Staying Abreast of New Biomarkers in Hematology/Oncology

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Abstract

There has been an increasing number of approvals for targeted therapies in oncology in the past decade, changing the treatment paradigm for many solid tumors and hematologic malignancies. At JADPRO Live 2023, presenters provided an in-depth review of cancer biomarkers, including testing methodology, recommended therapies, and how advanced practitioners can integrate results into clinical decision-making.

The identification of biomarkers based on oncogenic driver mutations has led to significant advancements in managing patients with cancer. At JADPRO Live 2023, Andrew Guinigundo, MSN, RN, CNP, ANP-BC, FAPO, Director of Precision Oncology at Cincinnati Cancer Advisors, and Grace Baek, PharmD, BCOP, Clinical Hematology/Oncology Pharmacist at Fred Hutchinson Cancer Center/UW Medicine, reviewed recently approved targeted cancer treatments, their corresponding biomarkers, and the clinical implications of these discoveries.

FLT3

FMS-like tyrosine kinase 3 (FLT3) is a membrane-bound receptor with parts including an extracellular ligand binding domain, a juxtamembrane dimerization domain, and an intracellular kinase domain. When it functions normally, FLT3 is expressed on CD34-positive hematopoietic stem cells and immature hematopoietic progenitors in the bone marrow, spleen, liver, and other organs. In the monomeric form, FLT3 wild type is inactive, but once it binds to a ligand, there is receptor activation via dimerization and phosphorylation of the tyrosine kinase domain. This results in regulation transcription, proliferation, and apoptosis. Its aberrant function can be in the form of an internal tandem duplication (ITD) or tyrosine kinase domain (TKD) mutation. Both of these types of mutations lead to cytokine-independent cellular proliferation.

FLT3 mutations are associated with multiple cancers, but notably they are found in 30% of acute myeloid leukemia (AML) cases. Among these, ITD is more common. *FLT3*-

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ITD carries a negative prognostic influence. US Food and Drug Administration (FDA)-approved targeted inhibitors for *FLT3*-ITD include quizartinib, gilteritinib, and midostaurin, and for *FLT3*-TKD, gilteritinib and midostaurin.

Quizartinib was approved in July 2023 for adult patients with newly diagnosed *FLT3*-ITD positive AML, in the induction and consolidation phases with cytotoxic chemotherapy and in post-consolidation maintenance as monotherapy. It has a black box warning of QTc prolongation. Quizartinib requires a *FLT3*-ITD positive result on an FDA-approved test.

"The turnaround time for this test is usually 2 to 7 days, but it could be longer if it is sent out," noted Dr. Baek.

The test is used during the workup of patients suspected of having AML as well as repeated at progression and relapse.

IDH

Isocitrate dehydrogenase (IDH) is expressed in the liver as well as heart and skeletal muscles. IDH1 is expressed in the cytoplasm and peroxisomes. When functioning normally, it plays a prominent role in glucose sensing and lipid metabolism. IDH2 in the mitochondria is involved in regulating oxidative respiration. Both IDH1/2 are active as homodimers and convert isocitrate to alpha-ketoglutarate, which is converted to nicotinamide adenine dinucleotide phosphate, which downstream manages cellular defense against oxidative damage. The aberrant function is seen with somatic gain-of-function mutations in *IDH1/2* at conserved arginine sites within the enzymatic active site. The mutated *IDH1/2* convert isocitrate to alpha-ketoglutarate, which is converted to oncometabolite 2-hydroxyglutarate. This competitively inhibits alpha-ketoglutarate dependent enzymes, including histone and DNA methylases, leading to epigenetic dysregulation, histone and DNA hypermethylation, and impaired cellular differentiation.

IDH1 mutations are seen in a variety of cancers. In AML, *IDH1* mutations are found in 6% to 9% of AML cases and are associated with older age at presentation, diploid or other intermediate-risk cytogenetics, as well as sustained platelet count at presentation. The prognostic significance of *IDH1* may vary.

"For instance, if we have *IDH*-mutated AML, generally it's associated with inferior outcomes compared with wild-type *IDH*. If there is *FLT3*-ITD with an *IDH* mutation and *NMP1* mutation, we see inferior outcomes as well," commented Dr. Baek.

The recently approved agent olutasidenib joins ivosidenib among FDA-approved agents targeting IDH1. This oral agent should be taken on an empty stomach and works by inhibiting mutated *IDH1*; R132H, L, S, G, and C proteins lead to decreased 2-hydroxyglutarate levels that are in hyperdrive with *IDH*-mutated leukemia cells. As a result, this restores hematopoietic differentiation and maturation leading to differentiation syndrome. Differentiation syndrome occurs in about 19% of patients with AML treated with IDH inhibitors. Systemic effects may include dyspnea, weight gain, fever, and acute renal failure. Interventions include holding the IDH1 inhibitor and starting treatment with steroids and supportive care.

Olutasidenib requires an *IDH1*-positive result based on an in vitro PCR assay looking to detect single nucleotide variants of five *IDH1* R132 mutations. This is utilized on blood and bone marrow aspirate samples. Clinicians should test for *IDH1* mutations during workup and repeat at progression or relapse. National Comprehensive Cancer Network (NCCN) Guidelines list IDH1 inhibitors in the induction category for patients not receiving intensive induction, as well as in the relapsed/refractory stage.

FGFR2

Fibroblast growth receptor number (FGFR) is a family of receptors 1 through 4 involved in several crucial cell functions such as angiogenesis, differentiation, development, survival, tissue repair and proliferation. The aberrant function is C-terminal truncation, which results in a shortened resulting protein, and then enhanced dimerization that turns on more readily or independent of FGF, the actual growth factor that stimulates that receptor (Figure 1).

In intrahepatic cholangiocarcinoma (iCCA), futibatinib, a tyrosine kinase inhibitor, binds to FGFR and inhibits FGR signaling.

"Think of futibatinib as the duct tape that you put over a light switch you don't want to turn on.

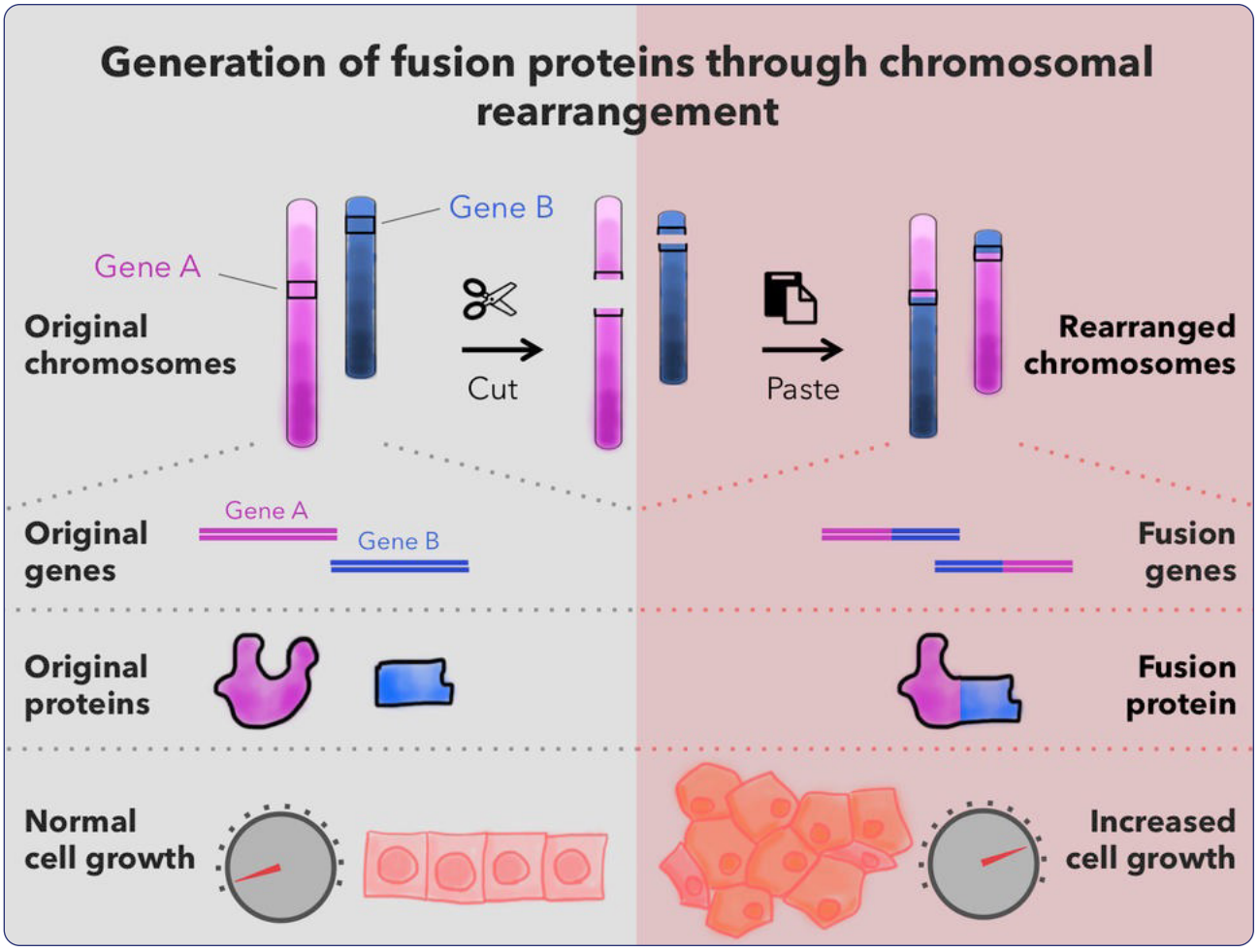

Figure 1. Fusion proteins, which can occur when parts of different chromosomal regions are joined, may drive the development of many cancers in children. Credit: Shannon McArdel, PhD, Harvard University SITN Blog, June 2017. CC BY-NC-SA 4.0.

That is what futibatinib does to that receptor," explained Mr. Guinigundo.

Futibatinib is indicated for the treatment of adult patients with previously treated unresectable, locally advanced or metastatic iCCA harboring *FGFR2* gene fusions or other rearrangements. TAS-120-101 was an open-label, single-arm trial that showed a 42% overall response rate and a duration of response of 9.7 months. Another FGFR tyrosine kinase inhibitor used in this setting is pemigatinib.

Mutations seen in iCCA include *IDH1/2* (20%), *BRAF* (3%–5%), *BAP1*, and *FGFR2* (10%–15%), which is found almost exclusively in small duct iCCA. Forty percent of iCCA tumors have an actionable biomarker. Of note, *IDH1/2* and *FGFR2* fusions in iCCA are mutually exclusive.

KRAS

The Kirsten rat sarcoma (*KRAS*) gene provides instructions for making a protein called K-Ras that is part of the RAS/MAPK signaling pathway.

"Think of it like a faucet. You turn on the faucet, and the signaling is flowing. You turn off the faucet, and the water stops. K-Ras is the protein that activates pathways involved in cell growth, differentiation, and survival," explained Mr. Guinigundo.

GTP is the active version, and it converts then to GDP when it is stimulated with K-Ras, acting as that faucet turning on or off.

"When you have the aberrant function, the feedback loop of GTP and GDP, or 'the faucet,' is stuck on, which can result in oncogenesis," said Mr. Guinigundo.

Adagrasib is an inhibitor of the GTPase family indicated for the treatment of adults with metastatic non–small cell lung cancer who have received one prior therapy. The companion diagnostic is Qiagen therascreen KRAS RGQ PCR, but there are many ways to check for KRAS.

In non–small cell lung cancer, *KRAS* G12C is most prevalent in nonsquamous histology. It accounts for 13% of non–small cell lung cancer driver mutations.

"It is interesting to understand that none of these mutations exist in a vacuum," said Mr. Guinigundo.

For example, a *KRAS* mutation with an *STK11* mutation or a *KRAS* mutation with a *KEAP1* mutation predicts a poor response to PD-L1 or PD-1 inhibitors. However, an anti-CTLA-4 therapy may overcome that. In lung cancer, *KRAS* wild-type disease does not have as good a progression-free survival and overall survival rate as *KRAS* mutated. *TP53* mutation has been shown to be a good prognostic indicator.

BCMA

B-cell maturation antigen (BCMA) is a transmembrane glycoprotein that is a member of the tumor necrosis factor receptor superfamily. In the nonmalignant context, BCMA is expressed on plasmablasts and plasma cells. BCMA binds ligands like APRIL and BAFF to regulate processes such as B-cell proliferation, maturation, survival, and differentiation into plasma cells. However, in the malignant context, there is overexpression and activation of BCMA. This is accomplished via a transcription factor called BLIMP1 that is present on malignant plasma myeloma cells leading to upregulation of nuclear factor-κB pathways, enhanced expression of genes critical for survival, growth, and adhesion. In addition, BCMA is present in plasmacytoid dendritic cells and promotes myeloma plasma cell survival in the bone marrow.

BCMA expression is prevalent in multiple myeloma. "However, there are no known associated patient or laboratory characteristics, and currently the jury is out on whether this biomarker has a prognostic impact," noted Dr. Baek.

Therapies recently approved for this biomarker include the bispecific T-cell engagers teclistamab and elranatamab, along with chimeric antigen receptor T-cell therapy. Teclistamab was approved in October 2022 and elranatamab in August 2023, both for the treatment of relapsed/refractory multiple myeloma in patients who have received at least four prior lines of therapy. These are both subcutaneous agents with step-up dosing regimens.

These agents work by binding not only BCMA but also CD3, which is expressed on the surface of T cells, leading to the activation of T cells, release of various proinflammatory cytokines, and lysis of multiple myeloma cells. Because of this mechanism of action, cytokine release syndrome occurs. Cytokine release syndrome is a systemic inflammatory response to excessive antigen-mediated immune stimulation. Systemic effects of this may include tachypnea, fever, hypotension, or hypoxia. Interventions include holding the BCMA-targeted agent or discontinuing it and starting steroids.

BCMA is typically not tested for outside of the context of clinical trials.

GPRC5D

Continuing the theme of multiple myeloma, another biomarker is G protein–coupled receptor, class C, group 5, member D (GPRC5D). In the nonmalignant context, GPRC5D is present in skin and keratinized tissues. Its physiologic function is currently not well characterized. In the malignant context, there is substantial expression on CD138-positive myeloma cells.

GPRC5D expression is prevalent among multiple myeloma cell lines, including heavily pretreated multiple myeloma. A newly approved target inhibitor is talquetamab, which fits in the same treatment niche as elranatamab and teclistamab in the NCCN Guidelines. In addition to binding the CD3 receptor, it also binds GPRC5D.

"Because of this mechanism of action, we often see cytokine release syndrome and neurologic toxicity with this agent," said Dr. Baek.

Talquetamab does not have a companion diagnostic, and it is not currently recommended to test for GPRC5D as standard of care.

BRCA1/2

The normal function of BReast CAncer Gene (*BRCA*) 1 and 2 is producing proteins that help repair DNA damage.

"I like to use the analogy of the spell checker. BRCA spell checks our DNA to make sure that new copies of the cells are correct," Mr. Guinigundo explained.

BRCA1 and *2* are part of the homologous recombination repair pathway and two of many homologous recombination deficiency (HRR) genes. Loss of BRCA function allows cells to accumulate mutations and genomic rearrangements that lead to cancer.

PARP inhibitors cause single-strand breaks in DNA that accumulate and cause double-strand breaks, which leads to apoptosis. One PARP inhibitor is olaparib, which is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious *BRCA*m metastatic castration-resistant prostate cancer (mCRPC). Any number of hereditary tests or next-generation sequencing on the tumor can find these types of mutations. Another therapy is talazoparib in combination with enzalutamide for patients with *HRR* gene-mutated mCRPC.

MMR

What is the difference between mismatch repair (MMR) and microsatellite instability (MSI)?

"You can have a mismatch repair but not have microsatellite instability. You can have microsatellite instability without having mismatch repair. You should be checking for both because sometimes the indication will be either/or," explained Mr. Guinigundo.

In its normal function, MMR corrects DNA mismatches generated during DNA replication, thereby preventing mutations from becoming permanent in dividing cells. The MMR system is required for cell cycle arrest and/or programmed cell death in response to certain types of DNA damage. It plays a role in the DNA damage response pathway that eliminates severely damaged cells and prevents both mutagenesis in the short term and tumorigenesis in the long term. Defects in MMR increase the spontaneous mutation rate. Microsatellites are regions of repeated DNA that change in length (show instability) when mismatch repair is not working properly (i.e., MSI-H).

"Do you ever have a copy of a form, and you make another copy because you don't have the original anymore? And as you continue making copies, it starts coming out crooked and the lines look all messed up," described Mr. Guinigundo. "That is what is happening here. You get an imperfect gene that's being copied, and now that problem is carrying forward and cancer arises."

Dostarlimab is an anti–PD-1 agent that in a study of 18 patients with locally advanced MMR deficient (dMMR) rectal cancer, 6 months of neoadjuvant treatment led to clinical complete responses in 100% of the study's first 14 patients (Cercek et al., 2022). It is indicated as a single agent for the treatment of adult patients with dMMR recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery.

FDA approval was also granted for pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumors, as determined by an FDA-approved test, who have progressed following prior treatment and have no satisfactory alternative treatment options.

ALK

Anaplastic lymphoma kinase (ALK) is a membrane-bound enzyme with tyrosine kinase activity. It is expressed on a number of different organs. When it functions normally, it undergoes receptor homodimerization, leading to activation of JAK/STAT, PI3K-AKT, mTOR, and MAPK pathways, which leads to the regulation of various processes. *ALK* mutations have been noted in cancers such as non–small cell lung cancer, anaplastic large cell lymphoma, and diffuse large B-cell lymphoma.

"But for inflammatory myofibroblastic tumor (IMT), which is a rare intermediate-grade neoplasm that can be treated with surgery but often requires more targeted therapies, rearrangements in *ALK* make up about half of IMT cases," said Dr. Baek.

Within IMTs, the most frequent *ALK* mutations are clonal rearrangements of *ALK* genes fused to TPM3 or 4. Instead of a homodimerization, there is heterodimerization leading to autophosphorylation activation of ALK and increased cell proliferation in survival. Beyond TPM3 and 4, there are other partners as well, such as CARS and CLTC.

Crizotinib is an FDA-approved targeted inhibitor for *ALK*-positive IMT patients. This oral medication works by inhibiting ALK and other receptor tyrosine kinases, leading to dampening of the activation and dysregulation of the gene expression signaling, and decrease of cell proliferation and survival in *ALK*-positive tumors.

The ALK assay for a patient suspected of having IMT can take anywhere from 3 to 10 days and relies on determining whether there is an ALK locus rearrangement using fluorescence in situ hybridization with a dual color break apart probe. Beyond this, testing may also include next-generation sequencing of biopsy samples, particularly for repeat biopsy samples if there is a concern for relapse.

ESR1

Up to 40% of patients with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2–negative metastatic breast cancer develop an estrogen receptor 1 (*ESR1*) mutation after initial endocrine therapy (Brett et al., 2021). Estrogen receptors are essential for sexual development and reproductive function but also play a role in other tissues such as bone. *ESR1* mutations usually develop 1 to 4 years after patients are on antiendocrine therapy for breast cancer and renders those tumors resistant to antihormonal therapy. It is therefore important to test for an *ESR1* mutation.

In the EMERALD trial, elacestrant (an oral selective ER degrader that binds to ERα) was compared with standard-of-care endocrine monotherapy (fulvestrant, anastrozole, letrozole, or exemestane). Progression-free survival was 3.8 months with elacestrant vs. 1.9 months in the standard-of-care arm, with a hazard ratio of 0.55. ●

Disclosure

Grace Baek has no relevant financial relationships to disclose. Andrew Guinigundo has served as a consultant for Amgen, Jazz, and Pharmacosmos, and on the speakers bureau for Amgen, Astellas, GSK, and Pfizer.

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