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Iniciativa científica de:
GECP lung cancer research

Enfermedad avanzada: tratamiento antidiana en mutaciones frecuentes

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EGFR mutations

First-Line Tyrosine Kinase Inhibitor With or Without Aggressive Upfront Local Radiation Therapy In Patients With EGFRm Oligometastatic Non-Small-Cell Lung Cancer: Interim Results of A Randomized Phase III, Open-Label ClinicalTrial (SINDAS) (NCT02893332).

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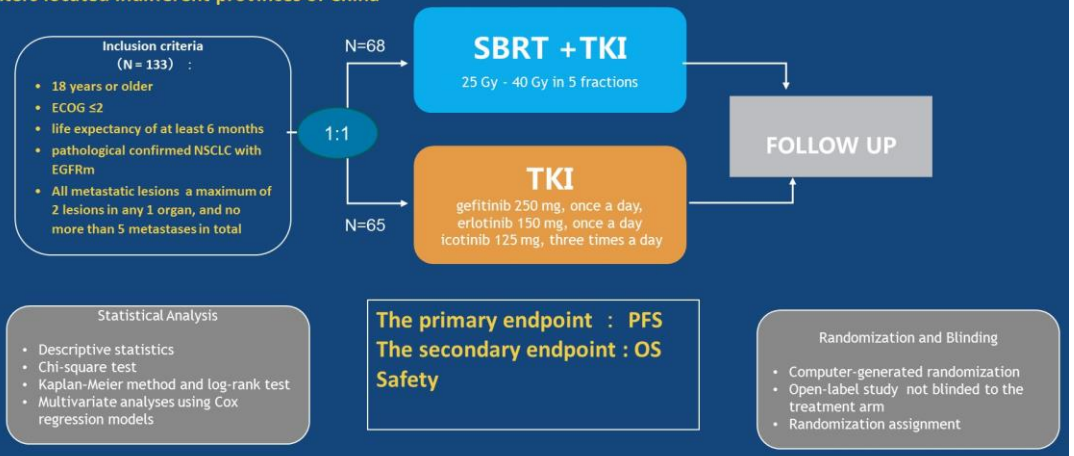
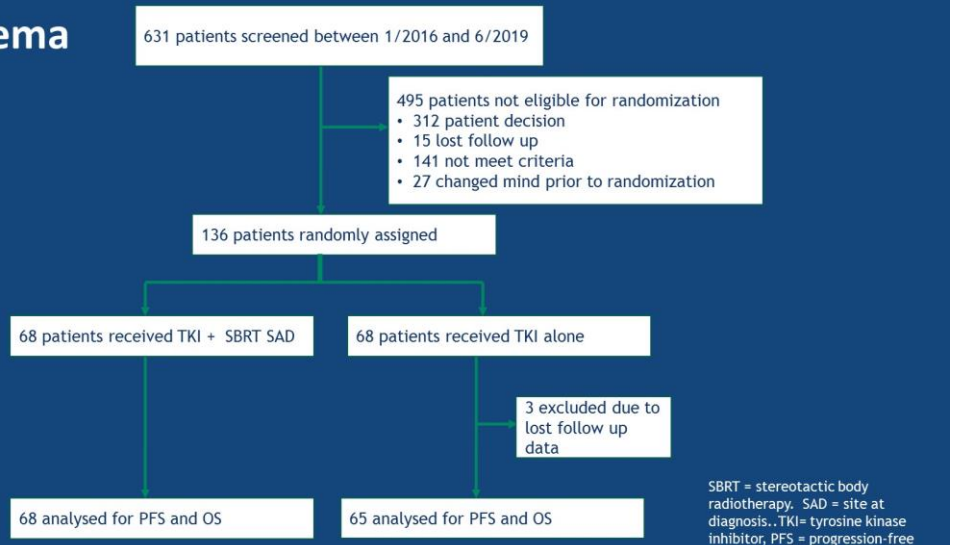
Study Design and Enrollment

2016.1—2019.6, Investigator-initiated, multicenter, open label, parallel-group, phase 3 randomized clinical trial from 5 centers located indifferent provinces of China

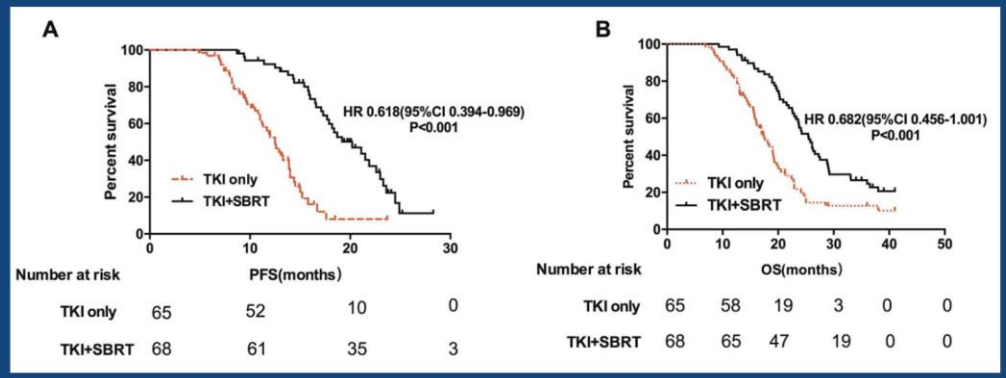


Study schema



SBRT = stereotactic body radiotherapy. SAD = site at diagnosis..TKI= tyrosine kinase inhibitor, PFS = progression-free survival; OS=overall survival

Kaplan-Meier plot of PFS (A) and OS (B)



SBRT=stereotactic body radiotherapy. HR=hazard ratio. (A) PFS and (B) OS. PFS,=progression-free survival; OS,=overall survival; C= confidence interval

EGFR mutations

Multivariate analyses Progression free survival

Clinicopathological Features	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Age (years) (≥ 63vs<63)	1.045	0.302-5.997	0.562			
Gender(Male vs Female)	0.978	0.429-2.230	0.957			
ECOG score (0vs 1-2)	0.372	0.117-0.876	0.014	0.502	0.220-0.746	0.019
T stage(T3-4 vs T1-2)	3.175	1.361-7.403	0.007	1.095	0.986-1.216	0.089
N stage(N2-3 vs <N0-1)	1.012	0.999-1.026	0.065			
Number of Mets (< 2 vs ≥3)	2.129	1.319-3.435	0.002	1.925	1.206-3.072	0.004
Mutation (19 vs 20 and 21 exon)	0.749	0.567-0.989	0.042	0.942	0.606-1.428	0.090
Treatment (TKI alone vsTKI + SBRT)	2.750	1.420-3.790	0.002	1.390	1.070-1.946	0.005

Multivariate analyses Overall Survival

Clinicopathological Features	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Age (years) (≥ 63vs<63)	1.014	0.710-1.480	0.330			
Gender(Male vs Female)	1.007	0.780-2.230	1.460			
ECOG score (0vs 1-2)	0.011	0.012-0.371	0.009	0.012	0.011-0.435	0.016
T stage(T3-4 vs T1-2)	3.520	1.190-7.620	0.001	2.060	1.080-5.540	0.017
N stage(N2-3 vs <N0-1)	2.450	1.320-5.960	0.013	1.560	1.190-3.690	0.062
Number of Mets (< 2 vs ≥3)	2.129	1.319-3.435	0.002	1.925	1.206-3.072	0.004
Mutation (19 vs 20 and 21 exon)	0.015	0.119-0.810	0.001	0.091	0.022-0.381	0.001
Treatment (TKI alone vsTKI + SBRT)	3.580	1.940-7.620	<0.001	2.110	1.310-5.970	0.004

Conclusion

- This randomized phase III study measuring upfront radiation to sites of diagnoses directly contributed to the improvement of both progression-free and overall survival with equivalent toxicity in EFGRm oligometastastic participants.
- The finding confirmed previous hypotheses of a benefit of consolidative SBRT for limited metastatic NSCLC.Our finding suggests aggressive local therapy to sites at diagnosis upfront should be explored further in large cohort phase 3 trials as a standard treatment option in this clinical scenario.

Take home points

- Adding SBRT to standard of care TKI treatment prolonged PFS and OS compared with TKI alone treatment
- Adding SBRT to TKI treatment was feasible and was not associated with any substantial increase in the toxicity profile of TKI alone treatment.
- Although this is an investigational interim report, the finding is suggestive of value in a further exploratory study.

EGFR mutations

NEJ026:
Final overall survival analysis of bevacizumab plus erlotinib treatment for NSCLC patients harboring activating EGFR-mutations

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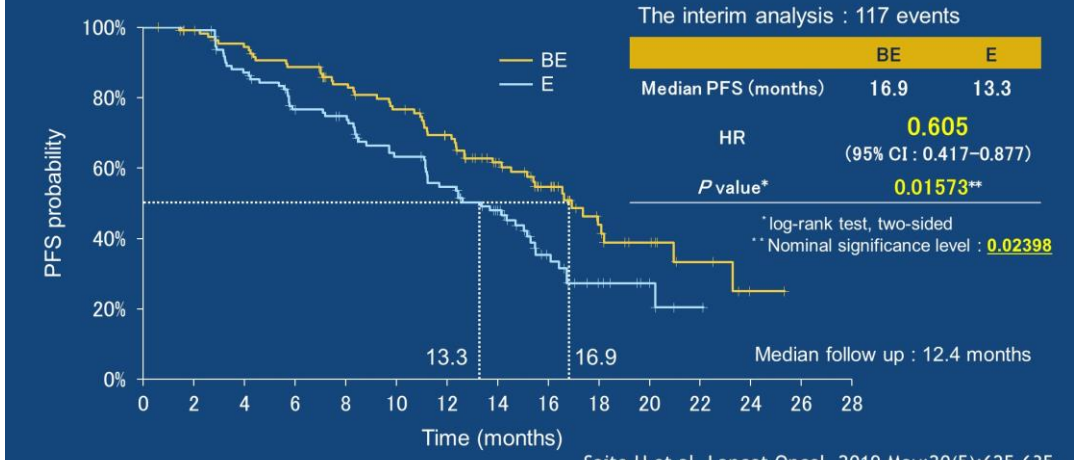
OS benefit of first line EGFR-TKI mono/combo treatment

	phase, n	Gefitinib	Erlotinib	Afatinib	Dacomitinib	Osimertinib	Gefitinib +CBDCA +PEM	Erlotinib +BEV	HR
FLAURA [1)]	III, 556	31.8				38.6			0.80
LUX-LUNG 7 [2)]	IIB, 319	24.5		27.9					
ARCHER1050 [3)]	III, 452	26.8			34.1				0.76
NEJ005 [4)]	II, 80						41.9*		
JO25567 [5)]	II, 154		47.4					47.0	
NEJ009 [6)]	III, 342	38.8					50.9		0.72
Noronha V, et al. [7)]	III, 350	17					n.r.		0.45

OS (months)

1) Ramalingam SS et al. N Engl J Med 2020; 2) Paz-Ares L et al. Ann Oncol. 2017; 3) Mok TS et al. J Clin Oncol 2018; 4) Oizumi S et al. ESMO Open 2018, * concurrent regimen; 5) Yamamoto N, et al. ASCO Annual Meeting 2018; Oral session #9007; 6) Hosomi Y et al. J Clin Oncol. 2020 7) Notonha V et al. J Clin Oncol. 2020

Primary endpoint : PFS by independent review



The interim analysis : 117 events

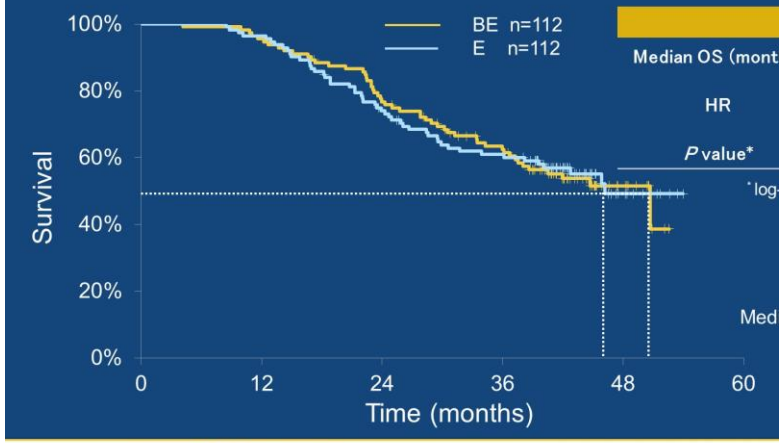
	BE	E
Median PFS (months)	16.9	13.3
HR	0.605 (95% CI : 0.417–0.877)	
P value*	0.01573**	

*log-rank test, two-sided
**Nominal significance level : 0.02398

Median follow up : 12.4 months

Saito H et al. Lancet Oncol. 2019 May;20(5):625-635.

Final Overall Survival



	BE	E
Median OS (months)	50.7	46.2
HR	1.007 (95% CI : 0.681–1.490)	
P value*	0.973	

*log-rank test

Median follow up : 39.2 months

EGFR mutations

Abstract ID: 9602

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Efficacy and safety of Alflutinib (AST2818) in patients with T790M mutation positive NSCLC: A phase IIb multicenter single arm study

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Abstract

Background:
Alflutinib (AST2818) is a third generation EGFR-TKI targeting both sensitizing EGFR and EGFR T790M mutations. This phase IIb, multicenter, single arm study (ALSC003, NCT03452592) aimed to assess the efficacy and safety of Alflutinib in patients with EGFR T790M mutated non-small cell lung cancer (NSCLC).

Methods:
Patients with centrally confirmed EGFR T790M mutation in tumor tissue, locally advanced or metastatic NSCLC who progressed after first/second-generation EGFR-TKIs or primary EGFR T790M mutation positive received 80 mg Alflutinib orally once daily. The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety. Efficacy was assessed by independent radiological review committee (IRRC) per RECIST 1.1. Safety was assessed by NCI CTCAE version 4.03.

Results:
From Jun 4, 2018 to Dec 8, 2018, 220 patients were enrolled. Patients were representative: median age 61, stage IV 96.4%, ECOG PS 1/2 77.3%/4.1%, CNS metastatic 39.5% (by IRRC). By Jan 29, 2020, the median follow-up time was 9.6 months. The ORR was 74.1% (163/220 [95% CI 67.8–79.7]). The DCR was 93.6% (206/220). The median PFS was 9.6 months (95% CI 8.2–9.7). Median OS was not yet reached. By Nov 6, 2019, 19 (65.5%) of 29 patients with measurable CNS metastases had an intracranial objective response, and the median PFS was 11.0 months (95% CI 8.3, NA). By Nov 6, 2019, 214 (97.3%) patients had at least one adverse events (AEs), which were mostly grade 1 or 2. The most common AEs were cough (49 [22.3%]), increased aspartate aminotransferase (37 [16.8%]), and upper respiratory tract infection (37 [16.8%]). Grade ≥ 3 AEs occurred in 53 (24.1%) patients. Drug related ≥ Grade 3 AEs assessed by investigator occurred in 22 (10.0%) patients.

Conclusions:
Alflutinib has promising efficacy and acceptable safety profile for the treatment of EGFR T790M mutated NSCLC patients.

Background

- Alflutinib (AST2818) is a newly developed, oral, irreversible third generation Epidermal growth factor receptor (EGFR) Tyrosine kinase inhibitor (TKI) targeting both sensitizing EGFR and EGFR T790M mutations.
- Preclinical studies revealed alflutinib had potent antitumor activity comparable to that of osimertinib (data on file).
- The phase I/II study (NCT02973763, NCT03127449) of aluflutinib has shown alflutinib is clinically effective with an acceptable safety profile in patients with EGFR T790M mutated advanced non-small cell lung cancer (NSCLC) , even in those with central nervous system (CNS) metastases.
- This phase IIb, multicenter, single arm study (ALSC003, NCT03452592) aimed to further assess the efficacy and safety of Alflutinib in patients with EGFR T790M mutated NSCLC.

Methods

- This is a phase IIb, multicenter, single arm study conducted at 46 centers in China.
- Eligible patients were aged 18 years or older, had histologically or cytologically confirmed locally advanced or metastatic NSCLC, not suitable for surgery or radiotherapy, radiologically progressed after first or second generation EGFR TKI with centrally confirmed EGFR T790M mutation, or with primary EGFR T790M mutation, had measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients with asymptomatic, stable CNS metastases not requiring steroids for at least 4 weeks before the first dose of alflutinib were allowed to be included.
- Eligible patients received alflutinib 80mg orally per day until disease progression or intolerable toxicity. Efficacy was evaluated every 6 weeks in the first 48 weeks, then every 12 weeks in the following weeks by independent radiological review committee (IRRC) using RECIST 1.1. Safety was assessed by NCI CTCAE version 4.03.
- The primary endpoint was objective response rate (ORR) by IRRC. Secondary endpoints included progression free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), clinical benefit rate (CBR) and safety.

Results

- From Jun 4, 2018 to Dec 8, 2018, 220 patients were enrolled in total.
- Baseline characteristics of patients were representative: median age 61, stage IV 96.4%, ECOG PS 1/2 77.3%/4.1%, CNS metastatic 39.5% (Table 1).

Table 1. Baseline patient characteristics (n=220)

Characteristics		No. of patient (%)
Age	Median (range)	61 (29-80)
Sex	Male	99 (45.0%)
	Female	121 (55.0%)
Stage	III	8 (3.6%)
	IV	212 (96.4%)
Smoking history	Smoker	60 (27.3%)
	Non-smoker	160 (62.7%)
Prior lines of therapy	0*	6 (2.7%)
	1	162 (73.6%)
	2	38 (17.3%)
	3	9 (4.1%)
	4	4 (1.8%)
	>5	1 (0.5%)
EGFR mutations in tumor	T790M	220 (100%)
	19del	133 (60.5%)
	L858R	81 (36.8%)
	19del + L858R	3 (1.4%)
	others	3 (1.4%)
ECOG PS	0	41 (18.6%)
	1	170 (77.3%)
	2	9 (4.1%)
CNS metastases by IRRC	Yes	87 (39.5%)
	No	133(60.5%)

* de novo T790M mutation

Efficacy
- At the data cut-off (DCO, Jan 29, 2020), the ORR and DCR by IRRC was 74.1% (163/220) and 93.6% (206/220) respectively (Table 2). At the DCO, the median follow-up of PFS was 9.6 months, the median PFS was 9.6 months (95% CI 8.2, 9.7) (Figure 1).
- Of the 220 enrolled patients, 87 had measurable and/or non-measurable CNS metastases, and 29 had one or more measurable CNS metastases assessed by IRRC. At DCO of Nov 6, 2019, the CNS ORR and DCR in patients with one or more measurable CNS lesions was 65.5% and 100% respectively. Median CNS PFS was 11.0 months (95% CI 8.3, NA) in patients with measurable and/or non-measurable CNS lesions.

Table 2. Summary of response to alflutinib assessed by IRRC

	N=220
Complete response (CR)	0
Partial response (PR)	163 (74.1%)
Stable disease (SD)	43 (19.5%)
Progressed disease (PD)	12 (5.5%)
Unevaluable (UE)	1 (0.5%)
Not evaluated	1 (0.5%)
ORR	74.10%
95% CI	67.8%-79.7%

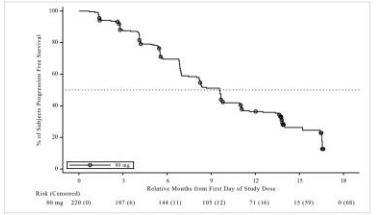

Figure 1. Kaplan-Meier estimates of PFS

Safety
- At the DCO of Nov 6, 2019, the median time of exposure to alflutinib was 9.7 months.
- 24.1%(53/220) of patients had grade ≥ 3 adverse events (AEs), and 10.0% (22/220) had drug-related grade ≥ 3 AEs. The most common drug related grade ≥ 3 AEs were increased aspartate aminotransferase (three [1.4%]), increased alanine aminotransferase (three [1.4%]) and increased γ-glutamyltransferase (three [1.4%]).
- 21.4%(47/220) of patients had serious AEs (SAEs) and 5.5% (12/220) had drug related SAEs.
- Only 8.6% (19/220) and 8.2% (18/220) of patients had diarrhea and rash of all grade respectively. No grade ≥ 3 diarrhea or rash were observed. Interstitial lung disease was observed in 1 patient (0.5%).
- Dose interruption and reduction were reported in 11.4% (25/220) and 2.3% (5/220) patients. Permanent discontinuation of alflutinib occurred in 3.6% (8/220) patients.
- 4 patients experienced AEs with death outcome, including CNS metastases (n=2), respiratory failure (n=1) and unknown death (n=1). The causality between study drug and first 3 events were assessed as probably not related by investigators, whereas the last one could not be determined due to the unknown cause of death.
- The detailed adverse events were listed in table 3.

Table 3. Treatment emerged adverse events (TEAEs, n=220)

TEAEs (overall rate ⩾10%)	Any Grade TEAEs	Grade ≥ 3 TEAEs	Grade ≥ 3drug related TEAEs by investigator
At least one TEAE	214(97.3%)	53(24.1%)	22(10.0%)
Cough	49(22.3%)	0	0
Upper respiratory tract infection	37(16.8%)	1(0.5%)	0
Increased aspartate aminotransferase	37(16.8%)	3(1.4%)	3(1.4%)
Increased alanine aminotransferase	35(15.9%)	3(1.4%)	3(1.4%)
Prolonged electrocardiogram QT	33(15.0%)	0	0
Urinary tract infection	30(13.6%)	1(0.5%)	1(0.5%)
Decreased white blood cell count	28(12.7%)	0	0
Anemia	27(12.3%)	2(0.9%)	0
Increased weight	24(10.9%)	0	0
Increased serum creatinine	22(10.0%)	0	0

Conclusions

- Aflutinib showed promising clinical antitumor activity in patients with EGFR T790M mutation NSCLC, including those with CNS metastases.
- Alflutinib also showed an acceptable and manageable safety profile.
- Therefore, alflutinib should be considered as a treatment option for NSCLC patients with EGFR T790M mutation.
- The randomized, double-blind phase III trial (NCT03787992, FLAG study) comparing alflutinib versus gefitinib as first line therapy in EGFR mutation positive, locally advanced or metastatic NSCLC patients is ongoing and the enrollment has been completed.

Acknowledgement

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Disclosure:
Ling Li, Yong Jiang are employees and shareholders of Shanghai Allist Pharmaceutical Inc. All other authors declare no competing interests.

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EGFR mutations

Osimertinib in Non-Small Cell Lung Cancer (NSCLC) with Atypical EGFR Activating Mutations: A Retrospective Multicenter Study

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Introduction

- Osimertinib is a 3rd-generation EGFR tyrosine kinase inhibitor (TKI) approved for 1st line treatment of metastatic non-small cell lung cancer (NSCLC) harboring EGFR Exon 19 del and L858R (representing >80% of EGFR-activating mutations) and patients with EGFR T790M (the most common resistance mutation to 1st or 2nd generation EGFR-TKI).[1-5]
- Clinical activity of osimertinib in less common EGFR activating mutations such as G719X, L861Q, S768I, and exon 20 insertion has been less extensively studied.[1-3,6]
- Afatinib is FDA approved for G719X, L861Q and S768I based on pooled analysis of LUX Lung 2, 3 and 6 with median PFS of 10.7 months (95% CI 5.6–14.7). [7]
- In a prospective, single-arm, phase II trial of osimertinib in 37 NSCLC patients with uncommon EGFR mutations by Cho et al 2020 in an Asian population median PFS was 8.2 months (95% CI 5.9-10.5) compared to median PFS of 18.9 months in FLAURA for EGFR Exon 19 del and L858R NSCLC.[8]

Study Objective

To evaluate real world clinical outcomes in a multi-institution, retrospective study in a series of patients with metastatic NSCLC treated with osimertinib who harbored at least one atypical EGFR mutation, excluding those with concurrent L858R, Exon 19 del, or T790M.

Methods

Inclusion Criteria

- Adult (≥18) patient with non-small cell lung cancer
- Atypical EGFR mutations confirmed on next generation sequencing, ddPCR, or other PCR/RT-PCR methods
- On osimertinib at any line of therapy
- Patients with previous or subsequent chemotherapy, 1st/2nd gen EGFR TKI therapy, and radiation therapy were included

Exclusion Criteria

- All individuals harboring an EGFR exon 19 deletion, L858R activating mutation, or T790M resistance mutation
- Patients with small cell lung cancer

Study Design

Study Type: Multi-center, Single-arm, Retrospective cohort analysis
Study population: 51 patients identified from six US academic institutions including:

- UC Davis Comprehensive Cancer Center
- UC San Diego Moores Cancer Center
- Stanford Cancer Institute
- Dana-Farber Cancer Institute
- MGH Cancer Center
- UCSF Hellen Diller Family Comprehensive Cancer Center

Number of patients with uncommon EGFR mutations: 51
Main outcomes: Time on osimertinib was employed as a surrogate endpoint for clinical benefit in this retrospective analysis.
Statistical Analysis: Kaplan-Meier analyses were generated with SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA)

Results

Table 1. Clinical and pathologic characteristics of the study population.

Median Age at Diagnosis (Range)	**65(44-83)**
Sex (%)	
Men	14(27.5)
Women	37(72.5)
ECOG (%)	
0	14(27.5)
1	28(54.9)
2	4(7.8)
3	1(2.0)
Unknown	4(7.8)
Smoking Status (%)	
Never smoked	22(43.1)
Former smoker	29(56.9)
Current smoker	0(0)
Average pack year (if smoker)	7.78
Histology (%)	
Adenocarcinoma	51(100)
Squamous cell carcinoma	0(0)
Line of Therapy (%)	
First Line	20(39.2)
Second Line	10(19.6)
≥3rd Line	21(41.2)
Prior EGFR TKI	28(54.9)
Race (%)	
Caucasian	30(58.8)
Asian	13(25.5)
Hispanic	1(2.0)
African American	2(3.9)
Other	5(9.8)
Stage at Diagnosis (%)	
I	6(11.8)
II	2(3.9)
III	6(11.8)
IV	37(72.5)

Table 2. Distribution of atypical EGFR mutations in the study population.

L861X (%)	**20(39.2)**
L861Q	14(27.5)
L816Q + L833F	2(3.9)
L861Q + K852N	1(2.0)
L861Q + G719A	1(2.0)
L861Q + L858M	1(2.0)
L861R + V774M	1(2.0)
G719X (%)	**14(27.5)**
G719A	7(16)
G719D	1(2.0)
G719S	1(2.0)
G719A + K757M	1(2.0)
G719A + E709A	1(2.0)
G719S + E709A	1(2.0)
G719A + L861Q	1(2.0)
G719A + S768I	1(2.0)
S768I (%)	**2(3.9)**
S768I	1(2.0)
S768I + G719A	1(2.0)
Exon 20 insertion (%)	**8(15.7)**
Other Mutations (%)	**10(19.6)**
V774M	2(3.9)
L747P	1(2.0)
Exon 18-25 duplication	1(2.0)
Exon 18 Deletion	1(2.0)
Exon 19 insertion	1(2.0)
G711A	1(2.0)
H773R	1(2.0)
L833V + H835L	2(3.9)

- Osimertinib has clinical activity as defined by time on treatment in this largest known retrospective cohort of atypical EGFR mutations treated with osimertinib.
- Clinical benefit appears lower than historical data for E19del and L858R.
- Patients with L861Q appeared to benefit the most from osimertinib, as well as one patient with an exon 19 insertion.

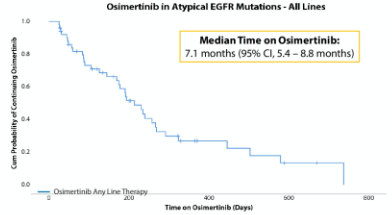

Figure 1. Kaplan-Meier survival analysis of time on osimertinib in overall population used in both first and subsequent line settings.

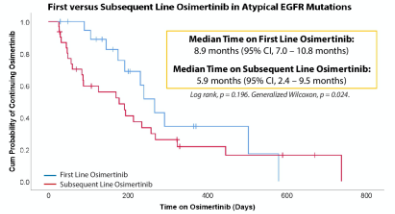

Figure 2. Kaplan-Meier survival analysis of time on osimertinib when used in the first line compared to subsequent line therapies.

Results (continued)

	Median Time on Osimertinib (95% CI)	
	Overall	**First Line**
S768I+G719X+L861Q	7.1 months (5.0 - 9.3), n = 34	8.9 months (1.7 - 16.1), n = 14
G719X	5.8 months (1.3 - 10.3), n = 14	5.8 months (no CI estimate), n = 4
L861Q	8.9 months (4.7 - 13.1), n = 19	19.3 months (no CI estimate), n = 10
Exon 20 Insertion	1.5 months (0.4 - 2.6), n = 8	8 months (no CI estimate), n = 2
Exon 19 Insertion	16.8 months, n = 1	16.8 months, n = 1
Other Mutations	7.7 months (0 - 17.9), n = 10	7.7 months (1.5 – 13.9), n = 4

Table 3. Median time on any line and first line osimertinib for various subgroups of patients harboring different EGFR mutations.

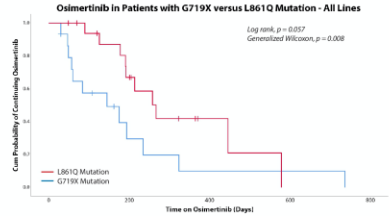

Figure 3. Kaplan-Meier survival analysis of time on osimertinib in patients with G719X versus L861Q EGFR point mutations in both first and subsequent line settings.

Discussion

- Osimertinib has activity in atypical EGFR mutations based on time on osimertinib in this retrospective analysis, though first line clinical benefit appears lower in this multicenter US cohort than PFS noted in EGFR E19del or L858R as described in FLAURA.[9]
- These results are similar to the results of the prospective phase II trial (Cho et al, 2019) conducted in Korea.[8]
- Patients with L861Q and Exon 19 insertion appeared to have the most benefit from osimertinib in this time on treatment analysis.
- More detailed analysis of this cohort is planned and further prospective studies are warranted to determine clinical benefit of osimertinib amongst diverse atypical EGFR-mutations.

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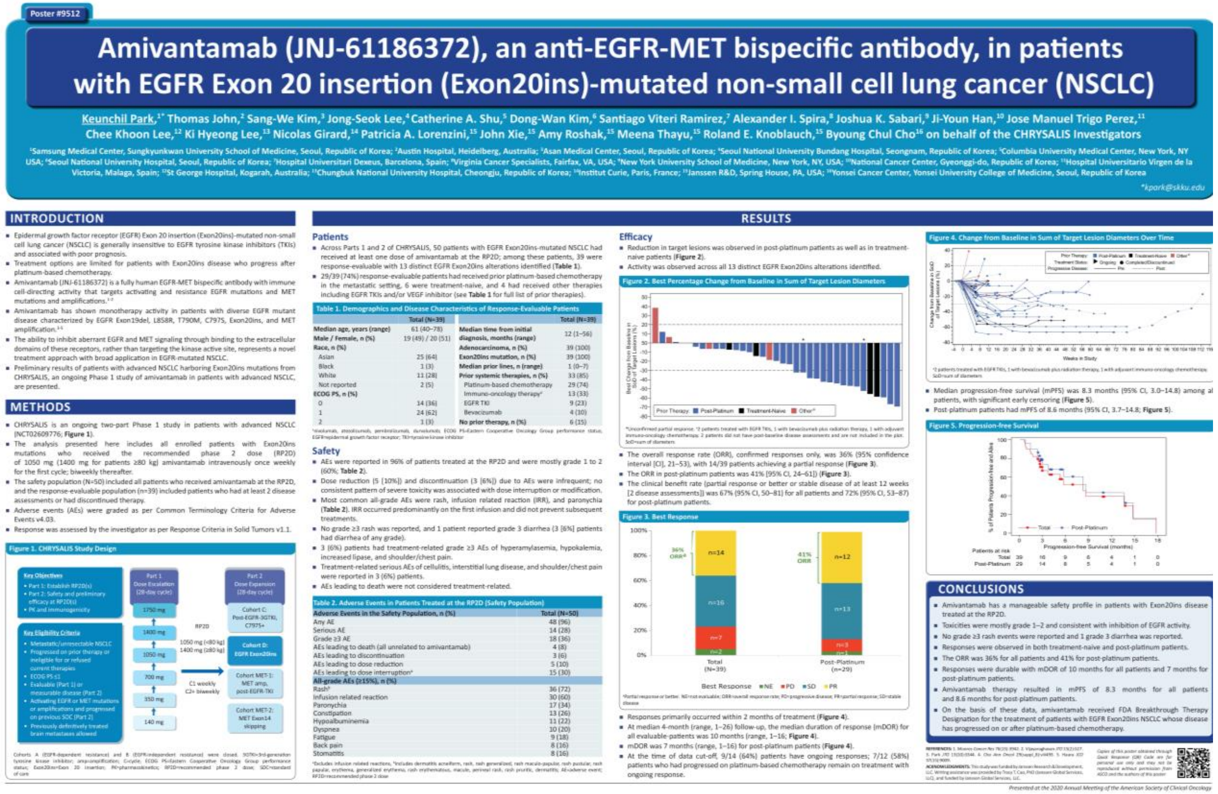
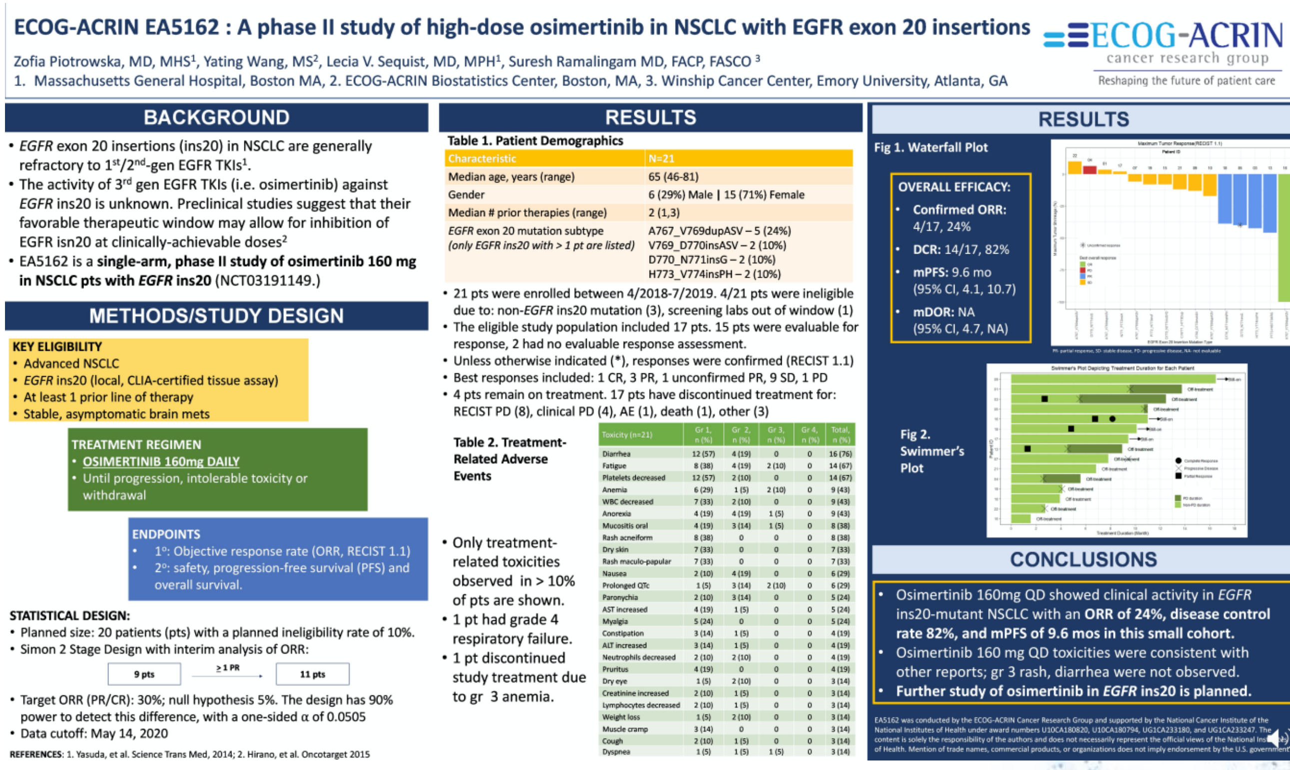
EGFR mutations



Poster #9512

Amivantamab (JNJ-61186372), an anti-EGFR-MET bispecific antibody, in patients with EGFR Exon 20 insertion (Exon20ins)-mutated non-small cell lung cancer (NSCLC)



ECOG-ACRIN EA5162 : A phase II study of high-dose osimertinib in NSCLC with EGFR exon 20 insertions

ECOG-ACRIN cancer research group
Reshaping the future of patient care

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BACKGROUND

- *EGFR* exon 20 insertions (ins20) in NSCLC are generally refractory to 1st/2nd-gen EGFR TKIs[1].
- The activity of 3rd gen EGFR TKIs (i.e. osimertinib) against *EGFR* ins20 is unknown. Preclinical studies suggest that their favorable therapeutic window may allow for inhibition of EGFR isn20 at clinically-achievable doses[2]
- EA5162 is a **single-arm, phase II study of osimertinib 160 mg in NSCLC pts with *EGFR* ins20** (NCT03191149.)

METHODS/STUDY DESIGN

KEY ELIGIBILITY
- Advanced NSCLC
- *EGFR* ins20 (local, CLIA-certified tissue assay)
- At least 1 prior line of therapy
- Stable, asymptomatic brain mets

TREATMENT REGIMEN
- OSIMERTINIB 160mg DAILY
- Until progression, intolerable toxicity or withdrawal

ENDPOINTS
- 1°: Objective response rate (ORR, RECIST 1.1)
- 2°: safety, progression-free survival (PFS) and overall survival.

STATISTICAL DESIGN:
- Planned size: 20 patients (pts) with a planned ineligibility rate of 10%.
- Simon 2 Stage Design with interim analysis of ORR:

9 pts → ≥ 1 PR → 11 pts

- Target ORR (PR/CR): 30%; null hypothesis 5%. The design has 90% power to detect this difference, with a one-sided α of 0.0505
- Data cutoff: May 14, 2020

REFERENCES: 1. Yasuda, et al. Science Trans Med, 2014; 2. Hirano, et al. Oncotarget 2015

RESULTS

Table 1. Patient Demographics

Characteristic	N=21
Median age, years (range)	65 (46-81)
Gender	6 (29%) Male | 15 (71%) Female
Median # prior therapies (range)	2 (1,3)
EGFR exon 20 mutation subtype (only EGFR ins20 with > 1 pt are listed)	A767_V769dupASV – 5 (24%) V769_D770insASV – 2 (10%) D770_N771insG – 2 (10%) H773_V774insPH – 2 (10%)

- 21 pts were enrolled between 4/2018-7/2019. 4/21 pts were ineligible due to: non-*EGFR* ins20 mutation (3), screening labs out of window (1)
- The eligible study population included 17 pts. 15 pts were evaluable for response, 2 had no evaluable response assessment.
- Unless otherwise indicated (*), responses were confirmed (RECIST 1.1)
- Best responses included: 1 CR, 3 PR, 1 unconfirmed PR, 9 SD, 1 PD
- 4 pts remain on treatment. 17 pts have discontinued treatment for: RECIST PD (8), clinical PD (4), AE (1), death (1), other (3)

Table 2. Treatment-Related Adverse Events

Toxicity (n=21)	Gr 1, n (%)	Gr 2, n (%)	Gr 3, n (%)	Gr 4, n (%)	Total, n (%)
Diarrhea	12 (57)	4 (19)	0	0	16 (76)
Fatigue	8 (38)	4 (19)	2 (10)	0	14 (67)
Platelets decreased	12 (57)	2 (10)	0	0	14 (67)
Anemia	6 (29)	1 (5)	2 (10)	0	9 (43)
WBC decreased	7 (33)	2 (10)	0	0	9 (43)
Anorexia	4 (19)	4 (19)	1 (5)	0	9 (43)
Mucositis oral	4 (19)	3 (14)	1 (5)	0	8 (38)
Rash acneiform	8 (38)	0	0	0	8 (38)
Dry skin	7 (33)	0	0	0	7 (33)
Rash maculo-papular	7 (33)	0	0	0	7 (33)
Nausea	2 (10)	4 (19)	0	0	6 (29)
Prolonged QTc	1 (5)	3 (14)	2 (10)	0	6 (29)
Paronychia	2 (10)	3 (14)	0	0	5 (24)
AST increased	4 (19)	1 (5)	0	0	5 (24)
Myalgia	5 (24)	0	0	0	5 (24)
Constipation	3 (14)	1 (5)	0	0	4 (19)
ALT increased	3 (14)	1 (5)	0	0	4 (19)
Neutrophils decreased	2 (10)	2 (10)	0	0	4 (19)
Pruritus	4 (19)	0	0	0	4 (19)
Dry eye	1 (5)	2 (10)	0	0	3 (14)
Creatinine increased	2 (10)	1 (5)	0	0	3 (14)
Lymphocytes decreased	2 (10)	1 (5)	0	0	3 (14)
Weight loss	1 (5)	2 (10)	0	0	3 (14)
Muscle cramp	3 (14)	0	0	0	3 (14)
Cough	2 (10)	1 (5)	0	0	3 (14)
Dyspnea	1 (5)	1 (5)	1 (5)	0	3 (14)

- Only treatment-related toxicities observed in > 10% of pts are shown.
- 1 pt had grade 4 respiratory failure.
- 1 pt discontinued study treatment due to gr 3 anemia.

RESULTS

Fig 1. Waterfall Plot

OVERALL EFFICACY:
- **Confirmed ORR:** 4/17, 24%
- **DCR:** 14/17, 82%
- **mPFS:** 9.6 mo (95% CI, 4.1, 10.7)
- **mDOR:** NA (95% CI, 4.7, NA)

Fig 2. Swimmer's Plot

CONCLUSIONS

- Osimertinib 160mg QD showed clinical activity in *EGFR* ins20-mutant NSCLC with an **ORR of 24%, disease control rate 82%, and mPFS of 9.6 mos in this small cohort.**
- Osimertinib 160 mg QD toxicities were consistent with other reports; gr 3 rash, diarrhea were not observed.
- **Further study of osimertinib in *EGFR* ins20 is planned.**

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ALK translocations

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Updated overall survival (OS) and safety data from the randomized, phase III ALEX study of alectinib (ALC) vs crizotinib (CRZ) in untreated advanced *ALK*+ NSCLC

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Summary

5-year survival rate: 62.5% with alectinib vs 45.5% with crizotinib:

ALC 62.5% | CRZ 45.5%

OS data remain immature at this updated analysis:

37% of events recorded in the ITT population

(stratified **HR 0.67** 95% CI 0.46–0.98)

No new safety signals were observed with alectinib with almost 3 times longer median treatment duration than crizotinib

Patients that had access to other ALK TKIs after first-line alectinib or crizotinib:

38.1% after first-line alectinib | **53.5%** after first-line crizotinib

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Background

- The global, randomized, phase III ALEX study (NCT02075840) compared the efficacy and safety of alectinib vs crizotinib in patients with untreated, advanced *ALK*+ non-small-cell lung cancer (NSCLC).[1]
- At the primary analysis (data cut-off, 9 Feb 2017), investigator-assessed progression-free survival (PFS) was significantly prolonged with alectinib vs crizotinib in the intent-to-treat (ITT) population: stratified hazard ratio (HR) 0.47, 95% confidence interval (CI) 0.34–0.65; p<0.001. Median PFS with alectinib was not reached (NR) vs 11.1 months with crizotinib.[1]
- Mature PFS data from ALEX (data cut-off, 30 Nov 2018) confirmed significant improvement in PFS for alectinib vs crizotinib (ITT stratified HR 0.43, 95% CI 0.32–0.58; median PFS 34.8 months vs 10.9 months with crizotinib).[2]
- At the 30 Nov 2018 data cut, OS data remained immature with 32% of events recorded (ITT stratified HR 0.69, 95% CI 0.47–1.02); the safety profile of alectinib compared favorably with that of crizotinib.[2]
- Here, we report updated OS, follow up anti-cancer therapies, and safety data from ALEX after a further 12 months of follow-up (data cut-off: 29 Nov 2019).

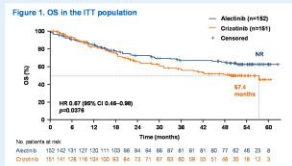
Methods

- Full details of the ALEX study design have been published previously.[1,3]
- In brief, patients aged ≥18 years with stage IIIB/IV *ALK*+ NSCLC (by central IHC [immunohistochemistry]), Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2 and no prior systemic therapy for advanced NSCLC were randomized to receive twice-daily alectinib 600mg or crizotinib 250mg until progressive disease (PD), toxicity, withdrawal or death.
- Patients with asymptomatic central nervous system (CNS) metastases were permitted, with CNS imaging performed in all patients at baseline and every 8 weeks until PD.
- Crossover between treatment arms was not permitted before PD. Further lines of therapy after PD were at the physician's discretion and based on treatment availability.
- Primary study endpoint: investigator-assessed PFS (RECIST v1.1); secondary study endpoints included independent review committee (IRC)-assessed PFS, objective response rate (ORR), IRC-assessed time to CNS progression, duration of response, OS and safety.
- Secondary study endpoints were analyzed using a hierarchical testing strategy to account for multiplicity.
- Kaplan-Meier methodology was used to estimate median OS for each treatment group along with 95% CIs.

Overall survival

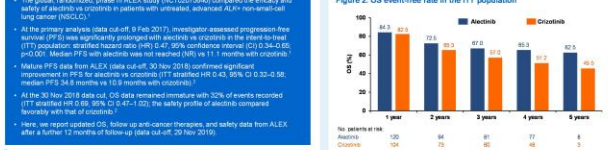
- The median duration of follow-up was 48.2 months (range 0.5–62.7) with alectinib and 23.3 months (range 0.3–60.6) with crizotinib.
- OS data remain immature with 37% of events recorded (stratified HR 0.67, 95% CI 0.46–0.98) (**Figure 1**).
- At the updated data cut-off, the median OS was NR with alectinib vs 57.4 months with crizotinib (95% CI 34.6–NR) (**Figure 1**).

Figure 1. OS in the ITT population



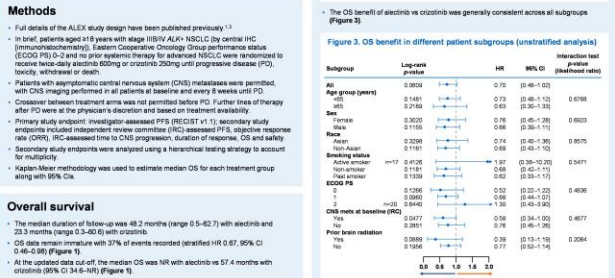
- The 5-year OS rate was 62.5% (95% CI 54.3–70.8) with alectinib vs 45.5% (95% CI 33.6–57.4) with crizotinib (**Figure 2**), with 34.9% and 8.6% of patients still on study treatment, respectively.

Figure 2. OS event-free rate in the ITT population



- The OS benefit of alectinib vs crizotinib was generally consistent across all subgroups (**Figure 3**).

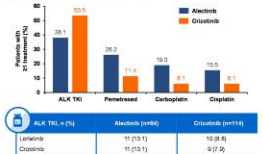
Figure 3. OS benefit in different patient subgroups (unstratified analysis)



Follow up anti-cancer therapies

- Overall, 21 patients died without PD and without receiving any follow up therapy.
- Among 84 patients in the alectinib arm and 114 patients in the crizotinib arm who experienced PD (including symptomatic deterioration), subsequent therapy was given in 60.7% and 63.2% of patients, respectively.
- ALK TKIs were administered to 38.1% of patients who progressed in the alectinib arm and to 53.5% of patients who progressed in the crizotinib arm (**Figure 4**).
- Lorlatinib and crizotinib were the most common ALK TKIs received in the alectinib arm (each 13.1%), compared with ceritinib and alectinib in the crizotinib arm (each 21.1%) (**Figure 4**).
- Other than ALK TKIs, the most common treatments received after PD in the alectinib and crizotinib arms were pemetrexed, carboplatin and cisplatin (**Figure 4**).

Figure 4. Most common follow up anti-cancer therapies in patients with PD (including symptomatic deterioration)



ALK TKI, n (%)	Alectinib (n=84)	Crizotinib (n=114)
Lorlatinib	11 (13.1)	10 (8.8)
Crizotinib	11 (13.1)	9 (7.9)
Brigatinib	8 (9.5)	11 (9.6)
Ceritinib	7 (8.3)	24 (21.1)
Alectinib	2 (2.4)	24 (21.1)
Ensartinib	1 (1.2)	0
Entrectinib	(0)	1 (0.9)

Table shows % of patients who received each treatment. Patients may have received more than one treatment. Treatment beyond progression on study treatment was allowed.

Safety

- Median treatment duration was 28.1 months with alectinib vs 10.8 months with crizotinib.
- No new safety signals were observed in this updated analysis of the ALEX data with almost three-times longer median treatment duration with alectinib vs crizotinib (**Table 1**).

Table 1. Safety summary

Event, n (%)	Alectinib (n=152)	Crizotinib (n=151)
All grade AEs	147 (97)	147 (97)
Serious AEs	59 (39)	48 (32)
Grade 3–5 AEs	79 (52)	85 (56)
Fatal AEs	7 (5)	7 (5)
AEs leading to treatment discontinuation	22 (15)	22 (15)
AEs leading to dose reduction	31 (20)	30 (20)
AEs leading to dose interruption	40 (26)	40 (27)

AE, adverse event

Conclusions and future directions

This is the first global randomized study of a next-generation ALK TKI to demonstrate a clinically meaningful improvement in OS vs crizotinib in treatment-naive, advanced *ALK*+ NSCLC

(5-year survival rate: 62.5% with alectinib vs 45.5% with crizotinib)

OS data remain immature.

No new safety signals were observed in this updated analysis of ALEX with almost three-times longer median treatment duration with alectinib vs crizotinib.

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Disclosures

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Poster 283

Correlation of Baseline Molecular and Clinical Variables With ALK Inhibitor Efficacy in ALTA-1L

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Background

- Emerging evidence suggests echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (*EML4-ALK*) variant status could impact outcome and acquired resistance[1]
- Brigatinib is a next-generation, central nervous system (CNS)-active ALK tyrosine kinase inhibitor (TKI) designed to have potent and broad activity against ALK mutants[2,3]
- The phase 3 ALTA-1L study evaluated efficacy and safety with brigatinib vs crizotinib in patients with ALK TKI–naive advanced ALK-positive NSCLC[4]
  - At the second interim analysis, brigatinib demonstrated superior efficacy compared with crizotinib with acceptable tolerability, making it a promising new first-line treatment option for ALK+ NSCLC[5]

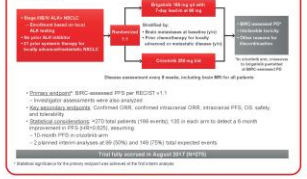
Objective

- We evaluated the impact of *EML4-ALK* fusion variants and other baseline molecular and clinical variables on the clinical efficacy of brigatinib vs crizotinib as first-line ALK TKI therapy in patients with ALK+ NSCLC in the ALTA-1L trial

Methods

Study Design

Figure 1. ALTA-1L: Phase 3, Open-label, Randomized, Multicenter Study (NCT02737501)



Exploratory Analysis

- Exploratory analyses were performed to assess molecular determinants of efficacy (PFS and confirmed ORR as assessed by BIRC) for brigatinib and crizotinib
- Blood samples were collected at screen from patients enrolled in both arms
- Cell-free DNA in plasma samples was analyzed by Resolution Bioscience ctDx Lung NGS panel, which includes the most frequently identified actionable driver oncogenes in NSCLC
- Mutation status of ALK and other oncogenes implicated in tumor biology were determined through molecular genetic analysis (NGS) of blood samples
- Baseline genetic mutations were characterized, and an analysis was conducted to assess their correlation with clinical efficacy outcomes (ORR, PFS) for both arms

Results

***ALK* Mutations**

Table 1. *ALK* Fusions Detected in Plasma

	Brigatinib n=124	Crizotinib n=127
ALK fusion detected at screen, n (%)	68 (54.8)	71 (55.9)
EML4-ALK fusion detected at screen, n (%)	57 (46.0)	64 (50.4)
EML4-ALK variant detected		
V1	25 (43.9)	30 (46.9)
V2	8 (14.0)	5 (7.8)
V3	23 (40.4)	21 (32.8)
V5	1 (1.8)	0
V6	2 (3.5)	7 (10.9)
EML4-ALK variant undetermined	0	1 (1.6)

- Brigatinib showed higher ORR and improved mPFS vs crizotinib in all variant subgroups (**Table 2**)

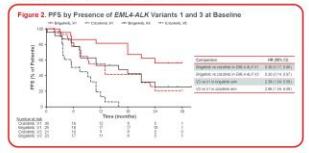
Table 2. Efficacy in Patients With Known *EML4-ALK* Fusions by Variant at Baseline

EML4-ALK variant	Brigatinib	Crizotinib	*P* value, log rank
V1, n	25	30	
ORR, %	84.0 (63.9–95.5*)	73.3 (54.1–87.7*)	
mPFS, mo	NR (16.5-NR*)	13.0 (7.4–24.0*)	0.0143
V2, n	8	5	
ORR, %	87.5 (47.3–99.7*)	60.0 (14.7–94.7*)	
mPFS, mo	16.0 (6.3-NR*)	11.0 (7.4-NR*)	0.661
V3, n	23	21	
ORR, %	82.6 (61.2–95.0*)	66.7 (43.0–85.4*)	
mPFS, mo	16.0 (7.6-NR*)	7.4 (3.7–12.9*)	0.0019

*95% CI

- Patients with V3 had worse PFS compared with V1 and V2 regardless of treatment (**Figure 2**)
- Brigatinib demonstrated superior PFS vs crizotinib regardless of *ALK* fusion variant, especially in the poor prognosis group of patients with V3

Figure 2. PFS by Presence of *EML4-ALK* Variants 1 and 3 at Baseline



***TP53* Mutations**

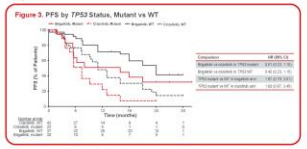
- Among patients with detectable *ALK* fusion, patients with *TP53* mutation showed numerically lower ORR and worse mPFS in both arms compared with patients with WT (**Table 3**)
- Brigatinib showed numerically improved ORR and mPFS compared with crizotinib regardless of *TP53* status

Table 3. Efficacy by *TP53* Status in Patients With *EML4-ALK* Fusion Types Detected in Plasma at Baseline (n=121)

	Brigatinib		Crizotinib	
TP53 mutation status	Mutant n=20	WT n=37	Mutant n=22	WT n=42
ORR				
Responders, n	15	33	13	30
ORR, % (95% CI)	75.0 (50.9–91.3)	89.2 (74.6–97.0)	59.1 (36.4–79.3)	71.4 (55.4–84.3)
PFS				
Events, n	11	19	16	27
mPFS, mo (95% CI)	16.0 (5.6-NR)	24.0 (18.0–NR)	7.4 (5.5–16.0)	11.0 (9.4–21.0)

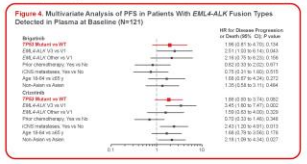
- Patients with *TP53* mutation showed a trend toward worse PFS regardless of treatment (**Figure 3**)

Figure 3. PFS by *TP53* Status, Mutant vs WT



- After adjusting for the potential confounding effect of molecular and clinical covariates, *TP53* mutation maintained a strong prognostic trend toward poor PFS (**Figure 4**)
- The independent prognostic effect of *EML4-ALK* fusion V3 was also verified in this analysis

Figure 4. Multivariate Analysis of PFS in Patients With *EML4-ALK* Fusion Types Detected in Plasma at Baseline (N=121)



Conclusions

- Brigatinib demonstrated superior efficacy compared with crizotinib as first-line therapy in patients, regardless of *EML4-ALK* fusion variant or *TP53* mutation status
- *EML4-ALK* fusion variant 3 detected in plasma appears to be a poor prognostic biomarker in ALK+ NSCLC
- There was also a nonsignificant trend toward *TP53* mutations detected in plasma appearing to be a separate, independent poor prognosis biomarker in ALK+ NSCLC
  - This trend persisted despite multivariate analyses and is worthy of further investigation in a larger sample size
  - Data from primary tumor sample analyses will provide additional information
  - Defining "higher risk" ALK+ advanced NSCLC may impact future clinical trial design and treatment options

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Abbreviations

ALK, anaplastic lymphoma kinase; ALK+, ALK gene-rearranged; bid, twice daily; BIRC, blinded independent review committee; CI, confidence interval; CNS, central nervous system; EML4, echinoderm microtubule-associated protein-like 4; HR, hazard ratio; ICNS, intracranial CNS; mPFS, median PFS; NGS, next-generation sequencing; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; qd, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; TP53, tumor protein p53; V, variant; WT, wild type

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ALK translocations

A Phase II Study of Lorlatinib in Patients with ALK-Positive Lung Cancer with Brain-Only Progression

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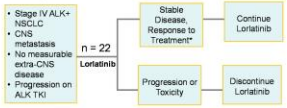
Background

- Anaplastic lymphoma kinase (ALK)-rearranged (ALK+) lung cancer is associated with a propensity towards central nervous system (CNS) dissemination.[1]
- Lorlatinib is a third-generation ALK tyrosine kinase inhibitor (TKI) developed to penetrate the CNS and overcome resistance to other less potent ALK TKIs.[2,3]
- In a global phase II study, lorlatinib induced intracranial responses in 53% of patients with measurable brain metastases at progression on a second-generation ALK TKI.[3]
- Among patients with pre-lorlatinib CNS metastases treated in the phase II study, the cumulative incidence of extra-CNS progression on lorlatinib exceeded the cumulative incidence of CNS progression.[4]
- As treatment discontinuation for extra-CNS progression can confound assessment of durability of intracranial response, we performed a phase II study (NCT02927340) to selectively evaluate the anti-tumor activity of lorlatinib in ALK+ patients with CNS-only disease.

Study Design

- 22 patients were enrolled at MGH and DFCI between 11/2016 and 1/2019
- Patients received lorlatinib at a starting dose of 100 mg QD
- The primary endpoint was intracranial disease control rate at 12 weeks per modified RECIST v1.1
- Secondary endpoints included intracranial objective response rate, duration of intracranial response, and intracranial progression-free survival.



*Treatment beyond progression permitted at Investigator discretion

Baseline Characteristics

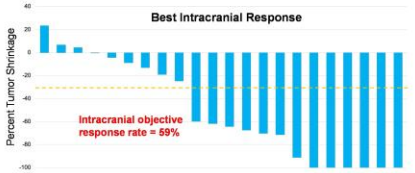
Characteristic	(n=22)
Age	
Median (range)	57.7 (21.6- 83.5)
Sex-no. (%)	
Male	12 (55)
Female	10 (45)
ECOG-no. (%)	
0	8 (36)
1	12 (55)
2	2 (9)
Brain Metastases-no. (%)	
Parenchymal Only	18 (82)
Leptomeningeal Only	0 (0)
Both	4 (18)
Previous CNS Radiation-no. (%)	
Stereotactic Radiosurgery	11 (50)
Whole or Partial Brain Radiotherapy	8 (36)
Previous Brain Lesion Resection-no. (%)	
Yes	6 (27)
Number of Prior ALK TKIs—no (%)	
1	5 (23)
2	11 (50)
3+	6 (27)
Number of Prior Chemo Lines—no (%)	
0	15 (68)
1+	7 (32)

- 4 (18%) patients had received both SRS and partial/whole brain radiation
- 6 (27%) patients had not received prior brain radiation
- Median time between brain radiation and lorlatinib was 21 months
- 21 (95%) patients had progressed on a second-generation TKI

Intracranial Response Rate

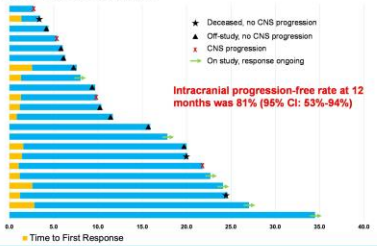
At 12 weeks, the intracranial disease control rate was 95%
- 3 complete and 10 partial responses
- 8 patients with stable disease

3 patients converted from partial to complete intracranial response after 12 weeks



Durability of Intracranial Response (Months)

Median intracranial PFS and intracranial DOR were not estimable due to a limited number of progression events.



Adverse Events Leading to Dose Reduction

	Grade 1-2	Grade 3	Grade 4
Cognitive Disturbance/ Memory Loss	7 (32%)	0	0
Emotional Lability	5 (23%)	0	0
Edema/Weight Gain	5 (23%)	0	0
Peripheral Neuropathy	3 (14%)	0	0
Confusion	2 (9%)	0	0
Fatigue	2 (9%)	0	0
Dyspnea	1 (5%)	0	0
Amylase Increase	1 (5%)	0	0
Lipase Increase	0	1 (5%)	0

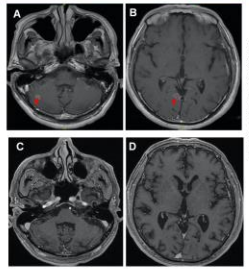
Patterns of Progression on Therapy

Intracranial Progression	Extracranial Progression: Yes	Extracranial Progression: No
Yes	1	3
No	5	13

With median follow-up of 14 months, 9 patients progressed:
- 3 CNS-only
- 5 extra-CNS only
- 1 combined extra-CNS + CNS

Four patients with ongoing CNS response continued treatment beyond extra-CNS progression.

Durable Intracranial Response to Lorlatinib



Pre-lorlatinib brain MRI demonstrates metastases (arrows) involving the right cerebellar (A) and occipital (B) regions. After 19 months of treatment, there was a significant decrease in size of the right cerebellar metastasis (C) and complete resolution of the occipital lesion (D).

Lorlatinib was discontinued after 19.5 months due to new symptomatic bone metastases.

Conclusions

- Lorlatinib induces durable intracranial responses in patients with CNS-only progression on second-generation ALK TKIs.
- The high rate of disease control with lorlatinib in CNS lesions resistant to a second-generation ALK TKI suggests that CNS-specific relapses are primarily driven by ALK-dependent mechanisms.
- Additional studies are needed to characterize the molecular basis of sensitivity to lorlatinib in this unique subgroup of patients.

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Lorlatinib for advanced ALK+ and ROS1+ non-small cell lung cancer (NSCLC): Efficacy and treatment sequences in the IFCT-1803 LORLATU expanded access program (EAP) cohort.

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Introduction

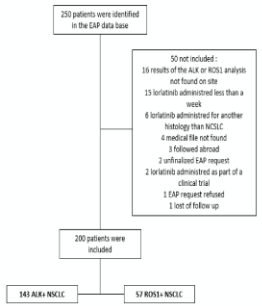
Lorlatinib, a third-generation tyrosine kinase inhibitor (TKI) targeting ALK and ROS1, has been made available in France starting October 2015 through an EAP for advanced, ALK+ or ROS1+ NSCLC after the failure of at least one ALK-TKI. The data regarding efficacy and safety of lorlatinib included in the different therapeutic sequences of ALK+ or ROS1+ NSCLC, are lacking besides the recently published phase II multicohort trials (1-2).

Objective

We aimed to determine the efficacy of lorlatinib in advanced ALK+ or ROS1+ NSCLC patients in real life setting after failure of at least one ALK TKI.

Methods

We report all consecutive patients with advanced, refractory, ALK or ROS1+ NSCLC enrolled in the French EAP of lorlatinib from October 2015 to June 2019. Data were collected from medical records by French Cooperative Thoracic Intergroup (IFCT) research study assistants on site. Primary endpoint was progression-free survival.



Results

Table 1: Demographics of the cohorts.

Characteristics	ALK+ (n=143)	ROS1+ (n=57)
Gender		
Male	63 (44.1%)	24 (42.1%)
Female	*80 (55.9%)*	*33 (57.9%)*
Median age (range)	60.9 (27.7-83.8)	59.3 (25.9-92.8)
Smoking status		
Current/former smoker	45 (32.4%)	22 (40%)
Never smoker	*94 (67.6%)*	*33 (60%)*
Unknown	4	2
Staging		
I-II	2 (1.4%)	3 (5.4%)
III	19 (13.5%)	6 (10.7%)
IV	*120 (85.1%)*	*47 (83.9%)*
Unknown	2	1
Histology		
Adenocarcinoma	*137 (95.8%)*	*51 (92.7%)*
Squamous	3 (2.1%)	1 (1.8%)
Other	3 (2.1%)	3 (5.5%)
Unkown	0	2

Table 2: Characteristics at lorlatinib iniation.

Characteristics	ALK+ (n=143)	ROS1+ (n=57)
Performance status		
0-1	*91 (74.6%)*	*40 (80%)*
≥2	31 (25.4%)	10 (20%)
Unknown	21	7
Previous lines		
1	4 (2.8%)	17 (29.8 %)
2	25 (17.5%)	17 (29.8%)
3	38 (26.6%)	9 (15.8%)
≥4	*76 (53.1%)*	*14 (24.6%)*
Previous treatment		
Chemotherapy	112 (78.3%)	38 (66.7%)
1st generation ALK TKI	*129 (90.2%)*	*56 (98.2%)*
2nd generation ALK TKI	*126 (88.1%)*	*12 (21.1%)*
Brain radiotherapy	64 (44.8%)	16 (28.1%)
Brain metastasis		
Present	*111 (78.2%)*	*35 (73.7%)*
Absent	31 (21.8%)	21 (26.3%)
Unknown	1	1

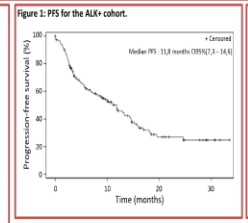
Table 3: Overall response to lorlatinib.

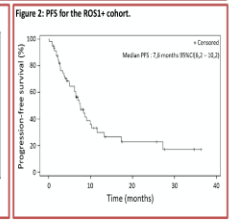
	ALK+ (n=143)	ROS1+ (n=57)
Best overall response		
Number of patients with available data	130 (90.9%)	51 (89.5%)
Complete response	10 (7.7%)	0 (0.0%)
Partial response	50 (38.5%)	24 (47.1%)
Stable disease	52 (40.0%)	21 (41.2%)
Progressive disease	16 (12.3%)	5 (9.8%)
Objective response rate	*60 (46.2%)*	*24 (47.1%)*
Disease control rate	*112 (86.2%)*	*45 (88.2%)*
Not evaluable	2 (1.5%)	1 (2%)
Central nervous system objective response rate (available data; %)*	*55 (/132; 41.7%)*	*20 (/53; 37.7%)*
Median duration of response (range, months)	*8.3 (0-29.9)*	*5.7 (0-34.5)*
Median follow up (CI95%, months)	15.6 (14.0-17.9)	14.5 (11.5-25.1)
Median lorlatinib duration (range, months)	7.4 (0.2-41.2)	7.3 (0.85-34.7)
Median lorlatinib duration beyond progression (range, months)	1.7 (0.1-22.1)	1.15 (0.03-25.3)

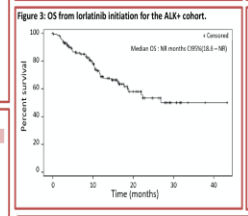
* Defined as the rate of intracranial tumor response according RECIST v1.1

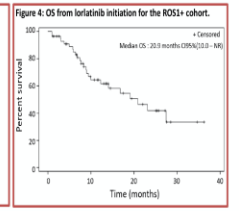
Table 4: Serious adverse events in patients treated with lorlatinib (reported in more than 1% of patients).

	ALK+ and ROS1+ (n = 200)			
	Grade≥3	Grade 3	Grade 4	Grade 5
Hypercholesterolaemia	21 (10.5%)	11 (5.5%)	10 (5%)	0 (0%)
Hypertriglyceridaemia	8 (4%)	5 (2.5%)	3 (1.5%)	0 (0%)
Cognitive effects	10 (5%)	9 (4.5%)	1(0.5%)	0 (0%)
Oedema	5 (2.5%)	5 (2.5%)	0 (0%)	0 (0%)
Peripheral neuropathy	4 (2%)	4 (2%)	0 (0%)	0 (0%)
Mood effects	4 (2%)	3 (1.5%)	1 (0.5%)	0 (0%)
Heart failure	3 (1.5%)	3 (1.5%)	0 (0%)	0 (0%)









Conclusions

These real-life results confirmed lorlatinib as a major treatment option for patients with advanced ALK+ or ROS1+ NSCLC after failure of at least one ALK-TKI.
In heavily treated advanced ALK NSCLC lorlatinib provides :
- a significant tumor response rate
- a long-lasting efficacy
- a central nervous system anti tumoral activity

In advanced ROS1+ NSCLC lorlatinib also displays an anti-tumoral activity despite a shorter efficacy.

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References

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