Investor Event

R&D / Science Day

January 24, 2024

eFFECTOR

Disclaimer

FORWARD-LOOKING STATEMENTS

This presentation contains forward-looking statements. All statements other than statements of historical facts contained in this presentation, including statements regarding the future clinical development of eFFECTOR Therapeutics, Inc.'s (eFFECTOR or the Company) product candidates, including expectations on enrollment and the timing of reporting data from ongoing clinical trials and initiating future clinical trials and the potential therapeutic benefits of tomivosertib and zotatifin, including based on its mechanism of action are forward-looking statements. In some cases, you can identify forward-looking statements by such terms as "may", "believe", "anticipate", "could", "should", "estimate", "expect", "intend", "plan", "project", "will", "forecast" and similar terms. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, but not limited to the risk that interim results of a clinical trial are not necessarily indicative of final results and one or more of the clinical outcomes may materially change as patient enrollment continues, following more comprehensive reviews of the data and as more patient data becomes available, including the risk that unconfirmed responses may not ultimately result in confirmed responses to treatment after follow-up evaluations; potential delays in the commencement, enrollment and completion of clinical trials; our dependence on third parties in connection with product manufacturing, research and preclinical and clinical testing; the results of preclinical studies and early clinical trials are not necessarily predictive of future results; the success of our clinical trials and preclinical studies for our product candidates is uncertain; we may use our capital resources sooner than expected and they may be insufficient to allow clinical trial readouts; regulatory developments in the United States and foreign countries; unexpected adverse side effects or inadequate efficacy of our product candidates that may limit their development, regulatory approval and/or commercialization, or may result in recalls or product liability claims; our ability to obtain and maintain intellectual property protection for our product candidates; our failure to meeting the continued listing requirements of the Nasdaq Capital Market could result in a delisting of our securities; and other risks described in the Company's prior press releases and filings with the Securities and Exchange Commission (SEC), including under the heading "Risk Factors" in the Company's annual report on Form 10-K and any subsequent filings with the SEC. Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond the Company's control, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in these forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements in this presentation, which speak only as of the date made. Except as required by applicable law, the Company does not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. All forward-looking statements are qualified in their entirety by this cautionary statement, which is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995.

MARKET AND INDUSTRY DATA

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

CLINICAL INVESTIGATION/FDA

This presentation concerns product candidates that are under clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). They are currently limited by Federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated.

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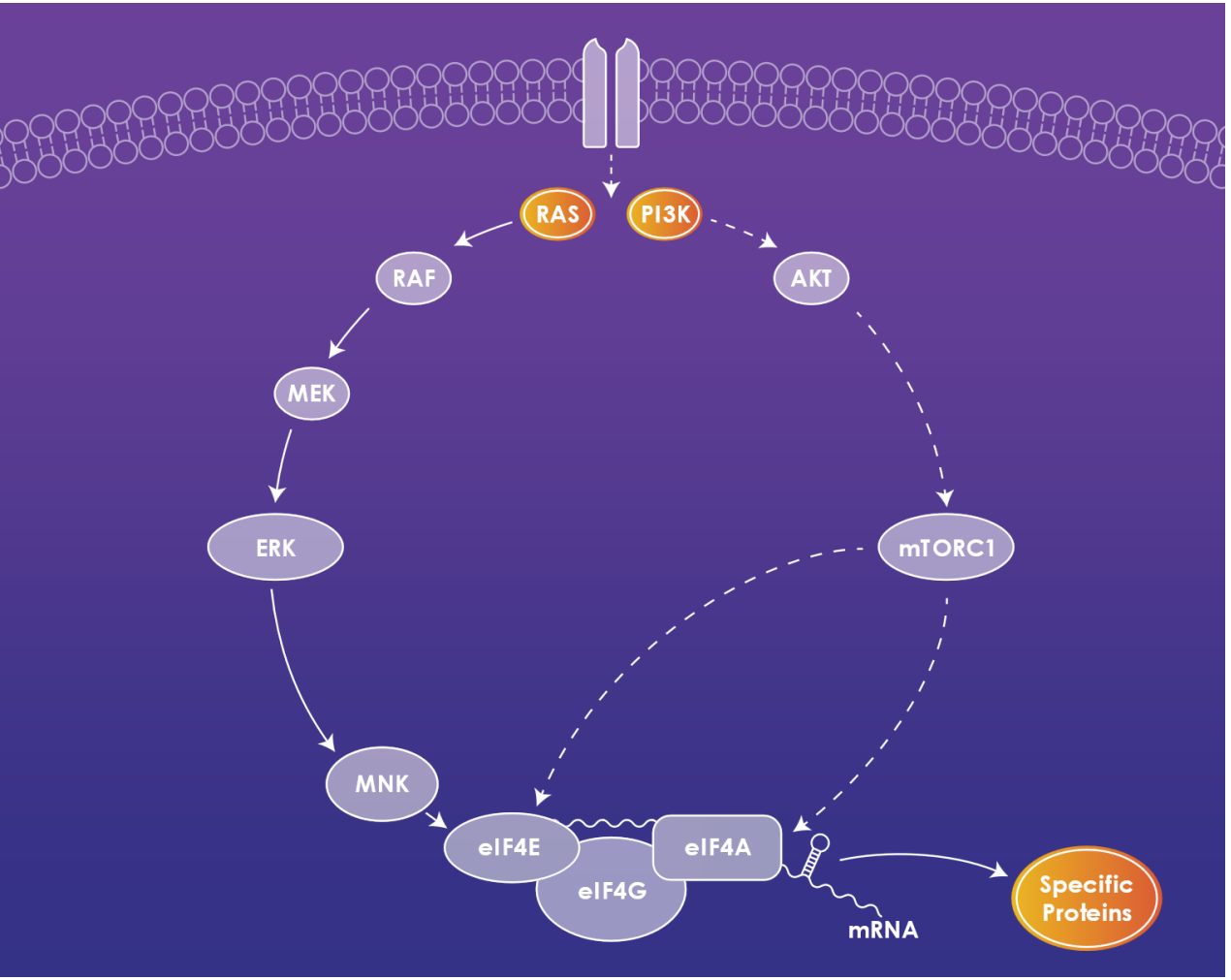
Agenda

	Company introduction	Steve Worland, Ph.D.
Tomivosertib	Unmet Need and SoC for 1st line PDL1+ NSCLC	Doug Warner, M.D.
	Non-Clinical Overview	Steve Worland, Ph.D.
	Clinical Overview & Next Steps	Doug Warner, M.D.
Zotatifin	Unmet Need and SoC for 2nd line ER+ BC	Kevin Kalinsky, M.D., M.S.
	Non-Clinical Overview	Steve Worland, Ph.D.
	Clinical Overview & Next Steps	Doug Warner, M.D.
	External Collaborations	Doug Warner, M.D.
	Closing Remarks	Steve Worland, Ph.D.
	Q&A	

Company Overview

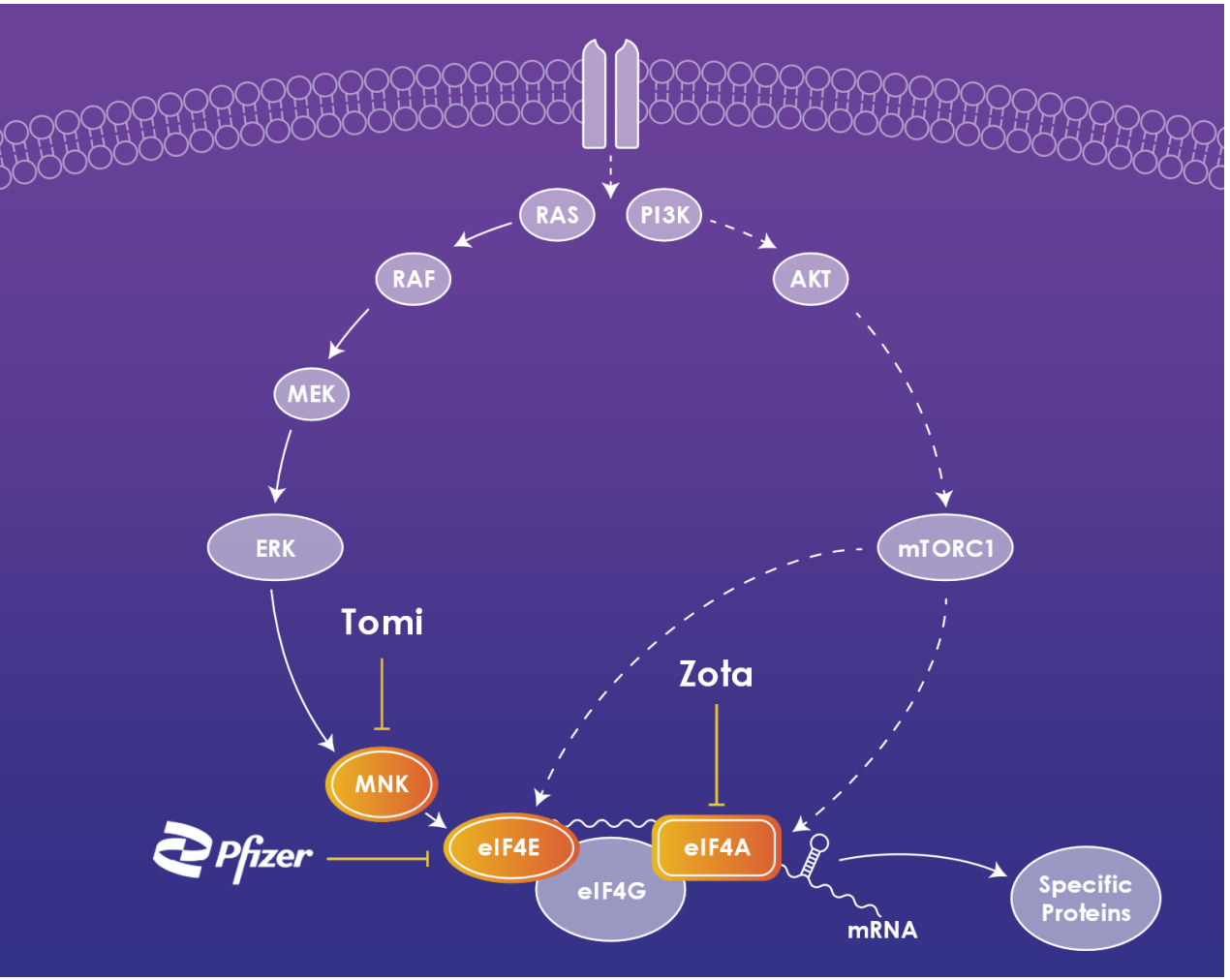
- Novel platform designed to **block upregulated production of specific oncoproteins** driven by oncogenic signaling
  - Next-generation targeted approach designed to broaden impact beyond addressing mutated oncogenes
  - Underlying technology licensed from UCSF, labs of Drs. Kevan Shokat and Davide Ruggero
  - Product candidates referred to as Selective Translation Regulator Inhibitors (STRIs)
- **Two wholly owned novel clinical assets**
  - Tomivosertib: MNK inhibitor in a **randomized P2b trial in NSCLC combined with pembrolizumab** with **top-line data anticipated Q1 2024**
  - Zotatifin: eIF4A inhibitor focused on **ER+ BC** with positive data presented in 2023 at ASCO and SABCS; **finalization of RP2D anticipated in 2024 to enable late development**
- Validating **partnership with Pfizer**
  - $507M partnership on third STRI product candidate targeting eIF4E
  - Retained option to co-promote and profit share in U.S.

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

Investment Highlights

- **Robust clinical pipeline with upcoming value inflection points**

Tomivosertib: Randomized Phase 2b in frontline non-small cell lung cancer (NSCLC) combined with pembrolizumab

- Topline results – Q1 2024
- Prior Phase 2a trial showed mPFS of 53 weeks in PD-L1 positive patients
- Additional clinical indications

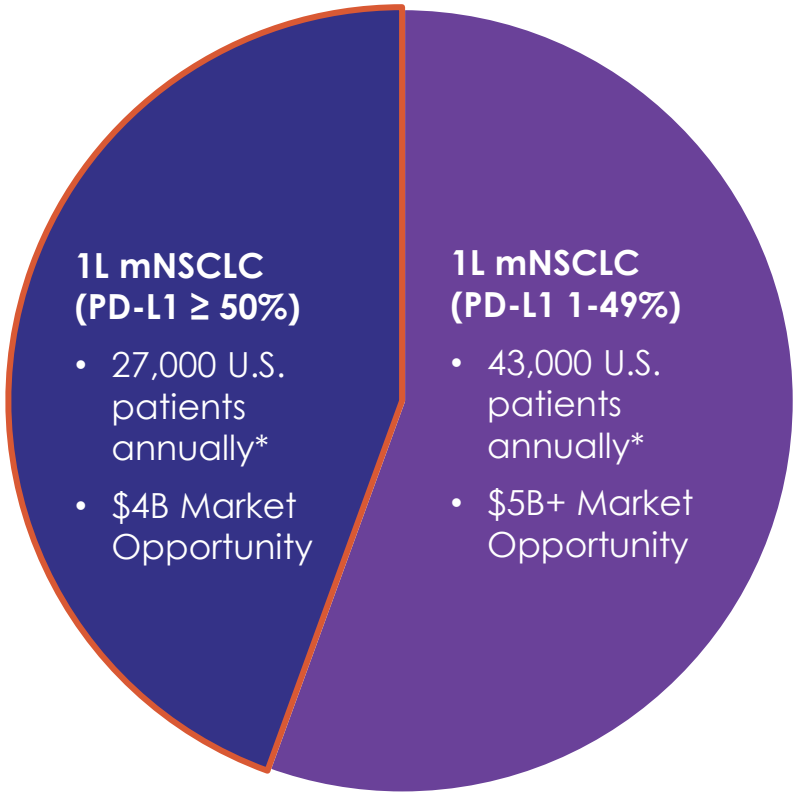
Zotatifin: Phase 2a expansion cohorts in ER^+ breast cancer and $KRAS^{mut}$ NSCLC

- Further data from dose escalation – H1 2024
- Positive Phase 2a data in ER+ BC presented in 2023 at ASCO and SABCS
  - 26% response rate and mPFS of 7.4 months as a triplet in heavily pretreated patients
- Additional clinical indications

- **Validating partnership with Pfizer**
  - $507M partnership on third STRI product candidate, with option to co-promote/profit share in U.S.
- **Q4 2023 ending cash of $18.4M expected to fund operations into Q3 2024**

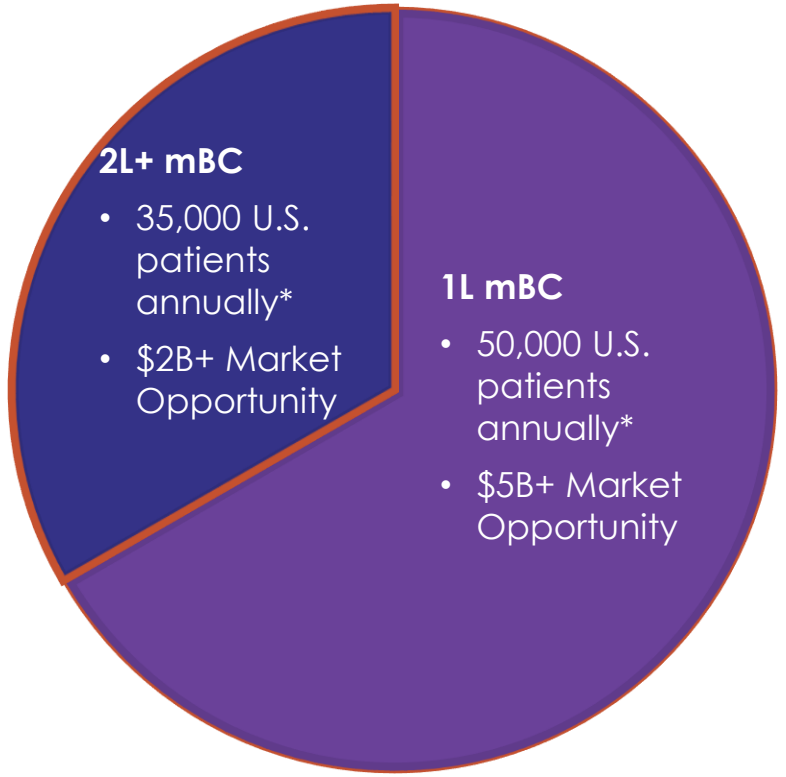
Potential Multi-Billion Dollar Indications in Two Tumor Types

Tomivosertib (NSCLC)



mNSCLC: Metastatic Non-Small Cell Lung Cancer

Zotatifin (ER+Breast Cancer)



mBC: Metastatic Breast Cancer

*Company estimates of sales potential based on analyst reports and annual sales of approved agents

Key: Lead indications

Robust Pipeline: Multiple STRIs in Development

Program (Target)	Discovery	Preclinical	Phase 1	Phase 2a	Phase 2b	Phase 3	Global Rights	Anticipated Milestones
Tomivosertib (MNKi)	1L NSCLC PD-L1 ≥50% - 1L in combo with pembro						eFFECTOR	Q1 2024 Topline data readout
Zotatifin (eIF4Ai)	Solid Tumors ER+ BC and KRAS NSCLC						eFFECTOR	H1 2024 Further data from dose escalation
External Collaborations								
eIF4Ei	Solid Tumors						Pfizer	$507M deal value with option to co-promote and profit share
Tomivosertib (MNKi)	Investigator-initiated trial at Northwestern in r/r AML						eFFECTOR	
Zotatifin (eIF4Ai)	Investigator-initiated trial at Stanford in ER+ HER2- breast cancer in pre-operative setting						eFFECTOR	

Experienced Leadership Team

Steve Worland, PhD
Founder, President, CEO and Director

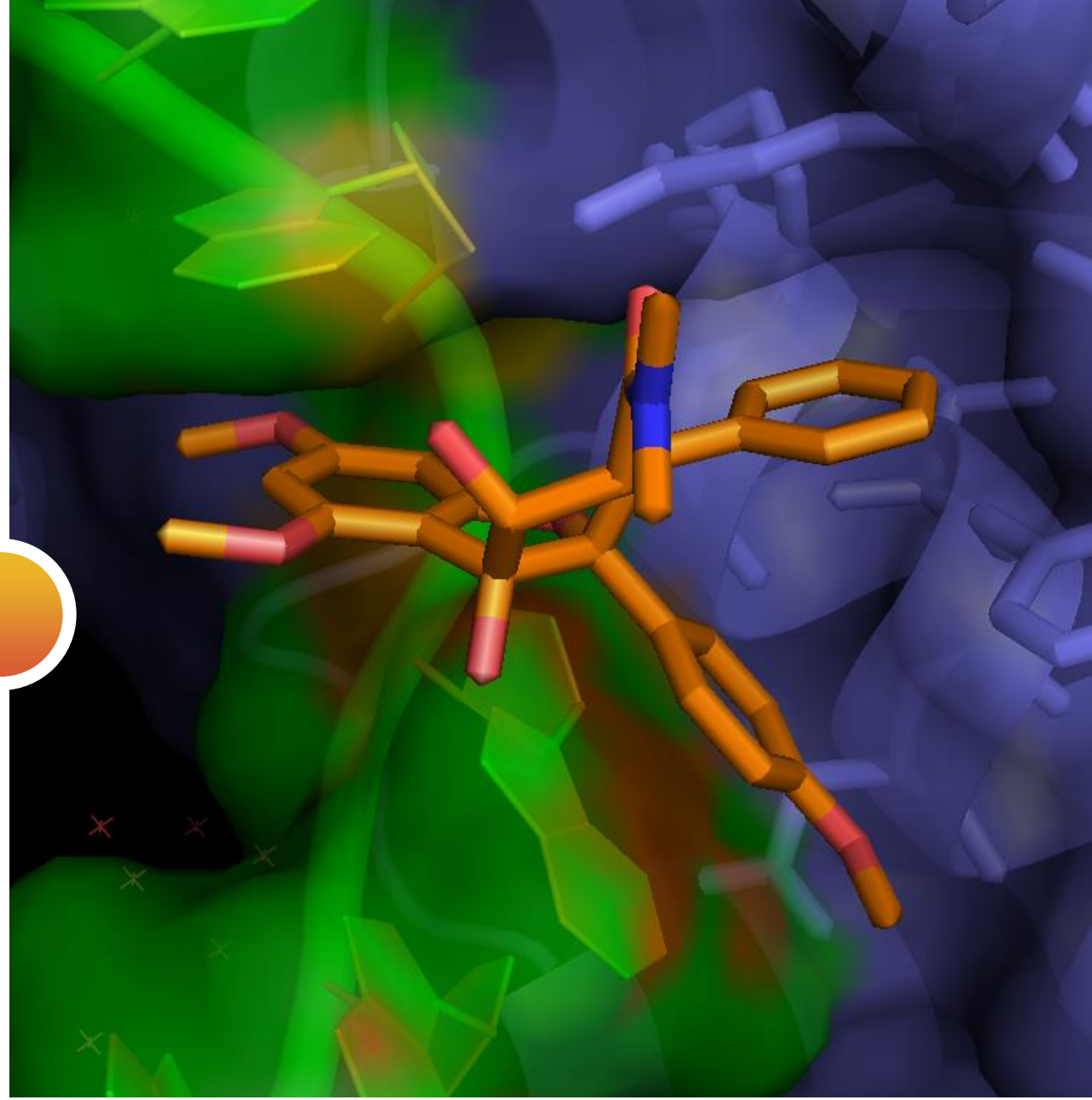
Doug Warner, MD, MBA
Chief Medical Officer

Mike Byrnes, MBA
Chief Financial Officer

Mayank Gandhi, MD
Chief Business Officer

Scientific Advisors	*Institution*	*Expertise*	*Clinical Advisors/ Key Investigators*	*Institution*	*Expertise*
Kevan Shokat, PhD	UCSF, EFTR Co-founder	Translation & KRAS	**Kapil Dhingra, MD**	Former Roche Oncology	Oncology Development
Davide Ruggero, PhD	UCSF, EFTR Co-founder	Translation	**Sarat Chandarlapaty, MD, PhD**	Memorial Sloan Kettering	Oncology Development
Jennifer Doudna, PhD	UC Berkeley	RNA, CRISPR Co-Inventor	**Funda Meric-Bernstam, MD**	MD Anderson	Oncology Development
Joan Brugge, PhD	Harvard	Oncogenic Signaling	**Ezra Rosen, MD, PhD**	Memorial Sloan Kettering	Oncology Development
Neal Rosen, MD, PhD	Memorial Sloan Kettering	Oncogenic Signaling	**Jennifer Caswell-Jin, MD**	Stanford Medicine	Oncology Development

Unmet Need and Current Standard of Care in PDL1+ NSCLC



In mNSCLC Pts Without Actionable Biomarkers, Pembro Mono or Combo with Chemo is the SoC Across Histologies & PD-L1 Status

NSCLC Treatment Map (US)[1]

Stage IV– no actionable biomarkers

Histology	PD-L1 status	1L		1L Maintenance Treatment	
Non-Squamous	≥50%	★ **Pembro** **Atezo** **Cemiplimab**	★ **Pembro + Plt CTx** Atezo + Plt CTx Atezo + beva + Plt CTx Nivo + ipi ± Plt CTx* Cemiplimab + Plt CTx Durva + tremelimuab + Plt CTx	**Pembro** Atezo Cemiplimab	**Pembro + pemetrexed** Atezo Atezo + bevacizumab Nivo + ipi Cemiplimab + pemetrexed Durva + tremelimuab + pemetrexed
	1-49%				
	<1% / unk.				
Squamous	≥50%	*Same Txs as above*	*Same Txs as above, except atezo-containing regimens not included*	*Same Txs as above*	**Pembro** Nivo + ipi Cemiplimab Durva
	1-49%				
	<1% / unk.				

NCCN: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf, Version 5.2023, November 8, 2023 [Accessed December 12, 2023]

Note: *Nivo + Ipi only available for PD-L1 TPS > 1%

Key: PD-(L)1 | Targeted Tx | CTx / RTx

Preferred regimen in NCCN guidelines

Standard of care ★ PD-L1 High Segment (>50%)

We Believe There is Significant Room for Improvement in Efficacy over the Current Benchmark in PD-L1 High Patients, Which is ~7 mo.

		KEYTRUDA (pembro)[1]		KEYTRUDA (pembro) + pemetrexed and platinum chemotherapy[2]
Indication		First-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations		First-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations
Dosing / Admin		KEYTRUDA 200 mg IV every 3 weeks		KEYTRUDA 200 mg, pemetrexed 500 mg/m^2, and choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min IV on Day 1 of each 21-day cycle for 4 cycles followed by KEYTRUDA 200 mg and pemetrexed 500 mg/m^2 IV every 3 weeks
Key Efficacy Data	***PD-L1 Status***	***TPS ≥ 1%***	***TPS ≥ 50%***	***All PD-L1 Segments***
	mOS	16.7	20.0	22.0
	mPFS	5.4	6.9	8.8
	ORR	27%	39%	48%
Key Safety Data	**Discontinuation due to adverse reactions**	19%		20%
	Most common adverse reactions resulting in permanent discontinuation	Pneumonitis (3.0%), Death due to unknown cause (1.6%), and Pneumonia (1.4%)		Pneumonitis (3%), Acute kidney injury (2%)
	Most frequent grade 3-5 adverse reactions	Pneumonia (7%), Pneumonitis (3.9%), Pulmonary embolism (2.4%), Pleural effusion (2.2%)		Nausea (3.5%), Diarrhea (5%), Vomiting (3.7%), Fatigue (12%)

1. KEYTRUDA Package Insert, https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf, Clinical Data from KEYNOTE-042
2. KEYTRUDA Package Insert, https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf, Clinical Data from KEYNOTE-189

Key: PD-L1 High Segment (>50%)

More Efficacious, Chemo-free Treatment Options are Key Unmet Needs in mNSCLC

Current Unmet Needs in Stage IV NSCLC

Lack of efficacious treatment options for patient with metastatic disease

~50% of patients are diagnosed with locally advanced / metastatic disease, which has a poor 5-year survival rate of 6-39%[1,2]

Lack of chemo-free, tolerable treatment options

Significant proportion of patients have poor performance score / experience cumulative toxicities from systemic therapies in earlier stages of disease, increasing the need for treatments with better tolerability than chemotherapy

Lack of treatment options for patients with primary or acquired resistance to IOs

Lack of efficacious options for patients who don't / no longer respond to IOs, especially with IO moving into earlier stages and lack of clarity on IO re-challenge in metastatic setting

1. https://www.cancer.org/cancer/types/lung-cancer/detection-diagnosis-staging/survival-rates.html
2. https://www.valueinhealthjournal.com/article/S1098-3015(21)01859-3/fulltext

Tomivosertib Faces Limited Competition for Chemo-Free and ADC-Free Regimens in the PD-L1 High Segment

NSCLC Future Treatment Map (US)[1,2]

Stage IV– no actionable biomarkers

Histology	PD-L1 status	1L		Maintenance Treatment	
Non-Squamous	≥50%	Pembro Atezo Cemiplimab **Tomivosertib + Pembro** **ADC Combos** **TIGIT Combos**	Pembro + Plt CTx Atezo + Plt CTx Atezo + beva + Plt CTx Nivo + ipi ± Plt CTx* Cemiplimab + Plt CTx Durva + tremelimuab + Plt CTx **Vibostolimab + Pembro**	Pembro Atezo Cemiplimab	Pembro + pemetrexed Atezo Atezo + bevacizumab Nivo + ipi Cemiplimab + pemetrexed Durva + tremelimuab + pemetrexed
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Squamous	≥50%	*Same Txs as above*	*Same Txs as above, except atezo containing regimens not included*	*Same Txs as above*	Pembro Nivo + ipi Cemiplimab Durva
	1-49%				
	<1% / unk.				

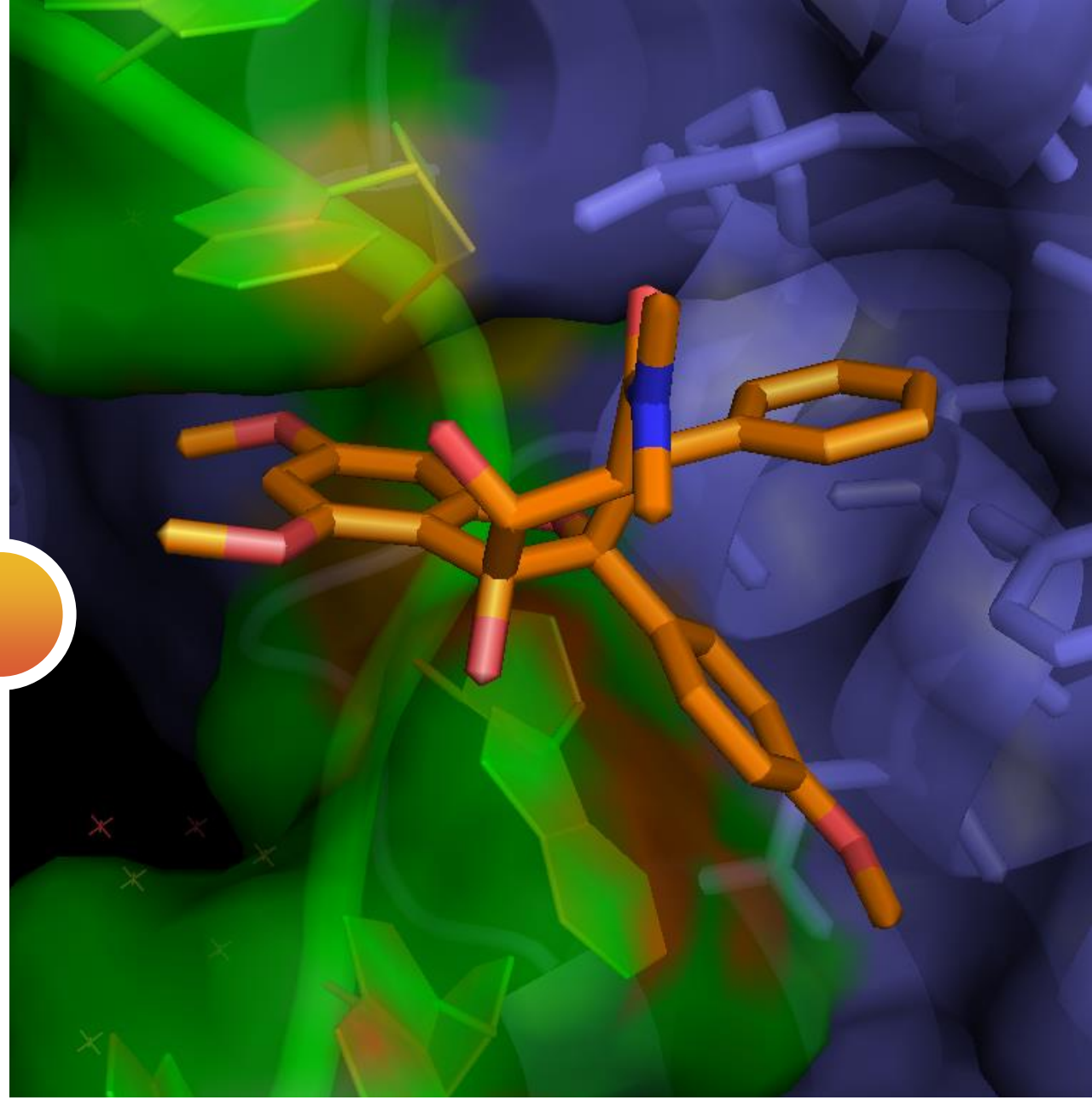
1. NCCN: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf, Version 5.2023, November 8, 2023 [Accessed December 12, 2023]
2. Clinicaltrials.gov

Note: *Nivo + Ipi only available for PD-L1 TPS > 1%
Competitive selection criteria: Assets in phase 3+, industry-sponsored trial, US trial site, 1L PD-LI + NSCLC, trial end date: >01-Jan-2023

Key: Tomi positioning

Potential Future Treatment Option

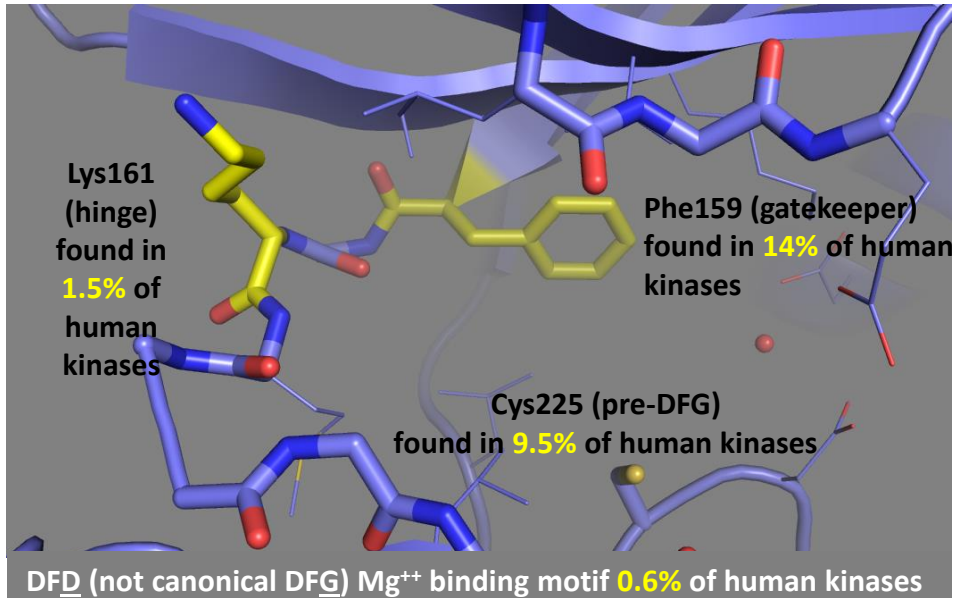
Non-Clinical Overview of Tomivosertib

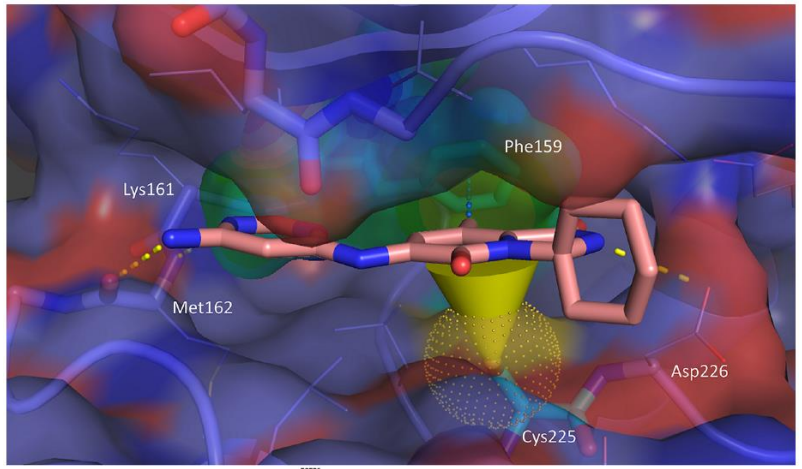


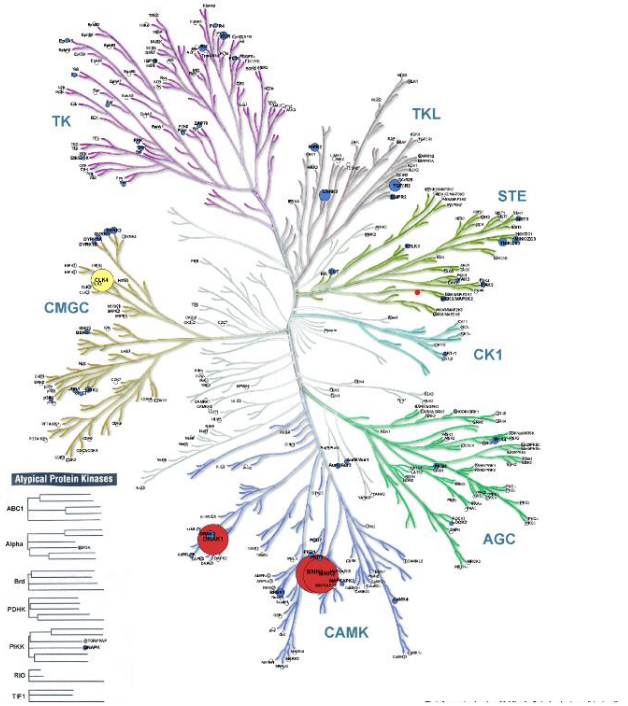
Tomivosertib Executive Summary

- Highly specific MNK inhibitor that enhances T cell function by **blocking production of** immunosuppressive factors including **PD-1, PD-L1, LAG3, TIM3 and IL-10**
- Phase 1 dose escalation program identified a generally well-tolerated dose that provided 90-100% target inhibition and demonstrated **single agent activity in B cell lymphomas**
- Phase 2a trial demonstrated clinical activity when added to patients not responding to checkpoint inhibitors
  - In patients with PD-L1 positive NSCLC, adding tomivosertib resulted in **mPFS of 53 weeks**
- Randomized, placebo-controlled Phase 2b trial in 1st line NSCLC, PD-L1 ≥ 50% in combination with pembrolizumab ongoing
  - **Topline PFS data anticipated Q1 2024**

Tomivosertib Is a Highly Selective Inhibitor of MNK1 and MNK2





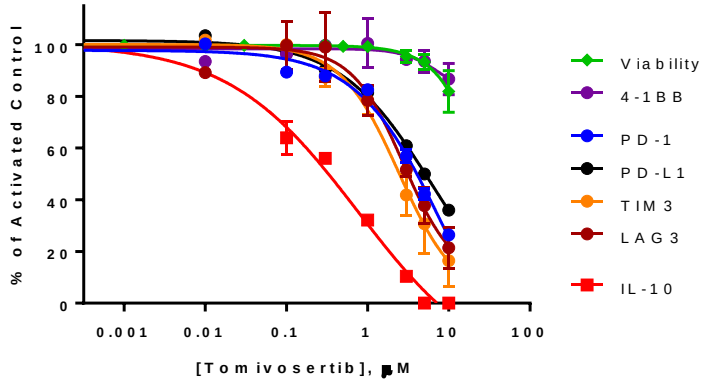


Lys161 + Phe159 + Cys225 + Asp228 occur together only in MNK 1 and 2 kinases in humans

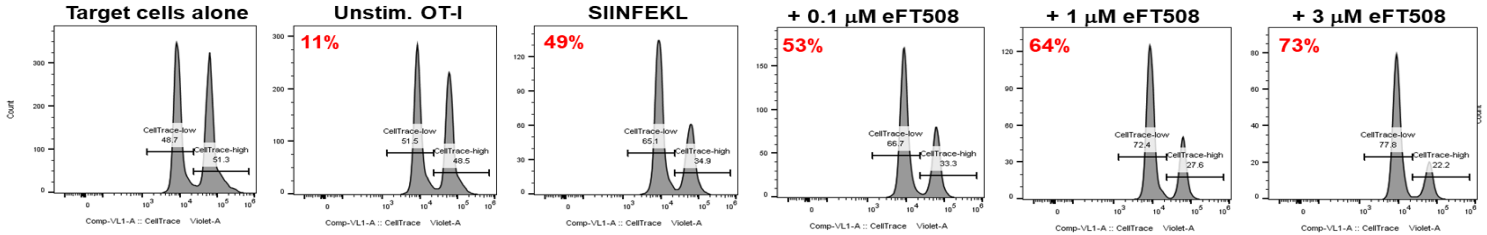
Reich et al., J Med Chem 2018

Tomivosertib Inhibited Checkpoint Protein Expression and Enhanced T Cell Function

- Tomivosertib blocks upregulation of immunosuppressive proteins induced by TCR activation but does not block expression of 4-1BB or T cell viability

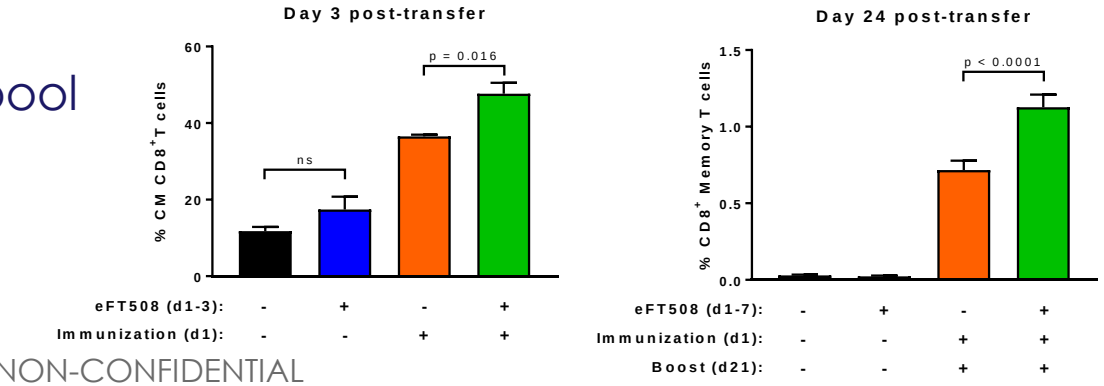


- Tomivosertib increases cytotoxic T cell function



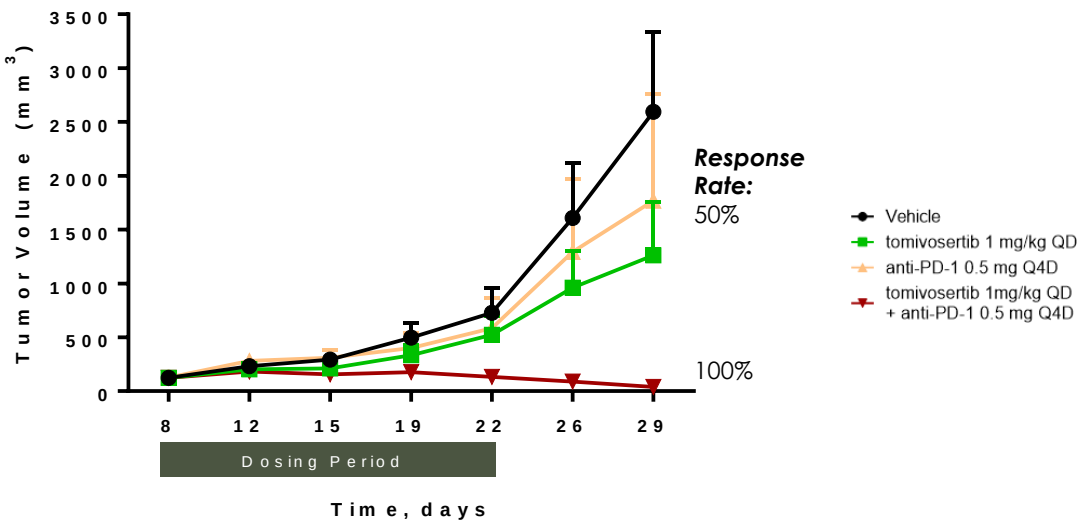
Red numbers represent % of cells killed following pulse with cognate antigen relative to unpulsed cells

- Tomivosertib enhances central memory pool and memory-recall responses *in vivo*

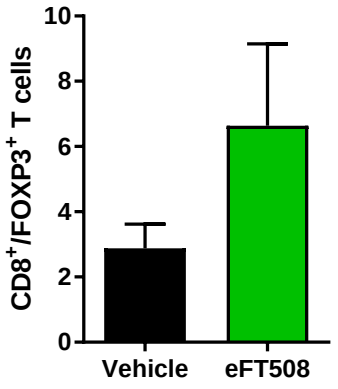


Tomivosertib Induced Changes in the Tumor Environment that Promote Anti-tumor Immune Activity

Anti-tumor Activity as Single Agent and Combined with Anti-PD-1

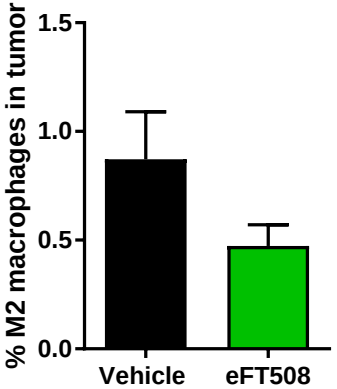


Tumor Infiltrating T Cells Single Agent



Day 4

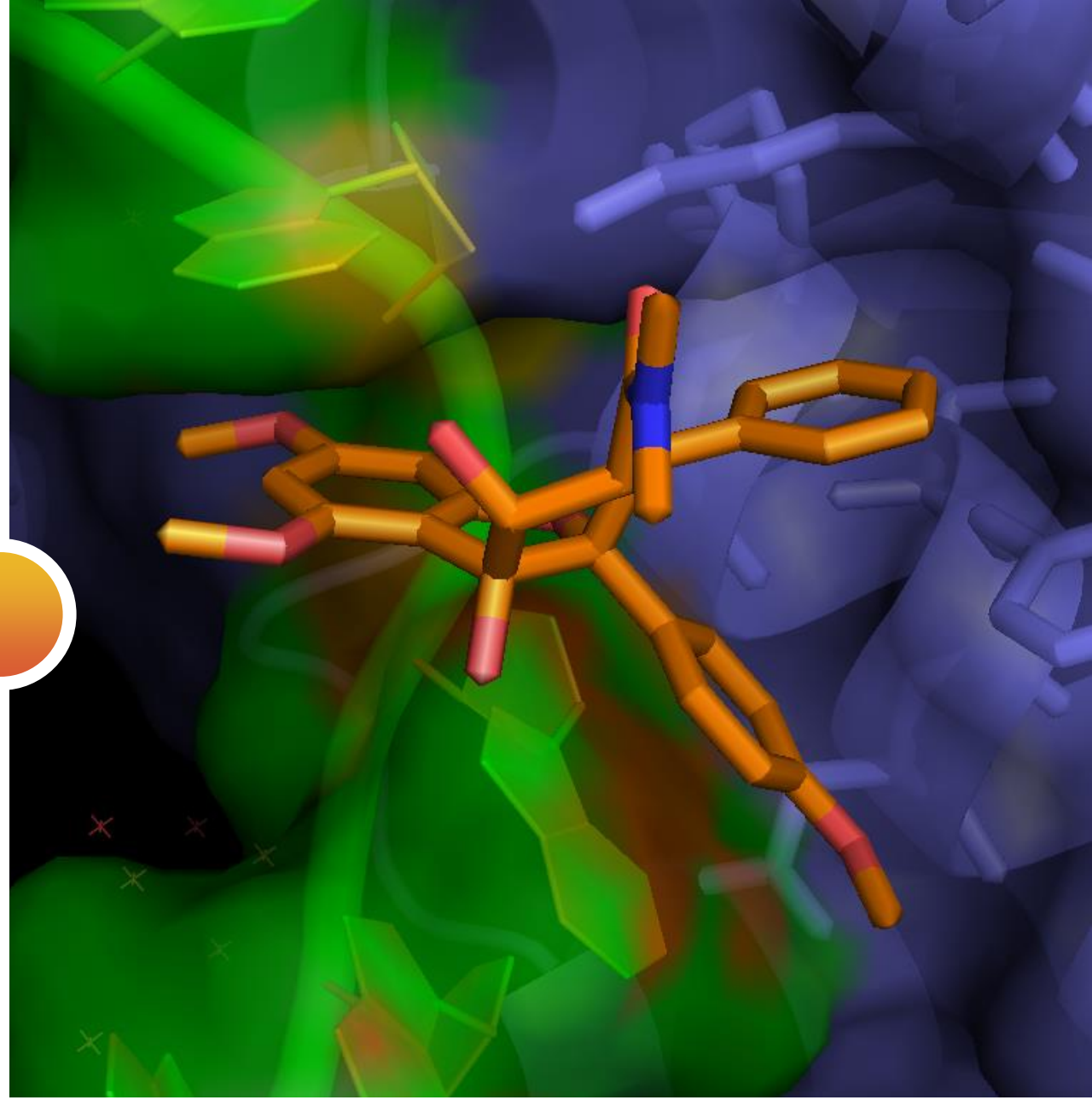
Tumor M2-Macrophage Single Agent



Day 7

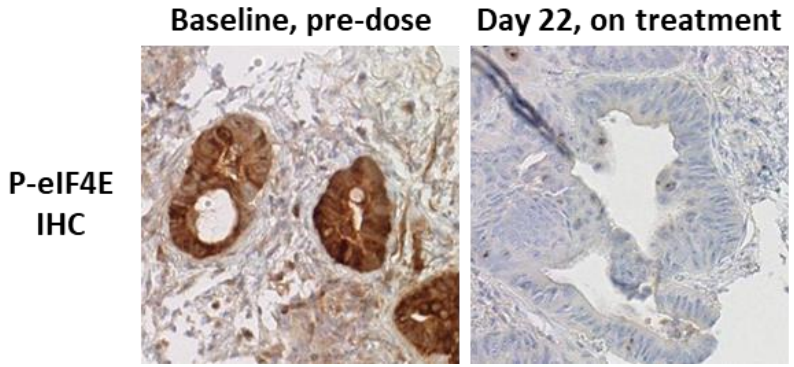
Tomivosertib treatment in CT-26 model resulted in tumor growth inhibition as a single agent and enhanced activity in combination with anti-PD-1, as well as an increase in lymphocytes that promote anti-tumor immunity and a decrease in immunosuppressive cell types that allow tumors to escape immune recognition.

Clinical Overview of Tomivosertib and Next Steps

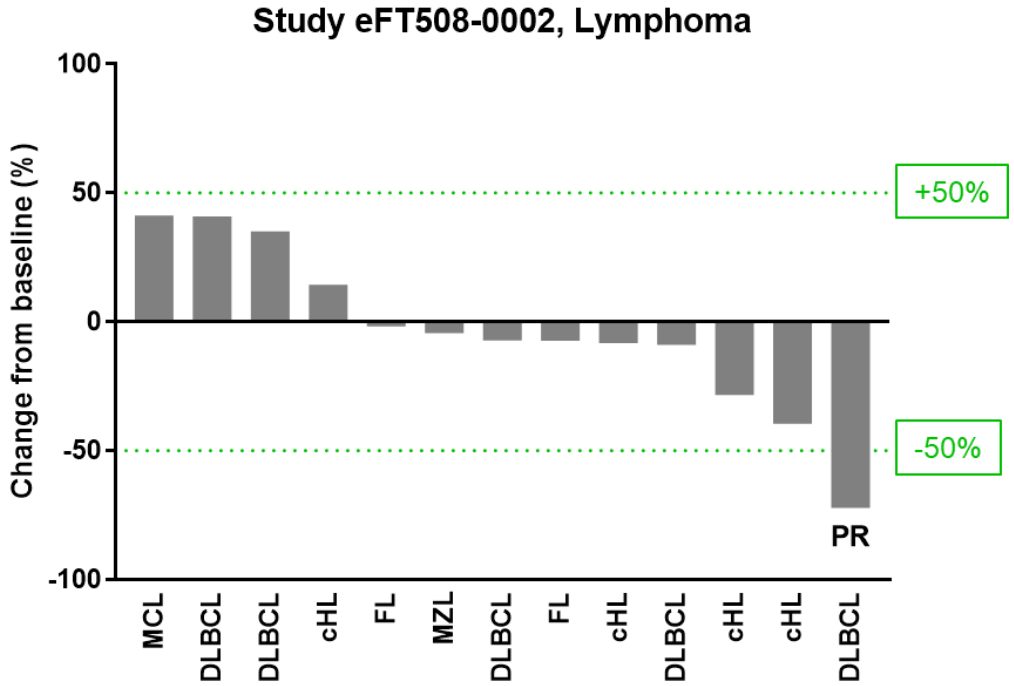


Tomivosertib: Generally Well Tolerated with Single-Agent Activity*

- Tomivosertib was generally well tolerated at the recommended Phase 2 dose (RP2D)
  - Low grade nausea, vomiting and tremors were most common treatment-emergent adverse events (TEAEs)
- MNK target was 90-100% inhibited at RP2D

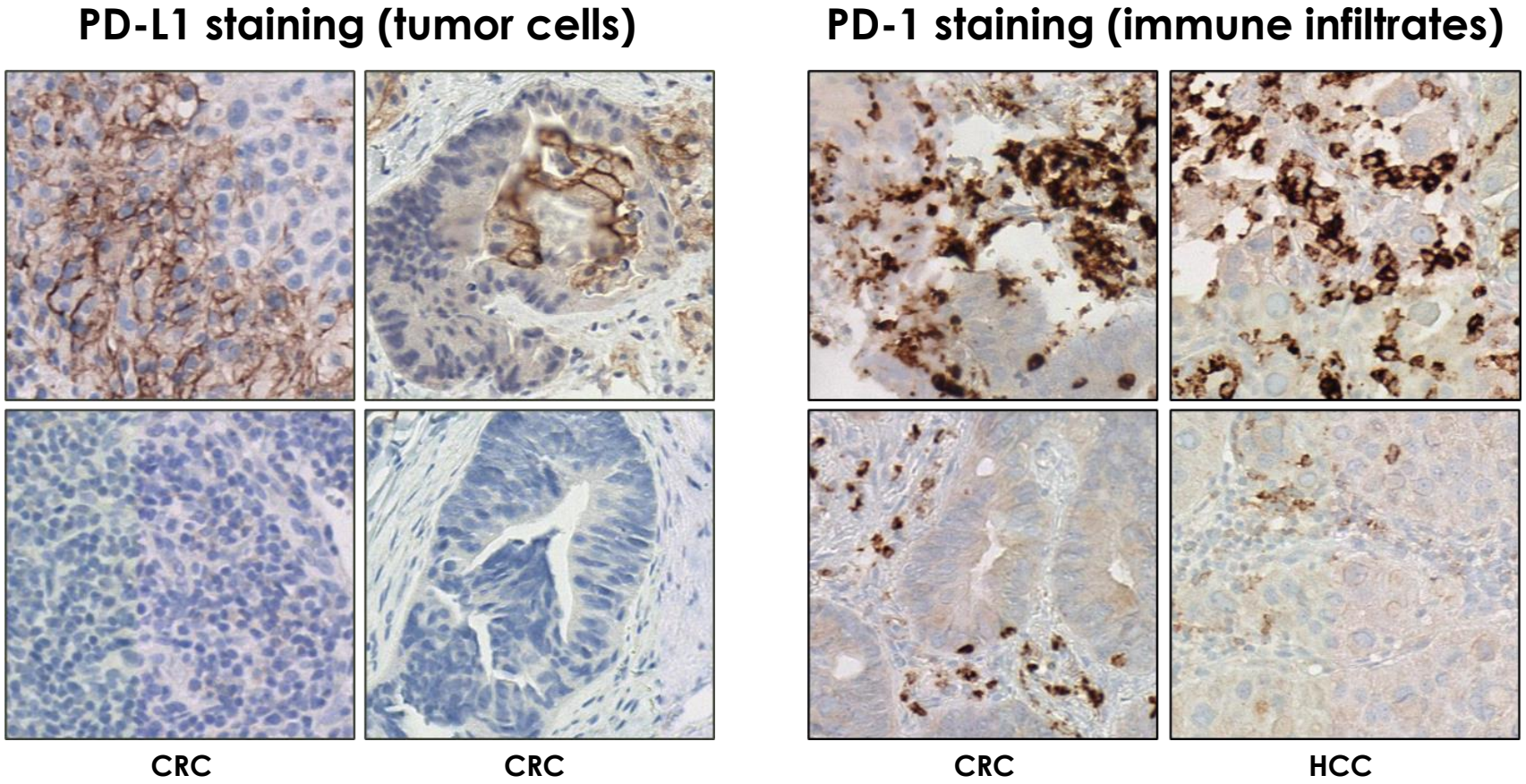


- Single agent activity was observed in lymphoma patients



*Data from completed studies as of September 2020. Lymphoma waterfall plot represents all patients with evaluable disease (n=13) out of 19 patients total enrolled.

Tomivosertib Reduced Checkpoint Protein Expression in Patient Biopsies



Tomivosertib Prolonged PFS When Combined with Anti-PD-(L)1 Agents

- Phase 2a trial (N=39)
  - Tomivosertib added on to patients not responding to anti-PD-(L)1 therapy, with no change or break in anti-PD-(L)1 regimen
  - Safety profile when combined with anti-PD-(L)1 agents comparable to anti-PD-L(1) agents alone
  - Showed encouraging activity in multiple tumor types*
- Clinical benefit was most prominent in NSCLC patients (N=17)
  - Increasing metastatic disease on anti-PD-(L)1 therapy prior to adding tomivosertib
    - 16 patients had RECIST-defined progressive disease, 17th patient had 13% increase in SLD score
  - Inflection in tumor growth and durable tumor control observed in many patients after adding tomivosertib
  - 2 confirmed partial responses (PR), including one which went on to confirmed CR on extension
    - 12% ORR compares favorably to 3% for vibostolimab+pembrolizumab in PD-(L)1 refractory setting**
  - **Adding tomivosertib substantially improved PFS, particularly in PD-L1+ patients**

**Data through study completion in September 2020; initial data presented at ASCO 2020; PR, CR and SLD (Sum of Long dimensions) as determined by RECIST 1.1 criteria.*

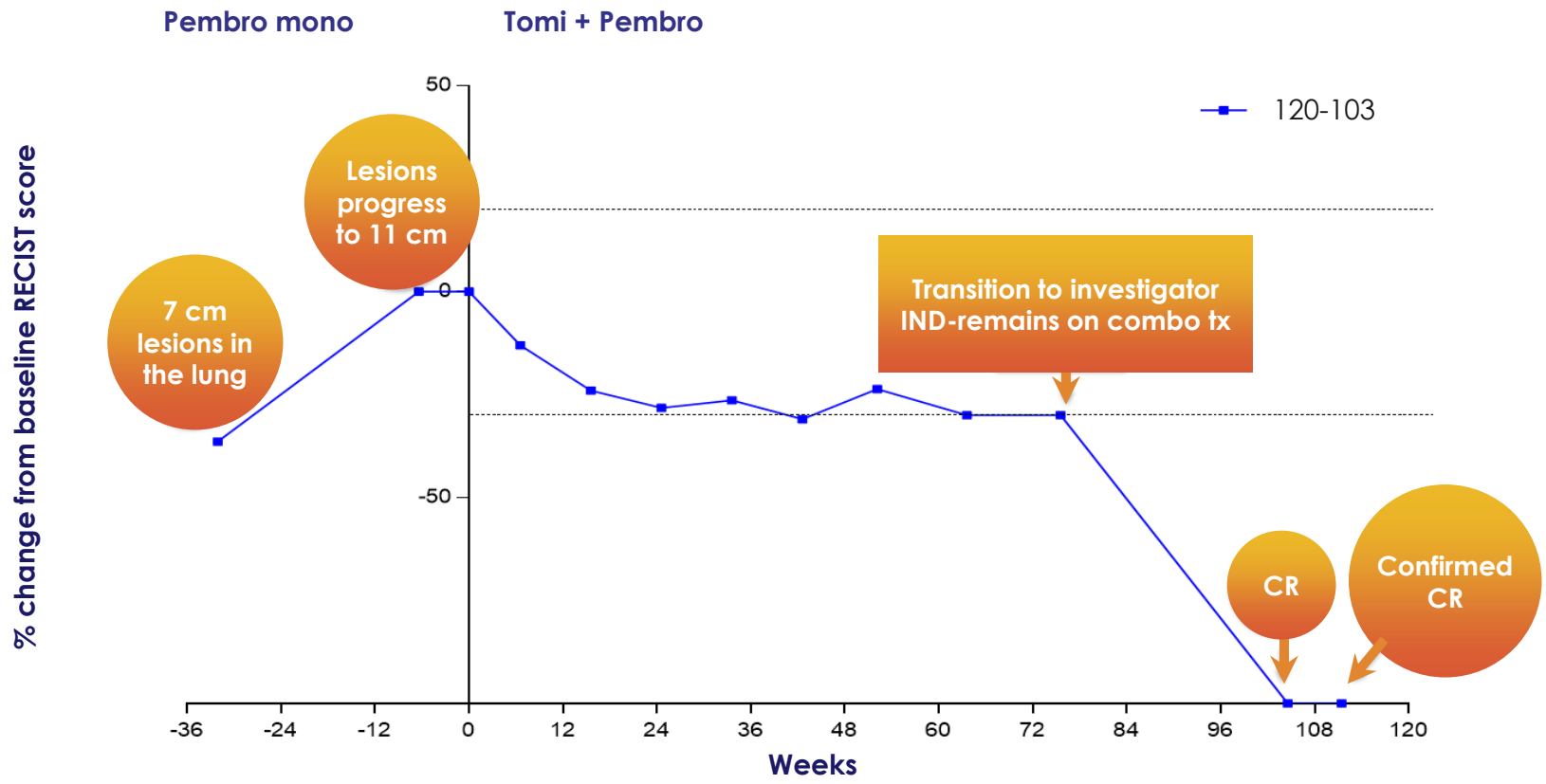
*FOR ILLUSTRATIVE PURPOSES ONLY: **Data for vibostolimab+pembrolizumab from trial NCT02964013. Differences exist between trial designs and subject characteristics, and caution should be exercised when comparing data across trials*

Tomivosertib Was Generally Well-Tolerated In Combination with Checkpoint Inhibitors in Phase 2a Trial

Tomivosertib 200 mg BID In Combination with Anti-PD-(L)1 Inhibitors (N=39)		
	Drug-related TEAEs	
MedDRA term	All Grades N(%)	Grade 3 or higher N(%)
Nausea	16 (41.0)	0 (0.0)
Tremor	15 (38.5)	0 (0.0)
Fatigue	11 (28.2)	0 (0.0)
Vomiting	9 (23.1)	0 (0.0)
Alanine aminotransferase increased	7 (17.9)	2 (5.1)
Aspartate aminotransferase increased	7 (17.9)	0 (0.0)
Diarrhea	7 (17.9)	0 (0.0)
Gamma-glutamyltransferase increased	7 (17.9)	1 (2.6)
Rash	5 (12.8)	0 (0.0)
Blood alkaline phosphatase increased	4 (10.3)	0 (0.0)
Decreased appetite	4 (10.3)	0 (0.0)
Dyspepsia	4 (10.3)	0 (0.0)
Headache	4 (10.3)	0 (0.0)
Insomnia	4 (10.3)	0 (0.0)

Tomivosertib-related Treatment-Emergent Adverse Events >10% Incidence from interim data at study conclusion.
Tomivosertib was dosed 200 mg BID in fasted state in combination with pembrolizumab, nivolumab, durvalumab or atezolizumab at approved dose of each anti-PD-(L)1 inhibitor.

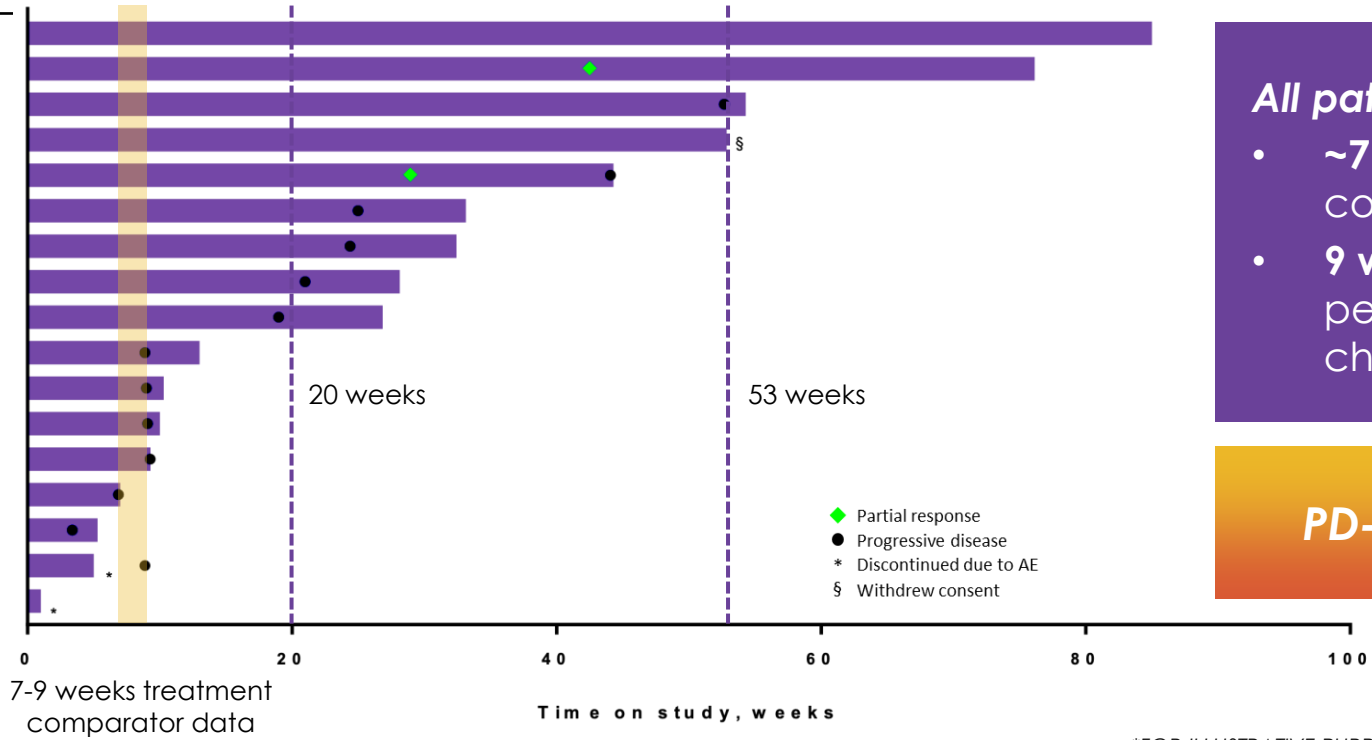
Example: Patient on Tomi/Pembro Combo With Confirmed Complete Response after ~2 Years



Patient was PD-L1>50%

Phase 2A: Demonstrated Extended PFS in NSCLC Patients Particularly Enriched in PD-L1+ Patients

Patient	CPI	PD-L1
115-103	Pembro	≥ 1%
120-103	Pembro	≥ 1%
113-102	Nivo	≥ 1%
113-103	Nivo	≥ 1%
104-101	Pembro	N.D.
106-103	Nivo	0
115-105	Durva	N.D.
111-101	Atezo	N.D.
106-104	Pembro	≥ 1%
106-107	Durva	≥ 1%
123-103	Pembro	0
105-102	Pembro	0
116-104	Nivo	0
108-106	Pembro	≥ 1%
123-101	Pembro	0
114-101	Nivo	0
112-104	Nivo	0



All patients: mPFS of **20 weeks** compared to

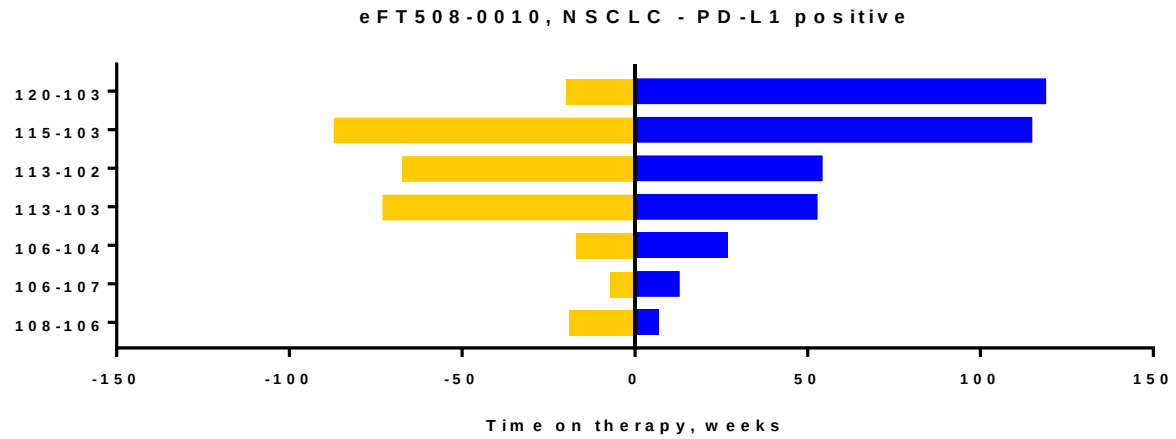
- **~7 weeks** for atezolizumab alone continued after progression and
- **9 weeks** for vibostolimab + pembrolizumab after progression on checkpoint inhibitor*

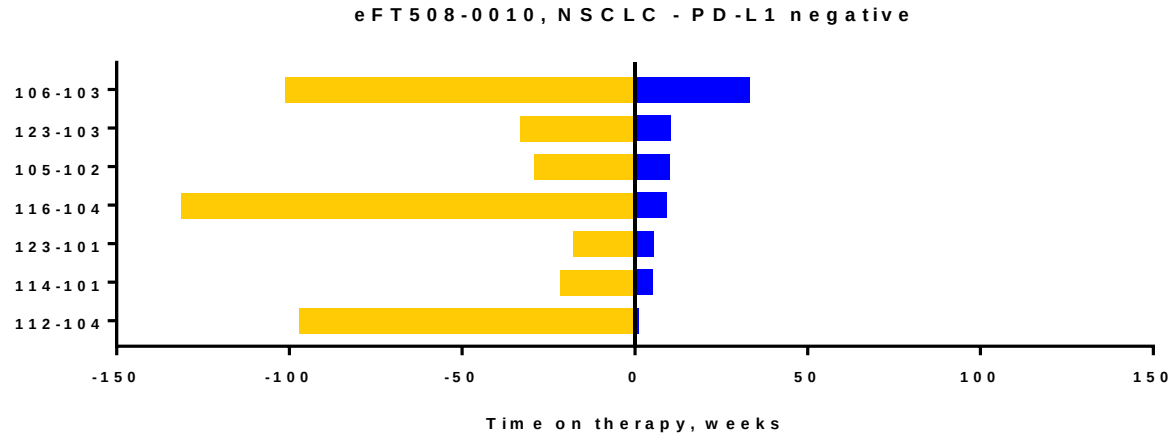
PD-L1+ patients: mPFS of 53 weeks

**FOR ILLUSTRATIVE PURPOSES ONLY: Data for atezolizumab from Treatment Beyond Progression (TBP) cohort in OAK trial. Data for vibostolimab+pembrolizumab from trial NCT02964013; Differences exist between trial designs and subject characteristics, and caution should be exercised when comparing data across trials*

Data through study completion in September 2020
Patients 115-103 and 120-103 continued treatment past study completion on Single Patient Expanded Access INDs

Longer Time on Tomi+CPI in PD-L1+ patients





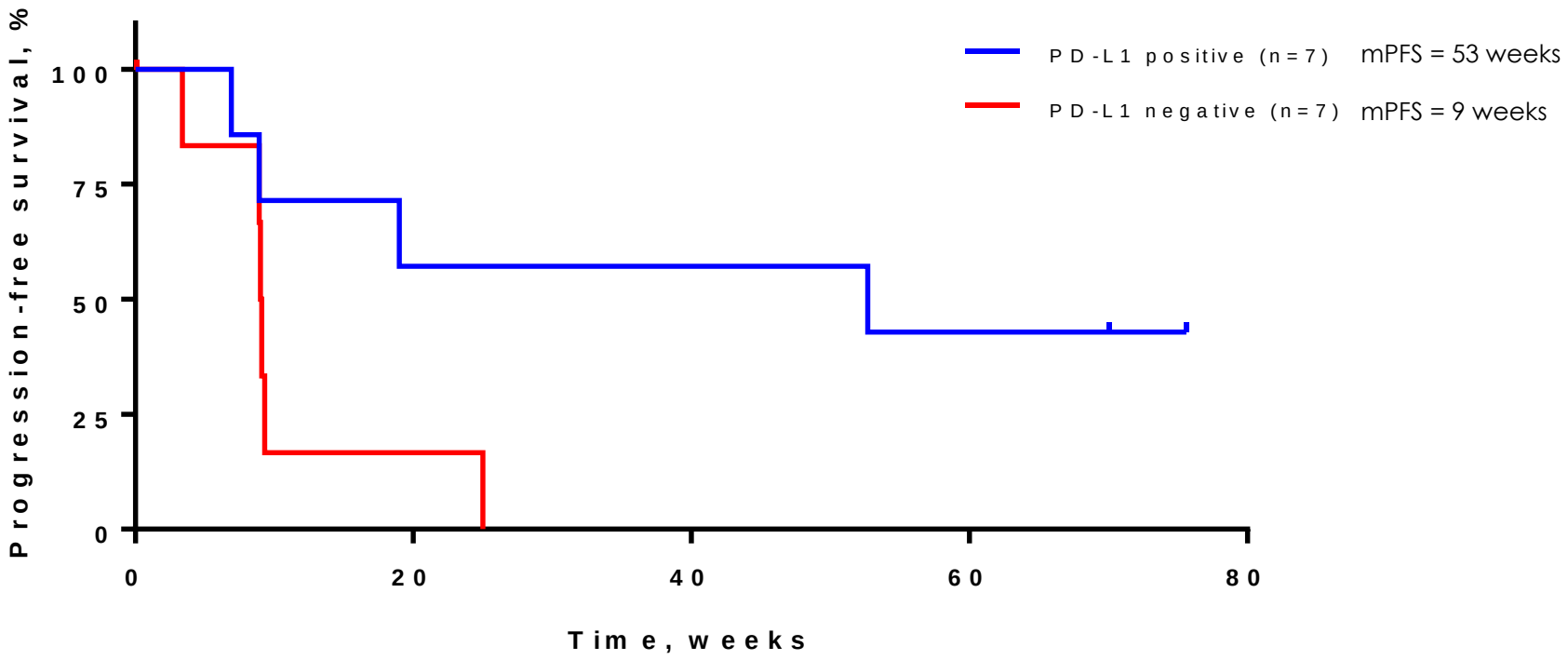
On tomi+CPI therapy

CPI immediately prior to adding tomi (Therapy -1)

Data through May 2021 for Patients 115-103 and 120-103 who continued treatment past study completion on Single Patient Expanded Access INDs

PD-L1 Positive Patients Showed Longer PFS

A post-hoc analysis of data from the Phase 2a trial showed that the median PFS in PD-L1 positive patients was 53 weeks vs 9 weeks in PD-L1 negative patients



**data as of study completion September 2020. PD-L1 status available from site communications or central testing for 14 of 17 patients. Analysis of median PFS between PD-L1 positive and negative patients is from Kaplan Meier analysis of PFS curves.*

PFS and OS for Tomi Added After PD in Phase 2a Trial Exceed PFS and OS in OAK Trial Treatment Beyond Progression Cohort

Criteria	EFTR Phase 2a Trial NSCLC subset	OAK Trial Treatment Beyond Progression Cohort[1]	OAK Trial Full Atezo Cohort[2]
ORR	11.8%	7.1%	13.6%
PFS	20.0 weeks	~6.5 weeks[3]	12.1 weeks
OS	19.0 months	12.7 months	13.8 months
PD-L1+ subset of pts[4] ORR PFS OS	 14.3% 53 weeks >20 months (not reached)	 7.5% not reported but not enriched in waterfall plot not reported	 18% 12.1 weeks 15.7 months

[1]Gandara et al., J. Thoracic Oncology 2018
[2]Rittmeyer et al., Lancet 2017
[3]reported as time to discontinue therapy
[4]PD-L1 detected on tumor cells or immune cells (TC or IC) in OAK trial, TC only in eFFECTOR trial

Differences exist between trial designs and subject characteristics, and caution should be exercised when comparing data across trials.

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

- Primary endpoint: Progression Free Survival (PFS)
- Secondary endpoints: OS, ORR, Safety

- **Topline data readout anticipated Q1 2024**

How We Define Success in KICKSTART

Clinically meaningful results:

- PFS Hazard Ratio (HR) of 0.65 (p ≤0.2)
  - HR of 0.65 corresponds to 50% improvement in PFS
- Illustrative example
  - mPFS in control arm is expected to be ~7 months*
  - 50% improvement corresponds to mPFS of ~11 months

We believe HR of 0.65 or better is achievable in KICKSTART:

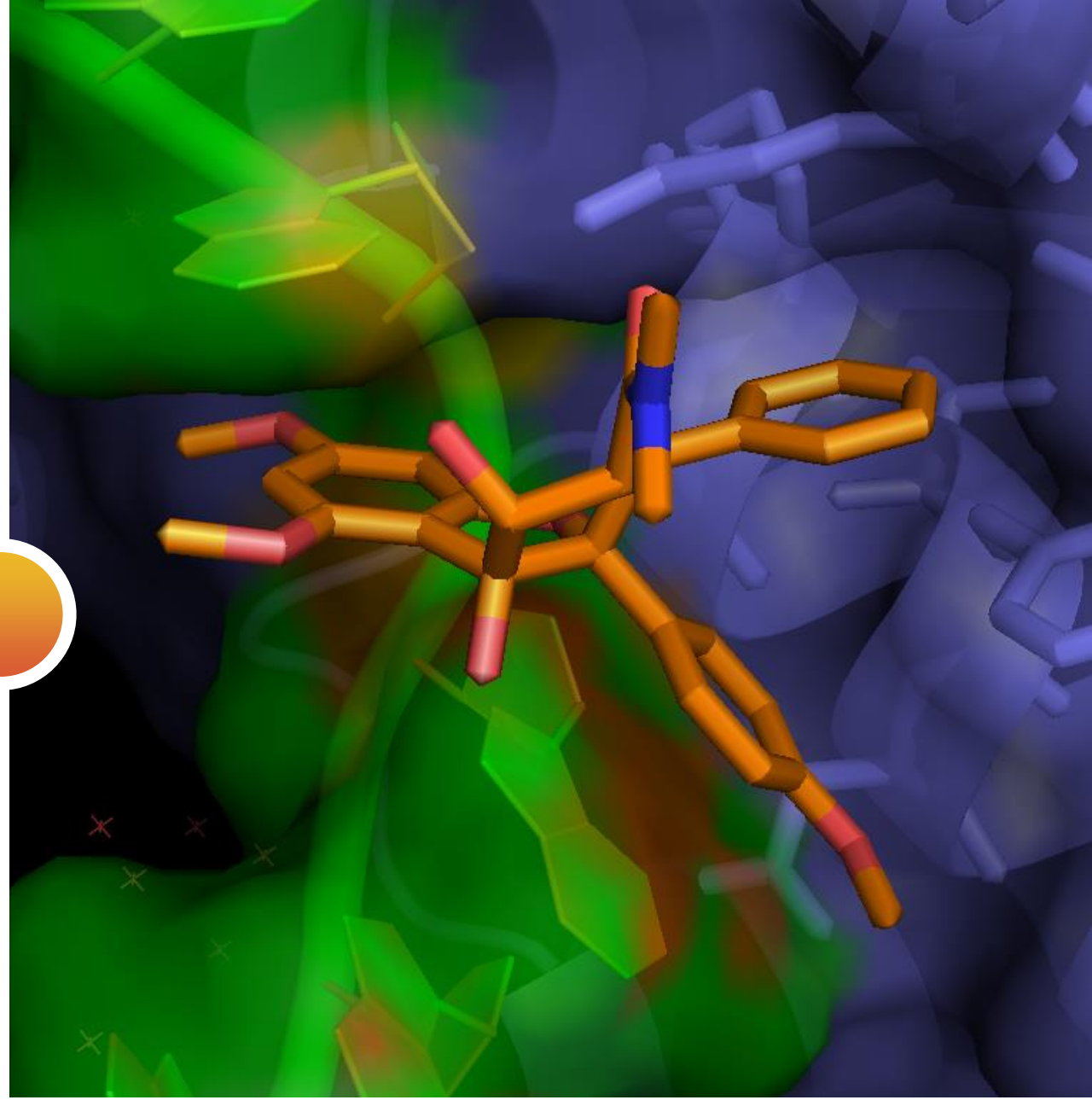
- In Phase 2a trial PFS benefit after progression was ~200% greater than comparator data from OAK trial
- KICKSTART is enrolling patients before progression
- KICKSTART is being enriched for PD-(L)1+ patients who demonstrated best results in Phase 2a (mPFS = 53 weeks)

* derived from KEYNOTE 042

Tomivosertib Development Plan

- Top-line results of primary analysis of KICKSTART Study anticipated Q1 2024
- Phase 3 planning including regulatory interactions and site selection anticipated during H2 2024
- Phase 3 registrational study design anticipated to be similar to KICKSTART
  - PD-L1 ≥ 50%
  - 1L NSCLC
  - Pembrolizumab + tomivosertib/placebo
- Anticipated Phase 3 clinical trial launch in H1 2025

Unmet Need and Current Standard of Care in ER+ BC



Unmet Need for Novel Second-Line+ Treatment for Patients With ER-Positive/HER2-Negative MBC

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Professor of Medicine
Director, Glenn Family Breast Center
Director, Breast Medical Oncology
Louisa and Rand Glenn Family Chair in Breast Cancer Research

Disclosures

Spouse, Stock: EQRX (Prior Employee), ADC Therapeutics

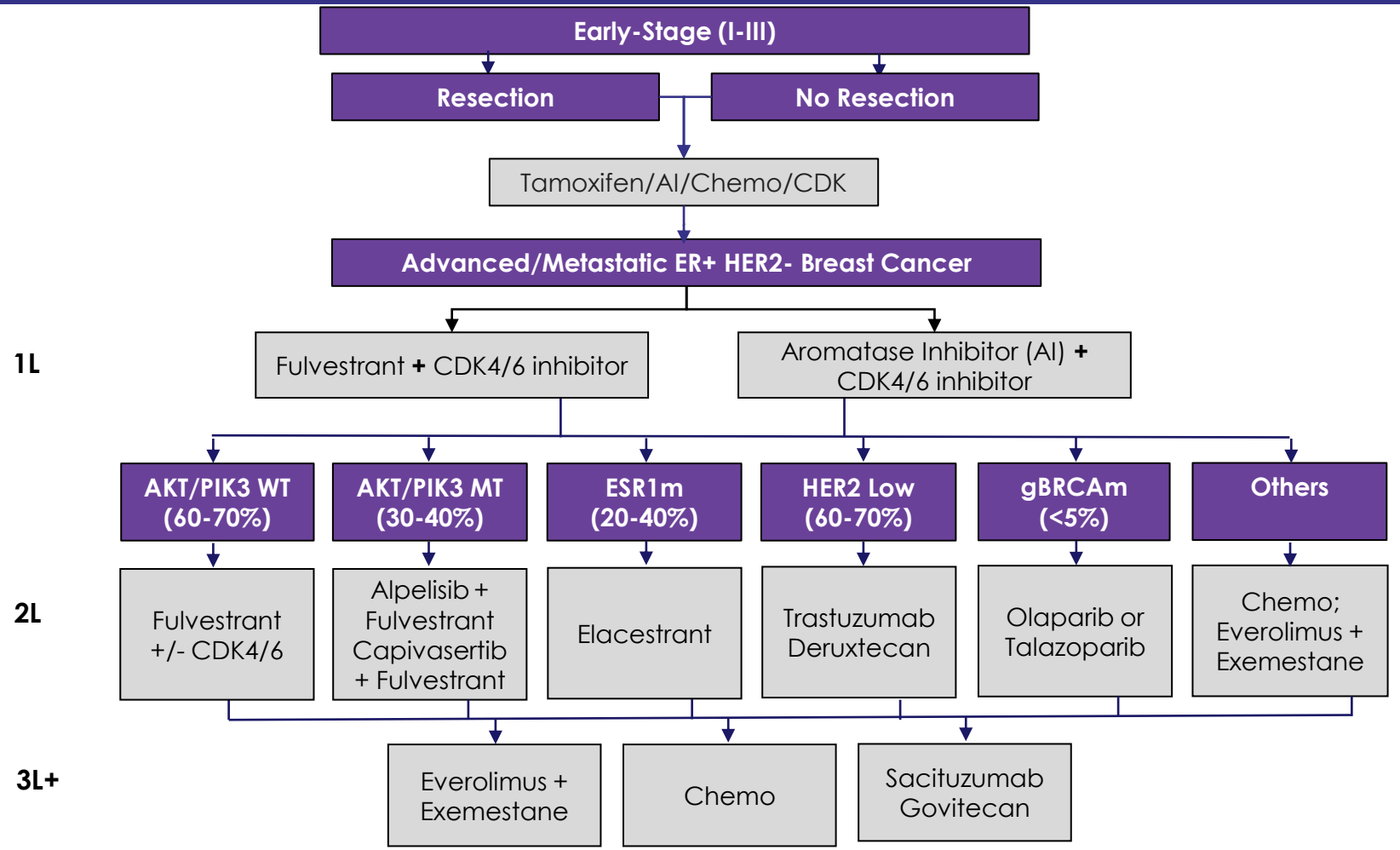
Advisory/Consulting: Genentech/Roche, Immunomedics, Seattle Genetics, AstraZeneca, Daiichi Sankyo, Puma Biotechnology, Mersana, Menarini Silicon Biosystems, Myovant Sciences, Takeda, Merck

Summary Data for First-line Combinations of CDK4/6 Inhibitors and ET in HR+/HER2-Breast Cancer: PFS and OS

	First-line Therapy				
	PALOMA-2[1-3] (N = 666)	**MONALEESA-2[4-6] (N = 668)**	**MONALEESA-3[7,8] (N = 726)**	**MONALEESA-7[8,9] (N = 672)**	**MONARCH-3[11-13] (N = 493)**
Endocrine partner	Letrozole	Letrozole	Fulvestrant	Letrozole, anastrozole, or tamoxifen + LHRH agonist	Letrozole
CDK4/6i	Palbociclib	Ribociclib	Ribociclib	Ribociclib	Abemaciclib
Median PFS, CDK4/6i + ET vs ET, mo	27.6 vs 14.5 (Δ13.1)[2]	25.3 vs 16.0 (Δ9.3)[5]	20.5 vs 12.8 (Δ7.7)[7]	23.8 vs 13.0 (Δ10.8)[9]	28.2 vs 14.8[12]
Hazard ratio	0.56	0.57	0.59	0.55	0.54
Median OS, CDK4/6i + ET vs ET, mo	53.9 vs 51.2[3]	63.9 vs 51.4[6]	67.6 vs 51.8[8]	58.7 vs 48.0[10]	67.1 vs 54.5 mo[13] (interim analysis)
Hazard ratio	0.956	0.76 **Significant**	0.67 **Significant**	0.76 **Significant**	0.75

1. Finn. NEJM. 2016;375:1925. 2. Rugo. Breast Cancer Res Treat. 2019;174:719. 3. Finn. ASCO 2022. Abstr LBA1003. 4. Hortobagyi. NEJM. 2016;375:1738. 5. Hortobagyi. Ann Oncol. 2018;29:1541. 6. Hortobagyi. NEJM. 2022;386:942. 7. Slamon. JCO.2018;36:2465. 8. Neven. Breast Can Res. 2023;25:103. 9. Tripathy. Lancet Oncol. 2018;19:904. 10. Lu. Clin Cancer Res. 2022;28:851. 11. Goetz. JCO. 2017;35:3638. 12. Johnston. NPJ Breast Cancer. 2019;5:5. 13. Goetz. ESMO 2022. LBA15.

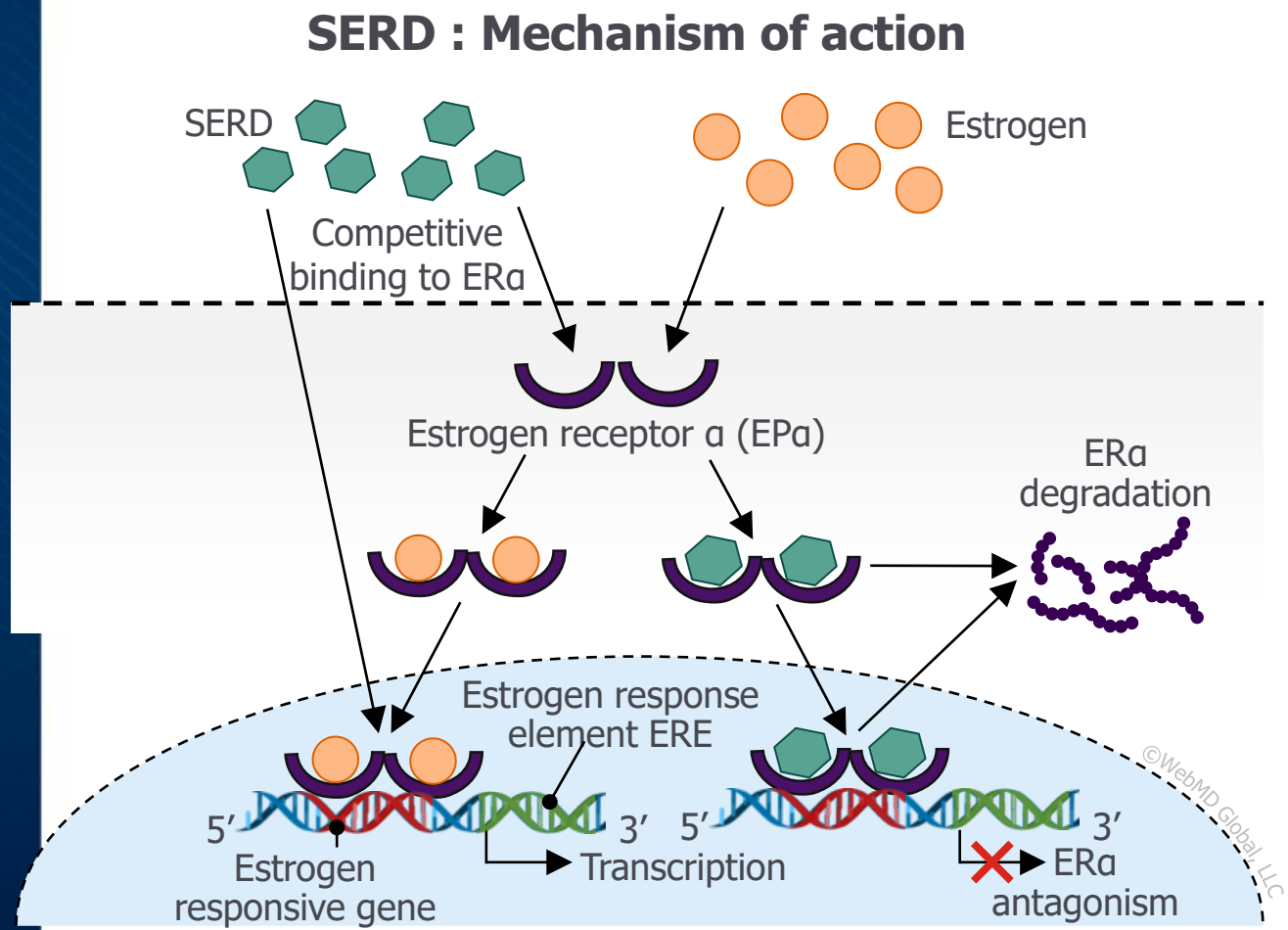
Treatment Algorithm in HR+, HER2- mBC

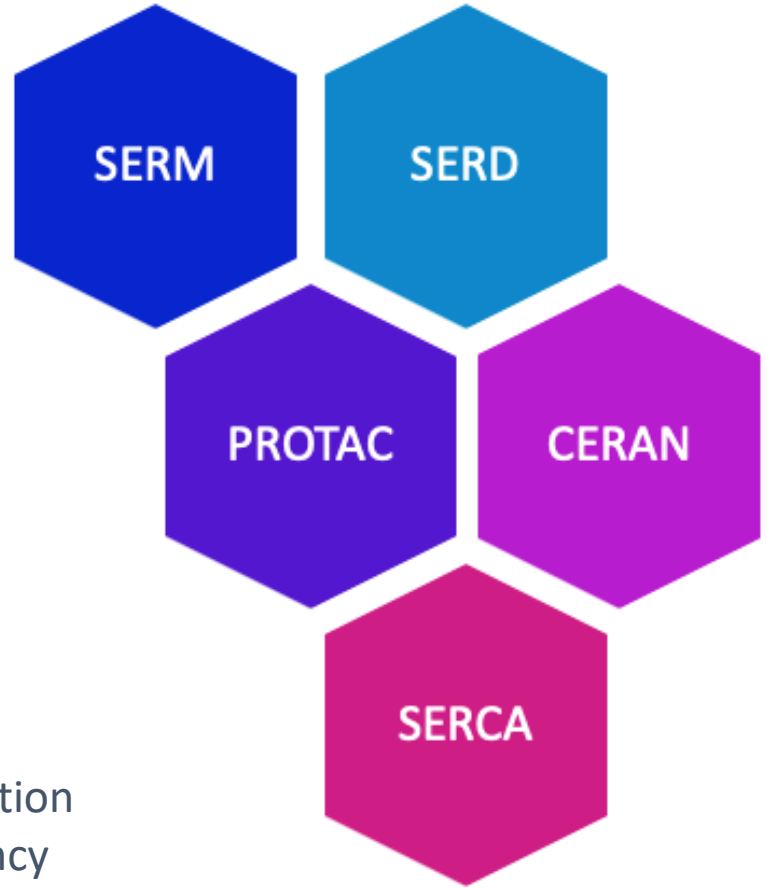


HER2-low defined as HER2 IHC 1+ or IHC 2+/ISH-; gBRCAm = germline BRCA mutant, SERM = selective estrogen receptor modulators, SERD = selective estrogen receptor degrader

eFFECTOR

Novel endocrine therapies may address endocrine resistance in MBC





Key advantages

- Oral formulation
- Higher potency
- Activity in ESR1 mutant MBC
- Activity in post-ET and CDK4/6i treated pts

Hernando et al, Int J Mol Sci 2021; slide adapted from Erika Hamilton

Prevalence of *ESR1* Mutations in Untreated vs Treated ER+/HER2- mBC

Treatment Setting	*ESR1* Mutation Prevalence[1-5]
At Initiation of First-Line ET	~5%
Second-Line	~33%
Third-Line	Up to 40%

1. Jeselsohn R et al. *Clin Cancer Res* 2014;20:1757-1767; **2.** Jeselsohn R et al. *Cancer Cell* 2018;33:173-186; **3.** Allouchery V et al. *Breast Cancer Res* 2018;20:40;
4. Schiavon G et al. Sci Transl Med 2015;7(313):313ra182; **5.** Brett JO et al. *Breast Cancer Res* 2021;23(1):85.

EMERALD Phase 3 Study Design

Inclusion Criteria

- Men and postmenopausal women with advanced/metastatic breast cancer
- ER-positive,[a] HER2-negative
- Progressed or relapsed on or after 1 or 2 lines of endocrine therapy for advanced disease, one of which was given in combination with a CDK4/6i
- ≤1 line of chemotherapy for advanced disease
- ECOG PS 0 or 1

Stratification Factors:

- *ESR1*-mutation status[f]
- Prior treatment with fulvestrant
- Presence of visceral metastases

R

1:1[b]

Elacestrant 400 mg daily[c]

Investigator's choice (SOC):
Fulvestrant
Anastrozole
Letrozole
Exemestane

PD or withdrawal criterion[d]

Follow Up

Two Primary Endpoints:[e]

- PFS in all pts
- PFS in *ESR1*-mut

[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Restaging CT scans every 8 weeks; [e]Blinded Independent Central Review; [f]*ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay (Guardant Health, Redwood City, CA).

PFS, progression-free survival; Pts, patients; R, randomized; SOC, standard of care.

Baseline Characteristics

Parameter	Elacestrant		SOC	
	All (N=239)	*ESR1*-mut (N=115)	All (N=239)	*ESR1*-mut (N=113)
Median age, years (range)	63.0 (24-89)	64.0 (28-89)	63.0 (32-83)	63.0 (32-83)
Gender, n (%) Female Male	233 (97.5) 6 (2.5)	115 (100) 0	238 (99.6) 1 (0.4)	113 (100) 0
ECOG PS, n (%) 0 1 >1	143 (59.8) 96 (40.2) 0	67 (58.3) 48 (41.7) 0	135 (56.5) 103 (43.1) 1 (0.4)	62 (54.9) 51 (45.1) 0
Visceral metastasis*, n (%)	163 (68.2)	81 (70.4)	170 (71.1)	84 (74.3)
Prior CDK4/6i, n (%)	239 (100)	115 (100)	239 (100)	113 (100)
Number of prior lines of endocrine therapy,** n (%) 1 2	129 (54.0) 110 (46.0)	73 (63.5) 42 (36.5)	142 (59.4) 97 (40.6)	69 (61.1) 44 (38.9)
Type of prior endocrine therapy, n (%)** **Fulvestrant** AI Tamoxifen	**70 (29.3)** 193 (80.8) 19 (7.9)	**27 (23.5)** 101 (87.8) 9 (7.8)	**75 (31.4)** 194 (81.2) 15 (6.3)	**28 (24.8)** 96 (85.0) 9 (8.0)
Number of prior lines of chemotherapy,** n (%) 0 1	191 (79.9) 48 (20.1)	89 (77.4) 26 (22.6)	180 (75.3) 59 (24.7)	81 (71.7) 32 (28.3)

*Includes lung, liver, brain, pleural, and peritoneal involvement
In the advanced/metastatic setting. **NCT03778931. Accessed March 29, 2023. https://clinicaltrials.gov/ct2/show/NCT03778931. Presented at: SACBS;2022.

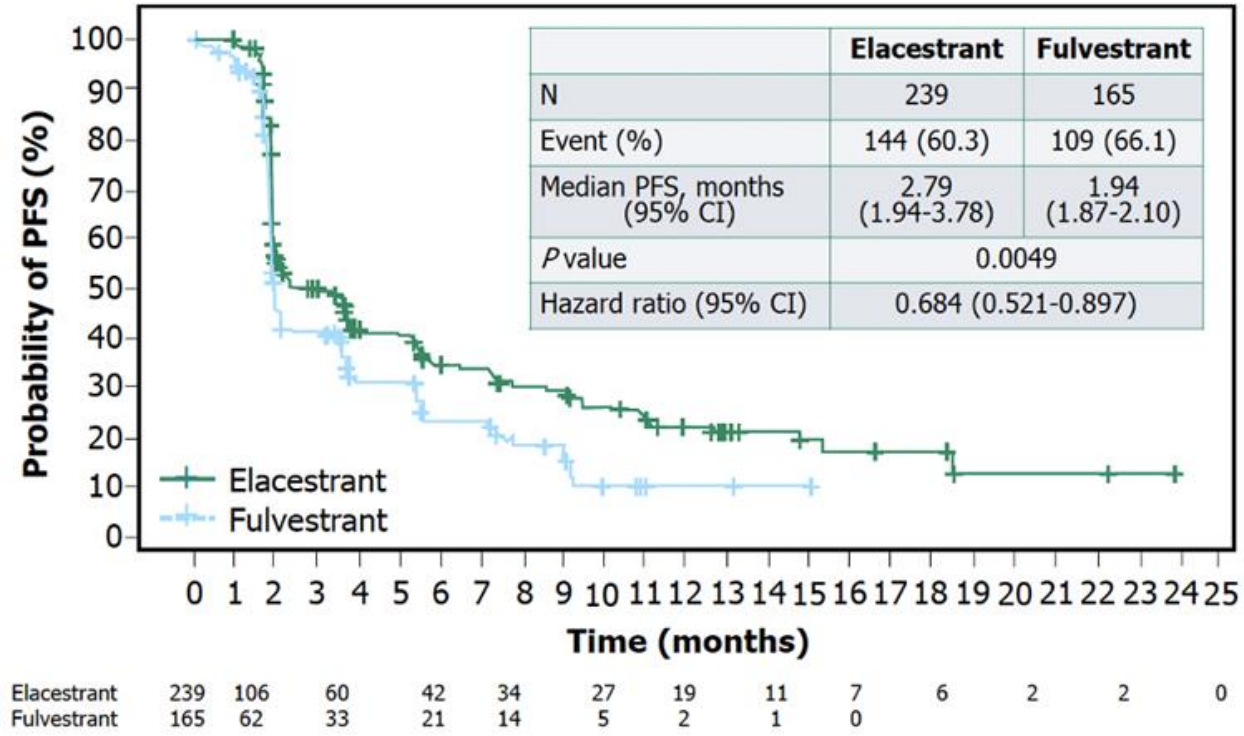
EMERALD study

PFS: Elacestrant vs Fulvestrant (All Patients and *mESR1* Group)

ITT

mPFS 2.79 vs 1.9 mon
HR 0.684 (0.52-0.90), p = 0.0049

All Patients



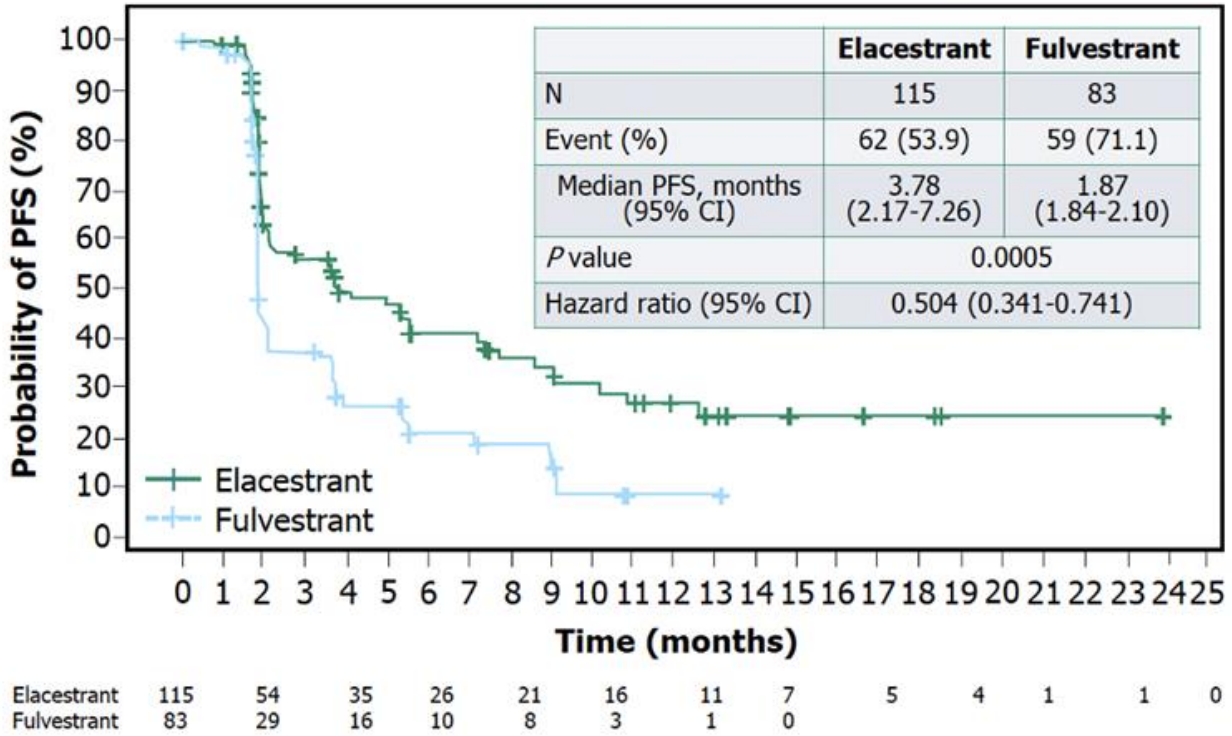
	Elacestrant	Fulvestrant
N	239	165
Event (%)	144 (60.3)	109 (66.1)
Median PFS, months (95% CI)	2.79 (1.94-3.78)	1.94 (1.87-2.10)
P value	0.0049	
Hazard ratio (95% CI)	0.684 (0.521-0.897)	

Elacestrant	239	106	60	42	34	27	19	11	7	6	2	2	0	
Fulvestrant	165	62	33	21	14	5	2	1	0					

mESR1

mPFS 3.78m vs 1.87m
HR 0.504 (0.34-0.74), p = 0.0005

Patients With Tumors Harboring *mESR1*



	Elacestrant	Fulvestrant
N	115	83
Event (%)	62 (53.9)	59 (71.1)
Median PFS, months (95% CI)	3.78 (2.17-7.26)	1.87 (1.84-2.10)
P value	0.0005	
Hazard ratio (95% CI)	0.504 (0.341-0.741)	

Elacestrant	115	54	35	26	21	16	11	7	5	4	1	1	0	
Fulvestrant	83	29	16	10	8	3	1	0						

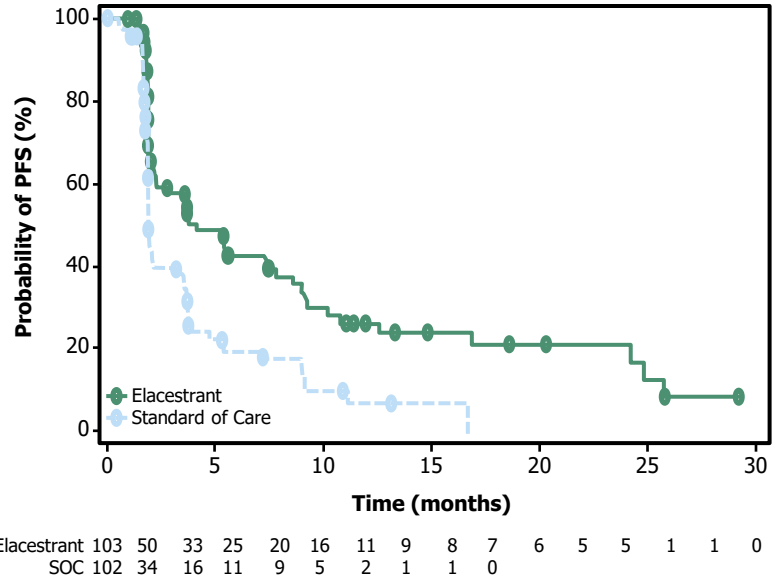
Bardia Aditya SABCS 2021

Emerald Toxicity

AEs[c] Occurring in ≥ 10% of Patients in Any Arm	Elacestrant		Total		Fulvestrant		AI	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	83 (35.0)[d]	6 (2.5)	43 (18.8)	2 (0.9)	26 (16.1)	0	17 (25.0)	2 (2.9)
Fatigue	45 (19.0)	2 (0.8)	43 (18.8)	2 (0.9)	35 (21.7)	1 (0.6)	8 (11.8)	1 (1.5)
Vomiting	45 (19.0)[e]	2 (0.8)	19 (8.3)	0	12 (7.5)	0	7 (10.3)	0
Decreased appetite	35 (14.8)	2 (0.8)	21 (9.2)	1 (0.4)	12 (7.5)	0	9 (13.2)	1 (1.5)
Arthralgia	34 (14.3)	2 (0.8)	37 (16.2)	0	28 (17.4)	0	9 (13.2)	0
Diarrhea	33 (13.9)	0	23 (10.0)	2 (0.9)	14 (8.7)	1 (0.6)	9 (13.2)	1 (1.5)
Back pain	33 (13.9)	6 (2.5)	22 (9.6)	1 (0.4)	16 (9.9)	1 (0.6)	6 (8.8)	0
AST increased	31 (13.1)	4 (1.7)	28 (12.2)	2 (0.9)	20 (12.4)	2 (1.2)	8 (11.8)	0
Headache	29 (12.2)	4 (1.7)	26 (11.4)	0	18 (11.2)	0	8 (11.8)	0
Constipation	29 (12.2)	0	15 (6.6)	0	10 (6.2)	0	5 (7.4)	0
Hot flush	27 (11.4)	0	19 (8.3)	0	15 (9.3)	0	4 (5.9)	0
Dyspepsia	24 (10.1)	0	6 (2.6)	0	4 (2.5)	0	2 (2.9)	0
ALT increased	22 (9.3)	5 (2.1)	23 (10.0)	1 (0.4)	17 (10.6)	0	6 (8.8)	1 (1.5)

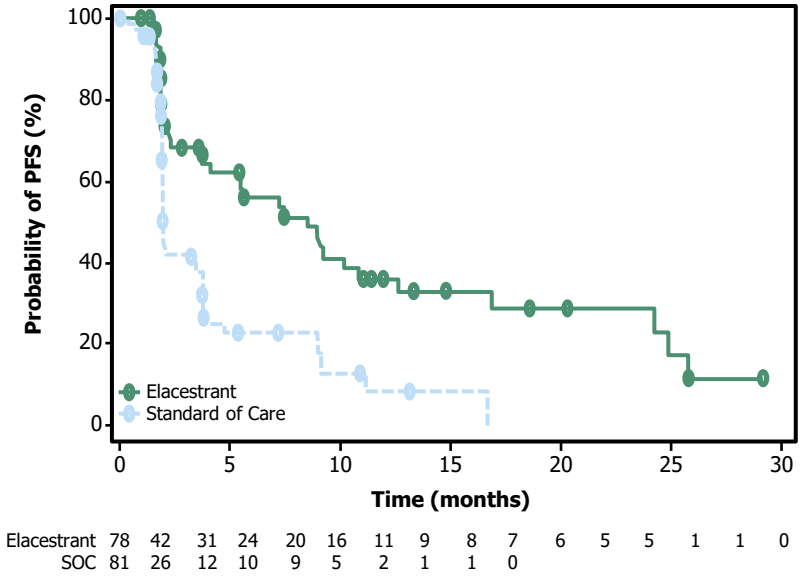
Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



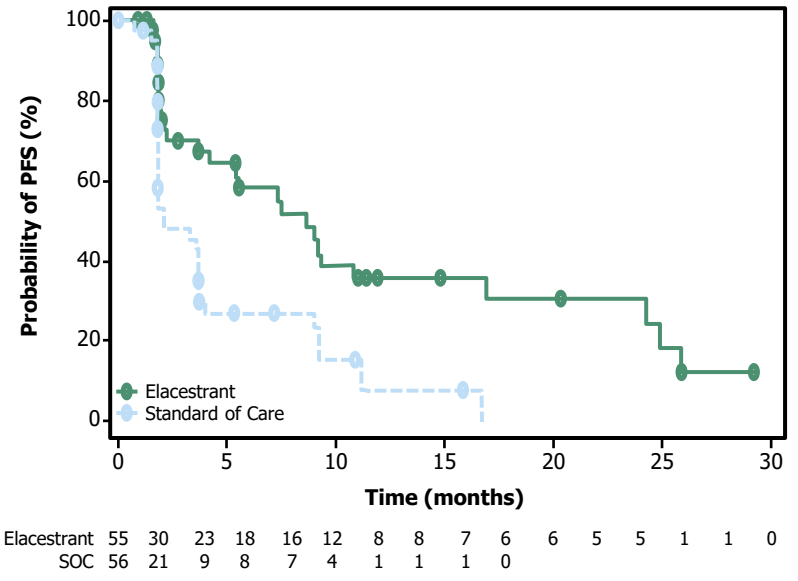
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

At least 12 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)	

At least 18 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

Various oral SERDs are being investigated on the horizon, pionERA is the is the only study addressing specific endocrine resistance and building on learnings from ESR1 mutation unmet need from previous studies

SERD	giredestrant (Roche)	elacestrant (Menarini)	camizestrant (AstraZeneca)	imlunestrant (Lilly)	amcenestrant* (Sanofi – discont.)
mBC					
1L PhIII +CDKi	**persevERA BC**[1] gired vs. let (+palbo) **pionERA BC**† gired vs. fulv (+CDKi) in ET-resistant	--	**SERENA-4**[9] cami vs. ana (+palbo) **SERENA-6**[10] cami vs. AI (+palbo/abema) in emerging *ESR1*m	--	**AMEERA-5**[17] amce vs. let (+palbo)
2L PhII–III	**acelERA BC**[2] PhII gire vs. PCE **evERA BC**[3] PhIII gired vs. PCE (+evero)	**EMERALD**[6] PhIII ela vs. PCE	**SERENA-2**[11] PhII cami (2 dose arms) vs. fulv	**EMBER-3**[14] PhIII imlu vs. PCE vs imlu+abema	**AMEERA-3**[18] amce vs. PCE
eBC					
Neoadj / WoO PhI–II	**coopERA BC**[4] PhII gired vs. ana (+palbo)	**ELIPSE**[7] PhI ela single-arm	**SERENA-3**[12] PhII cami (3 dose arms)	**EMBER-2**[15] PhI imlu (3 dose arms)	**AMEERA-4**[19] PhII amce vs. let **I-SPY EOP**[20] PhII amce+/-abema
Adjuvant PhIII	**lidERA BC**[5] gired vs. PCE, upfront	**TREAT**[8] ela vs. PCE, switch in rising ctDNA	**CAMBRIA-1**[13] cami vs PCE, switch	**EMBER-4**[16] imlu vs. PCE, switch	**AMEERA-6**[21] amce vs. tam, switch

* Discontinued clinical development of amcenestrant.
† Planned for 2023.
AI, aromatase inhibitor; amce, amcenestrant; ana, anastrozole; cami, camizestrant; CDKi, cyclin-dependent kinase inhibitor; ela, elacestrant; fulv, fulvestrant; gired, giredestrant; imlu, imlunestrant; let, letrozole; PCE: physician's choice endocrine therapy; tam, tamoxifen; WoO, window of opportunity. References in slide notes.

2022 ASCO® ANNUAL MEETING

A randomized phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition in patients with unresectable or metastatic hormone receptor positive, HER2 negative breast cancer: MAINTAIN Trial

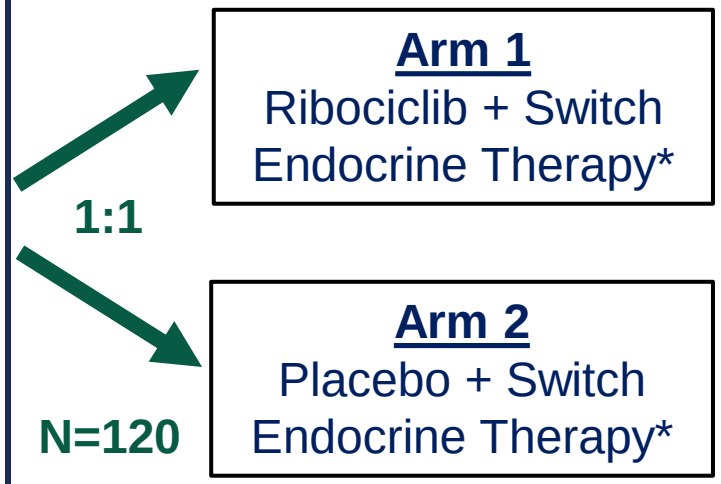
Kevin Kalinsky, Melissa K Accordino, Cody Chiuzan, Prabhjot Mundi, Meghna S Trivedi, Yelena Novik, Amy Tiersten, Amelia Zelnak, George Raptis, Lea Baer, Sun Y Oh, Erica Stringer-Reasor, Sonya Reid, Eleni Andreopoulou, William Gradishar, Kari B Wisinski, Anne O'Dea, Ruth O'Regan, Katherine D Crew, Dawn L Hershman

PRESENTED BY:
Kevin Kalinsky, MD, MS

Schema

Key Entry Criteria

- Men or Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- MBC
- Progression on ET + any CDK 4/6 inhibitor
- ≤ 1 line of chemotherapy for MBC
- Measurable or non-measurable
- PS 0 or 1
- Postmenopausal
  - GnRH agonist allowed if premenopausal
- Stable brain metastases allowed



Primary Endpoint

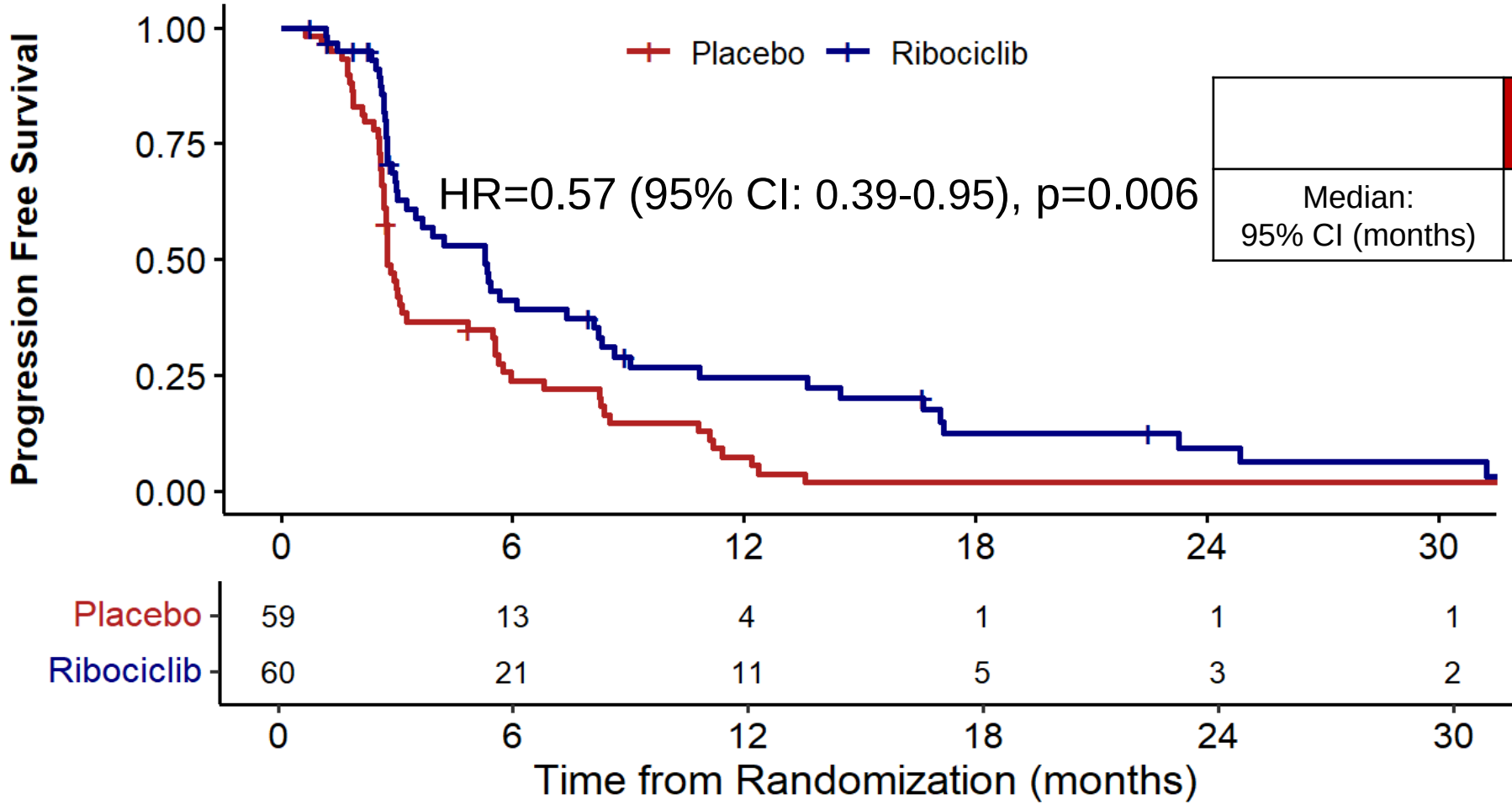
- Progression free survival
  - Locally assessed per RECIST 1.1

Secondary Endpoints

- Overall response rate
- Clinical benefit rate
- Safety
- Tumor and blood markers, including circulating tumor DNA

- Fulvestrant as endocrine therapy in pts with progression on a prior aromatase inhibitor for MBC and no prior fulvestrant; Protocol amended to allow exemestane as endocrine therapy if progression on prior fulvestrant (September 2018); Ribociclib 600 mg administered 3 weeks on/1 week off

Primary Endpoint: Progression Free Survival (PFS)

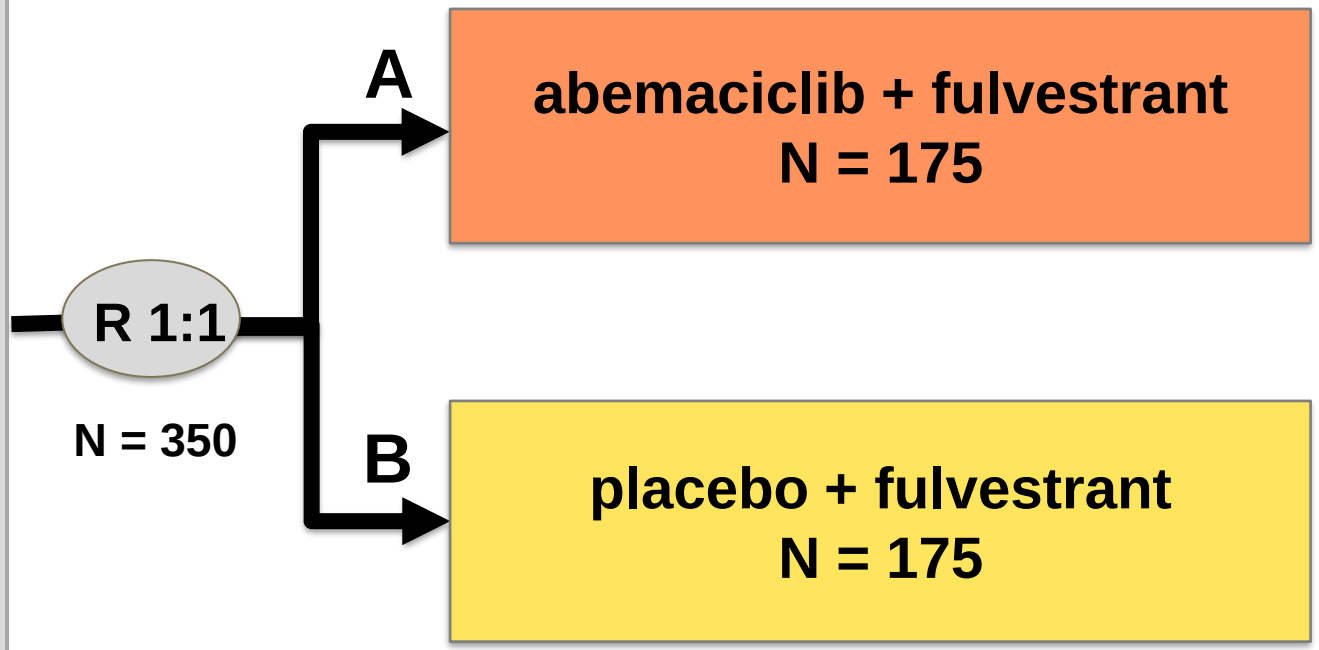


	Placebo + ET (n=59)	Ribociclib + ET (n=60)
Median: 95% CI (months)	**2.76** (2.66-3.25)	**5.29** (3.02-8.12)

postMONARCH (n=350)

Key Inclusion Criteria

- HR+, HER2- MBC
- Men, or pre- and postmenopausal women
- Prior therapy:
  - Advanced setting: Disease progression on CDK4 & 6 inhibitor plus an aromatase inhibitor (AI) as initial therapy, **OR**
  - Adjuvant setting: Disease recurrence on or after CDK4 & 6 inhibitor plus ET



Stratification Factors:

- Geography
- Presence of visceral metastasis
- Duration on prior CDK4 & 6 inhibitor-based regimen

Treatment continued until disease progression, unacceptable toxicity, or discontinuation criteria are met

Kalinsky K et al ASCO: Trials in Progress 2022

CAPItello-291: Study overview

Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia.
ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.
Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatment

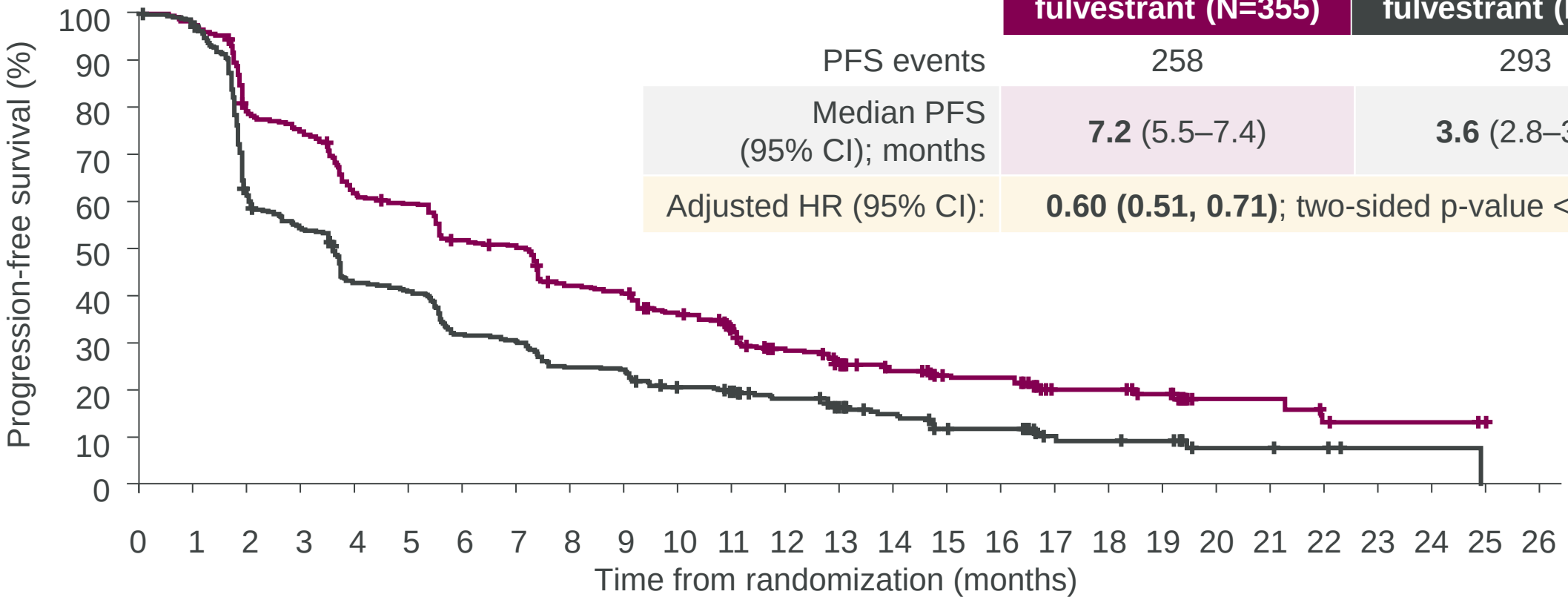
AKT pathway alterations

Alteration; n (%)		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Any AKT pathway alteration		**155 (43.7)**	**134 (38.0)**
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)
Non-altered		**200 (56.3)**	**219 (62.0)**
AKT pathway alteration not detected		142 (40.0)	171 (48.4)
Unknown		58 (16.3)	48 (13.6)
	No sample available	10 (2.8)	4 (1.1)
	Preanalytical failure	39 (11.0)	34 (9.6)
	Post analytical failure	9 (2.5)	10 (2.8)

AKT pathway alteration status was determined centrally using next-generation sequencing in tumor tissue with the FoundationOne®CDx assay (and Burning Rock assay in China)

Dual-primary endpoint: Investigator-assessed PFS in the overall population

	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
PFS events	258	293
Median PFS (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI):	**0.60 (0.51, 0.71)**; two-sided p-value <0.001	



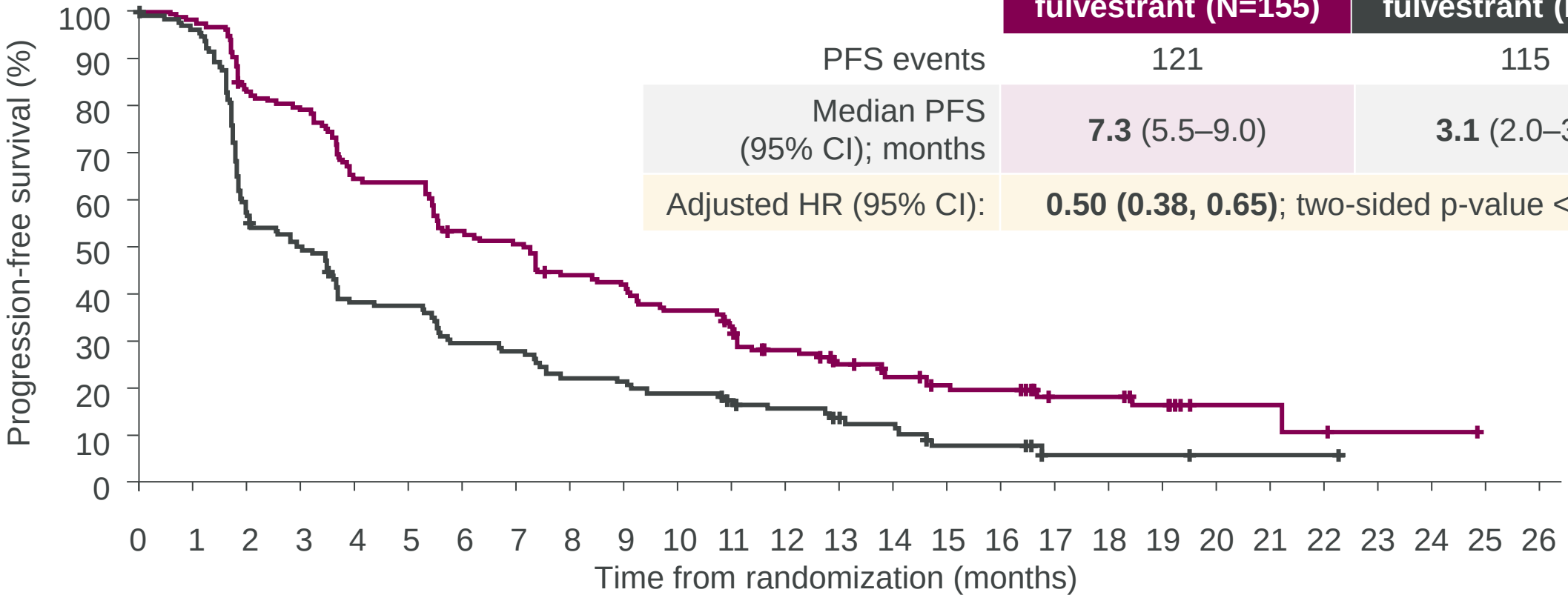
Number of patients at risk

Capivasertib + fulvestrant	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	25	21	8	8	5	2	2	1	0
Placebo + fulvestrant	353	329	207	182	142	136	106	100	83	81	66	59	51	41	33	24	23	12	11	10	4	4	3	1	1	0	0

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region.

Dual-primary endpoint: Investigator-assessed PFS in the AKT pathway-altered population

	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
PFS events	121	115
Median PFS (95% CI); months	**7.3** (5.5–9.0)	**3.1** (2.0–3.7)
Adjusted HR (95% CI):	**0.50 (0.38, 0.65)**; two-sided p-value <0.001	

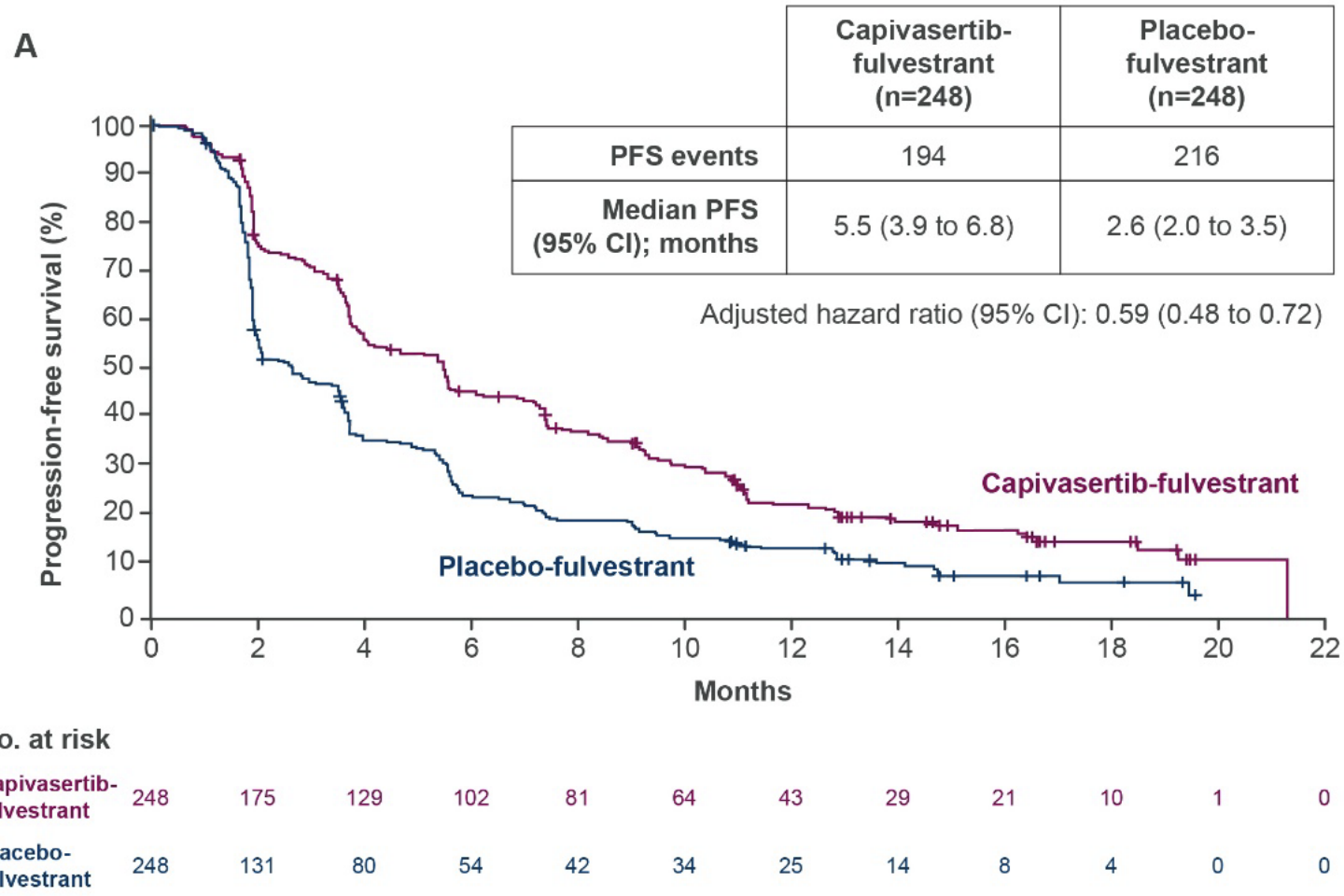


Number of patients at risk

Capivasertib + fulvestrant	155	150	127	121	99	97	80	76	65	62	54	49	38	31	26	22	21	12	12	9	3	3	2	1	1	0	0
Placebo + fulvestrant	134	124	77	64	48	47	37	35	28	27	24	20	17	14	11	6	6	2	2	2	1	1	1	0	0	0	0

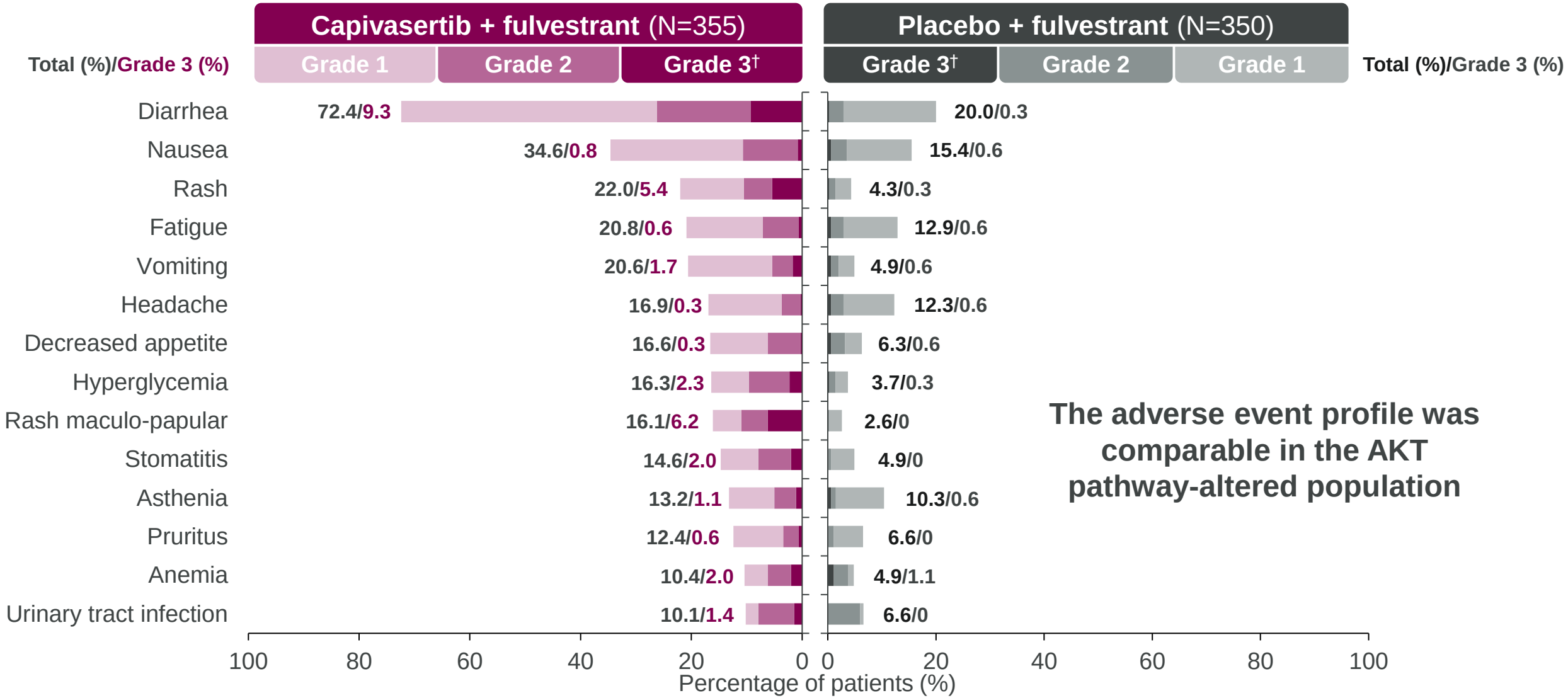
+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor.

Median PFS post-CDK4/6i remains limited



Turner et al NEJM 2022

Adverse events (>10% of patients) – overall population

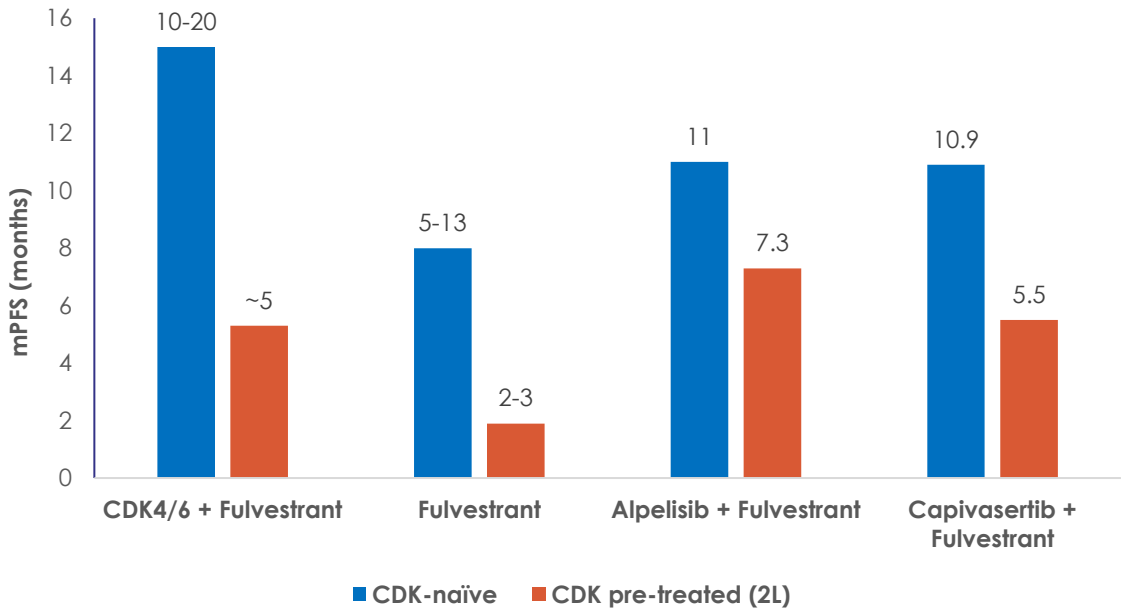


The adverse event profile was comparable in the AKT pathway-altered population

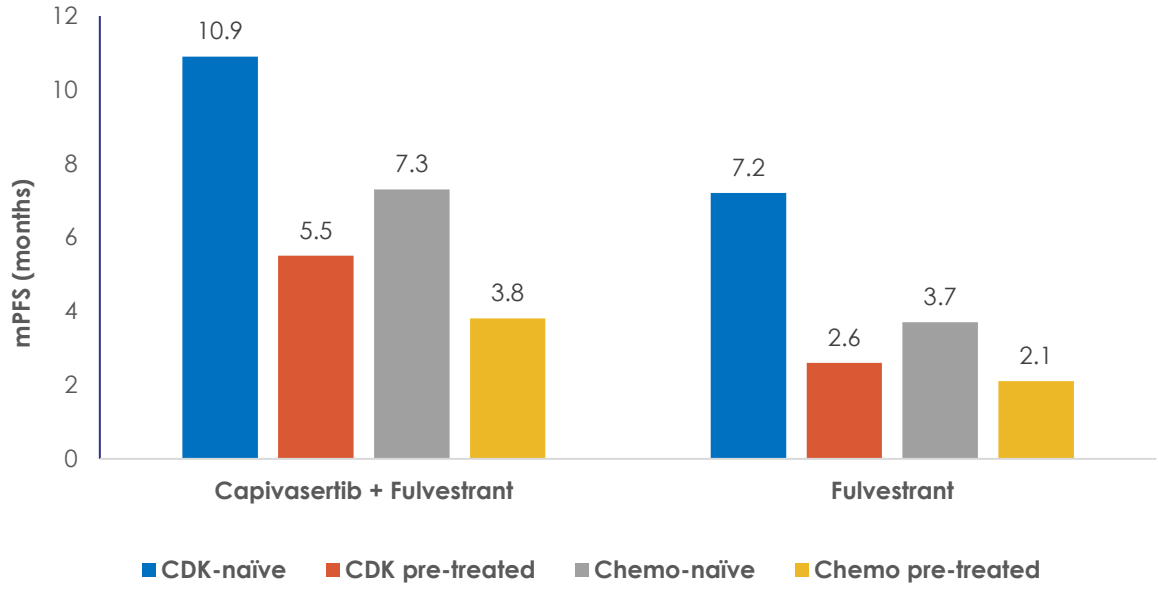
Adverse events of any grade related to rash (group term including rash, rash macular, maculo-papular rash, rash papular and rash pruritic) were reported in 38.0% of the patients in the capivasertib + fulvestrant arm (grade ≥3 in 12.1%) and in 7.1% of those in the placebo + fulvestrant group (grade ≥3 in 0.3%). †All events shown were Grade 3 except one case of Grade 4 hyperglycemia in the capivasertib + fulvestrant arm.

One Additional Prior Line of Treatment Decreases mPFS ~50% in mBC

Comparison of mPFS of SoC regimens based on prior CDK4/6 exposure



Comparison of mPFS of Fulvestrant +/- Capivasertib based on prior CDK4/6 or chemo exposure



CDK-naive trials: [2]PALOMA-3, MONALEESA-3, MONARCH-2; SOLAR-1; CAPItello-291

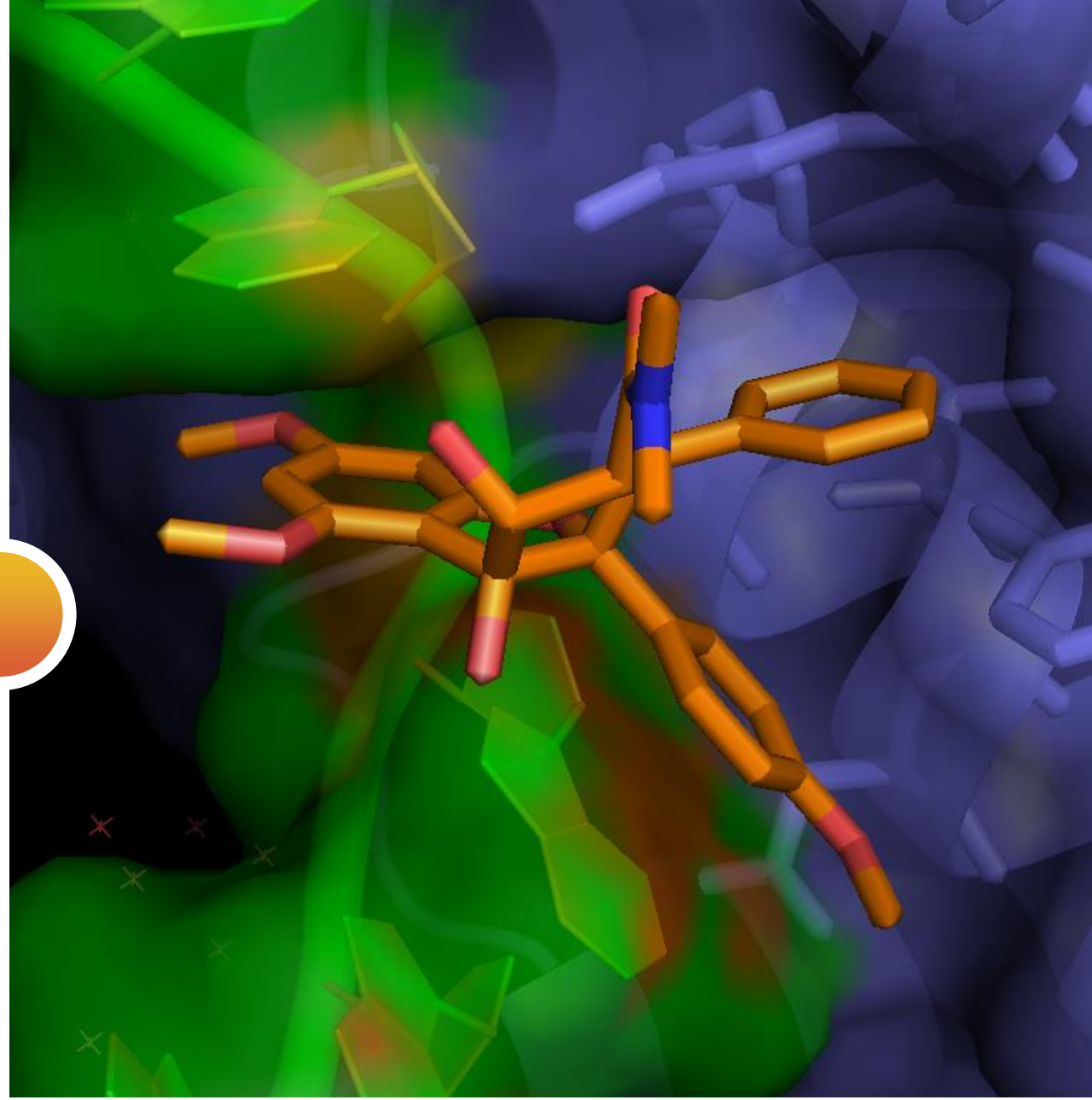
Post-CDK trials: EMERALD, VERONICA; MAINTAIN, PACE; BYLieve; CAPItello-291

Note: table is not based on head-to-head comparisons and caution should be exercised when comparing data across studies

Take Home

- **Advances in HR+/HER2- metastatic breast cancer have been made, including post-CDK4/6i**
- **Single agent elecestrant for those with durable response on CDK4/6i and *ESR1*m**
- **Fulvestrant + capivasertib approved for pts with PI3K pathway altered tumors**
- **Still significant room for improvement to increase the number of non-chemo/non-ADC containing regiments for patients with this subtype**
- **Need for agents with novel mechanisms of action/targets**

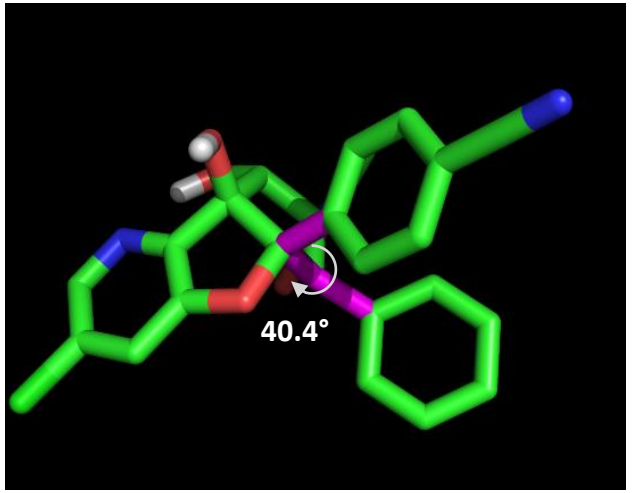
Non-Clinical Overview of Zotatifin



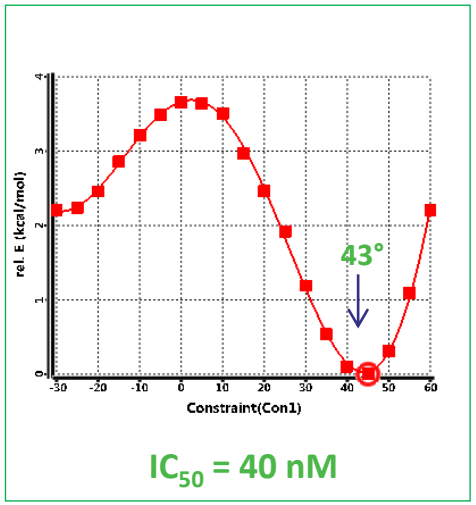
Zotatifin Executive Summary

- Highly selective inhibitor of eIF4A that blocks overproduction of cell cycle proteins and oncogenes driven by PI3K, RAS and ERα pathway signaling
  - Blocks **Cyclins D and E, CDKs 4 and 6, ERα,** KRAS, HER2 and other RTKs
  - Selectively down-regulates target proteins without broadly impacting protein translation and good tolerability at exposures efficacious in preclinical models
- Novel mechanism of action may address need to improve 2L+ treatment for ER+ breast cancer, especially for rechallenging with a CDK4/6 inhibitor
- Dose escalation and early expansion cohorts demonstrated safety, target engagement, highly selective down-regulation of target proteins and dose-dependent suppression of ctDNA
- Current focus of development is ZFA triplet (zotatifin + fulvestrant + abemaciclib) in 2nd line + ER^+ breast cancer with limited treatment options
  - Efficacy data presented at ASCO and SABCS exceeded our expectations for FA alone in late-line refractory patients
    - **26% response rate** and **7.4 month PFS**

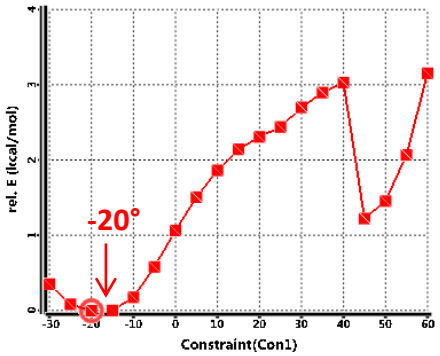
Zotatifin Discovery Driven by Deep Chemistry Knowledge



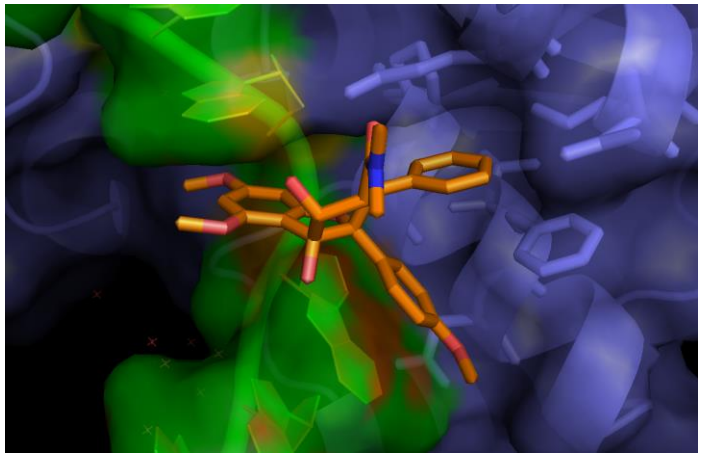
- A low energy Ar-Ar torsional angle of ~ 40° is most favored for potency in cell proliferation assay (ab initio 6-31G* DFT calculations)
  - Minimizes entropy penalty for binding
  - Unique finding not precedented in literature
- Corroborated by small molecule crystal structure
- Analysis was used to triage designs for SAR optimization



IC_{50} = 40 nM



IC_{50} >10 uM

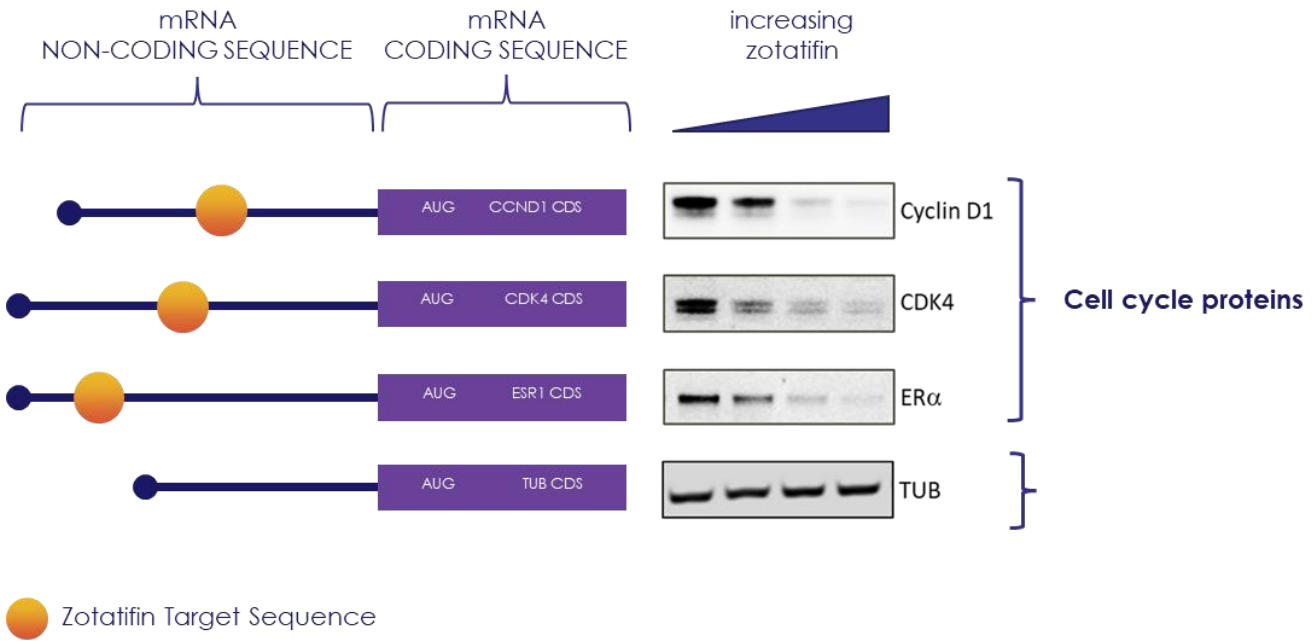


Experimental structure of natural product RocA bound to eIF4A and zotatifin RNA target sequence (Iwaski et al. Mol Cell 2019)

Ernst, Thompson et al. J Med Chem 2020

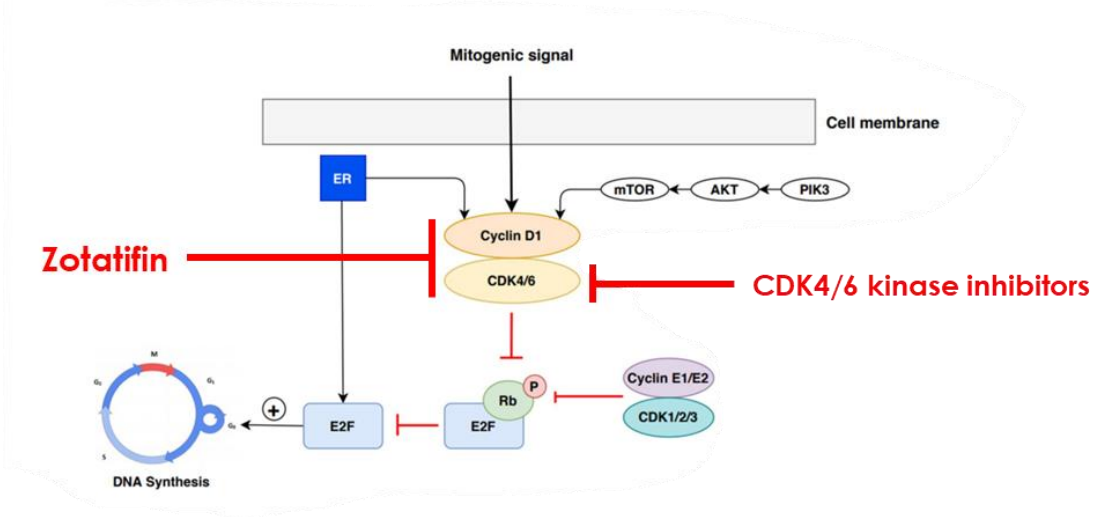
Preclinical Regulation of Translation by Zotatifin Selectively Suppressed a Specific Set of Cancer Driving Proteins

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



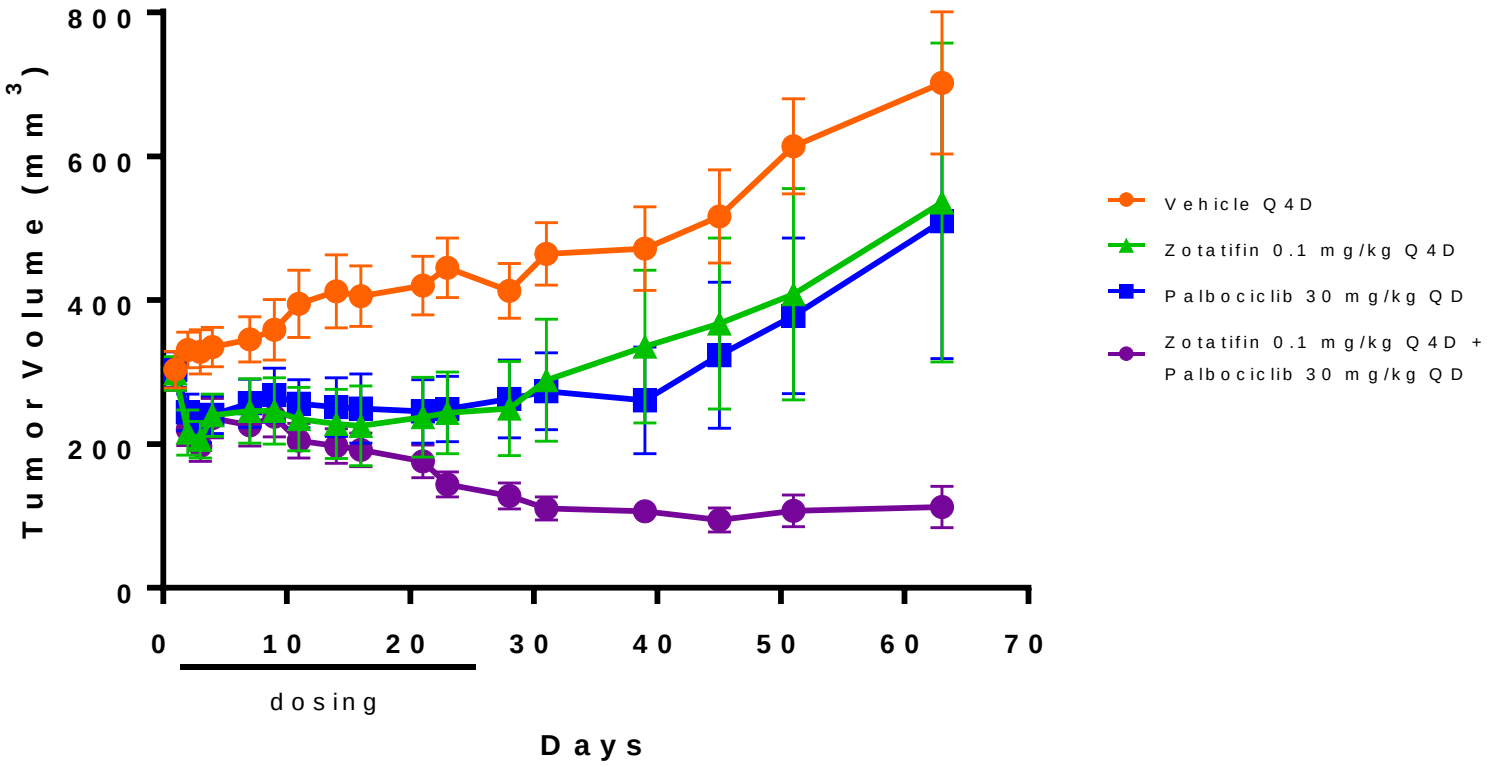
[1]Iwaski et al. 2019 Mol Cell (73) 738-748

Downregulation of Cyclin D1 and CDK 4/6 subunits by zotatifin is mechanistically distinct from kinase inhibitors

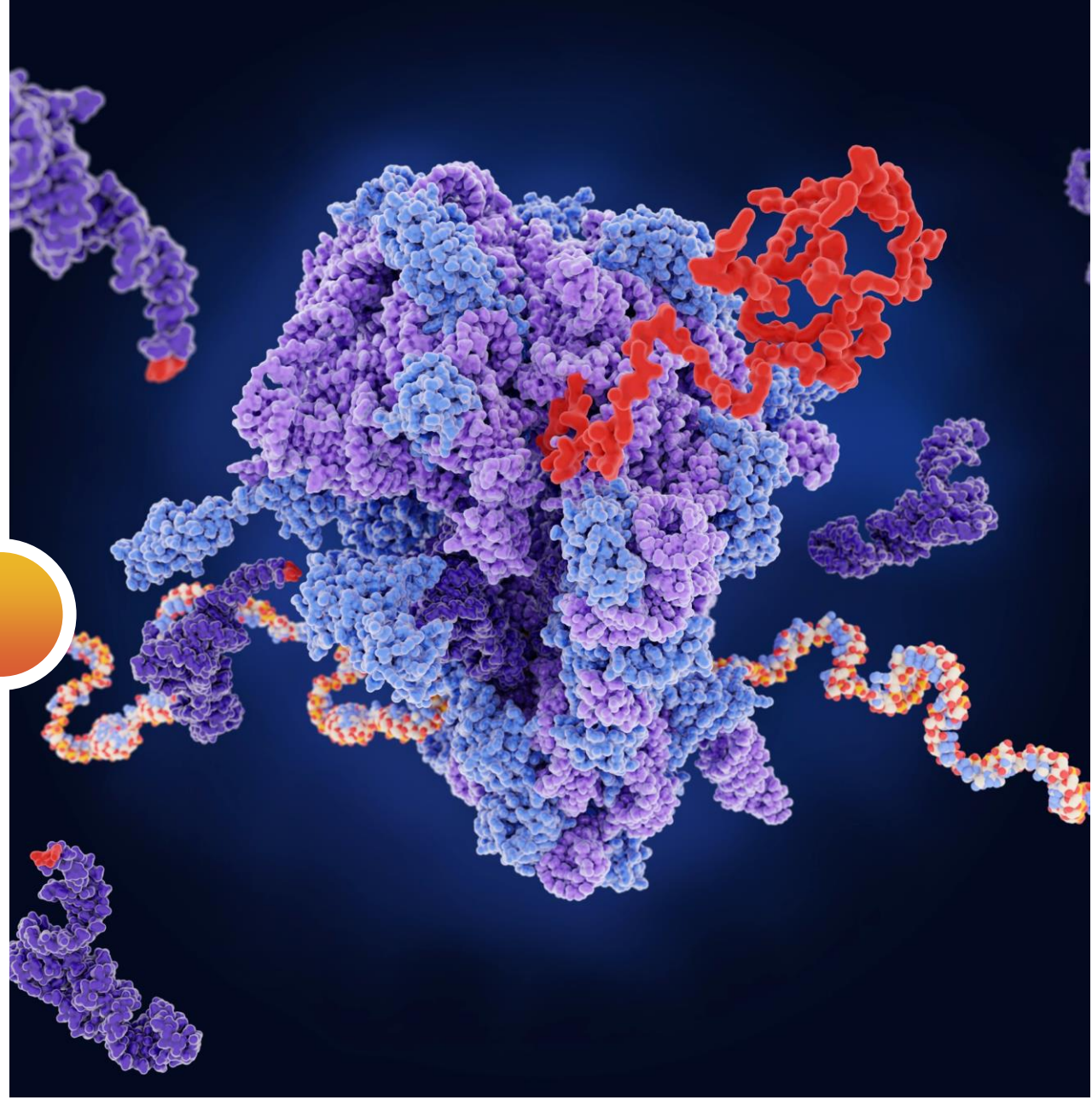


Zotatifin Downregulation of Cyclin D1 and CDK4/6 Designed To Complement CDK4/6 Inhibitors That Target Kinase Subunit

Zotatifin was active in preclinical models of ER+ BC and showed strong combination benefit with palbociclib



Clinical Overview of Zotatifin and Development Strategy in ER+ BC



eFFECTOR

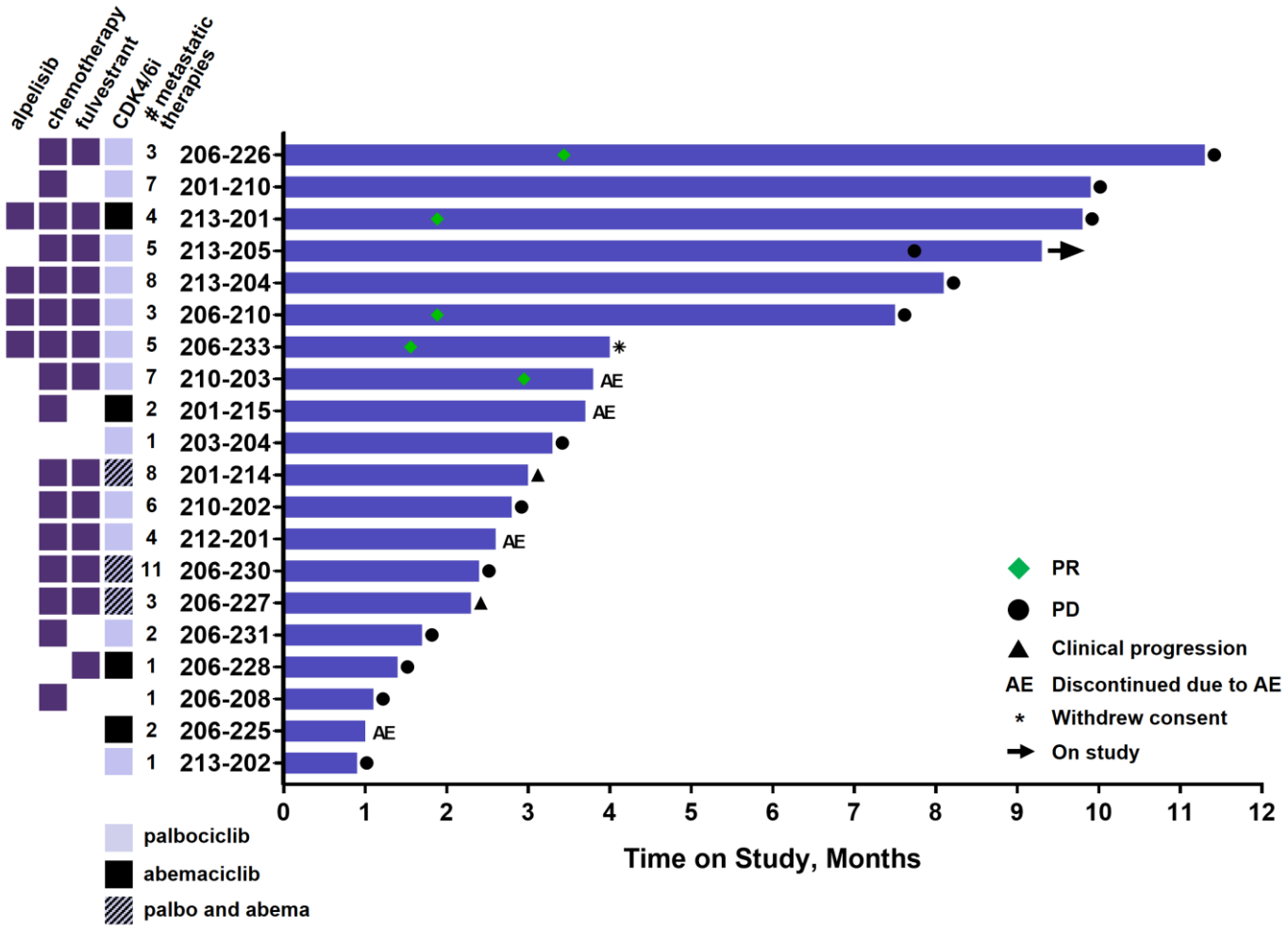
Zotatifin + Fulvestrant + Abemaciclib (ZFA) Triplet Expansion Cohort Trial Description and Patient Characteristics

- Phase 2a expansion cohort in ER+ BC in a Simon 2-stage design enrolled 20 patients
- Key eligibility criteria
  - 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
- Patients received zotatifin at 0.07 mg/kg on Days 1 and 8 of a 21-day cycle combined with fulvestrant and abemaciclib
- Primary endpoint is objective response rate per RECIST v1.1

Patient Characteristics and Prior Treatment History

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

ZFA Triplet Expansion Cohort (n=20)

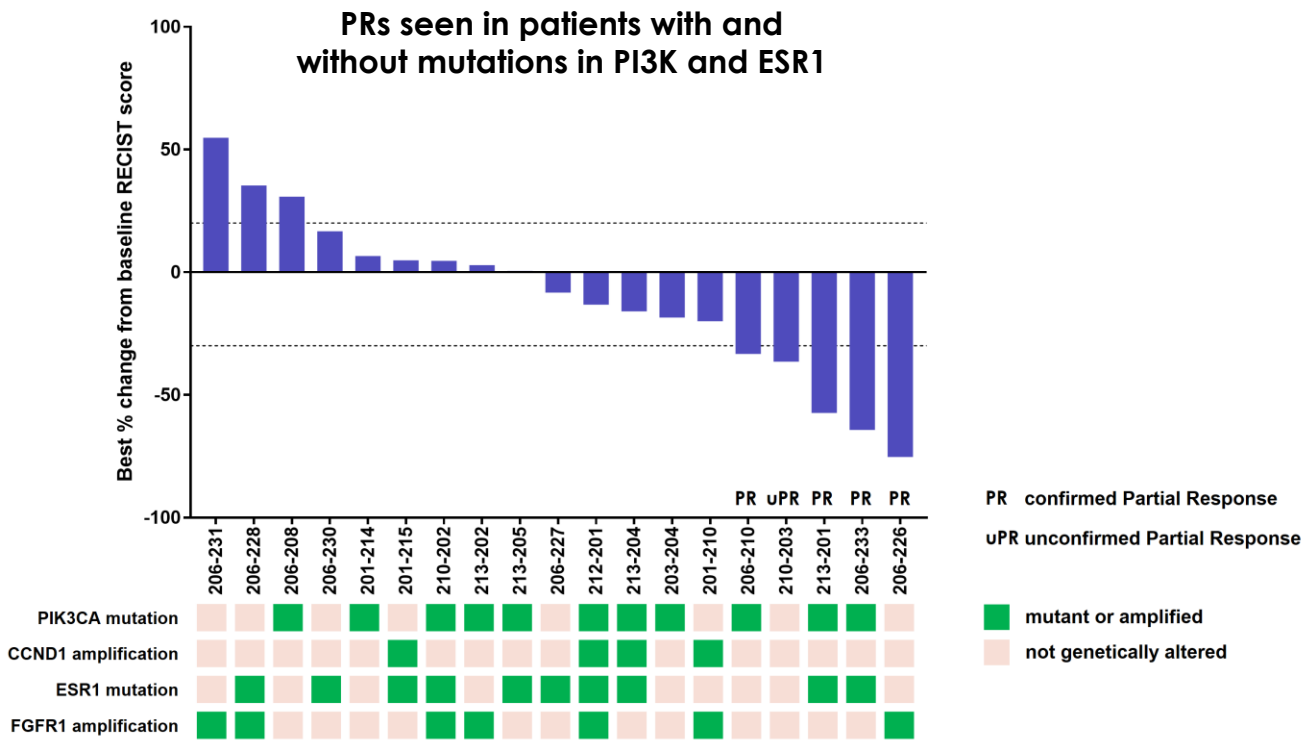


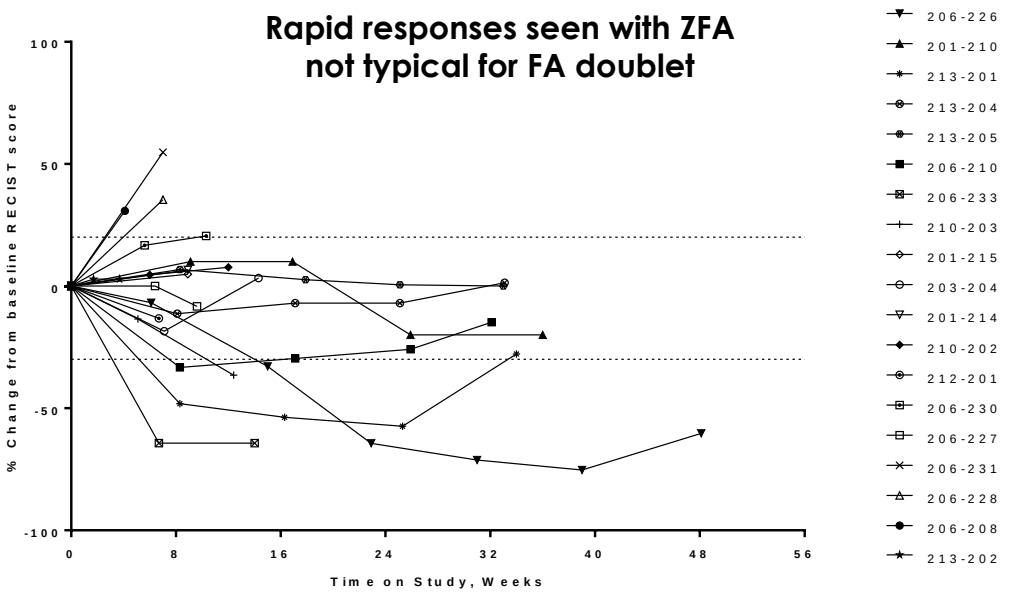
ORR, % (N)	26% (5)
DCR, % (N)	79% (15)
CBR24, % (N)	32% (6)
Median TTR, mo (range)	1.9 (1.6-3.5)
Median DOR, mo (range)	6.6 (1.7-7.7)

19 efficacy evaluable patients

Longest duration of treatment ~48 weeks

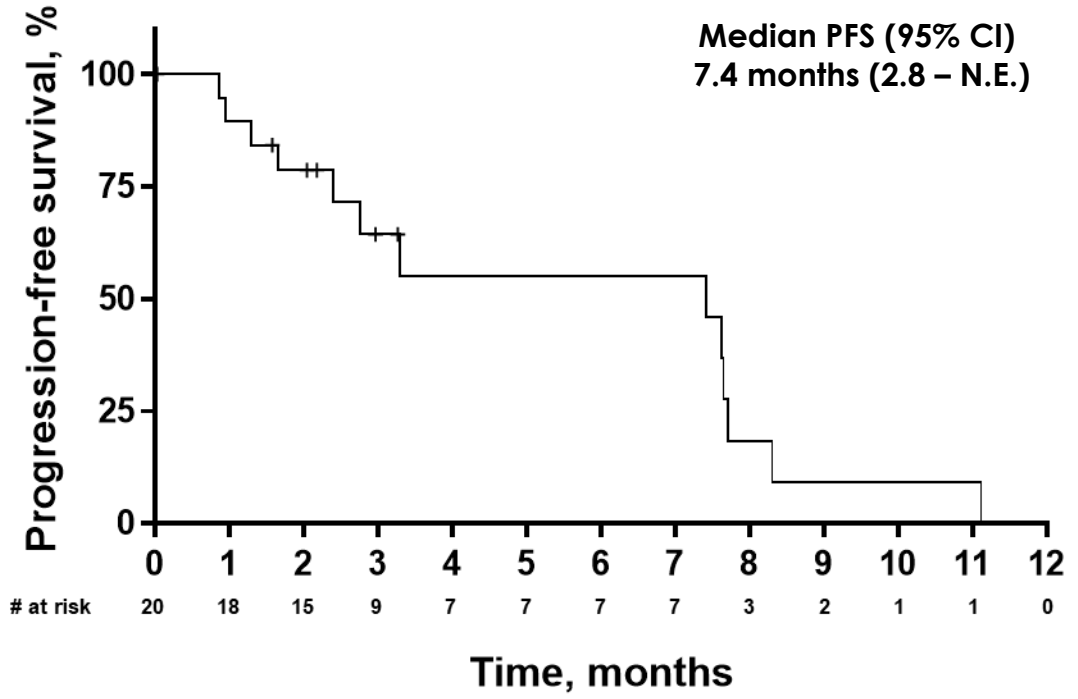
ZFA Efficacy Evaluation





Data as of 11/16/2023

ZFA Triplet Demonstrated Positive PFS Benefit



N.E., non-estimable

ZFA Details of Patients with PR or SD

Pt no	BoR	PIK3CA/ESR1 mutation/s (Y/N)	# Prior Line of Therapies for mBC*	Immediate Prior Therapy	Duration of immediate prior therapy	Time to PD on ZFA
206-226	PR	N	3	Pembro + Trodelvy	1.6 months	11.1 months
213-201	PR	Y (PIK3CA/ESR1)	4	Abema + Fulvestrant	1.5 months	9.5 months
206-210	PR	Y (PIK3CA)	3	Capecitabine	9 months	7.4 months
206-233	PR	Y (PIK3CA/ESR1)	4	Capecitabine	20.5 months	3.3 months (withdrew consent)
210-203	uPR	N	5	Gemcitabine	2.3 months	3.8 months (withdrew due to AE)
201-210	SD	N	7	Gemcitabine	3.0 months	9.9 months
213-204	SD	Y (PIK3CA/ESR1)	8	Gemcitabine	1.6 months	7.7 months
213-205	SD	Y (PIK3CA/ESR1)	5	Gemcitabine	1.2 months	7.6 months

*All patients had previously received CDK4/6i and chemo for mBC; all patients except 201-210 also received prior fulvestrant

ZFA Regimen Does As Well or Better Than Switching Both ET and CDK4/6i in MAINTAIN

		EFTR	MAINTAIN[1]	
		ZFA triplet CDK/F exposed n=19	Switch ET mono CDK exposed n=59	R + Switch ET CDK exposed n=60
Median prior lines		4	NR	NR
Prior therapies in metastatic setting	CDK4/6i	95%	100%	100%
	Fulvestrant	65%	0%	0%
	Chemo	75%	12%	7%
mPFS months		7.4	2.8	5.3
ORR (%)		26	11*	20*
CBR (%)		32#	25	43#

*excludes ~40% of pts without measurable disease

#excludes 1 pt (5%) from ZFA and 11 pts (18%) from MAINTAIN

Z = zotatifin, F = fulvestrant, A = abemaciclib, R = ribociclib, [1]Kalinsky et al., JCO 2023;
MAINTAIN Trial Design: All patients switched ET (83% switched from F) and of patients randomized to also receive R, it was a CDKi switch for 87% of patients

*Company estimate based on review of historical data for fulvestrant and abemaciclib.
DISCLAIMER: Differences exist between trial designs and subject characteristics, and caution should be exercised when comparing data across trials. No head-to-head clinical study has been conducted comparing Zotatifin to any other product or candidate.
Zotatifin interim data as of May 3, 2023 cut-off. Prior therapies presented for enrolled patients (n=20), responses for RECIST-evaluable patients (n=19).

ZFA 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)

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.

Q2W Dose Escalation Cohorts

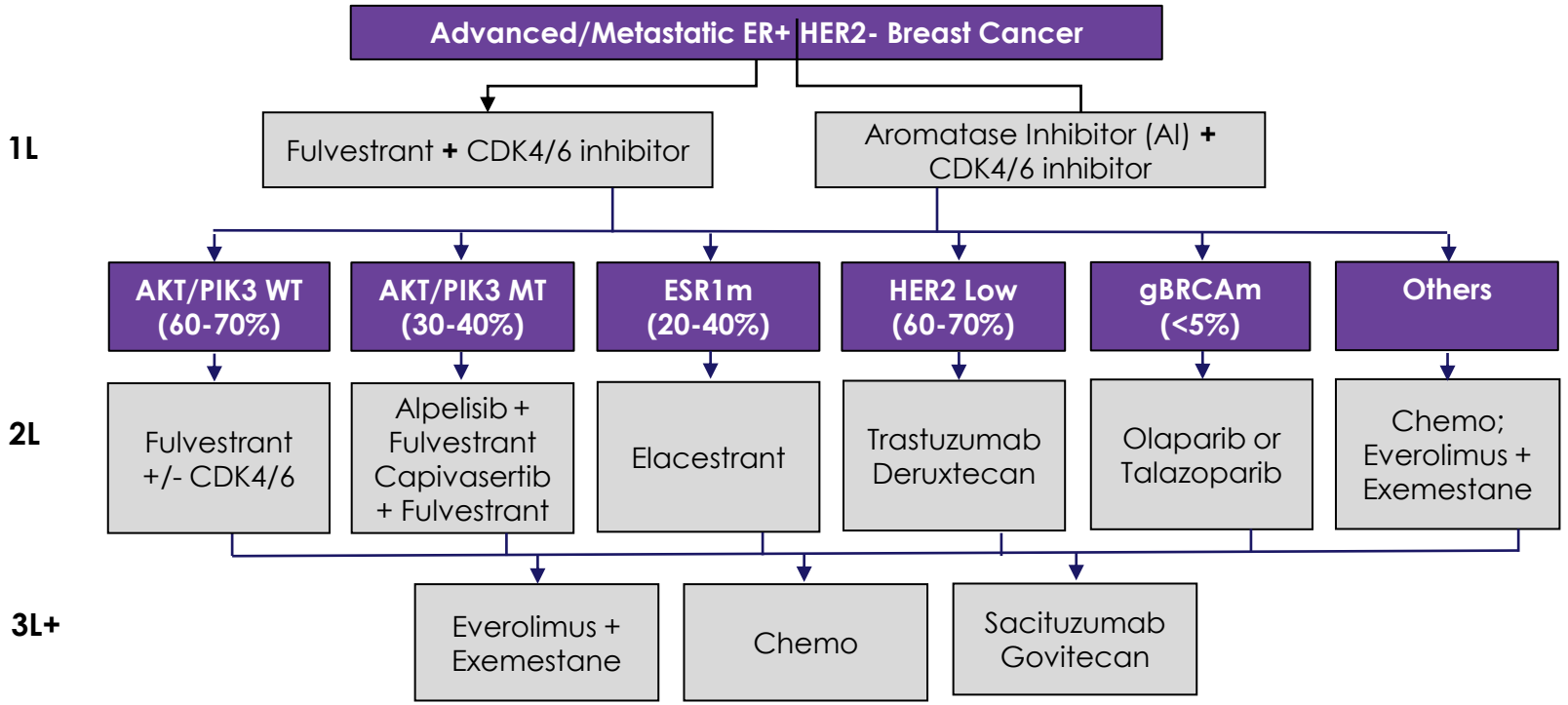
- Resumed dose escalation with Q2W dose schedule
- ZF doublet cohorts of 0.1, 0.14, and 0.2 mg/kg Q2W
  - No DLTs observed
  - PR in patient at 0.1 mg/kg Q2W dose
- ZFA triplet initiated at 0.1 mg/kg Q2W

Zotatifin Clinical Overview and Development Plan

- Zotatifin has shown compelling efficacy in highly refractory ER+ metastatic breast cancer population (median 4 prior lines of tx) in ZFA triplet
- Robust clinical safety seen across multiple cohorts
- Strong KOL feedback on high unmet need following first line CDK 4/6i and desire to retreat with CDK 4/6i
- Development plans include:
  - Finalization of dose and schedule in H1 2024
  - Evaluate ZFA triplet in randomized trial
    - Use FTD mechanism to align development strategy with FDA
    - POSTMonarch effect size will help inform study size

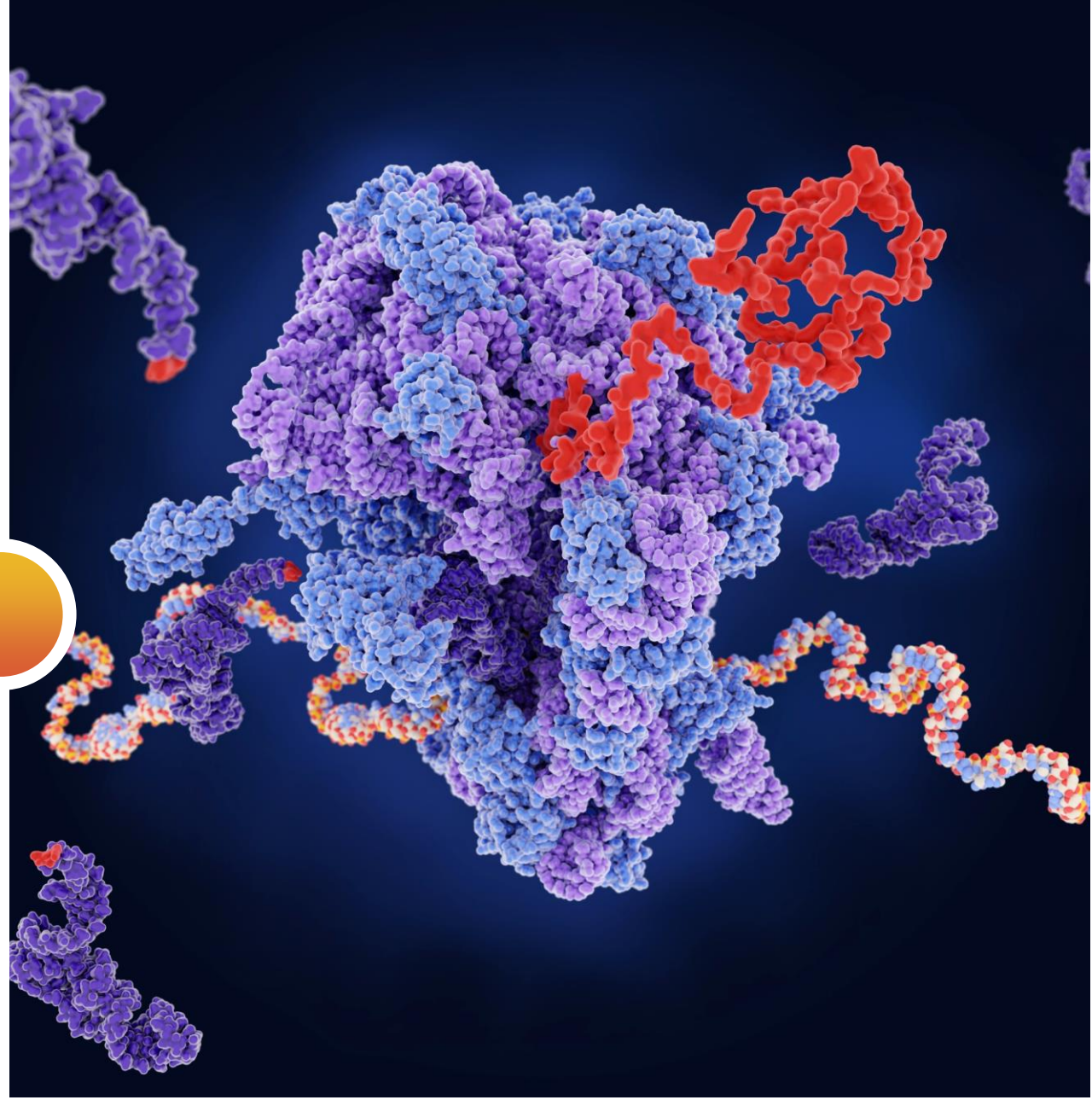
Zotatifin Product Development Strategy in ER+ Breast Cancer

- Seeking to establish zotatifin as a backbone of therapy in 2nd line plus ER+ BC
- **ZFA triplet**, intended to capitalize on synergy with CDK 4/6i, could treat a **broad, unrestricted population**
- Alternative regimens, e.g. combined with a SERD, PI3Ki or AKTi, could address specific resistant populations



HER2-low defined as HER2 IHC 1+ or IHC 2+/ISH-; gBRCAm = germline BRCA mutant, SERM = selective estrogen receptor modulators, SERD = selective estrogen receptor degrader

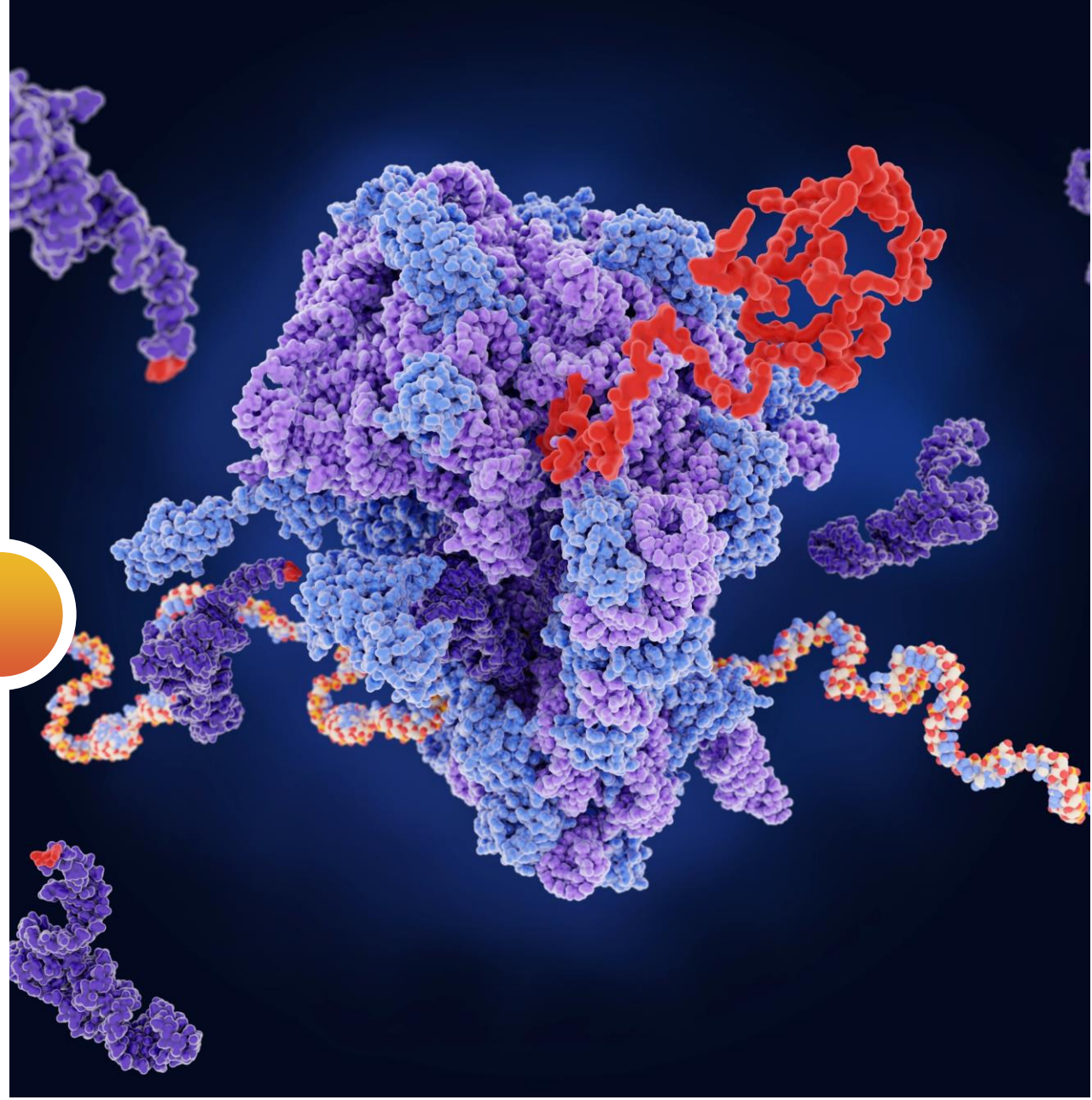
External Collaborations



Investigator Sponsored Trials

- **Stanford IST:** An umbrella, randomized pre-operative trial testing integrative subtype-targeted therapeutics in ER+/HER2- breast cancer (BC)
  - Genomic data used to identify "integrative clusters" in BC that predict higher risk of relapse
  - Zotatifin is evaluated in two high risk integrative clusters (amplifications of cyclin D1 and FGF3 or FGFR1) and in standard risk cohort
  - Patients randomized to receive one dose of zotatifin + fulvestrant or fulvestrant alone before surgery
    - Primary objective: assess change in tumor proliferative as measured by Ki67
- **Northwestern IST:** Phase 1 dose escalation study of tomivosertib in relapsed or refractory Acute Myeloid Leukemia
  - Trial designed to capitalize on previously published results that showed preclinical activity of tomivosertib in AML models
  - Once appropriate dose of tomivosertib is identified, plan to expand trial to test combination of tomivosertib with venetoclax and azacytidine

Closing Remarks



Multiple Upcoming Clinical Milestones

Anticipated Milestones		2024		2025	
		1H	2H	1H	2H
Tomivosertib	Top line data from P2b NSCLC frontline with pembro	●			
	Complete activities to enable registration trial(s)		●		
	Initiation of registration trial(s)				●
Zotatifin	Further data from dose escalation cohorts	●			
	Initiation of randomized trial(s)				●

Q&A