Tinengotinib in Advanced or Metastatic HR+/HER2- and TNBC: Efficacy and Biomarker Correlative Analysis from a Phase Ib/II Study

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Background

Patients with advanced/metastatic hormone receptor positive /human epidermal growth factor receptor 2 negative (HR+/HER2-) breast cancer (BC) often develop resistance to endocrine therapy and CDK4/6 inhibitors, while those with triple-negative BC (TNBC) usually lack effective targeted therapies after progression on chemotherapy or antibody drug conjugates. Tinengotinib, a novel multi-kinase inhibitor targeting FGFRs, VEGFRs, Aurora A/B, JAK1/2, and CSF1R, demonstrated preclinical activity in BC models, including those resistant to standard therapies. Here we present efficacy, safety and correlative biomarker data of tinengotinib monotherapy in patients with HR+/HER2- and TNBC from the Phase Ib/II trial TT420X1103 (NCT04742959).

Methods

Eligible patients with HR+/HER2- BC or TNBC with no effective standard therapeutic treatment options were enrolled. TNBC patients included acquired TNBC (aTNBC) disease, defined as patients initially diagnosed with HR+/HER2- BC but found to be transformed to TNBC at study entry. Tinengotinib was given as monotherapy at 10 mg or 12 mg daily dose (QD) dose levels, or 6 mg twice daily (BID) dose level, or as a combination therapy at 8mg with paclitaxel. Response was assessed per RECIST v1.1, and safety was evaluated per CTCAE v5.0. Biomarker sampling for circulating tumor DNA (ctDNA) analysis was completed at baseline, cycle 3, day 1 (C3D1), the time of response (partial response or complete response), the time of progression and end of treatment

Results

21 patients with advanced/metastatic breast cancer were treated with tinengotinib monotherapy at 10mg QD (n=3), 12mg QD (n=16), and 6mg BID (n=2).
All patients were female. The median age of patients was 58 (IQR 48-63), and all patients had an ECOG of 1. Of the 21 patients, 18 (85.7%) had Stage IV disease, and 18 (85.7%) had at least 3 lines of prior systemic therapy.

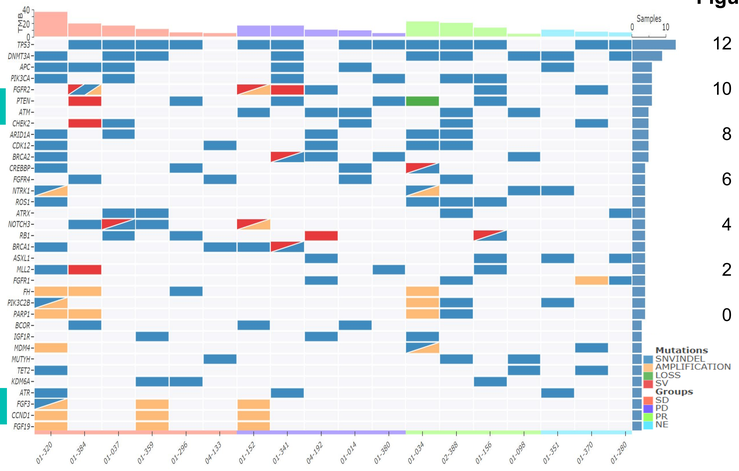
Table 1. Summary of Efficacy of tinengotinib monotherapy in patients with advanced/metastatic breast cancer (n=20)

	Total (n=20)	HR+HER2- (n=8)	TNBC (n=7)	aTNBC (n=5)
Objective Response Rate (ORR)	6 (30%)	3 (37.5%)	0 (0%)	3 (60%)
Median Duration of Response (DOR), months	4.17 (95% CI 2.92, NA)	4.17 (95% CI 3.48, NA)	0	3.89 (95% CI 2.92, NA)
Disease Control Rate (CR + PR + SD)	16 (75%)	6 (75%)	4 (57.1%)	5 (100%)

ctDNA Analysis – aTNBC and ROS1 as predictors of efficacy

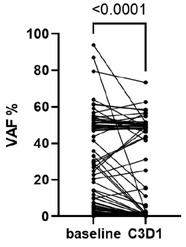
- Acquired TNBC (aTNBC) refers to patients who were originally diagnosed as HR+/HER2-, but at the time of study entry were found to have transformed to TNBC. Patients with aTNBC showed improved efficacy results (Progression Free Survival (PFS), Overall Response Rate (ORR) and Disease Control Rate (DCR)) when compared to TNBC.
- ROS1 mutations were found to have a statistically significant association with improved PFS and ORR and were more frequent in patients with aTNBC.

Figure 1. ctDNA Mutations Present at Baseline (n=18*)



Among 18 patients with ctDNA sampling TP53 (72%), DNMT3A (50%), APC (33%), PIK3CA (33%), FGFR2 (33%) and PTEN (33%) were the most common mutations.

Figure 2. C3D1 analysis of paired ctDNA samples (n=7)



There was reduction in variant allele frequency (VAF) of 7 patients from baseline to C3D1 ($p<0.0001$), indicating a molecular response with treatment.

Table 2. Efficacy in aTNBC vs TNBC (n=14*)

	aTNBC	TNBC
PFS (months)	4.3	2.6
ORR (%)	67%	0%
DCR (%)	100%	50%

TNBC: Triple Negative Breast Cancer
aTNBC: Acquired Triple Negative Breast Cancer (patients initially diagnosed with HR+/HER2- BC but found to be transformed to TNBC at study entry)

Figure 3A. Incidence of ROS1 Mutation vs Efficacy (n=18*)

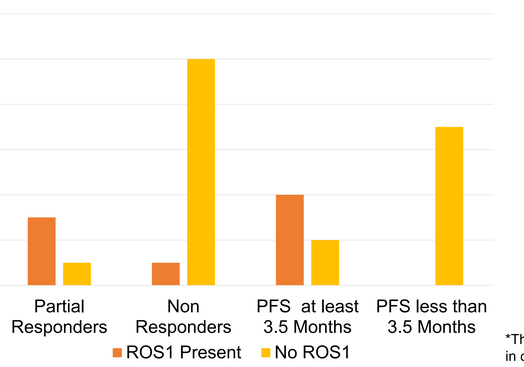
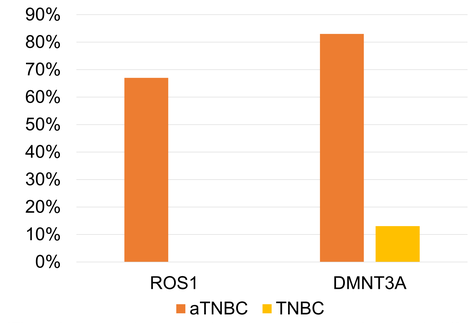


Figure 3B. Incidence of ROS1and DNMT3A in aTNBC vs TNBC (n=14*)



*These data sets include one patient who was treated with tinengotinib (8mg) in combination with paclitaxel, with a diagnosis of aTNBC. All other patients were treated with tinengotinib monotherapy.

Conclusions

- Tinengotinib exhibited promising clinical benefit and manageable safety profile for the treatment of HR+/HER2- BC or TNBC.
- The biomarker correlative analysis revealed that ROS1 mutations could be a potential predictive biomarker. Early reduction in ctDNA VAF may serve as a pharmacodynamic biomarker.
- Baseline genomic alterations in PIK3CA, PTEN, TP53, and RAD51D may contribute to primary resistance, while acquired resistance may be associated with emergence of mutations in pathways of RAS/MAPK, PI3K/AKT, RTK, MET, and cell cycle regulation.
- The improved clinical outcomes and enrichment of ROS1/DNMT3A mutations in aTNBC patients define this transformed subtype as a subgroup warranting further investigation.

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