

Biomarker Jeopardy

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

In the popular Biomarker Jeopardy session, Sandra E. Kurtin, PhD, ANP-C, AOCN[®], Alyssa Henglefelt, PharmD, BCOP, and Haleigh Mistry, MS, PA-C, 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 discussed guidelines for biomarker testing.

Biomarker expression is playing an increasingly important role with the continued approval of a growing number of targeted therapies. In a session called “Biomarker Jeopardy” during JADPRO Live Virtual 2021, Alyssa Henglefelt, PharmD, BCOP, HonorHealth – Virginia G. Piper Cancer Care Network, and Haleigh Mistry, MS, PA-C, The University of Texas MD Anderson Cancer Center, paired specific biomarkers with the tumor type for which their expression is used to determine targeted therapy, and Sandra E. Kurtin, PhD, ANP-C, AOCN[®], The University of Arizona Cancer Center, shared clinical pearls for each targeted therapy.

CD19 ANTIGEN AND ADCs

As Ms. Mistry explained, CD19 is an attractive therapeutic target for B-cell lymphomas because malignant B cells have high CD19 expression, which is currently preserved after treatment with standard chemoim-

munotherapy regimens (Chu et al., 2021). The CD19 antigen is expressed during B-cell development only after B-lineage commitment and is thus not present on hematopoietic stem cells. CD19 expression is lost during terminal plasma cell differentiation but maintained in hematologic B-cell malignancies (Chu et al., 2021). Antibody-drug conjugates (ADCs) are a promising class of immunotherapies with the potential to specifically target tumor cells and ameliorate the therapeutic index of cytotoxic drugs. They comprise monoclonal antibodies, cytotoxic payloads with inherent antitumor activity, and specialized linkers connecting the two.

In April 2021, the FDA approved the CD19 antibody-drug conjugate loncastuximab tesirine (Zynlonta) for adult patients with relapsed or refractory large B-cell lymphoma after two or more systemic lines of therapy. In clinical trials, loncastuximab demonstrated an overall response rate of 42% and a short median time-to-first

response of 6 weeks (Caimi et al., 2021). Encouraging responses were also seen in patients with high-risk characteristics, said Ms. Mistry, who noted pulmonary and peripheral edema as well extreme sensitivity to sun as common side effects.

According to Dr. Kurtin, sequencing of CD19-directed therapies will require additional study. In the pivotal study of loncastuximab, 15 out of 145 of patients went on to receive CAR-T and 7 (47%) had a response, including 6 (40%) with a complete response.

EGFR MUTATIONS: EXON 20 INSERTIONS

EGFR, or epidermal growth factor receptor, is a well-known member of the receptor tyrosine kinase (RTK) family. As Dr. Henglefelt explained, oncogenic transformation leads to constitutive activation to promote tumor cell proliferation and survival. In non-small cell lung cancer (NSCLC), *EGFR* mutations are one of the most common and druggable targets for treatment, and there are several locations where mutations may occur in the gene. Thus far, exon 20 insertions have been shown to be the third most common *EGFR* aberration found in NSCLC (Arcila et al., 2013).

The FDA approval of the first exon 20 insertion targeting drug, amivantamab (Rybrevant), requires the presence of this mutation for the treatment of advanced/metastatic NSCLC. According to Dr. Henglefelt, these abnormalities are best sequenced at the DNA level using polymerase chain reaction (PCR) or next-generation sequencing (NGS) testing modalities, like in Guardant360 CDx, which was approved by the FDA as the companion diagnostic for amivantamab. The use of *EGFR* testing diagnosis, in addition to other targetable mutations, is supported by consensus guidelines for all patients with stage IB or later disease.

“*EGFR* is commonly expressed in NSCLC,” said Dr. Kurtin, who noted that 64% of patients with NSCLC have these oncogenic driver mutations (Remon et al., 2020). “*EGFR* exon 20 insertion mutations, however, occur in only 2% to 3% of all NSCLC cases. These mutations are found more often in women, nonsmokers, and those with adenocarcinoma histology and confer inferior prognosis.”

AMINOPEPTIDASE AND PEPTIDE-DRUG CONJUGATE

Amionopeptidases are ZN2-dependent metalloproteinases that remove amino acids at the N-terminal position from oligopeptides and have been associated with multiple tumorigenic processes, such as proliferation, apoptosis, differentiation, angiogenesis, and motility.

Melphalan flufenamide (Pepaxto) is a first-in-class peptide-drug conjugate that targets aminopeptidases and rapidly releases alkylating agents inside cancer cells. Melphalan was indicated for relapsed or refractory multiple myeloma, and was the first triple-class refractory drug that was FDA approved (Mateo et al., 2020). Melphalan required failure of at least four prior lines of therapy, and patients had to have been disease refractory to at least one proteasome inhibitor, one immunomodulator agent, and one CD38-directed monoclonal antibody.

As Dr. Kurtin reported, however, data from the phase III OCEAN trial of melphalan flufenamide and low-dose dexamethasone compared to pomalidomide and low-dose dexamethasone in patients showed a higher mortality rate among patients treated with the melphalan flufenamide arm (Schjesvold et al., 2020). It was withdrawn from the US market in October 2021 (The ASCO Post, 2021).

VEGFR

Vascular endothelial growth factor receptors (VEGFR), like EGFR, are members of the RTK family. Overexpression and overactivation of these transmembrane proteins play a role in several tumor types, including renal cell carcinoma (RCC).

The FDA recently approved tivozanib (Fotivda), a VEGFR inhibitor, as subsequent therapy for clear cell RCC (FDA, 2021). Dr. Henglefelt noted that approval was not contingent upon a predictive biomarker or a companion diagnostic.

In clinical trials, reported adverse effects were in line with other VEGFR inhibitors already on the market, said Dr. Henglefelt. Common adverse effects included fatigue, hypertension, and stomatitis, among others (AVEO Pharmaceuticals, Inc., 2021). Examples of serious class effects, which are also labeled warnings by the manufacturer, include hypertensive crisis, thromboembolic events,

hemorrhagic events, proteinuria, and impaired wound healing.

“As we’ve come to know, many of these drugs [targeting RTK family transmembrane protein receptors] have off-target effects,” said Dr. Kurtin. “What’s unique about tivozanib is that it’s highly specific for VEGFR 1 through 3 with minimal residual effects on c-KIT and PDGFR-beta, which largely explains the toxicity profile of other multikinase inhibitors that have greater off-target effects and tend to be associated with more adverse events.”

B-CELL MATURATION ANTIGEN

An antigen with highly selective expression in malignant plasma cells, BCMA is a protein found on the surface of multiple myeloma cells in all patients with multiple myeloma. BCMA is an important target in multiple myeloma, said Ms. Mistry, because it is expressed in both normal and malignant plasma cells. An antibody-drug conjugate is an attractive therapeutic option because it enhances targeted killing of tumors while sparing normal tissue, which helps to minimize toxicity (Yu et al., 2020).

Belantamab mafodotin (Blenrep), a BCMA-directed antibody-drug conjugate, was approved by the FDA in August 2020 for relapsed or refractory multiple myeloma. Although relatively well-tolerated, said Ms. Mistry, ocular toxicity was a major off-target effect. Patients receiving belantamab should be seen by an ophthalmologist prior to and after receiving the drug.

“The belantamab mafodotin is a potent antimitotic agent that inhibits tubulin polymerization, making this an ideal payload, and the protease-resistant non-cleavable linker provides a stable option for delivery of that payload, making this drug behave in a more predictable way,” said Dr. Kurtin.

CDK4/6

Cyclin-dependent kinase (CDK) 4 and 6 play a crucial role in cell cycle regulation at the G1 to S phase transition. Under malignant conditions, said Dr. Henglefelt, tumor cells take advantage of this activity for proliferation and survival. Under the right conditions, however, scientists have learned how to leverage CDK4/6 inhibition to exert myeloprotective effects for hematopoietic stem and progenitor cells or HSPCs (Figure 1).

The underlying principle is based on whether a particular tumor type is dependent upon or independent from CDK 4 and 6 activity. Dependent cancers can be targeted for antineoplastic activity via CDK 4 and 6 inhibition (such as breast cancer), said Dr. Henglefelt, but independent cancers are less likely to be affected by this inhibition, which “creates a window for the protection of healthy cells.”

Trilaciclib (Cosela), a CDK4/6 inhibitor with a short half-life, is approved for supportive care in patients with extensive-stage small cell lung cancer (SCLC) receiving platinum/etoposide- or topotecan-containing regimens. Per consensus guidelines, trilaciclib may be used as a prophylactic option to decrease the incidence of chemotherapy-induced myelosuppression when administering these regimens for the treatment of extensive-stage SCLC.

PI3K-DELTA

PI3 kinase (PI3K)-delta is an intracellular signal transduction pathway that helps to promote metabolism, proliferation, cell survival, growth, and angiogenesis in response to extracellular signals. The aberrant function of PI3K-delta is cell survival of malignant cells with tumor overgrowth (Young & Staudt, 2013). PI3K signaling is also prominent in many of the B-cell malignancies.

“PI3K is a downstream intermediary in the BCR pathway, and it’s essential for the BCR-dependent B-cell survival,” said Ms. Mistry. “That’s why it’s an attractive target.”

Umbralisib (Ukoniq) is the first FDA approved PI3K-delta and CK1-epsilon inhibitor. It was approved in February of 2021 for patients with relapsed or refractory marginal zone lymphomas who have failed at least one prior anti-CD20-based regimen and for patients with relapsed or refractory follicular lymphoma who have received more than 3 lines of systemic therapy (Burris et al., 2018).

According to Ms. Mistry, the chemical structure of umbralisib differs from earlier PI3K-delta inhibitors such as idelalisib and duvelisib, which leads to an improved safety profile. Umbralisib (given intravenously) is associated with elevated liver enzymes, said Ms. Mistry, but infections such as pneumonitis and colitis occur less frequently than with idelalisib (oral) or duvelisib.

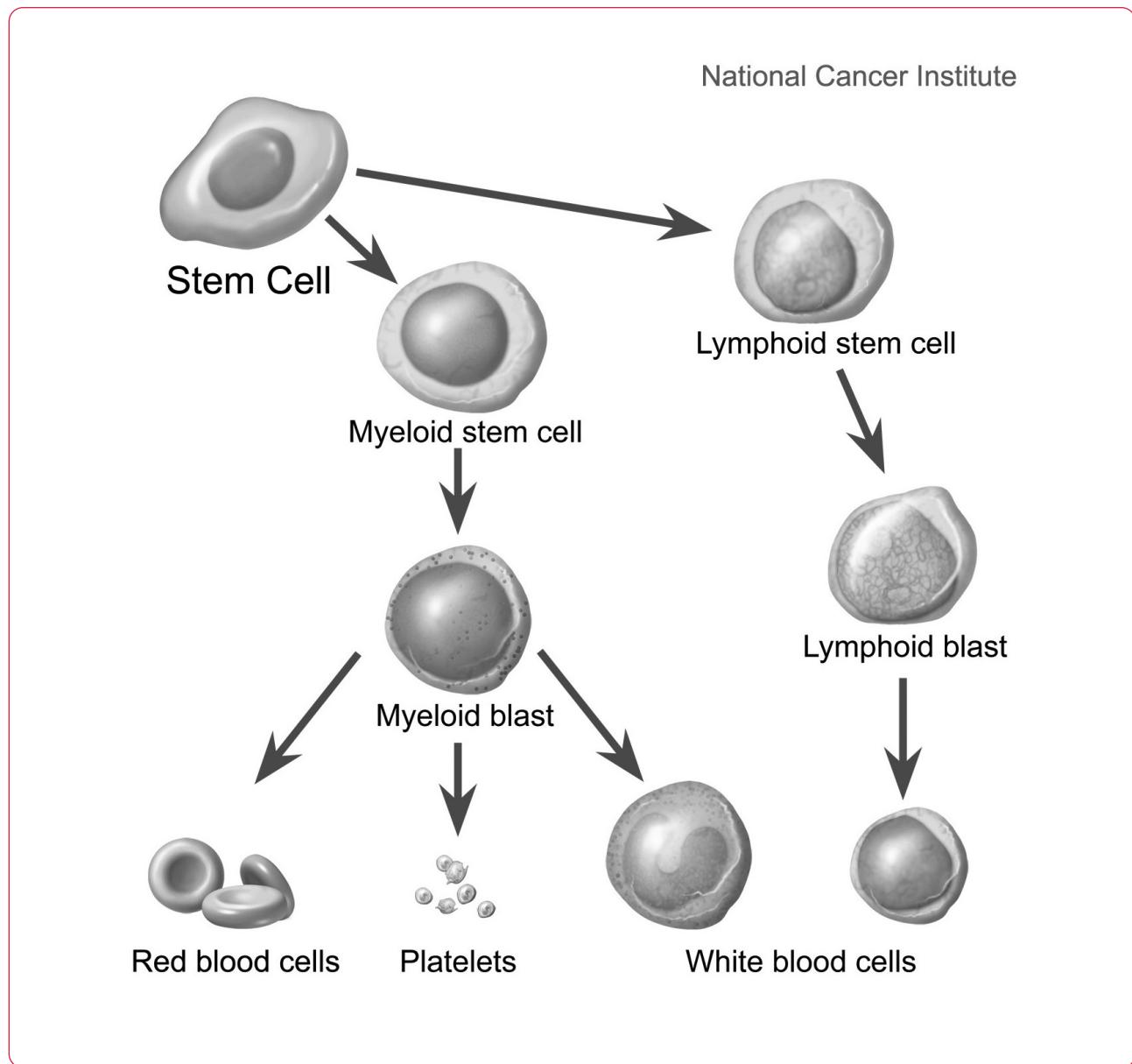


Figure 1. Stem cells maturing into one of three types of mature blood cells: red blood cells, platelets, and white blood cells. Precursor cells are also shown: stem cells, myeloid blasts, lymphoid stem cells, and lymphoid blasts. Stem Cells Maturing Into Blood Cells and Precursor Cells. Created by Alan Hoofring. Visuals Online. NIH: National Cancer Institute. Available at: <https://visualsonline.cancer.gov/>.

"This is a great example of one pathway with multiple isoforms where you see a big difference in the toxicity profile across the same class of drugs based on their target," said Dr. Kurtin. "The combination with CK1-epsilon inhibitor also adds an element of efficacy."

KRAS MUTATIONS

The *KRAS* gene encodes for the Kirsten rat sarcoma (KRAS) GTPase, a protein that contributes

to abnormal intracellular signaling of the RAS/RAF/MAP kinase pathway. Like *EGFR*, oncogenic transformation leads to constitutive activation for tumor survival, said Dr. Henglefelt, who noted that mutations in this family are estimated to occur in up to one third of all cancers (National Cancer Institute, 2021). In fact, *KRAS* mutations are believed to be the most prominent oncogenic driver of NSCLC, with the G12C variant accounting for approximately 40% of all *KRAS*-mutated

cases (Addeo et al., 2021; Hartley & Yi, 2021). Despite being a known oncogenic driver, however, Dr. Henglefelt noted that *RAS* mutations (the *RAS* family of oncogenes includes *KRAS*, *NRAS*, and *HRAS*) have been notoriously difficult to target.

“The FDA approval of sotorasib (Lumakras) as the first *KRAS* inhibitor was therefore a truly exciting breakthrough in oncology,” said Dr. Henglefelt.

Like *EGFR* exon 20 insertions, DNA-based testing such as PCR and NGS is preferred for the detection of *KRAS* mutations. As a predictive biomarker, *KRAS* testing is recommended by multiple consensus guidelines, particularly in advanced or metastatic NSCLC but also metastatic colorectal cancer, to guide treatment decisions.

As the first-in-class *KRAS* inhibitor, Dr. Henglefelt noted that the toxicity profile of sotorasib resembles other targeted oral therapies for NSCLC. In the pivotal CodeBreaK 100 trial, common adverse effects included nausea and diarrhea as well as fatigue and musculoskeletal pains (Amgen Inc, 2021). More severe effects, which are also labeled warnings, include hepatotoxicity, interstitial lung disease, and pneumonitis.

“We understand that *KRAS* proteins regenerate every 24 to 48 hours, thus requiring continuous suppression for therapeutic benefit, so this is a great example of understanding mechanism of action and targeted pathways and translating that into how we administer drugs for therapeutic benefit,” said Dr. Kurtin. “This is a very important new compound.”

COMPLEMENT COMPONENT 3

Complement Component 3 (C3) controls both C3b-mediated extravascular hemolysis and terminal complement-mediated intravascular hemolysis. Paroxysmal nocturnal hemoglobinuria (PNH) is a rare complement driven non-immune hemolytic anemia that is driven by complement inhibitors on CD55 and CD59 that converge at C3 convertase.

Pegcetacoplan (Empaveli) is a C3-based therapeutic combining APL-2 and pegcetacoplan. APL-2 is a compstatin that selectively binds to C3 inhibiting this cleavage by C3 convertases. It uses a PEG linker and serves as a molecular bridge to space apart these two moieties of the APL-1 peptide conjugated to either end of the linker (Mas-

telos et al., 2021).

“Pegcetacoplan acts proximally in the complement cascade, controlling both C3b-mediated extravascular hemolysis and terminal complement-mediated intravascular hemolysis, blocking all of that downstream activity,” said Dr. Kurtin.

Disclosure

Dr. Kurtin has served as a consultant for AbbVie, Amgen, BMS, Celgene, GSK, and Incyte. Ms. Misstry reported financial relationships with ADC Therapeutics, Bayer, AstraZeneca, and Genentech/Roche. Dr. Henglefelt had no conflicts of interest to disclose. ●

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