Frontline Ceritinib Doubles PFS in ALK-Rearranged Lung Cancer

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By Dave Levitan

The oral ALK inhibitor ceritinib provided a significant improvement in progression-free survival (PFS) over platinum-based chemotherapy in patients with previously untreated *ALK*-rearranged non–small-cell lung cancer (NSCLC), according to a new phase III study.

Crizotinib previously proved effective compared to chemotherapy in *ALK*-rearranged NSCLC, but most patients ultimately progress. "Ceritinib is a next-generation, selective oral ALK inhibitor with a 20 times greater potency than crizotinib in enzymatic assays," wrote study authors led by Jean-Charles Soria, MD, of the Institut Gustave Roussy in Villejuif, France.

The ASCEND-4 trial is a phase III randomized study comparing ceritinib (189 patients) to carboplatin or cisplatin (187 patients). All patients had stage IIIB/IV *ALK*-rearranged non-squamous NSCLC. The results were published online ahead of print in *Lancet*.

The study met its primary objective regarding PFS. The median PFS as assessed by a blinded independent review committee with ceritinib was 16.6 months, compared with 8.1 months in the chemotherapy group, for a hazard ratio of 0.55 (95% CI, 0.42–0.73; $P < .00001$). This was supported by a PFS assessment by the investigators. The PFS advantage was seen in patients with and without brain metastases. In those without brain metastases, the median PFS with ceritinib was 26.3 months compared with 8.3 months with chemotherapy, for an HR of 0.48 (95% CI, 0.33–0.69). In those with brain metastases the advantage did not reach significance; the median PFS was 10.7 months with ceritinib and 6.7 months with chemotherapy, for an HR of 0.70 (95% CI, 0.44–1.12). Ceritinib offered better PFS across other subgroups including age, race, and other factors as well, though sample sizes were too small in some to reach significance.

Overall survival (OS) data was not yet mature, but a trend toward an advantage with ceritinib was observed. The median OS with the study drug was not reached, and it was 26.2 months with chemotherapy, for an HR of 0.73 (95% CI, 0.50–1.08; $P = .056$). At 24 months, the estimated OS rates were 70.6% with ceritinib and 58.2% in the chemotherapy group. Of 145 patients who discontinued chemotherapy, 105 (72%) then received an ALK inhibitor.

Adverse events (AEs) that occurred more frequently with ceritinib included diarrhea, nausea, and vomiting, all of which were primarily grade 1 or 2. More patients in the ceritinib group (65%) had a grade 3 or 4 AE suspected to be related to the study drug than in the chemotherapy group (40%). Serious AEs related to study drugs were similar across the groups.

"The unprecedented median PFS … shows ceritinib to be an effective treatment for untreated *ALK*-rearranged NSCLC," the authors concluded.

In an accompanying editorial, Benjamin Solomon, MBBS, PhD, of Peter MacCallum Cancer Centre in Melbourne, Australia, noted that the efficacy of ceritinib did come with toxicity that often required dose interruption or reduction (80% of patients).

"An advantage of newer generation ALK tyrosine kinase inhibitors such as ceritinib over crizotinib is improved central nervous system penetration and activity against brain metastases, a frequent and clinically important problem in patients with *ALK*-rearranged NSCLC," Solomon wrote. He added that other ongoing or planned phase III trials involving alectinib, brigatinib, and other ALK inhibitors will soon shed more light on the optimal treatments for *ALK*-rearranged NSCLC.