

Transcript Details

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An Immunotherapy Combination as a First-Line Treatment for Extensive-Stage Small Cell Lung Cancer

Announcer:

Welcome to ReachMD.

This medical industry feature, titled “An Immunotherapy Combination as a First-Line Treatment for Extensive-Stage Small Cell Lung Cancer” is presented on behalf of Genentech, and the information presented is intended for physicians and consistent with FDA guidelines.

Dr. Evans:

Before we start our discussion, let’s go over some important disclosure information. First, this program is presented on behalf of Genentech and is consistent with FDA guidelines. I, along with Dr. Mudad have been compensated by Genentech to serve as speakers for this program.

Now, about the program, itself. It’s intended to provide general information about TECENTRIQ, or atezolizumab, and is not intended to be medical advice for any particular patient. Any adverse events included in this presentation today, have already been reported to Genentech drug safety, so no action is required by any member of the audience.

Lastly, this program may be monitored by Genentech to ensure adherence to program requirements and all materials are the property of Genentech and may not be recorded, photographed, copied, or reproduced.

So, now that we’ve reviewed that disclosure statement, Dr. Mudad, let’s dive right into our discussion.

Dr. Evans:

This is ReachMD and I’m Dr. Tracey Evans, the Director of Thoracic Oncology Research at Lankenau Institution for Medical Research. Joining me is Dr. Raja Mudad, a Thoracic Medical Oncologist and founding partner at Florida Precision Oncology. Dr. Mudad, thanks for being here, today.

Dr. Mudad:

Thanks for having me.

Dr. Evans:

Before we begin, let’s briefly review the indication, warnings and precautions for TECENTRIQ.

Announcer:

TECENTRIQ (atezolizumab) is a programmed death-ligand 1 or (PD-L1) blocking antibody indicated in combination with carboplatin and etoposide for the first-line treatment of adult patients with extensive-stage small cell lung cancer or (ES-SCLC).

Serious and sometimes fatal adverse reactions occurred with TECENTRIQ treatment. Warnings and precautions include severe and fatal immune-mediated adverse reactions, including pneumonitis, colitis, hepatitis, endocrinopathies, dermatologic adverse reactions, nephritis and renal dysfunction, and solid organ transplant rejection. Other warnings and precautions include infusion-related reactions, complications of allogeneic HSCT, and embryo-fetal toxicity.

Please see full Prescribing Information for additional Important Safety Information.

Dr. Evans:

Before we learn more about this treatment option, Dr. Mudad, can you tell us about the history of treating this disease?

Dr. Mudad:

There have been more than forty phase 3 trials since 1970. None leading to additional FDA approvals in first line extensive stage small lung cancer. So, there is a high, unmet need, with small cell lung cancer also having a low survival rate. Stage IV small cell lung cancer patients have a relative 5-year survival rate of about 3%.

Dr. Evans:

Then, the IMpower133 trial led to the emergence of immunotherapy as a significant therapeutic advancement and the first line treatment of extensive stage small cell lung cancer, when TECENTRIQ plus carboplatin and etoposide was FDA approved in March of 2019. Can you walk us through the trial design?

Dr. Mudad:

The IMpower133 was a phase 3, multi-center, randomized, double-blind, placebo-control trial in extensive stage small cell lung cancer in patients who had not received prior chemotherapy for extensive stage disease and who had a ECOG Performance Status of 0 or 1. The trial evaluated the superiority of using TECENTRIQ combination, up front. The co-primary endpoints were overall survival and progression-free survival.

Dr. Evans:

Thanks, Dr. Mudad. With that background in mind, could you highlight the results of IMpower133?

Dr. Mudad:

TECENTRIQ plus carbo and etoposide is the first and only immunotherapy combination with significantly superior overall survival and progression-free survival in first line, extensive stage small cell lung cancer patients. The IMpower133 trial showed a 30% reduction in the risk of death versus placebo plus carbo/etoposide with a p-value of 0.0069. The median overall survival was 12.3 months versus 10.3 months with placebo plus carbo/etoposide.

Adding TECENTRIQ to carbo and etoposide significantly improved the median progression-free survival. The median progression-free survival was 5.2 months versus 4.3 months with placebo plus carbo/etoposide with a p-value of 0.017.

Dr. Evans:

Okay. Now, continuing our discussion on the IMpower133 trial, Dr. Mudad, I see that there's almost 2 years' worth of additional follow up survival data. What were the findings there?

Dr. Mudad:

Nearly 2 years of exploratory follow-up overall survival data. Landmark analyses showed overall survival rates for the TECENTRIQ plus carbo/etoposide and placebo plus carbo/etoposide groups respectively were 52% and 39% at 12 months; 34% and 21% at 18 months; and 22% and 17% at 24 months. These landmark analyses were not powered to demonstrate statistically significant differences and no conclusions can be drawn from those analyses. The 12 and 24 months overall survival rates were pre-specified secondary endpoints. The 18 months overall survival rate was not pre-specified and is considered exploratory. The 24 months overall survival rates may be subject to change with longer follow-up. Safety analysis here was generally consistent with the safety observed in the initial analysis.

Dr. Evans:

Okay. Now, let's turn to the subject of infusion schedules for TECENTRIQ. Can you describe the dosing for us?

Dr. Mudad:

TECENTRIQ is administered via three flexible dosing options: as 840 mg every two weeks, as 1200 mg every three weeks, or as 1680 mg every four weeks. TECENTRIQ can be administered in a 30-minute infusion, if the initial 60-minute infusion is tolerated. We should administer TECENTRIQ prior to chemotherapy when given on the same day. We should not administer TECENTRIQ as an IV push or bolus. We should not co-administered other drugs through the same IV line. Refer to the respective prescribing information for carboplatin and etoposide for recommended dosing information.

Dr. Evans:

Thank you for that overview.

It's useful to know that you have the ability to choose a Q4 week, Q3 week, or a Q2 week infusion schedule for TECENTRIQ that helps meet your patient's needs.

Lastly, Dr. Mudad, let me open the floor to you for the final word. What would you like to reiterate or remind our audience of with regards to TECENTRIQ?

Dr. Mudad:

There are three reasons to choose TECENTRIQ plus carbo and etoposide. It is the first and only immunotherapy combination with significantly superior overall survival and progression-free survival in first line extensive stage small cell lung cancer patients. There are nearly two years of exploratory follow-up overall survival data and there are three flexible dosing options.

Dr. Evans:

That's a great comment for us to think on as we come to the end of today's program. I want to thank my guest, Dr. Raja Mudad for helping us better understand the role of TECENTRIQ in first line combination treatment for extensive stage small cell lung cancer. Dr. Mudad, it was great speaking with you, today.

Dr. Mudad:

Thanks so much for having me.

Dr. Evans:

For ReachMD, I'm Tracey Evans. Now, before we close, let's review some important safety information.

Announcer:

Serious Adverse Reactions

Please refer to the full Prescribing Information for important dose management information specific to adverse reactions.

Severe and Fatal Immune-Mediated Adverse Reactions

TECENTRIQ is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. The following immune-mediated adverse reactions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions can occur in any organ system or tissue and at any time after starting a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, they can also manifest after discontinuation of treatment.

Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue TECENTRIQ depending on severity. In general, if TECENTRIQ requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less, then initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Immune-Mediated Pneumonitis

TECENTRIQ can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-mediated pneumonitis occurred in 3% (83/2616) of patients receiving TECENTRIQ as a single agent, including fatal (<0.1%), Grade 4 (0.2%), Grade 3 (0.8%), and Grade 2 (1.1%) adverse reactions. Pneumonitis led to permanent discontinuation of TECENTRIQ in 0.5% and withholding of TECENTRIQ in 1.5% of patients. Systemic corticosteroids were required in 55% (46/83) of patients with pneumonitis.

Immune-Mediated Colitis

TECENTRIQ can cause immune-mediated colitis. Colitis can present with diarrhea, abdominal pain, and lower gastrointestinal (GI) bleeding. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated colitis occurred in 1% (26/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.5%) and Grade 2 (0.3%) adverse reactions. Colitis led to permanent discontinuation of TECENTRIQ in 0.2% and withholding of TECENTRIQ in 0.5% of patients. Systemic corticosteroids were required in 50% (13/26) of patients with colitis. Colitis resolved in 73% of the 26 patients. Of the 12 patients in whom TECENTRIQ was withheld for colitis, 8 reinitiated treatment with TECENTRIQ after symptom improvement; of these, 25% had recurrence of colitis.

Immune-Mediated Hepatitis

TECENTRIQ can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 1.8% (48/2616) of patients receiving TECENTRIQ as a single agent, including fatal (<0.1%), Grade 4 (0.2%), Grade 3 (0.5%), and Grade 2 (0.5%) adverse reactions. Hepatitis led to permanent discontinuation of TECENTRIQ in 0.2% and withholding of TECENTRIQ in 0.2% of patients. Systemic corticosteroids were required in 25% (12/48) of patients with hepatitis. Hepatitis resolved in 50% of the 48 patients. Of the 6 patients in whom TECENTRIQ was withheld for hepatitis, 4 reinitiated treatment with TECENTRIQ after symptom improvement; of these, none had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

TECENTRIQ can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated.

Adrenal insufficiency occurred in 0.4% (11/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (<0.1%) and Grade 2 (0.2%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of TECENTRIQ in 1 patient and withholding of TECENTRIQ in 1 patient. Systemic corticosteroids were required in 81% (9/11) of patients with adrenal insufficiency; of these, 3 patients remained on systemic corticosteroids. The single patient in whom TECENTRIQ was withheld for adrenal insufficiency did not reinitiate TECENTRIQ.

Hypophysitis

TECENTRIQ can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated.

Hypophysitis occurred in <0.1% (2/2616) of patients receiving TECENTRIQ as a single agent, including Grade 2 (1 patient, <0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of TECENTRIQ in 1 patient and no patients required withholding of TECENTRIQ. Systemic corticosteroids were required in 50% (1/2) of patients with hypophysitis. Hypophysitis did not resolve in these 2 patients.

Immune-Mediated Endocrinopathies (cont'd)

Thyroid Disorders

TECENTRIQ can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or medical management for hyperthyroidism as clinically indicated.

Thyroiditis occurred in 0.2% (4/2616) of patients receiving TECENTRIQ as a single agent, including Grade 2 (<0.1%) adverse reactions. Thyroiditis did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 1 patient. Hormone replacement therapy was required in 75% (3/4) of patients with thyroiditis. Systemic corticosteroids were required in 25% (1/4) of patients with thyroiditis. Thyroiditis resolved in 50% of patients. The single patient in whom TECENTRIQ was withheld for thyroiditis reinitiated TECENTRIQ, this patient did not have recurrence of thyroiditis.

Hyperthyroidism occurred in 0.8% (21/2616) of patients receiving TECENTRIQ as a single agent, including Grade 2 (0.4%) adverse reactions. Hyperthyroidism did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 0.1% of patients. Antithyroid therapy was required in 29% (6/21) of patients with hyperthyroidism. Of these 6 patients, the majority remained on antithyroid treatment. Of the 3 patients in whom TECENTRIQ was withheld for hyperthyroidism, 1 patient reinitiated TECENTRIQ; this patient did not have recurrence of hyperthyroidism.

Hypothyroidism occurred in 4.9% (128/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.2%) and Grade 2 (3.4%) adverse reactions. Hypothyroidism did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 0.6% of patients. Hormone replacement therapy was required in 81% (104/128) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 17 patients in whom TECENTRIQ was withheld for hypothyroidism, 8 reinitiated TECENTRIQ after symptom improvement.

Hypothyroidism occurred in 11% (277/2421) of patients with NSCLC and SCLC receiving TECENTRIQ in combination with platinum-based chemotherapy, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (5.7%) adverse reactions. Hypothyroidism led to permanent discontinuation of TECENTRIQ in 0.1% and withholding of TECENTRIQ in 1.6% of patients. Hormone replacement therapy was required in 71% (198/277) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 39 patients in whom TECENTRIQ was withheld for hypothyroidism, 9 reinitiated TECENTRIQ after symptom improvement.

Immune-Mediated Endocrinopathies (cont'd)

Type 1 Diabetes Mellitus, Which Can Present With Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated.

Type 1 diabetes mellitus occurred in 0.3% (7/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.2%) and Grade 2 (<0.1%) adverse reactions. Type 1 diabetes mellitus led to permanent discontinuation of TECENTRIQ in 1 patient and withholding of TECENTRIQ in 2 patients. Treatment with insulin was required for all patients with confirmed Type 1 diabetes mellitus and insulin therapy was continued long-term. Of the 2 patients in whom TECENTRIQ was withheld for Type 1 diabetes mellitus, both re-initiated TECENTRIQ treatment.

Immune-Mediated Nephritis with Renal Dysfunction

TECENTRIQ can cause immune-mediated nephritis

Immune-mediated nephritis with renal dysfunction occurred in <0.1% (1/2616) of patients receiving TECENTRIQ as a single agent, and this adverse reaction was a Grade 3 (<0.1%) adverse reaction. Nephritis led to permanent discontinuation of TECENTRIQ in this patient. This patient required systemic corticosteroids. In this patient, nephritis did not resolve.

Immune-Mediated Dermatologic Adverse Reactions

TECENTRIQ can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), DRESS, and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes.

Immune-mediated dermatologic adverse reactions occurred in 0.6% (15/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (<0.1%) and Grade 2 (0.2%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of TECENTRIQ in 0.1% and withholding of TECENTRIQ in 0.2% of patients. Systemic corticosteroids were required in 20% (3/15) of patients with dermatologic adverse reactions. Dermatologic adverse reactions resolved in 87% of the 15 patients. Of the 4 patients in whom TECENTRIQ was withheld for immune-mediated dermatologic adverse reactions, none re-initiated TECENTRIQ.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received TECENTRIQ or were reported with the use of other PD-1/PD-L1 blocking antibodies

- **Cardiac/Vascular:** Myocarditis, pericarditis, vasculitis
- **Nervous System:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy
- **Ocular:** Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss
- **Gastrointestinal:** Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis
- **Musculoskeletal and Connective Tissue:** Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatic
- **Endocrine:** Hypoparathyroidism
- **Other (Hematologic/Immune):** Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

Infusion-Related Reactions

TECENTRIQ can cause severe or life-threatening infusion-related reactions. Monitor for signs and symptoms of infusion-related reactions. Interrupt, slow the rate of, or permanently discontinue TECENTRIQ based on the severity.

For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses.

Infusion-related reactions occurred in 1.3% of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.2%) reactions.

The frequency and severity of infusion-related reactions were similar whether TECENTRIQ was given as a single-agent, in combination with other antineoplastic drugs in NSCLC and SCLC, and across the recommended dose range.

Complications of Allogeneic HSCT After PD-1/PD-L1 Inhibitors

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody.

Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause).

These complications may occur despite intervening therapy between PD-1/PD-L1 blockage and allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefits versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus, resulting in fetal death.

Verify pregnancy status of females of reproductive potential prior to initiating TECENTRIQ. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose.

Use In Specific Populations

Nursing Mothers

There is no information regarding the presence of TECENTRIQ in human milk, the effects on the breastfed infant, or the effects on milk production. As human IgG is excreted in human milk, the potential for absorption and harm to the infant is unknown. Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose.

Fertility

Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment.

Most Common Adverse Reactions

The most common adverse reactions (rate $\geq 20\%$) in patients who received TECENTRIQ in combination with other antineoplastic drugs for NSCLC and SCLC were fatigue/asthenia (49%), nausea (38%), alopecia (35%), constipation (29%), diarrhea (28%), and decreased appetite (27%).

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see full Prescribing Information for additional Important Safety Information.

Announcer:

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