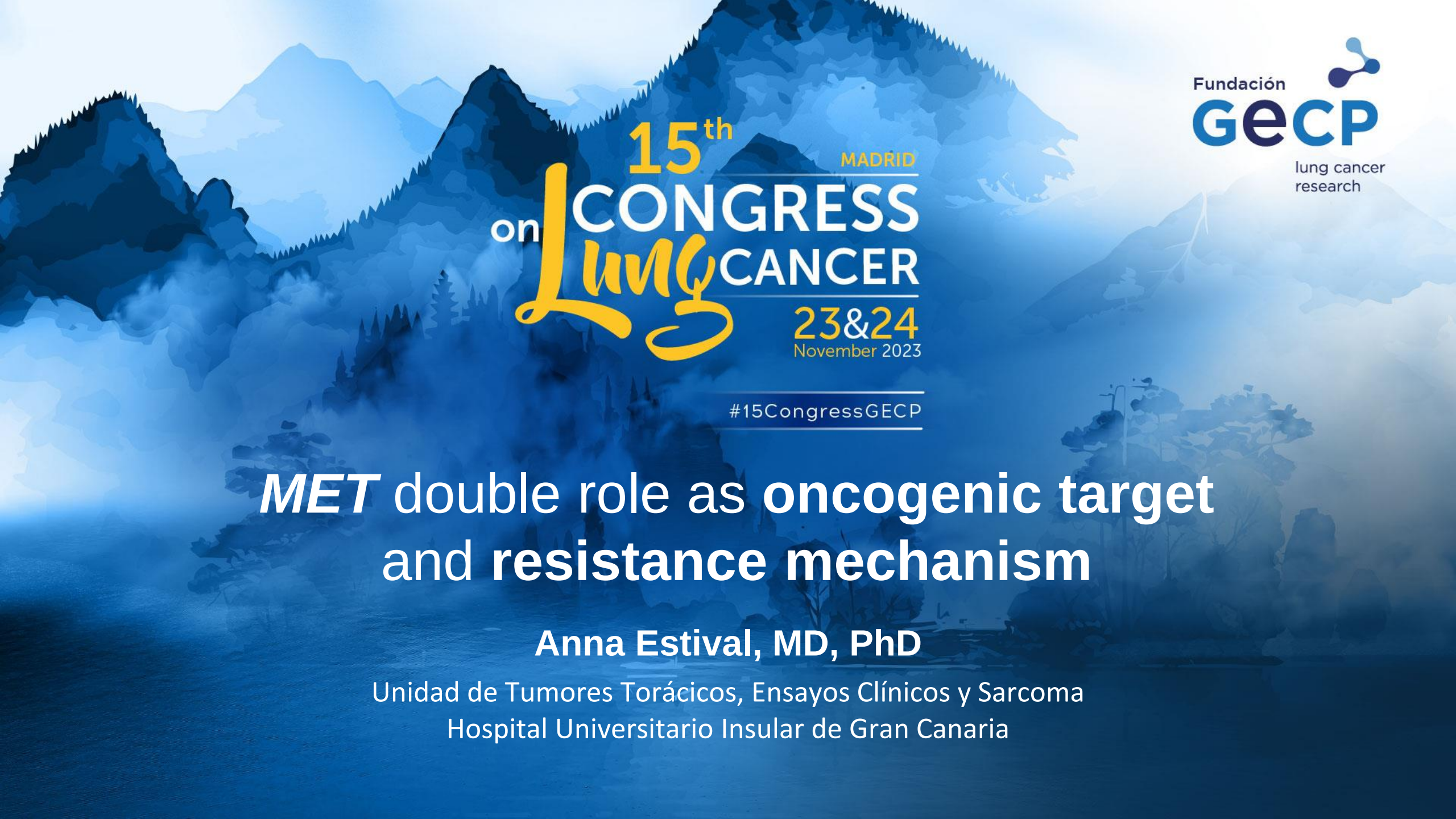


MET double role as **oncogenic target** and **resistance mechanism**

Anna Estival, MD, PhD

Unidad de Tumores Torácicos, Ensayos Clínicos y Sarcoma
Hospital Universitario Insular de Gran Canaria

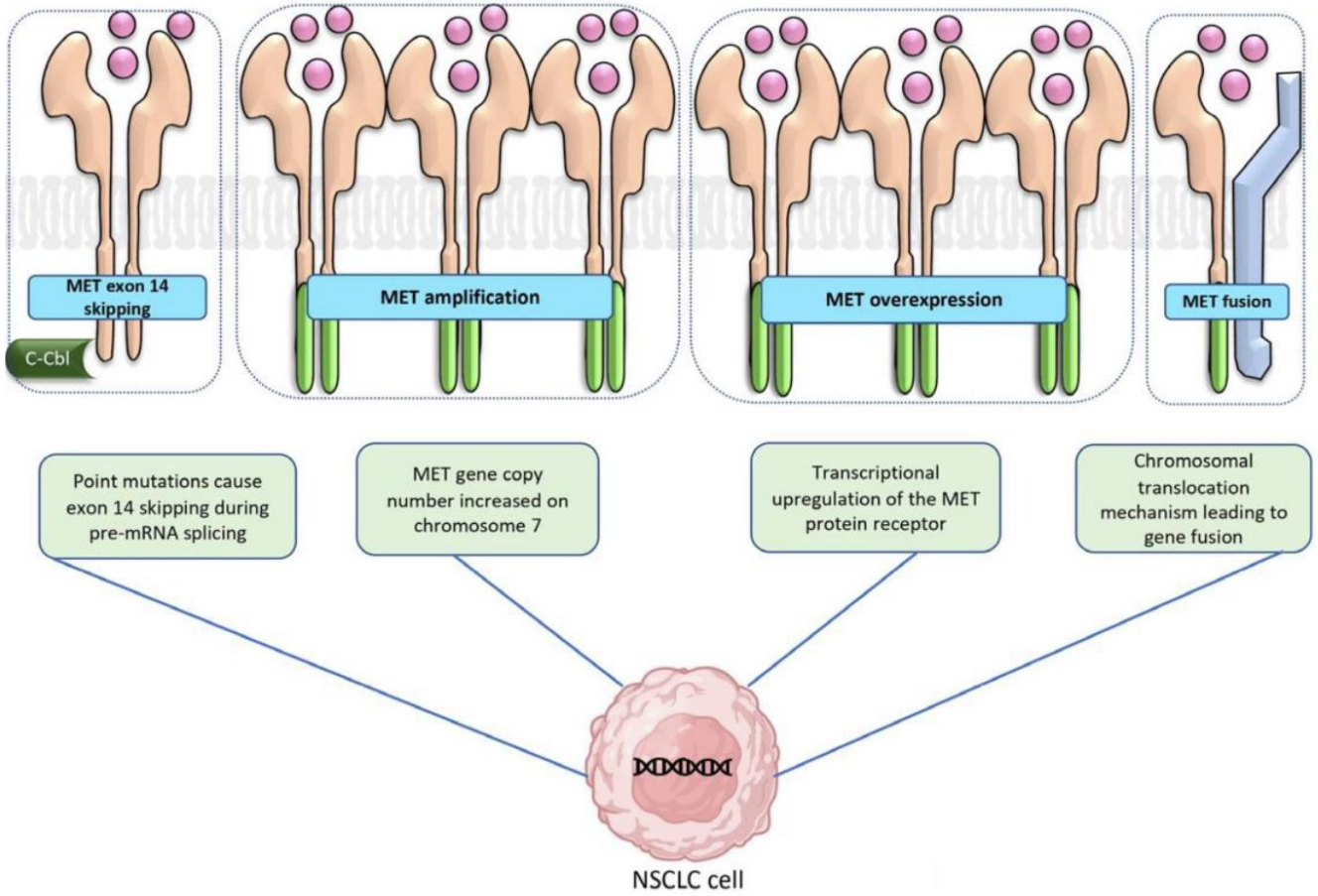
Disclousures

Consulting or **advisory** Role: Roche, MSD, Astrazeneca, Takeda, GSK.

Speaking: Bayer, Roche, MSD, Astrazeneca, Pharmamar, Takeda, GSK.

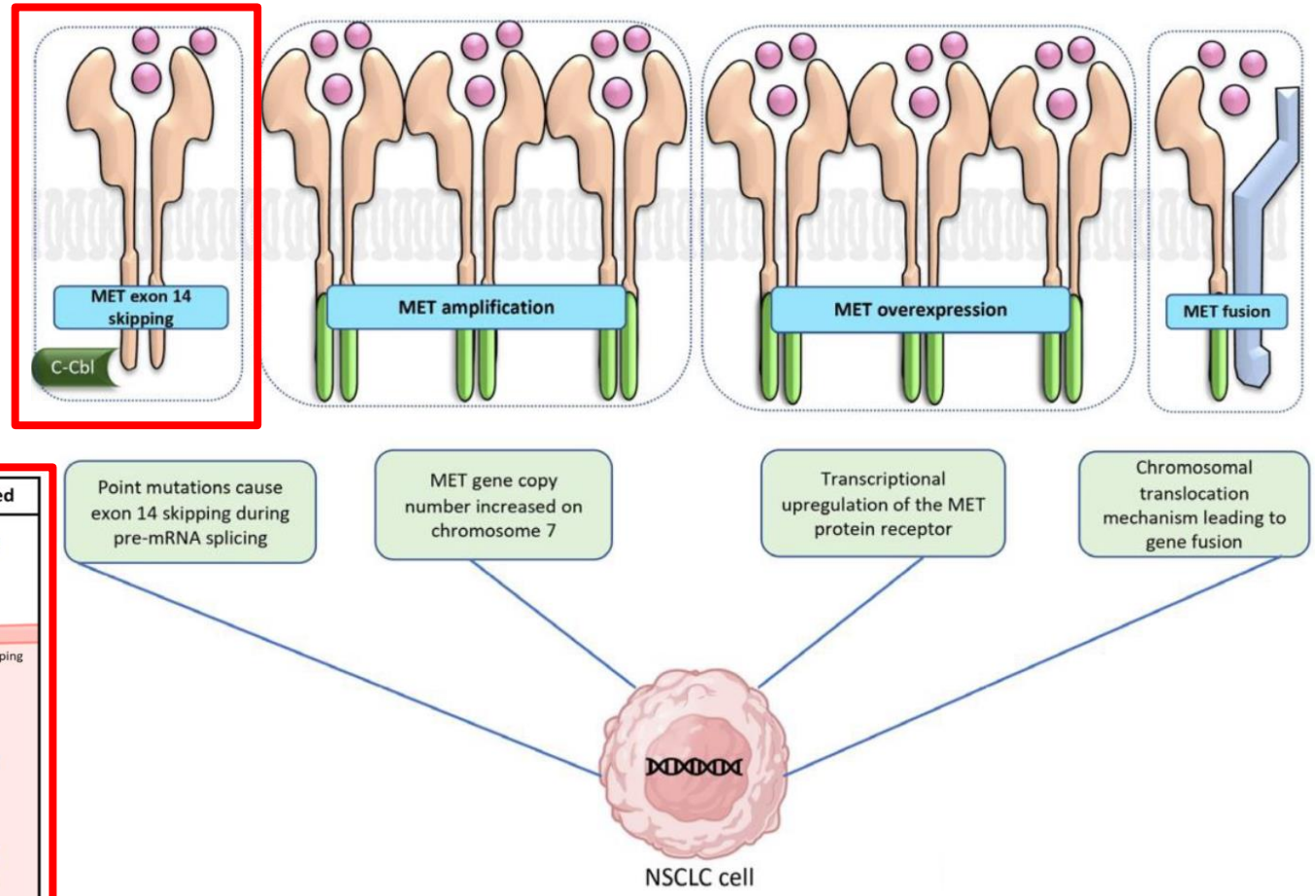
Conferences / **travel** expenses: Pfizer, MSD, Lilly, Roche, Astrazeneca, Pharmamar, Bayer, Takeda, BMS, Boehringer Ingelheim.

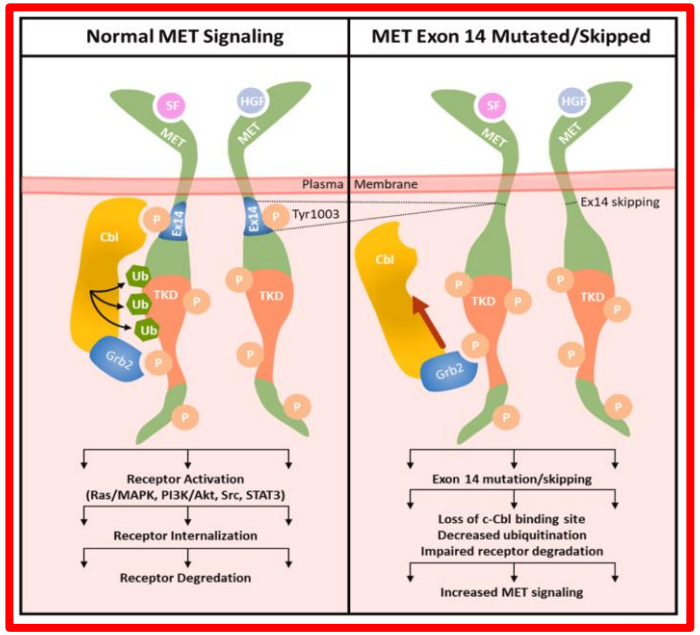
MET alterations



Spagnolo CC Int. J. Mol. Sci. 2023, 24, 10119 / N. Coleman et al. Lung Cancer 164 (2022) 56–68 / Remon J et al. Journal of Thoracic Oncology 2023 (18) 419–435

MET alterations





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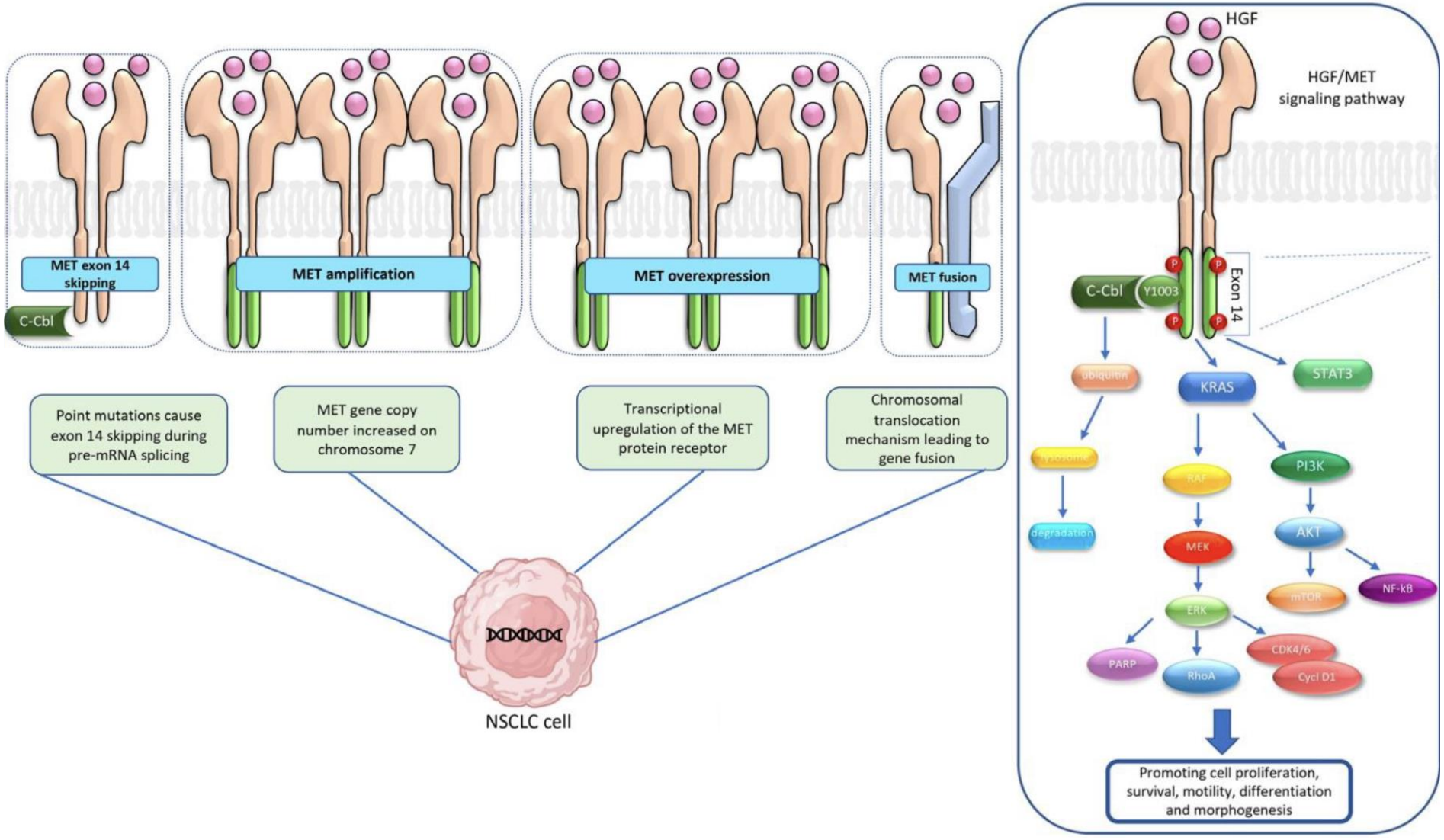


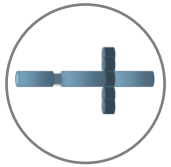
Spagnolo CC Int. J. Mol. Sci. 2023, 24, 10119 / N. Coleman et al. Lung Cancer 164 (2022) 56–68 / Remon J et al. Journal of Thoracic Oncology 2023 (18) 419–435

MET alteration as a primary – secondary oncogenic driver

MET alterations as **primary** drivers

***MET*ex14 skipping**

- ✓ 3% of adenocarcinomas
- ✓ 2% of squamous cell carcinomas
- ✓ 8–22% of **sarcomatoid** carcinomas



***MET* amplification**

Primary oncogenic driver in 1-5% of NSCLC

Frampton GM, et al. Cancer Discov 2015 / Schrock AB, et al. J Thorac Oncol 2016/ Reungwetwattana T, et al. Lung Cancer 2017 / Drilon A, et al. J Thorac Oncol 2016 / Ramalingam S, et al. ESMO 2018
Papadimitrakopoulou V, et al. ESMO 2018 / Lin J, et al. ASCO 2020 /Dagogo-Jack S. Clin Cancer Res 2020/Lin JJ, et al. Ann Oncol 2020 / Suzawa K, et al. JCO Precis Oncol 2019/ Wang W, et al. J Clin Oncol 2018

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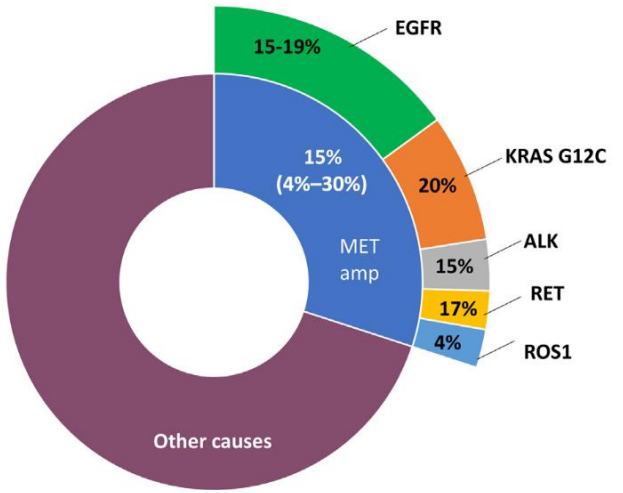
MET alterations as a mechanism of **acquired resistance (AR)**

***MET* amplification** is a secondary or co-driver in:

- ✓ Acquired **EGFR TKI** resistance (5%)
- ✓ **Osimertinib**: 19% on 2nd line

  15% on 1st line –> Main off-target mechanism of AR
- ✓ Acquired resistance to other TKIs (**ALK**, **ROS-1**, **RET**)



Frampton GM, et al. Cancer Discov 2015 / Schrock AB, et al. J Thorac Oncol 2016/ Reungwetwattana T, et al. Lung Cancer 20[illegible] / [illegible] et al. [illegible] / [illegible] et al. ESMO 2018
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***MET*ex14 skipping** and ***MET* fusions** (rare) → mechanism of resistance to TKIs

Frampton GM, et al. Cancer Discov 2015 / Schrock AB, et al. J Thorac Oncol 2016/ Reungwetwattana T, et al. Lung Cancer 2017 / Drilon A, et al. J Thorac Oncol 2016 / Ramalingam S, et al. ESMO 2018
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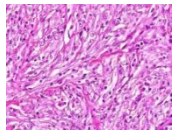
Where to seek for MET?

Patients with ***MET*ex14 skipping**

Older (median age 74 years) than those with *MET* amplification, and *EGFR* or *ALK* mutations

60 % current or former smokers

50–70% **female**



Sarcomatoid tumour

Wolf J, et al. EORTC/NCI/AACR Symposium 2018. /Awad MM, et al. J Clin Oncol 2016/ Wolf J, et al. N Engl J Med 2020/ Paik P, et al. N Engl J Med 2020

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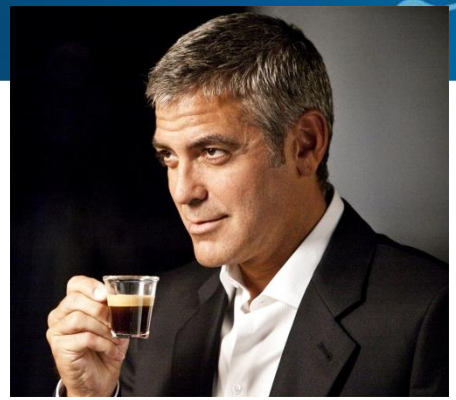

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- **60 % current or former smokers**
- 50–70% **female**
- **Sarcomatoid** tumour

Patients with ***MET* amplification**

- **Younger** (median age 64 years)
- More frequently current or former **smokers** (>90%)
- Predominantly **male**

Wolf J, et al. EORTC/NCI/AACR Symposium 2018. /Awad MM, et al. J Clin Oncol 2016/ Wolf J, et al. N Engl J Med 2020/ Paik P, et al. N Engl J Med 2020

Caso clínico

Hombre de 79 años

Ex fumador de 20 cigarrillos/día con DA de 40 paq-a.

HTA

EPOC leve

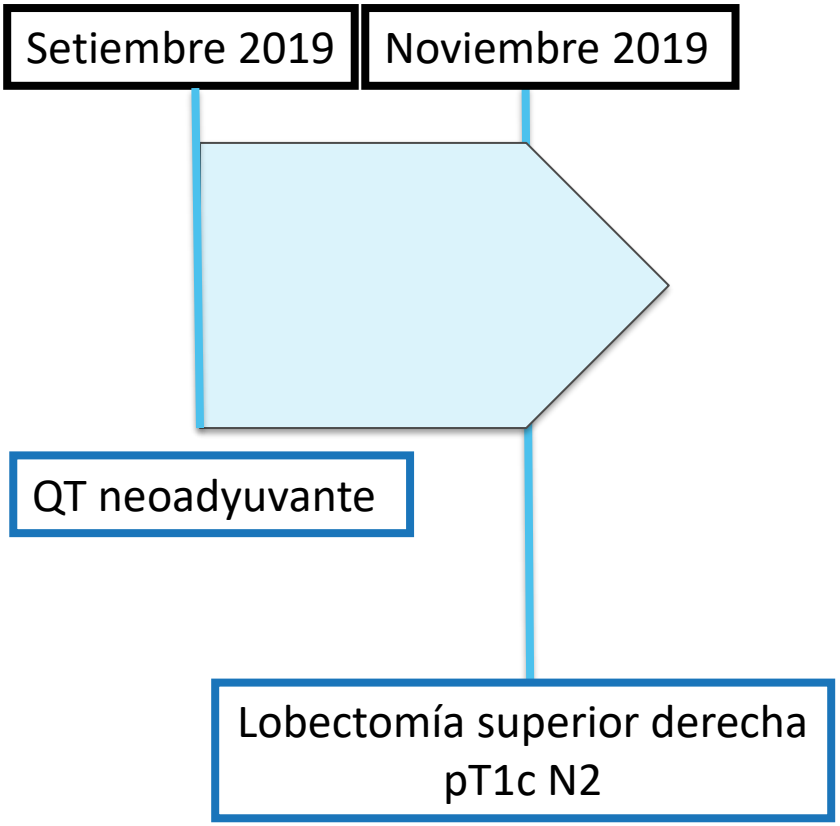
RTU por neoplasia vesical superficial en el 2010

Dx en setiembre 2019, a raíz de TAC de control de seguimiento

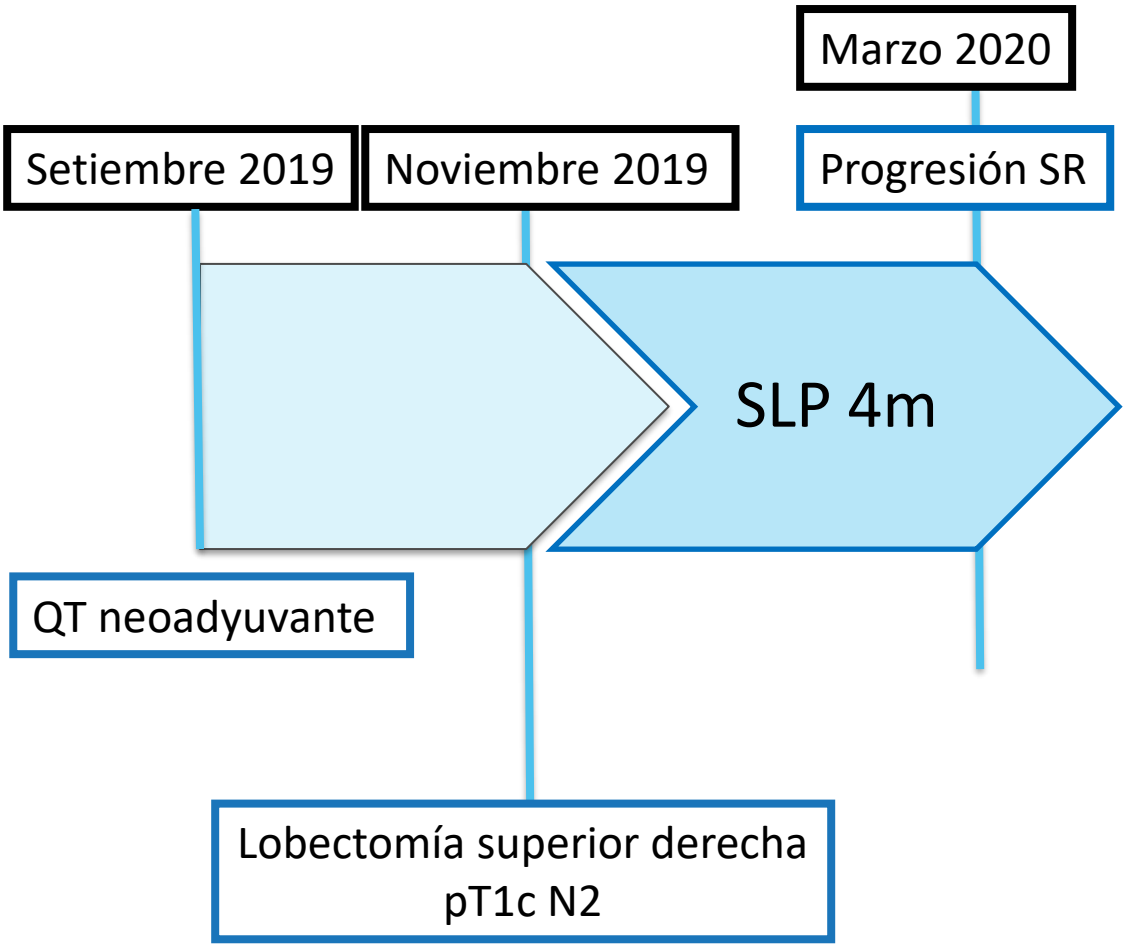
Carcinoma pleomórfico (con adenocarcinoma) LSD cT2N2M0.
PD-L1 80%. EGFR / ALK/ KRAS / ROS1 / BRAF negativos.

PS1. Exploración anodina.

Caso clínico



Caso clínico



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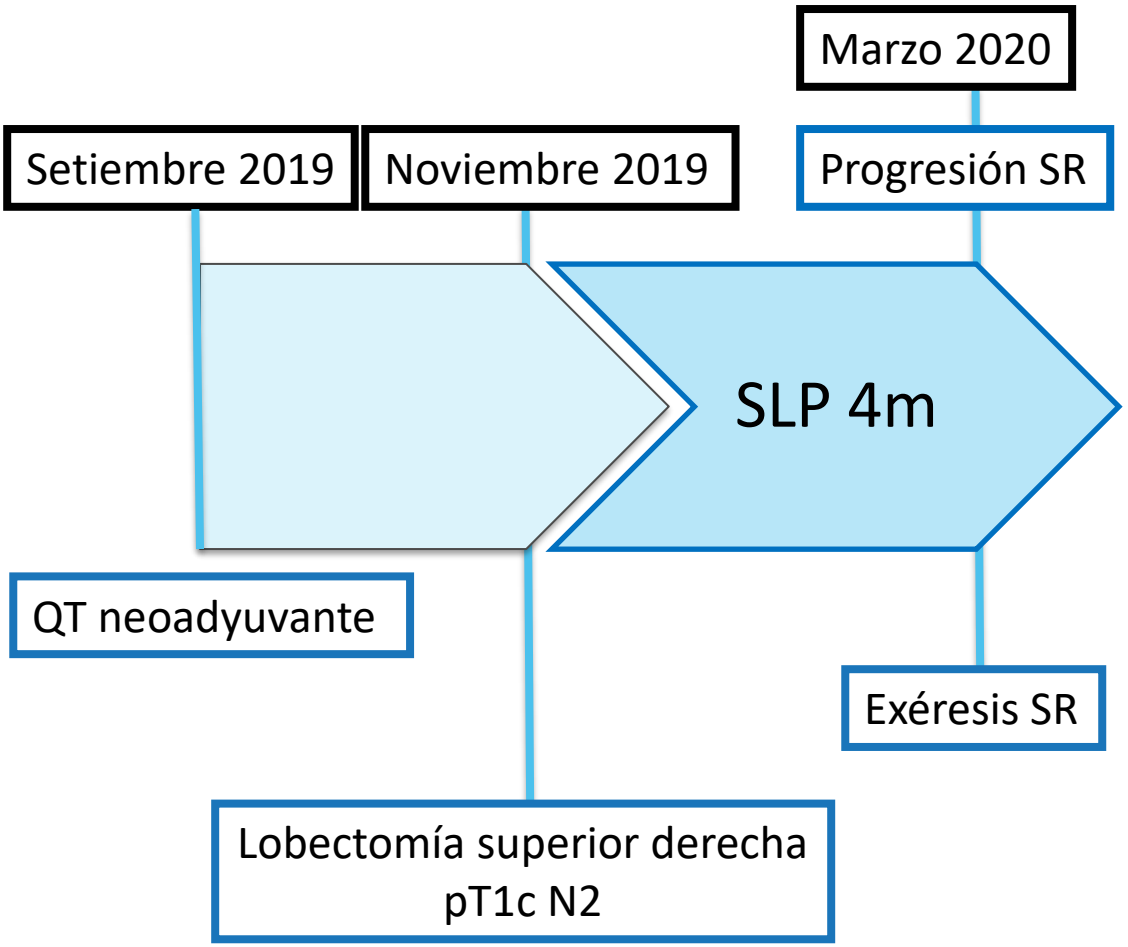

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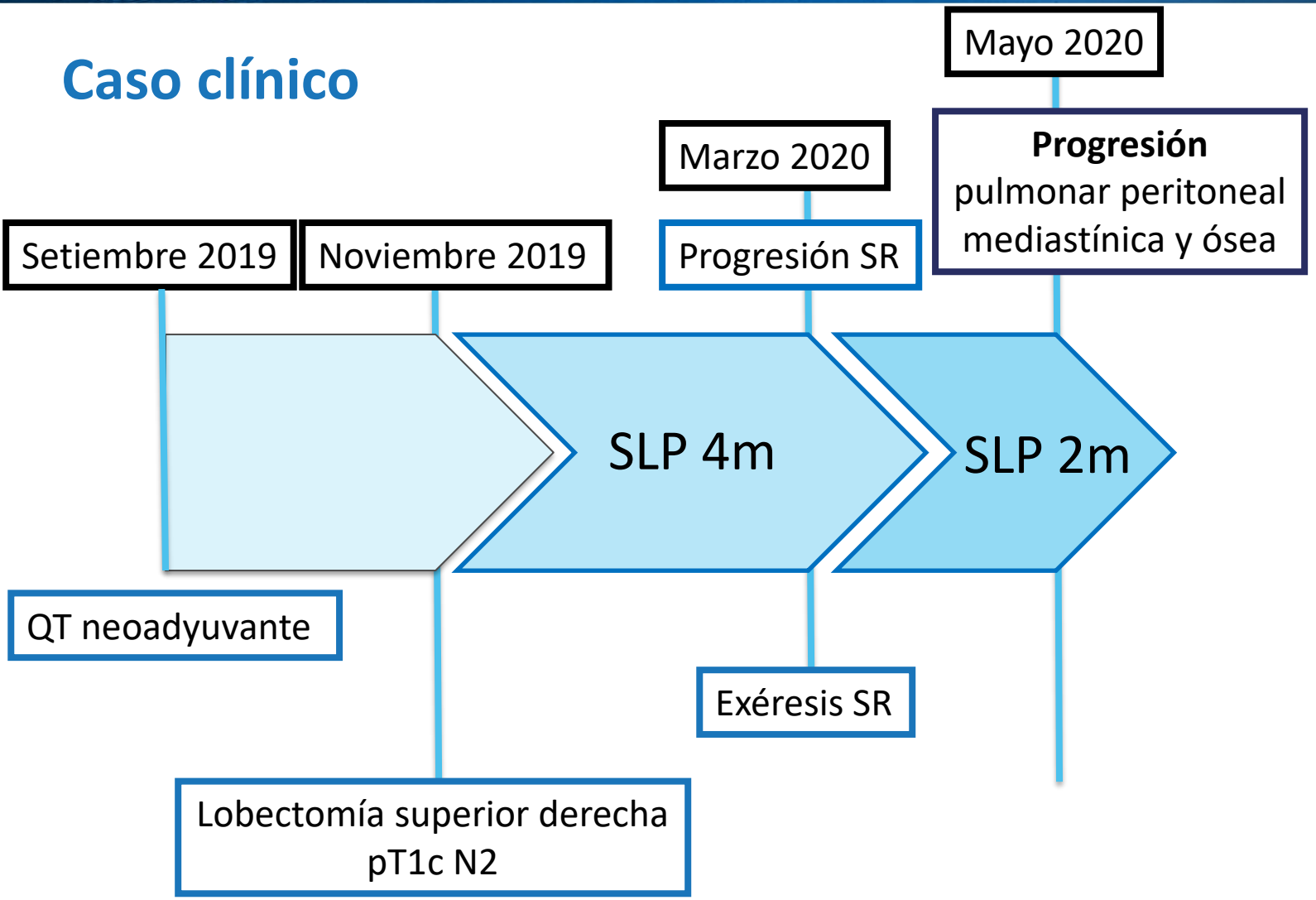

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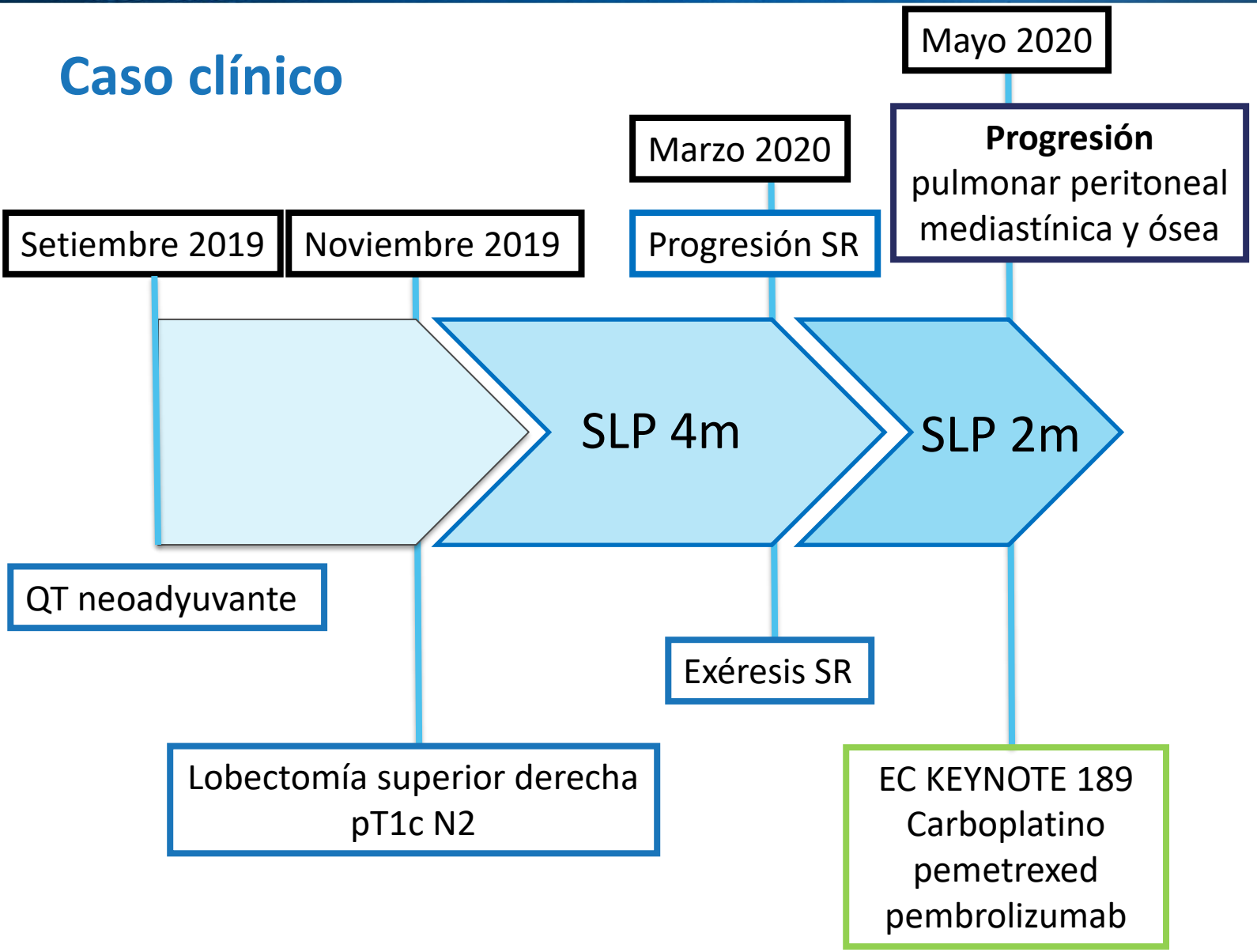

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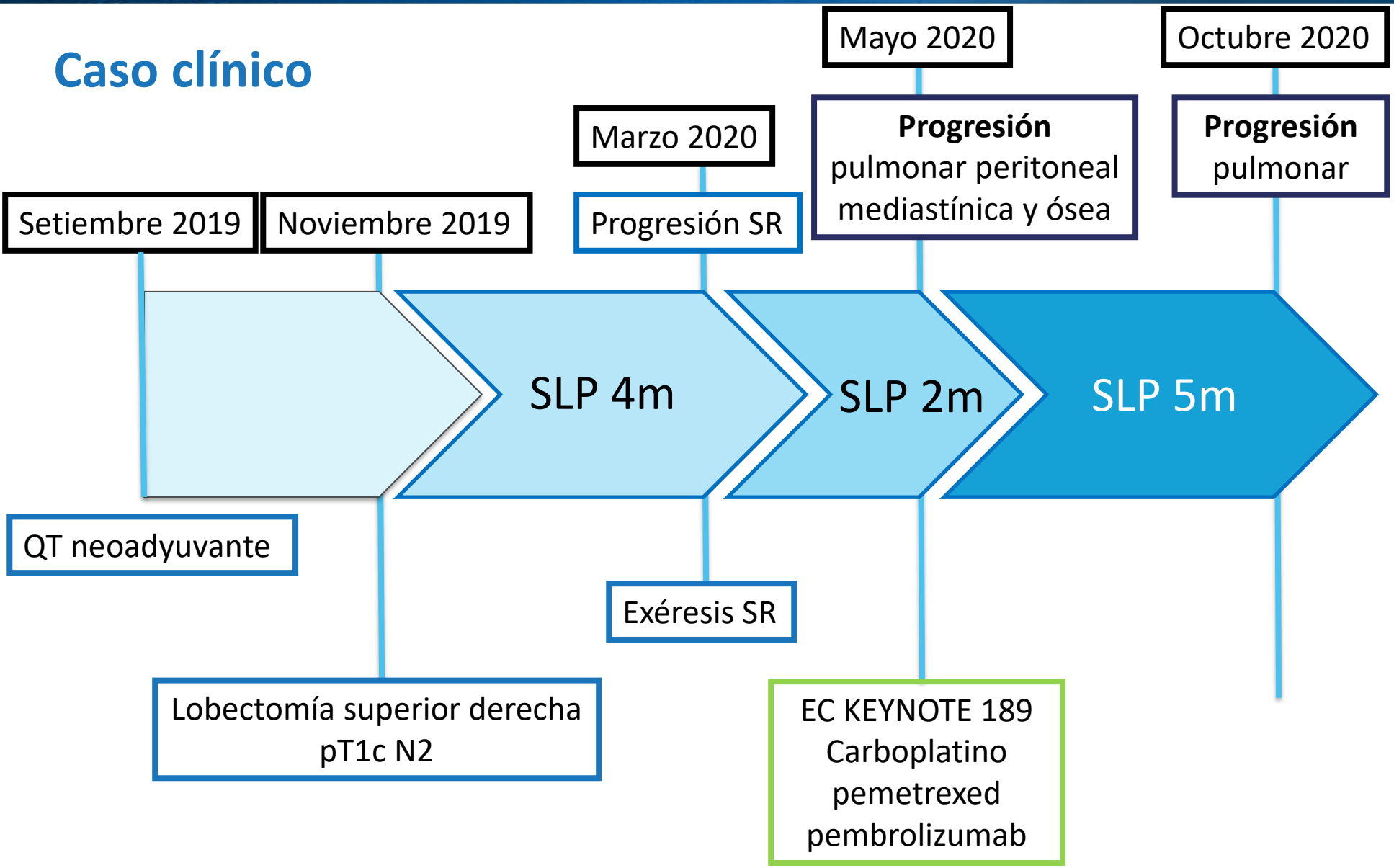

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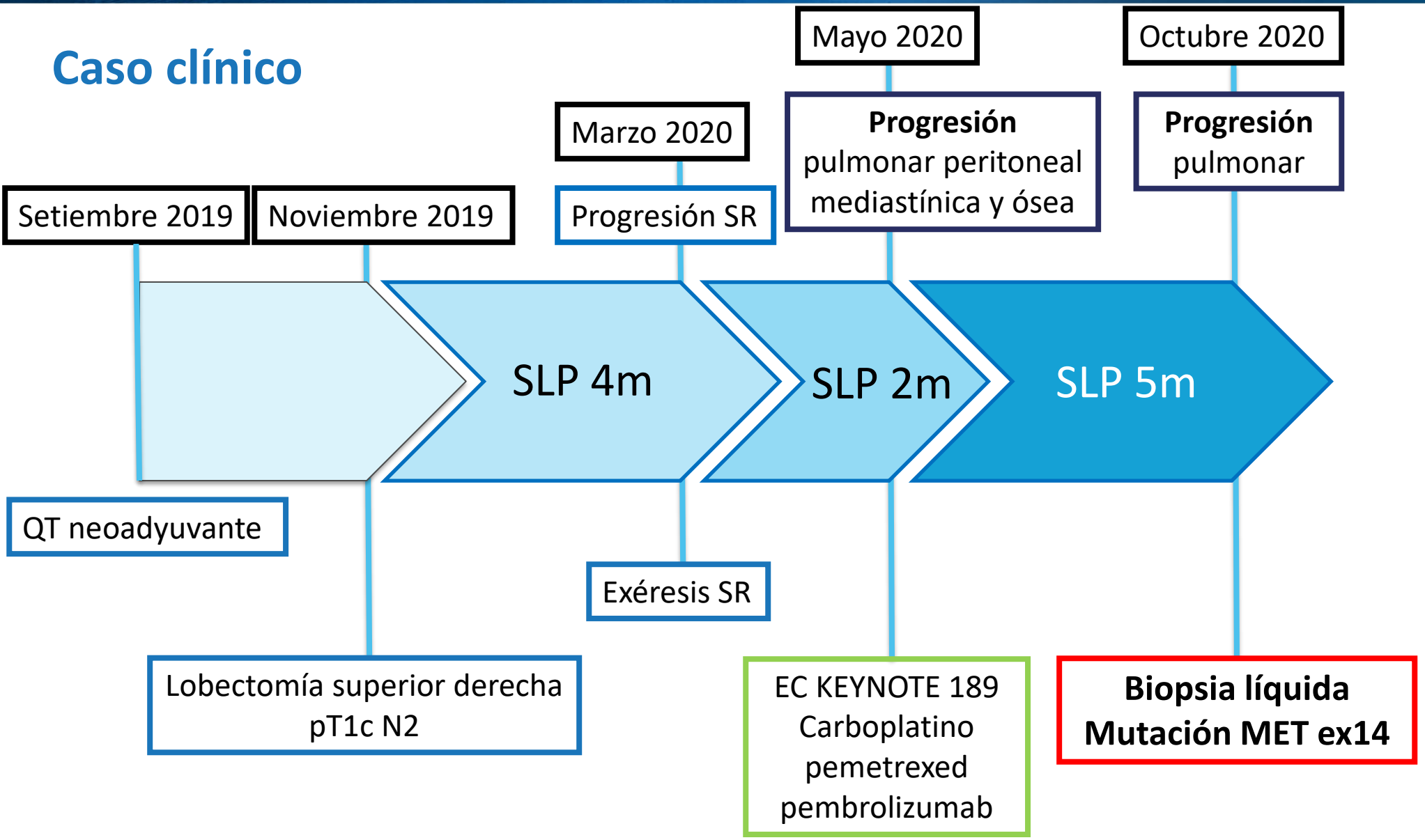

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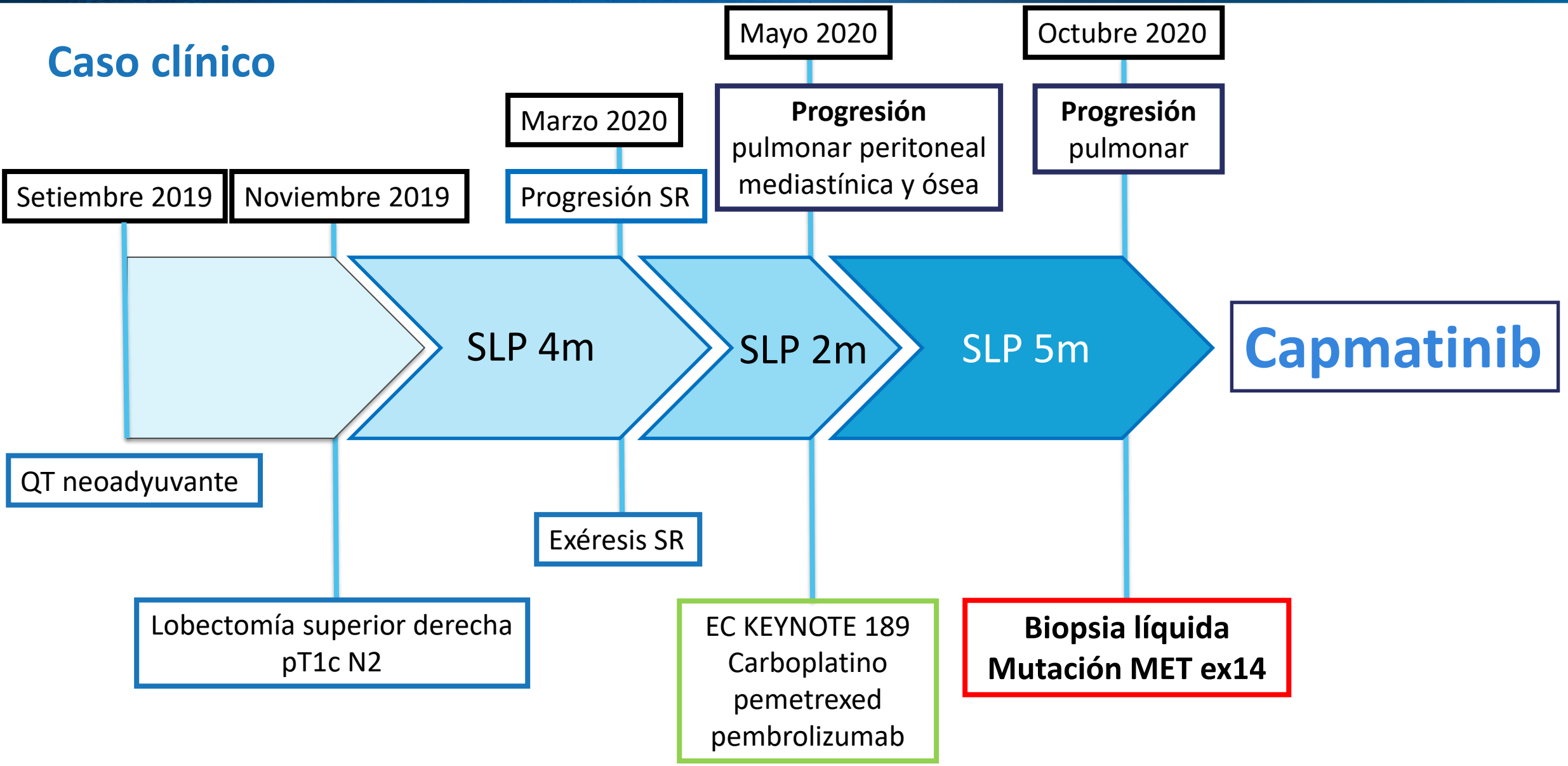
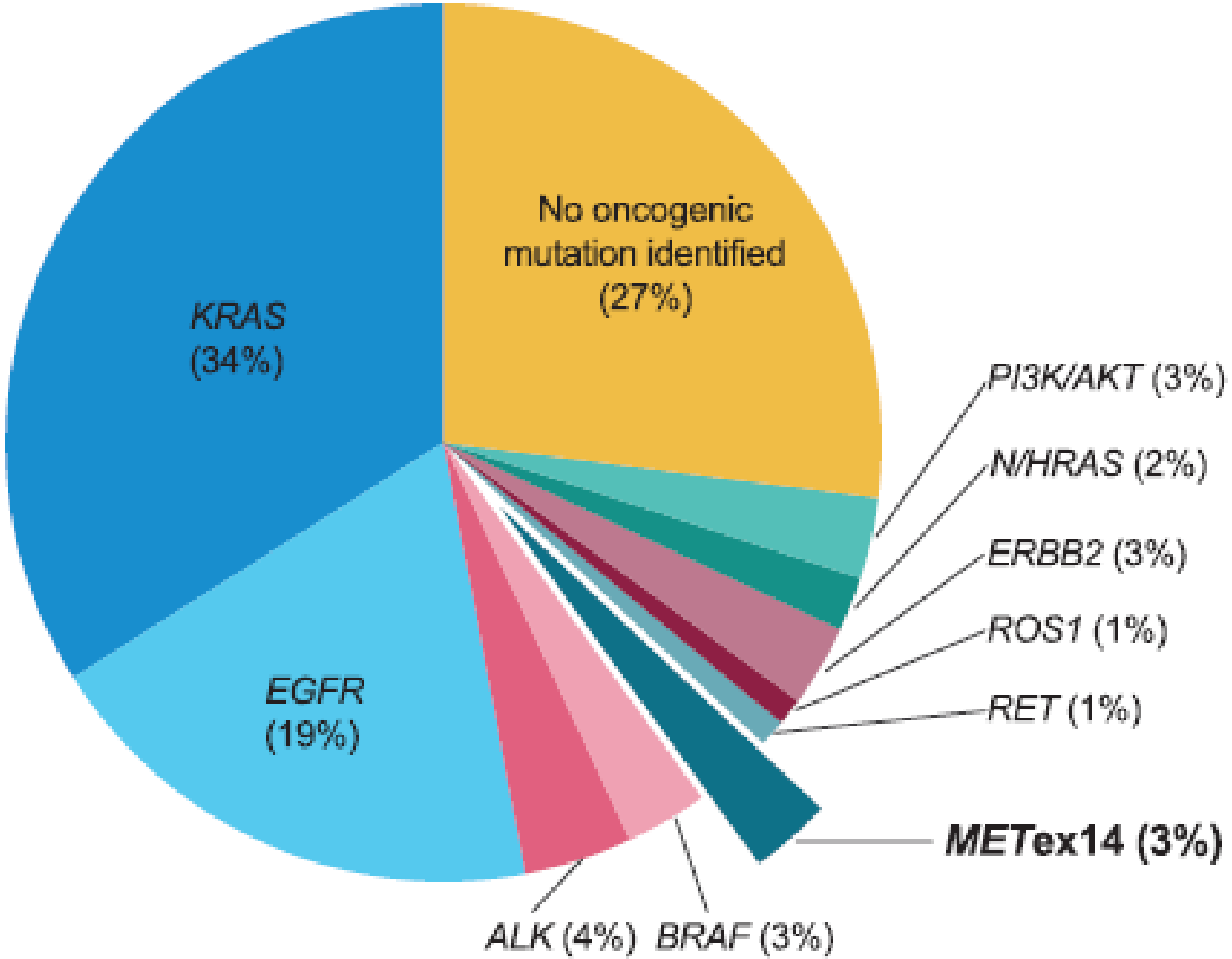


MET in NSCLC

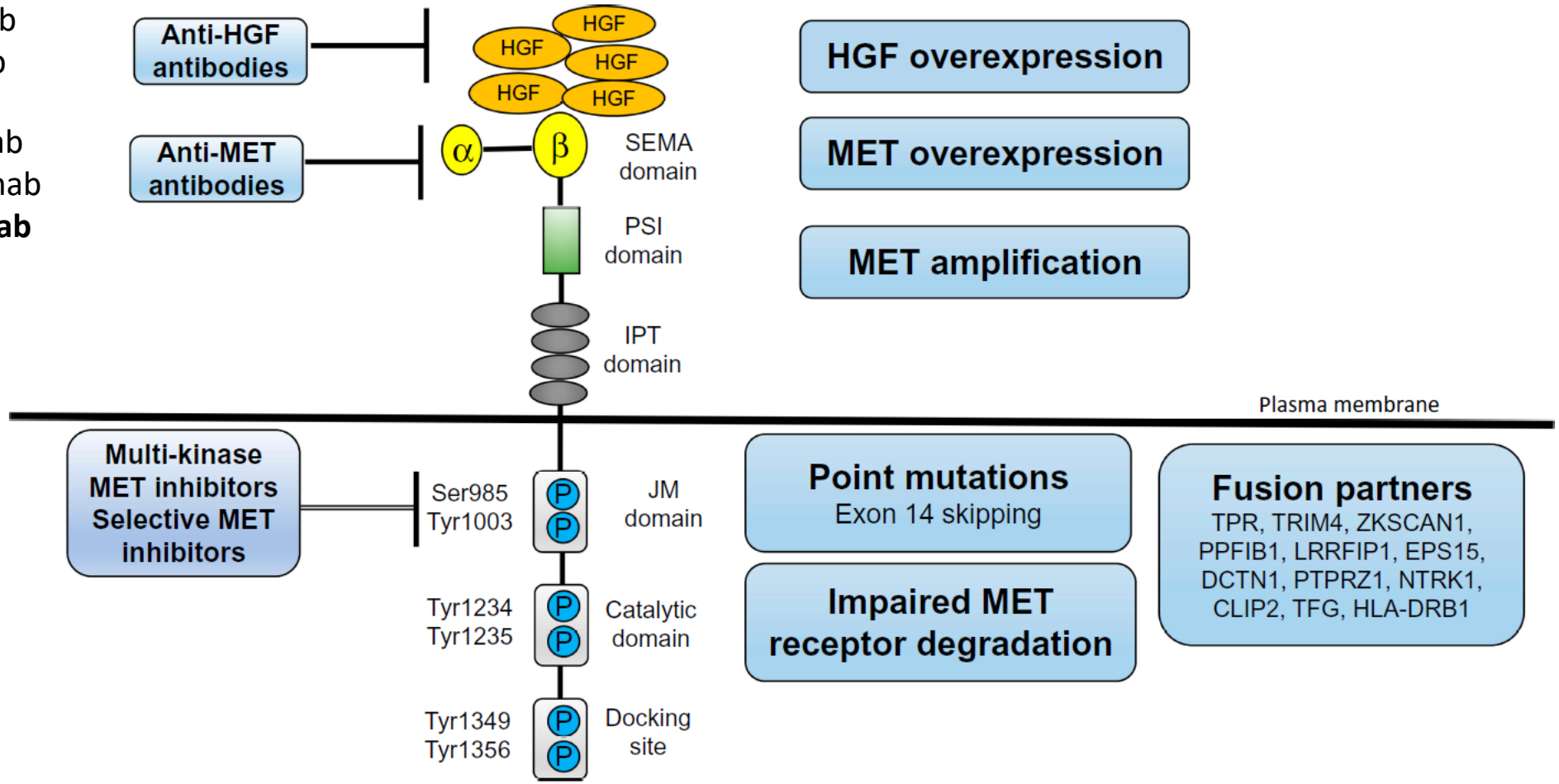


Hong L et al. Therapeutic Advances in Medical Oncology 2021

Ways to inhibit MET

Ficlatuzumab
Rilotuzumab

Onartuzumab
Emibetuzumab
Amivantamab



Hongge Liang et al. OncoTargets and Therapy 2020

Why to inhibit MET?

AwadMM, et al. Lung Cancer. 2019

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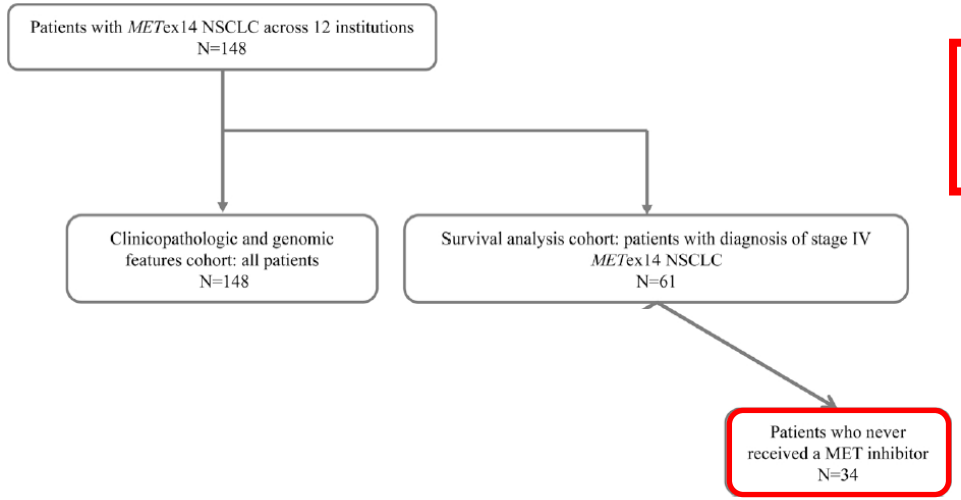
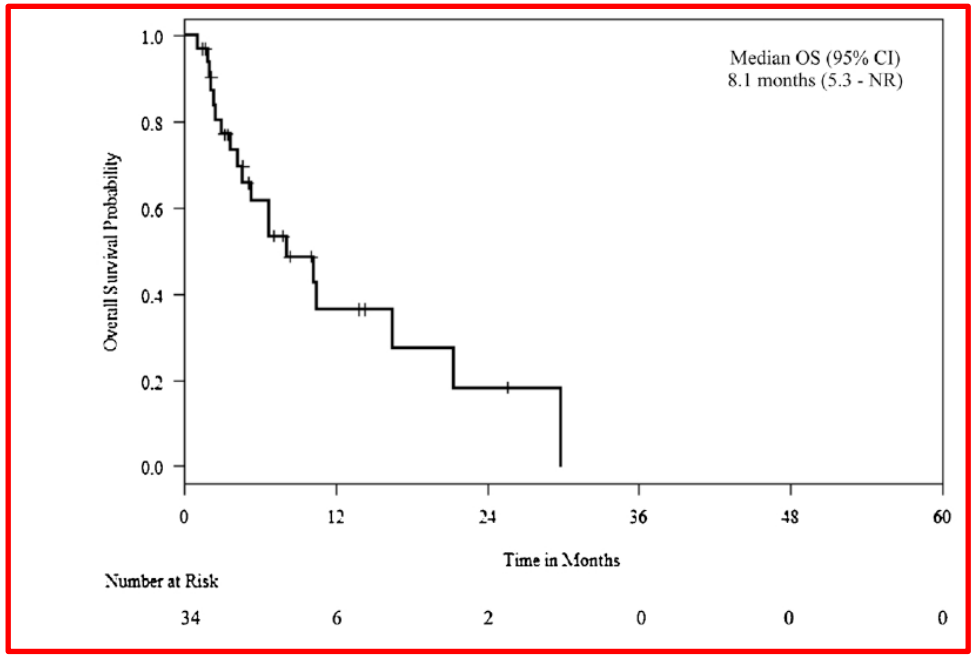


METex14 confers a bad prognosis

mOS 8.1m



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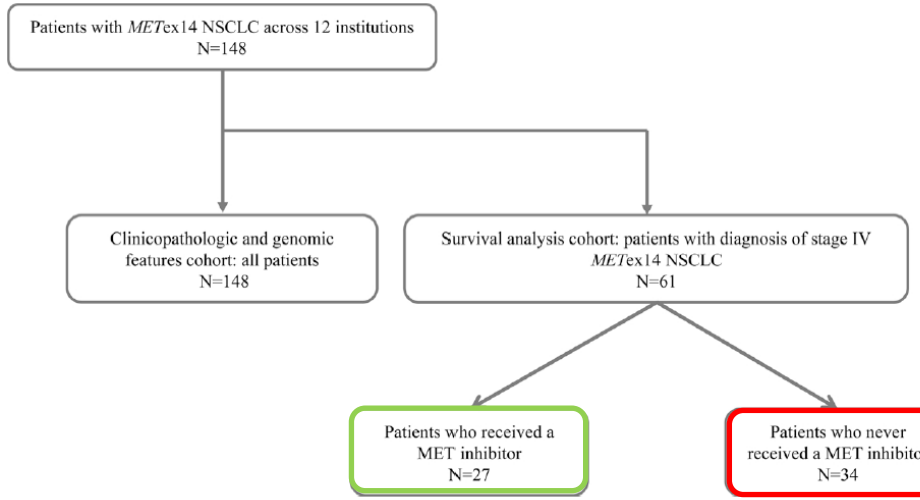

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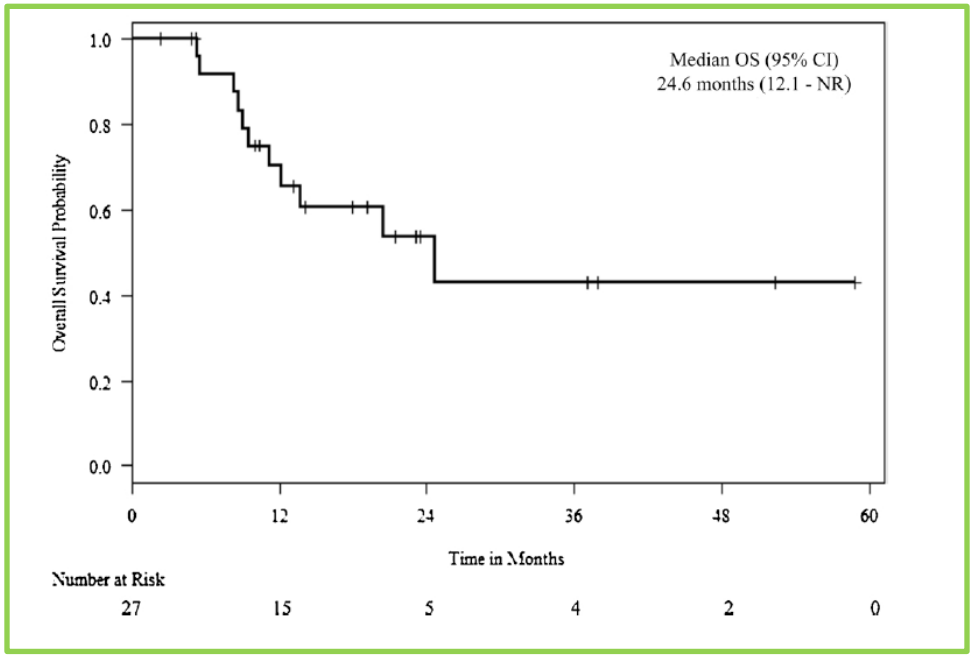
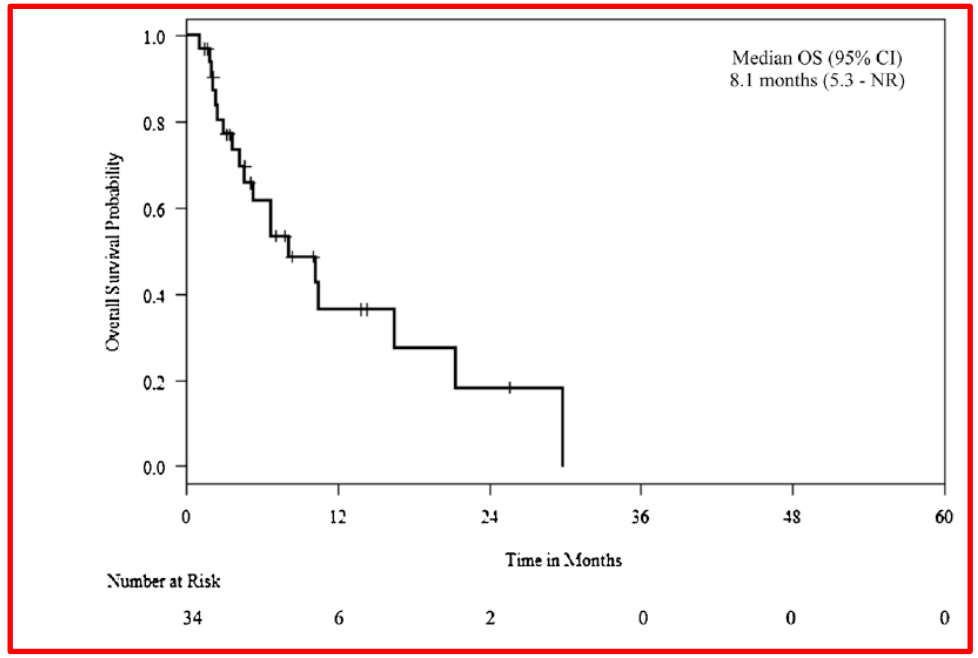
mOS 24.6 m



mOS 8.1m

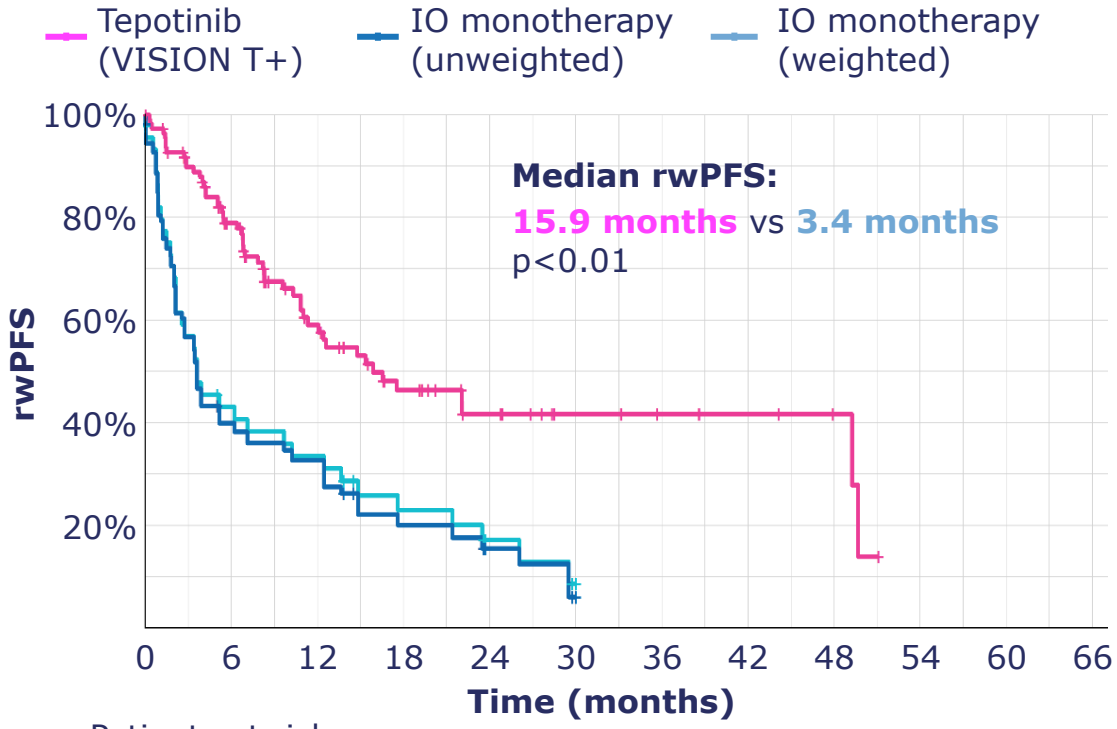


AwadMM, et al. Lung Cancer. 2019

Why to inhibit MET?

rwPFS for 1L (A) IO and (B) IO+CT compared with 1L tepotinib in VISION

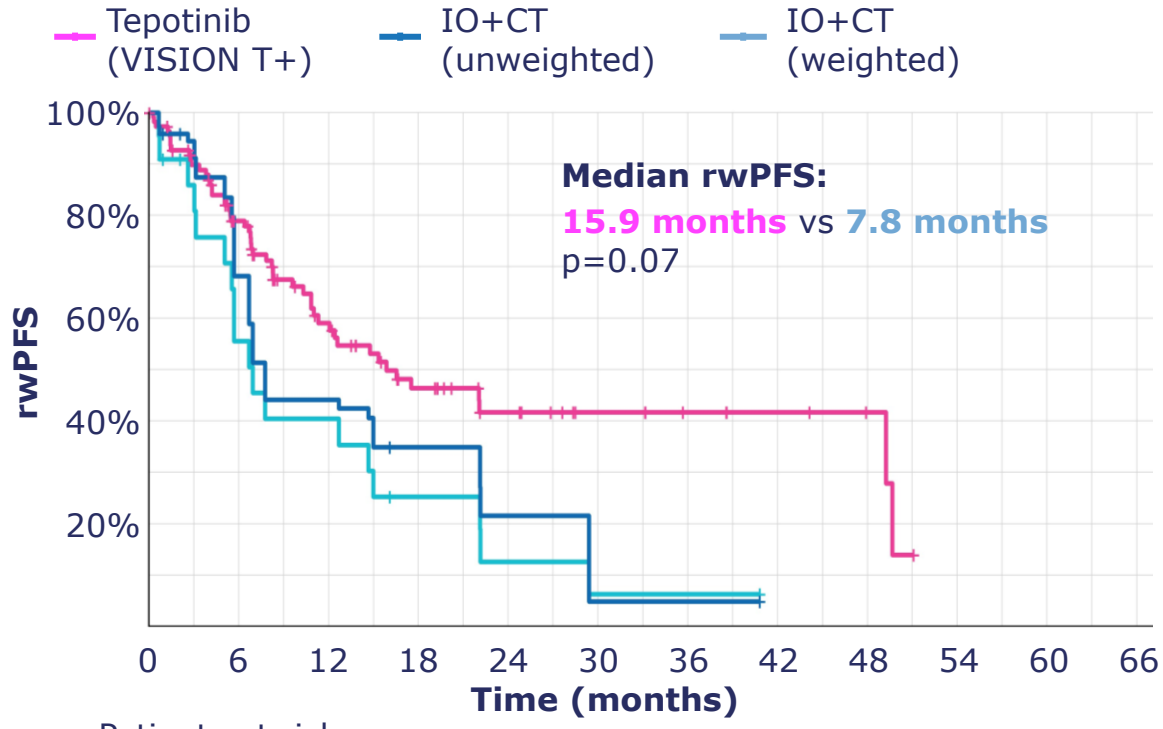
(A)



Patients at risk:

111	73	41	26	17	10	7	5	3	0	0	0
46	18	14	8	4	1	0	0	0	0	0	0
112	42	35	18	10	2	0	0	0	0	0	0

(B)

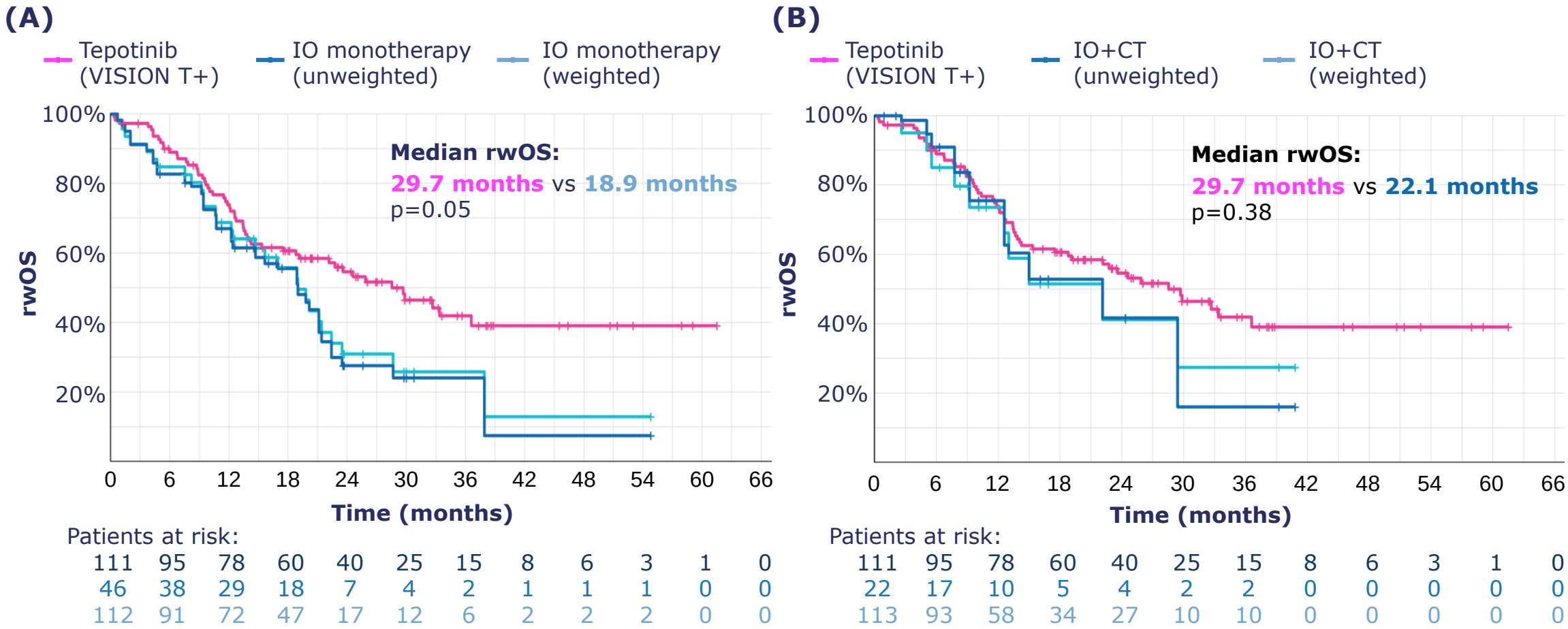


Patients at risk:

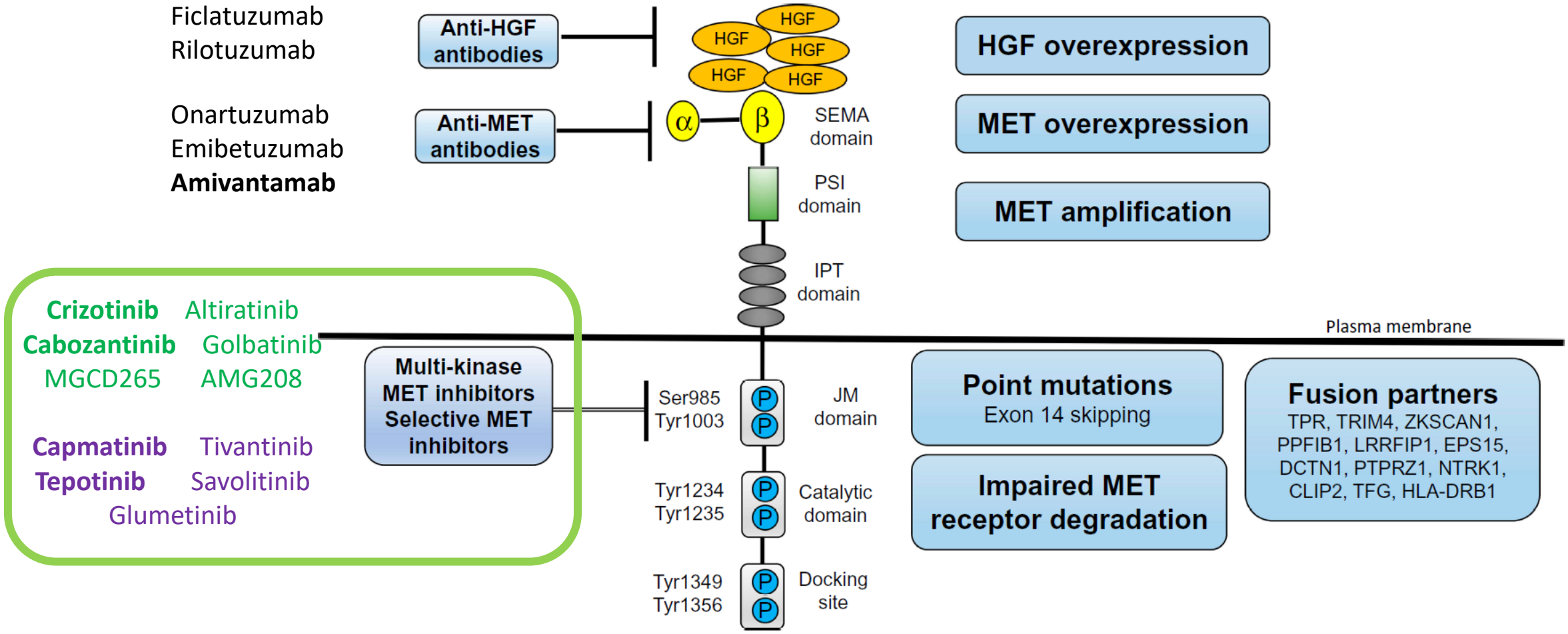
111	73	41	26	17	10	7	5	3	0	0	0
22	11	8	4	2	1	1	0	0	0	0	0
113	69	45	33	20	5	5	0	0	0	0	0

Why to inhibit MET?

ITC rwOS for 1L (A) IO and (B) IO+CT compared with 1L tepotinib in VISION



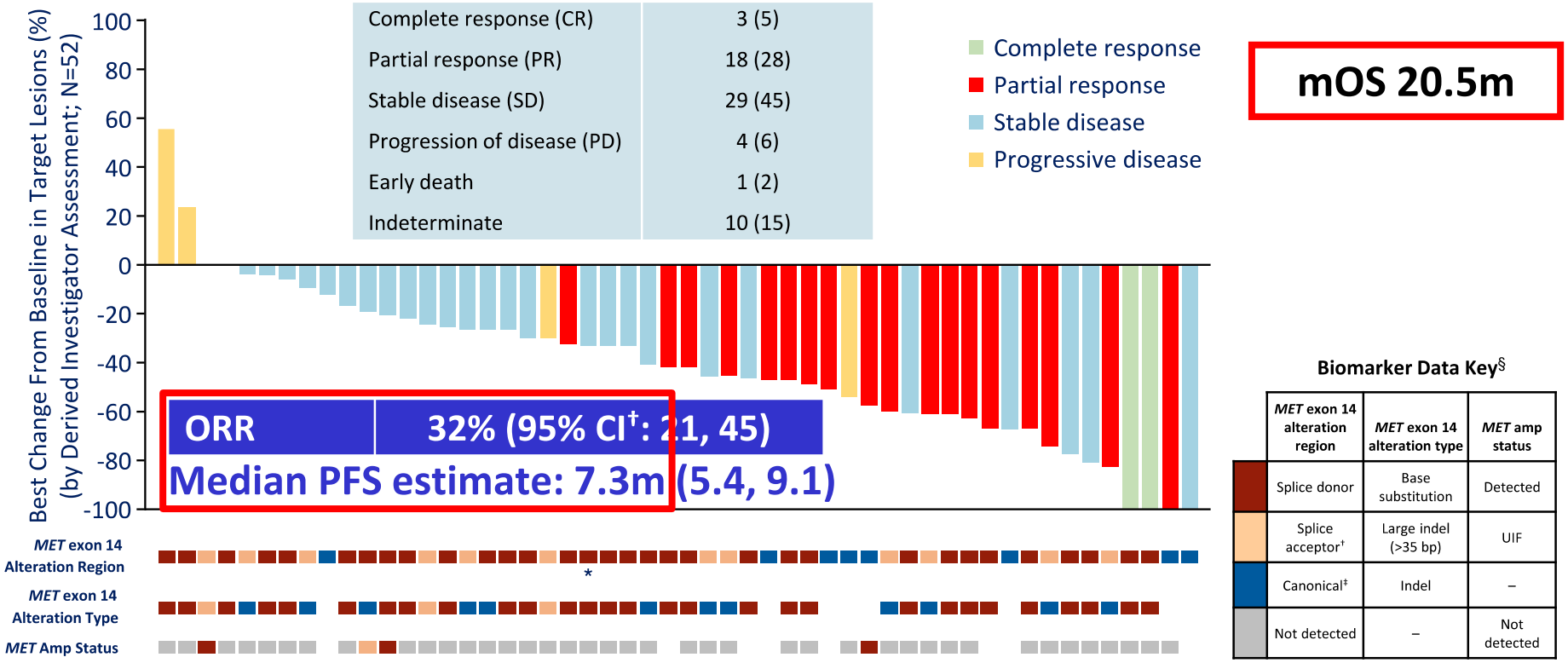
Ways to inhibit MET



Hongge Liang et al. OncoTargets and Therapy 2020

Crizotinib

PROFILE 1001: Crizotinib in METex14 NSCLC



mOS 20.5m

Biomarker Data Key§

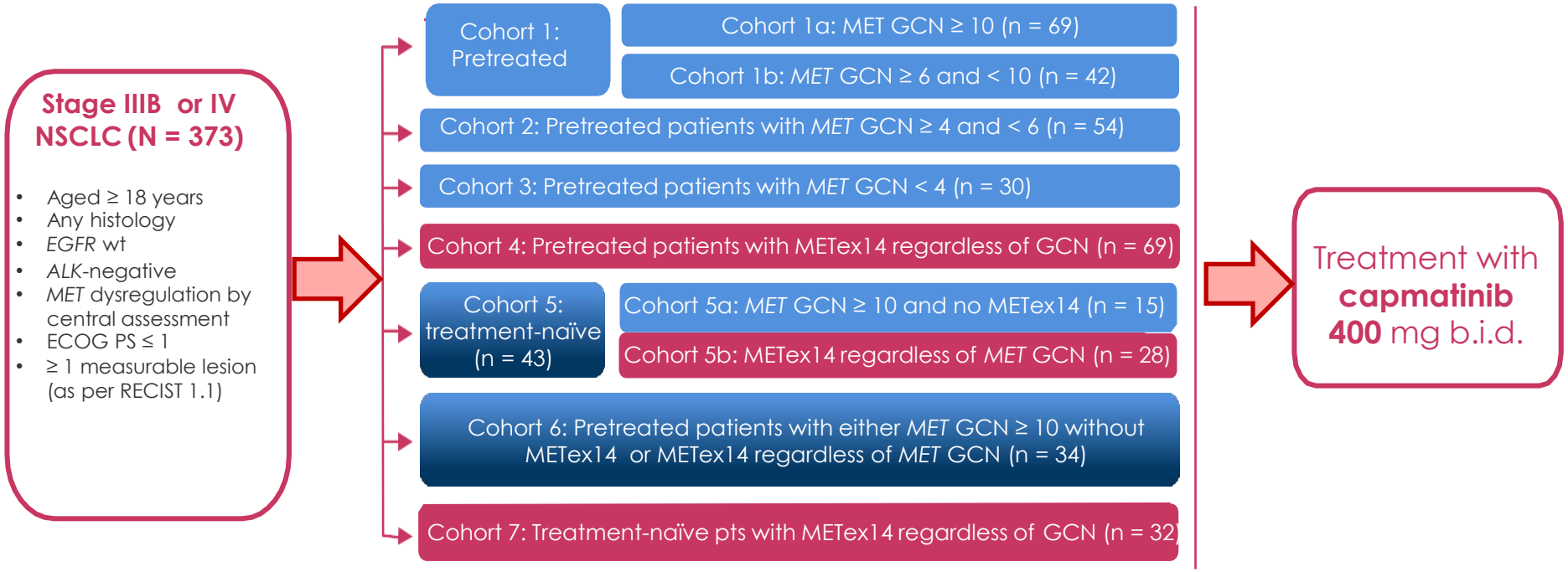
	MET exon 14 alteration region	*MET* exon 14 alteration type	*MET* amp status
	Splice donor	Base substitution	Detected
	Splice acceptor†	Large indel (>35 bp)	UIF
	Canonical‡	Indel	–
	Not detected	–	Not detected

*Alterations in both splice donor and acceptor regions. †Includes alterations in the Splice Acceptor Region, Polypyrimidine Tract, and Branching Point. ‡Includes *MET* exon 14 alterations that are not associated with DNA coding region information. §White space in biomarker data rows indicates no available sample for testing, not analyzable or no results reported. bp, base pairs; UIF, uninformative.

Drilon A, et al. Nat Med 2020;26:47-51

Capmatinib

GEOMETRY: *Phase II trial of capmatinib in patients with with METex14 or MET amplification*



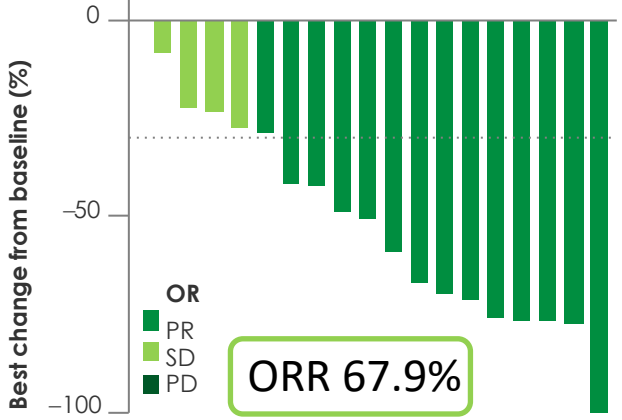
Endpoints	
Primary ORR[a] assessed by BIRC, by cohort	
Secondary	
- DoR assessed by BIRC, by cohort	- ORR and DoR assessed by investigator, by cohort
- TTR, DCR, and PFS[c] assessed by investigator and BIRC, by cohort	- OS by cohort
- Plasma concentration–time profiles and PK parameters	- AEs, vital signs, ECGs, and laboratory abnormalities

Wolf J, et al. N Engl J Med. 2020 / Wolf J, et al. Presented at ASCO 2021

Capmatinib

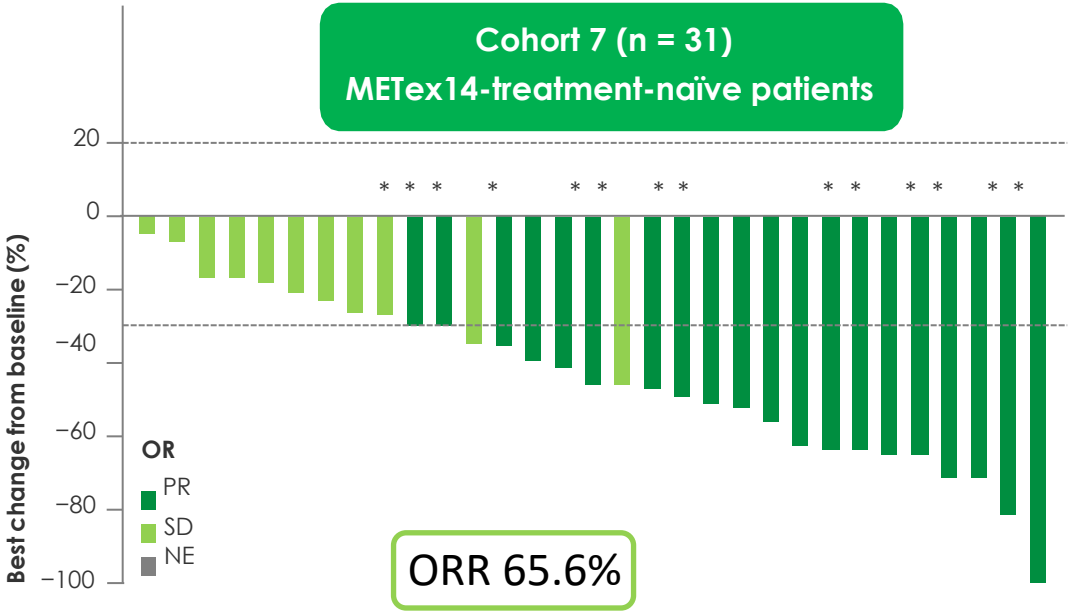
in METex14

Cohort 5b (n = 28)
METex14-treatment-naïve patients



ORR 67.9%

Cohort 7 (n = 31)
METex14-treatment-naïve patients



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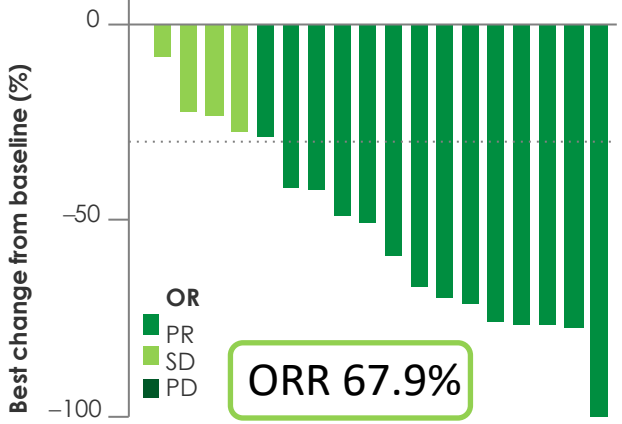

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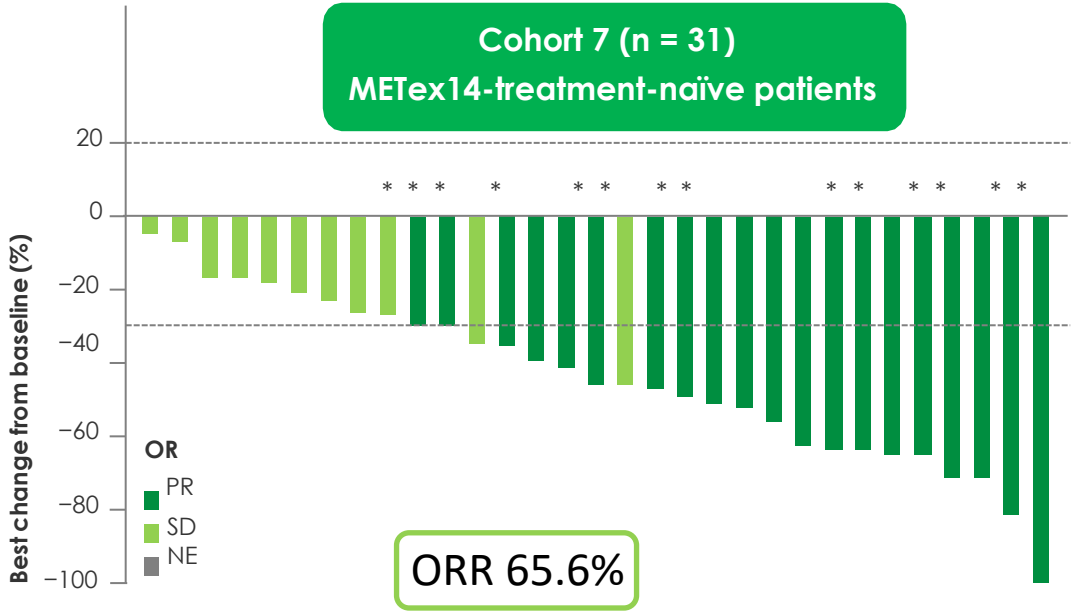
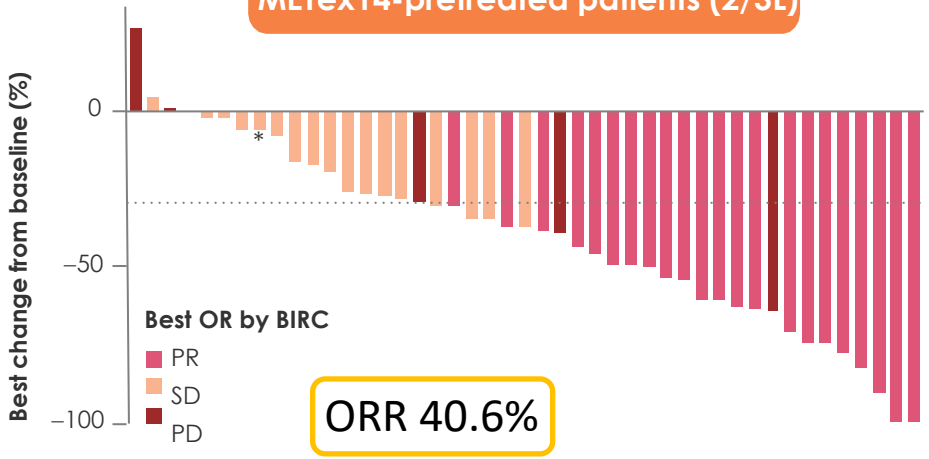


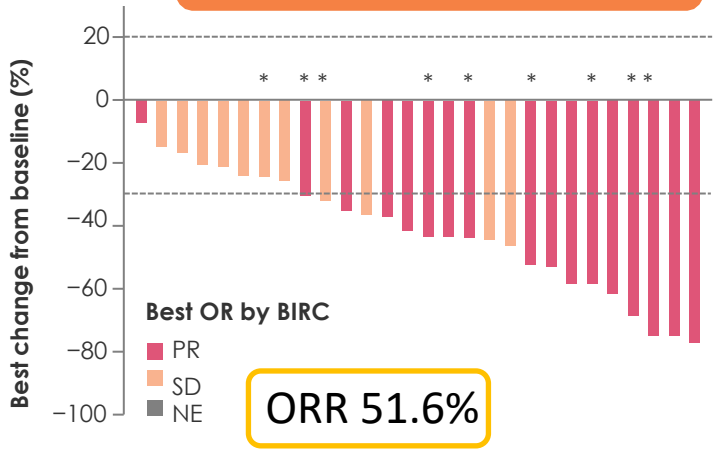
ORR 65.6%

Cohort 4 (n = 69)
METex14-pretreated patients (2/3L)



ORR 40.6%

Cohort 6 (n = 28)
METex14-pretreated patients (2L)



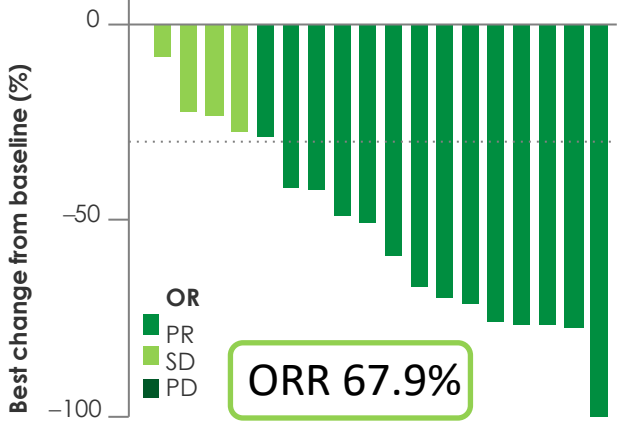
ORR 51.6%

Wolf J, et al. N Engl J Med. 2020 / Wolf J, et al. Presented at ASCO 2021

Capmatinib

in METex14

Cohort 5b (n = 28)
METex14-treatment-naïve patients



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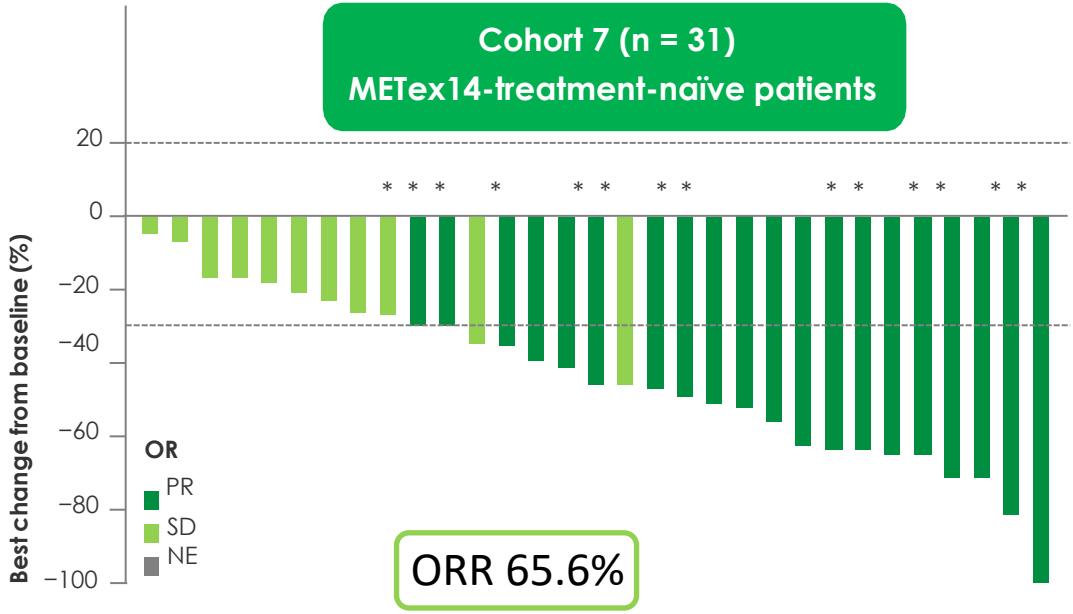

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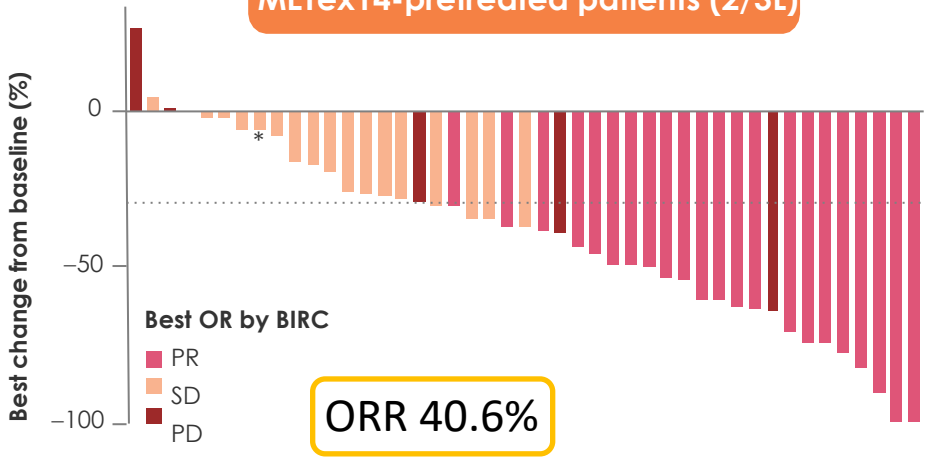

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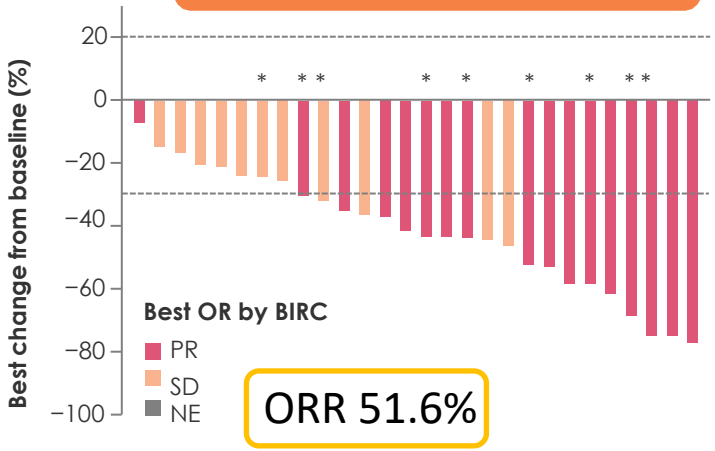
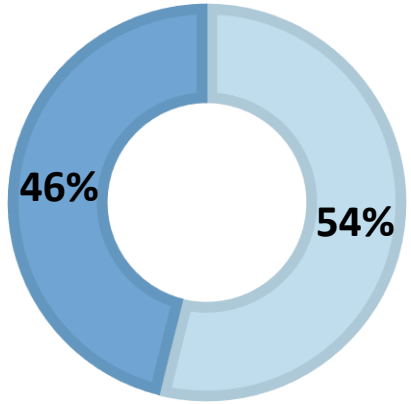
Cohort 6 (n = 28)
METex14-pretreated patients (2L)



ORR 51.6%

Intracranial response



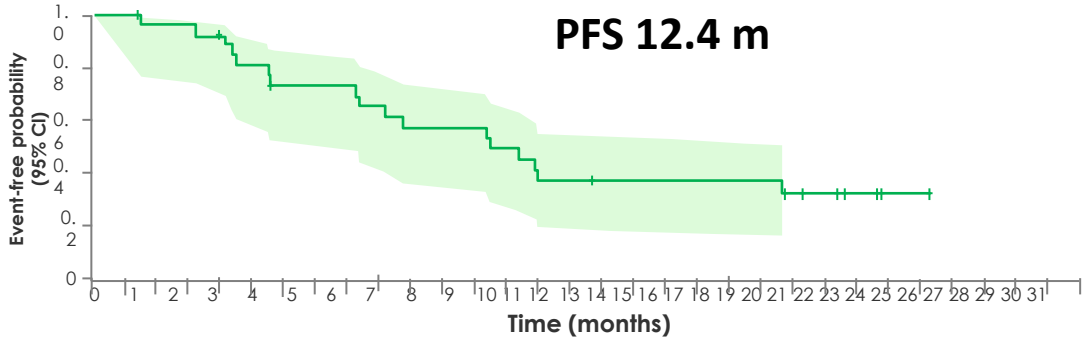
Wolf J, et al. N Engl J Med. 2020 / Wolf J, et al. Presented at ASCO 2021

Capmatinib

in METex14

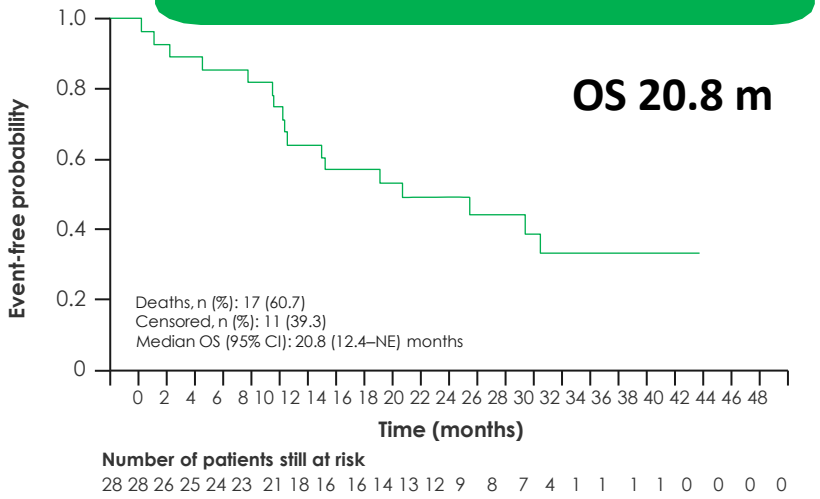
Cohort 5b (n = 28)
METex14- treatment-naïve patients

PFS 12.4 m



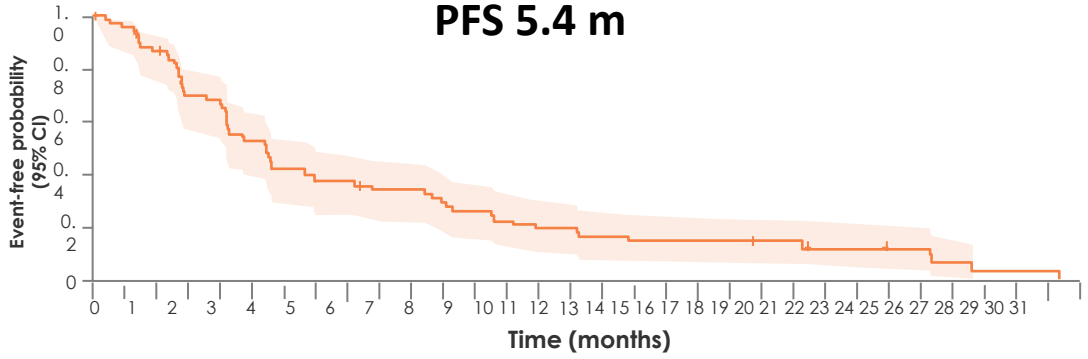
Cohort 5b (n = 28)
METex14- treatment-naïve patients

OS 20.8 m



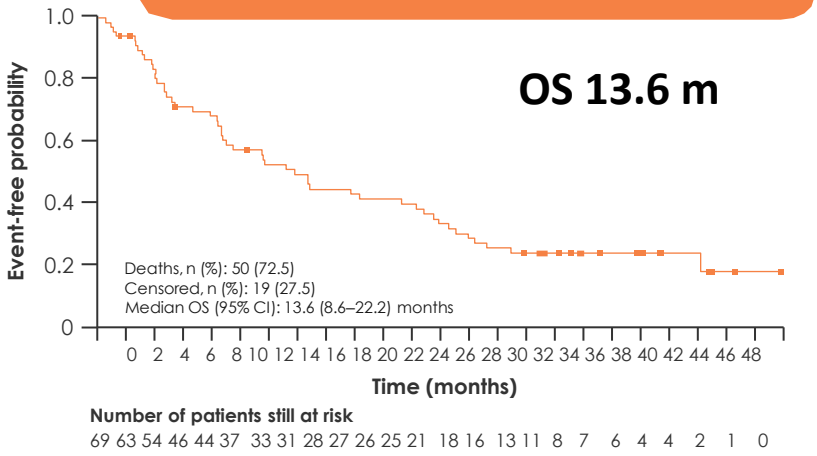
Cohort 4 (n = 69)
METex14-pretreated patients

PFS 5.4 m



Cohort 4 (n = 69)
METex14-pretreated patients

OS 13.6 m



Wolf J, et al. N Engl J Med. 2020 / Wolf J, et al. Presented at ASCO 2021

Capmatinib

in MET GCN ≥ 10

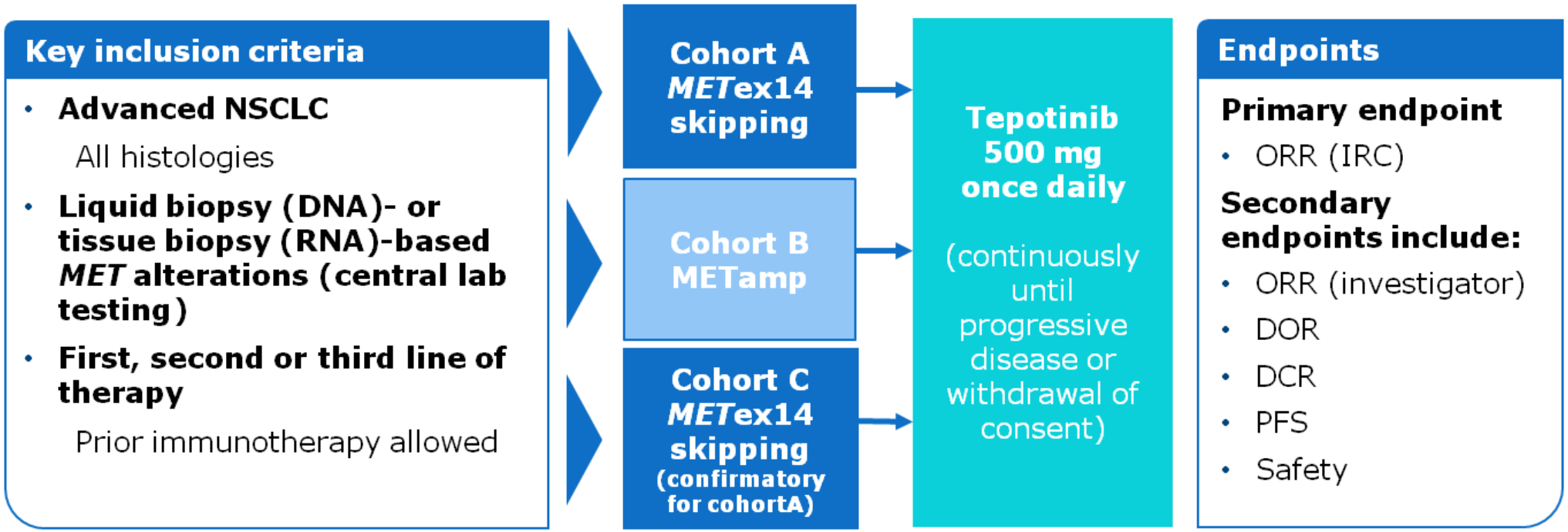
	Cohort 5a naïve (n=15)	Cohort 1a pretreated (n=69)
ORR % (95% CI)	**40** (16.3 -67.7)	29 (18.7 – 41.2)
DCR % (95% CI)	66.7 (38.4 - 88.2)	71 (58.8 – 81.3)
mPFS (95% CI)	4.17 m (1045 - 6.87)	4.07 (2.86 – 4.83)
mOS (95% CI)	9.56m (4.8 – NR)	10.61 (6.28 – 17.22)
mDoR (95% CI)	7.5 (2.6 - 14.3)	8.3 (4.2 – 15.4)

Cohorts 1b, 2 y 3 (MET **GCN < 10**) closed due to **futility**

Wolf J, et al. N Engl J Med. 2020 / Wolf J, et al. Presented at ASCO 2021

Tepotinib

***VISION**: Single-arm, Phase II trial of tepotinib in patients with NSCLC harboring MET alterations*



PaikPK, et al. N EnglJ Med 2020

Tepotinib *in METex14*

	Tissue Biopsy			Liquid Biopsy			Tissue/Liquid biopsy		
	1st Line	2nd Line	Overall	1st Line	2nd Line	Overall	1st Line	2nd Line	Overall
ORR	58.6%	49.5%	54.3%	58.9%	43.4%	51.7%	57.3%	45%	51.4%
mPFS (m)	15.9	11.5	13.7	10	8.2	8.9	12.6	11	11.2
mOS (m)	29.7	20.4	22.9	17.6	16.2	17.6	21.3	19.3	19.6

PaikPK, et al. Jama Oncol 2023

Tepotinib *in METex14*

	Tissue Biopsy			Liquid Biopsy			Tissue/Liquid biopsy		
	1st Line	2nd Line	Overall	1st Line	2nd Line	Overall	1st Line	2nd Line	Overall
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mOS (m)	29.7	20.4	22.9	17.6	16.2	17.6	21.3	19.3	19.6

ORR 50%
PFS 14m
OS 23m

PaikPK, et al. Jama Oncol 2023

Tepotinib *in METex14*

	Tissue Biopsy			Liquid Biopsy			Tissue/Liquid biopsy		
	1st Line	2nd Line	Overall	1st Line	2nd Line	Overall	1st Line	2nd Line	Overall
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ORR 50%
PFS 14m
OS 23m

ORR 50%
PFS 9m
OS 18m

PaikPK, et al. Jama Oncol 2023

Tepotinib *in METex14*

	Tissue Biopsy			Liquid Biopsy			Tissue/Liquid biopsy		
	1st Line	2nd Line	Overall	1st Line	2nd Line	Overall	1st Line	2nd Line	Overall
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ORR 50%
PFS 14m
OS 23m

ORR 50%
PFS 9m
OS 18m

Worse prognostic factors
↑ CNS involvement
↑Tumoral volume
Worse PS

PaikPK, et al. Jama Oncol 2023

Tepotinib *in METex14*

	Tissue Biopsy			Liquid Biopsy			Tissue/Liquid biopsy		
	1st Line	2nd Line	Overall	1st Line	2nd Line	Overall	1st Line	2nd Line	Overall
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mOS (m)	29.7	20.4	22.9	17.6	16.2	17.6	21.3	19.3	19.6
	ORR 50% PFS 14m OS 23m			ORR 50% PFS 9m OS 18m			ORR 50% PFS 11m OS 20m		

Worse prognostic factors
↑ CNS involvement
↑Tumoral volume
Worse PS

PaikPK, et al. Jama Oncol 2023

Tepotinib

in METampl

Key inclusion criteria

- **Advanced NSCLC**
  All histologies
- **Liquid biopsy (DNA)- or tissue biopsy (RNA)-based *MET* alterations (central lab testing)**
- **First, second or third line of therapy**
  Prior immunotherapy allowed

Cohort B METamp

Tepotinib 500 mg once daily

(continuously until progressive disease or withdrawal of consent)

		Overall (n=24)	1L (n=7)	2L (n=10)	3L (n=7)
Best overall response, n (%)	PR	10 (41.7)	5 (71.4)	3 (30.0)	2 (28.6)
	SD	1 (4.2)	0	1 (10.0)	0
	PD	5 (20.8)	1 (14.3)	2 (20.0)	2 (28.6)
	NE	8 (33.3)	1 (14.3)	4 (40.0)	3 (42.9)
ORR, n (%) [95% CI]		10 (41.7) [22.1, 63.4]	5 (71.4) [29.0, 96.3]	3 (30.0) [6.7, 65.2]	2 (28.6) [3.7, 71.0]

mPFS 4.2m

Le X, et al. J ClinOncol2021

Savolitinib

Phase II trial of Savolitinib in patients with NSCLC METex14+

Study population:

- Unresectable/metastatic PSC or other NSCLC
- *MET*ex14+ & EGFR/ALK/ROS1-
- Failed/or medically unfit for chemotherapy
- Naïve to *MET* inhibitor

Savolitinib treatment:

- 600mg (BW≥50kg), or
- 400mg (BW<50kg)

Orally, once daily, 21 days/cycle

Tumor evaluation by investigators

- 1st year: every 6 weeks
- After 1 year: every 12 weeks

(Independent review retrospectively)

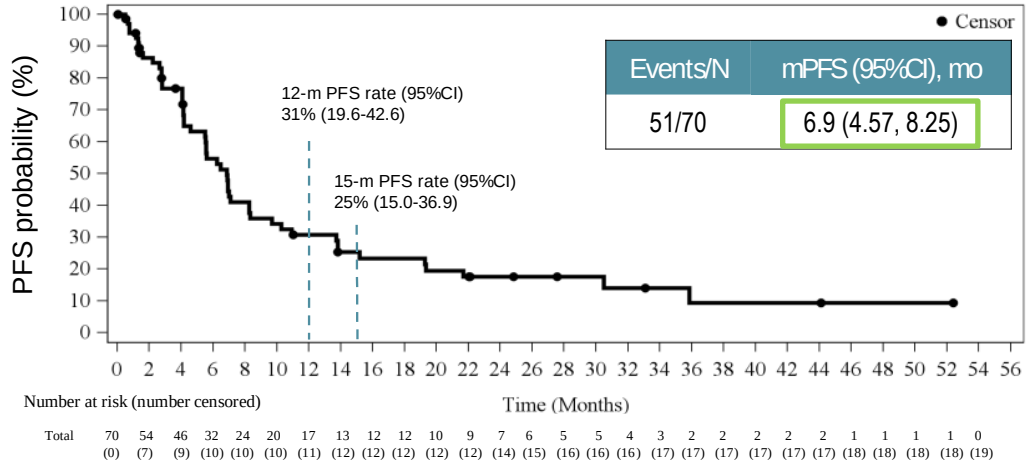
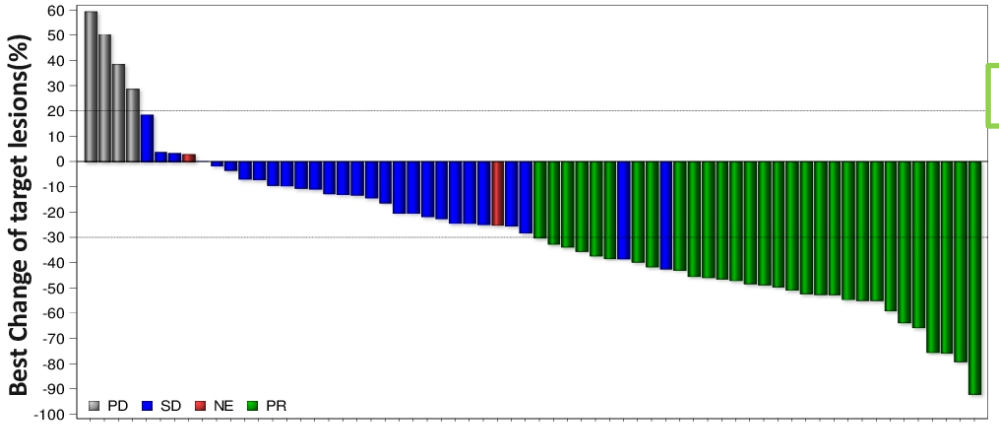
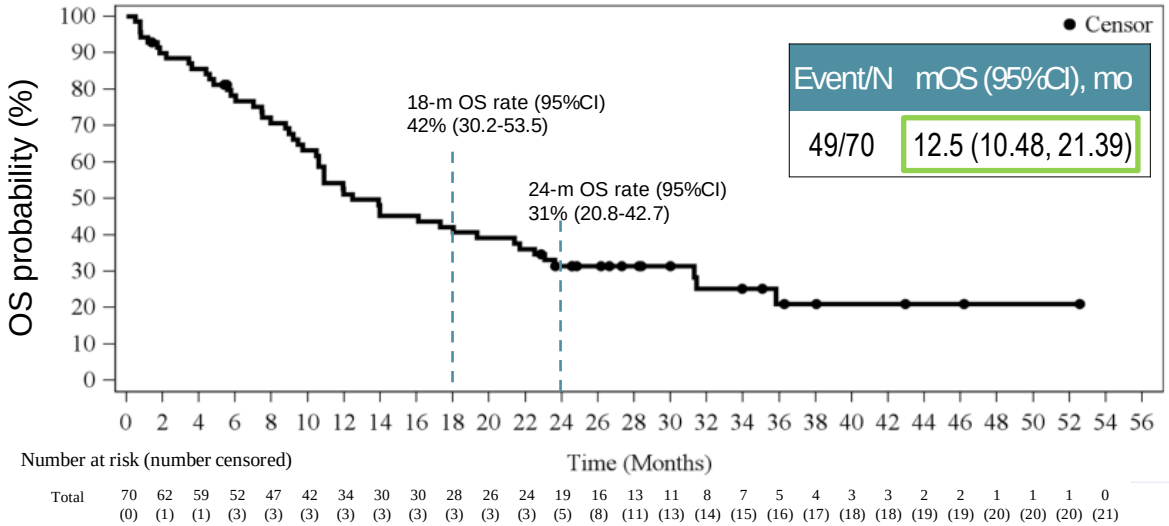


Figure 2. Tumor shrinkage in full analysis set per IRC



ORR: 49.2%

ORR 49%
mPFS 6.9m
mOS 12.5m



Shun Lu ELCC 2021

MET tirosin kinase inhibitors. Safety

Related AEs	Capmatinib (GEOMETRY) N=151		Tepotinib (VISION) N=255		Savolitinib (NCT02897479) N=70	
Discontinuation	12%		11%		14%	
	All Grade	Grade 3	All Grade	Grade ≥3	All Grade	Grade ≥3
Edema	50	11	63	7	54	9
Nausea	36	1	26	1	46	0
Creatinine incr.	19	0	18	1	-	-
AST incr.	6	3	7	2	37	13
ALT incr.	11	7	7	3	39	10
Fatigue	13	3	7	1	-	-
Hypoalbuminemia	-	-	16	2	23	0

Le, IASLC Targeted Therapies 2022

MET tirosin kinase inhibitors. Sumary

	CRIZOTINIB		CAPMATINIB		TEPOTINIB		SAVOLITINIB	
	PROFILE - 001		GEOMETRY-mono-1		VISION		NCT02897479	
Sample Size	1L 26	2L+43	1L 60	2L 100	1L 164	2L+ 241	1L 28	2L+ 42
Median Age	72		71	71	75	71	69	
ORR	25%	37%	67%	44%	56%	45%	46%	41%
mPFS (mo)	7.3		12.4	5.4	12.6	11	5.6	6.9
mOS (mo)	9.1		20.8	13.6	19.1	20	12.5	

Drilon, Nat Med 2020 / Wolf NEJM 2020 / Paik NEJM 2020 / Paik WCLC 2020 / Lu Lancet Resp Med 2021 / Le IASLC Targeted Therapies 2022

MET tirosin kinase inhibitors. Sumary

	CRIZOTINIB		CAPMATINIB		TEPOTINIB		SAVOLITINIB	
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✓ EMA approved

Drilon, Nat Med 2020 / Wolf NEJM 2020 / Paik NEJM 2020 / Paik WCLC 2020 / Lu Lancet Resp Med 2021 / Le IASLC Targeted Therapies 2022

MET tirosin kinase inhibitors. Sumary

	CRIZOTINIB		CAPMATINIB		TEPOTINIB		SAVOLITINIB	
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✓ EMA approved

😀

…on second line ?

Drilon, Nat Med 2020 / Wolf NEJM 2020 / Paik NEJM 2020 / Paik WCLC 2020 / Lu Lancet Resp Med 2021 / Le IASLC Targeted Therapies 2022

MET tirosin kinase inhibitors. Sumary

	CAPMATINIB	TEPOTINIB
FDA APPROVED	6 mayo 2020	3 febrero 2021
EMA APPROVED	20 junio 2022	16 febrero 2022
agencia española de medicamentos y productos sanitarios	1 marzo 2022	1 marzo 2022
Alta en financiación	1 marzo 2023	1 marzo 2023

MET tirosin kinase inhibitors. Sumary

	CAPMATINIB	TEPOTINIB
FDA APPROVED	6 mayo 2020	3 febrero 2021
EMA APPROVED	20 junio 2022	16 febrero 2022
agencia española de medicamentos y productos sanitarios	1 marzo 2022	1 marzo 2022
Alta en financiación	1 marzo 2023	1 marzo 2023

2 years

INADMISSIBLE

MET tirosin kinase inhibitors. Sumary

	CAPMATINIB		TEPOTINIB		GLUMETINIB		GUMAROTINIB	
	GEOMETRY-mono-1		VISION		GLORY		NCT04270591	
Sample Size	1L 60	2L 100	1L 164	2L+ 241	1L 42	2L+ 27	1L 44	2L 35
Median Age	71	71	75	71	-		68.5	
ORR	67%	44%	56%	45%	66.7%	51.9%	71%	60%
mPFS (mo)	12.4	5.4	12.6	11	NE	5.7	11.7	7.6
mOS (mo)	20.8	13.6	19.1	20	NE		NE	16.2

Wolf NEJM 2020 / Paik WCLC 2020 / Lu Lancet Resp Med 2021 / Lu S. AACR 2022 / Yu Y et al., eClinicalMedicine 2023

New ways to inhibit *MET*

Antibody-drug conjugate

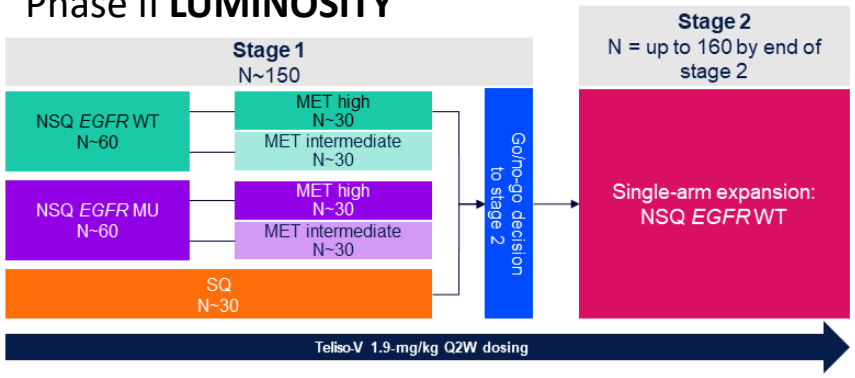
New ways to inhibit *MET*

Antibody-drug conjugate

Telisotuzumab Vedotin (teliso-v)

Telisotuzumab + monomethyl auristatin E (microtubule inhibitor + cytotoxin)

Phase II **LUMINOSITY**



Inclusion criteria

- Adult (≥18 years)
- Locally advanced/metastatic NSCLC
- c-Met–overexpressing*tumors (by central immunohistochemistry)
- ECOG performance status of 0 or 1
- ≤2 prior lines of systemic therapy, including ≤1 line of chemotherapy
- Adequate bone marrow, renal, and hepatic function

*Defined as ≥25% tumor cells at 3+ intensity (high, ≥50% 3+; intermediate, 25 to <50% 3+) for the NSQ cohort, and as ≥75% of tumor cells at 1+ intensity for the SQ cohort.

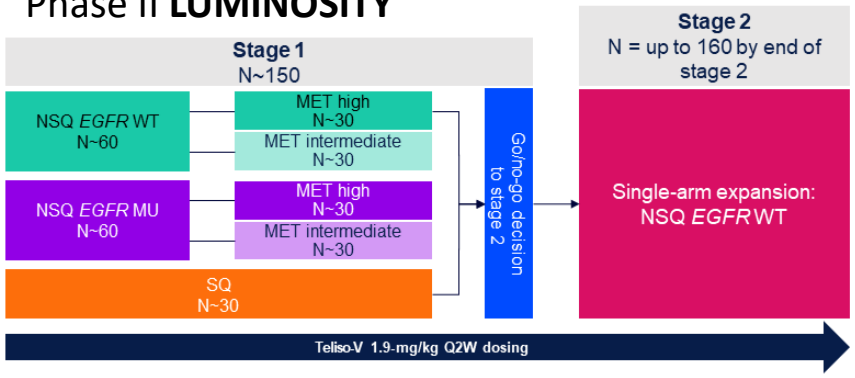
Dagogo J ASCO 2022 / Camidge DR, et al. J Clin Oncol 2022;40(suppl):Abstr 9016

New ways to inhibit *MET*

Antibody-drug conjugate

Telisotuzumab Vedotin (teliso-v)

Phase II **LUMINOSITY**



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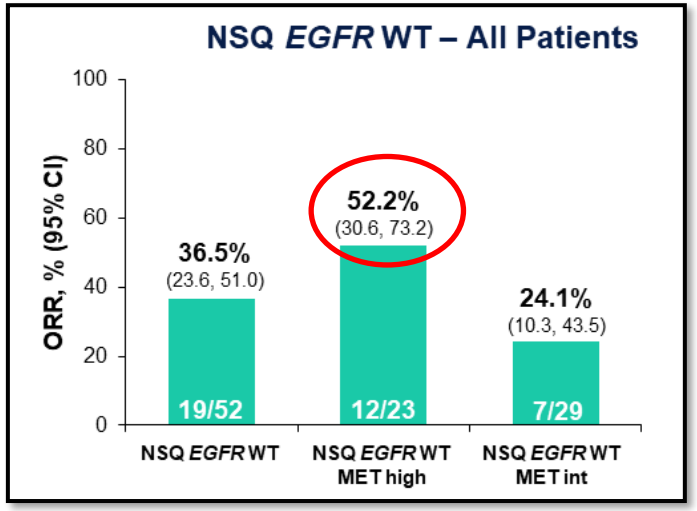
Telisotuzumab + monomethyl auristatin E (microtubule inhibitor + cytotoxin)

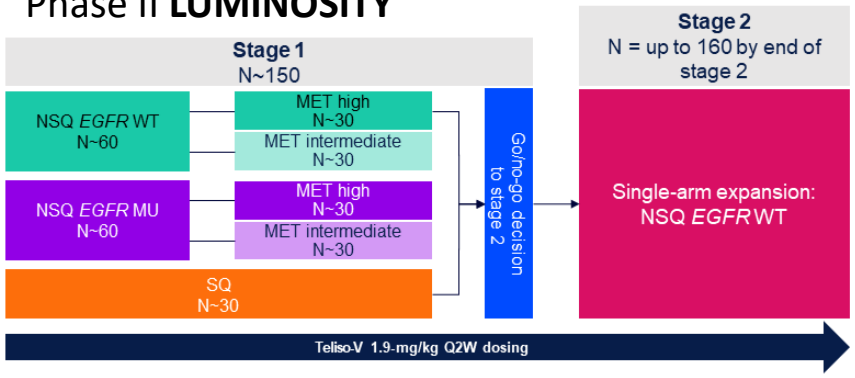


New ways to inhibit *MET*

Antibody-drug conjugate

Telisotuzumab Vedotin (teliso-v)

Phase II **LUMINOSITY**



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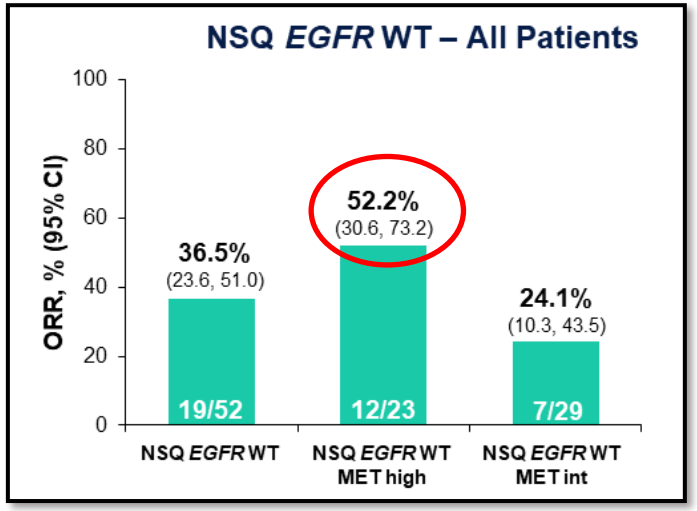
TEAEs, n (%)	Total N=136 Any Grade	Grade ≥3
Any TEAE	131 (96)	65 (48)
Most common any-grade TEAEs (≥10%)		
Peripheral sensory neuropathy	34 (25)	6 (4)
Nausea	30 (22)	1 (1)
Hypoalbuminemia	28 (21)	1 (1)
Peripheral edema	25 (18)	0
Blurred vision	25 (18)	1 (1)
Decreased appetite	24 (18)	0
Fatigue	22 (16)	5 (4)
Anemia	19 (14)	3 (2)
Dyspnea	19 (14)	4 (3)
Asthenia	18 (13)	3 (2)
Increased gamma-glutamyl transferase	18 (13)	3 (2)
Keratitis	18 (13)	0
Constipation	16 (12)	1 (1)
Cough	14 (10)	0
Diarrhea	14 (10)	0
Dizziness	14 (10)	0
Malignant neoplasm progression	14 (10)	11 (8)
Vomiting	14 (10)	1 (1)

Any TEAE related to Teliso-V*	104 (76)
Any serious TEAE	41 (30)
Any TEAE leading to Teliso-V discontinuation	45 (33)
Any TEAE leading to Teliso-V discontinuation possibly related to Teliso-V*	18 (13)
Any TEAE leading to death possibly related to Teliso-V*	2 (1) → n=1 sudden death, n=1 pneumonitis

*Per investigator assessment.
TEAEs, treatment-emergent adverse events; Teliso-V, telisotuzumab vedotin.

Pneumonitis reported in 9 (6.6%) patients, 3 of whom had grade ≥3 (2.2%) pneumonitis

Telisotuzumab + monomethyl auristatin E (microtubule inhibitor + cytotoxin)

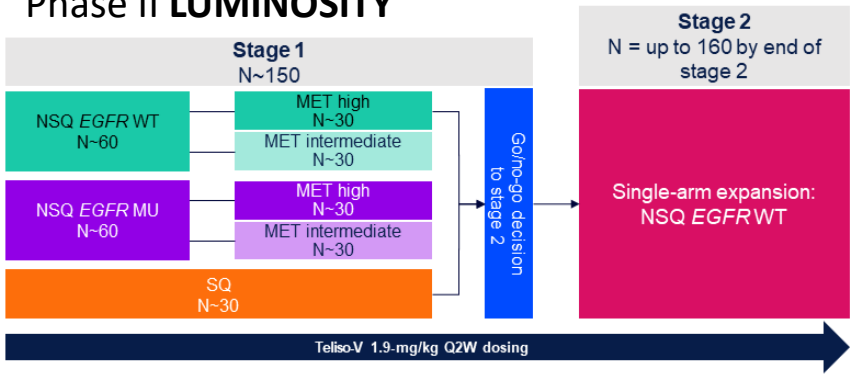


New ways to inhibit *MET*

Antibody-drug conjugate

Telisotuzumab Vedotin (teliso-v)

Phase II **LUMINOSITY**



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Nausea	30 (22)	1 (1)
Hypoalbuminemia	28 (21)	1 (1)
Peripheral edema	25 (18)	0
Blurred vision	25 (18)	1 (1)
Decreased appetite	24 (18)	0
Fatigue	22 (16)	5 (4)
Anemia	19 (14)	3 (2)
Dyspnea	19 (14)	4 (3)
Asthenia	18 (13)	3 (2)
Increased gamma-glutamyl transferase	18 (13)	3 (2)
Keratitis	18 (13)	0
Constipation	16 (12)	1 (1)
Cough	14 (10)	0
Diarrhea	14 (10)	0
Dizziness	14 (10)	0
Malignant neoplasm progression	14 (10)	11 (8)
Vomiting	14 (10)	1 (1)

Any TEAE related to Teliso-V*	104 (76)
Any serious TEAE	41 (30)
Any TEAE leading to Teliso-V discontinuation	45 (33)
Any TEAE leading to Teliso-V discontinuation possibly related to Teliso-V*	18 (13)
Any TEAE leading to death possibly related to Teliso-V*	2 (1)

n=1 sudden death, n=1 pneumonitis

*Per investigator assessment.
TEAEs, treatment-emergent adverse events; Teliso-V, telisotuzumab vedotin.

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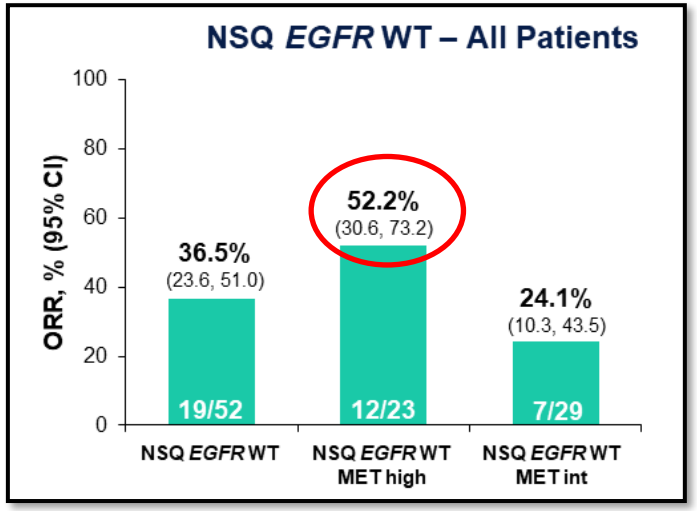
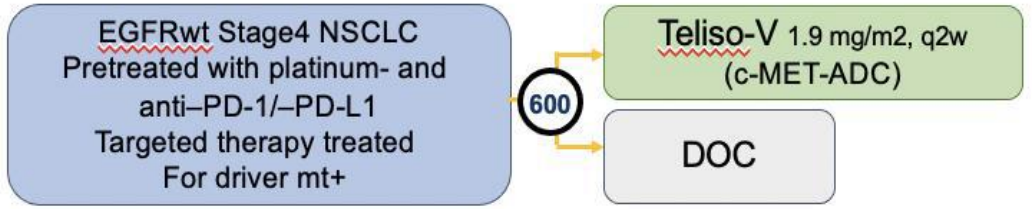


TeliMET NSCLC-01 **Phase III** TRIAL



New ways to inhibit *MET*

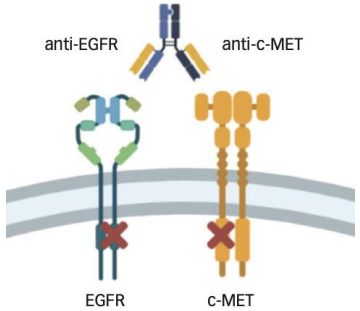
Bispecific antibodies

Krebs M et al. ASCO 2022

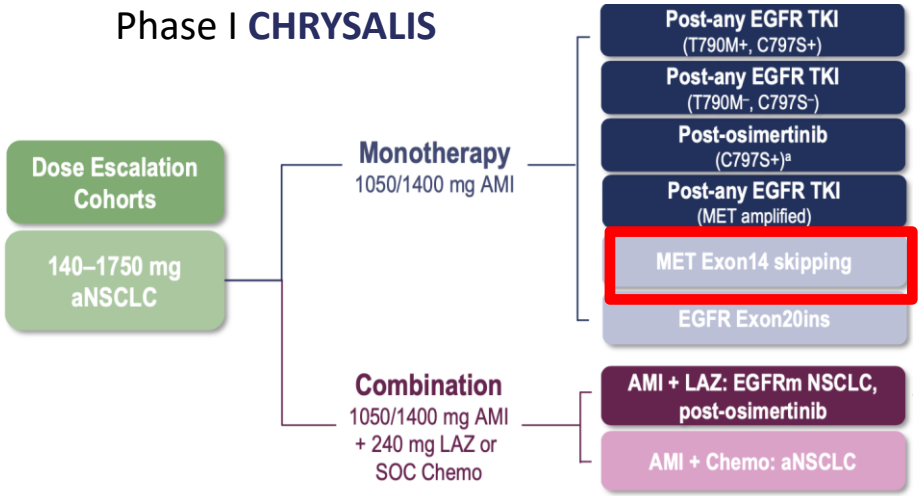
New ways to inhibit *MET*

Bispecific antibodies

Amivantamab



Phase I **CHRYSALIS**

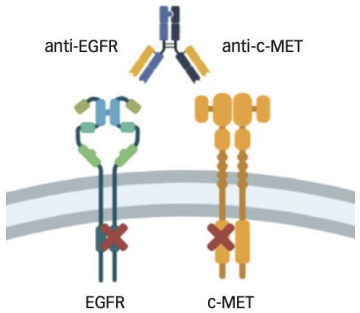


Krebs M et al. ASCO 2022

New ways to inhibit *MET*

Bispecific antibodies

Amivantamab



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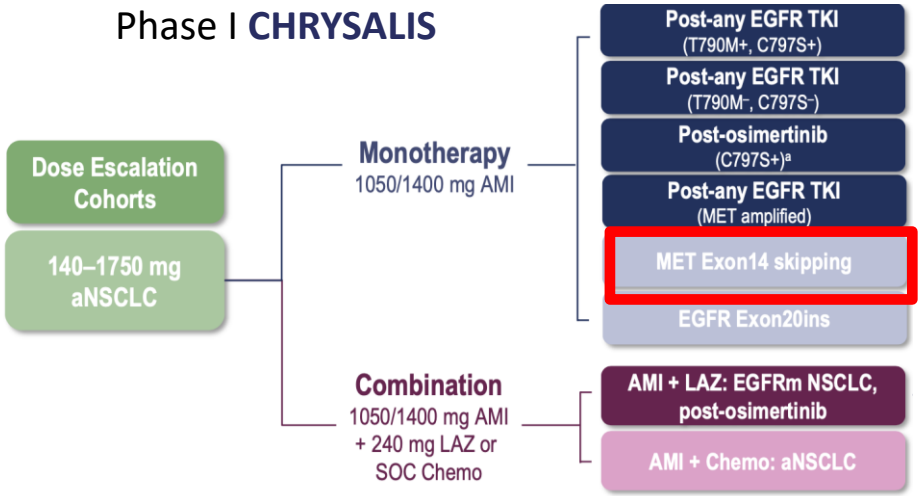
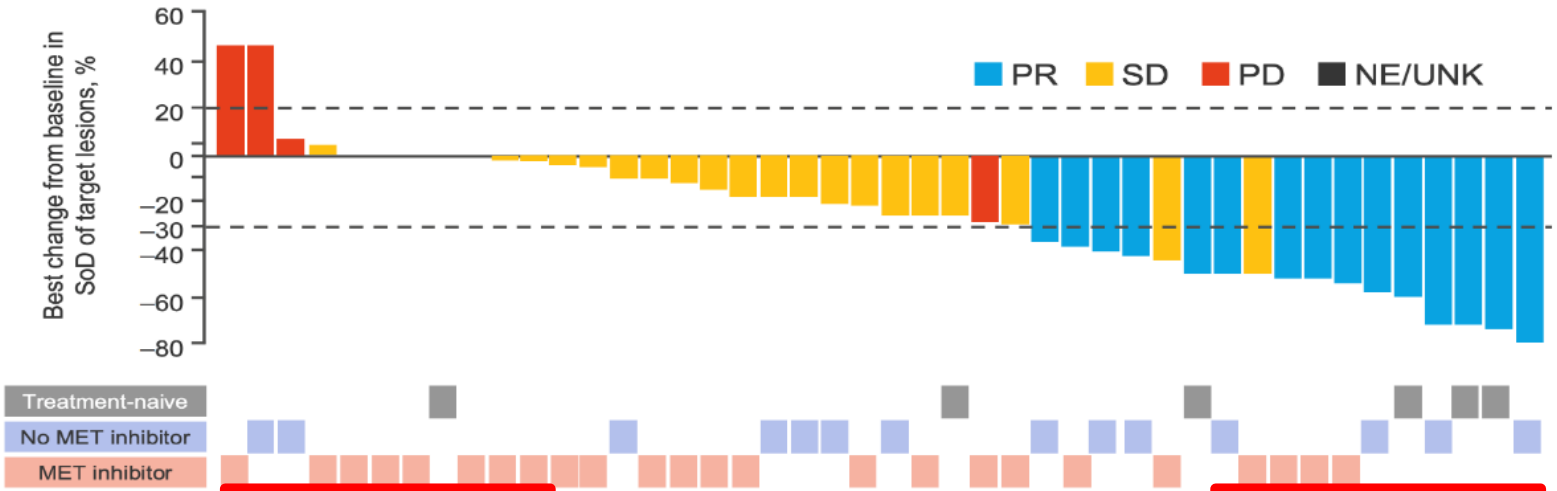




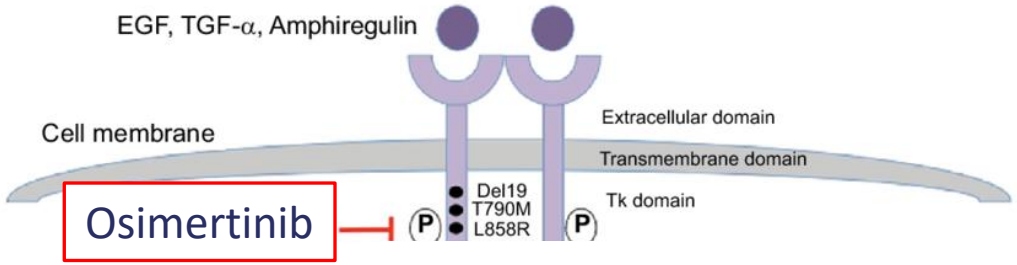
	Treatment-naïve 4 PRs/7; ORR 57%	No prior MET inhibitor 7 PRs/15; ORR 47%	Prior MET inhibitor 4 PRs/24; ORR 17%	All patients 15 PRs/46; ORR 33%
	Treatment-naive	No prior MET	Prior MET	All
mPFS, mo (95%CI)	NE (2.6, NE)	8.3 (1.5, 15.3)	4.2 (2.9, NE)	6.7 (2.9, 15.3)

Clinical benefit rate 59%

Treatment naïve 71%
No prior MET 53%
Prior MET 58%

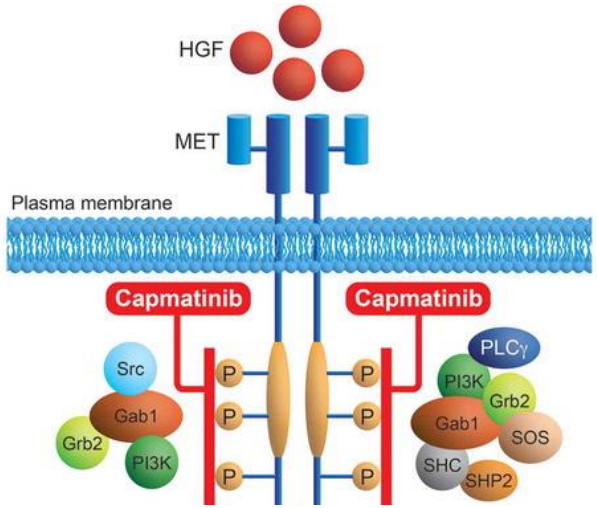
Krebs M et al. ASCO 2022

Inhibiting MET after EGFR TKI



Osimertinib

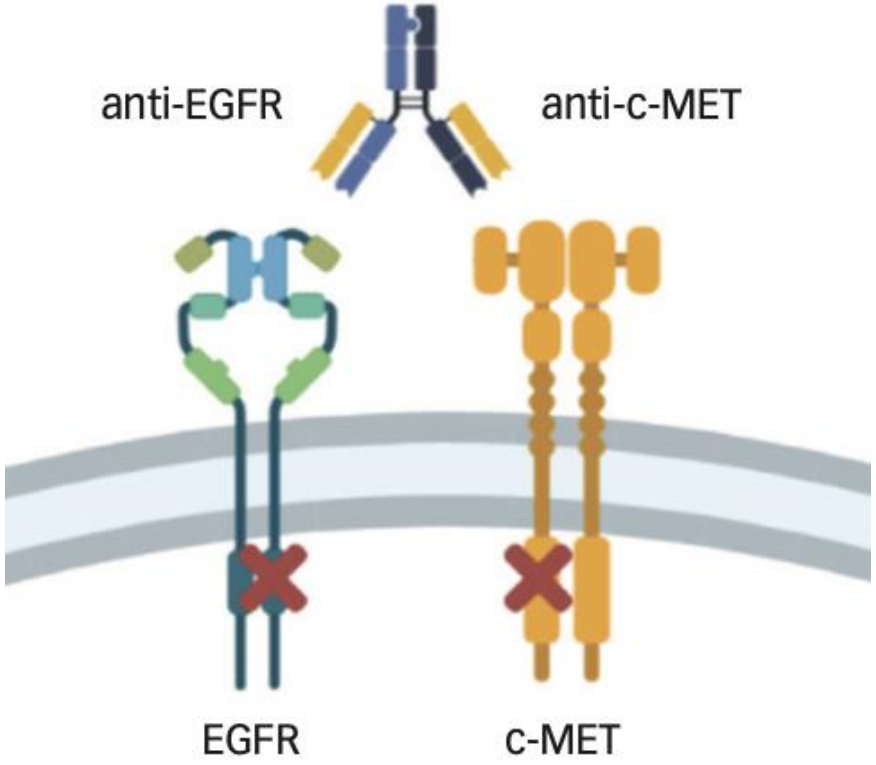
+



Tepotinib

Savolitinib

Crizotinib



Inhibiting MET after EGFR TKI

INSIGHT 2: Phase II study of advanced EGFRm NSCLC with METamp after progression on 1L Osimertinib

Key inclusion criteria

- Locally advanced or metastatic NSCLC with activating *EGFR* mutation
- Acquired resistance to 1L osimertinib
- *MET*amp detected by either central or local* FISH testing (TBx) or central NGS testing (LBx)†
- ECOG PS of 0 or 1
- Stable, treated brain metastases allowed

Tepotinib 500 mg QD
+
Osimertinib 80 mg QD‡

Tepotinib monotherapy arm#

Maxieres J. ESMO 2022 / Weng-Tan DS. ASCO 2023

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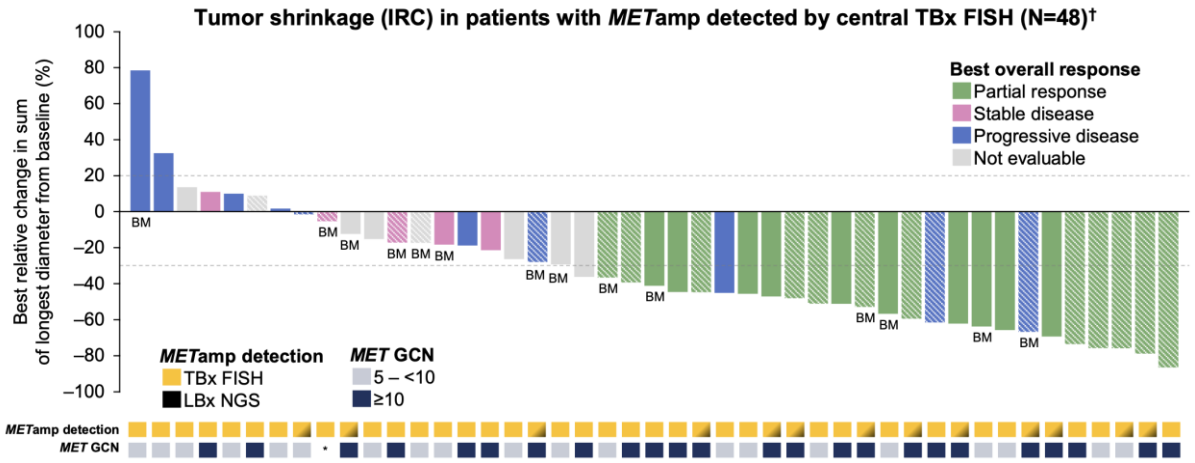
Tepotinib monotherapy arm#

Response	Tumor Tissue FISH+ (n = 98)
ORR, % (95% CI)	**43.9** (33.9-54.3)
Median DoR, mo (95% CI)	9.7 (5.6-NE)
Survival	**Tumor Tissue FISH+ (n = 98)**
Median PFS, mo (95% CI)	**5.4** (4.2-7.1)
Median OS, mo (95% CI)	NE (11.1-NE)



Response	Blood-Based NGS+ (n = 31)*
ORR, % (95% CI)	**51.6** (33.1-69.8)
Median DoR, mo (95% CI)	5.6 (2.9-NE)
Survival	**Blood-Based NGS+ (n = 31)***
Median PFS, mo (95% CI)	**4.6** (2.7-6.9)
Median OS, mo (95% CI)	NE (6.8-NE)

Maxieres J. ESMO 2022 / Weng-Tan DS. ASCO 2023

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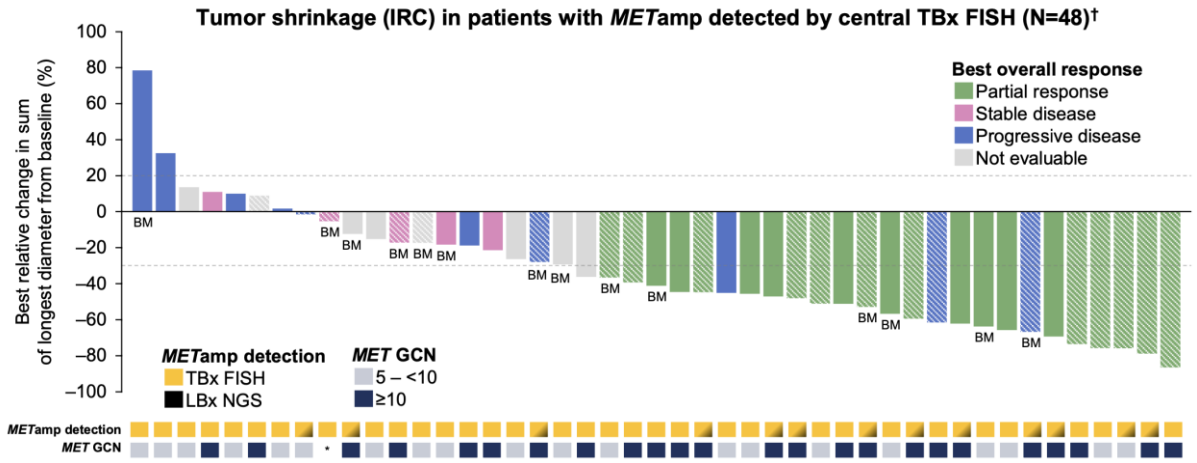

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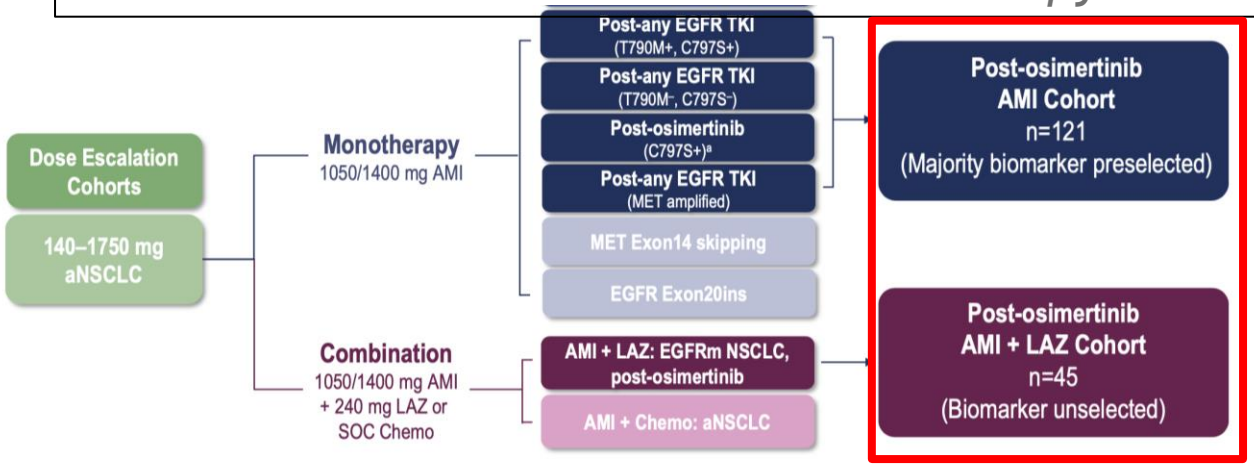
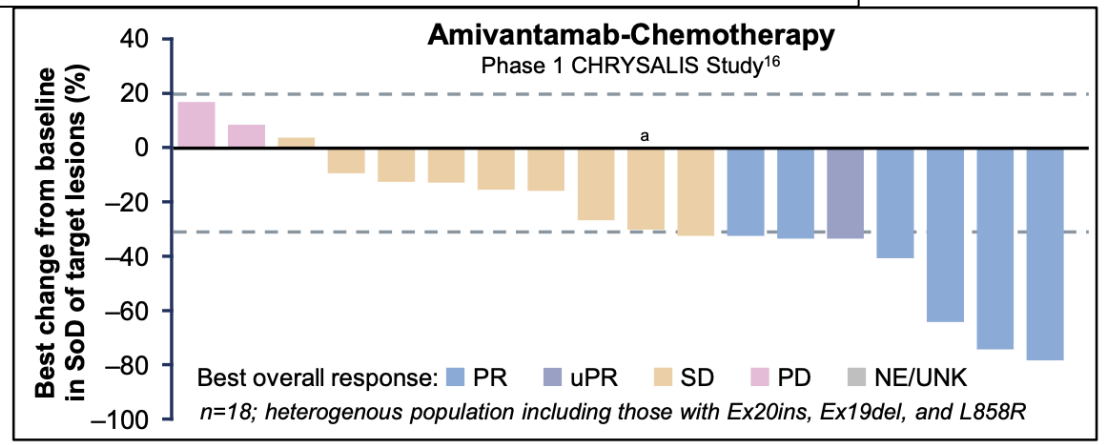
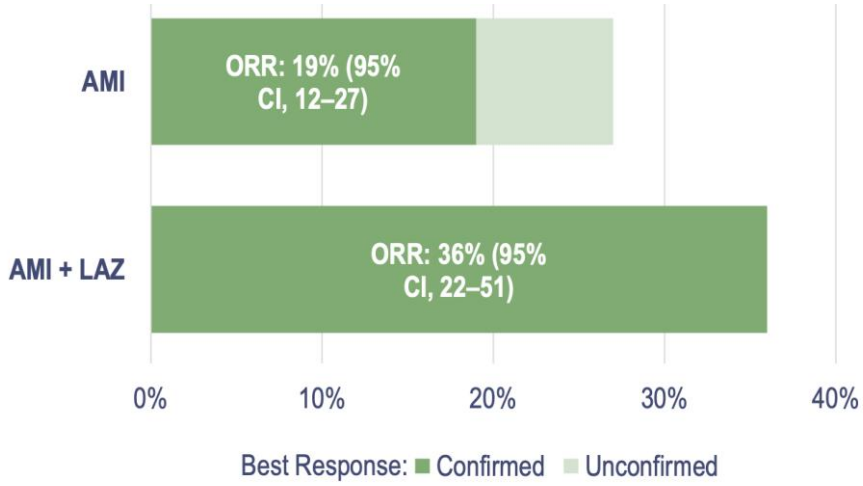
Maxieres J. ESMO 2022 / Weng-Tan DS. ASCO 2023

Inhibiting MET after EGFR TKI

CHRYSALIS: Phase I Amivantamab Monotherapy and + Lazertinib in Post-osimertinib EGFR- NSCLC







Leighl B. ESMO 2021 / Shu C, et al ASCO 2022

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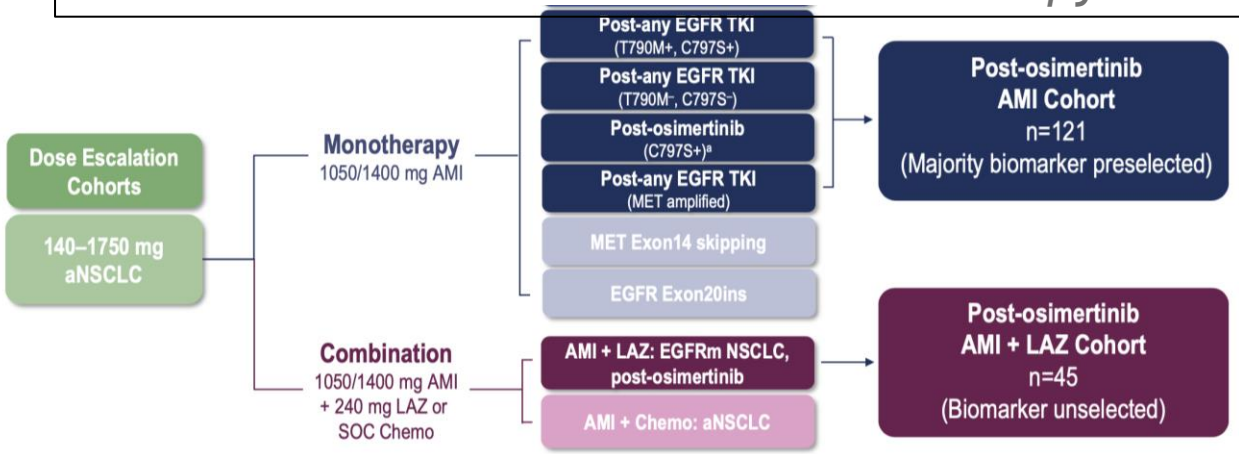
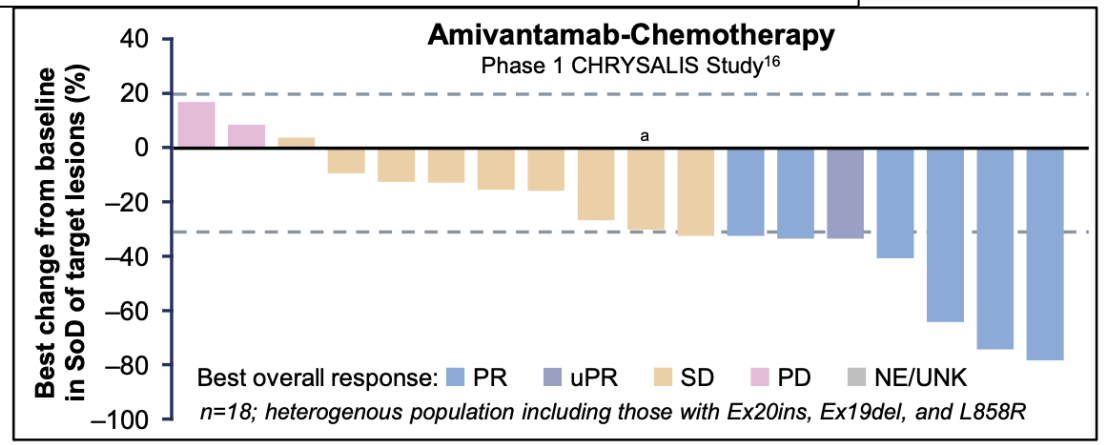
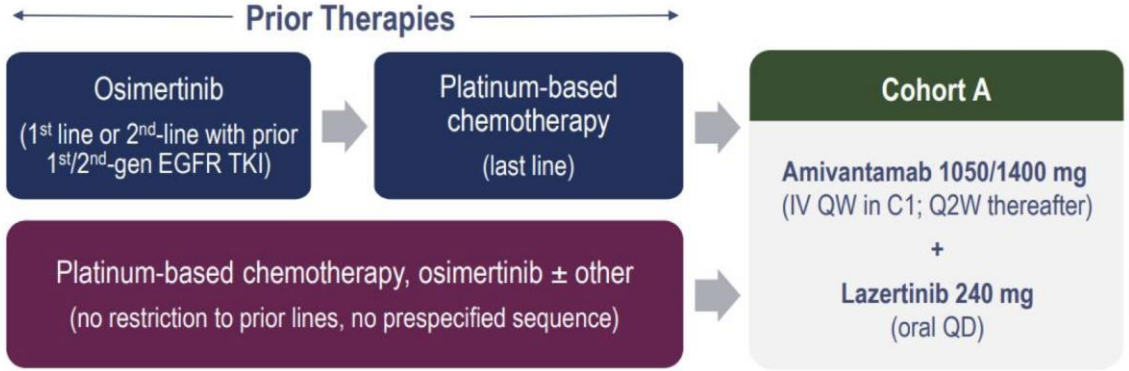
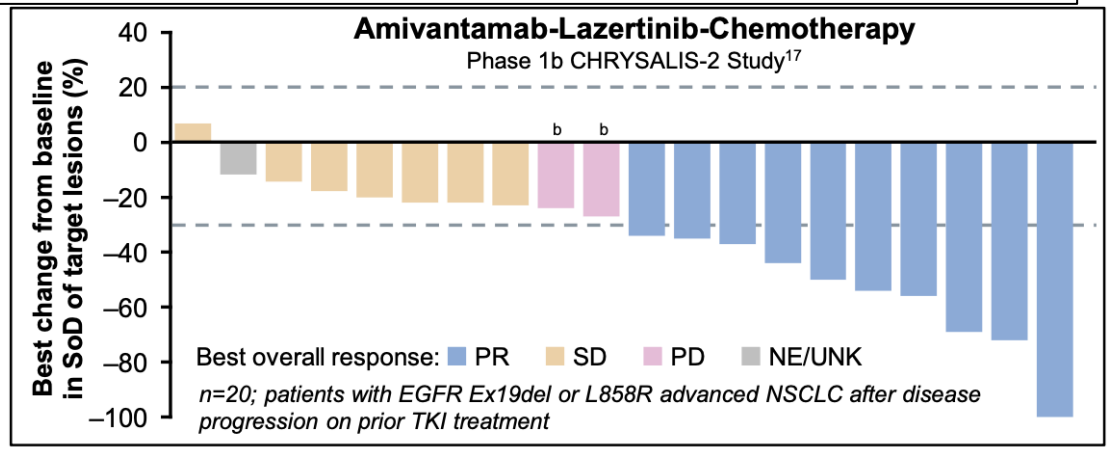




CHRYSALIS-2: Phase I Amivantamab + Lazertinib post- **osimertinib** and **chemotherapy** in EGFRm pts





Leighl B. ESMO 2021 / Shu C, et al ASCO 2022

Inhibiting MET after EGFR TKI

MARIPOSA-2: Phase III Amivantamab + Lazertinib + chemo vs Amivantamab + lazertinib vs chemotherapy post-osimertinib

1. Amivantamab-Chemotherapy (n=131)
2. Amivantamab-Lazertinib-Chemotherapy (n=263)
3. Chemotherapy (n=263)

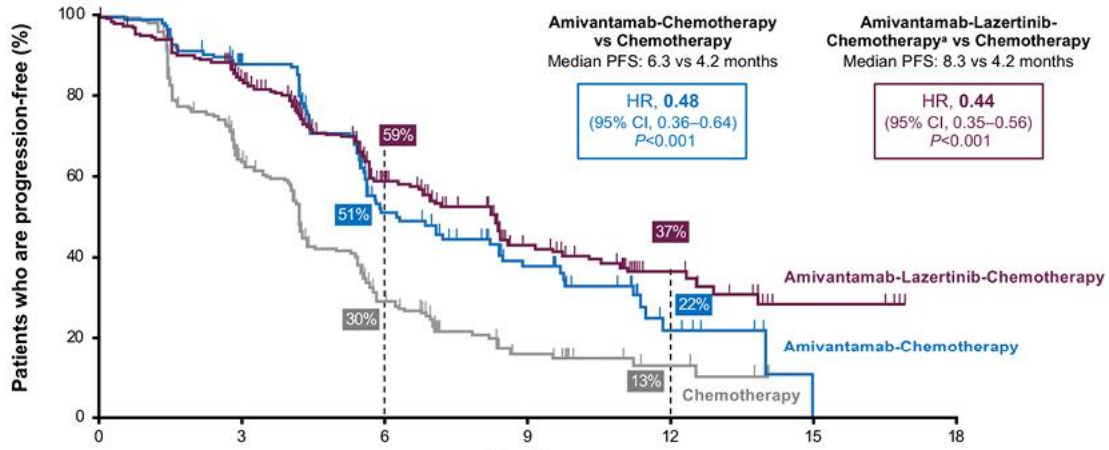
Amivantamab + Lazertinib + Chemotherapy and **Amivantamab + Chemotherapy** improved PFS, intracranial PFS, ORR, and other key endpoints versus **Chemotherapy** alone

Amivantamab-Chemotherapy vs **Chemotherapy**	**Amivantamab-Lazertinib-Chemotherapy** vs **Chemotherapy**
HR for disease progression or death, **0.48** (95% CI, 0.36–0.64); *P*<0.001	HR for disease progression or death, **0.44** (95% CI, 0.35–0.56); *P*<0.001

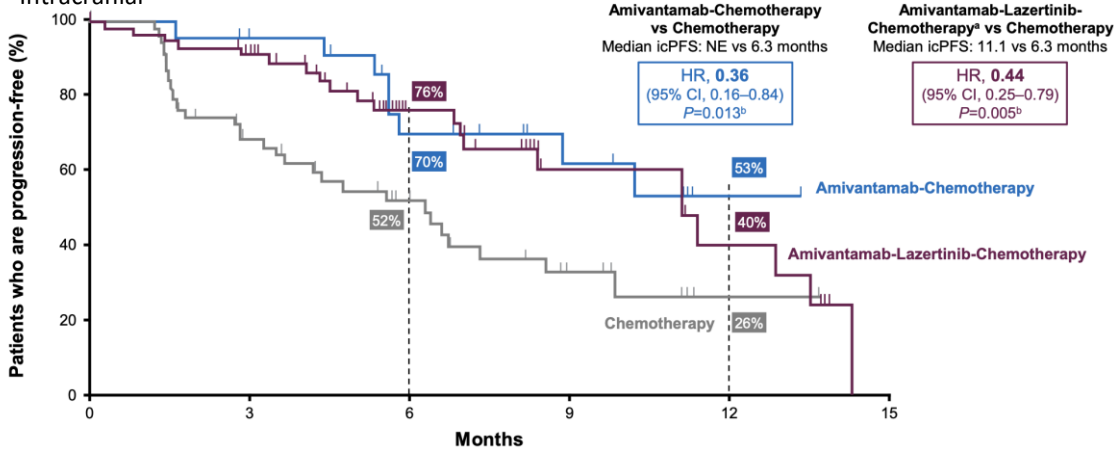
ORR by BICR

- 36% Chemotherapy
- 64% Amivantamab-Chemotherapy — OR=3.1, *P*<0.001
- 63% Amivantamab-Lazertinib-Chemotherapy — OR=3.0, *P*<0.001

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; PFS, progression-free survival



Intracranial



Passarano A, Annals of Oncology 2023

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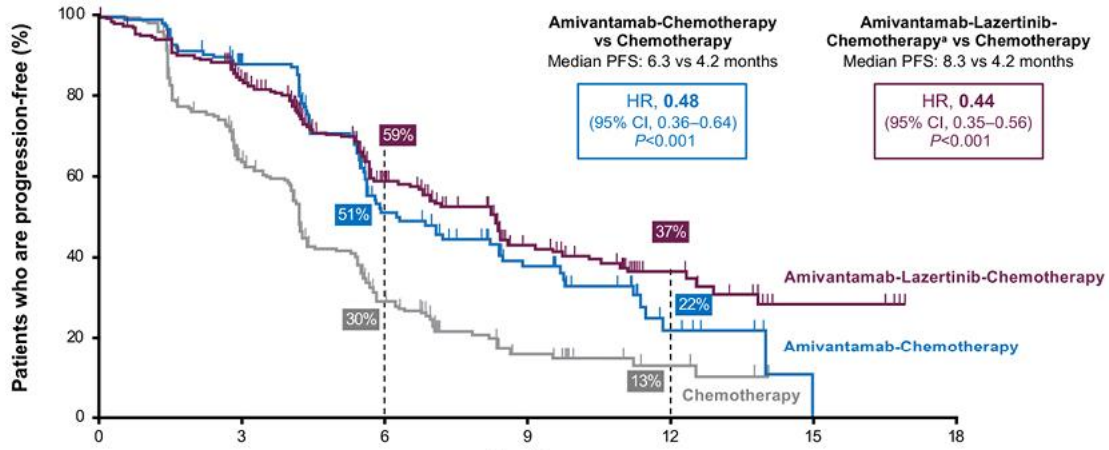

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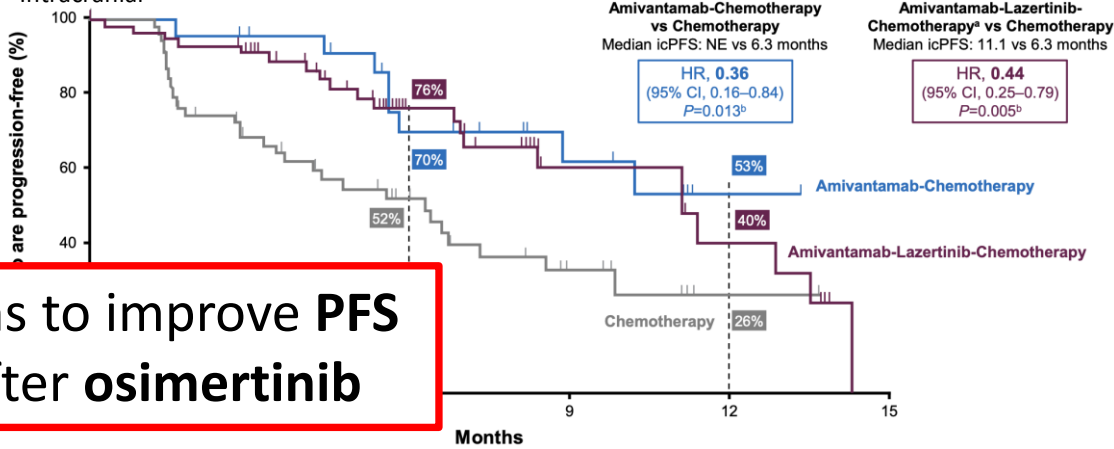


Amivantamab-combos → first regimens to improve **PFS** vs chemotherapy in ***EGFR*-m** NSCLC after **osimertinib**

Passarano A, Annals of Oncology 2023

Inhibiting MET and EGFR TKI

MARIPOSA: Amivantamab + Lazertinib vs Osimertinib as First-line Treatment in EGFR-m NSCLC

Key Eligibility Criteria

- Locally advanced or metastatic NSCLC
- Treatment-naïve for advanced disease
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0 or 1

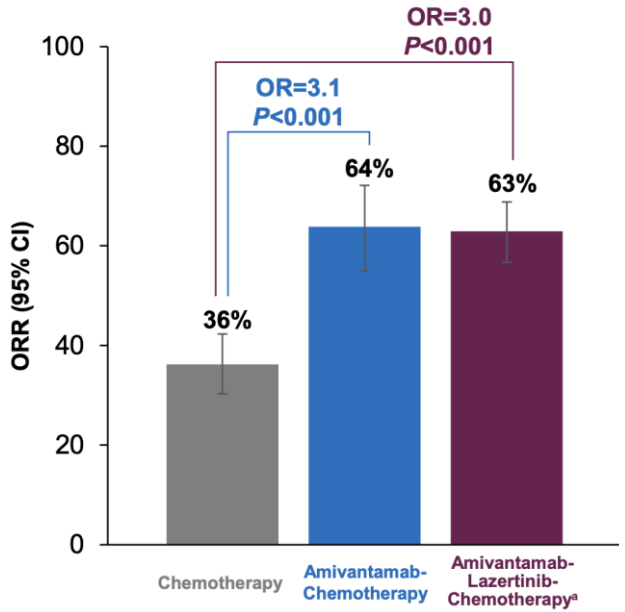
Stratification Factors

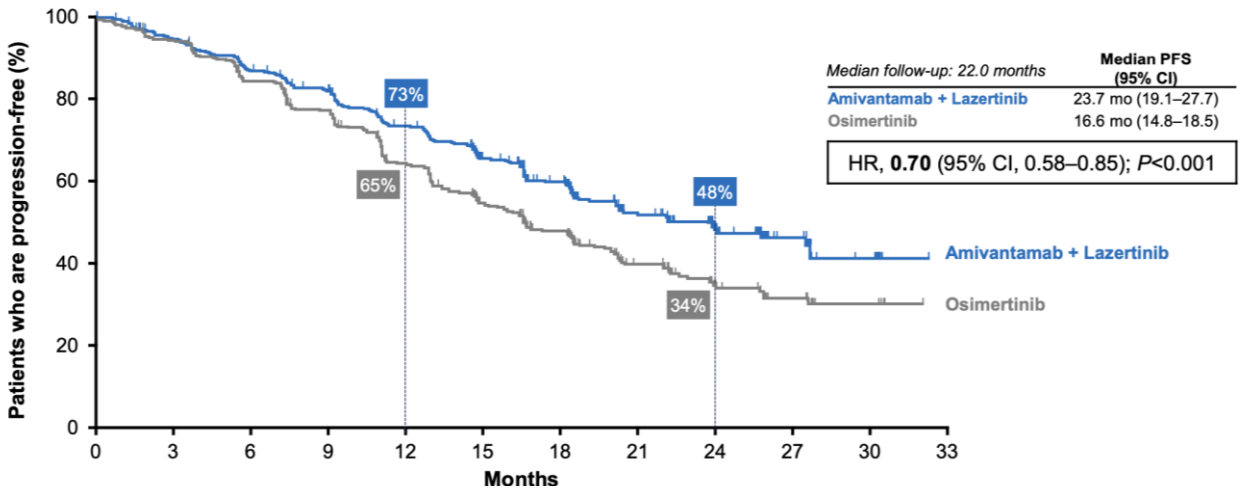
- *EGFR* mutation type (Ex19del or L858R)
- Asian race (yes or no)
- History of brain metastases[a] (yes or no)

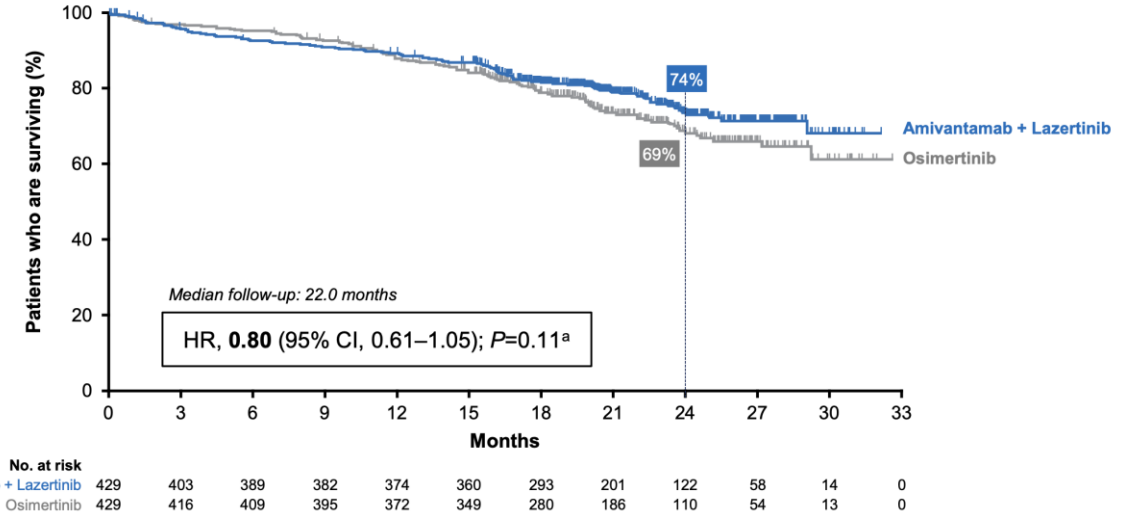
Serial brain MRIs were required for all patients[a]

2:2:1 Randomization (N=1074)

- **Amivantamab + Lazertinib** (n=429; open-label)
- **Osimertinib** (n=429; blinded)
- **Lazertinib** (n=216; blinded)

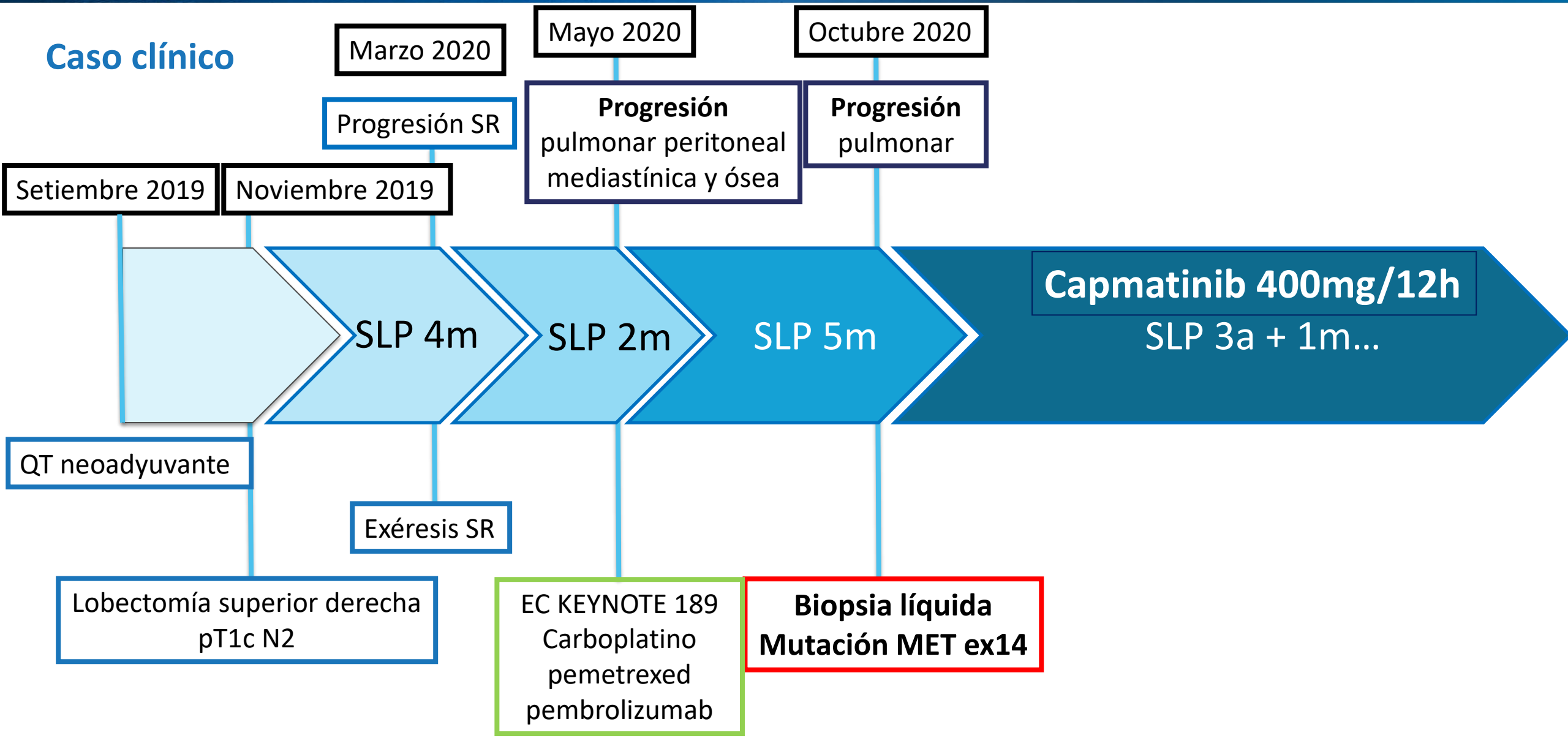






al. ESMO 2023

Caso clínico

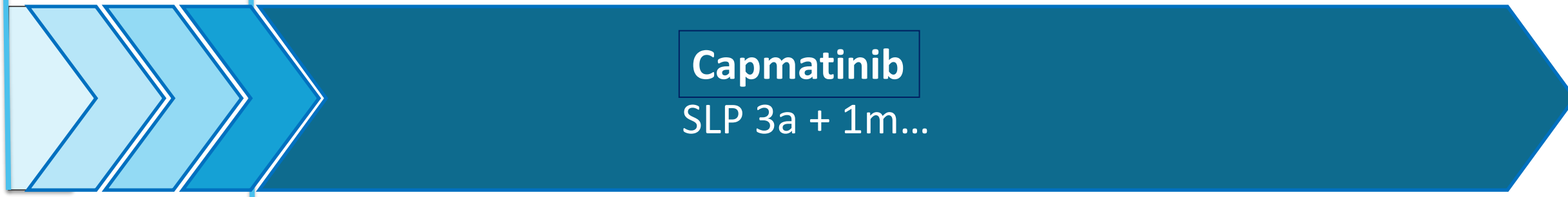


Caso clínico

Octubre 2020

Progresión pulmonar

Setiembre 2019



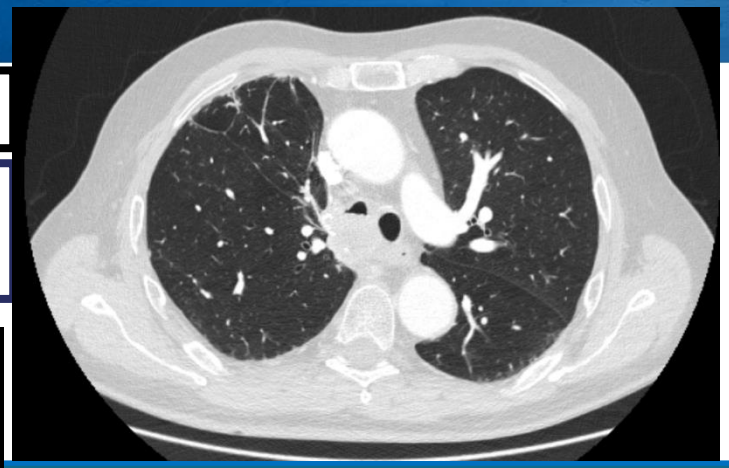
Capmatinib

SLP 3a + 1m…

Biopsia líquida
Mutación MET ex14

Caso clínico

Octubre 2020



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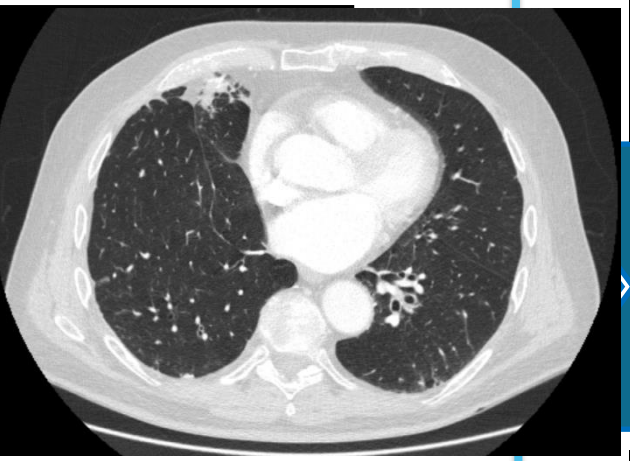

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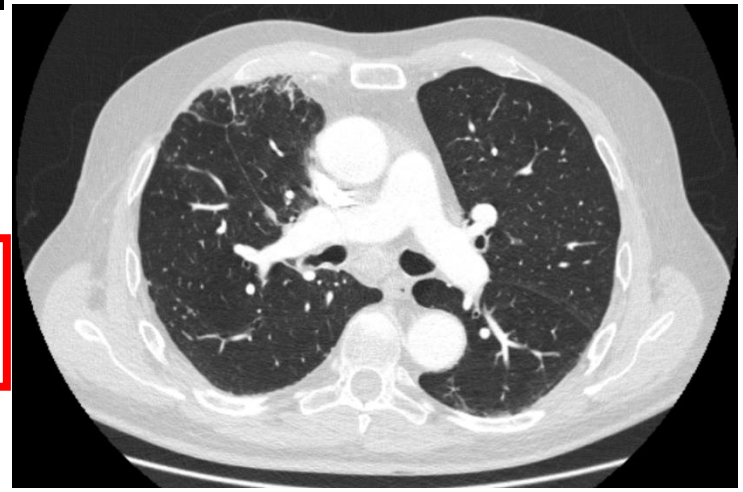

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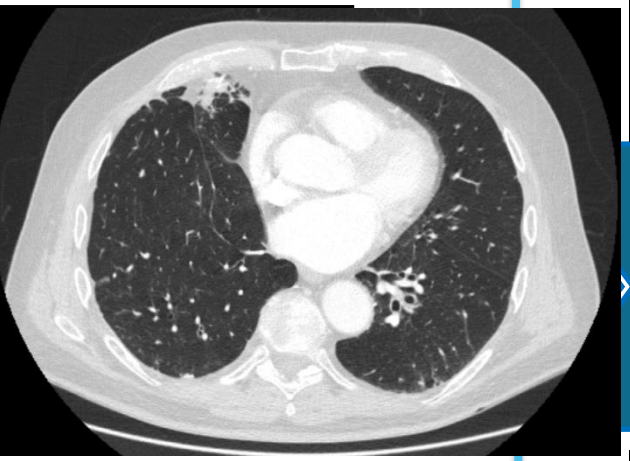

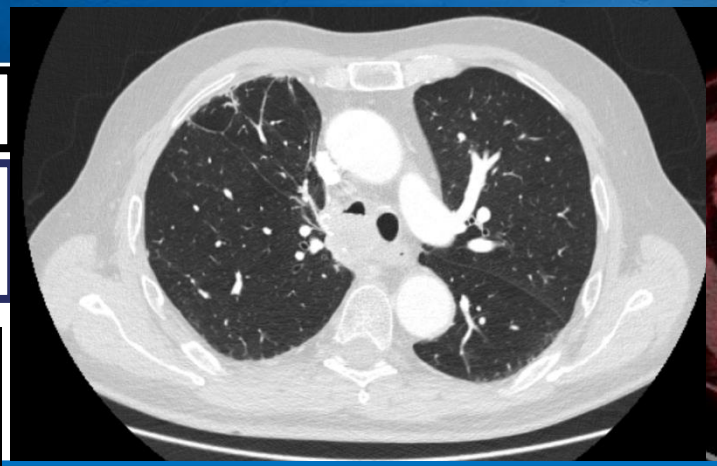

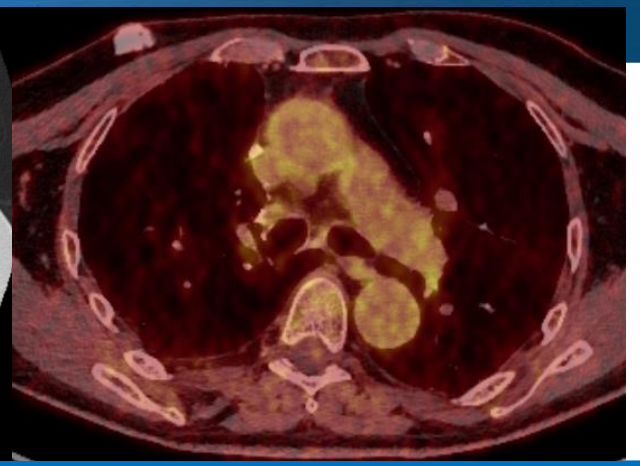

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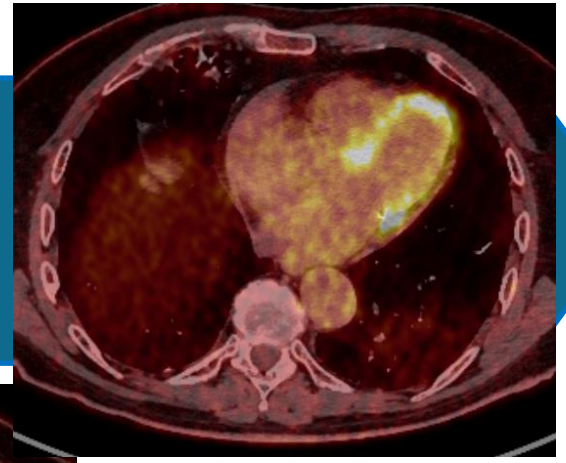

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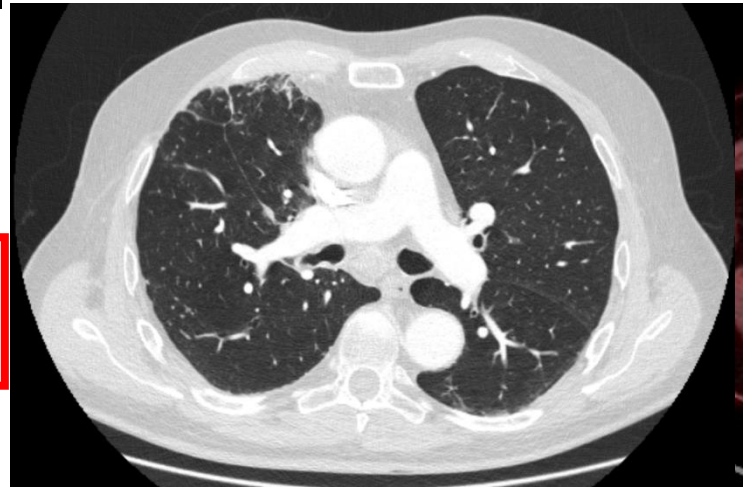
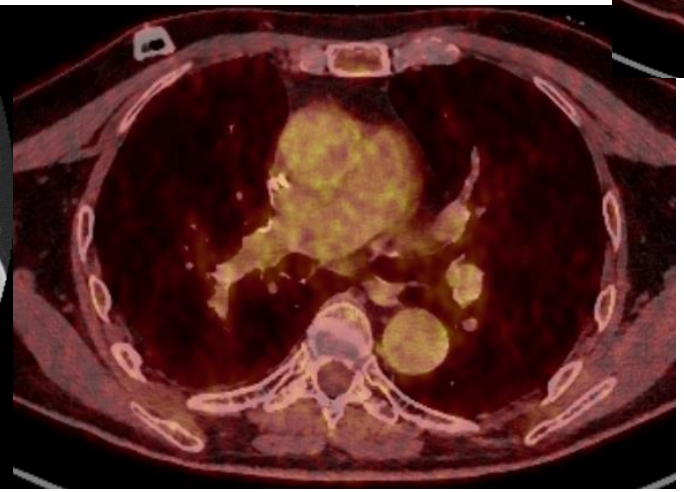
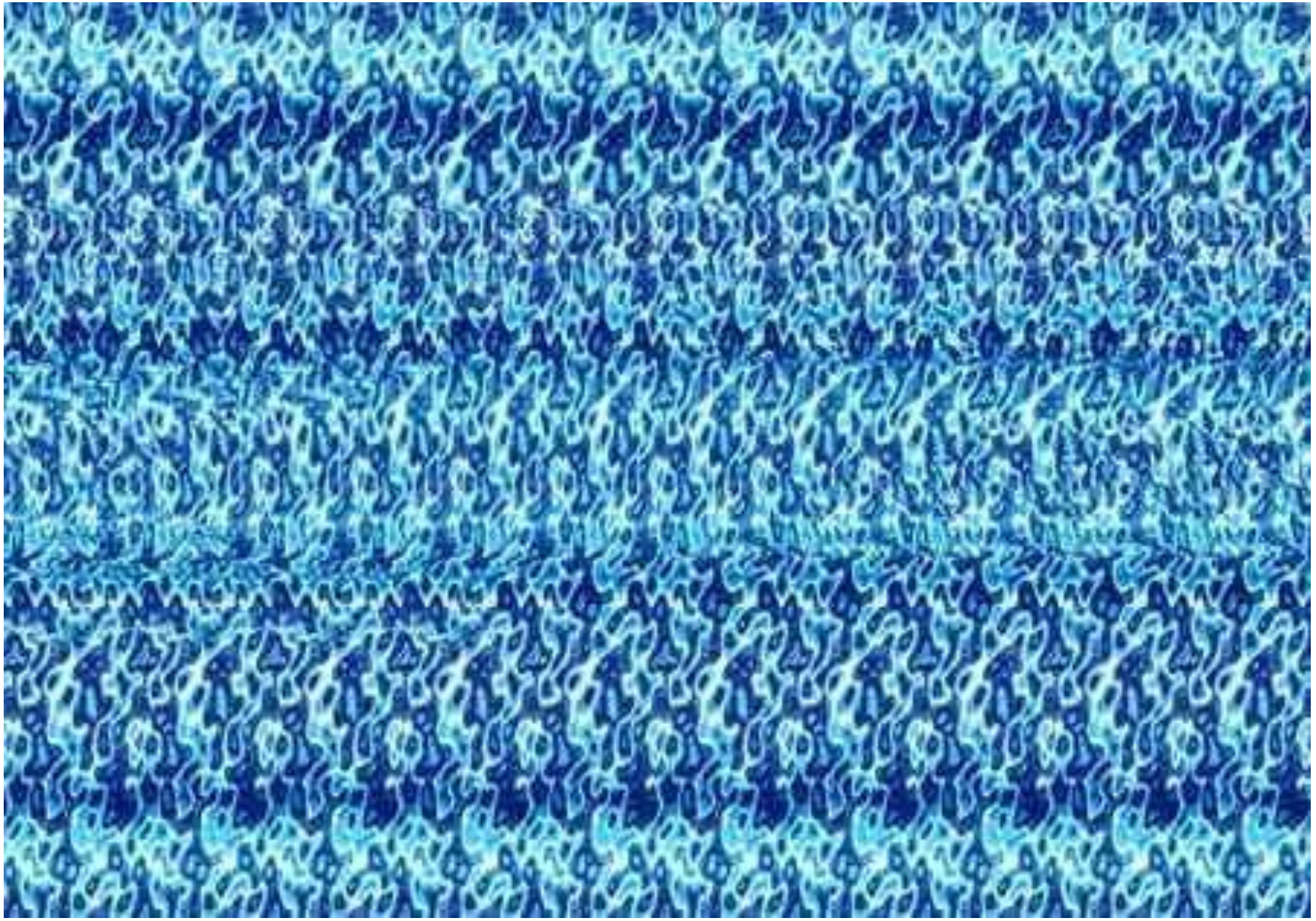




Respuesta completa

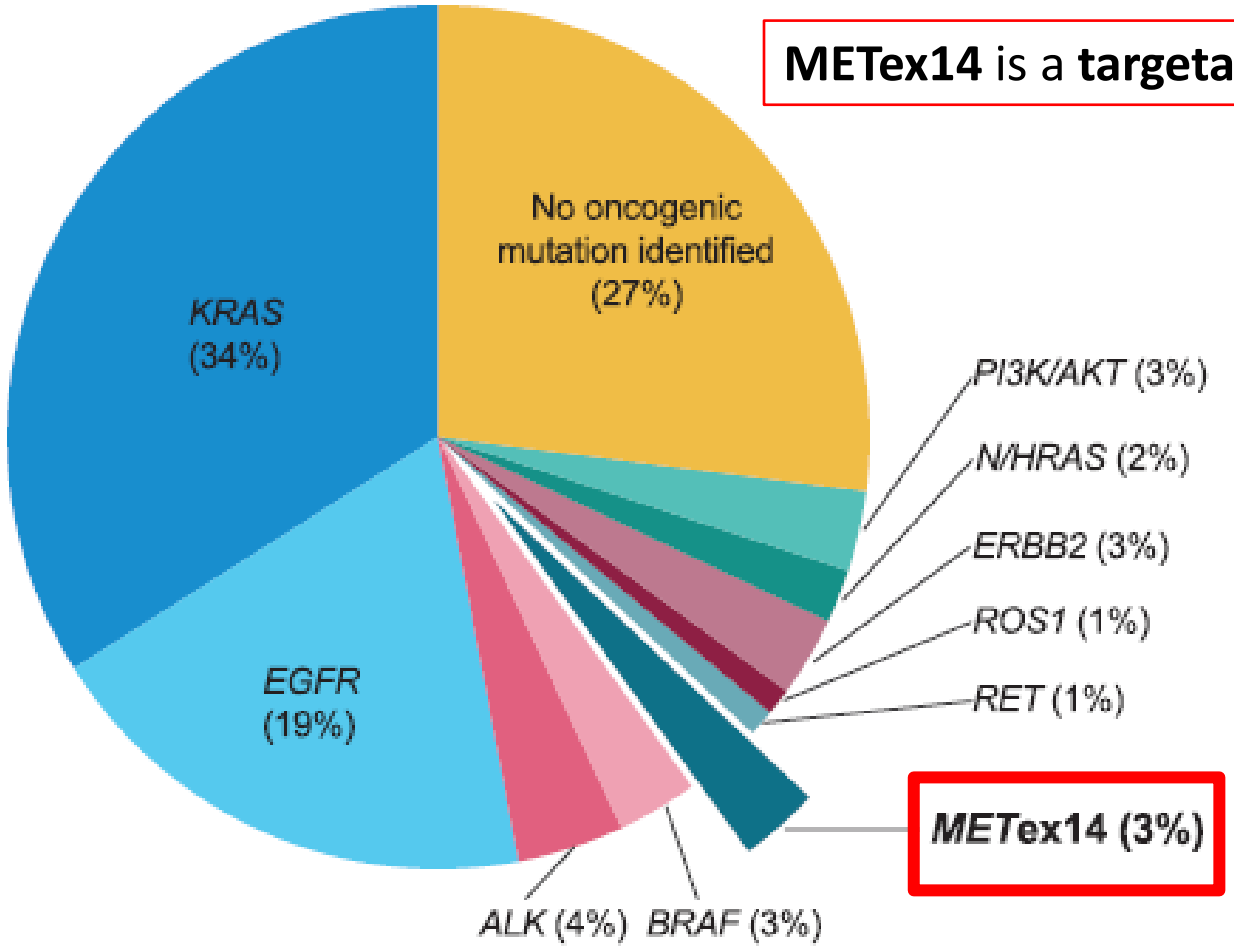
Take home message



Take home message

MET Exon 14 skip mut

METex14 is a **targetable** driver mutation and **should be tested**



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- ✓ **Capmatinib** and **tepotinib** are effective with the best efficacy in **1st** line
- ✓ Unfortunately, EMA approval is for **2nd** line.

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	ORR	mOS
Platin-doublet	25%	12 m
Pembro (PD-L1 high)	45%	26 m
CT/Pembro (PD-L1 high)	61%	22 m
Capmatinib / Tepotinib 1st line	55-70%	24 m
Capmatinib / Tepotinib 2nd-3rd line	40-50%	14 m

→ Median age of 70a
→ Less prone to respond on IO

Take home messages

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→ Median age of 70a
→ Less prone to respond on IO

→ Not sure about need to use IO / IO-Ch as a standar first line in this patients

Take home messages

MET as a secondary driver

- ✓ Role not only as a mechanism of resistance on **EGFR** but also to **other drivers**
- ✓ Outcomes with double blockage using TKIs are modest

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…but **antibodies drug conjugates** and **bispecific antibodies** are having promising results

Take home messages

MET as a secondary driver

✓ Role not only as a mechanism of resistance on **EGFR** but also to **other drivers**

✓ Outcomes with double blockage using TKIs are modest

…but **antibodies drug conjugates** and **bispecific antibodies** are having promising results

→ Is it time to use double blockage upfront?

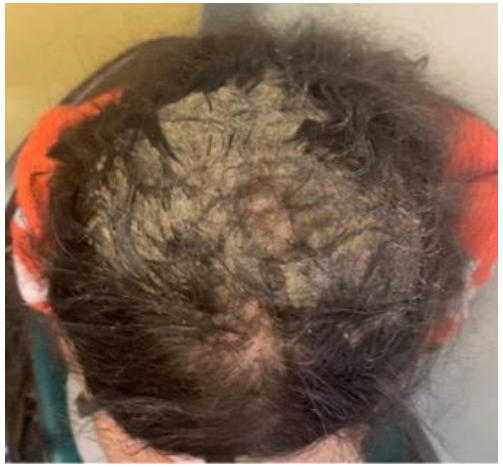
Take home messages

MET as a secondary driver

- ✓ Role not only as a mechanism of resistance on **EGFR** but also to **other drivers**
- ✓ Outcomes with double blockage using TKIs are modest

  …but **antibodies drug conjugates** and **bispecific antibodies** are having promising results

→ Is it time to use double blockage upfront?



"New" toxicities should also be taken into account

TEAEs, n (%)	Total N=136 Any Grade	Grade ≥3
Any TEAE	131 (96)	65 (48)
Most common any-grade TEAEs (≥10%)		
Peripheral sensory neuropathy	34 (25)	6 (4)
Nausea	30 (22)	1 (1)
Hypoalbuminemia	28 (21)	1 (1)
Peripheral edema	25 (18)	0
Blurred vision	25 (18)	1 (1)
Decreased appetite	24 (18)	0
Fatigue	22 (16)	5 (4)
Anemia	19 (14)	3 (2)
Dyspnea	19 (14)	4 (3)
Asthenia	18 (13)	3 (2)
Increased gamma-glutamyl transferase	18 (13)	3 (2)
Keratitis	18 (13)	0
Constipation	16 (12)	1 (1)
Cough	14 (10)	0
Diarrhea	14 (10)	0
Dizziness	14 (10)	0
Malignant neoplasm progression	14 (10)	11 (8)
Vomiting	14 (10)	1 (1)

Thank you

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Servicio Canario de la Salud
Complejo Hospitalario Universitario Insular - Materno Infantil


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Muchas Gracias