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A Phase 2 Randomized Trial of the IDO Pathway Inhibitor Indoximod in Combination With Taxane-based Chemotherapy for Metastatic Breast Cancer: Preliminary Data

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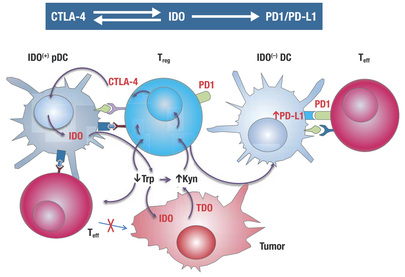
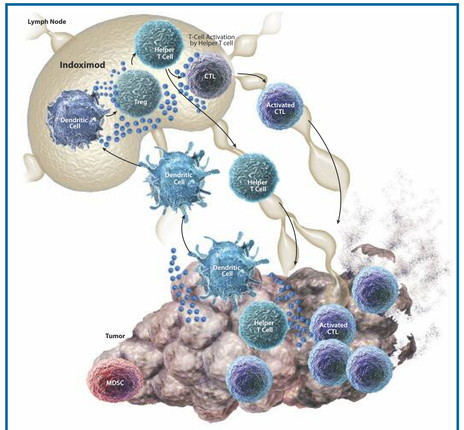
INTRODUCTION

- For patients with metastatic breast cancer, current treatments have unwanted side effects, responses to therapy are typically transient, and tumors ultimately become refractory to available therapies; thus, effective new therapies that are well tolerated are needed
- Indoleamine 2,3-dioxygenase (IDO) is a key immunomodulatory enzyme of acquired immune tolerance in normal and pathologic conditions, particularly in the tumor microenvironment, that allows tumors to thwart the host immune response (**Figure 1**)[1]
  - IDO inhibits CD8+ T cells and enhances the suppressor activity of regulatory T cells (Tregs)
- Indoximod (1-methyl-D-tryptophan) is an orally available, small molecule, broad IDO pathway inhibitor that has been shown to potentially interfere with multiple targets within the IDO pathway (**Figure 2**)
- Preclinical studies in MMTV-neu mouse models have shown that indoximod combined with chemotherapy had a greater in vivo antitumor effect than either agent alone[2]
- A Phase 1 trial combining docetaxel and indoximod demonstrated safety and responses in patients with metastatic solid tumors, including breast tumors[3]
  - 18% (4/22) of patients achieved a partial response (2 breast, 1 lung, 1 thymic)
- Based on these data, a Phase 2 trial evaluating indoximod in combination with taxane chemotherapy as first-line therapy in patients with metastatic breast cancer was initiated, and preliminary safety data will be presented



IDO, indoleamine 2,3-dioxygenase; TDO, tryptophan 2,3-dioxygenase; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; PD1, programmed death receptor 1; PD-L1, programmed death receptor ligand 1; pDC, plasmacytoid dendritic cell; T_{reg}, regulatory T cell; DC, dendritic cell; T_{eff}, effector T cell; Trp, tryptophan; Kyn, kynurenine.

Figure 1. IDO/TDO pathway and immune checkpoints.



Treg, regulatory T cell; CTL, cytotoxic T lymphocyte; MDSC, myeloid-derived suppressor cell.

Figure 2. Indoximod mechanism of action.

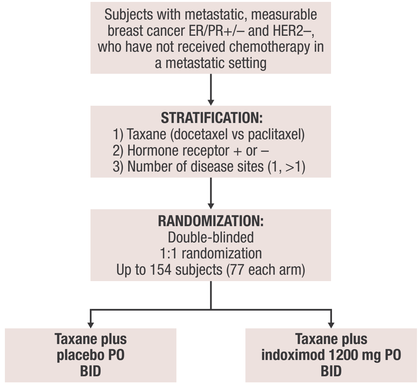
OBJECTIVES

- Primary endpoint: progression-free survival
- Secondary endpoints: overall survival, response rate per RECIST 1.1 criteria, safety, and immune response correlative assays

METHODS

Study Design

- This study is a 1:1 (indoximod:placebo) randomized, double-blinded, placebo-controlled, 2-arm, Phase 2 study; prior to randomization, patients are stratified to docetaxel or paclitaxel (**Figure 3**)
- For study arms 1A and 1B, treatment is intravenous docetaxel 75 mg/m^2 every 3 weeks on Day 8, plus placebo (1A) or oral indoximod 1200 mg (1B) BID on Days 1 to 14
- For study arms 2A and 2B, treatment is intravenous paclitaxel 80 mg/m^2 taken weekly for 3 out of 4 weeks, plus placebo (2A) or oral indoximod 1200 mg (2B) BID on Days 1 to 21
- Target enrollment is 154 patients across multiple clinical sites in the United States and Europe



ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; PO, orally; BID, twice daily.

Figure 3. Phase 2 randomization schema.

Eligibility

- Patients with measurable, histologically confirmed metastatic breast cancer
- No prior chemotherapies for metastatic disease; hormonal therapies are allowed
- ER/PR+/– and HER2–
- Eastern Cooperative Oncology Group Performance Status 0 to 1
- No active CNS disease
- No active autoimmune disease

Duration

- Treatment continues until disease progression, intercurrent illness or unacceptable toxicity that prevents further administration of treatment, or patient withdrawal
- Patients are followed for up to 5 years, until they are lost to follow up or death, whichever occurs first

RESULTS

- Baseline demographic characteristics are summarized in **Table 1**

Table 1. Patient Demographic Characteristics

Characteristic	Patients (N = 154)
Gender, n (%)	
Female	151 (98.1)
Male	3 (1.9)
Race, n (%)	
White	126 (81.8)
Black or African American	23 (14.9)
Asian	1 (0.6)
Other or unknown	4 (2.6)
Ethnicity, n (%)	
Hispanic or Latino	6 (3.9)
Not Hispanic or Latino	145 (94.2)
Not reported	3 (1.9)
Median age, y	58.0

Safety

- To date, 128 patients have evaluable safety data
- The most common indoximod-related AEs of any grade are summarized in **Table 2**
  - Fatigue (21%) was the most frequently reported AE that is possibly related to indoximod

Table 2. Indoximod-related AEs of Any Grade (Occurring in ≥5% of Patients)*

AE	Percentage of patients (n = 128)
Fatigue	21
Nausea	20
Diarrhea	13
Headache	12
Decreased appetite	9
Vomiting	9
Rash	8
Constipation	7
Increased aspartate aminotransferase	6
Blurred vision	5
Increased lacrimation	5

AE, adverse event.
*Includes all AEs considered by the Principal Investigator to be possibly, probably, or definitely related to the study treatment.

- The commonly observed taxane chemotherapy–associated AEs, including neutropenic fever, neuropathy, and edema, have been observed at the expected rates for taxane chemotherapy alone
- No immune-specific serious AEs have been observed
- No treatment-related deaths have been reported

CONCLUSIONS

- **For the 128 patients evaluable for safety, the regimen was generally well tolerated and aggregate data are similar to what is typically observed with taxanes**
- **No unexpected safety signals or immune-linked AEs were reported with the combination of indoximod with docetaxel or paclitaxel, suggesting that there is no additional toxicity with the addition of indoximod to taxane chemotherapy**
- **This Phase 2 trial has reached its targeted enrollment goal across multiple clinical sites in the United States and Europe**

References

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2. Muller AJ, et al. *Nat Med.* 2005;11(3):312-319.
3. Soliman HH, et al. *Oncotarget.* 2014;5(18):8136-8146.

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