IN FOCUS

Precision Oncology: 2023 in Review

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Summary: This article presents a review of recent major advances in precision oncology and the future implications of these advances, specifying the iterative progress achieved from the end of 2022 through 2023. We discuss the different classes of precision oncology drugs and associated biomarkers as well as the improvements in clinical trial design that have enabled the efficient testing of these drugs.

INTRODUCTION

The scope of precision oncology continues to expand as drugs with new mechanisms of action enable therapeutic intervention on a wider array of targets in broader, biomarker-selected patient populations. By virtue of the advances in our understanding of specific mutation-based clinical implications and the epistatic relationship between co-occurring mutations, as well as the role that the immune environment plays in therapy selection, the long-standing paradigm of matching a single gene to a single treatment is rapidly evolving.

This review, as the second installment in the Precision Oncology Year in Review series (1), uses OncoKB to offer a lens into the advances in precision oncology in 2023. On the basis of OncoKB, as of November 2023, twelve treatments were approved by the FDA for unique biomarker-selected indications, and six biomarker- and indication-specific treatments were listed in the National Comprehensive Cancer Network (NCCN) guidelines in the past year. In addition, compelling clinical evidence for two precision oncology therapies led to their inclusion as level 3 investigational agents in OncoKB (Table 1). Here we discuss the growing array of targetable molecular alterations as well as the proteomic and immunologic biomarkers that are increasingly guiding patient matching to novel classes of medications, including antibody–drug conjugates (ADC) and proteolysis-targeting chimeras (PROTAC)/protein degraders, and how the distinct biology of individual mutant alleles has contributed to drug development efforts.

CHIPPING AWAY AT THE UNDRUGGABLE

Over the past couple of years, novel approaches to drug design have resulted in new precision oncology therapies that are proving to be successful in addressing an increasing number of previously undruggable targets in the clinic. Epitomizing the cumulative results of these developments is our current emerging ability to target *KRAS*-mutant cancer, initiated with the success of selective $KRAS^{G12C}$ inhibitors.

The $KRAS^{G12C}$ inhibitors sotorasib and adagrasib, both of which trap $KRAS^{G12C}$ in its inactive GDP-bound state, previously received accelerated approval for $KRAS^{G12C}$-mutant non–small cell lung cancer (NSCLC). These inhibitors are now listed in the NCCN guidelines additional $KRAS^{G12C}$-mutant histologies, including for pancreatic and colorectal cancers (the latter indication's approval is in combination with either anti-EGFR monoclonal antibody inhibitors cetuximab or panitumumab). Another more potent $KRAS^{G12C}$ inhibitor of GDP-bound KRAS, divarasib, was shown to achieve an initial overall response rate (ORR) of 54% and progression-free survival (PFS) of 13.1 months in patients with NSCLC treated on a phase I trial (2).

$KRAS^{G12C}$ has a slightly increased affinity for GTP versus GDP, and this past year, the field pivoted to develop $KRAS^{G12C}$ inhibitors that trap the oncoprotein in its activated or so-called "on" form. For example, FMC-376 is a covalent inhibitor of both the activated and inactivated forms of $KRAS^{G12C}$, and RMC-6291, employs the formation of a so-called "tricomplex" between KRAS, cyclophilin A, and the drug to inhibit $KRAS^{G12C}$ in its activated state. There has also been a pronounced emphasis on combining $KRAS^{G12C}$ inhibitors with other agents this year. These combination strategies include supplementing $KRAS^{G12C}$ inhibitor treatment with drugs that target emerging biomarkers such as integrin beta 4 (3) as well as with immunotherapy, chemotherapy or other precision oncology drugs including those that target known resistance alterations arising in the receptor tyrosine kinase (RTK) or mitogen activated protein kinase (MAPK) pathways. Preliminary data on the combination of the $KRAS^{G12C}$ "off" inhibitor LY3537982 with pembrolizumab showed an ORR of 78% in NSCLC with no prior G12C inhibitor exposure and 25% after prior G12C inhibitor exposure (4).

Non-G12C KRAS alleles, including both mutant-selective and pan-KRAS inhibitors, are also being explored. For example, $KRAS^{G12D}$, the most common KRAS allele pan-cancer, is now potentially targetable by agents including RMC-9805, a tricomplex inhibitor; MRTX1133, a noncovalent inhibitor; and ASP3082, a protein degrader. Multiallele KRAS inhibitors such as RMC-6236 achieved clinical responses in G12D- and G12V-mutant cancers in a phase I trial (5). Lastly, pan-KRAS inhibitors that avoid inadvertant HRAS and NRAS activation by KRAS wild-type cells are in preclinical development (6).

Other targets previously considered undruggable include the YAP transcription coactivator, the phosphorylation and subse-

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Table 1. The changes in 2023 precision oncology landscape as documented by OncoKB

Level 1: Biomarkers listed in the tumor type–specific "Indications and Usage" section of the FDA drug label in 2023

			Evidence		
Molecular biomarker	Cancer type	Drug	Trial name(s)	*N*	Efficacy data
ERBB2 amplification	Colorectal cancer	Tucatinib + trastuzumab	MOUNTAINEER	84	ORR: 38% (95% CI: 28–49); CR: 3 (3.6%); PR: 29 (35%) Median DOR (*N* = 32): 12.4 mos (95% CI: 8.5–20.5)
ESR1 oncogenic ligand-binding domain missense mutations (310_547)	Breast cancer	Elacestrant	EMERALD	228	Elacestrant (*N* = 115): Median PFS: 3.8 mos (95% CI: 2.2–7.3) Fulvestrant or an AI (*N* = 113): Median PFS: 1.9 mos (95% CI: 1.9–2.1) HR: 0.55 (95% CI: 0.39–0.77) *P* < 0.0005
$BRAF^{V600E}$	Low-grade glioma (pediatric only)	Dabrafenib + trametinib	Study G2201	110	Dabrafenib + trametinib (*N* = 73): ORR: 46.6% (95% CI: 34.8–58.6) Placebo (*N* = 37): ORR: 10.8% (95% CI: 3.0–25.4) *P* < 0.001
ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11, NBN, PALB2, RAD51C oncogenic mutations	Prostate cancer	Talazoparib + enzalutamide	TALAPRO-2	399	HRR-gene mutated: Talazoparib (*N* = 200): Median Radiographic PFS (mos): NE (95% CI: 21.9-NE) Placebo (*N* = 199): Median Radiographic PFS: 13.8 mos (95% CI: 11.0–16.7) HR: 0.45 (95% CI: 0.33–0.61); *P* < 0.0001
BRCA1/2 oncogenic mutations	Prostate cancer	Talazoparib + enzalutamide	TALAPRO-2	155	*BRCA1/2* mutated: Talazoparib (*N* = 71): Median Radiographic PFS (mos): NE (95% CI: NE-NE) Placebo (*N* = 84): Median Radiographic PFS: 11.0 mos (95% CI: 8.3–11.1) HR: 0.20 (95% CI: 0.11–0.36)
		Olaparib + abiraterone + prednisone/ prednisolone	PROpel	85	Olaparib (*N* = 47): Median Radiographic PFS (mos): NR (95% CI: NR-NR) Median OS: NR (95% CI: NR-NR) Placebo (*N* = 38): Median Radiographic PFS: 8.0 mos (95% CI: 6.0–15.0) Median OS: 23 mos (95% CI: 18–34) HR for Radiographic PFS: 0.24 (95% CI: 0.12–0.45) HR for OS: 0.30 (95% CI: 0.15–0.59)
		Niraparib + abiraterone acetate + prednisone	MAGNITUDE	225	Niraparib (*N* = 113): Median Radiographic PFS: 16.6 mos (95% CI: 13.9-NE) Placebo (*N* = 112): Median Radiographic PFS: 10.9 mos (95% CI: 8.3–13.8) HR: 0.53 (95% CI: 0.36–0.79); *P* = 0.0014
FLT3 Internal Tandem Duplication	Acute myeloid leukemia	Quizartinib	QuANTUM- First	539	Quizartinib (*N* = 268): OS: 31.9 mos (95% CI: 21.0-NE) Placebo (*N* = 271): OS: 15.1 mos (95% CI: 13.2–26.2) HR: 0.78 (95% CI: 0.62–0.98); *P* = 0.032
Microsatellite instability-high	Endometrial cancer	Dostarlimab + carboplatin + paclitaxel	RUBY	122	Dostarlimab (*N* = 60): ORR: 73.8% (95% CI: 58.0–86.1) Median PFS: 30.3 mos (95% CI: 11.8-NR) Placebo (*N* = 62): ORR: 62.2% (95% CI: 46.5–76.2) Median PFS: 7.7 mos (95% CI: 5.6–9.7) HR for PFS: 0.29 (95% CI: 0.17–0.50); *P* < 0.0001
$BRAF^{V600E}$	Non–small cell lung cancer	Encorafenib + binimetinib	PHAROS	98	Treatment naïve (*N* = 59): ORR: 75% (95% CI: 62–85); CR: 15%; PR: 59% Previously treated (*N* = 39): ORR: 46% (95% CI: 30–63); CR: 10%; PR: 36%

IDH1 R132	Myelodysplastic Syndrome	Ivosidenib	AG120-C-001	18	Complete remission: 38.9% (95% CI: 17.3–64.3)
ROS1 Fusions	Non-small cell lung cancer	Repotrectinib	TRIDENT-1	127	ROS1-inhibitor treatment naïve (*N* = 71): ORR: 79% (95% CI: 68–88) ROS1-inhibitor pretreatment (*N* = 56): ORR: 38% (95% CI: 25–52)
PIK3CA, *AKT1* or *PTEN* Oncogenic Mutations	Breast Cancer	Capivasertib + fulvestrant	CAPItello-291	289	Capivasertib + fulvestrant (*N* = 155): Median PFS: 7.3 mos (95% CI: 5.5–9.0) Capivasertib + placebo (*N* = 134): Median PFS: 3.1 mos (95% CI: 2.0–3.7) HR: 0.50 (95% CI: 0.38-0.65); *P* < 0.0001
Level 2: Biomarkers listed in the treatment recommendations section of a tumor type–specific NCCN guideline in 2023					
$KRAS^{G12C}$	Pancreatic adenocarcinoma	Adagrasib	KRYSTAL-1	10	PR: 5/10 (50%)
		Sotorasib	CodeBreak 100	38	PR: 8/38 (21%) (95% CI: 10–37)
ESR1 oncogenic ligand-binding domain in-frame insertions or deletions	Breast cancer	Elacestrant	EMERALD	228	Elacestrant (*N* = 115): Median PFS: 3.8 mos (95% CI: 2.2–7.3) Fulvestrant *or an AI* (*N* = 113): Median PFS: 1.9 mos (95% CI: 1.9–2.1) HR: 0.55 (95% CI: 0.39–0.77); *P* < 0.0005
ERBB2 amplification	Biliary tract cancer	Trastuzumab + pertuzumab	MyPathway	39	PR: *N* = 9; SD: *N* = 11; ORR: 23% (95% CI, 11–39%)
ALK fusions	Inflammatory myofibroblastic tumors	Alectinib	A phase III trial of alectinib vs. crizotinib in pts with ALK+ NSCLC	303	Alectinib (*N* = 152): Median PFS: NR (95% CI, 17.7-NE) Crizotinib (*N* = 151): Median PFS: 11.1 mos (95% CI, 9.1–13.1) Case Study: 1 patient with SQSTM1-ALK fusion+ IMT had a PR to alectinib Case Study: 1 patient with SQSTM1-ALK fusion+ IMT had SD following treatment with alectinib
IDH1 oncogenic mutations	Oligodendroglioma	Ivosidenib	A phase I trial of ivosidenib in pts with IDH1 mt glioma	66	Non-enhancing glioma (*N* = 35): PR: 2.9%; SD: 85.7%; Median PFS: 13.6 mos (95% CI: 9.2–33.2) Enhancing glioma (*N* = 31): PR: 0%; SD: 45.2% Median PFS: 1.4 mos (95%CI: 1.0–1.9)
$KRAS^{G12C}$	Colorectal and rectal cancer	(Sotorasib or adagrasib) + (cetuximab or panitumumab)	KRYSTAL-1 Adagrasib or adagrasib + cetuximab	28	Combination therapy group (*N* = 28): ORR: 46% (95% CI: 28–66) Median PFS: 6.9 mos
			CodeBreak 101 Sotorasib + panitumumab	40	ORR: 30% (95% CI: 16.6–46.5)
Level 3: Biomarkers predictive of response to targeted agents as demonstrated by phase III clinical evidence, compelling phase I/II trial data in 2023					
$IDH1^{R132}$ and $IDH2^{R172}$	Oligodendroglioma, astrocytoma	Vorasidenib	INDIGO	331	Vorasidenib (*N* = 168): Imaging-based PFS: 27.7 mos (95% CI: 17.0-NE) Placebo (*N* = 163): Imaging-based PFS: 11.1 mos (95% CI: 11.0–13.7) HR for disease progression or death: 0.39 (95%CI: 0.27–0.56); *P* < 0.001
FGFR2 oncogenic mutations	Cholangiocarcinoma	RLY-4008	ReFocus	14	FGFR-inhibitor treatment naïve (*N* = 10): DCR: 70%; PR: 3/10 FGFR-inhibitor pretreatment (*N* = 4): PR: 1/4, SD: 2/4, PD: 1/4
FGFR2 fusions				75	FGFR-inhibitor treatment naïve (*N* = 25): ORR: 52% (95% CI: 31.3–72.2) Prior FGFR-inhibitor treatment (*N* = 50): ORR: 14% (95% CI: 5.8–26.7)

Abbreviations: AI, aromatase inhibitor; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; HRR: homologous recombination repair.

quent degradation target of the Hippo kinase cascade pathway. Mutation of Hippo pathway components, such as the tumor suppressor *NF2*, have been observed to arise in *IDH*-mutant-low-grade gliomas, mesotheliomas, and HPV-negative head and neck squamous cancers. Clinical responses were observed in an ongoing trial testing the YAP/TEAD inhibitor VT3989 (7), where the TEAD family of transcription factors are known to bind to and potentiate YAP oncogenic activity. Additionally, new targets such as cyclin E1, part of the cell-cycle pathway and often deregulated in cancer by amplification, are also being explored therapeutically, including to guide patient selection for treatment with the newly developed CDK2 inhibitor BLU-222.

ADVANCES IN MUTATION TARGETING

Kinases continue to represent the stronghold of the precision oncology armamentarium, with each year yielding novel kinase inhibitors that are characterized by improved potency, increased selectivity against specific kinase isoforms, or optimized mutant selectivity. This year, the FDA approved quizartinib, a more potent FLT3 and FLT3-ITD mutation type II inhibitor compared with earlier generation FLT3 inhibitors. Patients with acute myeloid leukemia (AML) that received quizartinib in addition to first-line chemotherapy achieved a median overall survival of 31.7 months compared with 15.1 months in patients who received first-line chemotherapy alone (8). In solid tumors, RLY-4008, an isoform-selective, covalent FGFR2 inhibitor designed to avoid off-target side effects associated with FGFR1 and FGFR4 inhibition, showed promising results in patients with FGFR2-positive cholangiocarcinoma (9). Trials testing FGFR3 selective inhibitors (TYRA-300 and LOXO-435) were also launched this year.

In addition to selectivity for individual mutations, inhibitors designed to selectively target single and compound acquired resistance mutations arising from treatment with earlier-generation ALK/ROS continue to be developed and approved. In November 2023, repotrectinib, a next-generation ROS1 and TRK inhibitor, was FDA-approved for ROS1 fusion-positive NSCLCs. Importantly, this drug demonstrated potent activity against ROS1 and NTRK TKI resistance mutations, including solvent front mutations. Relevant to the ROS1 approval, repotrectinib inhibited ROS1 fusion-positive NSCLCs bearing $ROS1^{G2032R}$ that arises after progression on crizotinib (10) or entrectinib. Currently in clinical trials are the TKIs NVL-520, a ROS1 selective agent that also targets $ROS1^{G2032R}$, as well as NVL-655, with activity against ALK fusion-positive NSCLCs harboring $ALK^{G1202R/L1196M}$ and $ALK^{G1202R/T1151M}$ compound resistance mutations. BLU-945, a reversible, wild-type-sparing inhibitor of EGFR+/T790M and EGFR+/T790M/C797S resistance mutants that maintains activity against the sensitizing mutations, especially L858R, similarly achieved responses in compound EGFR mutants (11).

Building on cumulative observations that pan-PI3K inhibition leads to hyperglycemia in treated PIK3CA-mutant patients with breast cancer that led to the 2019 approval of the PI3K-alpha-selective inhibitor alpelisib in combination with fulvestrant, the industry continues to pivot to wild-type sparing drug design. This year, the mutant selective inhibitor RLY-2608 was tested as monotherapy and in combination with fulvestrant in a phase I trial and neither severe nor dose-limiting hyperglycemia secondary to wild-type PI3Kα inhibition were observed thus far (12). Relatedly, 2023 saw the approval of the pan-AKT targeted inhibitor capivasertib for PIK3CA/AKT1/PTEN positive, hormone-receptor positive and HER2-negative patients with advanced cancer. The biomarker-based approval of capivasertib was surprising considering that published median progression free survival was 7.2 months in capivasertib/fulvestrant treated versus 3.6 months in placebo/fulvestrant and 7.3 months in capivasertib/fulvestrant versus 3.1 months in placebo/fulvestrant in the overall and AKT pathway-altered patient cohorts respectively.

In parallel with the development of newer kinase inhibitors, the indications for which meaningful clinical benefit has been observed for established kinase inhibitors have also continued to expand. For example, alectinib, initially developed for *ALK* fusion–positive NSCLC, has now been added to the NCCN guidelines for *ALK*-positive inflammatory myofibroblastic tumors. Combination dabrafenib plus trametinib, previously approved for $BRAF^{V600E}$-mutant solid tumors, received additional approval in the first-line setting for low-grade pediatric gliomas where treated patients achieved a median PFS of 20.1 months as well as a decreased rate of high-grade adverse events when compared with 7.4 months when treated with chemotherapy (13).

Other kinase inhibitors have been retired. Examples include Debio1347 for *FGFR1* amplifications and mobocertinib for *EGFR* exon 20 insertions. It is notable that sponsors decided not to pursue confirmatory studies mandated for regulatory approval for several drug indications despite their documented activity. Infigratinib previously received accelerated approval for FGFR2-positive cholangiocarcinoma based on a response rate of 23.1% (14), and the RET inhibitor pralsetinib previously showed an ORR of 71% among medullary thyroid cancers that had not been previously treated with cabozantinib and/or vandetanib (15).

Beyond kinase inhibitors, triple combination of different PARP inhibitors with hormone therapy abiraterone and steroid prenidsone were approved in 2023 for select patients with prostate cancer carrying mutations in genes involved in homologous recombination repair (HRR). PARP inhibitor olaparib or niraparib in combination with abiraterone and prenidsone received regulatory approval for metastatic, castration-resistant prostate cancer with *BRCA1/2* alterations. Additionally, following the TALAPRO-2 study testing the efficacy of combination treatment with PARP inhibitor talazoparib and androgen receptor inhibitor enzalutamide, resulted in the approval of this regimen for patients with HRR mutations, including in *BRCA1/2, ATR, FANCA, MLH1, MRE11, NBN, ATM, PALB2, CDK12, CHEK2,* and *RAD51C*. Notably, while the subgroup of all HRR-deficient pts shows statistical significance between the talazoparib + enzalutamide group versus placebo + enzalutamide, subgroup analysis indicates that this signal is likely primarily driven by BRCA2 presence (16). Indeed, analysis of treatment benefit in ATM- or CHEK2-mutant subgroups showed no significant PFS differences (16).

Lastly, the precision oncology drug ivosidenib targeting the mutant metabolic enzyme IDH1 previously developed for AML and cholangiocarcinoma, was added to the NCCN guidelines for *IDH1*-mutant oligodendrogliomas. The IDH1 inhibitor olutasidenib received approval for AML, following a study of IDH1 inhibitor–naïve relapsed/refractory AML, with an ORR of 48% and a median survival of 11.6 months (17). Beyond extending the range of histologies for which IDH1 inhibitors have been studied, IDH1/2-targeted drugs

such as vorasidenib, which achieved improved PFS versus placebo (27.7 vs. 11.1 months) in IDH1/2-mutant low-grade gliomas, are also being used for lower-grade tumors (18).

THE EVOLUTION OF PROTEIN TARGETING

Beyond DNA- and RNA-based targets, there has been significant expansion in drug development for protein targets. Among the most robust examples of protein targeting has been the evolution of therapies targeting HER2. Indications for the so-called naked or nonconjugated monoclonal anti-HER2 antibody trastuzumab when used in combination with the small molecule HER2 kinase inhibitor tucatinib have expanded. Combination tucatinib plus trastuzumab had previously been used with chemotherapy for breast cancer and gained regulatory approval for HER2-positive/RAS wild-type colorectal cancers this year. Similarly, the combination of trastuzumab and pertuzumab was newly included in the NCCN guidelines for biliary tract cancers.

For HER2 ADC therapy, a basket trial of trastuzumab deruxtecan (T-DXd) demonstrated the potential tumor-agnostic utility of protein expression using HER2 IHC for biomarker selection. The drug was previously approved for HER2-positive gastric and breast cancers, and preliminary data showed an ORR of 37% in patients with any tumor staining IHC 2+ or 3+ and 61% for the 3+ cohort (19).

Moving beyond HER2, a new wave of monospecific and bispecific ADCs have emerged, including those targeting receptor tyrosine kinases. For example, a number of ADCs and bispecifics are currently in trial for MET overexpression, including REGN5093-M114 and ABBV-400. A dual EGFRx-HER3-directed ADC, BL-B01D1, showed preliminary efficacy across a variety of tumor types, with an ORR of 62% in patients with EGFR-mutant NSCLC, 46% in nasopharyngeal carcinoma, and additional activity in small-cell lung cancer (SCLC) and head and neck squamous cell carcinoma (20). ABBV-011 is an ADC designed to target SEZ6, a tumor-specific cell-surface protein that has been found to be overexpressed in neuroendocrine tumors such as SCLC. Data from a phase I trial testing ABBV-011 in patients with relapsed or refractory SCLC, a patient population with limited molecularly targeted therapeutic options, showed an ORR of 25% (21).

Perhaps the most successful example within ADCs this year was the FDA approval of mirvetuximab soravtansine-gynx for patients with platinum-resistant ovarian, peritoneal, or fallopian tube cancer. Mirvetuximab soravtansine-gynx targets the folate receptor, FOLR1, which is overexpressed on the cell surface of many epithelial-derived cancers. Together with the drug, the VENTANA FOLR1 RxDx Assay was approved as a companion diagnostic for FOLR1 biomarker testing. Folate receptor alpha staining of 2+ by IHC in at least 75% of viable cells is required for a patient to be eligible for treatment (22). Efforts to target folate receptor alpha have evolved from ADCs to the smaller sized nanoparticle–drug conjugate ELU001, the latter drug designed to facilitate better tumor penetration.

Beyond ADCs, protein degradation therapy is making a comeback. This year saw the FDA approval of a next-generation selective estrogen receptor degrader, elacestrant, and the introduction of novel *KRAS* and *BRAF*^{V600E} degraders. Elacestrant received approval for patients with estrogen receptor (ER)–positive, endocrine therapy–refractory, HER2-negative breast cancer with an *ESR1* mutation. *ESR1* mutations have been associated with resistance to hormone therapy, due in part to estrogen independent signaling. Treatment with elacestrant notably improved PFS in *ESR1* mutant and wild-type patient cohorts, with an HR of 0.055 and 0.70, respectively, in a phase III trial (23). Combination strategies, such as with PI3K inhibition, are currently being explored.

PROTACs/protein degraders designed to address molecular alterations in known oncogenes, such as *KRAS* and *EGFR* were also tested in 2023. A bifunctional degradation activating compound of BRAF^{V600E}, CFT1946, that inhibits both the kinase activity of the oncoprotein as well as paradoxical MAPK activation by preventing oncoprotein dimerization entered clinical trials for patients with BRAF^{V600}-mutant disease.

IMMUNOMODULATORY THERAPY ADVANCES

Composite biomarkers, such as tumor mutational burden (TMB) and microsatellite instability (MSI) status, have continued to be used to tailor immunotherapeutic approaches to individual cancers, leading to further drug approvals. For example, the checkpoint inhibitor dostarlimab received regulatory approval in combination with chemotherapy for patients with MSI-high advanced or recurrent endometrial cancers. Recognition of the role of genomic instability events, such as chromothripsis, in oncogenesis is likely to propel further multi-omic biomarker development in the future.

Taking notes from the ADC playbook, immune-stimulating antibody conjugates (ISAC) have shown preliminary evidence of drug activity. BDC-1001 is an example of an ISAC consisting of a mAb conjugated to a Toll-like receptor TLR7/8 agonist that primes the microenvironment for immune rejection of the tumor by secretion of cytokines. By binding to a cell-surface protein such as HER2, ISACs are designed to elicit a phagocytic response and T cell–mediated antitumor immunity. Preliminary activity from BDC-1001 monotherapy and nivolumab combination cohorts across HER2-amplified or HER2 protein–expressing tumors was reported (24).

In addition, T-cell receptor (TCR) and neoantigen-based therapies including those with HLA restriction continue to be explored such as TCR therapies designed to address peptide neoantigens produced by mutant *PIK3CA*, *KRAS*^{G12D}, and *FLT3*, among other alterations.

TRIAL DESIGN EVOLUTION

As novel classes of drugs have emerged as viable options for patient treatment, the complexity of biomarkers has increased, and clinical trial design has similarly evolved and adapted to accommodate this increased complexity. In the age of precision oncology many molecularly selected therapies now achieve target inhibition at doses below the maximum tolerated dose (MTD). Moreover, as clinical responses become more durable, long-term tolerability beyond the dose-limiting toxicity period has come under scrutiny. This year, the FDA announced the launch of Project Optimus to facilitate improved dose-optimization strategies through multiple mechanisms, including by randomization of patients to different dose levels (25).

In parallel with the FDA guidance on optimizing dose have been efforts to expedite trials to enable early access to effective therapies. For combinations of established precision oncology

drugs and novel therapies, the FDA allowed the early introduction of combination therapy following a lead-in period of the new treatment to allow for characterization of toxicity, safety, pharmacodynamics, and pharmacokinetics. For example, preclinical data demonstrated that select tumors that have progressed on FDA-approved targeted oncogene inhibitors may be resensitized by adding PF-07284892, an inhibitor of the SHP2 tyrosine phosphatase. While most phase I trials require extensive testing of novel drugs as monotherapy prior to allowing combinations, recognition of the need to expedite combination therapy enabled patients to undergo a lead-in period on the SHP2 monotherapy, followed by the addition of the approved inhibitor at progression (26).

Trial designs also must account for changes in clinical characteristics of the patients being treated, including the inevitable shift of interventions to earlier-stage disease in place of focusing solely on late-stage disease or progression. Mirroring the use of blood-based testing for minimal residual disease in hematologic malignancies, circulating tumor DNA is increasingly being studied to define which patients with solid tumors will gain the greatest benefit from such earlier-stage interventions. For example, therapies are now being tested for patients who have no radiologic signs of disease, but who nonetheless have persistent molecular traces of cancer and who may benefit from therapeutic intervention.

Improving Access to Precision Oncology for All Patients

An additional trial design challenge derives from the need to ensure that all patients benefit from precision oncology's advances. Rates of genetic counseling tend to be lower in nonwhite patients, even when financial barriers are removed (27). Therapeutic approaches that rely on germline genetic differences may further accentuate disparities. In the immunotherapy space, modeling of antigen presentation contributing to HLA allele selection-based drug design has relied heavily on predominantly white patient populations. HLA alleles are known to differ between patients of different ancestries, and several immunologic therapies have been tailored for the HLA-A*02:01 allele, which is most common in white populations. Thus, for example, recent promising data generated by clinical testing of TAEST16001, a NY-ESO-1–directed TCR therapy given with IL2, showed a 41.7% response rate among 12 patients with soft-tissue sarcomas. Since only patients with the HLA-A*02:01 allele are eligible for treatment with TAEST16001, the promise of this drug may only be realized in a subset of patients (28). Indeed, in a pan-cancer study of more than 45,000 patients, those with African ancestry also had a lower rate of somatic actionable alterations (29). Extending the benefits of precision oncology to all patients requires identifying targetable germline and somatic variants across diverse populations, as well as ensuring that trial eligibility criteria and designs facilitate broad access.

CONCLUSION

Advances in precision oncology have enabled the development of multiple novel therapies and combinations this year. These have included treatments that more selectively inhibit their target of interest, including allele and isoform-specific inhibitors, as well as drugs like elacestrant for ESR1-mutant hormone receptor–positive breast cancer that are designed to address known mechanisms of resistance to previously approved therapies. The armamentarium of drugs for molecular alterations is also expanding, with many novel classes of therapies including ADCs, PROTACS/protein degraders, and TCR therapies designed to address protein and peptide targets. The design of clinical trials that support these developments has evolved to enable optimized dosing for tolerability and to facilitate accrual of patients with earlier-stage disease. As both novel drug mechanisms emerge and the biomarkers used to match patients to therapies evolve, cross-talk between precision oncology, molecular oncology, immuno-oncology, and proteomics is yielding therapeutic options for an expanded population of patients.

Authors' Disclosures

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