Phase 1/2 Dose Expansion Study Evaluating First-In-Class eIF4A Inhibitor Zotatifin In Patients with ER+ Metastatic Breast Cancer

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Background

Zotatifin is a highly selective inhibitor of eukaryotic translation initiation factor 4A (eIF4A) that provides a novel approach to cancer treatment by blocking production of specific proteins required for tumor growth and survival. eIF4A is a ribonucleic acid (RNA) helicase required to unwind secondary structures that inhibit translation initiation of specific messenger RNAs (mRNAs). eIF4A is activated by signaling through the PI3K and RAS pathways. Zotatifin forms a stable, inhibitory complex between eIF4A and defined nucleotide sequences present in the 5’ untranslated regions (5’-UTR) of certain mRNAs, thereby blocking production of proteins encoded by these mRNAs. Zotatifin target sequences are found in the 5’-UTR of mRNAs encoding the estrogen receptor, Cyclins D and E, CDK4, as well as several oncogenes and drivers of cell proliferation (HER2, ERBB3, FGFR1/2, EGFR, and KRAS). Zotatifin’s capacity to block production of these proteins leads to in vitro inhibition of tumor cell proliferation and induction of apoptosis and substantial in vivo anti-tumor activity in multiple tumor models, especially in ER+ breast cancer (BC), with strong, mechanism-based combination benefit observed when co-administered with the CDK4/6 inhibitor palbociclib.

Initial results from the first-in-human Phase 1/2 dose escalation and expansion study of zotatifin in solid tumors were reported at ASCO 2022[1]. Dose-dependent target engagement was demonstrated by rapid accumulation of a target mRNA, c-Jun, in circulating whole blood, reflecting the inhibitory complex of zotatifin, mRNA and eIF4A. Subsequent analysis also demonstrated dose-dependent decreases in circulating tumor DNA (ctDNA), including in patients who received zotatifin monotherapy. Zotatifin was well tolerated at the initial RP2D of 0.07 mg/kg given on Days 1 and 8 of a 21 day cycle and initial signs of clinical activity were observed, including partial responses and prolonged stable disease in metastatic ER+ BC. Expansion cohorts were opened in metastatic ER+ BC, including zotatifin in combination with fulvestrant (Z+F doublet) or with fulvestrant and abemaciclib (Z+F+A triplet). Based on accumulated safety information at the initial RP2D, dose escalation was resumed, using Z+F in patients with ER+ BC.

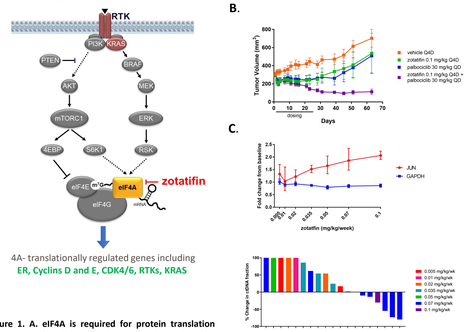


Figure 1. A. eIF4A is required for protein translation initiation and tumorigenesis. A. Oncogenic signaling through the PI3K and RAS pathways leads to activation of RNA helicase eIF4A. Activated eIF4A is required for efficient translation of mRNA encoding downstream effector proteins including ER and cyclins, and upstream pathway components including HER2 and other RTKs. **B. Pre-clinical efficacy of zotatifin**. Zotatifin inhibits tumor growth in mice bearing MDA-MB-361 xenografts and leads to sustained tumor regression post dosing in combination with palbociclib. **C**. **Target engagement in patients**. *Top panel*, dose-dependent changes in c-JUN RNA in patient whole blood. *Bottom panel*, dose dependent changes in ctDNA on C3D1 in patient whole blood assessed by FoundationOne assay. Increases >100% were capped at 100% for plotting.

Objectives

Primary objectives:

Parts 1, 1a and 1b (Dose escalation)

- To define the safety and tolerability of zotatifin monotherapy dosed QW or 2 wks on/1 wk off (Part1)[1], or zotatifin QW dosing (Part 1a)/zotatifin Q2W dosing (Part 1b) in combination with fulvestrant in patients with ER+ metastatic breast cancer
- To determine the MTD or RP2D for zotatifin monotherapy, and zotatifin QW/Q2W in combination with fulvestrant (Parts 1a and 1b)
- To evaluate the PK profile of zotatifin

Parts 2, 2a and 2b (Expansion cohorts)

- To evaluate the preliminary antitumor activity of zotatifin
- To determine the MTD or RP2D for zotatifin in combination therapy

Secondary objectives:

Parts 1, 1a and 1b

- To evaluate the preliminary antitumor activity of zotatifin

Part 2, 2a and 2b

- To assess the safety of zotatifin
- To assess progression free survival (PFS)
- To evaluate the PK profile of zotatifin in combination therapy

Exploratory objectives:

- To explore the effects of zotatifin on pharmacodynamic markers relating to drug mechanism
- To explore additional biomarkers to further elucidate mechanism of action, predict response to therapy, and understand potential resistance mechanisms

Methods

Study design and treatment

- Open label study in adult patients with metastatic or locoregionally recurrent ER+ breast cancer
- **Part 1**: 3+3 dose escalation scheme with intravenous administration of zotatifin monotherapy dosed QW or 2 wks on/1 wk off (Part 1)[1] or in combination with fulvestrant with QW dosing (Part 1a) and Q2W dosing (part 1b)
- **Part 2**: Expansion at MTD or RP2D as monotherapy or in combination with SOC on 1) days 1 and 8 of a 21-day cycle, 2) with QW administration (Part2a) or 3) with Q2W administration (Part 2b) as a Simon 2-stage design, with seven patients in stage 1 of each cohort

Patient eligibility - key inclusion criteria

- **Zotatifin + fulvestrant cohort (Z+F)**
  - Metastatic disease or locoregionally recurrent ER+ breast cancer
  - Minimum of one prior line of therapy for advanced/metastatic disease
  - Recurrence or progression on at least one line of endocrine therapy in the advanced/metastatic disease setting
  - Prior treatment has included a CDK4/6 inhibitor
- **Zotatifin + fulvestrant + abemaciclib cohort (Z+F+A)**
  - Metastatic disease or locoregionally recurrent ER+ breast cancer
  - Minimum of one prior line of therapy for advanced/metastatic disease
  - Recurrence or progression on at least one line of endocrine therapy in the advanced/metastatic disease setting

Response assessment

- Radiological tumor assessment at baseline and every 8 weeks
- Response assessment using RECIST v1.1

All data reported is interim prior to database lock (data cut-off 5/3/2023)

Results

Table 1. Patient characteristics and prior treatment history

Characteristic	Z+F (N=18)	Z+F+A (N=20)
Age, median (range), years	56 (40-72)	57 (38-82)
Race, N		
White	11	14
Black or African descent	4	2
Asian	1	1
American Indian or Alaska native	1	1
Other	1	2
ECOG PS, N (%)		
0	4 (22)	10 (50)
1	14 (78)	10 (50)
Visceral metastases, N (%)	16 (89)	15 (75)
Median number prior regimens for MBC (range)	5 (1-11)	4 (1-11)
≥ 2 prior ET for metastatic disease, N (%)	14 (78)	12 (60)
Type of prior therapy for MBC, N (%)		
CDK4/6 inhibitor	18 (100)	19 (95)
Fulvestrant	16 (89)	13 (65)
Chemotherapy	15 (83)	15 (75)
≥ 2 prior regimens for MBC	12 (67)	10 (50)

Table 2. Z+F+A triplet: summary of treatment-emergent adverse events

TEAE listing for Z+F+A, N=20	TEAEs (All Grades) N (%)	Grade 3 or Higher N (%)
Diarrhea	16 (80%)	3 (15%)
Nausea	15 (75%)	0 (%)
Vomiting	11 (55%)	0 (%)
Fatigue	11 (55%)	0 (%)
Dysgeusia	8 (40%)	0 (%)
Dry mouth	7 (35%)	0 (%)
Abdominal pain	6 (30%)	0 (%)
Anemia	6 (30%)	0 (%)
Dyspnea	6 (30%)	2 (10%)
Peripheral neuropathy	6 (30%)	0 (%)
Epistaxis	5 (25%)	0 (%)
Dehydration	4 (20%)	0 (%)
Muscle spasms	4 (20%)	0 (%)
Back pain	4 (20%)	0 (%)
Constipation	3 (15%)	0 (%)
Platelet count decreased	3 (15%)	1 (5%)
Blood creatine phosphokinase increased	3 (15%)	1 (5%)
Gastroesophageal reflux disease	3 (15%)	0 (%)
Pruritus	3 (15%)	0 (%)
Myalgia	3 (15%)	0 (%)

Table 3. Z+F doublet: summary of treatment-emergent adverse events

TEAE listing for Z+F, N=18	TEAEs (All Grades) N (%)	Grade 3 or Higher N (%)
Nausea	9 (50%)	0 (%)
Constipation	5 (28%)	0 (%)
Vomiting	5 (28%)	0 (%)
Fatigue	5 (28%)	0 (%)
Headache	4 (22%)	1 (6%)
Abdominal pain	4 (22%)	0 (%)
Anemia	4 (22%)	1 (6%)
Diarrhea	4 (22%)	1 (6%)
Dizziness	3 (17%)	0 (%)
Dry eye	3 (17%)	0 (%)
Dry mouth	3 (17%)	0 (%)
Alopecia	2 (11%)	0 (%)
Contusion	2 (11%)	0 (%)
Cough	2 (11%)	0 (%)
Dyspnea	2 (11%)	0 (%)
Non-cardiac chest pain	2 (11%)	0 (%)
Edema peripheral	2 (11%)	0 (%)
Sinus tachycardia	2 (11%)	0 (%)
Urinary tract infection	2 (11%)	0 (%)
Stomatitis	2 (11%)	0 (%)
Muscle weakness	2 (11%)	0 (%)
Oropharyngeal pin	2 (11%)	0 (%)

Treatment-emergent adverse events (TEAEs) are defined as AEs that start during or after initiating study therapy, or AEs with an onset prior to initiating study therapy that worsen after study therapy initiation. TEAEs >10% Incidence are reported by Preferred Term and Maximum Reported CTCAE Grade for Subjects. Percentage is calculated using the number of treated subjects as the denominator.

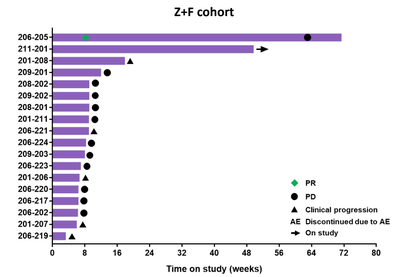
Results (continued) Expansion Cohorts

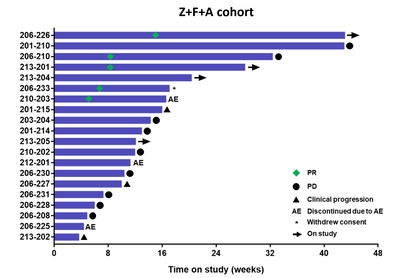
Table 4. Response summary

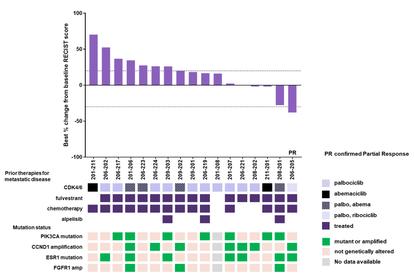
Characteristic	Z+F (N=17)	Z+F+A (N=19)
BOR (Unconfirmed responses), N (%)		
PR	1(5.9)	5 (26)
SD	6 (35)	9 (47)
PD	10 (59)	4 (21)
ORR (Confirmed CR/PRs), N (%)	1 (5.9)	4 (21)
DCR (CR, PR, or SD), N (%)	7 (41%)	14 (74)

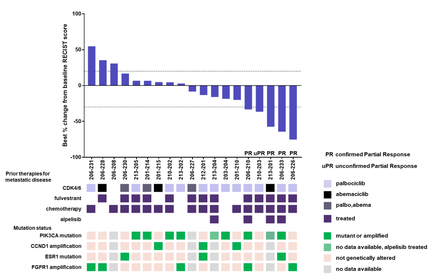
Evaluable population with at least 1 post-baseline measurement; SD was at least 5 weeks from start of treatment

Interim efficacy analysis – expansion cohorts





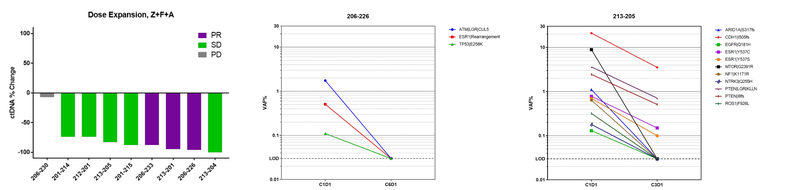




Evaluable population with at least 1 post-baseline measurement; SD was at least 5 weeks from start of treatment

Evaluable population with at least 1 post-baseline measurement; SD was at least 5 weeks from start of treatment

Interim ctDNA analysis – Z+F+A expansion cohort

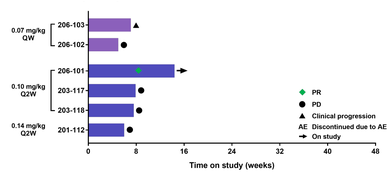


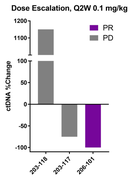
ctDNA was analyzed by GuardantInfinity assay. Changes in %ctDNA were calculated using the set of 74 cancer-associated genes validated in the Guardant360 assay. Variants of unknown significance and synonymous mutations were removed to plot specific allele changes. Samples were analyzed from C3D1 (Day 43) except for Patient 206-226 , where the available sample was from C6D1 (Day 106).

- 8 of 9 (89%) patients from Z+F+A triplet cohort with available samples showed >50% decrease in ctDNA
- All patients with >50% decrease in ctDNA showed PR or SD as best response
- Patient 206-226 had undetectable ctDNA (100% decrease) at Day 106 and a deep confirmed PR (RECIST -75%), ongoing at Week 40
- Patient 213-205 demonstrated an 83% reduction in ctDNA and an ongoing SD at Week 12

Results (continued) Resumed Dose Escalation

Interim efficacy analysis – Z+F dose escalation





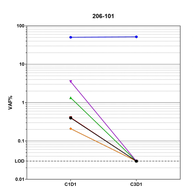
Confirmation of PR for 206-101 occurred after data cut-off

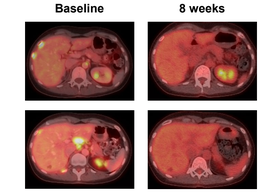
ctDNA analysis same as for Z+F+A, except C3D1 is Day 29

- No DLTs or SAEs observed to date in dose escalation cohorts
- 1 of 3 (33%) of Z+F patients dosed at 0.1 mg/kg Q2W had a confirmed PR

Patient 206-101

- Germline BRCA2^{mut} , prior biopsy showed HER2 2+, FISH negative
- ctDNA revealed ESR1, ERBB2 and BRCA2 mutations at baseline
- Four lines of prior therapy for metastatic disease, including
  - palbociclib + anastrozole
  - trastuzumab deruxtecan
  - abemaciclib + anastrozole
  - olaparib
  - Progressive disease was best response to all four prior lines
- ctDNA was undetectable after only two doses of zotatifin





Summary

Zotatifin had a manageable safety profile as the Z+F+A triplet

- The vast majority of adverse events were mild or moderate and there were no dose-limiting toxicities in expansion or dose-escalation cohorts

Zotatifin showed evidence of efficacy in heavily pretreated metastatic BC patients

- Zotatifin in combination with fulvestrant and abemaciclib (Z+F+A triplet) had a 26% ORR (four confirmed and one unconfirmed partial responses)
- All patients with responses had received prior CDK 4/6 inhibitor, fulvestrant, and chemotherapy

ctDNA decreases >50% were seen in 89% of patients dosed at 0.07 mg/kg

Less frequent dosing of zotatifin as a doublet showed evidence of activity

- Confirmed PR observed in a heavily pre-treated patient at 0.1 mg/kg Q2W combined with fulvestrant

Promising efficacy results compared favorably to published data for retreatment with CDK/endocrine therapy post progression

Data support continued development of the Z+F+A triplet in ER+ breast cancer and continued dose escalation of the Z+F doublet

Acknowledgements

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[1]F Meric-Bernstam et al. J Clin Oncol 40, 2022 (suppl 16; abstr 3081). Poster #73