A Phase 2 Study of Docetaxel in Combination with Indoximod in Metastatic Breast Cancer

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INTRODUCTION

Indoleamine 2,3 dioxygenase (IDO) is a tryptophan-catabolizing enzyme that tumors use to create a state of immunosuppression. [1,2] . The main function of the IDO pathway is the regulation of acquired local and peripheral immune tolerance in normal and pathological conditions, particularly in the tumor microenvironment.

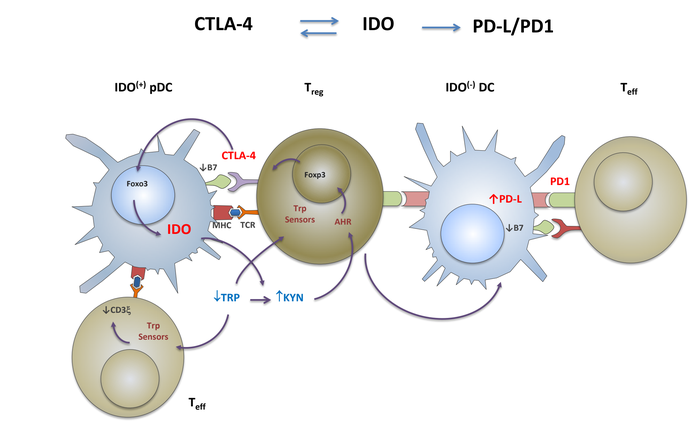
Indoximod (1-methyl-D-tryptophan) is a broad IDO pathway inhibitor as it has been shown to interfere with immunosuppression mediated by the IDO pathway.

Indoximod improved anti-tumor T cell responses and slowed the growth of tumors in several models, and the D-isomer was more effective than the L-isomer of the racemic mixture in shrinking tumors. [3,4]

Preclinical studies in MMTV-neu mouse models have shown that 1-methyl-tryptophan combined with chemotherapy was more effective in causing tumor regressions than either agent alone. A phase 1 trial combining docetaxel and indoximod demonstrated safety and responses in metastatic breast cancer patients.

KEY IMMUNE CHECKPOINTS

Figure 1



PHASE 1 STUDY DESIGN

Phase 1: Indoximod Plus Docetaxel

Treatment Plan:

- 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
- 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 1200 mg BID once docetaxel was increased to 75 mg/m^2

Treatment Duration

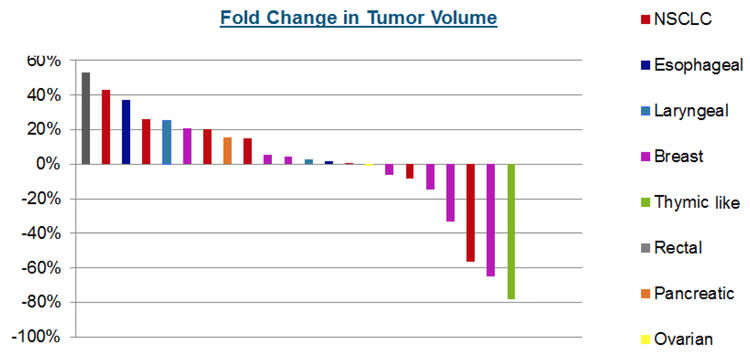
- Continued until disease progression or unacceptable toxicity

Disease Types	N (%)	Disease Types	N (%)
NSCLC	10 (34)	Uterine	1 (3)
Breast	8 (28)	Thymic like	1 (3)
Laryngeal	2 (7)	Liposarcoma	1 (3)
Esophageal	2 (7)	Rectal	1 (3)
Ovarian	2 (7)	Pancreas	1 (3)

Previous Therapies	Median
Any Systemic	5
Chemotherapy	3
Radiation	0

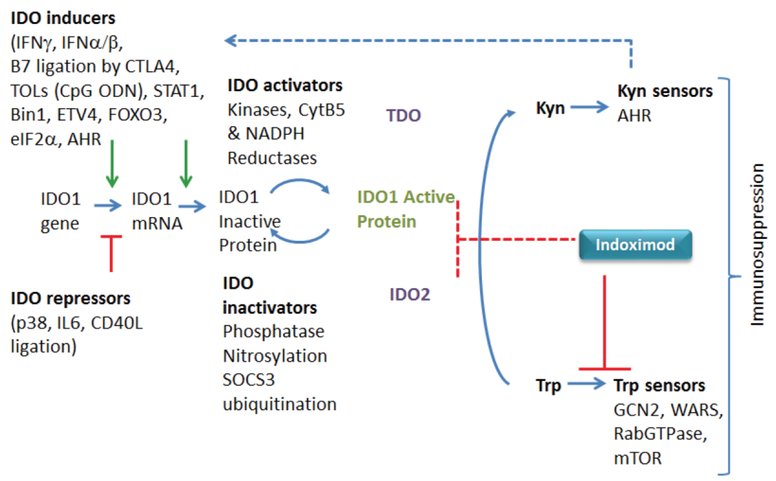
PHASE 1 STUDY RESULTS

- 18% (4/22) partial response rate (2 breast, 1 lung, 1 thymic like)
- 41% (9/22) rate of stable disease



IDO PATHWAY

Figure 2



PHASE 2 STUDY OVERVIEW

- The study is a 1:1 (indoximod:placebo) randomized, double-blinded, placebo controlled two arm phase 2 study.
- Treatment is docetaxel 75mg/m^2 IV D8 plus indoximod 1200mg PO BID D1-14 every 21 days or matching placebo.
- Target enrollment is 154 patients in multiple clinical sites all around the US.

Eligibility:

- Patients with measurable, histologically confirmed metastatic breast cancer
- No prior chemotherapies for metastatic disease
- ER/PR +/- and HER2 -
- ECOG PS 0-1
- No active CNS disease
- No active autoimmune disease

Objectives:

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

Duration:

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

STUDY SCHEMA

Subjects with metastatic, measurable breast cancer ER/PR +/- HER2 –, who have not received chemotherapy in metastatic setting

STRATIFICATION:
1) Hormone receptor + or –
2) Number of disease sites (1, >1)

RANDOMIZATION:
Double-blinded
1:1 randomization
Up to 154 subjects (77 each arm)

Docetaxel 75 mg/m^2 IV D8
Given q3wks
Plus placebo PO
BID D1-14

Docetaxel 75 mg/m^2 IV D8
given q3wks
plus indoximod 1200mg PO
BID D1-14

SUMMARY

- Well tolerated, novel agents which improve the efficacy of existing chemotherapy agents would prove quite useful in managing metastatic breast cancer.
- The phase 1b study of docetaxel plus indoximod demonstrated an excellent safety profile with no unexpected additional toxicities compare to docetaxel monotherapy.
- The phase 1b study informed safe and feasible phase 2 dosing of docetaxel at 75 mg/m^2 i.v. q3 weeks plus indoximod 1200 mg PO BID with the 1200 mg dose of indoximod as the maximally absorbable single oral dose.

REFERENCES

REFERENCES

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3. Hou et al, Cancer Research (2007)

CLINICAL TRIALS IDENTIFIER

Clinicaltrials.gov identifier: NCT01792050

For information on this study, see: http://clinicaltrials.gov/ct2/show/NCT01792050

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