

# Results of the Phase 1b Portion of a Phase 1/2 Trial of the Indoleamine 2,3-dioxygenase (IDO) Pathway Inhibitor Indoximod Plus Gemcitabine/nab-Paclitaxel for the Treatment of Metastatic Pancreas Cancer

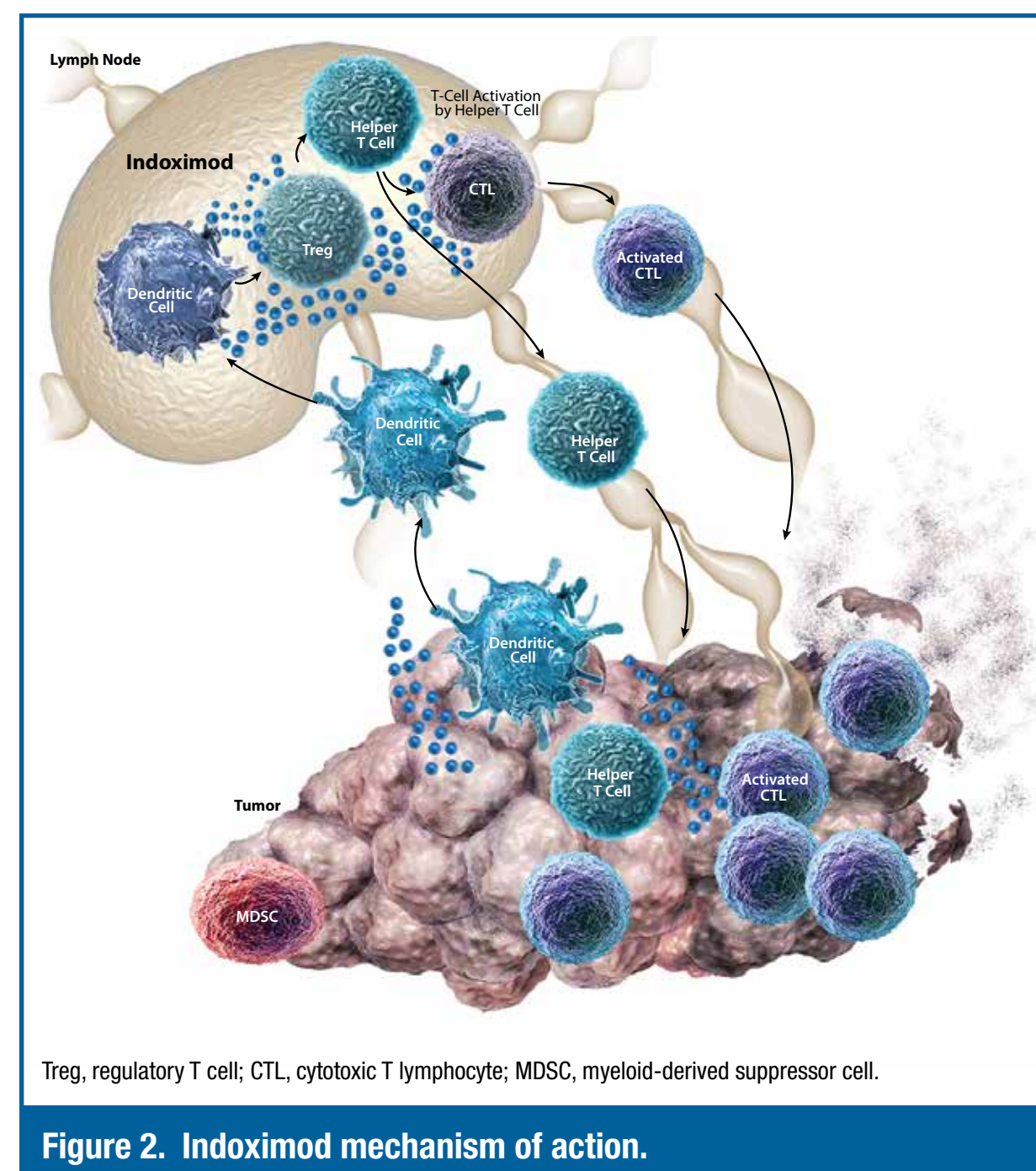
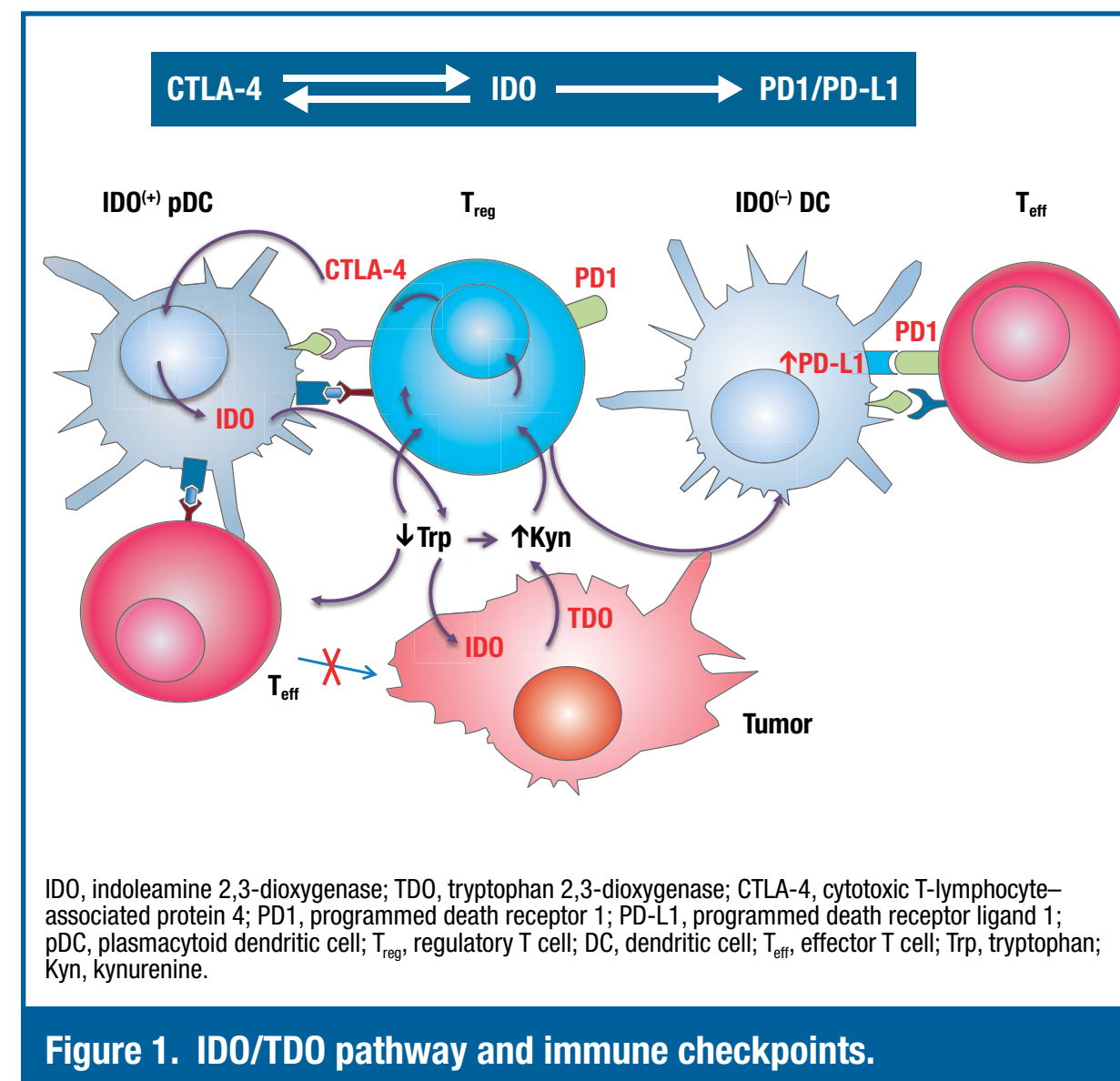
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## INTRODUCTION

- Pancreas cancer has limited treatment options and is projected to be the second deadliest malignancy by 2030<sup>1</sup>
- nab-paclitaxel was recently approved as combination treatment with gemcitabine for metastatic pancreas cancer<sup>2</sup>
  - A modest improvement in overall survival was observed with nab-paclitaxel plus gemcitabine compared with gemcitabine alone (8.5 months vs 6.7 months)<sup>3</sup>
  - This combination has become standard of care in metastatic pancreas cancer
- Immunotherapeutic approaches alone or in various combinations continue to show promise in multiple cancer types
- 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)<sup>4</sup>
  - IDO inhibits CD8+ T cells and enhances the suppressor activity of regulatory T cells (Tregs)
- Indoximod 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 models have demonstrated synergy between IDO pathway inhibition with indoximod and chemotherapy<sup>5</sup>
- A Phase 1 trial combining docetaxel and indoximod demonstrated safety and responses in patients with metastatic solid tumors<sup>6</sup>
  - No drug-drug interactions were noted, and 1200 mg indoximod was established as the maximum tolerated dose in combination with docetaxel
- Based on these findings, a Phase 1b/2 trial evaluating indoximod in combination with standard of care chemotherapy (gemcitabine and nab-paclitaxel) for patients with metastatic pancreas cancer was initiated, and preliminary data from the Phase 1b portion will be presented



## OBJECTIVES

- Primary endpoints for the Phase 1b component:
  - Determination of the recommended Phase 2 dose of indoximod when administered with gemcitabine and nab-paclitaxel
  - Identification of any regimen-limiting toxicity (RLT) of indoximod in combination with gemcitabine and nab-paclitaxel
    - RLTs are defined as grade 3/4 toxicities that are attributable to the investigational agent and result in delay of gemcitabine and nab-paclitaxel administration

## METHODS

### Study Design and Assessments

- Phase 1/2, open-label, standard 3+3 dose-escalation study design, with an 80-patient, Phase 2, single-arm expansion cohort
- Patients received indoximod according to their assigned dose cohort (600 mg/1000 mg/1200 mg oral twice-daily [BID] continuous dosing; Table 1)
- Gemcitabine (1000 mg/m<sup>2</sup> given intravenously on Days 1, 8, and 15 of 28-day cycles) and nab-paclitaxel (125 mg/m<sup>2</sup> given intravenously on Days 1, 8, and 15 of 28-day cycles) were administered in combination with indoximod in a standard 3+3 design (Table 1)
- Patients continue treatment until they experience disease progression or significant toxicity
- The RLT window was the first cycle (28 days) of treatment, but the recommended Phase 2 dose will include an assessment of toxicities that occur at later time points
- Target enrollment was up to 18 patients in the Phase 1b portion at multiple clinical sites across the United States, and 15 patients were required to complete the dose escalation; 80 patients will be enrolled in the Phase 2 portion

Table 1. Dose Levels in the Phase 1 Portion

Dose level	Indoximod (oral) × 28 days	nab-Paclitaxel (IV) weekly × 3	Gemcitabine (IV) weekly × 3
1	600 mg BID	125 mg/m <sup>2</sup>	1000 mg/m <sup>2</sup>
2	1000 mg BID	125 mg/m <sup>2</sup>	1000 mg/m <sup>2</sup>
3	1200 mg BID	125 mg/m <sup>2</sup>	1000 mg/m <sup>2</sup>

IV, intravenous; BID, twice daily.

### Eligibility

- Patients ≥18 years of age with histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas
- Life expectancy >3 months
- Karnofsky performance status ≥70
- Patients must have received no previous radiotherapy, surgery, chemotherapy or investigational therapy for the treatment of metastatic disease

## RESULTS

- A total of 15 patients were required to successfully escalate the Phase 1 study dose to 1200 mg BID
- Baseline demographic characteristics are summarized in Table 2
- In the indoximod 600 mg cohort, 2 patients were replaced after rapid deterioration and removal from the study due to underlying disease during the RLT window

Table 2. Baseline Demographic Characteristics

Characteristic	Indoximod + Gemcitabine/nab-Paclitaxel (N = 15)
Gender, n (%)	
Male	10 (66.7)
Female	5 (33.3)
Median age (range), years	68.3 (46-79)
Race, n (%)	
White	12 (80)
Black	3 (20)
Ethnicity, n (%)	
Hispanic	1 (6.7)
Non-Hispanic	13 (86.7)
Not available	1 (6.7)

### Safety and Tolerability

- The combination regimen was safe and well tolerated
- Most patients (80%) experienced an indoximod-related AE, and the most common indoximod-related AEs are summarized in Table 3
  - The most frequently reported indoximod-related AEs (all grades) were fatigue (40%) and weight loss, diarrhea, peripheral edema, and asthenia (20% each)
- One patient experienced an SAE (respiratory failure) possibly related to indoximod
- Only 1 RLT was reported (grade 3 ascites) in the study for a patient in the highest dose cohort

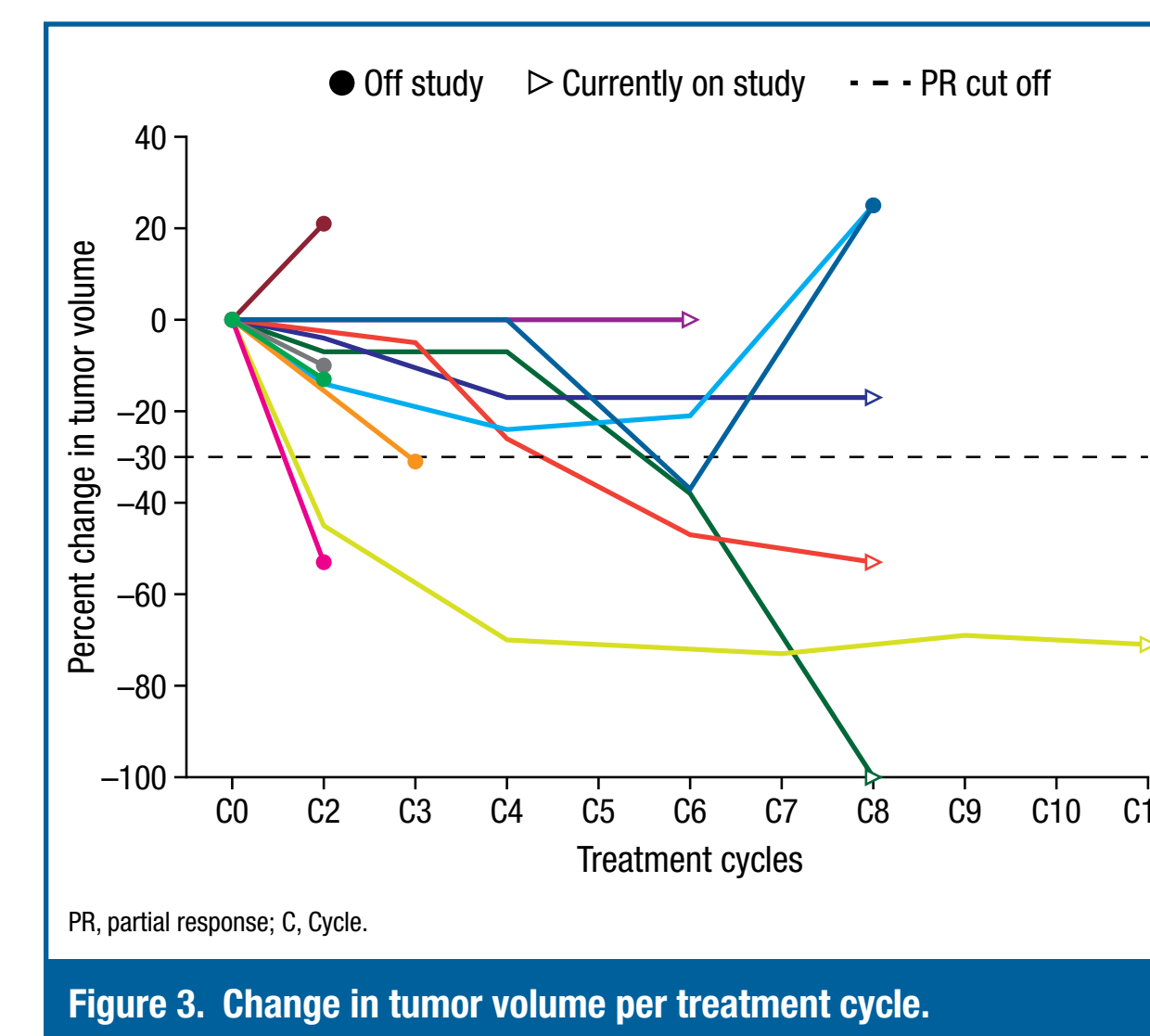
Table 3. Summary of the Most Common Indoximod-related AEs (>10% of Patients)\*

AE (any grade)	Number of patients, n (%)	AE (any grade)	Number of patients, n (%)
Fatigue	6 (40.0)	Decreased appetite	2 (13.3)
Weight loss	3 (20.0)	Nausea	2 (13.3)
Diarrhea	3 (20.0)	Myalgia	2 (13.3)
Peripheral edema	3 (20.0)	Rash	2 (13.3)
Asthenia	3 (20.0)	Decreased neutrophil count	2 (13.3)
Anemia	2 (13.3)	Decreased platelet count	2 (13.3)

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

### Antitumor Activity

- Response data for the 12 evaluable patients in the Phase 1b portion of the study are presented in Figure 3
  - At the time of this analysis, the response rate was 42% (5/12) and multiple durable responses ≥6 months were observed
  - A delayed response pattern was observed in multiple patients
  - One patient achieved a complete response (CR; 8%) at treatment Cycle 8



## CONCLUSIONS

- The combination of indoximod and gemcitabine/nab-paclitaxel was well tolerated in metastatic pancreas cancer
- When administered with gemcitabine/nab-paclitaxel, the recommended Phase 2 dose for indoximod was established as 1200 mg BID
- The objective response rate observed in this study (42%; including 1 CR) compares favorably with that observed for patients treated with gemcitabine/nab-paclitaxel in the MPACT trial (23%)<sup>3</sup>
- Collectively, the overall response rate, observance of a CR, and delayed and durable response patterns are promising for this combination regimen in metastatic pancreas cancer
- Furthermore, the delayed response pattern observed in multiple patients is suggestive of an immune-mediated mechanism of action
- This Phase 2 trial is actively enrolling patients at multiple sites across the United States. Currently, a total of 50 patients have been enrolled

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