Management of lung cancer with oncogenic driver mutations other than EGFR & ALK

Gogineni ratnakar

DM seminar

Division

- Background-driver mutations
- Prevalence
- Types of driver mutations in lung cancer
- Molecular testing
- Agents for driver mutations
- In our practice

Background driver mutations

Cancer-associated gene mutations

Driver

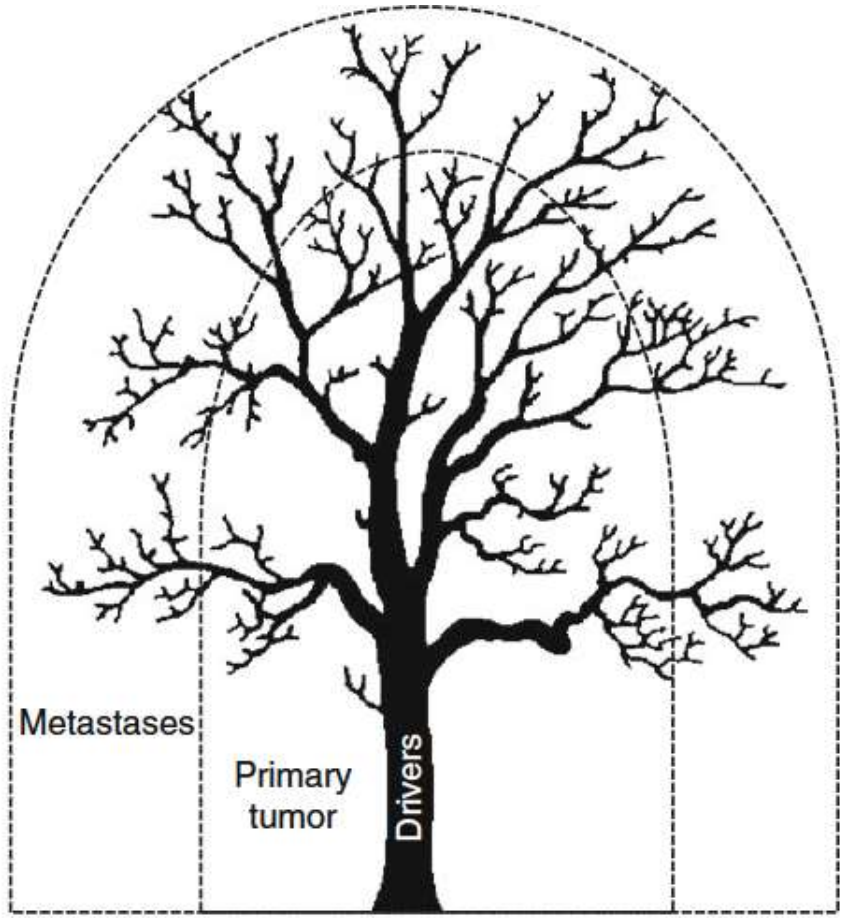
Passenger

Mutations that provide a selective growth advantage

Do not directly contribute to the ongoing proliferation

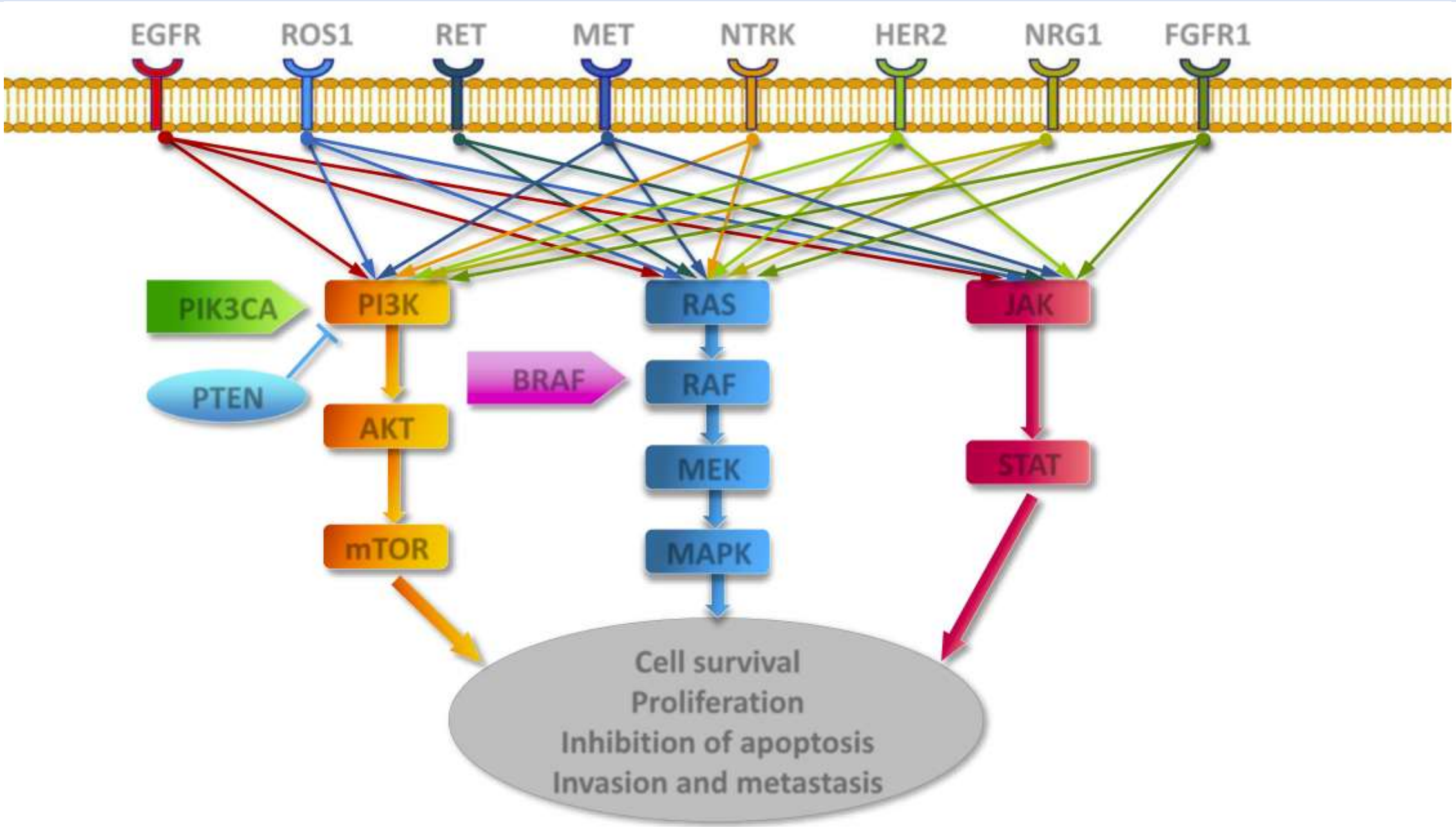
Tumorigenesis

Achilles heel

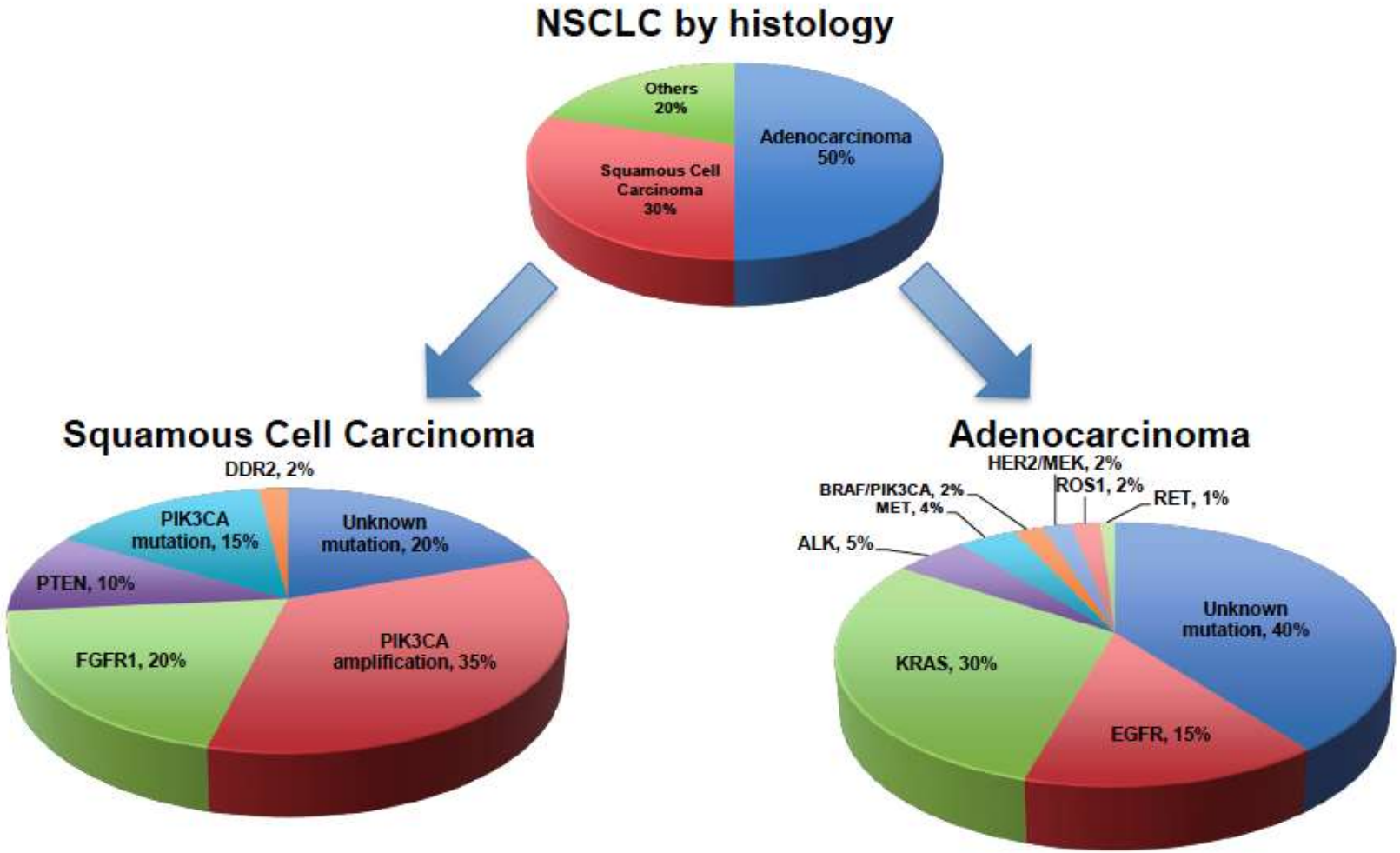


Principles of Cancer Genetics 2nd edition

Key signalling pathways of oncogenic drivers in NSCLC



NSCLC by histology and mutations



Transl Lung Cancer Res 2015;4(1):36-54

Clinical profile of lung cancer in North India: A 10-year analysis of 1862 patients from a tertiary care center

Anant Mohan[1], Avneet Garg[1], Aditi Gupta[1], Satyaranjan Sahu[1], Chandrashekhar Choudhari[1], Vishal Vashistha[2], Ashraf Ansari[1], Rambha Pandey[3], Ashu Seith Bhalla[4], Karan Madan[1], Vijay Hadda[1], Hariharan Iyer[1], Deepali Jain[5], Rakesh Kumar[6], Saurabh Mittal[1], Pawan Tiwari[1], Ravindra M Pandey[7], Randeep Guleria[1]

Pathological type (*n*=1862)	ADC	634 (34.0)
	SCC	532 (28.6)
	NCSLC (NOS)	338 (18.1)
	Small cell carcinoma (SCLC)	300 (16.1)
	Others	58 (3.2)
EGFR mutations (*n*=257)	Positive	65 (25.3)
	Negative	192 (74.7)
ALK rearrangement (*n*=192)	Positive	22 (11.5)
	Negative	170 (88.5)

Characteristics	Smokers	Nonsmokers	*P*
Age >60	797/1363 (58.5)	154/425 (36.2)	<0.001
Female	96/1363 (7)	203/425 (47.8)	<0.001
Education (above primary level education)	489/1120 (43.7)	182/358 (50.8)	0.018
Morphology			
ADC	340/1363 (24.9)	265/425 (62.3)	<0.001
SCC	476/1363 (34.9)	42/425 (9.9)	
Small cell carcinoma	261/1363 (19.1)	32/425 (7.5)	
NSCLC-NOS	266/1363 (19.5)	55/425 (13)	
EGFR mutation positivity, *n* (%)	23/129 (17.8)	37/117 (31.6)	0.012
ALK rearrangement positivity,	5/94 (5.3)	15/84 (17.9)	0.014

July 2016-October 2018-Harbin Cancer Hospital

5,003=adeno(3,243 tissues;1,760blood samples)

230=squamous(134 tissue;96 blood samples)

Genomic Profiling of Driver Gene Mutations in Chinese Patients With Non-Small Cell Lung Cancer

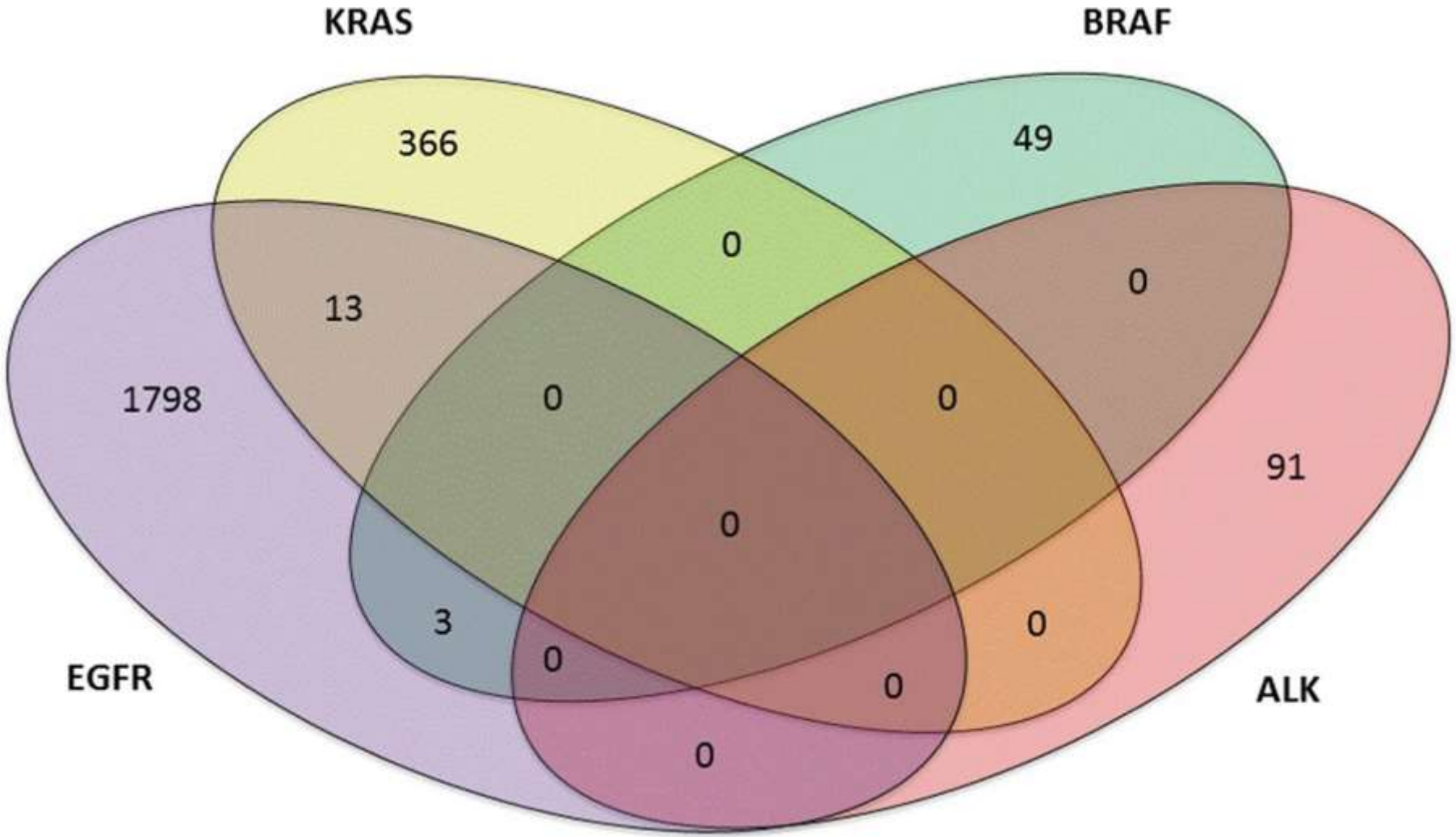
Hongxue Meng[1†], Xuejie Guo[2†], Dawei Sun[3†], Yuebin Liang[2], Jidong Lang[2], Yingmin Han[2], Qingqing Lu[2], Yanxiang Zhang[2], Yanxin An[2], Geng Tian[2], Dawei Yuan[2], Shidong Xu[3*] and Jingshu Geng[1*]*

TABLE 2 | Comparison of driver gene mutations of lung adenocarcinoma between mainland China (this study), Hong Kong (Diehl et al., 2008), Japan (Madic et al., 2012), Black, and White (George et al., 2015).

		Mainland China (3243)	Hong Kong (149)	Japan (411)	Black (146)	White (167)
		Mutant (%)	Mutant (%)	Mutant (%)	Mutant (%)	Mutant (%)
ALK	Rearrangement	2.8%	6.0%	5.0%	0.7%	0%
BRAF	V600E	1.3%	1.3%	0.7%	0.7%	1.2%
	Exon19del	20.6%	22.8%	–[a]	6.8%	6.0%
EGFR	L858R	28.1%	16.8%	–[a]	3.4%	4.2%
	Total	55.9%	43.0%	35.0%	11.6%	14.4%
HER2	Exon 20ins	2.1%	0.7%	1.7%	1.4%	0.6%
KRAS	G12/G13/Q61	11.7%	11.4%	8.5%	34.2%	33.5%
MET	Amplification	1.1%	1.3%	2.2%	2.1%	2.4%
PIK3CA	E542K/E545K/Q H1047L/R	2.9%	0.7%	2.7%	2%	2%
NRAS	G12/G13/Q61	0.7%	0.7%	0.5%	0%	1.2%
RET	Rearrangement	0.6%	–	1.1%	0%	1.2%
ROS1	Rearrangement	0.6%	2.0%	0.5%	0.7%	0%

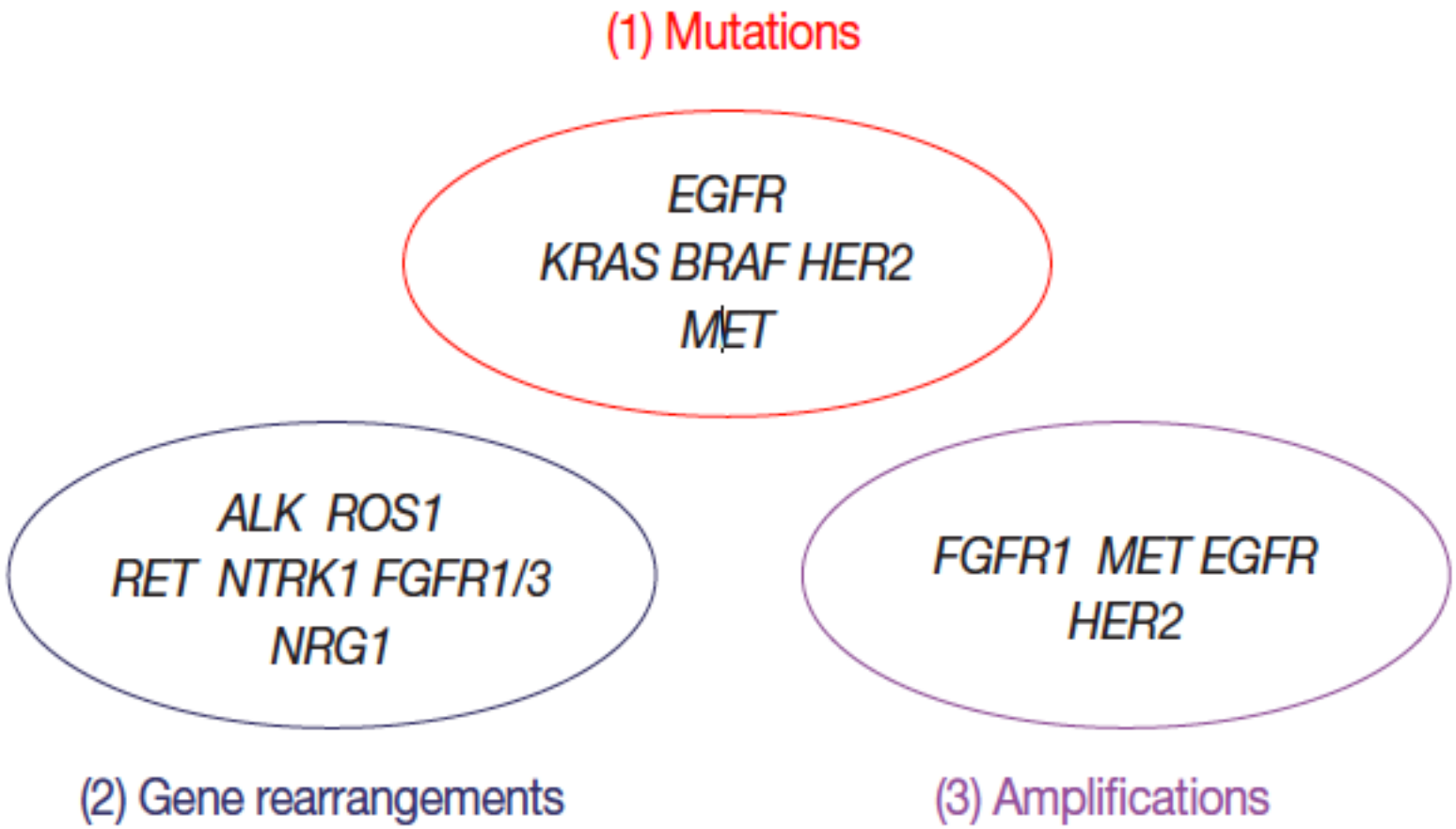
[a]*The mutation frequency was not mentioned in the related study.*

Mutually exclusive



Genomic Profiling of Driver Gene Mutations in Chinese Patients With Non-Small Cell Lung Cancer. Front. Genet. 10:1008. doi: 10.3389/fgene.2019.01008

Three categories of genotypes



Journal of Pathology and Translational Medicine 2017; 51: 242-254
https://doi.org/10.4132/jptm.2017.04.10

Diagnosis

Category	Mutation	Gene rearrangement	Amplification
DNA	Direct sequencing PCR-based methods NGS	FISH NGS	FISH qPCR NGS
RNA	RT-PCR (fusion transcript) NGS	Real-time PCR (mRNA overexpression)	
Protein	IHC (mutation-specific antibody)	IHC (protein expression)	IHC (protein overexpression)

CA CANCER J CLIN 2019;69:305–343

Gene	Representative subtypes or variants	Frequency	Method
Mutations			
EGFR	Exon 19 deletion, Exon 21 L858R, Exon 20 T790M	40%–50% in ADCsa 10%–20% in ADCsb	SCREENING METHODS 1. Sanger sequencing, 2. Next Generation Sequencing (NGS), 3. High Resolution Melt Analysis (HRMA) and 4. Pyrosequencing TARGETED METHODS 1. ddPCR 2. Real-time PCR 3. NGS
KRAS	G12X, G13X, G61X	5%–10% in ADCsa 20%–30% in ADCsb	Gene sequencing
BRAF	V600E	1%–4% in ADCs	NGS, pyrosequencing, AS-PCR
HER2	p.A775 G776insYVMA in exon 20	1%–2% in ADCs	NGS, multiple mutation testing
MET	Splice site mutations around or in exon 14	3%–4% in ADCs	NGS, FISH

CA CANCER J CLIN 2019;69:305–343

Diagnosis

Gene	Representative subtypes or variants	Frequency	Method
Gene fusions			
ALK	EML4-ALK, TGF-ALK, KIF5B-ALK	5% in ADCs	FISH,IHC,RT-PCR,NGS
ROS1	CD74-ROS1, EZR-ROS1, SLC34A2-ROS1, SDC4-ROS1	1% in ADCs	FISH,IHC,RT-PCR,NGS
RET	KIF5B-RET, CCDC6-RET	1% in ADCs	NGS, FISH, RT-PCR
NTRK1	MPRIP-NTRK1 and CD74-NTRK1, TPM3-NTRK1	< 1% in ADCs	NGS,IHC
FGFR1/3	FGFR3-TACC3, BAG4-FGFR1	1% in NSCLCs	NGS,RT-PCR
NRG1	CD74-NRG1, SLC3A2-NRG1, VAMP2-NRG1	7% in mucinous ADCs	NGS
Amplifications			
FGFR1	Gene amplification	13%–22% in SQCs	NGS
EGFR	Gene amplification	8%–9% in SQCs,	NGS
MET	Gene amplification	2%–4% in ADCs	NGS
HER2	Gene amplification	1%–2% in ADCs	NGS

Journal of Pathology and Translational Medicine 2017; 51: 242-254
https://doi.org/10.4132/jptm.2017.04.10

Table 2 FDA-approved companion diagnostic tests for NSCLC therapies

FDA-approved device	Manufacturer	Platform	Specimen	Therapy	Approximate turnaround time
therascreen EGFR RGQ PCR kit (47)	Qiagen	PCR	FFPE tumor tissue	Afatinib, gefitinib	1 to 7 days
FoundationOne CDx™ (48)	Foundation Medicine	NGS	FFPE tumor tissue	Afatinib, osimertinib, erlotinib, gefitinib, alectinib, crizotinib, ceritinib, dabrafenib plus trametinib	10 to 14 days
cobas *EGFR* Mutation Test v2 (49)	Roche	PCR	Plasma (K_2EDTA) or FFPE tumor tissue	Erlotinib, osimertinib	1 to 7 days
PD-L1 IHC 22C3 pharmDx (50)	Agilent Technologies	IHC	FFPE tumor tissue	Pembrolizumab	1 to 7 days
VENTANA *ALK* (D5F3) CDx Assay (51)	Roche/VENTANA Medical Systems	IHC	FFPE tumor tissue	Alectinib, crizotinib, ceritinib	1 to 3 days
Vysis *ALK* Break Apart FISH Probe Kit (52)	Abbott	FISH	FFPE tumor tissue	Alectinib, crizotinib, ceritinib	1 to 7 days
Oncomine™ Dx Target Test (53)	Thermo Fisher Scientific	NGS	FFPE tumor tissue	Crizotinib, dabrafenib plus trametinib, gefitinib	5 to 14 day

The table displays FDA-approved NSCLC therapies and companion diagnostics as of August 2018. Turnaround times are approximate. *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; FDA, Food and Drug Administration; FFPE, formalin-fixed, paraffin-embedded; FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry; K_2EDTA, dipotassium ethylenediaminetetraacetic acid; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction; PD-L1, programmed cell death ligand-1; RGQ, Rotor-Gene Q.

Spanish Society guidelines

Table 1 Essential biomarkers in NSCLC patients

Gene/protein	Predictive alteration	Methodology (in tissue)
EGFR	Mutation	PCR: sanger, real-time PCR and NGS
ALK	Rearrangement	IHC, FISH and NGS
ROS1	Rearrangement	IHC (screening), FISH and NGS
BRAF V600	Mutation	PCR: sanger, real-time PCR and NGS
PD-L1	Overexpression	IHC

EGFR epidermal growth factor receptor, *FISH* fluorescence in situ hybridisation, *H&E* haematoxylin/eosin, *IHC* immunohistochemistry, *NGS* next-generation sequencing, *NSCLC* non-small-cell lung cancer, *PCR* polymerase chain reaction, *PD-L1* programmed death ligand-1

Table 2 Other biomarkers of interest in NSCLC patients

Gene	Predictive alteration	Methodology (in tissue)
HER2	Mutation	PCR: sanger, real-time PCR and NGS
	Amplification	FISH, NGS, real-time PCR
MET	Mutation	NGS
	Amplification	FISH, NGS, real-time PCR
RET	Rearrangement	FISH and NGS
NTRK	Rearrangement	IHC (screening) and NGS
TMB	Mutations*	NGS

FISH fluorescence in situ hybridisation, *IHC* immunohistochemistry, *NGS* next-generation sequencing, *NSCLC* non-small-cell lung cancer, *PCR* polymerase chain reaction, *TMB* tumour mutation burden

*Measurement of somatic mutations present in tumour cells

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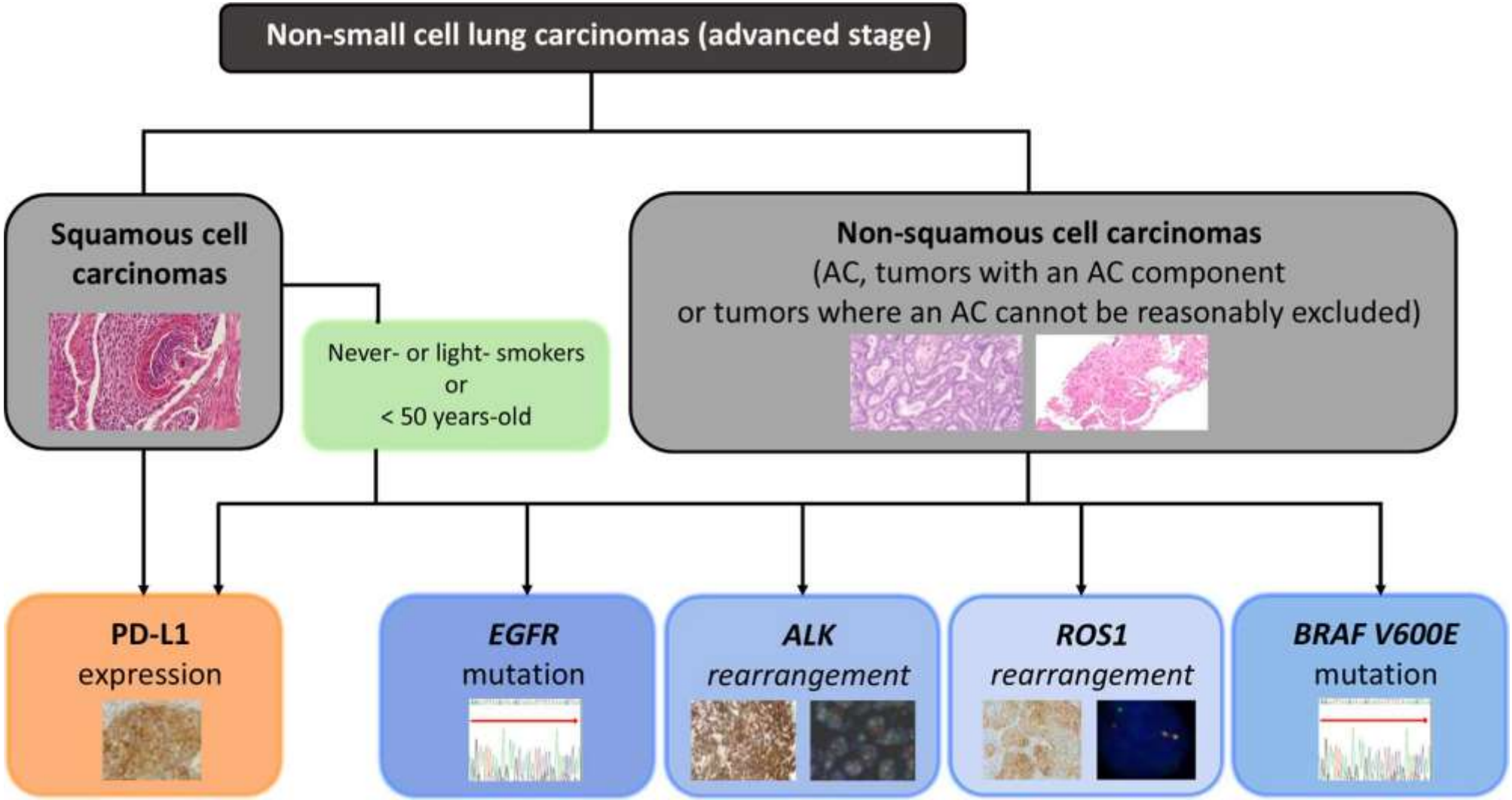
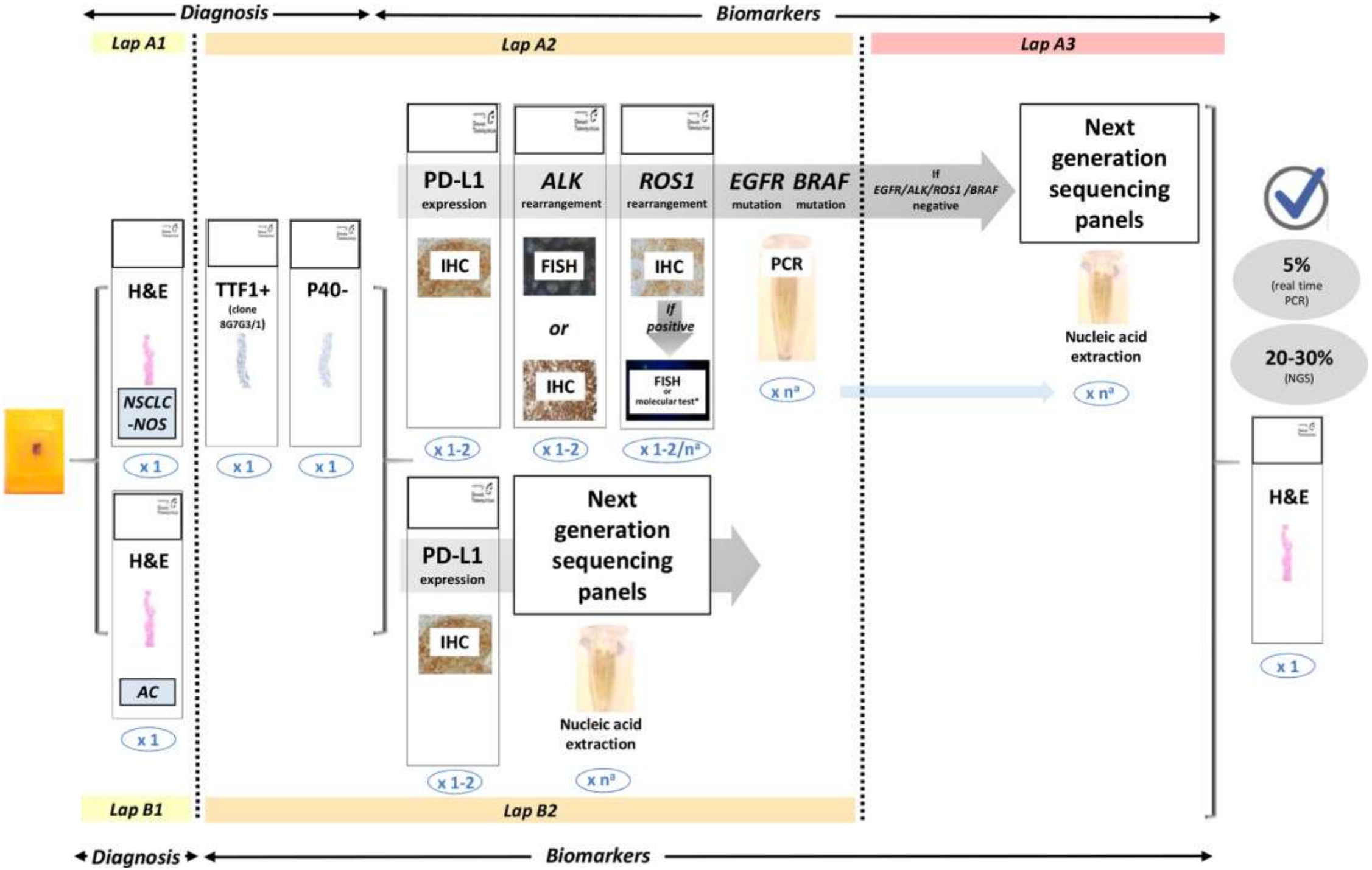


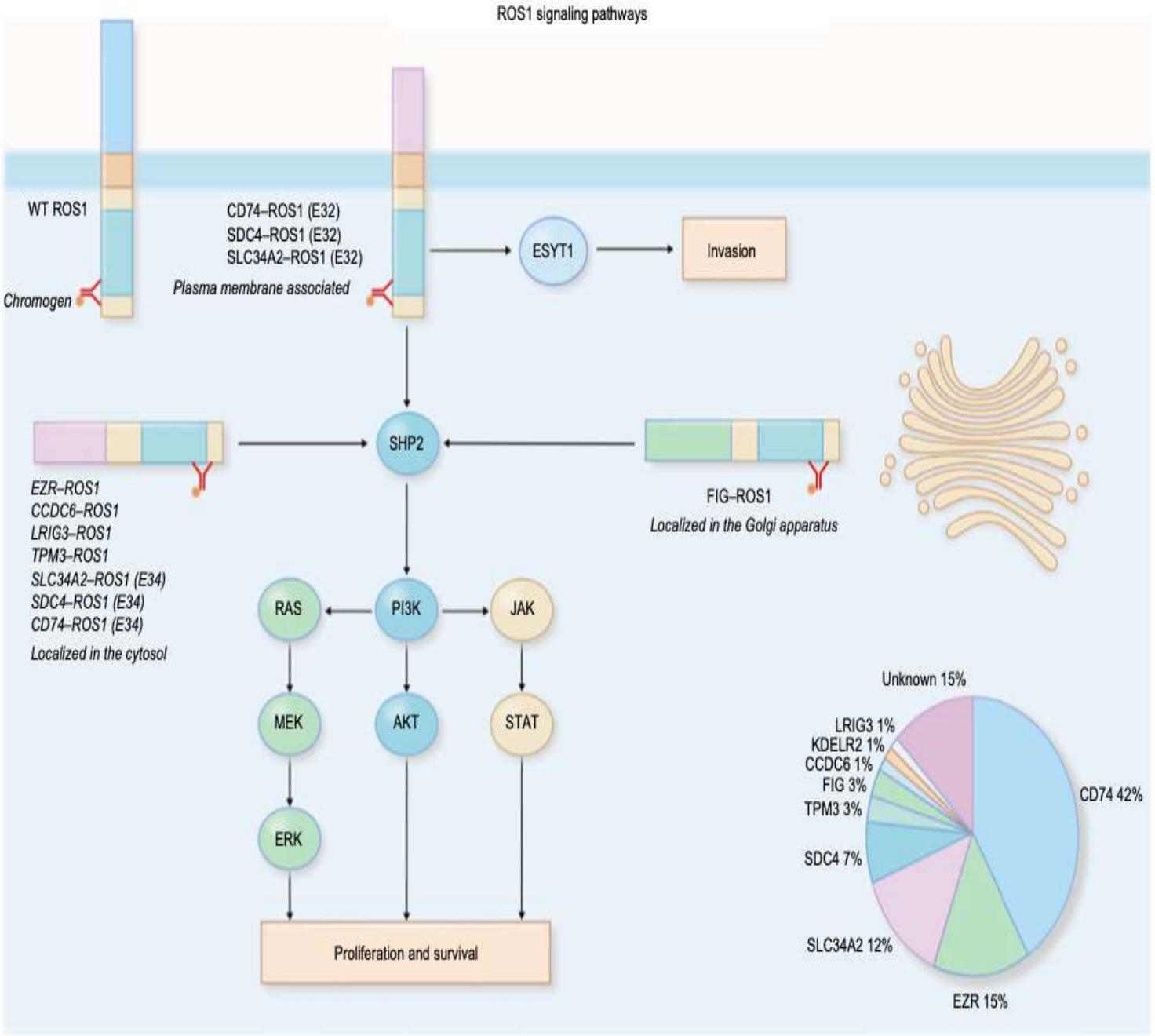
Clinical and Translational Oncology Spanish Society of Medical Oncology https://doi.org/10.1007/s12094-019-02218-4



Spanish Society guidelines

ROS1 oncogene

- Chromosome 6q22 - Receptor tyrosine kinase
- Fusion gene partners of ROS1 comprise several genes, including *CD74, EZR, FIG1, CCD6, KDELR2, LRI3, SDC4, SLC34A2, TPM3* and *TPD52L1*.
- 3′ region of the kinase domain of *ROS1* to the 5′ region of the partner gene

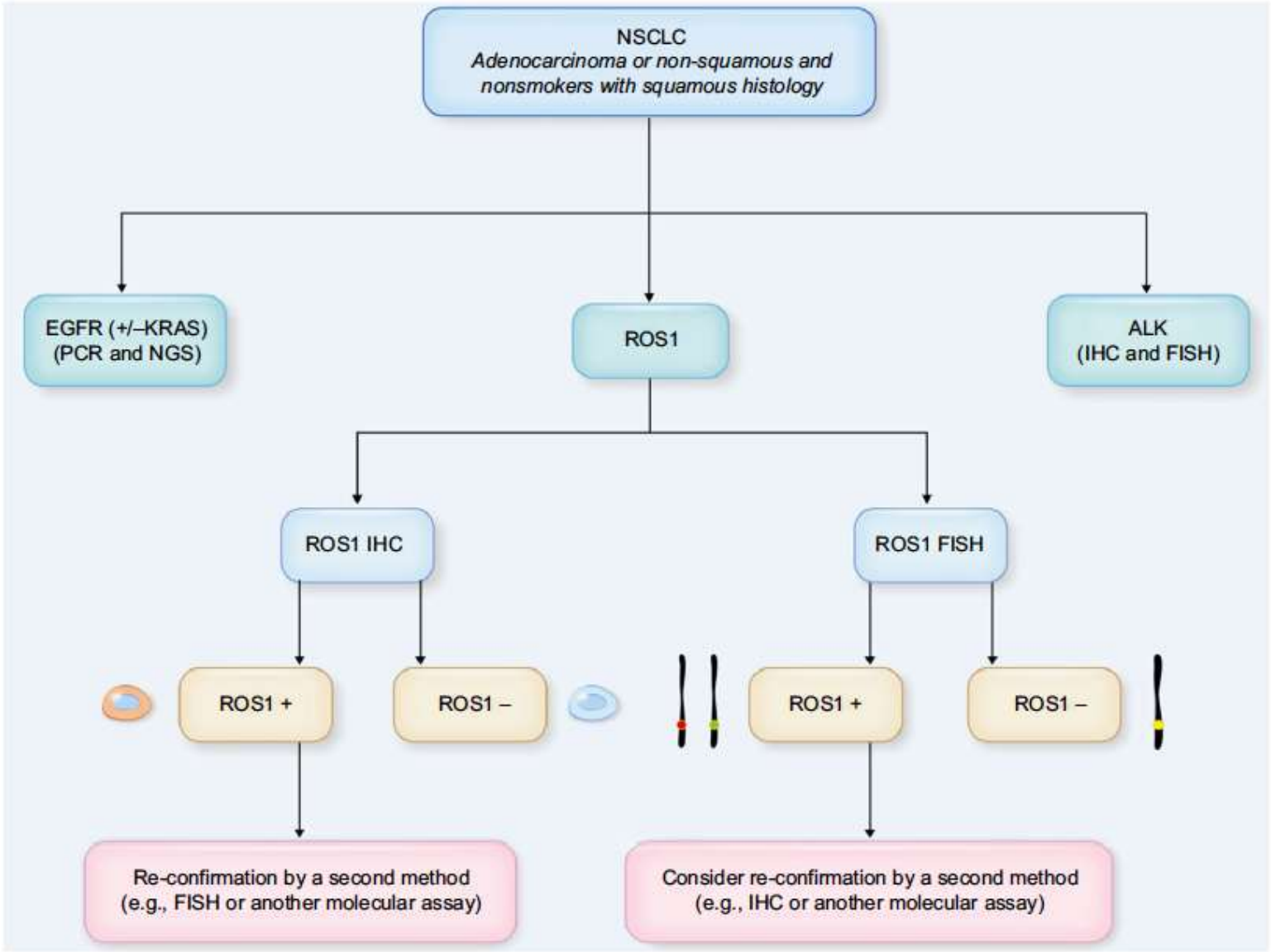


ROS1 oncogene

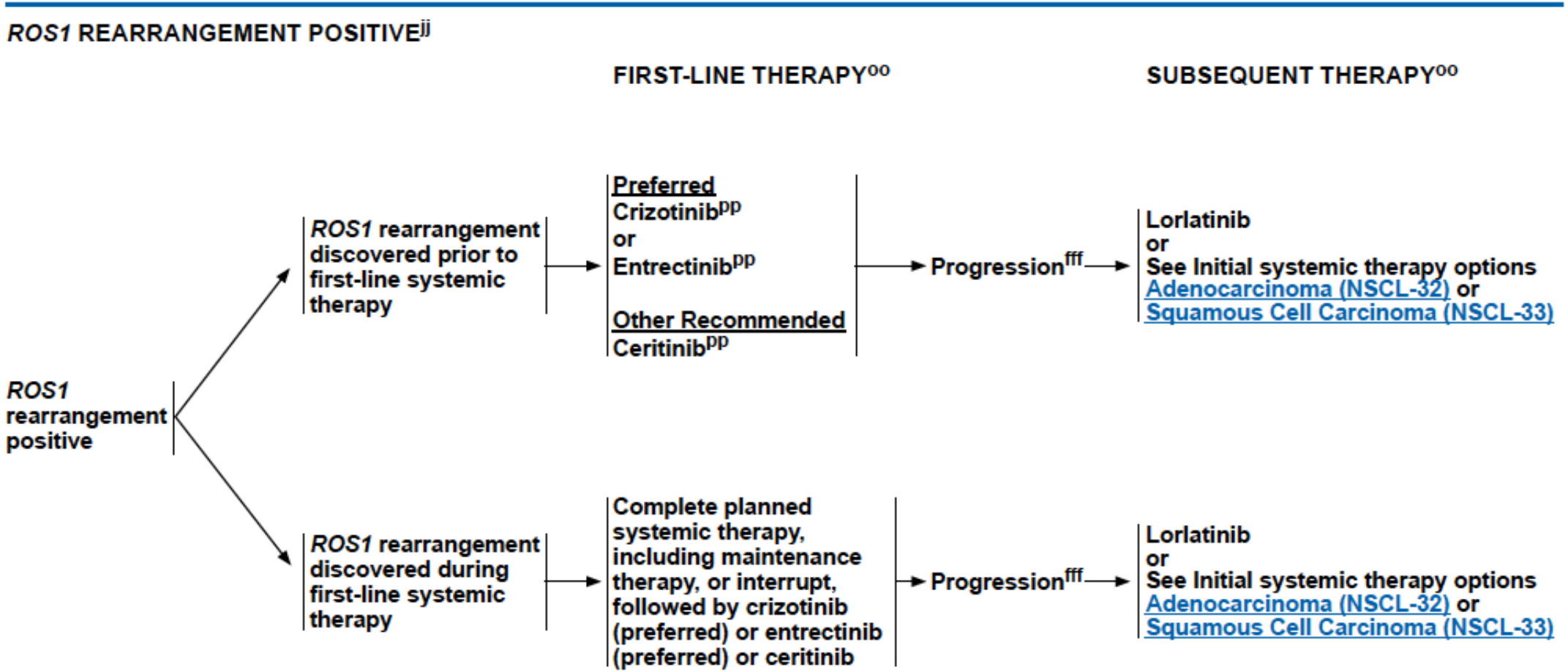
- ROS-1 (1–2%) NSCLC adenocarcinoma
- Overall survival irrespective of use of targeted therapy is longer
- Usually mutually exclusive with other mutations
- Young patients, Asian origin, women, never-smokers and adenocarcinoma
- Most frequent fusion partner being CD74 (40 to 45%)
- More susceptible to brain metastases
- lower ORR to crizotinib than non-CD74-ROS1

ROS1 oncogene

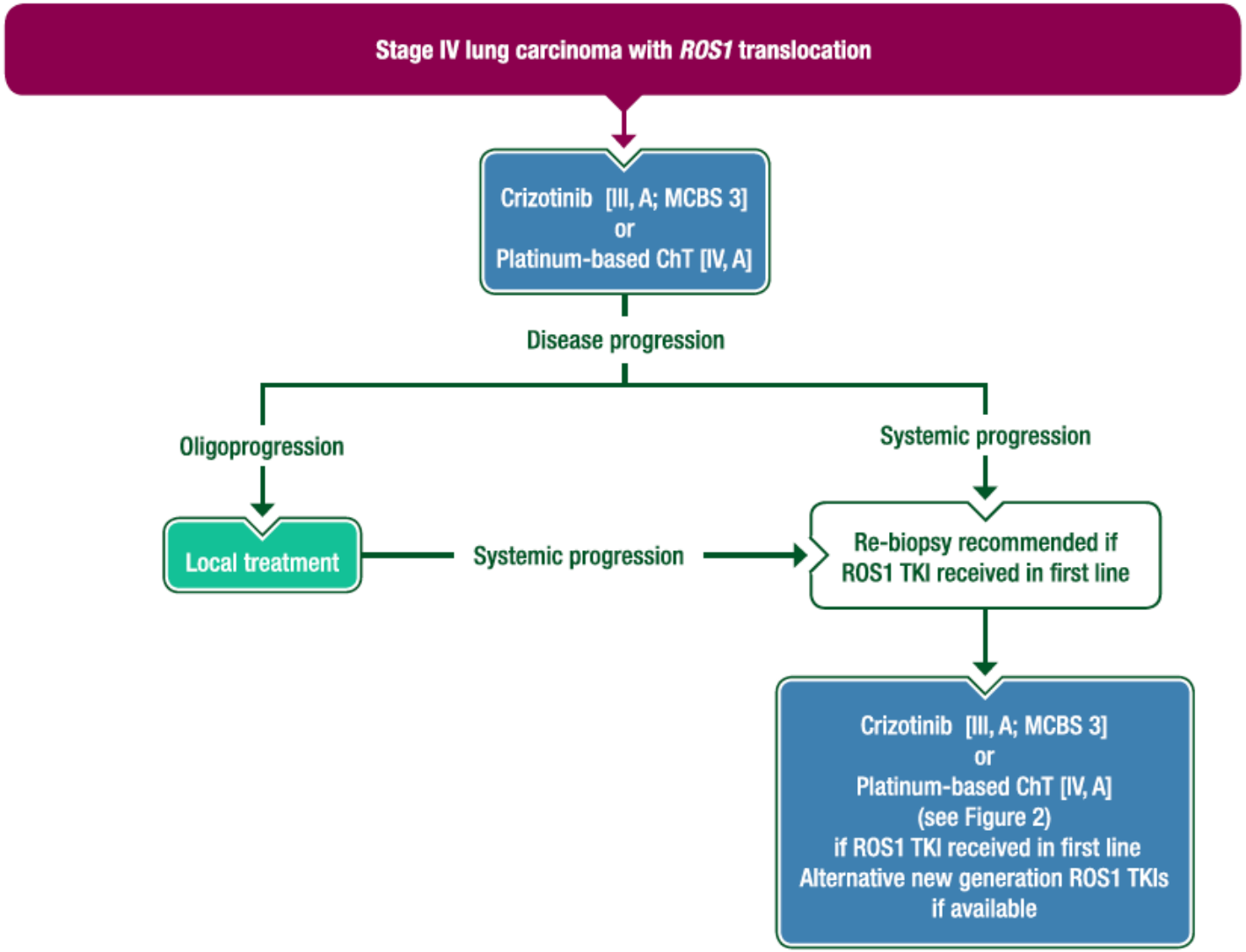
- ROS1 fusion detection methods include fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), reverse transcription-polymerase chain reaction (RT-PCR), and next-generation sequencing (NGS)



NCCN guidelines version 4.2020



ESMO-2018 Guidelines



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 20, 2014 VOL. 371 NO. 21

Crizotinib in *ROS1*-Rearranged Non–Small-Cell Lung Cancer

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Rationale-Crizotinib

- First-kinase domains of ALK and ROS1 share 77% amino acid identity within the ATP-binding sites.
- Second- cell-based assays for inhibition of autophosphorylation of different kinase targets, both ALK and ROS1 are sensitive to crizotinib, with a half-maximal inhibitory concentration of 40 to 60 nM
- Third-cell lines expressing ROS1 fusions, crizotinib potently inhibits ROS1 signaling and cell viability
- Finally-case reports have described marked responses to crizotinib in patients with ROS1-rearranged NSCLC

Open label, multi-center Phase 1 dose escalation, safety, pharmacokinetic and exploratory study

Eligible criteria

- Advanced NSCLC with a ROS1
- Age of at least 18 years
- ECOG status of 0 to 2
- Adequate organ function

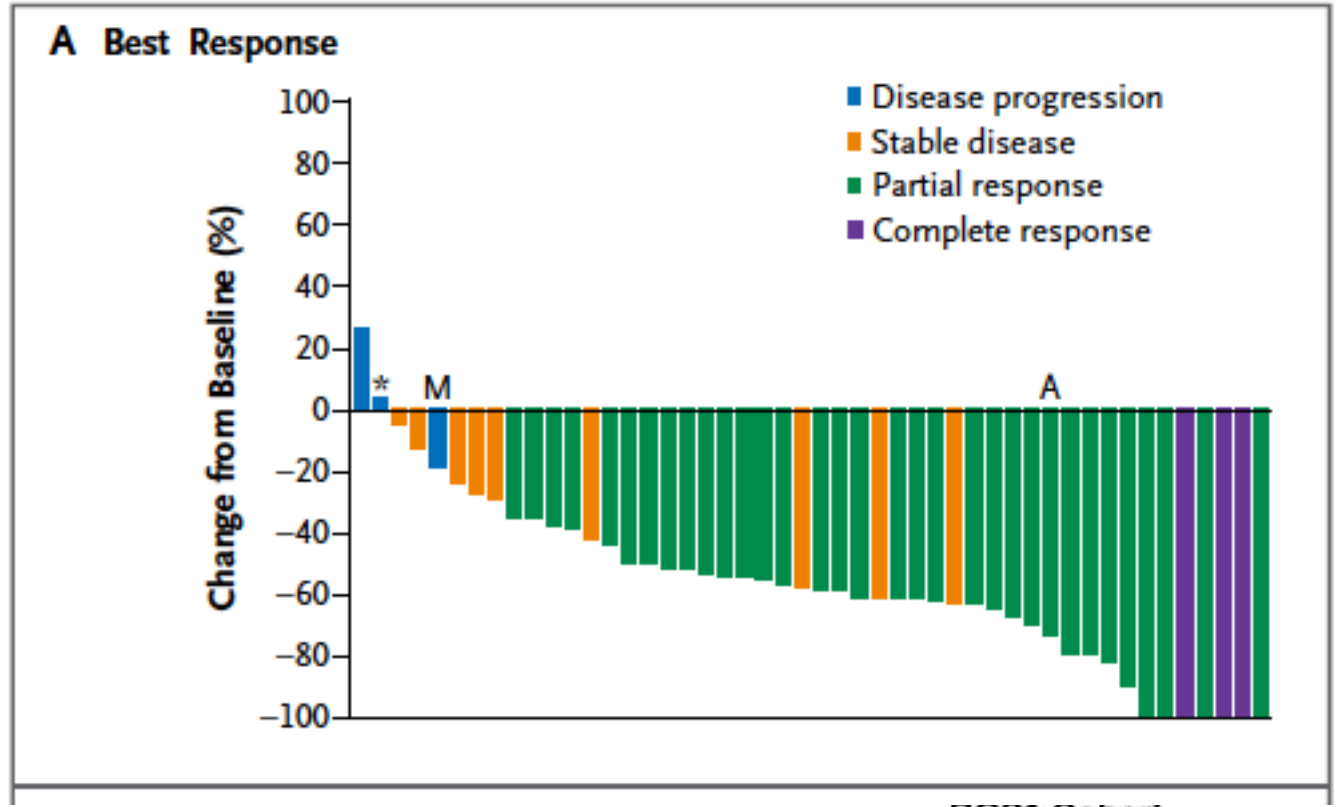
Intervention

- Crizotinib 50 mg dose-escalation phase to full dose of 250 mg twice daily 28 days cycle

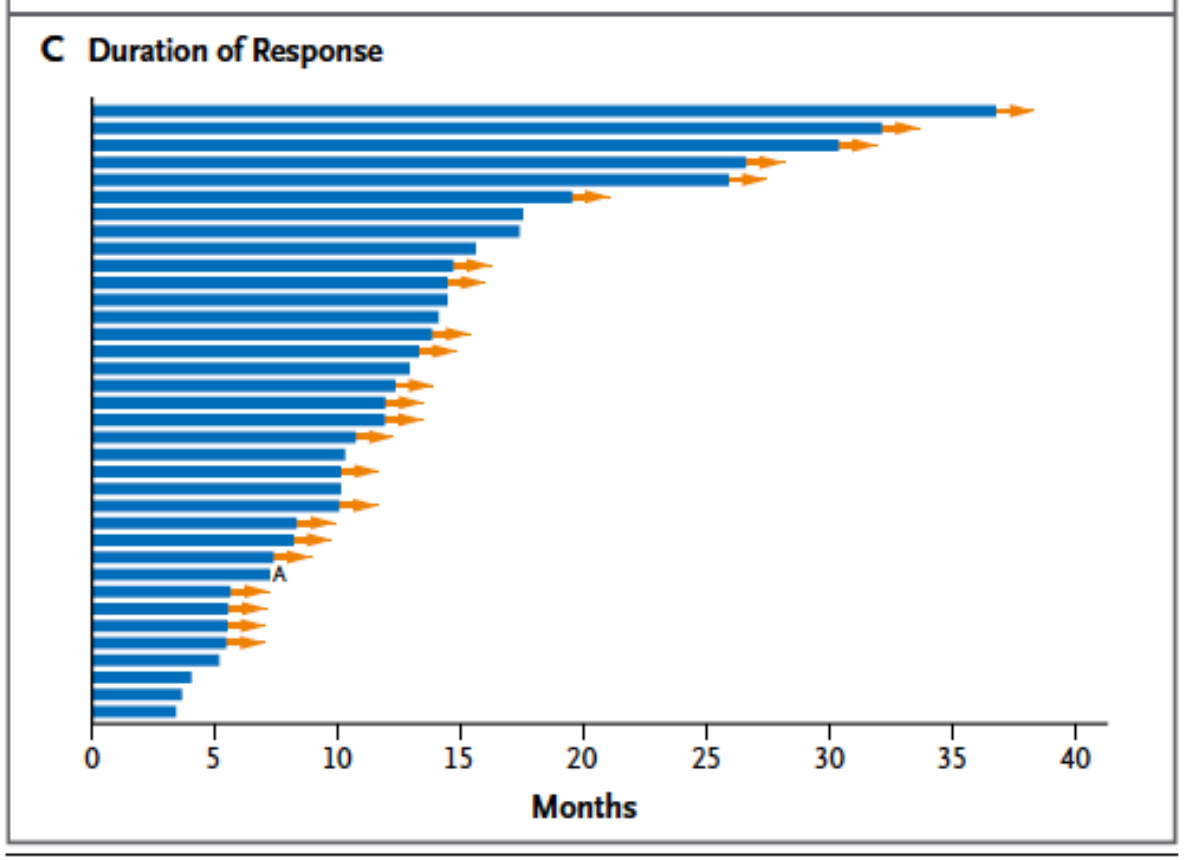
Treatment continued until the occurrence of RECIST-defined disease progression or clinical deterioration, unacceptable toxic effects, withdrawal from the study or death

Table 1. Characteristics of the Patients at Baseline.

Characteristic	ROS1 Cohort (N=50)
Age — yr	
Median	53
Range	25–77
Sex — no. (%)	
Male	22 (44)
Female	28 (56)
Race — no. (%)*	
White	27 (54)
Asian	21 (42)
Other	2 (4)
Smoking status — no. (%)	
Never smoked	39 (78)
Former smoker	11 (22)
Histologic type — no. (%)	
Adenocarcinoma	49 (98)
Squamous-cell carcinoma	1 (2)
ECOG performance status — no. (%)†	
0	22 (44)
1	27 (54)
2	1 (2)
Previous regimens for advanced disease — no. (%)	
0	7 (14)
1	21 (42)
>1	22 (44)

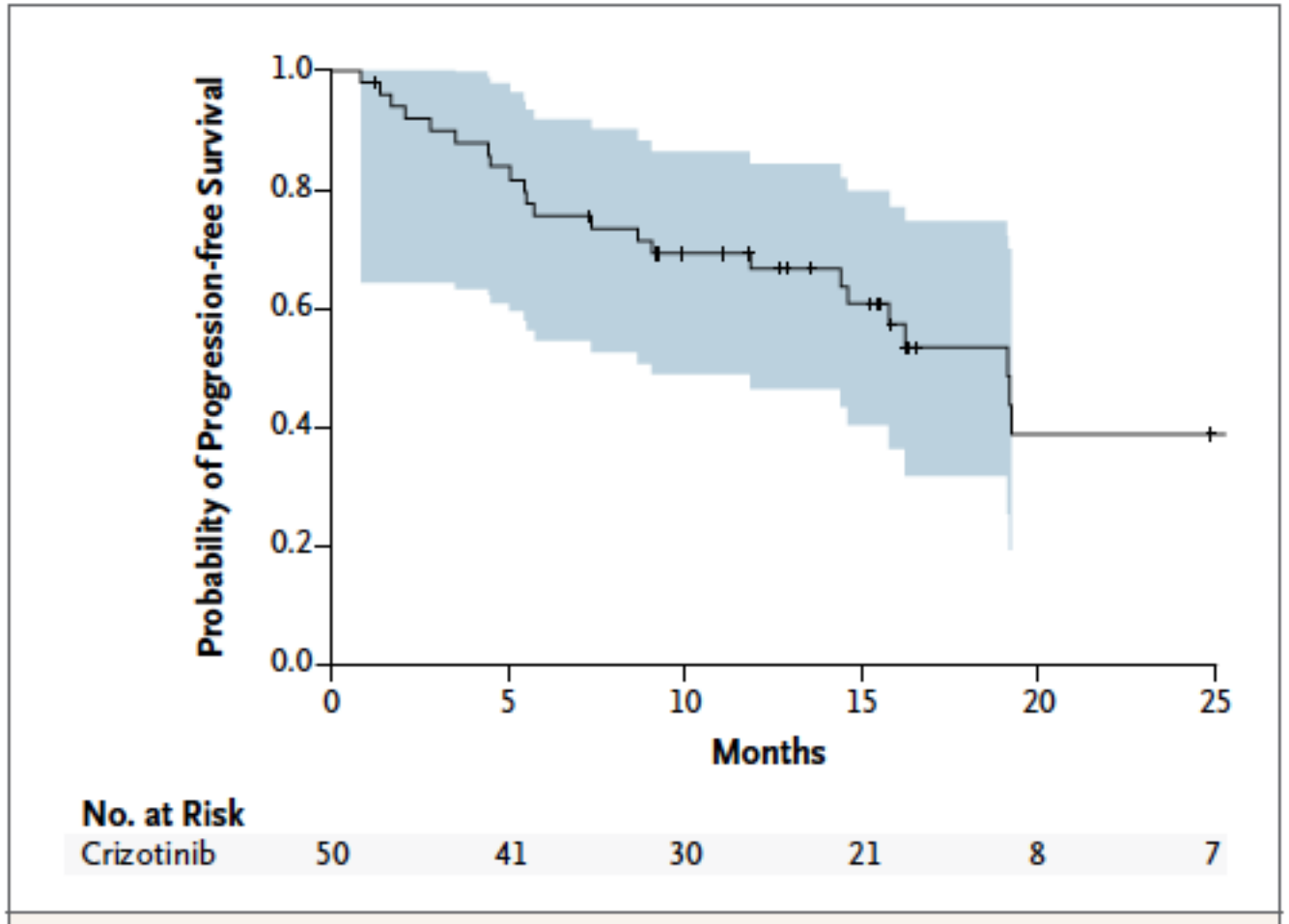


	ROS1 Cohort (N=50)
Type of response – no. (%)	
Complete response	3 (6)
Partial response	33 (66)
Stable disease	9 (18)
Progressive disease	3 (6)
Early death†	2 (4)
Objective response rate (%)	72
95% CI	58 - 84
Time to first response (wks)‡	
Median	7.9
Range	4.3 – 32.0
Duration of response (mos)§	
Median	17.6
95% CI	14.5 – NR



Among the 50 patients, the median duration of treatment was 64.5 weeks (range, 2.3 to 182.0), and 30 patients (60%) continued to re ceive crizotinib after the data cutoff date

Median progression-free survival was 19.2 months (95% CI, 14.4 to NR)



- Median follow-up for overall survival was 16.4 months (95% CI, 13.8 to 19.8)
- Nine of the 50 patients (18%) had died by the time of data cutoff
- The overall survival rate at 12 months was 85% (95% CI, 72 to 93)

Resistance to crizotinib

Secondary mutation that hinders drug binding27

and activation of epidermal growth factor

receptor, which enables cancer cells to bypass

crizotinib-mediated inhibition of ROS1 signalling pathway

FDA approved for the treatment of advanced

ROS1-rearranged NSCLC in March 2016

Table 2. Adverse Events.*

Adverse Event	Grade 1	Grade 2	Grade 3	All Grades
	number of patients (percent)			
Visual impairment	41 (82)	0	0	41 (82)
Diarrhea	21 (42)	1 (2)	0	22 (44)
Nausea	18 (36)	2 (4)	0	20 (40)
Peripheral edema	15 (30)	5 (10)	0	20 (40)
Constipation	16 (32)	1 (2)	0	17 (34)
Vomiting	15 (30)	1 (2)	1 (2)	17 (34)
Elevated aspartate aminotransferase	9 (18)	1 (2)	1 (2)	11 (22)
Fatigue	9 (18)	1 (2)	0	10 (20)
Dysgeusia	9 (18)	0	0	9 (18)
Dizziness	8 (16)	0	0	8 (16)
Elevated alanine aminotransferase	3 (6)	2 (4)	2 (4)	7 (14)
Hypophosphatemia	0	2 (4)	5 (10)	7 (14)
Decreased testosterone†	2 (9)	1 (5)	0	3 (14)
Neutropenia	1 (2)	0	5 (10)	6 (12)
Dyspepsia	5 (10)	0	0	5 (10)
Sinus bradycardia	5 (10)	0	0	5 (10)

		Median PFS	ORR	Duration of response	Time of first response	Median OS	Median duration of treatment
• AcSe´ phase II trial • 5606=patients • 78=ROS-1 2019	Crizotinib 250 mg twice daily	5.5 months with a 95% CI [4.2–9.1 months]	72%.			17.2 months with a 95% CI [6.8–32.8 months]	11.1 (1 day to 42.7 months) months
PROFILE 1001 2019 N=53	crizotinib at a starting dose of 250 mg twice daily	19.3 (15.2–39.1) months	72 (58–83)	24.7 (15.2–45.3) months	7.9 (4.3–103.6) weeks	51.4 (29.3–NR) months	22.4 months
EUROS1 Cohort	crizotinib (250mg two times per day) for	9.1 months	80%				

		Median PFS	ORR	Duration of response	Time of first response	Median OS	Median duration of treatment
EUCROSS N=34 open-label phase II trial	250 mg crizotinib twice daily	20.0 months (95% CI: 10.1–not reached)	70% (95% confidence interval [CI]: 51–85	20.0 months (95% CI: 10.1–not reached [NR])		Survival rates at 12 months and 24 months were 83% (95% CI: 69%–97%) and 63% (95% CI: 42–84)	
Phase II Study Yi-LongWu East Asian patients	crizotinib at a starting dose of 250 mg twice daily	15.9 95% CI 12.9 to 24.0	(71.7%) 95% CI(63.0 to 79.3)	19.7 95% CI 14.1 to NR		32.5 95% CI 32.5 to NR	

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Open-Label, Multicenter, Phase II Study of Ceritinib in Patients With Non–Small-Cell Lung Cancer Harboring *ROS1* Rearrangement

Sun Min Lim, Hye Ryun Kim, Jong-Seok Lee, Ki Hyeong Lee, Yun-Gyoo Lee, Young Joo Min, Eun Kyung Cho, Sung Sook Lee, Bong-Seog Kim, Moon Young Choi, Hyo Sup Shim, Jin-Haeng Chung, Yoon La Choi, Min Jeong Lee, Maria Kim, Joo-Hang Kim, Siraj M. Ali, Myung-Ju Ahn, and Byoung Chul Cho

Author affiliations and support information (if applicable) appear at the end of this article.

ABSTRACT

Ceritinib

- Ceritinib (LDK378) is a more potent and selective oral tyrosine kinase inhibitor of ALK and has shown promising clinical activity in both crizotinib-naiıve and crizotinib-treated patients
- Ceritinib demonstrated superior efficacy compared with standard second-line chemotherapy in patients with crizotinib-resistant ALK rearrangement
- Ceritinib crossed the blood-brain barrier

- Open-label, phase II study
- 10 academic hospitals across the Republic of Korea
- **Eligible criteria**
- Advanced NSCLC with a ROS1
- Age of at least 20 years
- ECOG status of 0 to 2
- Adequate organ function

- Ceritinib 750 mg/ day PO after 2-hour fasting in continuous 28-day treatment cycles
- Patients continued with ceritinib until objective evidence of disease progression or intolerance

Demography

Median follow-up was 14.0 months

Table 1. Baseline Characteristics

Characteristic	No. (%)
No. of patients	32
Age, years, median (range)	62 (35-79)
Female sex	24 (75)
WHO/ECOG performance status	
0	14 (44)
1	14 (44)
≥ 2	4 (13)
Smoking history	
Never-smoker	27 (84)
Former or current smoker	5 (16)
Tumor histology	
Adenocarcinoma	32 (100)
No. of previous treatment, median (range)	3 (2-7)
Months from diagnosis to initiation of ceritinib, median (range)	18.3 (2-96)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

- Objective response rate was 62% (95% CI, 45% to 77%)
- Duration of response was 21.0 months (95% CI, 17 to 25 months)
- Disease control rate was 81% (95% CI, 65% to 91%)

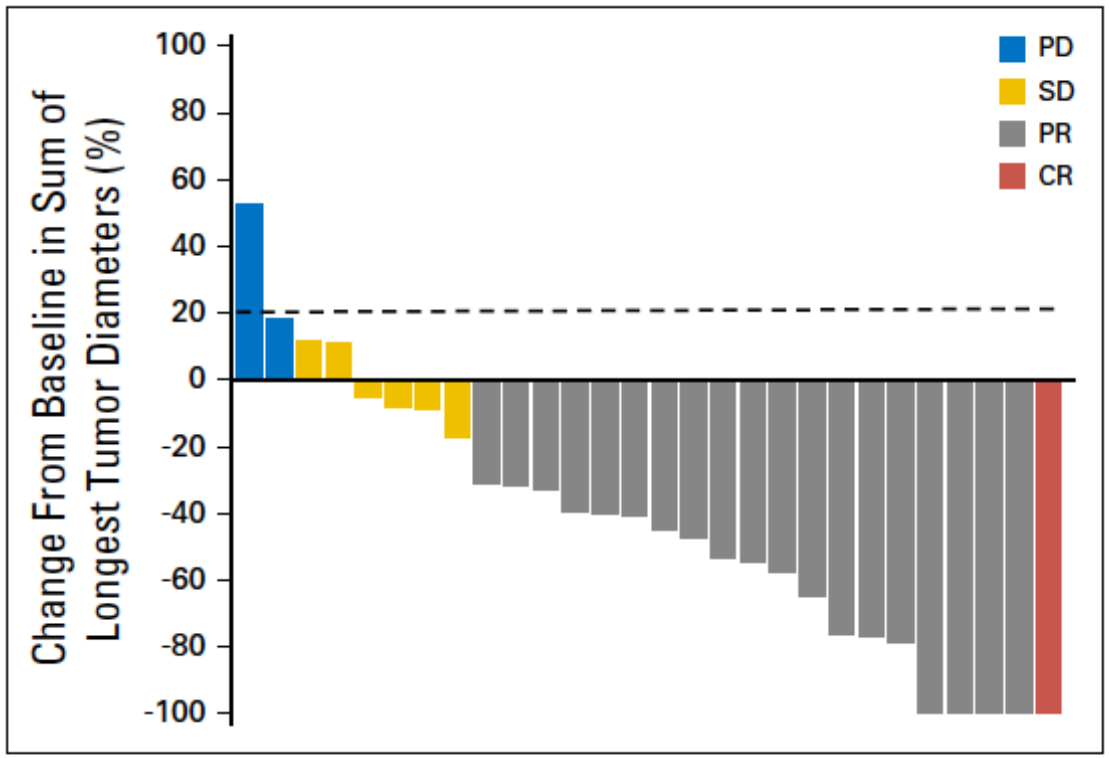


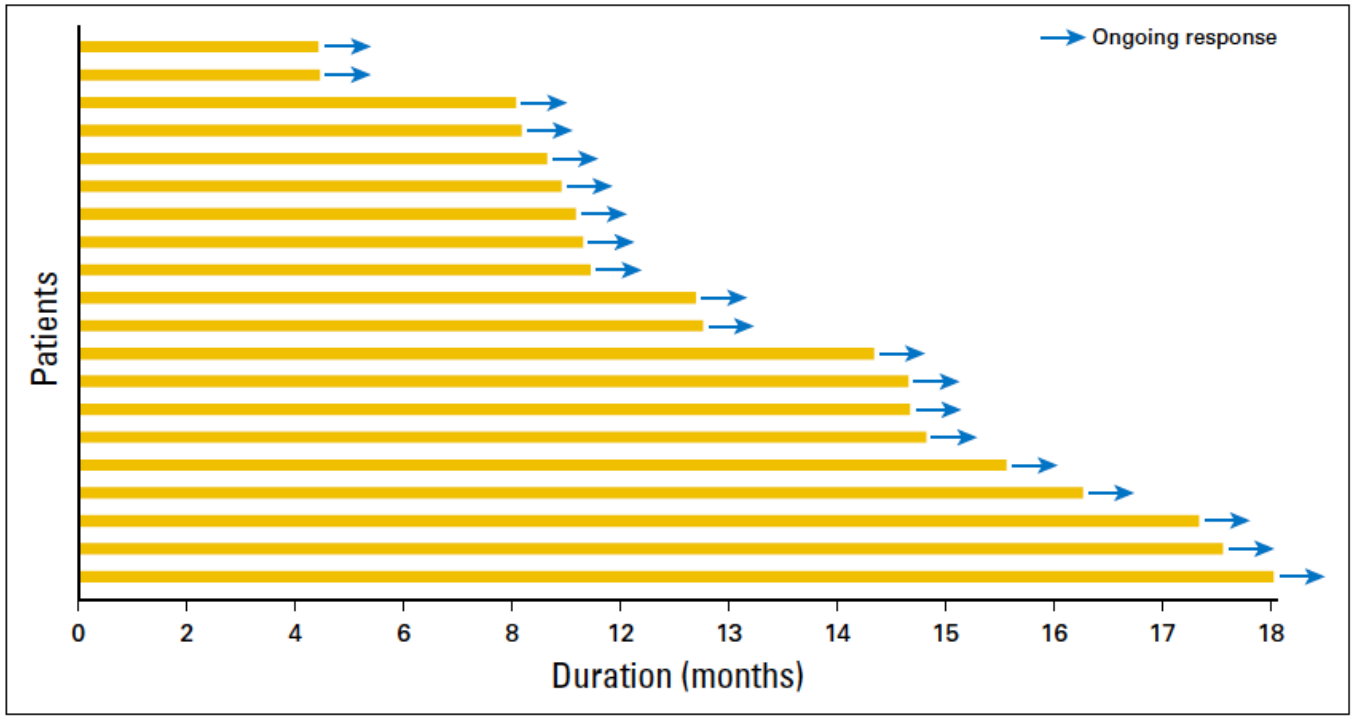
Fig 1. Best percentage change from baseline in tumor volume in patients with at least one postbaseline measurement. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Table 2. Independent Review Committee–Assessed Activity

Best Response	All Patients, No. (%)	Crizotinib-Naïve Patients, No. (%)
No. of patients	32	30
CR	1 (3)	1 (3)
PR	19 (59)	19 (63)
SD	6 (19)	6 (20)
PD	2 (6)	2 (7)
Not evaluable*	4 (12)	2 (7)
ORR, % (95% CI)	62 (45 to 77)	67 (48 to 81)
DCR (CR + PR + SD), % (95% CI)	81 (65 to 91)	87 (70 to 95)

Abbreviations: CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
*As a result of early death (n = 3) or withdrawal (n = 1) before first response evaluation.

- Median overall survival was 24 months (95% CI, 5 to43 months)
- Median progression-free survival was 9.3 months (95% CI, 0 to 22 months) for all patients and 19.3 months (95% CI, 1 to37 months) for crizotinib-naïve patients.



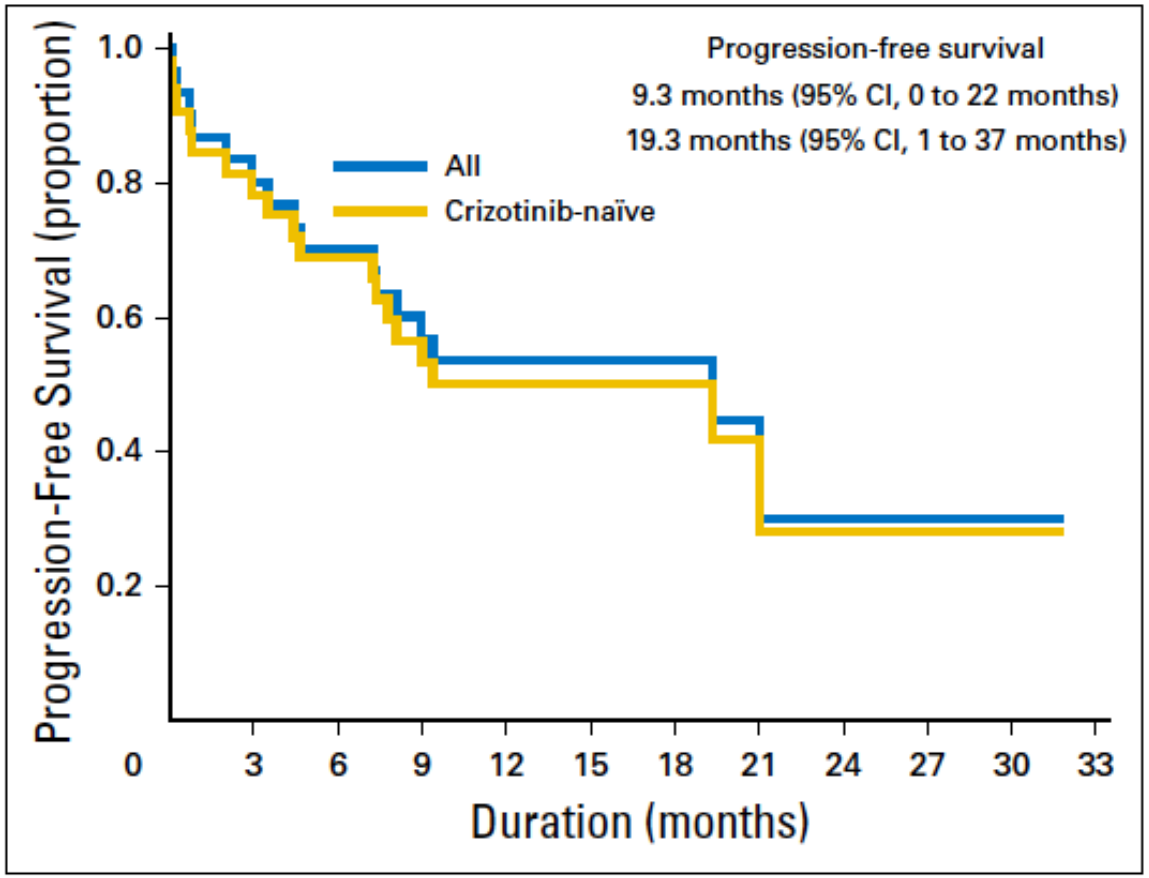


Table 3. Adverse Events That Occurred at Grades 1 to 2 in 10% or More Patients or at Grades 3 to 5

Adverse Event	Grade, No. (%)			
	1 to 2	3	4	5
Diarrhea	25 (78)	0	0	0
Nausea	19 (59)	1 (3)	0	0
Anorexia	18 (56)	1 (3)	0	0
Vomiting	17 (53)	0	0	0
Cough	15 (47)	0	0	0
Abdominal pain	13 (41)	0	0	0
Musculoskeletal pain	13 (41)	0	0	0
Fatigue	7 (22)	5 (16)	0	0
Dyspnea	7 (22)	0	0	1 (3)
Fever	6 (19)	0	0	0
Pruritus	5 (16)	0	0	0
Dyspepsia	4 (13)	0	0	0
Pneumonia	4 (13)	2 (6)	0	2 (6)
Dizziness	4 (13)	0	0	0
Infection	0	1 (3)	0	0
Dry mouth	0	1 (3)	0	0
Abdominal discomfort	0	1 (3)	0	0
Pleural effusion	0	1 (3)	0	0
Superior vena cava syndrome	0	1 (3)	0	0
Acute hepatitis	0	0	1 (3)	0
Laboratory abnormalities				
Blood creatinine increased	13 (41)	0	0	0
Alanine aminotransferase increased	10 (31)	2 (6)	1 (3)	0
Aspartate aminotransferase increased	9 (28)	3 (9)	1 (3)	0
Blood alkaline phosphatase increased	8 (25)	1 (3)	0	0
Hyperglycemia	4 (13)	3 (9)	1 (3)	0
Anemia	0	2 (6)	0	0
γ-Glutamyl transferase increased	0	1 (3)	0	0
Hyperuricemia	0	0	1 (3)	0

- Of the eight patients with brain metastases, intracranial disease control was reported in five (63%; 95% CI, 31% to 86%)
- The most common adverse events (majority, grade 1 or 2) for all treated patients were diarrhea (78%), nausea (59%), and anorexia (56%)

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†*

Summary

Background Recurrent gene fusions, such as *ROS1* fusions, are oncogenic drivers of various cancers, including non-small-cell lung cancer (NSCLC). Up to 36% of patients with *ROS1* fusion-positive NSCLC have brain metastases at the diagnosis of advanced disease. Entrectinib is a ROS1 inhibitor that has been designed to effectively penetrate and remain in the CNS. We explored the use of entrectinib in patients with locally advanced or metastatic *ROS1* fusion-positive NSCLC.

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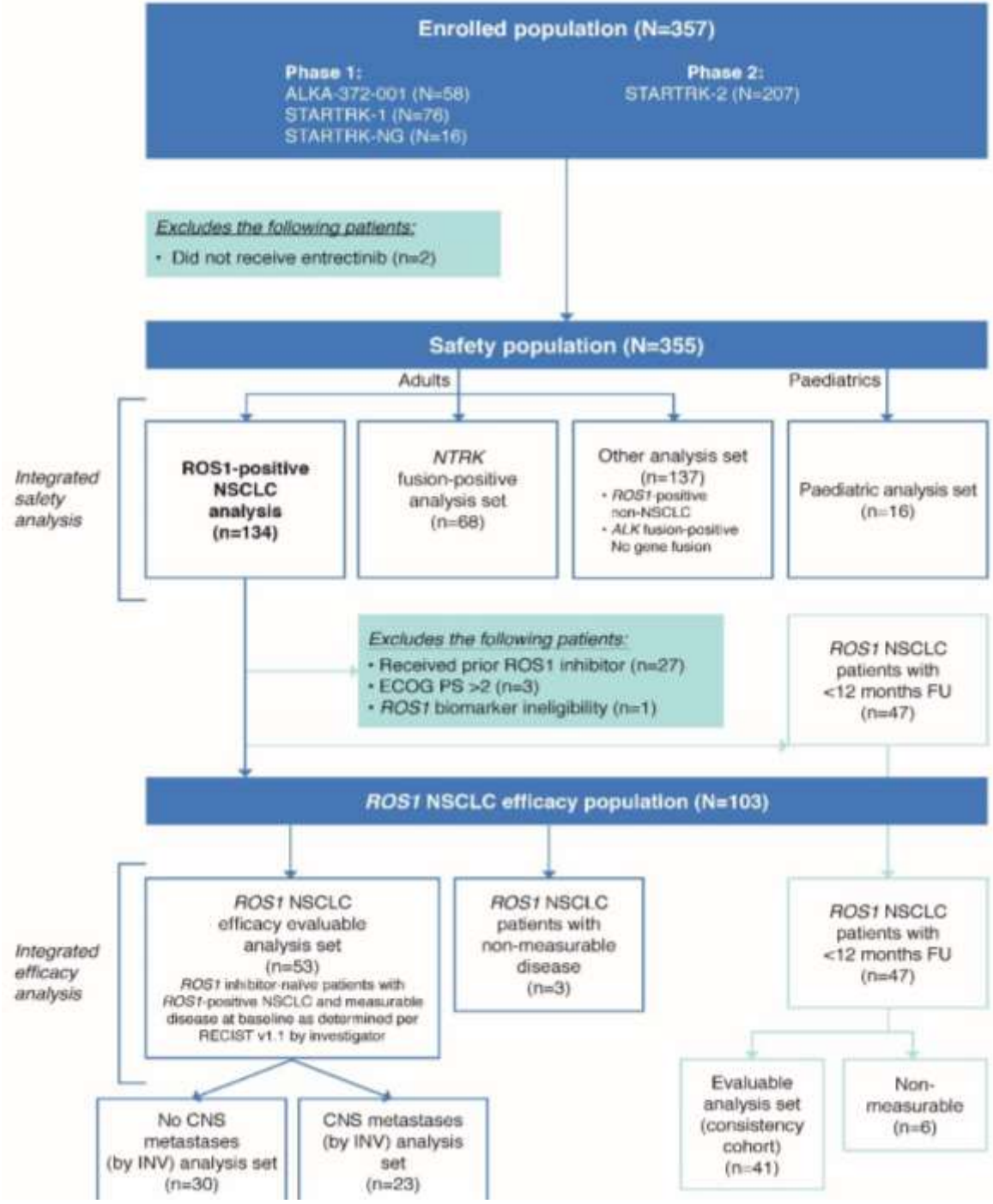
See Online/Comment

Entrectinib

- Entrectinib is a multikinase inhibitor against ROS1 (in addition to tropomyosin receptor kinase [TRK] A, B, and C and ALK
- In rat models entrectinib is 40 times more potent than crizotinib in vitro
- 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
- Up to 36% of patients with ROS1 fusion-positive NSCLC have brain metastases at the diagnosis of advanced disease

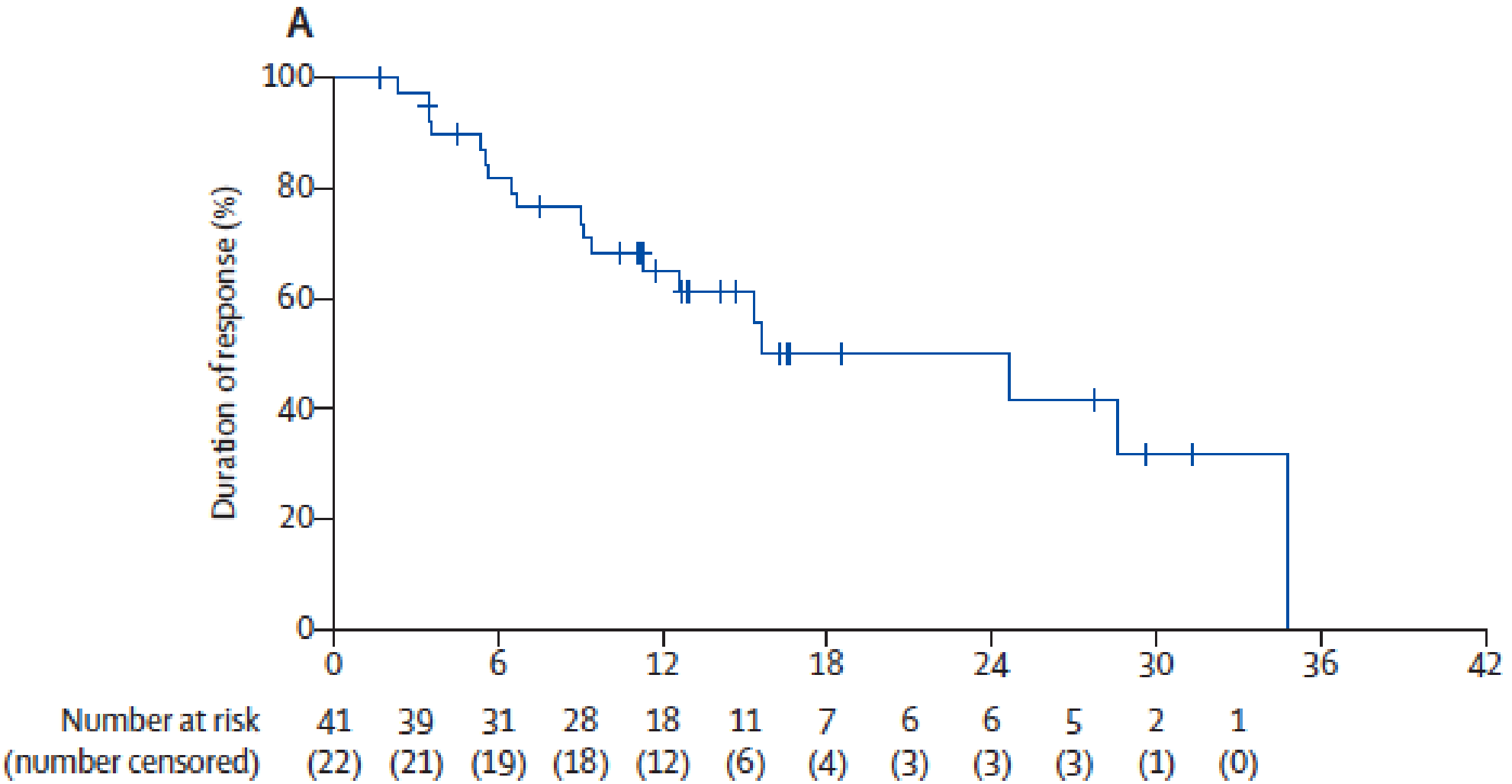
- Patients (aged ≥18 years),locally advanced ormetastatic solid tumours harbouring ROS1 fusions were enrolled in one of two phase 1 studies (ALKA-372-001or STARTRK-1) phase 2 global basket study(STARTRK-2)
- ALKA-372-001 was done at two cancer centres in Italy. STARTRK-1 was done at ten sites: one hospital 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

- For integrated efficacy analysis criteria:
- locally advanced or metastatic NSCLC - ROS1 fusion,
- they were ROS1 TKI naive,
- measurable disease
- ECOG performance status of 0–2
- Received at least 600 mg (one dose) of entrectinib

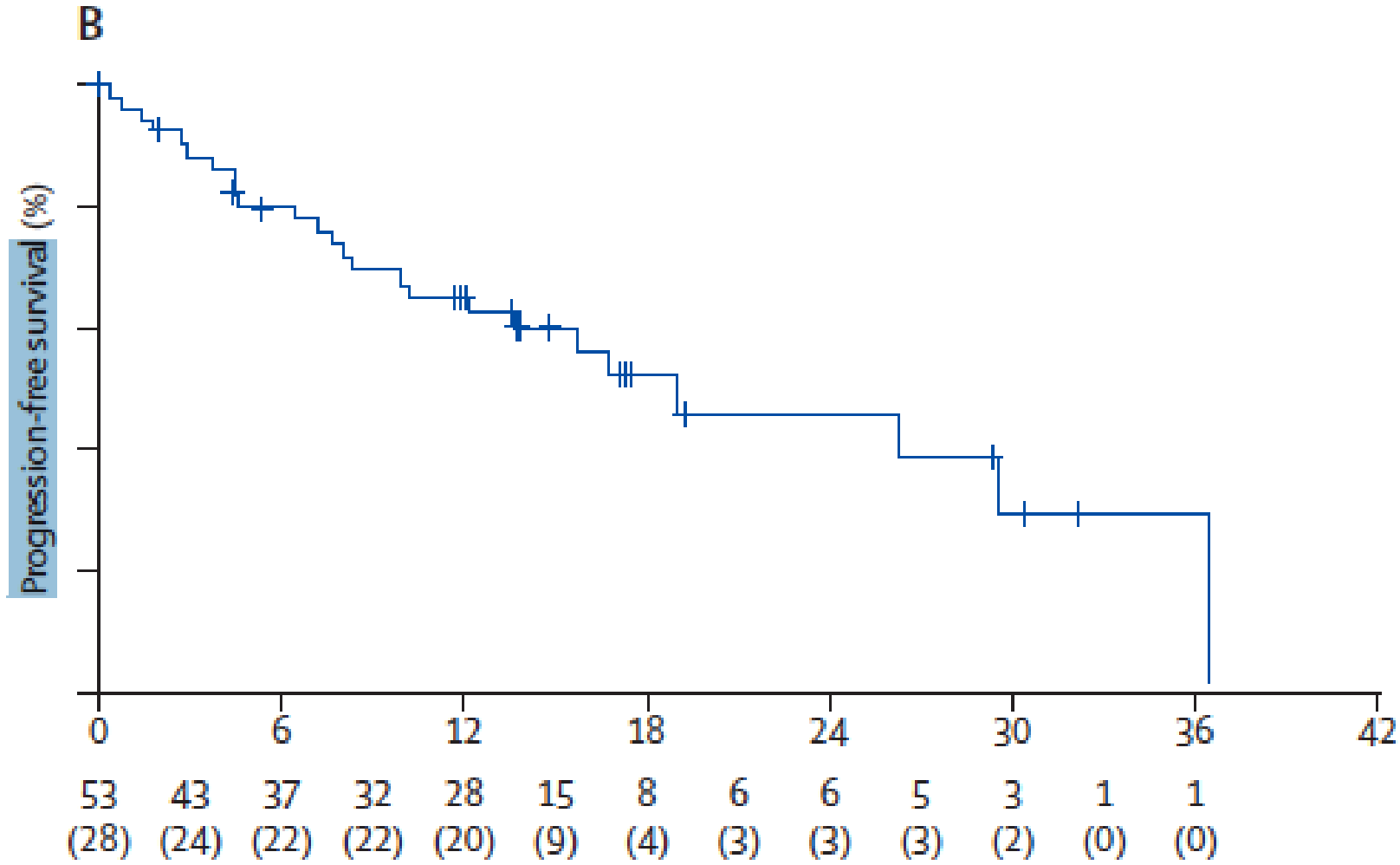

Enrolled population (N=357)
Phase 1:
ALKA-372-001 (N=58)
STARTRK-1 (N=76)
STARTRK-NG (N=16)
Phase 2:
STARTRK-2 (N=207)
Excludes the following patients:
• Did not receive entrectinib (n=2)
Safety population (N=355)
Adults
Paediatrics
Integrated safety analysis
ROS1-positive NSCLC analysis (n=134)
NTRK fusion-positive analysis set (n=68)
Other analysis set (n=137)
• ROS1-positive non-NSCLC
• ALK fusion-positive
No gene fusion
Paediatric analysis set (n=16)
Excludes the following patients:
• Received prior ROS1 inhibitor (n=27)
• ECOG PS >2 (n=3)
• ROS1 biomarker ineligibility (n=1)
ROS1 NSCLC patients with <12 months FU (n=47)
ROS1 NSCLC efficacy population (N=103)
Integrated efficacy analysis
ROS1 NSCLC efficacy evaluable analysis set (n=53)
ROS1 inhibitor-naive patients with ROS1-positive NSCLC and measurable disease at baseline as determined per RECIST v1.1 by investigator
ROS1 NSCLC patients with non-measurable disease (n=3)
ROS1 NSCLC patients with <12 months FU (n=47)
No CNS metastases (by INV) analysis set (n=30)
CNS metastases (by INV) analysis set (n=23)
Evaluable analysis set (consistency cohort) (n=41)
Non-measurable (n=6)

	All patients in integrated analysis (n=53)
Age, years	53 (46–61)
Sex	
Female	34 (64%)
Male	19 (36%)
Ethnicity	
White	31 (59%)
Asian	19 (36%)
Black or African–American	3 (6%)
Eastern Cooperative Oncology Group performance status	
0	20 (38%)
1	27 (51%)
2	6 (11%)
Smoking status	
Never smoker	31 (59%)
Previous or current smoker	22 (42%)
Histology*	
Adenocarcinoma	52 (98%)
Other†	1 (2%)
CNS disease present at baseline‡	23 (43%)
Measurable	5 (9%)
Not measurable	18 (34%)
Previous CNS disease treatment§	8 (35%)
Stereotactic radiotherapy	3 (13%)
Whole brain with or without stereotactic radiotherapy	5 (22%)
No previous CNS disease treatment§	15 (65%)
Number of previous systemic therapies	
0	17 (32%)
1	23 (43%)
2 or more	13 (25%)
Gene fusion	
CD74–ROS1	21 (40%)
SLC34A2–ROS1	7 (13%)
SDC4–ROS1	6 (11%)
EZR–ROS1	5 (9%)
TPM3–ROS1	2 (4%)
Unknown¶	12 (23%)

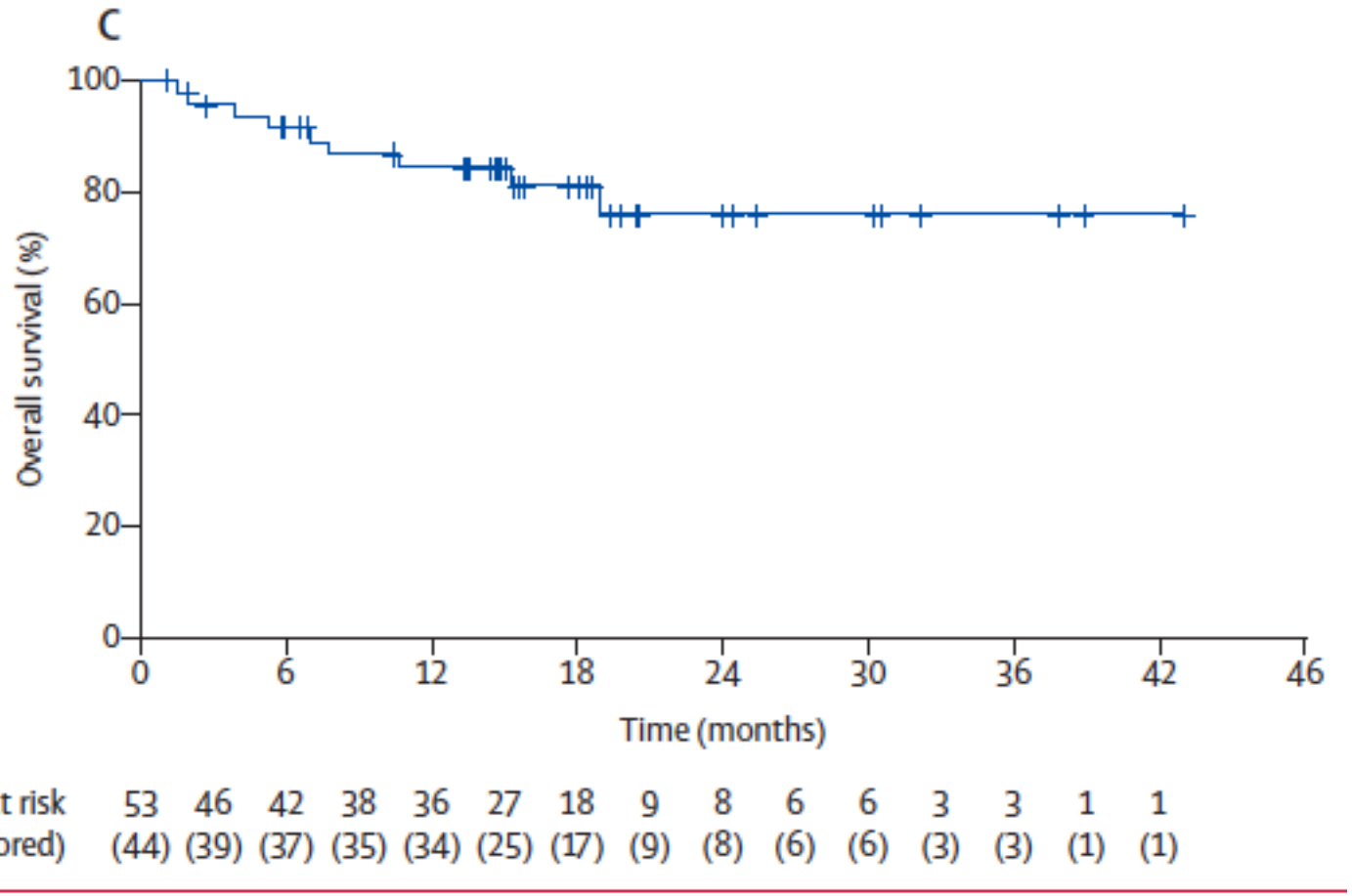
Duration of response			
Median, months (95% CI)	24·6 (11·4–34·8)	12·6 (6·5–NE)	24·6 (11·4–34·8)



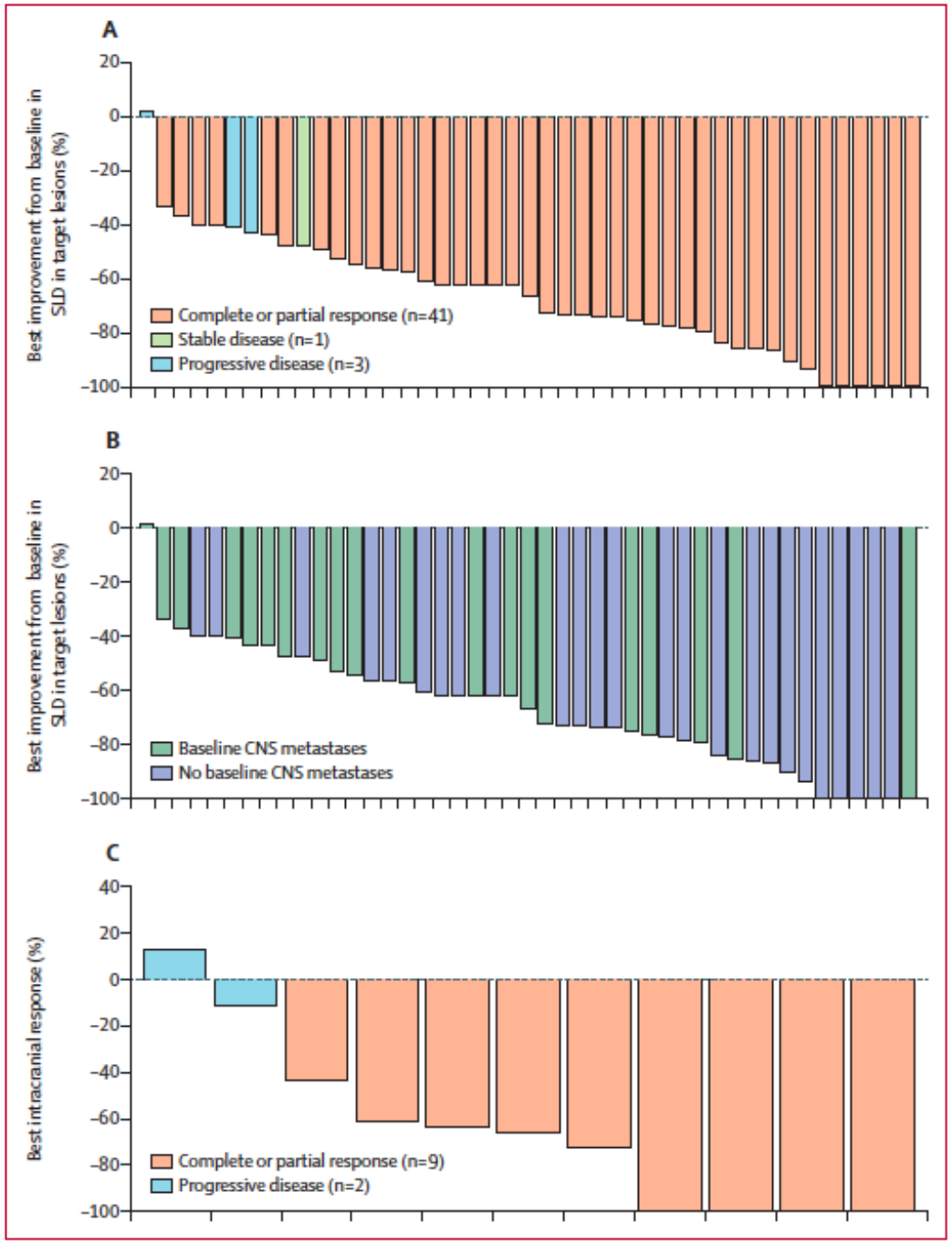
Progression-free survival			
Median, months (95% CI)	19·0 (12·2–36·6)	13·6 (4·5–NE)	26·3 (15·7–36·6)



- Median overall survival was not estimable (95% CI 15.1 to not estimable)
- At the time of data cut off, nine (17%) of 53 patients had died
- 45 (85%; 95% CI 74–95) patients were alive at 12 months
- 43 (82%; 70–93) were alive at 18 months



	Integrated efficacy-evaluable population (n=53)	Patients with baseline CNS disease (n=23)*	Patients with no baseline CNS disease (n=30)*
Objective responses, n; % (95% CI)	41; 77% (64–88)	17; 74% (52–90)	24; 80% (61–92)
Best overall response			
Complete response, n (%)	3 (6%)†	0	3 (10%)
Partial response, n (%)	38 (72%)†	17 (74%)	21 (70%)
Stable disease, n (%)	1 (2%)	0	1 (3%)
Progressive disease, n (%)	4 (8%)	4 (17%)	0
Non-complete response or non-progressive disease, n (%)	3 (6%)	0	3 (10%)
Missing or unevaluable, n (%)‡	4 (8%)	2 (9%)	2 (7%)
Duration of response			
Median, months (95% CI)	24·6 (11·4–34·8)	12·6 (6·5–NE)	24·6 (11·4–34·8)
Progression-free survival			
Median, months (95% CI)	19·0 (12·2–36·6)	13·6 (4·5–NE)	26·3 (15·7–36·6)
Intracranial activity	..	20·0‡	..
Overall response, n; % (95% CI)	..	11; 55% (32–77)	..
Best intracranial response			
Complete response, n (%)	..	4 (20%)	..
Partial response, n (%)	..	7 (35%)	..
Stable disease, n (%)	..	0	..
Progressive disease, n (%)	..	3 (15%)	..
Non-complete response or non-progressive disease, n (%)	..	4 (20%)	..
Missing or unevaluable, n (%)§	..	2 (10%)	..



	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

Lorlatinib in non-small-cell lung cancer with *ALK* or *ROS1* rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial

Alice T Shaw, Enriqueta Felip, Todd M Bauer, Benjamin Besse, Alejandro Navarro, Sophie Postel-Vinay, Justin F Gainor, Melissa Johnson, Jorg Dietrich, Leonard P James, Jill S Clancy, Joseph Chen, Jean-François Martini, Antonello Abbattista, Benjamin J Solomon

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Summary

Background Most patients with anaplastic lymphoma kinase (*ALK*)-rearranged or ROS proto-oncogene 1 (*ROS1*)-rearranged non-small-cell lung cancer (NSCLC) are sensitive to tyrosine kinase inhibitor (TKI) therapy, but resistance invariably develops, commonly within the CNS. This study aimed to analyse the safety, efficacy, and pharmacokinetic properties of lorlatinib, a novel, highly potent, selective, and brain-penetrant ALK and ROS1 TKI with preclinical activity against most known resistance mutations, in patients with advanced *ALK*-positive or *ROS1*-positive NSCLC.

Methods In this international multicentre, open-label, single-arm, first-in-man phase 1 dose-escalation study, eligible patients had advanced *ALK*-positive or *ROS1*-positive NSCLC and were older than 18 years, with an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate end-organ function. Lorlatinib was administered orally to patients at doses ranging from 10 mg to 200 mg once daily or 35 mg to 100 mg twice daily, with a minimum of three patients receiving each dose. For some patients, tumour biopsy was done before lorlatinib treatment to identify *ALK* resistance mutations. Safety was assessed in patients who received at least one dose of lorlatinib; efficacy was assessed in the intention-to-treat population (patients who received at least one dose of study treatment and had either *ALK* or *ROS1* rearrangement). The primary endpoint was dose-limiting toxicities during cycle 1 according to investigator assessment; secondary endpoints included safety, pharmacokinetics, and overall response. This study is ongoing and is registered with ClinicalTrials.gov, number NCT01970865.

Findings Between Jan 22, 2014, and July 10, 2015, 54 patients received at least one dose of lorlatinib, including 41 (77%) with *ALK*-positive and 12 (23%) with *ROS1*-positive NSCLC; one patient had unconfirmed *ALK* and *ROS1* status. 28 (52%) patients had received two or more TKIs, and 39 (72%) patients had CNS metastases. The most common treatment-related adverse events among the 54 patients were hypercholesterolaemia (39 [72%] of 54 patients), hypertriglyceridaemia (21 [39%] of 54 patients), peripheral neuropathy (21 [39%] of 54 patients), and peripheral oedema (21 [39%] of 54 patients). One dose-limiting toxicity occurred at 200 mg (the patient did not take at least 16 of 21 prescribed total daily doses in cycle 1 because of toxicities attributable to study drug, which were grade 2 neurocognitive adverse events comprising slowed speech and mentation and word-finding difficulty). No maximum tolerated dose was identified. The recommended phase 2 dose was selected as 100 mg once daily. For *ALK*-positive patients, the proportion of patients who achieved an objective response was 19 (46%) of 41 patients (95% CI 31–63); for those who had received two or more TKIs, the proportion of patients with an objective response was 11 (42%) of 26 patients (23–63). In *ROS1*-positive patients, including seven crizotinib-pretreated patients, an objective response was achieved by six (50%) of 12 patients (95% CI 21–79).

	Patients (n=54)
Age, years	
Mean (SD)	52 (13)
Median (IQR)	50 (43–58)
Sex	
Male	22 (41%)
Female	32 (59%)
Race*	
White	42 (78%)
Asian	7 (13%)
Other	5 (9%)
Histology	
Adenocarcinoma	51 (94%)
Other	3 (6%)
ECOG performance status†	
0	20 (38%)
1	31 (58%)
>1	2 (4%)
Brain metastases	
Present	39 (72%)
Absent	15 (28%)
***ALK* and *ROS1* status**	
ALK-positive	41 (76%)
ROS1-positive	12 (22%)
Unconfirmed‡	1 (2%)
Previous ALK or ROS1 TKI	
None	6 (11%)
One	20 (37%)
Two or more	28 (52%)

	Grade 1–2	Grade 3
Hypercholesterolaemia*	32 (59%)	5 (9%)
Hypertriglyceridaemia*†	18 (33%)	3 (6%)
Peripheral oedema	21 (39%)	0
Peripheral neuropathy*	21 (39%)	0
Cognitive effects*	12 (22%)	1 (2%)
Speech effects*	10 (19%)	0
Lipase increased†‡	7 (13%)	2 (4%)
Weight increased	6 (11%)	3 (6%)
Fatigue	8 (15%)	0
Mood effects*	8 (15%)	0
Amylase increased†‡	7 (13%)	0
AST increased	6 (11%)	1 (2%)
Constipation	7 (13%)	0
Tinnitus	7 (13%)	0
Vision disorder*	7 (13%)	0
Oedema	6 (11%)	0
Nausea	6 (11%)	0

Repotrectinib (TPX-0005)

- Repotrectinib is a next-generation ROS1/TRK/ALK TKI inhibiting ROS1
- 90-fold greater potency than crizotinib
- Preclinical studies showed effect against all known ROS1 fusion positive resistance mutations(most common ROS1 solvent-front mutation (SFM) G2032R)

Safety and preliminary clinical activity of repotrectinib in patients with advanced *ROS1* fusion-positive non-small cell lung cancer (TRIDENT-1 study).

- Confirmed diagnosis of locally advanced or metastatic solid tumor that harbours an ALK, ROS1, NTRK1-3gene rearrangement
- ECOG Performance Status score of 0-1
- Age ≥18

Methodology

Phase 1

- Phase 1a-dose escalation
- Phase 1b-food-effect sub-study
- Phase 1c dose escalation with food, and Midazolam drug-drug interaction sub-study

Repotrectinib dose 40 mg QD to 200 mg BID

DLTs
RP2D

Phase 2

Oral repotrectinib-6 distinct expansion cohorts

EXP-1: ROS1 TKI-naïve ROS1+ NSCLC

EXP-2: 1 Prior ROS1 TKI ROS1+ NSCLC

EXP-3: 2 Prior ROS1 TKIs ROS1+ NSCLC

EXP-4: ROS1 or ALK TKI-naïve ROS1+ or ALK+ solid tumors

EXP-5: TRK TKI-naïve NTRK+ solid tumors

EXP-6: TRK TKI-pretreated NTRK+ solid tumors

Results

- 75 pts were treated with dose levels from 40 mg QD to 200 mg BID
- Median number of prior TKI treatment was 1 (0-3) in 83% of TKI pre-treated

	TKI-naïve ROS1+ NSCLC (n=10)	**TKI-pre treated (n=18)**
ORR	90% (95% CI 56 - 100)	28% (95% CI 10 – 54)
DOR	Not reached	10.2 mos
Intracranial ORR	3/3 (100%)	2/4 (50%)
Intracranial DOR	5.5+; 7.2+; 14.85+ mo	5.5+;14.8+, mo

Results

- Subgroup analysis showed cORR 44% (95% CI 14 - 79) in 9 prior TKI pts and treated at dose levels of 160 mg QD or above
- Most AEs were manageable and grade (Gr) 1-2
- Common (> 20%) treatment-related AEs were dizziness (49%), dysgeusia (48%), paresthesia (28%), and constipation (20%).
- Four DLTs (Gr3 dyspnea/hypoxia (n = 1); Gr2 (n = 1) and Gr3 (n = 1) dizziness at 160 mg BID, and Gr3 dizziness (n = 1) at 240 mg QD)

DS-6051b

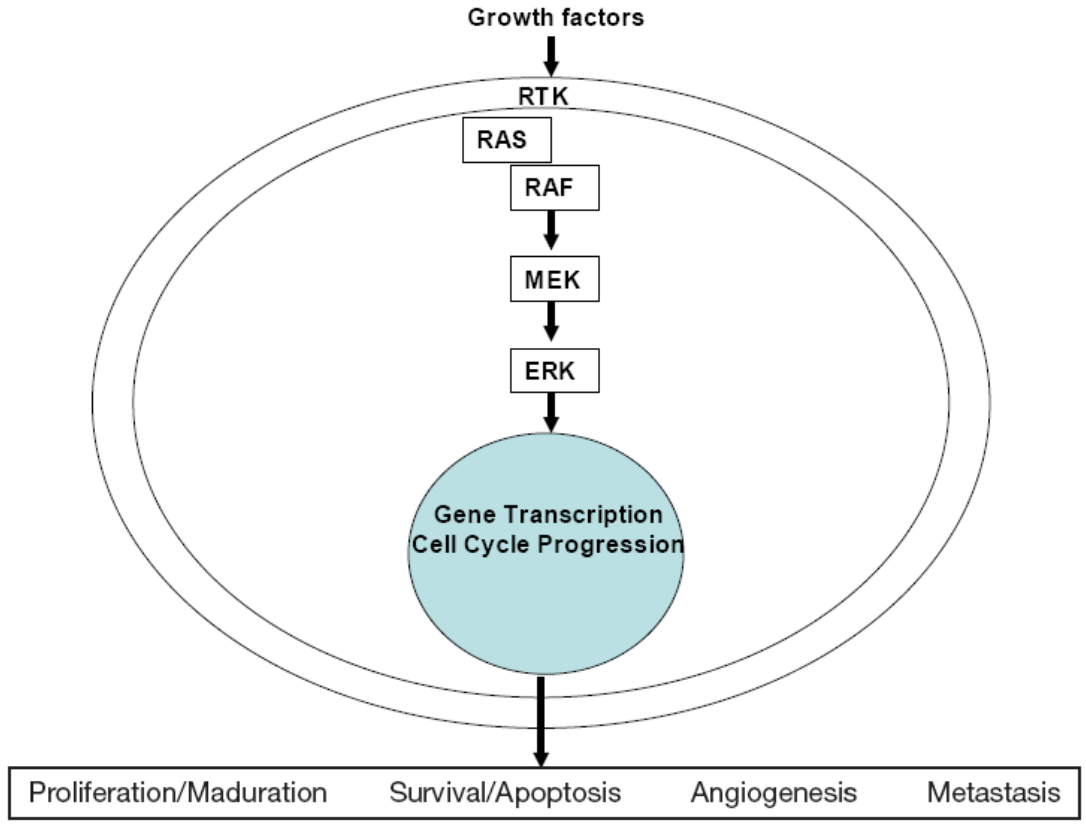
DS-6051b-oral, small molecule TKI with high affinity for ROS1 and NTRK kinases

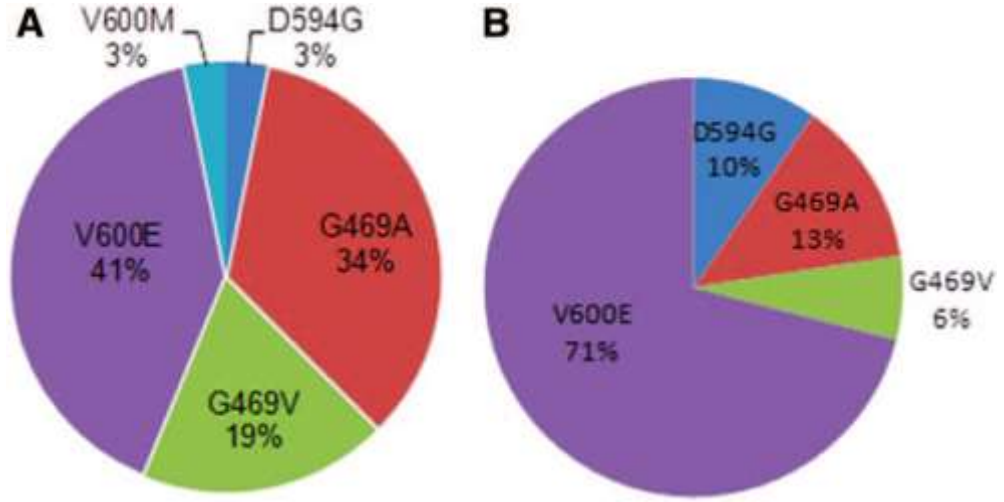
Targeted Agent	Clinical Trials	Phase	Patients Included	Results
DS-6051b[32]	NCT02675491	I	Advanced solid malignant tumors harboring either ROS1 or NTRK fusion.	n=15, ORR 58.3% in pts with target lesions, 66.7% in crizotinib-naïve pts, DCR 100%.
DS-6051b	NCT02279433	I/Ib	Solid tumors harboring ROS1 or NTRK1, NTRK2, or NTRK3 rearrangements	Ongoing

Targetable Driver genes	Incidence	Targeted Agent	Clinical Trials	Phase	Patients Included	Results	Approved or Recommended by
ROS1 rearrangements	1–2%	Crizotinib[11]	PROFILE 1001 (NCT00585195)	I	ROS1-rearranged NSCLC	n=50, ORR 72%, mPFS 19.2 mo	NCCN, FDA, EMA
		Ceritinib[23]	NCT01964157	II	ROS1-rearranged NSCLC	n=32, ORR 62%, DCR 81%, mPFS 9.3 mo for all pts, 19.3 mo for crizotinib-naive pts	NCCN
		Entrectinib (RXDX-101)[26]	ALKA-372-001 (EudraCT 2012–0001), STARTRK-1 (NCT02097810), STARTRK-2 (NCT02568267)	I/II	ROS1-rearranged NSCLC	n=53, ORR 77.4% (intracranial ORR, 73.9%), mDOR 24.6 mo, mPFS 19.0 mo (without CNS metastases: 26.3 mo; with CNS metastases: 13.6 mo)	NCCN, FDA
		Lorlatinib[31]	NCT01970865	II	ROS1-rearranged NSCLC	n=47, ORR 36.2%, mPFS 9.6 mo	NCCN
		DS-6051b[32]	NCT02675491	I	Advanced solid malignant tumors harboring either ROS1 or NTRK fusion.	n=15, ORR 58.3% in pts with target lesions, 66.7% in crizotinib-naive pts, DCR 100%.	
		DS-6051b	NCT02279433	I/Ib	Solid tumors harboring ROS1 or NTRK1, NTRK2, or NTRK3 rearrangements	Ongoing	
		Repotrectinib (TPX-0005)[33]	TRIDENT-1 (NCT03093116)	I/II	Solid malignancies harboring ALK, ROS1, NTRK1, NTRK2, or NTRK3 gene rearrangements	n=11, ORR 82% for TKI-naive pts, n=18, ORR 39% for pts pretreated with one TKI.	

BRAF

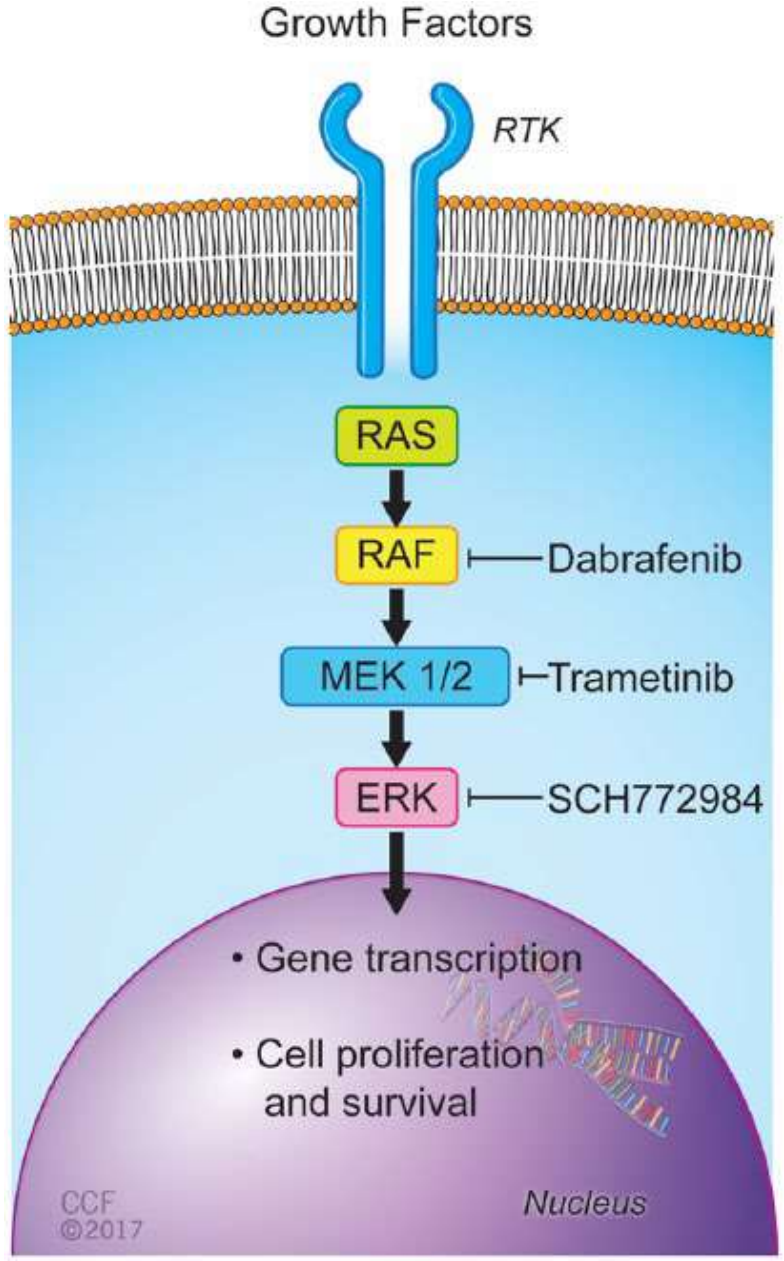
- BRAF is a serine/threonine kinase
- RAS/MAP/ERK signalling pathway
- Seen in 0.5% to 4.9% of lung cancers
- Adeno > squamous
- **Two type of mutations**
- PV600E & non-p.V600E BRAF-exon 11
- **BRAF p.V600E (glutamate to valine) exon 15-**
- 500 x kinase activity
- 1 to 2% of lung adenocarcinomas



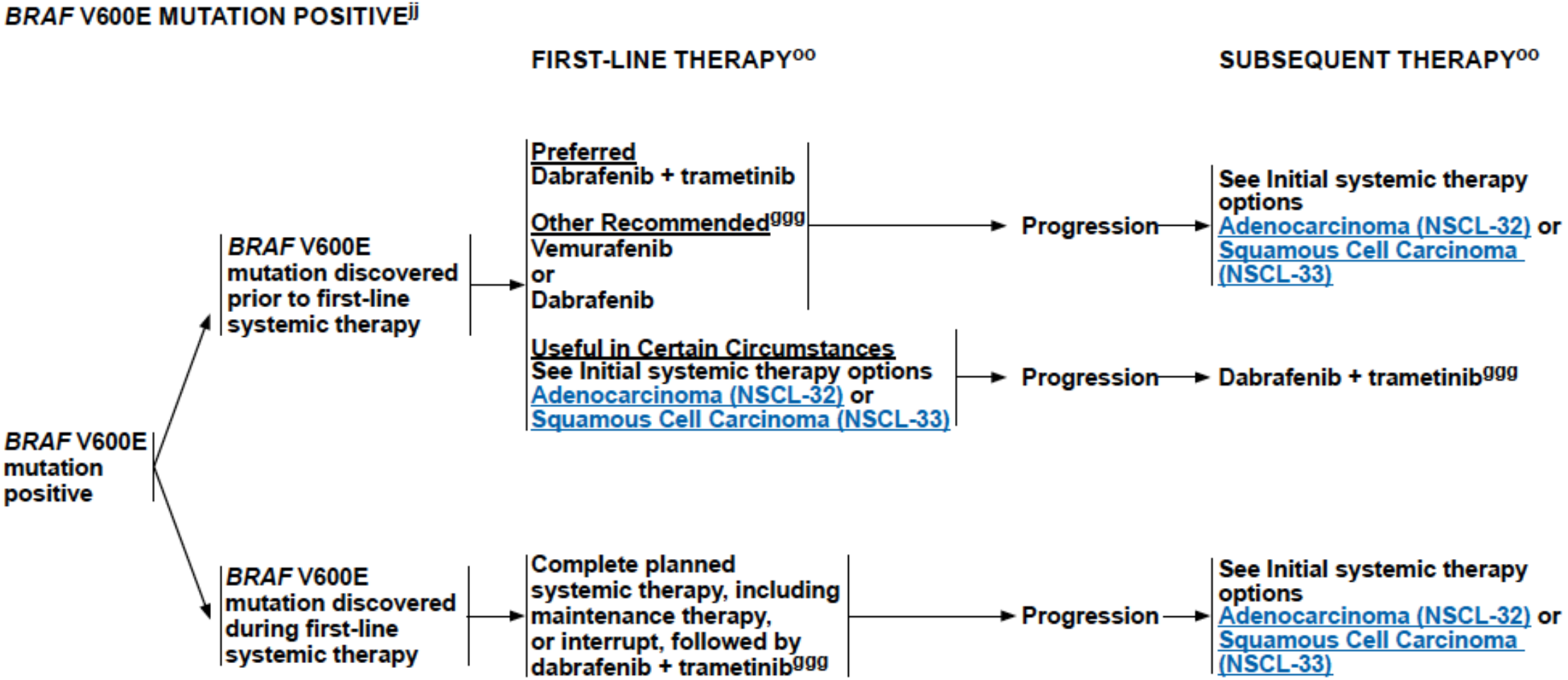


BRAF p.V600E

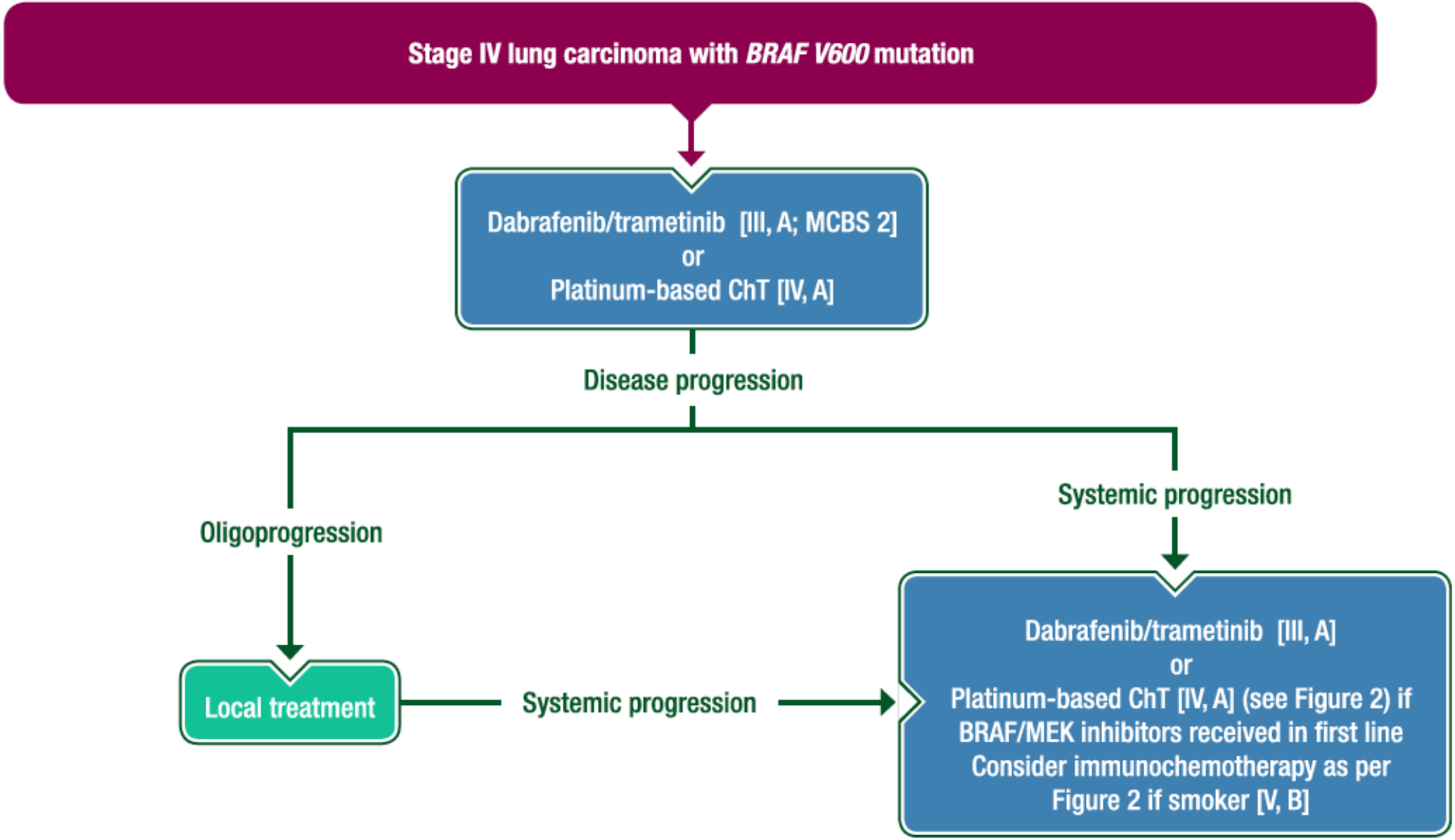
- Roughly 50% of BRAF-mutant NSCLC
- Frequent in females and never smokers
- Mutually exclusive of KRAS, EGFR, or ALK
- **Testing Methodologies:**
- Real-time PCR, Sanger sequencing & NGS
- Mutation specific IHC -antibodies against the p.V600E mutant protein (VE1)
- Currently insufficient evidence to support a recommendation either for or against BRAF p.V600E IHC (VE1) testing in NSCLC



NCCN guidelines version 4.2020



Single-agent vemurafenib or dabrafenib are treatment options if the combination of dabrafenib + trametinib is not tolerated


Stage IV lung carcinoma with *BRAF V600* mutation
Dabrafenib/trametinib [III, A; MCBS 2]
or
Platinum-based ChT [IV, A]
Disease progression
Oligoprogression
Local treatment
Systemic progression
Systemic progression
Dabrafenib/trametinib [III, A]
or
Platinum-based ChT [IV, A] (see Figure 2) if BRAF/MEK inhibitors received in first line
Consider immunochemotherapy as per Figure 2 if smoker [V, B]

BRAF and MEK inhibitors in melanoma

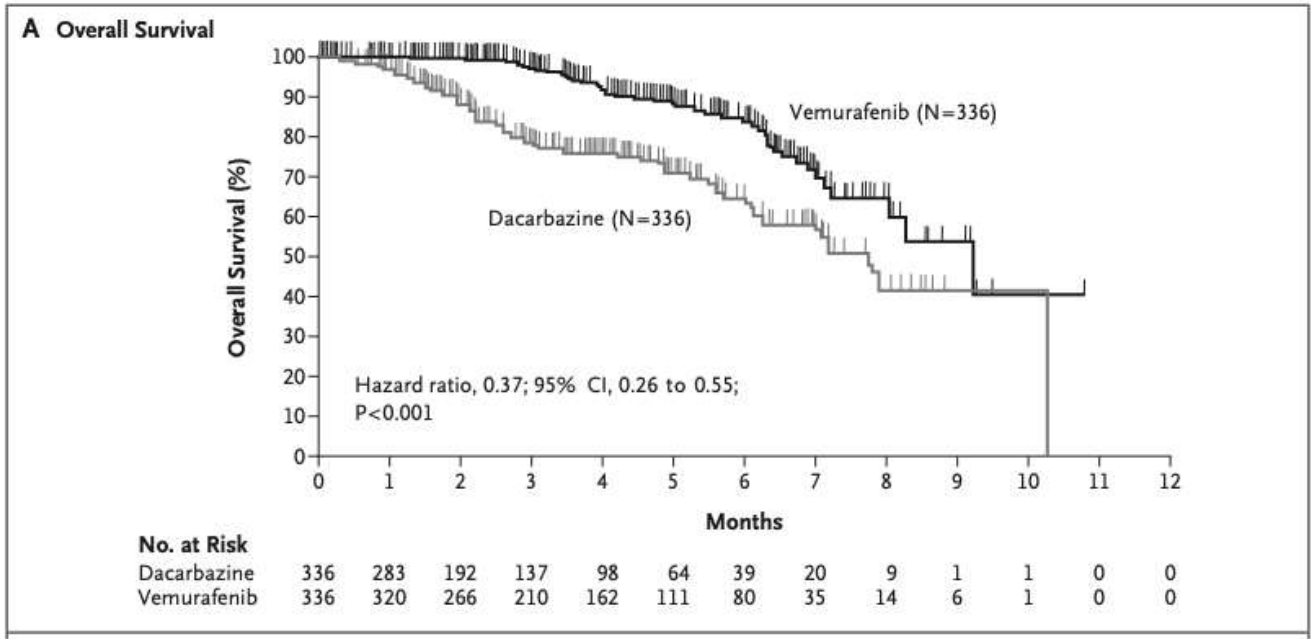
Phase 3 randomized clinical trial

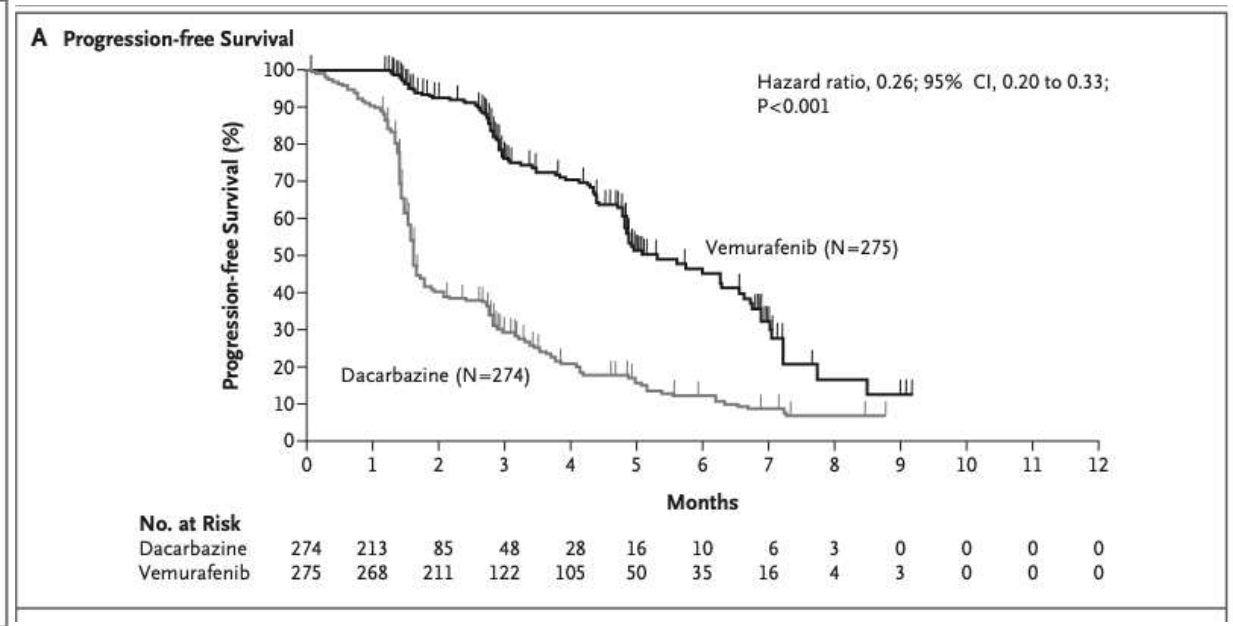
ORIGINAL ARTICLE

BRIM-3 Study Group*

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Progression -free survival (PFS) of 5.3 months and overall survival (OS) of 13.6 months with vemurafenib as compared with 1.6 months PFS and 9.7 months OS with dacarbazine in patients with BRAF V600E-mutated metastatic melanoma



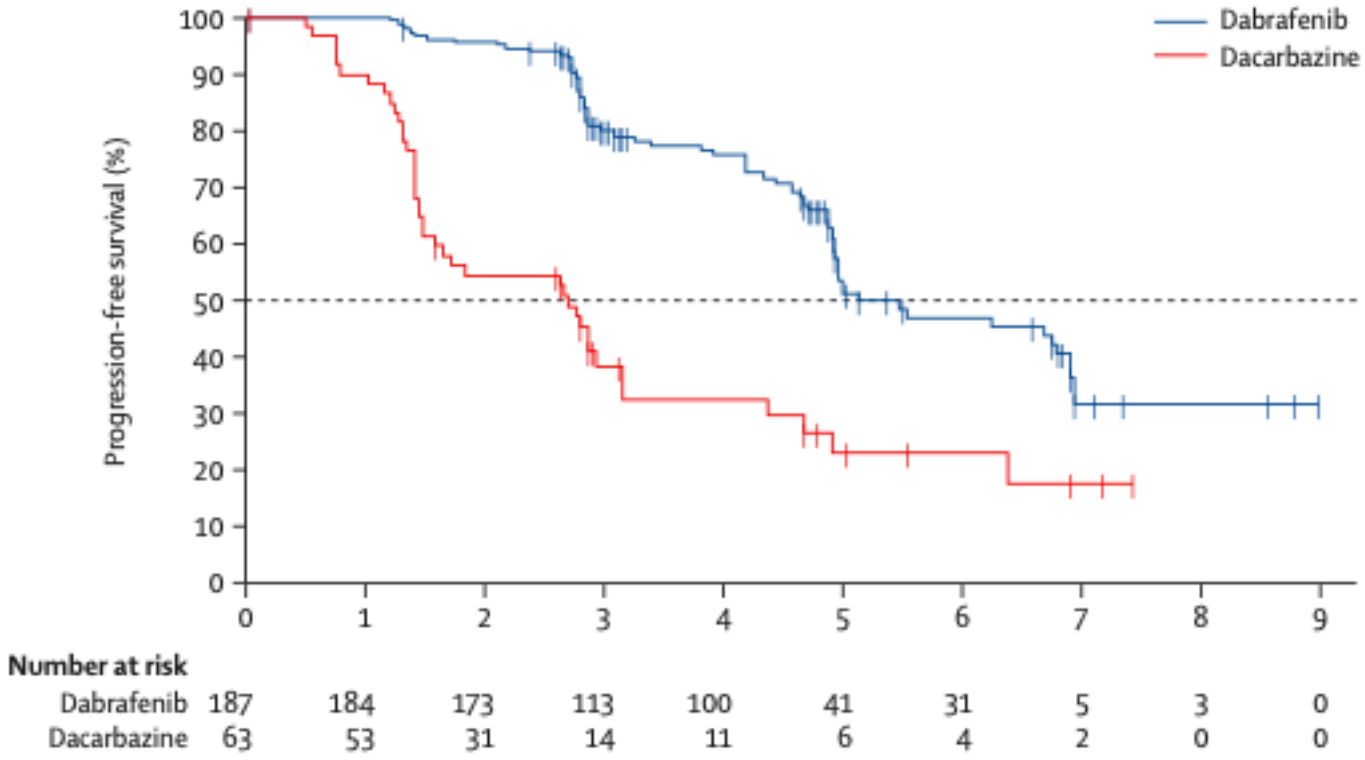


US FDA approved vemurafenib in 2011 for metastatic BRAF V600E-mutant melanoma

Dabrafenib in *BRAF*-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial

Axel Hauschild, Jean-Jacques Grob, Lev V Demidov, Thomas Jouary, Ralf Gutzmer, Michael Millward, Piotr Rutkowski, Christian U Blank, Wilson H Miller Jr, Eckhart Kaempgen, Salvador Martín-Algarra, Boguslawa Karaszewska, Cornelia Mauch, Vanna Chiarion-Sileni, Anne-Marie Martin, Suzanne Swann, Patricia Haney, Beloo Mirakhur, Mary E Guckert, Vicki Goodman, Paul B Chapman

Dabrafenib had longer PFS of 5.1 months as compared with 2.7 months with dacarbazine



	Dabrafenib (n=187)	Dacarbazine (n=63)
Complete response	6 (3%)	1 (2%)
Partial response	87 (47%)	3 (5%)
Stable disease*	78 (42%)	30 (48%)
Progressive disease	10 (5%)	23 (37%)
Not evaluable†	6 (3%)	6 (10%)
Response rate (complete+partial response, n [%, 95% CI])	93 (50%, 42·4–57·1)	4 (6%, 1·8–15·5)

Data are number of patients (%), unless otherwise stated. *Includes cases determined to have non-target disease only by independent review. †Includes two cases determined to have no disease at baseline or post-baseline assessment by independent review.

***Table 2*: Best confirmed response to treatment, by independent review**

Dabrafenib was approved by the US FDA in 2013 for BRAF V600E-mutated melanoma patients

Problem with BRAF

- Both vemurafenib and dabrafenib were well tolerated with only mild toxicities in both these clinical trials
- Longer follow up suggested that patients treated with BRAF inhibitors developed disease progression within 6 months of initiation of treatment due to development of resistance
- Patients developed secondary skin cancers, including squamous cell carcinoma and keratoacanthoma, mainly due to paradoxical activation of the MAPK pathway in BRAF nonmutant cells

MEK1/2 inhibitor-Trametinib

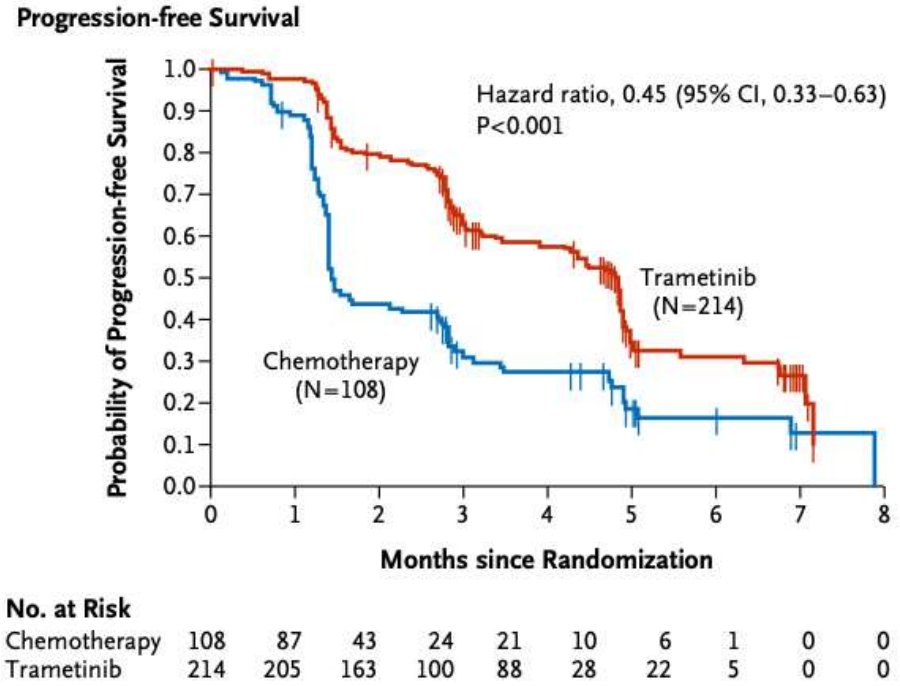
ESTABLISHED IN 1812 JULY 12, 2012 VOL. 367 NO. 2

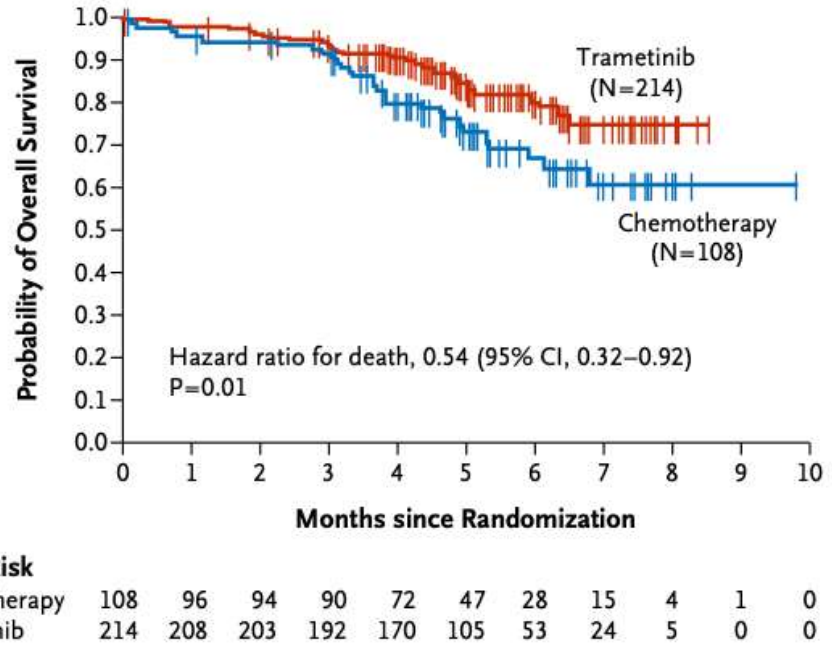
Improved Survival with MEK Inhibition in BRAF-Mutated Melanoma

Keith T. Flaherty, M.D., Caroline Robert, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Paul Nathan, M.D., Ph.D.,

METRIC Study Group*

Trametinib was associated with statistically significant improvement in response rate (22% versus 8%) and median PFS of 4.8 months as compared with 1.5 months with chemotherapy





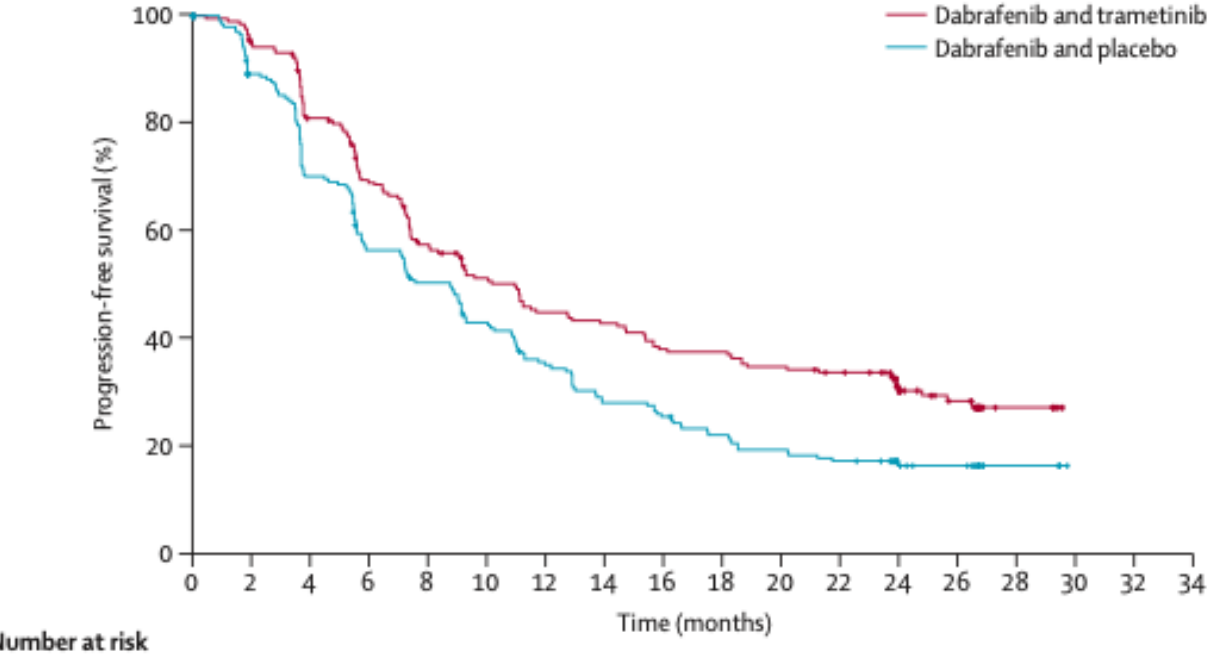
However later studies no statistically significant response of trametinib in patients who were previously treated with a BRAF inhibitor, indicating that BRAF inhibitor resistance mechanisms also confer resistance to MEK inhibitor monotherapy

Pre-clinical models of BRAF-mutant melanoma, synergistic antitumor activity and delay in emergence of acquired resistance was noted with combination of BRAF inhibitors with MEK inhibitors

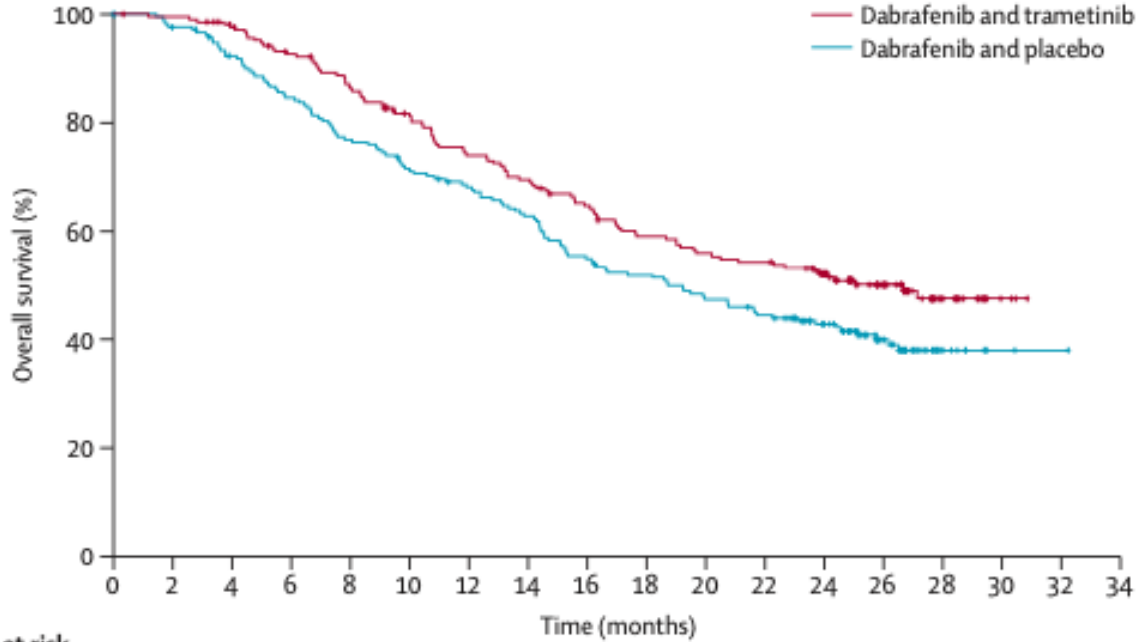
Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial

Georgina V Long, Daniil Stroyakovskiy, Helen Gogas, Evgeny Levchenko, Filippo de Braud, James Larkin, Claus Garbe, Thomas Jouary, Axel Hauschild,

Patients in the combination arm had a median PFS of 11 months and OS of 25.1 months as compared with PFS of 8.8 months and OS of 18.7 months in dabrafenib-only treated patients



Number at risk																		
Dabrafenib and trametinib	211	196	164	137	125	96	84	80	71	70	65	61	38	26	6	0	0	0
Dabrafenib and placebo	212	177	139	109	96	81	65	52	47	40	35	31	19	16	4	0	0	0



Number at risk																		
Dabrafenib and trametinib	211	208	200	187	174	159	144	135	124	112	106	103	88	53	21	3	0	0
Dabrafenib and placebo	212	206	191	175	159	147	138	127	111	104	95	88	70	42	10	2	1	0

Incidence of secondary skin cancers was lower in the combination arm (2%) as compared with the dabrafenib-only arm (9%)

BRAF and MEK inhibitors in NSCLC

- Early in vitro studies demonstrated efficacy in treatment of BRAF V600-mutated NSCLC using a single-agent BRAF inhibitor
- Preclinical studies also demonstrated that BRAF mutations predicted sensitivity of NSCLC cells to MEK inhibitors.
- Combination of BRAF and MEK inhibition was synergistic and delayed emergence of acquired resistance in NSCLC harbouring BRAF V600E mutation
- Early case reports documented a partial response (PR) to the isolated use of BRAF inhibitors in BRAF V600E-mutated NSCLC patients
- Durable response was noted in combination therapy of BRAF and MEK inhibitors

Retrospective study, 35 patients with advanced NSCLC with BRAF mutations were treated with different BRAF inhibitors including vemurafenib 960 mg BD,dabrafenib150 mg BD, or sorafenib 400 mg OD

TABLE 2. Tumor Parameters

Sample size (N)	35
NSCLC histology	
Adenocarcinoma	35 (100%)
Other	0
Stage at initial NSCLC diagnosis	
I and II	1 (3%)
III	4 (11%)
IV	30 (86%)
Metastatic sites of special interest	
Malignant effusion	10 (29%)
Brain metastases	6 (17%)
BRAF mutation	
V600E	29 (83%)
Non-V600E	6 (17%): G466V, G469A, G469L, G596V, V600K, K601E
Other driver mutations	
No	34 (97%)
Yes	1 (3%): KRAS V12

NSCLC, non–small-cell lung cancer.

Targeted Therapy for Patients with BRAF-Mutant Lung Cancer

Results from the European EURAF Cohort

TABLE 1. Patient Characteristics

Sample size (N)	35
Age at diagnosis	
Median years (range)	63 (42–85)
Gender	
Male	18 (51%)
Female	17 (49%)
Smoking status	
Never	14 (40%)
Former/current	16 (46%)
Unknown	5 (14%)
Country	
France	13 (37%)
Switzerland	10 (28%)
Germany	7 (20%)
The Netherlands	4 (11%)
Austria	1 (3%)
Systemic therapy	
Median lines (range)	3 (1–6)
Platinum-based frontline therapy	30 (86%)

Rapid tumor response was observed, with 2 patients noted to have complete response, 16 patients had a PR and 11 patients achieved stable disease.4 patients were reported to have progressive disease after treatment

TABLE 3. Drug Exposure

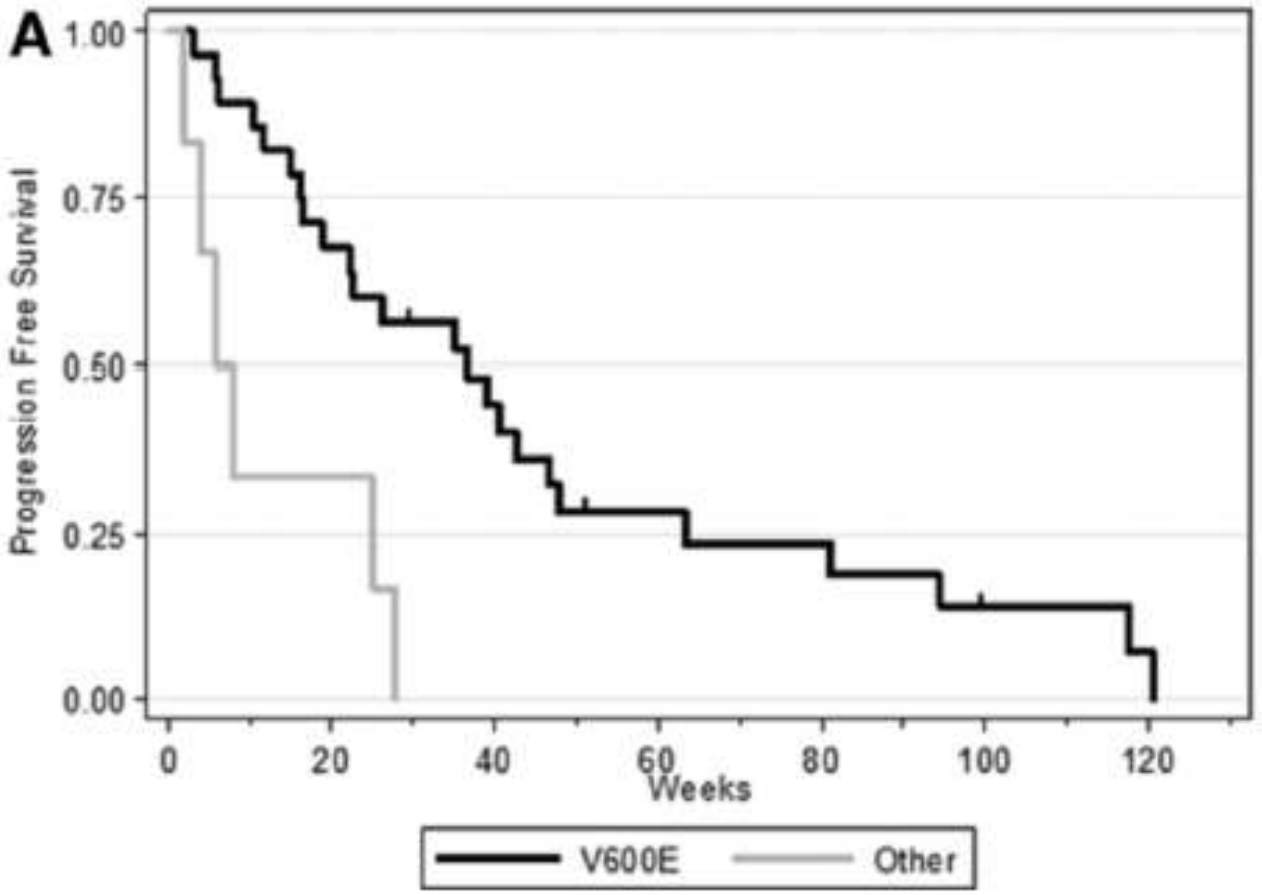
Sample size (N)	35
BRAF inhibitor therapy	35 (100%)
BRAF inhibitors and lines (total)	39
Vemurafenib	29
Dabrafenib	9
Sorafenib	1
Sequential BRAF inhibitors	
No	31 (89%)
Yes	4 (11%): 3× vemurafenib → dabrafenib and 1× sorafenib → vemurafenib
BRAF inhibitor used in	
First line	5 (14%)
Further lines	30 (86%)

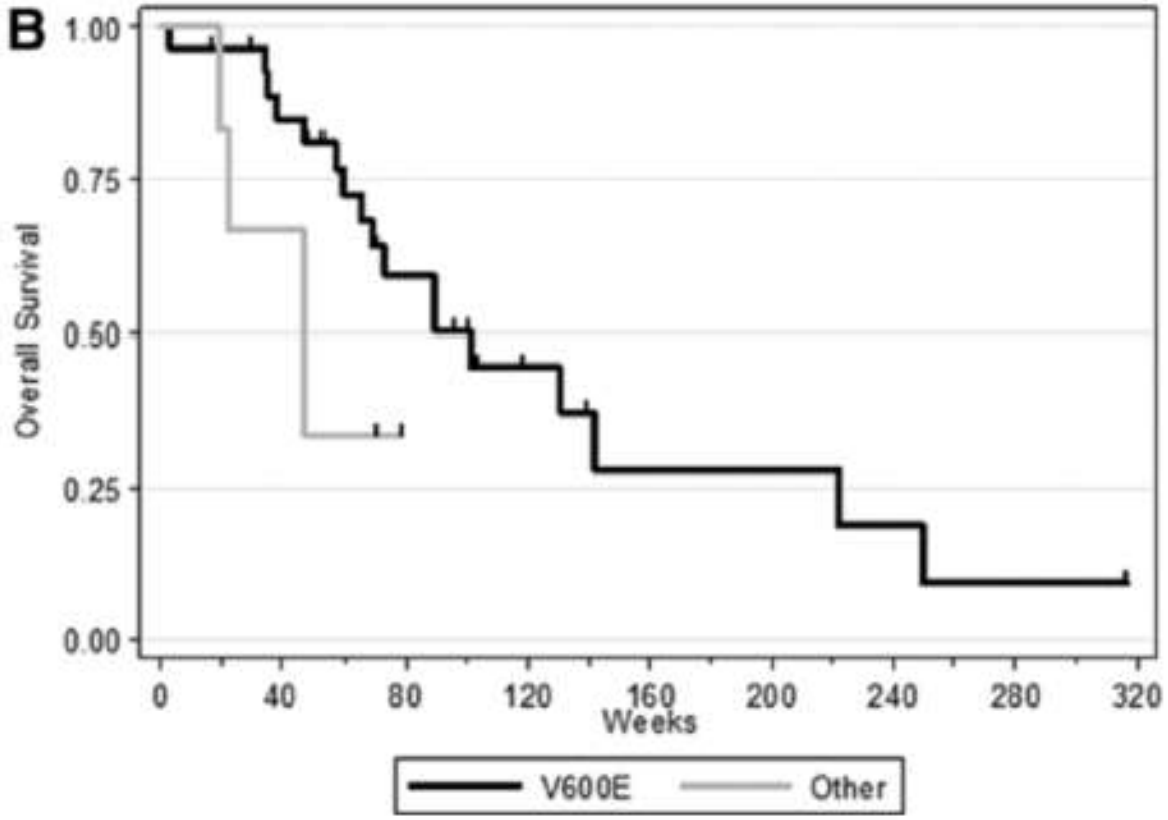
TABLE 4. Best Response with BRAF Inhibitor

	All Patients (N = 35)	V600E and Vemurafenib Subgroup (N = 25)
Data missing	1	1
Not measurable	1 (3%)	1 (4%)
CR	2 (6%)	2 (8%)
PR	16 (47%)	11 (46%)
SD	11 (32%)	10 (42%)
PD	4 (12%)	0
ORR	18 (53%; 95% CI: 35–70)	13 (54%; 95% CI: 33–74)
DCR	29 (85%; 95% CI: 69–95)	23 (96%; 95% CI: 79–100)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate; CI, confidence interval.

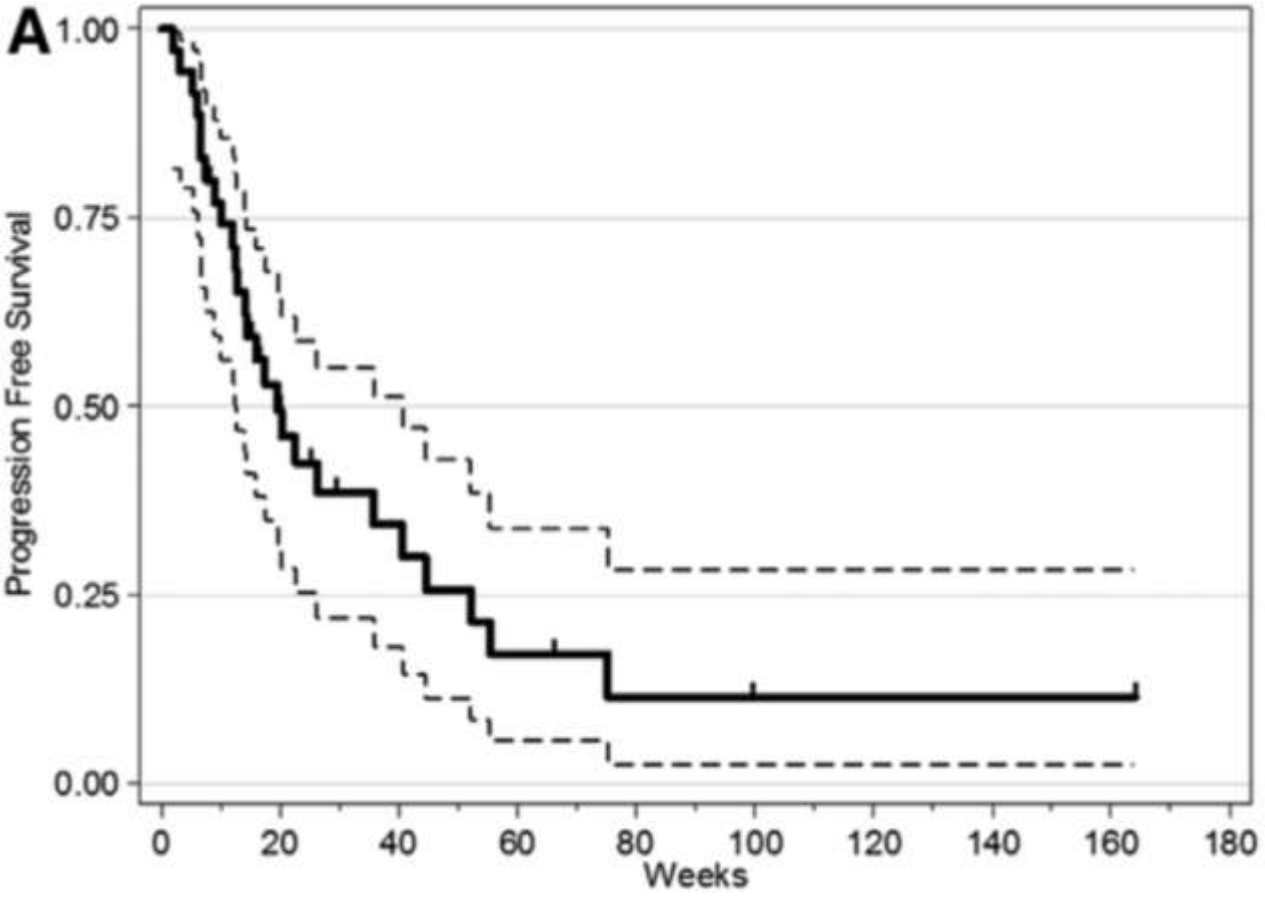
- First-line therapy, including chemotherapy, PFS was 37 wks (9.3 months) for V600E and 6 wks (1.5 months) for non-V600E
- OS -101 wks (25.3 months) for V600E and 47 weeks (11.8 months) for non-V600E

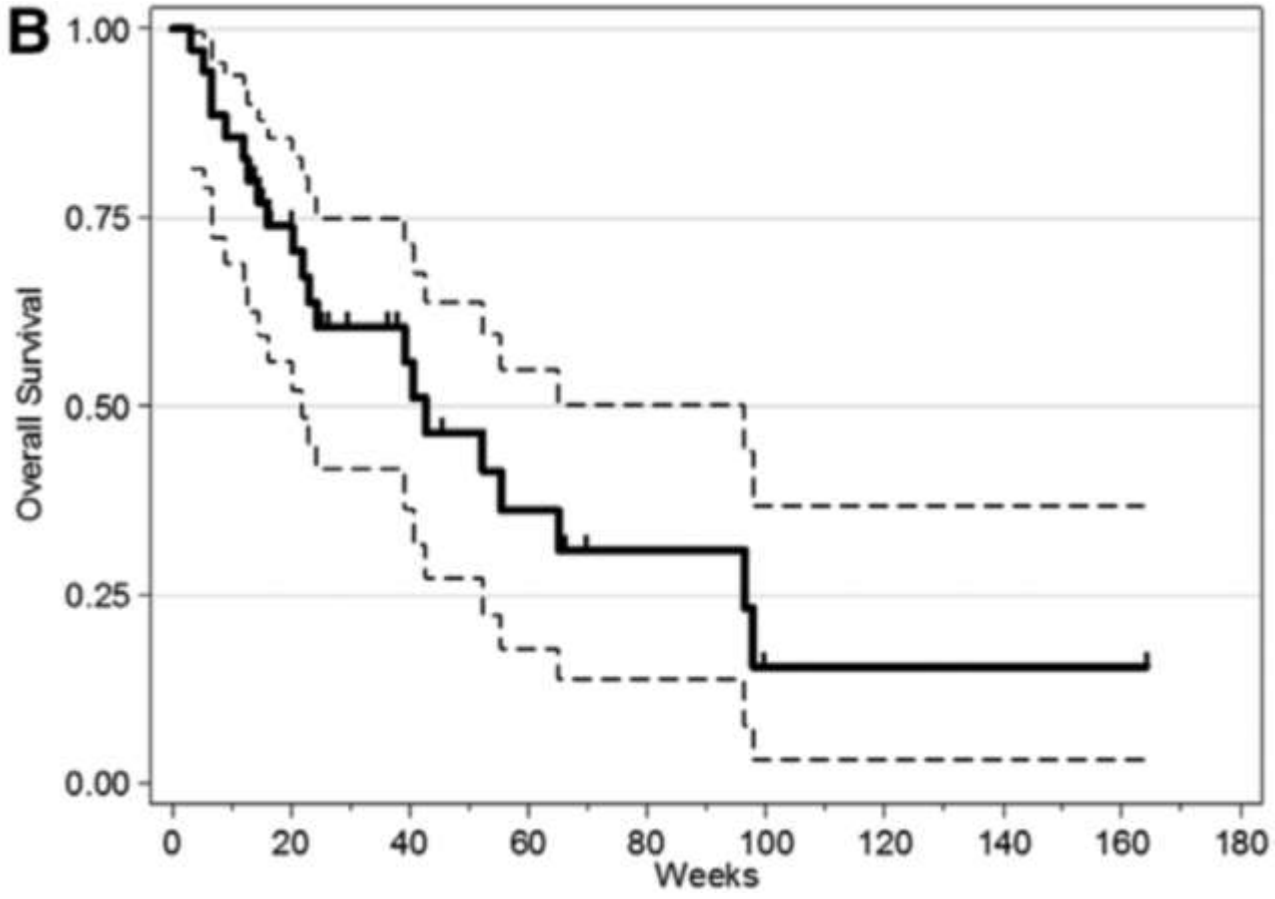


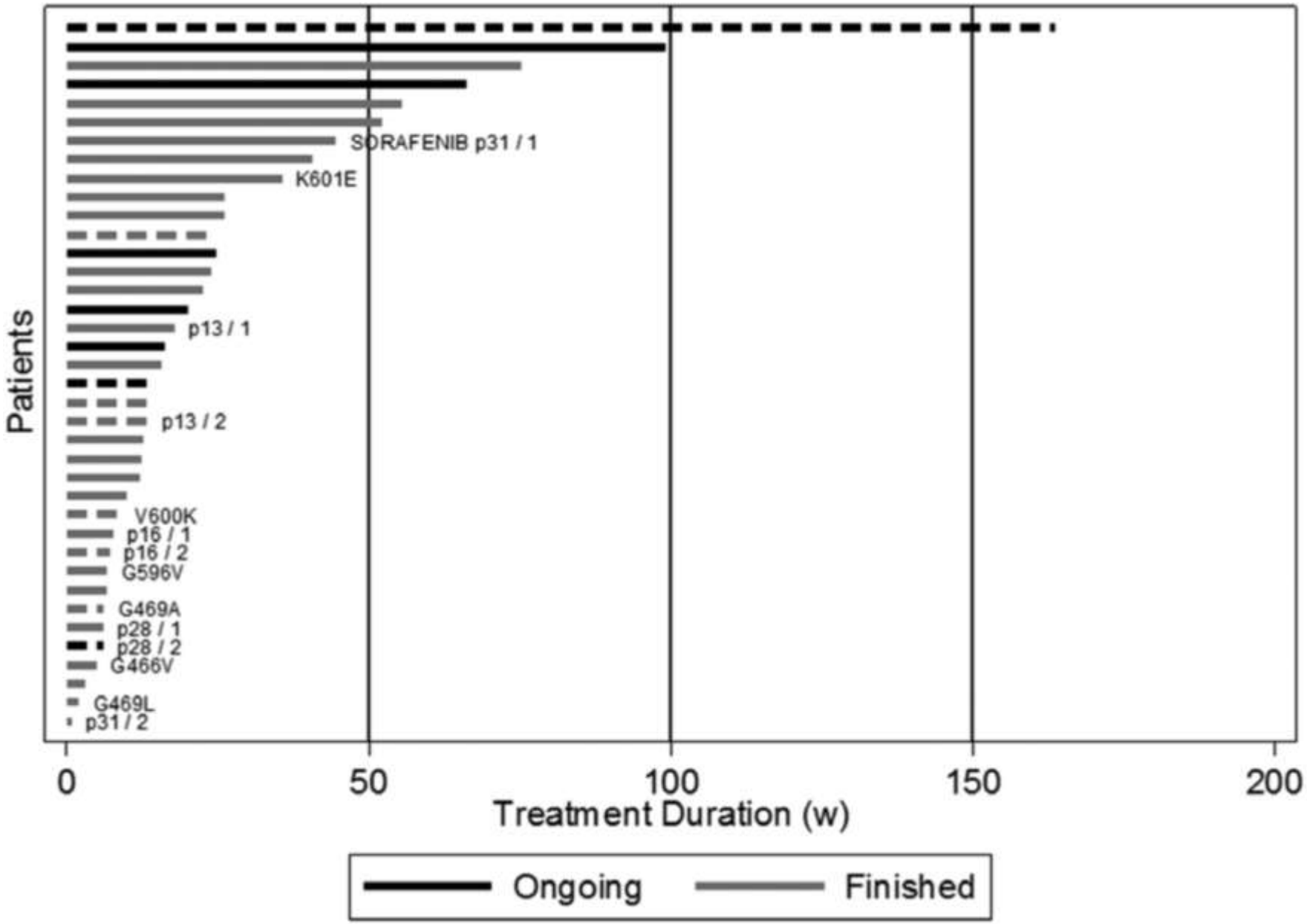


For BRAF therapy

- Median PFS was 20 weeks (5.0 months; 95% CI:12–41 weeks)
- OS was 43 weeks (10.8 months; 95% CI:22–96 weeks)

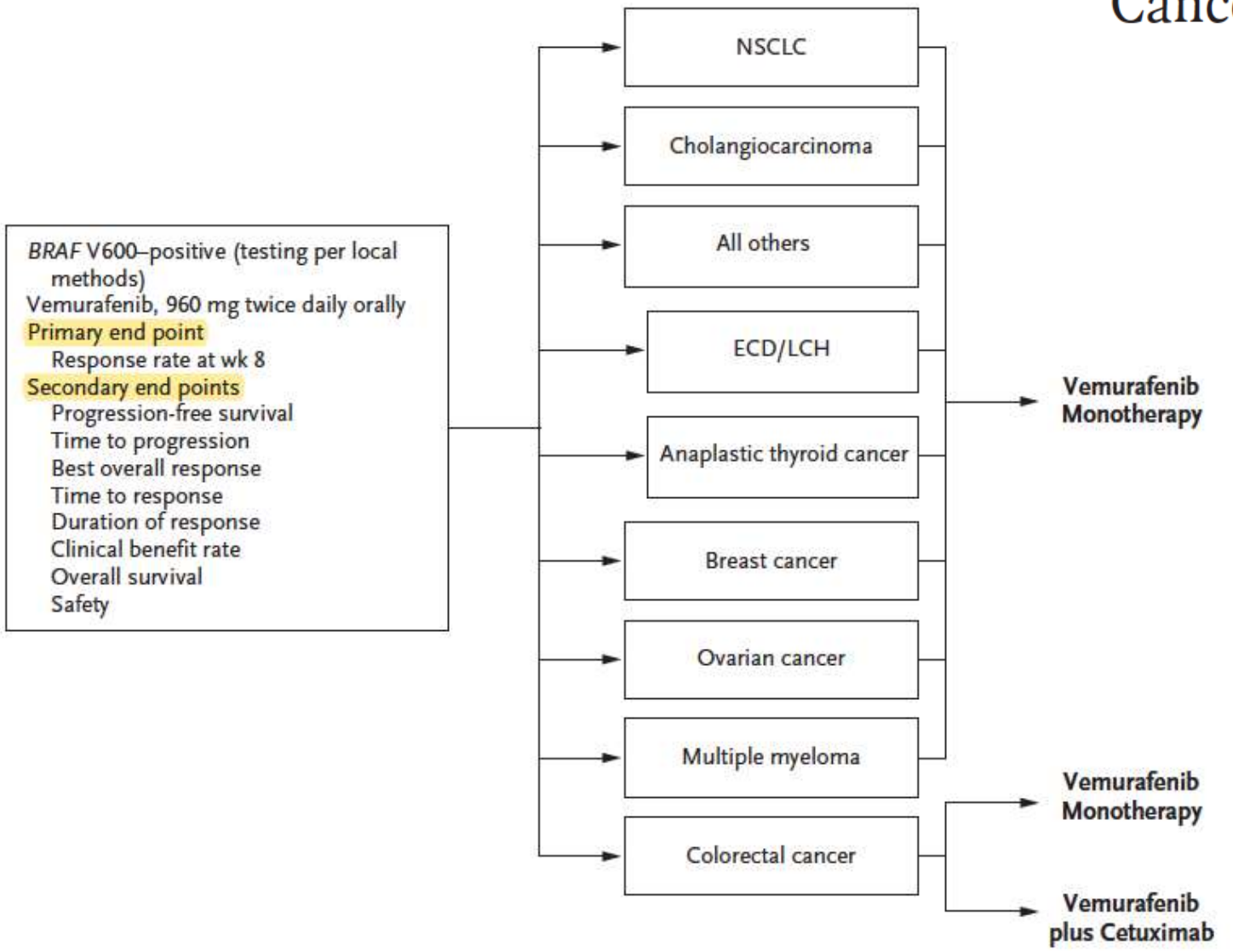






Median duration of BRAF therapy 17 weeks (4.3 months; range, 2–164 weeks

Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations



Prospective study which assessed response to vemurafenib monotherapy in BRAFV600-mutated nonmelanoma solid tumors including NSCLC

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline, According to Cohort.*

Characteristic	NSCLC (N=20)	Colorectal Cancer		Multiple Myeloma (N=5)	Cholangiocarcinoma (N=8)	ECD or LCH (N=18)	Anaplastic Thyroid Cancer (N=7)	Other† (N=27)
		Received Vemurafenib (N=10)	Received Vemurafenib + Cetuximab (N=27)					
Sex — no. (%)								
Male	14 (70)	5 (50)	10 (37)	4 (80)	3 (38)	7 (39)	4 (57)	9 (33)
Female	6 (30)	5 (50)	17 (63)	1 (20)	5 (62)	11 (61)	3 (43)	18 (67)
Yr of age — median (range)	61 (48–83)	59 (49–64)	63 (45–81)	64 (58–68)	53 (37–66)	64 (35–83)	65 (55–81)	55 (18–77)
ECOG performance status†								
0 or 1	16 (80)	10 (100)	25 (93)	4 (80)	7 (88)	15 (83)	4 (57)	22 (81)
≥2	4 (20)	0	2 (7)	1 (20)	1 (12)	3 (17)	3 (43)	5 (19)
Prior systemic therapies — no. (%)‡								
Any	19 (95)	10 (100)	27 (100)	5 (100)	8 (100)	11 (61)	7 (100)	21 (78)
None	1 (5)	0	0	0	0	7 (39)	0	6 (22)
1	10 (50)	1 (10)	5 (19)	0	2 (25)	2 (11)	5 (71)	6 (22)
2	4 (20)	2 (20)	11 (41)	2 (40)	1 (12)	7 (39)	1 (14)	5 (19)
≥3	5 (25)	7 (70)	11 (41)	3 (60)	5 (62)	2 (11)	1 (14)	10 (37)
Prior radiation — no. (%)	4 (20)	4 (40)	6 (22)	2 (40)	3 (38)	0	6 (86)	18 (67)
BRAF V600 mutation — no. (%)								
V600E	18 (90)	8 (80)	24 (89)	5 (100)	7 (88)	17 (94)	7 (100)	25 (93)
V600G	1 (5)	0	0	0	0	0	0	2 (7)
V600 unknown	1 (5)	2 (20)	3 (11)	0	1 (12)	1 (6)	0	0

* ECD denotes Erdheim–Chester disease, ECOG Eastern Cooperative Oncology Group, LCH Langerhans'-cell histiocytosis, and NSCLC non–small-cell lung cancer.

† Tumor types in this cohort included breast cancer, cervical cancer, brain tumors, head and neck cancer, esophageal and gastric cancers, pancreatic cancer, sarcoma, ovarian cancer, and tumors of unknown type.

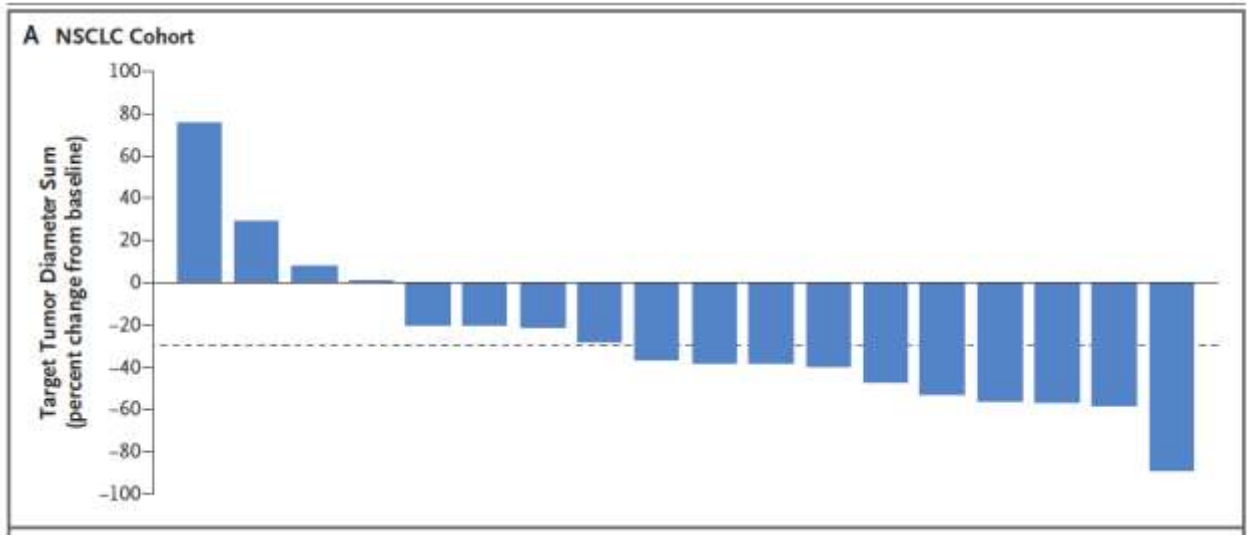
Table 2. Preliminary Best Response According to Cohort.*

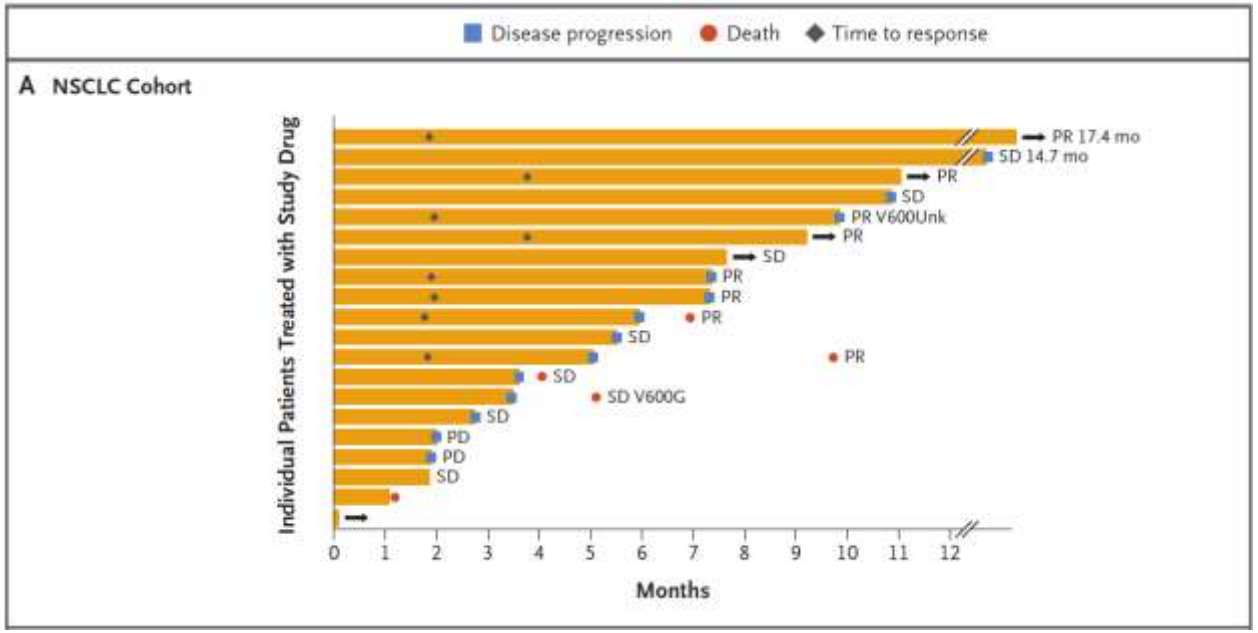
Variable	NSCLC (N=20)	Colorectal Cancer		Cholangio-carcinoma (N=8)	ECD or LCH (N=18)	Anaplastic Thyroid Cancer (N=7)
		Vemurafenib (N=10)	Vemurafenib + Cetuximab (N= 27)			
Patients with ≥1 postbaseline assessment — no.	19	10	26	8	14	7
Complete response — no. (%)	0	0	0	0	1 (7)	1 (14)
Partial response — no. (%)	8 (42)	0	1 (4)	1 (12)	5 (36)	1 (14)
Stable disease — no. (%)	8 (42)	5 (50)	18 (69)	4 (50)	8 (57)	0
Progressive disease — no. (%)	2 (11)	5 (50)	7 (27)	3 (38)	0	4 (57)
Missing data — no. (%)†	1 (5)	0	0	0	0	1 (14)
Overall response — no. (%) [95% CI]	8 (42) [20–67]	0	1 (4) [<1–20]	1 (12) [<1–53]	6 (43) [18–71]	2 (29) [4–71]

* The denominator for patients with a complete or partial response, stable disease, or progressive disease is the number of patients with a postbaseline assessment or early withdrawal. Of the 19 patients in the NSCLC cohort, 1 patient withdrew before the assessment of response but was included in the denominator for the efficacy assessment (as having had no response).

† All patients with missing data withdrew early.

- ORR-42% (95% confidence interval [CI], 20 to 67)
- Tumor regression seen in 14 of 19
- Median PFS- 7.3 months(95% CI, 3.5 to 10.8).
- 12-month rate of PFS -23%(95% CI, 6 to 46).
- Preliminary 12-month OS rate-66% (95% CI, 36 to 85).
- At cut-off date 5 patients were still receiving therapy
- Common adverse events in >20% of pts
- Most common adverse events were rash (68% of patients), fatigue (56%), and arthralgia (40%)





Efficacy of Vemurafenib in Patients With Non–Small-Cell Lung Cancer With *BRAF* V600 Mutation: An Open-Label, Single-Arm Cohort of the Histology-Independent VE-BASKET Study

Vivek Subbiah, MD[1]; Radj Gervais, MD[2]; Gregory Riely, MD, PhD[3]; Antoine Hollebecque, MD[4]; Jean-Yves Blay, MD, PhD[5]; Enriqueta Felip, MD, PhD[6]; Martin Schuler, MD[7]; Anthony Gonçalves, MD, PhD[8]; Antonio Italiano, MD, PhD[9]; Vicki Keedy, MD[10]; Ian Chau, MD[11]; Igor Puzanov, MD[12]; Noopur S. Raje, MD[13]; Funda Meric-Bernstam, MD[1]; Martina Makrutzki, MD[14]; Todd Riehl, PharmD[15]; Bethany Pitcher, MMath[16]; Jose Baselga, MD, PhD[3,17]; and David M. Hyman, MD[3,17]

PURPOSE To study whether *BRAF* V600 mutations in non–small-cell lung cancer (NSCLC) may indicate sensitivity to the BRAF inhibitor vemurafenib, we included a cohort of patients with NSCLC in the vemurafenib basket (VE-BASKET) study. On the basis of observed early clinical activity, we expanded the cohort of patients with NSCLC. We present results from this cohort.

METHODS This open-label, histology-independent, phase II study included six prespecified cohorts, including patients with NSCLC, and a seventh all-comers cohort. Patients received vemurafenib (960 mg two times per day) until disease progression or unacceptable toxicity. The primary end point of the final analysis was objective response rate (Response Evaluation Criteria in Solid Tumors, version 1.1). Secondary end points included progression-free survival, overall survival, and safety. Because the prespecified clinical benefit endpoint was met in the initial NSCLC cohort, the cohort was expanded.

TABLE 1. Baseline Characteristics

Characteristic	All Patients (N = 62)	Previously Untreated (n = 8)	Previously Treated (n = 54)
Median age (IQR), years	65 (59-74)	73 (65-79)	64 (57-72)
Age group, years			
18-64	30 (48)	2 (25)	28 (52)
65-84	30 (48)	5 (63)	25 (46)
≥ 85	2 (3)	1 (13)	1 (2)
Sex, No. (%)			
Male	35 (56)	5 (63)	30 (56)
Female	27 (44)	3 (38)	24 (44)
Smoking history, No. (%)			
Current smoker	1 (2)	0	1 (2)
Ex-smoker	36 (58)	3 (38)	33 (61)
Never smoked	25 (40)	5 (63)	20 (37)
ECOG performance status, No. (%)*			
0	16 (28)	3 (43)	13 (26)
1	31 (54)	4 (57)	27 (54)
2	10 (18)	0	10 (20)
No. of prior systemic therapies (%)		NA	
0	8 (13)		0
1	23 (37)		23 (43)
2	21 (34)		21 (39)
≥ 3	10 (16)		10 (19)
Median time since diagnosis (IQR), months	11.3 (4.4-23.8)	2.4 (1.7-3.9)	12.6 (7.9-26.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; NA, not applicable.
*All patients, N = 57; previously untreated, n = 7; previously treated, n = 50.

TABLE 2. Treatment Outcomes in Patients With Non–Small-Cell Lung Cancer

Outcome	All Patients (N = 62)	Previously Untreated (n = 8)	Previously Treated (n = 54)
Investigator-assessed best response, No. (%)			
CR	0	0	0
PR	23 (37)	3 (38)	20 (37)
SD	26 (42)	5 (63)	21 (39)
PD	8 (13)	0	8 (15)
Missing/not evaluable	5 (8)	0	5 (9)
ORR, % (95% CI)	37.1 (25.2 to 50.3)	37.5 (8.5 to 75.5)	37.0 (24.3 to 51.3)
CBR, % (95% CI)	48.4 (35.5 to 61.4)	62.5 (24.5 to 91.5)	46.3 (32.6 to 60.4)
Median survival, months (95% CI)			
OS	15.4 (9.6 to 22.8)	NE (6.0 to NE)	15.4 (8.2 to 22.8)
PFS	6.5 (5.2 to 9.0)	12.9 (4.0 to NE)	6.1 (5.1 to 8.3)

Abbreviations: CBR, clinical benefit rate; CR, complete response; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

	All patients	previously treated patients	previously untreated
Median treatment duration	6.0 months (IQR, 2.8 to 11.5 months)	5.7 months (IQR, 2.8 to 11.2 months)	12.0 months (IQR, 4.0 to 13.9 months)

TABLE 3. AEs Occurring in ≥ 20% of Patients Overall (N = 62)

AE	All Grades	Grade ≥ 3
Any AE	62 (100)	50 (81)
Nausea	25 (40)	3 (5)
Hyperkeratosis	21 (34)	0
Decreased appetite	20 (32)	5 (8)
Arthralgia	19 (31)	3 (5)
Diarrhea	18 (29)	0
Fatigue	18 (29)	3 (5)
Asthenia	17 (27)	3 (5)
Rash	17 (27)	0
Vomiting	17 (27)	1 (2)
Dyspnea	16 (26)	5 (8)
Alopecia	16 (26)	0
PPE syndrome	16 (26)	1 (2)
Melanocytic nevus	15 (24)	0
Seborrheic keratosis	15 (24)	1 (2)
Anemia	15 (24)	6 (10)
Pyrexia	14 (23)	1 (2)
Skin papilloma	14 (23)	0
Keratosis pilaris	13 (21)	0
Photosensitivity reaction	13 (21)	0
Dysgeusia	13 (21)	0

NOTE. All data are No. (%).

Abbreviations: AE, adverse event; PPE, palmar-plantar erythrodysesthesia.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Vemurafenib in non-small-cell lung cancer patients with $BRAF^{V600}$ and $BRAF^{nonV600}$ mutations

J. Mazieres[1*], C. Cropet[2], L. Montané[2], F. Barlesi[3], P. J. Souquet[4], X. Quantin[5], C. Dubos-Arvis[6], J. Otto[7], L. Favier[8], V. Avrillon[9], J. Cadranel[10], D. Moro-Sibilot[11], I. Monnet[12], V. Westeel[13], J. Le Treut[14], E. Brain[15], J. Trédaniel[16], M. Jaffro[17], S. Collot[17], G. R. Ferretti[18], C. Tiffon[19], C. Mahier-Ait Oukhatar[20] & J. Y. Blay[21]

- Advanced NSCLC
- BRAF mutations
- Measurable lesion
- ECOG PS < 2

BRAFV600

BRAFnonV600

- Vemurafenib PO 960 mg BD
- Until disease progression,
- Unacceptable toxicity

Primary objective

- objective response rate (ORR)

secondary efficacy outcomes

- Duration of response
- Progression-free survival (PFS)
- Overall survival (OS)

Safety - by clinical, biological, and cardiac evaluations

Tumour response was assessed every 8 weeks from baseline by CT scan using RECISTv1.1

Table 1. Demographics and disease characteristics

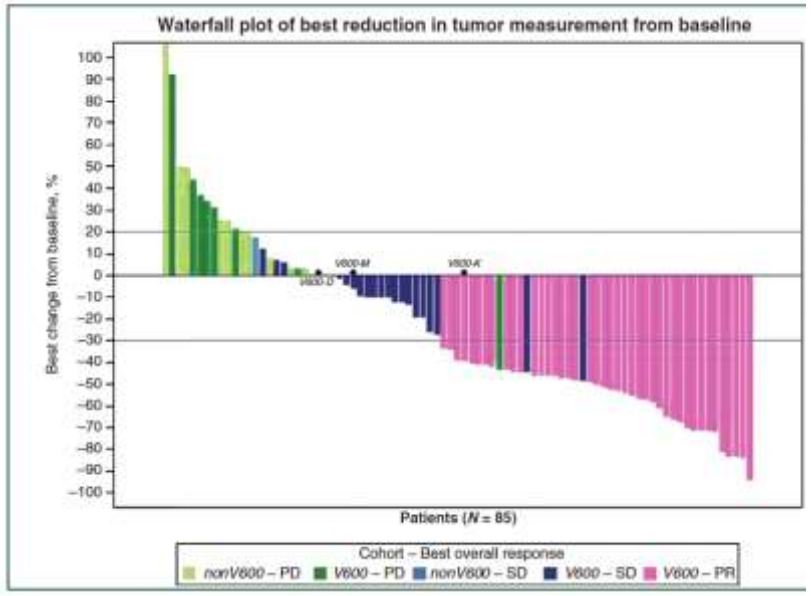
Characteristics	$BRAF^{V600}$ (N = 101)	$BRAF^{nonV600}$ (N = 17)
Age (years) [extreme]	68.0 [41.0; 85.0]	65.0 [34.0; 83.0]
Sex		
Male	51 (50.5%)	10 (58.8%)
Female	50 (49.5%)	7 (41.2%)
Tobacco		
smokers + ex-smokers	58 (69.0%)	12 (85.7%)
WHO PS[a]		
0	27 (27.0%)	4 (27.0%)
1	54 (54.0%)	7 (46.0%)
2	19 (19.0%)	4 (27.0%)
No. of previous lines of chemotherapy		
1	50 (49.5%)	3 (17.6%)
2	24 (23.8%)	8 (47.2%)
3 or more	6 (6.0%)	3 (17.6%)
Received any chemotherapy	80 (79.3%)	14 (82.4%)
Histology subtypes		
Adenocarcinoma	99 (98.0%)	17 (100%)
Undifferentiated carcinoma	2 (2.0%)	

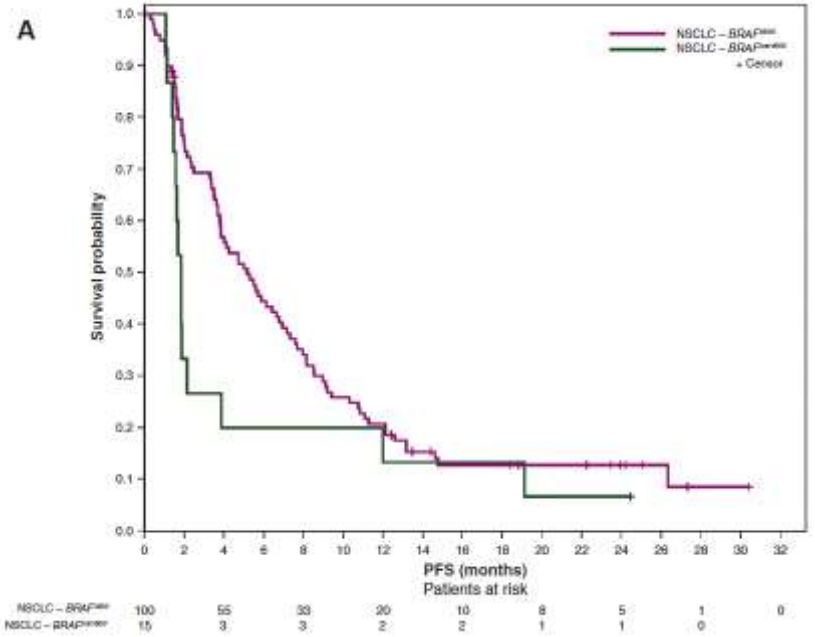
WHO PS, Performance status according to World Health Organization.
[a] *V600*: 1 missing data; *nonV600*: 2 missing data.

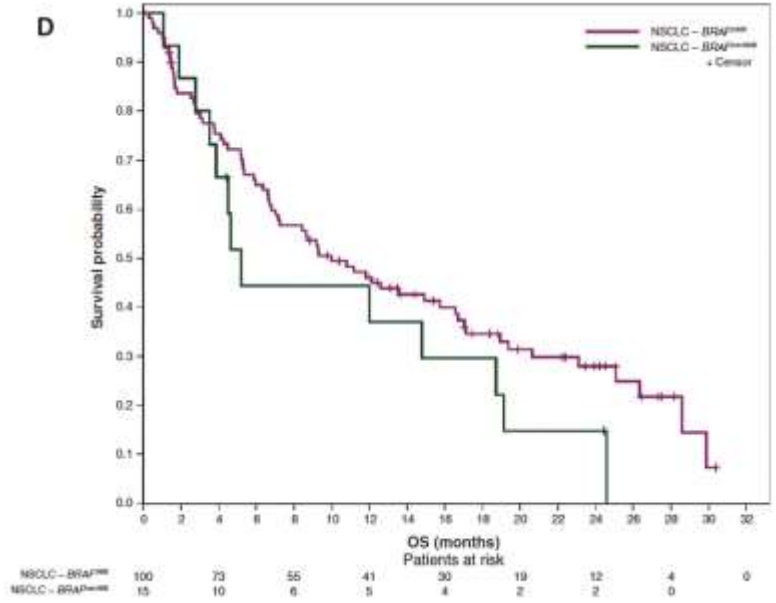
- Median duration of treatment was 3.3 months (range 0.03-27.4) Vs 1.5 months (range0.2-2.1)
- Treatment was modified (dose reductions and/or treatment delays) due to toxicity in 60 patients (60%) Vs 12 patients (80
- In the V600 cohort, 56 patients(56%) discontinued vemurafenib due to disease progression and 24 (24%) due to toxicity.
- In the nonV600 cohort,10 patients (67%) discontinued vemurafenib due to disease progression and 3 (20%) due to toxicity

Median follow-up of 23.9 months (95% CI 19.8-25.0)

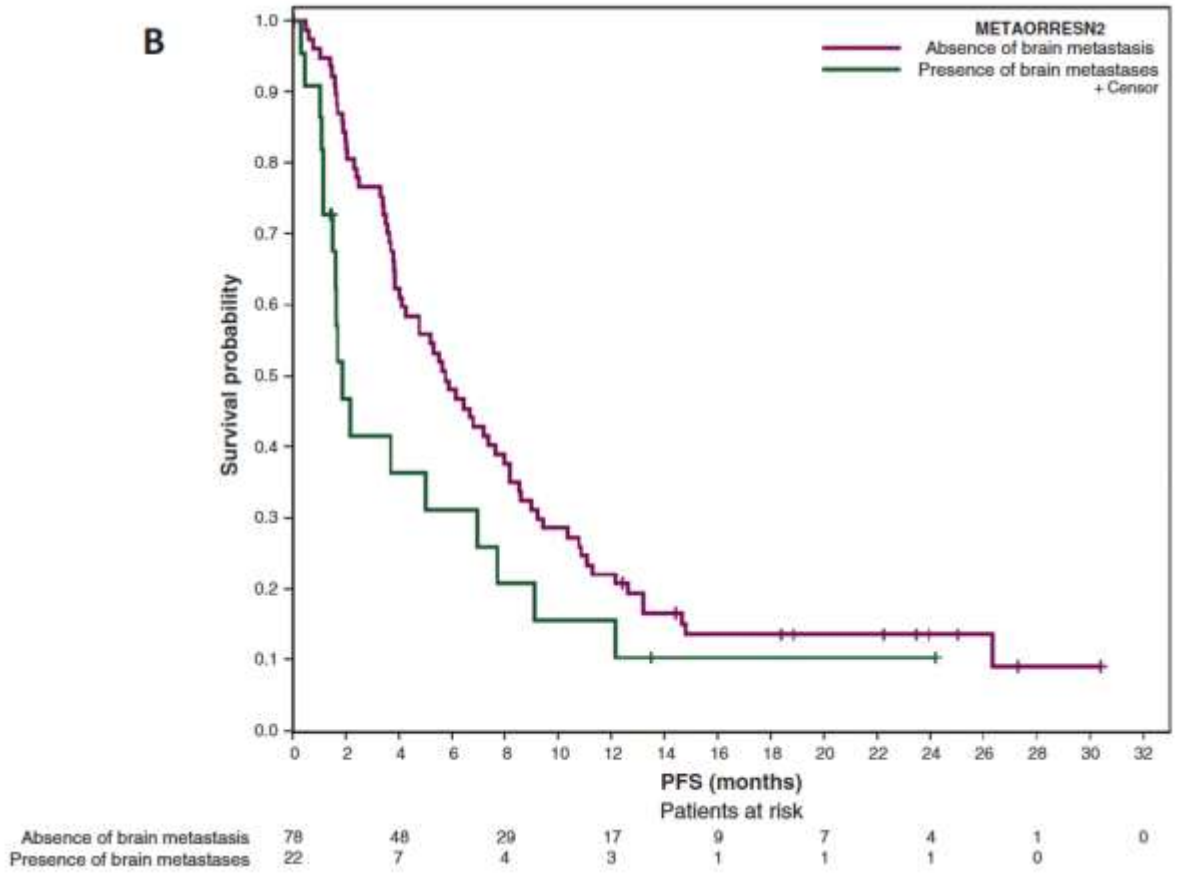
	BRAFV600 cohort	BRAFnonV600 cohort
Objective response rate	44.9% (95% CI 35.2%e54.8%)	5.9% (95% CI 0.2%-20.6%)
Median response duration	6.4 months (95% CI 5.1-7.3)	
Median PFS	5.2 months (95% CI 3.8e6.8)(V600-E) 3.8 months (V600-D), 5.9 months (V600-M), 2.1 and 6.8 months (2 pts V600-K)	1.8 months (95% CI 1.4-2.1)
Median OS	10 months (95% CI 6.8-15.7)	5.2 months (95% CI 2.8-18.7)

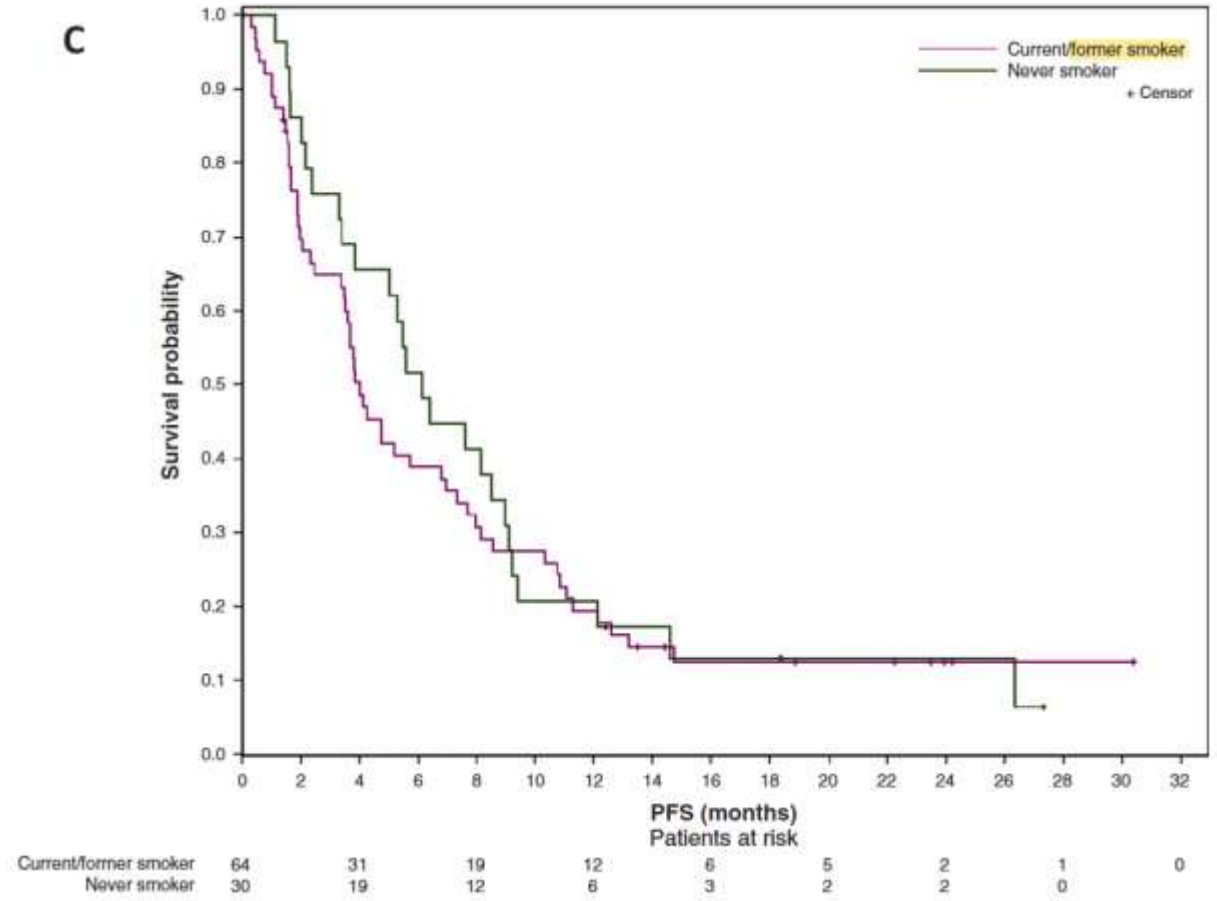


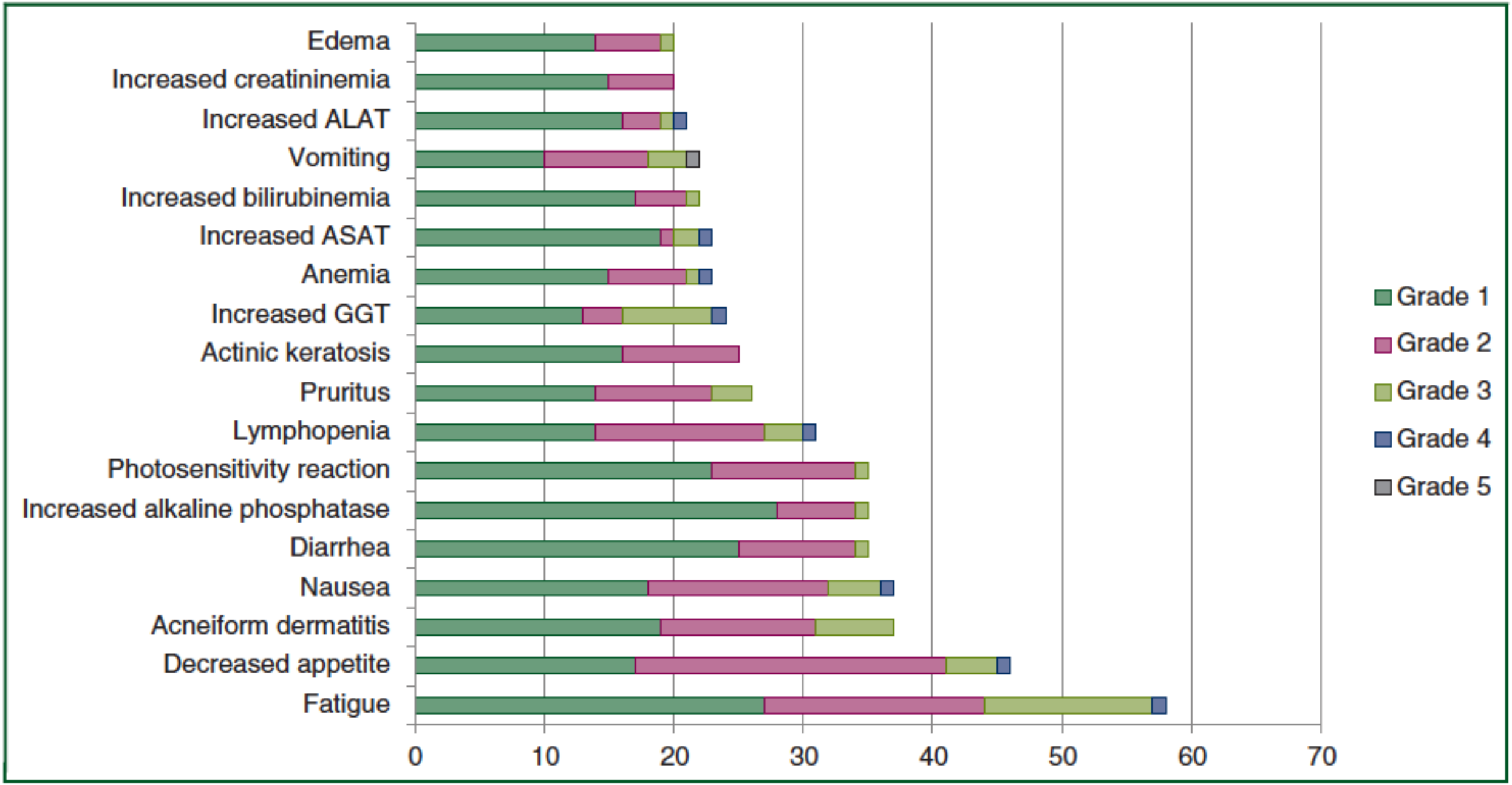




Median PFS-1.9 months (95% CI 1.5-3.9) in the 26 patients (22.6%) with brain metastasis and 5.4 months (95% CI 3.8-7.2) in the 89 patients (77.4%) without brain metastasis






Edema
Increased creatininemia
Increased ALAT
Vomiting
Increased bilirubinemia
Increased ASAT
Anemia
Increased GGT
Actinic keratosis
Pruritus
Lymphopenia
Photosensitivity reaction
Increased alkaline phosphatase
Diarrhea
Nausea
Acneiform dermatitis
Decreased appetite
Fatigue
0
10
20
30
40
50
60
70
Grade 1
Grade 2
Grade 3
Grade 4
Grade 5

Dabrafenib in patients with *BRAF*^{V600E}-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial

David Planchard, Tae Min Kim, Julien Mazieres, Elisabeth Quoix, Gregory Riely, Fabrice Barlesi, Pierre-Jean Souquet, Egbert F Smit, Harry J M Groen, Ronan J Kelly, B C Cho, Mark A Socinski, Lini Pandite, Christine Nase, Bo Ma, Anthony D'Amelio Jr, Bijoyesh Mookerjee, C Martin Curtis Jr, Bruce E Johnson

Dabrafenib plus trametinib in patients with previously treated *BRAF*^{V600E}-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial

David Planchard, Benjamin Besse, Harry J M Groen, Pierre-Jean Souquet, Elisabeth Quoix, Christina S Baik, Fabrice Barlesi, Tae Min Kim, Julien Mazieres, Silvia Novello, James R Rigas, Allison Upalawanna, Anthony M D'Amelio Jr, Pingkuan Zhang, Bijoyesh Mookerjee, Bruce E Johnson

Dabrafenib plus trametinib in patients with previously untreated *BRAF*^{V600E}-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial

David Planchard, Egbert F Smit, Harry J M Groen, Julien Mazieres, Benjamin Besse, Åslaug Helland, Vanessa Giannone, Anthony M D'Amelio Jr, Pingkuan Zhang, Bijoyesh Mookerjee, Bruce E Johnson

Phase 2, multicentre, non-randomised, open-label study

34 centres in ten countries within North America, Europe, and Asia

A-Dabrafenib 150 mg BD PO as second line or later treatment

B-Dabrafenib (150 mg BD PO) plus trametinib (2 mg OD PO) as second line

C-Dabrafenib (150 mg BD PO) plus trametinib (2 mg OD PO) as first-line treatment

Primary endpoint

- Overall response rate

Secondary endpoints

- Progression-free survival
- duration of response
- Disease control
- Overall survival
- pharmacokinetic assessment,
- Safety & tolerability of dabrafenib

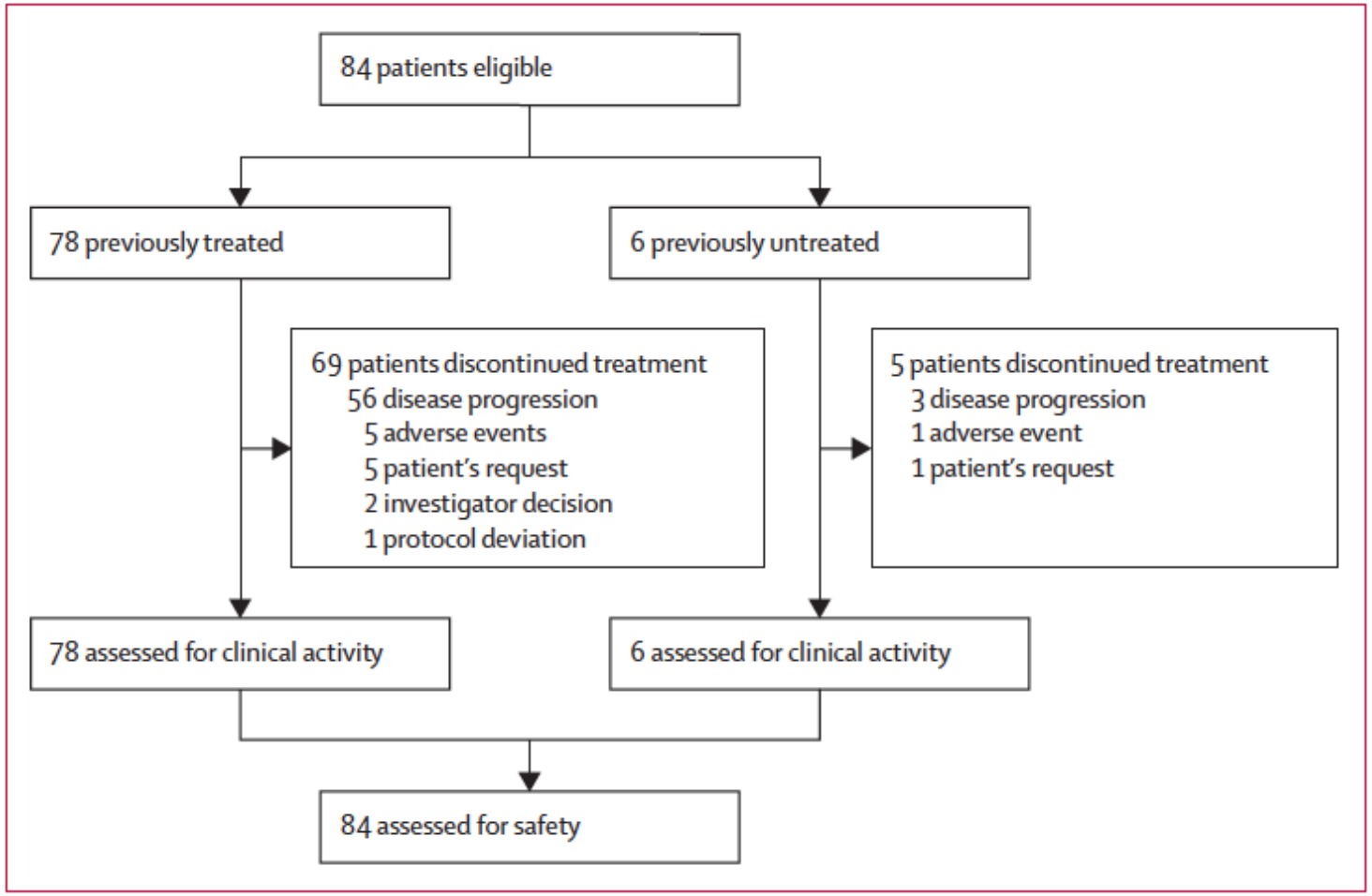
Inclusion Criteria

- Histologically or cytologically confirmed NSCLC stage IV with BRAF V600E mutation
- For Cohorts A and B, documented tumor progression (based on radiological imaging) after receiving at least one prior approved platinum-based chemotherapy regimen for advanced stage/metastatic NSCLC
- Cohort B < 3 prior systemic treatments
- Measurable disease [RECIST 1.1]
- At least 18 years of age
- Anticipated life expectancy of at least three months
- ECOG Performance Status of 0-2
- Must have adequate organ function

Exclusion criteria

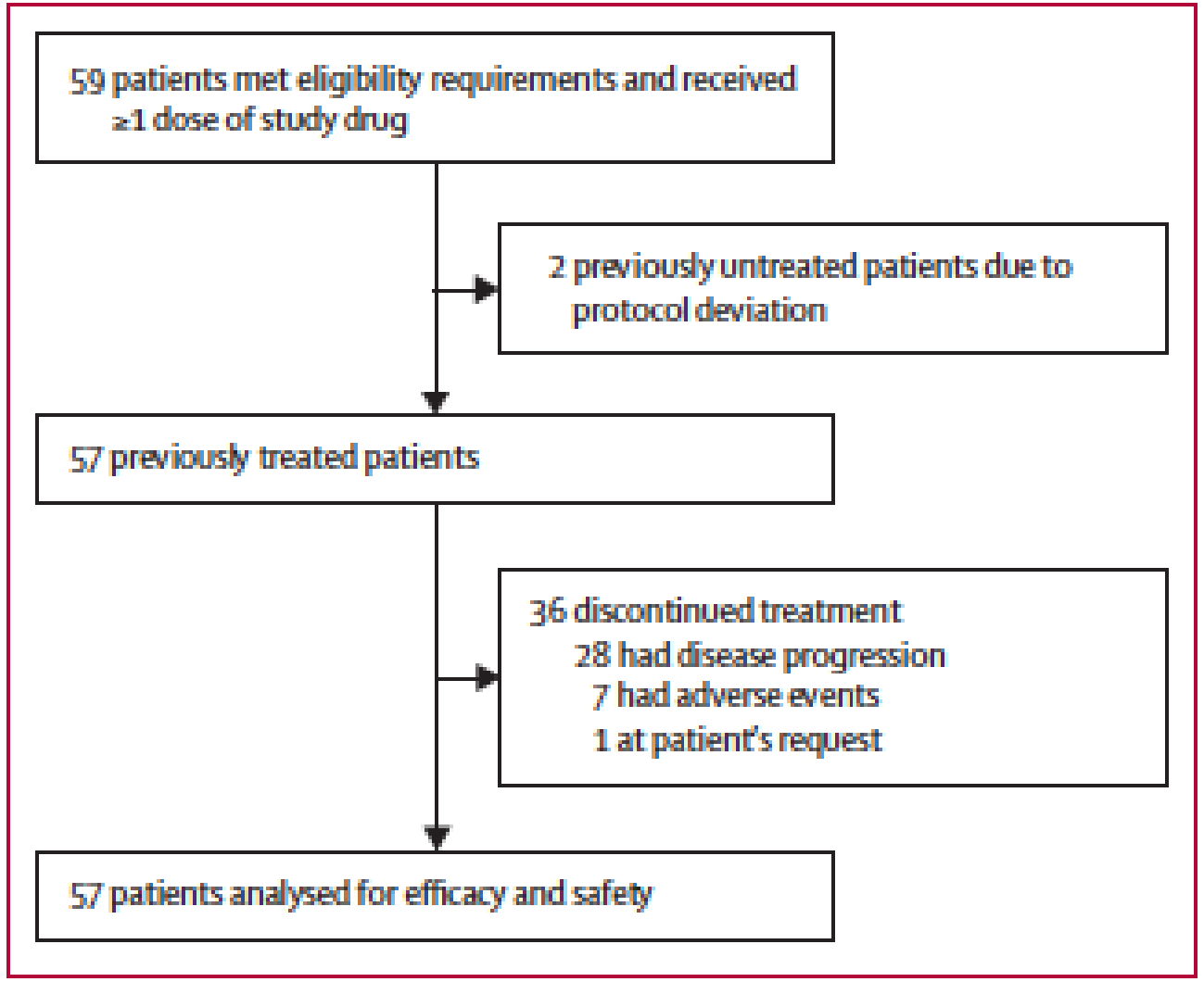
- Previously treated with a BRAF or MEK inhibitor or had
- Symptomatic or unstable brain metastases
- Anticancer treatment within 14 days of starting dabrafenib
- Treatment with an investigational anticancer drug within 14 days or five half-lives of starting dabrafenib
- Infection with hepatitis B or C virus
- History or signs of cardiovascular risk and pregnancy

Cohort-A



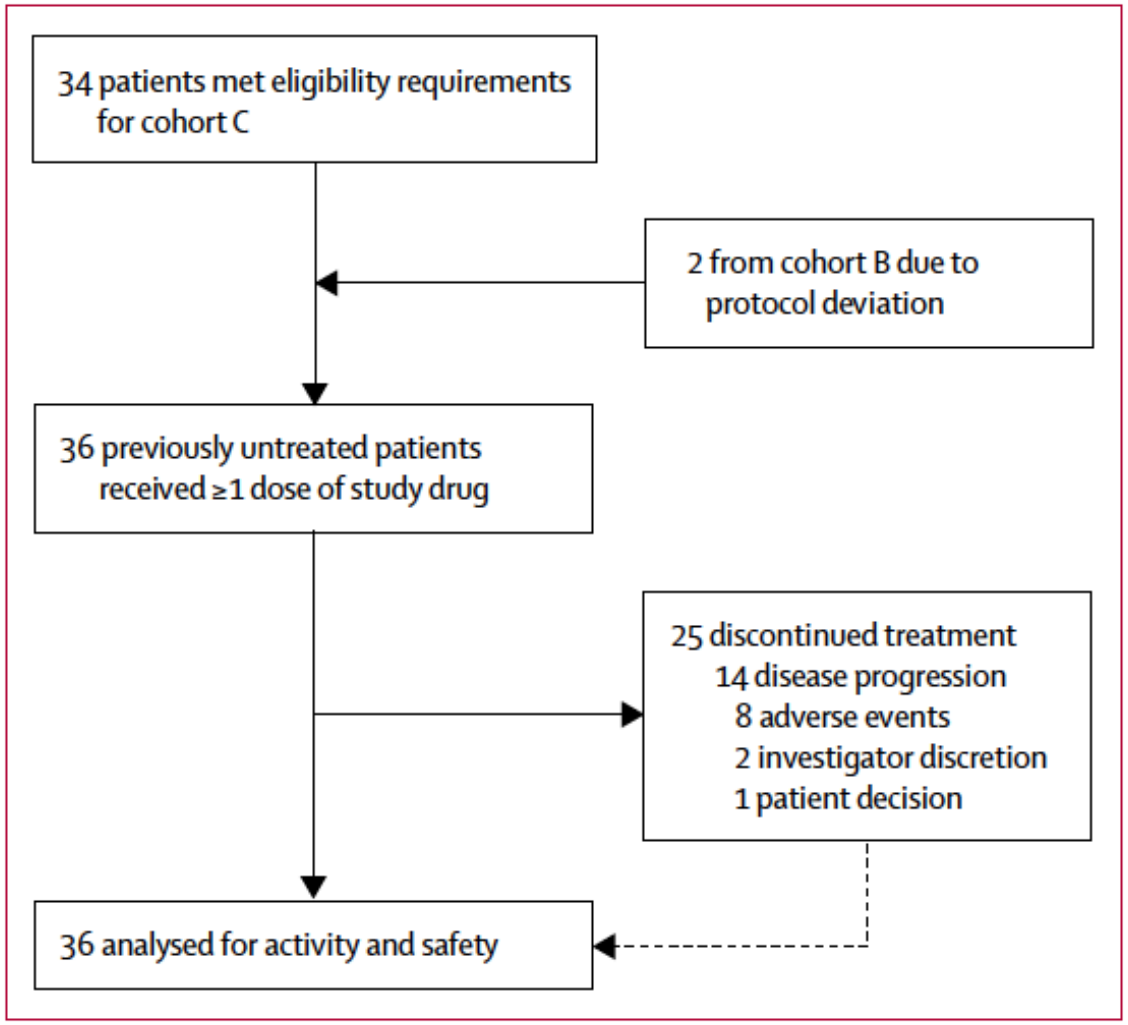
	Patients receiving dabrafenib as second-line or later treatment (n=78)
Age (years)	66 (28–85)
Sex	
Female	39 (50%)
Male	39 (50%)
Ethnic origin	
White	59 (76%)
Asian	17 (22%)
African American	2 (3%)
ECOG performance status	
0	16 (21%)
1	50 (64%)
2	12 (15%)
Smoking history	
Never smoker*	29 (37%)
Smoker ≤30 pack-years†	25 (32%)
Smoker >30 pack-years†	24 (31%)
Histology at diagnosis	
Adenocarcinoma	75 (96%)
Other‡	3 (4%)
Number of previous systemic regimens	
1	40 (51%)
2	14 (18%)
3	24 (31%)
Median (IQR) time since previous progression (months)§	1·1 (0·7–2·1)

Cohort-B



	Patients receiving dabrafenib plus trametinib as second-line or later treatment (n=57)
Age (years)	64 (58–71)
Sex	
Male	29 (51%)
Female	28 (49%)
Ethnic origin	
White	49 (86%)
Black	2 (4%)
Asian	4 (7%)
Mixed	1 (2%)
Missing	1 (2%)
ECOG performance status	
0	17 (30%)
1	35 (61%)
2	5 (9%)
Histology at initial diagnosis	
Adenocarcinoma*	56 (98%)
Large cell	1 (2%)
History of tobacco use	
Never smoker	16 (28%)
Current smoker	6 (11%)
Former smoker	35 (61%)
Smoking history†	
≤30 pack-years	22 (54%)
>30 pack-years	19 (46%)
Number of previous systemic regimens for metastatic disease	
1	38 (67%)
≥2	19 (33%)

Cohort-C



	All patients (n=36)
Age, years	67 (62–74)
Sex	
Female	22 (61%)
Male	14 (39%)
Race	
White	30 (83%)
Native American or other Pacific Islander	1 (3%)
Black or African American	1 (3%)
Asian	3 (8%)
Missing	1 (3%)
ECOG performance status	
0	13 (36%)
1	22 (61%)
2	1 (3%)
Histology at initial diagnosis	
Adenocarcinoma	32 (89%)
Adenosquamous carcinoma (predominantly adenocarcinoma)	1 (3%)
Adenosquamous carcinoma (predominantly squamous-cell carcinoma)	1 (3%)
Large-cell carcinoma	1 (3%)
NSCLC not otherwise specified	1 (3%)
Smoking history*	
Never	10 (28%)
Current	5 (14%)
Former	21 (58%)
Time smoked, years	30 (10–40)
Pack-years	
Median	18 (5–34)
<10	8 (22%)
10–30	9 (25%)
>30	7 (19%)

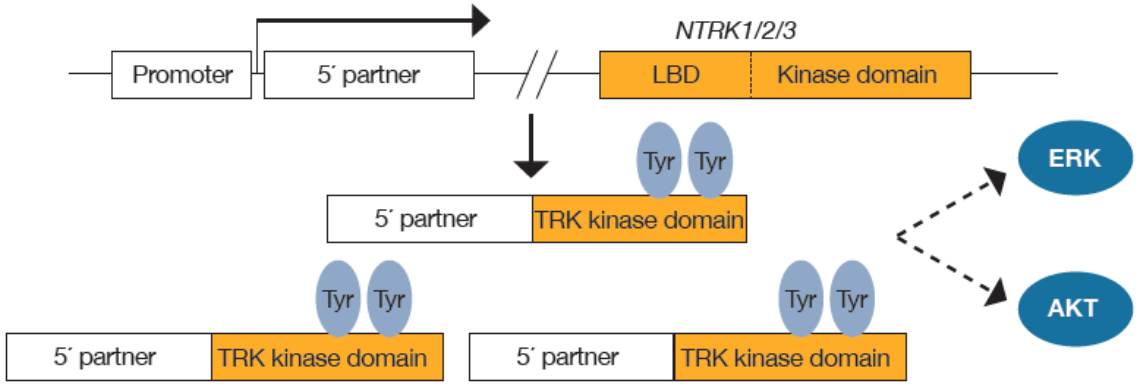
	Cohort -A Dabrafenib 150 mg BD PO as secondline or later treatment (n = 78)	Cohort -B Dabrafenib (150 mg BD PO) plus trametinib (2 mg OD PO) as secondline or later treatment (n = 57)	Cohort-C Dabrafenib (150 mg BD PO) plus trametinib (2 mg OD PO) as first-line treatment (n = 36)
Age (years)	66 (28–85)	64 (58–71)	67 (62–74)
Male	39 (50%)	29 (51%)	14 (39%)
Never smoker	29 (37%)	16 (28%)	10 (28%)
Smoker ⩽30 packyears	25 (32%)	22 (54%)	17 (47%)
Smoker >30 packyears	24 (31%)	19 (46%)	7 (19%)
Overall response rate (complete response + partial response)	26 (33%; 23–45%)	36 (63.2%; 49.3–75.6%)	23 (64%; 46–79%)
Disease control rate (complete response + partial response + stable disease)	45 (58%; 46–67%)	45 (78·9%; 66.1–88.6%)	27 (75%; 58–88%)

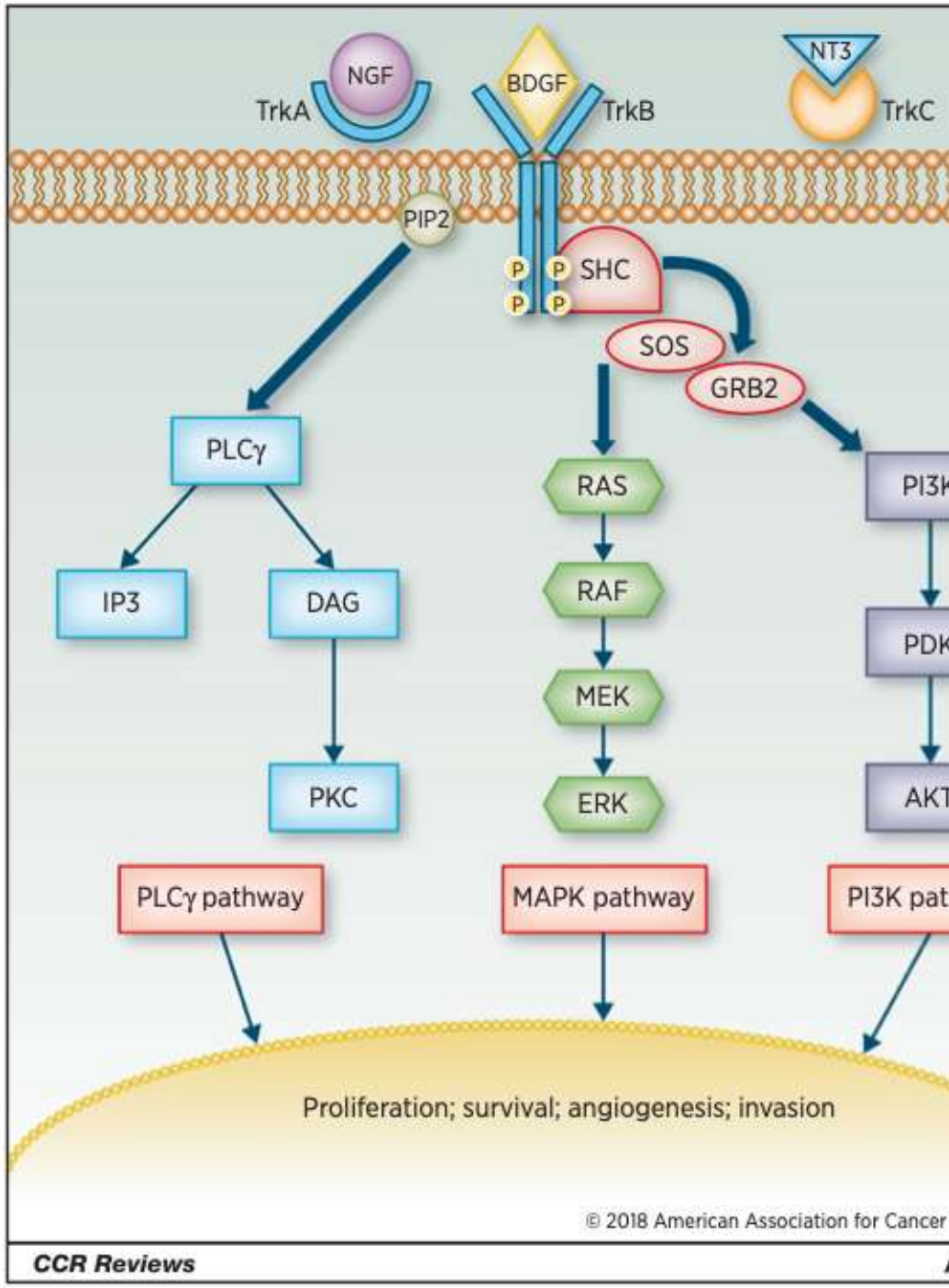
	Cohort -A dabrafenib 150 mg BD PO as secondline or later treatment (n = 78)	Cohort -B dabrafenib (150 mg BD PO) plus trametinib (2 mg OD PO) as secondline or later treatment (n = 57)	Cohort-C dabrafenib (150 mg BD PO) plus trametinib (2 mg OD PO) as first-line treatment (n = 36)
Progression-free survival (months)	5.5 (3.4–7.3)	9.7 (6.9–19.6)	10.9 (7.0–16.6)
Duration of response (months)	9.6 (5.4–15.2)	9.0 (6.9–18.3)	10.4 (8.3–17.9)
Overall survival	12.7 (7.3–16.3)	18.2 (14.3–not estimable)	24.6 (12.3–not estimable)
Adverse effects (grade 3–4)	Pyrexia - 2 (2%) Asthenia - 5 (6%) Anemia - 2 (2%) Squamous cell carcinoma - 10 (12%) Dyspnea - 2 (2%) Rash - 1 (1%) Hypertension - 1 (1%)	Pyrexia - 1 (2%) Asthenia - 2 (4%) Anemia - 3 (5%) Squamous cell carcinoma - 2 (4%) Dyspnea - 2 (4%) Rash - 1 (2%) Hypertension - 0 (0%)	Pyrexia - 4 (11%) Asthenia - 1 (3%) Anemia - 1 (3%) Squamous cell carcinoma - 1 (3%) Dyspnea - 2 (6%) Rash - 1 (3%) Hypertension - 4 (11%)

Targetable Driver genes	Incidence	Targeted Agent	Clinical Trials	Phase	Patients Included	Results	Approved or Recommended by
BRAF mutation	2–4%	Dabrafenib[77]	NCT01336634	II	Treated and untreated BRAFV600E + NSCLC	n=78, ORR 33%, mPFS 5.5 mo, mOS of 12.7 mo	
		Dabrafenib + trametinib[78]	NCT01336634	II	Untreated BRAFV600E+ NSCLC	n=36, ORR 64%, mPFS 10.9 mo, mOS 24.6 mo	NCCN, FDA, EMA
		Dabrafenib + trametinib[79]	NCT01336634	II	Chemotherapy-pretreated BRAFV600E+ NSCLC	n=57, ORR 63%, mPFS 10.2 mo, mOS 18.2 mo	NCCN, FDA, EMA

NTRK Rearrangements

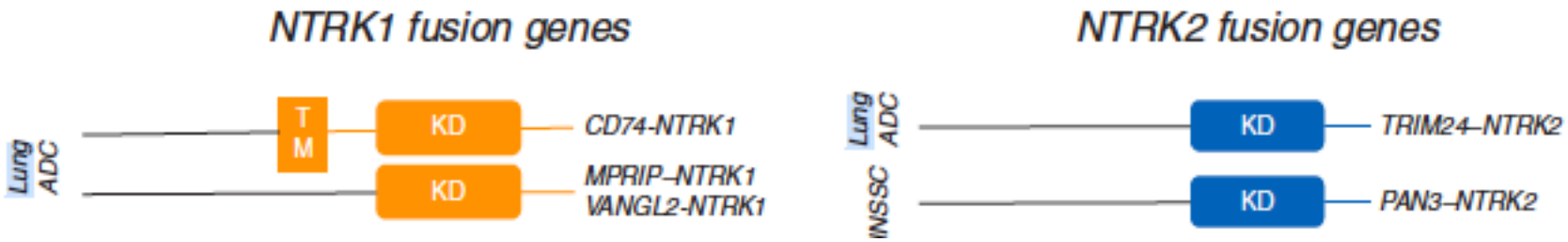
- Tropomyosin kinase receptors, TRKA, B and C are encoded by -*NTRK1, 2*, and *3*
- Fusion events with the kinase domain of *NTRK1, 2*, and *3* genes with various partners result in *NTRK* gene fusions, which are





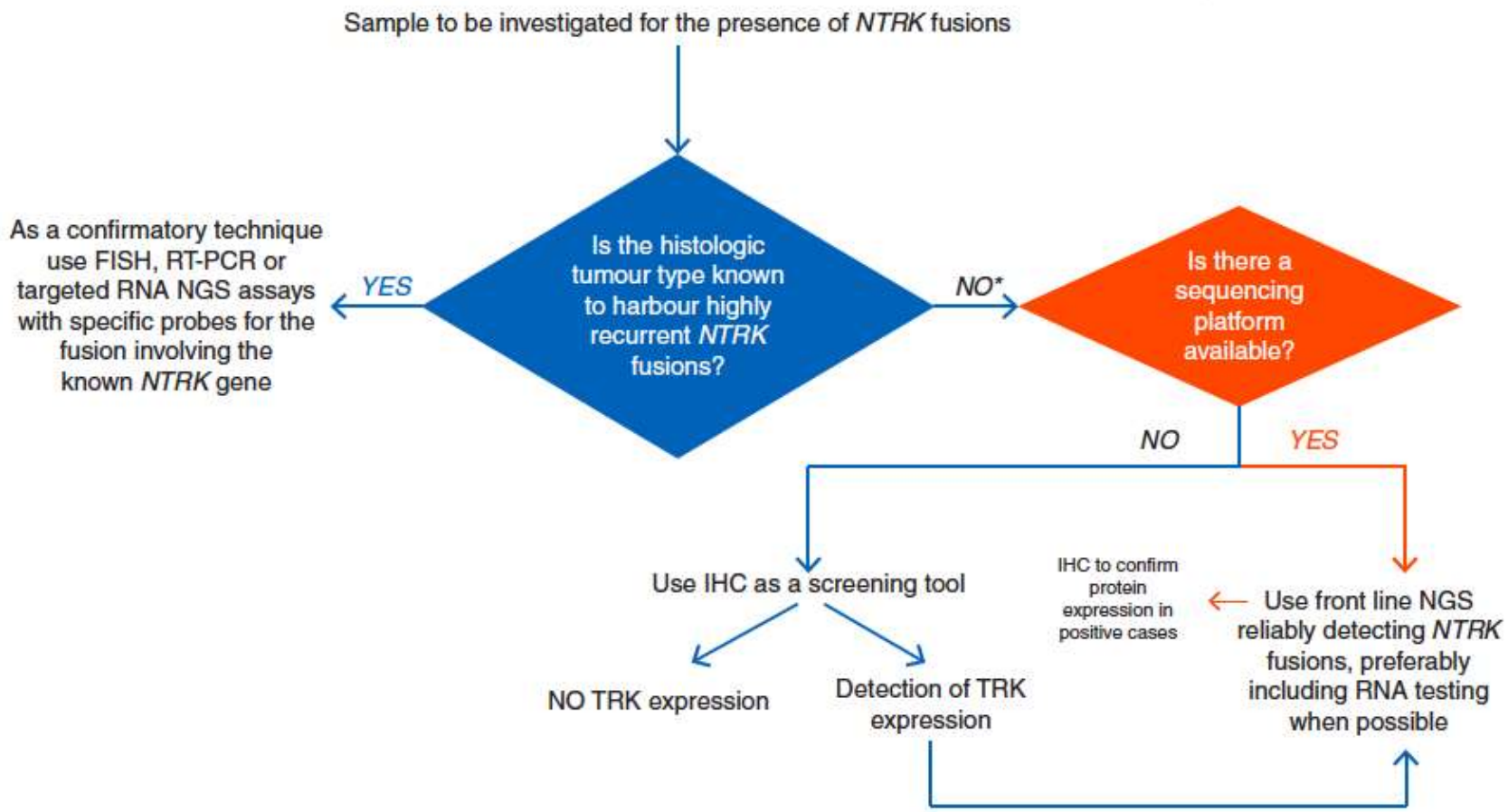
NTRK Rearrangements

- NTRK1 and NTRK2 rearrangements occur in 3 to 4% NSCLC
- CD74, MPRIP,SQSTM1, TRIM24 are their known fusion partners

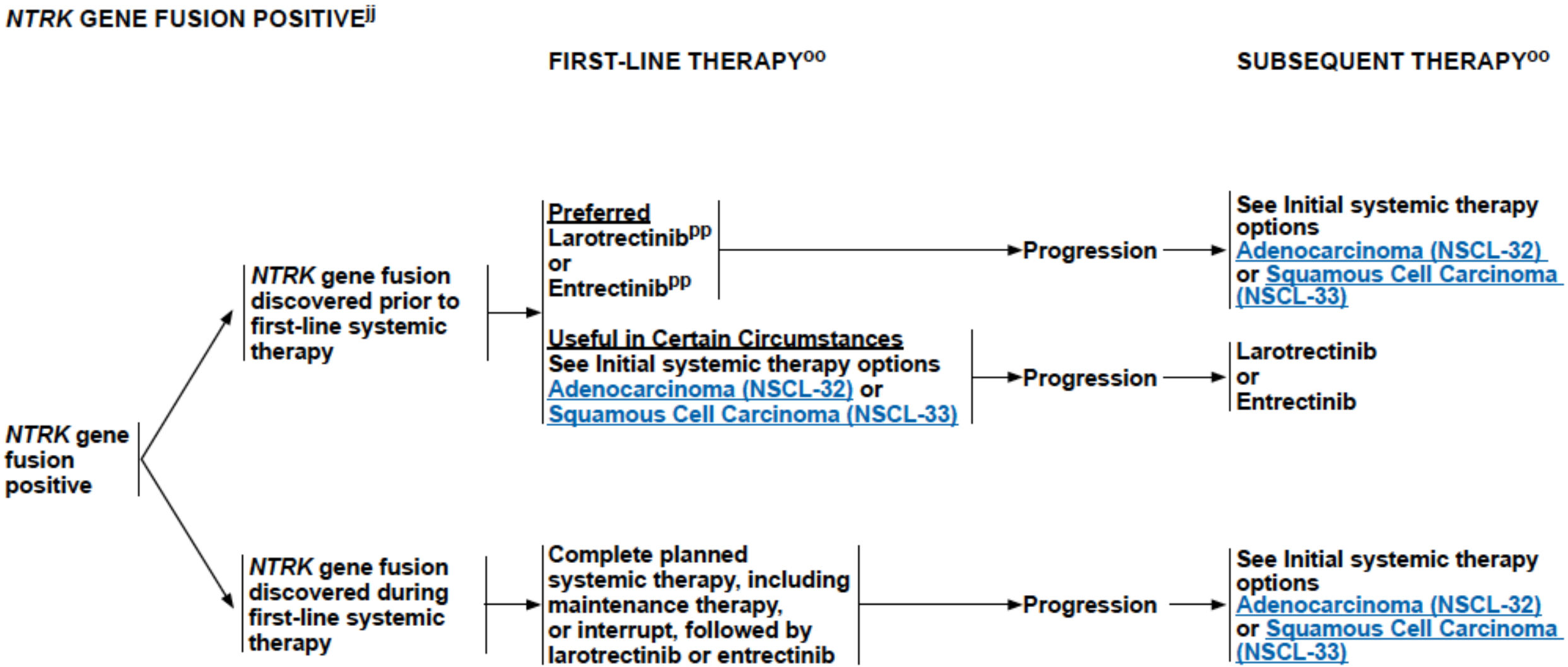


- *NTRK* gene fusions occur regardless of gender, age, and smoking history
- Mutually exclusive with *KRAS, EGFR, ALK, ROS1*, or other known drivers

NTRK Rearrangements-diagnosis(ESMO 2019)



FDA approved in MAY 2018



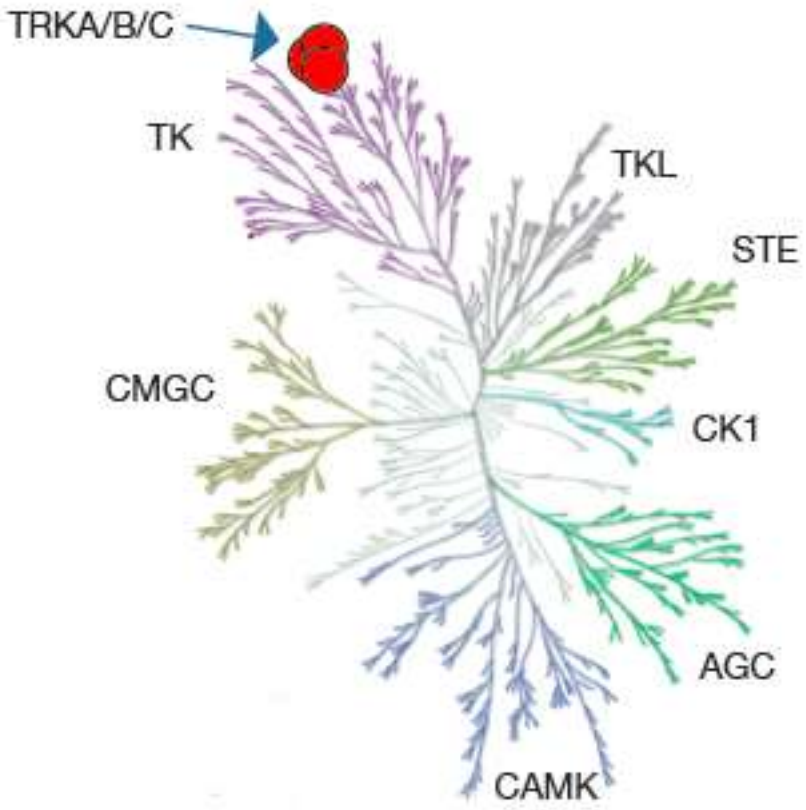
ORIGINAL ARTICLE

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and D.M. Hyman

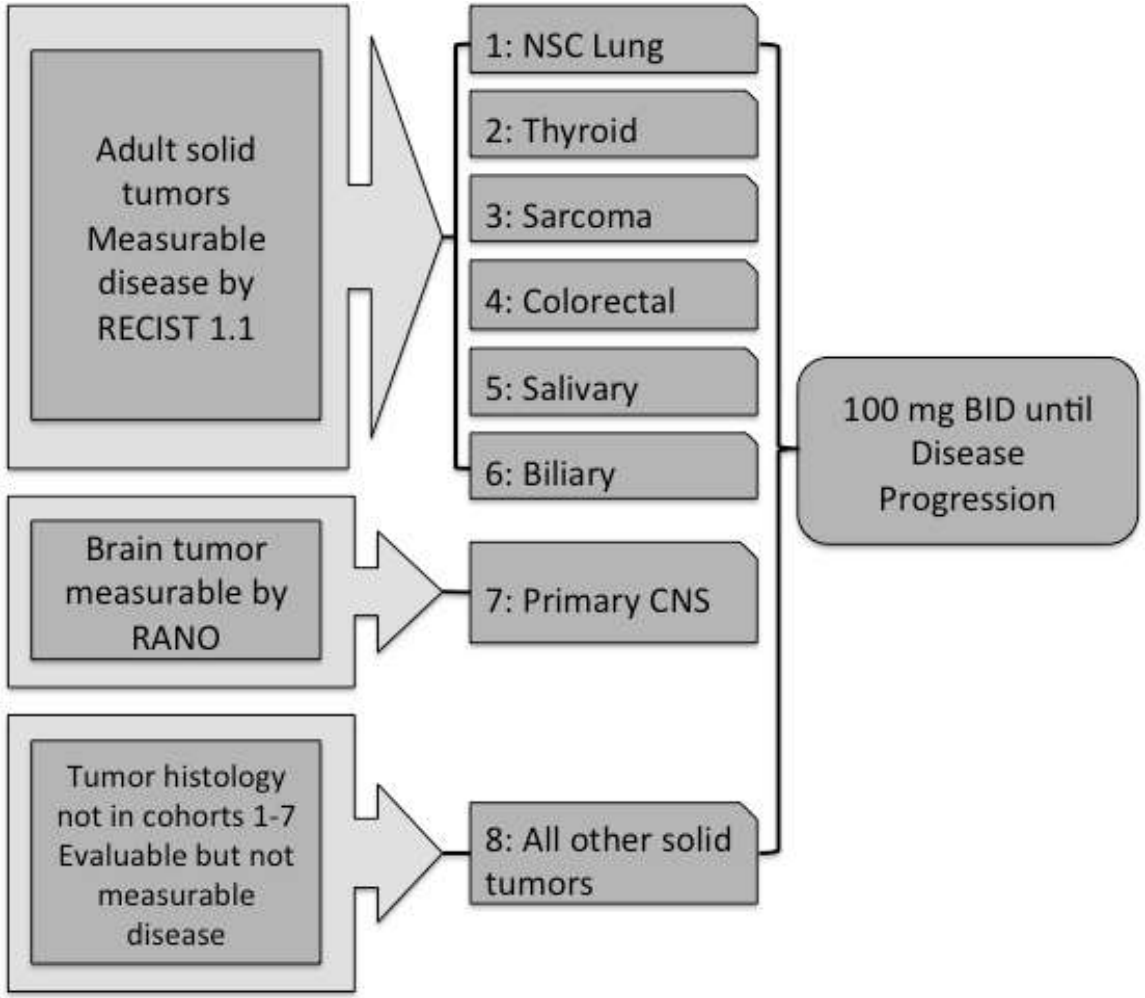
larotrectinib is potent and highly selective small-molecule inhibitor

of all three TRK proteins



Study design

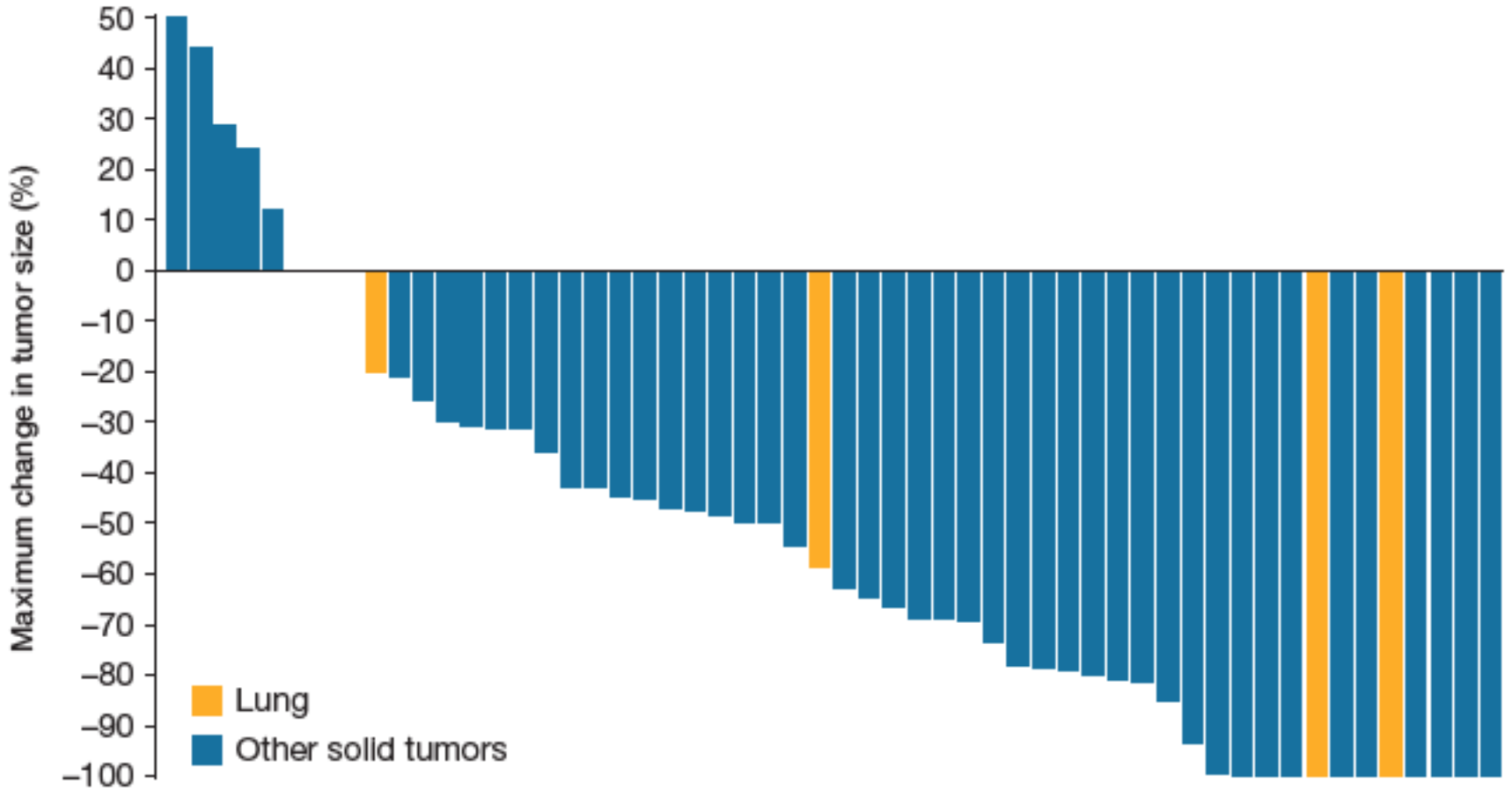
- The program involved three clinical studies:
- Phase 1 study involving adults,
- Phase 1–2 study involving children, and a
- Phase 2 “basket” study involving adolescents & adults
- For the primary analysis, 55 patients (aged 4 months to 76 years) with TRK fusion cancer detected by molecular profiling, were enrolled across 3 phases
- ORR is 75% regardless of tumor type
- Only 4 patients have lung cancer



Methodology

- Eligibility criteria - locally advanced or metastatic solid tumor, ECOG score of 0–3, adequate major organ function and no prior TRK-inhibitor therapy
- Patients received larotrectinib at 100 mg (BID) orally, until disease progression occurred or a lack of clinical benefit
- Tumor response was assessed by investigators and by independent radiology review at baseline and every 8 weeks for 1 year, and every 12 weeks thereafter until disease progression, according to RECIST v 1.1.
- Safety data were recorded until 28 days after the last dose of larotrectinib

	Gene fusion	Measurable disease	Best response	DOR (months)	Ongoing treatment
Patient 1	*ETV6-NTRK3*	No	SD*	>14.78*	Yes
Patient 2	*TPR-NTRK1*	Yes	PR	8.21	No**
Patient 3	*IRF2BP2-NTRK1*	No	CR	>20.27	Yes
Patient 4	*SQSTM1-NTRK1*	Yes	PR	>12.88	No



Durable responses (ranging from 8.21 to >20.27 months) were seen in 3 of 4 patients

Table 2: Safety profile of larotrectinib in overall study population (n=55)

	Adverse events regardless of attribution					Treatment-related adverse events		
	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade
	Percent of patients with event							
Increased ALT or AST	31	4	7	0	42	5	0	38
Fatigue	20	15	2	0	36	0	0	16
Vomiting	24	9	0	0	33	0	0	11
Dizziness	25	4	2	0	31	2	0	25
Nausea	22	7	2	0	31	2	0	16
Anemia	9	9	11	0	29	2	0	9
Diarrhea	15	13	2	0	29	0	0	5
Constipation	24	4	0	0	27	0	0	16
Cough	22	4	0	0	25	0	0	2
Increased body weight	11	5	7	0	24	0	0	11
Dyspnea	9	9	0	0	18	0	0	2
Headache	13	4	0	0	16	0	0	2
Pyrexia	11	2	2	2	16	0	0	0
Arthralgia	15	0	0	0	15	0	0	2
Back pain	5	9	0	0	15	0	0	0
Decreased neutrophil count	0	7	7	0	15	2	0	9

AST, aspartate aminotransferase; ALT, alanine aminotransferase; Modified from: Drilon et al. *N Engl J Med*. 2018; 378:731-39.
The adverse events listed here are those that occurred in at least 15% patients, regardless of attribution. The relatedness of the treatment to adverse events was determined by the investigators.

- 55 patients the majority of AE (93%) were grade 1 or 2, with few grade 3 or 4 events reported
- Adverse events leading to dose reduction occurred in only 15% of patients
- In NSCLC all have grade 1 adverse events reported, except for one grade 2 adverse event (decreased neutrophil count)

Results

- Three different categories of mutations were observed after larotrectinib progression and may represent resistance mechanisms, including substitutions in the solvent front (NTRK1 p.G595R, NTRK3 p.G623R), the gatekeeper position (NTRK1 p.F589L), and the xDFG position (NTRK1 p. G667S, NTRK3 p.G696A)
- FDA approved in MAY 2018

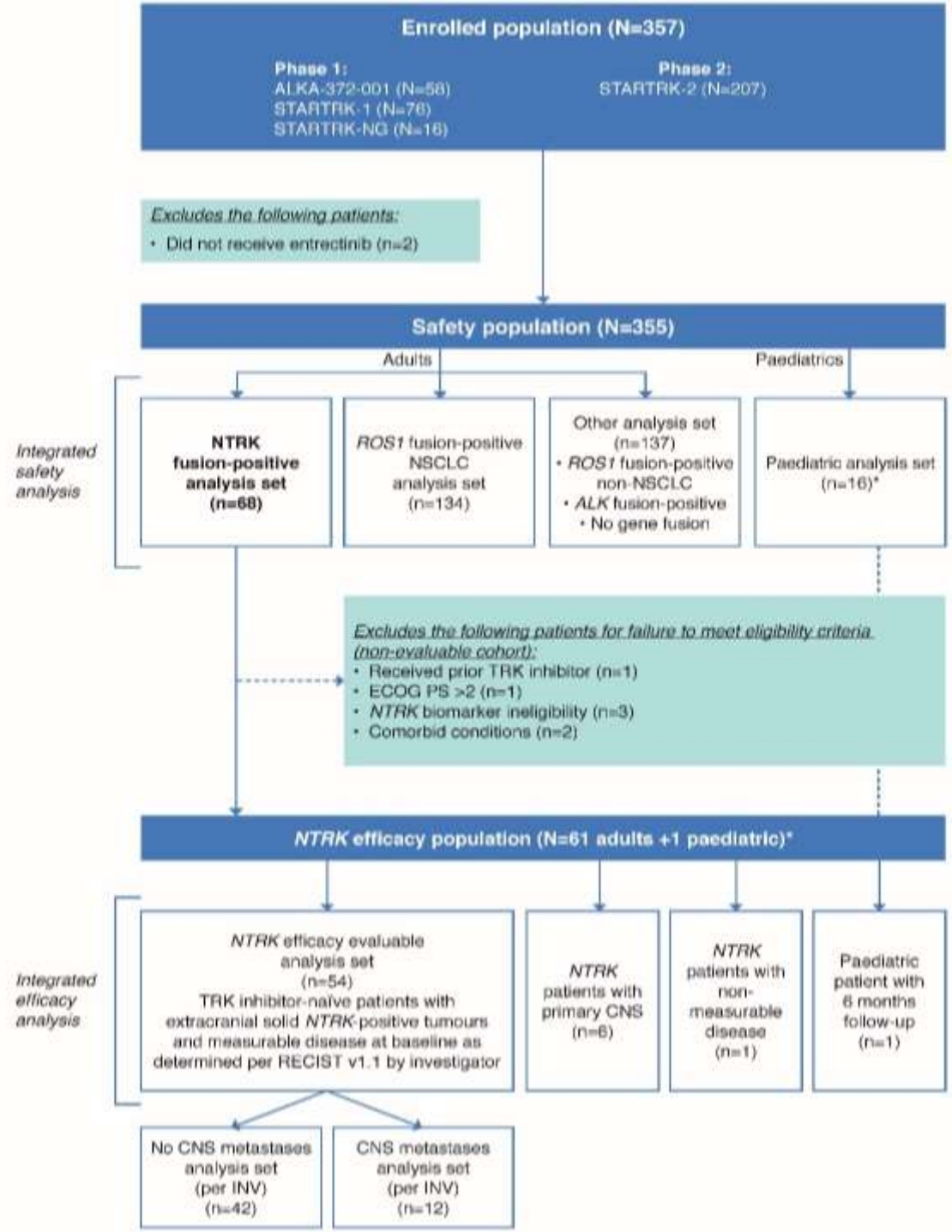
Entrectinib in patients with advanced or metastatic *NTRK* fusion-positive solid tumours: integrated analysis of three phase 1–2 trials

Robert C Doebele, Alexander Drilon*, Luis Paz-Ares, Salvatore Siena, Alice T Shaw, Anna F Farago, Collin M Blakely, Takashi Seto,*

- Entrectinib is a multikinase inhibitor against ROS1 (in addition to tropomyosin receptor kinase [TRK] A, B, and C and ALK
- Effectively cross the blood–brain barrier and be retained in the CNS
- Integrated database comprised the pivotal datasets of three, ongoing phase 1 or 2 clinical trials (ALKA-372-001,STARTRK-1, and STARTRK-2)

METHODOLOGY

- Patients aged 18 years or older
- Metastatic or locally advanced NTRK fusion-positive solid tumours.
- ECOG of 0–2 and could have received
- Previous anticancer therapy (except previous TRK inhibitors).
- Entrectinib orally 600 mg once per day in a capsule
- Primary endpoints- objective response and duration of response


Enrolled population (N=357)
Phase 1:
ALKA-372-001 (N=58)
STARTRK-1 (N=76)
STARTRK-NG (N=16)
Phase 2:
STARTRK-2 (N=207)
Excludes the following patients:
• Did not receive entrectinib (n=2)
Safety population (N=355)
Adults
Paediatrics
Integrated safety analysis
NTRK fusion-positive analysis set (n=68)
ROS1 fusion-positive NSCLC analysis set (n=134)
Other analysis set (n=137)
• ROS1 fusion-positive non-NSCLC
• ALK fusion-positive
• No gene fusion
Paediatric analysis set (n=16)*
Excludes the following patients for failure to meet eligibility criteria (non-evaluable cohort):
• Received prior TRK inhibitor (n=1)
• ECOG PS >2 (n=1)
• NTRK biomarker ineligibility (n=3)
• Comorbid conditions (n=2)
NTRK efficacy population (N=61 adults +1 paediatric)*
Integrated efficacy analysis
NTRK efficacy evaluable analysis set (n=54)
TRK inhibitor-naive patients with extracranial solid NTRK-positive tumours and measurable disease at baseline as determined per RECIST v1.1 by investigator
NTRK patients with primary CNS (n=6)
NTRK patients with non-measurable disease (n=1)
Paediatric patient with 6 months follow-up (n=1)
No CNS metastases analysis set (per INV) (n=42)
CNS metastases analysis set (per INV) (n=12)

	All patients in *NTRK* gene fusion-positive efficacy-evaluable population (n=54)
Age, years	58 (48–67)
Sex	
Female	32 (59%)
Male	22 (41%)
Race	
White	43 (80%)
Asian	7 (13%)
Other	4 (7%)
Eastern Cooperative Oncology Group performance status	
0	23 (43%)
1	25 (46%)
2	6 (11%)
Previous lines of systemic therapy	
0	20 (37%)
1	11 (20%)
2	14 (26%)
3	4 (7%)
≥4	5 (9%)
Previous treatment*	
Chemotherapy	46 (85%)
Targeted therapy	13 (24%)
Hormonal therapy	9 (17%)
Immunotherapy	7 (13%)
CNS metastases at baseline	
Yes	12 (22%)
No	42 (78%)
Previous radiotherapy to the brain	
Yes	7 (13%)
No	47 (87%)
Time from end of previous radiotherapy of the brain to first dose of entrectinib†	
<2 months	2 (29%)
2 to <6 months	4 (57%)
≥6 months	1 (14%)

All patients in *NTRK* gene fusion-positive efficacy-evaluable population (n=54)
(Continued from previous column)
Tumour type
Sarcoma‡ 13 (24%)
NSCLC 10 (19%)
Mammary analogue secretory carcinoma (salivary) 7 (13%)
Breast 6 (11%)
Thyroid 5 (9%)
Colorectal 4 (7%)
Neuroendocrine 3 (6%)
Pancreatic 3 (6%)
Gynaecological 2 (4%)
Ovarian 1 (2%)
Endometrial 1 (2%)
Cholangiocarcinoma 1 (2%)

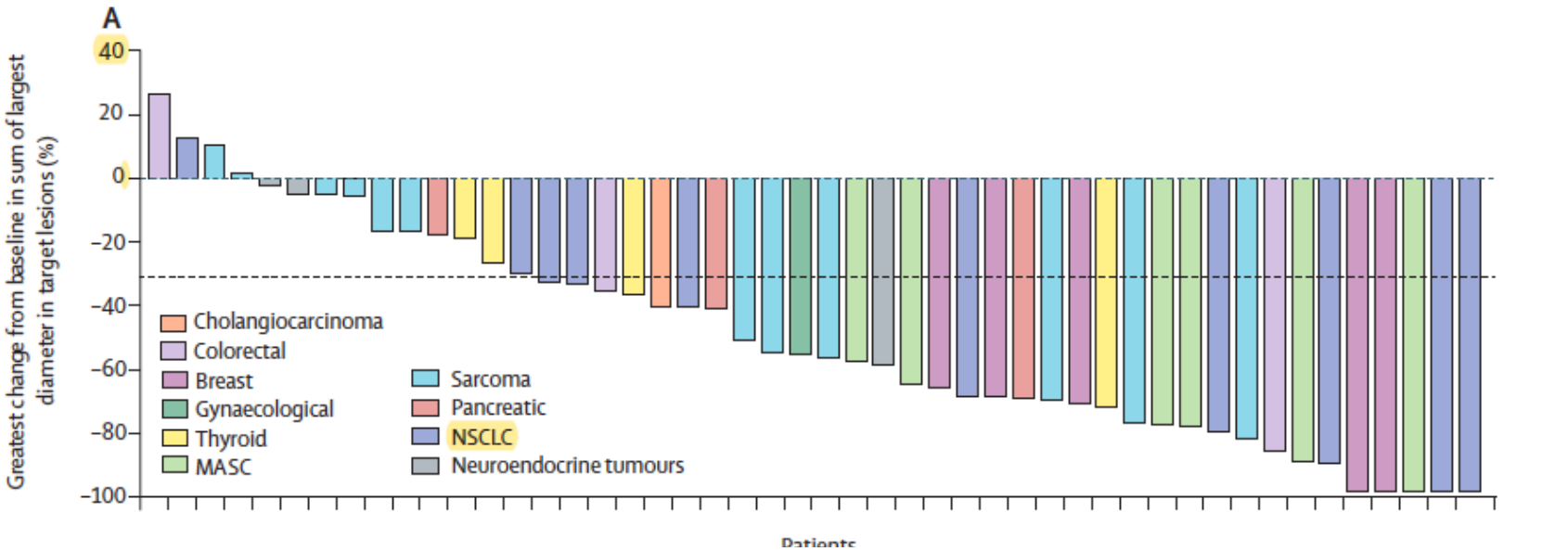
	Efficacy-evaluable population* (n=54)	Patients with baseline CNS disease† (n=12)	Patients with no baseline CNS disease*† (n=42)
Proportion of patients achieving a response	31 (57%)	6 (50%)	25 (60%)
Best overall response			
Complete response	4 (7%)	0	4 (10%)
Partial response	27 (50%)	6 (50%)	21 (50%)
Stable disease	9 (17%)	4 (33%)	5 (12%)
Progressive disease	4 (7%)	0	4 (10%)
Non-complete response or progressive disease	3 (6%)	0	3 (7%)
Missing or unevaluable‡	7 (13%)	2 (17%)	5 (12%)
Median duration of response, months	10·4 (7·1–NE)	NE	12·9 (7·1–NE)
Median progression-free survival, months	11·2 (8·0–14·9)	7·7 (4·7–NE)	12·0 (8·7–15·7)

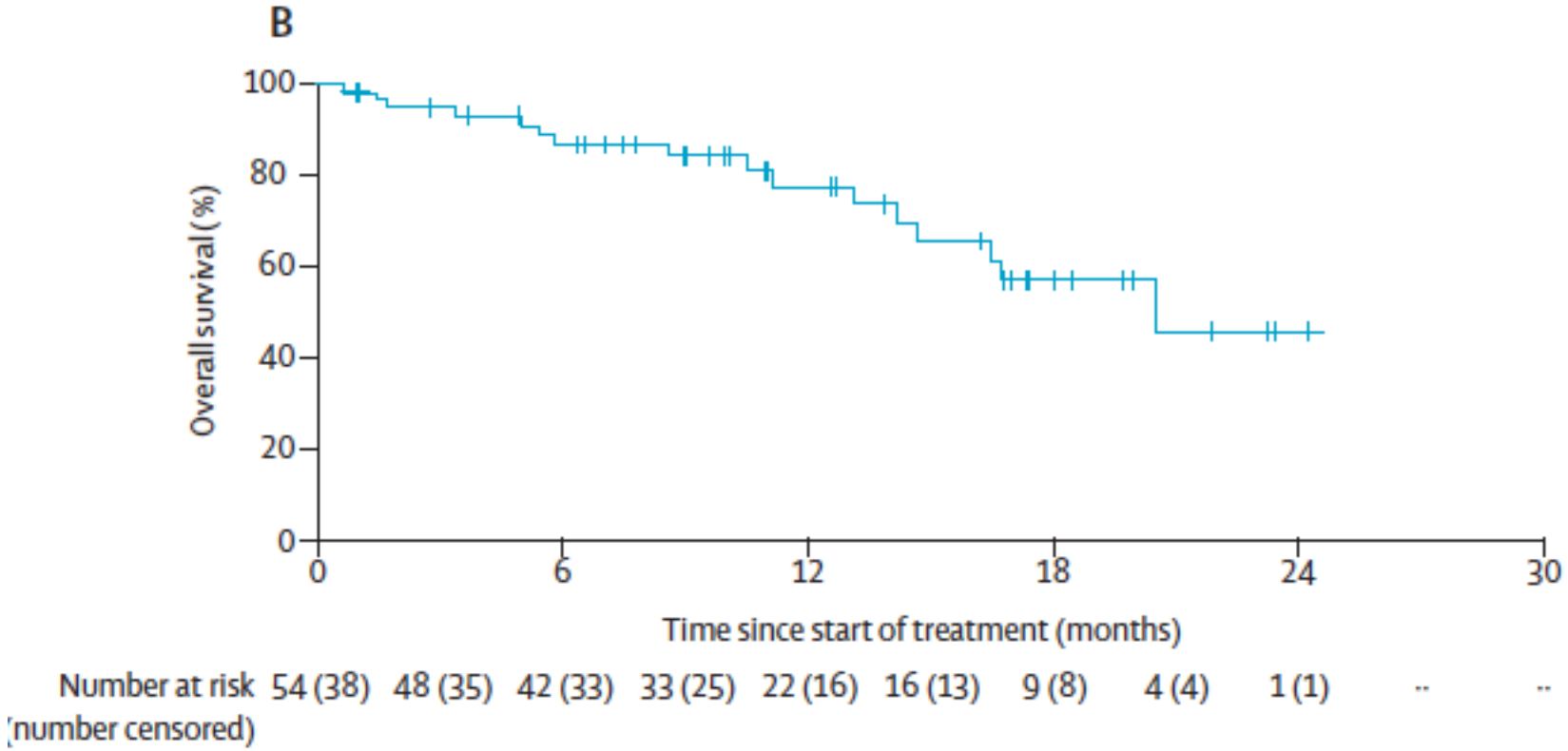
Data are n (%) or median (95% CI). NE=not estimable. *Systemic response. †CNS disease status determined by the investigator. ‡Missing or unevaluable included patients with no post-baseline scans available, missing subsets of scans at all time points, or patients who discontinued before obtaining adequate scans to evaluate or confirm response.

Table 2: **Activity outcomes**

In 54 patients

- ORR of 57.4%,
- Median PFS of 11.2m
- Median OS of 20.9m





- Median follow-up was 12.9 months 16 (30%) of 54 patients had died
- Median overall survival was 21 months (95% CI 14.9 to not estimable)

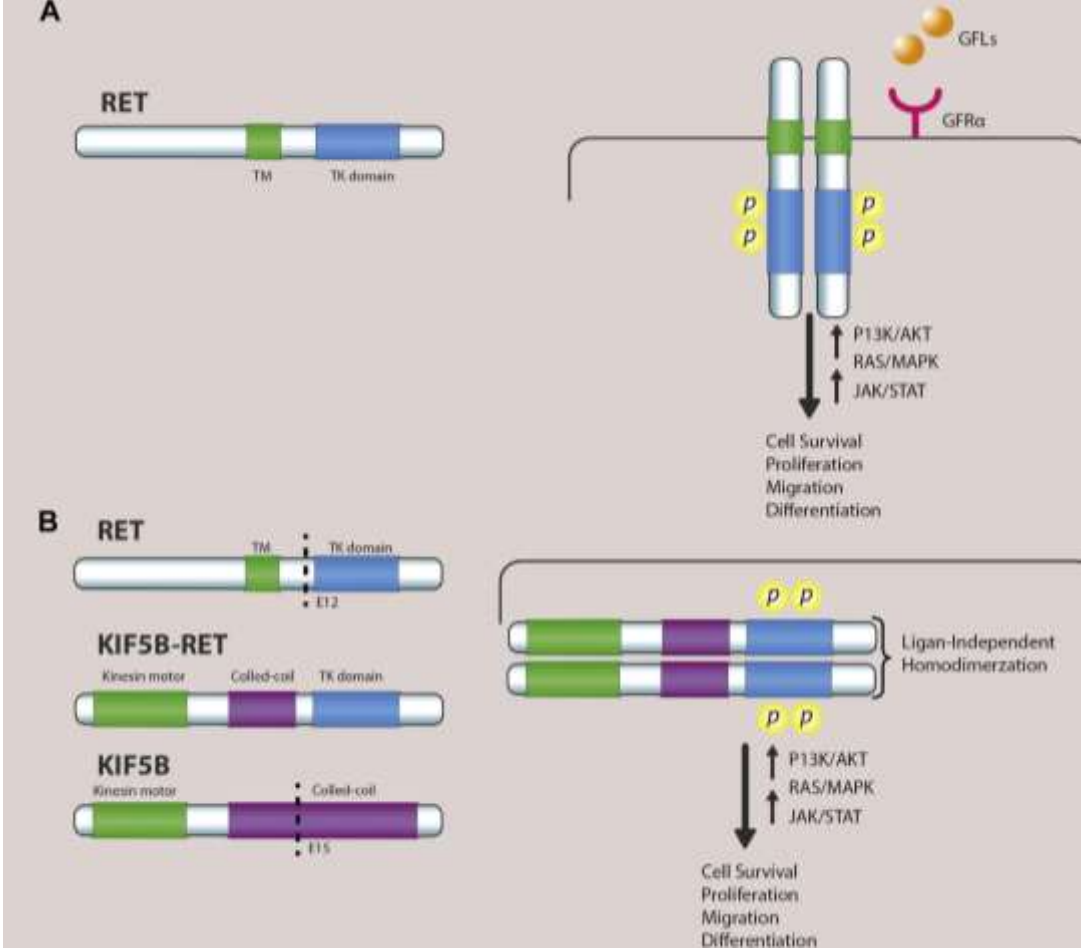
Adverse events

- Most common grade 3 or 4 treatment-related adverse events in both safety populations were increased weight (seven [10%] of 68 patients in the *NTRK* fusion-positive safety population and in 18 [5%] of 355 patients in the overall safety-evaluable population) and anaemia (8 [12%] and 16 [5%])
- The most common serious treatment-related adverse events were nervous system disorders (three [4%] of 68 patients and ten [3%] of 355 patients)
- On the basis of these and other data, entrectinib was granted accelerated approval by the US FDA in August, 2019

Targetable Driver genes	Incidence	Targeted Agent	Clinical Trials	Phase	Patients Included	Results	Approved or Recommended by
NTRK rearrangements	3–4%	Larotrectinib (LOXO-101)[92]	NCT02576431	II	NTRK fusion-positive solid tumors	n=55, ORR 75% regardless of tumor type, mDOR and mPFS were not reached.	NCCN, FDA, EMA
		LOXO-195	NCT03215511	I/II	NTRK fusion cancers treated with a prior TRK inhibitor	Ongoing	
		Entrectinib (RXDX-101)[96]	ALKA-372-001 (EudraCT 2012–0001), STARTRK-1 (NCT02097810), STARTRK-2 (NCT02568267)	I/II	NTRK fusion-positive solid tumors	n=54, ORR 57.4%, mPFS 11.2 mo, mOS 20.9 mo	NCCN, FDA, EMA

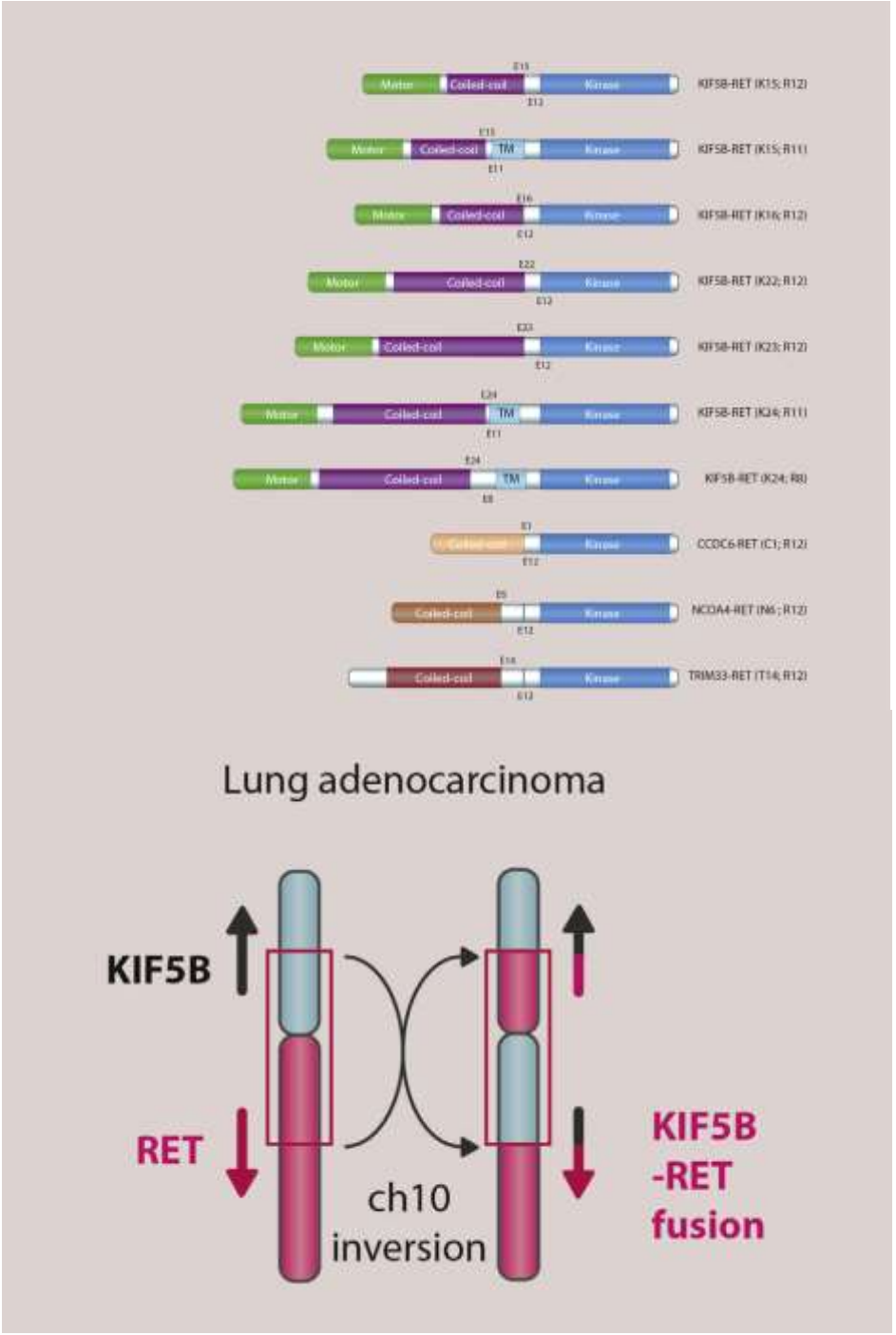
RET

- RET - chromosome 10q11.2
- Receptor tyrosine kinase
- 0.6% to 0.9% of NSCLCs & 1.2% to 2% of adeno
- In NSCLC, at least 12 different gene partners have been described for RET, including KIF5B, CCDC6,NCOA4, MYO5C, EPHA5, TRIM33, CLIP1, ERC1,PICALM, FRMD4A, RUFY2, TRIM24



RET

- Fusion of the tyrosine kinase domain gene with KIF5B (the most common, at (70%-90%)
- RET rearrangement is mutually exclusive
- Early lymph node metastases & advanced disease
- Usually younger & equal sex distribution.
- Histologic subtypes -mucinous/signet ring
- RET rearrangements can be detected by FISH, NGS, and
- RT-PCR, can be detected by IHC



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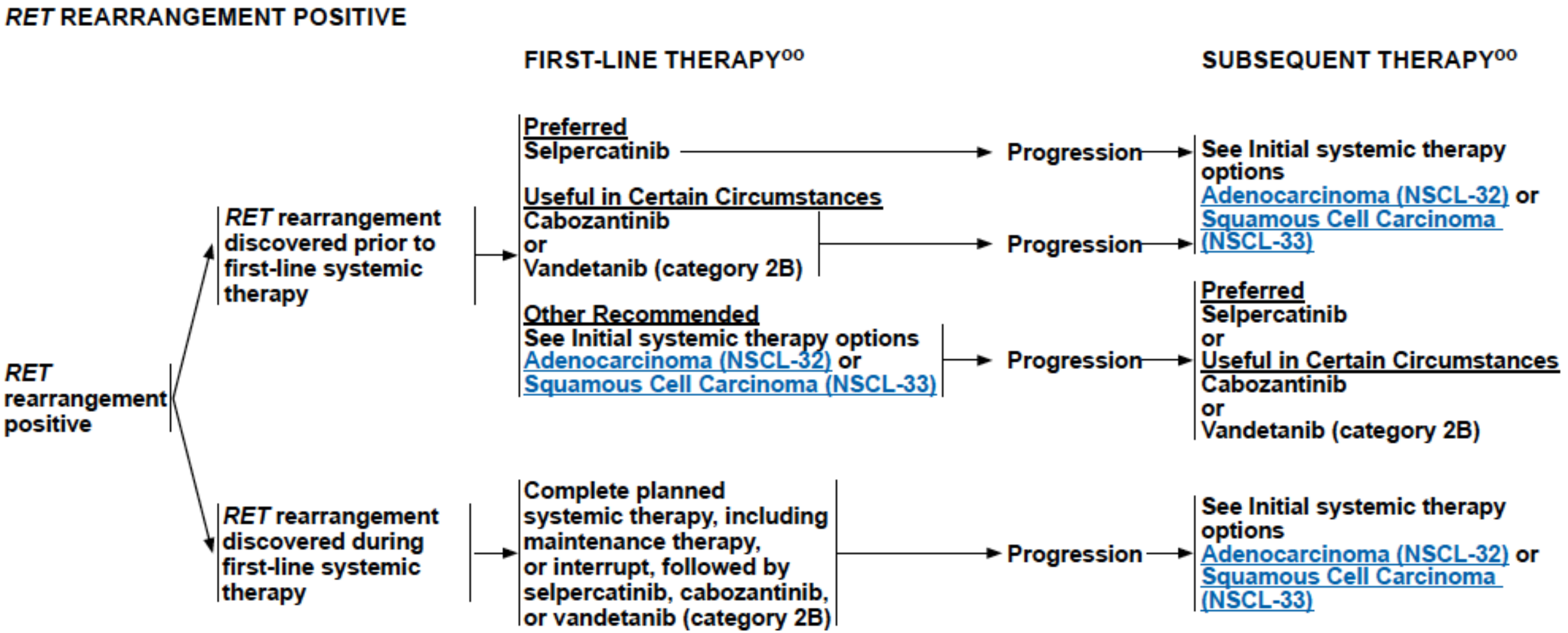

RET REARRANGEMENT POSITIVE
FIRST-LINE THERAPY[oo]
SUBSEQUENT THERAPY[oo]
RET rearrangement positive
RET rearrangement discovered prior to first-line systemic therapy
RET rearrangement discovered during first-line systemic therapy
Preferred
Selpercatinib
Progression
See Initial systemic therapy options
Adenocarcinoma (NSCL-32) or
Squamous Cell Carcinoma (NSCL-33)
Useful in Certain Circumstances
Cabozantinib
or
Vandetanib (category 2B)
Progression
Other Recommended
See Initial systemic therapy options
Adenocarcinoma (NSCL-32) or
Squamous Cell Carcinoma (NSCL-33)
Progression
Preferred
Selpercatinib
or
Useful in Certain Circumstances
Cabozantinib
or
Vandetanib (category 2B)
Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by selpercatinib, cabozantinib, or vandetanib (category 2B)
Progression
See Initial systemic therapy options
Adenocarcinoma (NSCL-32) or
Squamous Cell Carcinoma (NSCL-33)

Response to Cabozantinib in Patients with *RET* Fusion-Positive Lung Adenocarcinomas

Alexander Drilon[1], Lu Wang[2], Adnan Hasanovic[5], Yoshiyuki Suehara[4], Doron Lipson[6], Phil Stephens[6], Jeffrey Ross[6], Vincent Miller[6], Michelle Ginsberg[3], Maureen F. Zakowski[2], Mark G. Kris[1], Marc Ladanyi[4], and Naiyer Rizvi[1]

- Cabozantinib, a multi-tyrosine kinase inhibitor and potent inhibitor of RET, was chosen on the basis of the observation that the drug was most effective at inhibiting proliferation in a CCDC6-RET (RET/PTC1) fusion-positive papillary thyroid cancer cell line (IC 50 , 0.06 µmol/L) compared with vandetanib, sunitinib, and axitinib
- 3 patients with RETrearranged NSCLC were treated with cabozantinib
- 2 of these patients experienced partial responses by RECIST 1.1 criteria & the third had prolonged stable disease

Cabozantinib in patients with advanced *RET*-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial

Alexander Drilon, Natasha Rekhtman, Maria Arcila, Lu Wang, Andy Ni, Melanie Albano, Martine Van Voorthuysen, Romel Somwar, Roger S Smith, Joseph Montecalvo, Andrew Plodkowski, Michelle S Ginsberg, Gregory J Riely, Charles M Rudin, Marc Ladanyi, Mark G Kris

- Cabozantinib is a multikinase inhibitor with low nanomolar (IC50 5·2 nM) activity against RET, in addition to its activity against ROS1, MET, VEGFR2, AXL, TIE2 & KIT
- open-label, phase 2, singlearm trial ,single-centre in USA
- Aged 18 years or older
- Metastatic or unresectable lung cancers with RET rearrangement
- KPS greater than 70 & adequate haematological, renal, and hepatic function
- Measurable disease by the RECIST

Methodology

- Due to anti-VEGFR2 activity, we excluded patients if they had a history of significant bleeding, cavitary pulmonary lesions, tumours invading the tracheobronchial tree or major blood vessels, or a gastrointestinal disorder associated with a high risk of perforation or fistula formation
- Cabozantinib in tablet form at a starting dose of 60 mg orally once per day
- Patients were treated in 28-day cycles, until disease progression or unacceptable toxicity
- CT of the chest, abdomen, and pelvis at Baseline, 4 weeks after cabozantinib initiation, and every 8 weeks after the first response assessment scan (ie, we did scans at weeks 4, 12, 20, and so forth)
- RET-rearranged NSCLC screened by FISH or NGS

	Patients with *RET*-rearranged lung cancers who received cabozantinib (n=26)
Age	59 (54–67)
Sex	
Male	11 (42%)
Female	15 (58%)
Race	
White	19 (73%)
Asian	6 (23%)
African American	1 (4%)
Karnofsky performance status	
100	0
90	7 (27%)
80	19 (73%)
Cigarette smoking history	
Never smoker	17 (65%)
>0–15 pack years	8 (31%)
>15 pack years	1 (4%)
Previous chemotherapy regimens	
0	6 (23%)
1	13 (50%)
≥2	7 (27%)
Adenocarcinoma	26 (100%)
Fusion type	
KIF5B-RET	16 (62%)
CCDC6-RET	1 (4%)
TRIM33-RET	1 (4%)
CLIP1-RET	1 (4%)
ERC1-RET	1 (4%)
Unknown (FISH-positive)	6 (23%)
Brain metastases at baseline	
Not present	16 (62%)
Present, treated*	5 (19%)
Present, untreated, and asymptomatic	5 (19%)

Results

- 7 partial responses [overall response rate (ORR) 28%]
- ORR in patients with KIF5B-RET-rearranged NSCLC was 20%
- 50% in patients with different known RET fusion genes
- Median progression-free survival (mPFS) was 5.5 months
- Median overall survival (mOS) was 9.9 months

Adverse effects

- Treatment-related adverse events were predominantly grade 1 or grade 2, overall toxicity rate of 96.2%
- The most common treatment-related adverse events of any grade were increased ALT, AST, hypothyroidism, diarrhea, palmar plantar erythrodysesthesia, and skin hypopigmentation.
- The most common grade 3 AE-lipase elevation in four patients (15%), increased ALT in 2 (8%),decreased platelet count in 2 (8%) & hypophosphatemiain 2 (8%)
- 19 (73%) required a cabozantinib dose reduction grade 2 or grade 3 AE
- The most common reasons for dose reduction included palmar plantar erythrodysesthesia in seven patients (37%), fatigue in three patients (16%), and diarrhea in two patients (11%)

Vandetanib in patients with previously treated *RET*-rearranged advanced non-small-cell lung cancer (LURET): an open-label, multicentre phase 2 trial

Kiyotaka Yoh, Takashi Seto, Miyako Satouchi, Makoto Nishio, Noboru Yamamoto, Haruyasu Murakami, Naoyuki Nogami, Shingo Matsumoto, Takashi Kohno, Koji Tsuta, Katsuya Tsuchihara, Genichiro Ishii, Shogo Nomura, Akihiro Sato, Atsushi Ohtsu, Yuichiro Ohe, Koichi Goto

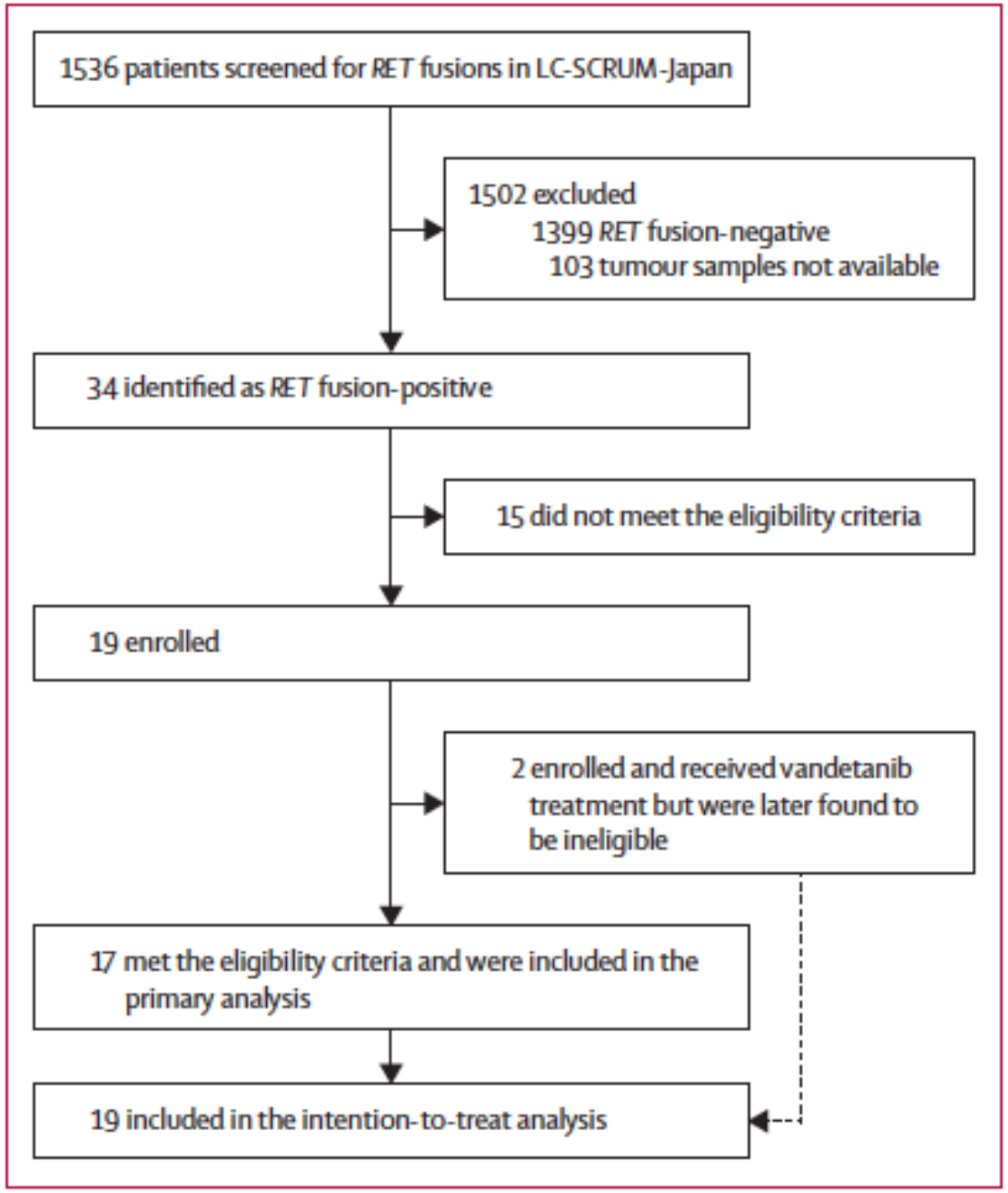
- Vandetanib is an oral receptor tyrosine kinase inhibitor that potently inhibits RET, EGFR, and VEGFR
- Preclinical studies have shown the antitumour activity of the RET inhibitor vandetanib in a lung adenocarcinoma cell line with the CCDC6-RET fusion
- 2 case reports showed tumour shrinkage after vandetanib treatment in patients with RET-rearranged NSCLC

Methodology

- Multicentre , single-arm, phase 2 trial,
- **Eligible Criteria**
- locally advanced or metastatic non-squamous NSCLC with RET rearrangement without EGFR mutations,
- Received one or more previous chemotherapy treatments
- Age 20 years or older
- ECOG of 2 or less,
- Adequate haematological and end-organ function, and
- Measurable disease according to (RECIST) version 1.1

Methodology

- Vandetanib was administered orally at a standard dose of 300 mg once daily in continuous 28-day cycles.
- Treatment continued til the identifi cation of RECIST-defineddisease progression by the investigator, unacceptable toxicity, death, or withdrawal from the study
- The tumour response was assessed on days 29, 57, 85, and every 8 weeks
- Primary endpoint –ORR
- Secondary endpoints- progression-free survival, disease control, response duration, overall survival, safety, and response to previous anticancer therapy before enrolment



	All patients (N=19)
Age (years)	59 (41–80)
Sex	
Male	5 (26%)
Female	14 (74%)
Ethnic origin	
East Asian	19 (100%)
Smoking history	
Never	13 (68%)
Former smoker	6 (32%)
Current smoker	0
Histology	
Adenocarcinoma	19 (100%)
Stage, TNM 2007	
3B	1 (5%)
4	18 (95%)
ECOG PS	
0	9 (47%)
1	8 (42%)
2	2 (11%)
Number of previous chemotherapy regimens	
1	7 (37%)
2	4 (21%)
≥3	8 (42%)
Type of *RET* fusion	
KIF5B-RET	10 (53%)
CCDC6-RET	6 (31%)
Unknown	3 (16%)*

- ORR - 53%
- Median PFS-4.7 months.
- OS rate at 12 months - 47%
- Median OS - 11.1 months

- The treatment response and survival outcome were much higher in patients with the CCDC6-RET fusionsubtype, with 83% ORR and mPFS of 8.3 months Vs 20% and 2.9 months, with KIF5BRET fusion variant

	All patients (N=19)	*KIF5B-RET* (N=10)	*CCDC6-RET* (N=6)	Unknown (N=3)
Tumour response				
Objective response	9 (47%; 24–71)	2 (20%; 3–56)	5 (83%; 36–100)	2 (67%; 9–99)
Disease control	17 (90%; 67–99)	9 (90%; 55–100)	6 (100%; 54–100)	2 (67%; 9–99)
Progression-free survival				
Median (months)	4·7 (2·8–8·5)	2·9 (1·1–15·7)	8·3 (4·7–8·5)	4·7 (1·0–10·9)
Overall survival				
Median (months)	11·1 (9·4–NR)	11·1 (3·0–NR)	NR (9·9–NR)	11·0 (9·4–13·5)
12 month (%)	47 (20–69)	42 (11–71)	67 (5–95)	33 (1–77)

Data are n (%; 95% CI), median (95% CI), or % (95% CI). NR=not reached. The response was assessed by an independent radiology review committee.

Table 2: **Efficacy by *RET* fusion type**

- 4/19 (21%) had an adverse event leading to the discontinuation of vandetanib
- 2/19 had rashes, and one patient each had pneumonitis and corneal opacity.
- 16 patients (84%) required a dose
- interruption because of an adverse event.
- A dose reduction in 10/19 (53%)
- MC AE were rash acneiform and HTN
- Serious AE were observed in two patients (11%) (total of three events: bacterial pneumonia [33%], prolonged QT corrected interval [33%], and rash [33%]

	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3 or 4
Hypertension	16 (84%)	0	5 (26%)	11 (58%)	0	11 (58%)
Diarrhoea	15 (79%)	5 (26%)	8 (42%)	2 (11%)	0	2 (11%)
Rash acneiform	12 (63%)	3 (16%)	6 (32%)	3 (16%)	0	3 (16%)
Dry skin	8 (42%)	4 (21%)	3 (16%)	1 (5%)	..	1 (5%)
Prolonged QT corrected interval	8 (42%)	2 (11%)	4 (21%)	1 (5%)	1 (5%)	2 (11%)
Anorexia	6 (32%)	4 (21%)	1 (5%)	1 (5%)	0	1 (5%)
Creatinine increased	6 (32%)	4 (21%)	2 (11%)	0	0	0
Vomiting	5 (26%)	4 (21%)	1 (5%)	0	0	0
Paronychia	5 (26%)	3 (16%)	2 (11%)	0	..	0
Proteinuria	5 (26%)	0	4 (21%)	1 (5%)	0	1 (5%)
Mucositis oral	4 (21%)	4 (21%)	0	0	0	0
Nausea	4 (21%)	2 (11%)	1 (5%)	1 (5%)	..	1 (5%)
Liver dysfunction	4 (21%)	3 (16%)	1 (5%)	0	0	0
Hypoalbuminaemia	4 (21%)	1 (5%)	3 (16%)	0	0	0
Photosensitivity	4 (21%)	2 (11%)	1 (5%)	1 (5%)	0	1 (5%)

Data are number of events (%). The highest grade of event for each patient was reported. Only one patient experienced a grade 4 adverse event (QT corrected interval prolonged).

Table 3: **Treatment-related adverse events that occurred in at least 20% of all treated patients**

Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring *RET* rearrangement: a phase II clinical trial

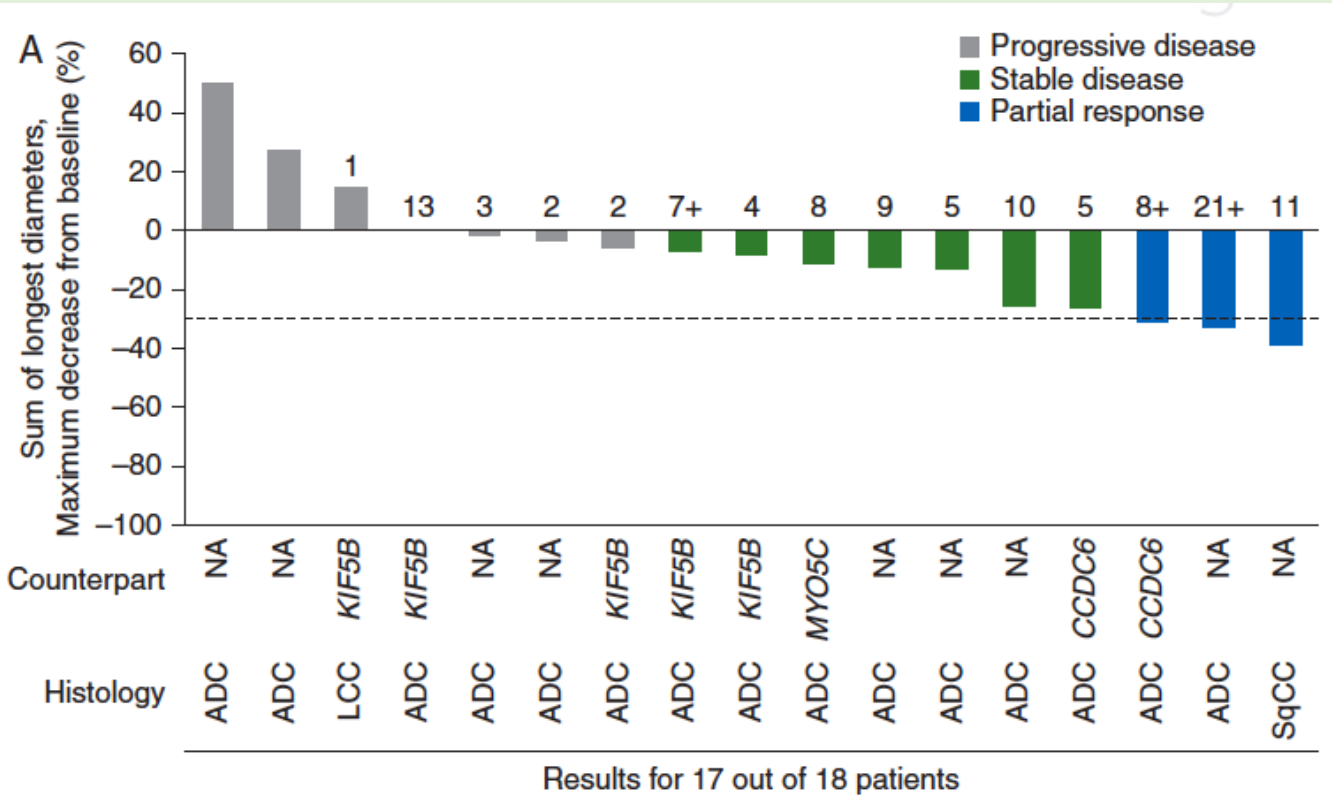
S.-H. Lee[1*‡], J.-K. Lee[2†‡], M.-J. Ahn[1], D.-W. Kim[2], J.-M. Sun[1], B. Keam[2], T. M. Kim[2], D. S. Heo[2], J. S. Ahn[1], Y.-L. Choi[3], H.-S. Min[4], Y. K. Jeon[4] & K. Park[1]

- Multi -center, open-label, phase II clinical trial examining the efficacy and safety of vandetanib
- Vandetanib 300 mg once daily
- Primary endpoint -objective response rate (ORR
- Secondary endpoints - (PFS), disease control rate (DCR), overall survival (OS), and safety

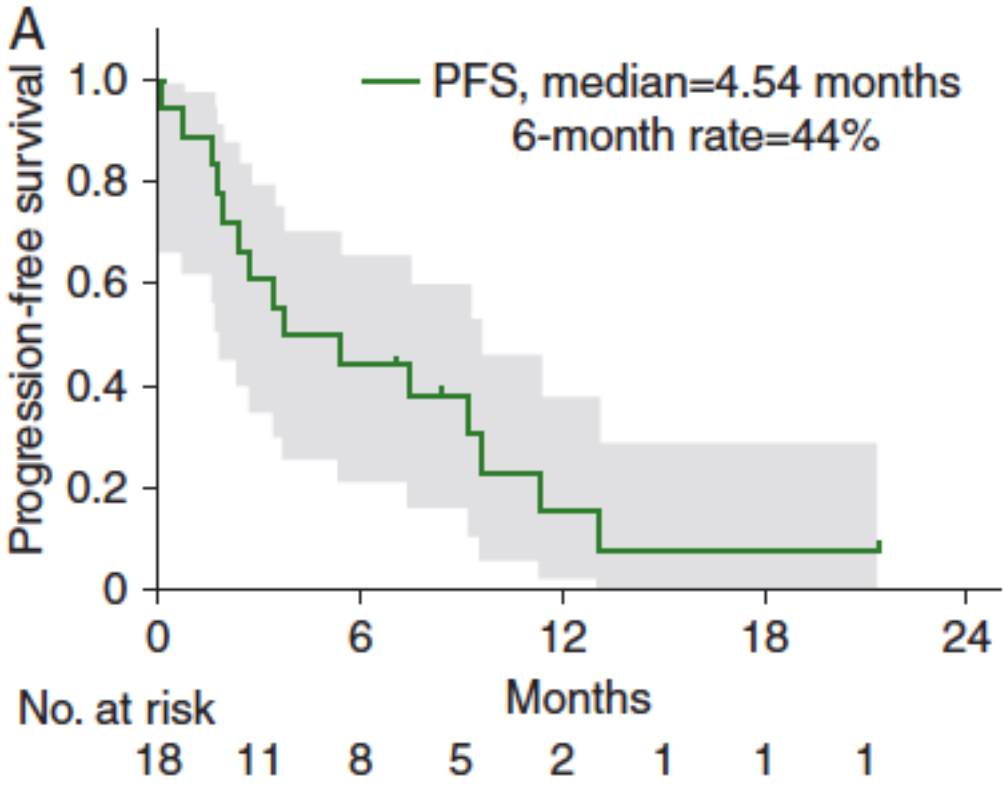
Table 1. Clinical and pathologic characteristics of study patients (n = 18)

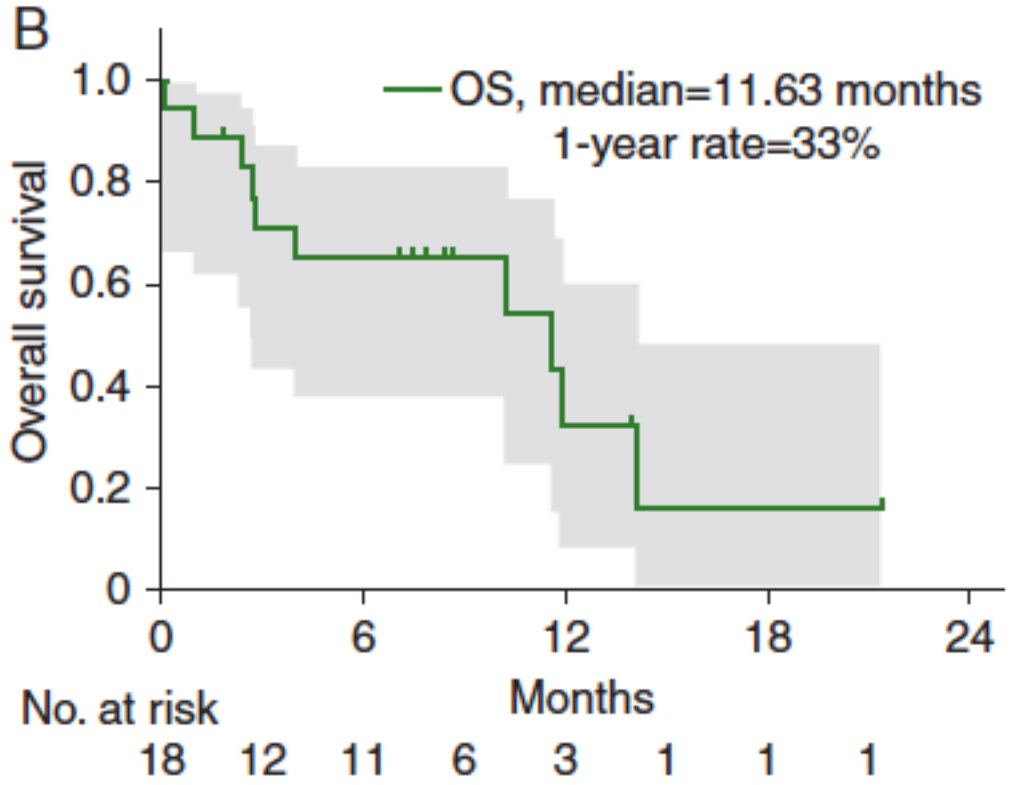
Characteristic	No.	%
Age, years		
Median	56	
Range	36 – 72	
Sex		
Female	6	33
Male	12	67
ECOG performance status		
0	2	11
1	13	72
2	3	17
Smoking history		
Never-smoker	11	61
Ever-smoker[a]	7	39
Tumor histology		
Adenocarcinoma	16	88
Squamous cell carcinoma	1	6
Large cell carcinoma	1	6
Number of prior chemotherapy regimens		
1	5	28
2	2	11
3	6	33
4	2	11
≥ 5	3	17

- 28% - KIF5B-RET rearrangement,
- 11% -CCDC6-RET-positive,
- 56% - unknown RET fusion gene,
- one patient (5%) MYO5C-RET rearrangement



- ORR - 18%
- mPFS - 4.5 months,
- mOS was 11.6 months
- 1-year OS rate was 33%





- Hypertension (16.89%), rash (13.72%), diarrhea (8.44%), acne(5.28%), xerosis (4.22%), and abdominal discomfort (3.17%) were the most frequent adverse events in the study patients
- Five patients experienced adverse events of grade 3:HTN (3, 18%), asymptomatic QTc prolongation in ECG (2, 12%), and elevated serum level of aminotransferases (1, 6%).
- Among these, four patients underwent dose reduction (28%)

Table 2. Summary of adverse events attributable to administration of vandetanib

Adverse event	Grade, *n*				Total (%)
	Grade1	Grade 2	Grade 3	Grade 4	
Hypertension	6	7	3	0	16 (89)
Rash	7	6	0	0	13 (72)
Diarrhea	7	1	0	0	8 (44)
Acne	3	2	0	0	5 (28)
Xerosis	4	0	0	0	4 (22)
Abdominal discomfort	3	0	0	0	3 (17)
Nail change	3	0	0	0	3 (17)
Pruritus	3	0	0	0	3 (17)
QTc prolongation	0	0	2	0	2 (11)
Asthenia	1	1	0	0	2 (11)
Decreased appetite	1	1	0	0	2 (11)
Increased AST and ALT	0	0	1	0	1 (6)
Nausea	1	0	0	0	1 (6)
Vomiting	1	0	0	0	1 (6)

A phase 2 study of lenvatinib in patients with *RET* fusion-positive lung adenocarcinoma☆

Toyoaki Hida[a,*,1], Vamsidhar Velcheti[b,1], Karen L. Reckamp[c], Hiroshi Nokihara[d], Pallavi Sachdev[e], Tomoki Kubota[f], Takuya Nakada[f], Corina E. Dutcus[e], Min Ren[e], Tomohide Tamura[g]

- Lenvatinib is a multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)1–3, fibroblast growth factor receptors (FGFR)1–4, platelet-derived growth factor receptor alpha (PDGFRα), RET, and KIT
- phase 2, multicenter, open-label study 14 study sites in 4 coun- tries (United States, Japan, Singapore, and Taiwan)
- Oral lenvatinib 24 mg once daily in 28-day cycles

Patient demographics and baseline characteristics.

Parameter	*KIF5B-RET* (n = 13)	*CCDC6-RET* (n = 12)	Total (N = 25)
Median age, years (range)	61.0 (34, 75)	65.5 (38, 78)	63.0 (34, 78)
Sex, n (%)			
Male	2 (15.4)	5 (41.7)	7 (28.0)
Female	11 (84.6)	7 (58.3)	18 (72.0)
Race, n (%)			
White	4 (30.8)	4 (33.3)	8 (32.0)
Asian	9 (69.2)	8 (66.7)	17 (68.0)
ECOG performance status, n (%)			
0	9 (69.2)	6 (50.0)	15 (60.0)
1	4 (30.8)	6 (50.0)	10 (40.0)
Smoking history, n (%)			
Never smoked	8 (61.5)	6 (50.0)	14 (56.0)
Current smoker	0 (0)	1 (8.3)	1 (4.0)
Former smoker	3 (23.1)	4 (33.3)	7 (28.0)
Unknown	2 (15.4)	1 (8.3)	3 (12)
Number of prior anticancer therapies, n (%)			
0	1 (7.7)	1 (8.3)	2 (8.0)
1	7 (53.8)	1 (8.3)	8 (32.0)
2	2 (15.4)	4 (33.3)	6 (24.0)
3	2 (15.4)	4 (33.3)	6 (24.0)
≥ 4	1 (7.7)	2 (16.7)	3 (12.0)
RET-targeted therapy,[a] n (%)			
Cabozantinib	0 (0)	3 (25.0)	3 (12.0)
Vandetanib	2 (15.4)	3 (25.0)	5 (20.0)
VEGF-targeted therapy,[a] n (%)			
Bevacizumab	6 (46.2)	4 (33.3)	10 (40.0)
BIBF 1120	0 (0)	1 (8.3)	1 (4.0)
Cabozantinib	0 (0)	3 (25.0)	3 (12.0)
Sorafenib	0 (0)	1 (8.3)	1 (4.0)
Vandetanib	2 (15.4)	3 (25.0)	5 (20.0)

Parameter	*KIF5B-RET* (n = 13)	*CCDC6-RET* (n = 12)	Total (N = 25)
Best overall response, n (%)			
Complete response	0 (0)	0 (0)	0 (0)
Partial response	2 (15.4)	2 (16.7)	4 (16.0)
Stable disease	6 (46.2)	9 (75.0)	15 (60.0)
Progressive disease	3 (23.1)	0 (0)	3 (12.0)
Not evaluable[a]	1 (7.7)	1 (8.3)	2 (8.0)
Unknown[b]	1 (7.7)	0 (0)	1 (4.0)
Objective response rate,[c] n (%)	2 (15.4)	2 (16.7)	4 (16.0)
(95% CI)	(1.9–45.4)	(2.1–48.4)	(4.5–36.1)
Disease control rate,[d] n (%)	8 (61.5)	11 (91.7)	19 (76.0)
(95% CI)	(31.6–86.1)	(61.5–99.8)	(54.9–90.6)
Clinical benefit rate,[e] n (%)	4 (30.8)	8 (66.7)	12 (48.0)
(95% CI)	(9.1–61.4)	(34.9–90.1)	(27.8–68.7)
Median PFS, months (95% CI)	3.6 (1.0–NE)	9.1 (2.3–10.2)	7.3 (3.6–10.2)
PFS rate, % (95% CI)[f]			
3 months	59.3 (27.5–81.0)	90.0 (47.3–98.5)	73.9 (50.6–87.5)
6 months	29.7 (5.1–60.9)	80.0 (40.9–94.6)	56.3 (31.9–75.0)
12 months	29.7 (5.1–60.9)	0 (NE–NE)	15.6 (1.0–47.4)
Median OS, months (95% CI)	11.4 (4.2–NE)	NE (4.3–NE)	NE (5.8–NE)
OS rate, % (95% CI)[f]			
3 months	84.6 (51.2–95.9)	91.7 (53.9–98.8)	88.0 (67.3–96.0)
6 months	60.6 (29.4–81.4)	75.0 (40.8–91.2)	67.8 (45.7–82.4)
12 months	40.4 (8.3–71.9)	66.7 (33.7–86.0)	54.5 (29.4–74.0)
24 months	40.4 (8.3–71.9)	NE (NE–NE)	54.5 (29.4–74.0)

Treatment-emergent adverse events that occurred in at least 10% of patients.

	KIF5B-RET (n = 13)		*CCDC6-RET* (n = 12)		Total (N = 25)	
Preferred term, n (%)	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Hypertension	9 (69)	8 (62)	8 (67)	6 (50)	17 (68)	14 (56)
Nausea	7 (54)	1 (8)	8 (67)	2 (17)	15 (60)	3 (12)
Decreased appetite	9 (69)	0 (0)	4 (33)	0 (0)	13 (52)	0 (0)
Diarrhea	4 (31)	0 (0)	9 (75)	2 (17)	13 (52)	2 (8)
Proteinuria	6 (46)	3 (23)	6 (50)	1 (8)	12 (48)	4 (16)
Vomiting	5 (39)	1 (8)	6 (50)	1 (8)	11 (44)	2 (8)
Headache	3 (23)	0 (0)	7 (58)	0 (0)	10 (40)	0 (0)
Fatigue	2 (15)	0 (0)	7 (58)	2 (17)	9 (36)	2 (8)
Decreased platelet count	5 (39)	1 (8)	2 (17)	0 (0)	7 (28)	1 (4)
Increased aspartate aminotransferase level	2 (15)	0 (0)	4 (33)	0 (0)	6 (24)	0 (0)
Constipation	2 (15)	0 (0)	4 (33)	0 (0)	6 (24)	0 (0)
Cough	3 (23)	0 (0)	3 (25)	0 (0)	6 (24)	0 (0)
Hyponatremia	2 (15)	2 (15)	4 (33)	3 (25)	6 (24)	5 (20)
Increased alanine aminotransferase level	2 (15)	0 (0)	3 (25)	0 (0)	5 (20)	0 (0)
Arthralgia	2 (15)	1 (8)	3 (25)	0 (0)	5 (20)	1 (4)
Dyspnea	2 (15)	0 (0)	3 (25)	1 (8)	5 (20)	1 (4)
Peripheral edema	4 (31)	0 (0)	1 (8)	0 (0)	5 (20)	0 (0)
Decreased weight	0 (0)	0 (0)	5 (42)	0 (0)	5 (20)	0 (0)
Dehydration	2 (15)	0 (0)	2 (17)	0 (0)	4 (16)	0 (0)
Dry mouth	1 (8)	0 (0)	3 (25)	0 (0)	4 (16)	0 (0)
Dry skin	1 (8)	0 (0)	3 (25)	0 (0)	4 (16)	0 (0)
Hypoalbuminemia	2 (15)	0 (0)	2 (17)	0 (0)	4 (16)	0 (0)
Pneumonia	1 (8)	1 (8)	3 (25)	3 (25)	4 (16)	4 (16)
Abdominal pain	0 (0)	0 (0)	3 (25)	0 (0)	3 (12)	0 (0)
Alopecia	0 (0)	0 (0)	3 (25)	0 (0)	3 (12)	0 (0)
Increased blood creatinine level	1 (8)	0 (0)	2 (17)	0 (0)	3 (12)	0 (0)
Dysphonia	1 (8)	0 (0)	2 (17)	0 (0)	3 (12)	0 (0)
Hypothyroidism	0 (0)	0 (0)	3 (25)	0 (0)	3 (12)	0 (0)
Musculoskeletal pain	2 (15)	0 (0)	1 (8)	0 (0)	3 (12)	0 (0)
Myalgia	3 (23)	0 (0)	0 (0)	0 (0)	3 (12)	0 (0)
Decreased neutrophil count	2 (15)	0 (0)	1 (8)	0 (0)	3 (12)	0 (0)
Palmar-plantar erythrodysesthesia syndrome	2 (15)	0 (0)	1 (8)	0 (0)	3 (12)	0 (0)
Pyrexia	3 (23)	0 (0)	0 (0)	0 (0)	3 (12)	0 (0)
Rash	1 (8)	0 (0)	2 (17)	0 (0)	3 (12)	0 (0)

- Grade ≥3 (TEAEs) - 23 (92%) patients
- TEAEs requiring dose reduction occurred in 16 (64%) patients.
- The most common TEAEs included hypertension(17.68%), nausea (15.60%), decreased appetite (13.52%),diarrhea (13.52%), proteinuria (48%), and vomiting (11.44%)

Summary of treatment-emergent adverse events, safety analysis set.

Parameter, n (%)	*KIF5B-RET* (n = 13)	*CCDC6-RET* (n = 12)	Total (N = 25)
TEAEs	13 (100.0)	12 (100.0)	25 (100.0)
Grade ≥ 3 TEAEs	12 (92.3)	11 (91.7)	23 (92.0)
Serious adverse events	6 (46.2)	7 (58.3)	13 (52.0)
Deaths	1 (7.7)	2 (16.7)	3 (12.0)
TEAEs leading to drug interruption	10 (76.9)	9 (75.0)	19 (76.0)
TEAEs leading to dose reduction	6 (46.2)	10 (83.3)	16 (64.0)
TEAEs leading to drug discontinuation	3 (23.1)	3 (25.0)	6 (24.0)

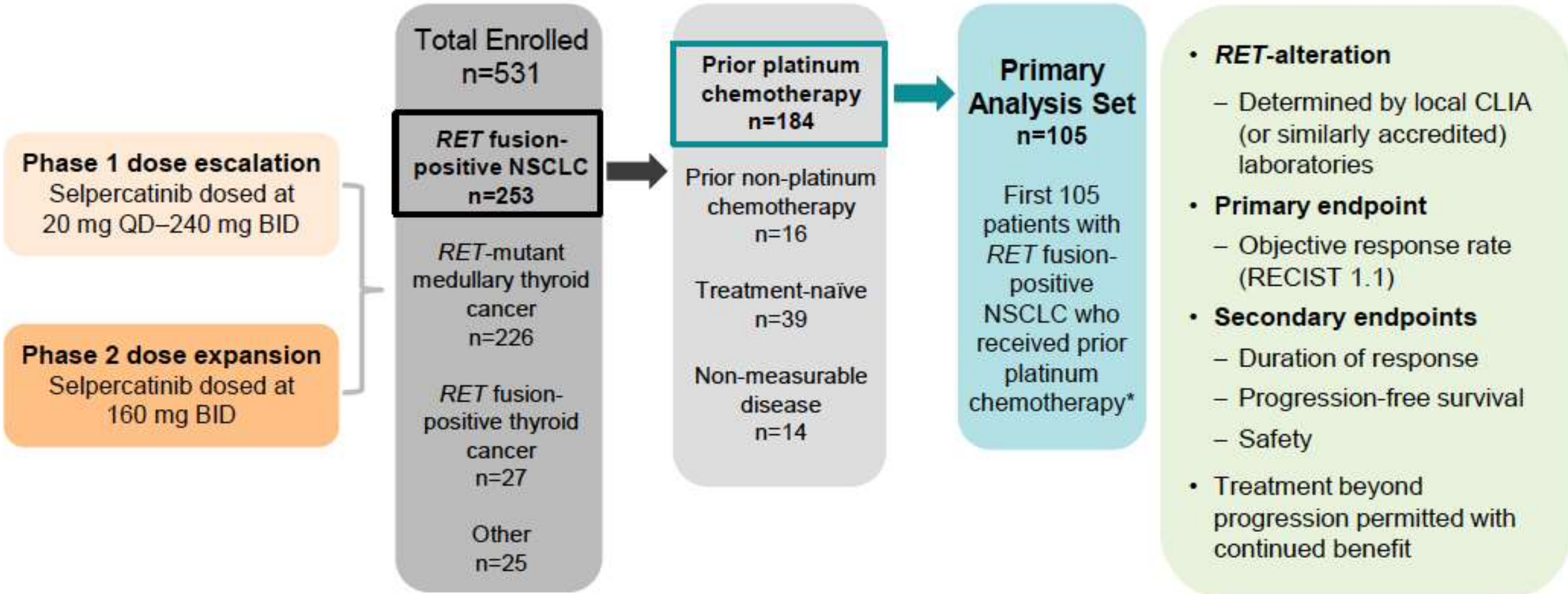
TEAE, treatment-emergent adverse event.

Registrational Results of LIBRETTO-001: A Phase 1/2 Trial of Selpercatinib (LOXO-292) in Patients with *RET* Fusion-Positive Lung Cancers

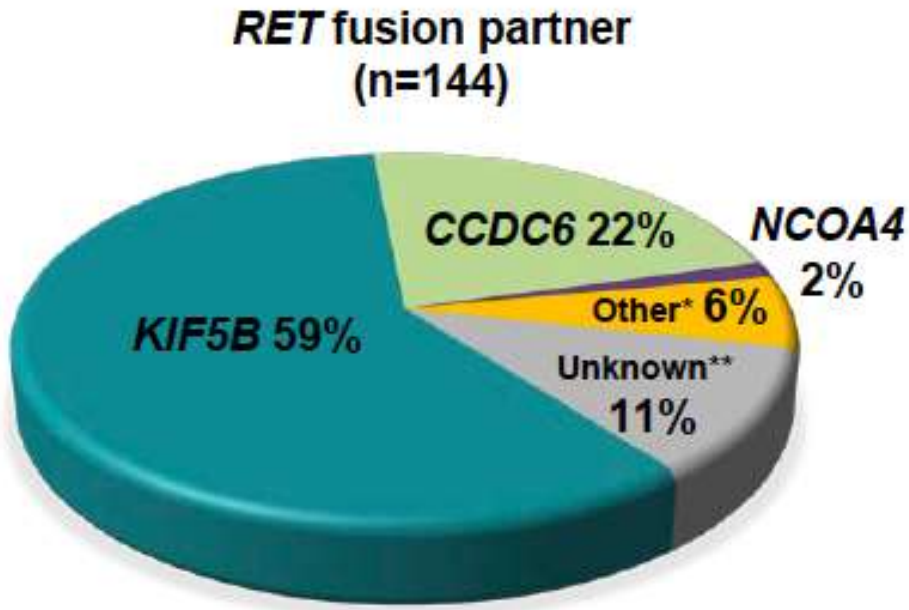
A. Drilon[1], G. Oxnard[2], L. Wirth[3], B. Besse[4], O. Gautschi[5], S.W.D. Tan[6], H. Loong[7], T. Bauer[8], Y.J. Kim[9], A. Horiike[10], K. Park[11], M.

- Selpercatinib is a novel, highly selective, ATP-competitive small molecule RET inhibitor that has significant CNS penetration, and a low potential for drug interactions
- Approved by the FDA for the treatment of advanced RETrearranged NSCLC and medullary thyroid cancers with a breakthrough therapy designation in September 2018
- Updated results of this study have been presented at the 2019WCLC

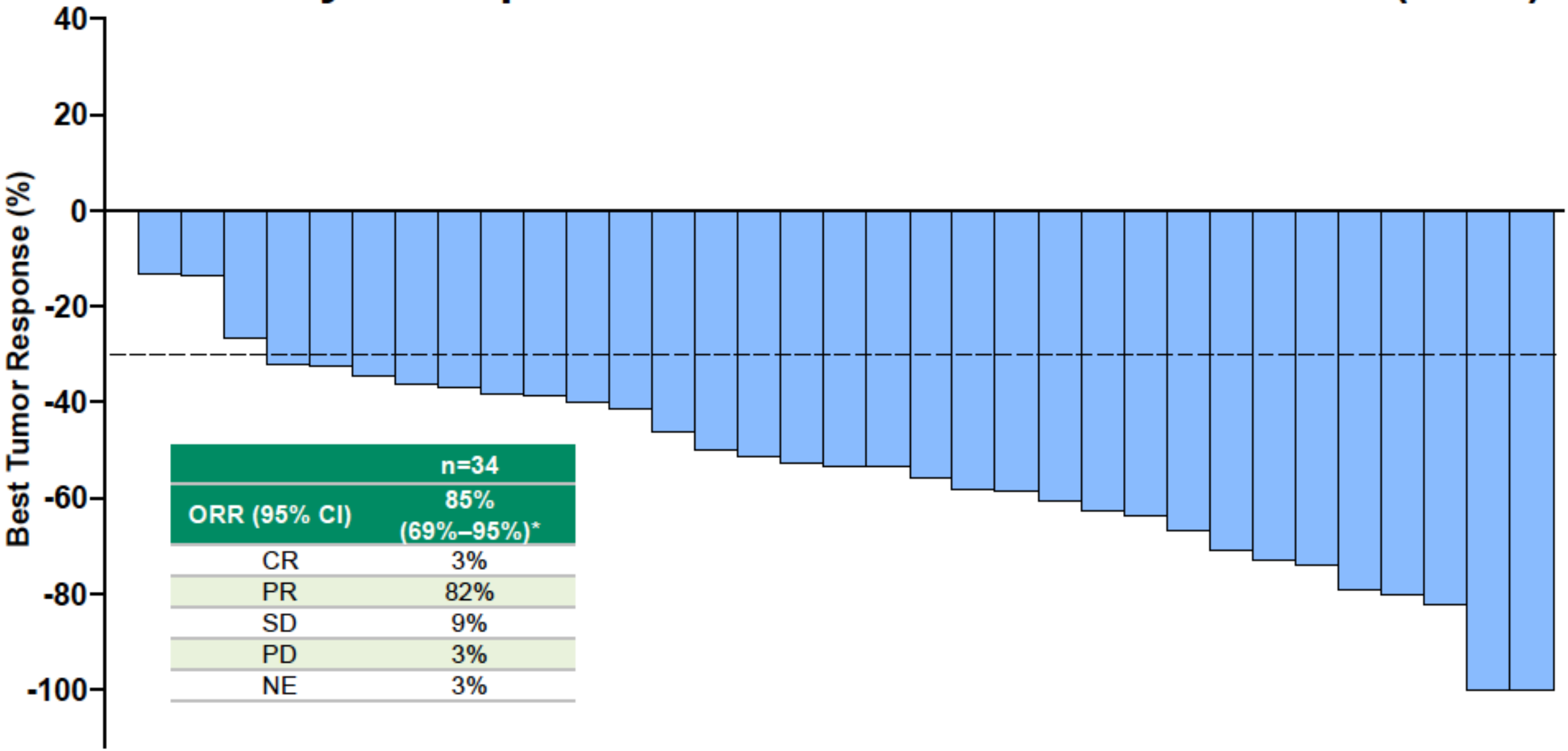
LIBRETTO-001: Selpercatinib in *RET*-altered cancers



Patient Characteristics	PAS (n=105)	Treatment-naïve (n=39)
Female / Male, n (%)	62 (59) / 43 (41)	22 (56) / 17 (44)
Median age (range), years	61 (23–81)	61 (23–86)
ECOG performance status, n (%)		
0	31 (30)	19 (49)
1	72 (69)	20 (51)
2	2 (2)	0
Median prior systemic regimens (range)	3 (1–15)	0
Prior platinum-based chemotherapy, n (%)	105 (100)	-
Prior PD-1/PD-L1 inhibitor, n (%)	58 (55)	-
Concurrent with platinum-based chemotherapy	9 (9)	-
Sequential to platinum-based chemotherapy	49 (47)	-
Prior multikinase inhibitor (MKI), n (%)	50 (48)	-
1	37 (35)	-
≥2	13 (12)	-
Brain metastases, n (%)‡	37 (35)	7 (18)
Measurable disease	104 (99)	39 (100)



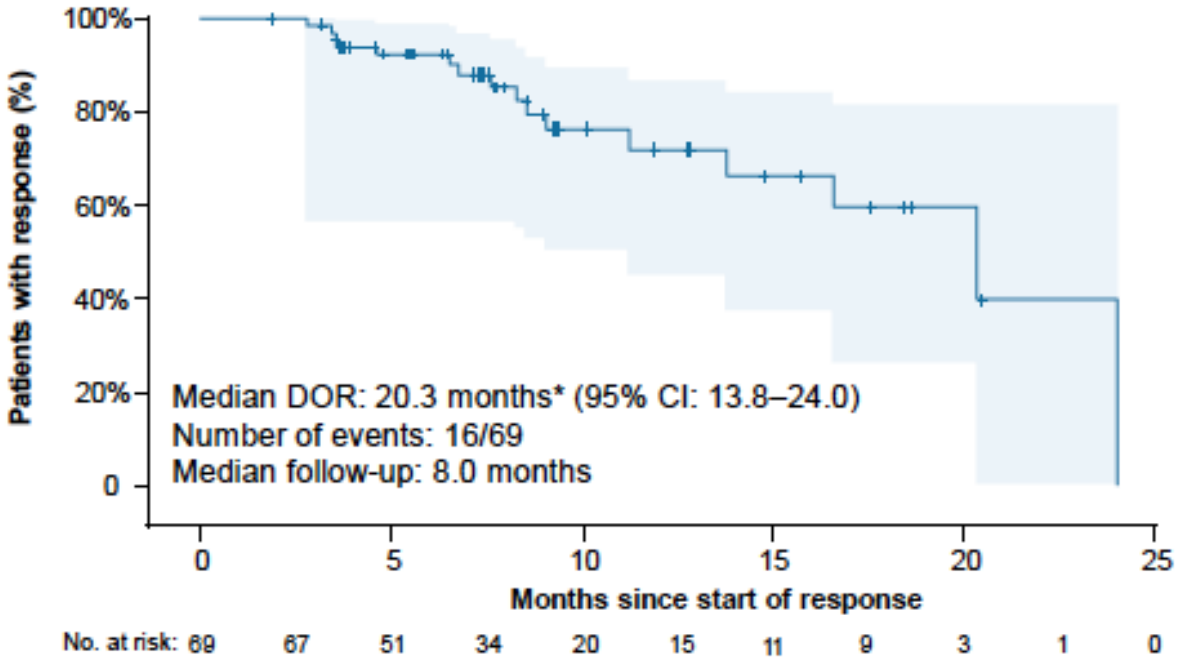
Efficacy of Selpercatinib: Treatment-naïve Patients (n=34)



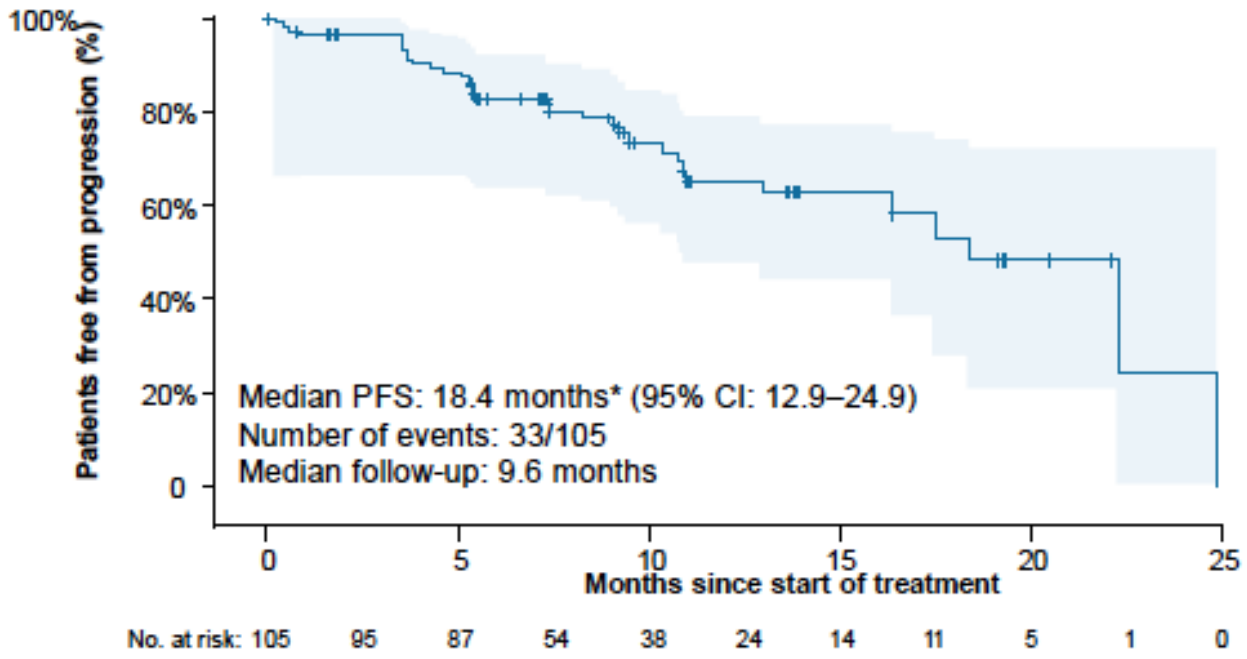
	n=34
ORR (95% CI)	85% (69%–95%)*
CR	3%
PR	82%
SD	9%
PD	3%
NE	3%

Durability of Selpercatinib Efficacy: Primary Analysis Set

Duration of response



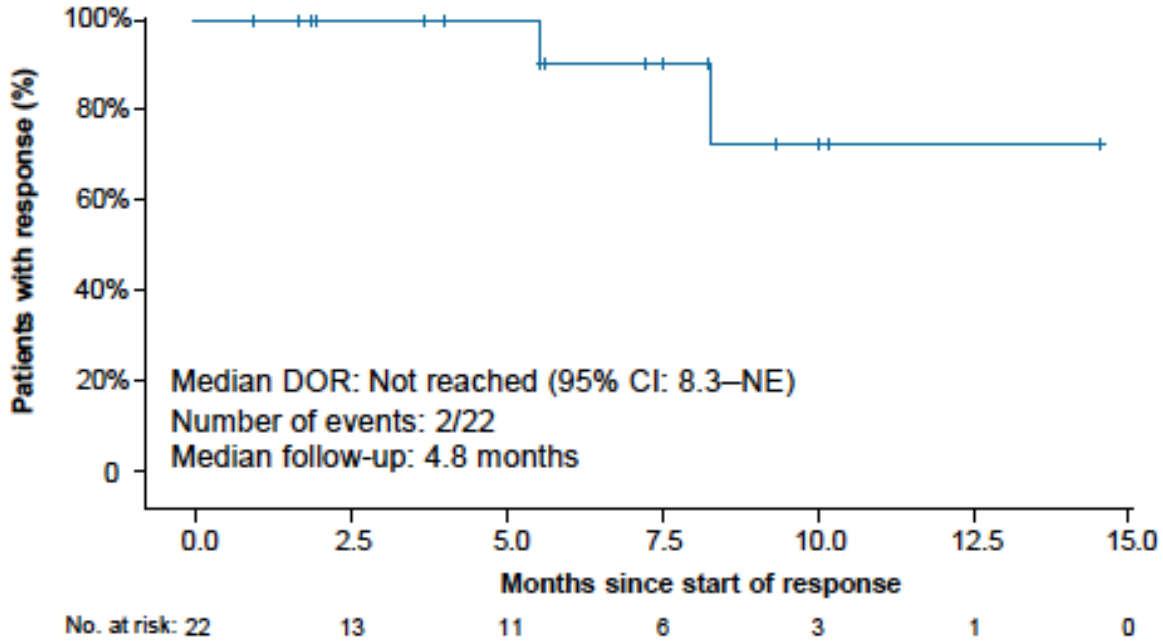
Progression-free survival



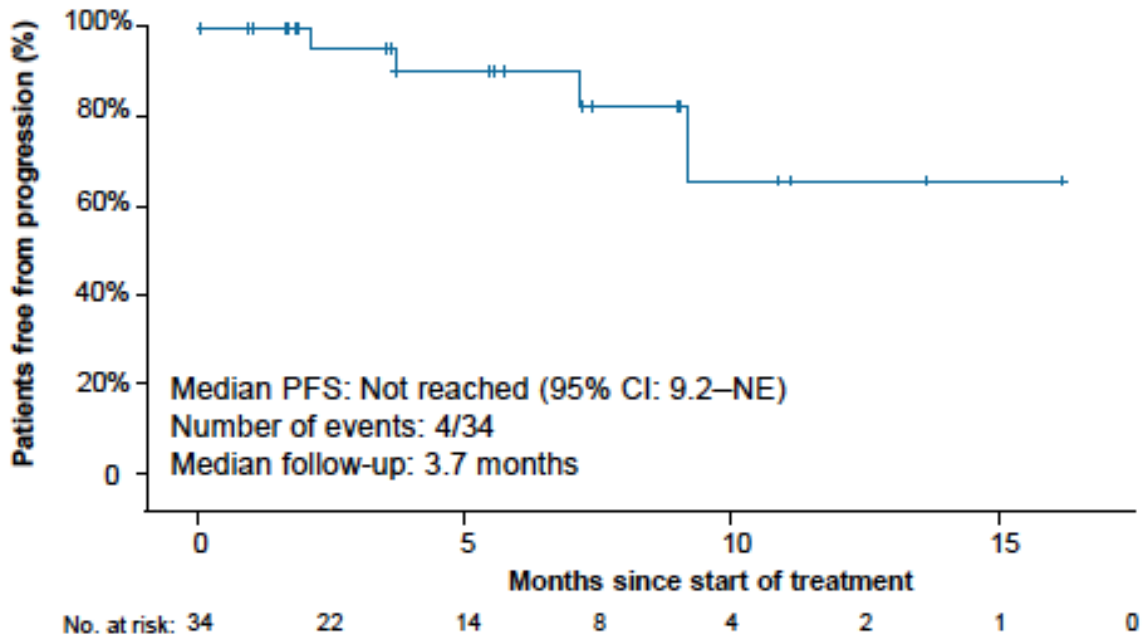
- Of 28 patients in the PAS that progressed, 23 continued treatment post-progression, for 0.2–16.4+ months
- ORR, DOR, PFS similar regardless of prior therapy (e.g. anti-PD-1/PD-L1, MKIs)

Durability of Selpercatinib Efficacy: Treatment-Naïve

Duration of response



Progression-free survival



Selpercatinib Safety Profile

	LIBRETTO-001 Safety Database, n=531							
	Treatment-emergent AEs (≥15% overall)					Treatment-related AEs		
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Dry mouth	29%	4%	–	–	32%	–	–	27%
Diarrhea	21%	8%	2%	–	31%	1%	–	16%
Hypertension	4%	11%	14%	<1%	29%	8%	<1%	18%
Increased AST	17%	5%	6%	1%	28%	4%	1%	22%
Increased ALT	13%	4%	7%	1%	26%	6%	1%	21%
Fatigue	15%	9%	1%	–	24%	<1%	–	14%
Constipation	19%	3%	<1%	–	22%	<1%	–	11%
Headache	15%	4%	1%	–	20%	<1%	–	7%
Nausea	15%	4%	<1%	–	19%	<1%	–	8%
Peripheral edema	16%	4%	<1%	–	19%	–	–	10%
Increased creatinine	14%	4%	–	<1%	18%	–	–	10%

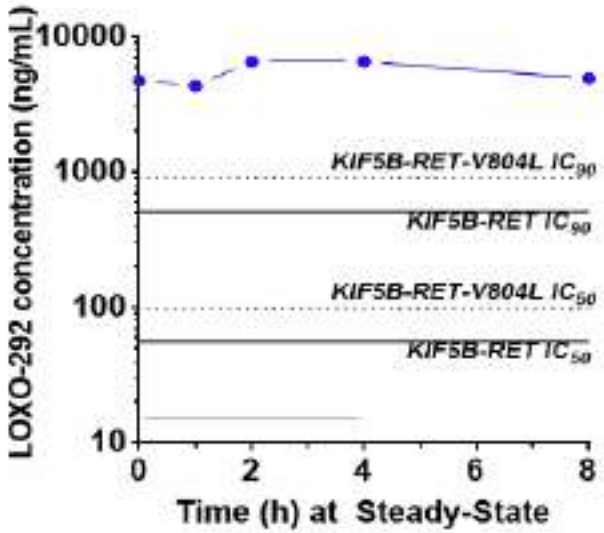
9 patients (1.7%) discontinued due to treatment-related AEs

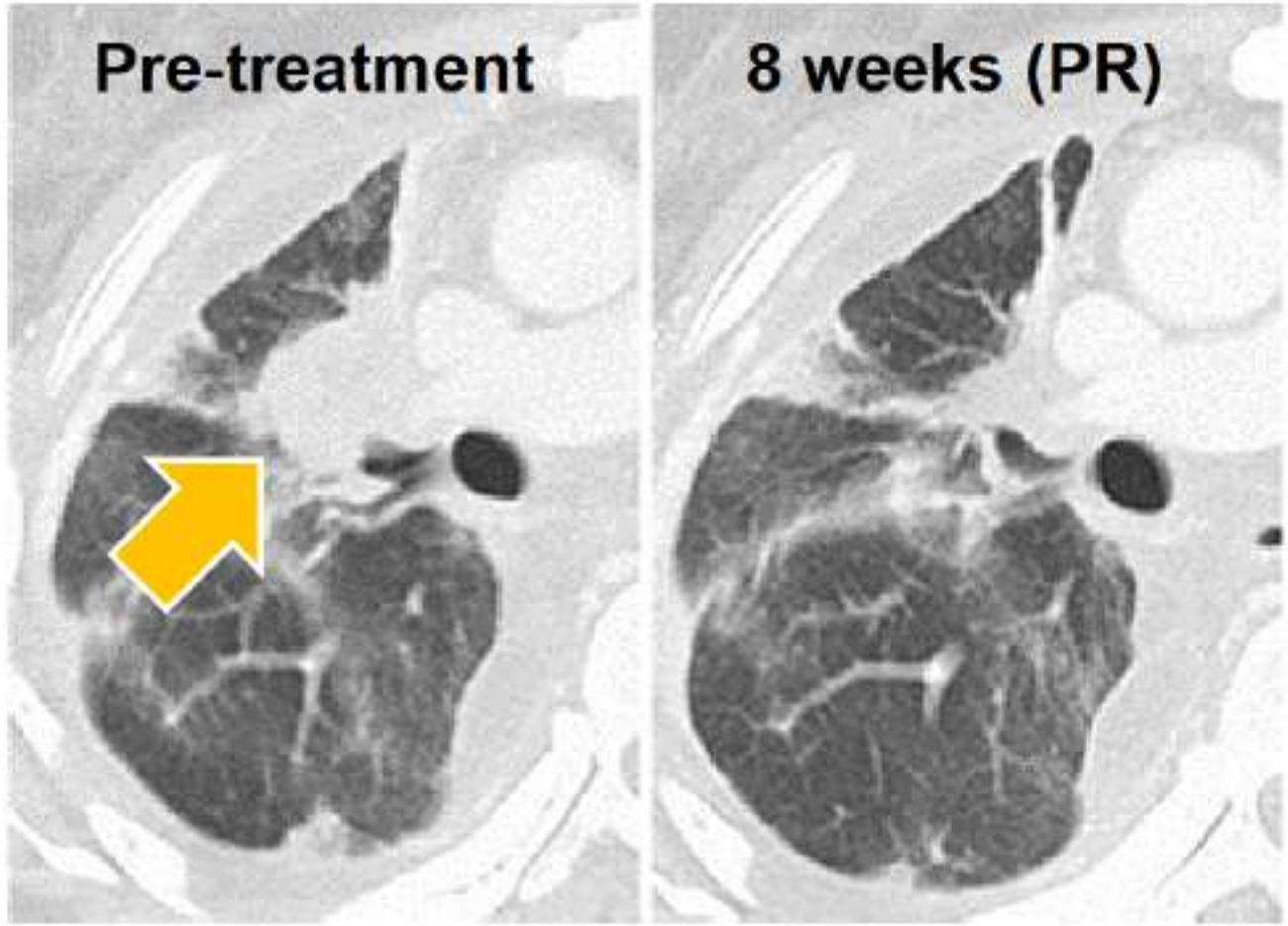
Selpercatinib Overcomes Acquired Gatekeeper Resistance

42-year-old woman with *KIF5B-RET* fusion-positive NSCLC

- 15 prior systemic therapy regimens
  - chemotherapy, immunotherapy, and investigational kinase inhibitors
- Acquired **RET V804L gatekeeper mutation** post-vandetanib therapy

Initiated selpercatinib at 160 mg BID



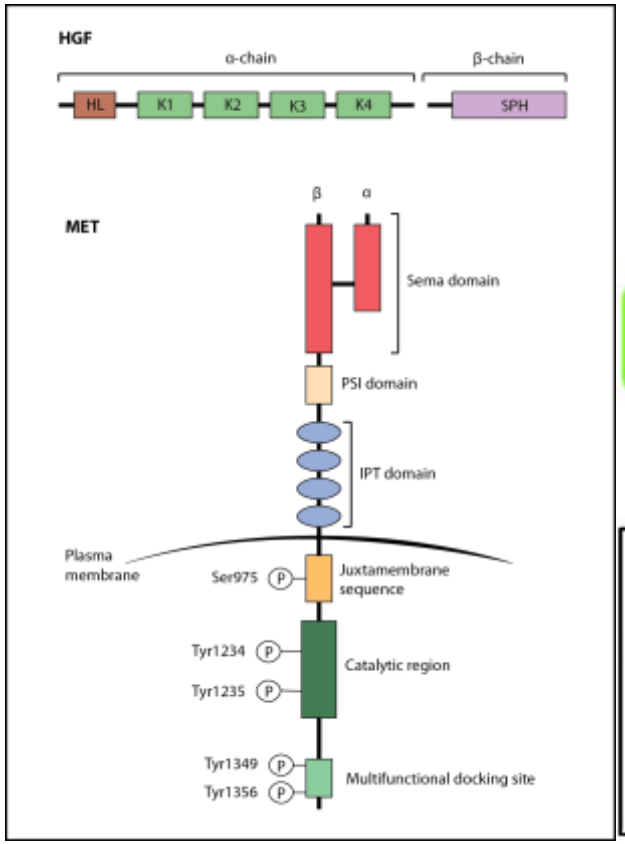


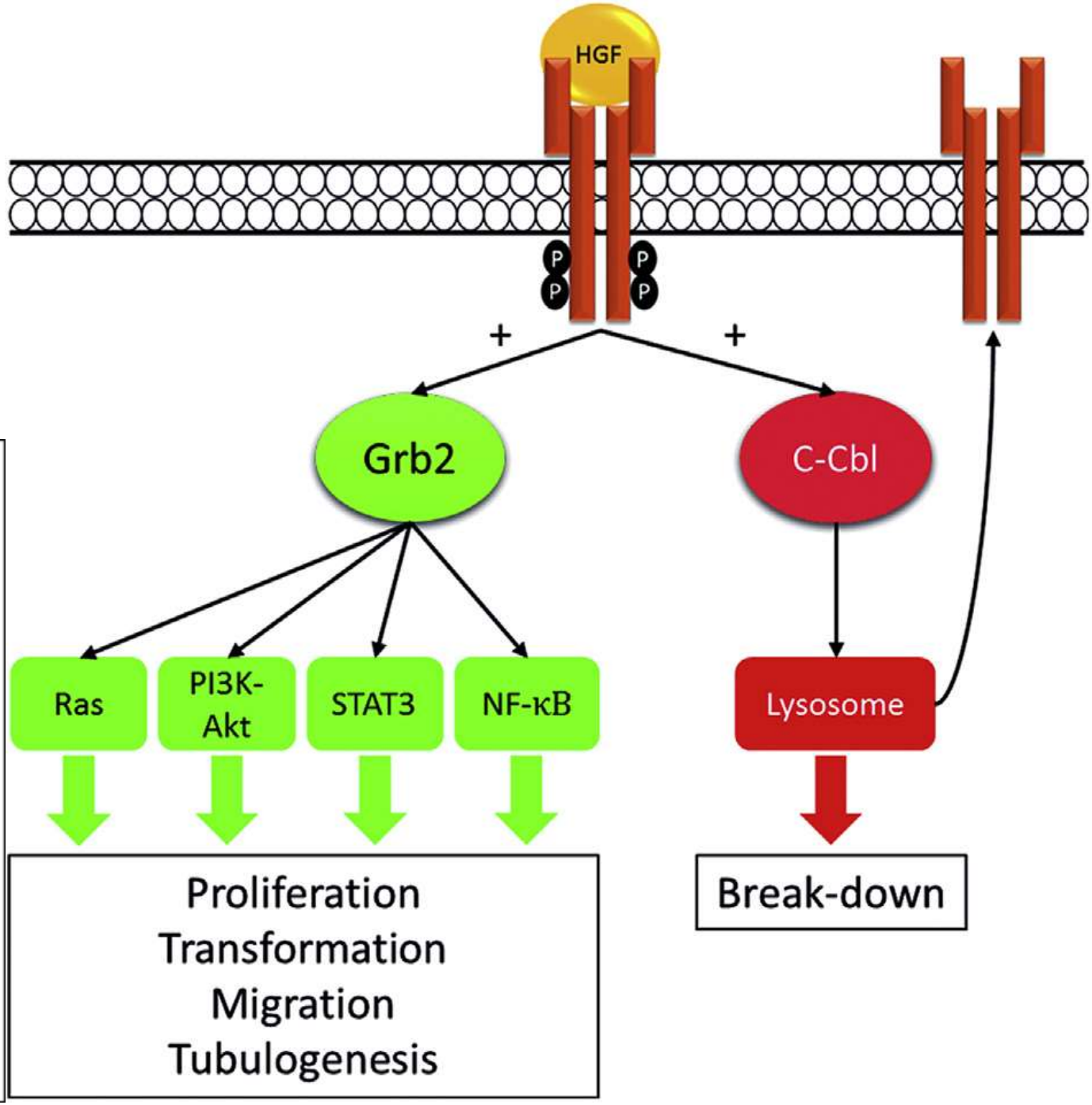
Decreased shortness of breath
Confirmed PR by RECIST 1.1
Remains on treatment at 11 months

Targetable Driver genes	Incidence	Targeted Agent	Clinical Trials	Phase	Patients Included	Results	Approved or Recommended by
RET rearrangements	1–2%	Vandetanib[48]	NCT01823068	II	RET-rearranged NSCLC	n=18, ORR 18%, mPFS 4.5 mo, mOS 11.6 mo	NCCN*
		Vandetanib[46]	UMIN000010095	II	RET-rearranged NSCLC	n=19, ORR 53%, mPFS 4.7 mo, mOS 11.1 mo	NCCN*
		Cabozantinib[45]	NCT01639508	II	RET-rearranged NSCLC	n=26, ORR 28%, mPFS 5.5 mo, mOS 9.9 mo	NCCN*
		Lenvatinib[47]	NCT01877083	II	RET-rearranged NSCLC	n=25, ORR 16%, mPFS 7.3 mo	
		Alectinib	NCT03131206	I/II	RET-rearranged NSCLC	Ongoing	
		Selpercatinib (LOXO-292)[51]	LIBRETTO-001 (NCT03157128)	I/II	RET-rearranged NSCLC	n=30, ORR 77%	FDA
		Selpercatinib (LOXO-292)[52]	LIBRETTO-001 (NCT03157128)	I/II	RET-rearranged NSCLC	n=105, ORR 68%, CNS ORR 91%, mDOR 20.3 mo, mPFS 18.4 mo for pre-treated pts. n=34, ORR 85%, mDOR, mPFS were not reached for treatment-naive pts.	FDA
		BLU-667[54]	NCT03037385	I	RET-rearranged NSCLC	n=11, ORR 45%	

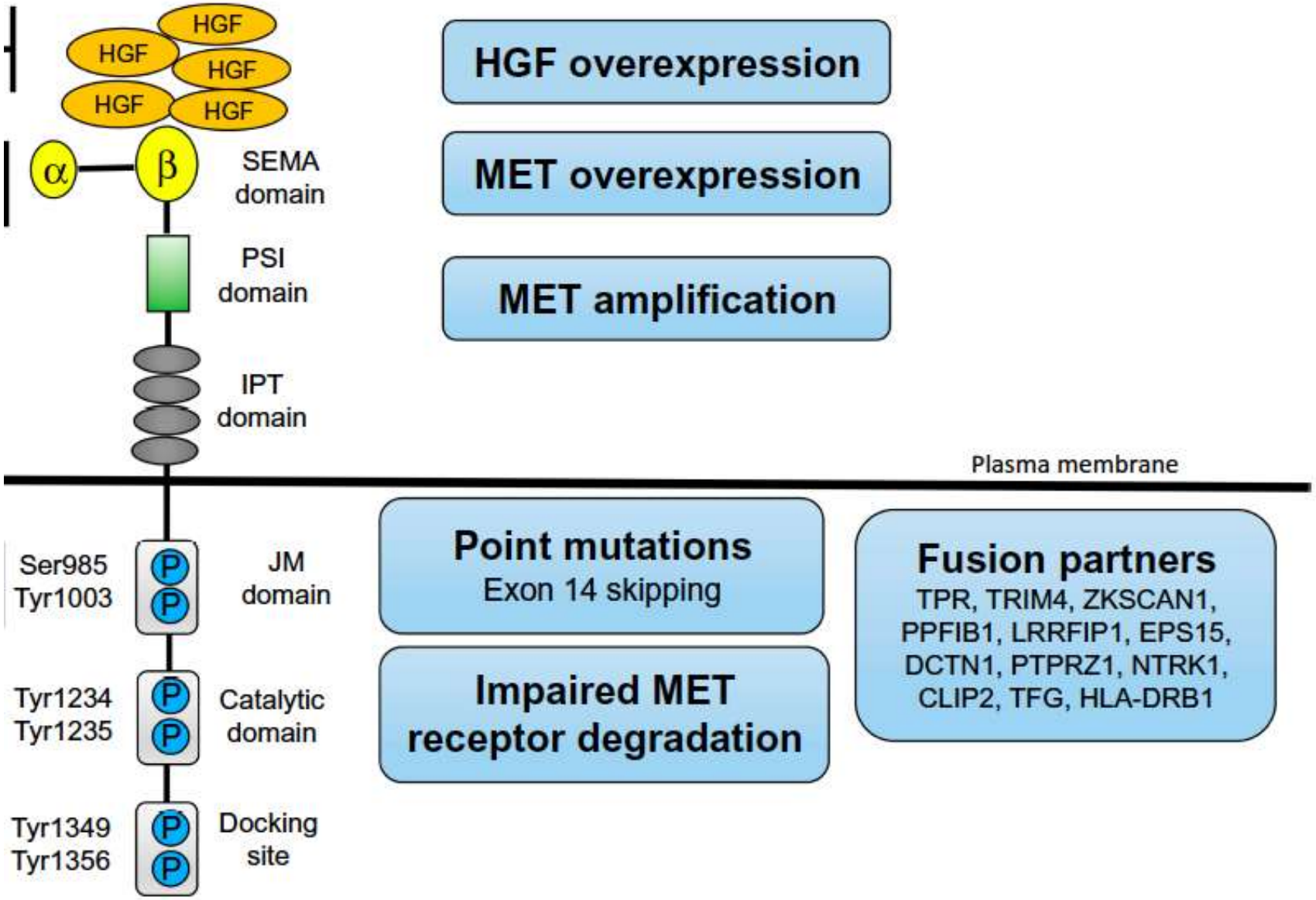
MET Pathway

- MET was first discovered as an oncogene that encodes for the tyrosine kinase receptor for HGF
- The gene for MET is located on chromosome 7q21-q31





Mechanism of MET/HGF axis dysregulation



MET Exon 14 Skipping Mutations

- MET exon 14 alterations (point mutations, deletions, insertions, and complex mutations) lead to decreased degradation of MET receptor, resulting in the activation of MET signalling and the tumorigenesis
- Seen in 3% of NSCLC cases
- More commonly found in females, elderly patients, non-smokers, pulmonary sarcomata carcinoma (PSC), and are associated with poor prognosis

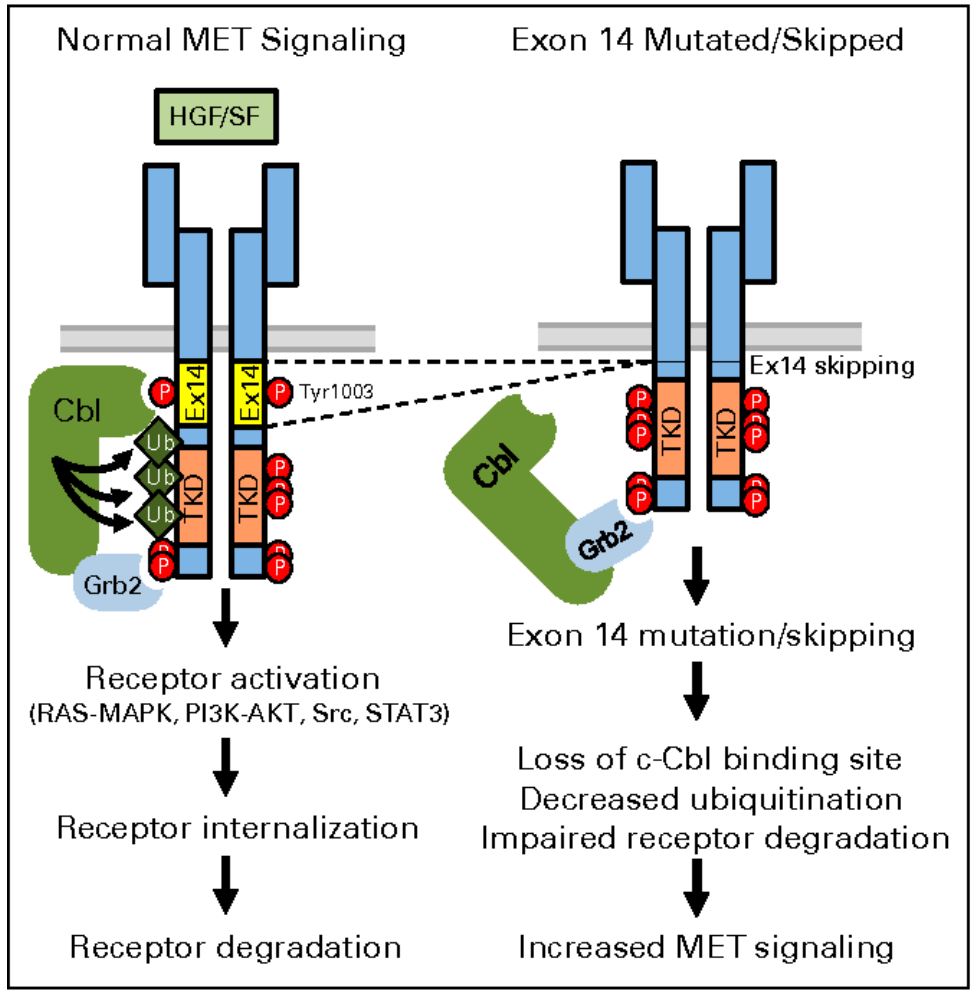


Fig 1 *MET* exon (Ex) 14 skipping results in impaired c-Met receptor degradation

MET Exon 14 Skipping Mutations

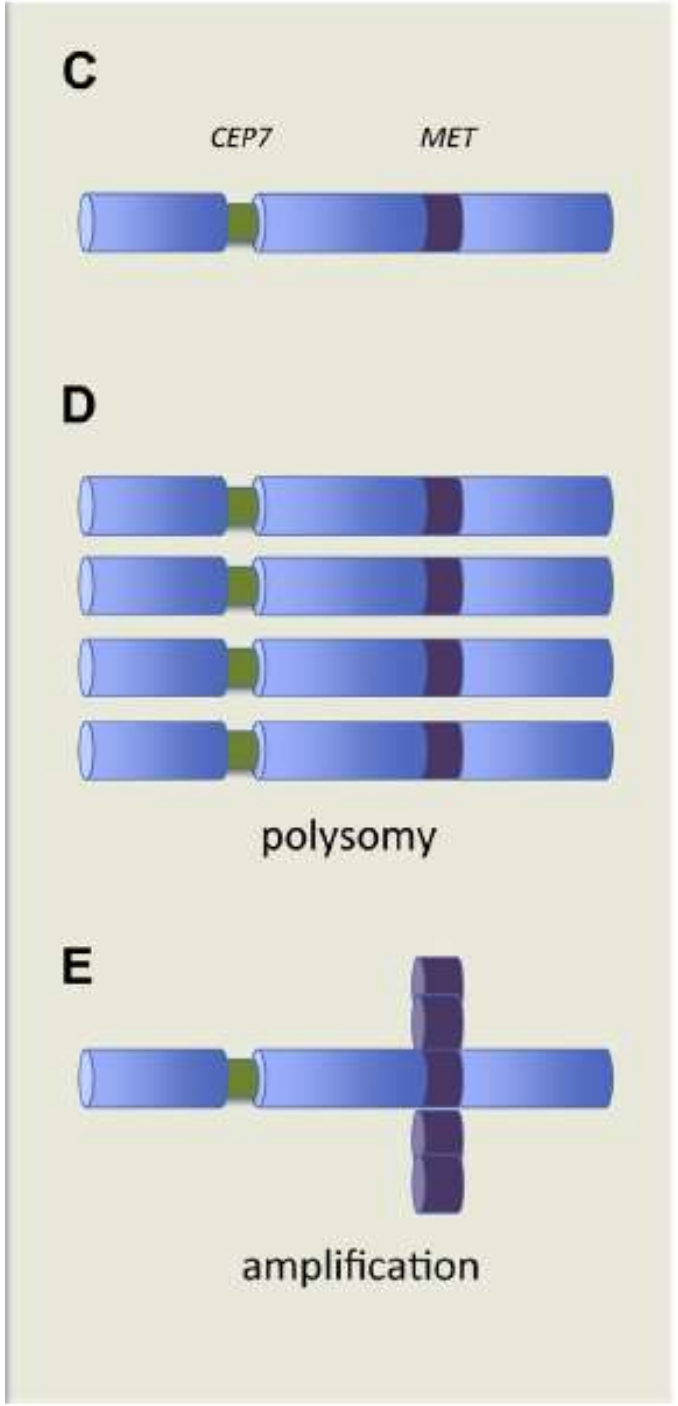
- Histological subtype of NSCLC, most commonly in sarcomatoid carcinoma (4.9% ~ 31%), followed by adenosquamous carcinoma (5%), adenocarcinoma (3%) and squamous cell carcinoma (2%)
- Targeted NGS-based assays-DNA-based testing used as screening followed by RNA based assays
- Quantitative reverse transcription PCR (qRT-PCR),sanger sequencing
- METex14 alterations are mutually exclusive with other drivers
- 20% of lung adenocarcinomas with MET exon 14–skipping mutations have concurrent high-level MET amplification

MET Amplification

- MET amplification was reported in 2–5% of NSCLC
- Not all amplifications are driver mutations
- Only high MET gene amplification act as drivers

Table 3. *MET*/CEP7 Ratio and Classification of *MET* Amplification

MET/CEP7 Ratio	*MET* Amplification Classification	Percentage of Total
<1.8	Negative	92.6
≥1.8 to ≤2.2	Low	3.6
>2.2 to <5.0	Intermediate	3.0
≥5.0	High	0.8
Total	—	100.0



MET Amplification

- Detected by IHC,Fluorescence in situ hybridization (FISH),Next generation sequencing and Quantitative PCR
- MET amplification is a potential resistance pattern of EGFR-TKIs in NSCLC, accounting for 50–60% of the first- and second-generation EGFR-TKIs acquired resistance accounting for 15–19% of the third generation EGFR-TKIs acquired resistance
- MET FISH-positive patients with advanced NSCLC have a poor overall survival

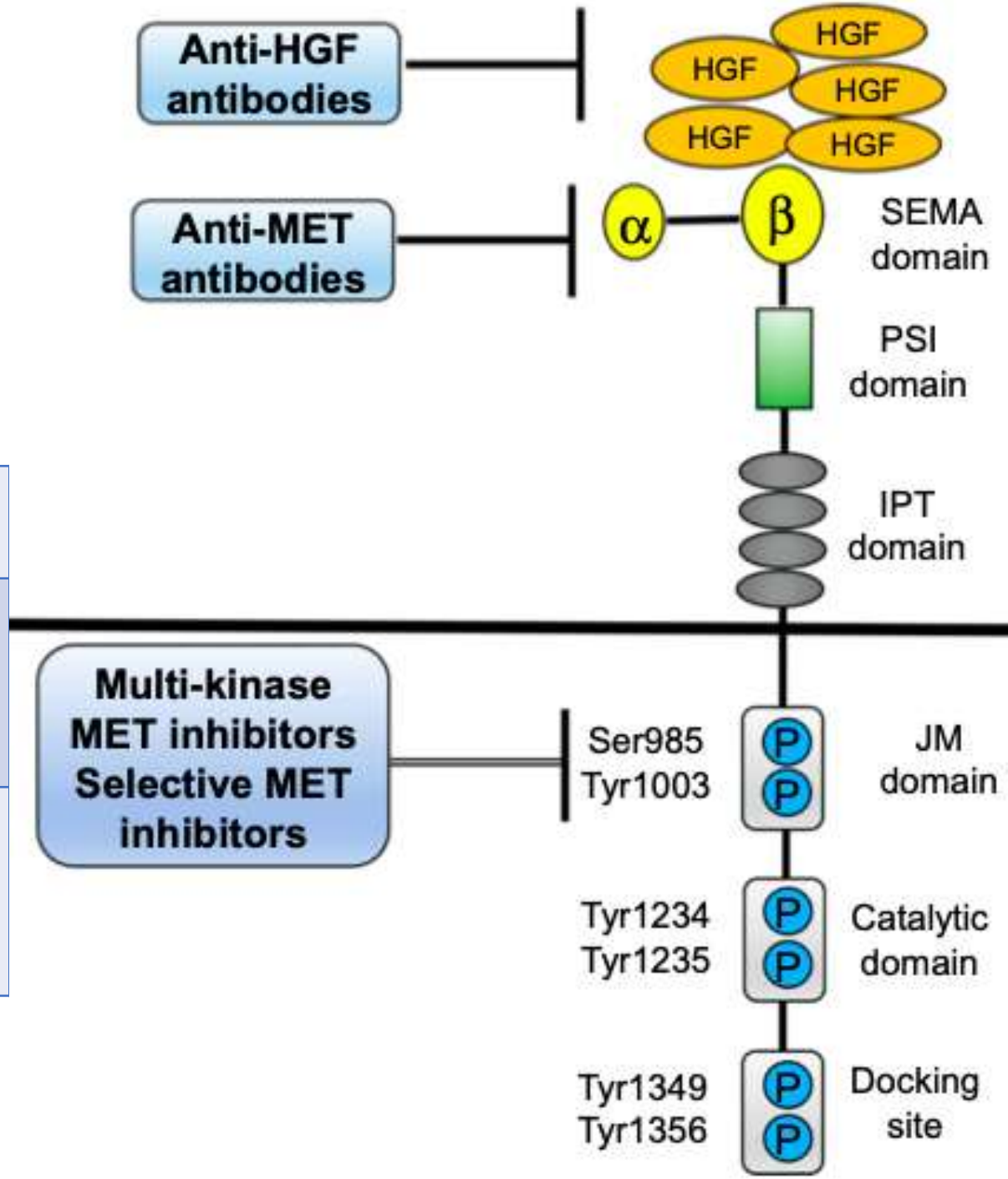
MET inhibitors-Small molecule TKIs

ATP competitive	
Type Ia MET-TKIs	• Crizotinib
Type Ib MET-TKIs	• Capmatinib • Tepotinib • Savolitinib
Type II MET-TKI	• Cabozantinib • Glesatinib • Merestinib
Type III MET-TKI	• Not available

ATP non-competitive	
• Tivantinib	
Selective	• **Tivantinib** • **Capmatinib** • **Savolitinib** • **Tepotinib**
Non-selective(multi-kinase)	• Cabozantinib • Foretinib • Crizotinib

MET inhibitors

Monoclonal antibodies (mAbs)	
Anti-MET	• Onartuzumab • Emibetuzumab
Anti-HGF	• Ficlatuzumab • Rilotumumab



Profile 1001:Crozotinib in MET exon 14

- Crizotinib is a multi-tyrosine kinase inhibitor that is approved for the treatment of ALK- or ROS1-rearranged advanced NSCLCs
- It has potent activity against MET and low nanomolar potency in cell lines that harbor MET exon 14 alterations
- Prospective, open label, multicentre phase 1 study to evaluate efficacy and ,safety of cirizotinib in NSCLSC including MET ex 14 expansion chort
- Intervention-crizotinib 250 mg BID
- Responses were based on derived investigator assessment per RECIST v1.0.
- From 11 September 2014 - 26 January 2018, 69 patients were enrolled

Patient characteristics at baseline

Patients with *MET*-exon-14-altered NSCLC	*n* = 69
Age — yr	
Median	72
Range	34–91
Sex — no. patients (%)	
Female	40 (58)
Male	29 (42)
Race — no. patients (%)	
White	50 (73)
Asian	11 (16)
Black/African American	2 (3)
Other	6 (9)
Smoking history — no. patients (%)	
Former	42 (61)
Never	26 (38)
Current	1 (1)
ECOG performance status — no. patients (%)	
0	19 (28)
1	49 (71)
2	1 (1)
Tumor histology — no. patients (%)	
Adenocarcinoma	58 (84)
Sarcomatoid carcinoma	6 (9)
Squamous cell carcinoma	3 (4)
Adenosquamous carcinoma	2 (3)
Prior treatments for advanced disease — no. patients (%)[a]	
0	26 (38)
1	29 (42)
>1	14 (20)
Local assay — no. patients (%)	
NGS	66 (96)
Reverse transcription PCR	3 (4)

The median duration of treatment was 7.4 months (95% CI, 5.5–9.1)

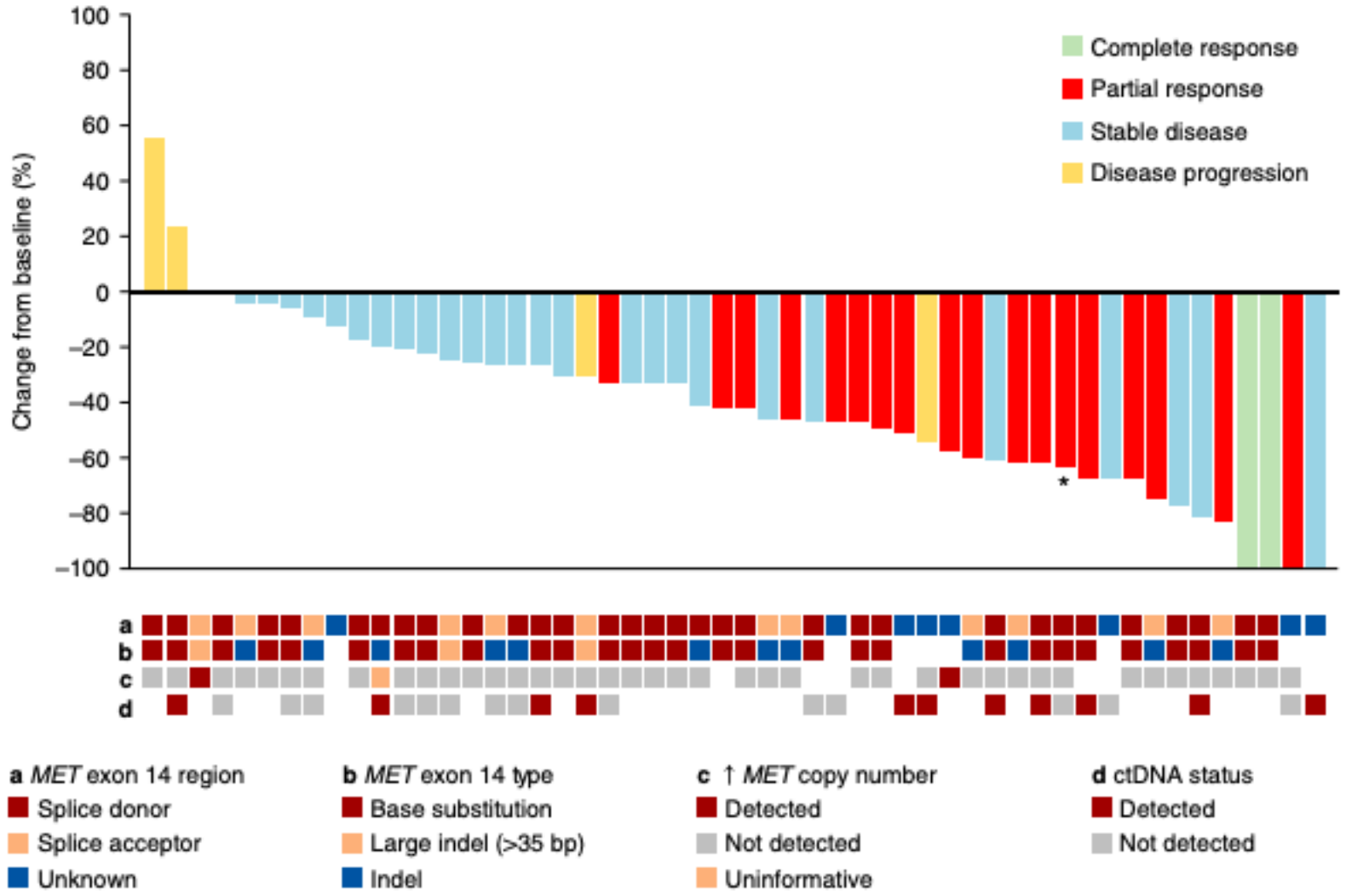
20 patients (29%) continued to receive crizotinib after the data cut off date

- 65 were response evaluable.

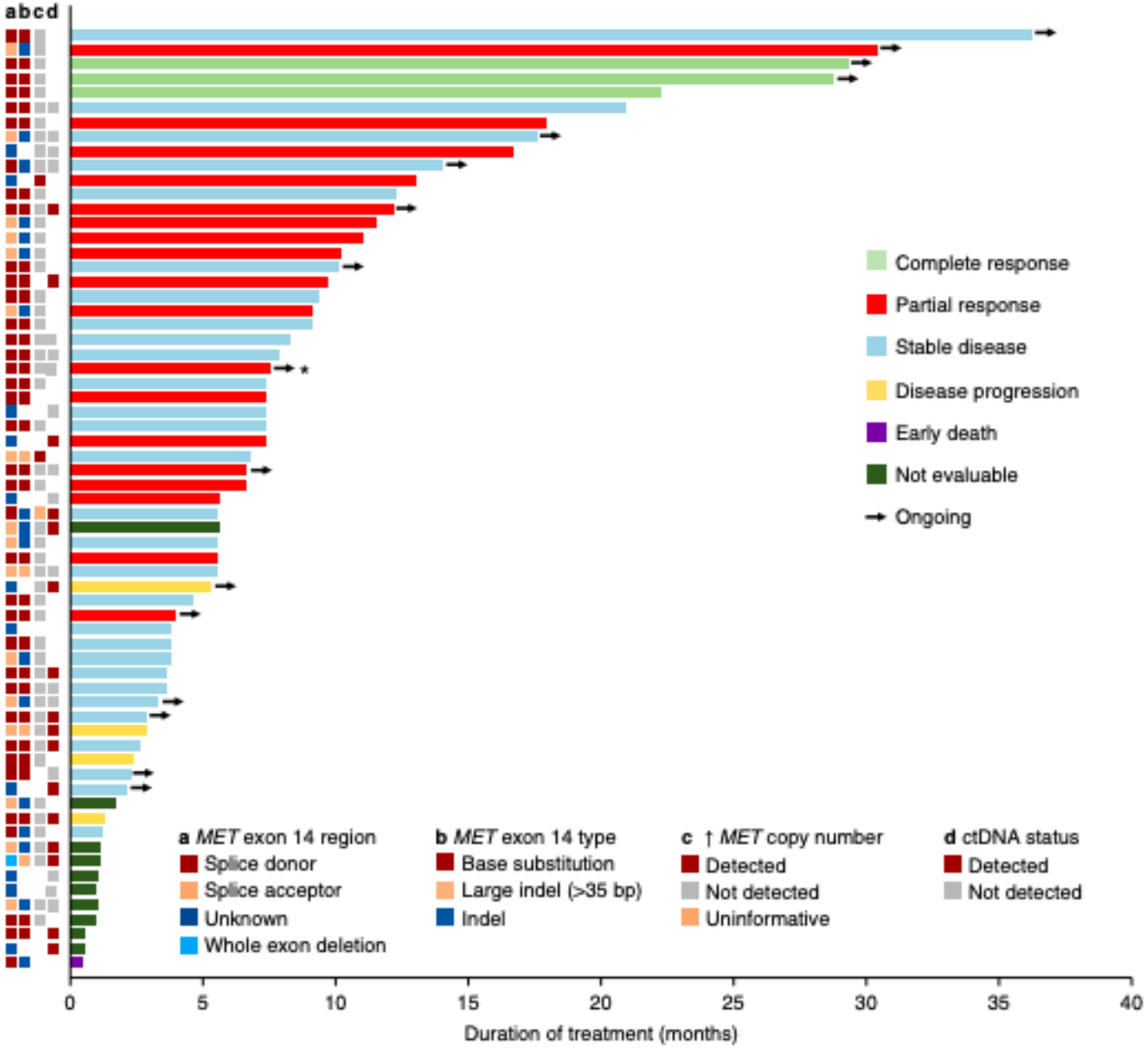
  ORR- 32% (95% CI, 21–45)

Among the 65 patients

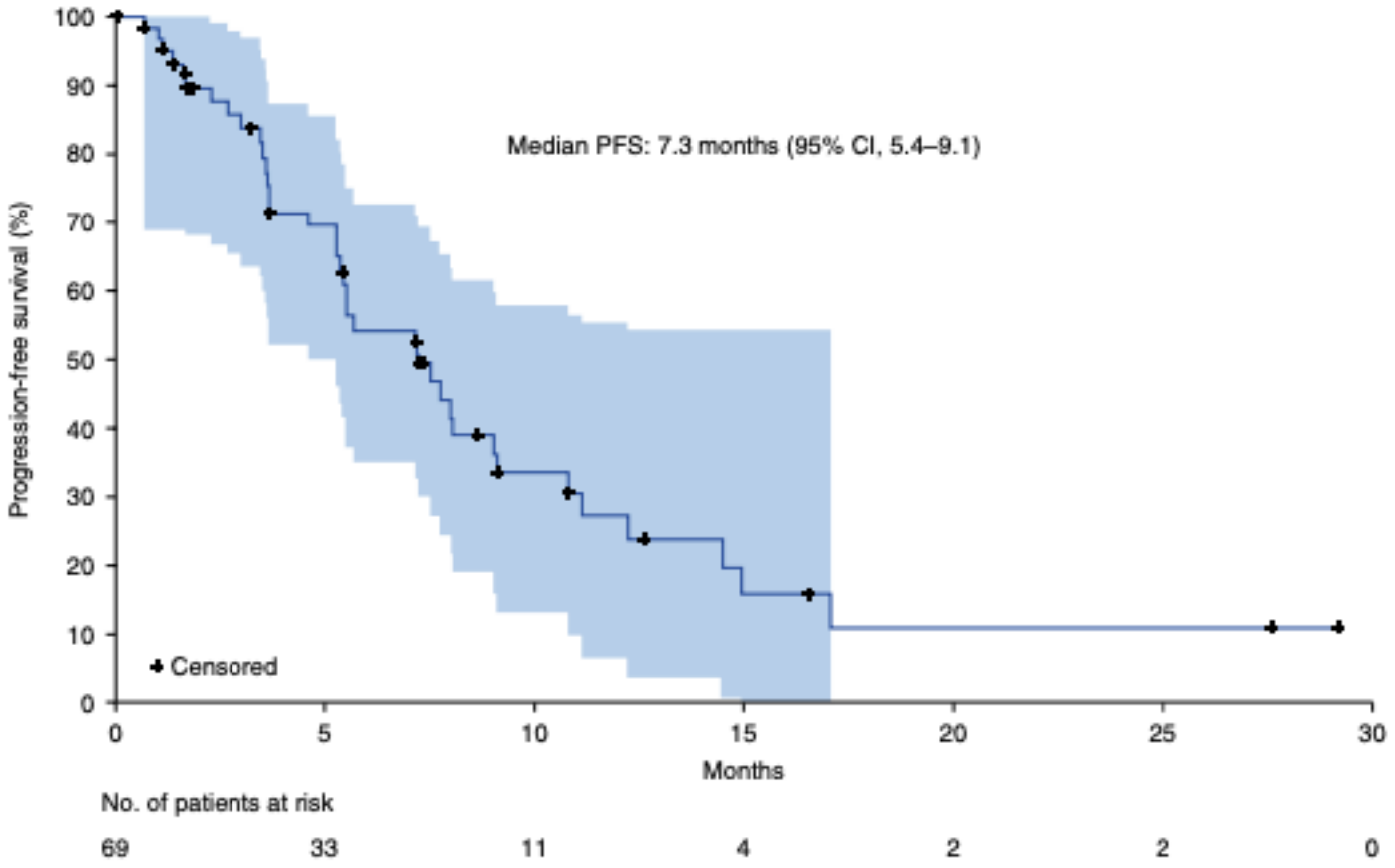
- Confirmed CR-3 (5%),
- Confirmed PR- 18 (28%)
- Stable disease- 29 (45%)
- Disease progression- 4 (6%)



- The median time to tumour response was 7.6 weeks (range, 3.7 to 16.3)
- Median duration of response was 9.1 months (95% CI, 6.4–12.7)
- Of 21 patients with an objective response, 12 (57%) had a duration of response of ≥6 months



- The median progression-free survival (PFS) was 7.3 months (95% CI, 5.4–9.1)
- Probability of being event-free at 6 months was 54% (95% CI, 39.2–66.9)
- Median overall survival (OS) was 20.5 months (95% CI, 14.3–21.8); OS data were not mature, with 24 patients (35%) having died and 28 (41%) still in follow-up
- Probability of survival at 6 and at 12 months was 87% (95% CI, 74.7–93.1) and 70% (95% CI, 54.7–81.1), respectively
- Estimated median duration of follow-up for OS was 11.5 months (95% CI, 7.9–16.7)



	MET exon 14-altered NSCLC (N = 65)	
Subgroup	**n/N with objective response[†]**	**ORR, % (95% CI)[‡]**
Age Group		
<65 yr	4/16	25.0 (7.3–52.4)
≥65 yr	17/49	34.7 (21.7–49.6)
Number of prior advanced/metastatic therapies		
0	6/24	25.0 (9.8–46.7)
≥1	15/41	36.6 (22.1–53.1)
Smoking history		
Never smoked	5/24	20.8 (7.1–42.2)
Smoker	1/1	100.0 (2.5–100)
Ex-smoker	15/40	37.5 (22.7–54.2)
Histology		
SCC	1/3	33.3 (0.8–90.6)
ACC	17/54	31.5 (19.5–45.6)
Sarcomatoid carcinoma	2/6	33.3 (4.3–77.7)
Other	1/2	50.0 (1.3–98.7)

- The most common TRAEs were edema (51%), vision disorder (45%), nausea (41%), diarrhea (39%) and vomiting (29%).
- Most TRAEs were grade 1 or 2.
- The most common (≥3%) grade 3 TRAEs were elevated transaminases (4%), and dyspnea (4%).
- There were three grade 4 TRAEs: hypophosphatemia, lymphopenia and pulmonary embolism.
- One patient had grade 5 treatment-related interstitial lung disease

Patients — no. (%) (N=69)	Any Grade	Grade 1	Grade 2	Grade 3§	Grade 4§
Any AE*†	65 (94)	14 (20)	30 (44)	17 (25)	3 (4)
Edema‡	35 (51)	23 (33)	11 (16)	1 (1)	0
Vision disorder‡	31 (45)	30 (44)	1 (1)	0	0
Nausea	28 (41)	20 (29)	8 (12)	0	0
Diarrhea	27 (39)	20 (29)	7 (10)	0	0
Vomiting	20 (29)	18 (26)	2 (3)	0	0
Fatigue	16 (23)	7 (10)	9 (13)	0	0
Constipation	14 (20)	11 (16)	2 (3)	1 (1)	0
Decreased appetite	13 (19)	8 (12)	5 (7)	0	0
Elevated transaminases‡	12 (17)	6 (9)	3 (4)	3 (4)	0
Bradycardia‡	11 (16)	9 (13)	1 (1)	1 (1)	0
Dysgeusia	10 (14)	10 (15)	0	0	0
Neuropathy‡	7 (10)	6 (9)	1 (1)	0	0

*There was 1 treatment-related grade 5 AE (interstitial lung disease, Extended Data Table 2).

TRAEs associated with a dose reduction or permanent treatment discontinuation occurred in 38% or 7% of patients

Conclusion

- Objective responses to crizotinib were observed independent of the MET exon 14 alteration splice site (ORR 12/37 (32%) for splice donor site and 5/16 (31%) for splice acceptor site) or mutation type (ORR 12/33 (36%) for base substitution and 5/20 (25%) for indel).
- The overall association of tumor response with MET exon 14 alteration (splice site region/mutation type, including patients with unknown MET exon 14 alteration status) was not significant (P=0.65)

Conclusion

- These outcomes clearly exceed those observed with second-line chemotherapy (ORR, 7–23%; median PFS, 2.4–4.5 months) and are comparable with that of first line platinum doublet-chemotherapy (ORR, 31–35%; median time to progression, 4.8–6.2 months)
- While these do not surpass the outcomes observed with select first-line chemoimmunotherapy combinations in unselected NSCLCs
- ORR of crizotinib in MET-exon-14-altered NSCLCs was lower compared with the ORRs of ~60–80% achieved with targeted therapy for other NSCLC drivers