ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

IMMUNOTHERAPY FOR PATIENTS WITH ACTIONABLE GENOMIC ALTERATIONS

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Paris, Friday 15th 2024

DECLARATION OF INTERESTS

Personal financial interests:

- None (since August 2021)

Institutional financial interests:

- Abbvie, ACEA, Amgen, Astra-Zeneca, Bayer, Bristol-Myers Squibb, Boehringer–Ingelheim, Eisai, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Genentech, Ipsen, Ignyta, Innate Pharma, Loxo, Novartis, Medimmune, Merck, MSD, Pierre Fabre, Pfizer, Sanofi-Aventis, Summit Therapeutics and Takeda

Non-financial interests:

- Principal Investigator for Astra-Zeneca, BMS, Innate Pharma, Merck, Mirati, Pierre Fabre and F. Hoffmann-La Roche, Ltd, sponsored trials (or ISR)

No other conflicts of interest

AGENDA

- Standard Checkpoints Inhibitors
- The role of VEGF inhibition
- TKIs and ICI combinations
- Current guidelines
- What the biology of AGA is telling us?
- What's next?

STANDARD CHECKPOINTS INHIBITORS

Alone or in combination (after TKI(s) exhaustion)

PD(L)1 MONOTHERAPY

Registry (Immunotarget)

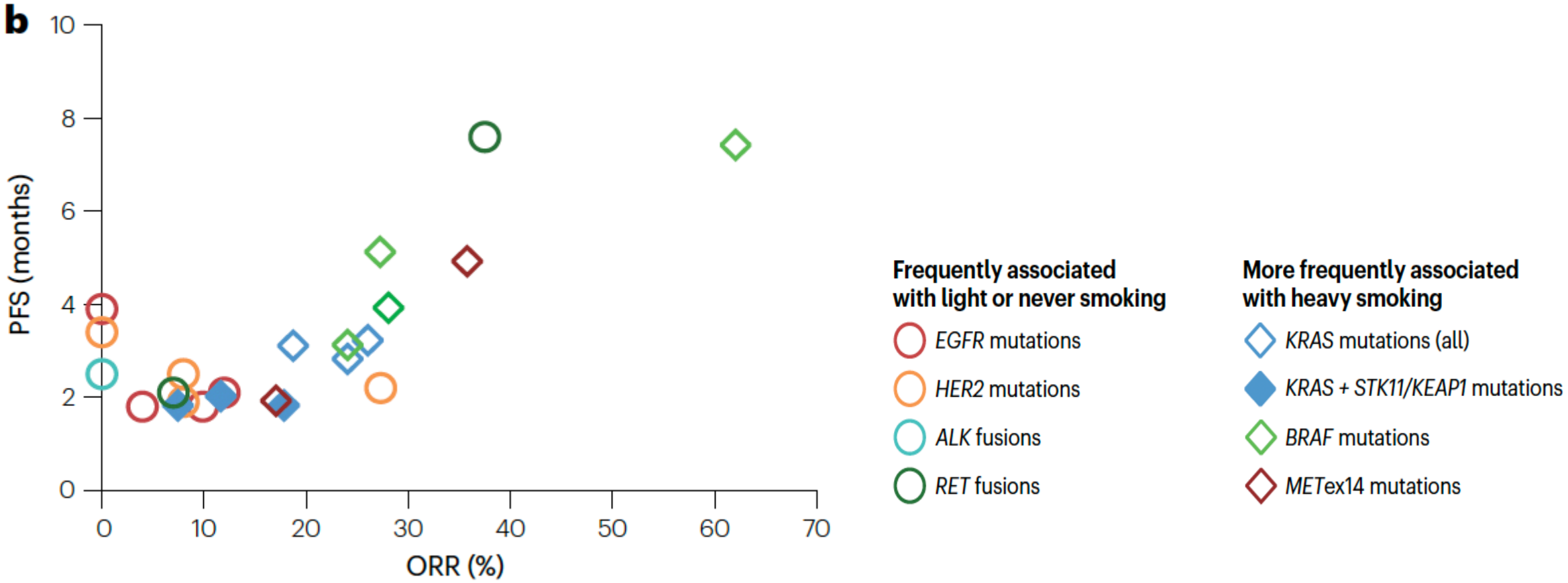
Table 2 Immune checkpoint inhibitor efficacy outcomes in various molecular alterations

		Best response (%)			PFS			OS
Driver	n	CR/PR	SD	PD	Median (months)	6 month PFS (%)	1 year PFS (%)	Median (months)
BRAF	38	28.1	28.1	43.8	3	35	19	13.6
KRAS	252	27.2	23.1	49.8	3.2	39	26	13.5
ROS1	5	20	0	80	NA	NA	NA	NA
MET	36	15.6	34.4	50	3.4	33	23	18.4
EGFR	110	11	18	71	2	16	6	8.8
HER2	23	9.5	28.6	61.9	3.5	34	17	10
RET	14	7.1	21.4	71.4	2.2	16	8	6.5
ALK	18	0	21.4	78.6	2.1	16	8	17

Mazieres J, et al. Ann Oncol 2019

PD(L)1 MONOTHERAPY

Subgroup analysis from randomized trials

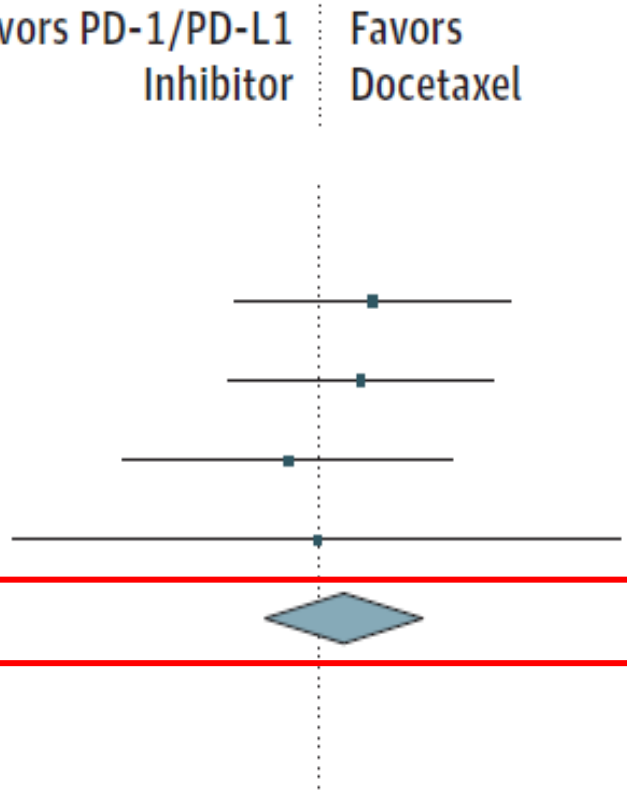


Otano I, et al. NRCO 2023

PD(L)1 MONOTHERAPY

EGFRm subgroup analysis from randomized trials

Trial	Hazard Ratio (95% CI)	Weight, %
EGFR mutated		
OAK	1.24 (0.71-2.18)	3.5
CheckMate 057	1.18 (0.69-2.02)	3.9
Keynote 010	0.88 (0.45-1.72)	2.5
POPLAR	0.99 (0.29-3.40)	0.7
Subtotal	1.11 (0.80-1.53)	10.6
Heterogeneity: $\chi^2_3 = 0.69$, $P = .88$; $I^2 = 0\%$		
Test for overall effect: $z = 0.61$ ($P = .54$)		



Lee, et al. JAMA Oncol 2018

PD(L)1 & CHEMOTHERAPY

EGFRm dedicated randomized trial: KN789 study

Key patient inclusion criteria

- Metastatic nonsquamous NSCLC
- EGFR mutation (Ex19del or L858R)
- TKI resistant
- ECOG PS 0–1

(n=492)

R 1:1

Pembrolizumab 200 mg + pemetrexed 500 mg/m^2 + platinum chemotherapy[a] q3w (4 cycles) (n=245)

→ Pembrolizumab 200 mg q3w (31 cycles) + pemetrexed 500 mg/m^2

Stratification

- PD-L1 TPS[b] (<50% vs. ≥50%)
- Treatment (with vs. without osimertinib)
- Region (East Asia vs. not East Asia)

Placebo + pemetrexed 500 mg/m^2 + platinum chemotherapy[a] q3w (4 cycles) (n=247)

→ Placebo q3w (31 cycles) + pemetrexed 500 mg/m^2

PD → Pembrolizumab 200 mg q3w (35 cycles)

Co-primary endpoints

- PFS (BICR, RECIST v1.1), OS

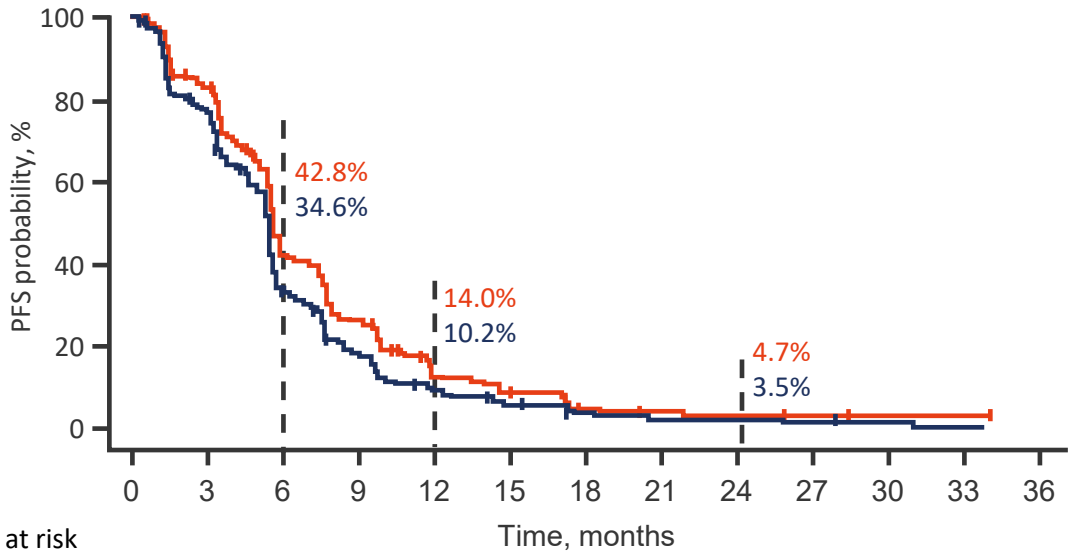
Secondary endpoints

- ORR, DoR, PROs, safety

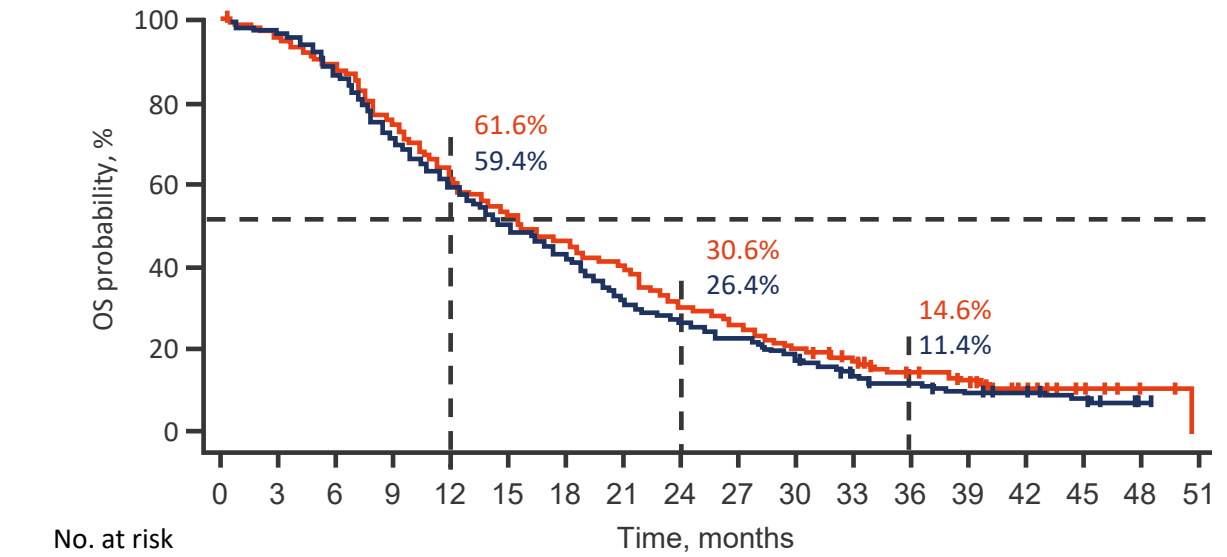
Yang JC, et al. J Clin Oncol 2023;41(suppl 16):Abstr LBA9000

PD(L)1 & CHEMOTHERAPY

EGFRm dedicated randomized trial: KN789 study



	Pembro + chemo (n=245)	Chemo (n=247)
Events, n (%)	198 (80.8)	214 (86.6)
mPFS, mo (95%CI)	5.6 (5.5, 5.8)	5.5 (5.4, 5.5)
HR (95%CI); p-value	0.80 (0.65, 0.97); 0.0122	



	Pembro + chemo (n=245)	Chemo (n=247)
Events, n (%)	214 (87.3)	224 (90.7)
mOS, mo (95%CI)	15.9 (13.7, 18.8)	14.7 (12.7, 17.1)
HR (95%CI); p-value	0.84 (0.69, 1.02); 0.0362	

Yang JC, et al. J Clin Oncol 2023;41(suppl 16):Abstr LBA9000

PD(L)1 & CHEMOTHERAPY

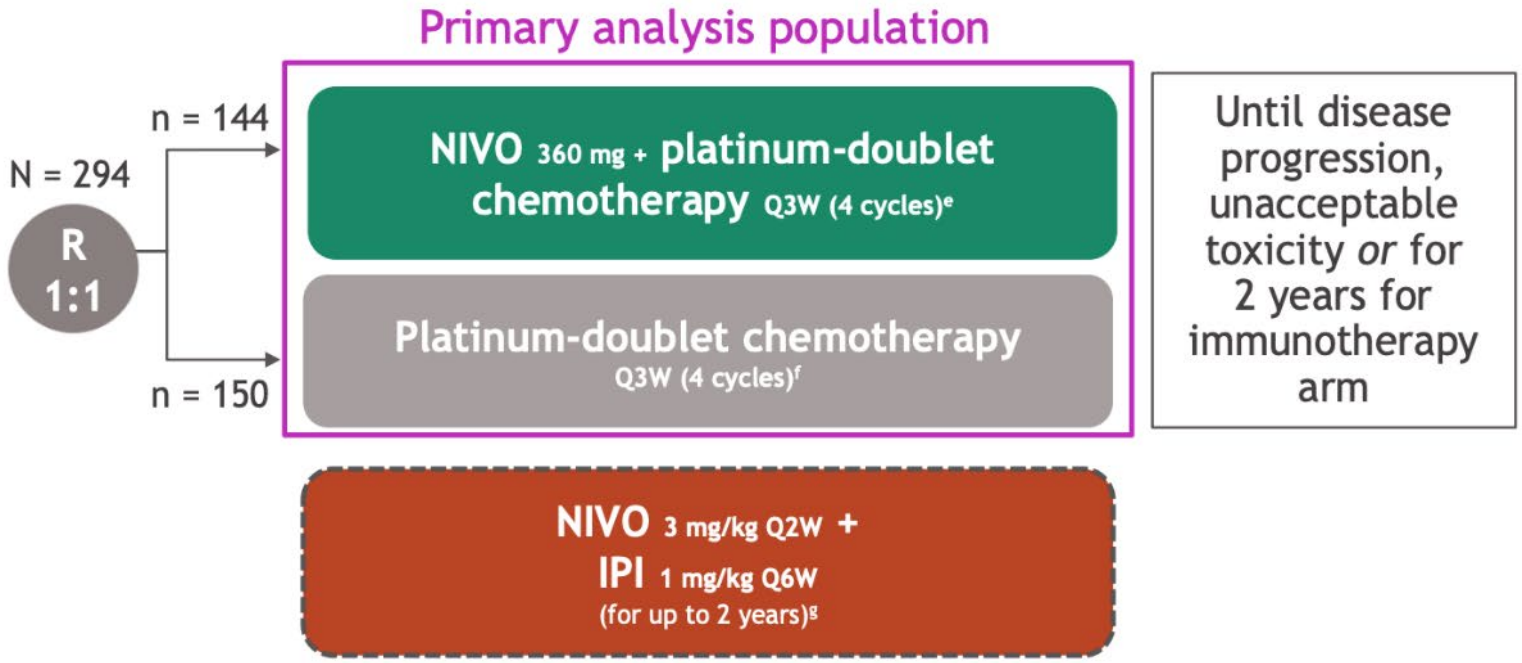
EGFRm dedicated randomized trial: CM722 study

Key eligibility criteria

- Recurrent *EGFR* mutation-positive metastatic or stage IV NSCLC
- Progressive disease after 1L first- or second-generation TKI without T790M mutation
- Progressive disease after 1L or 2L osimertinib, regardless of T790M mutation[b]
- ECOG PS 0-1

Stratified by

- Tumor PD-L1[c] (< 1%[d] vs ≥ 1%)
- Brain metastases
- Smoking history
- Prior osimertinib use[b]



Primary endpoint

- PFS by BICR

Secondary endpoints

- 9-mo and 12-mo PFS rates
- OS, ORR, DOR

Exploratory endpoints

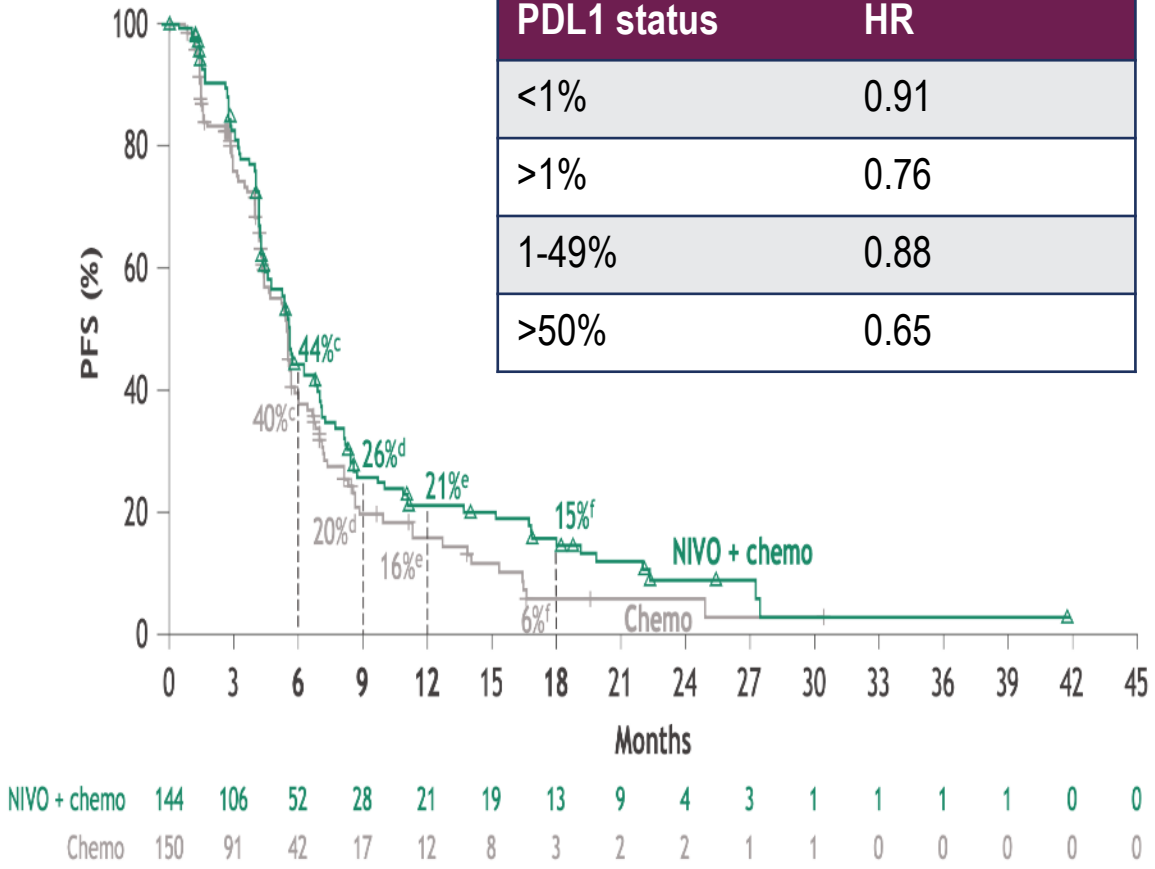
- Safety
- Efficacy by tumor PD-L1[c] status

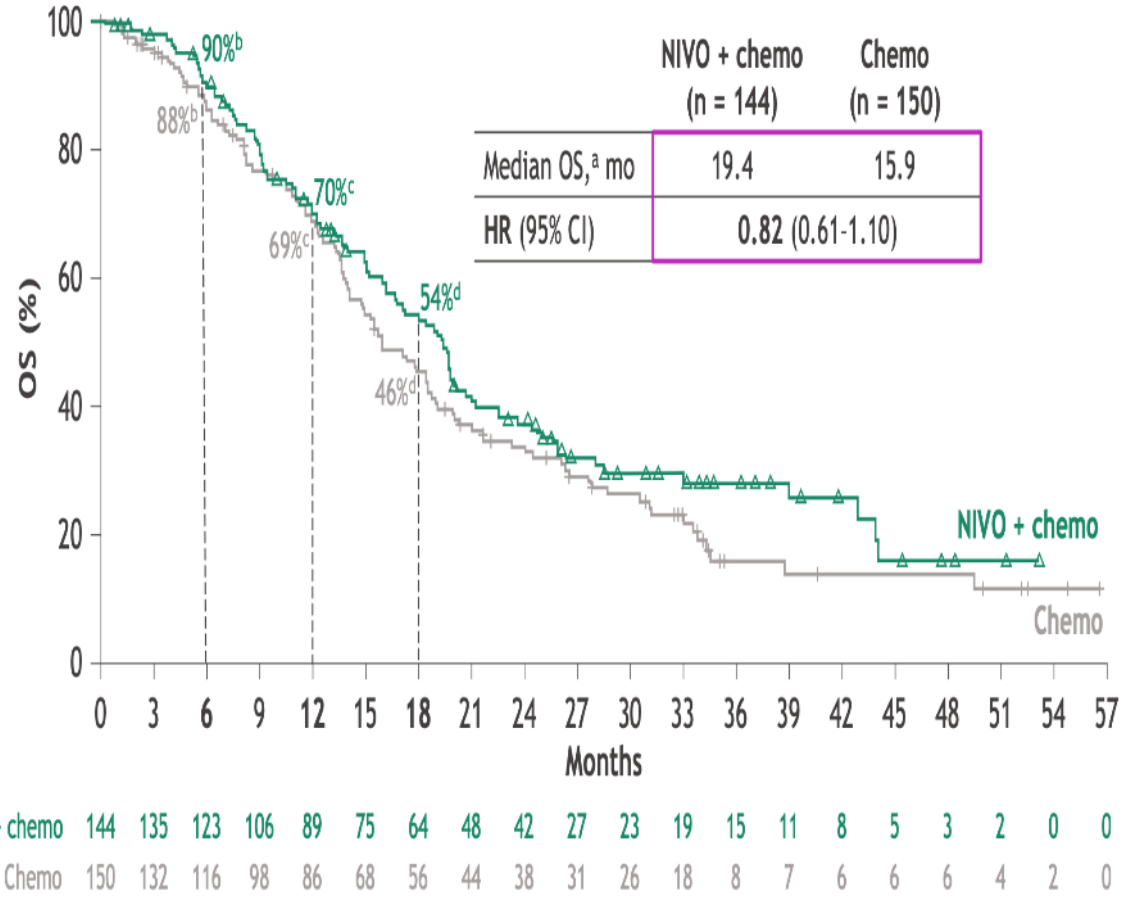
Mok T, et al. Ann Oncol 2022 (presented ESMO Asia) and J Clin Oncol 2024

PD(L)1 & CHEMOTHERAPY

EGFRm dedicated randomized trial: CM722 study

PDL1 status	HR
<1%	0.91
>1%	0.76
1-49%	0.88
>50%	0.65

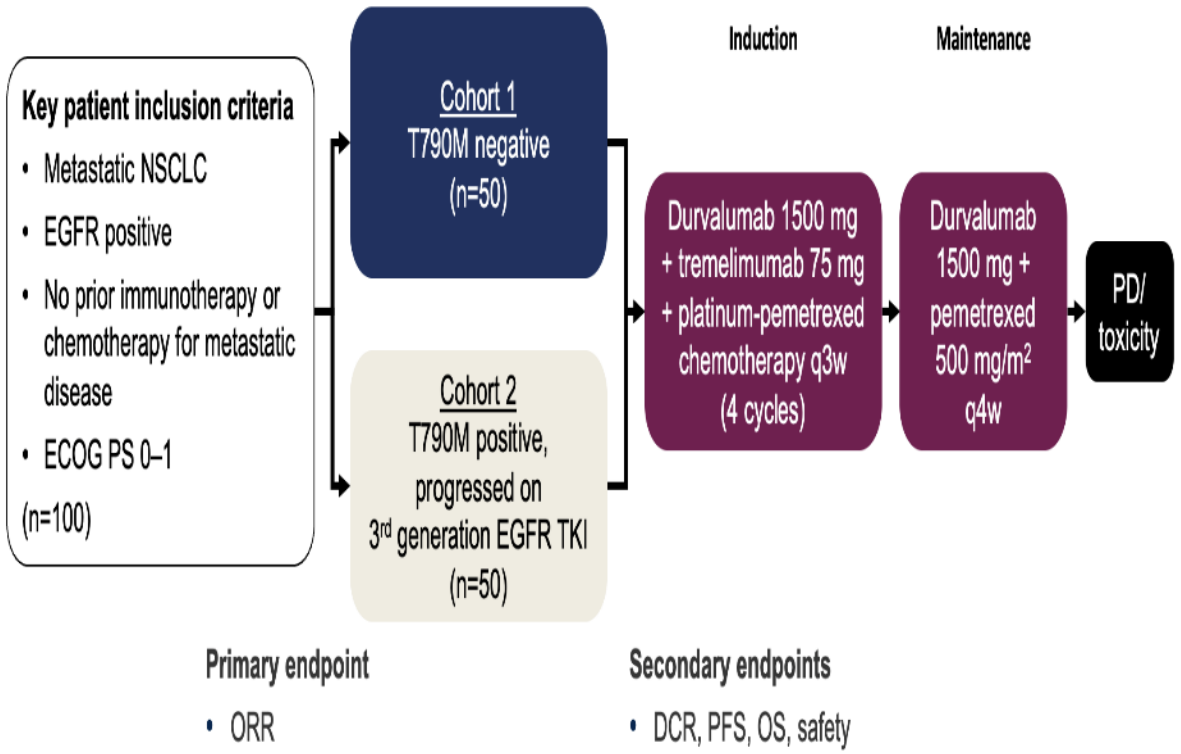


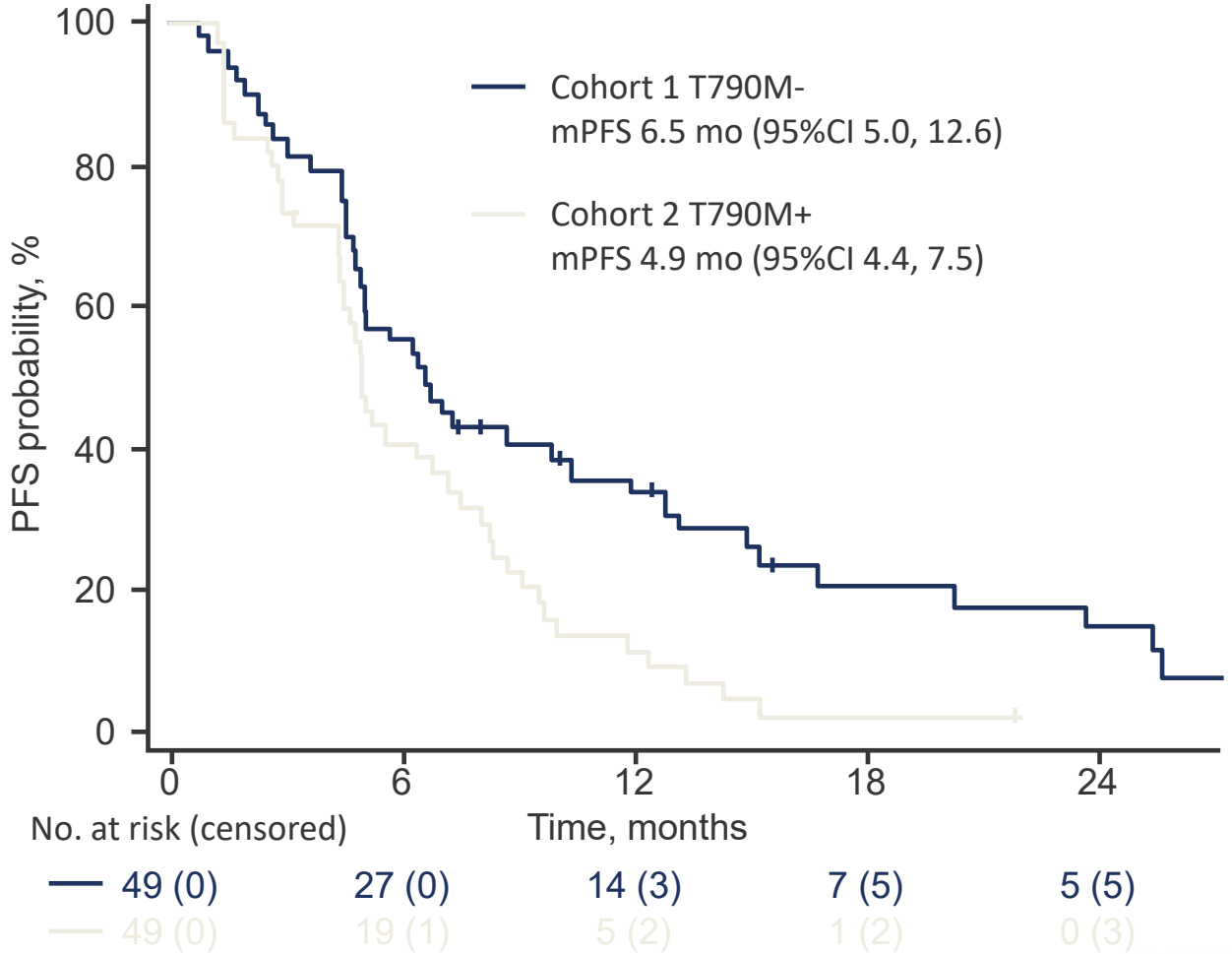


Mok T, et al. Ann Oncol 2022 (presented ESMO Asia) and J Clin Oncol 2024

PD(L)1 & CTLA4 & CHEMOTHERAPY

EGFRm dedicated randomized trial: Illuminate

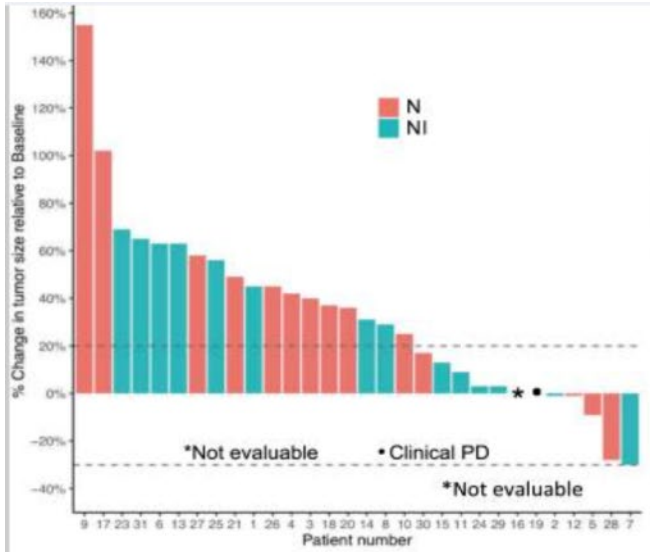


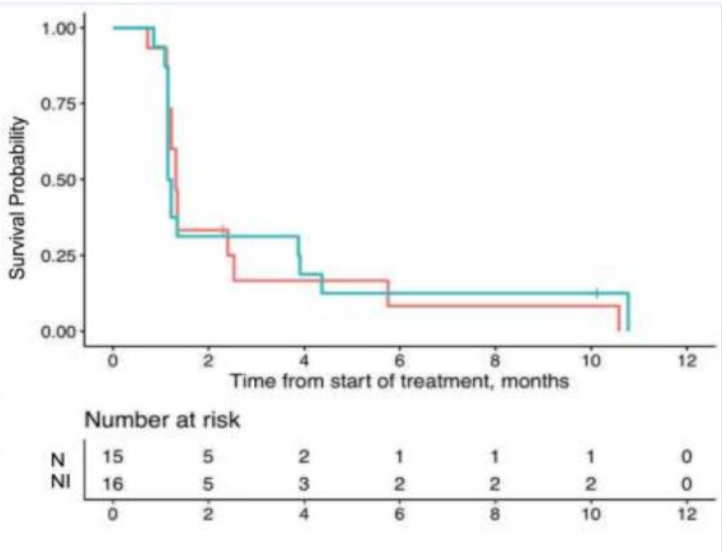


Lee C, et al. J Thorac Oncol 2023;18(suppl 9):Abstr OA09.04

PD(L)1 & CTLA4 AFTER CHEMOTHERAPY

EGFRm dedicated randomized trial: Checkmate 722





	N (%)	NI (%)	Total (%)
Partial response	0 (0.0)	1 (6.3)	1 (3.2)
Stable disease	6 (40.0)	6 (37.5)	12 (38.7)
PD	8 (53.3)	9 (56.3)	17 (54.8)

	Median PFS in months (95% CI)	3-month PFS rate (95% CI)	6-month PFS rate (95% CI)
N	1.31 (1.15–2.40)	16.7% (2.9%–40.2%)	8.3% (0.5%–30.6%)
NI	1.18 (1.15–3.88)	31.3% (11.4%–53.6%)	12.5% (2.1%–32.8%)
Overall	1.22 (1.15–1.35)	25.1% (11.5%–41.3%)	10.8% (2.8%–24.9%)

Lay G, et al. JTO Clin Res Rep 2022

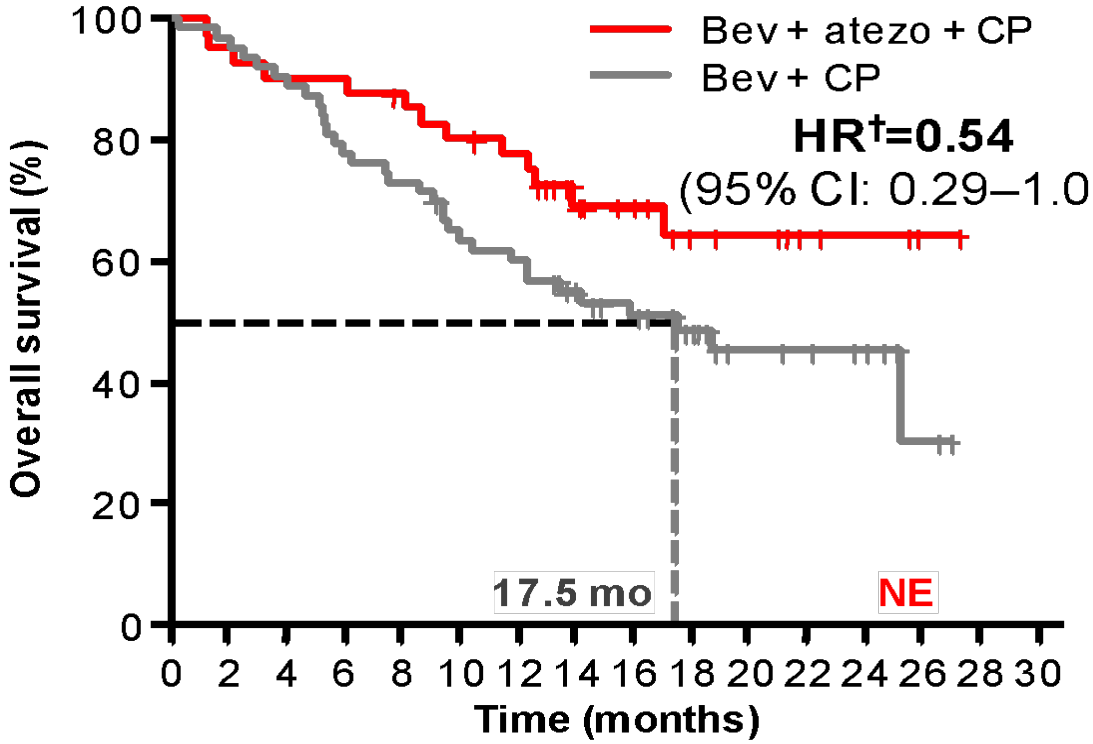
THE ROLE OF VEGF INHIBITION

Combined with PD(L)1 inhibitors +/- chemotherapy

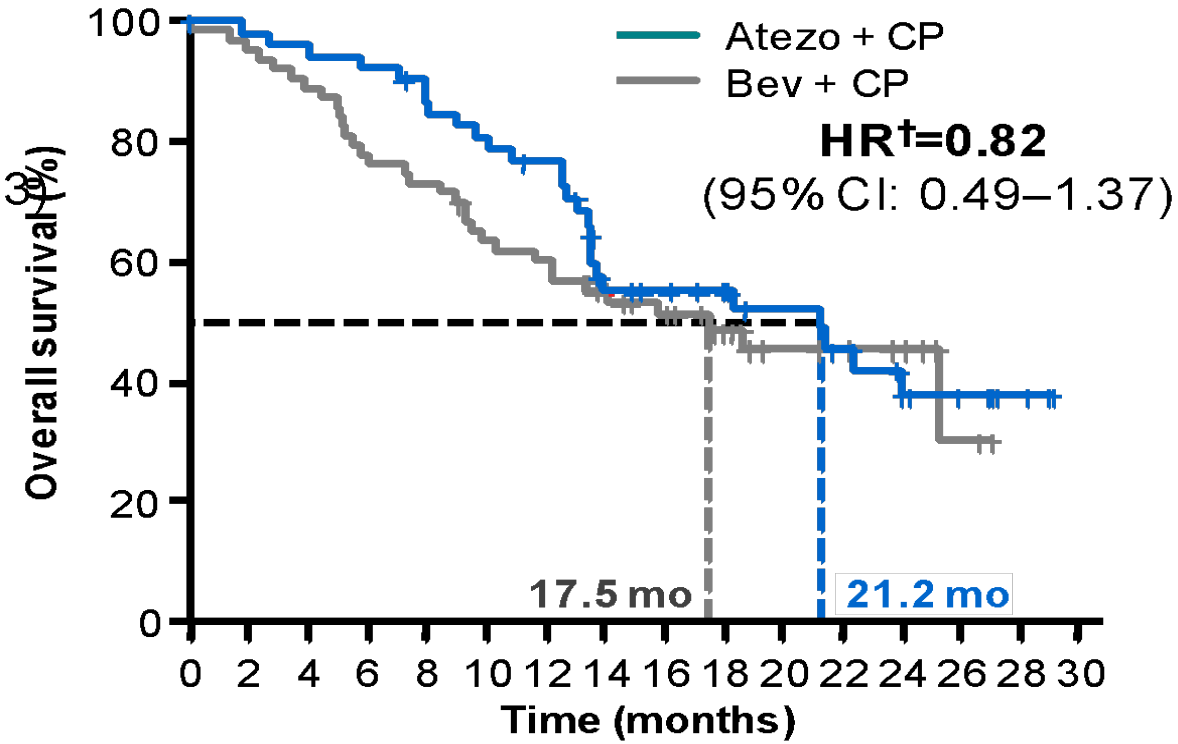
PD(L)1 & CHEMOTHERAPY+VEGFi

EGFRm subgroup analysis of IMP150 randomized trial

Double PD-L1 and VEGF inhibition on the top of chemotherapy



PD-L1 or VEGF inhibition on the top of chemotherapy



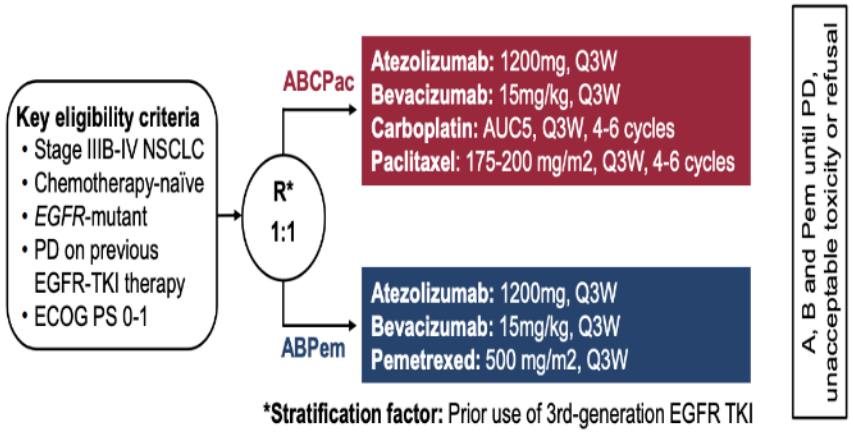
Socinski, et al. ASCO 2018 (Abs 9002);
Kowanetz, et al. AACR 2018 (Abs CT076)

ESMO

PD(L)1 & CHEMOTHERAPY+VEGFi

EGFRm dedicated randomized trial: ABC study

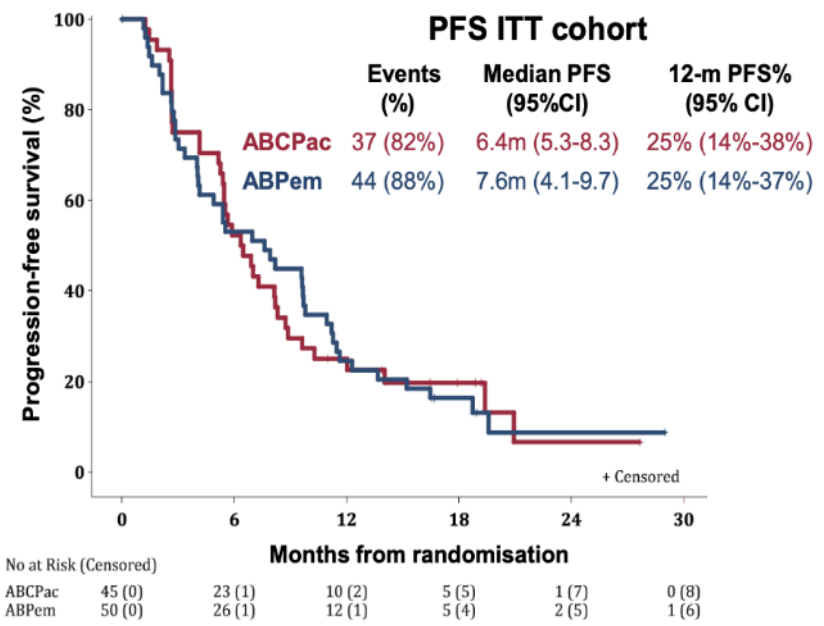
Study design: Randomised, non-comparative, international phase II trial

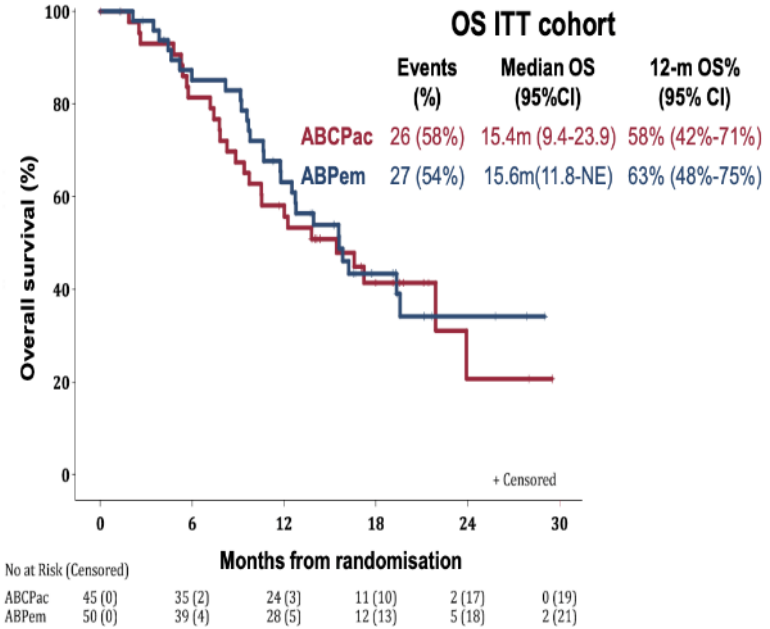


***Stratification factor:** Prior use of 3rd-generation EGFR TKI

Primary endpoint:

12-month PFS rate, by RECIST v1.1





The observed 12-m PFS rate of 25% with either ABCPac or ABPem was below the aspired rate of 37%.

Frueh M, et al. ESMO Open 2024 (presented at ELCC 2024)

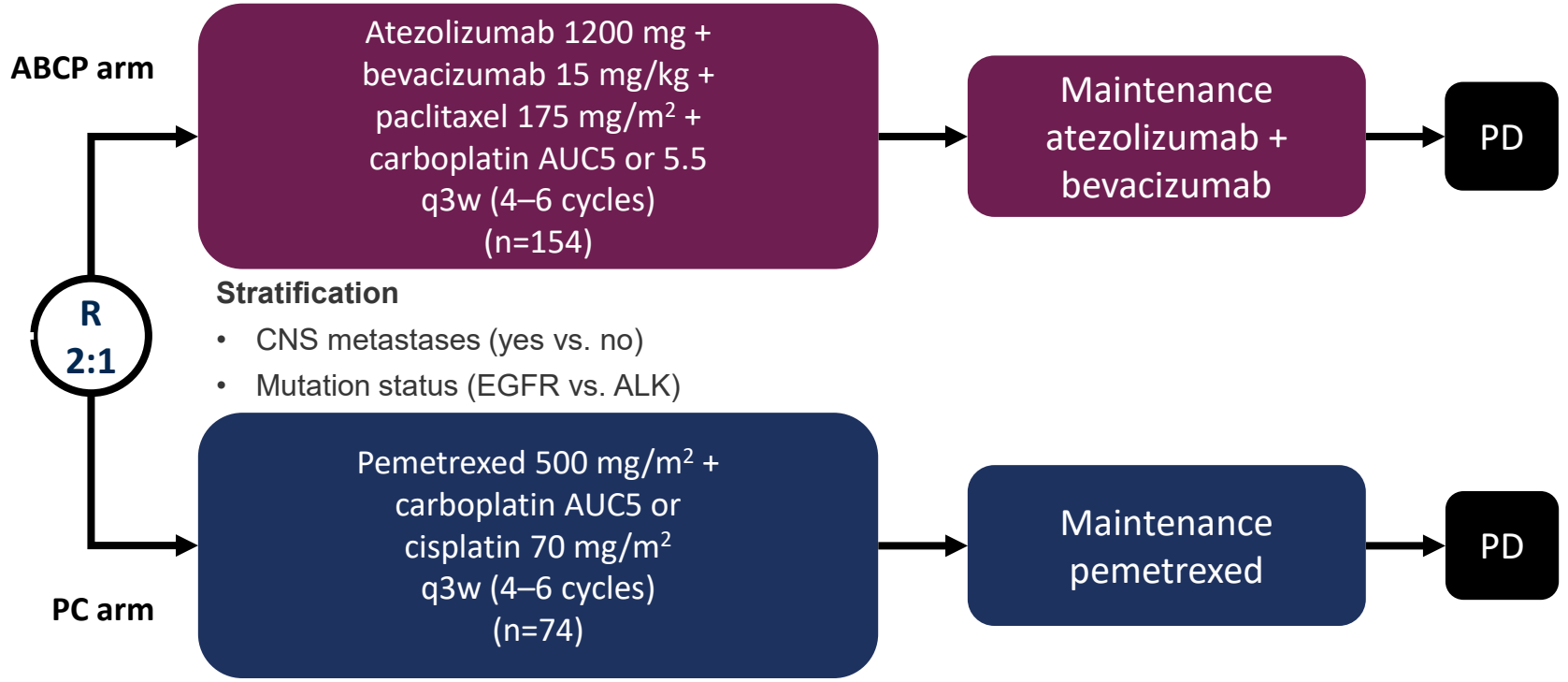
PD(L)1 & CHEMOTHERAPY+VEGFi

EGFRm/ALK dedicated randomized trial: ATTLAS, KCSG-LU19-04 study

Key patient inclusion criteria

- Stage IV nonsquamous NSCLC
- EGFR/ALK activating alteration
- Progressed on prior TKI
- ECOG PS 0–1

(n=225)



Primary endpoint

- PFS (investigator assessed)

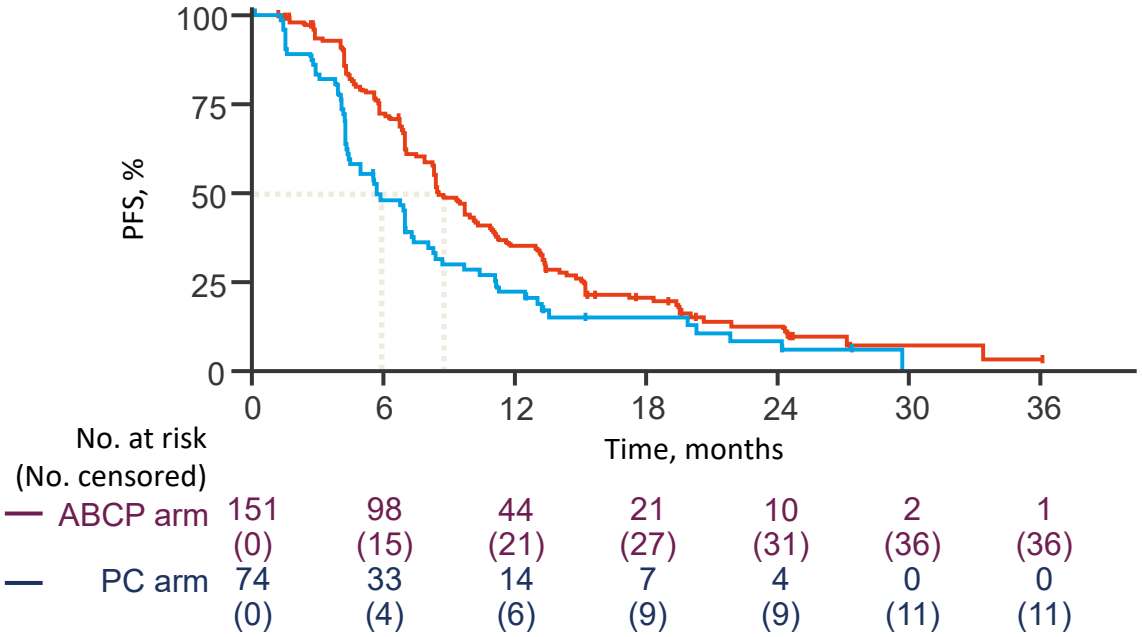
Secondary endpoints

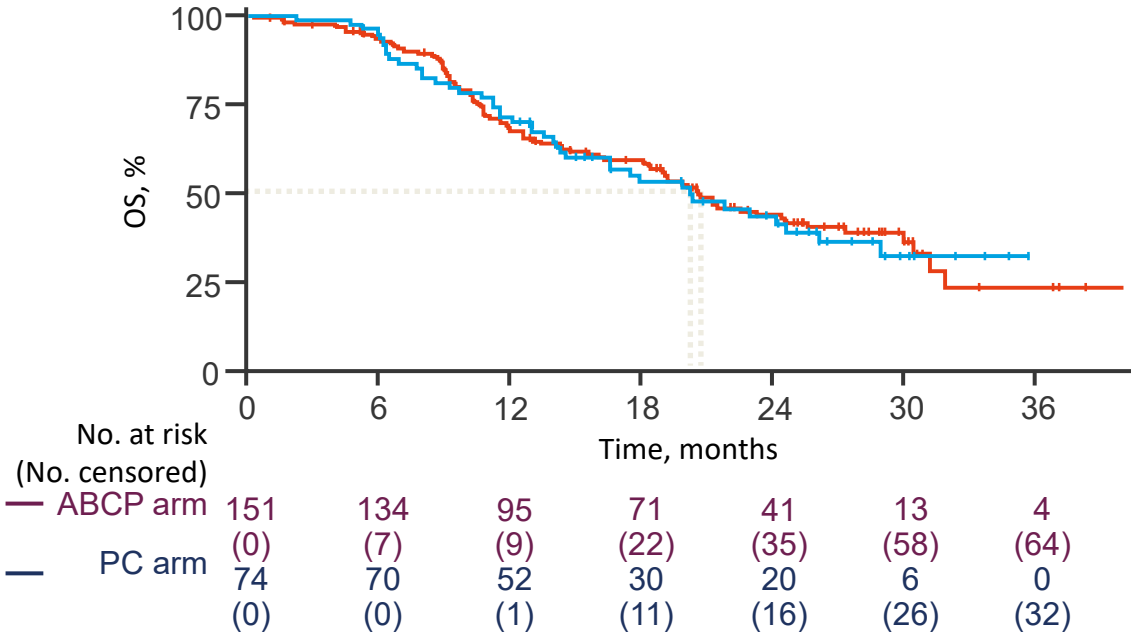
- OS, ORR, DoR, safety

Ahn M-J, et al. Ann Oncol 2023;34(suppl):Abstr LBA67

PD(L)1 & CHEMOTHERAPY+VEGFi

EGFRm/ALK dedicated randomized trial: ATTLAS, KCSG-LU19-04 study





	ABCP arm (n=154)	PC arm (n=74)
Events, n (%)	114 (75.5)	63 (85.1)
mPFS, mo (95%CI)	8.48 (8.18, 10.28)	5.62 (4.27, 7.22)
HR (95%CI); p-value	0.62 (0.45, 0.86); 0.004	

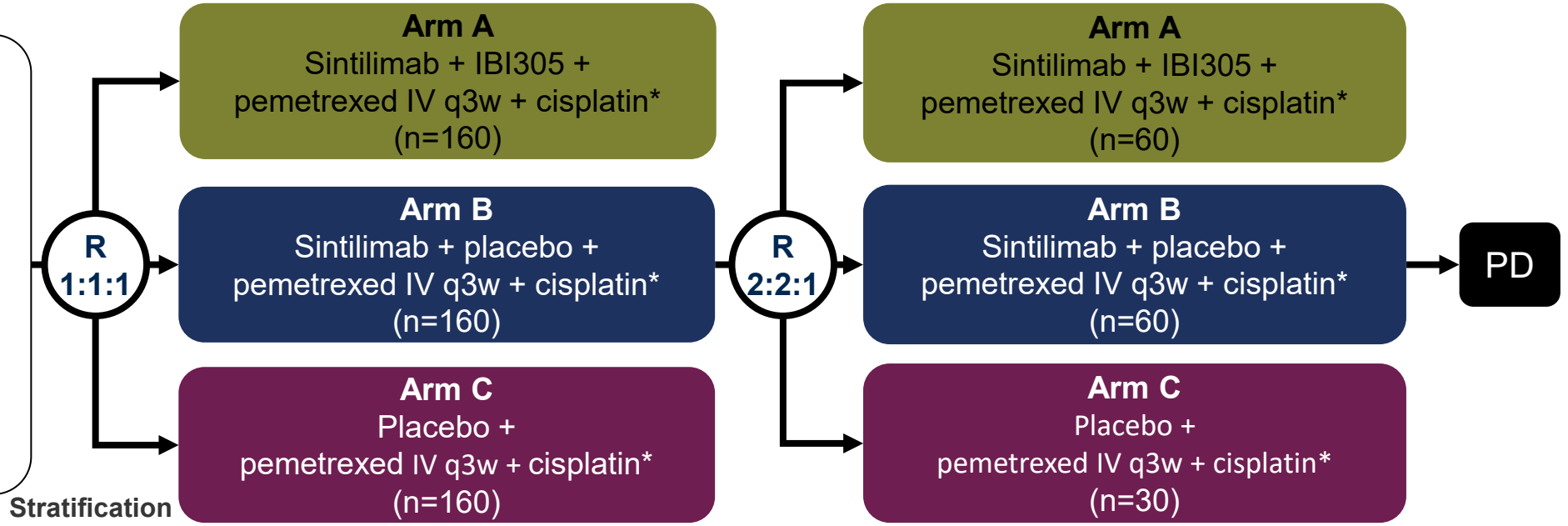
	ABCP arm (n=154)	PC arm (n=74)
Events, n (%)	83 (55.5)	42 (56.8)
mOS, mo (95%CI)	20.63 (18.14, 25.59)	20.27 (14.29, 26.12)
HR (95%CI); p-value	1.01 (0.69, 1.46); 0.975	

Ahn M-J, et al. Ann Oncol 2023;34(suppl):Abstr LBA67

PD(L)1 & CHEMOTHERAPY+VEGFi AFTER EGFR-TKI

EGFRm dedicated randomized trial: Orient-31 study

- Unresectable advanced/metastatic NSCLC
- EGFR mutant
- Progressed after EGFR-TKI
- Chemotherapy-naïve



Stratification

- Gender (male vs. female), brain metastases (yes vs. no)

Primary endpoint

- PFS (RECIST v1.1) for Arm B vs. C in this second interim analysis

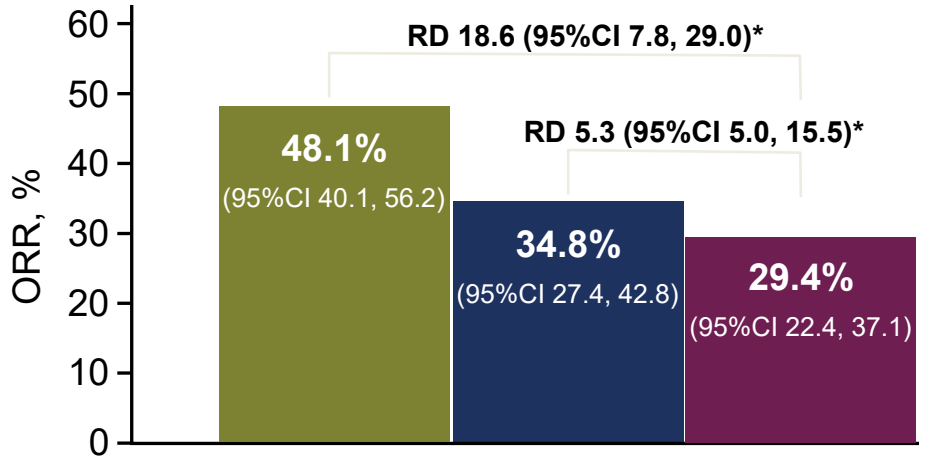
Secondary endpoints

- ORR, safety

Lu S, et al. ESMO 2022 (published by Wu et al. Lancet Oncol 2023)

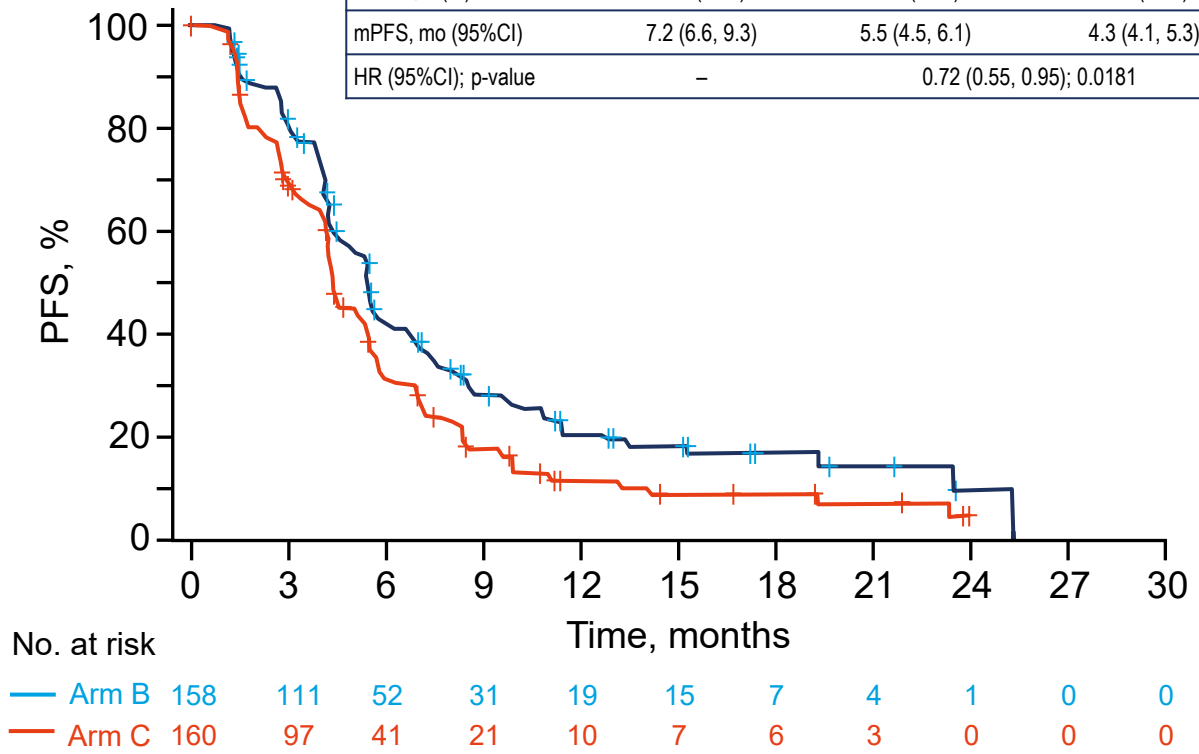
PD(L)1 & CHEMOTHERAPY+VEGFi AFTER EGFR-TKI

EGFRm dedicated randomized trial: Orient-31 study



	Arm A	Arm B	Arm C
DCR, % (95%CI)	86.1 (79.7, 91.1)	81.6 (74.7, 87.3)	75.6 (68.2, 82.1)
mDoR, mo (95%CI)	8.5 (5.6, 11.7)	7.4 (4.7, 12.0)	5.7 (4.1, 7.1)

	Arm A	Arm B	Arm C
Events, n (%)	102 (64.6)	108 (68.4)	125 (78.1)
mPFS, mo (95%CI)	7.2 (6.6, 9.3)	5.5 (4.5, 6.1)	4.3 (4.1, 5.3)
HR (95%CI); p-value	–	0.72 (0.55, 0.95); 0.0181	



Lu S, et al. ESMO 2022 (published by Wu et al. Lancet Oncol 2023)

PD(L)1 & CHEMOTHERAPY+VEGFi

EGFRm/ALK dedicated randomized trial: summary

Trial	IMpower150	IMpower151	ATTLAS (KCSG-LU19-04)	ORIENT-31
Country	26 countries	China	Korea	China
Treatment arm	Atezolizumab plus bevacizumab and chemotherapy (ABCP, N=34)	Atezolizumab plus bevacizumab and chemotherapy (ABCP, N=81)	Atezolizumab plus bevacizumab and chemotherapy (N=154)	Sintilimab plus IB305 plus chemotherapy (N=158)
Comparator arm	Atezolizumab plus carboplatin plus paclitaxel (ACP, N=45) Bevacizumab plus carboplatin plus paclitaxel (BCP, N=43)	Bevacizumab and chemotherapy (BCP, N=82)	Paclitaxel and carboplatin (N=74)	Sintilimab plus chemotherapy (N=156) Chemotherapy alone (N=160)
***EGFR* mutation (N)**				
Exon 19 deletion	15	50	70	80
Exon 21 L858R	11	26	75	70
T790M	1	14	NA	NA
Other	7	5	2	8
Post-3G TKI alone (quad arm)	0%	17.9% (N=14)	8.2% (N=12)	11% (N=7)
Smoking				
Current or former	14	NA for subgroup analysis	57	47
Never	20		97	111
Brain metastasis (N)	NA for subgroup analysis	NA for subgroup analysis	67	59
Primary endpoint	PFS and interim OS in the ITT wild-type population (excluding *EGFR* or *ALK* alteration)	Investigator-assessed PFS in the ITT population	Investigator-assessed PFS	IRRC-assessed PFS
Efficacy endpoints				
ORR	42%	NA for subgroup analysis	69.5%	45%
Median PFS (months)	10.2 (HR, 0.61, 95% CI: 0.36–1.03)	8.5 (HR 0.86, 95% CI: 0.61–1.21)	8.48 (HR 0.62, 95% CI: 0.45–0.86)	7.2 (HR 0.74, 95% CI: 0.57–0.97)
Median OS (months)	NR (HR 0.61, 95% CI: 0.29–1.28)	NA for subgroup analysis	20.63 (HR 1.01, 0.69–1.46)	21.1 (95% CI: 17.5–23.9)
Grade 3 or worse TRAEs	64%		53%	56%
Approvals				
FDA	No		No	No
EMA	Yes		No	No

Abbreviations: CI, confidence interval; *EGFR*, epidermal growth factor receptor; EMA, European Medicines Agency; FDA, Food and Drug Administration; HR, hazard ratio; IC, immune cells; IRRC, independent radiologic review committee; intention-to-treat, ITT; N, number; NA, not applicable; NR, not reached; ORR, objective response rate; OS, overall survival; PD-L1; programmed death-ligand 1; PFS, progression-free survival; TC, tumor cells; TRAEs, treatment-related adverse events.

Lee JB, et al. Lung Cancer: Targets and Therapy 2024

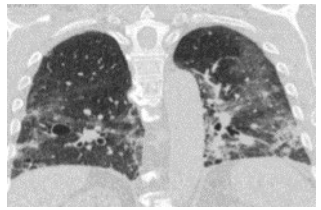
TKIs & ICI COMBINATIONS

Anything but easy

PD(L)1 & EGFR-TKI*

Early phases studies

Author, phase	Intervention	N = number of participants	Response rates %	Toxicity
EGFR positive				
Yang *et al.* [2019], phase I/II	TKI: erlotinib; gefitinib arm closed due to toxicity; ICI: Pembrolizumab	12	41.7	No G4 events; G3 AE 33%; ALT increased G1/2 25%; AST increased G1/2 25%; gefitinib arm closed due to G3/4 hepatotoxicity in 71.4% patients
Creelan *et al.* [2019], phase I	TKI: Gefitinib; ICI: Durvalumab	56	63	70%; combination therapy was associated with high discontinuation rate due to hepatotoxicity (>50%)
Gettinger *et al.* [2018], phase I	TKI: Erlotinib; ICI: Nivolumab	20	15	G3 events - 25% [5] • Raised AST [1] • Raised ALT [1] • Diarrhoea [2] • Weight loss [1]
Ahn *et al.* [2016], TATTON, Phase Ib	TKI: Osimertinib; ICI: Durvalumab	44	38	38% interstitial lung disease like events
Rudin *et al.* [2018], Phase Ib	TKI: Erlotinib; ICI: Atezolizumab	28	75	G3 AE in 43% • ALT rise 2 • Pyrexia 2 • Rash 2 • Diarrhoea 2



TKI, tyrosine kinase inhibitor, ICI, immune checkpoint inhibitor; G3, grade 3; G4, grade 4; AE, adverse event.

McLean L, et al. TLCR 2021
** few patients treated in 1st line*

PD(L)1 & ALK-TKI*

Early phases studies

Author, phase	Intervention	N = number of participants	Response rates %	Toxicity
ALK positive				
Spigel *et al.* [2018], Phase I/II	TKI: Crizotinib, ICI: Nivolumab	13	38	38% developed severe hepatoxicity leading to discontinuation of this combination; 2 patients died from their hepatotoxicity
Shaw *et al.* [2018], JAVELIN 101	TKI: Lorlatinib; ICI: Avelumab	28	46.4	54%; high triglycerides 14.3%; GGT increase 10.7%
Kim *et al.* [2018]	TKI: Alectinib; ICI: Atezolizumab	21	81	G3 62%; Rash/ALT rise/Pneumonitis
Felip *et al.* [2020], Phase Ib	TKI: Ceritinib, ICI: Nivolumab	36	First line 450 mg: 83; 300 mg: 60; Second line 450 mg: 50; 300 mg: 25	ALT rise 25%; GGT rise 22%; Amylase 14%

TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; G3, grade 3; G4, grade 4.

McLean L, et al. TLCR 2021
** few patients treated in 1st line*

OTHER CHECKPOINTS INHIBITORS

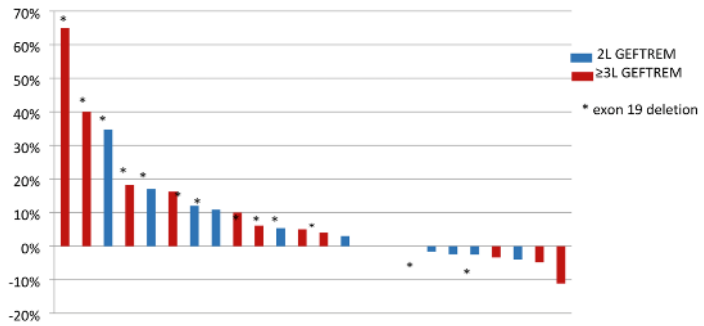
CTLA4 (Tremelimumab) / EGFRi (Gefitinib)

Baseline demographic and disease characteristics.

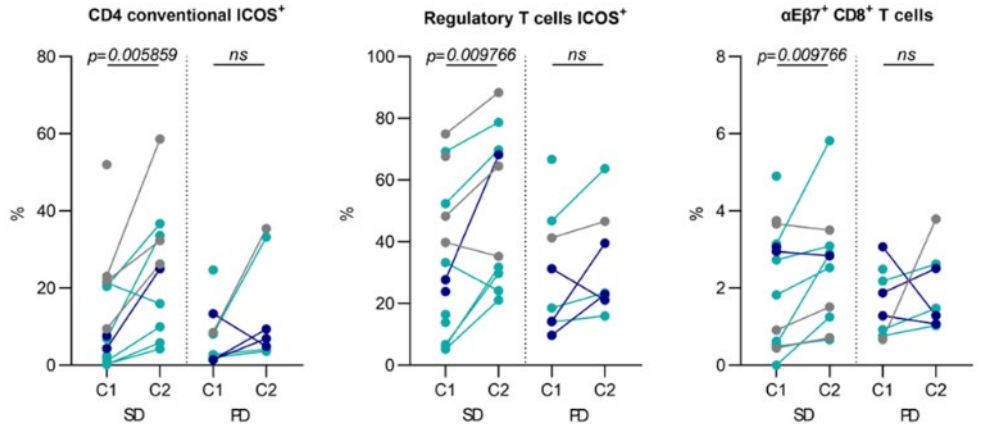
Clinical characteristics	N=27 (%)
Age, years [range]	63 [41-76]
Gender	
male	9 (33)
female	18 (67)
Smoking status	
non-smokers	18 (67)
former smokers	9 (33)
current	0
former	9
ECOG PS	
0	18 (67)
1	9 (33)
Histology	
adenocarcinoma	27 (100)
***EGFR* sensitizing mutation type**	
EGFR exon 19 deletion	19 (70)
EGFR exon 21 L858R mutation*	5 (19)
EGFR exon 18^	3 (11)
Stage disease at study initiation	
IVA	14 (52)
IVB	13 (48)
Metastatic sites	
Lung	18 (67)
Liver	1 (4)
Bone	12 (44)
Adrenal	2 (7)
Lymph nodes	8 (30)
Pleural	7 (26)
Brain	4 (15)
Number of treatment lines	
1 (GEFTREM 2L)	14 (52)
≥2 (GEFTREM≥3L)	13 (48)
First line treatment prior GEFTREM	
Erlotinib	6 (22)
Gefitinib	14 (52)
Platinum-based chemotherapy	7 (26)
Radiotherapy before clinical trial/sites	
No	18 (67)
Yes	9 (33)
brain	4
bone	4
mediastinum	1

Treatment outcomes of the combination of tremelimumab and gefitinib.

	Patients N=27 (%)	
Objective response		
complete response	0	
partial response	0	
Stable disease	18 (67)	
Progressive disease	7 (26)	
Not evaluable*	2 (7)	
Progression-free survival		
Number of events	27	
Median PFS, months (95% CI)	2.2 (1.8-4.2)	
GEFTREM 2L	4.2 (1.8-10.3)	*P* 0.01
GEFTREM ≥3L	1.8 (1.3-2.5)	
Overall survival		
Number of events	27	
Median OS, months (95% CI)	14.5 (7.1-37.8)	
GEFTREM 2L	24.4 (13.4-NR)	*P* 0.03
GEFTREM ≥3L	9.7 (3.3-14.3)	
OS rate (%)		
1-year	55	
2-year	33	
3-year	22	



In patients with SD, out of 114 blood biomarkers, a significant increase of memory CD4+, conventional CD4+ICOS+, ICOS+ regulatory (Treg) and CD103+β7+CD8+T cells (αEβ7+CD8+T cells) was observed



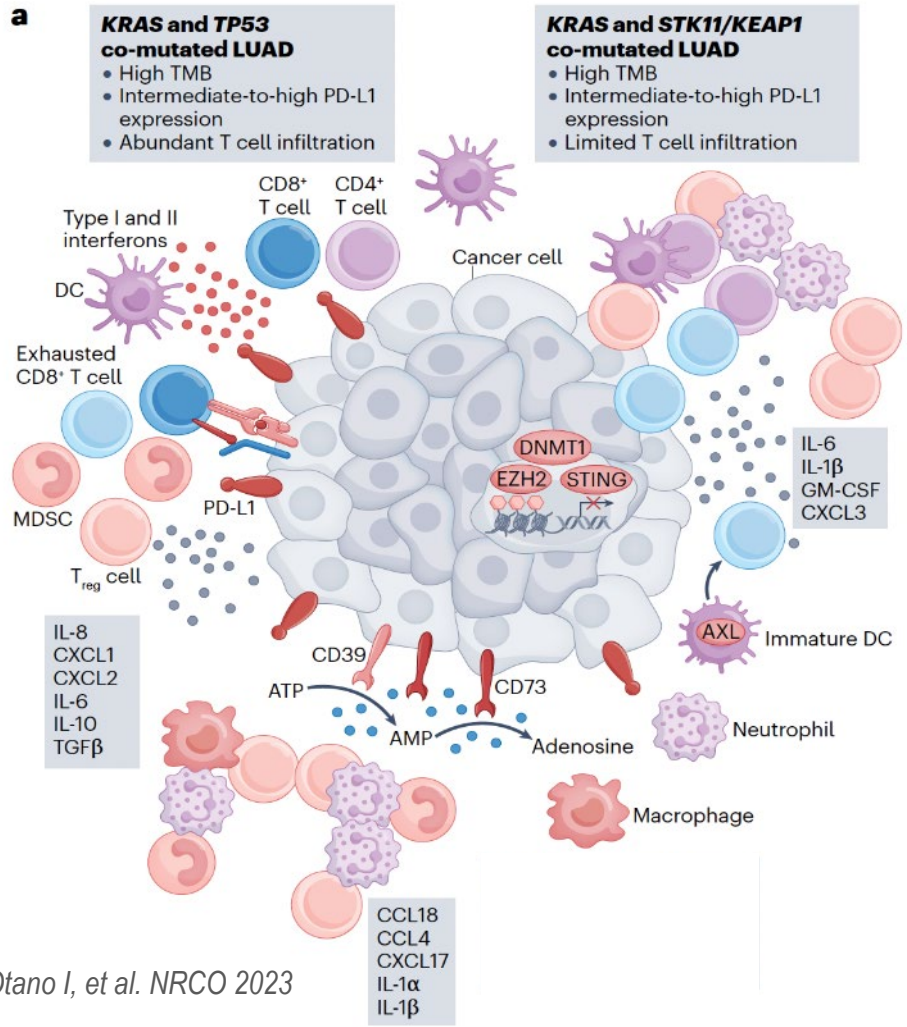
Riudavets M, et al. Lung Cancer 2022

THE SPECIAL CASE OF *KRASm*

Special genomic, immune contexture and management

KRASm AS A SPECIFIC AGA

Selected results



Otano I, et al. NRCO 2023

Drug	Trial	Sample Size	PFS (Months)	OS (Months)	ORR%
KRAS					
Chemo ICI	Nakajima EC et al. [27] 2022 FDA pooled analysis	1430 *KRASm* 39% (*n* = 557) *KRASwt* 61% (*n* = 873) (*KRAS* G12C *n* = 58)	Not reported	*KRASm* 22.4 (18.2-NR) vs. KRASwt 18.7 (16.0–25.2) *KRAS* G12C 20.8 (11.3-NR) [n = 58]	*KRASm* 46% vs. *KRASwt* 47% *KRAS G12C* 51%
ICI monotherapy	Nakajima EC et al. [27] 2022 FDA pooled analysis	1430 *KRASm* 39% (*n* = 557) *KRASwt* 61% (*n* = 873) [*KRAS G12C* (*n* = 45)]	Not reported	*KRASm* 16.2 (11.1-NR) (n = 135) vs. *KRASwt* 14.9 (12.2–6.6) (n = 322) *KRAS G12C* 11.8 (8.2-NR) (n = 45)	37% vs. 33% *KRAS G12C* 33%

KRASm AS A SPECIFIC AGA

Attention to some subgroups

Oncogenic driver	Anti-PD-(L)1 antibody-based treatment	*n*	ORR (%)	Median PFS (months)
KRAS mutations (any)	Anti-PD-(L)1 antibody monotherapy	246	26	3
	Anti-PD-(L)1 antibody monotherapy	135[a]	37[a]	NR
	Anti-PD-(L)1 antibody monotherapy	162	19	3
	Anti-PD-(L)1 antibody monotherapy	87 (MDACC cohort) 527 (CGDB cohort)	24 NR	3 4
	Sotorasib + pembrolizumab or atezolizumab	58	29	NR
	Chemotherapy + anti-PD-(L)1 antibody	219[a]	46[a]	NR
	Chemotherapy + bevacizumab + atezolizumab	80	NR	8
KRAS and *TP53* co-mutations	Anti-PD-(L)1 antibody monotherapy	56 (SU2C cohort) 7 (CheckMate 057 cohort)	36 57	3 NR
	Chemotherapy + bevacizumab + anti-PD-(L)1 antibody	41	NR	14
KRAS and *STK11* co-mutations	Anti-PD-(L)1 antibody monotherapy	54 (SU2C cohort) 6 (CheckMate 057 cohort)	7 0	2 NR
	Anti-PD-(L)1 antibody monotherapy	138	12	2
	Chemotherapy + bevacizumab + atezolizumab	34[b]	NR	6.0[b]
KRAS and *KEAP1* co-mutations	Anti-PD-1/PD-L1 monotherapy	101	18	2
	Chemotherapy + bevacizumab + atezolizumab	34[b]	NR	6[b]

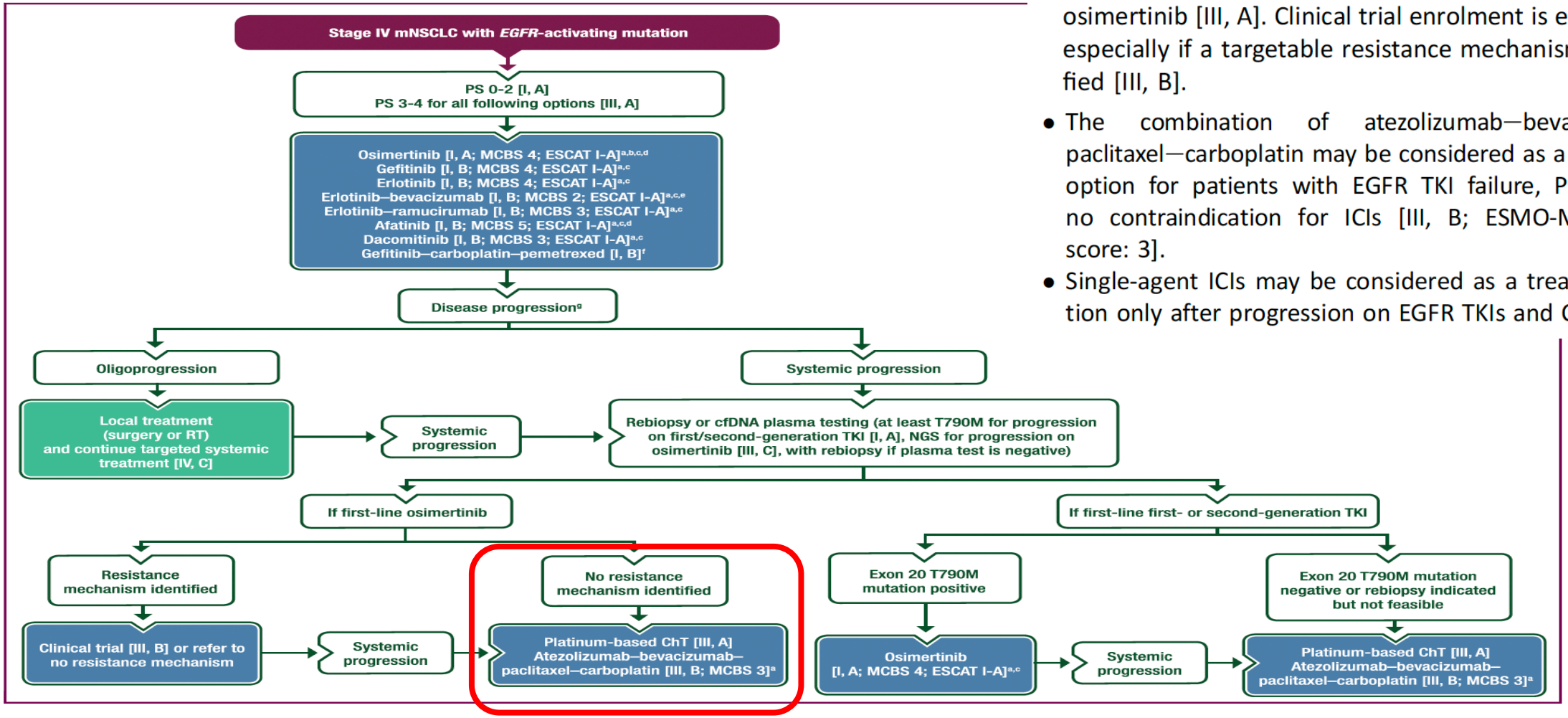
Otano I, et al. NRCO 2023

CURRENT GUIDELINES

ESMO, NCCN & ASCO

ESMO GUIDELINES

2023 (ex. EGFRm patients)

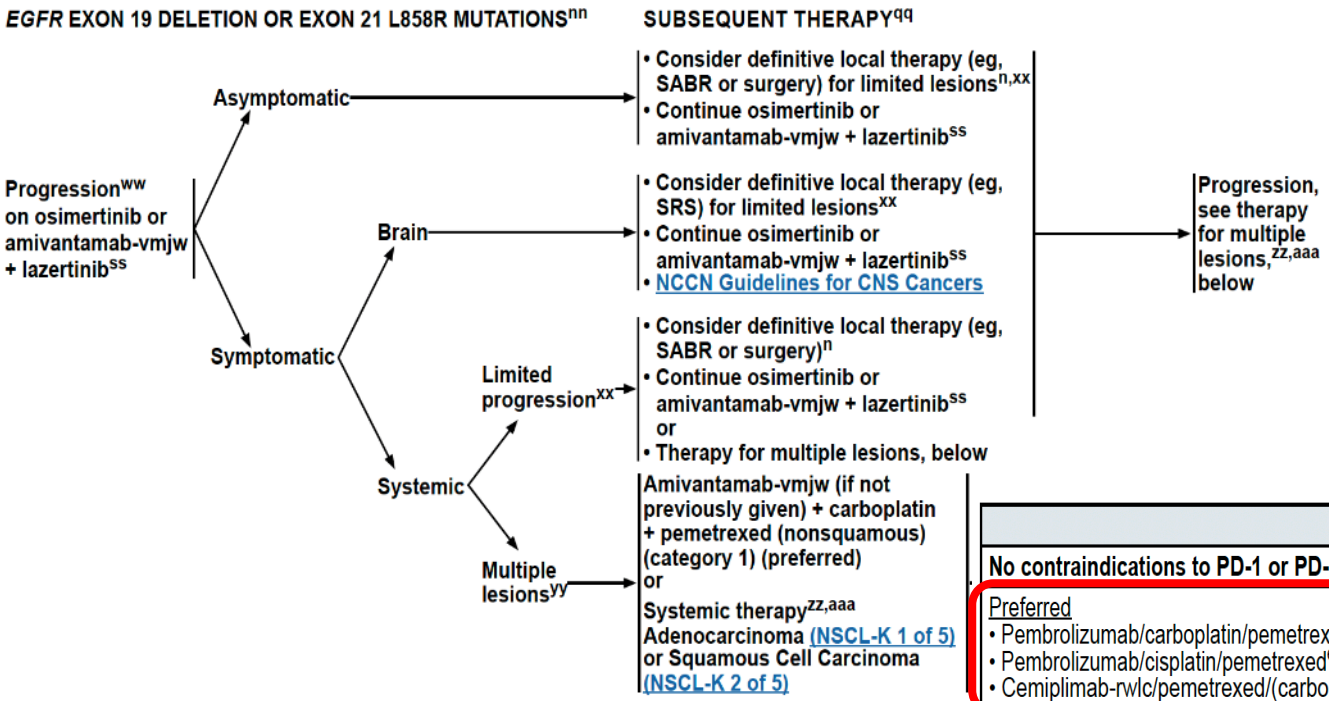


- Platinum-doublet ChT is the SoC upon progression on osimertinib [III, A]. Clinical trial enrolment is encouraged, especially if a targetable resistance mechanism is identified [III, B].
- The combination of atezolizumab—bevacizumab—paclitaxel—carboplatin may be considered as a treatment option for patients with EGFR TKI failure, PS 0-1 and no contraindication for ICIs [III, B; ESMO-MCBS v1.1 score: 3].
- Single-agent ICIs may be considered as a treatment option only after progression on EGFR TKIs and ChT [IV, C].

Hendriks L, et al. Ann Oncol 2023

NCCN GUIDELINES

v. 11/2024 (ex. EGFRm patients)



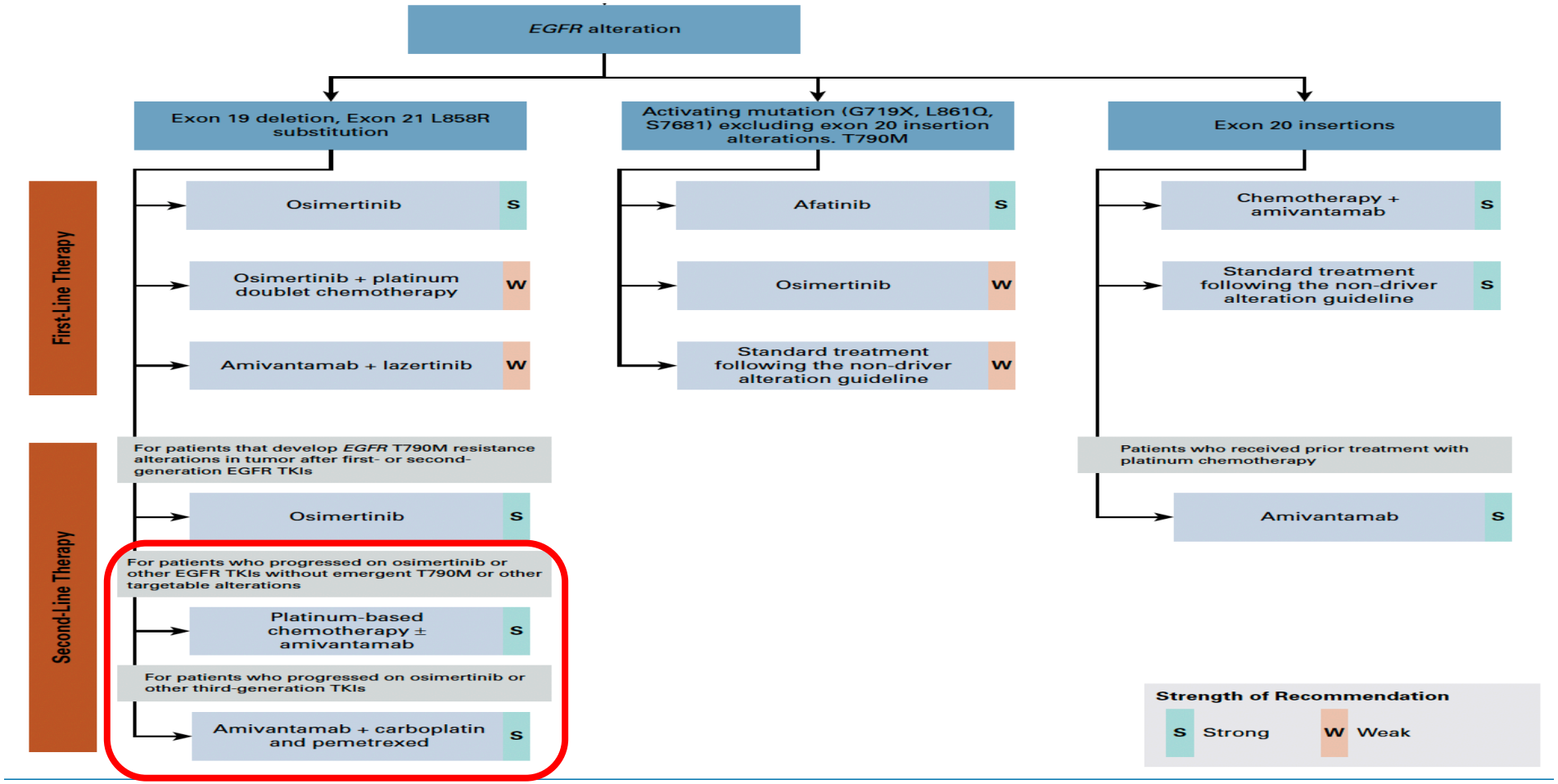
SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,c]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–1)	
No contraindications to PD-1 or PD-L1 inhibitors[d]	**Contraindications to PD-1 or PD-L1 inhibitors[d]**
Preferred • Pembrolizumab/carboplatin/pemetrexed[e] (category 1)[1,2] • Pembrolizumab/cisplatin/pemetrexed[e] (category 1)[2] • Cemiplimab-rwlc/pemetrexed/(carboplatin or cisplatin)[e] (category 1)[7] Other Recommended • Atezolizumab[f]/carboplatin/paclitaxel/bevacizumab[e,g,h,i,j] (category 1)[3] • Atezolizumab[f]/carboplatin/albumin-bound paclitaxel[e,4] • Nivolumab/ipilimumab[5,e] • Nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin)[e] (category 1)[6] • Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin)[e] (category 1)[7] • Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel[e] (category 1)[8] • Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/pemetrexed[e] (category 1)[8]	Useful in Certain Circumstances • Bevacizumab[g]/carboplatin/paclitaxel[h,i,j] (category 1)[9] • Bevacizumab[g]/carboplatin/pemetrexed[h,i,j,9,10] • Bevacizumab[g]/cisplatin/pemetrexed[h,i,j,11] • Carboplatin-combination therapy (category 1) ▸ Combination options include: albumin-bound paclitaxel[12] docetaxel,[13] etoposide,[14,15] gemcitabine,[16] paclitaxel,[17] or pemetrexed[18] • Cisplatin-combination therapy (category 1) ▸ Combinations options include: docetaxel,[13] etoposide,[19] gemcitabine,[17,20] paclitaxel,[21] or pemetrexed[20] • Gemcitabine/docetaxel (category 1)[22] • Gemcitabine/vinorelbine (category 1)[23]

Available online

ASCO GUIDELINES

Nov. 12, 2024 (ex. EGFRm patients)



Bazhenova L, et al J Clin Oncol 2024

WHAT THE BIOLOGY OF AGA IS TELLING US?

Understand AGA genomic and TME specificities

PDL1 EXPRESSION

At baseline, controversial results (related to different assays but not only)

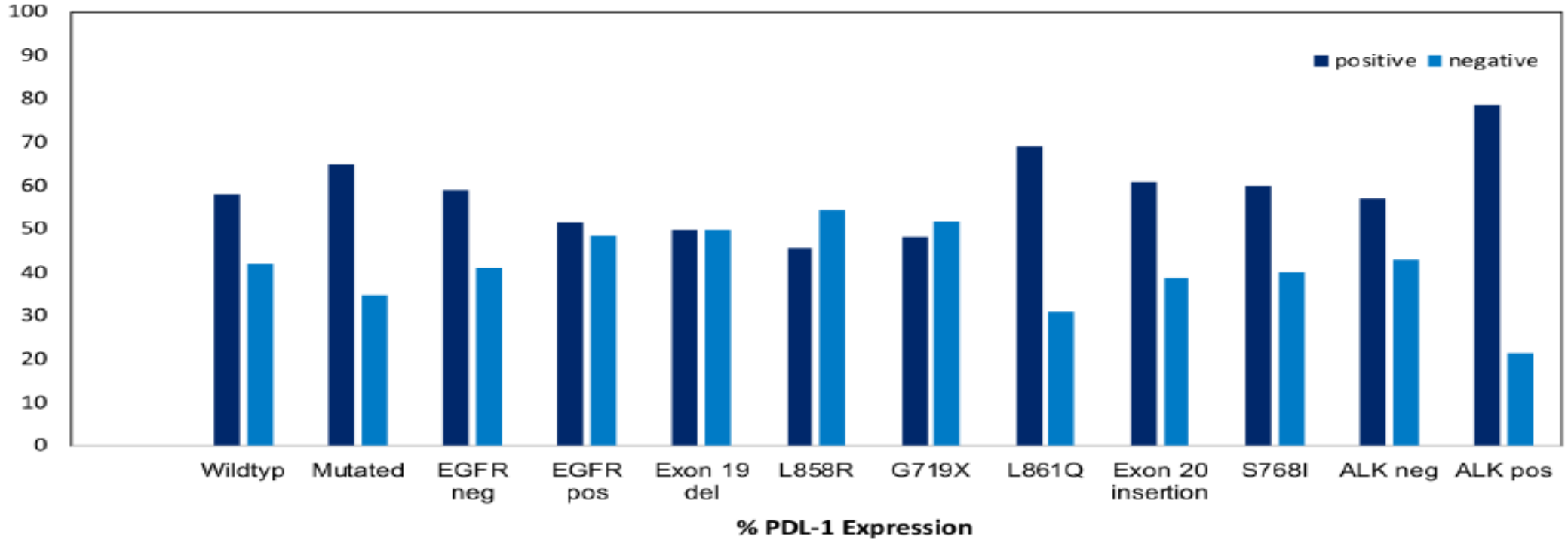
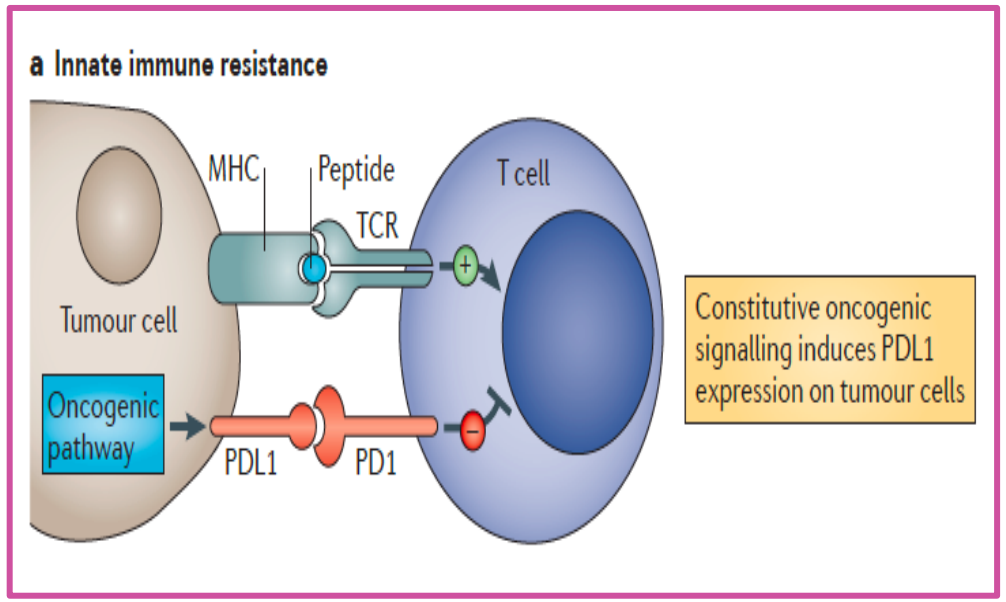


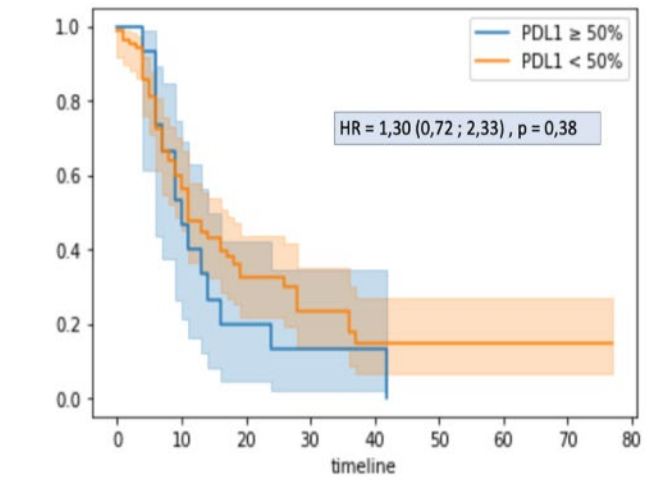
Figure 3 Relationship of programmed death-ligand 1 (PD-L1) expression with oncogene alterations.

Berghoff A et al., ESMO open 2019

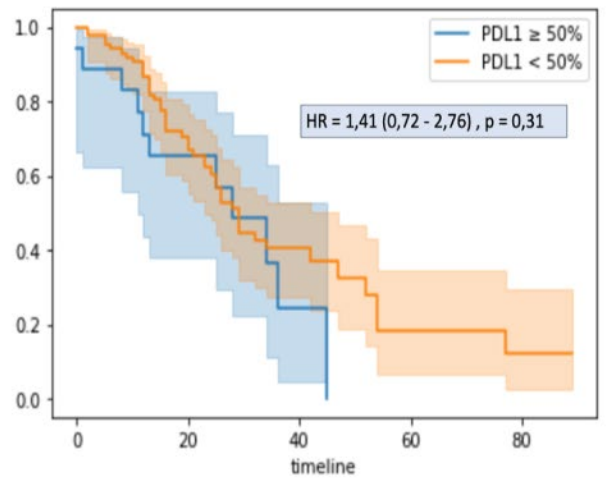
PDL1 EXPRESSION

A specific PDL1 expression mechanism with a possible adverse predictive value





PDL1 ≥ 50%									
At risk	17	7	3	2	1	0	0	0	0
Censored	1	3	3	3	4	4	4	4	4
Events	0	8	12	13	13	14	14	14	14
PDL1 < 50%									
At risk	84	45	17	10	5	3	1	1	0
Censored	0	4	16	19	21	23	25	25	26
Events	1	36	52	56	59	59	59	59	59



PDL1 ≥ 50%					
At risk	17	9	1	0	0
Censored	0	3	7	7	7
Events	1	6	10	11	11
PDL1 < 50%					
At risk	85	42	14	3	2
Censored	0	18	32	38	38
Events	0	25	39	44	45

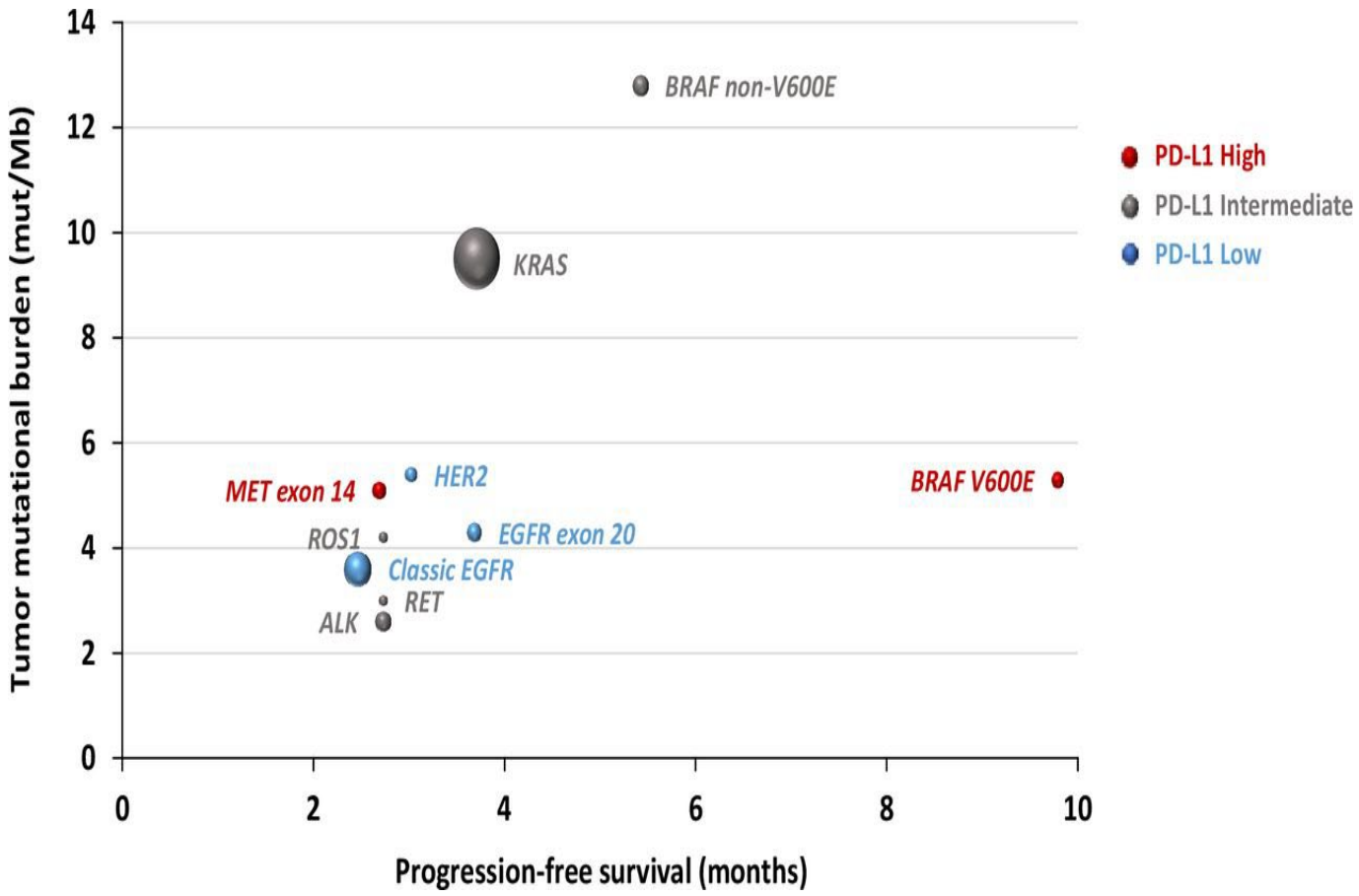
Pandoll DM, Nat Rev Cancer 2012;
Slomka J, et al. PLOSone 2024

TUMOR MUTATIONAL BURDEN

As expected, TMB is low in AGA

***EGFR/ALK+* NSCLC has low TMB[3]**

Variant	Median TMB
EML4-ALK	2.5
Non-EML4-ALK	2.7
ROS1 rearrangement	3.6
EGFR ex19del	3.6
EGFR L858R	3.8
BRAF V600E	3.8
EGFR T790M	4.5
MET ex14	4.5
KRAS mutation	9.0
BRAF non-V600E	10.8
POLE mutation	14.0
PD-L1 amplification	14.4
MSH2 alteration	18.0
MLH1 alteration	28.4



Schrock, et al. WCLC 2016 (Abs MA14.01);
Negrao M, et al. JITC 2021

CHARACTERISTICS OF AGA IMMUNE CONTEXTURE

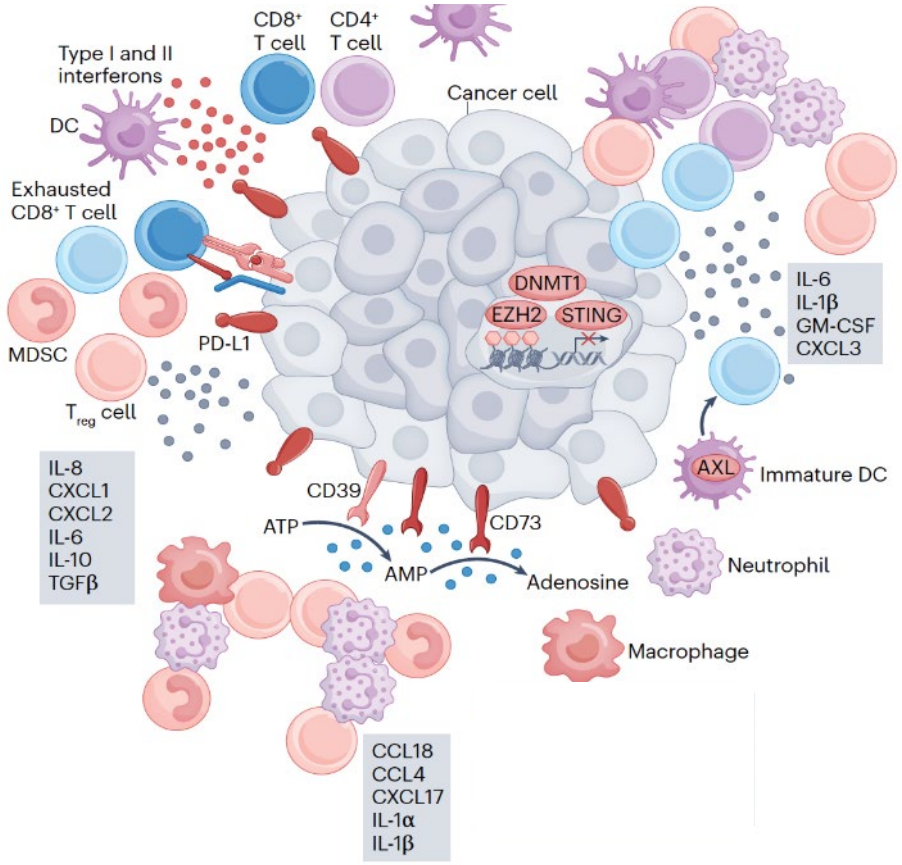
EGFRm as the example

Low TMB

Unreliable PDL1 expression

Low level of immunostimulatory cytokines (CCL3, CXCL9 and CXCL10)

Globally, a TME enriched in immunosuppressive cells such as MDSCs, Treg and tumour-associated macrophages



High levels of immunosuppressive

cytokines promoting MDSC and macrophages, from

- Tumour cells (CCL18, CXCL1, CXCL3 and IL-1β)
- T-cells (CCL4, CXCL17
- and IL-1β)
- Macrophages (CCL2 and CXCL17)

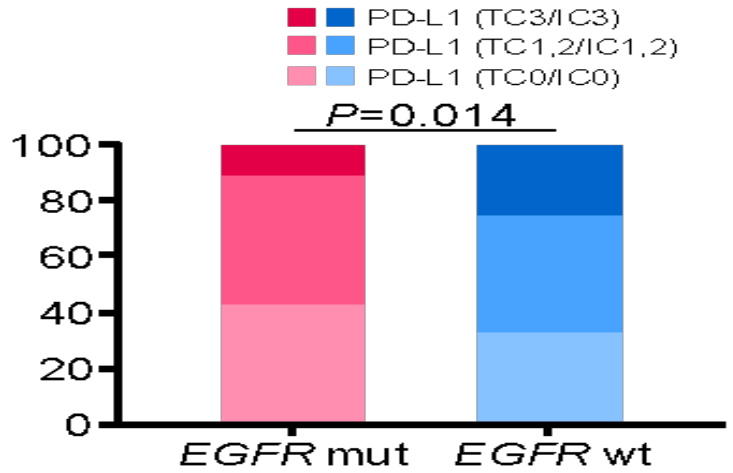
High levels of CD73 (adenosine)

Adapted from Otano I, et al. NRCO 2023

CD8+ PDL1+ TILS

After EGFR-TKIs, an increase has been reported in some cases

Lack of T-cell infiltration and low proportion of PD-L1+/CD8+ TILs[1,2]



	EGFR Mut+	
	Pre-TKI (N=62)	Post-TKI (N=63)
Concurrent PD-L1 expression and CD8+ TILs (IHC)		
PD-L1+ (≥50%) & high CD8+ TILs (grade 2–3)	1/48 (2.1%)	1/43 (2.3%)
PD-L1+ (≥5%) & high CD8+ TILs (grade 2–3)	1/48 (2.1%)	5/43 (11.6%)

EGFR TKIs trigger the secretion of CXCL10 (which recruits CD8+ T cells) and suppress the production of CCL22 (which recruits Treg cells)

Dong. Oncoimmunology 2017;
Gainor, et al. Clin Cancer Res, 2016.

WHAT'S NEXT?

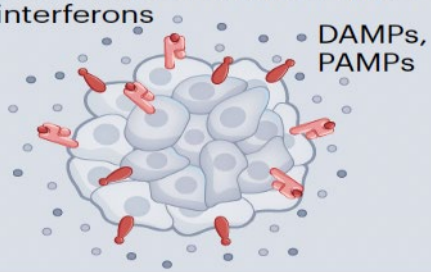
Overcome primary resistances to IO

VARIOUS OPTIONS

Theoritically

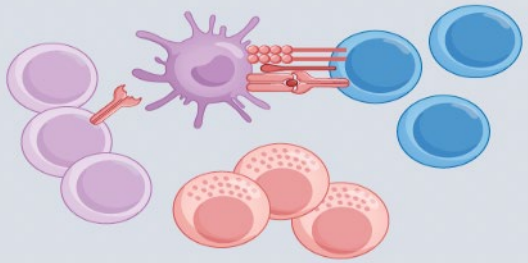
Immunogenic therapy

- Boost tumour immunogenicity
- Increase MHC I and II expression
- Elicit immunogenic cell death
- Release of DAMPs and PAMPs
- Upregulate expression of PD-L1
- Enhance DC maturation and antigen presentation
- Increase production of type I interferons



Immunostimulatory therapy

- Increase production of type I and II interferons
- Increase T cell activation and co-stimulation
- Recruit T cells and NK cell to the tumour
- Promote T cell memory phenotype



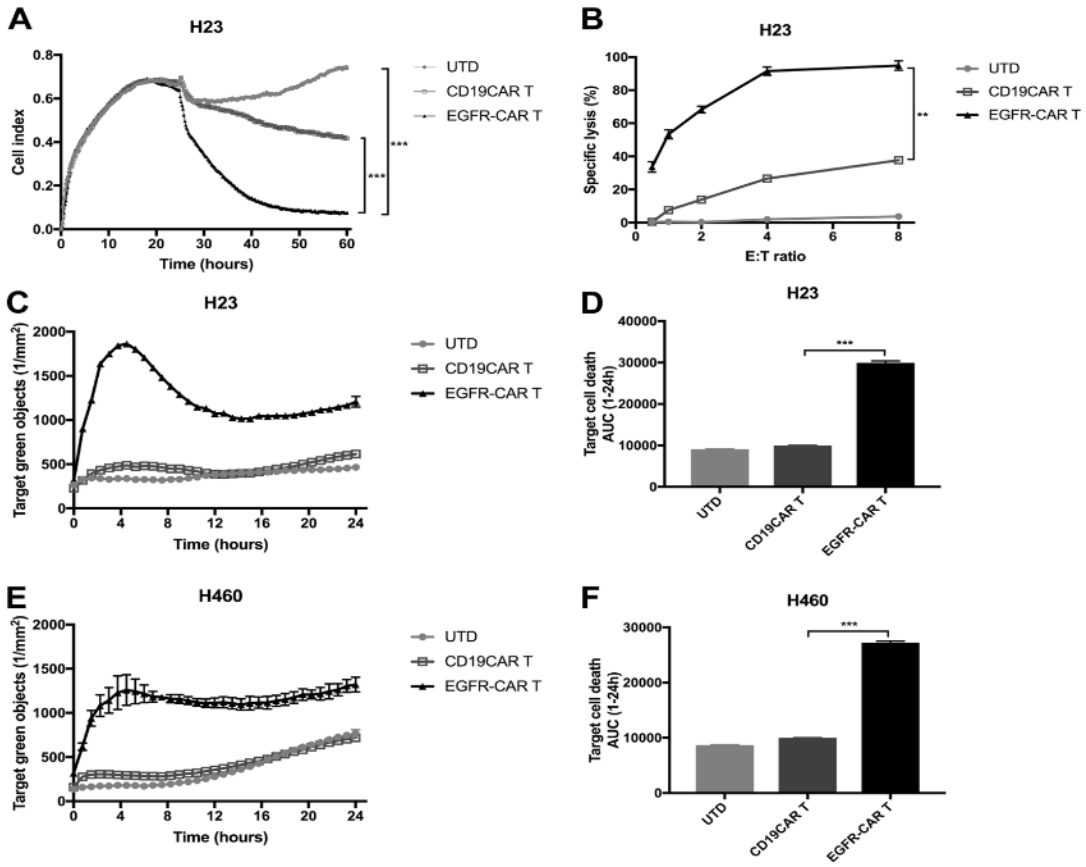
- Chemotherapy
- DDR-targeted therapies (PARP inhibitors)
- Epigenetic reprogramming
- Autophagy inhibition
- Anti-AXL agents
- MEK inhibitors

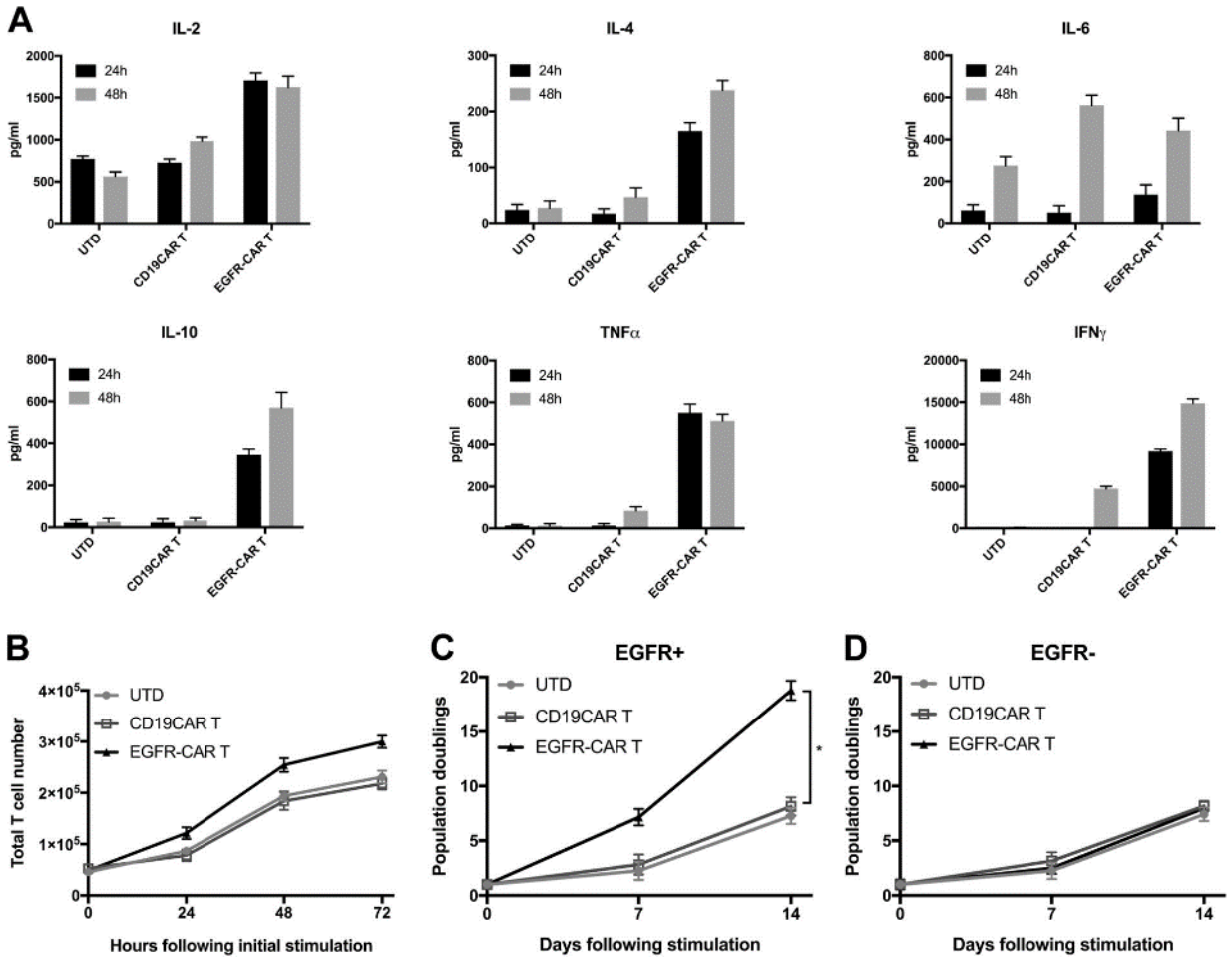
- Immune-checkpoint inhibitors (antagonistic antibodies targeting PD-(L)1, CTLA4, TIGIT, LAG3, TIM3 or BTLA)
- Co-stimulatory agonist targeting CD27, CD28, OX40, CD137 or GITR
- Anti-CD73 agents or other adenosine pathway inhibitors
- Anti-VEGF/VEGFR agents

Otano I, et al. NRCO 2023

CAR T CELL / CELL THERAPY

EGFRm in vitro / mouse model



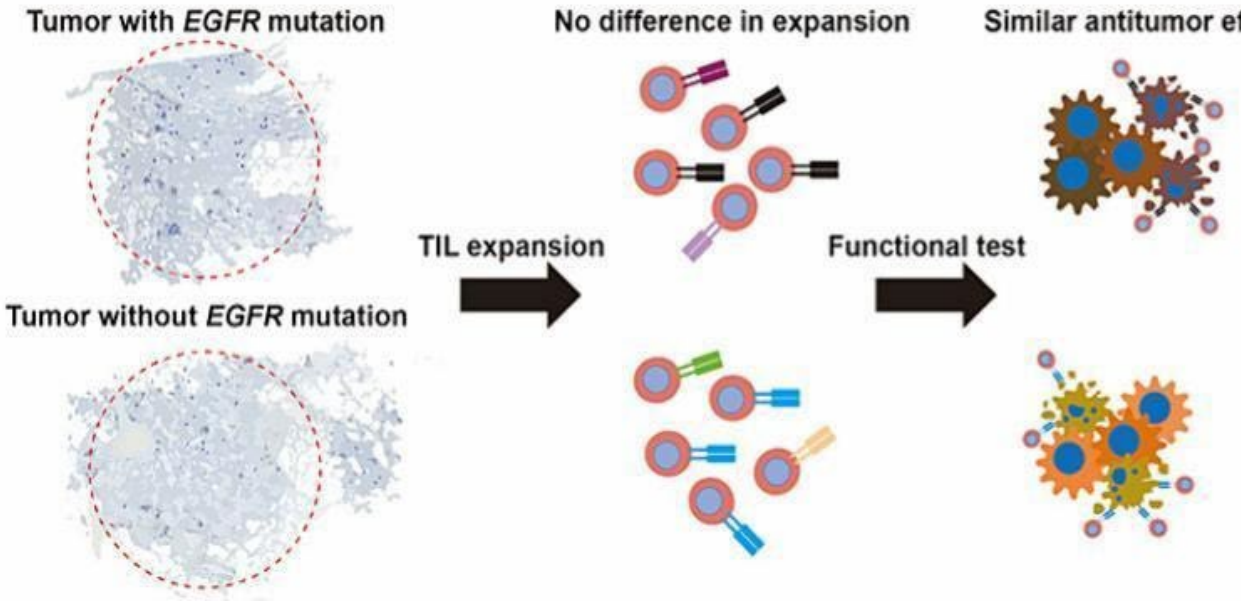


Li H, et al. Cell Death and Disease 2018

TILS / CELL THERAPY

EGFRm in vitro / in vivo

Expansion of Tumor-Infiltrating Lymphocytes in Non-Small Cell Lung Cancer: Clinical Potential and Efficacy in EGFR Mutation Subsets

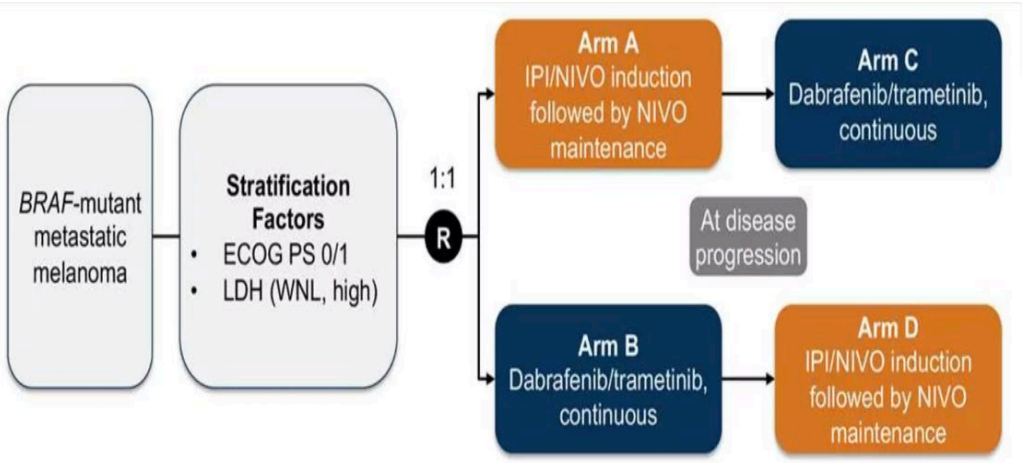


TILs expansion from 103 primary NSCLCs
TIL expansion observed in all cases, including EGFRm.
Increase in the median $CD4^+/CD8^+$ ratio and IFN-γ secretion in 13 out of 16 cases, including all three cases with EGFR mutations.
The cytotoxicity assay revealed enhanced tumor cell death in three of the seven cases, two of which had *EGFR* mutations.
In vivo functional testing in xenograft model showed a reduction in tumor volume.

Lee H, et al. Clin Immunol 2024

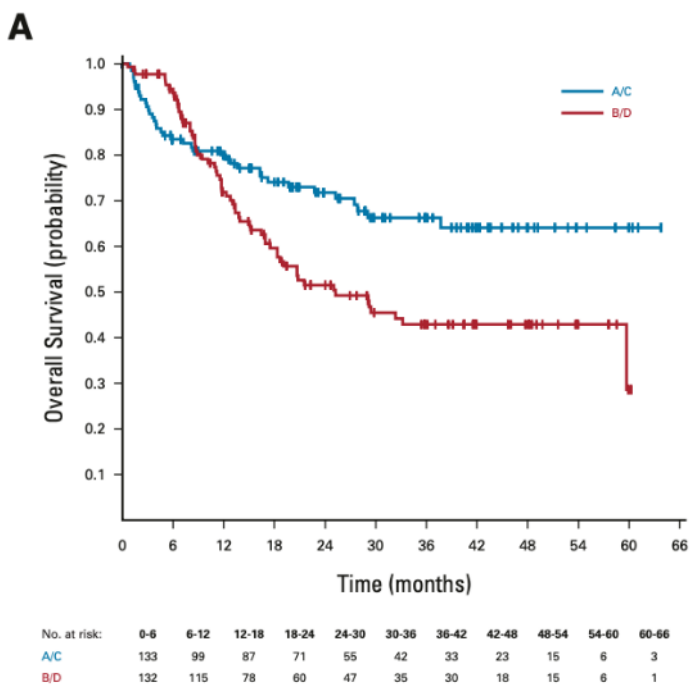
PD(L)1 & TKI: IMPACT OF THE SEQUENCE

Illustration with the DreamSeq trial (*BRAF*^{V600m} Melanoma)

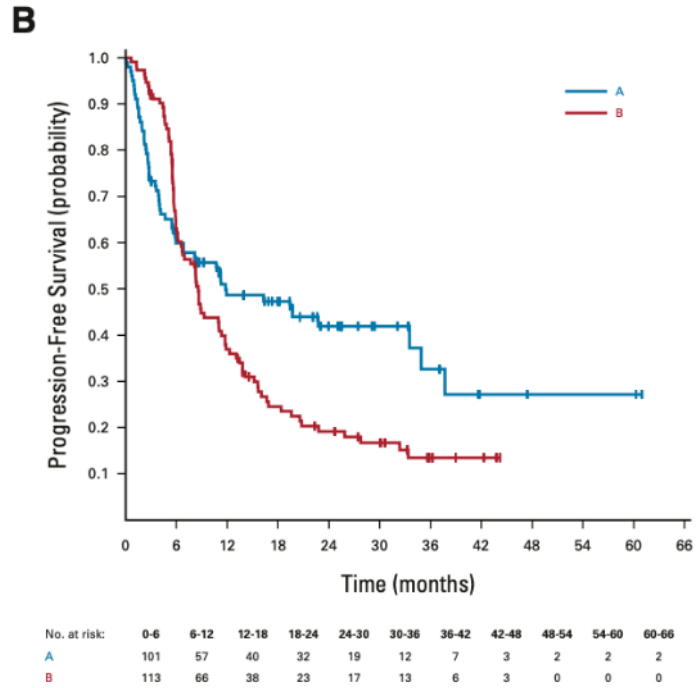


Primary endpoint: 2-year landmark OS (70% vs 50%)

- 90% power 2-year OS rate of 70% in arm A to C sequence vs 50% in arm B to D, two-sided type I error rate of 0.05



The 2-year OS rate was 71.8% (95% CI, 62.5 to 79.1) vs 51.5% (95% CI, 41.7 to 60.4) (*P* = .010, log-rank)

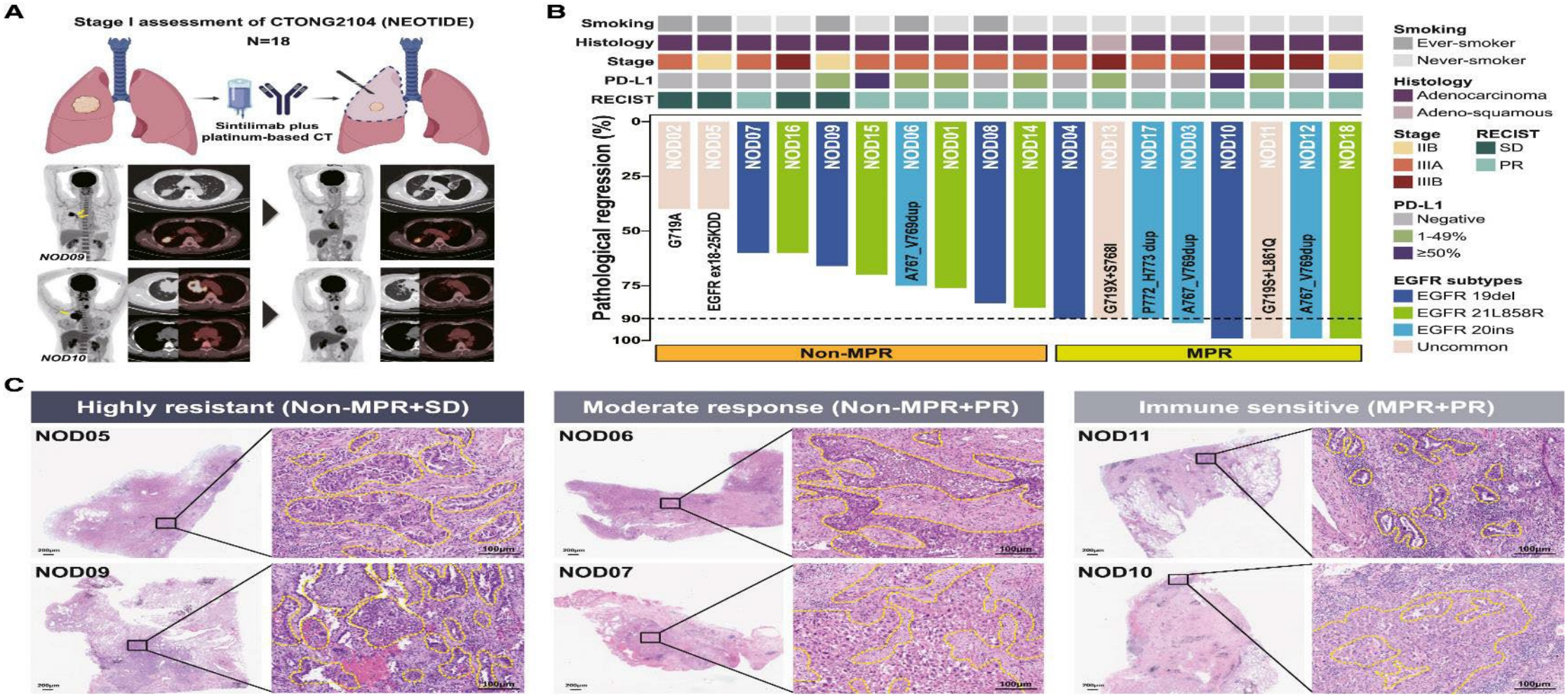


Median PFS 11.8 months [95% CI, 5.9 to 33.5] *v* 8.5 months [95% CI, 6.5 to 11.3] [*P* = .054, log-rank])

Atkins MB, et al. J Clin Oncol 2022

WOULD PERIOPERATIVE STRATEGY LOOK DIFFERENTLY?

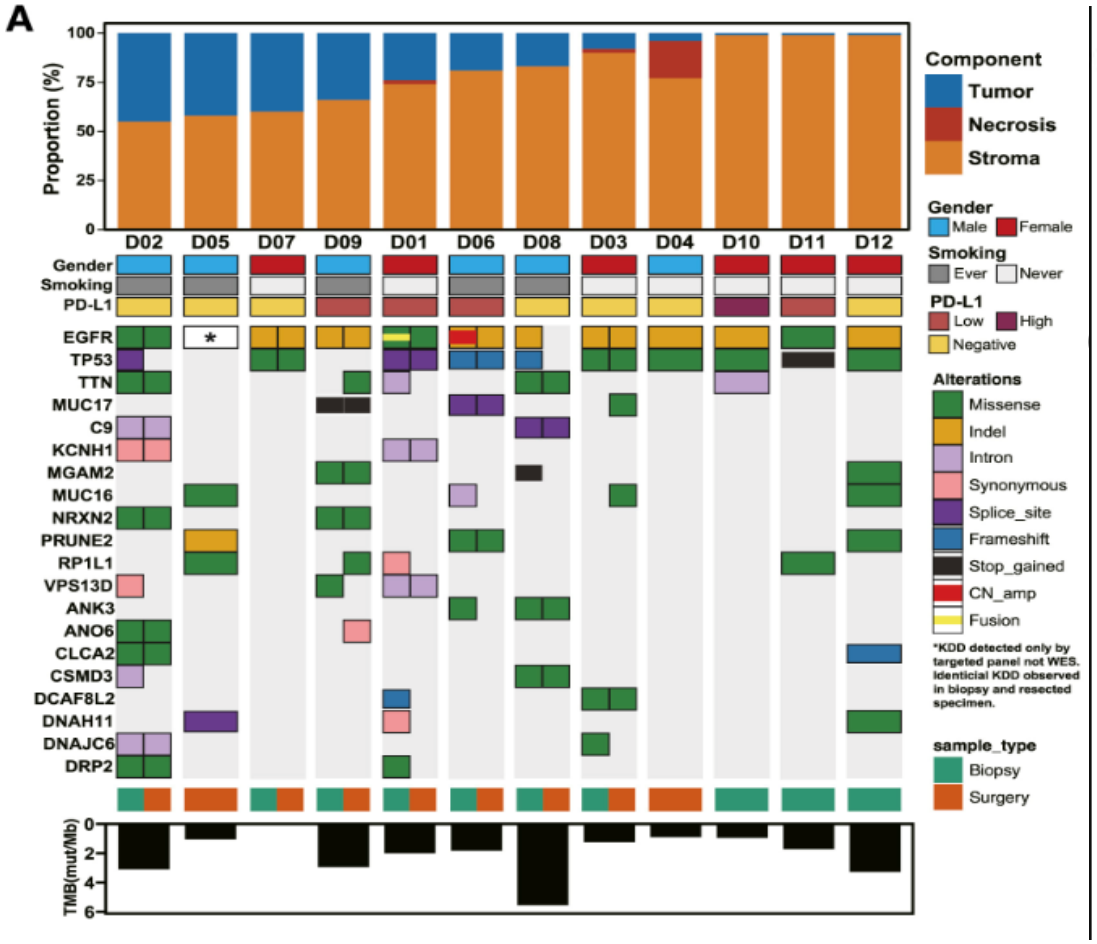
Neoadjuvant sintilimab & chemotherapy in *EGFRm* NSCLC: NEOTIDE/CTONG2104

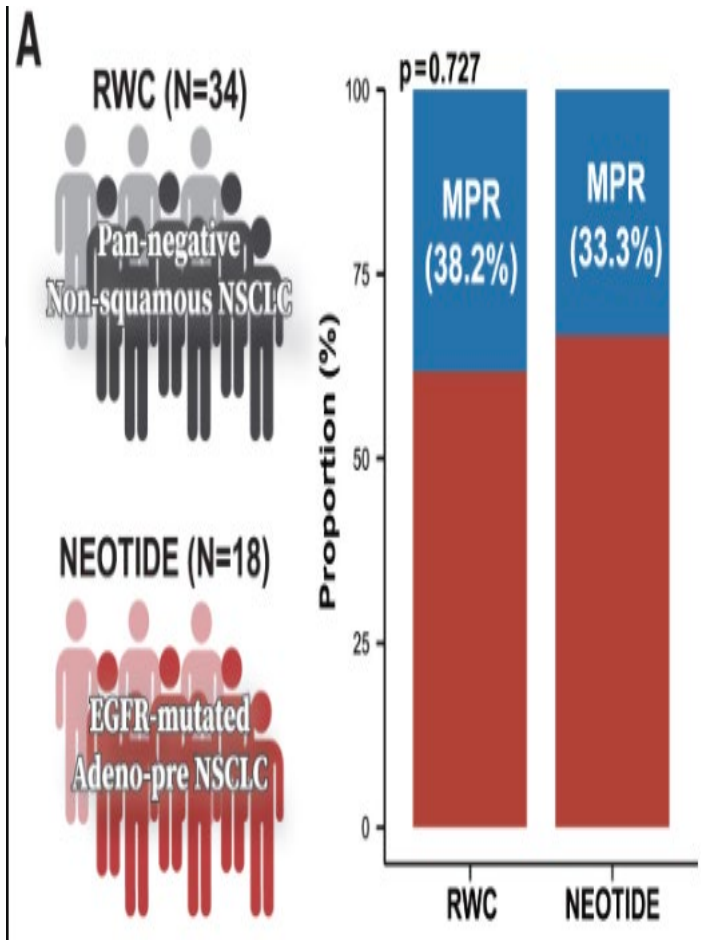


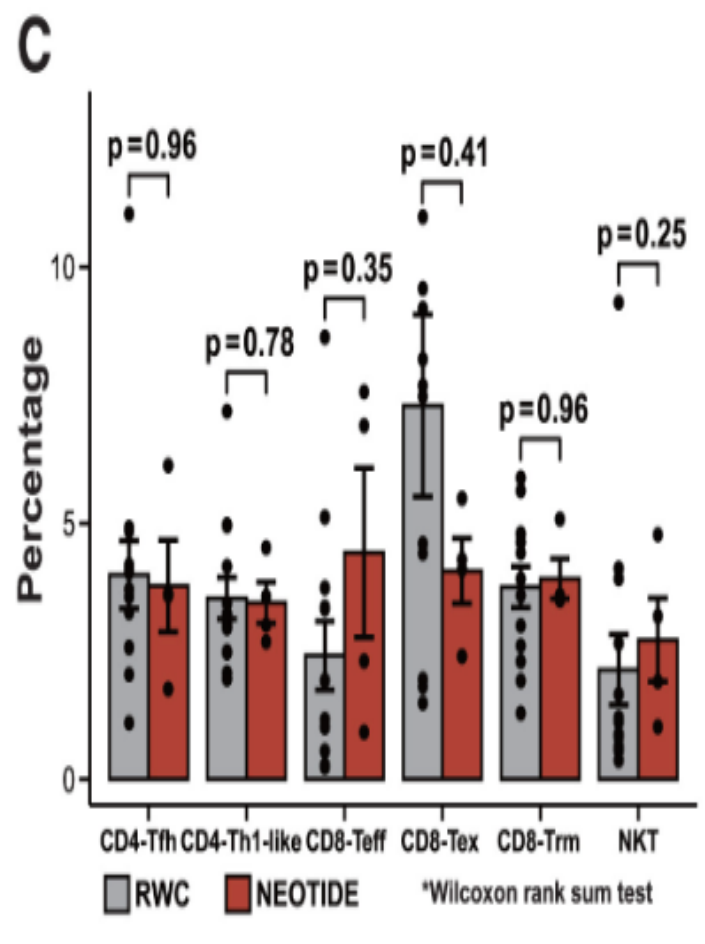
Zang C, et al. Cell Reports Med 2024

WOULD PERIOPERATIVE STRATEGY LOOK DIFFERENTLY?

Neoadjuvant sintilimab & chemotherapy in *EGFRm* NSCLC: NEOTIDE/CTONG2104)







Zang C, et al. Cell Reports Med 2024

TAKE HOME MESSAGES

- PD(L)1 Immune Checkpoints Inhibitors have low efficacy in advanced pts w AGA (except in *KRASm* & *BRAFm*)
  - Alone
  - In addition to standard platinum-based chemotherapy
  - In addition to VEGF inhibition
- AGA TME is enriched in immunosuppressive cytokines and cells (MDSCs, Treg and TAM)
- Targeted strategy (amivantamab) +/_ standard chemotherapy remains the SoC after TKI exhaustion
- New strategies (BiTES, Cell therapy, etc) are therefore being explored
- Extrapolation of these results in earlier setting should be made with caution

GOOD SCIENCE
BETTER MEDICINE
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Thank You

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