Biomarker Pursuit: Keeping Current With Novel Biomarkers in Hematology/Oncology

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Abstract

In the popular biomarker-focused session at JADPRO Live 2022, presenters paired biomarkers with tumor types for which their expression is most commonly used to determine targeted therapy, identified key assays used to measure common biomarkers, and reviewed recommendations and guidelines for biomarker testing.

Revolutionizing the way we diagnose, monitor, and treat cancer, biomarkers have emerged as a powerful tool to tailor therapy and improve outcomes for patients with cancer. In a session called "Biomarker Pursuit" during JADPRO Live 2022, Beth Faiman, PhD, MSN, APRN-BC, AOCN®, BMTCN, FAAN, FAPO, of Cleveland Clinic Taussig Cancer Center, Sandra E. Kurtin, PhD, ANP-C, AOCN®, FAPO, of The University of Arizona Cancer Center, and Rasheda Persinger, MSN, AGNP-C, AOCNP®, of Sibley Cancer Center, shared information about several key biomarkers associated with recent FDA-approved therapies, testing recommendations, and side effects of targeted therapies that advanced practitioners should be aware of.

HUMAN EPIDERMAL GROWTH FACTOR 2 (*HER2/ERBB2*)

As Ms. Persinger explained, the *HER2/ErbB2* gene is a member of the ErbB receptor tyrosine kinase family. Its normal function is to activate downstream signaling through the PI3K-AKT and MEK-ERK pathways. However, when the *HER2* gene is mutated, it leads to overactivation of these pathways, resulting in increased cell proliferation and resistance to apoptosis.

Fam-trastuzumab deruxtecan (Enhertu) is a drug that was approved by the US Food and Drug Administration (FDA) in August 2022 for the treatment of adult patients with unresectable or metastatic non–small cell lung cancer whose tumor harbors *HER2/ErbB2*

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mutations as detected by an FDA-approved test. The drug is indicated as a second-line therapy prior to other systemic therapy. The mechanism of action of fam-trastuzumab deruxtecan is a combination of a HER2-directed monoclonal antibody with a topoisomerase inhibitor payload. The topoisomerase is bound by a cleavable linker, and the HER2-directed monoclonal antibody provides targeted delivery of the cytotoxic agent. This leads to high-potency DNA damage and cell death. The FDA-approved testing for the *HER2/ErbB2* mutation can be done using tissue or liquid plasma if tissue is not available.

This mutation occurs in 2% to 4% of non–small cell lung cancers and can occur in exon 18 through 21 of the tyrosine kinase domain, extracellular region, and transmembrane region. The insertion exon 20 is different from *EGFR* exon 20 mutation, and *HER2* mutation is different from HER2 overexpression or amplification. Additionally, a 28% high propensity for brain metastases while on treatment compared to *KRAS* and *EGFR* mutations has been found.

JANUS KINASE 1 (*JAK1*)

The JAK-STAT pathway is a signaling pathway involved in myeloproliferative neoplasms, including myelofibrosis. The JAK-STAT pathway is activated by specific kinases called JAKs, one of which is *JAK1* (Schischlik & Kralovics, 2017). The activated JAKs and other mutations, such as *CALR* and *MPL*, upregulate receptors on myeloid cell lines, leading to an excess of cells in these disorders. Specifically, *JAK2* upregulates erythropoietin, thrombopoietin, and granulocyte colony-stimulating factor receptors, while *MPL* upregulates thrombopoietin and regulates megakaryopoiesis and *CALR* binds to the thrombopoietin receptor. The FLT3 pathway also cooperates with the JAK-STAT pathway and is expressed on immature hematopoietic cells, said Dr. Kurtin.

Pacritinib (Vonjo), a novel, low–molecular weight selective inhibitor of *JAK2* and *FLT3*, was granted accelerated approval by the FDA for the treatment of adults with intermediate or high-risk primary or secondary myelofibrosis with thrombocytopenia (Lamb, 2022). It is supplied in 100 mg capsules. The recommended dose is 200 mg twice daily.

As Dr. Kurtin explained, pacritinib works by inhibiting *JAK2*, *FLT3*, and *IRAK1* while not inhibiting *JAK1*, which helps to limit the effect on thrombocytopenia and immunosuppression. However, pacritinib is associated with potentially serious side effects, including anemia, thrombocytopenia, pneumonia, and cardiac failure.

LYMPHOCYTE-ACTIVATION GENE 3 PROTEIN

LAG-3 is a membrane protein that acts as an inhibitory immune checkpoint on tumor-infiltrating lymphocytes and negatively regulates T-cell function (Goldberg & Drake, 2011). When LAG-3 is upregulated, said Ms. Persinger, it negatively impacts T-cell proliferation and cytokine secretion, which can decrease the body's ability to fight tumors (Nguyen & Ohashi, 2015).

In contrast, the normal function of PD-1 is also an inhibitory immune checkpoint, but it is expressed on T-cell natural killer cells, B cells, and some myeloid cells, and limits and negatively regulates T-cell function. However, when PD-1 is upregulated, it also decreases the body's ability to fight tumors. According to Ms. Persinger, blocking the LAG-3 pathway or binding to the PD-1 receptor can promote more effective antitumor immunity.

The combination of nivolumab and relatlimab (Opdualag), which target the PD-1 and LAG-3 checkpoint, respectively, was approved by the FDA in March 2022 for unresectable or metastatic melanoma (Tawbi et al., 2022).

"The mechanism of action creates a dual antitumor synergistic effect," said Ms. Persinger, who noted that LAG-3 and PD-L1 expression are tested by immunohistochemistry tissue with an assay.

PYRUVATE KINASE ACTIVATOR

Pyruvate kinase deficiency (PKD), a rare genetic disorder that affects red blood cells, is caused by mutations in the L and R isozymes of pyruvate kinase, which are encoded by the *PKLR* gene located on chromosome 1q21. There can be up to 300 different mutations in this gene, and most patients have one or more missense mutations, which leads to PK deficiency. This in turn leads to a reduction in ATP, which is essential for the metabolic machinery required for aerobic metabolism and membrane integrity in red blood cells.

Pyruvate kinase deficiency can be diagnosed by a combination of tests that include G6PD, CD55, CD59 for paroxysmal nocturnal hemoglobinopathy, hemoglobin electrophoresis, PK enzyme activity, and PKR (Fattizzo et al., 2022). There is a genetic testing panel called Anemia ID that can be used to order all these tests in an electronic medical record. The main clinical manifestations of PKD are lifelong hemolysis and iron overload (Grace et al., 2018).

Mitapivat (Pyrukynd) is an oral small-molecule, allosteric activator of red cell pyruvate kinase that is designed to activate wild type and a variety of mutant red cell pyruvate kinase enzymes to increase ATP and is specifically indicated for the treatment of PKD (Al-Samkari & van Beers, 2021).

"The drug is available in a variety of tablets, and the dosing must be gradually increased to avoid acute hemolysis," said Dr. Kurtin, who noted that studies are also being conducted to explore the potential use of mitapivat in other chronic hemolytic diseases such as thalassemia and sickle cell anemia.

CYTOKINE AND COSTIMULATORY PATHWAYS INVOLVED IN ACUTE GVHD

As Dr. Kurtin explained, acute graft-vs.-host disease (GvHD) occurs in multiple phases, beginning with tissue damage and the release of inflammatory cytokines, which activate the immune system (Hill & Koyama, 2020). However, the problem with GvHD is that the activated immune system begins to attack the host, rather than just the invading cells.

Abatacept (Orencia) is a recombinant fusion protein that blocks co-stimulatory CD28-CD80/86 interactions, thereby inhibiting T-cell activation and proliferation and thus preventing the graft-vs.-host reaction (Martinez-Cibrian et al., 2021).

"This drug was already approved for autoimmune disorders and is now approved for prophylaxis of acute GvHD in combination with a calcineurin inhibitor and methotrexate," said Dr. Kurtin, who noted that abatacept is given intravenously over a series of days. Potentially serious side effects include atypical infections, hypersensitivity, exacerbation of chronic obstructive pulmonary disease, and immunosuppression.

BRAF V600E

The *BRAF* V600E mutation, which is a missense mutation in codon 600 of exon 15 (V600E) of the *BRAF* gene, occurs in multiple cancers and leads to the overactivation of the MAPK signaling pathway. This overactivation increases cell proliferation and resistance to apoptosis.

Trametinib (Mekinist), a MEK1 and MEK2 inhibitor, and dabrafenib (Tafinlar), a BRAF inhibitor, were approved by the FDA in June 2022 to treat patients with unresectable metastatic solid tumors with *BRAF* V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.

According to Ms. Persinger, dabrafenib and trametinib work by targeting the BRAF kinase and interfering with the MAPK signaling pathway. Testing for this mutation is FDA approved for tissue and/or liquid plasma. Although more commonly found in melanoma, *BRA*F V600E mutation also occurs in other forms of cancer.

The *BRAF* V600E mutation is the most common type of *BRAF* mutation, said Ms. Persinger, accounting for up to 90% of *BRAF*-mutant cancers. Dabrafenib and trametinib are FDA approved for treating *BRAF* V600E mutations but not for *BRAF* wild type.

ISOCITRATE DEHYDROGENASE 1

As Dr. Kurtin explained, reprogramming of cellular metabolism is a key fundamental characteristic of cancer. Mutations of *IDH1* and *IDH2* result in the conversion of alpha-ketoglutaric acid to an oncometabolite, D-2-hydroxyglutarate, which causes epigenetic regulation outside of the gene and hypermethylation. Somatic mutations in *IDH1* and *IDH2* are associated with leukemogenic development and progression of myeloid malignancies such as acute myeloid leukemia (AML), gliomas, cholangiocarcinoma, and chondrosarcoma. Although not very common in AML, *IDH1* mutations can be detected by next-generation sequencing on bone marrow.

Ivosidenib (Tibsovo) is an oral targeted small-molecule inhibitor of mutant *IDH,* which can be administered either in combination with

azacitidine or as a monotherapy. It has a category 1 recommendation by the National Comprehensive Cancer Network for patients with *IDH1* mutation as detected by an FDA-approved test. Potential serious side effects include differentiation syndrome, which is rare but can be well treated, leukocytosis, and QT prolongation. According to Dr. Kurtin, there may also be drug-drug interactions due to it being an oral compound.

BISPECIFIC GP100 PEPTIDE HLA-DIRECTED CD3 T-CELL ENGAGER

The glycoprotein called gp100 is a transmembrane-bound protein expressed in melanocytes, pigmented cells in the retina, and most malignant melanomas. gp100-derived peptides are targets of the antimelanoma cytotoxic T cells and T helper cells, making it a potential target for immunotherapy.

Tebentafusp-tebn (Kimmtrak) is an anti-gp100 immune monoclonal T-cell receptor that has been approved for HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. According to Ms. Persinger, tebentafusp works by binding to the HLA marker on uveal melanoma cells and activating CD3, which then releases inflammatory cytokines and cytolytic proteins, resulting in the direct lysis of tumor cells. Uveal melanoma is a rare subtype that accounts for less than 5% of melanoma cases and usually has a poor prognosis, occurring mainly in Caucasians. ●

Disclosure

Dr. Kurtin has served as a consultant for Agios, Amgen, AstraZeneca, Bristol Myers Squibb, Incyte, and Takeda. Ms. Persinger has served on the speakers bureaus for AstraZeneca and Guardant Health and as an advisor for AstraZeneca. Dr. Faiman has no relevant financial relationships to disclose.

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