Management of ROS and RET positive NSCLC

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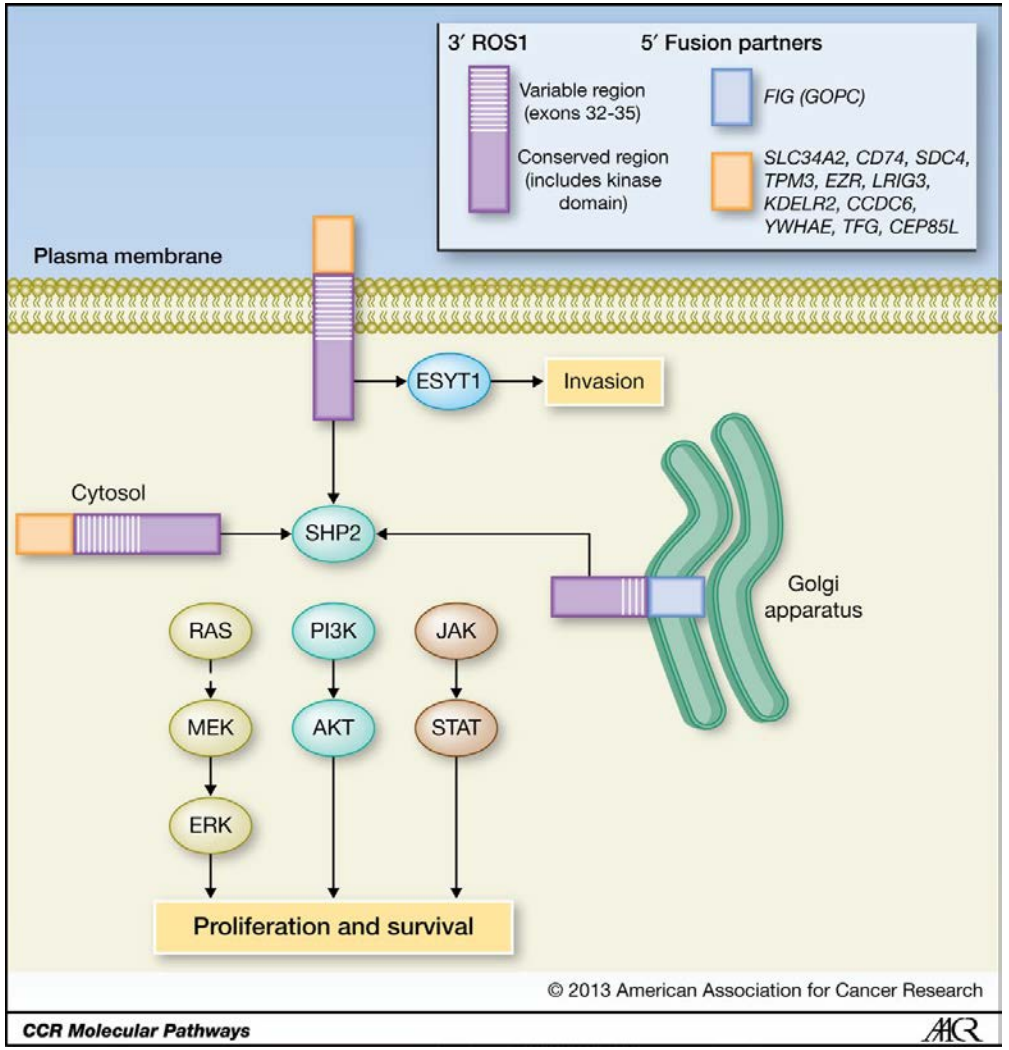
ROS1 fusions

Recurrent gene fusions are oncogenic drivers of various cancers.

ROS1 fusions include the kinase domaincontaining 3′ region of ROS1 fused to various 5′ or upstream partners, the most common of which is CD74 The resultant oncoprotein is characterised by constitutive kinase activation, increased downstream signalling, and ultimately tumour growth.

ROS1 fusions are enriched in non-small-cell lung cancers (NSCLCs) and are present in 1–2% of cases.

Typically, ROS1 fusions do not overlap with other canonical drivers, including NTRK fusions, in NSCLCs.



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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ORIGINAL ARTICLE

Crizotinib in *ROS1*-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001

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Background: In the ongoing phase I PROFILE 1001 study, crizotinib showed antitumor activity in patients with *ROS1*-rearranged advanced non-small-cell lung cancer (NSCLC). Here, we present updated antitumor activity, overall survival (OS) and safety data (additional 46.2 months follow-up) for patients with *ROS1*-rearranged advanced NSCLC from PROFILE 1001.

Patients and methods: *ROS1* status was determined by FISH or reverse transcriptase–polymerase chain reaction. All patients received crizotinib at a starting dose of 250 mg twice daily.

Results: Fifty-three patients received crizotinib, with a median duration of treatment of 22.4 months. At data cut-off, treatment was ongoing in 12 patients (23%). The objective response rate (ORR) was 72% [95% confidence interval (CI), 58% to 83%], including six confirmed complete responses and 32 confirmed partial responses; 10 patients had stable disease. Responses were durable (median duration of response 24.7 months; 95% CI, 15.2–45.3). ORRs were consistent across different patient subgroups. Median progression-free survival was 19.3 months (95% CI, 15.2–39.1). A total of 26 deaths (49%) occurred (median follow-up period of 62.6 months), and of the remaining 27 patients (51%), 14 (26%) were in follow-up at data cut-off. Median OS was 51.4 months (95% CI, 29.3 to not reached) and survival probabilities at 12, 24, 36, and 48 months were 79%, 67%, 53%, and 51%, respectively. No correlation was observed between OS and specific ROS1 fusion partner. Treatment-related adverse events (TRAEs) were mainly grade 1 or 2, per CTCAE v3.0. There were no grade ≥4 TRAEs and no TRAEs associated with permanent discontinuation. No new safety signals were reported with long-term crizotinib treatment.

Conclusions: These findings serve as a new benchmark for OS in *ROS1*-rearranged advanced NSCLC, and continue to show the clinically meaningful benefit and safety of crizotinib in this molecular subgroup.

Trial Registration Number: ClinicalTrials.gov identifier NCT00585195

Key words: crizotinib, non-small-cell lung cancer, *ROS1*, overall survival

Phase II Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced Non–Small-Cell Lung Cancer

Yi-Long Wu, James Chih-Hsin Yang, Dong-Wan Kim, Shun Lu, Jianying Zhou, Takashi Seto, Jin-Ji Yang, Noboru Yamamoto, Myung-Ju Ahn, Toshiaki Takahashi, Takeharu Yamanaka, Allison Kemner, Debasish Roychowdhury, Jolanda Paolini, Tiziana Usari, Keith D. Wilner, and Koichi Goto

ABSTRACT

Purpose

Approximately 1% to 2% of non–small-cell lung cancers (NSCLCs) harbor a c-ros oncogene 1 (*ROS1*) rearrangement. Crizotinib, an inhibitor of anaplastic lymphoma kinase (ALK), ROS1, and MET, has shown marked antitumor activity in a small expansion cohort of patients with ROS1-positive advanced NSCLC from an ongoing phase I study. We assessed the efficacy and safety of crizotinib in the largest cohort of patients with ROS1-positive advanced NSCLC.

Patients and Methods

This phase II, open-label, single-arm trial enrolled East Asian patients with ROS1-positive (assessed through validated AmoyDx assay [Amoy Diagnostics, Xiamen, China] at three regional laboratories) advanced NSCLC who had received three or fewer lines of prior systemic therapies. Patients were to receive oral crizotinib at a starting dose of 250 mg twice daily and continued treatment until Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1–defined progression (by independent radiology review [IRR]), unacceptable toxicity, or withdrawal of consent. The primary end point was objective response rate (ORR) by IRR.

Results

In the efficacy and safety analyses, 127 patients were included, with 49.6% still receiving treatment at data cutoff. ORR by IRR was 71.7% (95% CI, 63.0% to 79.3%), with 17 complete responses and 74 partial responses. ORRs were similar irrespective of the number of prior lines of therapy, and responses were durable (median duration of response, 19.7 months; 95% CI, 14.1 months to not reached). Median progression-free survival by IRR was 15.9 months (95% CI, 12.9 to 24.0 months). No new safety signals associated with crizotinib were reported.

Conclusion

This study demonstrated clinically meaningful benefit and durable responses with crizotinib in East Asian patients with ROS1-positive advanced NSCLC. Crizotinib was generally well tolerated, with a safety profile consistent with previous reports.

rizotinib treatment
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n were grade 1 or 2
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rade 3 or 4 TRAEs
which occurred in
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and 22.8% of pa-

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), and unknown in
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had a grade 5 AE
lure [n = 2], and

Table 3. Independent Radiology Review–Assessed ORR by Baseline Characteristics

Characteristic	Total Crizotinib (N = 127)	
	No. of Patients	ORR, % (95% CI)
Country		
China	53 of 74	71.6 (59.9 to 81.5)
Japan	17 of 26	65.4 (44.3 to 82.8)
Other	21 of 27	77.8 (57.7 to 91.4)
Sex		
Male	34 of 54	63.0 (48.7 to 75.7)
Female	57 of 73	78.1 (66.9 to 86.9)
Age-group		
< 65 years	78 of 106	73.6 (64.1 to 81.7)
≥ 65 years	13 of 21	61.9 (38.4 to 81.9)
Smoking history		
No	68 of 91	74.7 (64.5 to 83.3)
Yes	23 of 36	63.9 (46.2 to 79.2)
Baseline ECOG PS		
0	24 of 34	70.6 (52.5 to 84.9)
1	67 of 93	72.0 (61.8 to 80.9)
Brain metastases at baseline		
Yes	17 of 23	73.9 (51.6 to 89.8)
No	74 of 104	71.2 (61.4 to 79.6)
No. of prior regimens for advanced disease		
< 2	56 of 77	72.7 (61.4 to 82.3)
≥ 2	35 of 50	70.0 (55.4 to 82.1)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; PS, performance status.

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in which crizotinib
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63.0 to 79.3), simila
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trials.[17,18] Response
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similar to PROFILE
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in PROFILE 1001.
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Summary of ROS1+ crizotinib studies

The FDA and EMA approved crizotinib for the treatment of ROS1+ NSCLC (March and August 2016, respectively)

	PROFILE 1001	OxOnc	EUROS1	AcSé
Design	Prospective	Prospective	Retrospective	Prospective
Number	53	127	31	37
Population	Global (42% Asian)	East Asian (China, Japan, South Korea, Taiwan)	Europe	France
ROS1 detection method	Break-apart FISH	Amoy RT-PCR	Break-apart FISH	Break-apart FISH
ORR (%)	70%	71.7%	80%	69%
PFS (m)	19.3m	15.9m	9.1m	9.1m (update WCLC 5.5m)
mDoR (m)	17.6m	19.7m	NA	NA

Shaw AT. NEJM 2014; Mazieres J. JCO 2015; Wu YL. JCO 2018; Moro-Sibilot D. WCLC 2015, WCLC 2018

Ceritinib in *ROS1+* NSCLC

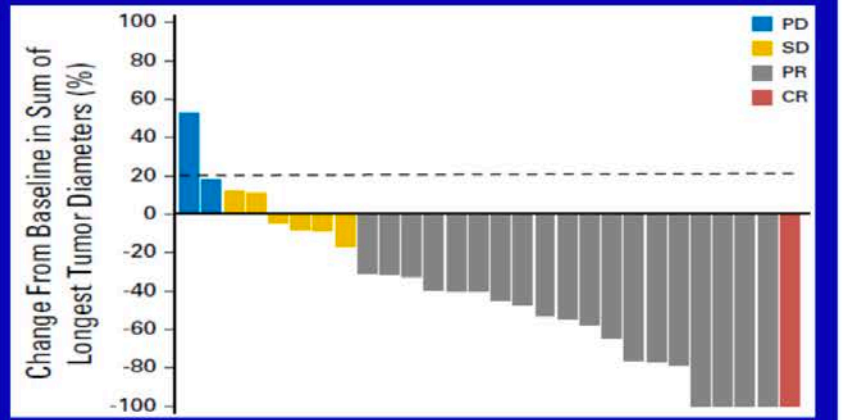
(Korean Nationawide Phase II Study)

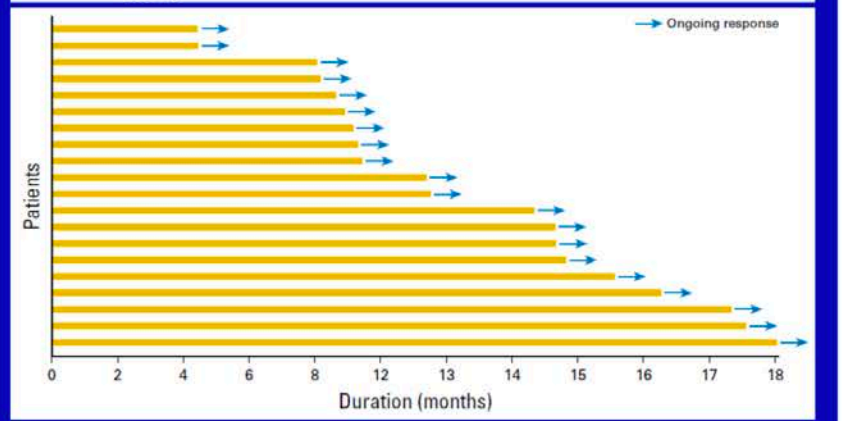
- 25% had brain metastasis at baseline
- iORR 25%, iDCR 63%

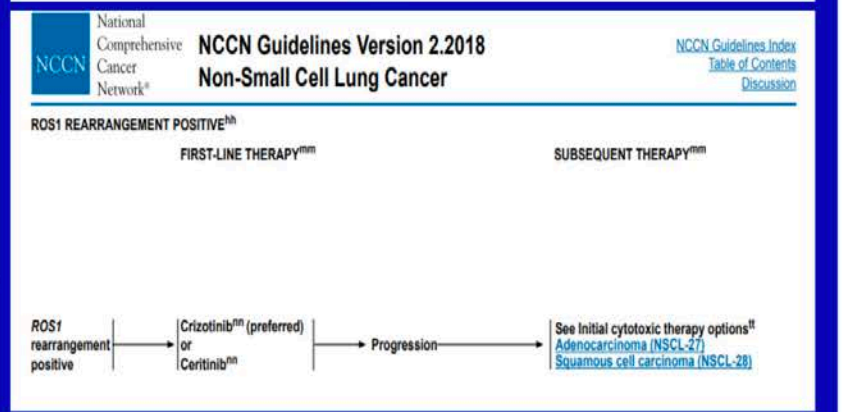
Efficacy	All (n=32; 2 crizotinib-pretreated)*	Crizotinib-naïve (n=30)
ORR, %	62	67
DoR, months (95% CI)	18.4 (8.0, 18.4)	
PFS, months (95% CI)	10.0 (2.5-17.4)	20.7 (4.7, NE)

***Two crizotinib-pretreated pts showed PD t… …itinib**

PROFILE 1001 (n= 53)
ORR 70%
mPFS 19.3 mo
(Shaw A, et al. ESMO 2016)



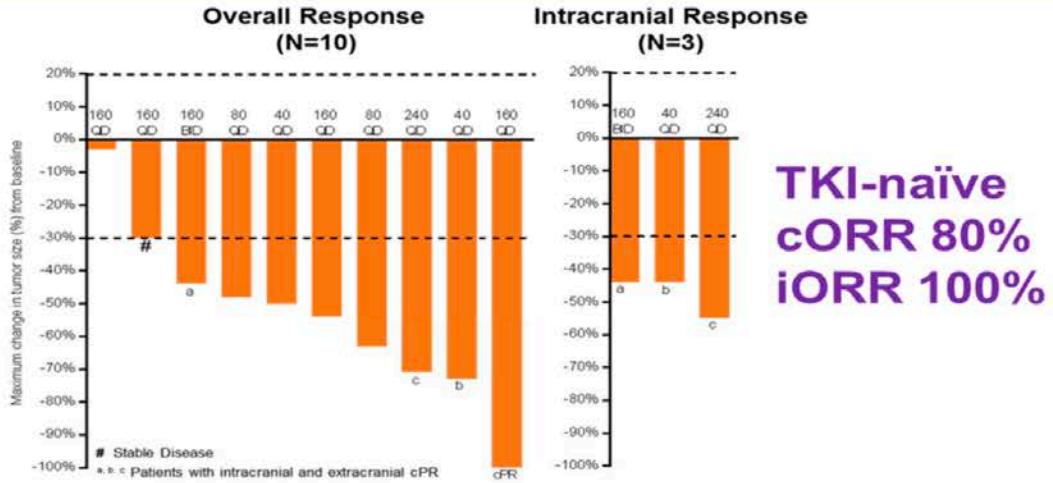




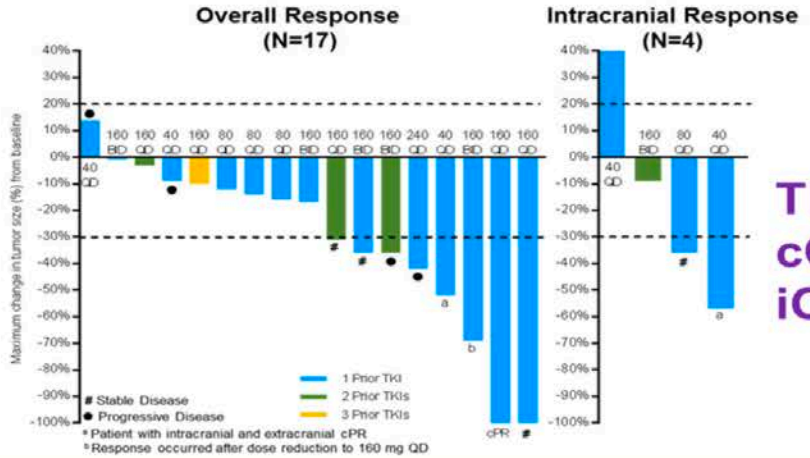
Lim SM, Cho BC. JCO 2017; https://www.nccn.org

Efficacy of Repotrectinib in TKI-naïve and TKI-pretreated ROS1+ NSCLC

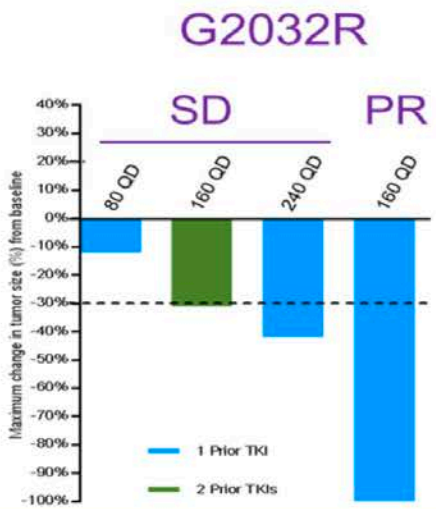
Lin JJ, Cho BC. WCLC 2018

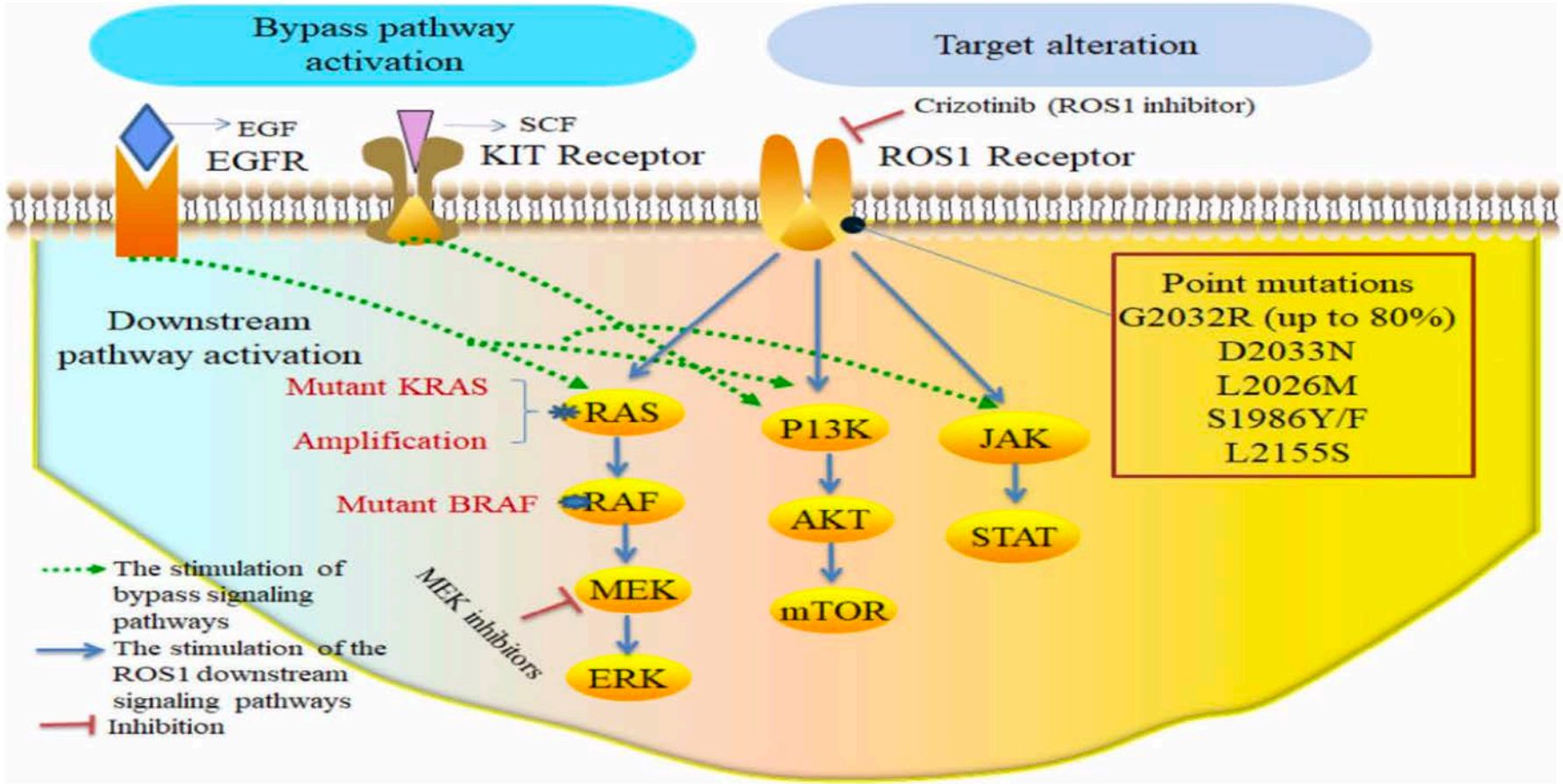


TKI-naïve
cORR 80%
iORR 100%



TKI-pretreated
cORR 18%
iORR 25%




Bypass pathway activation
Target alteration
EGF
EGFR
SCF
KIT Receptor
Crizotinib (ROS1 inhibitor)
ROS1 Receptor
Point mutations
G2032R (up to 80%)
D2033N
L2026M
S1986Y/F
L2155S
Downstream pathway activation
Mutant KRAS
Amplification
RAS
Mutant BRAF
RAF
MEK
ERK
P13K
AKT
mTOR
JAK
STAT
MEK inhibitors
The stimulation of bypass signaling pathways
The stimulation of the ROS1 downstream signaling pathways
Inhibition

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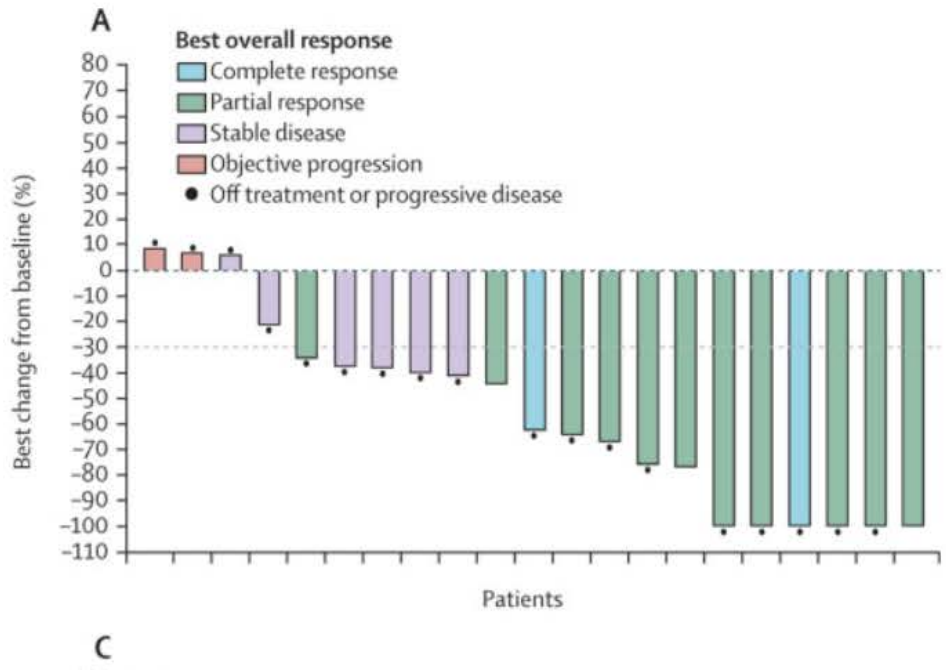
Lorlatinib in advanced *ROS1*-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1–2 trial

- 21 (30%) of 69 patients were TKI-naive, 40 (58%) had previously received crizotinib as their only TKI, and eight (12%) had previously received one non-crizotinib ROS1 TKI or two or more ROS1 TKIs.
- The estimated median duration of follow-up for response was 21·1 months (IQR 15·2–30·3). 13 (62%; 95% CI 38–82) of 21 TKI-naive patients and 14 (35%; 21–52) of 40 patients previously treated with crizotinib as their only TKI had an objective response.
- Intracranial responses were achieved in seven (64%; 95% CI 31–89) of 11 TKI-naive patients and 12 (50%; 29–71) of 24 previous crizotinib-only patients.


A
Best overall response
Complete response
Partial response
Stable disease
Objective progression
Off treatment or progressive disease
Best change from baseline (%)
80
70
60
50
40
30
20
10
0
-10
-20
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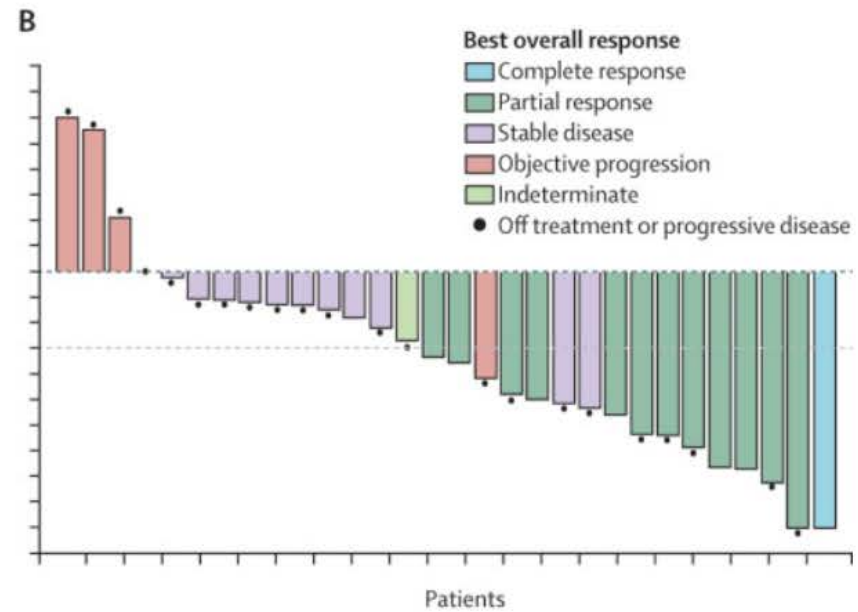
-50
-60
-70
-80
-90
-100
-110
Patients


B
Best overall response
Complete response
Partial response
Stable disease
Objective progression
Indeterminate
Off treatment or progressive disease
Patients

C

D

Updated data of ROS1-directed TKI in TKI-naïve patients

TKI-naïve	Study		N	ORR	PFS (months)	Patients with CNS metastases		
						N	ORR	PFS
Crizotinib	Profile 1001 et al[1-5]	phase 1-2, retrospective	32-127	69-80%	9.1-19.2	23[2]	73.9%	10.2
Ceritinib	A Korean study[6]	phase 2	30	63%	19.3	8	25%	6.0
Brigatinib	NCT01449461[7]	phase 1/2	1	1/1	21.6	N/A	N/A	N/A
Cabozantinib	NCT01639508[8]	phase 2	Ongoing					
DS-6051b	NCT02279433[10]	phase 1	10	80%	N/A	N/A	N/A	N/A
Entrectinib	ALKA-372-001+STARTRK-1+STARTRK-2[11]	phase 1/2	53	77.4%	19.0	23	73.9%	13.6
Lorlatinib	NCT01970865[9], Ph2(CohortEXP-6)[12]	phase 1-2	7-13	57-61.5%	21.0[12]	6[12]	66.7%	N/A
Repotrectinib	TRIDENT-1[13]	phase 1	10	80%	N/A	3	3/3	N/A

1. Shaw AT et al N Engl J Med 2014 Nov 20;371(21):1963-71. 2. Wu YL et al. J Clin Oncol 2018;36:1405-11. 3. Michels S et al. J Thor Oncol 2017;12:S379-80.4. Marasibilat P et al. J Thor Oncol 2015;10(2_suppl):S65.
5. Mazières J et al. J Clin Oncol 2015;33:992-9. 6. Lim SM et al. J Clin Oncol 2017;35:2613-18. 7.Getinger SN et al Lancet Oncol. 2016 Dec;17(12):1683-1696. 8.Drilon A et al Cancer Discov. 2017 Apr;7(4):400-409.
9.Shaw AT et al. Lancet Oncol 2017;18:1590–9.10.Nasaki K et al J Thorac Oncol 2017;12:S1069. 11.Doebele RC et al. 2018 WCLC OA02.0112.Ou SI et al. 2018 WCLC OA02.03.13.Lin JJ et al. 2018 WCLC OA02.02.

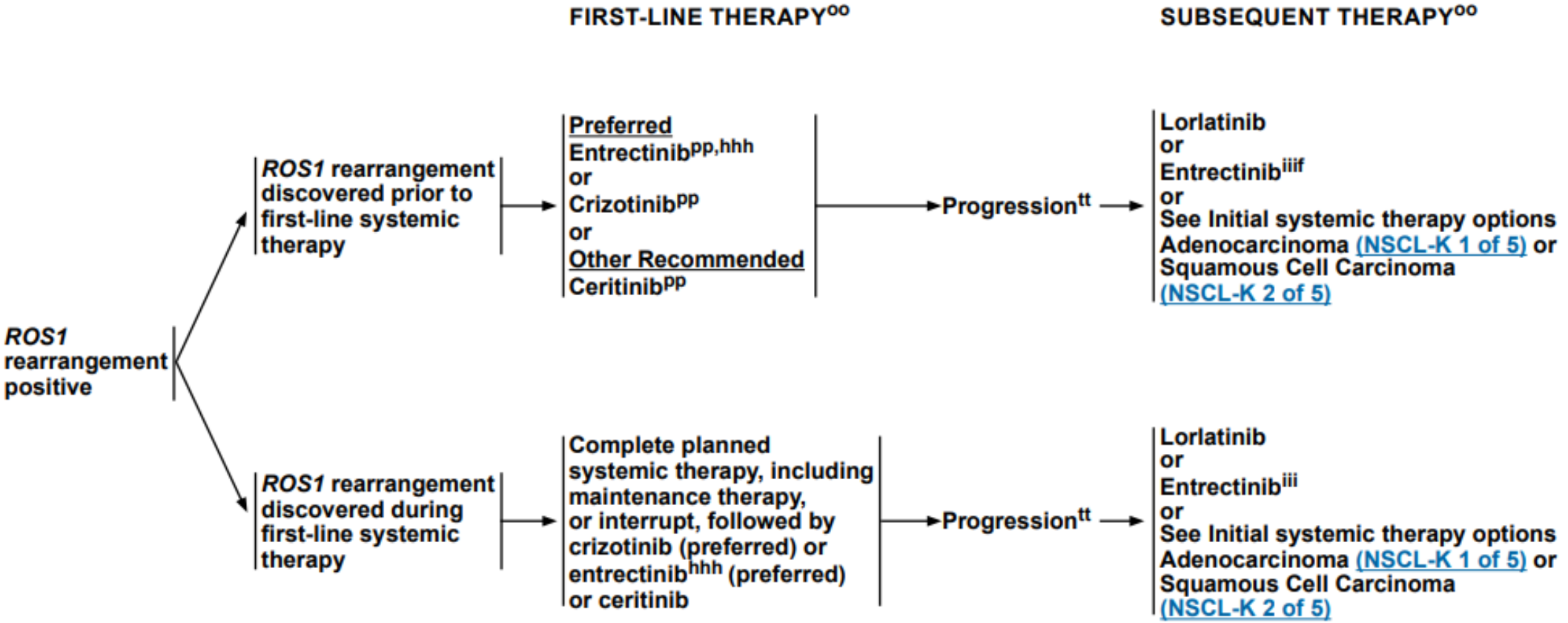
Updated data of ROS1-TKIs in TKI pretreated NSCLC

	TKI-naïve response rate	TKI-pretreated response rate	
Ceritinib[1]	19/30,63%	0/2	Phase 2
Brigatinib[2]	1/1	0/2	Phase 1/2
Entrectinib[3]	11/13,85%	0/6	Phase 1
DS-6051b[4]	8/10,80%	0/3	Phase 1
Lorlatinib[5]	8/13,61.5%	9/34,26.5%	Phase 2
Repotrectinib[6]	8/10,80%	3/17,18%	Phase 1

Further biomarker study is needed to identify the population benefit from Lorlatinib or Repotrectinib

1.Lim SM et al J Clin Oncol 2017 Aug 10;35(23):2613-2618. **2.**Gettinger SN et al Lancet Oncol. 2016 Dec;17(12):1683-1696. **3.**Drilon A et al Cancer Discov. 2017 Apr;7(4):400-409. **4.**Nosaki K et al J Thorac Oncol 2017;12:S1069. **5.**Ou SI et al. 2018 WCLC OA02.03 **6.**Lin JJ et al. 2018 WCLC OA02.02.

ROS1 REARRANGEMENT POSITIVE[ll]



Entrectinib in *ROS1* fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1–2 trials

Alexander Drilon, Salvatore Siena*, Rafal Dziadziuszko, Fabrice Barlesi, Matthew G Krebs, Alice T Shaw, Filippo de Braud, Christian Rolfo, Myung-Ju Ahn, Jürgen Wolf, Takashi Seto, Byoung Chul Cho, Manish R Patel, Chao-Hua Chiu, Thomas John, Koichi Goto, Christos S Karapetis, Hendrick-Tobias Arkenau, Sang-We Kim, Yuichiro Ohe, Yu-Chung Li, Young K Chae, Christine H Chung, Gregory A Otterson, Haruyasu Murakami, Chia-Chi Lin, Daniel S W Tan, Hans Prenen, Todd Riehl, Edna Chow-Maneval, Brian Simmons, Na Cui, Ann Johnson, Susan Eng, Timothy R Wilson, Robert C Doebele, on behalf of the trial investigators†*

Entrectinib

Entrectinib is a multikinase inhibitor with activity against ROS1 (in addition to tropomyosin receptor kinase [TRK] A, B, and C and ALK).

In ROS1 fusioncontaining cancer models, entrectinib is 40 times more potent than crizotinib in vitro.

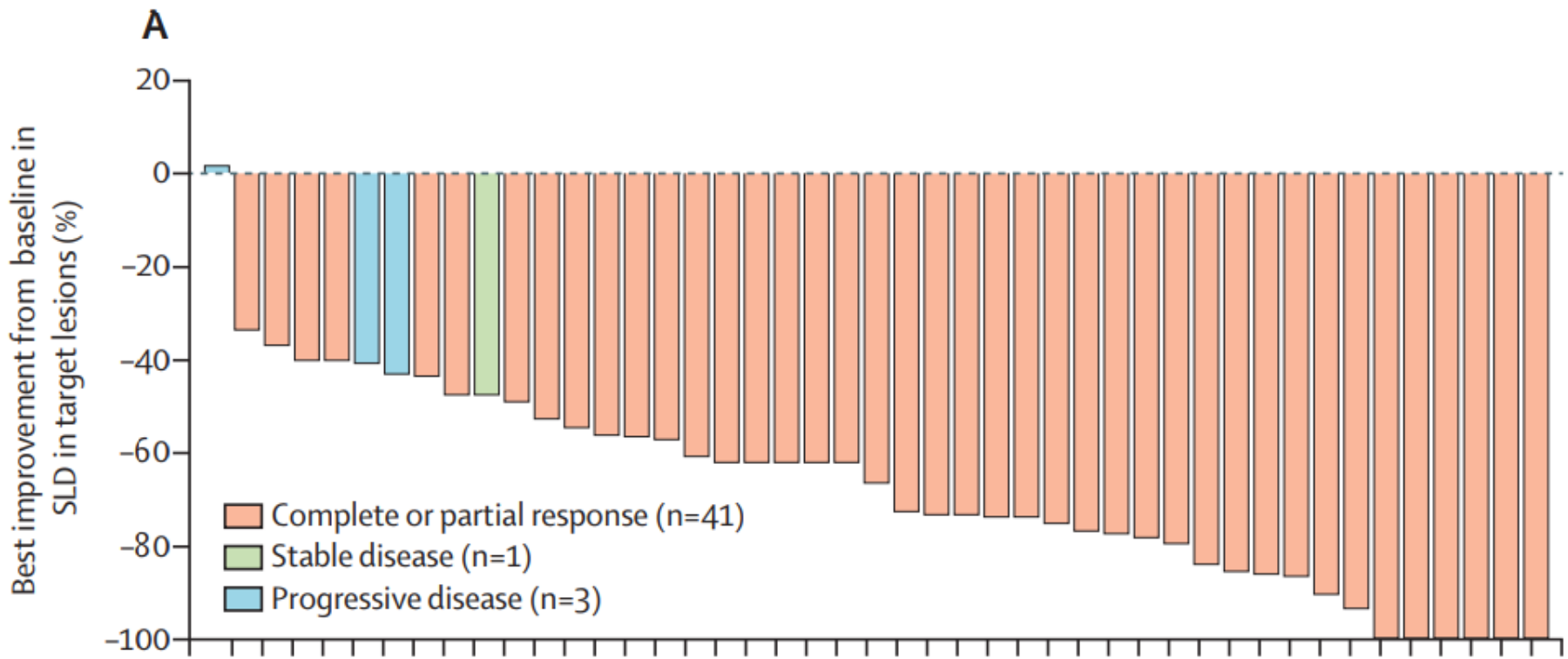
Moreover, it was designed with the ability to effectively cross the blood–brain barrier and be retained in the CNS.

In preclinical studies, entrectinib achieved substantial concentrations in the CNS, with a blood-to-brain ratio of 0·4–1·9 in mice, rats, and dogs.

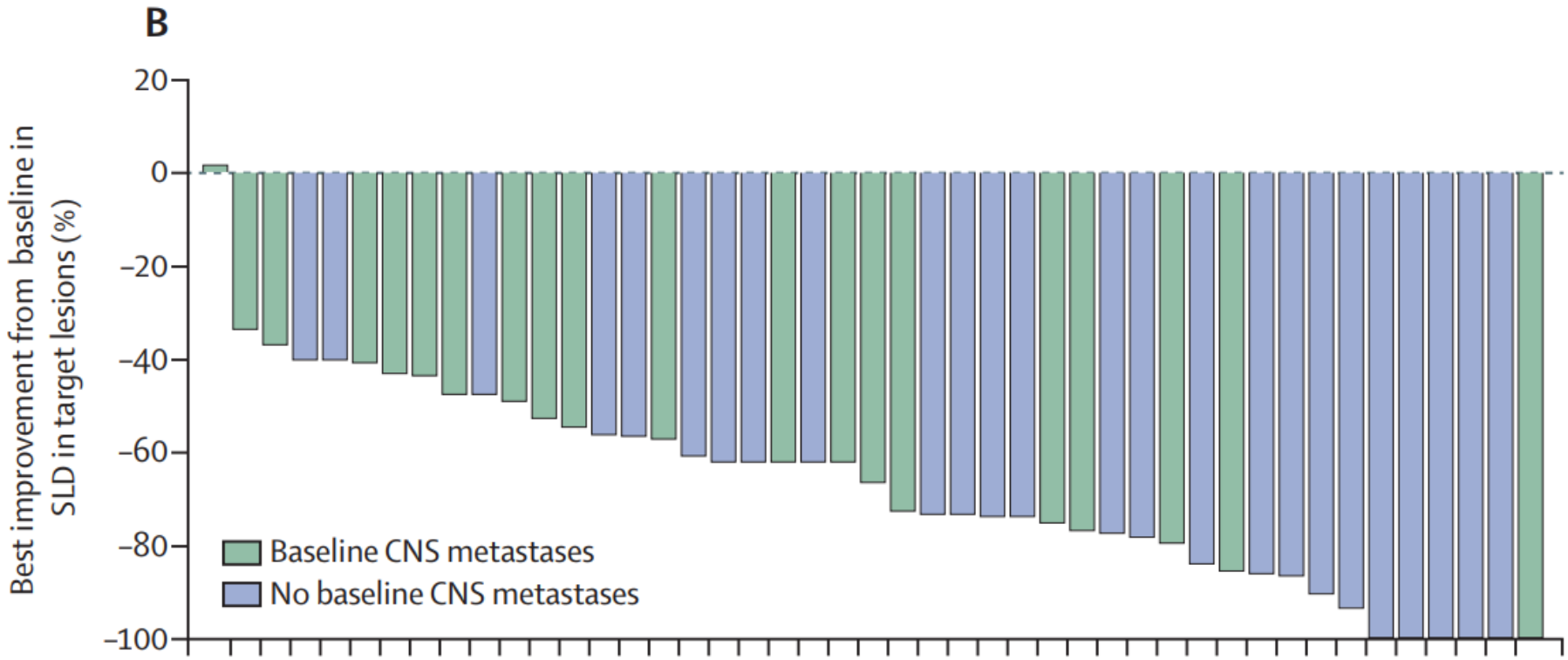
Entrectinib was detected in brain homogenates of these species after single or multiple doses.

Study design

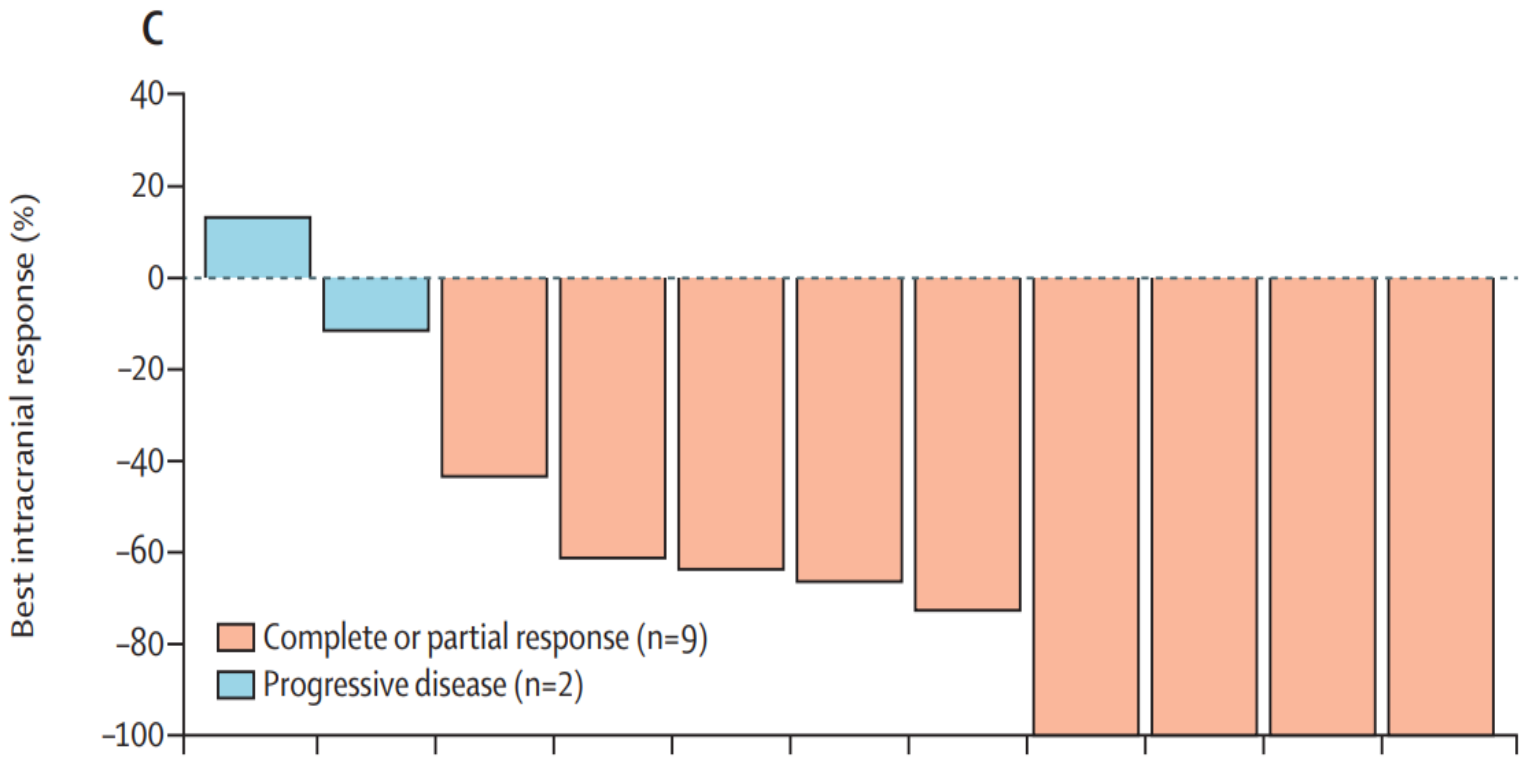
- Integrated analysis of 3 phase 1-2 trials
- Patients (aged ≥18 years) with locally advanced or metastatic solid tumours harbouring ROS1 fusions were enrolled in one of two phase 1 studies (ALKA-372-001 or STARTRK-1)11 or a phase 2 global basket study (STARTRK-2).
- **ALKA-372-001** was done at two cancer centres in Italy.
- **STARTRK-1** was done at ten sites: one hospital and seven cancer centres in the USA, one hospital in Spain, one centre in South Korea.
- **STARTRK-2** is ongoing at more than 150 sites (ie, cancer and medical centres, research institutes, hospitals, and universities) in 15 countries



(A) Best responses to entrectinib in the efficacy-evaluable population.

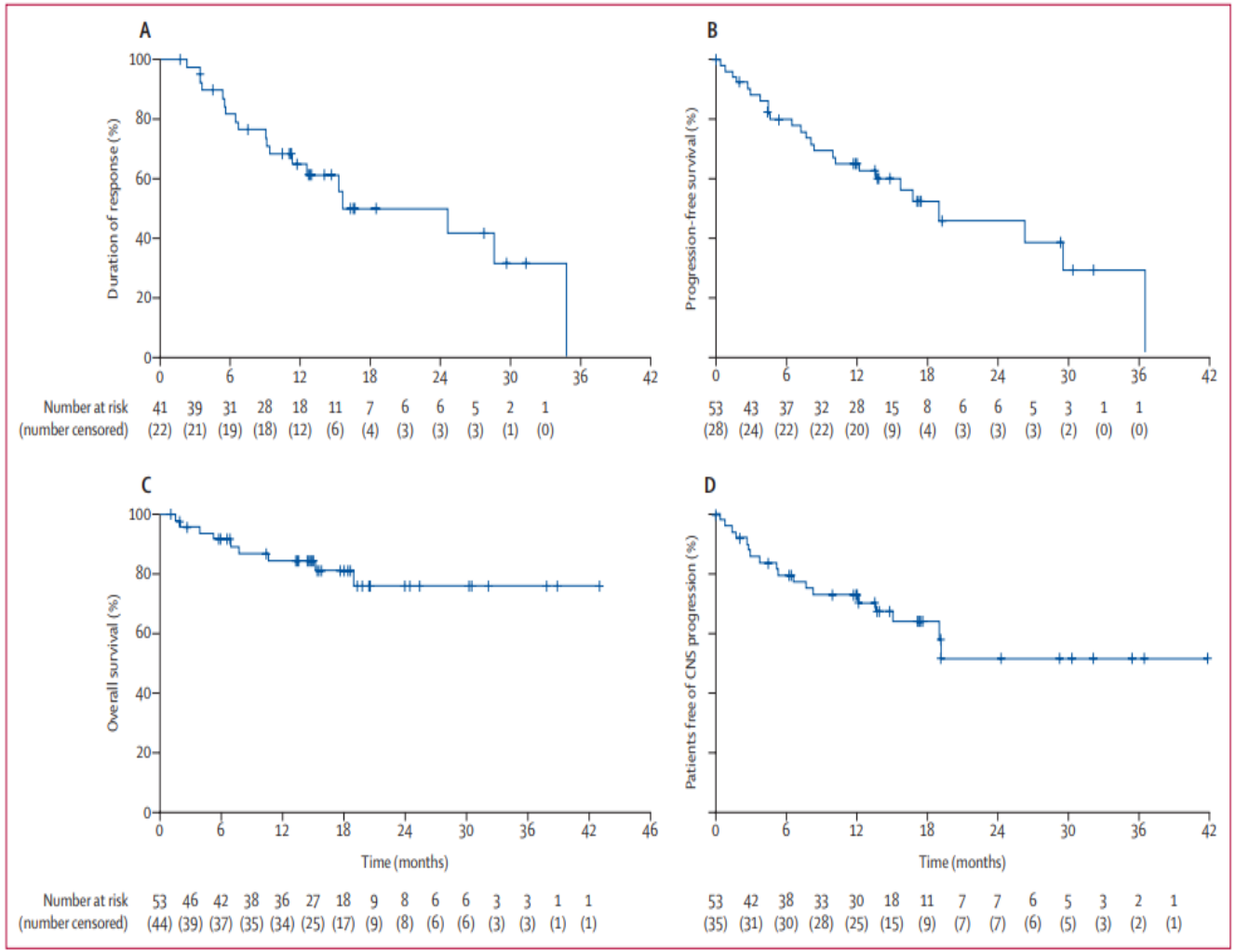


(B) Best responses for patients with and without baseline CNS disease.



(C) Best intracranial responses in patients with measurable CNS disease at baseline.

Time-to-event analysis



Response do not differ by upstream fusion partner (CD74 vs non CD74)

Disease control was durable with median PFS 19 months

Median duration of response 24.6m

- TOXICITIES:

	Grade 1–2	Grade 3	Grade 4
Dysgeusia	56 (42%)	1 (<1%)	0
Dizziness	43 (32%)	1 (<1%)	0
Constipation	44 (33%)	0	0
Diarrhoea	35 (26%)	3 (2%)	0
Weight increase	26 (19%)	10 (7%)	0
Fatigue	32 (24%)	0	0
Paraesthesia	23 (17%)	0	0
Nausea	23 (17%)	0	0
Peripheral oedema	22 (16%)	0	0
Myalgia	19 (14%)	2 (2%)	0
Vomiting	19 (14%)	0	0
Blood creatinine increase	17 (13%)	1 (<1%)	0
Aspartate aminotransferase increase	14 (10%)	2 (2%)	0
Alanine aminotransferase increase	13 (10%)	3 (2%)	0
Hyperaesthesia	12 (9%)	1 (<1%)	0
Arthralgia	12 (9%)	1 (<1%)	0
Anaemia	11 (8%)	1 (<1%)	0
Hyperuricaemia	11 (8%)	0	1 (<1%)
Rash	9 (7%)	2 (1%)	0
Pruritus	9 (7%)	1 (<1%)	0
Peripheral sensory neuropathy	8 (6%)	1 (<1%)	0
Cognitive disorder	8 (6%)	1 (<1%)	0
Muscular weakness	6 (4%)	1 (<1%)	0
Hypotension	6 (4%)	1 (<1%)	0
Neutropenia	5 (4%)	5 (4%)	0
Neutrophil count decrease	5 (4%)	3 (2%)	0
Ataxia	5 (4%)	1 (<1%)	0
Pyrexia	5 (4%)	1 (<1%)	0
Dysarthria	4 (3%)	1 (<1%)	0
Pain of skin	4 (3%)	1 (<1%)	0
Lymphocyte count decrease	2 (1%)	1 (<1%)	0
Blood creatine phosphokinase increase	2 (1%)	1 (<1%)	1 (<1%)
Hypophosphataemia	2 (1%)	1 (<1%)	0
Orthostatic hypotension	2 (1%)	1 (<1%)	0
Electrocardiogram QT prolonged	1 (<1%)	1 (<1%)	0
Amylase increased	1 (<1%)	1 (<1%)	0
Dehydration	0	2 (1%)	0
Limbic encephalitis	0	0	1 (<1%)
Anorectal disorder	0	0	1 (<1%)
Myocarditis	0	0	1 (<1%)
Myoclonus	0	1 (<1%)	0
Hypoxia	0	1 (<1%)	0
Hypertension	0	1 (<1%)	0
Cardiac failure	0	1 (<1%)	0

The safety population includes all patients with *ROS1* fusion-positive NSCLC across the three trials who received at least one dose of entrectinib (irrespective of dose or duration of follow-up). All treatment-related adverse events observed are shown. Data are n (%) of patients. Adverse events were encoded using Medical Dictionary for Regulatory Activities (version 21.0). NSCLC=non-small-cell lung carcinoma.

Table 3: **Treatment-related adverse events in the safety-evaluable population with *ROS1* fusion-positive NSCLC (n=134)**

- Outcomes exceed the activity of 1st line chemo &immunotherapy in NSCLC
- The current standard of care(i.e 1st line) for ROS 1 fusion +ve NSCLC
- FDA approved Aug 2019 for mets ROS 1 fusion +ve NSCLC
- Patients with intracranial metastases have a shorter overall duration of disease control than patients without intracranial disease

- This study had a high proportion of patients with baseline intracranial disease (>40%) when compared with trials of ROS1 TKIs such as crizotinib and ceritinib (listed as a potential first-line TKI for *ROS1* fusion positive NSCLC in the NCCN Guidelines) in TKI-naive, *ROS1* fusion-positive NSCLC.

- More pts of poor prognosis, still the RR, median PFS with ENTRECTINIB was similar to that with crizotinib & ceritinib.

- Pts with baseline brain mets:

  Median PFS : ENTRECTINIB(13.6m) > CRIZOTINIB(10.2M) OxOnc study

- Pts without baseline brain mets:

  Median PFS : ENTRECTINIB(26.3m) > CRIZOTINIB(18.8M) OxOnc study

Conclusion

Multiple options for ROS1 TKI-naive patients with advanced ROS1 fusion positive NSCLC.

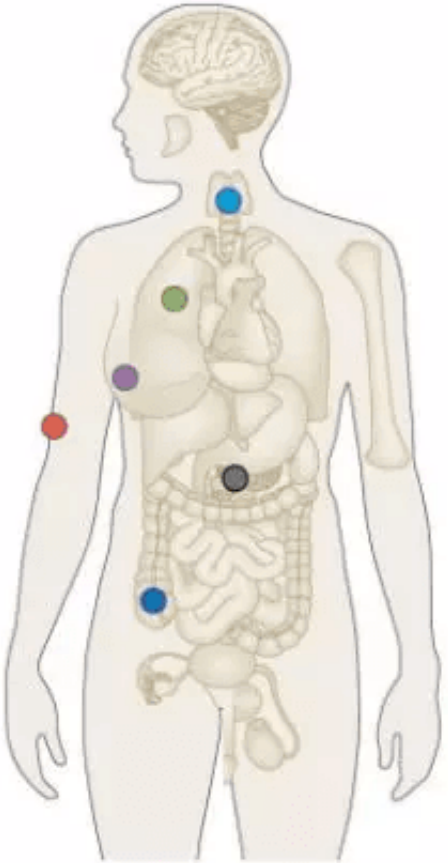
Drugs with both systemic and intracranial activity available

The safety profile of entrectinib is favourable, making it amenable to long-term dosing in this population in which durable disease control was observed.

These results underscore the need to routinely test for ROS1 fusions in the clinic to broaden therapeutic options for patients .

RET is activated by two major mechanisms in cancer

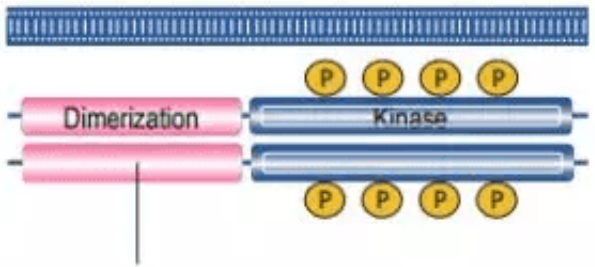
RET fusions



Non-small cell lung cancer (2%)

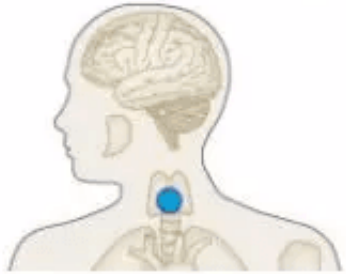
Papillary and other thyroid cancers (10–20%)

Pancreatic cancer (<1%)
Salivary gland cancer (<1%)
Spitz tumors (<1%)
Colorectal cancer (<1%)
Ovarian cancer (<1%)
Myeloproliferative disorders (<1%)
Many others (<1%)



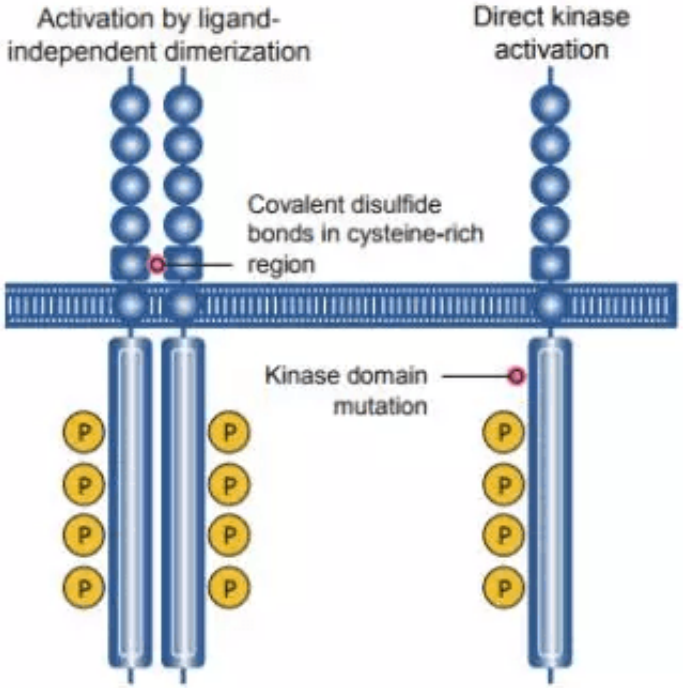
KIF5B (most common in lung cancer)
CCDC6* or *NCOA4 (most common in thyroid cancer)

RET mutations



Medullary thyroid cancer

sporadic (>60%)
hereditary (>90%)



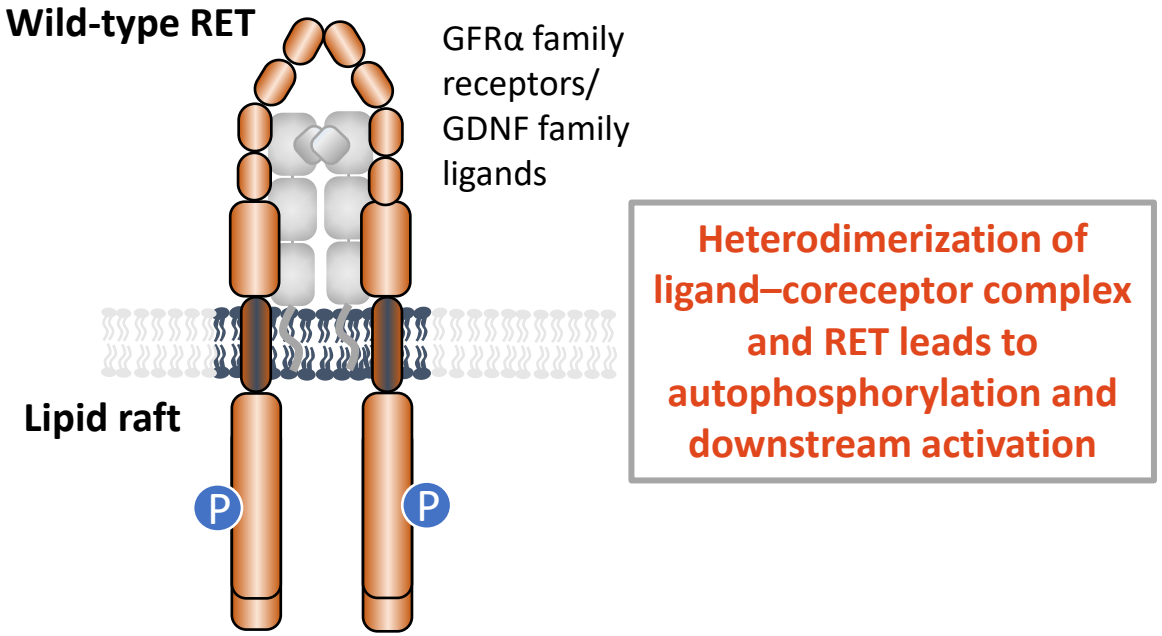
Common mutation: ***RET* M918T**

RET INHIBITORS

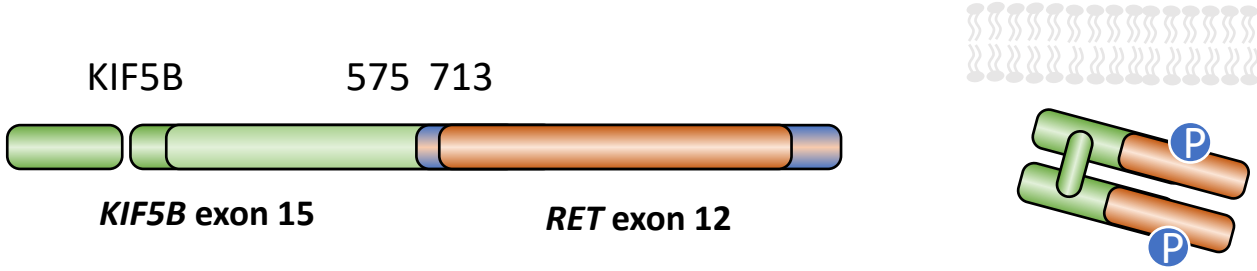
- Selpercatinib
- Pralsetinib
- Cabozantinib
- Vandetanib

RET Receptor Tyrosine Kinase and *RET* Fusions in NSCLC

- Normal role in neural, genitourinary development
- In cancer, *RET* gene rearrangements give rise to chimeric, cytosolic proteins with constitutively active RET kinase domain
  - 1%-2% of nonsquamous NSCLC
  - 10%-20% of papillary thyroid carcinoma
- Majority of *RET* fusions can be detected by DNA NGS but increased sensitivity with RNA NGS

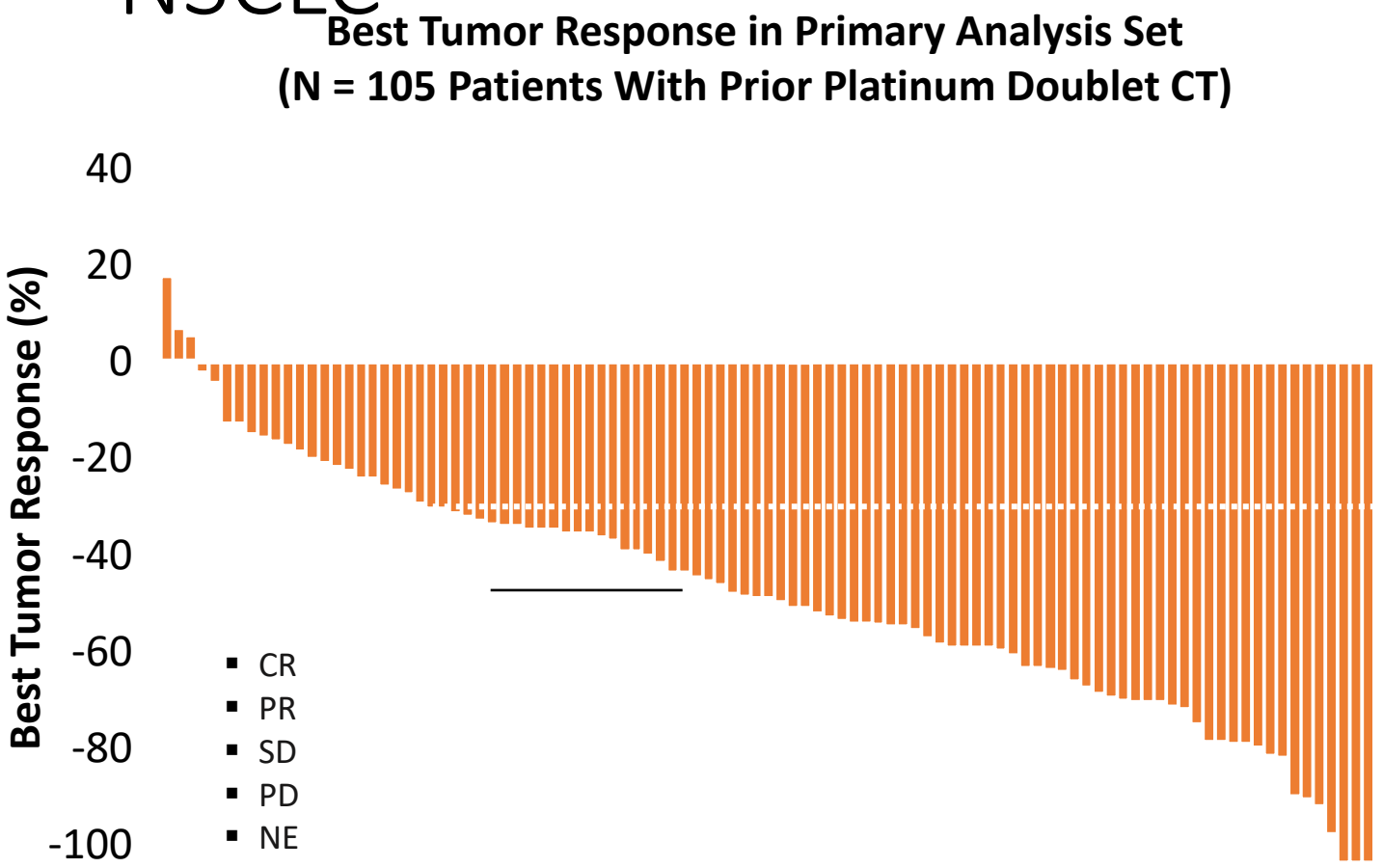


Most Common *RET* Translocation in Lung Adenocarcinoma: KIF5B-RET



Gautschi. JCO. 2017;13:1403. Ferrara. J Thorac Oncol. 2018;13:27. Kato. Clin Cancer Res. 2017;23:1988.
Wang . JCO. 2012;30:4352. Airaksinen. Nature Rev Neuroscience. 2002;3:383.

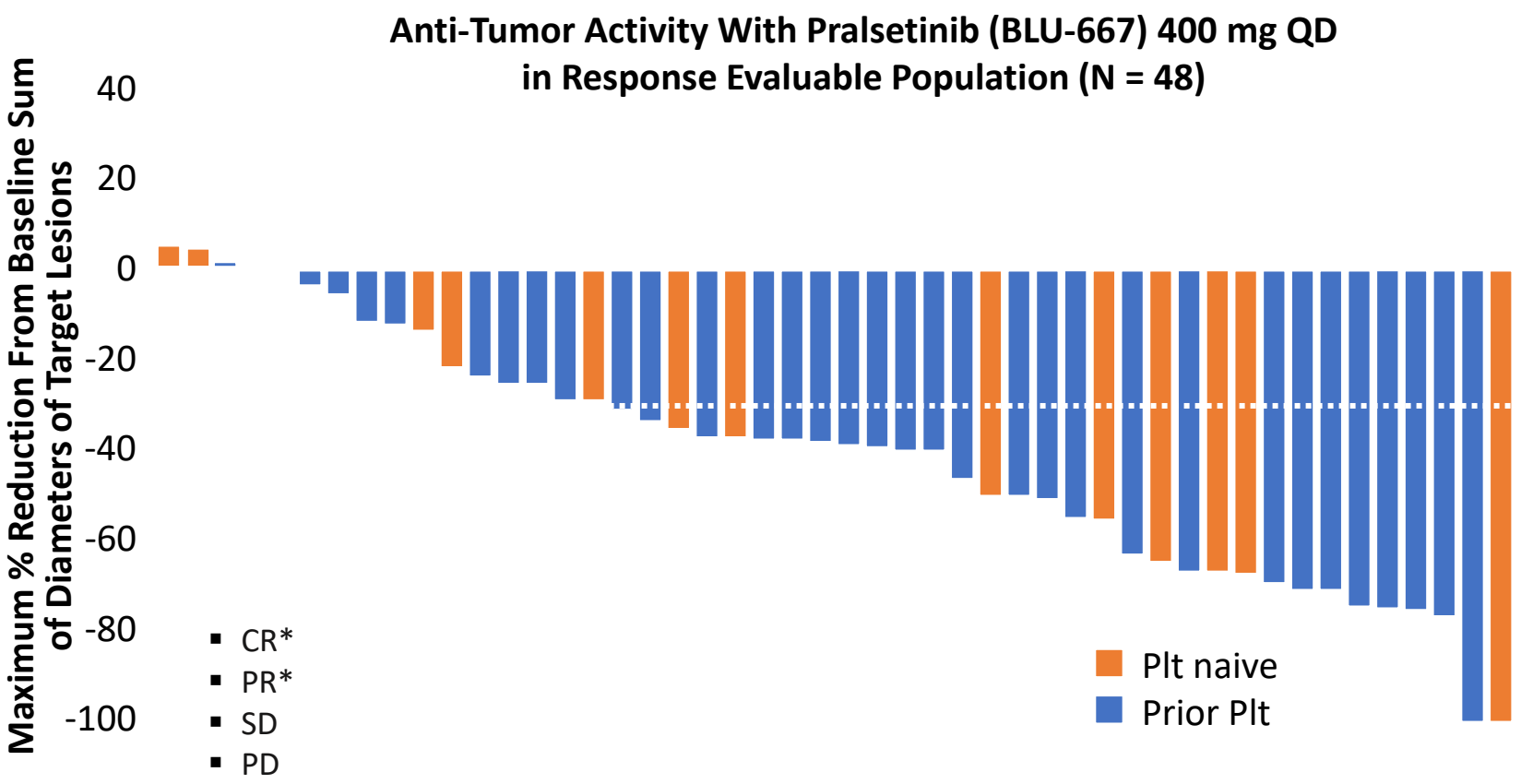
Phase I/II LIBRETTO-001: Efficacy With Selpercatinib (LOXO-292) in *RET* Fusion–Positive NSCLC



- Durability of response in primary analysis set
  - DoR: 20.3 mos
  - PFS: 18.4 mos
  - ORR, DoR, and PFS similar regardless of prior therapy
- Treatment-naive (n = 34)
  - ORR: 85%
  - DoR and PFS not reached

Drilon. WCLC 2019. Abstr PL02.08.

Phase I/II ARROW: Efficacy With Pralsetinib (BLU-667) in *RET* Fusion–Positive NSCLC



- Durability of response in response evaluable patients
  - DoR: not reached
- Anti-tumor activity regardless of prior ICI, *RET* fusion genotype, or presence of CNS mets
- 5/7 (71%) of treatment-naive patients had confirmed PR

Gainor. ASCO 2019. Abstr 9008.

n = 4 excluded. *Confirmed responses on 2 consecutive assessments as per RECIST 1.1.

SELPERCATINIB

- Mechanism of action- Selpercatinib inhibits wild-type **RET, multiple mutated RET isoforms, VEGFR1 and VEGFR3, and FGFR1, 2, and 3.**

- Administration-May administer with or without food

Indications

Non-small cell lung cancer, metastatic, RET fusion-positive:
Oral
Patients ≥50 kg: 160 mg twice daily
Patients <50 kg: 120 mg twice daily

Thyroid cancer, medullary, RET-mutant: Oral:
Patients ≥50 kg: 160 mg twice daily
Patients <50 kg: 120 mg twice daily

Thyroid cancer, RET fusion-positive: Oral:
Patients ≥50 kg: 160 mg twice daily
Patients <50 kg: 120 mg twice daily

Side effects

- Peripheral edema (33%), hypertension (35%), **Qtc prolongation (17%)**
- hyperglycemia (44%)
- Constipation (25%), diarrhea (37%), nausea (23%), vomiting (15%),
- dry mouth (39%)
- Anemia (27%) leukopenia (43%), lymphocytopenia (48%), thrombocytopenia (33%)
- Hepatic: **Serum Transaminitis (41-45%)**
- ILD, **pleural effusion (13%),**

Dose modification

Dose reduction	Patients <50 kg	Patients ≥50 kg
Initial (usual) dose	120 mg twice daily	160 mg twice daily
First dose reduction level	80 mg twice daily	120 mg twice daily
Second dose reduction level	40 mg twice daily	80 mg twice daily
Third dose reduction level	40 mg once daily	40 mg twice daily
Permanently discontinue selpercatinib if unable to tolerate 3 dose reductions		

Toxicity	Severity	Selpercatinib dose modification
Hemorrhagic events	Grade 3 or 4	Withhold selpercatinib until recovery to baseline or grade 0 or 1. Discontinue selpercatinib (permanently) for severe or life-threatening hemorrhagic events.
Hypersensitivity reactions	All grades	Withhold selpercatinib until resolution of the hypersensitivity event. Initiate corticosteroids (at a dose of 1 mg/kg prednisone [or equivalent]). Resume selpercatinib with the dose reduced by 3 dose levels while continuing corticosteroids. Increase dose by 1 dose level each week until achieving the dose administered prior to the onset of hypersensitivity, then taper corticosteroids.
	Recurrent hypersensitivity	Permanently discontinue selpercatinib.
Hypertension	Grade 3	Initiate or optimize hypertensive therapy. Withhold selpercatinib for grade 3 hypertension that persists despite management with optimal antihypertensive therapy. Resume selpercatinib at a reduced dose when hypertension is controlled.
	Grade 4	Discontinue selpercatinib.
QT interval prolongation	Grade 3	Withhold selpercatinib until recovery to baseline or grade 0 or 1, then resume selpercatinib at a reduced dose.
	Grade 4	Discontinue selpercatinib.
Other adverse reactions	Grade 3 or 4	Withhold selpercatinib until recovery to baseline or grade 0 or 1, then resume selpercatinib at a reduced dose.

PRALSETINIB

- Mechanism of action- Pralsetinib inhibits wild-type RET, oncogenic RET fusions and RET mutations, pralsetinib also inhibited DDR1, TRKC, FLT3, JAK1-2, TRKA, VEGFR2, PDGFRb, and FGFR1
- Indication-Non-small cell lung cancer, metastatic, RET fusion-positive: Oral: 400 mg once daily until disease progression or unacceptable toxicity.
- **Thyroid cancer, advanced or metastatic, RET fusion-positive: Oral:** 400 mg once daily until disease progression or unacceptable toxicity.
- **Thyroid cancer (medullary), advanced or metastatic, RET-mutant: Oral:** 400 mg once daily until disease progression or unacceptable toxicity.

Hemorrhagic events	Grade 3 or 4	Withhold pralsetinib until recovery to baseline or grade 0 or 1. Permanently discontinue pralsetinib for severe or life-threatening hemorrhagic events.
Hypertension	Grade 3	Initiate or optimize hypertensive therapy. Withhold pralsetinib for grade 3 hypertension that persists despite management with optimal antihypertensive therapy. Resume pralsetinib at a reduced dose when hypertension is controlled.
	Grade 4	Discontinue pralsetinib.
Pulmonary toxicity (interstitial lung disease [ILD])/pneumonitis)	Grade 1 or 2	Withhold pralsetinib until resolution, then resume pralsetinib at a reduced dose. Permanently discontinue pralsetinib for recurrent ILD/pneumonitis.
	Grade 3 or 4	Permanently discontinue pralsetinib for confirmed ILD/pneumonitis.
Other adverse reactions	Grade 3 or 4	Withhold pralsetinib until improvement to ≤ grade 2, then resume pralsetinib at a reduced dose. Permanently discontinue pralsetinib for recurrent grade 4 adverse reactions.

CABOZANTINIB

- Mechanism of action- It is a potent inhibitor of proinvasive receptor tyrosine kinases (RTKs), including AXL, FLT-3, KIT, MER, MET, RET, ROS1, TIE-2, TRKB, TYRO3, and VEGFR-1, -2, and -3
- Administration-Do not administer with food; administer on an empty stomach (at least 1 hour before or 2 hours after eating).

THANK YOU


Tata Memorial Hospital
(MPMMCC), Varanasi