BLU-667 Shows Good Activity Against Advanced Lung and Thyroid Cancers

RET inhibitor shrank tumors in more than half of people with non-small-cell lung cancer and aggressive thyroid cancer.

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An experimental therapy targeting the RET protein led to tumor shrinkage in about 60% of people with previously treated non-small-cell lung cancer (NSCLC) or medullary thyroid cancer with certain gene mutations, according to Phase I study results presented at the American Society of Clinical Oncology (ASCO) annual meeting this month in Chicago.

If these promising early findings are confirmed, BLU-667 could become another so-called site-agnostic medication designed to target cancers with specific genetic alterations anywhere in the body. The first, Vitrakvi (larotrectinib), was approved by the Food and Drug Administration (FDA) last November, and entrectinib—recently approved in Japan under the brand name Rozlytrek—could receive the FDA nod in August.

Cancer therapies have traditionally been developed, tested and prescribed for tumors in a specific part of the body. Site-agnostic targeted therapies could reduce the need for so many separate clinical trials and could help fill a gap for people with rare cancers that are not extensively studied.

BLU-667, from Blueprint Medicines, targets the RET receptor tyrosine kinase, which plays a role in cell proliferation. Oncogenic RET gene mutations and fusions (when one gene fuses with another) can drive the development of cancer. BLU-667 is highly specific for these mutations in cancer cells, meaning it should cause minimal damage to normal cells. There are currently no FDA-approved selective RET inhibitors; some multikinase inhibitors, such as Nexavar (sorafenib), block RET along with other targets, but these are more likely to cause side effects.

Although rare overall, RET alterations are found in around 90% of advanced medullary thyroid cancers, about 20% of papillary thyroid cancers and around 1% to 2% percent of non-small-cell lung cancers, the researchers noted as background.

At ASCO, Justin Gainor, MD, from Massachusetts General Hospital in Boston, presented the latest data on people with NSCLC treated with BLU-667 in the Phase I ARROW trial, while a poster from Matthew Taylor, MD, of Oregon Health and Science University in Portland, and colleagues described findings from the thyroid cancer cohort.

ARROW (NCT03037385) is evaluating the safety, tolerability and efficacy of BLU-667 in adults with RET-altered advanced solid tumors. The first part of the study tested different doses of the drug.

At last year's American Association for Cancer Research annual meeting, Vivek Subbiah, MD, of MD Anderson Cancer Center in Houston, presented interim findings showing that BLU-667 at doses of 60 milligrams or higher demonstrated good antitumor activity. The overall response rate, meaning complete or partial tumor shrinkage, was 37%, including five partial responses in NSCLC cancer patients and five partial responses and one complete response in thyroid cancer patients.

The ongoing second part of the study is enrolling participants into seven cohorts, all of whom will received BLU-667 at the selected dose of 400 mg taken by mouth once daily:

- Patients with RET-fusion NSCLC who were previously treated with platinum-based chemotherapy
- Patients with RET-fusion NSCLC who did not previously receive this chemotherapy
- Patients with RET-fusion medullary thyroid cancer who were previously treated with Cometriq (cabozantinib) or Caprelsa (vandetanib)
- Patients with RET-fusion medullary thyroid cancer who did not previously receive these drugs
- Patients with other RET-fusion tumors
- Patients with other RET-mutated tumors
- Patients with RET-fusion or RET-mutated tumors who were previously treated with another selective RET inhibitor, such as LOXO-292.

The NSCLC cohort included 120 participants, including 91 who had previously received platinum-based chemotherapy. Just over half were women, and the median age was 60. Two thirds reported they had never smoked. Other than RET, they had no other known targetable lung cancer driver mutations (such as ALK or ROS1). One in four had cancer that had spread to the brain. About 40% had previously tried checkpoint inhibitor immunotherapy.

Among the 48 patients with enough follow-up time to be evaluated, the overall response rate was 58% for the group as a whole and 60% for those with prior use of platinum chemotherapy. One person in the chemo-experienced group had a complete response. In addition, 38% in the full group and 40% in the prior chemotherapy group had stable disease with no further progression; two previously untreated patients had progressive disease. Responses were similar for people with or without prior checkpoint inhibitor use. BLU-667 was active against cancer in the brain, and seven of nine evaluated patients showed shrinkage of brain metastases.

Responses were "rapid and durable," mostly occurring by the first scan at week 8 of treatment, Gainor reported. Most participants (82%) were still on treatment at the time of the analysis, and

the median duration of response was not yet reached.

Gainor's presentation also reported that BLU-667 demonstrated good activity in people with other RET-fusion tumors, including two with metastatic pancreatic cancer and one with bile duct carcinoma in the liver.

The thyroid cohort included 64 participants with metastatic RET-mutated medullary thyroid cancer (MTC), 43 of whom had previously received Cometriq or Caprelsa, and nine people with advanced RET-fusion papillary thyroid cancer (PTC), a third of whom had received Nexavar or Lenvima (lenvatinib). Papillary carcinoma accounts for about 80% of all thyroid tumors; medullary cancer, which arises from a specific type of cell, is typically more aggressive. About two thirds were men, and the median age was 59 in the MTC group and 66 in the PTC group.

Among the 32 evaluable MTC patients, the overall response rate was 56% for the whole cohort and 63% for previously treated patients; all were partial responses. In addition, 41% in the full group and 31% in the treatment-experienced subgroup had stable disease, while one previously treated individual experienced disease progression. Five of the six evaluable PTC patients had partial responses, for an overall response rate of 83%. All MTC responders and all but one of the PTC patients were still on treatment at the time of the report, with the longest response approaching a year and half.

BLU-667 was generally safe and well tolerated. In the lung cancer cohort, 7% of participants stopped taking the drug because of treatment-related toxicities; none did so in the thyroid cancer cohort. Across both groups, the most common treatment-related adverse events were constipation, neutropenia (low white blood cell count), elevated AST liver enzyme levels and hypertension.

The FDA has granted BLU-667 a breakthrough therapy designation for progressive RET-fusion NSCLC and RET-mutated medullary thyroid cancer with no acceptable alternative treatments. Blueprint indicated that it plans to submit data supporting approval for lung cancer in early 2020 and for thyroid cancer by mid-2020.

The promise of site-agnostic medications points to the importance of genetic testing to match individuals with the targeted therapies most likely to work for them.

"ASCO 2019 has brought us hope for some of these elusive targets," said Christine Lovly, MD, PhD, of Vanderbilt University Medical Center in Nashville, who commented on the conference presentation. "We can expand the reach of precision medicine for lung cancer patients through improved uptake of tumor biomarker testing." She added that both smokers and those who never smoked should be tested for potentially targetable mutations.

Click here to read the NSCLC study abstract.

Click here to read the thyroid cancer study abstract.

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