#IASLCUPDATES

Iniciativa científica de:

GECP lung cancer research

LUNG CANCER UPDATES

IASLC HIGHLIGHTS

7-10 DE SEPTIEMBRE 2019

Con la colaboración de:

Bristol-Myers Squibb

illumina

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BARCELONA
Iniciativa científica de:
GECP lung cancer research

Targeted Therapies EGFR and ALK

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Con la colaboración de:
Bristol-Myers Squibb
illumina
Lilly

A Phase I/II trial of dasatinib and osimertinib in TKI naive patients with advanced EGFR mutant NSCLC

Study design

- Open-label, single-arm phase I/II trial of osimertinib and dasatinib (NCT02954523).
- EGFR-TKI naïve patients with advanced EGFR-mutant NSCLC. Patients with pleural or pericardial effusions excluded.
- Phase I utilized 3+3 design. Phase II uses two-stage sequential design (n=28).

Dose escalation schedule

Dose Level	Osimertinib	Dasatinib
Level 2	80 mg QD	70 mg BID
Level 1 (starting dose)	80 mg QD	50 mg BID
Level -1	80 mg QD	70 mg QD
Level -2	80 mg QD	50 mg QD

Key outcome measures

- Phase I: Maximum tolerated dose (MTD) and recommend phase 2 dose (RP2D)
- Phase II: Rate of non-response stratified by Cripto-1 expression in tumor

Demographics and disease characteristics (n=10)

Median age		70.5 (range: 48-83)
Sex	Female	9 (90%)
	Male	1 (10%)
Race	White	5 (50%)
	Asian	5 (50%)
Smoking status	Never	7 (70%)
	Former	3 (30%)
Performance status	0	5 (50%)
	1	5 (50%)
Histology	Adenocarcinoma	8 (80%)
	Adenosquamous	1 (10%)
	Undifferentiated carcinoma	1 (10%)
EGFR mutation	Exon 19 deletion	6 (60%)
	L858R	4 (40%)
Brain metastases at baseline		4 (40%)

Dose limiting toxicities

Dose levels	# of patients	# of DLTs	Details
2	3	0	
1	6	3 (50%)	G3 headache, myalgia G3 neutropenia* G3 rash
-1	1	0	

* Patient with history of AML in remission

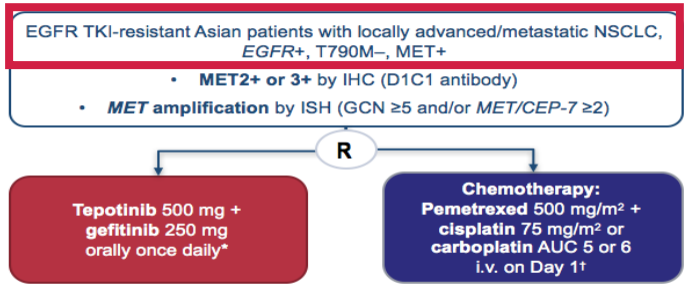
Treatment-related adverse events (TRAEs)

- Most TRAEs were grade 1 or 2 (92%).
- No grade 4 or 5 toxicities.
- Common side effects: pleural effusion (n=10), diarrhea (n=8), rash (n=7), thrombocytopenia (n=7), neutropenia (n=7), AST elevation (n=6), ALT elevation (n=6).
- Pleural effusion: Grade 1 (n=5), Grade 2 (n=4), Grade 3 (n=1) (4 underwent thoracentesis, 2 had PleurX placed).

Long-term outcomes to tepotinib plus gefitinib in patients with EGFR mutant NSCLC and MET dysregulation: 18 months follow-up

PHASE II INSIGHT STUDY (NCT01982955)

- Tepotinib is a highly selective, potent MET TKI with promising activity in NSCLC harboring *MET* alterations[1,2]



Primary endpoint: investigator-assessed PFS (RECIST v1.1)
Secondary endpoints include: ORR, OS, safety
Stratification factors: MET status (IHC2+ vs IHC3+ vs *MET* amplification), and prior EGFR TKI (gefitinib vs erlotinib vs icotinib vs afatinib)

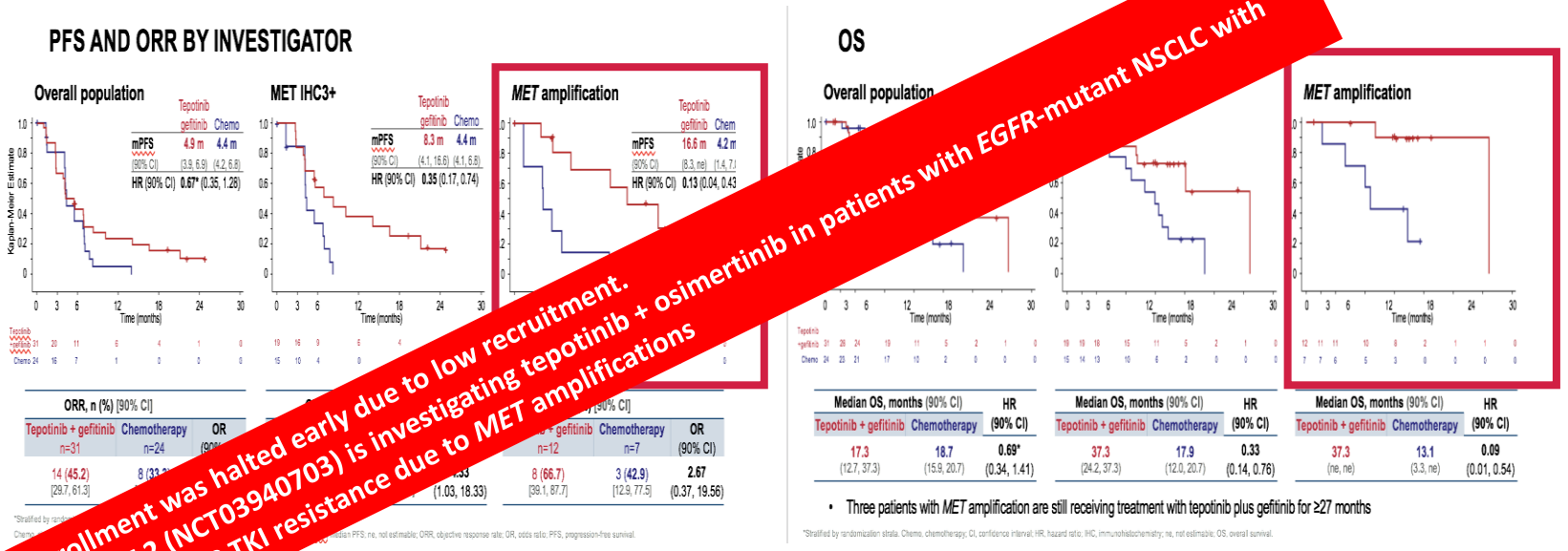
Due to low recruitment, enrolment was halted early with 55 of 156 planned patients enrolled

Baseline characteristics, n (%)	Tepotinib + gefitinib (n=31)	Chemotherapy (n=24)
Median age, years (range)	61.0 (42–76)	58.3 (42–82)
Male	11 (35.5)	12 (50.0)
Adenocarcinoma	30 (96.8)	24 (100)
Never smoker	21 (67.7)	16 (66.7)
Pre-planned subgroup analyses		
MET amplification	12 (38.7)	7 (29.2)
MET IHC3+	19 (61.3)	15 (62.5)

We report ≥18-month follow-up data on primary and secondary endpoints

Data cut 12-Dec-2018. AUC, area under concentration-time curve. *Treatment until disease progression, intolerable toxicity, or withdrawal of consent. †=<6 x 21 day cycles. EGFR, epidermal growth factor receptor; GCN, gene copy number; IHC, immunohistochemistry; ISH, in situ hybridization; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression free survival; RECIST, response evaluation criteria in solid tumours; TKI, tyrosine kinase inhibitor. 1. Cheng Y, et al. *Ann Oncol.* 2018;29(suppl 8) [abstract:13770]; 2. Paik P, et al. *J Clin Oncol.* 2019;37(suppl) [abstract 9005].

Enrollment was halted early due to low recruitment.
INSIGHT 2 (NCT03940703) is investigating tepotinib + osimertinib in patients with *EGFR*-mutant NSCLC with acquired EGFR TKI resistance due to *MET* amplifications



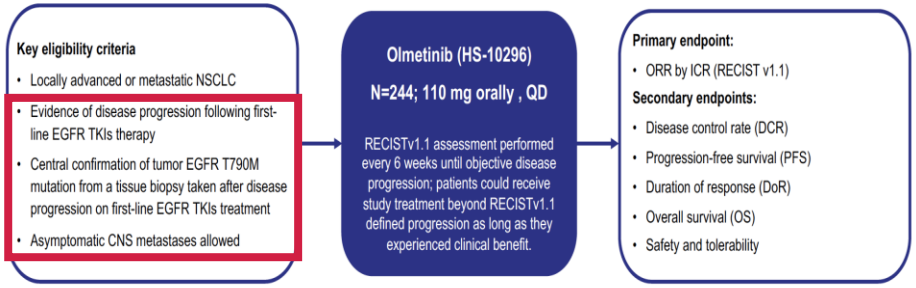
ORR 45.2%
mPFS 4.9 m
mOS 17.3 m

ORR 66.7%
mPFS 16.6 m
mOS 37.3 m

Wu Y et al. MA09.09

A Multicenter, Open-label, Single-arm, Phase II Study: The Third Generation EGFR Tyrosine Kinase Inhibitor Olmetinib (HS-10296) for Pretreated EGFR T790M-Positive Locally advanced or Metastatic Non-Small Cell Lung Cancer

Study Design



- The ORR by investigator (RECIST v1.1) for sensitivity analysis.
- A sample size of 238 patients achieving > 85% power to detect a difference of 0.1 (P0=0.45, P1=0.55) using a 2 sided binomial test with a significance level of 0.05.
- 244 Asian patients entered the study from 36 sites in mainland China (189 patients) and Taiwan (55 patients) between May 16, 2018 to Oct 23, 2018.
- RECIST, Response Evaluation Criteria In Solid Tumors. ICR, independent central review.

ClinicalTrials.gov Identifier: NCT02981108

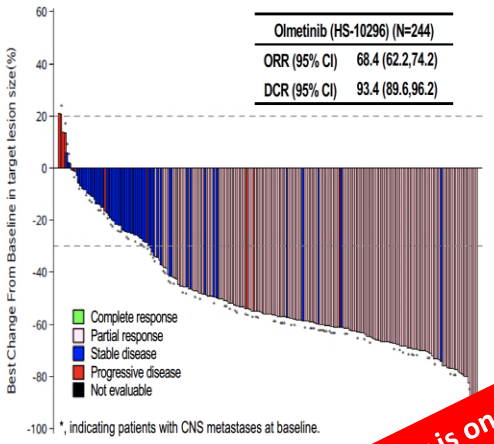
Demographics and Baseline Characteristics

Characteristics	Olmetinib (HS-10296) (N=244)
Age, median (range), years	61.0 (27~87)
Sex, %: Female / male	58.2 / 41.8
Brain metastases*, %: Yes / No	37.3 / 62.7
ECOG performance status,%: 0 / 1	34.8 / 65.2
Smoking status, %: Never / current / former	73.0 / 1.6 / 25.4
EGFR mutation# with T790M+,%: Ex19Del / L858R / others&	63.5 / 34.9 / 1.6
Previous anti-cancer treatment lines, %: 1 / 2 / 3	76.7 / 19.3 / 4.0

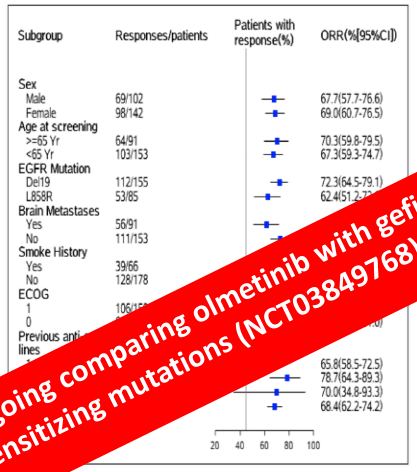
*, Brain metastases determined from baseline data of CNS lesion site, medical history, and/or surgery, and/or radiotherapy. #, EGFR mutation identified by cobas® EGFR Mutation Test. &, four patients without Ex19del or L858R mutation; one with G719X combined S768I mutation; other three without sensitizing EGFR mutation.

Primary Endpoint: ORR (ICR)

Olmetinib (HS-10296) (N=244)	
ORR (95% CI)	68.4 (62.2,74.2)
DCR (95% CI)	93.4 (89.6,96.2)

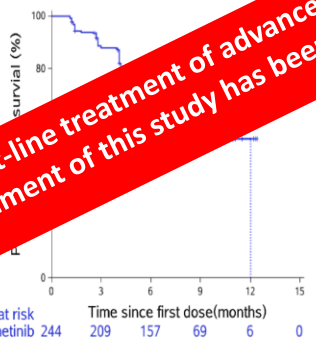


- Analysis of ORR by ICR was consistent with the investigator-based anal
- At the time of data cut-off (May 25, 2019), the median duratio



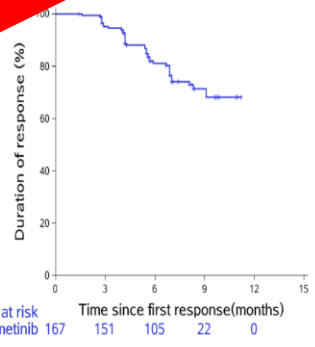
A phase III study is ongoing comparing olmetinib with gefinitib in first-line treatment of advanced NSCLC patients with EGFR sensitizing mutations (NCT03849768). The enrollment of this study has been completed

PFS



PFS	Olmetinib (HS-10296) (N=244)
Events (%)	97 (39.8)
Progression-free at 6 months (%) (95% CI)*	71.2 (64.9,76.6)
Progression-free at 9 months (%) (95% CI)	57.8 (50.8,64.1)
Progression-free at 12 months (%) (95% CI)	53.0 (44.9,60.4)
Median, months (95% CI)	NA (9.5,NA)

*, Estimated using the Kaplan-Meier method



DoR	Olmetinib (HS-10296) (N=167)
Estimated percentage remaining in response*	
at 6 months(95% CI)	88.8 (82.7,92.8)
at 9 months(95% CI)	74.4 (66.2,80.9)
at 12 months(95% CI)	69.0 (58.6,77.3)
Median, months (95% CI)	NA (NA,NA)

*, Estimated using the Kaplan-Meier method

ORR 68.4%
DCR 93.4%
PFS 12m 53.0%

Iniciativa científica de:
GeCP lung cancer research

Lu S et al. OA02.03

ALK…still debating the sequencing

National Comprehensive Cancer Network®

NCCN Guidelines Version 7.2019
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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Discussion

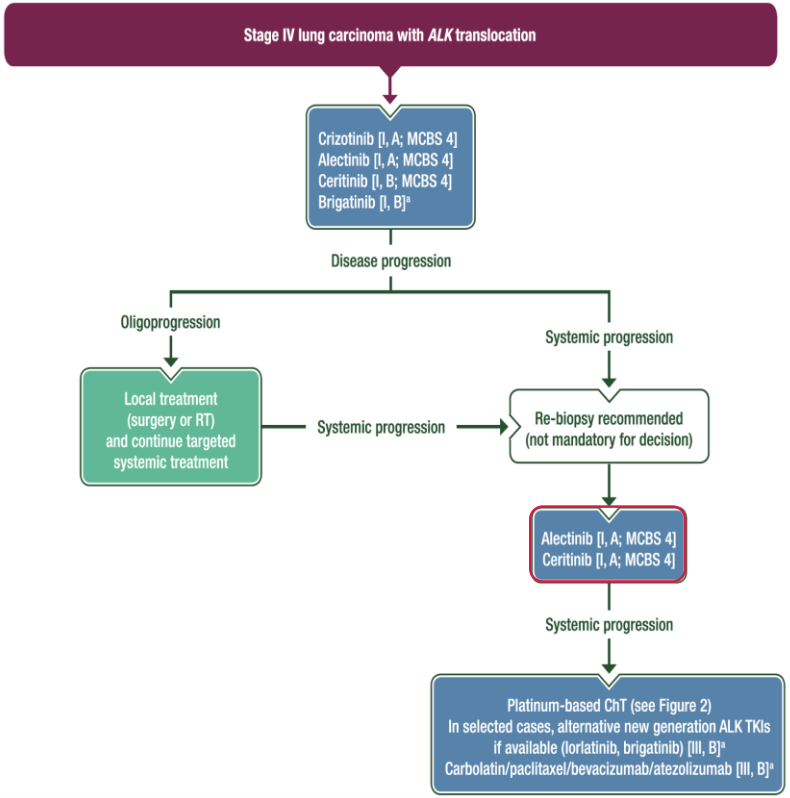
ALK REARRANGEMENT POSITIVE[hh]

SUBSEQUENT THERAPY[mm]

Progression on crizotinib[uu,vv]

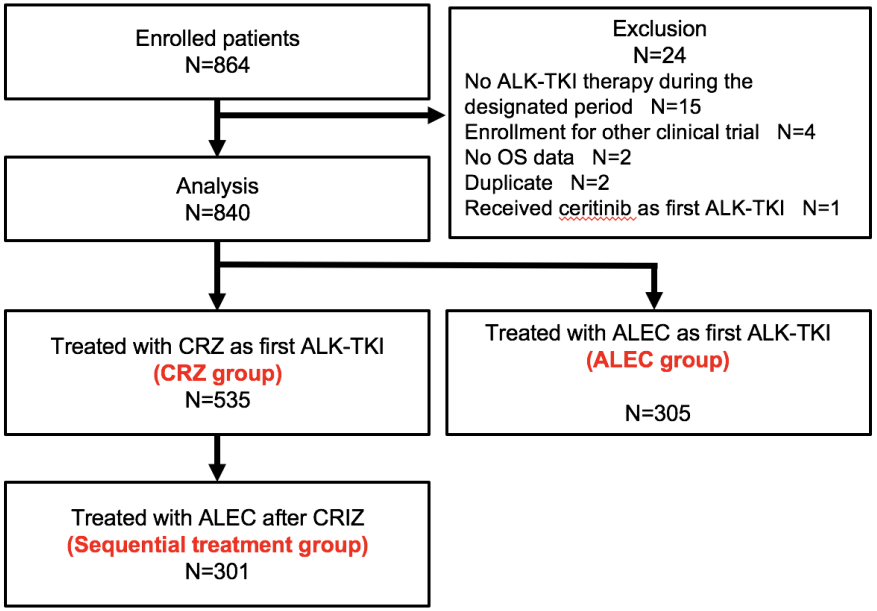
- Asymptomatic
  - • Consider definitive local therapy (eg, SABR or surgery) for limited lesions
    • Continue crizotinib
    or
    • Alectinib[nn,ww,xx] or brigatinib[nn,ww,xx] or ceritinib[nn,ww,xx]
- Symptomatic
  - Brain
    - • Consider definitive local therapy (eg, SRS) for limited lesions
      • Alectinib[nn,ww,xx] or brigatinib[nn,ww,xx] or ceritinib[nn,ww,xx]
      • See NCCN Guidelines for CNS Cancers
  - Systemic
    - Isolated lesion
      - • Consider definitive local therapy (eg, SABR or surgery)
        • Continue crizotinib
    - Multiple lesions
      - • Alectinib[nn,ww,xx] or brigatinib[nn,ww,xx] or ceritinib[nn,ww,xx]
        or
        • See Initial systemic therapy options[tt] Adenocarcinoma (NSCL-28) or Squamous Cell Carcinoma (NSCL-29)

Progression, Lorlatinib[yy] or See Initial systemic therapy options[tt] Adenocarcinoma (NSCL-28) or Squamous Cell Carcinoma (NSCL-29)



Planchard D, et al. Ann Oncol 2018

The impact of sequential therapy of crizotinib followed by alectinib: real world data analysis of 840 ALK-inhibitor naïve patients with NSCLC harboring ALK-rearrangement. WJOG9516L



Consort diagram

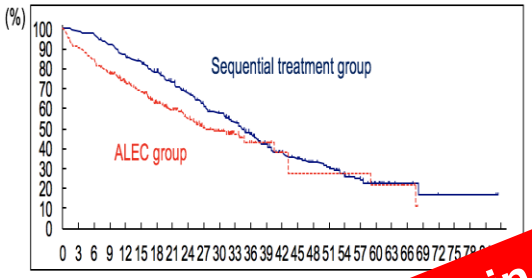
✓ A total of 846 patients with NSCLC harboring ALK rearrangement were enrolled in this research.

✓ Group definition as below: CRZ group, 535 patients received CRZ as first ALK-TKI; ALEC group, 305 patients received ALEC as first ALK-TKI; Sequential treatment group, patients received ALEC after CRZ failure in the CRZ group.

Watanabe S, et al. OA02.06

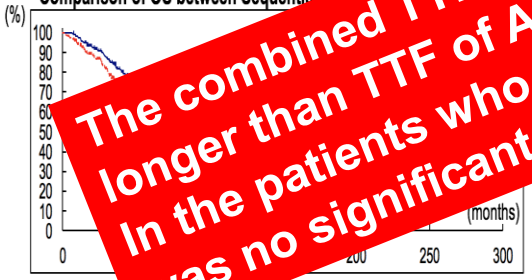
Patients treated with CRZ followed by ALEC (Sequential treatment group vs ALEC group)

Combined TTF vs. TTF of ALEC.



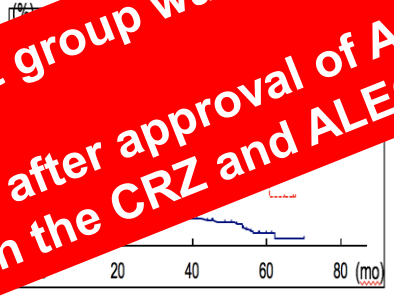
	CRZ followed by ALEC N=282	ALC N=302
Median, months	34.1	
HR [95%CI]		
p value		

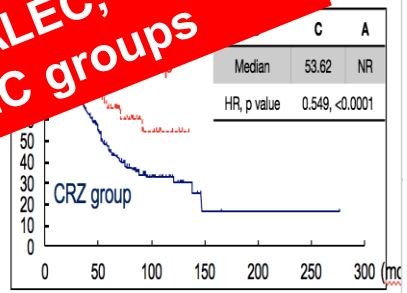
Comparison of OS between Sequential t

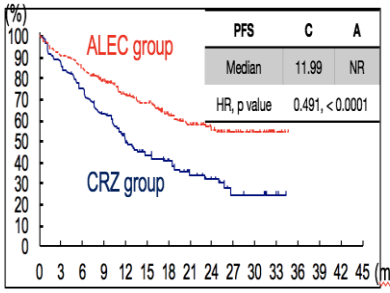


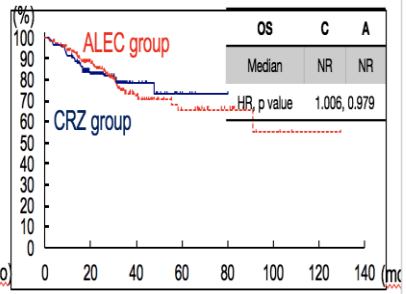
	N=305
N=301	
months	88.44 NR
HR [95%CI]	0.954 [0.689 – 1.319]
p value	0.7758

All patients and Patients who initiated ALK-TKI therapy after approval of ALEC









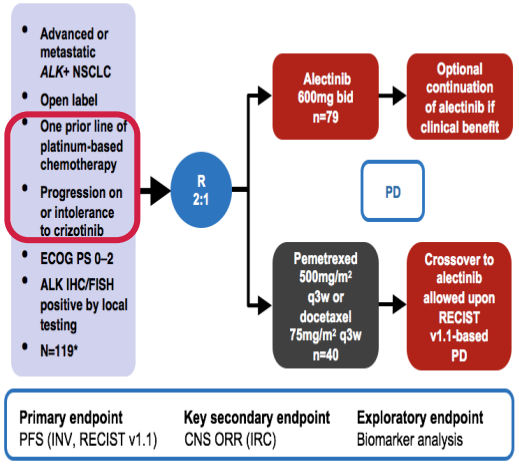
The combined TTF in the sequential treatment group was significantly longer than TTF of ALEC in the ALEC group. In the patients who started ALK-TKI therapy after approval of ALEC, there was no significant difference in OS between the CRZ and ALEC groups

Watanabe S, et al. OA02.06

Iniciativa científica de:
GECP lung cancer research

Final results from ALUR: efficacy, safety and biomarker data from a randomised, phase III, open-label study of alectinib versus pemetrexed or docetaxel in patients with previously-treated *ALK*+ NSCLC

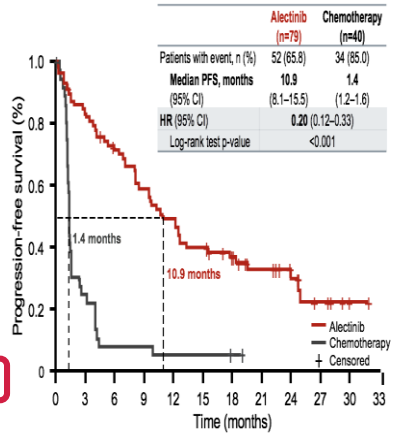
Study design & patient demographics



*Recruitment of patients continued after the primary analysis, in which 107 patients were enrolled
q3w, every three weeks

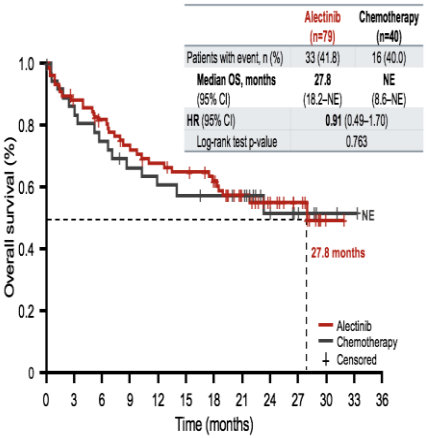
Baseline characteristics	Alectinib (n=79)	Chemotherapy (n=40)
Median age, years (range)	55.0 (21–82)	58.5 (37–80)
Male, n (%)	46 (58.2)	20 (50.0)
Race, n (%)		
Asian	6 (7.6)	8 (20.0)
Non-Asian	68 (86.1)	32 (80.0)
Unknown	5 (6.3)	0 (0.0)
Smoking status Never, n (%)	38 (48.1)	19 (47.5)
ECOG PS		
0 or 1 / 2, n (%)	73 (92.4) / 6 (7.6)	35 (87.5) / 5 (12.5)
CNS metastasis present, n (%)	52 (65.8)	28 (70.0)
Prior radiotherapy and CNS metastases status, n (%)		
No baseline CNS metastases	30 (38.0)	12 (30.0)
Baseline CNS metastases without prior radiotherapy	21 (26.6)	10 (25.0)
Baseline CNS metastases and prior radiotherapy	28 (35.4)	18 (45.0)

PFS (investigator assessed)



Data cut-off: 28 September 2018

Overall survival



- 17 (22.1%) patients received alectinib after disease progression
- 32 (86.5%) patients crossed over from chemotherapy to alectinib

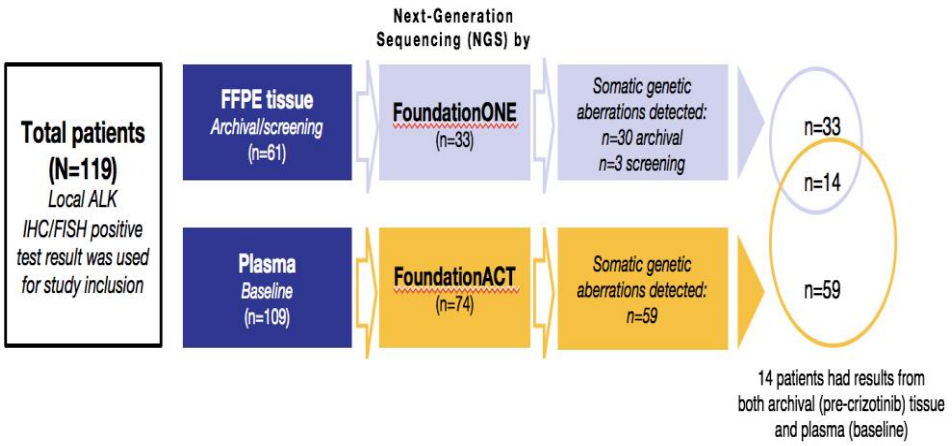
ORR (IR) 48.1%
icRR (IRC) 66.7%
mPFS 10.9 m
mOS 27.8 m

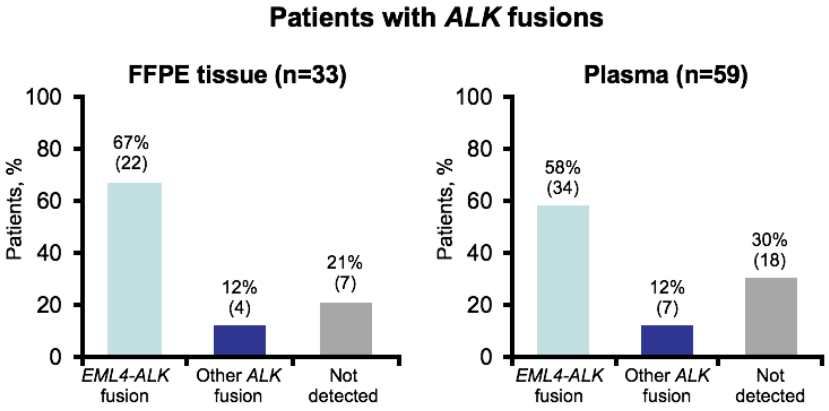
Wolf et al. OA02.07

Biomarkers: objectives & analysis

Objectives:

- To explore molecular factors in plasma (baseline) or tumour tissue (pre-crizotinib or baseline) for their association with treatment response





Exploratory analysis identified *ALK* fusions in tissue in 79% of patients (n=26) and in plasma in 70% of patients (n=41)

Wolf et al. OA02.07

Response rate by biomarker group (baseline plasma)

Patients were assigned to **biomarker groups** based on the presence of *ALK* fusions or mutations:

1. *ALK* fusion only
2. *ALK* fusion & *ALK* "resistance" mutation
3. *ALK* fusion not detected and mutations in other genes

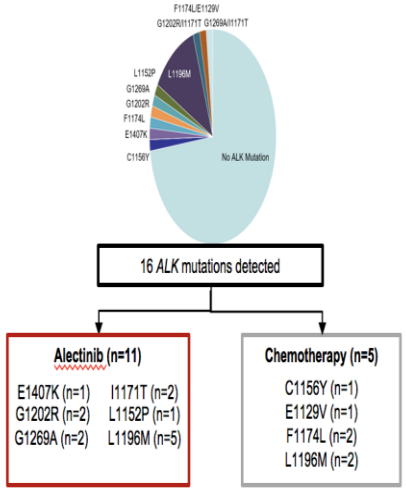
Overall response rate (investigator assessed)

	Alectinib		Chemotherapy	
Biomarker group	**n**	**ORR, n (%)**	**n**	**ORR, n (%)**
ITT	79	40 (51)	40	1 (3)
ALK fusion only	17	11 (65)	9	0 (0)
ALK fusion & mutation	10	6 (60)	5	0 (0)
ALK fusion not detected*	13	3 (23)	5	1 (20)

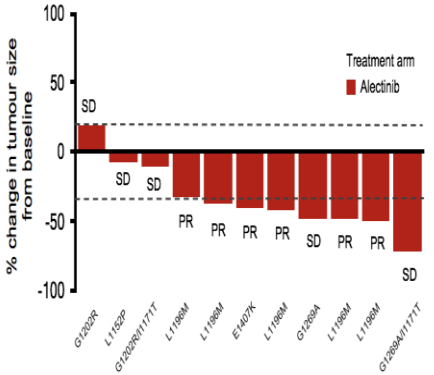
*and mutations in other genes

- In the alectinib arm, ORR was lower in patients without *ALK* fusions compared with patients that were *ALK*-fusion positive
- ORR was similar in patients treated with alectinib or chemotherapy in the 'other gene mutation' group
- In contrast to other groups, various driver mutations (i.e. *KRAS, EGFR, HER2, BRAF*), or a higher number of mutations, were found in cfDNA of patients in the 'other gene mutation' group

Secondary *ALK* mutations in plasma after first-line crizotinib therapy



Crizotinib resistance mutations in *ALK* were found in 27% (16/59) patients in plasma (baseline); some patients had more than one mutation



Patients with no post-baseline tumour assessment were not included in the waterfall plot
ORR confirmed by RECIST v1.1

Response	Alectinib (n=11)	Chemotherapy (n=5)
CR/PR, n (%)	6 (55)	0 (0)
SD/PD/NE, n (%)	5 (45)	5 (100)