15th MADRID CONGRESS on Lung CANCER

23&24 November 2023

#15CongressGECP

Fundación GECP lung cancer research

Session IX. Targeted therapies in NSCLC II

Next challenges. Resistance mechanisms

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Declaration of interests

Employment: Servicio Andaluz de Salud

Consultant/advisory role: MSD, BMS, Roche, AstraZeneca, Boehringer, Pfizer, Novartis, Eli Lilli, Merck, Regeneron

Talks in company's event: MSD, BMS, Roche, AstraZeneca, Pfizer, Sanofi, Regeneron

Research funding (institution): Roche, Pfizer, BMS

Outline

1. Resistance in oncogenic driven NSCLC
2. Evidence of drugs at progression
3. How to choose a therapy at progression
4. Local challenges
5. Take-home messages

Outline

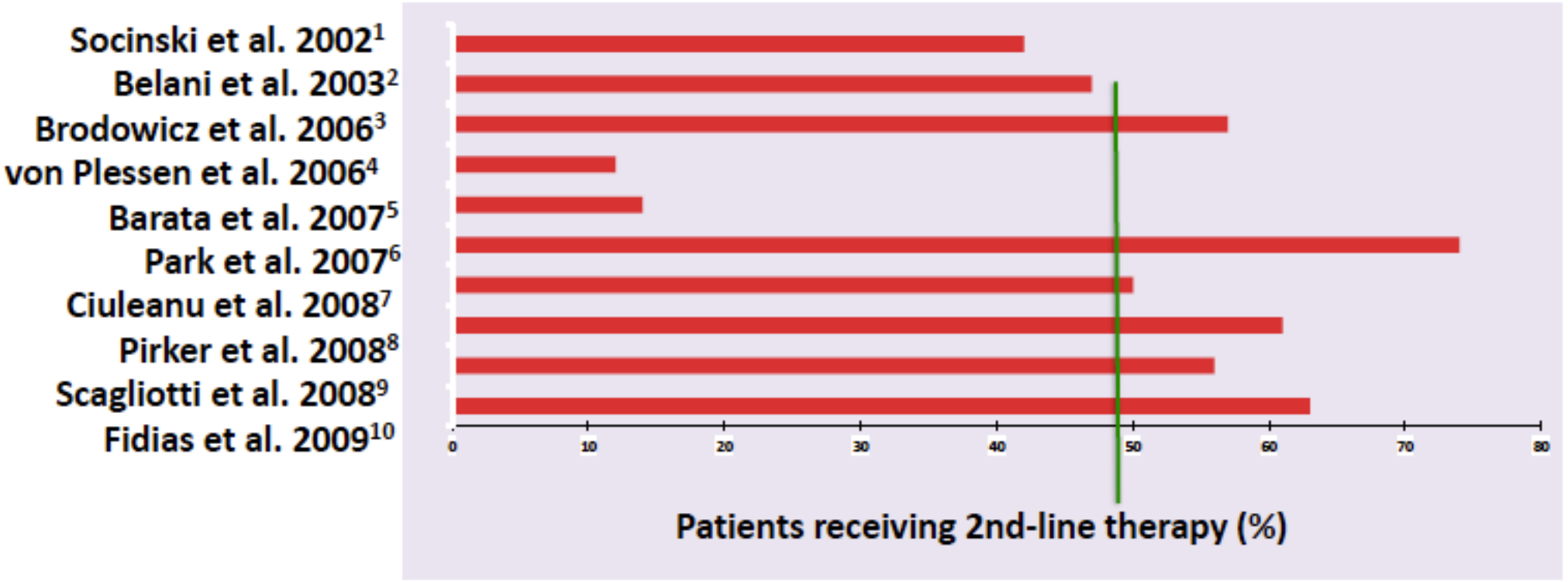
1. **Resistance in oncogenic driven NSCLC**
2. Evidence of drugs at progression
3. How to choose a therapy at progression
4. Local challenges
5. Take-home messages

Challenges in succesive therapies

- Pretreated patients
- Reduced performance status: tolerability becomes more important
- Low response rates: tumor control becomes important
- More symptomatic patients: symptom control and symptom improvement become important
- It is hard to show any improvement in efficacy...

Challenges in succesive therapies

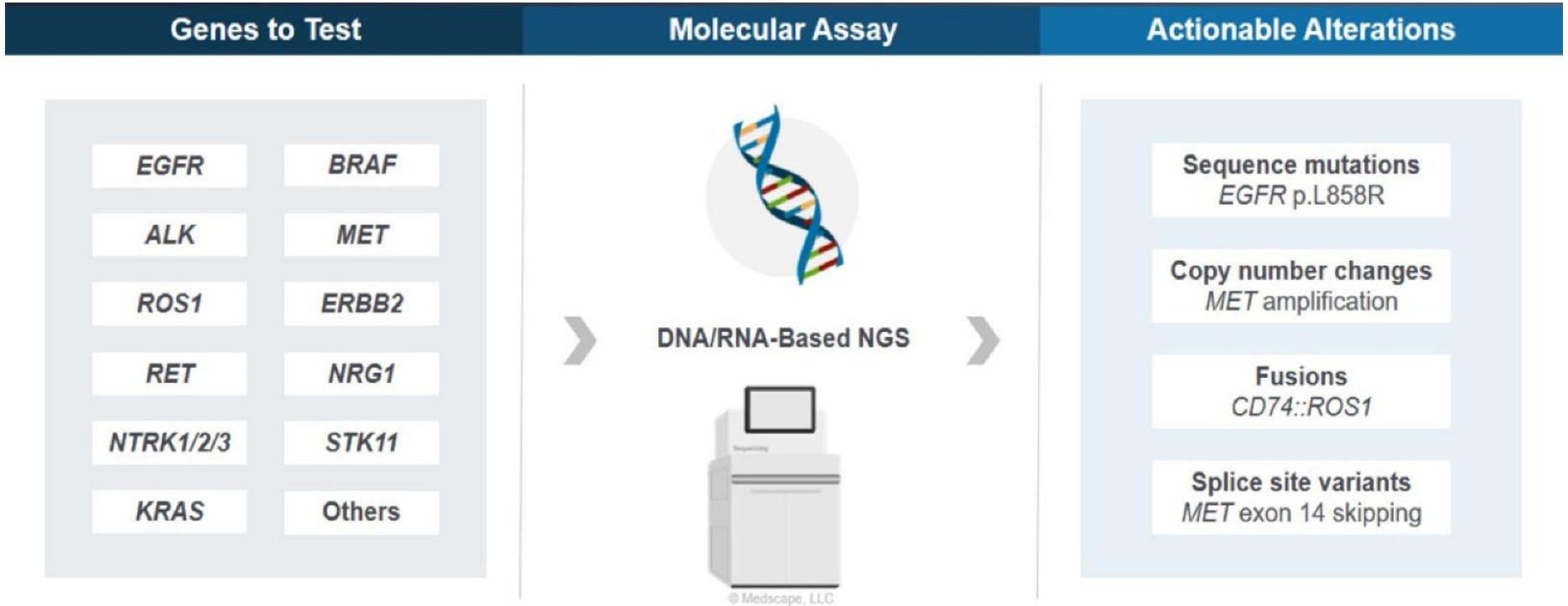
"Classic" 2nd line therapy



In recent studies, approximately 50% of patients did not receive second-line therapy

[1]J Clin Oncol 2002;20:1335–43; [2]J Clin Oncol 2003;21:2933–39; [3]Lung Cancer 2006;52:155–63; [4]Br J Cancer 2006;95:966–73; [5]J Thoracic Oncol 2007;2(Suppl. 4):S666 Abs. P2-235; [6]J Clin Oncol 2007;25:5233–39; [7]J Clin Oncol 2008;26(Suppl. 15S):426s Abs. 8011; [8]J Clin Oncol 2008;26(Suppl. 15S):6s Abs. 3; [9]J Clin Oncol 2008;26:3543–51; [10]J Clin Oncol 2009;27:

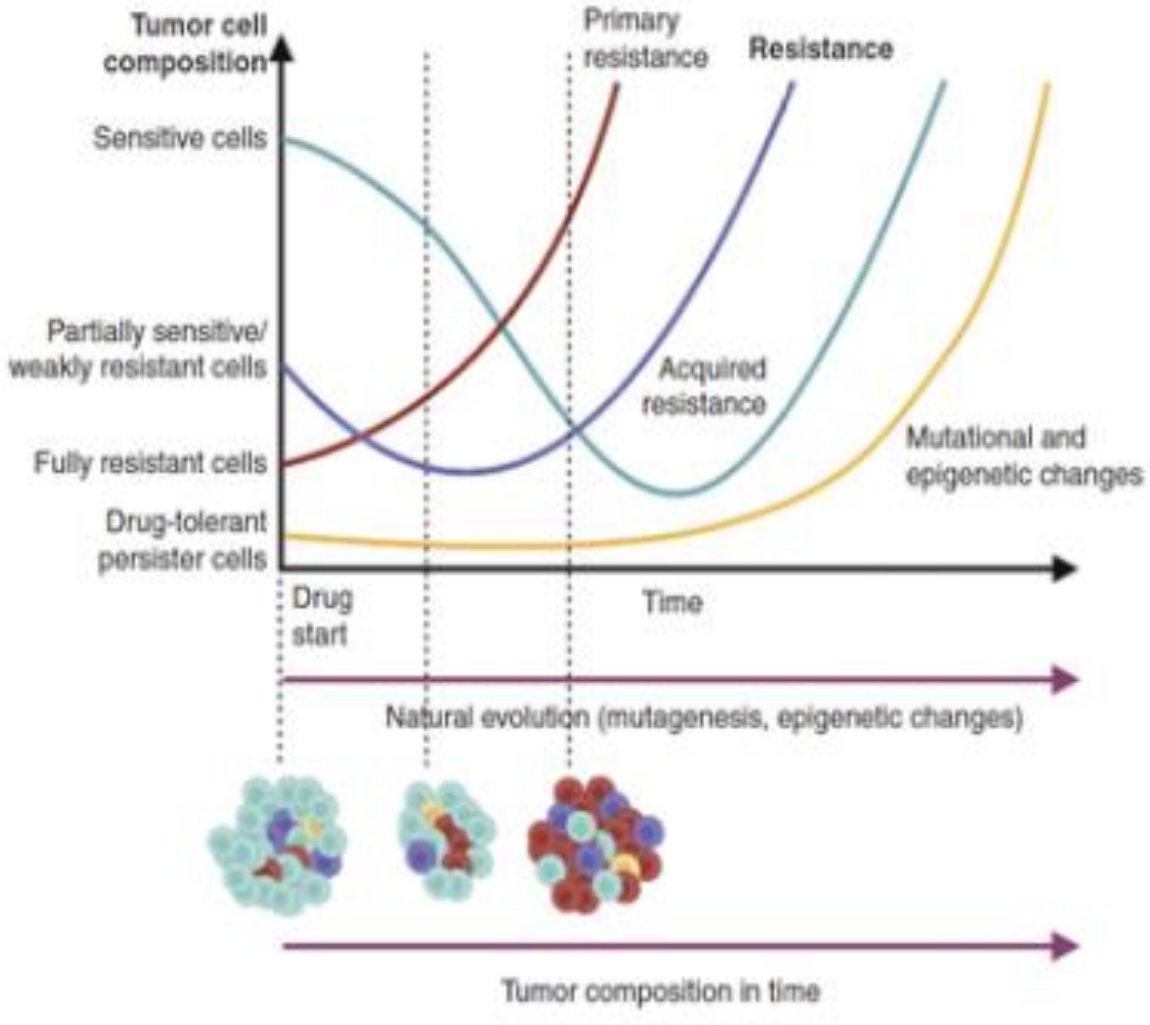
Molecular profiling



Broad molecular profiling of NSCLC using DNA/RNA-based NGS enables comprehensive, economical, and tissue-efficient strategy for guideline-complete genotyping

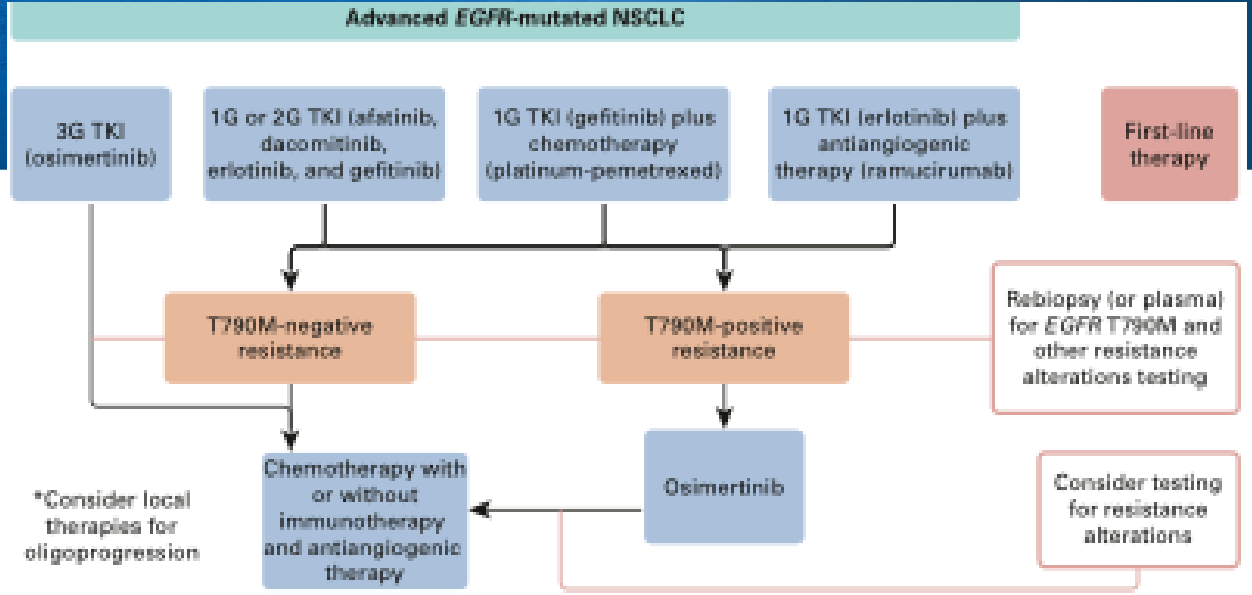
Pennell. JCO Precision Oncol 2020

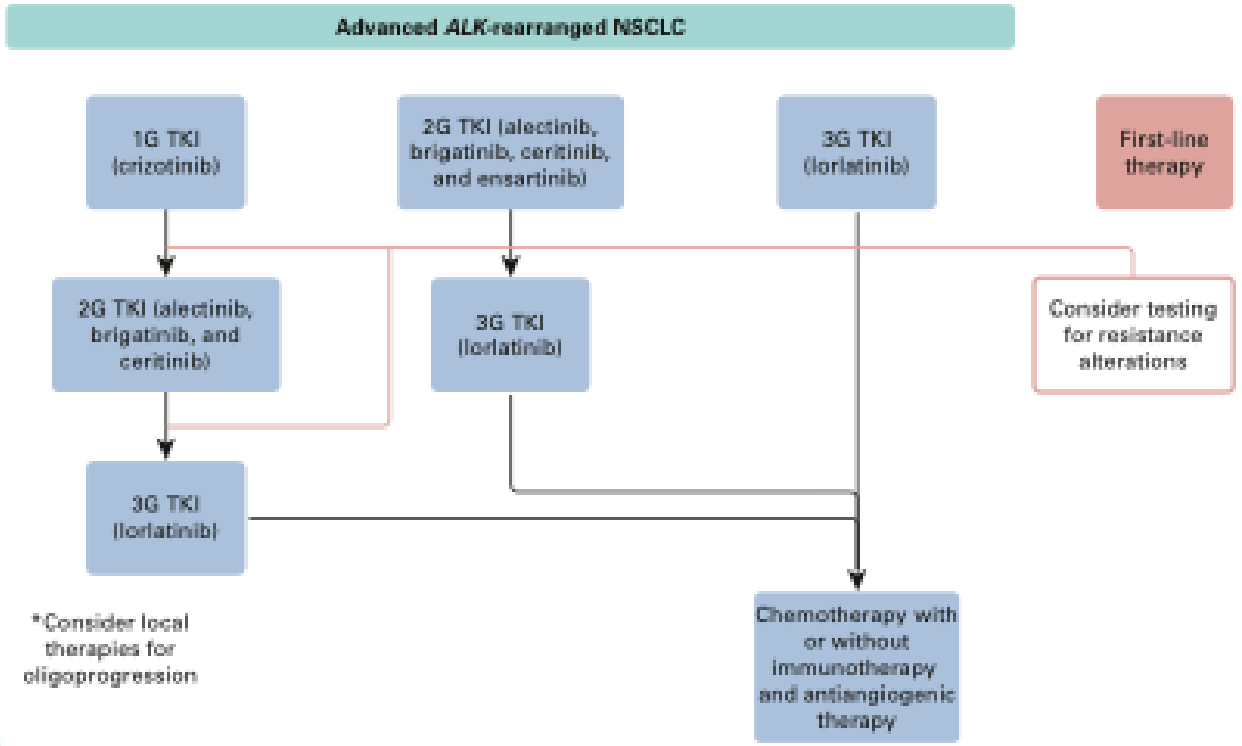
Today, all patients become resistant



Aldea. Cancer Discovery 2021

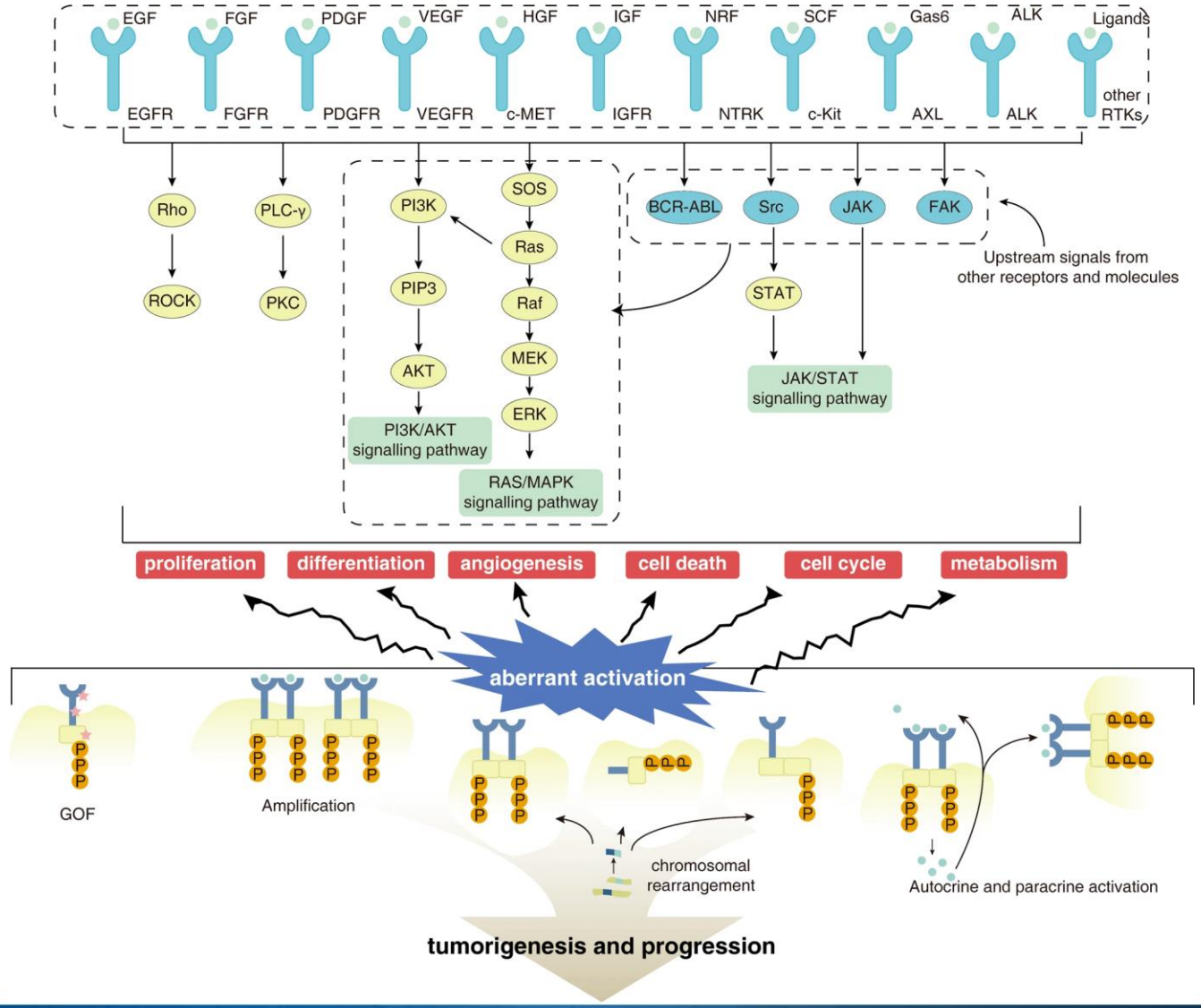
Algorithms



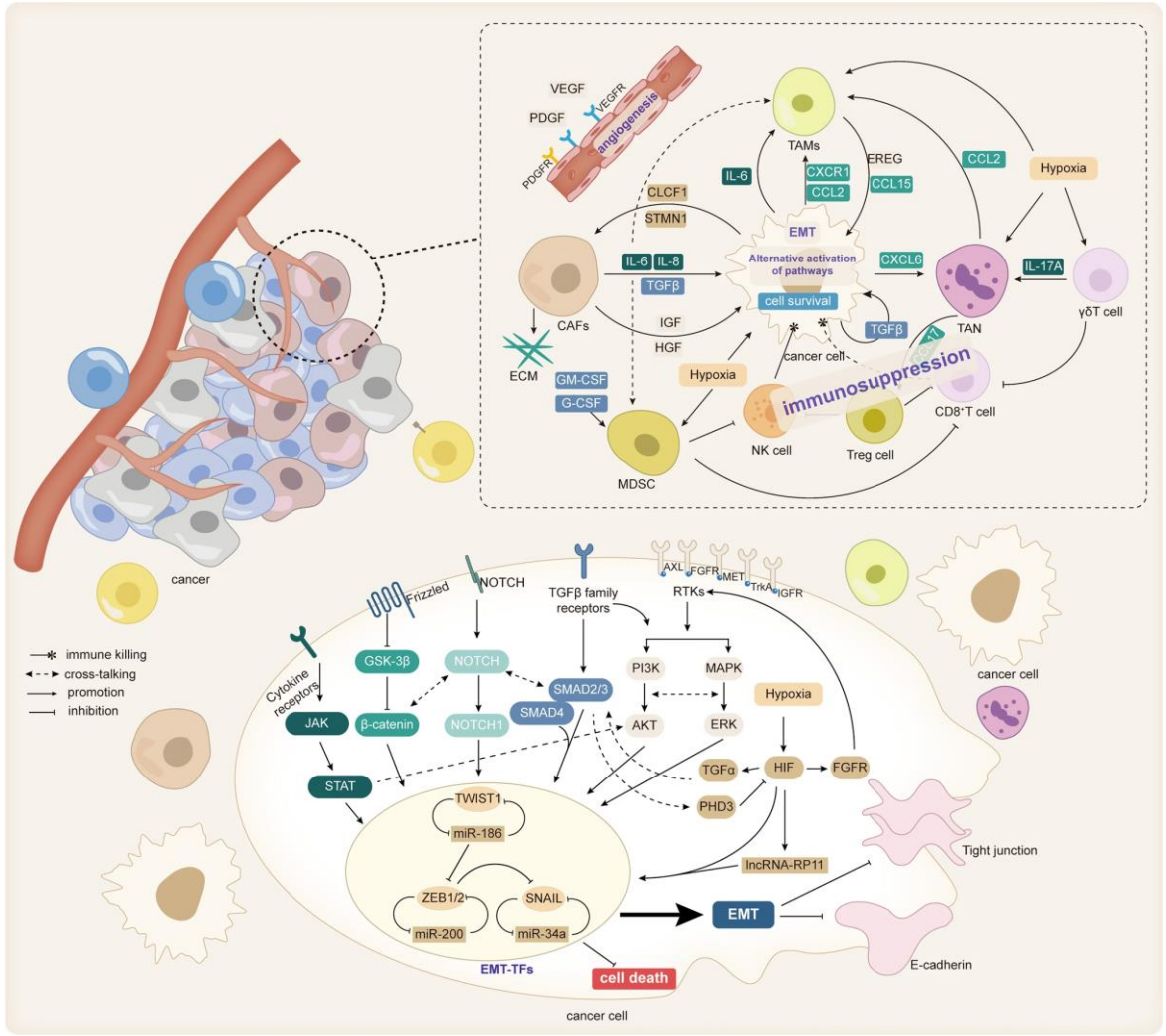


Tan. JCO 2022

Actionable genomic alterations

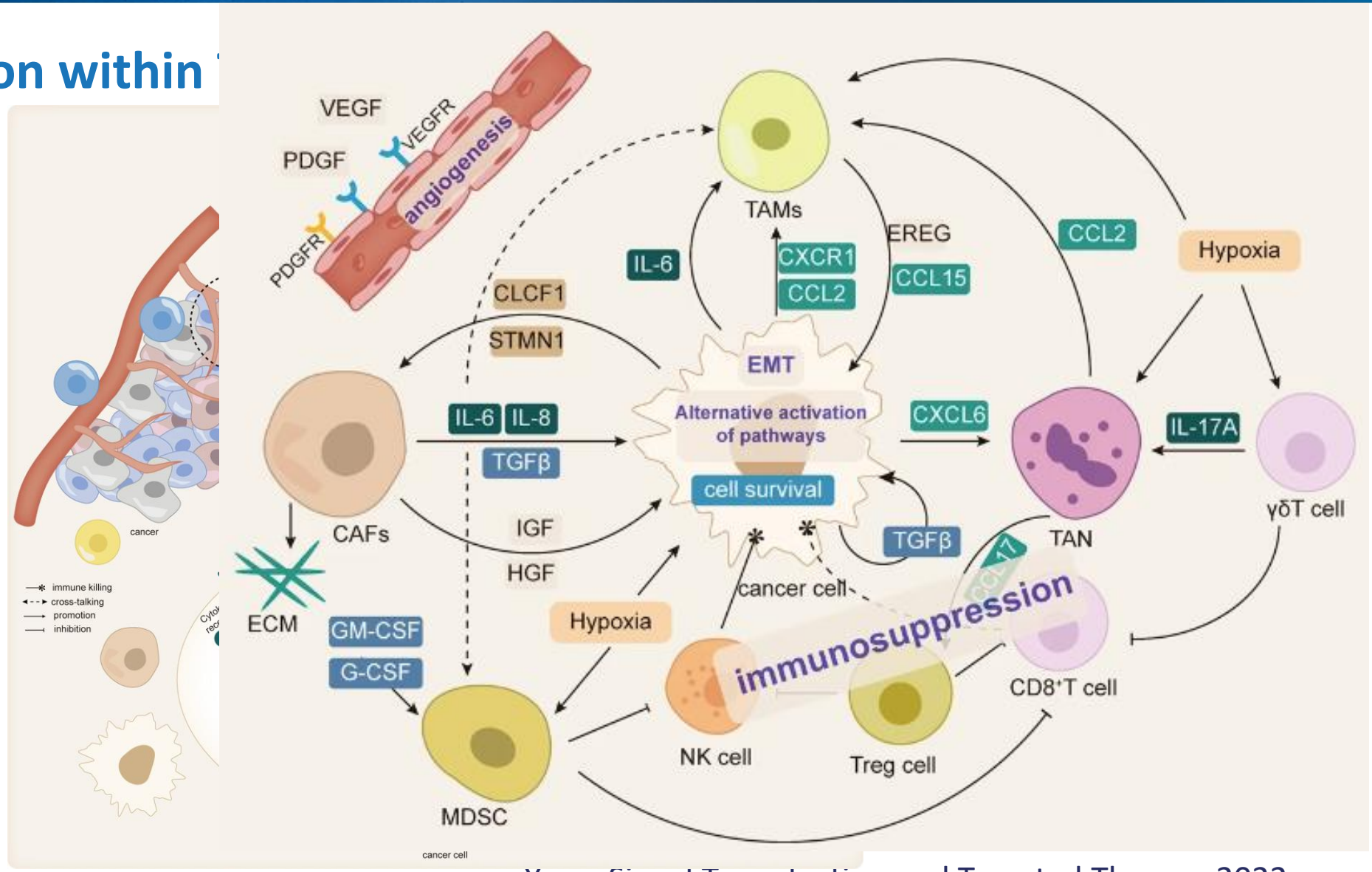


Cellular composition within TME and effect on TKI resistance



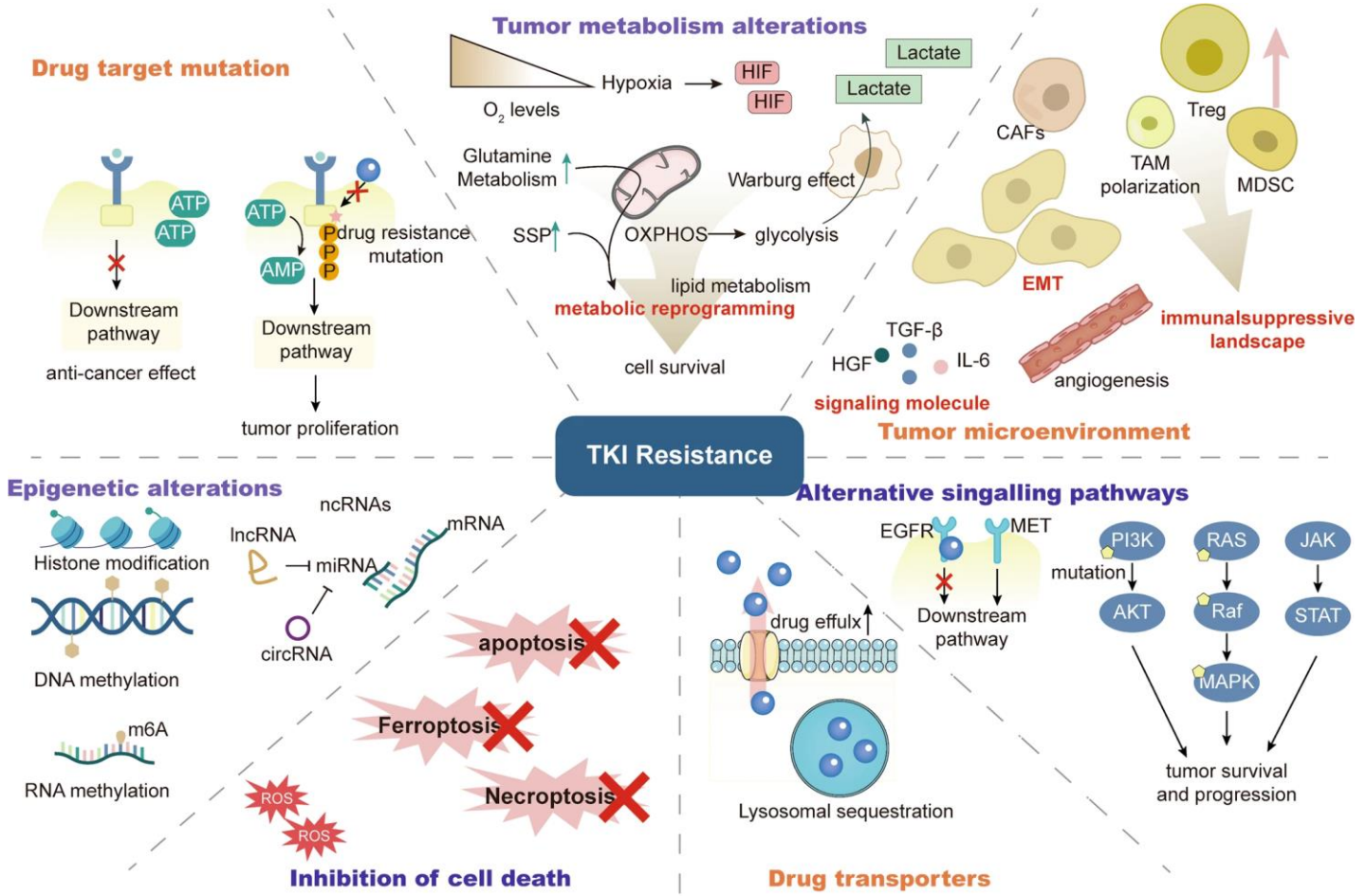
Yang. Signal Transduction and Targeted Therapy 2022

Cellular composition within



Yang. Signal Transduction and Targeted Therapy 2022

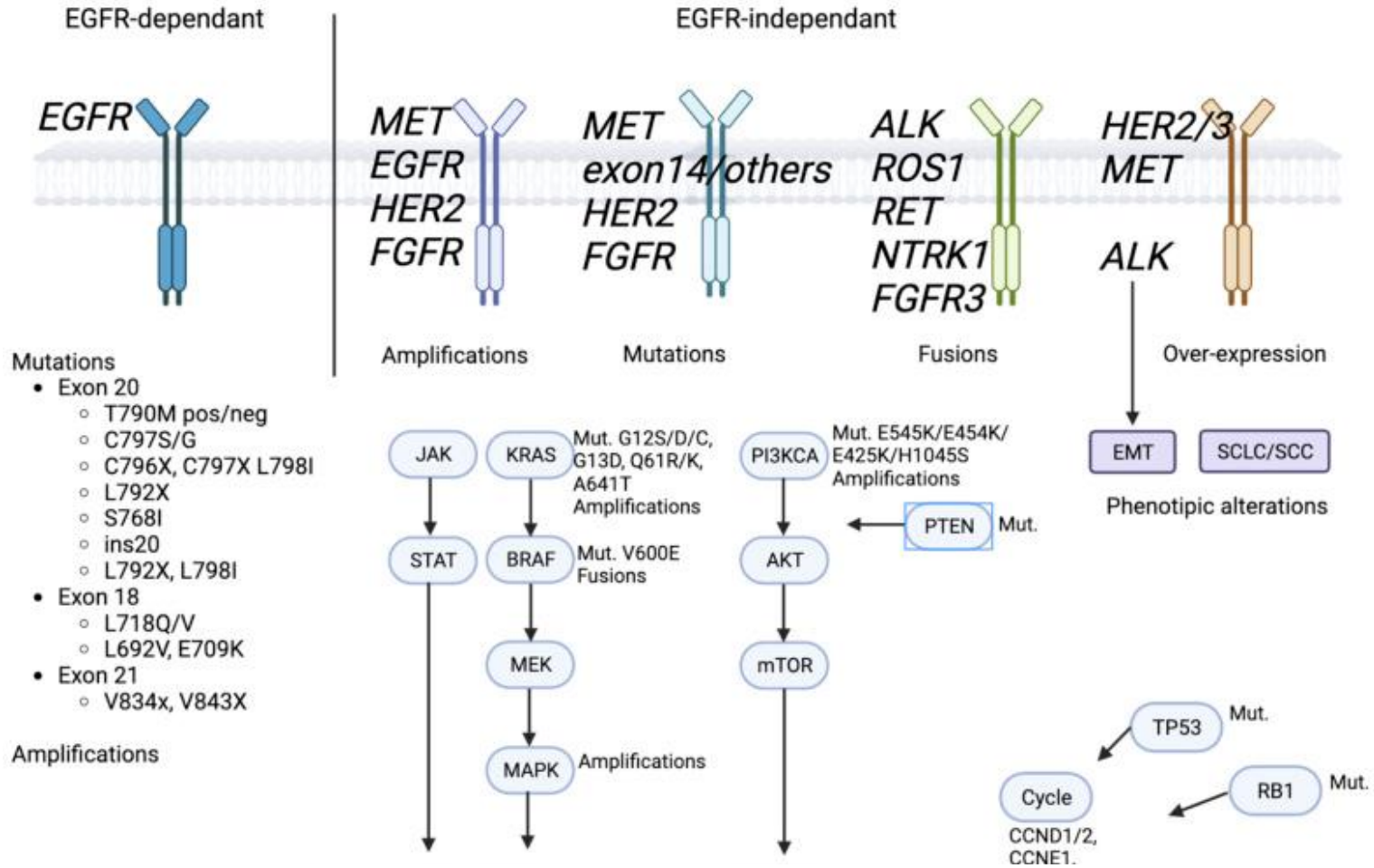
Overview of the mechanisms of tumor resistance to TKIs



Yang. Signal Transduction and Targeted Therapy 2022

Resistance to EFGR TKis

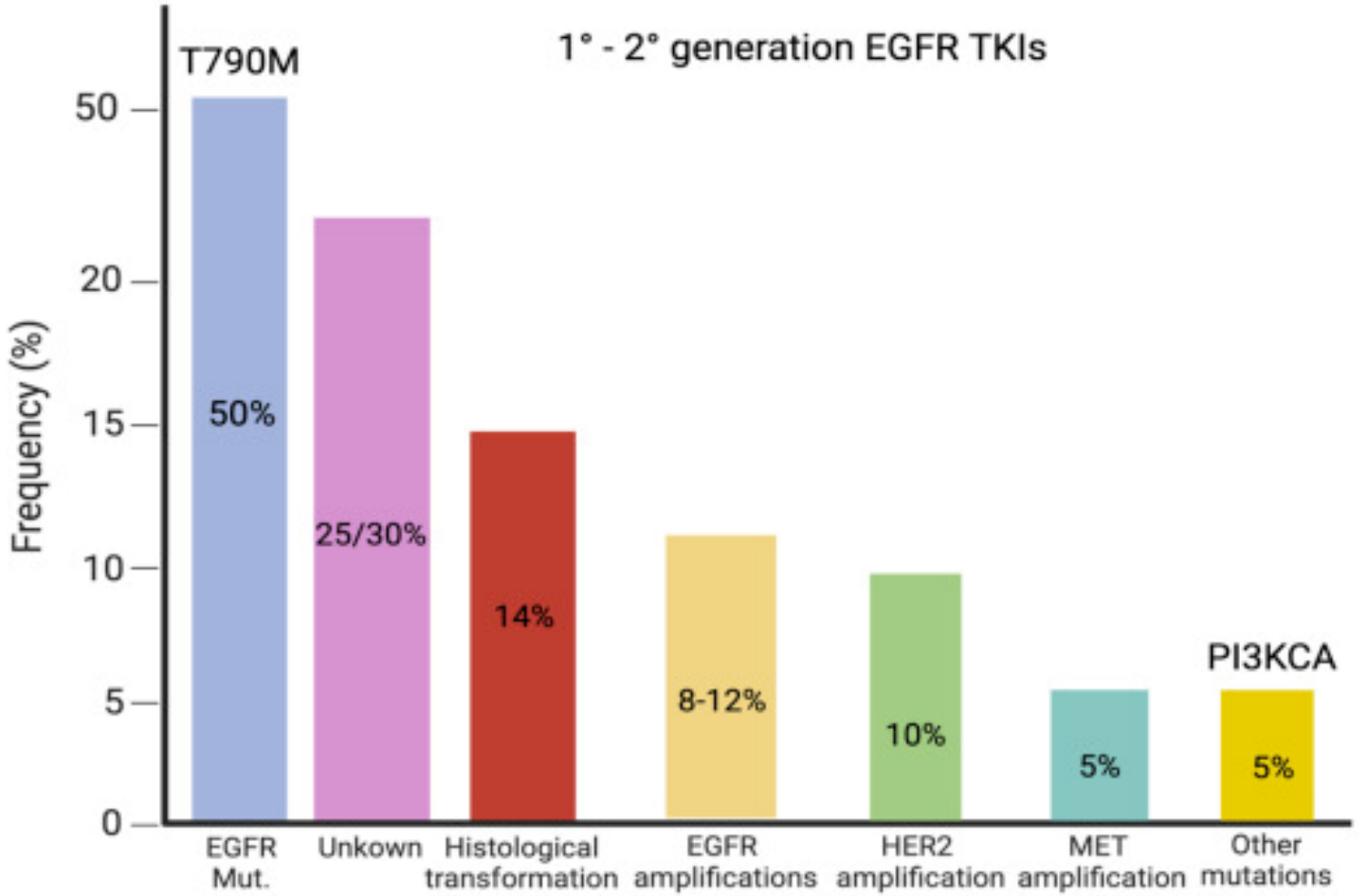
Known mechanisms of EGFR resistance



Laface. Pharmaceutics 2023

Resistance to EFGR TKis

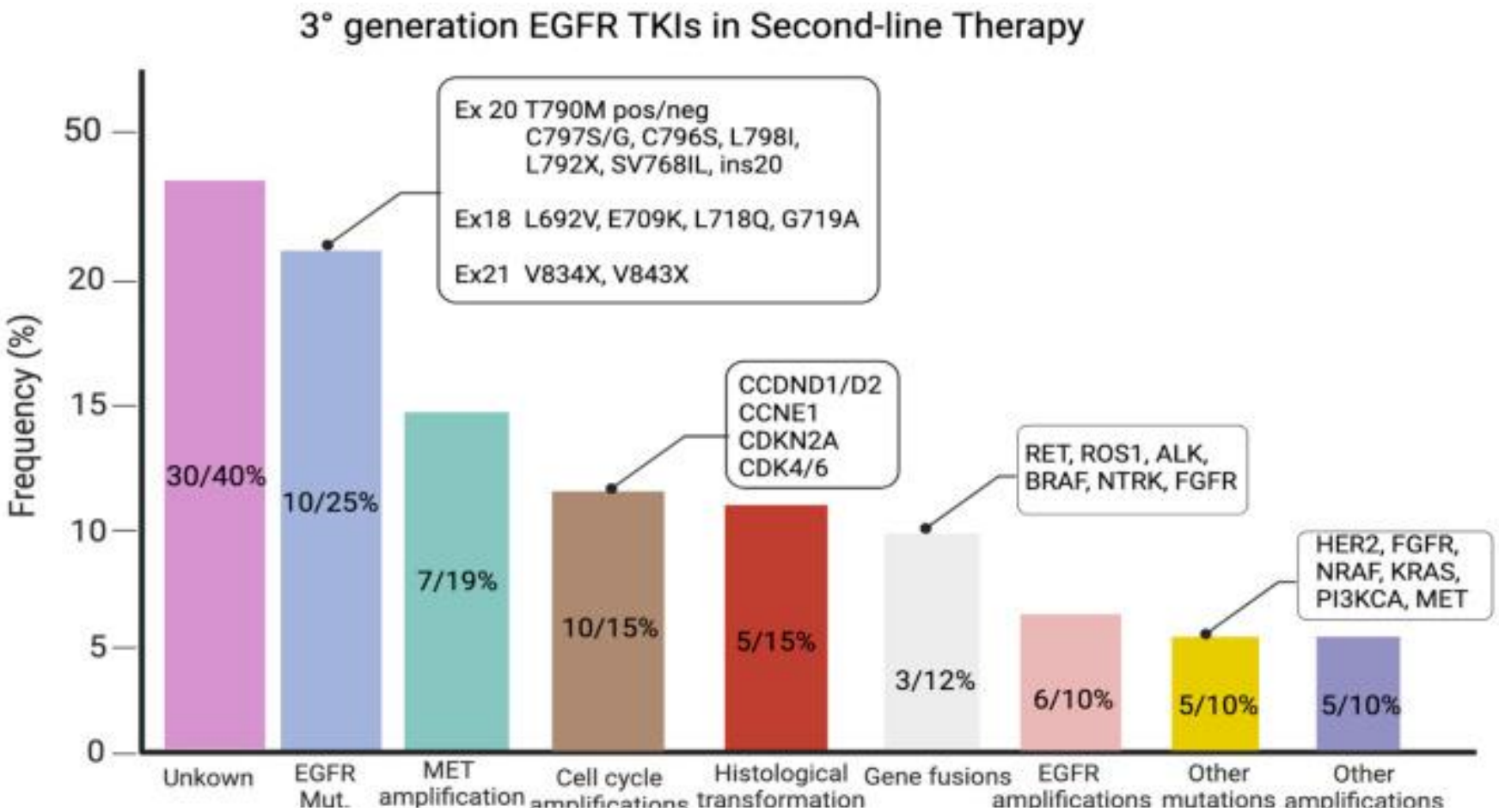
1st-2nd generation EGFR TKis



Laface. Pharmaceutics 2023

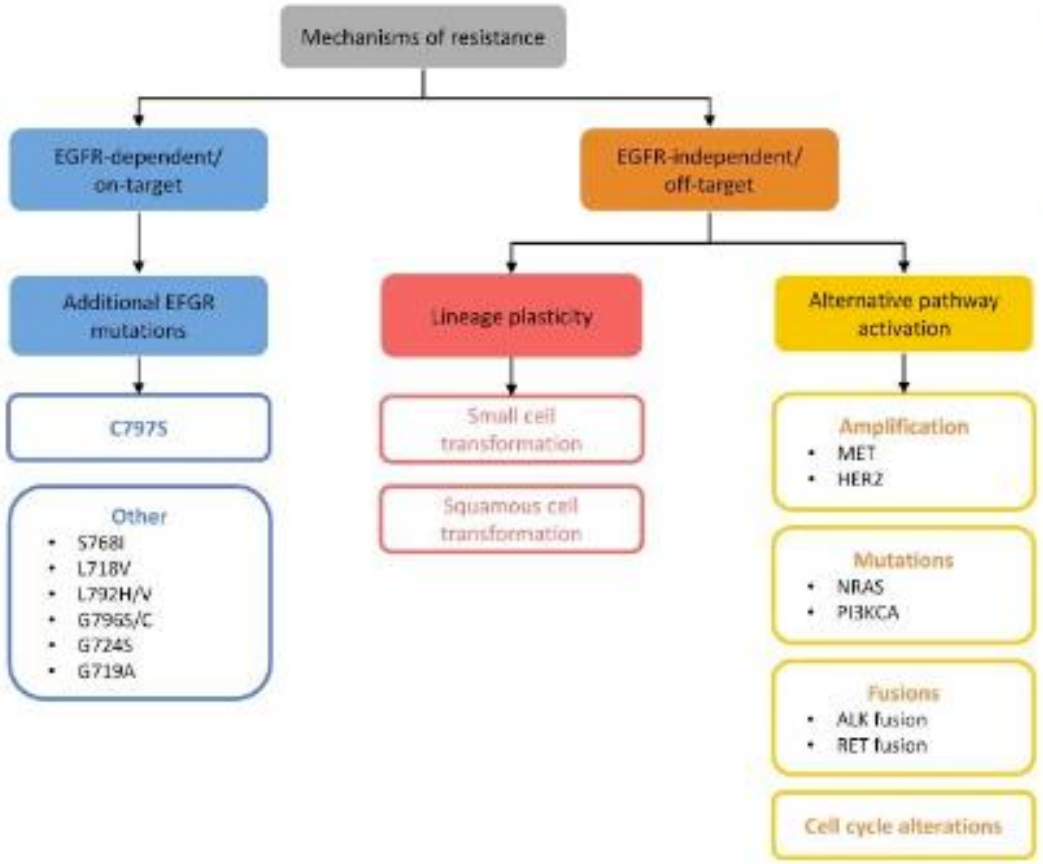
Resistance to EFGR TKis

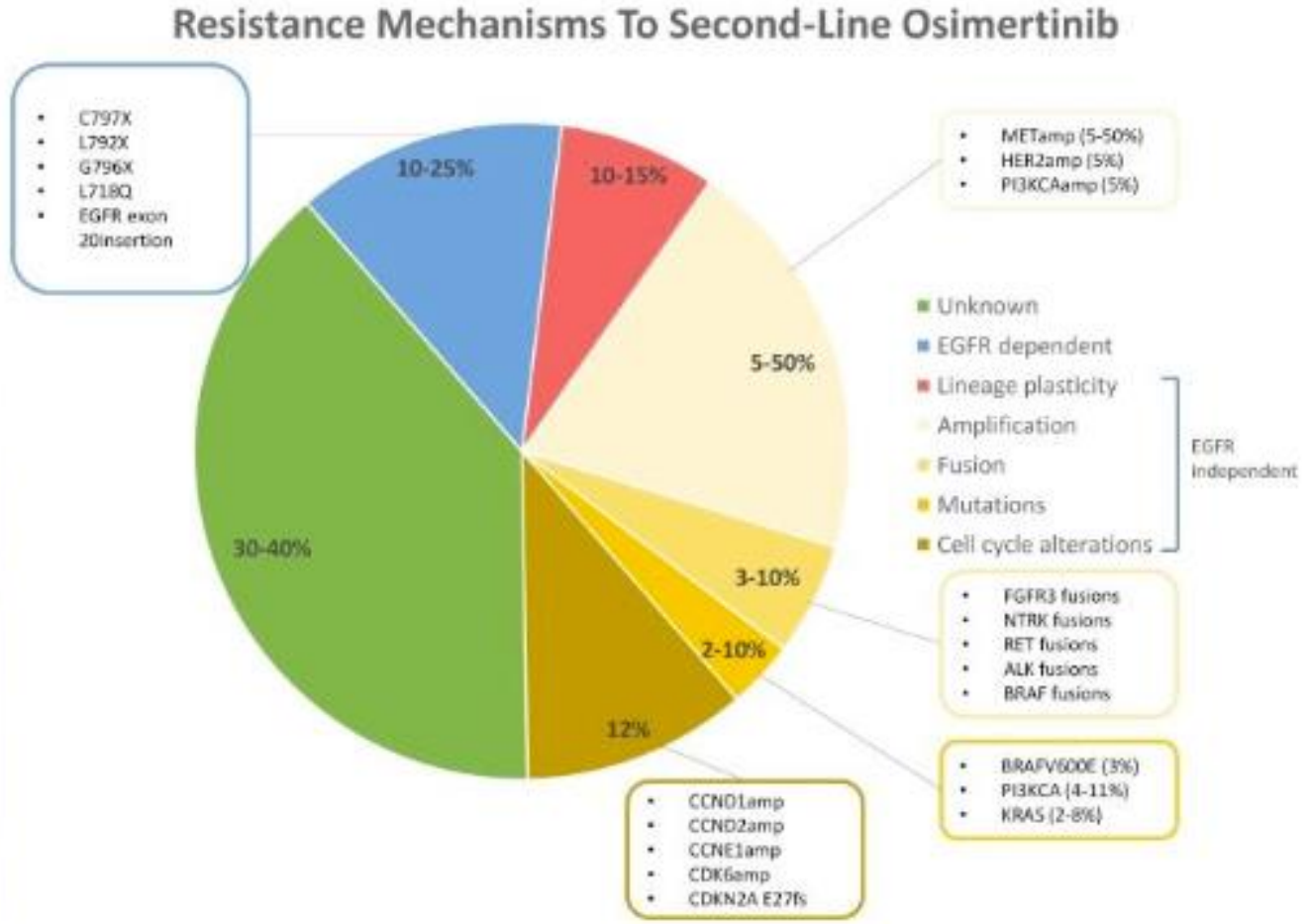
3rd generation EGFR TKis 2nd line therapy



Laface. Pharmaceutics 2023

Mechanisms of osimertinib resistance

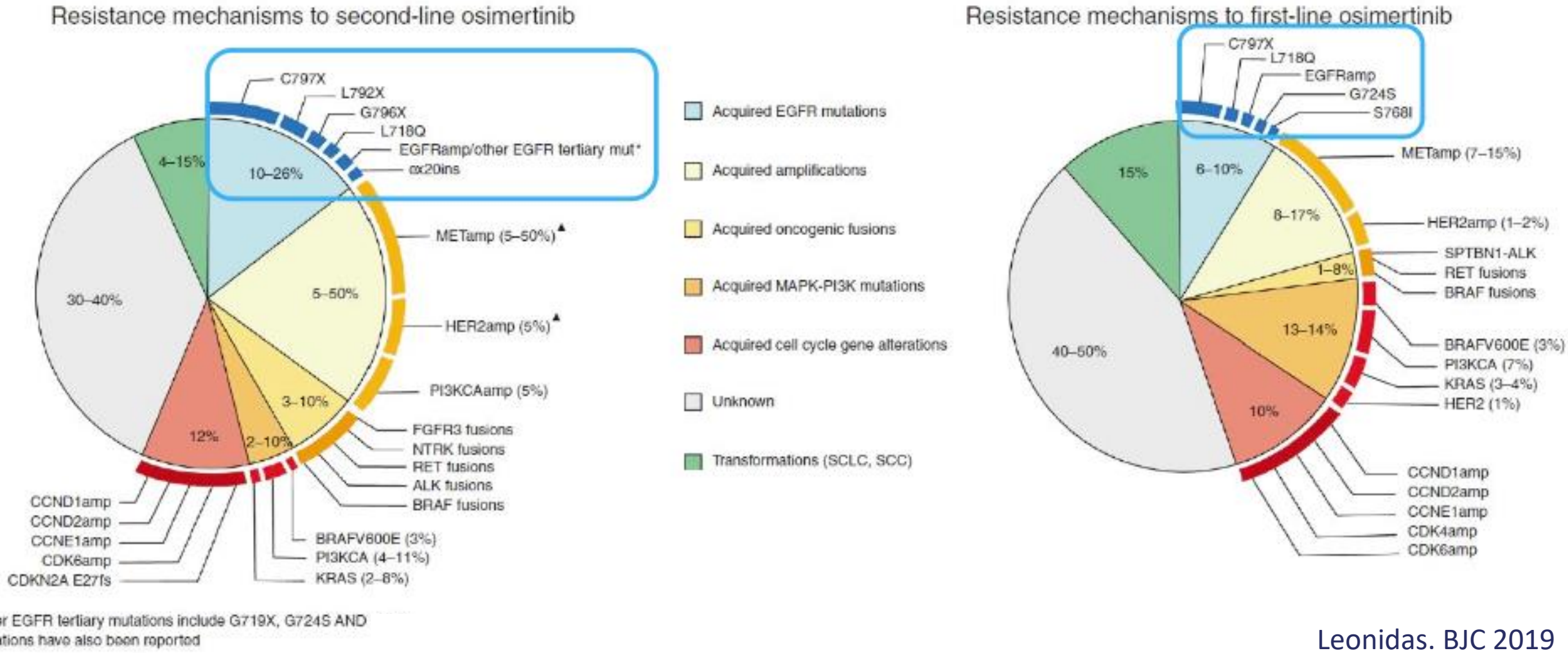




Schmid. Lung Cancer 2020

Resistance to EFGR TKis

EGFR dependent - secondary mutations



* Other EGFR tertiary mutations include G719X, G724S AND
▲ Mutations have also been reported

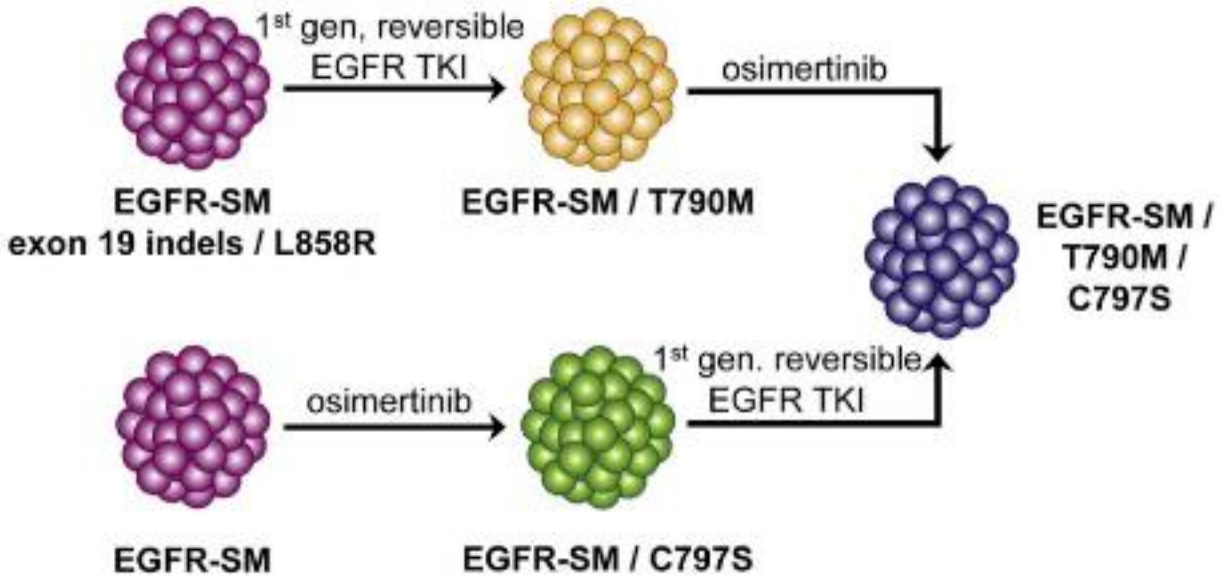
Leonidas. BJC 2019

Resistance to EFGR TKis

EGFR dependent – secondary mutations – C797S

EGFR inhibitor	*EGFR* mutant type (preclinical model prediction)			
	Sensitizing Mutation (SM) exon 19 indels / L858R	SM / C797S	SM / T790M	SM / T790M / C797S
Gefitinib (1st gen. reversible)				
Erlotinib (1st gen. reversible)				
Afatinib (2nd gen. irreversible)				
Dacomitinib (2nd gen. irreversible)				
Osimertinib (3rd gen. irreversible)				

resistant | sensitive



Rangachari. JTO 2019

Resistance to EFGR TKis

EGFR dependent – secondary mutations – C797S

EGFR inhibitor	Sens
	exon
Gefitinib (1st gen. reversible)	
Erlotinib (1st gen. reversible)	
Afatinib (2nd gen. irreversible)	
Dacomitinib (2nd gen. irreversible)	
Osimertinib (3rd gen. irreversible)	

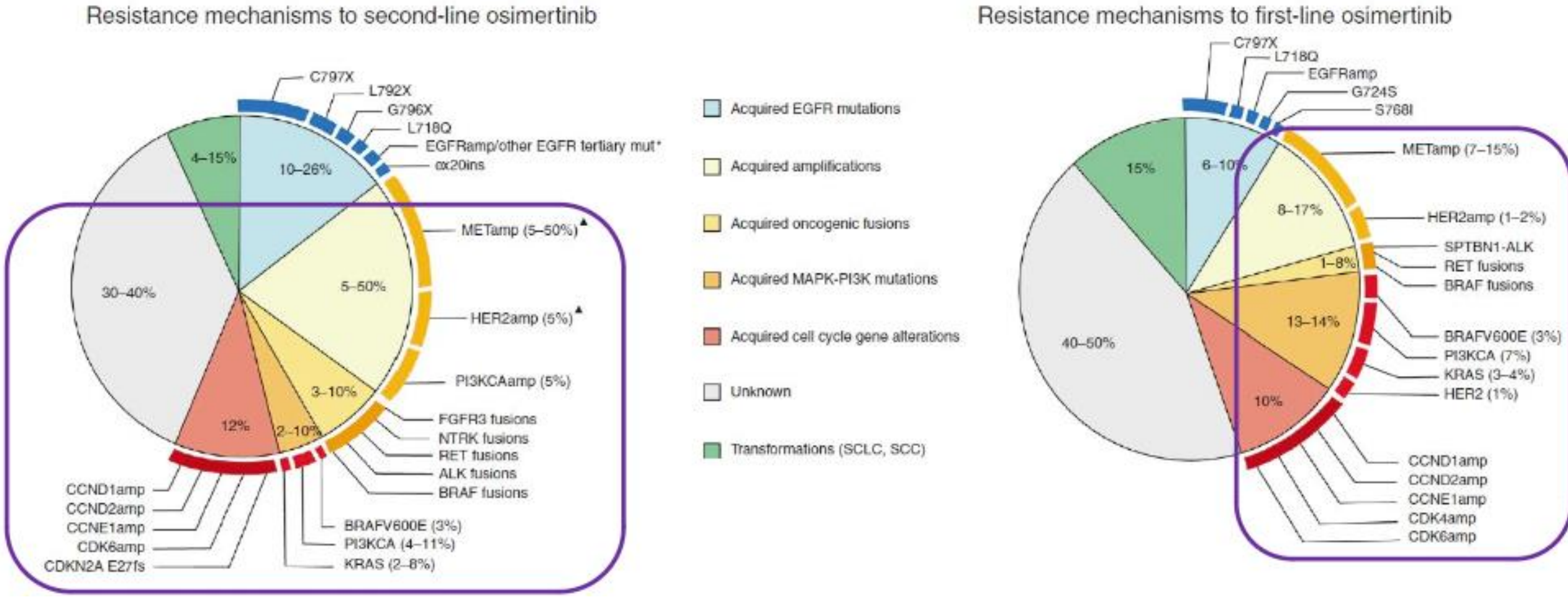
Drug	Mechanism	Status	Notes
Amivantamab	EGFR/MET Ab	Phase II	Approved for EGFR exon 20
BLU-945	EGFR TKI	Phase I/II	Inhibits EGFR T790M and C797S
BIU-701	EGFR TKI	Phase I	Does not inhibit EGFR T790M
BBT-176	EGFR TKI	Phase I	Inhibits EGFR T790M and C797S
JIN-A02	EGFR TKI	Pre-clinical	Inhibits EGFR T790M and C797S
JBJ-09-063	Allosteric inhibitor	Pre-clinical	Only works in L858R background

R-SM / 0M / 97S

Rangachari, JTO 2019. Calles SEOM 2023

Resistance to EFGR TKis

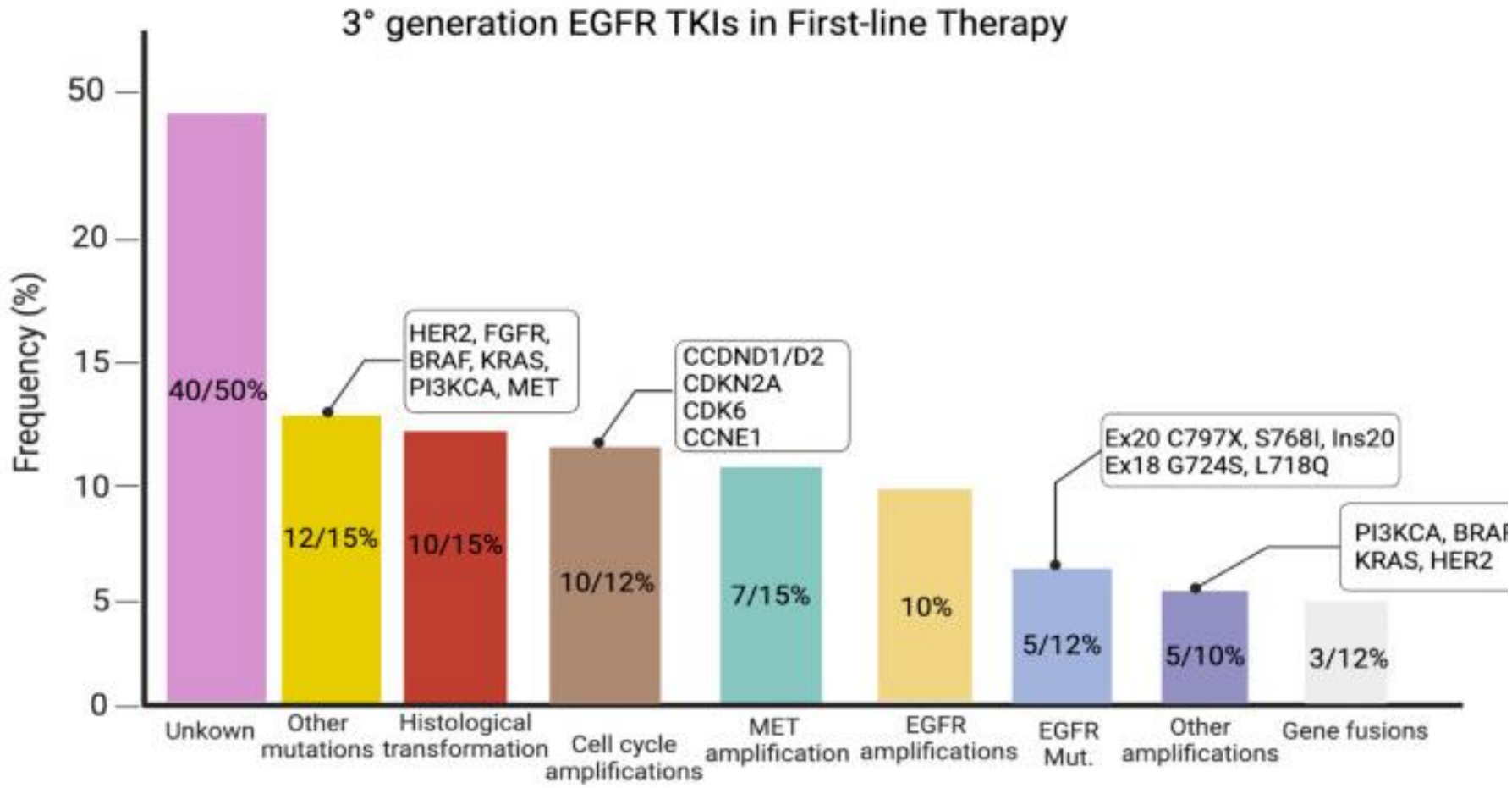
EGFRindependent – activation of bypass pathways



Leonidas. BJC 2019

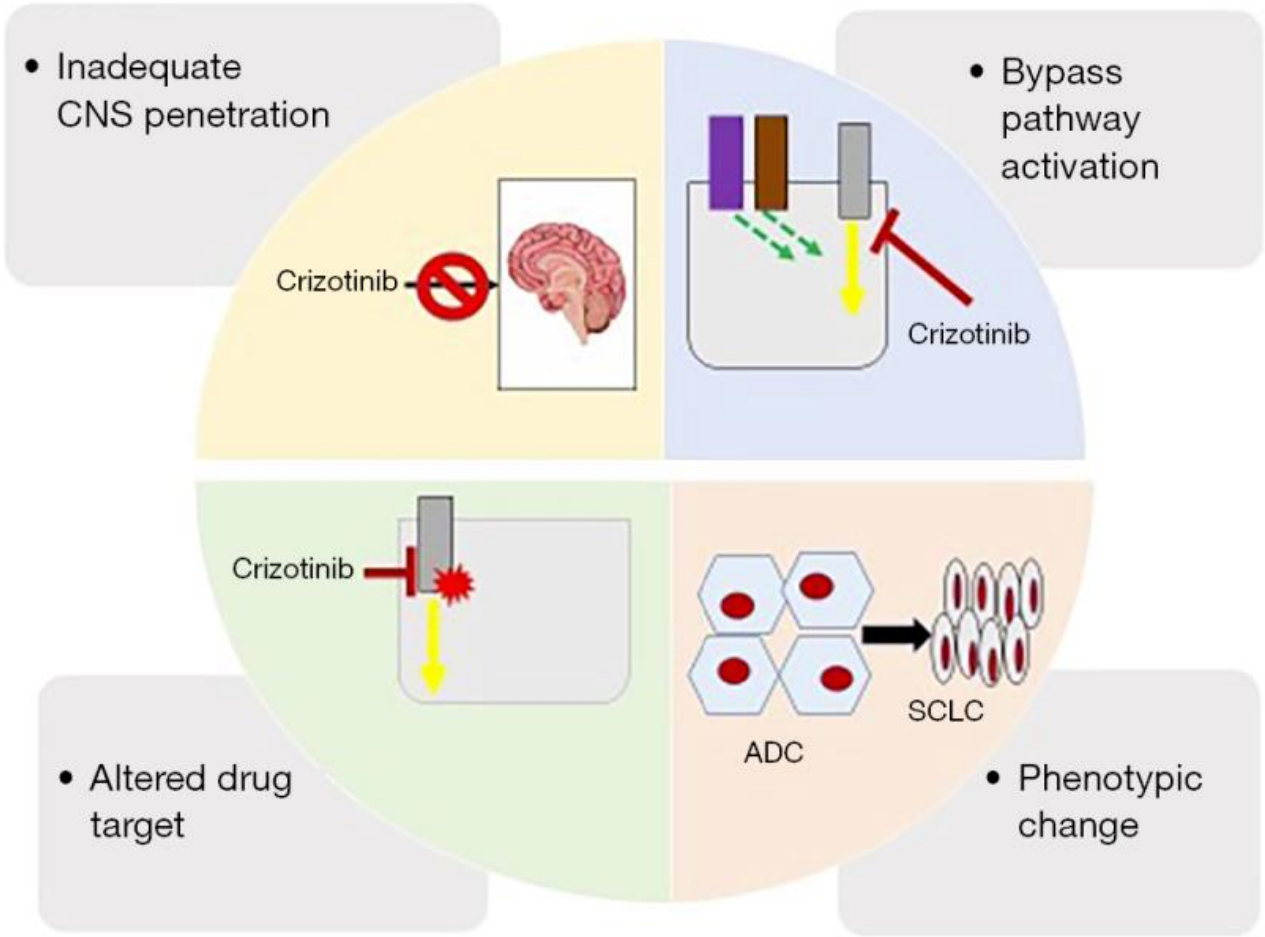
Resistance to EFGR TKis

3rd generation EGFR TKis 1st line therapy



Laface. Pharmaceutics 2023

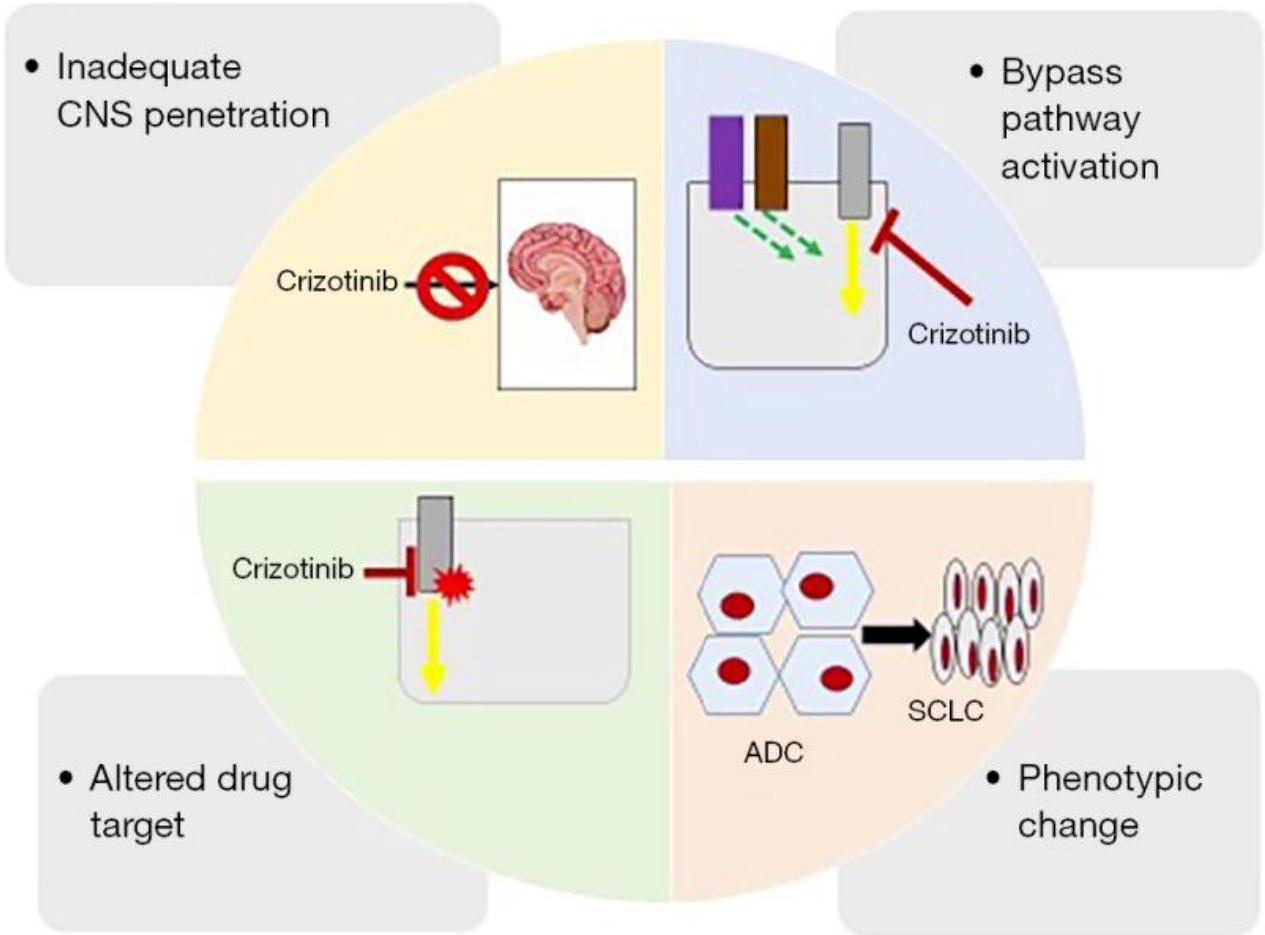
Acquired resistance to TKis and next therapies



García-Pardo, Prec Canc Med 2021. Calles, SEOM 2023

Acquired resistance to TKis and next therapies

Increase dose
Check Ddi
Change TKi



Combos
ADC
BsAb

Next-gen TKi
ADC
BsAb

Chemotherapy
(+/- TKi??)

García-Pardo, Prec Canc Med 2021. Calles, SEOM 2023

Outline

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2. **Evidence of drugs at progression**
3. How to choose a therapy at progression
4. Local challenges
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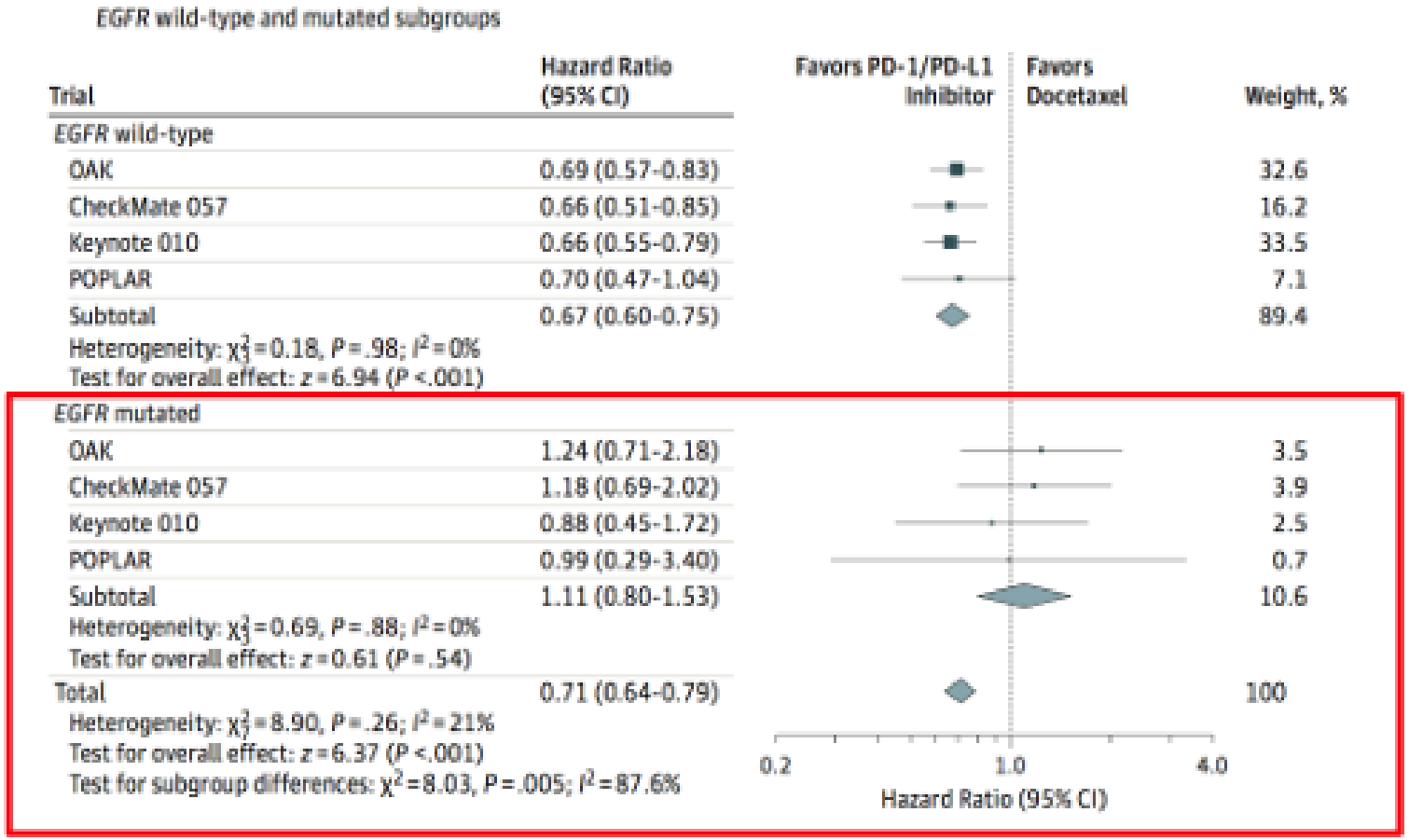
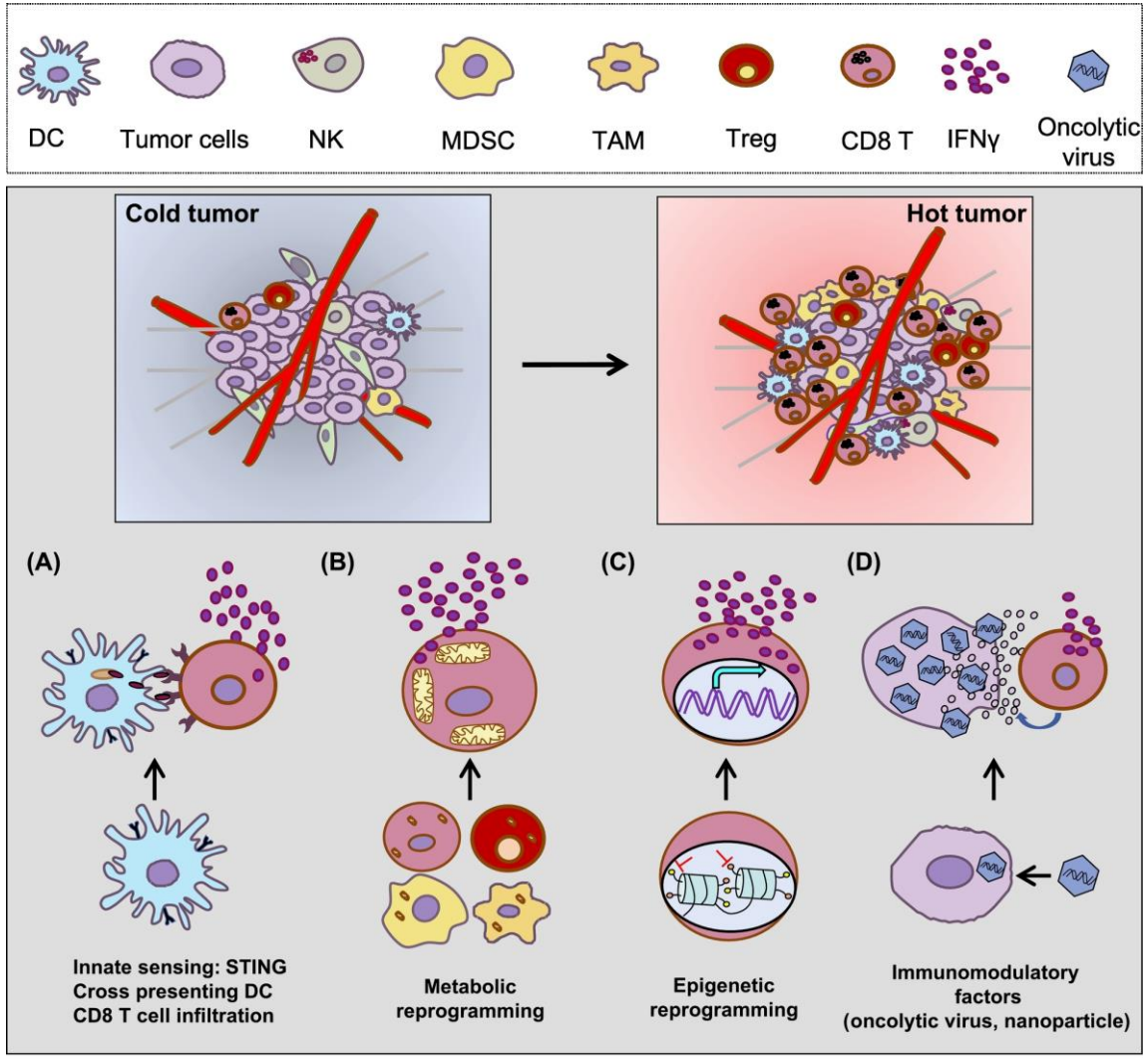
Monotherapy IO in EGFR/ALK/ROS1 NSCLC



Calles ASCO 2020

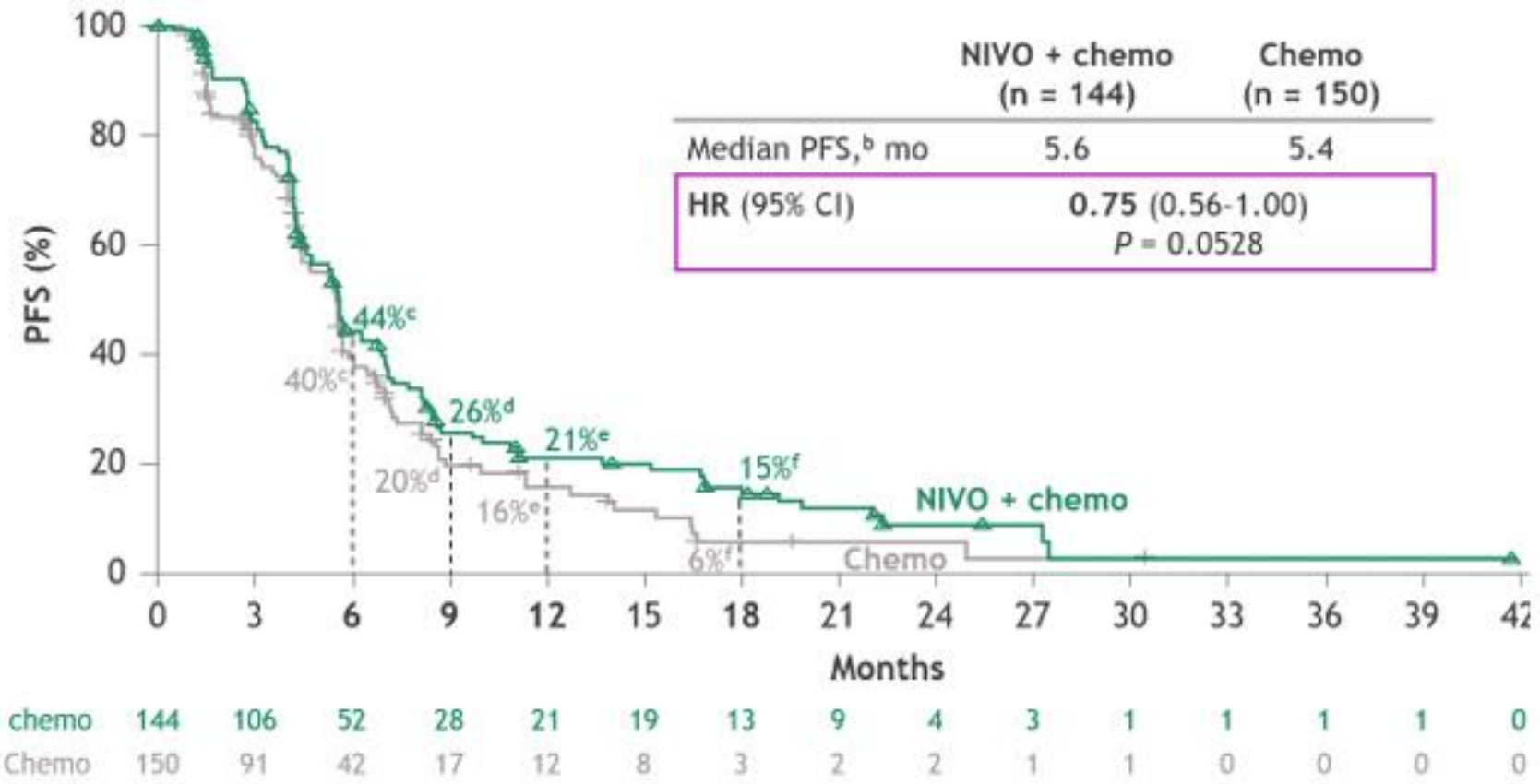
Turning cold tumors into hot tumors?



Duan. Tr Cancer 2021

IO + chemotherapy in EGFR NSCLC

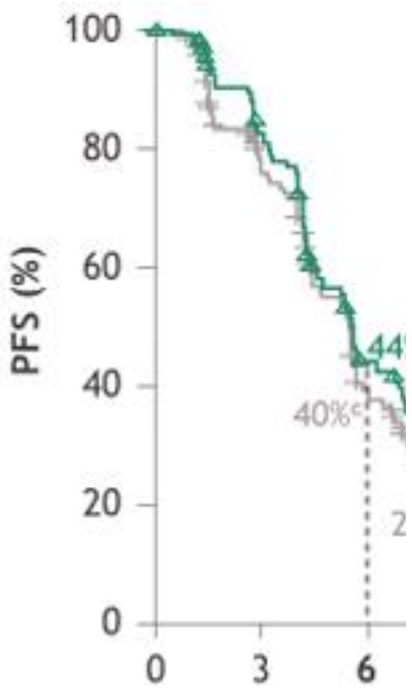
CheckMate 722



	NIVO + chemo (n = 144)	Chemo (n = 150)
Median PFS,[b] mo	5.6	5.4
HR (95% CI)	0.75 (0.56-1.00) *P* = 0.0528	

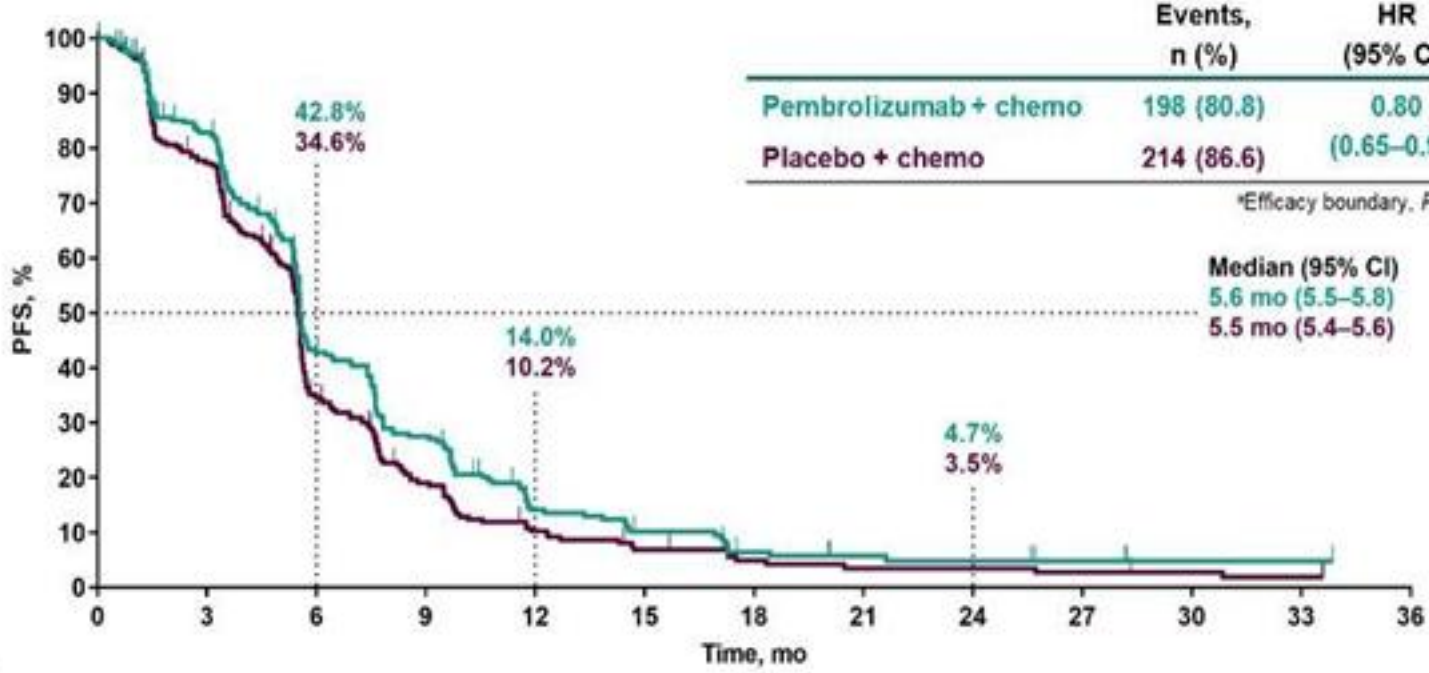
IO + chemotherapy in EGFR NSCLC

CheckMate 722



	0	3	6
NIVO + chemo	144	106	52
Chemo	150	91	42

Keynote 789



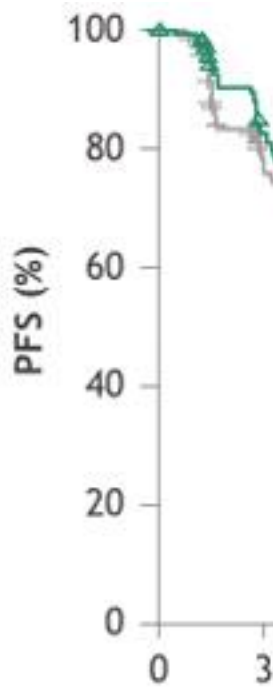
	Events, n (%)	HR (95% CI)	*P* value[a]
Pembrolizumab + chemo	198 (80.8)	0.80 (0.65–0.97)	0.0122
Placebo + chemo	214 (86.6)		

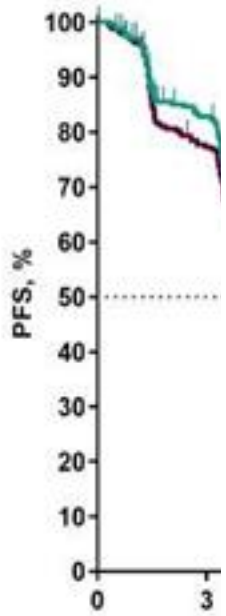
[a]Efficacy boundary, $P = 0.0117$ for PFS (IA2).

No. at risk													
Pembrolizumab + chemo	245	181	90	57	25	17	9	6	5	3	1	1	0
Placebo + chemo	247	184	75	37	19	12	7	5	5	4	3	2	0

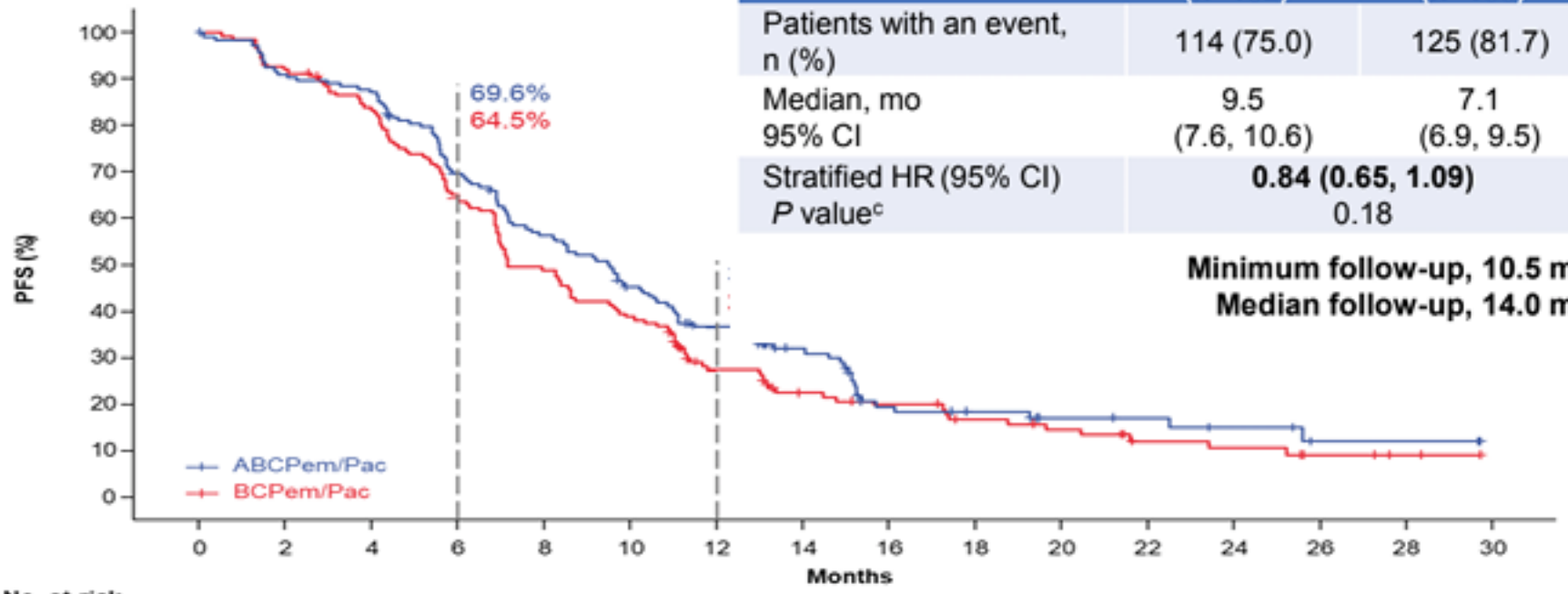
IO + chemotherapy in EGFR NSCLC

CheckMate 722 *Keynote 789* *ImPower 151*





No. at risk			
Pembrolizumab + chemo	245	181	
NIVO + chemo	144	10	
Placebo + chemo	247	184	
Chemo	150	91	



No. at risk																
ABCPem/Pac	152	136	130	102	82	64	47	33	17	14	10	9	7	3	3	0
BCPem/Pac	153	139	124	96	73	58	36	25	21	16	13	8	7	4	2	0

	ABCPem/Pac[b] (n=152)	BCPem/Pac[b] (n=153)
Patients with an event, n (%)	114 (75.0)	125 (81.7)
Median, mo 95% CI	9.5 (7.6, 10.6)	7.1 (6.9, 9.5)
Stratified HR (95% CI) *P* value[c]	**0.84 (0.65, 1.09)** 0.18	

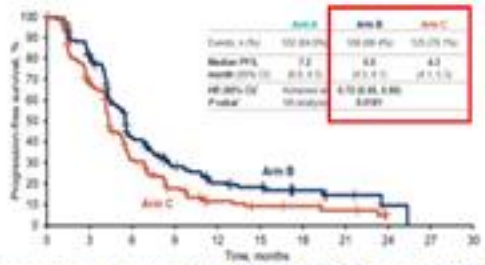
Minimum follow-up, 10.5 mo
Median follow-up, 14.0 mo

IO + chemotherapy + antiVEGF in EGFR NSCLC

ORIENT 131

Sintilimab +/- IBI305 plus chemotherapy

Study met primary endpoint of PFS (by IRRC) in Arm B vs Arm C



Secondary endpoint: ORR, DCR and DOR (by IRRC)

IO + chemotherapy + antiVEGF in EGFR NSCLC

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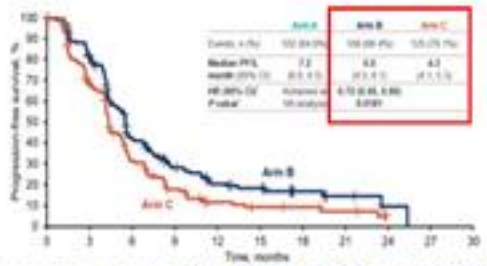
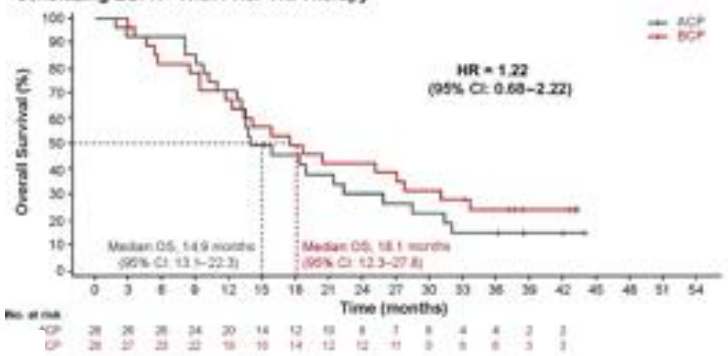


Secondary endpoint: ORR, DCR and DOR (by IRRC)

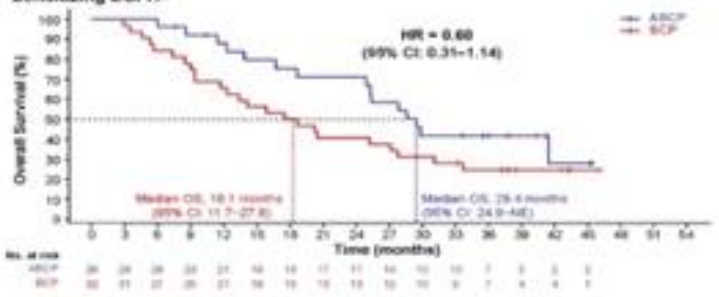
ImPower 150

Atezolizumab +/- Bevacizumab plus chemotherapy

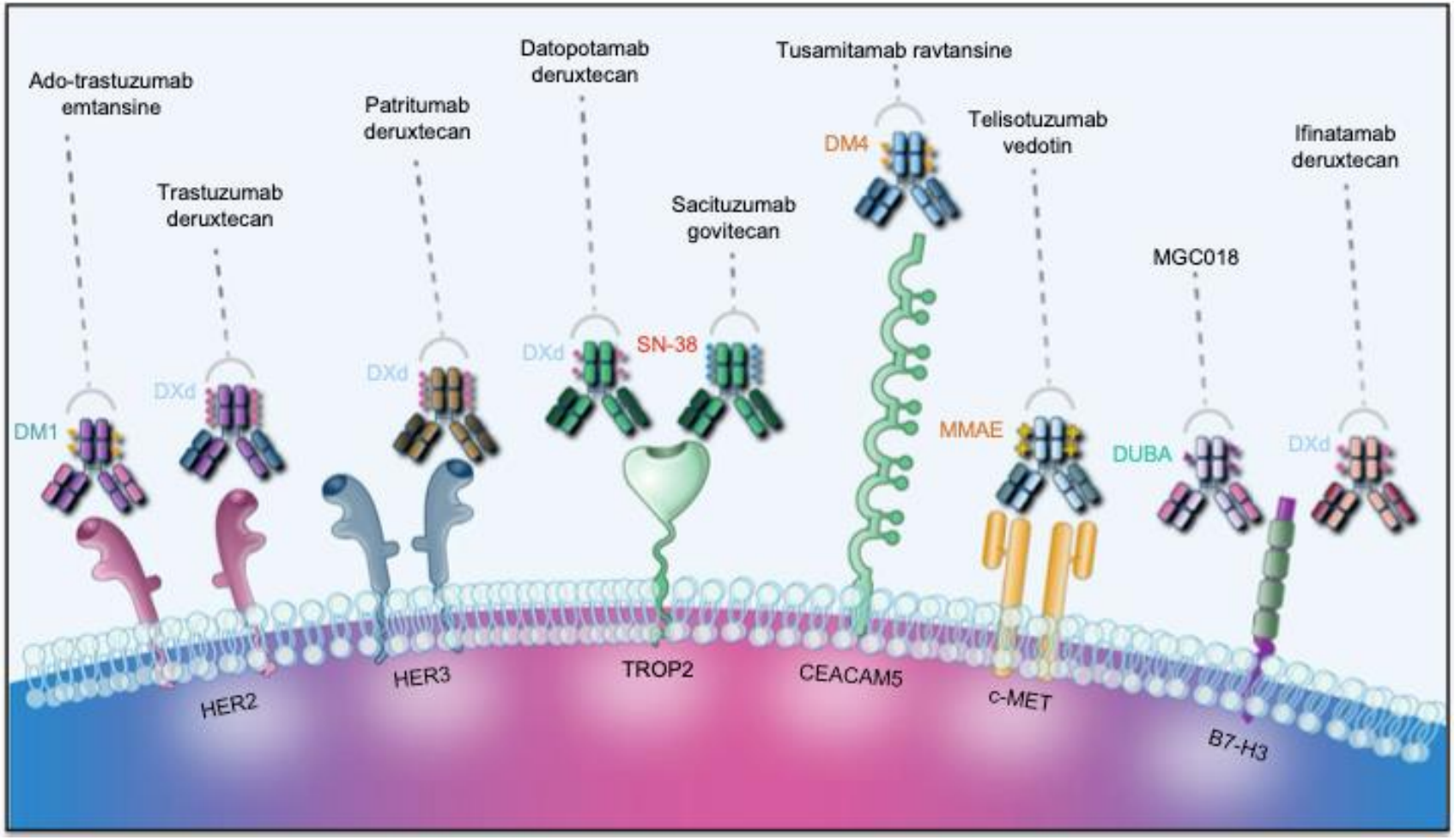
ACP versus BCP
Sensitizing *EGFR*+ With Prior TKI Therapy



ABCP versus BCP
Sensitizing *EGFR*+



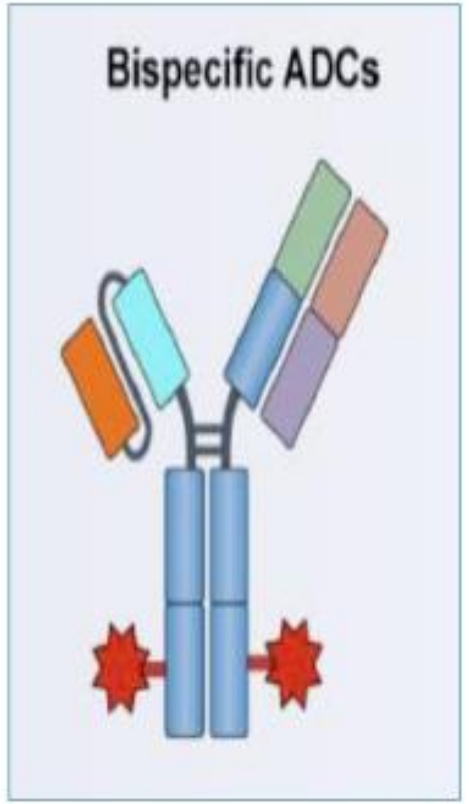
Overview of ADCs for lung cancer



Passaro. JCP 2023

Selection of ADCs for lung cancer

	Target	Drug	Payload	Linker	DAR
Biomarker selection not required	HER3	Patritumab-DXd	Topoisomerase Inhibitor	Cleavable	8
	TROP2	Sacituzumab govitecan	Topoisomerase Inhibitor	Cleavable	7.6
	TROP2	Datopotamab-DXd	Topoisomerase Inhibitor	Cleavable	4
Biomarker selection required	HER2*	Trastuzumab-DXd	Topoisomerase Inhibitor	Cleavable	8
	CEACAM5	Tusamitamab ravtansine	Microtubule Inhibitor	Cleavable	3.8
	c-Met	Telisotuzumab vedotin	Microtubule Inhibitor	Cleavable	3.1
	c-Met	ABBV-400[2]	Topoisomerase Inhibitor	Cleavable	–



Predictive biomarker required, others act as "agnostic" drugs such as Datopotomab Deruxtecan, anti-TROP2

Multiple Payloads in NSCLC

New generation ADC BL-B01D1: EGFR/HER3

Remón. ESMO 2023

Clinical trials in EGFR resistant NSCLC

Blaquier. Clin Cancer Res 2023

Drug and trial	Trial design	Outcomes	Toxicities G≥3
On and off target resistance			
Avimantamab + lazertinib CHRYSALIS	Phase I ORR, DoR, PFS, safety n=45, EGFR 2L prior osi, chemo naïve	ORR 36% DoR 9.6 mo PFS 4.9 mo	16% Discont. 4%
Amivantamab + lazertinib CHRYSALIS-2	Phase II cohort A ORR, DoR, PFS, OS, safety n=162 EGFR 3L prior osi and chemo	ORR 36% DoR 5.1 mo PFS 5.1 mo mOS 14.8 mo	Discont. 7%
Necitumumab + osimertinib NCT02496663	Phase I Cohort E ORR, PFS, safety n=18 EGFR 2L prior osi	ORR 16% PFS 2.3 mo	38% (rash 20%)
Selumetinib + osimertinib TATTON	Phase IB part B ORR, PFS, safety n=47 EGFR 2L prior Tki, n=35 prior 3GTKi	ORR 34% ORR 3GTKi 22.9% PFS 4.2 mo	23%

Clinical trials in EGFR resistant NSCLC

Drug and trial	Trial design	Outcomes	Toxicities G≥3
Off-target MET driven resistance			
Savolitinib + osimertinib TATTON	Phase IB part B1 ORR, PFS, safety n=69 EGFR mutant and MET amplified	ORR 33% DoR 7.9 mo PFS 4.4 mo	57%
Savolitinib + osimertinib SAVANNAH	Phase II ORR, DoR, PFS, safety n=109 EGFR mutant and MET amplified	ORR 49% DoR 9.3 mo PFS 7.1 mo	Not reported
Tepotinib + osimertinib INSIGHT 2	Phase II ORR n=70 EGFR mutant and MET amplified by FISH	ORR FuP>9 mo 54.5% (n=22) ORR FuP>3 m 45.8% (n=48)	23-9%

Blaquier. Clin Cancer Res 2023

Clin

Drug and trial	Trial design	Outcomes	Toxicities G≥3
Delivering targeted chemotherapy			
TDM-1 + chemotherapy TRAEMOS	Phase II ORR, PFS n=27 EGFR mutant HER2 positive by IHC or HER2 amplified	ORR 13% PFS 2.8 mo	21%
Patritumab deruxtecan NCT03260491	Phase I ORR, DoR, PFS, safety n=44 EGFR mutant 3L prior osi and chemotherapy	ORR 39% DoR 7 mo PFS 8.2 mo OS NE	54% Discont. 11%
Datopotamab deruxtecan TROPION-pantumor1	Phase I ORR, DoR, safety n=34 NSCLC with AGA	ORR 35% DoR 9.5 mo	54% Discont 14%
Telisotuzumab vedotin LUMINOSITY	Phase II Cohort EGFR ORR n=60 EGFR mut 3L	ORR 11.6% ORR 16.7% MET-high cohort	
Telisotuzumab vedotin + osimertinib NCT020990523	Phase I ORR, safety n=25 EGFR mut MET overexpresing prior osi	ORR 58%	32%

Summary combinations at TKI progression

	MET TKI + EGFR TKI			Bispecific Ab + EGFR TKI	ADC + EGFR TKI	ADC		CTx + IO	CTx + IO +antiangiogenic
STUDY NAME	ORCHARD	SAVANNAH	INSIGHT2	CHRYSALIS-2 COHORT D	Teliso-V + Osimertinib	TROPION -PanTumor01 (AGA)	U31402-A-U102	CM722 /KN789	ORIENT-31 /IMpower150
Drug	Osimertinib +Savolitinib	Osimertinib +Savolitinib	Osimertinib +Tepotinib	Amivantamab + Lazertinib	Teliso-V + Osimertinib	Datopotomab deruxtecan	Patritumab deruxtecan	IO + CTx	IO + CTx +Anti-angiogenic
n	N=20 (1L Osi)	N=193 (Prev Osi)	N=122 (1L Osi)	N=108 (Prev Osi)	N=25 (Prev Osi)	N=34	N=102 (Prev Osi)	N=294/492	N=158/59
Target	EGFR/MET	EGFR/MET	EGFR/MET	EGFR/MET	EGFR/MET	TROP2	HER3	-	-
Biomarker	NGS	MET IHC 3+ FGCN≥5 MET/CEP7≥2	GCN≥5 Liquid NGS MET/CEP7≥2	-	MET IHC	-	-	-	-
ORR	41%	32%	44%	30%	58%	35%	40%	31%/ 29%	44%/70%
mPFS	-	5.3 (4.2-5.8)	5.4	5.7 (4.0-8.2)	-	-	6.4 (5.3-8.3)	5.6/ 5.6	6.9/ 10.2
mDOR	NR	8.3 (6.9-9.7)	9.7	10.8 (5.5-NR)	-	9.5 (3.3-NR)	7.0 (3.1-NR)	6.7/ 6.3	8.3/ 11.1
Grade ≥ 3 TRAE	30%	45%	28%	9%	44%	26% (@6mg/kg)	32%	45%/ 55.9%	51%/ 64%

Calles. SEOM 2023

Summary combinations at TKI progression (till sept 2023)

	MET TKI + EGFR TKI			Bispecific Ab + EGFR TKI	ADC + EGFR TKI	ADC		CTx + IO	CTx + IO +antiangiogenic
STUDY NAME	ORCHARD	SAVANNAH	INSIGHT2	CHRYSALIS-2 COHORT D	Teliso-V + Osimertinib	TROPION -PanTumor01 (AGA)	U31402-A-U102	CM722 /KN789	ORIENT-31 /IMpower150
Drug	Osimertinib +Savolitinib	Osimertinib +Savolitinib	Osimertinib +Tepotinib	Amivantamab + Lazertinib	Teliso-V + Osimertinib	Datopotomab deruxtecan	Patritumab deruxtecan	IO + CTx	IO + CTx +Anti-angiogenic
n	N=20 (1L Osi)	N=193 (Prev Osi)	N=122 (1L Osi)	N=108 (Prev Osi)	N=25 (Prev Osi)	N=34	N=102 (Prev Osi)	N=294/492	N=158/59
Target	EGFR/MET	EGFR/MET	EGFR/MET	EGFR/MET	EGFR/MET	TROP2	HER3	-	-
Biomarker	NGS	MET IHC 3+ FGCN≥5 MET/CEP7≥2	GCN≥5 Liquid NGS MET/CEP7≥2	-	MET IHC	-	-	-	-
ORR	41%	32%	44%	30%	58%	35%	40%	31%/ 29%	44%/70%
mPFS	-	5.3 (4.2-5.8)	5.4	5.7 (4.0-8.2)	-	-	6.4 (5.3-8.3)	5.6/ 5.6	6.9/ 10.2
mDOR	NR	8.3 (6.9-9.7)	9.7	10.8 (5.5-NR)	-	9.5 (3.3-NR)	7.0 (3.1-NR)	6.7/ 6.3	8.3/ 11.1
Grade ≥ 3 TRAE	30%	45%	28%	9%	44%	26% (@6mg/kg)	32%	45%/ 55.9%	51%/ 64%

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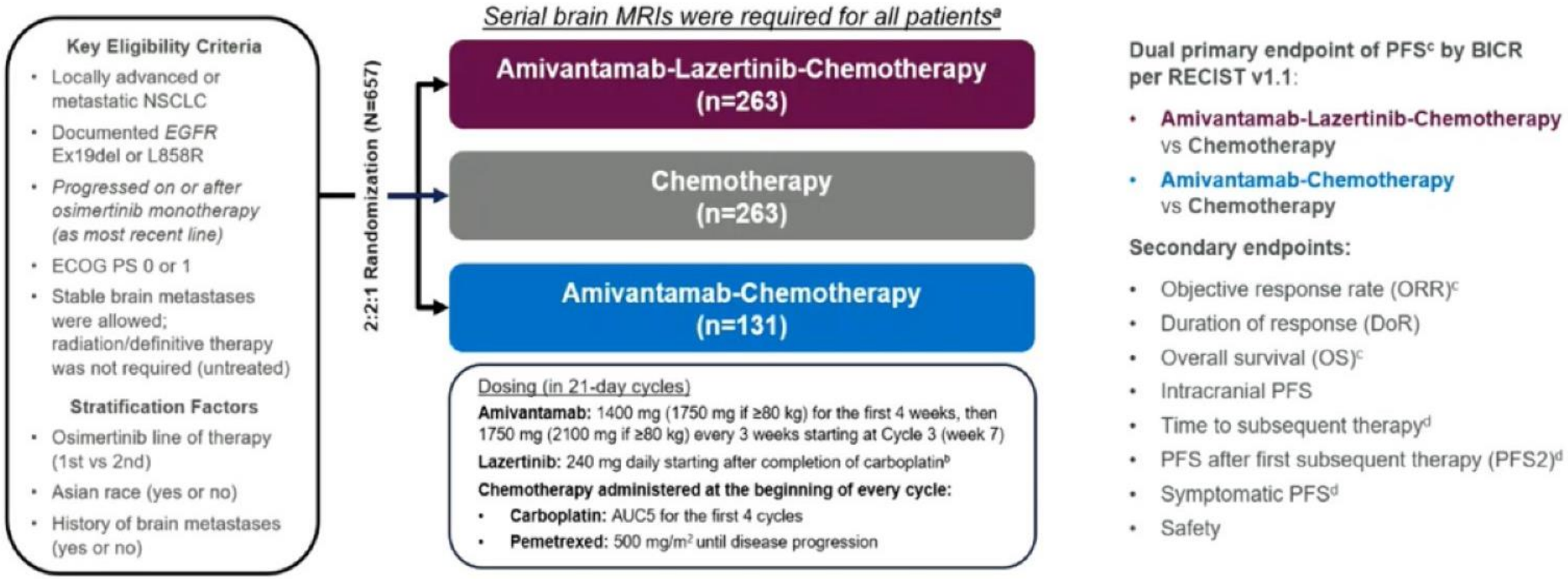
MARIPOSA-2

Trial design

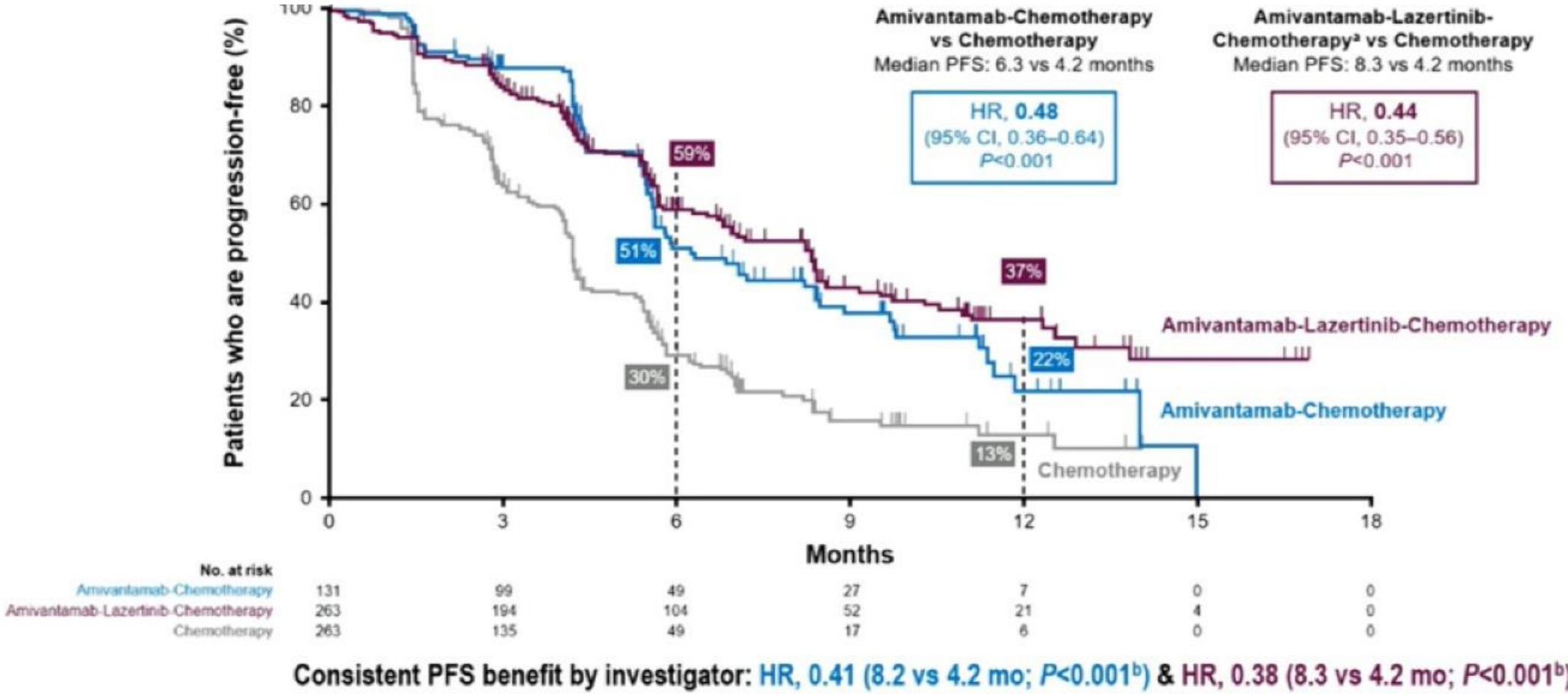


MARIPOSA-2 (ClinicalTrials.gov identifier: NCT04988295) enrollment period: December 2021 to April 2023; data cut-off: 10 July 2023.
[a]Patients who could not have MRI were allowed to have CT scans.
[b]All patients randomized before 7 November 2022 initiated lazertinib on the first day of cycle 1.
[c]Key statistical assumptions: 600 patient with 350 events across all 3 arms would provide approximately 83% and 93% power for amivantamab chemotherapy and amivantamab-lazertinib chemotherapy, respectively, vs chemotherapy to detect a HR of 0 65 using a log-rank test, with an overall 2-sided α of 0.05 (median PFS of 8.5 months for amivantamab-containing arms vs 5.5 for chemotherapy). Statistical hypothesis testing included PFS, ORR, and then OS.
[d]These secondary endpoints (time to subsequent therapy, PFS2, and symptomatic PFS) will be presented at a future congress
Passaro A, et al. Ann Oncol. 2023;34(Suppl 2):Abstract LBA15; Passaro A, et al. Ann Oncol. 2023;S0923-7534(23)04281-3.

Passaro. ESMO 2023

MARIPOSA-2

Progression-free survival by BICR



Consistent PFS benefit by investigator: HR, 0.41 (8.2 vs 4.2 mo; *P*<0.001[b]) & HR, 0.38 (8.3 vs 4.2 mo; *P*<0.001[b])

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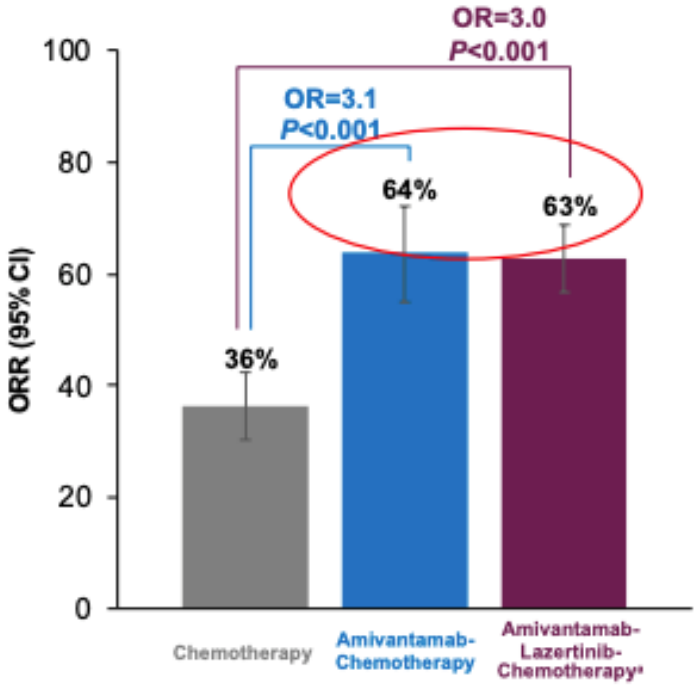
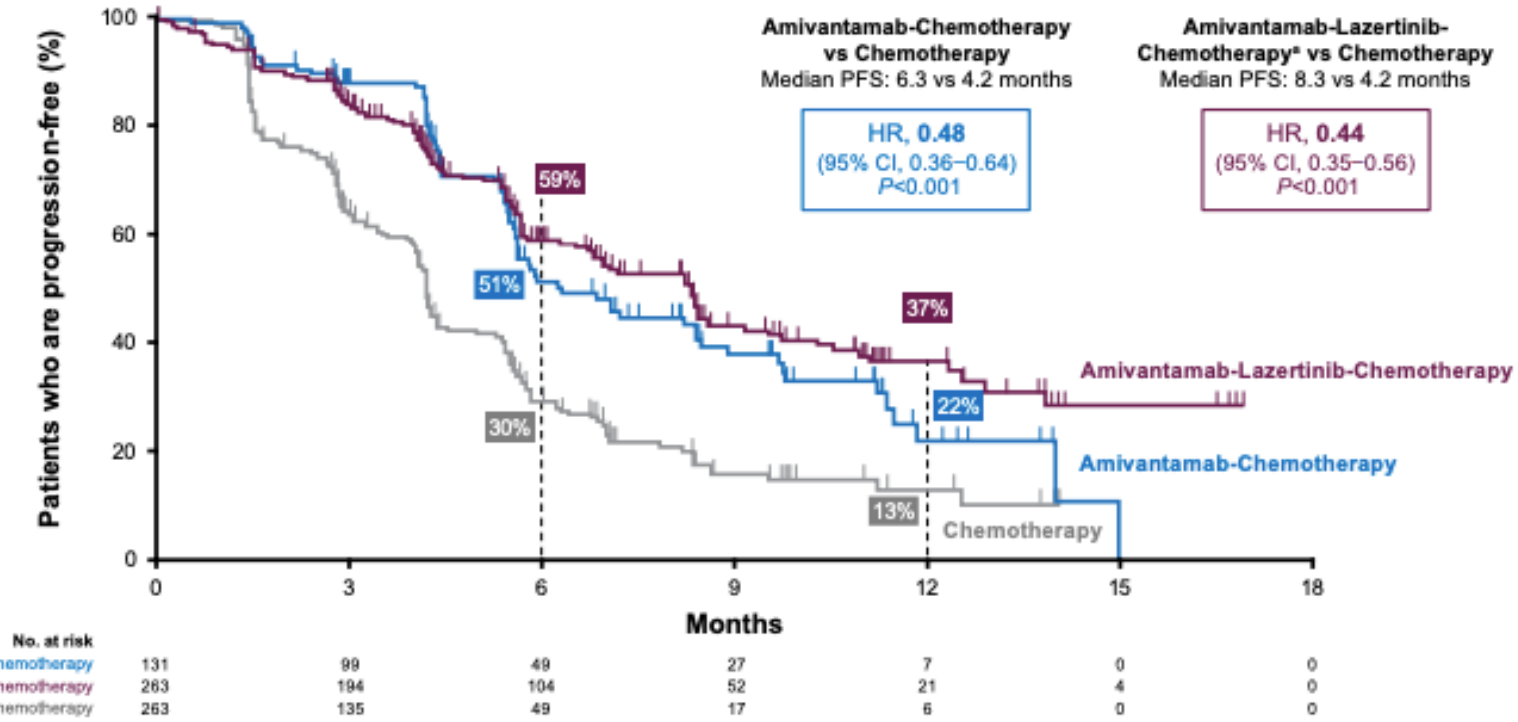
MARIPOSA-2

Progression-free survival by BICR and ORR





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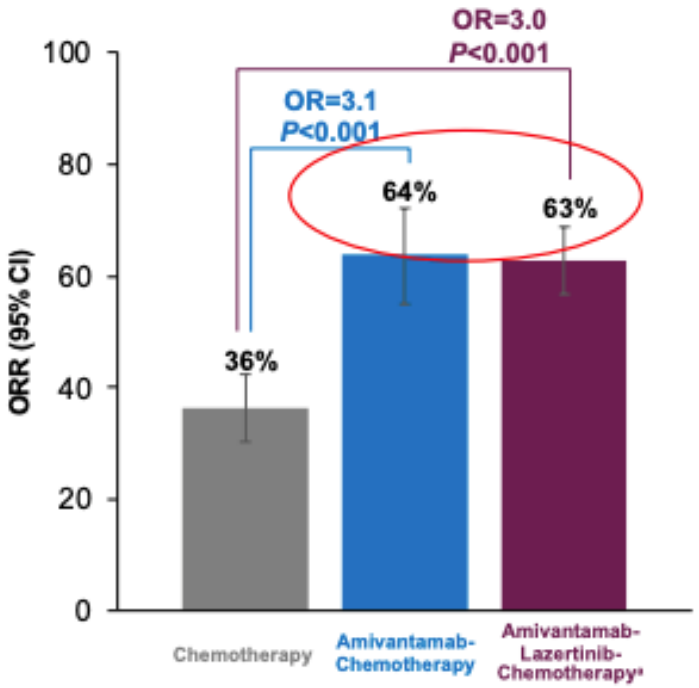
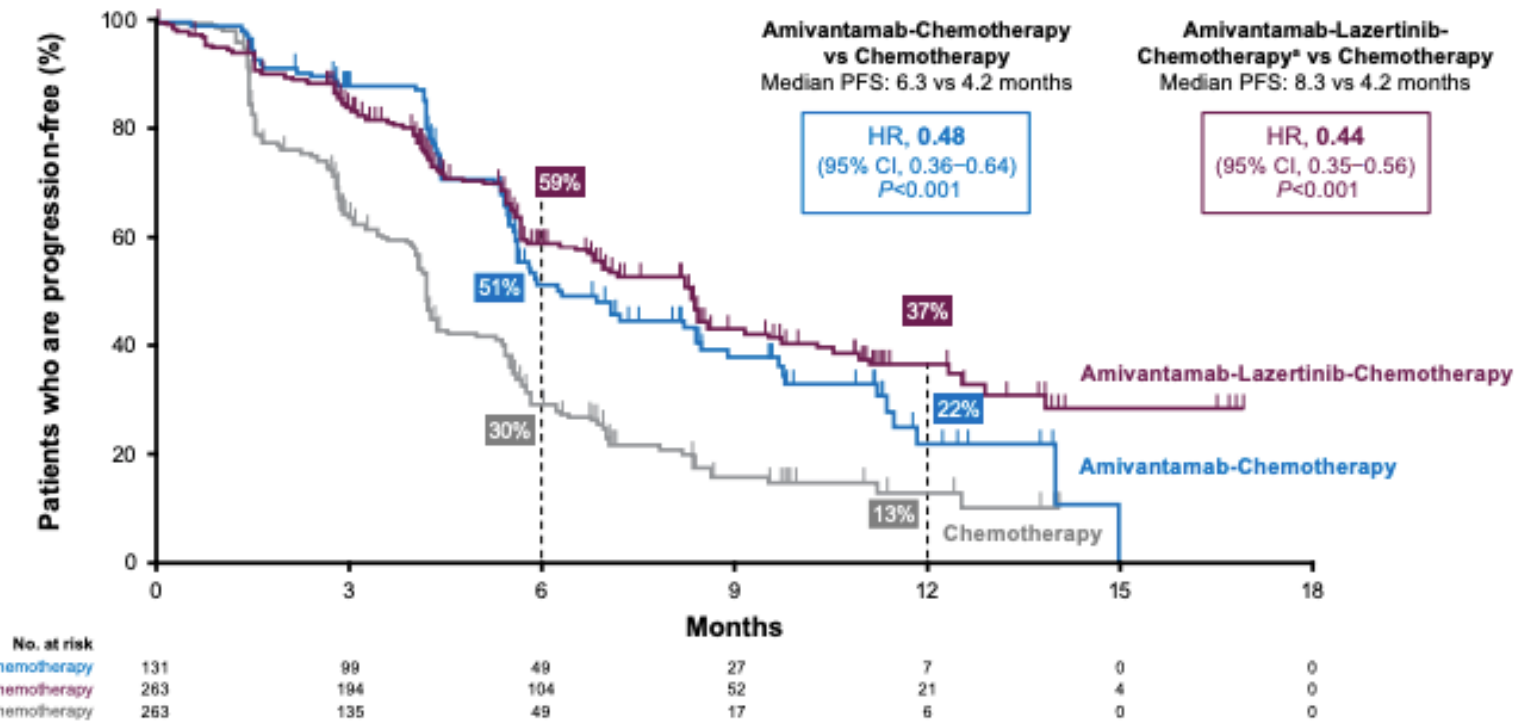
MARIPOSA-2

Progression-free survival by BICR and ORR

Amivantamab-chemo and amivantamab-lazertinib chemo reduced risk of progression or death by 52% and 56%, respectively (median FUP 8.7 mo)





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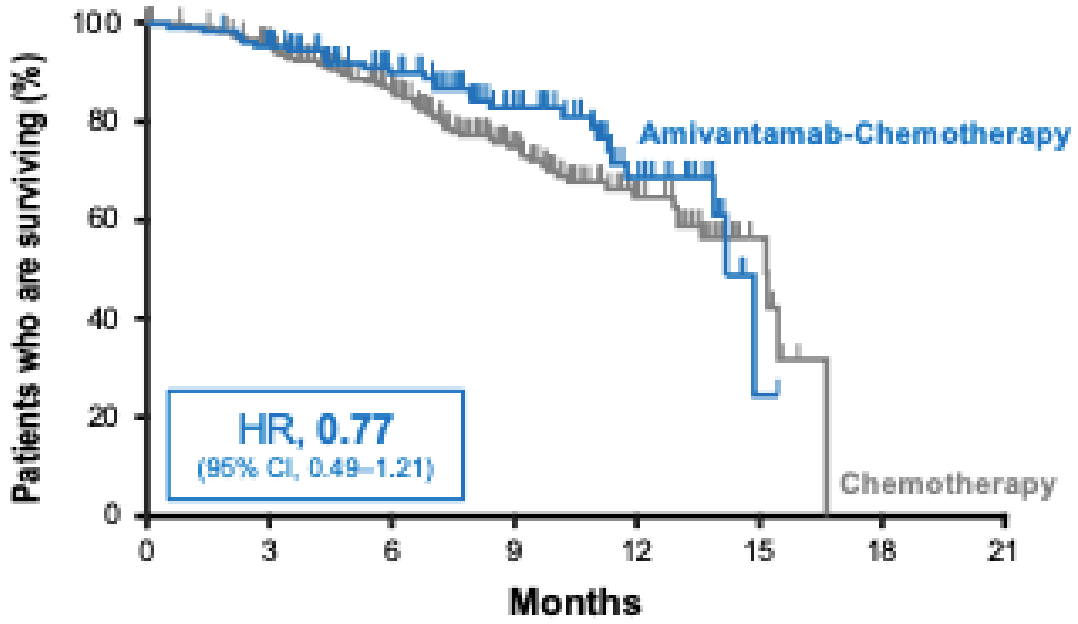
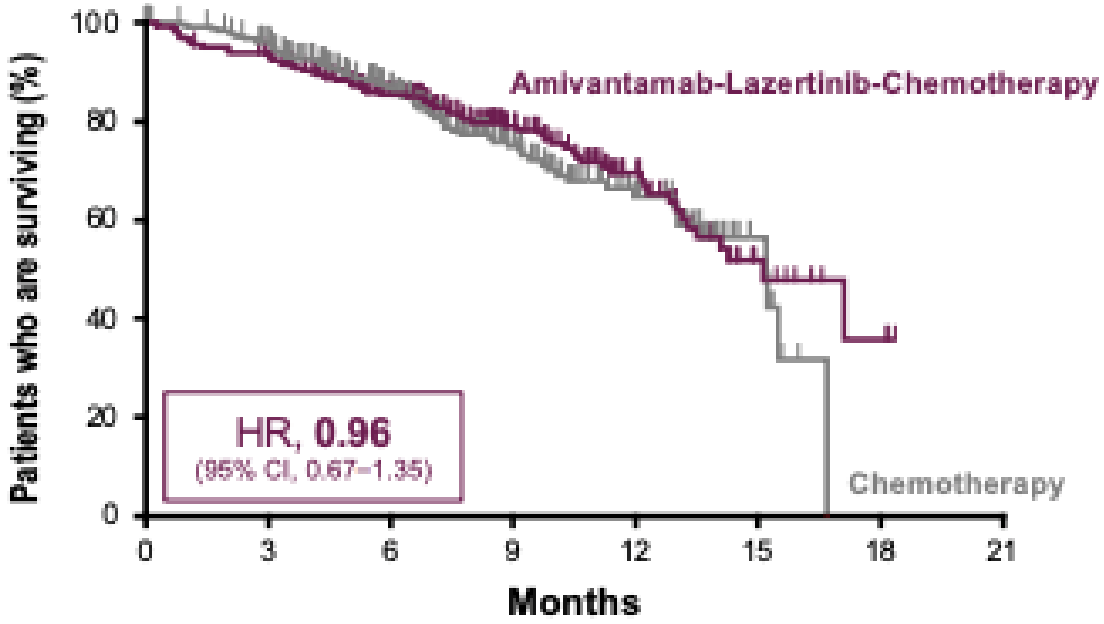
MARIPOSA-2

Early interim overall survival (8.7 mo)



No. at risk							
Amivantamab-Chemotherapy	131	122	89	54	24	1	0
Chemotherapy	263	229	158	85	39	8	0



No. at risk								
Amivantamab-Lazertinib-Chemotherapy	263	241	170	101	52	13	3	0
Chemotherapy	263	229	158	85	39	8	0	0

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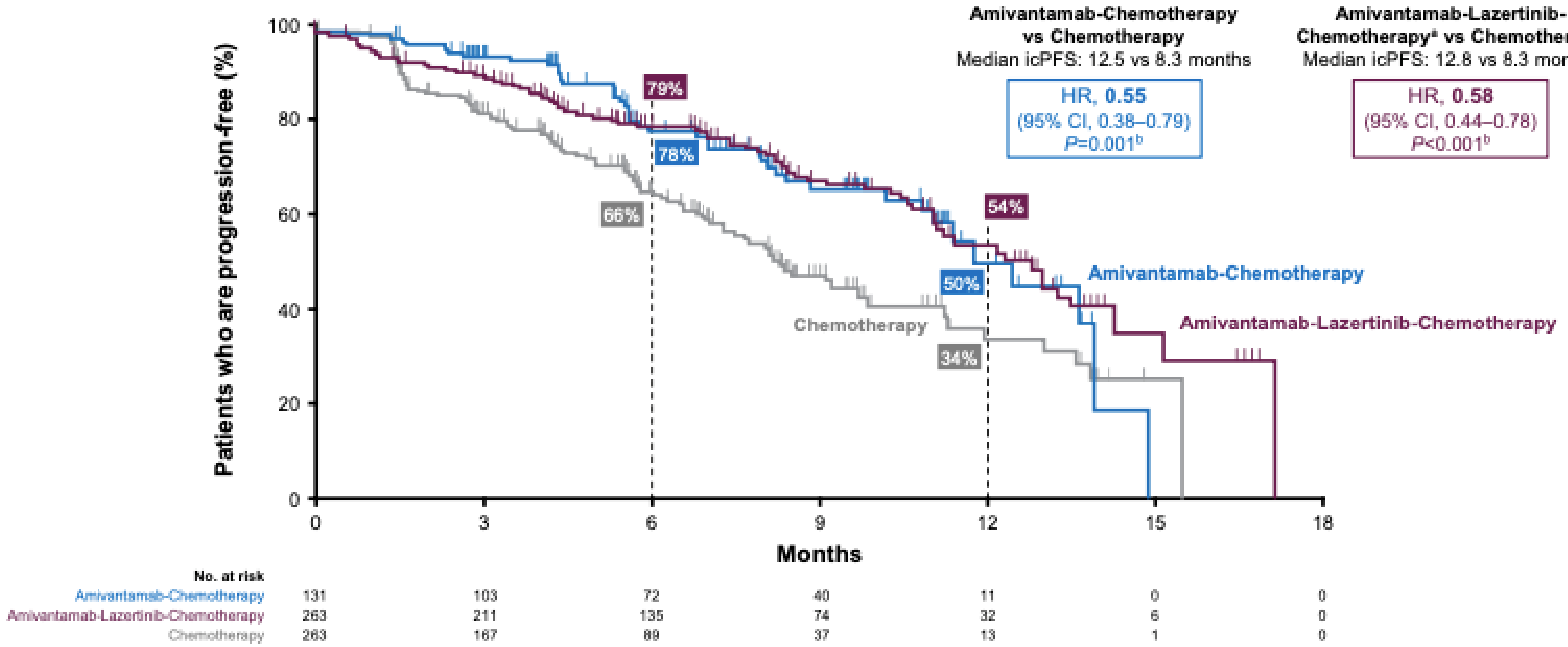
MARIPOSA-2

Intracranial progression-free survival by BICR



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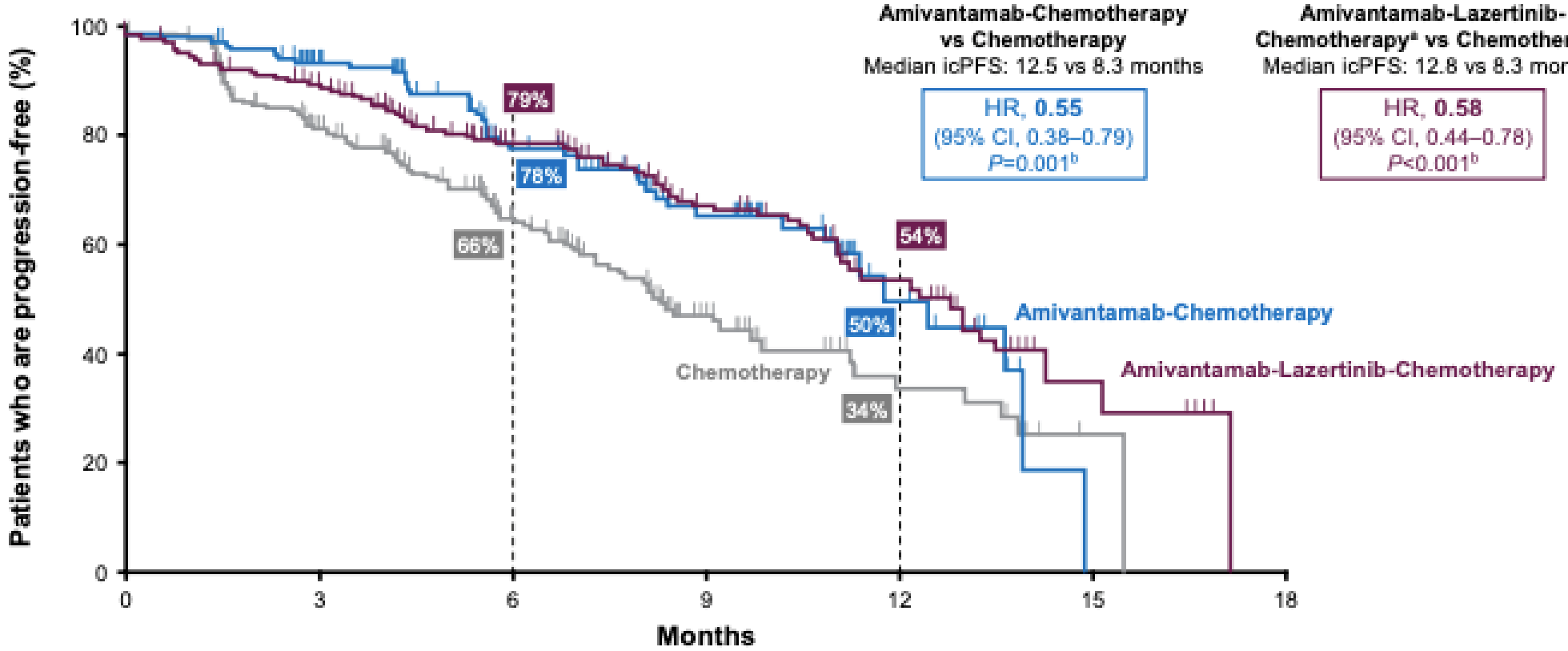
MARIPOSA-2

Intracranial progression-free survival by BICR

Lazertinib is adding benefit?
More mature data awaited



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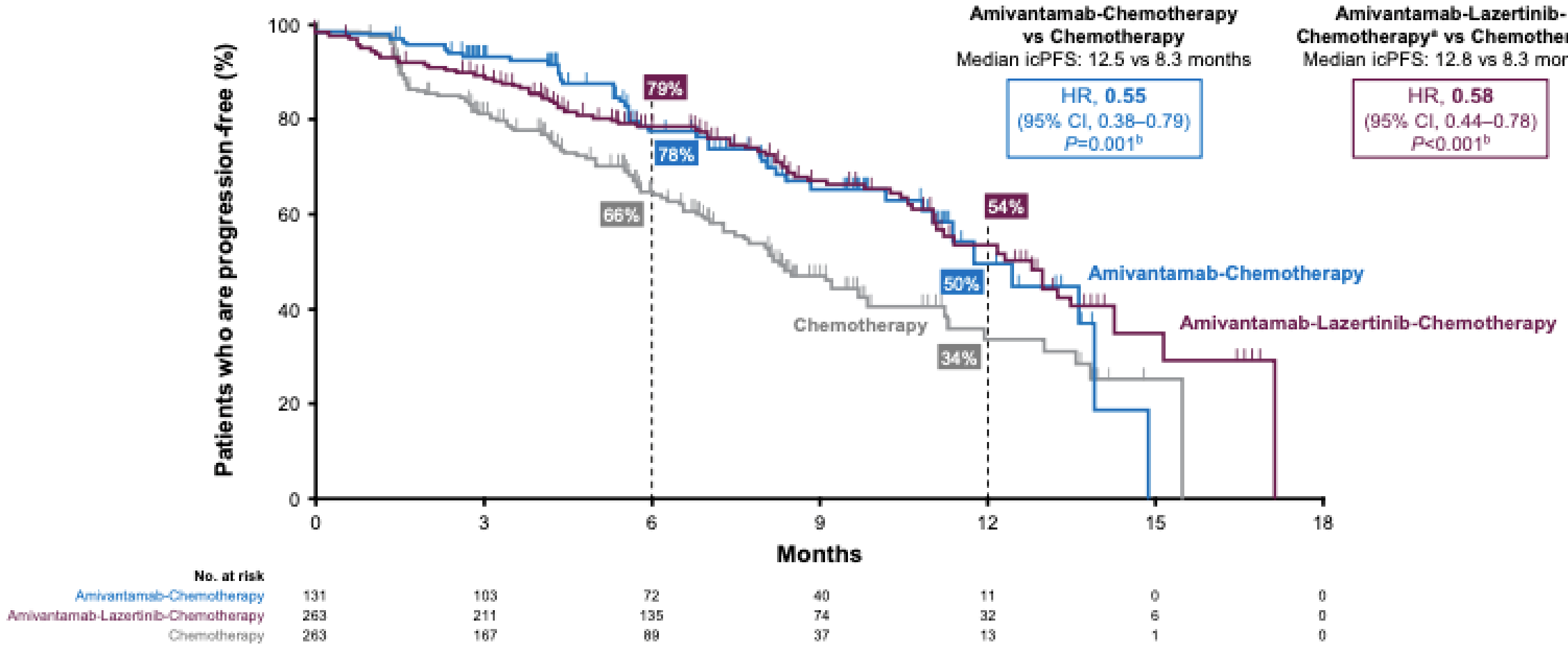
MARIPOSA-2

Intracranial progression-free survival by BICR



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Anti HER2 agents

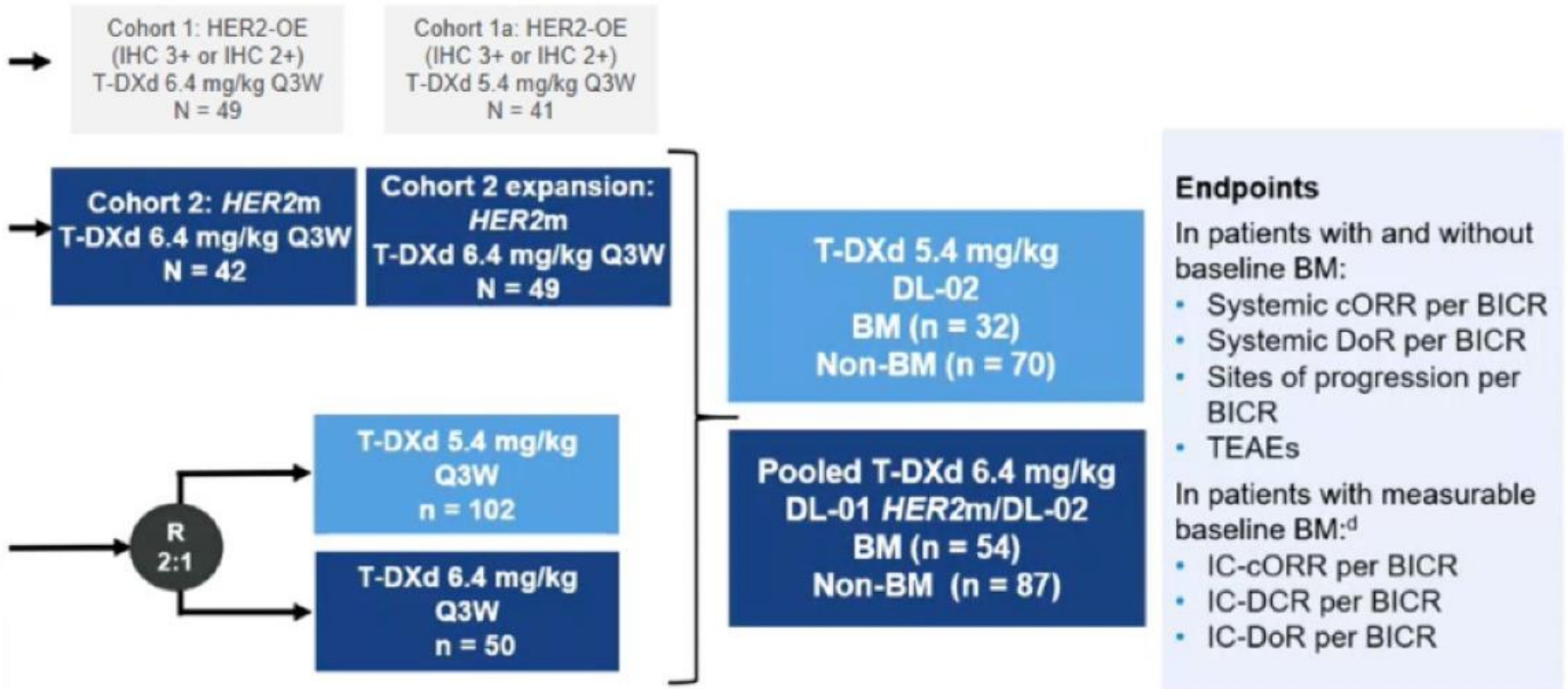
DESTINY-Lung 01 + DESTINY-Lung 02 pooled analysis with and without brain metastases

DESTINY-Lung01[a]

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed from or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- ECOG PS of 0 or 1
- Locally reported *HER2*m (Cohort 2)
- Asymptomatic BM allowed[c]

DESTINY-Lung02[b]

- Metastatic *HER2*m NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1
- Locally reported *HER2*m
- Asymptomatic BM allowed[c]



Endpoints

In patients with and without baseline BM:

- Systemic cORR per BICR
- Systemic DoR per BICR
- Sites of progression per BICR
- TEAEs

In patients with measurable baseline BM:[d]

- IC-cORR per BICR
- IC-DCR per BICR
- IC-DoR per BICR

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HER2 mutant patients

DESTINY-Lung 01 + DESTINY-Lung 02 pooled analysis with and without brain metastases: response (BICR)

	T-DXd 5.4 mg/kg DL-02 BM		Pooled T-DXd 6.4 mg/kg DL-01 *HER2*m/DL-02 BM	
	Prior treatment n = 8	No prior treatment n = 6	Prior treatment n = 14	No prior treatment n = 16
IC-cORR, n (%)[a]	**4 (50.0)**	**3 (50.0)**	**3 (21.4)**	**6 (37.5)**
95% CI[b]	15.7-84.3	11.8-88.2	4.7-50.8	15.2-64.6
CR	0	3 (50.0)	0	0
PR	4 (50.0)	0	3 (21.4)	6 (37.5)
SD	3 (37.5)	3 (50.0)	7 (50.0)	6 (37.5)
PD	1 (12.5)	0	3 (21.4)	1 (6.3)
NE	0	0	0	2 (12.5)
Missing	0	0	1 (7.1)	1 (6.3)
IC-DCR, n (%)[a]	**7 (87.5)**	**6 (100.0)**	**10 (71.4)**	**12 (75.0)**
95% CI[b]	47.3-99.7	54.1-100.0	41.9-91.6	47.6-92.7
IC-DoR, median, months[c]	**7.1**	**9.5**	**4.4**	**5.6**
95% CI[d]	3.6-NE	NE-NE	2.9-NE	2.9-NE
Time to IC progression, median, months	**2.8**	**NE**	**2.6**	**5.6**
Range	1.3-10.9	NE-NE	1.2-6.9	0.6-14.0

IC responses were similar in patients with or without prior BM treatment among patients with BM at baseline

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Datopotamab deruxtecan in 2L NSCLC with actionable genomic alterations

TROPION-Lung05 design

- **Dato-DXd** is a TROP2-directed ADC consisting of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a highly potent topoisomerase I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[1]
- In the **phase 1 TROPION-PanTumor01** study, Dato-DXd showed promising efficacy in patients with actionable genomic alterations[2]
- **TROPION-Lung05** (NCT04484142) is a **phase 2**, single-arm study evaluating Dato-DXd in patients with **advanced or metastatic NSCLC with actionable genomic alterations** that progressed on or after targeted therapy and platinum-based chemotherapy

Screening

Key inclusion criteria

- Stage IIIB, IIIC, or IV NSCLC
- Presence of ≥1 actionable genomic alteration (*EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*)
- ECOG PS of 0 or 1
- ≥1 line of targeted therapy
- 1 or 2 prior cytotoxic agent–containing therapies including platinum-based therapy in the metastatic setting
- Radiographic disease progression after targeted therapy

Treatment

Dato-DXd
6 mg/kg
Q3W

Endpoints[a]

Primary: ORR by BICR

Secondary:

- By BICR and investigator: DOR, DCR, CBR, PFS, TTR
- By investigator: ORR
- OS, safety, PK, immunogenicity

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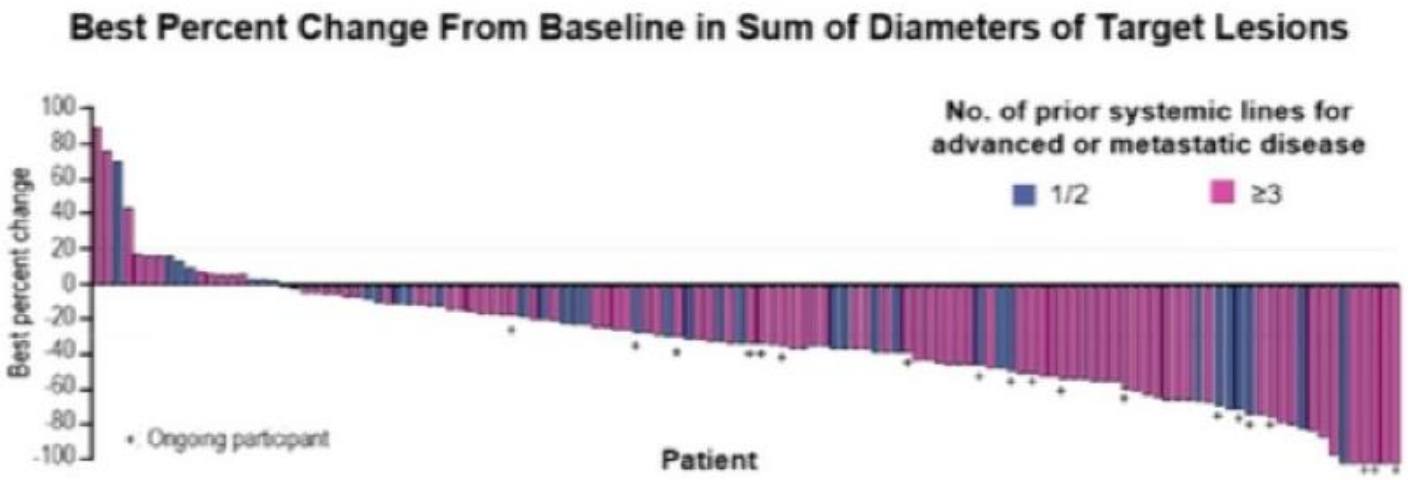
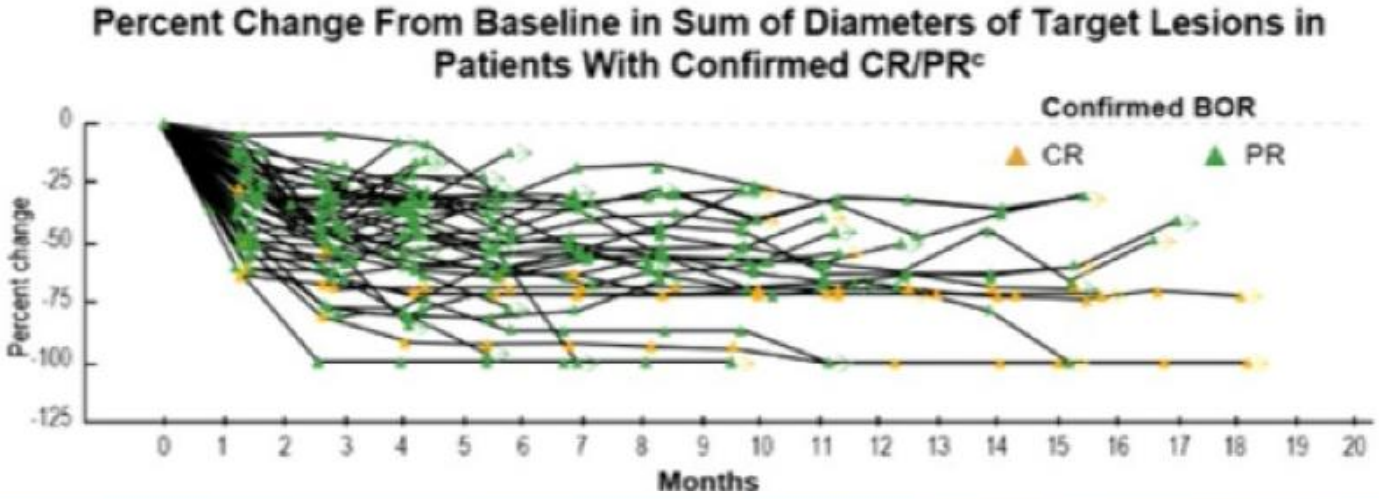
Datopotamab deruxtecan in 2L NSCLC with actionable genomic alterations

TROPION-Lung05: radiological response





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Datopotamab deruxtecan in 2L NSCLC with actionable genomic alterations

TROPION-Lung05: response (BICR)

Response per BICR	All treated patients (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI][a]	49 (35.8) [27.8-44.4]	34 (43.6) [32.4-55.3]	8 (23.5) [10.7-41.2]
Median DOR (95% CI), months	7.0 (4.2-9.8)	7.0 (4.2-10.2)	7.0 (2.8-8.4)
DCR confirmed, n (%) [95% CI][a]	108 (78.8) [71.0-85.3]	64 (82.1) [71.7-89.8]	25 (73.5) [55.6-87.1]
Median PFS, (95% CI), months[b]	5.4 (4.7-7.0)	5.8 (5.4-8.3)	4.3 (2.6-6.9)

BOR: In the overall population (N=137), 4 patients (3%) achieved a CR and 45 (33%) achieved a PR

***EGFR* subset:** Among patients with sensitizing or T790M mutations (N=68), the ORR was 49.1% in those previously treated with osimertinib

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Datopotamab deruxtecan in 2L NSCLC with actionable genomic alterations

TROPION-Lung05: safety profile and conclusions

- Antitumour activity with Dato-Dxd in heavily pretreated patients even those with genomic alterations
-
- Safety profile: manageable, nausea and stomatitis most frequent AEs

- Ongoing phase III trial TROPION-Lung01 assessing Dato-Dxd vs docetaxel in pretreated patients

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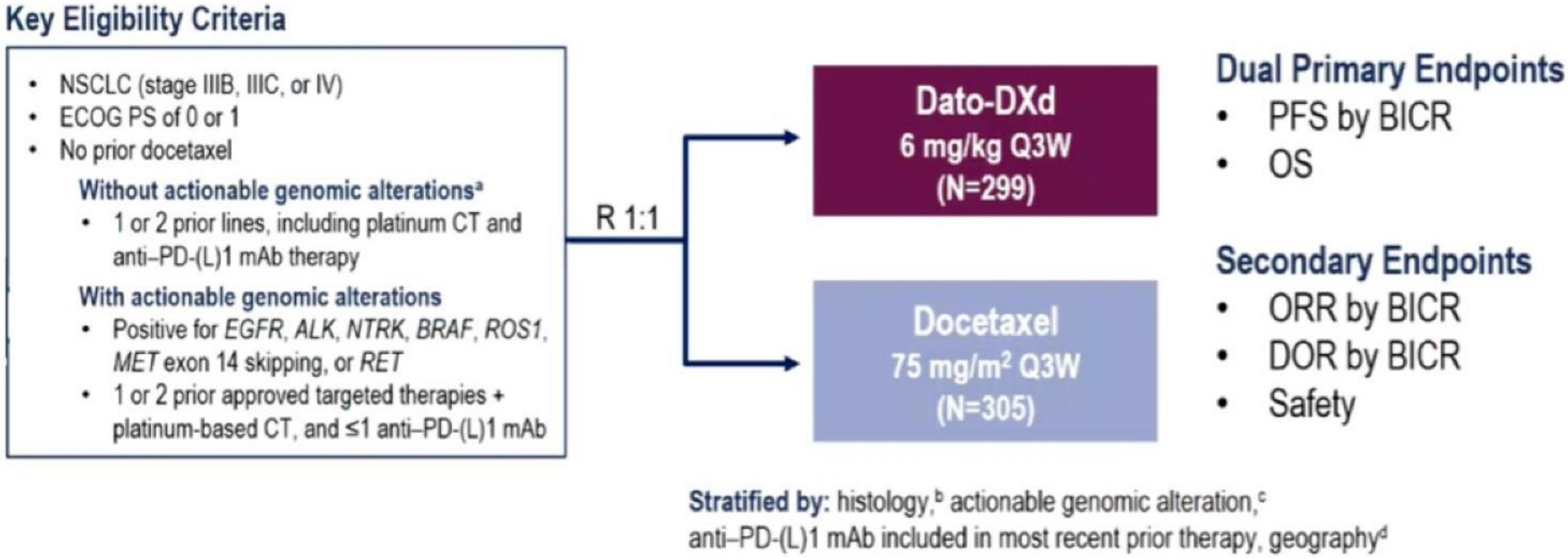
Phase III datopotamab deruxtecan vs docetaxel

TROPION-Lung01: design



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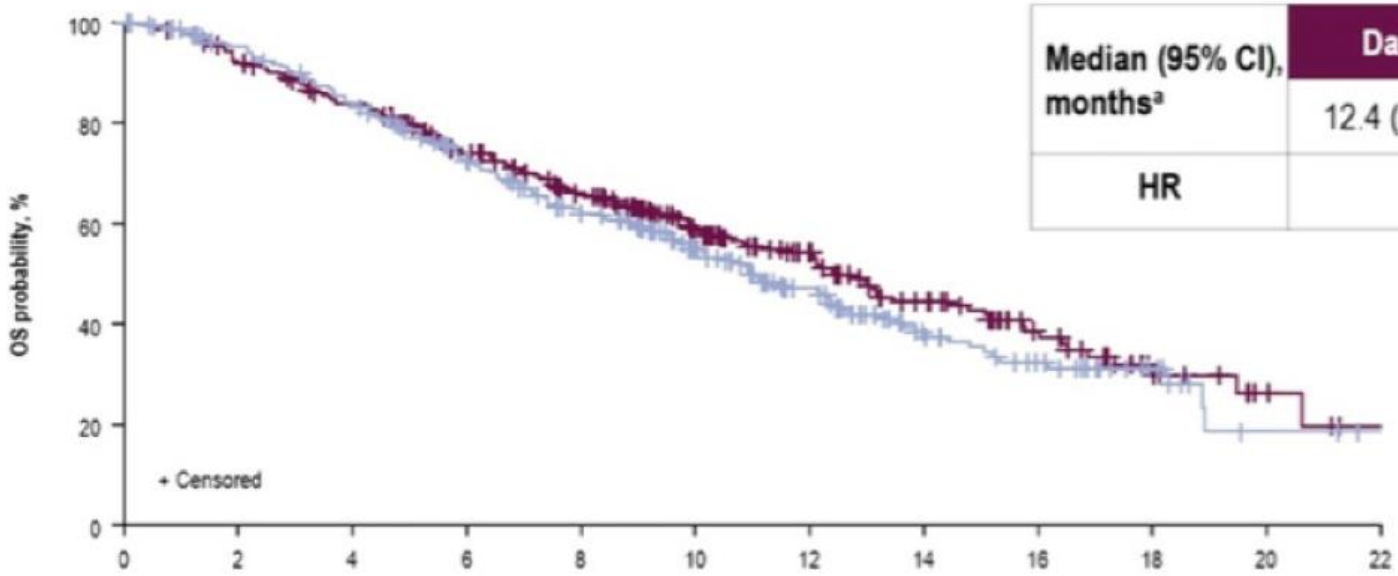
Phase III datopotamab deruxtecan vs docetaxel

TROPION-Lung01: interim overall survival



Median (95% CI), months[a]	Dato-DXd	Docetaxel
	12.4 (10.8-14.8)	11.0 (9.8-12.5)
HR	**0.90** (0.72-1.13)	

Information fraction at interim analysis (events/total events required): **74%.**

Non-squamous HR (95% CI): **0.77** (0.59-1.01); **Squamous HR** (95% CI): **1.32** (0.87-2.00)

Trial is continuing to final OS analysis

HR, hazard ratio; ITT, intention to treat; OS, overall survival.
[a]Median OS follow-up was 11.8 (95% CI, 11.3-12.7) and 11.7 (95% CI, 10.9-12.9) months for Dato-DXd and docetaxel, respectively.

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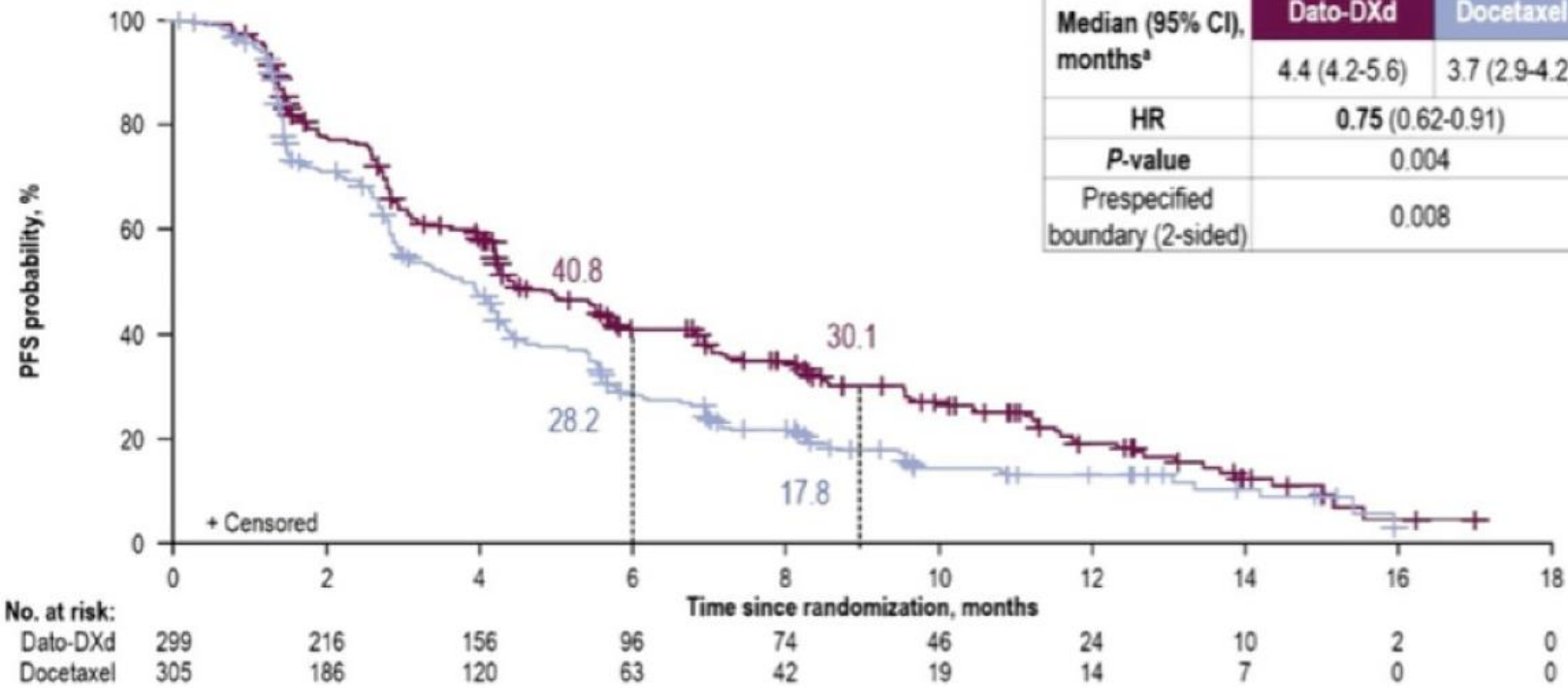
Phase III datopotamab deruxtecan vs docetaxel

TROPION-Lung01: progression-free survival



Median (95% CI), months[a]	Dato-DXd	Docetaxel
	4.4 (4.2-5.6)	3.7 (2.9-4.2)
HR	**0.75** (0.62-0.91)	
P-value	0.004	
Prespecified boundary (2-sided)	0.008	

	Dato-DXd	Docetaxel
ORR (95% CI), %[b]	**26.4** (21.5-31.8)	**12.8** (9.3-17.1)
DOR (95% CI), mo	**7.1** (5.6-10.9)	**5.6** (5.4-8.1)

CR, complete response; DOR, duration of response; HR, hazard ratio; ITT, intention to treat; ORR, objective response rate; PFS, progression-free survival; PR, partial response.
[a]Median PFS follow-up was 10.9 (95% CI, 9.8-12.5) and 9.6 (95% CI, 8.2-11.9) months for Dato-DXd and docetaxel, respectively. [b]Included 4 CRs and 75 PRs for Dato-DXd and 39 PRs for docetaxel.

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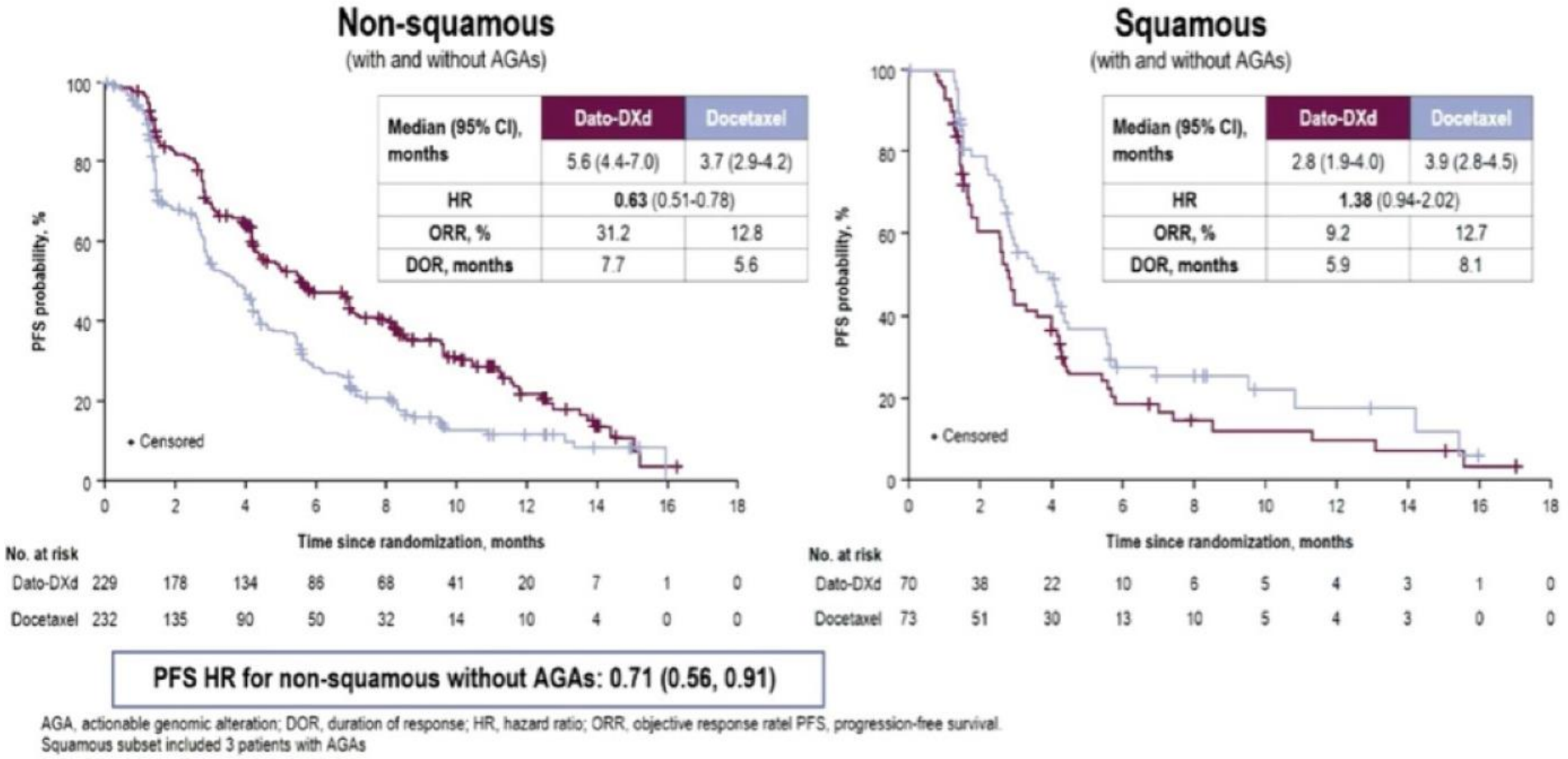
Phase III datopotamab deruxtecan vs docetaxel

TROPION-Lung01: progression-free survival by histology



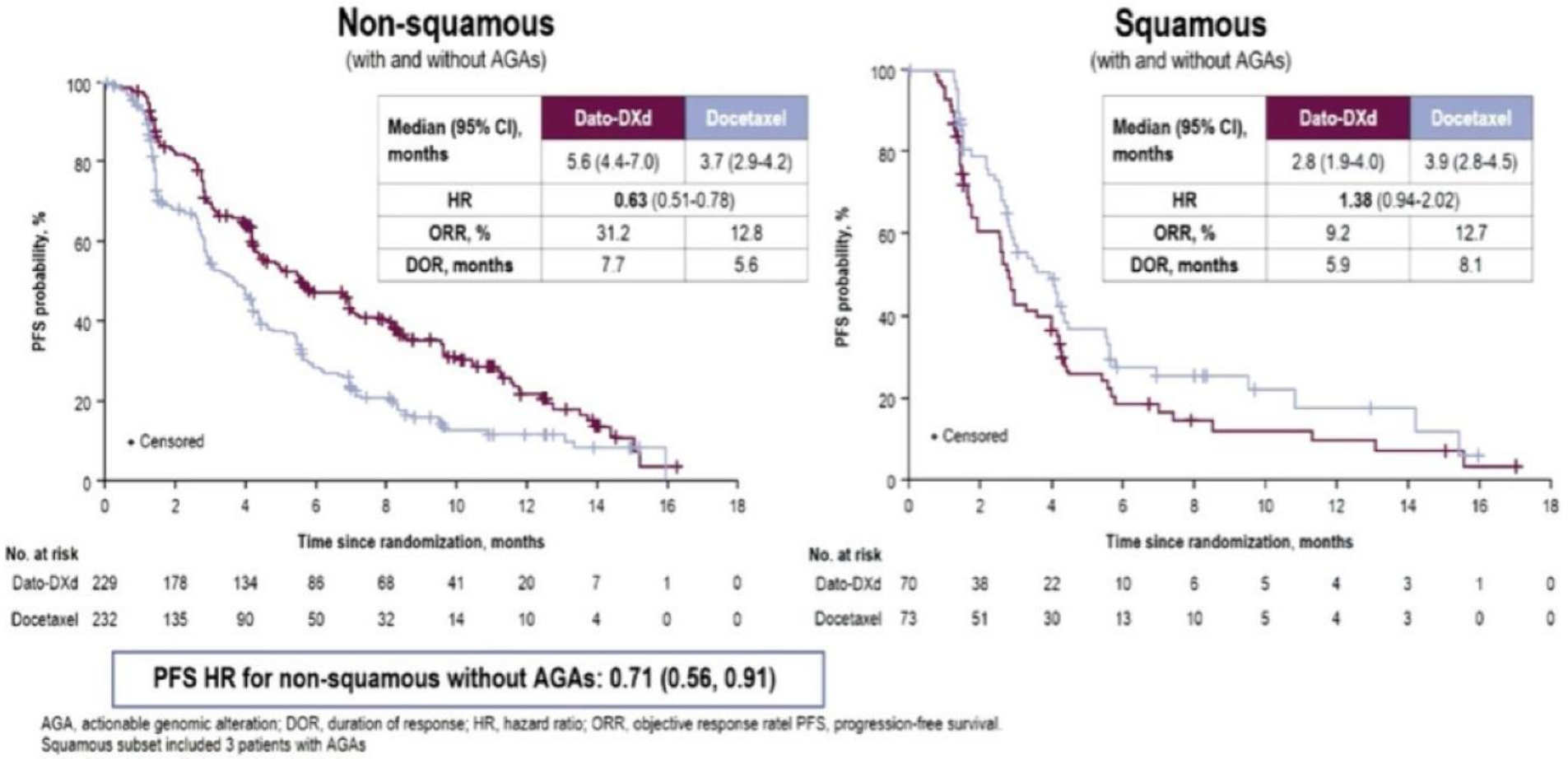
PFS HR for non-squamous without AGAs: 0.71 (0.56, 0.91)

AGA, actionable genomic alteration; DOR, duration of response; HR, hazard ratio; ORR, objective response ratel PFS, progression-free survival.
Squamous subset included 3 patients with AGAs

Lisberg. ESMO 2023

Phase III datopotamab deruxtecan vs docetaxel

TROPION-Lung01: progression-free survival by histology



PFS HR for non-squamous without AGAs: 0.71 (0.56, 0.91)

AGA, actionable genomic alteration; DOR, duration of response; HR, hazard ratio; ORR, objective response ratel PFS, progression-free survival.
Squamous subset included 3 patients with AGAs

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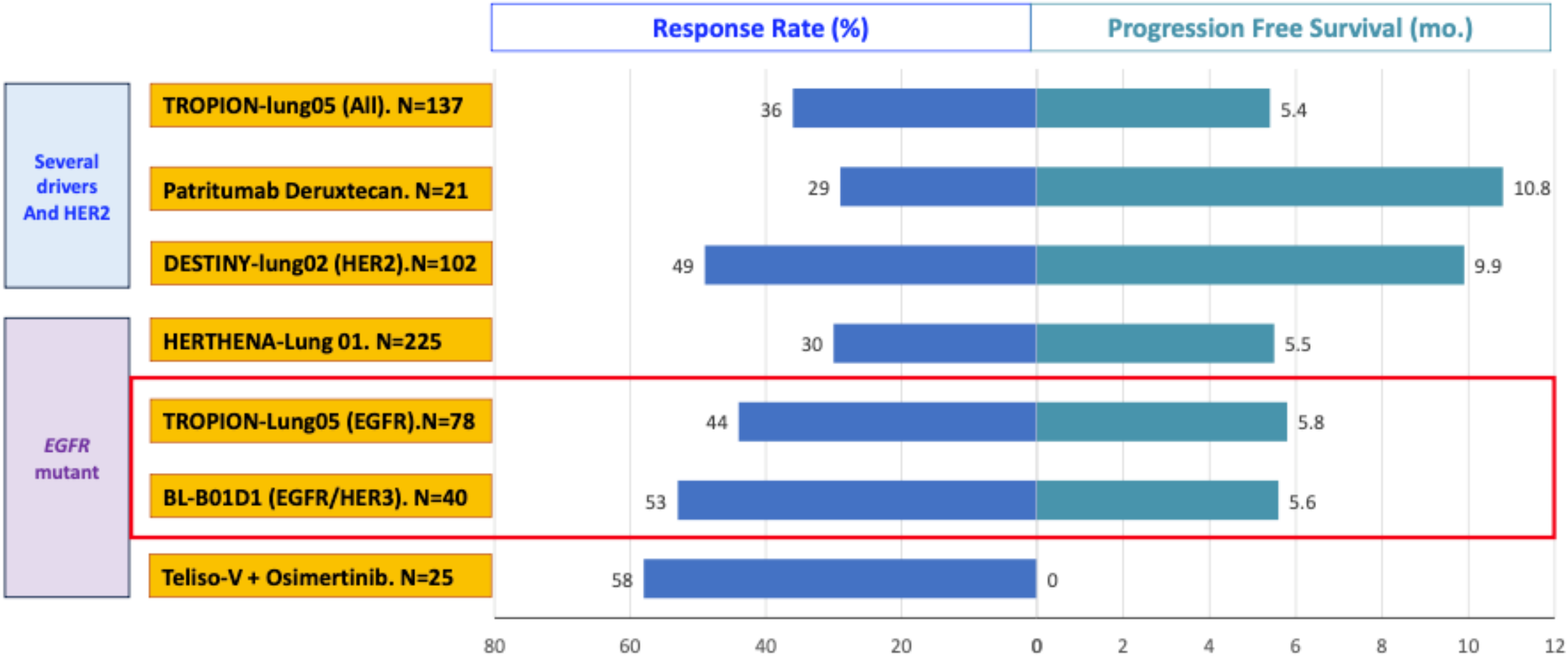
ADCs in oncogene-driven NSCLC



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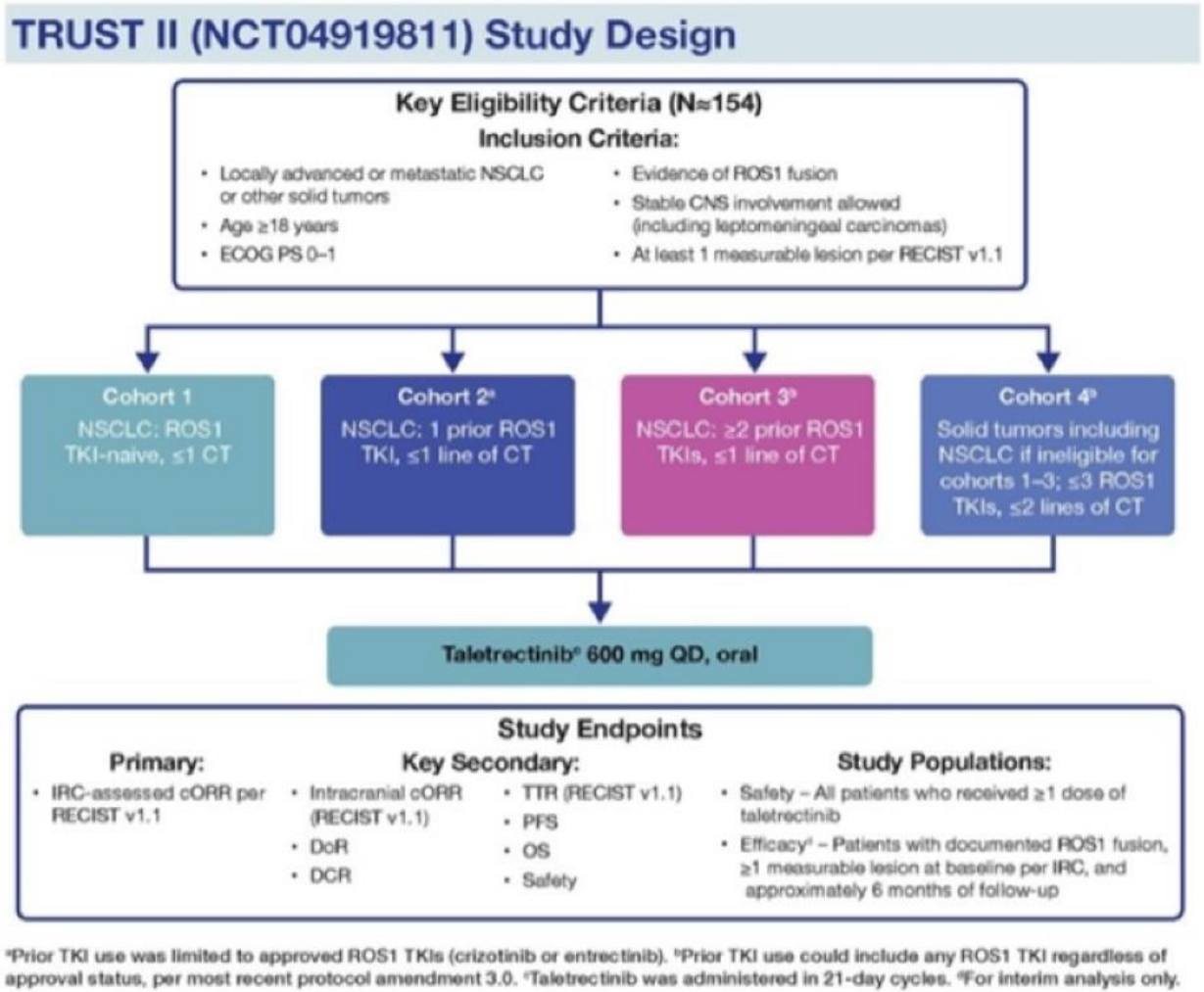
Taletrectinib in ROS1 NSCLC

TRUST-II study: design

- TRUST-II (NCT04919811), a global phase 2, multicenter, open-label, single-arm study in patients with ROS1+ tumors, has 4 cohorts



[a]Prior TKI use was limited to approved ROS1 TKIs (crizotinib or entrectinib). [b]Prior TKI use could include any ROS1 TKI regardless of approval status, per most recent protocol amendment 3.0. [c]Taletrectinib was administered in 21-day cycles. [d]For interim analysis only.

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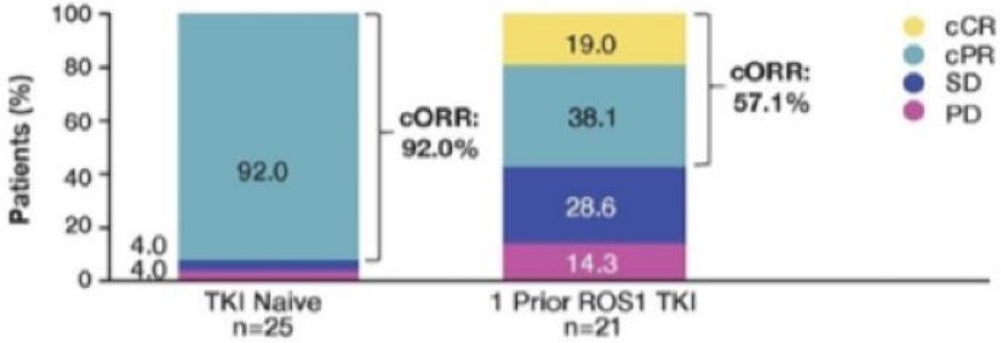
Taletrectinib in ROS1 NSCLC

TRUST-II study: responses

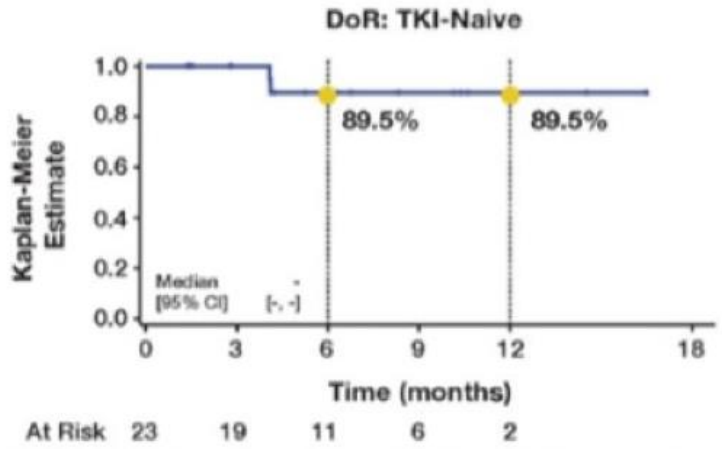
Responses by Cohort[a,b]

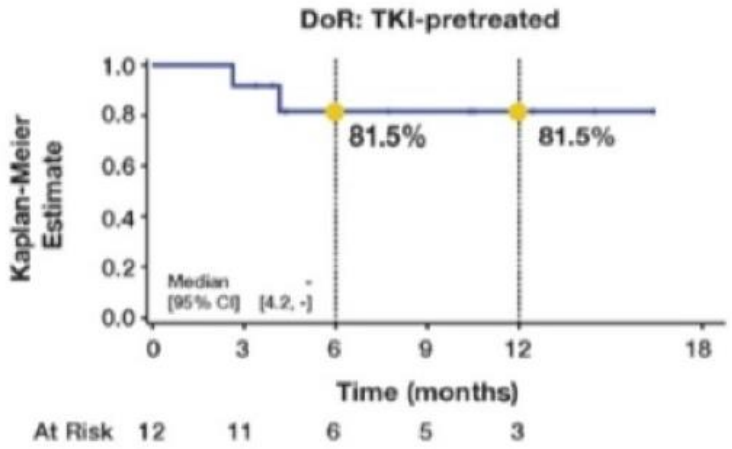


	TKI-Naive (n=25)	TKI-pretreated (n=21)
Median follow-up, months (95% CI)	8.1 (5.6, 11.7)	11.7 (5.5, 15.8)
Median PFS, months (95% CI)	NR (12.0, NR)	11.7 (4.0, NR)
12-month PFS rate, % (95% CI)	82.3 (59.2, 93.0)	42.6 (18.0, 65.5)

[a]Efficacy population. [b]Assessed by an independent review committee per RECIST v1.1.

Duration of response was not mature in either cohort



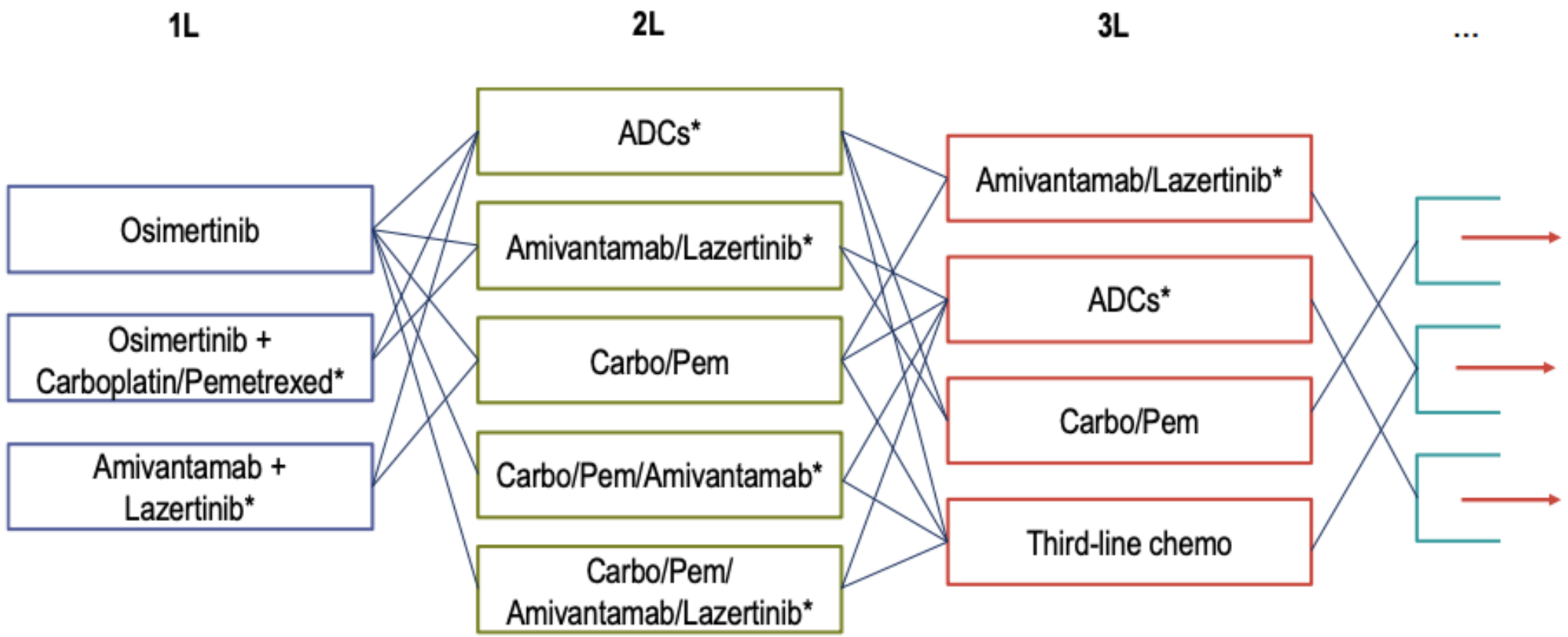


Perol. ESMO 2023

Outline

1. Resistance in oncogenic driven NSCLC
2. Evidence of drugs at progression
3. **How to choose a therapy at progression**
4. Local challenges
5. Take-home messages

Treatment Options for EGFRm NSCLC



*Experimental regimen, not yet approved.

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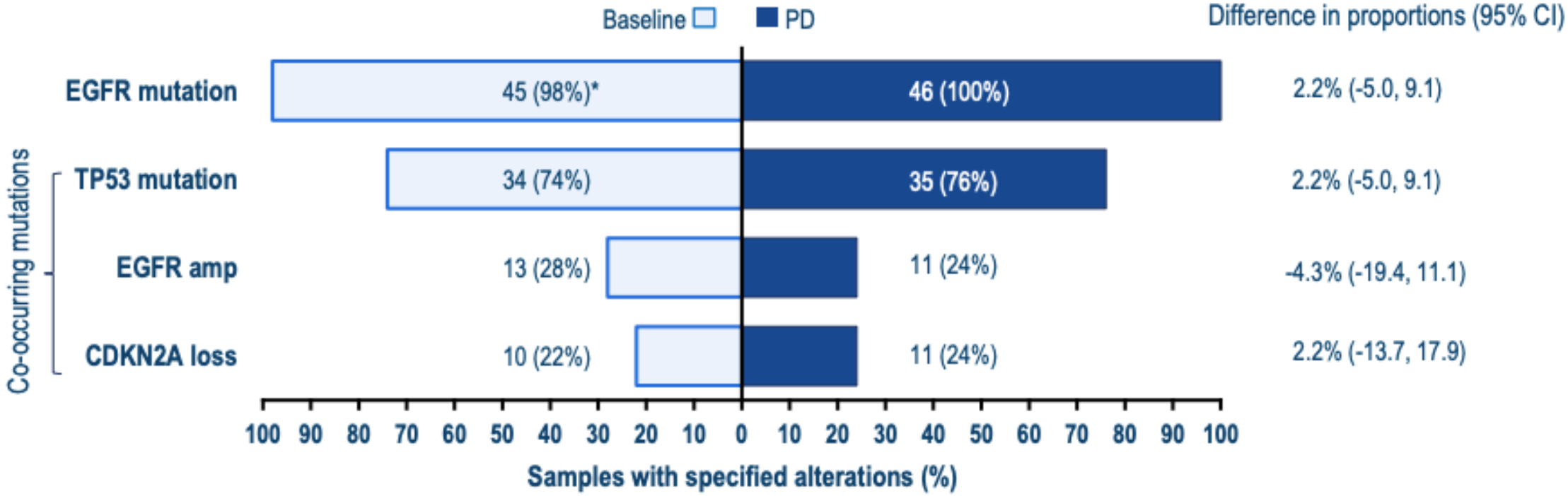
Difference between mutations from baseline to progression

ELIOS study: EGFR 1L to PD

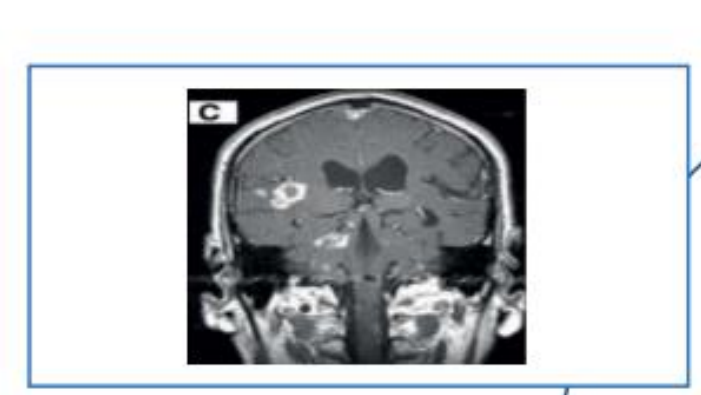
- High frequency mutations at baseline (EGFR, TP53 mutations, EGFR amplification and CDKN2A loss) did not differ significantly at PD



Paired biopsies in only 36% of patients

Piotrowska ESMO 2022

Challenges with ADCs in oncogene-driven NSCLC

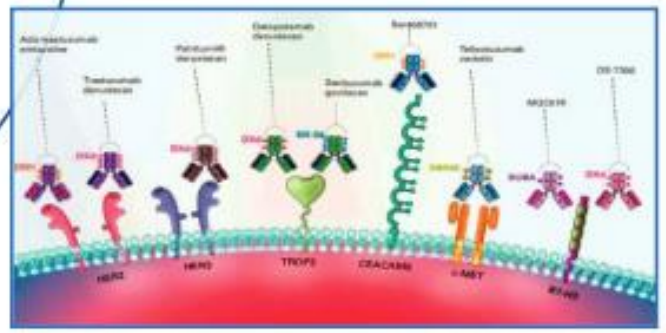


Brain penetration and activity

Monotherapy *v* combination

Best place in the sequence of treatment

Biomarker-agnostic Biomarker-driven

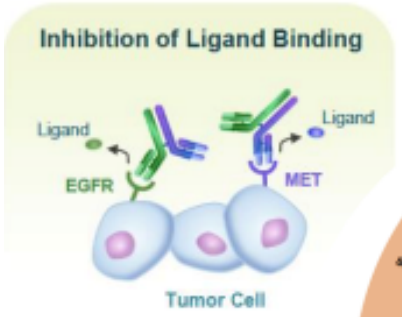


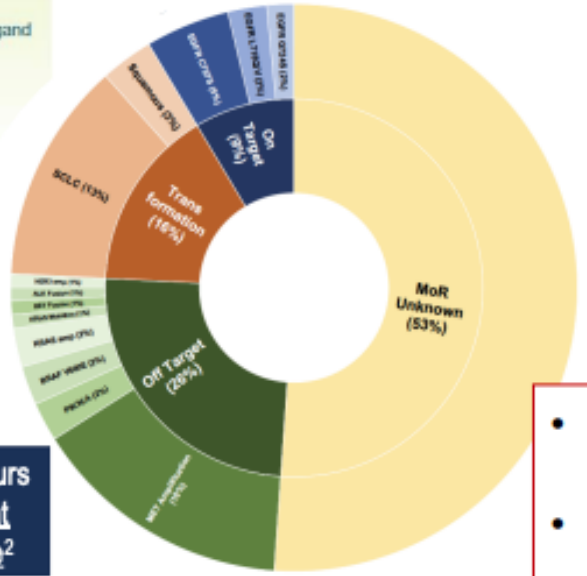
*

Hendriks and Remón. JCO 2023

How to select patients who benefit most from Amivantamab/Lazertinib?

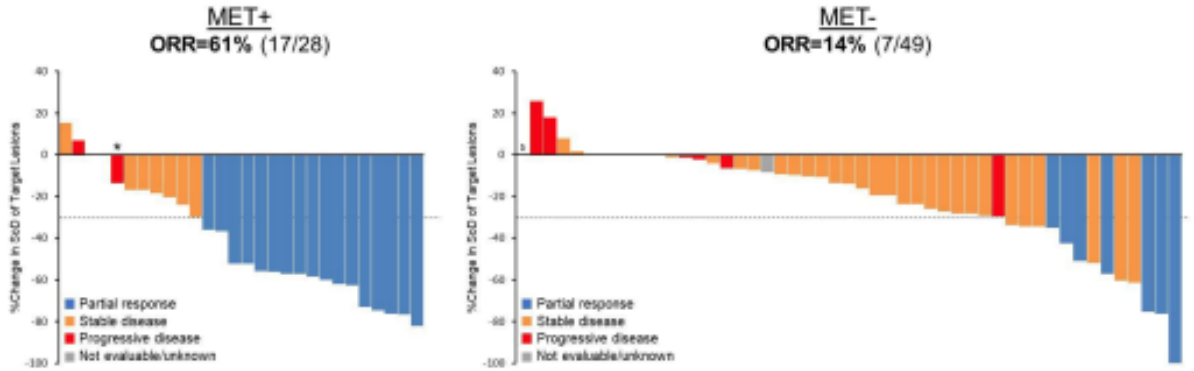
Amivantamab Mech of Action[1]





MET *Amplification* occurs in~ 16% of patients at osimertinib resistance[2]

Amivantamab/Lazertinib Post-TKI and Post-Chemotherapy: MET IHC+ may be correlated with response[3]



- The biology of EGFR-mutant NSCLC is different in the treatment-naïve vs. treatment-refractory setting.
- Careful examination of patient specimens collected on MARIPOSA and MARIPOSA-2 will be essential to identifying biomarkers of maximal response

1. Haura E, ASCO 2018; 2. Piotrowska Z, ASCO 2023 Abstract 9108, 3. Besse B, ASCO 2023 Abstract 9013.

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How do we move forward?

Potential baseline stratification factors

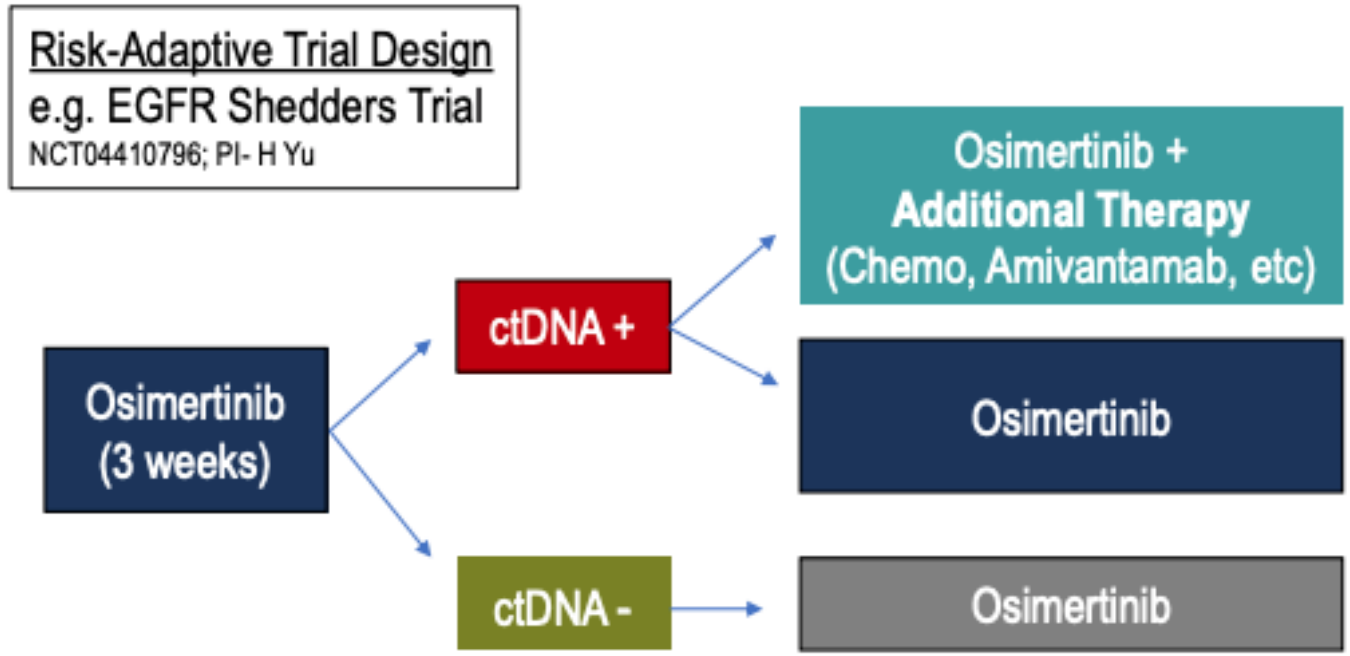
- Co-mutations (e.g., TP53, others)

Dynamic factors

- (Lack of) ctDNA clearance on treatment

Novel biomarkers

- Moving beyond NGS (multi-omic analyses)



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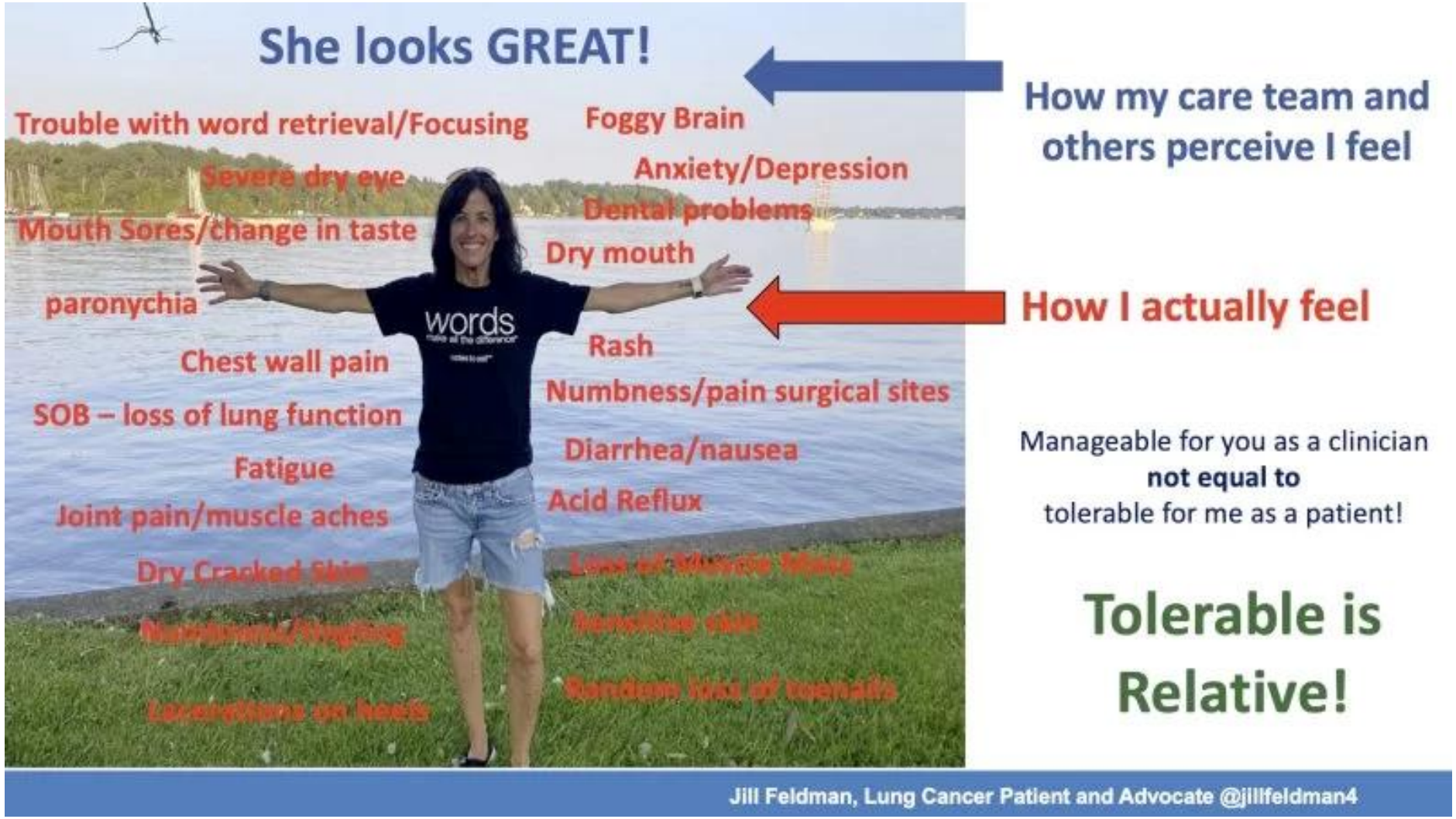
Patient preferences and tolerability



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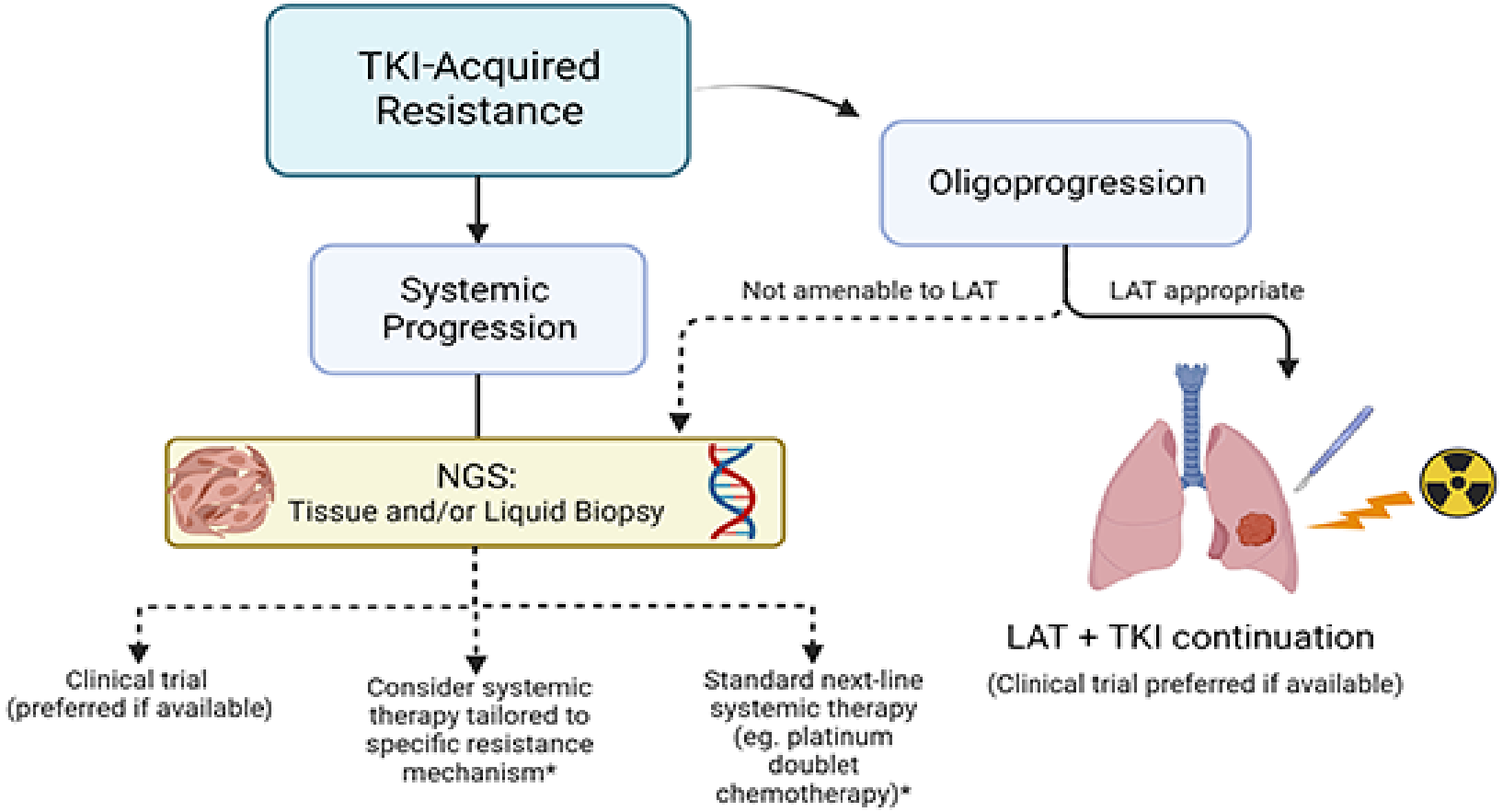
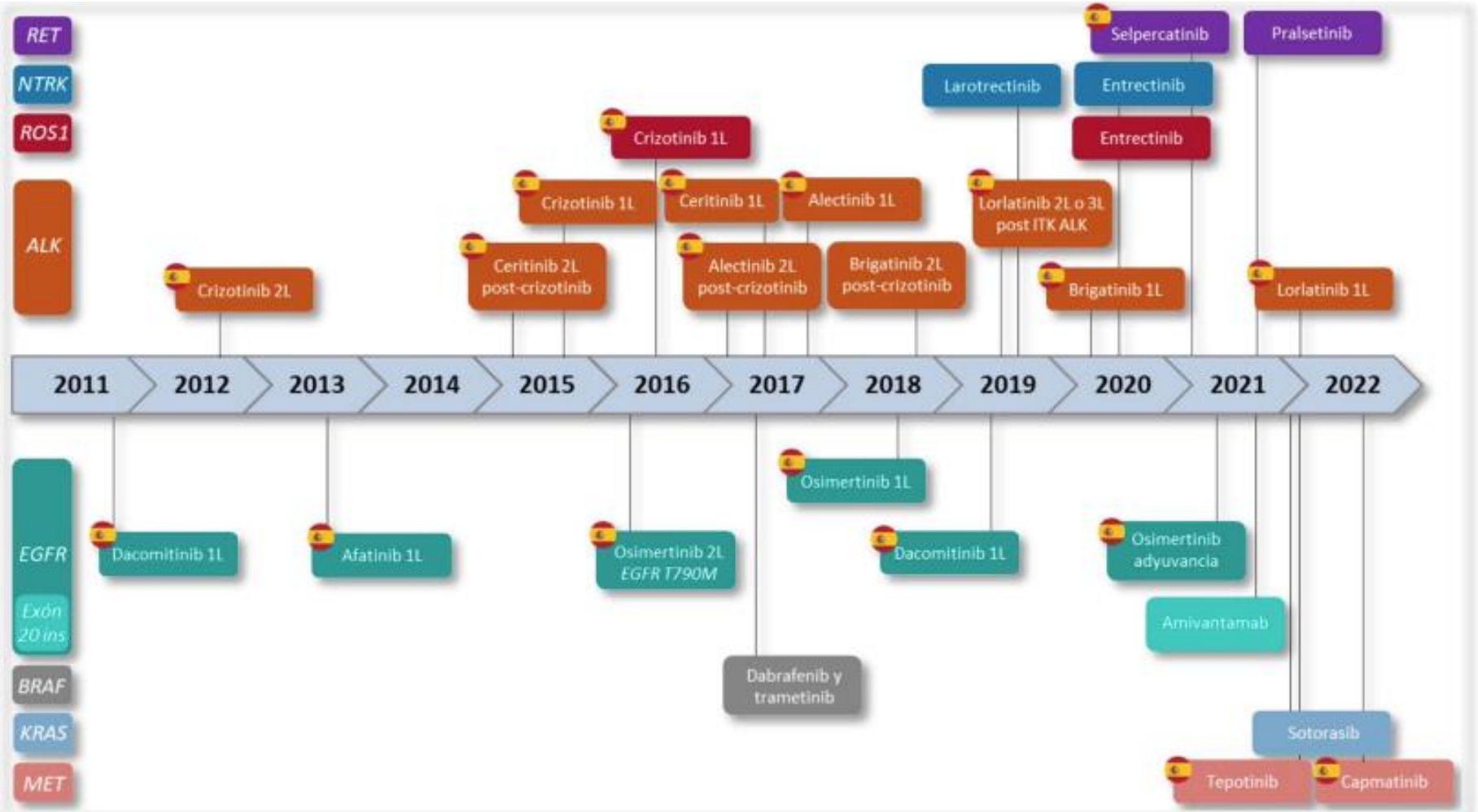
Local therapies at progression



Hubbeling. JCO 2022

Other “local” resistance mechanisms: availability in Spain



Calvo. Clin Transl Oncol 2023

Outline

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Take-home messages: challenges in resistance

1. Impact of molecular profiling in NSCLC therapy
2. In NSCLC with actionable genomic alterations, all patients become resistant
3. Patient profile: symptoms, comorbidities, preferences…
4. Drugs: impact of new generation Tkis, increasing knowledge about ADCs, no clear rule for IO…
5. Drugs: monotherapy vs combination
6. Understanding resistance: Biomarkers? Tissue *vs* liquid biopsy
7. Local therapies in local/oligometastatic progression
8. Availability of drugs

Muchas gracias

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