Zotatifin Program Update and Expansion Plans

June 5, 2022

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eFFECTOR

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Agenda for Today's Call

- **Introduction**
  - Kevan Shokat, Ph.D.
    Co-Founder, eFFECTOR Therapeutics
    Professor, Department of Cellular and Molecular Pharmacology, University of California San Francisco
    Howard Hughes Medical Investigator
- **Zotatifin Background**
  - Steve Worland, Ph.D.
    Co-Founder, President and CEO, eFFECTOR Therapeutics
- **Interim Clinical Data**
  - Funda Meric-Bernstam, M.D.
    Chair, Department of Investigational Cancer Therapeutics and Nellie B. Connally Chair in Breast Cancer
    University of Texas MD Anderson Cancer Center
- **Pharmacodynamic Markers & Zotatifin Clinical Plans**
  - Robert Sikorski, M.D., Ph.D.
    Senior Clinical Development Advisor, eFFECTOR Therapeutics
    Managing Director, Woodside Way Ventures
- **Future Outlook**
  - Steve Worland
- **Q&A**

Introduction

Kevan Shokat, Ph.D.

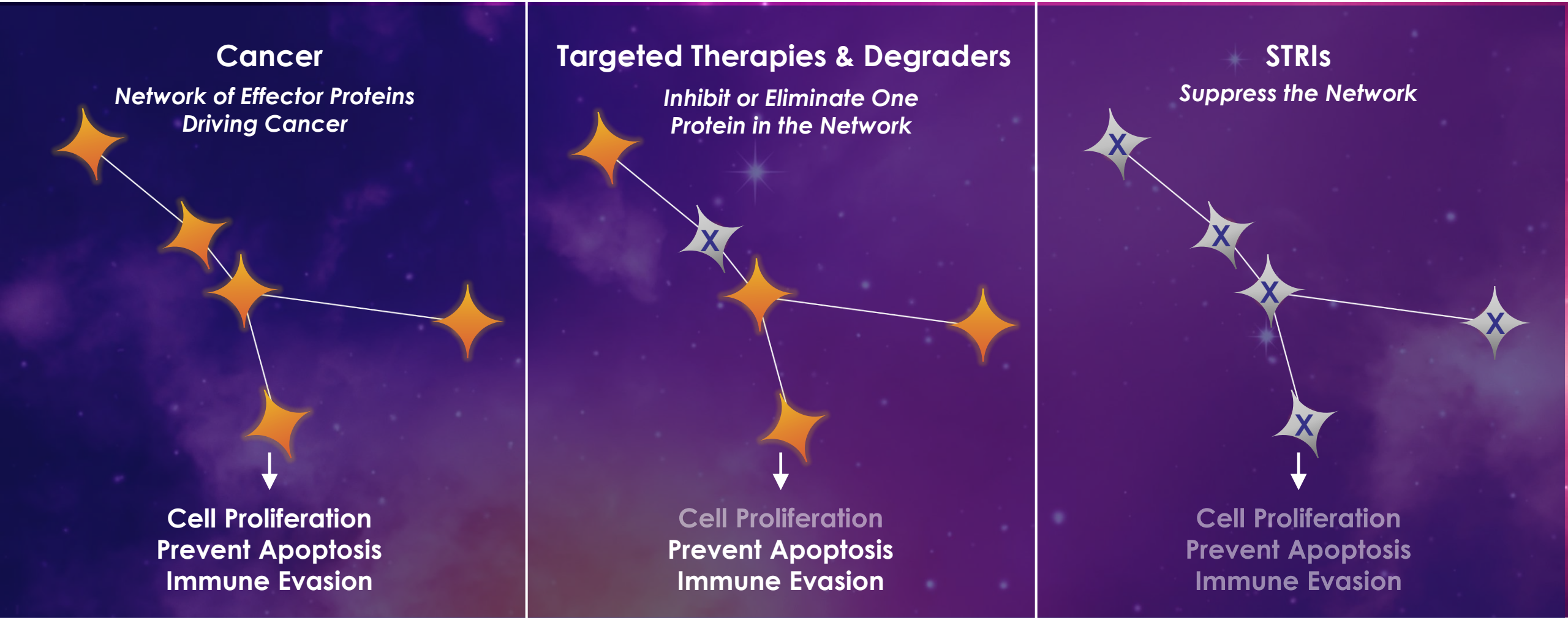
Co-Founder, eFFECTOR Therapeutics

Professor, Department of Cellular and Molecular Pharmacology, University of California San Francisco

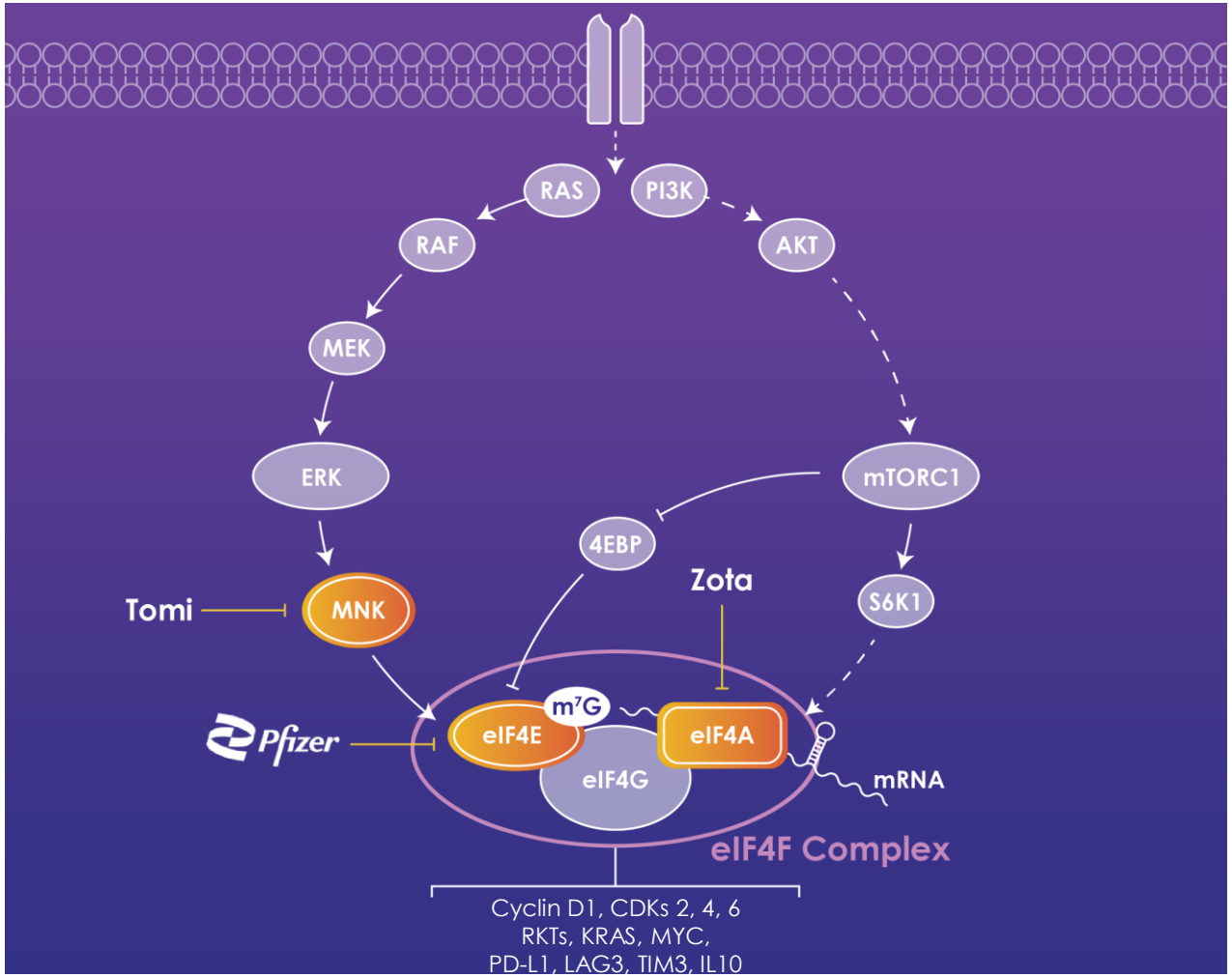
Howard Hughes Medical Investigator


A Network of
Cancer Drivers in a Universe
of Protein Synthesis

STRIs Can Suppress a Network of Cancer Driving Effector Proteins While Acting at a Single Target



STRI Platform: Targeting key node in cancer

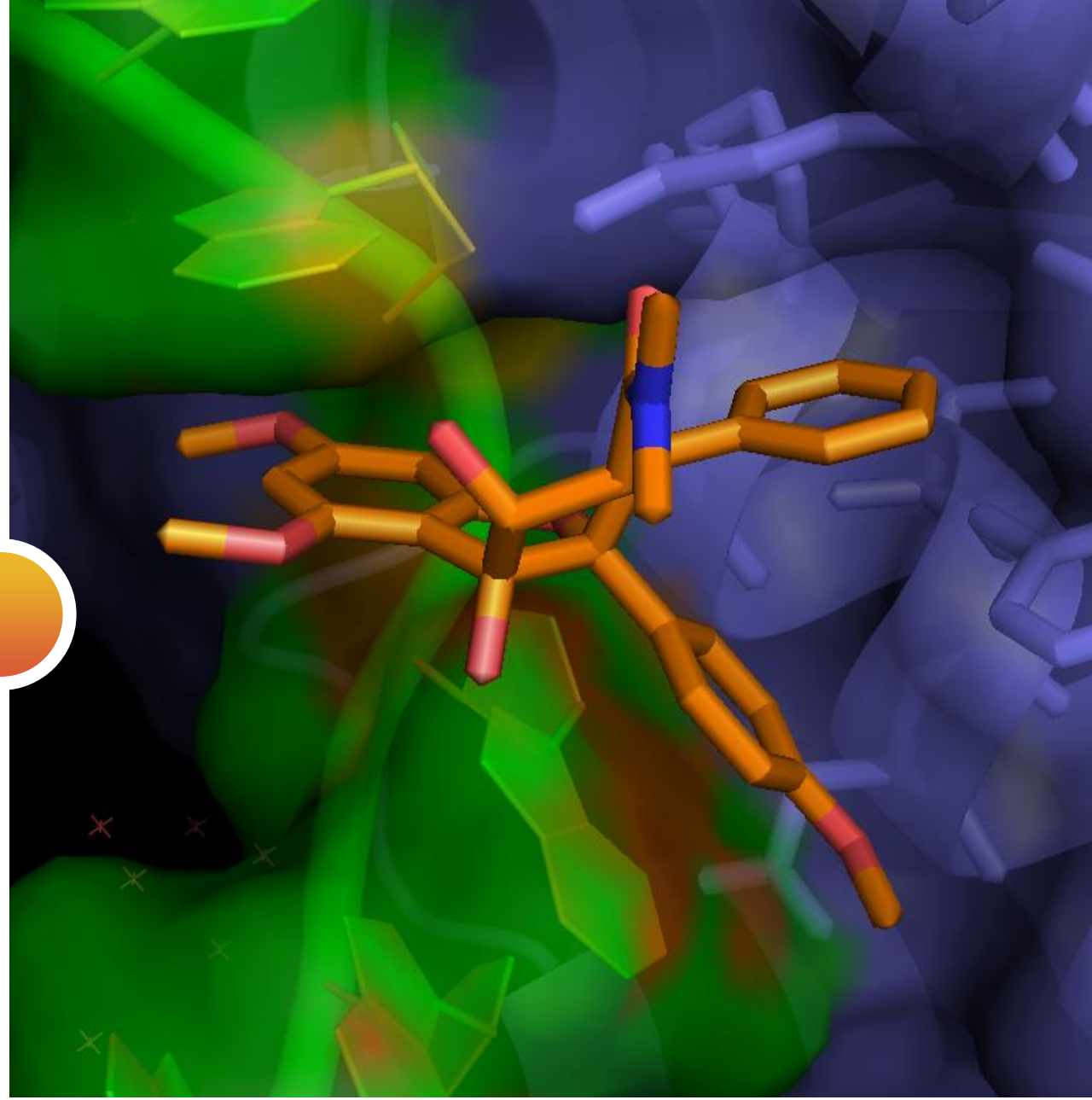


- Novel targets located at key node where two important cancer pathways converge and drive production of multiple disease-driving proteins
- Multiple potential advantages of inhibiting targets related to the eIF4F complex
  - ✓ Simultaneously decrease production of multiple cancer-driving proteins before they are synthesized
  - ✓ Strong combination potential due to down-regulation of key proteins that confer resistance to other single oncoprotein-targeted drugs
- eFFECTOR scientists invented three novel product candidates with strong intellectual property

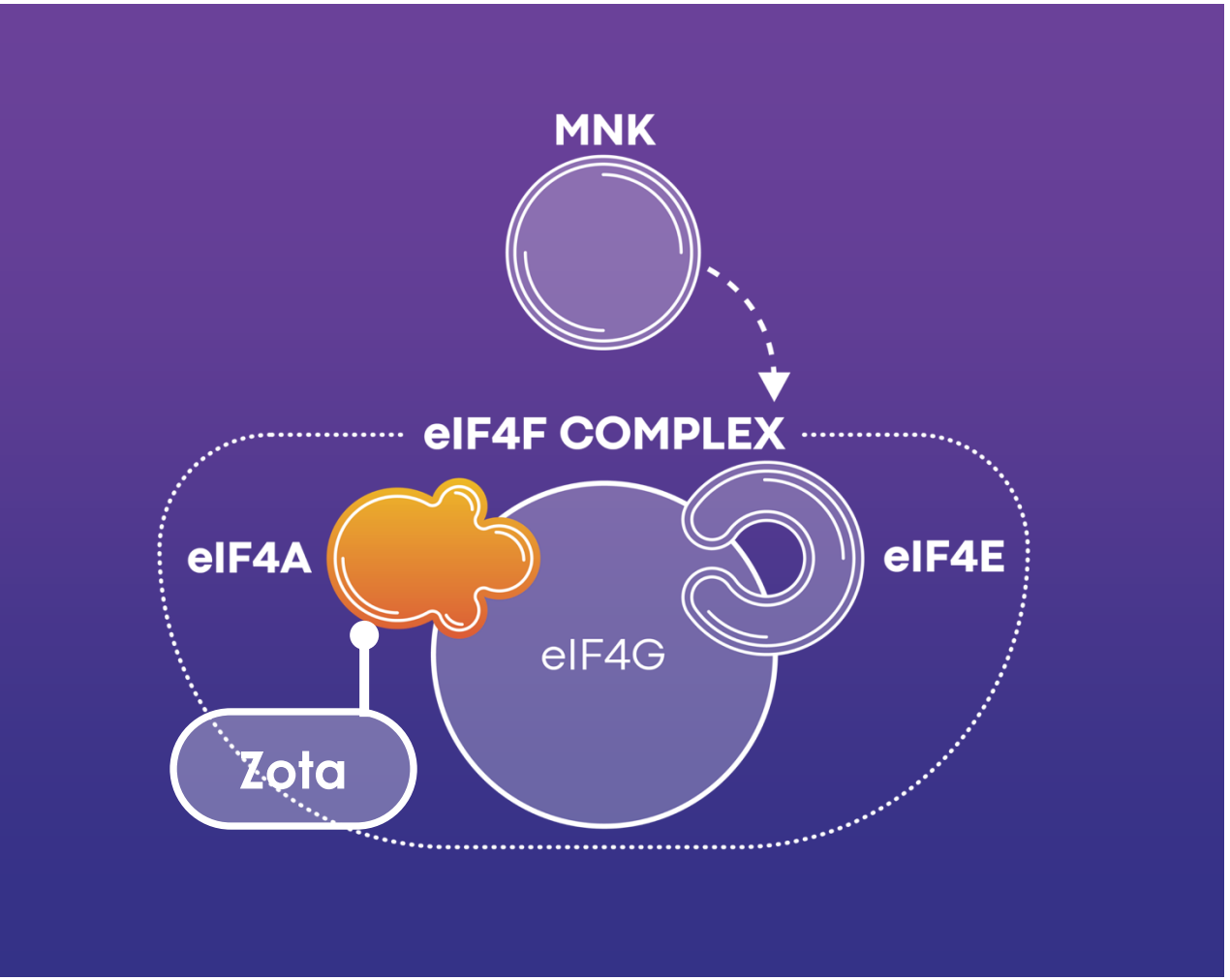
Zotatifin

Steve Worland. Ph.D.

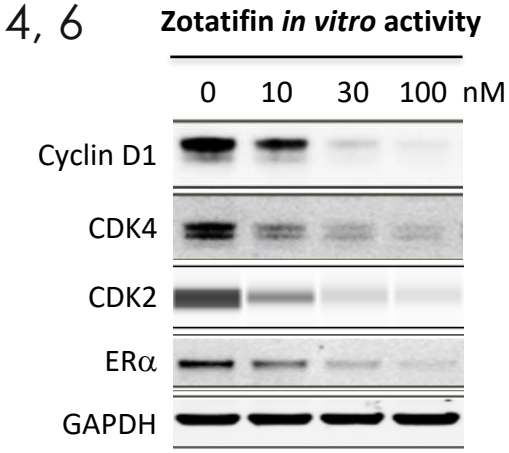
CEO, eFFECTOR Therapeutics



Zotatifin Designed to Inhibit Production of Key Proteins Driven by Upstream Oncogenes

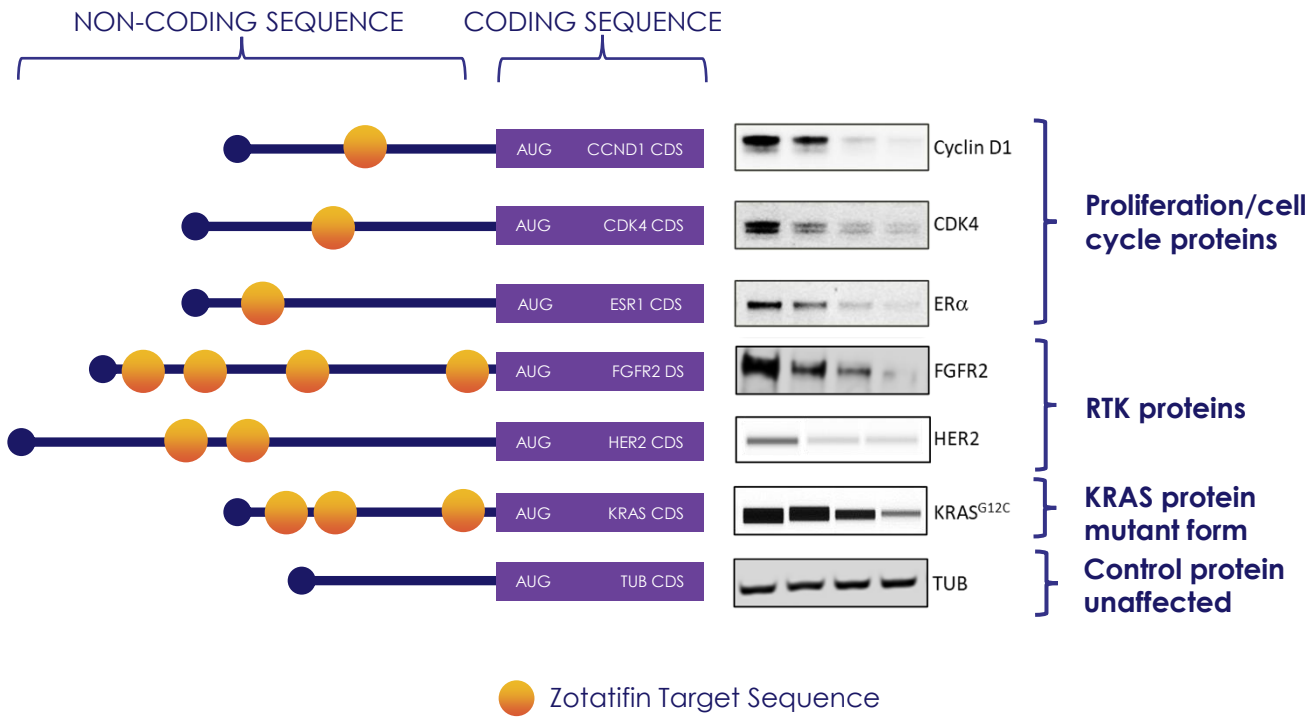


- Cancer signaling activates eIF4A to upregulate a network of tumor promoting proteins
- Zotatifin designed to suppress this network in a single product
- In preclinical studies, zotatifin was observed to downregulate cell-cycle proteins and oncoproteins including:
  - Cyclin D1 and CDKs 2, 4, 6
  - Estrogen receptor (ER)
  - RTKs and KRAS



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

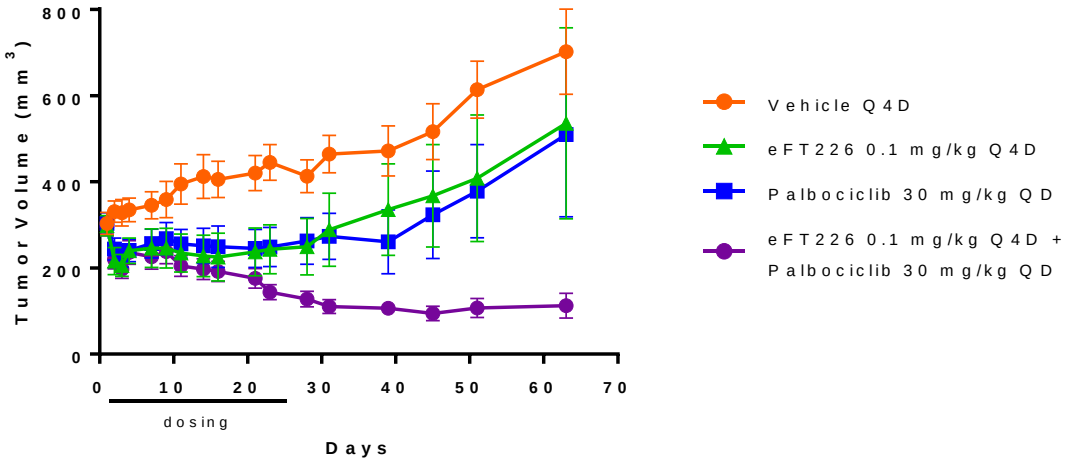
Zotatifin selectively bound specific sequences found in the 5' UTR of mRNAs of certain cancer-driving proteins



Zotatifin Demonstrated Single Agent and Combo Activity in Preclinical Studies

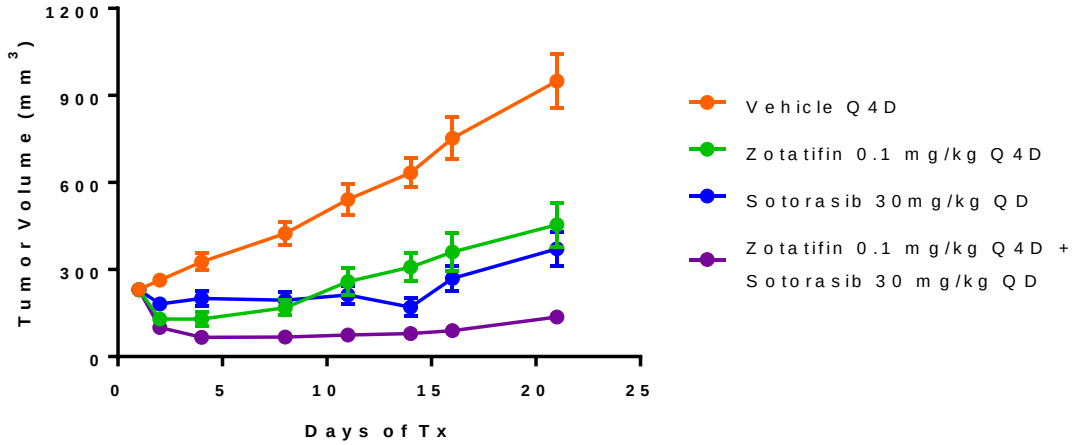
ER+ Breast Cancer Model

- Zotatifin demonstrated comparable single agent activity to palbociclib, marketed inhibitor of CDK4/6
- Strong combination activity observed with palbociclib



KRAS G12C NSCLC Model

- Zotatifin demonstrated comparable single agent activity to sotorasib, marketed inhibitor of KRAS G12C
- Strong combination activity observed with sotorasib



Overview of Results Presented at ASCO 2022

- **Demonstrated new pharmacodynamic mechanism of oncoprotein network suppression**
  - Highly selective with <1% deviation in overall protein levels
- **Was generally well-tolerated despite suppressing a network of cancer drivers**
  - Of 25 patients treated at RP2D:
    - No zotatifin-related G3/4/5 TEAEs
    - Only 2 patients with dose interruptions or reductions due to TEAEs
    - No patients discontinued zotatifin due to TEAEs
- **Early signals of clinical activity with focus on ER+ breast cancer**
  - Two PRs, including one not yet confirmed
  - Long SD in two ER+/FGFR1amp patients who had progressed on prior therapies

Interim Phase 1/2 Clinical Data

Funda Meric-Bernstam, M.D.

Chair, Department of Investigational Cancer Therapeutics and Nellie B. Connally Chair in Breast Cancer

University of Texas MD Anderson Cancer Center

Zotatifin Phase 1/2 Dose Escalation and Expansion Trial

Part 1 Dose Escalation

- Open label 3+3 dose escalation study
- Weekly IV zotatifin in 21 day cycle, switched to 2 weeks on/1 week off during dose escalation
- **Primary objectives**
  - Safety and tolerability as monotherapy
  - Maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D)
  - Evaluate PK
- **Secondary Objectives**
  - Preliminary antitumor activity of zotatifin as monotherapy
- **Exploratory objectives:**
  - Explore pharmacodynamic markers relating to drug mechanism
  - To explore additional biomarkers to further elucidate MOA, predict response to therapy, and understand potential resistance mechanisms

Part 2 Expansion

- Simon 2-stage design (Stage 1, N=7; Stage 2 N=7 or 11)
- **Primary objectives:**
  - Preliminary anti-tumor activity of zotatifin as monotherapy and as combination therapy
  - MTD or RP2D of zotatifin as combination therapy
- **Secondary objectives:**
  - Safety of zotatifin as monotherapy and as combination therapy
  - Progression free survival (PFS)
  - Evaluate PK profile of zotatifin in combination therapy

Expansion Cohorts

Tumors with mutational changes that may make them sensitive to zotatifin

EMBF ER+ BC, FGFR amp zotatifin monotherapy	Post-endocrine therapy No limit to prior lines
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
ECNS NSCLC, KRAS G12C zotatifin + sotorasib	Post-chemo/IO therapy No prior KRAS-targeted therapy

Patient Demographics & Baseline Characteristics

Characteristic		Part 1 (N=37)	Part 2 (N=17)
Age, median (range), years		62 (36-80)	55 (37-81)
Gender	Male	18	0
	Female	19	17
Race	White	30	13
	Black or African descent	1	4
	Asian	2	0
	Other	4	
Median number of prior metastatic therapies (range)		3 (0-9)	4 (1-11)
Primary diagnosis/cancer type, n (%)	Colorectal	11 (29.7)	
	Pancreatic	6 (16.2)	
	NSCLC	6 (16.2)	1 (5.9)
	Breast	4 (10.8)	16 (94.1)
	Cholangiocarcinoma	2 (5.4)	
	Melanoma	2 (5.4)	
	Other (1 patient/tumor type*)	6 (16.2)	

**appendiceal, ovarian, sarcoma, small bowel, testicular, unknown*

Safety Summary

zotatifin, mg/kg									
	Part 1, N (%)								Part 2, N (%)
Category	0.005[a] (N=3)	0.01[a] (N=3)	0.02[a] (N=3)	0.035[a] (N=7)	0.035[b] (N=3)	0.05[b] (N=3)	0.07[b] (N=8)	0.1[b] (N=7)	0.07[b] (N=17)
Subjects with TEAEs	3 (100)	3 (100)	2 (66.7)	7 (100)	3 (100)	3 (100)	8 (100)	7 (100)	15 (88.1)
Subjects with TEAEs related to zotatifin[c]	1 (33.3)	3 (100)	2 (66.7)	7 (100)	2 (66.7)	2 (66.7)	7 (87.5)	6 (85.7)	9 (52.9)
Subjects with DLTs	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (28.6)	1 (5.9)
Subjects with TESAEs	1 (33.3)	0 (0.0)	0 (0.0)	3 (42.9)	0 (0.0)	0 (0.0)	1 (12.5)	3 (42.9)	3 (17.6)
Subjects with TESAEs related to zotatifin[c]	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (28.6)	0 (0.0)
Subjects with CTCAE Gr 3/4 TEAEs	2 (66.7)	0 (0.0)	0 (0.0)	5 (71.4)	0 (0.0)	1 (33.3)	2 (25.0)	2 (28.6)	4 (23.5)
Subjects with CTCAE Gr 5 TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with CTCAE Gr 3/4 TEAEs related to zotatifin[c]	0 (0.0)	0 (0.0)	0 (0.0)	5 (71.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (28.6)	0 (0.0)
Subjects with CTCAE Gr 5 TEAEs related to zotatifin[1]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with TEAEs leading to dose interruption or reduction of zotatifin	1 (33.3)	0 (0.0)	0 (0.0)	4 (57.1)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (5.9)
Subjects with TEAEs leading to discontinuation of zotatifin	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)

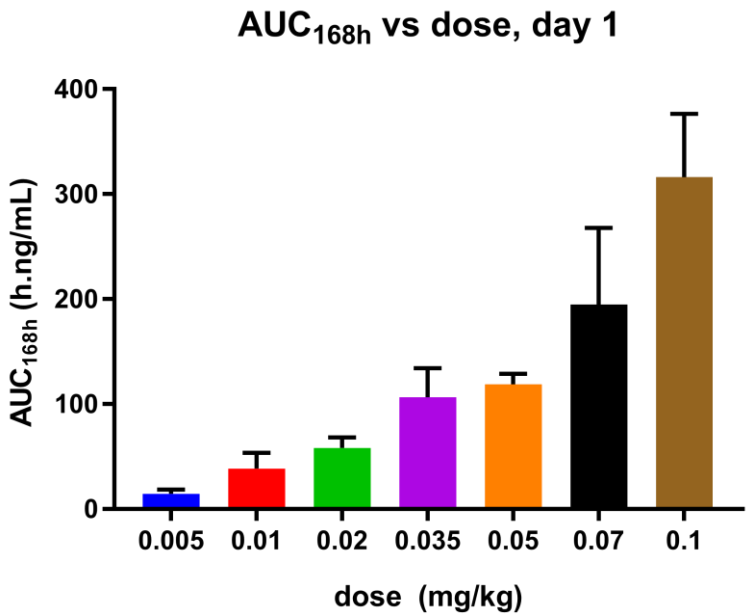
[a] Dosed on days 1, 8, and 15 of a 21 day cycle;
[b] Dosed on days 1 and 8 of a 21 day cycle;
[c] As assessed by the Investigator as possibly related.

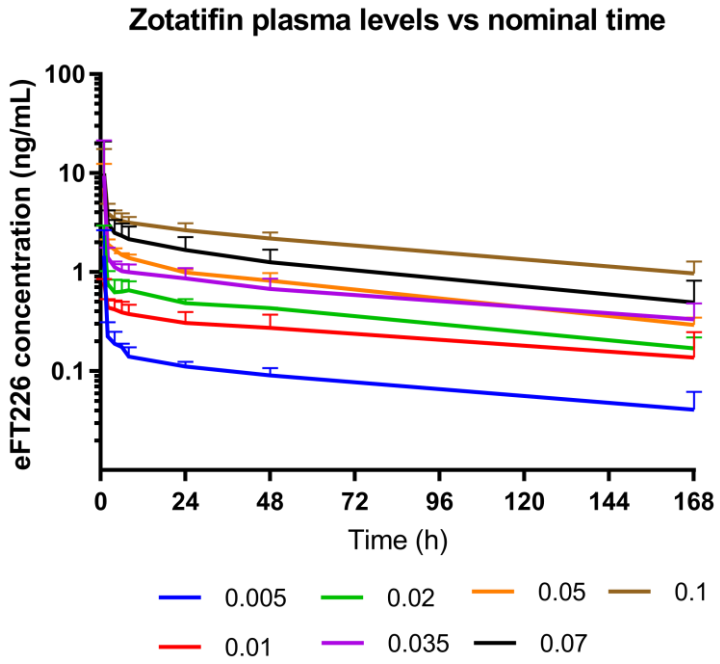
Zotatifin was Generally Well Tolerated at RP2D with No Zotatifin-Related Grade 3/4/5 TEAEs

zotatifin, mg/kg										
		Part 1, N (%)								Part 2, N (%)
MedDRA term	Grade	0.005[a] (N=3)	0.01[a] (N=3)	0.02[a] (N=3)	0.035[a] (N=7)	0.035[b] (N=3)	0.05[b] (N=3)	0.07[b] (N=8)	0.1[b] (N=7)	0.07[b] (N=17)
Fatigue	1-2	1 (33.3)	1 (33.3)	0 (0.0)	4 (57.1)	1 (33.3)	1 (33.3)	1 (12.5)	2 (28.6)	1 (5.9)
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	1-2	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (14.3)	3 (17.6)
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	3 (42.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)
Diarrhea	1-2	1 (33.3)	0 (0.0)	2 (66.7)	1 (14.3)	0 (0.0)	0 (0.0)	3 (37.5)	0 (0.0)	3 17.6)
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	1-2	0 (0.0)	1 (33.3)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	2 (25.0)	2 (28.6)	3 (17.6)
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1-2	0 (0.0)	1 (33.3)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (14.3)	2 (11.7)
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Dosed on days 1, 8, and 15 of a 21 day cycle;
[b] Dosed on days 1 and 8 of a 21 day cycle

Pharmacokinetics Support Intermittent Dosing





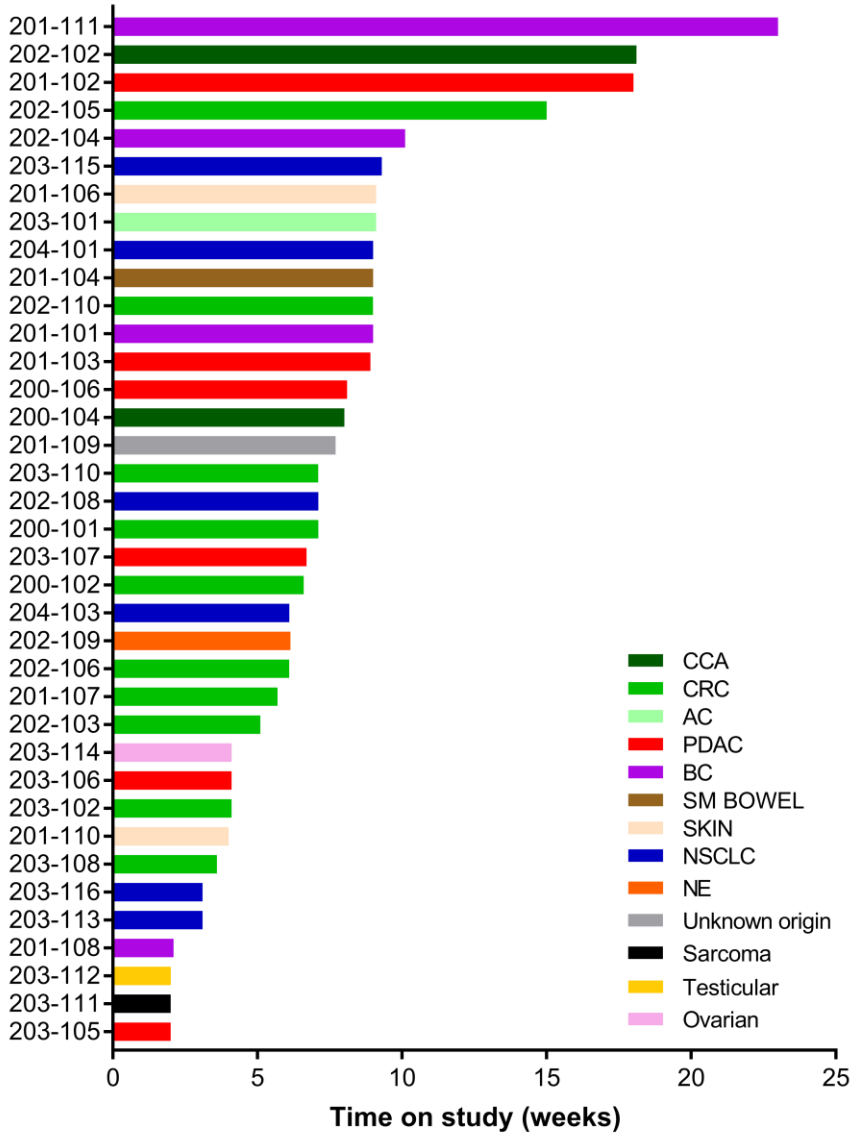
- Dose proportional exposure
- T ½ = 97 hr
- Accumulation Ratio (Day 8/Day 1) = 1.4

Part 1 Analysis in Mixed Population

- Typical Phase 1 patient population
  - Predominantly GI tumors
  - Median 3 prior lines of therapy for metastatic disease

Tumor Types				
GI	**NSCLC**	**Breast**	**Melanoma**	**Other**
19	6	4	2	6

- Patient 201-111 with ER^{+}/FGFR1^{amp} experienced stable disease for 23 weeks
  - Three prior lines of treatment for metastatic disease: goserelin; palbociclib+anastrazole; fulvestrant

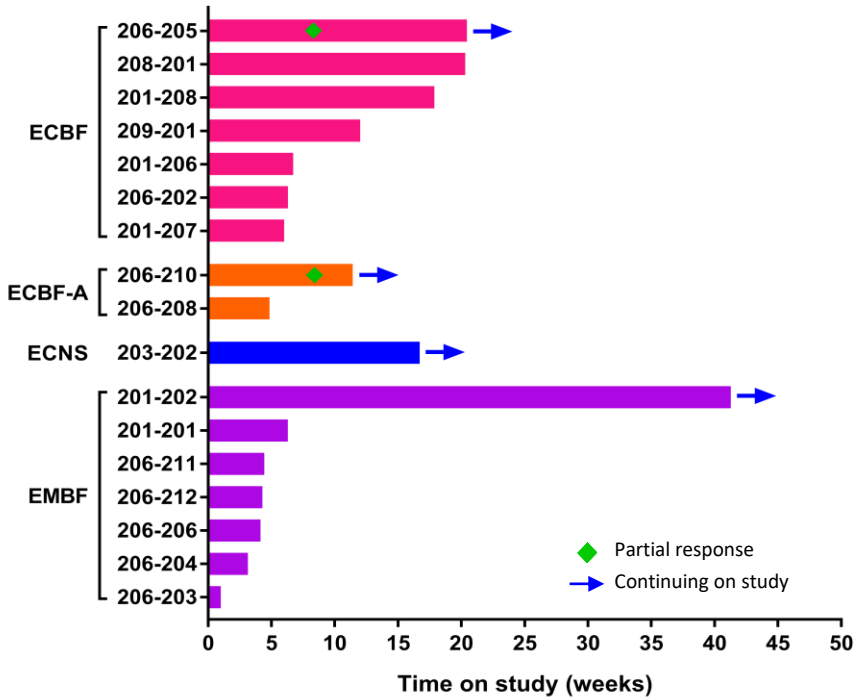


Zotatifin Generally Well Tolerated in First-in-Human Study

Key Findings in Part 1

- Target drug exposures were achieved
- 0.07 mg/kg dosed 2 weeks on/1 week off selected as RP2D
- Generally well tolerated at RP2D
  - AEs were mostly mild or moderate
- Above MTD, 2 of 7 patients had DLTs
  - G3 Anemia
  - G3 GI bleeding

Part 2 Interim Efficacy Analysis: Two* Partial Responses Observed in Combination with Fulvestrant in Breast Cancer Patients



*One PR awaiting confirmatory scan

	Part 2, Best Overall Response, N (%)			
zotatifin 0.07 mg/kg[a] (N)	CR/PR	SD	PD	Not evaluable
ECBF (N=7)	1 (14.3)	3 (42.9)	3 (42.9)	0 (0.0)
ECBF+ A (N=2)	1 (50.0)[b]	0 (0.0)	1 (50.0)	0 (0.0)
ECNS (N=1)	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)
EMBF (N=7)	0 (0.0)	1 (14.3)	3 (42.9)	3 (42.9)

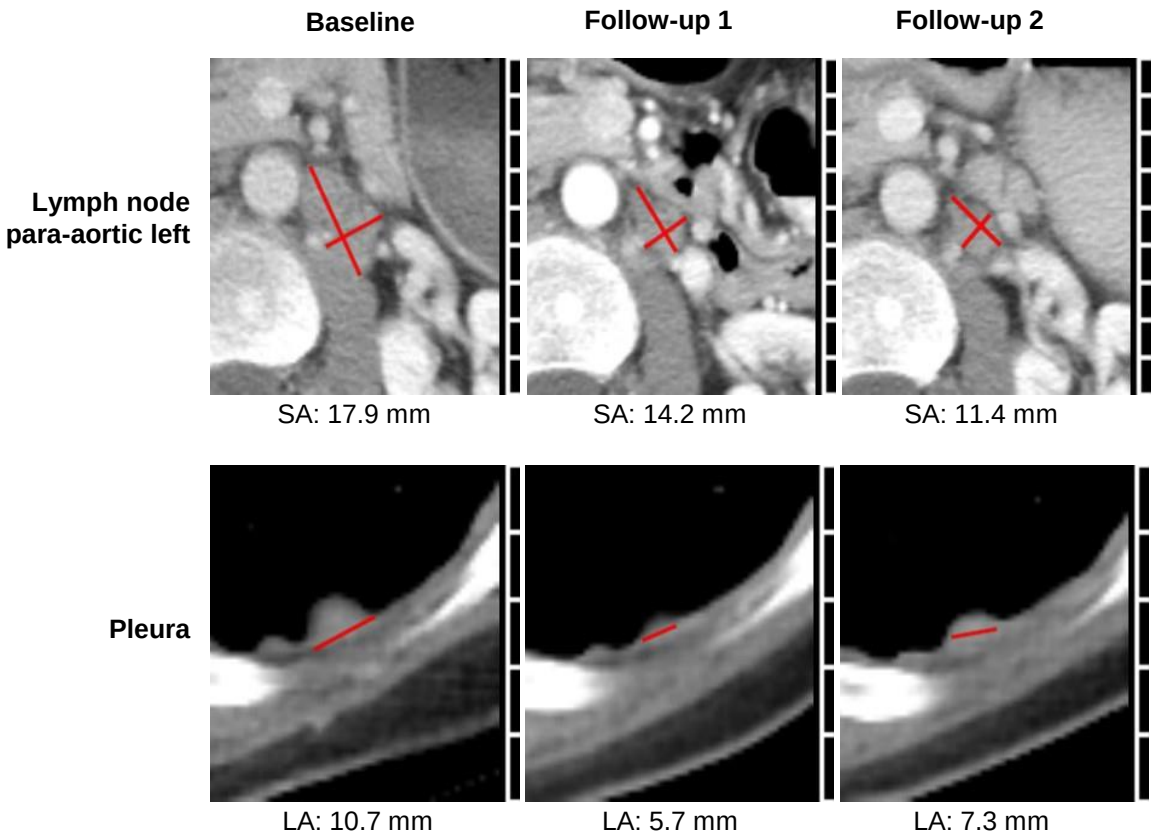
[a] *Dosed on days 1 and 8 of a 21 day cycle;* [b] *Awaiting confirmatory scan*
Reflects data through 5/02/2022

ECBF: Expansion, Combination, Breast, Fulvestrant
ECBF+ A: Expansion, Combination, Breast, Fulvestrant + Abemaciclib

ECNS: Expansion, Combination, NSCLC, Sotorasib
EMBF: Expansion, Monotherapy, Breast, FGFR

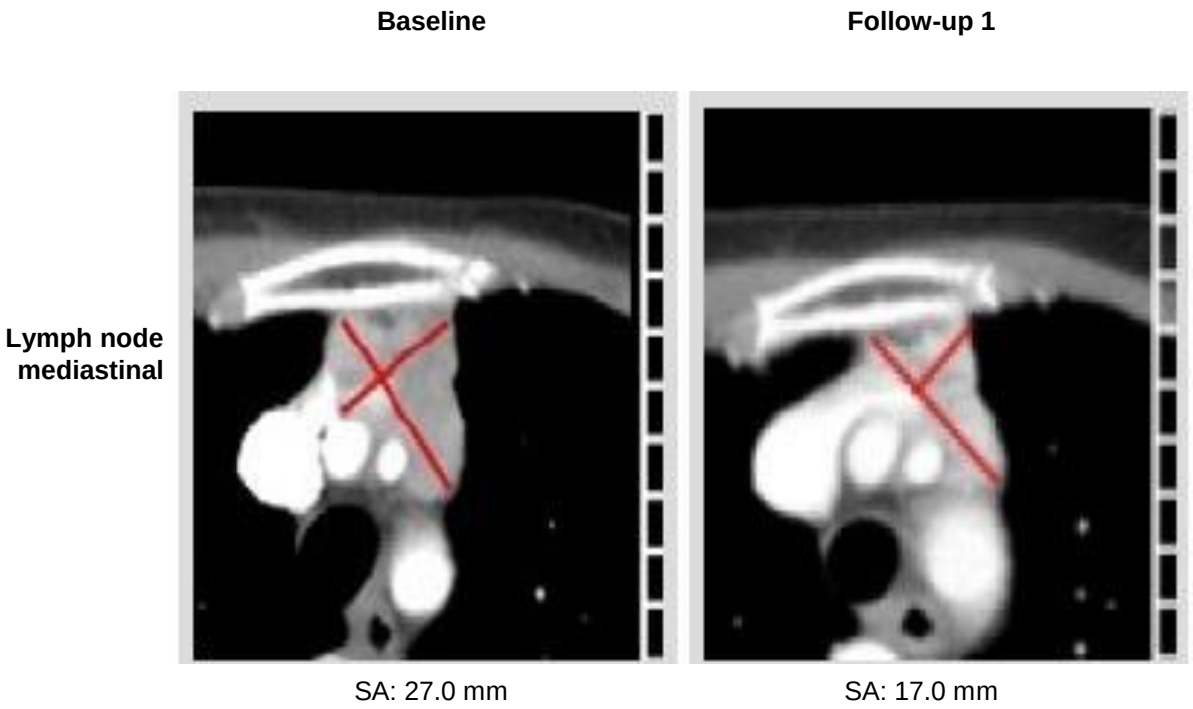
Case Study 1: ECBF Breast Cancer Patient with Confirmed PR

- Confirmed PR achieved with zotatifin in combination with fulvestrant
- Patient has amplified Cyclin D1 and ESR1 L536H mutation
- **Failed 7 lines of prior treatment** for metastatic disease
  - Endocrine therapy monotherapy
  - Endocrine therapy + multiple CDK4/6 inhibitors
  - Fulvestrant + everolimus
  - Three chemotherapies



Case Study 2: ECBF+A Breast Cancer Patient
PR Awaiting Confirmation

- Unconfirmed PR achieved with zotatifin in combination with fulvestrant and abemaciclib in first post-treatment scan
  - Awaiting confirmatory scan as of cutoff date
- Patient has PIK3CA Q546H and N1044K mutations
- **Failed 3 lines of prior treatment** for metastatic disease
  - Endocrine therapy + CDK4/6 inhibitor
  - Fulvestrant + alpelisib
  - Chemotherapy



Pharmacodynamics & Clinical Plans

Robert Sikorski, M.D., Ph.D.

Senior Clinical Development Advisor, eFFECTOR Therapeutics

Managing Director, Woodside Way Ventures

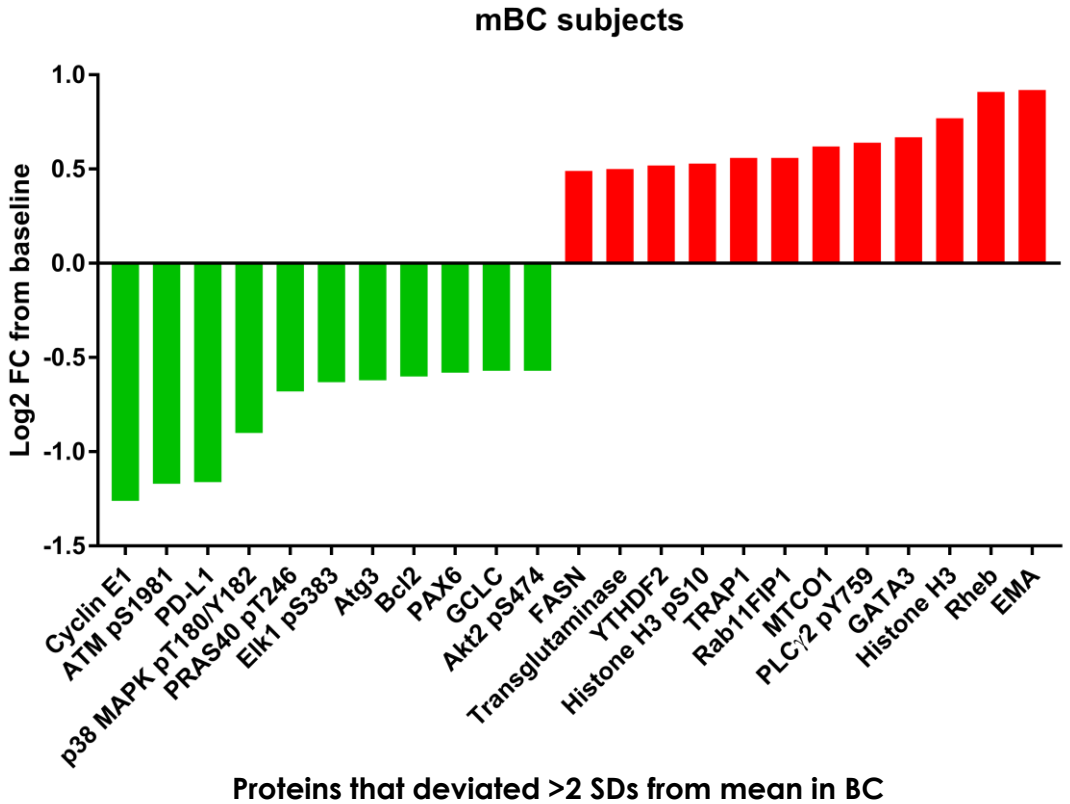
Modulation of Translation was Highly Selective with Less than 1% of Protein Expression Altered

Reverse Phase Protein Array Analysis of Pre- and On-Treatment Paired Biopsies

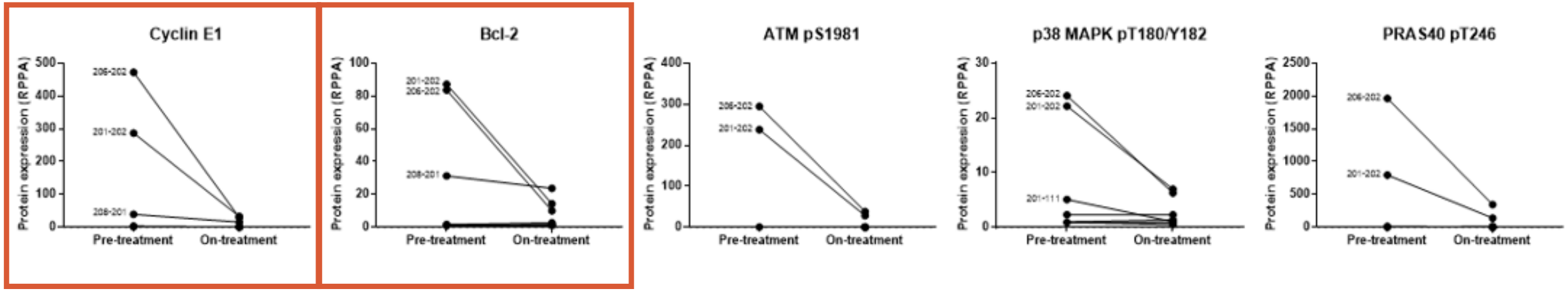
Less than 1% deviation in overall protein levels

Suppression of Cyclin E, Bcl2 and kinase signaling pathway phosphorylation

Average fold-change between pre- and on-treatment N=10 total, including 7 mBC		
	Proteins (~389)	**Phospho-protein markers (~95)**
10 subjects	0.99	0.95
7 mBC subjects	0.99	0.91



Reductions in Key Oncogenic Drivers Cyclin E1 and Bcl-2 Were Most Dramatic in Patients with Highest Pre-Treatment Levels



Trial Expansions Build on the Demonstrated PD Mechanism and Tolerability Profile of Zotatifin To Date

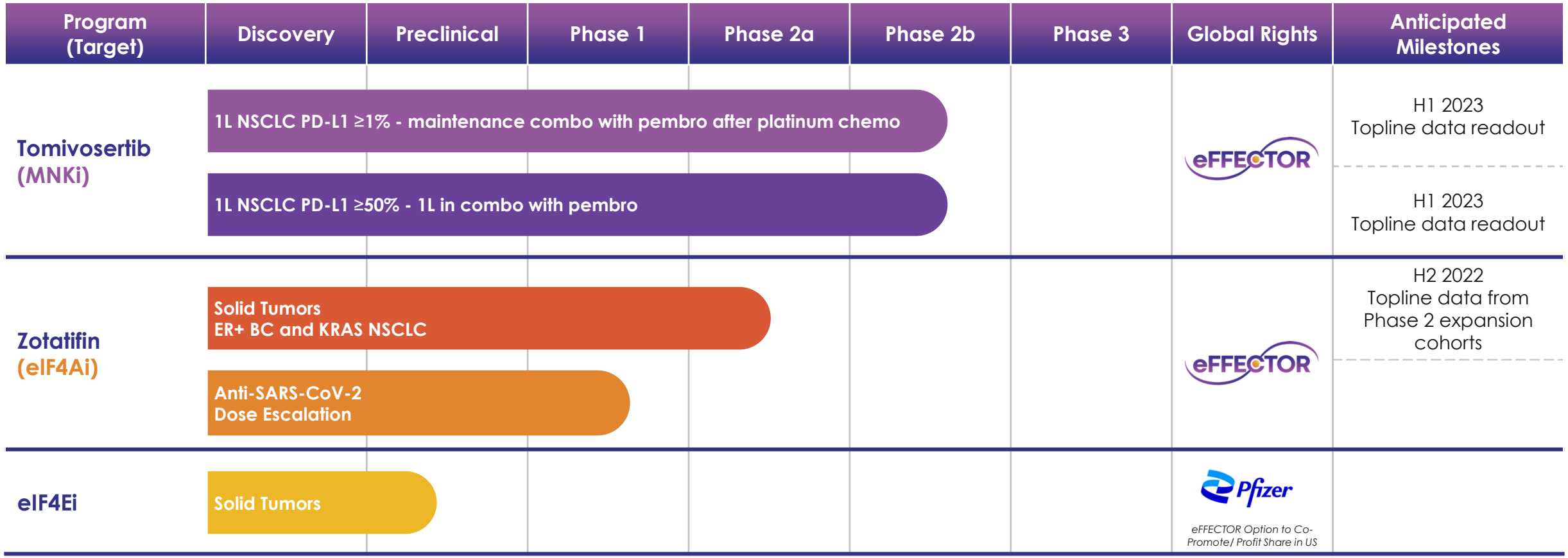
- **Clinical results showing general tolerability and signals of clinical activity support the development of a new potential class of medicines**
  - Patient in ECBF cohort with confirmed PR had Cyclin D1 amplification
  - Cyclin D1 one of the most consistently down-regulated proteins in preclinical models
- **Cohort ECBF has been expanded to 18 patients**
  - Combination with fulvestrant in patients whose disease has progressed on endocrine therapy and a cdk4/6 inhibitor
- **Adding new cohort in ER+ breast cancer in patients with Cyclin D1 amplification**
  - Combination with fulvestrant in patients whose disease has progressed on endocrine therapy and a cdk4/6 inhibitor
  - Cyclin D1 amplified in ~20% of ER+ breast cancer
  - Dataset in defined population that could support a path to registration

Future Outlook

Steve Worland, Ph.D.

CEO, eFFECTOR Therapeutics

Robust Pipeline: Multiple STRIs in Development



*Led by McGill University; funded by Stand Up to Cancer (SU2C) grant

Multiple Upcoming Clinical Milestones

	Anticipated Milestones	2022		2023		2024
		1H	2H	1H	2H	
Tomivosertib	Top line data from P2b NSCLC frontline with pembro			●		
	Top line data from P2b NSCLC frontline maintenance post platinum chemotherapy with pembro			●		
	Initiate P3 in NSCLC					●
Zotatifin	Initial ORR data from P2a expansion cohorts	✓				
	Top line data from P2a expansion cohorts		●			
	Initial ORR data from ER+ amplified Cyclin D1 cohort			●		
	Initiate potentially registrational P2b study				●	

Q&A