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Efficacy and Safety of Entrectinib in Locally Advanced or Metastatic *ROS1*-Positive Non-Small Cell Lung Cancer (NSCLC)

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Disclosures

- Robert C. Doebele declares the following potential conflicts of interest
  - Speaker or Advisory Board: Takeda, Ignyta, AstraZeneca, Bayer, Genentech, F. Hoffmann-La Roche
  - Stock shareholder: Rain Therapeutics
  - Grant/research support: Ignyta
  - Royalty, IP rights/patent holder: Abbott Molecular (patent license), Rain Therapeutics (patent license), and Ignyta (licensing fee for biologic materials)
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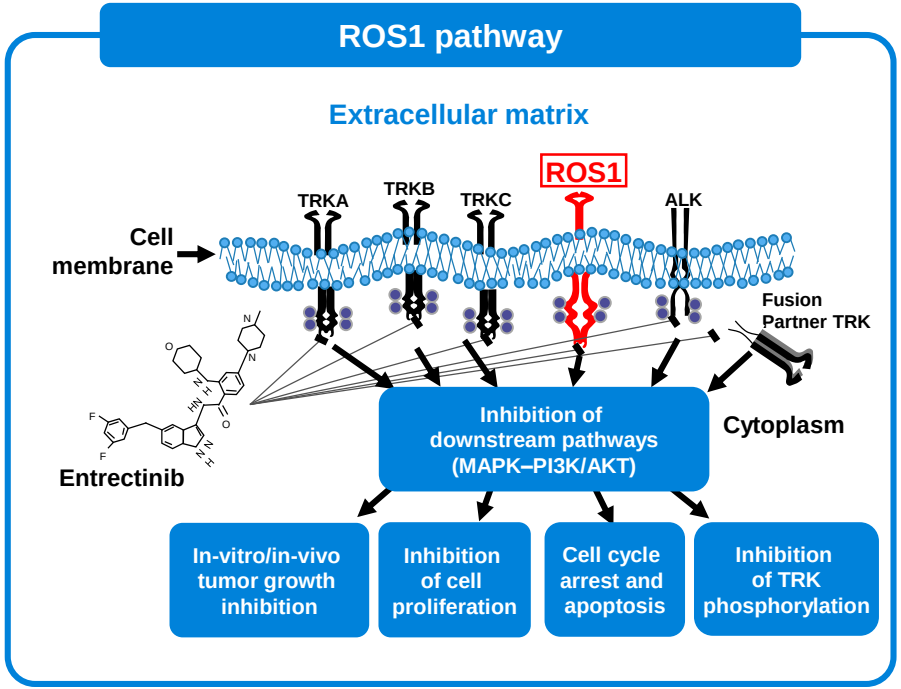
Entrectinib biology and pharmacology



Entrectinib is an oral, potent and selective ROS1/NTRK/ALK tyrosine kinase inhibitor that is CNS active[1,2]

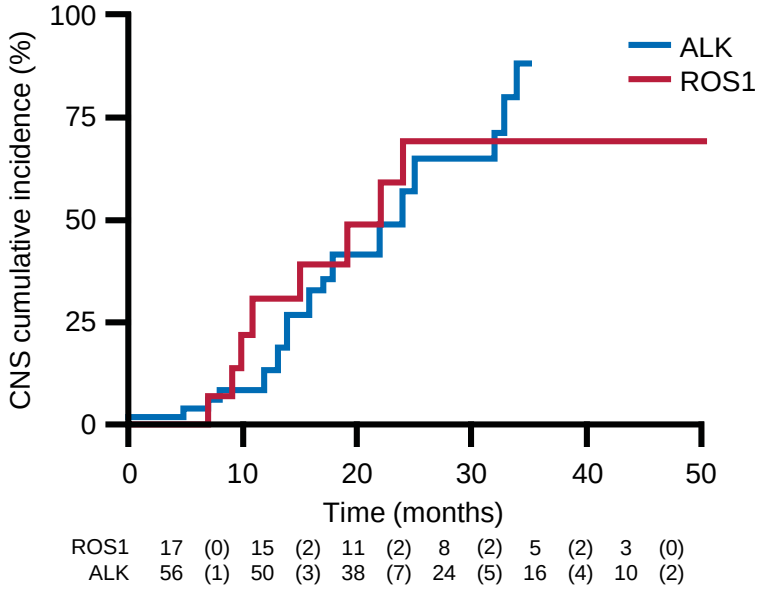
- **More potent ROS1 inhibitor** than crizotinib in preclinical studies[1]
- Potent pan-TRK inhibitor in clinical development; demonstrated clinical activity in multiple tumor histologies
- **Designed to cross the blood–brain barrier and remain within CNS**, with demonstrated clinical activity in primary brain tumors and secondary CNS metastases

1. Rolfo, et al. Expert Opin Investig Drugs 2015; 2. Ahn, et al. WCLC 2017

Brain metastases as an unmet need in patients with *ROS1*+ NSCLC

- *ROS1* fusions are oncogenic driver mutations occurring in 1–2% of NSCLC patients[1,2]
- Brain metastases are common in treatment-naïve stage IV *ROS1*+ NSCLC (36%), however, the incidence does not differ from other oncogene cohorts
- Current standard of care is crizotinib*; pivotal data from PROFILE 1001[3] (n=50):
  - ORR=72%; median PFS=19.2 months; median DOR=17.6 months[3]
- The CNS is a common first site of progression in patients with *ROS1*+ NSCLC receiving crizotinib (47%)
- Patients with *ROS1*+ tumors may also benefit from the use of a CNS-penetrant ROS1 inhibitor in the first-line setting

Cumulative development of brain metastases in NSCLC patients treated with crizotinib[4]

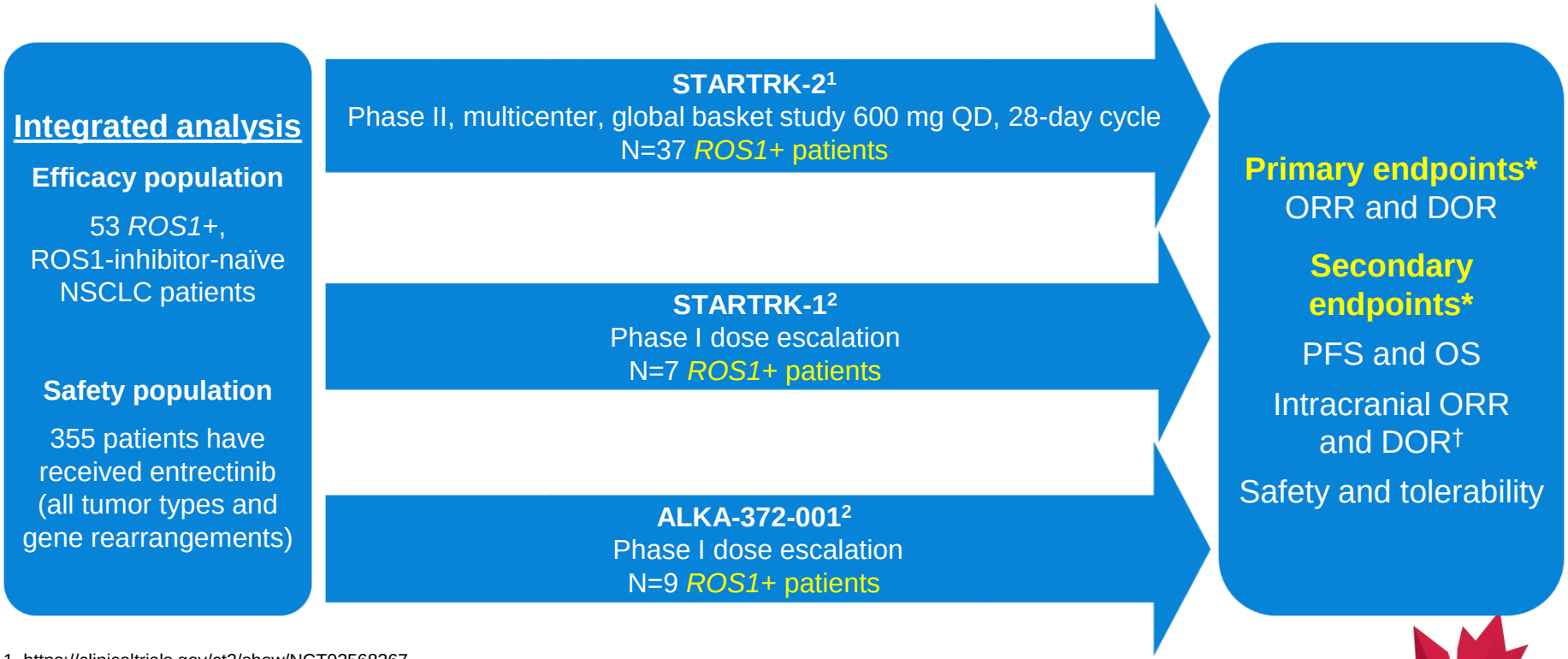


Risk table values = number at risk of CNS/death (number of CNS events)

1. Bergethon, et al. J Clin Oncol 2012; 2. Dugay, et al. Oncotarget 2017; 3. Shaw, et al. NEJM 2014; 4. Adapted from Patil, et al. J Thorac Oncol 2018; 5. Wu, et al. J Clin Oncol 2018

*Studies investigating crizotin b show variable outcomes/heterogeneity in patients, depending on the presence/absence of CNS disease and baseline ECOG PS[3,5]

Integrated analysis of three studies: entrectinib in *ROS1*+ NSCLC



1. https://clinicaltrials.gov/ct2/show/NCT02568267
2. Drilon, et al. Cancer Discov 2017

Data cut-off 31 May 2018

*BICR, blinded independent central review (RECIST v1.1)
†Patients with measurable and non-measurable CNS lesions at baseline

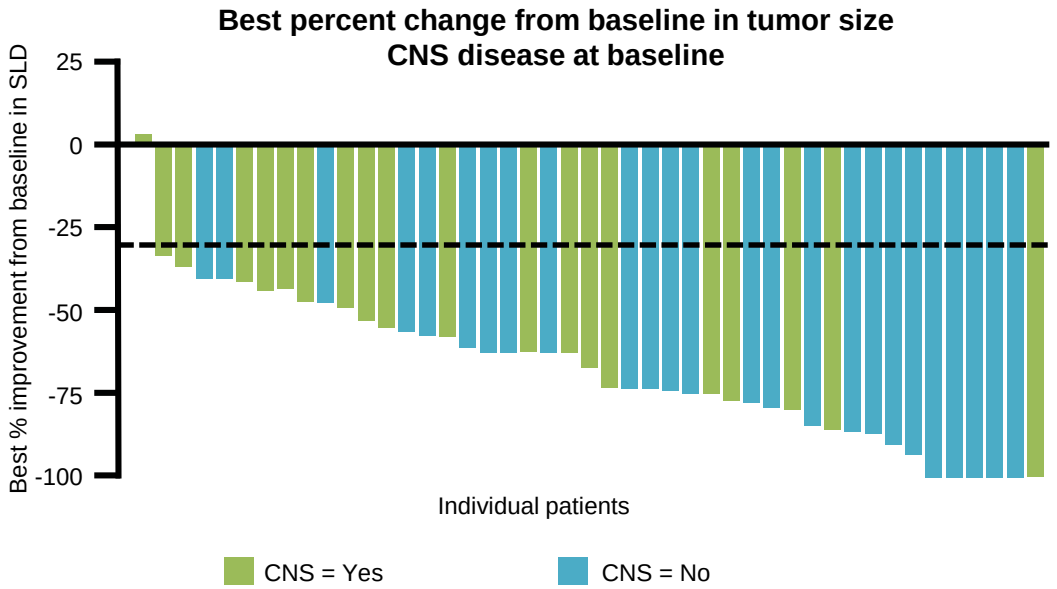
Baseline characteristics

Baseline characteristics		*ROS1*+ NSCLC population (N=53)
Age, years	Median (range)	53 (27, 73)
Sex	Female, %	64.2
Race	Asian/White, %	35.8/58.5
ECOG performance status, %	0 1 2	37.7 50.9 11.3
Smoking status, %	Never smoker Former/current smoker	58.5 41.5
Histology, n (%)	Adenocarcinoma	76.1
Prior lines of systemic therapy*,%	0 1–2 ≥3	13.2 39.7 47.1
CNS disease at baseline, n (%)		**23 (43.4)**

*Patients may have had multiple therapies. Data cut-off date: May 31 2018; ROS1-inihibitor-naïve patients with *ROS1*+ NSCLC (integrated analysis population)
ECOG, Eastern Cooperative Oncology Group

Objective response rate (BICR assessment)

Change in tumor size: *ROS1*+ NSCLC population



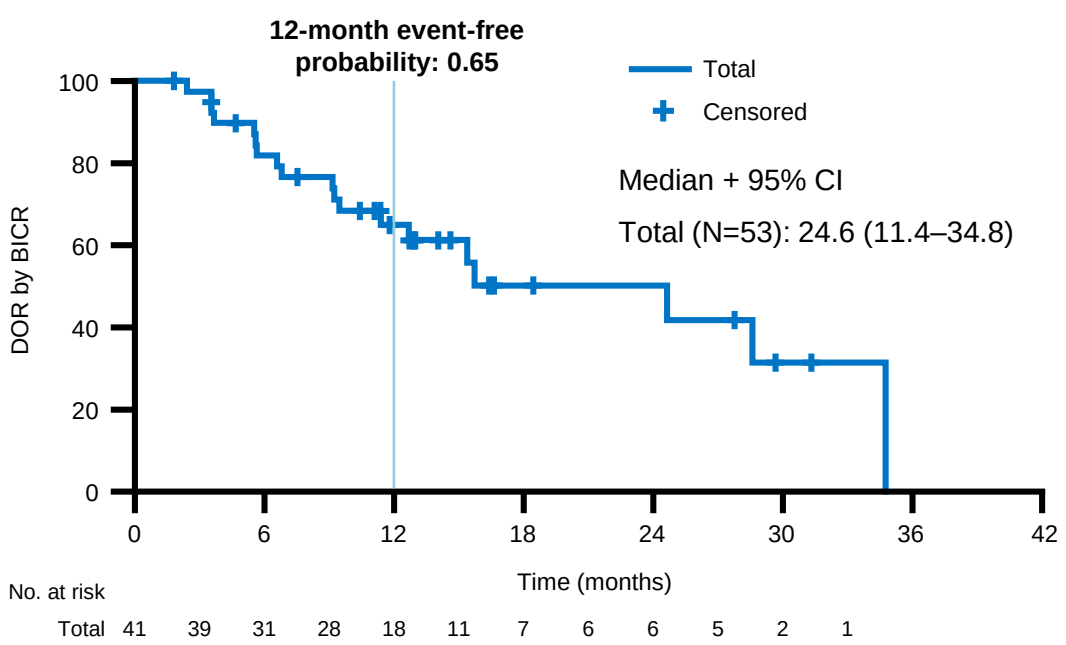
Subjects with missing SLD percent change were excluded from plot

n (%)	Total (N=53)	CNS disease at baseline (n=23)	No CNS disease at baseline (n=30)
ORR (95% CI)	**41 (77.4)** (63.8, 87.7)	**17 (73.9)** (51.6, 89.8)	**24 (80.0)** (61.4, 92.3)
CR	3 (5.7)	0	3 (10.0)
PR	38 (71.7)	17 (73.9)	21 (70.0)
SD	1 (1.9)	0	1 (3.3)
PD	4 (7.5)	4 (17.4)	0
Non-CR/PD	3 (5.7)	0	3 (10.0)
Missing or unevaluable	4 (7.5)	2 (8.7)	2 (6.7)
Clinical benefit rate* (95% CI)	41 (77.4) (63.8, 87.7)		

*Includes SD for at least 6 months. Data cut-off date: May 31 2018 (median follow up: 15.5 months), ROS1-inihibitor-naïve patients with *ROS1*+ NSCLC (integrated analysis population)

Duration of response (BICR assessment)

DOR, *ROS1*+ NSCLC



	Total (N=53)	CNS disease at baseline (n=23)	No CNS disease at baseline (n=30)
Pts included (responders), n	41	17	24
Pts with event, n (%)	19 (46.3)	6 (35.3%)	13 (54.2%)
PD, n Death, n	16 3	4 2	12 1
Time to event (months) Median 95% CI for median	 **24.6** (11.4, 34.8)	 **12.6** (6.5, NE)	 **24.6** (11.4, 34.8)

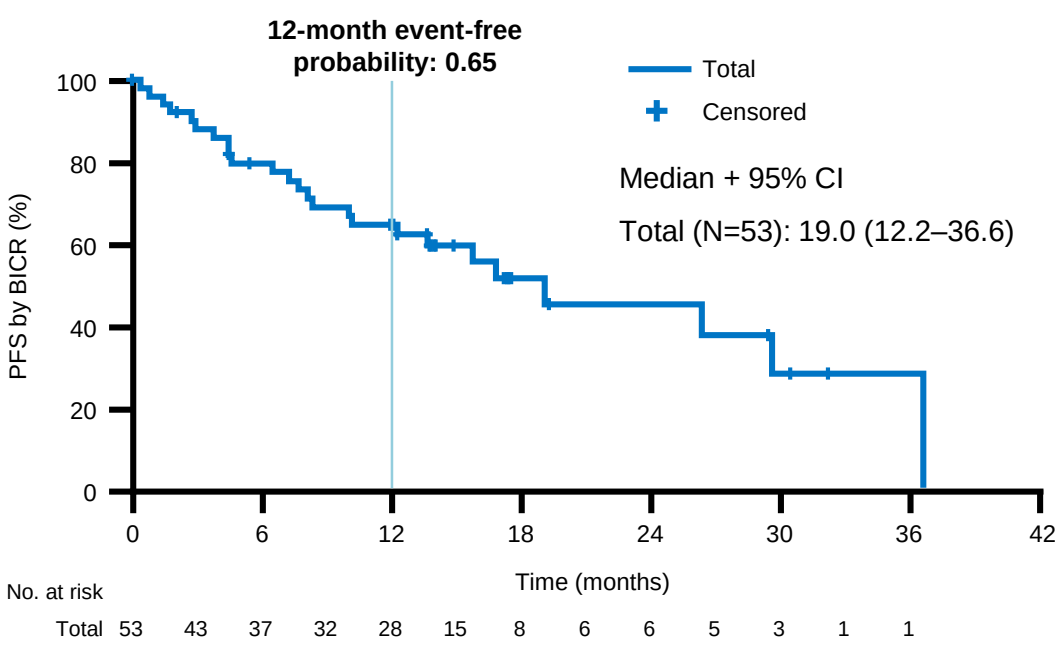
Median DOR 24.6 months (95% CI 11.4, 34.8)

Median follow up from first response: 16.6 months

Data cut-off date: May 31 2018, ROS1-inihibitor-naïve patients with *ROS1*+ NSCLC (integrated analysis population)
NE, not evaluable; PD, disease progression; Pts, patients

Progression-free survival (BICR assessment)

PFS, *ROS1*+ NSCLC



	Total N=53	CNS disease at baseline (n=23)	No CNS disease at baseline (n=30)
Pts with event, n (%)	25 (47.2)	11 (47.8)	14 (46.7)
PD, n	20	8	12
Death, n	5	3	2
Time to event (months)			
Median	**19.0**	**13.6**	**26.3**
(95% CI)	(12.2, 36.6)	(4.5, NE)	(15.7, 36.6)

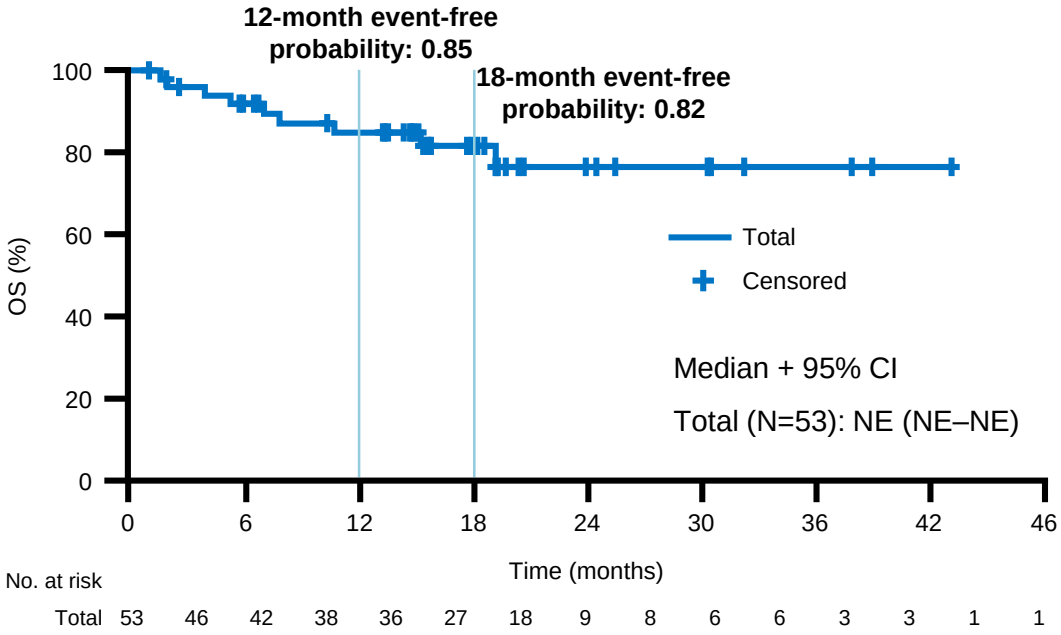
Median PFS 19.0 months (95% CI 12.2, 36.6)

Median follow up: 15.5 months

Data cut-off date: May 31 2018, ROS1-inihibitor-naïve patients with *ROS1*+ NSCLC (integrated analysis population)

Overall survival

Overall survival, *ROS1*+ NSCLC



	Total (N=53)
Pts with event	9 **(17.0%)**
Death	9
Time to event	
Median	NE
95% CI	NE

Median OS NE months (95% CI NE, NE)

Median survival follow up: 15.5 months

Data cut-off date: May 31 2018, ROS1-inihibitor-naïve patients with *ROS1*+ NSCLC (integrated analysis population)

Intracranial ORR and DOR (BICR assessment)

Intracranial response – CNS metastases at baseline by BICR (n=20*)	
Intracranial ORR, n (%) (95% CI)	**11 (55)** (31.53, 76.94)
CR PR SD PD Non CR/PD-Non evaluable	**4 (20.0)** 7 (35.0) 0 3 (15.0) 6 (30.0)
Intracranial median DOR, months (95% CI)	**12.9** (5.6, NE)
Patients with event, n (%) Disease progression, n Death, n	5 (45.5) 3 2
6 months Patients remaining at risk Event-free probability	 7 0.71

*Patients with assessable CNS metastases at baseline as per BICR
Data cut-off date: May 31 2018; ROS1-inihibitor-naïve patients with *ROS1*+ NSCLC (integrated analysis population)

Entrectinib safety summary

- 355 patients have been treated with entrectinib across 3 clinical studies
- Most AEs were Grade 1–2 and reversible
- Treatment-related AEs
  - **leading to discontinuation from study treatment: 3.9%**
  - leading to dose reduction: 27.3%
  - leading to dose interruption: 25.4%
  - serious AEs: 8.5%
  - no Grade 5 events

Most common (≥10%) treatment-related AEs, n (%)	Safety evaluable population (N=355)	
	All grades	Grade ≥3
Dysgeusia	147 (41.4)	1 (0.3)
Fatigue	99 (27.9)	10 (2.8)
Dizziness	90 (25.4)	2 (0.6)
Constipation	84 (23.7)	1 (0.3)
Nausea	74 (20.8)	0
Diarrhea	81 (22.8)	5 (1.4)
Weight increased	69 (19.4)	18 (5.1)
Paresthesia	67 (18.9)	0
Blood creatinine increased	54 (15.2)	2 (0.6)
Myalgia	54 (15.2)	2 (0.6)
Edema peripheral	50 (14.1)	1 (0.3)
Vomiting	48 (13.5)	0
Anemia	43 (12.1)	16 (4.5)
Arthralgia	44 (12.4)	2 (0.6)
Aspartate aminotransferase increased	39 (11.0)	4 (1.1)*

*One Grade 4 event (increased aspartate aminotransferase) and no Grade 5 events were evaluated by investigators to be related to study treatment
Data cut-off date: May 31 2018 (median duration of entrectinib treatment: 9.17 months (Q1, Q3: 4.60, 14.65), integrated analysis population

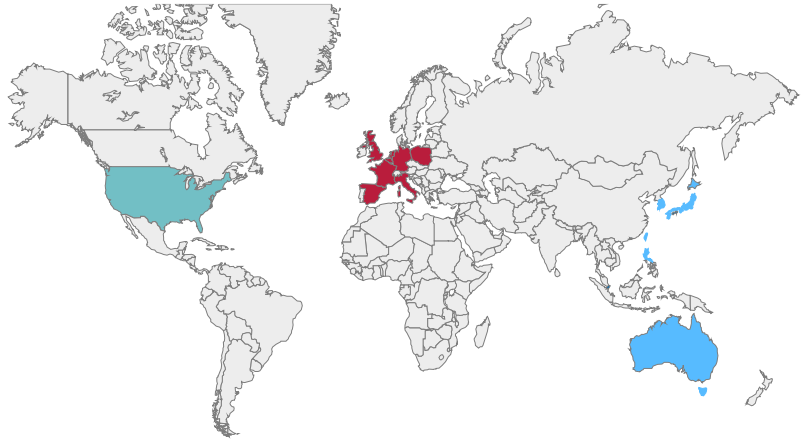
Overall conclusions

- In *ROS1*+ NSCLC patients treated with entrectinib, a clinically meaningful, deep and durable systemic response was observed in patients with and without CNS metastases
  - response rate 77.4%; median DOR 24.6 months
  - median PFS 26.3 months (without CNS metastases) and 13.6 months (with CNS metastases)
- Clinically meaningful and durable intracranial activity was also demonstrated in patients with baseline CNS disease
  - intracranial ORR 55%
  - intracranial mDOR 12.9 months
- Entrectinib was tolerable with a manageable safety profile
  - most of the AEs were managed with dose interruption/reduction and the discontinuation rate was low

Acknowledgments

- Thank you to all the patients and investigators who participated in the three studies

Study sites



Integrated analysis

STARTRK-2: 150+ sites in 15 countries
STARTRK-1: 10 sites in USA, Spain, South Korea
ALKA-372-001: 2 sites in Italy

North America	Europe	Asia Pacific
USA	Belgium	Australia
	France	Hong Kong
	Germany	Japan
	Italy	South Korea
	The Netherlands	Singapore
	Poland	Taiwan
	Spain	
	UK	

Summary of *ROS1*+ NSCLC trials with crizotinib or entrectinib

	Crizotinib				Entrectinib
Study name	PROFILE 1001	AcSé	OxOnc	EUCROSS	ALKA,STARTRK-1 & 2
Study type, location	Phase I, USA	Phase II, France	Phase II, East Asia	Phase II, Europe	Phase I and II, Global
No of Pts (% with CNS disease)	50 (NR)	37 (NR)	127 (18%)	29 (NR)	53 (43%)
Systemic ORR and DOR					
ORR by Investigator, % (95% CI)	72 (58, 84)	69 (52, 84)	NA	69 (49, 84)	76 (62, 86)
ORR by BICR, % (95% CI)	66 (51, 79)[1]	NA	72 (63, 79)	NA	77 (64, 88)
mDOR by investigator, months (95% CI)	17.6 (14.5, NR)	NA	NA	NA	16.6 (13.1, 21.4)
mDOR by BICR, months (95% CI)	18.3 (12.7, NR)[1]	NA	19.7 (14.1, NR)	NA	24.6 (11.4, 34.8)
Intracranial ORR and DOR by BICR					
Pts with CNS Disease at Baseline (n, by BICR)	NA	NA	23	NA	20[2]
IC-ORR (%) (95% CI)	NA	NA	NA	NA	75 (43, 95)[3] 55 (32, 77)[4]
IC-mDOR BICR (months)	NA	NA	NA	NA	12.9 (4.6, NE)[3] 12.9 (5.6, NE)[4]
Progression-Free Survival					
median, months (95% CI)					
by Investigator	19.2 (14.4, NR)	9.1 (5.4, NR)	NA	NA	15.5 (10, 19)
by BICR	NA	NA	15.9 (12.9, 24.0)	NA	19.0 (12, 37)
with CNS disease at baseline	NA	NA	10.2 (5.6, 13.1)	NA	13.6 (4.5, NE)
without CNS disease at baseline	NA	NA	18.8 (13.1, NR)	NA	26.4 (15.7, 36.6)
Patients remaining in follow-up for PFS, n (%)	25 (50)	NA	45 (35)	NA	28 (53)

1. Data for BICR reported in Xalkori EU Assessment Report or FDA benefit-risk summary for crizotin b in *ROS1*+ NSCLC (Kazandjian et al. 2016); 2. Sub-set of 53 patients with *ROS1*+ NSCLC with BICR-confirmed CNS disease at baseline; 3. Measurable intracranial lesions; 4. Measurable and non-measurable intracranial lesions. Source: Shaw et al. 2014; Moro-S bilot et al. 2015; Wu et al. 2018; Michels et al. 2017; Doebele, et al. 2018