Fusion Protein Shows Good Activity Against HPV-Related Cancer

Bintrafusp shrank tumors in about a third of patients with cervical, anal or head and neck cancer.

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A new type of immunotherapy targeting proteins that suppress immune response demonstrated promising activity against cancers caused by human papillomavirus (HPV), according to early study findings presented at the 2019 American Association for Cancer Research (AACR) annual meeting last week in Atlanta.

The researchers concluded that bintrafusp (also known as M7842 or MSB0011359C) has a "manageable safety profile" and "shows encouraging clinical efficacy" in people with HPV-positive cancers.

Estimates suggest that more than 30,000 people in the United States and 600,000 people worldwide are diagnosed with HPV-associated cancers each year, which include anal cancer, cervical cancer, other genital cancers and some head and neck cancers, particularly oral cancer. Almost all cervical cancer, 90 percent of anal cancer and 70 percent of oropharyngeal (mouth and throat) cancer is caused by HPV, according to the National Cancer Institute (NCI).

Bintrafusp is a bifunctional fusion protein created by fusing a receptor for TGF-beta to a monoclonal antibody that targets the PD-L1 checkpoint protein, which acts as a brake on T-cell activity. TGF-beta, which suppresses T cell and natural killer cell responses, promotes tumor growth, metastasis and resistance to treatment. Bintrafusp works as a trap to disable TGF-beta. The hybrid molecule therefore interferes with two pathways that tumors may use to evade the immune system, according to the NCI.

Julius Strauss of the NCI's Laboratory of Tumor Immunology and Biology presented the latest findings from a subgroup of patients with HPV-associated malignancies in a Phase I clinical trial evaluating bintrafusp for locally advanced or metastatic solid tumors that either have no effective standard therapy or do not respond to existing treatment. The TGF-beta pathway appears to play a critical role in HPV-associated malignancies and these tumors often have high PD-L1 expression, Strauss noted.

In the dose-escalation portion of the study, participants received bintrafusp at doses of 1, 3, 10 or

20 milligrams per kilogram once every two weeks until they experienced disease progression, unacceptable toxicity or withdrew for other reasons. An expansion cohort then received a fixed dose of 1,200 mg every two weeks. Previous results were published last year in the AACR's journal Clinical Cancer Research.

Strauss described 43 patients with previously treated HPV-associated cancers: 25 with cervical cancer, 14 with head and neck cancer and four with anal cancer. Of these, 36 had tumors that tested positive for HPV. Two thirds of the participants were women, with ages ranging from 34 to 78. Nearly 40 percent had tried three or more prior treatments.

Two people had complete responses, or full tumor regression, and 10 had partial responses, for an overall response rate of 27.9, rising to 30.6 percent for those with HPV-positive tumors, Strauss reported.

In addition, three more people had delayed partial responses after apparent disease progression (known as pseudo-progression), including one who ultimately had a 90 percent tumor reduction. Taking these patients into account, the clinical response rate was 34.9 percent for the whole group and 38.9 percent for those with HPV-positive tumors.

Responses were usually durable. At the data cutoff in early January, nearly 75 percent of responders still had not experienced disease progression. The median duration of response has not yet been reached because a majority are still responding. The two complete responders—both women with HPV-positive cervical cancer—remain on treatment with ongoing responses.

The median overall survival duration was 16.2 months for the whole group, but cannot yet be determined for those with HPV-positive tumors. The 12-month overall survival rates were 56.2 percent and 61.8 percent, respectively.

Bintrafusp was generally safe and well tolerated. The most common side effects were skin rash and itching. About 25 percent experienced severe (grade 3 or higher) treatment-related adverse events including anemia, various laboratory abnormalities and pneumonitis (lung inflammation). Several developed low-grade skin tumors or mucosal bleeding. Seven people discontinued treatment because of side effects.

The study's senior investigator, James Gully, MD, PhD, chief of the NCI's Genitourinary Malignancies Branch, previously told Cancer Health that one woman with metastatic cervical cancer had a complete response that has lasted more than two years so far. He suggested bintrafusp may be even more effective when combined with PD-1/PD-L1 checkpoint inhibitors such as Keytruda (pembrolizumab) or Tecentriq (atezolizumab).

Bintrafusp is being developed by a collaboration of GlaxoSmithKline and Merck KGaA. A Phase II study for people with HPV-associated malignancies is now underway. Ongoing or planned clinical trials will evaluate bintrafusp for a range of other cancers including breast cancer, colorectal cancer and non-small-cell lung cancer.

Click here to read the AACR study abstract.

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