Transcript Details

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When Apoptosis Becomes Impaired: Targeting BCL-2

ReachMD Announcer: Welcome to ReachMD. The following program, "When Apoptosis Becomes Impaired: Targeting BCL-2 " is developed and sponsored by AbbVie. This activity is intended for United States and Puerto Rico health care professionals only.

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Dr. Souers: Welcome to ReachMD. I'm Dr. Andy Souers from the oncology division at AbbVie.

Dr. Davids: And I'm Dr. Matthew Davids Associate Professor of Medicine at Harvard Medical School and the clinical research director in the division of lymphoma at Dana Farber Cancer Institute.

Dr. Souers: Together, we'll be discussing apoptosis, or what is also known as programmed cell death. This is a normal and highly regulated process that the body uses to dispose of aged or damaged cells. However, this critical process can become impaired, and in some cases this dysfunction can drive malignant transformation, tumor growth, and resistance to therapy.

Dr. Davids: We'll also focus on an important protein that regulates apoptosis, called BCL-2, and a treatment option designed to selectively bind and inhibit BCL-2. I'm looking forward to diving into all of this with you today, Andy.

Dr. Souers: Same here, Matt, so without further ado, let's talk about BCL-2. What do clinicians need to know about it?

Dr. Davids: So, BCL-2 is a member of a larger family of structurally related proteins that are either pro-apoptotic or anti-apoptotic. The dynamic balance between anti-apoptotic members such as BCL-2 as well as pro-apoptotic family members can help determine whether a cell undergoes apoptosis.

But let me turn back to you, Andy, for some more detail on how normal cells and cancer cells respond to stress, respectively. Can you provide some background information on that?

Dr. Souers: Certainly, in response to stress, normal cells, as well as certain cancer cells will actually increase the production of pro-apoptotic family members which promote cell death. Now in normal cells, this increased expression of pro-apoptotic proteins is sufficient to trigger apoptosis. In contrast, cancer cells sometimes express even higher levels of the anti-apoptotic protein BCL-2, which can keep pro-apoptotic members in check and thereby allow the cancer cells to survive.

So that leads to the question of how specifically higher expression of BCL-2 is able to allow these cancer cells to survive. Care to tackle that one, Matt?

Dr. Davids: Absolutely. So, the Increased expression of BCL-2 helps enable some cancer cells to resist apoptosis by binding and sequestering the pro-apoptotic proteins – essentially soaking them up like a sponge – and thus promoting their survival under stressful conditions. Preclinical studies have shown inhibition of BCL-2 in these cancer cells can cause a release of these pro-apoptotic proteins – like squeezing the sponge, and this can be sufficient to trigger apoptosis.

So clearly, BCL-2 is a key factor in the inhibition of apoptosis, and identifying that factor gave a therapeutic target which, in turn, led to the discovery of a drug called venetoclax that specifically inhibits BCL-2.

But before we dive into that, let's review some important safety information for Venetoclax.

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Indication
Venetoclax is a BCL-2 inhibitor indicated:

- For the treatment of adult patients with chronic lymphocytic leukemia (or CLL) or small lymphocytic lymphoma (or SLL).
- In combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (or AML) in adults:
  - who are age 75 years or older, or
  - who have comorbidities that preclude use of intensive induction chemotherapy.

Please stay tuned for a safety overview of venetoclax at the end of this program.

Dr. Davids: Now that we have a little more understanding on Venetoclax, Andy Dr. Souers, can you speak to this treatment option and how venetoclax actually targets BCL-2?

Dr. Souers: Absolutely. Co-developed by AbbVie and Genentech, venetoclax is an orally dosed small molecule designed to selectively bind and inhibit BCL-2. Upon binding BCL-2, venetoclax displaces the store of pro-apoptotic proteins in cancer cells. This can help cause a shift in the dynamic balance between the available BCL-2 and pro-apoptotic family members, thus triggering apoptosis. Now an important concept to understand is that cancer cells are highly primed to undergo apoptosis, whereas normal cells are not primed for apoptosis. This provides a therapeutic window so that venetoclax can selectively kill cancer cells.

But coming back to the preclinical studies you mentioned earlier that looked into the inhibition of BCL-2, can you elaborate on what those studies found, Matt?

Dr. Davids: Sure. So in these preclinical studies, when BCL-2 was inhibited by venetoclax, pro-apoptotic proteins were left free to promote pore formation in the mitochondria. Cytochrome C and other factors were subsequently released from the mitochondria, initiating the caspase activation cascade. And the activation of these proteolytic enzymes helped lead to apoptosis of the cell.

So that look back hopefully clarifies the precedent for this treatment approach. Andy, before we wrap up today, any closing comments for this discussion?

Dr. Souers: Absolutely, AbbVie Genentech and a number of key academic investigators such as yourself and colleagues at Dana Farber are continuing their research into the selective BCL-2 inhibitor, venetoclax. It is currently approved for the treatment of CLL and certain patients with AML.

Dr. Davids: Thanks for that reminder, Andy. Please stay tuned for some important safety information.

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Contraindications

- **Strong CYP3A Inhibitors:** Concomitant use with strong CYP3A inhibitors at initiation and during ramp-up phase in patients with CLL/SLL is contraindicated.

Warnings and Precautions

- **TLS:** Tumor lysis syndrome (or TLS), including fatal events and renal failure requiring dialysis, has occurred in patients treated with venetoclax. Anticipate TLS; assess risk in all patients. Premedicate with anti-hyperuricemics and ensure adequate hydration. Employ more intensive measures (intravenous hydration, frequent monitoring, and hospitalization) as overall risk increases.
- **Neutropenia:** Monitor blood counts. Interrupt dosing and resume at same or reduced dose. Consider supportive care measures.
- **Infections:** Fatal and serious infections such as pneumonia and sepsis have occurred in patients treated with venetoclax. Monitor for signs and symptoms of infection and treat promptly. Withhold venetoclax for Grade 3 and 4 infection until resolution and resume at same or reduced dose.
- **Immunization:** Do not administer live attenuated vaccines prior to, during, or after venetoclax treatment until B-cell recovery.
- **Embryo-Fetal Toxicity:** May cause embryo-fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.
- **Increased mortality in patients with multiple myeloma (or MM) when venetoclax is added to bortezomib and dexamethasone.** In a randomized trial in patients with relapsed or refractory MM, the addition of venetoclax to bortezomib plus dexamethasone, a use for

which venetoclax is not indicated, resulted in increased mortality. Treatment of patients with MM with venetoclax in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials.

Adverse Reactions

- In **CLL and SLL**, the most common adverse reactions (≥20%) for venetoclax when given in combination with obinutuzumab or rituximab or as monotherapy were neutropenia, thrombocytopenia, anemia, diarrhea, nausea, upper respiratory tract infection, cough, musculoskeletal pain, fatigue, and edema.
- In **AML**, the most common adverse reactions (≥30%) in combination with azacitidine or decitabine or low-dose cytarabine were nausea, diarrhea, thrombocytopenia, constipation, neutropenia, febrile neutropenia, fatigue, vomiting, edema, pyrexia, pneumonia, dyspnea, hemorrhage, anemia, rash, abdominal pain, sepsis, musculoskeletal pain, dizziness, cough, oropharyngeal pain, and hypotension.

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