Global Lung Cancer Academy

Global Lung Cancer Academy

Sharing Best Practices to Optimize Patient Care

14 November 2022

Sponsor: Sanofi Oncology & Regeneron

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Global Lung Cancer Academy

Welcome and Meeting Overview

Corey Langer, MD, FACP

Meet the faculty

CO-CHAIRS

Corey J. Langer, MD, FACP
University of Pennsylvania, PA, USA

Solange Peters, MD
University Hospital of Lausanne
Lausanne, Switzerland

FACULTY

Benjamin Besse, MD, PhD
Institute Gustave Roussy
Villejuif, France

Federico Cappuzzo, MD, PhD
AUSL della Romagna
Ravenna, Italy

Anne-Marie Dingemans, MD, PhD
Erasmus Medical Center
Rotterdam, the Netherlands

Enriqueta Felip, MD, PhD
Vall d'Hebron University Hospital
Barcelona, Spain

Umberto Malapelle, PhD
University of Naples Federico II
Naples, Italy

Luis Paz-Ares, MD, PhD
University Hospital October 12
Madrid, Spain

Johan Vansteenkiste, MD, PhD
University Hospital KU Leuven
Leuven, Belgium

Objectives of the program

- Discuss current evidence-based practices in the diagnosis and treatment of lung cancer
- Learn about current genomic testing practices and how these results inform treatment decisions
- Understand advances made in immunotherapy for lung cancer and how these agents are being used in clinical practice
- Gain insights into the latest developments in targeted therapies used for lung cancer
- Promote best practice cancer care via the review of clinical patient cases
- Recognize the major clinical trials underway to further develop treatment in lung cancer
- Learn about the regional challenges and differences in lung cancer treatment patterns in Europe

Day 2: Plenary Sessions

Monday, 14 November 2022 from 16.00 – 19.15 CET

Time	Title	Speaker
16.00 – 16.10 (10 min)	**Session Open** • ARS questions	Corey Langer
16.10 – 16.30 (20 min)	**Optimizing First-Line Therapy in NSCLC – Integration of Immunotherapy Into Frontline Regimens** • Optimal use of immunotherapeutic treatment choices in frontline NSCLC	Luis Paz-Ares
16.30 – 16.50 (20 min)	**Current Immunotherapy Options for Relapsed NSCLC** • Optimal use of immunotherapeutic treatment choices in relapsed NSCLC including considerations for potential rechallenge, and treatment selection mono vs combination therapy	Benjamin Besse
16.50 – 17.25 (35 min)	**Tumor Board Discussion** • Case 1 (10 min) • Case 2 (10 min) • Discussion & Q&A (15 min)	Moderator: Solange Peters Francesca Fusco Luis Angel Leon Mateos All faculty
17.25 – 17.35 (10 min)	***Break***	
17.35 – 17.50 (15 min)	**ALK Inhibitors in NSCLC** • Considerations for optimal use in clinical practice in patients with and without brain metastasis	Enriqueta Felip
17.50 – 18.05 (15 min)	**EGFR Inhibitors in NSCLC** • Considerations for optimal use in clinical practice	Johan Vansteenkiste
18.05 – 18.30 (25 min)	**Other Targets in NSCLC** • Considerations for optimal use of ROS1, NTRK, RET and MET inhibitors in clinical practice	Anne-Marie Dingemans
18.30 – 19.05 (35 min)	**Tumor Board Discussion** • Case 1 (10 min) • Case 2 (10 min) • Discussion & Q&A (15 min)	Moderator: Corey Langer May-Lucie Meyer Xander Verbeke All faculty
19.05 – 19.15 (10 min)	**Session Close** • ARS questions	Solange Peters

Question 1

In which country do you currently practice?

1. Austria
2. France
3. Germany
4. Italy
5. Poland
6. Spain
7. The Netherlands
8. United Kingdom
9. Other country in Europe
10. Outside Europe

Question 2

How would you describe your specialty?

1. General oncologist
2. Lung oncologist
3. General internal medicine
4. Pulmonologist
5. Fellow
6. Other

Question 3

Do you continue immunotherapy after progression in metastatic NSCLC?

1. No, I stop
2. Yes, I continue with the same drug
3. Yes, but I would consider switching to another immunotherapy
4. This completely depends on the situation
5. Other

Question 4

56-year-old male, heavy former tobacco enthusiast (50 pk/yr) presents with cough and pleuritic chest pain. CXR shows L pleural effusion and L hilar mass, confirmed on CT, which also discloses mediastinal LAD and a L adrenal mass measuring 3 cm. Pleural fluid cytology demonstrates adenocarcinoma, TTF1 positive. Cell block is sufficient for NGS testing; this proves positive for *KRAS* G12C mutation. PD-L1 is positive but at low level (10%). Brain MRI proves negative. Patient is treated with the KN-189 regimen (combination pemetrexed, carboplatin, and pembrolizumab) and sustains a PR with resolution of the L pleural effusion and shrinkage in the primary lung mass, mediastinal LAD, and L adrenal lesion. Scans after cycle 8 of maintenance pemetrexed + pembrolizumab show growth in the L adrenal mass and new hepatic lesions, all of which prove "hot" on PET. **Which of the following would NOT be appropriate therapy in the second-line setting?**

1. Sotorasib
2. Adagrasib
3. Selpercatinib
4. Combination ramucirumab and pembrolizumab

Global Lung Cancer Academy

Optimizing First-Line Therapy in NSCLC – Integration of Immunotherapy Into Frontline Regimens

Luis Paz-Ares, MD, PhD

i+12
Instituto de Investigación
Hospital 12 de Octubre

cnio SPANISH NATIONAL CANCER RESEARCH CENTRE

UNIVERSIDAD COMPLUTENSE MADRID

Optimizing First-Line Therapy in NSCLC – Integration of Immunotherapy Into Frontline Regimens

Luis Paz-Ares

Hospital Universitario 12 de Octubre

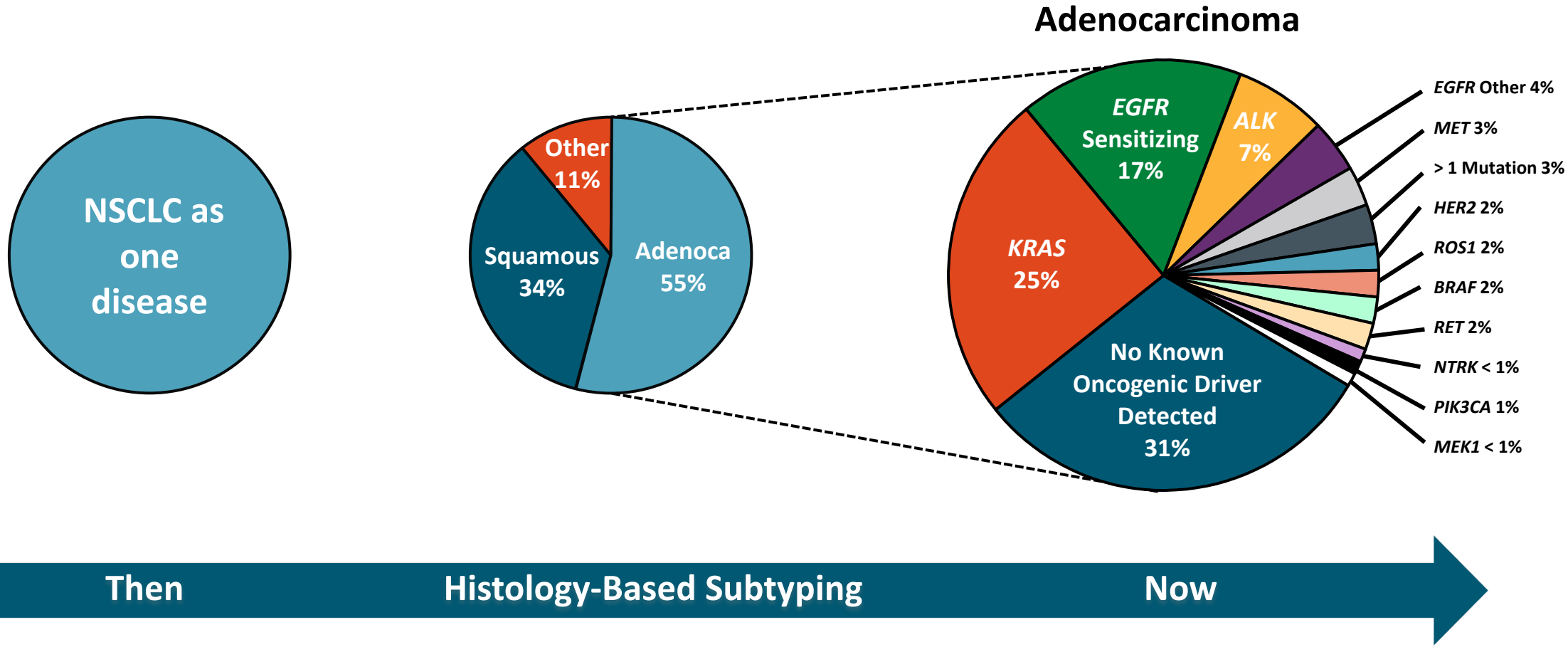
Conflicts of Interest (5 years)

Honoraria (self/family)– Scientific advice, speaker: Lilly, MSD, BMS, Roche, Pharmamar, Merck, Astra-Zeneca, Novartis, Boehringer, Celgene, Servier, Sysmex, Celgene, Amgen, Mirati, Pfizer, Ipsen,

Board Member– Genómica, Altum

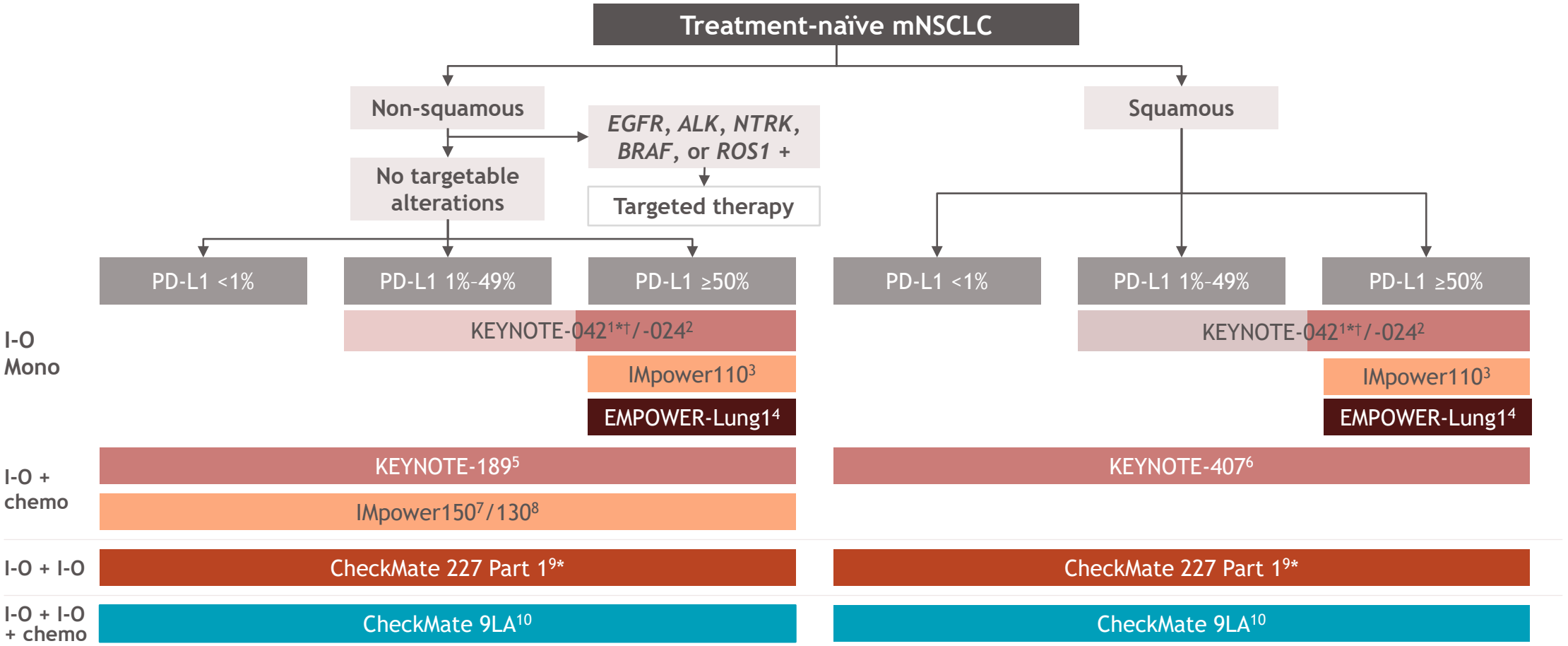
Research grants to Institution – MSD, BMS, Astra-Zeneca, Pfizer

Non-Small-Cell Lung Cancer: Not One Disease, but Many!



Li. JCO. 2013;31:1039. Tsao. J Thorac Oncol. 2016;11:613.

Increasing options available for 1L metastatic NSCLC



This diagram is intended for educational purposes only. It reflects the views of the presenter and not the current treatment landscape in mNSCLC.

*Regulatory status varies globally. †ESMO guidelines indicate that benefit driven mostly by high-expressors.

1. Cho BC et al. Poster presentation at WCLC 2020. Abstract FP13.04. 2. Reck M et al. *J Clin Oncol*. 2021;39(21):2339-2349. 3. Herbst RS et al. Poster presentation at WCLC 2020. Abstract FP13.03. 4. Sezer A et al. *Lancet* 2021;397:592-604. 5. Gray JE et al. Poster presentation at WCLC 2020. Abstract FP13.02. 6. Robinson AG et al. Oral presentation at ELCC 2021. Abstract 97O. 7. Socinski MA et al. Oral presentation at AACR 2020. Abstract CT216. 8. West H et al. Lancet Oncol 2019; 20(7):924-937. 9. Hellmann MD et al. *N Engl J Med*. 2018;378(22):2093-2104. 10. Paz-Arez L et al. *Lancet Oncol* 2021; 22(2):198-211.

Agenda

- IO Monotherapy
- Chemo plus IO
- IO plus IO combos

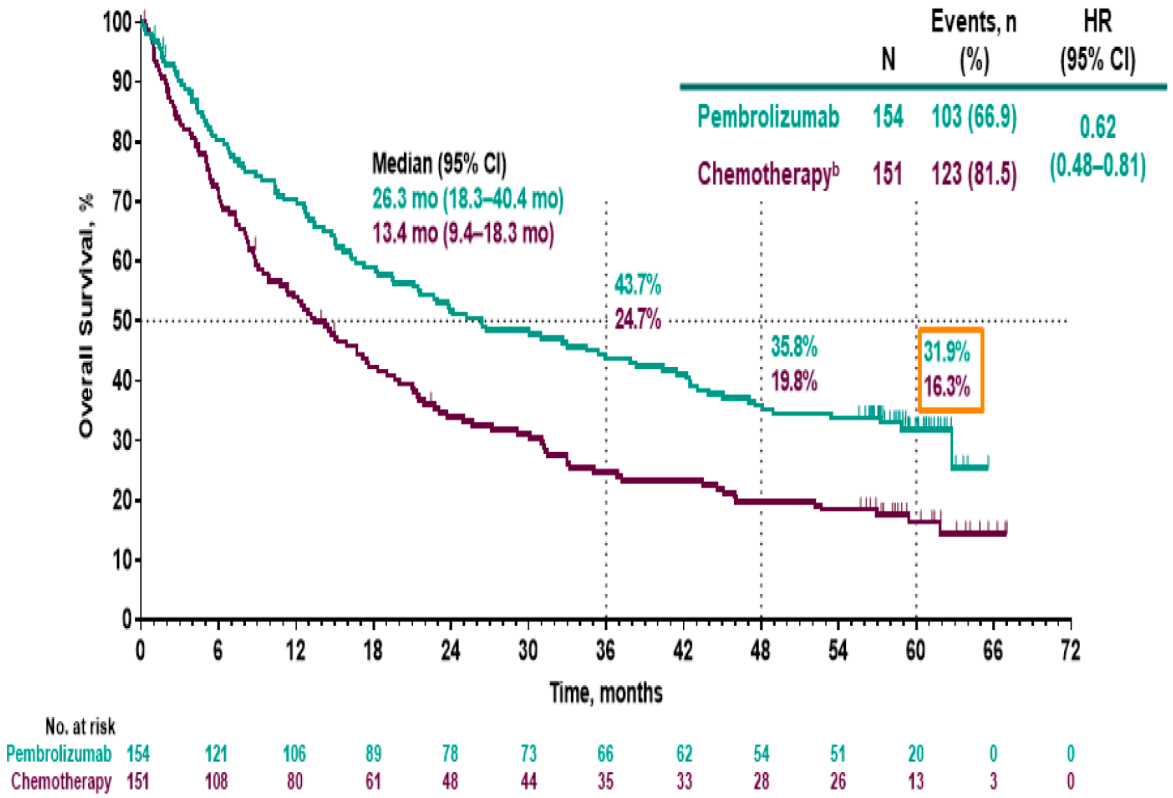
Agenda

- **IO Monotherapy**
- **Chemo plus IO**
- **IO plus IO combos**

KN 024 Trial - Update

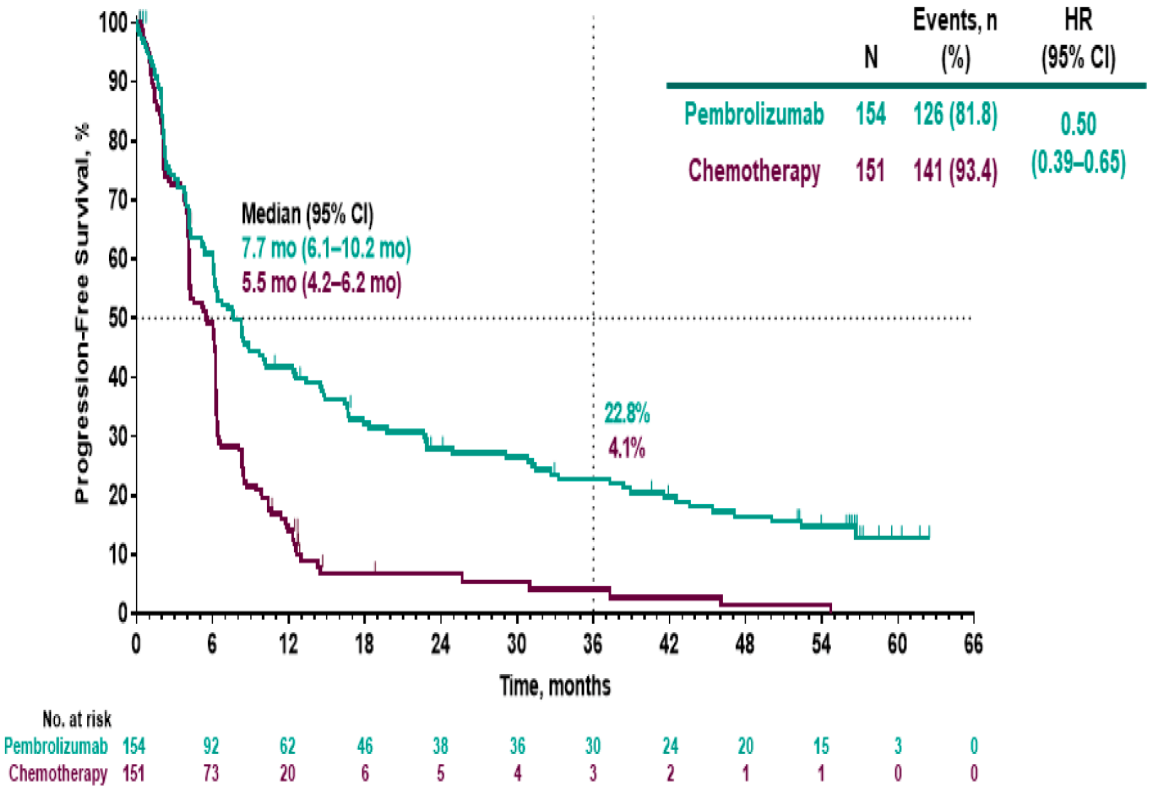
Median follow up: 59.9 months [range: 55,5–68.4])

Overall Survival[a]



Progression-Free Survival[a]

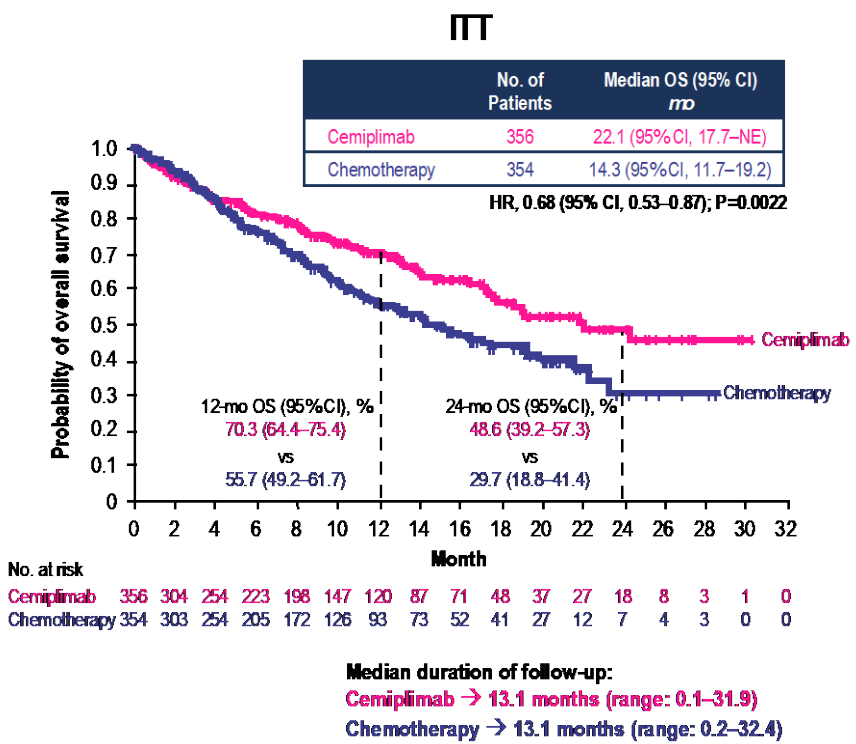
RECIST v1.1 per Investigator Review[b]

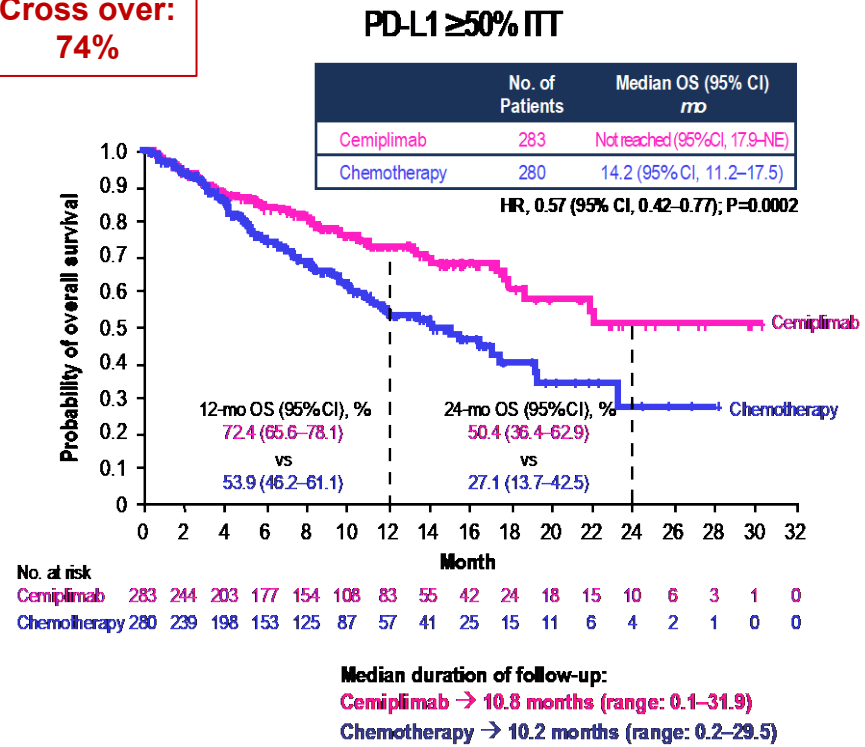


Brahmer JR, et al. Ann Oncol 2020;31(suppl):Abstr LBA51

Cemiplimab – Empower Lung 1Trial

Cross over: 74%





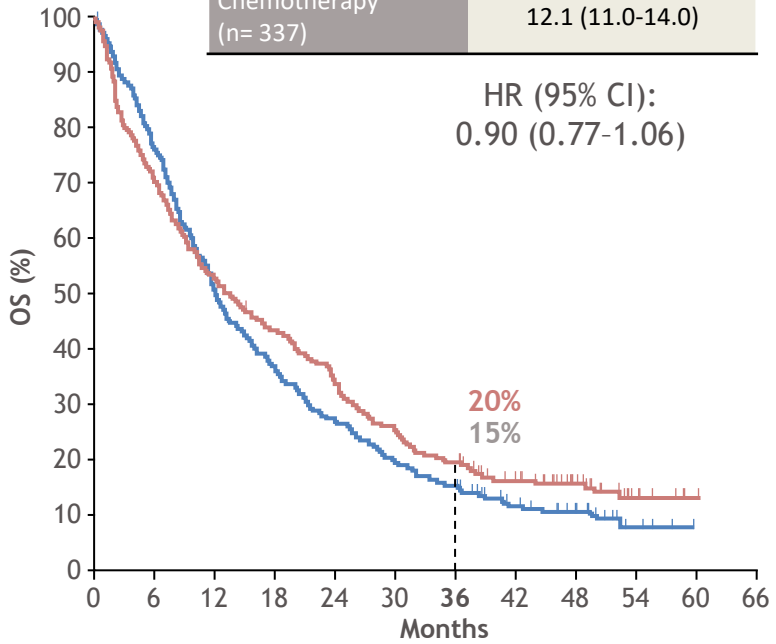
Sezer A, et al. Ann Oncol 2020;31(suppl):Abstr LBA52

Benefit from I-O monotherapy is limited in PD-L1 low or intermediate expressors

KEYNOTE-042: PD-L1 1-49%*[1]

	Median OS (95% CI), mo
Pembrolizumab (n=338)	13.4 (10.7-16.9)
Chemotherapy (n= 337)	12.1 (11.0-14.0)

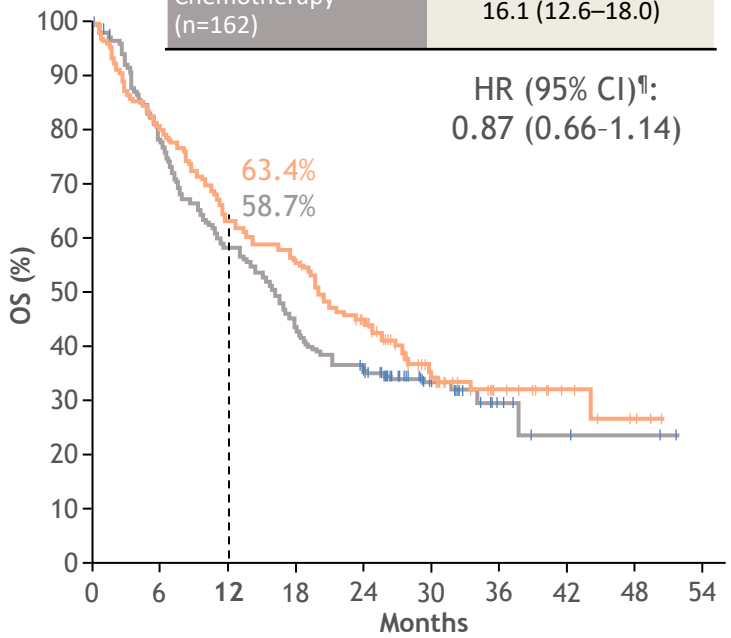
HR (95% CI): 0.90 (0.77–1.06)



IMpower110: PD-L1 TC2/3 or IC2/3[2†‡]

	Median OS (95% CI), mo
Atezolizumab (n=166)	19.9 (17.2–25.3)
Chemotherapy (n=162)	16.1 (12.6–18.0)

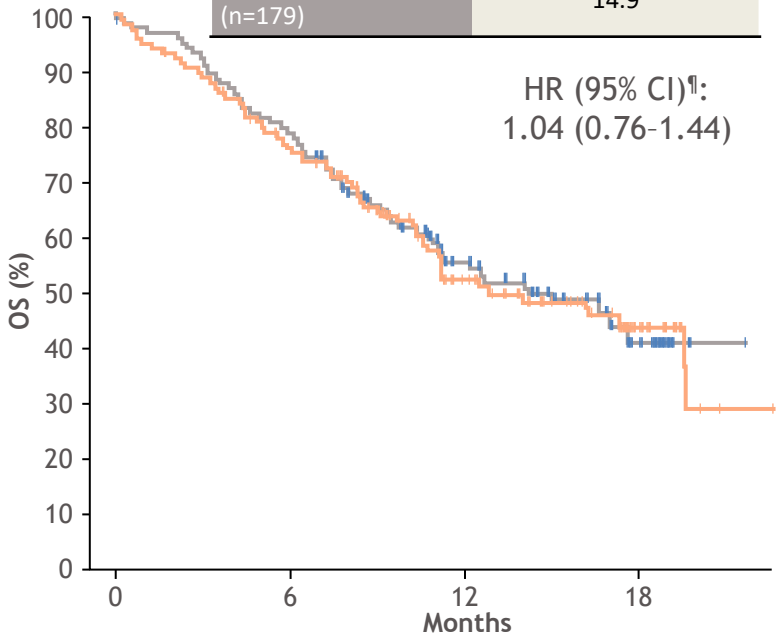
HR (95% CI)¶: 0.87 (0.66–1.14)



IMpower110: PD-L1 TC1/2 or IC1/2[3§‖]

	Median OS, mo
Atezolizumab (n=170)	12.9
Chemotherapy (n=179)	14.9

HR (95% CI)¶: 1.04 (0.76–1.44)



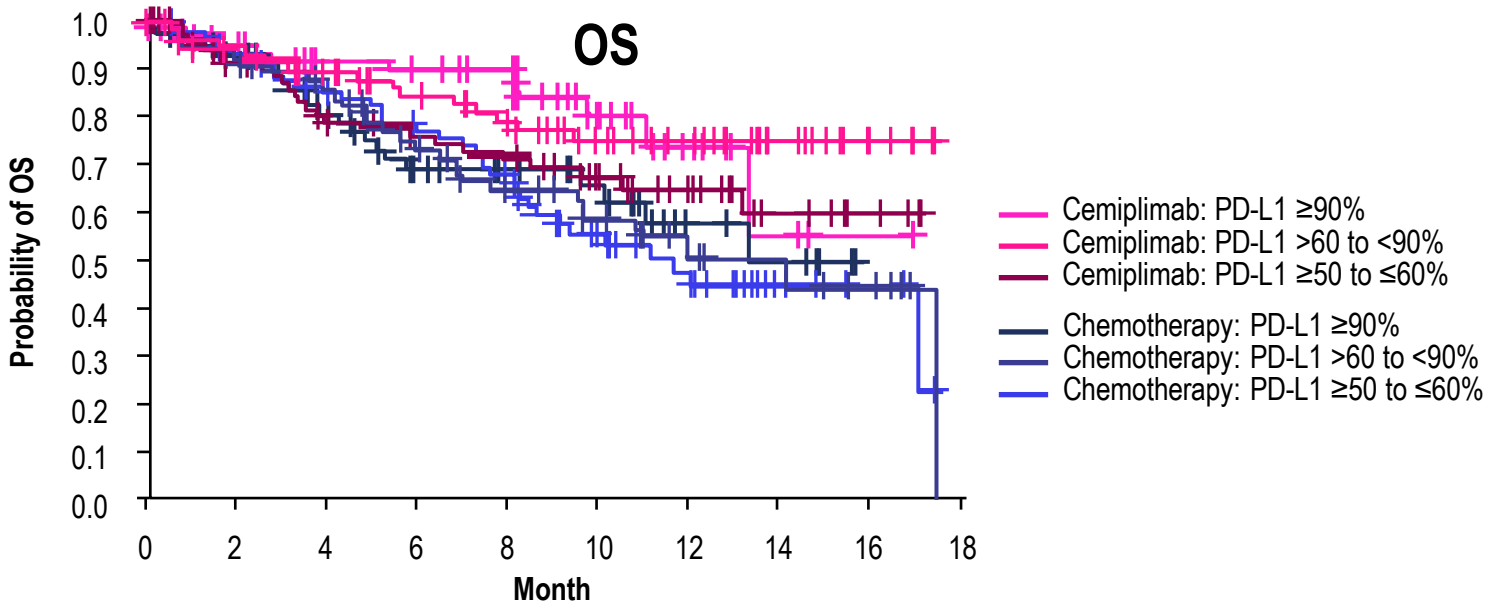
Slide intended for educational purposes only. Cross-study comparisons are not intended.

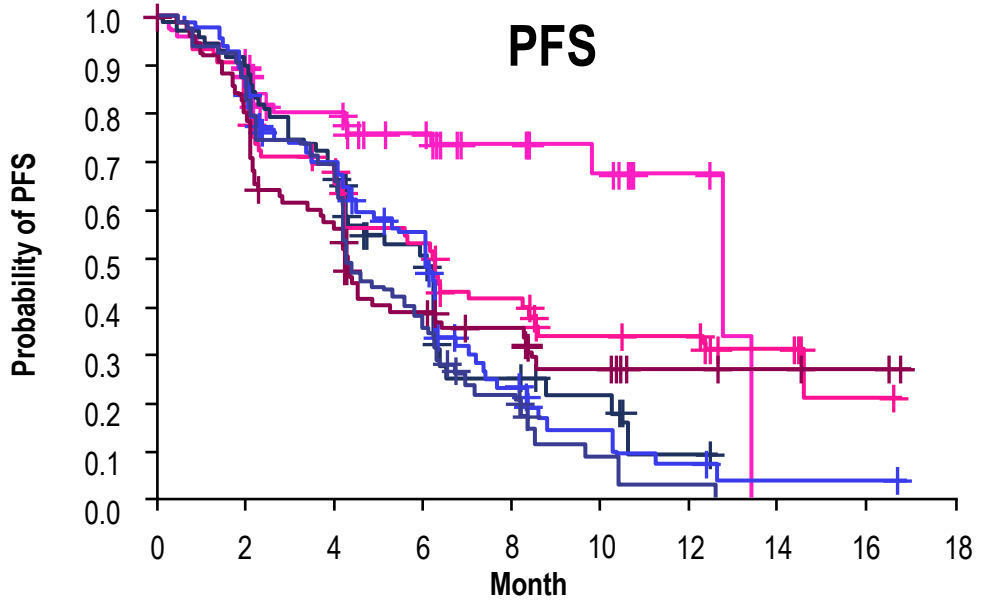
*Median follow-up time=46.9 months.[1] †Median follow-up time=31.3 months.[2] ‡TC2/3 or IC2/3 denotes PD-L1 expression on ≥5% of tumor or tumor-infiltrating cells respectively. §Median follow-up time=15.7 months.[3] ‖TC1/2 denotes PD-L1 expression on ≥1% and <50% of tumor cells or ≥1% and <10% tumor-infiltrating cells, respectively. ¶Stratified.[2,3]

1. Cho BC et al. Poster presentation at WCLC 2020. Abstract FP13.04. 2. Herbst RS et al. Poster presentation at WCLC 2020. Abstract FP13.03. 3. Herbst RS et al. Oral presentation at ESMO I-O 2019. Abstract LBA1.

EMPOWER Lung1 by PD-L1 Expression

PD-L1 Expression Levels Correlate with OS and PFS (N=475)





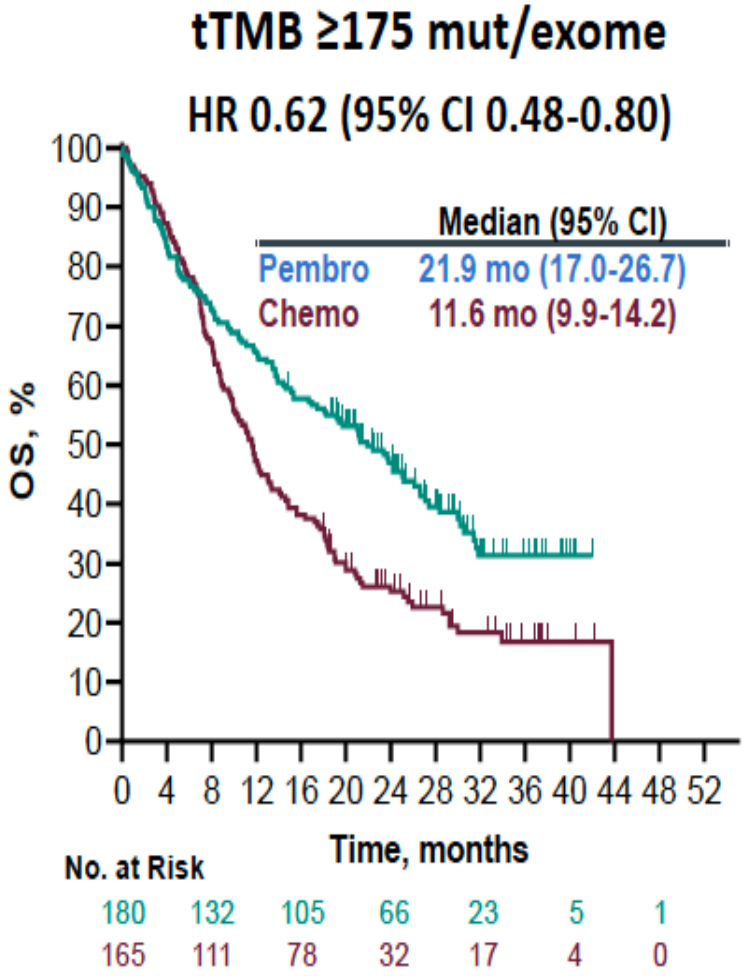
	Median, months (95% CI)			HR (95% CI)
	Cemiplimab (N=238)		Chemotherapy (N=237)	
≥90%	NR (13.4–NE)	vs	13.3 (10.2–NE)	0.54 (0.27–1.10)
>60 to <90%	NR (NE–NE)	vs	14.2 (9.6–17.5)	0.49 (0.26–0.92)
≥50 to ≤60%	NR (13.2–NE)	vs	11.7 (8.3–NE)	0.74 (0.44–1.24)

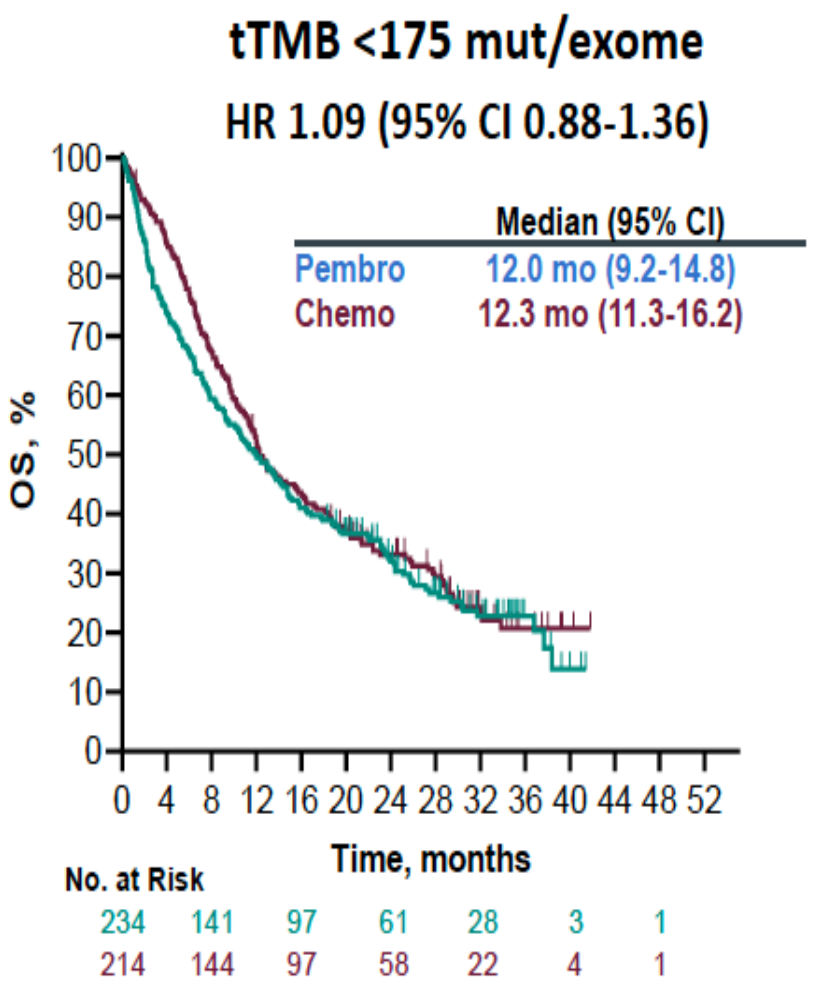
	Median, months (95% CI)			HR (95% CI)
	Cemiplimab (N=238)		Chemotherapy (N=237)	
≥90%	12.7 (9.8–13.4)	vs	6.1 (4.2–6.2)	0.33 (0.19–0.58)
>60 to <90%	6.2 (4.2–8.4)	vs	4.3 (4.1–5.9)	0.57 (0.38–0.85)
≥50 to ≤60%	4.3 (2.8–5.2)	vs	6.0 (4.4–6.2)	0.89 (0.61–1.29)

CI, confidence interval; HR, hazard ratio; NE, not evaluable; NR, not reached; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.

Kilickap et al. WLCC 2020

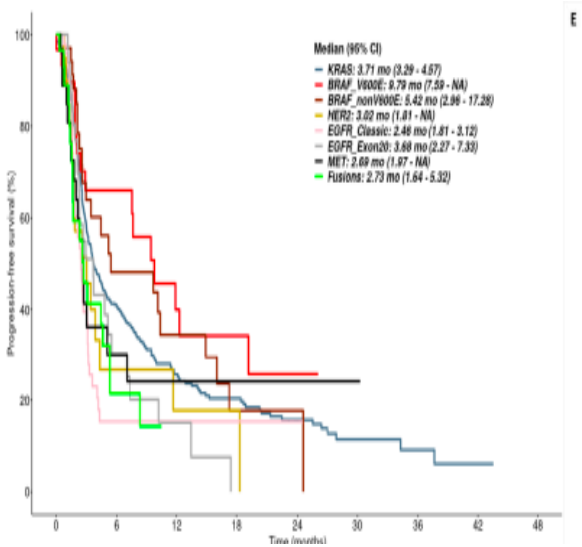
Pembro benefit may be restricted to PD-L1 ≥ 50% & TMB high

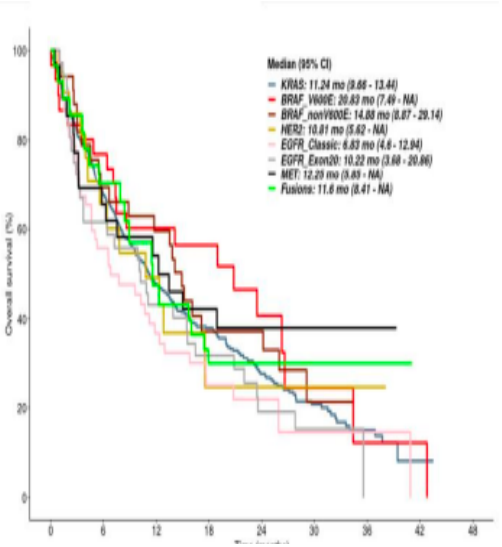


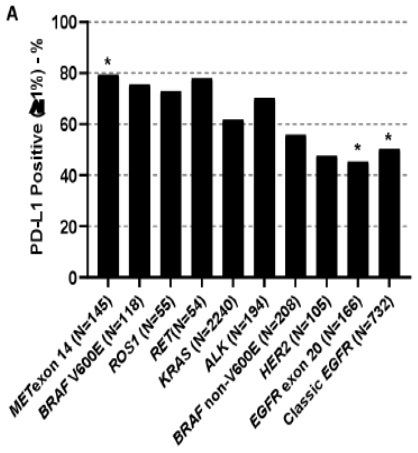


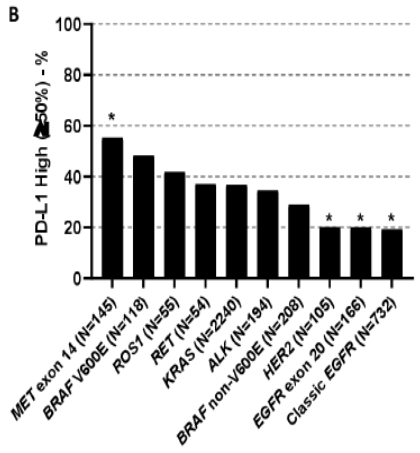
Herbst et al. ESMO 2019

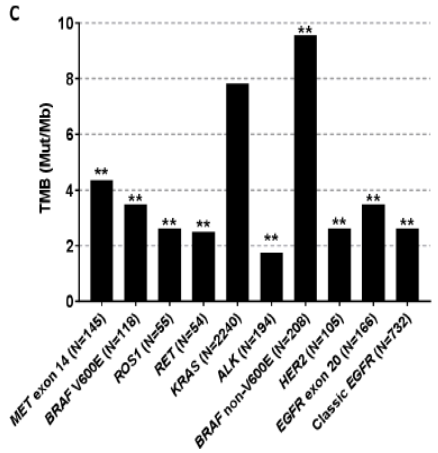
Individual Genomic Aberrations

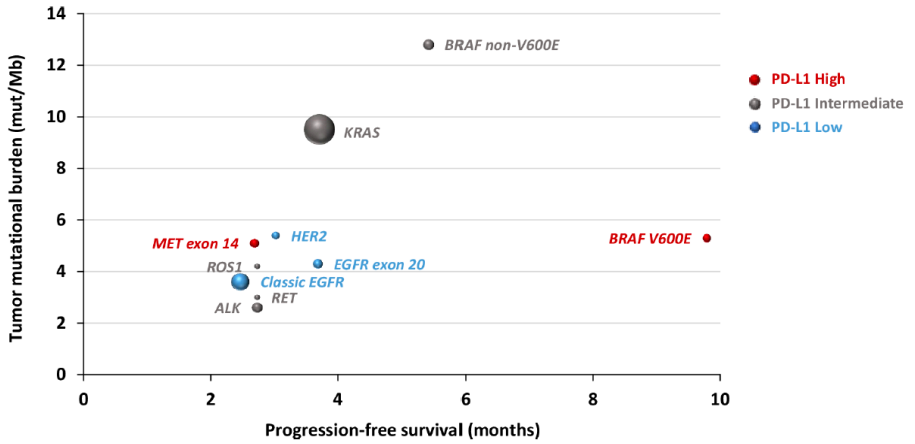






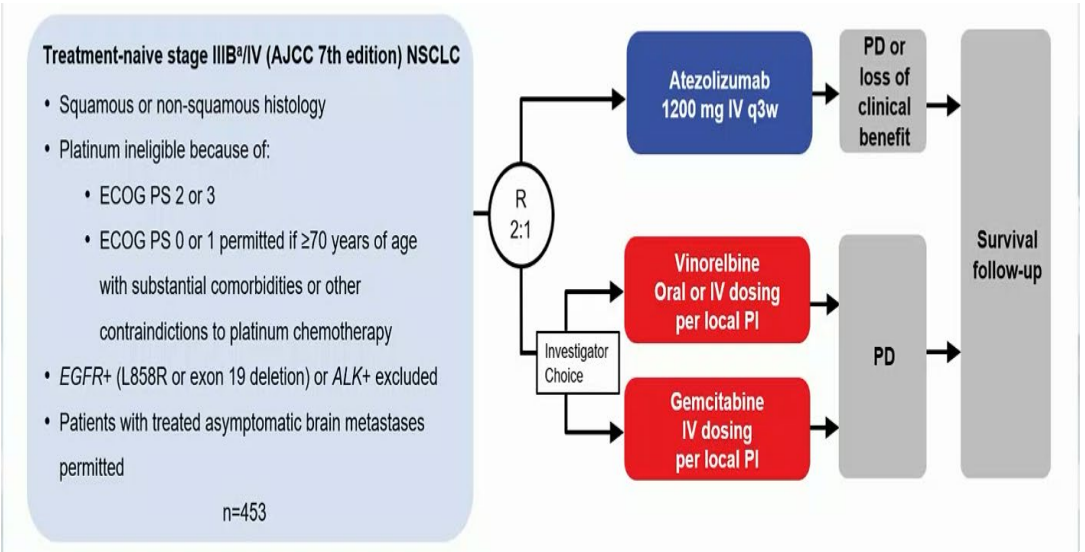


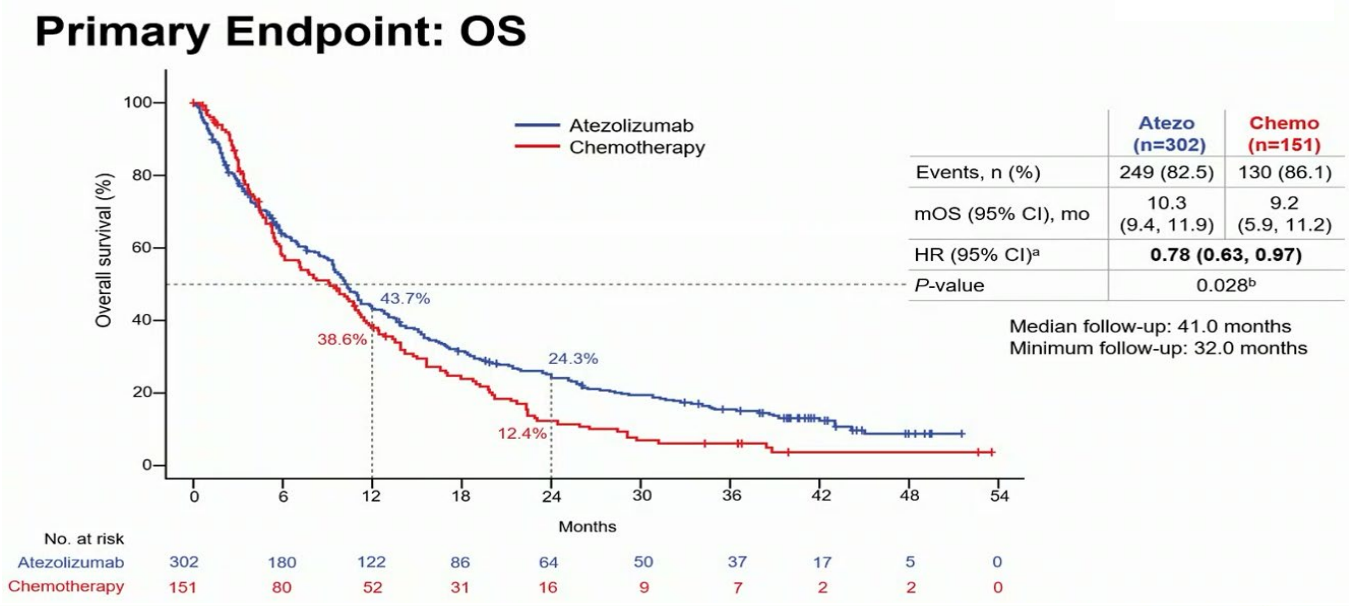




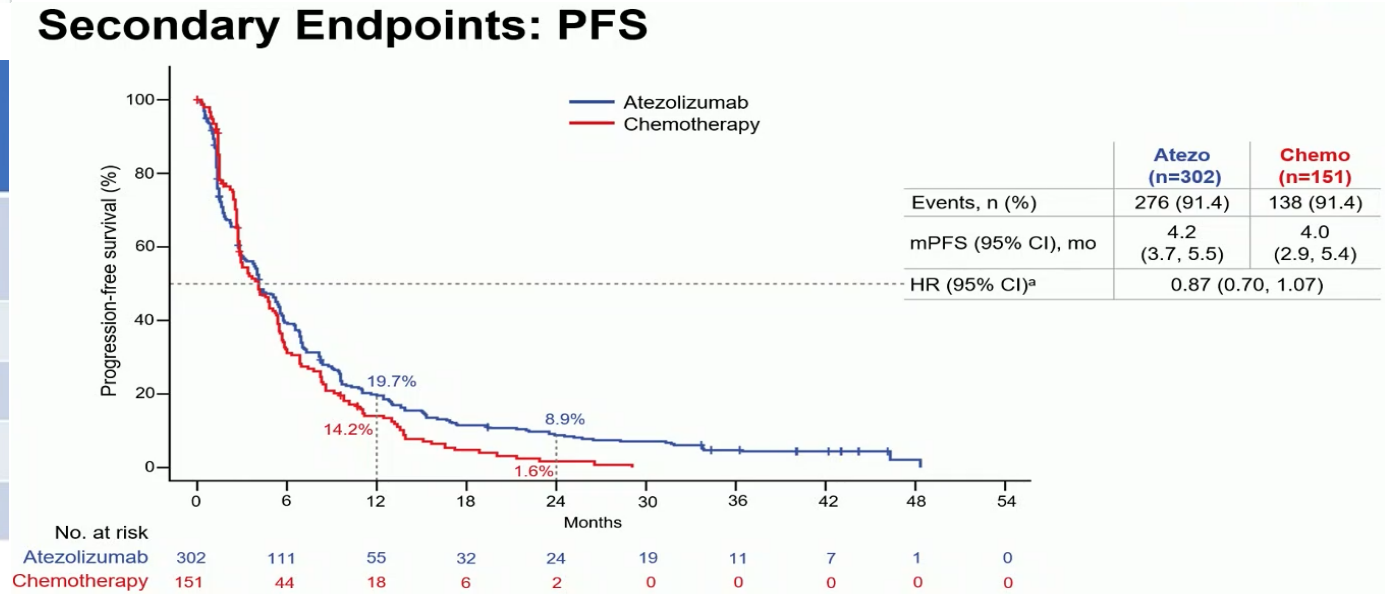
Negrao et al., JITC 2021

IPSOS trial: Atezo 1L in PS 2-3 patients/Elderly PS1





	Atezolizumab (n=302)	Chemotherapy (n=151)
Number of patients with any subsequent anti-cancer therapy, n (%)	**61 (20.2)**	**45 (29.8)**
Chemotherapy, n (%)	48 (15.9)	16 (10.6)
Cancer Immunotherapy, n (%)	4 (1.3)	28 (18.5)
TKI, n (%)	10 (3.3)	5 (3.3)
Other, n (%)	3 (1.0)	1 (0.7)



Lee et al. ESMO 2022;

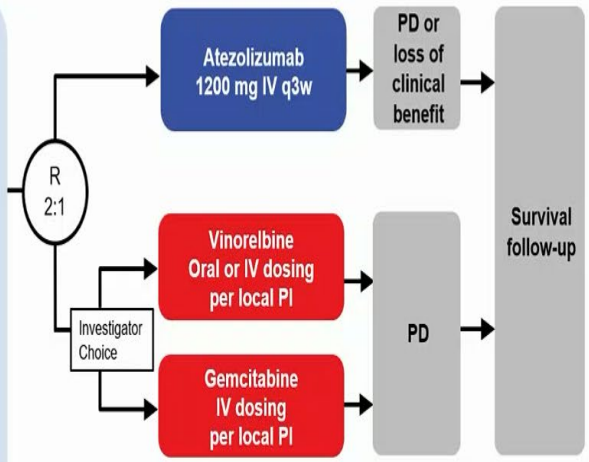
Vansteenkiste J. et al., atezolizumab in NSCLC (POPLAR)

IPSOS trial: Atezo 1L in PS 2-3 patients/Elderly PS1

Treatment-naive stage IIIB[a]/IV (AJCC 7th edition) NSCLC

- Squamous or non-squamous histology
- Platinum ineligible because of:
  - ECOG PS 2 or 3
  - ECOG PS 0 or 1 permitted if ≥70 years of age with substantial comorbidities or other contraindictions to platinum chemotherapy
- *EGFR*+ (L858R or exon 19 deletion) or *ALK*+ excluded
- Patients with treated asymptomatic brain metastases permitted

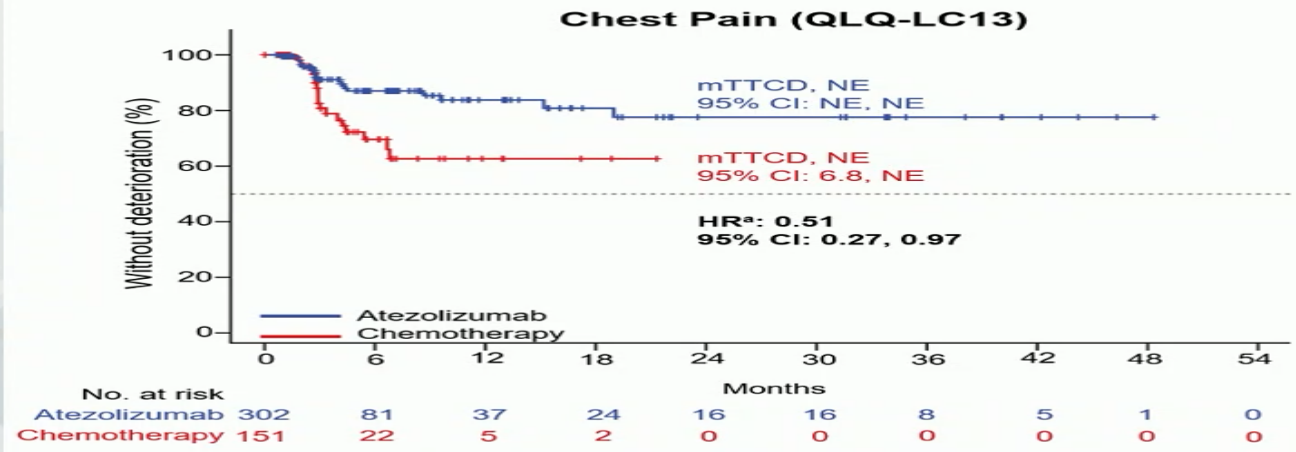
n=453

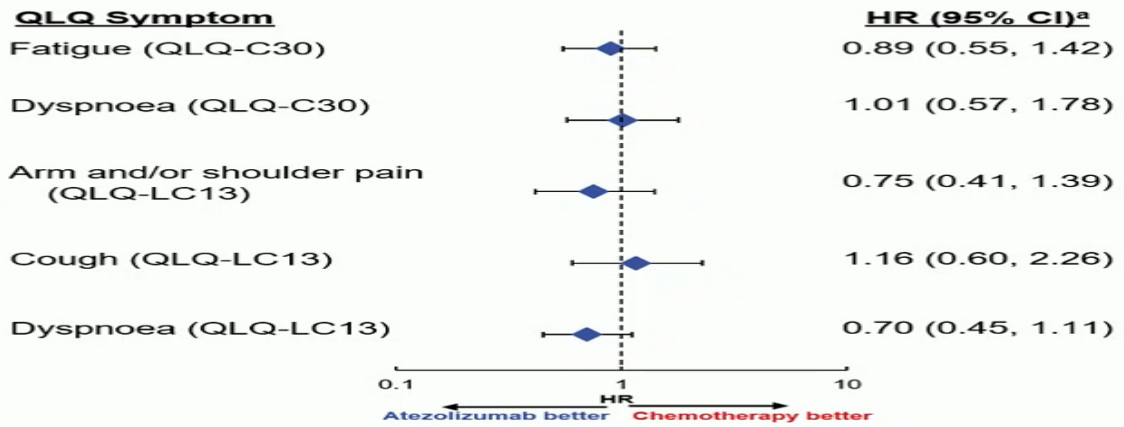


Safety Summary

	Atezolizumab (n=300)	Gemcitabine (n=63)	Vinorelbine (n=84)
Median treatment duration, months (range)	3.5 (0-51)	2.3 (0-13)	1.8 (0-21)
Median number of cycles initiated (range)	6.0 (1-73)	4.0 (1-19)	3.0 (1-31)
	Atezolizumab (n=300)	**Chemotherapy (n=147)**	
All-grade AE, n (%)	275 (91.7)	143 (97.3)	
Treatment-related AE	171 (57.0)	118 (80.3)	
Grade 3-4 AE, n (%)	136 (45.3)	71 (48.3)	
Treatment-related Grade 3-4 AE	49 (16.3)	49 (33.3)	
Serious AE, n (%)	146 (48.7)	53 (36.1)	
Treatment-related SAE	35 (11.7)	23 (15.6)	
Grade 5 AE, n (%)	35 (11.7)	13 (8.8)	
Treatment-related Grade 5 AE	3 (1.0)	4 (2.7)	
AE leading to discontinuation of study drug, n (%)	39 (13.0)	20 (13.6)	
AE leading to modification/interruption of study drug, n (%)	96 (32.0)	71 (48.3)	

Time to Confirmed Deterioration





Lee et al. ESMO 2022;

Vansteenkiste J. et al., atezolizumab in NSCLC (POPLAR)

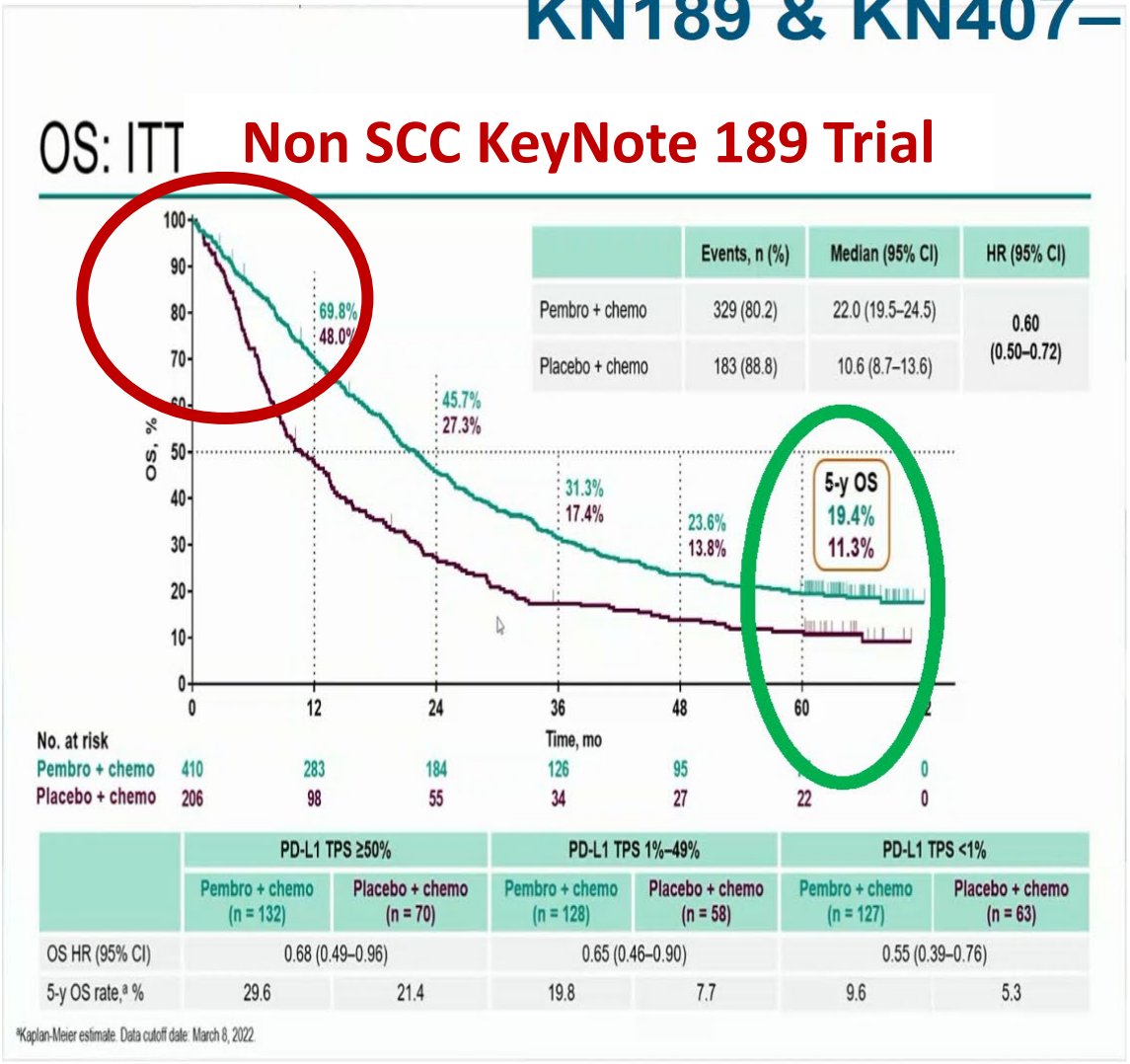
Agenda

- IO Monotherapy
- **Chemo plus IO**
- IO plus IO combos

PD-1/PD-L1 combos may enlarge the benefit

KN189 & KN407– 5 years update

OS: ITT Non SCC KeyNote 189 Trial



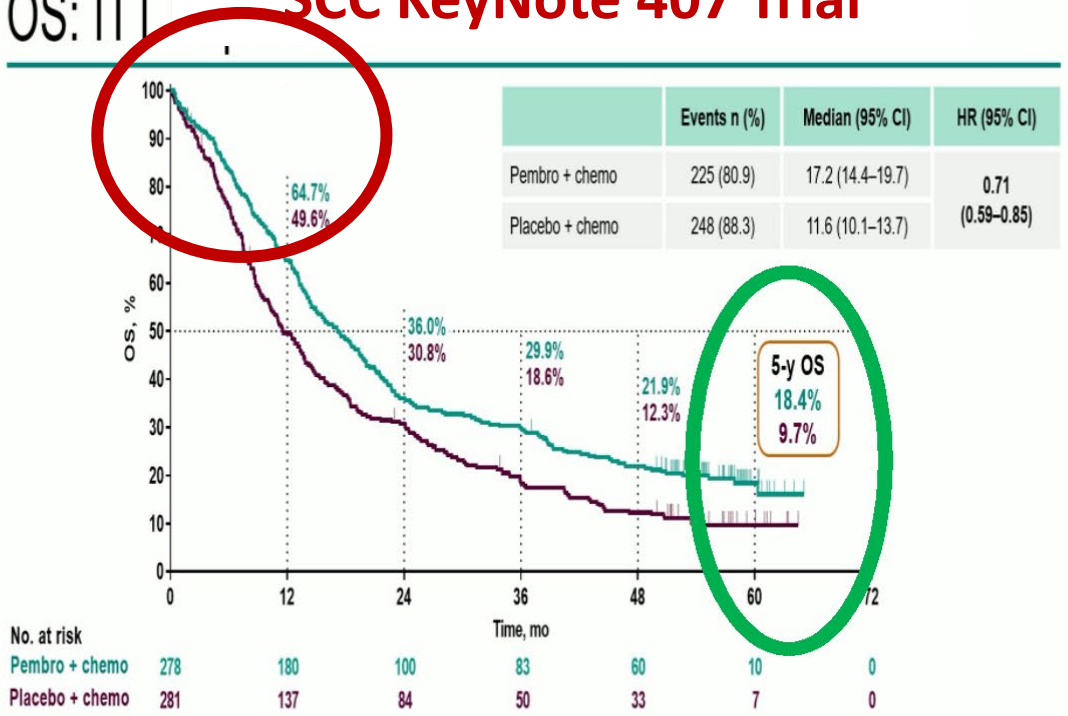
	Events, n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	329 (80.2)	22.0 (19.5–24.5)	0.60 (0.50–0.72)
Placebo + chemo	183 (88.8)	10.6 (8.7–13.6)	

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 132)	Placebo + chemo (n = 70)	Pembro + chemo (n = 128)	Placebo + chemo (n = 58)	Pembro + chemo (n = 127)	Placebo + chemo (n = 63)
OS HR (95% CI)	0.68 (0.49–0.96)		0.65 (0.46–0.90)		0.55 (0.39–0.76)	
5-y OS rate,[a] %	29.6	21.4	19.8	7.7	9.6	5.3

[a]Kaplan-Meier estimate. Data cutoff date: March 8, 2022.

Ghandi et al., NEJM 2018; Garassino et al., ESMO 2022

OS: ITT SCC KeyNote 407 Trial

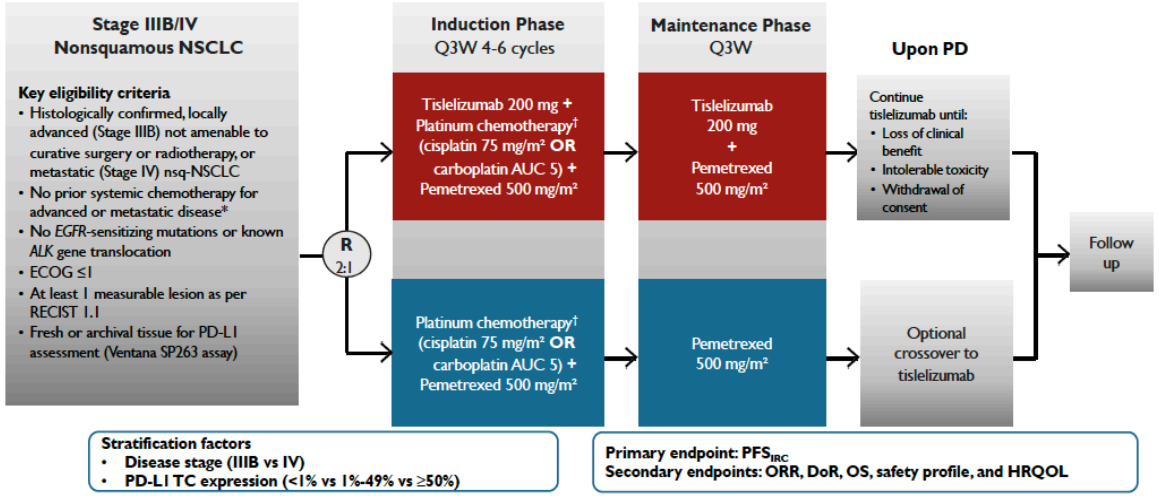


	Events n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	225 (80.9)	17.2 (14.4–19.7)	0.71 (0.59–0.85)
Placebo + chemo	248 (88.3)	11.6 (10.1–13.7)	

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 73)	Placebo + chemo (n = 73)	Pembro + chemo (n = 103)	Placebo + chemo (n = 104)	Pembro + chemo (n = 95)	Placebo + chemo (n = 99)
OS HR (95% CI)	0.68 (0.47–0.97)		0.61 (0.45–0.83)		0.83 (0.61–1.13)	
5-y OS rate,[a] %	23.3	8.3	20.6	7.6	10.7	13.1

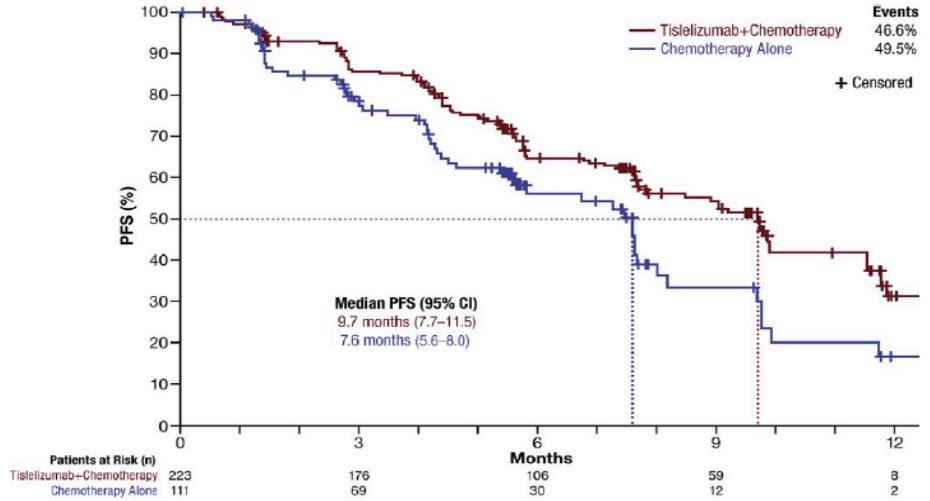
Paz-Ares et al., NEJM 2018; Novello et al., ESMO 2022

Rationale 304 Trial



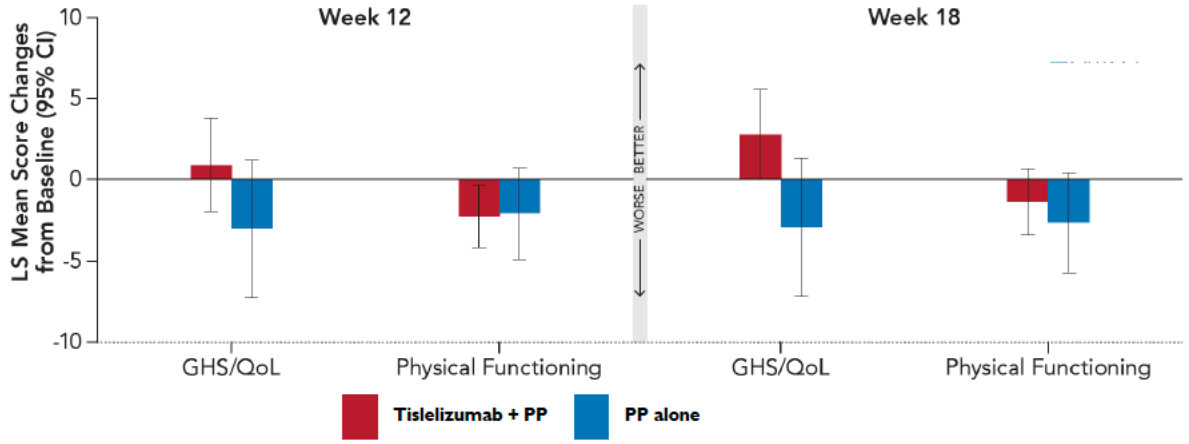
Progression-Free Survival as Assessed by IRC (ITT Population)

RATIONALE-304



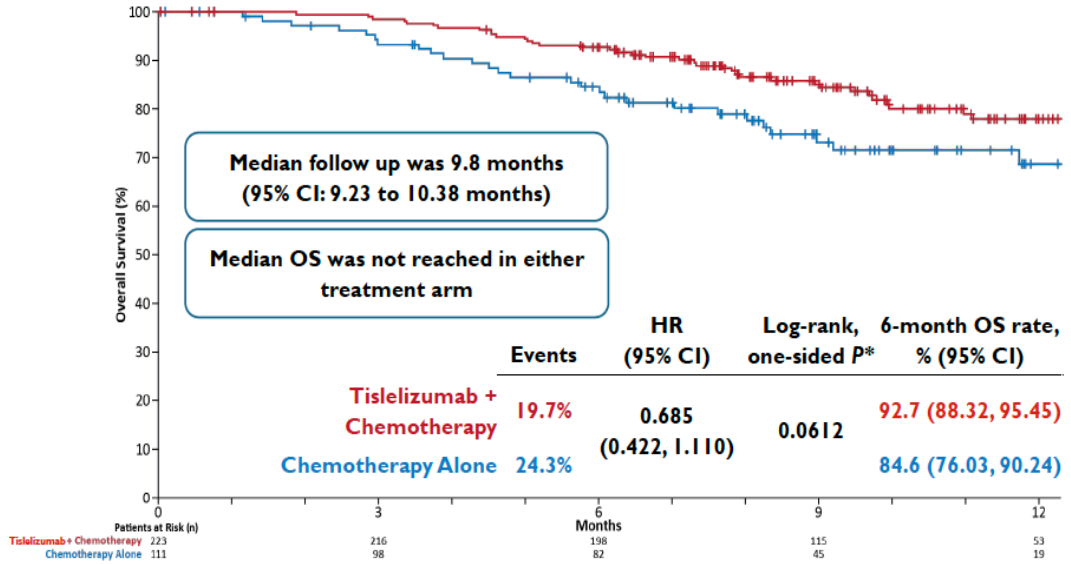
Change from Baseline in EORTC QLQ-C30 Subscales

RATIONALE-304



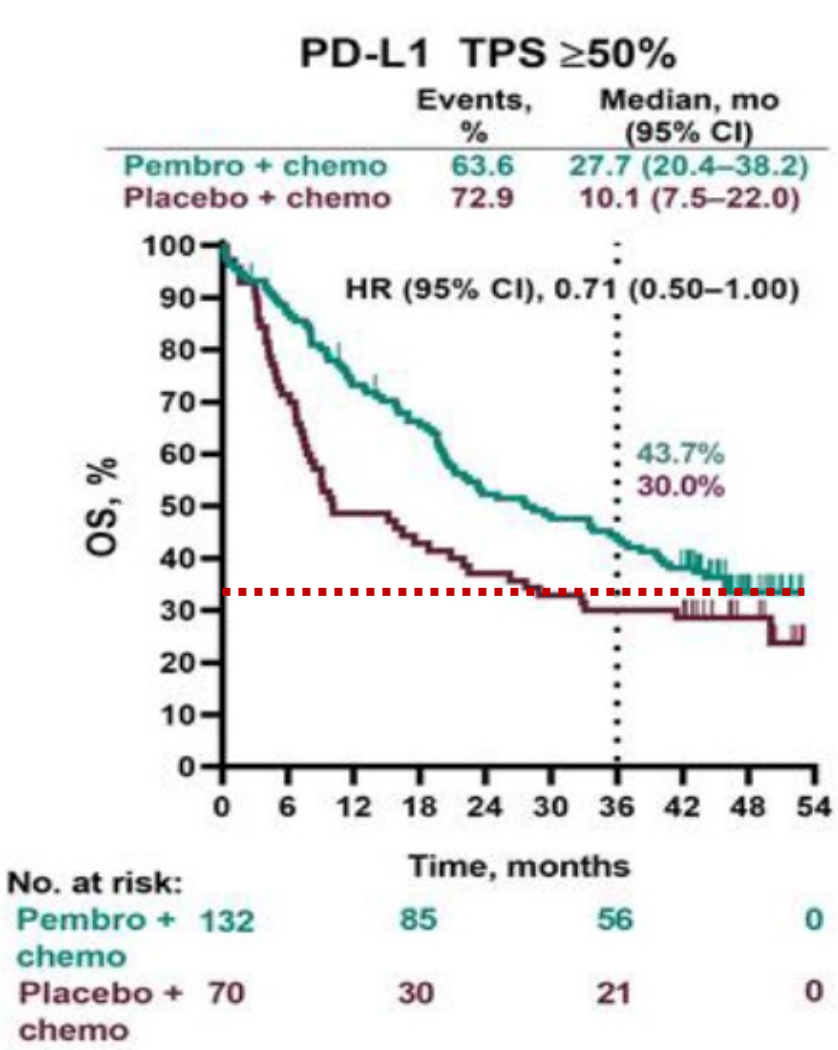
Overall Survival (ITT Population)

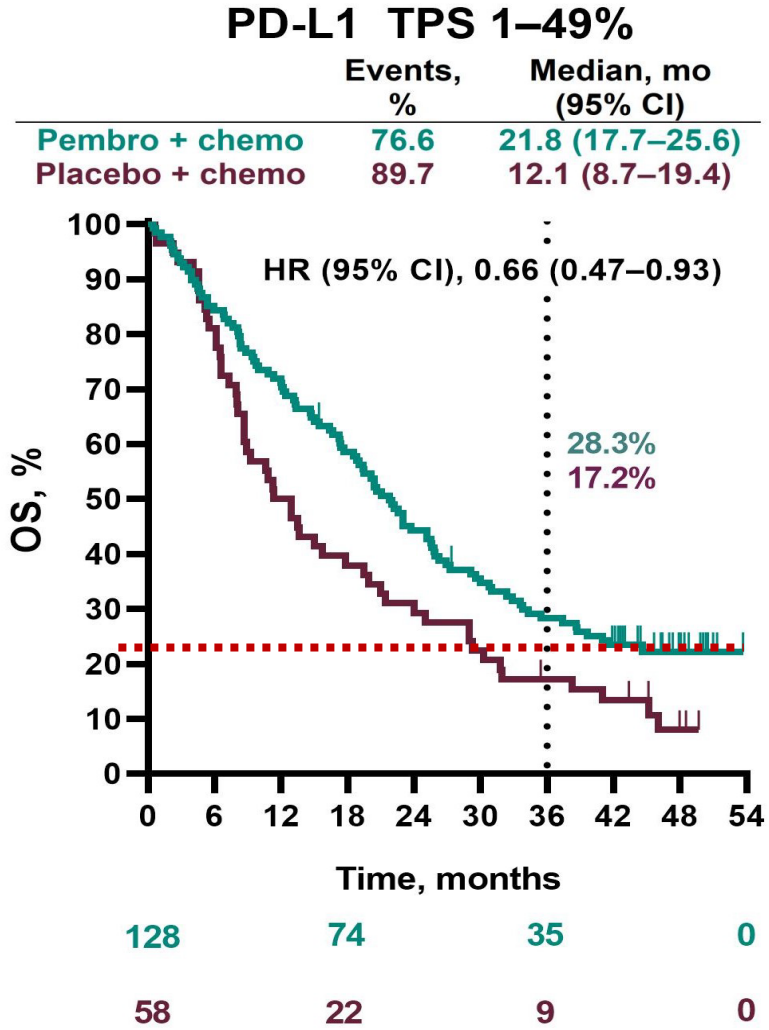
RATIONALE-304

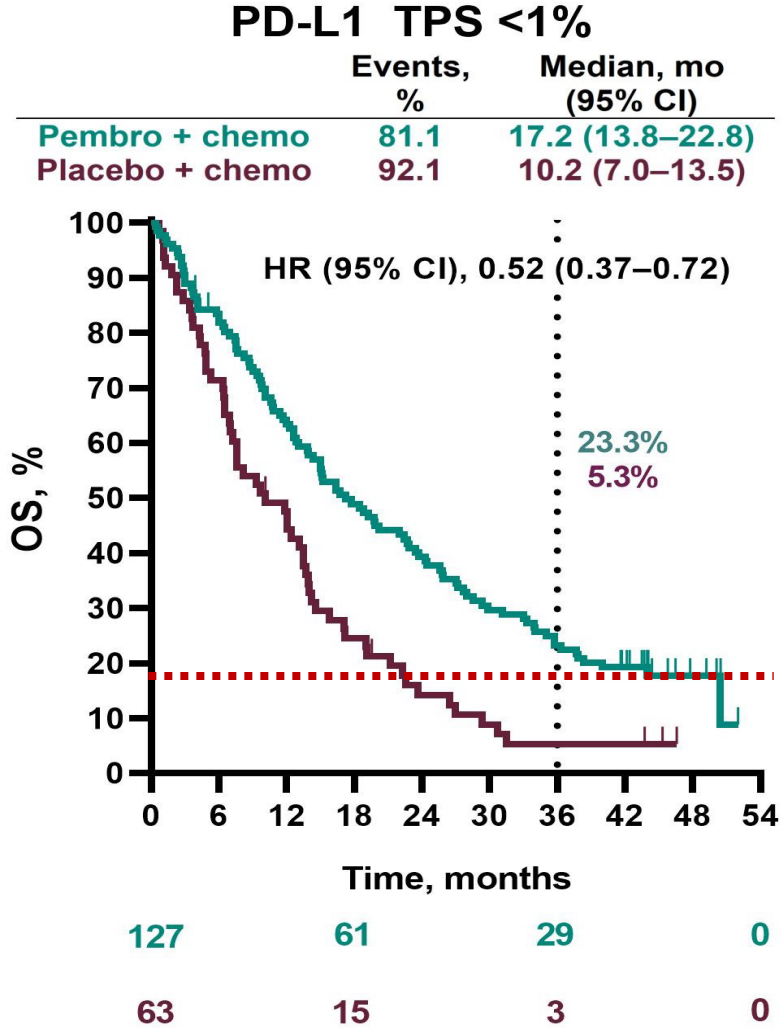


Lu et al. JTO 2021

KN 189 update (M Fup: 4 y)





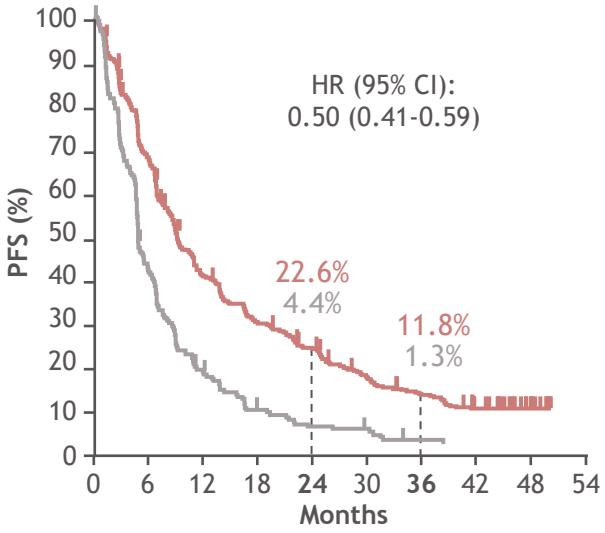


Gray et al. WLCC 2020

KEYNOTE-189: Pembro + chemo shows 3-year efficacy benefit across PD-L1 expression, with long-term outcomes driven by high PD-L1 expressors

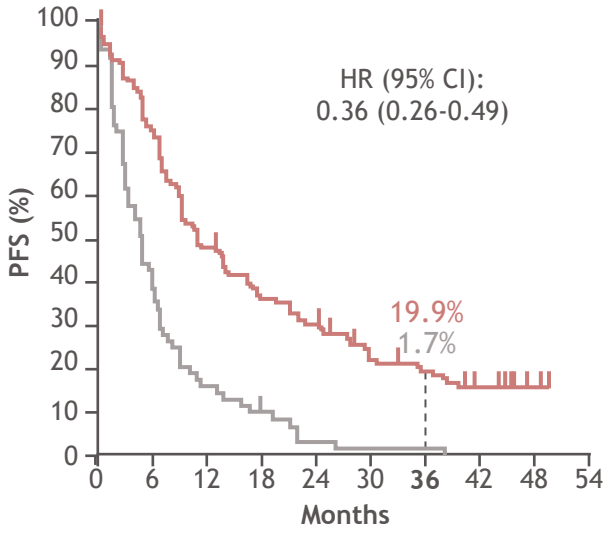
PFS, ITT Population*

	Median (95% CI) PFS, mo
Pembro + chemo	9.0 (8.1-10.4)
Placebo + chemo	4.9 (4.7-5.5)



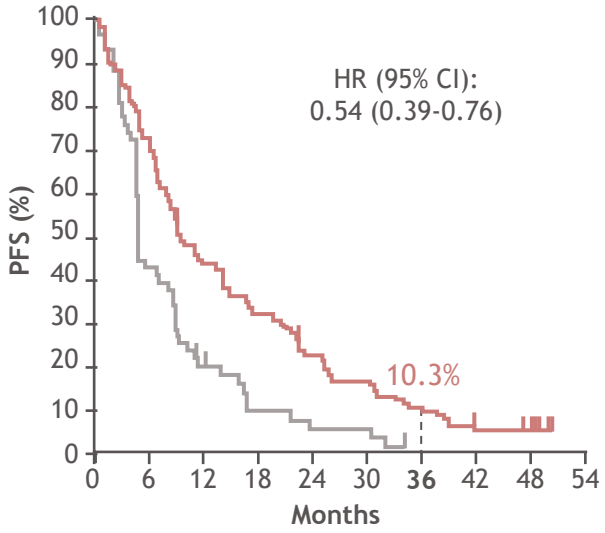
PFS, PD-L1 TPS ≥50%

	Median (95% CI) PFS, mo
Pembro + chemo	11.1 (9.1-16.4)
Placebo + chemo	4.8 (3.1-6.2)



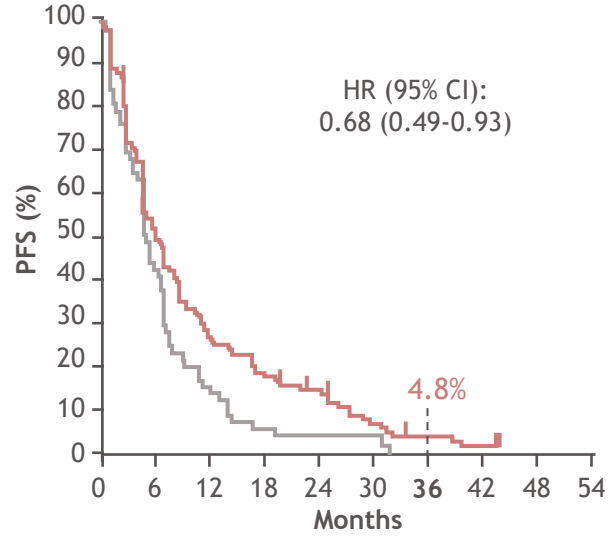
PFS, PD-L1 TPS 1-49%

	Median (95% CI) PFS, mo
Pembro + chemo	9.4 (8.1-13.8)
Placebo + chemo	4.9 (4.7-8.6)



PFS, PD-L1 TPS <1%

	Median (95% CI) PFS, mo
Pembro + chemo	6.2 (4.9-8.3)
Placebo + chemo	5.1 (4.5-6.8)



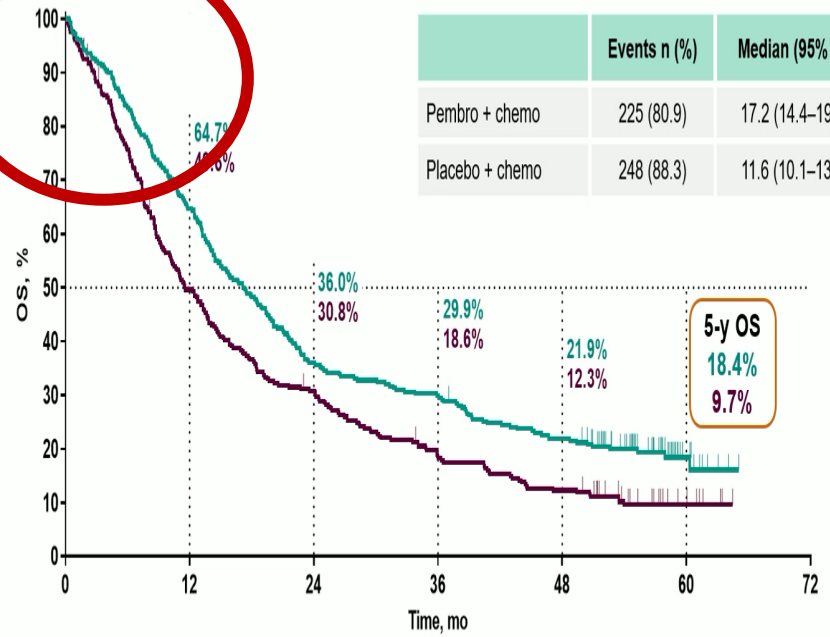
	ITT		PD-L1 TPS ≥50%		PD-L1 TPS 1-49%		PD-L1 TPS <1%	
	Pembro + chemo (n=410)	Placebo + chemo (n=206)	Pembro + chemo (n=132)	Placebo + chemo (n=70)	Pembro + chemo (n=128)	Placebo + chemo (n=58)	Pembro + chemo (n=127)	Placebo + chemo (n=63)
ORR, %	48.3	19.9	62.1	25.7	50.0	20.7	33.1	14.3
mDOR, mo	12.6	7.1	15.1	7.1	13.6	7.6	10.8	7.8

*Co-primary endpoint.

Gray JE et al. Poster presentation at WCLC 2020. Abstract FP13.02.

KN407 – 5 years update

OS: ITT Population

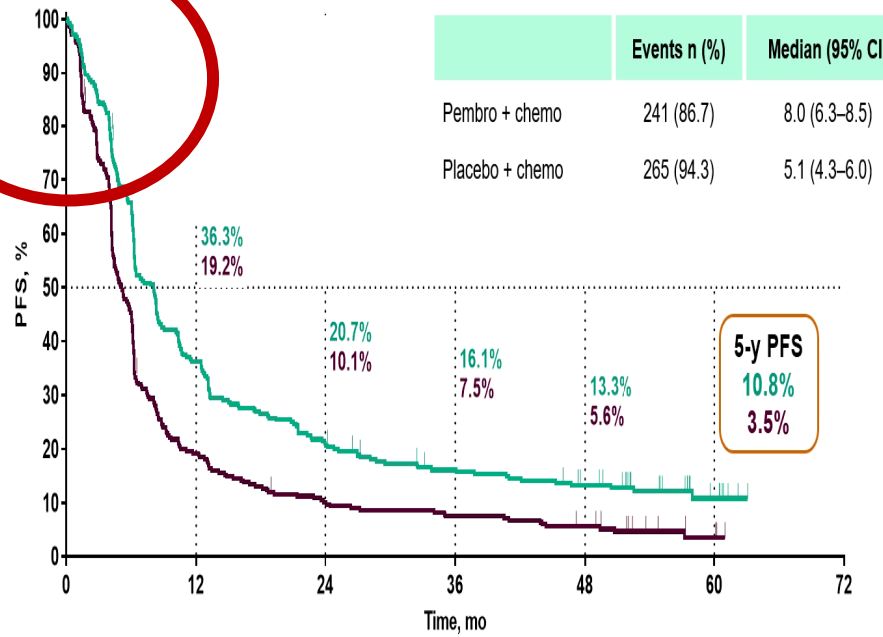


	Events n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	225 (80.9)	17.2 (14.4–19.7)	0.71 (0.59–0.85)
Placebo + chemo	248 (88.3)	11.6 (10.1–13.7)	

No. at risk							
Pembro + chemo	278	180	100	83	60	10	0
Placebo + chemo	281	137	84	50	33	7	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 73)	Placebo + chemo (n = 73)	Pembro + chemo (n = 103)	Placebo + chemo (n = 104)	Pembro + chemo (n = 95)	Placebo + chemo (n = 99)
OS HR (95% CI)	0.68 (0.47–0.97)		0.61 (0.45–0.83)		0.83 (0.61–1.13)	
5-y OS rate,[a] %	23.3	8.3	20.6	7.6	10.7	13.1

PFS[a]: ITT Population



	Events n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	241 (86.7)	8.0 (6.3–8.5)	0.62 (0.52–0.74)
Placebo + chemo	265 (94.3)	5.1 (4.3–6.0)	

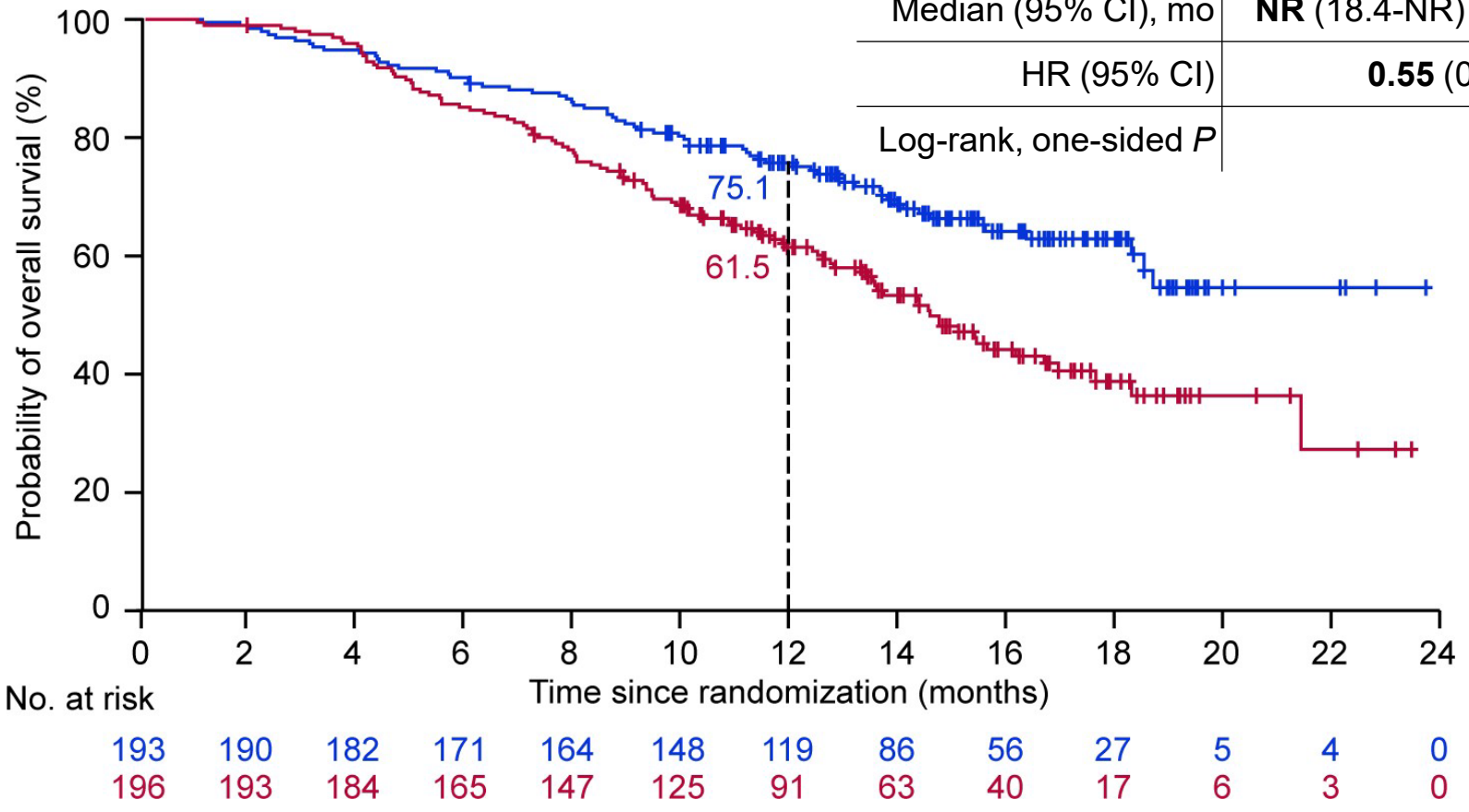
No. at risk							
Pembro + chemo	278	100	56	40	30	7	0
Placebo + chemo	281	53	27	20	14	1	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 73)	Placebo + chemo (n = 73)	Pembro + chemo (n = 103)	Placebo + chemo (n = 104)	Pembro + chemo (n = 95)	Placebo + chemo (n = 99)
PFS HR (95% CI)	0.48 (0.33–0.69)		0.60 (0.45–0.81)		0.70 (0.52–0.95)	
5-y PFS rate[b], %	15.0	NR	11.8	NR	7.1	6.7

S Novello et al. ESMO 2022

CameL-sq Trial - OS

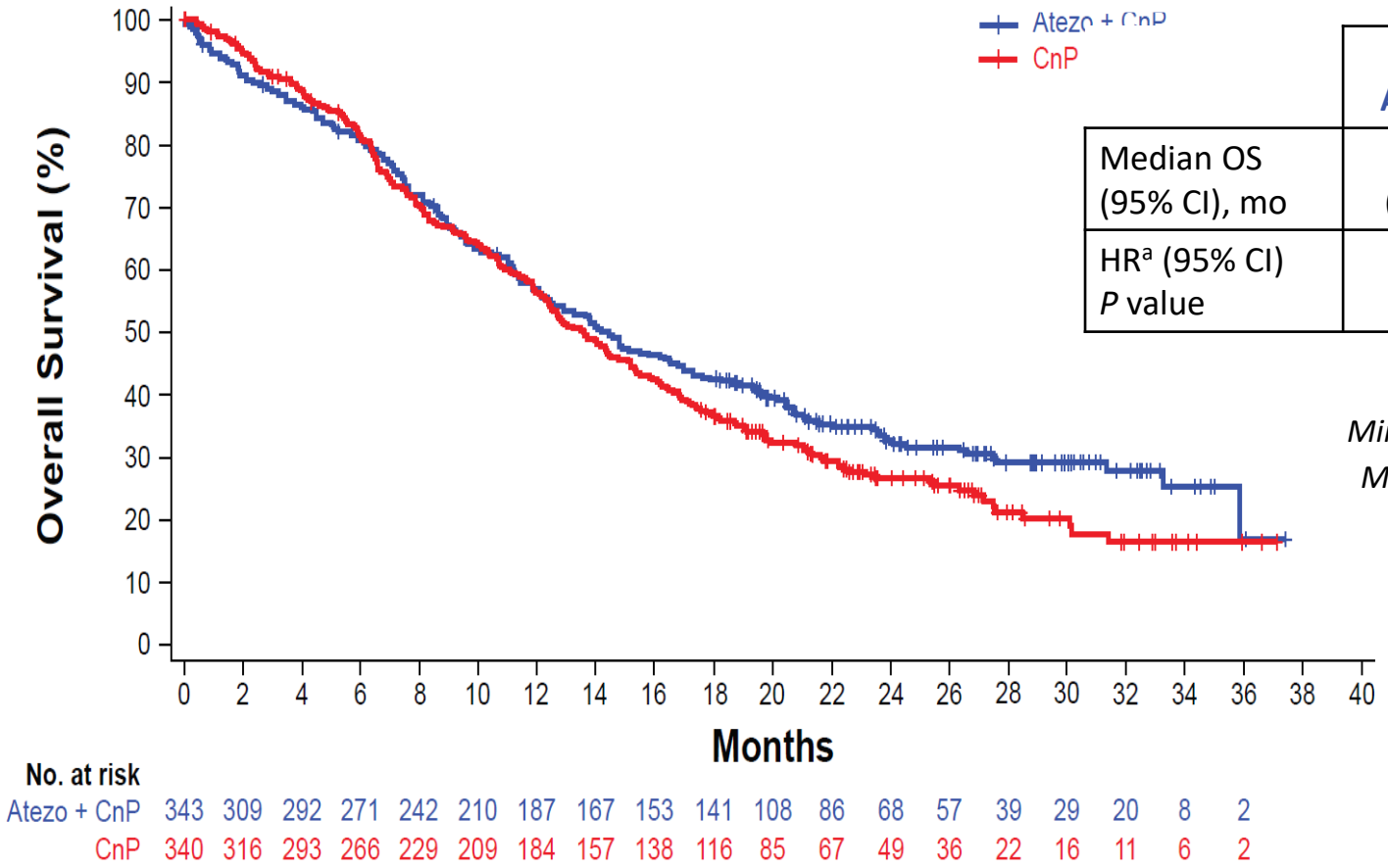
	Camrelizumab + chemotherapy	Placebo + chemotherapy
Median (95% CI), mo	**NR** (18.4-NR)	**14.5** (13.2-16.6)
HR (95% CI)	**0.55** (0.40-0.75)	
Log-rank, one-sided *P*	<0.0001	



Data cutoff: Nov.06, 2020
Median follow-up: 13.5 mo for camrelizumab+chemo, 11.6 mo for placebo+chemo
OS analyzed using a stratified one-sided log-rank test ;
HR estimated using a stratified Cox proportional hazards model.
46.9% of patients in the placebo+chemo group crossed over after PD.
NR, not reached

Zhou et al., ELCC 2021

IMpower 131 – CnP ± Atezolizumab
Final OS in the ITT population (Arm B vs Arm C)



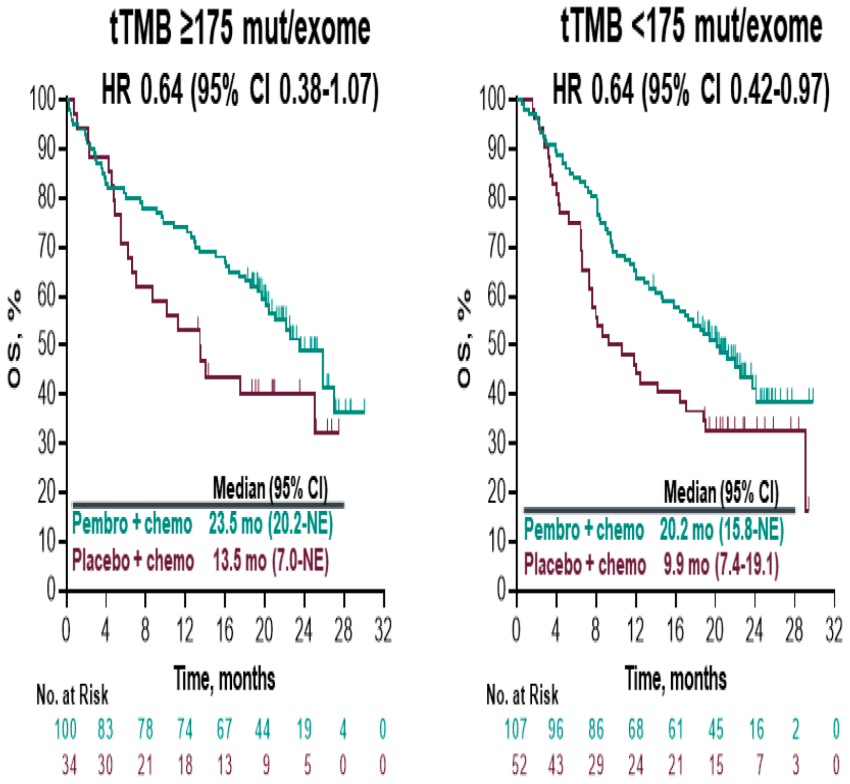
	Arm B: Atezo + CnP	Arm C: CnP
Median OS (95% CI), mo	14.2 (12.3, 16.8)	13.5 (12.2, 15.1)
HR[a] (95% CI) *P* value	0.88 (0.73, 1.05) 0.1581	

Minimum follow-up, 18.7 mo
Median follow-up, 25.5 mo

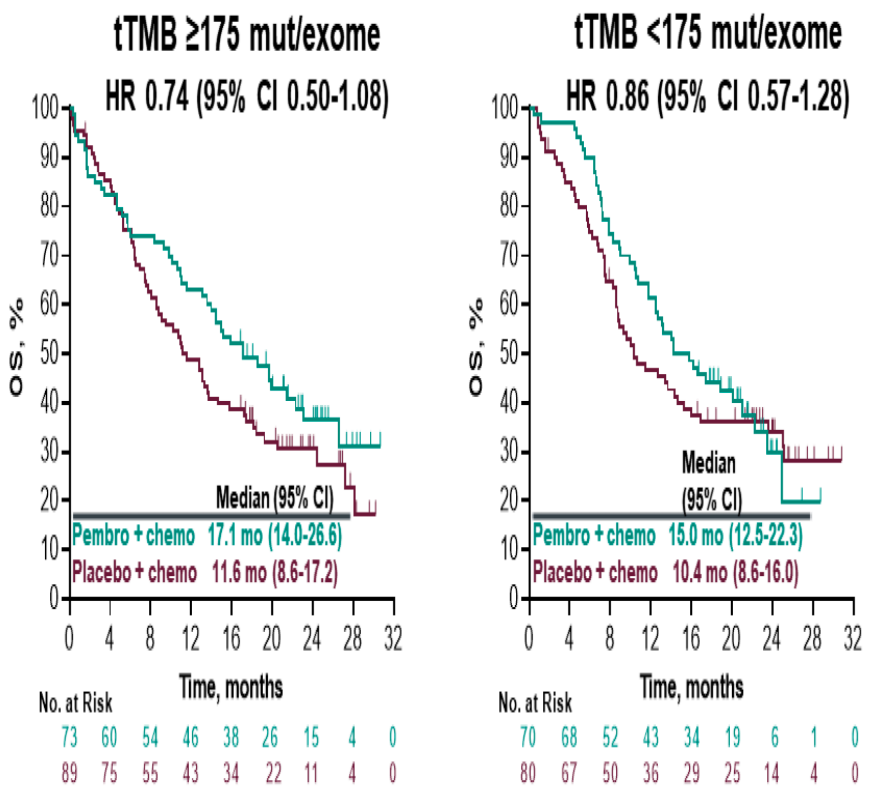
Jotte R et al., WLCC 2019

TMB may not predict outcome with Chemo-IO

Clinical Utility for OS in KEYNOTE-189: tTMB Cutpoint of 175 mut/exome

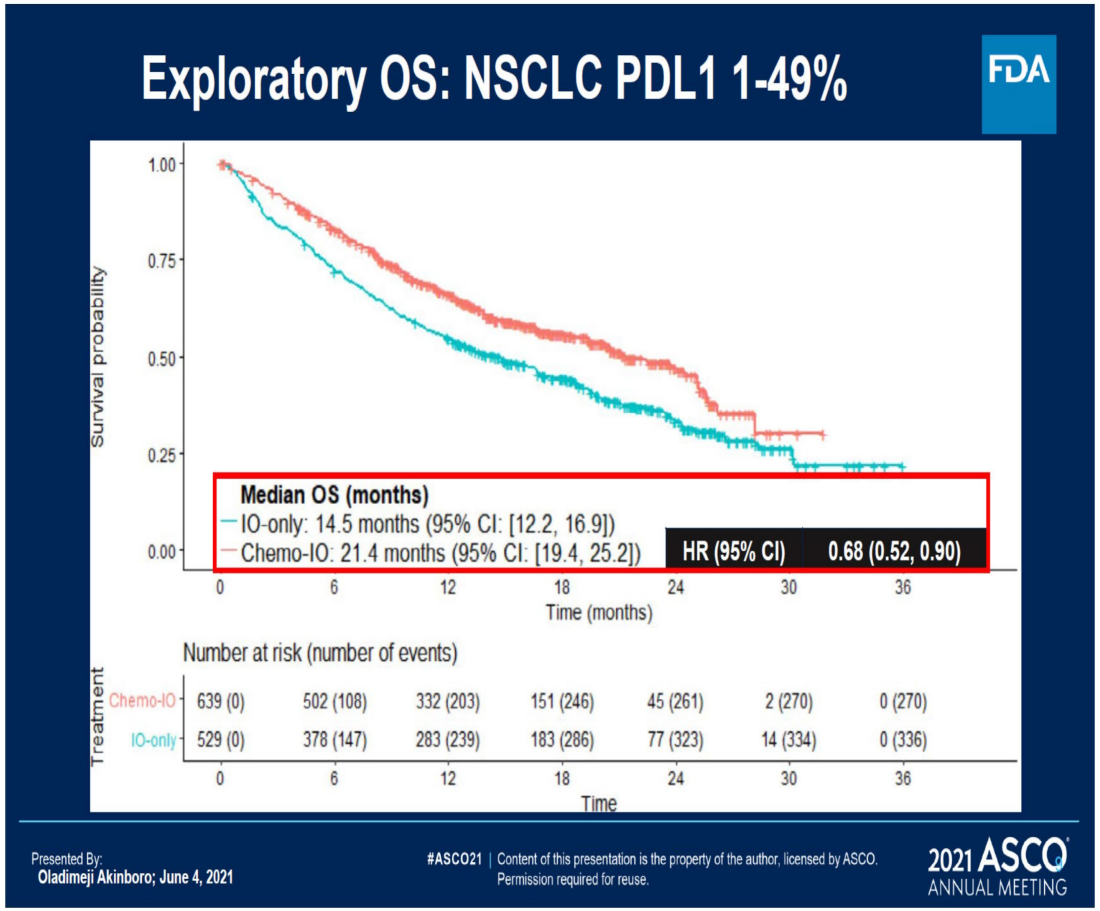


Clinical Utility for OS in KEYNOTE-407: tTMB Cutpoint of 175 mut/exome



Paz-Ares et al., ESMO 2019

IO alone *v* Chemo-IO in tumors with PD-L1 1-49%



Study	Investigational Treatment	Histology	PD-L1 1-49% OS HR (95% CI)
Keynote 042	Pembrolizumab alone	All NSCLC	0.92 (0.77-1.11)
Checkmate 227	NIVO/IPI	All NSCLC	0.94 (0.75-1.18)
Keynote 189	Pembro-Chemo	Non-squamous	0.55 (0.34-0.90)
Keynote 407	Pembro-Chemo	Squamous	0.57 (0.36-0.90)
Checkmate 9LA	NIVO/IPI + Chemo	All NSCLC	0.61 (0.44-0.84) (published) 0.70 (not included) (update)

MW Redman , ASCO 2021

Vansteenkiste J. et al., atezolizumab in NSCLC (POPLAR)

IO vs Chemo-IO in NSCLC PD-L1≥ 50%

Study Design

Pooled Analysis Population
- Advanced NSCLC
- PD-L1 TPS ≥50%
  - Excluded staining by tumor-infiltrating immune cells
- No sensitizing *EGFR* mutations or *ALK* alterations
- Clinical trial supported FDA approval of IO-based regimen

Chemo-IO

IO-only

Exploratory Primary Outcome measure
- OS

Other exploratory outcome measures
- PFS
- ORR

Sub-group analyses
- Age (yrs): *<65 vs 65-75 vs ≥75*
- ECOG PS: *0 vs. ≥ 1*
- Smoking history: *Never vs. Ever*

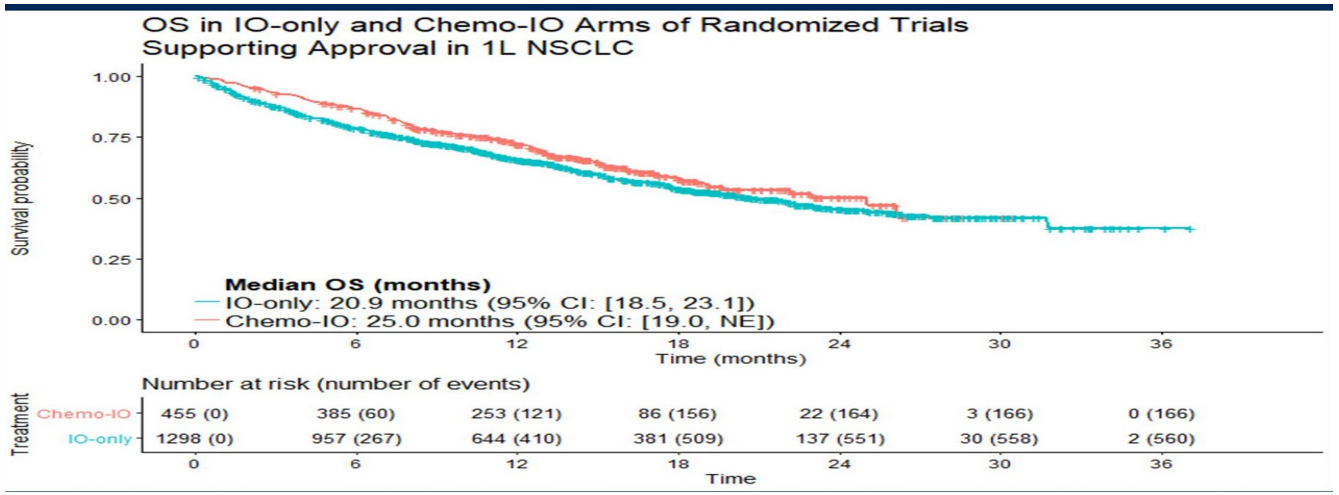
Chemo-IO Trials		IO-only Trials	
Trial	Investigational Regimen	Trial	Investigational Regimen
KEYNOTE-021*	**Pembrolizumab** + Chemo**	CheckMate 026	**Nivolumab****
KEYNOTE-189	**Pembrolizumab** + Chemo**	KEYNOTE-024	**Pembrolizumab****
KEYNOTE-407	**Pembrolizumab** + Chemo**	KEYNOTE-042	**Pembrolizumab****
IMpower150	**Atezolizumab** + Bevacizumab + Chemo***	IMpower110	**Atezolizumab****
IMpower130	**Atezolizumab** + Chemo**	CheckMate 227	**Nivolumab** + **Ipilimumab****
CheckMate-9LA	**Nivolumab** + **Ipilimumab** + Chemo**	EMPOWER-Lung 1	**Cemiplimab****

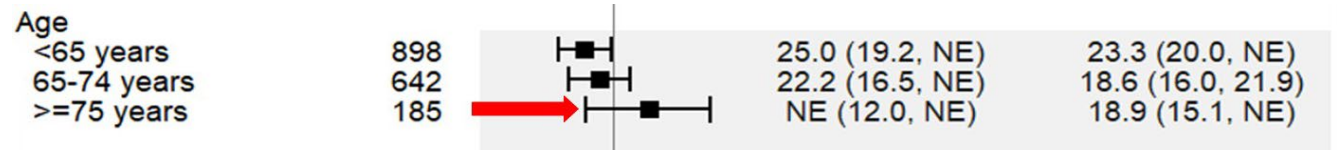
Chemo-IO *N*=455

IO alone *N*=1298

Chemotherapy *N*=1436

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

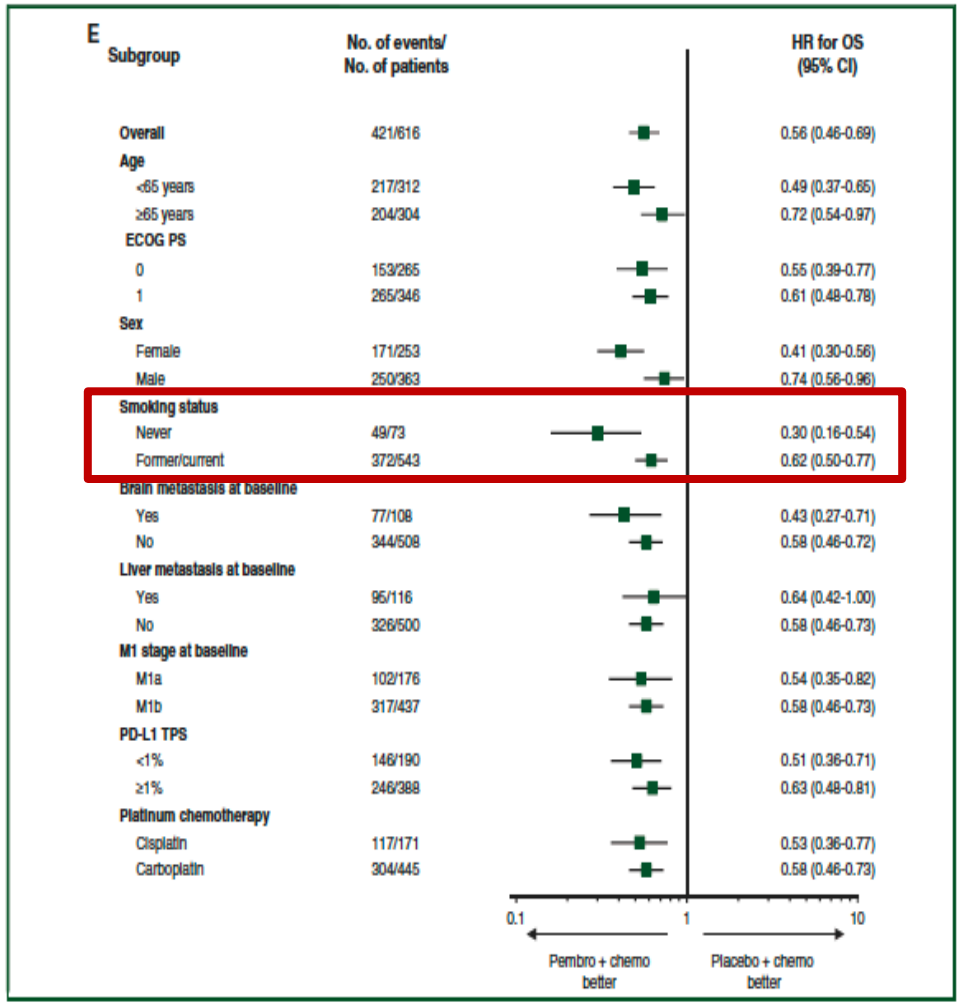




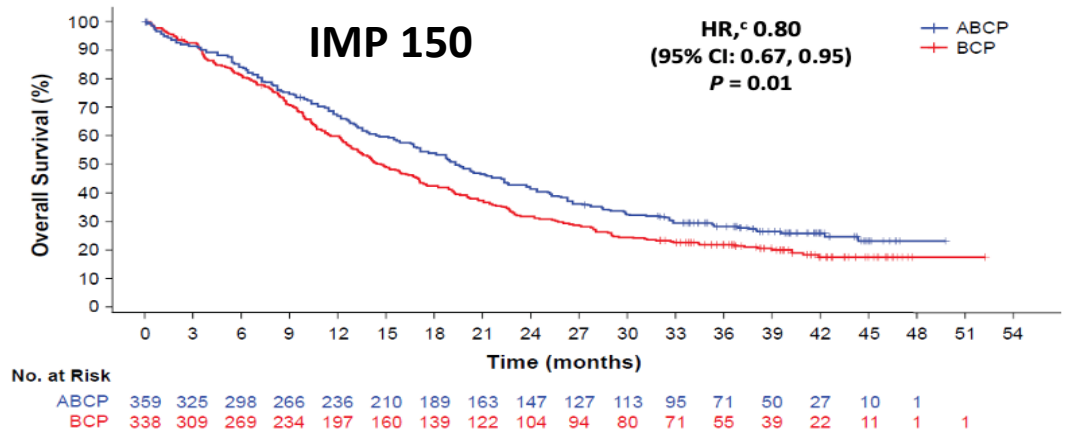
Akinboro et al. ASCO 2022

Smoking status and single genomic aberrations may not be as relevant with Chemo-IO

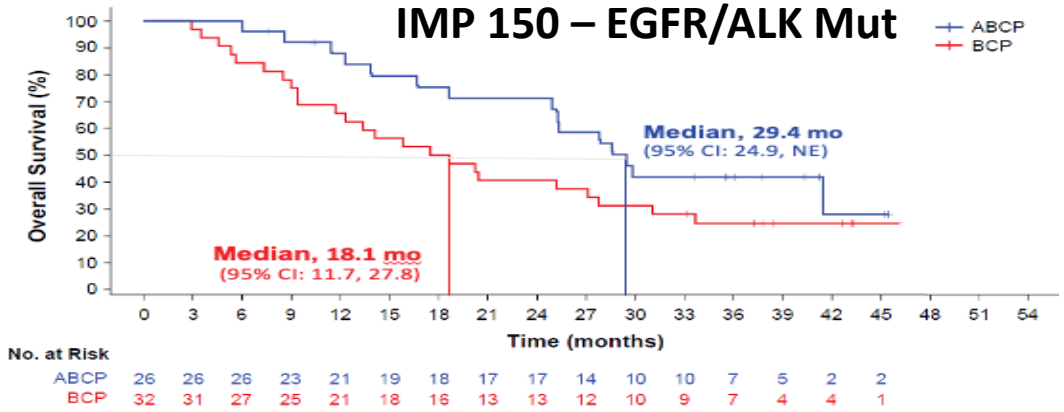
KN 189



Rodriguez-Abreu et al., Ann Oncol 2021



Arm B (atezo + bev + CP) vs Arm C (bev + CP)

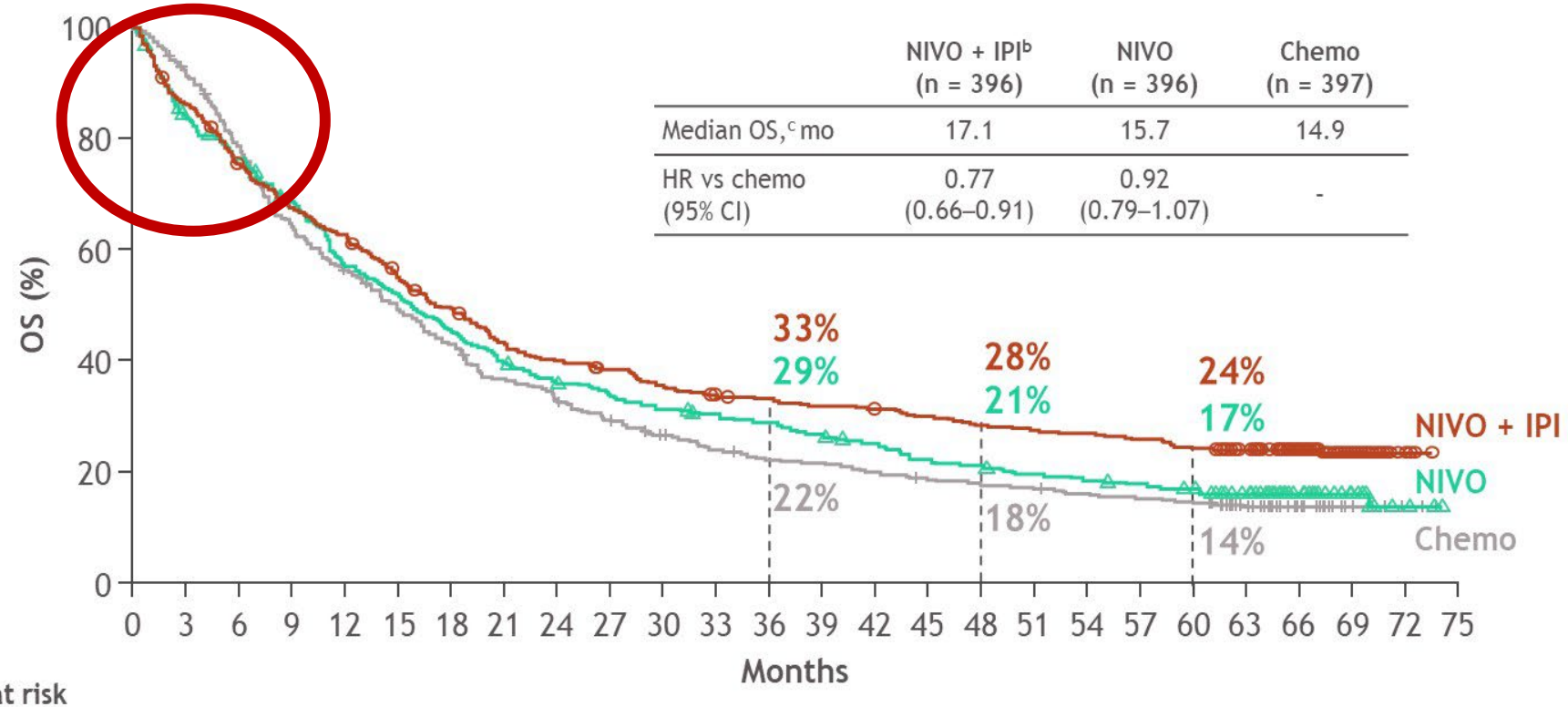


Socinski et al., ASCO 2020

Agenda

- IO Monotherapy
- Chemo plus IO
- **IO plus IO combos**

CM 227 Trial: 5-year OS in patients with PD-L1 ≥ 1%



	NIVO + IPI[b] (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median OS,[c] mo	17.1	15.7	14.9
HR vs chemo (95% CI)	0.77 (0.66–0.91)	0.92 (0.79–1.07)	-

No. at risk																										
NIVO + IPI	396	341	296	265	246	214	192	166	154	146	134	126	123	118	115	110	104	101	99	95	89	74	47	20	3	0
NIVO	396	330	299	265	220	201	176	153	139	129	119	112	108	98	91	80	75	70	66	63	59	46	27	12	3	0
Chemo	397	358	306	250	218	190	166	141	126	112	98	87	80	78	72	66	63	60	56	53	50	37	18	5	2	0

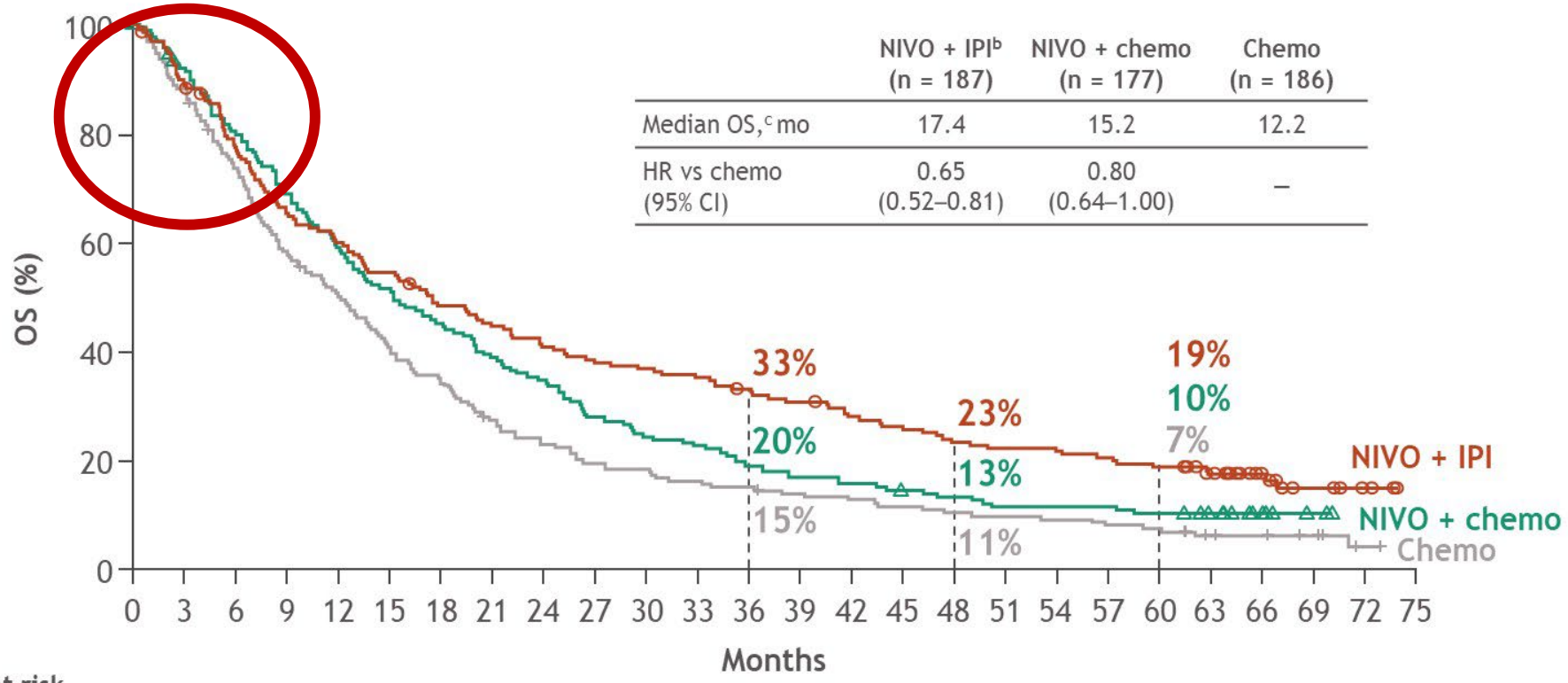
Database lock: February 15, 2022; minimum/median follow-up for OS: 61.3/66.7 months.

[a]In patients with PD-L1 ≥ 1% with a PFS event (per BICR), subsequent systemic therapy was received by 34% in the NIVO + IPI arm, 46% in the NIVO arm, and 48% in the chemo arm; subsequent immunotherapies by 7%, 9%, and 40%; subsequent chemo by 33%, 45%, and 25%, respectively. [b]NIVO + IPI vs NIVO HR was 0.84 (95% CI, 0.72–0.99). [c]Median OS 95% CI are 14.95–20.17 (NIVO + IPI), 13.27–18.14 (NIVO), and 12.71–16.72 (chemo).

BICR, blinded independent central review.

Brahmer et al. Asco 2022

CM 227: 5-year OS in patients with PD-L1 < 1%



	NIVO + IPI[b] (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
Median OS,[c] mo	17.4	15.2	12.2
HR vs chemo (95% CI)	0.65 (0.52–0.81)	0.80 (0.64–1.00)	–

No. at risk																										
NIVO + IPI	187	165	142	120	110	100	88	81	74	69	67	64	59	55	49	45	41	39	38	36	33	27	15	8	3	0
NIVO + chemo	177	159	139	119	102	88	78	67	60	48	42	39	34	29	27	24	22	19	19	19	17	14	7	2	0	0
Chemo	186	164	135	107	92	74	62	49	41	35	33	29	27	24	22	20	18	17	16	14	12	8	7	5	1	0

Database lock: February 15, 2022; minimum/median follow-up for OS: 61.3/66.7 months.

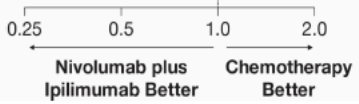
[a]In patients with PD-L1 < 1% with a PFS event (per BICR), subsequent systemic therapy was received by 44% in the NIVO + IPI arm, 39% in the NIVO + chemo arm, and 48% in the chemo arm; subsequent immunotherapies by 8%, 5%, and 33%; subsequent chemo by 43%, 37%, and 33%, respectively. [b]NIVO + IPI vs NIVO + chemo HR was 0.80 (95% CI, 0.63–1.00). [c]Median OS 95% CI are 13.21–22.05 (NIVO + IPI), 12.29–19.78 (NIVO + chemo), and 9.17–14.32 (chemo).

Brahmer et al. Asco 2022

CM 227: OS in patients subsets

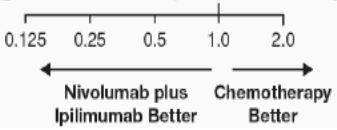
All Patients

Subgroup	Median Overall Survival, Months: Nivolumab plus Ipilimumab N=583	Chemotherapy N=583	Unstratified Hazard Ratio for Death (95% CI)
All the patients (N=1166)	17.1	13.9	0.73 (0.64–0.84)†
Age			
<65 yr (n=611)	16.6	14.2	0.70 (0.58–0.85)
≥65 to <75 yr (n=442)	18.7	13.0	0.76 (0.61–0.95)
≥75 yr (n=113)	15.1	12.4	0.84 (0.55–1.29)
Sex			
Male (n=778)	18.7	13.2	0.68 (0.57–0.80)
Female (n=388)	16.1	15.4	0.89 (0.70–1.12)
ECOG performance-status score			
0 (n=395)	24.4	18.8	0.70 (0.54–0.89)
1 (n=763)	14.8	11.3	0.77 (0.65–0.90)
Smoking status			
Never smoked (n=157)	15.3	16.1	0.96 (0.66–1.41)
Smoker (n=996)	17.4	13.5	0.72 (0.62–0.84)
Tumor histologic type‡			
Squamous (n=328)	15.0	9.2	0.62 (0.49–0.80)
Nonsquamous (n=838)	19.2	15.3	0.79 (0.67–0.93)
Liver metastases			
Yes (n=252)	10.3	10.4	0.82 (0.62–1.08)
No (n=914)	19.4	15.1	0.72 (0.62–0.85)
Bone metastases			
Yes (n=316)	12.2	8.8	0.68 (0.53–0.88)
No (n=850)	19.2	16.0	0.75 (0.64–0.89)
CNS metastases			
Yes (n=115)	16.8	13.4	0.64 (0.42–0.97)
No (n=1051)	17.2	14.0	0.75 (0.65–0.86)



PDL1 Negative Patients

Subgroup	Median Overall Survival, Months: Nivolumab plus Ipilimumab N=187	Chemotherapy N=186	Unstratified Hazard Ratio for Death (95% CI)
All randomized patients (N=373)	17.2	12.2	0.62 (0.48–0.78)†
Age			
<65 yr (n=205)	12.8	12.1	0.69 (0.50–0.94)
≥65 to <75 yr (n=136)	25.2	11.6	0.49 (0.32–0.75)
≥75 yr (n=32)	25.3	16.8	0.75 (0.31–1.82)
Sex			
Male (n=263)	19.4	11.0	0.55 (0.41–0.73)
Female (n=110)	15.3	13.6	0.83 (0.54–1.28)
ECOG performance-status score			
0 (n=126)	25.3	20.8	0.78 (0.50–1.23)
1 (n=244)	15.5	8.7	0.55 (0.42–0.74)
Smoking status			
Never smoked (n=50)	15.3	13.0	0.60 (0.32–1.15)
Smoked (n=322)	17.4	12.1	0.63 (0.49–0.82)
Tumor histologic type‡			
Squamous (n=92)	15.9	8.5	0.49 (0.30–0.79)
Nonsquamous (n=281)	17.5	13.1	0.67 (0.51–0.88)
Liver metastases			
Yes (n=96)	11.7	7.8	0.52 (0.32–0.83)
No (n=277)	17.8	13.9	0.65 (0.49–0.86)
Bone metastases			
Yes (n=108)	9.5	7.6	0.58 (0.37–0.89)
No (n=265)	19.6	14.5	0.64 (0.48–0.85)
CNS metastases			
Yes (n=34)	15.2	10.0	0.54 (0.24–1.22)
No (n=339)	17.8	12.2	0.62 (0.48–0.80)



Hellmann et al. NEJM 2019

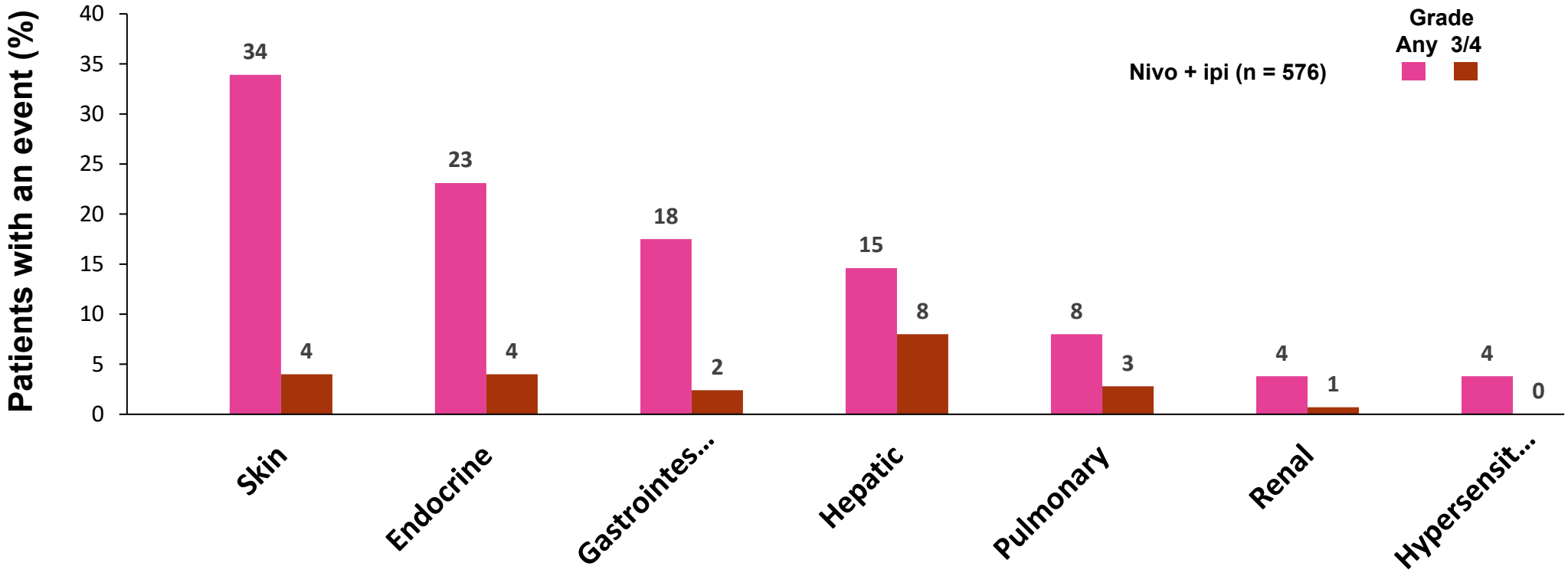
Safety Summary of Treatment-Related AEs

TRAE,[a] %	Nivolumab + ipilimumab (n = 576)		Chemotherapy (n = 570)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE	75	31	81	36
TRAE leading to discontinuation[b]	17	12	9	5
Most frequent TRAEs (≥15%)				
Rash	17	2	5	0
Diarrhea	16	2	10	1
Fatigue	13	1	18	1
Decreased appetite	13	<1	19	1
Nausea	10	<1	36	2
Constipation	4	0	15	<1
Anemia	4	2	32	11
Neutropenia	<1	0	17	9
Treatment-related deaths[c]	1		1	

- Median duration (range) of therapy was 4.2 months (0.03–24.0+) with nivolumab + ipilimumab and 2.6 months (0.03–22.1+) with chemotherapy
- Median number of doses of nivolumab (Q2W) and ipilimumab (Q6W) received were 9 and 3, respectively

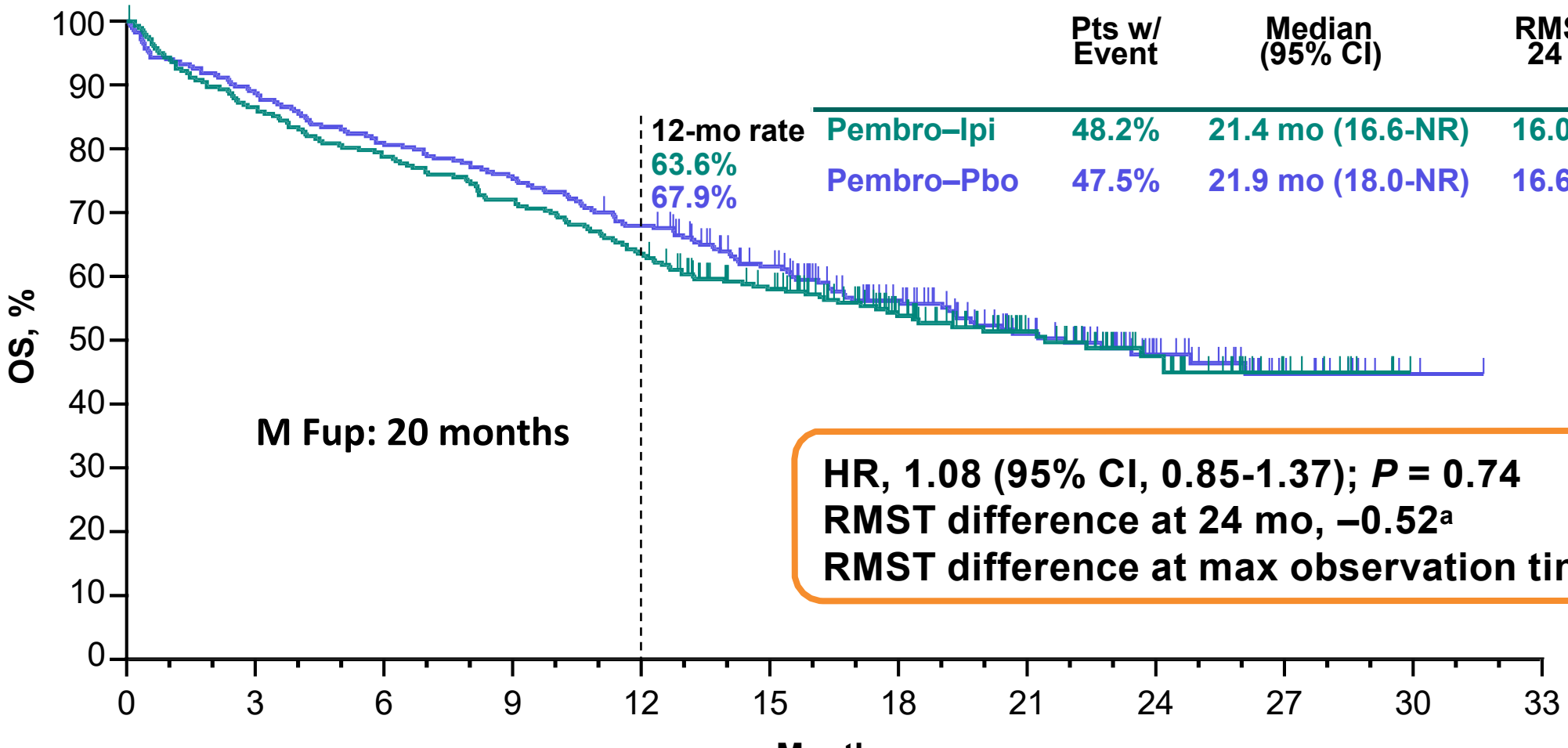
[a]Includes events reported between first dose and 30 days after last dose of study drug; [b]For nivo + ipi, these events include TRAEs leading to discontinuation of ipi or both study drugs; patients could not discontinue nivo without discontinuing ipi; [c]Treatment-related deaths in the nivo + ipi arm included myocarditis, acute tubular necrosis, pneumonitis (n = 3), circulatory collapse, and cardiac tamponade; deaths in the chemo arm included sepsis (n = 2), multiple brain infarctions, interstitial lung disease, thrombocytopenia, and febrile neutropenia with sepsis

Treatment-Related Select AEs in Patients Treated With Nivolumab + Ipilimumab[a,b]



Select AEs were events with potential immunologic etiology that required frequent monitoring/intervention; included events reported between first dose and 30 days after last dose of study drug.

KN 598: Overall Survival



	Pts w/ Event	Median (95% CI)	RMST at 24 mo	RMST at Max Time
Pembro–Ipi	48.2%	21.4 mo (16.6-NR)	16.09 mo	18.76 mo
Pembro–Pbo	47.5%	21.9 mo (18.0-NR)	16.61 mo	19.32 mo

HR, 1.08 (95% CI, 0.85-1.37); *P* = 0.74
RMST difference at 24 mo, –0.52[a]
RMST difference at max observation time, –0.56[a]

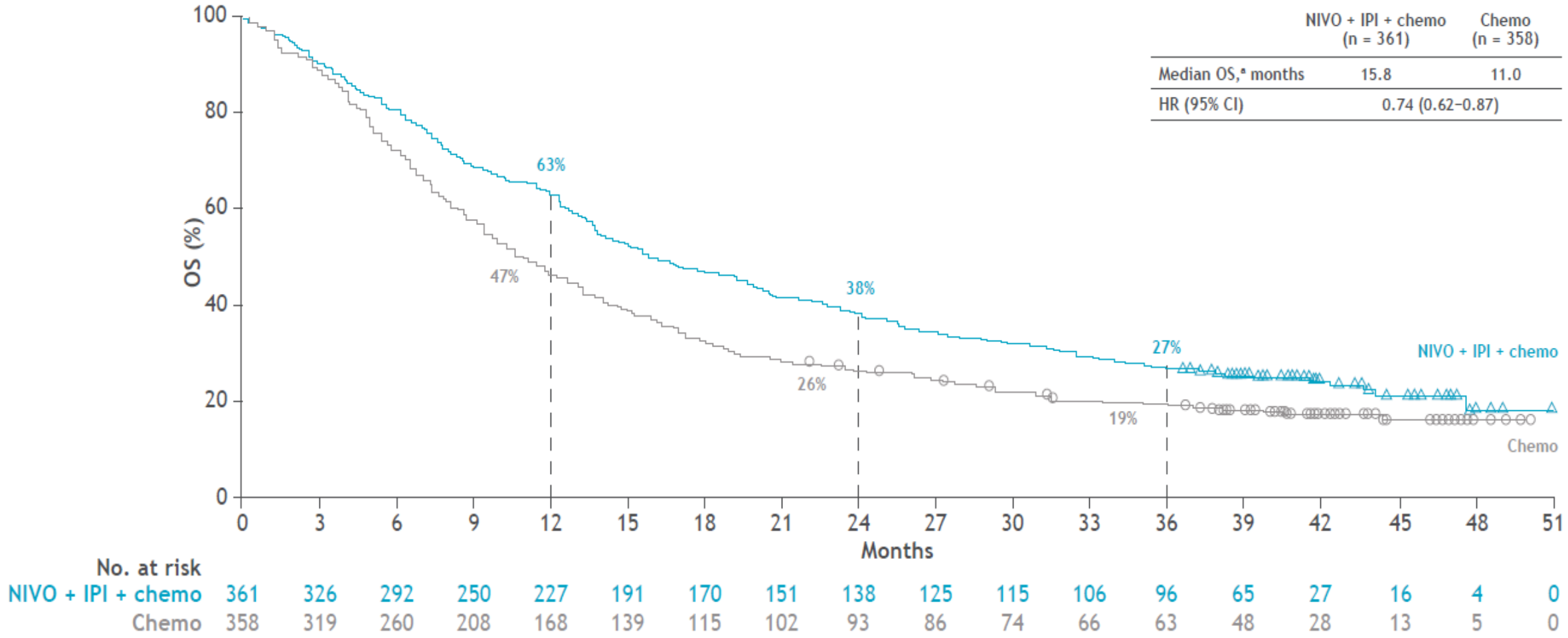
No. at risk

284	245	223	204	180	146	100	62	37	10	0	0
284	252	230	215	192	154	111	77	41	15	2	0

[a]Nonbinding futility criteria met.
Data cutoff date: Sep 1, 2020; median study follow-up was 20.6 months (range, 12.4–31.7 months).

Boyer et al. WLCC 2020

9 LA Trial 3-Year update: OS in all randomized patients

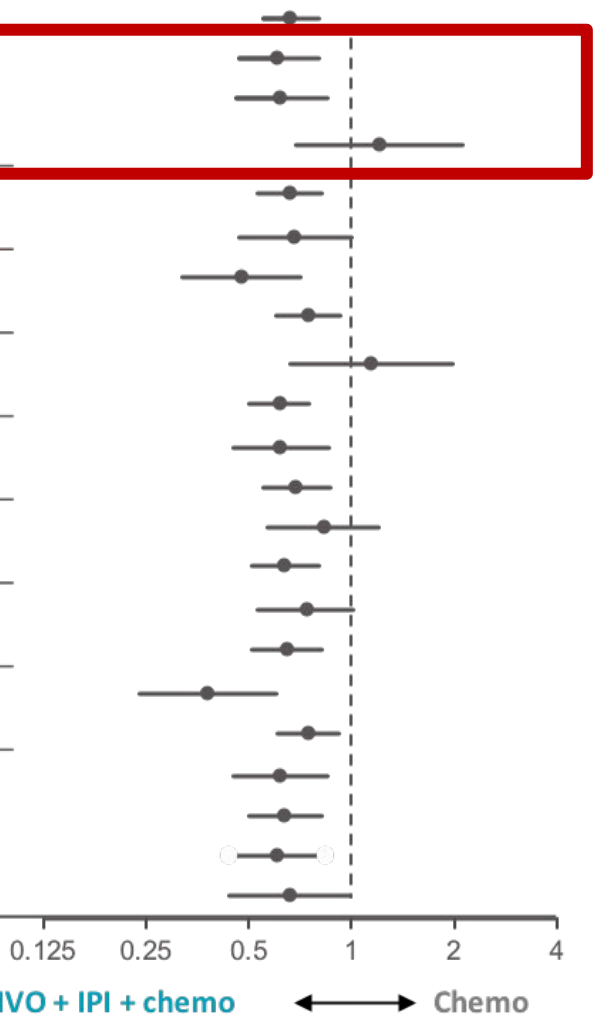


Database lock: February 15, 2022; minimum follow-up: 36.1 months.
[a]95% CI, 13.9-19.7 (NIVO + IPI + chemo) and 9.5-12.7 (chemo).

L Paz-Ares et al. ASCO 2022

9LA Regimen – OS According to Age

Subgroup	Median OS, mo		Unstratified HR
	NIVO + IPI + chemo n = 361	Chemo n = 358	
All randomized (N = 719)	15.6	10.9	0.66[a]
< 65 years (n = 354)	15.6	10.7	0.61
65 to < 75 years (n = 295)	19.4	11.9	0.62
≥ 75 years (n = 70)	8.5	11.5	1.21
Male (n = 504)	14.1	9.8	0.66
Female (n = 215)	19.4	15.8	0.68
ECOG PS 0 (n = 225)	NR	15.4	0.48
ECOG PS 1 (n = 492)	13.6	9.7	0.75
Never smoker (n = 98)	14.1	17.8	1.14
Smoker (n = 621)	15.6	10.4	0.62
Squamous (n = 227)	14.5	9.1	0.62
Non-squamous (n = 492)	17.0	11.9	0.69
Liver metastases (n = 154)	10.2	8.1	0.83
No liver metastases (n = 565)	19.4	12.4	0.64
Bone metastases (n = 207)	11.9	8.3	0.74
No bone metastases (n = 512)	20.5	12.4	0.65
CNS metastases (n = 122)	NR	7.9	0.38
No CNS metastases (n = 597)	15.4	11.8	0.75
PD-L1 < 1% (n = 264)	16.8	9.8	0.62
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.64
PD-L1 1–49% (n = 233)	15.4	10.4	0.61
PD-L1 ≥ 50% (n = 174)	18.0	12.6	0.66



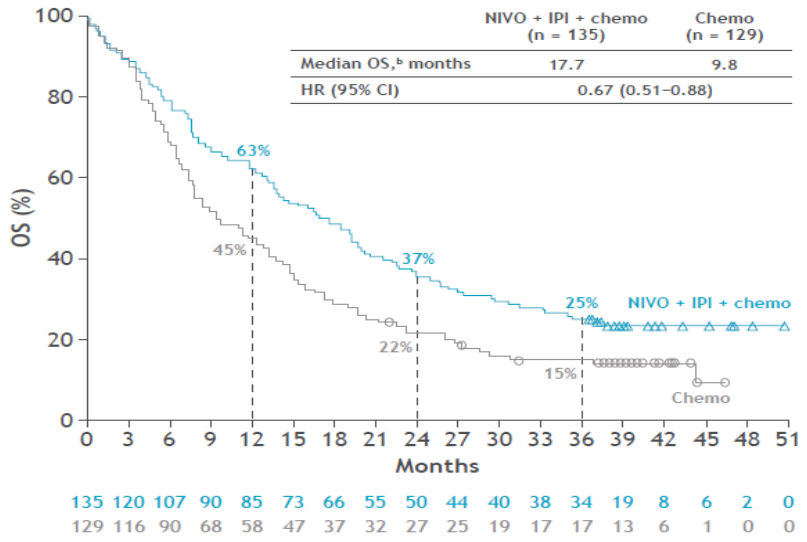
Minimum follow-up: 12.7 months.

[a]Stratified HR; unstratified HR was 0.67 (95% CI, 0.55–0.81).

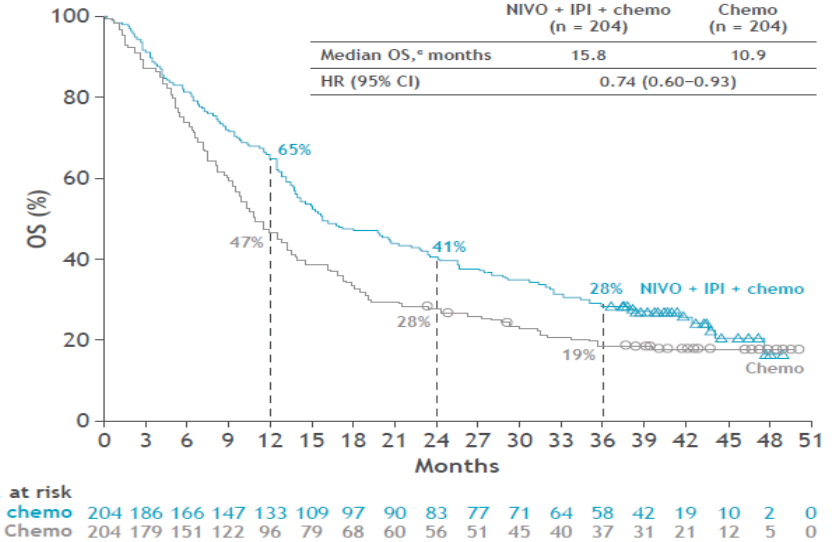
Reck M *et al.* ASCO 2020.

Overall survival by PD-L1 expression

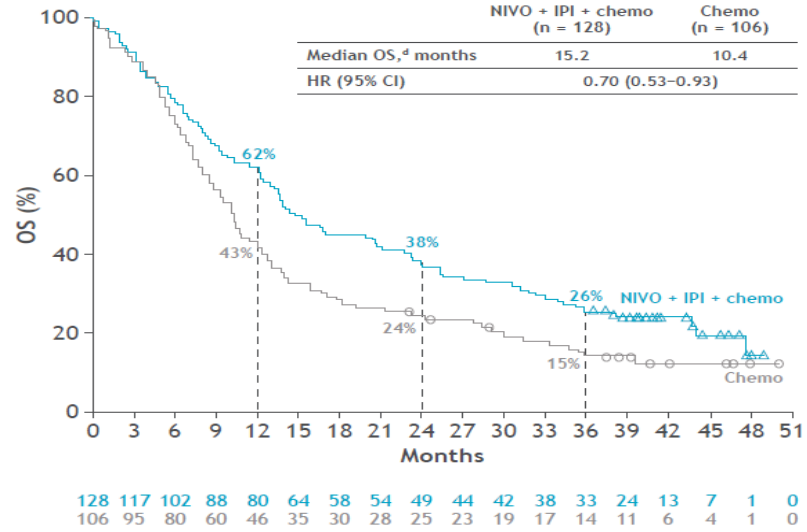
PD-L1 <1%



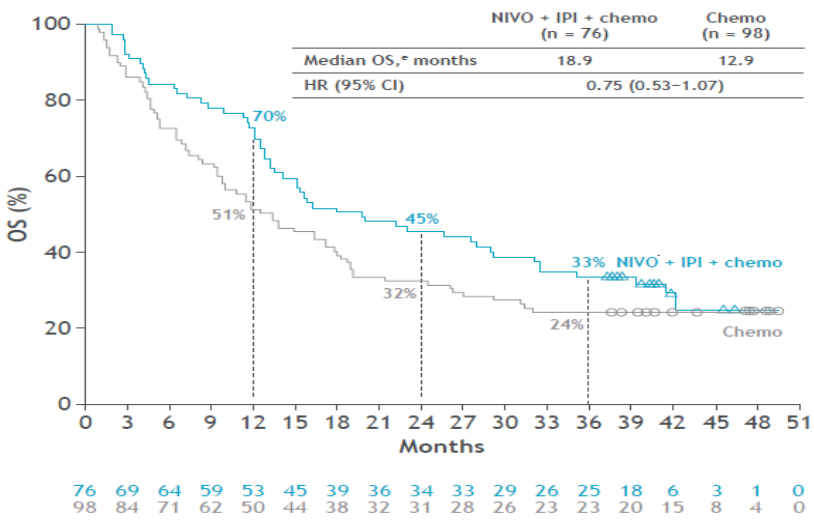
PD-L1 ≥1%



PD-L1 1-49%



PD-L1 ≥50%

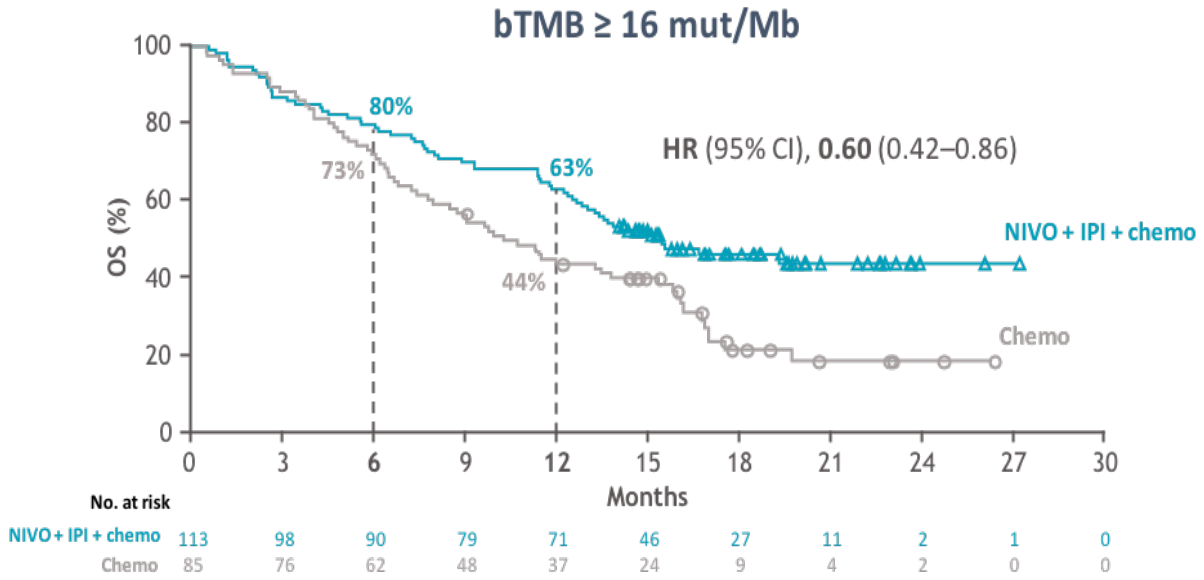


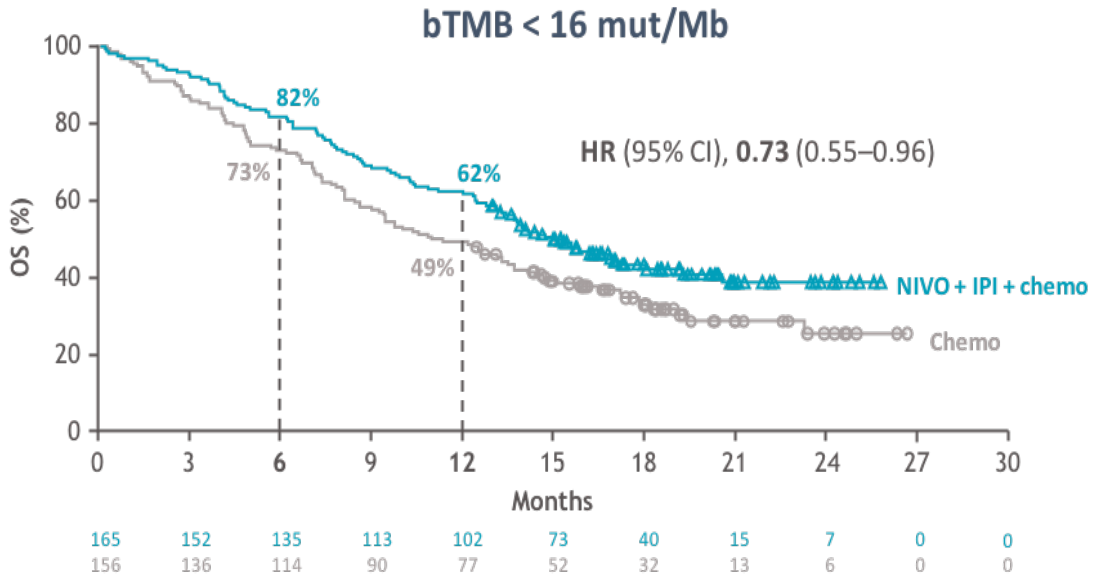
Database lock: February 15, 2022; minimum follow-up: 36.1 months.

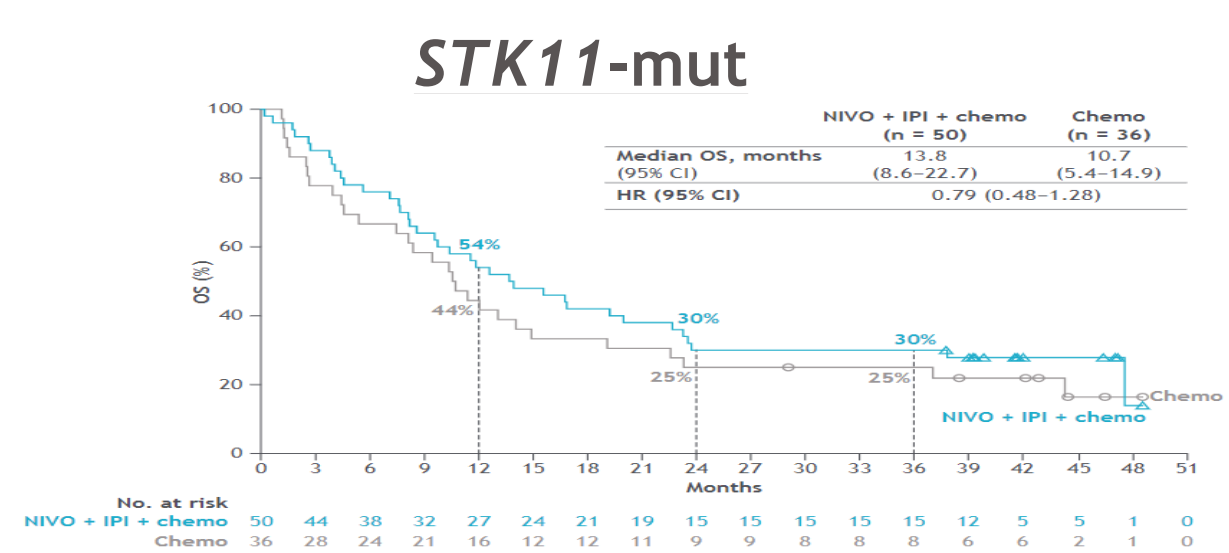
[a]95% CI, 13.7–20.3 (NIVO + IPI + chemo) and 7.7–13.5 (chemo); [b]95% CI, 13.8–22.2 (NIVO + IPI + chemo) and 9.5–13.2 (chemo); [c]95% CI, 12.6–21.2 (NIVO + IPI + chemo) and 8.7–12.4 (chemo); [d]95% CI, 13.1–29.1 (NIVO + IPI + chemo) and 9.4–17.6 (chemo).

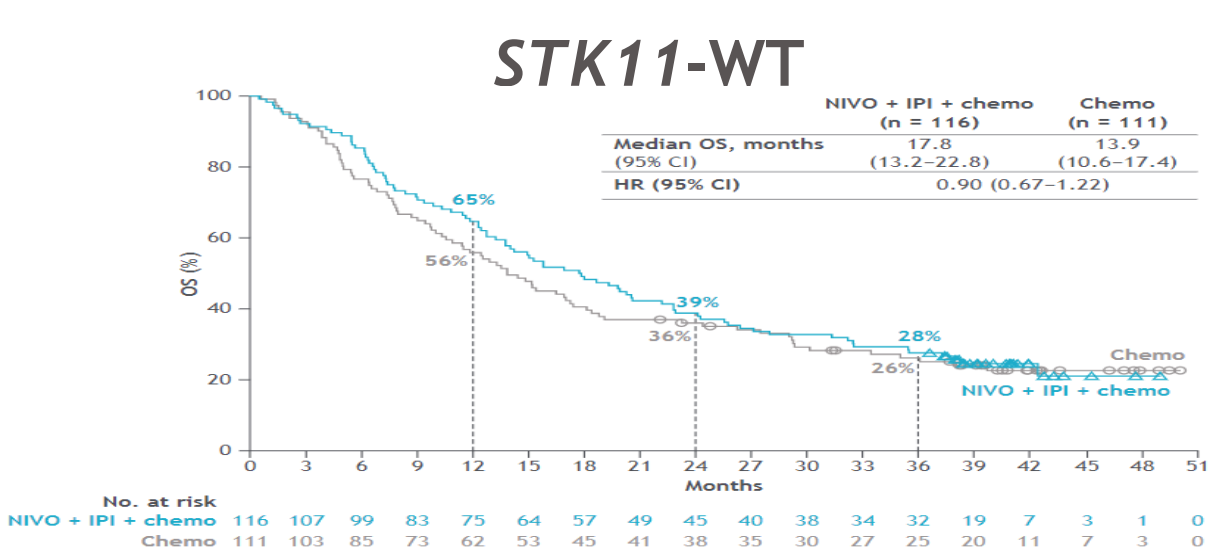
L Paz-Ares et al. ASCO 2022

9LA régimen - TMB and genomic aberrations are not predictive







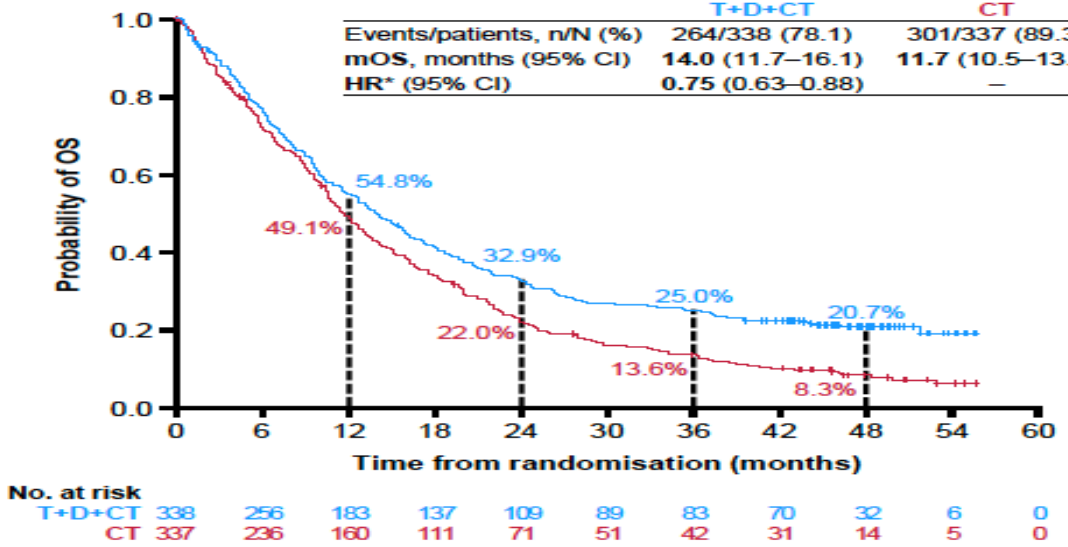


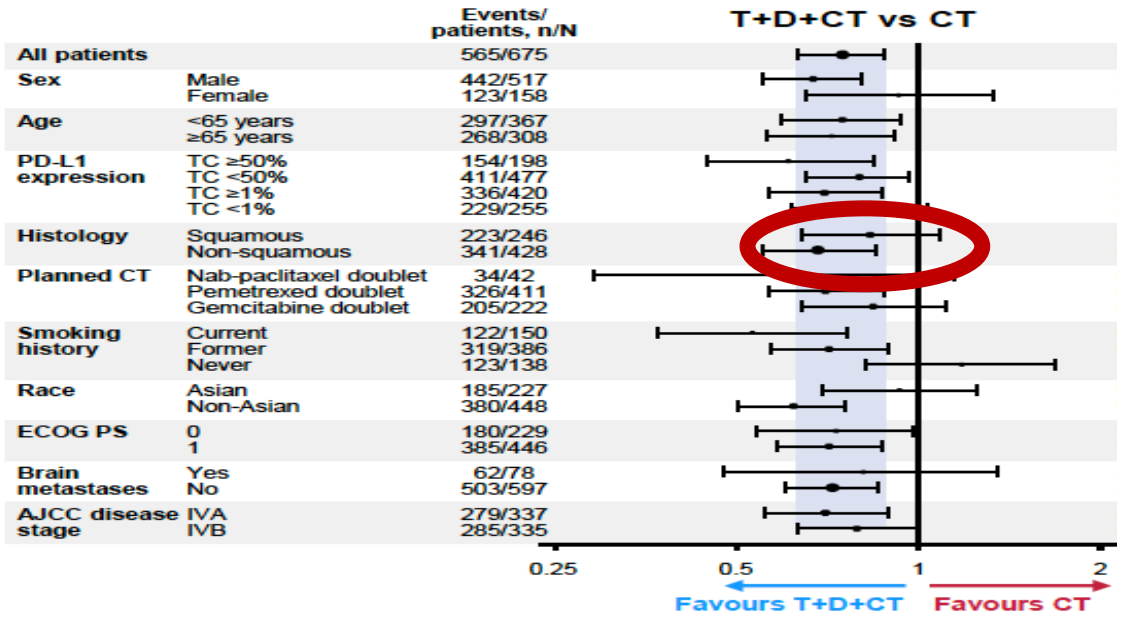
L Paz-Ares *et al.* ELCC 2021 & ASCO 2022.

POSEIDON trial – Updated Outcomes

T+D+CT vs CT

	T+D+CT	CT
Events/patients, n/N (%)	264/338 (78.1)	301/337 (89.3)
mOS, months (95% CI)	**14.0** (11.7–16.1)	**11.7** (10.5–13.1)
HR* (95% CI)	**0.75** (0.63–0.88)	–



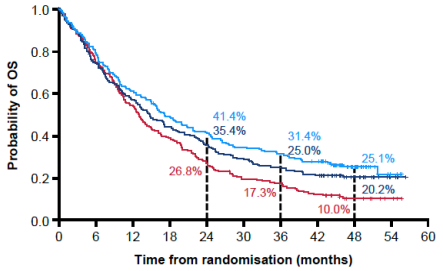


Updated OS by Histology

OS benefit with T+D+CT vs CT more pronounced in NSQ with HR 0.68 and estimated 31.4% alive at 3 yrs vs 17.3%

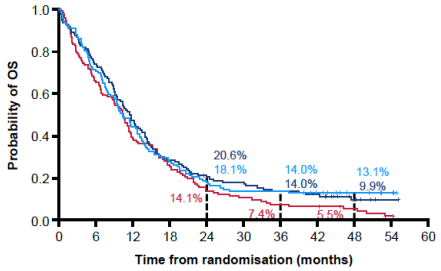
NSQ

	T+D+CT	D+CT	CT
Events/patients, n/N	158/214	162/209	183/214
mOS, months (95% CI)	**17.2** (14.9–21.8)	**14.8** (11.8–18.3)	**13.1** (10.6–15.1)
HR* (95% CI)	**0.68** (0.55–0.85)	**0.80** (0.64–0.98)	–



SQ

	T+D+CT	D+CT	CT
Events/patients, n/N	106/124	113/128	117/122
mOS, months (95% CI)	**10.4** (8.4–12.7)	**11.5** (9.4–14.0)	**10.5** (8.0–11.7)
HR* (95% CI)	**0.83** (0.64–1.08)	**0.81** (0.63–1.06)	–

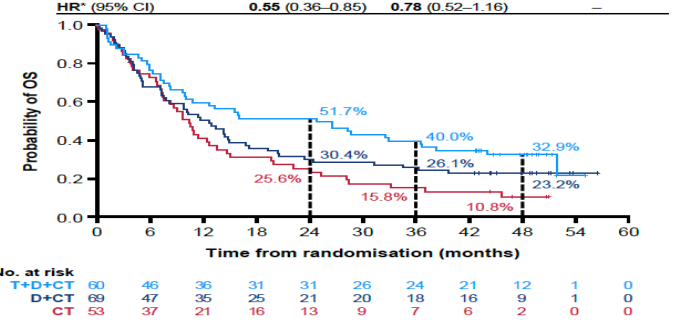


Updated OS by *KRAS* Mutation Status

OS benefit observed for T+D+CT vs CT in *KRAS*m with HR 0.55 and estimated 40.0% alive at 3 yrs vs 15.8%

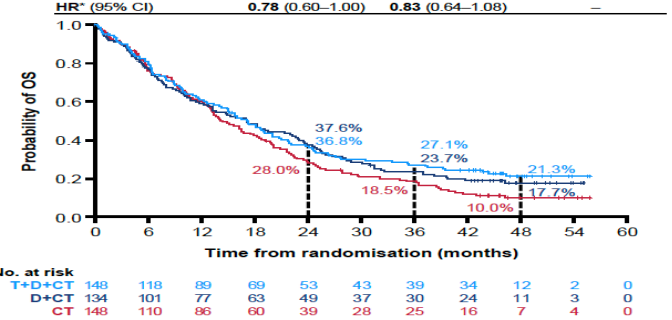
*KRAS*m

	T+D+CT	D+CT	CT
Events/patients, n/N	41/60	53/69	45/53
mOS, months (95% CI)	**25.7** (9.9–36.7)	**12.6** (7.5–16.9)	**10.4** (7.5–13.6)
HR* (95% CI)	**0.55** (0.36–0.85)	**0.78** (0.52–1.16)	–



*KRAS*wt

	T+D+CT	D+CT	CT
Events/patients, n/N	113/148	107/134	127/148
mOS, months (95% CI)	**17.1** (13.4–20.1)	**17.1** (12.3–22.6)	**14.4** (12.6–18.3)
HR* (95% CI)	**0.78** (0.60–1.00)	**0.83** (0.64–1.08)	–



M Johnson et al. ESMO 2022

Advanced NSCLC: IO Selection

- **IO Monotherapy**
- **Chemo plus IO**
- **IO plus IO combos**
- **Chemo plus IO-IO combos**

Tumor

- **PD-L1**
- Agressiveness
- Tumor burden
- Genomics/TMB

Patient

- PS
- Smoking
- Gender
- Comorbidities
- Convenience
- Expectations

Take home

- Novel immunotherapy strategies have impacted the natural history of advanced NSCLC patients
  - PD-1 inhibitors in PD-L1 $\geq$ 50
  - Chemo-IO in low/negative PD-L1 expressors
  - Dual IO combos
- Different treatment alternatives and combos should be consider according to tumor characteristics and patient health and expectations
- Multiparametric predictive biomarkers are required for personalized IO approaches

Gracias

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Global Lung Cancer Academy

Current Immunotherapy Options for Relapsed NSCLC

Benjamin Besse, MD, PhD

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Current Immunotherapy Options for Relapsed NSCLC

Benjamin Besse MD, PhD
Head, Clinical Research
Gustave Roussy Cancer Center
Chair, EORTC Scientific Chairs Council

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  4D Pharma, Abbvie, Amgen, Aptitude Health, AstraZeneca, BeiGene, Blueprint Medicines, Boehringer Ingelheim, Celgene, Cergentis, Chugai pharmaceutical, Cristal Therapeutics, Daiichi-Sankyo, Eli Lilly, EISAI, Genzyme Corporation, GSK, Inivata, IPSEN, Janssen, Onxeo, OSE immunotherapeutics, Pfizer, Roche-Genentech, Sanofi, Takeda, Tolero Pharmaceuticals, Turning Point Therapeutics

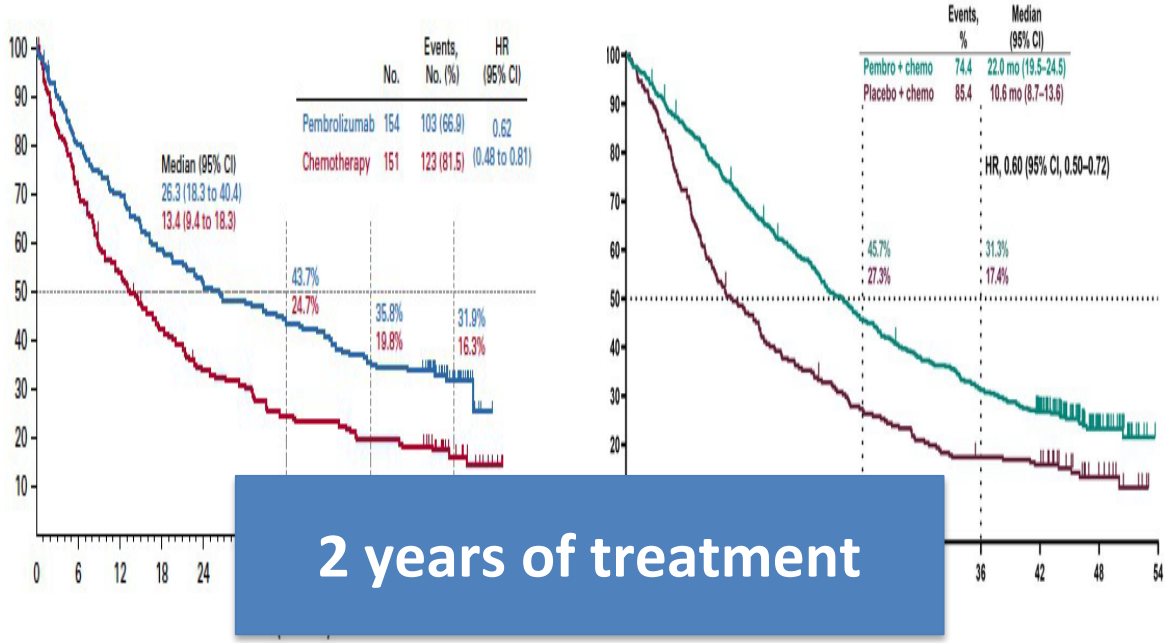
Relapsed NSCLC after immunotherapy

- **Patient stopped their previous immunotherapy regimen**
  - **Because end of treatment was planned**

ICI strategy is relevant in all stages of NSCLC

2016  2018

METASTATIC DISEASE
KEYNOTE 024 & 189



2 years of treatment

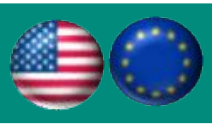
KEYNOTE-024 (PD-L1 ≥50%)
mOS: 26.3mo. / 5-y OS: 32%

KEYNOTE-189 (all comers)
mOS: 23 mo. / 3-y OS: 36%

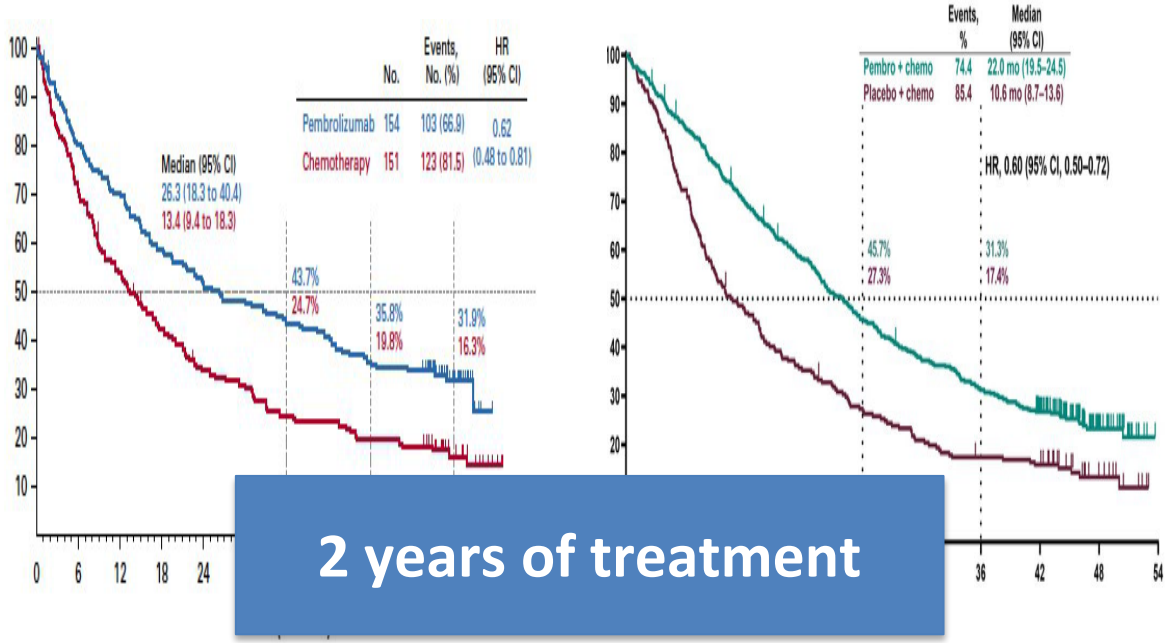
Reck – JCO 2021 * Gray – WCLC 2020 * Spigel – ASCO 2021 * Felip –Lancet 2021 (MDFS/OS: median disease free survival / Overall Survival. NE: Not Estimated)

Courtesy of J.Remon

ICI strategy is relevant in all stages of NSCLC

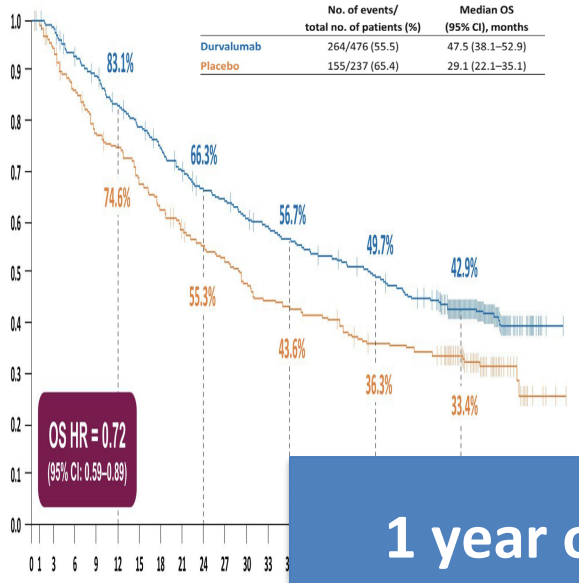
2016  2018 — 2018  PD-L1 ≥1% By the EMA — 2021  PD-L1 ≥1% Stage II-IIIA

METASTATIC DISEASE
KEYNOTE 024 & 189



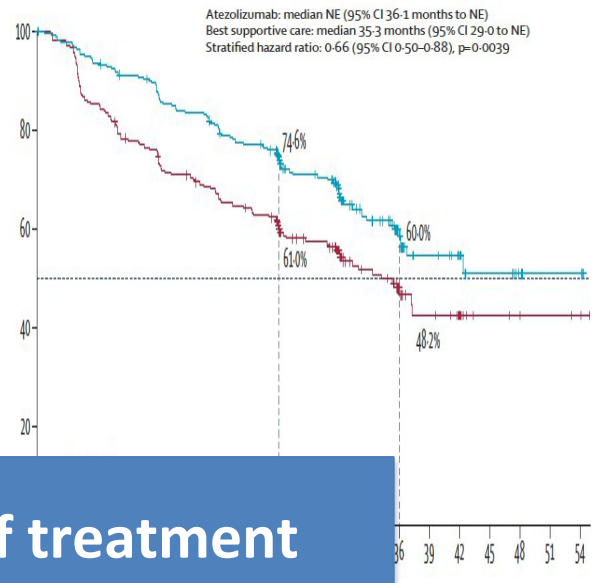
2 years of treatment

LOCALLY ADVANCED DISEASE
PACIFIC



1 year of treatment

EARLY-STAGE DISEASE
IMpower 010



KEYNOTE-024 (PD-L1 ≥50%)
mOS: 26.3mo. / 5-y OS: 32%

KEYNOTE-189 (all comers)
mOS: 23 mo. / 3-y OS: 36%

PACIFIC (all comers)
mOS: 47.5 mo. / 5-y OS: 43%

IMpower010 II-IIIA PD-L1≥1%
mDFS: NE mo. / 5-y DFS: 60%

Reck – JCO 2021 * Gray – WCLC 2020 * Spigel – ASCO 2021 * Felip –Lancet 2021 (MDFS/OS: median disease free survival / Overall Survival. NE: Not Estimated)

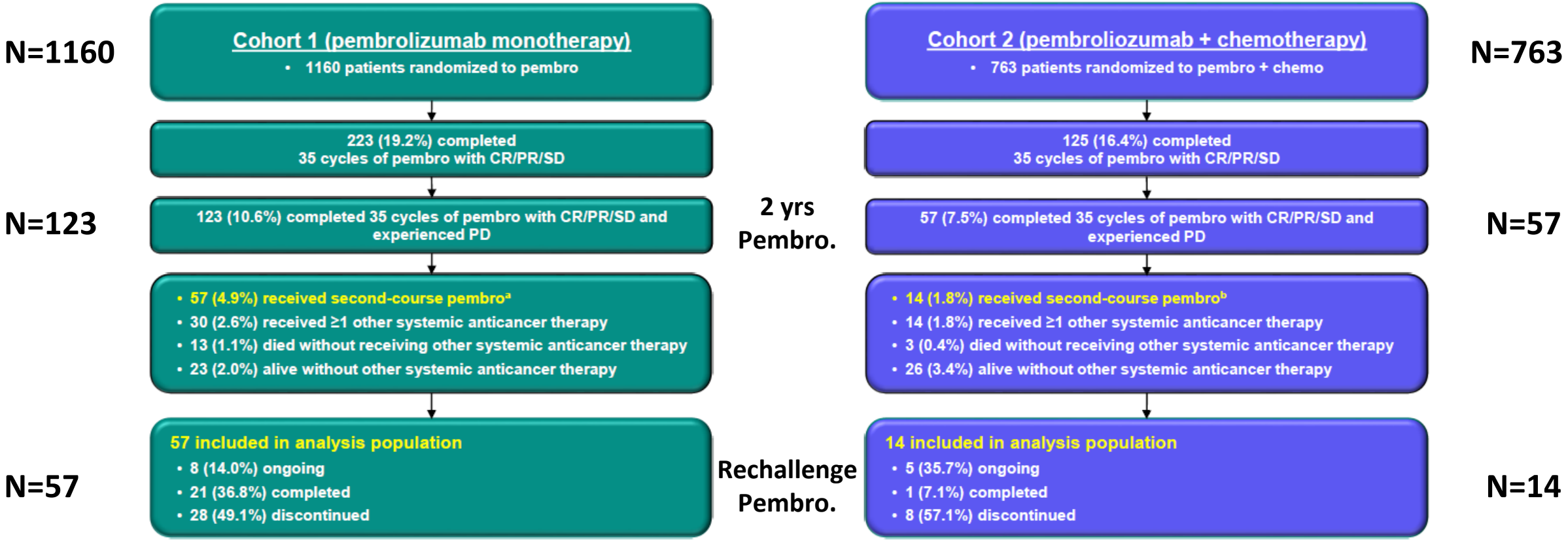
Courtesy of J.Remon

A patient with stage IV adenocarinoma has received 4 cycles of pemetrexed-carboplatin and pembrolizumab up to 2 years. He is off treatment for 18 months.
He has a diffuse relapse (bone, adrenal, lung).
What is your favorite option ?

- Docetaxel
- Docetaxel + nintedanib
- Pembrolizumab
- Paclitaxel-carboplatin
- Pemetrexed-carboplatin-pembrolizumab

Pembrolizumab rechallenge after 2 yrs pembrolizumab

A pooled analysis of 3 randomized phase III trials



- **Median duration on second course:** 8.3 mo (95% CI, 5.6–NR)
- **Remaining on second-course pembro at 6 mo:** 62.8% (95% CI, 48.5%–74.2%)

- **Median duration on second course:** 7.6 mo (95% CI, 1.4–NR)
- **Remaining on second course pembro at 6 mo:** 55.0% (95% CI, 25.8%–76.8%)

[a]1 patent completed 35 cycles after assessment of PD by BICR but PR per investigator; 1 patient did not complete 35 cycles because of CR assessment.
[b]2 patients did not complete 35 cycles but did receive 2 years of treatment.
Database cutoff dates: Jun 1, 2020 (KN024); Apr 28, 2021 (KN042); Oct 1, 2021 (KN598); Aug 28, 2020 (KN189); Sep 30, 2020 (KN407).

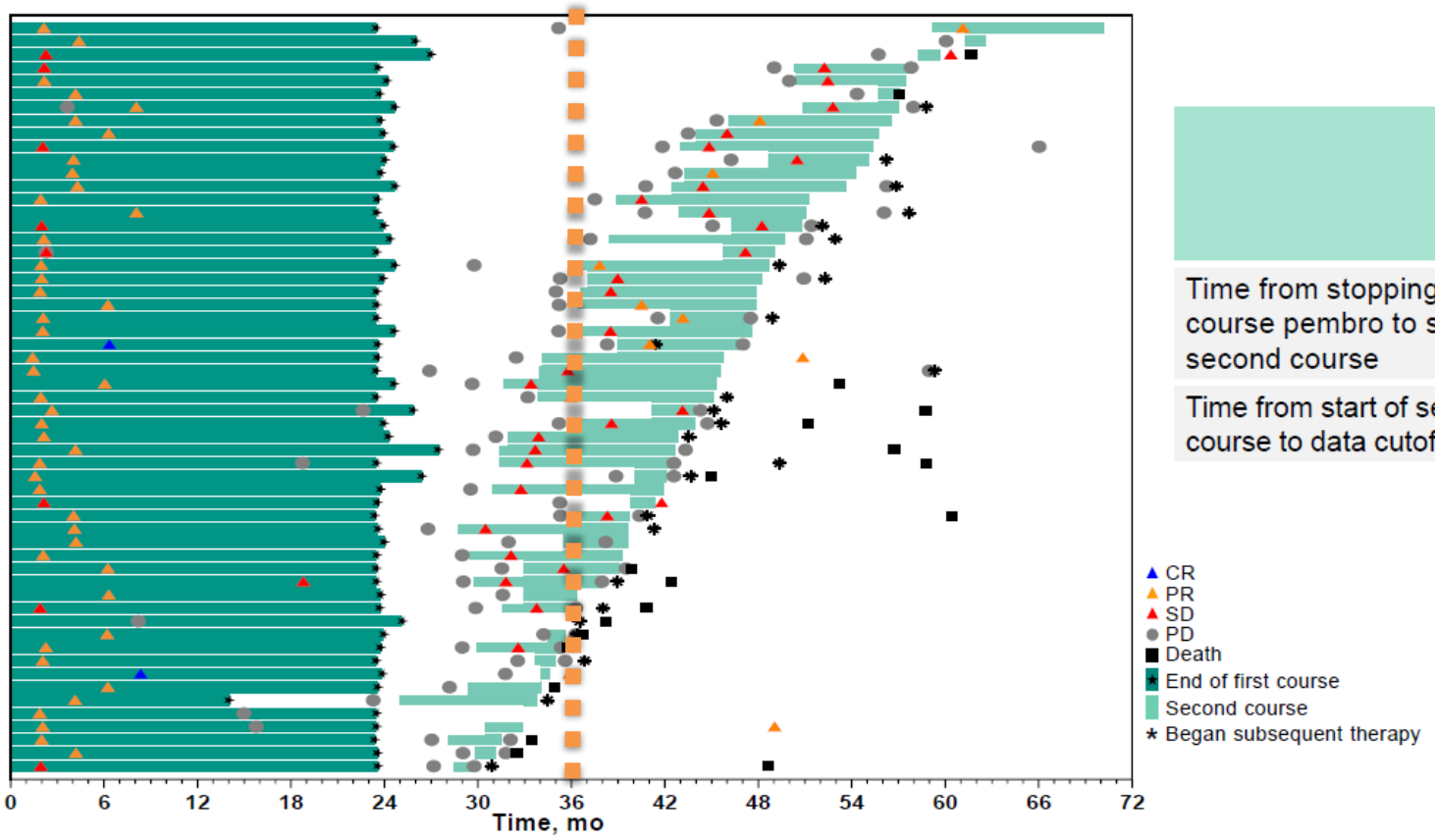
Rodiguez-Abreu WCLC 2022

Pembrolizumab rechallenge after 2 yrs pembrolizumab

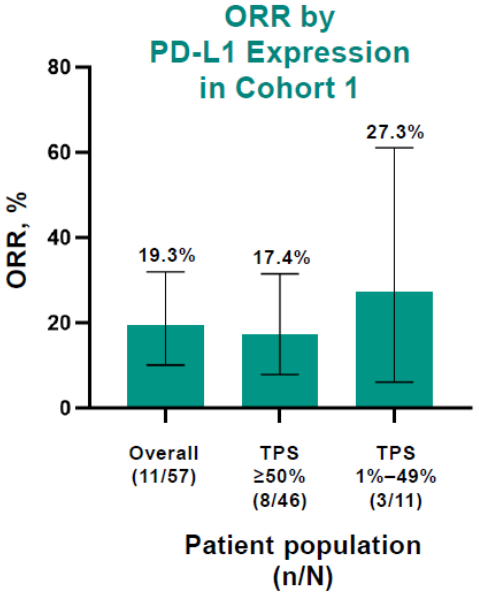
A pooled analysis of 3 randomized phase III trials

ORR = 19.3%
PFS = 10.3 mo
OS = 27.5 mo

Cohort 1 : rechallenge after pembrolizumab single agent



	Median (range), mo
Time from stopping first-course pembro to starting second course	12.0 (3.8–35.6)
Time from start of second course to data cutoff	21.5 (0.6–46.5)



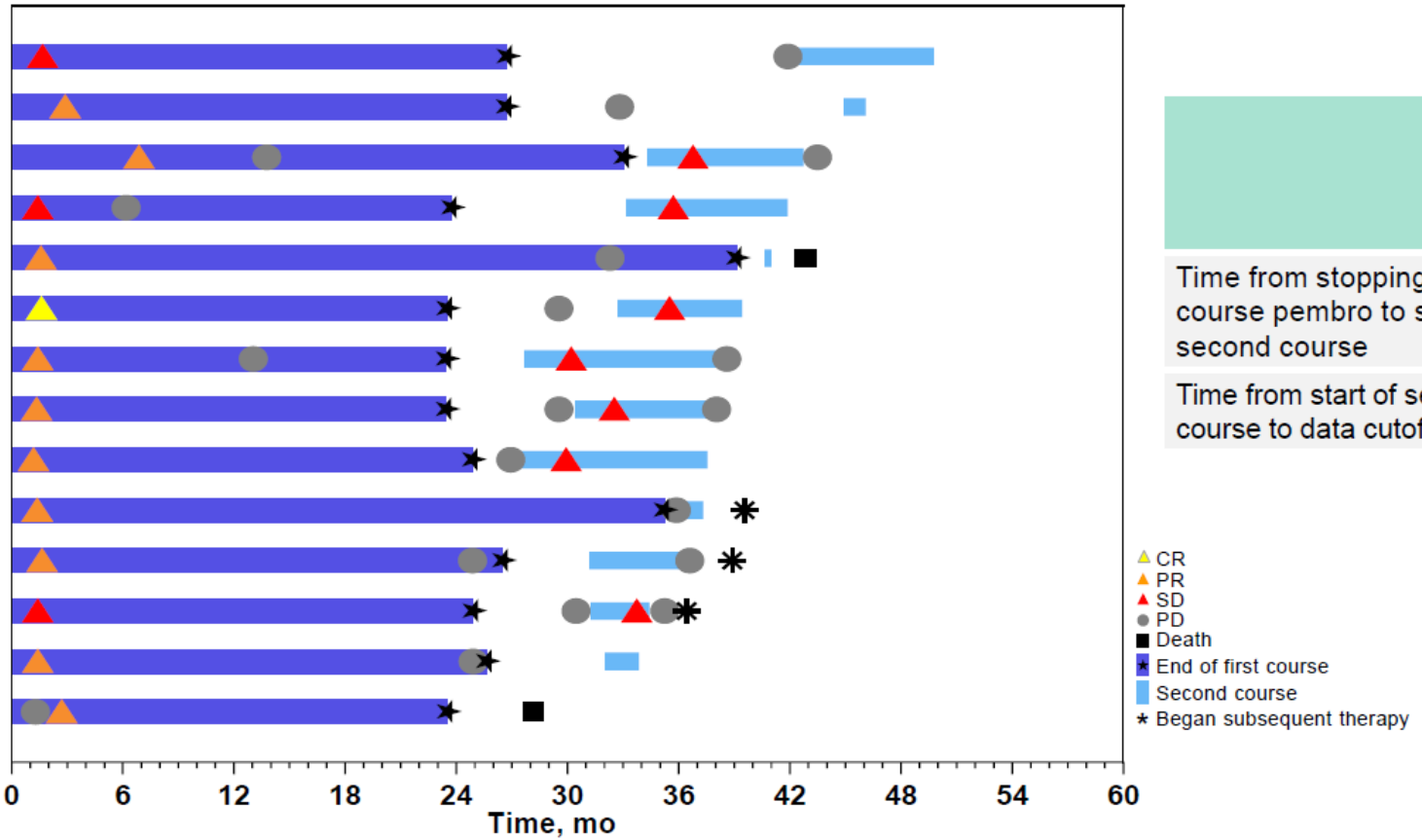
[a]Patient stopped treatment at cycle 21 due to CR assessed per investigator and not BICR (PR). At the time of progression, patient was eligible for second-course pembrolizumab, per protocol.
Database cutoff dates: Jun 1, 2020 (KN024); Apr 28, 2021 (KN042); Oct 1, 2021 (KN598); Aug 28, 2020 (KN189); Sep 30, 2020 (KN407).

Rodiguez-Abreu WCLC 2022

Pembrolizumab rechallenge after 2 yrs pembrolizumab

A pooled analysis of 3 randomized phase III trials

Cohort 2 : rechallenge after chemo-pembrolizumab



	Median (range), mo
Time from stopping first-course pembro to starting second course	5.4 (0.9–18.2)
Time from start of second course to data cutoff	10.3 (1.9–18.0)

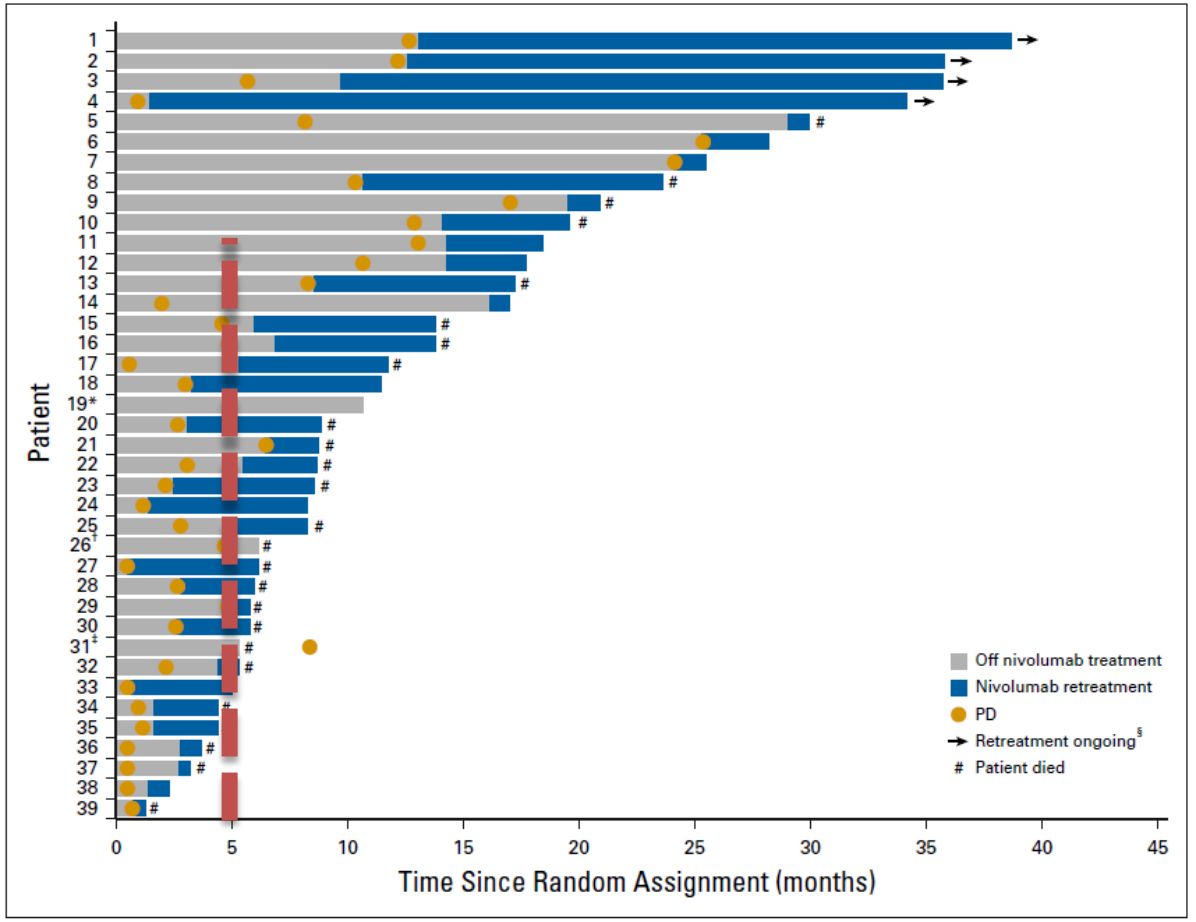
ORR = 0 %
PFS = 7.7 mo
OS = NR

Rodiguez-Abreu WCLC 2022

Nivolumab rechallenge after 1 yrs nivolumab

CheckMate 153: Continuous vs 1-Year Nivolumab

39 patients were retreated with nivolumab.



Watherhouse JCO 2020

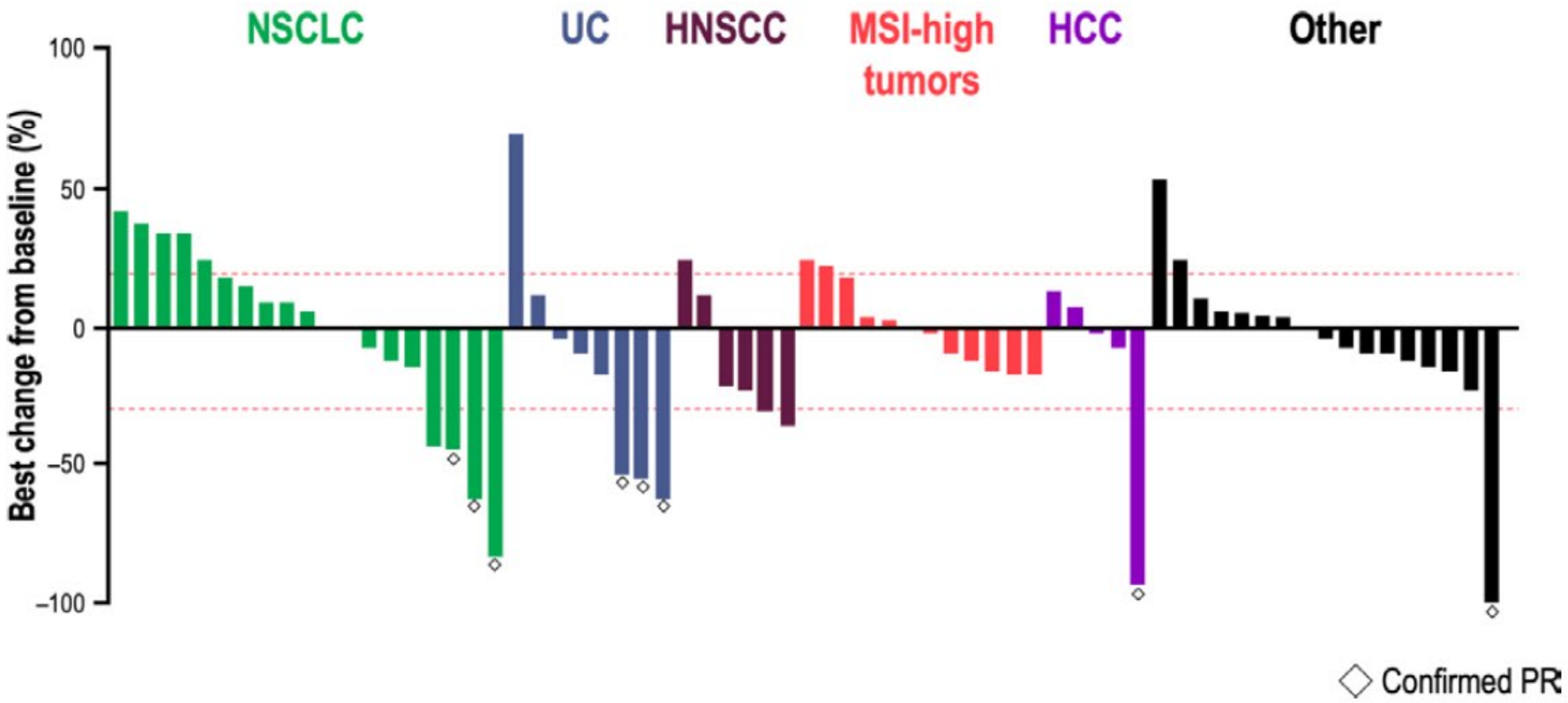
Durvalumab rechallenge after 1 yrs durvalumab

Phase I/II study evaluating durvalumab in advanced solid tumors (NCT01693562

. N=980 patients
. 168 stopped without DP at 1 yr

. 70 pts (41.7%) rechallenged

. Rechallenge:
11.4% PR
60% SD
22.9% PD



Sheth J Immunother Cancer. 2020

Durvalumab rechallenge after 1 yrs durvalumab

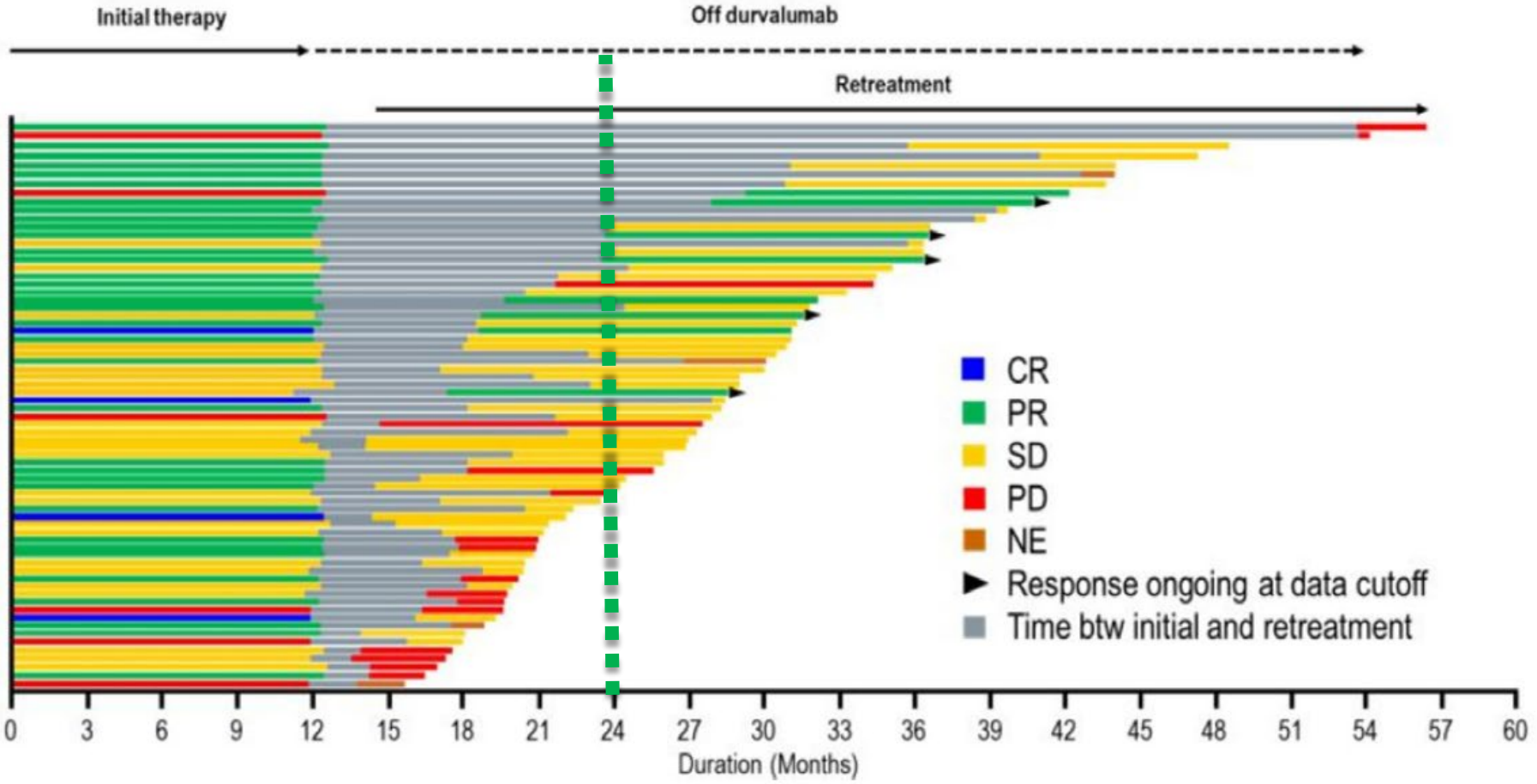
Phase I/II study evaluating durvalumab in advanced solid tumors (NCT01693562

. N=980 patients
. 168 stopped without DP at 1 yr

. 70 pts (41.7%) rechallenged

. Median time off treatment was 6.8 mo

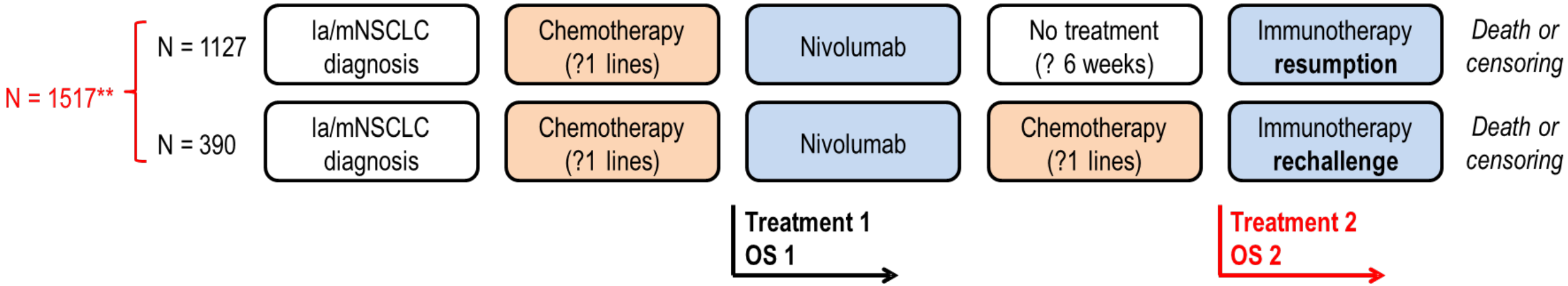
. Rechallenge:
median PFS 5.2 mo
Median OS 23.8 mo



Sheth J Immunother Cancer. 2020

Nivolumab – French cohort

1517 adult patients with locally advanced or metastatic NSCLC treated twice with immunotherapy

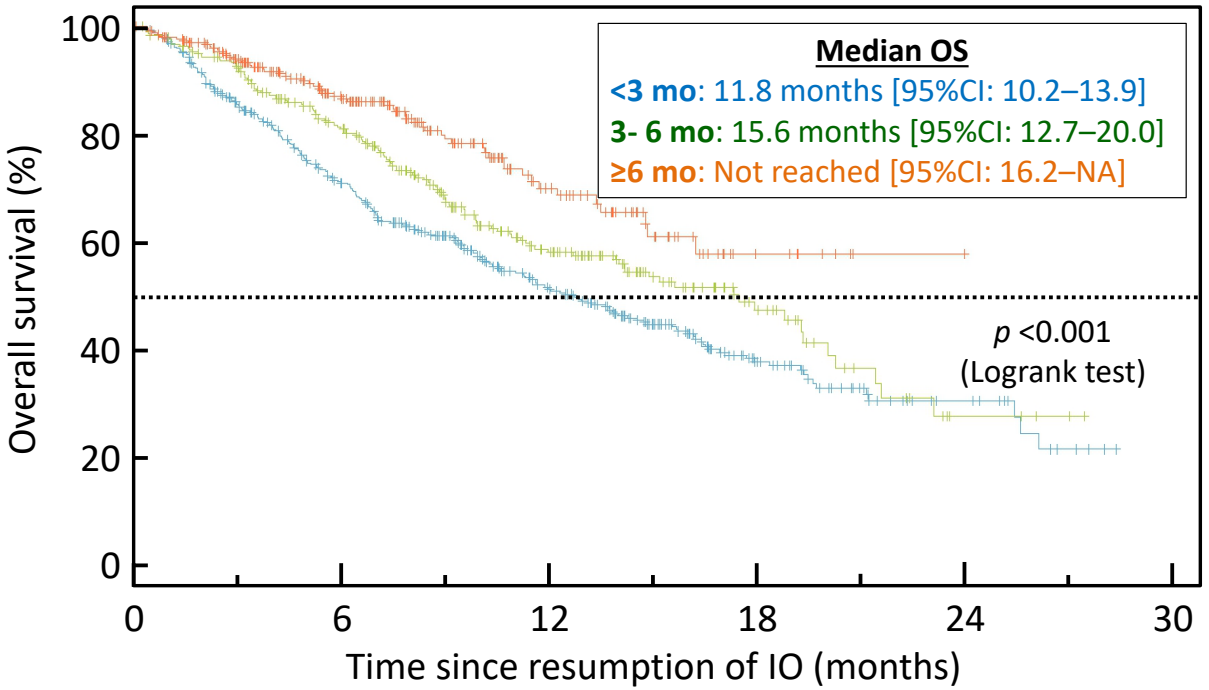


*Discontinuation was defined as no new treatment for ≥6 weeks after the previous treatment or death.
**1511 patients treated with nivolumab and 6 with pembrolizumab

Giaj Lebra WCLC 2019

Overall survival after rechallenge according to the previous benefit

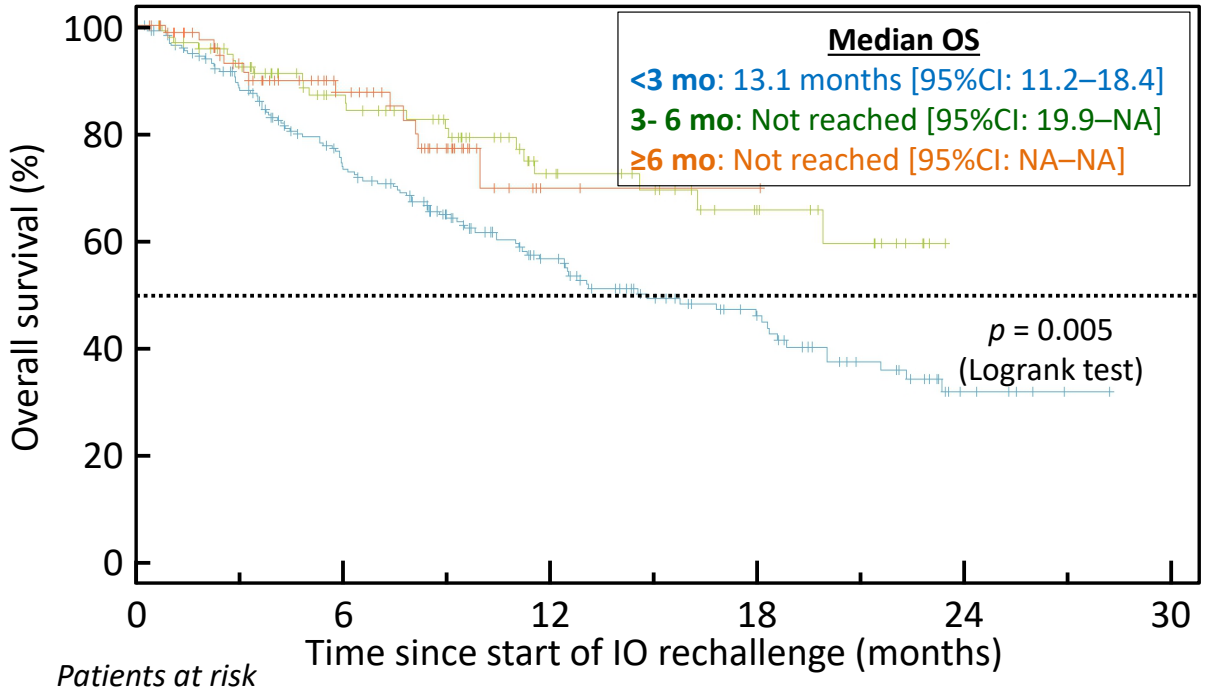
No treatment between the 2 ICI



Patients at risk

485	294	154	50	14	**<3 mo**
296	202	93	27	4	**3- 6 mo**
346	161	52	8	-	**≥6 mo**

Treatment between the 2 ICI



Patients at risk

210	129	70	38	8	**<3 mo**
94	58	27	14	-	**3- 6 mo**
86	38	2	-	-	**≥6 mo**

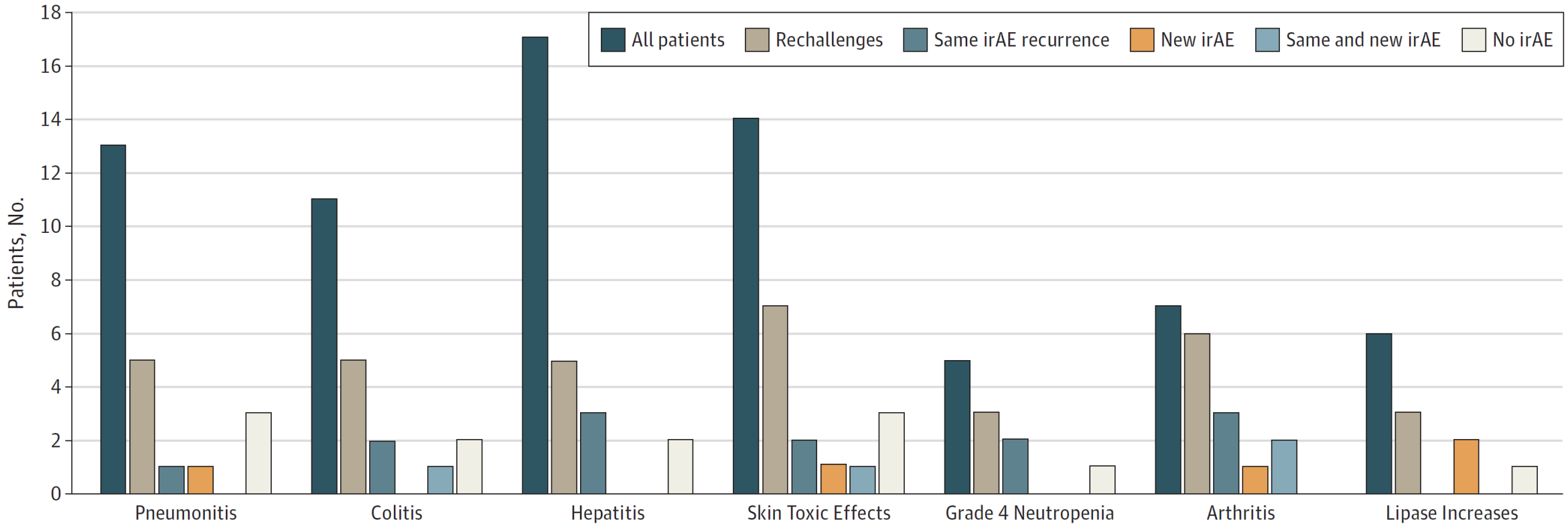
Giaj Levra Lung Cancer 2020

Relapsed NSCLC after immunotherapy

- **Patient stopped their previous immunotherapy regimen**
  - **Because end of treatment was planned**
  - **Because of a toxicity**

Which toxicities at rechallenge

n=93, any tumor type



	Pneumonitis	Colitis	Hepatitis	Skin Toxic Effects	Grade 4 Neutropenia	Arthritis	Lipase Increases
Recurrence of the same irAE	**20%**	**60%**	**60%**	**43%**	**67%**	**83%**	**0%**

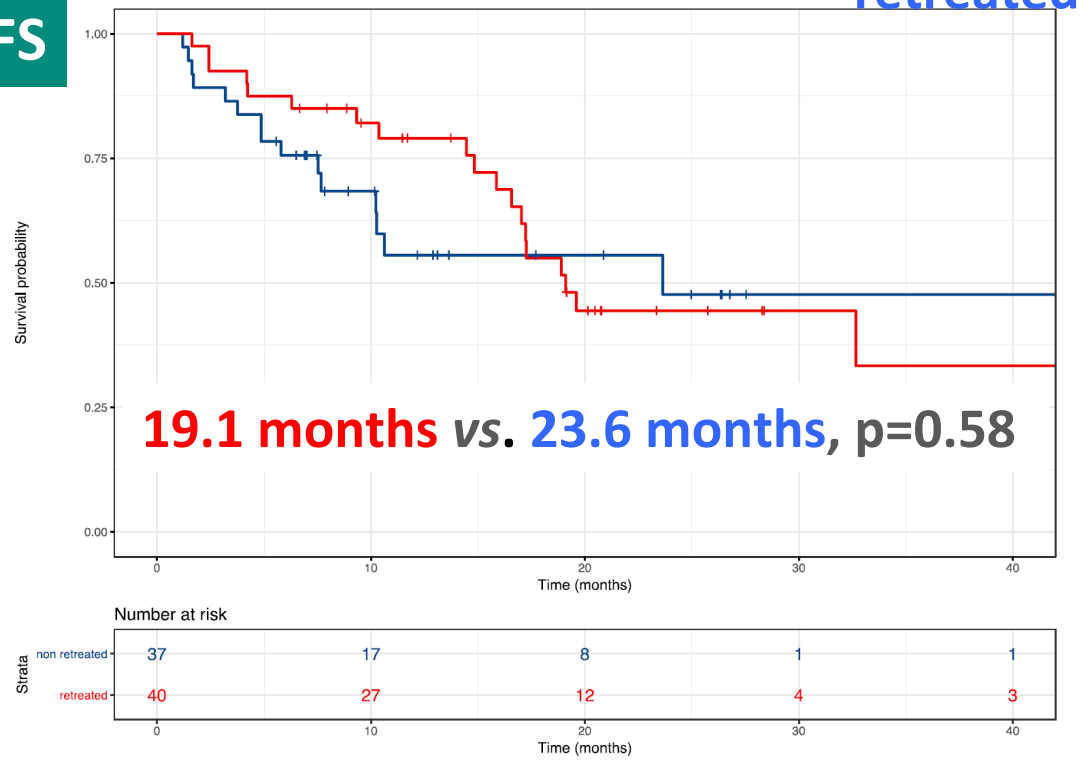
Simonaggio Jama Oncol 19

Outcome with rechallenge after irAEs

N= 93. Rechallenge 43%. Recurrent or new irAEs in 55%, not more severe than 1st irAEs

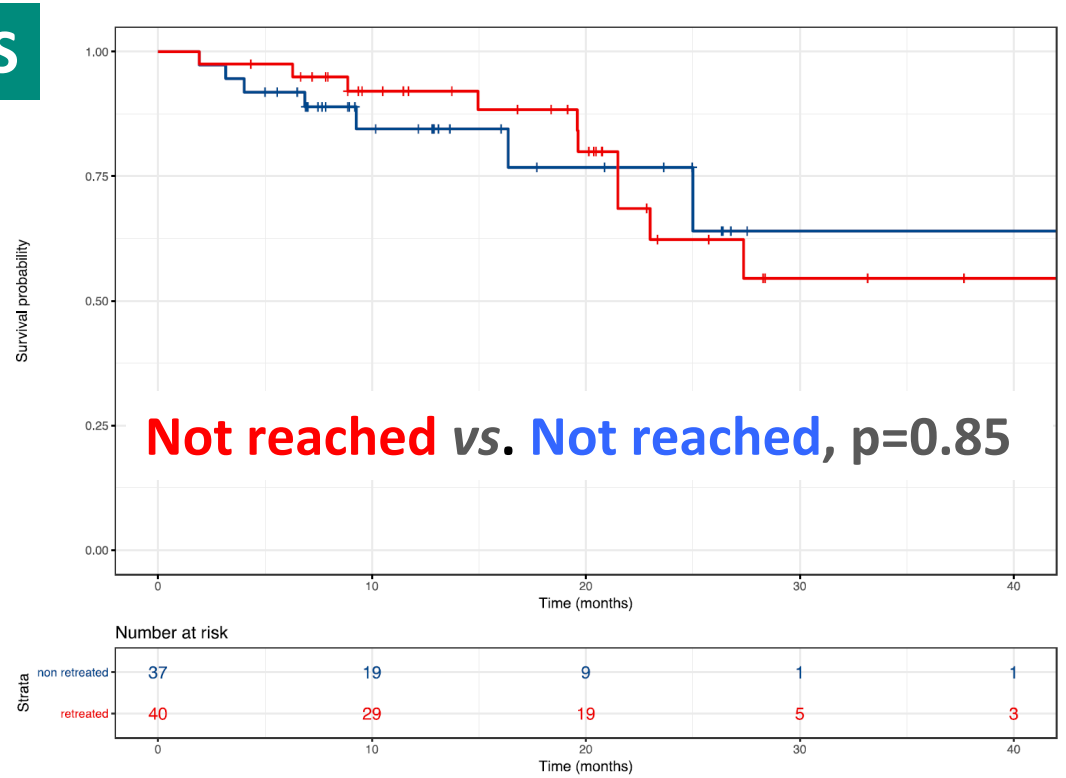
Retreated *vs*. non-retreated

PFS



19.1 months *vs*. 23.6 months, p=0.58

OS



Not reached *vs*. Not reached, p=0.85

Courtesy of J.Remon

Simonaggio Jama Oncol 19

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

Courtesy of J.Remon

ICI after ir-AE's with previous ICI

	Santini	Simonaggio	Abu-Sbeih	Naidoo	Pollack	Delaunay
N	482	93	167 with colitis	43 pneumonitis	80	64 ILD
Tumor	NSCLC	Multiple (N=15 NSCLC)	Multiple (N=27 NSCLC)	Multiple (N=9 NSCLC)	Melanoma	Multiple (N=45 NSCLC)
irAE's	68 (14%)	93	167	43	80	64
Retreat.	38	40	167	12	80	10
New/ Recurr.	52% (40% G≥3)	55% (60% G≥3)	34% (82% IS)	25% (0% G≥3)	18% (57% G≥3)	30% (0% G≥3)

~30-50% Retreated. ~30-50% New/Recurrent irAEs. ~50% G≥ 3. Not correlation with outcome

*For patients with previous RR to ICI. Ns: non significant. IS: 82% required immunosuppressive therapy

Santini – Cancer Immunol Res 2018 * Simonaggio – JAMA Oncol 2019 * Abu-Sbeih – JCO 2019 * Naidoo – JCO 2017 * Pollack – Ann Oncol 2018 * delaunay – ERJ 2017

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

Courtesy of J.Remon

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Interval irAE's - rechallenge	32 days (7–177)	27 days (7-168)	49 days (23-136)	-	58 days (14–395)*	-

*interval between last dose of combination therapy and the first dose of rechallenge

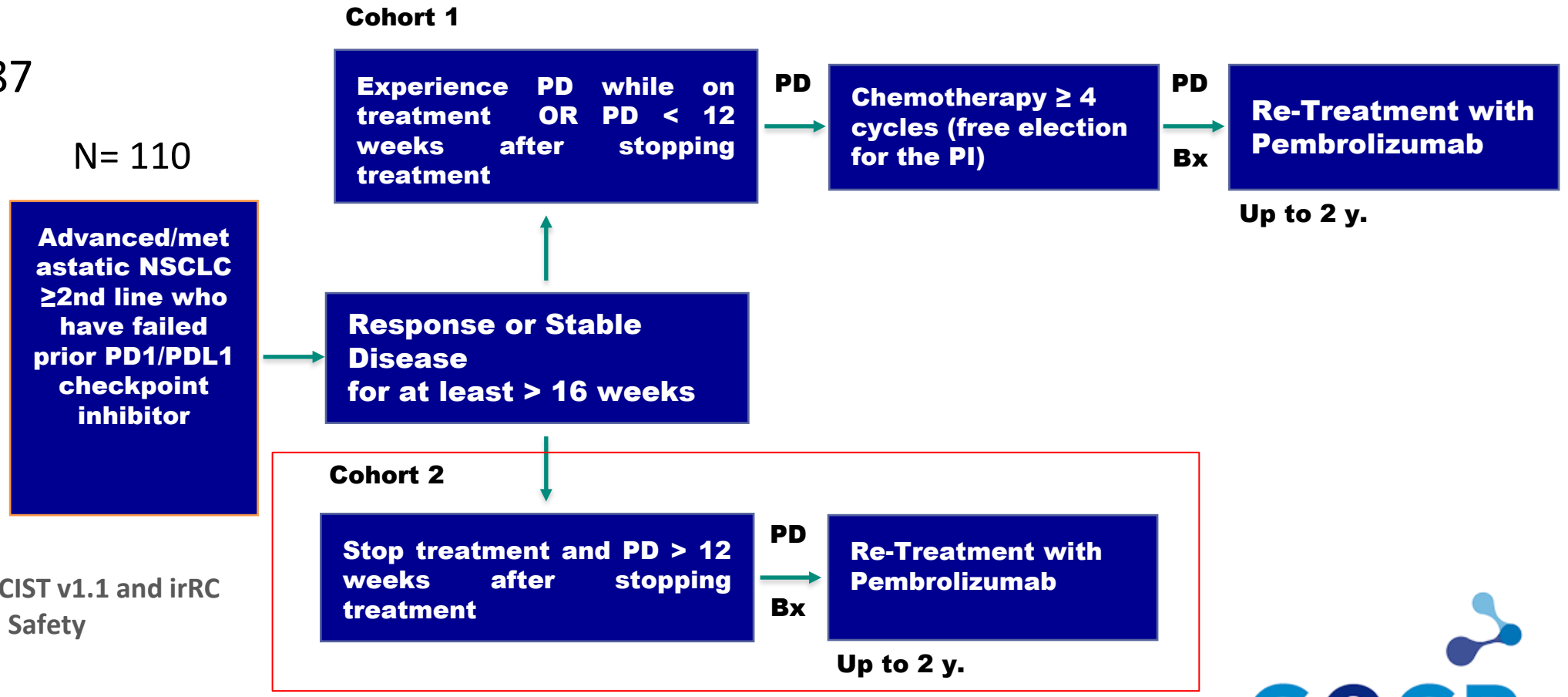
Santini – Cancer Immunol Res 2018 * Simonaggio – JAMA Oncol 2019 * Abu-Sbeih – JCO 2019 * Naidoo – JCO 2017 * Pollack – Ann Oncol 2018 * delaunay – ERJ 2017

Multi-center exploratory phase II trial of Pembrolizumab (200 mg) as second or further line with NSCLC who have failed to a prior treatment with anti-PDL1 drug

REPLAY

NCT03526887

N= 110



Primary: ORR by RECIST v1.1 and irRC
Secondary: PFS, OS, Safety

PI: Dr. Paz-Ares

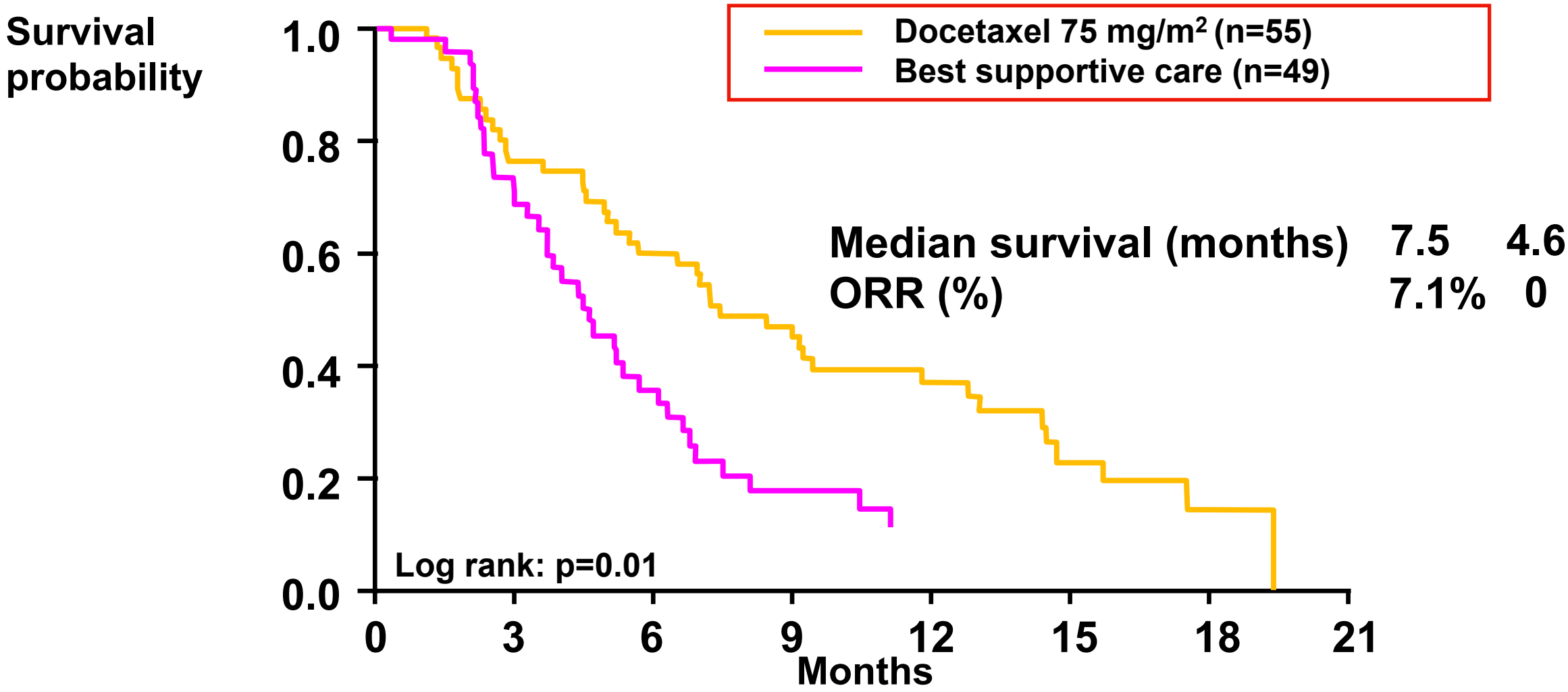
Courtesy of J.Remon

Relapsed NSCLC after immunotherapy

- **Patient stopped their previous immunotherapy regimen**
  - **Because end of treatment was planned**
  - **Because of a toxicity**

- **Patient is receiving first line immunotherapy (and chemoth.)**
  - **Docetaxel, standard of care**

Docetaxel – approved in 2000



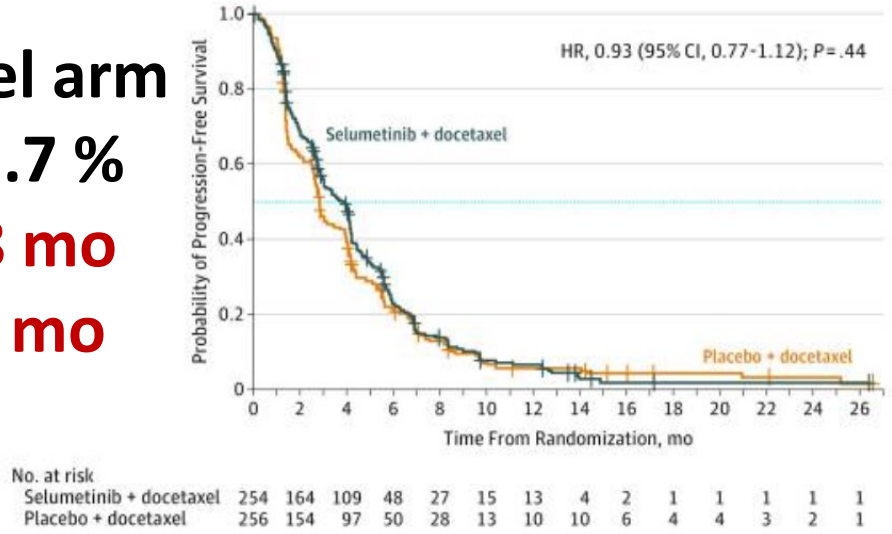
Shepherd JCO 2000

Impact of first line immunotherapy on docetaxel?

Efficacy of 2nd line docetaxel in patients with KRAS mutated NSCLC

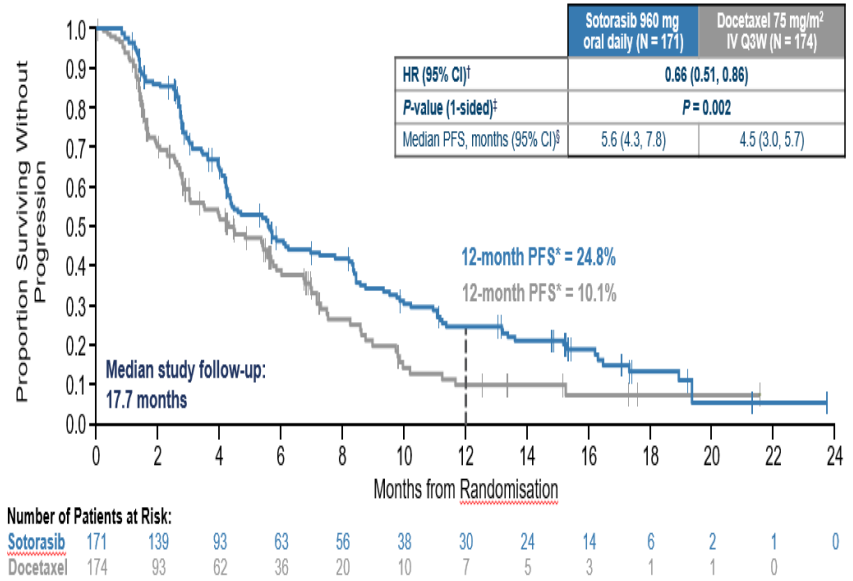
Docetaxel +/- selumetinib
After chemotherapy

Docetaxel arm
ORR 13.7 %
PFS 2.8 mo
OS 7.9 mo



Docetaxel vs sotorasib
After chemo-immunotherapy

Docetaxel arm
ORR 13.2 %
PFS 4.5 mo
OS 11.3 mo



Janne JAMA 2017
Johnson ESMO 2022

Relapsed NSCLC after immunotherapy

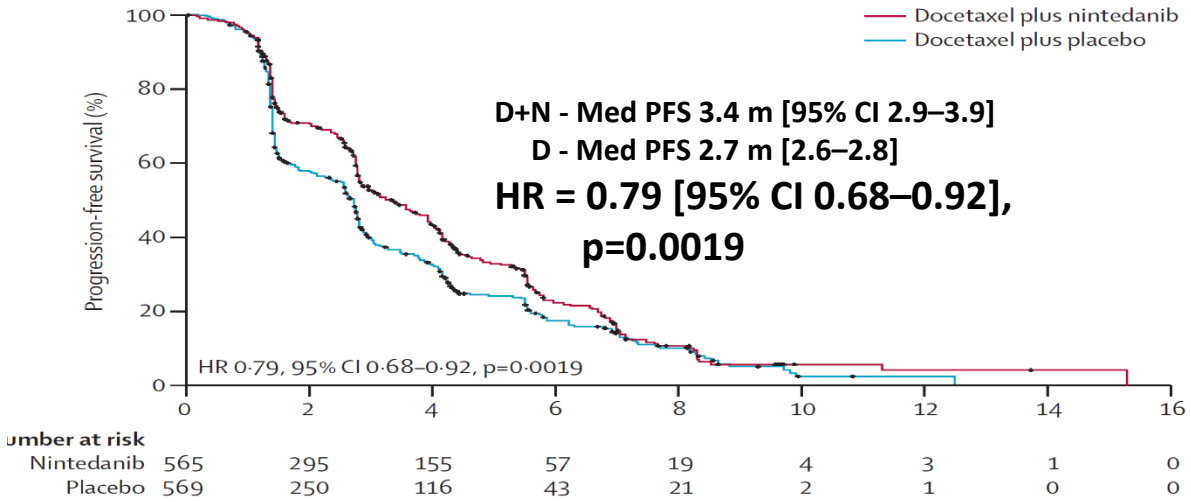
- **Patient stopped their previous immunotherapy regimen**
  - **Because end of treatment was planned**
  - **Because of a toxicity**

- **Patient is receiving first line immunotherapy (and chemoth.)**
  - **Docetaxel, standard of care**
  - **Current options**

Anti-angiogenic agents in 2nd line

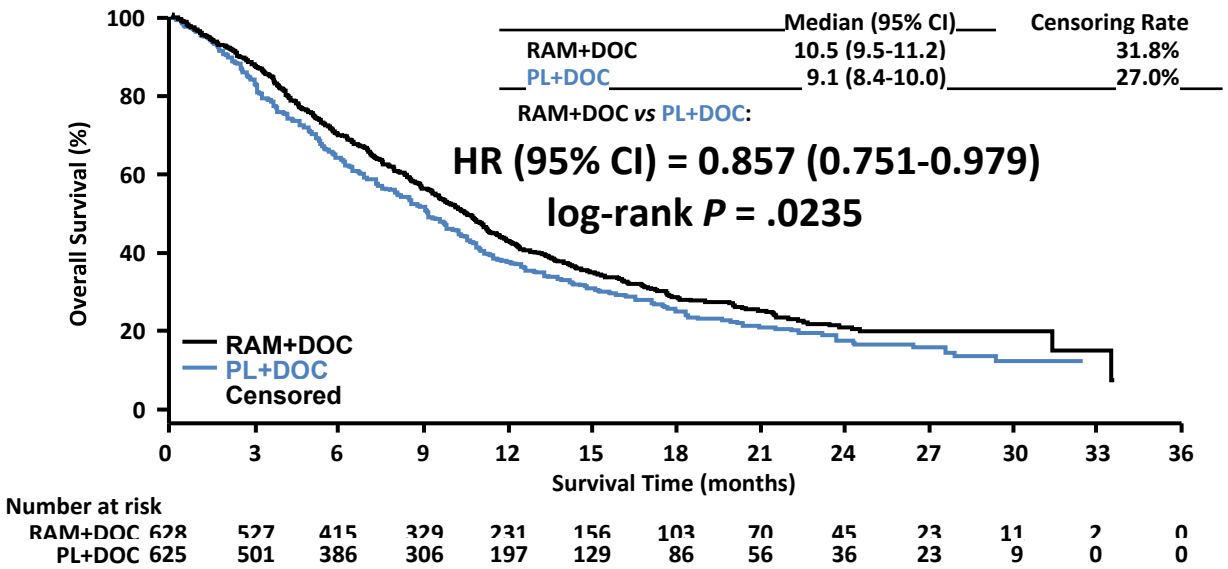
Data from randomized trials

PFS - Docetaxel +/- nindetanib



D+N - Med PFS 3.4 m [95% CI 2.9–3.9]
D - Med PFS 2.7 m [2.6–2.8]
HR = 0.79 [95% CI 0.68–0.92],
p=0.0019

OS - Docetaxel +/- ramucirumab



OS benefit in adenocarcinoma
PFS benefit in refractory pts
(HR= 0.67 (0.43-1.04,p=0.0725).

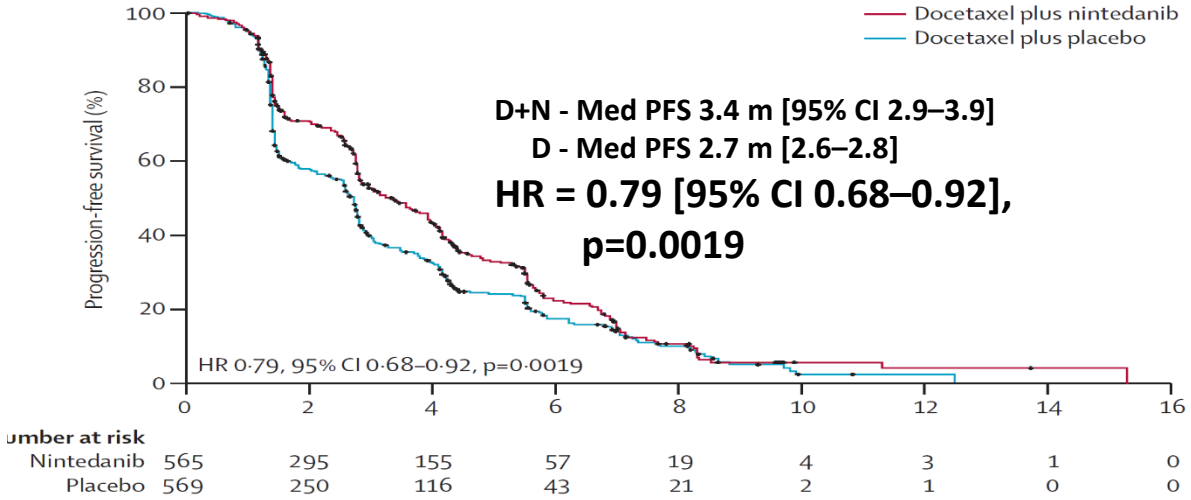
OS benefit in SCC and non SCC

Perol ASCO 14, Reck Lancet Oncol 14

Anti-angiogenic agents in 2nd line

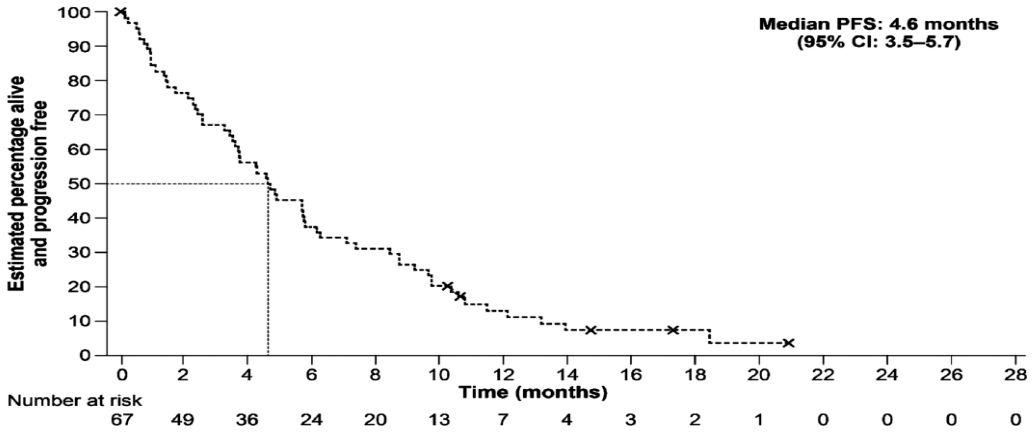
Impact of previous immunotherapy

PFS - Docetaxel +/- nindetanib



Median PFS Docetaxel + nintedanib : 3.4 mo
Median OS : 12.6 mo

PFS - Docetaxel + nintedanib



Median PFS Docetaxel + nintedanib : 4.6 mo
Median OS : 8;8 mo

Reck Lancet Oncol 14, Reck lung cancer 20

Anti-angiogenic agents in 2nd line

Trial after previous immunotherapy

Phase II randomized study of ramucirumab plus pembrolizumab versus standard of care for advanced non-small cell lung cancer previously treated with immunotherapy—Lung-MAP non-matched sub-study S1800A

Primary endpoint: OS

Secondary endpoints: RR, DCR, DoR, PFS, Toxicities

Stratified by 1) PD-L1 expression, 2) histology, 3) intent to receive ramucirumab in standard of care arm

NCT03971474

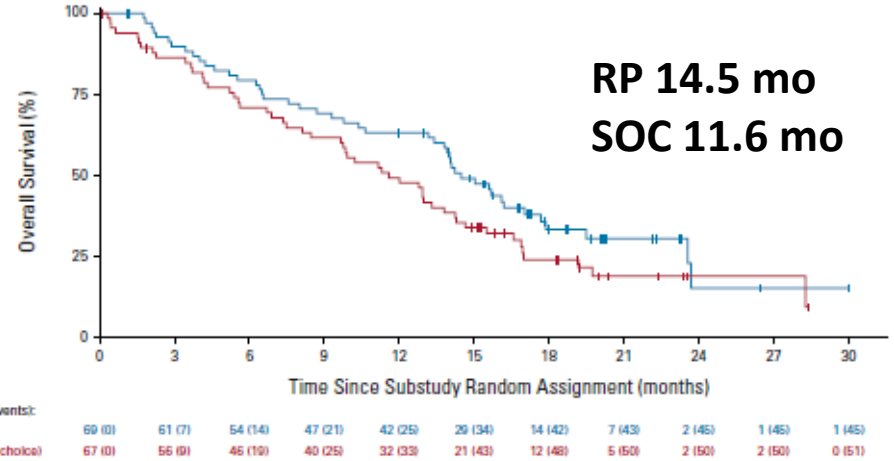
Randomization

R (1:1)
N= 130

ARM A
Investigator's Choice
Standard of Care
docetaxel + ramucirumab;
docetaxel; gemcitabine;
pemetrexed (nonSCC only)

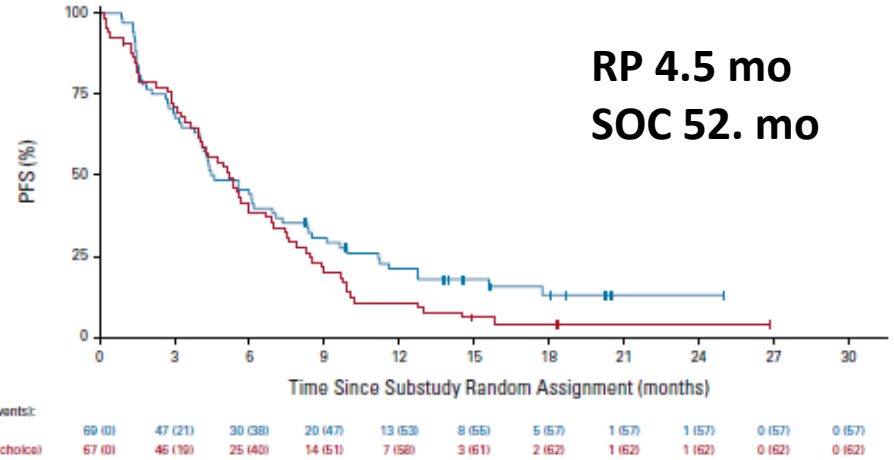
ARM B
Pembrolizumab
200 mg Q3W for
up to 35 cycles
+
Ramucirumab
10 mg/kg Q3W

OS



RP 14.5 mo
SOC 11.6 mo

PFS



RP 4.5 mo
SOC 52. mo

Reckamp JCO 2022

IFCT-1103 ULTIMATE study
Weekly paclitaxel + bevacizumab vs. docetaxel

- Advanced NSq-NSCLC

- Stratification factors
  - Center
  - PS (0-1 vs. 2)
  - Number of prior lines (1 vs. 2)
  - Prior exposure to bevacizumab (yes vs. no)

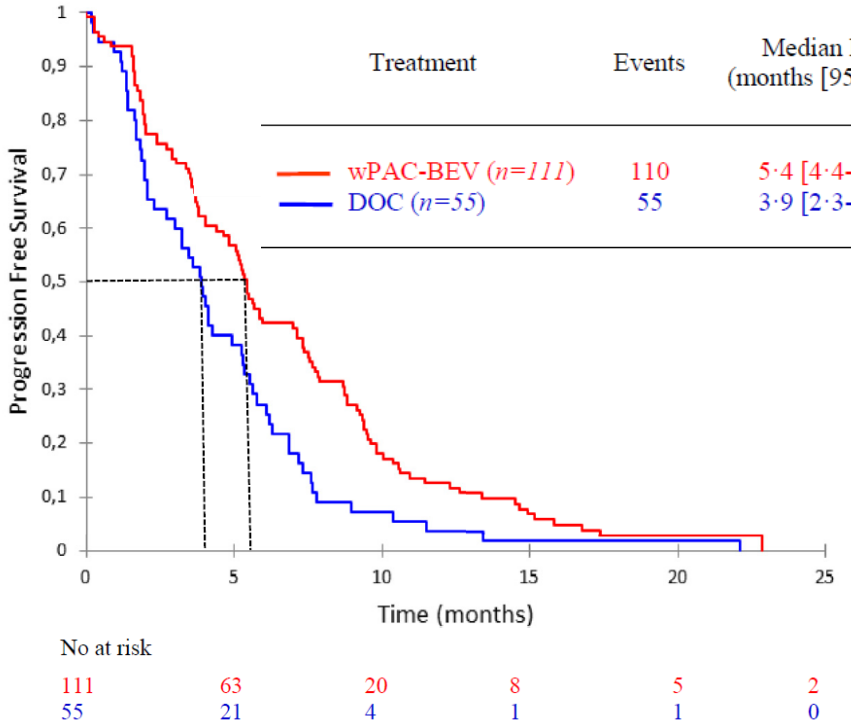
2:1 RANDOMIZE

Docetaxel 75 mg/m²
q3wks

Optional cross over at progression

Paclitaxel 90 mg/m² D1, D8, D15
Bevacizumab 10 mg/kg D1, D15
q4wks

PFS



Treatment	Events	Median PFS (months [95% CI])	Logrank test adjusted HR [95% CI]
wPAC-BEV (*n=111*)	110	5·4 [4·4-7·1]	
DOC (*n=55*)	55	3·9 [2·3-5·3]	0·61 [0·44-0·86] *p=0·006*

Cortot WCLC 16, Cortot EJC 2020

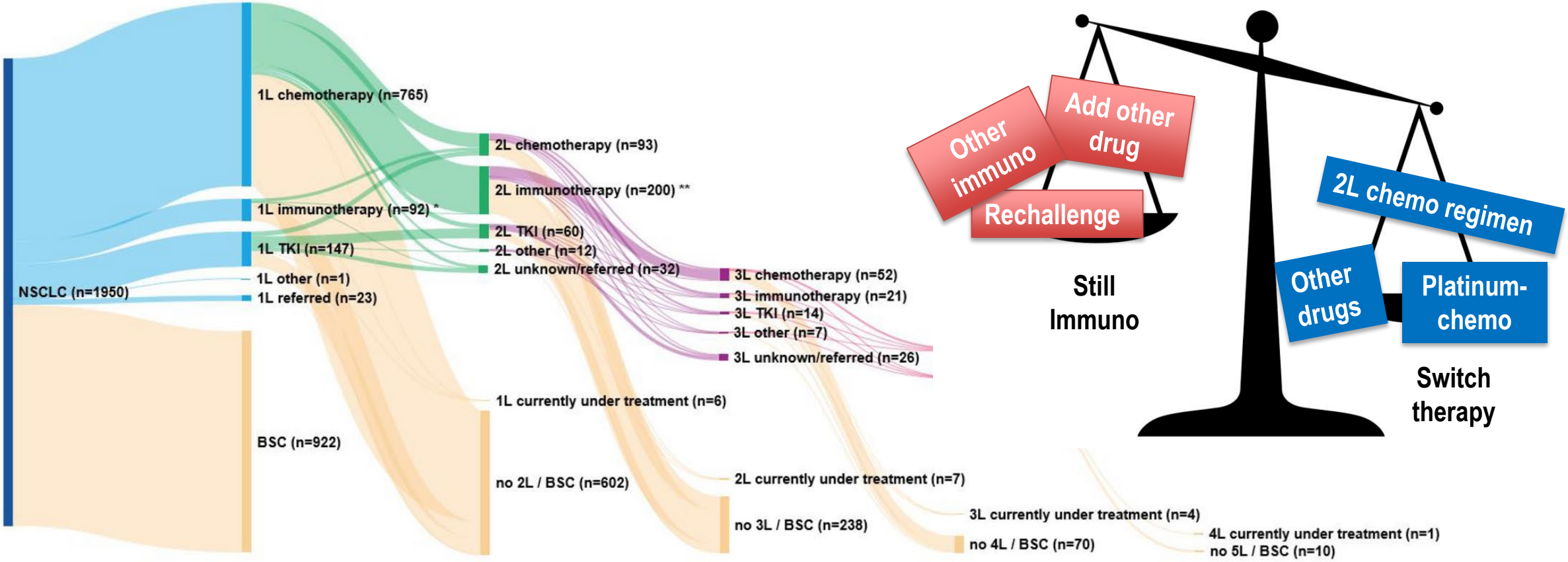
GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

Relapsed NSCLC after immunotherapy

- **Patient stopped their previous immunotherapy regimen**
  - **Because end of treatment was planned**
  - **Because of a toxicity**

- **Patient is receiving first line immunotherapy (and chemoth.)**
  - **Docetaxel, standard of care**
  - **Current options**
  - **Try to tackle immunoresistance**

We need more than docetaxel

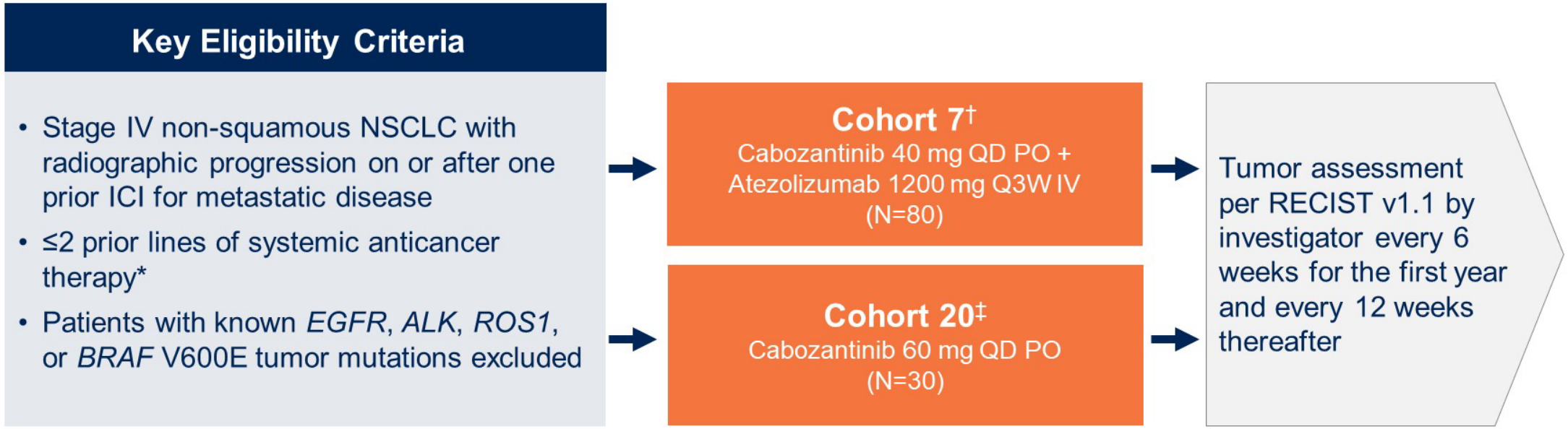


Courtesy of Laura Mezquita

Cramer-van der Welle CM et al, Scientific Reports 2021

Combination of VEGFR TKI + Immunotherapy

Example with cabozantinib and atezolizumab – COSMIC 021



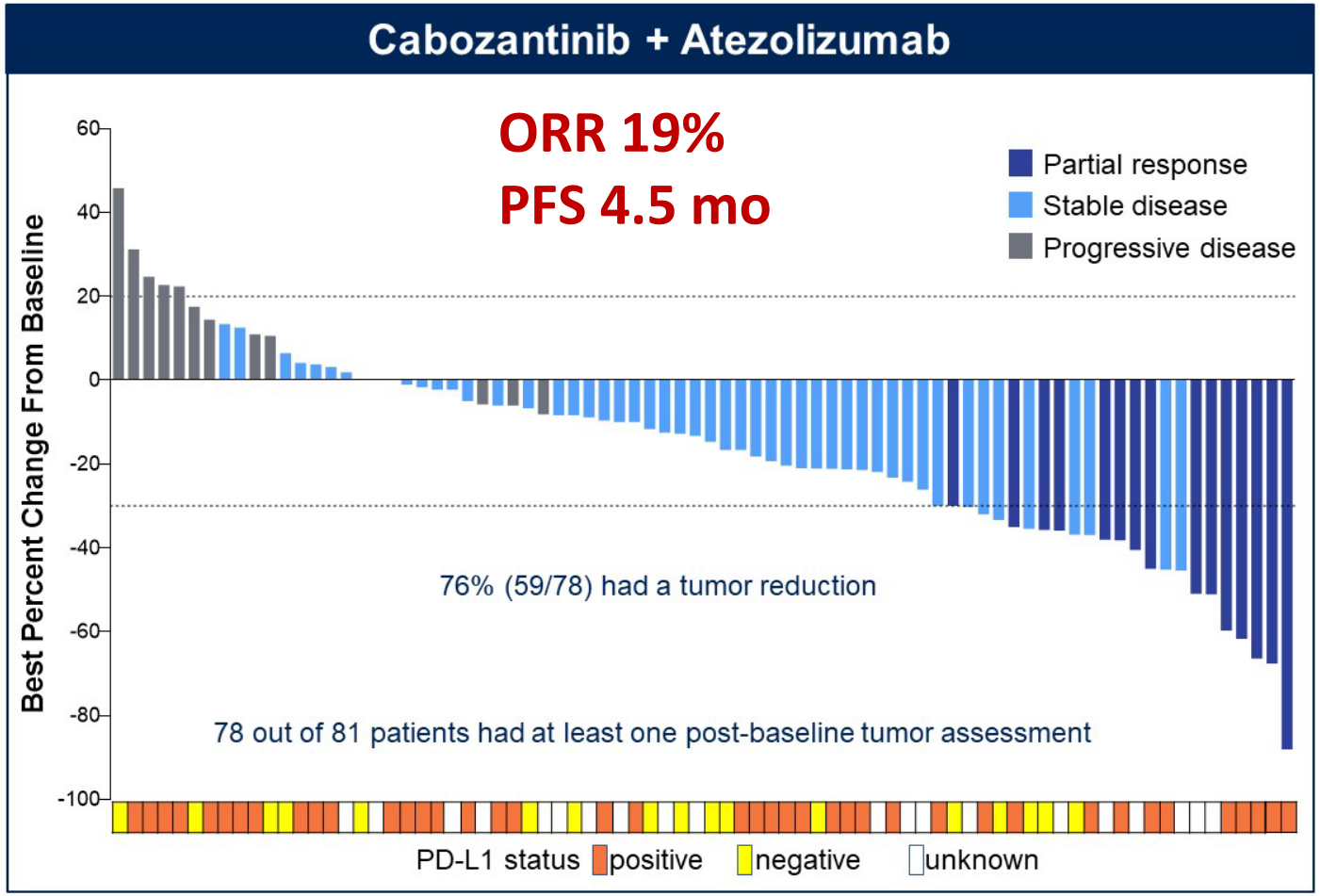
Primary endpoint:	ORR per RECIST v1.1 by investigator
Secondary endpoint:	Safety (AEs, SAEs, AESIs)
Exploratory endpoints:	DOR, PFS per RECIST v1.1 by investigator, OS

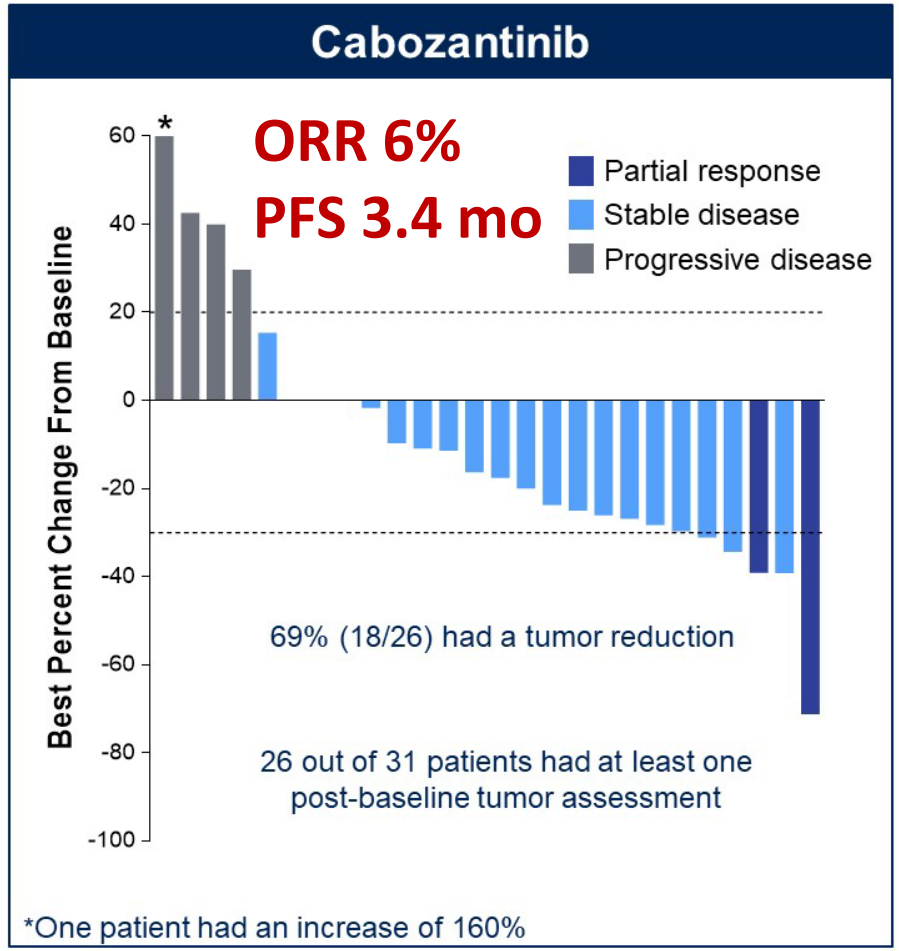
*Prior treatment with platinum-based chemotherapy was not required. †Patients were initially enrolled to cohort 7 (n=35). Following an initial assessment of clinical activity, subsequent patients were randomized between cohorts 7 and 20. ‡Patients in cohort 20 may receive combination therapy after radiographic disease progression per RECIST v1.1 by the investigator.
SAEs, serious adverse events; AESIs, adverse events of special interest

Neal ASCO 2022

Combination of VEGFR TKI + Immunotherapy

Example with cabozantinib and atezolizumab – COSMIC 021





Neal ASCO 2022

Combination of VEGFR TKI + Immunotherapy

Example with cabozantinib and atezolizumab – COSMIC 021

	Cabozantinib + Atezolizumab (N=81)		Cabozantinib (N=31)†	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TEAE, n (%)	81 (100)	43 (53)	31 (100)	22 (71)
Diarrhea	36 (44)	1 (1)	16 (52)	3 (10)
Decreased appetite	30 (37)	1 (1)	11 (35)	1 (3)
Fatigue	29 (36)	4 (5)	11 (35)	2 (6)
Nausea	28 (35)	2 (2)	15 (48)	2 (6)
Asthenia	24 (30)	5 (6)	12 (39)	3 (10)
Constipation	21 (26)	0	5 (16)	0
Pyrexia	20 (25)	0	2 (6)	0
AST increased	19 (23)	2 (2)	9 (29)	0
Hypertension	19 (23)	5 (6)	10 (32)	7 (23)
Vomiting	19 (23)	0	9 (29)	1 (3)
ALT increased	17 (21)	3 (4)	10 (32)	1 (3)
PPE	17 (21)	3 (4)	6 (19)	0
Hypomagnesemia	16 (20)	1 (1)	5 (16)	0
Weight decreased	16 (20)	3 (4)	4 (13)	2 (6)
Pneumonitis	3 (4)‡	0	0	0
Gastric ulcer hemorrhage	0	0	1 (3)§	0

AEs leading to cabozantinib dose reductions, n (%)	32 (40)
AEs leading to cabozantinib dose hold, n (%)	60 (74)

Neal ASCO 2022

ICB plus antiangiogenic

	COSMIC-021 Cohort 7	LUNG-MAP S1800A	MRTX-500	Phase II	Retrospective	Phase I
Schedule	Cabozantinib Atezolizumab	Ramucirumab Pembrolizumab	Sitravatinib Nivolumab	Bevacizumab Atezolizumab	Ramucirumab Atezolizumab	Lenvatinib Pembrolizumab
N	80	69	68	24	21	21
ORR (%)	19*	22	18	13	4.8	33**
PFS (mo.)	4.5*	4.5	5.7	5.6	3.4	NR
OS (mo.)	13.8*	14.5	14.9	14.0	16.5	NR
G≥3 TRAE (%)	53	42	66	4.2	43	42
Phase III	CONTACT1		SAPHIRE			

*RR: PD-L1<1%: 11% ; PD-L1≥1%: 20%. PFS: PD-L1<1%: 4.7; PD-L1≥1%: 5.4. OS: PD-L1<1%: 10.4 ; PD-L1≥1%: 17.8
** Include treatment naïve population.

Neal - ASCO 2022 * Reckamp –JCO 2022 * Leal –ESMO 2021 * Lee –JTO 2022 * Herzog –Lung Cancer 2022* Brose – ASCO 2019 * Taylor –JCO 2020
(There is no intention of cross trial comparison)

Courtesy of J.Remon

Combination of VEGFR TKI + Immunotherapy

- Ongoing multiarm randomized phase II trials exploring various IO combinations and potential biomarkers that may lead to specific phase III trials
- Many phase III trials are ongoing with single agent docetaxel as a shared comparator
  - Few are based on biomarker selection or make the distinction between primary and acquired resistance to CPI[1]
  - Identification of patients deriving benefit from these combinations may be difficult

Trial	2nd/3rd line target population	Experimental arm	Control	Primary endpoint
Sapphire NCT03906071	Non-squamous Prior PD-1/L1 therapy for ≥4 months	Sitravatinib + nivolumab	Docetaxel	OS
Contact-01 NCT04471428	All comers	Cabozantinib + atezolizumab	Docetaxel	OS
LEAP-008 NCT03976375	All comers	Lenvatinib + pembrolizumab	Docetaxel	PFS and OS

Perol ESMO 2021

Antibody drug conjugates (ADC) : CAECAM5

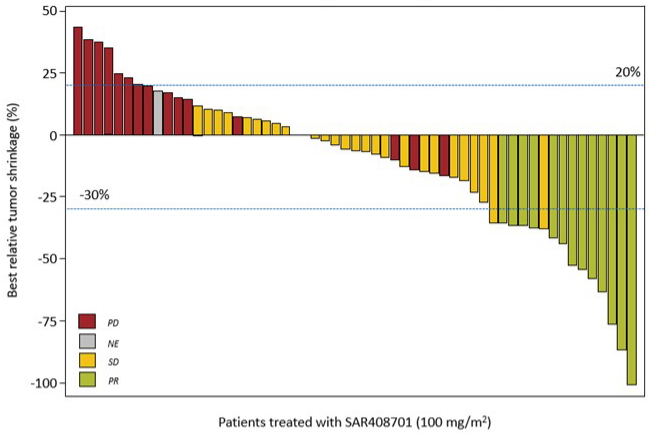
Example with tusamitamab ravtansine

Best Overall Response

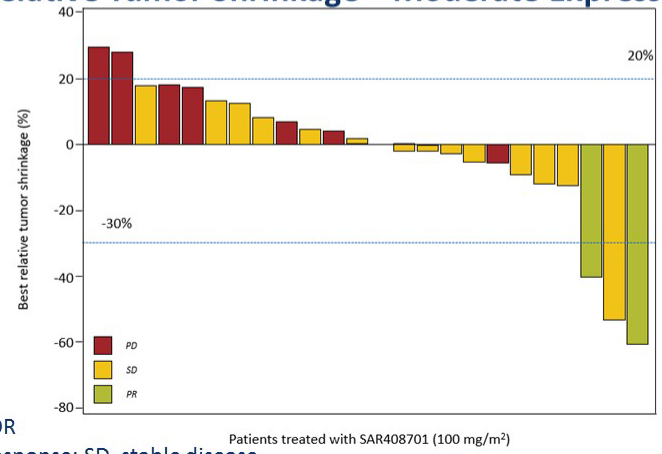
Overall Population

Response, n (%)	High expressors (n = 64)	Moderate expressors (n = 28)
ORR [95% CI]	13 (20.3%) [12.27-31.71]	2 (7.1%) [1.98-22.65]
Confirmed PR	13 (20.3%)	2 (7.1%)
SD	28 (43.8%)	15 (53.6%)
DCR	41 (64.1%)	17 (60.7%)
PD	21 (32.8%)	10 (35.7%)
NE	2 (3.1%)	1 (3.6%)

Best Relative Tumor Shrinkage – High Expressor Cohort



Best Relative Tumor Shrinkage – Moderate Expressor Cohort



Best relative tumor shrinkage: Patients who had unconfirmed PR (>30% decrease) were counted as SD for BOR
DCR, disease control rate; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Gazzah ASCO 2020

Antibody drug conjugates (ADC) : TROP2

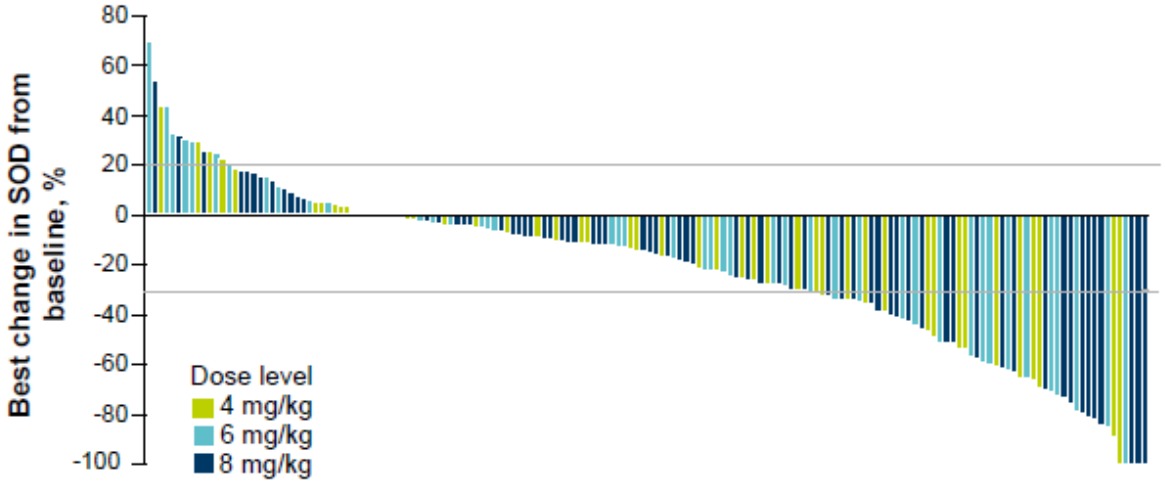
Example with datopotamab-deruxtecan – TROPION 01

Best Overall Response (BICR)

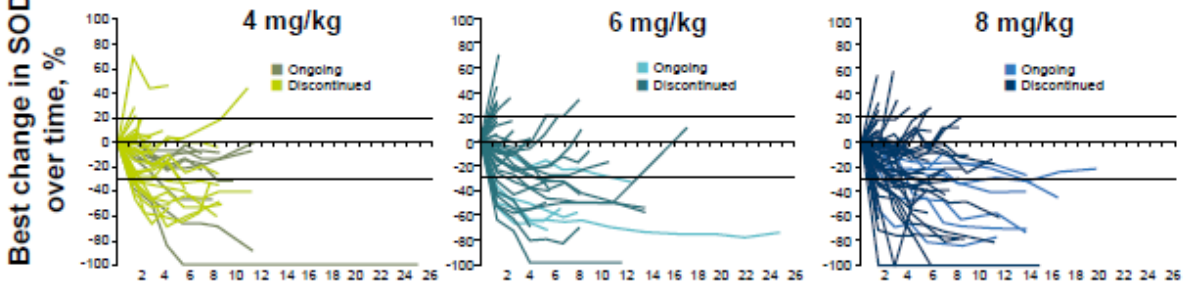
Patients[a]	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
ORR, n (%)[b]	12 (24)	14 (28)	19 (24)
CR, n (%)	0	0	1 (1)
PR, n (%)[b]	12 (24)	14 (28)	18 (23)
SD, n (%)	25 (50)	20 (40)	42 (53)
Non-CR/PD, n (%)	1 (2)	2 (4)	2 (3)
PD, n (%)	7 (14)	10 (20)	8 (10)
NE, n (%)	5 (10)	5 (10)	9 (11)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

- Antitumor activity was observed at 4-, 6-, and 8-mg/kg doses of Dato-DXd
- Most responses were durable over time, including a median duration of response of 10.5 months in the 6-mg/kg cohort

Best Change in Sum of Diameters (per BICR)



Change in Sum of Diameters of Target Lesion (per BICR) Over Time



Data cutoff: April 6, 2021.
BICR, blinded independent central review; CR, complete response; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SOD, sum of diameters; SD, stable disease.
[a] Includes response-evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. [b] ORR and CR/PR include 1 response in the 6-mg/kg cohort that is pending confirmation.

Meric Berstam ASCO 2021

Antibody drug conjugates (ADC) : TROP2

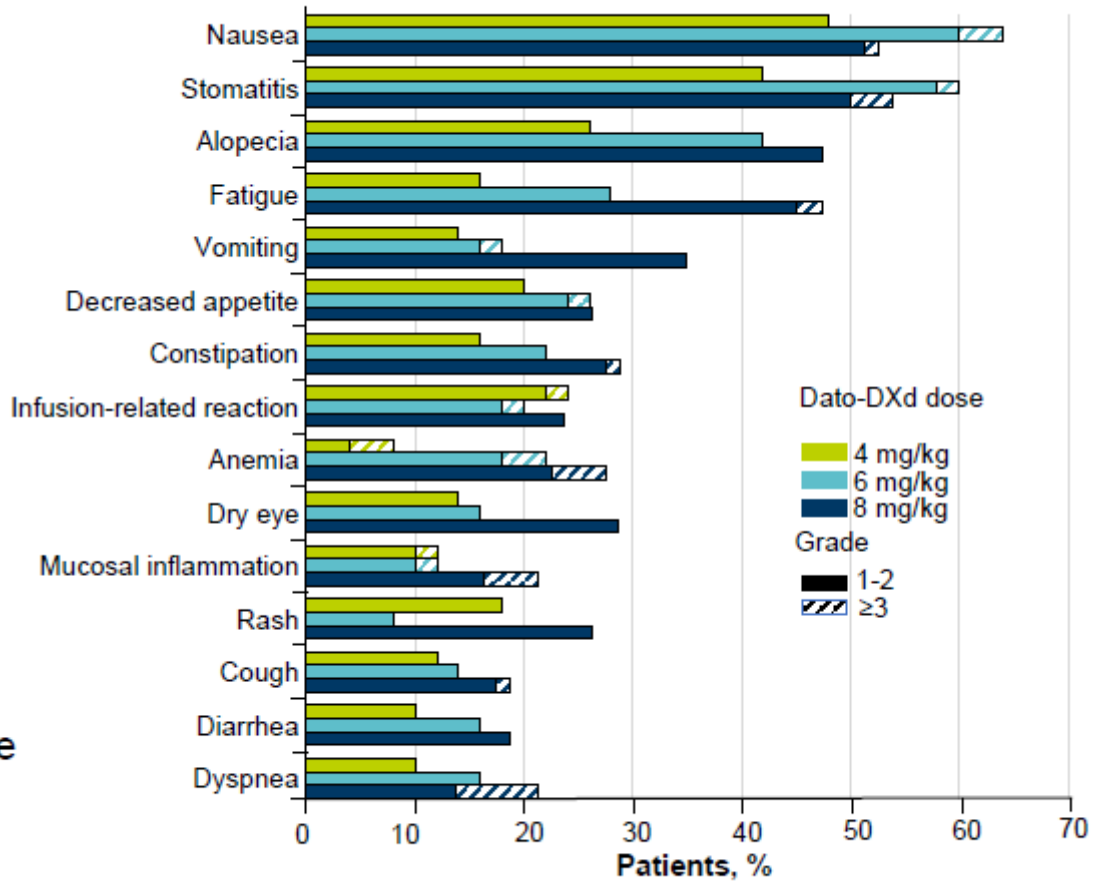
Example with datopotamab-deruxtecan – TROPION 01

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)

- The safety profile was manageable with mainly mild/moderate toxicity; TEAEs were primarily nonhematologic

TEAEs in ≥15% of Patients[b]



Data cutoff: April 6, 2021.
ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.
[a] Cases of ILD adjudicated as drug related comprised 5 patients in the 4-mg/kg cohort (1 grade 1, 3 grade 2, 1 grade 3), 3 patients in the 6-mg/kg cohort (2 grade 2, 1 grade 4), and 11 patients in the 8-mg/kg cohort (2 grade 1, 5 grade 2, 1 grade 3, 3 grade 5). [b] Of 180 patients (4 mg/kg [n=50]; 6 mg/kg [n=50]; 8 mg/kg [n=80]).

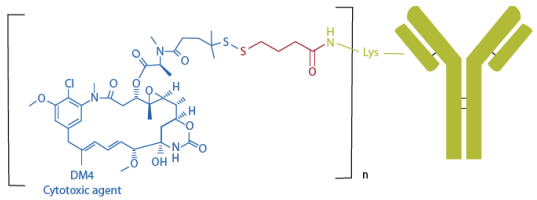
Meric Berstam ASCO 2021

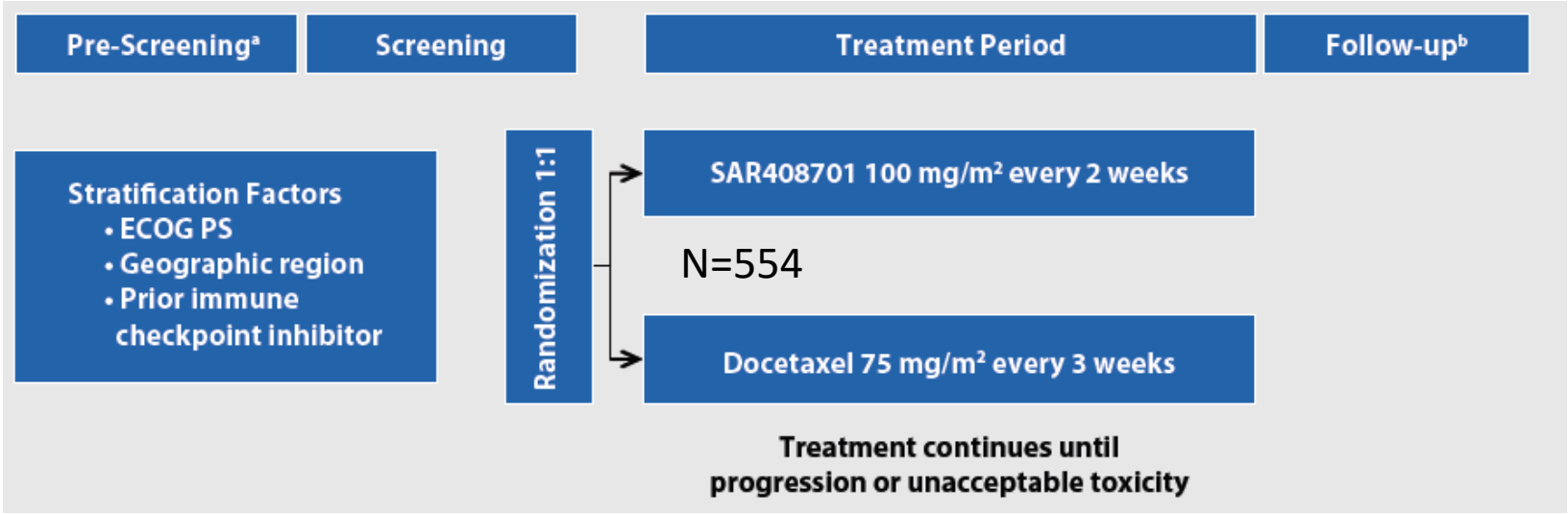
Antibody drug conjugates (ADC)

Example of ongoing phase III trials

CARMEN-LC03

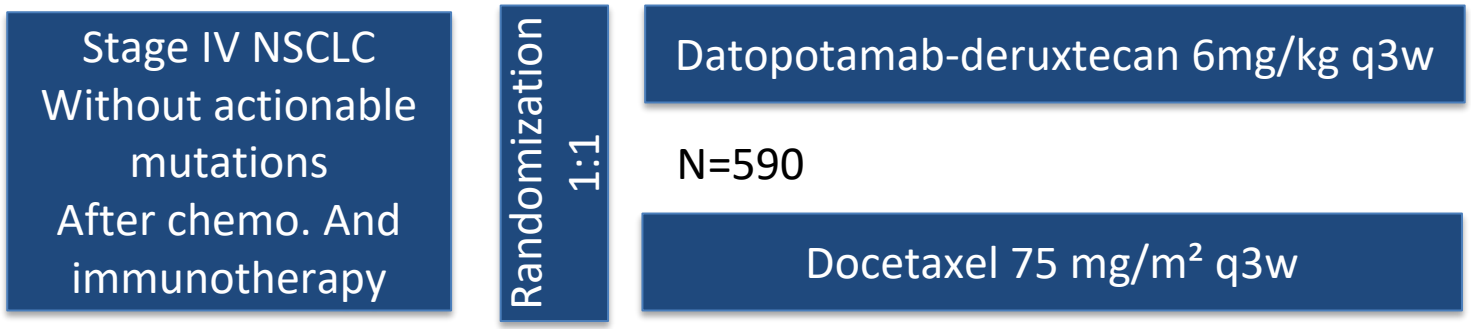
Restricted to CAECAM5 + NSCLC (by IHC)





TROPION-Lung01

All comers



Johnson ASCO 2020

Immunotherapy + “a booster”

Example of the ATRi ceralasertib

HUDSON:
Phase II multi-arm umbrella study

- Locally advanced or metastatic NSCLC
- Previous platinum-based chemotherapy
- Failure of prior anti-PD-(L)1 immunotherapy
- Suitable for new tumor biopsy / biopsy post-progression on anti-PD-(L)1 therapy
- No targetable alterations in *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, or *RET*

Central molecular screen,‡ ***n* = 255** (Jan 26, 2018–Apr 14, 2021)

Primary endpoint: ORR
Secondary endpoints: DCR, PFS, OS, safety and tolerability

Group A: biomarker-matched, *n* = 86

HRRm	Durvalumab + olaparib (PARPi), ***n* = 21**
LKB1	Durvalumab + olaparib (PARPi), ***n* = 21**
ATM	**Durvalumab + ceralasertib (ATRi), *n* = 21***
ATM	Single-agent ceralasertib (ATRi)*
CD73h	Durvalumab + oleclumab (CD73 mAb), ***n* = 23**
HER2e	Durvalumab plus trastuzumab deruxtecan (HER2i)†
HER2m	

Group B: biomarker-non-matched, *n* = 169

Primary resistance (disease progression ≤24 weeks)§	Acquired resistance (disease progression >24 weeks)#
Durvalumab + olaparib (PARPi), ***n* = 22**	Durvalumab + olaparib (PARPi) , ***n* = 23**
Durvalumab + danvatirsen (STAT3i), ***n* = 23**	Durvalumab + danvatirsen (STAT3i), ***n* = 22**
Durvalumab + ceralasertib (ATRi), *n* = 20	**Durvalumab + ceralasertib (ATRi), *n* = 25**
Durvalumab + oleclumab (CD73 mAb), ***n* = 9**	Durvalumab + oleclumab (CD73 mAb), ***n* = 25**
	Durvalumab + cediranib (VEGFi)†

*Ongoing. †Data not mature. ‡Immunohistochemistry was also performed. §/#Progression on prior anti-PD-(L)1 therapy within 24 weeks / after > 24 weeks.
ATM, ataxia telangiectasia mutated; ATRi, ataxia telangiectasia receptor inhibitor; CD73(h), (high expression of) cluster of differentiation 73; DCR, disease control rate; HER2e/i/m, human epidermal growth factor receptor 2 expression/inhibitor/mutated; HRRm, homologous recombination repair mutated; LKB1, LKB1/STK11 aberration; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PARPi, poly ADP ribose polymerase inhibitor; PD-(L)1, programmed death (ligand)-1; PFS, progression-free survival; STAT3i, signal transducer and activator of transcription 3 inhibitor; VEGFi, vascular endothelial growth factor inhibitor.

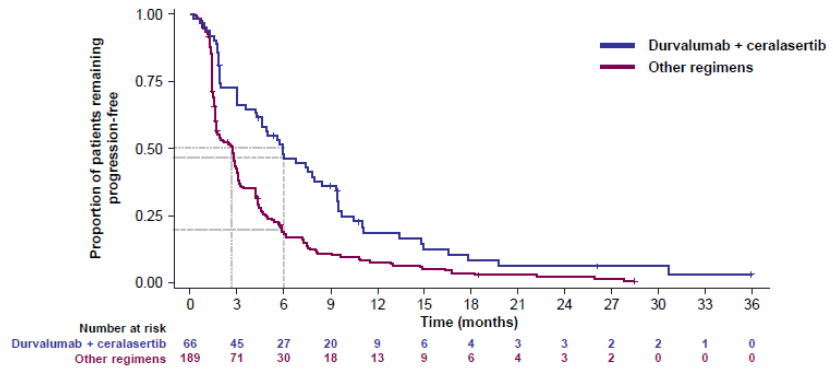
Besse WCLC 2022

Immunotherapy + “a booster”

Example of the ATRi ceralasertib

	Durvalumab + ceralasertib n=66	Durvalumab + olaparib n=87	Durvalumab + danvatirsen n=45	Durvalumab + oleclumab n=57
Median treatment duration, months Durvalumab* Other agent†	 7.3 6.3	 3.7 3.2	 2.8 2.8	 2.9 2.9
12-week disease control rate, %	60.6	36.8	26.7	29.8
24-week disease control rate, %	42.4	17.2	13.3	15.8
ORR, %	16.7%	4.6%	0%	1.8%

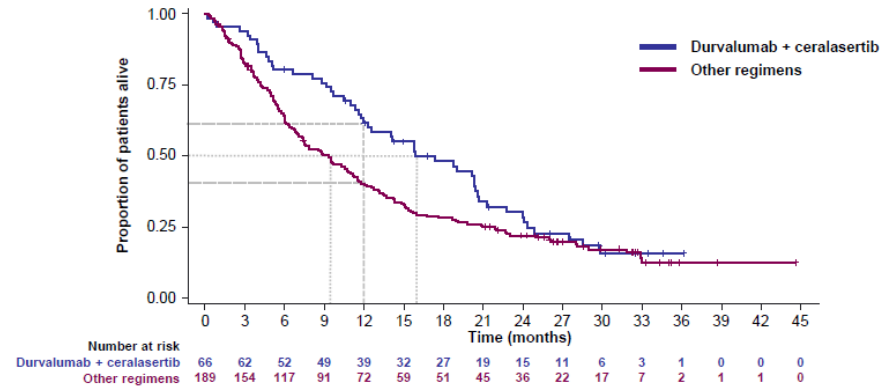
PFS



	Durvalumab + ceralasertib. n=66	Other regimens n=189	Durvalumab + olaparib, n=87	Durvalumab + danvatirsen, n=45	Durvalumab + oleclumab, n=57
Median PFS, months (80% CI)	6.0 (4.6–7.5)	2.7 (1.8–2.8)	2.7 (1.6–3.0)	2.9 (1.7–3.1)	1.8 (1.6–2.7)
6-month PFS, % (80% CI)	46.3 (37.9–54.2)	18.0 (14.5–21.9)	18.7 (13.5–24.5)	18.8 (11.5–27.6)	16.6 (10.8–23.6)

PFS, progression-free surv

OS



	Durvalumab + ceralasertib. n=66	Other regimens n=189	Durvalumab + olaparib, n=87	Durvalumab + danvatirsen, n=45	Durvalumab + oleclumab, n=57
Median OS, months (80% CI)	15.9 (14.1–20.3)*	9.4 (7.5–10.6)	9.4 (6.9–10.8)	7.9 (6.0–10.6)	11.0 (7.6–13.5)
12-month OS, % (80% CI)	61.6 (53.4–68.8)	39.7 (35.1–44.3)	40.8 (34.0–47.5)	28.8 (20.2–38.0)	46.2 (37.5–54.5)

*Data are still accruing; this median value for OS may change. OS, overall survival.

Besse WCLC 2022

Conclusion

- Rechallenge of immunotherapy is an option
  - Free interval > 1 year better?
- Need for new option beyond docetaxel
  - Immunotherapy + targeted therapies (VEGFRi, ATRi) ?
  - ADCs?
- Understanding the biology of primary and acquired resistance to immunotherapy is key

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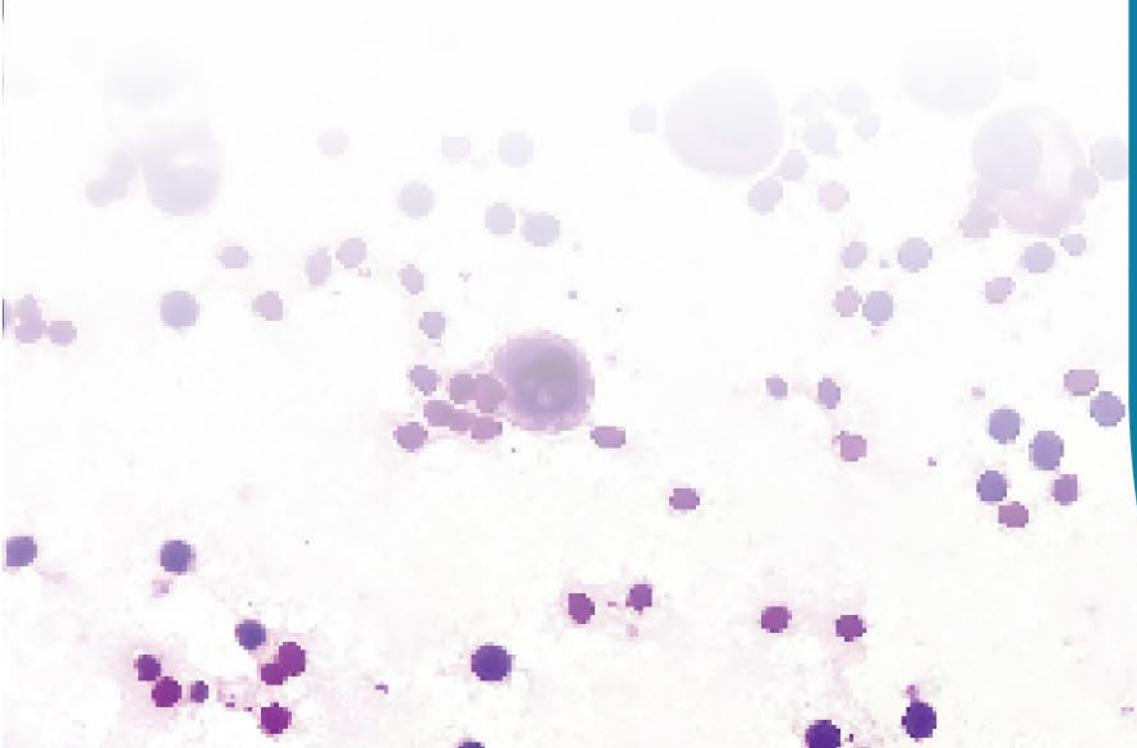
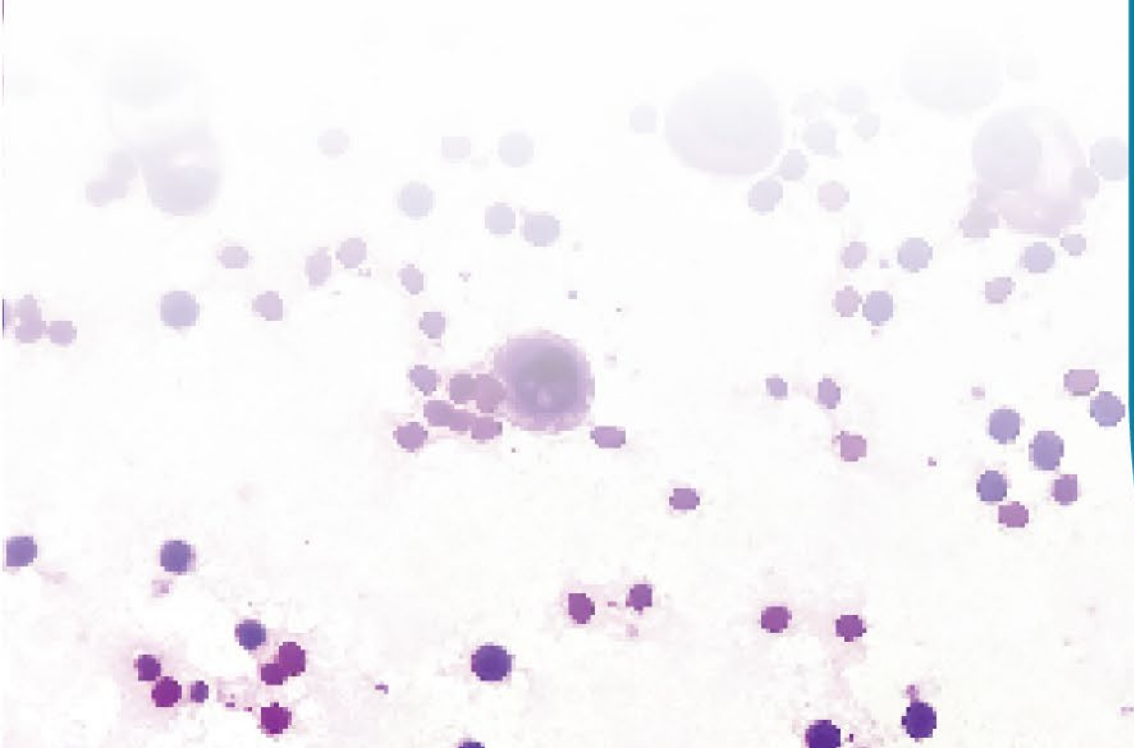


Tumor Board Discussion

Moderator: Solange Peters, MD

Case presenters: Francesca Fusco, MD, and Luis Angel Leon Mateos, MD

Global Lung Cancer Academy



Patient Case 1

Francesca Fusco, MD

Global Lung Cancer Academy

Sharing Best Practices to Optimize Patient Care in Europe

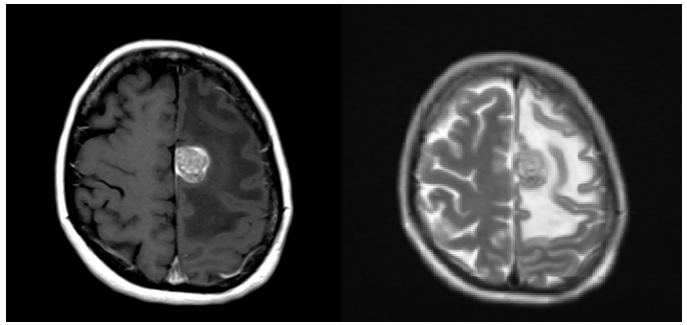
November 7 and 14, 2022

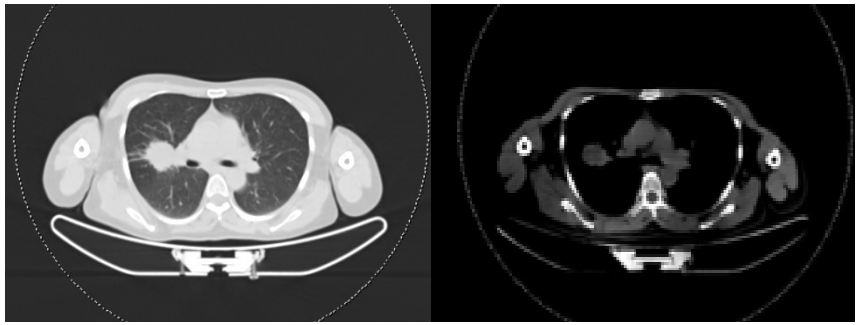
Local Case 1: First-Line Chemoimmunotherapy in NSCLC

Francesca Fusco, MD
Regina Elena National Cancer Institute
Rome, Italy

Case Presentation

- Woman, 47 years old, ECOG PS 0, current smoker (22 packs/year)
- No relevant medical history
- Symptoms: confusion and speech impairment
- February 6, 2021: brain MRI shows **single left frontal lesion** with perilesional edema. Chest-abdomen CT scan reveals **right upper lobe lung lesion**





Case Presentation

DIAGNOSIS	February 10, 2021: surgical **resection of frontal brain lesion** with histologically confirmed diagnosis of **metastasis of lung adenocarcinoma** (TTF-1 positive) IHC: **PD-L1 TPS 40%.** NGS: evidence of ***KRAS* G12A** mutation
STAGING	Staging: **cT2b** (41 mm) **cN2** (10R and 7) **pM1b** (single resected brain lesion) – Stage IV – TNM 8th Edition
MEDIASTINAL STAGING	April 27, 2021: EBUS-TBNA (station 7) with no evidence of cancer cells Staging: **cT2b** (41 mm) **cN1 (10R) pM1b** (single resected brain lesion)

ISG IRE

Case Presentation

What would you have done?

- Locoregional treatment
- First-line platinum-based chemotherapy
- First-line chemoimmunotherapy
- First-line immunotherapy

Case Presentation

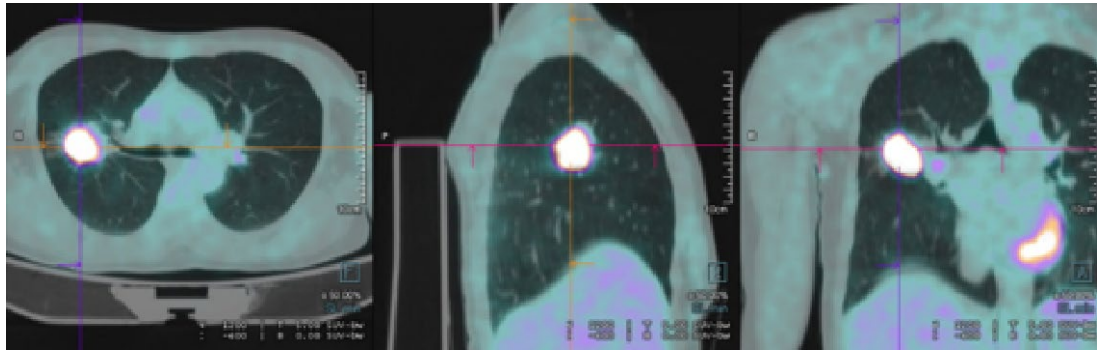
March 2, 2021: **SRS** (surgical bed) – 24 Gy in 3 fractions

May 25, 2021: first-line chemoimmunotherapy with **carboplatin AUC 5** on day 1, **pemetrexed 500 mg/m²** on day 1, **pembrolizumab 200 mg** on day 1 q3w
AEs: **anemia G2 and neutropenia G3**

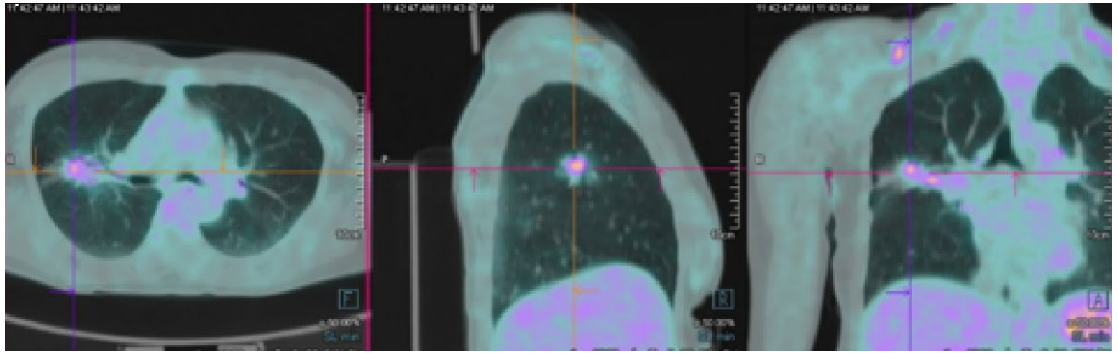
August 6, 2021: PET-CT scan performed after 4 cycles shows **partial response in the target lesion. Brain MRI: NED**

Case Presentation

Baseline
(March 2021)



+4 cycles
(August 2021)



Partial response on lung target lesion

Case Presentation

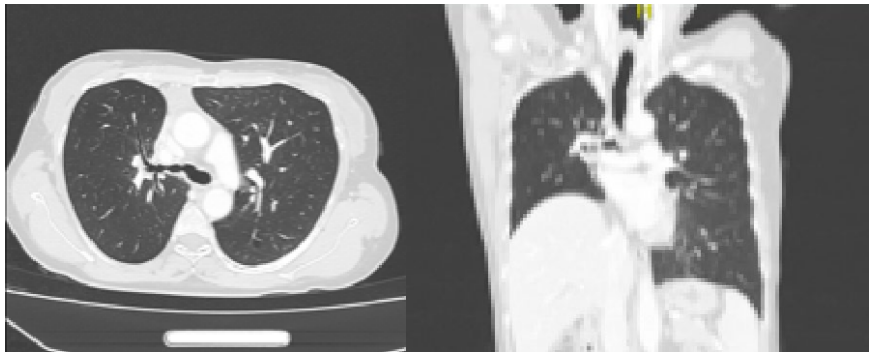
What would you have done?

- Maintenance therapy (pemetrexed and pembrolizumab)
- Locoregional treatment (surgery)
- Locoregional treatment (radiotherapy)

Case Presentation

August 24, 2021: **right upper lobectomy and mediastinal lymph node dissection** (1, 2R, 4R, 7, 8, 9R, 10R, 11R) with **pathologic complete response, ypT0 pN0** (0/16)

September 20, 2021: **maintenance therapy with pembrolizumab 200 mg** q3w (pemetrexed not included due to hematologic toxicity) for 1 year
Last tumor assessment (TB-CT scan) on September 2022: **NED**



Total body CT scan, September 2022

Case Presentation

What would you have done?

Continue maintenance treatment

Follow up

Thank you for your attention!

Thanks to My Team
Regina Elena National Cancer Institute – Rome

Medical Oncology 2 Division
Federico Cappuzzo, MD – Chief
Silvia Carpano, MD
Corrado Orciuolo, MD

Fellows
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Serena Ceddia, MD

Phase I Clinical Centre and Precision Oncology
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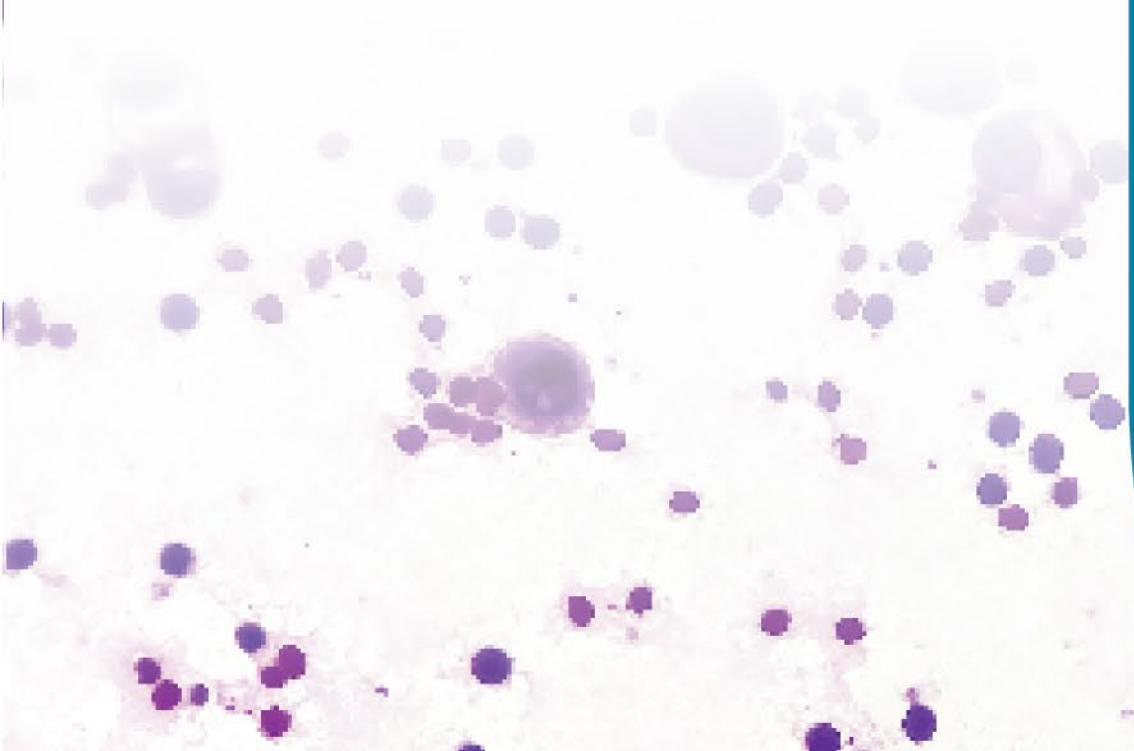
Global Lung Cancer Academy



Patient Case 2

Luis Angel Leon Mateos, MD

Global Lung Cancer Academy

Case 1: ALK Inhibitor

Luis León, MD
Medical Oncology Department
University Hospital Santiago de Compostela

Disclosures

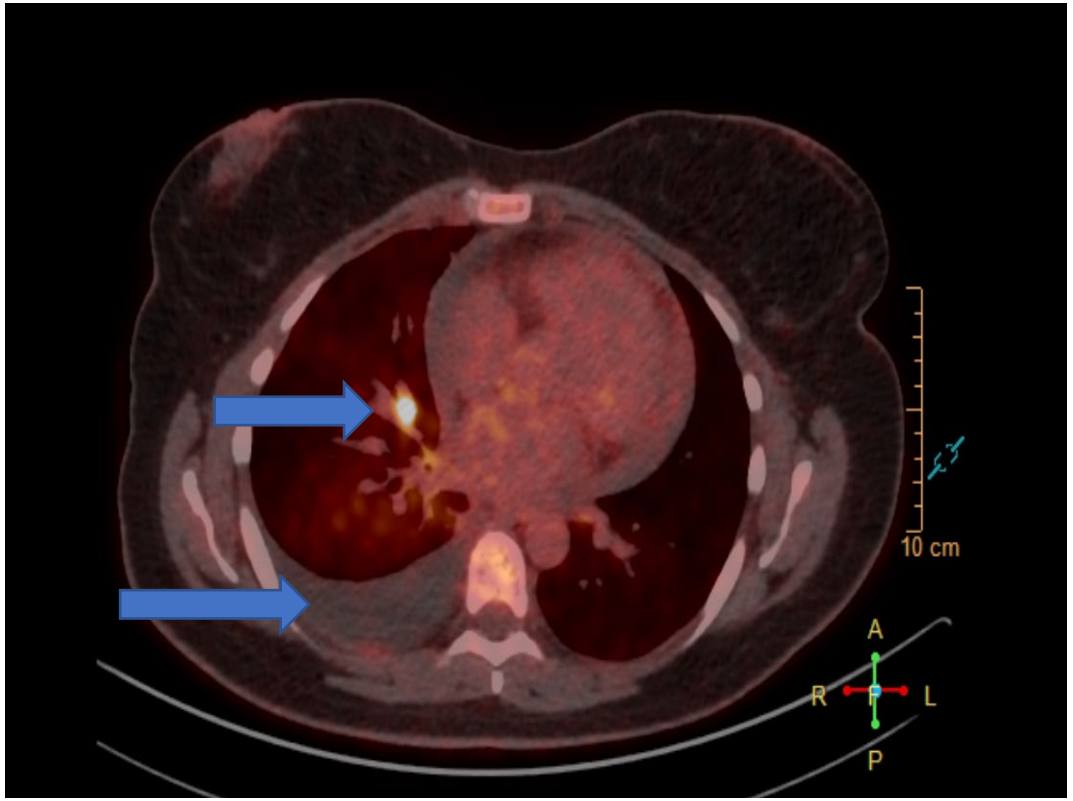
Consulting, advisory role or speaker: Pfizer, Boehringer, Novartis, Roche, Astra Zeneca, Sanofi, Bristol, Jansen, Pfizer, Astellas, MSD, Ipsen

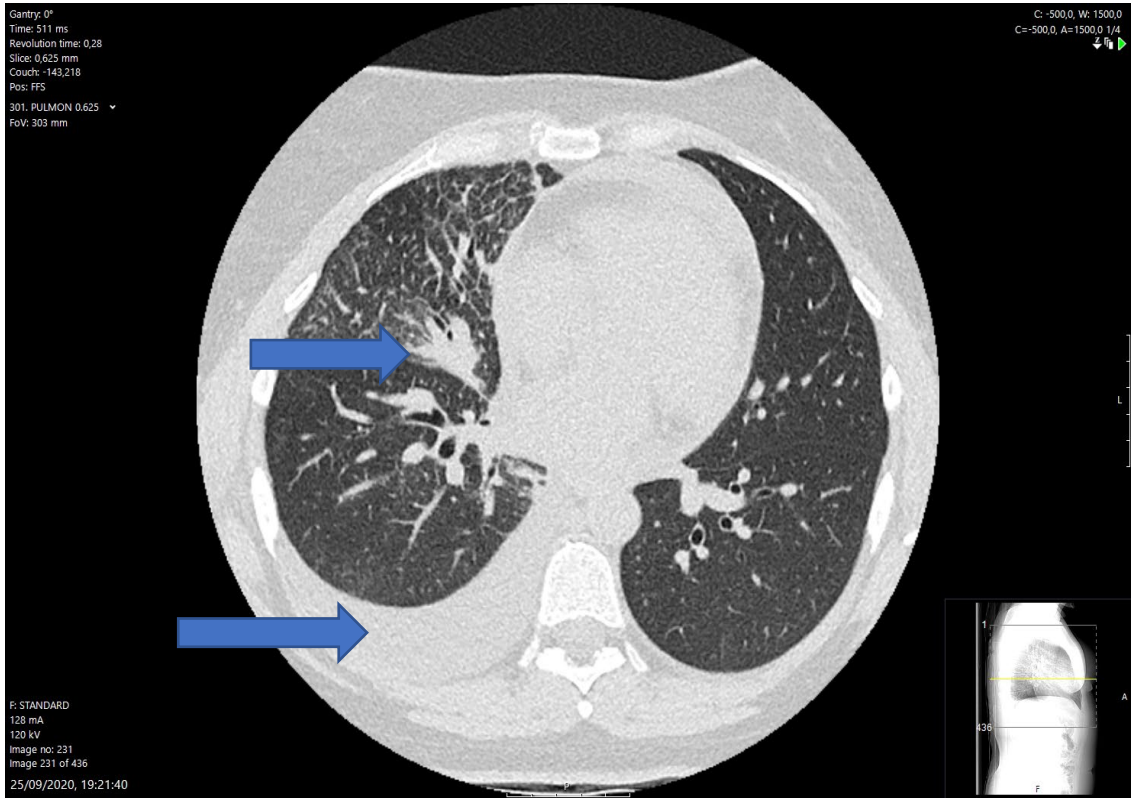
Grant or travel support: MSD, Ipsen, Sanofi, Jansen, Roche

Medical Background and Initial Diagnosis

- 37-year-old woman
- Smoker of 10 cigarettes/day (IPA 5)
- Autoimmune hypothyroidism; hiatal hernia
- In July 2020 starts with dyspnea
- Admission in August 2020 for pulmonary infiltrate; COVID-19 positive
- Bronchoscopy negative for malignancy

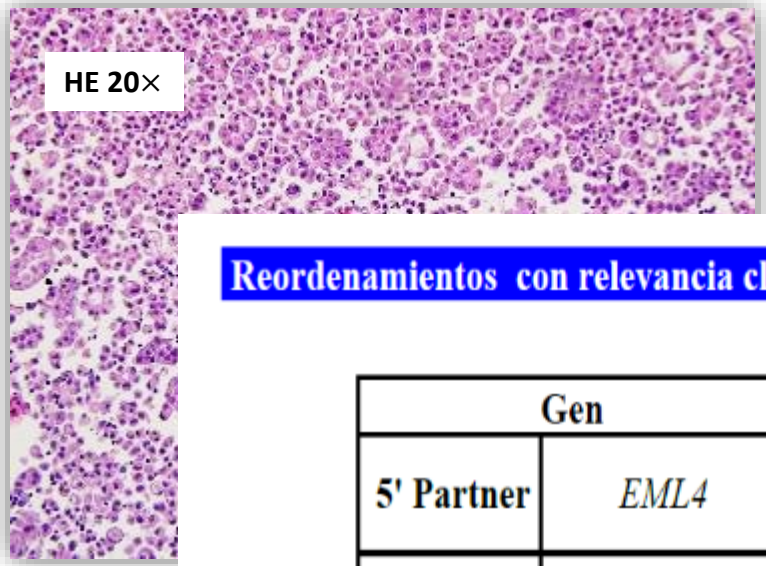
PET-CT Scan September 2020



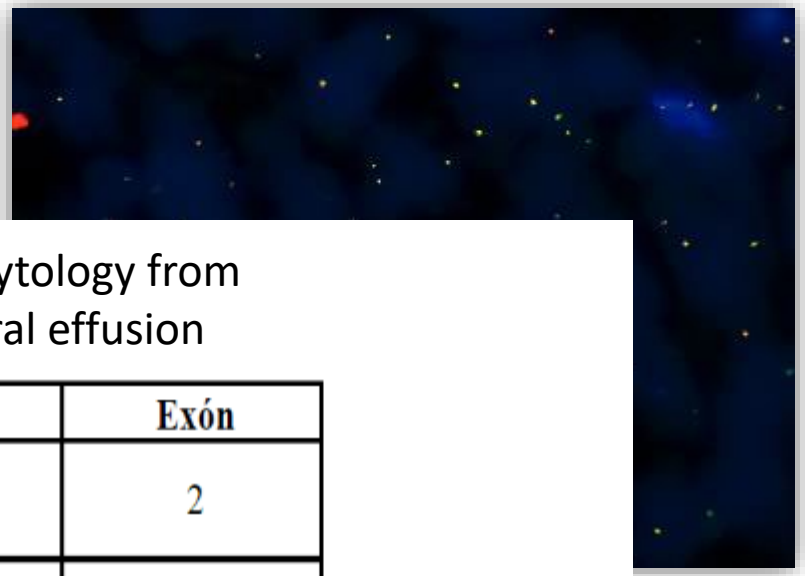


Lesion in middle lobe and pleural effusion

Pleural fluid: **adenocarcinoma**



Tissue: ***EML4-ALK* fusion variant 5**



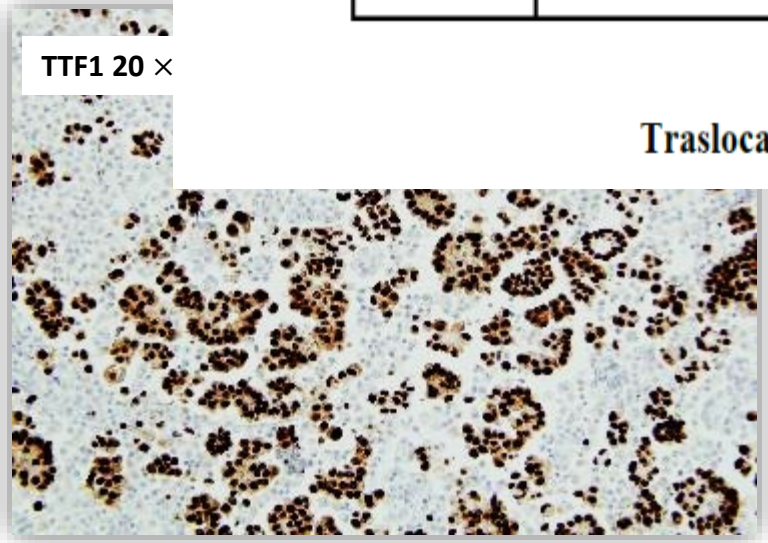
Reordenamientos con relevancia clínica

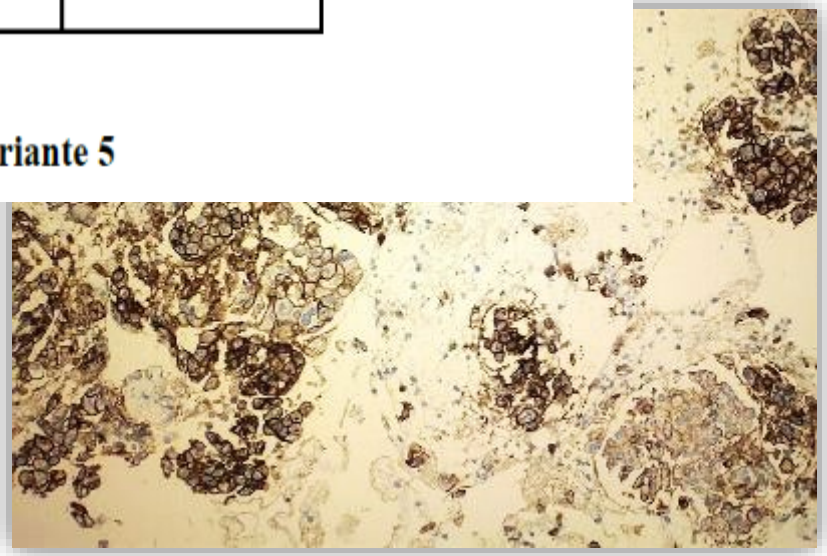
NGS, cytology from pleural effusion

Gen		Posición	Exón
5' Partner	*EML4*	2:42,475,889	2
3' Partner	*ALK*	2:29,447,252	19

Traslocación *EML4-ALK* variante 5

IHC: p





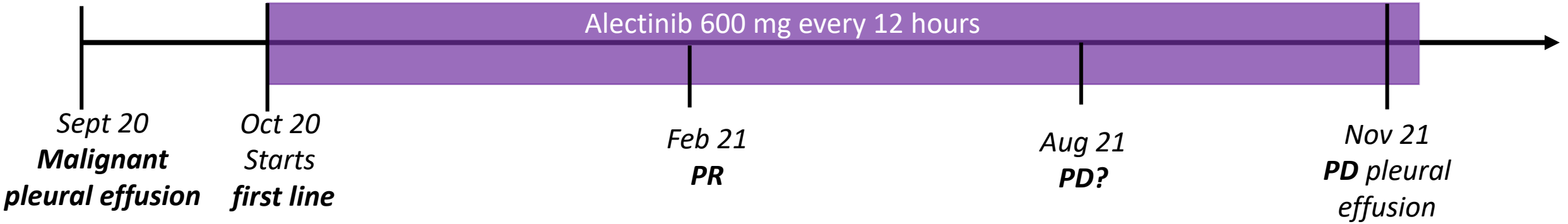
Question 1

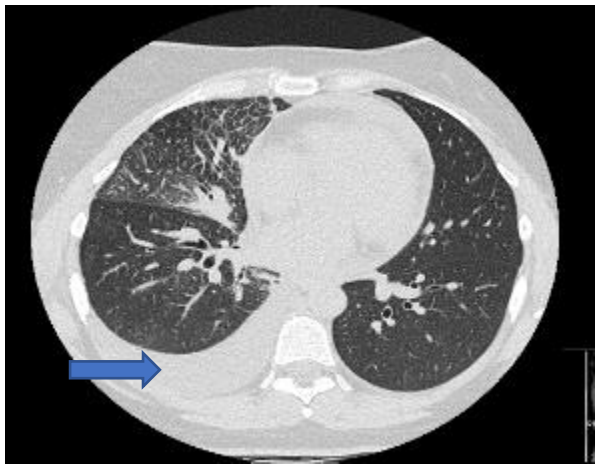
In this patient with stage IV lung adenocarcinoma with *ALK* variant 5 fusion and PD-L1 60%, which treatment would you initiate?

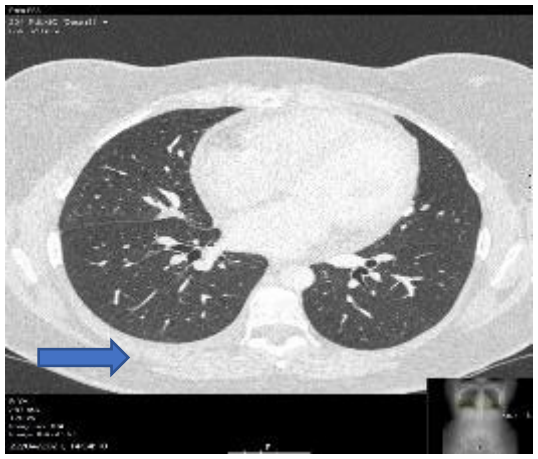
1. Crizotinib
2. Alectinib
3. Lorlatinib
4. Platinum doublet + immunotherapy

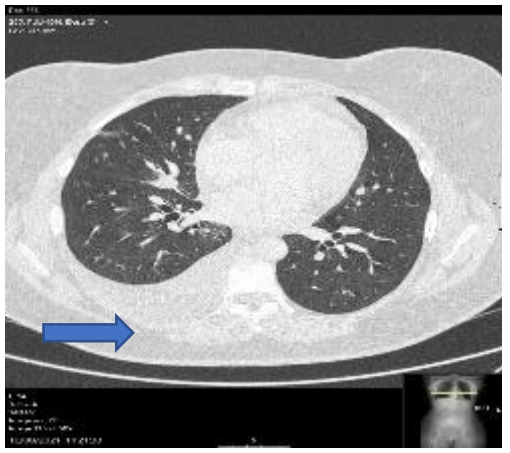
Woman, 37 years old
Smoker (IPA 5)
Autoimmune hypothyroidism

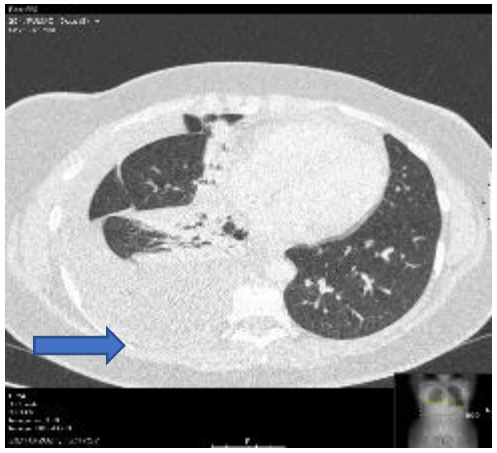
Stage IVA lung adenocarcinoma
Tissue
* ***EML4-ALK* fusion variant 5**
* PD-L1 60%



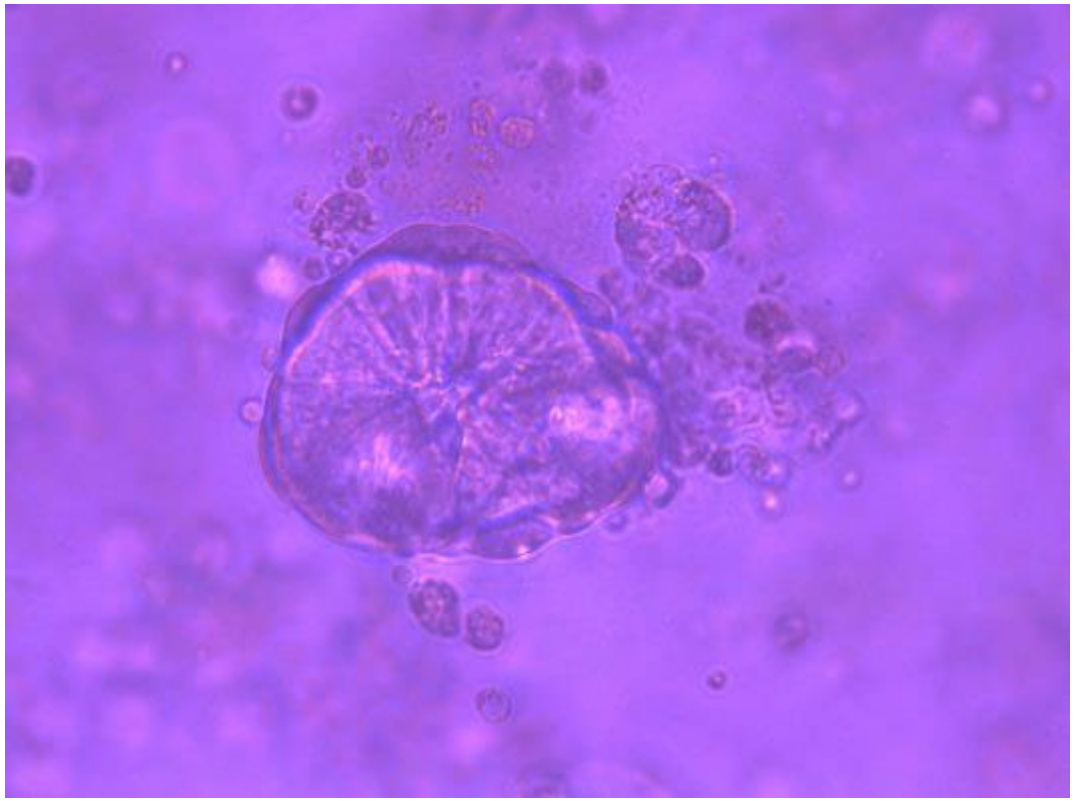


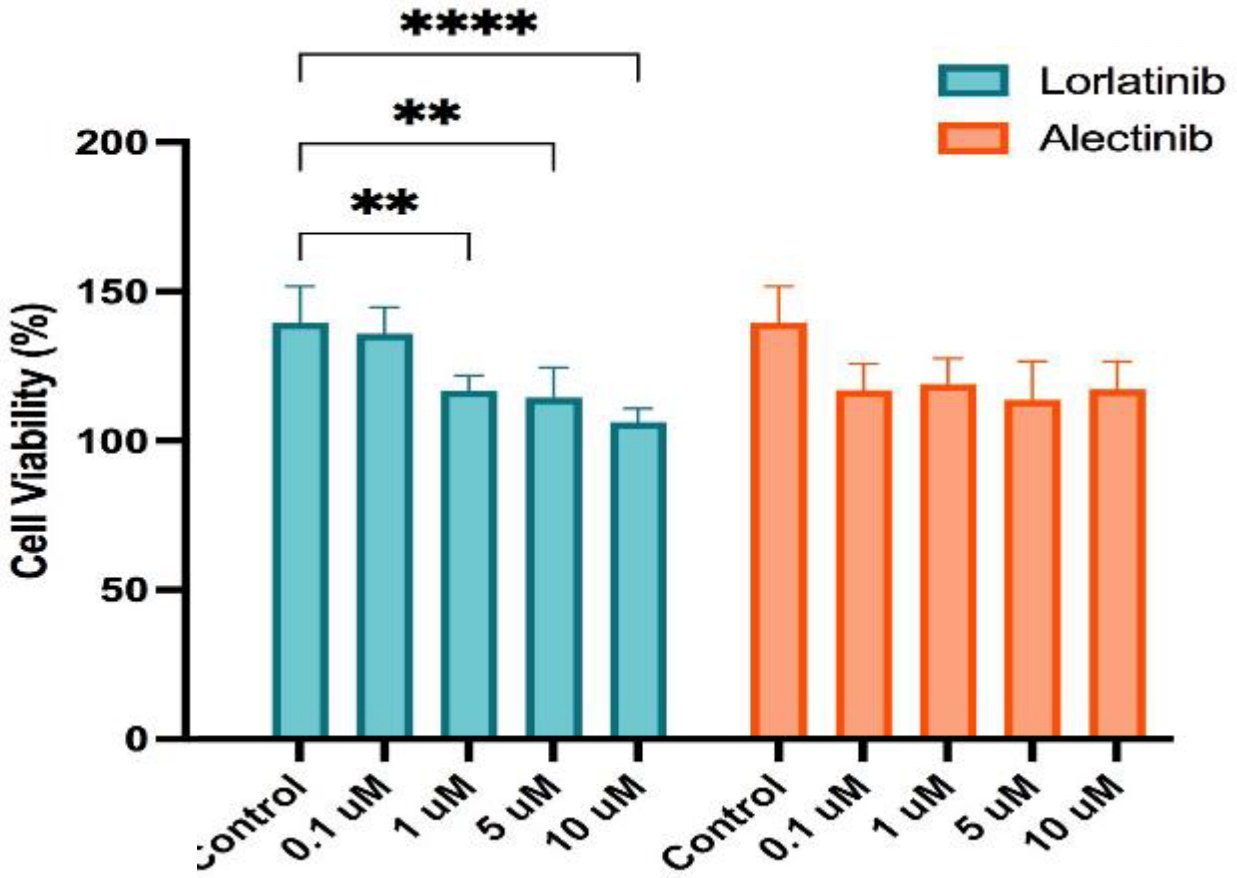






Organoids From Pleural Effusion



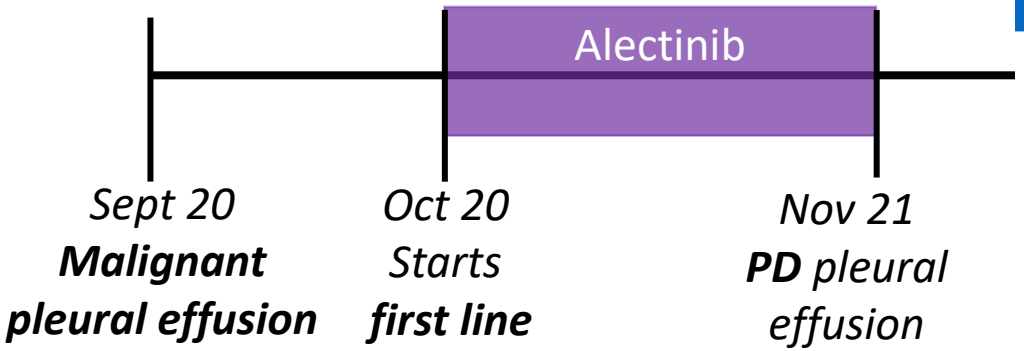


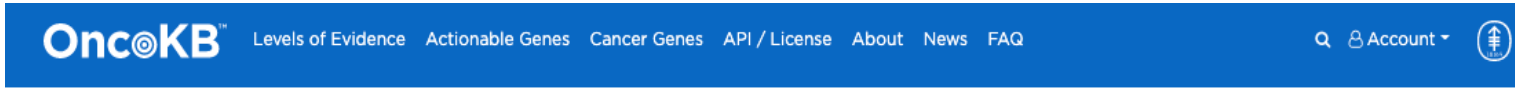
Courtesy of Patricia Mondelo and Miguel Abal.

⟹ NSCLC *ALK* Fusion Rearrangement

Woman, 37 years old
Smoker (IPA 5)
Autoimmune hypothyroidism

Stage IVA lung adenocarcinoma
Tissue
* ***EML4-ALK* fusion variant 5**
* **PD-L1 1%**





ALK G1202R

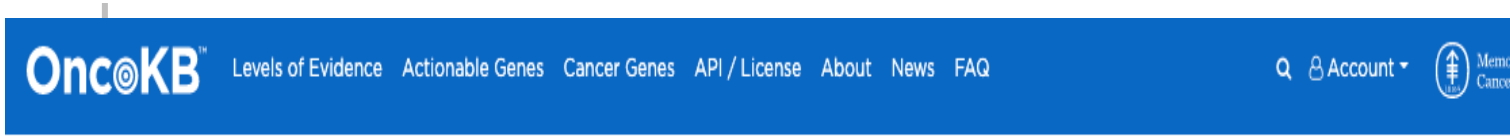
Resistance · Inconclusive · Level 1 · Level R2 · FDA Level 2

ALK, a receptor tyrosine kinase, is recurrently altered by chromosomal rearrangements in various cancer types including anaplastic large cell lymphoma, non-small cell lung cancer and inflammatory myofibroblastic tumors.

The ALK G1202R is a known resistance mutation.

Non-Small Cell Lung Cancer

"Promising clinical data with lorlatinib in *ALK* pts with G1202R"



ALK F1174L

Oncogenic · Gain-of-function · Level 1 · FDA Level 2

ALK, a receptor tyrosine kinase, is recurrently altered by chromosomal rearrangements in various cancer types including anaplastic large cell lymphoma, non-small cell lung cancer and inflammatory myofibroblastic tumors.

The ALK F1174L mutation is known to be oncogenic.

Select a cancer type

Is lorlatinib active in *ALK* F1174L?

Nov 11, 2021

ddPCR **pleural effusion** → *G1202R* 33.16%
F1174L 0.12%

ddPCR **plasma** → *F1174L* 0.13%

Question 2

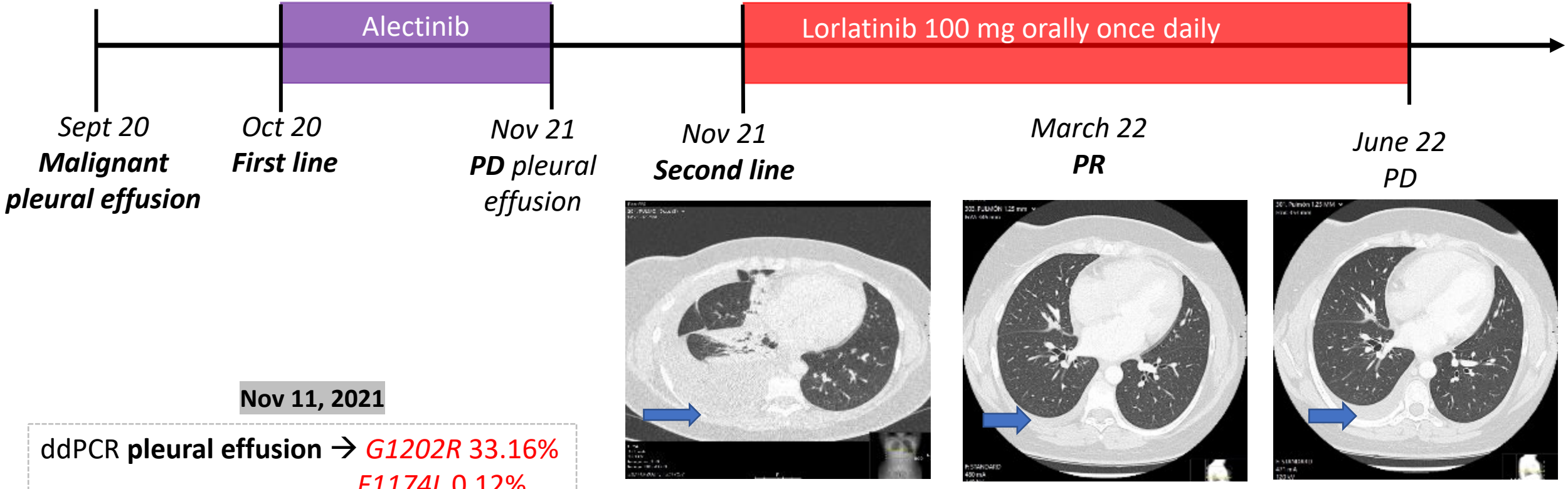
The study in tissue, pleura, or plasma after progression to alectinib:

1. Only has academic interest, not useful for decision-making
2. Tissue biopsy is only useful to know if there is histologic transformation
3. The study of secondary resistance mutations can be useful for treatment selection
4. Resistance in patients with *ALK* fusions is not related to activation of bypass signaling pathways

Stage IVA lung adenocarcinoma

Tissue

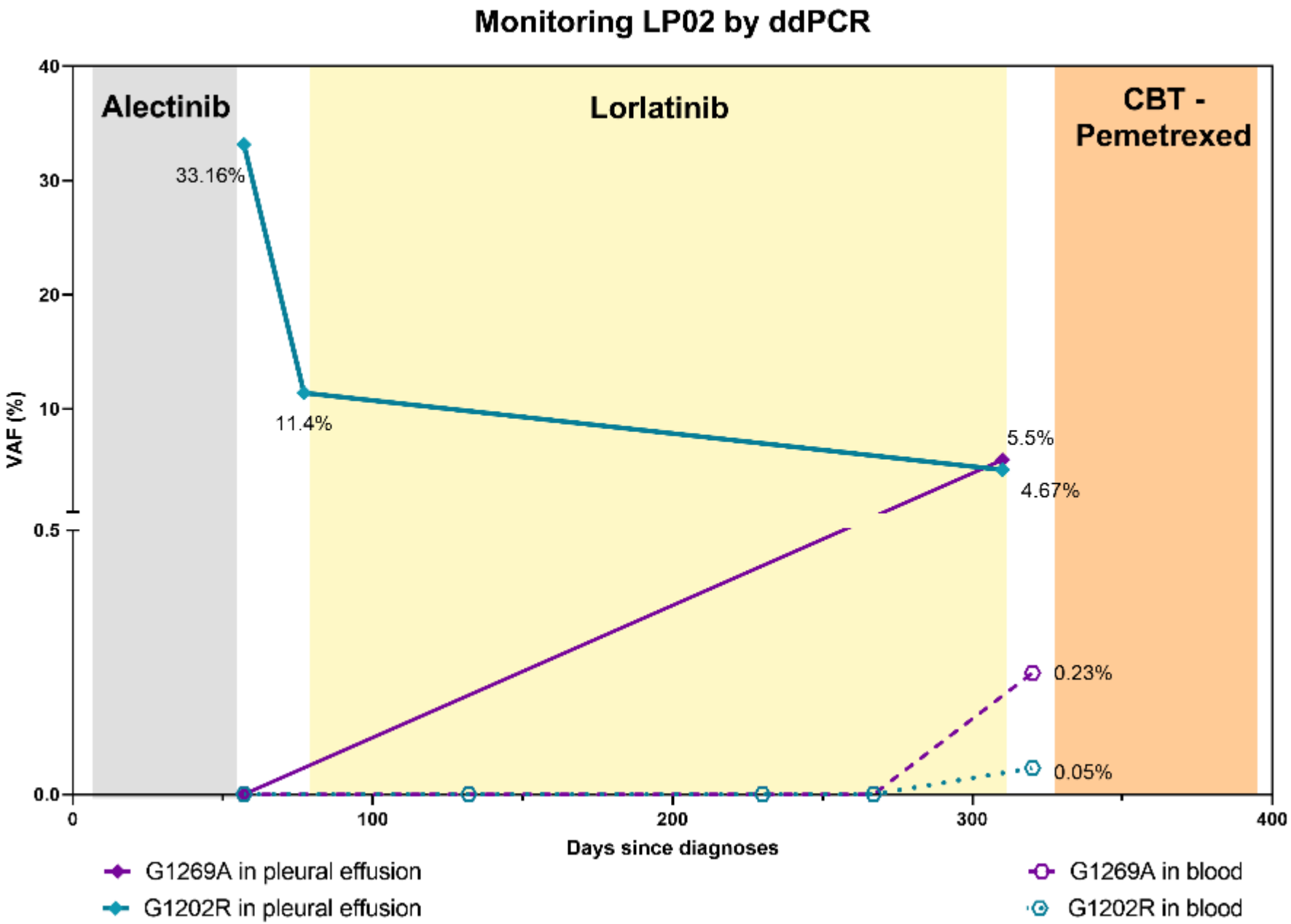
* ***EML4-ALK* fusion variant 5**
* **PD-L1 1%**



Nov 11, 2021

ddPCR **pleural effusion** → *G1202R* 33.16%
F1174L 0.12%

ddPCR **plasma** → *F1174L* 0.13%


Monitoring LP02 by ddPCR
Alectinib
Lorlatinib
CBT - Pemetrexed
33.16%
11.4%
5.5%
4.67%
0.23%
0.05%
VAF (%)
40
30
20
10
0.5
0.0
0
100
200
300
400
Days since diagnoses
G1269A in pleural effusion
G1202R in pleural effusion
G1269A in blood
G1202R in blood

Conclusions

1. The introduction of new TKIs is improving the survival of *ALK* fusion NSCLC patients

2. Knowledge of the mechanisms of drug resistance can guide the choice of treatment

3. Tissue and liquid biopsy are complementary tools in the management of these patients

Global Lung Cancer Academy

SERVIZO GALEGO de SAÚDE | Área Sanitaria de Santiago de Compostela e Barbanza

Thank you!

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Global Lung Cancer Academy

Tumor Board Discussion

Moderator: Solange Peters, MD

All faculty

Global Lung Cancer Academy

BREAK

Global Lung Cancer Academy

ALK Inhibitors in NSCLC

Enriqueta Felip, MD, PhD

ALK Inhibitors in NSCLC
Considerations for Optimal Use in Clinical Practice in Patients With and Without Brain Metastases

Enriqueta Felip, MD, PhD
Vall d'Hebron University Hospital, Barcelona, Spain

Global Lung Cancer Academy

November 14, 2022

Disclosures

- Dr Enriqueta Felip has the following relationships to disclose
  - Advisory role or speaker's bureau: Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, F. Hoffman-La Roche, GlaxoSmithKline, Ipsen, Janssen, Medscape, Merck KGaA, MSD, Novartis, Peptomyc, PeerVoice, Pfizer, Regeneron, Sanofi, Seagen, Takeda, and Turning Point Therapeutics
  - Independent board member: Grifols
  - Research funding: Fundación Merck Salud, Grant for Oncology Innovation, and Merck Healthcare KGaA

Metastatic *ALK*+ NSCLC: CNS Metastases

- Patients with *ALK* translocations have among the highest incidence of CNS metastases across the NSCLC oncogene groups
  - In newly diagnosed patients with *ALK*+ NSCLC, the incidence of brain metastases ranges from 20%–30%, and it is estimated that 50%–60% will develop brain metastases during the course of their disease
  - The incidence of brain metastases in *ALK*+ NSCLC patients increases over time and with subsequent lines of therapy
- Durable control of brain metastases in patients with brain metastases and prevention of brain metastases in those without them at the point of diagnosis remain unmet treatment needs

Patil T, et al. *J Thorac Oncol*. 2018;13:1717-1726; Wang W, et al. *Oncol Res Treat*. 2019;42:599-606; Zhang Z, et al. *J Thorac Dis*. 2019;11:1397-1409.

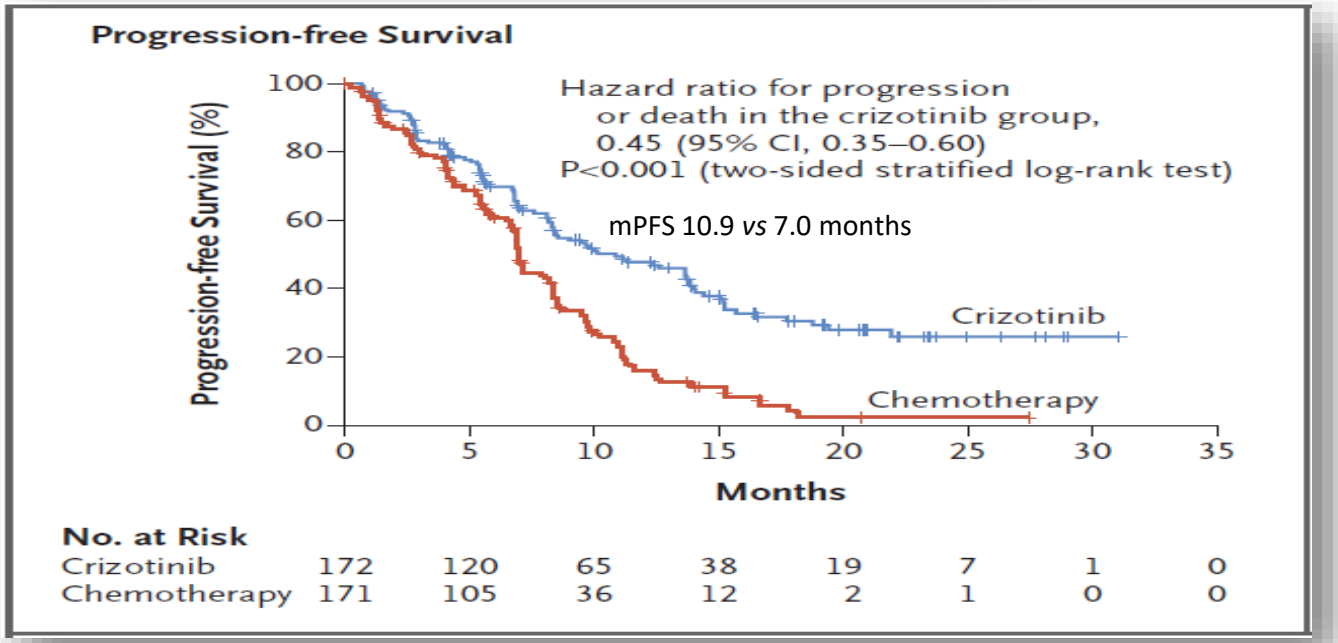
ALK+: Crizotinib as First Line

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer

Benjamin J. Solomon, M.B., B.S., Ph.D., Tony Mok, M.D., Dong-Wan Kim, M.D., Ph.D., Yi-Long Wu, M.D., Kazuhiko Nakagawa, M.D., Ph.D., Tarek Mekhail, M.D., Enriqueta Felip, M.D., Ph.D., Federico Cappuzzo, M.D., Jolanda Paolini, B.Sc., Tiziana Usari, B.Sc., Shrividya Iyer, Ph.D., Arlene Reisman, M.P.H., Keith D. Wilner, Ph.D., Jennifer Tursi, M.Sc., and Fiona Blackhall, M.D., Ph.D., for the PROFILE 1014 Investigators*



The Common Sites of Relapse on Crizotinib

	ALK inhibitor-naive	Post-ALK inhibitor
Brain	31-40%	**58-71%**
Lung	75%	34-68%
Bone	31-44%	42-58%
Liver	27-36%	37-42%

Solomon BJ, et al. *N Engl J Med*. 2014;371:2167-2177; Camidge DR, Doebele RC. *Nat Rev Clin Oncol*. 2012;9:268-277.

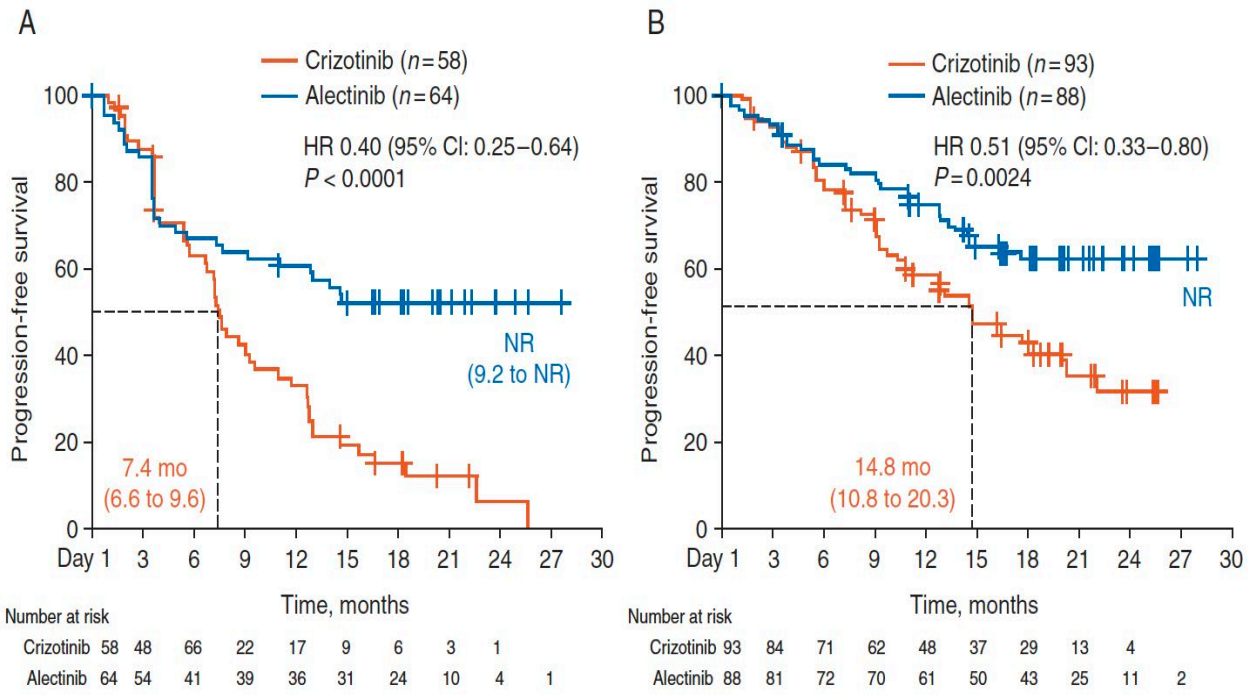
First-Line *ALK*+: PFS Outcomes From the ALEX, ALTA-1L, and CROWN Trials

Efficacy Data	ALEX[1]		ALTA-1L[2]		CROWN[3]	
	Alectinib (n = 152)	Crizotinib (n = 151)	Brigatinib (n = 137)	Crizotinib (n = 138)	Lorlatinib (n = 147)	Crizotinib (n = 149)
Median PFS, months	34.8	10.9	24.0	11.1	Not reached	9.3
HR (95% CI)	0.43 (0.32–0.58)		0.48 (0.35–0.66)		0.27 (0.18–0.39)	
PFS rate at 36 months, % (95% CI)	46.4 (CI not reported)	13.5 (CI not reported)	43.0 (34.0–51.0)	19.0 (12.0–27.0)	63.5 (CI not reported)	18.9 (CI not reported)
Median duration of follow-up, months	37.8		40.4		36.7	

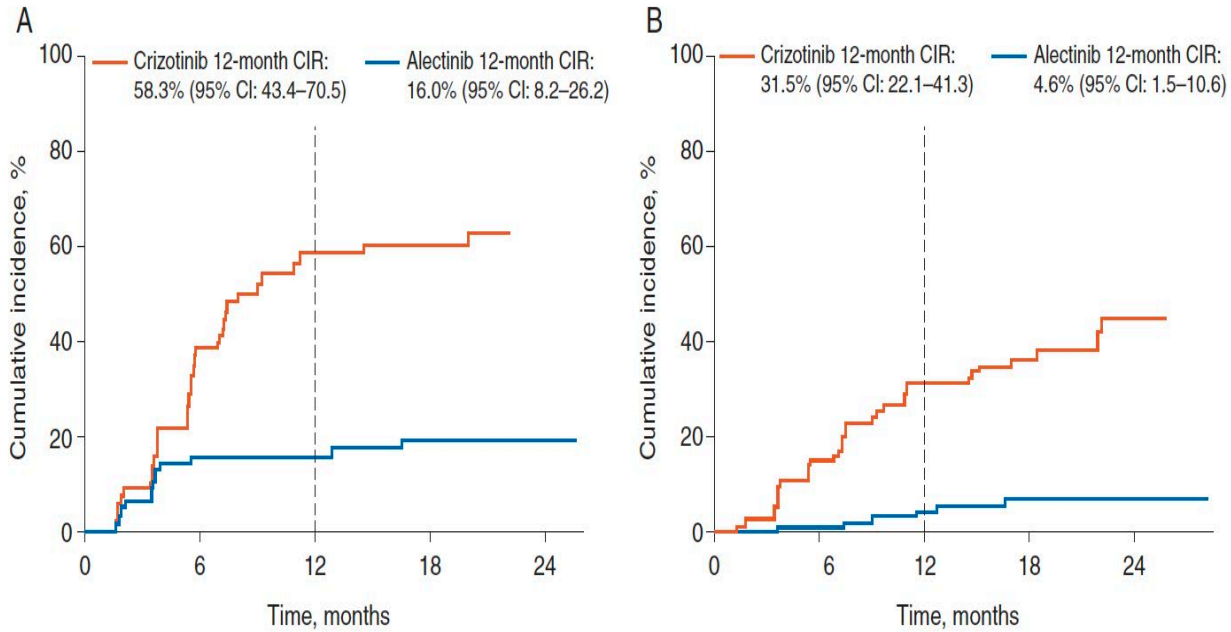
1. Mok T, et al. *Ann Oncol*. 2020;31:1056-1064; 2. Tiseo M, et al. ELCC 2022. Abstract 29P; 3. Solomon B, et al. AACR 2022. Abstract CT223.

Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (*ALK*+) non-small-cell lung cancer: CNS efficacy results from the ALEX study

S. Gadgeel[1*], S. Peters[2], T. Mok[3], A. T. Shaw[4], D. W. Kim[5], S. I. Ou[6], M. Pérol[7], A. Wrona[8], S. Novello[9], R. Rosell[10], A. Zeaiter[11†], T. Liu[11], E. Nüesch[11], B. Balas[11] & D. R. Camidge[12]



PFS according to CNS metastatic status at baseline
(A) Patients with CNS metastases at baseline
(B) Patients without CNS metastases at baseline

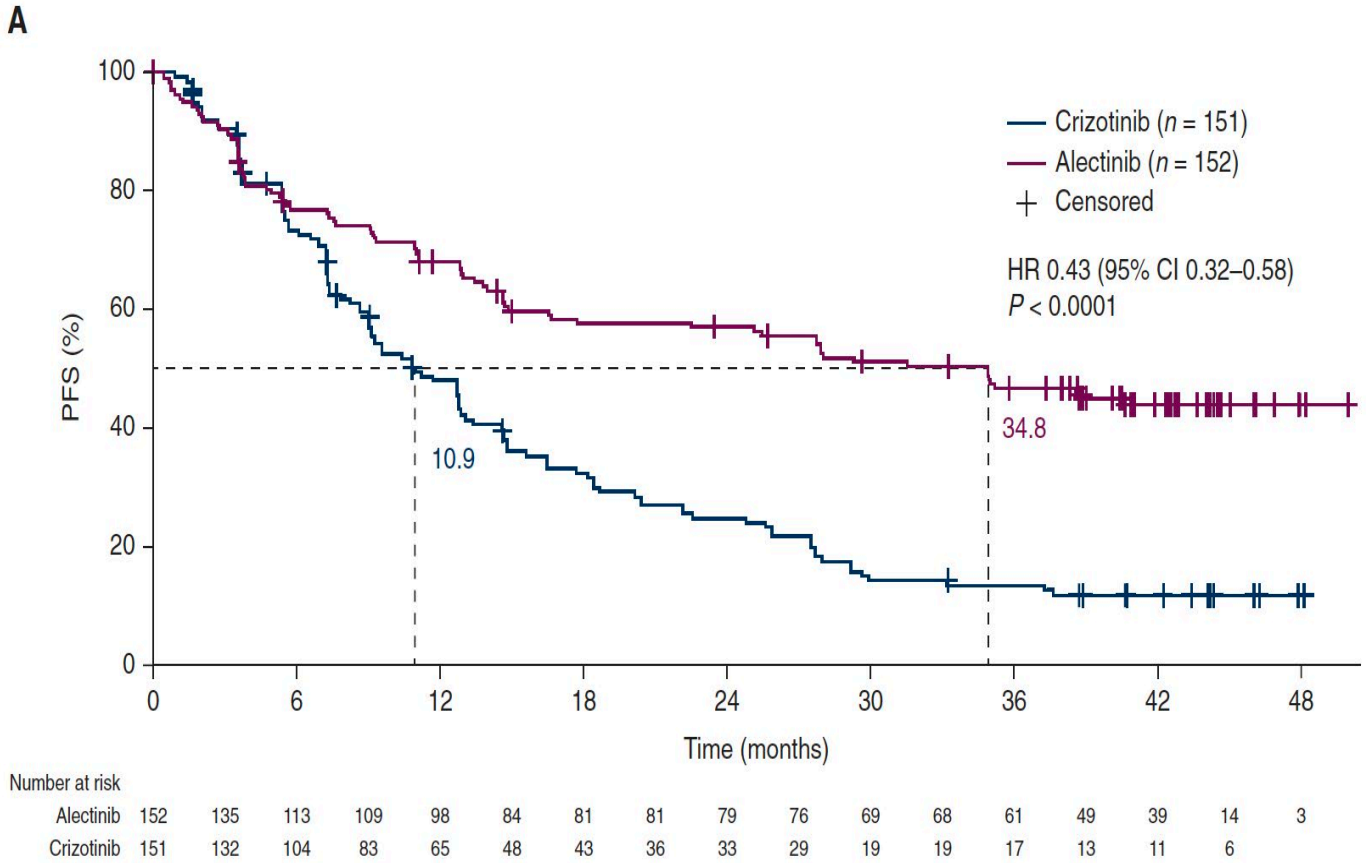


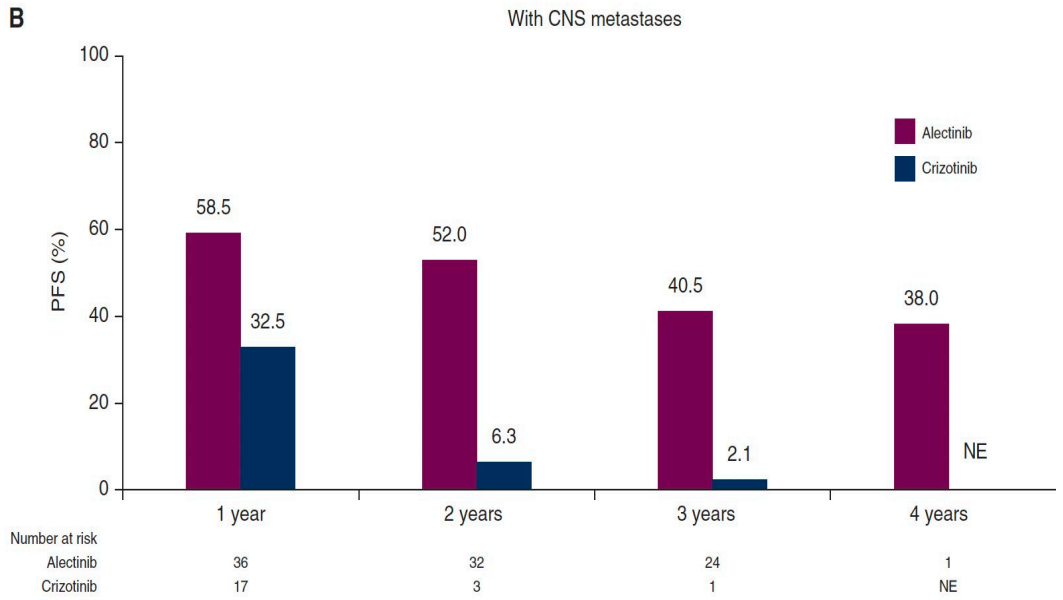
Cumulative incidence rate of CNS PD
(A) Patients with CNS metastases at baseline
(B) Patients without CNS metastases at baseline

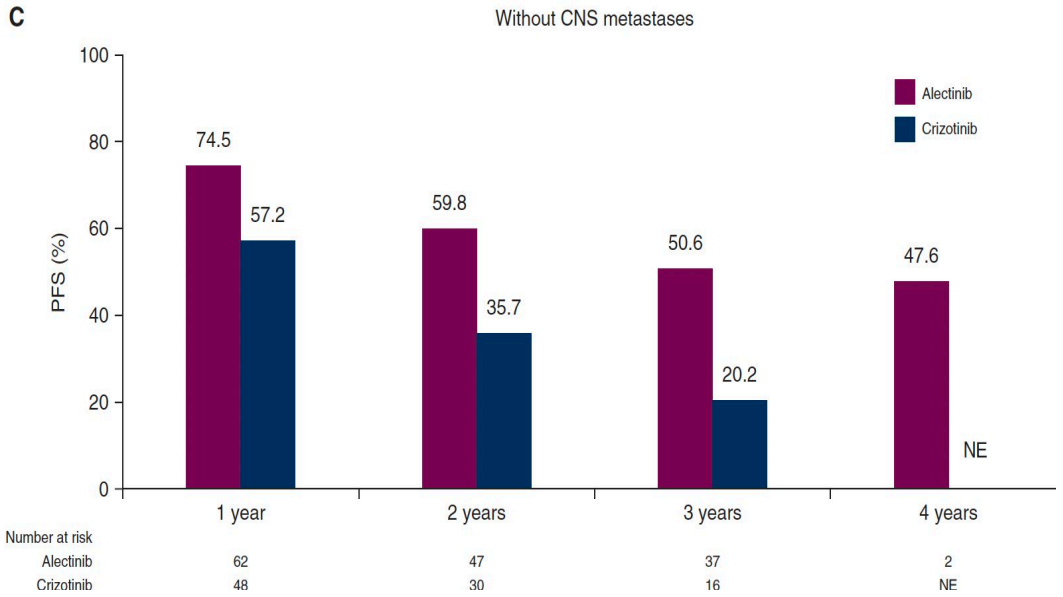
Gadgeel S, et al. *Ann Oncol.* 2018;29:2214-2222.

Updated overall survival and final progression-free survival data for patients with treatment-naive advanced *ALK*-positive non-small-cell lung cancer in the ALEX study

T. Mok[1], D. R. Camidge[2], S. M. Gadgeel[3], R. Rosell[4], R. Dziadziuszko[5], D.-W. Kim[6], M. Pérol[7], S.-H. I. Ou[8], J. S. Ahn[9], A. T. Shaw[10†], W. Bordogna[11], V. Smoljanović[11], M. Hilton[11], T. Ruf[11], J. Noé[11] & S. Peters[12*]







(A) Kaplan-Meier plot of investigator-assessed PFS in the intent-to-treat population, and PFS rates (B) in patients with baseline CNS metastases, and (C) in patients without baseline CNS metastases

Mok T, et al. *Ann Oncol*. 2020;31:1056-1064.

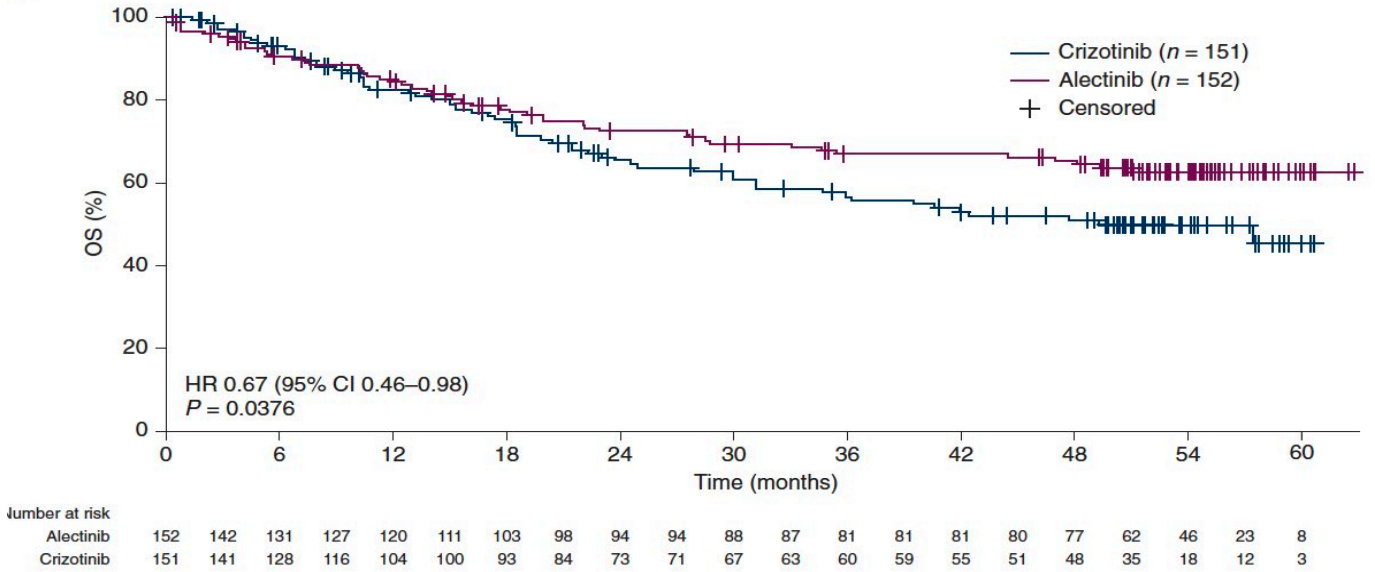
Updated overall survival and final progression-free survival data for patients with treatment-naive advanced *ALK*-positive non-small-cell lung cancer in the ALEX study

T. Mok[1], D. R. Camidge[2], S. M. Gadgeel[3], R. Rosell[4], R. Dziadziuszko[5], D.-W. Kim[6], M. Pérol[7], S.-H. I. Ou[8], J. S. Ahn[9], A. T. Shaw[10†], W. Bordogna[11], V. Smoljanović[11], M. Hilton[11], T. Ruf[11], J. Noé[11] & S. Peters[12*]

A) Kaplan-Meier plot of investigator-assessed OS in the intent-to-treat population (stratified analysis) and
B) OS subgroup analysis (unstratified analysis)

Mok T, et al. *Ann Oncol*. 2020;31:1056-1064.

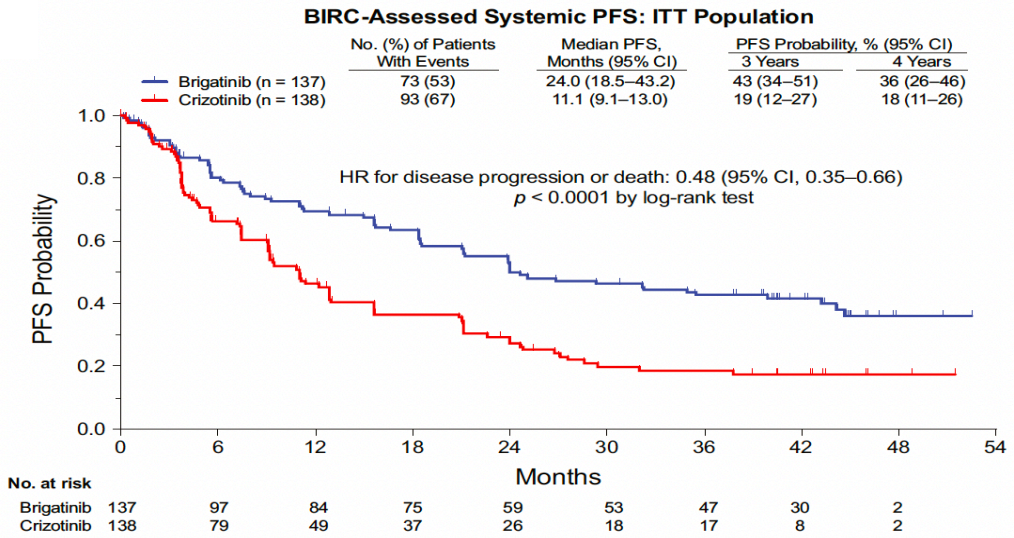
A

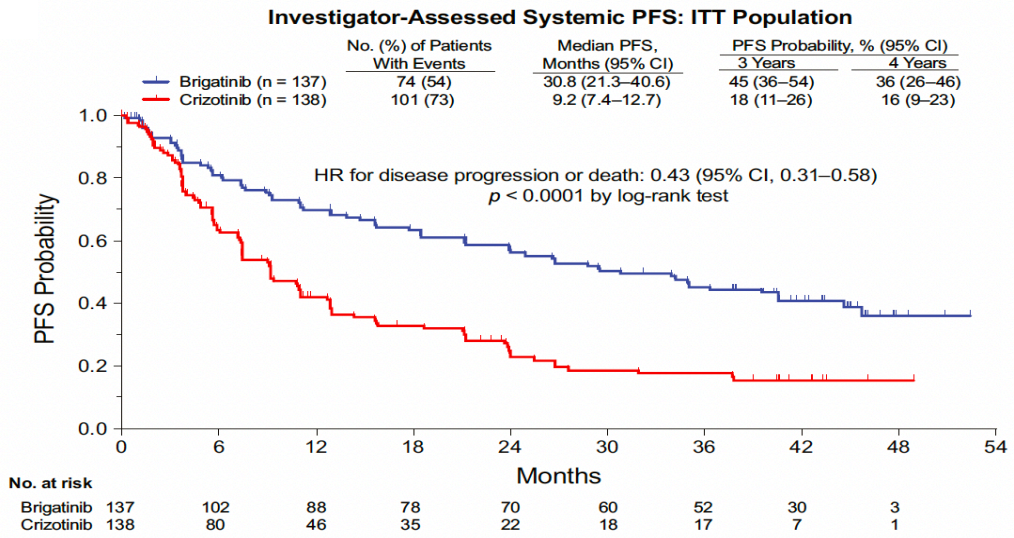


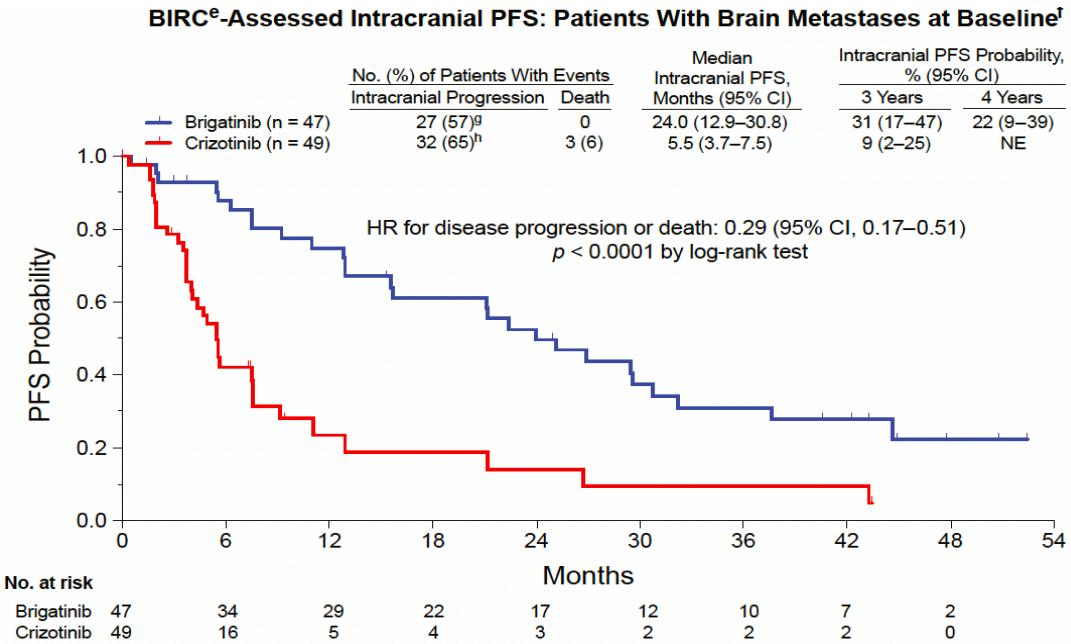
B

Name		Level	Log-rank *P* value	Hazard ratio	95% CI	Interaction test *P* value (likelihood ratio)
All		n/a	0.0609	0.70	(0.48–1.02)	
Age group (years)		< 65	0.1481	0.73	(0.48–1.12)	0.6768
		≥ 65	0.2189	0.63	(0.30–1.33)	
Sex		Female	0.3020	0.76	(0.45–1.28)	0.6923
		Male	0.1155	0.66	(0.39–1.11)	
Race		Asian	0.3298	0.74	(0.40–1.36)	0.8575
		Non-Asian	0.1161	0.69	(0.43–1.10)	
Smoking status	*n* = 17	Active smoker	0.4126	1.97	(0.38–10.20)	0.5471
		Non-smoker	0.1181	0.68	(0.42–1.11)	
		Past smoker	0.1339	0.62	(0.33–1.17)	
ECOG PS		0	0.1266	0.52	(0.22–1.22)	0.4636
		1	0.0960	0.68	(0.44–1.07)	
	n = 20	2	0.6440	1.30	(0.43–3.90)	
CNS mets at baseline (IRC)		Yes	0.0477	0.58	(0.34–1.00)	0.4677
		No	0.2851	0.76	(0.45–1.26)	
Prior brain radiation		Yes	0.0889	0.39	(0.13–1.19)	0.2064
		No	0.1956	0.77	(0.52–1.14)	

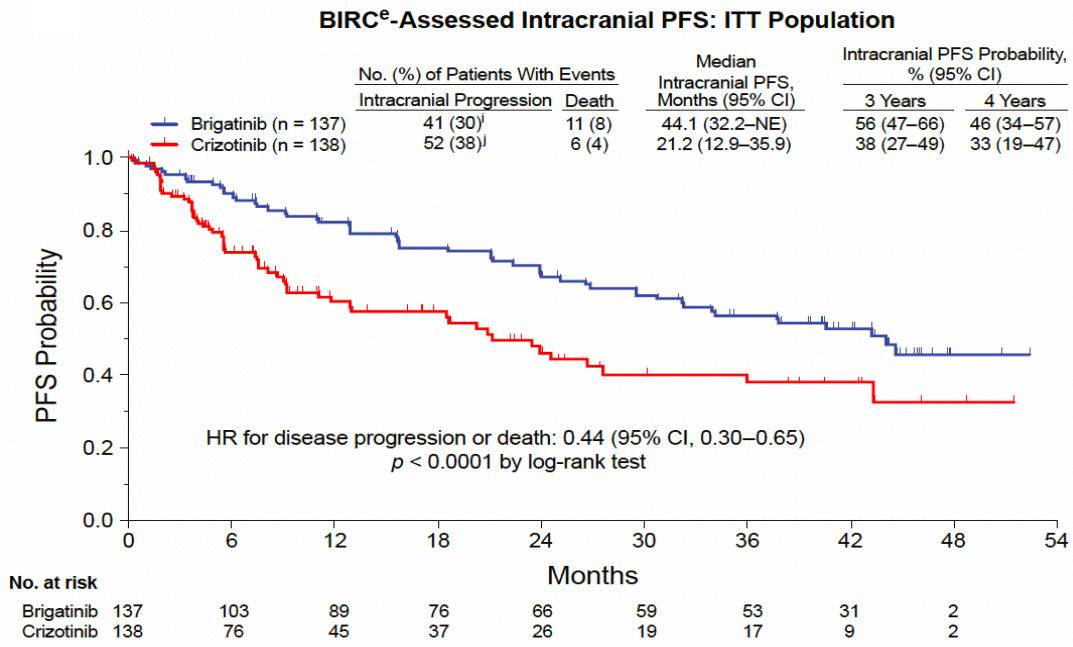
Brigatinib Versus Crizotinib in ALK Inhibitor–Naive Advanced ALK-Positive NSCLC: Final Results of Phase 3 ALTA-1L Trial





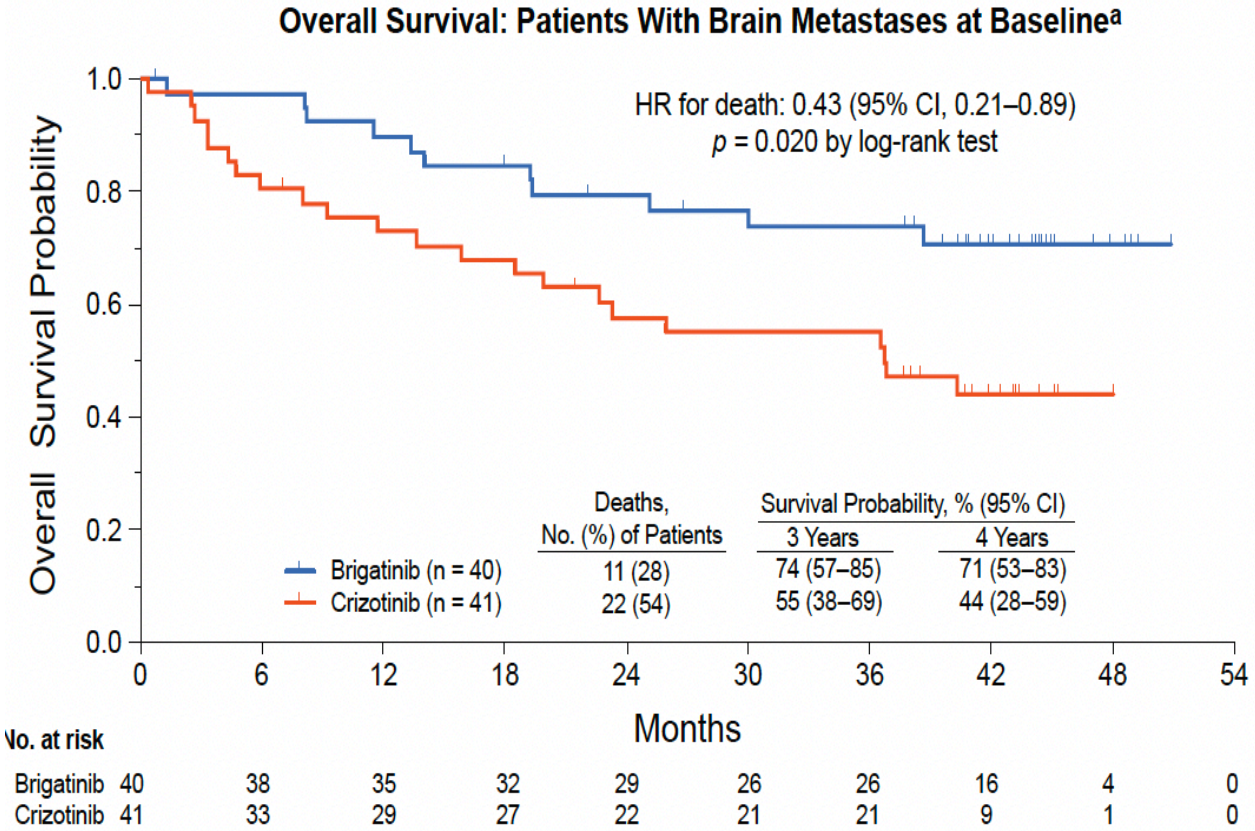


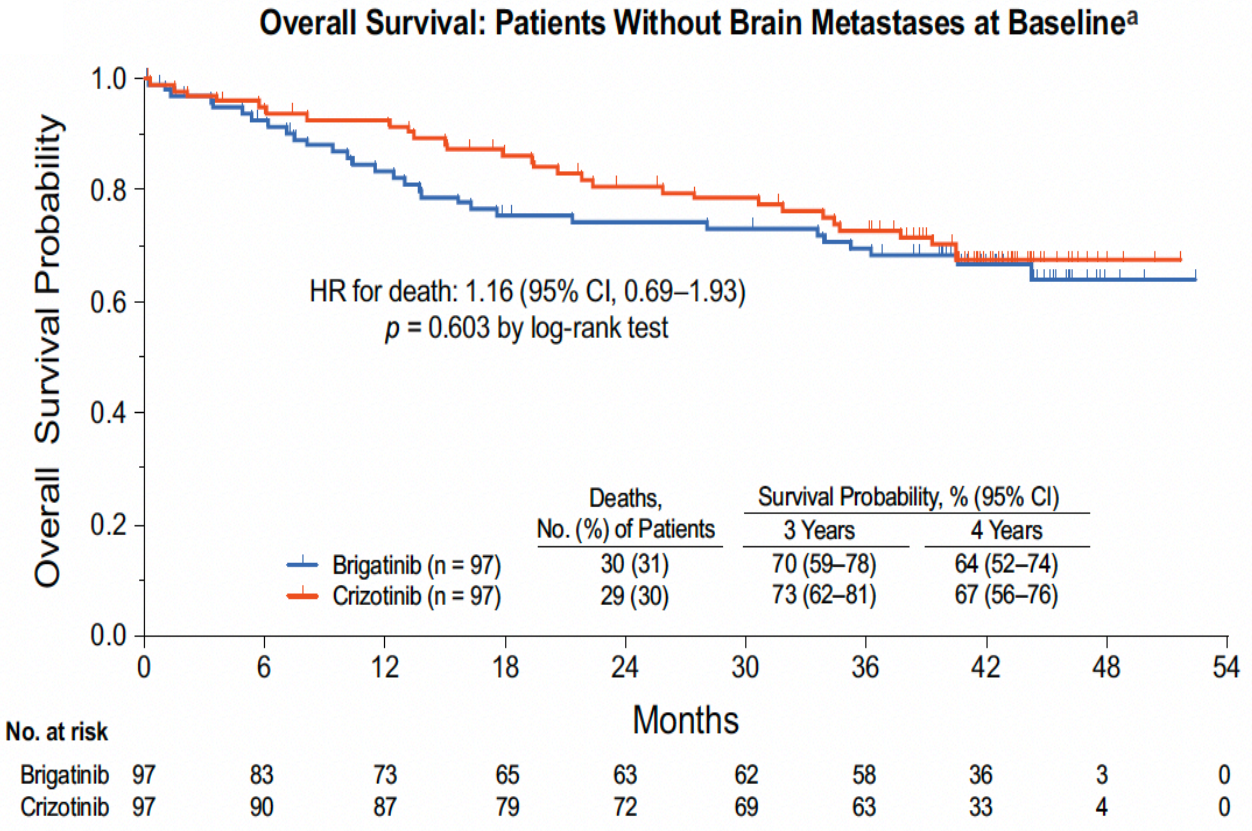
F



Camidge DR, et al. *J Thorac Oncol.* 2021;16:2091-2108.

Brigatinib Versus Crizotinib in ALK Inhibitor–Naive Advanced ALK-Positive NSCLC: Final Results of Phase 3 ALTA-1L Trial

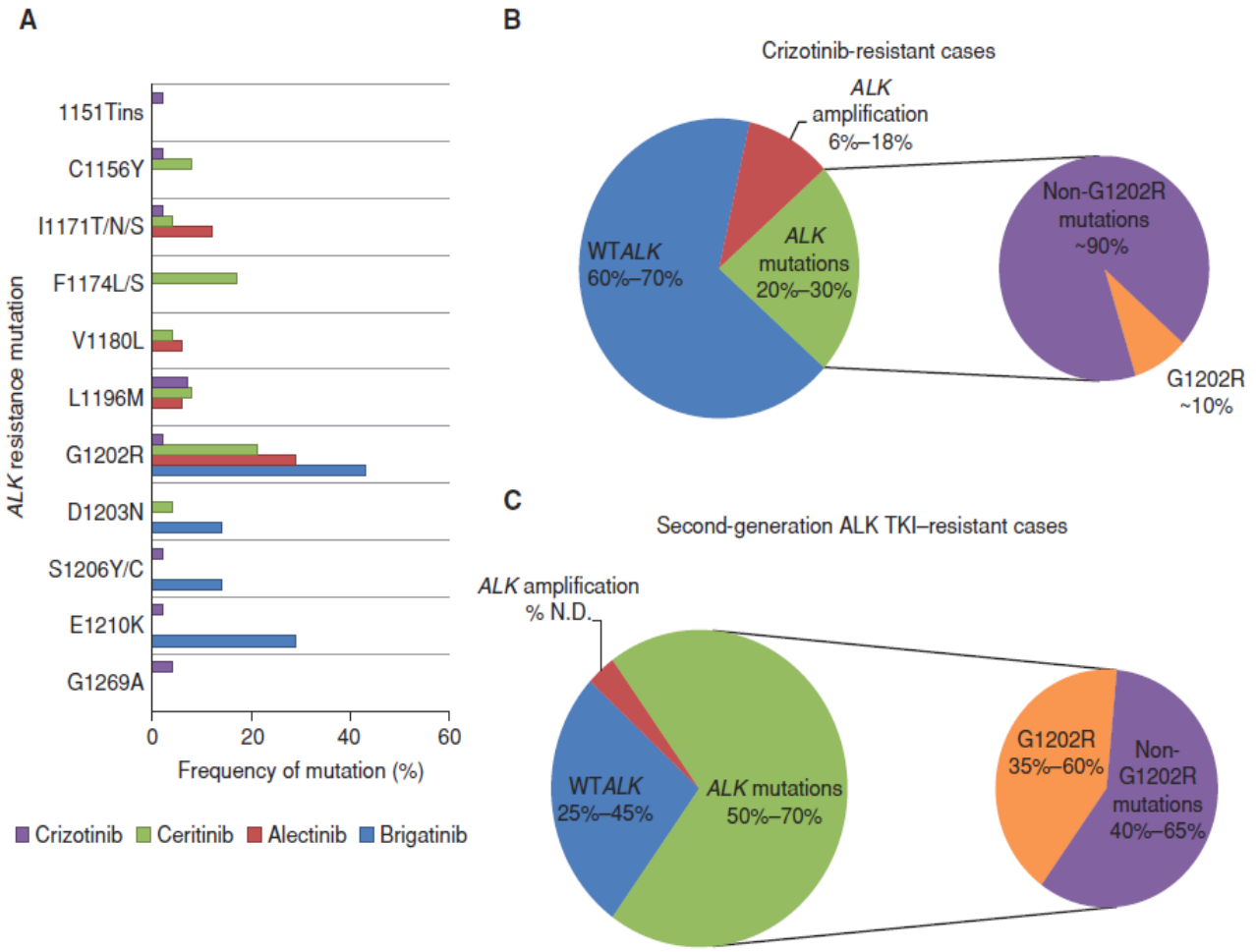




Camidge DR, et al. *J Thorac Oncol.* 2021;16:2091-2108.

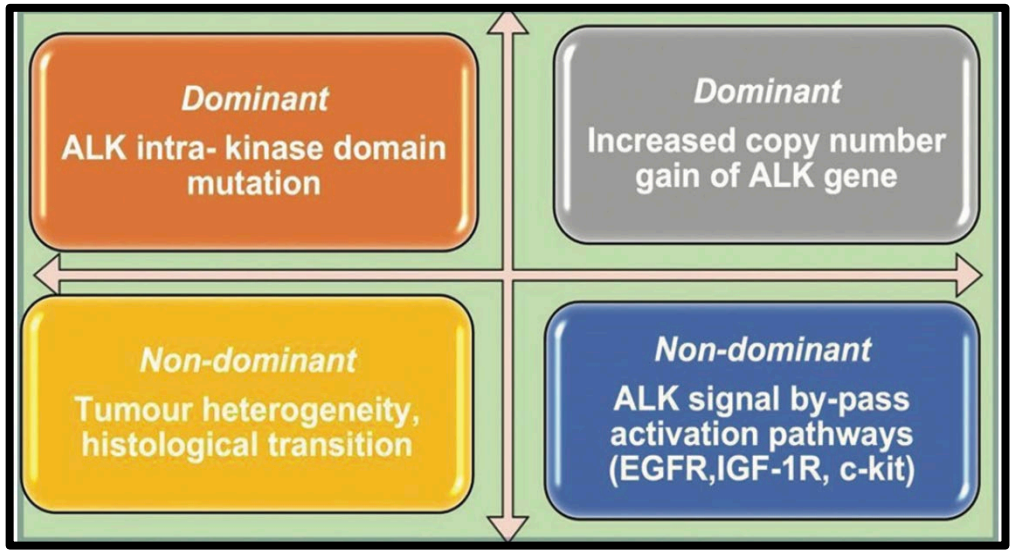
Acquired Resistance Mechanisms[1]

ALK dependent
- *ALK* secondary resistance mutations
- *ALK* amplification



ALK independent
- Bypass tracks
- Lineage changes

ALK TKI	Bypass Pathway	Reference
Crizotinib	*EGFR* activation	Katayama et al 2012
	cKIT amplification	Katayama et al 2012
	IGF-1R signaling	Lovely et al 2014
	SRC signaling	Crystal et al 2014
Crizotinib/ceritinib[2]	*MAPK* pathway	Doebele et al 2012
	RAS pathway	Dardaei et al 2018
Alectinib[3]	*MET* amplification	Gouji et al 2014

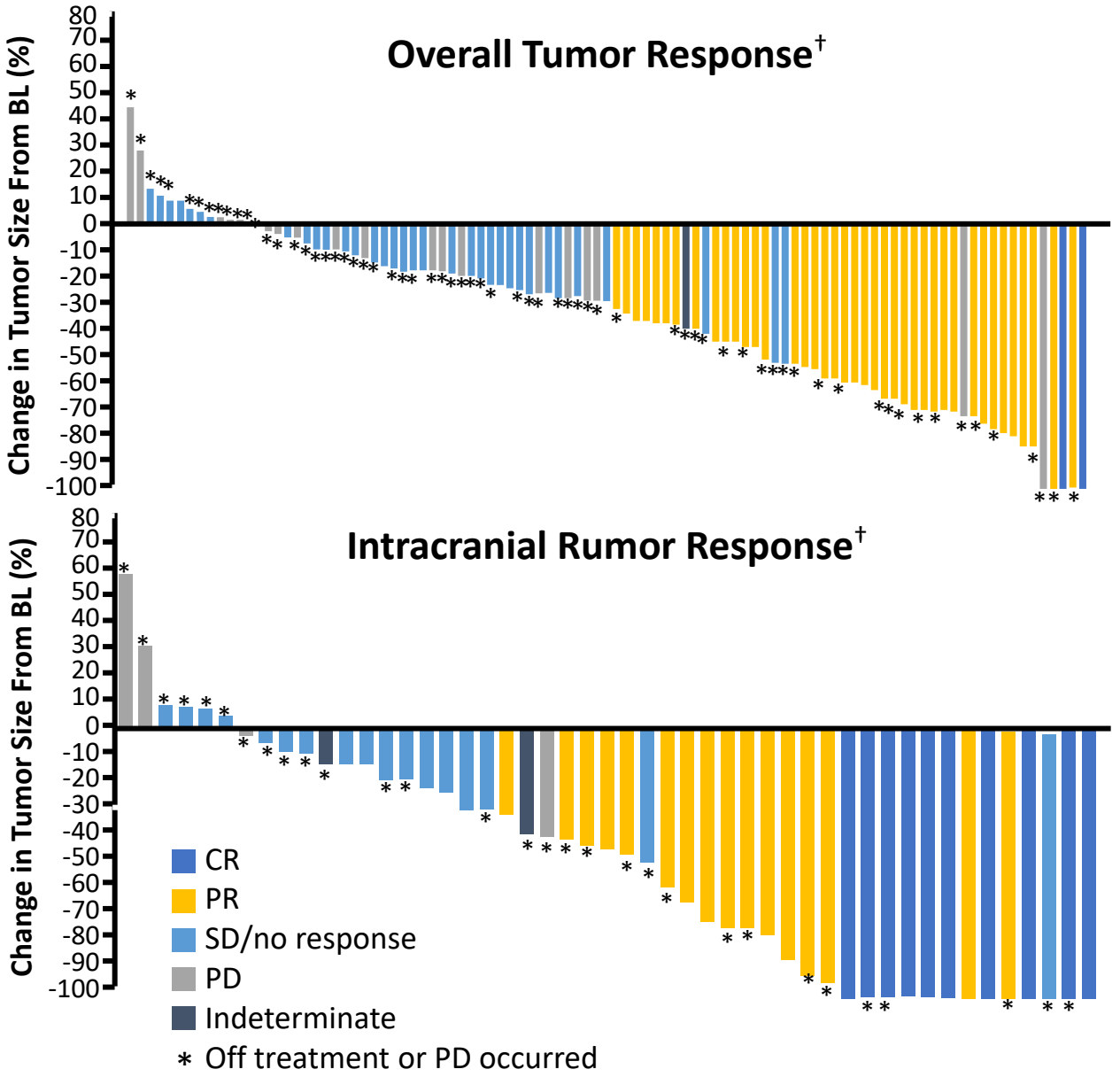


1. Gainor JF, et al. *Cancer Discov*. 2016;6:1118-1133; 2. Dardaei L, et al. *Nat Med.* 2018;24:512-517;
3. Gouji T, et al. *J Thorac Oncol.* 2014;9:e27-e28.

Phase II Lorlatinib: Efficacy in Patients With ≥2 Prior ALK TKIs (± CT)

- Pooled data from EXP4 (2 ALK TKIs ± CT), EXP5 (3 ALK TKIs ± CT): 111 patients
  - 83 patients (75%) had brain metastases at baseline

Outcome	N = 111
ORR, n (%) ▪ Intracranial ORR, n/N (%)	43 (39) 26/49 (53)
Median DOR, mo (95% CI)	NR (5.5–NR)
Median PFS, mo (95% CI)	6.9 (5.4–9.5)



†Patients with ≥1 on-study target lesion assessment as per ICR were included in overall and intracranial tumor response analysis.

Solomon BJ, et al. *Lancet Oncol*. 2018;19:1654-1667.

Intracranial and extracranial efficacy of lorlatinib in patients with *ALK*-positive non-small-cell lung cancer previously treated with second-generation ALK TKIs

E. Felip[1*], A. T. Shaw[2], A. Bearz[3], D. R. Camidge[4], B. J. Solomon[5], J. R. Bauman[6], T. M. Bauer[7], S. Peters[8], F. Toffalorio[9], A. Abbattista[9], H. Thurm[10], G. Peltz[11], R. Wiltshire[12] & B. Besse[13,14]

We report updated efficacy data as of cutoff date May 14, 2019.

Table 3. Intracranial and extracranial efficacy

	≥1 prior second-generation ALK TKI (EXP3B-5)	1 prior second-generation ALK TKI (EXP3B)	≥2 prior ALK TKIs (EXP4-5)
Intracranial with ≥1 measurable CNS lesion			
N	57	9	48
IC-ORR, *n* (%)	32 (56.1)	6 (66.7)	26 (54.2)
95% CI	42.4-69.3	29.9-92.5	39.2-68.6
Best overall response, *n* (%)			
Complete response	12 (21.1)	2 (22.2)	10 (20.8)
Partial response	20 (35.1)	4 (44.4)	16 (33.3)
Stable disease/no response	16 (28.1)	0	16 (33.3)
Progressive disease	6 (10.5)	2 (22.2)	4 (8.3)
Indeterminate	3 (5.3)	1 (11.1)	2 (4.2)
Duration of IC objective response,[a] months			
Median	12.4	20.7	12.4
95% CI	6.0-37.1	4.1-37.1	6.0-16.7
Extracranial			
N	139	28	111
EC-ORR, *n* (%)	51 (36.7)	9 (32.1)	42 (37.8)
95% CI	28.7-45.3	15.9-52.4	28.8-47.5
Best overall response, *n* (%)			
Complete response	5 (3.6)	1 (3.6)	4 (3.6)
Partial response	46 (33.1)	8 (28.6)	38 (34.2)
Stable disease/no response	55 (39.6)	13 (46.4)	42 (37.8)
Progressive disease	21 (15.1)	4 (14.3)	17 (15.3)
Indeterminate	12 (8.6)	2 (7.1)	10 (9.0)
Duration of EC objective response,[a] months			
Median	9.7	NE	7.1
95% CI	6.1-33.3	6.8-NE	5.6-32.2

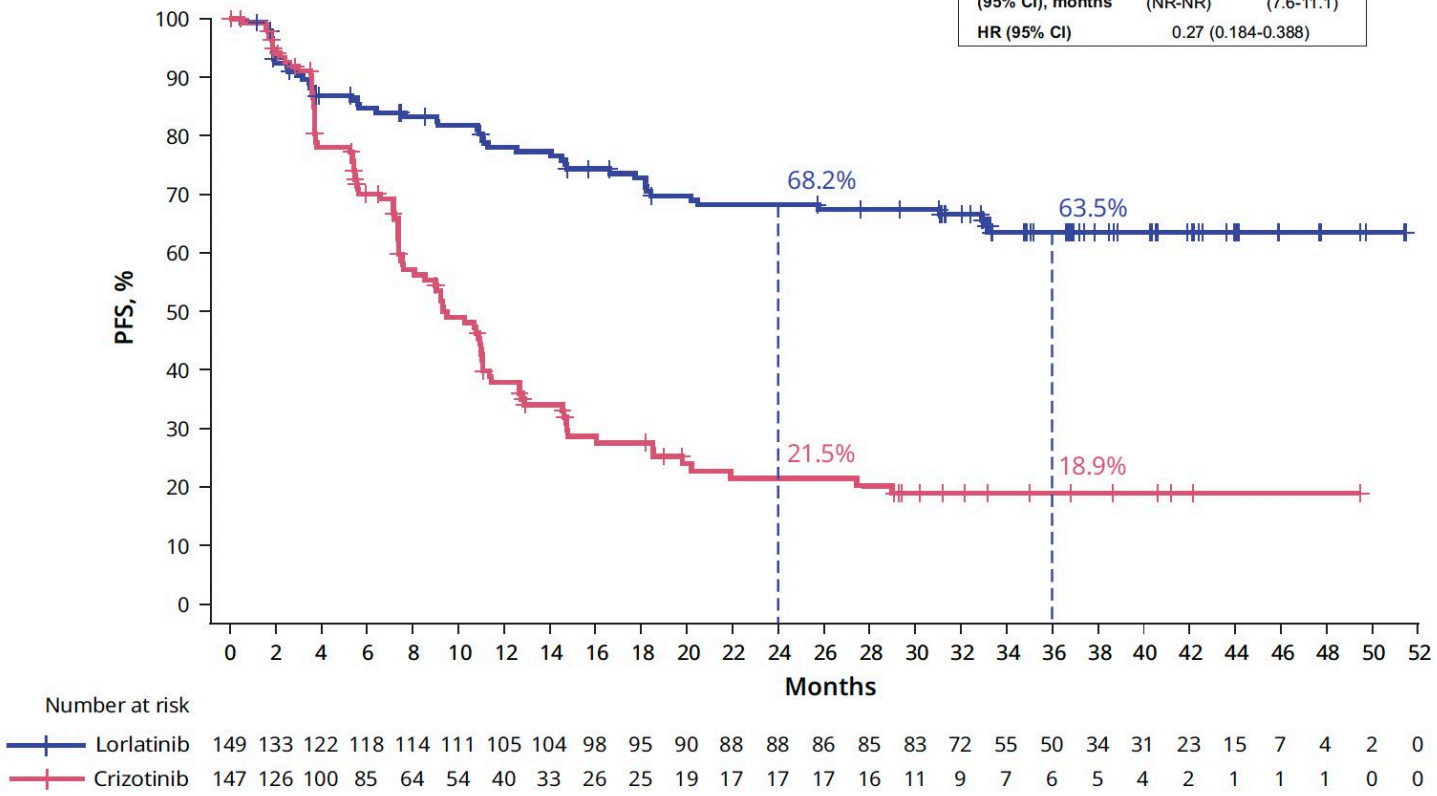
Felip E, et al. *Ann Oncol*. 2021;32:620-630.

Updated Efficacy and Safety From the Phase 3 CROWN Study of First-Line Lorlatinib vs Crizotinib in Advanced Anaplastic Lymphoma Kinase (*ALK*)–Positive Non-Small Cell Lung Cancer (NSCLC)

PFS by BICR

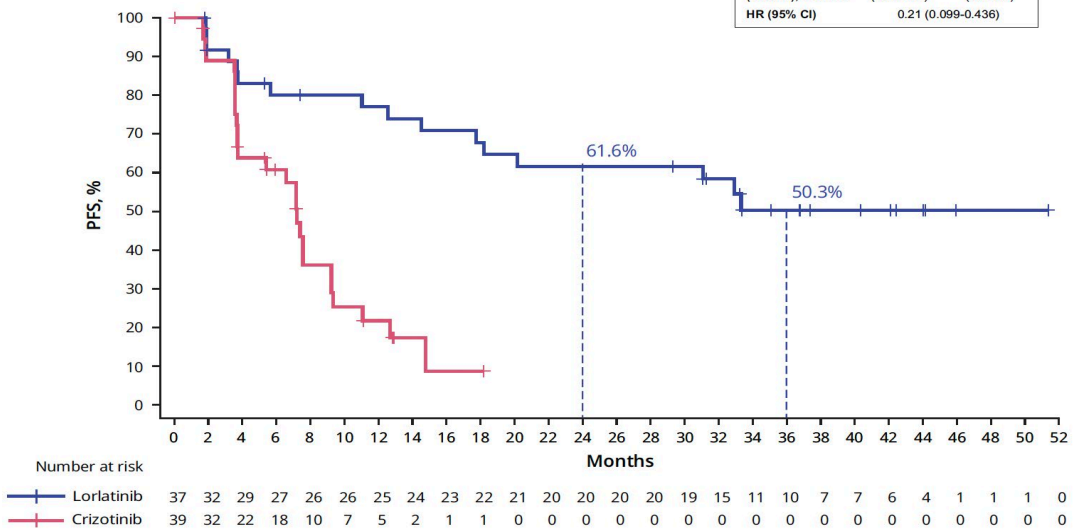
A. ITT population

	Lorlatinib (n=149)	Crizotinib (n=147)
Events	49	92
PFS, median (95% CI), months	NR (NR-NR)	9.3 (7.6-11.1)
HR (95% CI)	0.27 (0.184-0.388)	



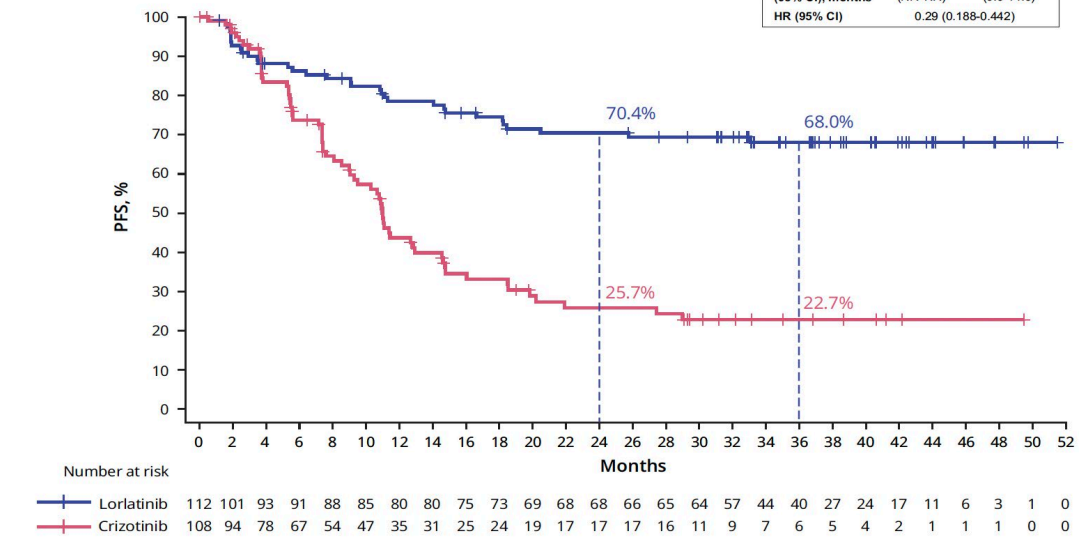
B. Patients with baseline brain metastases

	Lorlatinib (n=37)	Crizotinib (n=39)
Events	16	27
PFS, median (95% CI), months	NR (18.2-NR)	7.2 (3.7-9.2)
HR (95% CI)	0.21 (0.099-0.436)	



C. Patients without baseline brain metastases

	Lorlatinib (n=112)	Crizotinib (n=108)
Events	33	65
PFS, median (95% CI), months	NR (NR-NR)	11.0 (9.0-14.6)
HR (95% CI)	0.29 (0.188-0.442)	



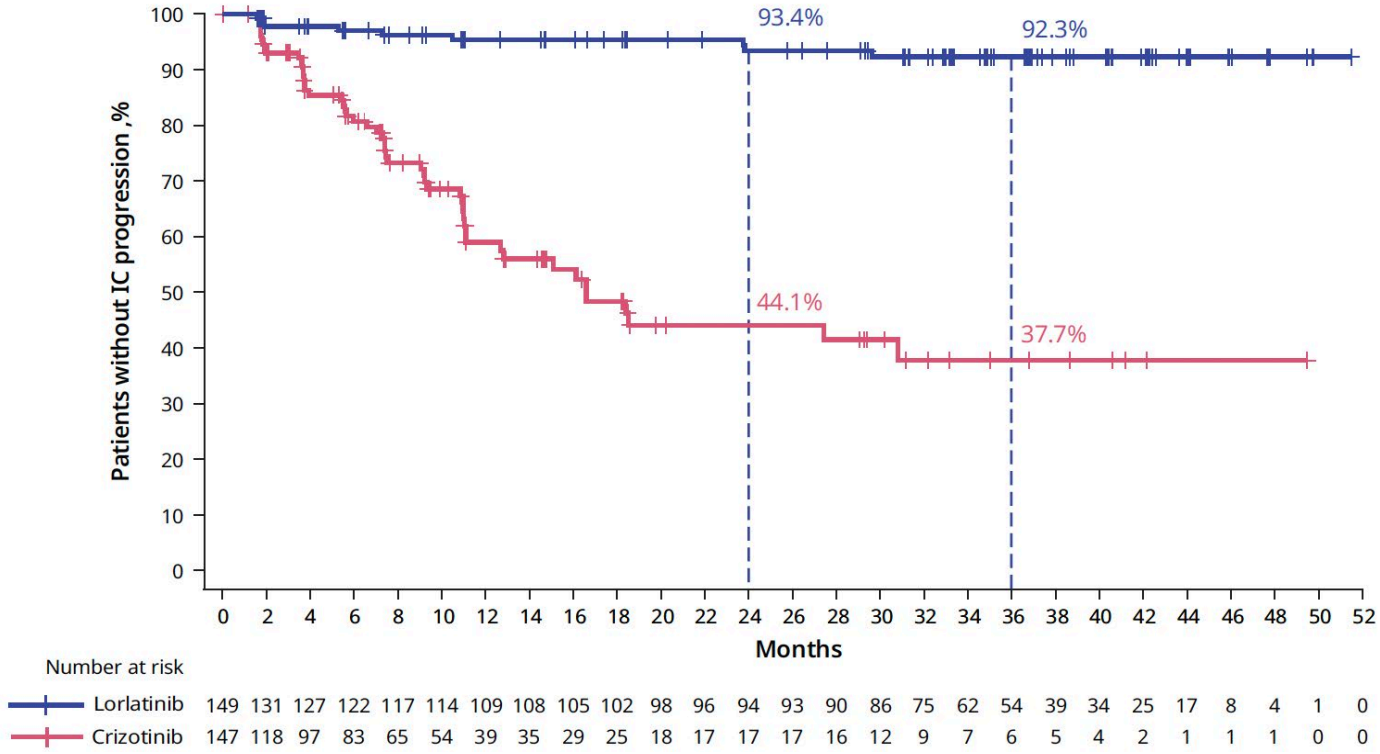
Solomon B, et al. AACR 2022. Abstract CT223.

Updated Efficacy and Safety From the Phase 3 CROWN Study of First-Line Lorlatinib vs Crizotinib in Advanced Anaplastic Lymphoma Kinase (*ALK*)–Positive Non-Small Cell Lung Cancer (NSCLC)

Time to IC progression by BICR

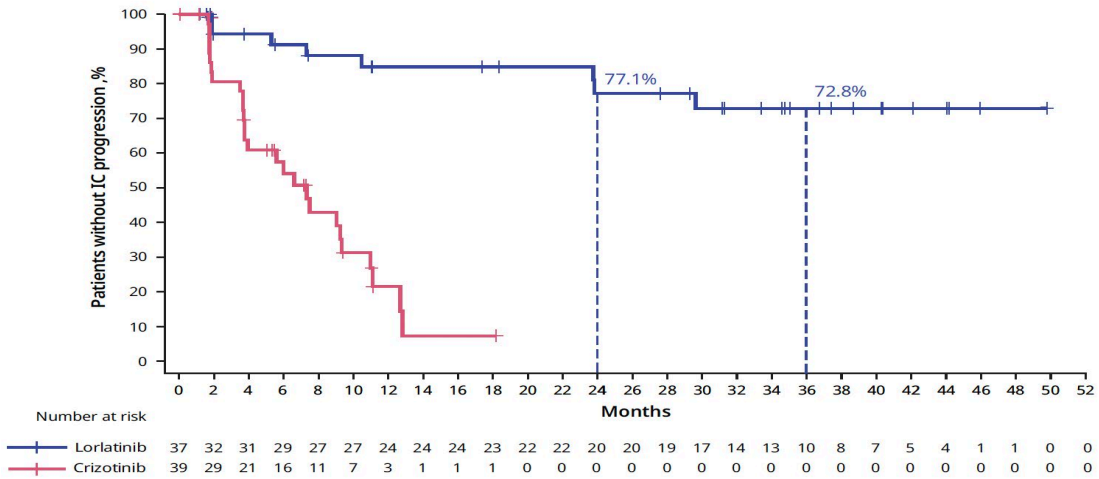
A. ITT population

	Lorlatinib (n=149)	Crizotinib (n=147)
Events	9	51
PFS, median (95% CI), months	NR (NR-NR)	16.6 (11.1-NR)
HR (95% CI)	0.08 (0.040-0.174)	



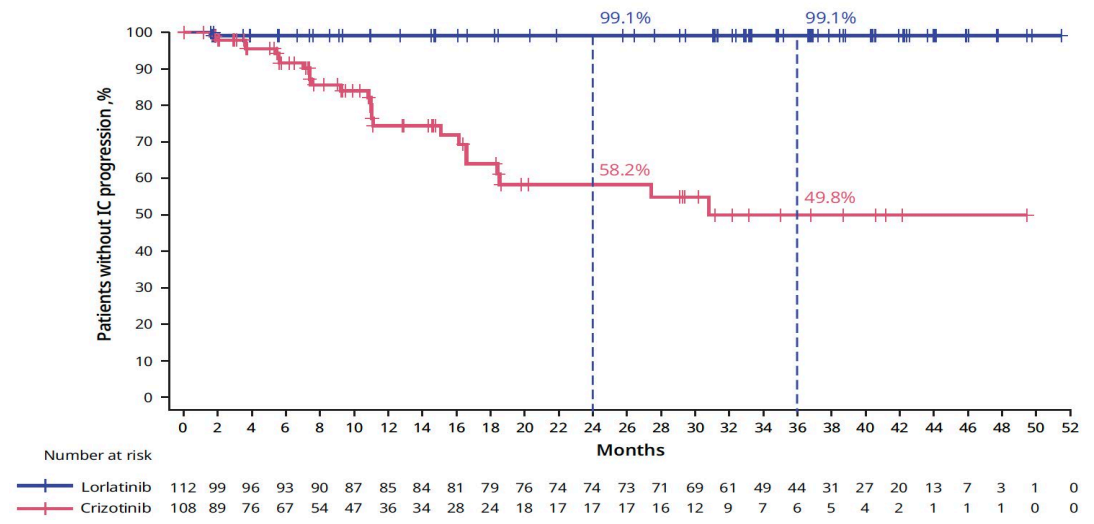
B. Patients with baseline brain metastases

	Lorlatinib (n=37)	Crizotinib (n=39)
Events	8	26
TTP, median (95% CI), months	NR (NR-NR)	7.3 (3.7-9.3)
HR (95% CI)	0.10 (0.037-0.268)	



C. Patients without baseline brain metastases

	Lorlatinib (n=112)	Crizotinib (n=108)
Events	1	25
TTP, median (95% CI), months	NR (NR-NR)	30.8 (18.4-NR)
HR (95% CI)	0.02 (0.002-0.136)	



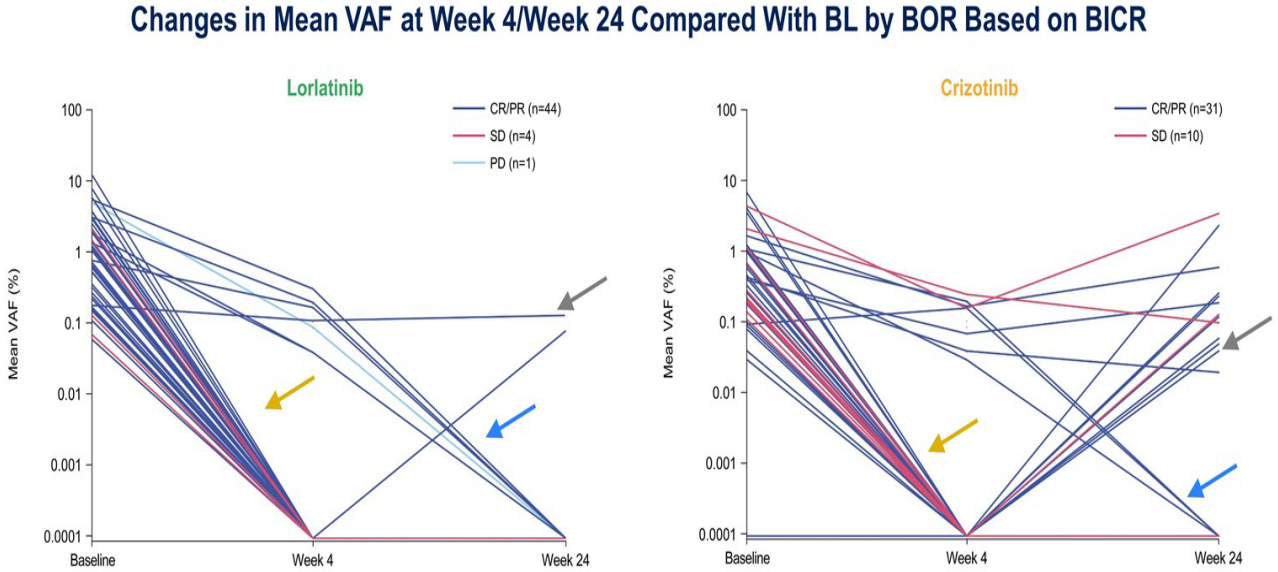
Solomon B, et al. AACR 2022. Abstract CT223.

First-Line Treatments for *ALK*+ NSCLC: Most Commonly Reported AEs of Any Grade Occurring in ≥20% of Patients, %

CROWN Lorlatinib (n = 149)[1]	ALEX Alectinib (n = 152)[2]	ALTA-1L Brigatinib (n = 136)[3]
Hypercholesterolemia (70) Hypertriglyceridemia (64) Edema (55) Increased weight (38) Peripheral neuropathy (34) Cognitive effects (21) Diarrhea (21)	Constipation (37) Anemia (26) Fatigue (22) Blood bilirubin increased (22)	Diarrhea (58) Increased blood CPK (50) Cough (36) Nausea (33) Hypertension (32) Increased AST (26) Back pain (26) Dyspnea (24) Headache (24) Increased lipase (24) Increased ALT (23) Vomiting (22) Fatigue (21) Pruritus (21) Constipation (20) Arthralgia (20)

1. Shaw AT, et al. *N Engl J Med*. 2020;383:2018-2029; 2. Mok T, et al. *Ann Oncol*. 2020;31:1056-1064; 3. Camidge DR, et al. *J Thorac Oncol.* 2021;16:2091-2108.

Early Circulating Tumor (ct) DNA Dynamics and Efficacy of Lorlatinib: Analysis From the CROWN Study



- Most patients had early decrease in *ALK* VAF, but it was less sustained in crizotinib-treated patients
- Presumably clonal resistance mechanism covered by lorlatinib?

Soo RA, et al. ASCO 2021. Abstract 9011.

Resistance mechanisms to lorlatinib or crizotinib in treatment-naive patients with *ALK*+ advanced non-small cell lung cancer

Table 3: Summary of potential resistance mechanisms against lorlatinib or crizotinib

Resistance mutation at EOT	Lorlatinib n=26	Crizotinib n=80
New single *ALK* mutation, n (%)	0	6 (8)
ALK compound mutation, n (%)	0	2 (2)
Bypass mechanism, n (%)[a]	9 (35)	10 (12)
MAPK pathway aberration	3 (12)	1 (1)
PI3K/mTOR/PTEN pathway aberration	2 (8)	0
RTK pathway aberration	4 (15)	5 (6)
Cell cycle pathway aberration	2 (8)	5 (6)
Other mutation, n (%)	9 (35)	15 (19)

[a]Each sample could harbor >1 bypass mechanism.

Felip E, et al. ESMO 2022. Abstract 1008P.

Thanks!!!

efelip@vhio.net

Global Lung Cancer Academy

EGFR Inhibitors in NSCLC

Johan Vansteenkiste, MD, PhD

Disclosures [update 09/2022, alphabetical]

- **Research funding at University Hospitals KU Leuven**
  - **MSD**

- **Advisory functions**
  - **AstraZeneca, BMS, Daiichi-Sankyo, Janssen, Merck, MSD, Novartis, PDCline, Pfizer, Roche, Sanofi**

- **Lectures**
  - **AstraZeneca, BMS, Janssen, Novartis, Roche, Sanofi**

- **Others**
  - **None**

ANNALS OF ONCOLOGY

ESMO

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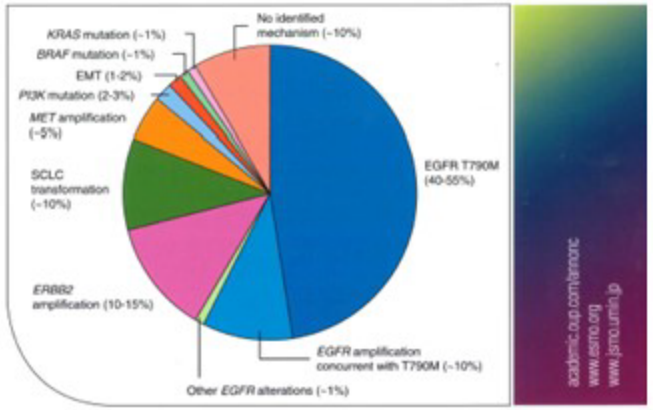
Ann Oncol 29 Suppl 1, 2018

EGFR Mutant Non-small-cell Lung Cancer

Guest Editor: J. F. Vansteenkiste



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JSMO

Editorial

Ann Oncol 29 Suppl 1: i1-i2, 2018

Tyrosine kinase inhibition of EGFR: a successful history of targeted therapy for NSCLC since 20 years

The first-in-human dosing of the Epidermal Growth Factor Receptor tyrosine kinase inhibitor (EGFR-TKI) ZD1839 (later gefitinib) goes back to April 1998, by now almost 20 years ago. In several randomized controlled trials have established the role of first-generation EGFR-TKIs as preferred first-line therapy for *EGFR* mutant tumours. Gefitinib and erlotinib gained global approval in this setting, while icotinib is approved in China. The second-generation drugs are different because of their irreversible binding to EGFR, and because of their broader inhibition of the different members of the human epidermal receptor (HER) fam-

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESMO expert consensus statements on the management of *EGFR* mutant non-small-cell lung cancer

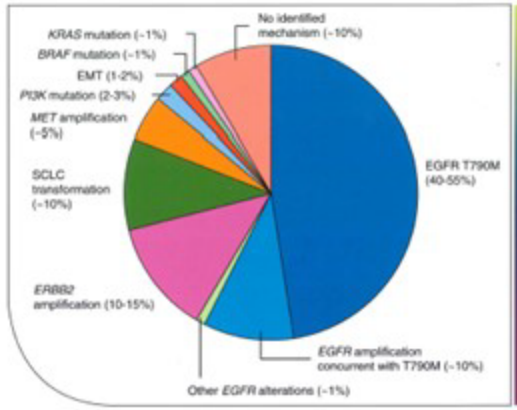
A. Passaro[1*], N. Leighl[2†], F. Blackhall[3,4†], S. Popat[5,6,7†], K. Kerr[8†], M. J. Ahn[9], M. E. Arcila[10], O. Arrieta[11], D. Planchard[12], F. de Marinis[1], A. M. Dingemans[13], R. Dziadziuszko[14], C. Faivre-Finn[15], J. Feldman[16], E. Felip[17], G. Curigliano[18], R. Herbst[19], P. A. Jänne[20], T. John[21], T. Mitsudomi[22], T. Mok[23], N. Normanno[24], L. Paz-Ares[25], S. Ramalingam[26], L. Sequist[27], J. Vansteenkiste[28], I. I. Wistuba[29], J. Wolf[30], Y. L. Wu[31], S. R. Yang[7], J. C. H. Yang[32], Y. Yatabe[33], G. Pentheroudakis[34] & S. Peters[35]

Ann Oncol 33:466-487, 2022

ANNALS OF ONCOLOGY
ESMO
Ann Oncol 29 Suppl 1, 20

EGFR Mutant Non-small-cell Lung Cancer

Guest Editor: J. F. Vansteenkiste



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- **Case study**
- **Optimal 1st line therapy**
  - **Osimertinib**
  - **Sequencing?**
  - **Other 3rd generation TKIs**
- **Failure post-osimertinib**
  - **Extra pathway**
  - **Intra pathway**
  - **Histologic transformation**
  - **No specific findings**
- **Uncommon *EGFR* mutations**
- **Conclusion**

Editorial

Ann Oncol 29 Suppl 1: i1-i2, 2018

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driving innovation in oncology

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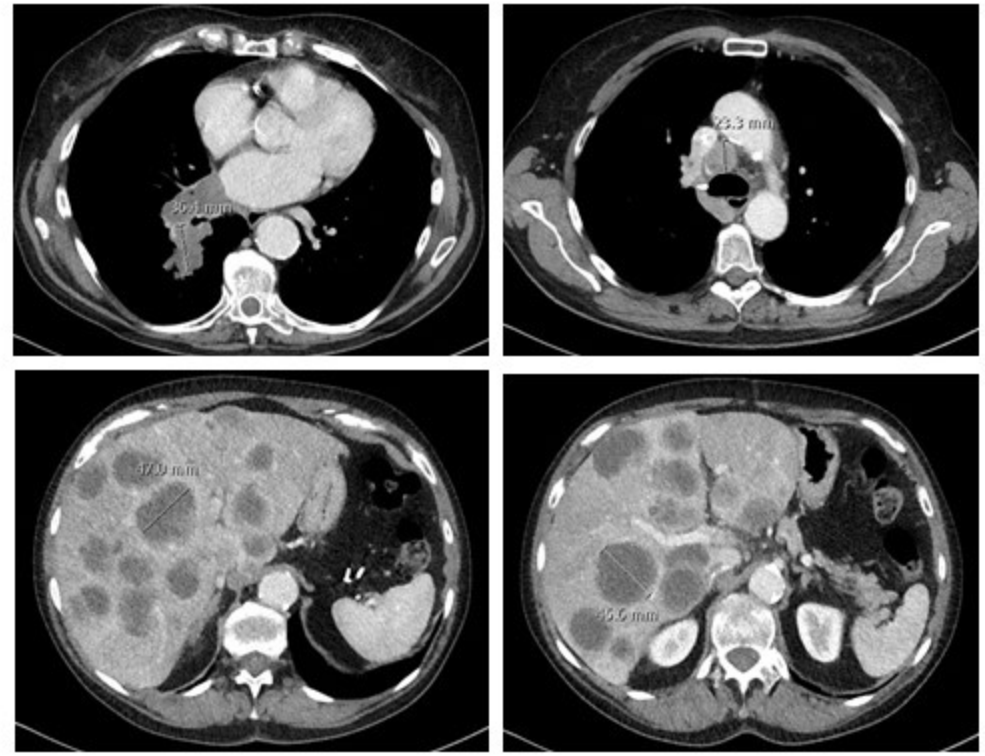
Ann Oncol 33:466-487, 2022

Case study: 69 year old female

- Current smoker (35 packyears) – housewife
- Medical history
  - 2000: epilepsy/headache -> diagnosis of right frontal brain lesion: low-grade glioma. Conservative approach, anti-epileptic agents
  - 2004: coronary disease – stent placement
- 01/2019: rapid deterioration of general condition
  - Fatigue, weight loss 77 -> 68 kg, WHO PS 2, cough since 4 months
  - Lab: CRP 82 mg/L, abnormal AST/ALT, CEA 85, normal renal function
  - Brain MRI: glioma, otherwise normal
- Bronchoscopy-EBUS
  - Endobronchial normal – EBUS: multiple TBNA samples
  - Pathology:
    - NSCLC favor adeno
    - IHC: PD-L1 60%, ALK/ROS1/NTRK negative. NGS pending



Stage IVb: T2a N2 M1c

➢ **RECIST v1.1: 148 mm**

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Case study: 69 year old female
> polling question

- **Which of the following options do you prefer?**
  1. **Wait for NGS**
  2. **Start carboplatin-pemetrexed & pembrolizumab**
  3. **Start carboplatin-paclitaxel-bevacizumab & atezolizumab**
  4. **Start carboplatin-pemetrexed**

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Case study: 69 year old female
> continued

- Carboplatin-pemetrexed cycle 1
- Day 15 of cycle 1:
  - Slight symptomatic improvement
  - NGS: EGFR exon 19 deletion mutation !

- 03/2019: start Osimertinib -> PR with RECIST v1.1 from 148 to 28 mm (liver normal, intrathoracic dimensions)

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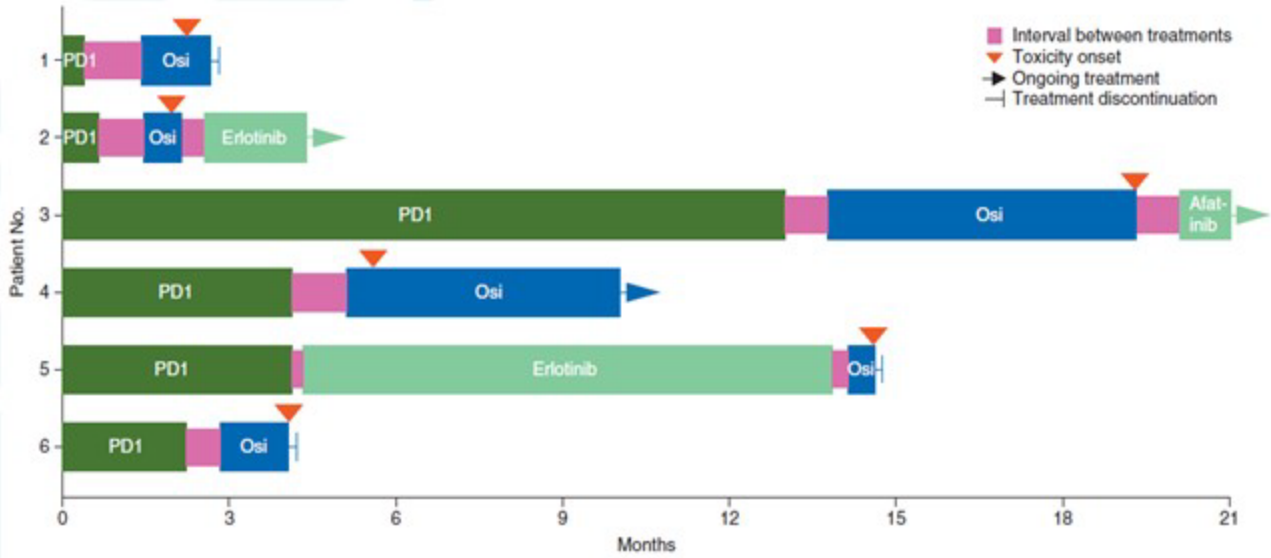
Case study: 69 year old female
> immunotherapy in EGFRmut+ patients

ESMO ORIGINAL ARTICLE

Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib

A. J. Schoenfeld[1], K. C. Arbour[1], H. Rizvi[1], A. N. Iqbal[1], S. M. Gadgeel[2], J. Girshman[3], M. G. Kris[1], G. J. Riely[1], H. A. Yu[1*†] & M. D. Hellmann[1*†]



Schoenfeld et al, Ann Oncol 30:839-844, 2019

- Patients with EGFR-mutant NSCLC who were treated with PD-(L)1 blockade and EGFR-TKIs, irrespective of drug or sequence of administration (total n=126)
- 15% (6/41) of patients with sequential PD-(L)1 blockade followed by osimertinib developed a severe irAE
- Severe irAEs were most common among those who began osimertinib <3 months of prior PD-(L)1 blockade (5/21 or 24%)
- No severe irAEs were identified among patients treated with osimertinib followed by PD-(L)1
- IrAEs occurred at a median onset of 20 days after osimertinib
- All patients with irAEs required steroids and most required hospitalization

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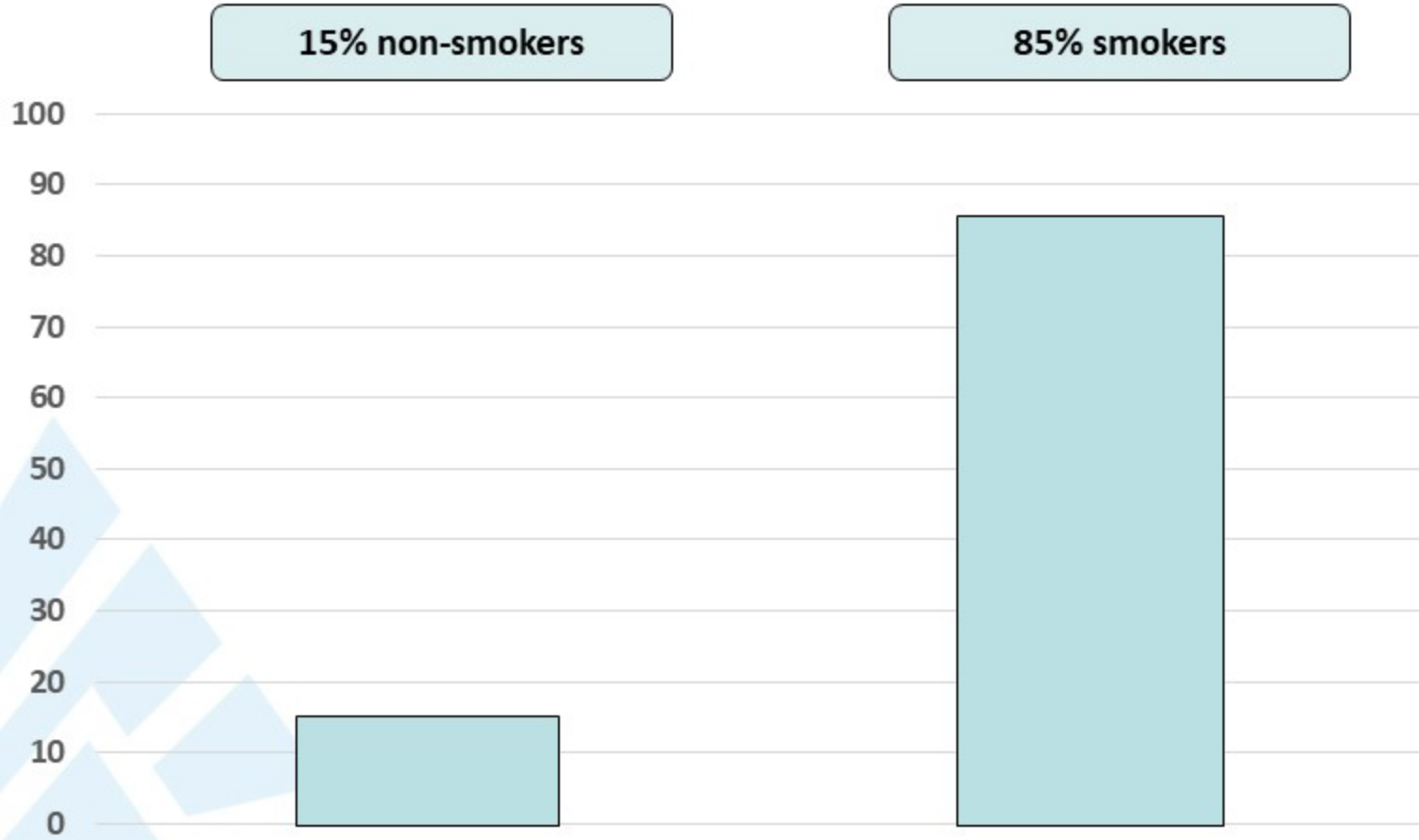
NSCLC

> EGFR – smoking paradox



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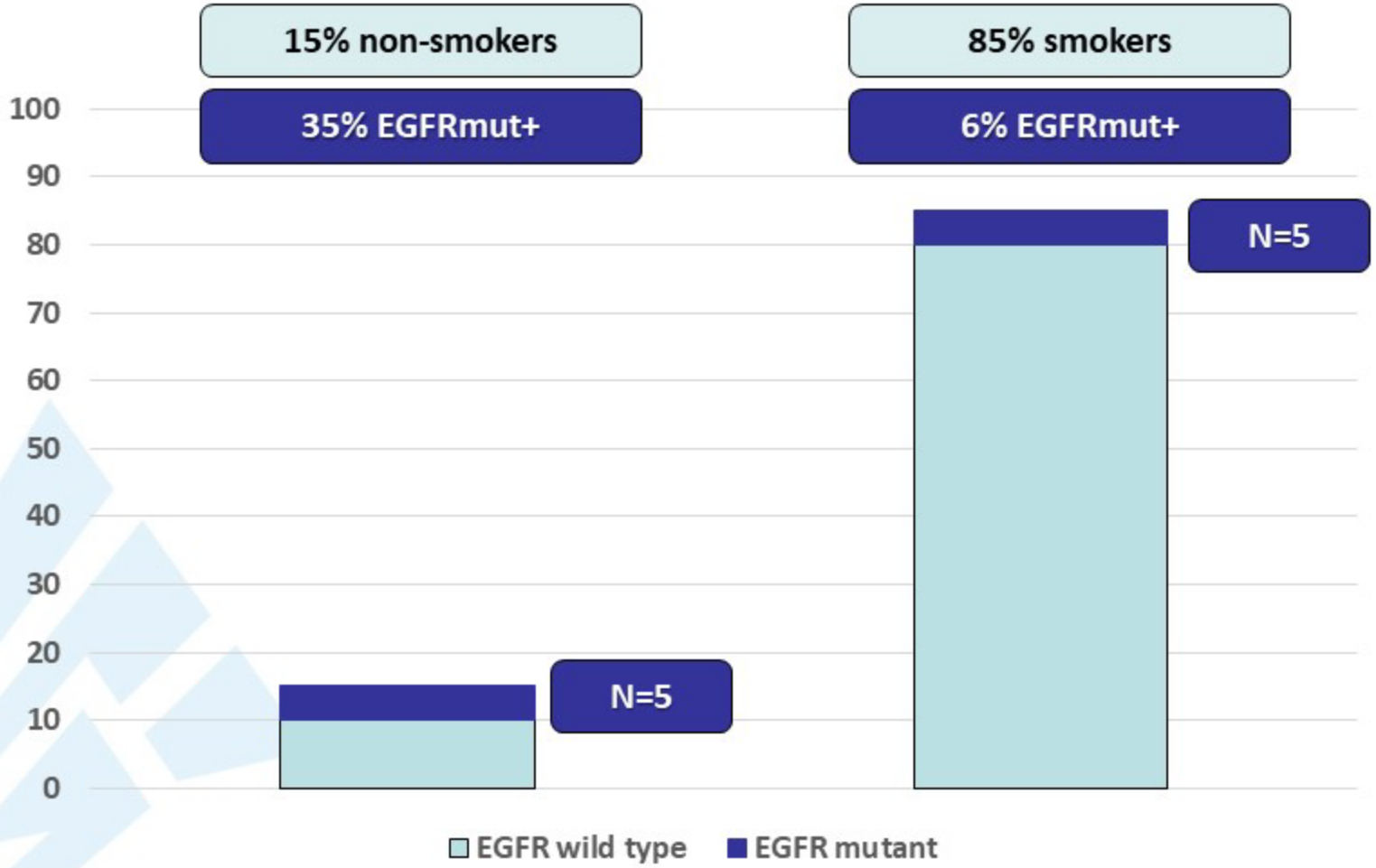

➢ Adenocarcinoma or NSCLC-NOS: always test for EGFR

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NSCLC *EGFR*mut+

- Case study
- Optimal 1st line therapy
  - Osimertinib
  - Sequencing?
  - Other 3rd generation TKIs
- Failure post-osimertinib
  - CNS failure
  - Histologic transformation
  - Known molecular mechanism
  - No specific findings
- Uncommon *EGFR* mutations
- Conclusion

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> FLAURA ph3 trial

FLAURA study
- **Advanced NSCLC, untreated**
- **EGFRmut+** (del19, L858R)
- **PS 0-1**
- **Stable brain mets allowed**

1° endpoint: PFS (investigator)

The NEW ENGLAND JOURNAL of MEDICINE

This article was published on November 18, 2017, at NEJM.org.

Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.-C. Su, J.E. Gray, S.-M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, and S.S. Ramalingam, for the FLAURA Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

This article was published on November 21, 2019, at NEJM.org.

Overall Survival with Osimertinib in Untreated, *EGFR*-Mutated Advanced NSCLC

S.S. Ramalingam, J. Vansteenkiste, D. Planchard, B.C. Cho, J.E. Gray, Y. Ohe, C. Zhou, T. Reungwetwattana, Y. Cheng, B. Chewaskulyong, R. Shah, M. Cobo, K.H. Lee, P. Cheema, M. Tiseo, T. John, M.-C. Lin, F. Imamura, T. Kurata, A. Todd, R. Hodge, M. Saggese, Y. Rukazenkov, and J.-C. Soria, for the FLAURA Investigators*

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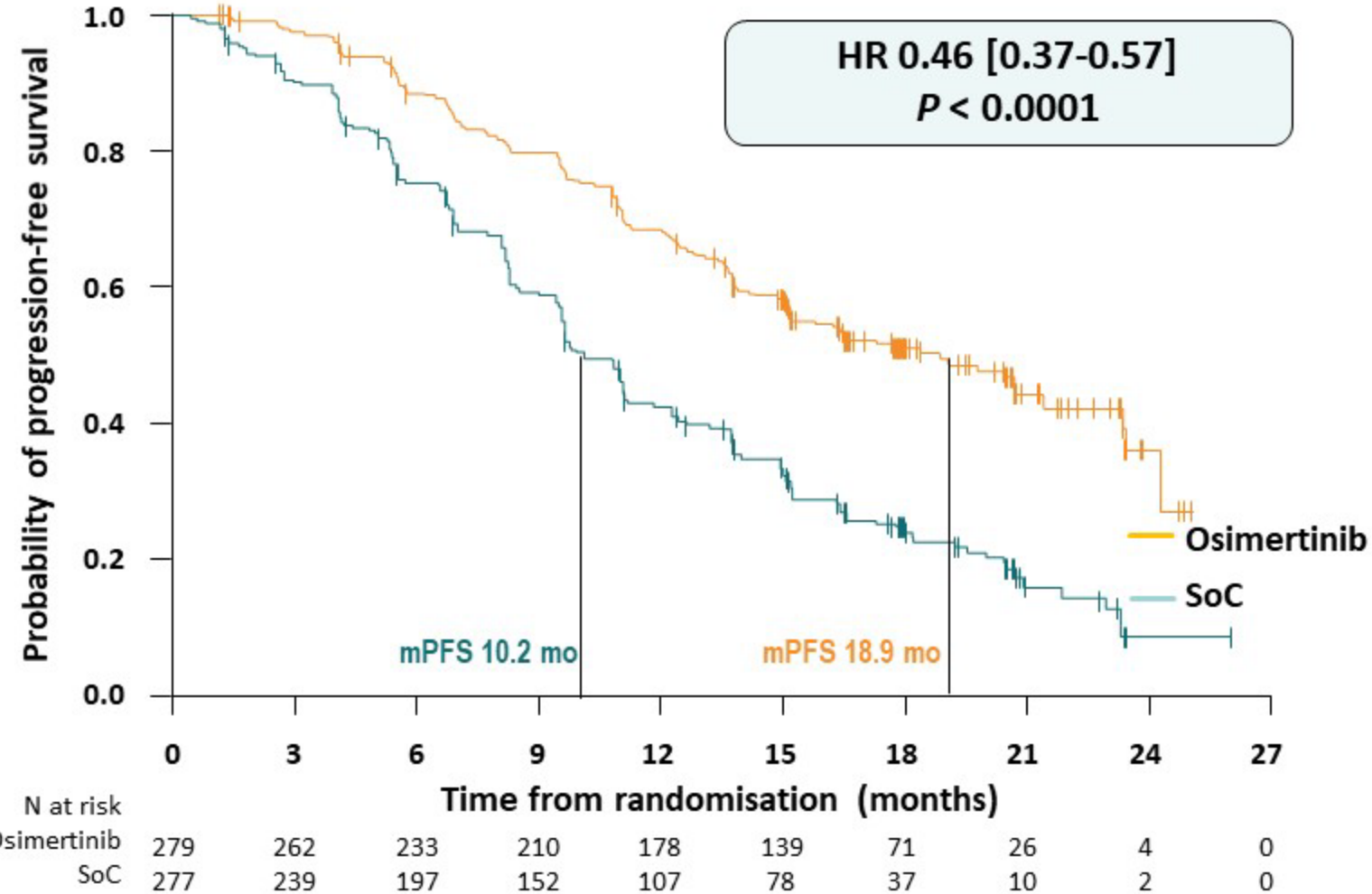
> ph3 osimertinib *vs.* SoC-TKI: PFS (by investigator)



Ramalingam et al, ESMO 2017 *and* Soria et al, N Engl J Med 378:113-125, 2018

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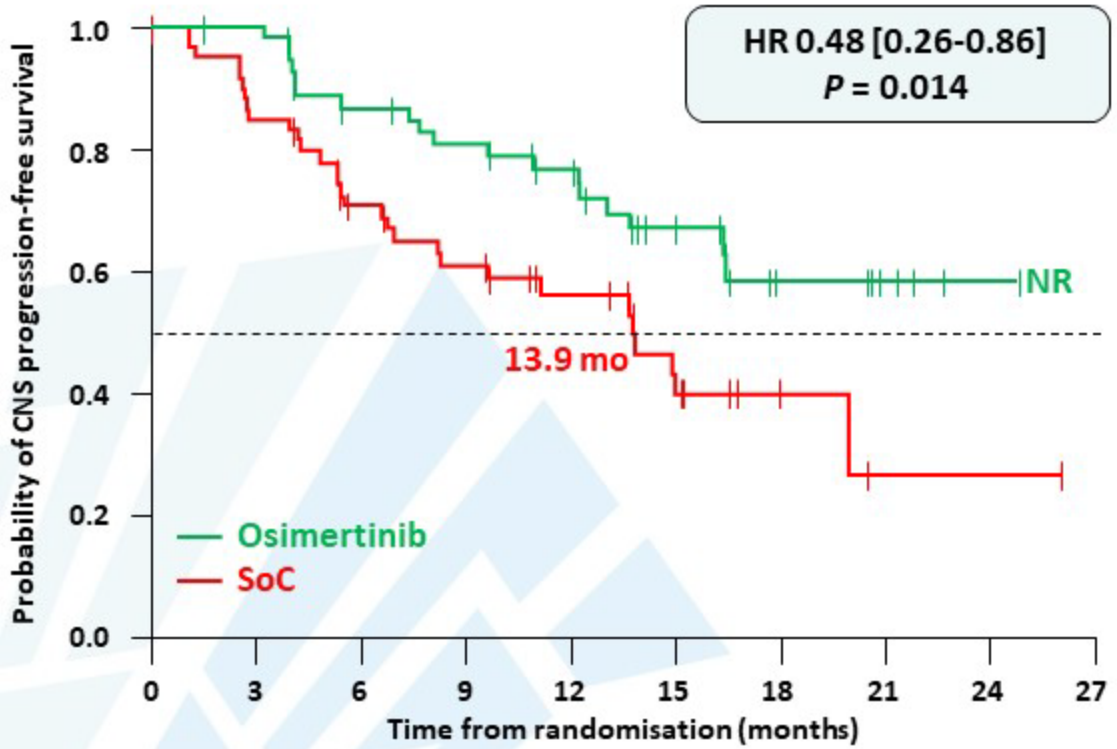
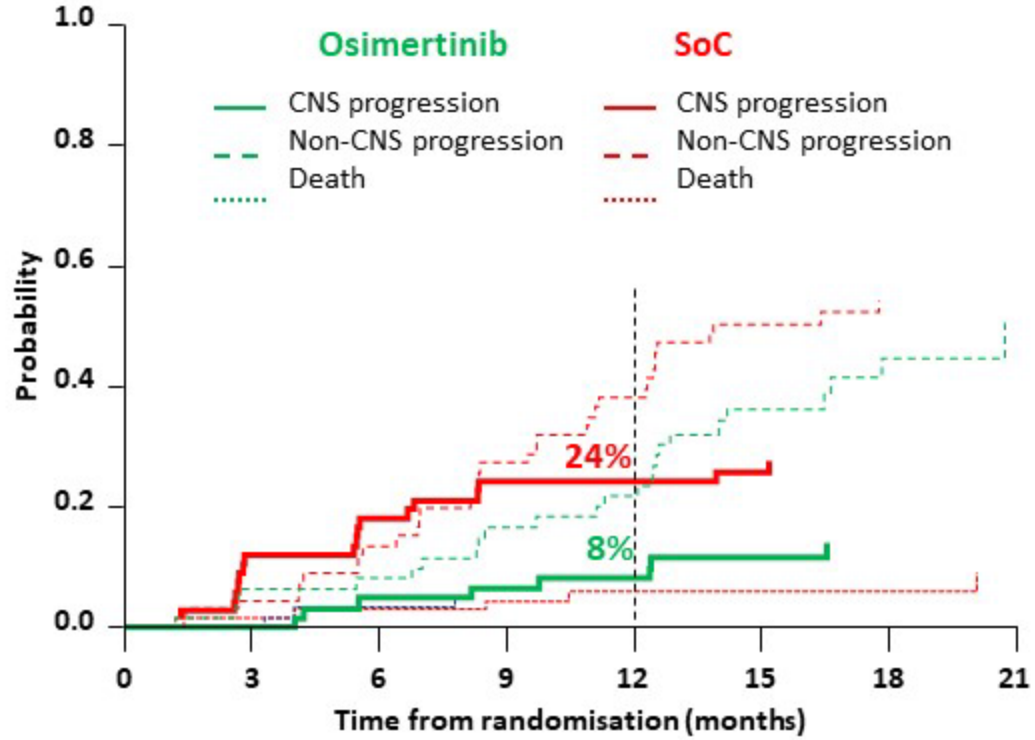
> ph3 osimertinib CNS analysis: CNS-PFS and competing risks





Vansteenkiste et al, ESMO-ASIA 2017 *and* Reungwetwattana et al, J Clin Oncol 36:3290-3297, 2018

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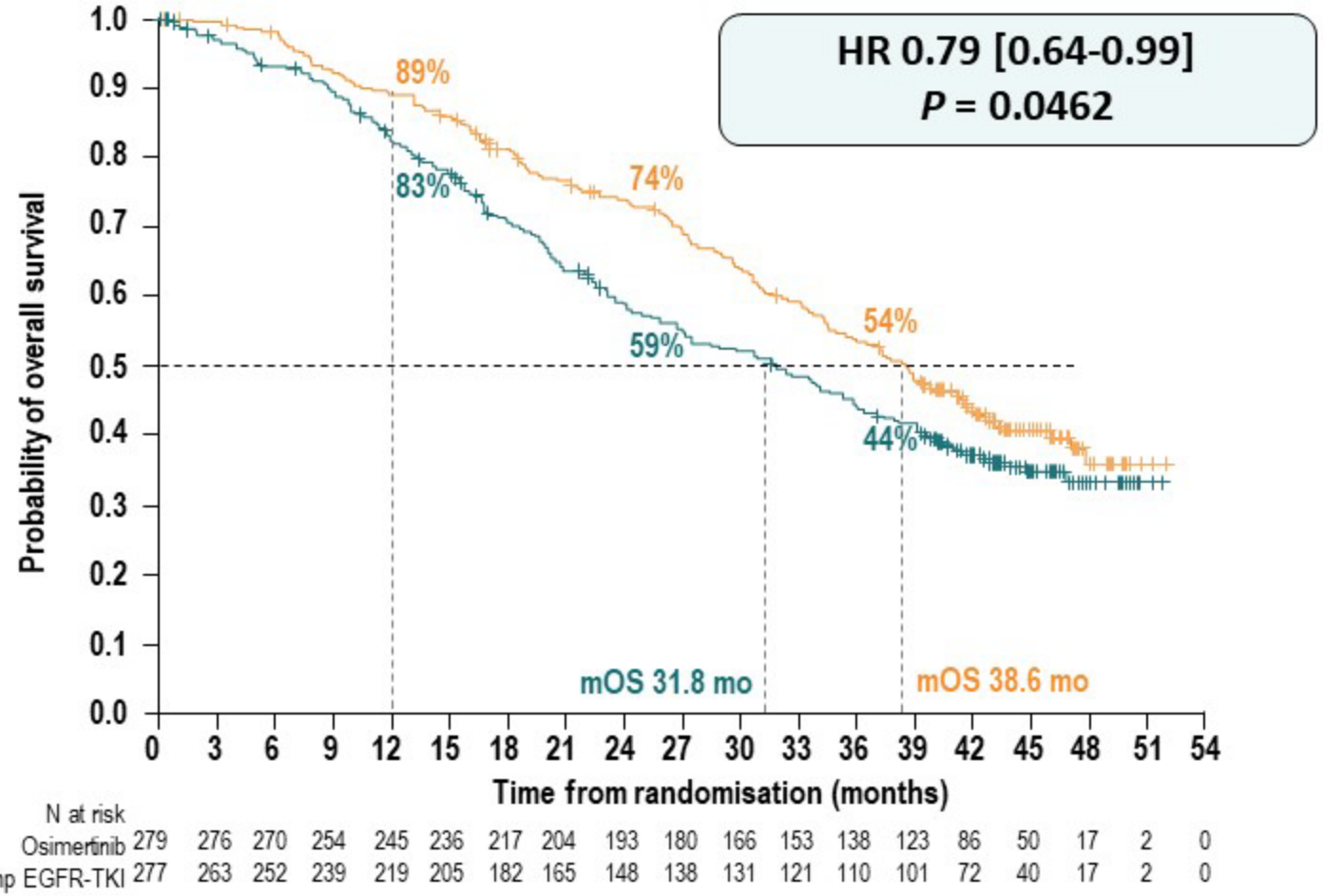
> ph3 osimertinib *vs.* SoC-TKI: OS final analysis*



* 321 deaths in 556 patients at data cut-off: 58% maturity

Ramalingam et al, ESMO 2019 *and* N Engl J Med 382:41-50, 2020

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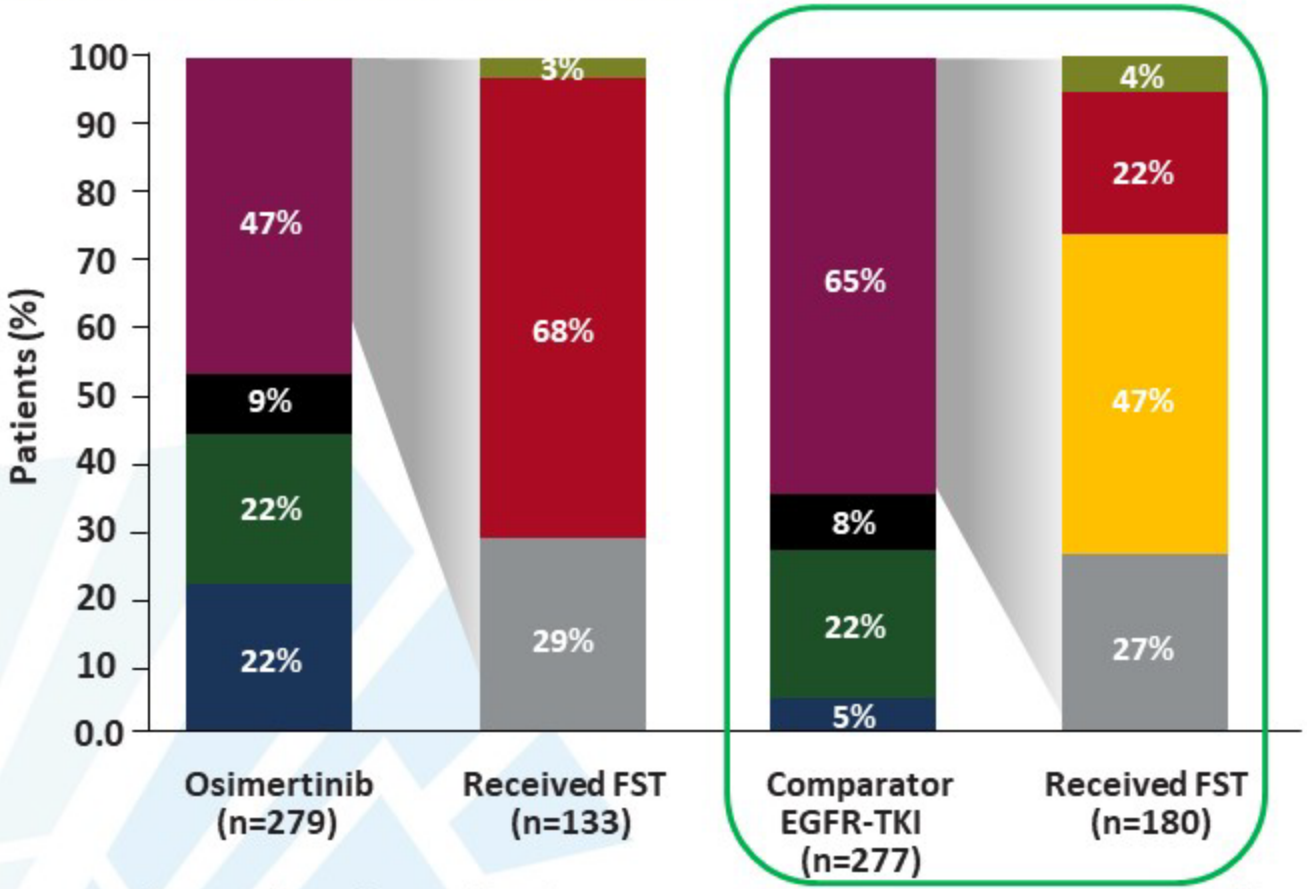
> ph3 osimertinib: further therapies



Patient disposition

- Received first subsequent (second-line) anti-cancer treatment
- No subsequent anti-cancer treatment (alive)
- No subsequent anti-cancer treatment (dead)
- Still on study treatment

First subsequent (second-line) anti-cancer therapies

- Other*
- Cytotoxic chemotherapy†
- Osimertinib
- EGFR-TKI containing regimen, other than osimertinib

- **180/277 of patients in the comparator EGFR-TKI arm received a subsequent treatment (65%)**
- **85/277 of these patients received osimertinib (31%)**

Ramalingam et al, ESMO 2019

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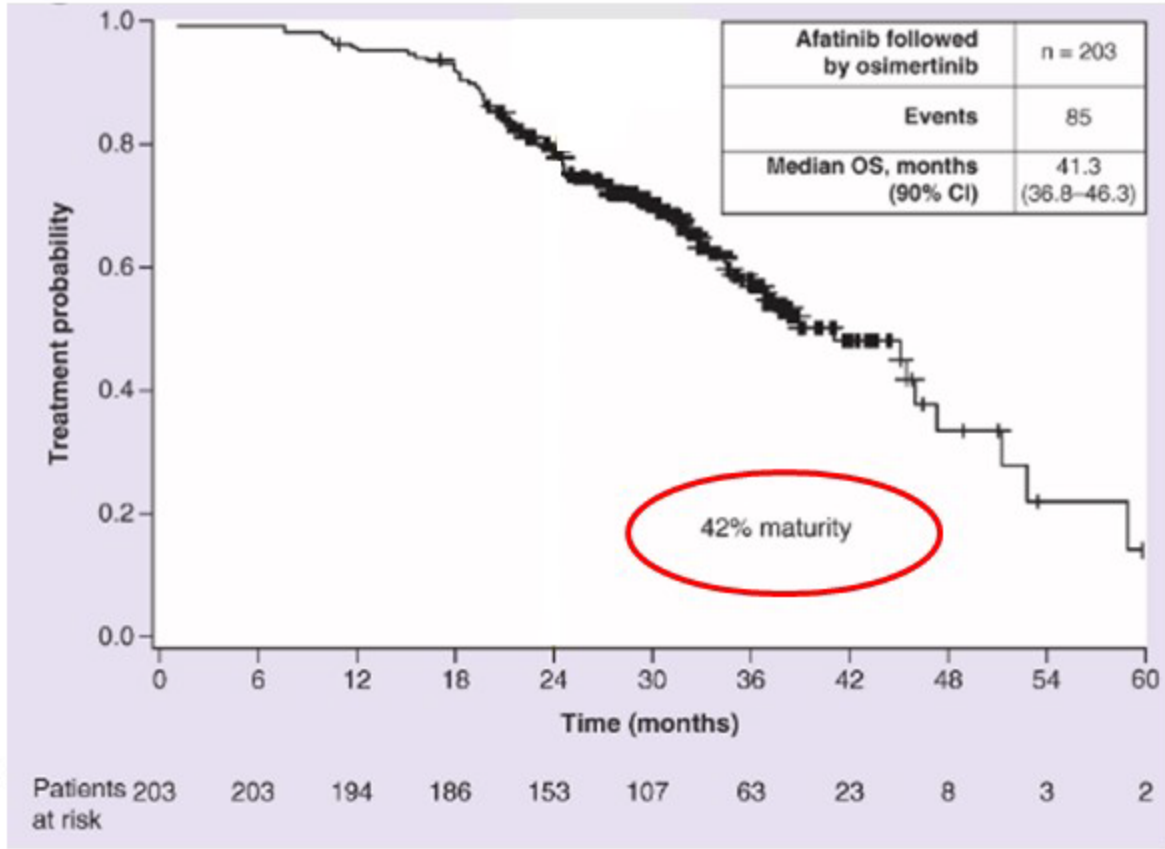
> sequencing? Ph2 GIOTAG study

retrospective real-world study of sequential therapy with Afatinib followed by Osimertinib

EGFRmut+ NSCLC → **SoC TKI** → *Further therapy* → *T790M+* → **3rd gen TKI**



Hochmair et al, Fut Oncol 15:2905-2914, 2019

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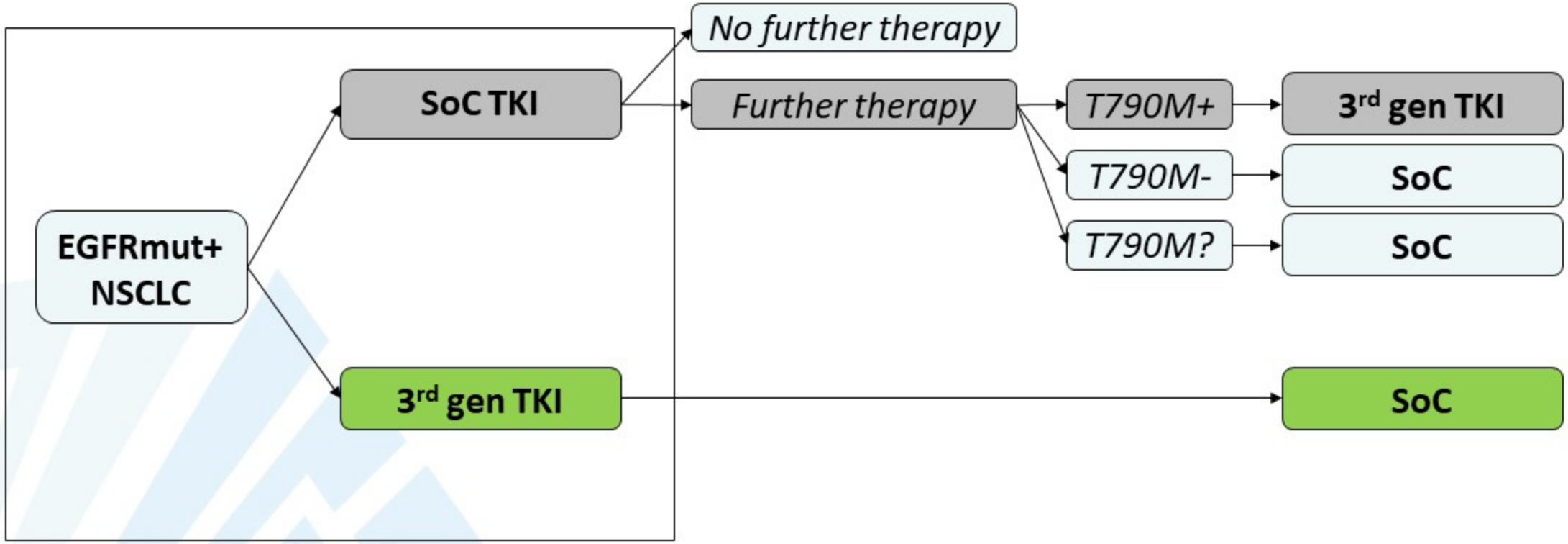
> sequencing? *Loss of best drug* paradigm



- FLAURA: superior PFS, superior PFS2, superior OS, and superior CNS control with novel strategy

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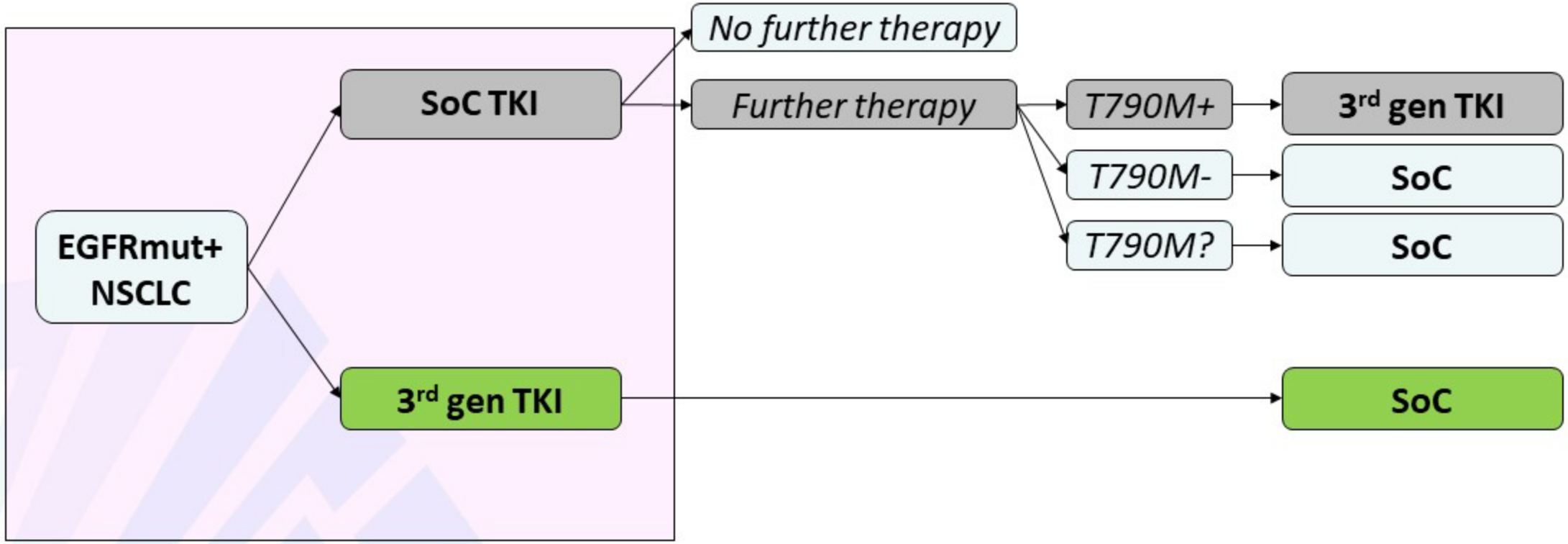

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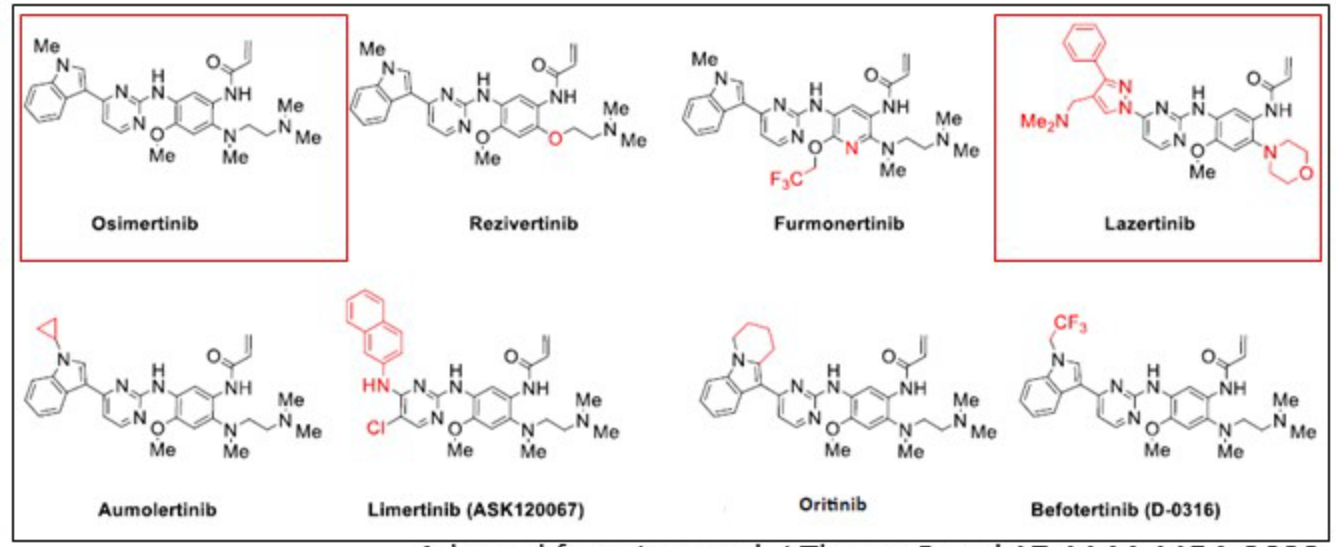
NSCLC *EGFR*mut+
> other 3rd generation TKIs

- **Lazertinib**
  - **Approval in South-Korea for T790M+**
  - **International ph3 trial in 1st line**
  - **Co-development with JNJ in Amivantamab program**

- **Chinese me-too compounds**
  - **No novelty**
  - **Trials in Chinese population only**
  - **May not meet FDA or EMA criteria**
  - **Results available for 2 trials [AENEAS[1], FURLONG[2]]**
  - **Others expected 2023**



Adapted from Lau et al, J Thorac Oncol 17:1144-1154, 2022

1 Lu et al, J Clin Oncol 40: 3162-3171, 2022
2 Shi et al, Lancet Respir Med online June 2, 2022

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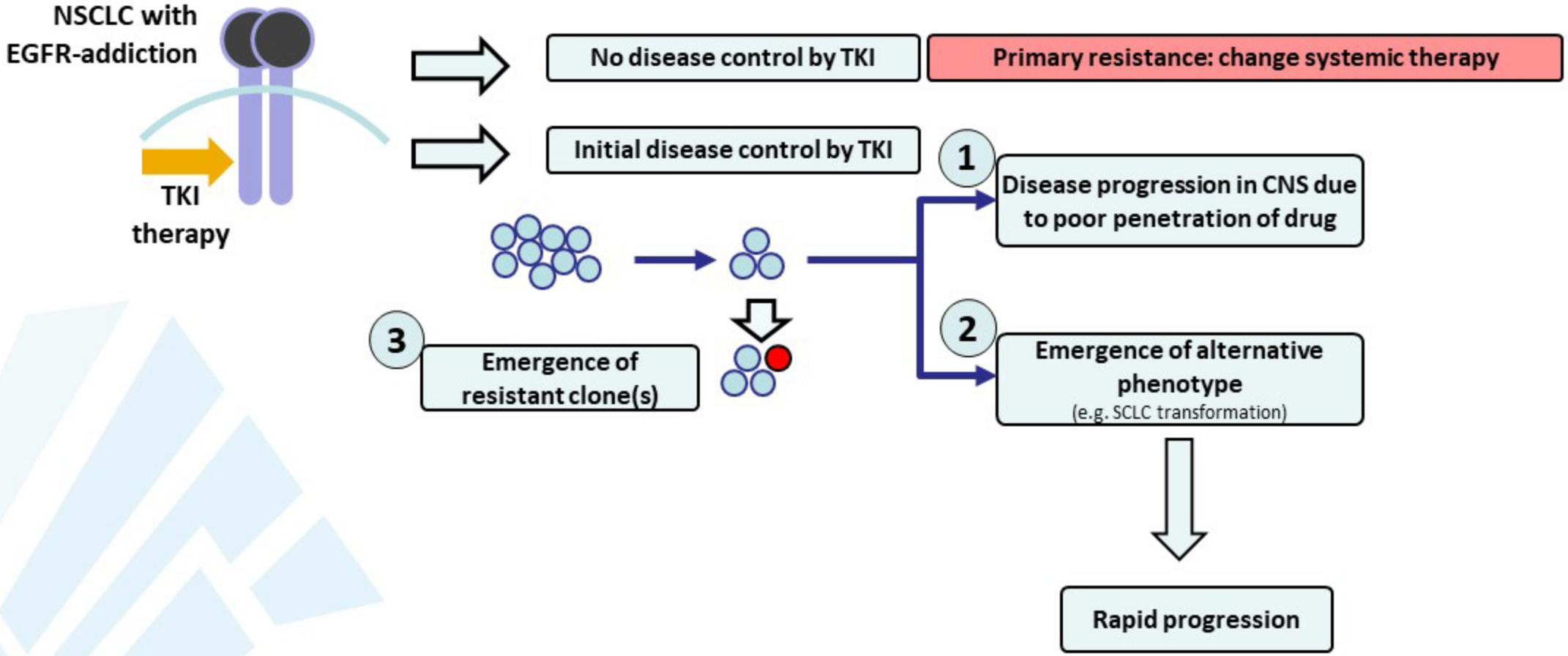
> patterns of resistance to 1L Osimertinib



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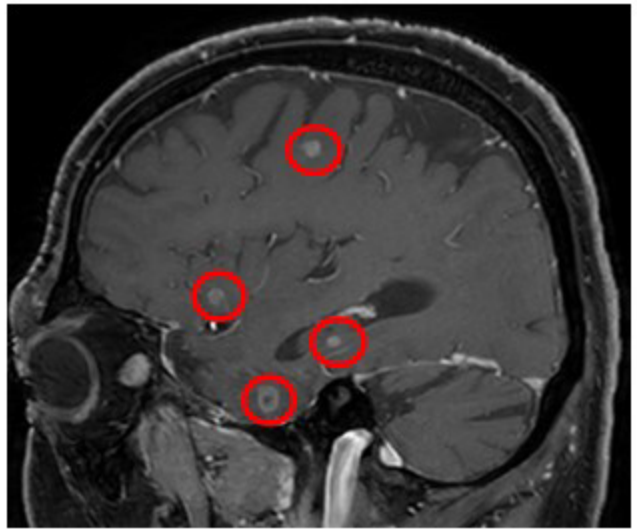
> resistance to 1L Osimertinib

1 **Disease progression in CNS due to poor penetration of drug**



- **Far less common with Osimertinib, compared to 1st/2nd gen TKI**

Oligobrain (≤3) *and* **Lesions <3-4 cm** → **'Local ablative therapy' (SRS/surgery)**

Multiple brain (>3) *or* **Large lesions** → **WBRT**

Multiple brain (>3) *or* **Large lesions** → **Osimertinib 160 mg/d Other systemic therapy**

→ **Continue Osimertinib**

(?) Osimertinib 160 mg/d[1]

Other systemic therapy

1 Yang et al, J Clin Oncol 38:538-547, 2020

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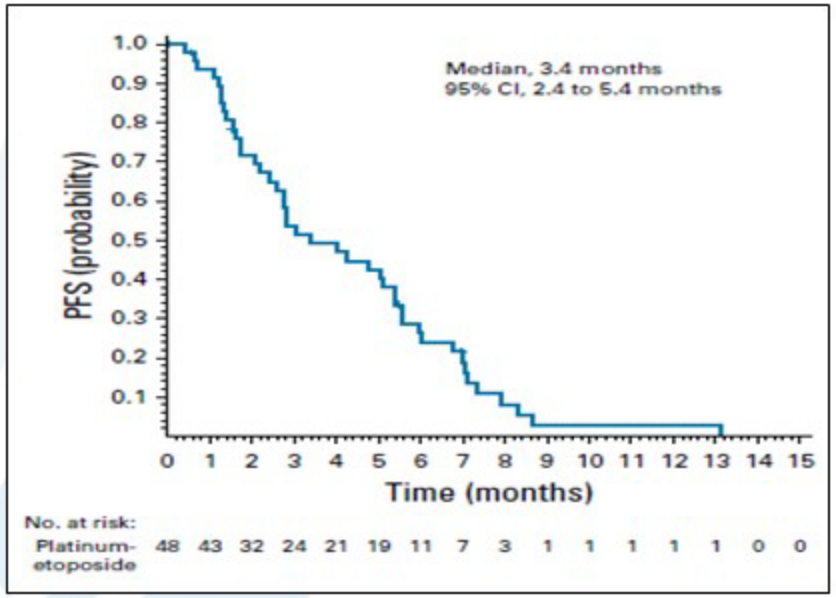
NSCLC *EGFR*mut+

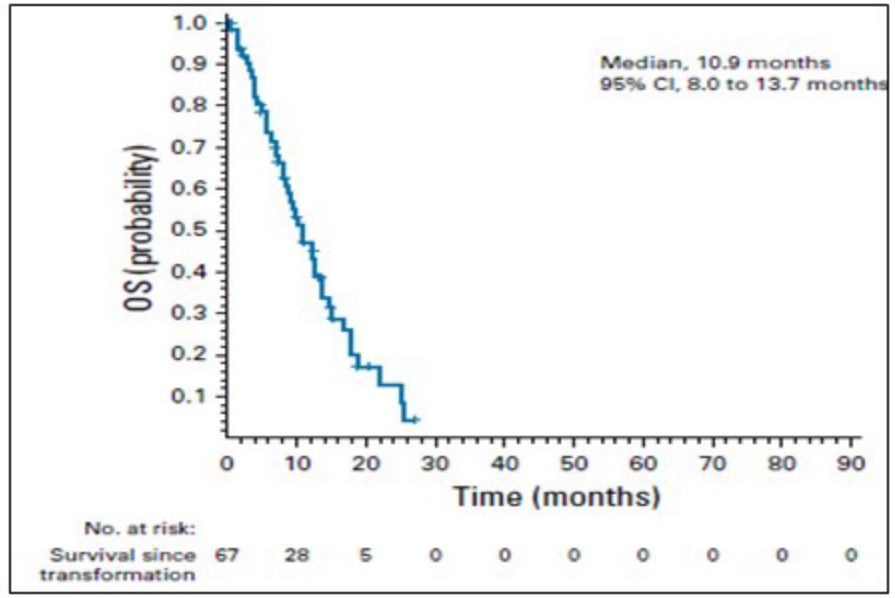
> resistance to 1L Osimertinib

2

Emergence of alternative phenotype [10-15%]
(e.g. SCLC transformation)

- **Histology adapted chemotherapy**
- **(?) continue Osimertinib [NCT03567642]**





Marcoux et al, J Clin Oncol 37:278-285, 2019

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> resistance to 1L osimertinib: ESMO treatment recommendations

3

Emergence of resistant clone(s)

Symptomatic

PS 3–4
Best supportive care

ORR ≈30%
median PFS ≈5-6 months

PS 0–1
- Platinum doublet ± bevacizumab
- Carboplatin-paclitaxel + bevacizumab + atezolizumab (if fit and no contraindication to immunotherapy)

PS 2
- Platinum doublet
- Single agent chemotherapy (pemetrexed, gemcitabine, docetaxel)

Asymptomatic or oligoprogression

- Continue Osimertinib
- Local ablative treatment if limited lesions (RT or surgery)

➢ **Note: role of immunotherapy in this setting -> topic of ongoing clinical trials (KN-789 ; CM-722)**

➢ **Note: role of continuing Osimertinib with platinum doublet -> to be evaluated in clinical trials**

Planchard et al, *Ann Oncol* 29 Suppl 4:iv192–237, 2018; updated online 15 September 2020

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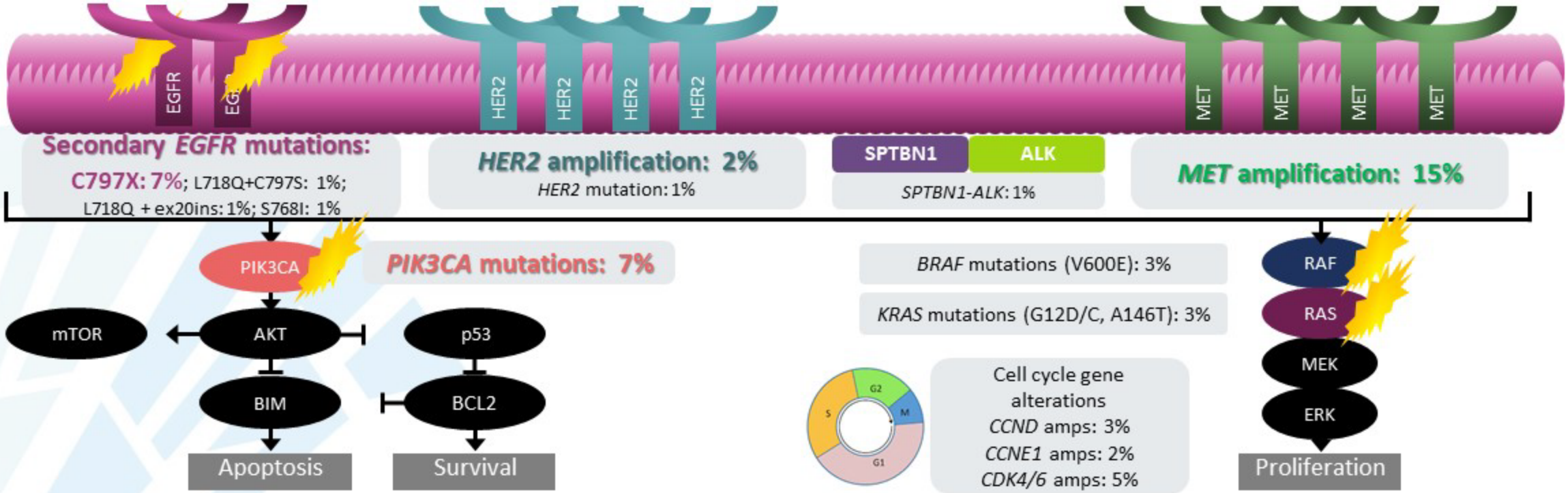
> resistance to 1L Osimertinib: FLAURA ctDNA analysis (n=91)

- **Intra-pathway ('on target'): most common resistance mechanism was *EGFR* C797S mutation**
- **Bypass pathway ('off-target'): most common resistance mechanism was *MET* amplification**
  - Other mechanisms included *HER2* amplification, *PIK3CA, RAS* pathway mutations, CDK amplifications



Ramalingham et al, ESMO 2018

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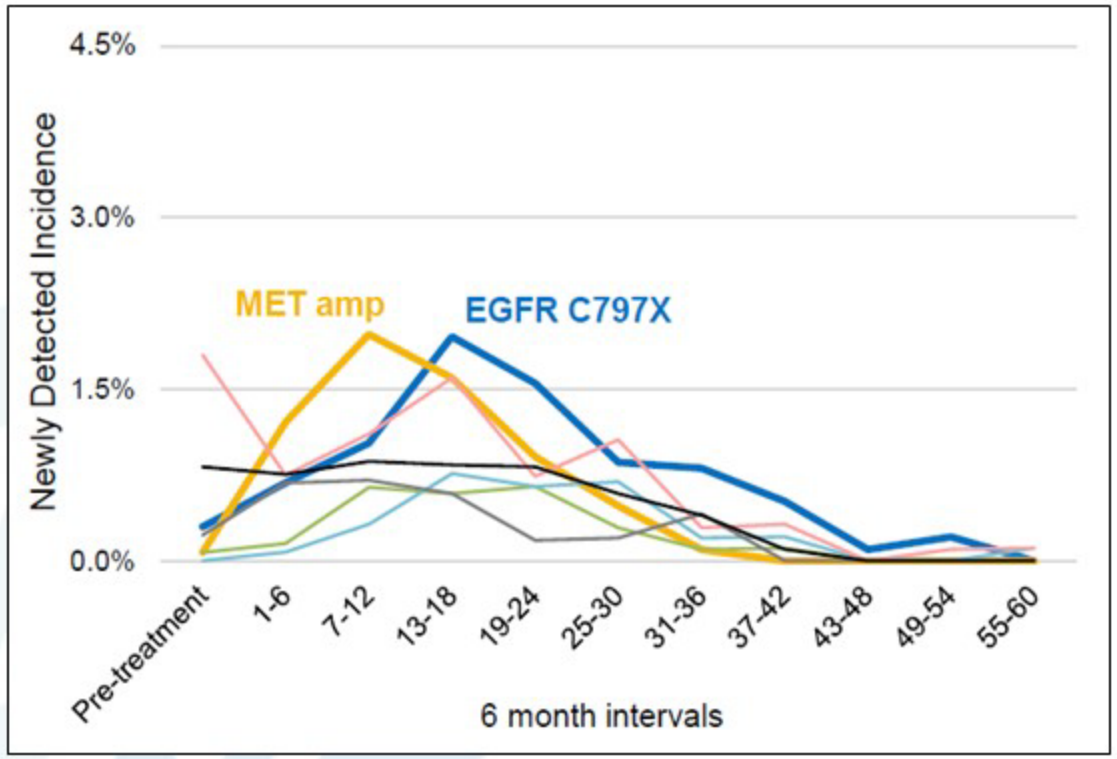
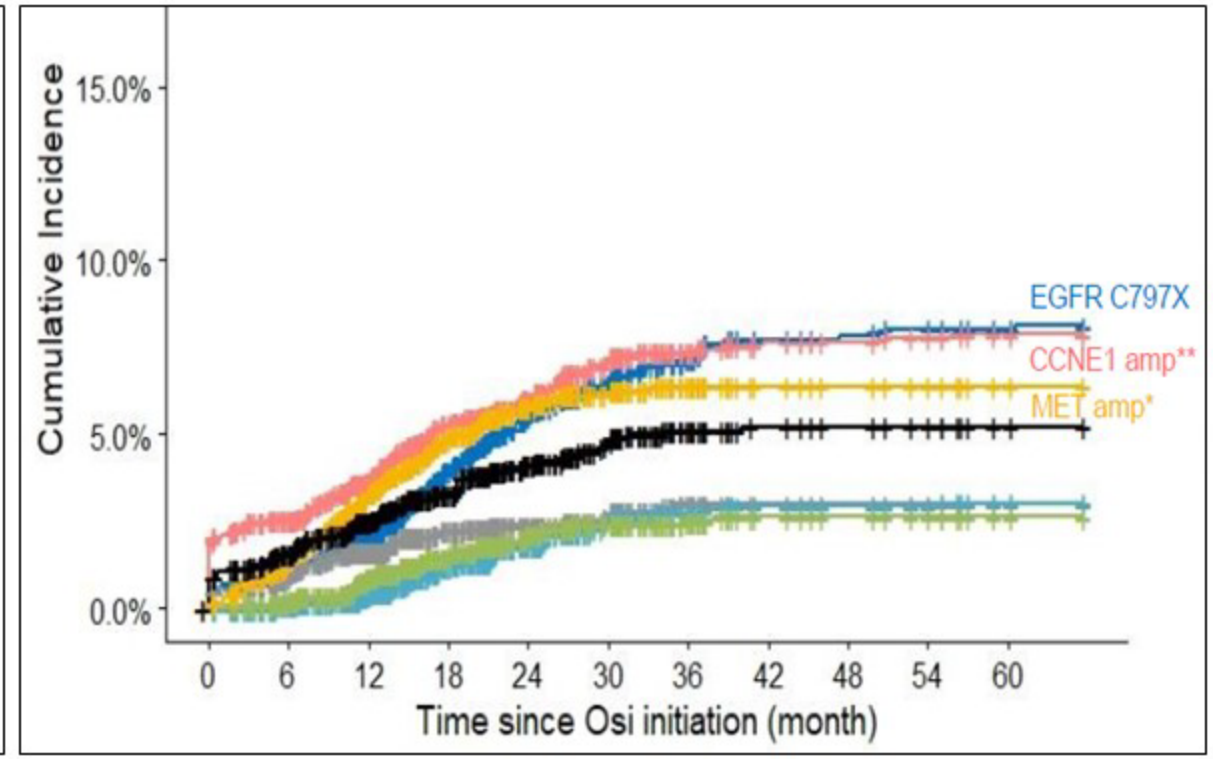
> resistance to 1L Osimertinib: INFORM database (n=1337)

- **INFORM: database with de-identified records of US advanced cancer patients with clinical cfDNA results** [testing either Guardant360 CDx or Guardant360]





EGFR C797 MET amp

BRAF V600 EGFR L718 CCNE1 amp PIK3CA E542 PIK3CA E545

Ramalingham et al, WCLC 2022

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> off-target druggable alterations: the MET amplification example

	NCT01610336[1]	TATTON (NCT02143466)[2]	INSIGHT2 (NCT03940703)[3]
Phase	**1b/2**	**1b** [expansion B cohorts and D cohort]	**2**
Treatment arms	**Capmatinib (400 mg/d) + Gefitinib (250 mg/d)**	**Savolitinib (600/300 mg/d) + Osimertinib (80 mg/d)**	**Tepotinib 500 mg/d + Osimertinib 80 mg/d**
Patients (n)	**161**	**69 / 51 / 18 / 36**	**88**
Molecular group	**Biomarker seeking study 'MET dysregulation'**	***MET* amplified*** **MET* GCN ≥5 and/or *MET/CEP7* ≥2	***MET* amplified***
ORR (%)	**27** [47 if GCN >6]	**30 / 65 / 67 / 64**	**55**
mPFS (months)	**Variable** [5.5 if GCN >6]	**5.4 / 9.0 / 11.0 / 9.1**	**NR**
TREAs ≥grade 3 (%)	**57**	**57**	**24**
Most common TRAEs	**Nausea/Fatigue Peripheral edema**	**Fatigue Nausea / Decreased appetite**	**Diarrhea/Paronychia Peripheral edema**
Discontinuation for AEs	**N=27 (17%)**	**N=38 (28%)**	**N=6 (7%)**
Ph3 vs. plat-pemetrexed	**GeoMETry-E NCT04816214**	**Saffron NCT05261399**	

1 Wu et al, J Clin Oncol 36:3101-3109, 2018
2 Sequist et al, Lancet Oncology 21:373-386, 2020
3 Mazieres et al, ESMO 2022, LBA52

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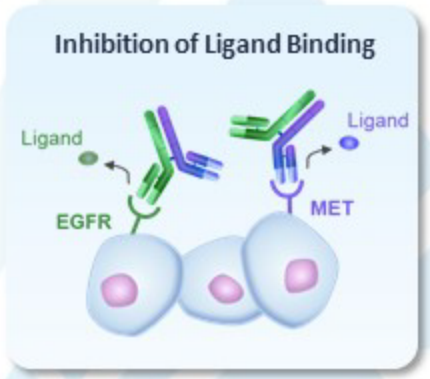
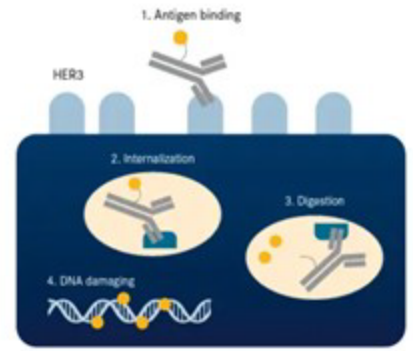
> on-target alterations

- **Platinum-pemetrexed is standard**
- **Alternatives**
  - **Adding anti-EGFR monoclonal, e.g. Afatinib+Cetuximab[1] – toxicity!**
  - **Adding Gefitinib in case of resistance mutation *in trans* with T790M[2] (2nd line use of Osimetinib)**
- **"Mutation agnostic" options**



Lazertinib + Amivantamab
Bispecific antibody
CHRYSALIS-1 study[3]
- **ORR 36%**
- **mDoR 9.6 mo**
- **mPFS 4.9 mo**



Patritumab-Deruxtecan
Antibody-drug conjugate
HERTHENA-1 study[4]
- **ORR 39%**
- **mDoR 7.0 mo**
- **mPFS 8.2 mo**

1 Horn et al, Lung Cancer 113:51-58, 2017
2 Arulanda et al, J Thorac Oncol 12:1728-1732, 2017
3 Bauml et al, ASCO 2021, abstr 9006
4 Janne et al, Cancer Discov 12:74-89, 2022

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- Case study
- Optimal 1st line therapy
  - Osimertinib
  - Sequencing?
  - Other 3rd generation TKIs
- Failure post-osimertinib
  - CNS failure
  - Histologic transformation
  - Known molecular mechanism
  - No specific findings
- Uncommon *EGFR* mutations
- Conclusion

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NSCLC *EGFR*mut+
> uncommon (sensitizing) mutations

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

Treatment outcome of atypical *EGFR* mutations in the German National Network Genomic Medicine Lung Cancer (nNGM)

M. Janning[1,2,3,4], J. Süptitz[5], C. Albers-Leischner[4], P. Delpy[1,6,7], A. Tufman[8], J.-L. Velthaus-Rusik[4], M. Reck[9], A. Jung[10,11], D. Kauffmann-Guerrero[8], I. Bonzheim[12], S. Brändlein[13], H.-D. Hummel[14], M. Wiesweg[15], H.-U. Schildhaus[16], J. A. Stratmann[17], M. Sebastian[17], J. Alt[18], J. Buth[19], I. Esposito[19], J. Berger[20], L. Tögel[21], F. C. Saalfeld[22], M. Wermke[22], S. Merkelbach-Bruse[23], A. M. Hillmer[23,24], F. Klauschen[10,11], C. Bokemeyer[4], R. Buettner[23], J. Wolf[5†] & S. Loges[1,2,3,4*†], National Network Genomic Medicine Lung Cancer (nNGM)

- 10-30% of all *EGFR* mutations, sensitivity to classical EGFR-TKIs highly heterogeneous
- Retrospective, multi-center study of the nNGM: 856 cases with atypical EGFR mutations[1]
- Three groups
  1. Clear response data for G719X, L861Q, S768I, or compound mutations
  2. Variable response data for very rare *EGFR* mutations (single point, ex18 deletions, ex19 insertions)
  3. Ex20 insertions: notoriously resistant to all generations of standard EGFR-TKIs
- Suggested therapy
  1. Afatinib[2] or Osimertinib[3]
  2. TKI, or platinum-pemetrexed chemotherapy for mutations with limited or missing data
  3. Platinum-pemetrexed in 1st line, EMA approval for Amivantamab 2nd line use[4]

1 Janning et al, Ann Oncol 33:602-615, 2022
2 Yang et al, Lancet Oncol 16:830-838, 2015
3 Cho et al, J Clin Oncol 38:488-495, 2020
4 Park et al, J Clin Oncol 39:3391-3402, 2021

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NSCLC *EGFR*mut+

- Case study
- Optimal 1st line therapy
  - Osimertinib
  - Sequencing?
  - Other 3rd generation TKIs
- Failure post-osimertinib
  - CNS failure
  - Histologic transformation
  - Known molecular mechanism
  - No specific findings
- Uncommon *EGFR* mutations
- Conclusion

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NSCLC *EGFR*mut+
> conclusion

- *EGFR* mutation is a prime story in personalized oncology
  - From first Gefitinib dosing (1998) to contemporary 1st line Osimertinib (3-year survival >50%)

- Unraveling clinical types & mechanisms of acquired resistance: work in progress
  - Role of ablative therapies in oligoprogression
  - Drugs targeting MET-amplification: proof of principle of adapted targeted therapy
  - Emerging "mutation agnostic" options

- New combination strategies in 1st line – not adopted as standards (yet)
  - EGFR-TKI + anti-angiogenic: prolongation of PFS, not OS. Increased toxicity and loss of convenience
  - EGFR-TKI + chemotherapy: no data with Osimertinib -> wait for FLAURA2 phase 3 trial results
  - "Pre-emptive strategies", e.g. EGFR-TKI + MET-inhibition -> ongoing early trials

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Thank you for your kind attention

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Global Lung Cancer Academy

Other Targets in NSCLC

Anne-Marie Dingemans, MD, PhD

Erasmus MC
Universitair Medisch Centrum Rotterdam

Cancer Institute

Other targets in NSCLC
ROS1, RET, MET, NTRK

Global Lung Cancer Academy
November 14th 2022

Prof Anne-Marie C. Dingemans, Respiratory Physician

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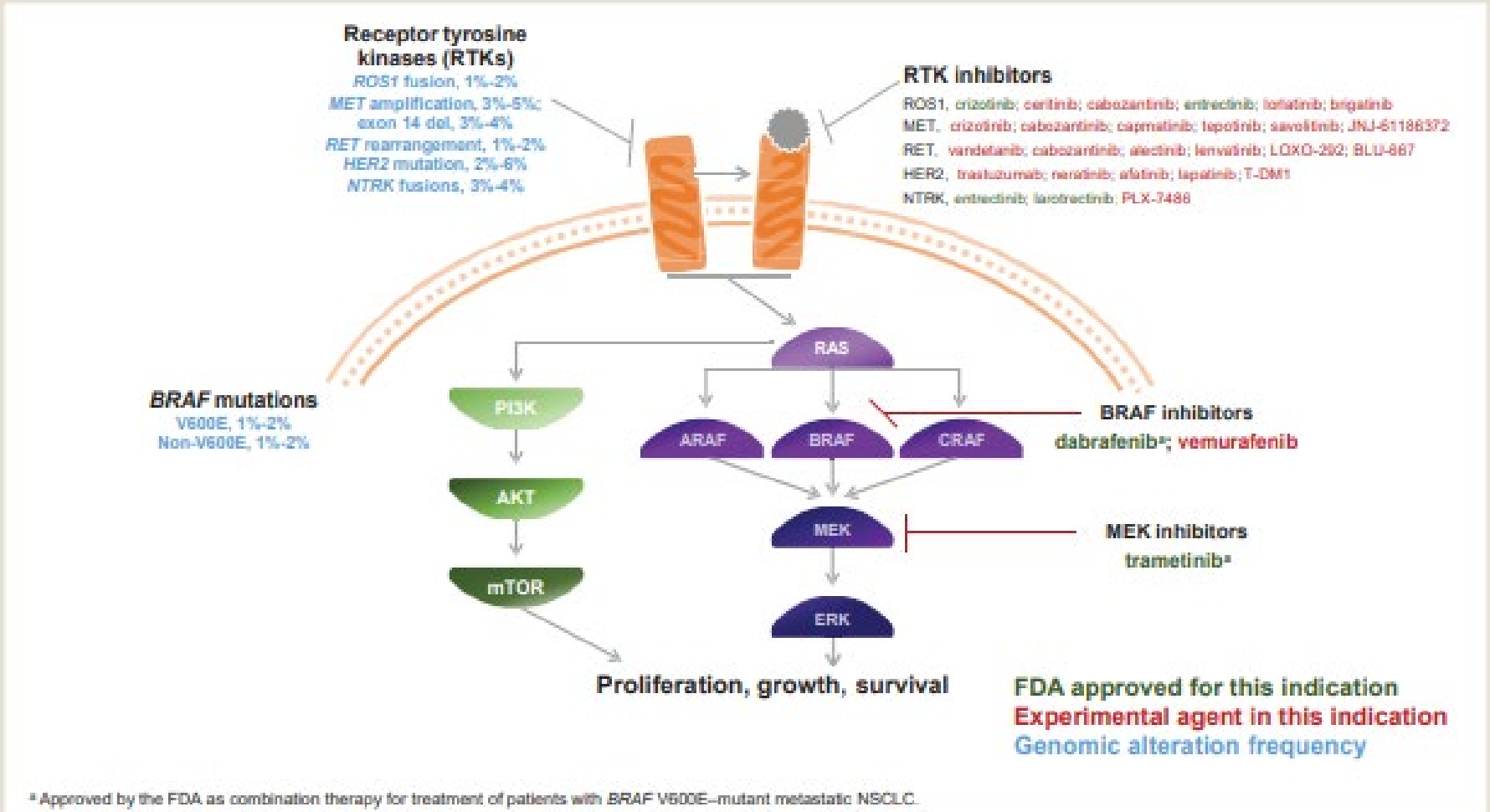
Disclosures Anne-Marie Dingemans
All paid to institute

Erasmus MC Cancer Institute

Commercial Interest	Relationship(s)
Roche	Advisory Board, Steering Committee
Eli Lilly	Honorarium
Boehringer Ingelheim	Advisory Board
Astra Zeneca	Honorarium, Advisory Board
Jansen	Honorarium (industry sponsored symposium)
Chiesi	Honorarium
Amgen	Advisory Board, research support
Pfizer	Honorarium
Bayer	Advisory Board
Takeda	Honorarium. IDMC
Pharmamar	Advisory Board
Sanofi	Advisory Board
Daiichi	Advisory Board

Figure 1 Targeting Rare Oncogenic Alterations in Non–Small-Cell Lung Cancer

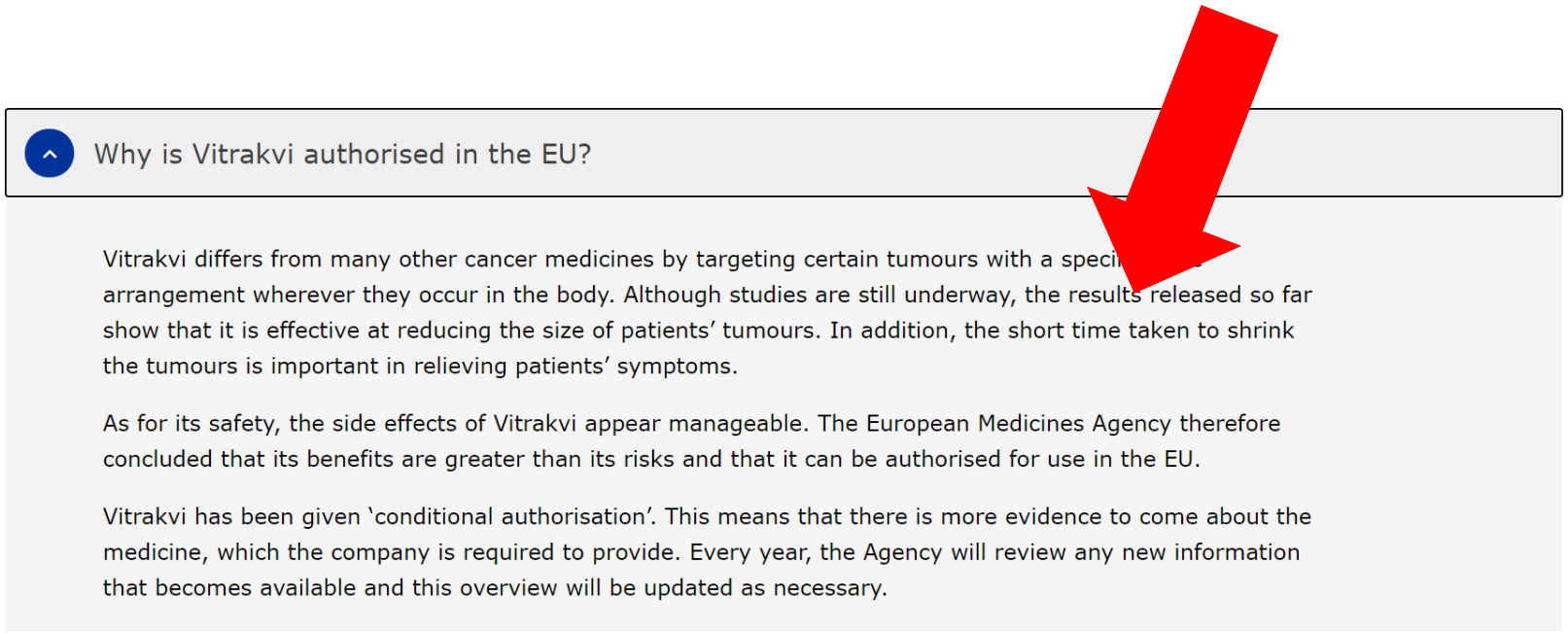


[a] Approved by the FDA as combination therapy for treatment of patients with *BRAF* V600E–mutant metastatic NSCLC.

Marmarelis ME, Langer CJ. *Clin Lung Cancer.* 2020;21:395-406.

Rare Cancers ≠ RCT

- Single arm phase II
- Readout: waterfall plot
- Overall Response Rate
- Duration of Response
- Toxicity
- Intracerebral efficacy



Why is Vitrakvi authorised in the EU?

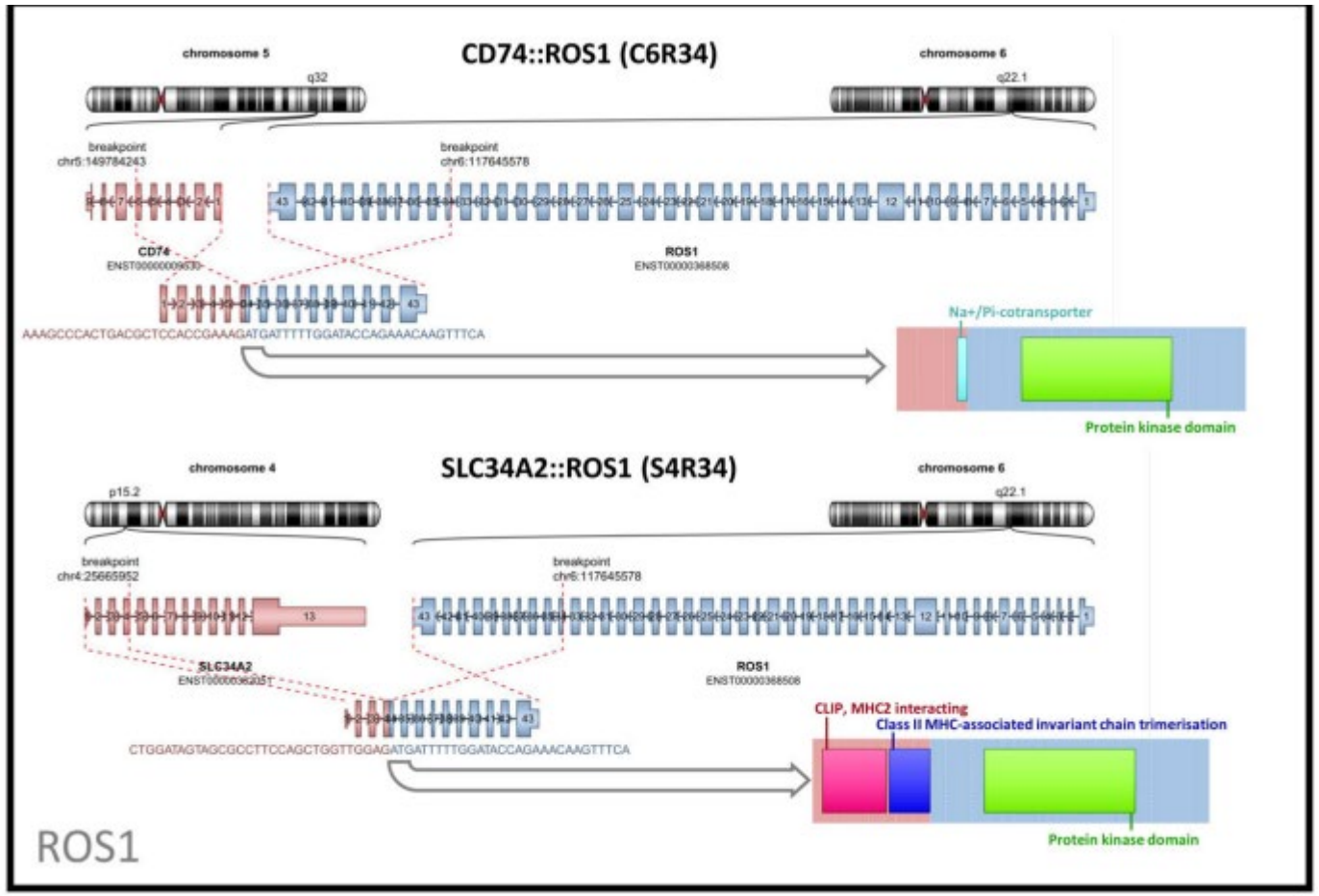
Vitrakvi differs from many other cancer medicines by targeting certain tumours with a speci… arrangement wherever they occur in the body. Although studies are still underway, the results released so far show that it is effective at reducing the size of patients' tumours. In addition, the short time taken to shrink the tumours is important in relieving patients' symptoms.

As for its safety, the side effects of Vitrakvi appear manageable. The European Medicines Agency therefore concluded that its benefits are greater than its risks and that it can be authorised for use in the EU.

Vitrakvi has been given 'conditional authorisation'. This means that there is more evidence to come about the medicine, which the company is required to provide. Every year, the Agency will review any new information that becomes available and this overview will be updated as necessary.

Larotrectinib EMA Approval 10/2019

ROS1 fusion



Method	
IHC	Screening
FISH	
(RNA-based) NGS	Fusion partner

Kazdal, *Genes Chromosomes Cancer 2022;61:244-260*

Crizotinib
PROFILE 101

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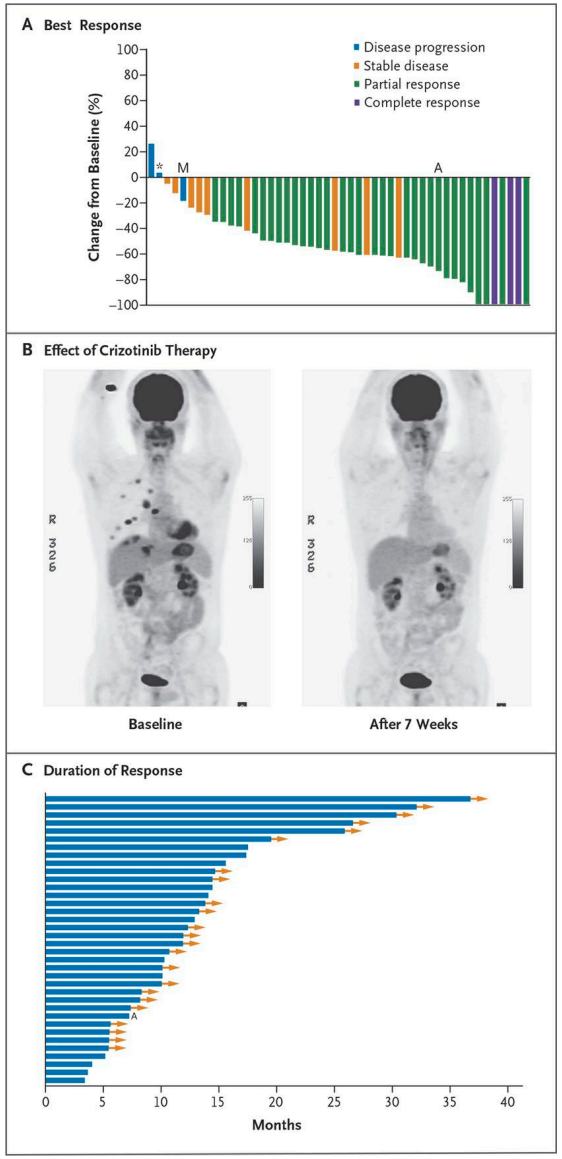

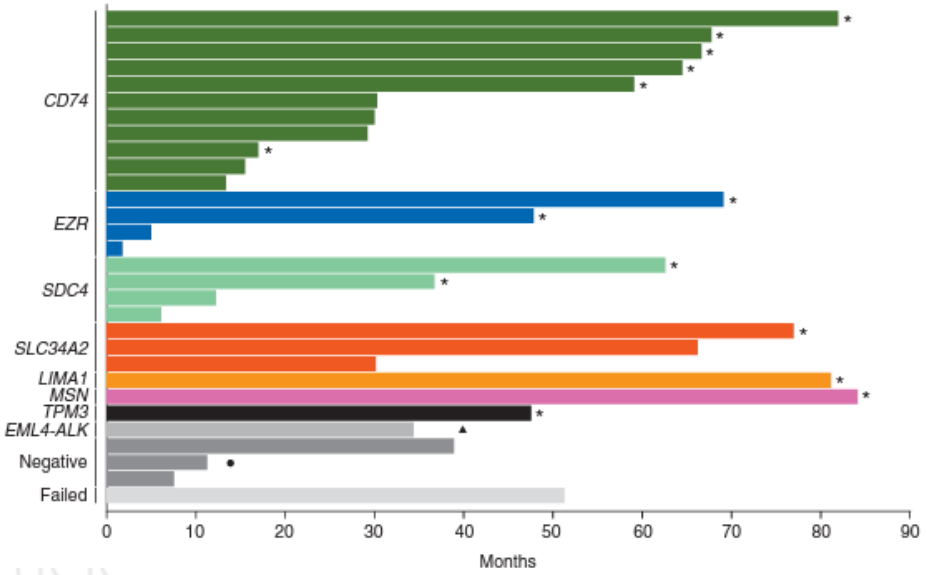

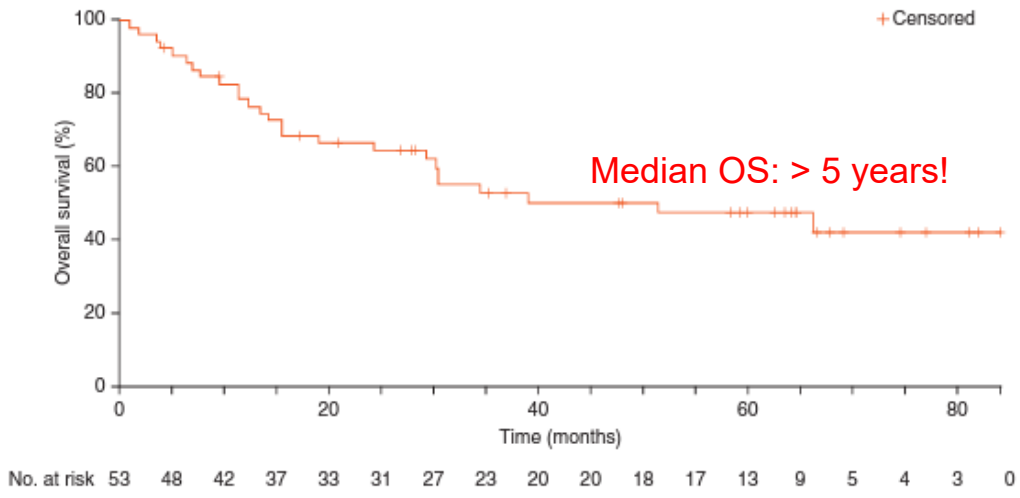

Median OS: > 5 years!

Shaw, *NEJM, 2014;371:1963-1971*
Shaw, *Annals of Oncology 2019;30:1121-1126*

Entrectinib
ALKA-372-001 / STARTK-1/STARTK-2

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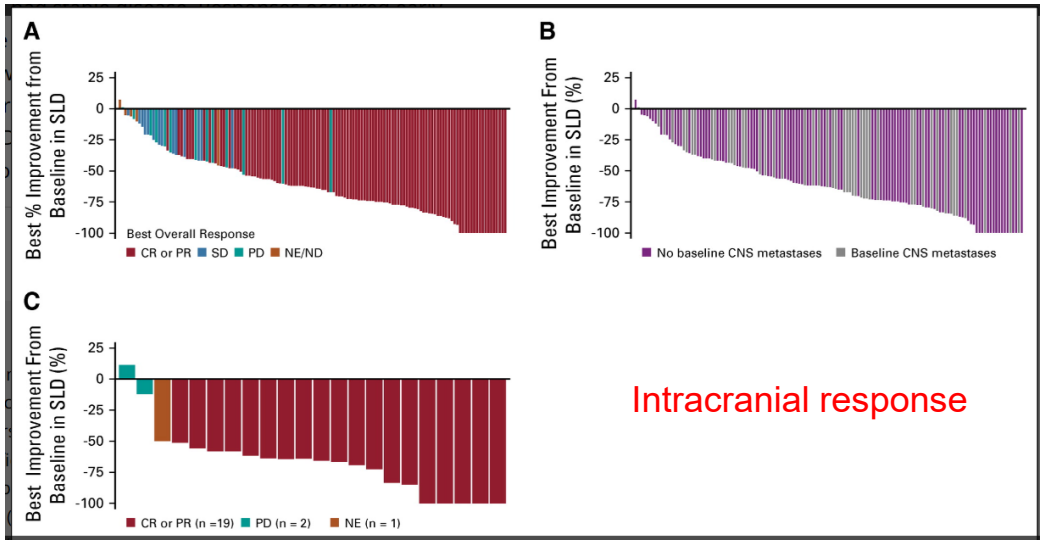
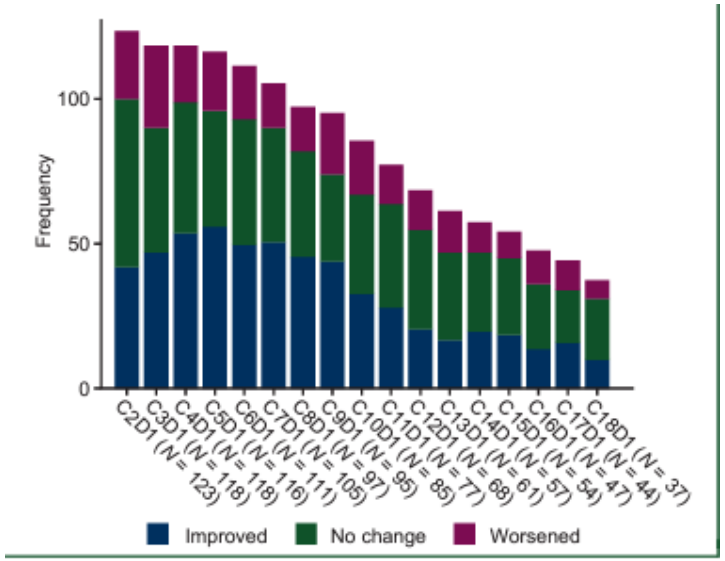
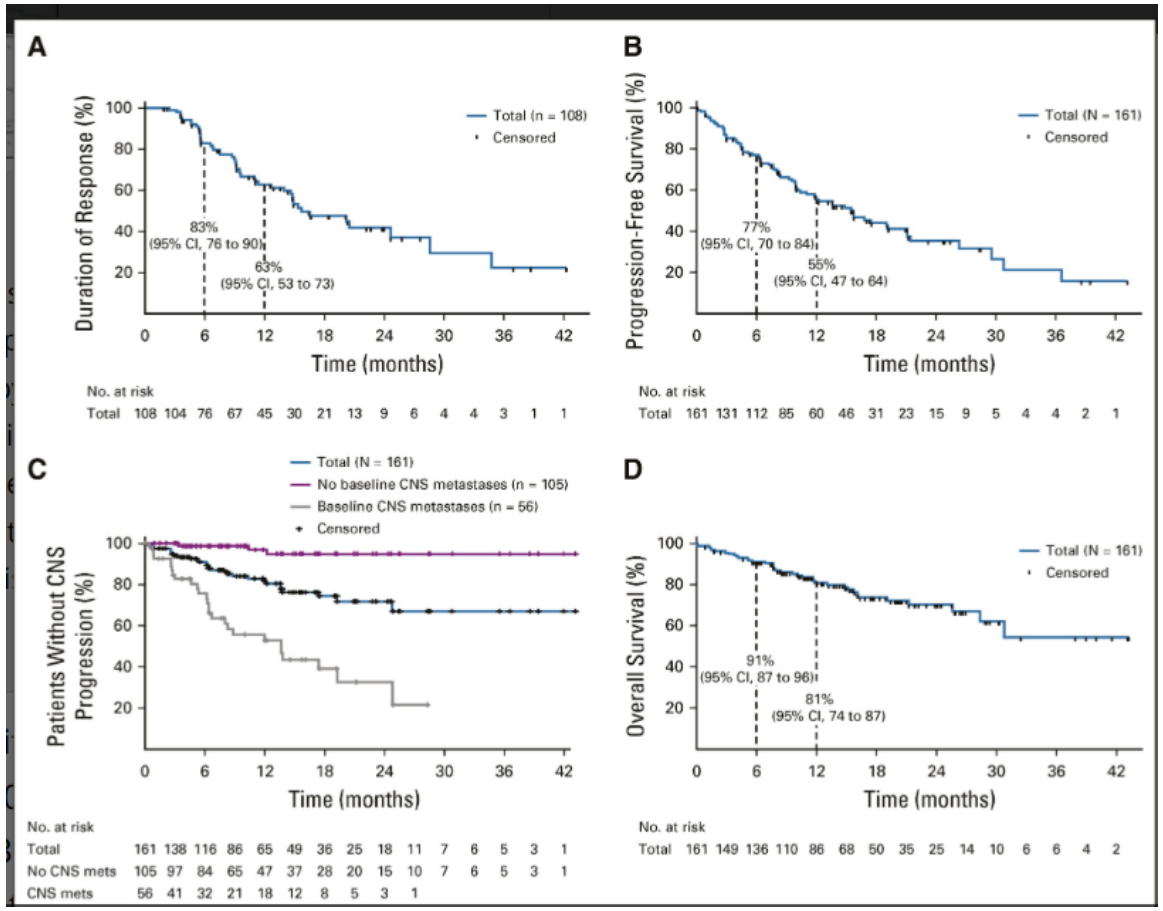


Intracranial response





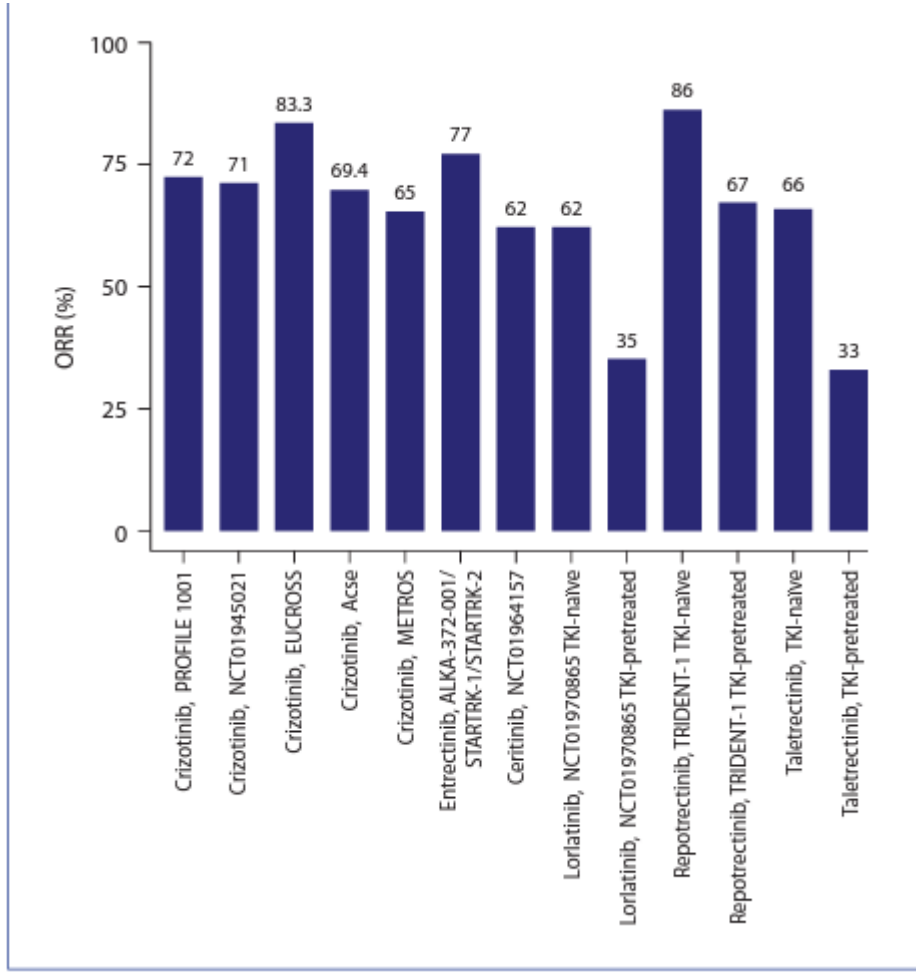
Dziadziuszko, *JCO 2021;39:1253-1263*
Paz-Ares, *ESMO open;2021*

Targeting ROS1

Table 2. Clinical activity of ROS1 TKIs.

ROS1 TKI	Clinical trial	Setting	Outcomes
Crizotinib	PROFILE 1001	Advanced ROS1$^+$ NSCLC	mPFS 19 months; mOS 51.4 months 72% ORR
Crizotinib	NCT01945021	Advanced ROS1$^+$ NSCLC	mPFS 15.9 months; 71% ORR
Crizotinib	EUCROSS	Advanced ROS1$^+$ NSCLC	mPFS 16.8 months; 83.3% ORR
Crizotinib	Acsé	Advanced ROS1$^+$ NSCLC	mPFS 5.5 months; mOS 17.2 months 69.4% ORR
Crizotinib	METROS	Advanced ROS1$^+$ NSCLC	mPFS 22.8 months; mOS not reached; 65% ORR
Entrectinib	ALKA-372-001, STARTRK-1, STARTRK-2	Advanced ROS1$^+$ NSCLC	mPFS 19 months; mOS not reached 77% ORR; 55% intracranial ORR
Ceritinib	NCT01964157	Advanced ROS1$^+$ NSCLC	mPFS 9.3 months; mOS 24 months; ORR 62%
Lorlatinib	NCT01970865	TKI-pre-treated ROS1$^+$ NSCLC	mPFS 21 months (TKI naive); mPFS 8.5 months (TKI pre-treated); 62% ORR (TKI naive); 35% ORR (TKI pre-treated)
Repotrectinib	TRIDENT-1	TKI-pre-treated ROS1$^+$ NSCLC	86% ORR (TKI naive); 40–67% ORR (TKI pre-treated)
Taletrectinib	NCT02279433, NCT02675491	TKI-pre-treated ROS1$^+$ NSCLC	66% ORR (TKI naive); 33% ORR (TKI pre-treated)

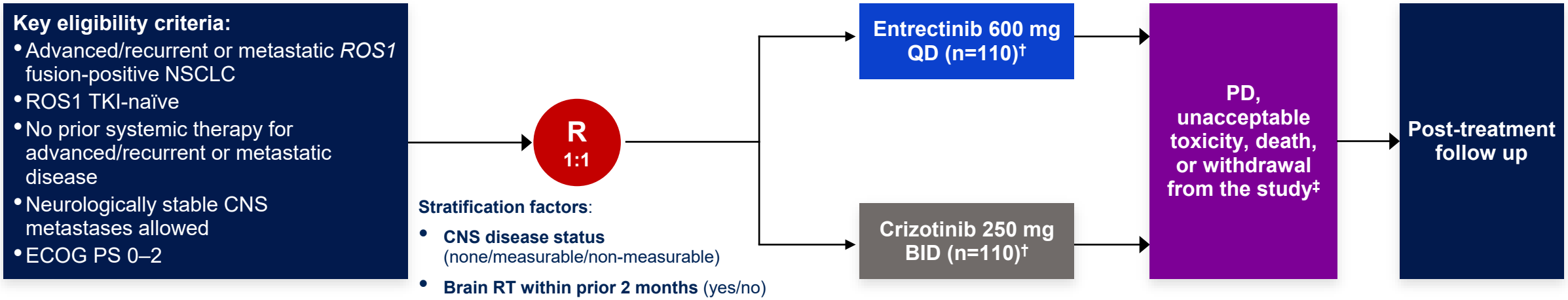
mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small-cell lung cancer; ORR, overall response rate; TKI, tyrosine kinase inhibitor.



Marinelli, *Drugs in Contaxt 2022;11*

Study design

- This is a **randomized, open-label, multicenter, phase 3 head-to-head trial**, designed to compare the efficacy and safety of entrectinib vs crizotinib in adult patients with:
  - ROS1 TKI-naïve advanced/recurrent or metastatic *ROS1* fusion-positive NSCLC
  - With or without CNS metastases that are neurologically stable



NCT04603807

Randomization will be performed centrally via an interactive voice or web-based response system (IxRS); †Estimates based on planned enrollment; ‡Patients with radiographic disease progression or isolated asymptomatic CNS progression may continue treatment at the investigator's discretion

BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD, progressive disease; QD, once daily; R, randomized; RT, radiotherapy

Dingemans, *ASCO 2022 TiP*

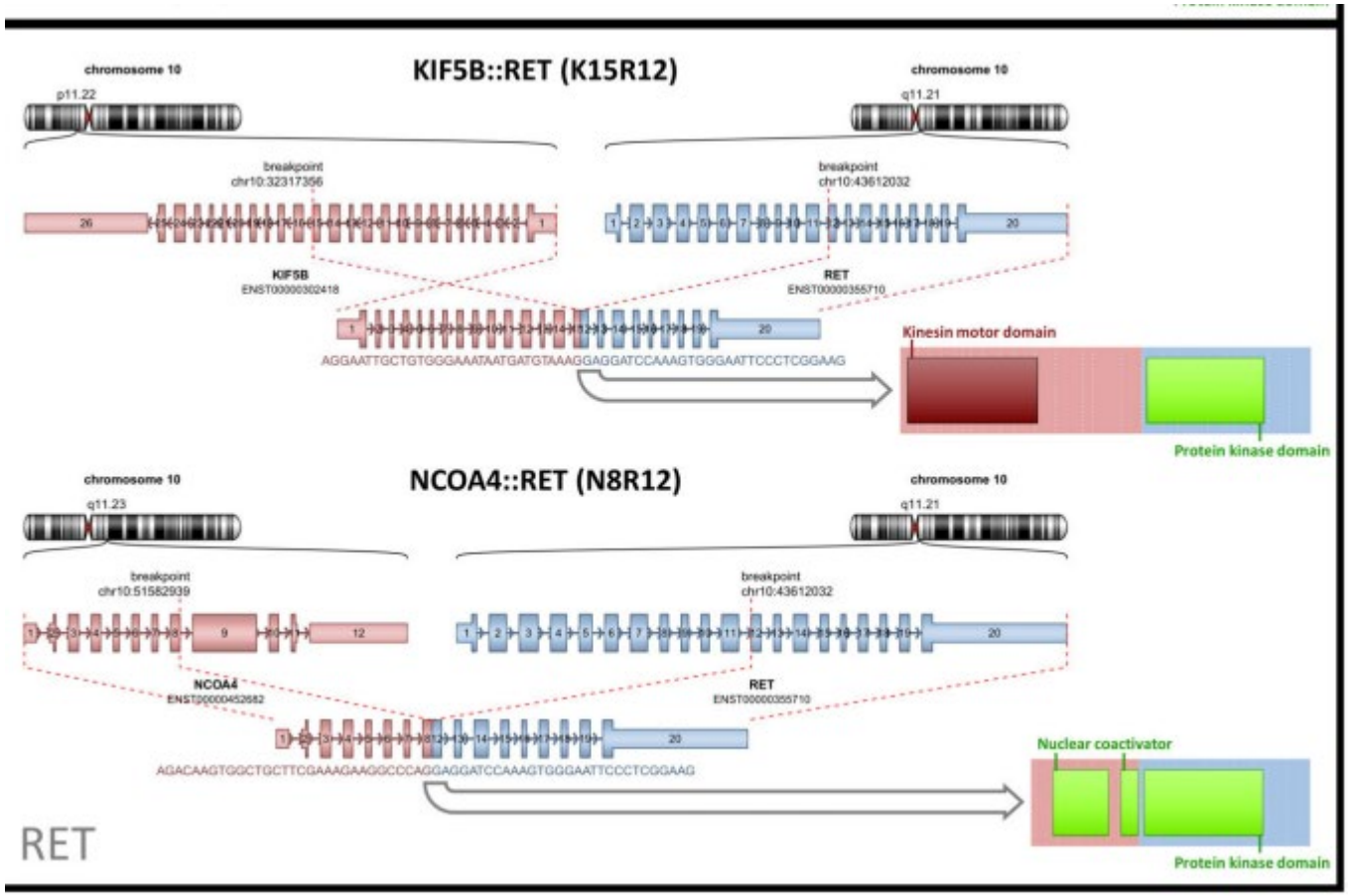
ROS1 translocation

	crizotinib	entrectinib
N	53	161
Dose	250 mg QD	600 mg OD
Biomarker	+	+
ORR (%(95% CI)	72 (58-83)	67 (59.3-74.3)
Time to response (weeks (95% CI)	7.9 (4.3-103.6)	
DoR (mts (95% CI)	24.7 (15.2-45.3)	15.7 (13.9-28.6)
Intracranial RR	82% 19/22	62%
Toxicity		
Special toxicity	Visual disturbance, edema	See NTRK
		
		first line

Dziadziuszko, *JCO 2021;39:1253-1263*
Shaw, *Annals of Oncology 2019;30:1121-1126*

This is not intended as a head-to-head comparison

RET translocations



Method	
IHC	Screening
FISH	
(RNA-based) NGS	Fusion partner

Not restricted to Adenocarcinoma!

Kazdal, *Genes Chromosomes Cancer 2022;61:244-260*

Pralsetinib
ARROW trials

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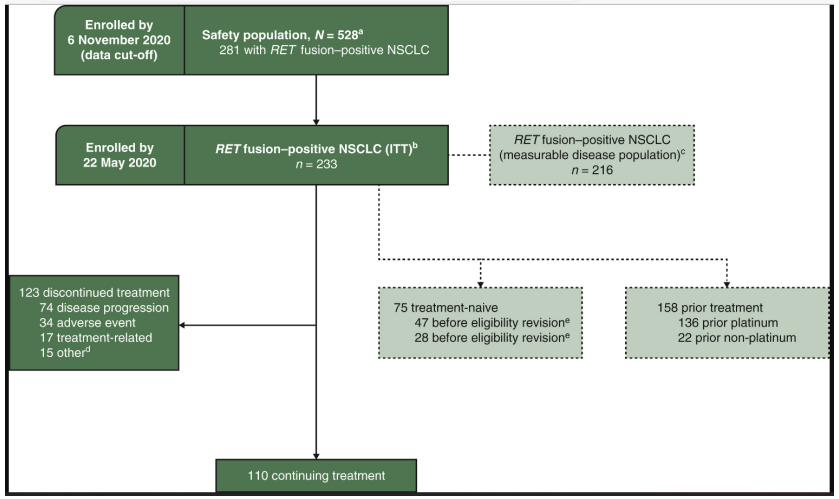

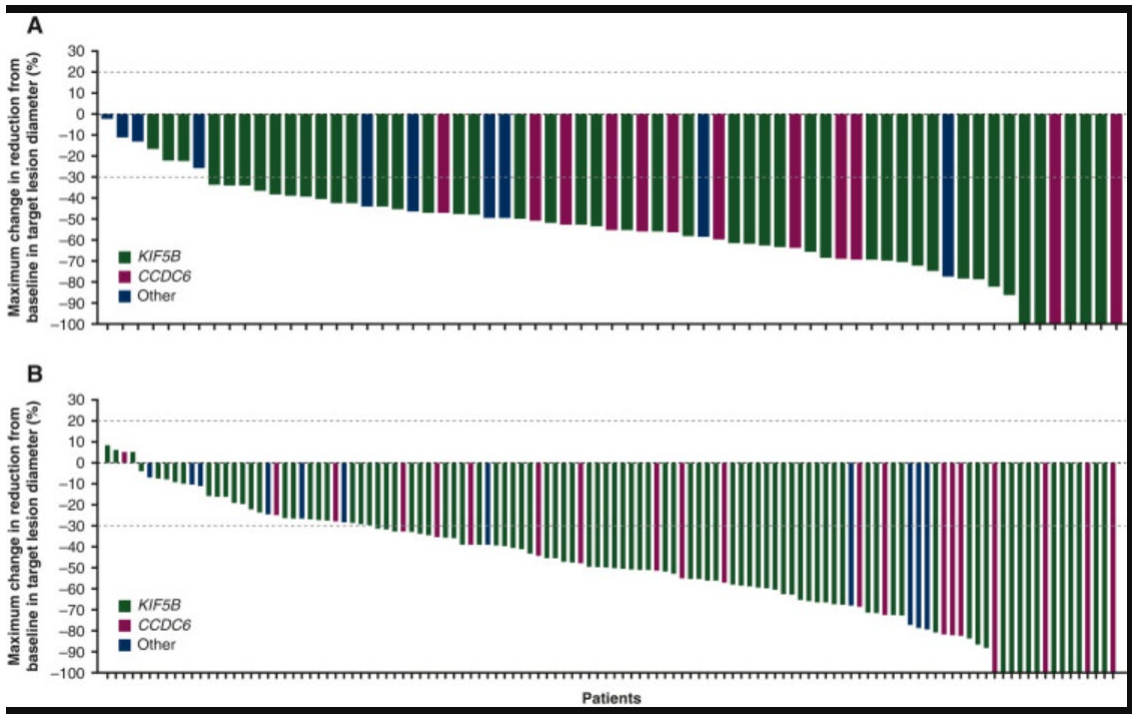

Treatment naive (N=75):
ORR 72% (95% CI 60-82)

Prior treatment (N=136)
ORR 59% (95% CI 50-67)

Griesinger, *Annals of Oncology 2022;33:1168-11778*

Selpercatinib
Libretto-001

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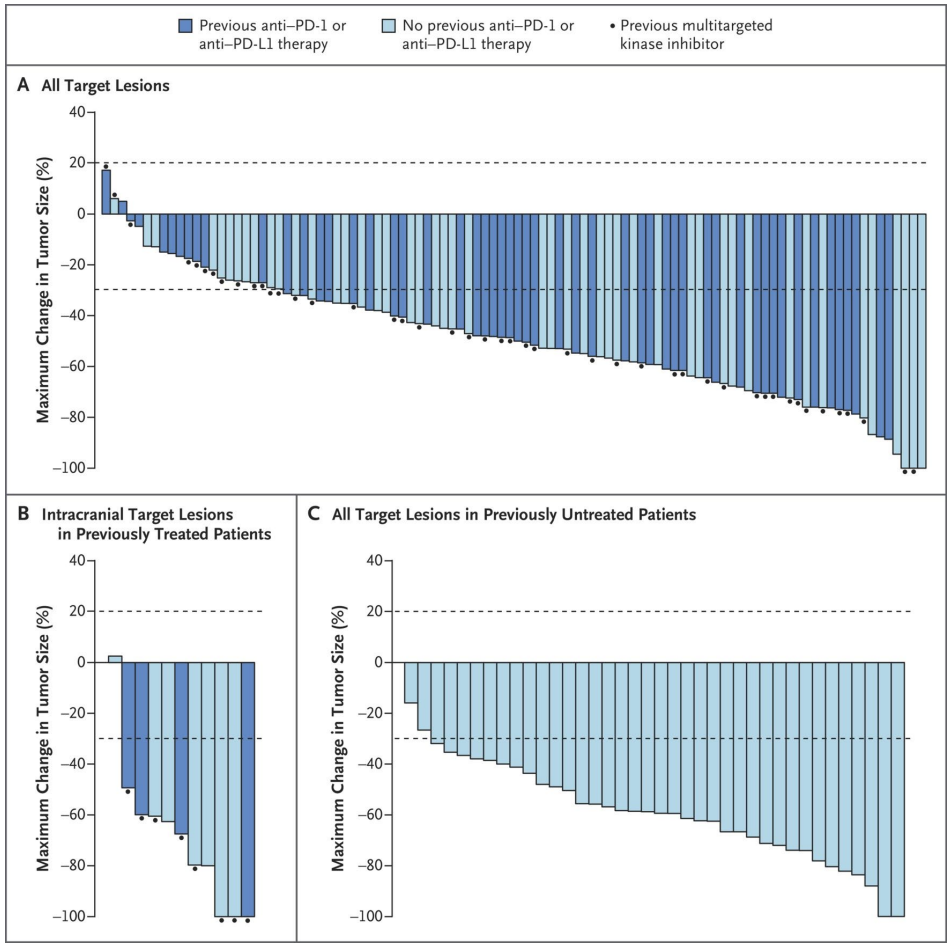
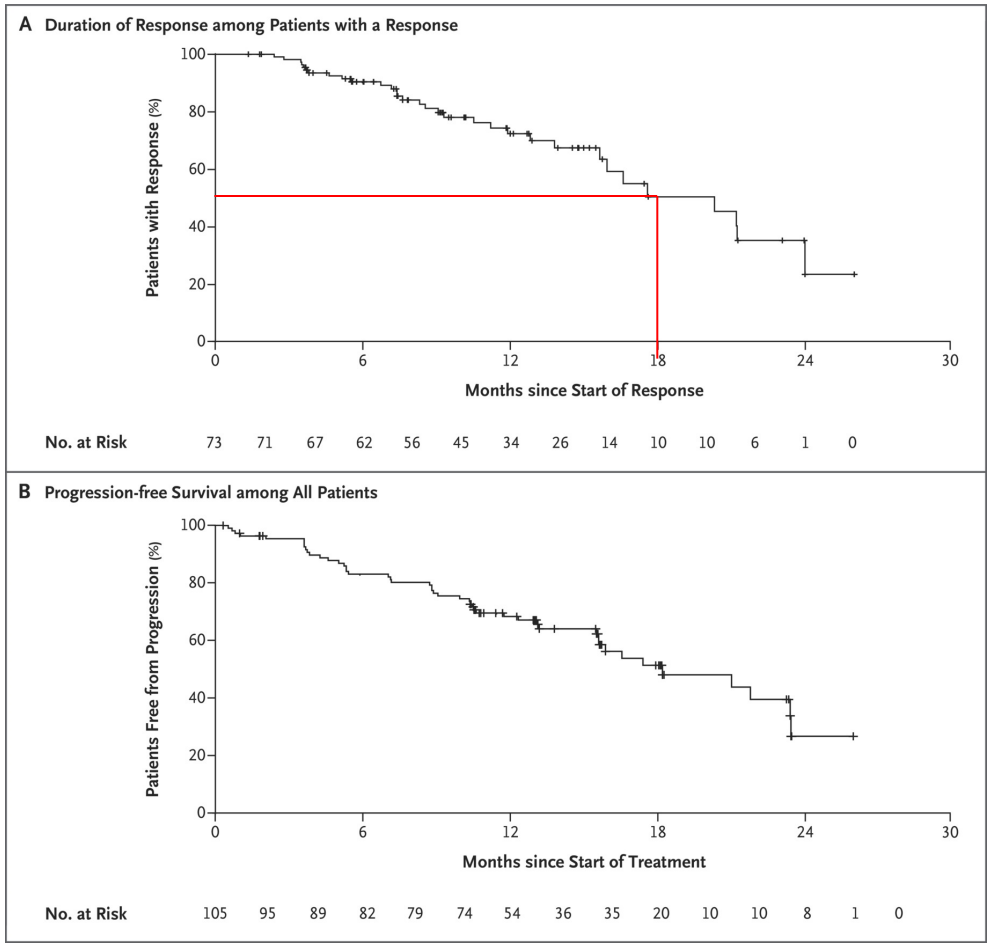
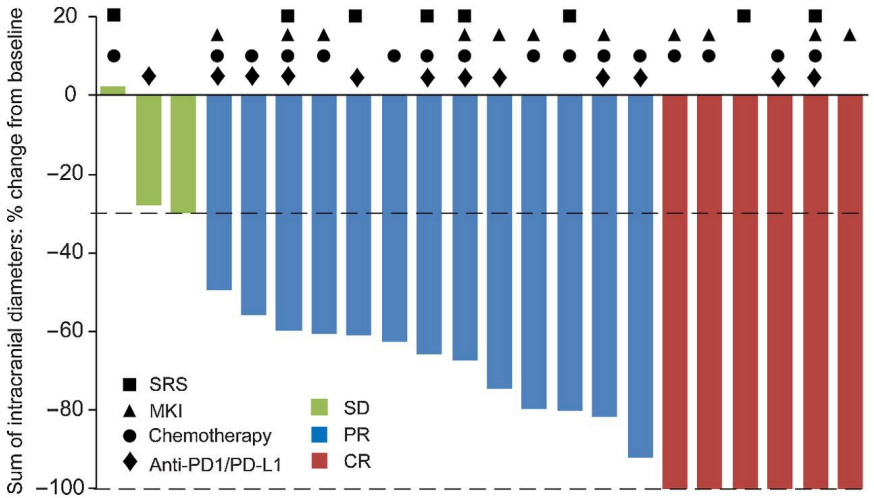
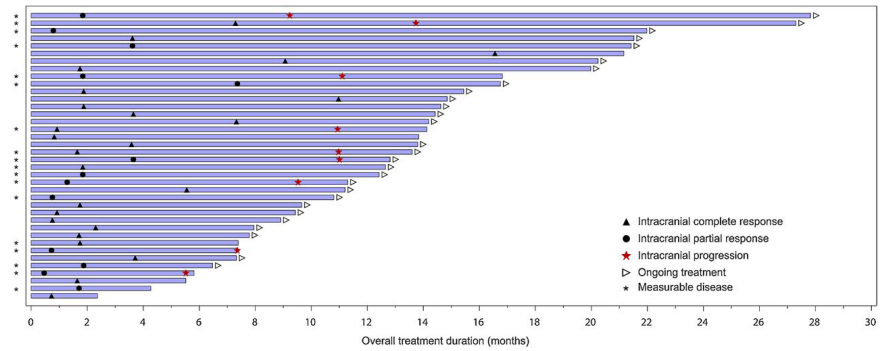


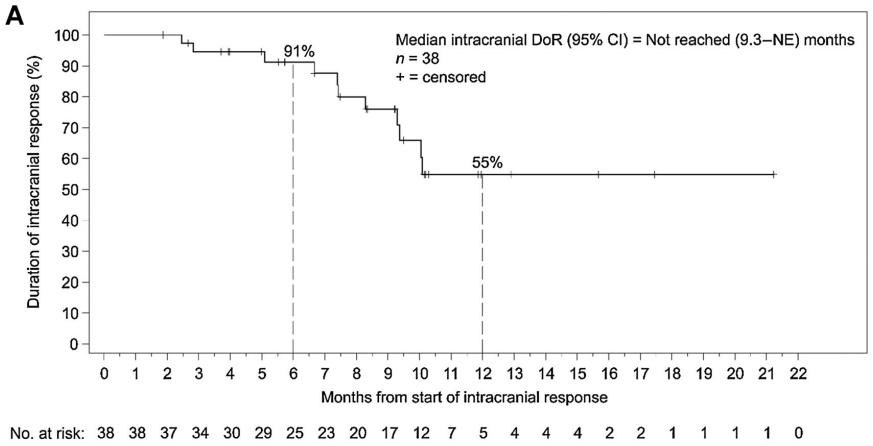


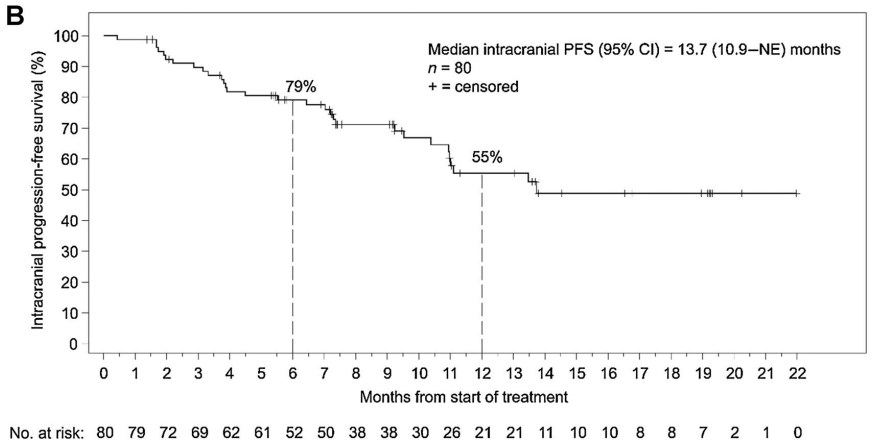
Drilon, *NEJM 2020;383:813*

Selpercatinib: intracranial efficacy (LIBRETTO-001)









Subbiah, *Clin Cancer Res. 2021;27(15):4160-4167*

Change in global health status/quality of life from baseline by cycle of Selpercatinib

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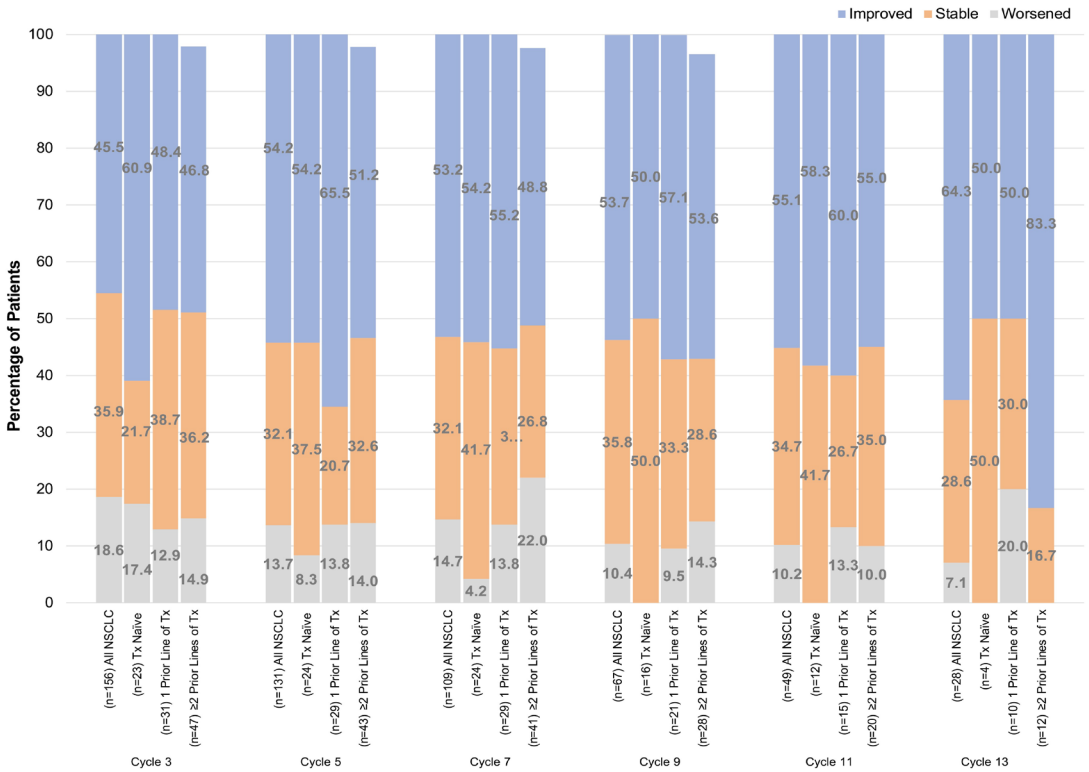

N=253

Clinical meaningful improvements of global health status: 61 – 67%

improved

stable

worsened

Minchon, *The Oncologist 2022;27:22-29*

RET translocation

	selpercatinib		pralsetinib		
	untreated	pretreated	untreated	Pretreated platinum	Pretreated non-platinum
N	39	105	75	136	22
Dose	160 mg QD		400 OD		
ORR (%(95% CI)	85 (70-94)	64 (54-73)	72 (60-82)	59 (50-67)	73 (50-89)
Time to response			1.8 (0.9-6.1)	1.8 (1.3-11.4)	1.8 (1.6-5.5)
DoR (mts (95% CI)	NE (12 –NE)	17.5 (12-NE)	NR (9.0 – NR)	22.3 (15.1-NR)	NR (9.2-NR)
Intracranial RR	82% 19/22		70% 7/10, 3 CR		
Toxicity gr ¾	38%		52%	56%	
Special toxicity	Hypertension, increase transaminases		Hypertension, neutropenia, anemia, increase transaminased, pneumonitis (2%)		
					
					

This is not intended as a head-to-head comparison

Drilon, *NEJM 2020;383:813*
Subbiah, *Clin Cancer Res. 2021;27(15):4160-4167*
Griesinger, *Annals of Oncology 2022;33:1168-11778*

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Current approaches to target cMET

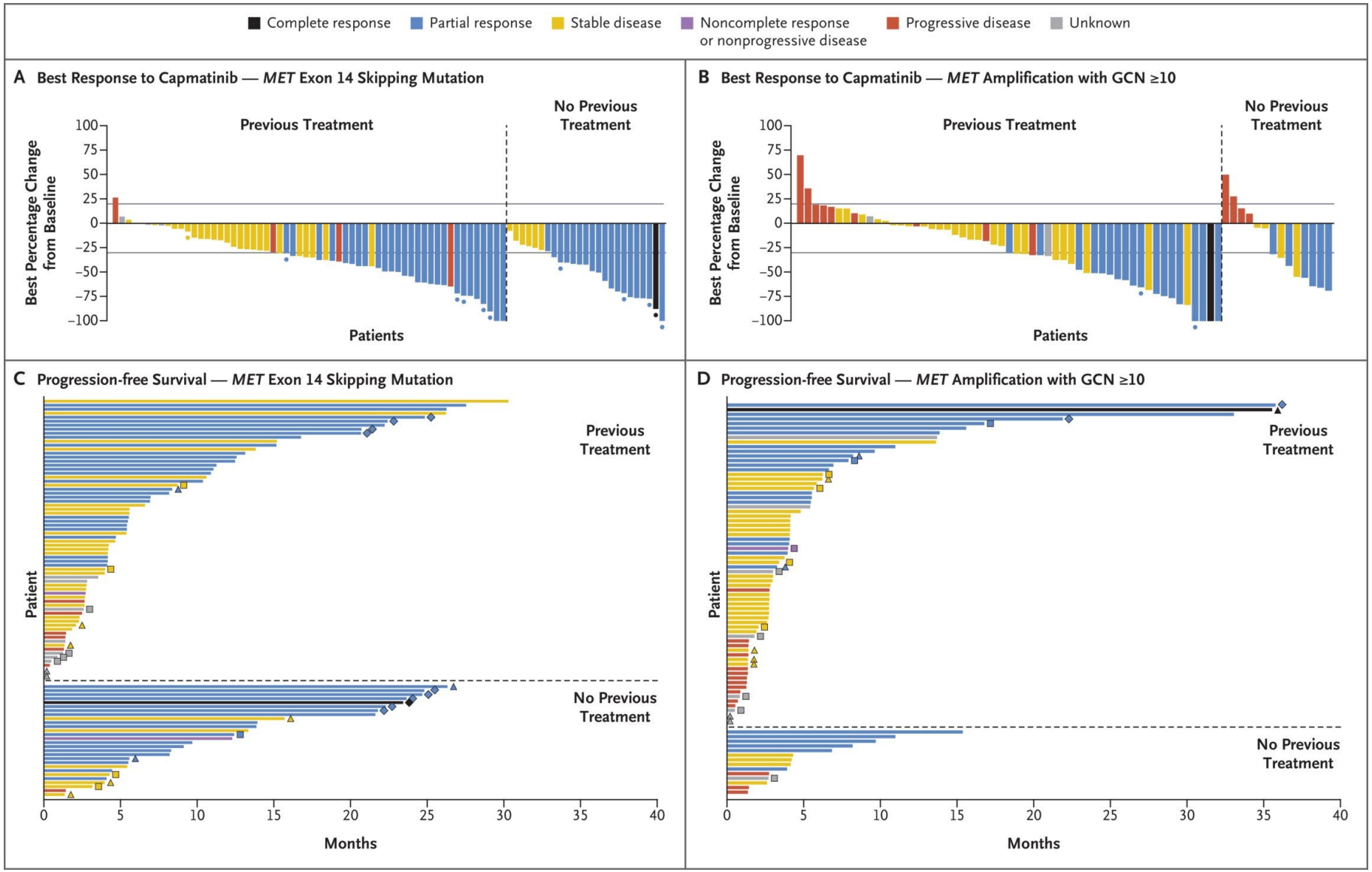
- **Different mechanisms of MET activation**
  - cMET overexpression, amplification, exon 14 skipping mutations, fusions, heterodimerisation
- **Convergent resistance mechanisms for several RTKs**
  - EGFR, KRAS, RET-rearranged NSCLC[1,2,3]
  - Significant cross-talk in pathways
- **Capmatinib and tepotinib (Class Ib) approved for MET exon 14 skipping mutations**
  - GEOMETRY[4]
    - **2/3L** ORR 41%, PFS 5.4 m
    - **1L** ORR 68% PFS 12.4 m
  - VISION[5]
    - **2/3L** ORR 47.7%, PFS 11.1 m
    - **1L** ORR 54.7%, PFS 15.3 m

Sarcomatoid Lung Cancer

Category	Drug	Status
TKI		
Type Ia	Crizotinib	Approved in ALK/ROS
Type Ib	Capmatinib Tepotinib	Approved Approved
Type II	Cabzantinib	Approved in RCC
Type III	Tivantinib	Failed phase III
Antibodies		
Anti HGF	Ficlatuzumab	Failed phase II
Anti cMET	Ornatuzumab	Failed phase III
cMET-EGFR Bispecific Ab	Amivantamab	Approved EGFR ex20ins

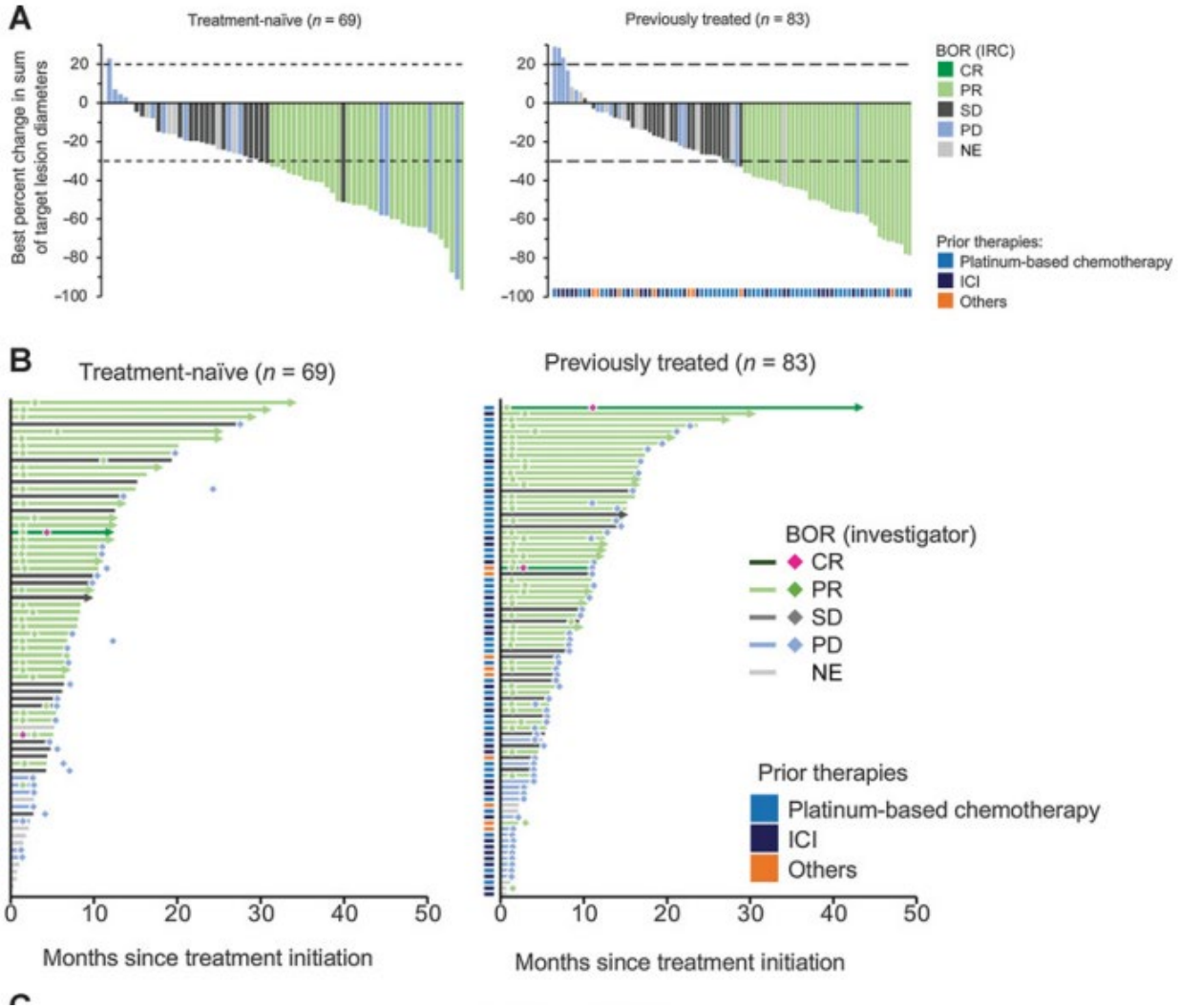
1. Chua et al. CCR 2021; 2. Awad et al. NEJM 2021; 3. Lin et al. Ann Oncol 2020; 4. Wolf et al. NEJM 2020; 5. Paik et al. NEJM 2020

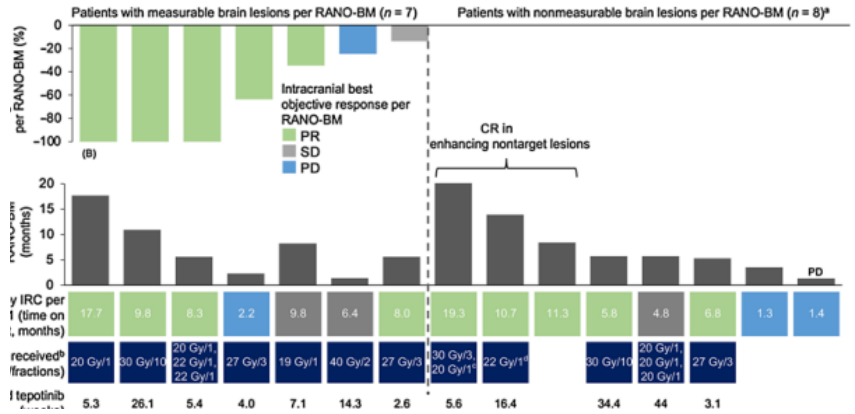
Capmatinib



Wolf, *NEJM 2020;383:944-957*

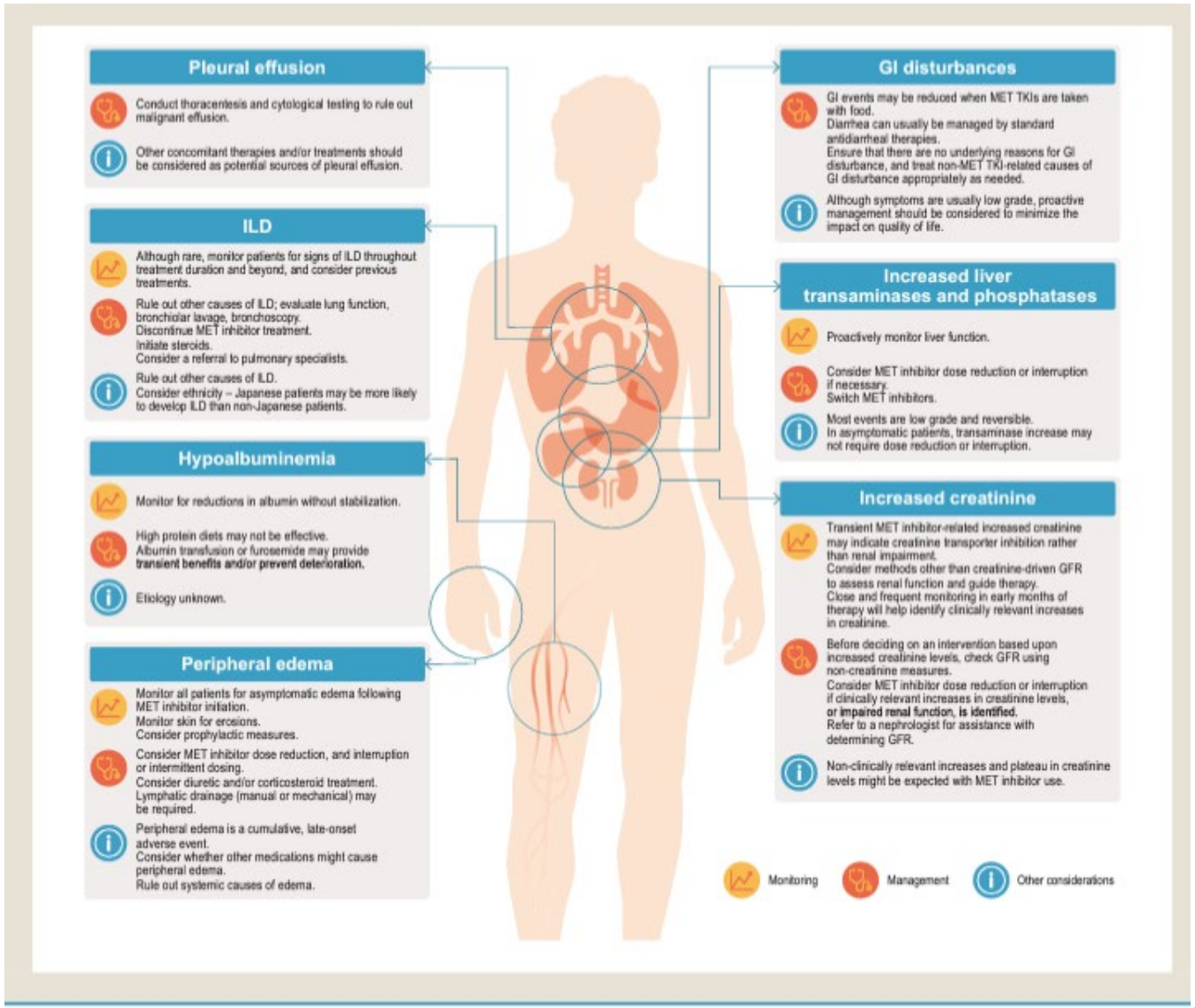
Tepotinib
Ph II, Vision trial





Le, *CCR, 2022:28:1117-1126*

Toxicity of MET TKI in *MET*ex14



Cortot, *Clinical Lung Cancer, 2022;23:195-207*

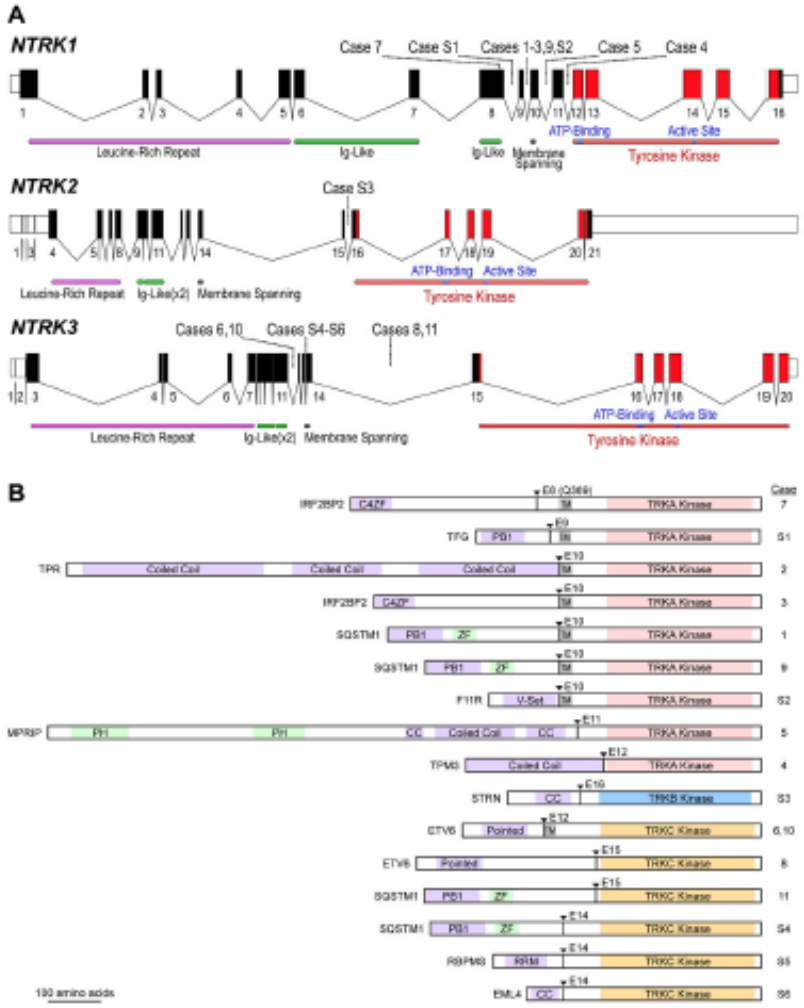
METex14 skipping mutation

	capmatinib		tepotinib	
	untreated	pretreated	unteated	pretreated
N	28	69	69	83
Dose	400 mg QD		450 OD	
ORR (%(95% CI)	68 (48 – 84)	41 (29-53)	45 (33-57)	45 (35-56)
Time to response	68% at 1st assessment	82% at 1st assessment		
DoR (mts (95% CI)	12.6 (5.6 – NE)	9.7 (5.6 -13)	10.8 (6.9- NE)	11.1 (9.5 – 18.5)
Intracranial RR	7/13, 4 CR		5/7, 3 CR	
Toxicity gr ¾	46%		24%	
Special Toxicity	Peripheral edema, nausea		Peripheral edema, pneumonitis	
				
				

This is not intended as a head-to-head comparison

Wolf, *NEJM 2020;383:944-957*
Le, *CCR, 2022:28:1117-1126*

NTRK fusions: A rare event in lung cancer

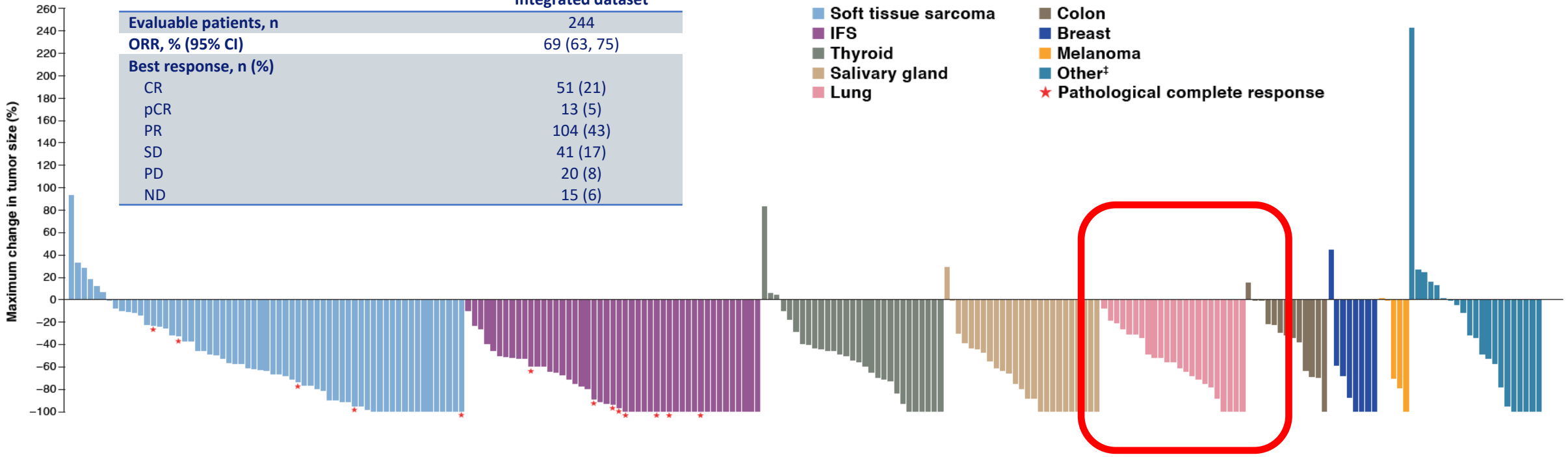


	MGH	MSKCC	Total	Frequency, % (95% CI)
NSCLC screened	1804	3068	4872	
NTRK1	2	4	6	0.12 (0.05-0.27)
NTRK2	0	1	1	0.02 (0.00-0.11)
NTRK3	2	2	4	0.08 (0.02-0.21)
All *NTRK* fusions	4	7	11	0.23 (0.11-0.40)

CI, confidence interval; MGH, Massachusetts General Hospital; MSKCC, Memorial Sloan Kettering Cancer Center; NSCLC, non-small cell lung cancer.
Farago AF, et al. *JCO Precis Oncol.* 2018:PO.18.00037.

Larotrectinib: Tumour response (N=234)

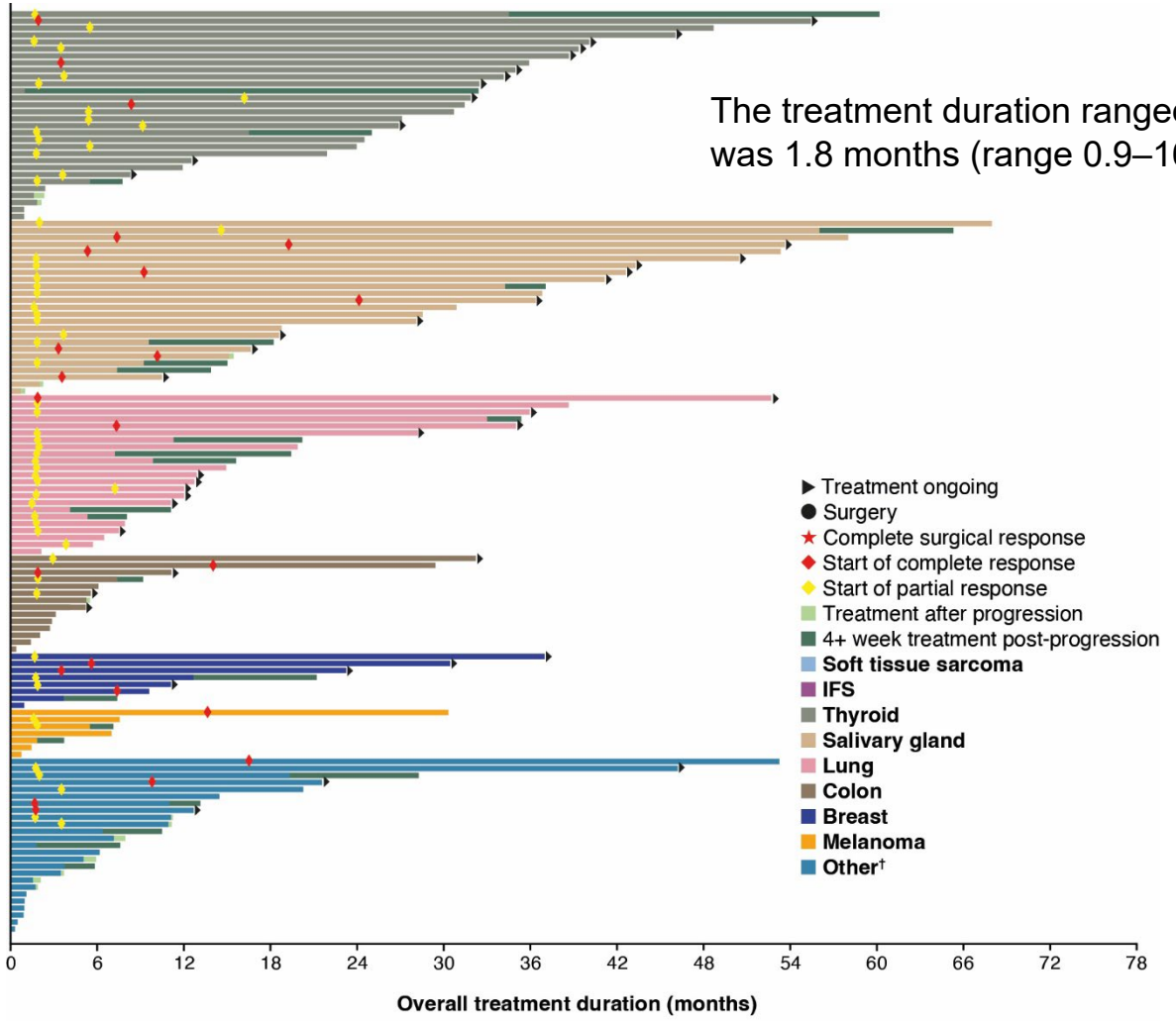
	Integrated dataset
Evaluable patients, n	244
ORR, % (95% CI)	69 (63, 75)
Best response, n (%)	
CR	51 (21)
pCR	13 (5)
PR	104 (43)
SD	41 (17)
PD	20 (8)
ND	15 (6)



CR, complete response; IFS, infantile fibrosarcoma; ND, not determined; ORR, overall response rate; pCR, pathological complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Drilon A, et al. *J Clin Oncol.* 2022;40(16_suppl):3100-3100.

Larotrectinib: Treatment duration



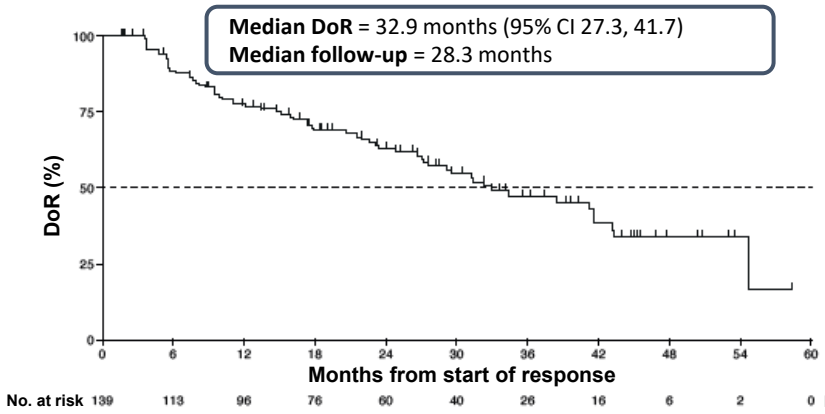
The treatment duration ranged from 0.1 to 67.9 months and median TTR was 1.8 months (range 0.9–16.2)

IFS, infantile fibrosarcoma; TTR, time to response.

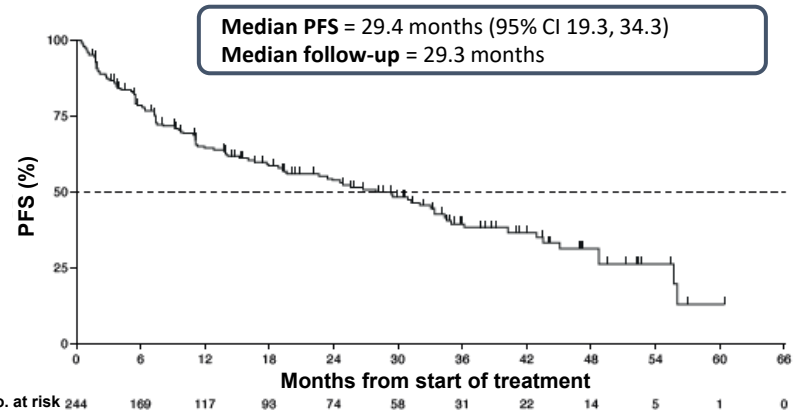
Drilon A, et al. *J Clin Oncol.* 2022;40(16_suppl):3100-3100.

Larotrectinib: Median duration of response: 32.9 MTS

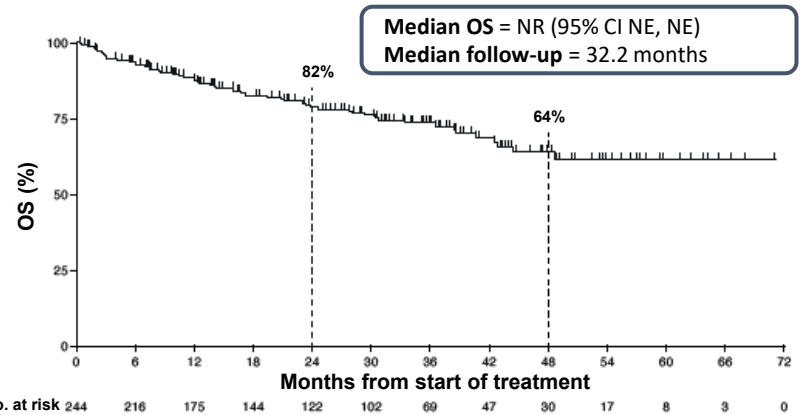
DoR



PFS



OS



Efficacy assessments for subset of patients enrolled with a minimum follow-up of 28 months*

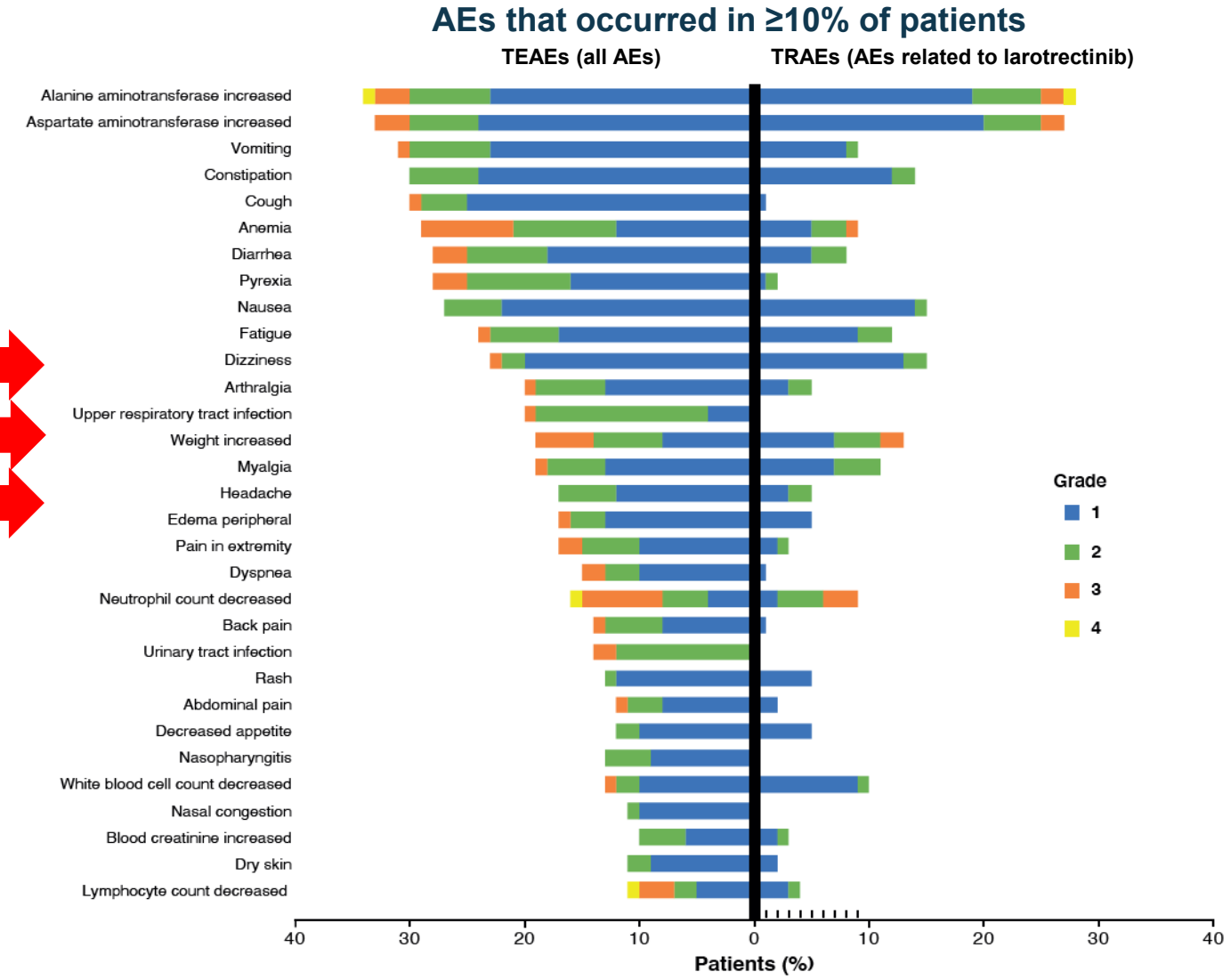
	Exploratory dataset
Evaluable patients, n	164
ORR, % (95% CI)	74 (67, 81)
Median DoR, months, (95% CI)	34.5 (27.6, 43.3)
Median follow-up, months	34.1

CI, confidence interval; DoR, duration of response; MTS, months; NE, non-estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Drilon A, et al. *J Clin Oncol.* 2022;40(16_suppl):3100-3100.

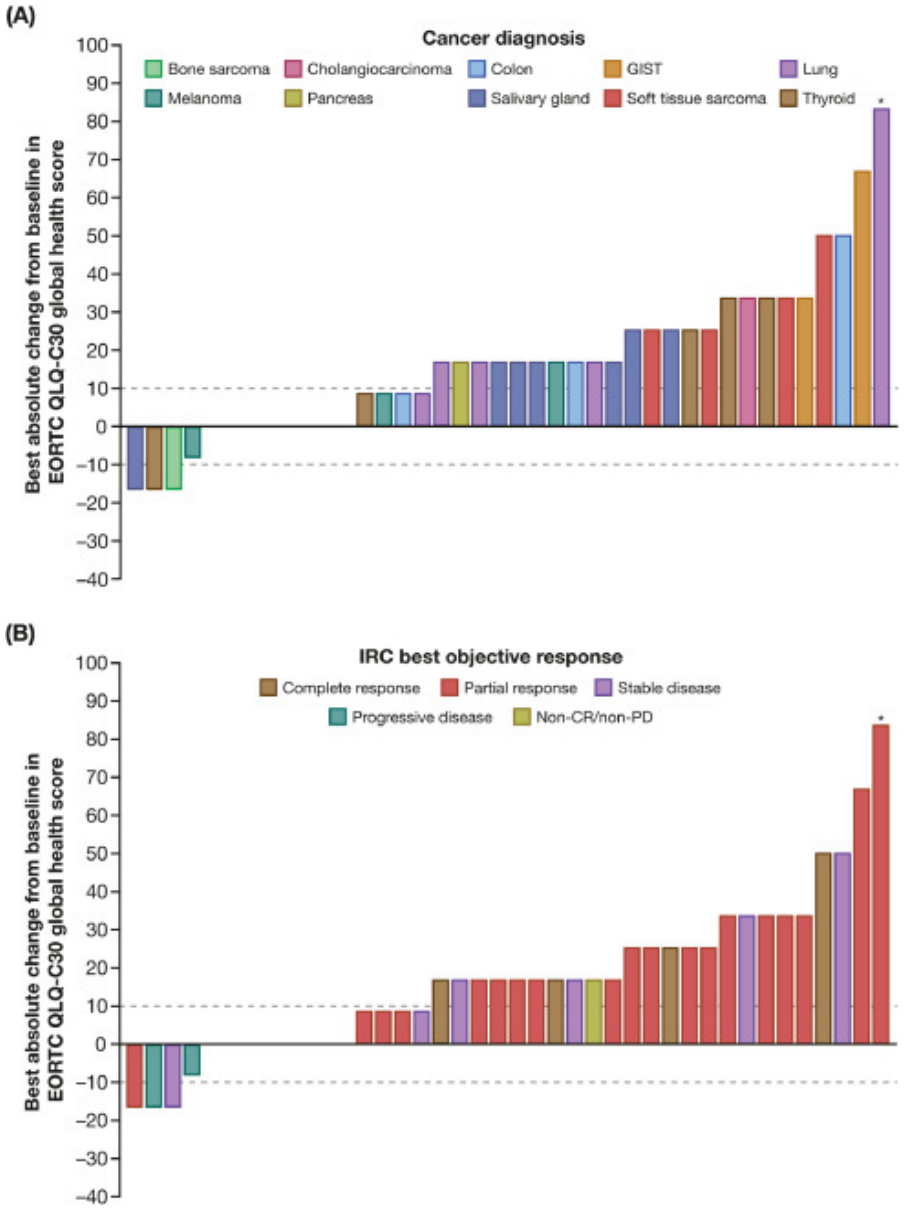
Acceptable toxicity; but on-target under reported?

- There were no new or unexpected safety signals, with a longer follow-up than the previous report and with 83 patients (34%) on larotrectinib treatment for ≥24 months
  - Fifty-three patients (20%) had grade 3 or 4 TRAEs
  - Five patients (2%) discontinued treatment due to TRAEs
    - Emotional poverty, hypoventilation, neutropenia, and decrease in neutrophil count occurred in one patient each
    - ALT increases and AST increases both occurred in one patient



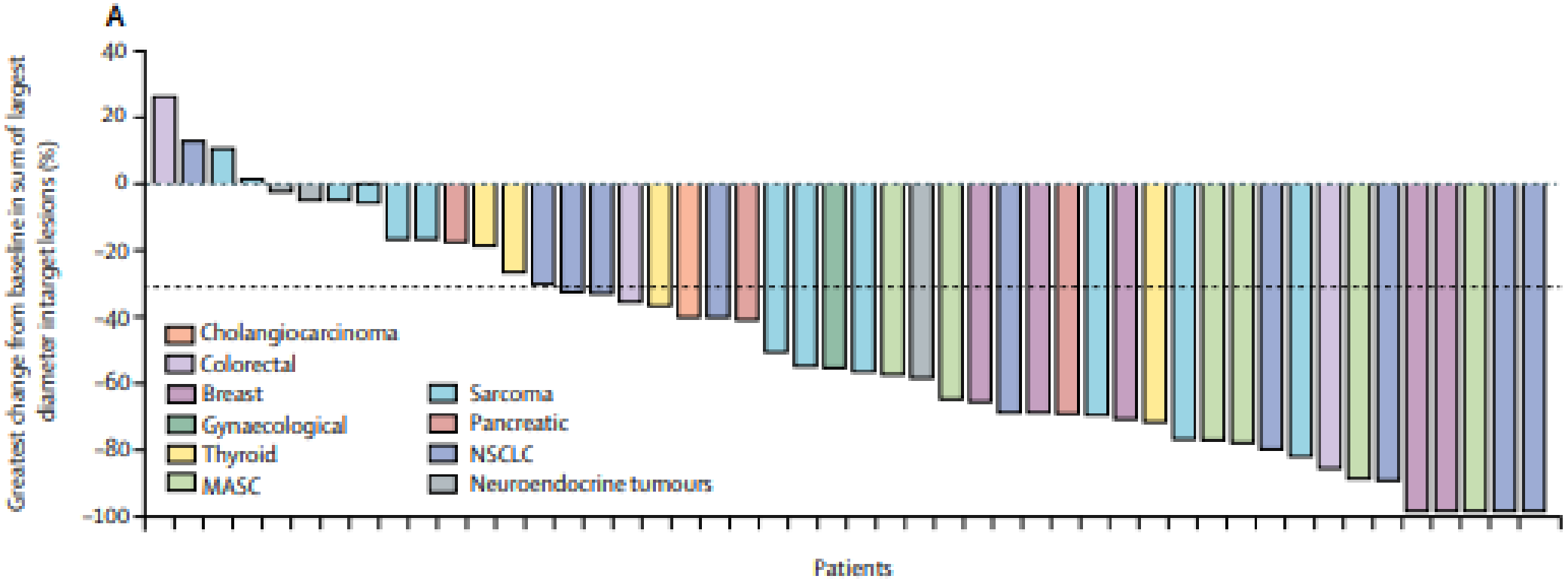
AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
Drilon A, et al. *J Clin Oncol.* 2022;40(16_suppl):3100-3100.

Larotrectinib: QOL



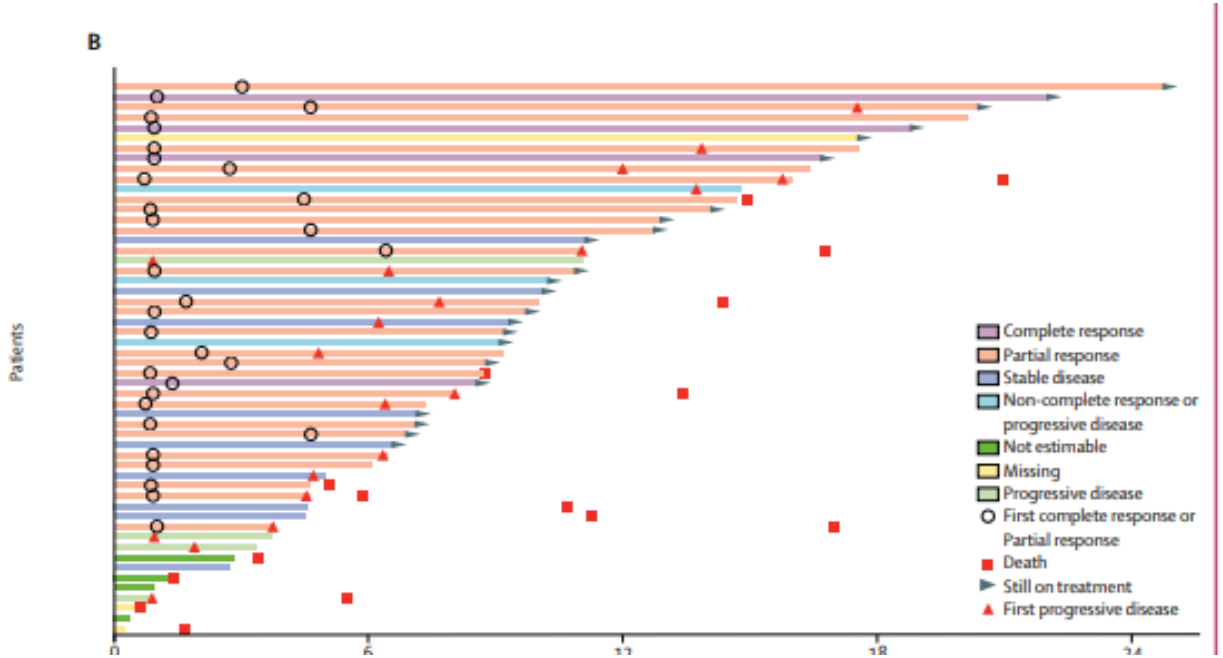
GIST, gastrointestinal stromal tumour; QOL, quality of life.
Kummar S, et al. *Curr Probl Canc.* 2021;45:100734.

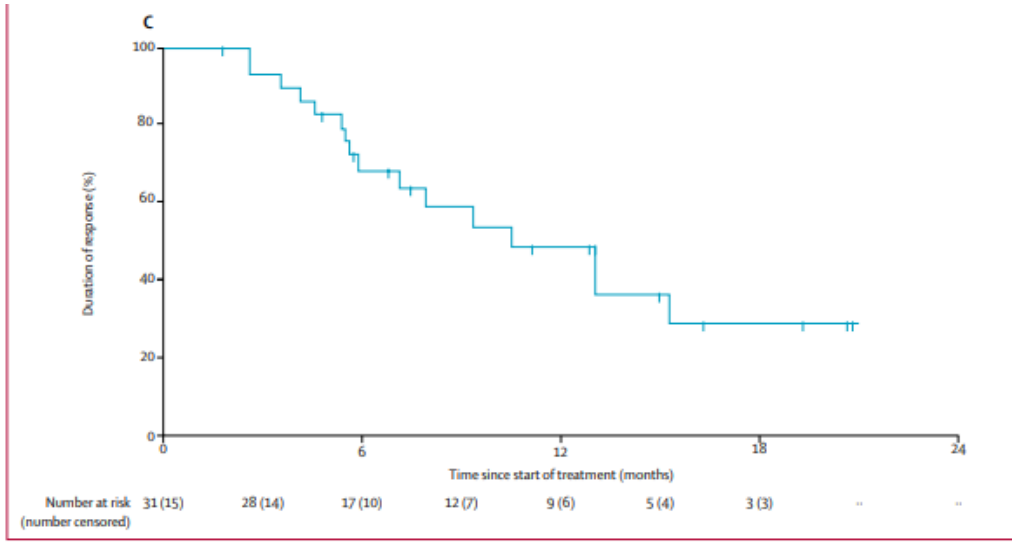
Entrectinib ORR: 57% (95% CI 43-71); N=54



CI, confidence interval; MASC, mammary analogue secretory carcinoma; NSCLC, non-small cell lung cancer; ORR, overall response rate.
Doebele RC, et al. *Lancet Oncol.* 2020;21:271–282.

Entrectinib: Median time to response ‘rapid’
Duration of response: 10 MTS (95% CI, 7.1 – NE)

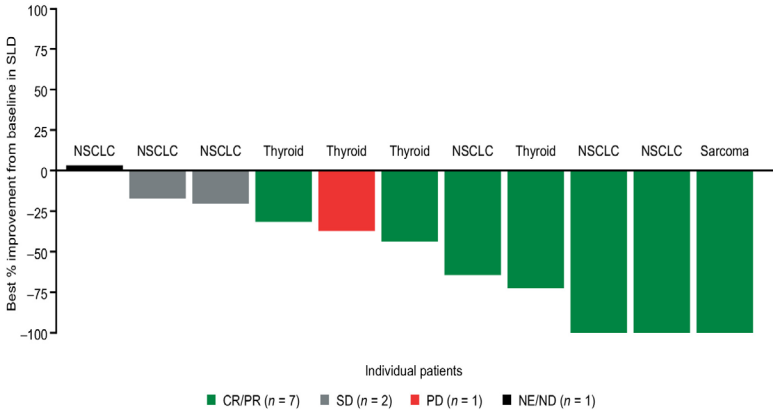


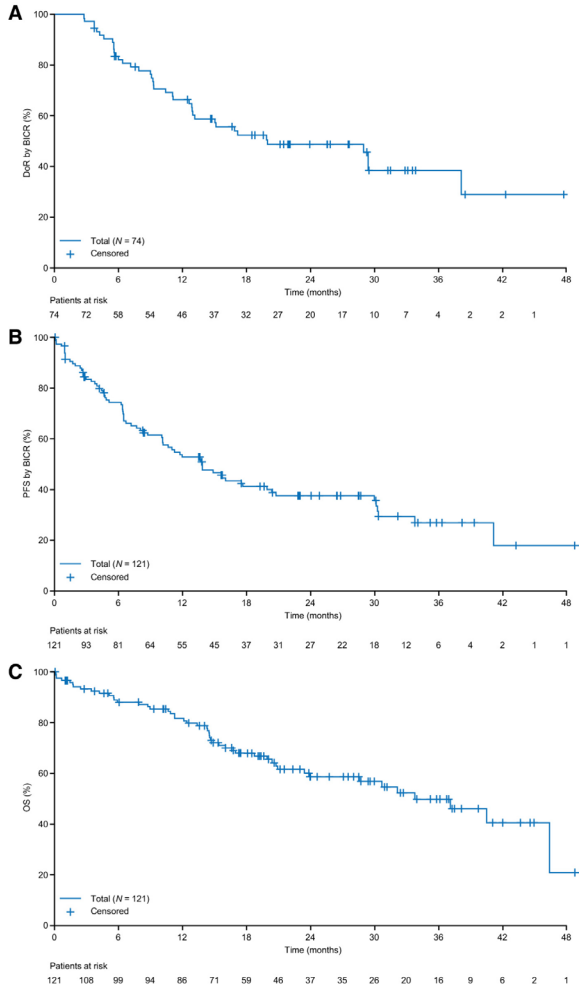


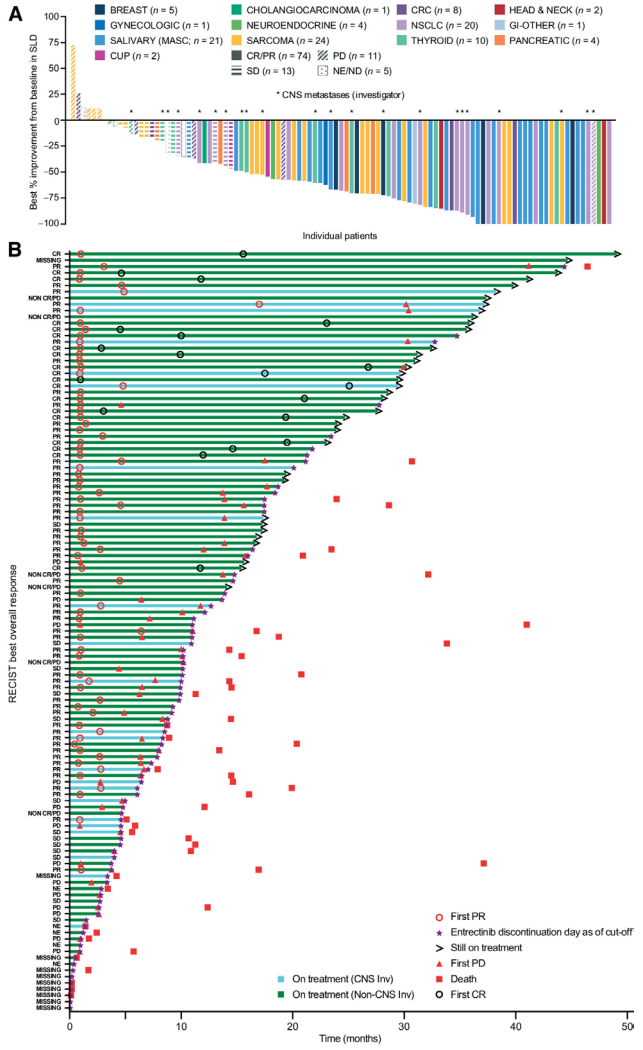
CI, confidence interval; MTS, months; NE, non-estimable
Doebele RC, et al. *Lancet Oncol.* 2020;21:271-282.

Update entrectinib: STARTRK-1 and STARTRK-2

Intracranial response







Demetri GD, et al. *Clin Cancer Res.* 2022;28:1302-1312.

Acceptable toxicity: But on-target under reported?
N=119

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Dose reductions: 15%

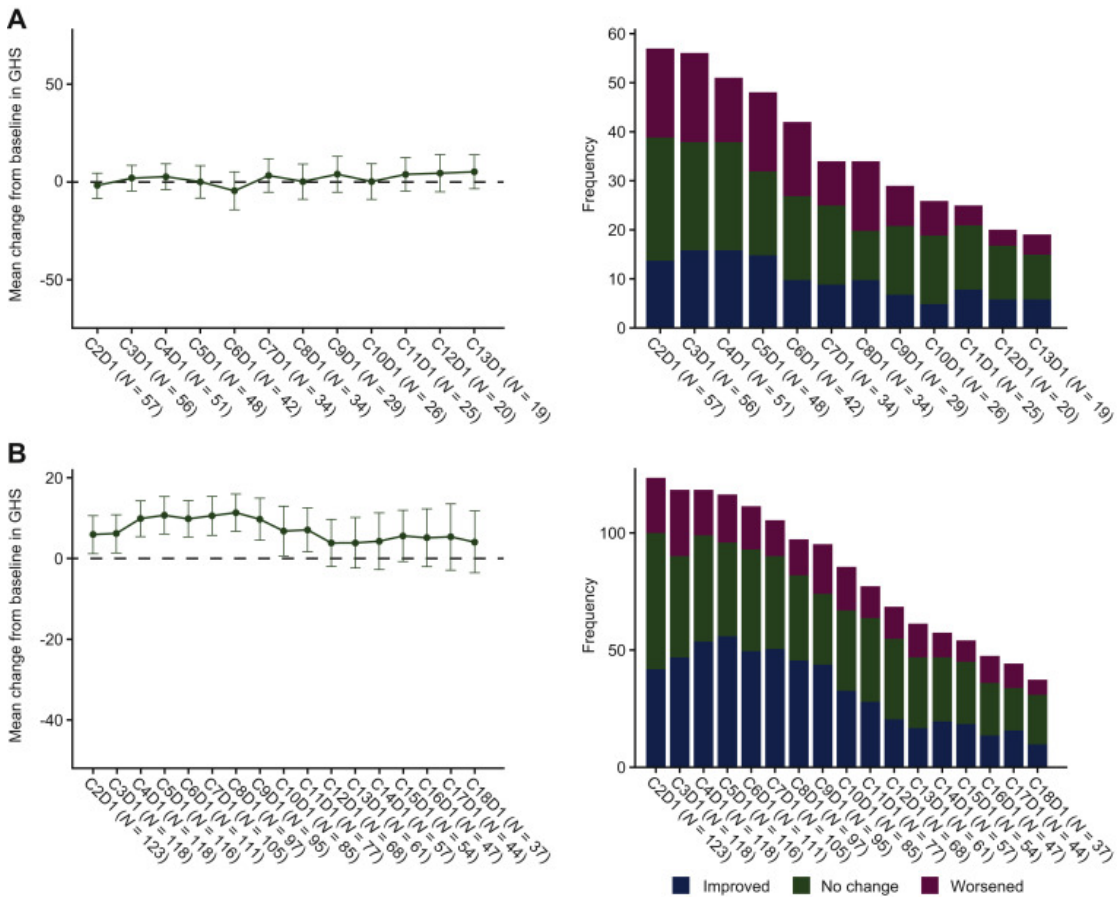
Table 2. Adverse events: Listed below are adverse events reported in at least 10% of the patients ($n = 119$) with advanced solid tumors who received entrectinib on either phase I trial (ALKA-372-001 or STARTRK-1) and that were deemed by the investigators to be related to study drug

Adverse event, *n* (%)	Grade 1	Grade 2	Grade 3	All grades ($n = 119$)
Fatigue/asthenia	28 (24)	22 (19)	5 (4)	55 (46)
Dysgeusia	47 (40)	3 (3)	0	50 (42)
Paresthesia	34 (29)	0	0	34 (29)
Nausea	29 (24)	4 (3)	0	33 (28)
Myalgia	23 (19)	4 (3)	0	27 (23)
Diarrhea	19 (16)	3 (3)	1 (1)	23 (19)
Vomiting	19 (16)	1 (1)	0	20 (17)
Arthralgia	12 (10)	6 (5)	1 (1)	19 (16)
Dizziness	14 (12)	5 (4)	0	19 (16)
Constipation	12 (10)	2 (2)	0	14 (12)
Weight increase	4 (3)	6 (5)	2 (2)	12 (10)

NOTE: There was only one Grade 4 treatment-related adverse event: eosinophilic myocarditis on STARTRK-1. No treatment-related Grade 5 events were reported.

Drilon A, et al. *Canc Discov.* 2017;7:400-409.

PROM STARTRK-2 entrectinib (ROS1 and NTRK)



Paz-Ares L, et al. *ESMO Open.* 2021;6:100113.

TRK-inhibitor: On-target toxicity

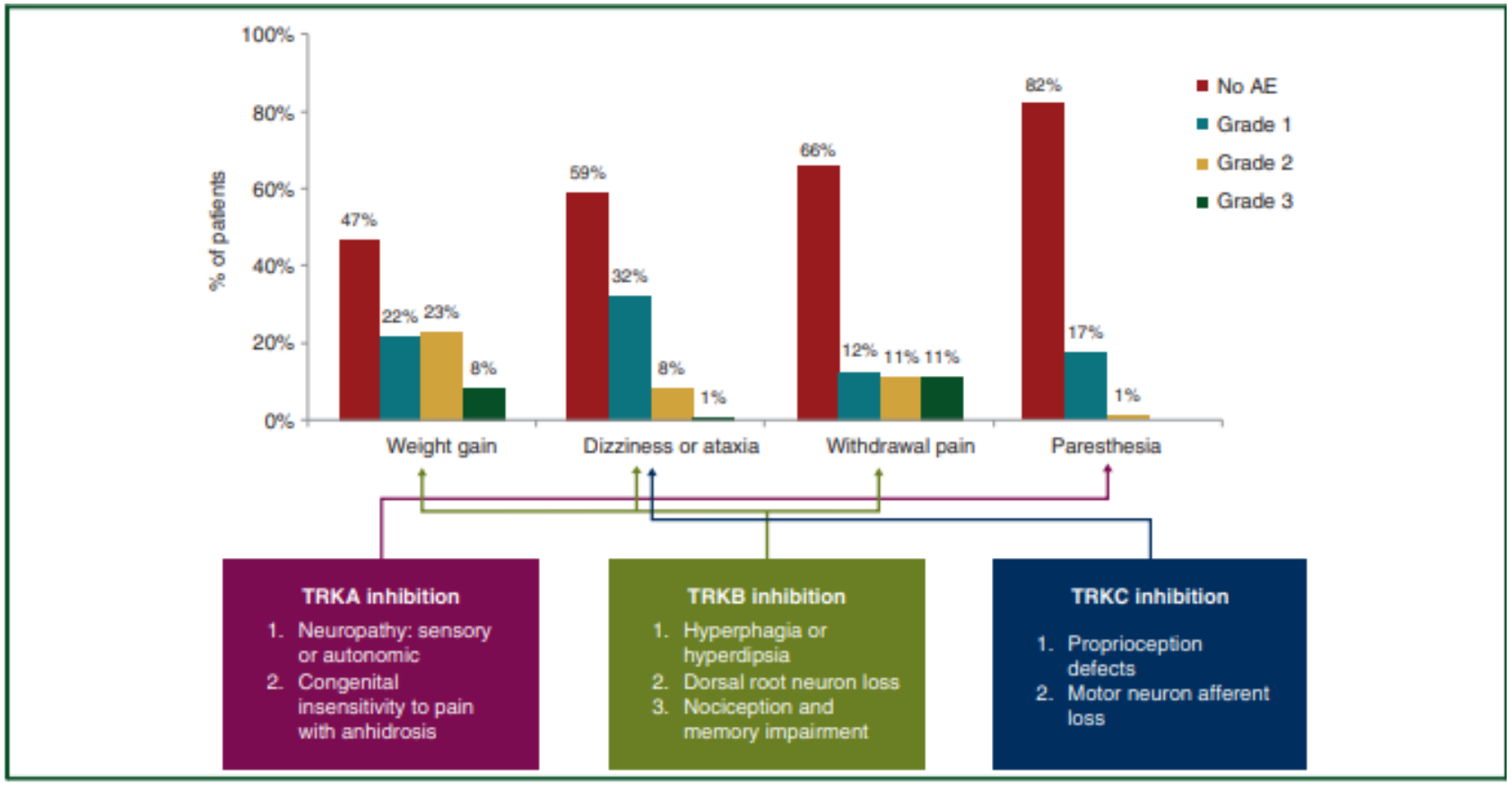


Figure 1. Neurologic adverse events observed with TRK inhibition.
The frequency of weight gain, dizziness with or without ataxia, withdrawal pain, and paresthesias are summarized. The frequency of each adverse event is displayed according to the worst grade the patient experienced during therapy. For withdrawal pain, only patients who had dose interruptions and were at risk for this event were

Liu D, et al. *Ann Oncol*. 2020;31:1207-1215.

Treatment of adverse events

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Table 2. Supportive medication

Adverse event	Agent(s)	Mechanism of action	Dose and schedule
Weight gain	Liraglutide	GLP-1 analog	0.6—3.0 mg once/day
	Orlistat	Inhibits fat absorption	60—120 mg three times/day
	Phentermine/topiramate combination	Increases norepinephrine release; GABA receptor agonist	3.75/23—15/92 mg once/day
	Lorcaserin	5-HT_{2C} receptor agonist	10 mg twice/day
	Naltrexone/bupropion combination	μ-Opioid receptor antagonist; dopamine and norepinephrine reuptake inhibitor	8/90—16/180 mg once or twice/day
	Metformin	Modulates hypothalamic appetite regulatory centers	500—2000 mg once/day
Dizziness (ataxia or vertigo)	Meclizine	H_1 histamine receptor antagonist, suppresses vestibular stimulation, anticholinergic	25—50 mg once/day
	Scopolamine	Antagonizes histamine and serotonin	1 Patch every 3 days
Dizziness (orthostasis)	Midodrine	α_1 Adrenergic receptor agonist, increases vascular tone	5—10 mg three times/day
	Fludrocortisone	Mineralocorticoid	0.05—0.2 mg once/day
	Droxidopa	Metabolized to norepinephrine, induces vasoconstriction	100 mg three times/day (1.8 g/day maximum)
Withdrawal pain	Nonsteroidal anti-inflammatory agents	COX-1/COX-2 inhibitors	Per agent/label
	Opioids	Opioid receptor agonists	Per label
	Gabapentin/pregabalin	GABA analog	Per label

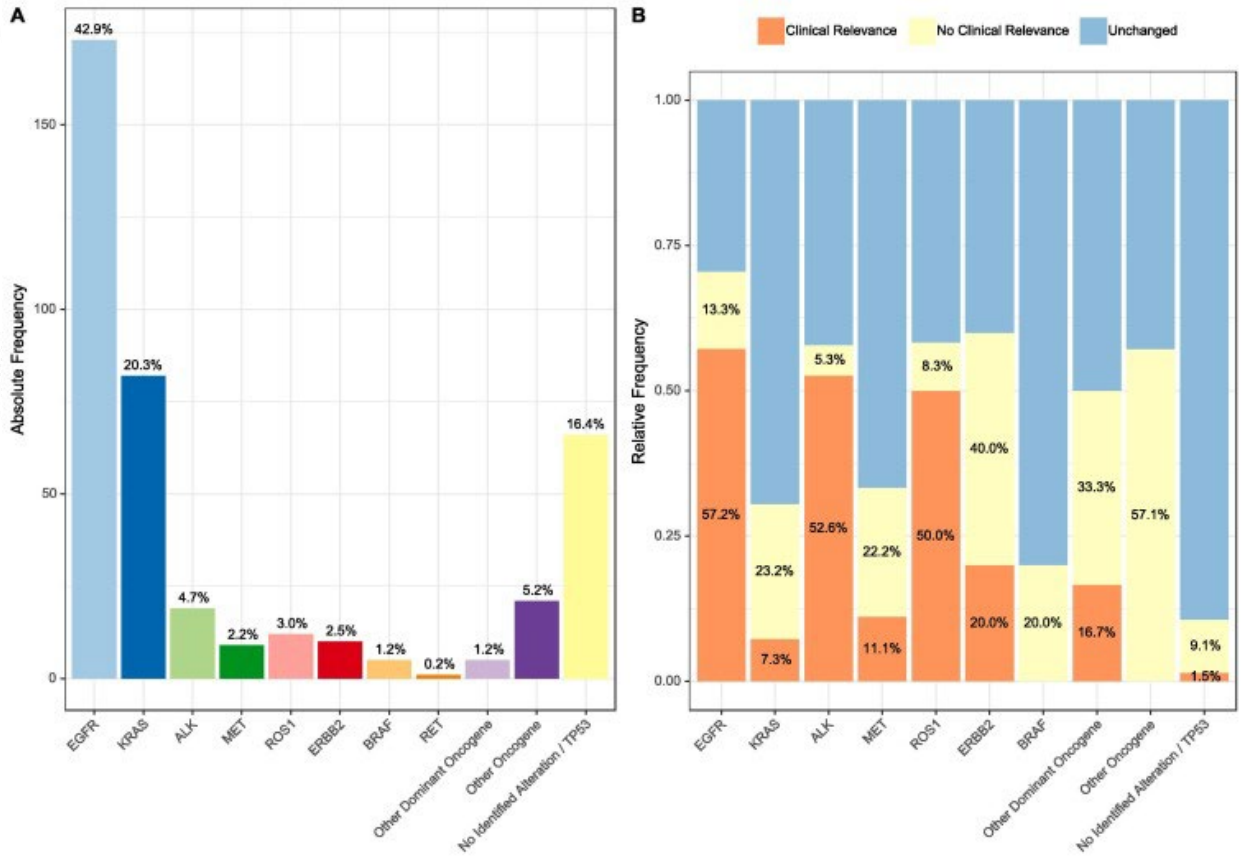
COX, cyclo-oxygenase; GABA, gamma-aminobutyric acid; GLP-1, glucagon-like peptide 1.
Liu D, et al. *Ann Oncol.* 2020;31:1207-1215.

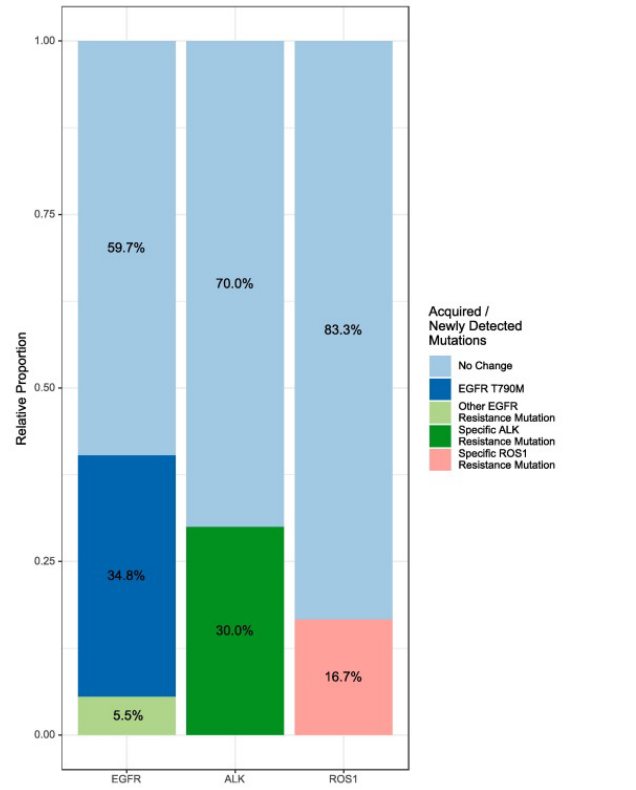
Treating rare mutations: Efficacy assessments

	LAROTRECTINIB[1,2]	ENTRECTINIB[3]
Overall response	69% (95% CI 63-75)	61% (95% CI 51.9-69.9)
Early response/ time to response	1.8 mts (range 0.9-16.2)	0.95 mts
Durable response	32.9 mts (95% CI 27.3-41.7)	20.0 mts (95% CI 13.0-38.2)
CNS activity (RR)	8/10	15/26
PFS	29.4 mts (95% CI 19.3-34.3)	13.8 mts (95% CI 10.1-19.9)
Tolerability: Grade 3-4	20%	41.5%
		
		

This is not intended as a head-to-head comparison.
CI, confidence interval; CNS, central nervous system; PFS, progression-free survival; RR, response rate.
1. Drilon A, et al. *J Clin Oncol.* 2022;40(16_suppl):3100-3100; 2. Drilon A, et al. *J Clin Oncol.* 2022;40(16_suppl):9024-9024; 3. Demetri GD, et al. *Clin Cancer Res.* 2022;28:1302-1312.

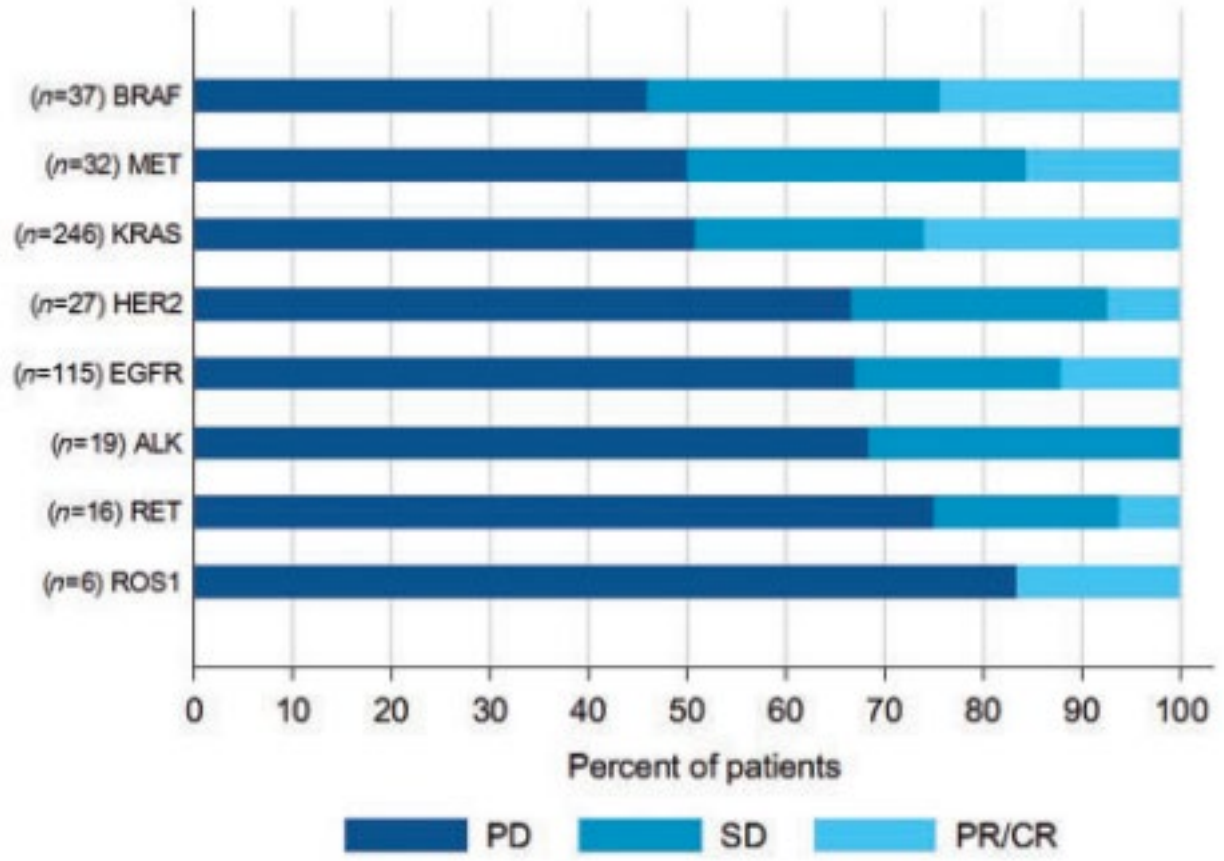
Rare mutations AND resistance: rebiopsy!





Scheffler, *Lung Cancer, 2022;168:10-20*

Immunotherapy?



Mazieres, Ann Oncol 2019;30”1321

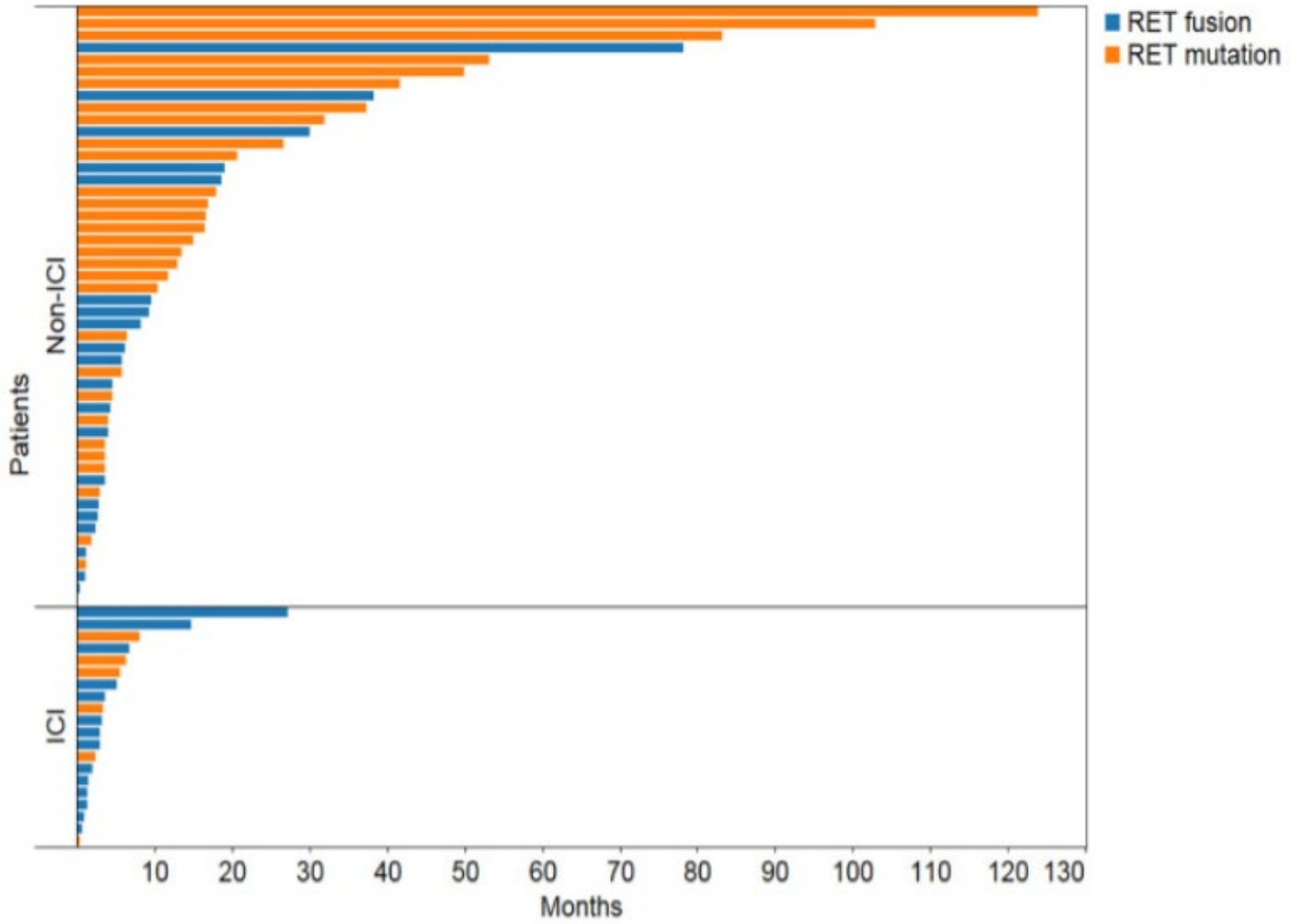
TABLE 3 | Efficacy of ICIs in NSCLS with *c-MET* mutations.

Reference	Characteristics	ORR, %	mPFS, months	mOS, months since start of ICI
Sabari JK. et al. (12)	*cMET exon 14* skipping mutation (n=147)	17	1.9	18.2
Mazieres J., et al. (31)	*cMET exon 14* skipping mutation and *cMET* amplification (n=36)	49	3.4	18.4
Guisier F., et al. (47)	*cMET* mutant (n=30)	36	4.9	13.4
Dudnik- E., et al. (46)	*cMET exon 14* skipping mutation (n=148)	12	4	NR (not reached)
	cMET amplification (n=54)	25	4.9	NR (not reached)
Mayenga M., et al. (56)	*cMET exon 14* skipping mutations, 2nd line immunotherapy (n=13)	46.2		

ICIs, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; ORR, overall response rate; mPFS, median progression-free survival; mOS, median overall survival.

Seegobin et al, Frontiers in Oncol 2021;11

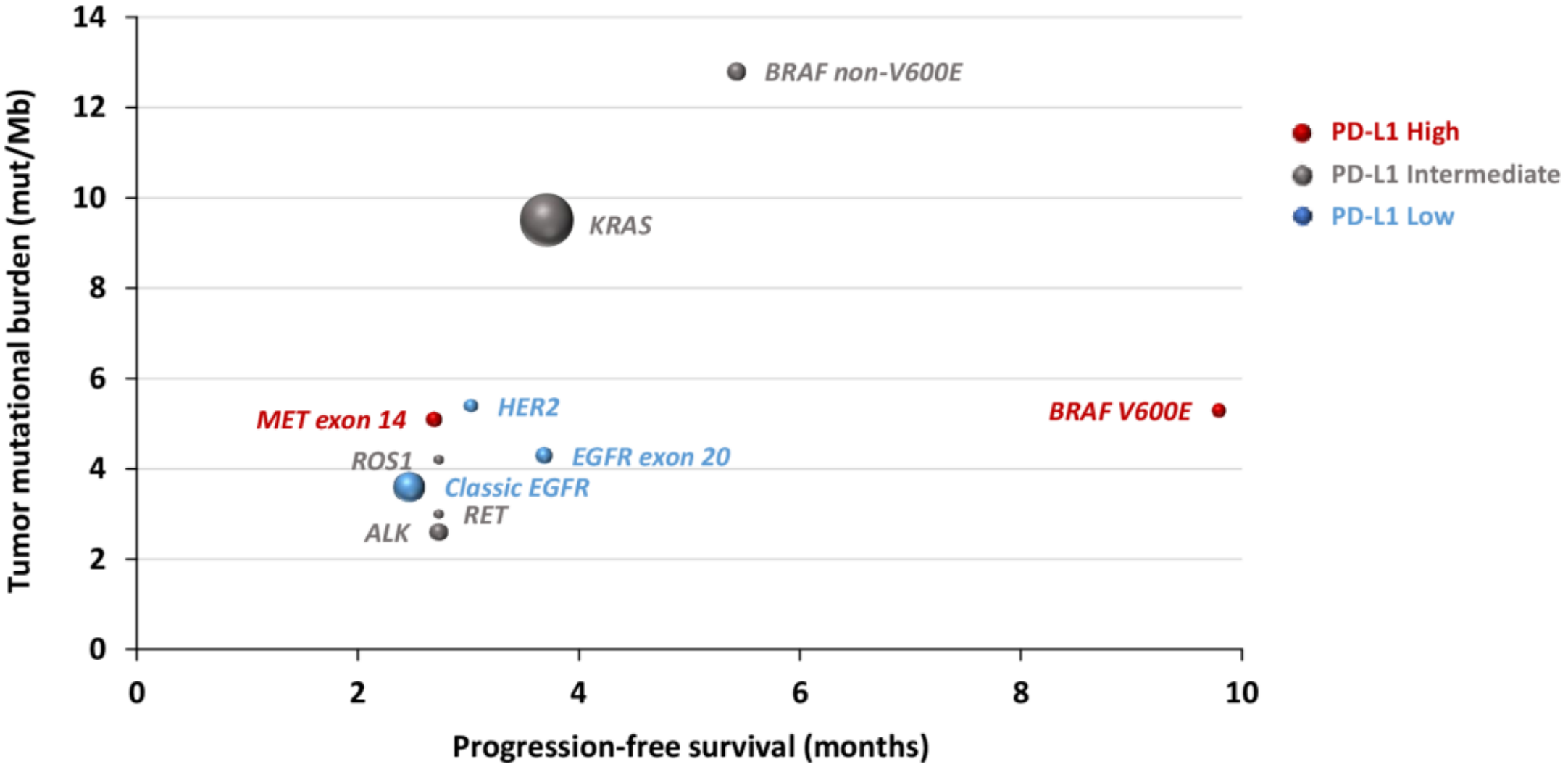
Immunotherapy



Retrospective review MD Anderson
Referal phase I

Risk for treatment discontinuation
HR=0.31, 95% CI 0.16-0.62

Hegde, *ESMO Open 2020;5*



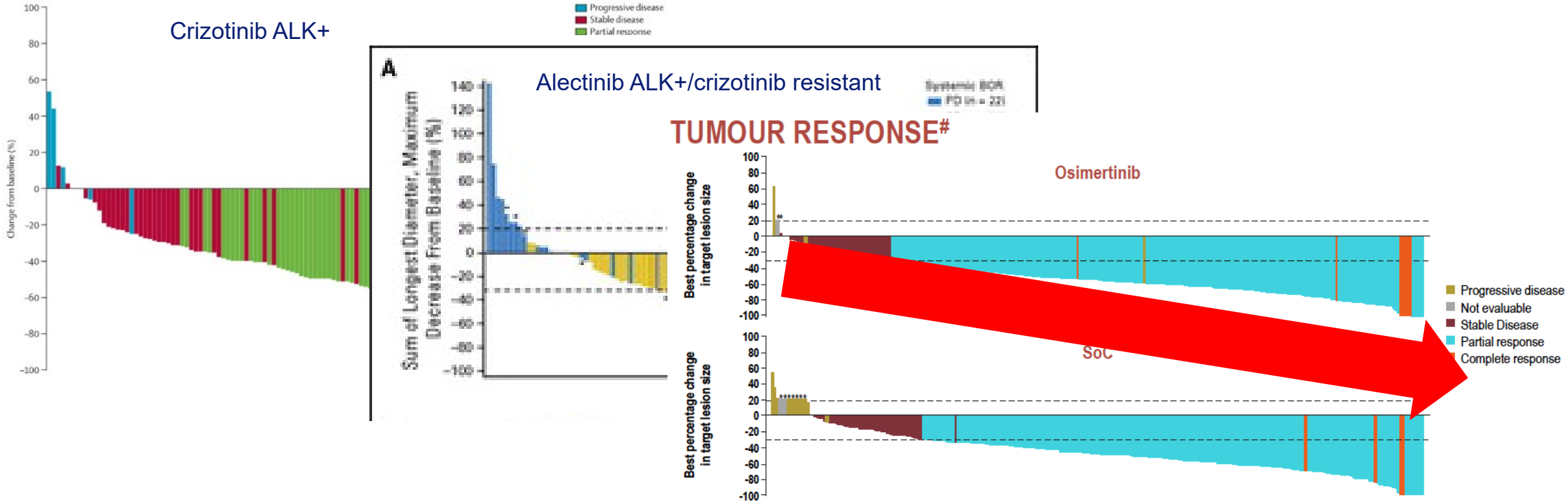
Negrao et al, J Immunother Cancer 2021;9:e002891

Rare disease ----→>>>> RCT?

Erasmus MC Cancer Institute

	DRUG	Trial name	number	N		comparator
RET fusion	praseltinib	AcceleRET	NCT04222972	226	1:1	Platinum=based chamo +/- pembrolizumab
RET fusion	Selpercatinib	LIBRETTO-431	NCT04194944	250	1:1	Platinum-based + pemetrexed +/- pembrolizumab
*MET*ex14 skipping	Capmatinib	GeoMetry-III	NCT04427072	90	2:1	docetaxel

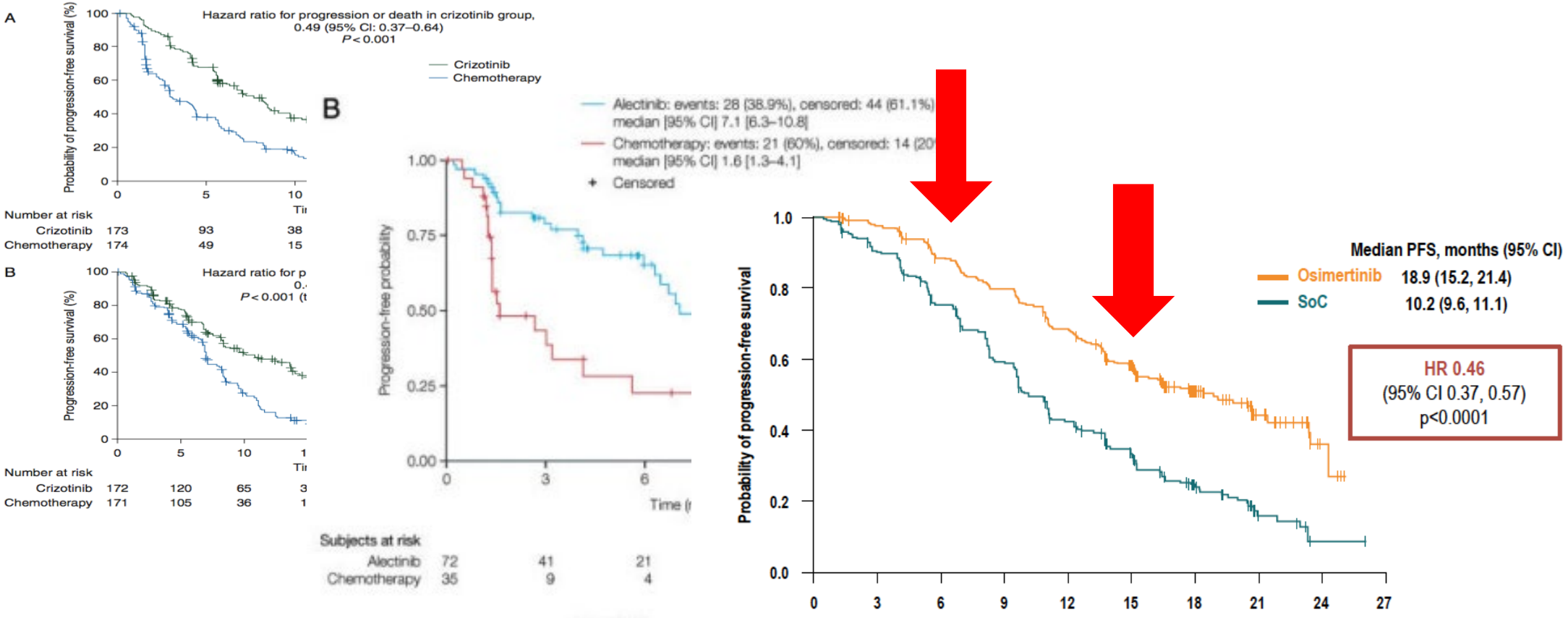
The typical “right target – right drug” waterfall plot



Camidge DR, et al. *Lancet Oncol.* 2012;13:1011-1019; Ou SHI, et al. *J Clin Oncol.* 2016;34:661-668; Ramalingam S, et al. Presented at ESMO 2017. Abstract LBA2_PR.

Erasmus MC Cancer Institute

The typical “right target – right drug” phase III PFS curve



CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; SoC, standard of care.

Shaw AT, et al. *N Engl J Med.* 2013;368:2385-2394; Novello, *Ann Oncol.* 2018;29:1409; Soria JC, et al. *N Engl J Med.* 2018;378:113-125.

Other mutations

Clinical equipoise, also known as **the principle of equipoise**, provides the ethical basis for medical research that involves assigning patients to different treatment arms of a clinical trial.The term was first used by Benjamin Freedman in 1987. In short, clinical equipoise means that there is genuine uncertainty in the expert medical community over whether a treatment will be beneficial.

Global Lung Cancer Academy

Tumor Board Discussion

Moderator: Corey Langer, MD, FACP

Case presenters: May-Lucie Meyer, MD, and Xander Verbeke, MD

Global Lung Cancer Academy

Patient Case 1

May-Lucie Meyer, MD

ALK

Case Presentation

May-Lucie Meyer, MD

Gustave Roussy, Villejuif (France)

Disclosure

- I have no conflicts of interest to declare

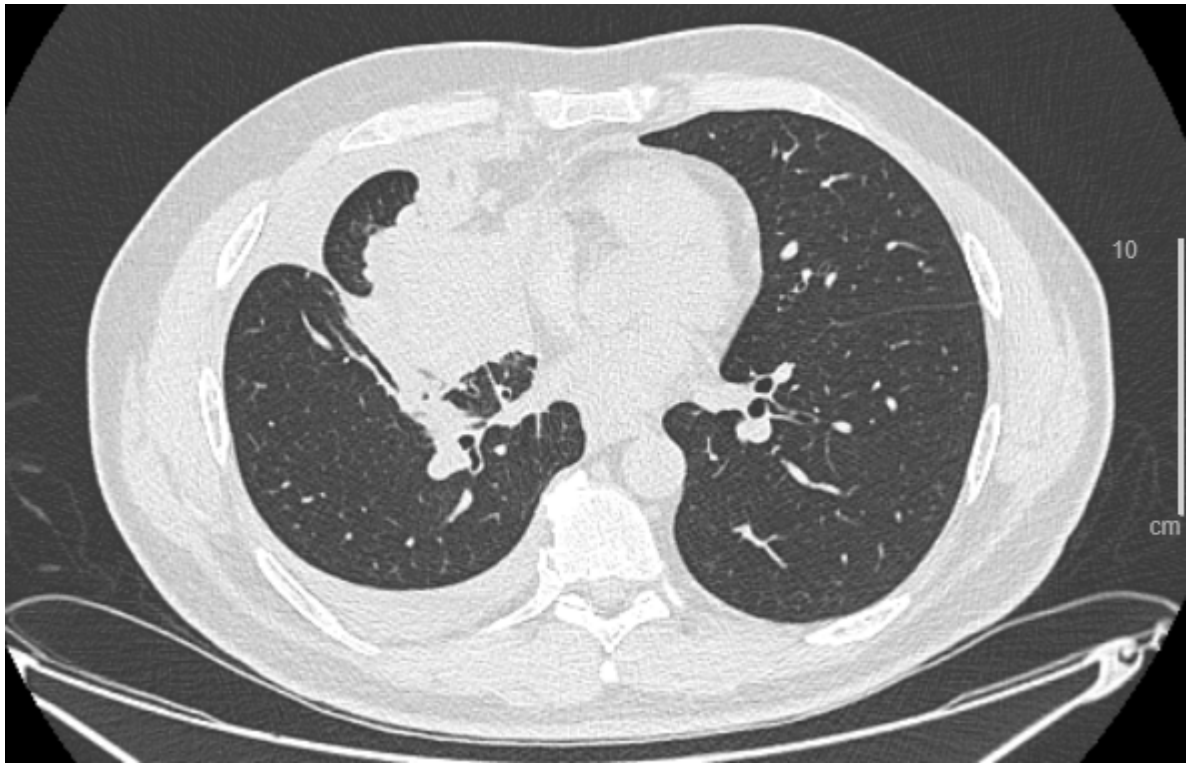
The Patient

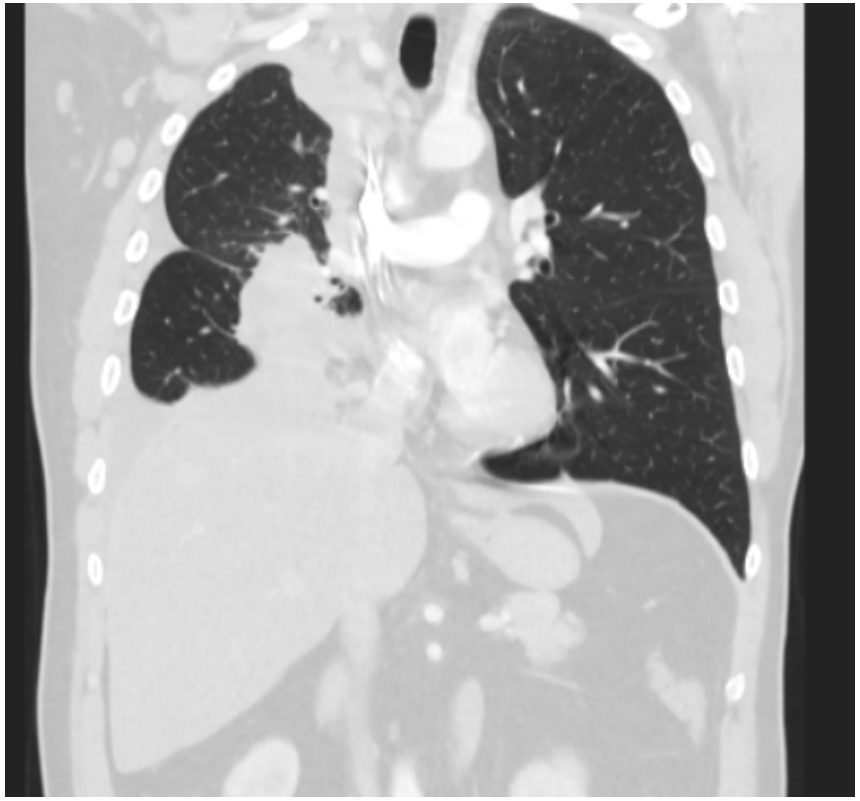
- 55-year-old man, reports increasing dyspnea
  - Arterial hypertension
  - Occasional smoker, <10 packs/year
  - Familial history: brother with pleural mesothelioma
  - No asbestos exposure
  - Lives in Martinique

Clinical Exam

- PS 0, good general condition
- Normal vital signs, SpO2 95% breathing air
- Physiologic auscultation, no palpable adenopathy

CT Scan September 15, 2020





- **PET-CT showed lung, pleural, nodal, and bone lesions**
- Normal brain MRI

Fibroscopy and Biopsy October 20, 2020

- Adenocarcinoma, TTF-1 positive, *ALK* positive, PD-L1 negative

Diagnosis

- Lung adenocarcinoma, T4N3M1c, stage IV, *ALK* positive on IHC, PD-L1 negative

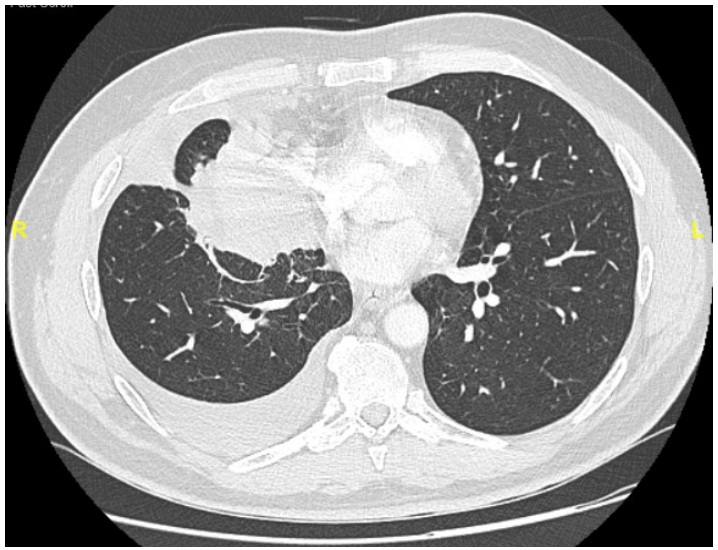
What Do You Do?

- Start chemotherapy + immunotherapy
- Start TKI
- Start 2 cycles of chemotherapy doublet, ask for molecular biology, and adapt
- Wait for molecular biology before starting any treatment

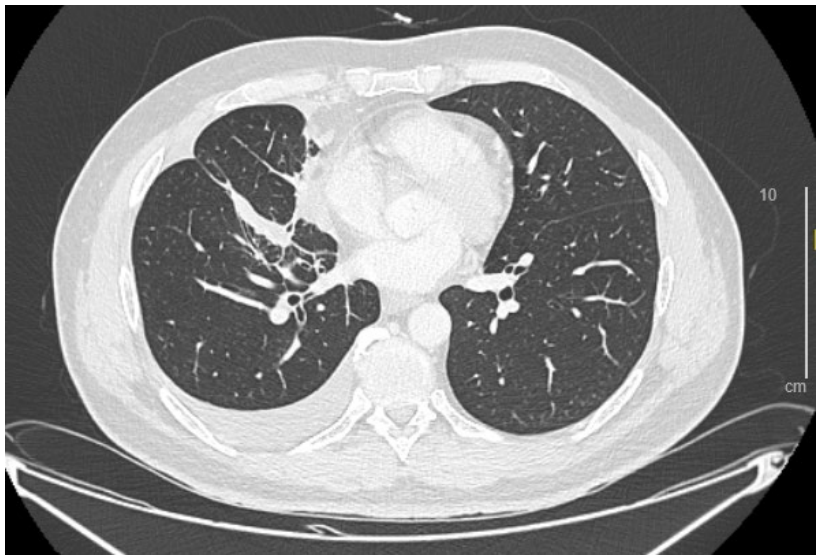
First-Line Treatment

- Alectinib 600 mg bid, started October 30, 2020
- Good tolerance
- Toxicities: asthenia G1, photosensitivity G1

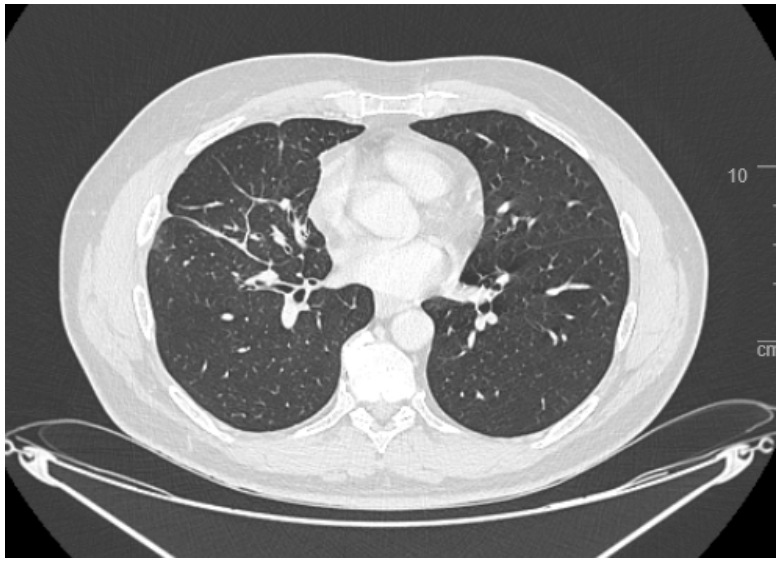
Evolution on Alectinib



September 22, 2020



December 23, 2020

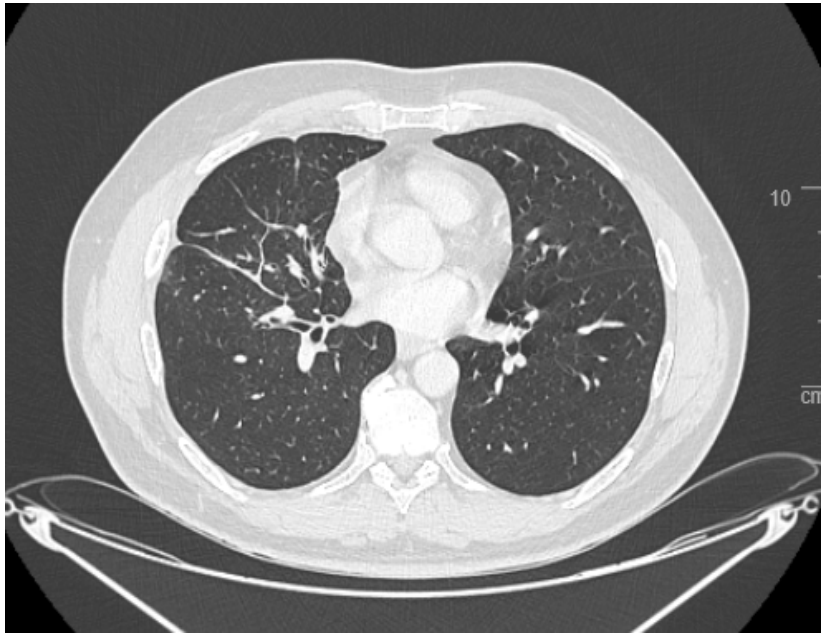


May 17, 2021

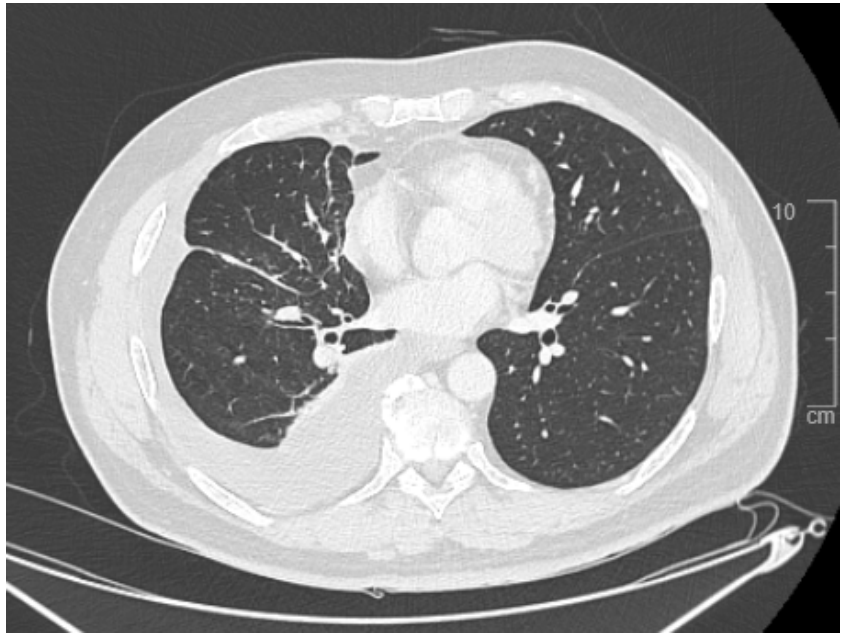
After 18 Months of Treatment. . . .

- Patient still in good general condition, but reports cough grade 1

After 18 Months of Treatment. . . .

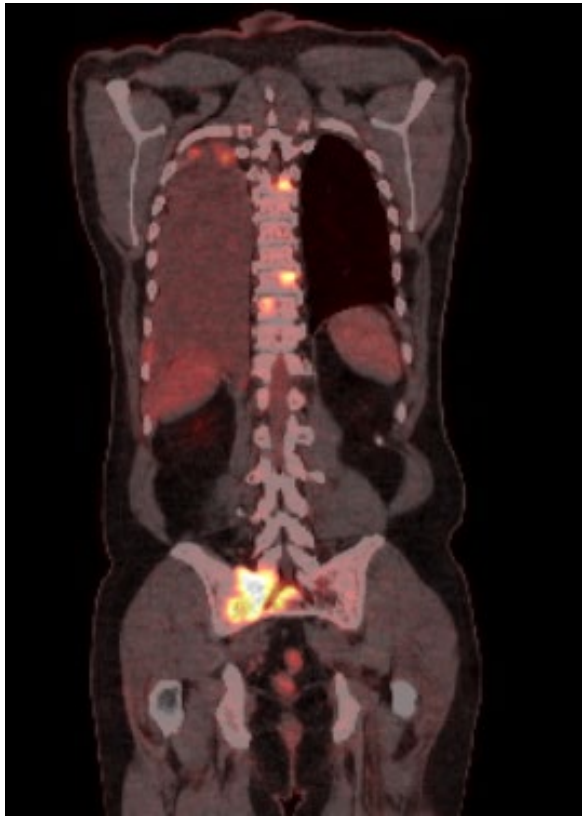


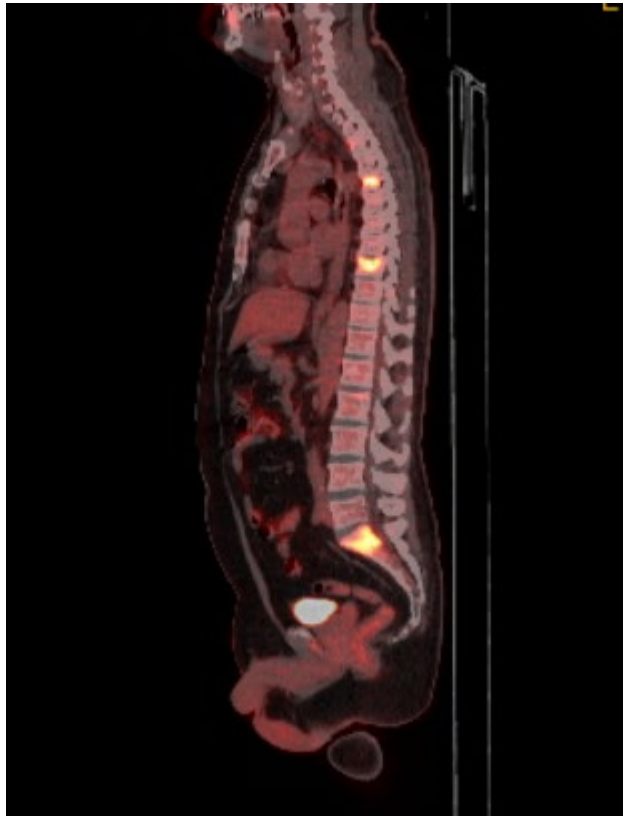
May 17, 2021 (nadir)

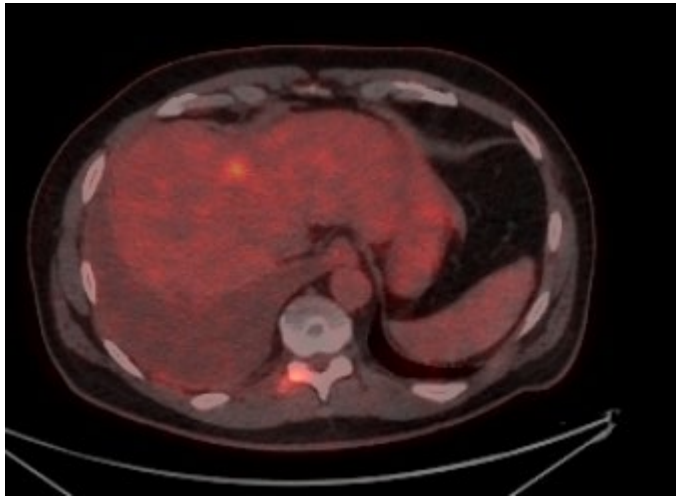


April 27, 2022

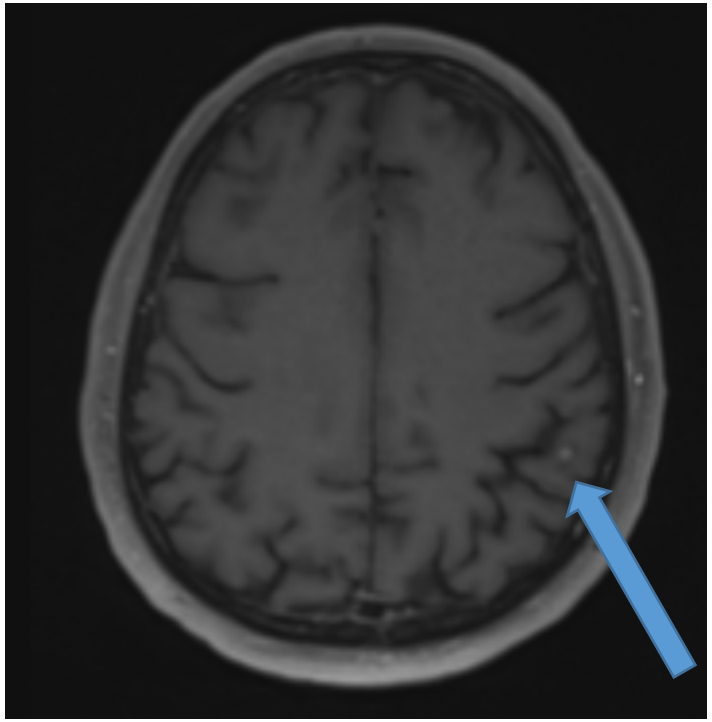
PET-CT May 13, 2022

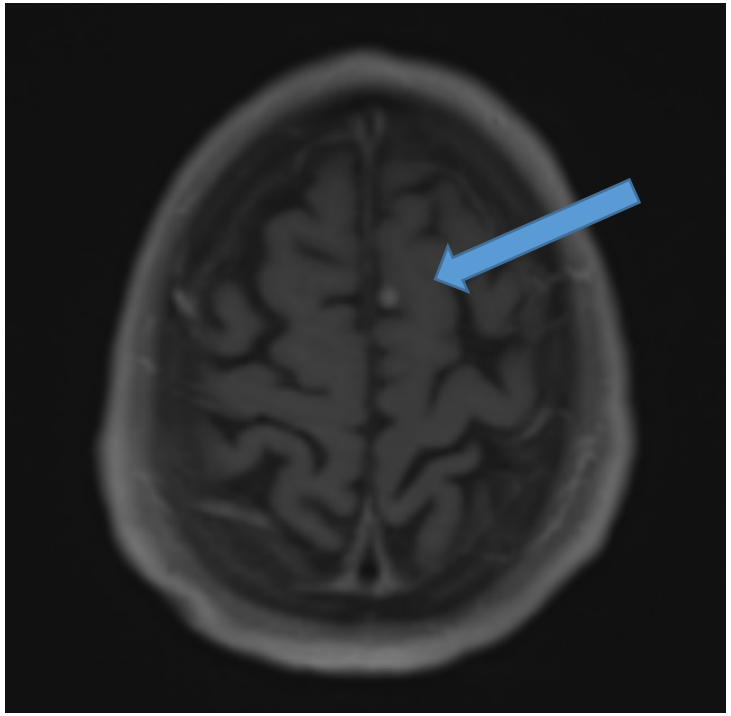






Brain MRI May 13, 2022





Liquid Biopsy May 12, 2022

- FoundationOne NGS assay

Genomic Signatures

Blood Tumor Mutational Burden - 0 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Elevated Tumor Fraction Not Detected

Gene Alterations

For a complete list of the genes assayed, please refer to the Appendix.

ALK EML4-ALK fusion

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Alectinib** (p. 6), **Brigatinib** (p. 6), **Ceritinib** (p. 7), **Crizotinib** (p. 8), **Lorlatinib** (p. 9)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 10)

What Do You Do?

- Continue alectinib; radiation to bone, liver, and brain lesions
- Stop alectinib, start lorlatinib
- Stop alectinib, start lorlatinib, and radiation to the brain
- Stop alectinib, start chemotherapy

What We Did

- Lorlatinib 100 mg started on June 1, 2022

After 3 Weeks of Treatment

- Decrease of cough and dyspnea
- Visual hallucinations, depression with suicidal thought

How Do You Adapt the Treatment?

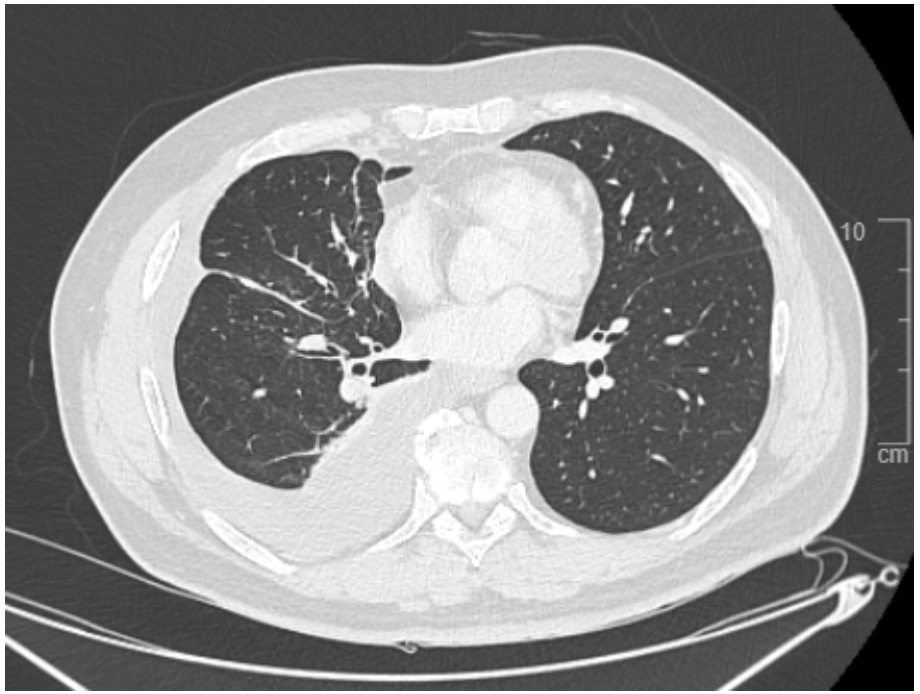
- Stop lorlatinib, refer to psychiatrist, wait for approval to start again at 50 mg
- Stop lorlatinib, restage, and consider chemotherapy
- Decrease dose to 50 mg/d, refer to psychiatrist
- Continue at 100 mg/d, refer to psychiatrist

After 2 Months of Lorlatinib

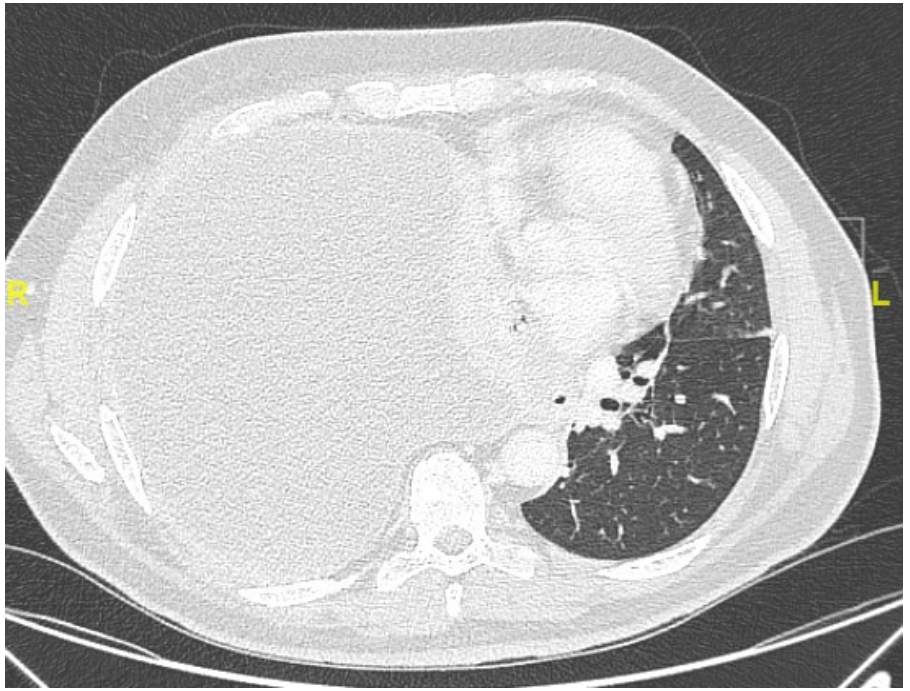
- Patient reports an increasing dyspnea
- Clinical exam: PS 2, auscultation with no sound on the right chest
- Patient was transferred to the emergency department

After 2 Months of Lorlatinib

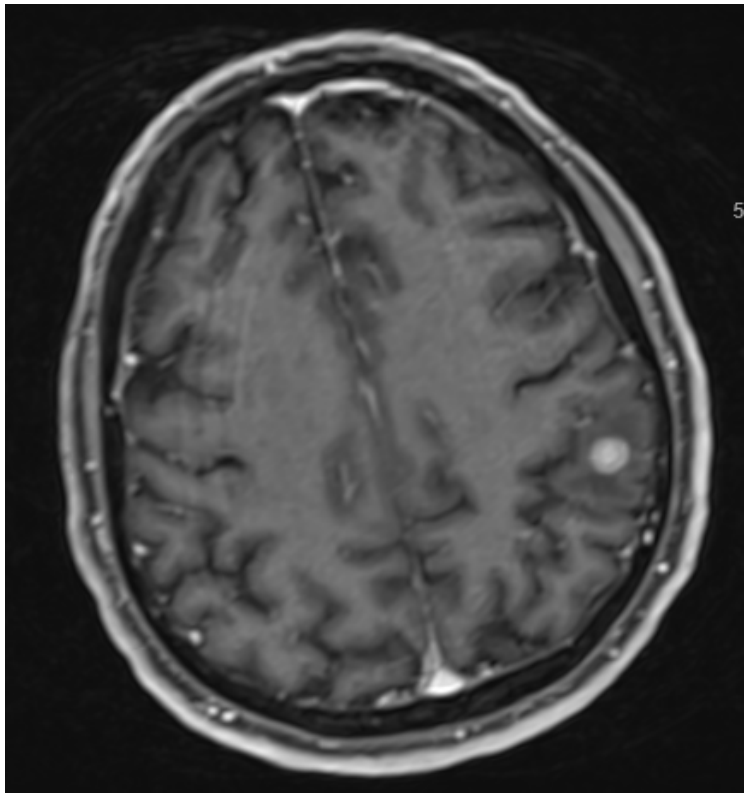
April 27, 2022

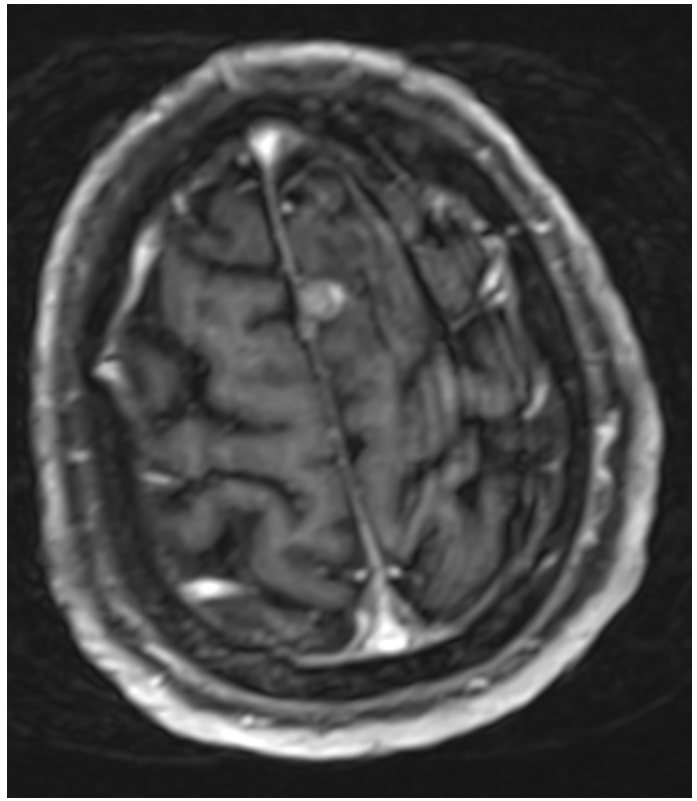


July 25, 2022



Brain MRI July 24, 2022



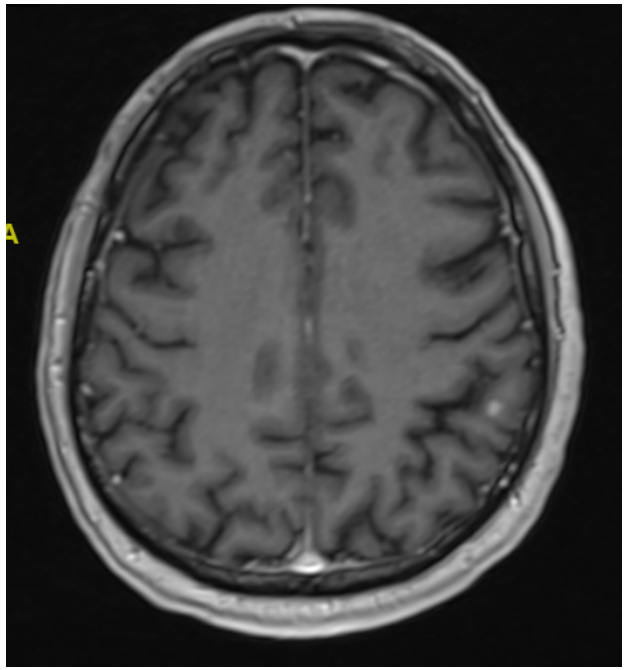


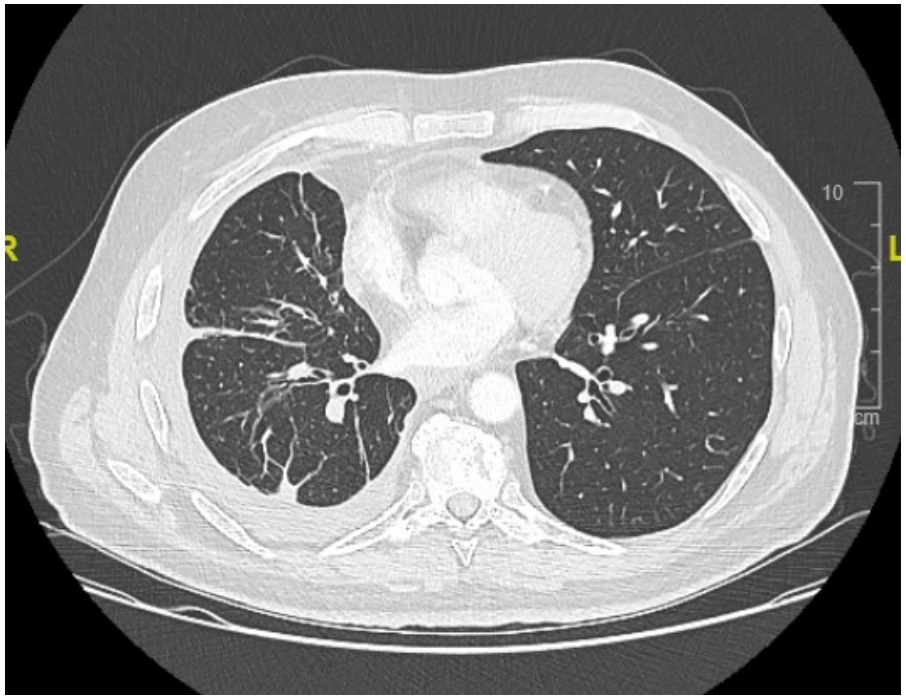
Third-Line Treatment

- Carboplatin AUC 5 and pemetrexed 500 mg/m^2
- C1D1 August 10, 2022

After 4 Cycles of Chemotherapy

- Partial response on brain, lung, liver, bone





Today

- Pemetrexed maintenance
- Returned to Martinique, next evaluation in December

Fusion *EMLA4-ALK* + fusion *ST7-MET* on the last bone biopsy

Next lines?
Possible role of crizotinib (alone or in combination)
Clinical trial with fourth-generation ALK inhibitors
Taxanes

Thank you!

Global Lung Cancer Academy

Patient Case 2

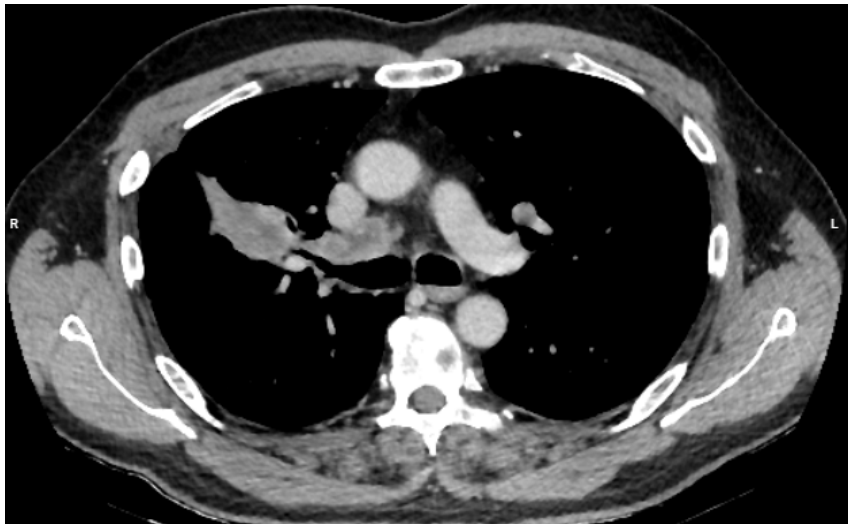
Xander Verbeke, MD

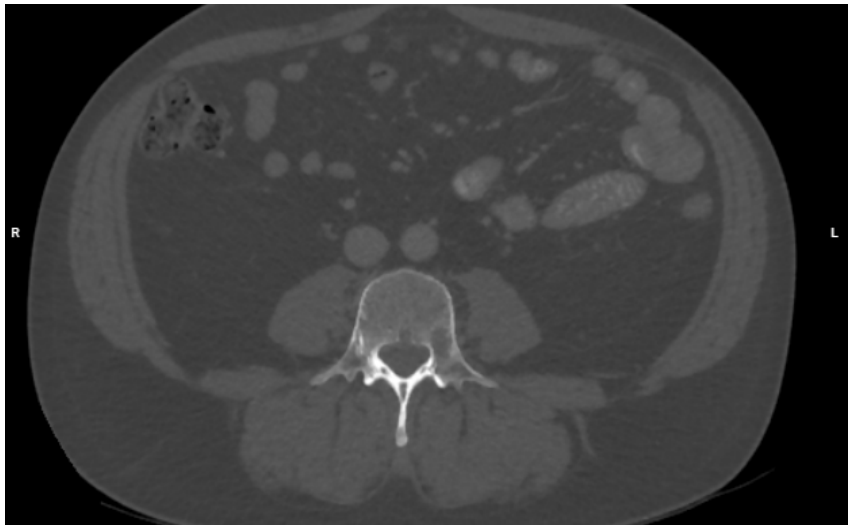
Global Lung Cancer Academy

Dr Xander Verbeke

University Hospital of Leuven

November 14, 2022





Case Presentation

Patient characteristics

- 58-year-old man
- Second opinion
- History of degenerative lumbar disease
- Substance abuse
  - Never-smoker
  - Drinks half a bottle of wine a day (at time of diagnosis)
- No medication
- Profession
  - Butcher

First presentation

- May 2021: worsening of lower-back pain in the last 3 months

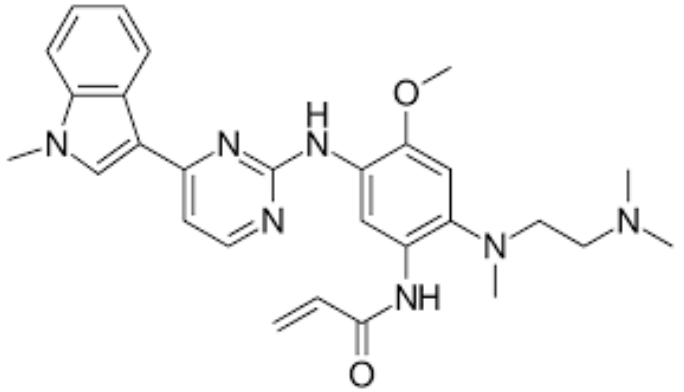
Tissue Is the Issue

Tissue sampling

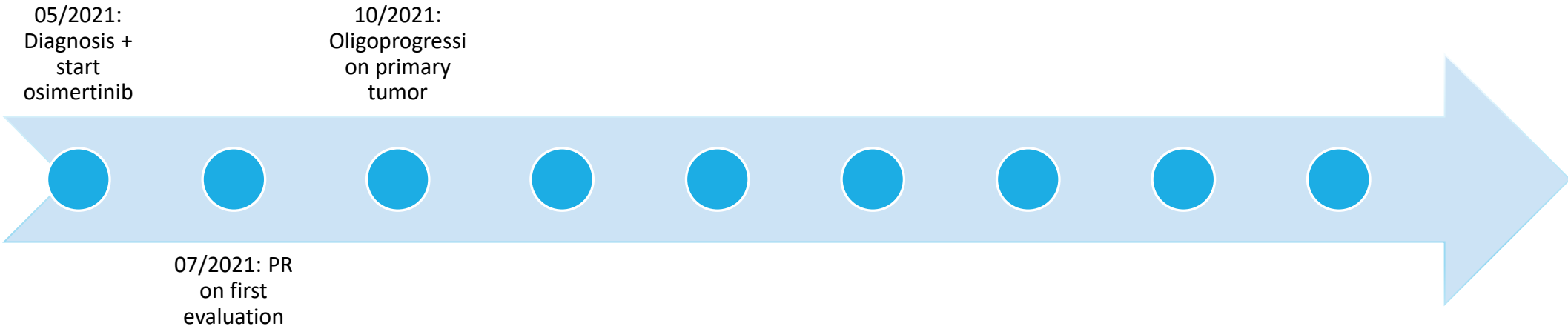
- LN7 and LN10R
  - TTF1 positive, p40 negative
  - PD-L1 0%, *ALK* and *ROS1* negative
  - NGS: *EGFR* exon 19 del and *TP53* mutation

EGFR positive cT2a pN2 cM1c – stage IVb nonsquamous NSCLC

Start first-line osimertinib



First-Line Therapy: Oligoprogression



Q1

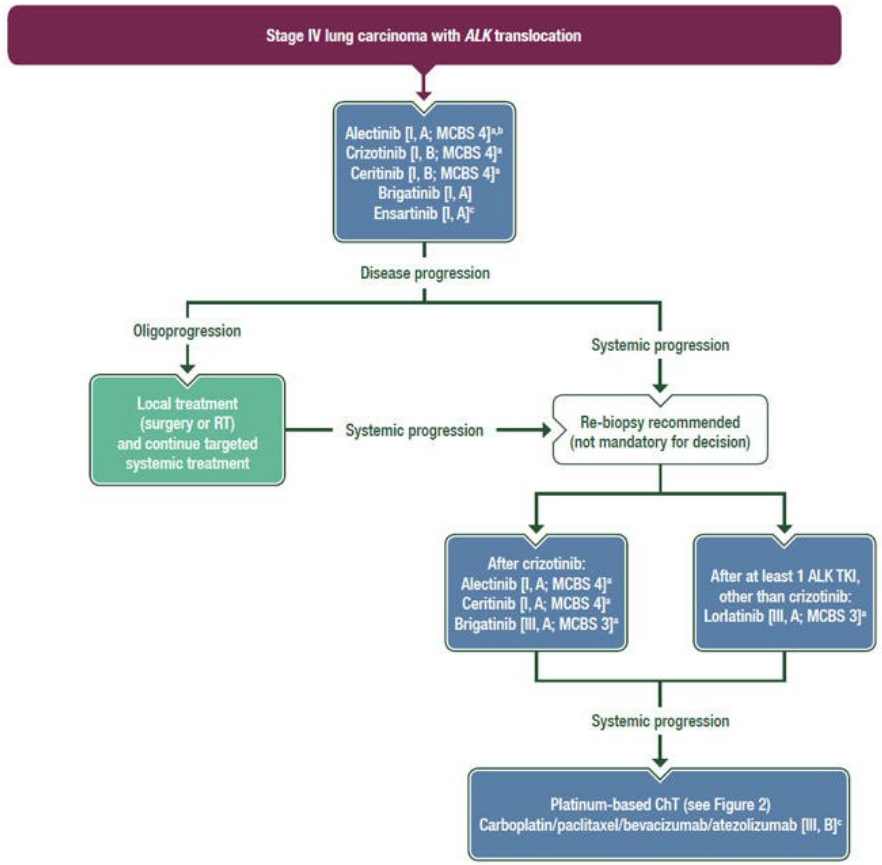
What is your next step?

1. Switch to platinum doublet
2. Switch to platinum doublet + PD-L1/PD-1 inhibitor
3. Switch to a different TKI
4. Rebiopsy tumor
5. SBRT on the primary tumor and continue osimertinib

Q1 – Answer

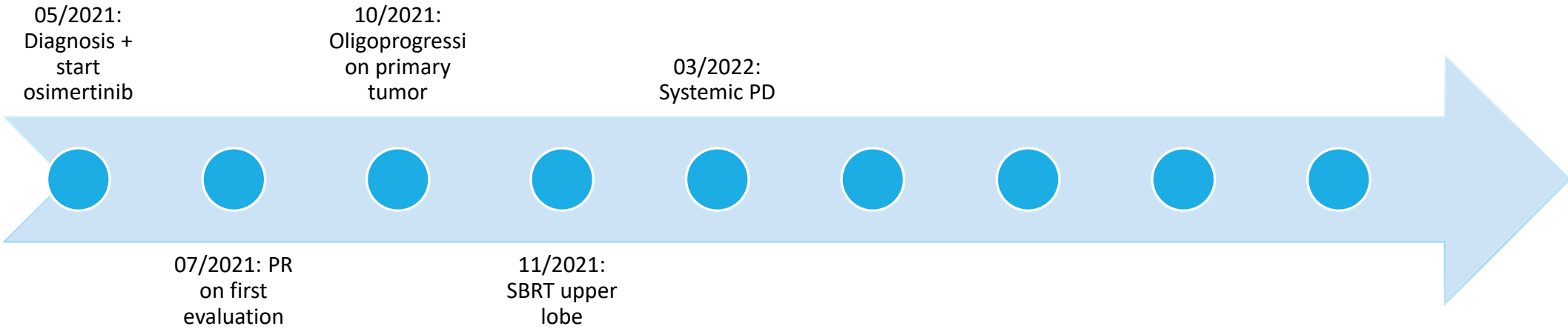
What is your next step?

1. Switch to platinum doublet
2. Switch to platinum doublet + PD-L1/PD-1 inhibitor
3. Switch to a different TKI
4. Rebiopsy tumor
5. **SBRT on the primary tumor and continue osimertinib**

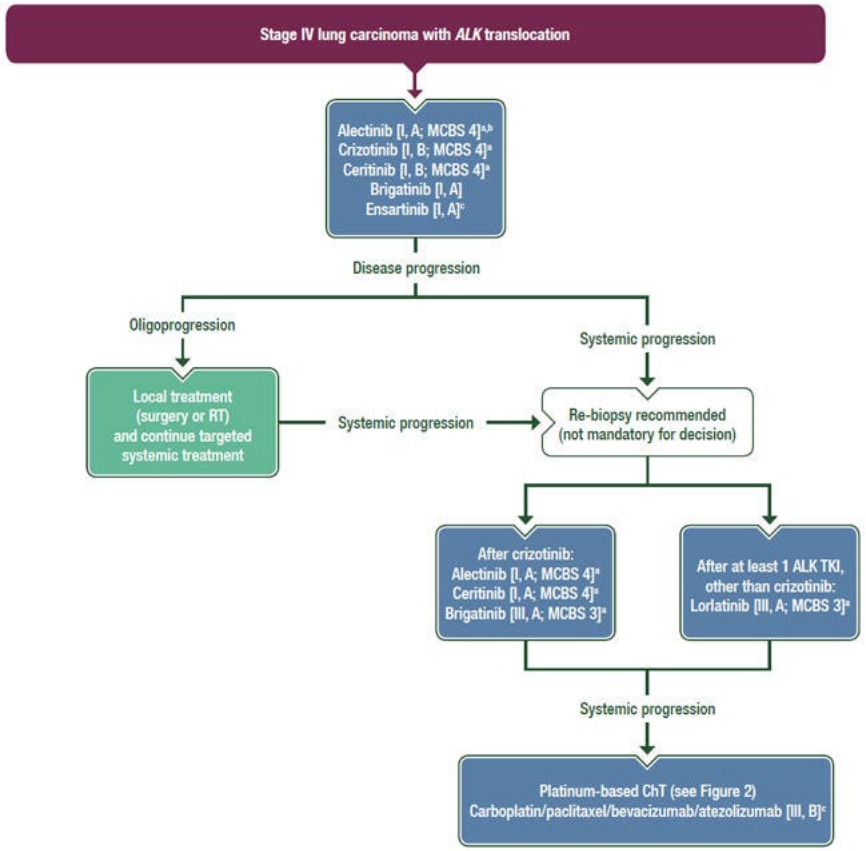


Planchard D, et al. *Ann Oncol*. 2018;29(suppl 4):iv192-iv237.

First-Line Therapy: Systemic PD



Systemic PD



Planchard D, et al. *Ann Oncol*. 2018;29(suppl 4):iv192-iv237.

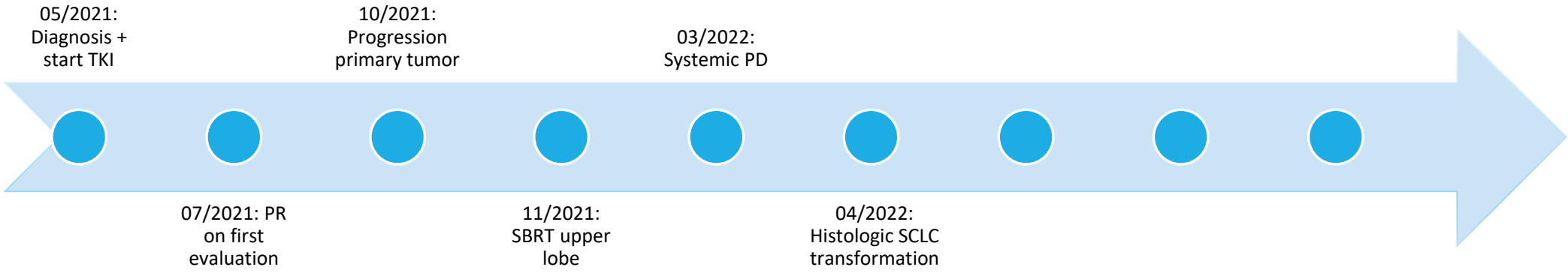
Systemic PD: Rebiopsy

New biopsy (liver)
- Synaptophysin positive
- Chromogranin positive
- Ki67 90%
- *EGFR* mutant – exon 19 del

→ Histologic transformation to SCLC

EGFR-Mutant Adenocarcinomas That Transform to Small-Cell Lung Cancer and Other Neuroendocrine Carcinomas: Clinical Outcomes

Nicolas Marcoux, MD[1,12]; Scott N. Gettinger, MD[2]; Grainne O'Kane, MD[3]; Kathryn C. Arbour, MD[4]; Joel W. Neal, MD[5]; Hatim Husain, MD[6]; Tracey L. Evans, MD[7,13]; Julie R. Brahmer, MD[8]; Alona Muzikansky, MA[1]; Philip D. Bonomi, MD[9]; Salvatore del Prete, MD[10]; Anna Wurtz, BS[2]; Anna F. Farago, MD, PhD[1]; Dora Dias-Santagata, PhD[1]; Mari Mino-Kenudson, MD[1]; Karen L. Reckamp, MD[11]; Helena A. Yu, MD[4]; Heather A. Wakelee, MD[5]; Frances A. Shepherd, MD[3]; Zofia Piotrowska, MD[1]; and Lecia V. Sequist, MD, MPH[1]



Marcoux N, et al. *J Clin Oncol*. 2019;37:278-285.

EGFR-Positive Transformation to SCLC

Resistance to EGFR TKI is well known

- *T790M*, c-*MET* . . .

Transformation to SCLC

- Rare: 3%–10% of all patients who develop resistance to TKI
  - Phenotypic switch or SCLC + NSCLC at baseline?
- *EGFR* founder mutation often maintained after transformation
- Can occur at any time of the disease (~16–20 mo)
  - Longer interval to transformation in *EGFR* wild-type NSCLC (~26 mo)
- Risk: *TP53* and/or *RB1* mutation
  - *EGFR/TP53/RB1* positive
    - ~43 × higher risk of SCLC transformation vs *EGFR* positive, *TP53* negative, *RB1* negative
    - Shorter time to discontinuation of TKI vs *EGFR/TP53* positive and *EGFR* positive only
  - Transformation likely a clonal evolution event

Q2

What is your choice of therapy?

1. PD-L1/PD-1 inhibitor
2. Platinum-etoposide
3. Platinum-etoposide + PD-L1/PD-1 inhibitor
4. Platinum-etoposide + continuation of osimertinib
5. Best supportive care

EGFR-Positive HT to SCLC: Treatment

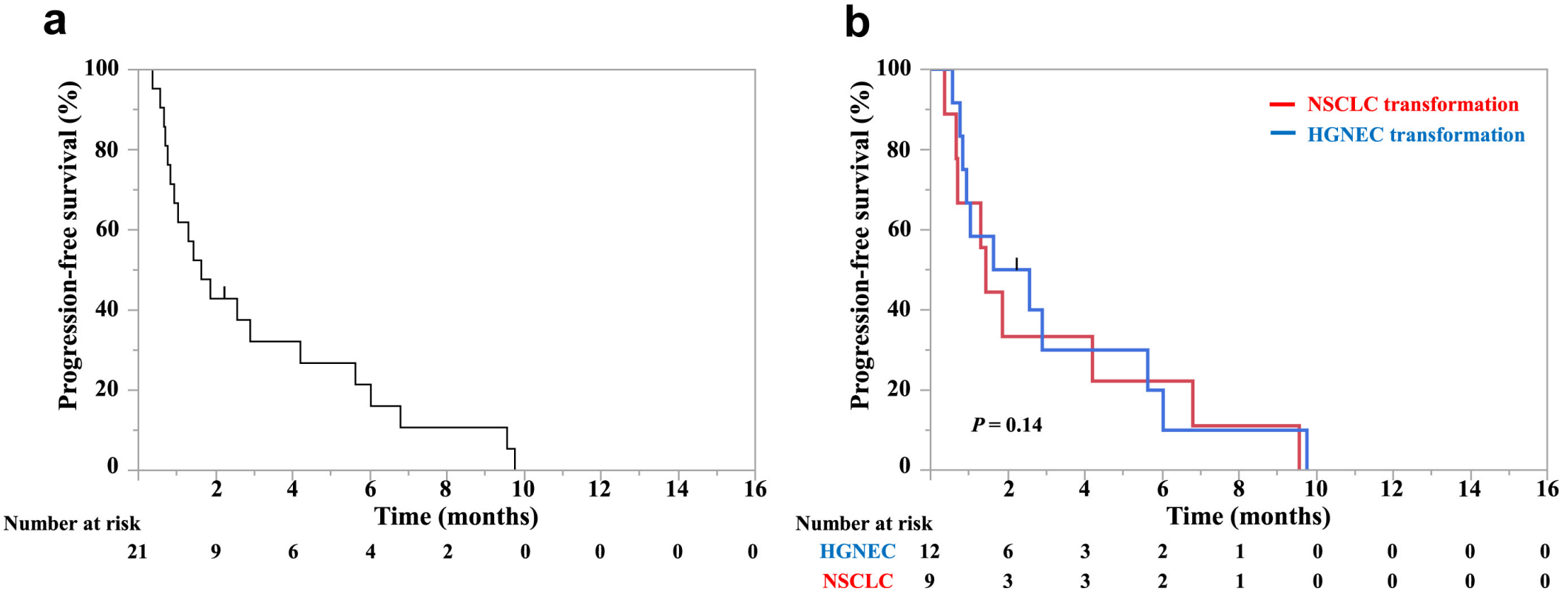
Therapy Received	No. (%)
Received before transformation to SCLC	n = 58
EGFR TKI	58 (100)
Erlotinib	49 (84)
Afatinib	13 (22)
Third-generation EGFR TKI	19 (33)
Osimertinib	18 (31)
Investigational	5 (9)
Checkpoint inhibitor	4 (7)
Cytotoxic chemotherapy	21 (36)
Platinum-doublet regimens	20 (34)
Bevacizumab	9 (16)
Received after SCLC transformation (or after diagnosis for de novo SCLC)	n = 65*
Cytotoxic chemotherapy	63 (97)
Platinum-etoposide	53 (82)
Other platinum-combination	7 (11)
Taxane	21 (32)
Campthotecin (topotecan, irinotecan)	12 (18)
Temozolamide	4 (6)
EGFR TKI	34 (52)
Checkpoint inhibitor	17 (26)
PD-1 or PD-L1 monotherapy	9 (14)
Ipilumumab plus nivolumab	8 (12)

Received after transformation to HGNEC, n (%)	Patients (n = 59)
Cytotoxic chemotherapy (not including immunotherapy)	51 (86)
Immune checkpoint inhibitors	12 (20)
PD-1/PD-L1 inhibitor monotherapy	7 (12)
Nivolumab + ipilimumab	1 (2)
Platinum-doublet + PD-1/PD-L1 inhibitor	4 (7)
EGFR-TKI rechallenge	21 (36)
No anticancer therapy	5 (8)
Received after transformation to another NSCLC subtype, n (%)	**Patients (n = 15)**
Cytotoxic chemotherapy (not including immunotherapy)	9 (60)
Immune checkpoint inhibitors	9 (60)
PD-1/PD-L1 inhibitor monotherapy	7 (47)
Platinum-doublet + PD-1/PD-L1 inhibitor	2 (13)
EGFR-TKI rechallenge	5 (33)
No anticancer therapy	1 (7)

EGFR, epidermal growth factor receptor; HGNEC, high-grade neuroendocrine carcinoma; NSCLC, non–small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Marcoux N, et al. *J Clin Oncol*. 2019;37:278-285; Fujimoto D, et al. *Eur J Cancer*. 2022;166:41-50.

EGFR-Positive HT to SCLC: ICI



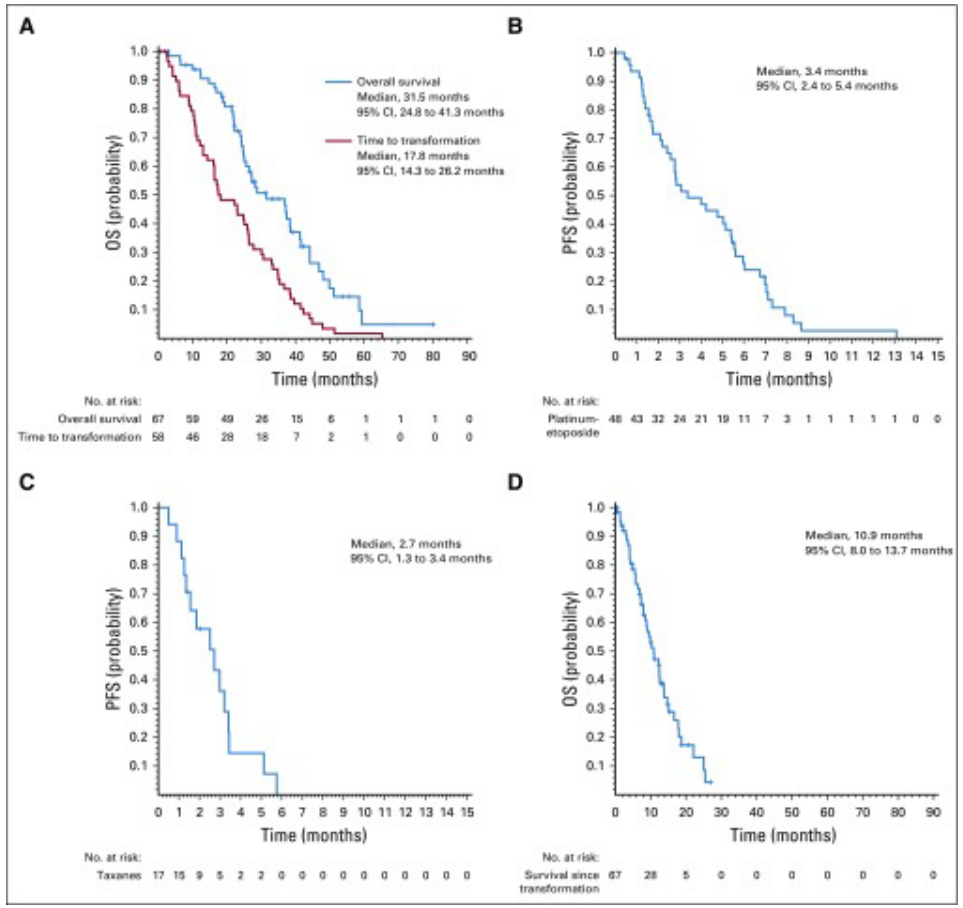
Fujimoto D, et al. *Eur J Cancer.* 2022;166:41-50.

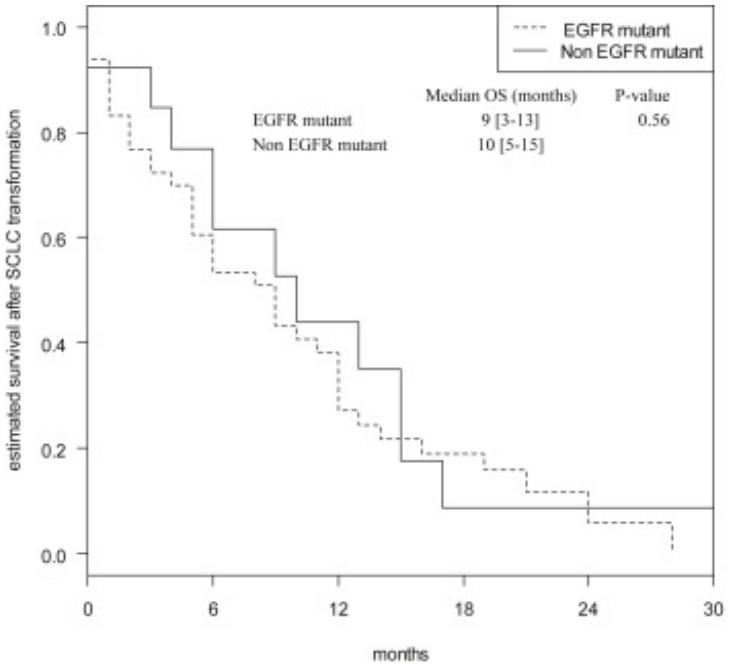
Q2 – Answer

What is your choice of therapy?

1. PD-L1/PD-1 inhibitor
2. **Platinum-etoposide**
3. Platinum-etoposide + PD-L1/PD-1 inhibitor
4. Platinum-etoposide + continuation of osimertinib
5. Best supportive care

EGFR-Positive Transformation to SCLC: Prognosis

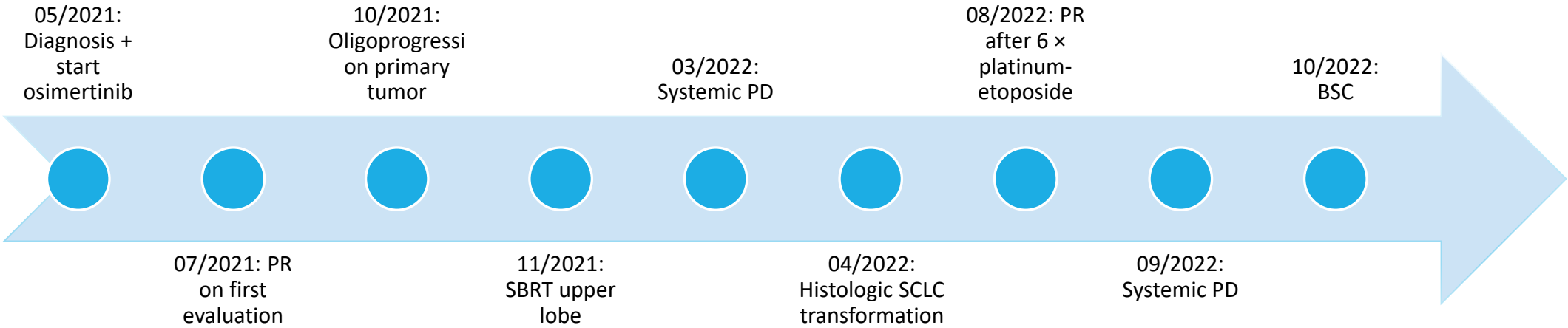




Time (months)	0	6	12	18	24	30
N at risk	61	35	19	7	3	1
EGFR mutant	48	25	14	6	2	0
Non EGFR mutant	13	10	5	1	1	1

Marcoux N, et al. *J Clin Oncol*. 2019;37:278-285; Ferrer L, et al. *J Thorac Oncol.* 2019;14:130-134.

Back to the Case



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Global Lung Cancer Academy

Tumor Board Discussion

Moderator: Corey Langer, MD, FACP

All faculty

Global Lung Cancer Academy

Session Close

Solange Peters, MD

Meeting evaluation

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Repeat Question 4

56-year-old male, heavy former tobacco enthusiast (50 pk/yr) presents with cough and pleuritic chest pain. CXR shows L pleural effusion and L hilar mass, confirmed on CT, which also discloses mediastinal LAD and a L adrenal mass measuring 3 cm. Pleural fluid cytology demonstrates adenocarcinoma, TTF1 positive. Cell block is sufficient for NGS testing; this proves positive for *KRAS* G12C mutation. PD-L1 is positive but at low level (10%). Brain MRI proves negative. Patient is treated with the KN-189 regimen (combination pemetrexed, carboplatin, and pembrolizumab) and sustains a PR with resolution of the L pleural effusion and shrinkage in the primary lung mass, mediastinal LAD, and L adrenal lesion. Scans after cycle 8 of maintenance pemetrexed + pembrolizumab show growth in the L adrenal mass and new hepatic lesions, all of which prove “hot” on PET. Which of the following would NOT be appropriate therapy in the second-line setting?

1. Sotorasib
2. Adagrasib
3. Selpercatinib
4. Combination ramucirumab and pembrolizumab

Thank you!

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