Targeted oral therapy reduces disease burden and improves symptoms for patients with rare blood disorder in trial

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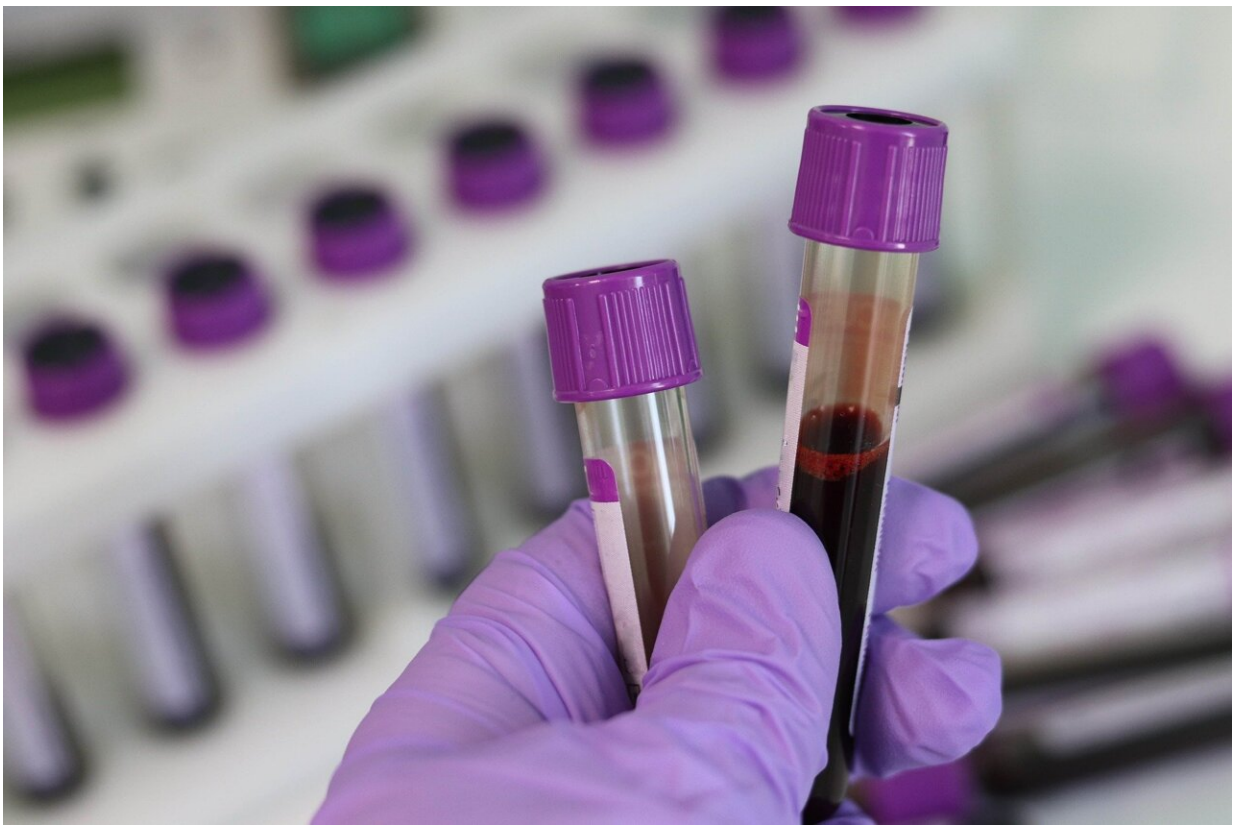

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The targeted therapy bezuclastinib was safe and rapidly reduced markers of disease burden while also improving symptoms for patients with a

rare blood disorder called nonadvanced system mastocytosis, according to results of the Phase II SUMMIT trial reported by researchers at The University of Texas MD Anderson Cancer Center.

The findings, presented at the 2023 American Society of Hematology (ASH) Annual Meeting, demonstrate that all participants treated with bezuclastinib achieved at least a 50% reduction in markers of disease burden and 63% reported their disease symptoms eased within 12 weeks. That number increased to 78% after an additional eight weeks of treatment, at which time all patients also reported an improvement in pain symptoms.

"The era of targeted therapy offers hope, not just for alleviating symptoms but for getting to the root of the condition," said principal investigator Prithviraj Bose, M.D., professor of Leukemia. "Bezuclastinib provides precision targeting without the typical central nervous system or bleeding side effects often associated with similar drugs."

Systemic mastocytosis (SM) is a rare disease marked by the buildup of malignant mast cells in the bone marrow and other tissues. These high levels of abnormal mast cells can lead to a multitude of symptoms due to the release of chemicals called mediators. SM can range from non-advanced (NonAdvSM) to advanced disease (AdvSM), with symptoms that can include brain fog and skin rashes to gut issues and life-threatening anaphylaxis.

In up to 95% of patients, SM is driven by the KIT D816V gene mutation. Treatments targeting this mutated kinase have been used for AdvSM variants, but they are known to have off-target activity that can cause toxicities that restrict dosing and, therefore, limit efficacy.

There are two variants within NonAdvSM: indolent systemic

mastocytosis (ISM) and smoldering systemic mastocytosis (SSM). ISM, which affects the majority of patients with SM, is characterized mostly by symptoms related to mast cell degranulation and mediator release. SSM is identified by a higher mast cell burden, marked by high levels of blood enzymes like serum tryptase, but without resulting organ damage.

Bezuclastinib is a potent type-1 tyrosine kinase inhibitor that blocks mutant KIT D816V activity while sparing other kinases, minimizing the potential for off-target side effects. In a separate, prior studies, the drug demonstrated minimal brain penetration in animals and no central nervous system toxicities in patients with AdvSM.

The first part of the SUMMIT trial followed 20 patients with NonAdvSM for a median duration of seven months. The majority were female (75%) with a median age of 50. Seventy-five percent of patients had the KIT D816V mutation, and all had moderate-severe symptoms. Patients were treated with either 100 or 200 mg of bezuclastinib or with placebo. All patients continued to receive their baseline anti-mediator treatments throughout the trial.

Researchers evaluated the efficacy of bezuclastinib through multiple patient-reported outcome measures and changes in markers of disease burden, such as serum tryptase, bone marrow mast cell percentage and KIT D816V mutation allele burden.

Patients who received the 100 mg dose experienced a median reduction in symptoms of 48.5% after 12 weeks. During this period, none of the patients in the placebo group reported significant improvement in their overall symptoms. However, after transitioning those patients to bezuclastinib treatment, 67% reported an improvement in their symptoms after four weeks.

After 20 weeks, more patients observed greater improvements in

dermatological symptoms (78%), gastrointestinal symptoms (33%) and cognitive symptoms (33%) compared to the 12-week mark.

Adverse events generally were mild and reversible, with the most frequent being a change in hair color, nausea and peripheral edema. No serious adverse events related to bezuclastinib were reported in the 100 mg or 200 mg cohorts.

"This drug may offer great promise in the treatment of non-advanced systemic mastocytosis," Bose said. "As we move forward, our aspiration is to optimize the dosage while maintaining a robust safety profile."

To further assess the drug's efficacy in patients with NonAdvSM, next steps for the SUMMIT trial include comparing bezuclastinib against placebo once the optimal dose has been determined. Part Ib of the trial will investigate 100mg and 150 mg daily doses that use a different formulation of the drug, and those results are expected in 2024, Bose explained.

More information: Abstract

Provided by University of Texas M. D. Anderson Cancer Center

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