Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/navigating-nsclc/updates-from-pacific-study-its-impact-on-unresectable-stage-III-nsclc-treatment-landscape/10955/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Updates From the PACIFIC Study & Its Impact on the Unresectable Stage III NSCLC Treatment Landscape

Voice Over:

IMFINZI® (durvalumab) is indicated for the treatment of adult patients with unresectable Stage III non-small cell lung cancer whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

Serious, potentially fatal risks were seen with IMFINZI in the PACIFIC trial. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonitis or radiation pneumonitis (7%) and pneumonia (6%).

Immune-mediated adverse reactions, including immune-mediated pneumonitis, hepatitis, colitis, endocrinopathies (including thyroid disorders, adrenal insufficiency, type 1 diabetes, and hypophysitis), nephritis, dermatologic reactions, and other immune-mediated adverse reactions; infection; and infusion-related reactions were reported in patients receiving IMFINZI in the PACIFIC trial.

The most common adverse reactions were cough, fatigue, pneumonitis or radiation pneumonitis, upper respiratory tract infections, dyspnea, and rash.

Advise women not to become pregnant or breastfeed during treatment with IMFINZI and for at least 3 months after the last dose.

The safety and effectiveness of IMFINZI have not been established in pediatric patients.

Please refer to the Important Safety Information and the full Prescribing Information for important dosage modification and management information specific to adverse reactions.

Announcer:
Welcome to ReachMD. This medical industry feature titled “Updates from the PACIFIC Study & Its Impact on the Unresectable Stage III NSCLC Treatment Landscape” is sponsored by AstraZeneca. This program is intended for physicians. Here’s your host, Dr. Jennifer Caudle.

Dr. Jennifer Caudle (host):
Coming to you live from the ASTRO annual meeting in Chicago, I’m your host, Dr. Jennifer Caudle, from ReachMD, and joining me today is Dr. Timothy Kruser, an Assistant Professor of Radiation Oncology at Northwestern Memorial Hospital in Chicago, to discuss recent updates from the PACIFIC trial and how this is impacting the non-small cell lung cancer treatment landscape.

Dr. Caudle:
Dr. Kruser, thank you so much for being with us today.

Dr. Kruser:
Thank you, Dr. Caudle, for the opportunity to talk about this exciting data.

Dr. Caudle:
Absolutely. Well, I’m definitely excited, so let’s jump right in. New data from the PACIFIC study were recently released at ASCO 2019. So, Dr. Kruser, can you tell us what this update is and really how it’s impacting the treatment landscape for unresectable stage III non-small cell lung cancer?

Dr. Kruser:
Yes, I’m excited to share with the audience this update, which is an update of the overall survival data of the PACIFIC study. As we

know, the PACIFIC study was first presented in 2017 where the progression-free survival data was outlined. The *New England Journal* article in 2018 demonstrated a statistically significant benefit in terms of overall survival, establishing and solidifying durvalumab after chemoradiotherapy as a standard of care for patients with stage III non-small cell lung cancer who don't progress. The data was thereafter updated at ASCO in Chicago in the summer of 2019, and it mirrored and solidified the role of durvalumab in this setting and provides more optimism for our patients.

Dr. Caudle:
Excellent. Now, can you provide your perspective on the treatment landscape for unresectable stage III non-small cell lung cancer before the approval of IMFINZI? In particular, what were some of the challenges for patients really during that time?

Dr. Kruser:
Yes, concurrent chemoradiotherapy has been the standard of care for about 20 years for patients with stage III non-small cell lung cancer. It's important to note that even with all the new medical therapies available, curative intent chemoradiotherapy still remains an integral part of the care for these patients. That said, the outcomes have been relatively underwhelming. We faced high rates of metastatic disease in these patients, and really, for 20 years we haven't had a breakthrough, not until the PACIFIC data came out, which we're going to talk about a little bit more, but it's really exciting and has provided a lot more optimism for patients facing this problem.

Dr. Caudle:
Sure. Well, that's really helpful to understand, and I think we should really talk about the PACIFIC trial. Let's start. Can you provide a brief summary of the PACIFIC study design?

Dr. Kruser:
Yes. The PACIFIC study was a phase 3 randomized study, double-blinded, placebo-controlled, where 713 patients with stage III non-small cell lung cancer whose disease had not progressed after chemoradiotherapy were randomized either to IMFINZI or placebo. The medication arms were delivered every 2 weeks for 12 months until either disease progression or adverse reactions.

Dr. Caudle:
Excellent. So, let's now go to efficacy. Let's hear more about this data. What can you tell us about the efficacy data?

Dr. Kruser:
In 2017, the first *New England Journal of Medicine* article came out highlighting that the median progression-free survival had been improved with IMFINZI from 5.6 months up to 16.8 months, so an 11.2-month improvement, and this was statistically significant.

Dr. Kruser:
Thereafter, in 2018, and in very exciting fashion, the overall survival data came out, again in the *New England Journal of Medicine*. At that 2-year time point, the median survival had not yet been reached in the IMFINZI arm, whereas in the placebo arm, it was about 29 months. Again, these differences were statistically significant and in favor of the IMFINZI arm and established IMFINZI as the standard of care following concurrent chemoradiotherapy for patients with stage III non-small cell lung cancer who haven't progressed following their treatment. Thereafter, as I mentioned before, at ASCO the 3-year data came out. It's important to note that this was a post-hoc analysis and the study was not powered for this point, but nonetheless, it was in line with the 2-year survival outcomes. So, at 3 years, the median survival had still not been reached in the IMFINZI arm, where again, for the placebo arm, it was about 29 months.

Dr. Caudle:
Okay.

Dr. Kruser:
Analysis at 3 years showed that 57% of patients were still alive in the IMFINZI arm versus about 44% in the placebo arm.

Dr. Caudle:
Okay, great. Now, thank you for that overview of the overall survival data for IMFINZI. There are important safety data for IMFINZI that physicians really should be aware of. Can you talk us through some of those?

Dr. Kruser:
Yes, it's important to note that there are some very serious side effects that are potentially fatal

Dr. Caudle:
Right.

Dr. Kruser:
When we look at the PACIFIC data, the most common serious adverse reactions were radiation pneumonitis, or pneumonitis, which is

about 7% of patients, and pneumonia at 6%, and those were the rates in the IMFINZI arm. Looking at the study as a whole, there was 29% of patients in the IMFINZI arm who had a serious adverse reaction versus 23% in the placebo arm. The common adverse reactions—not necessarily serious but common in the IMFINZI arm—were radiation pneumonitis, pneumonia, upper respiratory infections, cough, dyspnea and rash. It's important to note that the rate of discontinuing IMFINZI due to these adverse reactions was about 15%, whereas it was 10% in the placebo arm.

Dr. Caudle:
Okay. All right. Now, I'd like to sort of go back and maybe take a 50,000-foot view and I'd like you to talk about how the release of this overall data, the PACIFIC trial, etc., has impacted your practice. How have you changed, or your practice changed as a result of what we're learning from this?

Dr. Kruser:
I think this has really injected a sense of optimism into this space. When I was going through training, there tended to be a bit of nihilism when treating patients with stage III non-small cell lung cancer, especially in light of the poor outcomes that had become common to expect, so with this improvement in overall survival, this has established a standard of care and really makes us more optimistic about pursuing aggressive treatment in these patients, and in that context, these patients really need to have multidisciplinary consultation to make sure all treatment options have been presented to them, including chemoradiotherapy and IMFINZI.

Dr. Caudle:
Absolutely. Well, your perspective is very helpful. It's nice to hear about the optimism that you feel. So, let's go back to the real world and give some maybe real-world examples of how all of this has changed your day-to-day management of patients. What's changed?

Dr. Kruser:
Yes, I think the biggest thing that has changed is that we now think of stage III lung cancer as something that's going to merit a long treatment course. So, we used to think about 6 weeks of chemoradiotherapy as the standard, and somewhat we were kind of racing to this finish line of 6 weeks. I really try to, in my practice, highlight the patients that the chemoradiotherapy is now a component of a treatment package that's going to include 12 months of IMFINZI following the completion of chemoradiotherapy if all goes well.

Dr. Kruser:
So, we really like to minimize the chance that patients are going to go through this and have side effects that preclude them from moving on to IMFINZI thereafter, so that can include really proactive management of their side effects and coordinating supportive care with our chemotherapy colleagues, but also using advanced radiation techniques such as IMRT to minimize any esophagitis that might make the patient feel poorly at the end of their treatment course.

Dr. Caudle:
Okay. Now, Dr. Kruser, I want to talk a little bit about patients who maybe have refused treatment or maybe those patients who want to wait. Have you had experiences with patients in those situations, and what's your approach in each case?

Dr. Kruser:
So, again, I try early on to set the expectation with my patients that the IMFINZI for 12 months is part of the entire course that they're going to go through because we really want to minimize the likelihood that patients are going to drop off given the significant benefits we saw with IMFINZI in the PACIFIC study. Again, we like to be proactive about our side effect management, to minimize any problems the patients are having at the end of the 6 weeks, and again, utilize the best radiation we can to keep all of their abilities to go on to restaging scans and continuation with IMFINZI to be as smooth as possible and to get them on to that important part of their treatment package.

Dr. Caudle:
Okay, great. Now, before we close—and this has been a really great discussion—do you have any final takeaways for our audience?

Dr. Kruser:
I would just say that I think this is a really exciting time to be a radiation oncologist and any oncologist who's focused on lung cancer.

Dr. Caudle:
Sure.

Dr. Kruser:
And certainly, no patient wants to find themselves in this scenario, but that said, the outcomes are much better now than they had been in prior eras.

Dr. Caudle:
Right.

Dr. Kruser:
I would just reiterate for the audience that IMFINZI and the PACIFIC study have shown statistically significant improvement in overall survival at 2 years and that the ASCO data at 3 years showed that over half of patients are still alive that go through the PACIFIC regimen, so therefore, the PACIFIC regimen is a comprehensive treatment plan and offers improved outcomes and a lot more optimism in this disease setting.

Dr. Caudle:
Excellent. Thank you so much for explaining that, and it's really been great having an opportunity to really learn more about the recent data as well as your personal experiences with this treatment approach for patients with unresectable stage III non-small cell lung cancer. I really would like to thank you, Dr. Timothy Kruser, for sharing your thoughts with us today. It was wonderful having you on the program.

Dr. Kruser:
Thank you, Dr. Caudle. It was a pleasure to be here.

Important Safety Information

There are no contraindications for IMFINZI® (durvalumab).

IMFINZI can cause serious, potentially fatal adverse reactions including immune-mediated pneumonitis, hepatitis, colitis, endocrinopathies, nephritis, dermatologic reactions, other immune-mediated adverse reactions, infection, and infusion-related reactions. Please refer to the full Prescribing Information for important dosage modification and management information specific to adverse reactions.

Immune-Mediated Pneumonitis

IMFINZI can cause immune-mediated pneumonitis, defined as requiring use of corticosteroids. Fatal cases have been reported. Monitor patients for signs and symptoms of pneumonitis and evaluate with radiographic imaging when suspected. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold IMFINZI for Grade 2 pneumonitis; permanently discontinue for Grade 3 or 4 pneumonitis.

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, pneumonitis occurred in 5% of patients, including Grade 3 (0.8%), Grade 4 (<0.1%), and Grade 5 (0.3%) pneumonitis. Pneumonitis led to discontinuation of IMFINZI in 1.5% of the 1889 patients. The incidence of pneumonitis (including radiation pneumonitis) was higher in patients in the PACIFIC study who completed treatment with definitive chemoradiation within 42 days prior to initiation of IMFINZI (34%) compared to patients in other clinical studies (2.3%) in which radiation therapy was generally not administered immediately prior to initiation of IMFINZI. In the PACIFIC study, the incidence of Grade 3 pneumonitis was 3.4% and of Grade 5 pneumonitis was 1.1% in the IMFINZI arm. In the PACIFIC study, pneumonitis led to discontinuation of IMFINZI in 6% of patients.

The frequency and severity of immune-mediated pneumonitis were similar whether IMFINZI was given as a single agent in patients with various cancers or in combination with chemotherapy in patients with ES-SCLC.

Immune-Mediated Hepatitis

IMFINZI can cause immune-mediated hepatitis, defined as requiring use of corticosteroids. Fatal cases have been reported. Monitor patients for signs and symptoms of hepatitis during and after discontinuation of IMFINZI, including clinical chemistry monitoring. Administer corticosteroids for Grade 2 or higher elevations of ALT, AST, and/or total bilirubin. Withhold IMFINZI for ALT or AST greater than 3 but less than or equal to 8 times the ULN or total bilirubin greater than 1.5 but less than or equal to 5 times the ULN; permanently discontinue IMFINZI for ALT or AST greater than 8 times the ULN or total bilirubin greater than 5 times the ULN or concurrent ALT or AST greater than 3 times the ULN and total bilirubin greater than 2 times the ULN with no other cause.

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, hepatitis occurred in 12% of patients, including Grade 3 (4.4%), Grade 4 (0.4%), and Grade 5 (0.2%) hepatitis. Hepatitis led to discontinuation of IMFINZI in 0.7% of the 1889 patients.

Immune-Mediated Colitis

IMFINZI can cause immune-mediated colitis, defined as requiring use of corticosteroids. Administer corticosteroids for Grade 2 or greater colitis or diarrhea. Withhold IMFINZI for Grade 2 colitis or diarrhea; permanently discontinue for Grade 3 or 4 colitis or diarrhea.

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, colitis or diarrhea occurred in 18% of patients, including Grade 3 (1.0%) and Grade 4 (0.1%) immune-mediated colitis. Diarrhea or colitis led to discontinuation of IMFINZI in 0.4% of the 1889 patients.

Immune-Mediated Endocrinopathies

IMFINZI can cause immune-mediated endocrinopathies, including thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, and hypophysitis/hypopituitarism. Monitor patients for clinical signs and symptoms of endocrinopathies.

- Thyroid disorders—Monitor thyroid function prior to and periodically during treatment. Initiate hormone replacement therapy or medical management of hyperthyroidism as clinically indicated. Withhold IMFINZI for Grades 2–4 hyperthyroidism, until clinically stable. Continue IMFINZI for hypothyroidism.
  In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, hypothyroidism occurred in 11% of patients, while hyperthyroidism occurred in 7% of patients. Thyroiditis occurred in 0.9% of patients, including Grade 3 (<0.1%). Hypothyroidism was preceded by thyroiditis or hyperthyroidism in 25% of patients.

- Adrenal insufficiency—Administer corticosteroids as clinically indicated and withhold IMFINZI until clinically stable for Grade 2 or higher adrenal insufficiency. In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, adrenal insufficiency occurred in 0.7% of patients, including Grade 3 (<0.1%) adrenal insufficiency.

- Type 1 diabetes mellitus—Initiate treatment with insulin as clinically indicated. Withhold IMFINZI for Grades 2–4 type 1 diabetes mellitus, until clinically stable. In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, type 1 diabetes mellitus occurred in <0.1% of patients.

- Hypophysitis—Administer corticosteroids and hormone replacement as clinically indicated and withhold IMFINZI until clinically stable for Grade 2 or higher hypophysitis. Hypopituitarism leading to adrenal insufficiency and diabetes insipidus occurred in <0.1% of 1889 patients with various cancers who received IMFINZI.

Immune-Mediated Nephritis

IMFINZI can cause immune-mediated nephritis, defined as evidence of renal dysfunction requiring use of corticosteroids. Fatal cases have occurred. Monitor patients for abnormal renal function tests prior to and periodically during treatment with IMFINZI. Administer corticosteroids as clinically indicated. Withhold IMFINZI for creatinine greater than 1.5 to 3 times the ULN; permanently discontinue IMFINZI and administer corticosteroids in patients with creatinine greater than 3 times the ULN.

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, nephritis (reported as any of the following: increased creatinine or urea, acute kidney injury, renal failure, decreased glomerular filtration rate, tubulointerstitial nephritis, decreased creatinine clearance, glomerulonephritis, and nephritis) occurred in 6.3% of the patients including Grade 3 (1.1%), Grade 4 (0.2%), and Grade 5 (0.1%) nephritis. IMFINZI was discontinued in 0.3% of the 1889 patients.

Immune-Mediated Dermatologic Reactions

IMFINZI can cause immune-mediated rash. Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN) has occurred with other products in this class. Administer corticosteroids for Grade 2 rash or dermatitis lasting for more than 1 week or for Grade 3 or 4 rash or dermatitis. Withhold IMFINZI for Grade 2 rash or dermatitis lasting longer than 1 week or Grade 3 rash or dermatitis; permanently discontinue IMFINZI in patients with Grade 4 rash or dermatitis.

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, 26% of patients developed rash or dermatitis and 0.4% of the patients developed vitiligo. Rash or dermatitis led to discontinuation of IMFINZI in 0.1% of the 1889 patients.

Other Immune-Mediated Adverse Reactions

IMFINZI can cause severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system. While immune-mediated reactions usually manifest during treatment with IMFINZI, immune-mediated adverse reactions can also manifest after discontinuation of IMFINZI. For suspected immune-mediated adverse reactions, exclude other causes and initiate corticosteroids as clinically indicated. Withhold IMFINZI for Grade 3 immune-mediated adverse reactions, unless clinical judgment indicates discontinuation; permanently discontinue IMFINZI for Grade 4 adverse reactions.

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% each in 1889 patients who received IMFINZI: aseptic meningitis, hemolytic anemia, immune thrombocytopenic purpura, myocarditis, myositis, and ocular

inflammatory toxicity, including uveitis and keratitis. In patients who received IMFINZI in clinical studies outside of the pooled dataset, myasthenia gravis occurred at an incidence of less than 0.1%. Permanently discontinue IMFINZI if myasthenia gravis does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory and/or autonomic insufficiency. Additional clinically significant immune-mediated adverse reactions have been seen with other products in this class (see Warnings and Precautions Section 5.7 of IMFINZI full Prescribing Information).

Infection

IMFINZI can cause serious infections, including fatal cases. Monitor patients for signs and symptoms of infection and treat as clinically indicated. Withhold IMFINZI for Grade 3 or 4 infection, until clinically stable.

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, infections occurred in 43% of patients, including Grade 3 (8%), Grade 4 (1.9%), and Grade 5 (1.0%). The overall incidence of infections in IMFINZI-treated patients in the PACIFIC study (56%) was higher compared to patients in other clinical studies (38%) in which radiation therapy was generally not administered immediately prior to initiation of IMFINZI. In patients with UC in Study 1108 (n=182), the most common Grade 3 or higher infection was urinary tract infections, which occurred in 4% of patients. In patients with Stage III NSCLC in the PACIFIC study, the most common Grade 3 or higher infection was pneumonia, which occurred in 5% of patients.

Infusion-Related Reactions

IMFINZI can cause severe or life-threatening infusion-related reactions. Monitor patients for signs and symptoms of an infusion-related reaction. Interrupt or slow the rate of infusion for Grades 1–2 infusion-related reactions; permanently discontinue for Grades 3–4 infusion-related reactions.

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, infusion-related reactions occurred in 2.2% of patients, including Grade 3 (0.3%).

Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman. There are no data on the use of IMFINZI in pregnant women. Advise pregnant women of the potential risk to a fetus and advise women of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of IMFINZI.

Lactation

There is no information regarding the presence of IMFINZI in human milk; however, because of the potential for adverse reactions in breastfed infants from IMFINZI, advise women not to breastfeed during treatment and for at least 3 months after the last dose.

Most Common Adverse Reactions

- In patients with Stage III NSCLC in the PACIFIC study (IMFINZI n=475), the most common adverse reactions (≥20% of patients) were cough (40%), fatigue (34%), pneumonitis or radiation pneumonitis (34%), upper respiratory tract infections (26%), dyspnea (25%), and rash (23%). The most common Grade 3 or 4 adverse reaction (≥3%) were pneumonitis/radiation pneumonitis (3.4%) and pneumonia (7%).
- In patients with Stage III NSCLC in the PACIFIC study (IMFINZI n=475), discontinuation due to adverse reactions occurred in 15% of patients in the IMFINZI arm. Serious adverse reactions occurred in 29% of patients receiving IMFINZI. The most frequent serious adverse reactions (≥2% of patients) were pneumonitis or radiation pneumonitis (7%) and pneumonia (6%). Fatal pneumonitis or radiation pneumonitis and fatal pneumonia occurred in <2% of patients and were similar across arms.

The safety and effectiveness of IMFINZI have not been established in pediatric patients.

Indication

IMFINZI is indicated for the treatment of adult patients with unresectable Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

Please see complete Prescribing Information, including Medication Guide.

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