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TRANSCRIPT

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Targeting the DNA Damage Response: Updates from the 2021 SABCS

Announcer:
You're listening to *Project Oncology* on ReachMD. On this episode, sponsored by Lilly, we're going to hear from medical oncologist and physician-scientist Dr. Timothy Yap, who's an Associate Professor in the Department for Investigational Cancer Therapeutics and the Department of Thoracic/Head and Neck Medical Oncology at the University of Texas MD Anderson Cancer Center. Dr. Yap joins us to discuss his presentation given at the 2021 San Antonio Breast Cancer Symposium titled, "Targeting the DNA Damage Response: Moving Beyond PARP Inhibitors." Here's Dr. Yap now.

Dr. Yap:
I had the pleasure of speaking about the latest developments and using PARP inhibitors and other DNA damage response, or DDR, inhibitors to target breast cancer, where we are now trying to really build on the success that we have seen with PARP inhibitor monotherapy, and treating BRCA-mutated breast cancer, both in the metastatic and adjuvant settings.

The great news is that the DDR therapies and landscape is rapidly expanding beyond PARP inhibitors, and this has really been facilitated by the discovery of novel precision targets, enabled by cancer genome sequencing and modern CRISPR technologies. And this has, in turn, enabled us to use biomarker-driven patient selection strategies to guide the development of novel DDR agents in clinical trials. We now have multiple DDR agents currently in early Phase 1 and 2 clinical trial development, including inhibitors against ATR, WEE1, ATM, DNA-PK, CHK1, and RAD51, as well as new agents that have recently entered the clinic, such as PKMYT1 and USP1 inhibitors. I think this truly does show that the DDR synthetic lethal concept is much bigger than just BRCA-mutated cancers and PARP inhibitors, and that we are just at the tip of the iceberg.

In my talk, I discussed the use of ATR inhibitors in molecularly selected cancers, including breast cancer, where we have seen early promising activity in BRCA1 and BRCA2-mutated breast cancer patients, who had previously received a PARP inhibitor. We are also seeing early activity in breast cancer patients with other molecular subtypes, including ATM loss of function alterations. I also discussed the development of rational PARP inhibitor combinations, to build on the success of PARP inhibitor monotherapy. And such promising combinations include the use of PARP inhibitors with other DDR agents, such as WEE1 or ATR inhibitors, antibody drug conjugates such as sacituzumab govitecan, immunotherapy agents such as PD1 and PD-L1 inhibitors, and also potent and selective molecularly targeted agents, which can induce chemical BRCAness and sensitize homologous recombination proficient tumors, such as BRCA1 and BRCA2-mutated, wild-type, triple negative breast cancers to PARP inhibitors. And such partner drugs may include BAT inhibitors, that have been shown to induce chemical BRCAness and are showing promise in combination with PARP inhibitors in early phase clinical trials.

The key lessons or takeaways are that we now have multiple DDR agents currently in early Phase 1 and 2 clinical trial development, including inhibitors against ATR, WEE1, ATM, DNA-PK, CHK1, and RAD51, as well as new agents that have recently entered the clinic, such as PKMYT1 and USP1 inhibitors. And I do believe that this shows that the DDR synthetic lethal concept is much bigger than just BRCA-mutated cancers and PARP inhibitors, and that we are just at the tip of the iceberg.

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