Early trial results show benefits of FGFR inhibitors and PARP/ATR inhibitor combinations in multiple tumor types

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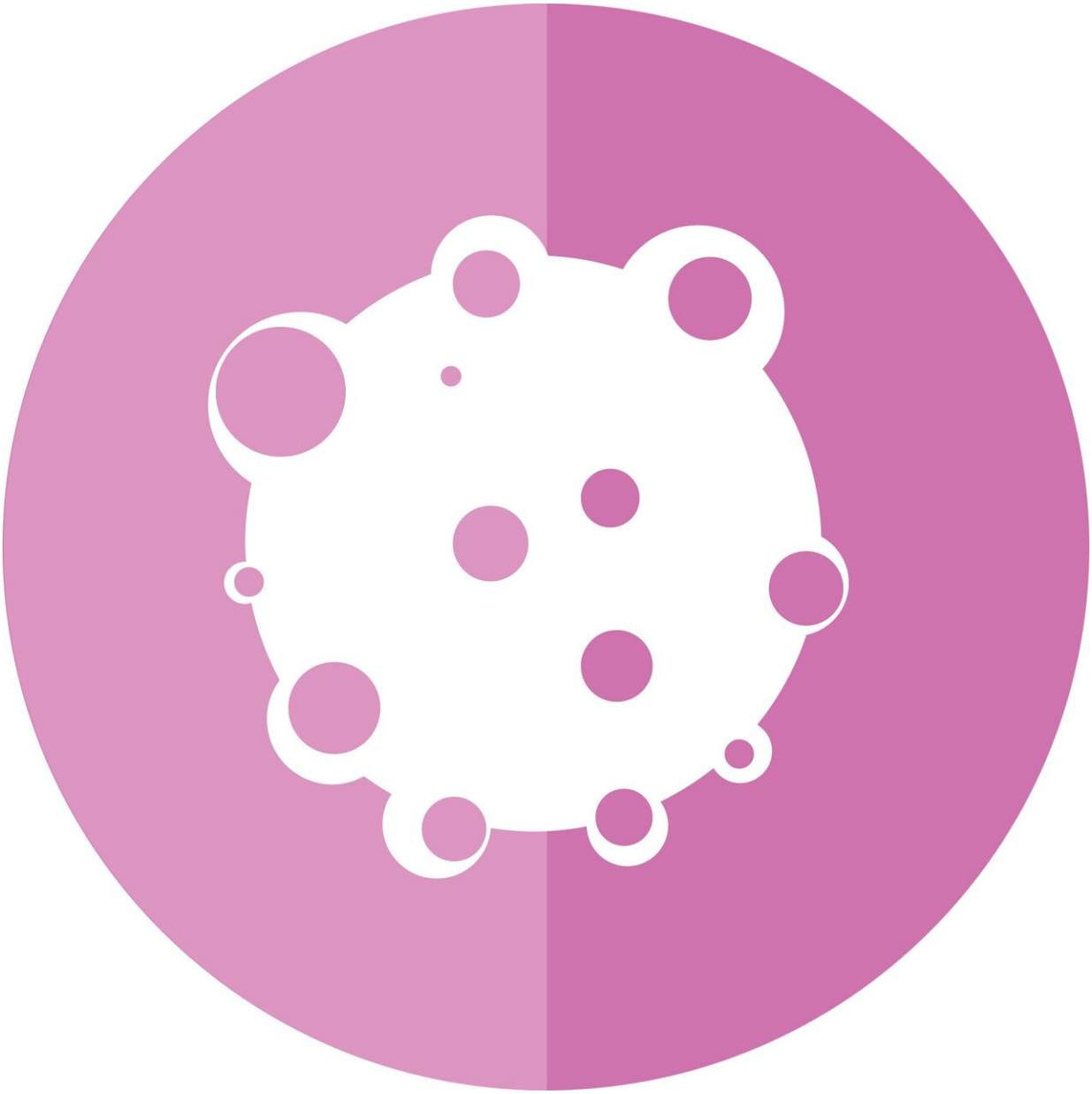

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Researchers from The University of Texas MD Anderson Cancer Center presented promising findings from multiple clinical trials today at the American Association for Cancer Research (AACR) Annual Meeting 2023.

The studies, which describe results from a novel FGFR inhibitor and from new PARP/ATR inhibitor combinations, were featured in a plenary session highlighting novel biomarker-driven molecularly targeted therapy trials. Information on all MD Anderson AACR Annual Meeting content can be found at MDAnderson.org/AACR.

Basket trial results suggest wider population may benefit from FGFR inhibitor pemigatinib (Abstract CT016)

The FIGHT-207 trial, led by Jordi Rodon, M.D., Ph.D., associate professor of Investigational Cancer Therapeutics, demonstrated promising early signs of clinical benefit and unveiled potential mechanisms of primary and secondary resistance following treatment with the selective FGFR inhibitor pemigatinib in patients with advanced FGFR-altered solid tumors.

Pemigatinib achieved responses across multiple tumor types, with the highest objective response rate (26.5%) in the cohort containing patients with FGFR1-3 fusions. These include responses in glioblastoma and pancreatic cancers, which were not known to respond to FGFR inhibitors, and patients with previously unreported FGFR alterations.

The researchers also found that certain co-occurring mutations correlated with patient responses. For example, BAP1 mutations were associated with higher response rates, while TP53 alterations were associated with lower response rates.

"This study highlights the value of basket trials as a discovery tool. Instead of grouping by cancer type, this trial grouped cohorts based on types of mutations," Rodon said. "There remain a lot of unknowns with FGFR inhibitors, with FGFR mutations that drive sensitivity and resistance, and with tumor types where these alterations drive growth. This basket trial allowed us to explore these unknowns from a mutational rather than a histological point of view to see what other types of patients may benefit."

FGFR alterations drive cancer progression in multiple tumor types, making them a promising target for therapies. However, a lack of target selectivity in first-generation FGFR inhibitors frequently led to intolerable toxicities, limiting their effectiveness in the clinic. Pemigatinib overcomes that by selectively targeting certain FGFR proteins commonly found in cancers; the drug previously was approved by the Food and Drug Administration (FDA) for use in refractory cholangiocarcinoma and myeloid/lymphoid neoplasms (MLNs) with fibroblast growth factor receptor 1 (FGFR1) rearrangement.

The open-label, single-arm Phase II basket study was designed to evaluate the efficacy and safety of pemigatinib in patients with previously treated unresectable or metastatic solid tumors harboring FGFR mutations or fusions/rearrangements. The trial enrolled 111 patients and grouped participants into three cohorts based on the specific type of FGFR alteration. Patients were 56% female with a median age of 62; 56% had more than two prior lines of therapy.

Safety was consistent with previous studies of pemigatinib, with the

most common adverse events being hyperphosphatemia, or excess phosphorous in the blood, in 84% of patients, followed by stomatitis (53.2%), alopecia (41%), diarrhea (39%) and constipation (33%.) Of these, only stomatitis (9%) occurred at a grade 3 level or higher in more than 1% of patients.

PARP and ATR inhibitors in combination show promising early results (Abstract CT018)

Two trials led by Timothy A. Yap M.D., Ph.D., associate professor of Investigational Cancer Therapeutics, showed encouraging results for treating solid tumors with DNA damage response alterations using a combination of PARP and ATR inhibitors. Notably, anti-tumor activity was seen in patients with tumors that had previously shown resistance to PARP inhibitors or platinum-based therapies.

The researchers studied combinations of the ATR inhibitor camonsertib with each of three currently approved PARP inhibitors, niraparib, talazoparib and olaparib. The clinical benefit rate (CBR) for all patients in this heavily pretreated population was 48%, with an overall response rate (ORR) of 18% in the niraparib group and 10% in each of the groups treated with talazoparib and olaparib. The high molecular response rate using circulating tumor DNA further confirmed treatment effect and offered a mechanistic explanation for the durable clinical benefit.

The highest response rates were seen in patients with ovarian cancer. Among 19 patients, the ORR was 32% and CBR was 58%, with a median progression-free survival of about seven months and treatment of at least 16 weeks ongoing in nine patients.

"We really need better approaches with PARP inhibitors to maximize their benefit, and pre-clinical data support combinations with ATR inhibitors. This study was designed to evaluate the optimal combination

from a tolerability and toxicity standpoint," Yap said.

PARP inhibitors have been approved for certain cancer types since 2014, but not all patients respond and those that do often build up resistance, limiting their clinical effectiveness. To overcome these problems, researchers studied the effectiveness of combining them with an ATR inhibitor.

ATR inhibitors are similar to PARP inhibitors in that they target the DNA damage repair pathway. In cells with defects in repair pathways, this causes a buildup of cell damage and ultimately cell death. Pre-clinical studies suggest that, since the two work toward the same goal using different mechanisms, the combination of the two makes them more effective than either one alone.

The two Phase I/II trials include a total of 107 patients, with 90 evaluable for efficacy at the time of the AACR data cut off. Patients received a median of three prior lines of therapy, including 39% of patients having previously been treated with a PARP inhibitor and 78% of patients who were platinum-resistant or refractory.

The challenge in bringing these combinations to the clinic has been overcoming the overlapping toxicities associated with both inhibitors. In this trial, both drugs were given at low intermittent doses based on strong pre-clinical modeling data supporting this novel approach.

"Using this dosing technique, we were able to get combinatorial efficacy without the severe toxicity," Yap said. "We were very excited to see responses even in patients who previously had been treated with a PARP inhibitor and were resistant to it, which is a critical area of unmet need that is urgently required in the clinic."

In general, the combinations were well tolerated. The most common

adverse events were short-term reversible hematological side effects, such as anemia, with no prophylactic growth factors required in the study. Dose optimization in molecularly driven tumor-specific expansion cohorts is ongoing.

More information: Conference: www.aacr.org/meeting/aacr-annual-meeting-2023/

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