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***Poziotinib is an investigational drug not approved by the FDA**

A Phase 2 Study of Poziotinib* in Patients with HER2-positive Metastatic Breast Cancer Previously Treated with HER2 Therapies

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INTRODUCTION

- HER2 is overexpressed in roughly 20-25% of breast cancers (BC) and is a prognostic marker[1,2]
- Several targeted drug therapies have been approved by the US Food and Drug Administration (FDA) to treat HER2-positive BC including trastuzumab, lapatinib, pertuzumab, T-DM1
- The current challenge of treating HER2 metastatic BC patients remains the very low response rate whose medical need is unmet and who have progressed with multiple approved therapies and treatment combinations
- Poziotinib (HM781-36B) is a novel pan-HER inhibitor that irreversibly blocks signaling through the EGFR family of tyrosine-kinase receptors and inhibits the proliferation of tumor cells
- To date, poziotinib has been studied in 21 studies in USA, Korea and European countries in patients with lung and other advanced cancers including exon 20 mutations

OBJECTIVES

This study evaluates the safety and clinical activity of poziotinib in adult patients with HER2-positive metastatic breast cancer who have received at least 2 HER2-therapies (trastuzumab and T-DM1). The study objectives are as follows:

Primary

1. To establish the dosing schedule to be in used in the clinical development
2. To evaluate the objective response rate (ORR) of poziotinib in patients with HER2-positive metastatic breast cancer (MBC) who have received prior HER2 regimens for MBC

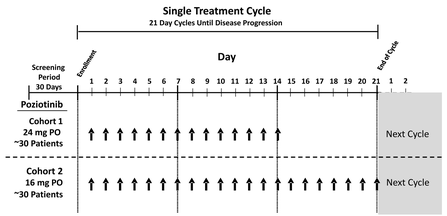
Key Secondary

1. To assess the safety and tolerability of poziotinib in metastatic BC
2. To evaluate progression-free survival (PFS), disease control rate (DCR), time to progression (TTP)

STUDY DESIGN

- Open-label, multi-center study in patients with HER2-positive MBC who have received at least 2 prior HER2-directed treatment including trastuzumab and T-DM1
- Multi-cohort study to establish the dose regimen with the cohort design below
  - Cohort 1: 24 mg (three 8-mg tablets once daily) for 2 weeks, rest 1 week
  - Cohort 2: 16 mg (two 8-mg tablets once daily) continuous dosing
- ORR assessed by Response Evaluation Criterion in Solid Tumors (RECIST, v1.1)

Figure 1. Trial Schema



METHODS

Key Inclusion Criteria

- Histopathologically confirmed primary breast cancer with metastatic lesions
- Confirmed HER2 overexpression or gene-amplified tumor via immunohistochemistry [IHC] with IHC 3+ or IHC 2+ with confirmatory fluorescence *in situ* hybridization [FISH]+
- At least 2 prior HER2-directed therapy regimen(s) for MBC, including trastuzumab and T-DM1
- Adequate hematologic, hepatic and renal function defined by
  - ANC ≥1.0x10^9/L
  - Platelet count ≥100x10^9/L
  - Hemoglobin ≥9 g/dL
  - Total bilirubin ≤1.5 mg/dL; if hepatic metastases present, ≤2.5 mg/dL
  - AST/SGOT, ALT/SGPT, GGT ≤2.5xULN; if hepatic metastases present, ≤5.0xULN
  - Creatinine ≤2.2 mg/dL or calculated creatinine clearance ≥40 mL/min
- Measurable disease as per RECIST, v1.1 at Screening

Key Exclusion Criteria

- Previous treatment with poziotinib
- Brain metastases that are symptomatic or require therapy to control symptoms; history of radiation, surgery, or other therapy including steroids to control symptoms from brain metastases within 15 days of enrollment
- Received anticancer chemotherapy, biologics, immunotherapy, cure-intent radiotherapy or investigational treatment within 15 days, except for hormone, palliative or supportive therapy
- History of congestive heart failure (CHF) Class III/IV as per NYHA functional classification or serious cardiac arrhythmias requiring treatment
- Has left ventricular ejection fraction (LVEF) <50% by either echo or MUGA
- Confirmed clinically significant or recent acute gastrointestinal disease presenting with diarrhea and/or enteritis as a main symptom

RESULTS

Cohort 1 (Poziotinib 24 mg)

Patient Disposition

- 33 patients were enrolled
  - 30 evaluable for efficacy
  - 3 patients died before first post-baseline tumor assessment
- 32 patients discontinued and 1 completed 2-years (34 cycles) treatment
  - 22 disease progression; 4 adverse events; 4 death; 2 withdrawal of consent

Baseline Characteristics

- Female patients with majority <65 yrs old and White
- Most patients had Stage IV breast cancer and median number of previous HER2 therapy was 3 with a range from 2 to 5 therapies
- All 33 patients received trastuzumab, 32 (97%) received T-DM1, and 25 (76%) received pertuzumab

Cohort 2 (Poziotinib 16 mg)

Patient Disposition

- 34 patients were enrolled
  - 27 evaluable for efficacy
  - 7 patients discontinued before first post-baseline tumor assessment (3 adverse events, 3 withdrawal of consent, 1 death)
- 34 patients discontinued the treatment
  - 14 disease progression; 12 adverse events; 4 withdrawal of consent; 1 death; 3 other reasons

Baseline Characteristics

- Female patients with majority <65 yrs old and White
- Most patients had Stage IV breast cancer and median number of previous HER2 therapy was 3 with a range from 2 to 5 therapies
- All 34 patients received trastuzumab, 33 (97%) received T-DM1, and 26 (76%) received pertuzumab

RESULTS *CONTINUED*

Table 1. Key Baseline Characteristics

Characteristic	Cohort 1 Poziotinib 24 mg (N = 33)	Cohort 2 Poziotinib 16 mg (N = 34)
Age (years)		
Median (range)	59 (29, 94)	59 (33, 86)
<65 yrs, n (%)	25 (75.8)	24 (70.6)
≥65 yrs, n (%)	8 (24.2)	10 (29.4)
Race, n (%)		
White	30 (90.9)	29 (85.3)
Black or African American	1 (3.0)	4 (11.8)
Asian	2 (6.1)	0
Other	0	1 (2.9)
Hispanic or Latino ethnicity, n (%)	5 (15.2)	5 (14.7)
Stage, n (%)		
IIIA	0	3 (8.8)
IIIC	1 (3.0)	1 (2.9)
IV	32 (97.0)	30 (88.2)
ECOG, n (%)		
0	20 (60.6)	16 (47.1)
1	11 (33.3)	16 (47.1)
2	2 (6.1)	2 (5.9)

Table 2. Prior Therapy

	Cohort 1 Poziotinib 24 mg (N = 33)	Cohort 2 Poziotinib 16 mg (N = 34)
Number of Prior HER2 Therapy, median (range)	3 (2, 5)	3 (2, 5)
Prior HER2 Therapy, n (%)		
Trastuzumab + T-DM1	5 (15.2)	8 (23.5)
Trastuzumab + T-DM1 + lapatinib	3 (9.1)	0
Trastuzumab + pertuzumab	1 (3.0)	0
Trastuzumab + pertuzumab + lapatinib	0	1 (2.9)
Trastuzumab + T-DM1 + pertuzumab	12 (36.4)	16 (47.1)
Trastuzumab + T-DM1 + pertuzumab + lapatinib	11 (33.3)	8 (23.5)
Trastuzumab + T-DM1 + pertuzumab + lapatinib + neratinib	1 (3.0)	1 (2.9)
Patients with trastuzumab, T-DM1 and pertuzumab, n (%)	24 (72.7)	25 (73.5)
Number of Prior Lines of Therapy, median (range)	7 (2, 13)	4 (2, 16)

Table 3. Poziotinib Drug Exposure

	Cohort 1 Poziotinib 24 mg (N = 33)	Cohort 2 Poziotinib 16 mg (N = 34)
Number of Cycles, median (range)	3 (1, 34)	2 (1, 31)
Duration of Treatment (days), median (range)	56.0 (1, 707)	45.5 (3, 660)
Days of Treatment Administered, median (range)	41.0 (1, 475)	34.5 (3, 581)
Average Daily Dose (mg) per Duration of Treatment, median (range)	11.2 (5.0, 24.0)	11.9 (5.0, 16.0)
Average Daily Dose (mg) per Days of Treatment Administered, median (range)	20.0 (11.7, 24.0)	16.0 (11.7, 16.0)
Relative Dose Intensity, RDI (%), median (range)	61.7 (7.1, 100.0)	55.2 (14.3, 99.0)
Patients with Dose Reduction, n (%)	22 (66.7)	16 (47.1)
Last Dose Level, n (%)		
24 mg	11 (33.3)	n/a
16 mg	13 (39.4)	18 (52.9)
12 mg	9 (27.3)	14 (41.2)
10 mg	0	1 (2.9)
8 mg	0	1 (2.9)

RDI=100*Total Actual Dose Taken / (336 x Number of Cycles)

Poziotinib Drug Exposure

Cohort 1 (poziotinib 24 mg)

- Median number of cycles was 3.0 with one patient who completed up to 34 cycles
- Median duration of treatment of 56.0 days with one patient who completed 707 days
- Median relative dose intensity was 61.7%

Cohort 2 (poziotinib 16 mg)

- Median number of cycles was 2.0 with one patient who completed up to 31 cycles
- Median duration of treatment of 45.5 days with one patient who completed 660 days
- Median relative dose intensity was 55.2%

Table 4. Efficacy Results (Evaluable Population)

Efficacy outcome	Cohort 1 Poziotinib 24 mg (N = 30)	Cohort 2 Poziotinib 16 mg (N = 27)
ORR (CR+PR), % [95% CI]	23.3 [9.9, 42.3]	22.2 [8.6, 42.3]
DCR (CR+PR+SD), % [95% CI]	46.7 [28.3, 65.7]	63.0 [42.4, 80.6]
Best Overall Response, n (%)		
Complete Response (CR)	0	3 (11.1)
Partial Response (PR)	7 (23.3)	3 (11.1)
Stable Disease (SD)	7 (23.3)	11 (40.7)
Progressive Disease (PD)	15 (50.0)	7 (25.9)
Not Evaluable (NE)	1 (3.3)	3 (11.1)
PFS (months), median (range)	3.0 (0.9, 10.8)	4.9 (0.1, 19.8)
DoR (months), median (range)	5.6 (3.0, 9.6)	13.8 (4.4, 18.7)

- ORR=Overall Response Rate; DCR=Disease Control Rate; PFS=Progression-free Survival; DoR=Duration of Response
- The Evaluable Population consists of all patients who are enrolled, complete at least one cycle of poziotinib treatment, and have at least one evaluable post-baseline tumor response evaluation using RECIST, v1.1
- Results are derived by Sponsor based on RECIST, v1.1, and include criteria below:
  - CR/PR requires confirmation scan that is ≥4 weeks from previous scan
  - Patient needs to be on-treatment for ≥6 weeks when SD is evaluated

Figure 2. Progression-free Survival (Evaluable Population)

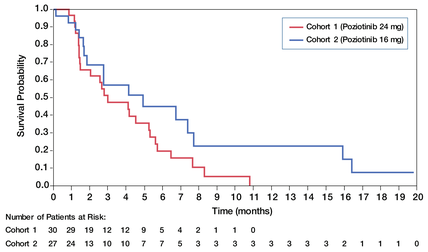


Figure 3. Swimmers Plot (Responders only)

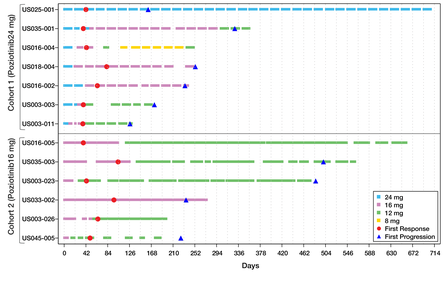


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Table 5. Adverse Events Summary

	Cohort 1 Poziotinib 24 mg (N = 33) n (%)	Cohort 2 Poziotinib 16 mg (N = 34) n (%)
Any AE	33 (100.0)	34 (100.0)
Any grade ≥3 AE	24 (72.7)	29 (85.3)
Any treatment-related AE	33 (100)	33 (97.1)
Any treatment-related ≥3 AE	22 (66.7)	25 (73.5)
Any serious AE	14 (42.4)	16 (47.1)
Any treatment-related serious AE	9 (27.3)	7 (20.6)
Any AE leading to discontinuation	7 (21.2)	13 (38.2)
Any treatment-related AE leading to discontinuation	6 (18.2)	10 (29.4)
Any AE with outcome of death	3 (9.1)	1 (2.9)

Table 6. Most Common (≥20%) Treatment-Related AEs

Efficacy outcome	Cohort 1 Poziotinib 24 mg (N=33)		Cohort 2 Poziotinib 16 mg (N=34)	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Diarrhea	29 (87.8)	10 (30.3)	29 (85.3)	10 (29.4)
Rash	20 (60.6)	6 (18.2)	15 (44.1)	4 (11.8)
Fatigue	15 (45.2)	1 (3.0)	13 (38.2)	0
Stomatitis	13 (39.4)	2 (6.1)	16 (47.1)	1 (2.9)
Vomiting	13 (39.4)	1 (3.0)	8 (23.5)	0
Nausea	11 (33.3)	2 (6.1)	14 (41.2)	1 (2.9)
Decreased appetite	10 (30.3)	0	11 (32.4)	0
Dry skin	9 (27.3)	0	5 (14.7)	0
Mucosal inflammation	8 (24.2)	2 (6.1)	2 (5.9)	0
Dermatitis acneiform	7 (21.2)	2 (6.1)	10 (29.4)	2 (6.1)
Rash maculo-papular	3 (9.1)	1 (3.0)	8 (23.5)	4 (11.8)

SUMMARY AND CONCLUSIONS

- Study evaluated 24 mg daily and 16 mg daily intermittent starting doses to evaluate safety and efficacy in advanced and metastatic BC who failed multiple prior treatments
- Majority (at least 75%) patients received at at least 3 prior HER2 therapies (range from 2 to 5) including trastuzumab, pertuzumab, T-DM1 and other approved therapies
- Patients with intermittent 24 mg were able to stay longer on therapy with higher dose intensity
- There were similar treatment-related AEs in both dose groups which included diarrhea and rash
- Poziotinib demonstrated clinical activity in both dose groups with confirmed ORR of 23% and 22% respectively in these heavily pre-treated metastatic breast cancer patients

REFERENCES

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