

12º SIMPÓSIO
INTERNACIONAL DE

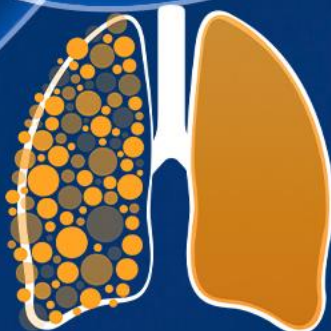
CÂNCER DE PULMÃO

2ª JORNADA ONCONNECTION MULTICARE

2024

GERENCIAMENTO E PRODUÇÃO

RV+
EVENTOS MÉDICOS



12º SIMPÓSIO
INTERNACIONAL DE
**CÂNCER DE
PULMÃO**
2ª JORNADA ONCONNECTION MULTICARE
2024

O papel da mutação METex14 no tratamento da doença avançada.

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Pesquisador Associado - Laboratório de Imuno-Oncologia - CIPE

Presidente-Eleito - Grupo Brasileiro de Oncologia Torácica

Vice-Presidente - Lung Cancer Steering Committee - LACOG

Assessor Técnico-científico - Medicina de precisão em Oncologia - Grupo Fleury

Declaração de Conflito de Interesse

De acordo com a Norma 1595/2000 do Conselho Federal de Medicina e com a RDC 96/2008 da ANVISA, declaro que:

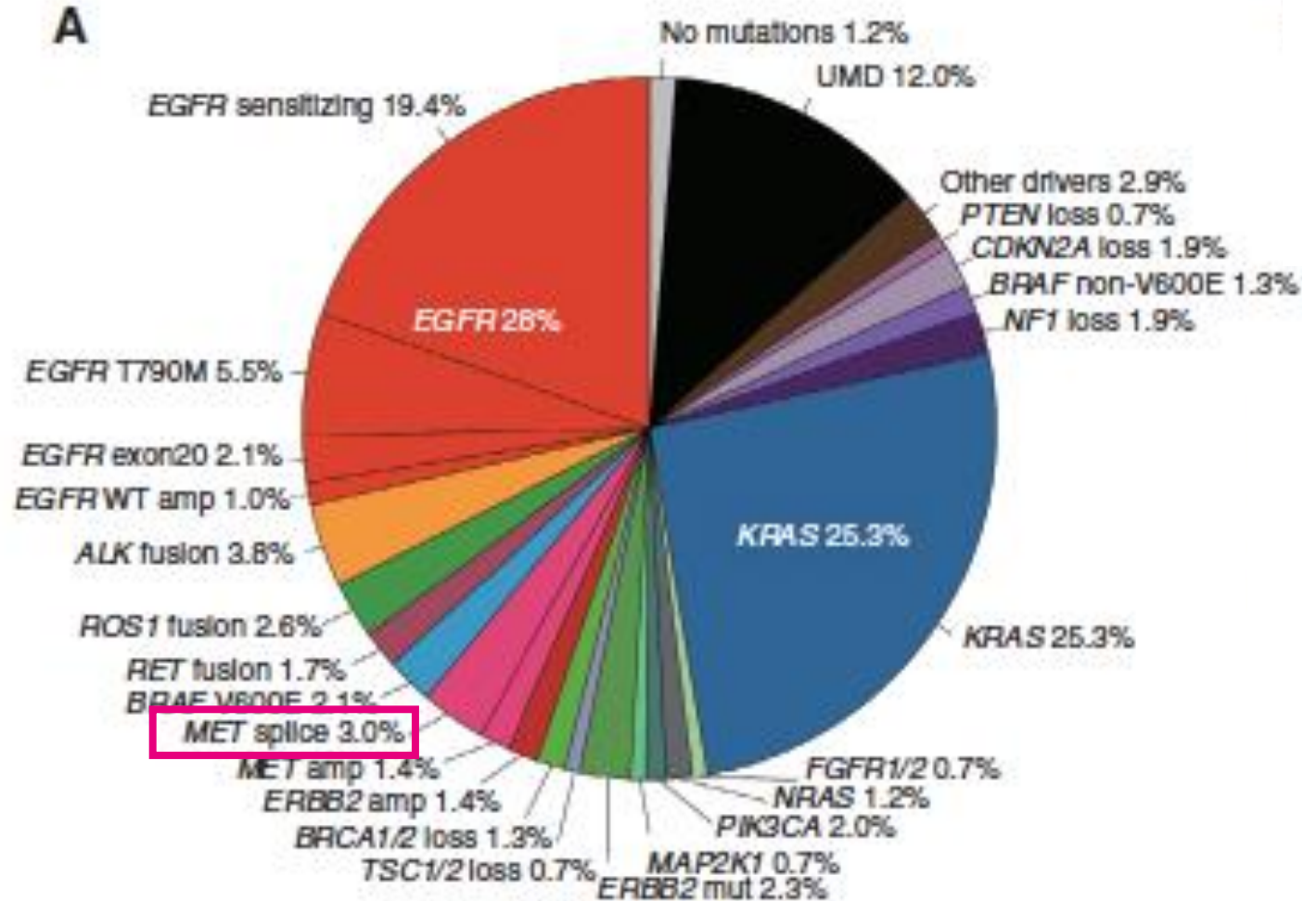
Pesquisa Clínica: como médico investigador, participei de estudos patrocinados por: **BMS, Janssen, MSD, Roche, Syneos**

Apresentações: como palestrante convidado, participei dos eventos de: **MD Health, Amgen, Astra-Zeneca, BMS, Novartis, MSD, Sanofi, Daichii-Sankyo, Roche**

Consultoria: como membro de *advisory boards*, participei de reuniões com: **Roche, MSD, Astra-Zeneca, Novartis, Janssen, BMS, Lilly, Pfizer, Daichii-Sankyo, Cristália**

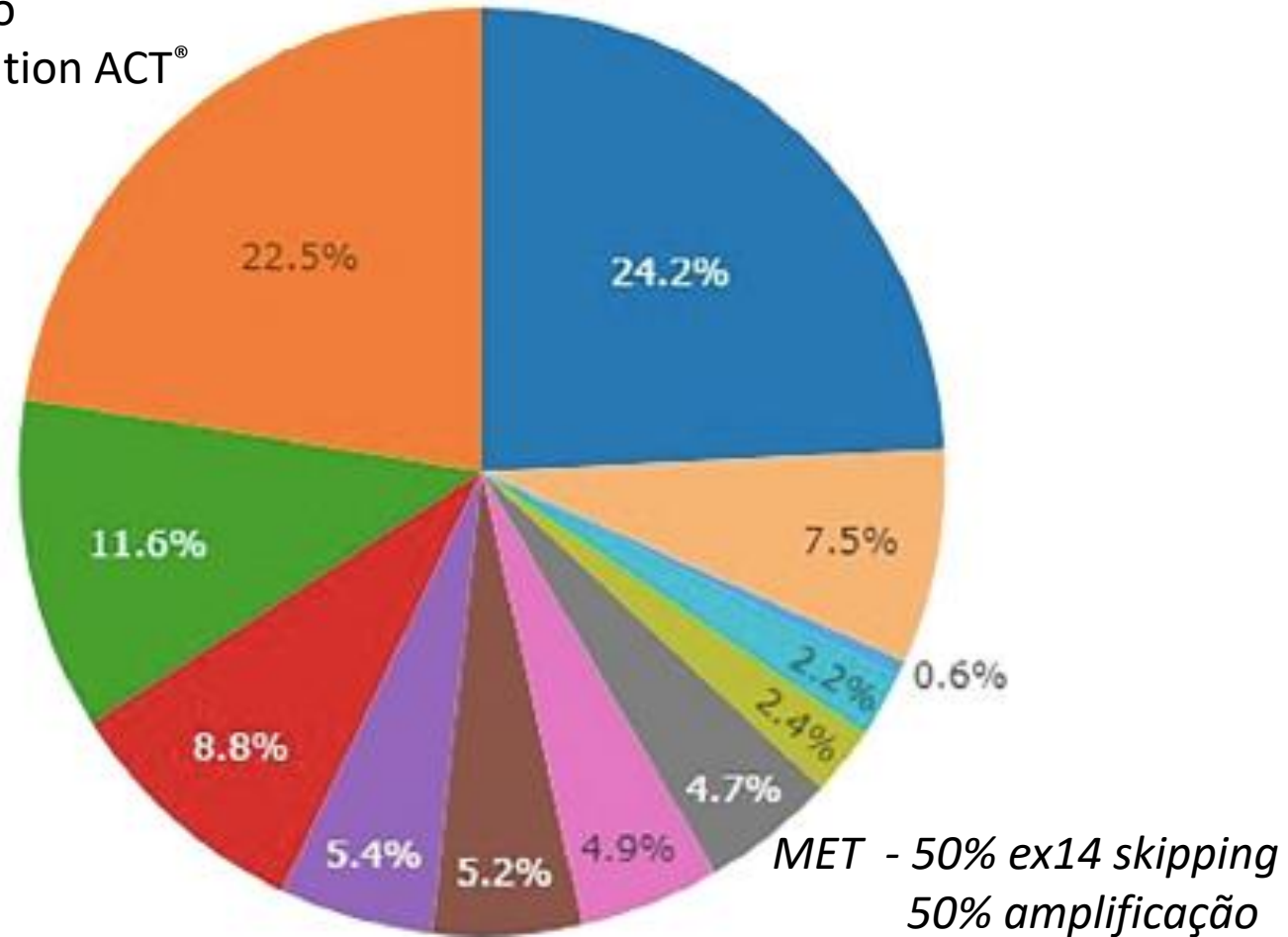
CPCNP são várias doenças genomicamente definidas

N=860
Adenocarcinoma
Estádio IV
MSK-IMPACT



Alteração genômica em *MET* em CPCNP no Brasil

N=513 CPCNP não escamoso
Foundation One® ou Foundation ACT®

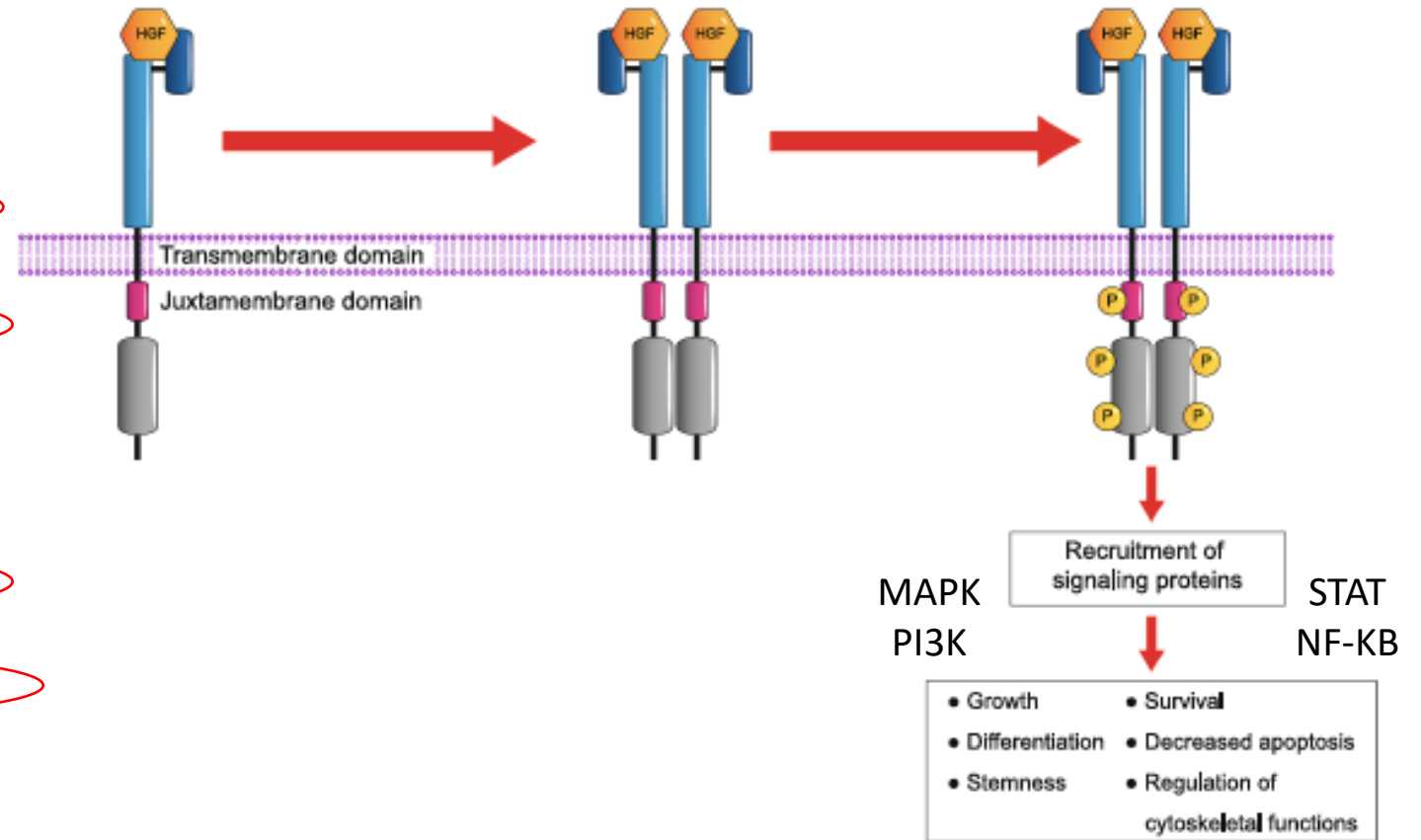
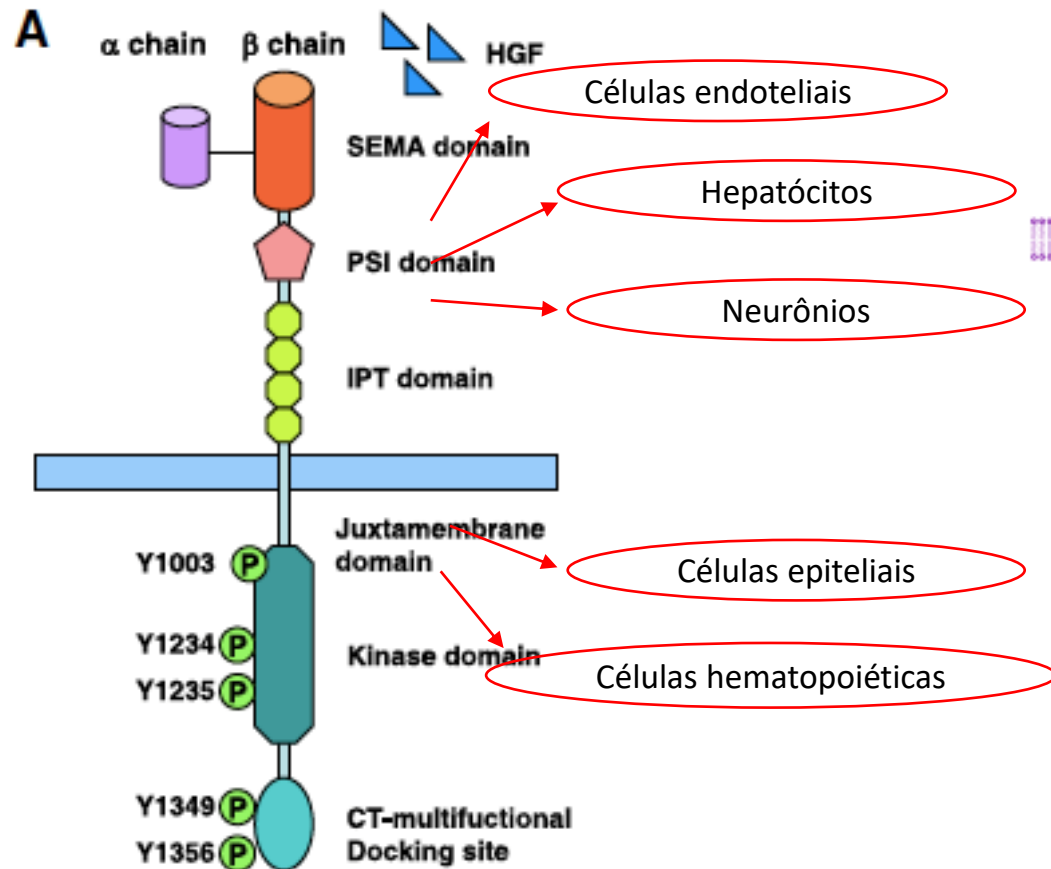


MET no seu estado normal

Cromossomo 7q31

190 KDa

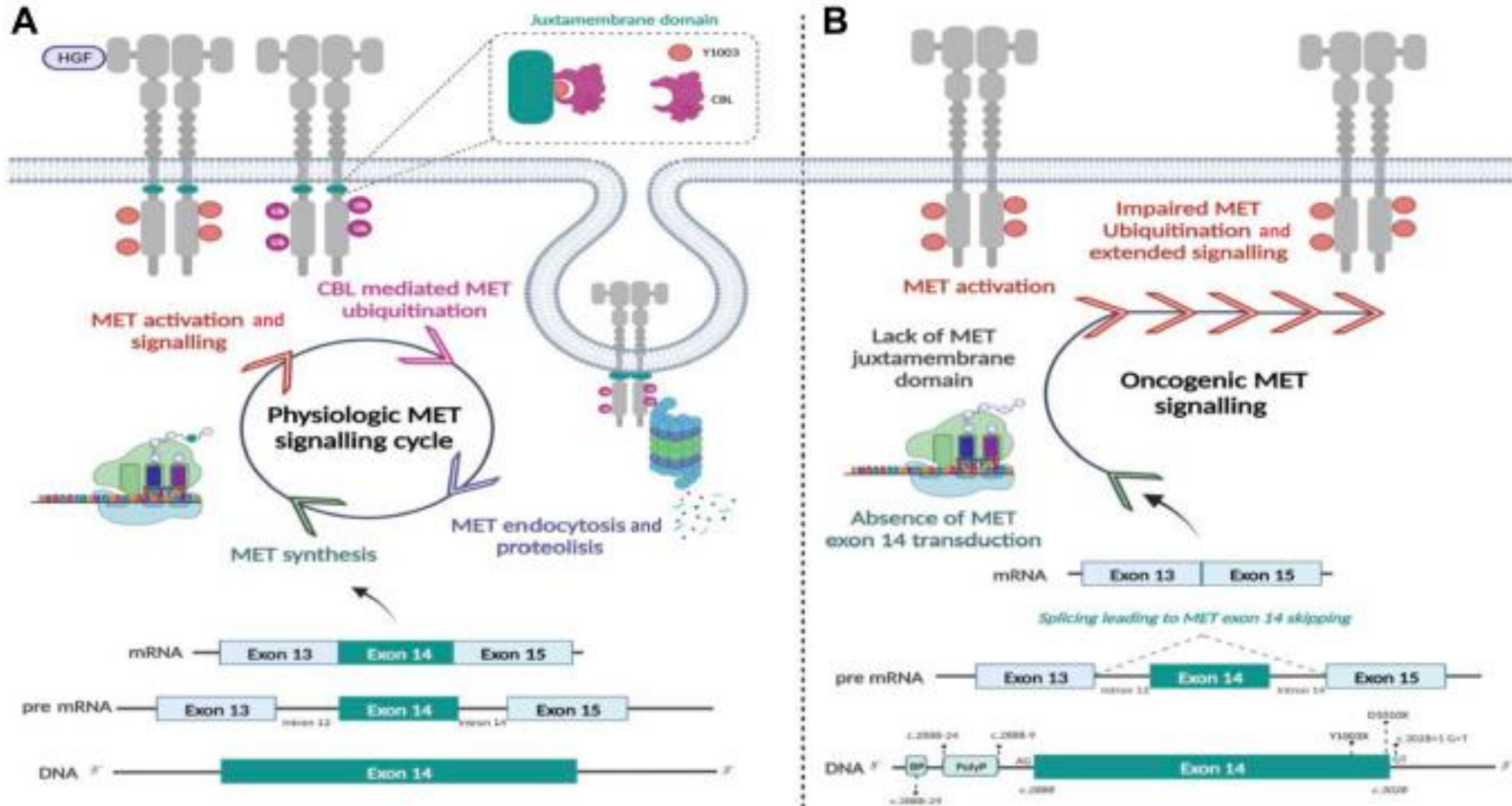
Ligante HGF



Wang Q, et al. J Hemat Oncol. 2019; 12:63; epub online ahead of print.

Salgia R, et al. Cancer Treat Reviews. 2020; 87:102022, epub online ahead of print.

Impacto funcional da mutação *MET* *ex14 skipping*



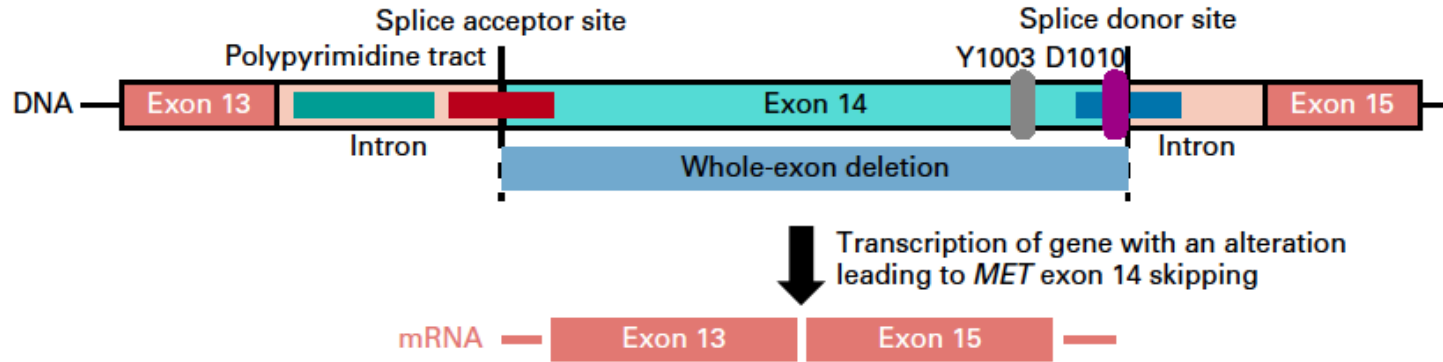
Awad MM, et al. J Clin Oncol. 2016; 34:721-730.

Salgia R, et al. Cancer Treat Reviews. 2020; 87:102022, epub online ahead of print.

Remon J, et al. J Thorac Oncol. 2022; S1556-0864(22)01865-2, epub online ahead of print.

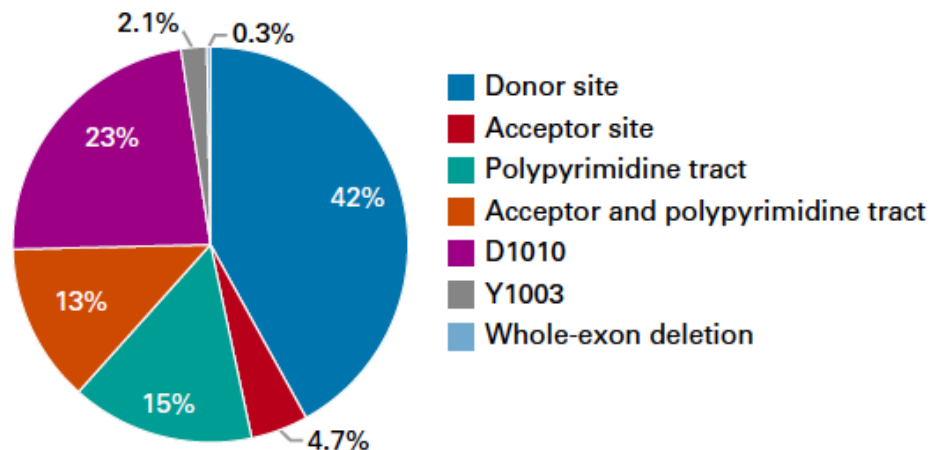
Tipos de mutação que geram *skipping* do éxon 14 do *MET*

A



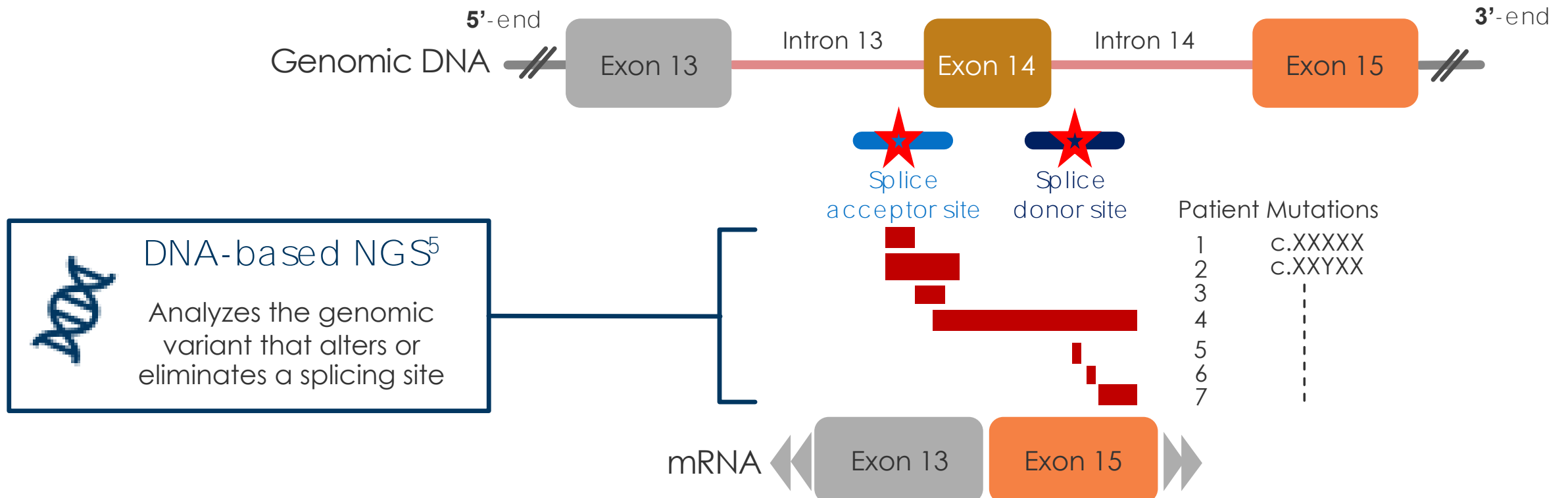
MyCancer Genome
CiViC
OncoKB

B



Avaliação da *METex14 skipping* - DNA

Aberrant splicing and *METex14*²⁻⁴



METex14, *MET* exon 14 skipping mutation; mRNA, messenger-RNA; NGS, next generation sequencing.

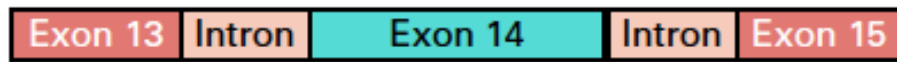
1. Drilon A, et al. *Clin Cancer Res.* 2015;21(16):3631-3639; 2. Frampton GM, et al. *Cancer Discov.* 2015;5:850-859; 3. Drilon A. *Clin Cancer Res.* 2016;22(12):2832-2835; 4. Shah R, et al. *Oncology & Haematology Review.* 2020;16(2):100-110; 5. Pruis MA, et al. *Lung Cancer.* 2020;140:46-54.

Quando a análise for realizada apenas em DNA, métodos que empregam captura híbrida têm melhor desempenho

“Amplicon based”

“Hybrid capture”

A



Genomic alteration

Deletions or mutations that abolish primer binding

Deletions or mutations within amplification region that do not affect primer binding

Detection of *MET* exon 14 skipping

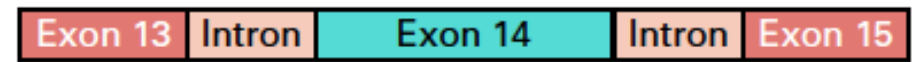
No

Yes

★ Mutation

— Deletion

B



Probe 1

Probe 2

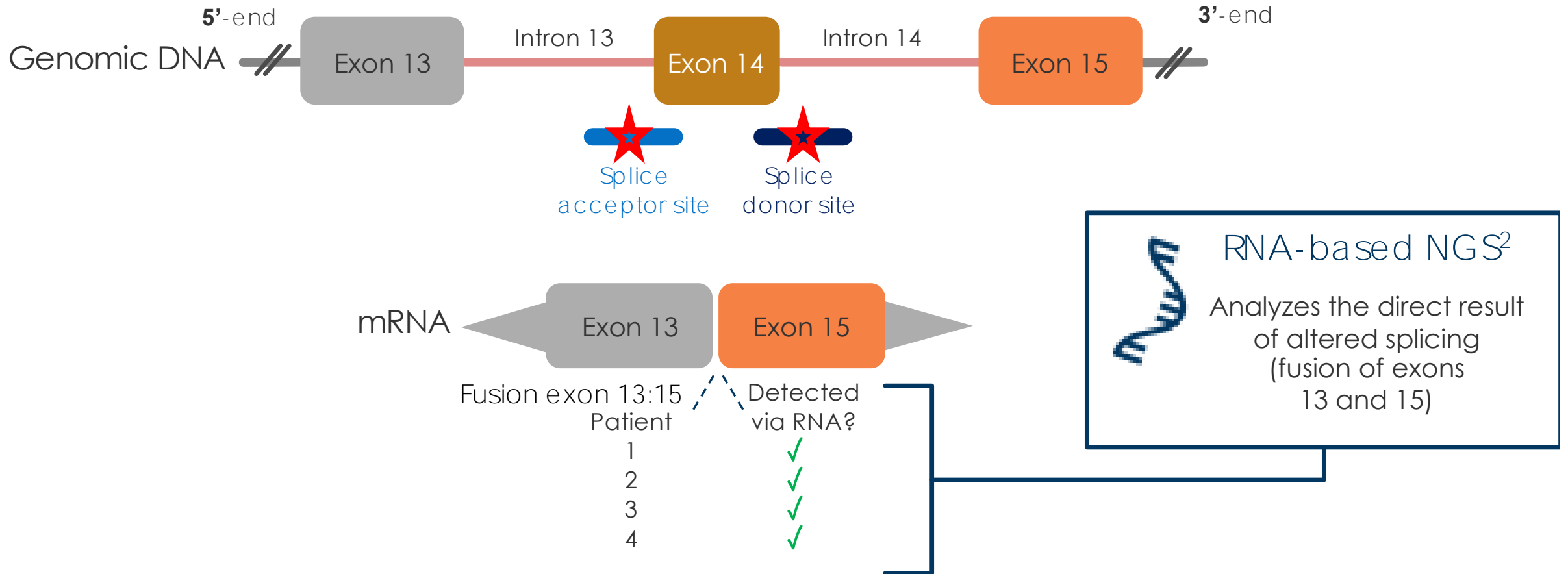
Detection of *MET* exon 14 skipping

Yes

Yes

Avaliação da *MET*ex14 skipping - RNA

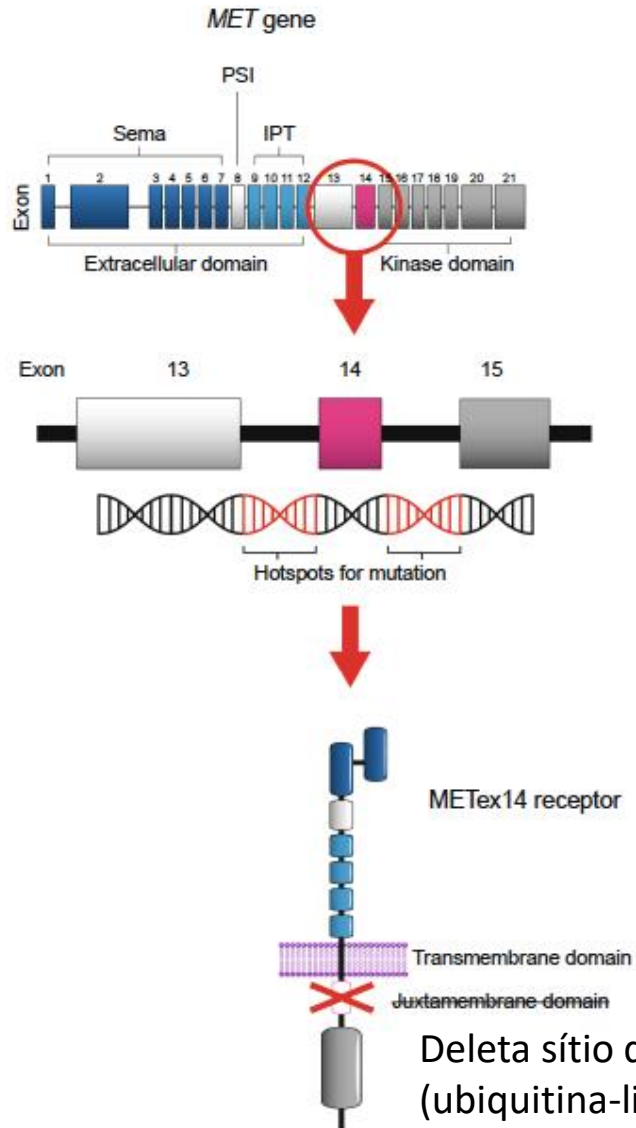
Aberrant splicing and *MET*ex14^{2,4,5}



*MET*ex14, *MET* exon 14 skipping mutation; mRNA, messenger-RNA; NGS, next generation sequencing.

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Mutação *skipping* do éxon 14 do gene *MET*

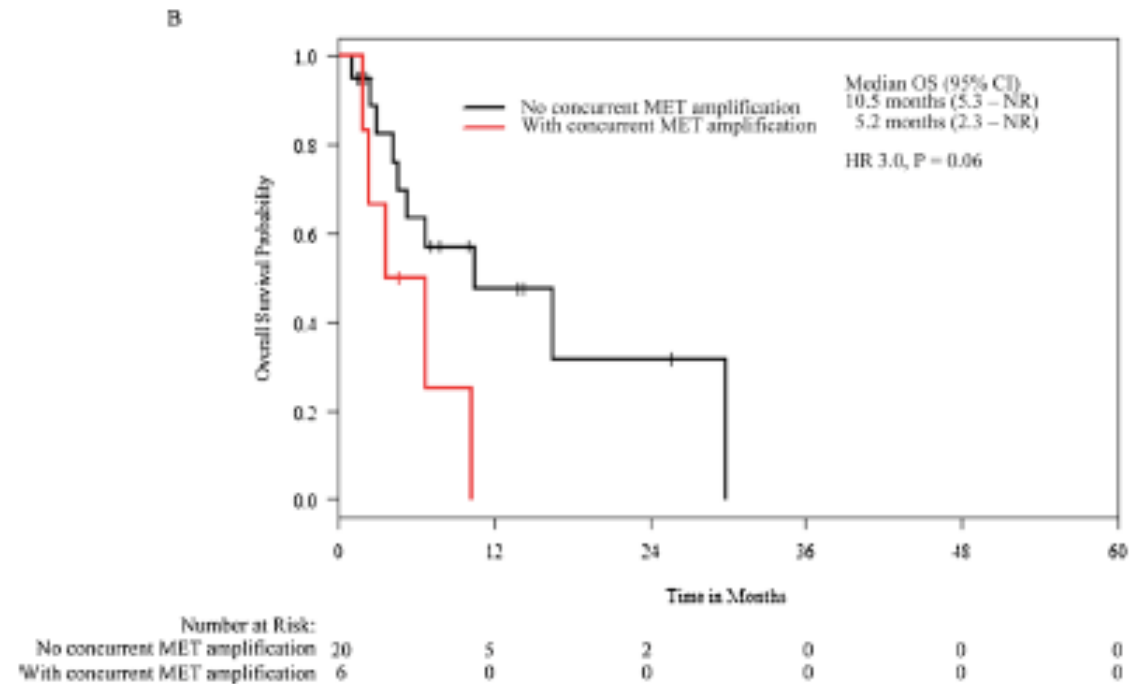
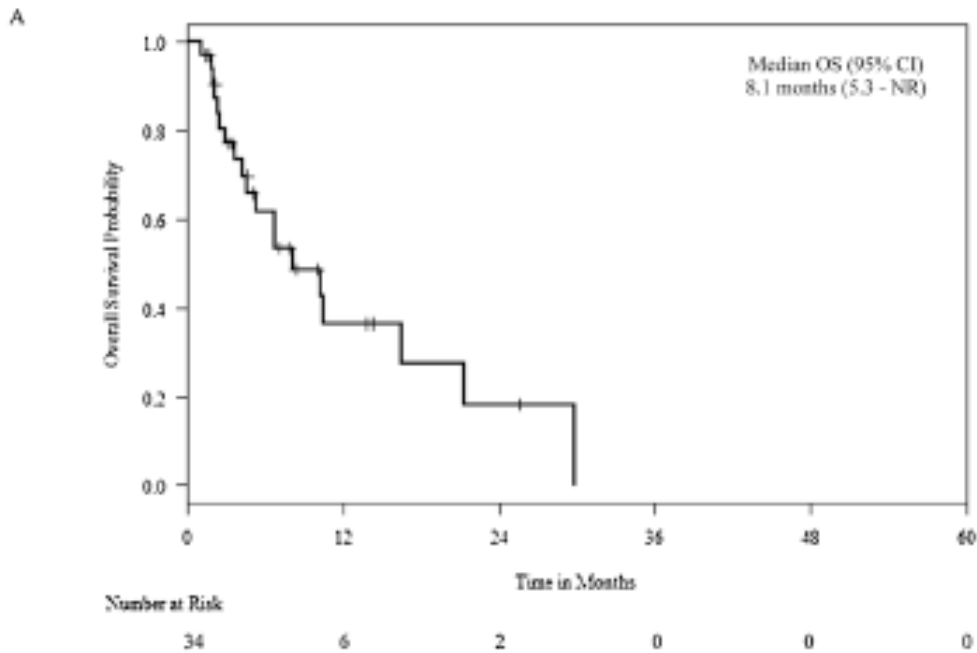


- Mutações que geram *skipping* do éxon 14 são encontradas em 2,7% dos CPCNP.
 - Associada com mau prognóstico.
 - Mais comum em idosos.
 - 50% fumantes.
- Frequência por histologia:
Adenocarcinoma – 2,8%
Carcinoma escamoso – 3,0%
Carcinoma adenoescamoso – 8,2%
Carcinoma sarcomatoide – 7,7%

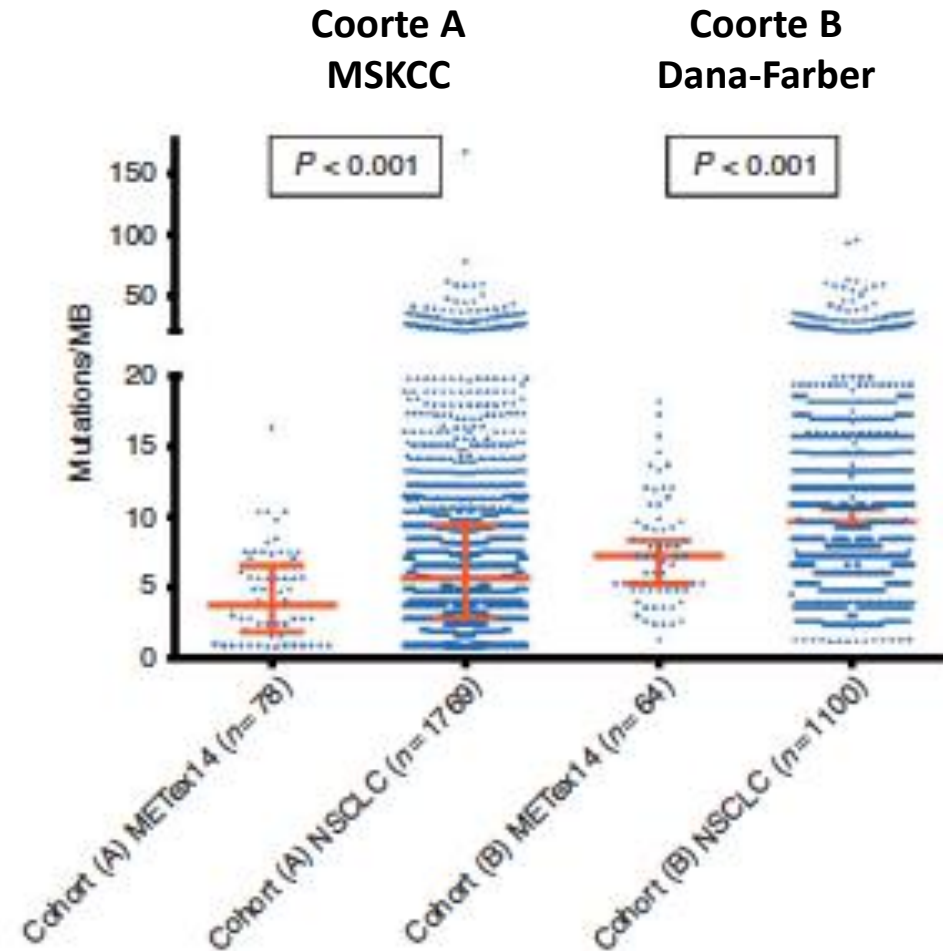
Mutação *METex14* e sobrevida

Análise retrospectiva
12 centros acadêmicos
N=64 → 34 nunca receberam um inibidor de MET

Pacientes que nunca receberam inibidor de MET



Clinical characteristics	No. (%) (N = 147)
Age, median (range), years	73 (44–91)
Sex	
Male	58 (39)
Female	89 (61)
Smoking history, pack years	
0	52 (35)
1–10	30 (21)
>10	65 (44)
Pack years (median, range)	6 (0–125)
Tumor histology	
Adenocarcinoma	109 (74)
Sarcomatoid	28 (19)
Adenosquamous	5 (3.5)
Squamous	5 (3.5)
Stage at diagnosis	
I	39 (27)
II	15 (10)
III	25 (17)
IV	68 (46)
Metastatic/recurrent disease	
Yes	101 (69)
No	46 (31)

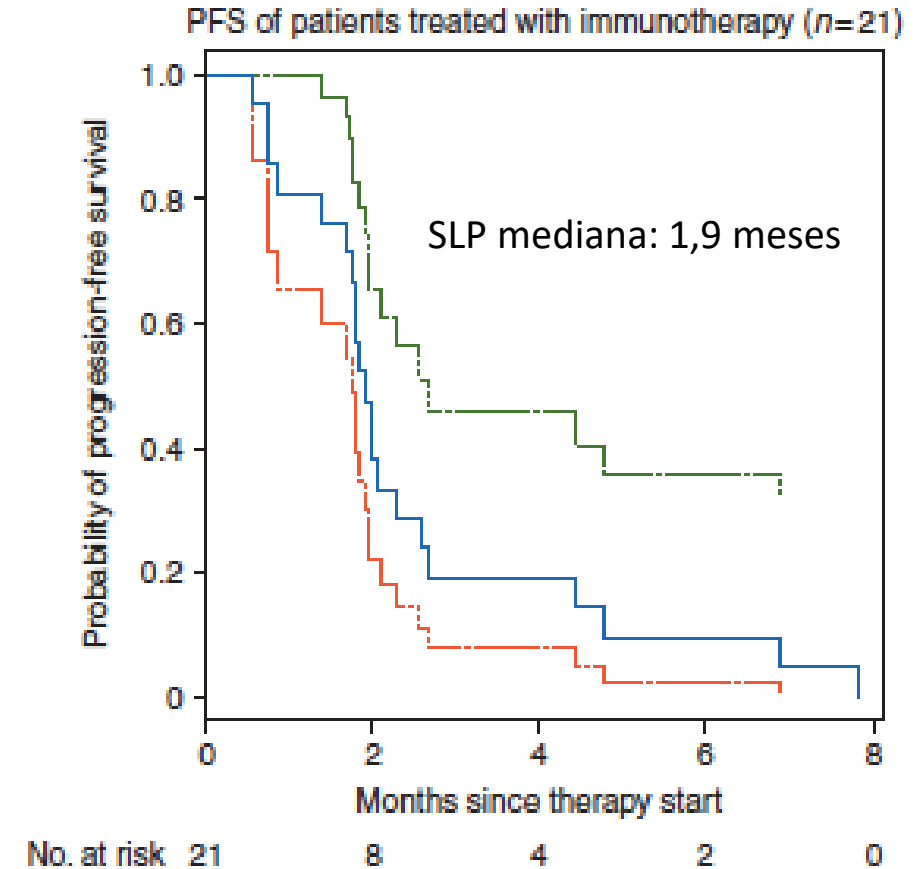
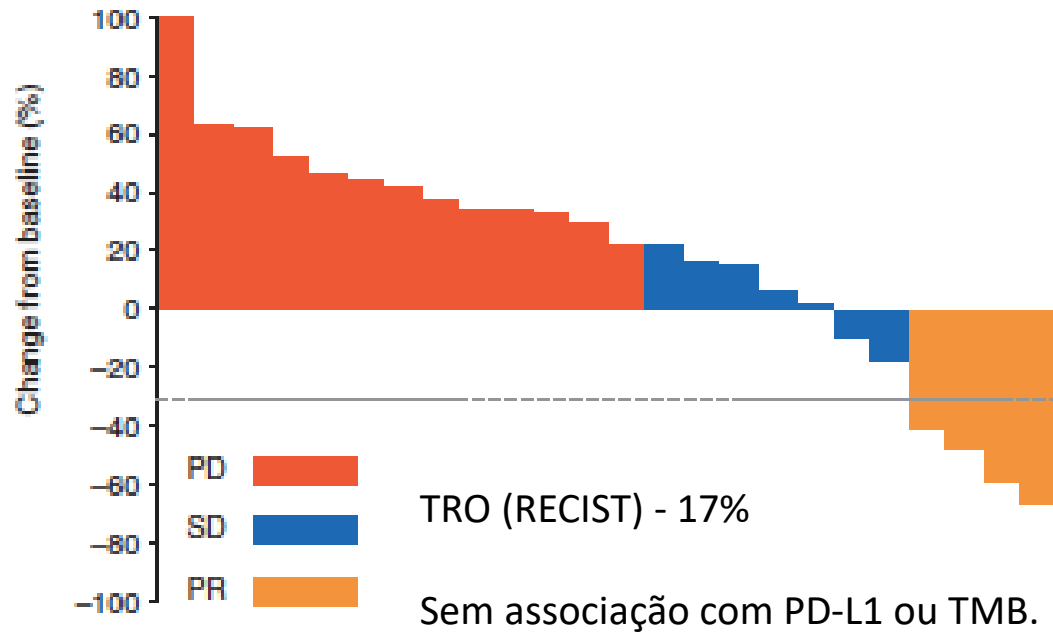


22 receberam IO monoterapia

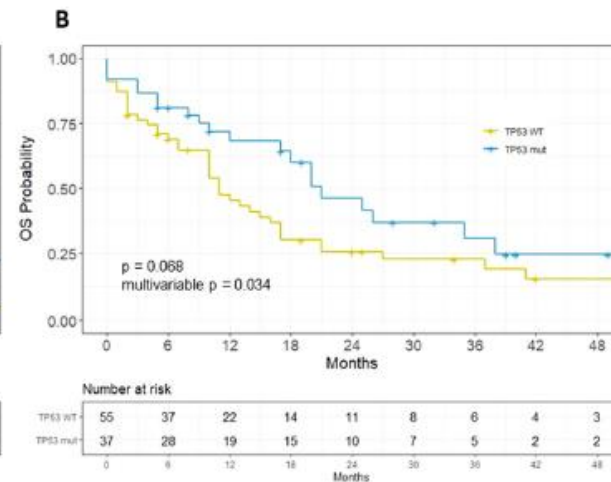
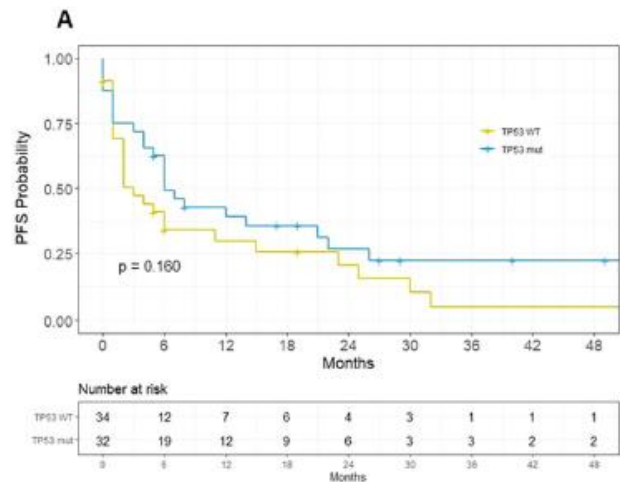
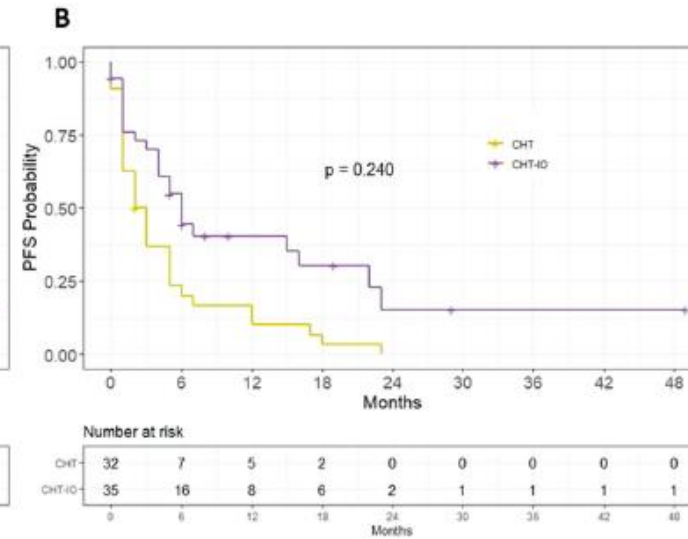
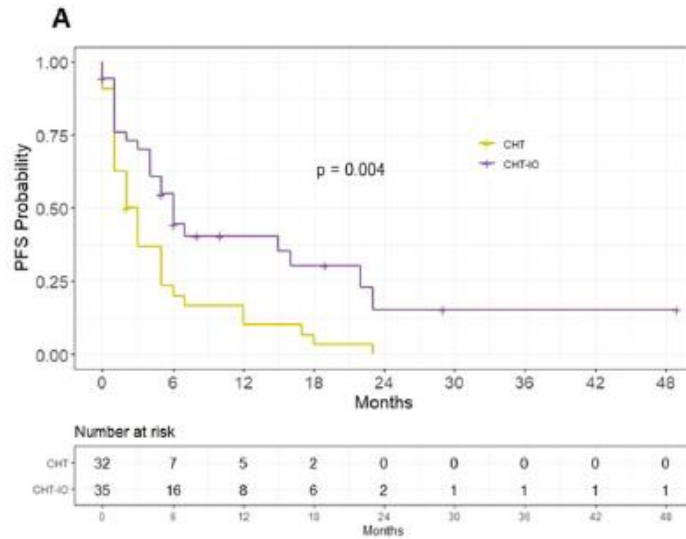
2 receberam IO+IO

11 foram tratados em 1L

63% tinham PD-L1 ≥ 1%



ME_{Tex}14 skipping – quimioimunoterapia primeira linha



Co-mutação em *TP53*
associada a pior
prognóstico

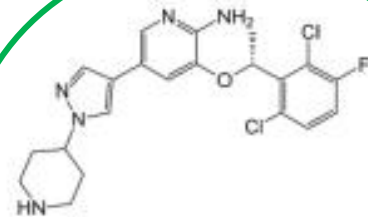
Inibidores de MET

Inibidor não seletivo

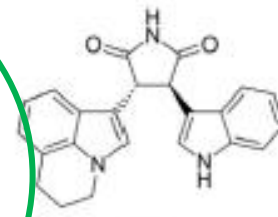
Tipo Ia – ligam-se ao sítio de ligação

do ATP e inibem forma ativa

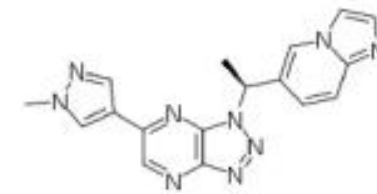
Interage com resíduo G1163



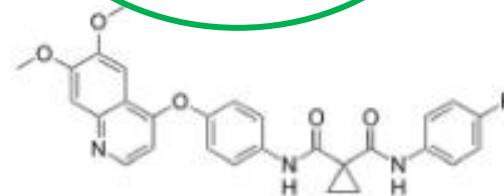
Crizotinib (PF-02341066)
- FDA-approved as an ALK inhibitor
- Inhibit MET, ALK, ROS1 and RON
- IC₅₀ for MET: 0.0002 μM



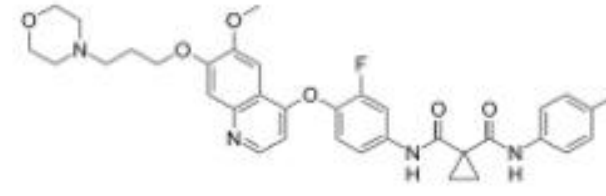
Tivantinib (ARQ197)
- Phase II combined with erlotinib in NSCLC
- Inhibit MET
- IC₅₀ for MET: N/A



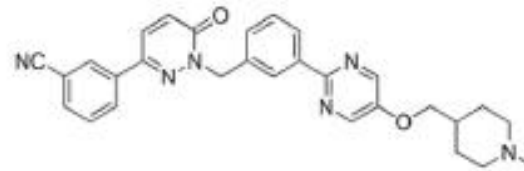
Savolitinib (HMPL-504; AZD6094)
- Phase II with NSCLC
- Inhibit MET
- IC₅₀ for MET: 0.003 μM



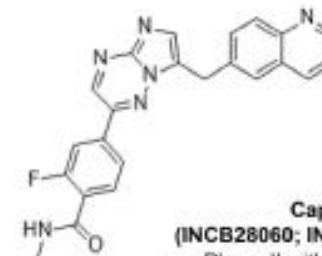
Cabozantinib (XL184, BMS907351)
- FDA-approved for renal and thyroid cancers
- Inhibit MET, VEGFR2, AXL and RET
- IC₅₀ for MET: 0.0013 μM
- Phase II with NSCLC



Foretinib (XL880; EXEL-2880; GSK1363089; GSK089)
- Inhibit MET and VEGFR2
- IC₅₀ for MET: 0.0004 μM
- Phase I in combination with erlotinib in NSCLC



Tepotinib (EMD 214063)
- Phase II with MET-altered NSCLC
- Inhibit MET
- IC₅₀ for MET: 0.001 μM



Capmatinib (INC28060; INC280, NVP-INC280)
- Phase II with NSCLC
- Inhibit MET
- IC₅₀ for MET: 0.00013 μM

Fase I/II – Coorte extendida

N=69

Critérios de elegibilidade

- CPCNP estágio IV
- Alterações no éxon 14 do gene *MET*
- Doença mensurável por RECIST 1.1
- ECOG PS 0–1
- Idade ≥ 18 anos (≥ 20 anos no Japão)

Plano estatístico: um estágio, ≥ 7 respostas em 33 pacientes incluídos para detectar uma TRO $\geq 30\%$ com poder de 90% e $p < 0,05$ (unicaudal).
Expandido para 68 para avaliar segurança.

Crizotinibe 250mg 2xdia VO a cada 28 dias (contínuo)

Status de ex14 *MET* (mutação ou amplificação) avaliado localmente.
Confirmação central retrospectiva por Foundation One CDx em tecido.
Avaliação em plasma com PlasmaSELECT R-64 (*baseline* e fim de tratamento).

Mantido até progressão,
deterioração clínica,
toxicidade limitante, retirada
de consentimento ou morte

Início do estudo: Setembro de 2014

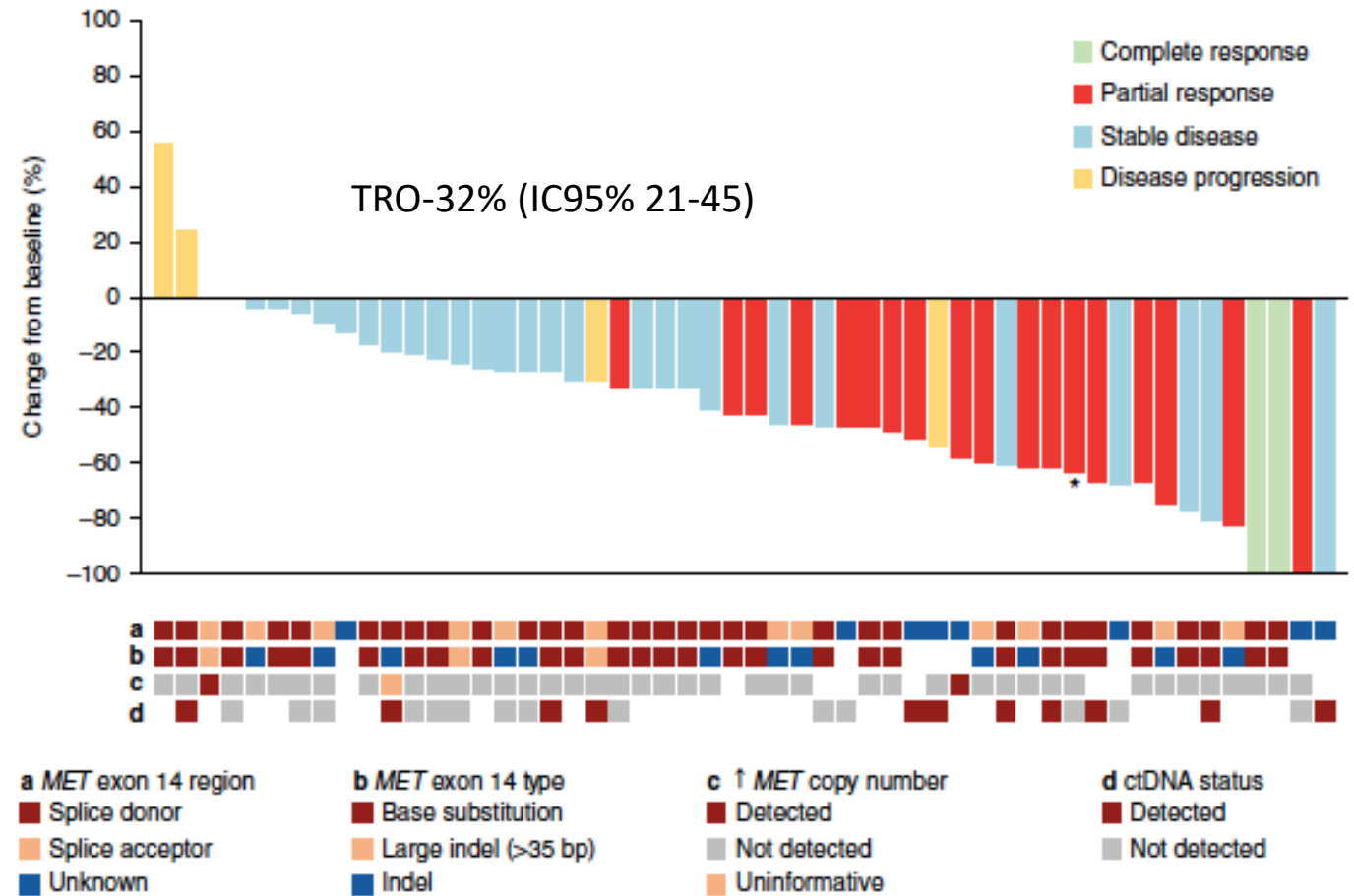
Fim do estudo: Janeiro de 2018

Desfecho Primário: TRO RECIST v1.1

Desfecho secundário: DoR, TPR, SLP, SG, segurança

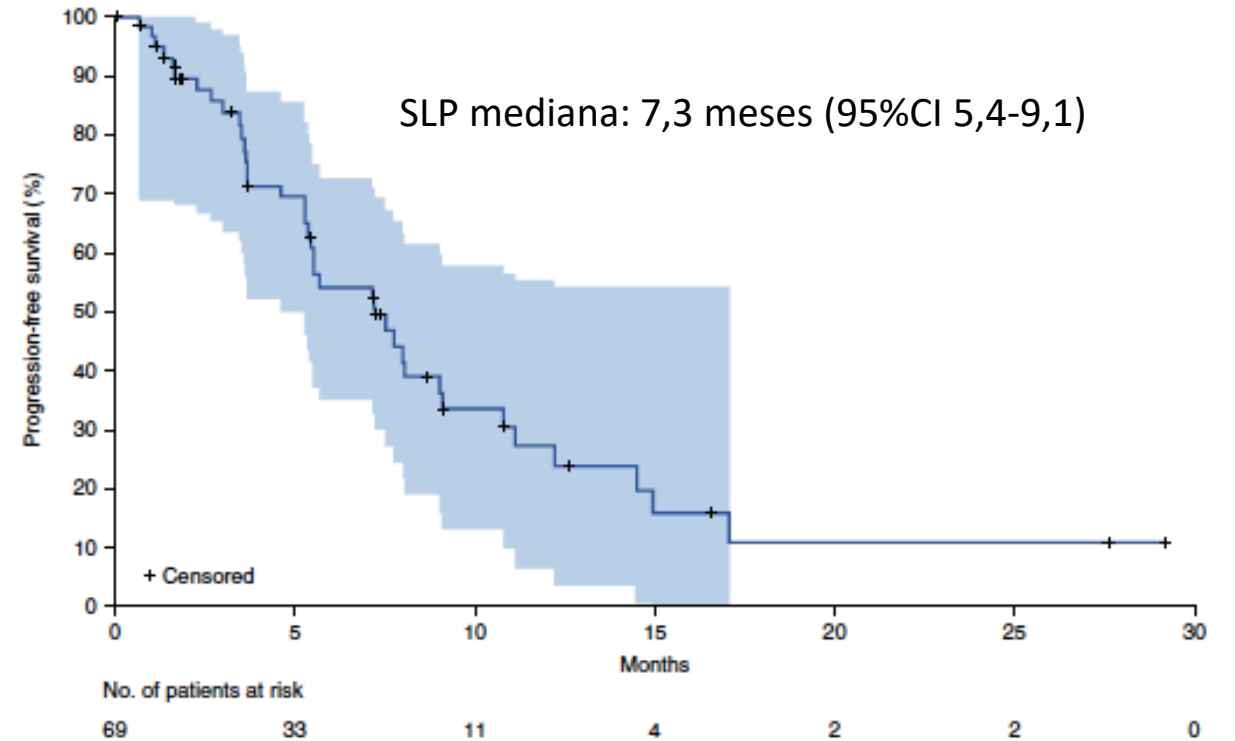
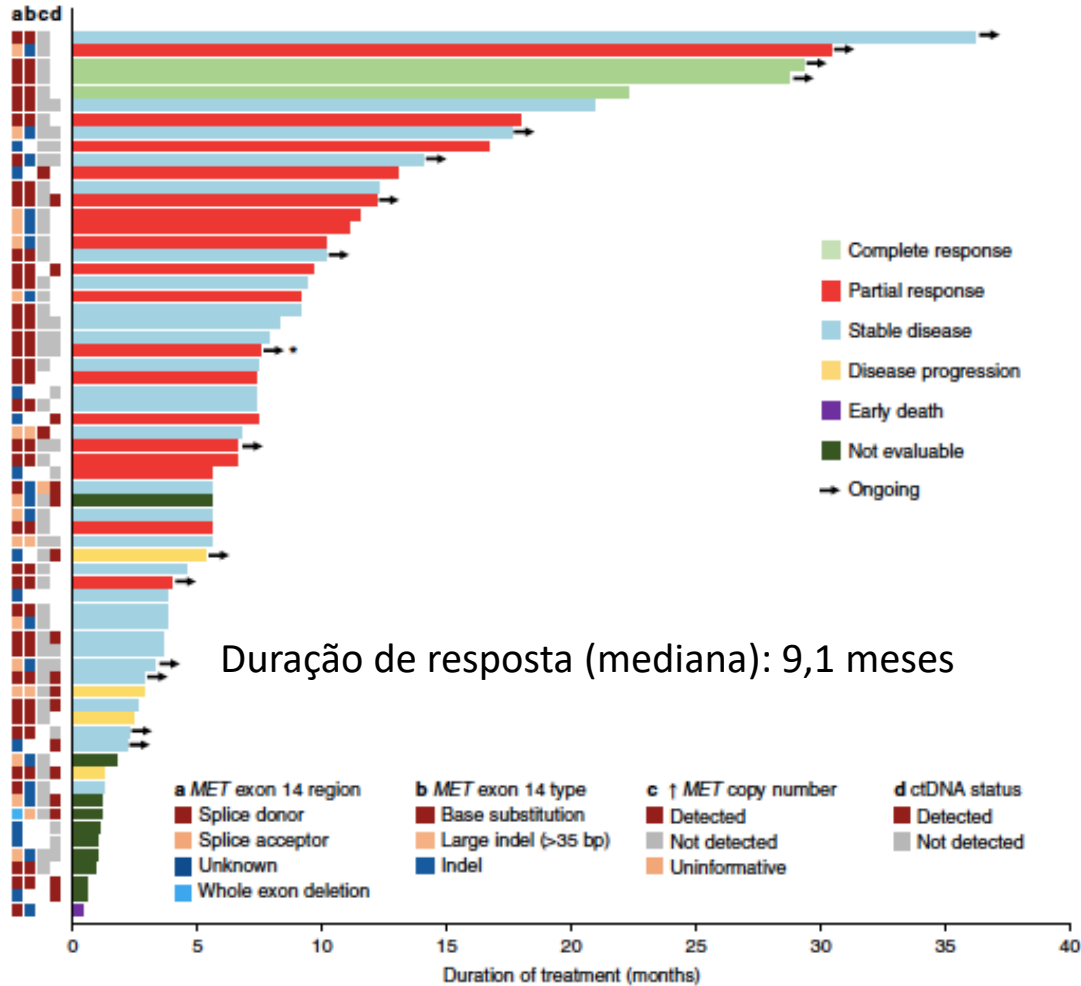
PROFILE 1001 - Características clínicas e TRO

Patients with <i>MET</i> -exon-14-altered NSCLC		n = 69
Age — yr		
Median	72	
Range	34-91	
Sex — no. patients (%)		
Female	40 (58)	
Male	29 (42)	
Race — no. patients (%)		
White	50 (73)	
Asian	11 (16)	
Black/African American	2 (3)	
Other	6 (9)	
Smoking history — no. patients (%)		
Former	42 (61)	
Never	26 (38)	
Current	1 (1)	
ECOG performance status — no. patients (%)		
0	19 (28)	
1	49 (71)	
2	1 (1)	
Tumor histology — no. patients (%)		
Adenocarcinoma	58 (84)	
Sarcomatoid carcinoma	6 (9)	
Squamous cell carcinoma	3 (4)	
Adenosquamous carcinoma	2 (3)	
Prior treatments for advanced disease — no. patients (%) ^a		
0	26 (38)	
1	29 (42)	
>1	14 (20)	



20% com comutações: *TP53*, *MDM2*, *CDKN2A*

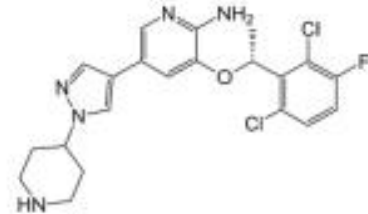
PROFILE 1001 - Duração de resposta e SLP



Outros estudos com crizotinibe

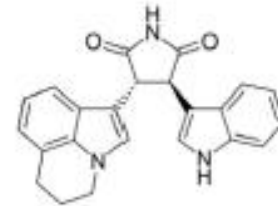
Drug	Nonselective TKI		
	CRIZOTINIB ³²⁻³⁴		
Dose	250 mg BID		
Trial	PROFILE		
	1001	AcSé	METROS ^a
Line	≥1	≥2	≥2
N	69	25	26
RR (%)	32 ^b	40	27
DoR (mo)	9.1	NR	NR
PFS (mo)	7.3	3.6	4.4
OS (mo)	20.5	9.5	5.4
G3 TRAE's (%)	25	NR	NR
Dose R (%)	38	NR	15
Disc (%)	7	24	6

Inibidores de MET



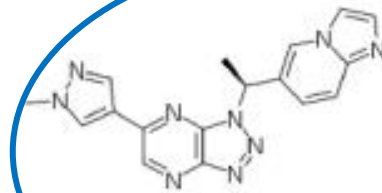
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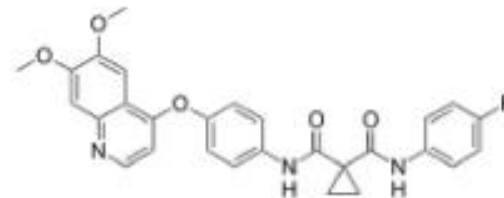
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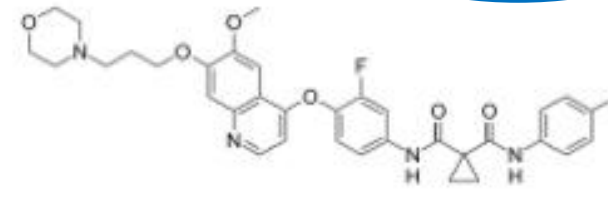
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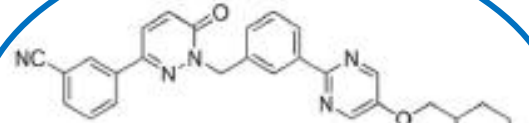
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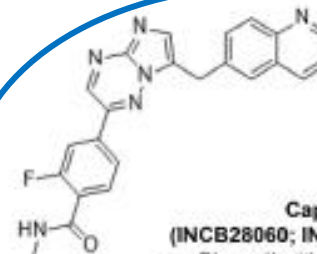
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Tepotinib (EMD 214063)

- Phase II with MET-altered NSCLC
- Inhibit MET
- IC₅₀ for MET: 0.001 µM



Capmatinib (INC28060; INC280, NVP-INC280)

- Phase II with NSCLC
- Inhibit MET
- IC₅₀ for MET: 0.00013 µM

Inibidores seletivos
Tipo Ib – ligam-se ao sítio
de ligação do ATP e
inibem forma ativa
Não interagem com
resíduo G1163

GEOMETRY mono-1 – Desenho do estudo

Fase II – *Open label*, multicêntrico

N=364

Stage IIIB or IV NSCLC
EGFR nonmutated (negative for L858R and exon 19 deletion) and ALK-rearrangement negative
ECOG performance-status score of 0 or 1
≥1 Measurable lesion (RECIST, version 1.1)
Asymptomatic or neurologically stable brain metastases allowed

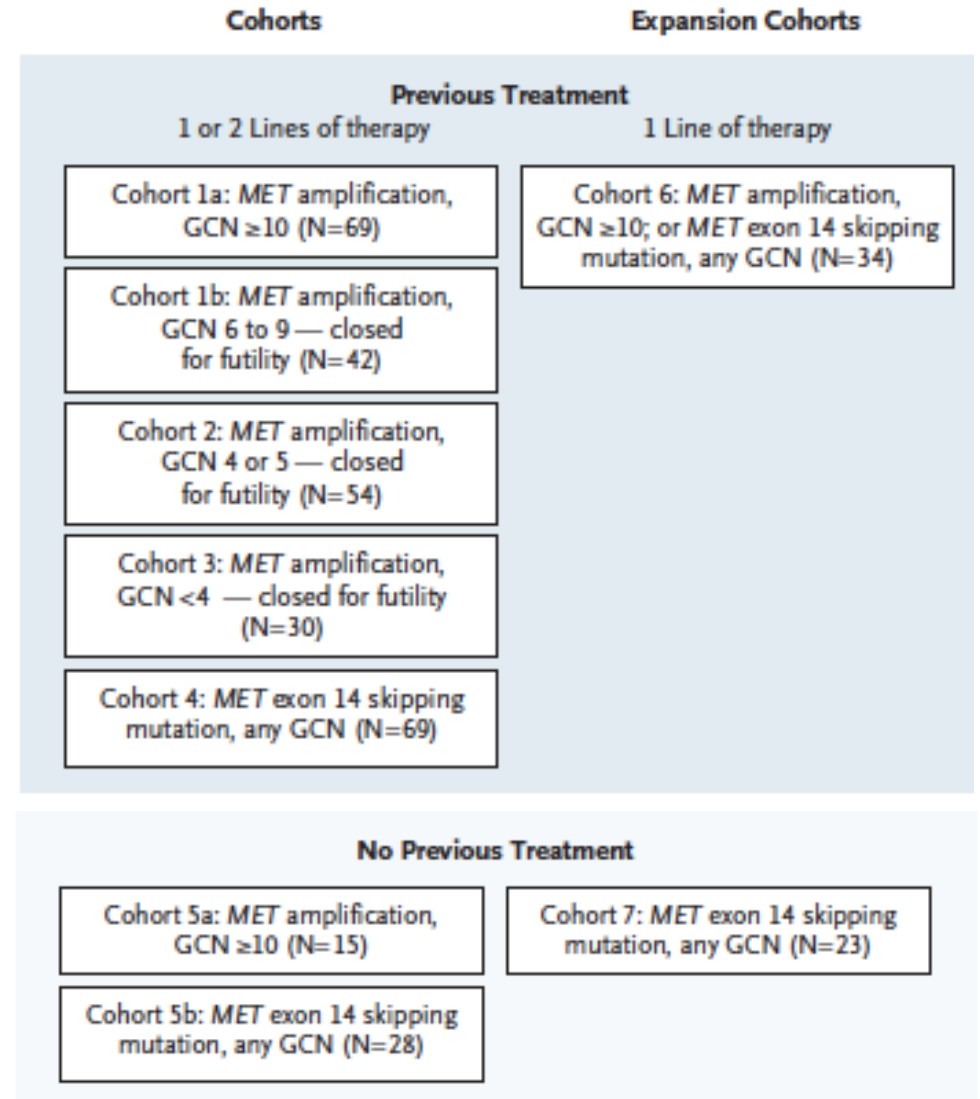
Capmatinib, 400 mg tablet twice daily
(02 comp. de 200mg)

Mutação *skipping* éxon 14 de MET ou amplificação de MET – Avaliação central

Desfecho Primário: TRO (CRIC) por RECIST v1.1

Desfecho secundário: DoR, TPR, SLP, segurança

Data *cutoff* para análise de eficácia: Janeiro de 2020



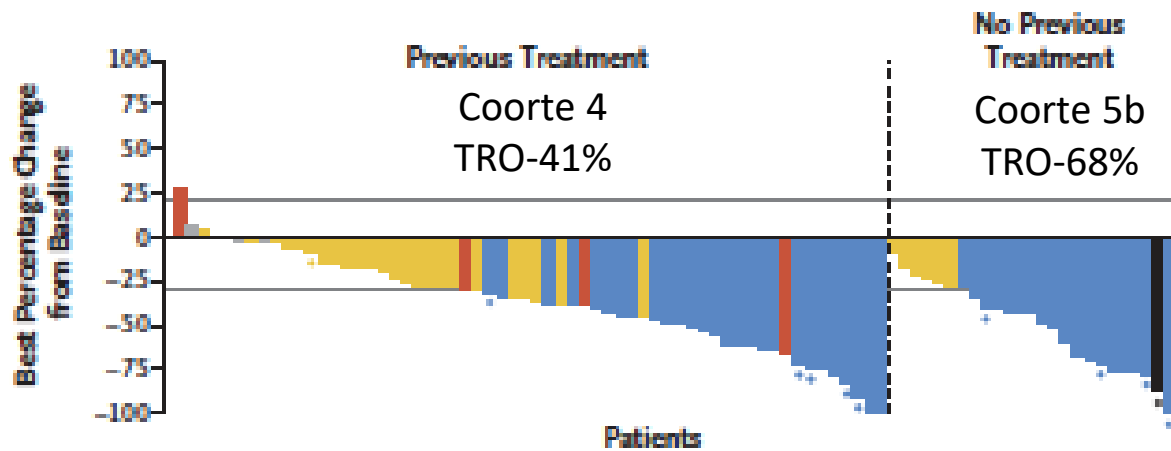
GEOMETRY mono-1 – Características clínicas

Characteristic	NSCLC with MET Exon 14 Skipping Mutation		NSCLC with MET Amplification				
	Cohort 4 (N=69)	Cohort 5b (N=28)	Cohort 1a (N=69)	Cohort 5a (N=15)	Cohort 1b (N=42)	Cohort 2 (N=54)	Cohort 3 (N=30)
Age							
Median (range) — yr	71 (49–90)	71 (57–86)	61 (33–76)	70 (49–86)	60 (36–76)	64 (39–84)	63 (38–78)
≥65 yr — no. (%)	55 (80)	25 (89)	28 (41)	10 (67)	13 (31)	24 (44)	14 (47)
→ Female sex — no. (%)	40 (58)	18 (64)	15 (22)	4 (27)	21 (50)	15 (28)	11 (37)
ECOG performance-status score — no. (%)†							
0	16 (23)	7 (25)	17 (25)	4 (27)	14 (33)	23 (43)	9 (30)
≥1	53 (77)	21 (75)	52 (75)	11 (73)	28 (67)	31 (57)	21 (70)
Smoking history — no. (%)							
→ Never smoked	40 (58)	18 (64)	5 (7)	2 (13)	7 (17)	11 (20)	7 (23)
Former smoking	27 (39)	9 (32)	54 (78)	8 (53)	29 (69)	34 (63)	20 (67)
Current smoking	2 (3)	1 (4)	10 (14)	5 (33)	6 (14)	9 (17)	3 (10)
Histologic findings — no. (%)							
Adenocarcinoma	53 (77)	25 (89)	57 (83)	11 (73)	35 (83)	48 (89)	22 (73)
Squamous-cell carcinoma	6 (9)	2 (7)	7 (10)	2 (13)	2 (5)	4 (7)	5 (17)
Large-cell carcinoma	1 (1)	0	2 (3)	1 (7)	1 (2)	0	1 (3)
Other	9 (13)	1 (4)	3 (4)	1 (7)	4 (10)	2 (4)	2 (7)
→ Brain metastases at baseline — no. (%)‡	11 (16)	3 (11)	26 (38)	7 (47)	14 (33)	18 (33)	6 (20)
No. of previous lines of antineoplastic therapy — no. (%)§							
1	51 (74)	NA	41 (59)	NA	27 (64)	28 (52)	9 (30)
2	16 (23)	NA	27 (39)	NA	15 (36)	26 (48)	21 (70)
3	2 (3)	NA	1 (1)	NA	0	0	0

GEOMETRY mono-1 – Taxa de resposta

■ Complete response
 ■ Partial response
 ■ Stable disease
 ■ Noncomplete response or nonprogressive disease
 ■ Progressive disease
 ■ Unknown

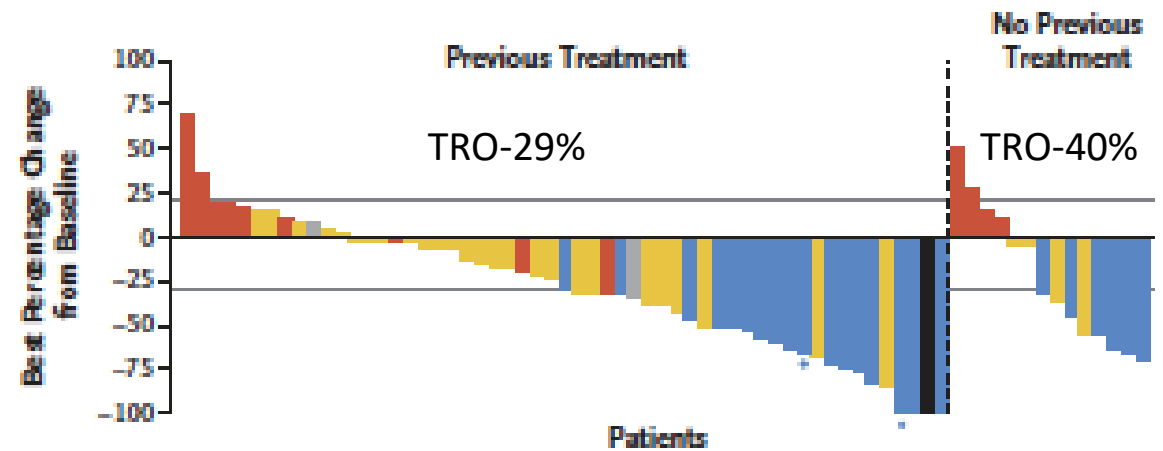
A Best Response to Capmatinib — MET Exon 14 Skipping Mutation



Duração de resposta mediana Coorte 4: 9,7 meses

Duração de resposta mediana Coorte 5b: 12,6 meses

B Best Response to Capmatinib — MET Amplification with GCN ≥ 10



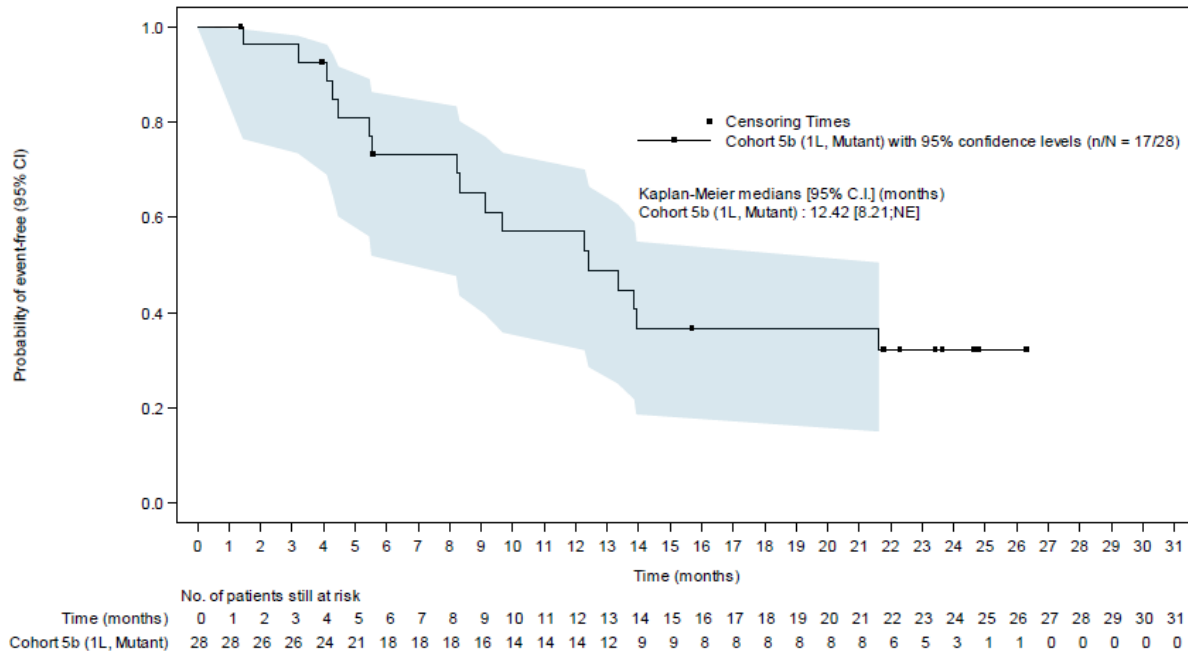
Metástase cerebral: 14

Resposta intracraniana: 7/13 (54%)

GEOMETRY mono-1

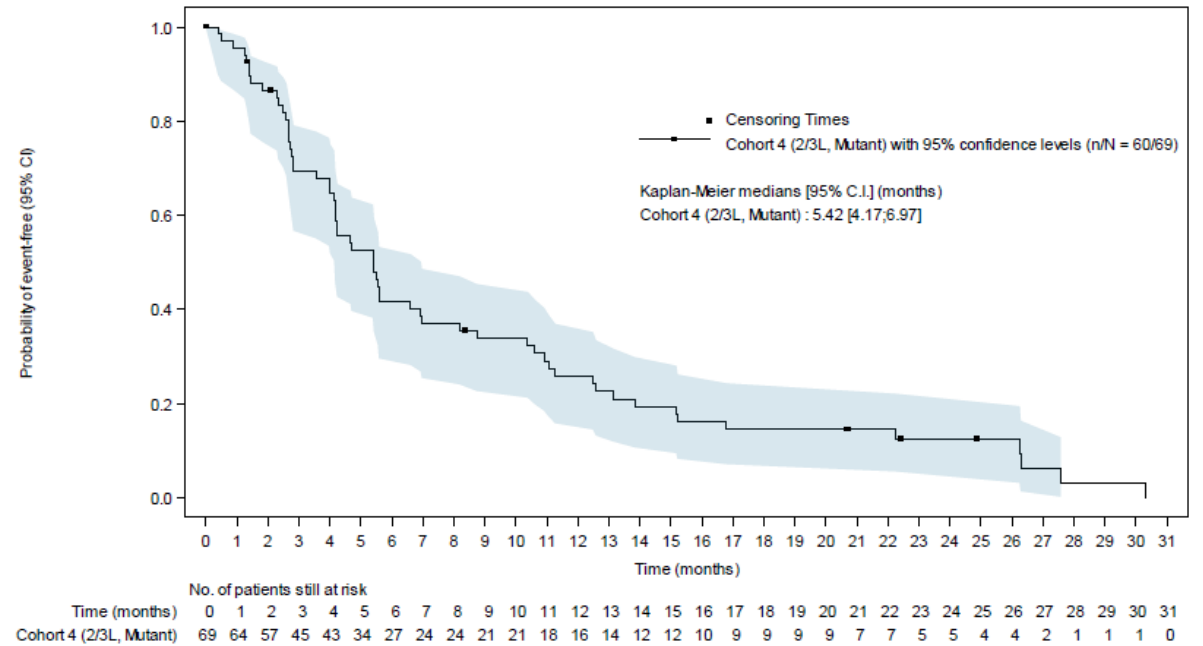
Sobrevida livre de progressão – skipping ex14

1ª Linha Coorte 5b



SLP mediana: 12,4 meses

2ª Linha Coorte 4

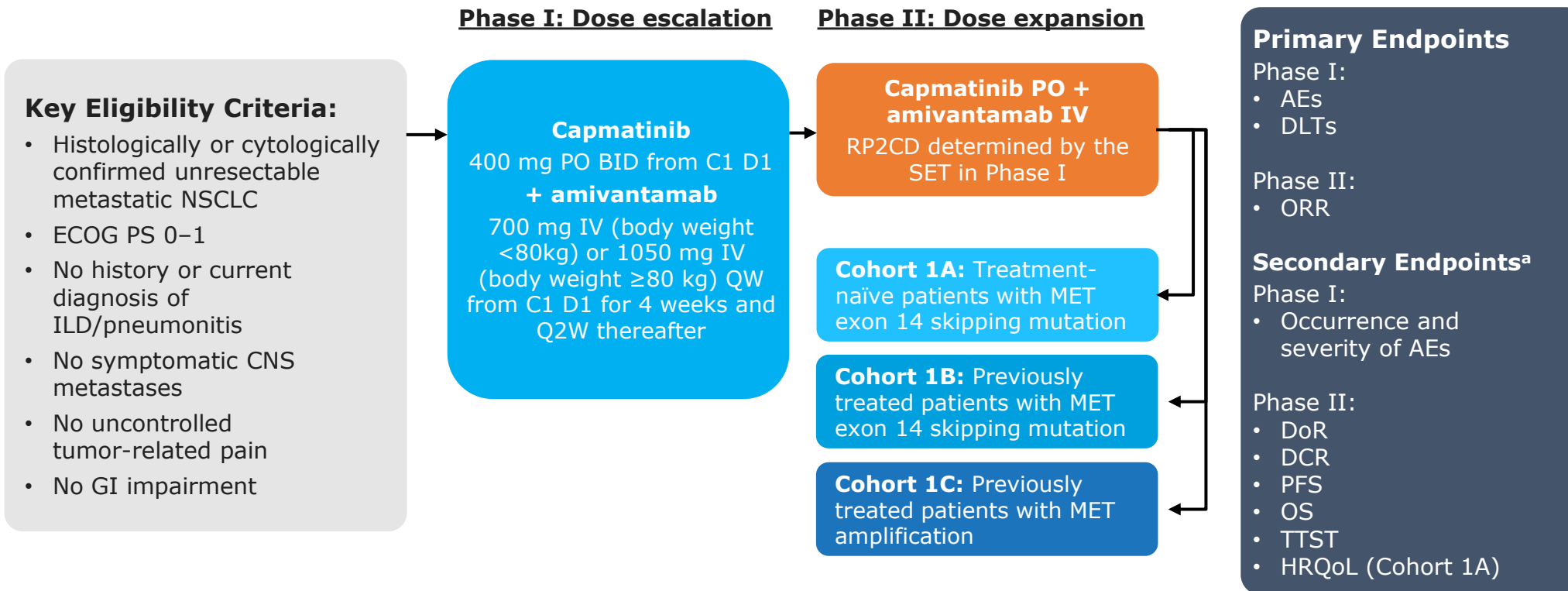


SLP mediana: 5,4 meses

METalmark* (NCT05488314)

 A **Phase I/II** study evaluating the safety and efficacy of **amivantamab** and **capmatinib** combination therapy in **unresectable metastatic NSCLC**

N=~147



Please refer to disclaimer slide

*Not yet recruiting. ^aNot a complete list of secondary endpoints.

AEs, adverse events; BID, twice daily; C, cycle; CNS, central nervous system; D, day; DCR, disease control rate; DLTs, dose limiting toxicities; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; ILD, interstitial lung disease; IV, intravenous; MET, mesenchymal-epithelial transition factor; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; PS, performance status; Q2W, every 2 weeks; QW, weekly; RP2CD, recommended phase 2 combination dose; TTST, time to subsequent therapy.



Fase II – *open label*, multi-coorte

N=99

Critérios de elegibilidade

- CPCNP metastático ou localmente avançado
- Sem mutação de *EGFR* ou rearranjo de *ALK*
- Mutação *skipping* éxon 14 do gene *MET*
- Doença mensurável por RECIST 1.1
- ECOG PS 0–1
- Idade ≥ 18 anos

Plano estatístico: análise primária de eficácia após a inclusão de pelo menos 60 pacientes com pelo menos 9 meses de seguimento. TRO de 40-50% limite inferior do IC 95% (Clopper-Pearson) de pelo menos 20%.

Tepotinibe 450mg (02 comp. 225mg) 1xdia VO contínuo

Mutação do éxon 14 do gene *MET* foi avaliado centralmente no plasma pelo método Guardant 360 ou em tecido com teste Oncomine Focus.

Início do estudo: Setembro de 2016

Fim do estudo: Janeiro de 2020

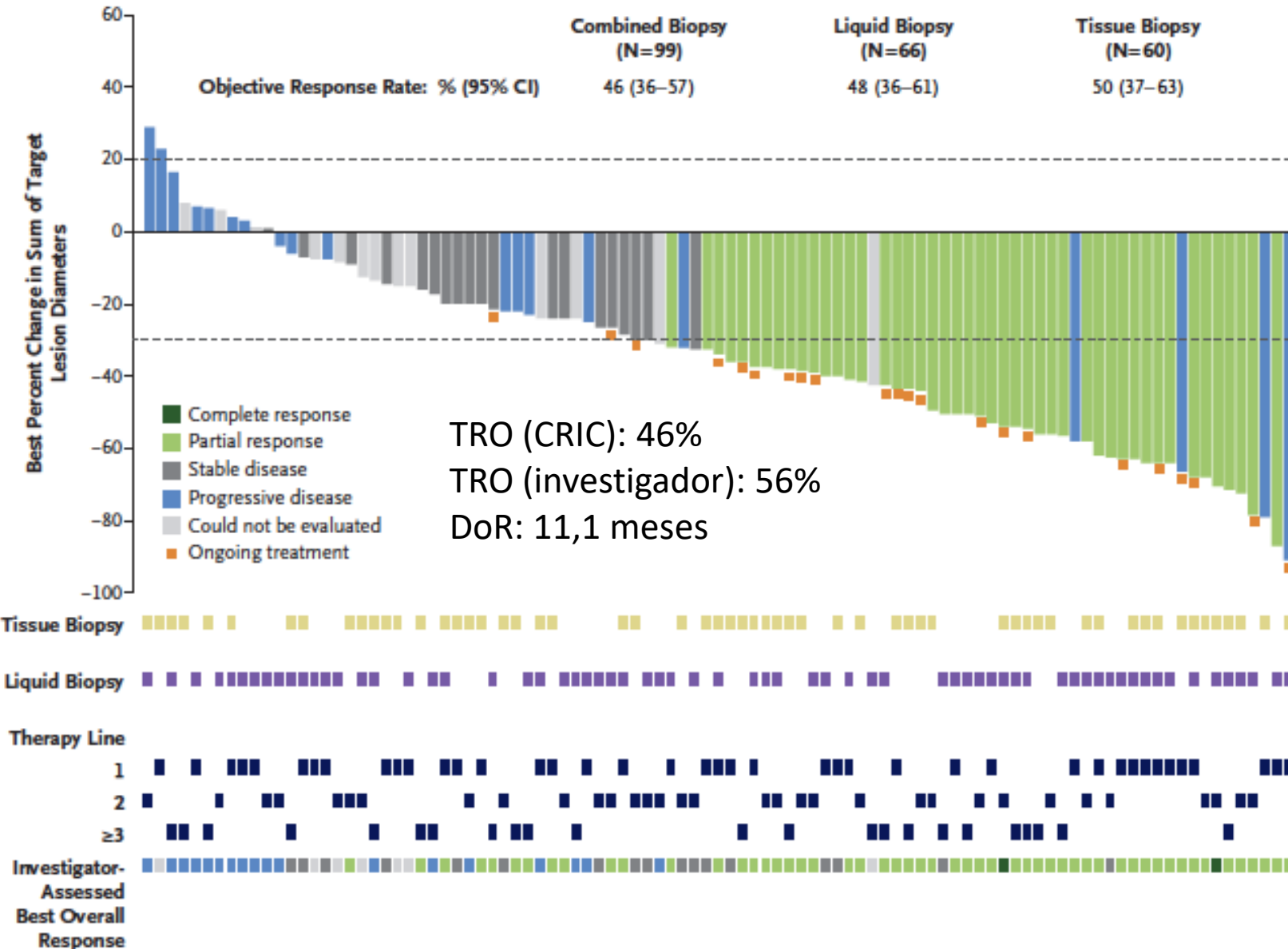
Desfecho Primário: TRO (CRIC) RECIST v1.1

Desfecho secundário: TRO (investigador), DoR, SLP, SG

VISION – Características clínicas

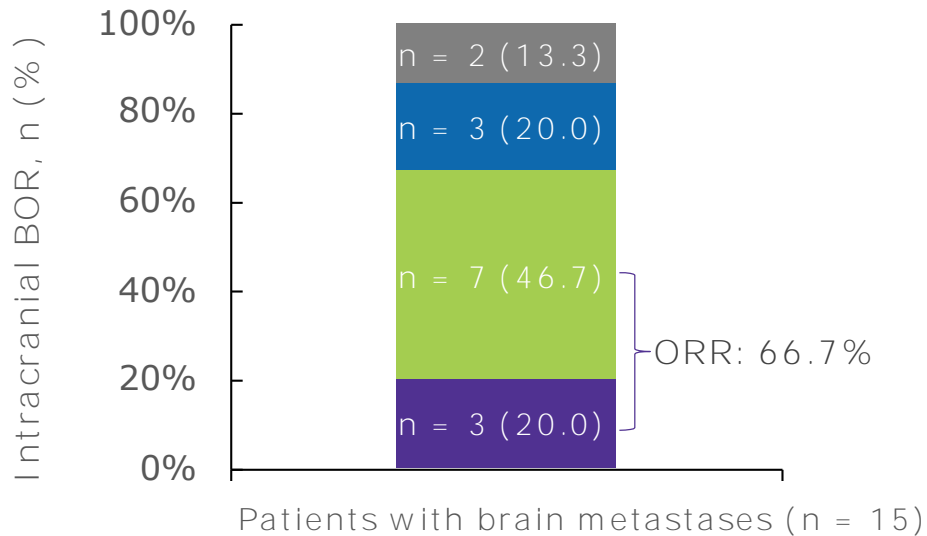
Characteristic	Liquid Biopsy (N=66)	Tissue Biopsy (N=60)	Combined Biopsy (N=99)
→ Median age (range) — yr	74 (49–88)	74 (41–94)	74 (41–94)
Sex — no. (%)			
Male	32 (48)	39 (65)	54 (55)
Female	34 (52)	21 (35)	45 (45)
Race — no. (%)†			
Asian	11 (17)	15 (25)	21 (21)
White	52 (79)	44 (73)	74 (75)
Smoking history — no. (%)‡			
Yes	28 (42)	30 (50)	46 (46)
→ No	34 (52)	22 (37)	45 (45)
ECOG performance-status score — no. (%)§			
0	14 (21)	16 (27)	22 (22)
1	52 (79)	44 (73)	77 (78)
Histologic subtype — no. (%)¶			
Adenocarcinoma	58 (88)	56 (93)	89 (90)
Squamous	6 (9)	3 (5)	7 (7)
Sarcomatoid	1 (2)	0	1 (1)
Previous courses of therapy for advanced or metastatic disease — no. (%)			
→ 0	29 (44)	27 (45)	43 (43)
1	22 (33)	19 (32)	33 (33)
≥2	15 (23)	14 (23)	23 (23)
→ Brain metastases as identified by independent review — no. (%)	9 (14)	3 (5)	11 (11)

VISION – Taxa de resposta



VISION – Atividade em SNC (RANO-BM)

- Complete response
- Partial response
- Stable disease
- Progressive disease



Patients with brain metastases (n = 15)		
Intracranial ORR, n (%) [95% CI]	Overall (n = 15)	10 (66.7) [38.4, 88.2]
	Treatment-naïve (n = 10)	6 (60.0) [26.2, 87.8]
	Previously treated (n = 5)	4 (80.0) [28.4, 99.5]
Intracranial DOR	Median, months (95% CI)	ne (0.9, ne)

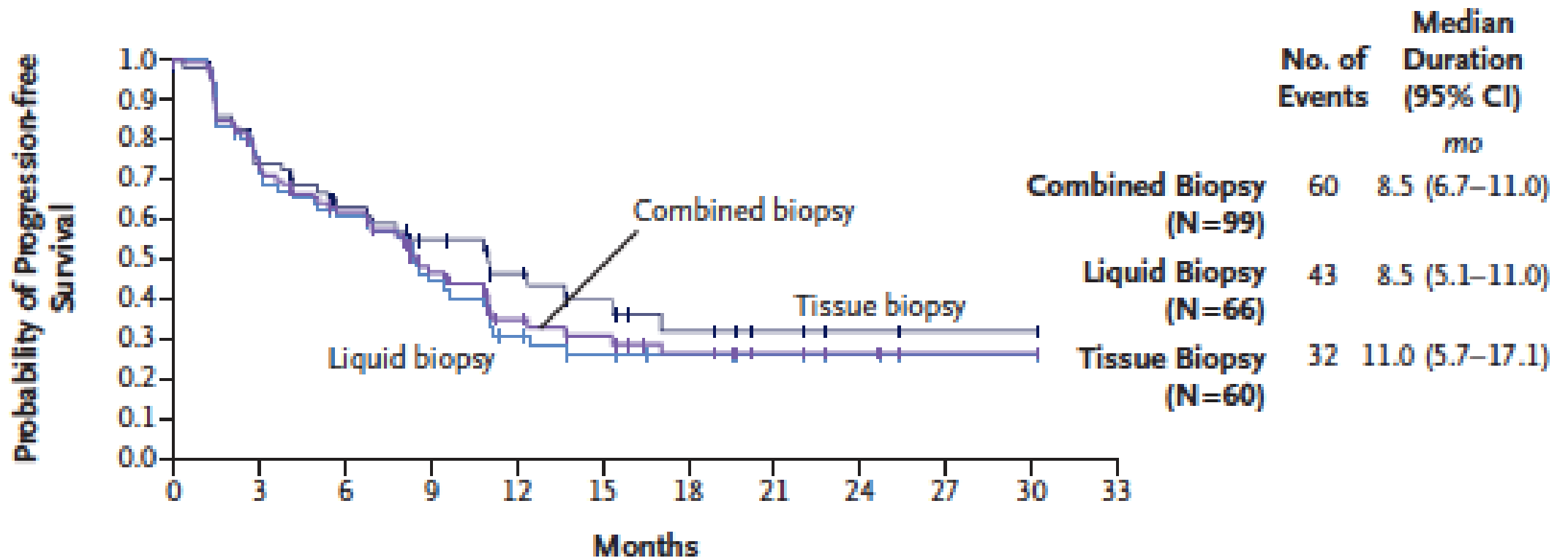


Of 15 patients with brain metastases target lesions evaluable by RANO-BM (12 patients had received prior brain radiotherapy), the intracranial ORR was 66.7%

BOR, Best overall response; CI, Confidence interval; DOR, Duration of response; ne, Not estimable; ORR, Objective response rate; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases.

Mazieres et al. JAMA Oncol. 2023;9(9):1260-1266.

VISION – Sobrevida livre de progressão



No. at Risk

Combined biopsy	99	67	53	33	20	15	10	6	4	1	1	0
Liquid biopsy	66	44	36	23	14	10	8	6	4	1	1	0
Tissue biopsy	60	42	32	22	16	11	7	4	2	1	1	0

Savolitinibe – Desenho do estudo

Fase II – *open label*, braço único, multicêntrico

N=84

Critérios de elegibilidade

- CPCNP metastático ou localmente avançado
- Sem mutação de *EGFR* ou rearranjo de *ALK* e *ROS1*
- Mutação *skipping* éxon 14 do gene *MET*
- Doença mensurável por RECIST 1.1
- ECOG PS 0–1
- Idade ≥ 18 anos

Início do estudo: Novembro de 2016

Fim do estudo: Agosto de 2020

Plano estatístico: TRO de 55% com limite inferior do IC 95% de pelo menos 30%, com poder de 92% e um alfa unicaudado de 0,025.

Savolitinibe 600mg (se ≥ 50 Kg) ou 400mg (se < 50 Kg) 1xdia VO contínuo

Mutação do éxon 14 do gene *MET* foi avaliado centralmente no plasma pelo método de Sanger inicialmente e após emenda pelo teste Geneseeq Tetradecan em tecido.

Desfecho Primário: TRO (CRIC) RECIST v1.1

Desfecho secundário: TRO (investigador), DoR, SLP, SG

Savolitinibe – Características clínicas

Age	
Median age, years	68.7 (65.4-74.7)
<75 years	54 (77%)
≥75 years	16 (23%)
Sex	
Female	29 (41%)
Male	41 (59%)
Weight	
<50 kg	8 (11%)
≥50 kg	62 (89%)
Smoking history	
Never	42 (60%)
Current or former	28 (40%)
Disease characteristics	
ECOG performance status*	
0	12 (17%)
1	57 (81%)
3	1 (1%)
Time from primary diagnosis to first dose, months	3.4 (0.2-35.9)
Disease stage*	
III	5 (7%)
IV	65 (93%)

Histology	
Pulmonary sarcomatoid carcinoma	25 (36%)
Pleomorphic carcinoma	15 (21%)
Spindle cell carcinoma	8 (11%)
Giant cell carcinoma	1 (1%)
Carcinosarcoma	1 (1%)
Other NSCLC subtypes	45 (64%)
Adenocarcinoma	40 (57%)
Squamous carcinoma	3 (4%)
Adenosquamous carcinoma	1 (1%)
NSCLC, not otherwise specified	1 (1%)
Number of previous systemic treatments for advanced disease	
0	28 (40%)
1	32 (46%)
2	5 (7%)
3	3 (4%)
≥4	2 (3%)
Type of previous systemic treatment for advanced disease	
Chemotherapy	39 (56%)
Immunotherapy	3 (4%)
Targeted therapy	5 (7%)
Other	16 (23%)

Savolitinibe – Taxa de resposta

	IRC-assessed (n=70)	Investigator-assessed (n=70)
Best overall response		
Confirmed complete response	0	0
Confirmed partial response	30 (43%)	33 (47%)
Stable disease	27 (39%)	24 (34%)
Non-complete response or non-progressive disease	1 (1%)	0
Progressive disease*	7 (10%)	8 (11%)
Could not be determined†	5 (7%)	5 (7%)
Objective response rate	30 (42.9%, 31.1-55.3)	33 (47.1%, 35.1-59.5)
Disease control rate	58 (82.9%, 72.0-90.8)	57 (81.4%, 70.3-89.7)
Median time to response, months	1.4 (1.4-1.5)	1.4 (1.4-1.5)
Median duration of response, months	8.3 (5.3-16.6)	6.9 (4.9-12.5)
Median progression-free survival, months	6.8 (4.2-9.6)	6.9 (4.6-8.3)
6-month progression-free survival (95% CI)	52.0% (38.6-63.8)	54.6% (41.3-66.1)
12-month progression-free survival (95% CI)‡	31.9% (20.3-44.2)	30.7% (19.6-42.6)

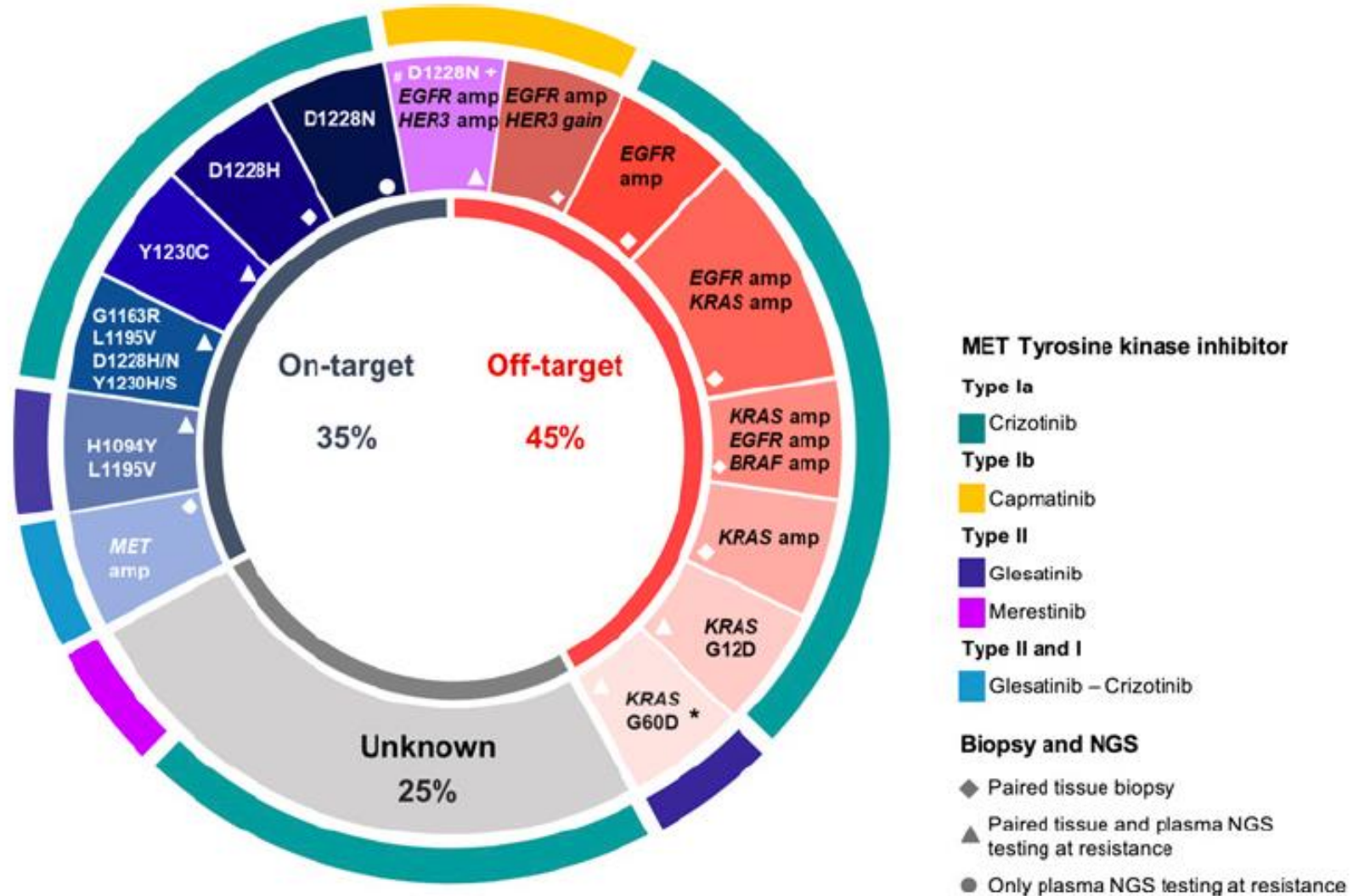


Co-mutação em *TP53* associada com pior resposta e menor SLP.
Amplificação de *MET* associada com melhor resposta.

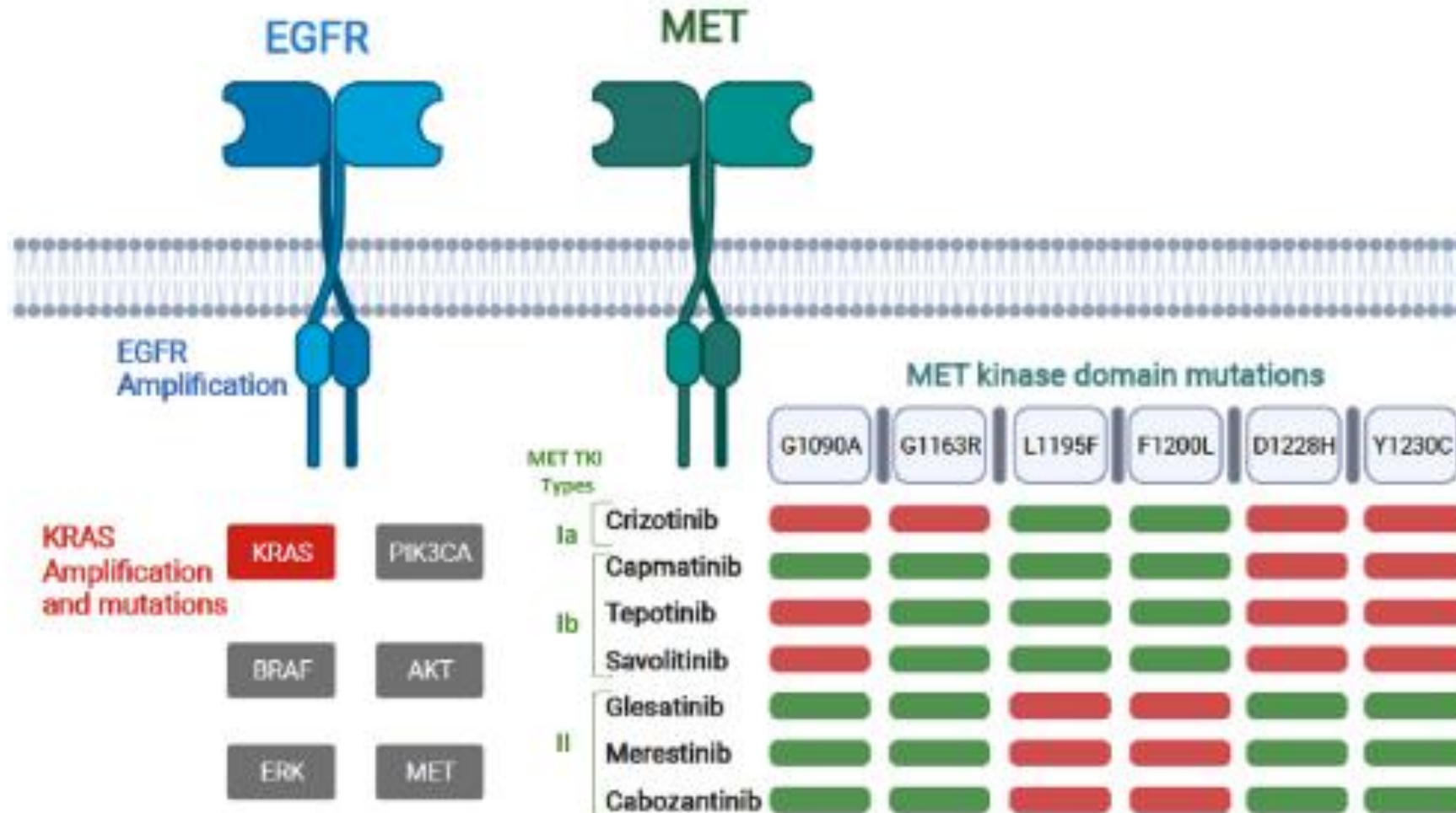
Comparação do perfil de toxicidade dos inibidores de MET

	Tepotinib ²¹ N = 152 (Reported TRAEs in ≥5% Patients/Treatment) % All-grade / ≥3 (Unless Stated)	Capmatinib ²⁷ N = 151 ^a (Reported TRAEs in ≥10% Patients in Any Cohort) % All-grade / ≥3 (Unless Stated)	Savolitinib ³² N = 70 (Reported TRAEs in ≥25% Patients) % All-grade / ≥3 (Unless Stated)	Crizotinib ³⁶ N = 69 (Reported TRAEs in ≥10% Patients) % All-grade / ≥3 (Unless Stated)
AEs	98	97 / 66	100 / 64	
TRAEs	89 / 28	88 / 46	100 / 46	94 / 29
TRAEs Leading to Dose Reduction	33 / NR	NR	NR	38 / NR
TRAEs Leading to Discontinuation	11 / NR	12 / 8	14 / NR	7 / NR
Serious TRAEs	15 / NR	15 / 13	24 / 14	NR
Deaths (Related or Potentially Related to Treatment)	Respiratory failure and dyspnea	Pneumonitis	Tumor lysis syndrome	Interstitial lung disease
<i>Most Frequently Reported TRAEs in ≥ 10% of Patients</i>				
Peripheral Edema	63 / 7	50 / 11	54 / 9	51 / 1 ^{b,c}
Nausea	26 / 1	36 / 1	46 / 0	41 / 0
Diarrhea	22 / 1	9 / 0	NR	39 / 0
Increased Creatinine	18 / 1	19 / 0	NR	NR
Hypoalbuminemia	16 / 2	NR	23 / 0	NR
Increased Amylase	11 / 3	8 / 4	NR	NR
Increased Lipase	9 / 3	9 / 7	NR	NR
Decreased Appetite	8 / 1	13 / 1	20 / 0	19 / 0
Fatigue	7 / 1	13 / 3	NR	23 / 0
Increased AST	7 / 2	6 / 3	37 / 13	17 / 4 ^{b,d}
Increased ALT	7 / 3	11 / 7	39 / 10	17 / 4 ^{b,d}

Maioria dos mecanismos de resistência a MET-TKI são *off-target*

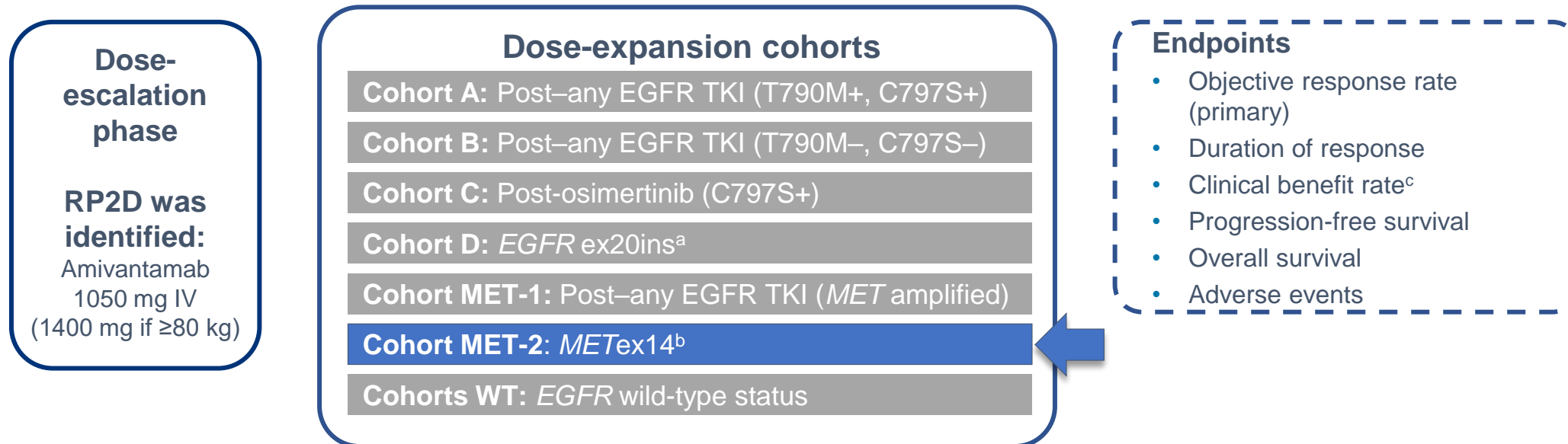


Mecanismos de resistência adquirida a MET-TKI



CHRYSALIS coorte METex14: desenho do estudo

- Fase I, aberto, multi-coorte – Escalonamento de dose (140-1750 mg) e coorte de expansão
- As of June 19, 2023, 97 patients had been enrolled in the *MET*ex14 cohort, with a median follow-up of 10.0 months



All cohorts are now closed

CHRYSALIS also included 2 additional combination cohorts:

- *Amivantamab + lazertinib*
- *Amivantamab + carboplatin-pemetrexed*

ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion mutation; IV, intravenous; MET, mesenchymal-epithelial transition factor; *MET*ex14, *MET* exon 14 skipping mutation; NGS, next-generation sequencing;

NSCLC, non-small cell lung cancer; RP2D, recommended phase 2 dose; SD, stable disease; TKI, tyrosine kinase inhibitor.

^aCohort D was presented at WCLC 2020 (Sabari, JK. *J Thorac Oncol.* 2021;16(3):S108-109. OA04.04).

^bPrimary *MET*ex14 mutation by NGS of tumor tissue or ctDNA; all patients must have failed or be ineligible for standard of care therapy.

^cPercentage of patients with confirmed response or SD of ≥11 weeks duration.

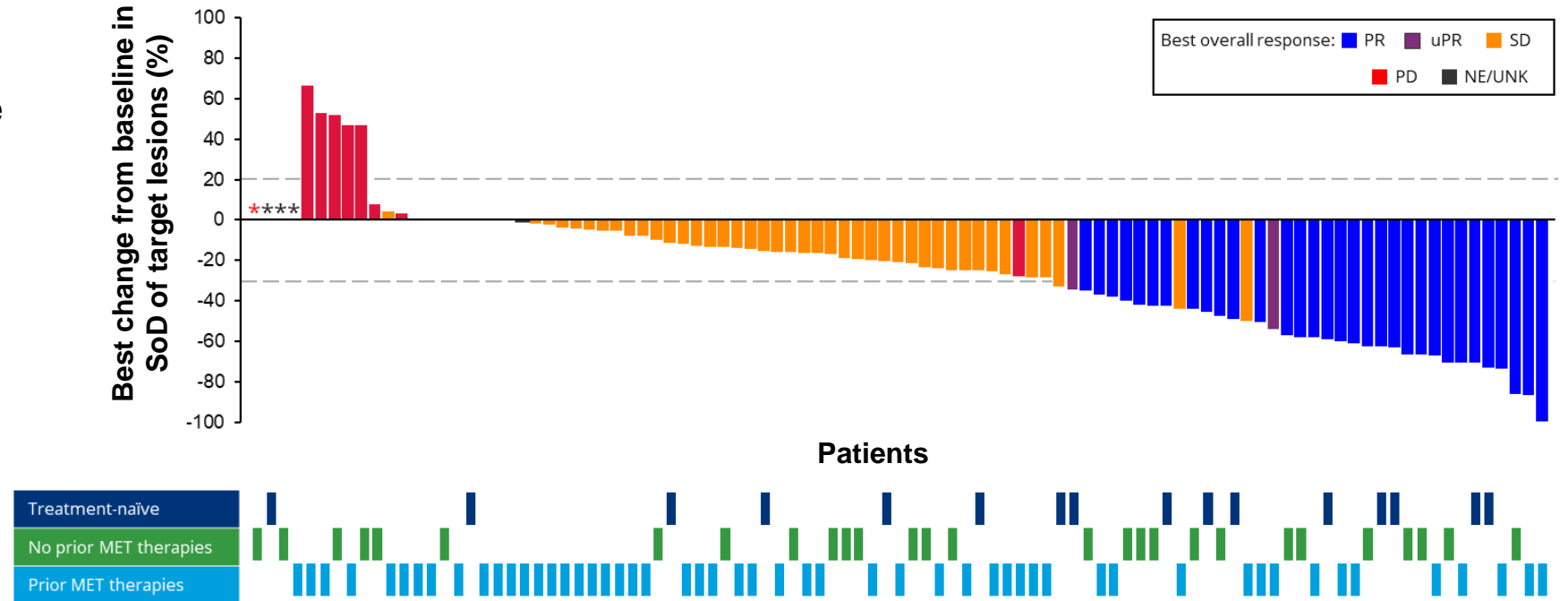
CHRYSALIS coorte METex14: características basais

Characteristic, n (%)	Treatment-naïve (n = 16)	Previously treated		Total (n = 97)
		No prior MET therapies (n = 28)	Prior MET therapies (n = 53)	
Median age, years (range)	70 (57–86)	69 (49–83)	71 (43–88)	70 (43–88)
Female / male	8 (50) / 8 (50)	15 (54) / 13 (46)	29 (55) / 24 (45)	52 (54) / 45 (46)
Race				
Asian	10 (63)	16 (57)	21 (40)	47 (49)
White	6 (38)	9 (32)	23 (43)	38 (39)
Black	0	0	2 (4)	2 (2)
Not reported	0	3 (11)	7 (13)	10 (10)
History of brain metastases	1 (6)	4 (14)	9 (17)	14 (14)
ECOG PS				
0	7 (44)	4 (14)	8 (15)	19 (20)
1	9 (56)	23 (82)	45 (85)	77 (79)
2	0	1 (4)	0	1 (1)
History of smoking: yes / no	10 (63) / 6 (38)	14 (50) / 14 (50)	26 (49) / 27 (51)	50 (52) / 47 (48)
Median number of prior lines (range)	0	1 (1–4)	3 (1–10)	2 (0–10)

CHRYSALIS coorte METex14: atividade anti-tumoral

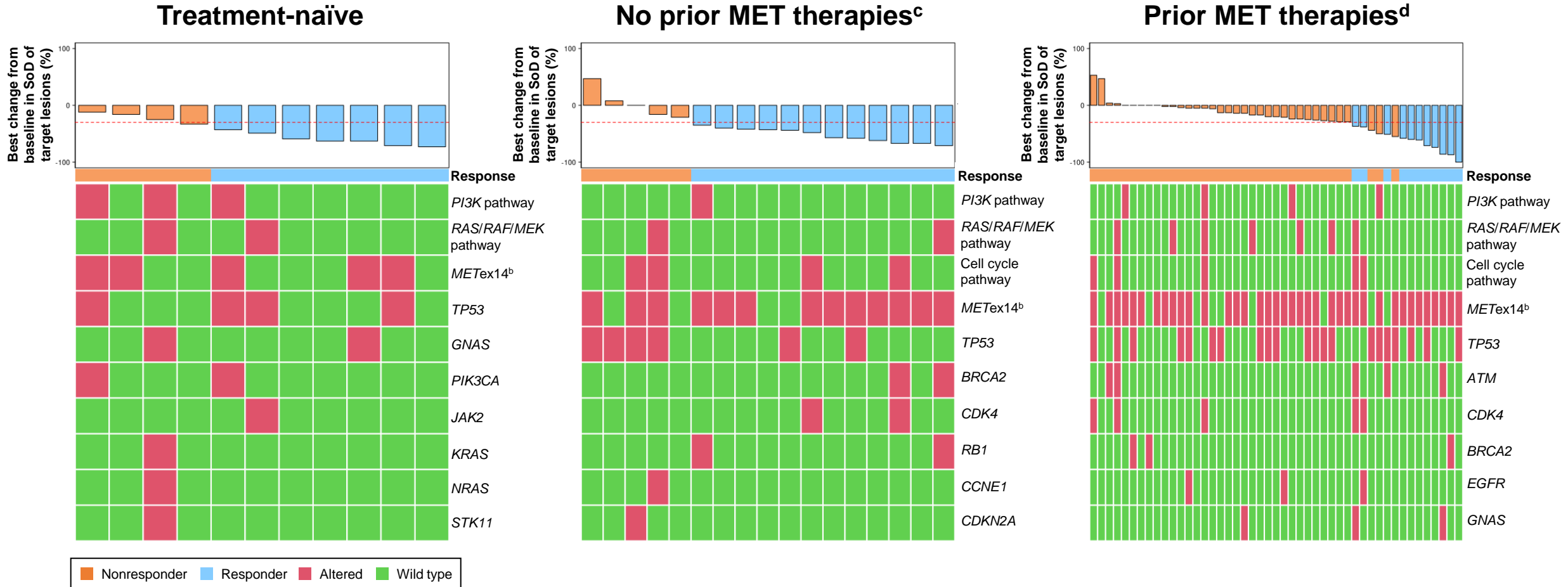
- The **ORR^a was 33%**, with a total of 32 PRs observed
- Responses to amivantamab were observed in both treatment-naïve and prior treatment settings
 - Treatment-naïve:
8 PRs / 16; **ORR^a = 50%**
 - No prior MET therapies:
13 PRs / 28; **ORR^a = 46%**
 - Prior MET therapies:
11 PRs / 53; **ORR^a = 21%**

Best change from baseline in SoD of target lesions



Comutações não se associaram com resposta

- Amivantamab activity did not correlate with any co-occurring genomic alterations detected by ctDNA^a



ctDNA, circulating tumor DNA; MET, mesenchymal-epithelial transition factor; METex14, MET exon 14 skipping mutation; NGS, next-generation sequencing; SoD, sum of diameters.

^aThe top 10 most common pathways/alterations for each subgroup are shown. ^bAll patients had primary METex14 mutation confirmed by NGS of tumor tissue or ctDNA. ^cAdditional alterations not shown included ERBB2, KRAS, and PIK3CA. ^dAdditional alterations not shown included MET amplification, MET D1228N, MET Y1230C, MET Y1230S, CCND1, KIT, KRAS, PIK3CA, PTEN, RB1, ALK, ERBB2, and FGFR3.

Perfil de segurança

AEs (≥20%) by preferred term, n (%)	Median follow-up: 10.0 months (n = 97)	
	Total	Grade ≥3
Associated with EGFR inhibition		
Paronychia	47 (48.5)	0
Dermatitis acneiform	40 (41.2)	1 (1.0)
Rash	37 (38.1)	1 (1.0)
Stomatitis	27 (27.8)	0
Pruritus	20 (20.6)	0
Associated with MET inhibition		
Hypoalbuminemia	37 (38.1)	2 (2.1)
Peripheral edema	36 (37.1)	4 (4.1)
Other		
Infusion-related reaction	70 (72.2)	4 (4.1)
Fatigue	28 (28.9)	2 (2.1)
Dyspnea	22 (22.7)	5 (5.2)
Hypokalemia	22 (22.7)	3 (3.1)
Nausea	21 (21.6)	0
Decreased appetite	21 (21.6)	0
Alanine aminotransferase increased	20 (20.6)	2 (2.1)
AEs of special interest by grouped term, n (%)		
Rash ^a	76 (78.4)	3 (3.1)
Venous thromboembolism ^b	8 (8.2)	2 (2.1)
Interstitial lung disease ^c	4 (4.1)	1 (1.0)

- The majority of AEs were grade 1 to 2
- Treatment-related dose interruptions, reductions, and discontinuations of amivantamab were seen in 24 (24.7%), 12 (12.4%), and 9 (9.3%) patients, respectively
- Cumulative grouped rash^a AEs occurred in 76 (78.4%) patients, with 3 (3.1%) grade ≥3
- Treatment-emergent VTE^b events were reported by 8 (8.2%) patients, with 2 (2.1%) grade ≥3 (none were grade 5)
- ILD^c was seen in 4 (4.1%) patients, of which 1 (1.0%) was grade 3
- No new safety signals were found

AE, adverse event; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; MET, mesenchymal-epithelial transition factor; *MET*_{ex14}, *MET* exon 14 skipping mutation; VTE, venous thromboembolism.

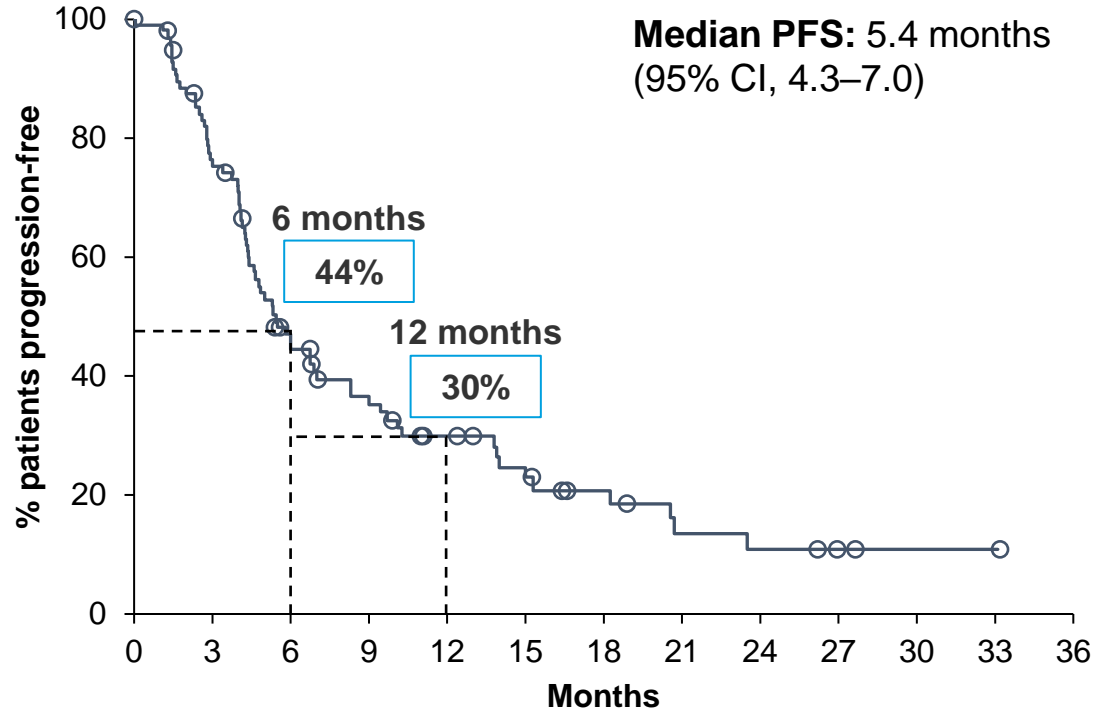
^aGrouping includes the following related preferred terms: dermatitis acneiform, rash, folliculitis, rash maculo-papular, skin exfoliation, rash pustular, skin lesion, dermatitis, dermatitis exfoliative generalized, dermatitis infected, erythema, rash erythematous, rash pruritic.

^bGrouping includes the following related preferred terms: pulmonary embolism, deep vein thrombosis, embolism; anticoagulant use for either VTE prophylaxis (1/97 [1.0%]) or medical history of VTE (0/97) was infrequent.

^cGrouping includes the following related preferred terms: ILD and pneumonitis.

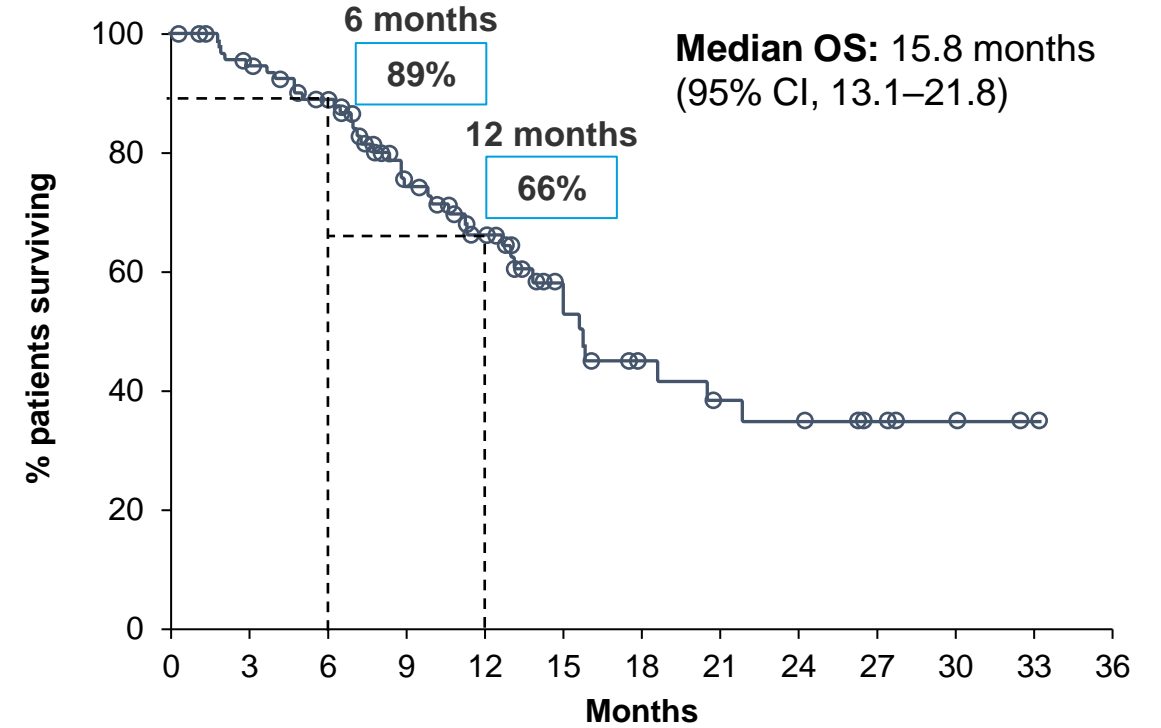
Amivantamabe – Sobrevida Global e Livre de Progressão

PFS (n = 97)



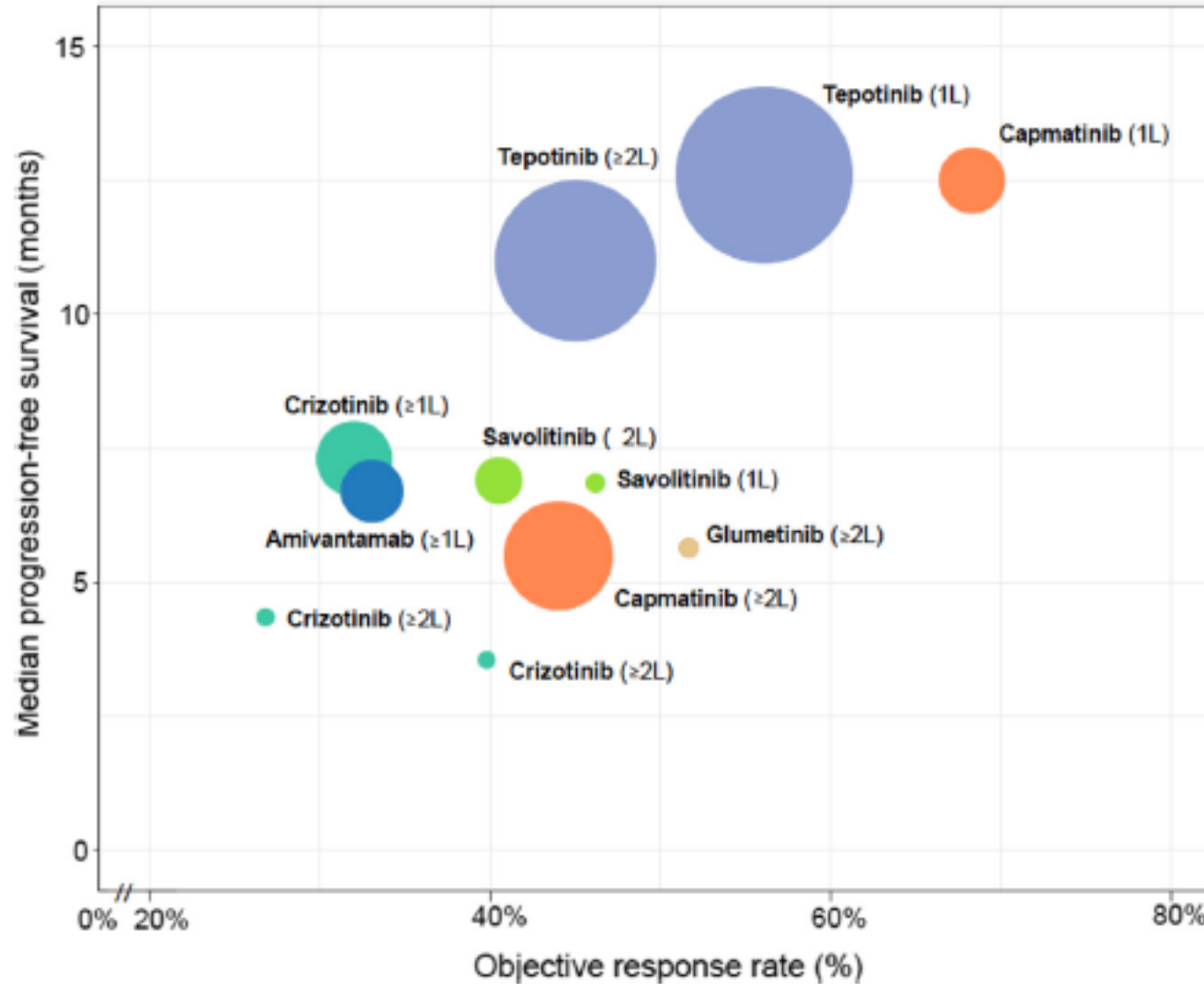
No. at risk	97	69	36	27	19	14	9	5	4	2	1	1	0
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OS (n = 97)



No. at risk	97	87	77	51	38	22	14	11	10	6	2	1	0
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Comparação da atividade das diversas terapias para CPCNP metastático com mutação METex14 skipping



- Mutações *METex14 skipping* são identificadas em 3 a 4% dos CPCNP e estão associadas, em algumas coortes, a pior prognóstico.
- Crizotinibe apresenta atividade limitada contra esses tumores (não aprovado para essa indicação).
- Capmatinibe e tepotinibe estão aprovados no Brasil e apresentam taxa de resposta que varia entre 68% (capmatinibe em primeira linha) a 43% (tepotinibe).
- Savolitinibe e amivantamabe também apresentam atividade contra estes tumores (ainda não aprovados).
- Edema periférico e sintomas gastrointestinais são os efeitos adversos mais comuns.
- Teliso-V (ADC) a caminho – resultados animadores com o fase II – LUMINOSITY (amplificação de MET).



Obrigado!

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GERENCIAMENTO E PRODUÇÃO

