Potential of Targeted Protein Degradation: Early Results for ARV-110

BY DANIEL P. PETRYLAK, MD

Proteolysis targeting chimeras, also called PROTAC protein degraders, are emerging as an exciting class of small molecule therapies for cancer and other diseases. Unlike conventional inhibitors or antagonists, which block the enzymatic or signaling activity of their target proteins, PROTAC molecules harness a system present within every cell that clears away damaged or unwanted proteins. They achieve this via a dual-binding action: one end of the PROTAC molecule selectively binds the target protein; the other end binds an E3 ubiquitin ligase, triggering the ubiquitination system that tags the target protein for proteasomal degradation.

This novel mode of action differentiates PROTAC protein degraders from conventional small molecule therapies in at least two ways. First, PROTAC molecules do not need to bind a target protein's active site, which should allow them to bypass resistance mechanisms the target has to conventional therapies.

Second, a PROTAC molecule is not itself degraded or consumed by the process it triggers; instead, the molecule "recycles" to degrade hundreds of copies of its target protein, making PROTAC protein degraders potentially more efficacious than conventional small molecules and offering the potential for lower dosing and a stronger overall safety profile.

While many biopharma companies have disclosed programs in targeted protein degradation, only one thus far has advanced such a program into clinical testing. In March 2019, a Phase I/II trial of ARV-110, a first-in-class PROTAC protein degrader targeting androgen receptor (AR), began for patients with metastatic, castration-resistant prostate cancer (mCRPC) (NCT03888612). I have had the pleasure of being the lead investigator on this pioneering clinical trial.

In an oral presentation at the 2020 ASCO Annual Meeting, I presented data from the dose-escalation portion of the trial. These early, but promising, results highlight ARV-110's safety and activity in this heavily pretreated cohort of mCRPC patients; but just as importantly, the data offer the first evidence that PROTAC protein degraders, as a new therapeutic modality, can be safe and effective in humans.

So, what else do we need to understand to fully prove and harness the potential of targeted protein degradation as a therapeutic modality? Let me explain.

Targeted AR Degradation in mCRPC

The trial is an excellent first-in-human test case for PROTAC technology for two reasons: AR is a well-known driver of prostate cancer; and, while mCRPC patients have more therapeutic options than they did

DANIEL P. PETRYLAK, MD, is Professor of Medicine (Medical Oncology) and of Urology, as well as Co-Leader of Cancer Signaling Networks, at Yale Cancer Center.

25 years ago (*Cancer* 1993;71(3 Suppl):1098-109), these options can control disease but do not cure it. Thus, despite extensive pretreatment, the androgen receptor remains a target in castration-resistant prostate cancer.

Anti-androgenic therapies have been the mainstays of prostate cancer treatment. Prostate cancer tumors develop resistance through AR point mutations and other receptor and ligand alterations, such as up-regulation of wild-type AR and increased androgen production, that render them insensitive or resistant to anti-androgen treatments. Once prostate cancer has developed resistance to one anti-androgen therapy, such as abiraterone, another therapy with a similar mechanism, such as enzalutamide, is unlikely to be effective.

Clinical trials have demonstrated that earlier use of chemotherapy and anti-androgen therapies, when initially patients are still sensitive to primary androgen blockade, imparts a greater impact on survival than when the same agents are used in castration-resistant disease. This means patients today live longer and have a better quality of life. But it also means that, if or when they progress, they may have exhausted the available treatment options; so, there is an urgent need for new options in this patient group.

Overall, the wider variety of targeted therapies with differing mechanisms we have against AR, the better the therapeutic landscape will be for prostate cancer patients at any stage of the disease. That is what makes ARV-110 an intriguing chapter in the prostate cancer story: it has a completely novel mechanism of action against AR. This gives it the potential to address the immediate needs of mCRPC patients who are resistant to conventional therapies, as well as the potential to treat patients at all stages of the disease.

Early Findings From Phase I

ARV-110 is designed to degrade wild-type AR, as well as forms of AR harboring point mutations, including T878A, H875Y, F877L and M895V, that occur in 5-7 percent of mCRPC patients and confer resistance to abiraterone, enzalutamide, and other anti-androgen therapies. In preclinical models ARV-110 does not degrade the L702H AR mutation or the AR-V7 splice variant, each of which occurs in 3-10 percent and about 30 percent of patients, respectively.

The Phase I dose-escalation trial of ARV-110 has recruited men with mCRPC, regardless of AR mutation status, who had at least two previous systemic therapies—at least one of which was abiraterone or enzalutamide. The decision not to limit the number of prior therapies was based on the fact that the androgen receptor is expressed throughout the course of castration-resistant disease. In fact, many of the trial participants have received a mean of six prior lines of therapy.

The trial uses a standard "3+3" design and, as of April 2020, has tested four once-daily doses: 35, 70, 140, and 280 mg. Also, as of April 2020, 22 patients have been recruited and the maximum tolerated dose has not been reached, so recruitment and dosing escalation continue past the 280 mg dose.

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Preliminary results from the trial provide answers to the three main questions faced by any new therapeutic modality: 1) Is it safe? 2) Does it work against its target as expected? 3) Does it have a therapeutic effect?

First, ARV-110 has been well-tolerated at the four doses tested so far, although a potential drug-drug interaction was identified in two trial patients who had concurrent use of rosuvastatin. One of these two patients received 280 mg of ARV-110 and experienced grade 4 dose-limited toxicity of elevated aspartate transaminase/alanine transaminase (AST/ALT) levels (transaminitis) followed by acute renal failure, and discontinued use of ARV-110. The second patient received 70 mg ARV-110 and experienced grade 3 AST/ALT, which resolved after removal of rosuvastatin, and the patient was retreated with ARV-110. Subsequent in vitro studies indicated ARV-110 inhibits breast cancer resistance pump (BCRP), a substrate of rosuvastatin. Based on these initial data supporting a potential drug-drug interaction, concomitant use of rosuvastatin was prohibited and no other related incidents of grade 3 or 4 transaminitis have since been reported.

Second, the data demonstrate ARV-110-mediated degradation of AR in tumors. Analysis of biopsies of a metastatic liver lesion taken from one patient detected a 70-90 percent reduction in AR levels after 6 weeks of ARV-110 treatment (280 mg) compared with the pretreatment baseline. This is the first time a PROTAC protein degrader has been shown to degrade its target in the human body.

Third, two of the seven patients who both received ≥140 mg doses of ARV-110—140 mg being the minimum dose that had a therapeutic effect in preclinical animal models—and lacked the L702H and AR-V7 forms of AR that ARV-110 cannot degrade had confirmed responses determined by PSA50 (≥50% reduction in PSA levels) and/or RECIST (Response Evaluation Criteria in Solid Tumors). As of April 2020, the patient with the confirmed PSA50 response had remained on ARV-110 for 30 weeks with no evidence of progression; the other patient, whose response was confirmed by PSA50 and RECIST, had remained on ARV-110 treatment for 18 weeks. These results provide early support for targeted degradation of AR in mCRPC with resistance to antiandrogen therapy.

Better Understanding Markers of Response

The trial has raised other intriguing findings around response that will require additional data to explore more fully.

Genomic analysis of patients who received 140 or 280 mg doses of ARV-110 reveals an association between the presence of ARV-110-degradable forms of AR and therapeutic response, as measured by reductions in PSA levels. This suggests the possibility of enriching future trials of ARV-110 based on the AR mutational status of patients' tumors.

However, the association between AR status and ARV-110 response may not be governed simply by the presence or absence of ARV-110-degradable AR in the tumor. This is especially true when we remember that a patient's tumor may harbor several AR forms and mutations, have different levels of wild-type androgen receptor expression, or develop new androgen receptor mutations over time.

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For example, the two confirmed responders described previously both harbored two of the AR mutations (H875Y and T878A) associated with resistance to abiraterone and enzalutamide that ARV-110 degrades. But a third patient, whose PSA levels decreased about 20 percent in response to treatment with 140 mg of ARV-110, harbored an ARV-110-degradable AR mutant (T878A) and the non-degradable AR-V7 splice variant. This raises the possibility that the two non-degradable forms of AR are not markers of insensitivity to ARV-110, as we might initially assume. Indeed, when we consider that some tumors with AR-V7 also up-regulate wild-type AR, we realize the biology underlying the response to ARV-110 may be complex.

Of course, these preliminary data from the trial make it difficult to understand what drives response to ARV-110. As we gather additional data in this clinical trial of ARV-110, we hope to understand more clearly which subpopulations of mCRPC patients will benefit most from it.

The Future of ARV-110

Opportunities to prove a new therapeutic modality in patients do not come along every day. The fact that ARV-110, the first-in-human PROTAC protein degrader, has demonstrated anti-tumor effects in these heavily pretreated mCRPC patients, and at these doses, is remarkable and encouraging. Still, it is important to underscore that we are still very early in clinical of evaluation of ARV-110. We need much more data to demonstrate that targeted protein degradation is a viable therapeutic modality.

Nevertheless, these early results for ARV-110 suggest the technology could eventually deliver on its promise of targeting proteins that are currently difficult, if not impossible, to drug with existing therapeutic modalities. About 80 percent of proteins fall into this "undruggable" category, including many that are critical to cancer cell growth, such as Ras, p53, and the anti-apoptotic protein BCL2. Some antisense therapies have succeeded in down-regulating anti-apoptotic proteins to treat liquid tumors, but have been less successful in treating solid tumors. PROTAC proteins degraders might be able to down-regulate those genes in solid tumors and offer a wider population of cancer patients the new options they need and deserve. OT