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.

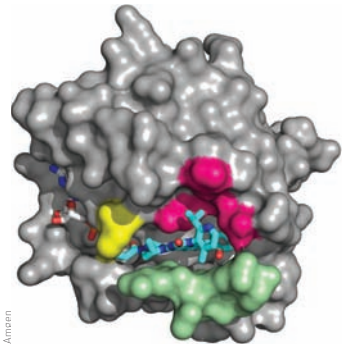
Ultimately, "the holy grail here will be to develop PROTACs that recruit E3 ligases expressed specifically in diseased, not healthy, tissue," Ciulli said. Meanwhile, "we have very encouraging first efficacy data" with ARV-110 that—together with its good safety profile so far—"will no doubt give a big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



The yellow area indicates where AMG 510 covalently binds to KRAS^{G12C}.

progression-free survival was 4 months across all doses, and 4.2 months for those treated with 960 mg.

David Hong, MD, of The University of Texas MD Anderson Cancer Center in Houston, presented findings from a CodeBreak 100 cohort that enrolled patients with various solid tumors. Of 22 evaluable patients, three—one each with appendix cancer, melanoma, and endometrial cancer—achieved partial responses. In addition, 13 patients had stable disease, of whom three, all with pancreatic cancer, also experienced tumor shrinkage by nearly 30%, Hong observed.

AMG 510's safety profile was similar to what had previously been reported, the investigators said. Mild diarrhea, nausea, and fatigue were the main side effects, and no dose-limiting toxicities were seen.

"The response rate does seem to be lower in colorectal cancer compared to the NSCLC data shown last year," Hong remarked. "This inconsistency suggests that either KRAS^{G12C} is not the dominant driver in colorectal cancer, or other pathways, such as WNT and EGFR, mediate oncogenic signaling beyond KRAS."

Fakih, too, noted "more durable disease control" in the NSCLC cohort, adding that response differences "may be partly related to higher EGFR expression" in colorectal cancer versus NSCLC. Blocking KRAS^{G12C} can lead to compensatory phosphorylation of EGFR, in turn activating the MAPK pathway—and this compensation, being triggered "to a much greater extent in colorectal cancer cells, would mitigate AMG 510's antitumor activity," he explained.

A recent preclinical study has shown just that, pinpointing EGFR signaling as the main route by which colorectal cancer dodges KRAS^{G12C} inhibition (Cancer Discov 2020 May 19 [Epub ahead of print]). In various models, "the addition of an EGFR inhibitor was synergistic," Fakih said. "This has significant implications, suggesting the need for vertical blockade of both EGFR and KRAS to achieve optimal benefit."

As such, researchers have launched the multiarm CodeBreak 101 trial, using a "master protocol approach" that allows "rapid evaluation of different agents in combination with AMG 510, based on solid preclinical rationale," Fakih added. Drugs currently being tested include not only EGFR inhibitors but also SHP2 inhibitors, as well as anti–PD-1 immunotherapies.

Other translational and correlative studies are ongoing, Hong said, because "as of now, we don't have any evidence or data that clearly differentiate responders from nonresponders" to AMG 510.

With more KRAS-targeting contenders on the horizon, too—Mirati Therapeutics' MRTX849, as well as candidates from Revolution Medicines and Oncogenuity—a therapeutic area once considered undruggable is expected to flourish. *–Alissa Poh* ■

Tumors Appear Rife with Bacterial Lodgers

Intracellular bacteria are widespread in different tumor types, forming distinct populations that may play a critical role in shaping the microenvironment of cancers, according to a comprehensive survey of more than 1,000 tumor microbiomes across seven cancer types (Science 2020;368:973–80).

Scientists had previously linked tumor-residing bacteria to carcinogenesis and therapeutic responses, but the phenomenon seemed limited to a handful of pathogenic microbes influencing tumors mostly at mucosal surfaces. The new findings instead suggest that these intratumoral bacterial communities are far more diverse and pervasive, penetrating deep into protected body sites typically considered sterile, such as the brain.

"This is a really important initial step in showing that intratumoral microbes are found all over the body and that they're real—we're not just dealing with contamination, which has been a concern in the past," says Chloe Atreya, MD, PhD, of the University of California, San Francisco, who cowrote a commentary about the research (Science 2020;368:938–9). "It opens a door to a whole other facet of the microenvironment that we hadn't really been considering."

To catalogue the cancer microbiome, a team led by Ravid Straussman, MD, PhD, of Weizmann Institute of Science in Rehovot, Israel, and Noam Shental, PhD, of the Open University of Israel in Ra'anana, quantified bacterial DNA found in 1,010 tumor samples and 516 normal controls. They sequenced 16S ribosomal RNA—a common probe for bacterial detection—and discovered more than 500 bacterial species colonizing tumor tissue, albeit to a different extent in each cancer type and with different mixes of species.

More than 60% of breast, pancreatic, and bone tumors tested positive for bacterial DNA, compared with fewer than 25% of lung cancers, melanomas, and ovarian tumors. In brain cancers, bacterial DNA was detectable in about 45% of samples. The microbiome of breast tumors proved the most diverse of those tested. The authors also documented associations between specific bacteria and tumor type, smoking history, and immunotherapy responses, suggesting that targeting the microbes might improve survival.

The results dovetail with those reported earlier this year by Rob Knight, PhD, and his colleagues at the University of California, San Diego, who showed that signatures of microbial DNA and RNA are pervasive across human tumors (Nature 2020;579:567–74).

However, the Israeli-led team went beyond that earlier finding, notes Eytan Ruppin, MD, PhD, of the NCI's Cancer Data Science Laboratory, who was not involved in either study. In addition to looking at genomic data, Straussman and Shental's group used immunostaining, electron microscopy, and cytogenetic techniques to show that bacteria are mostly found inside cancer and immune cells rather than in the surrounding matrix. "It's a landmark contribution," Ruppin says.

Susan Bullman, PhD, of the Fred Hutchinson Cancer Research Center in