Updates on Clinical Trials of Opdualag for Metastatic Melanoma

Melanoma Research Alliance interviews Dr. Hussein Tawbi, who led a clinical trial on the immunotherapy drug Opdualag.

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In March of 2022, the melanoma community celebrated the FDA approval of nivolumab + relatlimab (brand name Opdualag), a new treatment for patients with metastatic melanoma that combines two different immunotherapies, nivolumab and relatlimab, into one medicine.

This summer, at the American Society of Clinical Oncology (ASCO) Annual Meeting, we caught up with Dr. Hussein Tawbi, professor of melanoma medical oncology at the University of Texas MD Anderson Cancer Center, who led the phase 2-3 RELATIVITY-047 clinical trial, to learn any updates on these important results. Dr. Tawbi's answers, provided below, have been lightly edited for clarity and length.

Could you provide some updates on new data reported from the RELATIVITY-047 trial?

Dr. Hussein Tawbi: We are really excited about our data from the RELATIVITY-047 clinical trial, the study that led to FDA approval of Opdualag as a first line therapy for patients with metastatic melanoma.

We're excited because the trial has given us the opportunity to treat patients with a combination that offers additional benefit over the single agent treatment nivolumab with only a modest increase in toxicity. This is counter to the use of combinations like ipilimumab + nivolumab, which have been used over the last 10 years and gives us more benefit, but leads to more toxicity. It's gratifying to see that we are targeting new immune checkpoint proteins that give us benefit with less toxicity.

RELATIVITY-047 was a randomized Phase 2/3 trial comparing nivolumab + relatlimab vs nivolumab alone. The primary endpoint was progression free survival (PFS). Progression free survival is the amount of time the patient does not have progression of disease while on treatment with the combination versus the single agent. The first data we reported was after only 13 months of patient follow-up, because the data was compelling and had not met the primary endpoint. This data was reported and led to FDA approval.

We were happy with the results, but the truth is, we really needed more time to follow patients so that we could more thoroughly comprehend the results. There was enthusiasm about this study because our median patient follow-up time is a little over two years (25 months); and our minimum follow-up was 21 months. We were very confident about the results which show that progression free survival on nivolumab + relatlimab combination therapy remains very solidly better than treatment with the single agent nivolumab.

We now report that the one year PFS now is 48% with nivolumab + relatlimab therapy versus 37% from nivolumab therapy alone. The hazard ratio is almost a 20% decrease in risk of progression of disease or death for patients. The median PFS is 10 months for patients receiving nivolumab + relatlimab combination therapy compared to 4.6 months for patients receiving nivolumab therapy alone. So really great results.

What are the implications of these updated results for patients?

Dr. Tawbi: As this treatment combination becomes available for more patients, we want to try to inform practicing oncologists of what to expect after therapy. Therefore, we looked at what subsequent therapies were administered to patients after disease progression while enrolled in the trial. We found that patients who progressed on the combination therapy were treated with immunotherapy and targeted therapy afterwards in the second line. We then reported progression free survival 2 (PFS2) in patients, which is the amount of time it takes for disease to progress on the second line therapy. We observed that PFS2 is remarkably better for patients who received the combination therapy nivolumab + relatlimab than those who received nivolumab alone. We did not apply statistical significance to this data because it's an exploratory endpoint and not a primary end point.

There was some speculation from prior reports that maybe ipilimumab + nivolumab combination therapy wouldn't work as well in patients who had already received nivolumab + relatlimab. However, this was only reported in a very small retrospective study which indicated that the response rate was only 10%. In our study, patients treated with ipilimumab + nivolumab in the second line seem to have comparable response rates of about 20-25% post nivolumab + relatlimab or nivolumab only treatment, which is what we expected. We were happy to say that treatment with combination nivolumab + relatlimab (Opdualag) does not undermine treatment with a second line CTLA4 + PD-1. Similarly, BRAF and MEK inhibitors seem to work just as well in the second line in patients from both arms of the study.

How did treatment with nivolumab + relatlimab impact melanoma specific survival?

Dr. Tawbi: The last and the most exciting data we have is on melanoma specific survival. While treating patients for melanoma, some may unfortunately succumb due to other causes as our trial population has a median age of 60 to 63 years old. Patients were followed for several years, and some have been followed for five years now. We analyzed how many patients died due to melanoma and how many did not. We found that melanoma specific survival was 60% for those who received the combination therapy, and the hazard ratio indicates a 20% decrease in melanoma specific deaths when compared to those who received single agent nivolumab.

Although the difference was not statistically significant, the confidence interval doesn't cross one, which implies that there may be real benefit. Most excitingly, we observed a very clear plateau in patient survival after several years on treatment. So, this is really, really good news.

How did patients with brain metastases do in the trial?

Dr. Tawbi: The Relativity-047 phase three clinical trial did not include patients with brain metastases. In current practice, patients with brain metastases are treated with ipilimumab + nivolumab and not nivolumab + relatlimab based on the existing data. At MD Anderson, we think this is a really important issue that hasn't been addressed and we believe in generating the data. So, we are conducting a clinical trial at treating melanoma patients that have asymptomatic brain metastases with nivolumab + relatlimab to determine whether the combination therapy has activity in the brain. This new trial is very similar to the previous CheckMate-204 study conducted with ipilimumab + nivolumab including patients with asymptomatic brain metastases. We've already treated five patients and our goal is to enroll approximately 30 patients. I can't share the results yet, but this is a very important patient population, and the clinical trial is of vital importance.

Clinical trials, like the Relativity-047 study, are critically important not only to get a therapy like Opdualag approved, but also to help clinicians understand how best to use available therapies to maximize patient care. We are so appreciative of Dr. Tawbi for taking the time to speak to us about the evolving results from this study. Learn more about clinical trials at CureMelanoma.org/Clinicaltrials.

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