

Zedoresertib and Lunresertib Combination Shows Promising Antitumor Activity

Zedoresertib and lunresertib are both investigational targeted therapies that create synthetic lethality by blocking cell cycle proteins.

April 19, 2026 By MD Anderson Cancer Center

- Phase I trial provides early clinical proof-of-concept supporting the combination of zedoresertib and lunresertib in certain advanced solid tumors.
- Zedoresertib, which targets WEE1, and lunresertib, a PKMYT1 inhibitor, are both investigational therapies that create synthetic lethality by blocking cell cycle proteins.
- Combination achieved notable responses in ovarian cancer at the preliminary recommended Phase II dose, with a 50% overall response rate across all patients and a 60% rate in patients with *CCNE1* amplification.
- This combination has been granted FDA Fast Track Designation in patients with ovarian cancer harboring *CCNE1* amplification, *FBXW7* or *PPP2R1A* deleterious mutations.

For patients with advanced solid tumors harboring specific genetic alterations, the first-in-class synthetic lethal combination of WEE1 inhibitor zedoresertib plus PKMYT1 inhibitor lunresertib demonstrated promising antitumor activity and was generally well-tolerated, according to Phase I MYTHIC trial data reported by researchers at The University of Texas MD Anderson Cancer Center.

Based on these data, the combination was granted Food and Drug Administration (FDA) Fast Track Designation in patients with [ovarian cancer](#) harboring these genetic alterations. Results were presented today in the clinical trials plenary session at the [American Association for Cancer Research \(AACR\) Annual Meeting 2026](#) by principal investigator [Timothy Yap, MBBS, PhD](#), professor of [Investigational Cancer Therapeutics](#) and vice president and head of clinical development in UT MD Anderson's [Therapeutics Discovery](#) division.

“This combination demonstrated strong synergy in preclinical studies, and we have now demonstrated its great potential as a novel therapeutic option for patients across multiple tumor types – especially for those with ovarian cancer,” Yap said. “Patients with cancers harboring *CCNE1* amplification and *FBXW7* and *PPP2R1A* mutations represent areas of unmet clinical need, for which this combination could provide a new treatment option.”

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What are zedoresertib and lunresertib, and how do they work?

Zedoresertib, developed by Debiopharm, is a highly selective and brain-penetrant WEE1 kinase inhibitor. The WEE1 protein is a critical gatekeeper of the cell cycle that can help cancer cells survive DNA damage by ensuring that DNA repair occurs before cell division takes place. Inhibiting WEE1 with zedoresertib, therefore, pushes cancer cells with DNA damage – such as those with *CCNE1* amplification-induced replication stress – into mitosis earlier, leading to cell death through apoptosis.

Similarly, lunresertib, developed by Repare Therapeutics and licensed to Debiopharm, is a highly selective PKMYT1 kinase inhibitor that regulates the cell cycle via a different pathway, creating synthetic lethality in tumors with specific genetic mutations, such as *FBXW7* or *PPP2R1A*, or *CCNE1* amplification.

Both zedoresertib and lunresertib work well together in multiple tumor types *in vivo*, showing durable regressions following both continuous and intermittent zedoresertib treatment. The combination was also well-tolerated in preclinical studies.

What were the main objectives and who was treated in the MYTHIC trial?

The primary objectives of the Phase I MYTHIC trial were to determine the safety and tolerability of zedoresertib plus lunresertib, as well as to identify the maximum tolerated dose. Additionally, the researchers evaluated preliminary antitumor activity, pharmacokinetics and pharmacodynamics.

The ongoing trial had enrolled 62 patients at data cutoff with advanced resistant/refractory solid tumors harboring *CCNE1* amplification and/or *FBXW7* and/or *PPP2R1A* mutations, including but not limited to patients with ovarian, [colorectal](#), [pancreatic](#) and [breast cancer](#). Investigators are examining treatment doses from 150 mg to 260 mg daily of zedoresertib plus 60 mg or 80 mg of lunresertib on a three-on-four-off schedule.

What were the results of combining zedoresertib and lunresertib?

The overall disease control rate for 54 evaluable patients across all dosing levels was 68.5%. In 51 patients with target lesions, 26 showed tumor shrinkage and 10 patients achieved a radiological response.

Among patients with advanced ovarian cancers harboring *CCNE1* amplification, *FBXW7* or *PPP2R1A* mutations, 80% showed consistent tumor shrinkage, with durable responses observed. At least 10 patients (37%) remained on treatment for more than 16 weeks, and five patients (18.5%) remained on treatment for longer than 32 weeks.

The molecular response rate (MRR) was 47% for all patients across all dose levels. In patients with advanced ovarian cancer, the MRR was 67%.

The safety profile was manageable and consistent with either inhibitor as a monotherapy. The most commonly reported side effects were Grade 1 or 2 nausea, vomiting and asthenia, or generalized fatigue.

Given the promising antitumor activity and manageable safety profile, researchers will continue to optimize dosing and scheduling of this combination across the various tumor types represented in this study.

The study was funded by Debiopharm and Repare Therapeutics. A complete list of collaborating authors and their disclosures can be found with the [abstract](#).

This [news release](#) was published by the University of Texas MD Anderson Cancer Center on April 19, 2026.

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