Biomarker BINGO

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Abstract

This JADPRO Live session tested attendees' knowledge on biomarkers and their use in determining targeted therapy for certain tumor types, key assays used to measure common biomarkers, and guideline-endorsed biomarker testing recommendations.

The selection of cancer therapy is increasingly based on the presence of relevant biomarkers. At JADPRO Live 2019, Lauren Held, PharmD, BCOP, of Seattle Cancer Care Alliance, Sandra Kurtin, PhD, ANP-C, AOCN®, of University of Arizona Cancer Center, and Lee Schwartzberg, MD, FACP, of West Cancer Center discussed a number of specific biomarkers and the tumor types for which their expression is commonly used to determine targeted therapy. The trio of presenters also identified key assays used to measure common biomarkers and evaluated guideline-endorsed biomarker testing recommendations.

NEUROTROPHINS AND TROPOMYOSIN RECEPTOR KINASE (NTRK)

As Dr. Schwartzberg reported, *NTRK* are a family of genes that normally promote central nervous system development and are involved in cancerous fusion products. Larotrectinib is the first of a new class of inhibitors of TRK and is approved by the U.S. Food & Drug Administration (FDA) for adult and pediatric patients with solid tumors with an *NTRK* gene fusion without a known acquired resistance mutation, who have no satisfactory alternative treatments. According to Dr. Schwartzberg, Chief Medical Director of West Cancer Center, larotrectinib has potent activity against all three of the TRKs and has demonstrated an 80% response rate across a host of different tumors (Drilon et al., 2018). A second TRK inhibitor, entrectinib, was recently approved for the same indication.

"This is an area of rapidly growing excitement," said Dr. Schwartzberg. Table 1 describes the methods of detecting TRK fusions.

VENETOCLAX AND BCL2

As Dr. Held reported, venetoclax inhibits BCL2, a family of proteins located on the mitochondrial membrane (Del Gaizo Moore & Letai, 2013). Venetoclax is currently being studied in a variety of malignancies but is approved for both chronic lymphocytic leukemia (CLL) and

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Table 1. Methods of Detecting TRK Fusions

Method	Pros	Cons	Comments
IHC	Potential local implementation	Significant FN, FP Requires dedicated tissue and limits multi-target testing	May be used as screening diagnostic, but confirmation of *NTRK* gene fusion is recommended
FISH	Potential local implementation	Interpretation can be challenging Significant FN, FP Requires dedicated tissue and limits multi-target testing	In order to detect fusions at multiple locations, such as the 3 *NTRK* genes, multiple FISH tests would need to be run
RT-PCR	Fast, relatively inexpensive	No novel fusion partner detection May or may not be multiplexed with other fusion targets	Designed to identify only known translocation partners and breakpoints
NGS	Sensitive, specific molecular testing Simultaneously get mutation information for multiple targets	Expensive and longer turnaround time	RNA-NGS testing may be preferable to DNA-NGS testing because it identifies actively transcribed chimeric fusions

Note. IHC = immunohistochemistry; FISH = fluorescence in situ hybridization; RT-PCR = reverse transcriptase polymerase chain reaction; NGS = next-generation sequencing; FN = false negative; FP = false positive.

acute myeloid leukemia (AML). With CLL, said Dr. Held, a clinical hematology/oncology pharmacy specialist, venetoclax is usually given with a CD20 monoclonal antibody or as monotherapy, comes in a starter pack, and is dosed over 5 weeks and a weekly ramp-up. When giving the drug, she added, it's important to assess for tumor lysis syndrome prior to initiation, administer appropriate hydration and antihyperuricemics, and ensure adequate lab monitoring.

In AML, venetoclax is indicated in combination with azacitidine or decitabine, or low-dose cytarabine in patients at least 75 years who may not tolerate intensive chemotherapy. The dosing is different and there is a daily ramp-up over 4 days. Dr. Held also advised dose reductions for concomitant CYP3A4 inhibitors.

ALTERATIONS IN *RET*

As Dr. Schwartzberg reported, rearranged during transfection proto-oncogene (RET) is a receptor tyrosine kinase with a role in normal organogenesis and maintenance of several adult tissue types. Alterations in *RET* are predictive of response to RET inhibitors and associated with negative prognosis in medullary thyroid carcinoma. A high frequency of *RET* alterations occur in multiple endocrine neoplasia type 2 (> 98%), medullary thyroid carcinoma (40%–80%), papillary thyroid carcinoma (7%–27%), and anaplastic thyroid carcinoma (4.0%–16.7%). *RET* alterations are also reported in non–small cell lung cancer (0.7%–2.0%) and pheochromocytoma/paraganglioma (3%–6%) but rarely in other solid tumors.

"There are several drugs that work against *RET*-altered cancers," said Dr. Schwartzberg, who noted that, in patients with medullary thyroid cancer, cabozantinib improved progression-free survival compared to placebo (Gautschi et al., 2017).

"Cabozantinib has activity that is clinically meaningful, but other receptor tyrosine kinases have also demonstrated responses against RET," he added.

While current RET inhibitors are all multi-tyrosine kinase inhibitors, more targeted drugs should be available in the near future, which should lead to less toxicity, Dr. Schwartzberg reported (Figure 1).

JAK-STAT PATHWAY AND GVHD

Dr. Kurtin, a hematology/oncology nurse practitioner, reported that JAK-STAT is a well-characterized signaling pathway involved in normal hematopoiesis, inflammation, and immune function. JAKs mediate signaling of multiple cytokine receptor family members, including interleukins, interferons, and hematopoietic stimulating proteins, said Dr. Kurtin, who noted that cytokines

are surrogate markers of inflammation in peripheral blood.

Ruxolitinib, which inhibits the JAK-STAT pathways, including IFNγ and other inflammatory cytokines, is indicated for steroid-refractory acute graft-vs.-host disease (GVHD) in adults and pediatric patients 12 years and older.

While targeting the JAK-STAT pathways can reduce the severity of acute GVHD, said Dr. Kurtin, there are some tradeoffs; the use of ruxolitinib requires the monitoring of potential adverse events. Clinicians should monitor hemoglobin and platelet count for cytopenias and transfuse as needed. In addition, dose modifications may be required for renal impairment. There is also a risk of infection and non-melanoma skin cancer, said Dr. Kurtin, so patients should be assessed for signs and symptoms.

SINE COMPOUNDS AND EXPORTIN 1

As Dr. Held explained, SINE compounds inhibit exportin 1 (XPO1) and nuclear export of tumor suppressor proteins (TSPs). Accumulation of TSPs in the nucleus leads to cell cycle arrest, which, in turn, leads to apoptosis, said Dr. Held, who noted that increased expression of XPO1 has been observed and correlated in several solid and hematologic malignancies.

Selinexor is a SINE compound approved for relapsed/refractory multiple myeloma in combination with dexamethasone in patients who have received at least four prior therapies and are refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

As Dr. Held reported, data from the STORM clinical trial that led to FDA approval showed significant toxicities associated with selinexor, including thrombocytopenia, anemia, fatigue, nausea, and hyponatremia (Chari et al., 2019).

"Patients taking selinexor have progressed through essentially all of our regimens in multiple myeloma, so they probably are not going to have great blood counts and are most likely thrombocytopenic prior to initiating," said Dr. Held. "We've had one patient on selinexor and had to dose reduce her within the first 2 weeks, which I would usually expect with this drug" (Table 2).

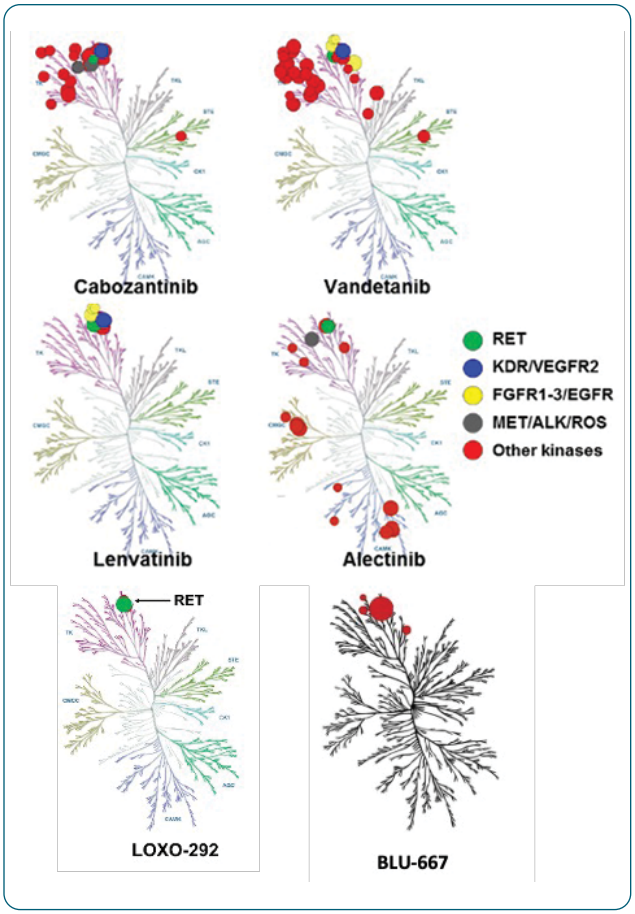

Figure 1. Current RET inhibitors are multi-tyrosine kinase inhibitors, but more targeted drugs are coming.

PIK3CA MUTATIONS

Dr. Schwartzberg reported that PI3 kinase signaling is critical in normal cells and tumor growth, and approximately 40% of patients with hormone receptor–positive, HER2-negative breast cancer present with *PIK3CA* activating gain-of-function mutations. Targeting the PI3K α-isoform may decrease toxicity compared with a pan-PI3Ki, said Dr. Schwartzberg.

Alpelisib, an α-specific PIK3CA inhibitor, was recently approved for the treatment of breast cancer with mutations in *PIK3CA*. Results of the SOLAR 1 trial showed that in combination with fulvestrant vs. fulvestrant alone in metastatic hormone receptor–positive, HER2-negative breast cancer, alpelisib led to a doubling of progression-free survival. According to Dr. Schwartzberg, however, the toxicity associated with alpelisib is fairly substantial.

Table 2. Adverse Events of Selinexor

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Total (N = 123)
Thrombocytopenia	12 (10%)	6 (5%)	31 (25%)	41 (33%)	90 (73%)
Anemia	7 (6%)	22 (18%)	53 (43%)	1 (1%)	83 (67%)
Fatigue	16 (13%)	43 (35%)	31 (25%)	0	90 (73%)
Nausea	34 (28%)	42 (34%)	12 (10%)	0	88 (72%)
Hyponatremia	18 (15%)	0	26 (21%)	1 (1%)	45 (37%)

Note. Warnings and precautions include thrombocytopenia, neutropenia, gastrointestinal toxicity, hyponatremia, infections, neurological toxicity, and embryo-fetal toxicity. Information from Chari et al. (2019); Karyopharm Therapeutics (2019).

"Because PIK3CA is important in insulin regulation in the normal host, hyperglycemia is an on-target effect," said Dr. Schwartzberg. "Diarrhea and other gastrointestinal toxicities are also a concern with alpelisib."

ISOCITRATE DEHYDROGENASE 1 (*IDH1*) MUTATION

As Dr. Kurtin explained, isocitrate dehydrogenase (IDH) is an enzyme that plays a crucial role in gene regulation and tissue homeostasis. *IDH* mutations can either be *IDH1* or *IDH2* mutations, said Dr. Kurtin, who noted that *IDH1* occurs in the cytoplasm and *IDH2* occurs in the mitochondria.

Ivosidenib is recently approved for both relapsed/refractory and newly diagnosed AML with *IDH1* mutation in patients over 75 years or who have comorbidities that preclude intensive chemotherapy. *IDH* mutations require detection by an FDA-approved test (the Abbott RealTime Qualitative Assay). As Dr. Kurtin reported, ivosidenib comes with a black box warning for differentiation syndrome, which can develop as early as one day after the start of therapy and during the first 3 months of treatment. Symptoms include fever, cough or difficulty breathing, rash, decreased urinary output, hypotension, rapid weight gain, or swelling of arms or legs.

"It's very important to initiate dexamethasone 10 mg IV every 12 hours (or equivalent dose) as soon as symptoms occur for a minimum of 3 days and until symptoms resolve," said Dr. Kurtin.

SMOOTHENED (SMO)

As Dr. Held explained, smoothened is a protein encoded by the *SMO* gene, which is involved in the sonic hedgehog (Shh) signaling pathway. The Shh pathway is essential for normal embryonic development and plays a role in adult tissue maintenance, renewal, and regeneration.

Glasdegib inhibits SMO involved with downstream signaling effects that lead to cell proliferation and apoptotic suppression. Glasdegib is approved for newly diagnosed AML in combination with low-dose cytarabine in adult patients who are at least 75 years of age or who have comorbidities that preclude intensive induction chemotherapy. Although there is a black box warning about embryo-fetal toxicity, said Dr. Kurtin, the drug is generally well tolerated. Adverse reactions include anemia, fatigue, hemorrhage, febrile neutropenia, musculoskeletal pain, nausea, edema, thrombocytopenia, dyspnea, decreased appetite, dysgeusia, mucositis, constipation, and rash (Lear et al., 2014).

ADDITIONAL BIOMARKERS

The presenters also discussed the following biomarkers and therapeutic agents:

- Tagraxofusp targets the α receptor chain for interleukin, which requires activation of CD123
- Emapalumab primarily targets interferon gamma (IFNγ).
- ^{177}Lu-dotatate binds to somatostatin receptors in neuroendrocrine tumors.
- Moxetumomab pasudotox-tdfk regulates the activity of the B-cell receptor pathway through CD22
- Erdafitinib targets mutations or fusions in the FGFR transmembrane receptor tyrosine kinase gene.
- Fostamatinib is a spleen tyrosine kinase (SYK) inhibitor, which impairs phagocyto-

sis of antibody-coated platelets.
- Polatuzumab vedotin is a CD79b-directed monoclonal antibody conjugated to the cytotoxic agent MMAE, which is a microtubule inhibitor. ●

Disclosure

Dr. Kurtin has acted as a consultant for AbbVie, Celgene, Janssen, Genentech, Incyte, and Takeda. Dr. Schwartzberg has acted as a consultant for Amgen, AstraZeneca, Genentech/Roche, and Pfizer. Dr. Held has no conflicts of interest to disclose.

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