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Examining a Therapeutic Modality for 2L+ mNSCLC

Announcer:
Welcome to *Project Oncology* on ReachMD.

This medical industry feature, titled *"Examining a Therapeutic Modality for 2L+ mNSCLC,"* is sponsored by Novocure.

Here's your host, Dr. Gates Colbert.

Dr. Colbert:
Despite improvements in the first-line setting, 80 percent of patients with non-small cell lung cancer will progress. Even with the use of first-line immune checkpoint inhibitors, the five-year overall survival rate is approximately 18 percent.[1] Join us as we explore an FDA-approved therapeutic modality in second line for metastatic NSCLC that aims to address this unmet need.

This is ReachMD, and I'm Dr. Gates Colbert. Today, we'll examine the mechanism of action and data on the efficacy, safety, and impact on patient quality of life associated with Optune Lua®, the Tumor Treating Fields, or TTFields, therapy for metastatic non-small cell lung cancer.

Joining our discussion is Dr. Eric Nadler who's a medical oncologist at Texas Oncology-Baylor Charles A. Sammons Cancer Center in Dallas, Texas and the Medical Director of U.S. Oncology Health Informatics and Internet Technology.

Dr. Nadler, welcome to the program.

Dr. Nadler:
I'm excited. And thank you all for coming today and participating in this program to learn about innovations in non-small cell lung cancer.

Dr. Colbert:
Before we delve into Optune Lua, let's take a moment here to review the Important Safety Information.

Announcer:
Optune Lua Indication for Use and Important Safety Information

Indication For Use – Metastatic non-small cell lung cancer
Optune Lua® is intended as a treatment concurrent with PD-1/PD-L1 inhibitors or docetaxel for adult patients with metastatic non-small cell lung cancer who have progressed on or after a platinum-based regimen.

Contraindications
Do not use Optune Lua in patients with an electrical implant. Use of Optune Lua together with electrical implants has not been tested and may lead to malfunctioning of the implanted device.

Do not use Optune Lua in patients known to be sensitive to conductive hydrogels. In this case, skin contact with the gel used with Optune Lua may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions, such as a fall in blood pressure and breathing difficulty.

Warnings and Precautions
Optune Lua can only be prescribed by a healthcare provider that has completed the required certification training provided by Novocure® (the device manufacturer).

Do not prescribe Optune Lua for patients who are pregnant, whom you think might be pregnant, or who are trying to get pregnant, as the safety and effectiveness of Optune Lua in these populations have not been established.

The most common (≥10%) adverse events involving Optune Lua concurrent with PD-1/PD-L1 inhibitors or docetaxel were dermatitis, musculoskeletal pain, fatigue, anemia, dyspnea, nausea, cough, diarrhea, anorexia, pruritus, leukopenia, pneumonia, respiratory tract infection, localized edema, rash, pain, constipation, skin ulcers, and hypokalemia.

Other potential adverse effects associated with the use of Optune Lua include treatment related skin toxicity, allergic reaction to the adhesive or to the gel, overheating of the array leading to pain and/or local skin burns, infections at the site where the arrays make contact with the skin, local warmth and tingling sensation beneath the arrays, medical device site reaction, muscle twitching, and skin breakdown or skin ulcer.

If the patient has an underlying serious skin condition on the chest, evaluate whether this may prevent or temporarily interfere with Optune Lua treatment.

Please see the Optune Lua Instructions For Use (IFU) for complete information regarding the device's indications, contraindications, warnings, and precautions at OptuneLuaHCP.com

Dr. Colbert:
Now that we've heard that Important Safety Information, let's briefly examine the treatment landscape and the unmet need and second-line setting for metastatic non-small cell lung cancer. Dr. Nadler, can you tell us more about the development of second-line treatment options?

Dr. Nadler:
Absolutely. The current options for second-line treatment of non-small cell lung cancer are unfortunately limited, so there's need for new treatments that can improve survival without increasing toxicity.[2] This is where modalities like Tumor Treating Fields, can come into play. Optune Lua is an innovative, wearable device for patients with metastatic non-small cell lung cancer that have progressed on or after platinum-based therapy. It is a noninvasive, antimitotic treatment that uses alternating electrical fields to kill cancer cells. Tumor Treating Fields therapy is delivered by a portable, wearable medical device and two pairs of transducer arrays, which are essentially adhesive bandages with biocompatible insulated ceramic discs covered by a hydrogel.[3]

Dr. Colbert:
How interesting. So what's the history of Tumor Treating Fields therapy? And has this treatment modality been used for other indications?

Dr. Nadler:
Yes, actually the first clinical trial for Tumor Treating Fields started back in 2006. To date, Tumor Treating Fields therapy has received FDA approvals for three indications.[4–9]

Dr. Colbert:
Thanks for this background. Now let's dive into the mechanism of action for Tumor Treating Fields. Dr. Nadler, can you explain how this modality targets cancer cells?

Dr. Nadler:
Sure. What we know based on preclinical data is that Tumor Treating Fields exert forces on charged molecules to kill cancer cells without stimulating or significantly heating the surrounding tissue. Tumor Treating Fields uses a frequency range of 100 to 500 kilohertz to inhibit cancer cells and cause cell death, while sparing healthy cells due to their differing properties, such as divisional rate, morphology, and the electrical properties themselves. Tumor Treating Fields are tuned to different frequencies depending on tumor cell type. For example, at a frequency of 150 kilohertz, it's been shown to inhibit non-small cell lung cancer cells in vitro. [3,10-15]

Now the mechanism of action at cancer cells involves disruption of mitosis. Tumor Treating Fields exerts physical forces on the electrically charged components of the cancer cells, disrupting the assembly of the mitotic spindle, leading to impaired cell division and possibly tumor cell death. [3,16,17]

Per preclinical *in vitro* modeling data, this process activates a downstream immune response:[18]

- enhancing the recognition of tumor cells by the immune system,
- leading to T-cell infiltration at the tumor site, and
- initiating a systemic antitumor response which can lead to increased cancer cell surveillance throughout the body.

Dr. Colbert:
For those just tuning in, you're listening to *Project Oncology* on ReachMD.

I'm Dr. Gates Colbert, and today I'm speaking with Dr. Eric Nadler about the mechanisms and clinical data of the Tumor Treating Fields therapy Optune Lua in treating metastatic non-small cell lung cancer.

Now that we've discussed the history and mechanism of action underlying this unique treatment modality, I'd like to shift over to the efficacy and safety data for Optune Lua. Dr. Nadler, how was the study designed and what were the patient characteristics?

Dr. Nadler:
So the LUNAR study was a global phase 3 clinical trial that investigated Optune Lua when concurrently administered with either a PD-1/PD-L1 inhibitor or docetaxel in patients with metastatic non-small cell lung cancer who progressed on or after platinum-based therapy.[3,19]

This trial enrolled 291 patients, randomized one to one to receive either Tumor Treating Fields therapy plus a PD-1/PD-L1 inhibitor or docetaxel, or PD-1/PD-L1 inhibitor or docetaxel alone. The primary endpoint was overall survival in the Tumor Treating Fields therapy arm versus a PD-1/PD-L1 inhibitor or docetaxel alone. Key secondary endpoints included overall survival for patients treated with Tumor Treating Fields therapy plus a PD-1/PD-L1 inhibitor or docetaxel, compared to the inhibitor or docetaxel alone.[3]

The key eligibility criteria included patients aged 22 or older, with the median age being 65, who had metastatic non-small cell lung cancer and progressed on or after platinum-based therapy, along with an ECOG performance status of zero to two.[3]

Looking at the study population, baseline demographics were well-balanced across all treatment subgroups and 68 percent of patients had an ECOG performance status of one. Most patients had only one prior line of systemic therapy, and about one-third of patients in the study had prior immune checkpoint inhibitor therapy. Notably, only four percent of patients were re-treated with an immunotherapy as part of their prior treatment regimen.[3,20]

In terms of histology, there was a relative even split of patients with non-squamous and squamous histology, at 57 percent and 43 percent, respectively.[3]

And overall, 16 percent of patients had PD-L1 expression of less than one percent, 27 percent had PD-L1 expression between one and 49 percent, and 10 percent had PD-L1 expression over 50 percent. As PD-L1 status assessment wasn't mandated at the time of enrollment, 46 percent of patients had unknown PD-L1 status.[19]

Dr. Colbert:
And how did Optune Lua perform in terms of the study endpoints?

Dr. Nadler:
The study met its primary endpoint with the statistically significant improvement in overall survival and this was the first significant overall survival improvement demonstrated by a second-line, or latter, treatment for metastatic non-small cell lung cancer in eight years.[21] There was a 3.3-month improvement in median overall survival between the Tumor Treating Fields plus a PD-1/PD-L1 inhibitor or docetaxel group versus the PD-1/PD-L1 inhibitor or docetaxel alone arm, at 13.2 months and 9.9 months, respectively. And this was associated with the 24 percent reduction in the risk of death.[3,19]

Next, the subgroup receiving Tumor Treating Fields with a PD-1/PD-L1 inhibitor had a statistically significant overall survival benefit with a median OS benefit of 19 months compared to the 10.8 months in the group receiving PD-1/PD-L1 inhibitors alone. This represents a 37 percent reduction in the risk of death with a hazard ratio of 0.63 and a P value of 0.024. Looking at one-year survival, for Tumor Treating Fields plus a PD-1/PD-L1 inhibitor, the survival rate was 61 percent compared to 46 percent with a PD-1/PD-L1 inhibitor alone.[3]

And finally, in the docetaxel subgroup, there was a numeric trend toward improved overall survival in the Tumor Treating Fields plus docetaxel subgroup, but it was not statistically significant. Here, the median overall survival was 11.1 months with the Tumor Treating Fields plus docetaxel versus 8.9 months with docetaxel alone with a hazard ratio of 0.88 and a P value of 0.47.[3]

Dr. Colbert:
And now let's turn to the Tumor Treating Fields safety data. What were the results from the LUNAR trial here?

Dr. Nadler:
When we look at the safety data, we see that Optune Lua did not add systemic toxicity. About 40 percent of patients who received a PD-

1/PD-L1 inhibitor/docetaxel alone reported any serious adverse event, compared to almost 55 percent of patients who received Tumor Treating Fields with PD-1/PD-L1 inhibitor or docetaxel. In addition, there was no difference in the rate of grade three or four pneumonitis or other systemic adverse events.[3,22]

There were no reports of device-related grade four toxicities or deaths.[3]

In fact, adverse events were balanced between treatment arms, except for dermatitis. Skin-related adverse events were reported in 63.1 percent of patients treated with Optune Lua, which were mostly mild to moderate. Six patients reported grade three skin toxicity requiring a treatment break, with all cases resolving. In the LUNAR study, skin irritation improved with topical medications. Regular relocation of the transducer arrays is recommended for continuous use. The arrays are moved two centimeters from the original mapping upon the first array change and then back to the original mapping on the second change and so on.[3,22,23]

So I'd encourage healthcare providers to proactively manage patients for dermatologic reactions. This involves ensuring patients are educated on dermatologic toxicity and well-informed about the importance of reporting symptoms as soon as they occur, the use of water-based skin barriers, appropriate prophylactic topical agents, and regular monitoring with prompt treatment. The goal is to get ahead of adverse skin reactions to hopefully allow patients to remain on treatment longer.[23,24]

Dr. Colbert:
Thanks for walking us through the safety data. Now let's explore the patient experience with Tumor Treating Fields. How did it impact the patients' quality of life in the LUNAR trial?

Dr. Nadler:
Patients treated with Optune Lua reported no significant differences in health-related quality of life compared to those receiving a PD-1/PD-L1 inhibitor or docetaxel alone. Quality of life scores remained stable and mean global health status scores were similar across treatment groups at both baseline and 54 weeks.[19]

Dr. Colbert:
And that brings us near the end of our program. So, Dr. Nadler, what key takeaways would you like to leave with our audience?

Dr. Nadler:
So Optune Lua is an FDA-approved, wearable treatment that uses Tumor Treating Fields to disrupt mitotic activity of metastatic non-small cell lung cancer cells without adding systemic toxicity.[3]

The LUNAR study demonstrated a 3.3-month improvement in median overall survival in patients treated with Optune Lua plus a PD-1/PD-L1 inhibitor/docetaxel versus either treatment alone, and an 8.2-month improvement in Tumor Treating Fields plus a PD-1/PD-L1 inhibitor compared to the inhibitor alone.

Patients treated with Tumor Treating Fields and docetaxel showed a trend toward improved median overall survival compared to those treated with docetaxel alone, with a 2.2-month increase, though it did not achieve statistical significance.[3]

Importantly, there were no additional systemic toxicities reported in the LUNAR study, and the most common device-related adverse event was mild-to-moderate skin irritation.[3]

Dr. Colbert:
Thank you for breaking down all of the key information as we end our discussion today.

I want to thank my guest, Dr. Eric Nadler, for his comprehensive overview of Tumor Treating Fields and its potential in treating metastatic non-small cell lung cancer.

Dr. Nadler, it was great speaking with you today.

Dr. Nadler:
It's really an exciting time. Thank you.

Announcer:
This medical industry feature was sponsored by Novocure. If you missed any part of this discussion or to find others in this series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge.

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