A phase I study of Ad.p53 DC vaccine in combination with indoximod in metastatic solid tumors.

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BACKGROUND

Indoleamine 2,3 dioxygenase (IDO) is an inducible tryptophan-catabolizing enzyme that downregulates the immune response. Many tumor cell types overexpress IDO to avoid elimination by tumor infiltrating cytotoxic T cells.[1] This makes IDO a key target for reversing tumor associated immunosuppression. Indoximod (1-methyl-D-tryptophan, 1-MT) is an oral IDO pathway inhibitor that blocks the downstream effects of IDO enzyme activation.[2] Phase I data of indoximod demonstrated that it has good bioavailability and an excellent safety profile. Ad.p53 is a replication incompetent adenovirus used for generating autologous DC vaccines directed against wild type p53 epitopes. This vaccine has been used in previous multiple clinical trials including small cell lung cancer (SCLC) patients. When Ad.p53 DC vaccine was given to SCLC patients after progressing on platinum chemotherapy, it increased the rate of response to salvage paclitaxel to 50% in patients who responded immunologically to the vaccine.[3] Published preclinical data suggested that blockade of IDO with indoximod enhances the adoptive immunologic response to antigens and dendritic cell (DC) vaccines in LLC mouse models.[4, 5] Based on this data we initiated a phase I/II trial combining Ad.p53DC vaccine plus indoximod. The goal of the phase I trial was to establish dosing and safety of the combination.

METHODS

Study design: Phase I 3+3 dose escalation design.
Study endpoints: Safety/toxicity (primary), recommended phase 2 dosing (primary), response rate to vaccine and subsequent salvage therapy (secondary)
Study treatment: Seven indoximod dose levels (100 mg, 200 mg, 400 mg, 800 mg QD then 800 mg, 1,200 mg, and 1,600 mg PO BID) + up to 6 (1-5x10^6 cells) Ad.p53 DC vaccinations SQ given on weeks 1,3,5,10,13,16. Patients underwent pheresis once for each set of three vaccines produced in our cellular therapy facility. If patients had minor progression, stable disease, or a response on week 6 scans they went on to get the vaccines on weeks 10,13,16. Treatment will continue until disease progression or unacceptable toxicity. DLT rules are 1st cycle ≥G3 AE related to treatment
Patient population: Adult patients with metastatic solid tumors that were p53+ (>5% nuclear staining by IHC), measurable disease, no restriction on prior lines of therapy.
Eligibility: Standard eligibility/exclusion criteria applied along with exclusion of patients previously treated with ipilimumab.

PATIENT INFORMATION

Indoximod dose level	Number patients accrued	Number of vaccines given per patient
1 (100mg QD)	4	3 (2 pts), 2 (1 pt), 0 (1 pt)
2 (200mg QD)	3	3 (1 pt), 2 (2 pts)
3 (400mg QD)	4	6 (1pt), 3 (2 pts), 1 (1 pt)
4 (800mg QD)	6	3 (4 pts), 2 (2 pts)
5 (800mg BID)	6	3 (3 pts), 1 (2 pts), 0 (1 pt)
6 (1200mg BID)	3	3 (3 pts)
7 (1600mg BID)	6	6 (1 pt), 5 (1 pt), 3 (4 pts)

PATIENT DEMOGRAPHICS

Female	28
Male	4
White	27
Black	4
Hispanic	1
Median Age	52 (range = 29-73)
Median # prior therapies	2 (range = 0-6)
Tumor types	22 breast, 4 colon, 2 gastric, 1 ovarian, 1 NSCLC, 1 oropharynx, 1 sarcoma

AGGREGATE SAFETY DATA (Treatment related and unrelated)

ADVERSE EVENT	Events (N)	%	G1	G2	G3	G4	G5
Fatigue	**26**	81%	**20**	**6**	**0**	**0**	**0**
Anemia	16	50%	7	6	3	0	0
Hyperglycemia	13	41%	11	2	0	0	0
Alk phos increased	12	38%	8	1	3	0	0
Nausea	**12**	38%	**11**	**0**	**1**	**0**	**0**
Anorexia	10	31%	7	3	0	0	0
AST increased	10	31%	7	1	1	1	0
Lymphopenia	10	31%	8	2	0	0	0
Hypoalbuminemia	9	28%	6	2	1	0	0
Dyspnea	9	28%	6	1	1	0	1
Headache	8	25%	8	0	0	0	0
Hyponatremia	7	22%	5	0	2	0	0
ALT increased	7	22%	5	2	0	0	0
White blood cell decreased	7	22%	7	0	0	0	0
Constipation	7	22%	5	1	1	0	0
Bone pain	6	19%	4	2	0	0	0
Peripheral neuropathy	6	19%	5	1	0	0	0
Edema limbs	5	16%	5	0	0	0	0
Neutropenia	5	16%	3	1	0	1	0
Vomiting	5	16%	5	0	0	0	0
Dehydration	4	13%	3	1	0	0	0
Abdominal pain	4	13%	0	3	1	0	0
Diarrhea	4	13%	4	0	0	0	0
Cough	4	13%	4	0	0	0	0
Fever	3	9%	2	1	0	0	0
Hypokalemia	3	9%	3	0	0	0	0

ADVERSE EVENT	Events (N)	%	G1	G2	G3	G4	G5
Back pain	3	9%	2	1	0	0	0
Chest wall pain	3	9%	2	1	0	0	0
Weakness lower limb	3	9%	3	0	0	0	0
Alopecia	3	9%	2	1	0	0	0
Urinary tract infection	3	9%	0	3	0	0	0
Hypotension	3	9%	2	0	1	0	0
Flu like symptoms	2	6%	2	0	0	0	0
Pain	2	6%	2	0	1	0	0
Hypocalcemia	2	6%	2	0	0	0	0
Hypoglycemia	2	6%	2	0	0	0	0
Blood bilirubin increased	2	6%	1	0	1	0	0
Platelet count decreased	2	6%	1	0	0	1	0
Hemolysis	2	6%	0	2	0	0	0
Arthralgia	2	6%	1	1	0	0	0
Rash maculo-papular	2	6%	2	0	0	0	0
Skin infection	2	6%	0	0	2	0	0
Breast pain	2	6%	1	1	0	0	0
Hypernatremia	1	3%	0	1	0	0	0
Creatinine increased	1	3%	0	1	0	0	0
Febrile neutropenia	1	3%	0	0	1	0	0
Ascites	1	3%	0	1	0	0	0
Pleural effusion	1	3%	0	1	0	0	0
Respiratory failure	1	3%	0	0	0	0	1
Pain of skin	1	3%	0	1	0	0	0
Glaucoma	1	3%	0	1	0	0	0
Acute kidney injury	1	3%	0	1	0	0	0

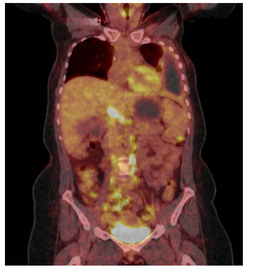
Adverse events in **bold** represent expected toxicities for indoximod

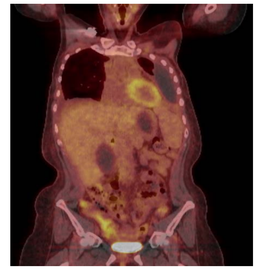
RESPONSE DATA

Response to Initial Study Treatment	
Stable disease	3
Progressive disease	26
Not Evaluable	3

Post vaccination response to subsequent chemotherapy

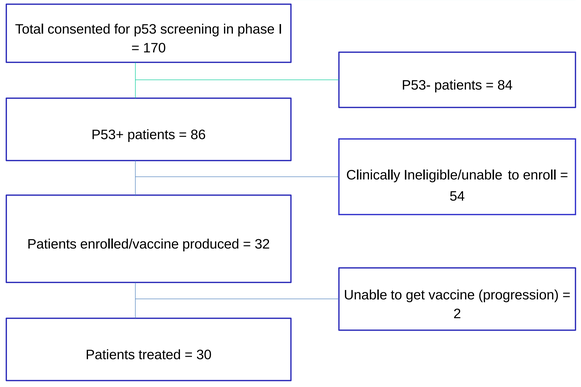
Tumor	# Prior chemotherapy lines	Subsequent treatment	Response
Breast	4	carboplatin/gemcitabine	CR
Colon	3	notch inhibitor trial	PD
Colon	5	NA	NA
Breast	3	NA	NA
Colon	3	Irinotecan	NA
Breast	2	Navelbine	PR
Breast	2	NA	NA
Breast	0	carboplatin/gemcitabine	PR
Breast	0	carboplatin/gemcitabine	PR
Breast	1	carboplatin/gemcitabine/ Bevacizumab	PR
Breast	2	Gemcitabine	SD
Breast	2	carboplatin/gemcitabine	SD
Breast	1	carboplatin/gemcitabine	PR
Breast	3	navelbine/trastuzumab	PD
Breast	2	Eribulin	PD
Breast	0	NA	NA
Breast	3	paclitaxel/bevacizumab	PD
Breast	1	carboplatin/gemcitabine	PD
Breast	0	carboplatin/paclitaxel	NA
Breast	2	Navelbine	PD
Lung	6	NA	NA
Breast	2	Eribulin	PD
Breast	2	Eribulin	PD
Breast	3	carboplatin/gemcitabine	PD
GI	4	TEM1 mAb trial	PD
Breast	1	carboplatin/gemcitabine	PD
Ovarian	1	carboplatin/PARPi trial	NA
Head and Neck	0	NA	NA
GI	5	NA	NA
Breast	2	gemcitabine	PR
Sarcoma	2	pazopanib	SD
Colon	3	NA	NA





Breast cancer patient refractory to 2 prior chemotherapy treatments has complete response to 5th line carboplatin/gemcitabine after study treatment. This was durable lasting over 11 months.

PATIENT FLOW DIAGRAM



CONCLUSIONS

- The combination of Ad.p53DC and indoximod was well tolerated 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.
- The maximally administered dose of indoximod was 1600mg PO BID in combination with the Ad.p53DC vaccine. This is the phase 2 dose currently in use for this combination.
- 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 had an objective response (36%). For 11 patients treated with gemcitabine based therapy, 6 patients had an objective response (54%). 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.
- The phase 2 trial in metastatic breast cancer patients is currently accruing. Patients will be followed for their response to salvage chemotherapy with gemcitabine based therapy following the study treatment. Immune correlates looking at vaccine response rates are planned.

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