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Report from the World Conference on Lung Cancer (WCLC)

Improving survival in lung cancer

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PROLONGING SURVIVAL IN ADVANCED NSCLC

TRIAL SUMMARY: Next-generation ALK inhibitors

Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK-positive non-small cell lung cancer. *NEJM*. 2018 Sep 25. doi: 10.1056/NEJMoa1810171. [Epub ahead of print] Presented at WCLC, September 2018, Toronto.

The next-generation anaplastic lymphoma kinase (ALK) inhibitor, brigatinib, has demonstrated effectiveness in patients with ALK-positive non-small cell lung cancer (NSCLC) that is refractory to crizotinib. This phase 3 trial sought to compare the efficacy of brigatinib and crizotinib in patients with advanced ALK-positive NSCLC who have not previously received an ALK inhibitor. A total of 275 patients were randomized to receive either 180 mg once daily of brigatinib or 250 mg twice daily of crizotinib. The primary endpoint was progression-free survival (PFS), and secondary endpoints were objective response rate (ORR) and intracranial response.

Results: A first interim analysis was conducted when 50% of 198 expected events of disease progression or death had occurred. The median followup at the time of this analysis was 11.0 months in the brigatinib group and 9.3 months in the crizotinib group.

The estimated 12-month PFS was higher with brigatinib, 67% (95% confidence interval [CI]: 56–75) vs 43% (95% CI, 32–53) with crizotinib. ORR was 71% (95% CI, 62–78) with brigatinib vs 60% (95% CI, 51–68) with crizotinib. Intracranial response among patients with measurable lesions was 78% (95% CI, 52–94) with brigatinib and 29% (95% CI, 11–52) with crizotinib. No new safety concerns were noted.

COMMENTARY: Targeting ALK in patients with ALK-positive lung cancer results in high tumour response rates and prolonged survival.[1] Progression on crizotinib is often due to development of brain metastases resulating from poor central nervous system (CNS) drug penetration.[2] Alectinib, a CNS-penetrant ALK inhibitor has greater efficacy than crizotinib in the treatment-naive ALK-positive lung cancer setting, showing a PFS of 34.8 months in the ALEX trial.[3]

Brigatinib is another next-generation ALK inhibitor that has shown activity in patients refractory to crizotinib and crosses the blood-brain barrier.[4] At the 2018 World Conference on Lung Cancer, the authors reported on results of the first preplanned interim analysis of brigatinib vs crizotinib in the first-line setting for treatment-naive ALK-positive NSCLC patients.[5] Median followup was 9.3 months in the brigatinib arm and 11 months in the crizotinib arm of the trial.

This open-label phase 1/3 clinical trial randomized 275 patients 1:1 between brigatinib and crizotinib until progression or intolerable toxicity. Crossover to the brigatinib arm was permitted on blinded independent review committee of progression on crizotinib. Approximately a third of patients entered the trial with brain metastases, nearly half of whom had been pretreated with radiation.

This first analysis showed a superior PFS in patients who received brigatinib as compared with crizotinib (HR 0.49), with the median PFS not yet not reached in the brigatinib arm. The crizotinib arm thus far appears to perform similar to previous ALK inhibitor trials.[1,3] There was a 24% increase in 1-year PFS in the brigatinib arm as compared to crizotinib.

Subgroup analysis showed that patients with brain metastases at the time of enrolment derived the greatest benefit (HR 0.20), but this likely reflects the fact that this patient population drives early progression events. The most frequent site of progression in patients with brain metastases at enrolment was within the brain. The median PFS of crizotinib-treated patients with baseline brain metastases was 5.6 months, in contrast to brigatinib, where the median PFS for this patient subset was not yet reached. The intracranial response rate of patients with any brain metastases at baseline was 67% with brigatinib, as compared with 29% in the crizotinib arm, emphasizing the CNS penetrance of brigatinib.[4]

The proportion of patients with measurable brain metastases at enrolment was similar in this trial to that in the ALEX trial.[3,5] The response rate to crizotinib in patients with measurable brain metastases is 29% in the ALTA-1L trial, as compared with 50% in the ALEX trial.[6] The response rate for brigatinib and alectinib in these populations is similar, at 78% and 81% respectively. However, ALTA-1L reported median intracranial PFS, while the ALEX trial reported cumulative incidence of CNS progression at 1 year, which makes cross-trial comparison more difficult.[5,6]

The safety profile of brigatinib was as expected from earlier trials, with early-onset pneumonitis (within 14 days of drug initiation) seen in 3% of brigatinib-treated patients.[5] Increased levels of creatine phosphokinase (CPK), lipase or amylase were observed in between 3% and 10% of brigatinib patients, without any evidence of myalgia, myositis or pancreatitis. This led to twice as many dose reductions in the brigatinib arm (30% of patients) as seen in the alectinib group. The benefit of treatment was maintained at these lower doses.

The data from this study are immature, but brigatinib shows better efficacy than crizotinib, and a magnitude of benefit that is likely similar to alectinib in treatment-naive patients. The most effective sequencing of different ALK inhibitors remains an open question, and decisions are likely to be driven by knowledge of patterns of resistance to the various inhibitors and prospective selection of the most effective inhibitor for the contemporaneous resistance mechanism. Overall survival in both studies, although broadly informative, will be influenced by post-trial treatment.

At the WCLC, discussant Professor Fiona Blackhall also made the valid point that crizotinib may no longer be the appropriate choice for randomized controlled trials of new ALK inhibitors in the treatment-naive space.

In the Canadian landscape, brigatinib adds to our armamentarium against ALK-positive NSCLC. With the option of crizotinib, ceritinib, alectinib and now brigatinib, the future looks brighter for our patients.

IN BRIEF

Already known

- Crizotinib is the first anaplastic lymphoma kinase (ALK) inhibitor to demonstrate an improvement in progression-free survival (PFS) over platinum-based chemotherapy in advanced ALK-positive non-small cell lung cancer (NSCLC) patients.
- Alectinib, a central nervous system (CNS)-penetrant ALK tyrosine kinase inhibitor (TKI), has greater efficacy in treatment-naive ALK-positive NSCLC than crizotinib.

What this study showed

- Brigatinib is more effective than crizotinib in treatment-naive ALK-positive NSCLC, with greatest benefit seen thus far in patients with brain metastases at enrolment.

Next steps

- Brigatinib is another option for first-line treatment of ALK positive NSCLC with an acceptable toxicity profile. The optimal sequencing of ALK inhibitors and the most efficacious first-line inhibitor are yet to be confirmed.

References

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