Zotatifin Clinical Data and Corporate Update

January 5, 2023

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Zotatifin Clinical Data and Corporate Update

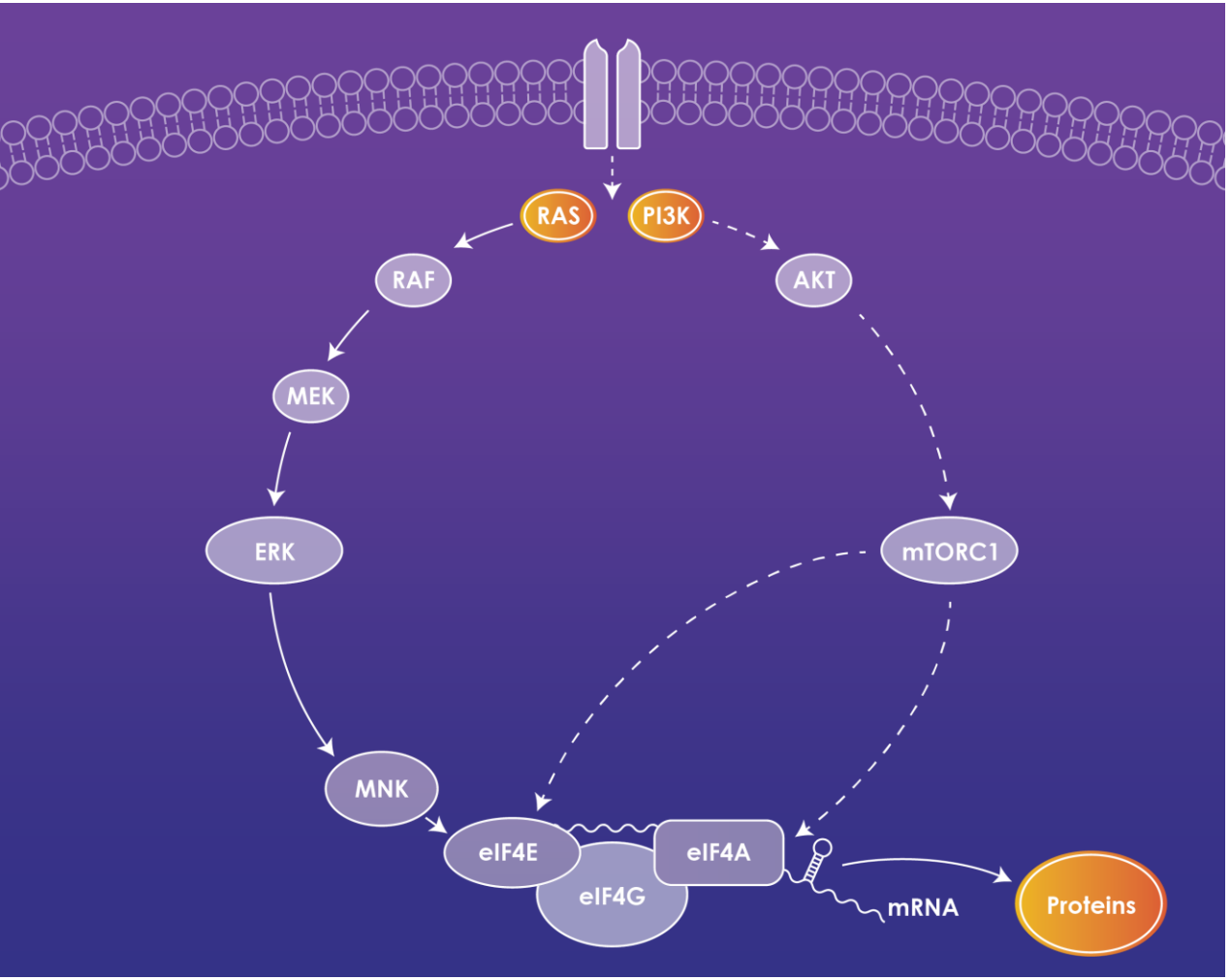
Participants

- Steve Worland, Ph.D., President & CEO
- Doug Warner, M.D., Chief Medical Officer
- Mike Byrnes, Chief Financial Officer

Agenda

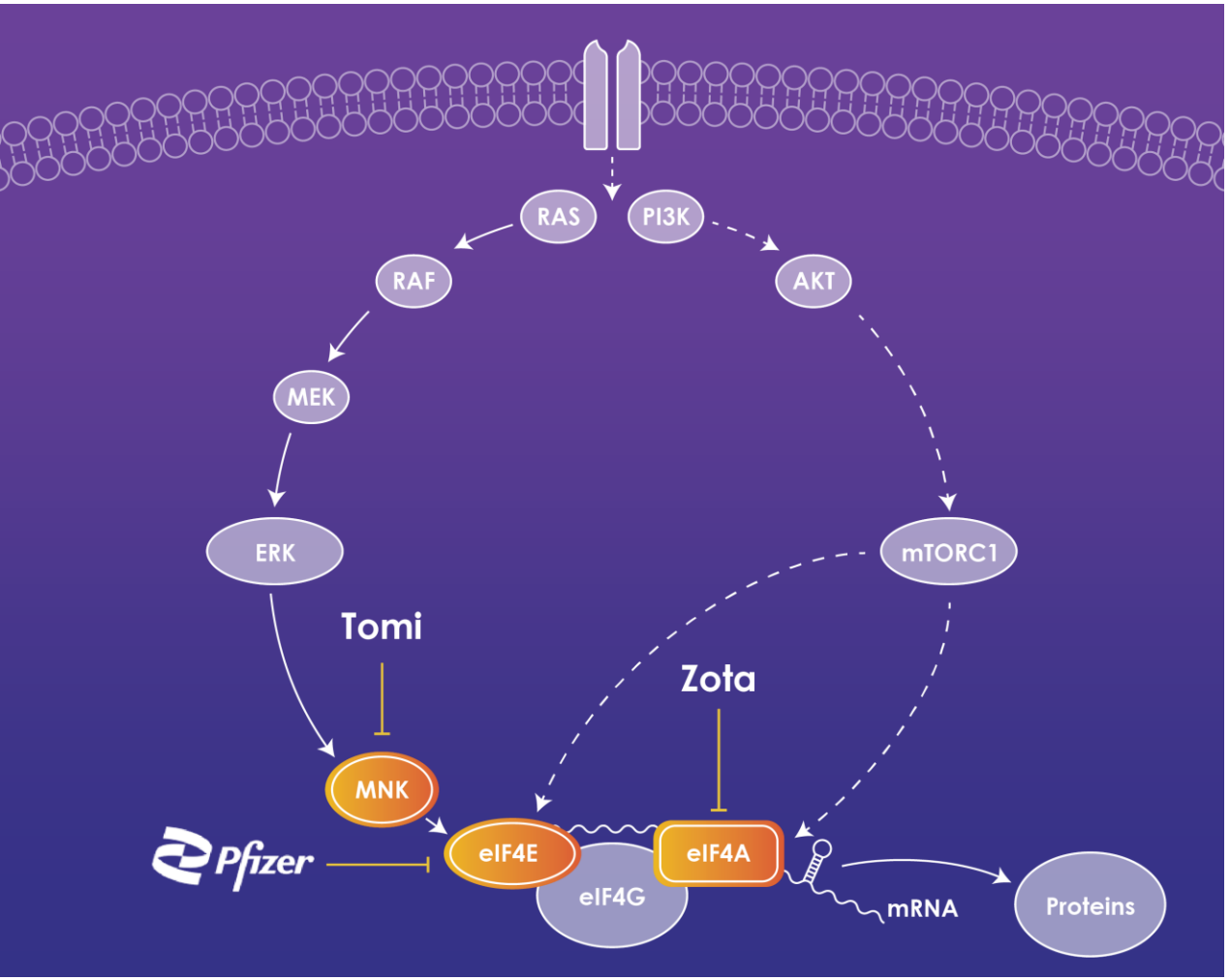
- Introductory Remarks
- Zotatifin Oncology Update
- Zotatifin COVID Update
- Tomivosertib Update
- Business Update and Closing Remarks
- Q&A

Oncogenic Signaling Selectively Activates Translation to Drive Production of Specific Tumor-Promoting Proteins



- Multiple signaling pathways, including **RAS** and **PI3K**, activate mRNA translation to drive production of **specific proteins**
- Tumors are dependent on upregulated protein production for growth, avoidance of apoptosis, and immune evasion
- eFFECTOR is taking the novel approach to block oncogenic signaling at the point of mRNA translation
- Potential **benefits** to targeting translation
  - Certain tumors are **acutely dependent** on upregulated protein production
  - Numerous **opportunities to combine** with agents acting elsewhere in these pathways or in complementary pathways

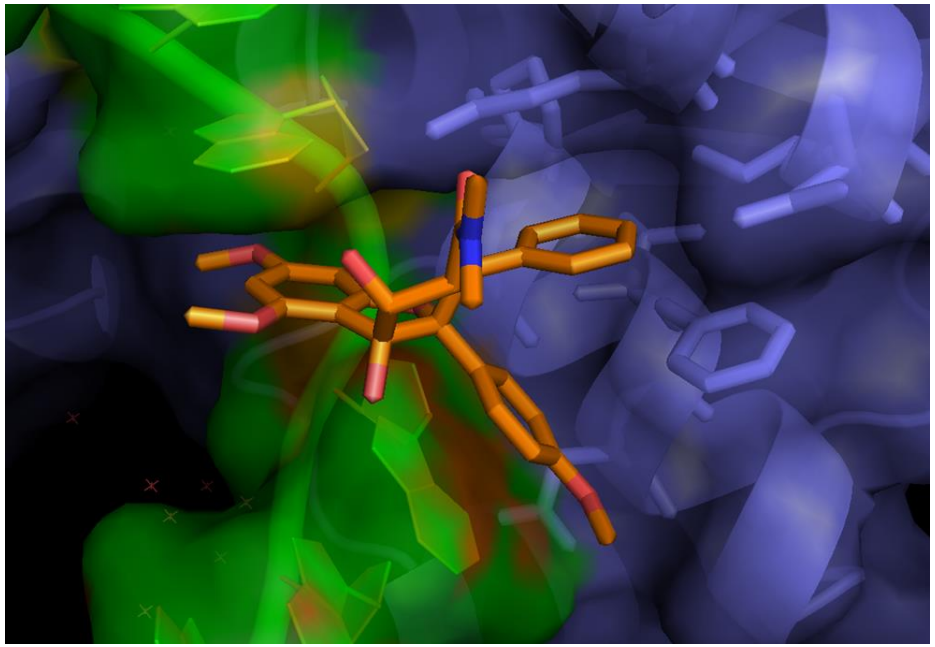
Selective Translation Regulator Inhibitor (STRI) Platform: Controlling the Outputs of Tumor-driving Pathways



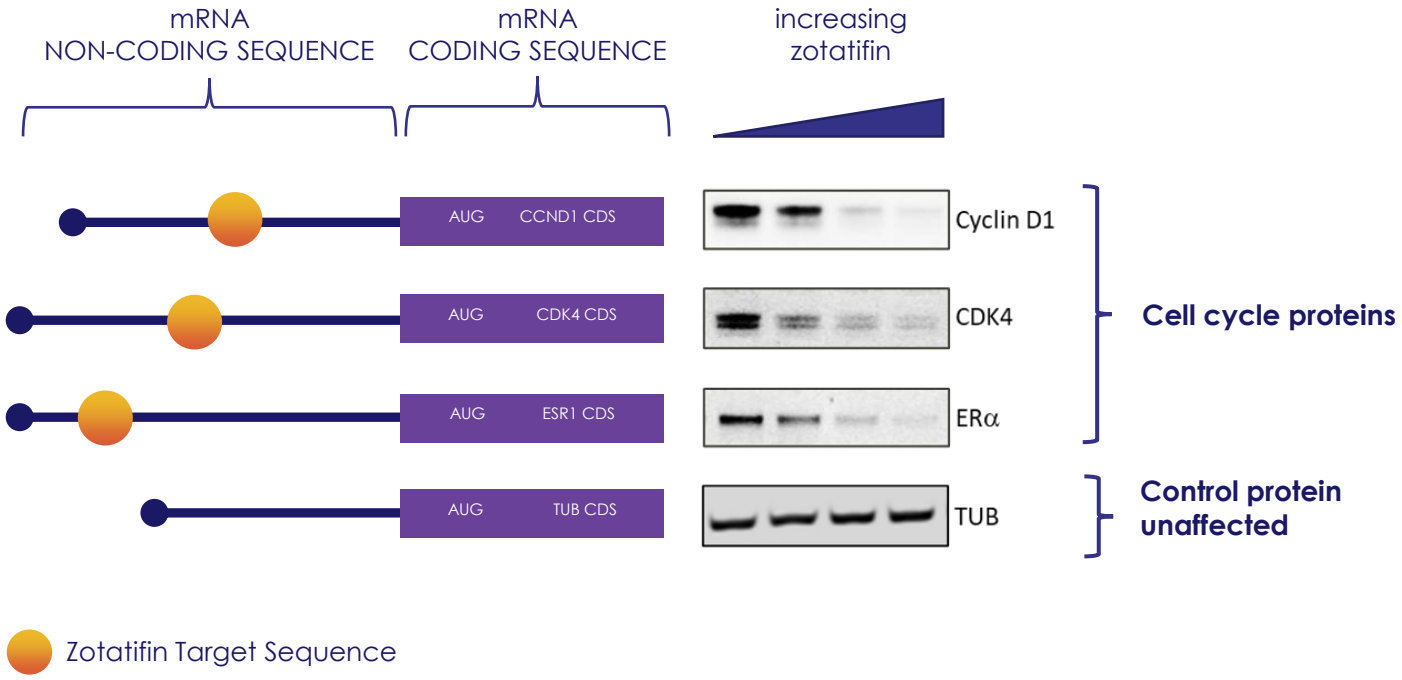
- Focused on three targets that drive translation:
  - **MNK:** kinase phosphorylates RNA-binding proteins
  - **eIF4A:** helicase unwinds RNA secondary structures
  - **eIF4E:** binds 5'-cap of mRNA
- Each target controls production of a distinct set of proteins
  - STRI platform enabled identification of regulated proteins and vulnerable tumor types
- eFFECTOR invented novel product candidates with strong intellectual property to address each of the three targets

Preclinical Regulation of Translation by Zotatifin Selectively Suppressed a Specific Set of Cancer Driving Proteins

Zotatifin selectively bound specific sequences found in the 5' non-coding region of mRNAs encoding certain cancer-driving proteins



Experimental structure of natural product RocA bound to eIF4A and zotatifin RNA target sequence[1]



[1]Iwaski et al. 2019 Mol Cell (73) 738-748

Zotatifin Phase 1/2 Dose Escalation and Expansion Trial

Part 1 Dose Escalation

- Open label 3+3 design in mixed population
- Weekly dosing transitioned to two weeks on/one week off
- **Primary Objectives** include
  - Safety, tolerability, MTD and RP2D
- **Secondary Objectives** include
  - Preliminary anti-tumor activity

Part 2 Expansion Cohorts

- Simon 2-stage design (Stage 1, N=7; Stage 2, N=11)
- Dose of 0.07 mg/kg given on Day 1 and 8 of 21-day cycle
- **Primary Objectives** include
  - Preliminary anti-tumor activity as monotherapy and in combination
  - MTD or RP2D of zotatifin as combination therapy
- **Secondary Objectives** include
  - Safety of zotatifin as monotherapy and as combination therapy
  - Progression free survival (PFS)

Expansion Cohorts in ER+ BC Combined with fulvestrant +/- abemaciclib

ECBF ER+ BC zotatifin + fulvestrant	Post-endocrine and CDK4/6 therapy No limit to prior lines
ECBF + A ER+/HER2- zotatifin + fulvestrant + abemaciclib	Post-endocrine therapy No limit to prior lines

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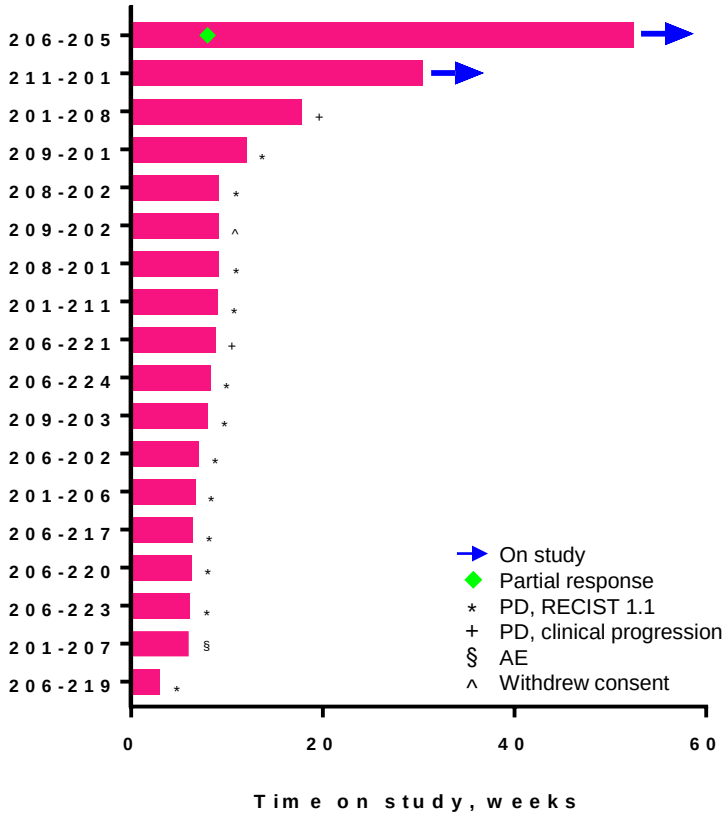
ECBF Cohort
Zotatifin plus Fulvestrant

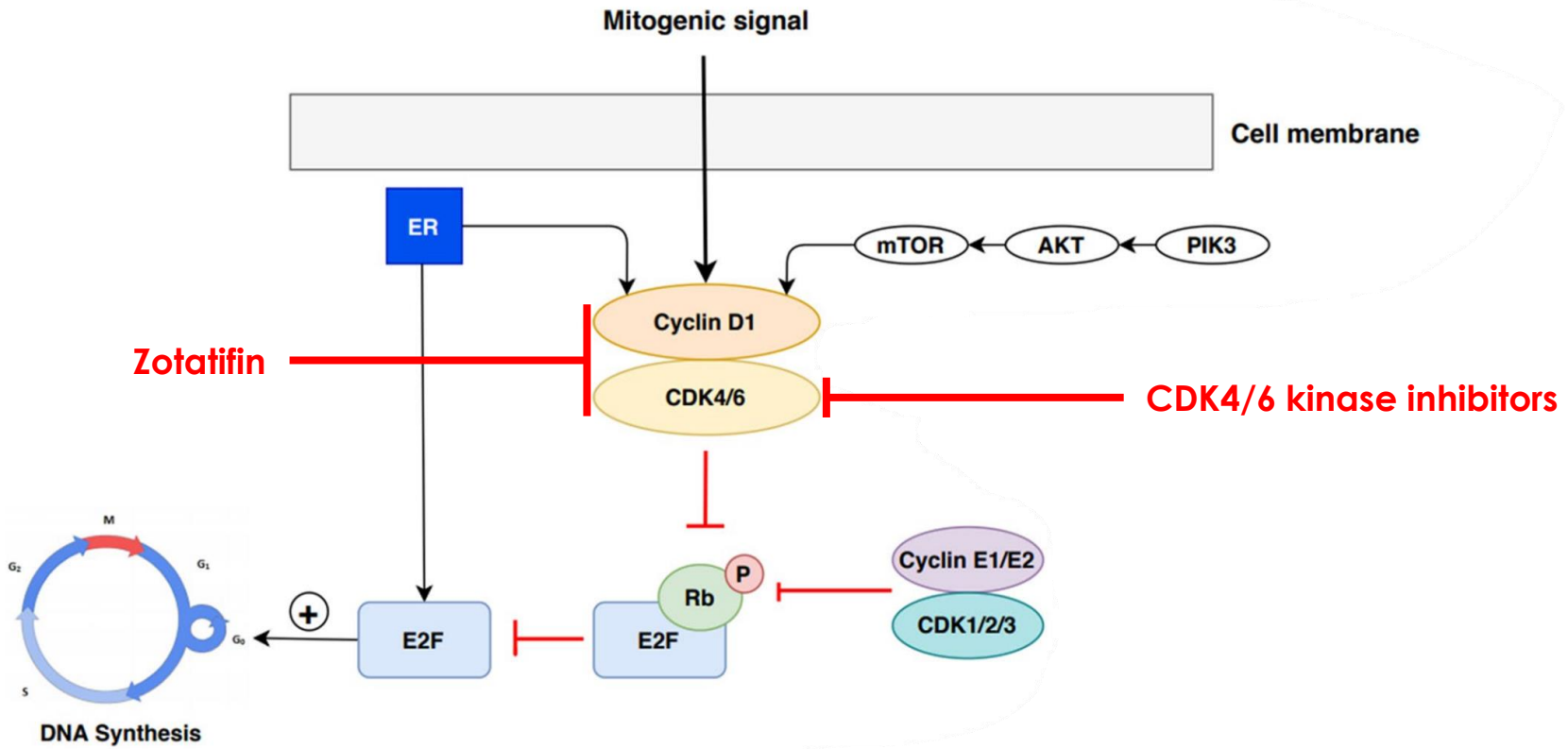


Genetics and Prior Treatments

- 206-205
  - Confirmed PR continuing at Week 52
  - Cyclin D1^{amp}, ESR1^{mut}
  - 7 lines of prior treatment including fulvestrant, palbociclib and ribociclib
- 211-201
  - Stable Disease ongoing at Week 30
  - PIK3CA^{mut}
  - 3 lines of prior treatment including fulvestrant and abemaciclib

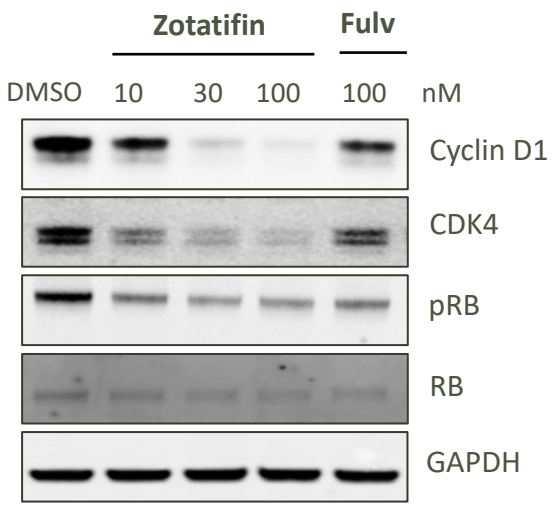
Preliminary results from ongoing trial prior to database lock
Data cutoff December 15, 2022

Zotatifin Downregulation of Cyclin D1 and CDK4/6 Designed To Complement CDK4/6 Inhibitors That Target Kinase Subunit

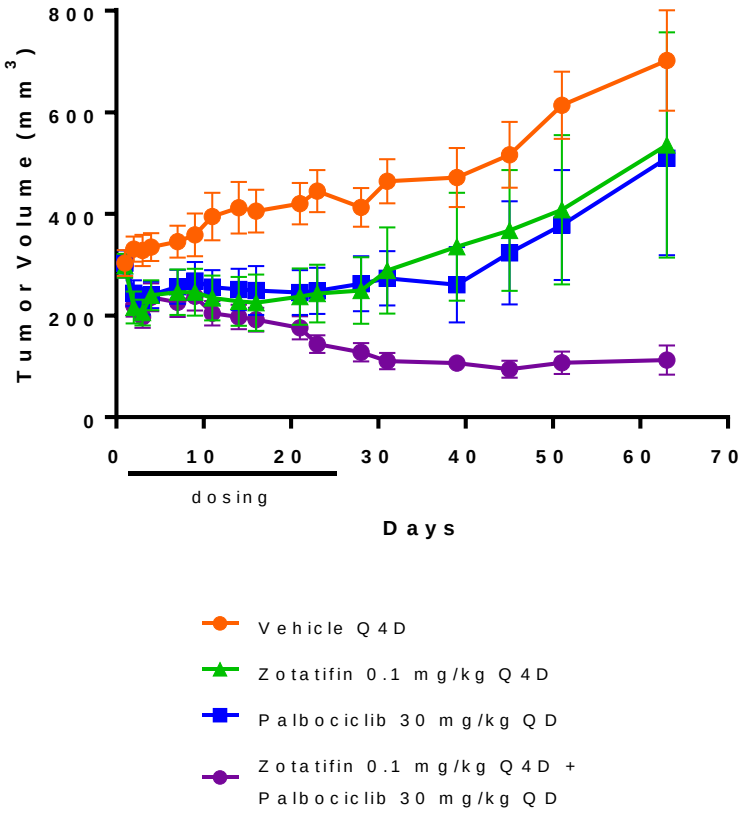


Zotatifin Downregulated Cyclin D1 and CDK4/6 *in vitro* Combination of Zotatifin with Palbociclib Was Highly Active *in vivo*

Zotatifin Blocked Production of Key Cell Cycle Targets in Cells

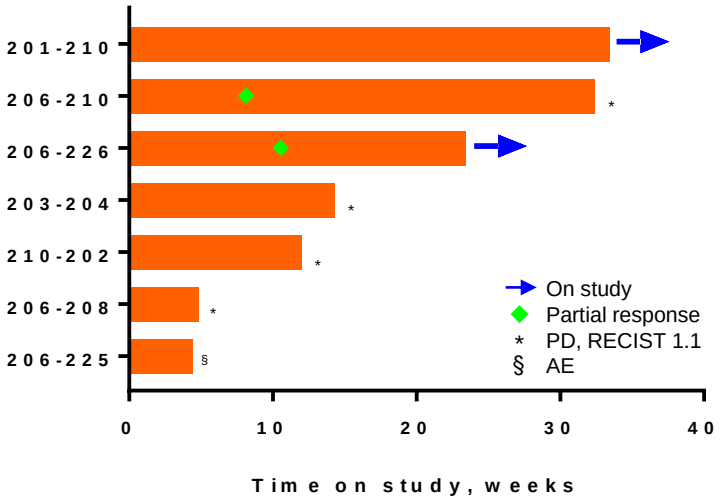


Zotatifin Was Active in Preclinical Models of ER+ BC and Showed Combination Benefit with Palbociclib



ECBF+A Cohort
Zotatifin plus Fulvestrant and Abemaciclib

ORR 29% (2/7)
CBR 43% (3/7)



Clinical Benefit Rate (CBR) defined as proportion of patients with Confirmed Responses or Stable Disease lasting ≥ 24 weeks

Genetics and Prior Treatments

- 201-210
  - Stable Disease continuing at Week 33
  - Cyclin D1^{amp}, FGFR1^{amp}
  - 7 lines of prior treatment including palbociclib
- 206-210
  - Confirmed PR, PFS of 28 Weeks
  - PIK3CA^{mut}
  - 3 lines of prior treatment including palbociclib, fulvestrant and alpelisib
- 206-226
  - Confirmed PR ongoing at Week 23
  - FGFR1^{amp}, NSD3^{amp}
  - 3 lines of prior treatment including palbociclib and fulvestrant

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Preliminary results from ongoing trial prior to database lock
Data cutoff December 15, 2022

ECBF Cohort (Zotatifin plus Fulvestrant) Summary of Treatment-Emergent Adverse Events

TEAE Listing for ECBF	TEAEs (All Grades) N (%)	Grade 3 or Higher N (%)
	n=18	n=18
Nausea	7 (39%)	0 (%)
Constipation	5 (27%)	0 (%)
Abdominal pain	4 (22%)	0 (%)
Anemia	4 (22%)	1 (6%)
Diarrhea	4 (22%)	1 (6%)
Vomiting	4 (22%)	0 (%)
Dizziness	3 (17%)	0 (%)
Dry eye	3 (17%)	0 (%)
Dry mouth	3 (17%)	0 (%)
Fatigue	3 (17%)	0 (%)
Headache	3 (17%)	0 (%)
Alopecia	2 (11%)	0 (%)
Aspartate aminotransferase increased	2 (11%)	0 (%)
Contusion	2 (11%)	0 (%)
Cough	2 (11%)	0 (%)
Dyspnea	2 (11%)	1 (6%)
Hypotension	2 (11%)	1 (6%)
Non-cardiac chest pain	2 (11%)	0 (%)
Edema peripheral	2 (11%)	0 (%)
Sinus tachycardia	2 (11%)	0 (%)
Urinary tract infection	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. Preliminary results with data cutoff of December 15, 2022.

ECBF+A Cohort (Zotatifin plus Fulvestrant and Abemaciclib) Summary of Treatment-Emergent Adverse Events

TEAE Listing for ECBF+A	TEAEs (All Grades) N (%)	Grade 3 or Higher N (%)
	n=7	n=7
Diarrhea	5 (71%)	0 (%)
Nausea	4 (57%)	0 (%)
Dry mouth	3 (43%)	0 (%)
Fatigue	3 (43%)	0 (%)
Vomiting	3 (43%)	0 (%)
Constipation	2 (29%)	0 (%)
Dysgeusia	2 (29%)	0 (%)
Dyspnea	2 (29%)	0 (%)
Epistaxis	2 (29%)	0 (%)
Muscle spasms	2 (29%)	0 (%)
Myalgia	2 (29%)	0 (%)
Atrial fibrillation	1 (14%)	1 (14%)
Blood creatine phosphokinase increased	1 (14%)	1 (14%)
Corona virus infection	1 (14%)	0 (%)
Ear congestion	1 (14%)	0 (%)
Gastroesophageal reflux disease	1 (14%)	0 (%)
Hypomagnesaemia	1 (14%)	0 (%)
Limb discomfort	1 (14%)	0 (%)
Muscular weakness	1 (14%)	0 (%)
Non-cardiac chest pain	1 (14%)	0 (%)
Esophagitis	1 (14%)	0 (%)

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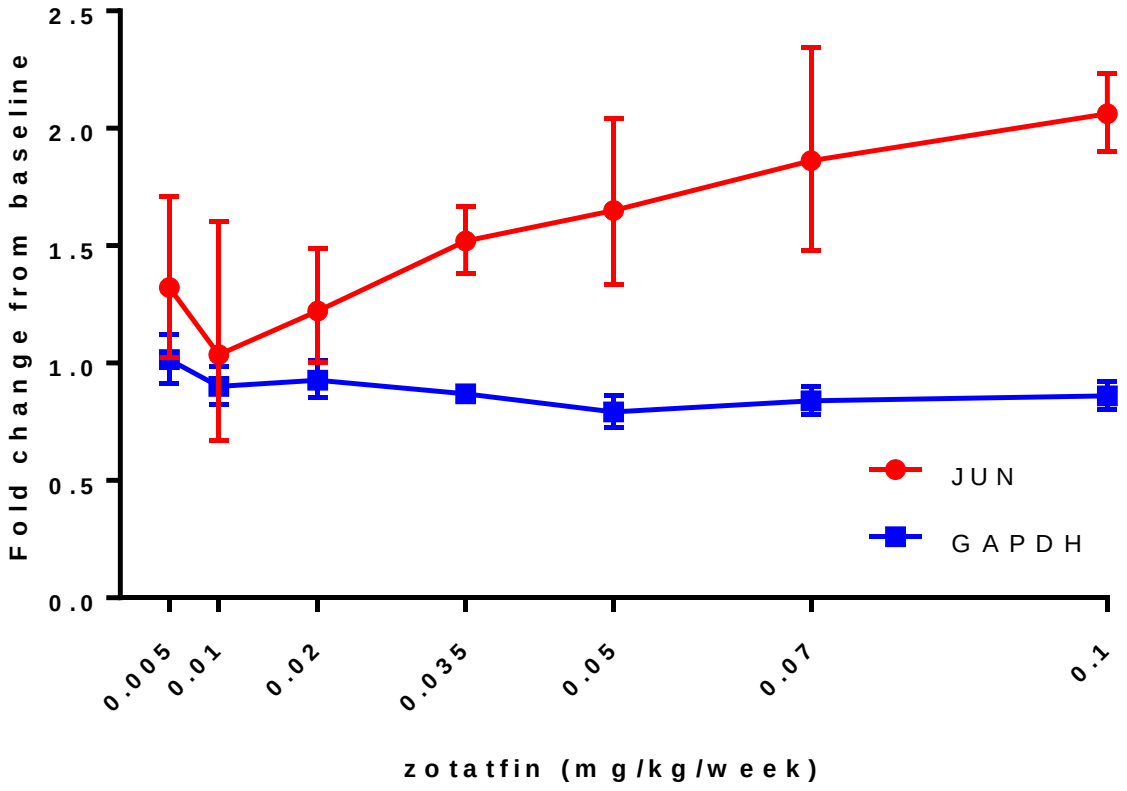
ECBF+A Cohort (Zotatifin plus Fulvestrant and Abemaciclib) Summary of Treatment-Emergent Adverse Events, cont'd

TEAE Listing for ECBF+A	All TEAEs (All Grades) (N %)	Grade 3 or Higher N(%)
	n=7	n=7
Pain in extremity	1 (14%)	0 (%)
Palpitations	1 (14%)	0 (%)
Pleural effusion	1 (14%)	0 (%)
Presyncope	1 (14%)	0 (%)
Proteinuria	1 (14%)	1 (14%)
Pruritus	1 (14%)	0 (%)
Rash maculo-papular	1 (14%)	0 (%)
Rhabdomyolysis	1 (14%)	1 (14%)
Sinus tachycardia	1 (14%)	0 (%)
Stomatitis	1 (14%)	0 (%)
Thrombocytopenia	1 (14%)	0 (%)
Vertigo	1 (14%)	0 (%)
Vision blurred	1 (14%)	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. Preliminary results with data cutoff of December 15, 2022.

eIF4A Target Engagement Was Assessed by Stabilization of Zotatifin-Sensitive RNA in Whole Blood

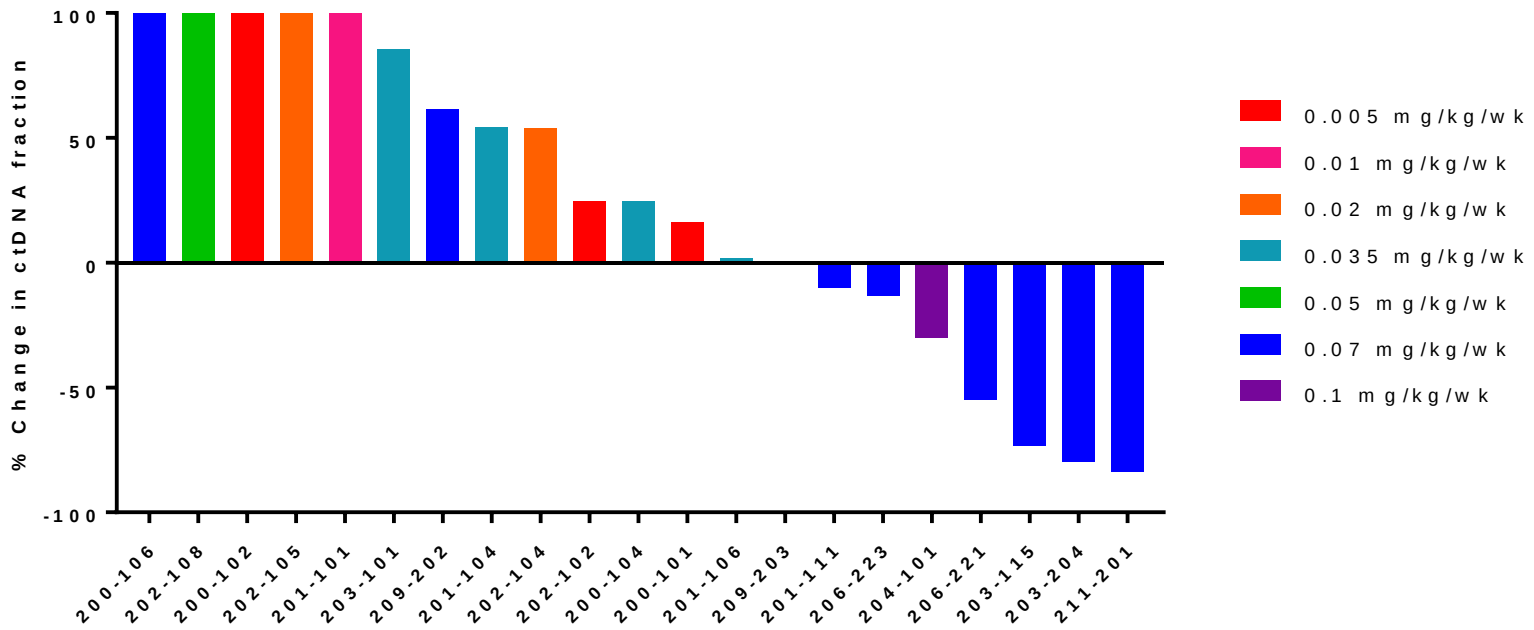
Formation of ternary complex between zotatifin, eIF4A and RNA resulted in selective, dose-dependent stabilization of JUN RNA relative to housekeeping gene GAPDH



RNA levels in whole blood, assayed by Nanostring ® methodology, are plotted as geometric mean of fold-induction 4 and 8 hrs after zotatifin administration
Preliminary results with a data cutoff of December 15, 2022

eIF4A Target Engagement Was Assessed by Changes in Fraction of Circulating Tumor DNA (ctDNA)

Fraction of ctDNA decreased at higher doses of zotatifin



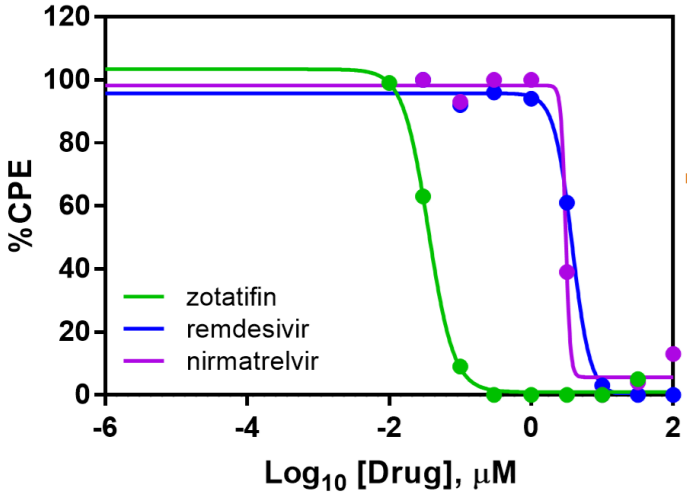
Fraction of ctDNA relative to total DNA was measured at baseline and after treatment with zotatifin. % change in ctDNA fraction after treatment relative to baseline is plotted. Preliminary results with a data cutoff of December 15, 2022

Good Safety Results with Zotatifin To Date Motivate Additional Dose Escalation

- Resumed dose escalation at 0.1 mg/kg dosed every other week (Q2W)
  - Preclinical *in vivo* data showed full retention of anti-tumor activity with extended-interval dosing
- Also plan to resume testing weekly (QW) dosing, starting at 0.07 mg/kg
  - Testing weekly dosing in case relationships between pharmacokinetics, pharmacodynamics and activity are different between human disease and mouse models
- Expect data from both dosing regimens 2H 2023

Zotatifin Well Positioned as Host-Directed Therapeutic for COVID-19 and Beyond

Zotatifin observed to be more potent *in vitro* than remdesivir and nirmatrelvir*



Phase 1b Double-Blind Trial Ongoing

- N=36, non hospitalized patients with mild to moderate COVID-19 severity
- Sequential cohort dosing:
  - 0.01 mg/kg
  - .02 mg/kg
  - .035 mg/kg

Future Development

- Continued widespread COVID-19 cases and potential for future zoonotic transmissions suggests pressing need for continued development of novel anti-coronavirus therapeutics

- Zotatifin inhibits eIF4A, preventing production of the viral proteins needed for SARS-CoV-2 replication
- Sub-cutaneous formulation with single injection aligns with Test to Treat initiative
- COVID-19 program funded by $5M cooperative agreement with DARPA and UCSF
- **Enrollment in all three cohorts now completed**

Topline safety and antiviral data expected in 1H 2023

*tested head-to-head in same assay against Omicron BA.2 strain of SARS-CoV-2

KICKSTART: Randomized, Double-blind, Phase 2b Trial In Treatment-Naïve NSCLC Patients w/ PD-L1 ≥50%

- Tomi dosed 100 mg BID with food
- Progression Free Survival (PFS) is primary endpoint

- **Topline data readout anticipated 2H 2023**

Multiple Upcoming Clinical Milestones

Anticipated Milestones		2023		2024
		1H	2H	
Tomivosertib	Top line data from P2b NSCLC frontline with pembro		●	
	Initiate P3 in NSCLC			●
Zotatifin Oncology	Initial ORR data from remaining 11 patients in ECBF+A P2a (n=18) expansion cohort	●		
	Data from P1b dose escalation cohorts		●	
	Initiate potentially registrational P2b study			●
Zotatifin COVID-19	Top line data from Phase 1b study	●		

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Q&A

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