



American Association for Cancer Research

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To interview Yousef N. Zakharia, contact Julia Gunther at julia.gunther@aacr.org or 215-446-6896 (office) or 267-250-5441 (cell). For a photo of Zakharia, click [here](#). Visit our [newsroom](#).

Adding the IDO-pathway Inhibitor Indoximod to Pembrolizumab Improved the Melanoma Response Rate

WASHINGTON — Adding the investigational immunotherapy indoximod to the FDA-approved immunotherapy pembrolizumab (Keytruda) increased the proportion of patients with advanced melanoma who responded to treatment compared with previously reported response rates for pembrolizumab monotherapy, according to interim results from a [phase I/II clinical trial](#) presented here at the [AACR Annual Meeting 2017](#), April 1-5.

“In the phase III [KEYNOTE-006](#) clinical trial that led the FDA to approve the immune checkpoint inhibitor pembrolizumab as an initial treatment for patients with advanced melanoma, the overall response rate was [33 percent](#), meaning 33 percent of patients had partial or complete shrinkage of their tumors,” said [Yousef N. Zakharia, MD](#), assistant professor in the Department of Internal Medicine at the University of Iowa, Iowa City. “We set out to investigate whether we could improve upon this response rate by adding an inhibitor of the IDO pathway to pembrolizumab treatment.

“We are excited to share interim results from the phase II portion of this clinical trial, because the data show that 52 percent of patients treated with a combination of pembrolizumab and the IDO-pathway inhibitor indoximod had a partial or complete response without significant added toxicities,” continued Zakharia, who is also coleader of the early phase clinical trials program at the Holden Comprehensive Cancer Center at the University of Iowa.

“It is noteworthy that this trial did not exclude ocular melanoma, which has been shown to be more aggressive and less responsive to available systemic treatment,” added Zakharia. “Most comparable trials do not allow patients with ocular melanoma. When the results are considered without the ocular melanoma patients (9 out of 60), the response rate in cutaneous and nonocular melanoma is actually 59 percent. These robust data are very promising, but we need to confirm the clinical benefit in a larger, randomized trial.”

Zakharia explained that the normal function of the IDO pathway is to keep the immune system in check, preventing it from responding inappropriately; for example, it helps prevent the immune system of a pregnant woman from attacking her baby. “However, some tumors hijack the pathway, using it to prevent the immune system from attacking and destroying the tumors, suggesting that it could be a good target for cancer immunotherapy,” he said.

Previously [reported](#) results from the phase Ib portion of the clinical trial showed that the combination of indoximod and an FDA-approved immune checkpoint inhibitor called ipilimumab (Yervoy) was well tolerated and caused no increase in toxicity compared with the immune checkpoint inhibitor used alone.

In the phase II portion of the clinical trial, patients received indoximod and FDA-approved immune checkpoint inhibitor therapy of the treating physician's choice, either ipilimumab, pembrolizumab, or nivolumab (Opdivo). Most patients received indoximod (1200 mg orally twice every day) with pembrolizumab, which was infused at the standard dose of 3 mg/kg every 21 days.

The new data being reported were obtained with a January 2017 cutoff data. After a median follow up of 10.5 months, six of 60 patients had a complete response and 25 had a partial response, giving an overall response rate of 52 percent. The most common adverse events were fatigue, diarrhea, and nausea.

"The trial is still accruing patients and we are continuing to monitor all of the patients enrolled so far," said Zakharia. "This interim analysis represents the largest reported number of melanoma patients treated with the combination of an IDO-pathway inhibitor and standard checkpoint inhibitors to date."

According to Zakharia, the main limitation of the study is that the clinical trial had no control arm, which means that a large-scale, placebo-controlled randomized clinical is needed to confirm the current results.

This study was funded by NewLink Genetics. Zakharia has received scientific conference travel support from NewLink Genetics.

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About the American Association for Cancer Research

Founded in 1907, the American Association for Cancer Research (AACR) is the world's first and largest professional organization dedicated to advancing cancer research and its mission to prevent and cure cancer. AACR membership includes more than 37,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and patient advocates residing in 108 countries. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, biology, diagnosis, and treatment of cancer by annually convening more than 30 conferences and educational workshops, the largest of which is the AACR Annual Meeting with nearly 19,500 attendees. In addition, the AACR publishes eight prestigious, peer-reviewed scientific journals and a magazine for cancer survivors, patients, and their caregivers. The AACR funds meritorious research

directly as well as in cooperation with numerous cancer organizations. As the Scientific Partner of Stand Up To Cancer, the AACR provides expert peer review, grants administration, and scientific oversight of team science and individual investigator grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and other policymakers about the value of cancer research and related biomedical science in saving lives from cancer. For more information about the AACR, visit www.AACR.org.

Abstract: CT117

Presentation Session: [CTSY04 - Novel Immuno-oncology Agent Clinical Trials](#), Tuesday, April 4, 10:30 a.m.-12:45 p.m. ET, Ballroom C, Level 3

Title: Interim analysis of the Phase 2 clinical trial of the IDO pathway inhibitor indoximod in combination with pembrolizumab for patients with advanced melanoma

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Background: The indoleamine 2,3-dioxygenase (IDO) pathway is a key counter-regulatory mechanism that normally inhibits immune responses when appropriate. In the setting of cancer, IDO pathway-mediated immune suppression is exploited by tumors in order to prevent and defeat anti-tumor immunity. Small-molecule inhibitors of the IDO pathway, such as indoximod, are an increasingly validated class of potential cancer therapeutics. Additionally, pre-clinical tumor models have shown complementary effects with indoximod / anti-PD1 checkpoint inhibitor treatment combinations. A clinical trial was developed based upon these data.

Methods: Upon successful completion of a Phase 1b dose escalation cohort, metastatic melanoma patients were enrolled in a single arm Phase 2 trial evaluating the addition of indoximod to standard of care checkpoint inhibitors approved for melanoma. Treating physicians were allowed to administer their choice of approved checkpoint inhibitor. The large majority of patients received indoximod with pembrolizumab and this interim report is limited to those patients. Indoximod was administered continuously in 21 days cycles (1200mg po twice daily) concurrently with pembrolizumab (3mg/kg q21 days). Study endpoint is best overall response (objective response rate (ORR) = complete response rate (CR) + partial response rate (PR)) per site reported RECIST criteria.

Results: At time of data cut-off, 60 patients had received indoximod /pembrolizumab and were evaluable for response, defined as having at least one follow-up imaging study performed. The ORR was 52% (31/60) with a CRR of 8% (5/60). The combination was well tolerated. The most frequently reported adverse events (regardless of attribution), occurring in $\geq 20\%$ of subjects, were fatigue, diarrhea, nausea, arthralgia, headache, cough, rash, pruritus, and hypertension. The most frequently reported laboratory abnormalities (regardless of attribution), were anemia (17%) and hyperglycemia (17%).

Conclusions: The interim analysis of the combination of indoximod and pembrolizumab demonstrates an ORR of 52% which compares favorably with the established ORR for pembrolizumab alone. Updated data to be presented. NCT02073123.