Phase 2 Trial of the IDO Pathway Inhibitor Indoximod Plus Checkpoint Inhibition for the Treatment of Patients With Advanced Melanoma

9512

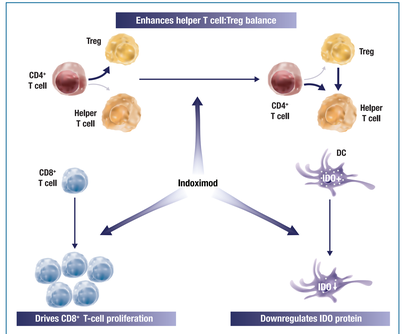
Yousef Zakharia,[1,*] Olivier Rixe,[2] John H. Ward,[3] Joseph J. Drabick,[4] Montaser F. Shaheen,[5] Mohammed M. Milhem,[1] David H. Munn,[6] Jiayi Yu,[7] Eugene Paul Kennedy,[7] Nicholas N. Vahanian,[7] Charles J. Link,[7] Robert R. McWilliams[8]

[1]University of Iowa Hospitals and Clinics, Holden Comprehensive Cancer Center, Iowa City, IA; [2]University of New Mexico Comprehensive Cancer Center, Albuquerque, NM; [3]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [4]Penn State Milton S. Hershey Medical Center, Palmyra, PA; [5]University of Arizona Cancer Center, Tucson, AZ; [6]Georgia Cancer Center, Augusta University, Augusta, GA; [7]NewLink Genetics Corporation, Ames, IA; [8]Mayo Clinic, Rochester, MN.

*Presenting author.

INTRODUCTION

- Melanoma is the fifth most common cancer in the United States, and the rates of new cases continue to increase each year[1,2]
- Despite improvements in overall survival (OS) rates of patients with stage IV metastatic melanoma with novel immunotherapies and targeted agents, the disease remains refractory to therapy[3]
- The indoleamine 2,3-dioxygenase (IDO) pathway mediates immunosuppressive effects through the metabolism of tryptophan (Trp) to kynurenine (Kyn), triggering downstream signaling through the Trp sensors general control nonderepressible 2 (GCN2) and mammalian target of rapamycin (mTOR) and the Kyn sensor aryl hydrocarbon receptor (AhR)[4-7]
- Indoximod is an orally administered, small-molecule IDO pathway inhibitor that reverses the immunosuppressive effects of low Trp and high Kyn that result from IDO activity (**Figure 1**)[8]
- Indoximod has immunostimulatory effects involving 3 main cell types: $CD8^+$ T cells, T regulatory cells (Treg), and dendritic cells (DCs) through the following mechanisms:
  - Reverses the effects of low Trp by increasing proliferation of effector T cells
  - Directly reprograms Treg into helper T cells
  - Downregulates IDO expression in DCs
- IDO is upregulated in many human tumors and tumor-draining lymph nodes, including malignant melanoma[9-11]
- Preclinical data and an increasing body of clinical data support evaluating the combination of a checkpoint inhibitor with an IDO pathway inhibitor as potential treatment for advanced melanoma[13,14]



Treg, T regulatory cell; DC, dendritic cell; IDO, indoleamine 2,3-dioxygenase.
Indoximod inhibits the effects of the IDO pathway, preventing Treg activation and myeloid-derived suppressor cell recruitment, promoting effector T-cell activation and proliferation, reprogramming of Treg to Th17-helper-like T cells, and DC activation.

Figure 1. Mechanism of action of indoximod.

METHODS

Study Design and Treatment

- Phase 2, single-arm, open-label study (ClinicalTrials.gov Identifier: NCT02073123)
- Patients received indoximod 1200 mg orally twice daily with an approved standard of care checkpoint inhibitor dosed per approved US product label:
  - Concomitant ipilimumab 3 mg/kg intravenously (IV) on Day 1 of each 21-day cycle for 4 cycles
  - Nivolumab 240 mg IV every 2 weeks
  - Pembrolizumab 2 mg/kg IV every 3 weeks
- Patients continued treatment until they experienced disease progression or significant toxicity
- Patients were followed clinically and radiographically at 12 weeks after treatment initiation and then every 8 weeks for tumor evaluation
- In part 2 of this study, patients were only enrolled to receive pembrolizumab
- Up to 20 patients were enrolled in an expansion cohort that required paired pretreatment and on-treatment core needle biopsies of the same lesion

Patients

- Eligible patients were ≥18 years of age with unresectable stage III or IV advanced melanoma and an Eastern Cooperative Oncology Group performance status of 0 to 2
- Exclusions included prior therapy with an immune checkpoint inhibitor or indoximod and systemic therapy within the previous 28 days

Assessments

- The safety and tolerability of combination therapy were assessed in all patients receiving ≥1 dose of study medication in the phase 2 and biopsy cohorts
- Efficacy was assessed in patients who received ≥1 dose of study medication and had ≥1 postbaseline response evaluation (efficacy evaluable population)
- The primary efficacy endpoint was overall response rate (ORR; complete response [CR] + partial response [PR]) based on Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.1, by site report
- Secondary objectives included median progression-free survival (PFS) and OS
- Scoring for programmed death-ligand 1 (PD-L1) expression was conducted using a validated assay for clone 22C3[15]
- Biopsies from patients in the expansion cohort underwent multiplex immunofluorescence staining for IDO1 and Ki67, with total IDO expression evaluated using IDO scores as previously described,[16] with minor modifications

RESULTS

Patients

- A total of 131 patients were enrolled and included in the safety population (**Table 1**)
- The efficacy evaluable population included 85 patients with cutaneous/mucosal melanoma who received indoximod + pembrolizumab, including the biopsy expansion cohort
- Among patients in the biopsy cohort, paired samples from before and during treatment were available from 11 patients

Table 1. Patient Disposition

Study cohort	N
Phase 1	9
Phase 2	101
Efficacy evaluable	70
Uveal melanoma	15
Treated with ipilimumab	4
Treated with nivolumab	4
Off study prior to first on-treatment imaging study	8
Adverse event	3
Progression	4
Withdrew	1
Biopsy Cohort	21
Efficacy evaluable	15
Uveal melanoma	3
Off study prior to first on-treatment imaging study	3
Adverse event	2
Withdrew	1
Totals	
Safety population	131
Efficacy evaluable population + biopsy cohort	85

- Patients in the efficacy evaluable population + biopsy cohort were a median 61.5 years of age and 56% were male (**Table 2**)

Table 2. Demographics and Baseline Characteristics

Characteristic	Indoximod + pembrolizumab (N = 85)*
Median age (range), y	61.5 (27-88)
Male, n (%)	56 (66)
White, n (%)	83 (98)
Disease stage,† n (%)	
IIIB	4 (5)
IIIC	6 (7)
IV	75 (88)
LDH above ULN, n (%)	22 (26)
ECOG performance status of 0 or 1, n (%)	85 (100)
Prior therapy, n (%)	
Radiation	14 (16)
Systemic‡	16 (19)

LDH, lactate dehydrogenase; ULN, upper limit of normal; ECOG, Eastern Cooperative Oncology Group; BRAF, B-Raf proto–oncogene, serine/threonine kinase; IL-2, interleukin 2.
*Excludes uveal melanoma patients.
†Data missing for 2 patients in the efficacy evaluable population.
‡Includes BRAF and IL-2, but treatment with a checkpoint inhibitor was not allowed per protocol.

Efficacy

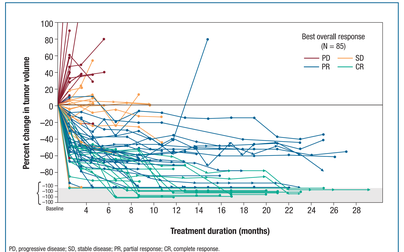
- The ORR was 53% in the efficacy evaluable + biopsy cohort population (**Table 3**)
  - CR was achieved by 18% of patients, and 73% of patients achieved disease control (CR + PR + stable disease)
- Median PFS in the efficacy evaluable + biopsy cohort population was 12.4 months (95% confidence interval: 7.1, 24.9)

Table 3. Response Rates and PFS*

Response status	Efficacy evaluable population (N = 70)*			Efficacy evaluable population + biopsy cohort (N = 85)*		
	Overall (N = 70)	Prior systemic therapy (N = 15)†	Prior radiation therapy (N = 13)	Overall (N = 85)	Prior systemic therapy (N = 16)†	Prior radiation therapy (N = 14)
PFS, median months (95% CI)	13.2 (9.0, 24.9)	–	–	12.4 (7.1, 24.9)	–	–
ORR, n (%)	**38 (54)**	**9 (60)**	**9 (69)**	**45 (53)**	**10 (63)**	**9 (64)**
CR	13 (19)	5 (33)	5 (38)	15 (18)	5 (31)	5 (36)
PR	25 (36)	4 (27)	4 (31)	30 (35)	5 (31)	4 (29)
SD	14 (20)	2 (13)	3 (23)	17 (20)	2 (13)	3 (21)
DCR	52 (74)	11 (73)	12 (92)	62 (73)	12 (75)	12 (86)
PD	18 (26)	4 (27)	1 (8)	23 (27)	4 (25)	2 (14)

PFS, progression-free survival; CI, confidence interval; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; DCR, disease control rate; PD, progressive disease; BRAF, B-Raf proto-oncogene, serine/threonine kinase; IL-2, interleukin 2.
*Excludes uveal melanoma patients.
†Prior systemic therapy includes BRAF inhibitors and IL-2.

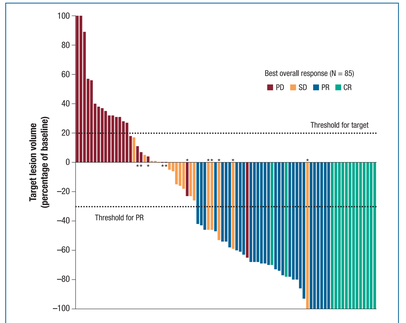
- Change in tumor volume per treatment cycle over time is shown in **Figure 2**
  - OR and PR responses were achieved as early as 12 weeks
  - Many patients who achieved CR or PR had durable and ongoing responses



PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

Figure 2. Change in tumor volume per treatment cycle according to best overall response.

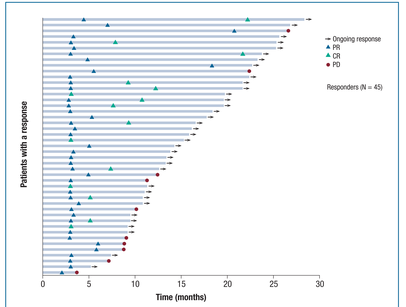
- The best response in target lesion volume in these patients with advanced melanoma shows significant depth of response (**Figure 3**)



PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; RECIST, Response Evaluation Criteria in Solid Tumors. All responses were assessed per RECIST, version 1.1. CR patients in whom the best response in change in tumor volume is not –100% have target lesions that are pathological lymph nodes of <10 mm. PR patients with a reduction in tumor volume of –100% are not CR patients due to nontarget lesions that are stable or have not completely resolved. SD or PD patients with a reduction in tumor volume of ≥30% are not responders due to either unequivocal nontarget lesion progression or an unconfirmed response.
*Patients who progressed due to new nontarget lesions.

Figure 3. Best response in target lesion volume by patient relative to baseline.

- Among responding patients, the combination of indoximod and pembrolizumab provides durable, ongoing responses with continued treatment (**Figure 4**)



PR, partial response; CR, complete response; PD, progressive disease.

Figure 4. Duration of response by patient.

PD-L1–positive patients

- Among 41 patients with tissue samples available for PD-L1 staining, 22 (54%) were positive for PD-L1 (**Table 3**)
- ORR for PD-L1–positive patients was 77% compared with 42% for PD-L1–negative patients

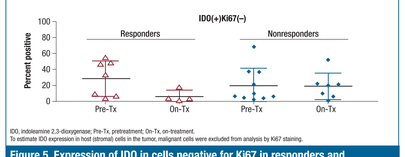
Table 4. Response by PD-L1 Status*

PD-L1 status	Efficacy evaluable population*
Tissue available, n/N (%)	41/70 (59)
PD-L1(+) staining	22/41 (54)
PD-L1(–) staining	19/41 (46)
Overall response rate by PD-L1, n/N (%)	
PD-L1(+) patients	17/22 (77)
PD-L1(–) patients	8/19 (42)

PD-L1, programmed death-ligand 1.
*Excluding the biopsy cohort.

Immunohistochemistry

- Results from immunofluorescence assays demonstrated that IDO(+)Ki67(–) cells, most likely representing DCs expressing IDO, tend to decrease IDO expression upon treatment in responders (**Figure 5**)



IDO, indoleamine 2,3-dioxygenase; Pre-Tx, pretreatment; On-Tx, on-treatment.
To estimate IDO expression in host (stromal) cells in the tumor, malignant cells were excluded from analysis by Ki67 staining.

Figure 5. Expression of IDO in cells negative for Ki67 in responders and nonresponders, before and after treatment.

Safety

- The combination of indoximod and a checkpoint inhibitor was generally well tolerated with limited grade 3/4 treatment-related adverse events (AEs)
- The most common (≥10% of patients) treatment-related AEs are shown in **Table 5**
- 21 patients (16.0%) discontinued due to treatment-related AEs (**Table 6**)
- Serious treatment-related AEs are shown in **Table 7**; no treatment-related AEs led to death

Table 5. Most Common (≥10% of Patients) Treatment-related AEs in the Safety Population

AE, n (%)	All grades (N = 131)	Grade 3/4 (N = 131)
Total	**127 (96.9)**	**13 (9.9)**
Fatigue	78 (59.5)	3 (2.3)
Pruritus	50 (38.2)	0
Rash	37 (28.2)	2 (1.5)
Diarrhea	34 (26.0)	4 (3.1)
Nausea	34 (26.0)	1 (0.8)
Arthralgia	25 (19.1)	1 (0.8)
Decreased appetite	24 (18.3)	0
Headache	23 (17.6)	0
Constipation	19 (14.5)	0
Rash maculopapular	16 (12.2)	3 (2.3)
Vomiting	16 (12.2)	0
Hypothyroidism	14 (10.7)	0

AE, adverse event.

Table 6. Treatment-related AEs That Led to Discontinuation

AE, n (%)	All grades (N = 131)
Total	**21 (16.0)**
Rash	4 (3.1)
ALT increased	3 (2.3)
Lipase increased	3 (2.3)
Amylase increased	2 (1.5)
AST increased	2 (1.5)
Colitis	2 (1.5)
Gastritis	2 (1.5)
Alkaline phosphatase increased	1 (0.8)
Blood bilirubin increased	1 (0.8)
Diarrhea	1 (0.8)
Fatigue	1 (0.8)
Hearing loss	1 (0.8)
Hepatitis/pancreatitis	1 (0.8)
Interstitial nephritis	1 (0.8)
Knee arthritis	1 (0.8)
Pneumonitis	1 (0.8)
Thrombocytopenia	1 (0.8)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 7. Treatment-related Serious AEs

AE, n (%)	All grades (N = 131)
Total	**14 (10.7)**
Colitis	2 (1.5)
Abdominal pain	1 (0.8)
ALT increased	1 (0.8)
Appendicitis	1 (0.8)
Arthritis	1 (0.8)
Deafness	1 (0.8)
Dehydration	1 (0.8)
Diarrhea	1 (0.8)
Dyspnea	1 (0.8)
Gastritis	1 (0.8)
Hyperglycemia	1 (0.8)
Myositis	1 (0.8)
Pneumatosis	1 (0.8)
Pneumonitis	1 (0.8)
Thrombocytopenia	1 (0.8)
Tubulointerstitial nephritis	1 (0.8)

AE, adverse event; ALT, alanine aminotransferase.

CONCLUSIONS

- **The combination of indoximod and checkpoint inhibition demonstrated an ORR of 53% and CR of 18% in these patients with advanced melanoma, and nearly three-quarters achieved disease control**
- **Responses to indoximod and checkpoint inhibition were deep and durable, with median PFS exceeding 1 year**
- **Combination therapy was generally well tolerated**

Acknowledgments

This study (ClinicalTrials.gov Identifier: NCT02073123) is funded by NewLink Genetics Corporation. Medical writing and editorial support were provided by Jason McDonough, PhD, CMPP, of MedErgy, and were funded by NewLink Genetics Corporation.

References

1. Siegel RL, et al. *CA Cancer J Clin.* 2017;67(1):7-30.
2. Surveillance Epidemiology and End Results (SEER). SEER cancer stat facts: melanoma of the skin. http://seer.cancer.gov/statfacts/html/melan.html. Accessed May 15, 2018.
3. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology™: Melanoma, v2.2018. https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/PDF/melanoma.pdf. Accessed May 15, 2018.
4. McGaha TL, et al. *Immunol Rev.* 2012;249(1):135-157.
5. Munn DH, et al. *Immunity.* 2005;22(5):633-642.
6. Metz R, et al. *Oncoimmunology.* 2012;1(9):1460-1468.
7. Opitz CA, et al. *Nature.* 2011;478(7368):197-203.
8. Brincks EL, et al. Presented at: Annual Meeting of the American Association for Cancer Research (AACR); April 14-18, 2018; Chicago, IL. Abstract 3753.
9. Uyttenhove C, et al. *Nat Med.* 2003;9(10):1269-1274.
10. Gerlini G, et al. *J Invest Dermatol.* 2010;130(3):898-901.
11. Lee JH, et al. *Clin Cancer Res.* 2005;11(1):107-112.
12. Lee JR, et al. *Lab Invest.* 2003;83(10):1457-1466.
13. Zakharia Y, et al. Presented at: Annual Meeting of the American Society of Clinical Oncology (ASCO); June 3-7, 2016; Chicago, IL. Abstract 3075.
14. Holmgaard RB, et al. *J Exp Med.* 2013;210(7):1389-1402.
15. Daud AI, et al. *J Clin Oncol.* 2016;34(34):4102-4109.
16. Rubel F, et al. *J Invest Dermatol.* 2018;138(3):679-687.

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from ASCO and the authors of this poster.