2015 European Cancer Congress (ECC)

TKI Targeted at T790M Lung Cancer Mutations Yields High Rate of Disease Control

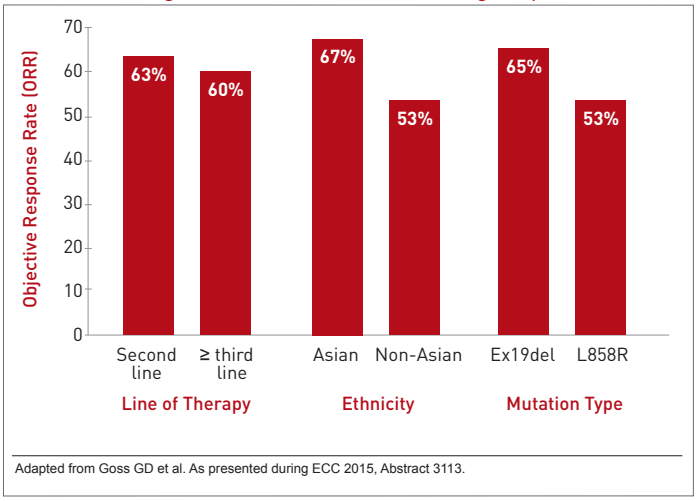
Vienna - In advanced non-small cell lung cancer (NSCLC) patients who have developed the epidermal growth factor receptor (EGFR) T790M mutation, a novel second-line targeted agent continues to demonstrate high rates of disease control, according to data presented at the 2015 European Cancer Congress. Although the data were from pooled Phase 2 data, the high rates of activity and favorable safety profile are likely to advance this agent toward regulatory approval.

Focus on EGFR and T790M Mutations

Data from the pooled analysis of two Phase 2 trials showed that overall, "the ORR [objective response rate] was 61% by independent central review and the disease control rate was 91%," reported Dr. Glenwood Goss, Director, Lung Cancer Program, Ottawa Hospital Cancer Centre, Ontario. The results are consistent with initial safety and efficacy data published last year (Jänne PA et al. *N Engl J Med* 2015;372: 1689-99). The data have attracted attention because NSCLC patients with driver EGFR mutations who acquire resistance to first-line tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib, or afatinib, now have limited treatment options.

Most reassuring in these Phase 2 trials was the consistency of the activity of AZD9291, an oral TKI selective for both EGFR and T790M resistance mutations, across patient stratifications. This included line of therapy (second vs. third), ethnicity (Asian vs. non-Asian), and mutation type (Figure 1). In the pooled data with 411 patients, of which 98.5% had EGFR T790M mutations confirmed in a central laboratory, 31% received AZD9291 as a second-line therapy and 69% as a third-line therapy. Non-Asians represented 40% of the study population, while Ex19del was the most common T790M mutation subtype (68%) followed by L858R (29%).

FIGURE 1 | High ORR (>50%) across Subgroups



Adapted from Goss GD et al. As presented during ECC 2015, Abstract 3113.

AZD9291 has been well tolerated. Although diarrhea and rash were each reported by 38% of patients, grade 3 or higher of these events were observed in less than 1%. Only 4% of patients discontinued therapy for adverse events. Consistent with the potential for this therapy to extend disease control, a large proportion of patients remained on therapy with durable disease control at the most recent data cut-off.

Goal is to transform advanced NSCLC into a chronic disease that can be controlled by a sequence of therapies targeted at underlying mutations.

The Phase 2 data were drawn from multicenter trials that enrolled patients from Europe, North America, and Asia. Molecular studies to confirm T790M status were mandatory. Patients with stable brain metastases were permitted into the trial. In separate data that evaluated the patient experience with AZD9291, treatment satisfaction was high (score 9.1 of 10). Asked specifically to rate difficulty with adverse events, patients gave AZD9291 a score 2.1 out of 10, suggesting good tolerability.

Conclusion

In the context of its tolerability, the efficacy of AZD9291 may be another advance toward the goal of transforming advanced NSCLC into a chronic disease that can be controlled by a sequence of therapies targeted at underlying mutations identified with molecular profiling. NSCLC driven by EGFR mutations represent about one third of the disease. Currently, there is no approved drug for patients with EGFR mutations who develop T790M resistance to currently available TKIs.●

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