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...
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

### Table 1. Methods of Detecting TRK Fusions

| Method   | Pros                                         | Cons                                               | Comments                                                                                                                                   |
|----------|----------------------------------------------|----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| IHC      | Potential local implementation               | Significant FN, FP                                 | May be used as screening diagnostic, but confirmation of \textit{NTRK} gene fusion is recommended                                             |
| FISH     | Potential local implementation               | Interpretation can be challenging                   | In order to detect fusions at multiple locations, such as the 3 \textit{NTRK} genes, multiple FISH tests would need to be run            |
| RT-PCR   | Fast, relatively inexpensive                 | No novel fusion partner detection                  | Designed to identify only known translocation partners and breakpoints                                                                   |
| NGS      | Sensitive, specific molecular testing         | Expensive and longer turnaround time                | RNA-NGS testing may be preferable to DNA-NGS testing because it identifies actively transcribed chimeric fusions                       |
|          | Simultaneously get mutation information for multiple targets |                                                     |                                                                                                                                          |

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.
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).

**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.
“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).
- 177Lu-dotatate binds to somatostatin receptors in neuroendocrine 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.

References
Chari, A., Vogl, D. T., Gavriatopoulou, M., Nooka, A. K., Yee, A. J., Huff, C. A.,...Jagannath, S. (2019). Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. New England Journal of Medicine, 381(8), 727–738. http://doi.org/10.1056/NEJMoa1903455
Del Gaizo Moore, V., & Letai, A. (2013). BH3 profiling-measuring integrated function of the mitochondrial apoptotic pathway to predict cell fate decisions. Cancer Letters, 332(2), 202–205. https://doi.org/10.1016/j.canlet.2011.12.021
Drilon, A., Laetsch, T. W., Kummar, S., DuBois, S. G., Lassen, U. N., Demetri, G. D.,...Hyman, D. M. (2018). Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. New England Journal of Medicine, 378(8), 731–739. http://doi.org/10.1056/NEJMoa1714448
Gautschi, O., Milia, J., Filleron, T., Wolf, J., Carbone, D. P., Owen, D.,...Drilon, A. (2017). Targeting RET in patients with RET-rearranged lung cancers: results from the global, multicenter RET registry. Journal of Clinical Oncology, 35(13), 1403–1410. http://doi.org/10.1200/JCO.2016.70.9352
Karyopharm Therapeutics. (2019). Xpovio (selinexor) packages insert. Retrieved from https://www.karyopharm.com/wp-content/uploads/2019/07/NDA-212306-SN-0071-Prescribing-Information-01July2019.pdf
Lear, J. T., Corner, C., Dziewulski, P., Fife, K., Ross, G. L., Varma, S., & Harwood, C. A. (2014). Challenges and new horizons in the management of advanced basal cell carcinoma: A UK perspective. British Journal of Cancer, 111(8), 1476–1481. http://doi.org/10.1038/bjc.2014.270