15th CONGRESS on Lung CANCER

MADRID

23&24 November 2023

#15CongressGECP

Fundación GECP lung cancer research

Sesión IX: What other new targets are coming?

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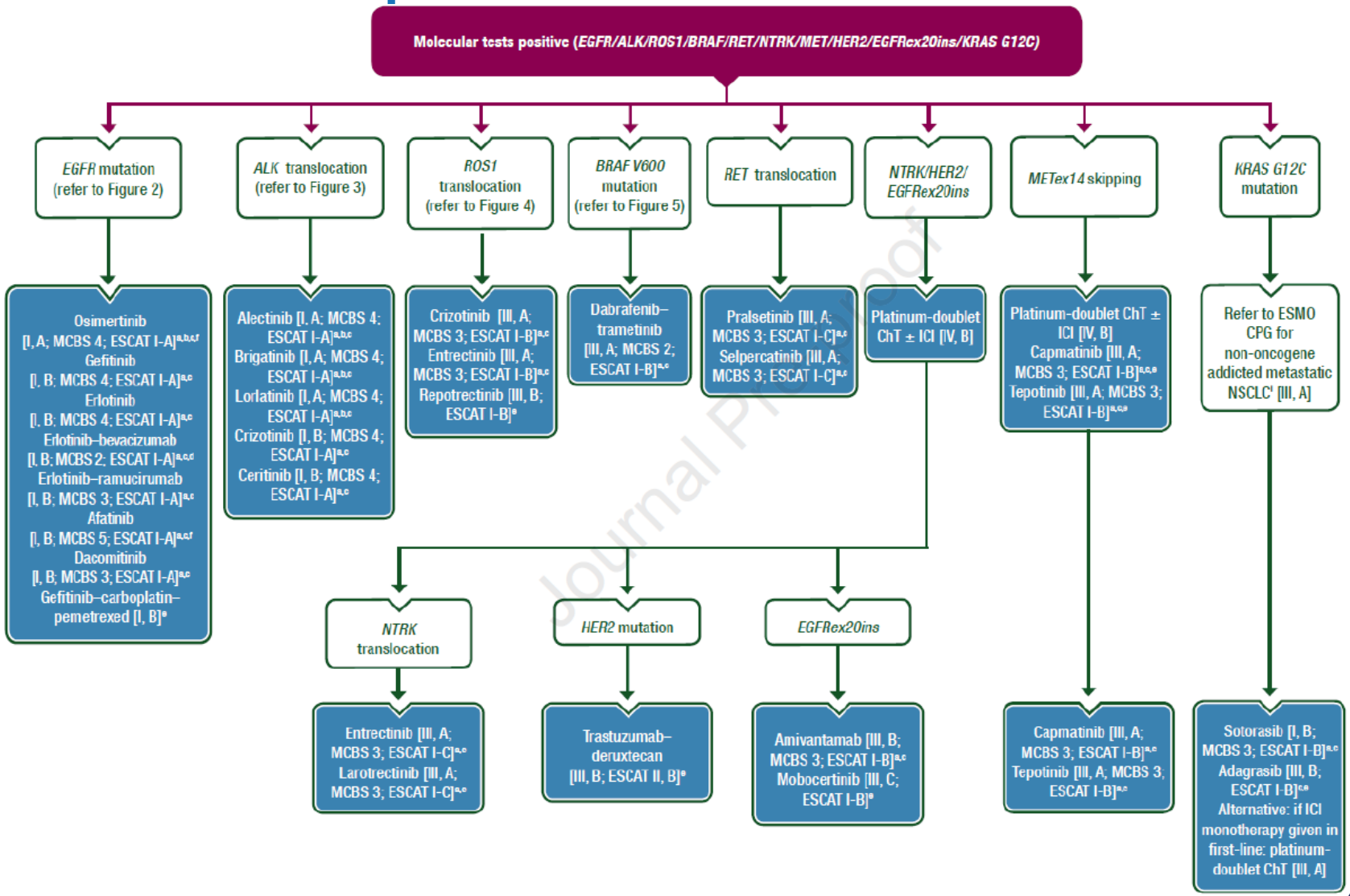
Disclosure

- Educational fees: Astra Zeneca,, Merck Sharp and Dohme, and Roche.

- Consultancy/Advisoryboard: Astra Zeneca, Merck Sharp and Dohme, Novartis, Sanofi

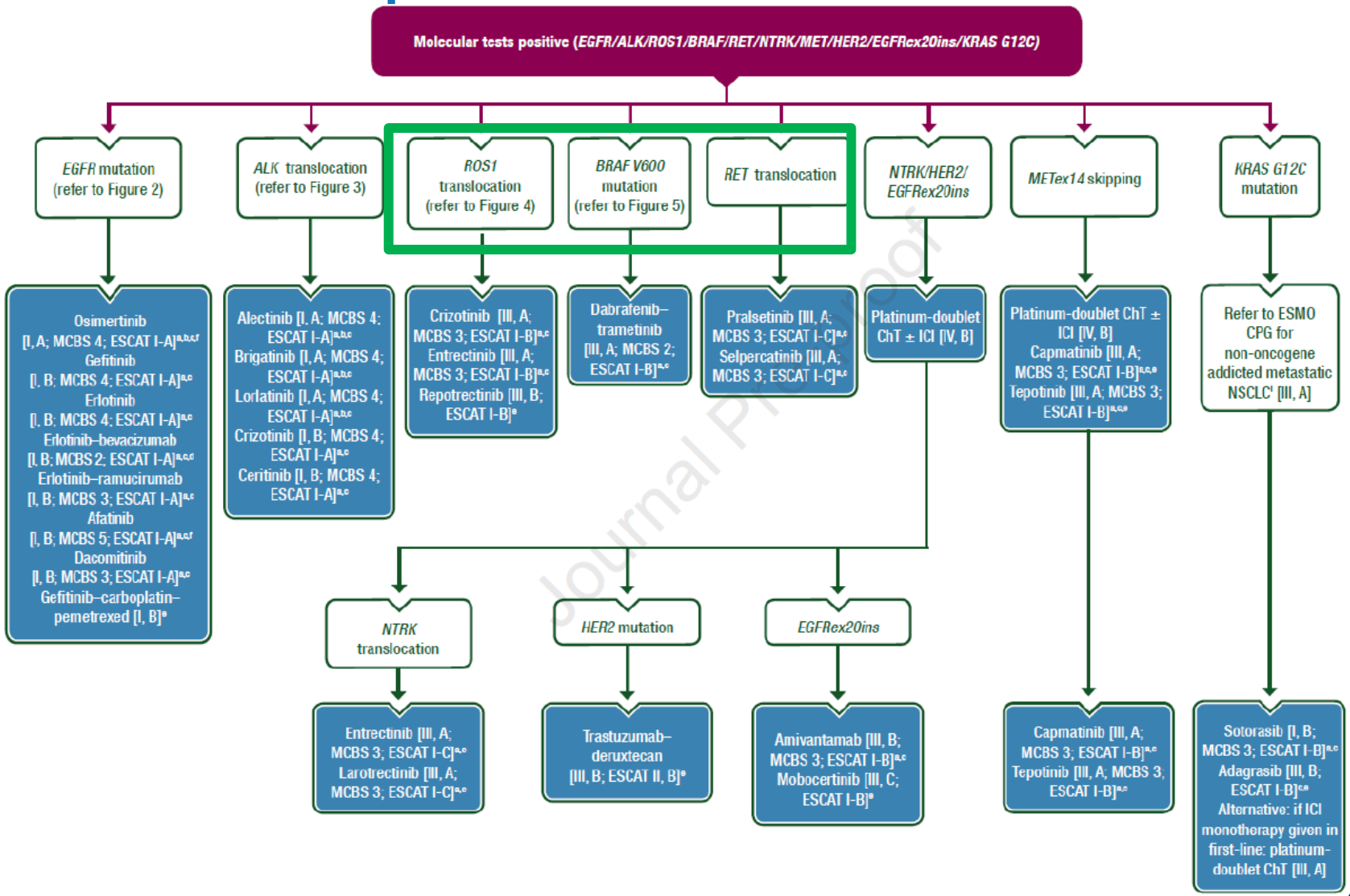
- Presenter/Speaker bureau: Astra Zeneca, Gilead, Roche, Merck Sharp and Dohme, Pfizer, Sanofi, Takeda

Molecular biomarker positive advanced NSCLC



Annals of Oncol 2023 S0923 7534(22)04781-0

Molecular biomarker positive advanced NSCLC



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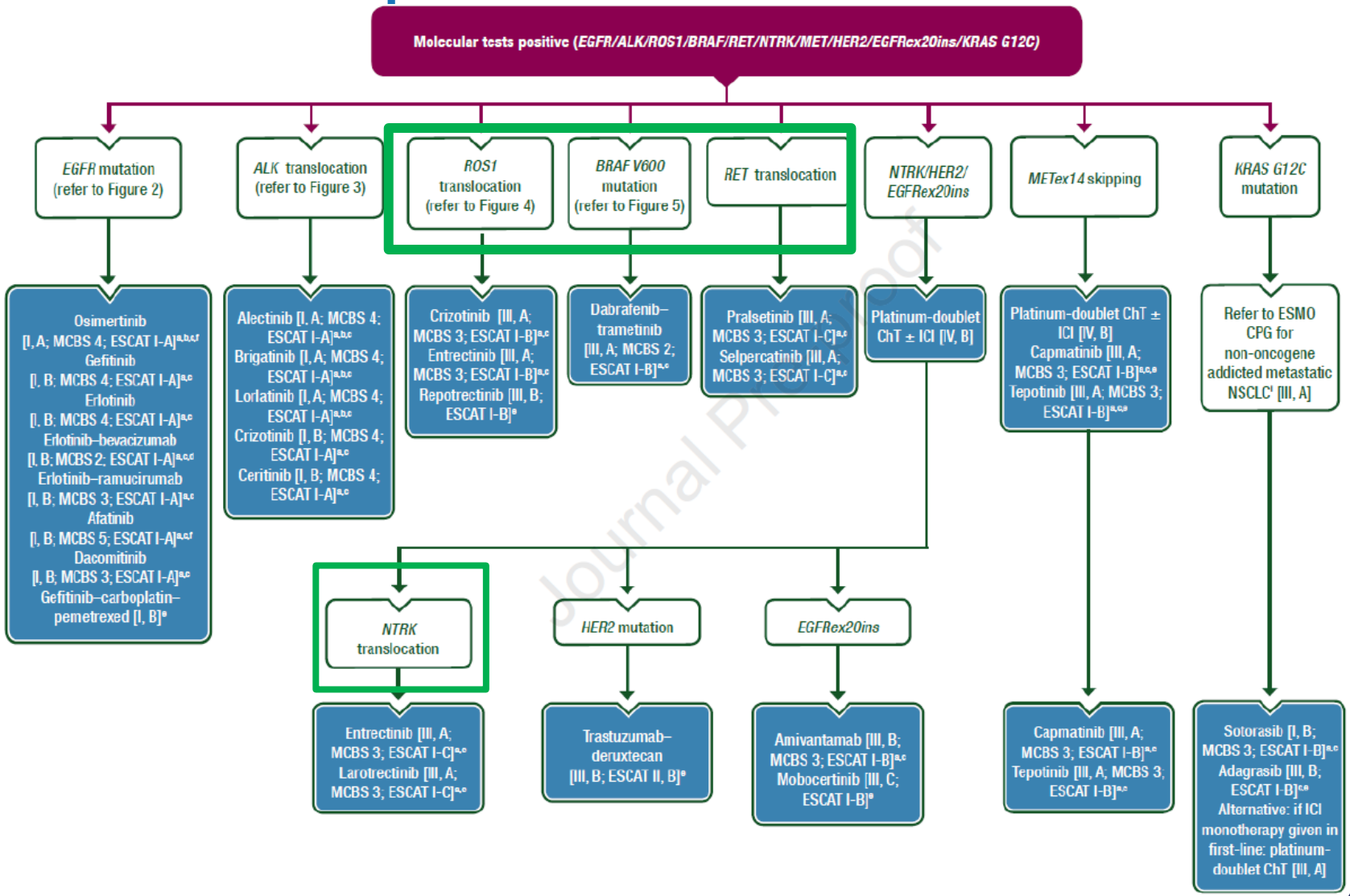
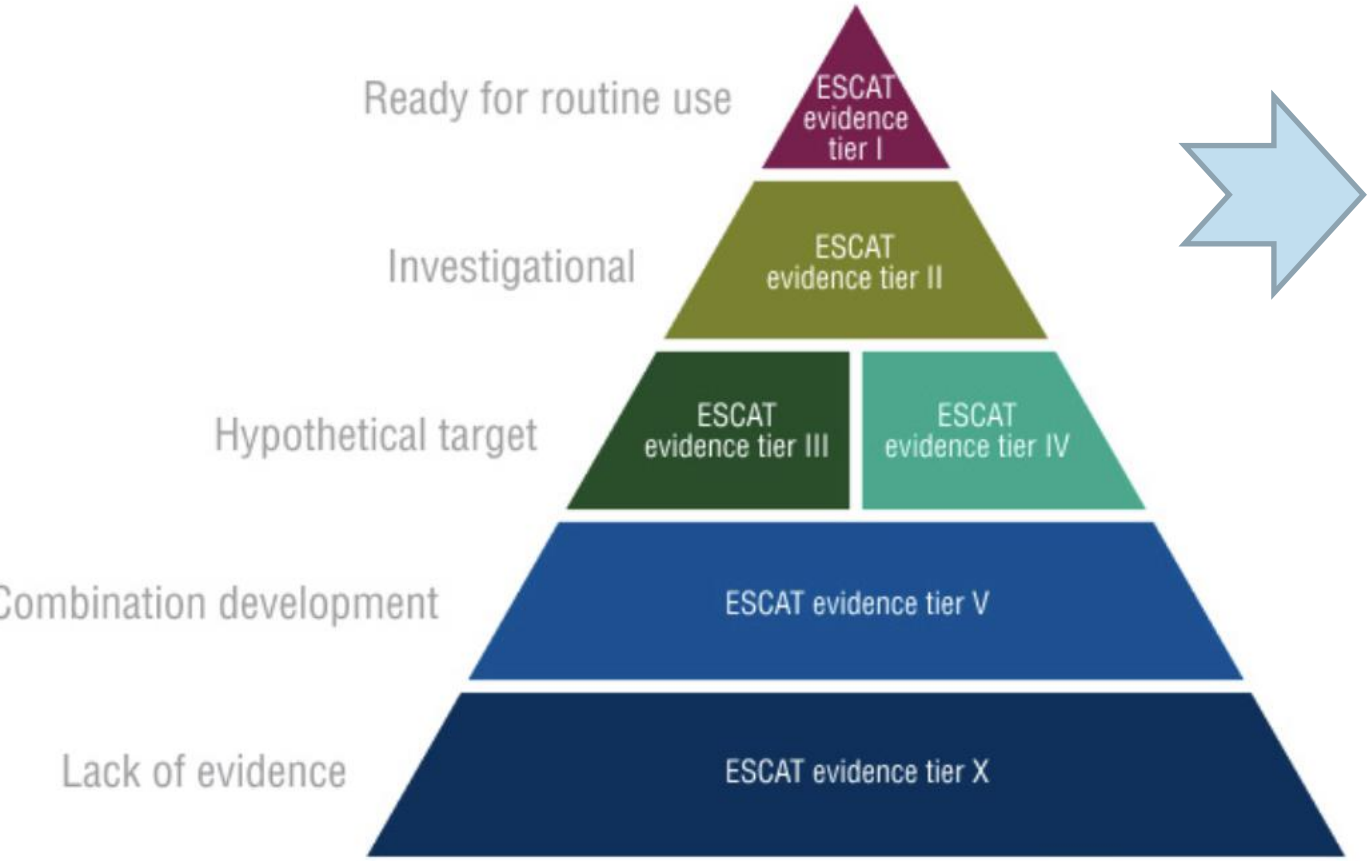
Molecular biomarker positive advanced NSCLC



Annals of Oncol 2023 S0923 7534(22)04781-0

ESMO Scale of Clinical Actionability for molecular Targets (ESCAT)

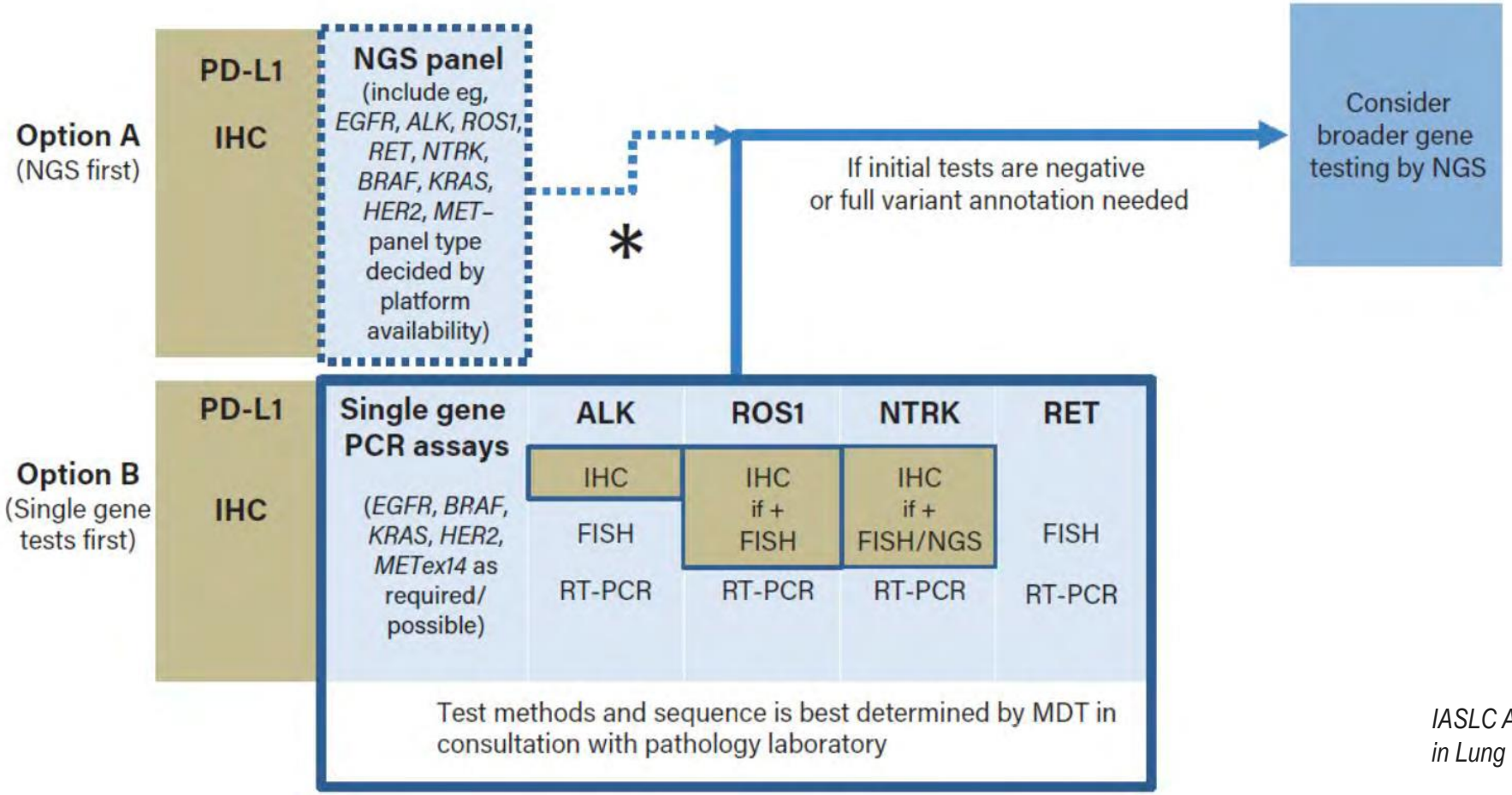


Gene	Alteration	ESCAT
	ESCAT TIER EVIDENCE I	
EGFR	Common mutations (Del19, L858R)	IA
	Acquired T790M exon 20	IA
	Uncommon (G719X exon 18, L861Q exon 21, S768I exon 20)	IB
ALK	Fusions (mutations as mechanism of resistance)	IA
MET	Mutations ex 14 skipping	IB
$BRAF^{v600}$	Mutations	IB
ROS1	Fusions (mutations as mechanism of resistance)	IB
NTRK	Fusions	IC
RET	Fusions	IC
	ESCAT TIER EVIDENCE II-III	
$KRAS^{G12C}$	Mutations	IIB
EGFR	Exon 20 insertion	IIB
ERBB2	Hotspot mutations and Amplifications	IIB
MET	Focal amplifications (acquired resistance on EGFR TKI)	IIB
BRCA 1/2	Mutations	IIIA
PIK3CA	Hotspot mutations	IIIA
NRG1	Fusions	IIIB

MoseleF., et al. Ann Oncol.2020

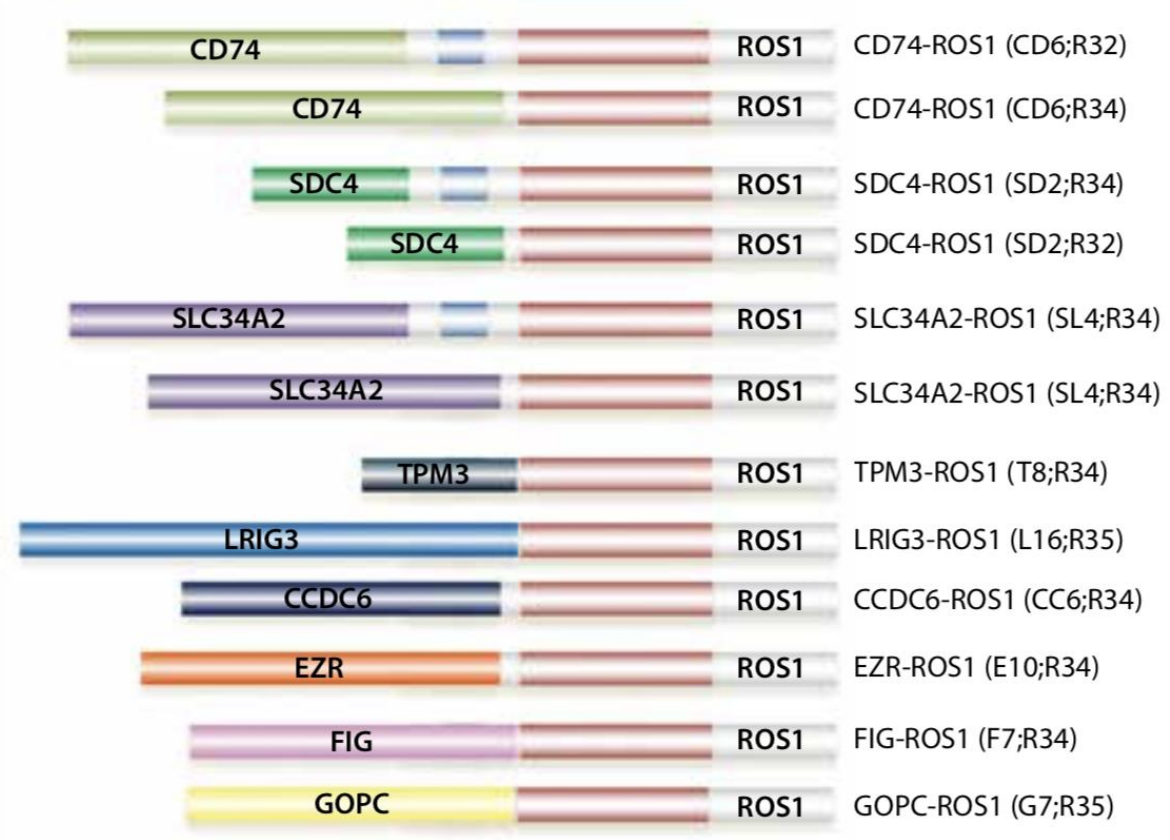
Diagnostic

Implement sensible workflows with several feed-back loops



IASLC Atlas of Molecular Testing for Targeted Therapy in Lung Cancer. 2023

ROS 1



Paciente mas joven. (54ª)
Adenocarcinoma 98%
No fumador
Histología: Células en anillo de sello

DrilonA et al. Nat Rev ClinOncol. 2021 Jan;18(1):35-55.

ROS 1

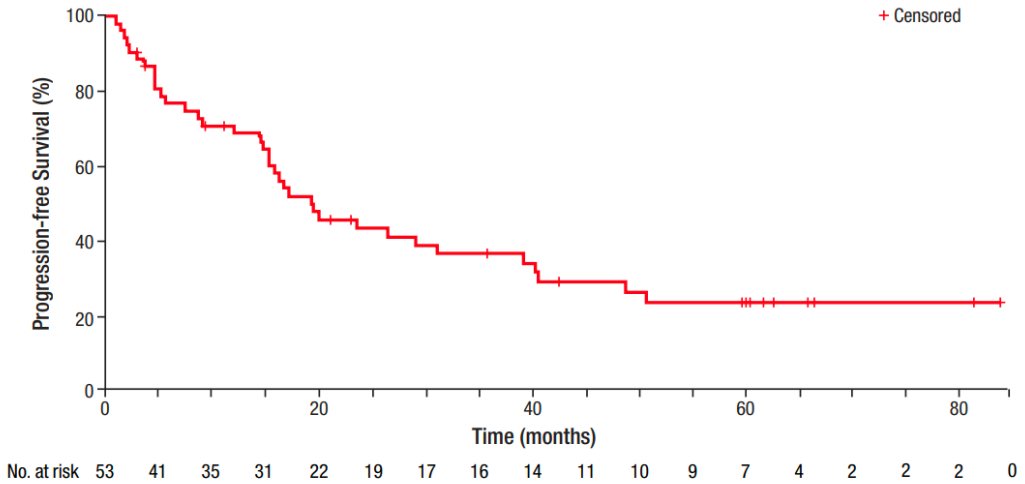
Crizotinib. PROFILE 1001

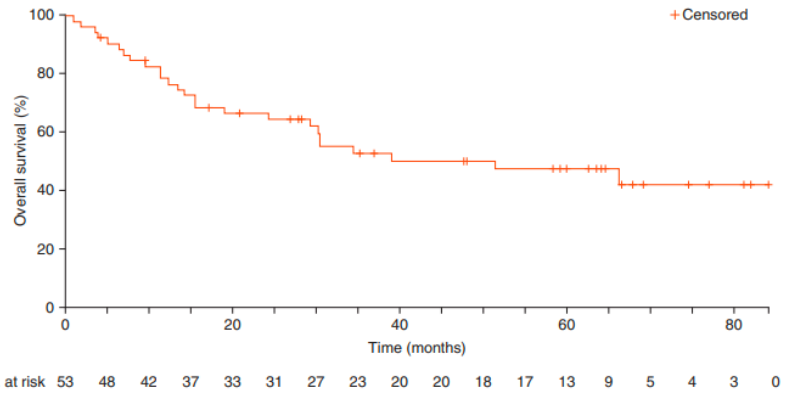
ORR 72%

Table 2. Antitumor activity end points

End points	*ROS1*-rearranged NSCLC (*N* = 53)
ORR, % (95% CI)[a]	72 (58–83)
CR, *n* (%)	6 (11)
PR, *n* (%)	32 (60)
SD (≥6 weeks), *n* (%)	10 (19)
PD, *n* (%)	3 (6)
Not evaluated[b]	2 (4)
Median time to first tumor response, weeks (range)[c]	7.9 (4.3–103.6)
Median duration of response, months (95% CI)[d,e]	24.7 (15.2–45.3)
Median PFS, months (95% CI)[d,f]	19.3 (15.2–39.1)

PDF 19.3m





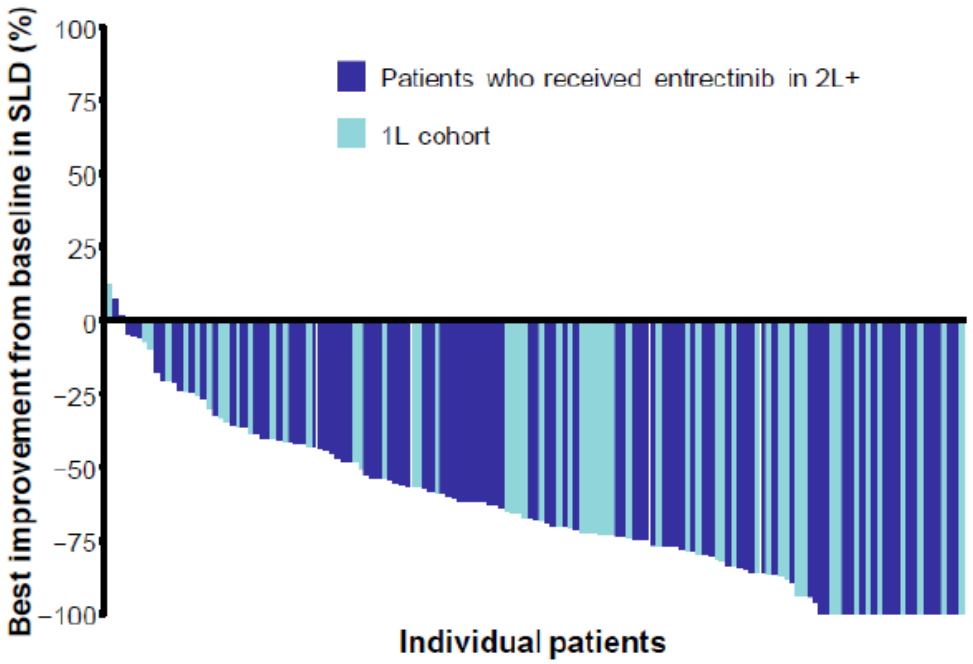
OS 51 meses

Figure 1. Overall survival. Shown is the Kaplan–Meier curve estimating overall survival (OS) among the 53 ROS1-positive NSCLC patients treated with crizotinib in PROFILE 1001. After a median follow-up of 62.6 months, median OS was 51.4 months. Vertical lines on the curve indicate censoring of data.

ROS 1

Entrectinib STARTRKn1-2 Trial

Entrectinib demonstrated robust and durable responses regardless of baseline CNS status



ORR 67%

	Overall efficacy population (N=172)	Baseline CNS metastases* (n=60)	No baseline CNS metastases* (n=112)	First-line population† (n=67)
ORR, n (%) [95% CI]	**116 (67.4) [59.9–74.4]**	**38 (63.3) [49.9–75.4]**	**78 (69.6) [60.2–78.0]**	**46 (68.7) [56.2–79.4]**
CR	23 (13.4)	4 (6.7)	19 (17.0)	10 (14.9)
PR	93 (54.1)	34 (56.7)	59 (52.7)	36 (53.7)
SD	16 (9.3)	6 (10.0)	10 (8.9)	7 (10.4)
PD	16 (9.3)	8 (13.3)	8 (7.1)	5 (7.5)
Non CR / PD	10 (5.8)	2 (3.3)	8 (7.1)	6 (9.0)
Missing / unevaluable	14 (8.1)	6 (10.0)	8 (7.1)	3 (4.5)
Median DoR, months [95% CI]	**20.4 [14.8–34.8]**	**14.6 [11.0–20.4]**	**28.6 [14.9–38.6]**	**35.6 [13.9–38.8]**

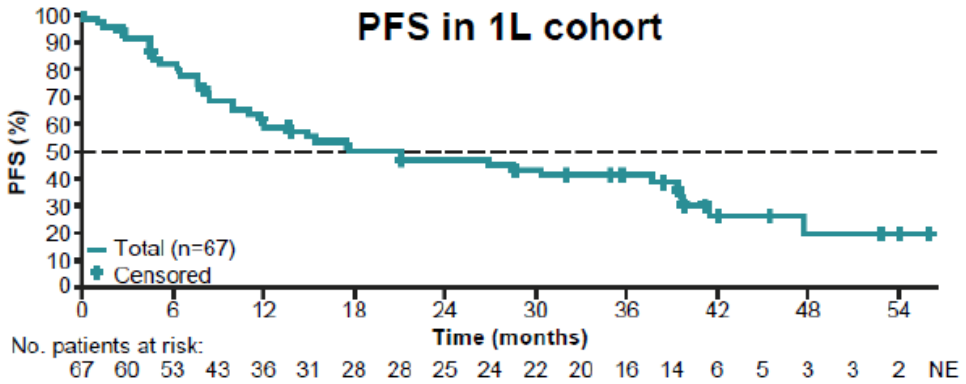
Fan Y, WCLC 2022

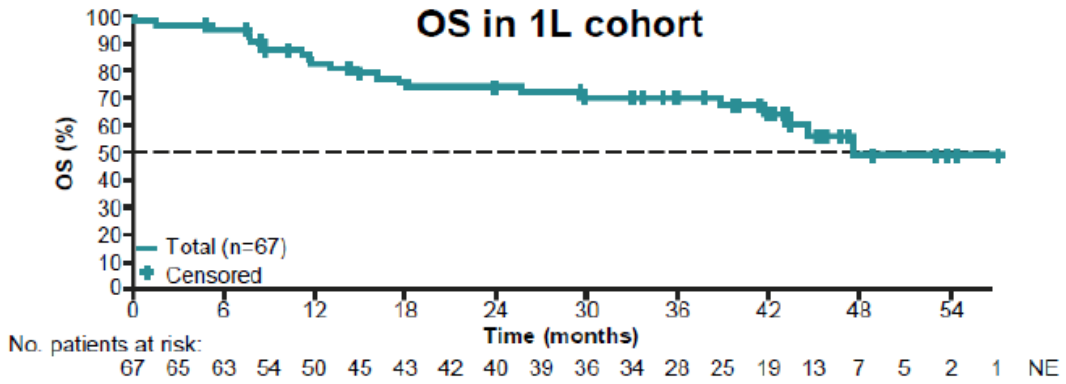
ROS 1

Entrectinib STARTRKn1-2 Trial

PFS 16.8%

	Overall efficacy population (N=172)	Baseline CNS metastases* (n=60)	No baseline CNS metastases* (n=112)	First-line population† (n=67)
Median PFS, months [95% CI]	**16.8** [12.2–22.4]	**11.8** [7.2–15.7]	**25.2** [15.7–36.6]	**17.7** [11.8–39.4]
Median OS, months [95% CI]	**44.1** [40.1–NE]	**28.3** [17.0–44.6]	**NE** [41.8–NE]	**47.7** [43.2–NE]





Data cut-off: 02 Aug 2021. *Investigator-assessed CNS metastases; †Exploratory analysis.
OS, overall survival; PFS, progression-free survival

Intracranial efficacy	Overall efficacy population (n=51)*	First-line cohort (n=23)*†
IC-ORR, n (%) [95% CI]	**25 (49.0)** [34.8–63.4]	**14 (60.9)** [38.5–80.3]

Fan Y, WCLC 2022

ROS 1

Entrectinib STARTRKn1-2 Trial

Entrectinib had a manageable safety profile in patients with *ROS1* fusion-positive NSCLC

- The **most frequent TRAEs** were **dysgeusia** (43%), **weight increase** (38%), **dizziness** (35%), **constipation** (32%) and **diarrhea** (30%)
- **TRAEs** led to **dose interruption, reduction** and **discontinuation** in **36%**, **35%** and **7%** of patients, respectively

N (%)	Safety population (N=247)
Patients with TRAE	234 (95)
Patients with serious TRAE	35 (14)
Patients with Grade ≥3 TRAE	107 (43)
Patients with TRAE leading to dose interruption	89 (36)
Patients with TRAE leading to dose reduction	86 (35)
Patients with TRAE leading to discontinuation	17 (7)
Patients with AE leading to death	16 (6)
Patients with TRAE leading to death	1 (<1)

Data cut-off: 02 Aug 2021.
AE, adverse event; TRAE, treatment-related adverse event

Fan Y, WCLC 2022

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Por fin aprobado en España 1/12/2023

Data cut-off: 02 Aug 2021.
AE, adverse event; TRAE, treatment-related adverse event

Fan Y, WCLC 2022

ROS 1

Lorlatinib

N= 69 (54 yr, 57%F)

TKI naive

N=21

ORR 62%

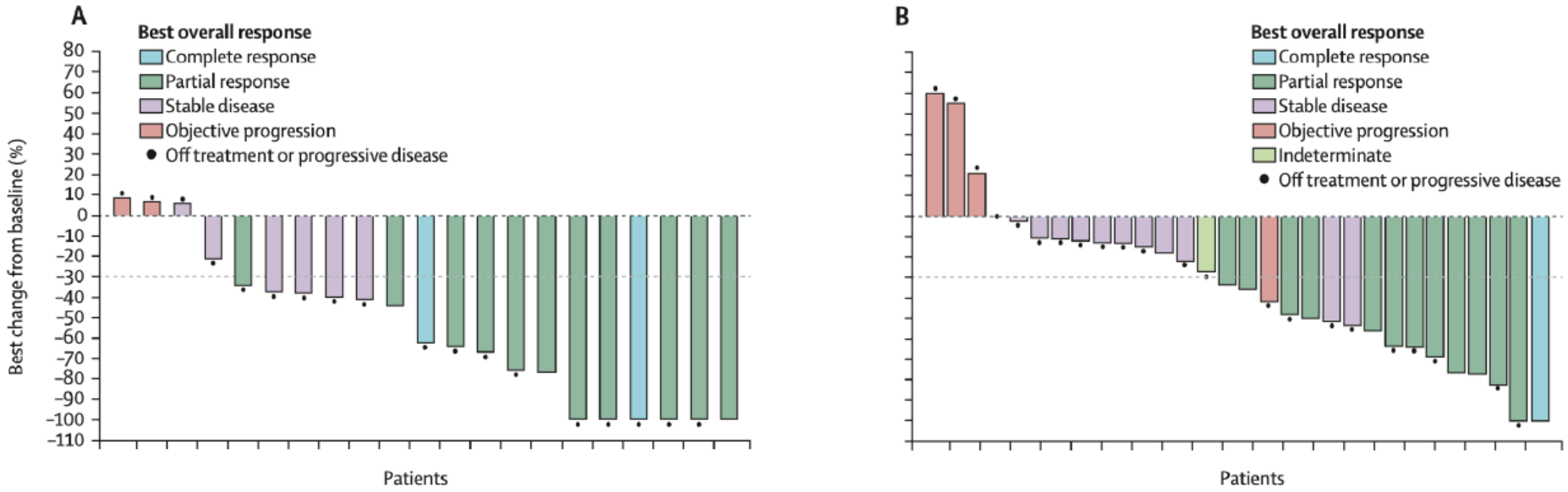
DoR: 25.3 m

Preview crizo only

N= 40

ORR 35%

DoR 13.8 m



Shaw A. Lancet Oncol2018

ROS 1

Lorlatinib

Effect according to resistant mutation

	TKI-naive*	Any previous ROS1 TKI†	
		No mutations	≥1 mutation
Circulating free DNA			
Number of patients with analysable samples	17	33	6
Best overall response			
Complete response	2 (12%)	1 (3%)	0
Partial response	8 (47%)	8 (24%)	0
Stable disease	5 (29%)	14 (42%)	5 (83%)
Objective progression	2 (12%)	4 (12%)	1 (17%)
Indeterminate‡	0	6 (18%)	0
Responders	10 (59%)	9 (27%)	0
Tumour tissue (de novo)			
Number of patients with analysable samples	7	11	5
Best overall response			
Complete response	1 (14%)	0	0
Partial response	4 (57%)	1 (9%)	2 (40%)
Stable disease	2 (29%)	6 (55%)	3 (60%)
Objective progression	0	2 (18%)	0
Indeterminate‡	0	2 (18%)	0
Responders	5 (71%)	1 (9%)	2 (40%)

Data are n (%) unless otherwise specified. TKI=tyrosine kinase inhibitor.
*All TKI-naive patients had no mutations. †Includes patients treated with

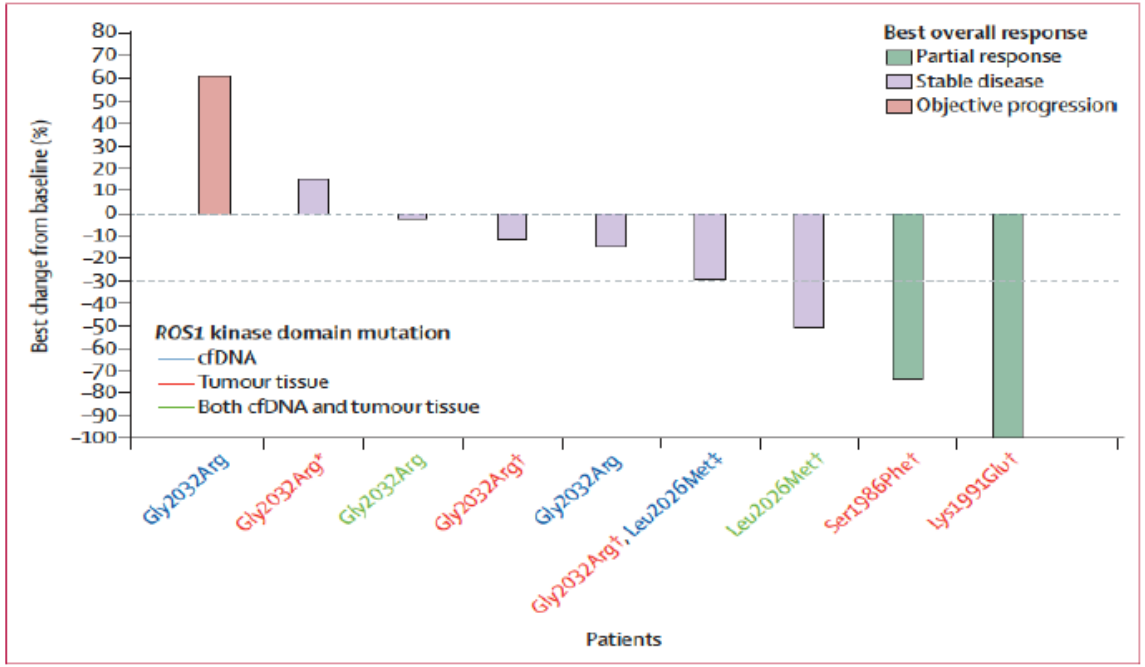
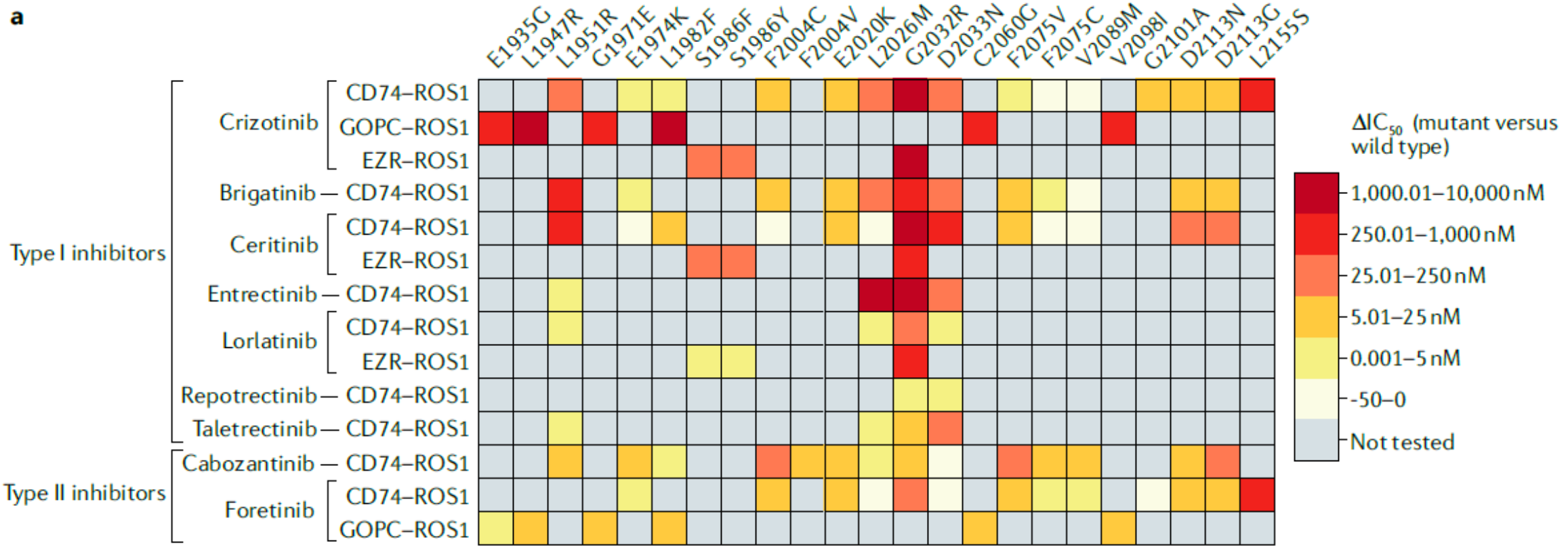


Figure 2: **Best percentage change in tumour size from baseline in patients with at least one *ROS1* kinase domain mutation in cfDNA or tumour tissue (archival or de-novo)**
All patients had received prior crizotinib. The dashed line shows a 30% reduction in target lesions, which is the threshold for partial response. cfDNA=circulating free DNA. *Patient previously received crizotinib and DS6051B. †*ROS1* mutation found in de-novo tumour sample. §Patient previously received crizotinib and ceritinib, and also had the silent Ile2025Ile mutation in cfDNA.

Shaw A. Lancet Oncol2018

ROS 1

***On**-target resistance (ROS1-dependent): ROS kinase domain point mutations*



DrilonA et al. Nat Rev ClinOncol. 2021 Jan;18(1):35-55.

ROS 1

Repotrectinib : TRIDENT-- 1 Trial

Metástasis cerebrales incluibles

Phase 1/2 patient eligibility

- Locally advanced or metastatic solid tumors harboring *ROS1* or *NTRK1-3* gene fusion
- Treated or untreated asymptomatic CNS metastases and/or leptomeningeal carcinomatosis allowed

Phase 1[a] dose escalation cohorts

RP2D
160 mg QD x 14 days, then 160 mg BID[b]

Phase 2 dose expansion cohorts

ROS1+ advanced NSCLC

TKI-pretreated (EXP-2, -3, and -4)

EXP-1	EXP-2	EXP-3	EXP-4
ROS1 TKI-naïve	1 prior ROS1 TKI AND 1 prior platinum-based chemo	2 prior ROS1 TKIs AND no prior chemo	1 prior ROS1 TKI AND no prior chemo
(n = 110)[c]	(n = 60)[c]	(n = 40)[c]	(n = 60)[c]

- MRI was mandated for all patients with and without baseline brain metastases in phase 2 at screening and at protocol-specified intervals until progression
- Primary efficacy population includes patients pooled from phases 1[e] and 2 that began repotrectinib treatment at least 8 months before data cutoff date of June 20, 2022

Phase 2 (*ROS1*+ advanced NSCLC cohorts)

Primary endpoint

cORR by BICR using RECIST v1.1

Key secondary endpoint

icORR by mRECIST v1.1 in patients with measurable brain metastases

Data cutoff date: June 20, 2022.

[a]Phase 1 primary endpoints: DLT, MTD, RP2D. [b]Based on tolerability. [c]N's for expansion cohorts indicate enrollment targets. [d]MRI brain scans performed at Cycle 3 day 1 (± 7 days), every 2 cycles (± 7 days) up to Cycle 19 and then every 3 cycles (± 7 days) up to Cycle 37 and then every 4 cycles (± 7 days); brain CT was acceptable if brain MRI was contraindicated. [e]Patients from phase 1 received 40 mg QD to 160 mg QD and 160 mg BID. [f]By RECIST v1.1.

Lin et al. ASCO 2023

ROS 1

Repotrectinib : TRIDENT-- 1 Trial

	ROS1 TKI-naïve (n = 71)	1 prior ROS1 TKI AND no prior chemo (n = 56)	1 prior ROS1 TKI AND 1 prior platinum-based chemo (n = 26)	2 prior ROS1 TKIs AND no prior chemo (n = 18)
Median follow-up, months	18.1	15.5	21.3	14.1
Patients with CNS mets,[a] n (%)	18 (25)	24 (43)	10 (38)	8 (44)
cORR,[b] % (95% CI)	89 (65-99)	33 (16-55)	40 (12-74)	12 (0.3-53)
CR, n (%)	1 (6)	0 (0)	0 (0)	1 (12)
PR, n (%)	15 (83)	8 (33)	4 (40)	0 (0)
SD,[b] n (%)	1 (6)	11 (46)	3 (30)	1 (12)
DOR,[c] % (95% CI)				
≥ 6 months	100 (100-100)	62 (29-96)	50 (1-99)	100 (100-100)
≥ 12 months[d]	93 (79-100)	–	–	–
PFS,[c] % (95% CI)				
≥ 6 months	94 (83-100)	57 (35-78)	40 (10-70)	12 (0-35)
≥ 12 months[d]	87 (71-100)	–	–	–
Patients without CNS mets, n (%)	53 (75)	32 (57)	16 (62)	10 (56)
cORR,[b] % (95% CI)	75 (62-86)	41 (24-59)	44 (20-70)	40 (12-74)
CR, n (%)	3 (6)	3 (9)	1 (6)	0 (0)
PR, n (%)	37 (70)	10 (31)	6 (38)	4 (40)
SD,[b] n (%)	10 (19)	14 (44)	5 (31)	2 (20)
DOR,[c] % (95% CI)				
≥ 6 months	87 (77-98)	92 (76-100)	71 (38-100)	50 (1-99)
≥ 12 months[d]	84 (72-96)	–	–	–
PFS,[c] % (95% CI)				
≥ 6 months	90 (81-98)	75 (59-91)	38 (12-63)	30 (2-58)
≥ 12 months[d]	77 (65-89)	–	–	–

ORR 89%

ORR 75%

ORR 12%
Solo 12 pacientes

ORR 40%

[a]Including patients with measurable and non-measurable lesions. [b]By RECIST v1.1. [c]DOR and PFS were calculated by Kaplan-Meier estimates. [d]Not reported for TKI-pretreated cohorts due to small number of patients at risk.

Lin et al. ASCO 2023

ROS 1

Repotrectinib : TRIDENT-- 1 Trial

	ROS1 TKI-naïve	1 prior ROS1 TKI AND no prior chemo
Patients with CNS metastases at baseline, n	18	24
Measurable, n	8	12
icORR,[b] % (95% CI)	88 (47-100)[a,c]	42 (15-72)
CR, n (%)	1 (12)	0
PR, n (%)	6 (75)	5 (42)

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≥ 6 months	100 (100-100)	62 (29-96)	50 (1-99)	100 (100-100)
≥ 12 months[d]	93 (79-100)	–	–	–
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PFS,[c] % (95% CI)				
≥ 6 months	90 (81-98)	75 (59-91)	38 (12-63)	30 (2-58)
≥ 12 months[d]	77 (65-89)	–	–	–

ORR 89%

ORR 75%

ORR 12% Solo 12 pacientes

ORR 40%

[a]Including patients with measurable and non-measurable lesions. [b]By RECIST v1.1. [c]DOR and PFS were calculated by Kaplan-Meier estimates. [d]Not reported for TKI-pretreated cohorts due to small number of patients at risk.

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ROS 1

Repotrectinib : TRIDENT-- 1 Trial. Safety and BM protection

TRIDENT-1: repotrectinib in *ROS1*+ NSCLC with/without CNS metastases

Safety summary in patients with *ROS1*+ NSCLC with or without baseline CNS metastases per investigator assessment[a]

	With baseline CNS metastases (n = 118)		Without baseline CNS metastases (n = 178)	
AE, n (%)	TEAEs	TRAEs	TEAEs	TRAEs
Any AEs	116 (98)	109 (92)	178 (100)	169 (95)
Any grade ≥ 3 AEs	52 (44)	27 (23)	96 (54)	41 (23)
Serious AEs	31 (26)	6 (5)	74 (42)	11 (6)
AEs leading to dose reduction	38 (32)	34 (29)	62 (35)	54 (30)
AEs leading to drug interruption	48 (41)	32 (27)	92 (52)	61 (34)
AEs leading to treatment discontinuation	8 (7)	3(3)	18 (10)	9 (5)
AEs leading to death	7 (6)	0	8 (4)	0

- Rate of nervous system AEs was similar in patients with *ROS1*+ NSCLC with or without CNS metastases
  - Dizziness was observed in 57% and 63% of patients with or without CNS metastases, respectively (mostly grade 1-2), and did not lead to treatment discontinuation

[a]Safety analysis population includes all patients with *ROS1*+ NSCLC in phase 1 and phase 2 who received at least 1 dose of repotrectinib.

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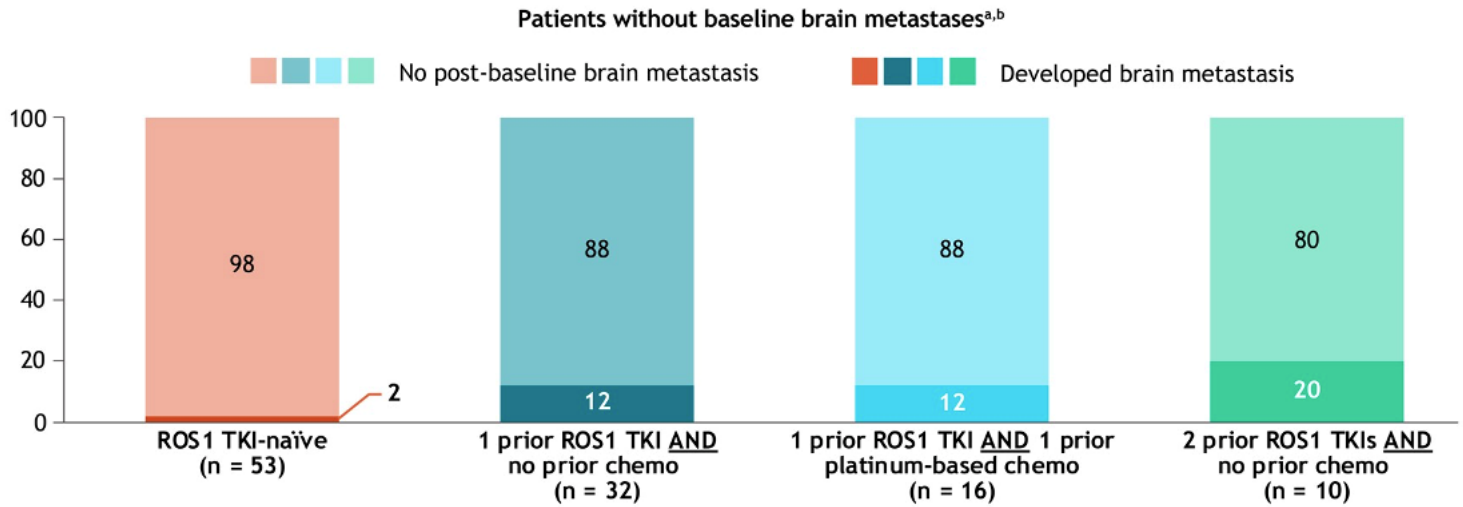

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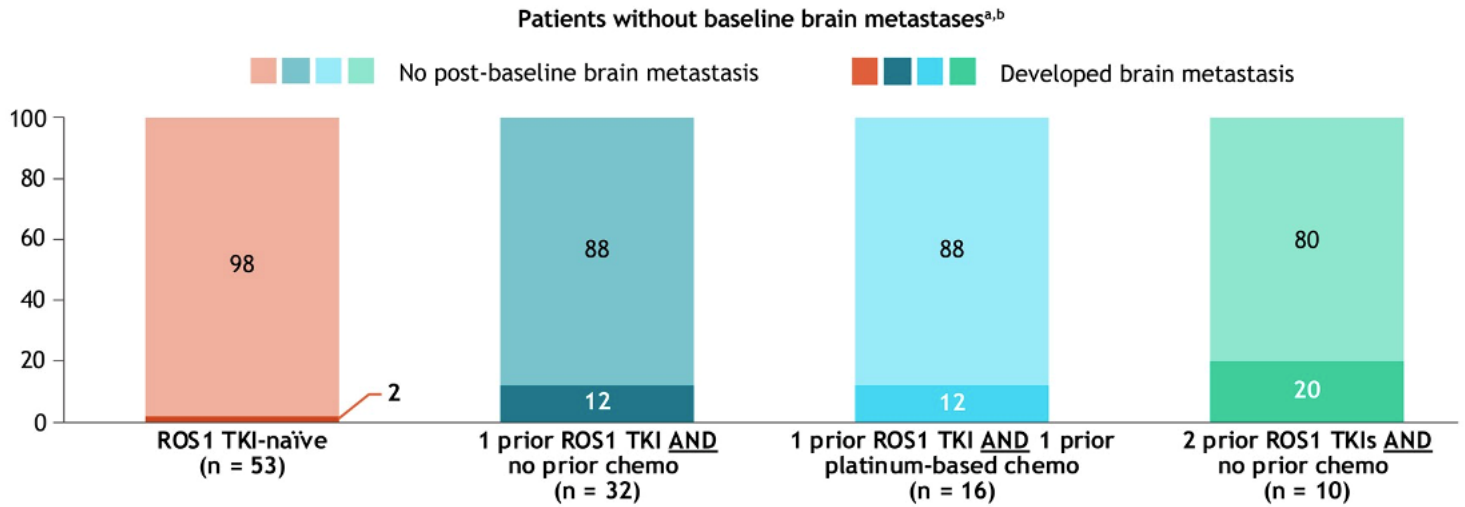
AEs leading to death	7 (6)	0	8 (4)	

- Rate of nervous system AEs was similar in patients with *ROS1*+ NSCLC with or without CNS meta
  - Dizziness was observed in 57% and 63% of patients with or without CNS metastases, respect and did not lead to treatment discontinuation

[a]Safety analysis population includes all patients with *ROS1*+ NSCLC in phase 1 and phase 2 who received at least 1 dose of repotrectinib.



Solo 1 paciente desarrollo mtx en SNC en cohorte naïve

Lin et al. ASCO 2023

ROS 1

Repotrectinib : TRIDENT-- 1 Trial. Safety and BM protection

AUGTYRO™ FDA approval 15 noviembre2023 independiente de la línea de tratamiento

TRIDENT-1: repotrectinib in *ROS1*+ NSCLC with/without CNS metastases

Safety summary in patients with *ROS1*+ NSCLC with or without baseline CNS metastases per investigator assessment[a]

	With baseline CNS metastases (n = 118)		Without baseline CNS metastases (n = 178)	
AE, n (%)	TEAEs	TRAEs	TEAEs	TRAEs
Any AEs	116 (98)	109 (92)	178 (100)	
Any grade ≥ 3 AEs	52 (44)	27 (23)	96 (54)	
Serious AEs	31 (26)	6 (5)	74 (42)	
AEs leading to dose reduction	38 (32)	34 (29)	62 (35)	
AEs leading to drug interruption	48 (41)	32 (27)	92 (52)	
AEs leading to treatment discontinuation	8 (7)	3(3)	18 (10)	
AEs leading to death	7 (6)	0	8 (4)	

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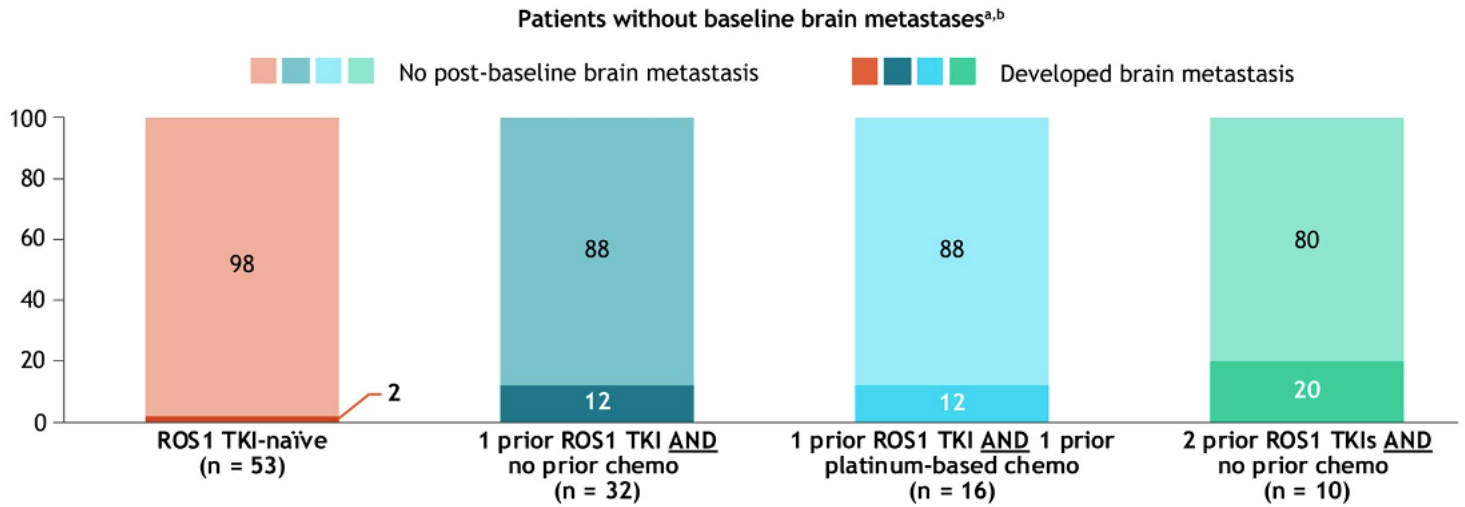


Solo 1 paciente desarrollo mtx en SNC en cohorte naïve

Lin et al. ASCO 2023

ROS 1

Taletrectinib: TRUST I phase II

Key Eligibility Criteria

Inclusion Criteria:

- Locally advanced or metastatic NSCLC
- Age ≥18 years
- ECOG PS 0-1
- Evidence of ROS1 fusion in tumor tissue

Stage 1 Lead-in (n=6)

- Taletrectinib 400 mg QD
- Taletrectinib 600 mg QD

Stage 2 (n~100)

- **Cohort 1: ROS1 TKI-naïve** Taletrectinib 600 mg QD
- **Cohort 2: Crizotinib-pretreated** Taletrectinib 600 mg QD

Endpoints

Primary:
IRC-assessed cORR per RECIST 1.1

Secondary:

- DoR
- DCR
- IC-ORR
- PFS
- TTR (RECIST1.1)
- OS

Key Demographics	TKI-Naïve N=67 (%)	Crizotinib-Pretreated N=42 (%)	Total[a] N=109 (%)
Male, n (%)	28 (41.8)	16 (38.1)	44 (40.4)
Age, median (range)	54 (26, 75)	52 (31, 77)	54 (26, 77)
ECOG PS 0/1, n (%)	11 (16.4)/ 56 (83.6)	17 (40.5)/ 25 (59.5)	28 (25.7)/ 81 (74.3)
Adenocarcinoma, n (%)	64 (95.5)	38 (90.5)	102 (93.5)
Prior chemotherapy, n (%)	15 (22.4)	14 (33.3)	29 (26.6)
Non-smoker/current smoker, n (%)	62 (92.5)/ 5 (7.5)	42 (100.0)/0	104 (95.4)/ 5 (4.6)
Brain Metastasis, n (%)	8 (11.9)	16 (38.1)	24 (22.0)

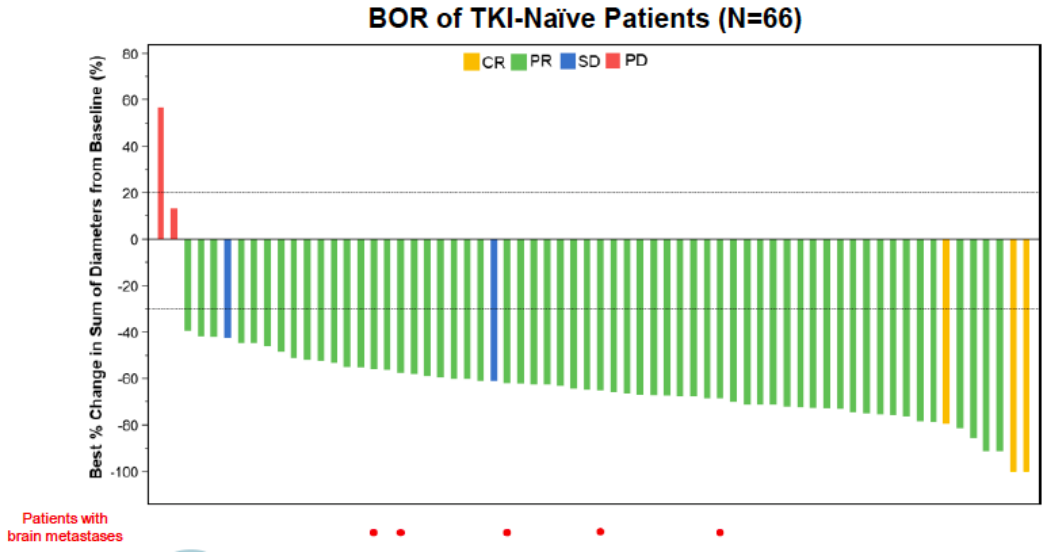
Li et al ELCC 2023

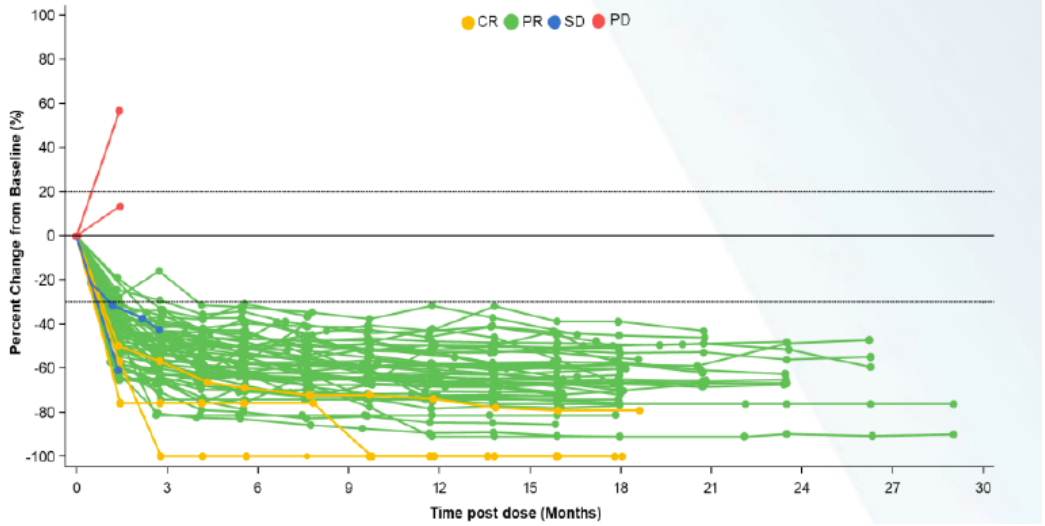
ROS 1

Taletrectinib: TRUST I phase II. Cohort TKI Naïve

ORR 92%

Responses	Taletrectinib efficacy (n=67)
IRC-assessed cORR, % (95% CI)	92.5 (83.4 – 97.5)
DCR, % (95% CI)	95.5 (87.5 –99.1)
Median TTR, months (Range)	1.4 (1.2, 4.2)
mDoR, months (min, max)	NR (1.3 – 27.6)
mPFS, months (min, max)	NR (0.0 – 29.0)





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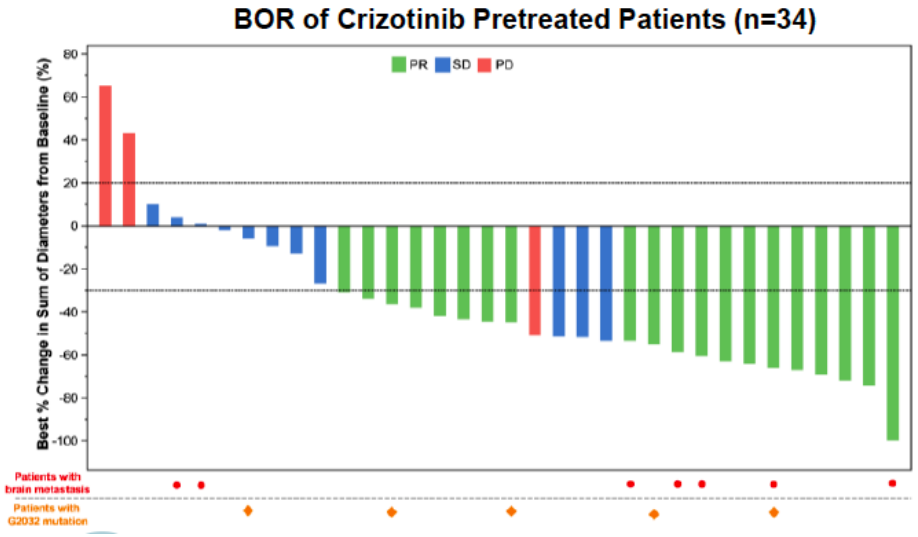
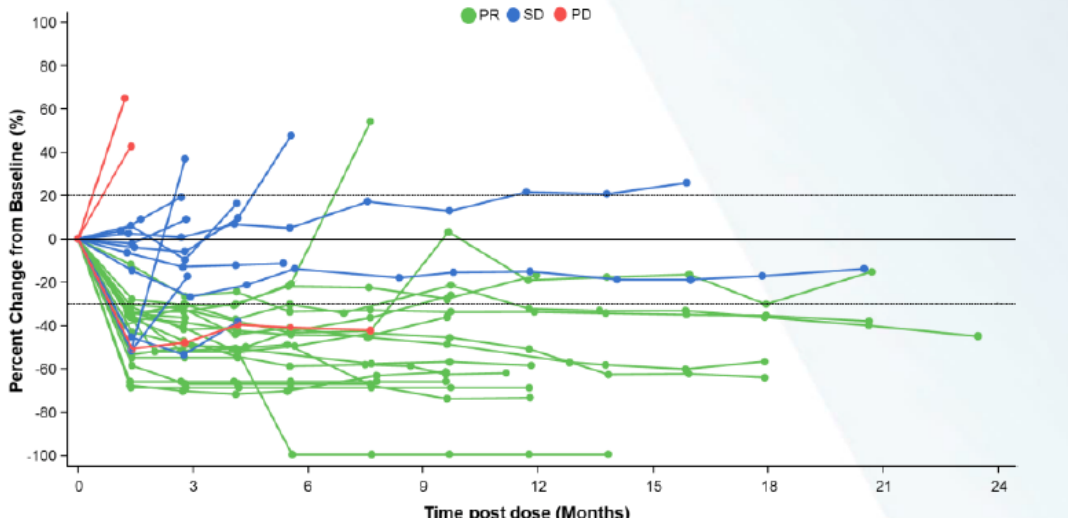
ROS 1

Taletrectinib: TRUST I phase II. Cohort Crizotinib pretreated

ORR 52.6%

Responses	Taletrectinib Efficacy (n=38)
IRC-assessed cORR, % (95% CI)	52.6 (35.8 – 69.0)
DCR, % (95% CI)	81.6 (65.7 – 92.3)
Median TTR, months (Range)	1.4 (1.2 – 4.1)
mDoR, months (min, max)	NR (1.4 – 22.2)
mPFS, months (min, max)	9.8 (0.0 – 23.5)
G2032R ORR,[b] %, n/N	80.0 (4/5)





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ROS 1

Taletrectinib: TRUST I phase II. Cohort Crizotinib pretreated

Patients with TEAEs (≥15%): Taletrectinib 600mg Safety Population (N=178)

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5[b] n (%)	Any Grade N (%)
AST increased	86 (48.3)	28 (15.7)	12 (6.7)	0	0	126 (70.8)
ALT increased	69 (38.8)	32 (18.0)	13 (7.3)	0	0	114 (64.0)
Diarrhea	81 (45.5)	22 (12.4)	6 (3.4)	0	0	109 (61.2)
Vomiting	56 (31.5)	18 (10.1)	3 (1.7)	0	0	77 (43.3)
Nausea	65 (36.5)	8 (4.5)	2 (1.1)	0	0	75 (42.1)
Anemia	39 (21.9)	20 (11.2)	4 (2.2)	0	0	63 (35.4)
WBC count decreased	24 (13.5)	12 (6.7)	4 (2.2)	0	0	40 (22.5)
Neutrophil count decreased	18 (10.1)	8 (4.5)	8 (4.5)	4 (2.2)	0	38 (21.3)
Hepatic function abnormal	20 (11.2)	5 (2.8)	12 (6.7)	0	0	37 (20.8)
Dizziness	34 (19.1)	2 (1.1)	1 (0.6)	0	0	37 (20.8)

Por la inhibición dual con TRK

Li et al ELCC 2023

ROS 1

Taletrectinib. TRUST II Interim analysis

TRUST II (NCT04919811) Study Design

Key Eligibility Criteria (N=154)

Inclusion Criteria:

- Locally advanced or metastatic NSCLC or other solid tumors
- Age ≥18 years
- ECOG PS 0–1
- Evidence of ROS1 fusion
- Stable CNS involvement allowed (including leptomeningeal carcinomas)
- At least 1 measurable lesion per RECIST v1.1

Cohort 1
NSCLC: ROS1 TKI-naive, ≤1 CT

Cohort 2[a]
NSCLC: 1 prior ROS1 TKI, ≤1 line of CT

Cohort 3[b]
NSCLC: ≥2 prior ROS1 TKIs, ≤1 line of CT

Cohort 4[b]
Solid tumors including NSCLC if ineligible for cohorts 1–3; ≤3 ROS1 TKIs, ≤2 lines of CT

Taletrectinib[c] 600 mg QD, oral

Study Endpoints

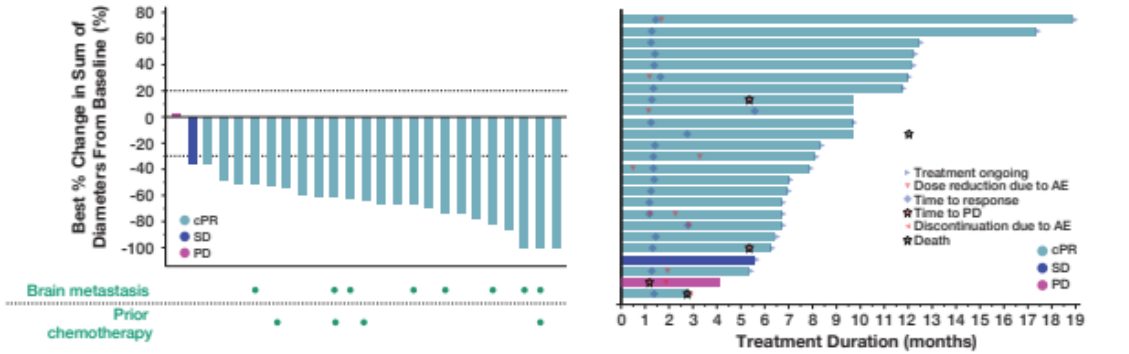
Primary:
- IRC-assessed cORR per RECIST v1.1

Key Secondary:
- Intracranial cORR (RECIST v1.1)
- DoR
- DCR
- TTR (RECIST v1.1)
- PFS
- OS
- Safety

Study Populations:
- Safety – All patients who received ≥1 dose of taletrectinib
- Efficacy[d] – Patients with documented ROS1 fusion, ≥1 measurable lesion at baseline per IRC, and approximately 6 months of follow-up

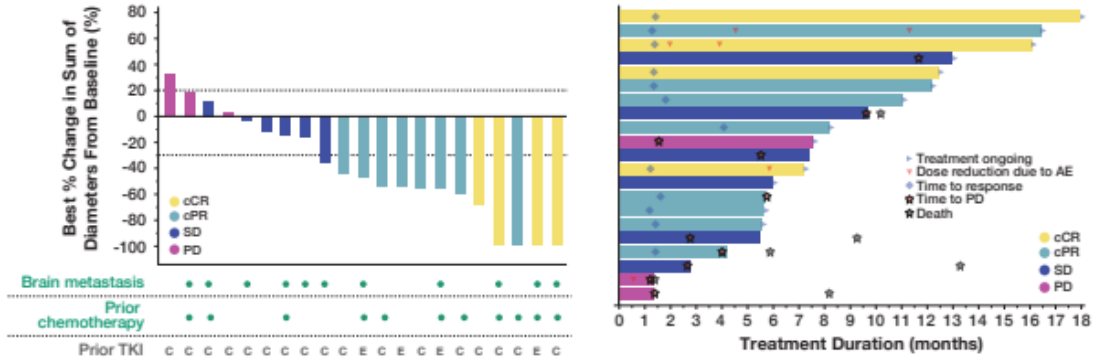
Efficacy in ROS1 TKI-Naive Patients (TKI-Naive; n=25)

- cORR: 92.0% (95% CI: 74.0, 99.0)



Efficacy in ROS1 TKI-Pretreated Patients (TKI-pretreated; n=21)

- cORR: 57.1% (95% CI: 34.0, 78.2)
- 17 patients (81%) in Cohort 2 received crizotinib (C); 4 (19%) received entrectinib (E)



Perol et al ESMO 2023 1371P

ROS 1

Taletrectinib. TRUST II Interim analysis

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Taletrectinib[c] 600 mg QD, oral

Study Endpoints

Primary:
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Key Secondary:
- Intracranial cORR (RECIST v1.1)
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- DCR
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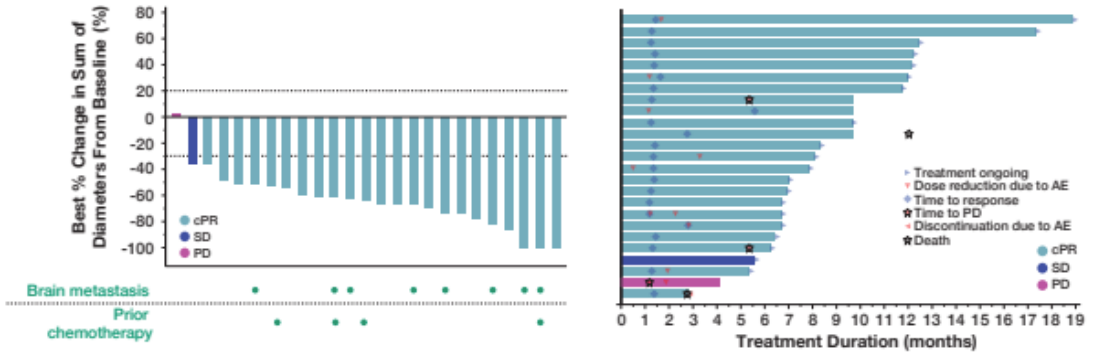

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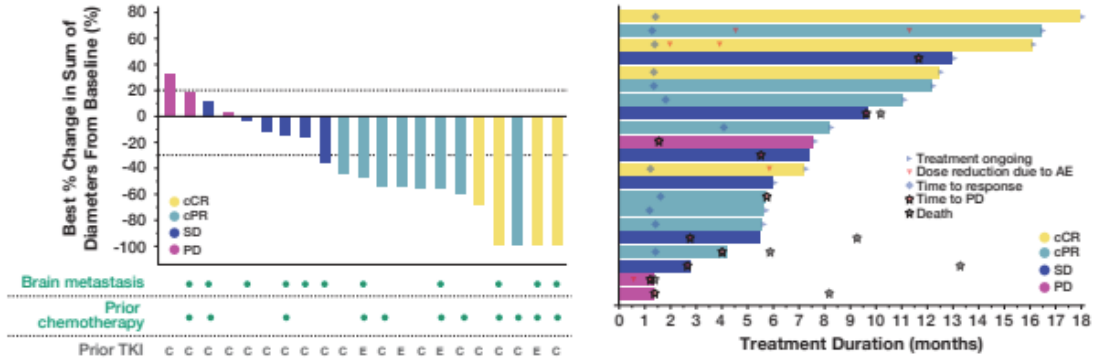


Perol et al ESMO 2023 1371P

ROS 1

NVL 520 (Zidesamitinib)

ARROS-1 Study Design

Phase 2 Cohorts Designed to Support Registration for Either Niche or Broad Patient Population

Phase 1

- Dose Level 6
- Dose Level 5
- Dose Level 4
- Dose Level 3
- Dose Level 2
- Dose Level 1

PURPOSE

- ✓ Safety / Tolerability
- ✓ Determine/Confirm RP2D

Phase 2

COHORT	TUMOR TYPE	PRIOR ROS1 TKI	PRIOR CHEMO/I-O**	DETAIL
2a	ROS1-positive NSCLC	Naive	≤ 1	
2b	ROS1-positive NSCLC	1*	Naive	*Subset analysis for G2032R*
2c	ROS1-positive NSCLC	1*	1	*Subset analysis for G2032R*
2d	ROS1-positive NSCLC	2+	≤ 1	*Subset analysis for G2032R*
2e	Any ROS1-positive Solid Tumor***	Any	Any	*Exploratory Cohort*

Cohorts 2a, 2b, 2c, and 2d were designed to support registration

*Either crizotinib or entrectinib; ** Platinum-based chemotherapy ± immunotherapy; *** Includes NSCLC who do not qualify for any of the other cohorts
I-O: Immunotherapy; RP2D: Recommended Phase 2 Dose; TKI: Tyrosine Kinase Inhibitor

Nuvalent results

- 2 TKIS: 48- 50%
- ROS1 G2032R. ORR 78%
- CNS icORR 78- 100%

100 mg/dia

Nuvalent report 2022
Drilon et al. Cancer Discovery 2023

ROS 1

NVL 520 (Zidesamitinib)

		Name	Cell line	Fusion	Mutation	Crizotinib	Entrectinib	Lorlatinib	Taletrectinib	Repotrectinib	NVL-520
A	Wild-type ROS1 fusion	HCC78	Human cancer cell line	SLC34A2–ROS1	–	45	5.3	0.9	15	7.7	<0.7
		MGH193-1	Patient-derived cell line	EZR–ROS1	–	18	8.7	0.4	5	2.1	1
		Ba/F3	Engineered mouse pro–B cell line	CD74–ROS1	–	40	19	1.2	21	4.6	1.3
				EZR–ROS1	–	5.9	12	0.5	11	2.9	0.3
				GOPC(L)–ROS1	–	33	11	0.3	7.6	3.5	0.2
				GOPC(S)–ROS1	–	110	36	0.3	9.9	2.7	0.2
				CEP85L–ROS1	–	30	13	0.4	6.2	2.1	0.2
		Average potency across 7 wild-type ROS1 fusion cell lines				30	13	0.5	9.7	3.3	0.4
B	ROS1 fusion with G2032R mutation	MGH9018-1	Patient-derived cell line	CD74–ROS1	G2032R	1,100	610	500	190	32	5.1
		Ba/F3	Engineered mouse pro–B cell line	CD74–ROS1	G2032R	950	880	320	84	25	3.6
				EZR–ROS1	G2032R	630	830	42	19	8.8	0.7
				GOPC(L)–ROS1	G2032R	1,600	1,200	91	27	11	1.1
				GOPC(S)–ROS1	G2032R	1,200	>3,000	>100	>100	>100	6.6
				SLC34A2–ROS1	G2032R	440	220	14	9.4	3.8	0.2
		Average potency across 6 ROS1 G2032R fusion cell lines				920	850	98	44	18	1.6
C	ROS1 fusion with other resistance mutations	Ba/F3	Engineered mouse pro–B cell line	CD74–ROS1	S1986F	39	26	<0.3	NA	0.84	<0.6
				CD74–ROS1	F2004C	35	60	0.3	13	3.2	0.02
				EZR–ROS1	F2004C	28	66	0.5	13	3.5	0.01
				CD74–ROS1	F2004V	35	38	0.5	8.5	2.5	0.01
				EZR–ROS1	F2004V	11	51	0.6	10	3.6	0.2
				CD74–ROS1	L2026M	110	41	0.8	NA	3.3	1.5
				CD74–ROS1	D2033N	77	79	0.4	NA	2.5	1
				EZR–ROS1	G2101A	25	8.4	0.4	9.3	1.8	0.4

Cell viability IC_{50} (nmol/L)

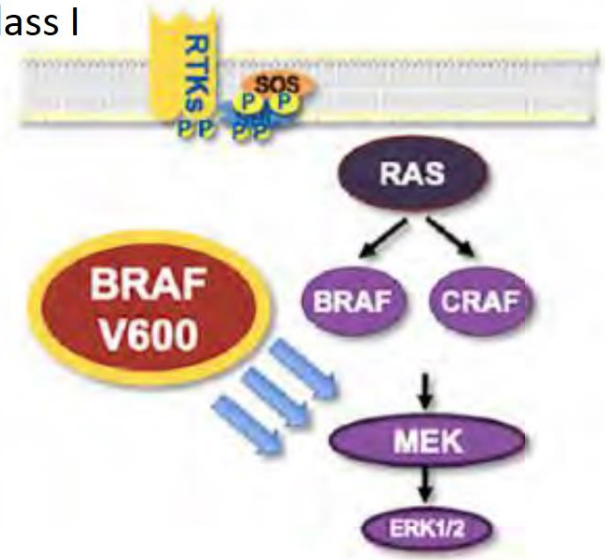
10^{-1} 10^{0} 10^{1} 10^{2} 10^{3}

et al. Cancer Discovery 2023

BRAF

Deleciones
Fusiones

Class I

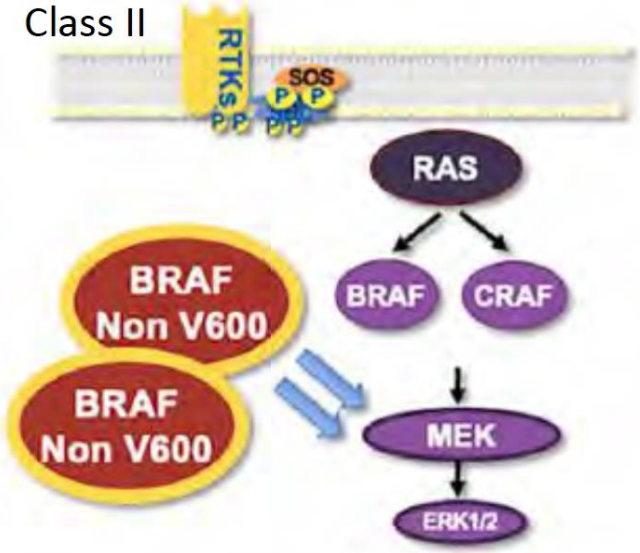


50-62%

Class I BRAF mutant:
- RAS-independent
- higher kinase activity
- monomers
- V600E/K/D/R/M/G

95-96% are *V600E*

Class II

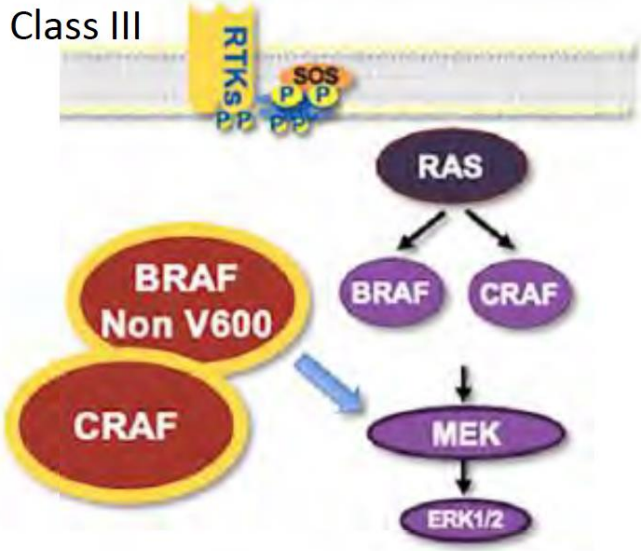


16.5 – ~25%

Class II BRAF mutant:
- RAS-independent
- Intermediate kinase activity
- Homodimers
- BRAF dimers
- non-V600 point mutations

(G496A/V/S/R, G464E/V/R, R462I, I463S, E586K, L485W, L597Q/R/S/V, A598V, T599I, K601E/N/T, A727V, P367L/S)

Class III



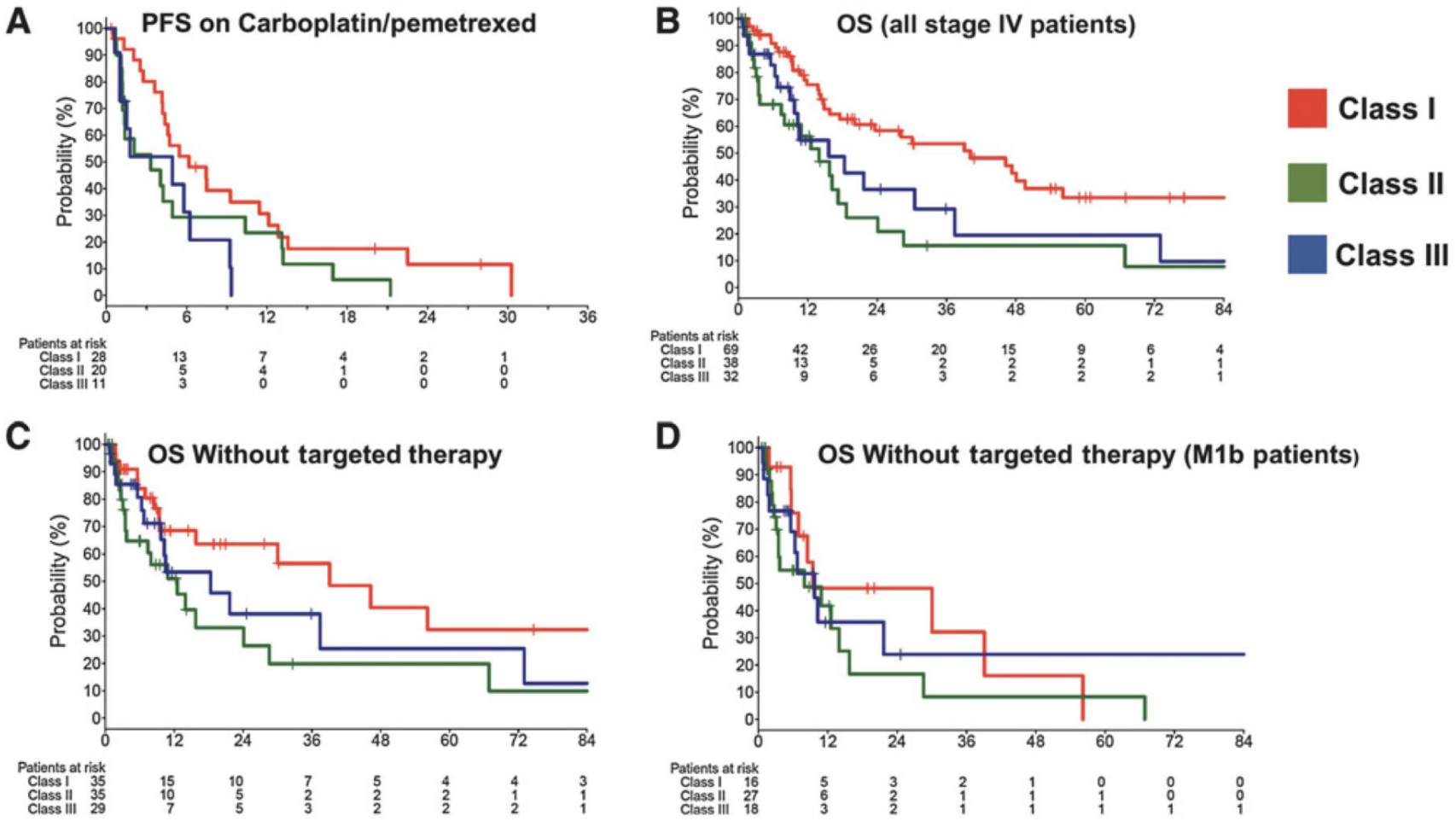
17.5- ~25%

Class III BRAF Mutant:
- RAS-dependent
- compromised kinase activity
- wild-type CRAF heterodimer
- G466A/E/V/R/L, S467A/E/L, G469E, K483M, N581Y/I/S, D287H/Y, V459L, F595L, D594A/E/G/H/N/V/Y, G596A/C/D/R

RiudavetsM et al. Lung Cancer 2022;

BRAF

Outcomes by mutation class. N: 107



Dagogo Jack, Clin Cancer Res, 2019

BRAF

Retrospective studies evaluating immunotherapy in BRAF lung cancer

	Sample size	*Type of ICIs and treatment line*	*PD-L1 ≥ 50%*	*ORR* n (%)	*DCR* n (%)	*Median PFS* mo. (95%CI)	*Median OS* mo. (95%CI)	*Reference*
Multicentre Israeli retrospective study	12 (V600E)	≥2 lines 75%	42%	3/12 (25)	–	3.7 (1.6–6.6)	–	Dudnik E, et al. *JTO*, 2018
	10 (non-V600E)	≥2 lines 40%	50%	3/9 (33)	–	4.1 (0.1–19.6)	–	
IMMUNOTARGET registry [a]	43	Nivolumab 89.6% ≥2 lines 94.5%	55.6%	9/37 (24.3)	11/37 (29.7)	3.1 (1.8–4.6)^	18.0 (7.2–32.7)	Mazières J, et al. *Ann Oncol*, 2019
Italian Expanded Access Program[b]	11	Nivolumab 2 line 100%	–	1/11 (9.1)	1/11 (9.1)	–	10.3 (2.1–18.5)	Rihawi K, et al. *JTO*, 2019
French Lung Cancer Group (GFPC)[c]	26 (V600E)	Nivolumab 69% ≥2 lines 88%	38%	6/23 (26.1)	14/23 (60.9)	5.3 (2.1 - NR)	22.5 (8.3 - NR)	Guisier F, et al. *JTO*, 2020
	18 (non-V600E)	Nivolumab 89% ≥2 lines 94%	11%	6/17 (35.3)	9/17 (52.9)	4.9 (2.3 - NR)	12.0 (6.8 - NR)	

PDL1 status	<1%	1-49%	≥50%	High TMB
BRAF V600E	26%	32%	42%	25%
BRAF Non-V600E	40%	10%	50%	0%

RiudavetsM et al. Lung Cancer 2022;

BRAF

Clinical features

BRAF V600E

Adenocarcinoma
Females 3:1
Micropapillary-predominant 80% cases
40% light/never smokers

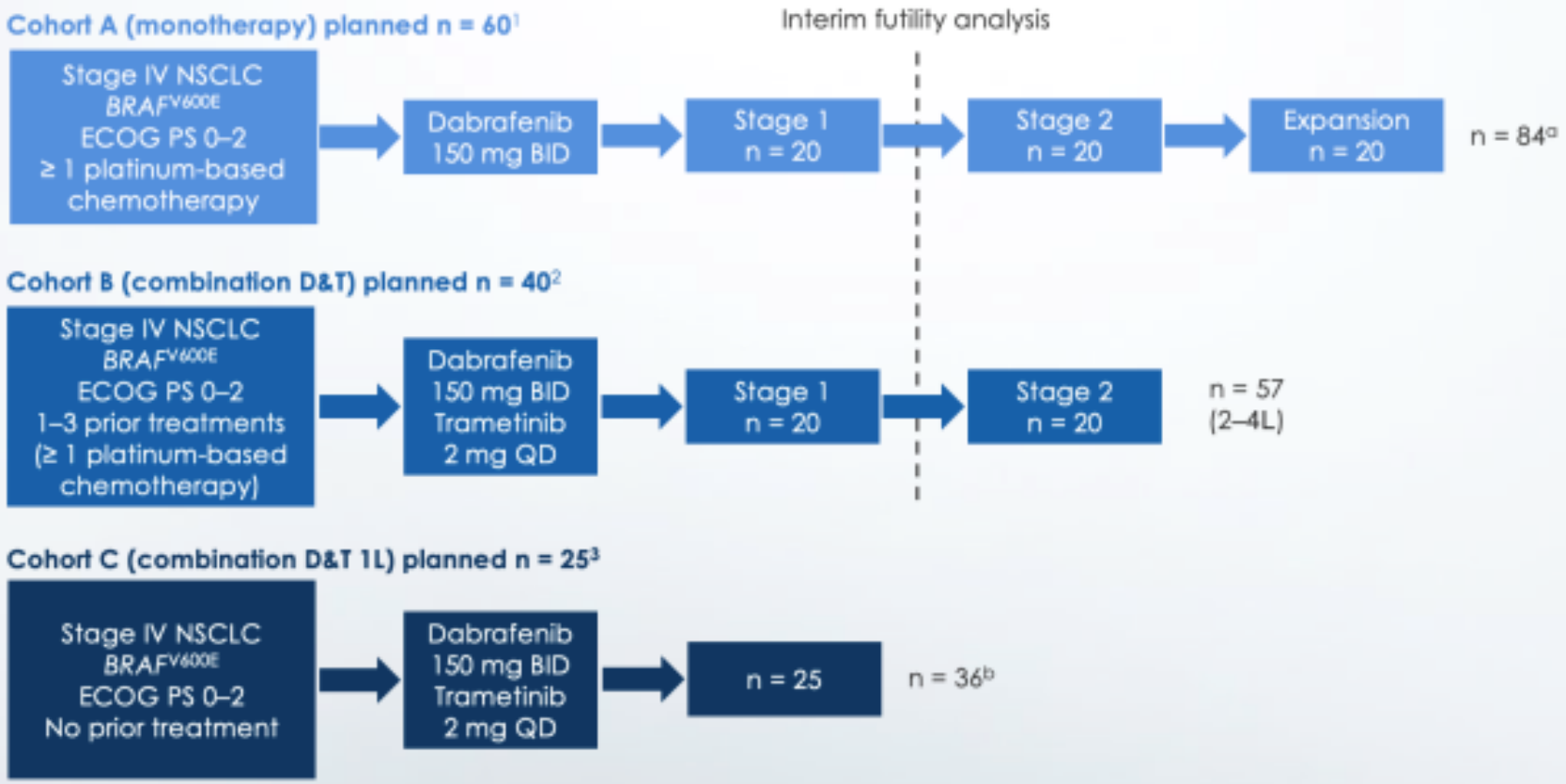
Non-V600 BRAF mutations

Almost all adenocarcinoma
Almost all male
More mucinous cases??
> 90% smokers

Dagogo Jack, Clin Cancer Res, 2019
RiudavetsM et al. Lung Cancer 202

BRAF V600E

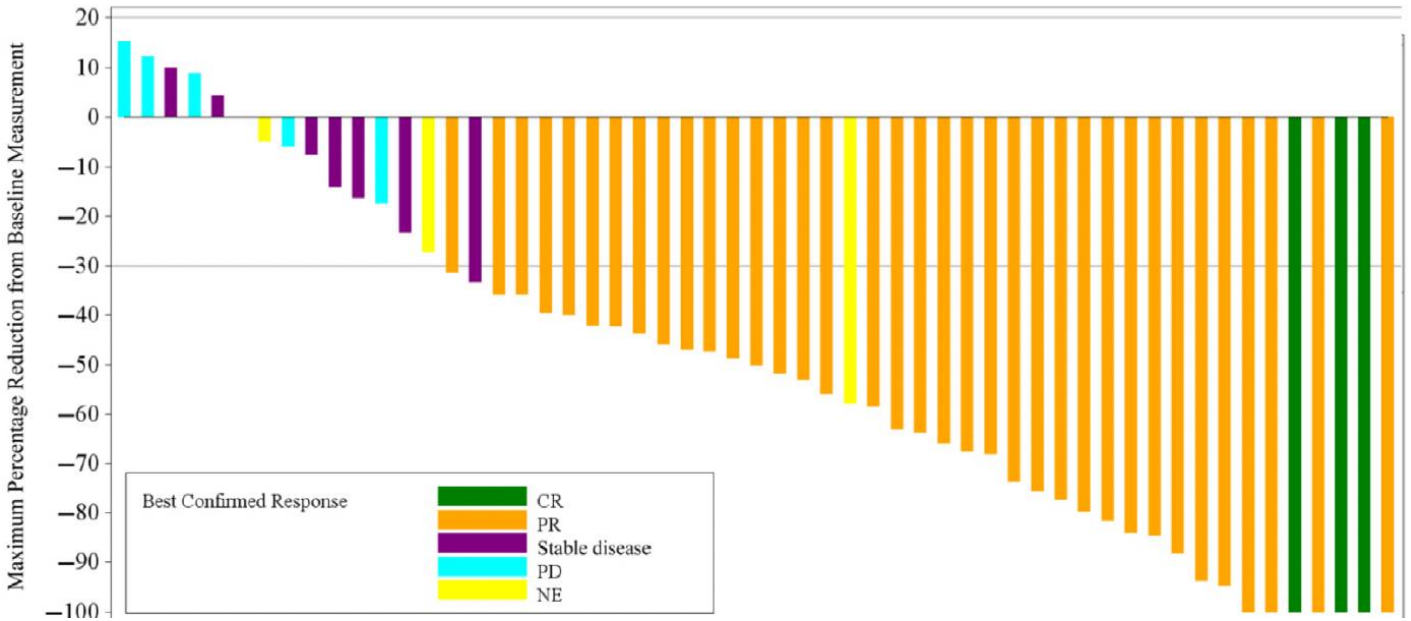
BRF113928 study: Design



Planchardet al. J ThoracOncology2022

BRAF V600E

BRF113928 study: ORR

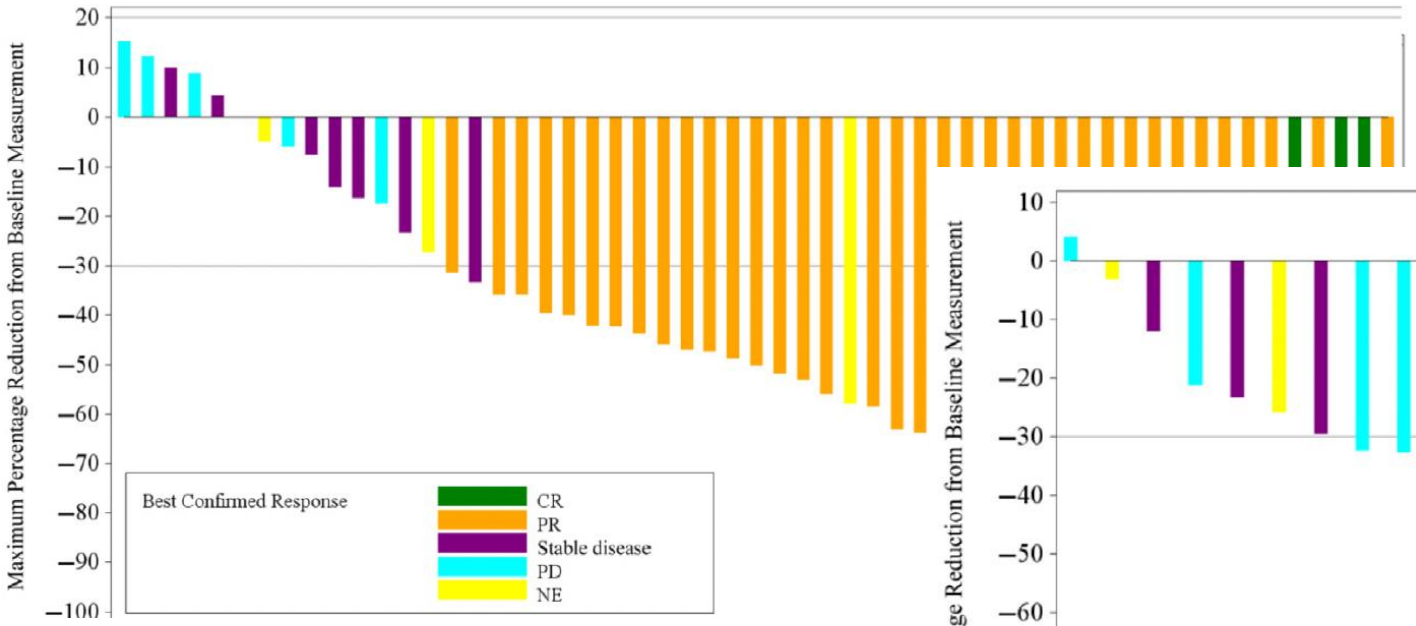


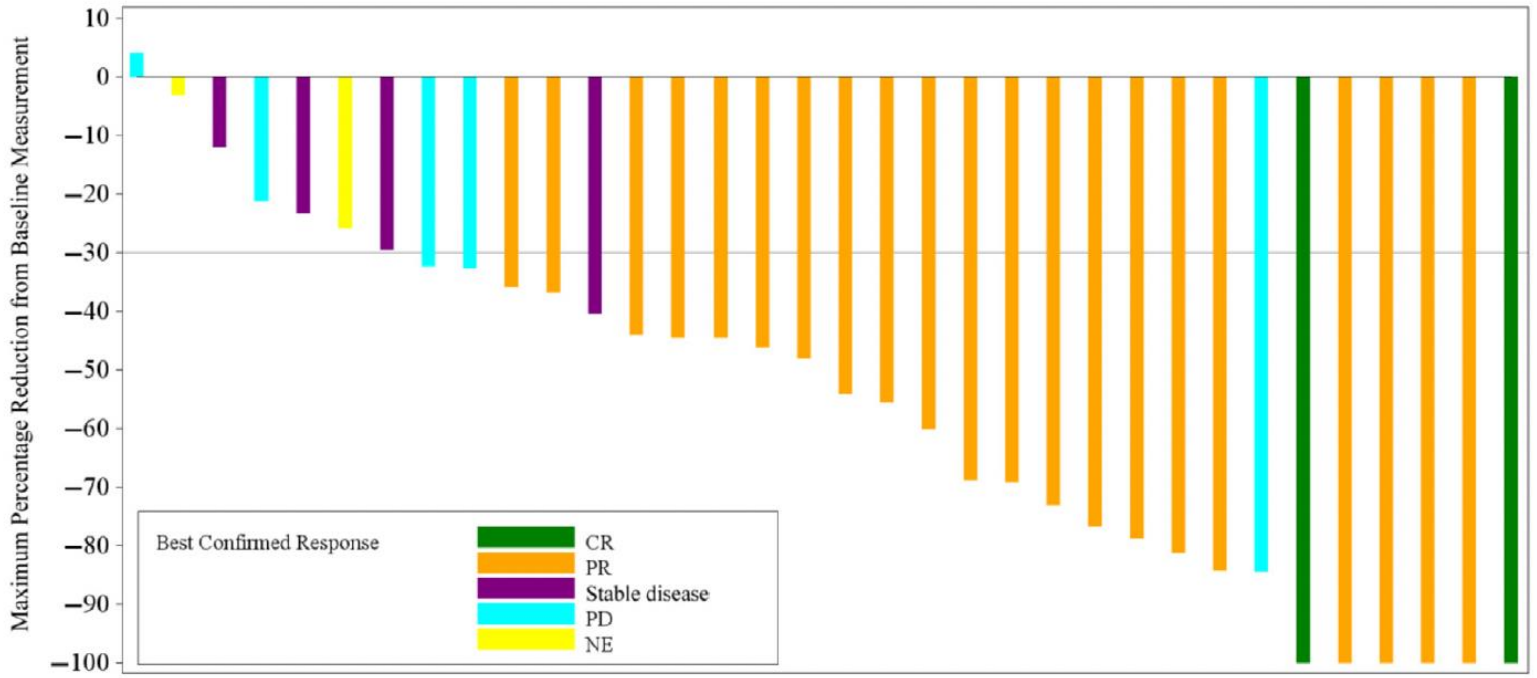
ORR pretreated 68.4%
CR 5%

Planchardet al. J ThoracOncology2022

BRAF V600E

BRF113928 study: ORR





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Planchardet al. J ThoracOncology2022

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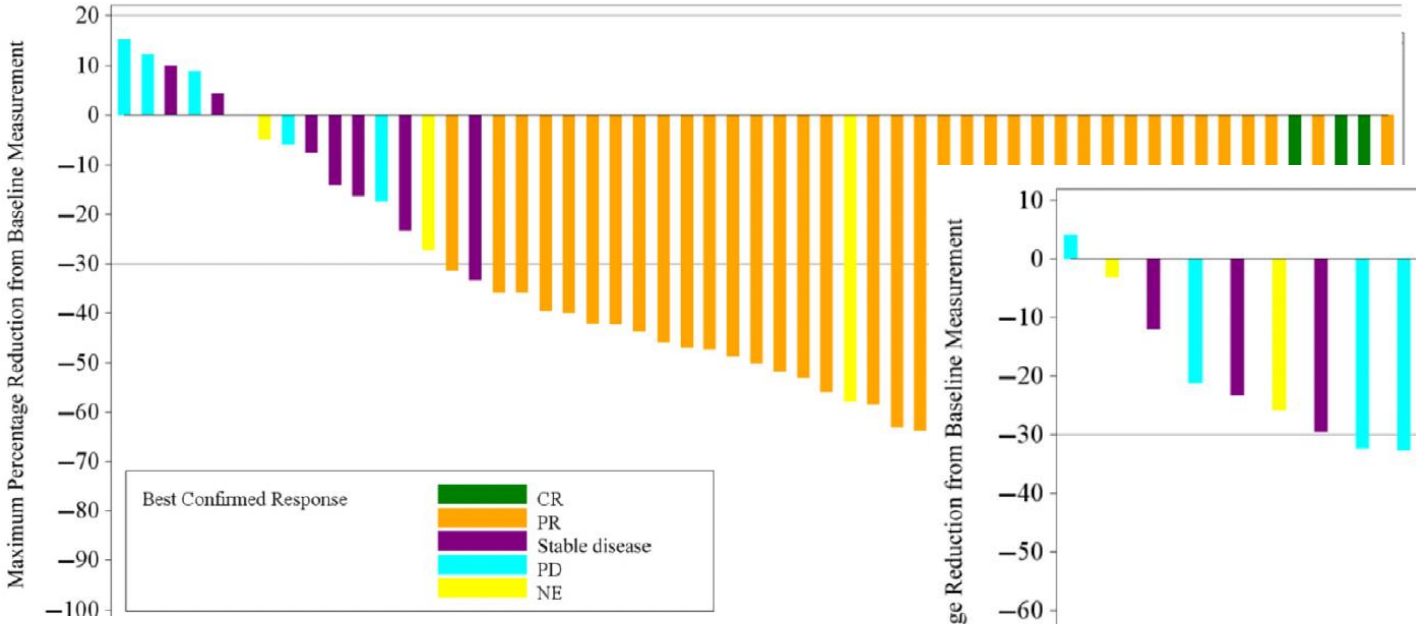
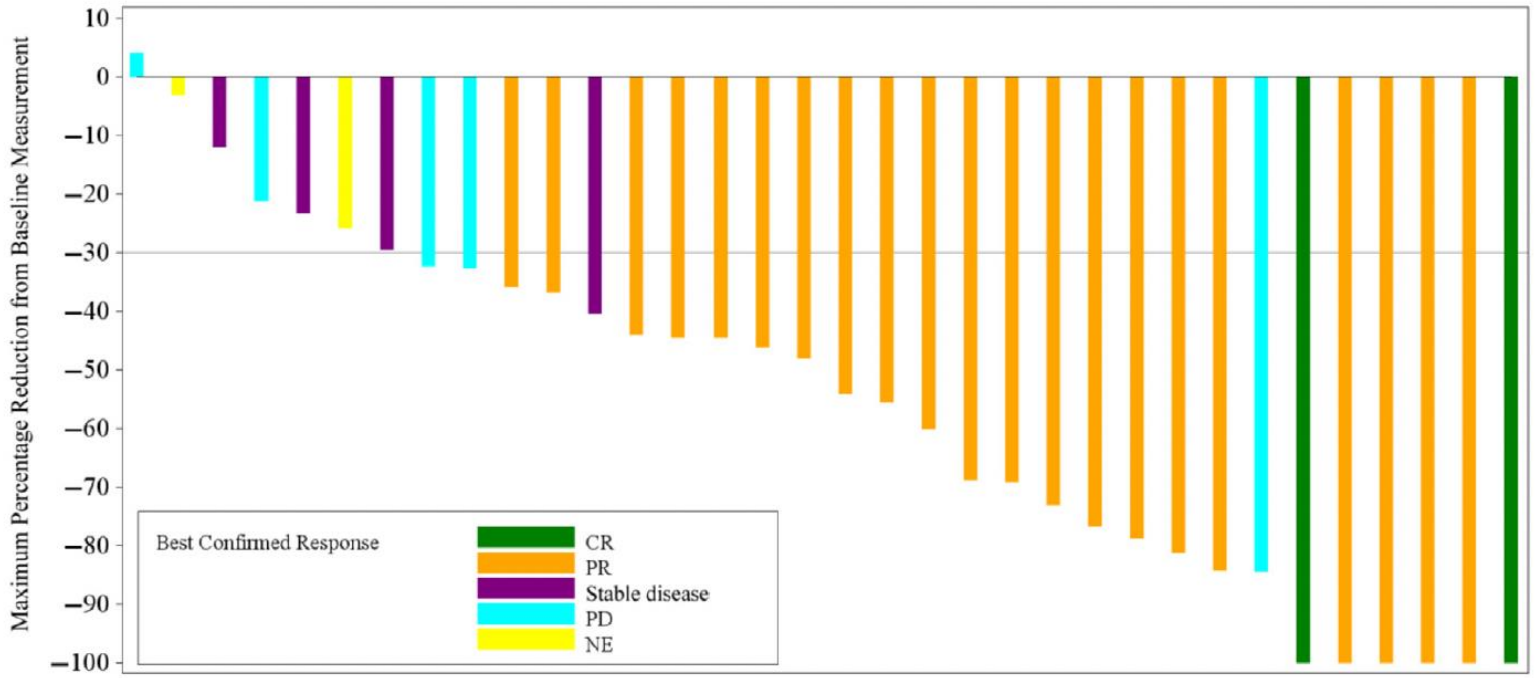


ORR Naïve 63.9%



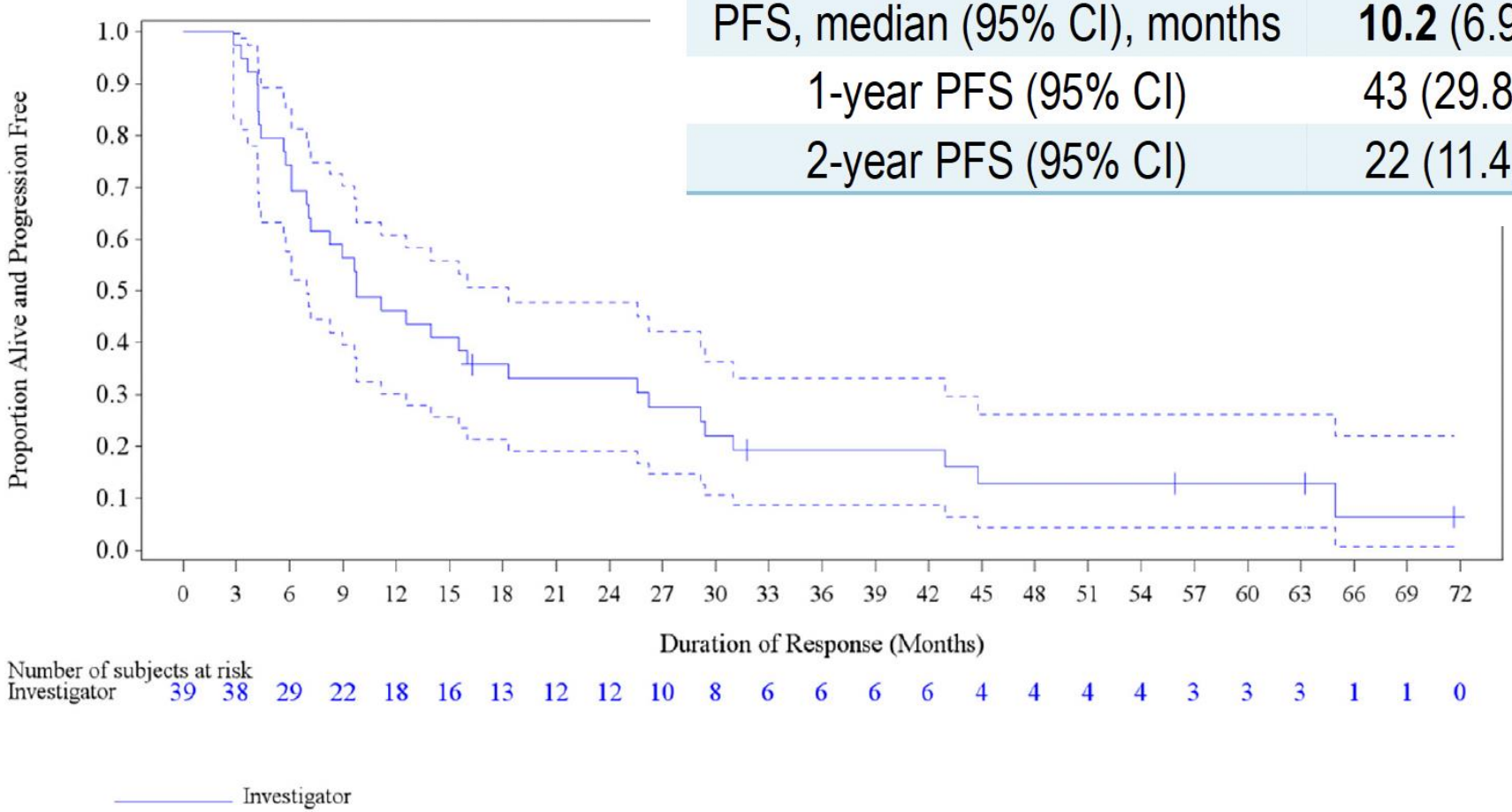
ORR pretreated 68.4%
CR 5%

Planchardet al. J ThoracOncology2022

BRAF V600E

BRF113928 study: PFS Cohort B

	Investigator assessment (n=57)	IRC assessment (n=57)
PFS, median (95% CI), months	**10.2** (6.9, 16.7)	8.6 (5.2, 16.8)
1-year PFS (95% CI)	43 (29.8, 55.7)	41 (28.5, 53.9)
2-year PFS (95% CI)	22 (11.4, 35.6)	27 (14.6, 41.1)

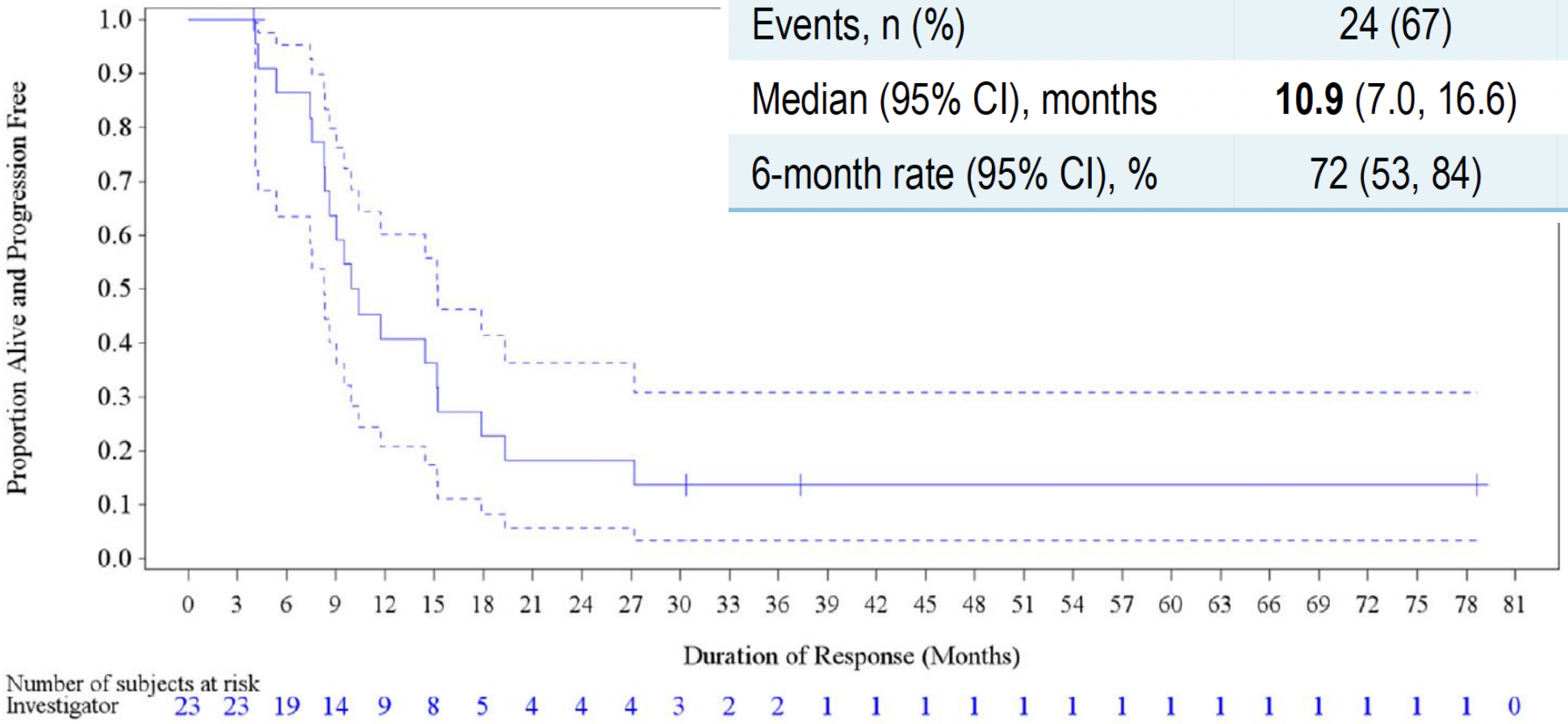


Planchardet al. J ThoracOncology2022

BRAF V600E

BRF113928 study: PFS Cohort C

	Investigator assessed (n=36)	IRC assessed (n=36)
Events, n (%)	24 (67)	22 (61)
Median (95% CI), months	**10.9** (7.0, 16.6)	**14.6** (7.0, 22.1)
6-month rate (95% CI), %	72 (53, 84)	69 (51, 82)



Planchard et al. J ThoracOncology2022

BRAF V600E

Pharos study

PHAROS (NCT03915951):
A single-arm, open-label, multicenter, phase 2 study

Key eligibility criteria

- Metastatic BRAF V600E–mutant NSCLC
- ECOG performance status 0 or 1
- No *EGFR* mutation, *ALK* fusion, or *ROS1* rearrangement
- No more than 1 prior line of treatment in the advanced setting
- No prior treatment with BRAF or MEK inhibitor
- No symptomatic brain metastases

Patients enrolled

- Treatment naïve n=59
- Previously treated n=39

Encorafenib: 450 mg QD

Binimetinib: 45 mg BID

28-day cycles

Treat until progression or unacceptable toxicity

***BRAF* mutation testing**

- Determined locally by PCR- or NGS-based assay; sent to central laboratory[a]
- Pleural fluid, fresh and archived tissue, and fine needle aspiration were acceptable

Primary endpoint

- ORR[b] by IRR

Secondary endpoints

- ORR by investigator
- DOR, DCR, PFS, and TTR (all by IRR and investigator)
- OS
- Safety

Exploratory endpoints

- Biomarker and pharmacokinetic analyses

Riely et al. ASCO 2023

BRAF V600E

Pharos study. ORR

ORR 75%

ORR 46%

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

Riely et al. ASCO 2023

BRAF V600E

Pharos study. ORR

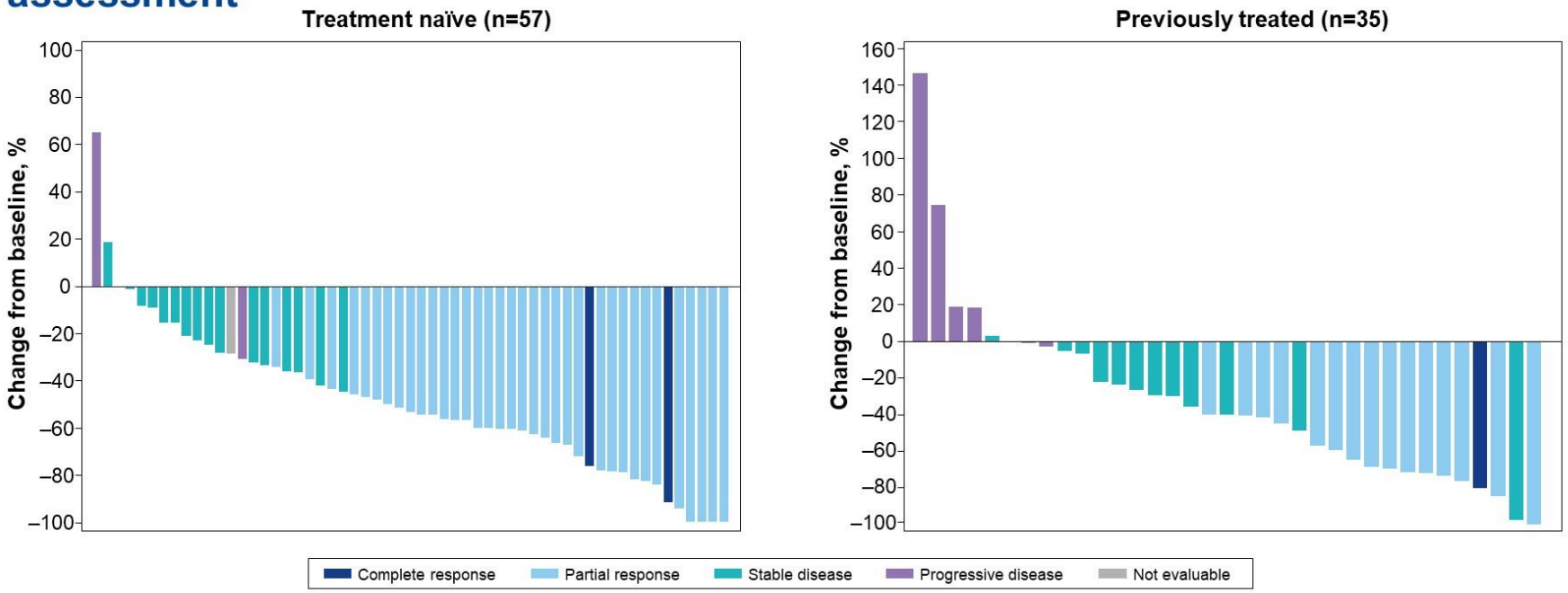
ORR 75%

ORR 46%

Encorafenib plus binimetinib in metastatic BRAF-V600E mutant NSCLC

Objective response rate (95% CI), %[a]	
Complete response	
Partial response	
Stable disease	
Progressive disease	
Disease control rate at 24 weeks (95% C	
Duration of response, median (95% CI), r	
Duration of response ≥12 months, n/N (%	
Time to response, median (range), montl	

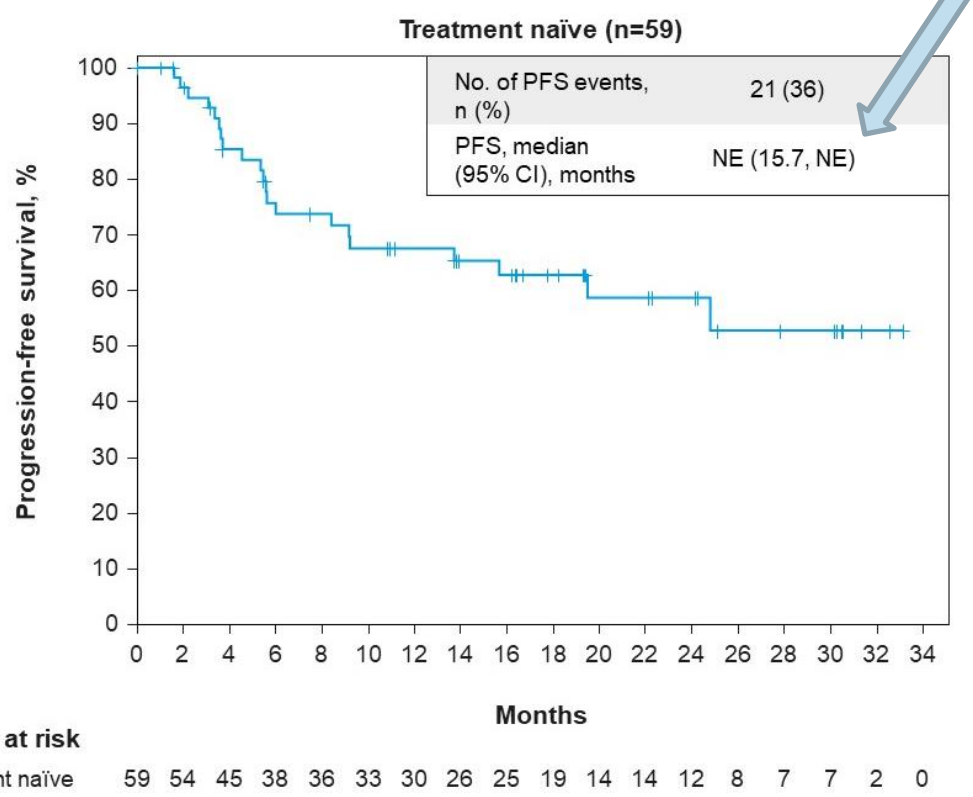
Change from baseline in the sum of diameters of target lesions by investigator assessment[a]

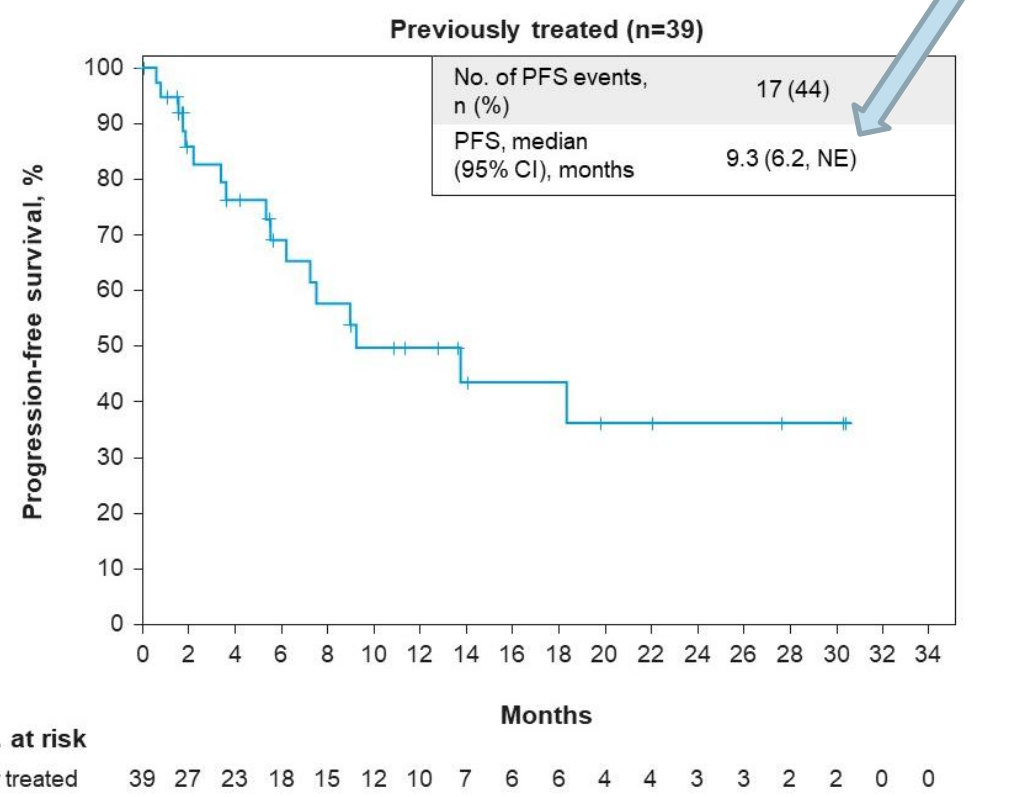


Riely et al. ASCO 2023

BRAF V600E

Pharos study : PFS





- The median duration of follow-up for PFS by IRR was 18.2 months (95% CI, 16.4, 22.3 months) in treatment-naïve patients and 12.8 months (95% CI, 9.0, 19.8 months) in previously treated patients

BRAF V600E

All grades	D + T	E + B
Fever	46%	↓ 22%
Nausea	40%	50%
Vomiting	35%	29%
Diarrhea	34%	43%
Fatigue	28%	32%
Oedema	23%	↓11%
SAEs	56%	↓41%
Reduction	35%	↓24%
Discont.	12%	15%

BRAF V600E

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Fever	46%	↓ 22%
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Dabrafenib + Trametinib FDA y EMA approved 2017

NO financiación España

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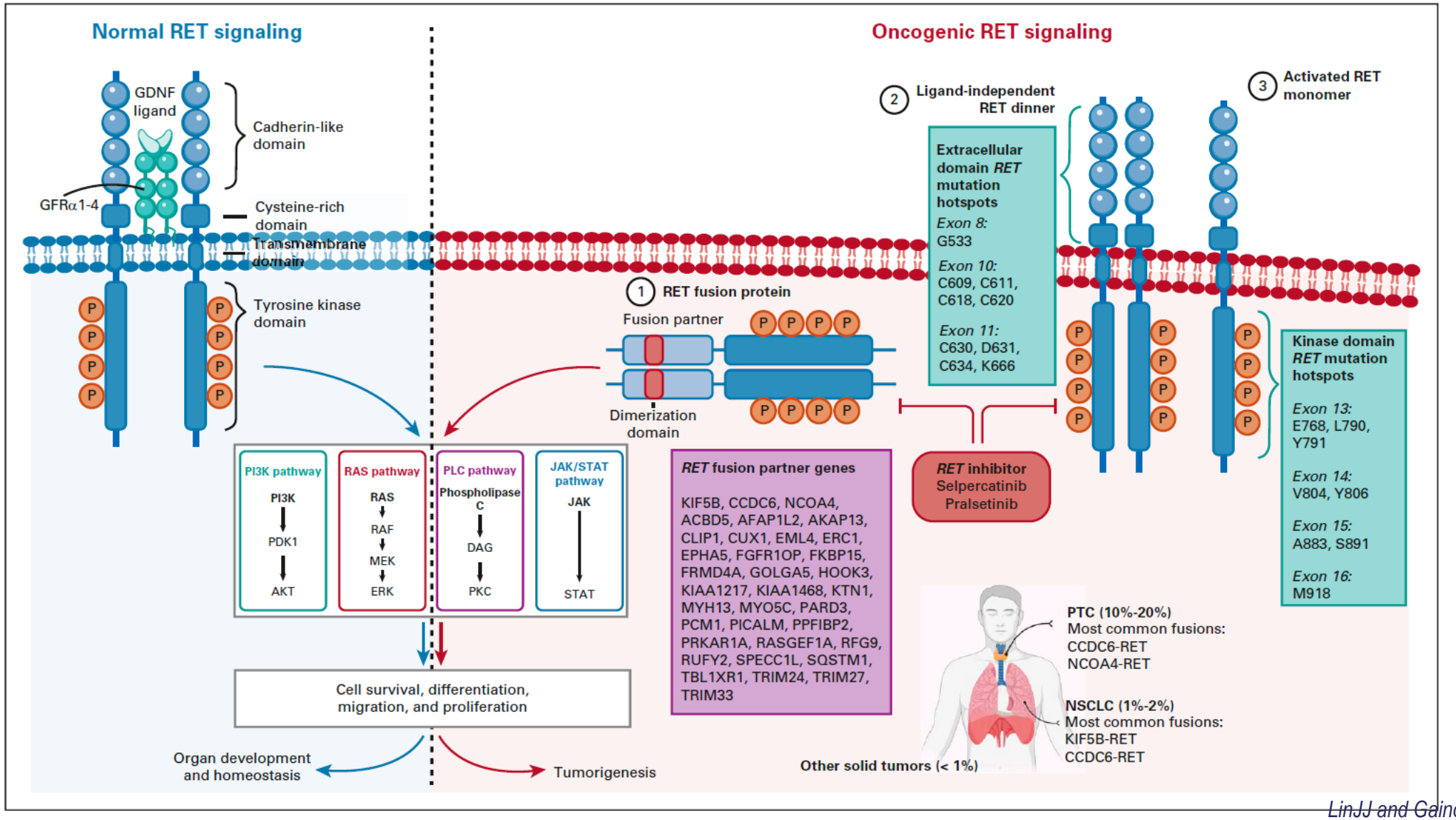
Dabrafenib + Trametinib FDA y EMA approved 2017
NO financiación España

Encorafenib + Binimetinib FDA approval October 2023

RET



LinJJ and GainorJ. ClinOncol2023

RET

Diagnostico

FISH	
Advantages	Low input material Short turnaround time Usually high specificity and sensitivity Low cost
Challenges	Interpretation (not only for the *NCOA4* partner!)

Real-time PCR	
Advantages	Low input material Short turnaround time Usually high specificity and sensitivity Low cost
Challenges	Design of the kit (width) RNA failure rate

RET

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NGS	
Advantages	Comprehensive Usually high specificity and sensitivity
Challenges	Longer turnaround time High input material for some panels High cost Design of the panel (width) Reduced sensitivity of DNA-only NGS for fusions RNA failure rate

RET

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Si resultado no significativo/negativo y alta sospecha

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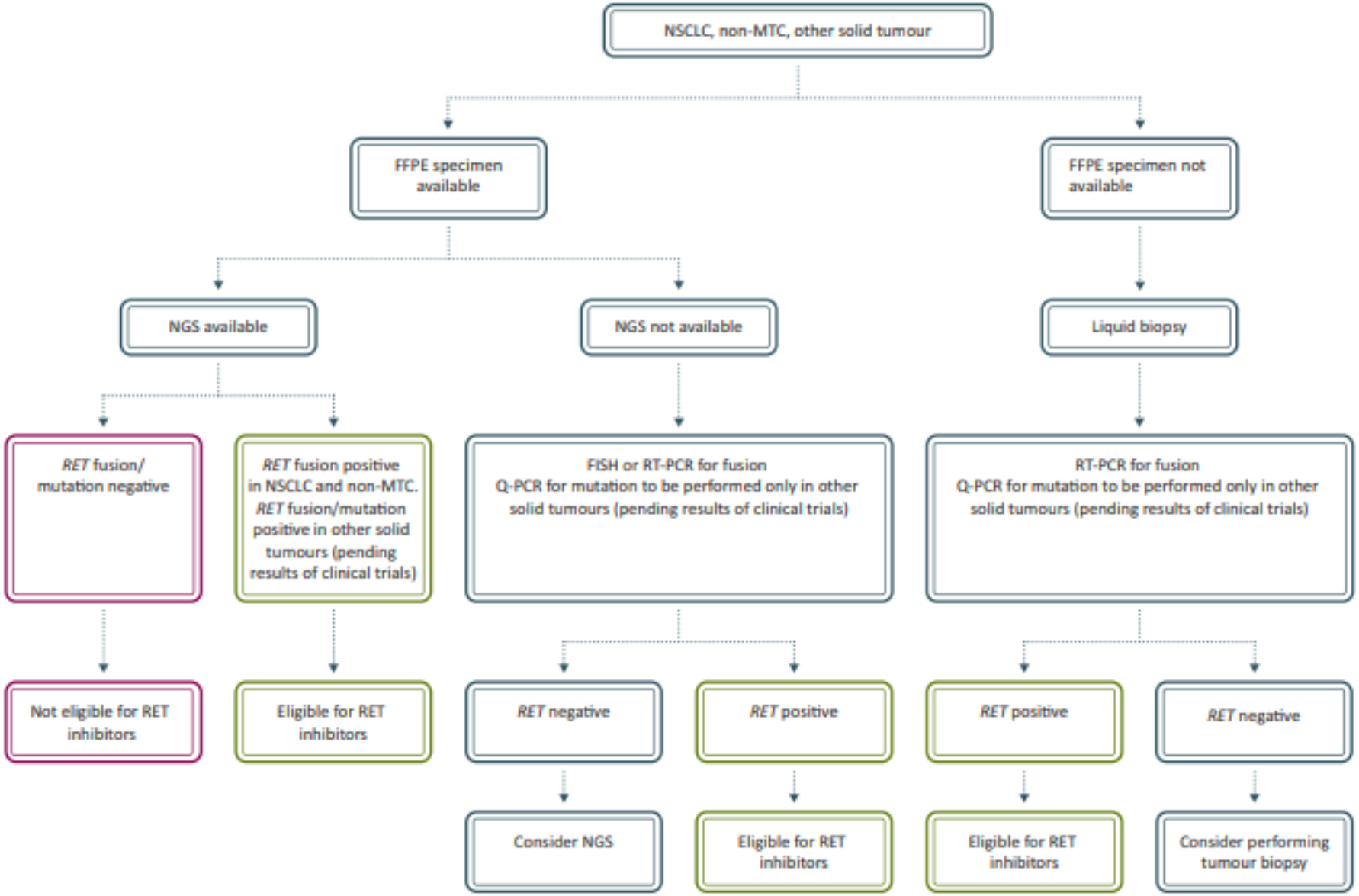
Diagnostico



Belli C, et al. Ann Oncol2021;32(3):337-350.

RET

Restrospective non-specificmultikinase RET inhibitors

Escasa eficacia
mOS 6.8m

Table 2. Best Response to RET Inhibitor Therapy

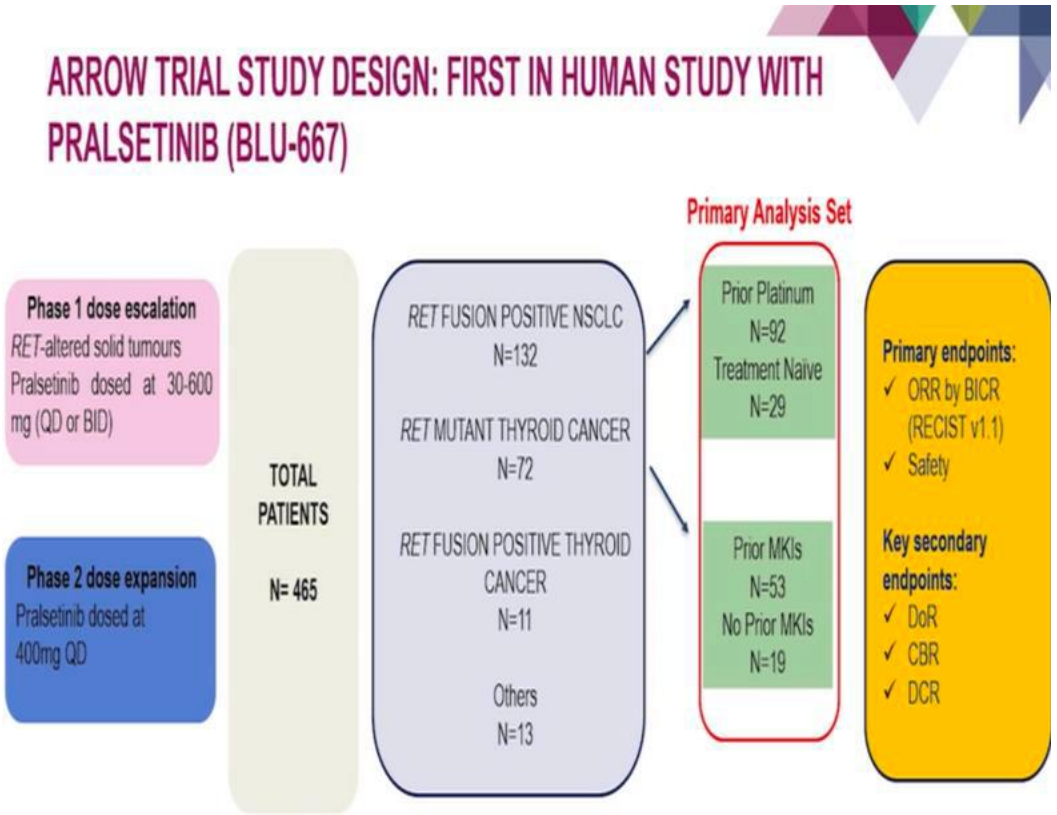
RET Inhibitor	Complete Response	Partial Response	Stable Disease	Disease Progression	Not Evaluable	Missing Data
All agents (n = 53)	2 (4%)	11 (22%)	16 (32%)	20 (40%)	1 (2%)	3
Cabozantinib (n = 21)	1 (5%)	6 (32%)	5 (26%)	7 (37%)	0	2
Vandetanib (n = 11)	0	2 (18%)	3 (27%)	6 (55%)	0	0
Sunitinib (n = 10)	0	2 (22%)	3 (33%)	3 (33%)	1 (11%)	1
Sorafenib (n = 2)	0	0	2	0	0	0
Alectinib (n = 2)	0	0	0	2	0	0
Lenvatinib (n = 2)	0	1	0	1	0	0
Nintedanib (n = 2)	1	0	1	0	0	0
Ponatinib (n = 2)	0	0	2	0	0	0
Regorafenib (n = 1)	0	0	0	1	0	0

NOTE. The best response to a multikinase inhibitor with activity against RET is summarized for 53 patients with advanced *RET*-rearranged lung cancers.

Gautschiet al, JCO 2017

RET

Pralsetinib: ARROW Phase I



Preteated:

TR 59.6% (RC 7.1%; RP 52.5%)

mDoR: 22.4m (95% CI 14.8-39.4)

mPFS 16.4 m(95% CI 11.4–22.3)

Treatment naive:

TR 75.4% (RC 5.8%; RP 69.6%)

mDoR: 13.4m (95% CI 9.4-NR)

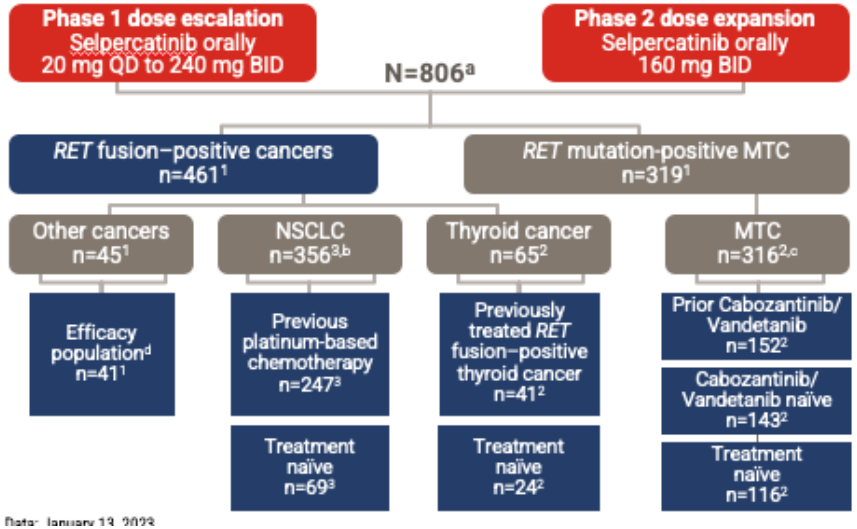
mPFS 13.2 m(95% CI 9.2–21.1)

INTRACRANEL RESPONSE: 52%

GainorJF, et al. LancetOncol2021.

RET

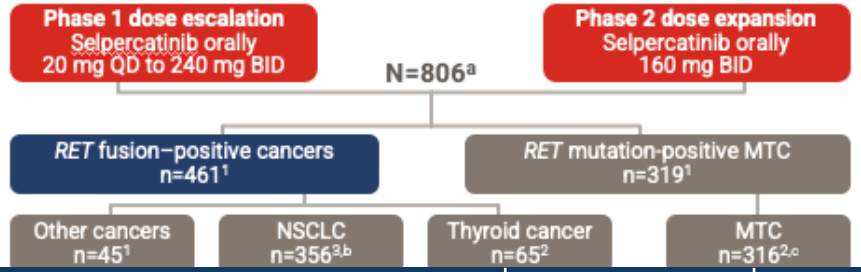
Selpercatinib, LIBRETTO 001



Drilon A, et al. J Clin Oncol. 2022; doi:10.1200/JCO.22.00393

RET

Selpercatinib, LIBRETTO 001



Patient Characteristics		Prior Platinum (n=247)	Treatment Naïve (n=69)
Median age, y (range)		61.0 (23, 81)	63.0 (23, 92)
Sex (%)	Female	56.7	62.3
	Male	43.3	37.7
Race (%)	White	43.7	69.6
	Asian	47.8	18.8
	Black	4.9	5.8
ECOG PS (%)	0	36.4	36.2
	1	60.7	58.0
	2	2.8	5.8
Never smoked (%)		66.8	69.6
Median prior systemic regimens (range)		2 (1,15)	0
Prior platinum-based chemotherapy (%)		100	-
Prior PD-1/PD-L1 inhibitor (%)		58.3	-
Prior MKI (%)		34.4	-

Drilon A, et al. J Clin Oncol. 2022; doi:10.1200/JCO.22.00393

RET

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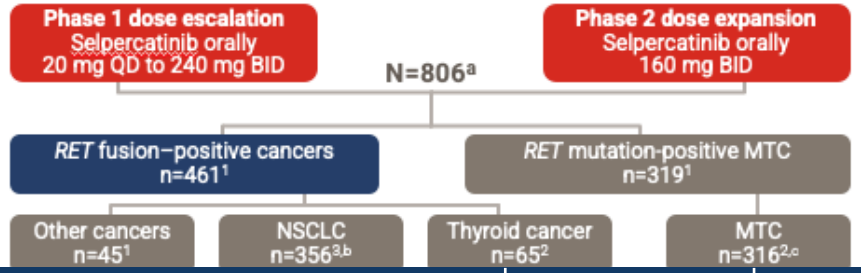

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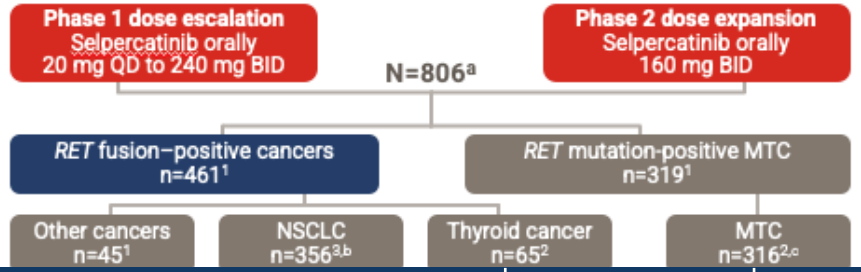
Prior MKI (%)		34.4	-

	Prior Platinum (n=247)	Treatment Naïve (n=69)
ORR by IRC, % (95% CI)	61 (55, 67)	84 (73, 92)
Median DOR estimate, mo (95% CI)	28.6 (20.4, NE)	20.2 (13, NE)
Median follow-up, mo	21.2	20.3
DOR rate at 12 mo, %	73.1	66.1
Median PFS estimate, mo (95% CI)	24.9 (19.3, NE)	22.0 (13.8, NE)
Median follow-up, mo	24.7	21.9
Censoring rate, %	55.9	53.6

Drilon A, et al. J Clin Oncol. 2022; doi:10.1200/JCO.22.00393

RET

Selpercatinib, LIBRETTO 001



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ORR 84 %

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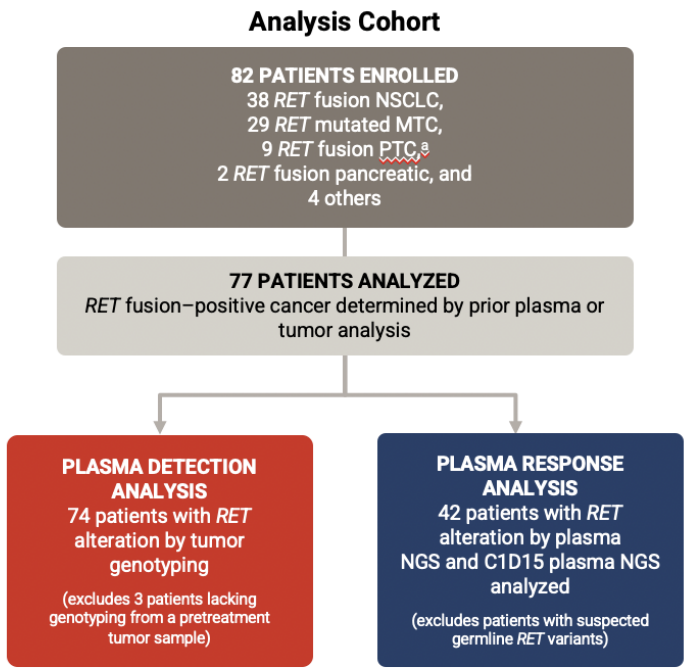
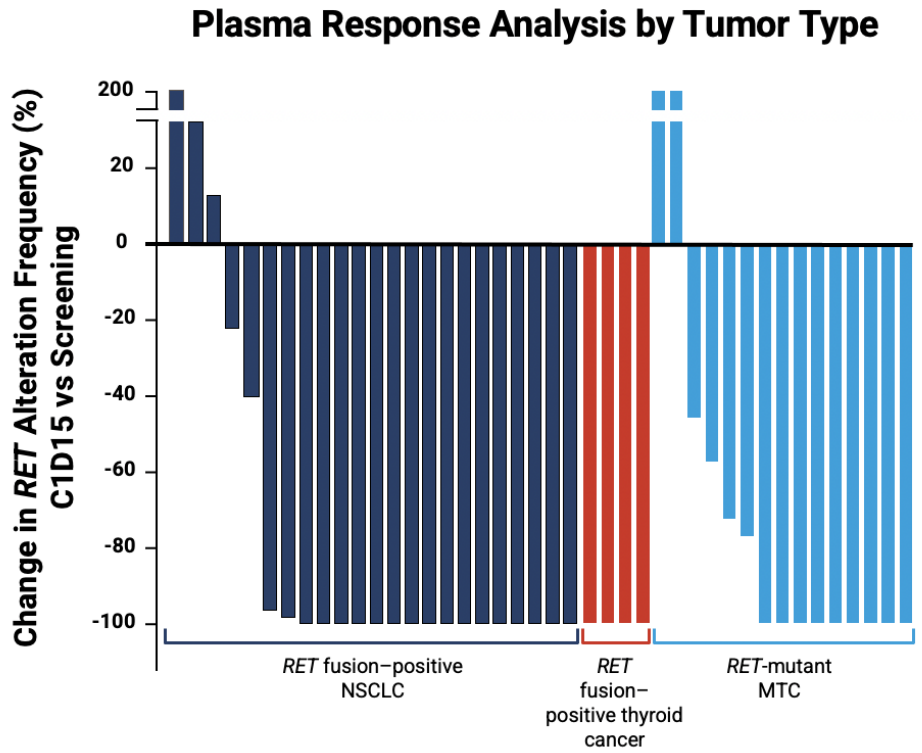
RET

Selpercatinib. LIBRETTO 001

Correlation Between *RET* Fusions in Circulating Tumor DNA and Tumor Response



Patients enrolled as of April 2, 2018. Follow-up as of July 19, 2018.
[a]Includes 1 patient with poorly differentiated thyroid cancer.



Drilon A, et al. J Clin Oncol. 2022; doi:10.1200/JCO.22.00393

RET

Selpercatinib: Libretto 431

Key Eligibility Criteria

- Stage IIIB-IIIC[1], IV non-squamous NSCLC
- No prior systemic therapy for metastatic disease
- *RET* fusion identified via NGS or PCR
- ECOG PS 0-2
- Symptomatic CNS metastases excluded

Stratification factors:

- Geography (East Asian vs. non-East Asian)
- Brain metastases (present vs. absent/unknown)[2]
- Investigator's choice of treatment with pembrolizumab

R 2:1[3]

Selpercatinib (160 mg BID)
N= 159

Carboplatin (AUC 5) or **Cisplatin** (75 mg/m^2)
+ **Pemetrexed** (500 mg/m^2)
+/- **Pembrolizumab** (200 mg)
N= 102

Optional Crossover → **Selpercatinib** (Upon BICR confirmed PD)

Gated Primary Endpoints: PFS by blinded independent central review (BICR) in ITT-Pembrolizumab[4] and ITT population
Secondary Endpoints:

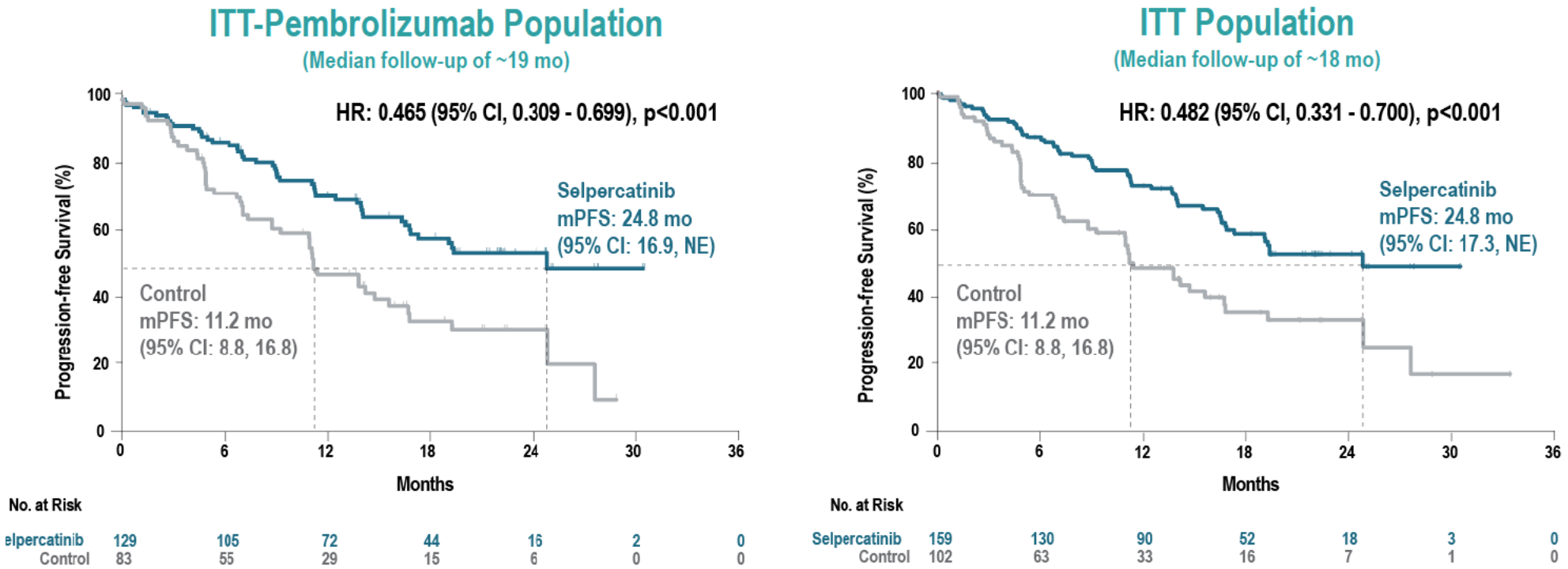
- **Efficacy** ([OS, ORR, DOR], CNS [ORR, DOR, time to progression][5])
- **Safety**
- **Patient Reported Outcomes** (NSCLC-SAQ [tertiary endpoint EORTC QLQ-C30])

[1] Not suitable for radical surgery or radiation therapy
[2] Investigator assessed

Loong et al ESMO 2023

RET

Selpercatinib: Libretto 431

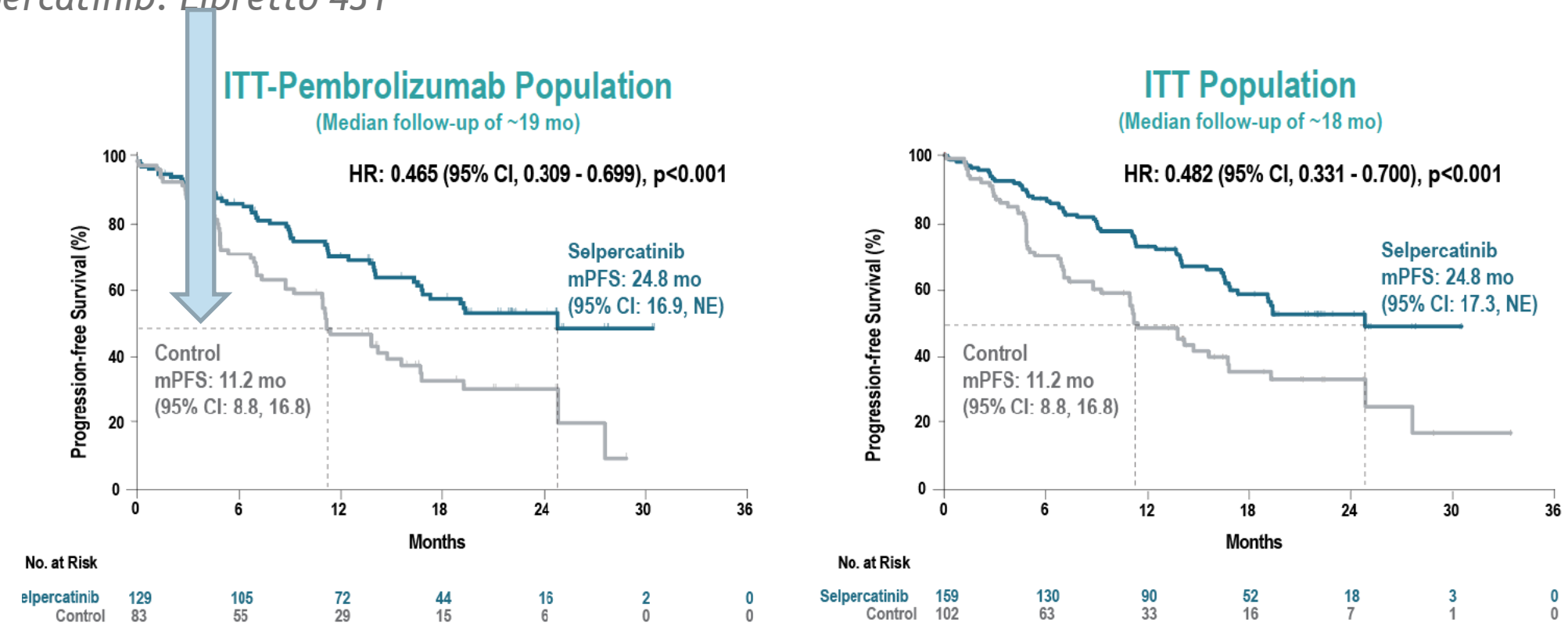


The primary endpoints were met, as selpercatinib resulted in a statistically significant improvement in PFS in both pre-specified populations

Loong et al ESMO 2023

RET

Selpercatinib: Libretto 431



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Loong et al ESMO 2023

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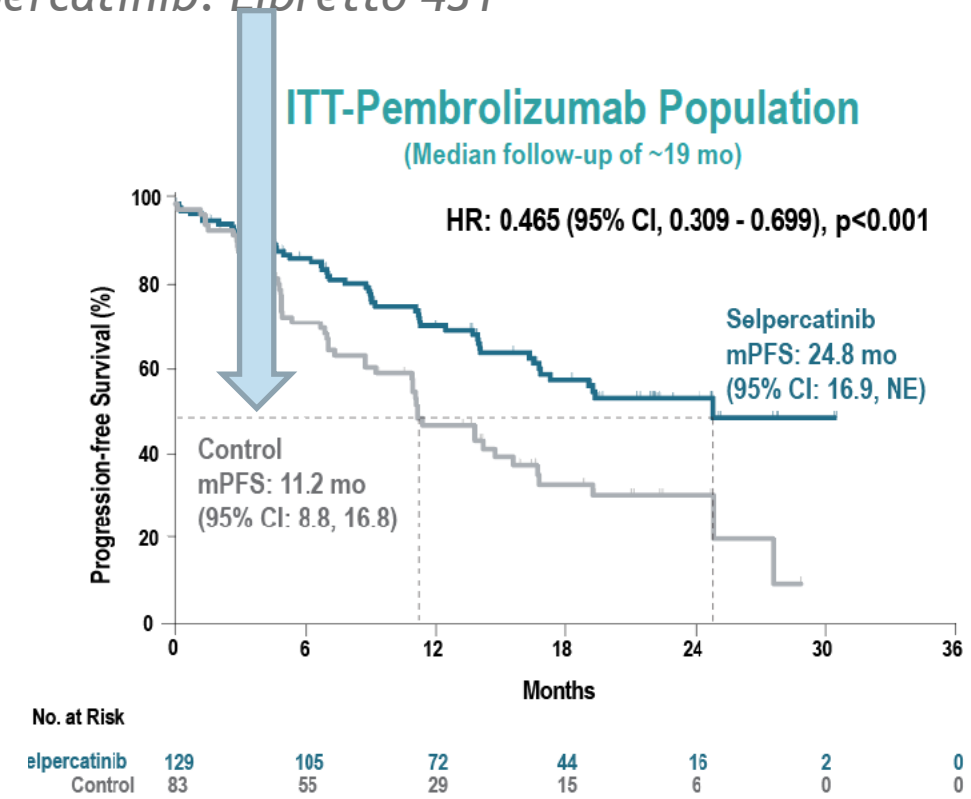

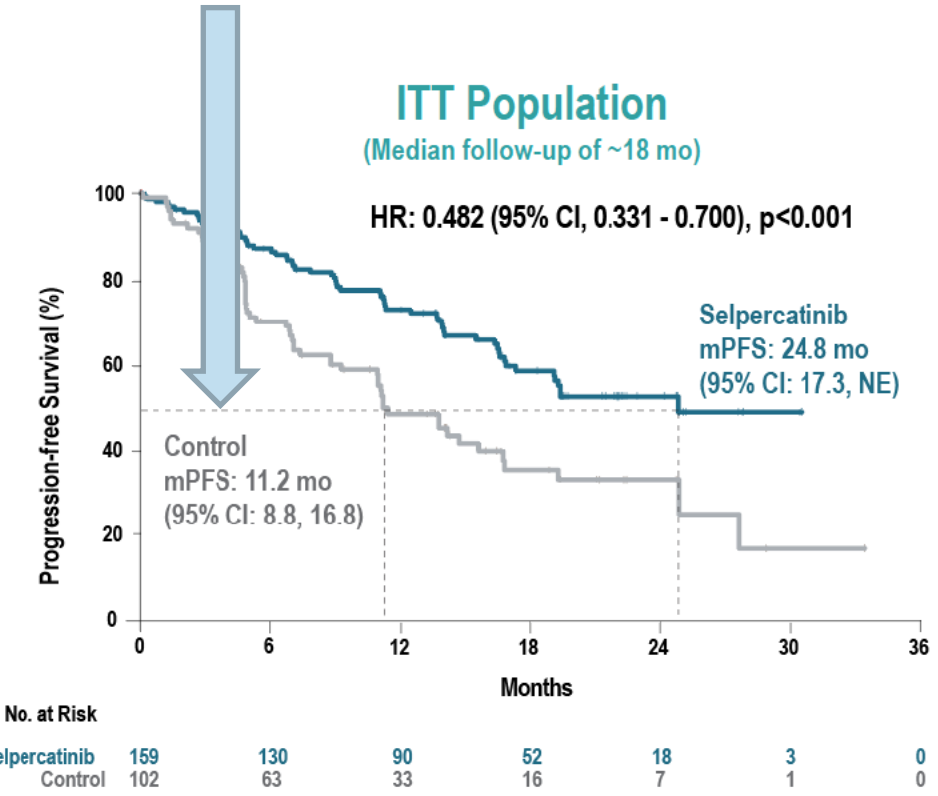

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Loong et al ESMO 2023

RET

Selpercatinib: Libretto 431

ORR 83.7 %

Systemic Outcomes

	Selpercatinib N= 129	Control N= 83
ORR, %	83.7	65.1
Median DOR, mo (95% CI)	24.2 (17.9, NE)	11.5 (9.7, 23.3)

Overall Survival immature (censoring rate ~80%) and confounded by crossover (75% effective rate)[1]: HR 0.961 (95% CI: 0.503, 1.835)

iRC 35%

Intracranial Outcomes[2]

	Selpercatinib N= 17	Control N= 12
Intracranial ORR, %	82.4	58.3
Intracranial CR, %	35.3	16.7
12-mo Intracranial DOR Rate, % (95% CI)	76.0 (42.2, 91.6)	62.5 (14.2, 89.3)
Median Intracranial PFS, mo (95% CI)	16.1 (8.8, NE)	10.4 (3.8, NE)

Loong et al ESMO 2023

RET

Selpercatinib: Libretto 431

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Intracranial Outcomes[2]

	Selpercatinib N= 17	Control N= 12
Intracranial ORR, %	82.4	58.3
Intracranial CR, %	35.3	16.7
12-mo Intracranial DOR Rate, % (95% CI)	76.0 (42.2, 91.6)	62.5 (14.2, 89.3)
Median Intracranial PFS, mo (95% CI)	16.1 (8.8, NE)	10.4 (3.8, NE)

Risk of CNS Progression

Without CNS Metastases at Baseline	Selpercatinib (N= 99)	Control (N= 51)
12-month CIR, % (95% CI)	1.1% (0.1, 5.2)	14.7% (5.7, 27.6)
Cause-specific HR[1] (95% CI)	0.17 (0.04, 0.69)	

With CNS Metastases at Baseline	Selpercatinib (N= 21)	Control (N= 21)
12-month CIR, % (95% CI)	25.7% (8.8, 46.7)	33.3% (14.3, 53.8)
Cause-specific HR[1] (95% CI)	0.61 (0.19, 1.92)	

Loong et al ESMO 2023

RET

Selpercatinib: Libretto 431

ORR 83.7 %

Systemic Outcomes

	Selpercatinib N= 129	Control N= 83
ORR, %	83.7	65.1
Median DOR, mo (95% CI)	24.2 (17.9, NE)	11.5 (9.7, 23.3)

Overall Survival immature (censoring rate ~80%) and confounded by crossover (75% effective rate)[1]: HR 0.961 (95% CI: 0.503, 1.835)

iRC 35%

Intracranial Outcomes[2]

	Selpercatinib N= 17	Control N= 12
Intracranial ORR, %	82.4	58.3
Intracranial CR, %	35.3	16.7
12-mo Intracranial DOR Rate, % (95% CI)	76.0 (42.2, 91.6)	62.5 (14.2, 89.3)
Median Intracranial PFS, mo (95% CI)	16.1 (8.8, NE)	10.4 (3.8, NE)

Risk of CNS Progression

Without CNS Metastases at Baseline	Selpercatinib (N= 99)	Control (N= 51)
12-month CIR, % (95% CI)	1.1% (0.1, 5.2)	14.7% (5.7, 27.6)
Cause-specific HR[1] (95% CI)	0.17 (0.04, 0.69)	

With CNS Metastases at Baseline	Selpercatinib (N= 21)	Control (N= 21)
12-month CIR, % (95% CI)	25.7% (8.8, 46.7)	33.3% (14.3, 53.8)
Cause-specific HR[1] (95% CI)	0.61 (0.19, 1.92)	

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RET

Selpercatinib: Libretto 431

ORR 83.7 %

Systemic Outcomes

	Selpercatinib N= 129	Control N= 83
ORR, %	83.7	65.1
Median DOR, mo (95% CI)	24.2 (17.9, NE)	11.5 (9.7, 23.3)

Overall Survival immature (censoring rate ~80%) and confounded by crossover (75% effective rate)[1]: HR 0.961 (95% CI: 0.503, 1.835)

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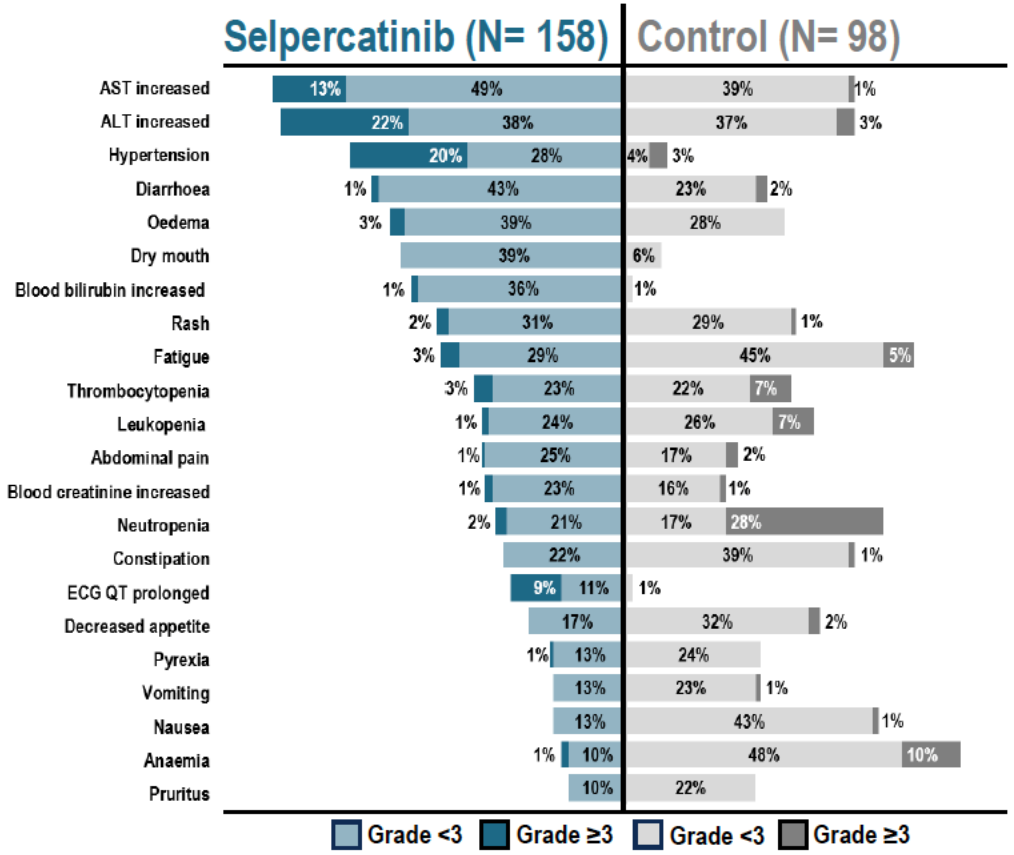
RET

Selpercatinib: Libretto 431 . Safety



Any grade treatment-emergent adverse events (TEAEs) occurring in ≥20% of patients in either study arm

Aes discontinuación: 10%
G3 70%
Aes dose reduction 51%

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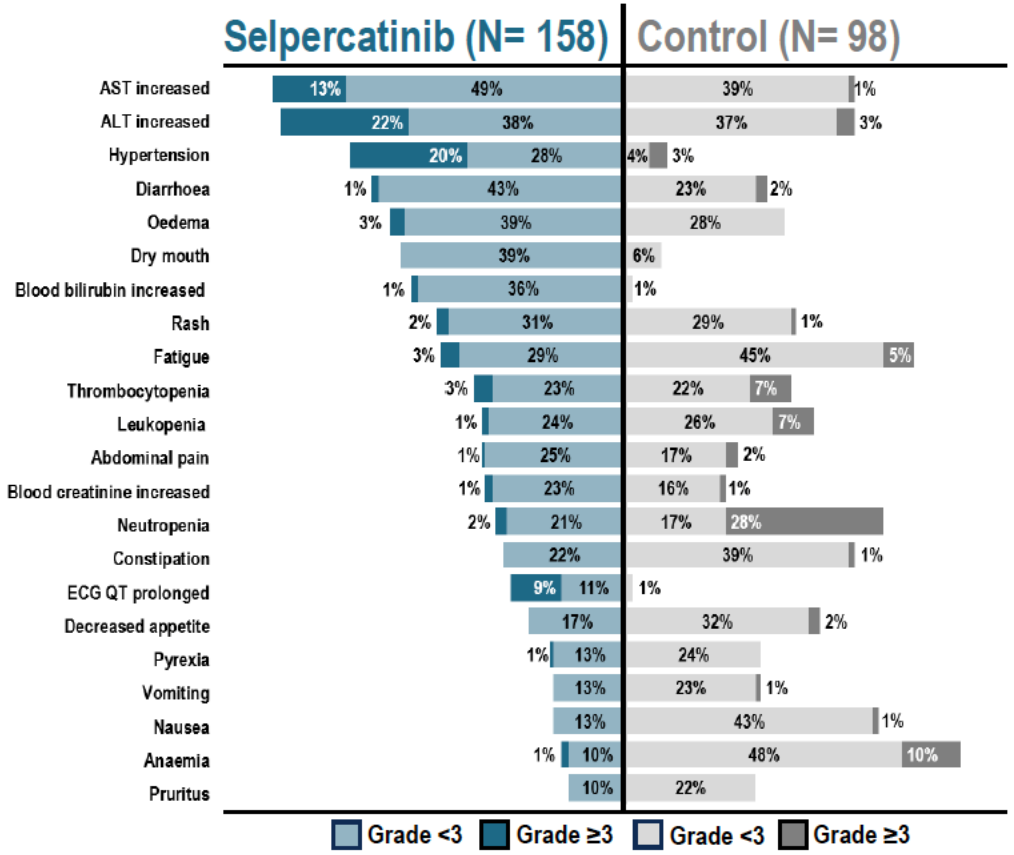
RET

Selpercatinib: Libretto 431 . Safety



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DAR la mejor terapia ANTES

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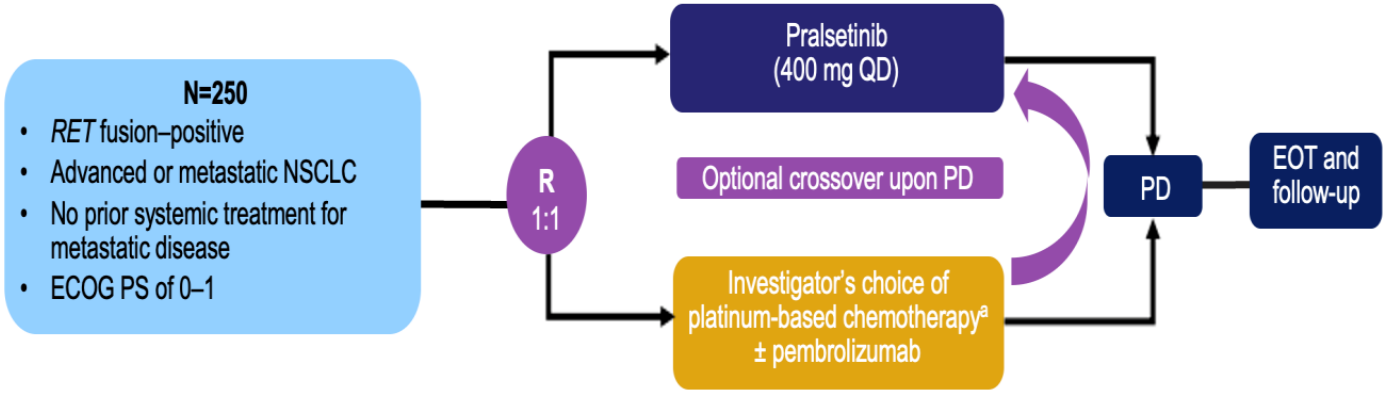
RET

Praseltinib: fase III pendiente

AcceleRET Lung

- International, open-label, randomized, phase 3 study (NCT04222972) in patients with *RET* fusion–positive NSCLC
- Efficacy and safety of pralsetinib vs investigator's choice of platinum-based chemotherapy regimen as first-line



- Stratification factors include intended pembrolizumab use if randomized to the investigator's choice arm, history of brain metastases, and ECOG PS
- Crossover to receive pralsetinib will be allowed for patients randomized to the investigator's choice arm upon PD confirmed by central review assessment

RET

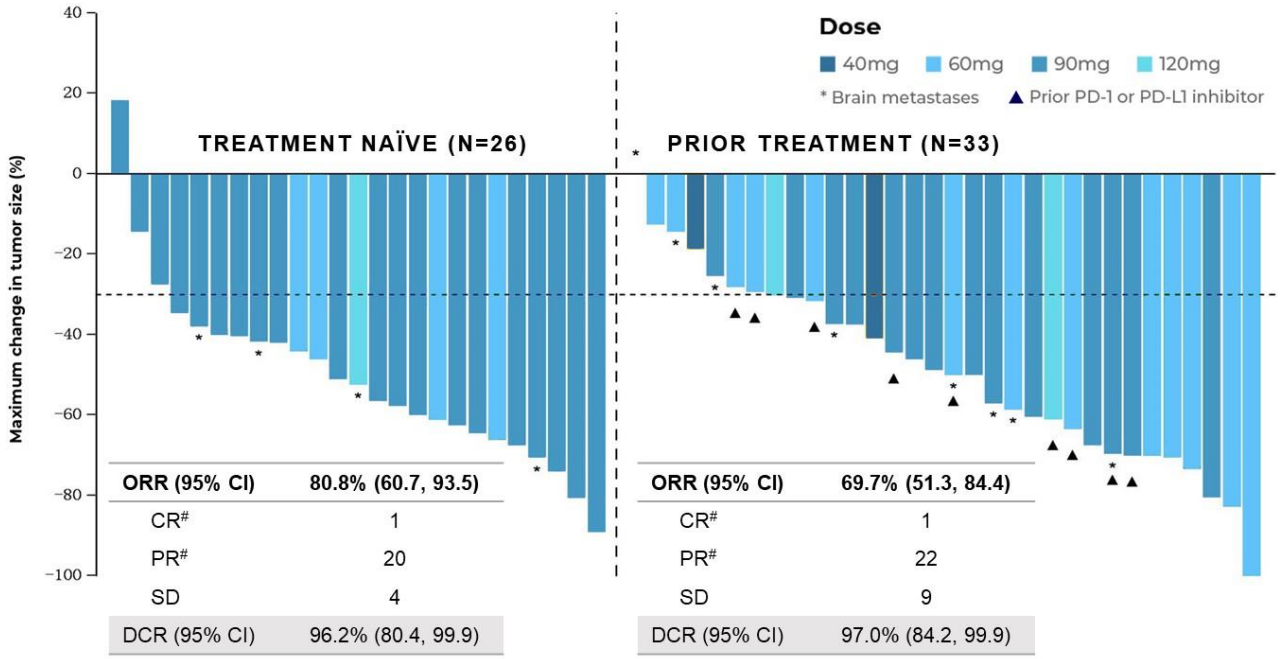
Nuevos inhibidores RET

KL590586 (A400/EP0031) active

regardless of RET fusion or prior checkpoint inhibitor

CHANGE IN TUMOR SIZE FOR PATIENTS WITH NSCLC ADMINISTERED KL590586 40-120MG QD

 # All responses are confirmed on two consecutive assessments as per RECIST 1.1.



ORR (95% CI)	**80.8% (60.7, 93.5)**
CR#	1
PR#	20
SD	4
DCR (95% CI)	96.2% (80.4, 99.9)

ORR (95% CI)	**69.7% (51.3, 84.4)**
CR#	1
PR#	22
SD	9
DCR (95% CI)	97.0% (84.2, 99.9)

Data cut-off date: 20 Apr 2023.

PRESENTED BY: Qing Zhou, Prof

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RET

Nuevos inhibidores RET

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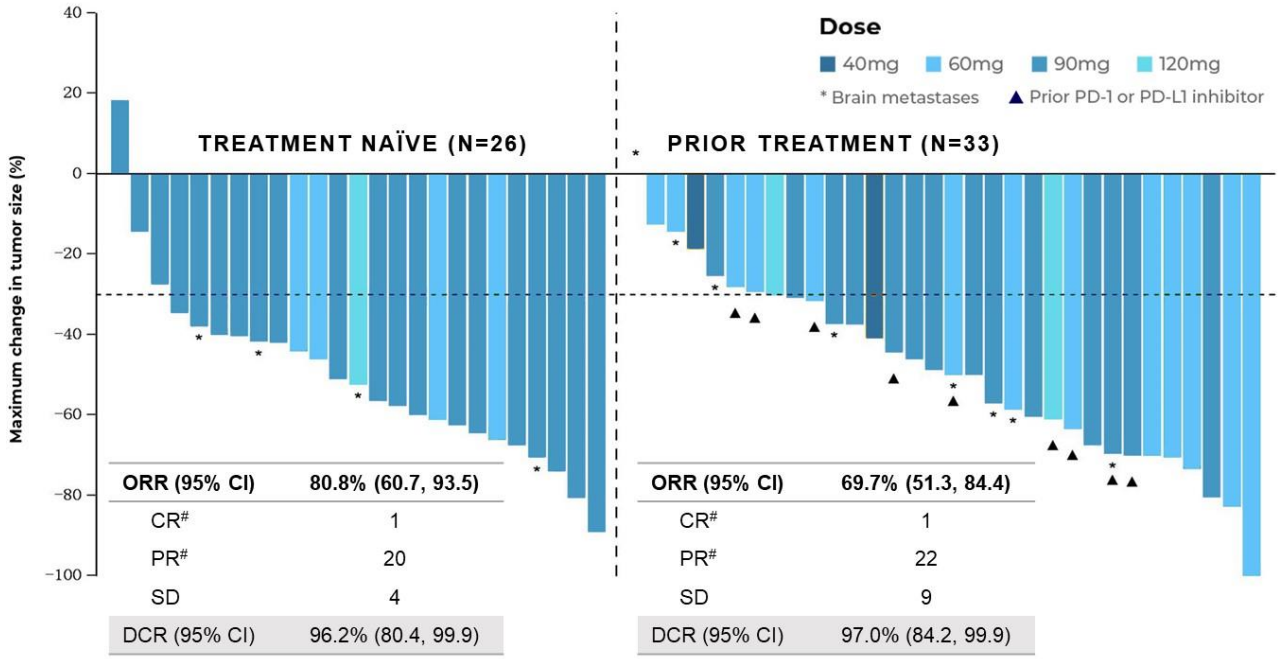


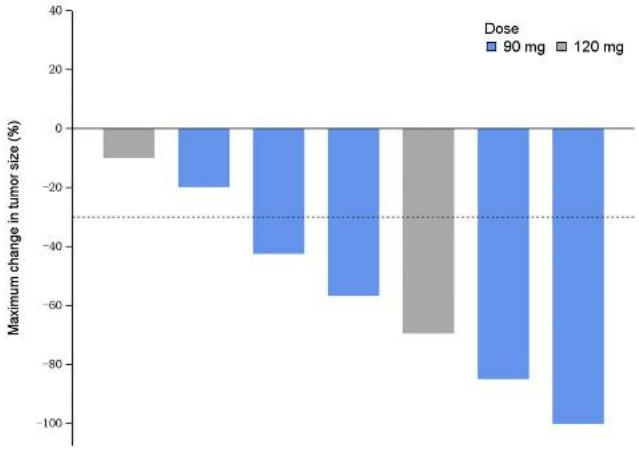
	TREATMENT NAÏVE (N=26)	PRIOR TREATMENT (N=33)
ORR (95% CI)	80.8% (60.7, 93.5)	69.7% (51.3, 84.4)
CR#	1	1
PR#	20	22
SD	4	9
DCR (95% CI)	96.2% (80.4, 99.9)	97.0% (84.2, 99.9)

Data cut-off date: 20 Apr 2023.

KL590586 (A400/EP0031) is active

in patients pretreated with 1st gen SRI

TARGET LESION RESPONSE IN NSCLC PATIENTS WITH PRIOR 1ST GEN SRI TREATMENT



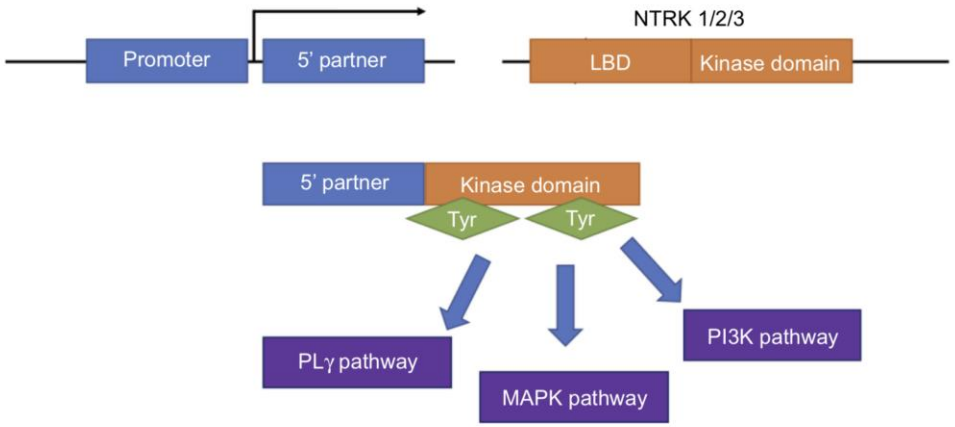
PRESENTED BY: Qing Zhou, Prof

Zhou et al ASCO 2023

NTRK

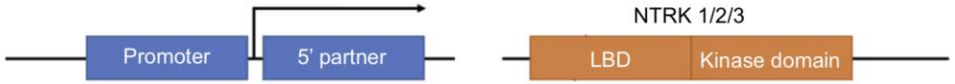
Garrido et al. ClinTranslOncol.2021.

NTRK



Garrido et al. ClinTranslOncol.2021.

NTRK



Low prevalence of NTRK gene fusions and of NTRK expression:
- Lung cancer
- Colon, breast, thyroid cancer
- Melanoma
- Cholangiocarcinoma, pancreatic cancer
- Spitzoid tumour
- Papillary thyroid carcinoma

Routine molecular testing

YES
- TRK included
- TRK not included → If known drivers are negative

NO → **Perform panTRK IHC screening** → If positive

Low prevalence of NTRK gene fusions, but frequent NTRK expression:
- Neuroendocrine tumours
- Glioma
- Sarcomas
- GIST

High prevalence of NTRK gene fusions:
- Infantile fibrosarcoma
- Secretory carcinoma of salivary gland and breast
- Congenital mesoblastic nephroma

Routine FISH testing

YES → If FISH is negative

NO

Broad NGS testing that includes NTRK genes

Garrido et al. ClinTranslOncol.2021.

NTRK

Larotrectinib

Study Design

Adult phase I trial (NCT02122913)
- Age ≥18 years
- Advanced solid tumors

n=1

Phase II basket trial (NAVIGATE, NCT02576431)
- Age ≥12 years
- Advanced solid tumors
- TRK fusion cancer

n=19

20 patients with TRK fusion lung cancer

TRK fusion status determined by local CLIA-accredited (or similar) laboratories

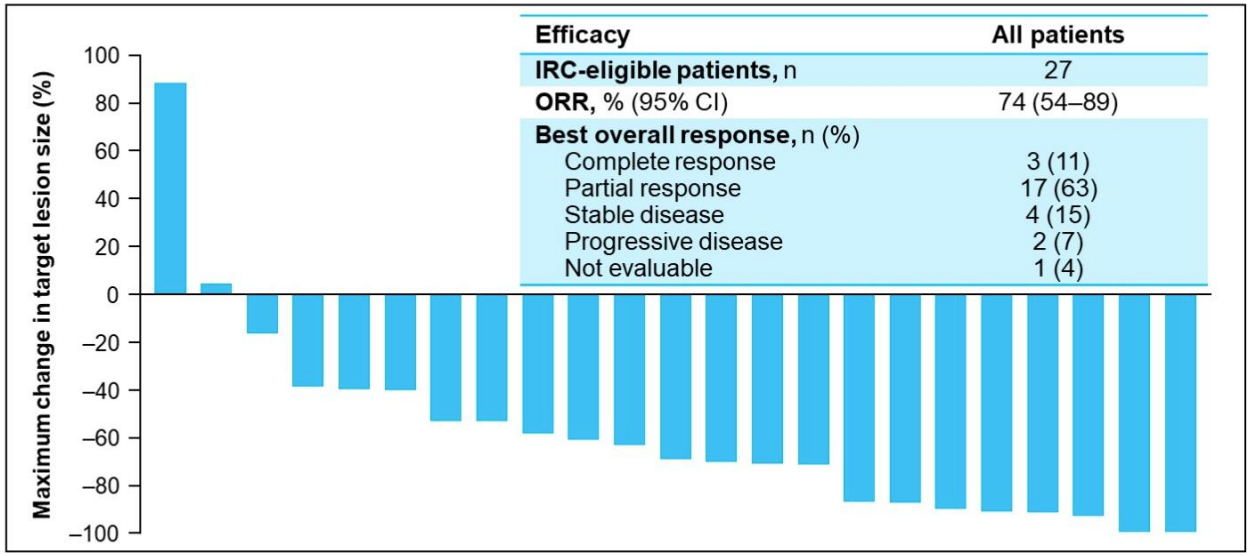
Data cut-off: July 20, 2020

Primary endpoint
- Best ORR per IRC and INV (RECIST v1.1)

Secondary endpoints
- Duration of response
- Progression-free survival
- Overall survival
- Safety

Larotrectinib dose
- Larotrectinib, 100 mg BID continuously
- 28-day cycles

Figure 2. Maximum change in target lesion size following treatment in patients with TRK fusion lung cancer (n=23)†



Efficacy	All patients
IRC-eligible patients, n	27
ORR, % (95% CI)	74 (54–89)
Best overall response, n (%)	
Complete response	3 (11)
Partial response	17 (63)
Stable disease	4 (15)
Progressive disease	2 (7)
Not evaluable	1 (4)

Lin ESMO 2023

NTRK

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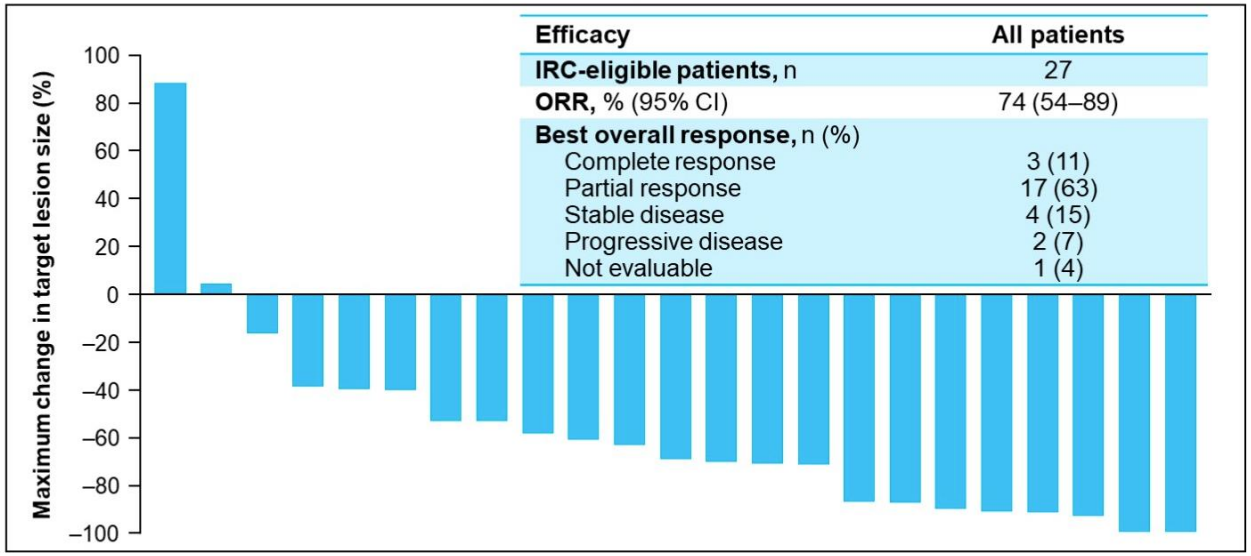

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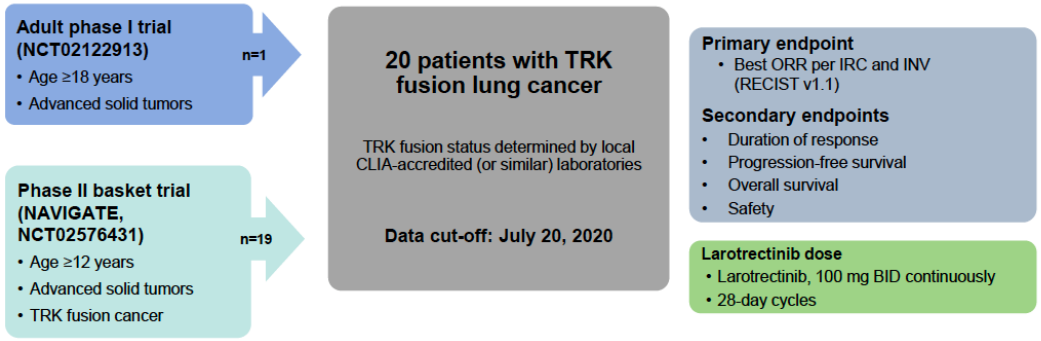
Median PFS, months (95% CI)	**33.0 (11.3–NE)**
Median follow-up, months	24.7
12-month PFS, % (95% CI)	70 (51–89)
24-month PFS, % (95% CI)	52 (29–74)

Lin ESMO 2023

NTRK

Larotrectinib

Study Design



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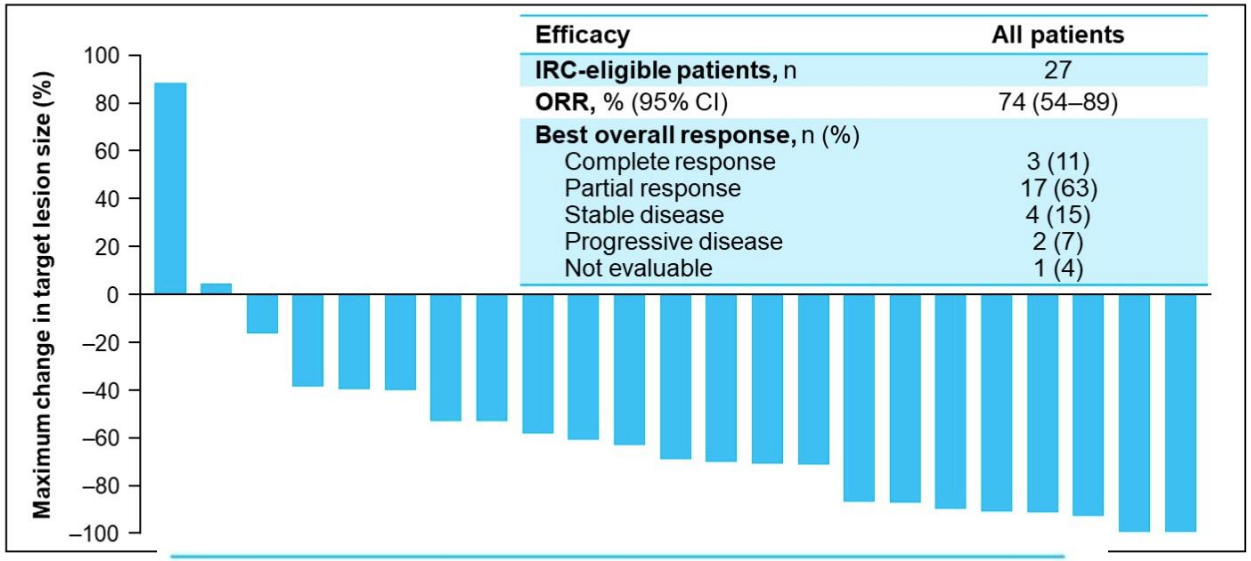

Median OS, months (95% CI)	**39.3 (17.2–NE)**
Median follow-up, months	23.1
12-month OS, % (95% CI)	89 (76–100)
24-month OS, % (95% CI)	67 (48–86)

Lin ESMO 2023

NTRK

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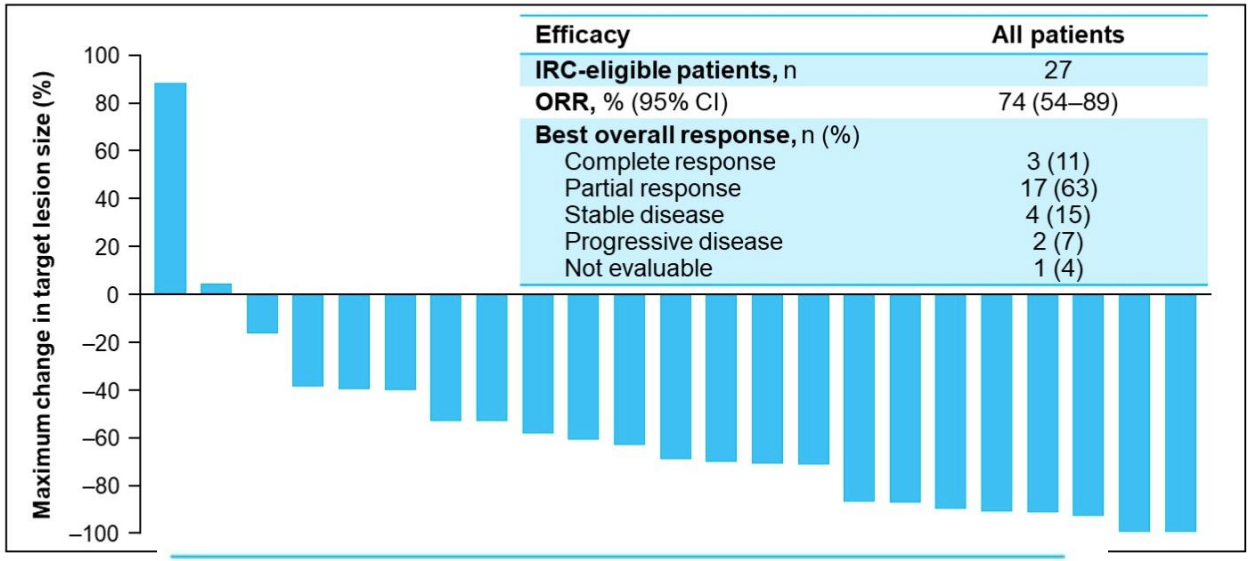

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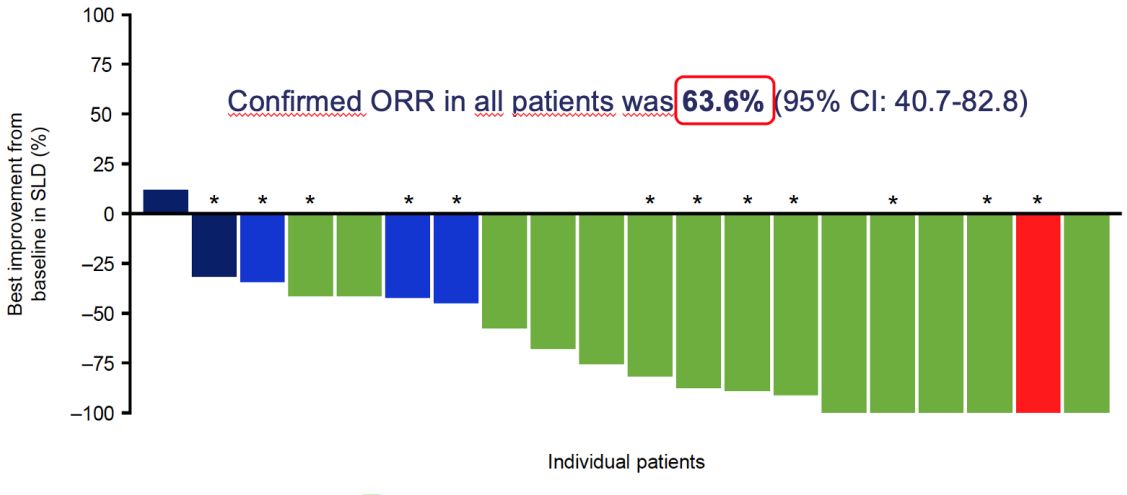
Financiacion ESPAÑA 1/10/2023

Lin ESMO 2023

NTRK

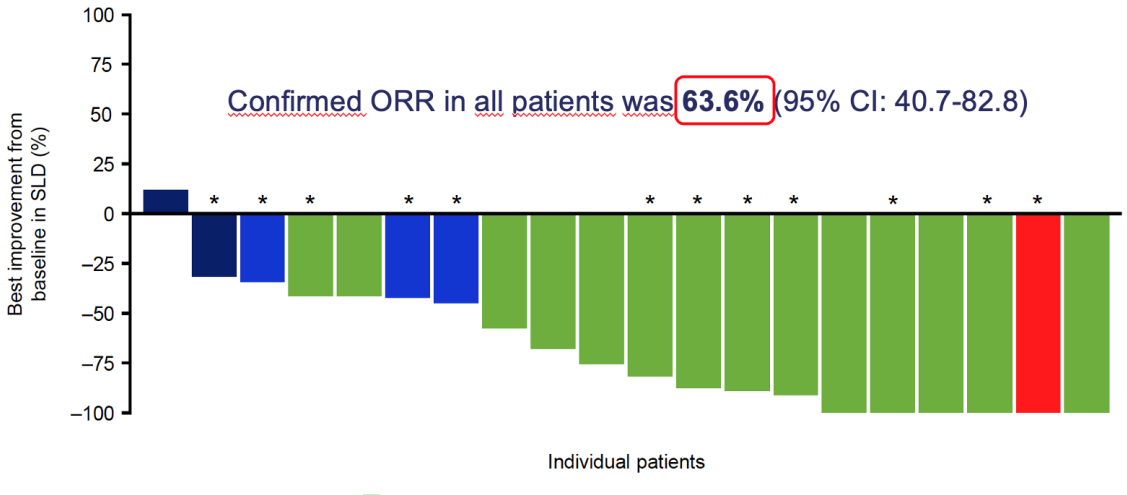
Entrectinib ALKA/ STARTRKn1-2 Trial. N: 2



Median time to event, months (95% CI)	All patients (N=22)	Baseline CNS metastases* (n=13)	No baseline CNS metastases* (n=9)
DoR	19.9 (10.4–29.4)†	29.4 (13.0–NE)‡	19.9 (9.2–NE)§
PFS	14.9 (6.5–30.4)	13.8 (4.5–NE)	17.8 (10.1–NE)
OS	NE (20.8–NE)	NE (5.9–NE)	NE (20.8–NE)

NTRK

Entrectinib ALKA/ STARTRKn1-2 Trial. N: 2



Financiacion ESPAÑA 1/12/2023

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NTRK

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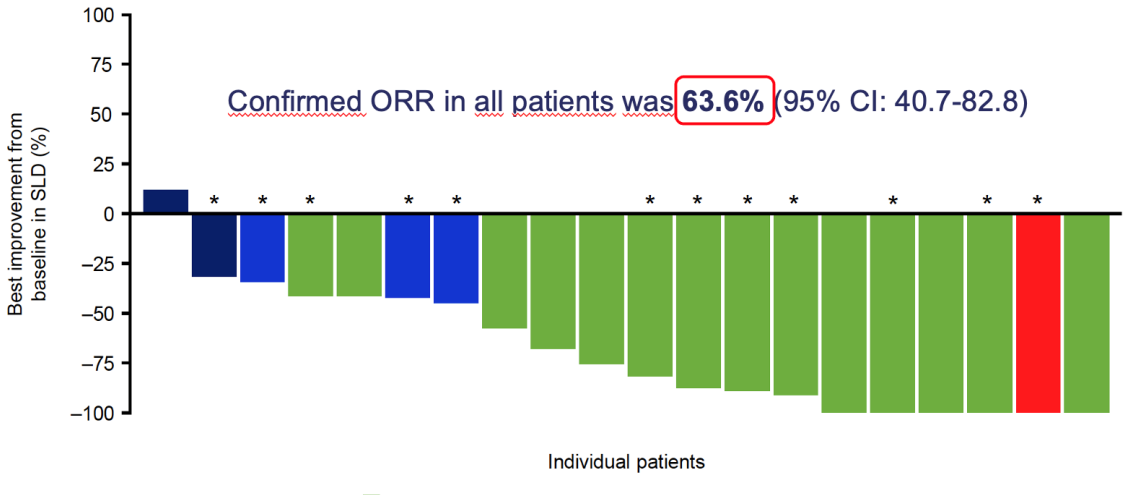

Financiacion ESPAÑA 1/12/2023

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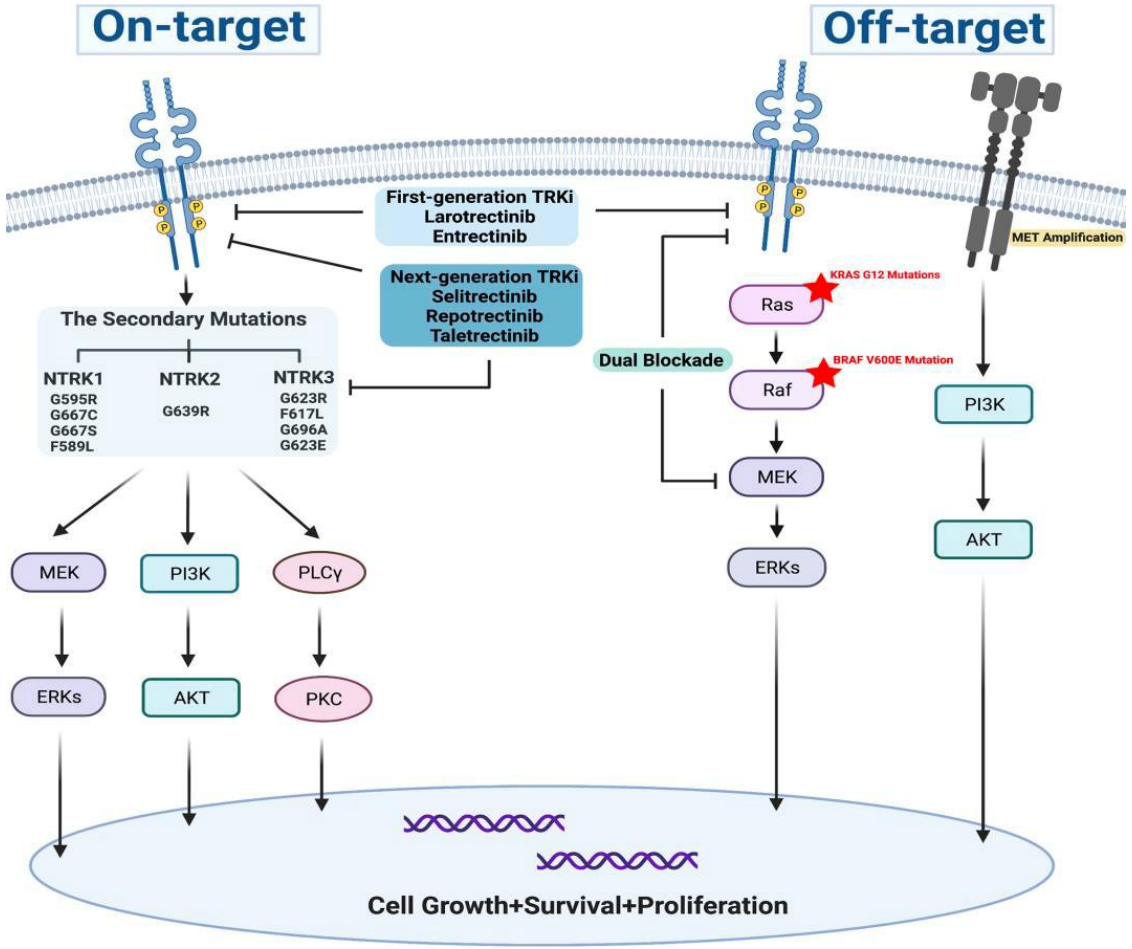
OS	NE (20.8–NE)	NE (5.9–NE)	NE (20.8–NE)

NTRK

Mechanism of resistance



Liu Reviem Frontiers 2023

NTRK

Repotrectinib. TRIDENT -1

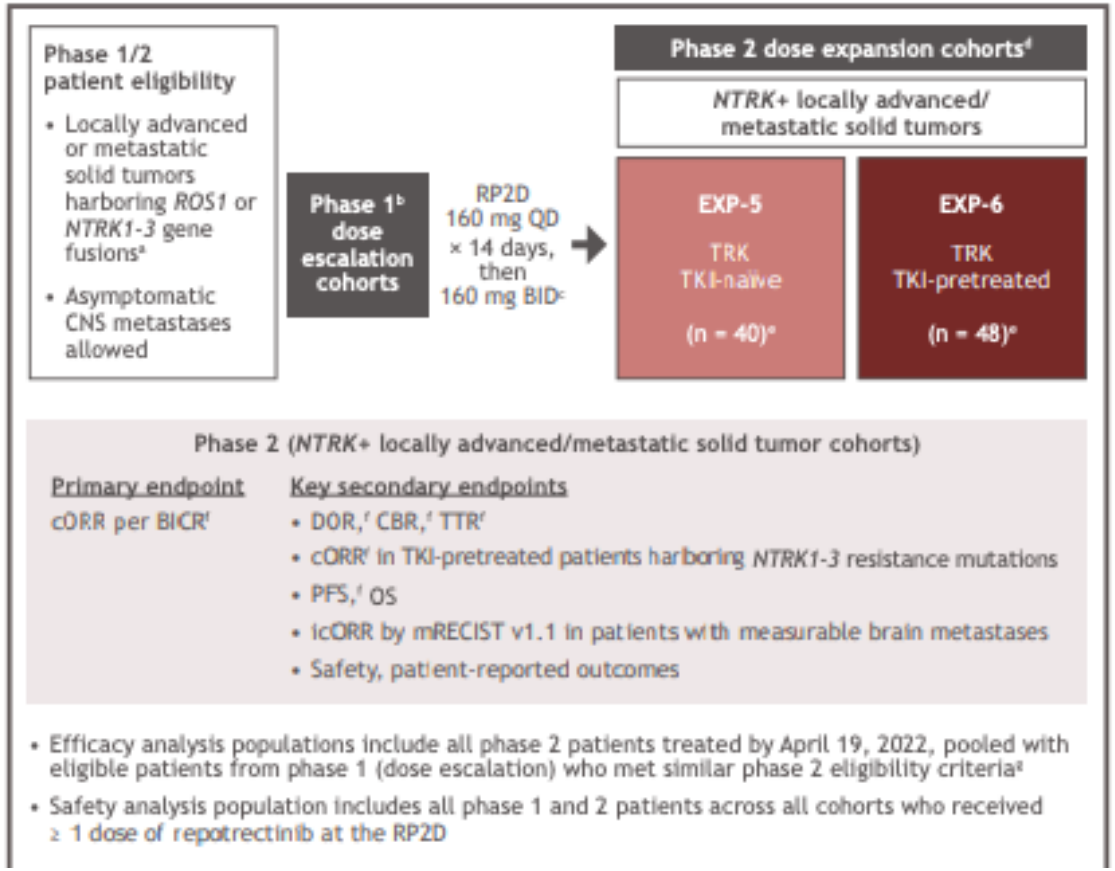


Table 2: Efficacy in TRK TKI-naïve and TKI-pretreated patients with *NTRK*+ NSCLC

	TRK TKI-naïve patients with *NTRK*+ NSCLC (n = 21)	TRK TKI-pretreated patients with *NTRK*+ NSCLC (n = 14)
cORR,[a] % (95% CI) CR, n (%) PR, n (%)	62 (38–82) 2 (10) 11 (52)	43 (18–71) 0 6 (43)
CBR,[a] % (95% CI)	86 (64–97)[b]	57 (29–82)[c]
12-mo DOR, % (95% CI)	92 (76–100)	44 (1–88)
12-mo PFS, % (95% CI)	64 (43–86)	23 (0–49)
Median time to response, mo (range)	1.8 (1.6–3.9)	1.9 (1.8–2.0)

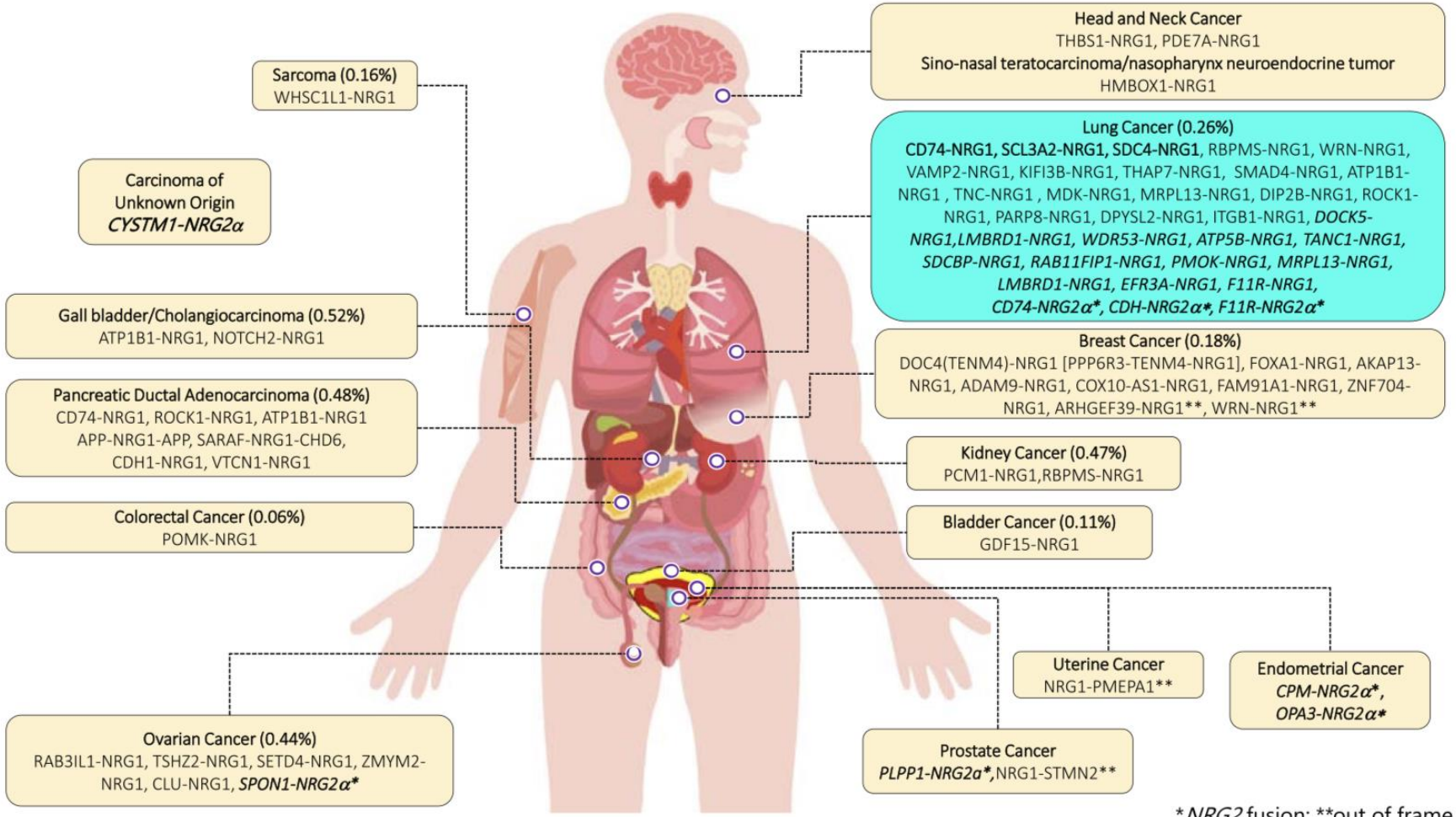
[a]By RECIST v1.1. [b]CBR was defined as CR + PR + SD: 24% (n = 5) and 5% (n = 1) of patients, respectively, had SD or PD. [c]CBR was defined as CR + PR + SD: 14% (n = 2) and 21%

FDA breakthrouh therapy Oct 2021
Approval China after TKI progression Agosto 2023

Solomon et al . ESMO 2022 1372P

NRG1 & NRG2

Distribution of fusions

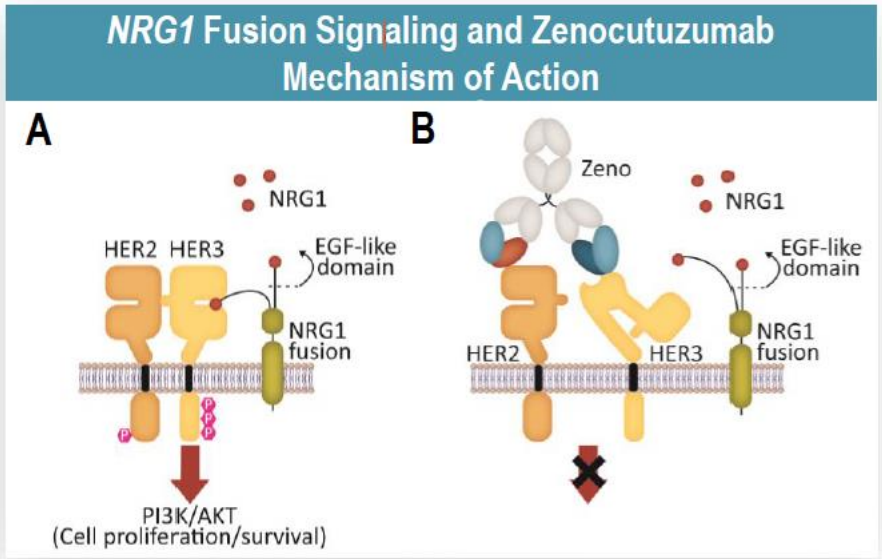


**NRG2* fusion; **out of frame

Nagasaka et al. Trends in Cancer, March 2022, Vol. 8, No. 3

NRG1

Zenocutuzumab : eNRGy Trial



Schram M et al. ASCO 2022

NRG1

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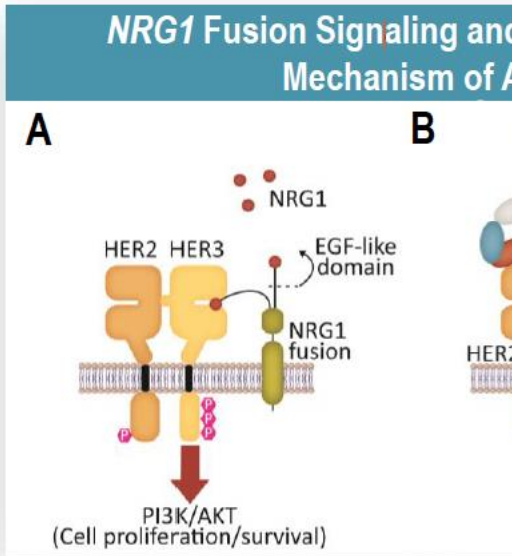

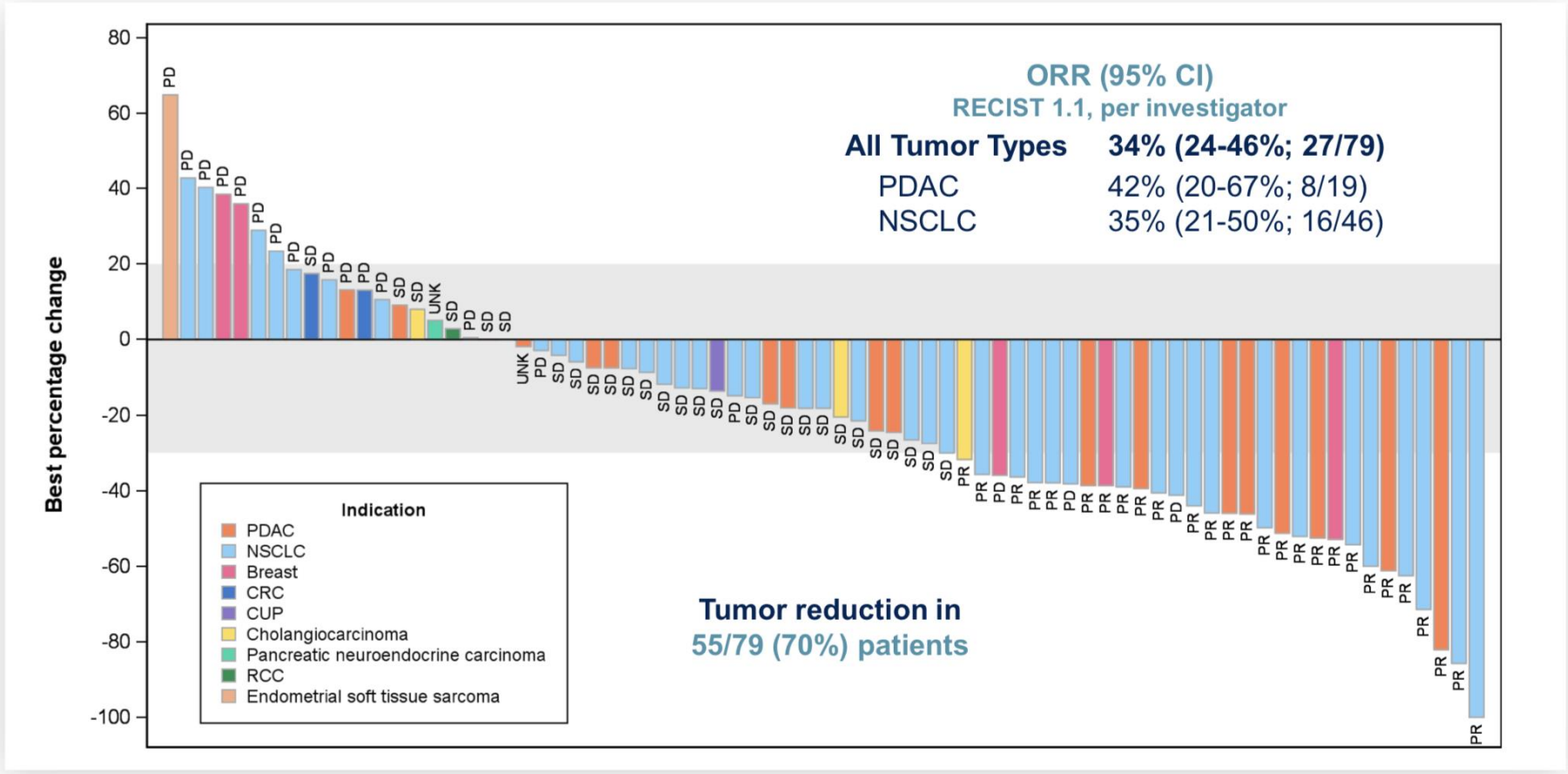

Schram M et al. ASCO 2022

NRG1

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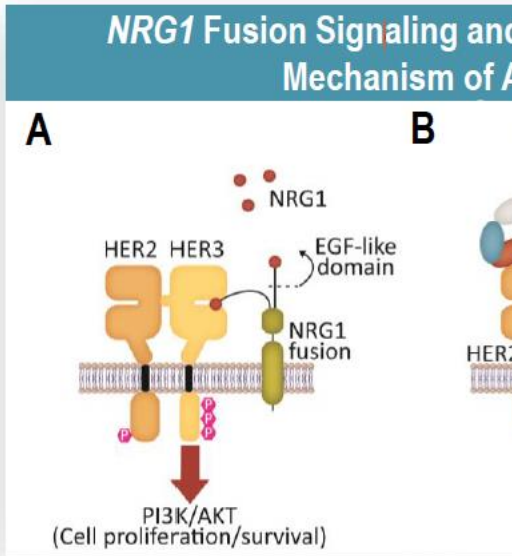
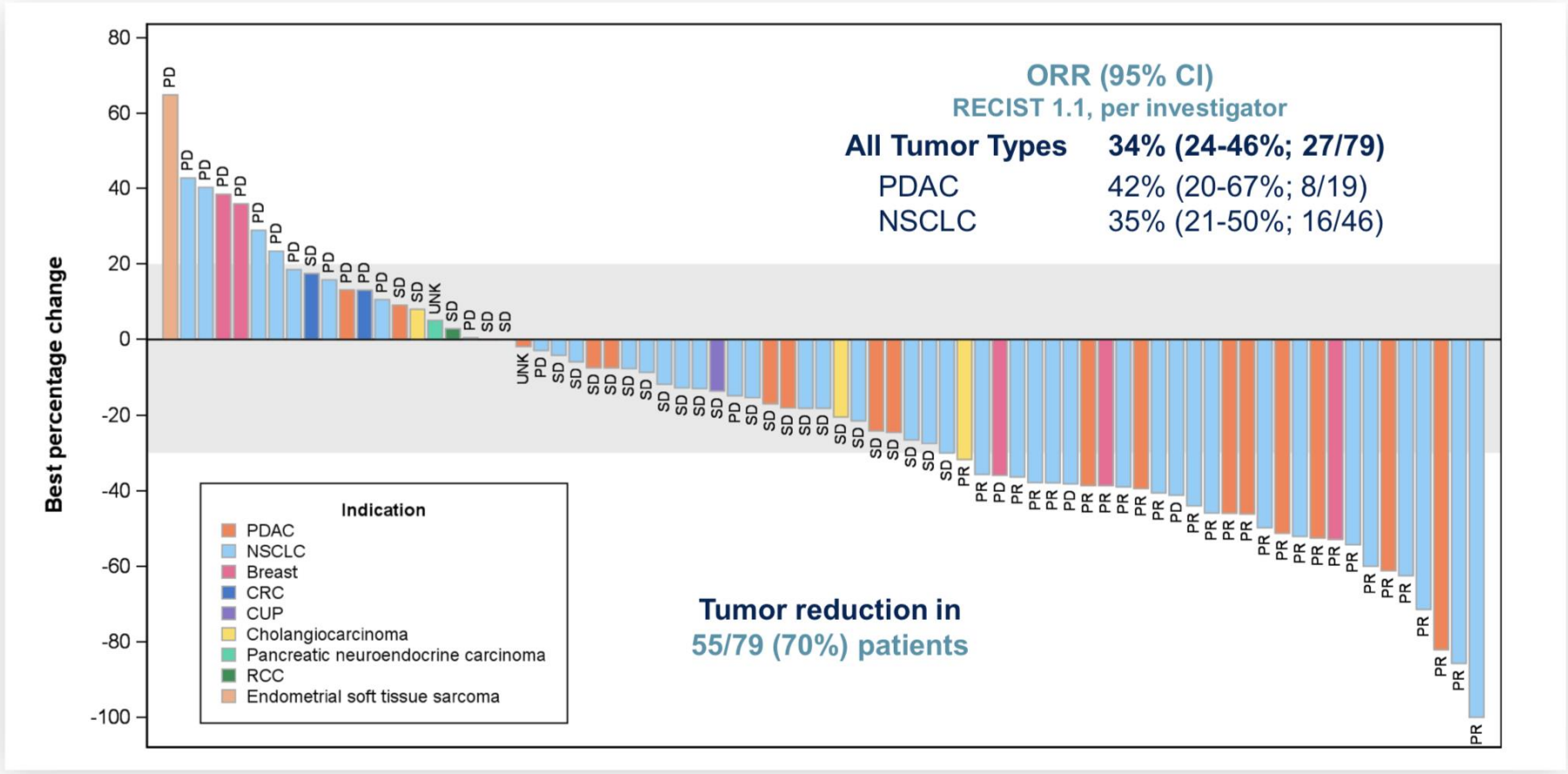


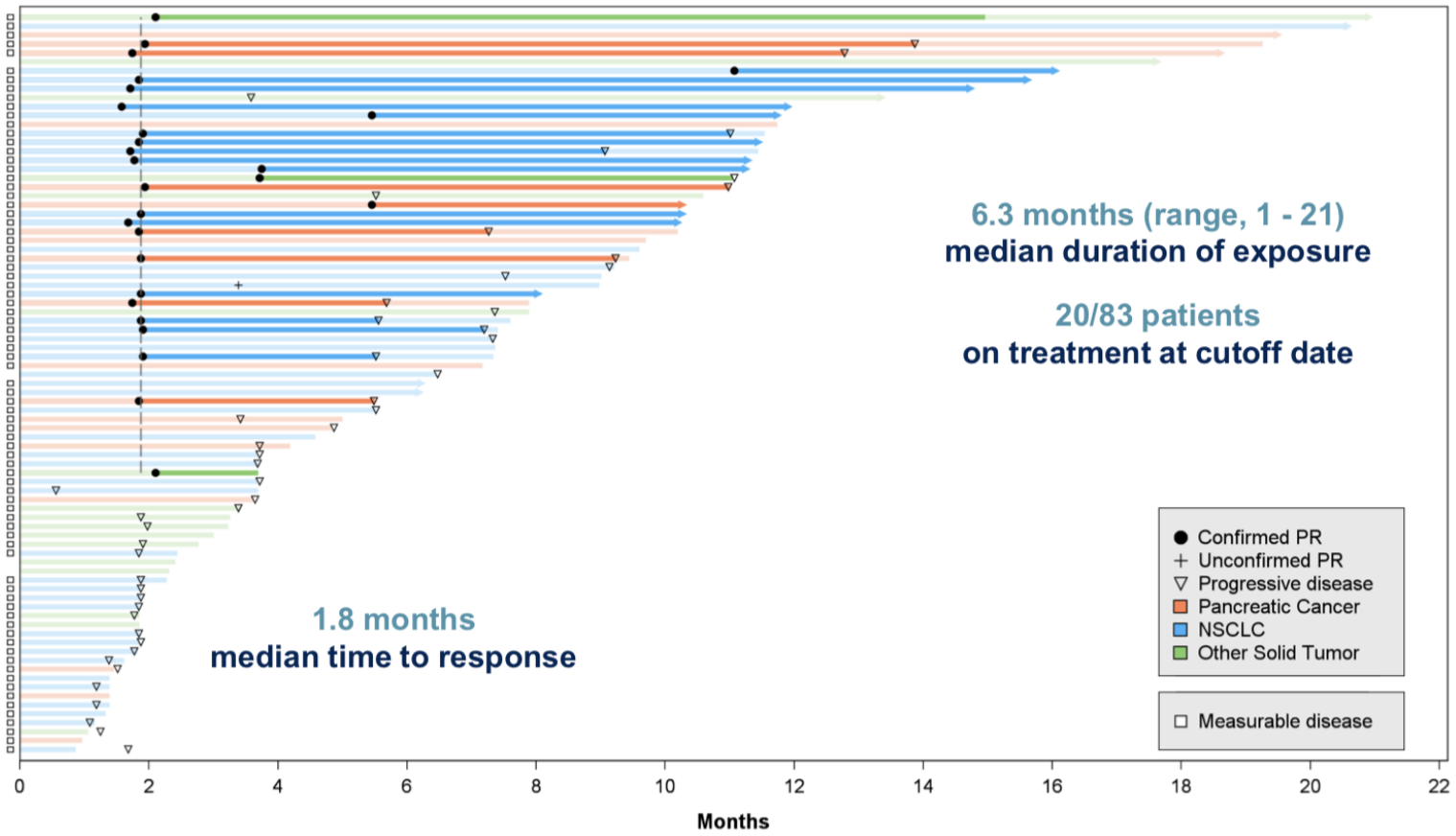


Schram M et al. ASCO 2022

NRG1

Zenocutuzumab. eNRGy Trial

Time to Response and Time on Therapy



FDA Fast track Designation

Schram M et al. ASCO 2022

NRG1

Zenocutuzumab. eNRGy Trial

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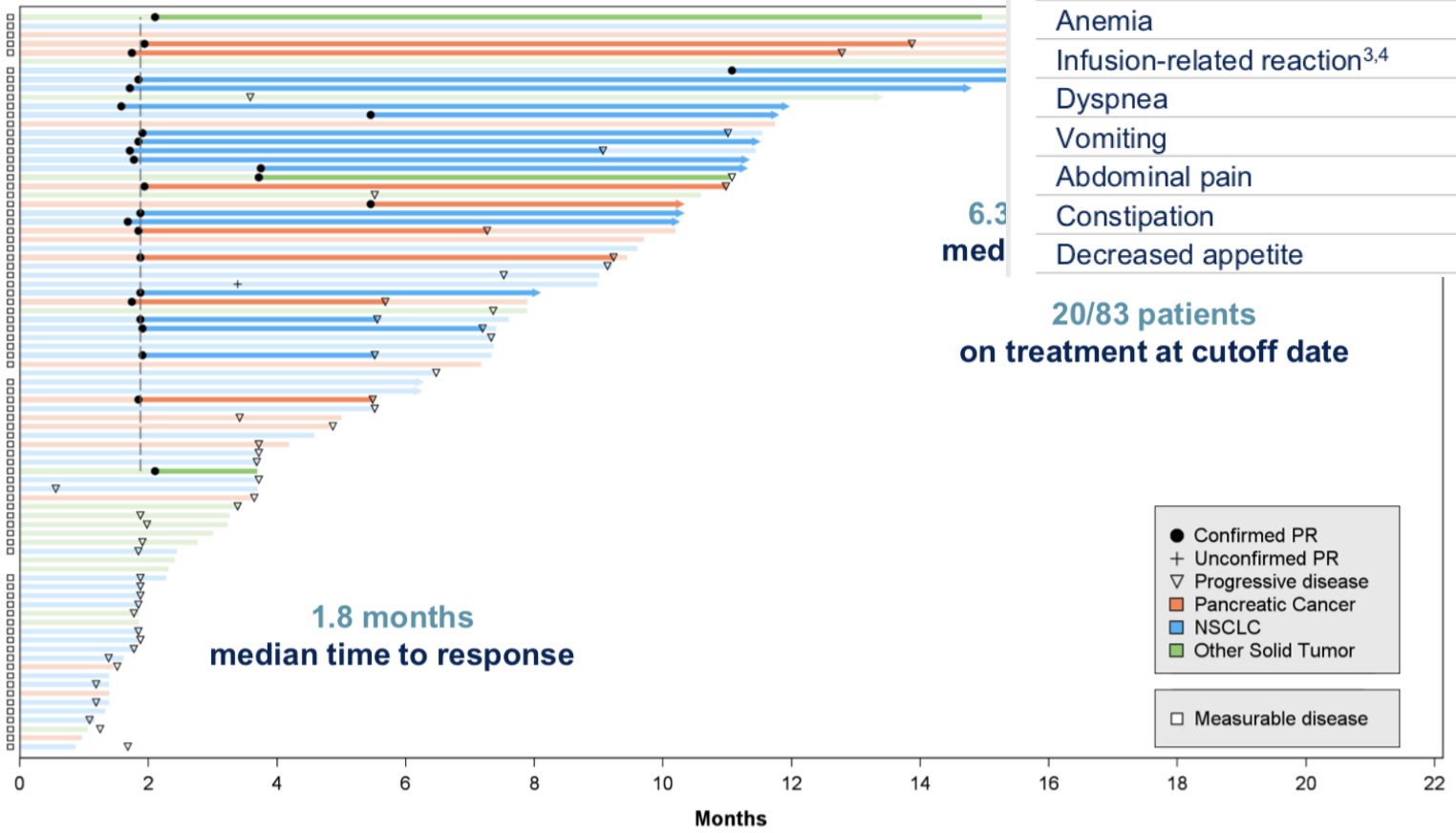

AEs Irrespective of Causality (>10%)			
	ALL GRADES	GRADE 3-4	GRADE 5
Patients with ≥1 AE	92%	36%	3%
Diarrhea	32%	2%	-
Asthenia/fatigue	30%	4%	-
Nausea	20%	1%	-
Anemia	19%	3%	-
Infusion-related reaction[3,4]	15%	1%	0.5%
Dyspnea	14%	4%	-
Vomiting	13%	0.5%	-
Abdominal pain	12%	1%	-
Constipation	11%	-	-
Decreased appetite	10%	0.5%	-

FDA Fast track Designation

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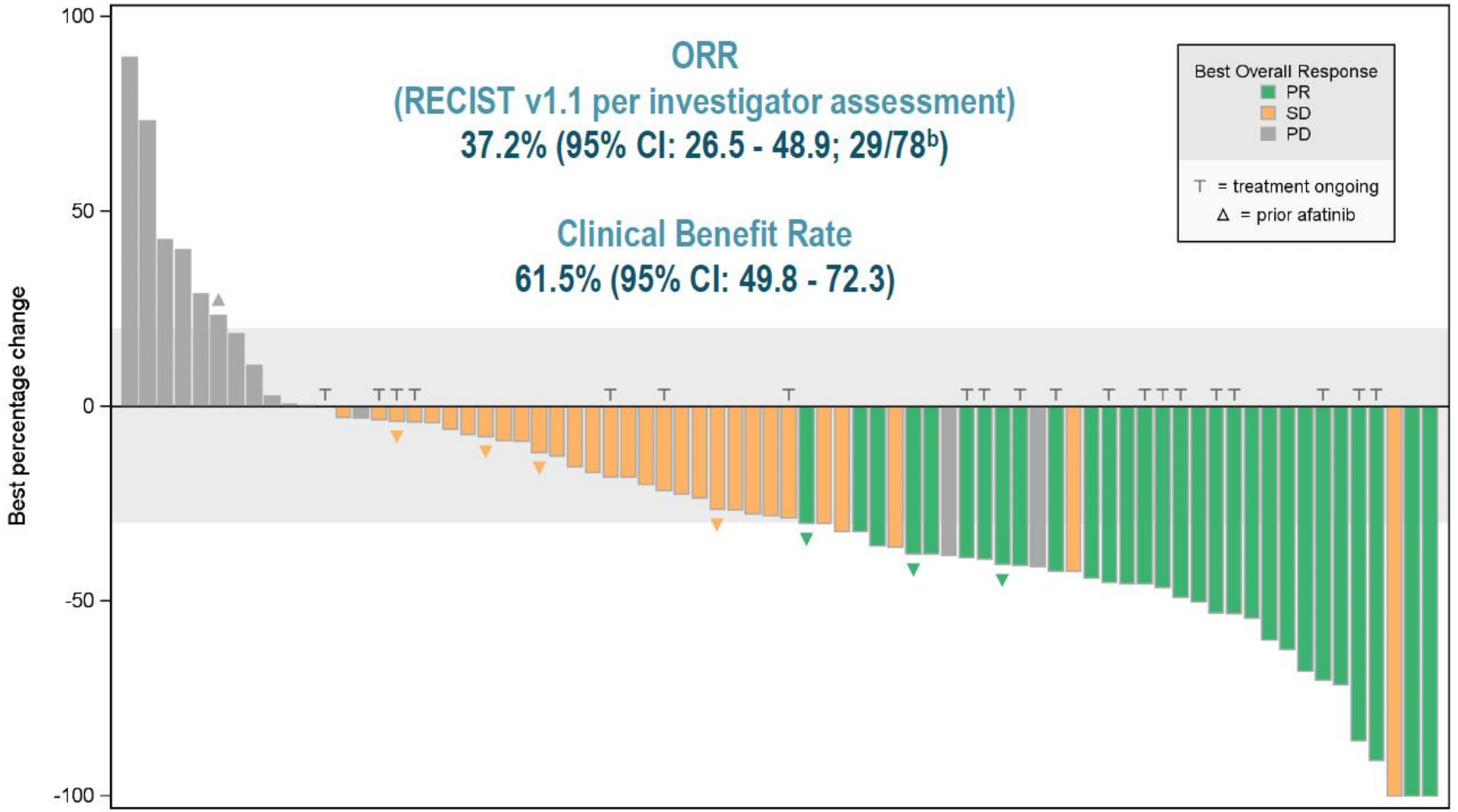
NRG1

Zenocutuzumab. eNRGy Trial + EAP Program Lung. N: 105



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NRG1

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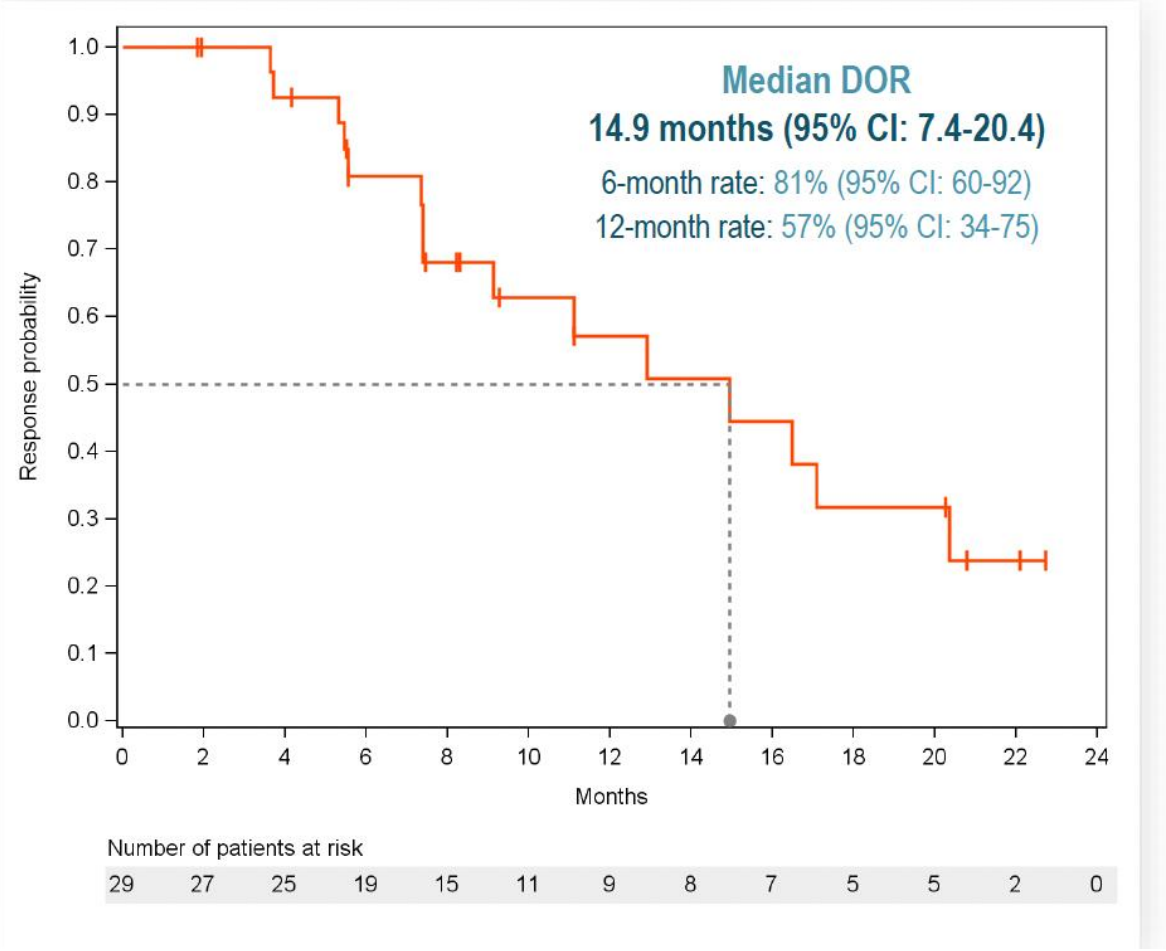

	Related TEAEs (≥10% patients and all Grade 3-4) n (%)	
	All grades	Grades 3-4
≥1 TEAE	115 (61)	11 (6)
Diarrhea	33 (17)	3 (2)
Infusion-related reactions[b]	23 (12)	0
Fatigue	18 (10)	0
Nausea	16 (8)	2 (1)
Vomiting	11 (6)	1 (1)
Anemia	7 (4)	1 (1)
Constipation	5 (3)	0
ALT increased	5 (3)	1 (1)
AST increased	5 (3)	2 (1)
Decreased appetite	5 (3)	1 (1)

•Infusion-related reactionsbin 23 of 189 (12%) patients, with no grade 3 or greater events

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FGFR 1-3

FIND trial: Erdafitinib Lung cancer

FIND – overview

Molecular prescreening (archive tumor sample) of NSCLC patients for **FGFR mutations** with NGS in **NGM Cologne and nNGM** Germany.
NSCLC samples without genetic alteration are sent for central hybrid capture (Archer) to **NGM Cologne** for determination of **FGFR translocations***.

Confirmation of activating alteration: **FIND molecular board**

*Inclusion of patients with local NGS results possible

Clinical screening
CT, MRT, Lab, ctDNA, biopsy (fresh frozen and FFPE)

↓

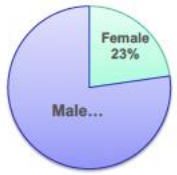
Erdafitinib 8-9 mg p.o qd ← CT every 8 weeks

Results of stage 1 of 2-stage Simon design (n=22):

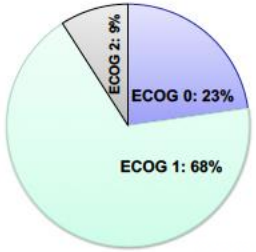
Parameters	Patients (n=22)
Recruitment time (m/y)	7/2019 - 9/2022
Patients recruited (n)	26
Screening failures (n)	4
Age mean y (range)	65 (38,86)

FGFR-alteration	Patients (n)	Cohort
FGFR3-TACC3	7	1
FGFR3 S249C	5	2
FGFR3 R248C	1	2
FGFR3 K5650E	1	2
FGFR3 G370C	1	2
FGFR3 S249C	1	3
IKBKB-FGFR1	1	3
FGFR2 K509M	1	3
WHSC1L1-FGFR1	1	3
FGFR3 P772L	1	3
FGFR2-CIT	1	3
FGFR1 Ex7inv	1	3

Sex



ECOG performance status



Best response	cohort 1 n (%) FGFR fusions	cohort 2 n (%) FGFR mutations
Complete response	0	0
Partial response	2 (29%)*	0
Stable disease	1 (14%)	4 (50%)
Progressive disease	1 (14%)	1 (13%)
Missing	3 (43%)	3 (38%)
Total	7 (100%)	8 (100%)

* 1 PR was unconfirmed PR

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Take home message

- *BUSCAR + BUSCAR + BUSCAR*
- *Diseñar adecuadamente los ensayos clínicos y ajustados a la escasa población*
- *Aprobaciones rápidas (SPAIN is different)*


15th
MADRID
CONGRESS
on Lung CANCER
23&24
November 2023
#15CongressGECP
Fundación
GECP
lung cancer
research
Muchas Gracias