A PHASE 2 DOUBLE-BLINDED, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF INDOXIMOD IN COMBINATION WITH A TAXANE CHEMOTHERAPY IN METASTATIC BREAST CANCER

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BACKGROUND

- Indoleamine-2,3-dioxygenase (IDO1) is a tryptophan metabolizing enzyme in the kynurenine pathway that promotes an immunosuppressive tumor microenvironment. Tryptophan depletion induces cell cycle arrest of CD8+ and NK T cells and activation of immunosuppressive CD4+ T regulatory cells.[1,2]
- Overexpression of IDO correlates with poor prognosis in some cancers, but the data is conflicting in breast cancer.[3]
- T lymphocyte proliferation arrest due to tryptophan shortage caused by IDO1 overactivity can be partly reverted by systemic treatment with an inhibitor of the IDO pathway, such indoximod (1-methyl-D-tryptophan).[4] Pre-clinical models of breast cancer showed synergistic anti tumor activity when indoximod was added to taxanes. In a prior phase I trial testing indoximod in combination with docetaxel in pretreated metastatic solid tumors, including breast cancer, 17% of patients achieved a partial response.[5]

OBJECTIVES

- **Primary objective:** PFS after treatment with docetaxel or paclitaxel in combination with indoximod or placebo in metastatic breast cancer.
- **Secondary objectives:** median OS, objective response rate (ORR) measured by RECIST, safety profile

METHODS

Study design: Double-blinded, multicenter, randomized (1:1), placebo-controlled phase 2 study in patients with HER2 negative metastatic breast cancer. (ClinicalTrials.gov: NCT01792050)

Treatment: Indoximod PO 1200 mg BID on d1-14 with docetaxel 75mg/m^2 q21days (phase 1 determined dose) or indoximod PO 1200mg BID on d1-21 with weekly paclitaxel 80mg/m^2 3 weeks on 1 week off.

Eligibility criteria: Women or men, ≥ 18 yo, ECOG 0-1, ER/PR +/–, HER2 negative metastatic breast cancer, disease measurable on imaging, no prior exposure to chemotherapy in the metastatic setting, normal organ and marrow function, treated and stable CNS disease. No autoimmune disease or immunodeficiency, or prior immunotherapy allowed.

Statistical design: A sample size of 154 evaluable patients was designed to detect an HR of 0.64 with one sided alpha of 0.1 and beta of 0.2 at 95 PFS events (assuming 10% dropout).

IDO expression: IHC using Ventana Discovery XT auto-stainer optimized protocols with IDO1 10.1 Ab. Aperio digital pathology scoring cutoff of ≥16.5 (median) on IHC on tumor cells was chosen to classify IDO expression of low and high.

RESULTS

Characteristic	Indoximod (n=85)	Placebo (n=79)
Age (years)		
Median	58.0	57.0
Range	29-76	29-85
Female sex no. (%)	84 (98.8)	77 (97.5)
Race no. (%)		
White	71 (83.5)	66 (83.5)
African American	12 (14.1)	10 (10.7)
Asian	1 (1.2)	0
Other	1 (1.2)	3 (3.8)
Baseline Height (cm)		
Median	164.5	162.0
Range	137.2-181.0	149.0-178.0
Baseline weight (kg)		
Median	74.10	73.85
Range	46.8-129.4	46.0-134.0
ECOG no. (%)		
0	41 (48.8)	43 (54.4)
1	41 (48.8)	35 (44.3)
ER status no. (%)		
Negative	23 (27.1)	23 (29.1)
Positive	62 (72.9)	56 (70.9)
Disease sites no. (%)		
1	20 (23.5)	13 (16.5)
>1	65 (76.5)	66 (83.5)
Choice of Taxane		
Docetaxel	62 (72.9)	59 (74.7)
Paclitaxel	23 (27.1)	20 (25.3)

Table 1. Demographics

Adverse Events	Indoximod arm (n = 85)		Placebo arm (n = 79)	
	Any grade n. (%)	≥ grade 3 n. (%)	Any grade n. (%)	≥ grade 3 n. (%)
Alopecia	38(44.7)	0	51(64.6)	0
Fatigue	52(61.2)	6(7.1)	36(45.6)	4(5.1)
Nausea	40(47.1)	2(2.4)	38(48.1)	2(2.5)
Diarrhea	30(35.3)	1(1.2)	31(39.2)	6(7.6)
Constipation	24(28.2)	0	27(34.2)	1(1.3)
Edema	26(30.6)	1(1.2)	23(29.1)	1(1.3)
Vomiting	20(23.5)	3(3.5)	28(35.4)	1(1.3)
Headache	19(22.4)	1(1.2)	24(30.4)	2(2.5)
Anemia	28(32.9)	7(8.2)	15(19.0)	3(3.8)
Neuropathy	19(22.4)	0	19(24.1)	1(1.3)
Anorexia	17(20.0)	1(1.2)	19(24.1)	0
Arthralgia	17(20.0)	0	16(20.3)	0
Bone pain	19(22.4)	2(2.4)	14(17.7)	3(3.8)
Dizziness	11 (12.9)	0	19 (24.1)	0
Dysgeusia	12 (14.1)	0	17 (21.5)	0
Lymphopenia	18 (21.2)	3 (3.5)	10 (12.7)	3 (3.8)
Hyperglycemia	20 (23.5)	3 (3.5)	7 (8.9)	0
Cough	17 (20.0)	0	10 (12.7)	0

Table 2. Most common treatment-emergent adverse events (≥ 20% in any treatment arm)

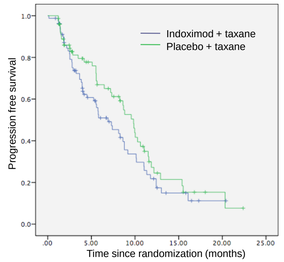

Fig. 1. PFS Kaplan-Meier curve

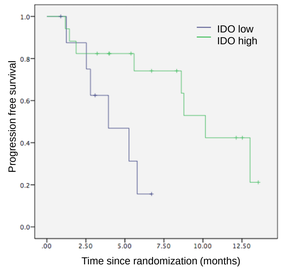

Fig. 2. Indoximod arm PFS Kaplan-Meier curve

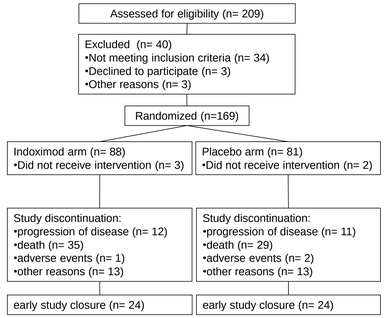

Fig. 3. Consort diagram

RESULTS

- The study enrolled patients between 26 Aug 2013 and 17 Aug 2017, and was prematurely discontinued due to lack of efficacy. (Fig. 3)
- Patient characteristics and demographics were generally distributed evenly for each arm. (Table 1)

Efficacy:

An updated analysis using the documented progression on scans or date of death showed:

- A median PFS of 6.9 months (95% CI, 4.8-8.9) for patients in the indoximod arm and 9.5 months (95% CI, 8.1-10.9) in the placebo arm (HR 1.3, 95% CI 0.8-1.9). (Fig.1)
- A median OS of 19.4 months (95% CI, 14.5-24.4) in the indoximod group and 20.6 months (95% CI, 18.6-22.5) in the placebo group (HR 1.0, 95% CI 0.6-1.6).
- Three subjects (3.5%) in the indoximod arm and two (2.5%) in the placebo arm achieved a complete response. 31 (36.5%) subjects achieved partial response in the indoximod arm and 27 (34.2%) in the placebo group. ORR was not significantly different between the arms.

IDO Expression:

- An exploratory analysis of IDO staining in 52 archival available samples (26 in the indoximod arm and 26 in the placebo arm) suggested a difference in median PFS in patients who received indoximod with high IDO (17 pts) compared to low IDO expression (9 pts) (median PFS 10.1 vs 3.9 months; p=0.018)(Fig.2). Median OS was 24.0 months in patients with high IDO vs 12.6 months in patients with low IDO. Stratification factors were balanced in the two groups.
- This difference was not noted in the placebo arm between IDO low and high subjects.

Safety:

- Adverse events of ≥grade 3 in severity occurred in 51 subjects (60.0%) in the indoximod arm and in 48 subjects (60.8%) in the placebo arm.
- Most common adverse events are shown in table 2.
- Anemia, fatigue, lymphopenia, hyperglycemia, extremities pain, and cough were reported with a higher incidence (≥5% difference) in the indoximod arm, but they were manageable.

CONCLUSIONS

- Indoximod combined with taxane chemotherapy in HER2- metastatic breast cancer patients did not demonstrate a benefit compared to placebo in an unselected population.
- Higher tumor IDO expression may select for patients who could benefit more from IDO/TDO inhibitors and should be investigated as a predictive biomarker in prospective studies.

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