Efficacy and Safety of Tenalisib, a PI3K δ/γ and SIK3 inhibitor in Patients with Locally Advanced or Metastatic Breast Cancer: Initial results from a Phase II study

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INTRODUCTION

Hyperactivation of PI3K pathway is implicated in malignant transformation, progression, and resistance to endocrine therapy in breast cancer. Salt Inducible Kinase- 3 (SIK3) is highly expressed in breast cancer and elevated SIK3 has shown to contribute to tumorigenesis. Tenalisib (RP6530), a PI3K δ/γ and SIK-3 inhibitor has been evaluated in patients with haematological malignancies and demonstrated encouraging activity in T-cell lymphoma. Tenalisib's major metabolite (IN0385) shows potent SIK-3 inhibition. Preclinical studies in breast cancer cell lines have demonstrated that tenalisib potentiates the activity of taxol and doxorubicin. Tenalisib potentiated the activity of fulvestrant by inhibiting cell growth and causing cell cycle arrest in both MCF-7 and ZR.75.1 breast cancer cell lines.

Figure 1: Study Design

Key Eligibility Criteria

- HR+/HER2- locally advanced or Metastatic Breast Cancer (MBC)
- Progressed following at least one line of therapy
- At least one measurable lesion
- ECOG PS ≤ 2

Group 1: Tenalisib (800mg PO, BID) (N=20)

Group 2: Tenalisib (1200mg PO, BID) (N=20)

Primary end point:
Percentage of patients without disease progression at the end of 6 months.

Secondary end point:
ORR, PFS, CBR

METHODS

- Phase II, randomized, open-label study, to evaluate the preliminary efficacy and safety of tenalisib at two dose levels.
- Both dose groups ran in parallel.
- Tenalisib was given orally in a 28-day cycle until disease progression. (NCT05021900).
- Disease was re-assessed using RECIST version 1.1 at C3D1 (± 7 days) and approximately 8 weeks thereafter (± 7 days), and/or at the EOT and/or as clinically indicated.
- As an exploratory analysis, change from baseline in cytokine/chemokine levels post treatment with tenalisib and change in gene expression profiles from tumour biopsy samples post treatment with tenalisib were measured.

DEMOGRAPHICS

Table 1: Baseline Characteristics and Patient Demographics

Parameters	800 mg BID (n=20)	1200 mg BID (n=20)	All (n=40)
Age, years, Median (range)	62.4 (31-71)	64.2 (51-71)	63.8 (31-71)
Median time from initial diagnosis to first dose of tenalisib treatment, months (range)	47 (7-179)	59 (6-195)	49 (6-195)
de novo metastasis n (%)	6 (30)	5 (25)	11 (27.5)
Stage IVA/IVB, n	10/10	9/11	19/21
Site of disease/metastasis, n			
• *Breast*	14	6	20
• *Lung*	8	12	20
• *Lymph node*	14	14	28
• *Liver*	8	9	17
• *Bone*	12	13	25
No. of metastatic sites, n			
• *≥ 3*	15	15	30
ECOG status, 0/1/2, n	11/9/0	8/12/0	19/21/0
Subtypes, n			
• *ER+, PR+ / ER+, PR- / TNBC*	15/ 5/ 0	16/3/1	31/8/1
Prior Therapies given in advanced/metastatic setting			
Median no. of prior therapies (range)	2 (1-5)	1 (1-5)	1.5 (1-5)
Median no. of prior endocrine therapies, (range)	1.5 (0-3)	1 (0-2)	1 (0-3)
Patients who received chemotherapy, n (%)	9 (45)	10 (50)	19 (47.5)
Last Prior Therapy			
• Aromatase inhibitors	8	8	16
• Tamoxifen	-	1	1
• Fulvestrant	7	5	12
• Chemotherapy agents	6	6	12
Endocrine resistance status#			
• Primary Resistance, n (%)	9 (45)	5 (28)	14 (37)
• Secondary Resistance, n (%)	11 (55)	13 (72)	24 (63)

#Primary endocrine resistance is defined as a relapse within 2 years of adjuvant endocrine treatment or disease progression during the first 6 months of first-line endocrine therapy in metastatic setting. Secondary resistance was defined as relapse ≥ 2 years while the patient was receiving adjuvant ET, relapse <12 months after end of adjuvant ET or progression ≥ 6 months while the patient was received ET in metastatic setting.

SAFETY

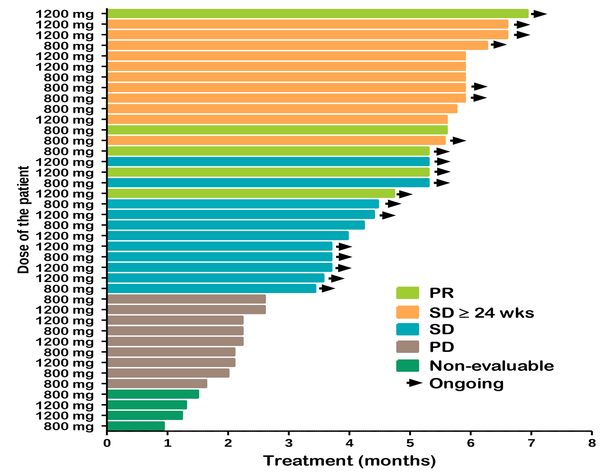
- Majority of the reported AEs were mild to moderate in severity.
- The most common AEs of any grade were transaminitis, GGT elevation, Increased ALP, fatigue and rash. G3 AEs mainly limited to transaminitis, GGT elevation.
- Transaminitis, GGT elevation were managed with a short course of steroids.
- Discontinuations due to related AEs were infrequent (5%). There were no unexpected TEAEs.
- Dose reduction due to related AEs occurred in three patients (7.5%).

Table 2: Incidence of All Related Adverse Events

Adverse Event	800 mg BID (N=20)		1200 mg BID (N=20)		All (N=40)	
	Any grade,%	Grade ≥3, %	Any Grade, %	Grade ≥3, %	Any grade,%	Grade ≥3, %
Increased ALT	40	15	50	10	45	12.5
Increased GGT	40	10	55	15	42.5	12.5
Increased AST	40	10	40	15	40.0	12.5
Rash	15	5	10	-	12.5	2.5
Increased ALP	5	5	10	-	7.5	2.5
Fatigue	-	-	15	-	7.5	-
Pain	5	-	10	-	7.5	-
Neutropenia	5	5	-	-	2.5	2.5
Allergic Reaction	5	5	-	-	2.5	2.5
Elevated Creatinine	-	-	5	-	2.5	-
Hypokalemia	-	-	5	-	2.5	-
Vertigo	5	-	-	-	2.5	-
Vomiting	5	-	-	-	2.5	-
Dysgeusia	-	-	5	-	2.5	-
Urinary tract infection	5	-			2.5	

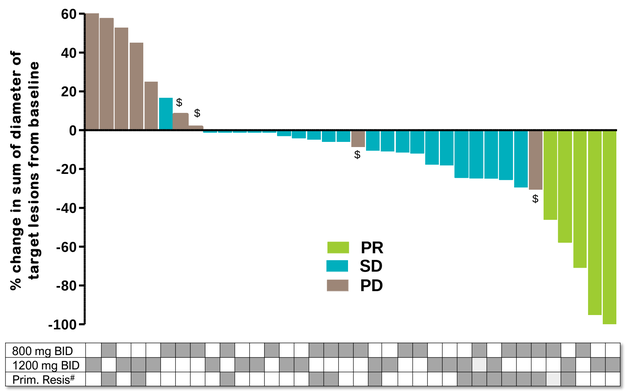
RESULTS

Figure 2: Duration of treatment and Clinical response



- As of 13 May 2022,
  - The median duration of treatment was 4.31 months and ranged from 0.93 to 6.93+ months.
  - 19 (47.5 %) patients continue to be on the study.
  - 13 (32.5%) patients have been treated for ≥ 24 weeks of Tenalisib.

Figure 3: Tumor Response



$PD due to the new lesion; #no of patients with primary resistance.
Data for four patients who were non evaluable prior to C3D1 is not captured

- Out of 14 patients who had primary resistance to endocrine therapy, one patient had partial response and the overall Disease Control Rate (DCR) was 71%.

Parameters	800 mg BID (N=20)	1200 mg BID (N=20)	All (N=40)
• Complete Response, n	-	-	-
• Partial Response, n	2	3	5
• Stable disease, n	11	11	22
• Progressive disease, n	5	4	9
• Objective Response rate (ORR), %	-	-	12.5
• Disease Control rate (DCR), %	-	-	67.5

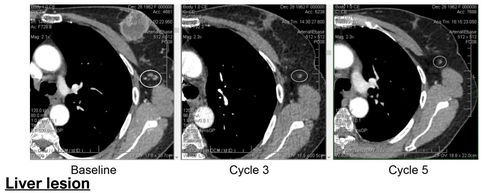
- Median time to onset of response was 1.8 months
- Correlation of response with gene expression profiles by RNA sequencing from tumour biopsy samples post treatment with tenalisib and analysis of cytokine/chemokine levels post tenalisib treatment are underway.

RAPID RESPONSE

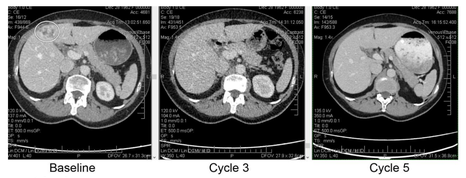
Figure 4: CT Scan images of a patient who showed PR

- 68-year-old female who had extensive disease with lesions on breast, liver, bone, lymph node.
- At C3D1, there was 75% (lymph node), 57% (breast) and 100% (liver) reduction in lesion diameters.
- At C5D1, breast lesion further reduced by 100% with lymph node normalized.

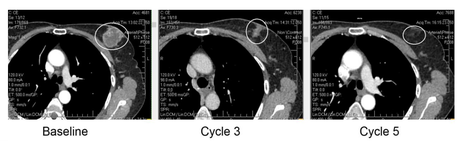
Lymph node



Liver lesion



Breast lesion



CONCLUSIONS

- Tenalisib was well tolerated at both 800 mg BID and 1200 mg BID dose levels.
- Based on the current data, Tenalisib showed encouraging preliminary efficacy as a single agent in patients with advanced MBC.
- Overall efficacy response in both primary and secondary resistant MBC continues to be encouraging and supports further development of Tenalisib in patients with HR+ and HER2- MBC.

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