Abstract #3020

Phase 2 trial of the indoleamine 2,3-dioxygenase pathway (IDO) inhibitor indoximod plus gemcitabine / nab-paclitaxel for the treatment of metastatic pancreas cancer:interim analysis

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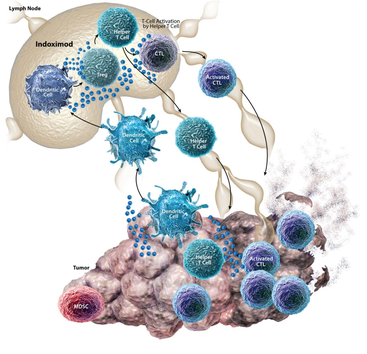
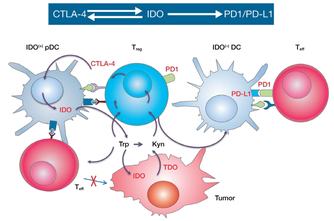
INTRODUCTION

- Pancreas cancer has limited treatment options and is projected to be the second deadliest malignancy by 2030[1]
- Nab-paclitaxel was recently approved as combination treatment with gemcitabine for metastatic pancreas cancer[2]
  - A modest improvement in overall survival was observed with nab-paclitaxel plus gemcitabine compared with gemcitabine alone 8.5 months vs 6.7 months)[3]
  - This combination has become a 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 immuno-modulatory enzyme of acquired immune tolerance in normal and pathologic conditions, particularly in the tumor micro-environment, that allows tumors to thwart the host immune response **(Figure 1)**[4]
- IDO inhibits CD8+ T cells and enhances the suppressor activity of regulatory T cells (Tregs)
- Indoximod is an orally available small molecule. It is a 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[5]
- A Phase 1 trial combining docetaxel and indoximod demonstrated favorable safety profile and evidence of clinical activity in patients with metastatic solid tumors[6]
- Based on these findings, a Phase 1b/2 trial evaluating indoximod in combination with standard of care chemo-therapy (gemcitabine and nab-paclitaxel) for patients with metastatic pancreas cancer was initiated
- Phase 1b results were presented at ASCO GI in January 2016[7]



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

Figure 2. Indoximod mechanism of action.



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.

OBJECTIVES

- Primary endpoint for Phase 2 study:
  - Overall Survival
- Secondary endpoints
  - Objective response rate
  - Progression free survival

METHODS

Study Design and Assessments

- Phase 2, single arm, open-label study
- Phase 2 dose of indoximod set at 1200mg oral twice-daily [BID] continuous dosing
- Gemcitabine (1000 mg/m^2 given intravenously on Days 1, 8, and 15 of 28-day cycles) and nab-paclitaxel (125 mg/m^2 given intravenously on Days 1, 8, and 15 of 28-day cycles) were administered in combination with indoximod in 28 day cycles
- Patients continue treatment until they experience disease progression or significant toxicity
- Cross sectional imaging is performed every 2 cycles per protocol. Response for this interim analysis was determined by local radiologist review per standard RECIST criteria
- Target enrollment is 80 patients in the Phase 2 portion
- For purposes of this interim analysis, patients from both Phase 1b and Phase 2 are included in evaluation of response including those patients in Phase 1b treated at doses below the Phase 2 dose
- Only patients enrolled in the trial long enough to have at least cycle 4 imaging available for review were included in this analysis

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 45 patients had been enrolled in the trial long enough to have cycle 4 imaging available at data cut off of May 16, 2016
- Response data is available on 31 patients at time of data cut off and no response data available on the following 14 patients:
  - 5 patients died within 30 days of starting study treatment
  - 1 patient withdrew from study to an serious adverse event (SAE)
  - 8 subjects withdrew before or shortly after starting treatment
    - 6 treated < 2 weeks – never treated, ineligible, rapid deterioration
    - 2 treated to start cycle 2 – subjects withdrew

Table 2. Baseline Demographic Characteristics

Characteristic	Indoximod + Gemcitabine/nab-Paclitaxel (N = 45)
Gender, n (%)	
Male	27 (60)
Female	18 (40)
Median age (range), years	64.0 (46-79)
Race, n (%)	
White	34 (75)
Black	8 (18)
Asian	2 (5)
Other	1 (2)

Safety and Tolerability

- The combination regimen was safe and well tolerated
- The most frequently reported adverse events (regardless of attribution) occurring in ≥ 10% of patients, were anemia, constipation, diarrhea, nausea, vomiting, fatigue, peripheral edema, abdominal pain, decreased appetite, weight loss, dizziness, fever, peripheral neuropathy, alopecia, rash, hypotension, hypokalemia, hyponatremia, ALT increased, AST increased, alk phos increased, platelet count decreased, white blood cell count decreased, and neutrophil count decreased

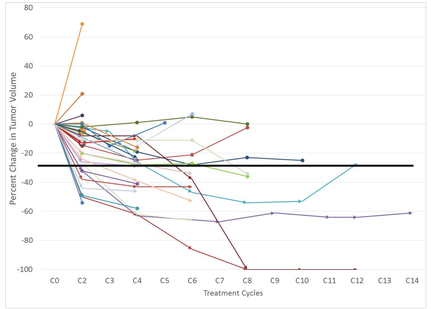
Table 3. Summary of Indoximod-related SAEs *

SAE	SAE
Respiratory Failure	Pneumonitis
Colitis	Fever
Hypotension	Flu-like syndrome
Renal Insufficiency	Intractable Vomiting
Infection (x2)	

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

Antitumor Activity

- Response data for the 31 evaluable patients in the Phase 1b and 2 portions of the study are presented in **Figure 3**
  - At the time of this analysis, objective response rate (CR + PR) was 45% (14/31) and multiple durable responses ≥6 months were observed
  - A delayed response pattern was observed in multiple patients
  - Two patients achieved a complete response (CR; 6%), both at treatment Cycle 8



Black bar =partial response threshold , C, Cycle.

Figure 3. Change in tumor volume per treatment cycle.

Biochemical Response

- Serial serum CA19-9 levels are available for 24 patients and are presented in **Figure 4**
  - 58% (14/24) had a reduction in CA19-9 of ≥80% during treatment period
  - Delayed responses were observed

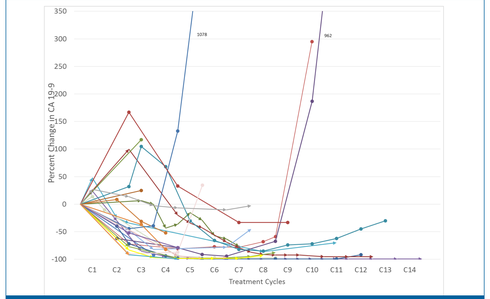


Figure 4. Change in CA19-9 per treatment cycle.

CONCLUSIONS

- **The combination of indoximod and gemcitabine/nab-paclitaxel continues to be well tolerated in metastatic pancreas cancer**
- **The objective response rate observed in this study (45%; including 2 CRs) is promising and remains consistent with the rate seen in the Phase 1b portion of the study (42%).**
- **The 45% ORR compares favorably with that observed for patients treated with gemcitabine/nab-paclitaxel in the MPACT trial (23%)[3]**
- **Furthermore, the delayed response pattern observed in multiple patients is suggestive of an immune-mediated mechanism of action**
- **One SAE of special immunological significance (pan-colitis) was observed.**
- **Collectively, the overall response rate, observance of CRs, and delayed and durable response patterns are promising for this combination regimen in metastatic pancreas cancer**
- **This Phase 2 trial is actively enrolling patients at 11 sites across the United States. Currently, a total of 95 patients (80 in Phase 2) have been enrolled.**
- **Plans for an expansion cohort with serial tumor biopsies is currently underway.**

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