June 2018

OncPathways®

FTase Inhibition Holds Promise for RAS Targeting and Beyond

By William Pass, DVM

For more than 20 years, researchers have known that the RAS pathway is involved in a wide variety of cancer types. RAS proteins normally switch between an active state, which is bound by guanosine triphosphate, and an inactive state, which is bound by guanosine diphosphate, to regulate cell-cycle progression. In cancer, the mutant *RAS* gene becomes locked in the active state, causing uncontrolled cell proliferation.[1] Such mutations are found in 30% of all neoplasms, with a higher prevalence in colon cancer (~50%) and pancreatic cancer (~90%).[2]

Unfortunately, mutant *RAS* has proved to be a challenging therapeutic target. After early attempts at direct targeting were unsuccessful, subsequent research with indirect targeting led to predominantly disappointing results. No drugs are currently approved that directly target *RAS* activity.[1,3]

Despite this rocky terrain, recent success with tipifarnib, a biologically active drug known as a farnesyltransferase inhibitor (FTI), brings promise for treating solid tumors and hematological malignancies. In time, FTIs may be utilized in a variety of cancer types and other diseases as associated pathways become better defined.

Farnesyltransferase

Farnesyltransferase (FTase) is an enzyme that plays a key role in RAS posttranslational processing (**FIGURE**).[1,4] Specifically, FTase is responsible for farnesylation, a type of prenylation, in which a hydrophobic group is added to the C-terminal CAAX motif of a RAS protein. Prenylation allows for RAS membrane binding and subsequent downstream signaling; without it, mutant *RAS* becomes inert, thereby halting uncontrolled cell proliferation.[5]

Although targeting FTase initially appeared to be a logical way to stop RAS membrane binding, a major obstacle lies in enzymatic redundancy. Researchers have found that RAS prenylation can also be achieved by geranylgeranyltransferase, which means that blocking FTase does not necessarily stop RAS membrane localization. This scenario likely explains the disappointing results of earlier FTI trials.[2] Recent research, however, exploits the fact that not all RAS isoforms are so dynamic.[6]

The RAS family isoforms are KRAS, NRAS, and HRAS. Of these 3, HRAS exclusively relies upon FTase for prenylation, which means that FTIs are still effective in *HRAS*-driven cancer types.[3] Ongoing research into this subclass of RAS proteins is yielding promising results.

Tipifarnib Effective for *HRAS*-Mutant HNSCC

A study by Alan L. Ho, MD, PhD, a medical oncologist and the Geoffrey Beene Junior Faculty Chair at Memorial Sloan Kettering Cancer Center, is investigating the efficacy of tipifarnib, a first-in-class, highly selective FTI that competitively binds to the CAAX motif of FTase. Treatment with tipifarnib has

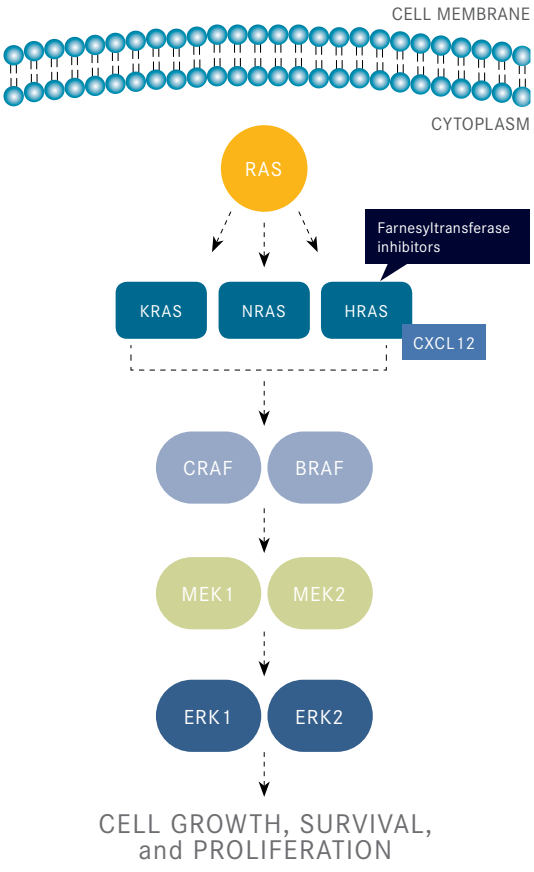
ALAN L. HO, MD, PHD

Also in this issue...

PARP Inhibitors Are Making an Impact in Breast Cancer
(page 4)

Harvard Expert Sees Potential in BCL-2 Combos
(page 7)

FIGURE. FTI INHIBITION AND RAS SIGNALING



The use of a farnesyltransferase inhibitor (FTI) may provide an indirect attack on aberrant activity of members of the RAS protein family, particularly HRAS. The chemokine CXCL12 also signals through HRAS and may be a biomarker for FTI inhibition.

produced partial responses in 4 of 6 patients with *HRAS*-mutant head and neck squamous cell carcinoma (HNSCC).[7]

"This evidence is the first to really demonstrate that mutant *HRAS* is a target in cancer with FTIs," Ho said in an interview. "The activity we've seen [with tipifarnib] is rapid and durable and has translated into clinical benefit in a number of different ways."[8]

Treated patients had HNSCC and an *HRAS* mutation, with no available curative treatments. Tipifarnib was administered orally at 900 mg twice daily during alternating weeks in a 28-day cycle. Of the 4 responding patients, 2 responded for over 1 year. The patients who did not respond maintained stable disease during the trial, and tumor size decreased in all patients.

Ho said that the objective response rate of 67% (95% CI, 22%-95%) "is a remarkable response rate for a previously treated patient population."

The phase II trial was initiated in light of previous research surrounding HRAS susceptibility and anecdotal evidence that tipifarnib was effective in some patients as a single agent. Tipifarnib has been used in over 70 studies that included more than 5000 patients, and is relatively well tolerated, with less than 25% of patients discontinuing treatment due to adverse events (AEs).

Among 27 patients treated across 3 cohorts in the study, grade ≥3 treatment-emergent AEs included myelosuppression (neutropenia, 31%; anemia, 19%; and thrombocytopenia, 15%), gastrointestinal disturbances (15%), and increased creatinine (11%).

The study is currently ongoing with 2 other patient cohorts, including a group of patients with *HRAS*-mutant thyroid carcinoma and a group of patients with squamous cell carcinoma not of the head and neck.[7]

Tipifarnib May Target CXCL12/CXCR4

Previous studies' results have shown that tipifarnib can generate major responses in some patients with myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML), but the overall activity and molecular mechanisms behind these responses has remained unclear. Although this mystery has thus far precluded drug registration, recent research suggests that tipifarnib may target the CXCL12/CXCR4 pathway.[9]

The CXCL12 (stromal cell-derived factor-1)/CXCR4 (CXC receptor 4) axis plays a part in a variety of neoplastic events, including metastasis, survival, and angiogenesis. As a homeostatic chemokine, CXCL12 controls secondary lymphoid tissue architecture and hematopoietic cell trafficking. CXCR4 activity is thought to involve the RAS-activated signaling pathway, although exact mechanisms are unknown. CXCR4 is broadly expressed on hematopoietic cells such as B lymphocytes, T lymphocytes, CD34-positive hematopoietic stem cells (HSCs), macrophages, monocytes, eosinophils, and neutrophils. Further expression of CXCR4 can be found on colon, lung, heart, brain, liver, kidney, epithelial, endothelial, and some progenitor cells. Functional CXCR4 is expressed on several types of tissue-committed stem cells and embryonic pluripotent stem cells, allowing them to invade and/or migrate along CXCL12 gradients.[10]

Previous research has found that CXCL12/CXCR4 signaling causes the bone marrow to retain neoplastic cells, which protects them from apoptosis. Findings from clinical trials in patients with multiple myeloma and non-Hodgkin lymphoma showed that treatment with plerixafor, a small molecule inhibitor of CXCR4, prompted cellular egress from bone marrow, thereby increasing collection yield for later HSC transplant. Additionally, a mouse model of acute promyelocytic leukemia revealed that treatment with a CXCR4 antagonist improved the efficacy of cytarabine, as bone marrow protection was lost when neoplastic cells were released into circulation. These findings affirm that increased CXCL12/CXCR4 causes cell retention in the bone marrow, making it an attractive target in bone marrow neoplasia.

In a 2014 study involving patients with AML, treatment with tipifarnib at 300 mg twice daily for 3 weeks led to response rates of up to 20%.[11] However, patient-specific responses could not be correlated with blast karyotype, clinical features, FTase inhibition, or *RAS* mutation status. With regard to this finding, the researchers noted that a reliable predictor of response to tipifarnib was still lacking.

Fortunately, Antonio Gualberto, MD, PhD, and his team at Kura Oncology, Inc. may be closing in on an answer. In recent findings presented at the 2017 American Society of Hematology Annual Meeting, investigators showed that tipifarnib may target the CXCL12/CXCR4 pathway.[9] In patients with AML and MDS, tipifarnib was most effective when high levels of CXCL12 were found in the bone marrow. The researchers concluded that a high level of CXCR4 compared with a low level of the antagonistic receptor CXCR2 may serve as a reliable biomarker for tipifarnib in bone marrow neoplasia.

In a group of 58 patients with relapsed or refractory AML who were treated with tipifarnib, the quintile expressing the highest CXCR4/CXCR2 ratios achieved progression-free survival (PFS) times nearly double those of all other patients (57 days vs 29 days; $P = .026$). When tipifarnib was administered to another cohort of 15 patients with chronic myelomonocytic leukemia, the tertile with the highest CXCR4/CXCR2 ratios achieved a PFS of 280 days compared with 84 days for those with lower levels ($P = .015$).

"Analysis of CXCR4 and CXCR2 expression in bone marrow aspirates of mononuclear cells revealed an association between the ratio of CXCR4 to CXCR2 and the clinical activity of tipifarnib," investigators reported. This correlation "was consistent across endpoints, clinical settings, and indications," they added. Ongoing phase II clinical trials aim to elucidate these findings by researching upstream and downstream farnesylated targets in the CXCL12/CXCR4 pathway.

TABLE. ONGOING STUDIES OF TIPIFARNIB

Tumor Type	Estimated Enrollment	Phase (ClinicalTrials.gov identifier)
HRAS-mutant squamous head and neck cancer	36	II (NCT02383927)
Peripheral T-cell lymphoma	30	II (NCT02464228)
Myelodysplastic syndromes	58	II (NCT02779777)
Chronic myelomonocytic leukemia	20	II (NCT02807272)

The researchers noted that tipifarnib has a safety profile at least as favorable as best supportive care including hydroxyurea. With older and more frail patients with AML, tipifarnib could be a more attractive option than chemotherapy, particularly when a high CXCR4/CXCR2 ratio is detected.

The future of FTIs

Although combination therapies have yielded mixed results, FTIs may increase sensitivity to chemotherapeutics or radiation with appropriate timing, particularly in *HRAS*-mutant cancer types.[5] In light of the recent successes with tipifarnib in *HRAS*-mutant HNSCC, more combination studies may be forthcoming. Kura Oncology, a biopharmaceutical company headquartered in San Diego, California, has 4 ongoing clinical trials investigating tipifarnib in HNSCC and myeloid malignancies (**TABLE**).

Following a meeting with the FDA, the company said it plans to initiate a registration-directed phase II trial in patients with *HRAS*-mutant HNSCC in the second half of 2018. The single-arm study, to be called AIM-HN, would seek to enroll at least 59 patients with recurrent or metastatic disease.[12]

At press time, tipifarnib remains the only FTI undergoing clinical trials for use in cancer treatment, while previously investigated FTIs BMS-214662, CP-609,754, and AZD3409 remain dormant, according to a search of the ClinicalTrials.gov website. Outside of the cancer arena, however, research with other FTIs continues.

Of note, lonafarnib is undergoing clinical trials for Hutchinson-Gilford Progeria Syndrome (HGPS), a terminal illness that causes premature aging. In patients with HGPS, progerin is the protein thought to be responsible for blocking normal cell function, and as farnesylation is required for progerin activity, lonafarnib could be the first therapeutic drug for this rare disease. Completed trials have recorded increased survival times in treated patients.[13]

To date, more than 50 proteins are known to undergo posttranslational farnesylation, and additional activity may be elucidated in the future. Further research is needed to better understand associated pathways. As early trials using FTIs to indirectly target the RAS pathway are found, blocking farnesylation is inadequate as a therapeutic strategy for all tumors with *RAS* mutations.

However, ongoing research shows that *HRAS*-mutant varieties appear susceptible to tipifarnib due to a lack of redundant enzymes. Along the same optimistic lines, research into the CXCL12/CXCR4 pathway is defining which patients with hematological malignancies are likely to respond to FTI therapy and illuminating associations with the RAS pathway. As research clarifies the complex network of pathways that drive neoplasia and other diseases, more patient-specific therapies may be on the horizon. ■

For a complete list of references, see article on *OncLive.com*.

PARP Inhibitors Are Making an Impact in Breast Cancer

By Silas Inman and Jason Harris

Following in the footsteps of ovarian cancer, the development of PARP inhibitors for patients with *BRCA*-mutant metastatic breast cancer is progressing rapidly, signaling a potential new era for targeted therapies in the treatment paradigm for the disease.

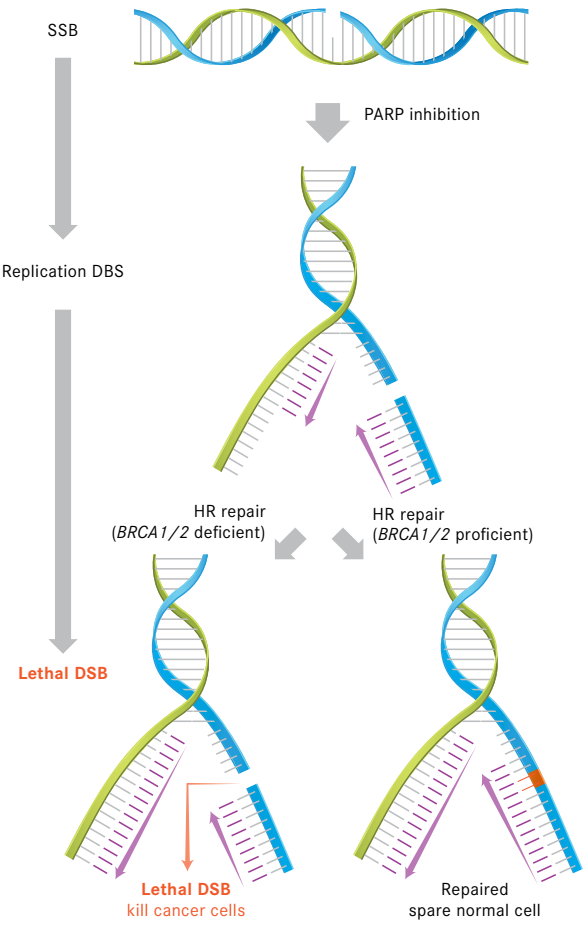
In January 2018, the FDA approved olaparib (Lynparza) for treating patients with germline *BRCA*-positive, HER2-negative metastatic breast cancer who have previously received chemotherapy. In addition to olaparib, investigators are exploring 4 other PARP inhibitors in breast cancer: talazoparib (BMN 673), niraparib (Zejula), rucaparib (Rubraca), and veliparib (ABT-888).

Each drug has demonstrated a different level of "PARP trapping," defined as a process whereby the PARP inhibitor complex "locks" onto damaged DNA, interrupting its ability to replicate and ultimately causing cell death.[1] Talazoparib has exhibited the highest level of PARP trapping, followed by niraparib, rucaparib, olaparib, and veliparib, according to Debu Tripathy, MD, who discussed the emerging PARP landscape during the *35th Annual* Miami Breast Cancer Conference® in March.


DEBU TRIPATHY, MD

"We know now that the PARP inhibitors exist on a spectrum of biological properties. Those with the highest so-called PARP trapping activity sequester the PARP enzyme and make it unavailable to the DNA repair machinery," said Tripathy, professor and chair of the Department of Breast Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston. "Not only does this correlate with higher potency but [also] more toxicity when combined with cytotoxic chemotherapy."

FIGURE. IMPACT OF TARGETING PARP



PARP inhibition blocks DNA single-strand breaks (SSBs), which can convert to double-strand breaks (DSBs). DSBs are typically repaired through homologous recombination (HR). *BRCA1/2* mutations disable HR repair, resulting in lethality.

© Recreated by Julianne Costello from He JX, Yang CH, Miao ZH. *Acta Pharmacol Sin*. 2010;31(9):1172-1180. doi: 10.1038/aps.2010.103.

Rationale for PARP InHibition in Breast Cancer

PARP inhibition has been a clinical target in breast cancer for nearly 2 decades. In 2010, Mark Robson, MD, who would go on to become part of the research team that published the landmark OlympiAD trial for olaparib, and Elizabeth A. Comen, MD, discussed the rationale for targeting PARPs, a family of enzymes involved in DNA damage repair and many other cellular functions, in triple-negative breast cancer (TNBC).[2]

Through their enzymatic activity, PARPs coordinate the base excision repair (BER) pathway to mend single-strand breaks (SSBs) in DNA. If SSBs go unrepaired, they can lead to a more dangerous form of DNA damage, the double-strand break (DSB). PARP1 also has been implicated in the homologous recombination pathway of DNA repair, which relies upon the activity encoded by *BRCA1/2* genes, as well.

TABLE. SELECTED ONGOING LATE-STAGE PARP INHIBITOR TRIALS IN BREAST CANCER

Agent/Industry Developer	Trial Description	Patient Population	Estimated Enrollment
Olaparib (Lynparza)[a] AstraZeneca	Phase III Olaparib vs placebo (OlympiA; NCT02032823)	g*BRCA*-mutant, high-risk HER2-negative, primary BC	1800
	Olaparib + chemotherapy (PARTNER; NCT03150576)	Neoadjuvant TNBC or g*BRCA*-mutant BC	527
Talazoparib (BMN 673) Pfizer	Phase III Talazoparib vs physician's choice of chemotherapy (EMBRACA; NCT01945775)[b]	g*BRCA*-mutant previously treated advanced/metastatic BC	431
Niraparib (Zejula)[a] Tesaro	Phase III Niraparib vs physician's choice chemotherapy (BRAVO; NCT01905592)[b]	g*BRCA*-mutant, HER2-negative previously treated advanced/ metastatic BC	306
Rucaparib (Rubraca)[a] Clovis Oncology	Phase II Rucaparib + cisplatin vs cisplatin (NCT01074970)[b]	TNBC with *BRCA1/2* mutations after preoperative chemotherapy	135
Veliparib (ABT-888) AbbVie	Phase III Carboplatin + paclitaxel with veliparib or placebo (BROCADE 3; NCT02163694)[b]	g*BRCA*-mutant, HER2-negative advanced/ metastatic unresectable BC	512
	Carboplatin + paclitaxel with veliparib or placebo followed by AC; or paclitaxel with placebo followed by AC (NCT02032277)[b]	Neoadjuvant early-stage TNBC	634

AC indicates doxorubicin (Adriamycin)/cyclophosphamide; BC, breast cancer; g*BRCA*, germline *BRCA* mutation; TNBC, triple-negative breast cancer.

[a]FDA has approved for ovarian cancer. Olaparib also is approved in breast cancer.

[b]Active but not recruiting participants.

When *BRCA1/2* genes are mutated, the homologous recombination repair mechanism fails to function, promoting genomic instability and, therefore, cancer-causing activity. Drugs that inhibit PARP activity in cancers with homologous recombination pathway or *BRCA* defects promote cell killing directly and are believed to enhance the activity of DNA-damaging chemotherapies (**FIGURE**).[2,3]

This has made PARP inhibitors attractive anticancer therapies for ovarian and breast cancers with homologous recombination deficiencies and *BRCA* mutations. Findings from several studies have estimated that the prevalence of *BRCA* mutations in TNBC ranges from approximately 11% to nearly 20%.

In the OlympiAD trial findings, which showed a progression-free survival (PFS) benefit for olaparib, Robson et al noted that cells lacking functional *BRCA1/2* are sensitive to PARP inhibition. Investigators believe that this sensitivity can be caused by several mechanisms, including PARP trapping.[4]

In ovarian cancer, clinical trial findings have shown that *BRCA* mutations are not always needed to generate a response from PARP inhibition. Results from the phase III ENGOT-OV16/NOVA showed that niraparib improved PFS for some patients with platinum-sensitive, recurrent ovarian cancer who did not have a germline *BRCA* (g*BRCA*) mutation, although the benefit was more pronounced among those who did.[5]

Patients with a g*BRCA* mutation had a median PFS of 21.0 months with niraparib compared with 5.5 months for placebo (HR, 0.27; 95% CI, 0.17-0.41; P <.001). Median PFS also favored the niraparib group in the overall non-g*BRCA* cohort (9.3 vs 3.9 months; HR, 0.45; 95% CI, 0.34-0.61; P <.001) and among patients without a mutation who had a homologous recombination deficiency (12.9 vs 3.8 months; HR, 0.38; 95% CI, 0.24-0.59; P <.001).

To date, no PARP inhibitor has shown similar results in humans with nonmutated breast cancer. However, in results published in 2017, talazoparib induced regression in 5 of 13 patient-derived xenografts (PDXs) largely generated from residual tumors following neoadjuvant chemotherapy. Activity was seen in 3 of the 10 responsive PDXs derived from tumors that had not responded to neoadjuvant therapy. Four of 5 talazoparib-sensitive models did not harbor known deleterious g*BRCA1/2* mutations.[6]

Nevertheless, most of the later-stage clinical trials investigating the leading PARP inhibitor candidates in breast cancer are being conducted in patients with *BRCA* mutations (**TABLE**).

Phase III Findings for PARP Inhibition

Olaparib, which is approved in several ovarian cancer settings, gained its breast cancer indication based on findings from OlympiAD, a phase III trial that randomized 302 patients with HER2-negative, g*BRCA1/2*-mutated metastatic breast cancer to receive 300-mg olaparib tablets twice daily (n = 205) or chemotherapy treatment of physician's choice (n = 97).[4]

In the study, the median PFS was 7.0 months in the olaparib arm versus 4.2 months with standard chemotherapy (HR, 0.58; 95% CI, 0.43-0.80; P = .0009).

The objective response rate (ORR) was 59.9% with olaparib versus 28.8% with chemotherapy. Median overall survival (OS) rates were not different between the 2 arms; however, Tripathy noted that the data were still immature. The median OS was 19.3 months with olaparib and 19.6 months for chemotherapy (HR, 0.90; 95% CI, 0.63-1.29; *P* = .5665).

There was a more pronounced benefit for the PARP inhibitor in patients with TNBC. In those with hormone receptor–negative, HER2-negative disease, there was a 57% reduction in the risk of progression or death with olaparib versus chemotherapy (HR, 0.43; 95% CI, 0.29-0.63). In patients with HER2-negative, hormone-receptor–positive breast cancer, the reduction in progression or death was 18% with olaparib, which was not statistically significant (HR, 0.82; 95% CI, 0.55-1.26).

In another phase III study, EMBRACA, patients were randomly assigned to oral talazoparib at 1 mg daily (n = 287) or physician's choice of therapy (n = 144). All patients in the trial had *BRCA*-mutant advanced breast cancer.[7]

At a median follow-up of 11.2 months, the median PFS was 8.6 months (95% CI, 7.2-9.3) with talazoparib compared with 5.6 months (95% CI, 4.2-6.7) with physician's choice of therapy (HR, 0.54; 95% CI, 0.41-0.71; *P* <.0001). The 1-year PFS rate was 37% with talazoparib versus 20% with chemotherapy. In patients with central nervous system metastasis, the median PFS was 5.7 months with talazoparib versus 1.6 months for chemotherapy (HR, 0.32; 95% CI, 0.15-0.68; *P* = .0016). The ORR was 62.6% versus 27.2%, respectively.

At the interim analysis, the OS was 22.3 months with talazoparib versus 19.5 months for chemotherapy (HR, 0.76; 95% CI, 0.54-1.06; *P* = .105), which showed a hint of improvement, Tripathy said. The OS rates at 24 months were 45% and 37% for talazoparib and chemotherapy, respectively. The 36-month OS rates were 34% and 0%, respectively.

"Randomized trials of olaparib and talazoparib show longer PFS with PARP inhibition compared with single-agent chemotherapy in *BRCA*-mutation–associated metastatic breast cancer," Tripathy said. "There's a hint of greater activity in hormone-receptor–negative and non–platinum-exposed [patients]. There's no difference yet apparent in survival, but the data are not [yet] mature."

With both agents showing similar efficacy, the adverse events (AEs) become a differentiating factor between the 2 PARP inhibitors. With olaparib, the most common AEs were nausea (58%), anemia (40%), vomiting (30%), fatigue (29%), neutropenia (27%), diarrhea (21%), and headache (20%). For talazoparib, the most common AEs were anemia (53%), fatigue (50%), nausea (49%), neutropenia (35%), headache (33%), alopecia (25%), vomiting (25%), diarrhea (22%), and constipation (22%).

"There were differences in toxicity," Tripathy said. "Anemia might be more frequent with talazoparib and neutropenia, although it is not seen as frequently as in the chemotherapy groups. I will point out that fatigue is a common event, although it might be a little more common with talazoparib."

An OS Benefit for Olaparib?

Updated data from the OlympiAD trial presented at the 2018 American Association for Cancer Research Annual Meeting showed that, although the study was not powered to demonstrate a statistically significant difference in OS, olaparib was associated with a 2.2-month improvement in OS (19.3 vs 17.1 months; HR, 0.90; 95% CI, 0.66-1.23; *P* = .513). At the final OS data cut-off (64% maturity), nearly 13% of patients remained on olaparib and no patients remained on chemotherapy.[8]

"OlympiAD is the first phase III trial to demonstrate disease control with a PARP inhibitor in *BRCA*-mutated HER2-negative metastatic breast cancer," Sean Bohen, executive vice president of Global Medicines Development and chief medical officer at AstraZeneca, said in a statement. "[Although] the trial was not powered to show overall survival compared [with] chemotherapy, the results are another encouraging marker in the use of Lynparza for this patient population."

Previously reported findings also showed that olaparib more than doubled ORRs (52% vs 23%) and improved quality-of-life scores.

Ongoing PARP Inhibitor Studies

Combinations are a logical next step for the PARP inhibitors, with early findings already available for veliparib plus carboplatin and paclitaxel from the phase II BROCADE-2 trial.[9] The median PFS was 14.1 months (95% CI, 11.5-16.2) for the veliparib arm and 12.3 months (95% CI, 9.3-14.5) for the placebo group (HR, 0.789; 95% CI, 0.536-1.162; *P* = .231). The ORR was 77.8% for veliparib versus 61.3% for placebo.

The phase III BROCADE-3 study is currently assessing the efficacy and tolerability of carboplatin and paclitaxel with veliparib or placebo for patients with HER2-negative, *BRCA*-associated advanced breast cancer. The study has fully accrued with a primary completion date of May 31, 2018 (NCT02163694).

Beyond these studies, PARP inhibitors are being explored with a variety of partners, Tripathy noted. "Trials are ongoing in the adjuvant setting, in biomarker-specified *BRCA* wild-type, and in combinations with radiation therapy, immunotherapy, signal transduction inhibitors—such as PI3K/mTOR, Wee1 kinase inhibitors—and CDK4/6 inhibitors," he said.

The phase II SWOG 1416 study is exploring other potential markers that could predict response to PARP inhibitors. This trial includes an arm of patients with g*BRCA* mutations along with other arms to assess other DNA-repair–associated markers, such as high levels of homologous repair deficiency or mutations in homologous repair genes (NCT02595905). The estimated primary completion date for this study is October 2021. ■

For a complete list of references, see article on *OncLive.com*.

Harvard Expert Sees Potential in BCL-2 Combos

By Jane de Lartigue, PhD

The prospect of developing anticancer strategies that target the apoptotic pathway most likely lies in combinations involving members of the B-cell lymphoma-2 (BCL-2) protein family, according to Anthony G. Letai, MD, PhD, a leading investigator in the field.

In his laboratory at Dana-Farber Cancer Institute in Boston, Massachusetts, where he is an associate professor of medicine, Letai focuses on investigating apoptotic dysfunction's role in tumor maintenance. In particular, he is interested in understanding the interactions among the BCL-2 protein family members, which include myeloid cell leukemia-1 (MCL-1). Letai, who also is an associate professor at Harvard Medical School, has led efforts to translate BH3 mimetics that target BCL-2 family members to the clinic.


ANTHONY G. LETAI, MD, PHD

In an interview with *OncologyLive®*, Letai discussed the complex nature of apoptosis and efforts to target the process.

Q: How does apoptosis fit into the hallmarks of cancer?

A: Both the older and newer constructs of Hanahan and Weinberg's "Hallmarks of Cancer" list "resisting cell death" as a hallmark. The concept is that a lot of the bad things cancers do, such as overexpress oncogenes, invade and metastasize out of their native locations, and proliferate relentlessly, should provoke apoptotic signaling (apoptosis is a prominent form of programmed cell death) that should kill the cancer cells. The fact that some cancer cells escape this level of control suggests that they have selected for evasion of programmed cell death. Indeed, many mouse genetic models of impaired apoptosis display accelerated oncogenesis, supporting programmed cell death as 1 level of control of cancer.

However, some have taken this to mean that cancer cells in established tumors are more resistant to programmed cell death than normal cells are. This is probably incorrect. In fact, most cancers are more sensitive to cell death signaling than most normal tissues are. This is the main reason conventional chemotherapy, targeting the ubiquitous elements of DNA and microtubules, ever demonstrates a therapeutic index.

Cancer cells may select for blocks in apoptosis that enable it to escape endogenous death signaling induced by oncogenesis, but there is no mechanism for them to foresee future exposure to chemotherapy and select for the extra apoptotic blocking that resistance to these agents would require. This often results in cancer cells that survive, but just barely. Of course, this principle exists on a broad spectrum, with leukemias and other blood cancers being the most primed for apoptosis, in concert with their broad chemosensitivity. Many solid tumors, however, exhibit more profound blocking, which yields less chemosensitivity.

Q: What is the role of MCL-1 in that hallmark ability?

A: MCL-1 is one of the proteins of the BCL-2 family that regulate apoptosis. It is a so-called antiapoptotic protein, as it opposes commitment to apoptotic cell death by binding and sequestering proapoptotic proteins. Theoretically–and demonstrated in mouse models–high levels of MCL-1 expression can facilitate tumorigenesis. In human tumors, amplification of the *MCL-1* locus is one of the more common somatic genetic abnormalities.

However, what is more important from a therapeutic perspective is whether or not the tumor cell is dependent on MCL-1 function to stay alive, and this is a phenotype that is not easily identified by somatic genetic alterations. MCL-1–dependent tumor cells are good candidates for targeting with MCL-1–inhibiting drugs.

Q: How is MCL-1 being targeted for anticancer therapy?

A: The most direct way is via small molecules that compete for the pocket in MCL-1 that is required to bind the BH3 domain of proapoptotic proteins. These so-called BH3 mimetic drugs inhibit the homodimerization that is necessary for MCL-1 function. BH3 mimetics can displace proapoptotic proteins that are already bound by MCL-1, allowing them to progress with commitment to programmed cell death. Right now, the companies that are furthest along with BH3 mimetic small-molecule antagonists of MCL-1 include Novartis (in a partnership with Servier), AstraZeneca, and Amgen.

An alternative way to target MCL-1 is via CDK9 (cyclin-dependent kinase 9) inhibition. CDK9 regulates transcriptional elongation, and its inhibition selectively depletes cells of proteins with a short half-life. MCL-1 is such a protein and is depleted by CDK9 inhibition. Of course, this is a "dirtier" way to inhibit MCL-1 function–only clinical experience will reveal if it is more or less effective, or more or less toxic, than BH3 mimetic MCL-1 inhibition.

Q: How might MCL-1 inhibitors be used in hematologic malignancies? Do you think they might be effective in solid tumors?

A: BCL-2 is an antiapoptotic cousin of MCL-1. Based on work my lab and others have done and based on clinical experience, it looks like chronic lymphocytic leukemia is pretty homogeneously dependent on BCL-2 and sensitive to BCL-2 inhibition. B-cell acute lymphoblastic leukemia and blastic plasmacytoid dendritic cell neoplasm (a rare blood cancer) are likely quite similar.

So far, we have not identified a blood cancer that is quite so homogeneously dependent on MCL-1. What we see more often are significant subsets of disease, like acute myelogenous leukemia or myeloma that is MCL-1 dependent. I think this is where we will first see their single-agent activity, and clinical trials are ongoing. I think that clinical response rate will improve when treatment is driven by predictive biomarkers of MCL-1 dependence. Also, as we have seen for BCL-2 inhibition, I expect that response rates and durability of response will significantly increase as MCL-1 inhibitors are brought into combinations.

I think that when this is done, MCL-1 inhibitors, as I think for BCL-2 inhibitors, will find very broad application across hematologic malignancies. I am very excited about the possibility of combining BCL-2 and MCL-1 inhibitors. There may be toxicity issues to sort out, but I believe that whoever finds a way to combine these 2 will have an extremely powerful combination therapy with very broad applicability.

For solid tumors, it is simply harder to get them to undergo apoptosis, as they are generally less primed for apoptosis. Therefore, I suspect there will be limited single-agent activity of MCL-1 inhibitors. However, as in blood cancers, I think that the use of good predictive biomarkers, as well as incorporation into combinations, will facilitate penetration of MCL-1 inhibitors (and BCL-2 inhibitors) into solid tumors. I expect that progress in solid tumors will lag behind that in blood cancers, as it will be much easier to accumulate the necessary proof-of-principle data in the latter, which are more primed for apoptosis. ■