Therapies targeting DNA damage response show promising antitumor activity

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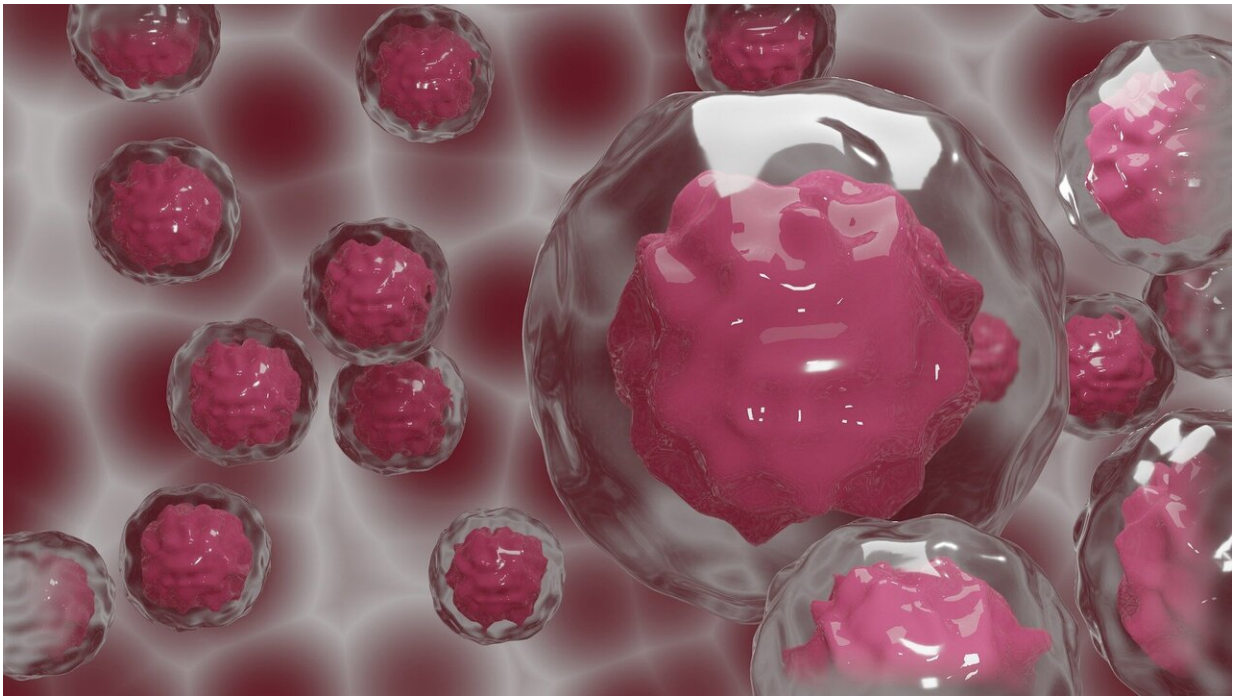

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Results from early-stage clinical trials show two drugs that target the DNA damage response (DDR) pathway in cancers—ATR inhibitor elimusertib and PARP inhibitor AZD5305—are safe and clinically beneficial in treating patients with advanced solid tumors. Principal investigator Timothy Yap, M.B.B.S., Ph.D., associate professor of Investigational Cancer Therapeutics, today presented new data from the

trials at the American Association for Cancer Research (AACR) Annual Meeting 2022.

"DDR orchestrates a complex network of mechanisms that detects and repairs damage to DNA, such as double strand breaks and replication stress," Yap explained. "However, when DDR defects occur, it promotes uncontrolled cancer cell growth and enables cells to evade apoptosis. The studies suggest that PARP1-selective and ATR inhibitors, which block two key mediators of the DDR signaling pathway, are a promising class of new drugs that offer significant therapeutic potential for patients with cancers harboring synthetic lethal genomic alterations in DDR pathways."

Expansion trial of ATR inhibitor shows encouraging clinical activity against DDR defects (Abstract CT006)

In a Phase Ib expansion trial, elimusertib—a potent and highly selective ATR inhibitor—demonstrated promising antitumor activity against a range of advanced solid tumors with different putative deleterious DDR alterations.

ATR is a critical component of the DDR network that is activated by DNA damage or replication stress. By binding to ATR and blocking ATR-mediated signaling, ATR inhibitors prevent DNA damage checkpoint activation, disrupt DNA damage repair and stop the growth of tumor cells, Yap explained.

In the study, 143 patients with advanced solid tumors with different putative deleterious DDR alterations—including 45 gynecologic cancers, 24 colorectal cancers, 19 HER2-negative breast cancers, 19 castration-resistant prostate cancers, and 36 advanced cancers with loss of alternative DDR protein ATM—received at least one dose of elimusertib. Thirty-two patients with ATM protein loss and/or mutations

were enrolled in the dose escalation arm of the study.

The most frequent drug-related grade ≥3 treatment emergent adverse events (TEAEs) were hematologic, including anemia (65.7%) and neutropenia (47.6%). Overall, these hematologic TEAEs were reversible and manageable with dose interruptions or reductions and supportive measures, and infrequently resulted in permanent drug discontinuation. An alternative schedule of three days on and 11 days off, which also was explored, may reduce the risk of hematologic events and offer a potential alternative to be further evaluated in future studies of elimusertib.

Elimusertib achieved clinical benefit with disease control for at least 16 weeks in approximately 35% of patients enrolled in the three days on, four days off dose expansion, with durable objective responses observed across a variety of cancer types. Results showed a durable clinical benefit lasting greater than six months in 27.8% of patients with advanced ovarian cancer, including those resistant to platinum-based therapy and those who previously had received PARP inhibitor therapy. In patients with ATM loss, the best overall response included RECIST partial responses in 8.9% of patients and RECIST stable disease in 55.9% of patients, with durable clinical benefit lasting >6 months in 26.5% of patients.

"While we observed durable responses and prolonged stable disease in patients with ATM alterations and *BRCA1* and *BRCA2* defects, including patients previously treated with PARP inhibitor therapy, further studies are needed to better identify molecular biomarkers to predict which patients are most likely to benefit from elimusertib monotherapy," Yap said. "Rational combination studies are also ongoing and investigating elimusertib in combination with the PARP inhibitor niraparib and with the PD-1 inhibitor pembrolizumab."

The trial was supported by Bayer. A full list of co-authors and their disclosures can be found here.

Next-generation PARP1-selective inhibitor demonstrates promising clinical activity with a favorable safety profile (Abstract CT007)

Results from the Phase I/IIa PETRA trial showed that AZD5305, a potent and highly selective next-generation PARP1 inhibitor and trapper, achieved maximal target engagement and promising clinical activity with a favorable safety profile. The targeted therapy demonstrated significantly improved pharmacokinetics and exposure above target than could be achieved with first-generation PARP inhibitors.

In addition to blocking PARP enzymatic activity, first-generation PARP inhibitors trap PARP1 and PARP2—two repair proteins that activate the DDR pathway—to the sites of DNA damage to prevent DNA repair and to selectively kill cancer cells. However, a growing body of evidence shows that only PARP1 inhibition and trapping is required for synthetic lethality in cancers with homologous recombination repair (HRR) deficiency.

"By selectively inhibiting and trapping PARP1, AZD5305 achieved greater antitumor efficacy across select tumor and molecular subtypes, more durable target inhibition and superior tolerability compared to first-generation dual PARP1/2 inhibitors in preclinical models," Yap said. "These exciting trial results of AZD5305 demonstrate that we can build on the success of first-generation PARP inhibitors by providing important clinical proof of concept for this innovative strategy. We were able to achieve substantially improved safety, pharmacokinetics, pharmacodynamics and promising efficacy in patients with different molecularly-driven cancers with AZD5305."

In the first-in-class, first-in-human trial, researchers enrolled and treated

61 patients with advanced breast, ovarian, prostate or pancreatic cancer bearing germline or somatic *BRCA1/2*, *PALB2* or *RAD51C/D* mutations with AZD5305.

Of the 40 evaluable patients, 10 achieved RECIST partial responses and 11 achieved RECIST stable disease across doses, tumor types and mutation types and were independent of prior PARP inhibitor use.

The most common grade ≥3 TEAE, irrespective of causality, was anemia (14.8%), followed by neutropenia (6.6%) and thrombocytopenia (3.3%). Only two patients (3.3%) required a dose reduction after experiencing treatment-related grade 3 neutropenia and grade 1 thrombocytopenia. At the time of data cutoff, there were no dose-limiting toxicities, treatment-related serious adverse events or treatment discontinuations. Overall, AZD5305 was well tolerated with low rates of nausea and hematological toxicity compared to first-generation PARP inhibitors.

The drug achieved robust and durable pharmacodynamic target engagement across all dose levels, measured by the inhibition of poly ADP-ribosylation (PARylation), which showed that AZD5305 led to maximal target engagement of at least 90%.

Researchers are currently conducting expansion trials to evaluate the drug's efficacy in PARP inhibitor-naïve populations and dose escalations of combination therapies, including trastuzumab deruxtecan and datopotamab deruxtecan.

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

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