Phase 2 Trial of the FASN Inhibitor, Denifanstat (TVB-2640), Plus Trastuzumab in Combination with Paclitaxel or Endocrine Therapy for Patients with HER2+ Metastatic Breast Cancer Resistant to Trastuzumab

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INTRODUCTION

- Fatty Acid Synthase (FASN) is a key lipogenic enzyme co-regulated with HER2 and highly expressed in ER+ and HER2+ breast cancer (BC).[1]
- FASN targeting downregulates HER2 expression.[2]
- Our preclinical studies have demonstrated that FASN inhibition can sensitize or restore sensitivity to trastuzumab, paclitaxel and endocrine therapy (ET) in HER2+ BC models.[2,3]
- Denifanstat (formerly TVB-2640) is a novel FASN inhibitor that demonstrated promising clinical activity and safety in a prior phase I trial as either monotherapy or in combination with paclitaxel.[4]
- The primary objective of this study was to evaluate the objective tumor response rate (ORR) of denifanstat plus trastuzumab (H) in combination with paclitaxel (T) or ET in patients (pts) with HER2+ metastatic BC (MBC) resistant to H.

METHODS

- Two independent, phase II clinical trials were initiated to assess the efficacy and safety of denifanstat plus H in combination with T (Cohort A) or ET (Cohort B).
- Key inclusion criteria included HER2+ MBC resistant to HER2-directed therapy, measurable disease, unlimited prior ET (ER+ disease and ET resistance required in Cohort B), ≤6 prior chemotherapy or antibody drug conjugate regimens, and confirmation of HER2+ MBC on a pre-registration biopsy.
- Denifanstat was administered 100 mg/m^2 orally once daily. TH (weekly) or H plus ET (fulvestrant or aromatase inhibitor) were administered at standard dose and schedule.
- Blood was collected on Cycle 1 Day 1 (C1D1), C1D8 and C2D1 for serum FASN analysis. An additional MBC tumor biopsy was collected on C2D1 for correlative studies.
- A 2-stage Simon design with a safety-run in was used to test the null hypothesis that the true objective response rate (ORR) is at most 5% against the alternative that it is at least 20%. With a sample size of 32 pts per cohort, if ≥4 responses are seen, this design has a 90% chance of rejecting the null hypothesis at a 0.10 level of significance.
- Both trials were closed to enrollment early due to slow accrual.

RESULTS

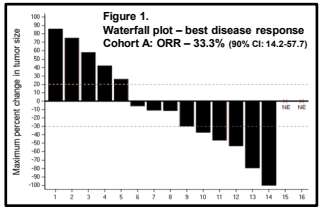
- From August 2017 - February 2024, 33 pts with HER2+ MBC pre-registered, of which 17 registered. One progressed prior to therapy.
- 16 pts were evaluable (received ≥1 dose of therapy): Cohort A- 15 pts and Cohort B- 1 pt. Pt characteristics are provided in Table 1.
- The most common reason for ineligibility was HER2-negative status on central review of the pre-registration biopsy (7 of 16 pts).

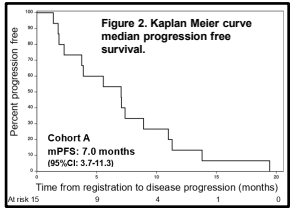
TABLE 1. PATIENT CHARACTERISTICS

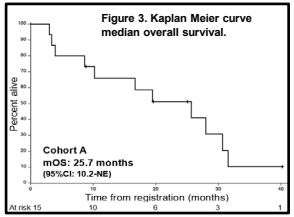
	EVALUABLE PTS (N=16)
Cohort A	15
Cohort B	1
Median Age (range)	57 (35-80)
Race	
Asian	2 (12.5)
Black	1 (6.3%)
White	13 (81.3%)
Ethnicity – Non-Hispanic	16 (100%)
ECOG PS	
0	11 (68.8%)
1	5 (31.3%)
Most common sites of MBC	
Bone	11 (68.8%)
Liver	12 (75.0%)
Lung	9 (56.3%)
Lymph nodes	10 (62.5%)
Prior chemotherapy for MBC	
None*	2 (12.5%)
Taxane	12 (87.5%)
Anthracycline	2 (12.5%)
Platinum	1 (6.3%)
Capecitabine	3 (18.8%)
Vinorelbine	1 (6.3%)
Prior ET for MBC	
None	6 (37.5%)
Anastrozole	4 (25.0%)
Exemestane	1 (6.3%)
Fulvestrant	4 (25.0)
Letrozole	6 (37.5)
Ovarian function suppression	3 (18.8%)
Prior HER2-directed therapy for MBC	
None	2 (12.5%)
Lapatinib	3 (18.8%)
H + Pertuzumab	9 (56.3%)
T-DM1	10 (62.5%)
Other agents for metastatic disease	
CDK 4/6 inhibitor	3 (18.8%)
PD-L1 inhibitor	1 (6,3%)

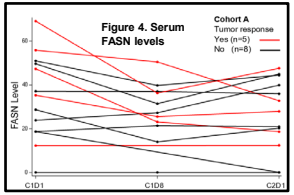
TABLE 2. ADVERSE EVENTS

	GRADE regardless of attribution		
	2	3	4
Alopecia	2 (13%)	0	0
Anemia	3 (20%)	1 (7%)	0
Blurred vision	1 (7%)	0	0
Constipation	1 (7%)	0	0
Cough	1 (7%)	1 (7%)	0
Dry eye	1 (7%)	0	0
Dyspnea	1 (7%)	1 (7%)	0
Fatigue	5 (33%)	1 (7%)	0
Hypertension	0	1 (7%)	0
Leukocytosis	0	1 (7%)	0
Lymphocyte count decreased	1 (7%)	1 (7%)	0
Neutrophil count decreased	2 (13%)	3 (20%)	0
Mucositis oral	1 (7%)	1 (7%)	0
Pain	1 (7%)	0	0
Palmar-plantar erythrodysesthesia	6 (40%)	0	0
Peripheral motor neuropathy	3 (20%)	1 (7%)	0
Peripheral sensory neuropathy	5 (33%)	0	0
Pleural effusion	0	2 (13%)	0
Pneumonitis	1 (7%)	0	1 (7%)
Pruritus	0	1 (7%)	0
White blood cell decreased	2 (13%)	2 (13%)	0









COHORT A

- All 15 pts have discontinued protocol therapy due to disease progression (n=12) or AE (n=3).
- Median cycles administered was 4 (range 1-15).
- AEs are summarized in Table 2. Seven of 15 pts had a grade 3 or 4 AE attributed to therapy. There were no grade 5 events.
- The confirmed ORR was 33.3% (Fig. 1).
- mPFS and mOS were 7.0 months and 25.7 months (Fig. 2 & 3)
- Median C1D1 FASN level was 32.7 ng/mL (IQR: 18.7 to 49.6 ng/mL). Change in levels over time are shown in Fig. 4.
- There was little association found between C1D8 or C2D1 levels and time to disease progression (data not shown).
- Tumor FASN, p-AKT, p-S6 expression by IHC are in progress

COHORT B

- The 1 pt experienced stable disease as best response and maintained it through end of cycle 8.
- The only grade 3+ AE reported was grade 3 ALT increase.
- The pt was alive 2.6 years post-registration.

DISCUSSION

- Denifanstat combined with TH provided clinical antitumor activity in pts with HER2+ MBC resistant to trastuzumab.
- Nearly half of pts experienced a grade 3 or 4 AE attributed to the therapy, and 20% stopped treatment due to AE.
- Further study of denifanstat, H plus ET will be necessary to draw safety and efficacy conclusions.
- Additional correlative studies and analyses are in progress.

REFERENCES

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