PEOPLE


Moffitt Cancer Center

John Cleveland, PhD, became director and executive vice president of Moffitt Cancer Center in Tampa, FL, replacing Thomas Sellers, PhD. Most recently, Cleveland served as the associate director of basic science at Moffitt. Previously, he was a professor and chair of the Department of Cancer Biology at the Scripps Research Institute in La Jolla, CA, and held various leadership roles at St. Jude Children's Research Hospital, based in Memphis, TN. Cleveland's research focuses on the molecular pathogenesis of cancer, including how oncogenes and tumor suppressors regulate cancer cell growth and survival.

Proof-of-Concept with PROTACs in Prostate Cancer

The first clinical data are in for Arvinas's proteolysis-targeting chimeras (PROTAC), with ARV-110, the biotech's androgen receptor (AR) PROTAC, showing some efficacy in men with metastatic castration-resistant prostate cancer (mCRPC). Preliminary data from the ongoing phase I trial were presented by Daniel Petrylak, MD, of Yale University in New Haven, CT, during the 2020 American Society of Clinical Oncology Annual Meeting, May 29–31.

PROTACs—first conceptualized by Yale's Craig Crews, PhD, who founded Arvinas—are designed as a ternary complex: ARV-110 consists of a "warhead" at one end that goes after the AR, another end that recruits a specific ubiquitin E3 ligase, and a linker to help orient both the target protein and the ligase.

"All three regions play a role in [ARV-110's] specificity and potency," Petrylak said. The goal is to hobble the AR signaling axis—on which mCRPC relies—by tagging the AR with ubiquitin so it can be shuttled to the proteasome for degradation.

Among 12 patients treated with ARV-110 at or above 140 mg—the preclinically determined minimum dose for tumor growth inhibition—Petrylak reported that two experienced reductions in PSA levels by 74% and 97%, respectively; the latter patient also had a confirmed partial response. Both men had two AR mutations, T878A and H875Y, associated with resistance to enzalutamide (Xtandi; Pfizer) and abiraterone acetate (Zytiga; Janssen). Five other patients who did not respond to treatment were found to have different AR alterations, L702H or AR-V7, which preclinical models had shown were nondegradable by ARV-110.

Although biopsy specimens "are generally difficult to obtain in mCRPC, due to a paucity of measurable lesions," Petrylak said, tissue analyses were performed where possible, and "preliminary evidence of ARV-110–mediated AR degradation was seen."

ARV-110 was well tolerated, with low-grade nausea and diarrhea being the most common side effects. These safety data support further dose escalation, Petrylak added, and "once we've settled on a recommended phase II dose, an expansion cohort will be started."

A key advantage with PROTACs is that "they can be used in more than one round of degradation," noted study discussant Edward Yeh, MD, of the University of Missouri in Columbia. Unlike conventional inhibitors, which need to remain latched to their protein of interest for efficacy, after a single PROTAC briefly brings target and E3 ligase together, it can repeat this process multiple times.

PROTACs "act like a catalyst," explained Alessio Ciulli, PhD, of the University of Dundee in Scotland, UK. "They can be highly effective at degradation while binding to only a small proportion of their target—say, less than 10%—at any one time."

This feature also "means that even if the target protein's concentration varies a lot within cells, it shouldn't matter too much," Ciulli added, and "the same rationale is applicable to the ligase-recruitment end of the ternary complex." As such, although E3 ligase expression may be different in different cancers—which Yeh thought could be a potential complication for PROTACs as a therapeutic strategy—to Ciulli, this issue can be mitigated by PROTACs' catalyst-like function.

Overall, "it's a very exciting class of therapies," Yeh said of PROTACs. Between myriad oncogenic targets and more than 600 ubiquitin E3 ligases alone, researchers will have no shortage of candidates to pursue. In time, he suggested, the field could expand its sights to include still more E3 ligases corresponding to other ubiquitin-like proteins such as SUMO and SENP1.

Ultimately, "the holy grail here will be to develop PROTACs that recruit E3 ligases expressed specifically in diseased, not healthy, tissue," Ciulli said. Meanwhile, "we have very encouraging first efficacy data" with ARV-110 that—together with its good safety profile so far—"will no doubt give a big boost of confidence to degrader drug hunters."
–Alissa Poh ■

AMG 510 Shows Activity beyond NSCLC

In June 2019, Amgen's AMG 510 generated considerable buzz as the first small-molecule inhibitor to successfully target $KRAS^{G12C}$ in patients with non–small cell lung cancer (NSCLC). A year later, the latest data highlighted during the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting, May 29–31, indicate activity with AMG 510, albeit more modest, in other solid tumor types.

AMG 510, also called sotorasib, irreversibly binds to the cysteine amino acid that replaces glycine in mutant KRAS, keeping the protein locked in an inactive GDP-bound state. $KRAS^{G12C}$ occurs in approximately 13% of patients with NSCLC, said Marwan Fakih, MD, of City of Hope Comprehensive Cancer Center in Duarte, CA; it is rarer (3%) in malignancies such as colorectal and appendix cancers.

At ASCO, Fakih reported updated results from the colorectal cancer cohort of Amgen's ongoing CodeBreak 100 trial. Among 42 evaluable patients, three responded partially to AMG 510—all of whom received the highest dose, 960 mg—and another 29 saw their disease stabilize. The median