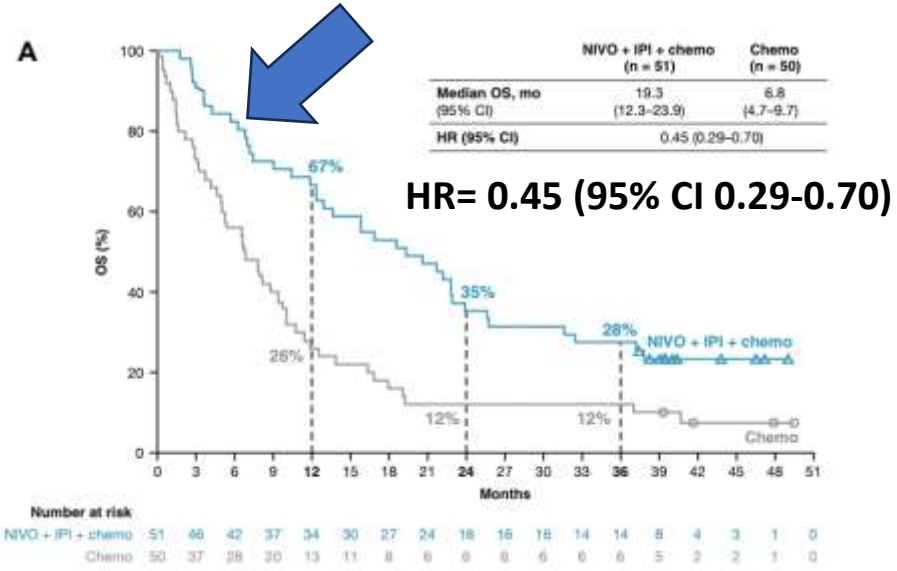
The combination of IO-IO + QMT in **treated** mCNS patients improved OS compared to chemotherapy.

CheckMate-227[1]
1L IPI + NIVO vs chemotherapy



Greater benefit in terms of OS in patients with brain metastases (HR=0.63) compared to those without brain metastases (HR=0.76).

CheckMate-9LA[2]
1L IPI + NIVO + CTx2 vs chemotherapy



Greater benefit in terms of OS in patients with brain metastases (HR=0.45) compared to those without brain metastases (HR=0.80).

(1) Reck et al. J Thorac Oncol 2023; (2) Paz-Ares et al. J Thorac Oncol 2023

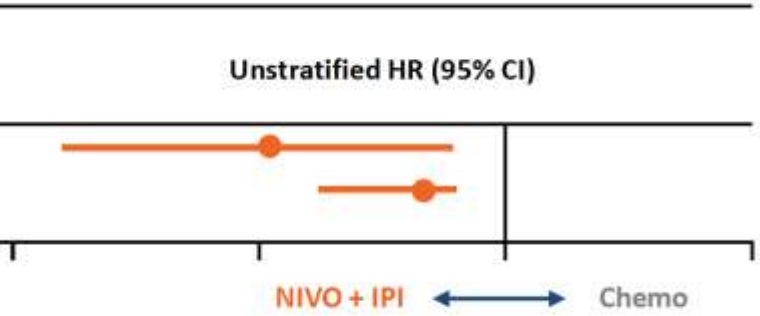
Clinical factors

Brain metastases

"Compensatory" effect of anti-CTLA4 addition

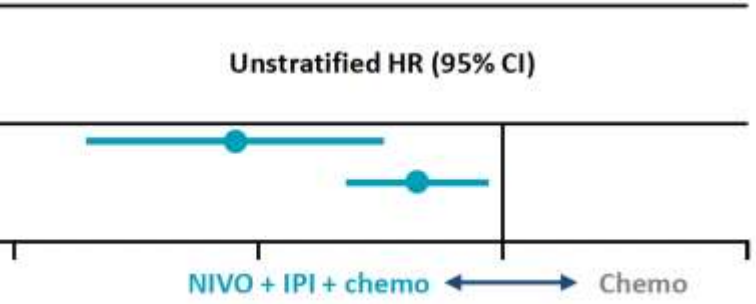
Checkmate 227

Subgroup	Median OS, mo NIVO + IPI (n = 583)	Chemo (n = 583)	Unstratified HR
CNS metastases (n = 135)	17.4	13.7	0.60
No CNS metastases (n = 1031)	17.1	13.9	0.77



Checkmate 9LA

Subgroup	Median OS, mo NIVO + IPI + chemo (n = 361)	Chemo (n = 358)	Unstratified HR
CNS metastases (n = 123)	19.9	7.9	0.49
No CNS metastases (n = 596)	15.6	11.8	0.81

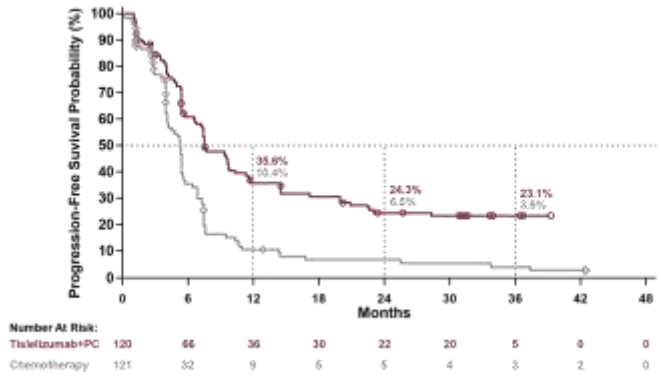


1. Borghaei H, et al. AACR Annual Meeting 2020. Abstract CT221 (CheckMate 227). 2. Reck M, et al. 2021 ASCO. Abstract 9000 (CheckMate 9LA).

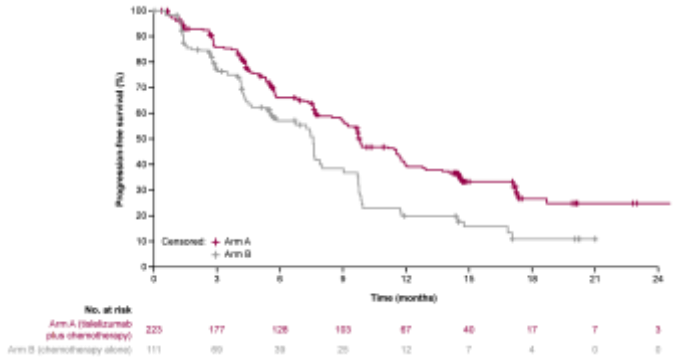
Clinical factors

Locally advanced

Rationale 307 (sq)

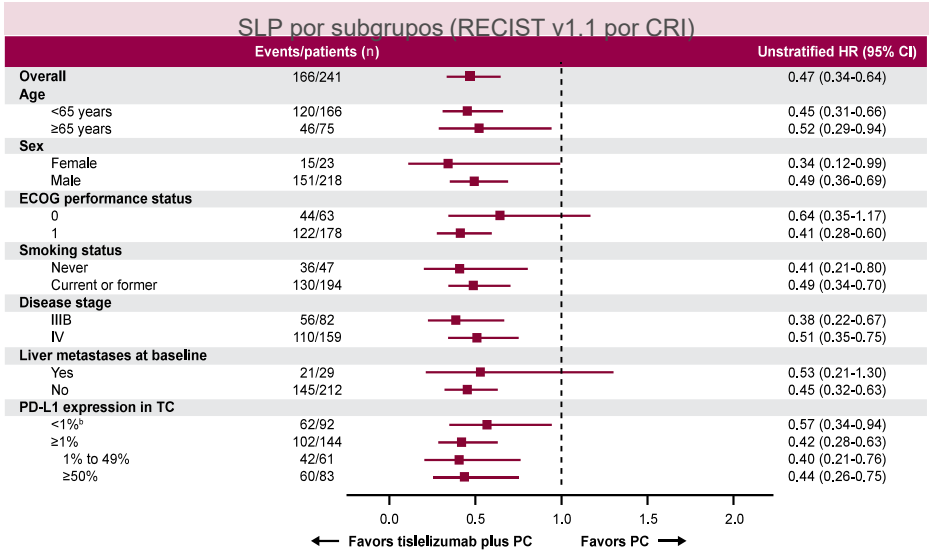


Rationale 304 (non sq))



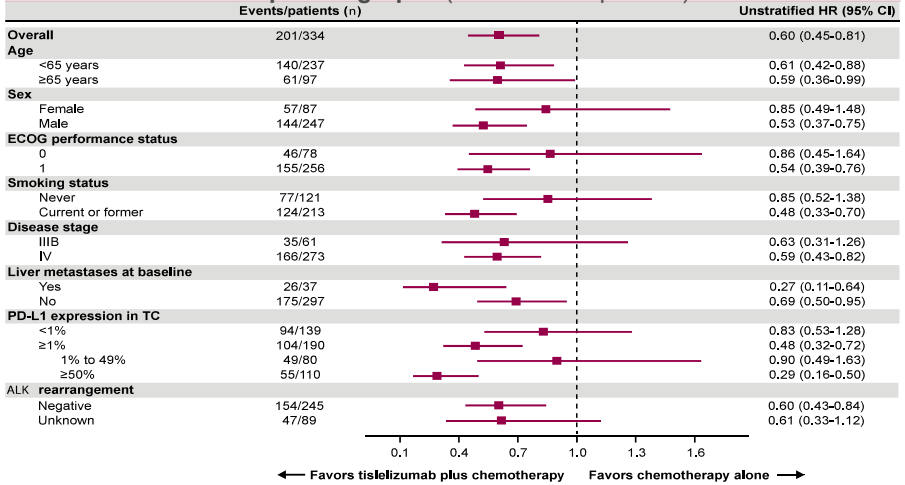
Estadios IIB: 34%

SLP por subgrupos (RECIST v1.1 por CRI)



Estadios IIB: 18%

SLP por subgrupos (RECIST v1.1 por CRI)



1. **1.** Wang J, et al. ESMO Open. 2024;9(10):103727.
2. Lu S, et al. ESMO Open. 2024;9(10):103728

Outline

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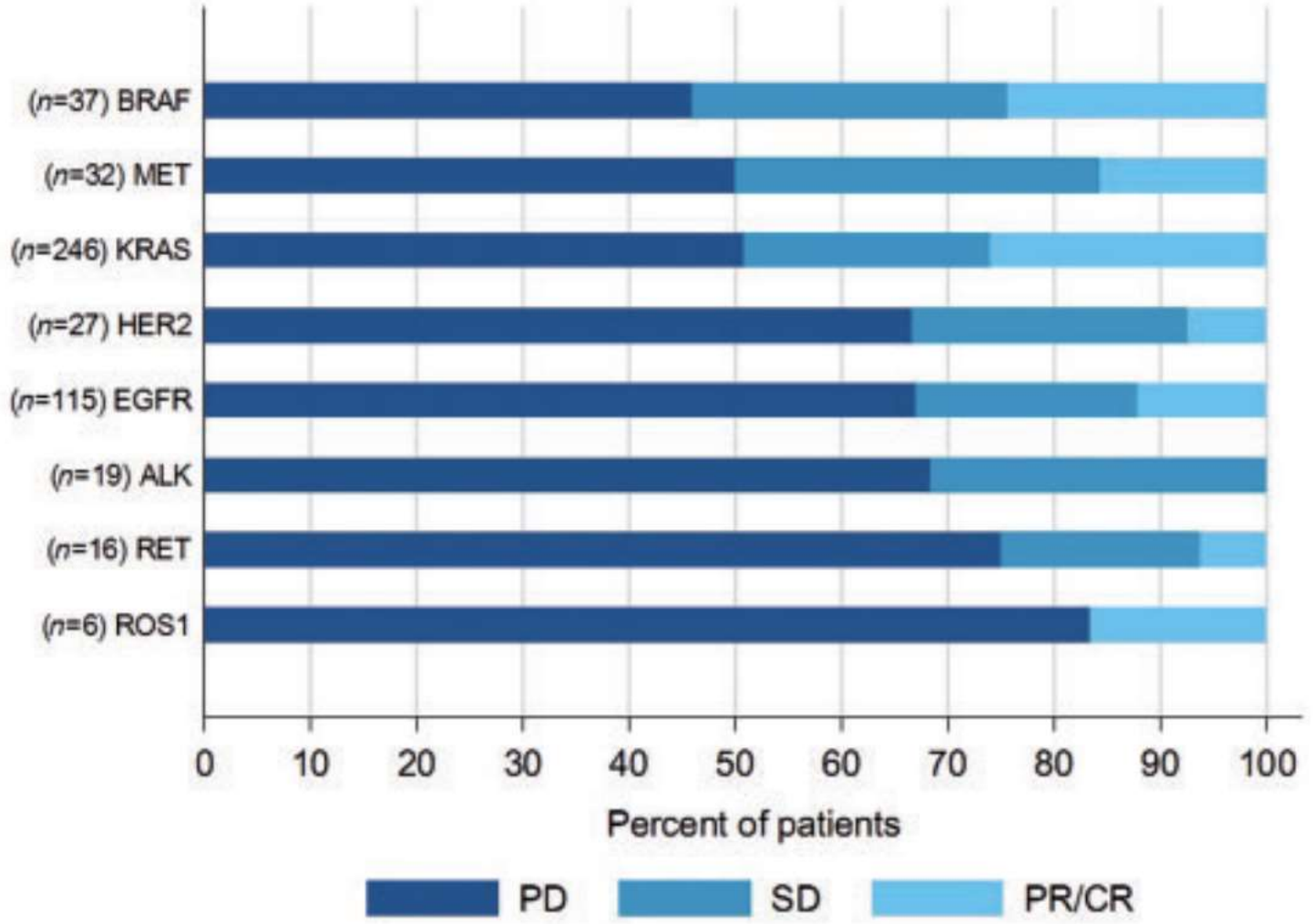
Oncogene addicted

Benefit not generalizable

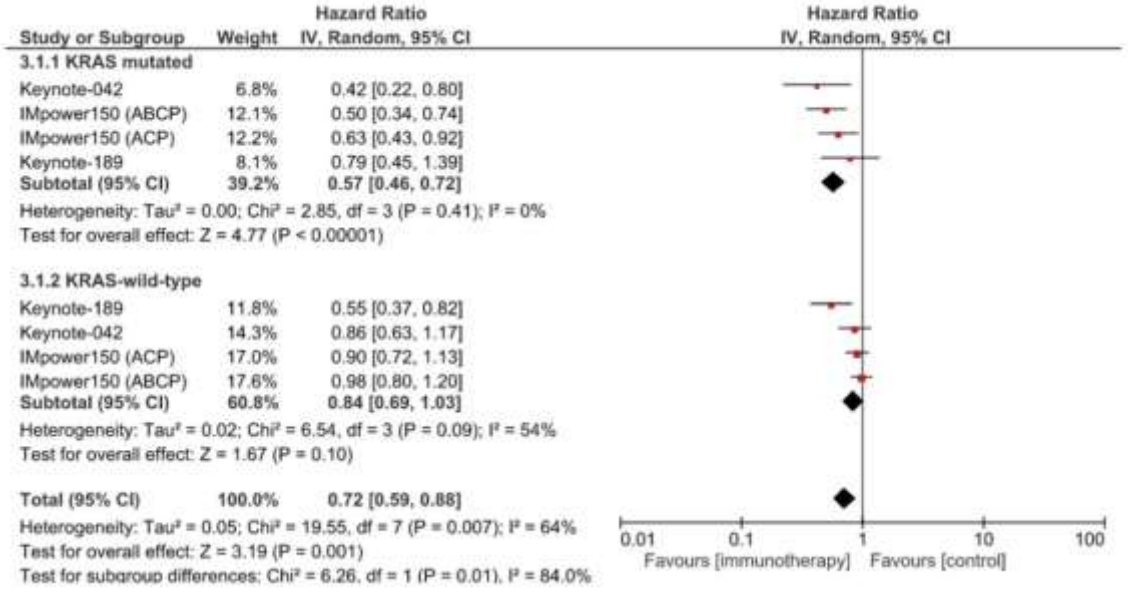


Mazieres. Ann Oncol 2019;30:12321

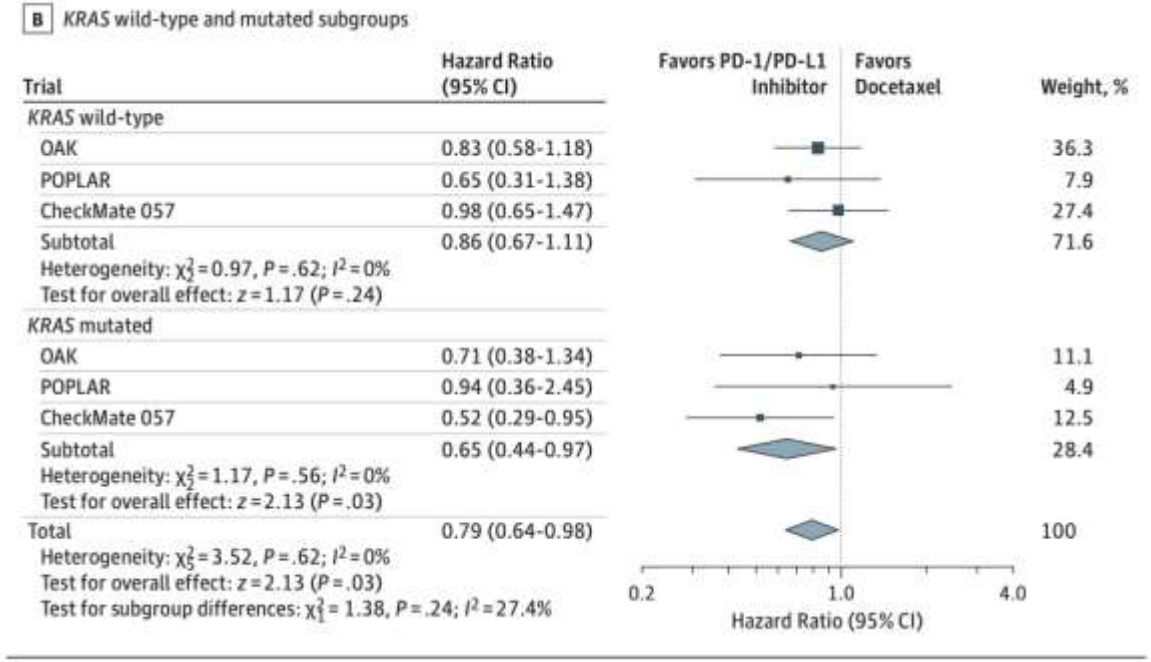
Oncogene addicted

Benefit not generalizable

KRAS Meta-analysis



Landre. Cancer Immunol Immunother. 2022 Mar;71(3):719



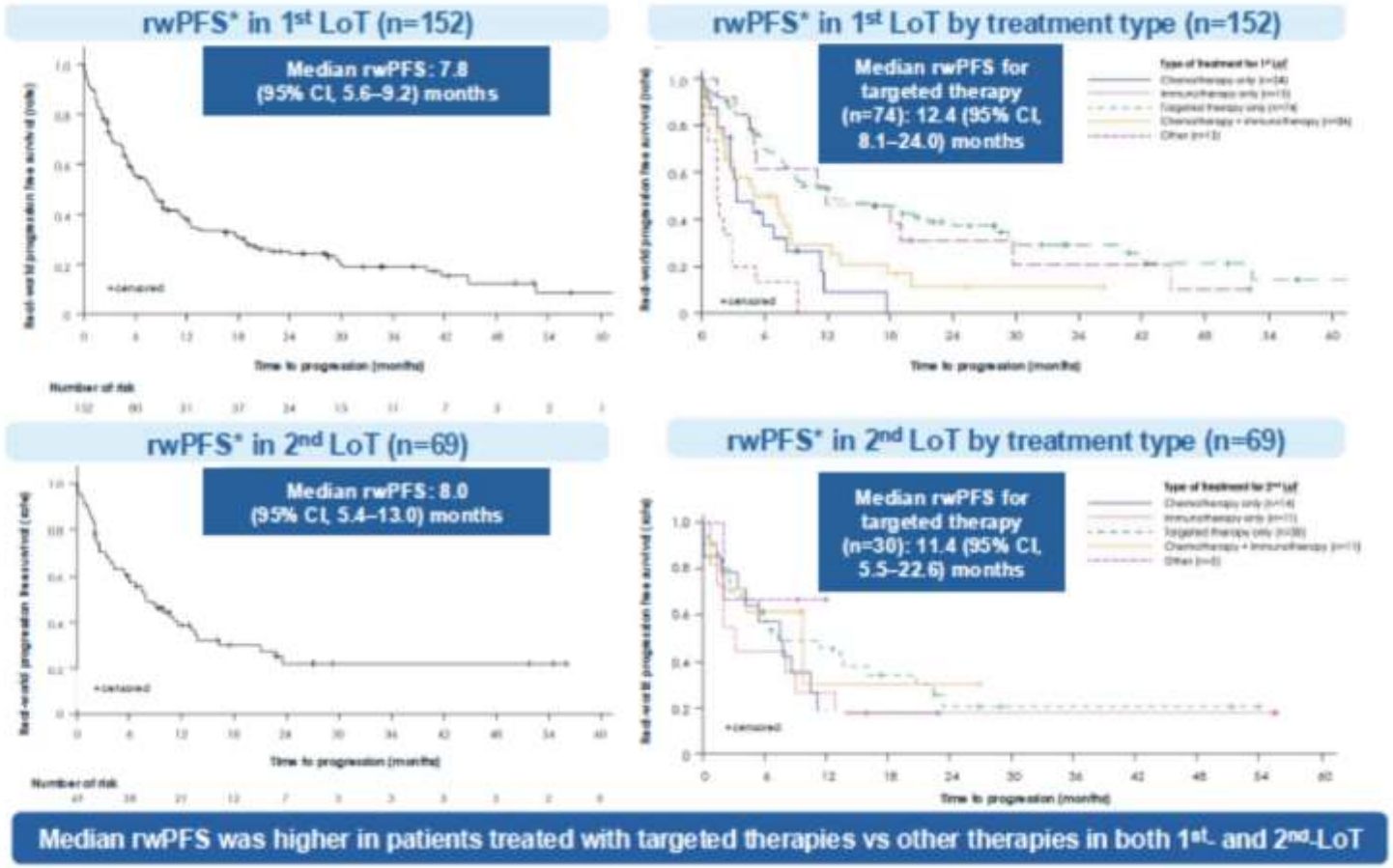
Lee. AMA Oncol. 2018 Feb 1;4(2):210

Oncogene addicted

Benefit not generalizable

BRAF

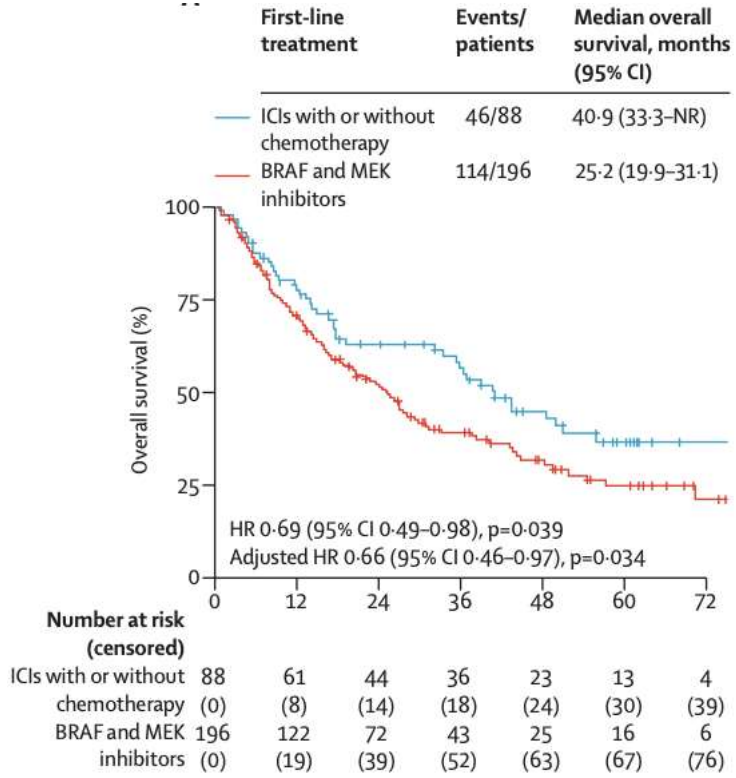
OCTOPUS



Planchard D. ELCC 2025 (Poster 86P)

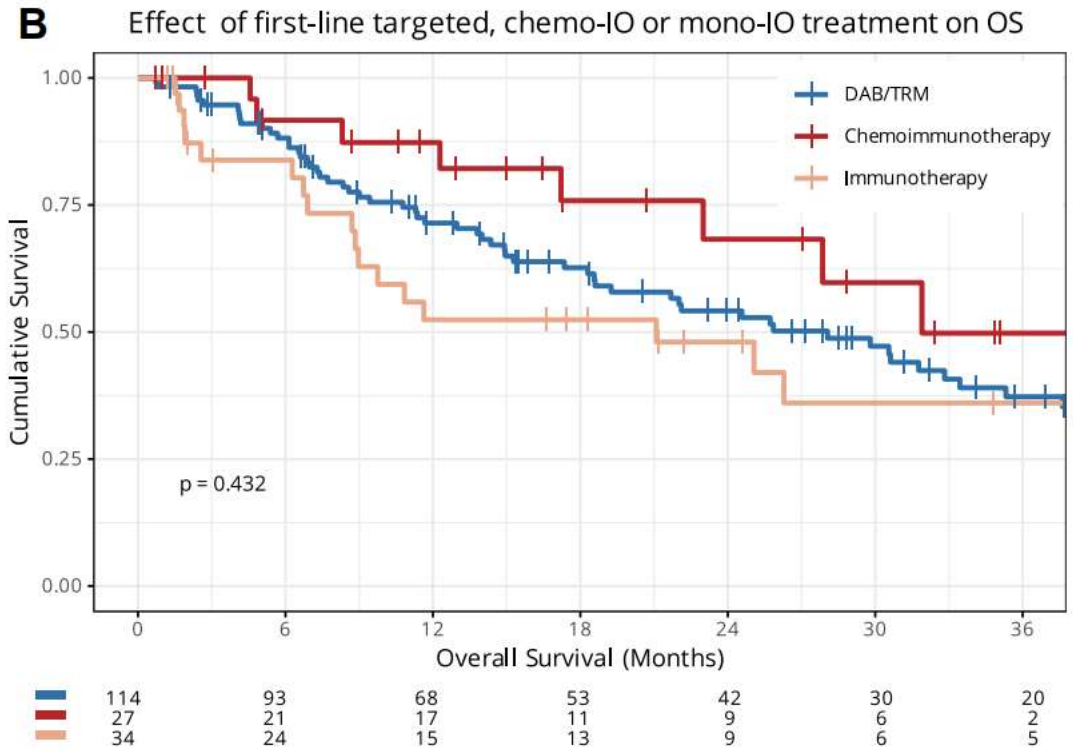
Oncogene addicted

Benefit not generalizable



Di Federico. Lancet Oncol 2025;26:1357

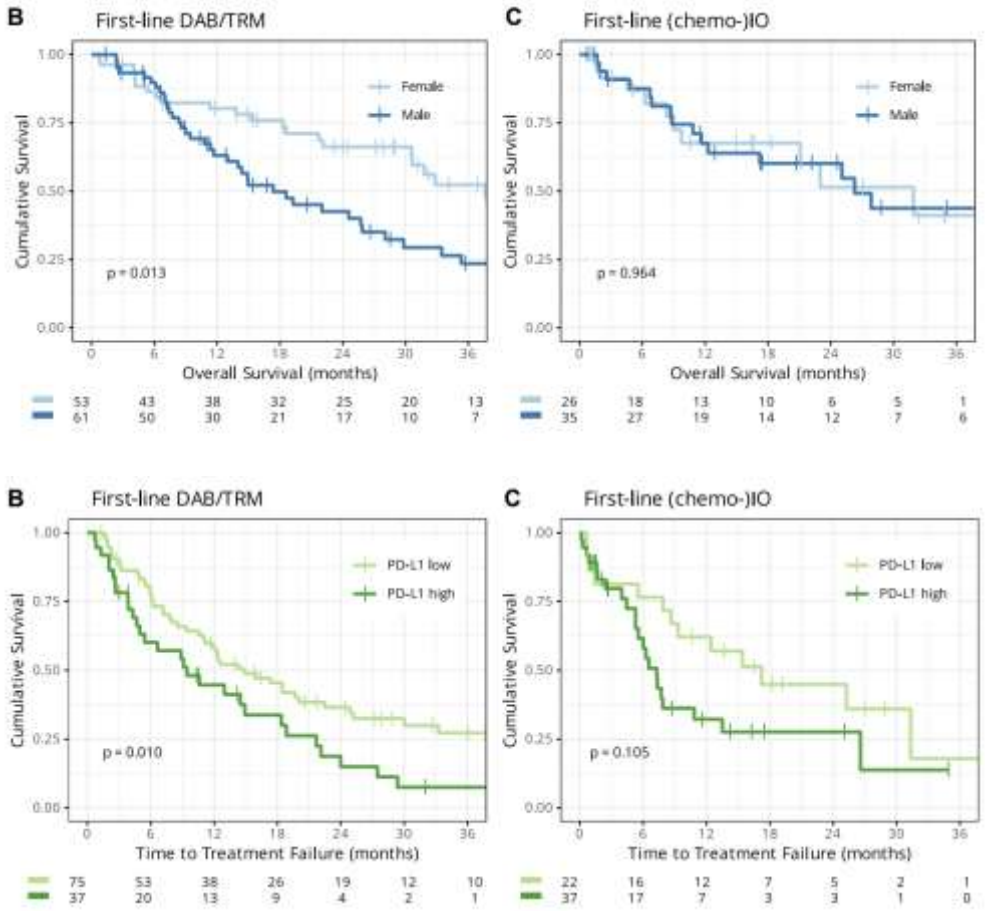
BRAF



Wiesweg. J Thor Oncol 2025;20:1328

Oncogene addicted

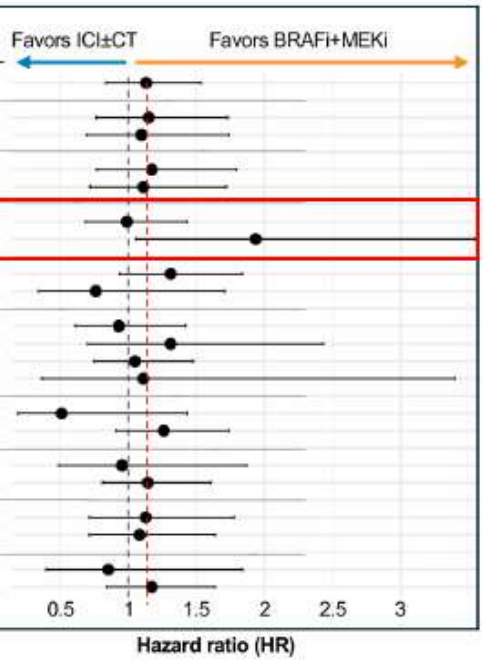
Benefit not generalizable



Wiesweg. J Thor Oncol 2025;20:1328

BRAF

Subgroup		N	PFS HR (95% CI)	P value
Overall		284	1.13 (0.83-1.53)	0.43
Age (years)	<70	159	1.15 (0.76-1.73)	0.51
	≥70	125	1.10 (0.69-1.74)	0.70
Sex	Male	136	1.17 (0.77-1.79)	0.46
	Female	148	1.11 (0.72-1.71)	0.63
Smoking status	Ever	191	0.99 (0.68-1.43)	0.95
	Never	91	1.94 (1.06-3.55)	0.03
ECOG PS	0-1	228	1.31 (0.93-1.84)	0.12
	≥2	44	0.76 (0.34-1.71)	0.51
PD-L1 TPS	≥50%	134	0.93 (0.61-1.42)	0.74
	1-49%	83	1.31 (0.70-2.43)	0.40
	≥1%	217	1.05 (0.75-1.48)	0.78
	<1%	39	1.11 (0.36-3.40)	0.86
Metastatic sites	>3	32	0.51 (0.19-1.43)	0.20
	≤3	252	1.26 (0.91-1.74)	0.16
Brain metastasis	Yes	48	0.95 (0.49-1.87)	0.89
	No	236	1.14 (0.81-1.61)	0.45
Bone metastasis	Yes	106	1.13 (0.72-1.77)	0.61
	No	178	1.08 (0.71-1.64)	0.71
Liver metastasis	Yes	48	0.85 (0.40-1.84)	0.68
	No	236	1.17 (0.84-1.64)	0.35



Di Federico. Lancet Oncol 2025;26:1357

Oncogene addicted

Benefit not generalizable

PHAROS

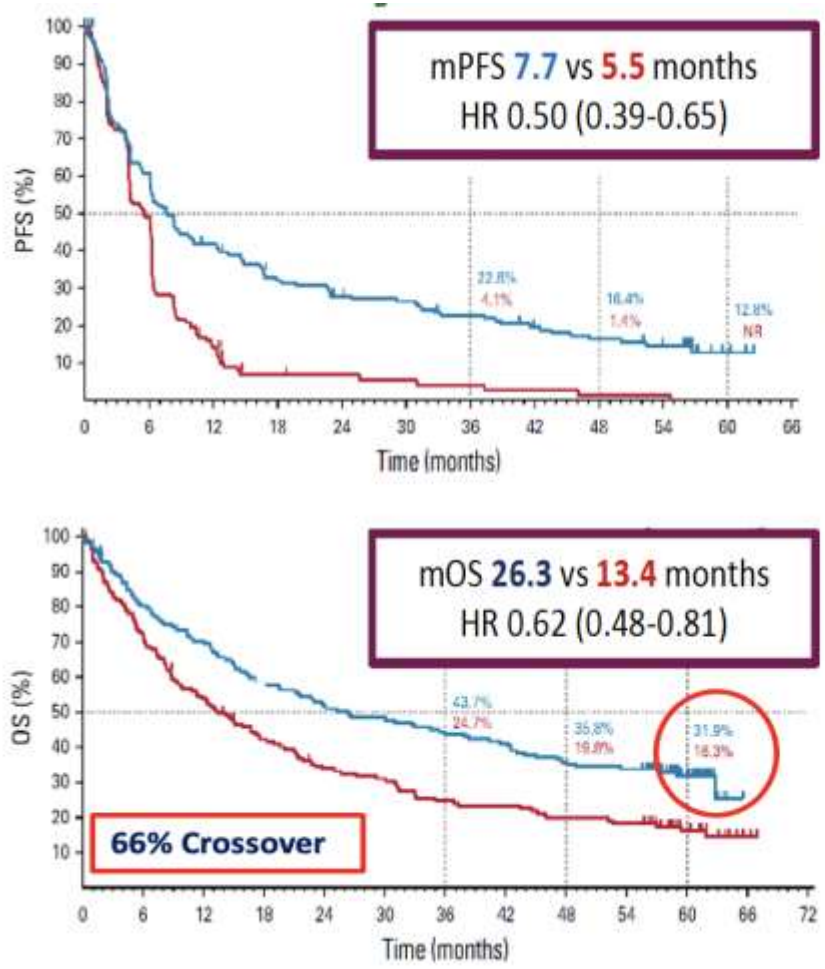
Characteristic	Treatment-Naïve				Previously Treated			
	No.	ORR,[a] % (95% CI)	mPFS,[a] Months (95% CI)	mOS, Months (95% CI)	No.	ORR,[a] % (95% CI)	mPFS, Months[a] (95% CI)	mOS, Months (95% CI)
Age group								
<65 years	23	74 (52 to 90)	24.9 (5.6 to NE)	51.2 (19.8 to NE)	13	38 (14 to 68)	9.0 (1.9 to NE)	32.6 (3.4 to NE)
≥65 years	36	75 (58 to 88)	30.4 (15.7 to NE)	39.3 (25.4 to NE)	26	54 (33 to 73)	9.3 (6.2 to 24.8)	22.7 (14.1 to 31.1)
Sex								
Female	33	70 (51 to 84)	30.7 (15.7 to NE)	47.6 (21.5 to NE)	19	53 (29 to 76)	9.3 (7.4 to 24.8)	30.3 (20.7 to NE)
Male	26	81 (61 to 93)	30.2 (9.2 to NE)	51.2 (19.6 to NE)	20	45 (23 to 69)	7.3 (3.6 to NE)	14.7 (6.7 to NE)
ECOG PS								
0	19	74 (49 to 91)	30.7 (15.7 to NE)	NE (35.7 to NE)	7	86 (42 to 100)	18.4 (7.4 to NE)	32.2 (22.7 to NE)
1	40	75 (59 to 87)	30.4 (9.2 to NE)	32.9 (20.3 to 61.4)	32	41 (24 to 59)	7.5 (5.4 to 24.8)	20.0 (9.1 to 32.6)
Smoking status								
Current/former	41	71 (55 to 84)	24.8 (9.2 to NE)	35.7 (20.3 to NE)	28	46 (28 to 66)	9.0 (6.2 to NE)	20.0 (9.1 to 32.6)
Never	18	83 (59 to 96)	41.8 (16.6 to NE)	61.4 (61.4 to NE)	11	55 (23 to 83)	18.4 (3.6 to NE)	32.2 (8.6 to NE)
Previously treated with IO								
No			NA		15	33 (12 to 62)	9.0 (3.6 to 18.4)	20.7 (8.6 to NE)
Yes			NA		24	58 (37 to 78)	13.8 (6.2 to NE)	26.6 (14.1 to NE)

Johnson. J Clín Oncol 2025

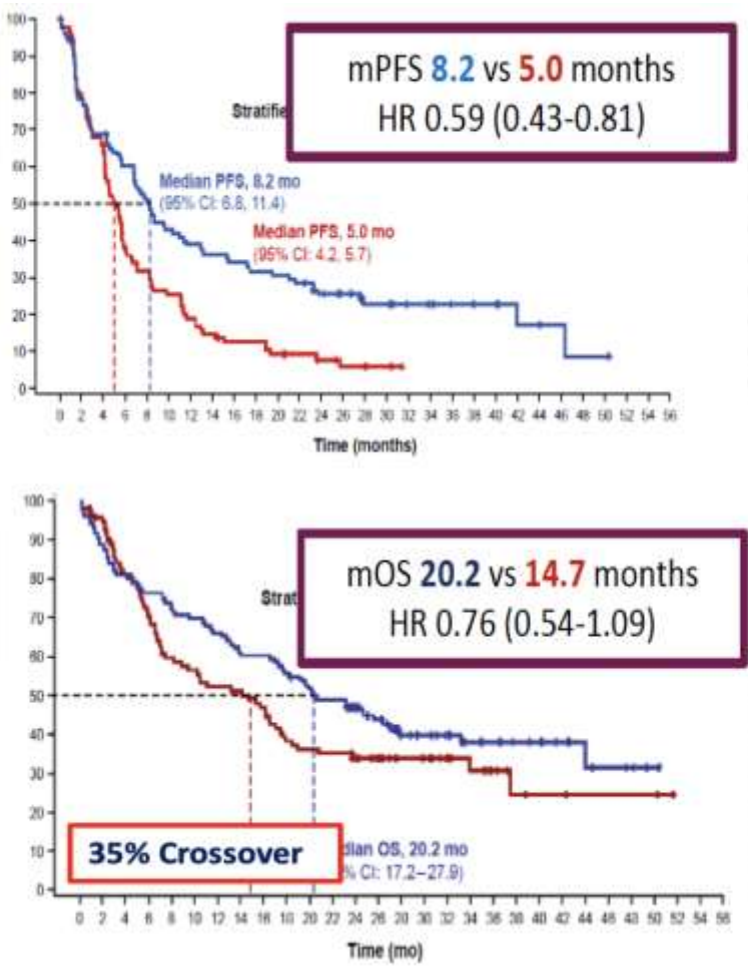
PD-L1

PD-L1≥50%

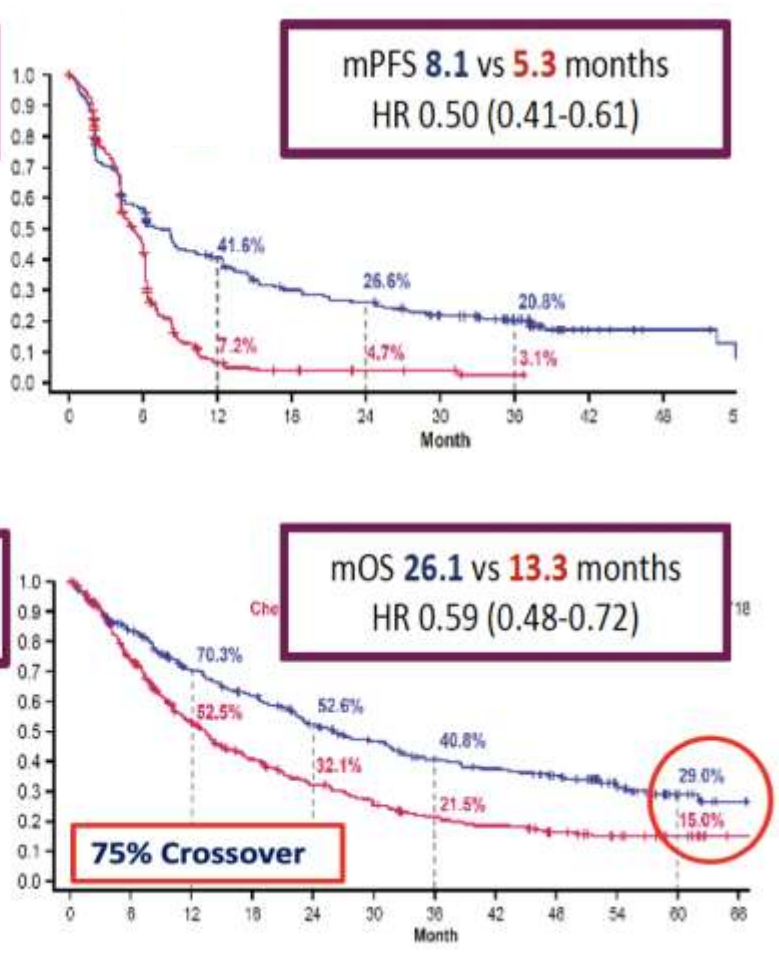
Keynote-024



Impower110



Empower lung1

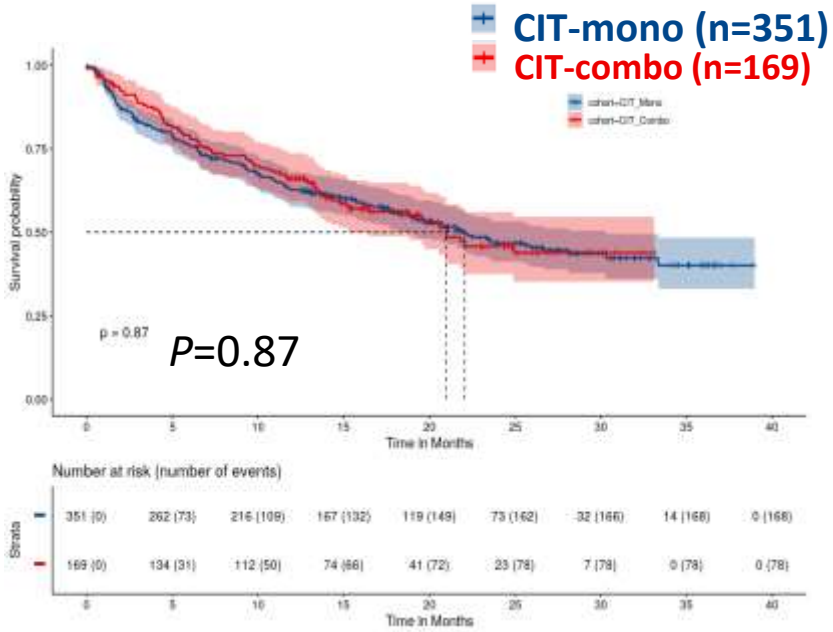


Reck JCO 2021 ; Jassem JTO 2021; Kilickap WCLC 2024

PD-L1

PD-L1≥50%

RWD in PD-L1 =/> 50%



P=0.87

Time
(months)

Flatiron Health: Data from 141,013 advanced NSCLC and PD-L1≥50%

FDA data: 9084 patients, 12 trials, patients with PD-L1≥50%

Exploratory OS, PFS, and ORR: NSCLC PD-L1 ≥50%

	Chemo-IO (*N*=455)	IO-alone (*N*=1,298)
OS		
Median, months (95% CI)	25.0 (19.0, NE)	20.9 (18.5, 23.1)
HR (95% CI)	0.82 (0.62, 1.08)	
PFS		
Median, months (95% CI)	9.6 (8.4, 11.1)	7.1 (6.3, 8.3)
HR (95% CI)	0.69 (0.55, 0.87)	
ORR		
% (95% CI)	61 (56, 66)	43 (41, 46)
Odds ratio	1.2 (1.1, 1.3)	

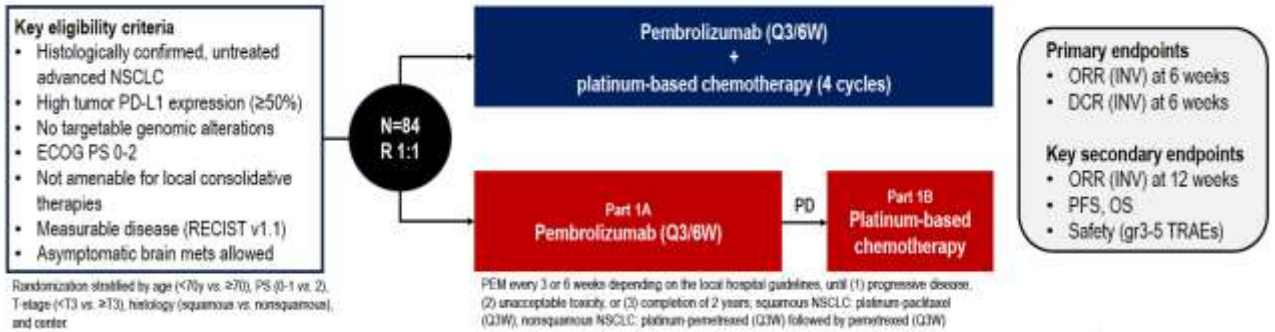
Abbreviations: Chemo-IO=platinum-based doublet chemotherapy plus immunotherapy; CI=confidence interval; HR-hazards ratio; IO=immunotherapy; *N*=number; NSCLC=non-small-cell lung cancer; NE=not estimable; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival.

Peters et al ESMO 2021 ; Akinboroo et al ASCO 2022

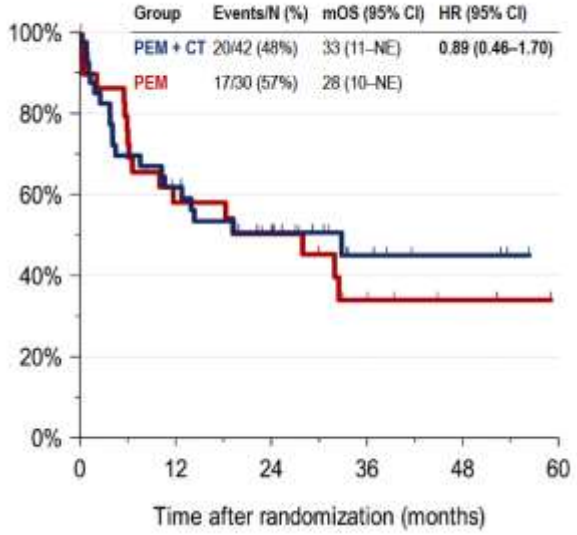
PD-L1

PD-L1≥50%

PAULIEN

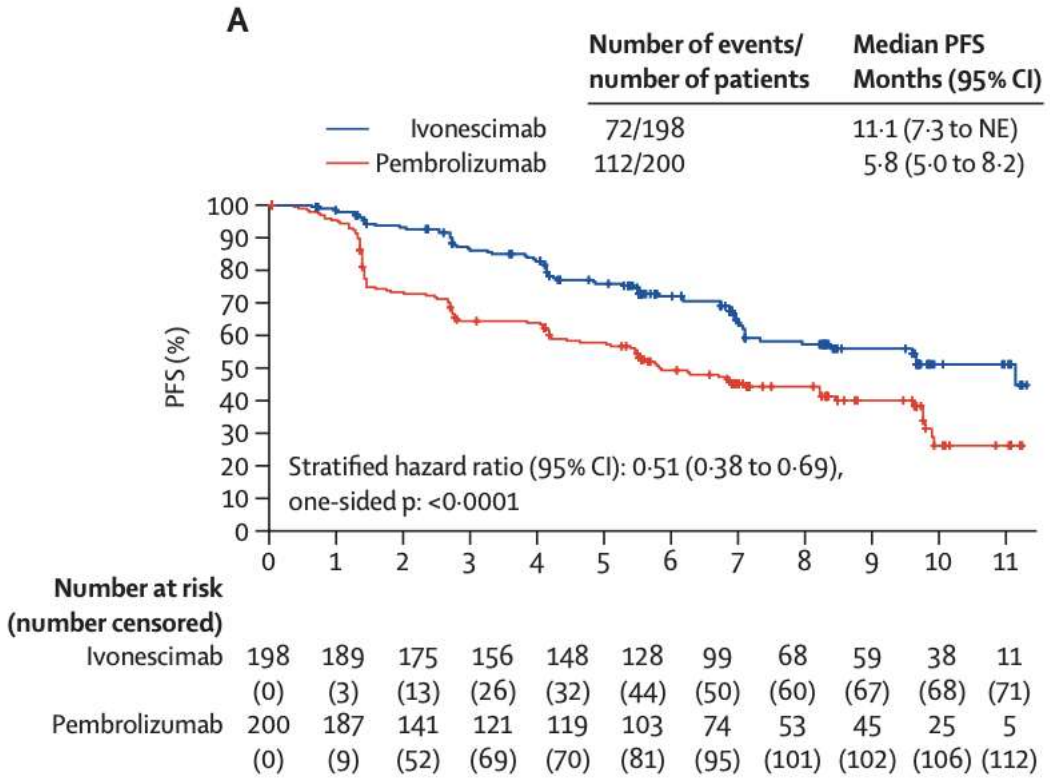


Overall survival



Houda. ESMO 2025

HARMONi-2

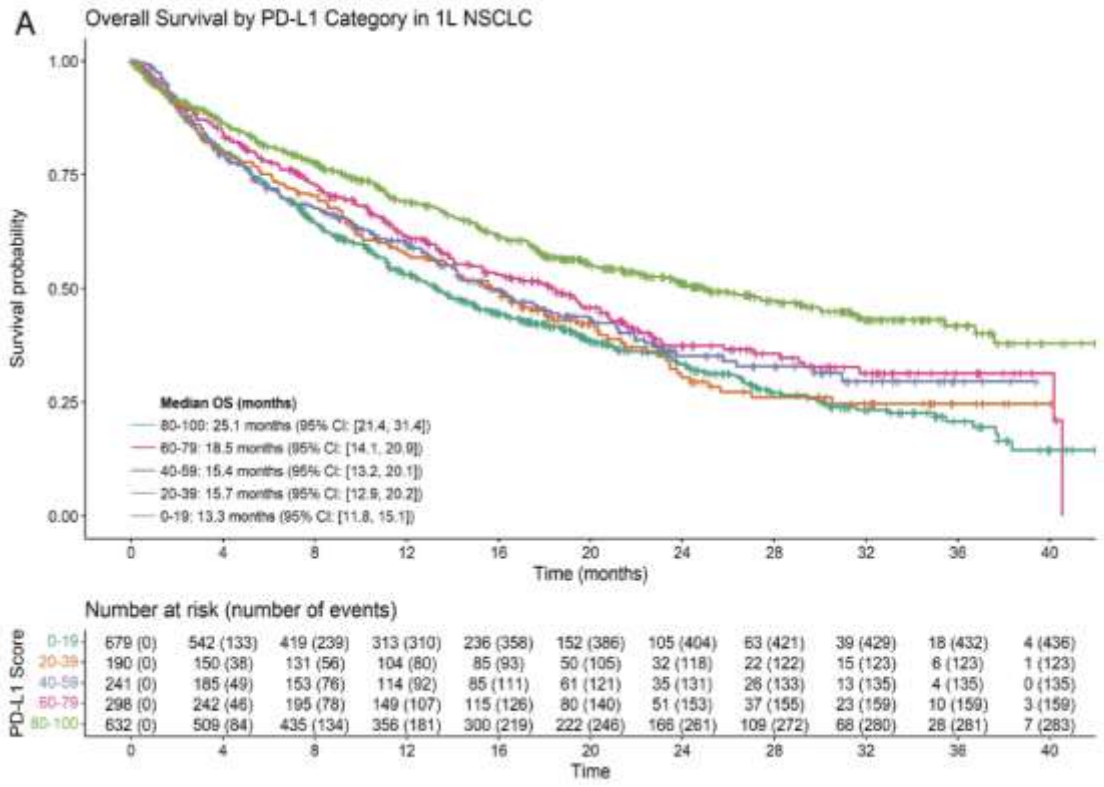


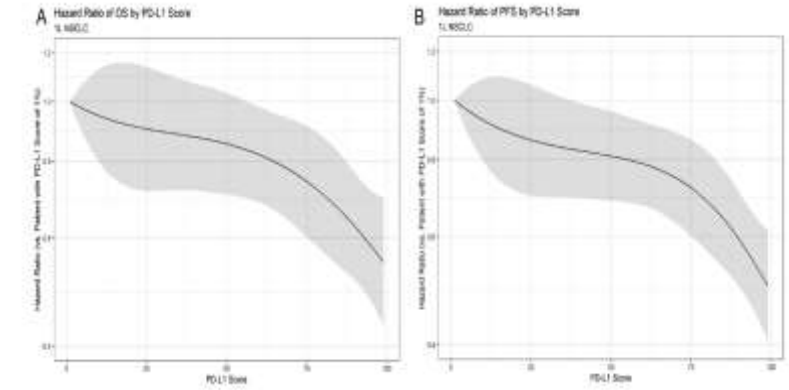
Number at risk (number censored)

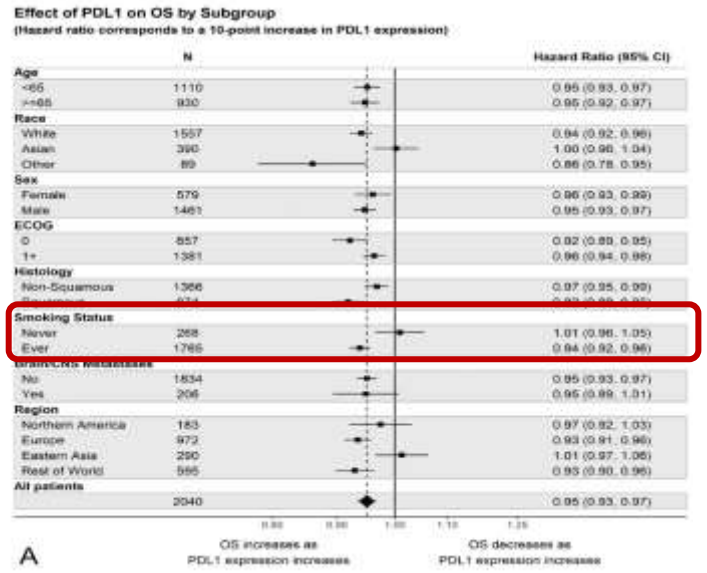
Ivonescimab	198 (0)	189 (3)	175 (13)	156 (26)	148 (32)	128 (44)	99 (50)	68 (60)	59 (67)	38 (68)	11 (71)
Pembrolizumab	200 (0)	187 (9)	141 (52)	121 (69)	119 (70)	103 (81)	74 (95)	53 (101)	45 (102)	25 (106)	5 (112)

Xiong. Lancet 2025; 405: 839–49

Pooled Analysis 11 Prospective Clinical trials
PD-L1 expression effect







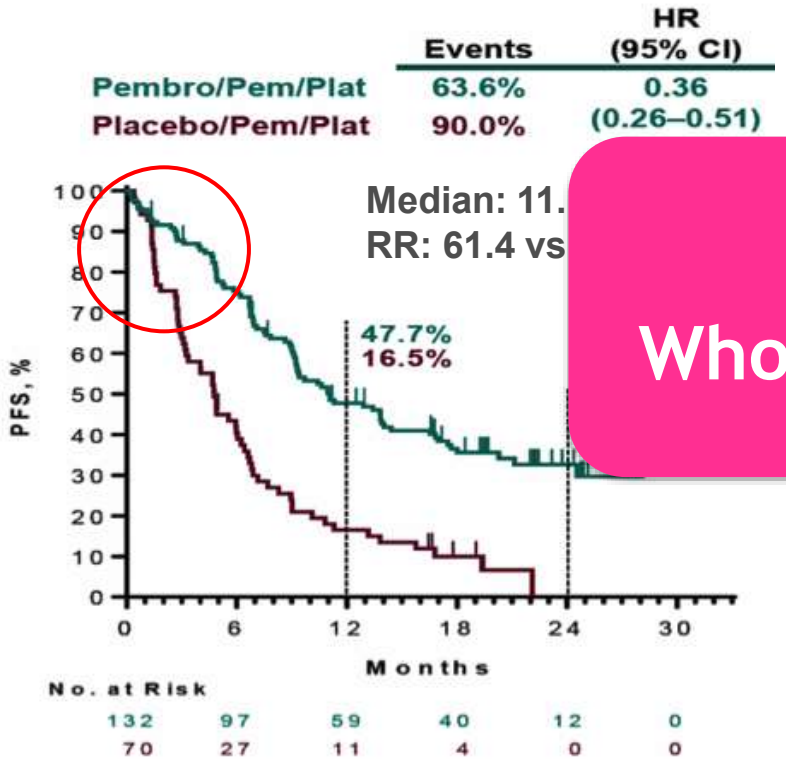
Vallejo J et al. Oncologist 2024

PD-L1

≥50%

PFS in PD-L1 High NSCLC

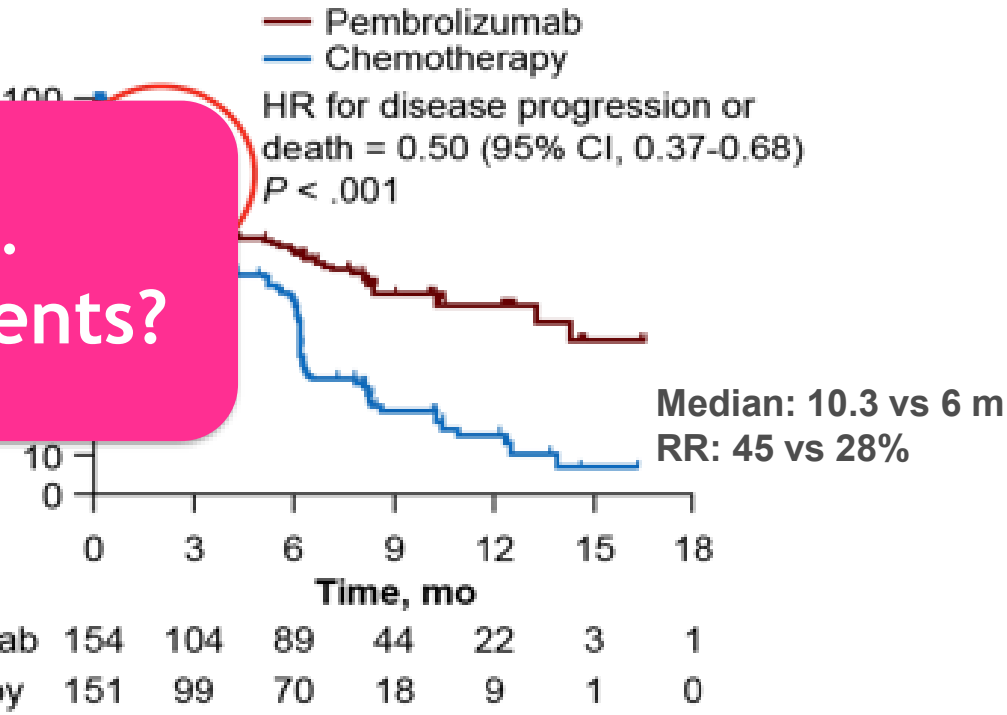
KN-189 (TPS ≥50%)



PFS: HR = 0.36
(95% CI, 0.26-0.51; *P* = .0001)

The challenge…
Who are these patients?

KN-024



PFS: HR = 0.50
(95% CI, 0.37-0.68; *P* < .001)

Gadgeel ASCO 2019; Gandhi, NEJM 2018; Reck, NEJM 2016

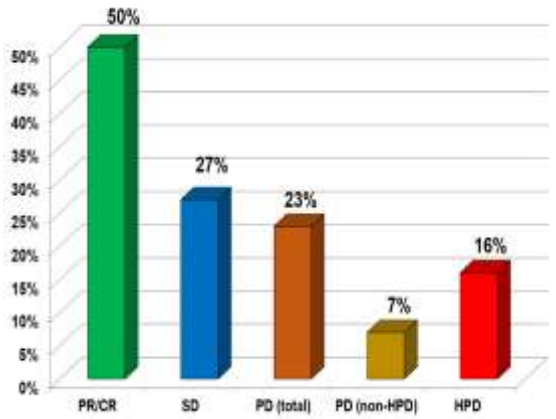
PD-L1

≥50%

PD-L1 High NSCLC

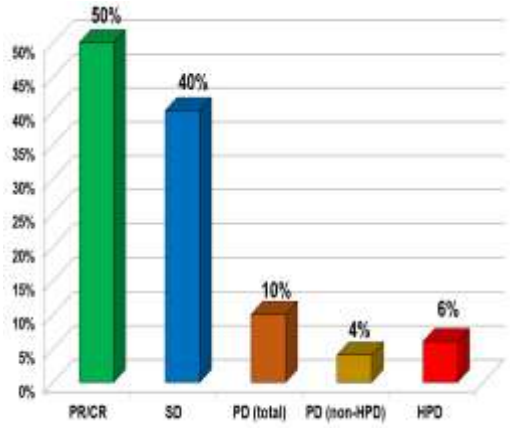
Tumor burden…not easy to define

Single agent ICI
PD-L1 ≥ 50%

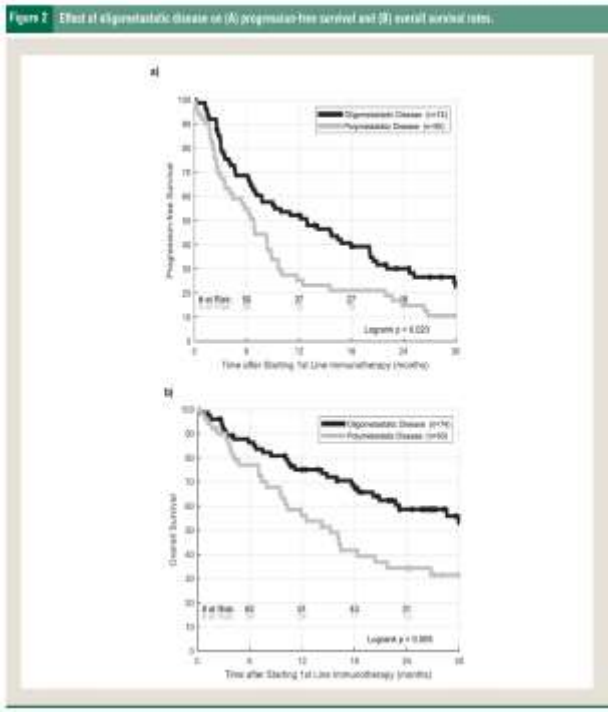


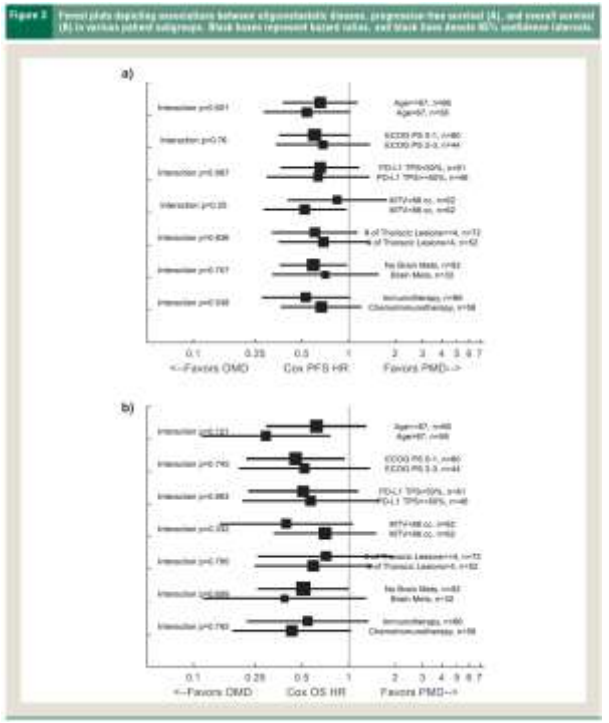
N=44

Chemo + ICI
All comers



N=50





HPD occurs in up to 16% of PD_L1 TPS ≥50% pts upon first-line single agent ICI and is associated with por baseline PS, dNLR>3 and poor survival after adjustement fo potential prognostic variables

For advanced NSCLC patients receiving first-line IMT, the **presence of extrathoracic OMD and low volumetric disease burden on PET are favorable prognostic factors**

Ferrara R, et al. ESMO 2020. Andraos et al. Clin Lung Cancer 2022

Chemo-ICB is«globally» registered regardless of PD-L1

Study Name	Hysto	PDL1	ICB* in Experimental arm	HR OS (95% CI)
KN189	Non-Sq	All	Pembrolizumab	0.60 (0.5 - 0.72)
Impower 130	Non-Sq	All	Atezolizumab	0.79 (0.64 - 0.98)
Impower 150	Non-Sq	All	Atezolizumab+ Bevacizumab	0.80 (0.67 - 0.95)
CAMEL	Non-Sq	All	Camrelizumab	0.74 (0.58 - 0.93
RATIONALE 304	Non-Sq	All	Tislelizumab	0.87 (0.65 - 1.17)
ORIENT 11	Non-Sq	All	Sintilimab	0.65 (0.50 - 0.85)
RATIONALE 307	Sq	All	Tislelizumab	0.68 (0.46 - 1.01)
ORIENT 12	Sq	All	Sintilimab	0.56 (0.35 - 0.90)
KN407	Sq	All	Pembrolizumab	0.71 (0.58- 0.88)
CM9LA	NSCLC	All	Nivolumab Ipilimumab	0.74 (0.63- 087)
POSEIDON	NSCLC	All	Durvalumab +/- Tremelimumab	0.77 (0.65-0.92)
EMPOWER-Lung3	NSCLC	All	Cemiplimab	0.71 (0.53-0.91)

PD-L1

PD-L1 neg

Primary endpoint
- OS

Key eligibility criteria
- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0-1

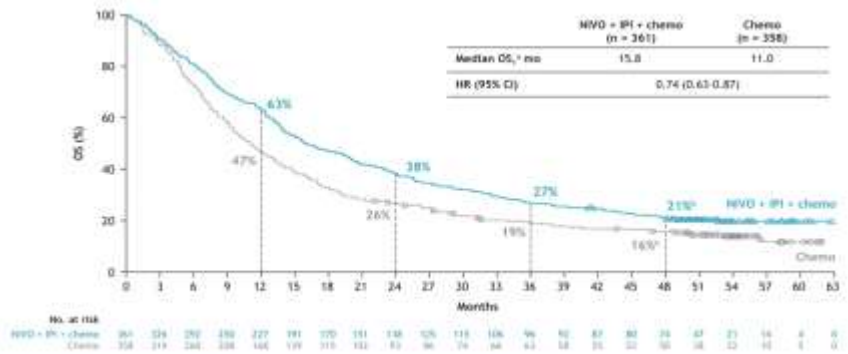
Stratified by PD-L1[b] (< 1%[c] vs ≥ 1%), sex, and histology (SQ vs NSQ)

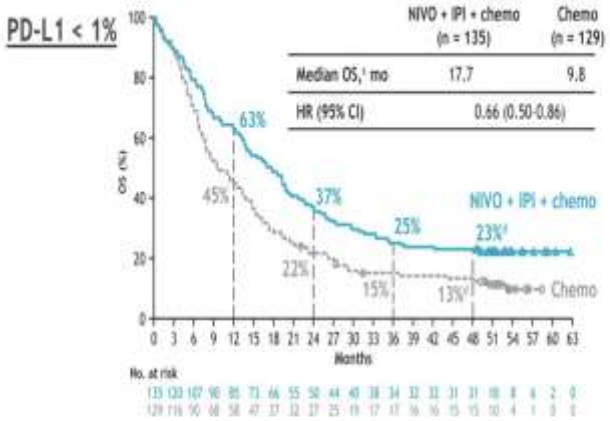
N = 719 → R 1:1

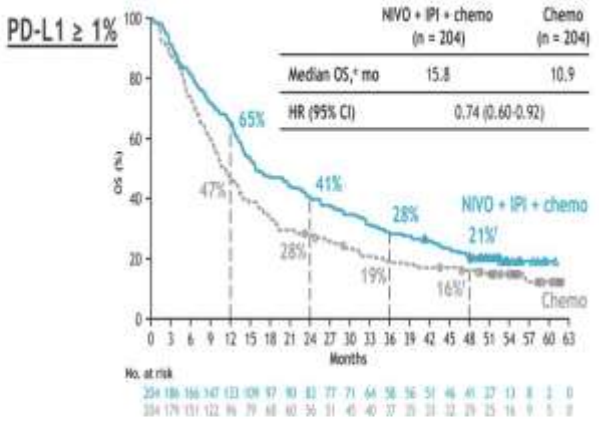
- n = 361: **NIVO** 360 mg Q3W + **IPI** 1 mg/kg Q6W + **Chemo**[d] Q3W (2 cycles)
- n = 358: **Chemo**[d] Q3W (4 cycles) with optional pemetrexed maintenance (NSQ)

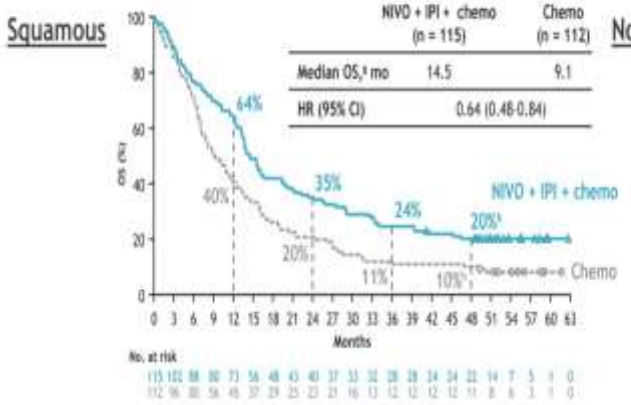
Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

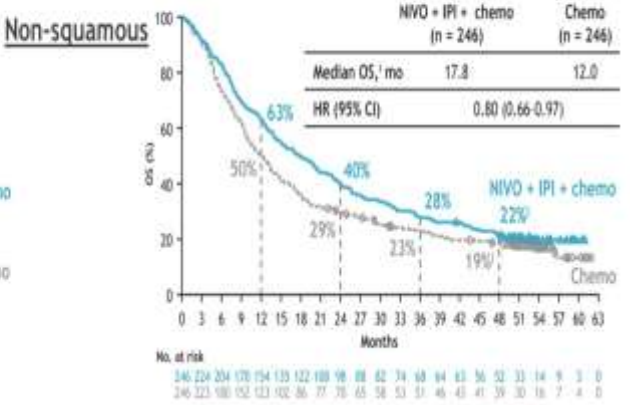
OS: 15.8 vs. 11.0
HR 0.74 (0.61-0.87)
4y OS: 21% vs. 16%









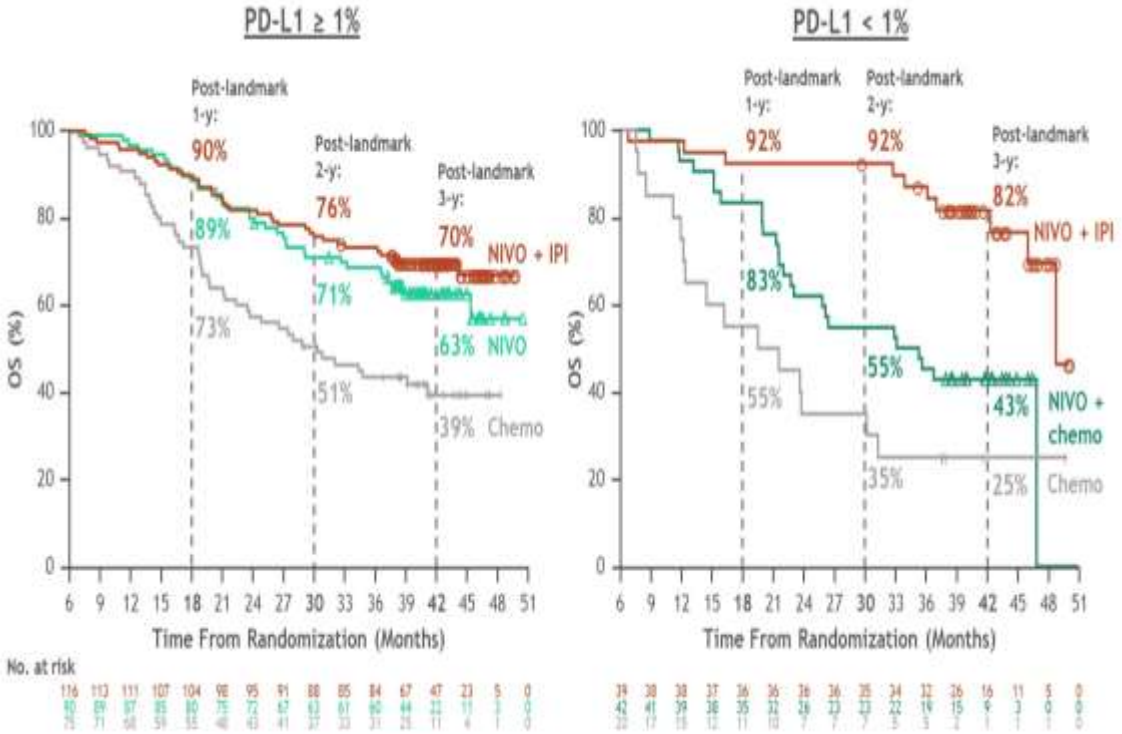


Carbone. J Immu Cancer 2024

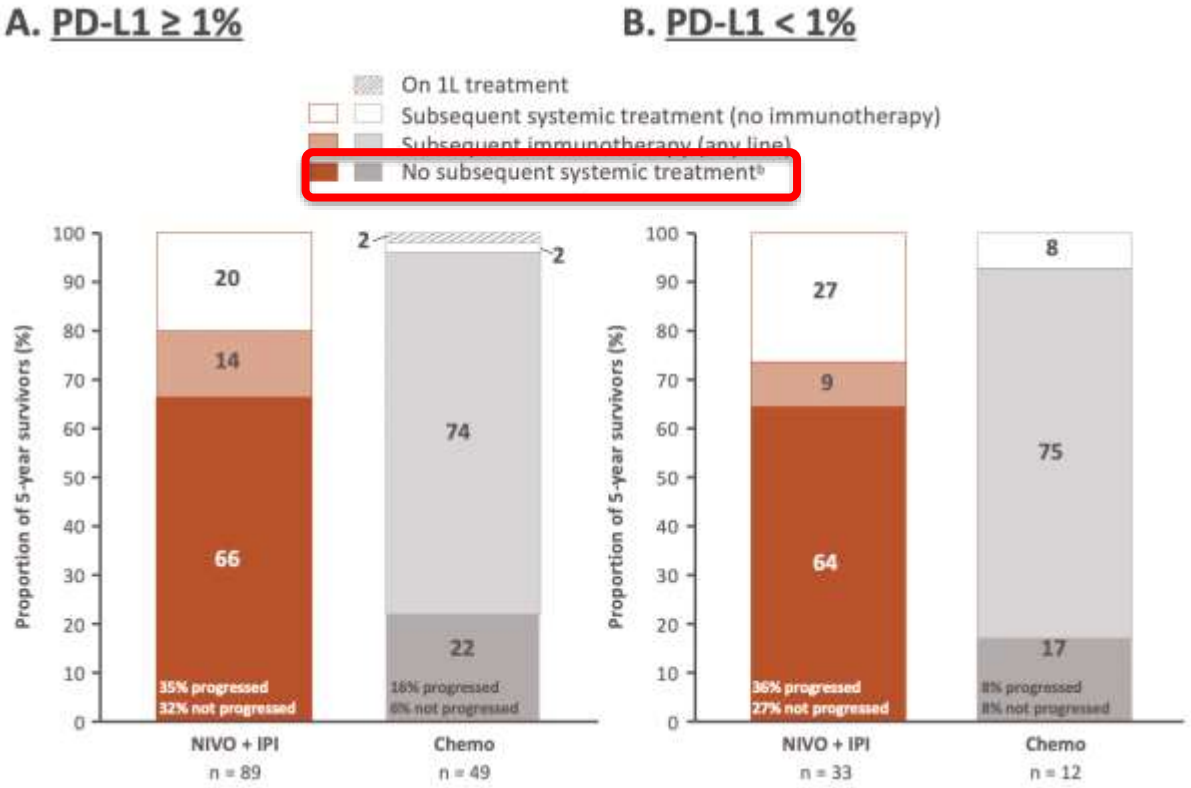
PD-L1

PD-L1 neg

CM227: Post-landmark OS in CR/PR PD-L1≥ 1% and PD-L1< 1%



CM 227: Treatment status in 5-year survivors

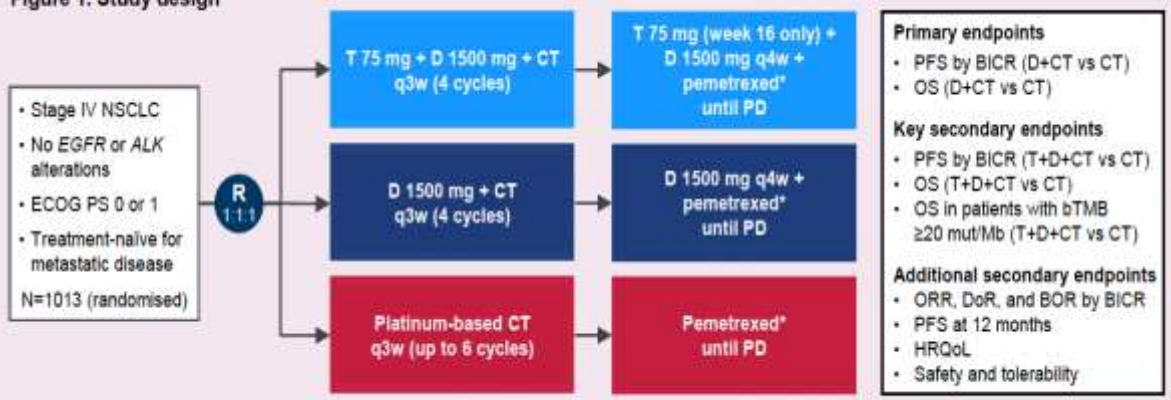


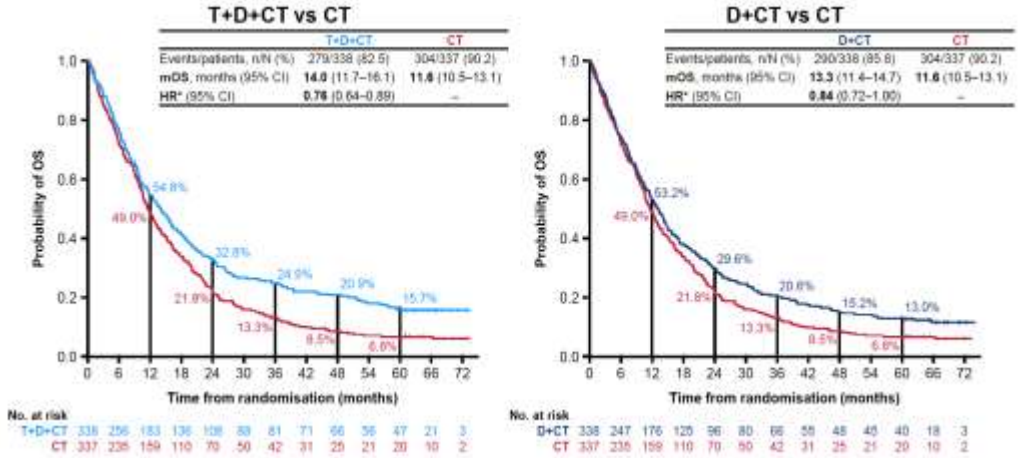
Ramalingam et al ASCO 2020; Brahmer J, et al. ASCO 2022

PD-L1

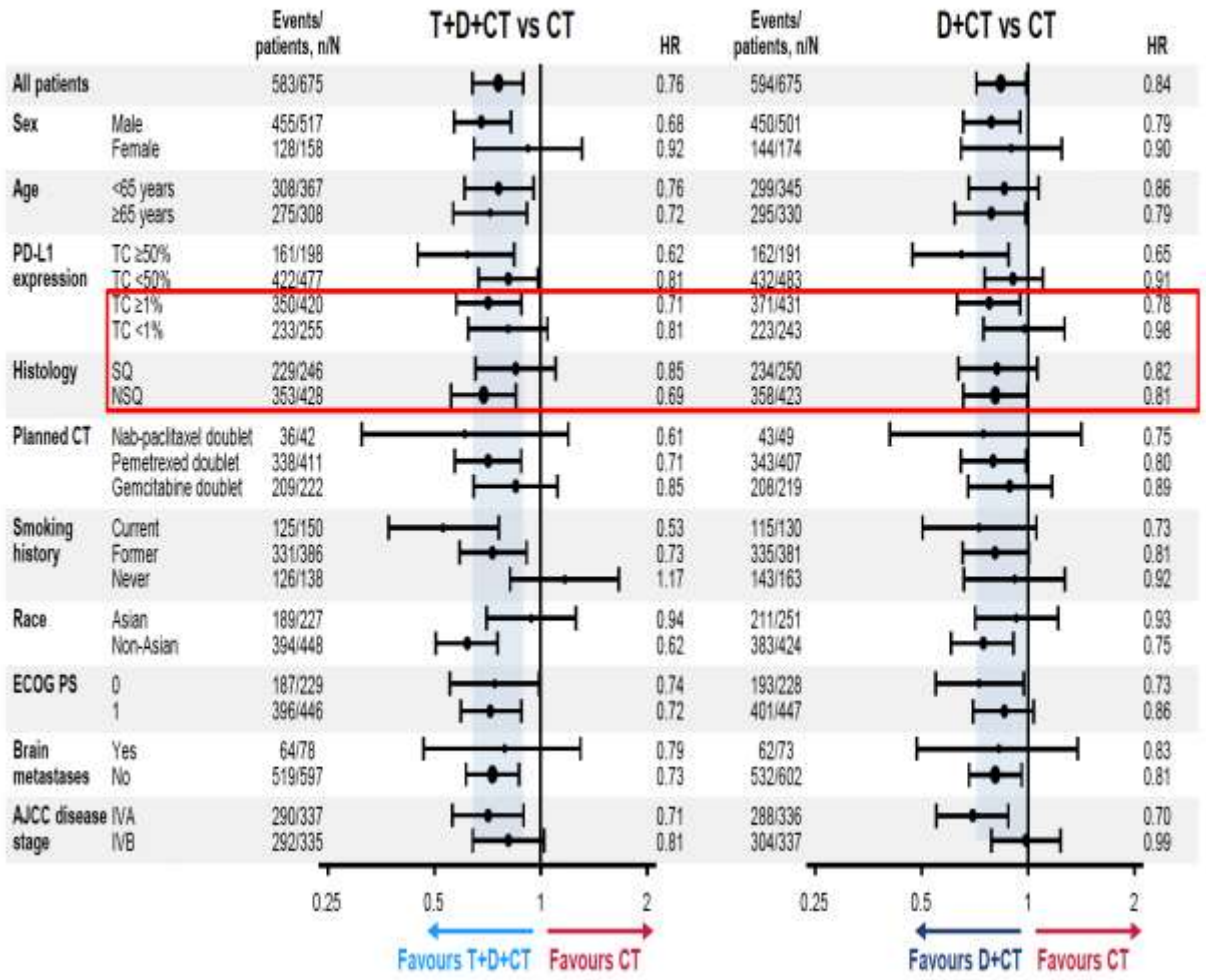
PD-L1 neg

Figure 1. Study design





OS Update: Subgroup Analysis



Petes S ESMO IO 2023
Johnson M, et al J Clin Oncol 2023

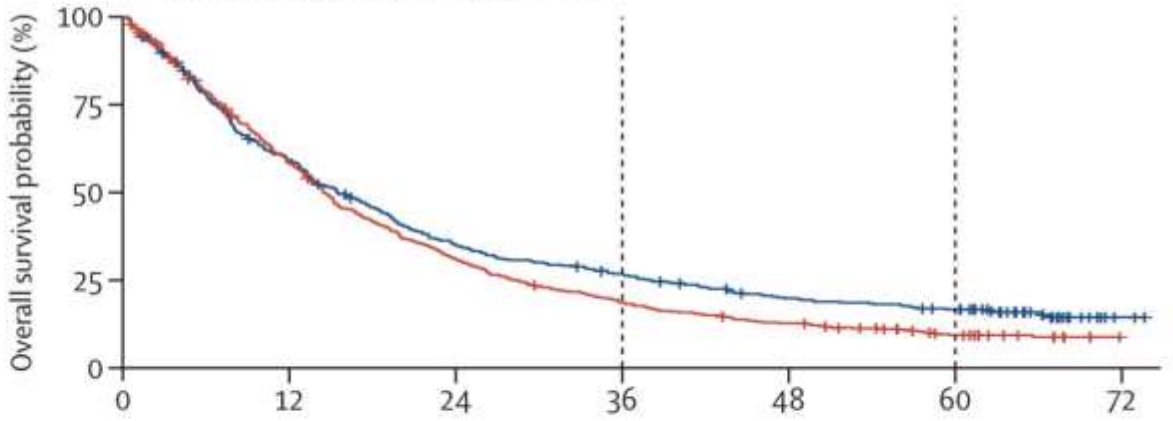
PD-L1

PD-L1 neg

Meta-análisis, individual data

	Reconstructed events/patients	Median overall survival, months (95% CI)	3-year overall survival, rate (95% CI)	5-year overall survival, rate (95% CI)
Dual CTLA-4 and PD-L1 or PD-1 blockade	367/447	15·5 (13·6–18·5)	26·8% (22·9–31·3)	16·6% (13·4–20·6)
Single PD-L1 or PD-1 blockade	452/512	14·5 (13·4–15·9)	18·7% (15·5–22·4)	9·3% (7·0–12·3)

HR 0·85; 95% CI 0·74–0·98; p=0·021



Number at risk (censored)							
Dual CTLA-4 and PD-L1 or PD-1 blockade	447 (0)	260 (7)	152 (10)	114 (12)	81 (16)	61 (23)	3 (77)
Single PD-L1 or PD-1 blockade	512 (0)	292 (11)	155 (12)	92 (13)	62 (14)	36 (25)	1 (59)

Di Federico. Lancet Oncol 2025;26:1443

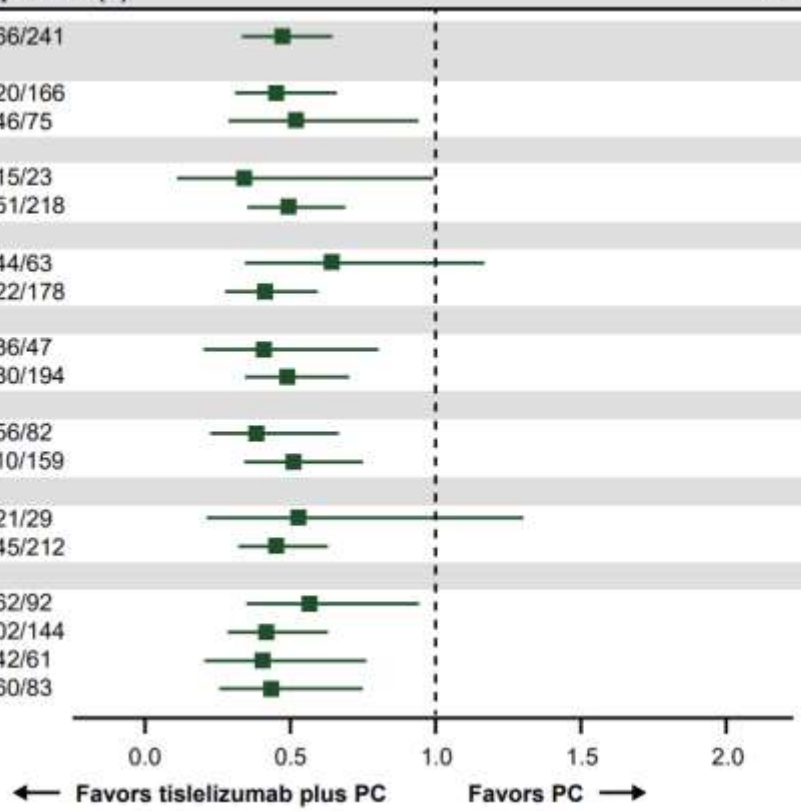
PD-L1

PD-L1 neg

Carbo/paclit vs carbo/paclit/tislelizumab (PFS)

C

	Events/patients (*n*)	Unstratified HR (95% CI)
Overall	166/241	0.47 (0.34-0.64)
Age		
<65 years	120/166	0.45 (0.31-0.66)
≥65 years	46/75	0.52 (0.29-0.94)
Sex		
Female	15/23	0.34 (0.12-0.99)
Male	151/218	0.49 (0.36-0.69)
ECOG performance status		
0	44/63	0.64 (0.35-1.17)
1	122/178	0.41 (0.28-0.60)
Smoking status		
Never	36/47	0.41 (0.21-0.80)
Current or former	130/194	0.49 (0.34-0.70)
Disease stage		
IIIB	56/82	0.38 (0.22-0.67)
IV	110/159	0.51 (0.35-0.75)
Liver metastases at baseline		
Yes	21/29	0.53 (0.21-1.30)
No	145/212	0.45 (0.32-0.63)
PD-L1 expression in TC		
<1%[b]	62/92	0.57 (0.34-0.94)
≥1%	102/144	0.42 (0.28-0.63)
1% to 49%	42/61	0.40 (0.21-0.76)
≥50%	60/83	0.44 (0.26-0.75)



Wang. ESMO Open 2024;9

TMB

TMB : no standardized methodology and threshold in NSCLC

Line of Tx	Clinical Trial	Analysis	Study Therapy	Assay	Cutpoint	Survival	Hazard Ratio	
							High TMB	Low TMB
Anti-PD-1 or PD-L1 vs. chemo								
1L	CM-26	E	Nivo	WES	243 mut/exome	PFS	0.62 (0.38-1.00)	1.82 (1.30-2.55)
1L	KN-042	E	Pembro	WES	175 mut/exome	PFS	0.75 (0.59-0.95)	1.27 (1.04-1.55)
1L	MYSTIC	E	Durva	F1CDx	10 mut/Mb	OS	0.70 (0.47-1.06)	1.26 (0.90-1.77)
2L	KN-010	E	Pembro	WES	175 mut/exome	PFS	0.59 (0.40-0.87)	1.09 (0.72-1.63)
2/3L	POPLAR	E	Atezo	F1	16.2 mut/Mb	PFS	0.49 (0.19, 1.3)	1.28 (0.77, 2.12)
					9.9 mut/Mb	PFS	0.49 (0.25-0.93)	2.41 (1.24-4.67)
Anti-PD1 or PD-L1 + anti-CTLA-4 vs. chemo								
1L	CM-227	P	Nivo + Ipi	F1CDx	10 mut/Mb	PFS	0.58 (0.41-0.81)	1.07 (0.84-1.35)
					10 mut/Mb	OS	0.68 (0.51-0.91)	0.75 (0.59-0.94)
1L	MYSTIC	E	Durva + Treme	F1CDx	10 mut/Mb	OS	0.72 (0.48-1.09)	1.39 (1.00-1.92)
Anti-PD1 + chemo vs. chemo								
1L	KN-189	E	Pembro + Chemo	WES	175 mut/exome	PFS	0.32 (0.21-0.51)	0.51 (0.35-0.74)
1L	KN-407	E	Pembro + Chemo	WES	175 mut/exome	PFS	0.57 (0.41-0.81)	0.68 (0.48-0.96)
1L	RATIONALE-307[a]	E	Tisle + Chemo	OncoScreen	10 mut/Mb	PFS	0.44 (0.27-0.72)	0.57 (0.36-0.91)
					12 mut/Mb		0.34 (0.19-0.62)	0.61 (0.40-0.93)
					14 mut/Mb		0.29 (0.13-0.65)	0.57 (0.39-0.82)
Anti-PD-1 + anti-CTLA-4 + chemo vs. chemo								
1L	CM-9LA	E	Nivo + Ipi + Chemo	F1CDx	10 mut/Mb	PFS	0.74 (0.51-1.08)	0.75 (0.55-1.02)
						OS	0.49 (0.34-0.70)	0.83 (0.63-1.10)
Anti-PD-L1 + anti-CTLA-4 vs. ICI								
1L	MYSTIC	E	Durva + Treme	F1CDx	10 mut/Mb	OS	1.00 (0.65-1.54)	1.09 (0.79-1.50)

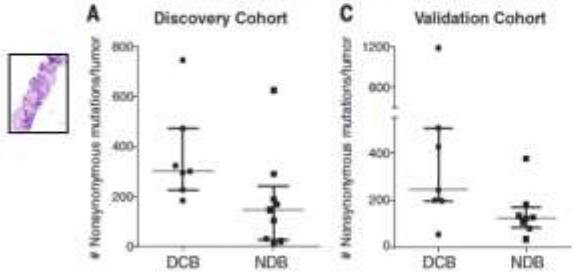
Kenudson, JTO 2022

TMB

TMB as a biomarker

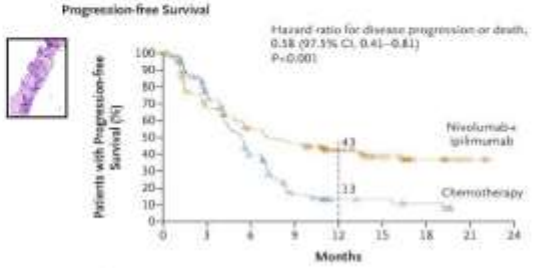
Anti-PD-1 (Nivolumab)[1]

WES, cut off ≥178 mutations



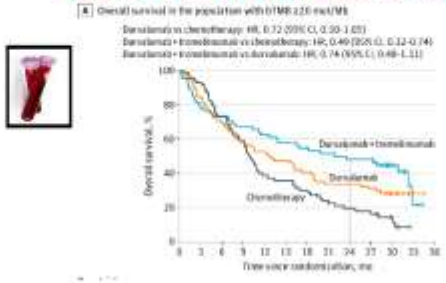
Anti-PD-1+CTLA-4 (Nivolumab + Ipilimumab; CheckMate 227)[2]

Tissue NGS panel, cut off >10 mutations/Mb



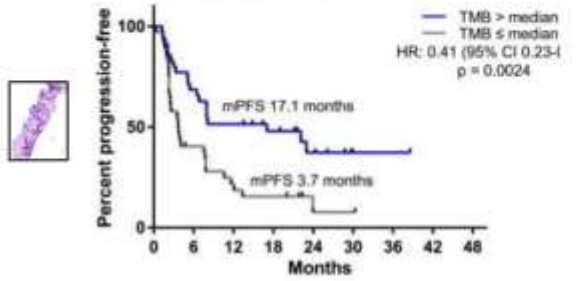
Anti-PDL-1+CTLA-4 (Durvalumab + Tremelimumab; MYSTIC)[3]

Blood NGS panel, cut off ≥20 mutations/Mb



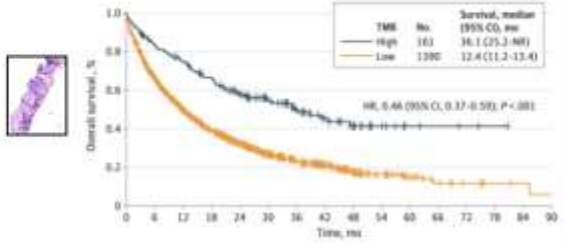
Anti-PD-1+CTLA-4 (Nivolumab + Ipilimumab; CheckMate 012)[4]

WES, cut off ≥158 mutations (median)



Anti-PD-1/PD-L1 (Multicenter)[5]

Tissues NGS panels, >19 mutations/Mb



It is another (more) imperfect biomarker:

- **Several methodologies and samples:**
  - Tissue: WES (≥ 243, 178, 158, 75 mts); NGS panels (>10, >19 mts/Mb). Including indels ?
  - Blood: NGS panels (≥20, 14.5, 16 and 20 mts/Mb).
- **Tissue TMB:**
  - No predictive value in patients treated with ICI + chemo.
- **Blood TMB:**
  - It has been suggested to be a prognostic biomarkers.
- **FDA approved tissue TMB (2021) for solid tumors** (Keynote 158; no NSCLC case was included, >10 mut/Mb).

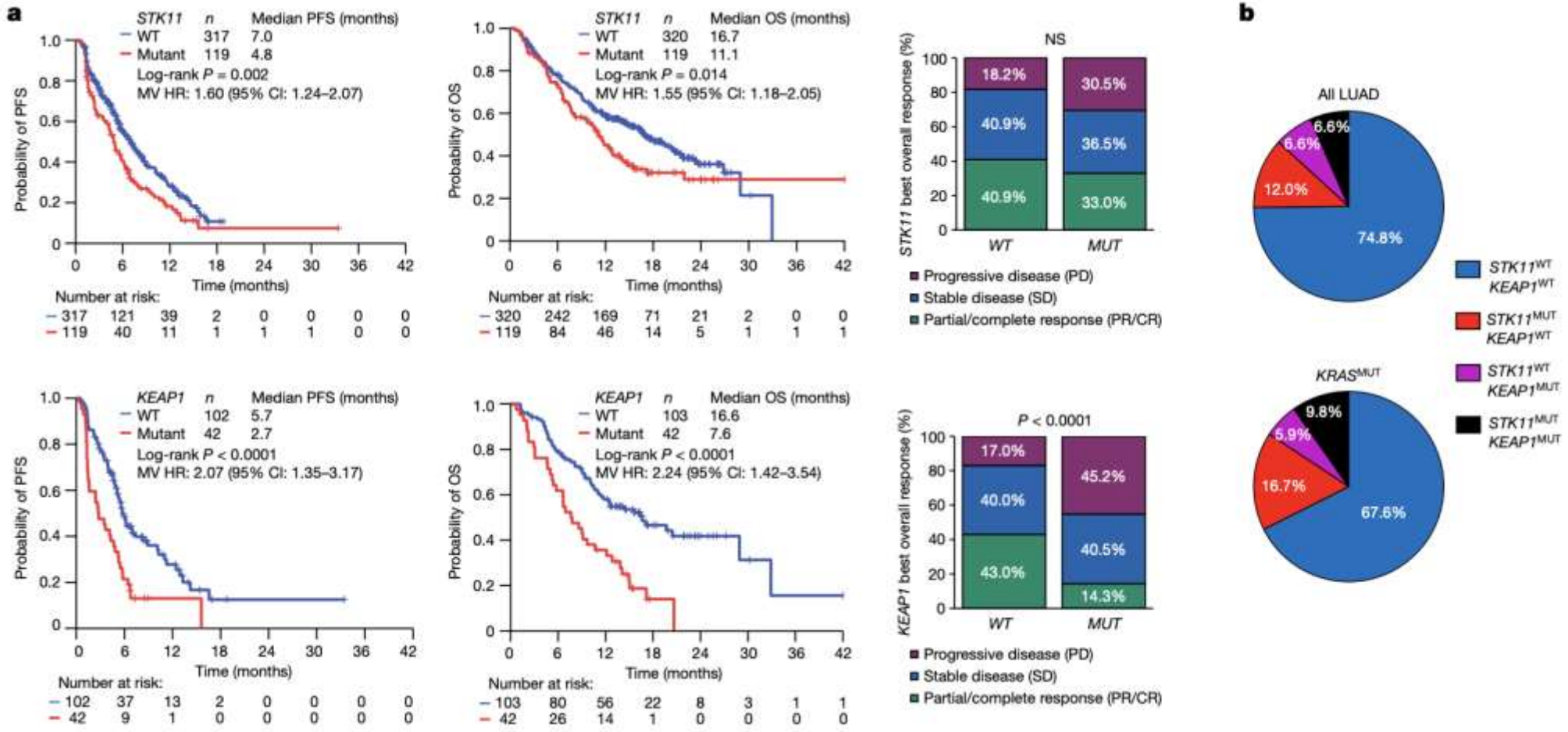
1. Rizvi NA et al. *Science.* 2015;348(6230):124-128; 2. Hellman MD et al. *N Engl J Med.* 2018;378(22):2093-2104; 3. Rizvi NA et al. *JAMA Oncol.* 2020;6(5):661-674; 4. Hellman MD et al. *Cancer Cell.* 2018;33(5):843-852; 5. Ricciuti B et al. *JAMA Oncol.* 2022;8(8):1160-1168.

Mod from S Peters, ESMO 2025

STK11/KEAP1

STK11 and KEAP1 mutations occur frequently in NSCLC

Co-mutations constitute major determinants of tumor molecular diversity



Skoulidis, Nature 2024;635:462

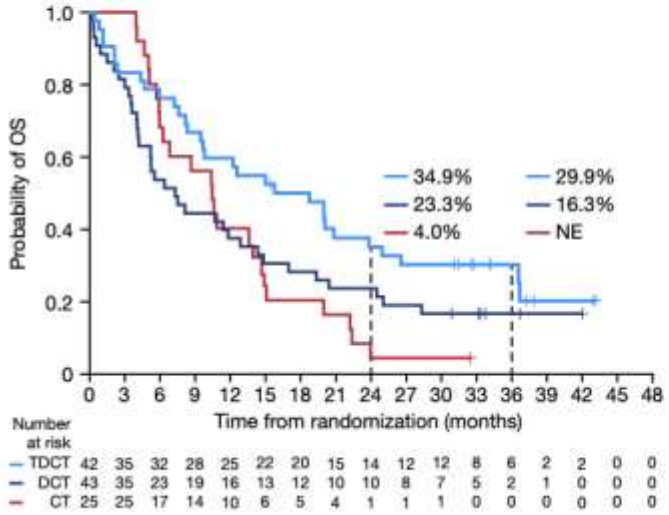
STK11/KEAP1

STK11 and KEAP1 mutations occur frequently in NSCLC

b

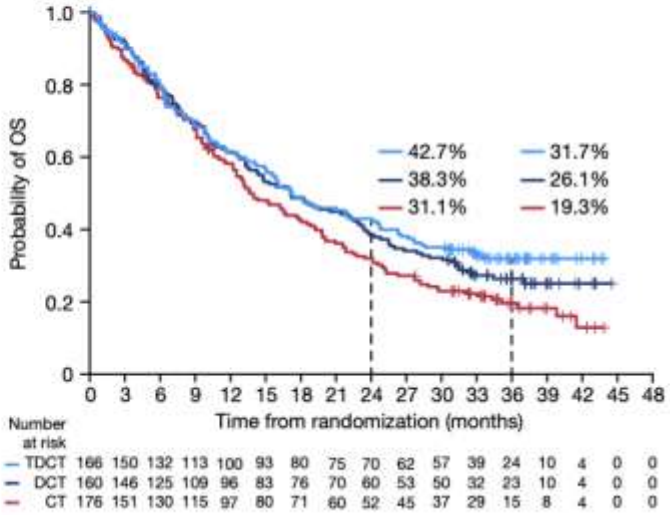
STK11^{MUT} and/or *KEAP1*^{MUT}

	TDCT	DCT	CT
mOS (months) (95% CI)	15.8 (9.5–23.8)	7.3 (4.2–12.9)	10.5 (6.0–14.7)
HR versus CT (95% CI)	0.50 (0.29–0.87)	0.90 (0.53–1.52)	–
HR versus DCT (95% CI)	0.64 (0.40–1.04)	–	–

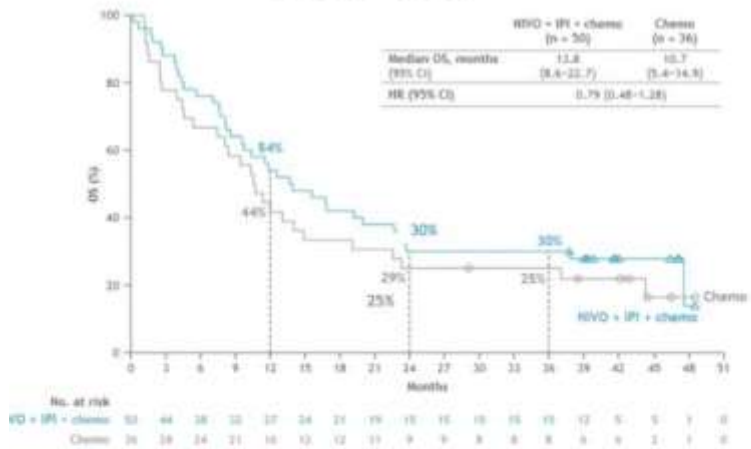


STK11^{WT} and *KEAP1*^{WT}

	TDCT	DCT	CT
mOS (months) (95% CI)	17.2 (14.2–24.1)	17.1 (13.3–22.6)	13.7 (12.0–17.8)
HR versus CT (95% CI)	0.74 (0.58–0.95)	0.81 (0.63–1.04)	–
HR versus DCT (95% CI)	0.90 (0.69–1.17)	–	–

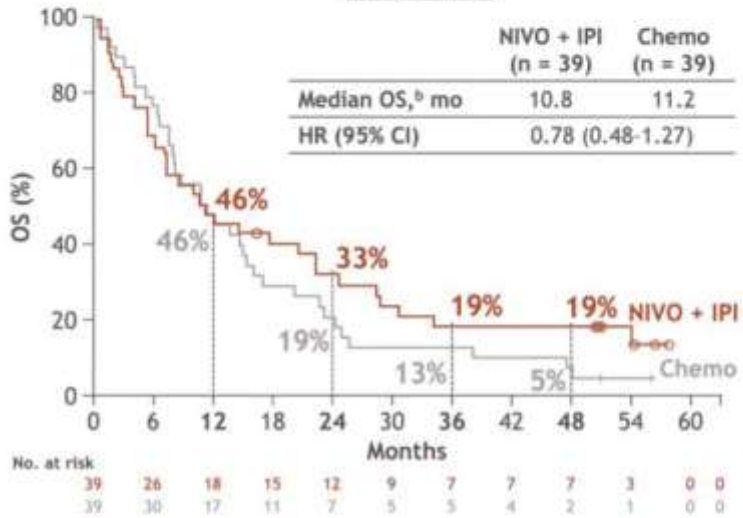


STK11-mut



STK11-mut

	NIVO + IPI (n = 39)	Chemo (n = 39)
Median OS,[b] mo	10.8	11.2
HR (95% CI)	0.78 (0.48-1.27)	



Skoulidis, Nature 2024;635:462
Paz-Ares LG, et al. Oral presentation at ASCO 2022 (Abstract LBA 9026)
Peters S, et al. Poster presented at WCLC 2022 (Poster OA 15.04)
Ramalingam, S.S. et al. (2021). Annals of Oncology, 32. doi:10.1016/j.annonc.2021.10.020

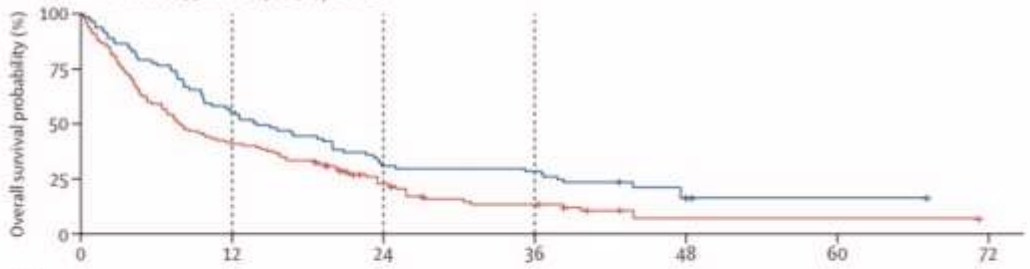
STK11

Meta-análisis; individual data

A *STK11* mutated

	Reconstructed events/patients	Median overall survival, months (95% CI)	1-year overall survival, rate (95% CI)	2-year overall survival, rate (95% CI)	3-year overall survival, rate (95% CI)
Dual CTLA-4 and PD-L1 or PD-1 blockade	65/81	13·9 (9·8–20·8)	55·6% (45·7–67·5)	30·9% (22·3–42·8)	28·4% (20·1–40·1)
Single PD-L1 or PD-1 blockade	102/120	7·8 (6·4–12·9)	40·8% (32·9–50·7)	22·7% (16·1–32·0)	13·4% (8·1–22·2)

HR 0·67; 95% CI 0·49–0·91; p=0·012

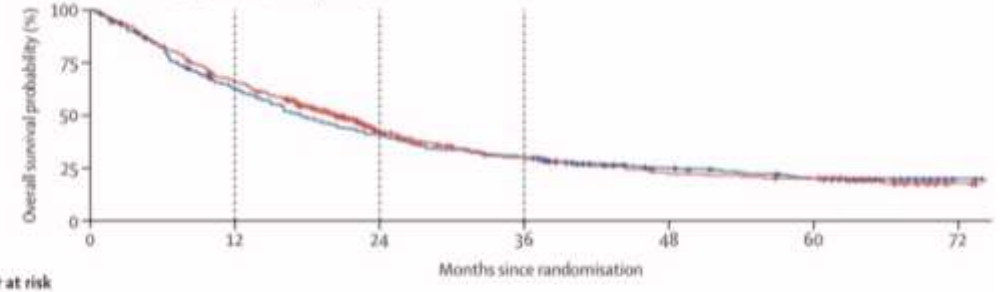


Number at risk (censored)							
Dual CTLA-4 and PD-L1 or PD-1 blockade	81 (0)	45 (0)	25 (0)	23 (0)	7 (9)	4 (12)	0 (16)
Single PD-L1 or PD-1 blockade	120 (0)	49 (0)	21 (8)	11 (10)	2 (16)	2 (16)	0 (18)

B *STK11* wild-type

	Reconstructed events/patients	Median overall survival, months (95% CI)	1-year overall survival, rate (95% CI)	2-year overall survival, rate (95% CI)	3-year overall survival, rate (95% CI)
Dual CTLA-4 and PD-L1 or PD-1 blockade	221/293	17·4 (15·2–21·7)	62·5% (57·2–68·4)	41·1% (35·8–47·2)	29·9% (25·0–35·7)
Single PD-L1 or PD-1 blockade	221/337	20·4 (17·3–23·5)	66·3% (61·4–71·6)	42·1% (36·9–48·1)	30·1% (24·6–36·8)

HR 1·04; 95% CI 0·87–1·26; p=0·65



Number at risk (censored)							
ual CTLA-4 and PD-L1 or PD-1 blockade	293 (0)	178 (7)	117 (7)	85 (7)	47 (34)	34 (38)	3 (69)
Single PD-L1 or PD-1 blockade	337 (0)	220 (4)	93 (59)	43 (89)	31 (90)	27 (91)	2 (114)

Di Federico. Lancet Oncol 2025;26:1443

Outline

concl
molecular
clinical
intro

16th CONGRESS Lung CANCER

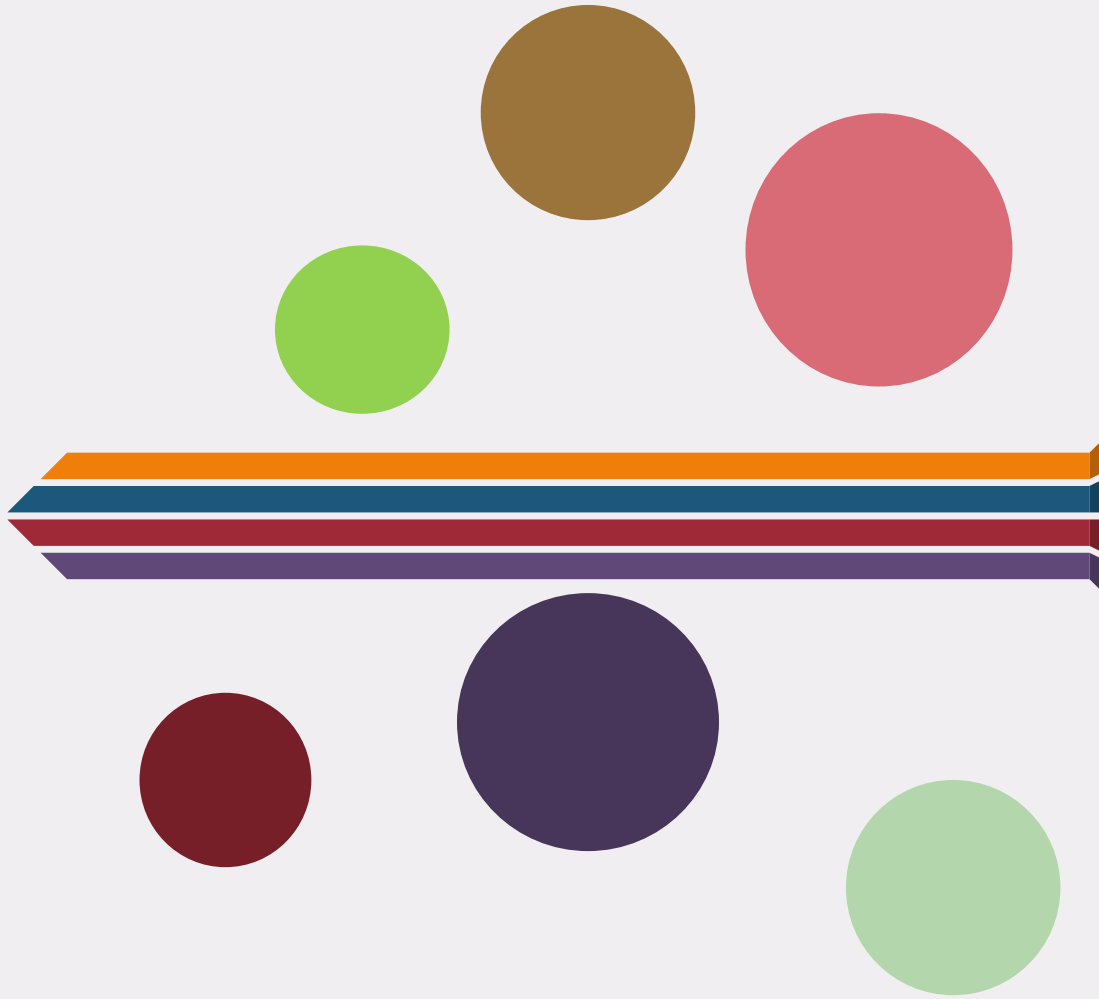
BARCELONA 27/28 NOVEMBER 2025

GECP lung cancer research

4

CONCL

Conclusions



PD-L1< 50%: CT/IO > CT alone. Undisputed standard independent of PD-L1 and histology.

PDL1>50%. Single agents is a perfect option but not for all. Not in never smokers?

CTLA-4: in negative PD-L1, in STK11/KEAP1; in brain mets?

Learning to identify patients who may develop hyperPD

Conclusions