Biomarker Jeopardy

PRESENTED BY SANDRA E. KURTIN, PhD, ANP-C, AOCN®, ALYSSA HENGLEFELT, PharmD, BCOP, and ALLYSON PRICE, MPAS, PA-C

Abstract

The popular Biomarker Jeopardy session returned this year at JADPRO Live 2020. Sandra E. Kurtin, PhD, ANP-C, AOCN®, led the session, and was joined by Alyssa Henglefelt, PharmD, BCOP, and Allyson Price, PA-C. Using a Jeopardy format, they identified specific biomarkers while discussing targeted therapies and class effects APs should be aware of.

As oncology continues to move towards precision medicine with targeted therapies, biomarker expression is playing an increasingly important role. In a session led by Sandra E. Kurtin, PhD, ANP-C, AOCN®, during JADPRO Live Virtual 2020, Alyssa Henglefelt, PharmD, BCOP, HonorHealth, Virginia G. Piper Cancer Care Network, and Allyson Price, PA-C, MD Anderson Cancer Center, paired specific biomarkers with the tumor type for which their expression is most commonly used to determine targeted therapy.

NUCLEOSIDE METABOLIC INHIBITOR

As Ms. Price explained, nucleoside metabolic inhibitors work by inhibiting DNA methyltransferase with the unique ability to increase systemic exposure through bioavailability. The normal function of DNA methylation is a process of silencing or suppression that prevents overexpression of certain types of genes. In aberrant functions, however, there is oversuppression leading to hypermethylation, transcriptional silencing, and eventually, tumor development.

In July 2020, the FDA approved oral decitabine plus cedazuridine (Inqovi) based on evidence from two clinical trials of 213 patients with myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML). The trials were conducted at 51 sites in the United States and Canada. In the first trial, 18% of patients treated with cedazuridine experienced complete response (morphologic improvement in bone marrow and hematologic complete or partial recovering in counts) that lasted about 9 months. In the second trial, 21% of patients treated with cedazuridine experienced complete response that lasted about 7.5 months.

“As advanced practitioners, it’s really important for us to have oral options now since we know that there is going to be continuity of this treatment,” said Ms. Price.

In acute myeloid leukemia (AML), these drugs act at the DNA level to restore normal gene expression of-
ten “turned off” by malignant cells. Oral azacitidine (Vidaza) was approved in September 2020 as maintenance for AML for patients in first complete response. Data from the phase III trial showed that azacitidine extended patients’ lives by nearly 10 months compared with placebo (24.7 months vs. 14.8 months with placebo) and resulted in a 31% reduction in the risk of death (Wei et al., 2020).

**MET EXON 14 SKIP MUTATION**

Mesenchymal epithelial transition (MET) is a receptor tyrosine kinase that functions as a transmembrane protein and provides an option for the targeted treatment of non–small cell lung cancer (NSCLC). As Dr. Henglefelt explained, aberrant signaling from this transmembrane protein tends to lead to oncogenic transformation, thereby driving tumor growth and survival.

In the case of MET specifically, said Dr. Henglefelt, researchers have identified druggable targets for patients with MET exon 14 skip mutations (METex14), which are the result of aberrant intron splicing during the formation of mature messenger RNA. MET amplification is also being researched as a prospective therapeutic target. Overall, it is estimated that approximately 3% to 4% of patients with NSCLC harbor MET exon 14 skip mutations.

Capmatinib (Tabrecta), a selective MET kinase inhibitor, was approved for the treatment of metastatic NSCLC harboring MET exon 14 skip mutations based on data from the GEOMETRY mono-1 trial.

“As a class, this group of inhibitors has been shown to produce gastrointestinal symptoms and peripheral edema,” said Dr. Henglefelt (Wolf et al., 2020). Based on its selectivity, capmatinib was also uniquely shown to create transient increases in serum creatinine. This phenomenon is generally reversible and is attributed to off-target renal transport inhibition with this drug, said Dr. Henglefelt.

**CD19**

As Ms. Price reported, CD19 is a surface protein expressed early in B-cell maturation (Table 1). CD19 is one of the most reliable surface biomarker for B cells, said Ms. Price, who noted that it is expressed from pre-B cells until the terminal differentiation to plasma cells. Interestingly, CD19 is maintained in B-cell malignancies.

Tafasitamab-cxix (Monjuvi), a CD19 antibody, was approved in July 2020 for combination with lenalidomide in adults with relapsed refractory diffuse large B-cell lymphoma who may not be candidates for stem cell transplant.

“This is important because we know that approximately 40% of these patients are refractory to front-line chemotherapies and may not respond to normal cytotoxic therapy,” said Ms. Price. “Because of the expression of CD19, we can treat these patients with antibodies earlier on when B cells are first starting to developing. It also gives us treatment options in a patient population that has been difficult to treat.”

Studies of tafasitamab showed an overall response of 55% with a partial response of 18%.

**FIBROBLAST GROWTH FACTOR RECEPTORS**

The normal functions of fibroblast growth factor receptors (FGFR) include cellular proliferation, survival, migration, and differentiation. Just like with MET, however, alterations that produce aberrant signaling can ultimately lead to enhanced tumor cell proliferation, migration, and angiogenesis. Abnormalities have been identified within multiple members of the FGFR family of proteins (FGFR1 to FGFR4) and across multiple tumor types.

According to Dr. Henglefelt, FGFR2 fusions and rearrangements are the most common type of FGFR abnormality identified in patients with intrahepatic cholangiocarcinoma (10%–16% of all patients).

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**Table 1. CD19 Normal and Aberrant Function**

| Normal function | Normal B cells |
|-----------------|----------------|
| Aberrant function | Neoplastic B cells |

- Recruits signaling proteins to membrane and works with C19/CD21 complex to decrease threshold for B-cell receptor signaling pathways
- Vital in B-cell development
- Preserved expression in B-cell malignancies after differentiation; earlier markers of B cells—eliminate earlier
- Used in MRD setting (compared to CD20 expressed later)
Subsequent research and development of these aberrations ultimately led to the approval of pemigatinib (Pemazyre), a selective inhibitor of FGFR1, FGFR2, and FGFR3 (Facchinetti et al., 2020), as a subsequent treatment option for patients with advanced and metastatic cholangiocarcinoma harboring FGFR2 fusions or rearrangements.

As Dr. Henglefelt reported, class effects of these drugs include hyperphosphatemia, nail changes, and ocular disorders (Abou-Alfa et al., 2020). The hyperphosphatemia is thought to be related to FGFR1 inhibition, as this particular receptor demonstrates a known role in phosphate homeostasis.

**TROP2**

Trophoblast cell-surface antigen 2 (TROP2) is a transmembrane protein overexpressed in a wide variety of tumor types, including breast cancer (Table 2). Sacituzumab govitecan-hziy (Trodelvy), a TROP2 monoclonal antibody conjugated with SN-38, was granted accelerated approval by the FDA for metastatic triple-negative breast cancer based on the results of a basket trial (IMMU-132). The drug is also being explored in several other solid epithelial cancers (Zaman et al., 2019).

According to Dr. Henglefelt, the adverse event profile is similar to other monoclonal antibodies in that infusion reactions are possible. The SN-38 linker (an active metabolite of irinotecan) can also lead to nausea, vomiting, diarrhea, and myelosuppression. However, the incidence of severe adverse events appears to be lower with this drug than with conventional irinotecan, “which is really great for our patients,” said Dr. Henglefelt.

**SMAD2/3 SIGNALING**

In MDS/CMML, overactivation of SMAD2/3 signaling pathways causes anemia due to impaired erythroid maturation. Luspatercept (Reblozyl) was approved in April 2020 for patients with low- to intermediate-risk MDS/CMML with two or more red blood cell units over 8 weeks based on data from the MEDALIST trial, which showed an overall improvement of transfusion needs (Feixnaux et al., 2020). As Ms. Price reported, 38% of patients receiving luspatercept achieved four-unit or greater reduction of transfusion over an 8-week period, or they had an increase in their hemoglobin of about 1.5 over that 8-week period. This differs from erythroid-stimulating agents and is the first erythroid maturation agent.

“This is exciting because we are seeing a different target that is not dealing with DNA methylation but rather with maturation of erythrocytes,” said Ms. Price.

**PARP ENZYMES**

Overexpression of poly(ADP-ribose) polymerase or PARP enzymes leads to accumulation of mutations and malignant transformations. As Dr. Henglefelt explained, however, research has not been focused specifically on PARP enzymes themselves, but rather on other portions of the DNA repair process that make tumors susceptible to PARP inhibition (e.g., tumor cells with BRCA1 and BRCA2 mutations and others related to homologous recombination repair [HRR] and deficiency [HRD]).

Niraparib (Zejula), a PARP1 and PARP2 inhibitor, was originally indicated as monotherapy for HRD-positive, recurrent ovarian cancer but was also approved recently as maintenance therapy after platinum-based treatment in the first-line setting, regardless of HRD status, based on the PRIMA trial (González-Martín et al., 2019).

Thus far, class effects are fairly consistent in terms of myelosuppression, gastrointestinal toxicity (e.g., nausea), and fatigue, but niraparib seems to be associated with a greater incidence of thrombocytopenia compared with other PARP inhibitors.

**METHYLTRANSFERASE INHIBITOR**

When aberrant, the histone methyltransferase pathway can lead to transcriptional changes resulting in unregulated cell proliferation in both solid and liquid tumors. In particular, EZH2 gain-of-function mutations have been seen in hemato-

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**Table 2. TROP2 Targeting**

| Normal function | Aberrant function |
|-----------------|-------------------|
| Proliferation and self-renewal regulation (beta-catenin) | Tumor growth, migration, and invasion |
| Transmembrane glycoprotein → intracellular calcium signaling | TROP2 upregulated in many cancers, particularly solid epithelial malignancies |
| Implicated in MAPK, Raf, and NF-κB pathways | |

*Note. Information from Hope et al. (2020); Zaman et al. (2019).*
logic malignancies, and overexpression has been detected in solid tumors.

According to Dr. Henglefelt, the activity of EZH2 inhibitors in epithelioid sarcoma, a rare type of soft tissue sarcoma, is unique. Tazemetostat (Tazverik) was first granted an accelerated approval in January 2020 for patients with locally advanced or metastatic epithelioid sarcoma, and then was also approved in June 2020 for patients with relapsed/refractory EZH2-positive follicular lymphoma who had received two prior treatments. Ms. Price reported that the follicular lymphoma approval was based on data that showed median duration of overall response of 10.9 months (Morschhauser et al., 2020).

“The availability of this oral medication definitely gives us more options for patients with relapsed/refractory disease,” said Ms. Price.

Disclosure
Dr. Kurtin has acted as a consultant for Celgene and Incyte. Dr. Henglefelt and Ms. Price had no conflicts of interest to disclose.

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