Editorial

Expanding therapies for crizotinib refractory *ALK*-rearranged non-small cell lung cancer

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Since the discovery of the EML4-ALK fusion oncogene in 2007, there have been three drugs approved by the U.S. Food and Drug Administration for the treatment of *ALK* rearranged lung cancer. The reported frequency of *ALK*-rearrangement is between 4–7% in unselected advanced non-small cell lung cancer (NSCLC) (1-3), with an associated clinical phenotype of adenocarcinoma in never or light smokers, and younger patients (2,3). Crizotinib received FDA accelerated approval status in 2011 and full approval in 2013, reflecting both highly efficient drug development and approval (4). Initial phase III evidence of benefit with crizotinib, came from the PROFILE 1007 study (5) which compared crizotinib to chemotherapy following failure of first line chemotherapy. There were benefits in progression free survival (PFS) (3.0 to 7.7 months, HR 0.49), response rate (65% *vs.* 20%) and quality of life. Data for first-line crizotinib are from the PROFILE 1014 (6) study with crizotinib compared to platinum/pemetrexed chemotherapy. The crizotinib group had longer median PFS (10.9 *vs.* 7 months, HR 0.45), and superior objective response rate (74% *vs.* 45%), establishing crizotinib as initial therapy for *ALK*-rearranged lung cancer patients.

Mechanisms for emergence of resistance to crizotinib have now been characterized: with secondary mutations of the *ALK* kinase domain or amplification of the *ALK* fusion gene identified; the commonest of these are L1196M and G1269A (7,8). There are also documented mechanisms that bypass *ALK* and directly affect the downstream signalling pathways, such as alterations in EGFR, insulin like growth factor and KIT (7,8). Resistance frequently develops in brain, although this may be related to poor cerebrospinal fluid (CSF) penetration. For example, the CSF penetration of crizotinib is extremely low, and approximately half of patients go on to develop brain metastases despite crizotinib therapy (9). The intracranial relapse rate may be a result of both poor drug CSF penetrance (ratio plasma: CSF levels 0.0026) (9), natural history of *ALK* disease and pressure on diverse clonal groups promoting resistance in the brain. In oligometastatic progression, maintenance of crizotinib and addition of local treatment modalities results in improved overall survival compared to a group ceasing crizotinib in the same situation (10).

Ceritinib was the second *ALK* inhibitor approved for use by the FDA, in crizotinib refractory patients with *ALK*-rearranged lung cancer. In the ASCEND-1 trial (11,12), response was seen in 56% of 83 patients with prior *ALK* inhibitor treatment and 72% of 163 *ALK* inhibitor-naïve patients; with prolonged duration of response 8.3 and 17.0 months respectively. Tolerance was acceptable with low rates of grade 3 or greater toxicity. The phase II ASCEND-2 (13) and ASCEND-3 (14) trials of ceritinib in pre-treated and treatment naïve patients respectively, were presented at 2015 ASCO meeting and showed durable responses and safety outcomes in both groups consistent with those seen in ASCEND-1. Phase III confirmatory studies of ceritinib are underway.

Brigatinib is still under development and the results of the phase II ALTA study (15) were reported at ASCO 2016, showing an ORR of 54%, median PFS (at 180 mg) of 12.9 months, intracranial PFS of 15.6 months with the 90 mg dose and not yet reached with 180 mg daily.

Alectinib, the most recently approved second generation

ALK inhibitor in 2015, is an oral tyrosine kinase inhibitor of *ALK*. Pre-clinical data suggest high potency inhibition of *ALK*, anti-tumor effect in xenograft models and significant CSF penetrance and activity in xenograft brain metastases models (16). The initial phase I dose finding study from Japan, was published by Seto in *JCO* 2013. It led to a dose of 300 mg being approved in Japanese patients, although maximum-tolerated dose was not reached. 46 patients were treated with the recommended dose, of whom 43 achieved an objective response (93.5%; 95% CI, 82.1–98.6) including two complete responses (4.3%; 0.5–14.8) and 41 partial responses (89.1%; 76.4–96.4) (17). The North American study (AF-002JG) recommended a dose of 600 mg bid. Objective responses were noted in 24 of 44 patients (55%), with a confirmed complete response in 2 (2%), and partial response in 23 (52%). Sixteen (36%) patients had stable disease; the remaining four (9%) had progressive disease (18).

More recently, Ou *et al.* have published their global phase II experience with alectinib in crizotinib refractory *ALK*-rearranged lung cancer patients (16). Patients received 600 mg twice daily, and exploratory evaluation of alectinib plasma levels between 6 white and 20 Asian patients did not demonstrate marked differences. Of 138 patients treated, 122 were evaluable for response and 84 (61%) had brain metastases at baseline. The objective response rate was 52.2%, with a disease control rate of 79%. Median PFS was 8.9 months (95% CI, 5.6 to 11.3 months). In the chemotherapy group (96 with IRC response evaluable), response rate was 45% (95% CI, 35% to 55%) and disease control rate was 77% (95% CI, 67% to 85%); in the treatment naive group (26 response evaluable patients) ORR was 69% (95% CI, 48% to 86%).

The overall CNS response rate was 57%, with 27% achieving a complete CNS response; with CNS duration of response 10.3 months (95% CI, 7.6 to 11.2 months). Only 35 patients had measurable brain lesions at baseline, The response rate was higher in 23 patients who had not had previous brain irradiation with 10 of 23 achieving a CNS CR. The rate of systemic progression was less than the rate of CNS progression but a limitation of the study was that patients without baseline brain metastases did not have routine brain imaging during the study, thus potentially underestimating CNS progression. Alectinib-related adverse events (any grade) were constipation (33%), fatigue (26%), myalgia (23%), and asthenia (18%). Grade 3 to 4 AEs did not occur in more than 5% of patients treated with alectinib. Alectinib seems a more tolerable treatment than crizotinib, particularly with respect to gastrointestinal side effects.

Alectinib is a highly promising treatment for *ALK* rearranged crizotinib-refractory lung cancer. In terms of drug selection for patients with brain metastases, whilst acknowledging cross trial comparison limitations, we note the intracranial response rate for ceritinib was 36%, 67% for brigatinib and 57% for alectinib in patients with measurable CNS lesions at baseline, although patient numbers are small. Alectinib appears to have the most favourable toxicity profile, with fewer gastrointestinal side effects than ceritinib, and without the concerns about pneumonitis associated with brigatinib.

Excitement about alectinib is also influenced by the presentation of the J-ALEX trial at the ASCO 2016 Annual Meeting. In this phase II study, 207 Japanese patients with treatment naive *ALK* positive NSCLC were randomly assigned to alectinib or crizotinib. PFS was not reached (95% CI, 20.3–not estimated) in alectinib group while it was 10.2 months (95% CI, 8.2–12.0) in the crizotinib group. PFS HR of alectinib arm to crizotinib arm was 0.34 (99.6826% CI, 0.17–0.70, P<0.0001) (19). All subgroups appeared to benefit including those with brain metastases receiving alectinib (HR PFS 0.08; 95% CI, 0.01–0.61). The results of the global randomized ALEX trial of first line alectinib versus crizotinib are pending, with the expectation that it will be preferred for patients presenting with brain metastases. However its availability in many parts of the world is currently limited by lack of drug access.

This research adds to the growing evidence to support the use of alectinib in the treatment of *ALK* rearranged NSCLC, particularly in patients with brain metastases, adding a valuable tool to our therapeutic armamentarium. Ongoing development of other compounds is also eagerly awaited, including lorlatinib with high CNS penetration (20), ensartinib and CEP-37440.

Mechanisms of resistance to alectinib have been elucidated and have shown to be overcome by ceritinib (8), paving the way for treatment algorithms with sequential therapies. We are entering an era in which biopsy data, as well as disease kinetics and presence of cerebral metastases will guide treatment decisions in *ALK* rearranged disease (21). Sequential therapy, novel TKIs, immunotherapy combinations and possibly combinations of targeted agents may be the future of overcoming resistance in *ALK*-rearranged lung cancer.

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