Sotorasib provides durable clinical benefit for patients with non-small cell lung cancer and KRAS mutations

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In the phase II CodeBreak 100 trial, sotorasib provided durable clinical benefit with a favorable safety profile in patients with pretreated non-

small cell lung cancer (NSCLC) and who harbor KRAS p.G12C mutations, validating CodeBreak 100's phase I results, according to research presented today at the International Association for the Study of Lung Cancer World Conference on Lung Cancer.

Outcome in patients with advanced NSCLC on second- or third-line therapies is poor, with a response rate of less than 20% and median progression-free survival of fewer than four months. Approximately 13% of patients with lung adenocarcinomas harbor KRAS p.G12C mutations.

Sotorasib is a first-in-class small molecule that specifically and irreversibly inhibits KRAS p.G12C. In the phase I cohort of the CodeBreak 100 trial, sotorasib was well tolerated and demonstrated a confirmed response rate of 32.2%, a median duration of response of 10.9 months, and a median progression-free survival of 6.3 months in 59 patients with heavily pretreated NSCLC.

Results from the registrational phase II portion of this multicenter, international study, led by Dr. Bob Li, of Memorial Sloan Kettering Cancer Center in New York City, were presented for the first time.

Researchers enrolled 126 patients who met the following inclusion criteria:

- Presence of a centrally confirmed KRAS p.G12C mutation;
- Disease progression on anti-PD-1/PD-L1 immunotherapy and/or platinum-based combination chemotherapy, or targeted therapy if EGFR, ALK, and ROS1 alterations had been previously identified; and
- Fewer than or equal to three prior lines of therapy.

Patients with untreated active brain metastases were excluded.

Enrolled patients were followed for a median period of 12.2 months. An independent blinded central review of the patients found that 124 patients had at least one measurable lesion at baseline and were evaluated for efficacy. Of these, 46 patients experienced a confirmed response (three complete responses and 43 partial responses), resulting in an objective response rate of 37.1% (95% Cl: 28.6-46.2). The median time to objective response was 1.4 months, the median duration of response was 10 months (95% CI: 6.9-11.1), and 43% of responders remained on treatment without progression. The disease control rate was 80.6% (95% Cl: 72.6-87.2).

Median progression-free survival was 6.8 months (95% Cl: 5.1-8.2).

Treatment-related adverse events (TRAEs) of any grade occurred in 88 (69.8%) patients and led to discontinuation in nine (7.1%) patients. Grade 3 TRAEs were reported in 25 (19.8%) patients; those that occurred most commonly were alanine aminotransferase increase (8/126, 6.3%), aspartate aminotransferase increase (7/126, 5.6%), and diarrhea (5/126, 4.0%). There were no treatment-related deaths.

"This is a historic milestone in [lung] cancer therapy. After four decades of scientific efforts in targeting KRAS, sotorasib has potential to be the first targeted treatment option for this patient population with a high unmet need," said Dr. Li.

Further clinical trials of sotorasib, either alone or in combination with other cancer drugs, are ongoing in an effort to benefit more patients.

In December 2020, Amgen submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) and Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for sotorasib, for the treatment of patients with KRAS p.G12C-mutated locally advanced or metastatic NSCLC, following at least one

prior systemic therapy. The NDA is being reviewed under the FDA's Real-Time Oncology Review pilot program and has been granted Breakthrough Therapy designation.

Provided by International Association for the Study of Lung Cancer