Saruparib demonstrates early efficacy in breast cancers with DNA repair defects in Phase I/II trial

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The first-in-class PARP1-selective inhibitor saruparib demonstrated encouraging early efficacy and a favorable safety profile in patients with homologous recombination repair (HRR)-deficient breast cancers, according to results from the Phase I/II PETRA trial led by researchers at The University of Texas MD Anderson Cancer Center.

Results from the first-in-human trial were presented at the American Association for Cancer Research (AACR) Annual Meeting 2024 by Timothy Yap, M.B.B.S., Ph.D., professor of Investigational Cancer Therapeutics and vice president and head of clinical development in the Therapeutics Discovery division.

A total of 31 patients with advanced breast cancers harboring HRR deficiency mutations received the optimal recommended dose of 60 mg of saruparib. The objective response rate was 48.8% with a median progression-free survival of 9.1 months. The drug had favorable tolerability as well as pharmacokinetic and pharmacodynamic responses.

"Saruparib is a first-in-class, highly selective and potent new generation PARP1-selective inhibitor with a wide therapeutic index," Yap said. "The favorable safety profile of saruparib together with the low dose-reduction rate compared to approved PARP inhibitors may allow patients to remain on treatment longer at an optimal dose, offering maximal pharmacokinetic exposure and pharmacodynamic engagement, which could lead to improved efficacy."

Poly-ADP ribose polymerase (PARP) inhibition previously was shown

to be particularly effective in cancers harboring gene mutations that negatively affect DNA repair, such as BRCA1/2 mutations, because these cancers rely even more than others on PARP proteins to repair any DNA damage. By inhibiting PARP proteins, these cancers are unable to repair their DNA, leading to an inability to replicate and, ultimately, cell death.

Saruparib is a new-generation oral inhibitor selectively targeting PARP1, whereas previous PARP inhibitors targeted both PARP1 and PARP2. While these first-generation inhibitors have become the standard of care for certain cancers, the improved safety profile of saruparib could allow for more combinations with other treatments and opportunities to bring the benefits of PARP inhibitors to patients in earlier disease stages.

The trial included 141 patients who were eligible for safety analysis at a 60 mg dose. Of these, only 14.2% had to reduce dosage and just 3.5% had to discontinue treatment due to treatment-related adverse events. The most common adverse events were anemia, neutropenia, thrombocytopenia, fatigue and asthenia.

According to Yap, the safety profile of this heavily pretreated patient population compared favorably to Phase III data from approved first-generation PARP inhibitors. In follow-up to these findings, rational saruparib combination strategies currently are being tested, including clinical evaluation in the Phase III trial setting, Yap noted.

More information: ABSTRACT CT014: https://www.abstractsonline.com/pp8/#!/20272/presentation/11430

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