

13 Apr 2021 |

AACR Round-Up: Zentalis, Pieris, Hookipa And Eli Lilly

DNA Damage Response Inhibitors, Fusion Proteins And KRAS Inhibitors

by [John Davis](#)

Zentalis outlines promising antitumor activity associated with its WEE1 inhibitor, Phase II trials are planned for Pieris Pharmaceuticals' fusion protein in HER2-positive cancers, while HPV-positive cancers are being targeted by Hookipa's immunotherapeutics in arenavirus vectors, and Eli Lilly is planning early-stage clinical trials with its next-generation KRAS inhibitor.

Zentalis's WEE1 Inhibitor Active In Advanced Cancers

Inhibitors of DNA damage response proteins are in the spotlight after the success of PARP inhibitors, and [Zentalis Pharmaceuticals](#)'s WEE1 inhibitor, ZN-c3, has been associated with promising antitumor activity in a Phase I study in heavily pre-treated, refractory cancer patients.

WEE1 is a protein involved in DNA damage responses, and its inhibition leads to the accumulation of damaged DNA in cancer cells leading to cell death. Zentalis believes ZN-c3 has the potential to be a best-in-class small molecule.

In the Phase I study, there were two partial responses, in one ovarian cancer and one colorectal cancer patient, and three unconfirmed partial responses, one in non-small cell lung carcinoma and two in uterine serous carcinoma patients, according to data presented during a late-breaking session during the virtual American Association of Cancer Research (AACR) meeting.

The compound was well tolerated, and as well as identifying a dose for the Phase II portion of the study, US biotech Zentalis said it was planning a Phase I/II study of ZN-c3 in combination with chemotherapy in osteosarcoma, to start in the third quarter of 2021. ZN-c3 is also being evaluated in combination with chemotherapy in a Phase Ib study in patients with advanced ovarian cancer, and a Phase II study of ZN-c3 as a monotherapy for uterine serous carcinoma is planned for this year.

Analysts at Biomedtracker noted that an oral dose of 300mg every day with continuous dosing is the recommended Phase II dose of ZN-c3 when used as a monotherapy, while SVBLEerink analysts noted that all responders had *TP53* mutations, and in patients with uterine serous carcinoma, there were two unconfirmed responses in five evaluable patients, giving an overall response rate of around 40%.

This response rate is higher than that seen with [AstraZeneca PLC](#)'s early-stage WEE inhibitor, adavosertib, the SVBLEerink analysts report. Tumor responses in CRC and ovarian cancer appeared to deepen over time, and colon cancer patients seem particularly sensitive to ZN-c3 therapy, noted Jefferies analysts. "The data are extremely promising," commented Zentalis CEO Anthony Sun.

Pieris's Fusion Protein Cinrebafusp Alfa in HER2-Positive Cancers

In eight evaluable patients in the high-dose cohort of a monotherapy trial with US biotech [Pieris Pharmaceuticals, Inc.](#)'s bispecific compound, cinrebafusp alfa, the fusion protein was associated with one complete response in patients with HER2-positive malignancies, one partial response and three patients developing stable disease, giving an objective response rate of 25%, reported Sarina Piha-Paul of the MD Anderson Cancer Center, Houston.

Cinrebafusp alfa was well tolerated and increases in CD8-positive T-cells, NK cells and cytotoxic activity in the tumor microenvironment appeared to be dose-dependent, Piha-Paul noted. Cinrebafusp alfa has a HER2-targeting moiety and another that activates the 4-1BB pathway, and

AACR Round-Up: BMS, Lilly, iTeos, Affimed, Treovir, Revolution And Cardiff

By [Mandy Jackson](#) and [Joseph Haas](#)

12 Apr 2021

iTeos presents early anti-TIGIT results, Affimed reports 100% response rate in Hodgkin lymphoma, Treovir will start a pivotal Phase II after Phase I pediatric glioma study, updates in KRAS-mutated cancers from Revolution Medicines and Cardiff Oncology, plus Opdivo plus chemo shows complete responses in neoadjuvant lung cancer and Lilly's Retevmo is active in additional tumors.

[Read the full article here](#)

showed clinical activity in both hot and “cold tumors”, and in those with low HER2-expressing tumors, she added.

Pieris is planning a Phase II study of cinrebafusp alfa combined with ramucirumab ([Eli Lilly and Company](#)'s VEGF2 receptor 2 blocker, Cyramza) and paclitaxel to treat HER2 high-expressing gastric cancer, and in combination with tucatinib ([Seagen Inc.](#)'s HER2 inhibitor, Tukysa) in HER2 low-expressing gastric cancer. (PS142053)

Hookipa Targets HPV-Associated Cancers

US/Austria biotech [HOOKIPA Pharma Inc.](#) is using arenavirus vectors for its immunotherapy approach to the treatment of HPV16-positive cancers, and reported encouraging preliminary immunogenicity data from the first patients treated in an ongoing Phase I/II clinical study of two different vectors, HB-201 and HB-202, expressing the same antigen, an E7E6 fusion protein derived from HPV16.

All five patients who received single doses of HB-201 or HB-202 produced T-cells specific to HPV16 two weeks after administration, and the candidates also increased gamma-interferon levels, indicating their immune systems were activated, according to late-breaking data presented at the AACR meeting.

“Our novel arenavirus platform has the potential to be a new class of immunotherapeutics,” commented Hookipa CEO Joern Aldag. Further data read-outs are expected in the coming months, he added.

The early results provide optimism for clinical outcomes including efficacy, noted JMP analysts. The vectors produced substantial levels of directed CD8-positive T-cells, they pointed out.

Lilly's Preclinical KRAS Inhibitor

The development of KRAS-G12C inhibitors is a hot area, with lead product [Amgen, Inc.](#)'s sotorasib already awaiting US approval and [Mirati Therapeutics, Inc.](#)'s adagrasib in late-stage clinical studies. ([Also see "Mirati's KRAS Inhibitor Gains Edge On Efficacy, But Safety Trails Amgen's Competing Drug"](#) - Scrip, 26 Oct, 2020.)

After a previously developed KRAS inhibitor developed by Eli Lilly failed in Phase I due to toxicity concerns, company researchers have now presented preclinical data on another candidate, LY3537982, showing it to be highly selective. Phase I studies are planned for this year. ([Also see "Lilly Points To Six-Month Growth Instead Of Pandemic Impacted Q2"](#) - Scrip, 30 Jul, 2020.)

SCRIP

CITELINE COMMERCIAL

LY3537982 in *in vitro* studies occupied more than 90% of its target, and induced tumor regression in animal models, noted Sheng-Bin Peng and colleagues. Other KRAS-G12C inhibitors in development have relatively modest activity, possibly due to incomplete target occupancy, the researchers add.