ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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The Development of ATR Inhibitors

Timothy A. Yap, MBBS, PhD
Ransom Horne, Jr Endowed Professor for Cancer Research
Therapeutics Discovery Division and Department of Investigational Cancer Therapeutics (Phase I Program)
The University of Texas MD Anderson Cancer Center
Houston, Texas

H&O What is the ataxia telangiectasia and Rad3-related (ATR) protein, and what makes it a good target in cancer?

TY The ATR protein is a serine threonine kinase and a member of the phosphoinositide 3-kinase (PI3K) family. ATR is a central mediator of the cellular replication stress response that controls cell division, safeguarding the genomic integrity of all the body's cells. It is activated when DNA becomes damaged. ATR is a good target in cancer for multiple reasons; for example, by inhibiting ATR, we can target the elevated replication stress and/or DNA repair deficiency found in cancer cells.

H&O What unmet need are ATR inhibitors designed to address?

TY Right now, we do not have any approved drugs for cancers with *ATM* mutations apart from poly(ADP-ribose) polymerase (PARP) inhibitors in metastatic castration-resistant prostate cancer, so that is an area of unmet clinical need. Second, we need agents for patients with a *BRCA1* or *BRCA2* mutation who have already received a PARP inhibitor and whose disease either did not respond (primary drug resistance) or initially responded but then stopped responding (acquired or secondary drug resistance). These patients need better therapeutic options after PARP inhibition. ATR inhibitors also have the potential to target alterations in *CDK12*, *CHEK1*, *CHEK2*, *RNASEH2A*, *RNASEH2B*, and *ATRX*, in addition to the *ATM*, *BRCA1*, and *BRCA2* mutations. These mutations are found in a range of cancers, including those for which PARP inhibitors are not approved, such as lung and colorectal cancers. An ATR inhibitor could provide this option, either as monotherapy or in combination with a partner agent.

H&O Which ATR inhibitors are being developed?

TY Many different ATR inhibitors are being developed, both as monotherapy and in combination with other classes of drugs. Some are in late preclinical testing and others are in phase 1, 2, or 3 clinical testing. We have good evidence that ATR inhibition synergizes with the effects of other drugs, including cytotoxic chemotherapy agents, antibody-drug conjugates, targeted therapeutics such as PARP inhibitors, and immunotherapeutic agents.

The agent that is farthest along is ceralasertib, from AstraZeneca. In a phase 1 trial, we had established the recommended phase 2 dose of ceralasertib in combination with carboplatin in patients with advanced solid tumors.[1] We also observed preliminary evidence of antitumor activity. A phase 2 umbrella study, called HUDSON, evaluated various combination regimens in patients with pretreated advanced non–small cell lung cancer (NSCLC).[2] The study examined objective response rate, median progression-free survival, and median overall survival. The investigators found that clinical benefit was greater in patients who received the programmed death ligand 1 (PD-L1) inhibitor durvalumab (Imfinzi, AstraZeneca) plus ceralasertib than in patients who received durvalumab plus a PARP inhibitor, a STAT3 antisense oligonucleotide, or an anti-CD73 monoclonal antibody. These findings led to the ongoing phase 3 randomized LATIFY clinical trial, which is currently assessing this combination in patients with pretreated NSCLC (NCT05450692).

Tuvusertib, from Merck, is another ATR inhibitor that is being examined in multiple clinical trials. In the phase 1 DDRiver Solid Tumors 301 study, tuvusertib demonstrated a manageable safety profile and achieved pharmacokinetic drug exposure–related target engagement, showing preliminary signals of antitumor activity in patients with metastatic or locally advanced unresectable solid tumors.[3] This study also looked at tuvusertib in combination with the PARP inhibitor niraparib (Zejula, GSK) in patients with metastatic or locally advanced unresectable solid tumors (NCT04170153). In addition, different phase 2 studies are looking at the use of tuvusertib: the DDRiver NSCLC 322 study of tuvusertib in combination with cemiplimab (Libtayo, Sanofi-Aventis/Regeneron) in checkpoint inhibitor–resistant advanced NSCLC (NCT05882734), the DDRiver EOC 302 study of tuvusertib plus the DNA damage response inhibitor lartesertib or niraparib in biomarker-selected PARP-resistant ovarian cancer (NCT06433219), and the JAVELIN DDRiver Bladder study of tuvusertib in combination with avelumab (Bavencio, EMD Serono/Pfizer) in checkpoint inhibitor–resistant advanced urothelial cancer (NCT06424717).

Camonsertib, from Repare Therapeutics, has been examined in several studies. For example, the phase 1/2 TRESR study in advanced solid tumors found that camonsertib was very well tolerated, with a robust pharmacokinetic-pharmacodynamic profile and antitumor activity in patients who had advanced solid tumors harboring loss-of-function alterations in DNA damage response genes.[4] The phase 1/2 ATTACC study evaluated camonsertib plus either niraparib or olaparib (Lynparza, AstraZeneca) in patients with advanced solid tumors (NCT04972110), and the MYTHIC trial is testing the combination of camonsertib and the novel PKMYT1 inhibitor lunresertib in patients with cancers harboring *CCNE1* amplifications, *FBXW7* mutations, or *PPP2R1A* mutations.[5]

Another agent that is being examined is ART0380, from Artios. A preclinical study found that ART0380 had potent, selective antitumor activity in a range of preclinical cancer models with differing degrees of *ATM* loss of function.[6] This preclinical study was followed by a phase 1 study, which found that ART0380 is well tolerated and clinically active in patients with advanced solid cancers, including those with *ATM* alterations.[7] ART0380 is also being evaluated as a monotherapy and in combination with chemotherapy in several phase 2 expansion cohorts and trials.[8]

H&O What side effects are seen with ATR inhibitors?

TY The most common and clinically important side effect to date is reversible anemia, which we believe to be a class effect. Erythroblast precursors are vulnerable to iron-dependent reactive oxygen species (ROS) and are exceptionally susceptible to ATR inhibitors through a mechanism mediated by enhanced ferroptosis. ATR inhibition thus leads to dose-dependent suppression of erythroblast proliferation and differentiation, profoundly affecting reticulocytes and contributing to the development of anemia. In the laboratory and subsequently in the clinic, we have been able to mitigate this side effect by modifying ATR inhibitor doses and schedules. For example, when we administer these agents on an intermittent dosing schedule instead of continuously, we observe fewer cases and lower grades of anemia and myelosuppression in general. This strategy potentially lets us maximize target and pathway inhibition while allowing sufficient time for erythroid precursor maturation and recovery of the hemoglobin level and other blood parameters. Before we pursue such intermittent dosing schedules, extensive preclinical modeling will be essential for developing the optimal trial design. To date, we have evaluated different intermittent dosing schedules, and different schedules have worked for different ATR inhibitors. For example, intermittent schedules can mean anything ranging from a 4-days-on, 3-days-off schedule to a 1-week-on, 2-weeks-off schedule, or a hybrid or combination variation of these schedules. It remains important to think outside the box for creative scheduling solutions, especially when it comes to combination regimens for which alternating schedules may be needed to mitigate the overlapping toxicities observed with concurrent combinations.[9]

H&O What types of cancer may be targeted with ATR inhibitors?

TY Several types of cancers may be targeted with ATR inhibitors. As we have seen with PARP inhibitors, we expect ATR inhibitors to work in the so-called canonical types of cancer, which include breast, prostate, ovarian, and pancreatic cancer. These are tumor types in which PARP inhibitors have already been approved and in which ATR inhibition may also be effective, including in the setting of PARP inhibitor resistance. ATR inhibition may also help us reach beyond these tumor types to include cancers such as NSCLC—in which ceralasertib is being assessed—and colorectal cancer.[10]

H&O Do all patients with cancer require molecular testing?

TY We should always consider somatic and germline molecular testing in patients with cancer. Multiple alterations will sensitize cancers to ATR inhibitors, and we need to find out the best way to measure some of these alterations. With *ATM* alterations, a key question is, how do we best measure *ATM* loss of function? Should it be done by using comprehensive next-generation sequencing

panels to look for pathogenic *ATM* mutations? Or should we be using immunohistochemistry to look for ATM loss of protein? In addition, is a tumor more likely to respond to an ATR inhibitor if it has both an *ATM* pathogenic mutation and associated *ATM* loss of function by immunohistochemistry rather than having just one or the other? Can some patients have tumors with ATM loss of protein caused by an epigenetic alteration? All these questions are being investigated. Just to add to the complexity, we also know that zygosity is very important—that is, response rates are likely to be higher if we are targeting tumors with biallelic vs monoallelic loss of function of *ATM*, *BRCA1*, or *BRCA2*. Whether these mutations are germline or somatic is also important. In addition, whether the tumor has co-mutations is likely to play a key role in its sensitivity and/or resistance to ATR inhibitors and other agents. In the future, I expect that we will eventually be looking at a tumor's overall mutational signature rather than just a single mutation, or that we will use a functional assay to assess homologous recombination to decide which agent or agents to administer. We are currently actively working on these predictive biomarker assays because if we can identify the right molecular alterations in the relevant tumor types for these agents, we should be able to establish the optimal role of ATR inhibitors in cancer medicine and ultimately improve patient outcomes.

Disclosures

Dr Yap's institution has a commercial interest in DNA damage response and other inhibitors (IACS30380/ART0380 licensed to Artios). He is a consultant for AbbVie, Acrivon Therapeutics, Adagene, Almac Group, Alterome Therapeutics, Aduro Biotech, Amgen, Amphista Therapeutics, Artios Pharma, Astex Pharmaceuticals, AstraZeneca, Athena Bioscience, Atrin Pharmaceuticals, Avenzo Therapeutics, Avoro Capital, Axiom Biotechnologies, Baptist Health System, Bayer, BeiGene, BioCity Biopharma, Blueprint Medicines, BMS, Boxer Capital Management, BridGene Biosciences, C4 Therapeutics, Calithera Biosciences, Cancer Research UK, Carrick Therapeutics, Circle Pharma, Clovis Oncology, Cybrexa Therapeutics, Daiichi Sankyo, Dark Blue Therapeutics, Debiopharm, Diffusion Pharmaceuticals, Duke Street Bio, 858 Therapeutics, EcoR1 Capital, Ellipses Pharma, EMD Serono, Entos Pharmaceuticals, FoRx Therapeutics, F-Star Biotechnology, Genesis Therapeutics, Genmab, Glenmark Pharmaceuticals, GLG Pharma, Globe Life Sciences, Greywolf Therapeutics, GSK, Guidepoint, Ideaya Biosciences, Idience, Ignyta, I-Mab, Immunesensor Therapeutics, Impact Therapeutics, Institut Gustave Roussy, Intellisphere, Janssen, Joint Scientific Committee for Phase I Trials in Hong Kong, Kyn Therapeutics, Kyowa Kirin, Lumanity, MEI Pharma, Mereo BioPharma Group, Merck, Merit Pharmaceutical, Monte Rosa Therapeutics, Natera, Nested Therapeutics, Nexus Pharmaceuticals, Nimbus Therapeutics, Novocure, Odyssey Therapeutics, OHSU, OncoSec Medical, Ono Pharmaceutical, Onxeo, PanAngium Therapeutics, Pegascy, Pfizer, Piper Sandler, Plexium, Pliant Therapeutics, Prelude Therapeutics, ProLynx, Protai Bio, Radiopharm Theranostics, Repare Therapeutics, resTORbio, Roche, Ryvu Therapeutics, SAKK (Swiss Group for Clinical Cancer Research), Sanofi, Schrodinger, Servier, Synnovation Therapeutics, Synthis Therapeutics, Tango, TCG Crossover, TD2 Oncology, Terremoto Biosciences, Tessellate Bio, Terns Pharmaceuticals, Thryv Therapeutics, TOLREMO Therapeutics, Tome Biosciences, Trevarx Biomedical, Varian Medical Systems, Veeva Systems, Versant, Vibliome Therapeutics, Voronoi, XinThera, Zai Lab, and ZielBio. He has received grants or research support from Artios, AstraZeneca, Bayer, BeiGene, BioNTech, Blueprint, BMS, Boundless Bio, Clovis, Constellation Pharmaceuticals, CPRIT, Cyteir Therapeutics, Department of Defense, EMD Serono, Exelixis, Forbius, F-Star, Genentech, Gilead, Golfers Against Cancer, GSK, Haihe Biopharma, Ideaya, Immunesensor, Insilico Medicine, Ionis Pharmaceuticals, Ipsen, Jounce Therapeutics, Karyopharm Therapeutics, KSQ Therapeutics, Kyowa Kirin, Lilly, Merck, Mirati Therapeutics, Novartis, NIH/NCI, Pfizer, Pliant, Prelude, Ribon Therapeutics, Regeneron, Repare, Roche, Rubius Therapeutics, Sanofi, Scholar Rock, Seagen, Synnovation Therapeutics, Tango Therapeutics, Tesaro, V Foundation, Vivace Therapeutics, Zenith Therapeutics, and Zentalis Pharmaceuticals.

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