IASLC 2022 World Conference on Lung Cancer
AUGUST 6-9, 2022 | VIENNA, AUSTRIA

ALK, *ROS1*, and *BRAF* Positive Lung Cancer

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DISCLOSURES

Has no relevant financial relationships

Discussion Outline

1. ***ALK – Sequencing Next-Generation TKI Therapies***
   MA13.03 – Integrated Efficacy and Safety of Brigatinib Following Alectinib Treatment in the ALTA-2 and J-ALTA Studies

2. ***ROS1 – Further Data with Entrectinib and Lorlatinib***
   MA13.04 – Entrectinib in Patients with ROS1 Fusion-Positive (ROS1-fp) NSCLC: Updated Efficacy and Safety Analysis

   P2.14-02 – TP53 Mutations Affect Sensitivity to Lorlatinib in ROS1Positive NSCLC: Final Results of the PFROST Trial

3. ***BRAF – Supportive Care Insights***
   EP08.02-070 – High Incidence of Peridiagnosis Thromboembolic Events in Patients with BRAF Mutant Lung Cancer

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Integrated Efficacy and Safety of Brigatinib Following Alectinib Treatment in the ALTA-2 and J-ALTA Studies

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Chao Family Comprehensive Cancer Center, University of California, Irvine, School of Medicine

Next-Generation ALK Inhibitors vs Crizotinib

	Alectinib	Brigatinib	Lorlatinib
Clinical trial	ALEX[9,18]	ALTA-1L[17,22]	CROWN[11]
OR (%) (95% CI)	82.9 (76.0–88.5)	74 (66–81)	76 (68–83)
Median			NE)
Median (95% C			NE)*
Median			NE)
HR for disease progression or death (95% CI)	0.47 (0.34–0.65)	0.48 (0.35–0.66)	0.28 (0.19–0.41)
OS rates (%) (95% CI)	5-year OS rate 62.5% (54.3–70.8)	3 year-OS probability 71% (62–78)	NA
Median OS, HR (95% CI)	0.67 (0.46–0.98)	0.81 (0.53–1.22)	0.72 (0.41–1.25)

Ongoing questions:
1. Preferred choice in the first-line setting?
2. **Sequencing of next-generation agents?**

Study Schema

Overview of Integrated Study Design

ALTA-2 (NCT03535740), post-alectinib cohort (n=86)[1]

Single arm, open-label study conducted in Asia, Europe, North America, and Australia

- Locally advanced or metastatic *ALK*+ NSCLC[a]
- Disease progression on alectinib
- ≤3 lines of systemic therapy for metastatic disease (included crizotinib prior to alectinib)

Brigatinib 180 mg QD (7-day lead-in at 90 mg QD)

Primary endpoint:
Confirmed BIRC-assessed ORR
Secondary endpoints:
DoR, PFS, OS, safety

J-ALTA (NCT03410108), main cohort (n=47)[2]

Single arm, open-label study conducted in Japanese patients

- Locally advanced or metastatic *ALK*+ NSCLC[a]
- Disease progression on alectinib ± prior crizotinib

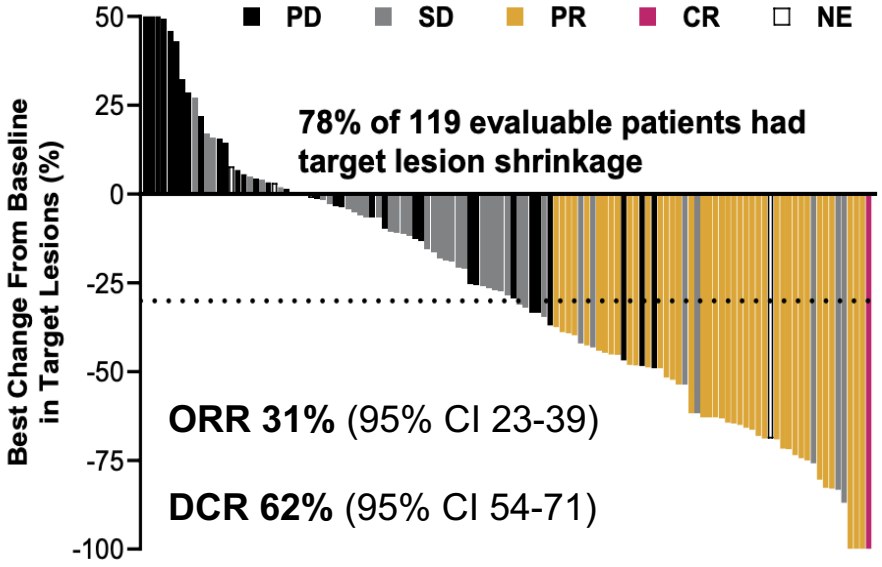
[a] Patients with asymptomatic brain metastases at screening were eligible for enrollment

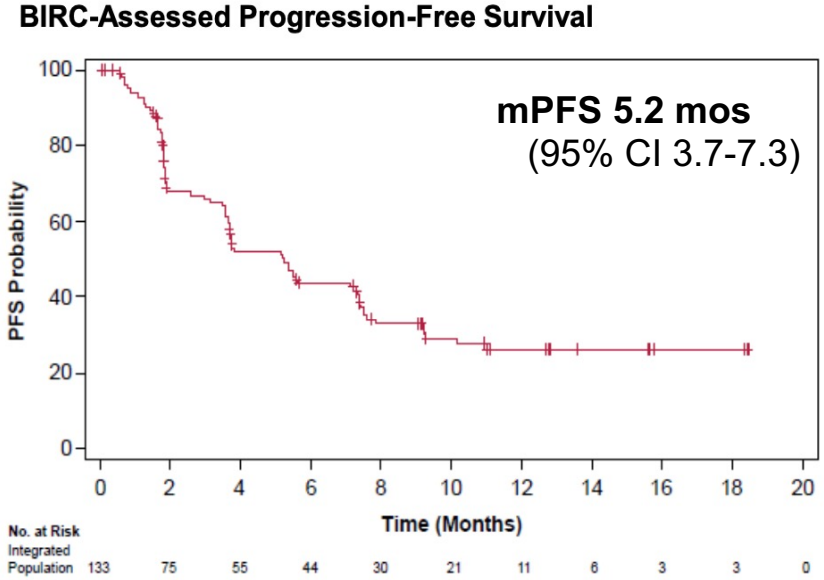
Patient Demographics

Characteristic, n (%)	Integrated Population N = 133
Age, median (range), years	54 (22–82)
Female, n (%)	68 (51)
Brain metastases at baseline by BIRC	66 (50)
Stage IV disease at study entry	131 (98)

Prior anticancer therapies	
Alectinib only	77 (58)
Crizotinib and alectinib	56 (42)
Chemotherapy for metastatic disease	41 (31)
2 prior therapies	53 (40)
3 prior therapies	24 (18)
Duration of prior alectinib, median (range), mo	15 (1–65)
Best response to prior alectinib as CR/PR	96 (72)

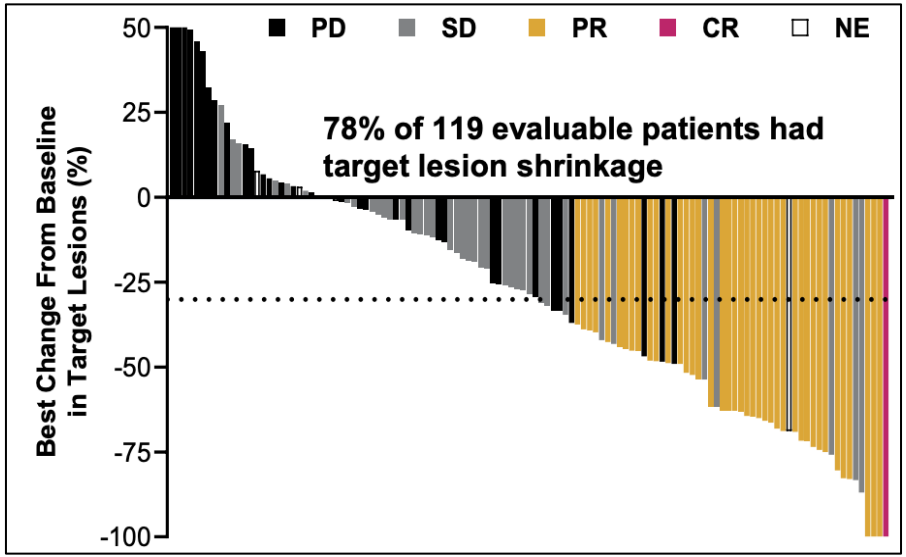
Efficacy of Brigatinib After Alectinib



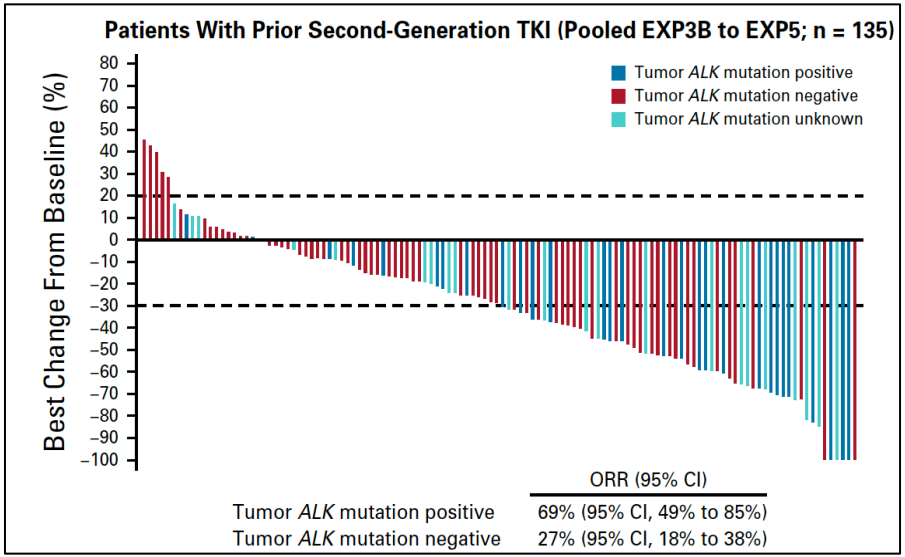


Post-Alectinib Targeted Therapy Options

Brigatinib - ORR 31%, PFS 5.2 months



Lorlatinib - ORR 40%, PFS 6.9 months



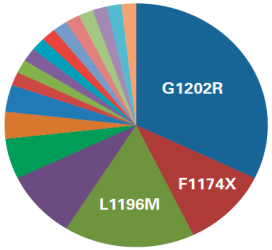
Ou et al, WCLC Abstract MA13.03, 2022
Shaw et al, *J Clin Oncol*, 2019

Post-Alectinib Therapy Options

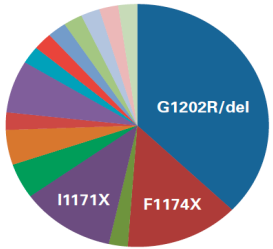
ALK+ NSCLC
Progression on alectinib

Tissue/blood NGS

cfDNA



Tumor Tissue (archival or de novo)



G1202R/del F1174X L1196M I1171X G1269A D1203N E1210K/Q
R1113Q G1128A E1129V T1151M/K C1156Y V1180L L1198F
P1213H P1329S F1245C N1335K L1122V E1161D R1192P

- Lorlatinib
- Brigatinib
- Platinum-doublet chemotherapy

Ou et al, WCLC Abstract MA13.03, 2022
Shaw et al, *J Clin Oncol*, 2019

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Entrectinib in Patients with *ROS1* Fusion-Positive NSCLC: Updated Efficacy and Safety Analysis

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**Currently at Taipei Cancer Center and Taipei Medical University Hospital, Taipei, Taiwan*

Updated Integrated Analysis (STARTRK-1, STARTRK2, ALKA-372-001)

ALKA-372-001
Phase I, dose-escalation study
NTRK / *ROS1* fusion-positive tumors

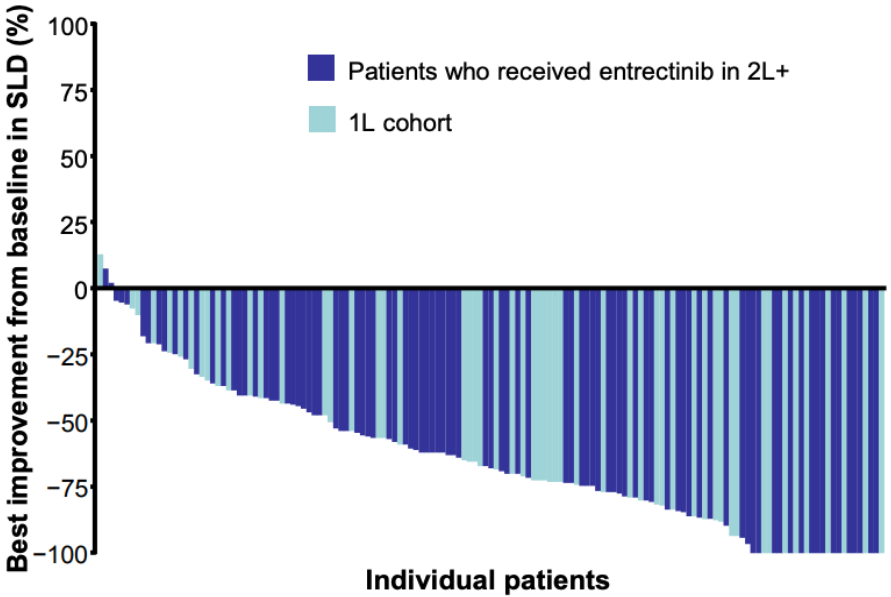
STARTRK-1
Phase I, dose-escalation study
NTRK / *ROS1* fusion-positive tumors

STARTRK-2
Phase II, multicenter, global basket study
NTRK / *ROS1* fusion-positive tumors

	Overall efficacy population N=172	First-line population* n=67
Median age, years (range)	54.5 (20–86)	55.0 (33–86)
Female, n (%)	113 (65.7)	41 (61.2)
ECOG PS, n (%) 0 / 1 / 2	66 (38.4) / 90 (52.3) / 16 (9.3)	25 (37.3) / 37 (55.2) / 5 (7.5)
Smoking status, n (%) Never smoker / Previous or current smoker	111 (64.5) / 61 (35.5)	42 (62.7) / 25 (37.3)
Prior lines of systemic therapy in metastatic setting, n (%) 0 / 1 / ≥2	67 (39.0) / 65 (37.8) / 40 (23.3)	NA
CNS metastases at baseline by investigator, n (%) Yes / No	60 (34.9) / 112 (65.1)	26 (38.8) / 41 (61.2)

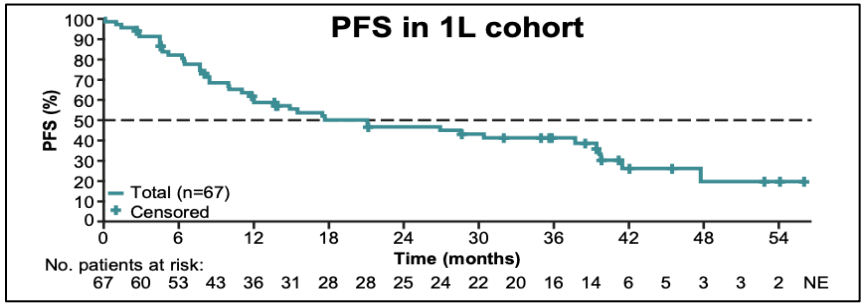
All patients in the overall efficacy population were ROS1 TKI-naive

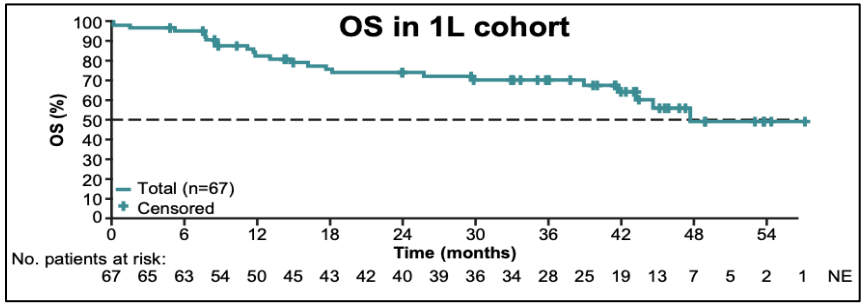
Efficacy of Entrectinib



	Overall efficacy population (N=172)	Baseline CNS metastases* (n=60)	No baseline CNS metastases* (n=112)	First-line population† (n=67)
ORR, n (%) [95% CI]	116 (67.4) [59.9–74.4]	38 (63.3) [49.9–75.4]	78 (69.6) [60.2–78.0]	46 (68.7) [56.2–79.4]

Efficacy of Entrectinib





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

Intracranial Efficacy of Entrectinib

Intracranial efficacy	Overall efficacy population (n=51)*	First-line cohort (n=23)*†
IC-ORR, n (%) [95% CI]	**25 (49.0)** [34.8–63.4]	**14 (60.9)** [38.5–80.3]
CR	8 (15.7)	3 (13.0)
PR	17 (33.3)	11 (47.8)
SD	0	0
PD	10 (19.6)	2 (8.7)
Non-CR / PD	12 (23.5)	6 (26.1)
Missing / non evaluable	4 (7.8)	1 (4.3)
Median IC-DoR, months [95% CI]	**12.9** [7.6–22.5]	**12.9** [7.6–22.2]
No. remaining at risk (% event free): 6 / 12 mos	19 (79) / 14 (58)	12 (86) / 9 (64)
Median IC-PFS, months [95% CI]	**12.0** [6.7–15.6]	**15.6** [7.7–21.1]
No. remaining at risk (% event free): 6 / 12 mos	33 (70) / 23 (48)	18 (78) / 13 (57)

Data cut-off: 02 Aug 2021. *In patients with BICR-assessed CNS metastases at baseline; †Exploratory analysis.
BICR, blinded independent central review; IC, intracranial

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TP53 Mutations Affect Sensitivity to Lorlatinib in *ROS1* Positive NSCLC: Final Results of the PFROST Trial

L. Landi *et al*
National Cancer Institute Regina Elena
Rome, Italy

PFROST Trial Schema

***ROS1*-positive NSCLC**
1. **Prior crizotinib**
2. **RECIST measurable disease**
3. **ECOG 0-2**
4. **Asymptomatic brain metastases and leptomeningeal disease allowed**

NGS (NEOSelect or NEOLiquid) on baseline tissue or liquid specimens

Lorlatinib 100 mg qd

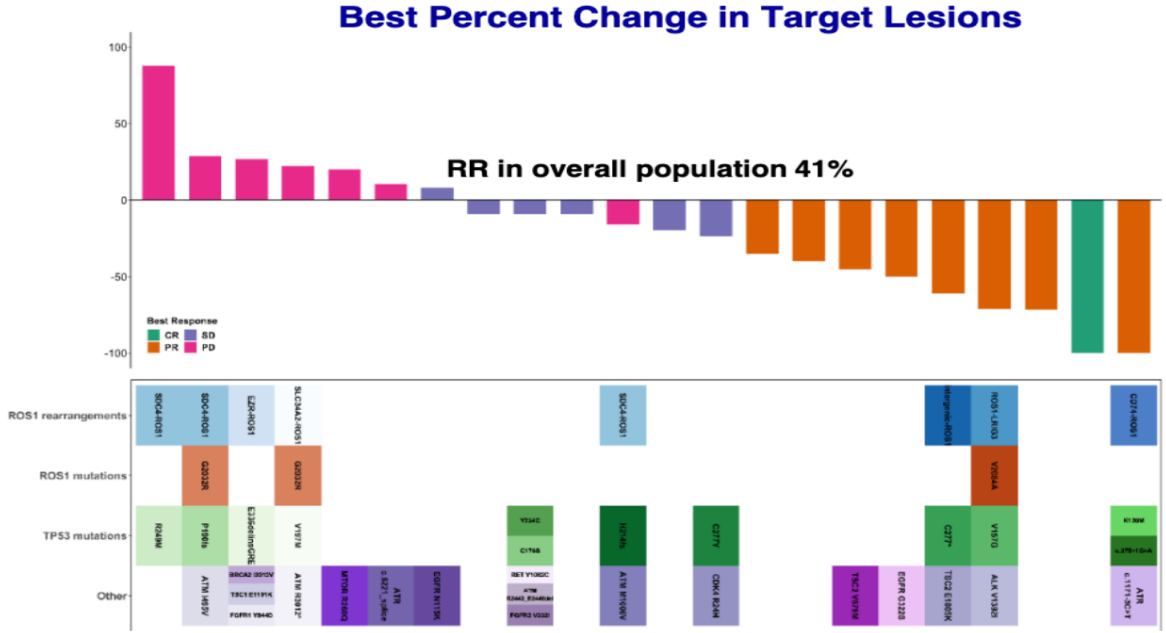
Primary Endpoint:
- ORR

Secondary Endpoints:
- PFS
- OS
- Safety
- Biomarker assessment

Patient Demographics

	N 22	% 100
Age, median (range)	56 (39-82)	
Male/Female	8/14	36.3/63.6
ECOG PS 0/1/2	8/14/0	36.3/63.6/0
Never Smoker/Past Smoker/Current smoker	13/7/2	59.1/31.8/9.1
Previous therapy lines, 1/2/>2	4/16/2	18.2/72.7/9.1
Number of disease sites, 1/2/>2	1/5/16	4.5/22.8/72.7
Brain mets at baseline	15	68.1
Availability of plasma at baseline	21	90.9
TP53 mutations	11	52.3

Overall Efficacy of Lorlatinib (Entire Cohort)

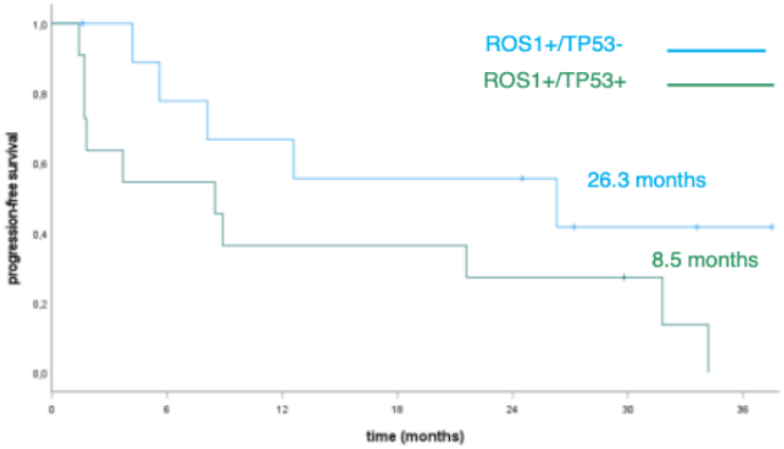


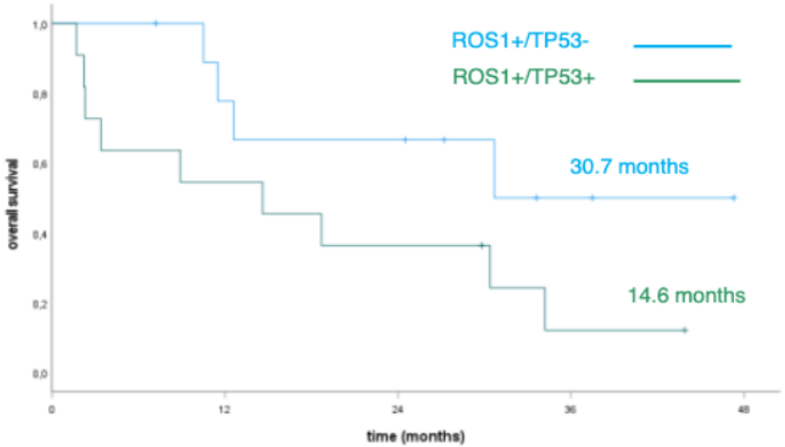
- **Entire cohort (n = 22)**
  PFS 8.9 months (95% CI 2.2-15.8)
  OS 30.4 months (95% CI 10.6-50.2)

- **Baseline brain metastases (n = 15)**
  PFS 8,5 months (95% CI 4.3-12.7)
  OS 30.4 months (95% CI 0-62.4)

Efficacy of Lorlatinib With *TP53* Mutations

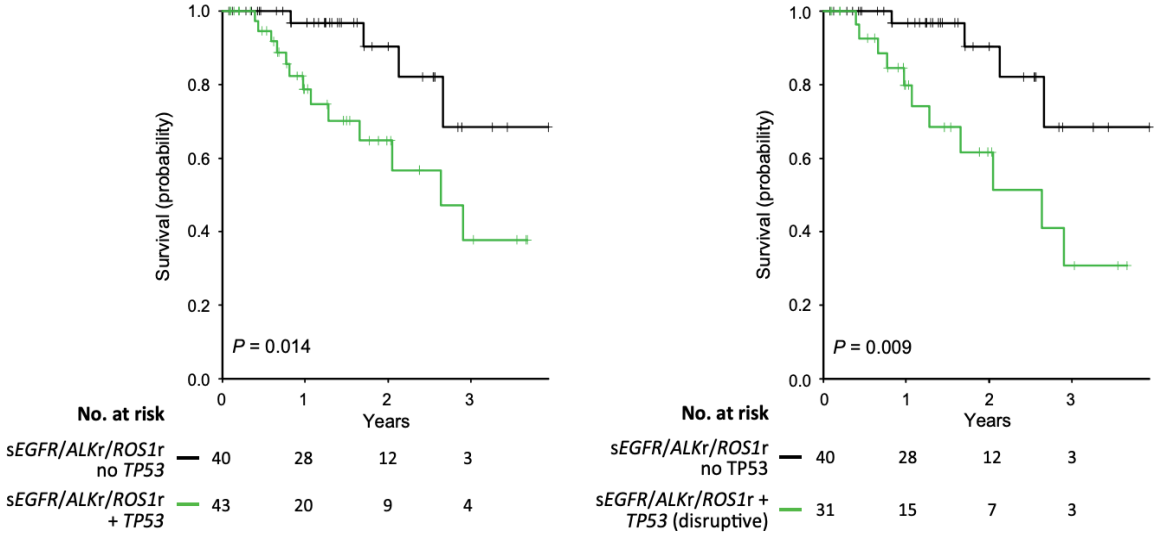
PFS and OS according to TP53 status





ORR – 27.3% (*ROS1+/TP53+*) vs 50% (ROS1+/TP53-)

TP53 Mutations in Driver-Mutated Lung Cancer



- Negative effect of concurrent *TP53* mutations has been suggested in earlier studies of *EGFR/ALK/ROS1* (see figure)
- PFROST results suggest ongoing negative effect of *TP53* mutations even with more effective, CNS-penetrant, next-generation therapies
- Highlights the value of NGS testing

Aisner et al, *Clin Cancer Res*, 2018

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High Incidence of Peridiagnosis Thromboembolic Events in Patients with *BRAF*-mutant Lung Cancer

I. Aparicio Salcedo *et al*
Hospital General Universitario Gregorio Maranon
Madrid, Spain

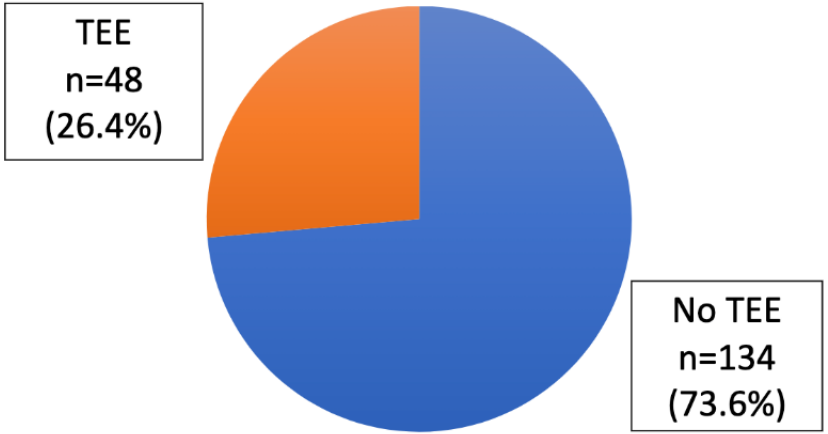
Retrospective Multi-Center Study

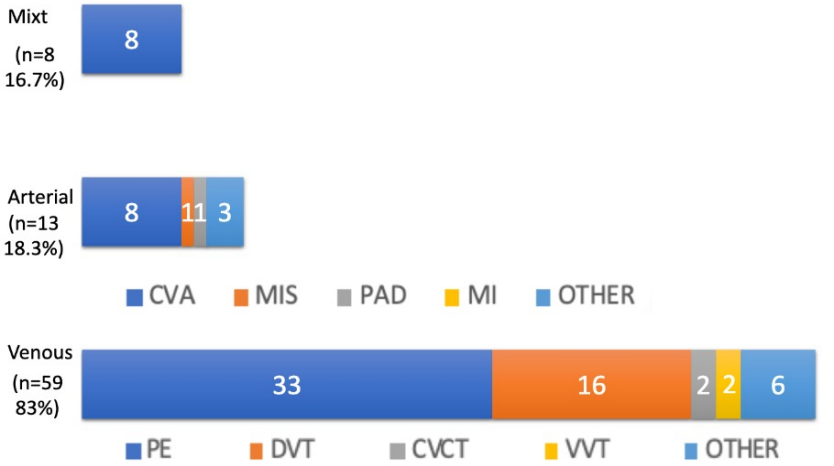
Variable	n (%)
Sex: Male	107 (58.8%)
Female	75 (41.2%)
Mean Age at diagnosis (range)	59.7 (57.8-71.6)
Smoking status: Former/Current	153 (83.9%)
Never	29 (15.9%)
ECOG: 0-1	151 (83%)
≥2	31 (16.9%)
Histology: Adenocarcinoma	159 (87.4%)
Squamous	7 (3.8%)
NOS	16 (8.8%)
Stage IV: De novo	134 (73%)
Relapsed	48 (26.4%)
BRAF mutation: V600E	70 (38.5%)
non-V600E	112 (61.5%)
PDL1: <1%	51 (33.1%)
1-49%	48 (31.2%)
≥50%	55 (35.7%)
NOS	28 (15.3%)
CVC: No	169 (92.9%)
Yes	13 (7%)
Khorana Risk Score: 1-2	143 (78.1%)
3-4	34 (17.5%)
NE	6 (3.3%)
Previous thrombosis history: No	161 (89.4%)
Yes (arterial)	13 (7.2%)
Yes (venous)	6 (3.3%)
Regular treatment with anticoagulants or antiplatelet agents:	42 (23%)
CVRF (HBP, DL , DM)	109 (60%)

NOS: not otherwise specified, CVC: central venous catheter; CVRF: cardiovascular risk factors (high blood pressure, dyslipidemia, diabetes).

Incidence of Thromboembolic Events

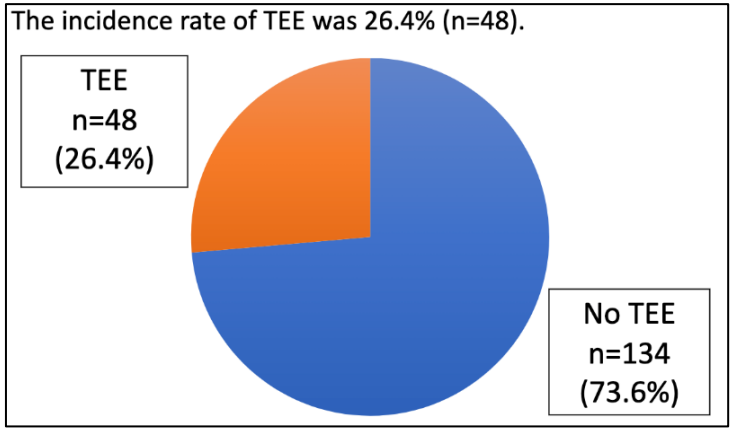
The incidence rate of TEE was 26.4% (n=48).





CVA: cerebrovascular accident; MIS: mesenteric ischemia; PAD: peripheral arterial disease; MI:myocardial infarction; Other (arterial): aorta artery (2), carotid artery; PE: pulmonary embolism; DVT: deep venous thrombosis; CVCT: thrombosis associated with CVC; VVT: visceral venous thrombosis; Other (venous): superficial venous thrombosis, superior vena cava, jugular vein, subclavian vein.

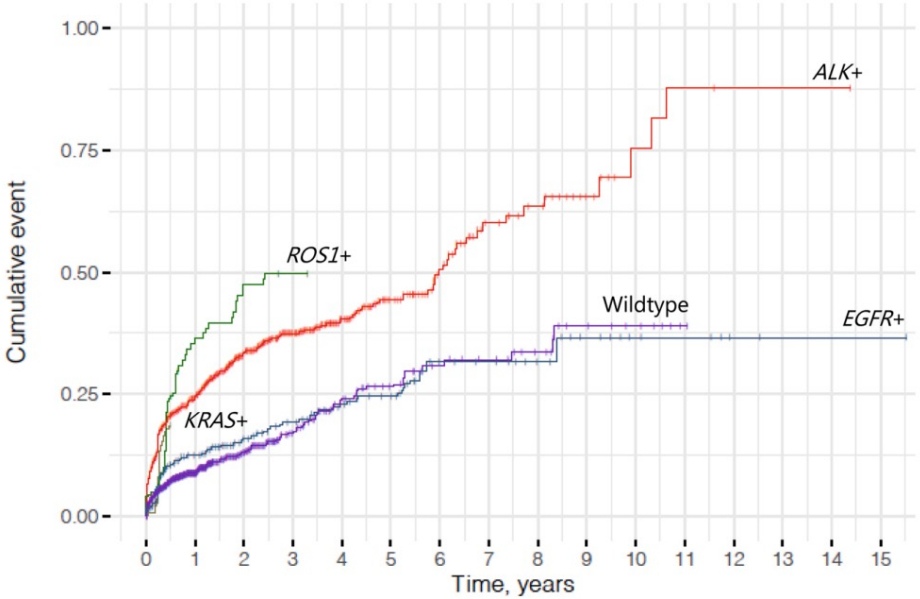
Associated Clinical Outcomes



TEE = thromboembolic event

- Median time to onset of TEE: 1.5 months
- Incidence not associated with history of thrombosis, type of BRAF mutation (V600E/non-V600E), type of therapy), or Khorana risk score
- Worse outcomes associated with TEE:
  mOS 10.5 vs 19.4 months (TEE vs non-TEE; p 0.4)
  mOS 9.8 vs 41 months (arterial vs venous TEE; p 0.01)

Comparison to Other Drivers in Lung Cancer?



- *ALK* and *ROS1* mutations have been associated with an increased risk of VTE (e.g., incidence rates 17% and 30%, respectively, versus ~7% for *EGFR* or wild-type).
- How *BRAF* mutations compare to these other drivers warrants further investigation.

Zhu et al, *Lung Cancer*, 2021

Conclusions

- Sequencing next-generation targeted therapies, such as brigatinib after progression on alectinib, is feasible and effective in *ALK*-rearranged NSCLC.
- Entrectinib and lorlatinib are effective therapies in *ROS1*-rearranged NSCLC, but concurrent *TP53* mutations may still portend a worse prognosis.
- Attention to thromboembolic events may be warranted in *BRAF*-positive NSCLC.