A phase I study of indoximod in combination with docetaxel in metastatic solid tumors.

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Abstract No. 3026

RATIONALE

Indoximod is an orally administered immunotherapy agent that inhibits the IDO pathway. The IDO pathway regulates immune response by suppressing T-cell function and enabling local tumor immune escape. Recent studies have demonstrated that the IDO pathway is active in many cancers, both within tumor cells as a direct defense against T-cell attack, and also within antigen presenting cells in tumor draining lymph nodes resulting in peripheral tolerance to tumor associated antigens (TAAs). Cancers may use the IDO pathway to facilitate survival, growth, invasion and metastasis of malignant cells expressing TAAs that might otherwise be recognized and attacked by the immune system. [1-3] Preclinical studies found that indoximod increased the anti-tumor T-cell response and reduced the number of circulating regulatory T cell (Tregs), thereby slowing tumor growth. [4] IDO pathway inhibitors are another class of immune checkpoint inhibitors akin to the recently developed antibodies targeting CTLA-4 and PD-1 that are potential breakthroughs in cancer therapy.

Pre-clinical studies in a murine MMTV-Neu model evaluated tumor responses with indoximod alone and in combination with a panel of conventional chemotherapies. Indoximod in combination with paclitaxel produced 30% tumor regression while either agent alone demonstrated growth retardation but no tumor regression. Additionally, increased tumor cell death was observed histologically after treatment with the indoximod/paclitaxel combination when compared to single agent. This effect was lost when mice underwent CD4+ T cell depletion previous to treatment. [5] This suggested that the observed combination effect could be attributed to immune response. An initial phase I study of indoximod as a single agent demonstrated good oral bioavailability and a favorable safety profile. Based on these findings, a phase I trial was designed to study the safety of the chemotherapy agent docetaxel in combination with indoximod, in patients with metastatic tumors.

STUDY DESIGN

- **Eligibility:** patients with at least one metastatic solid malignancy, age ≥18, life expectancy >4 months, and normal organ/marrow function
- **Exclusion criteria:** chemotherapy within the past 3 weeks, untreated brain metastases, active autoimmune disease, GI disease causing malabsorption, prior experimental immunotherapy consisting of targeted monoclonal antibodies
- **Treatment plan:** a 3+3 design to determine Maximum Tolerated Dose (MTD). DLT rule was 1st cycle ≥G3 non-heme AEs or ≥G4 heme AEs despite supportive care or that delayed therapy >14d.
  - -Docetaxel (60 mg/m^2) administered for cohorts 1-4 and docetaxel (75 mg/m^2) for cohort 5 (Table 2)
  - Indoximod administered continuously during 21 day cycles
  - Indoximod given orally in escalating dose cohorts of 300 mg BID, 600 mg BID, 1000 mg BID, 2000 mg BID, and finally at 1200mg BID once docetaxel was increased to (75 mg/m^2) (Table 2)
- **Duration:** treatment continued until disease progression or unacceptable toxicity prevented further treatment

DEMOGRAPHICS

Patient Characteristics	
Age	
Mean +/- SD	53 +/- 10
Disease Types, n (%)	
Lung: NSCLC	10 (34)
Breast	8 (28)
Laryngeal	2 (7)
Esophageal	2 (7)
Ovarian	2 (7)
Uterine	1 (3)
Thymus	1 (3)
Liposarcoma	1 (3)
Rectal	1 (3)
Pancreas	1 (3)
Previous Therapies (Median)	
Any Systemic	5
Chemotherapy	3
Radiation	0

Table 1: Patient Demographics

ENDPOINTS

1. Primary Endpoint:

a. *Safety/toxicity:* Adverse events described via Common Terminology Criteria for Adverse Events (CTCAE) 4.0

2. Secondary Endpoints:

a. *Pharmacokinetic Data*

-High performance liquid chromatography used to characterize PK data

-PK measurements drawn on C1D1 (Cycle 1, Day 1) after a single dose of indoximod was given and then on C1D8 (Cycle 1, Day 8) after the morning dose of indoximod was given. (drawn at 0,1,2,4,8,12,24, and 48 hours)

-PK data was compared to known data for indoximod and docetaxel to assess for possible PK interactions

b. *Overall Response Rate*

-Complete Response/ Partial Response per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria for the indoximod/docetaxel combination

RESULTS

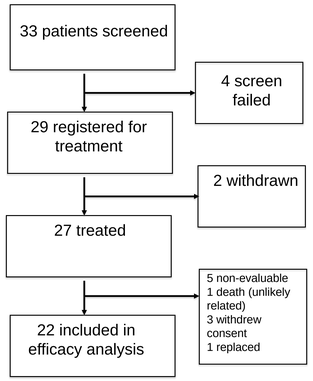


Figure 1: Patient flow diagram

Cohort	Docetaxel (mg/m2)	Indoximod (mg) BID	No. Treated	Dose Limiting Toxicity
1	60	300	7	Grade 3 Dehydration
2	60	600	6	Grade 5 Colitis
3	60	1000	6	Grade 3 Skin infection
4	60	2000	2	Grade 3 Hypotension Grade 3 Mucositis
5	75	1200	6	none

Table 2: Dose Escalation

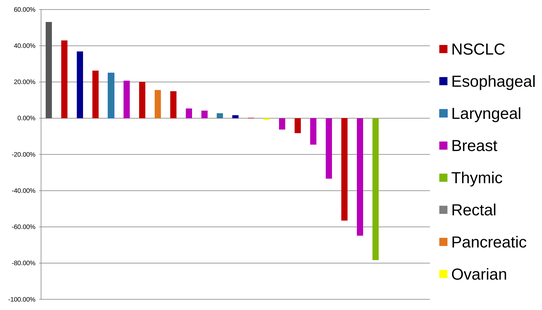


Figure 2: Waterfall plot showing percent change in tumor volume. Eight patients obtained a reduction in tumor volume as shown on the right of the figure. Half of these responders were breast cancer patients. Overall there was encouraging activity achieved with the indoximod/docetaxel combination.

Objective Response Rate	Number of patients, n (%)
Complete Response	0
Partial Response	4 (18)
Stable Disease > 6 Months	1 (4)
Stable Disease < 6 Months	8 (36)
Progressive Disease	9 (41)

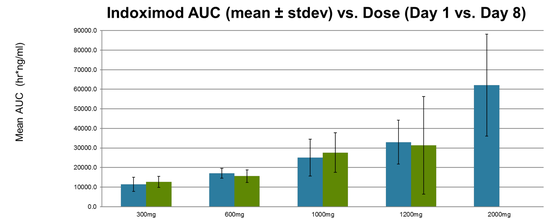
Table 3: Overall Response Rate

Toxicity	Grade 1, n(%)	Grade 2, n(%)	Grade 3, n(%)	Grade 4, n(%)	Grade 5, n(%)
Hematologic					
Anemia	12(41)	8(28)	1(3)	0	0
Leukopenia	0	0	1(3)	2(7)	0
Lymphopenia	0	0	2(7)	0	0
Neutropenia	0	0	1(3)	3(10)	0
Thrombocytopenia	0	0	1(3)	0	0
Endocrine					
Hyperglycemia	11(38)	8(28)	1(3)	0	0
Infection					
Febrile Neutropenia	0	0	4(14)	0	0
GI Infection	0	0	1(3)	0	0
Gram Negative Infection	0	0	1(3)	0	0
Pneumonia	0	0	2(7)	0	0
Sepsis	0	0	0	1(3)	0
Skin Infection	0	0	1(3)	0	0
Tooth Abscess	0	0	1(3)	0	0
Gastrointestinal					
Abdominal Pain	0	0	1(3)	0	0
Anorexia	8(28)	0	0	0	0
Bowel Perforation	0	0	0	1(3)	0
Colitis	0	0	0	0	1(3)*
Constipation	8(28)	0	0	0	0
Dehydration	0	0	2(7)*	0	0
Diarrhea	8(28)	0	0	0	0
Nausea	10(34)	0	1(3)	0	0
Oral Mucositis	0	0	1(3)*	0	0
Vomiting	8(28)	0	0	0	0
Metabolic					
Hypercalcemia	0	0	1(3)	0	0
Hypoalbuminemia	9(31)	0	2(7)	0	0
Hypocalcemia	0	0	1(3)	1(3)	0
Hypokalemia	0	0	1(3)	0	0
Hyponatremia	0	0	4(14)	0	0
Pulmonary					
Cough	6(21)	0	0	0	0
Dyspnea	8(28)	0	1(3)	0	0
Pleuritic Chest Pain	0	0	1(3)	0	0
Renal					
Increased Creatinine	0	0	1(3)	0	0
Hematuria	0	0	1(3)	0	0
Vascular					
Hypotension	0	0	3(10)*	0	0
Muskuloskeletal					
Alopecia	8(28)	0	0	0	0
Arthralgia	0	0	1(3)	0	0
Bone Pain	0	0	1(3)	0	0
Neurologic					
Peripheral Neuropathy	7(24)	0	1(3)	0	0
Weakness	0	0	1(3)	0	0
Constitutional Symptoms					
Fatigue	13(45)	13(45)	0	0	0
Pain					
Headache	0	0	2(7)	0	0
Jaw Pain	0	0	1(3)	0	0
General Disorders					
Multi-Organ Failure	0	0	0	1(3)	1(3)

Table 4: All grade 3/4/5 toxicities, and any grade 1/2 toxicity present in >25% patients, regardless of causality, during all cycles. The most common adverse events included grade 1 anemia and fatigue. The most common high grade toxicities included grade 3 febrile neutropenia and hyponatremia.

***Dose Limiting Toxicities**

PHARMACOKINETICS



Indoximod Terminal half-life = 11.3 (±5.0) hours (n=23)
(Both 2000mg patients did not get day 8 PK)

Docetaxel Pharmacokinetics

Cycle 1 Day 1		t1/2 (hr)	Cmax (ng/mL)	AUC(0-48hr) (hr*ng/mL)	AUC(0-INF) (hr*ng/mL)	Vol. of Distribution (L)	Clearance (L/hr)
60mg/m^2	(n=20)	19.9	1660.7	3634.9	4082.4	1145.5	38.7
75mg/m^2	(n=3)	28.1	1974.6	3842.6	4631.2	1805.1	43.1

CONCLUSIONS

Docetaxel plus indoximod demonstrated an excellent safety profile with no unexpected additional toxicities compared to docetaxel monotherapy

There were no drug-drug interactions between indoximod and docetaxel noted

Encouraging activity was seen in a population of pre-treated patients with metastatic disease

The recommend phase 2 dose of docetaxel 75mg/m2 i.v. q3weeks plus indoximod 1200mg PO BID is safe and feasible. The 1200mg dose of indoximod is the maximally absorbable single oral dose based on additional single agent PK data.

A phase II study of docetaxel/indoximod in metastatic breast cancer patients is now open to accrual

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This trial was supported by the National Cancer Institute N01 contract # N01-CM-62208 and conducted through the Southeast Phase 2 Consortium (SEP2C)