BMS Immuno-Oncology Video 3 Title: Immuno-Oncology Approaches in the Lung – Dr. Jack West

I'm Dr. Jack West. I'm glad to have you here for the third installment of this ongoing series about immuno-oncology, presented by Bristol-Myers Squibb.

Last time, you heard about how the immune system functions to attack tumor cells in the lungs and how those tumor cells can develop the ability to fight back. Today, we'll focus on cutting edge research of immune-based pathways in lung cancer.

Even though the incidence of lung cancer is declining, it still accounts for about 14% of cancer diagnoses in both men and women in the US, with about 230,000 estimated new cases diagnosed in 2013 alone.1 only prostate and breast cancer have a higher incidence.

But despite being third in incidence, lung cancers cause the most deaths of any tumor type. In 2013 they accounted for 27% of all cancer-related deaths in the US—or nearly 160,000—underscoring the need for continuing research seeking to advance the treatment landscape.

You heard in previous talks about immunosurveillance and the mechanisms that tumor cells can adopt to evade that surveillance.

Immuno-oncology research—which focuses on the interactions between the immune system and cancer cells—is uncovering potential new therapeutic strategies that work with the immune system to attack tumor cells.

Immunotherapies can be divided into passive therapies and active therapies.

Passive immunotherapies are defined by the fact that they typically don't engage the adaptive immune system. Instead, they target tumor-related antigens through the adoptive transfer of immunomodulators, monoclonal antibodies, or T-cells that have been activated outside of the patient.5

Since the adaptive immune system usually isn't involved, passive immunotherapies generally don't produce immunological memory for specific antigens.

The second group of immunotherapies—active immunotherapies—are designed to engage the patient's adaptive immune system and launch an immune response against tumor cells.

Since active immunotherapies work with the adaptive immune system, they can also elicit immunological memory.

Current research in active immunotherapy strategies includes vaccinating patients against tumor-associated antigens, enhancing immune cell function, or modulating immune activity.

The development of active immunotherapies is an emerging area of immuno-oncology research and will be our focus here, starting with vaccines.

Perhaps the most familiar use of vaccines is in the prevention or treatment of certain infectious diseases. The use of pathogen-related antigens to immunize patients can create immunological memory and provide immunity.6

Cancer vaccines use this same concept to direct an immune response against cells displaying tumor-associated antigens.

Peptide-based vaccines are currently being investigated in the treatment of lung cancer, and include a synthetic peptide intended to elicit a response against the tumor-associated adhesion protein

Mucin-1.

“Cellular vaccines directed against specific tumor antigens are also an active area of clinical research and include dendritic cells that have been primed with tumor antigens in vitro. These cells are then transferred to a patient, where they may induce an antitumor response through B- and T-cell activation.

Other clinical studies are investigating vaccines composed of exogenous, irradiated tumor cells that have been transfected with genes—such as cytokines and growth factors—intended to drive an immune response after administration to patients.

Another area of research into active immunotherapies is focused on activity within the tumor microenvironment.

As you heard about earlier in this series, lung tumors are capable of using a variety of strategies to suppress immune activity—specifically the activity of cytotoxic T-cells, or CTLs—within their microenvironment.

Lung tumors are known to express immunosuppressive molecules like indoleamine 2, 3-dioxygenase, or IDO, which inhibits T-cell activity by limiting tryptophan levels.2,8 Ongoing clinical research is investigating how targeting IDO may affect tumor-induced immunosuppression.

Interestingly, vaccination against IDO also appears to induce an overall reduction in T cells T along with myeloid-derived suppressor cells, or MDSCs, are among the immunosuppressive cells known to be recruited to the tumor microenvironment.

These immunosuppressive cells are also being directly targeted in immuno-oncology research. Preclinical and clinical studies are using chemical- or antibody-based methods to inhibit MDSCs, either to help limit tumor growth or to augment the response to a separate vaccine.

Now, in addition to recruiting immunosuppressive cells and releasing immunosuppressive molecules, lung tumors can act to inhibit CTL function through immune checkpoints.2,12 Much of the current research being done regarding immuno-oncology involves targeting immune checkpoint pathways.

As you heard earlier, CTLs are responsible for eliminating pathogens, infected host cells, and tumor cells.

However, if left unchecked, CTLs can also injure healthy host cells and cause a breakdown in self-tolerance. It’s therefore important for the immune system to be able to modulate CTL activity so that healthy cells aren’t damaged by an immune response.

Immune checkpoints are part of this modulatory mechanism. They’re a collection of signaling systems—including the examples that we’re showing here—that allow antigen-presenting cells, or APCs, to inhibit T-cell activity when needed.

Checkpoints are activated through binding of a ligand on an APC to its receptor on a CTL.12 Subsequent inhibitory signaling within the T-cell limits immune activity, 12 in some cases leading to CTL apoptosis.2”

So obviously, immune checkpoints can be good things, as they help to prevent autoimmunity.

But research has shown that tumor cells can exploit this system by expressing checkpoint ligands themselves to suppress CTL activity directed against them.

Some of the checkpoints that have been implicated in immunosuppression by lung tumors are PD-1, B7-H3, and B7-H4.

We know that expression of these B7 homologs or the PD-1 ligand on lung tumor cells is associated with decreased immune activity against tumors.

It also appears that CTLA-4 activity may generally suppress CTL activity, allowing for tumor growth.16

Inhibiting immune checkpoints may therefore help restore CTL activity. And a major area of immuno-oncology research is focused on doing just that.

The investigational compounds that target checkpoints don't specifically target tumor cells or antigens, but are instead designed to modulate immune activity.

A number of monoclonal antibody-based therapies directed against immune checkpoint pathways are currently in development for lung cancer.

The potential of immunotherapies makes this an incredibly exciting time in the field of immuno-oncology.

In this series we've just been able to scratch the surface of what is happening in immuno-oncology research. This field represents a new way of looking at how tumor cells interact with their environment and how we can use that knowledge to investigate novel therapeutic avenues.

We hope that you've enjoyed this series and have found it informative. Thank you for joining us.