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19-23 DE OCTUBRE 2018, MUNICH

TERAPIAS DIRIGIDAS I (ALK, EGFR)

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1379PD. Impact of the EML4-ALK variant on the efficacy of alectinib in untreated ALK+ advanced NSCLC in the global phase III ALEX study

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Impact of the *EML4-ALK* variant on the efficacy of alectinib in untreated *ALK*-positive advanced non-small-cell lung cancer in the global phase III ALEX study

1379PD

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INTRODUCTION

- *ALK*+ NSCLC is a subset of lung cancer characterised by an oncogene rearrangement resulting in a structural alteration of the chromosome, leading to expression of constitutively active ALK fusion proteins.[1–3]
- The most common *ALK* fusion partner is *EML4*.[4] Both located on chromosome 2, the breakpoint of the *ALK* gene occurs at exon (ex) 20, whereas the *EML4* breakpoint varies, resulting in different fusion proteins.[4–6]
- The most common *EML4-ALK* fusions are variant 1 (ex13 of *EML4*, ~43%), variant 2 (ex20 of *EML4*, ~9%) and 3a/b (ex6a/b of *EML4*, ~40%); particular variants may influence response to therapy, e.g. variant 1 was associated with worse outcome than variant 3 in patients treated with the third-generation ALK inhibitor, lorlatinib.[4–7]
- Alectinib is a CNS-active ALK inhibitor. The phase III ALEX trial of alectinib versus crizotinib,[8] led to the approval of alectinib for the first-line treatment of *ALK*+ NSCLC[9]
  - 9 Feb 2017 cut-off: median progression-free survival (PFS) not reached for alectinib vs 11.1 months for crizotinib; HR 0.47 (95% CI: 0.34–0.65)[8]
  - 1 Dec 2017 cut-off: median PFS alectinib 34.8 vs crizotinib 10.9 months; HR, 0.43 (95% CI: 0.32–0.59).[9]
- Here we report efficacy data from the ALEX trial stratified by *EML4-ALK* variant.

METHODS

- In ALEX (NCT02075840), 303 patients were randomised 1:1 to receive twice-daily alectinib 600mg or crizotinib 250mg until disease progression, toxicity, withdrawal or death.
- Eligible patients with advanced NSCLC were tested for *ALK*+ by VENTANA ALK (D5F3) immunohistochemistry at central laboratories. Patients had no prior systemic treatment for advanced NSCLC and Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; asymptomatic brain metastases were permitted.
- Tissue and plasma samples were collected at baseline.
- PFS, overall response rate (ORR) and duration of response (DoR) were determined by investigator (INV) and Independent Review Committee (IRC; RECIST v1.1).
- *ALK* fusion variants were detected by a hybrid-capture, next-generation sequencing (NGS) test using proprietary computational algorithms that enabled variant calls to be accurately detected by discriminating sequencing artefacts from real mutations
  - Plasma samples were analysed using the FOUNDATIONACT® platform, which analyses circulating tumour DNA to identify clinically relevant genomic alterations
  - Tissue samples were analysed using the FOUNDATIONONE® platform, which identifies somatic genomic alterations in genes known to be drivers of solid tumours
  - Both methods identify substitutions, insertions/deletions, copy number changes and rearrangements.
- Comparison between treatment groups for PFS was based on a stratified log-rank test at a 5% level of significance (two-sided).
- ORR was calculated using the Clopper-Pearson method with treatment groups compared using a stratified Mantel-Haenszel test.
- At the primary data cut-off (9 Feb 2017), the median duration of follow-up was 18.6 months with alectinib and 17.6 months with crizotinib
  - To allow comparison with the original study results, the primary data cut-off was used.

RESULTS

Biomarker evaluable population

- Baseline characteristics were broadly similar between the biomarker evaluable population (BEP) subgroups (Table 1) and comparable with the intent-to-treat (ITT) population.
- PFS within the tissue and plasma BEP subgroups was longer with alectinib than crizotinib, and comparable with the ITT population (plasma BEP: HR 0.40 [95% CI: 0.27–0.57], p<0.0001; tissue BEP: HR 0.57 [95% CI: 0.36–0.84], p=0.0042).

Table 1. Selected baseline characteristics of the plasma and tissue BEP subgroups

	Total population (N=303)	Plasma BEP		Tissue BEP	
		Crizotinib (n=116)	Alectinib (n=107)	Crizotinib (n=99)	Alectinib (n=107)
Age, <65 years, n (%)	233 (76.9)	87 (75.7)	81 (75.7)	76 (79.2)	80 (74.8)
Median age, years	56	55	58	54	58
Smoking status, n (%) Non-smoker	190 (62.7)	76 (66.1)	64 (59.8)	61 (63.5)	63 (58.9)
ECOG PS, n (%) 0 or 1	283 (93.4)	107 (93.0)	97 (90.6)	88 (91.7)	101 (94.4)
2	20 (6.6)	8 (7.0)	10 (9.4)	8 (8.3)	6 (5.6)
CNS lesions*	122 (40.3)	45 (39.1)	45 (42.1)	35 (36.5)	45 (42.1)

*Measurable and non-measurable

ALK rearrangements

- The percentage of *ALK* rearrangements detected by NGS was similar in plasma (55%) and tissue (57%) samples.
- The prevalence of all three common *EML4-ALK* variants was broadly similar between the BEP subgroups (Table 2).

Table 2. Prevalence of *EML4-ALK* variants in plasma and tissue BEP subgroups

	Plasma BEP			Tissue BEP		
n (%)	Total (N=136)	Crizotinib (n=68)	Alectinib (n=67)	Total (N=124)	Crizotinib (n=56)	Alectinib (n=68)
EML4-ALK V1	52 (37.5)	28 (41.2)	22 (32.8)	53 (42.7)	28 (43.7)	25 (41.7)
EML4-ALK V2	22 (16.3)	12 (17.6)	10 (14.9)	13 (10.5)	5 (7.8)	8 (13.3)
EML4-ALK V3a/b	49 (36.3)	24 (35.3)	25 (37.3)	48 (37.1)	25 (39.1)	21 (35)
EML4-ALK other variants	8 (5.9)	2 (2.9)	6 (9.0)	12 (9.7)	6 (9.4)	6 (10.0)
Missing	5 (4.4)	2 (2.9)	4 (6.0)	0 (0.0)	0 (0.0)	0 (0.0)

Plasma BEP: V1 = 2 single nucleotide variant (SNV), V2 = 0 SNV, V3 = 0 SNV; Tissue BEP: V1 = 3 SNV, V2 = 1 SNV, V3 = 1 SNV

Efficacy

PFS

- PFS, assessed by INV and IRC, was longer with alectinib versus crizotinib in all *EML4-ALK* variant populations in both the plasma and tissue BEP subgroups, apart from IRC-assessed PFS in patients with variant 2 in the tissue BEP subgroup (Figure 1).
- There were no significant differences in median PFS by INV between the three common *EML4-ALK* variant populations in the plasma (alectinib p=0.378; crizotinib p=0.832) or tissue (alectinib p=0.092; crizotinib p=0.058) BEP subgroups.

ORR

- ORR by INV was higher with alectinib versus crizotinib in *EML4-ALK* variant populations 1 and 3a/b in both the plasma (Figure 2A) and tissue (Figure 2B) BEP subgroups; however, the ORR by INV for variant 2 was higher with crizotinib in the tissue, but not the plasma subgroup.
- ORR by IRC was higher with alectinib in all *EML4-ALK* variant populations in both the plasma (Figure 2C) and tissue (Figure 2D) BEP subgroups.
- There was no significant difference in ORR (INV) between the *EML4-ALK* variant populations in plasma (alectinib p=0.364; crizotinib p=0.407) or tissue (alectinib p=0.103; crizotinib p=0.275).

Figure 1. PFS by *EML4-ALK* variants in plasma and tissue BEP subgroups for (A) plasma and (B) tissue by INV and by (C) plasma and (D) tissue by IRC

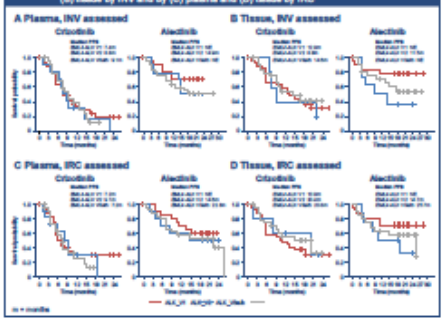
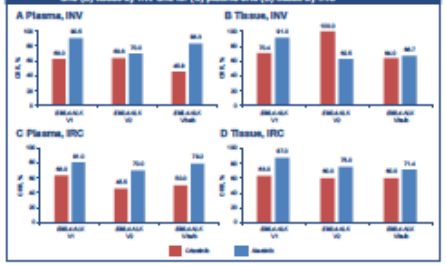


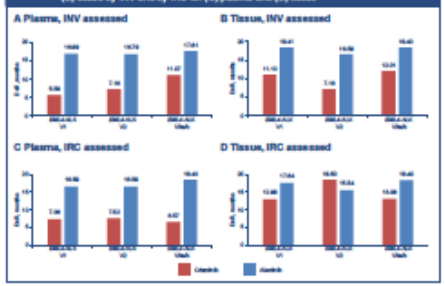
Figure 2. Response rate by *EML4-ALK* variant in plasma and tissue subgroups for (A) plasma and (B) tissue by INV and for (C) plasma and (D) tissue by IRC



Duration of response

- Median DoR by INV and IRC was longer with alectinib versus crizotinib in all *EML4-ALK* variant populations, in both the plasma and tissue BEP subgroups, except in variant 2 IRC-assessed patients in the tissue subgroup (Figure 3).

Figure 3. DoR by *EML4-ALK* variants in plasma and tissue BEP subgroups for (A) plasma and (B) tissue by INV and by IRC for (C) plasma and (D) tissue



CONCLUSIONS

- This study represents the largest analysis of ALK inhibitor efficacy by *EML4-ALK* variant type in a prospective phase III randomised clinical trial.
- Greater efficacy was demonstrated with alectinib compared with crizotinib in patients with *ALK*+ NSCLC regardless of *EML4-ALK* variant; tissue V2 INV-assessed ORR and IRC-assessed PFS and DoR were the only exceptions, and were likely due to low patient numbers.
- The prevalence of *EML4-ALK* variants in ALEX are consistent with previous reports; in contrast to other studies, efficacy across variants was similar.

ACKNOWLEDGEMENTS

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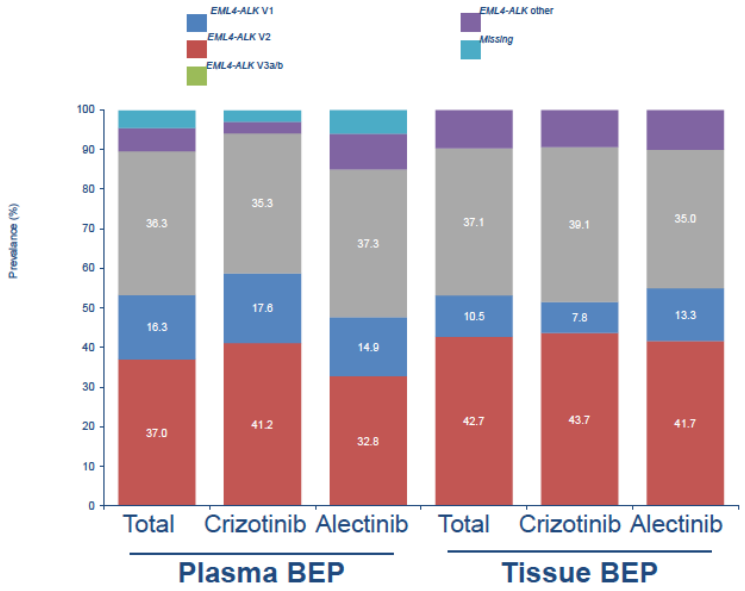
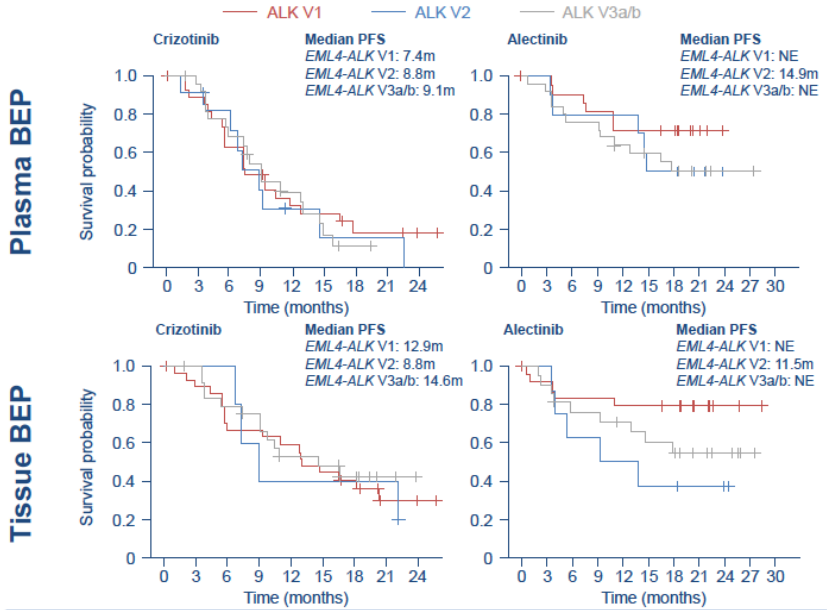
Prevalence of *EML4-ALK* variants



Prevalence of the *EML4-ALK* variants was broadly similar between the BEP subgroups and was consistent with previous reports[1,2]

Variant 2 was less prevalent in both subgroups

PFS by INV in *EML4-ALK* variant populations



The ALEX study demonstrated a greater PFS (INV and IRC*) efficacy benefit of alectinib compared with crizotinib in patients with *ALK*+ NSCLC, regardless of *EML4-ALK* variant

There was no significant PFS difference across variant type for patients treated with crizotinib or alectinib

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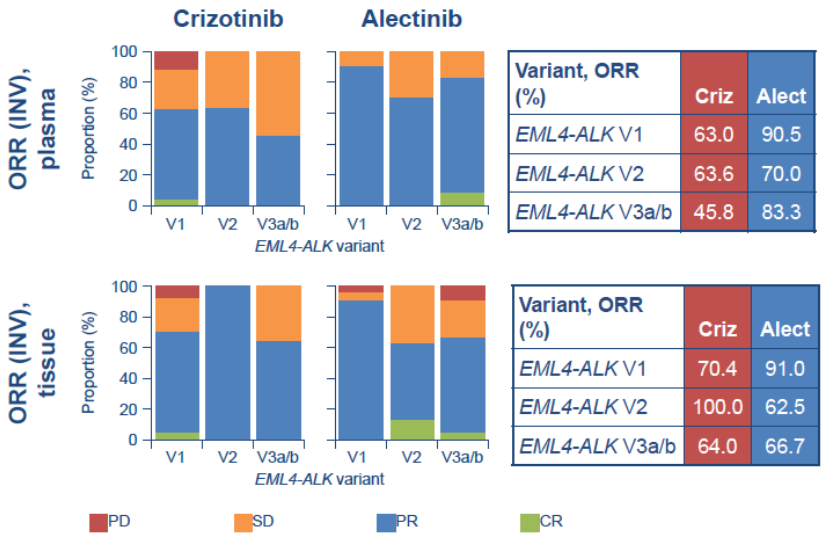
ORR in *EML4-ALK* variant populations



Variant, ORR (%)	Criz	Alect
EML4-ALK V1	63.0	90.5
EML4-ALK V2	63.6	70.0
EML4-ALK V3a/b	45.8	83.3

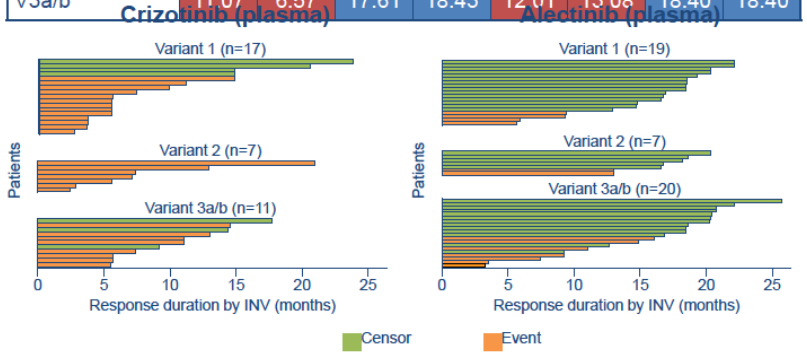
Variant, ORR (%)	Criz	Alect
EML4-ALK V1	70.4	91.0
EML4-ALK V2	100.0	62.5
EML4-ALK V3a/b	64.0	66.7

Alectinib demonstrated a greater ORR (INV) compared with crizotinib in the *EML4-ALK* variant populations 1 and 3a/b. ORR (INV) was higher with crizotinib for variant 2 in the tissue; however, variant 2 had smaller sample size

Alectinib demonstrated a higher ORR (IRC*) in all three variant populations compared with crizotinib

DoR in *EML4-ALK* variant populations

	Plasma median DoR, months				Tissue median DoR, months			
	Crizotinib		Alectinib		Crizotinib		Alectinib	
Variant	INV	IRC	INV	IRC	INV	IRC	INV	IRC
EML4-ALK V1	5.59	7.36	16.89	16.59	11.10	12.98	18.41	17.64
EML4-ALK V2	7.16	7.52	16.79	16.59	7.16	18.50	16.59	15.54
EML4-ALK V3a/b	11.07	6.57	17.61	18.43	12.01	13.08	18.40	18.40



DoR (by INV and IRC) was longer with alectinib versus crizotinib in all three *EML4-ALK* variant populations, in both tissue and plasma

La eficacia de Alectinib es superior frente a Crizotinib independientemente de la variante EML4-ALK

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LBA57. Overall survival results of ceritinib in ALKi-naïve patients with ALK-rearranged NSCLC (ASCEND-3)

ASCEND-3: A Single-arm, Open-label, Multicenter Phase 2 Study of Ceritinib in ALKi-naive Adult Patients (pts) With ALK-rearranged (ALK+) Non-small Cell Lung Cancer (NSCLC)

Advanced or metastatic ALK+ NSCLC
- ALK inhibitor naïve
- 0 to 3 lines of chemotherapy
- WHO PS 0–2

Certinib at 750 mg/d
- Continuous oral dosing
- Once daily
- 28 day cycle
- Treatment continued until unacceptable toxicity, discontinuation of treatment at the discretion of the investigator or patient, initiation of new anticancer therapy and/or death

- **Primary objective:** Determination of ORR per RECIST (investigator assessed)
- **Secondary Objectives:** Determination of DOR,

	N = 124
Age (median), years (range)	56 (27-82)
Age category, n (%)	
< 65 years	94 (75.8)
Sex, n (%)	
Female	74 (59.7)
Race, n (%)	
Caucasian	48 (38.7)
Black	1 (0.8)
Asian	74 (59.7)
Other	1 (0.8)
WHO performance status, n (%)	
0	46 (37.1)
1	69 (55.6)
2	9 (7.3)
Tumor histology/cytology, n (%)	
Adenocarcinoma	120 (96.8)

Primary endpoint: investigator assessed ORR
Secondary endpoint: ORR (BIRC), PFS (investigator and BIRC)
N=124; 39,5% with brain mets; 25% ≥ 3 prior non-ALK TKI therapies

LBA57. Overall survival results of ceritinib in ALKi-naïve patients with ALK-rearranged NSCLC (ASCEND-3)

GRADE 3/4 TOXICITIES

- Nausea (8%)
- Vomiting (6%)
- Diarrhea (3%)
- Increased ALT (24%)/AST(12%)/GGT(19%)
- Aes (all grade) requiring dose interruption (79%) or dose adjustment (65%)

Felip et al. Vs. Prior studies of ceritinib in ALK TKI naïve patients

Study	N	ORR (%)	PFS (months)	OS (months)
Felip et al	124	64-68	16.6-19.4	**51.3**
Kim et al	83	72	18.4	
Soria et al	189	73	16.6	

Shaw et al. NEJM 2014; Kim et al. Lancet Oncol 2016; Soria et al. Lancet 2017

LBA57. Overall survival results of ceritinib in ALKi-naïve patients with ALK-rearranged NSCLC (ASCEND-3). CONCLUSIONS

- The ASCEND-3 study met its objectives and the final analysis results are consistent with the previous analysis
- Ceritinib led to high rate of durable responses and prolonged PFS in the ALKi-naïve patients with ALK+ NSCLC, irrespective of brain metastases at baseline
- Median OS was prolonged (51.3 months) and clinically relevant in ALKi-naïve patients with ALK+ NSCLC, who are previously treated with ≤ 3 lines of chemotherapy
- The safety profile is consistent with the previous analysis and with the known safety profile of ceritinib. AEs were manageable with dose reductions / interruptions. No new safety signals identified
- Quality of life was generally maintained during ceritinib treatment
- These results further support the positive benfit-risk profile of ceritinib in ALKi-naïve patients with ALK-rearranged NSCLC

Shaw et al. NEJM 2014; Kim et al. Lancet Oncol 2016; Soria et al. Lancet 2017

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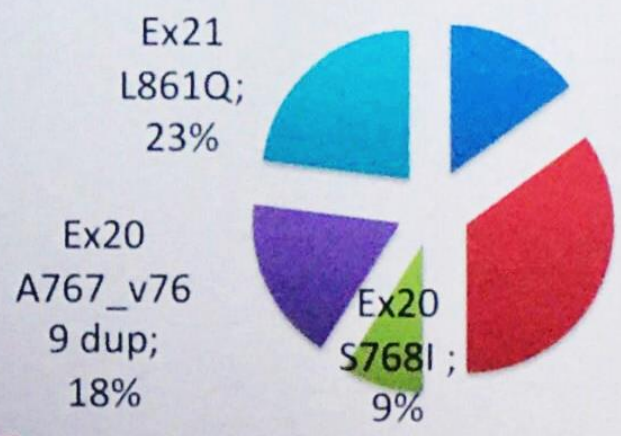
Results

UNCOMMON MUTATIONS (N=95/857) – 11% OF TOTAL EGFR Muts



Exon 20 ins not reported

27 (28%) presented with another co-mutation

9% with L858R

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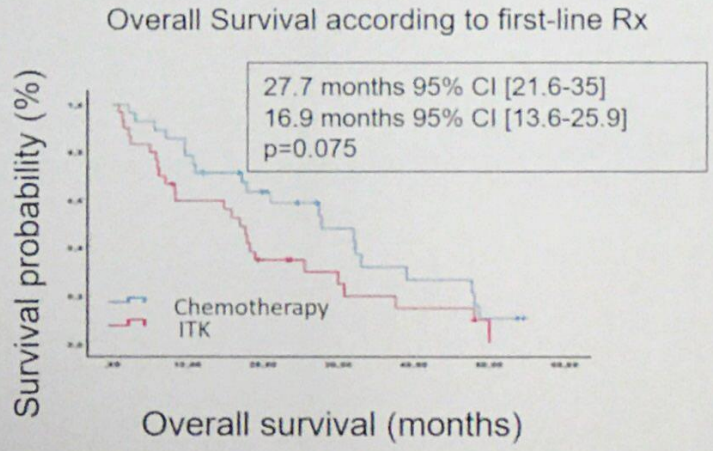
Overall Survival



Mutation	OS (mos)	95% CI
Ex21 L861Q	8.95	5.0-NA
Ex18 G719X	18.2	8.4-NA
Ex18 E709X	17.7	17.2-NA
Ex20 A767_v769 dup	16.9	7.1-NA
Ex20 S768I	29.75	1.5-NA

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OS According to Treatment

Treatment Group	No	Median OS (mos)	95% CI
Chemo only	13	20.9	11-NA
Chemo and EGFR-TKI	27	18.9	16.9-37.6
EGFR- TKI only	10	4.2	1.5-NA

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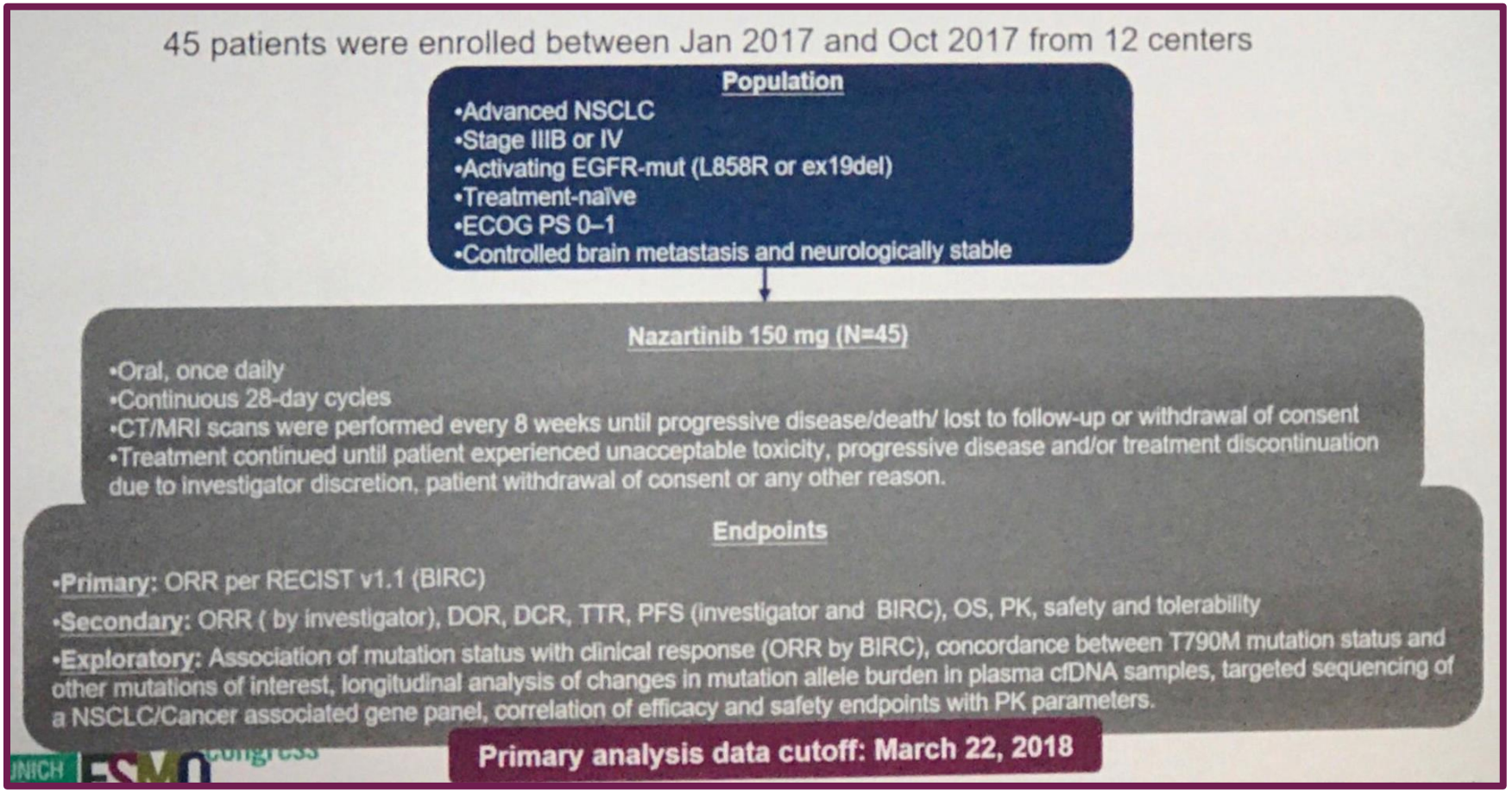
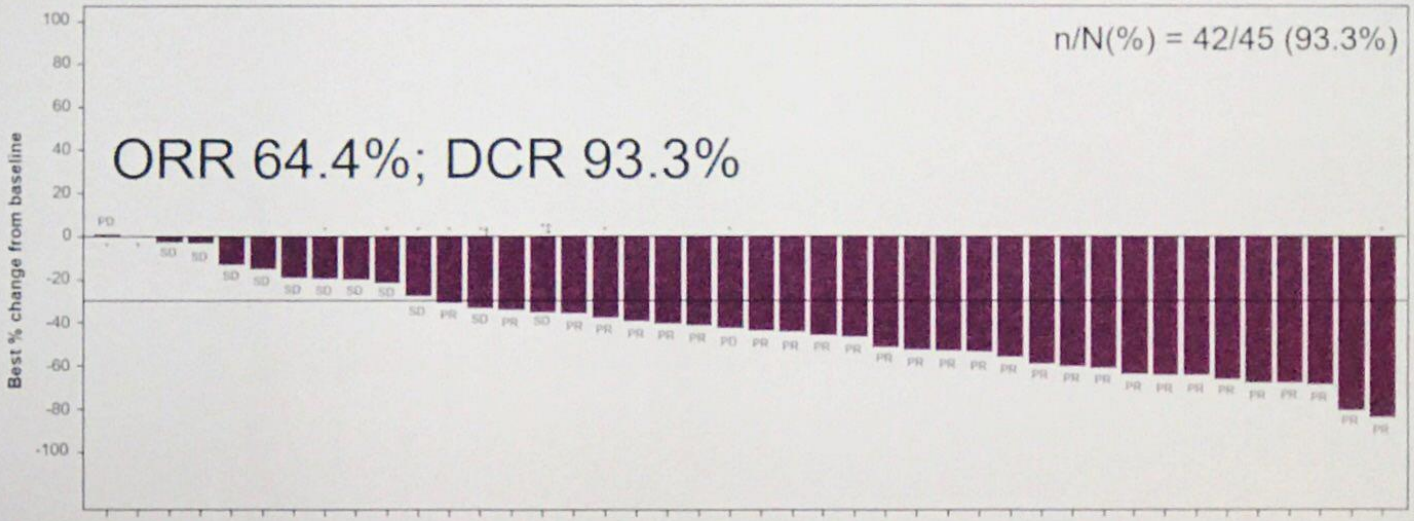
LBA61. Phase II results for single-agent nazartinib (EGF816) in adult patients (pts) with treatment-naïve EGFR-mutant non-small cell lung cancer NSCLC



LBA61. Phase II results for single-agent nazartinib (EGF816) in adult patients (pts) with treatment-aïve EGFR-mutant non-small cell lung cancer NSCLC

WATERFALL PLOT OF BEST PERCENTAGE CHANGE FROM BASELINE IN TARGET LESION DIAMETER PER BIRC



* Patient discontinued treatment
† SD-UNK-PR (SD BOR) by central
‡ PR-SD (SD BOR), by central
Evaluable patients: Patients who have an adequate tumor assessment at baseline and started treatment ≥ 15 weeks before the data cut-off.
n=number of patients with a baseline and at least one post-baseline assessment of target lesions based on investigator assessment.
Patients with BOR=UNK(No valid post-baseline assessment), Non-CR/Non-PD are not presented, 1 CR patient with non-measurable disease not presented
BIRC, Blinded Independent Review Committee; BOR, best overall response; PR, partial response; RP2D, recommended phase 2 dose; SD, stable disease; UNK, unknown

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SUMMARY OF RESPONSE ON BRAIN METASTASES PER BIRC

	N=45
Patients with brain metastasis at baseline, n/N (%)*	18/45 (40.0)
Patients with brain metastasis in non-target lesions only	17/18 (94.4)
Patients with brain metastasis in target lesions only	1/18 (5.6)
Patients with new brain lesions post baseline	1/18 (5.6)
Best response of brain non-target lesions, n/M† (%)	
Absent/normalized	9/17 (52.9)
Present	7/17 (41.2)
Unknown	1/17 (5.9)
Best % change from baseline in patient with brain target lesion	-38.5%
Patients without brain metastasis at baseline, n/N (%)	27/45 (60.0)
Patients with new brain metastasis post baseline, n/M‡ (%)	1/27 (3.7)

*Patients with valid post-baseline assessment and full brain metastasis data
†Patients with brain metastasis in non-target lesions only at baseline
‡Patients without brain metastasis at baseline
BIRC, Blinded Independent Review Committee

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- Effective 3rd gen EGFR-TKI with good brain penetration
- PFS, DoR and OS not mature yet
- Higher incidence of G ≥ 3 rash than Osimertinib
- Do we need another 3rd gen EGFR-TKI?