A Phase 2 Study of Ad.p53 DC Vaccine in Combination with Indoximod in Metastatic Solid Tumors

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INTRODUCTION

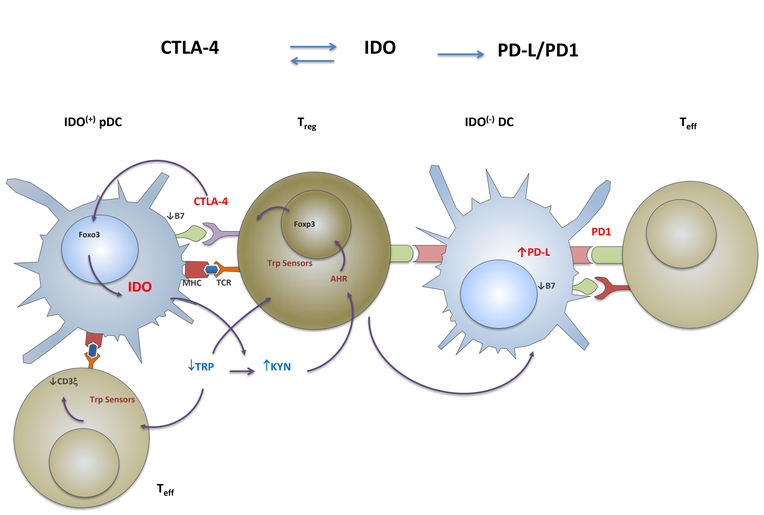
Indoleamine 2,3 dioxygenase (IDO) is an inducible tryptophan-catabolizing enzyme that downregulates the immune system. Many tumor cell types overexpress IDO to avoid elimination by infiltrating cytotoxic T cells [1-3]. The main function of the IDO pathway is the regulation of acquired local and peripheral immune tolerance in normal and pathological conditions, particularly in the tumor microenvironment.

Indoximod (1-methyl-D-tryptophan / D1MT) is an IDO pathway inhibitor. Published preclinical data suggests that blockade of the IDO pathway with indoximod enhances the immunologic response to dendritic cell (DC) vaccines.

Ad.p53 is an adenovirus used for generating DC vaccines directed against p53 epitopes. Ad.p53 when given to previously treated SCLC patients significantly increased their response rate to subsequent chemotherapy. Data showing a similar trend for enhanced response to subsequent chemotherapy was presented in breast cancer patients who were treated in the phase I trial using Ad.p53DC and indoximod [4].

The primary endpoint in this phase 2 study is the response rate of the combination of indoximod + Ad.p53 in metastatic breast cancer patients. Secondary endpoints include safety, PFS, OS, and immunologic correlates.

KEY IMMUNE CHECKPOINTS

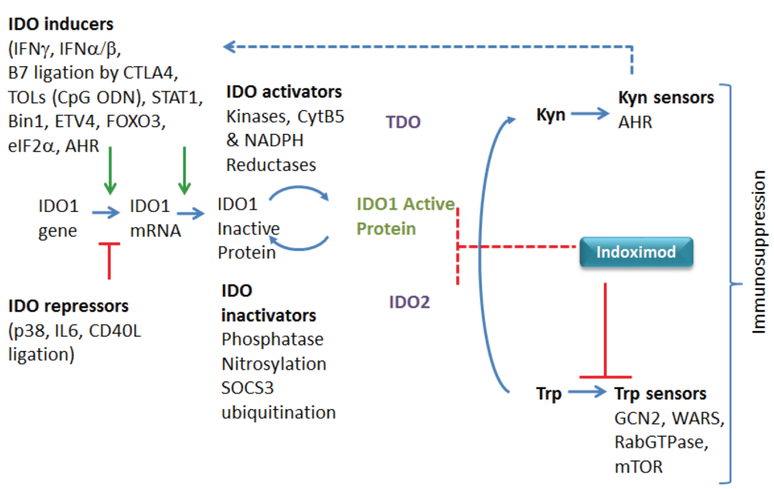


PRIOR CLINICAL EXPERIENCE

The phase 1 Ad.p53DC plus indoximod study showed [4]:

- The maximally administered dose of indoximod was 1600mg PO BID in combination with the Ad.p53DC vaccine
- Initial response to the study treatment was stable disease in 3 patients (2 breast and 1 colon)
- Encouragingly, out of 19 patients treated with subsequent chemotherapy, 7 (36%) had an objective response
- For 11 patients treated with gemcitabine based therapy, 6 (54%) patients had an objective response
- One patient with MBC had a CR in 5th line treatment after vaccination.
- This supports the hypothesis that immunotherapy treatments may sensitize patients to subsequent lines of therapy

IDO PATHWAY



STUDY OVERVIEW

This phase 2 study uses a single arm, Simon two stage design. Study treatment consists of 1600 mg PO BID of indoximod given continuously along with up to 6 fixed doses of Ad.p53DC SQ vaccinations q2 weeks.

First stage of accrual is 12 patients with one response required for progression into the second stage of 25 additional patients. The study design is based on the alternative hypothesis of a 20% response rate, with 90% power to detect this level of activity with a significance of .09 (assuming a total of 4 responses out of 37 are observed).

Eligibility

Patients with measurable, metastatic breast cancer, <3 lines of prior chemotherapy in metastatic setting, p53 immunohistochemistry >5% in archival tumor specimen, ECOG 0-2, no autoimmune disease.

Primary Objectives

- Efficacy (objective response rate) of the combination Ad.p53 DC vaccine plus indoximod followed chemotherapy in metastatic breast cancer patients whose tumor expresses mutated p53 by IHC
- An objective response rate of at least 40% as determined by RECIST is desired for this vaccine followed by chemotherapy study treatment on the intent-to-treat basis

Secondary Objectives

- Percentage of p53 specific IFNγ ELISPOT responders at week 5 and 16
- PFS on the study treatment
- Response and PFS on the subsequent chemotherapy, if administered
- The effects of indoximod on serum kynurenine / tryptophan ratio, C reactive protein, and circulating T-regulatory cells (CD4+, 25+, CD127low, FoxP3+) by flow cytometry at each vaccination point on study when compared their corresponding baseline

STUDY SCHEMA

Week #																				
0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
	V		V		V					V			V			V					
DAILY 1-MT							DAILY 1-MT														
I, C			I		I		C			I			I			I, C					

V = Ad.p53 DC VACCINE SQ
1-MT = ORAL DAILY INDOXIMOD
I = IMMUNOLOGIC TESTING (ELISPOT, T-REG FLOW)

C = CT SCANS FOR RESPONSE

1-MT MAINTENANCE PHASE: A patient who demonstrates stable disease after completion of the 6th vaccine can proceed to single agent indoximod maintenance for up to 6 monthly cycles. Monthly visits with safety labs (CMP, CBC, Pituitary function testing) and every 2 months CT scans will be performed. At progression patient receives chemotherapy. Response CT scans on chemo are every 6 weeks (+/- 5 WORK DAYS) or as clinically indicated.

FOLLOW UP: Visits for ELISPOT evaluation at 3, 6, AND 12 months after completion of study treatment if possible. Every 3 month telephonic follow up with patient/ providers thereafter for up to 5 years or until death.

SUMMARY

- Novel therapies such as combination immunotherapy that can offer clinical benefits with less toxicity are needed
- The combination of Ad.p53DC and indoximod was well tolerated in a phase 1 study with no DLTs and no serious treatment related adverse events. The safety profile was consistent with the known monotherapy safety profile for each agent. Any treatment discontinuation was due to disease progression

Trial Status:

- Accrual to the first stage of this trial is completed and the study remains open with some of the patients still undergoing study treatment
- Patients will be followed for their response to salvage chemotherapy following the study treatment
- Immune correlates looking at vaccine response rates are planned

REFERENCES

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3. Godin-Ethier, J., et al., Indoleamine 2,3-dioxygenase expression in human cancers: clinical and immunologic perspectives. Clin Cancer Res, 2011. 17(22): p. 6985-91.
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CLINICAL TRIALS IDENTIFIER

Clinicaltrials.gov identifier: **NCT01042535**

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