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1299P Real-world treatment patterns, clinical outcomes and EGFR/T790M testing practices in patients with EGFRm advanced NSCLC and 1L EGFR TKI therapy: A retrospective multinational study (REFLECT)

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Background: Epidermal growth factor receptor tyrosine kinase inhibitors (TKIs) have shown efficacy for the treatment of EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC). However, patients (pts) progress despite initial response to 1st/2nd generation (1G/2G) TKIs.

Methods: Clinical characteristics, treatment patterns, attrition rate and survival outcomes were assessed in a retrospective study of 896 pts initiating first line (1L) TKI between Jan 2015 - Jun 2018 in 49 sites in 7 European countries and Israel (data collection: May to Dec 2019). Kaplan-Meier methods were used to estimate median progression free survival (mPFS), overall survival (mOS) and time to treatment discontinuation (mTTD) [months (m) and (95% CI)] from 1L start.

Results: Baseline characteristics: median age 68 y; 64.1% female; 51.3% never smokers; 53.9% exon 19 deletion, 31.4% L858R, 14.7% uncommon EGFR mutations; 22.1% brain metastases; 69.6% ECOG 0-1. 1L TKI: 45.4% afatinib, 27.3% erlotinib, 27.2% gefitinib. Median follow-up from 1L start: 21.5 m. 14.6% pts continued 1L therapy at data collection. Of 765 pts stopping 1L, reasons were 75.0% progression, 11.2% death and 13.7% other. 1L mPFS was 13.0 (12.3,14.1) m and mTTD 12.6 (11.8,13.3) m. 32.7% (250/765) did not receive any 2L therapy. 515 pts started 2L therapy [chemotherapy 31.7% (163/515); osimertinib 59.8% (308/515)]. Of 395 pts discontinuing 2L, reasons were 59.7% progression, 22.0% death and 18.2% other. 2L median duration was 2.3 (2.0,2.8) m for chemotherapy and 10.9 (9.4,12.4) m for osimertinib. 20.4% (183/896) pts received 3L, of which 16.4% received osimertinib, and 6.1% (55/896) pts started 4L. Of 765 pts stopping 1L, 76.1% were tested for T790M at any time with 40.0% positive. 262/306 positive, 34/275 negative and 12/314 untested pts received osimertinib in 2L. In total 44.3% (339/765) started osimertinib post-1L. Overall mOS was 26.2 (23.6,28.4) m.

Conclusions: This is one of the largest studies with European pts treated with 1L 1G/2G TKIs. In real-world setting, 1/3 of pts never received 2L therapy, 3/4 were tested for T790M and <1/2 received osimertinib after 1L. More efficient use of EGFR TKIs is needed for better outcomes.

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1300P Intracranial efficacy of brigatinib (BRG) vs crizotinib (CRZ): Updated results from the ALTA-1L trial

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Background: BRG, a next-generation ALK tyrosine kinase inhibitor (TKI), has robust overall and intracranial efficacy in CRZ-resistant ALK+ NSCLC. At first ALTA-1L interim analysis (IA) in patients (pts) with TKI-naive ALK+ NSCLC, the primary endpoint,

blinded independent review committee (BIRC)-assessed PFS, was met (HR, 0.49; $P<0.001$; NCT02737501). Similarly, intracranial PFS (iPFS) in the ITT population was significantly improved with BRG vs CRZ (HR, 0.42; $P=0.0006$). Here we report updated intracranial efficacy from the second IA.

Methods: This open-label, multicenter study enrolled pts with TKI-naive stage IIIB/IV ALK+ NSCLC. Pts were stratified by presence of baseline (BL) brain metastases and history of chemotherapy for advanced disease and randomized 1:1 to BRG 180 mg qd with 7-day lead-in at 90 mg or CRZ 250 mg bid. Primary endpoint was BIRC-assessed PFS (RECIST v1.1). Secondary endpoints included intracranial ORR (iORR) and iPFS. The second IA was planned at ~75% of 198 expected PFS events.

Results: Of 275 randomized pts (BRG/CRZ, n=137/138), 34%/36% had BL brain metastases (BIRC-assessed). 13%/14% had prior brain radiotherapy, with whole brain radiation and stereotactic radiosurgery balanced across arms. At data cutoff (28 June 2019; median follow-up [BRG/CRZ], 24.9/15.2 mo, 150 events), iPFS in the ITT population remained significantly improved with BRG (HR, 0.45 [95% CI, 0.29–0.69]; log-rank $P=0.0001$). Additional intracranial efficacy results are presented in the table. Radiological overall disease progression occurred in (BRG vs CRZ) 54 (39%) vs 74 (54%) pts as assessed by BIRC and 50 (36%) vs 84 (61%) pts as assessed by investigator; of these, brain was the first site of disease progression more frequently in pts treated with CRZ: (CRZ vs BRG) 31 (42%) vs 17 (31%) pts by BIRC and 22 (26%) vs 7 (14%) pts by investigator.

Table: 1300P

BIRC-Assessed Endpoint	BRG	CRZ	*P* Value
All patients (ITT), n	137	138	
iPFS events, n (%)	40 (29)	51 (37)	
Median iPFS, mo	32 (30–NR[a])	24 (13–NR[a])	
2-yr iPFS, %	65 (55–73[a])	50 (38–60[a])	
iPFS HR	0.45 (0.29–0.69[a])		0.0001[b]
Any baseline brain metastases by BIRC, n	47	49	
iPFS events, n (%)	21 (45)	32 (65)	
Median iPFS, mo	24 (13–NR[a])	6 (4–8[a])	
2-yr iPFS, %	48 (30–63[a])	15 (5–32[a])	
iPFS HR	0.31 (0.17–0.56[a])		<0.0001[b]
Confirmed iORR, %	66 (51–79[a])	16 (7–30[a])	<0.0001[c]
Measurable brain metastases, n	18	23	
Confirmed iORR, %	78 (52–94[a])	26 (10–48[a])	0.0014[c]

NR, not reached [a]95% CI; [b]Log-rank; [c]Cochran-Mantel-Haenszel test.

Conclusions: BRG demonstrated superior intracranial activity vs CRZ in pts with ALK TKI-naive ALK+ NSCLC in ALTA-1L.

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1301P Blood first assay screening trial (BFAST) in patients (pts) with 1L NSCLC: ALK+ cohort updated biomarker analyses

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Background: BFAST (NCT03178552) is a global, multi-cohort study evaluating the relationship between blood-based next-generation sequencing (NGS) detection of actionable genetic alterations in circulating tumour DNA and activity of targeted therapies/immunotherapy in pts with 1L advanced NSCLC. In the *ALK+* cohort, investigator-assessed objective response rate (ORR) was 87.4% and 12-month progression-free survival (PFS) rate was 78.4% with alectinib. We present updated *ALK+* cohort biomarker analyses (median follow-up: 18.2 months).

Methods: Pts aged ≥18 with stage III/IV *ALK+* NSCLC (detected by blood-based NGS) received oral alectinib 600mg twice daily. Pre-treatment plasma samples were analysed for: co-occurring genetic alterations, *ALK* allele frequency, *EML4* variants; their association with clinical outcomes was explored (adjusted [adj.] for sex, disease stage, performance and smoking status).

Results: Of detected ALK fusions, 84% were EML4-ALK fusions. The most common EML4 variants (V) were V1 (34%) and V3 (33%), and the most common co-mutation was TP53 (44%). Pts with wild-type TP53 had improved 12-month PFS rate vs pts with mutated TP53 (89.4 vs 63.2%, respectively; adj. hazard ratio [HR] 0.31; 95% CI 0.14–0.68; P=.004). Worse 12-month PFS rate was seen for high (73.8%) vs low (81.5%) ALK allele frequency (50% allele cut-off [5.56 copies/mL; range: 0.43–686.28 copies/ml]: adj. HR 0.49; 95% CI 0.22–1.09; p=.08). No significant difference was seen in 12 month PFS rate between EML4 (78.9%) and non-EML4 (71.4%) fusions (adj. HR 0.91; 95% CI 0.33–2.49; p=.846) or EML4 V1 (87.5%) and V3 (74.1%) (adj. HR 0.53; 95% CI 0.18–1.55; p=.244). No significant difference in ORR was observed among the categories analysed.

Conclusions: Molecular heterogeneity in *ALK+* NSCLC may influence clinical efficacy of ALK inhibitors such as alectinib. Larger, more mature datasets are needed to identify and validate additional biomarkers predictive of limited benefit from ALK inhibitors.

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