VII CONVEGNO NAZIONALE DELLA
RETE ONCOLOGICA SIFaCT

Oltre il modello mutazionale e l'oncologia di precisione:
la medicina personalizzata

ONCOFARMA

Milano 23-24 Giugno 2023

Sifact
SOCIETÀ ITALIANA DI FARMACIA CLINICA E TERAPIA

Management dei pazienti affetti da NSCLC

Giuseppe Lo Russo MD;PhD
Fondazione IRCCS Istituto Nazionale dei Tumori
Milano

Obiettivi dei trattamenti vecchi e nuovi

Malattia localizzata→GUARIGIONE (Chirurgia, Terapie Neoadiuvante, Adiuvante e Concomitante ad RT definitiva)

Malattia avanzata/metastatica→CONTROLLO DELLA MALATTIA (Terapie sempre sistemiche: CHEMIOTERAPIA, IMMUNOTERAPIA, TERAPIE BIOLOGICHE)

Cosa dobbiamo sapere per decidere la terapia?

- ✓**PATIENT**
- ✓SCLC: Histological diagnosis and staging
- ✓NSCLC early stages: Histological diagnosis and staging *(EGFR,PD-L1, ALK)*
- ✓Squamous NSCLC advanced disease: PD-L1
- ✓Non-squamous NSCLC advanced disease: PD-L1, EGFR, ALK , ROS1,BRAF, NTRK

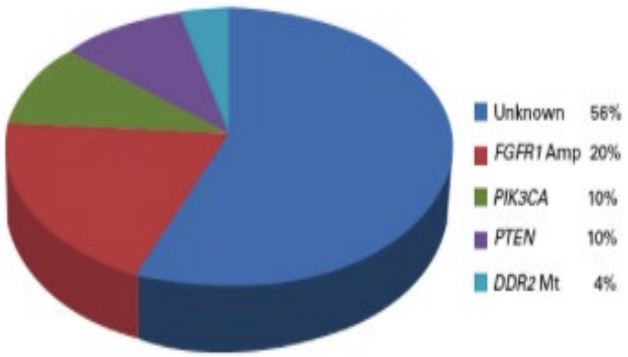
Cosa dovremmo sapere già oggi?

PD-L1	
Single nucleotide variations (SNVs)	EGFR, BRAF, HER2 ,KRAS
Insertions and deletions (indels)	EGFR
Copy number variations (CNVs)	MET, HER2
Rearrangements	ALK, ROS1, RET, NTRK
Splice variants	MET

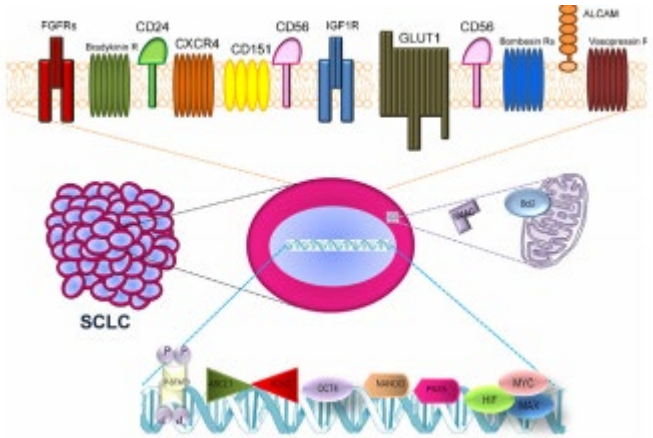
Cosa potremo sapere in futuro?

PD-L1 Status, TMB, MSI status

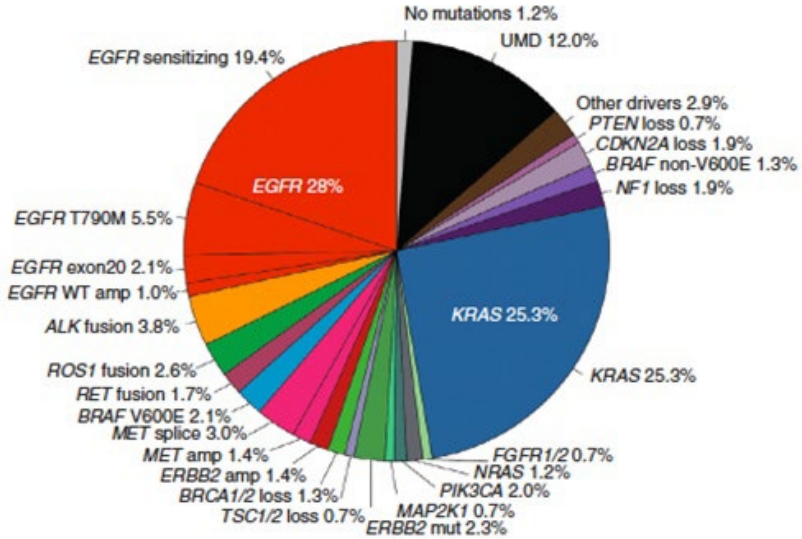
Squamous cell carcinoma



Small cell lung cancer

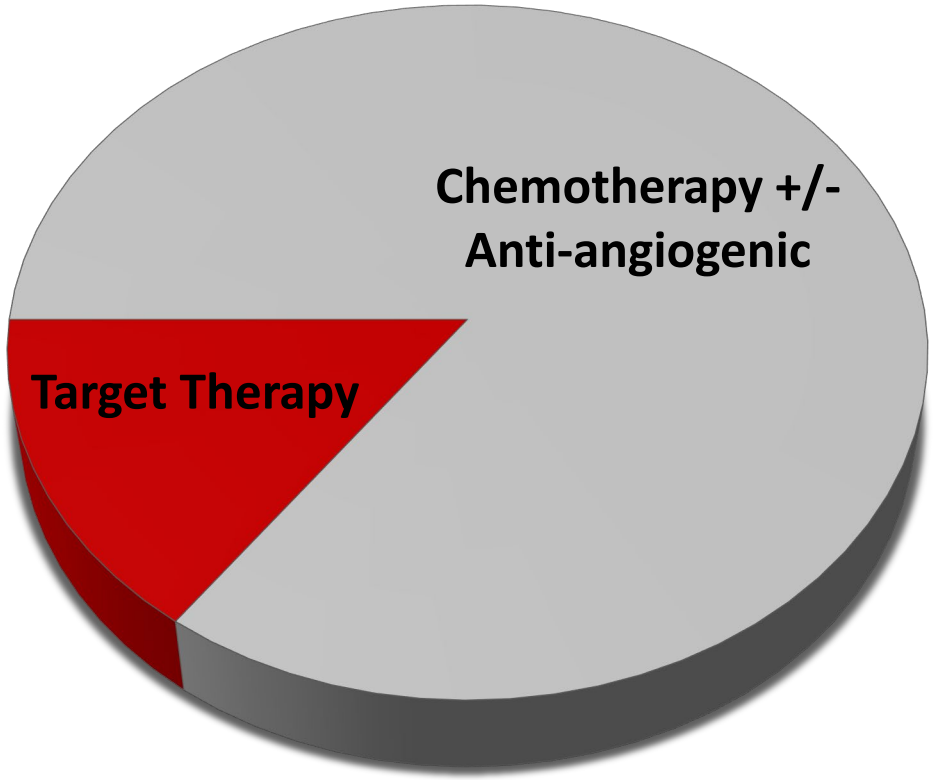


Adenocarcinoma

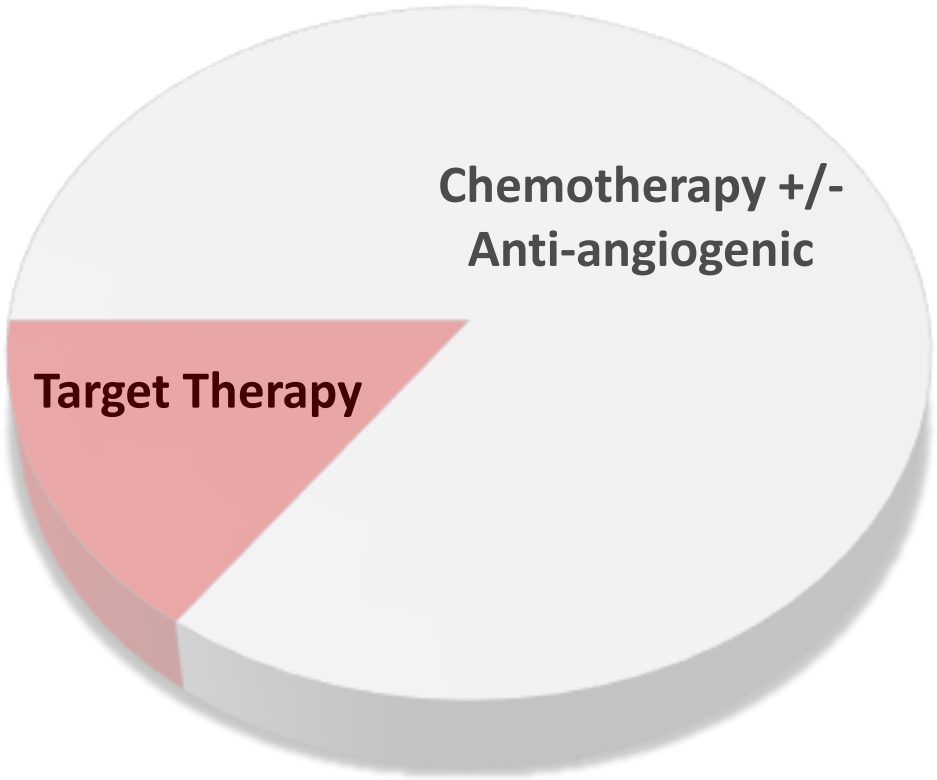


Teicher BA, 2014

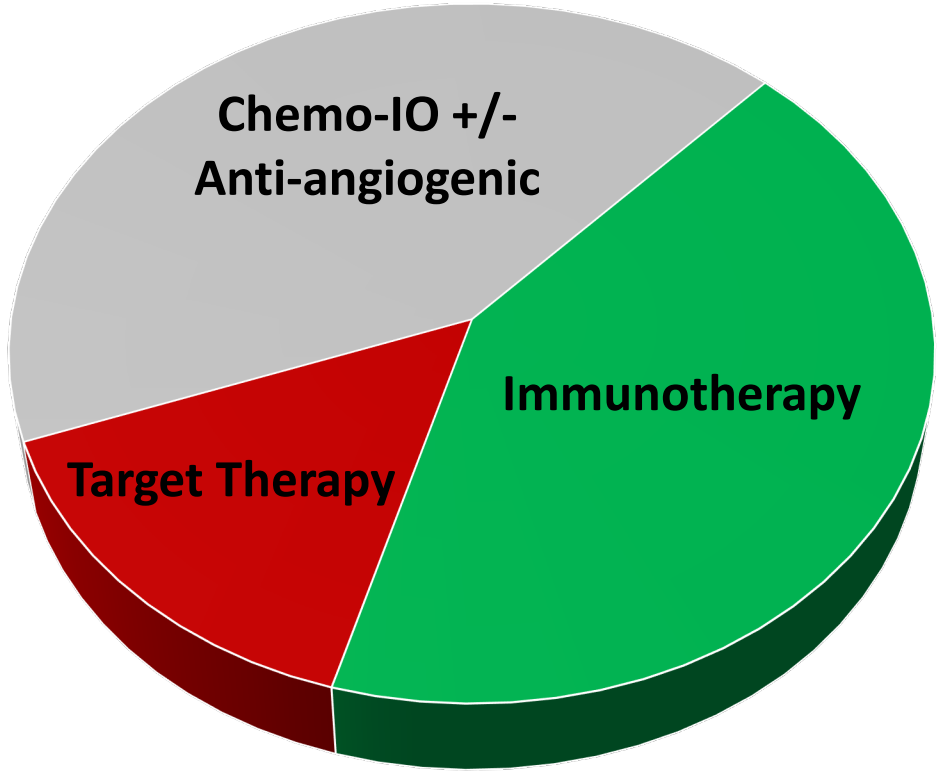
Pochi anni fa….



Pochi anni fa….



….Oggi



Italian Therapeutic algorithms 2023

- NSCLC I: Surgery or RT (If no possible surgery)
- NSCLC STAGES II-III AFTER SURGERY: Platinum based adjuvant CHT (cisplatin + vinorelbine) + 3 years adjuvant osimertinib if EGFR + or 1 year adjuvant atezolizumab if PD-L1 ≥ 50%
- NSCLC STAGES IIIa-b: Platinum based neoadjuvant CHT
- NSCLC STADI IIIb-c: Concomitant CHT + RT→ 1 years durvalumab (only if pd-l1 ≥ 1%)
- Oncogene addicted advanced NSCLC (ALK,ROS1,BRAF,EGFR, NTRK) (18%): target therapies
- Non Oncogene addicted advanced NSCLC PD-L1 ≥ 50%(27%): Pembrolizumab OR Cemiplimab OR Atezolizumab → Platinum based CHT
- Non Oncogene addicted advanced NSCLC PD-L1<50% (55%): Platinum based CHT + Pembrolizumab OR Nivolumab + ipilimumab + CHT (2 CYCLES)→ Docetaxel +/- nintedanib

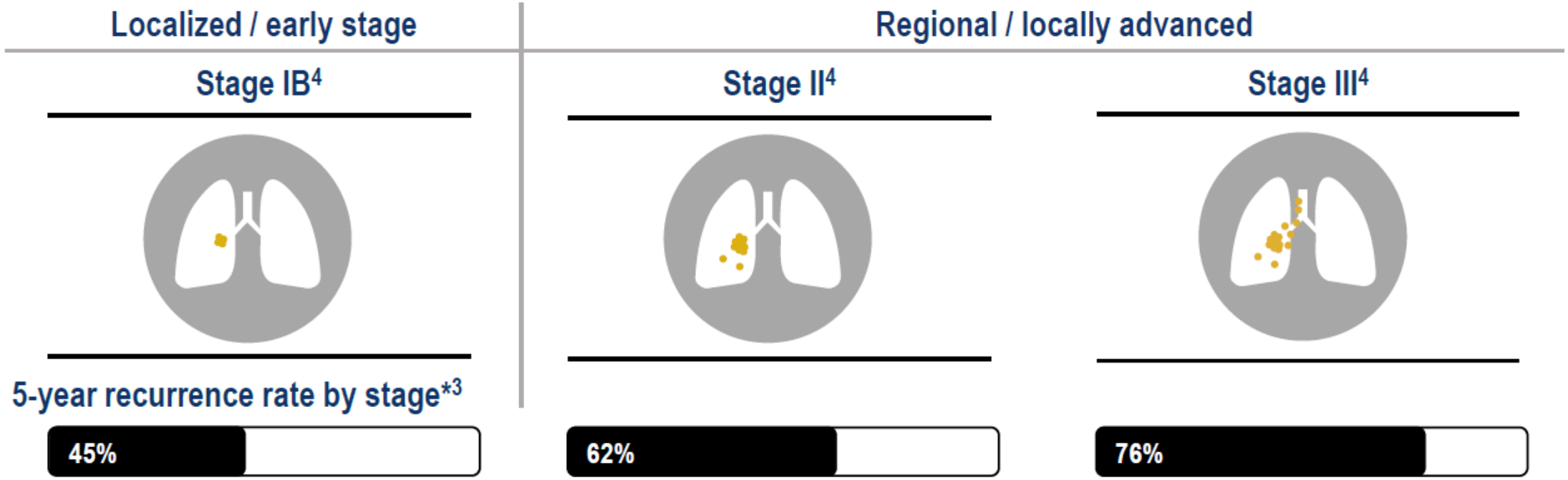
Early stages NSCLC: (Stages I-IIIA)

Standard:

- NSCLC I: Surgery or RT (If no possible surgery)

- NSCLC STAGES II-III AFTER SURGERY: Platinum based adjuvant CHT (cisplatin + vinorelbine) + 3 years adjuvant osimertinib if EGFR or 1 year adjuvant Atezolizumab if PD-L1 ≥ 50%

Why adjuvant chemotherapy?

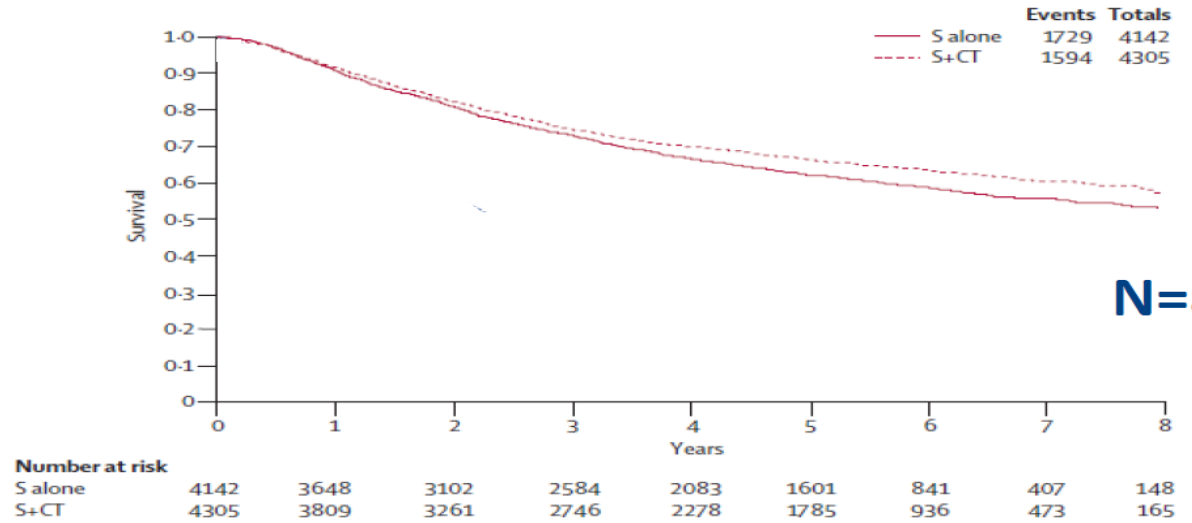


Courtesy of R Herbst

Why adjuvant chemotherapy?

Adjuvant treatments destroy the micrometastasis

Meta-analysis
IGR-MRC
CT vs no CT



N=8447

HR = 0.87 (0.81-0.93) p<0.000001

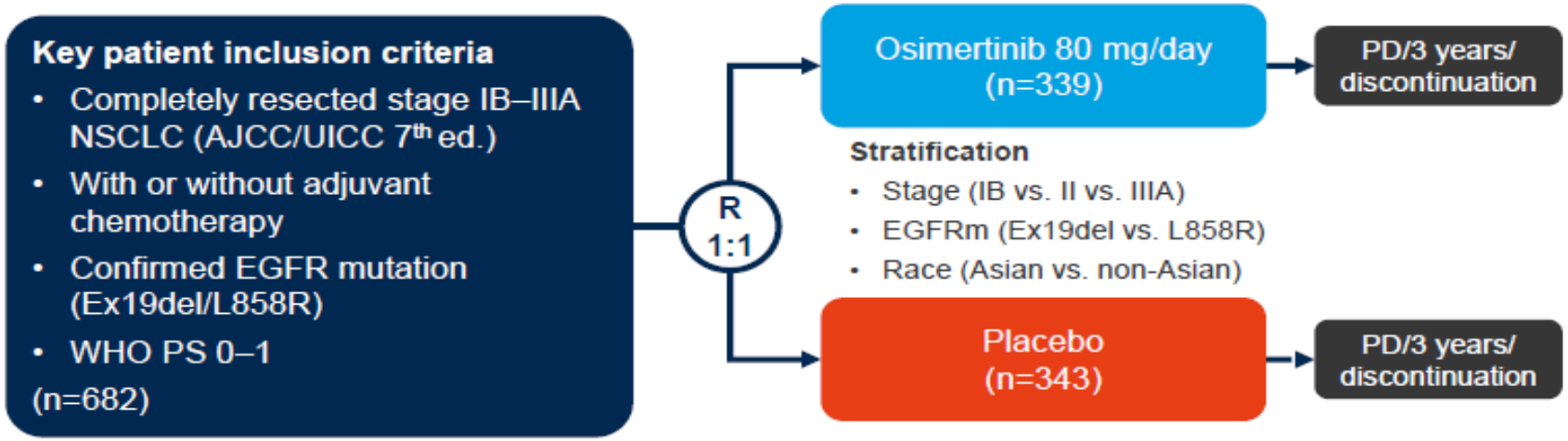
Absolute benefit 4% at 5 yrs

Lancet 2010; 375: 1267–77

Adjuvant treatment in EGFR +

LBA47: Osimertinib as adjuvant therapy in patients (pts) with resected EGFR-mutated (EGFRm) stage IB–IIIA non-small cell lung cancer (NSCLC): updated results from ADAURA – Tsuboi M, et al

- **Study objective**
  - To evaluate the updated efficacy and safety of adjuvant osimertinib in patients with resected EGFR-mutated NSCLC in the ADAURA study



Primary endpoint
- DFS (in stage II/IIIA)

Secondary endpoints
- DFS (overall population[a]), OS, HRQoL, safety

[a]Stage IB, II and IIIA

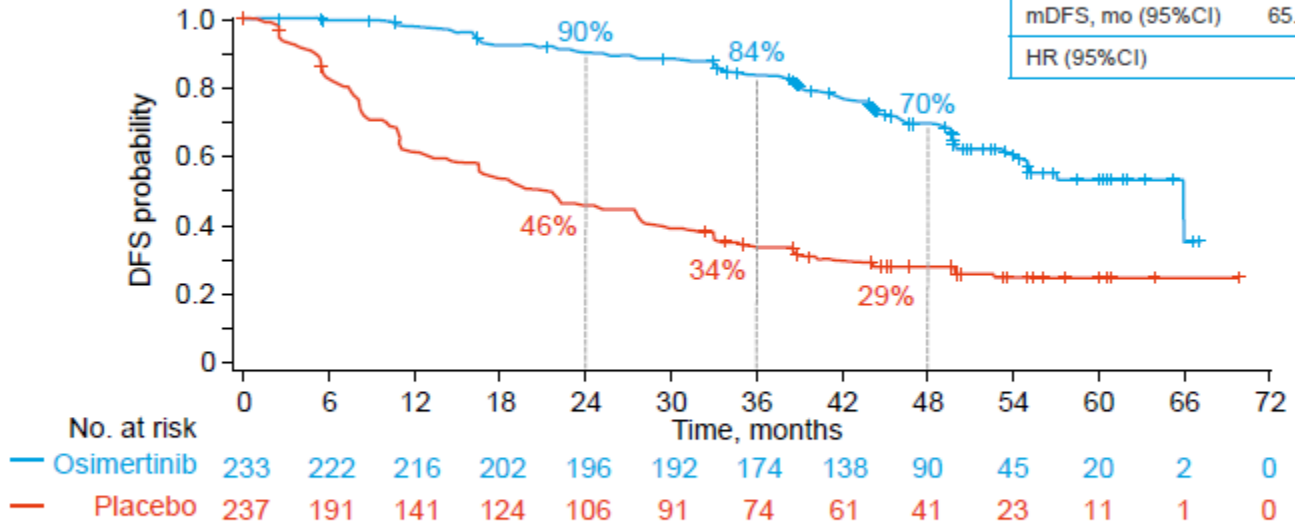
Tsuboi M, et al. Ann Oncol 2022;33(suppl):Abstr LBA47

Adjuvant treatment in EGFR+

- **Key results**

Disease-free survival in stage II/IIIA patients

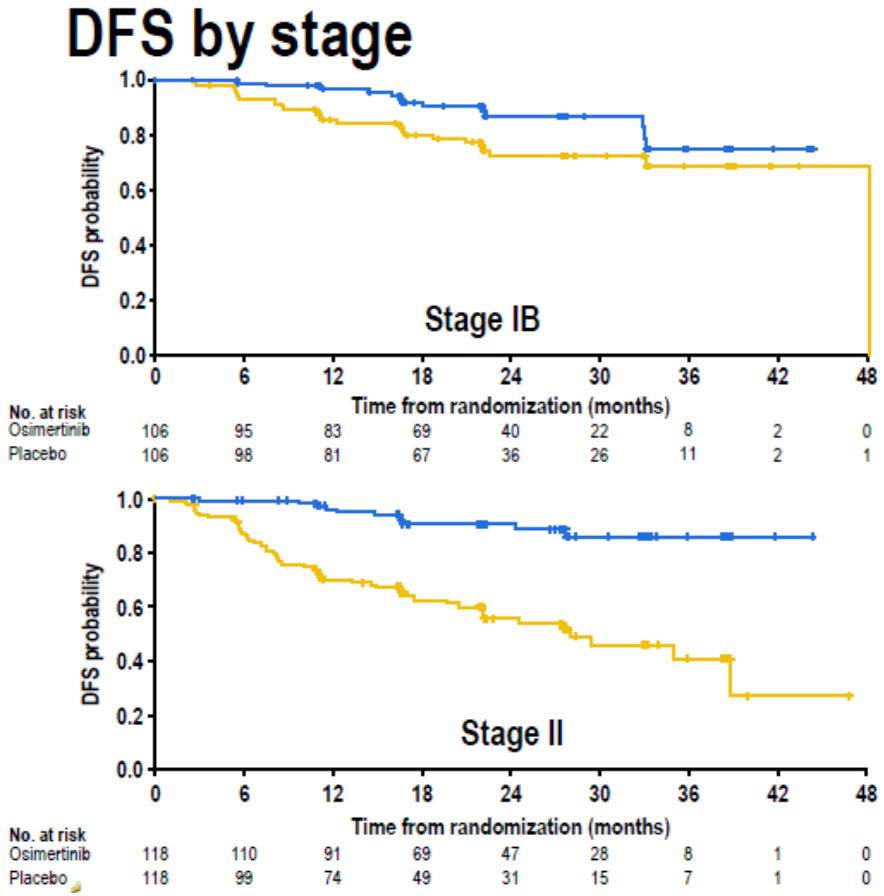
	Osimertinib (n=233)	Placebo (n=237)
mDFS, mo (95%CI)	65.8 (54.4, NC)	21.9 (16.6, 27.5)
HR (95%CI)	0.23 (0.18, 0.30)	



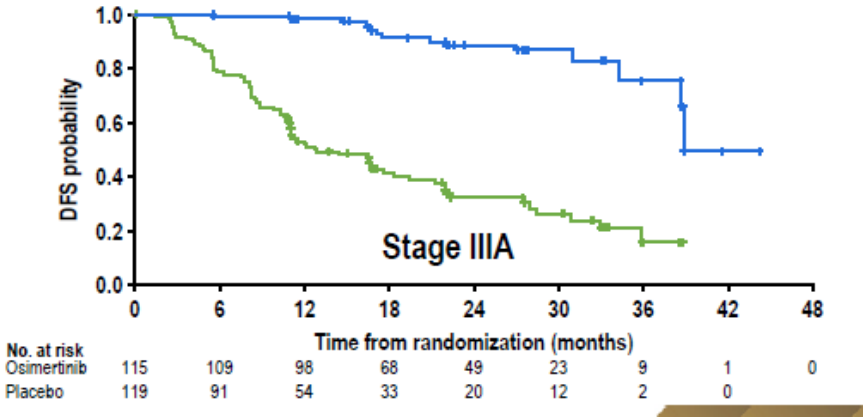
– In the overall population, mDFS was 65.8 mo (95%CI 61.7, NC) and 28.1 mo (95%CI 22.1, 35.0) in the osimertinib and placebo arms, respectively (HR 0.27 [95%CI 0.21, 0.34])

Tsuboi M, et al. Ann Oncol 2022;33(suppl):Abstr LBA47

Adjuvant treatment in EGFR+



	Stage IB	Stage II	Stage IIIA
2 year DFS rate, % (95% CI)			
– Osimertinib	87 (77, 93)	91 (82, 95)	88 (79, 94)
– Placebo	73 (62, 81)	56 (45, 65)	32 (23, 42)
Overall HR (95% CI)	0.50 (0.25, 0.96)	0.17 (0.08, 0.31)	0.12 (0.07, 0.20)



Majem M et al, JTO 2021

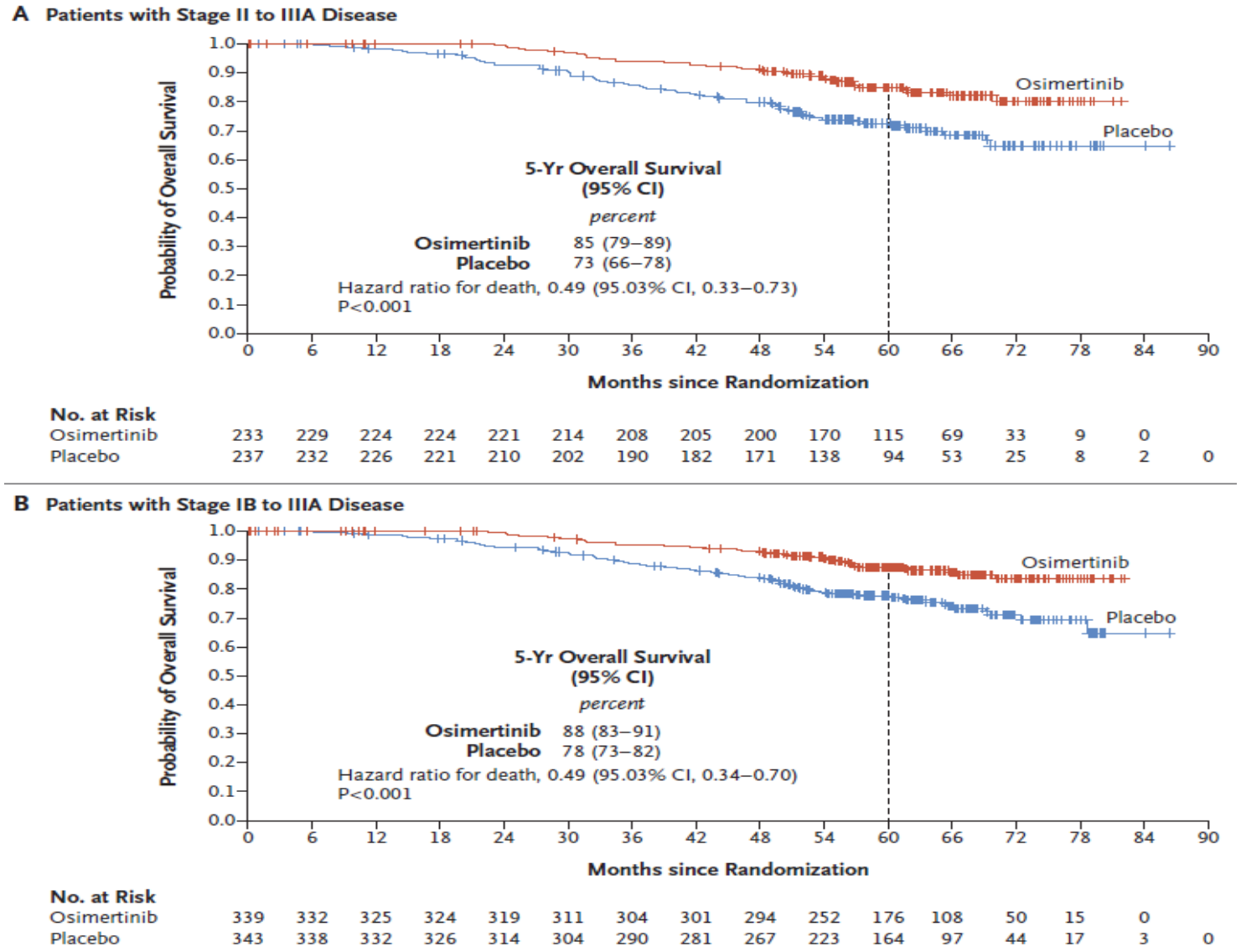
Adjuvant treatment in EGFR+

TEAEs, n (%)	Osimertinib (n=337)	Placebo (n=343)
Any	330 (98)	309 (90)
Grade ≥3	79 (23)	48 (14)
Serious	68 (20)	47 (14)
Led to discontinuation	43 (13)	9 (3)
Led to dose reduction	42 (12)	3 (1)
Led to dose interruption	91 (27)	43 (13)
Led to death	1 (<1)	2 (1)

TRAEs, n (%)	Osimertinib (n=337)	Placebo (n=343)
Any	308 (91)	199 (58)
Grade ≥3	36 (11)	7(2)
Serious	10 (3)	2 (1)
Led to death	0	0 (0)

Tsuboi M, et al. Ann Oncol 2022;33(suppl):Abstr LBA47

Adjuvant treatment in EGFR+

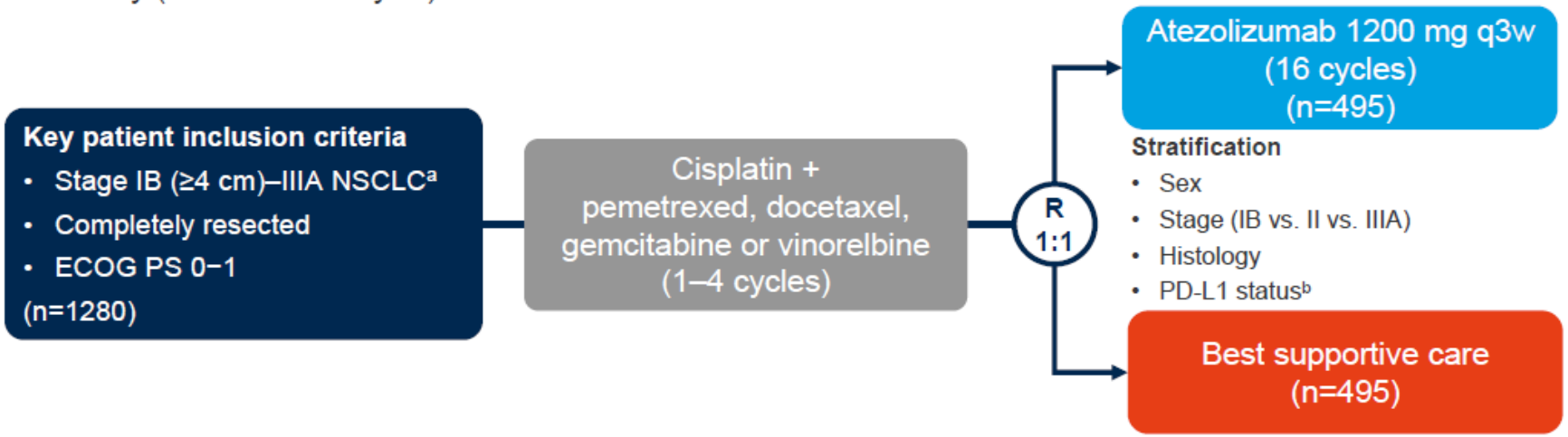


Herbst R et al; NEJM 2023

Adjuvant IO

PL03.09: IMpower010:Overall Survival Interim Analysis of a Phase III Study of Atezolizumab vs Best Supportive Care in Resected NSCLC – Felip E, et al

- **Study objective**
  - To evaluate the efficacy and safety of atezolizumab in patients with resected NSCLC in the IMpower010 study (an interim analysis)

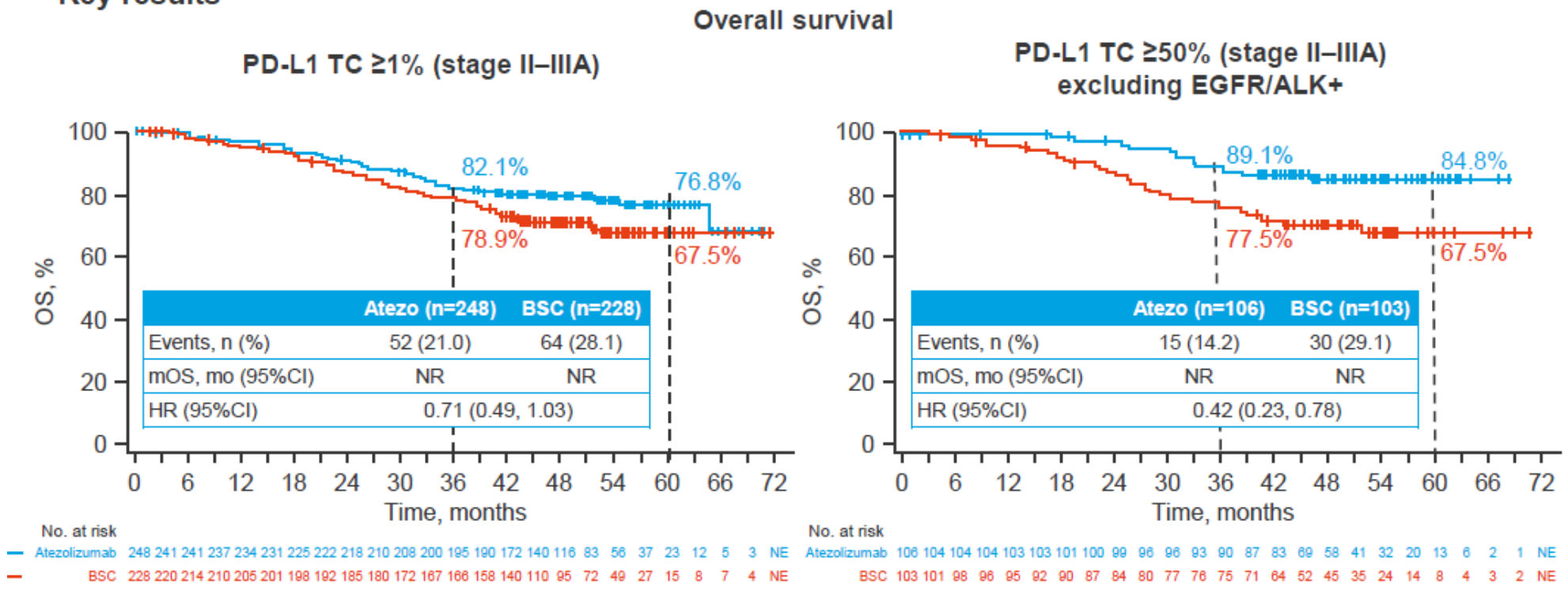


[a]Per American Joint Committee on Cancer (AJCC) cancer staging manual, 7th edition;
[b]TC2/3 and any IC vs. TC0/1 and IC2/3 vs. TC0/1 and IC0/1

Felip E, et al. J Thorac Oncol 2022;17(suppl):Abstr PL03.09

Adjuvant IO

- **Key results**



Felip E, et al. J Thorac Oncol 2022;17(suppl):Abstr PL03.09

Adjuvant IO

	Atezolizumab	BSC
All randomized (stage II–IIIA), n	442	440
Events, n (%)	115 (26.0)	116 (26.4)
mOS, mo (95%CI)	NR	NR
HR (95%CI)	0.95 (0.74, 1.24)	
ITT (stage IB–IIIA), n	507	498
Events, n (%)	127 (25.0)	124 (24.9)
mOS, mo (95%CI)	NR	NR
HR (95%CI); p-value	0.995 (0.78, 1.28); 0.9661	

TRAEs, %	Atezolizumab (n=495)	BSC (n=495)
Any	67.9	0
Grade 3–4	10.7	0
Serious	7.5	0
Grade 5	0.8	0
Led to dose interruption (atezolizumab)	28.7	0
Led to withdrawal	18.2	0
AESIs (atezolizumab)		
Any	52.1	9.5
Grade 3–4	7.9	0.6
Required corticosteroids	12.3	0.8

Felip E, et al. J Thorac Oncol 2022;17(suppl):Abstr PL03.09

Locally advanced resectable NSCLC (Stages II-IIIB)

Standard

NSCLC STAGES IIIa-b: Platinum based neoadjuvant CHT

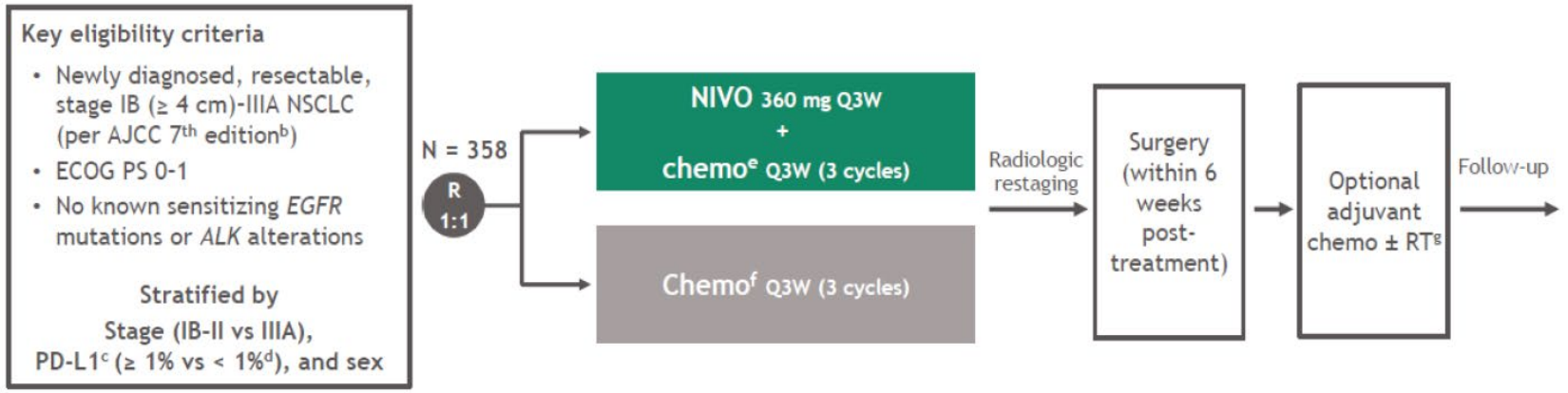
Neoadjuvant IO or IO-IO

Trial		N	Stage	% stage III	Surgery (%)	RR-RECIST (%)	MPR (%)	pCR (%)
CM159	Nivolumab x 2	21	I-IIIA	33	95	10	45	10
LCMC3	Atezolizumab x 2	181	IB-IIIB (8^{th})	48	88	NR	20	6
PRINCEPS	Atezolizumab x 1	30	I-IIIA	30	93	7	14	0
IONESCO	Durvalumab x 3	50	IB-IIIA	4	93	9	19	7
GAO	Sintilimab x 2	40	IA-IIIB	45	93	20	41	11
NEOSTAR	Nivolumab x 3	23	I-IIIA	22	96	22	22	9
	Nivo. x 3 + Ipi. x 1	21		19	81	19	38	29
NEO-COAST	Durvalumab (D)	27	I-IIIA	7	86	7	11	4
	D + oleclumab	21		24	86	5	19	10
	D + monalizumab	20		15	90	15	30	31
	D + danvatirsen	16		31	100	6	31	13
NEO-Predict	Nivolumab x 2	30	IB-IIIA (8^{th})	13	100	10	27	
	Nivo. + Relatlimab x 2	30		10	100	27	30	

Adapted from Hendriks L. ELCC 2023

Neoadjuvant CHT-IO

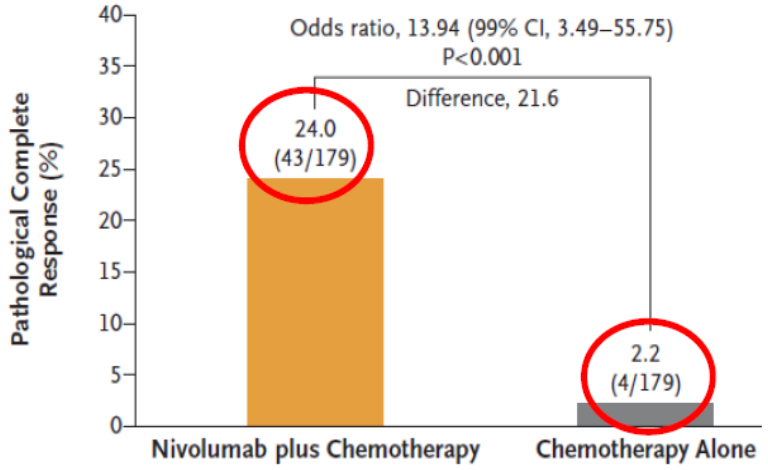
Neoadjuvant CT-IO vs CT: CheckMate 816
Study design

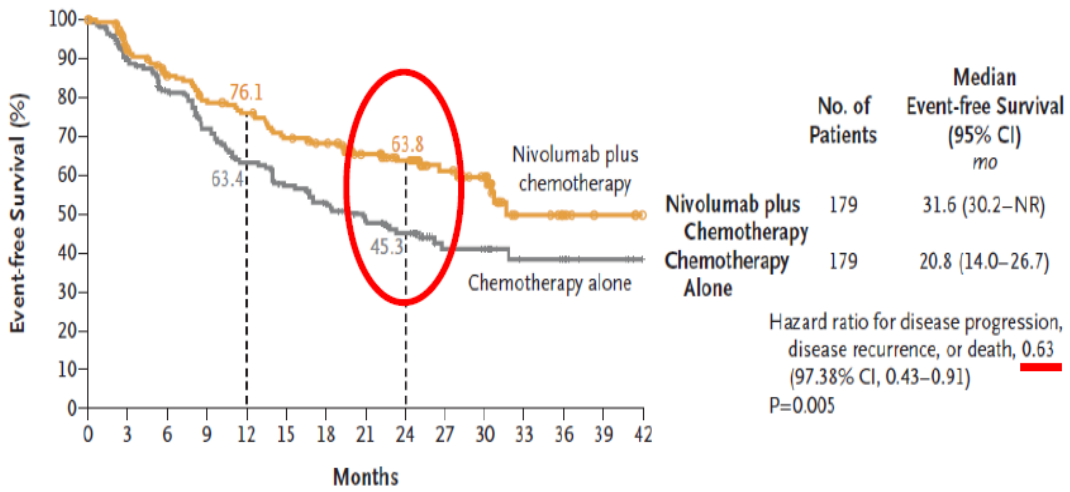


Girard et al, AACR'22

Neoadjuvant CHT-IO

Primary end-points: pCR and EFS



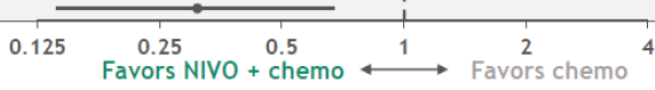


Forde PM et al. NEJM'22

Neoadjuvant CHT-IO

CheckMate 816: EFS Subgroup Analysis

	Median EFS[a], mo		Unstratified HR (95% CI)	Unstratified HR
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	32	21		0.63
< 65 years (n = 176)	NR	21		0.57
≥ 65 years (n = 182)	30	18		0.70
Male (n = 255)	31	17		0.68
Female (n = 103)	NR	32		0.46
North America (n = 91)	NR	NR		0.78
Europe (n = 66)	32	21		0.80
Asia (n = 177)	NR	16		0.45
ECOG PS 0 (n = 241)	NR	23		0.61
ECOG PS 1 (n = 117)	30	14		0.71
Stage IB-II (n = 127)	NR	NR		0.87
Stage IIIA (n = 228)	32	16		0.54
Squamous (n = 182)	31	23		0.77
Non-squamous (n = 176)	NR	20		0.50
Current/former smoker (n = 318)	32	22		0.68
Never smoker (n = 39)	NR	10		0.33
PD-L1 < 1% (n = 155)	25	18		0.85
PD-L1 ≥ 1% (n = 178)	NR	21		0.41
PD-L1 1-49% (n = 98)	NR	27		0.58
PD-L1 ≥ 50% (n = 80)	NR	20		0.24
TMB < 12.3 mut/Mb (n = 102)	30	27		0.86
TMB ≥ 12.3 mut/Mb (n = 76)	NR	22		0.69
Cisplatin (n = 258)	NR	21		0.71
Carboplatin (n = 72)	NR	11		0.31

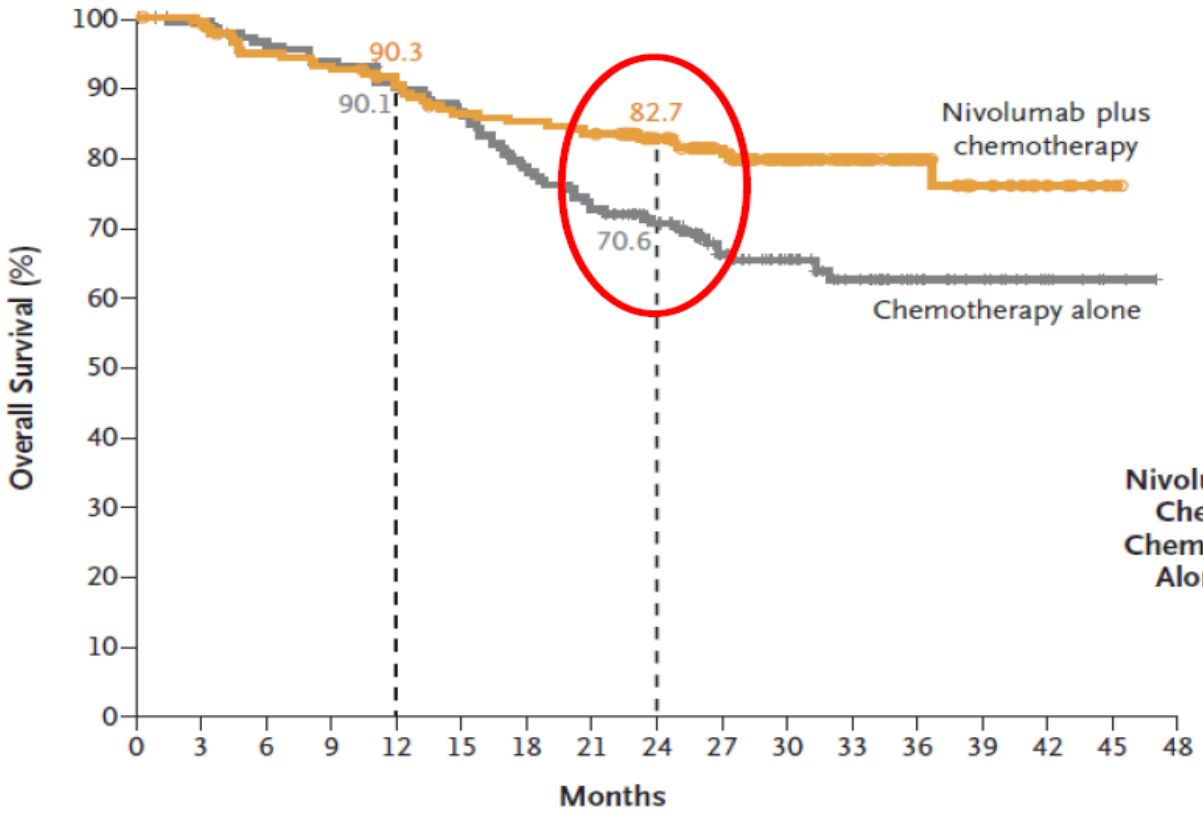


[a]Per BICR.

[4]Girard et al, AACR'22

Neoadjuvant CHT-IO

Secondary end-point: OS

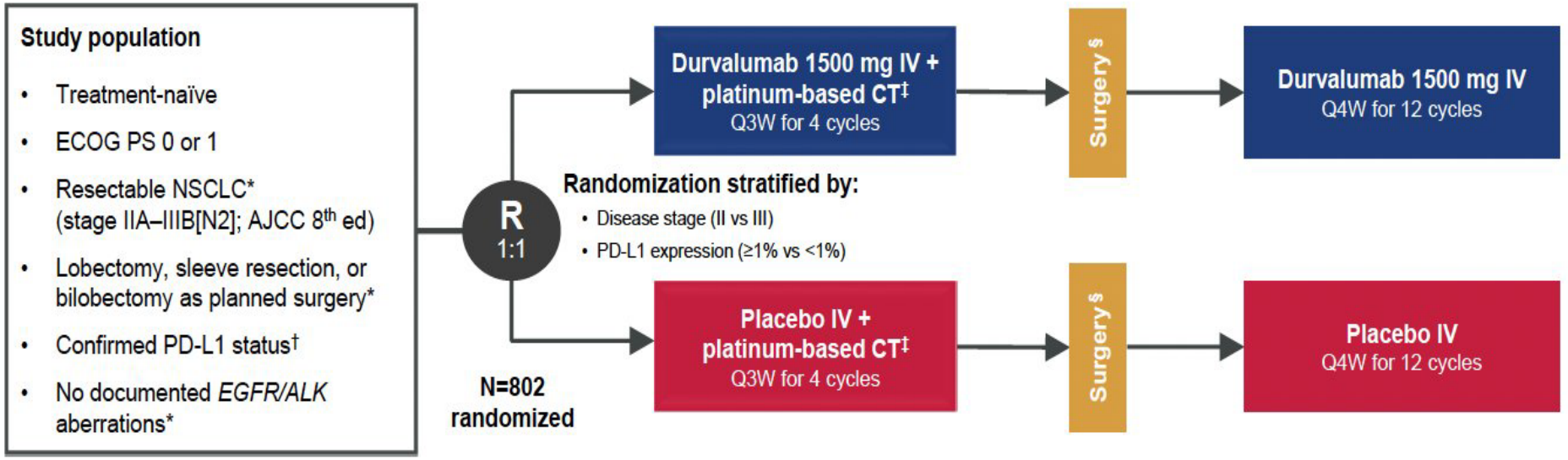


	No. of Patients	Median Overall Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	NR (NR–NR)
Chemotherapy Alone	179	NR (NR–NR)

Hazard ratio for death, 0.57
(99.67% CI, 0.30–1.07)
P=0.008

Forde PM et al. NEJM'22

Neoadjuvant CHT-IO→IO



Endpoints: All efficacy analyses performed on a modified population that excludes patients with documented *EGFR/ALK* aberrations¶

Primary:

- pCR by central lab (per IASLC 2020[1])
- EFS using BICR (per RECIST v1.1)

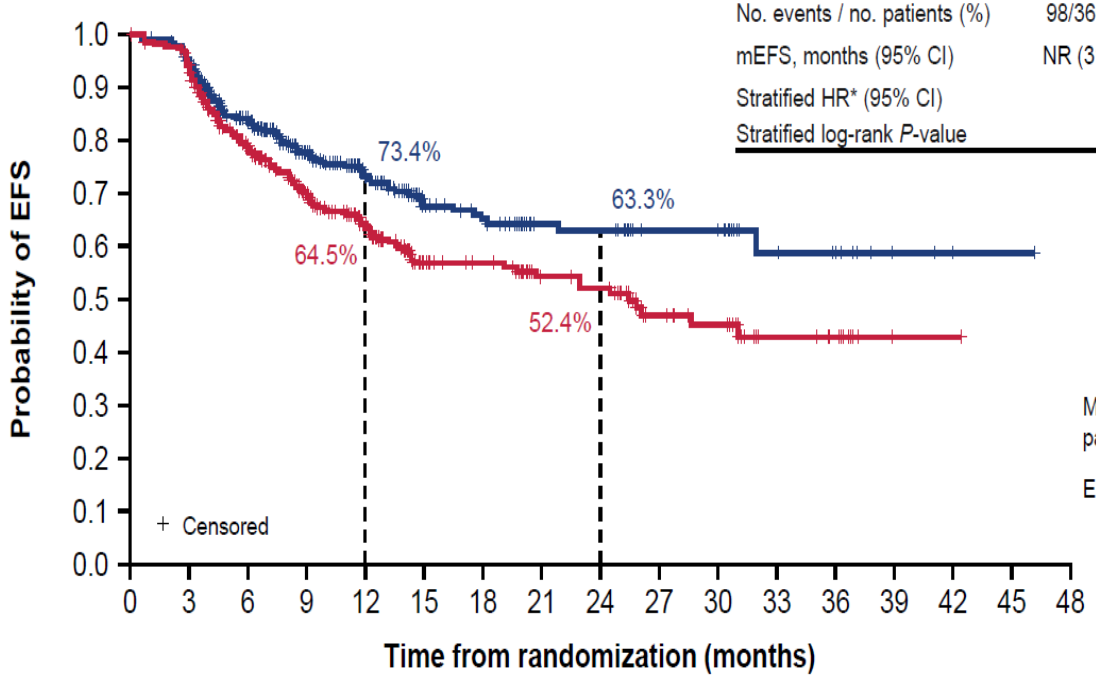
Key secondary:

- MPR by central lab (per IASLC 2020[1])
- DFS using BICR (per RECIST v1.1)
- OS

Adapted from Heymach JV. AACR 2023

Neoadjuvant CHT-IO→IO

	D arm	PBO arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9–NR)	25.9 (18.9–NR)
Stratified HR* (95% CI)	0.68 (0.53–0.88)	
Stratified log-rank *P*-value	0.003902	



Median follow-up (range) in censored patients: 11.7 months (0.0–46.1)

EFS maturity: 31.9%

No. at risk:																	
D arm	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
PBO arm	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

Adapted from Heymach JV. AACR 2023

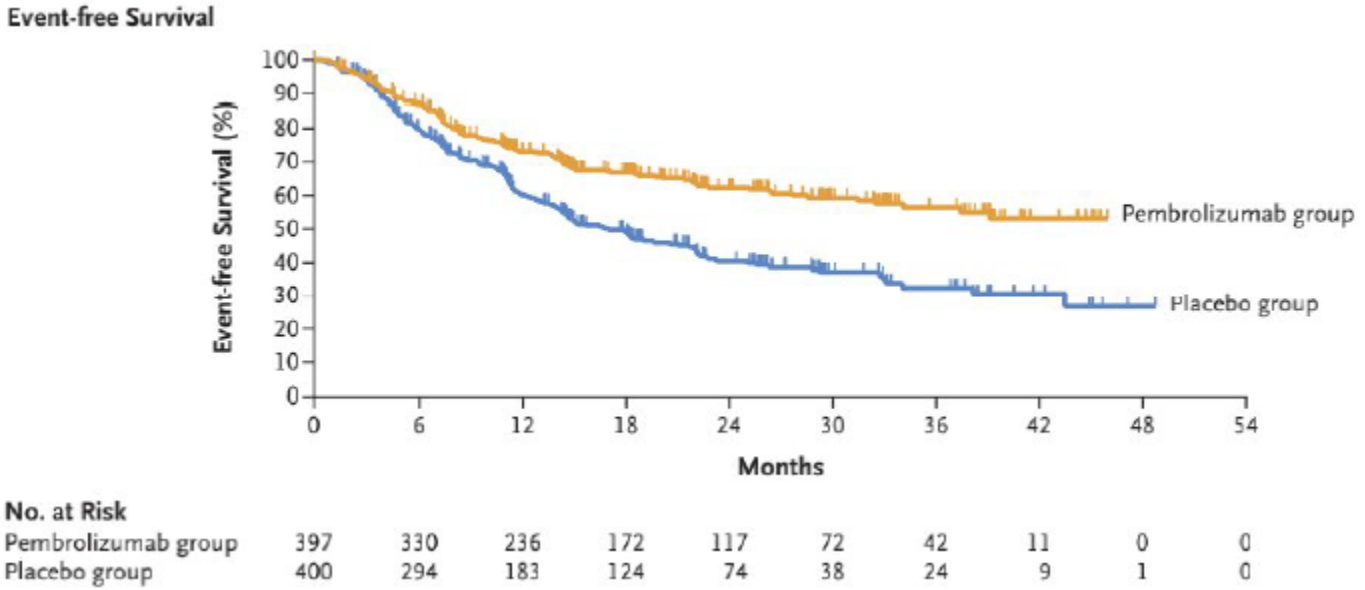
Neoadjuvant CHT-IO→IO

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

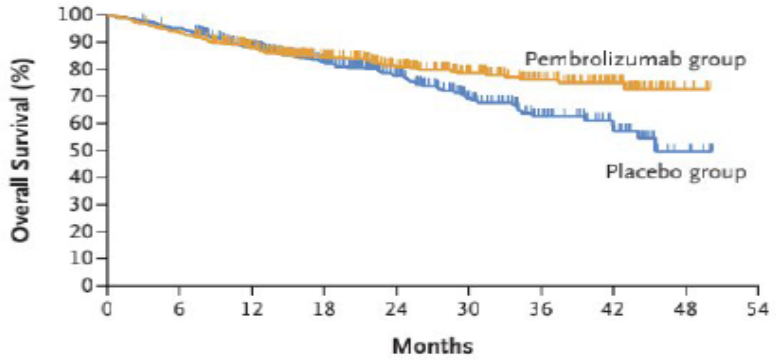
Perioperative Pembrolizumab for Early-Stage Non–Small-Cell Lung Cancer

H. Wakelee, M. Liberman, T. Kato, M. Tsuboi, S.-H. Lee, S. Gao, K.-N. Chen, C. Dooms, M. Majem, E. Eigendorff, G.L. Martinengo, O. Bylicki, D. Rodríguez-Abreu, J.E. Chaft, S. Novello, J. Yang, S.M. Keller, A. Samkari, and J.D. Spicer, for the KEYNOTE-671 Investigators*



No. at Risk

Pembrolizumab group	397	330	236	172	117	72	42	11	0	0
Placebo group	400	294	183	124	74	38	24	9	1	0



No. at Risk

Pembrolizumab group	397	370	313	232	170	118	76	41	5	0
Placebo group	400	379	316	225	153	91	54	30	6	0

Wakelee et al; NEJM 2023

Neoadjuvant TKI

Oncogene	(Neo) adjuvant	Study	Phase	Stage	Regimen	No.	Primary endpoint
EGFR mutation	Adjuvant	ICTAN (NCT01996098)	III	IIA–IIIA	CT vs CT + icotinib for 6 or 12 mo	318	DFS
		CORIN (NCT02264210)	II	IB	Clinical observation vs icotinib for 12 mo	128	OS
		ALCHEMIST (NCT02193282)	III	IB (T ≥ 4cm) – IIIA	CT vs CT + erlotinib for 2 y	450	OS
		APEX (NCT04762459)	III	II–IIIA	CT vs CT + Almonertinib for 3 y vs Almonertinib for 3 y	606	DFS
	Neoadjuvant	NeoADAURA (NCT04351555)	III	II–IIIB (N2)	Osimertinib vs osimertinib + CT vs placebo + CHT → surgery → investigator choice (osimertinib for 3 y)	328	MPR
		ANSWER (NCT04455594)	II	IIIA N2	Almonertinib vs Erlotinib/CT	168	ORR
		NeoIpower (NCT05104788)	II	II–IIIB	Icotinib + CT for 2 cycles → surgery	27	MPR
		NCT04201756	II	III	Afatinib 16 weeks → surgery → Afatinib for 1 y	47	ORR
		NCT03749213	II	IIIA N2	Icotinib for 8 w → surgery → icotinib for 2 y	36	ORR
ALK rearrangement	Adjuvant	ALCHEMIST (NCT02193282)	III	IB (T ≥ 4 cm) – IIIA	CT vs CT + crizotinib for 2 y	450	OS
		NCT05241028	II	IB (T ≥ 4 cm) – IIIA	Ensartinib for 3 y	80	3 y–DFSR
	Neoadjuvant	ALINA (NCT03456076)	III	IB (T ≥ 4 cm) – IIIA	CT vs alectinib for 2 y	255	DFS
		ALNeo (NCT05015010)	II	III	Alectinib 2cycles → surgery → alectinib for 2 y	33	MPR
RET	Adjuvant	LIBRETTO–432 (NCT04819100)	III	IB–IIIA	Surgery/radiation → selpercatinib for 3 y	170	EFS
MET	Neoadjuvant	Geometry–N (NCT04926831)	II	Stages IB–IIIA, N2 and selected IIIB (T3N2 or T4N2)	Capmatinib → surgery → adjuvant capmatinib	38	MPR
Other mutations *ALK/ ROS1/BRAF/ RET/ NTRK*	Neoadjuvant	NAUTIKA1 (NCT04302025)	II	II–III	TKI 2cycles → Surgery → CT + TKI for 2 y (alectinib, entrectinib, pralsetinib, vemurafenib + cobimetinib)	60	MPR

Liu SY et al, Lung Canc 2022

Locally advanced unresectable NSCLC

Standard:

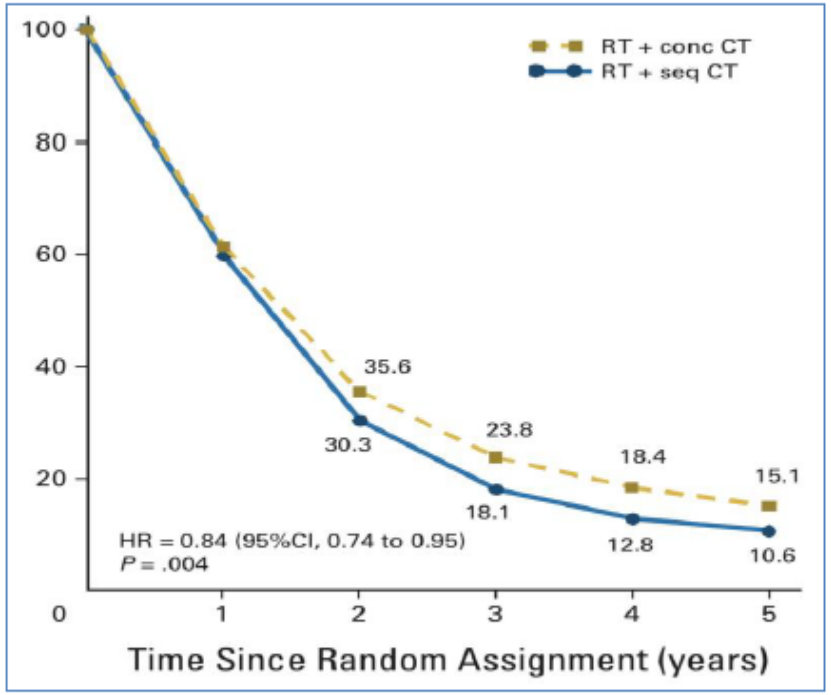
NSCLC STADI IIIb-c: Concomitant CHT + RT→ 1 year durvalumab
(only if pd-l1 ≥ 1%)

CHT-RT

Results of treatment in unresectable stage III NSCLC

- Sequential CT/RT: MST 13.7 months and 5-year OS 10.6%[1]
- Concurrent therapy:
  - Meta-analysis[1]: MST 17 months and 5-year OS 15.1%
  - PROCLAIM[2] (standard arm): MOS 25 months, 37% 3-y OS
  - RTOG 0617[3] (standard arm): MOS 28.7 months and 58% 2-y OS

Although the goal is to cure, less than 25% of patients are alive at 5 years



[1]Auperin A, et al. *J Clin Oncol*. 2010.[2]Senan S, et al. *J Clin Oncol*. 2016.
[3]Bradley J et al, Lancet Oncol 2015

Consolidation CT following CHT-RT has not resulted in improved survival times compared with concurrent CHT-RT alone

Study	Design	Conclusion
CALGB 39801[2]	Induction therapy prior to concurrent CRT vs CRT alone	**No improvement in survival**
HOG LUN 01–24[3]	Consolidation docetaxel vs CRT alone	
KCSG-LU05-04[4]	Consolidation docetaxel + cisplatin vs CRT alone	
PROCLAIM[5]	Concurrent CRT followed by consolidation pemetrexed vs standard CRT	
RTOG 0617[6]	Concurrent CRT + cetuximab vs concurrent CRT alone	
CALGB 30605[7,*]	Addition of erlotinib to RT vs RT alone after induction CT	
START[8]	Addition of MUC1 immunotherapy vs placebo after CRT	

.

1. Hanna N. *Am Soc Clin Oncol Educ Book*. 2015:e442-e447. 2. Vokes EE, et al. *J Clin Oncol*. 2007;25:1698-1704. 3. Hanna N, et al. *J Clin Oncol*. 2008;26:5755-5760. 4. Ahn JS, et al. *J Clin Oncol*. 2015;33:2660-2666.
5. Senan S, et al. *J Clin Oncol*. 2016;34:953-962. 6. Bradley JD, et al. *Lancet Oncol*. 2015;16:187-199. 7. Lilenbaum R, et al. *J Thorac Oncol*. 2015;10:143-147. 8. Butts C, et al. *Lancet Oncol*. 2014;15:59-68.

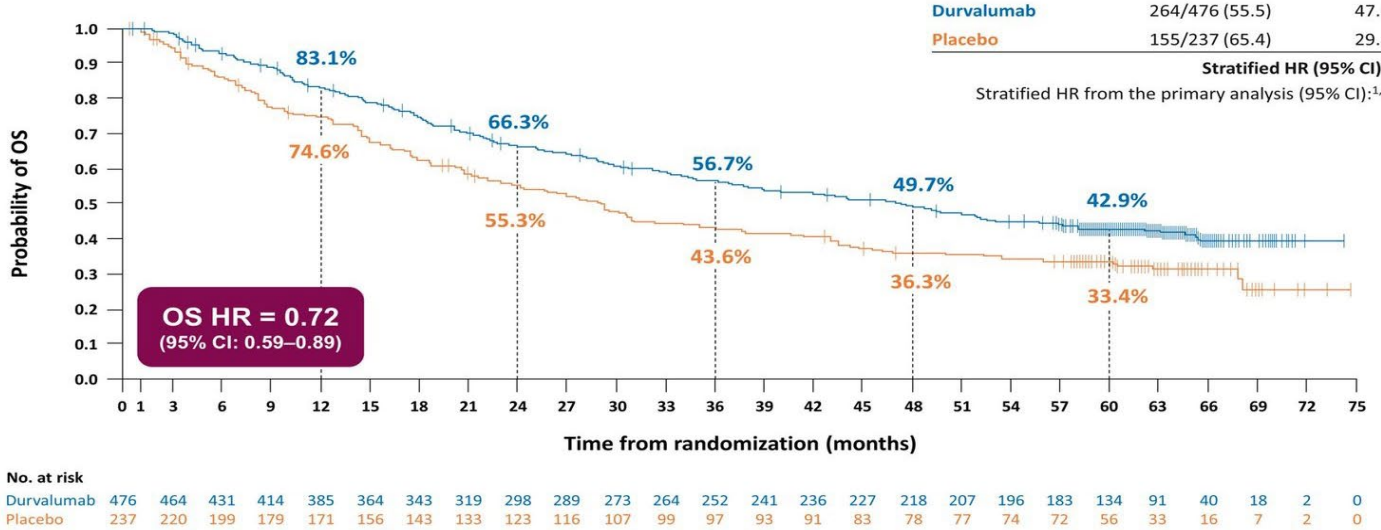
CHT-RT→IO: Pacific Study

Updated OS (ITT)

	No. of events/ total no. of patients (%)	Median OS (95% CI), months
Durvalumab	264/476 (55.5)	47.5 (38.1–52.9)
Placebo	155/237 (65.4)	29.1 (22.1–35.1)

Stratified HR (95% CI): 0.72 (0.59–0.89)

Stratified HR from the primary analysis (95% CI):[1,2] 0.68 (0.53–0.87)



No. at risk

Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival

Data cutoff: 11 January 2021 (median follow-up: all patients, 34.2 months [range, 0.2–74.7]; censored patients, 61.6 months [range, 0.4–74.7]).

1. Antonia SJ, et al. New Engl J Med 2018;379:2342–50; 2. European Medicines Agency. Durvalumab (Imfinzi). Summary of product characteristics 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf 5. [Accessed April 2021]

DR SPIGEL; ASCO 2021

CHT-RT→IO

How can we go further ? ICI consolidation intensification

CTRT	ICI (antiPD(L)1)	ICI (other than antiPDL1)
LUN 16-081 Phase 2 (n=108) cRTCT plus Nivolumab/Ipillimumab 6 months vs Nivolumab 6 months		Anti CTLA4
SKYSCRAPER 03 Phase 3 (n=800) cRTCT plus Atezolizumab + Tiragolumab 1 year vs Durvalumab		Anti TIGIT
COAST Phase 2 (n=300) cRTCT plus Durvalumab+ Oleclumab or Durvalumab + Monalizumab vs Durvalumab		Anti CD73 Anti NK
PACIFIC 9 (n=999) cRTCT plus Durvalumab+ Oleclumab or Durvalumab + Monalizumab or Durvalumab + Placebo		Anti CD73 Anti NK

elcc European Lung Cancer Congress 2023

Adapted from Guillerm S. ELCC 2023

CHT-RT→IO

How can we go further ? Concurrent ICI and CTRT

CTRT	ICI
ICI (antiPDL1 or anti PD1)	
DETERRED Phase 2 (n=30) cCTRT + Atezolizumab	Atezolizumab 1 year (anti PDL 1)
NICOLAS Phase 2 (n=80) cRTCT or seqRTCT + Nivolumab	Nivolumab 1 year (anti PD 1)
KEYNOTE 799 Phase 2 (n=216) cRTCT + Pembrolizumab	Pembrolizumab 1 year (anti PD 1)

elcc European Lung Cancer Congress 2023

Adapted from Guillerm S. ELCC 2023

CHT-RT→IO

How can we go further ? Induction intensification

ICI +/- CT	CTRT	ICI
DEDALUS trial phase 2 Durvalumab + induction CT then durvalumab and RT		Durvalumab 12 months
BRIDGE trial phase 2 Durvalumab + induction CT then durvalumab and RT *Patients initially not eligible to cCTRT because of large tumor volumes*		Durvalumab 12 months
AFT 16 trial phase 2 Atezolizumab then cCTRT		Atezolizumab 12 months
APOLO trial phase 2 Atezolizumab + induction CT then cCTRT		Atezolizumab 12 months

elcc European Lung Cancer Congress 2023

Adapted from Guillerm S. ELCC 2023

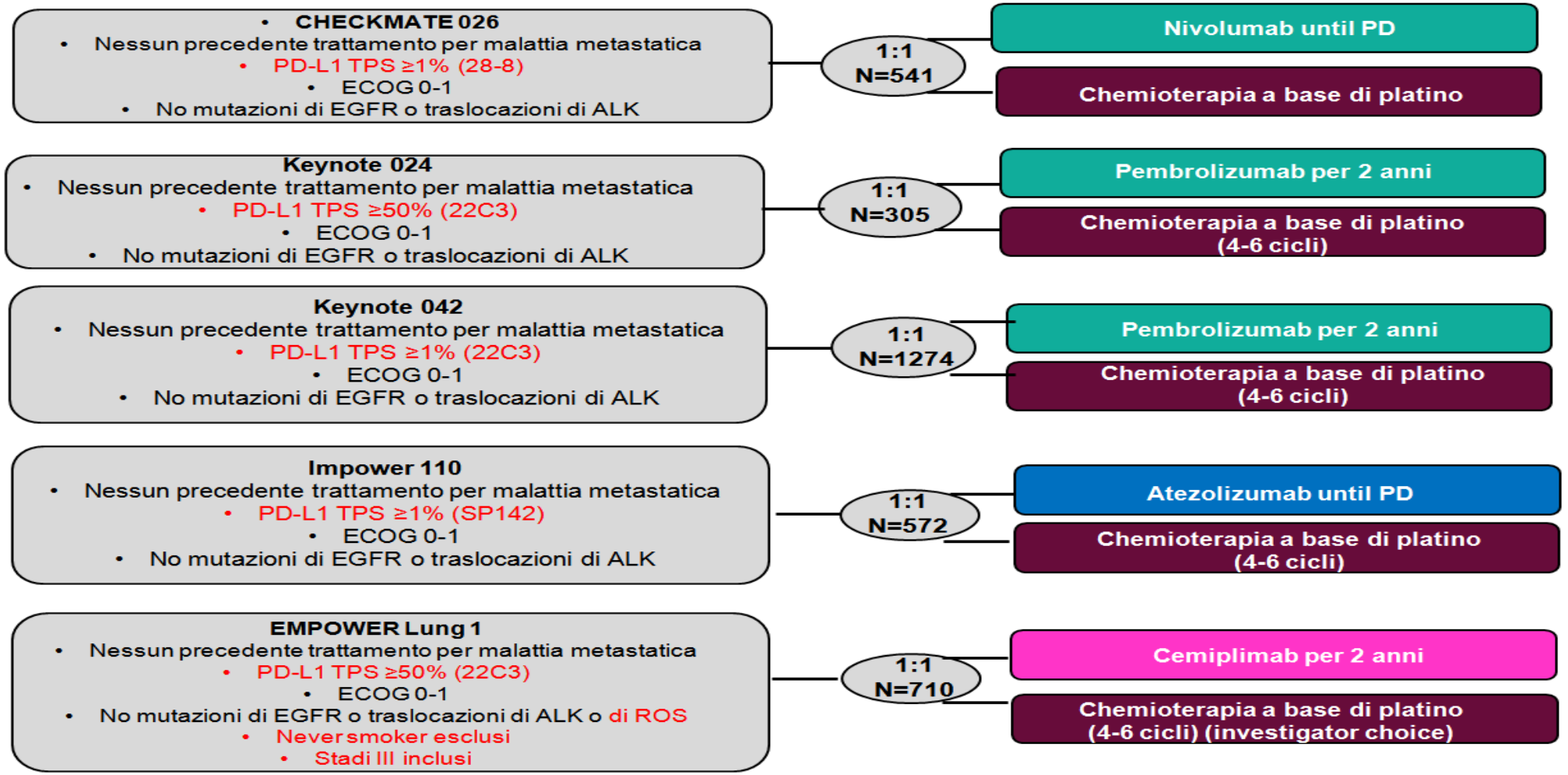
Non oncogene addicted advanced NSCLC (first line)

Standard:

- Non Oncogene addicted advanced NSCLC PD-L1 ≥ 50%(30%): Pembrolizumab OR Cemiplimab OR Atezolizumab → Platinum based CHT

- Non Oncogene addicted advanced NSCLC PD-L1<50% (55%): Platinum based CHT + IO OR Nivolumab + ipilimumab + CHT (2 CYCLES)→ Docetaxel +/- nintedanib

1 linea anti-PD-1/PD-L1 in monoterapia in pazienti selezionati per PD-L1

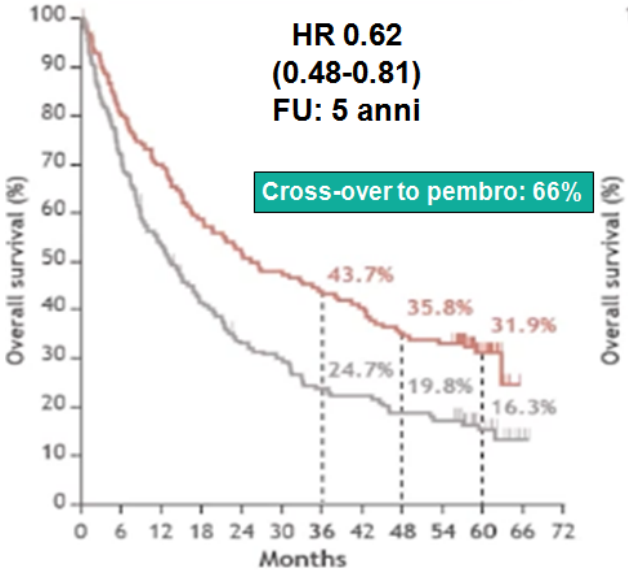


Courtesy R Ferrara

1 linea anti-PD-1/PD-L1 in monoterapia in pazienti selezionati per PD-L1

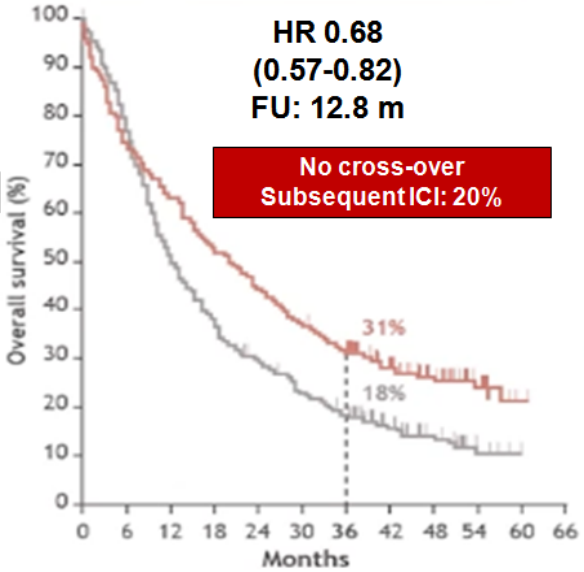
KEYNOTE 024 PD-L1 ≥ 50%

	ORR	Median OS
Pembro (n=154)	45%	26.3 (18.3-40.4)
Chemo (n=151)	28%	13.4 (9.4-18.3)



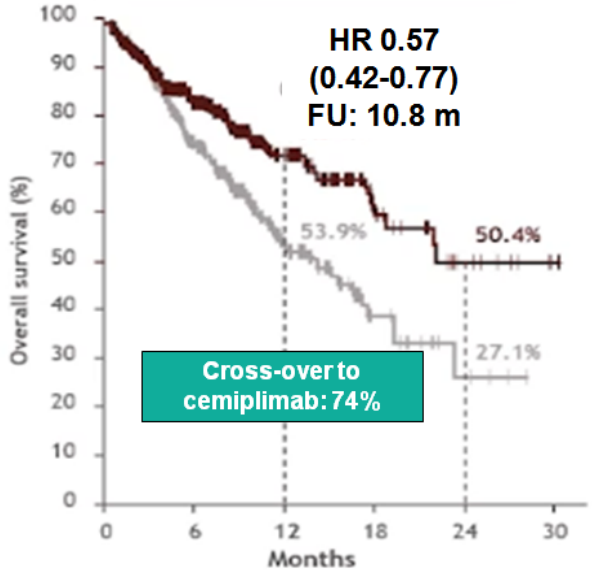
KEYNOTE 042 PD-L1 ≥ 50%

	ORR	Median OS
Pembro (n=299)	39%	20 (15.9-24.2)
Chemo (n=300)	32%	12.2 (10.4-14.6)



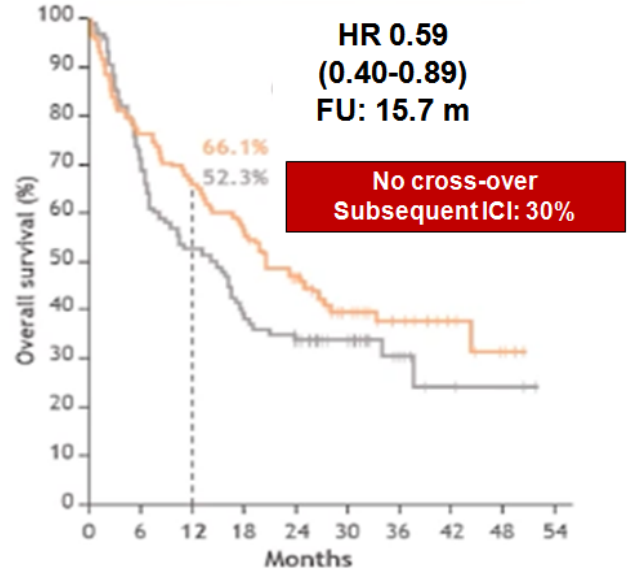
EMPOWER Lung 1 PD-L1 ≥ 50%

	ORR	Median OS
Cemiplimab (n=283)	39%	NR (17.9-NE)
Chemo (n=280)	20%	14.2 (11.2-17.5)



Impower 110: PD-L1 ≥ 50% or TC ≥10% IC

	ORR	Median OS
Atezo (n=107)	38%	20.2 (16.5-NE)
Chemo (n=98)	29%	13.1 (7.4-16.5)



Dei pazienti con alta espressione di PD-L1 trattati con anti-PD 1/PD-L1 in prima linea:

40% risponde

40-50% è vivo a 2 anni (20-26 mesi sopravvivenza mediana)

30% è vivo a 5 anni

Anti-PD-1 e anti-PD-L1 outcome simili

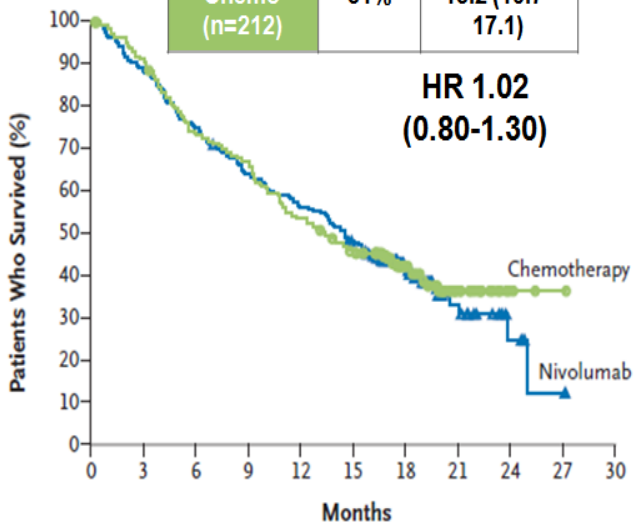
Reck JCO 2021, Mok Lancet 2019, Sezer Lancet 2021, Herbst NEJM 2020

1 linea anti-PD-1/PD-L1 in monoterapia in pazienti selezionati per PD-L1

CHECKMATE 026 OS
PD-L1≥ 5%

	ORR	Median OS
Nivo (n=211)	26%	14.4 (11.7-17.4)
Chemo (n=212)	31%	13.2 (10.7-17.1)

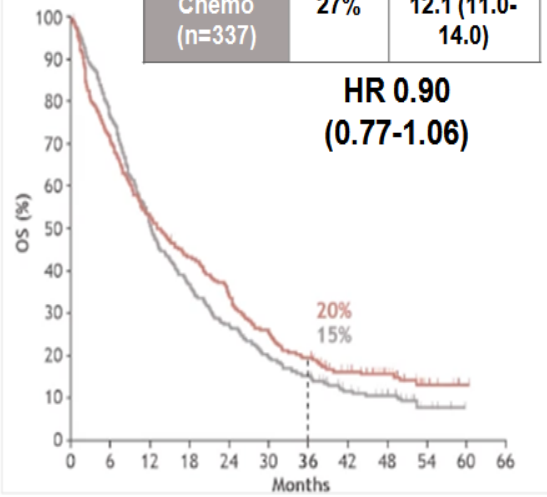
HR 1.02
(0.80-1.30)



KEYNOTE 042 OS
PD-L1 1-49%

	ORR	Median OS
Pembro (n=338)	27%	13.4 (10.7-16.9)
Chemo (n=337)	27%	12.1 (11.0-14.0)

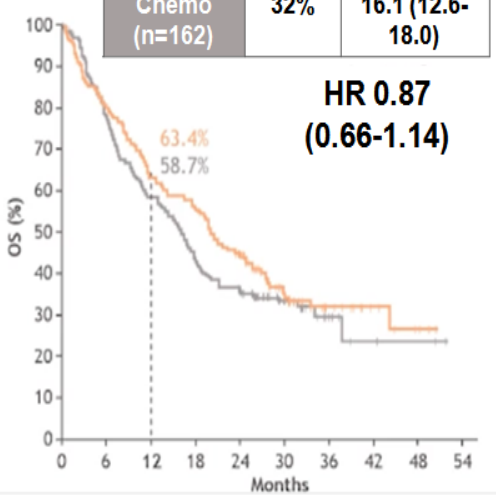
HR 0.90
(0.77-1.06)



Impower 110 OS
PD-L1 TC2/3 or IC 2/3

	ORR	Median OS
Atezo (n=166)	31%	19.9 (17.2-25.3)
Chemo (n=162)	32%	16.1 (12.6-18.0)

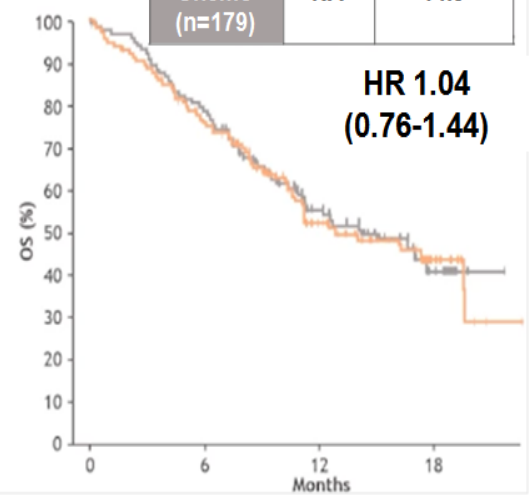
HR 0.87
(0.66-1.14)



Impower 110 OS
PD-L1 TC1/2 or IC 1/2

	ORR	Median OS
Atezo (n=170)	NA	12.9
Chemo (n=179)	NA	14.9

HR 1.04
(0.76-1.44)



Nei pazienti con PD-L1 basso/intermedio: anti-PD-1/PD-L1 in prima linea non è superiore alla chemioterapia a base di platino né in risposta né in sopravvivenza

Carbone NEJM 2017, Mok Lancet 2019, Herbst NEJM 2020

1 linea anti-PD-1/PD-L1 in monoterapia tossicità

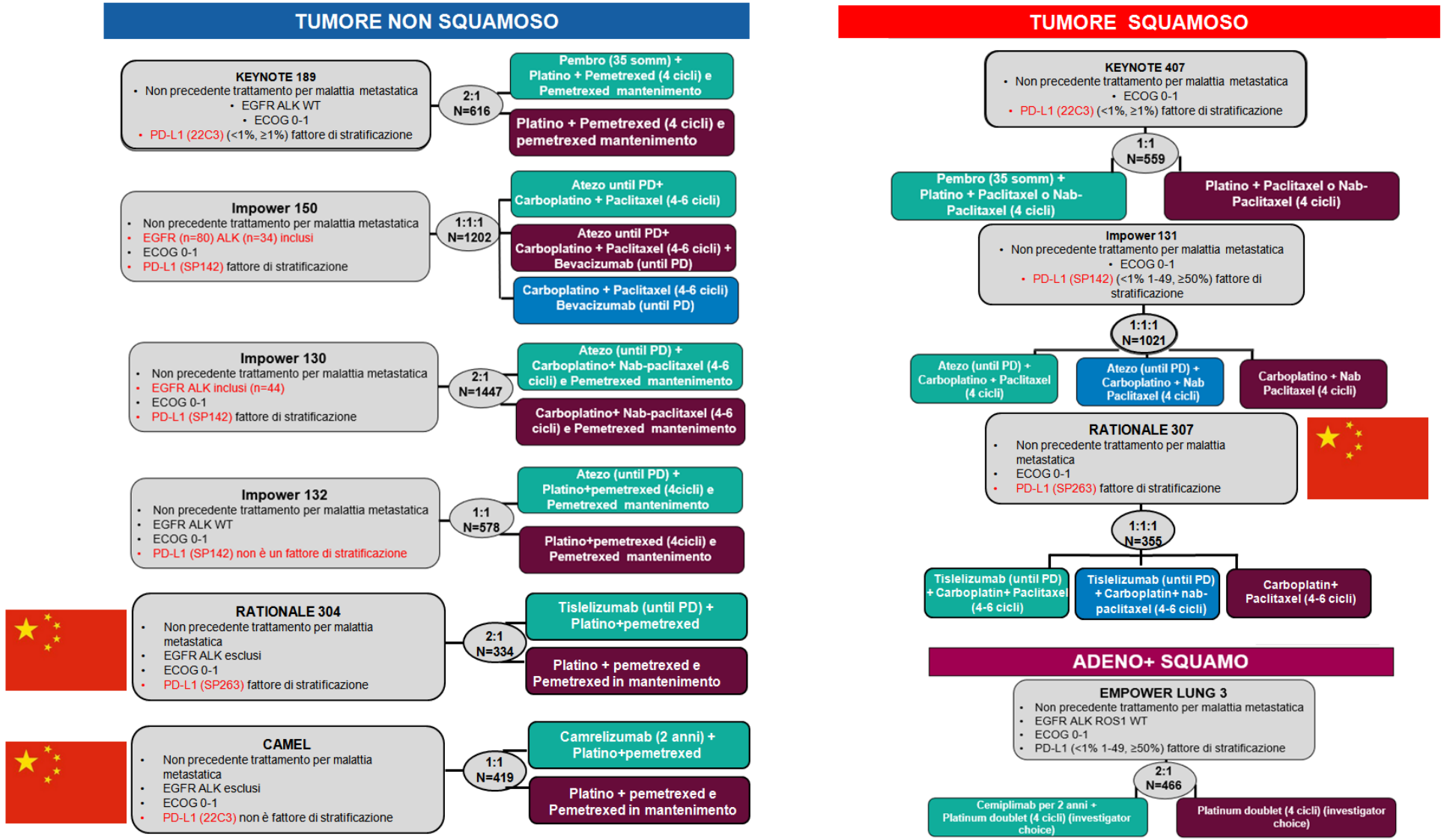
	KEYNOTE-024[1] (PD-L1 ≥50%)		KEYNOTE-042[2] (PD-L1 ≥1%)		EMPOWER-Lung 1[3,4] (PD-L1 ≥50%)		IMpower110[5] (PD-L1 ≥1%)*	
	Pembro (n=154)	Chemo (n=150)	Pembro (n=636)	Chemo (n=615)	Cemiplimab (n=355)	Chemo (n=342)	Atezo (n=286)	Chemo (n=263)
All TRAEs (%)	77.6	90.0	63.8	90.1	57.5	88.6	62.9	85.2
Grade 3-5 TRAEs (%)	31.2	53.3	18.9	41.6	14.1	39.2	14.3 (Grade 3-4)	44.9 (Grade 3-4)
TRAEs, leading to discontinuation (%)	13.6	10.7	9.1	9.6	5.1†	3.5†	7.3‡	17.1‡
TRAEs, leading to death (%)	1.3	2.0	2.0	2.3	2.5	2.0	0	0.4

15-30% dei pazienti con alta espressione di PD-L1 può avere delle tossicità immuno relate di grado 3-4.

1-2% sono le morti tossiche legate al trattamento

Reck JCO 2021, Mok Lancet 2019, Sezer Lancet 2021, Herbst NEJM 2020

1 linea anti-PD-1/PD-L1 + CHT: Attività ed efficacia

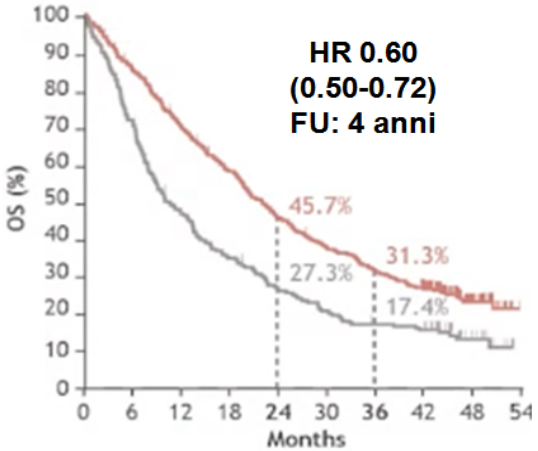


Courtesy R Ferrara

1 linea anti-PD-1/PD-L1 + CHT: Attività ed efficacia

KEYNOTE 189 OS ITT

	ORR	Median OS
Pembro + chemo (n=410)	48%	22.0 (19.5-24.9)
Chemo (n=206)	19%	10.6 (8.7-13.6)



Immuno in II linea (cross over or subsequent): 54%

PD-L1 ≥50%

	ORR	Median OS
Pembro + chemo (n=132)	62%	27.7 (20.4-38.2)
Chemo (n=70)	26%	10.1 (7.5-22)
HR 0.71 (0.50-1.00)		
3 year OS rate (pembro): 44%		

PD-L1 1-49%

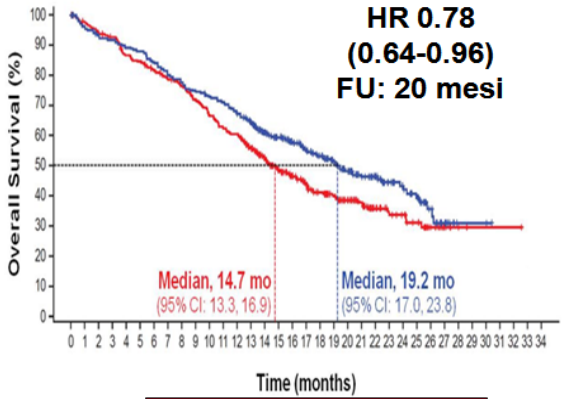
	ORR	Median OS
Pembro + chemo (n=128)	50%	21.8 (17.7-25.9)
Chemo (n=58)	21%	12.1 (8.7-19.4)
HR 0.66 (0.47-0.93)		
3 year OS rate (pembro): 28%		

PD-L1 <1%

	ORR	Median OS
Pembro+chemo (n=127)	33%	17.2 (13.8-22.8)
Chemo (n=63)	14%	10.2 (7.0-13.5)
HR 0.52 (0.37-0.72)		
3 year OS rate (pembro): 23%		

Impower 150 OS ITT EGFR ALK WT

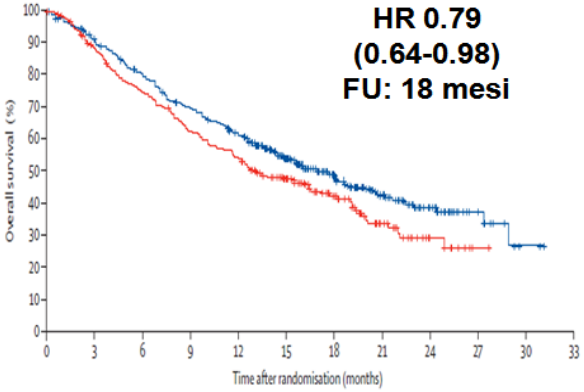
	ORR	Median OS
Atezo + chemo (n=359)	63%	19.2 (17.0-23.8)
Chemo (n=337)	48%	14.7 (13.3-16.9)



No cross over ma subsequent ICI: 32%

Impower 130 OS ITT EGFR-ALK WT

	ORR	Median OS
Atezo + chemo (n=483)	49%	18.6 (16.0-21.2)
Chemo (n=240)	32%	13.9 (12.0-18.7)



Cross over consentito + subsequent ICI: 60%

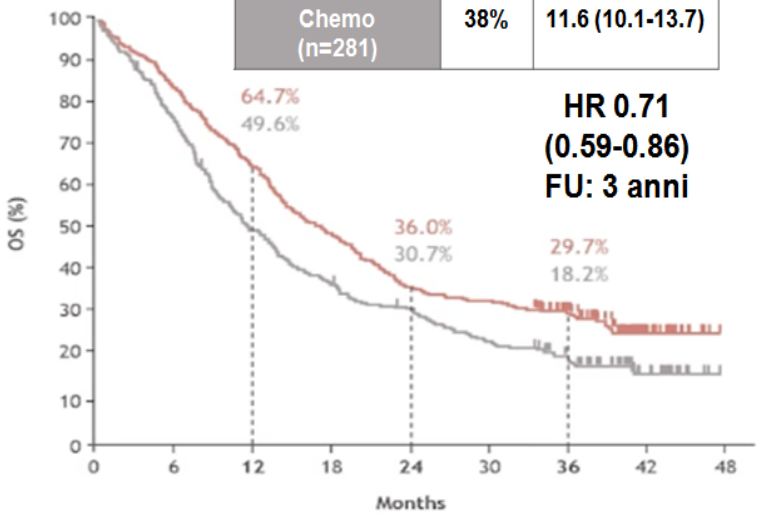
Dei pazienti con adenocarcinoma polmonare trattati con anti-PD-1/PD-L1 + CT a base di platino:
50% risponde (fino al 60% nei PD-L1 TPS ≥ 50%)
40-50% è vivo a 2 anni (18-22 mesi sopravvivenza mediana, >24 mesi nei PD-L1 TPS ≥ 50%)
20-30% è vivo a 3 anni (>40% nei PD-L1 TPS ≥ 50%)
Beneficio osservato in tutte le categorie di PD-L1
Code delle curve negli studi Impower tendono a sovrapporsi

Gray JTO 2021, Socinski NEJM 2018, West Lancet Oncology 2019

1 linea anti-PD-1/PD-L1 + CHT: Attività ed efficacia

KEYNOTE 407 ITT OS

	ORR	Median OS
Pembro + chemo (n=278)	60%	17.2 (14.4-19.7)
Chemo (n=281)	38%	11.6 (10.1-13.7)

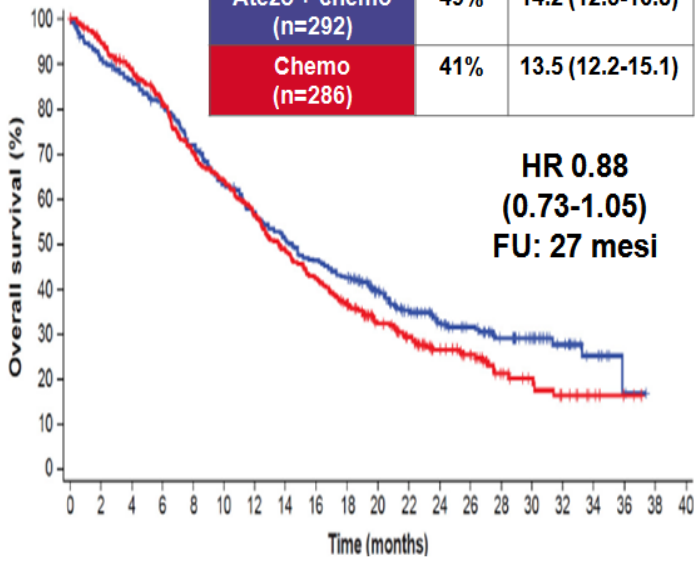


HR 0.71
(0.59-0.86)
FU: 3 anni

Cross over a pembro: 50%

Impower 131 ITT OS

	ORR	Median OS
Atezo + chemo (n=292)	49%	14.2 (12.3-16.8)
Chemo (n=286)	41%	13.5 (12.2-15.1)

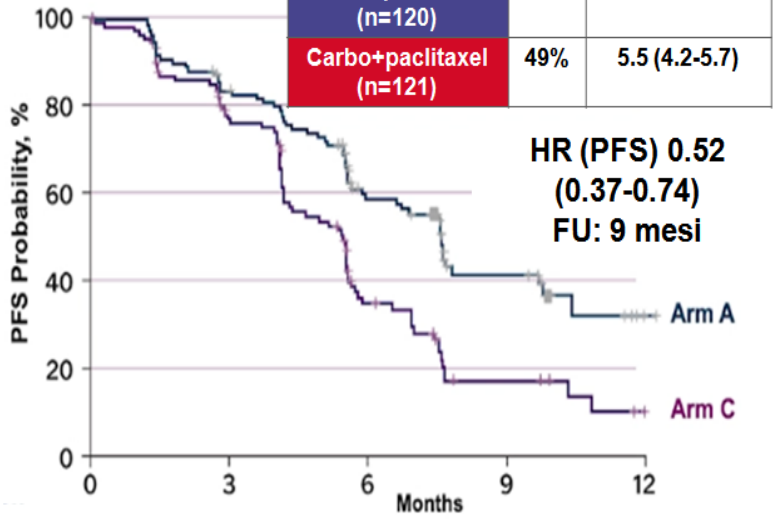


HR 0.88
(0.73-1.05)
FU: 27 mesi

No cross over
ma subsequent ICI: 43%

RATIONALE 307 PFS ITT

	ORR	Median OS
Tisle + carbo+paclitaxel (n=120)	72%	7.6 (6.0-9.8)
Carbo+paclitaxel (n=121)	49%	5.5 (4.2-5.7)



HR (PFS) 0.52
(0.37-0.74)
FU: 9 mesi

Nell'istologia squamosa:

- Buoni tassi di risposta 60% fino a >70% (tislelizumab) ma OS tendenzialmente inferiore ad adenocarcinoma (17 vs 22 mesi)
- Pembro + chemo aumenta OS indipendentemente da PD-L1
- Atezolizumab + chemo non migliora OS

Paz-Ares NEJM 2018, Jotte JTO 2020, Wang JAMA Onc 2021

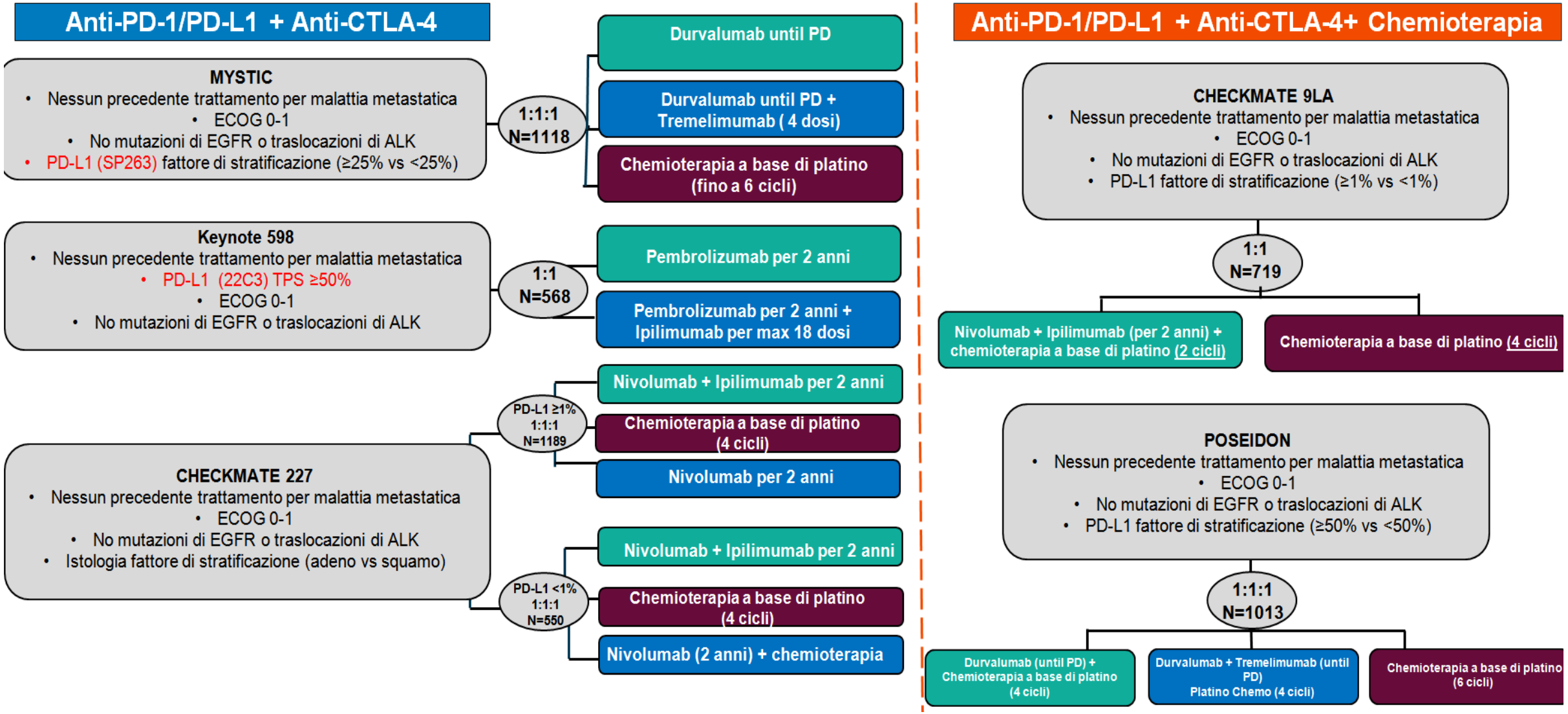
1 linea anti-PD-1/PD-L1 + CHT: Tossicità

	KEYNOTE-189 (NSQ)[1]		KEYNOTE-407 (SQ)[2]		IMpower150 (NSQ)[3,4]	
	Pembro + chemo (n=405)	Placebo + chemo (n=202)	Pembro + chemo (n=278)	Placebo + chemo (n=280)	Atezo + chemo + bev (n=393)	Chemo + bev (n=394)
All (TR)AEs, %	92.8*	90.6*	98.6†	98.2†	94.4*	95.4*
Grade 3-5 (TR)AEs, %	52.1*	42.1*	74.1†	69.6†	55.7* (Grade 3-4)	47.7* (Grade 3-4)
Tossicità Immunorelate %	26	13	35			
Tossicità Immunorelate Grado 3-4%	11	4	13			
Morti tossiche legate al trattamento	2	1	4	2	3	2

50% fino a 70% dei pazienti trattati con chemioterapia+ anti-PD-1/PD-L1 in prima linea può avere delle tossicità di grado 3-4 10-15% sono tossicità immunorelate grado 3-4
2% le morti tossiche legate al trattamento

Gadgeel JCO 2020, Paz-Ares NEJM 2018, Socinski NEJM 2018

1 linea anti-PD-1/PD-L1 + altri immunoterapici +/- chemioterapia a base di platino

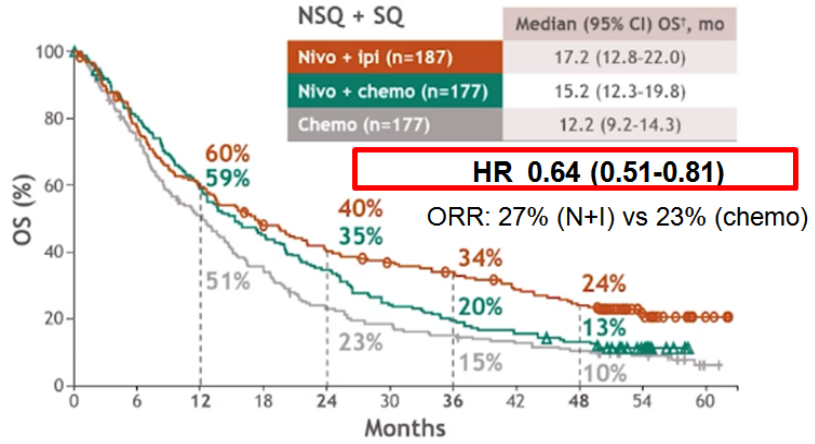


Courtesy R Ferrara

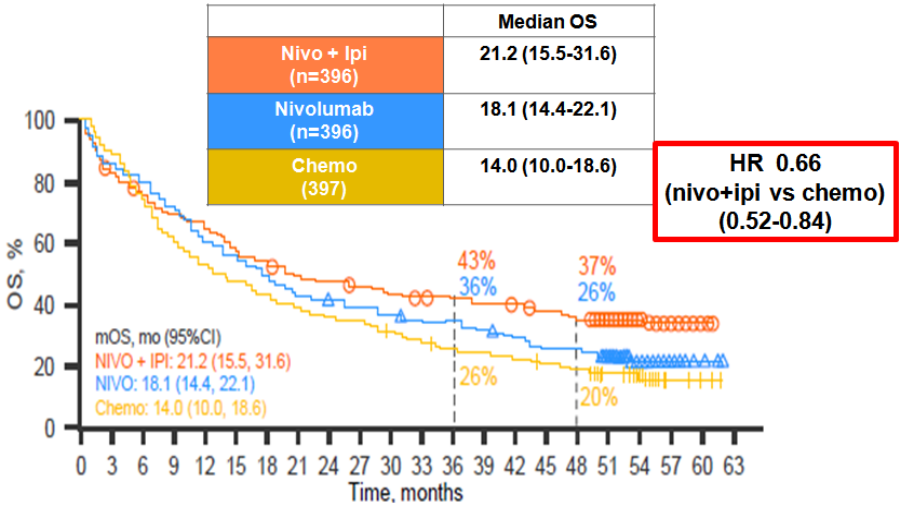
1 linea anti-PD-1/PD-L1 + altri immunoterapici +/- chemioterapia a base di platino

PD-L1 <1%

Checkmate 227 OS 4 anni follow up

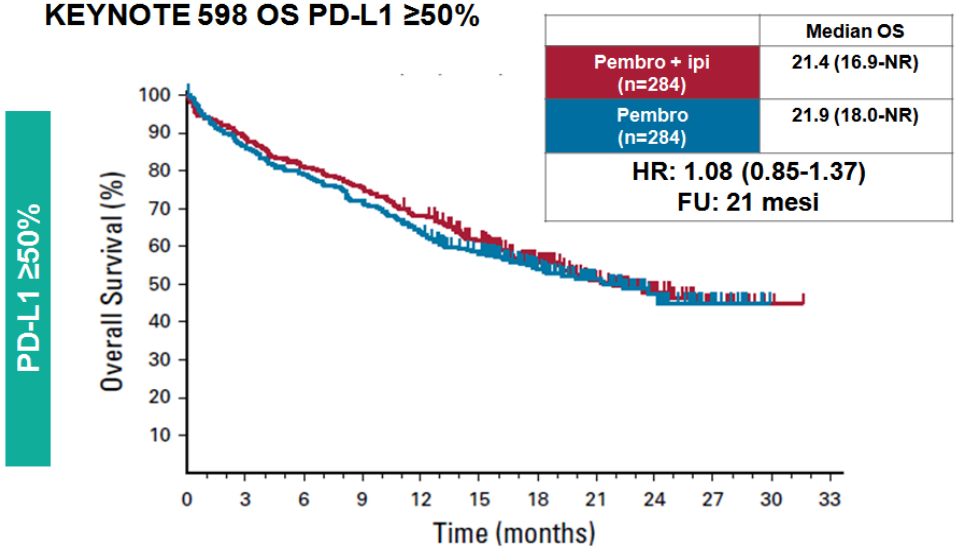


PD-L1 ≥50%



PD-L1 ≥50%

KEYNOTE 598 OS PD-L1 ≥50%



Tasso di risposte : 30%
Sopravvivenza mediana 17-21 mesi
25-30% dei pazienti vivi a 4 anni
HR sembra favorire la combo Nivolumab + Ipilimumab per pazienti con PD-L1 <1% e PD-L1 ≥50% (ma analisi esploratorie)
Pembro + Ipi non superiore al solo Pembro nei pazienti con PD-L1 ≥50%

Paz-Ares ASCO 2021, Boyer JCO 2021

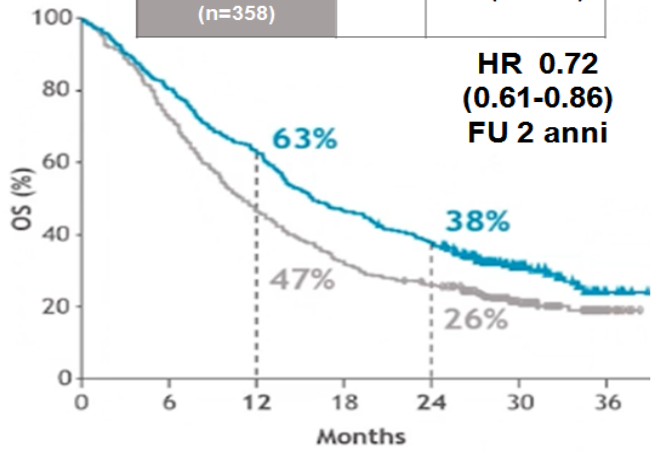
1 linea anti-PD-1/PD-L1 + altri immunoterapici +/- chemioterapia a base di platino

2 cicli chemio (short course)

No cross over ma subsequent ICI: 34%

CHECKMATE 9LA OS ITT

	ORR	Median OS
Nivo+Ipi+chemo (n=361)	38%	15.8 (13.9-19.7)
Chemo (n=358)	25%	11.0 (9.5-12.7)

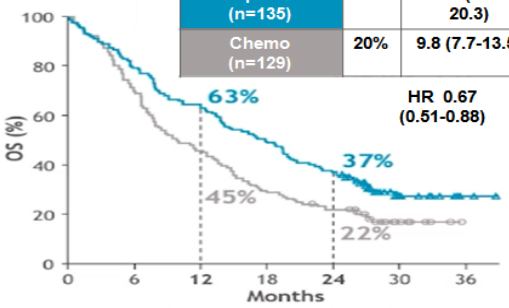


Tripletta anti-PD-1 + CTLA-4 + chemo:

- **40% risposte**
- **OS mediana 14-16 mesi**
- **30-40% sopravviventi a 2 anni**
- **No differenze a seconda dei livelli di PD-L1**

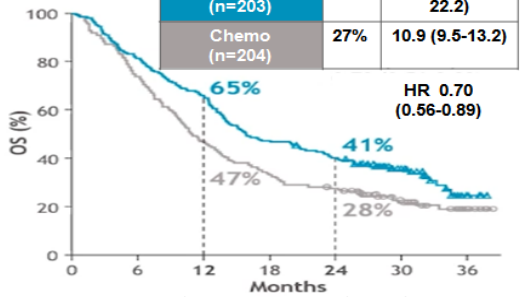
PD-L1 <1%

	ORR	Median OS
Nivo+Ipi+chemo (n=135)	31%	17.7 (13.7-20.3)
Chemo (n=129)	20%	9.8 (7.7-13.5)



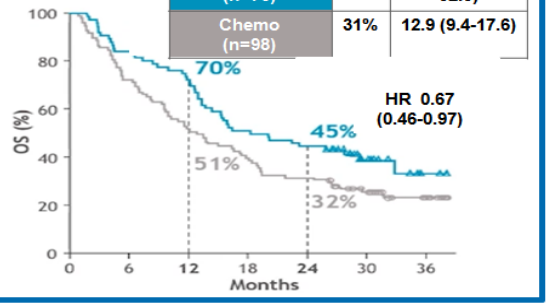
PD-L1 ≥1%

	ORR	Median OS
Nivo+Ipi+chemo (n=203)	43%	15.8 (13.8-22.2)
Chemo (n=204)	27%	10.9 (9.5-13.2)



PD-L1 ≥50%

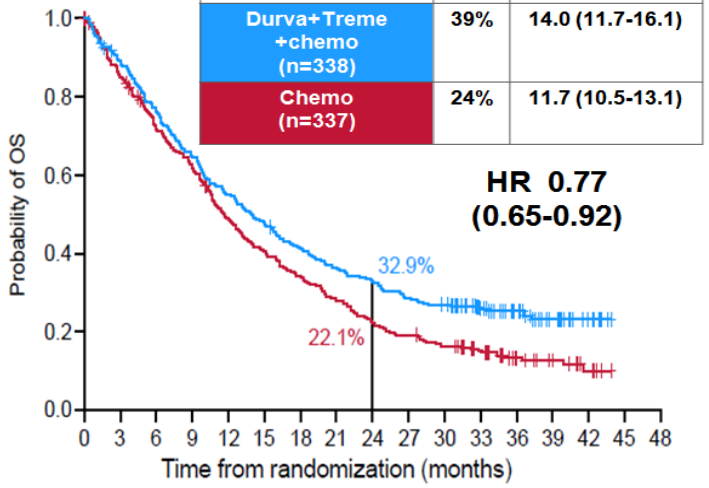
	ORR	Median OS
Nivo+Ipi+chemo (n=76)	50%	18.9 (13.1-32.5)
Chemo (n=98)	31%	12.9 (9.4-17.6)



4 cicli chemio + mantenimento se istologia non squamosa

POSEIDON OS

	ORR	Median OS
Durva+Treme +chemo (n=338)	39%	14.0 (11.7-16.1)
Chemo (n=337)	24%	11.7 (10.5-13.1)



- **30% sopravviventi a 2 anni con durvalumab e tremelimumab**
- **Ma se braccio di controllo fosse chemo+ anti-PD-1/PD-L1: anti-CTLA-4 sarebbe davvero un valore aggiunto?**

Reck ESMO Open 2021, Johnson WCLC 2021

1 linea anti-PD-1/PD-L1 + altri immunoterapici +/- chemioterapia a base di platino: tossicità

	CheckMate 227[1]								CheckMate 9LA[2]			
	All randomized (PD-L1 ≥1% and <1%)				PD-L1 ≥1%		PD-L1 <1%		All randomized			
	Nivo + Ipi (n=576)		Chemo (n=570)		Nivo (n=391)		Nivo + chemo (n=172)		Nivo + ipi + chemo (n=358)		Chemo (n=349)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAE*, %	77	33	82	36	66	20	92	56	92	48	88	38
TRAEs leading to discontinuation of any regimen component	18	12	9	5	12	7	14	8	22	18	8	5
Treatment-related deaths	1		1		<1		2		2		2	

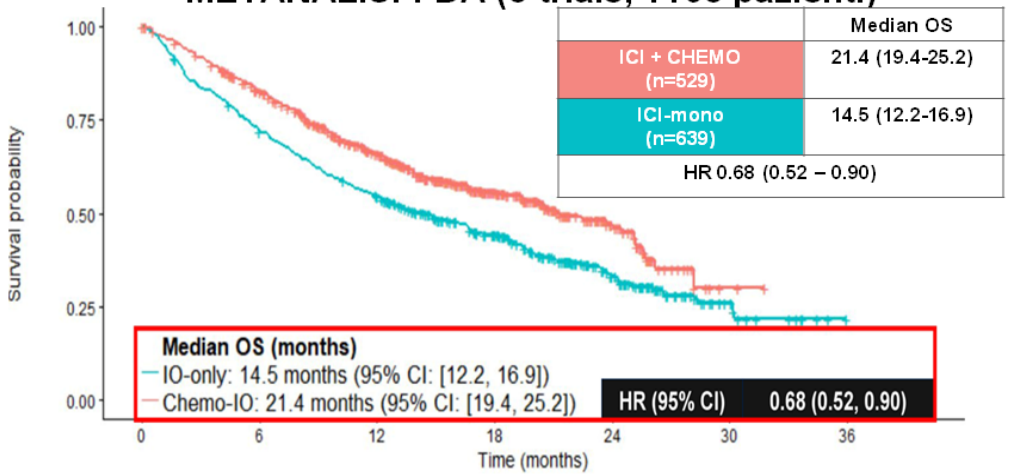
Rate di eventi avversi di grado 3-4 (30% nivolumab+ipilimumab, 50% con aggiunta di chemio) e morti tossiche (2%) non aumentano in maniera significativa con aggiunta dell'anti-CTLA-4

Hellmann NEJM 2019, Paz-Ares Lancet Oncology 2021

ICI in monoterapia o in combinazione con chemio a seconda dell'espressione di PD-L1

PD-L1 1-49%

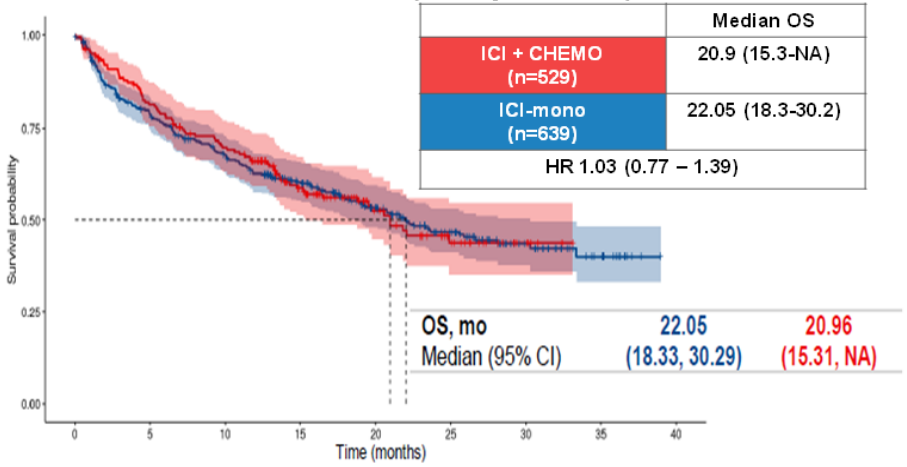
METANALISI FDA (8 trials, 1168 pazienti)



	Median OS
ICI + CHEMO (n=529)	21.4 (19.4-25.2)
ICI-mono (n=639)	14.5 (12.2-16.9)
HR 0.68 (0.52 – 0.90)	

PD-L1 ≥50%

Dati real-world (520 pazienti)

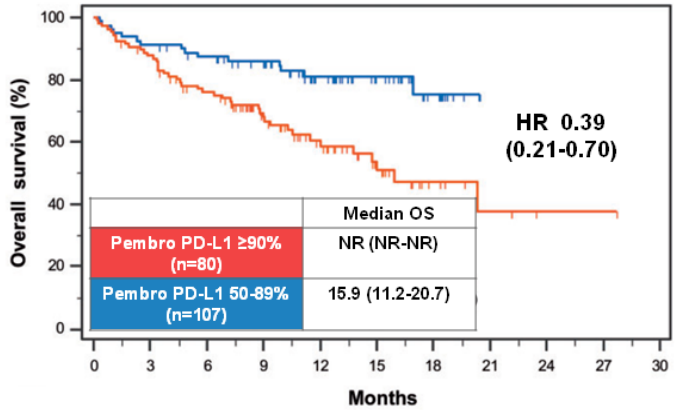


	Median OS
ICI + CHEMO (n=529)	20.9 (15.3-NA)
ICI-mono (n=639)	22.05 (18.3-30.2)
HR 1.03 (0.77 – 1.39)	

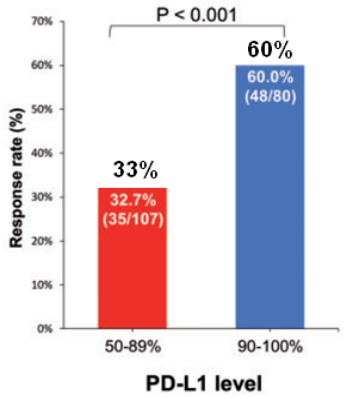
Ankinboro ASCO 2021, Peters ESMO 2021, Aguilar Ann of Oncology 2019, Sezer Lancet 2021

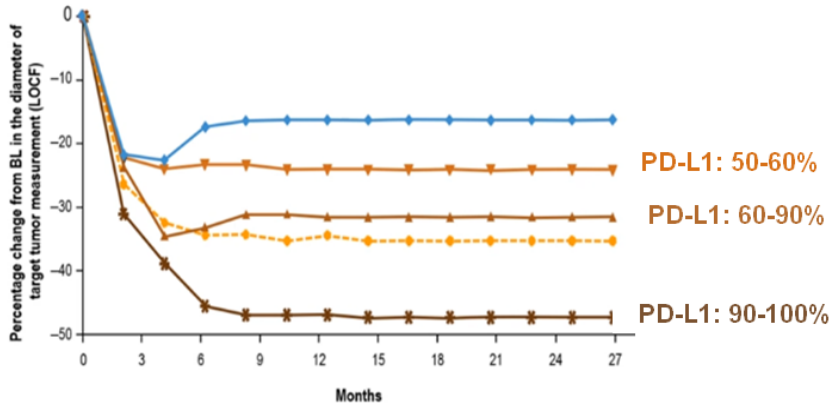
PD-L1 ≥ 90%

PD-L1 ≥ 90% correla con migliore sopravivenza globale



PD-L1 ≥ 90% correla con più alto ORR (60%) e soprattutto con maggiore profondità della risposta



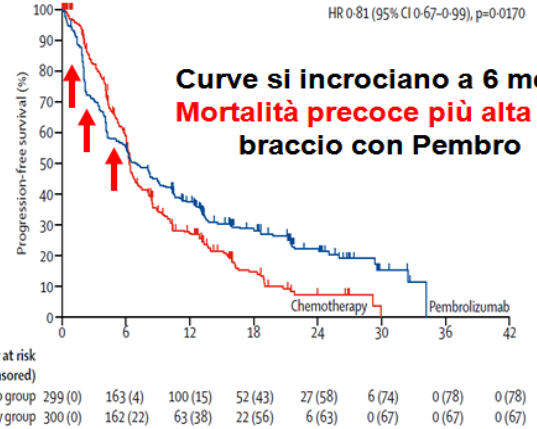


Courtesy R Ferrara

Progressione rapida e mortalità precoce

ICI in monoterapia

KEYNOTE 042 PFS PD-L1 ≥50%



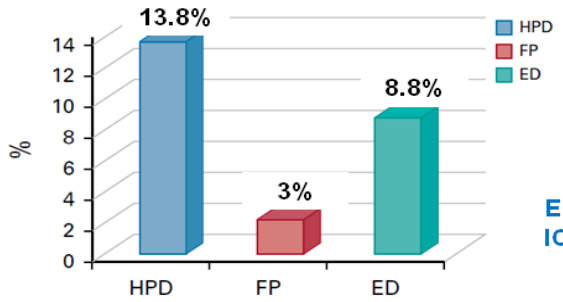
Curve si incrociano a 6 mesi:
Mortalità precoce più alta nel braccio con Pembro

406 pazienti, ICI in 2 linea

16% classificato come HPD, FP o ED

HPD: differenza in velocità di crescita
FP= RECIST >50% alla prima rivalutazione
ED: morte in 12 settimane

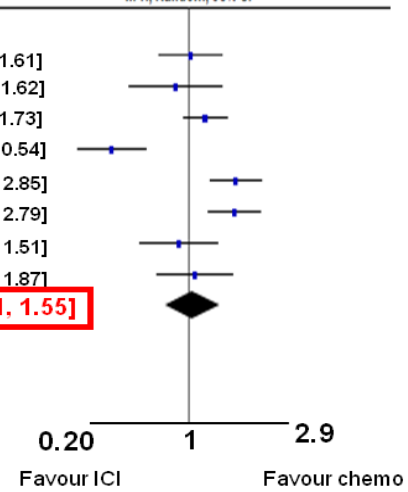
Overlap HPD e ED: 55%



ED= morte nei primi 3 mesi
ICI in monoterapia vs chemo

	Immunotherapy Events	Total	Standard Treatment Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
7 trials						
CHECKMATE 026 (Nivo)	34	271	33	270	12.8%	1.03 [0.66, 1.61]
BFAST (Atezo)	14	145	17	146	10.6%	0.83 [0.42, 1.62]
CHECKMATE 227 (N+I)	77	583	61	583	13.9%	1.26 [0.92, 1.73]
KEYNOTE 024 (Pembro)	18	154	53	151	12.4%	0.33 [0.20, 0.54]
MYSTIC (Durvalumab)	71	374	36	372	13.4%	1.96 [1.35, 2.85]
MYSTIC (Durva + Treme)	69	372	36	372	13.4%	1.92 [1.32, 2.79]
EMPOWER Lung 1 (Cemiplimab)	1	283	24	280	11.6%	0.87 [0.49, 1.51]
IMPOWER 110 (Atezolizumab)	25	277	23	277	11.8%	1.09 [0.63, 1.87]
Subtotal (95% CI)		2459		2451	100.0%	1.05 [0.71, 1.55]
Total events	329		283			

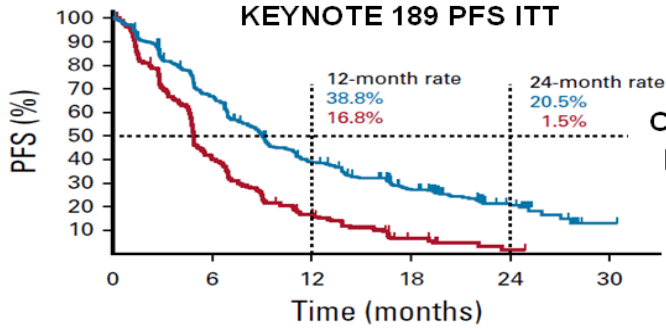
Heterogeneity (I square): 84%
Test for overall effect: 0.26, p=0.80



Ferrara JCO PO 2020, Viscardi ESMO 2021

ICI + chemioterapia

KEYNOTE 189 PFS ITT



Curve si separano presto e restano separate

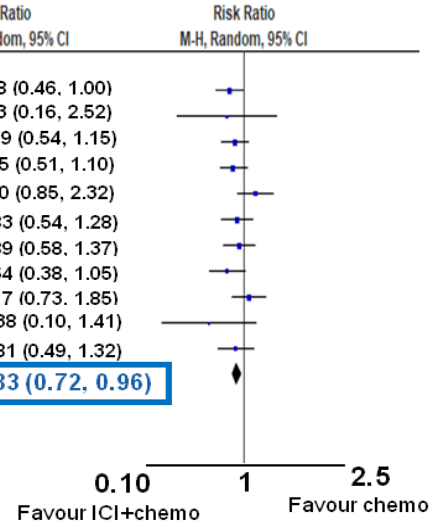
No. at risk:

Pembro	410	266	149	91	28	1
Placebo	206	81	31	8	1	0

ED= morte nei primi 3 mesi
ICI +chemo vs chemo

	ICI+ others Events	Total	Standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
10 trials						
IMPOWER 130 (Atezo+CT)	52	483	38	240	13.4%	0.68 (0.46, 1.00)
KEYNOTE 021 (Pembro+CT)	3	60	5	63	1.1%	0.63 (0.16, 2.52)
POSEIDON (Durva+CT)	42	338	53	337	14.3%	0.79 (0.54, 1.15)
POSEIDON (Durva+Treme+CT)	40	338	53	337	13.8%	0.75 (0.51, 1.10)
IMPOWER 131 (Atezo+CT)	34	343	24	340	8.2%	1.40 (0.85, 2.32)
IMPOWER 132 (Atezo+CT)	34	292	40	286	11.2%	0.83 (0.54, 1.28)
CHECKMATE 9LA (Nivo+Ipi+CT)	35	361	39	358	10.9%	0.89 (0.58, 1.37)
KEYNOTE 407 (Pembro+CT)	22	278	35	281	8.0%	0.64 (0.38, 1.05)
IMPOWER 150 (Atezo+CT)	36	359	29	337	9.4%	1.17 (0.73, 1.85)
CAMEL (Camre+CT)	3	205	8	207	1.2%	0.38 (0.10, 1.41)
KEYNOTE 189 (Pembro+CT)	37	410	23	206	8.5%	0.81 (0.49, 1.32)
Subtotal (95% CI)		3467		2992	100.0%	0.83 (0.72, 0.96)
Total events	338		347			

Heterogeneity (I square): 3%
Test for overall effect: 2.52, p=0.01



27% di aumento del rischio relativo di mortalità precoce con ICI mono vs ICI + chemio [Risk ratio: 1.27 (0.83; 1.92)]

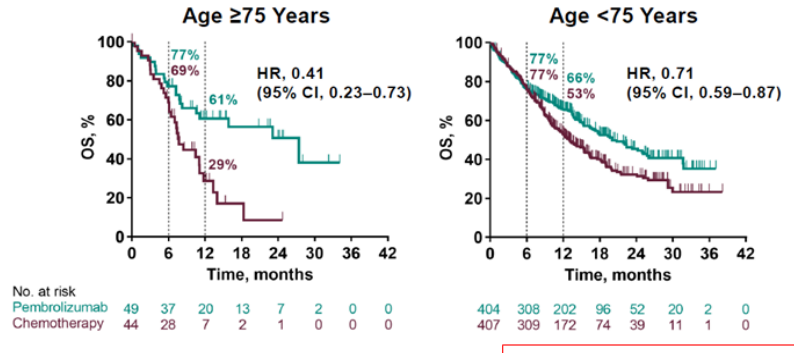
Courtesy R Ferrara

Popolazioni particolari: anziani, non fumatori, ECOG PS-2

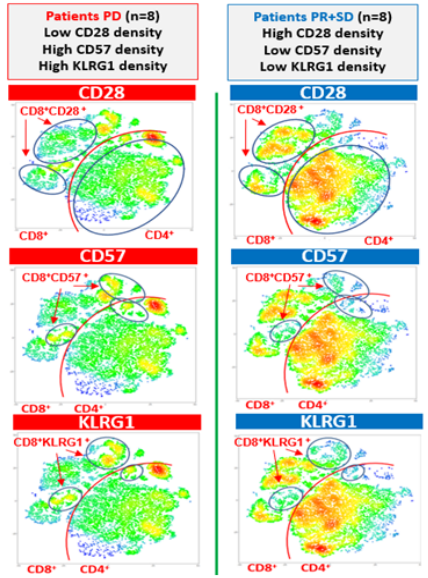
ANZIANI: Età anagrafica non importante, controlla età immunologica!

ETA' ANAGRAFICA

Età immunologica può predire meglio di quella anagrafica il **non-beneficio** da ICI



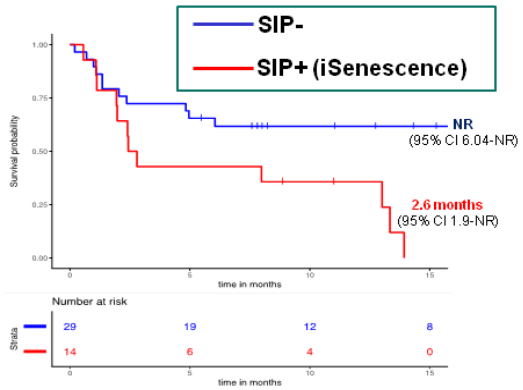
ETA' IMMUNOLOGICA



iSenescence: fenotipo delle T-cell circolanti **CD28-CD57+KLRG1+**

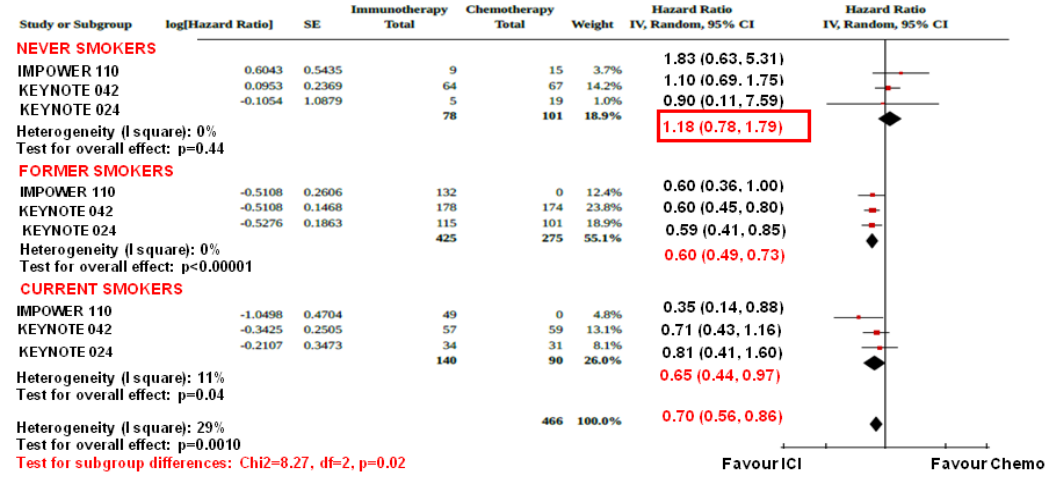
- **28%** dei pazienti con NSCLC hanno **linfociti senescenti**

SIP+ = iSenescence



NON FUMATORI: Controlla prima tutti i possibili driver molecolari!

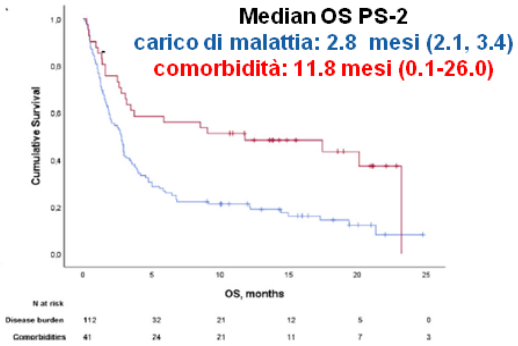
OS ICI single agent vs chemotherapy in PD-L1 ≥ 50% according to **smoking status**

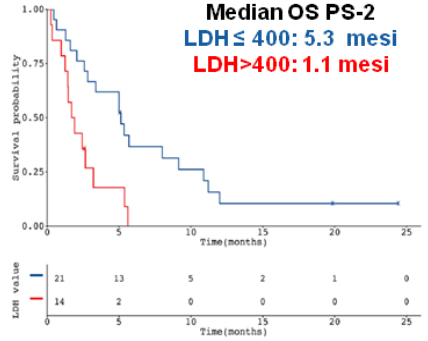


PS ≥ 2 : se è da carico di malattia «effetto LAZZARO» è raro con ICI!

Se è il carico di malattia (i.e: LDH alto) ICI sopravvivenza mediana < 3mesi

Pembro I linea PS2 PD-L1 TPS ≥50%





Nosaki Lung Cancer 2019, Ferrara Clinical Cancer Research 2020, Ferrara Cochrane System Reviews 2021, Facchinetti EJC 2020, Lobefaro Lung Cancer 2021

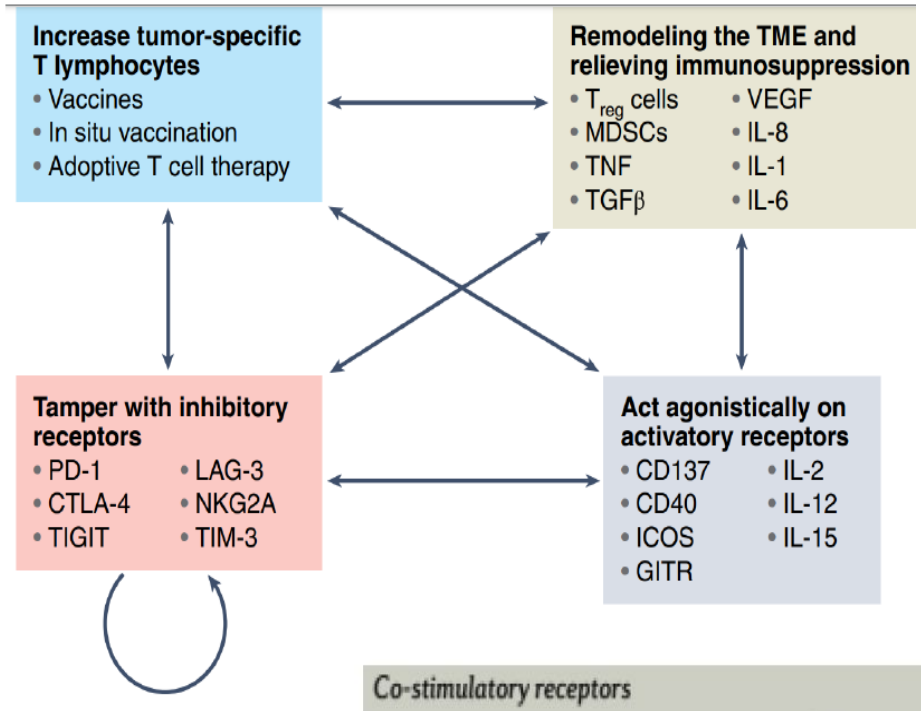
NSCLC WT LATER LINES

Standard:

- Non Oncogene addicted advanced NSCLC PD-L1>50%(30%): Pembrolizumab OR Cemiplimab OR Atezolizumab → Platinum based CHT

- Non Oncogene addicted advanced NSCLC PD-L1<50% (55%): Platinum based CHT + IO OR Nivolumab + ipilimumab + CHT (2 CYCLES)→ Docetaxel +/- nintedanib

IO VECCHIE E NUOVE STRATEGIE



Co-inhibitory receptors				
CTLA4	CD80/86	Limits initial T cell activation and proliferation	FDA-approved	Ipilimumab, tremelimumab
PD1	PD-L1	Inhibits the activity of effector T cells	FDA-approved	Nivolumab, pembrolizumab, durvalumab, atezolizumab
LAG3	MHC II	Inhibits the activity of effector T cells via the KIEELE motif, which is functionally linked with T_{reg} cell-mediated immunosuppression	Phase III trial ongoing	Relatlimab
TIM-3	Galectin-9 CEACAM1	Triggers $CD8^+$ T cell apoptosis and/or exhaustion	Phase II trials ongoing	Cobolimab, sabatolimab
TIGIT	CD155, CD112	Downregulation of T cell and NK cell function	Phase II trials ongoing	Tiragolumab
BTLA	HVEM	Suppression of downstream activation of TCR signalling via SH2	Phase I trials ongoing	Icatolimab

Co-stimulatory receptors				
GITR	GITRL	Promotes activation and proliferation of effector T cells and a reduction in T_{reg} cells	Phase II trials ongoing	TRX518, BMS-986156
OX40	OX40L	Promotes survival, but not priming, of both effector and memory T cells	Phase II trials ongoing	GSK3174998, MEDI6469, PF-04518600
4-1BB	4-1BBL	Promotes T cell proliferation and mitochondrial function and biogenesis	Phase I trials ongoing	Utomilumab, urelumab
ICOS	ICOSL	Promotes TCR co-stimulation and T_{reg} cell stimulation	Phase I trials ongoing	Vopratelimab, KY1044, GSK3359609

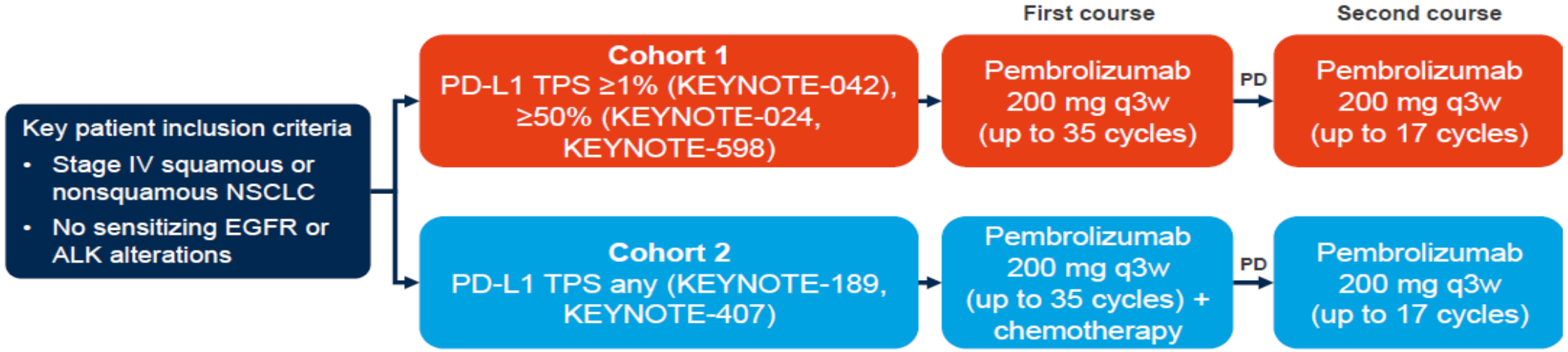
Kraehenbuhl, Nature Reviews 2022

Sanmamed, Nature Cancer review 2022

IO-SECOND COURSE

OA15.06: Pooled Analysis of Outcomes With Second-Course Pembrolizumab Across 5 Phase 3 Studies of Non-Small-Cell Lung Cancer – Rodriguez-Abreu D, et al

- **Study objective**
  - To evaluate the efficacy and safety of second-course pembrolizumab in patients with NSCLC across five KEYNOTE studies



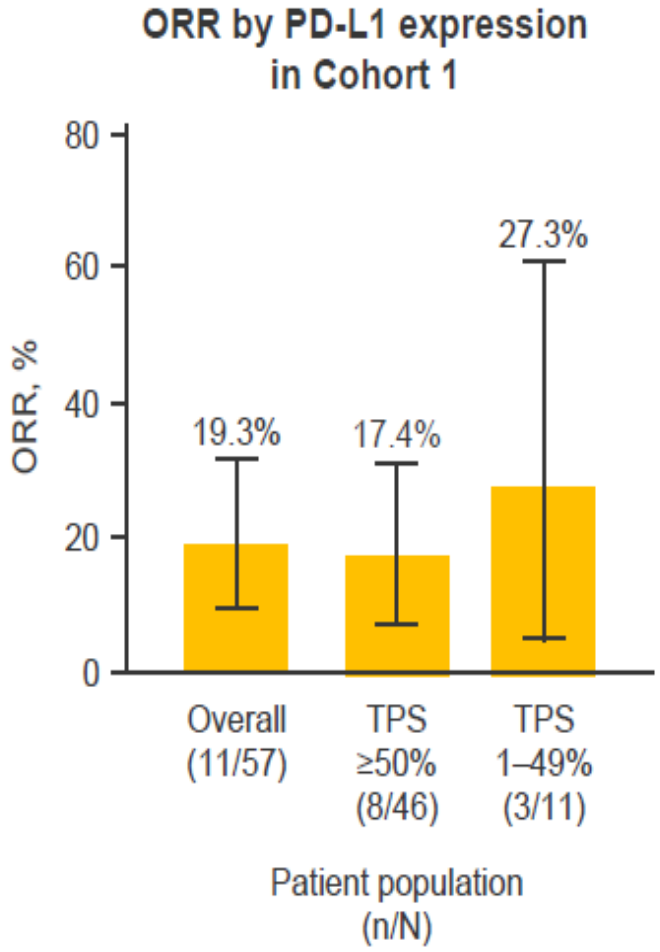
Endpoints

- ORR, DCR, DoR, OS, PFS, safety

Rodriguez-Abreu D, et al. J Thorac Oncol 2022;17(suppl):Abstr OA15.06

IO-SECOND COURSE

	Cohort 1 (pembrolizumab) (n=57)	Cohort 2 (pembrolizumab + chemo) (n=14)
ORR, % (95%CI)	19.3 (10.0, 31.9)	0 (0, 23.2)
DCR, % (95%CI)	73.7 (60.3, 84.5)	50.0 (23.0, 77.0)
BOR, n (%)		
CR	0	0
PR	11 (19.3)	0
SD	31 (54.4)	7 (50.0)
PD	8 (14.0)	2 (14.3)
NA	7 (12.3)	5 (35.7)
mDoR, mo (range)	NR (0.0+ to 20.0+)	–
DoR ≥6 mo, %	78.8	–
mOS, mo (95%CI)	27.5 (21.7, NR)	NR (NR, NR)
6-mo OS, % rate (95%CI)	85.1 (72.4, 92.3)	85.1 (52.3, 96.1)
mPFS, mo (95%CI)	10.3 (5.6 ,14.0)	7.7 (1.8, NR)
6-mo PFS rate, % (95%CI)	60.8 (46.0, 72.7)	54.5 (22.9, 78.0)



Rodriguez-Abreu D, et al. J Thorac Oncol 2022;17(suppl):Abstr OA15.06

IO-SECOND COURSE

AEs, n (%)	Cohort 1 (pembrolizumab) (n=57)		Cohort 2 (pembrolizumab + chemo) (n=14)	
Treatment-related	14 (25)		14 (29)	
Grade 3–4	3 (5)		1 (7)	
Led to discontinuation	1 (1)		0	
Led to death	0		0	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Immune-mediated	5 (9)	1 (2)	0	0
Hyperthyroidism	1 (2)	0	0	0
Hypothyroidism	3 (5)	0	0	0
Severe skin reactions	1 (2)	1 (2)	0	0
Thyroiditis	1 (2)	0	0	0

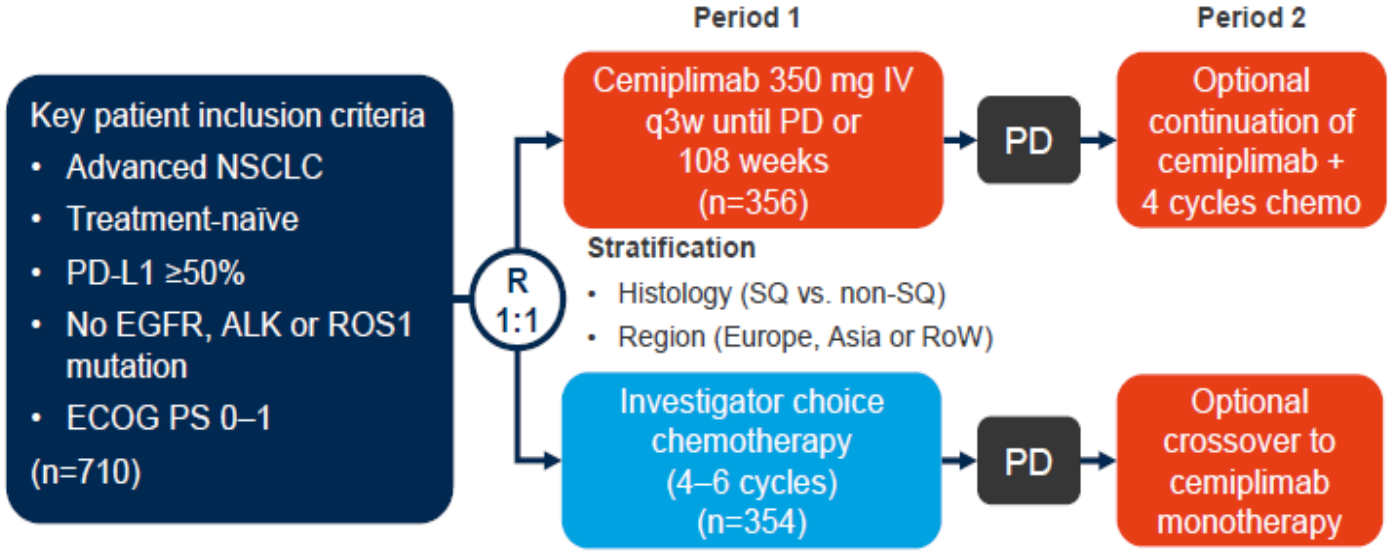
- **Conclusions**
  - In patients with metastatic NSCLC, second course pembrolizumab demonstrated promising clinical benefit and had a manageable safety profile

Rodriguez-Abreu D, et al. J Thorac Oncol 2022;17(suppl):Abstr OA15.06 .

IO-CHT BEYOND PD

LBA54: Three years survival outcome and continued cemiplimab (CEMI) beyond progression with the addition of chemotherapy (chemo) for patients (pts) with advanced non small cell lung cancer (NSCLC): the EMPOWER-Lung 1 trial – Özgüroğlu M, et al

- **Study objective**
  - To evaluate the updated efficacy and safety of 1L cemiplimab in patients with advanced NSCLC in the EMPOWER-Lung 1 study

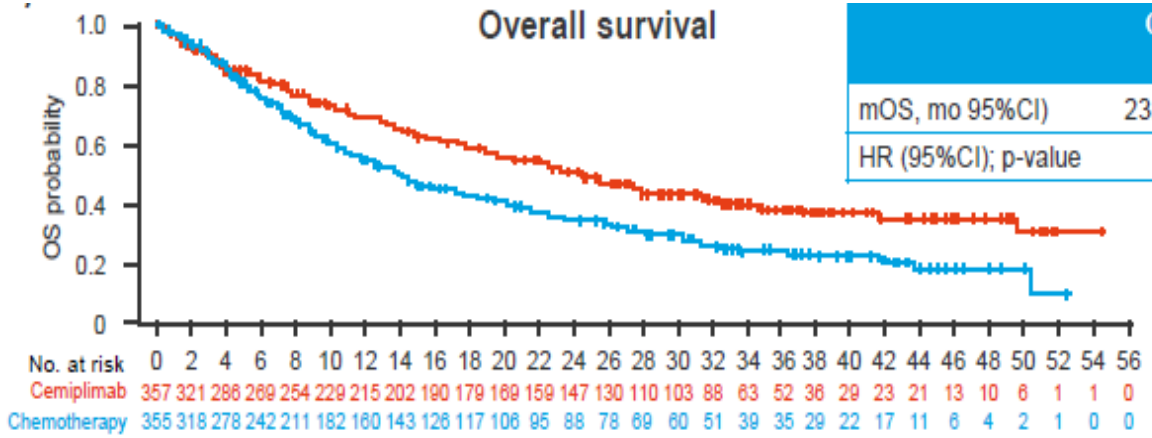


Primary endpoints
- OS, PFS

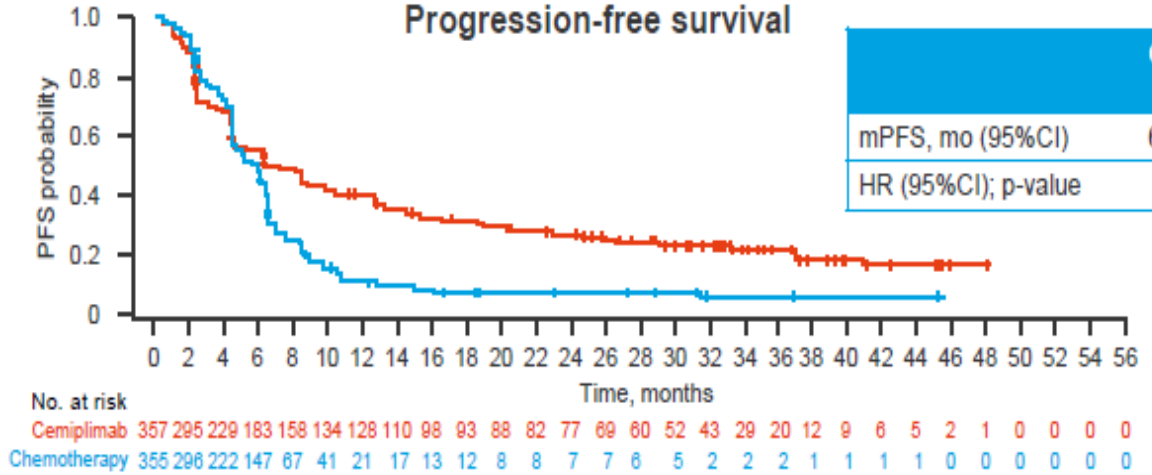
Secondary endpoints
- ORR, DoR, HRQoL, safety

Özgüroğlu M, et al. Ann Oncol 2022;33(suppl):Abstr LBA54

IO-CHT BEYOND PD



	Cemiplimab (n=357)	Chemotherapy (n=355)
mOS, mo 95%CI)	23.4 (19.4, 27.4)	13.7 (11.2, 16.2)
HR (95%CI); p-value	0.63 (0.52, 0.77); 0.0001	



	Cemiplimab (n=357)	Chemotherapy (n=355)
mPFS, mo (95%CI)	6.3 (4.6, 8.3)	5.3 (4.3, 6.0)
HR (95%CI); p-value	0.56 (0.47, 0.67); 0.0001	

Data cut-off: 4 March 2022

Özgüroğlu M, et al. Ann Oncol 2022;33(suppl):Abstr LBA54

IO-CHT BEYOND PD

AEs, n (%)	Cemiplimab (n=356)		Chemotherapy (n=343)	
	Any grade	Grade 3–5	Any grade	Grade 3–5
TEAE				
Any	330 (92.7)	163 (45.8)	329 (95.9)	177 (51.6)
Led to discontinuation	32 (9.0)	20 (5.6)	17 (5.0)	10 (2.9)
Led to death	36 (10.1)	36 (10.1)	33 (9.6)	33 (9.6)
TRAE				
Any	223 (62.6)	65 (18.3)	310 (90.4)	137 (39.9)
Led to discontinuation	26 (7.3)	5 (4.2)	15 (4.4)	10 (2.9)
Led to death	10 (2.8)	10 (2.8)	7 (2.00	7 (1.0)

Immune-related AEs, n (%)	Cemiplimab (n=356)		Chemotherapy (n=343)	
	Any grade	Grade 3–5	Any grade	Grade 3–5
Any	80 (22.5)	17 (4.8)	8 (2.3)	1 (0.3)
Led to discontinuation	16 (4.5)	9 (2.5)	0	0
Led to death	2 (0.6)	2 (0.6)	0	0

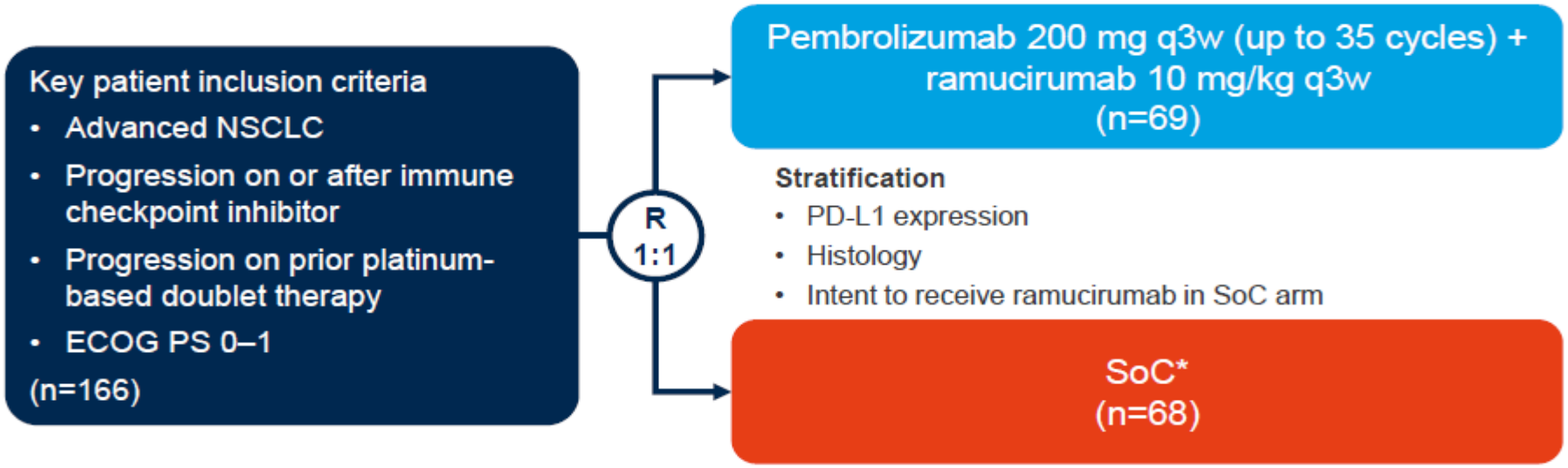
- **Conclusions**
  - In patients with advanced NSCLC, 1L cemiplimab continued to demonstrate improved survival benefit compared with chemotherapy and had a manageable safety profile
  - In an exploratory analysis, cemiplimab + chemotherapy continued beyond progression showed encouraging responses

Özgüroğlu M, et al. Ann Oncol 2022;33(suppl):Abstr LBA54

IO-ANTIANGIOGENIC DRUGS BEYOND PD

9004: Overall survival from a phase II randomized study of ramucirumab plus pembrolizuma versus standard of care for advanced non–small cell lung cancer previously treated with immunotherapy: Lung-MAP nonmatched substudy S1800A – Reckamp KL, et al

- **Study objective**
  - To evaluate the efficacy and safety of pembrolizumab + ramucirumab in previously treated patients with advanced NSCLC in a Lung-MAP substudy



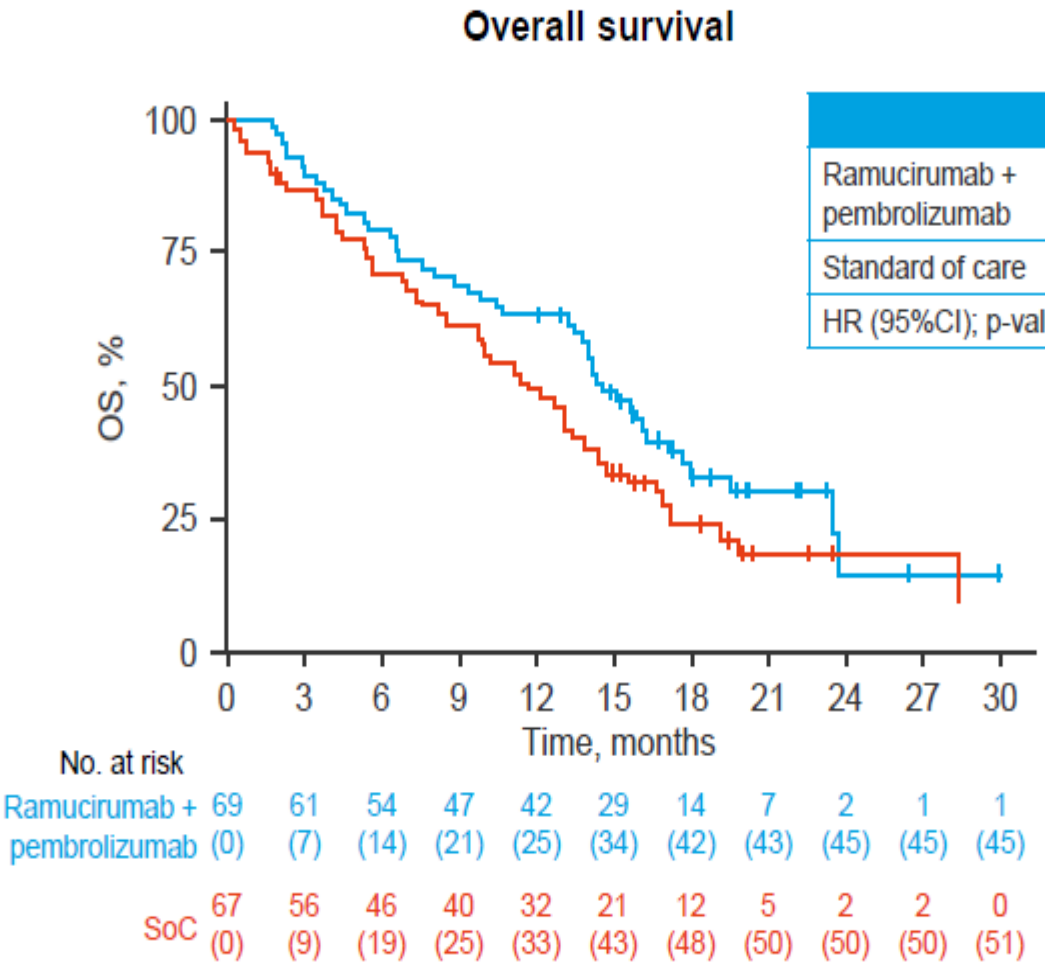
Primary endpoint
- OS

Secondary endpoints
- DoR, PFS, safety

*Investigator's choice: docetaxel ± ramucirumab, pemetrexed (nonsquamous only), gemcitabine

Reckamp KL, et al. J Clin Oncol 2022;40(suppl):Abstr 9004

IO-ANTIANGIOGENIC DRUGS BEYOND PD



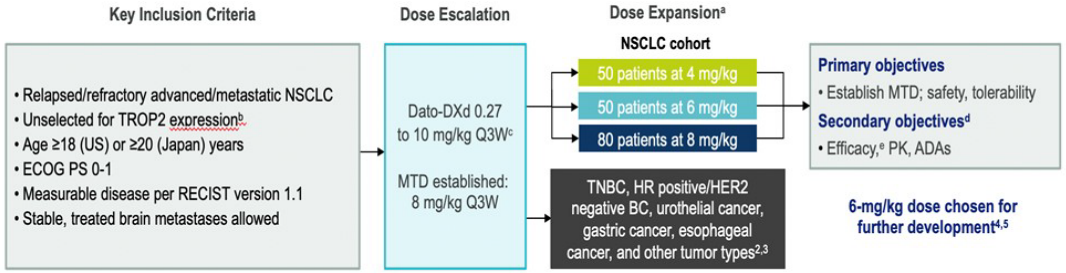
	n	Events	mOS, mo (80%CI)
Ramucirumab + pembrolizumab	69	45	14.5 (13.9, 16.1)
Standard of care	67	51	11.6 (9.9, 13.0)
HR (95%CI); p-value			0.69 (0.51, 0.92); 0.05

Reckamp KL, et al. J Clin Oncol 2022;40(suppl):Abstr 9004

DRUG CONJUGATE ANTIBODY

Datopotamab deruxtecan in previously treated metastatic NSCLC (TROPION-PanTumor01 phase I, NSCLC cohort)

Garon WCLC 2021

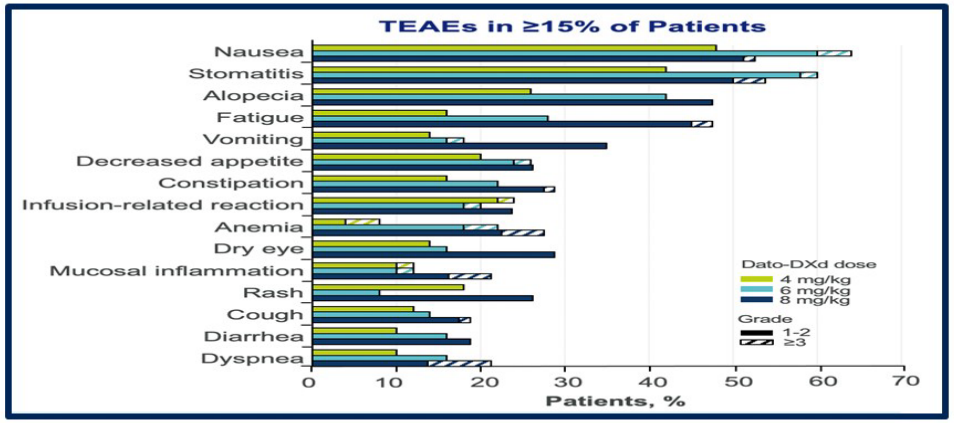


Best Overall Response (BICR)

Patients[a]	Dato-DXd dose 4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
ORR, n (%)[b]	12 (24)	14 (28)	19 (24)
CR, n (%)	0	0	1 (1)
PR, n (%)[b]	12 (24)	14 (28)	18 (23)
SD, n (%)	25 (50)	20 (40)	42 (53)
Non-CR/PD, n (%)	1 (2)	2 (4)	2 (3)
PD, n (%)	7 (14)	10 (20)	8 (10)
NE, n (%)	5 (10)	5 (10)	9 (11)
DOR, median (95% CI), mo	NE (2.8-NE)	10.5 (5.6-NE)	9.4 (5.8-NE)

Overall Safety Summary

Patients, n (%)	Dato-DXd dose 4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
TEAE	49 (98)	49 (98)	80 (100)
Grade ≥3	15 (30)	27 (54)	46 (58)
Drug-related TEAE	47 (94)	41 (82)	78 (98)
Grade ≥3	7 (14)	13 (26)	28 (35)
Serious TEAE	10 (20)	24 (48)	40 (50)
Grade ≥3	10 (20)	18 (36)	37 (46)
Dose adjustments			
TEAEs associated with discontinuation	8 (16)	7 (14)	19 (24)
TEAEs associated with dose interruption	4 (8)	15 (30)	29 (36)
TEAEs associated with dose reduction	1 (2)	5 (10)	23 (29)
ILD adjudicated as drug related[a]	5 (10)	3 (6)	11 (14)
Grade ≤2	4 (8)	2 (4)	7 (9)
Grades 3-4	1 (2)	1 (2)	1 (1)
Grade 5	0	0	3 (4)



In NSCLC datopotamab deruxtecan activity was observed irrespective of TROP 2 expression *Lisberg ASCO 20*

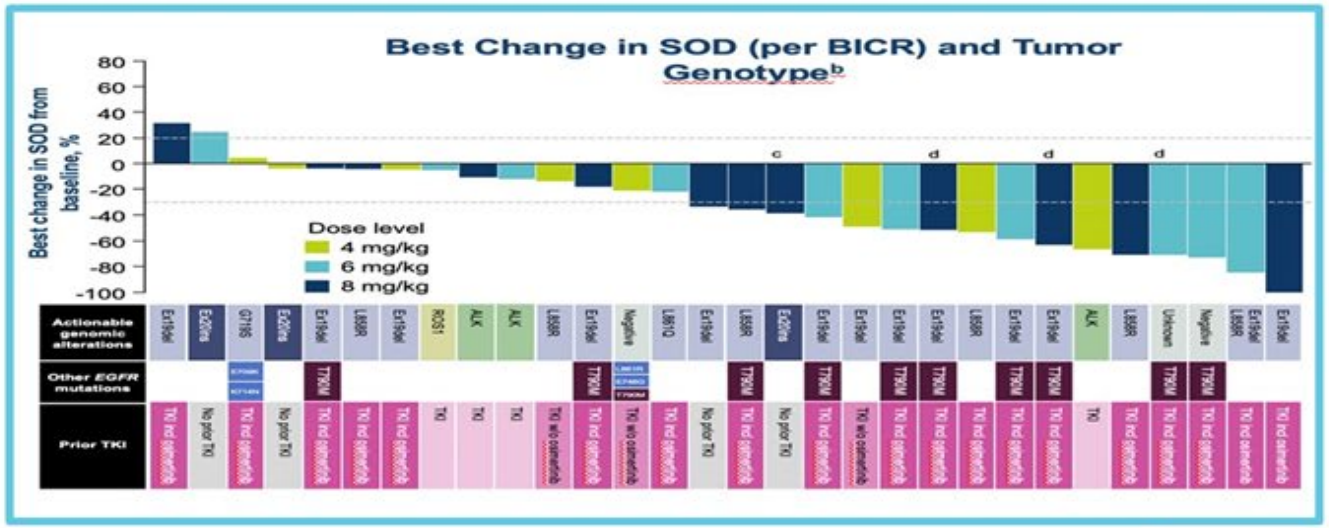
Adapted by E Felip ; ASCO 2023

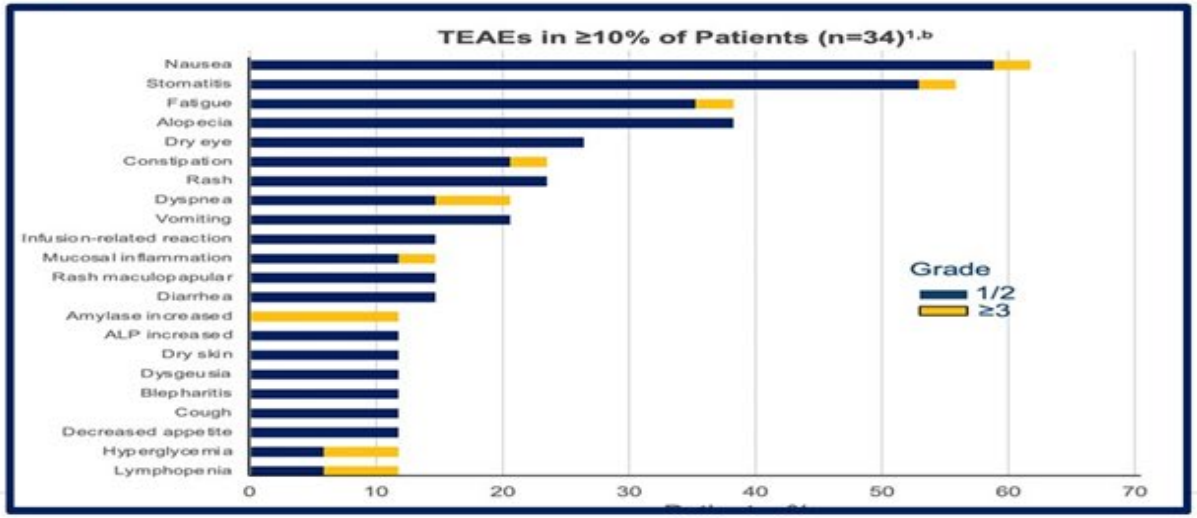
DRUG CONJUGATE ANTIBODY

Garon ESMO 2021

Best Overall Response (per BICR)

Patients[a]	Dato-DXd n=34
ORR, n (%)	12 (35)
CR	0
PR	12 (35)
SD, n (%)	14 (41)
Non-CR/PD, n (%)	2 (6)
PD, n (%)	2 (6)
NE, n (%)	4 (12)
DOR, median (95% CI), mo	9.5 (3.3-NE)





Adapted by E Felip ; ASCO 2023

KRAS G12C

Standard: IO or CHT platinum based +/- IO→ EAP target therapy

K-RAS G12C

Second line. Adagrasib and Sotorasib

	Adagrasib[1, 2]	Sotorasib[3,4]
N efficacy (safety)	112 (116)	172 (174)**
ORR (95% CI)	43 (34.5-52.6)	41 (33.3-48.4)**
mDOR months (95% CI)	8.5 (6.2 to 13.8),	12.3 (7.1-15)**
mPFS months	6.5 (4.7 to 8.4)	6.3 (*5.3 to 8.2)***
mOS months	12.6(9.2 to 19.2)	12.5 (10- 17.8)**
Median follow up, months	15.6	24.9**
icORR (prospective untreated brian mets cohort)	6/19 32%	NR
icDOR*	NR (4.1-NE)	NR
icPFS*	4.2 (3.8-NE)	NR
Approval	FDA	FDA, EU, Canada

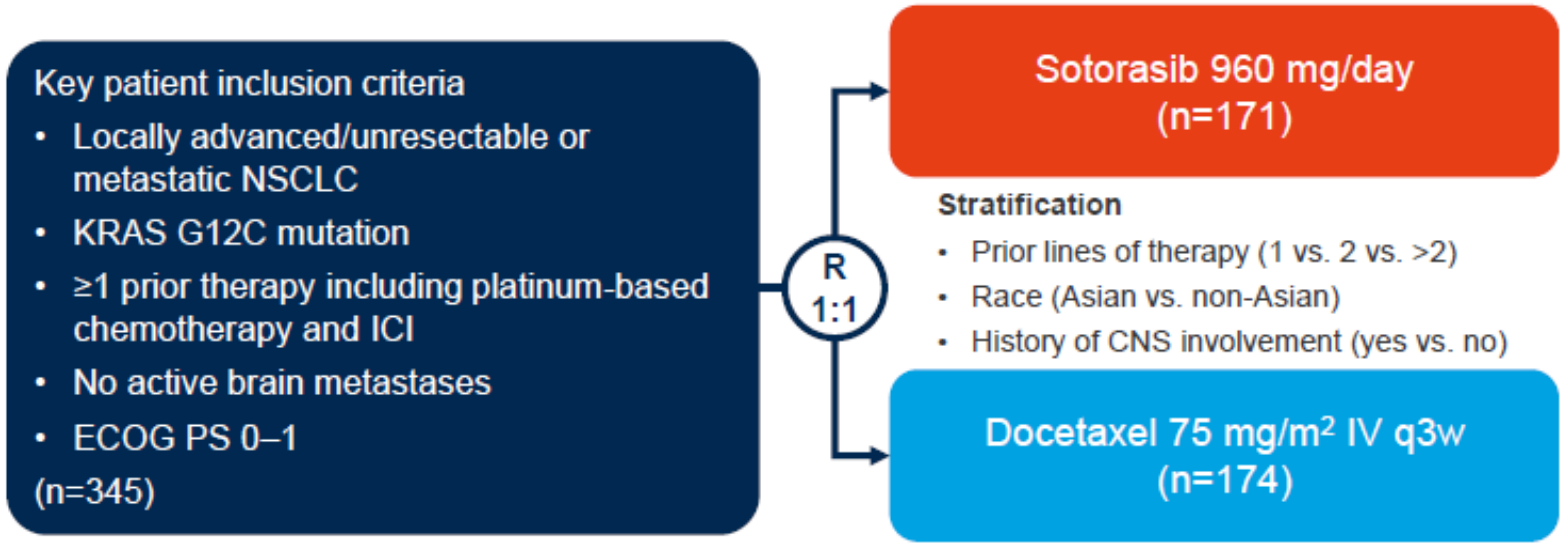
* median follow up 6.6 months, ** from updated pooled analysis by Dy et all

[1] Janne PA et al NEJM 2022, [2] Sabari et al ASCO 2022 [3,] Skoulidis et al NEJM 2021 [4] Dy et al AACR 2022

K-RAS G12C

LBA10: Sotorasib versus docetaxel for previously treated non-small cell lung cancer with KRAS G12C mutation: CodeBreaK 200 phase III study – Johnson ML, et al

- **Study objective**
  - To evaluate the efficacy and safety of sotorasib in previously treated patients with NSCLC and KRAS G12C mutation in the phase 2 CodeBreaK 200 study



Primary endpoint

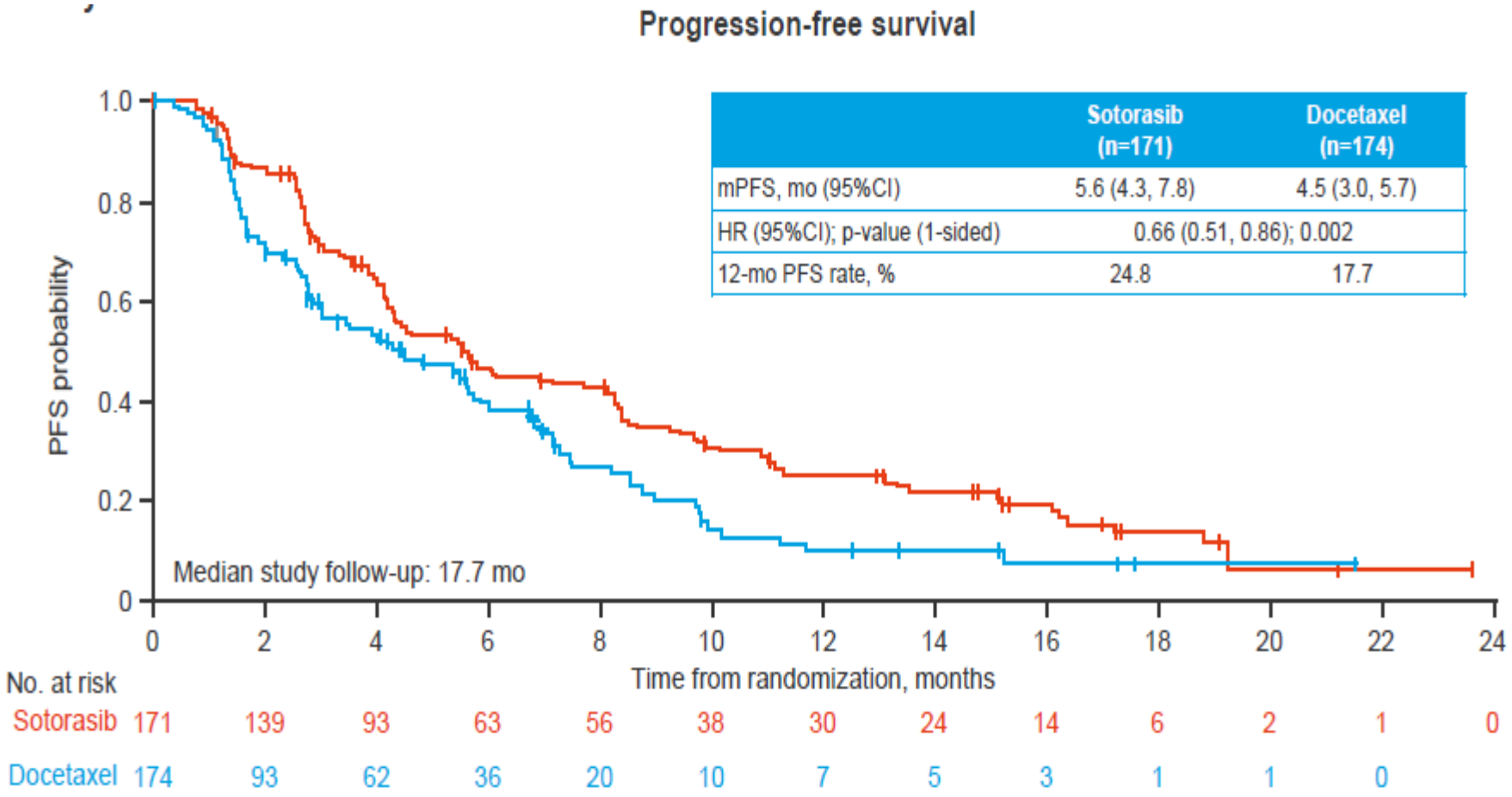
- PFS (BICR)

Secondary endpoints

- OS, ORR, DoR, TTR, DCR, safety

Johnson ML, et al. Ann Oncol 2022;33(suppl):Abstr LBA10

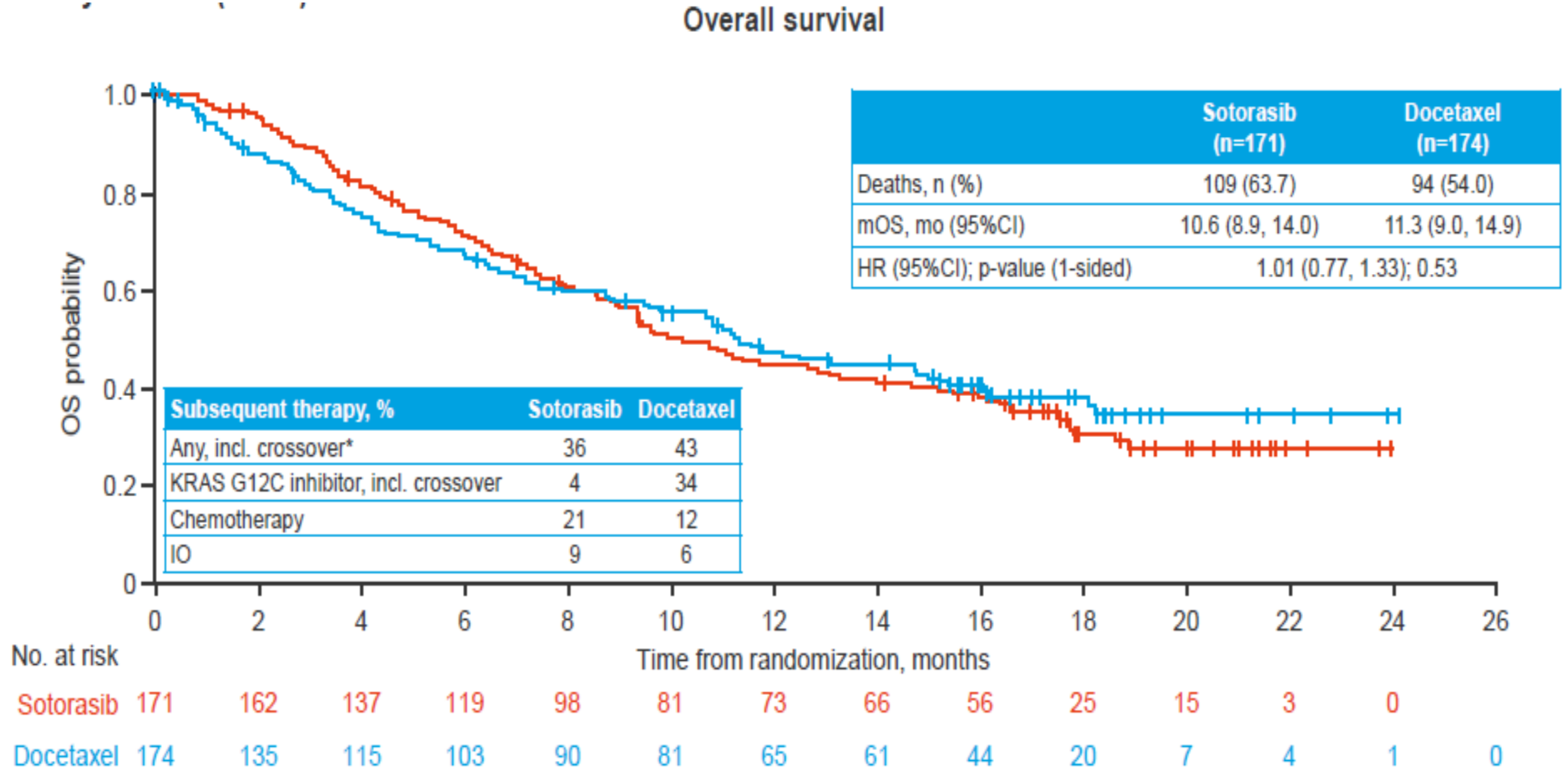
K-RAS G12C



	Sotorasib (n=171)	Docetaxel (n=174)
mPFS, mo (95%CI)	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)
HR (95%CI); p-value (1-sided)	0.66 (0.51, 0.86); 0.002	
12-mo PFS rate, %	24.8	17.7

Johnson ML, et al. Ann Oncol 2022;33(suppl):Abstr LBA10

K-RAS G12C



	Sotorasib (n=171)	Docetaxel (n=174)
Deaths, n (%)	109 (63.7)	94 (54.0)
mOS, mo (95%CI)	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)
HR (95%CI); p-value (1-sided)	1.01 (0.77, 1.33); 0.53	

Subsequent therapy, %	Sotorasib	Docetaxel
Any, incl. crossover*	36	43
KRAS G12C inhibitor, incl. crossover	4	34
Chemotherapy	21	12
IO	9	6

*16.4% and 5.2% of patients in the sotorasib and docetaxel arms, respectively, were treated beyond progression

Johnson ML, et al. Ann Oncol 2022;33(suppl):Abstr LBA10

K-RAS G12C

Outcomes	Sotorasib (n=158)*	Docetaxel (n=129)*
ORR, % (95%CI)	28.1 (21.5, 35.4)	13.2 (8.6, 19.2)
DCR, % (95%CI)	82.5 (75.9, 87.8)	60.3 (52.7, 67.7)
Tumour shrinkage, %	80.4	62.8
Responders, n	48	23
mTTR, mo (range)	1.4 (1.2–8.3)	2.8 (1.3–11.3)
mDoR, mo (95%CI)	8.6 (7.1, 18.0)	6.8 (4.3, 8.3)

TRAEs, n (%)	Sotorasib (n=169)	Docetaxel (n=151)
Any grade	119 (70.4)	130 (86.1)
Grade ≥3	56 (33.1)	61 (40.4)
Serious	18 (10.7)	34 (22.5)
Led to dose interruption	60 (35.5)	23 (15.2)
Led to dose reduction	26 (15.4)	40 (26.5)
Led to discontinuation	16 (9.5)	17 (11.3)
Led to death	1 (0.6)	2 (1.3)

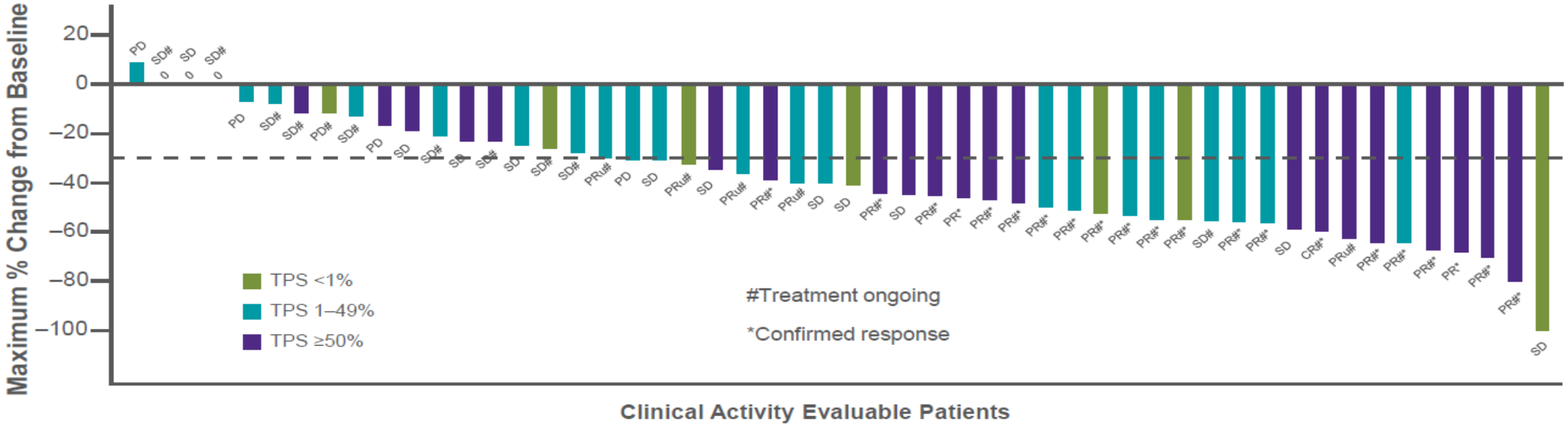
- **Conclusions**
  - In previously treated patients with locally advanced/unresectable or metastatic NSCLC, sotorasib demonstrated significant improvement in PFS compared with docetaxel and was generally well-tolerated
  - Sotorasib also demonstrated improvements in other outcomes over docetaxel, although there was no difference noted in OS, however, the study was not powered to detect a statistical difference

*Patients without baseline target lesions, post-baseline per cent change or NE were excluded

Johnson ML, et al. Ann Oncol 2022;33(suppl):Abstr LBA10

K-RAS G12C

Adagrasib + Pembrolizumab in Treatment-Naïve KRAS^{G12C}-mutated NSCLC: KRYSTAL-7 Best Tumor Change from Baseline



- Objective responses were observed in 49% (26/53)[a] of patients across all PD-L1 levels, with a disease control rate of 89% (47/53)
- Responses were observed in 59% (13/22)[a] of patients with PD-L1 TPS ≥50%, 48% (10/21)[a] with PD-L1 TPS 1–49%, and 30% (3/10)[a] with PD-L1 TPS <1%

Clinical activity evaluable population (n=53). One patient had only one post-baseline tumor assessment of PD due to new lesion; target lesions were not measured, therefore not included in the plot. Responses include target lesion tumor regression, as well as non-target lesion assessment
[a]Includes confirmed and unconfirmed CR/PR
Data as of 30 August, 2022. Median follow-up 3.5 months

Janne PA ; ESMO IO 2022

K-RAS G12C

Adagrasib + Pembrolizumab in Treatment-Naïve KRAS^{G12C}-mutated NSCLC: KRYSTAL-7 Treatment-Related Adverse Events

Most Frequent TRAEs	Concurrent 400 mg BID Adagrasib + Pembrolizumab (n=75)				
TRAEs, %	**Any grade**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Any TRAEs	83%	15%	24%	40%	4%[a]
Most frequent TRAEs[b], %					
Nausea	48%	24%	19%	5%	0%
Diarrhea	43%	33%	5%	4%	0%
Vomiting	24%	13%	9%	1%	0%
ALT increased	21%	7%	7%	8%	0%
AST increased	21%	7%	5%	9%	0%
Fatigue	21%	9%	8%	4%	0%
Decreased appetite	20%	11%	9%	0%	0%
Amylase increased	16%	5%	11%	0%	0%

- There were no Grade 5 TRAEs
- Median time to onset for ALT increase and AST increase was 26 and 37 days, respectively; only 1 patient experienced new onset treatment-related ALT/AST increase after 3 months
- TRAEs led to adagrasib dose reduction in 23/75 (31%) patients and to dose interruption in 31/75 (41%) patients
- TRAEs led to discontinuation of both drugs in 2/75 (3%) patients and only pembrolizumab in 2/75 (3%)[c] patients

[a]Gr 4 TRAEs comprised 1 case each of pneumonitis, neutropenia and pulmonary embolism. [b]Occurring in >15% of patients (any grade). Additional TRAEs of interest include 1 (1%) patient with Gr 1 blood bilirubin increased, 1 (1%) with Gr 2 pancreatitis, 2 (3%) with Gr 3 hepatitis, 8 (11%) with Gr 3 lipase increased, 2 (3%) with Gr 3–4 pneumonitis, and 2 (3%) with Gr 1–2 QT prolongation. [c]No patients discontinued only adagrasib due to a TRAE
Data as of 30 August, 2022. Median follow-up 3.5 months. Median duration of treatment 2.0 months

Janne PA ; ESMO IO 2022

Oncogene addicted advanced NSCLC

Standard:

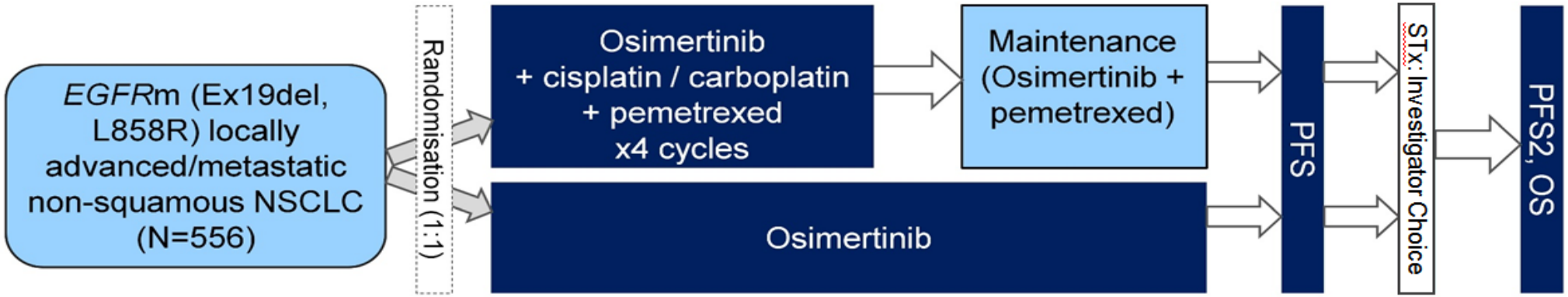
- Oncogene addicted advanced NSCLC (ALK,ROS1,BRAF,EGFR, NTRK) (18%): target therapies

EGFR COMMON MUTATIONS

Standard: Osimertinib→ CHT platinum based

Potenziamento della I linea

FLAURA2 Design: Chemotherapy + Osimertinib



- Osimertinib given at a dose of 80 mg QD during induction and maintenance
- The osimertinib dose can be reduced to 40 mg QD for management of AEs; chemotherapy dose interruption/reduction is to be prioritised over reduction/interruption of osimertinib
- Randomisation will be stratified by race, WHO PS (0 vs 1), and tissue *EGFR* mutation test at enrolment
- Planned to involve approximately 248 sites in 27 countries

Abbreviations: AE, adverse event; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PFS2, time from randomisation to second progression or death on a subsequent treatment; QD, once daily; STx, subsequent treatment; vs, versus; WHO, World Health Organization

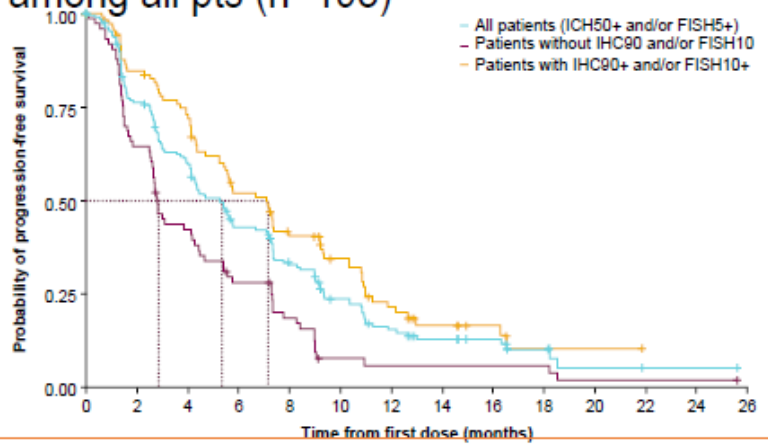
Ramalingam et al, presented at ESMO 2017, Ann Oncol (2017) 28 (suppl_5): v605-v649; Soria et al, N Engl J Med, 2018

Resistance mechanism in EGFRm NSCLC

Combining MET + EGFR TKIs in MET-positive pts

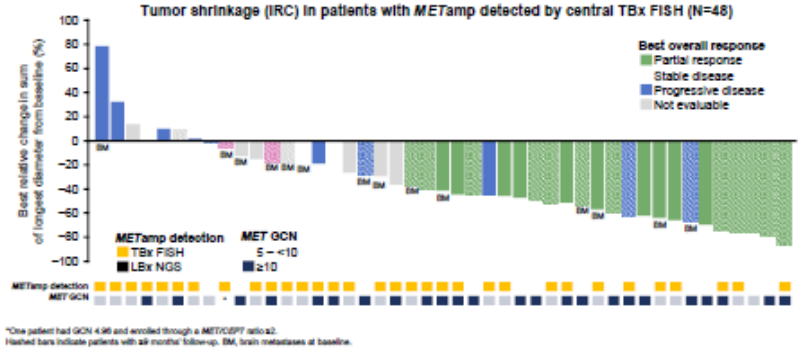
Osimertinib + Savolitinib (SAVANNAH)[1]

PFS among all pts (n=193)



	ORR	mPFS
IHC50+/FISH 5 (low cutoff; n= 193)	32%	5.3 mo
IHC90+/FISH 10 (high cutoff; n=108)	49%	7.1 mo

Osimertinib + Tepotinib (INSIGHT-2)[2]



*One patient had GCN 4.96 and enrolled through a MET/CEP7 ratio ≥2.
Hashed bars indicate patients with ≥8 months' follow-up. BM, brain metastases at baseline.

Tepotinib plus osimertinib (IRC)

	METamp by central TBx FISH		METamp by central LBx NGS	
Follow-up	≥8 months (N=22)	≥3 months (N=48)	≥8 months (N=16)	≥3 months (N=23)
ORR (95% CI)	54.5% (32.2, 75.6)	45.8% (31.4, 60.8)	50.0% (24.7, 75.3)	56.5% (34.5, 76.8)
BOR, n (%)				
PR	12 (54.5)	22 (45.8)	8 (50.0)	13 (56.5)
SD	2 (9.1)	5 (10.4)	1 (6.3)	1 (4.3)
PD	4 (18.2)	10 (20.8)	5 (31.3)	5 (21.7)
NE	4 (18.2)	11 (22.9)*	2 (12.5)	4 (17.4)

Similar ORRs were reported according to METamp GCN (TBx FISH):
Patients with ≥3 months' follow-up (N=48): ≥10 GCN: 51.9% (95% CI: 31.9, 71.3) (N=27); 5–9 GCN: 40.0% (95% CI: 19.1, 63.9) (N=20)†

Tepotinib monotherapy (IRC)

	METamp by central TBx FISH
Follow-up	≥8 months (N=12)
ORR (95% CI)	8.3% (0.2, 38.5)
BOR, n (%)	
PR	1 (8.3)
SD	2 (16.7)
PD	8 (66.7)
NE	1 (8.3)

Seven patients switched to tepotinib plus osimertinib and five of them are still on combination treatment

1. Ahn MJ, WCLC 2022; 2. Mazieres J, ESMO 2022

Resistance mechanism in EGFRm NSCLC

Targeting EGFR C797S Mutations

- Limited data for 1st gen EGFR TKIs
- "4th gen" EGFR TKIs with activity against C797S are now entering the clinic
  - BLU-945
  - BDTX-1535
  - THE-349
  - H002
  - BAY 2927088
  - JIN-A02
  - BBT-176
  - EAI045, and others

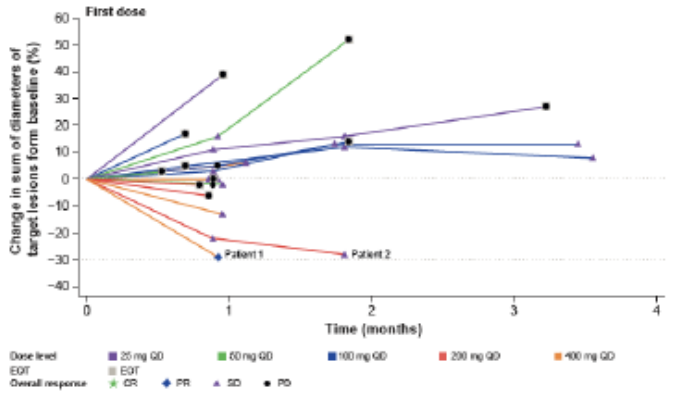
BLU945

	1G	3G	4G		Potential combinations	
EGFR mutational coverage[a]	Gefitinib	Osimertinib	BLU-701	BLU-945	BLU-701 + osimertinib	BLU-701 + BLU-945
L858R (LR)						
ex19del						
LR or ex19del / T790M						
LR or ex19del / C797S						
LR or ex19del / T790M / C797S						

[a]Based on biochemical IC_{50}.
1G, first generation; 3G, third generation; 4G, fourth generation; IC_{50}, half-maximal inhibitory concentration.

$IC_{50} \leq 10$ nM
10 nM < $IC_{50} \leq 50$ nM
$IC_{50} > 50$ nM

Figure 5: Dose-dependent tumor shrinkage with BLU-945 treatment[a,b]



Conti C, AACR 2021; Shum E, AACR 2021

ALK , ROS1

Standard ALK: alectinib→ lorlatinib→ CHT platinum based

Standard ROS1: Entrectinib → CHT platinum based

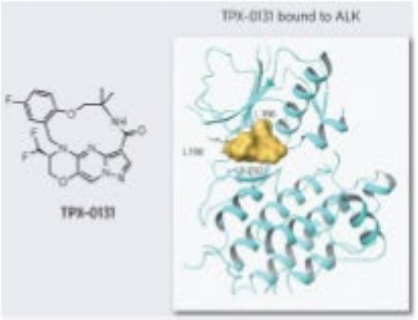
ALK

Overcoming ALK-Dependent Resistance to Lorlatinib: Novel 4th-Generation ALK TKIs

TPX-0131 (NCT04849273)

Ba/F3 EML4-ALK		TPX-0131	Crizotinib*	Alectinib*	Brigatinib*	Ceritinib*	Lorlatinib*
L1196M/L1198F	N=3	<0.2	252	2250	253	1410	1310
L1198F/C1156Y	N=3	<0.2	19.3	776	102	1310	140
G1202R/C1156Y	N=3	0.2	745	2420	810	1800	521
G1202R/L1196M	N=2	0.7	808	>10000	1100	1260	4780
G1202R/L1198F	N=3	<0.2	188	3000	2040	2010	1710
G1202R/G1269A	N=3	9.9	705	7200	164	303	636
G1202R/G1269A/L1204V	N=3	14.9	634	6740	176	345	673
G1202R/G1269A/L1198F	N=3	0.2	596	>10000	907	1670	6330

* Proxy reagents purchased from commercial sources



Cui JJ et al., AACR 2020; Brion WM et al., Mol Cancer Ther 2021

NVL-655 (NCT05384626)

	Cell with ALK fusion	NUV-655	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
No kinase domain mutations	NCI-H2228 (EML4-ALK v3)	0.70	90	55	13	13	< 1.1
	NCI-H3122 (EML4-ALK v1)	2.0	180	48	22	22	3.5
	Wild-type	1.6	270	90	25	42	4.2
G1202R+ mutations	G1202R	< 0.73	950	570	1600	400	120
	G1202R/L1196M	7.0	1500	1400	2200	820	3900
	G1202R/G1269A	3.0	1100	350	1300	240	970
	G1202R/L1198F	2.0	170	1300	2200	470	720

Slide courtesy of Jessica Lin, MD

Pelish HE et al., AACR 2021

2°Gen ROS1 TKI inhibitors

Compound	# of pts	ORR	PFS	CNS activity	Activity in pts with baselin G2032R	Common AEs
Repotrectinib	56	38% (only 1 prior TKI +_no chemo)	NR	42% (5/12) with measurable CNS	59% (10/17)	Dizziness, dysgeusia, constipation, paresthesia
Taletrectinib	38 (China)	50% (prior crizotinib)	NR	92% (11/12) with CNS mets (TKI naïve+ crizotinib pre-treated)	80% (4/5)	Diarrhea, nausea, vomiting, ALT/AST increase
NVL-520	21	48% 53% (9/17) ≥2 prior ROS1 TKI + ≥1 chemo 50% (9/18) with prior lorlatinib or repotrectinib	NR	Cases of CNS response reported	78% (7/9)	No DLTs or TR-SAEs or dizziness reported

Cho BC et al, AACR-NCI-EORTC 2022. Li W et al. ASCO 2022. Drilon A et al, EORTC-NCI-AACR 2022.

NTRK

Standard: entrectinib /larotrectinib→ CHT platinum based +/- IO

Next Gen NTRK TKI inhibitors

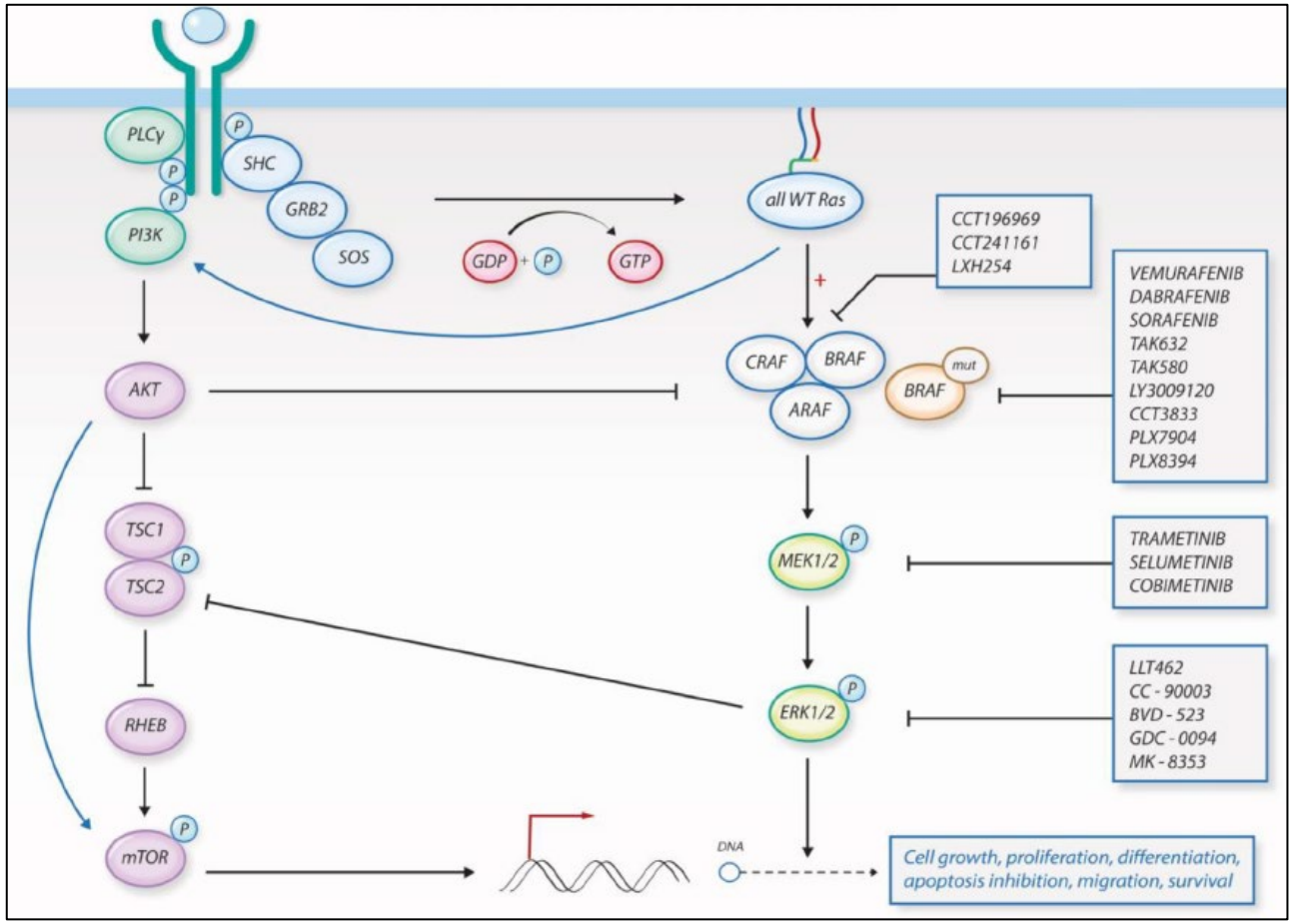
Study	Phase	Drug	Pt population
NCT03215511	I/II	selitrectinib	Children and adults with advanced NTRK fusion + solid tumor with prior TRK inhibitor, no satisfactory treatment option
NCT03093116 (TRIDENT-1)	I/II	repotrectinib	Pts ≥12 yo with advanced solid tumor with NTRK, ROS1 or ALK
NCT04094610	I/II	repotrectinib	Children and young adults with advanced malignancies with NTRK, ROS1 or ALK
NCT04617054	II	taletrectinib	Children and young adults with advanced malignancies with NTRK fusion, no prior TKI

Patel JD., TTLC 2023

BRAF V600E

Standard: dabrafenib + trametinib → CHT platinum based +/- IO

BRAF mutations in NSCLC



Demographics

- Exclusive from EGFR, ALK & ROS1
- Up to 5% in adenocarcinomas
- Worse outcomes
- V600E: Reduced platinum sensitivity

BRAF Point Mutations

- 50% V600E
- 50% other V600 and non-V600

- V600E: non-mucinous adk with micropapillary growth pattern and high TTF-1 expression (more in never/light smokers)
- Non-V600E: various morphologies, including mucinous component

Leonetti et al., Cancer Treat Rev (2018); 66:82-94

BRAF V600E NSCLC

	Previously Treated				Treatment Naive
	VE-Basket trial **vemurafenib** (n=20)	AcSé trial **vemurafenib** (n=100)	BRF113928 **dabrafenib** (n = 78)	BRF113928 **Dabrafenib Plus Trametinib** (n = 57)	BRF113928 **Dabrafenib Plus Trametinib** (n = 36)
Male	14 (70%)	-	39 (50%)	29 (51%)	14 (39%)
Never smoker	7 (35%)	-	29 (37%)	16 (28%)	10 (28%)
ORR % (95% CI)	42 (20-67)	44.9	33 (23–45)	67 (53–79)	64 (46-79)
PFS, median (95% CI)	**7.3** (3.5-10.8)	**5.2**	**5.5** (3.4–7.3)	**10.2** (6.9–16.7)	**10.9** (7.0-16.6)
OS, median (95% CI)	NA	9.3	12.7 (7.3–16.3)	18.2 (14.3–NE)	24.6 (12.3-NE)

Courtesy of S. Gadgeel

PHAROS study: efficacy and safety results

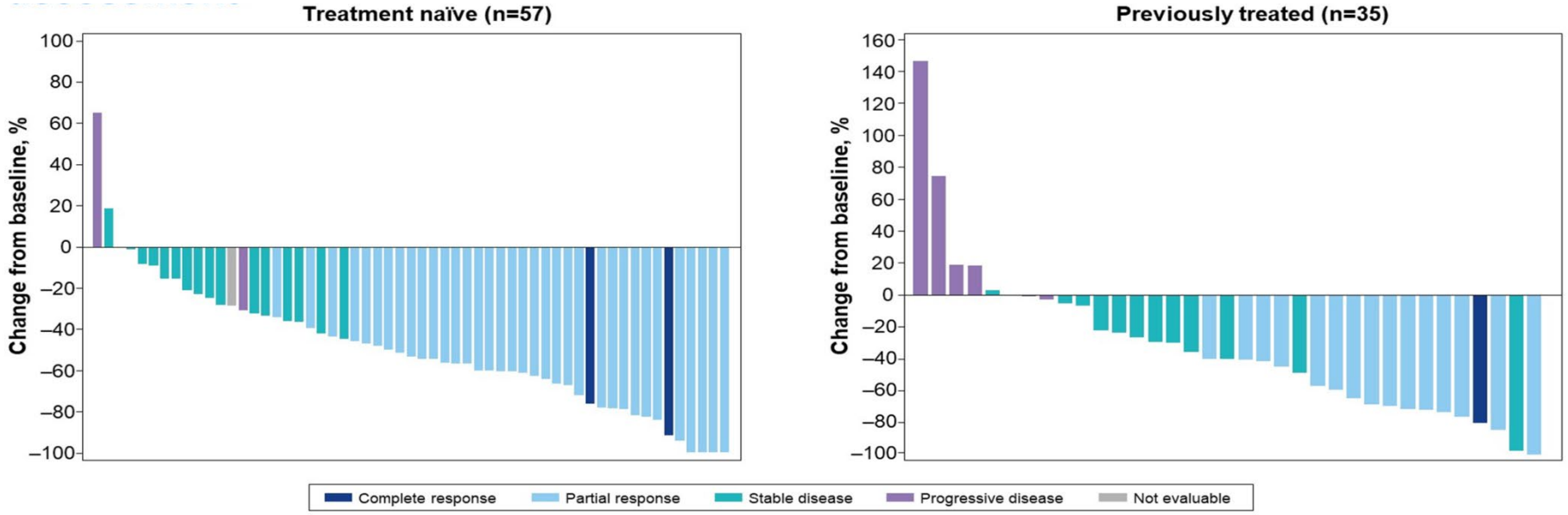
Antitumor activity endpoints by IRR

	Treatment naïve (n=59)	Previously treated (n=39)
Objective response rate (95% CI), %[a]	75 (62, 85)	46 (30, 63)
Complete response	9 (15)	4 (10)
Partial response	35 (59)	14 (36)
Stable disease	10 (17)	13 (33)
Progressive disease	2 (3)	3 (8)
Disease control rate at 24 weeks (95% CI), %	64 (51, 76)	41 (26, 58)
Duration of response, median (95% CI), months	NE (23.1, NE)	16.7 (7.4, NE)
Duration of response ≥12 months, n/N (%)	26/44 (59)	6/18 (33)
Time to response, median (range), months	1.9 (1.1-19.1)	1.7 (1.2-7.3)

Encorafenib plus binimetinib in metastatic BRAF-V600E mutant NSCLC
Incidence of TRAEs of any grade >10% in all patients

	Overall (N=98)		
	Any grade	Grade 3	Grade 4
Any TRAEs, n (%)[a]	92 (94)	37 (38)	3 (3)[b]
Nausea	49 (50)	3 (3)	0
Diarrhea	42 (43)	4 (4)	0
Fatigue	31 (32)	2 (2)	0
Vomiting	28 (29)	1 (1)	0
Anemia	18 (18)	3 (3)	0
Vision blurred	17 (17)	1 (1)	0
Constipation	13 (13)	0	0
ALT increased	12 (12)	5 (5)	0
AST increased	12 (12)	7 (7)	0
Pruritus	12 (12)	0	0
Blood creatine phosphokinase increased	11 (11)	0	0
Edema peripheral	11 (11)	0	0

Note: Any-grade abdominal pain, alopecia, asthenia, and dry skin occurred in 10% of patients; any-grade pyrexia occurred in 8% of patients.
ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **TRAE**, treatment-related adverse event.
[a]One patient died due to intracranial hemorrhage, which was assessed as treatment related by the investigator. [b]Grade 4 TRAEs were colitis, disseminated intravascular coagulation, increased γ-glutamyl transferase, and hyponatremia.

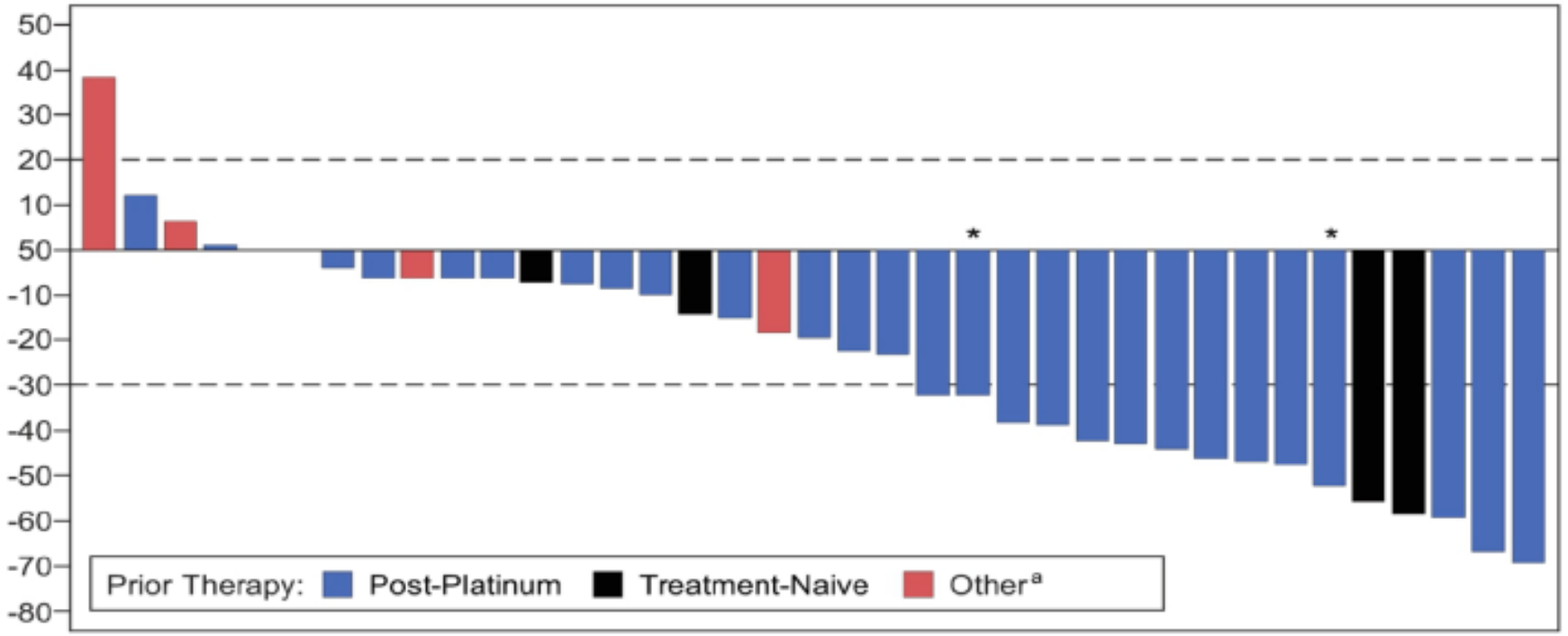


EGFR EX 20 INSERTION

Standard: CHT platinum based +/- IO→ EAP target therapy

EGFR EX 20 INSERTION

Amivantimab: Anti-EGFR-MET Bispecific Ab and Exon20ins in NSCLC



Paik ASCO 20

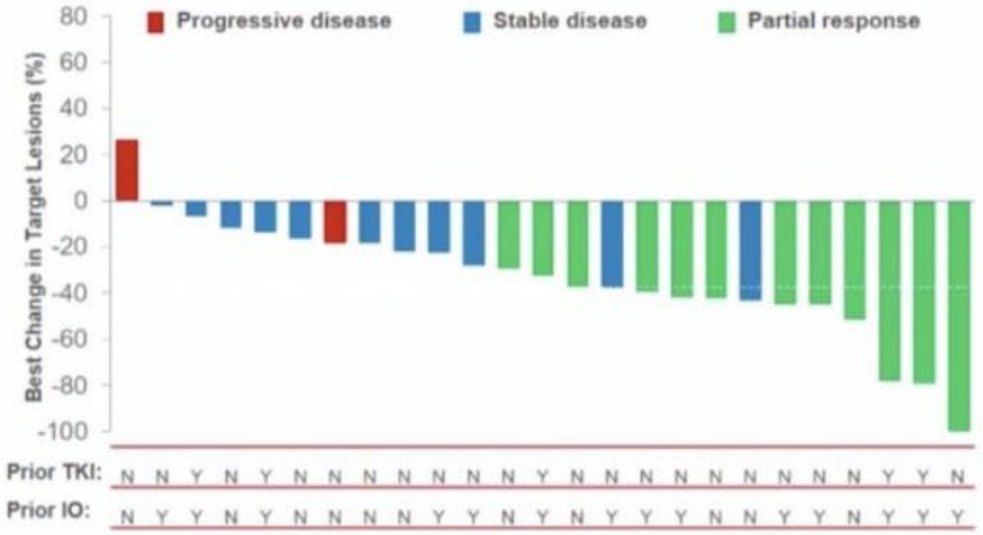
RR 36%

Median PFS 8.3 MO

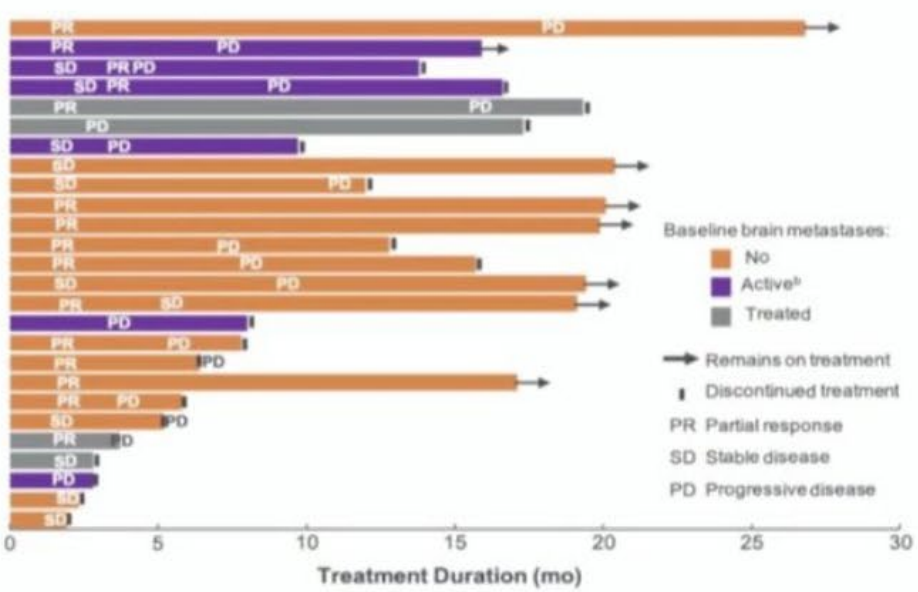
EGFR EX 20 INSERTION

Response to Mobocertinib in Patients With *EGFR* Exon 20 Insertions Treated at 160 mg qd (n=28)[a]

Antitumor Activity



Overall Response and Time on Treatment



IO, immuno-oncology therapy; TKI, tyrosine kinase inhibitor
[a] Two patients had no postbaseline assessment and are not included in figures
[b] Active brain metastases were either never treated or progressed after radiation

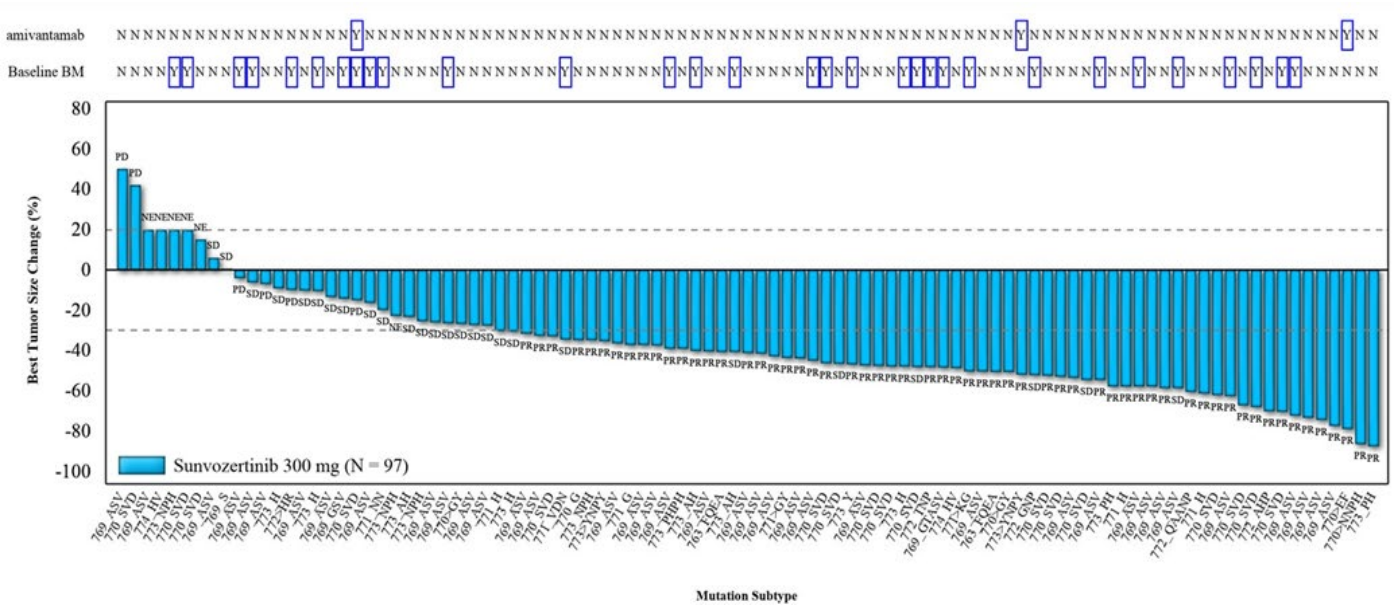
- **Mobocertinib at recommended phase 2 dose (160 mg qd) showed antitumor activity in patients with *EGFR* exon 20 insertion mutations**
  - **43% confirmed objective response rate (n=12/28) with 13.9-month median duration of response and 7.3-month median progression-free survival in all patients, including those with baseline central nervous system metastases**

Presented at the ESMO 2020 Virtual Annual Meeting, September 19-21, 2020

7

EGFR EX 20 INSERTION

SUNVOZERTINIB



Common TEAE by PT	N = 104 All Grade	N = 104 ≥ Grade 3
Diarrhea	70（67.3）	8（7.7）
Blood CPK increase	60（57.7）	18（17.3）
Rash	56（53.8）	1（1.0）
Anemia	51（49.0）	6（5.8）
Blood creatinine increase	39（37.5）	0（0.0）
Paronychia	34（32.7）	2（1.9）
Body weight decrease	30（28.8）	1（1.0）
White blood cell decrease	27（26.0）	0（0.0）
Lipase increase	27（26.0）	2（1.9）
Vomiting	25（24.0）	1（1.0）
Decreased appetite	25（24.0）	2（1.9）
Mouth ulceration	24（23.1）	0（0.0）

M Wang; ASCO 2023

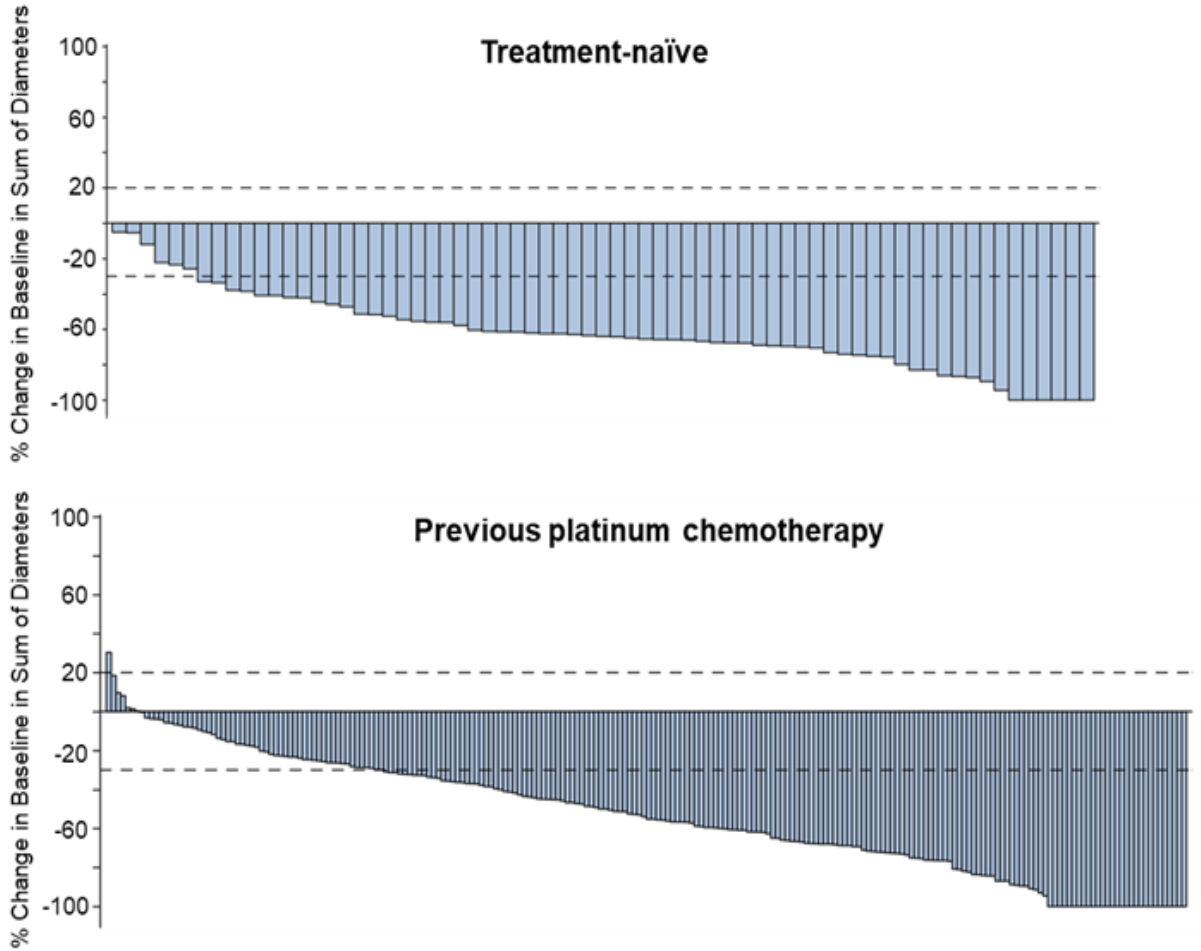
RET

Standard: CHT platinum based +/- IO→ Selpercatinib or Pralsetinib

Selpercatinib Efficacy

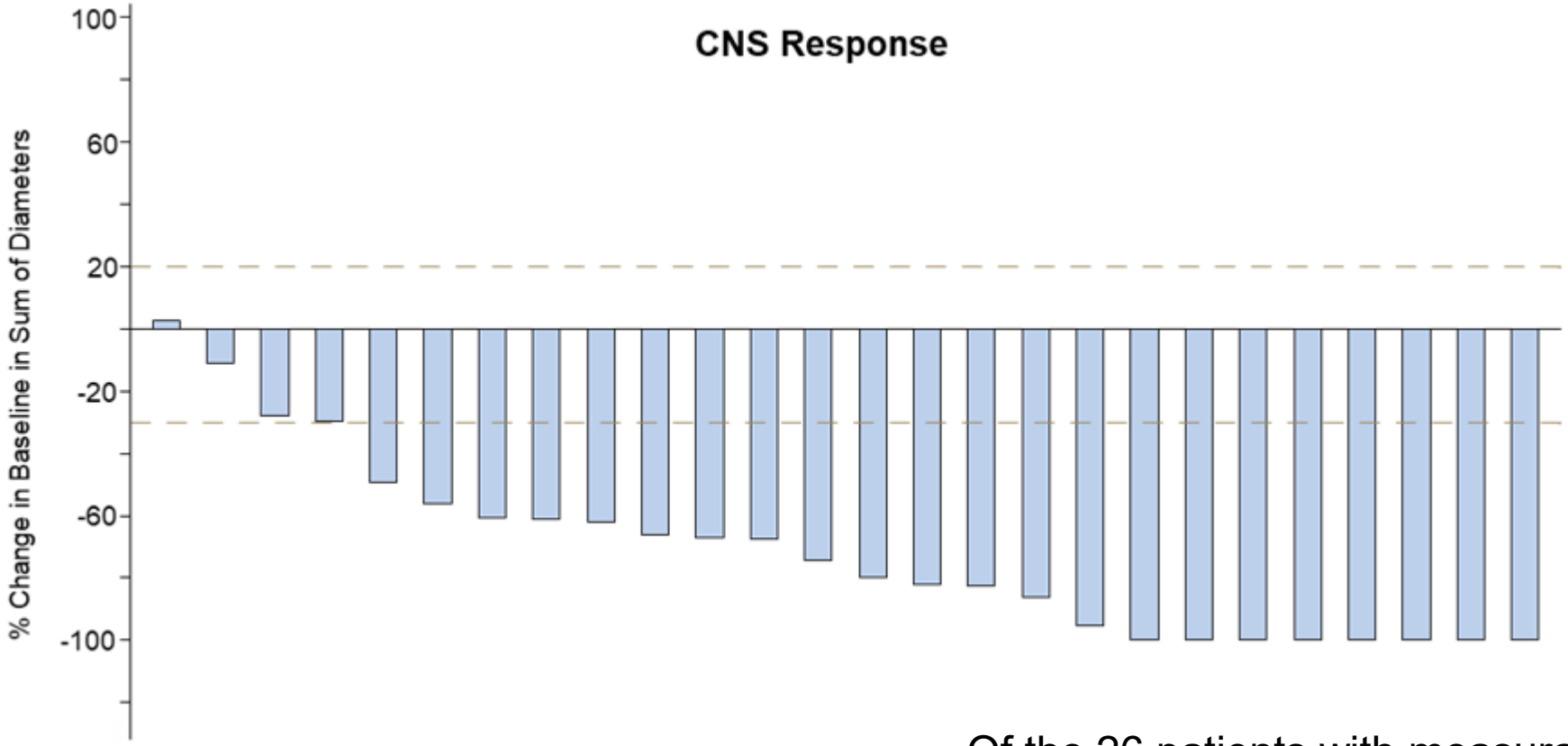
Response	Treatment-naïve (N=69)	Previous platinum chemotherapy (N=247)
Objective response by IRC—% (95% CI)	84.1 (73.3, 91.8)	61.1 (54.7, 67.2)
Duration of response		
Median —mo (95% CI)	20.2 (13.0, NE)	28.6 (20.4, NE)
Censoring rate (%)	55.2	60.9
1-yr DoR—% (95% CI)	66.1 (51.6, 77.3)	73.1 (64.9, 79.7)
2-yr DoR—% (95% CI)	41.6 (25.6, 56.8)	55.8 (46.4, 64.2)
Median duration of follow-up—mo	20.3	21.2
Progression-free survival		
Median —mo (95% CI)	22.0 (13.8, NE)	24.9 (19.3, NE)
Censoring rate— n (%)	37 (53.6)	138 (55.9)
1-yr PFS — % (95% CI)	70.6 (57.8, 80.2)	70.5 (64.1, 76.0)
2-yr PFS — % (95% CI)	41.6 (26.8, 55.8)	51.4 (44.3, 58.1)
Median duration of follow-up—mo	21.9	24.7
Overall survival		
Patients with censored data—n (%)	49 (71.0)	169 (68.4)
1-yr OS —% (95% CI)	92.7 (83.3, 96.9)	87.9 (83.0, 91.4)
2-yr OS —% (95% CI)	69.3 (55.2, 79.7)	68.9 (62.2, 74.7)
3-yr OS —% (95% CI)	57.1 (35.9, 73.6)	58.5 (49.7, 66.3)
Median duration of follow-up —mo	25.2	26.4

Note: ORR was consistent regardless of prior therapy or ethnicity (data not shown)



Drillon ELCC 2022

Selpercatinib CNS Response



Of the 26 patients with measurable CNS disease, 22 had a confirmed best response of CR or PR

Drillon ELCC 2022

Selpercatinib Adverse Events

	Any Causality		Related to Treatment	
N=356, n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥1 AE	356 (100.0)	263 (73.9)	341 (95.8)	143 (40.2)
Edema	178 (50.0)	2 (0.6)	124 (34.8)	2 (0.6)
Diarrhea	184 (51.7)	15 (4.2)	114 (32.0)	8 (2.2)
Fatigue	153 (43.0)	8 (2.2)	78 (21.9)	3 (0.8)
Dry Mouth	163 (45.8)	0	151 (42.4)	0
Hypertension (AESI)	141 (39.6)	68 (19.1)	95 (26.7)	49 (13.8)
AST increased	149 (41.9)	37 (10.4)	122 (34.3)	24 (6.7)
ALT increased	147 (41.3)	53 (14.9)	120 (33.7)	41 (11.5)
Abdominal pain	101 (28.4)	5 (1.4)	28 (7.9)	1 (0.3)
Constipation	96 (27.0)	5 (1.4)	34 (9.6)	2 (0.6)
Rash	130 (36.5)	4 (1.1)	83 (23.3)	4 (1.1)
Nausea	112 (31.5)	4 (1.1)	40 (11.2)	2 (0.6)
Blood creatinine increased	92 (25.8)	10 (2.8)	50 (14.0)	1 (0.3)
Headache	94 (26.4)	3 (0.8)	23 (6.5)	0
Cough	87 (24.4)	0	9 (2.5)	0
Dyspnea	84 (23.6)	16 (4.5)	10 (2.8)	0
Vomiting	78 (21.9)	4 (1.1)	19 (5.3)	2 (0.6)
ECG QT prolongation (AESI)	74 (20.8)	21 (5.9)	57 (16.0)	14 (3.9)
Thrombocytopenia	74 (20.8)	20 (5.9)	52 (14.6)	13 (3.7)
Decreased appetite	73 (20.5)	1 (0.3)	34 (9.6)	0
Pyrexia	79 (22.2)	1 (0.3)	21 (5.9)	1 (0.3)
Urinary tract infection	70 (19.7)	8 (2.2)	2 (0.6)	0

- Of the 34 (9.6%) patients who discontinued due to AE, 11 (3.1%) were deemed related to study treatment per the investigator
- No grade 5 TRAEs were observed

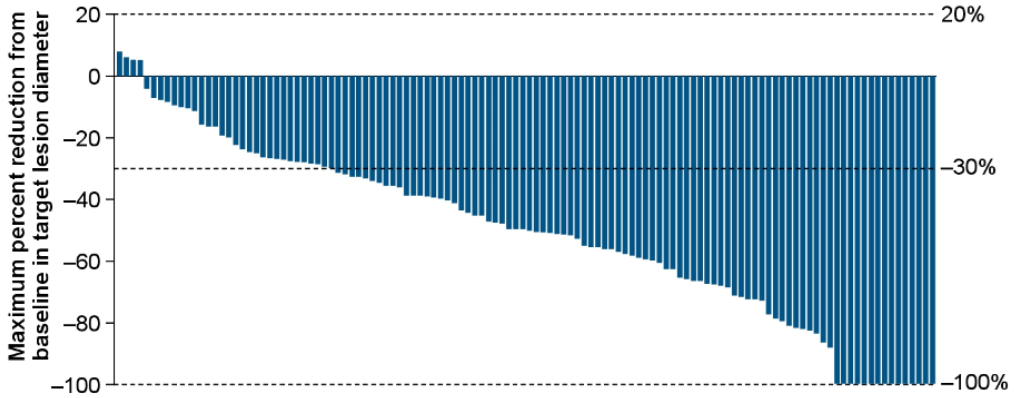
Drillon ELCC 2022

Pralsetinib Efficacy

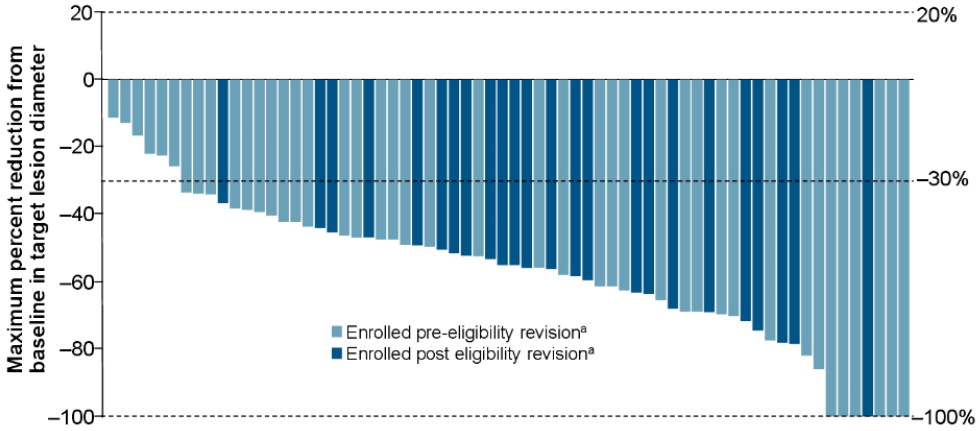
	Measurable disease population					
	RET fusion–positive NSCLC (n=216)	Treatment-naïve			Prior treatment	
		All (n=68)	Pre-eligibility revision (n=43)[a]	Post eligibility revision (n=25)[a]	Prior platinum (n=126)	Prior non-platinum (n=22)
ORR, % (95% CI)	**69 (62–75)**	**79 (68–88)**	**74 (59–87)**	**88 (69–98)**	**62 (53–70)**	**73 (50–89)**
Best overall response, n (%)						
CR	9 (4)	4 (6)	4 (9)	0	5 (4)	0
PR	139 (64)	50 (74)	28 (65)	22 (88)	73 (58)	16 (73)
SD	50 (23)	9 (13)	7 (16)	2 (8)	37 (29)	4 (18)
PD	10 (5)	3 (4)	3 (7)	0	5 (4)	2 (9)
NE	8 (4)	2 (3)	1 (2)	1 (4)	6 (5)	0
DCR, % (95% CI)[b]	92 (87–95)	93 (84–98)	91 (78–97)	96 (80–100)	91 (85–96)	91 (71–99)
CBR, % (95% CI)[c]	77 (71–82)	82 (71–91)	79 (64–90)	88 (69–98)	74 (65–81)	77 (55–92)
mDOR, mo (95% CI)	22.3 (15.1–NR)	NR (9.0–NR)	11.0 (7.4–NR)	NR (NR–NR)	22.3 (15.1–NR)	NR (9.2–NR)
mPFS, mo (95% CI)[d]	16.4 (11.0–24.1) n=233	13.0 (9.1–NR) n=75	10.9 (7.7–NR) n=47	NR (NR–NR) n=28	16.5 (10.5–24.1) n=136	12.8 (9.1–NR) n=22

[a]Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naïve patients eligible for standard platinum-based therapy who had previously not been permitted. [b]Confirmed CR or PR or SD. [c]CR or PR or SD of ≥16 weeks. [d]Evaluated in all patients with *RET* fusion–positive NSCLC who initiated 400 mg QD pralsetinib by May 22, 2020.
CI, confidence interval; mDOR, median duration of response; mo, month; mPFS, median progression-free survival; NE, not evaluable; NR, not reached; PD, progressive disease.

Tumor shrinkage in patients with prior platinum-based chemotherapy



Tumor shrinkage in treatment-naïve patients



[a]Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naïve patients eligible for standard platinum-based therapy who had previously not been permitted.

Curigliano et al. Poster 9089. Presented at ASCO, 4–8 June 2021, Virtual

Pralsetinib CNS activity

	All (n=15)
CNS ORR, % (95% CI)	53.3 (26.6–78.7)
Complete response, n (%)	3 (20.0)
Partial response, n (%)	5 (33.3)
Median DOR, months (95% CI)[a]	n=8 11.5 (9.2–NR)
Median follow-up (95% CI)	29.7 (24.1–35.3)

Of the 15 patients, 14 had prior platinum treatment and one was treatment naïve

Besse B, et al. ESMO 2022 (Abs 1170P)

Pralsetinib Safety

n=281, n (%)	Any causality		Treatment related	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with any AE	280 (99.6)	231 (82.2)	265 (94.3)	176 (62.6)
Anaemia	151 (53.7)	65 (23.1)	119 (42.3)	55 (19.6)
AST increased	137 (48.8)	18 (6.4)	125 (44.5)	11 (3.9)
Constipation	125 (44.5)	2 (<1)	76 (27.0)	2 (<1)
Hypertension	103 (36.7)	50 (17.8)	75 (26.7)	39 (13.9)
ALT increased	101 (35.9)	13 (4.6)	92 (32.7)	9 (3.2)
Neutrophil count decreased	88 (31.3)	40 (14.2)	87 (31.0)	37 (13.2)
Diarrhoea	84 (29.9)	7 (2.5)	50 (17.8)	3 (1.1)
Cough	81 (28.8)	1 (<1)	15 (5.3)	1 (<1)
Pyrexia	81 (28.8)	2 (<1)	22 (7.8)	0
White blood cell count decreased	77 (27.4)	16 (5.7)	74 (26.3)	15 (5.3)
Fatigue	75 (26.7)	6 (2.1)	46 (16.4)	5 (1.8)
Blood creatinine increased	70 (24.9)	2 (<1)	48 (17.1)	1 (<1)
Neutropenia	64 (22.8)	30 (10.7)	60 (21.4)	26 (9.3)
Dyspnoea	62 (22.1)	8 (2.8)	5 (1.8)	1 (<1)
Pneumonia	56 (19.9)	36 (12.8)	18 (6.4)	12 (4.3)

Overall, 10% of patients discontinued pralsetinib due to treatment-related adverse events

Besse B, et al. ESMO 2022 (Abs 1170P)

Next Gen RET TKI inhibitors

Drugs	Clinical trials (NCT#)
LOXO-260	phase I/II trial (NCT05241834) expanded access trial (NCT05225259)
HM06/TAS0953	phase I/II margaRET trial (NCT04683250)
TPX-0046	phase I/II SWORD-1 trial (NCT04161391)
APS03118	phase I/II trial (NCT05653869)
EP0031-101/A400	phase I/II trial (NCT05443126) phase I/II trial, China

Solomon et al, JTO 2020.
Drilon A, TTLC 2023

MET

Standard: IO or CHT platinum based +/- IO→ EAP target therapy

MET

	Non-Selective	Selective TKI							
	CRIZOTINIB PROFILE 1001	CAPMATINIB GEOMETRY Mono-1		TEPOTINIB VISION (A+C) (TBx)		SAVOLITINIB		GLUMETINIB GLORY	
IC_{50} (nM)	26,5	0.6		3.0		2.1		0.42	
Dose	250 mg BID	400 mg BID		500 mg QD		400-600 mg QD		300 mg QD	
Line	≥1	1	≥2	1	≥2	1	≥2	1	≥2
N	69	60	100	111	97	28	42	42	27
RR (%)	32	68.3	44	56.8	49.5	46.4	40.5	66.7	51.9
DoR (mo.)	9.1	16.6	9.7	46.4	10.2	5.6	9.7	NE	5.1
PFS (mo.)	7.3	12.4	5.4	15.3	11.5	6.9	6.9	NE	5.7
OS (mo.)	20.5	25.5	13.6	25.9	20.4	10.9	19.4	NR	NR
Comments	Shorter PFS in ctDNA positive at baseline	Higher activity in 1st line *vs.* ≥2nd line		The RR regardless Age, line & type of previous therapy		Sarcom. *vs.* others RR: 40% *vs.* 44% PFS: 5.5 *vs.* 6.9			
		2022	2022 (2nd)	2021	2021 (2nd)	2021			

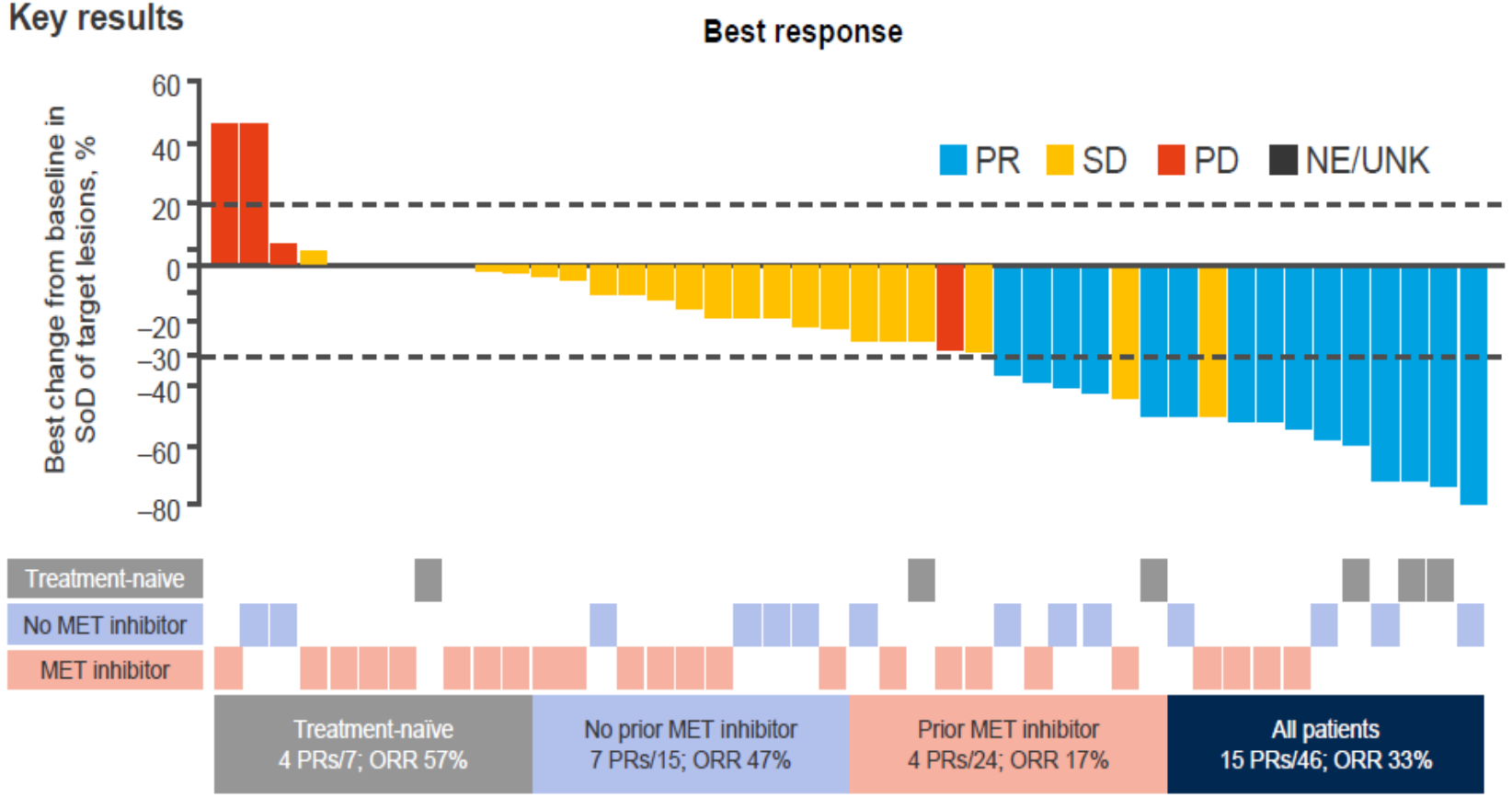
ıon Slide

Drilon –Nature Med 2020 * Wolf –ELCC 2022 * Wolf – ASCO 2021 * Thomas – WCLC 2022 * Lu – Lancet Resp Med 2021 * Lu – ELCC 2022 * Lu – AACR 2022

MET

9008: Amivantamab in patients with NSCLC with MET exon 14 skipping mutation: Updated results from the CHRYSALIS study – Krebs M, et al

- Key results



Krebs M, et al. J Clin Oncol 2022;40(suppl):Abstr 9008

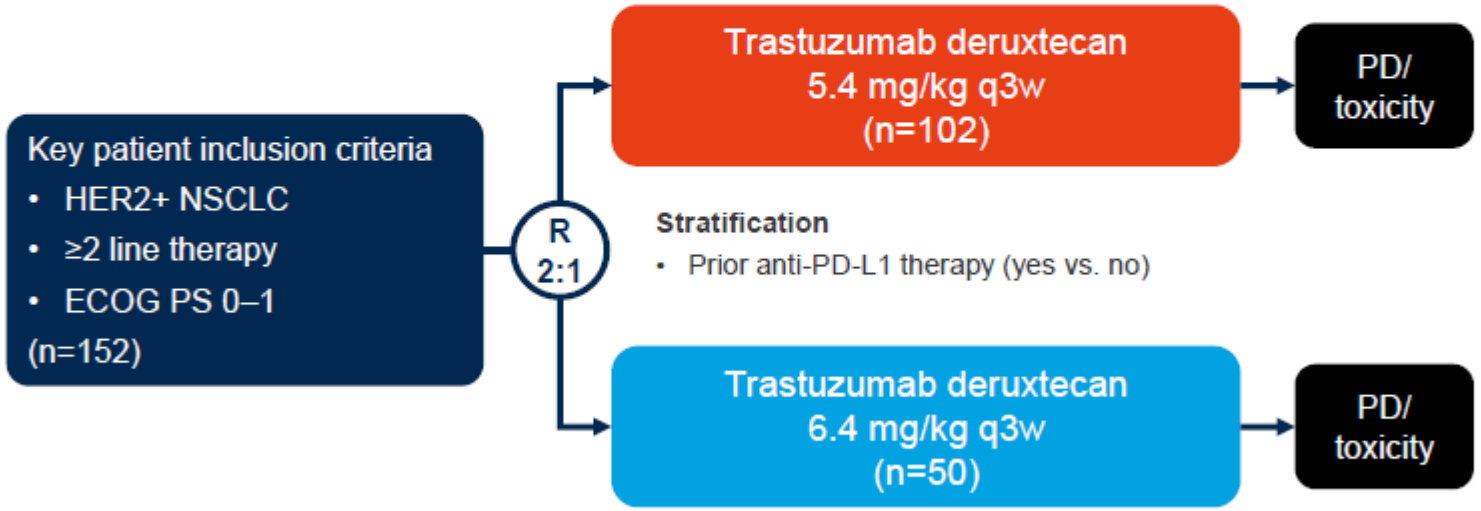
HER 2

Standard: CHT platinum based +/- IO→ EAP target therapy

HER 2

LBA55: Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-mutant metastatic non–small cell lung cancer (NSCLC): Interim results from the phase 2 DESTINY-Lung02 trial – Goto K, et al

- **Study objective**
  - To evaluate the efficacy and safety of two doses of trastuzumab deruxtecan in previously treated patients with advanced HER2-mutated NSCLC in the phase 2 DESTINY-Lung02 study



Primary endpoint
- ORR (BICR)

Secondary endpoints
- OS, PROs, PK, safety

Goto K, et al. Ann Oncol 2022;33(suppl):Abstr LBA55

HER2

- **Key results**

Response assessment by BIRC in the pre-specified early cohort

	Trastuzumab deruxtecan 5.4 mg/kg (n=52)	Trastuzumab deruxtecan 6.4 mg/kg (n=28)
Confirmed ORR, n (%) [95%CI]	28 (53.8) [39.5, 67.8]	12 (42.9) [24.5, 62.8]
BOR, n (%)		
CR	1 (1.9)	1 (3.6)
PR	27 (51.9)	11 (39.3)
SD	19 (36.5)	14 (50.0)
PD	2 (3.8)	1 (3.6)
NE	3 (5.8)	1 (3.6)
DCR, n (%) [95%CI]	47 (90.4) [79.0, 96.8]	26 (92.9) [76.5, 99.1]
mDoR, mo (95%CI)	NE (4.2, NE)	5.9 (2.8, NE)
Median time to initial response, mo (range)	1.4 (1.2–5.8)	1.4 (1.2–3.0)
Median follow-up, mo (range)	5.6 (1.1–11.7)	5.4 (0.6–12.1)

- Trastuzumab deruxtecan 5.4 mg/kg did not reach mDoR at the time of cut-off, therefore, an additional 90-day follow-up was conducted and the ORR (confirmed by BIRC) was 57.7 (95%CI 43.2, 71.3)

Goto K, et al. Ann Oncol 2022;33(suppl):Abstr LBA55

HER2

TRAEs, %	Trastuzumab deruxtecan 5.4 mg/kg (n=101)	Trastuzumab deruxtecan 6.4 mg/kg (n=50)
Any grade	92.1	100
Grade ≥3	31.7	58.0
Led to drug discontinuation	7.9	16.0
Led to drug reduction	9.9	26.0
Led to drug interruption	13.9	30.0
Leading to death	1.0	2.0

Adjudicated drug-related ILD, n (%)	Trastuzumab deruxtecan 5.4 mg/kg (n=101)	Trastuzumab deruxtecan 6.4 mg/kg (n=50)
Any grade	6 (5.9)	7 (14.0)
Grade 1	3(3.0)	1 (2.0)
Grade 2	2 (2.0)	6 (12.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	0	0
Cases resolved, n (%)	3 (50.0)	1 (14.3)
Median time to onset, days (range)	67.5 (40–207)	41.0 (36–208)

- **Conclusions**
  - In previously treated patients with advanced HER2-mutated NSCLC, trastuzumab deruxtecan 5.4 mg/kg demonstrated clinically meaningful activity, which was similar to 6.4 mg/kg, and had a favourable safety profile over the higher dose

Goto K, et al. Ann Oncol 2022;33(suppl):Abstr LBA55