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. Initial data from expansion cohorts in metastatic ER+ BC, including zotatifin in combination with fulvestrant or with fulvestrant and abemaciclib (Z+F+A triplet), as well as data from resumed dose escalation, were presented at ASCO 2023[2]. Here we present mature data from the Z+F+A triplet as well as additional data from further dose escalation in combination with fulvestrant.

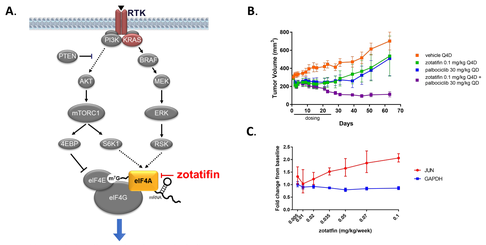


Figure 1. A. eIF4A is required for protein translation initiation and tumorigenesis. A. Oncogenic signaling through the PI3K and RAS pathways leads to activation of eIF4A, which is required for efficient translation of mRNA encoding downstream effector proteins including ER and cyclins, and upstream 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**. Dose-dependent changes in c-JUN RNA in patient whole blood.

Objectives and Methods

Primary objectives:

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

- To define the safety, tolerability, MTD or RP2D of zotatifin monotherapy and in combination with fulvestrant

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

- To evaluate antitumor activity of zotatifin monotherapy and combination therapy

Secondary objectives:

Part 2, 2a and 2b

- To assess the safety of zotatifin and progression free survival (PFS)

Exploratory objectives:

- To explore the effects of zotatifin on pharmacodynamic markers relating to drug mechanism, response to therapy, and potential resistance mechanisms

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 iv administration of zotatifin monotherapy or in combination with fulvestrant dosed QW, 2 wks on/1 wk off, or Q2W
- **Part 2**: Expansion at MTD or RP2D as monotherapy or in combination with SOC as a Simon 2-stage design

Patient eligibility - key inclusion criteria

- **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
- **Part 1b: dose escalation, zotatifin + fulvestrant cohort Q2W**
  - 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

Response assessment

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

Results

All data reported is interim prior to database lock (data cut-off 11/17/2023)

Table 1. Patient characteristics and prior treatment history

Characteristic	Z+F+A (N=20)	Part 1b (N=9)
Age, median (range), years	57 (38-82)	62 (38-71)
Race, N		
White	14	6
Black or African descent	2	0
Asian	1	2
American Indian or Alaska native	1	0
Other	2	1
ECOG PS, N (%)		
0	10 (50)	4 (44)
1	10 (50)	5 (56)
Visceral metastases, N (%)	15 (75)	9 (100)
Median number prior regimens for MBC (range)	4 (1-11)	4 (2-5)
≥ 2 prior ET for metastatic disease, N (%)	12 (60)	8 (89)
Type of prior therapy for MBC, N (%)		
CDK4/6 inhibitor	19 (95)	9 (100)
Fulvestrant	13 (65)	6 (67)
Chemotherapy	15 (75)	6 (67)
≥ 2 prior regimens for MBC	10 (50)	4 (44)

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

Preferred term, N=20	All Grades, N (%)	Grade 3 or 4, N (%)
Nausea	14 (70)	0 (0)
Vomiting	11 (55)	0 (0)
Fatigue	10 (50)	0 (0)
Diarrhea	9 (45)	1 (5)
Anemia	6 (30)	2 (10)
Dry mouth	6 (30)	0 (0)
Peripheral sensory neuropathy	6 (30)	0 (0)
Dehydration	4 (20)	0 (0)
Muscle spasms	4 (20)	0 (0)
Blood creatine phosphokinase increased	4 (20)	2 (10)
Dysgeusia	4 (20)	0 (0)
Stomatitis	4 (20)	0 (0)
Platelet count decreased	3 (15)	1 (5)
Abdominal pain	3 (15)	0 (0)
Hypertriglyceridemia	3 (15)	0 (0)

Zotatifin-related 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 ≥ 15% 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.

Table 3. Part 1b (Z+F): summary of zotatifin-related treatment-emergent adverse events

Preferred term	0.10 mg/kg, N=3 Grades 1 or 2 N (%)	0.14 mg/kg, N=3 Grades 1 or 2 N (%)	0.2 mg/kg, N=3 Grades 1 or 2 N (%)
Vomiting	2 (67)	0 (0)	2 (67)
Nausea	2 (67)	0 (0)	1 (33)
Anemia	0 (0)	2 (67)	0 (0)
Headache	1 (33)	0 (0)	1 (33)
Fatigue	0 (0)	0 (0)	2 (67)
Diarrhea	0 (0)	0 (0)	1 (33)
Dry mouth	0 (0)	0 (0)	2 (67)
Peripheral sensory neuropathy	0 (0)	0 (0)	1 (33)
Dehydration	0 (0)	1 (33)	0 (0)
Muscle spasms	1 (33)	0 (0)	0 (0)
Abdominal pain	0 (0)	0 (0)	1 (33)
Hypertriglyceridemia	0 (0)	1 (33)	0 (0)
Infusion related reaction	0 (0)	0 (0)	1 (33)
Muscular weakness	0 (0)	0 (0)	1 (33)
Myalgia	1 (33)	0 (0)	0 (0)
Constipation	1 (33)	0 (0)	0 (0)
Dysgeusia	0 (0)	0 (0)	1 (33)
Polydipsia	0 (0)	0 (0)	1 (33)
Palmar-plantar erythrodysaesthesia	0 (0)	0 (0)	1 (33)
Vision blurred	0 (0)	0 (0)	1 (33)
Tinnitus	0 (0)	0 (0)	1 (33)
Candida infection	0 (0)	0 (0)	1 (33)
Epistaxis	1 (33)	0 (0)	0 (0)

Zotatifin-related 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. All TEAEs are reported by Preferred Term and Maximum Reported CTCAE Grade for Subjects. Percentage is calculated using the number of treated subjects as the denominator.

- **In Part 1b, no zotatifin-related grade 3 or 4 TEAEs were observed**

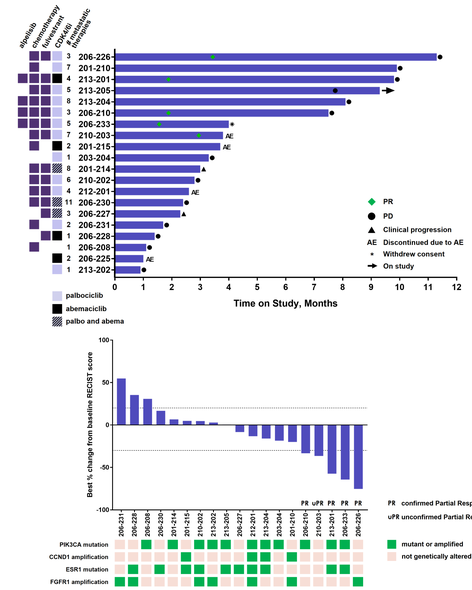
Results (continued) Z+F+A Cohort

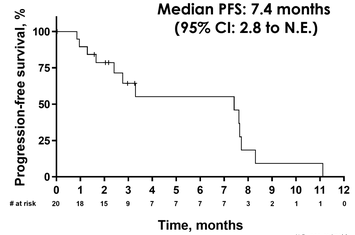
Table 4. Response summary

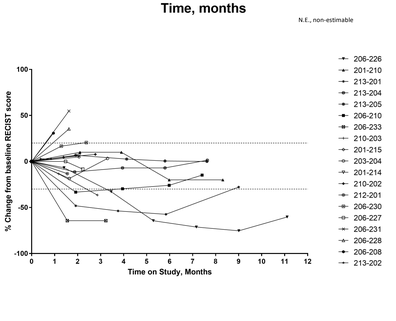
Characteristic	Z+F+A (N=19)
BOR (Unconfirmed responses), N (%)	
PR	5 (26)
SD	10 (53)
PD	4 (21)
ORR (Confirmed CR/PRs), N (%)	4 (21)
DCR (CR, PR, or SD), N (%)	15 (79)
CBR24, N (%)	6 (32)
Median TTR , months (range)	1.9 (1.6 - 3.5)
Median DOR, months (range)	6.6 (1.7 – 7.7)

- **5 PRs (4 confirmed) in Z+F+A triplet cohort**
- **Responses seen in patients with or without ESR1 and PIK3CA mutations**
- **All 5 patients with PRs had progressed on prior treatment with fulvestrant and a CDK4/6 inhibitor, including Patient 213-201 who progressed on abemaciclib and fulvestrant immediately prior to study entry**
- **All 5 patients with PRs had received one or more lines of prior chemotherapy**

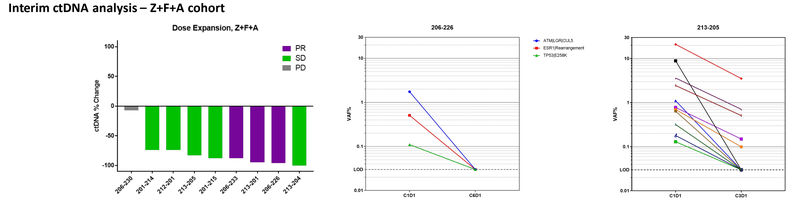
Efficacy analysis – Z+F+A cohort







Interim ctDNA analysis – Z+F+A cohort

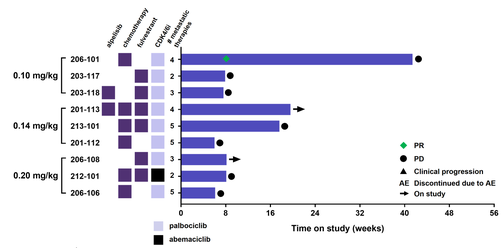


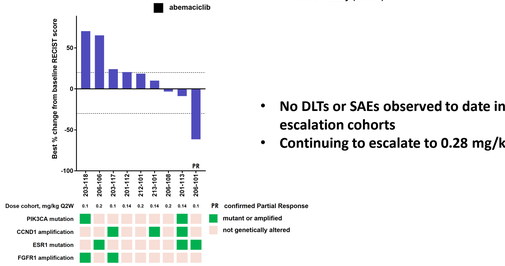
ctDNA was analyzed by Guardant Infinity assay. Changes in % ctDNA were calculated using the set of 74 cancer-associated genes validated in the Guardant360 assay. Variants of unknown significance and synonymous mutations were removed to plot specific allele changes. Samples were analyzed from C3D1 (Day 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%) for 11 months**
- **Patient 213-205 demonstrated an 83% reduction in ctDNA and SD for 7.6 months**

Results (continued) Part 1b, Dose Escalation

Interim efficacy analysis – Part 1b (Z+F) dose escalation





- **No DLTs or SAEs observed to date in dose escalation cohorts**
- **Continuing to escalate to 0.28 mg/kg Q2W**

Summary

Zotatifin had a manageable safety profile

- The vast majority of adverse events were mild or moderate and there were no dose-limiting toxicities in resumed 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) led to a mPFS of 7.4 months and responses in 26% of evaluable patients (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 evaluable 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

- Median PFS in the Z+F+A triplet of 7.4 months compares favorably to other reports of activity in late line ER+ BC patients in the post-CDK4/6i setting, including a mPFS of 5.3 months observed in the MAINTAIN study[3] with less heavily treated patients than reported here

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. 2022 J Clin Oncol 40 (suppl 16: abstr 3081).
[2]Rosen, et al. 2023 J Clin Oncol 41 (suppl 16: abstr 1080).
[3]Kalinsky, et al. 2023 J Clin Oncol 41(24):3003-4013.