



celcuity

EXPANDING TREATMENT OPTIONS

## **Celcuity Science Day**

**Unlocking the Potential of Treating Cancers with  
PI3K/mTOR Involved Signaling**

**September 21, 2023**

# Forward-Looking Statements

This presentation contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 relating to our business, operations, and financial condition. Forward-looking statements include but are not limited to statements based on current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our preclinical and clinical results and expected timing thereof, our plans to develop and commercialize gedatolisib, our first internally developed drug candidate, and the anticipated market opportunity at that time, our plans to research, discover and develop additional product candidates, our planned milestones and timing of achieving such milestones, the scope, protocol, and costs of our clinical development program and upcoming clinical trials for gedatolisib, including but not limited to our VIKTORIA-1 Phase 3 clinical trial and our Phase 1b/2 CELC-G-201 clinical trial, the expected results of VIKTORIA-1 and CELC-G-201, including but not limited to the anticipated efficacy of gedatolisib in combination with fulvestrant and with or without palbociclib, the anticipated efficacy of gedatolisib in combination with darolutamide, the expected timing of funding of tranches under the Company’s debt financing facility, any potential benefits resulting from Breakthrough Therapy designation for gedatolisib, and other expectations with respect to Celcuity’s lead product candidate, gedatolisib, our beliefs related to the perceived advantages of our CELsignia tests compared to traditional molecular or other diagnostic tests and its CELsignia platform. Words such as, but not limited to, “may,” “will,” “would,” “should,” “could,” “look forward to,” “believe,” “predict,” “expect,” “anticipate,” “intend,” “continue,” “ongoing,” “target,” “goal,” “plan,” “potential,” or “estimate,” and similar expressions or words, identify forward-looking statements.

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# Celcuity Leadership Team and External Speakers Participating Today

## Celcuity Participants



**Brian Sullivan**  
Chief Executive Officer  
Co-Founder



**Lance Laing, PhD**  
Chief Scientific Officer  
Co-Founder



**Igor Gorbachevsky, MD**  
Chief Medical Officer

## External Key Opinion Leaders



**Sara Hurvitz, MD**  
Professor of Medicine  
Head, Division of Hematology & Oncology  
Sr. Vice President, UW Medicine,  
Fred Hutch Cancer Center



**Karim Fizazi, MD, PhD**  
Professor of Medicine  
GETUG President  
Head, GU Group,  
Institute Gustav Roussy  
University of Paris Saclay

# Agenda

Topic	Session	Presenter
	Overview of Gedatolisib's Potential	Brian Sullivan
Scientific Overview	Importance of PI3K/mTOR as an Anti-Cancer Target	Lance Laing, PhD
	Gedatolisib Differentiation – Nonclinical	Lance Laing, PhD
	Gedatolisib PK and Safety Overview	Igor Gorbachevsky, MD
Prostate Cancer	KOL Presentation: 2L SOC and PI3K/mTOR in Prostate Cancer	Karim Fizazi, MD, PhD
	Gedatolisib for Prostate Cancer	Igor Gorbachevsky, MD
Breast Cancer	KOL Presentation: SOC and Future Landscape in HR+/HER2- ABC	Sara Hurvitz, MD
	Gedatolisib for Breast Cancer	Igor Gorbachevsky, MD
	Wrap-up	
	Q&A	Brian Sullivan

# Introduction and Overview

**Brian Sullivan**

CEO and Co-Founder

# Focused on Treating Cancers Involving the PI3K/mTOR Pathway

## One of the most important oncogenic pathways

### PI3K/mTOR (PAM) regulates key metabolic functions

- Plays a key role promoting tumor cell proliferation
- Cross-regulates other oncogenic pathways
- Affects immune response by regulating tumor microenvironment

## Most highly altered of all signaling pathways<sup>1</sup>

### Proportion of alterations correlates to pathway's role as a cancer driver

<b>PI3K/mTOR</b>	<b>38%</b>
RAS	15%
HER2	8%
EGFR	5%

## Largest untapped drug development opportunity in solid tumors

### Breast and prostate cancers involve PAM pathway

- **>500,000** addressable patient population in US, 5EU, and Japan
- Nominal penetration of PAM drugs in these markets

(1) cBioPortal References: Cerami et al., Cancer Discov. 2012, and Gao et al., Sci. Signal, 2013;



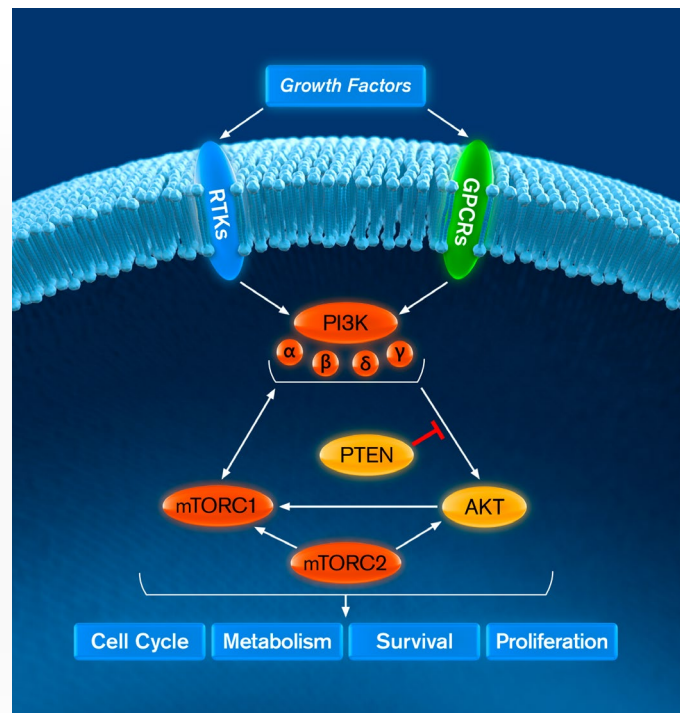
# Difficult to Safely and Efficaciously Inhibit PI3K/mTOR

Maximum efficacy requires inhibition of all Class I PI3K isoforms and mTORC1 and mTORC2

## Multiple pathway components must be targeted

Feedforward and feedback loops between PI3K isoforms, AKT, and mTOR cross-activates uninhibited sub-units

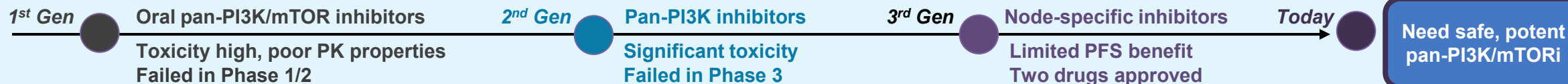
Induces compensatory resistance that reduces efficacy



## Therapeutic window for oral PI3K/mTOR inhibitors is narrow

Difficult to optimize pathway inhibition without inducing undue toxicity

Orally administered pan-PI3K or pan-PI3K/mTOR inhibitors induced unacceptable toxicity



# Gedatolisib is a Potential First-in-Class PI3K/mTOR Inhibitor

Breakthrough Therapy Designation granted for 2L HR+/HER2- advanced breast cancer indication

## Highly Differentiated Mechanism

- Inhibits all PI3K/mTOR nodes at **low or sub-nanomolar** concentrations
- **More potent & cytotoxic** than other PAM inhibitors being developed for breast or prostate cancer

## Compelling Efficacy

- Gedatolisib + ET + CDK4/6 in HR+/HER2- ABC patients
- **79% ORR, 48.6 months mPFS** in 1L patients<sup>1</sup>
- **63% ORR, 12.9 months mPFS** in 2L patients<sup>2</sup>

## Well-Tolerated

- Nominal Grade 3, no Gr 4 TEAE's as a single agent
- **Only 4% treatment discontinuation** due to AE with Phase 3 dosing in combination with palbociclib and fulvestrant<sup>2</sup>

## Addressing Large Patient Populations

- **Breast Cancer:** Enrolling Phase 3 trial for 2L patients with HR+/HER2- ABC
- **Prostate Cancer:** Phase 1b/2 trial for 2L patients with mCRPC in Q1 '24
- **211,000 1L/2L patients** in US, 5EU, Japan<sup>3</sup>



# Current Clinical Development Programs

## 2<sup>nd</sup> Line HR+/HER2- Advanced Breast Cancer (ABC)

Pivotal Phase 3 clinical trial for gedatolisib with fulvestrant +/- palbociclib is enrolling

- Enrolling patients with **HR+/HER2- advanced breast cancer** who progressed on CDK4/6 therapy
- Breakthrough Therapy Designation for this indication
- Expect to report top-line primary analysis data for:
  - PIK3CA WT patients in 2H 2024
  - PIK3CA MT patients in 1H 2025

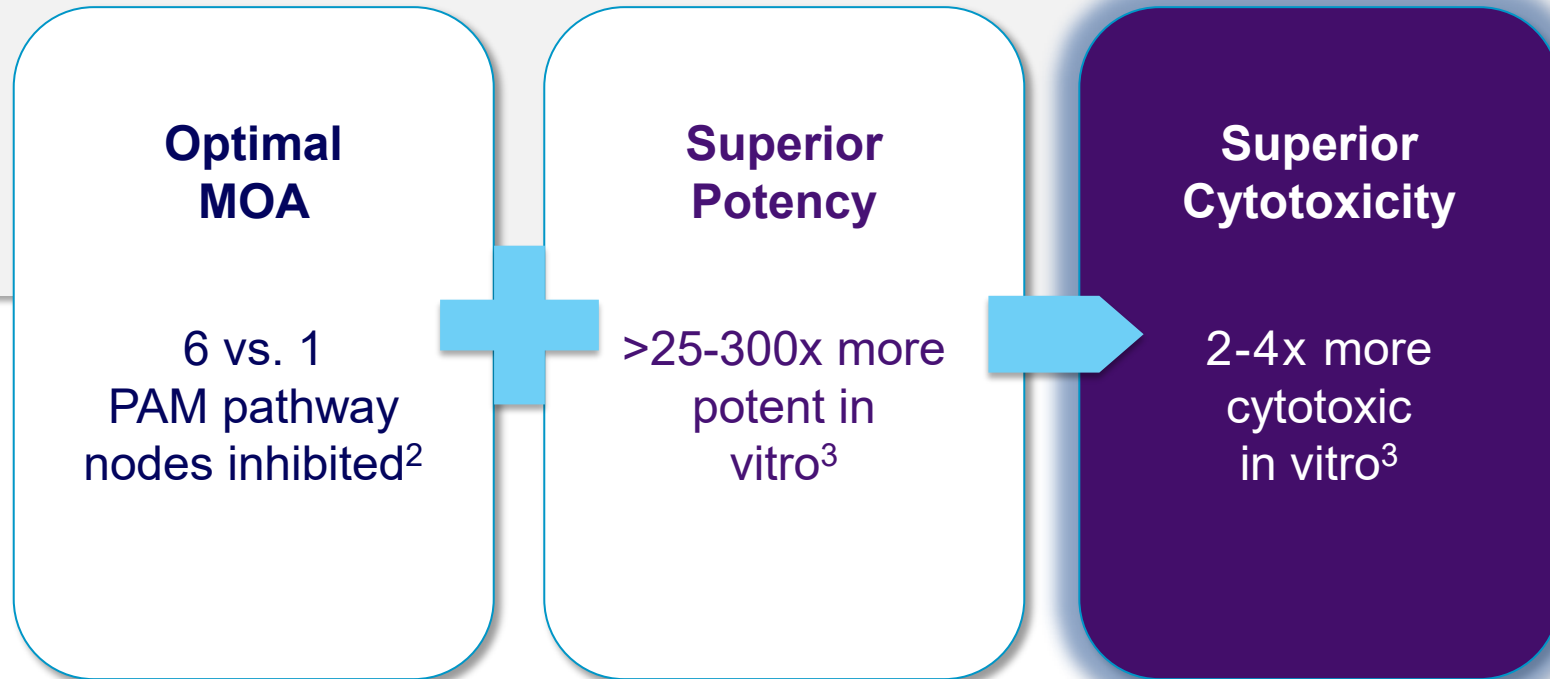
## 2<sup>nd</sup> Line Metastatic Castration Resistant Prostate Cancer (mCRPC)

Phase 1b/2 clinical trial for gedatolisib with darolutamide

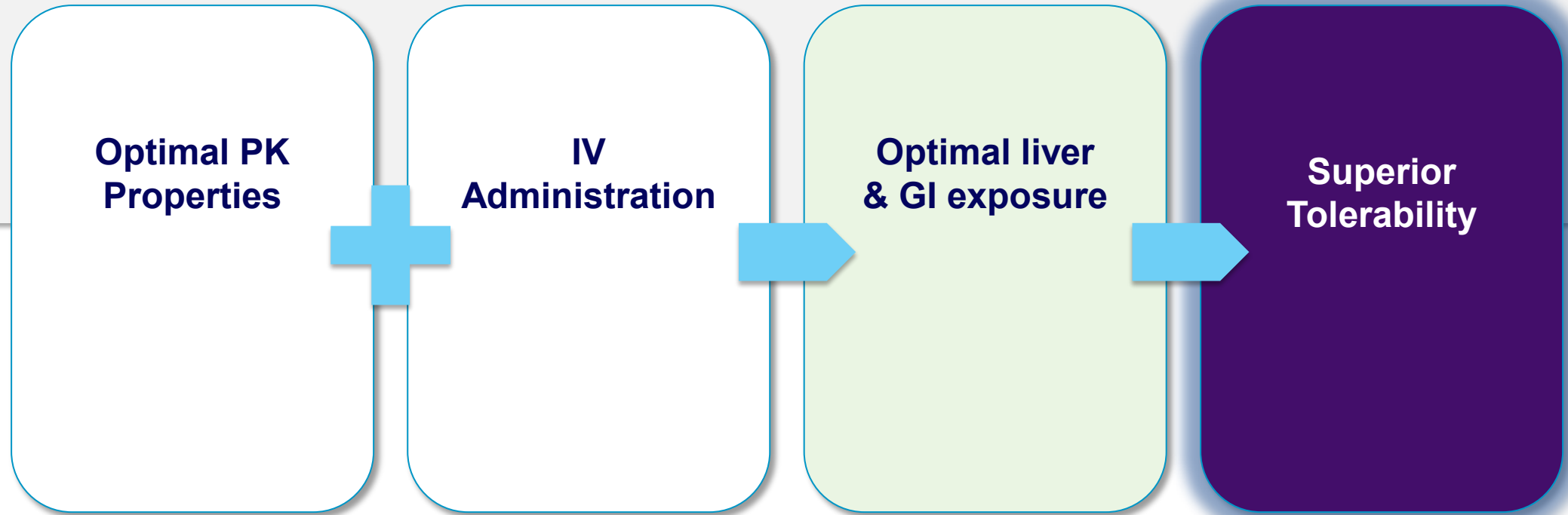
- Will enroll patients with who progressed on androgen receptor (AR) therapy
- Entered into Clinical Trial Collaboration Agreement with Bayer to provide darolutamide for Phase 1b/2 study
- Expect to enroll first patient in Q1 '24
- Expect to report initial data in 1H '25

# Mechanism of Action (MOA) & Potency Induce Superior Cytotoxicity

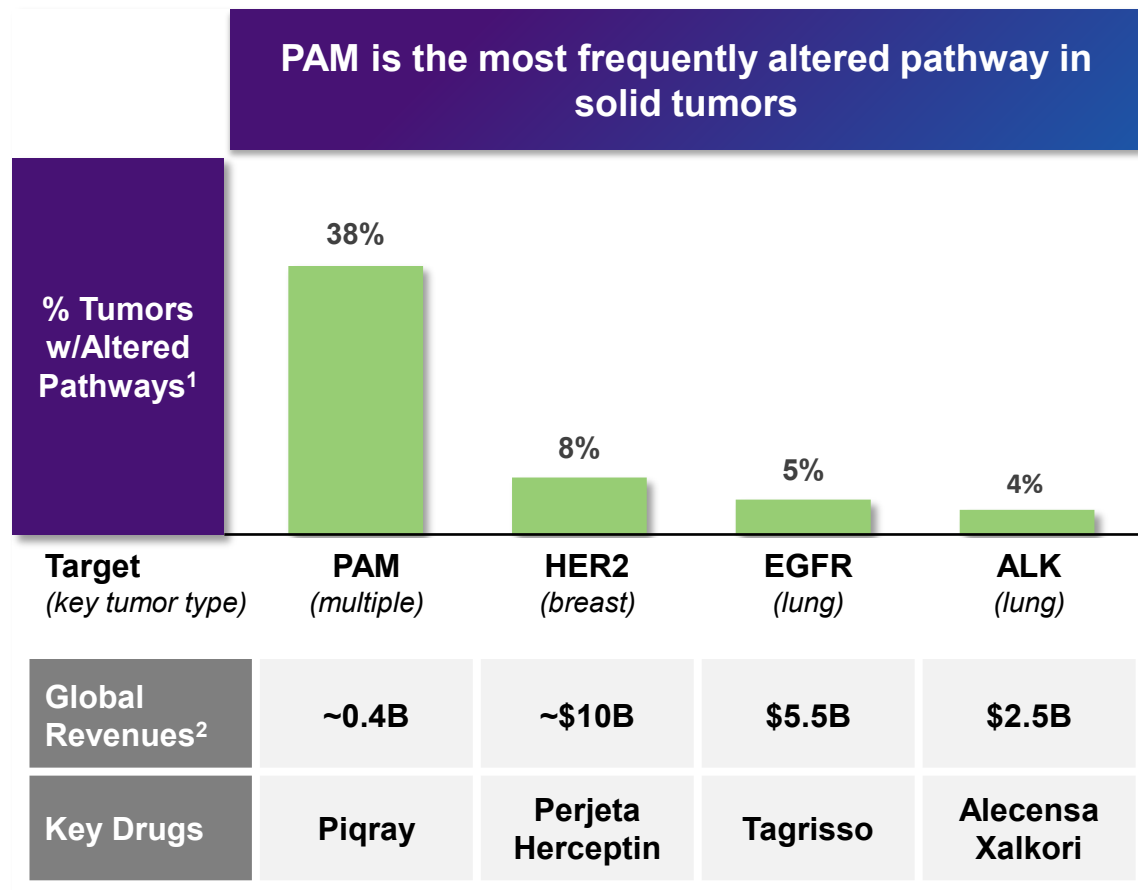
Gedatolisib vs. approved PAM inhibitors assessed in 34 breast and prostate cancer cell lines<sup>1</sup>



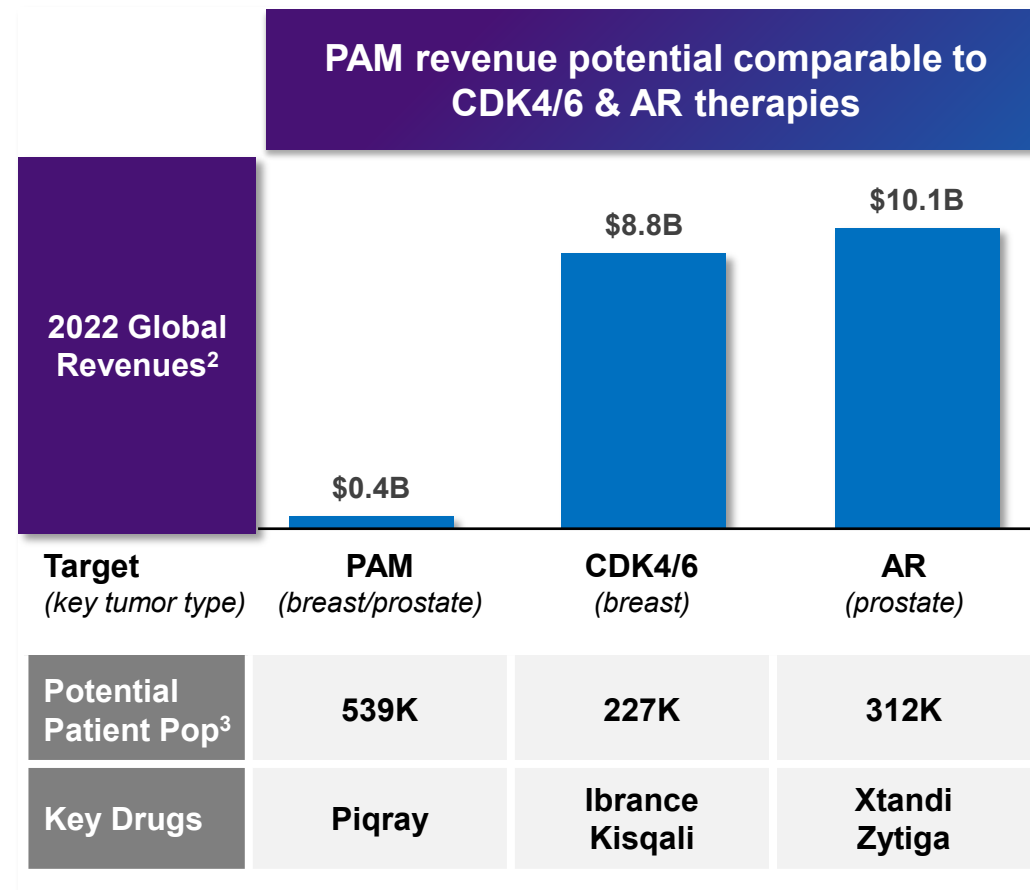
# Gedatolisib Is Well Tolerated - Unlike Earlier PI3K/mTOR or Pan-PI3K Inhibitors



# The PAM Pathway is the Most Underdeveloped Target in Solid Tumors

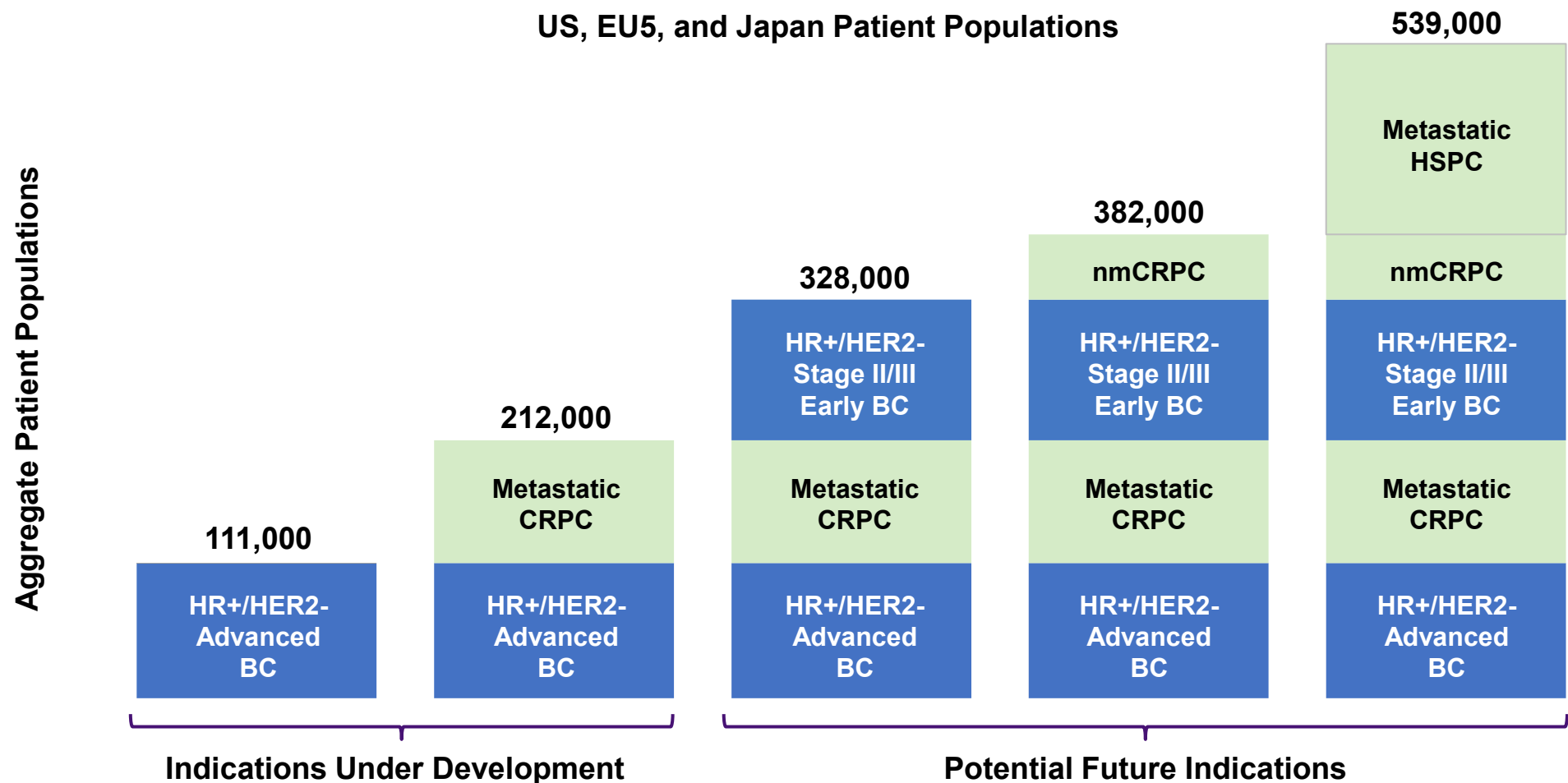


Drug revenues from PAM inhibitors are a small fraction of other targeted therapy classes

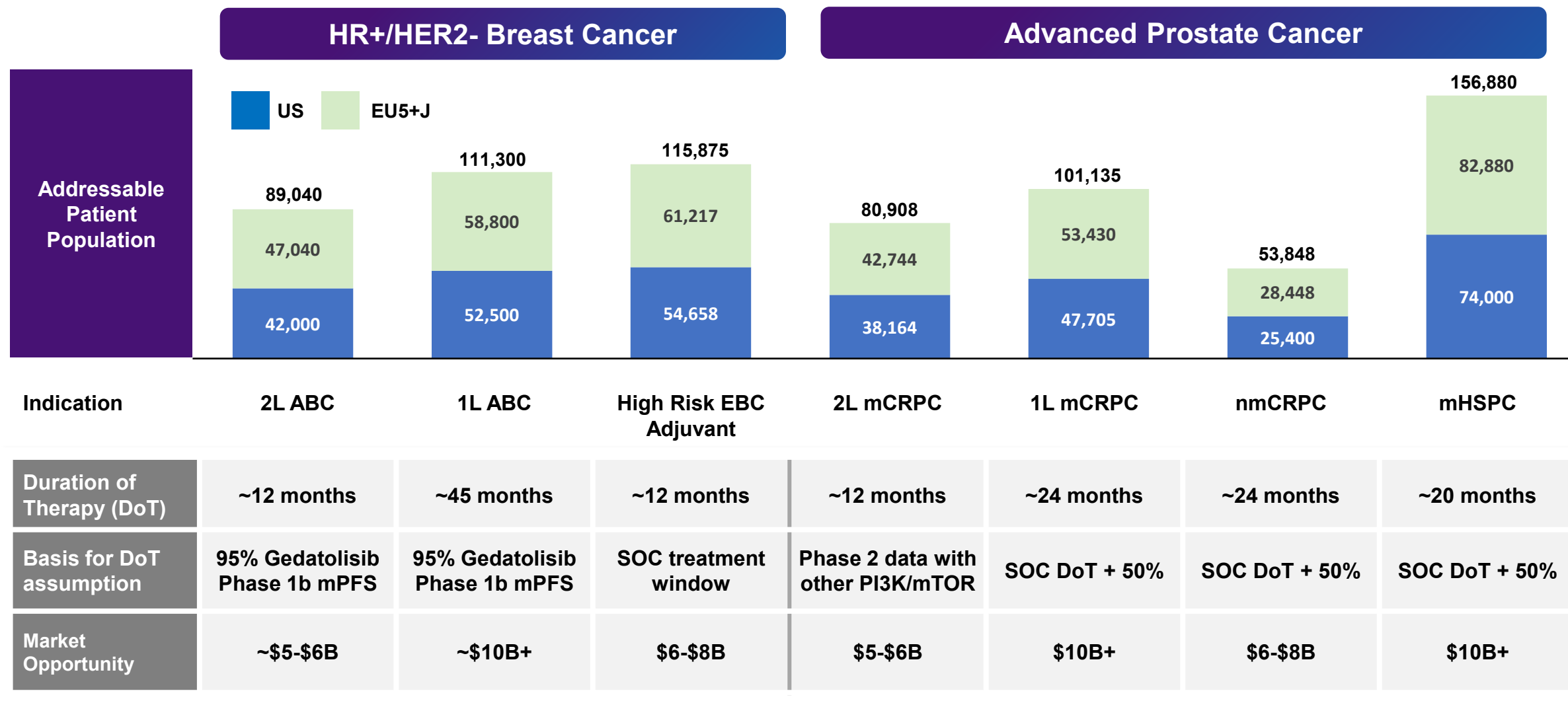


PAM potential patient population is not tumor specific like CDK4/6 or AR inhibitors

# Addressable Patient Population in Breast and Prostate Cancer



# Multiple potential blockbuster indications in both tumor types





# Key Themes for Today's Meeting

Significant untapped potential to effectively treat PAM pathway involved cancers

1

- The PAM pathway is one of the most important, yet underdeveloped, targets in cancer

2

- Gedatolisib's differentiated MOA and PK profile result in a highly potent and cytotoxic PAM inhibitor

3

- **Very compelling data in 1L and 2L patients with HR+/HER2- ABC**
- Gedatolisib combined with CDK4/6i + hormonal therapy has potential to replace currently available standard-of-care

4

- **Uniquely positioned to advance multiple potential blockbuster indications in breast and prostate cancer**
- Cash & cash equivalents of \$146M at end of Q2 '23 expected to fund operations through data readouts in ABC and mCRPC

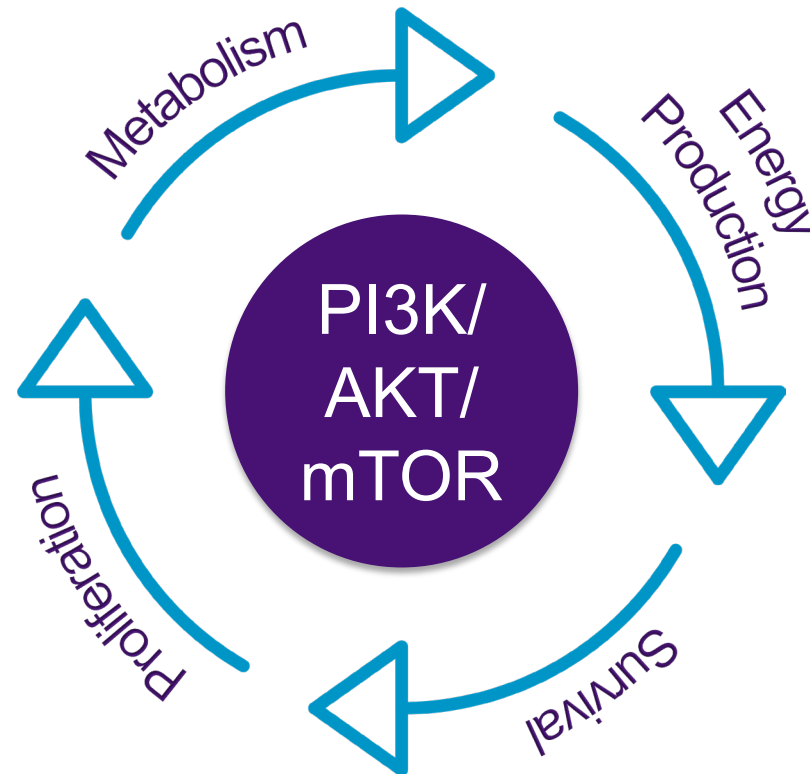
# The Importance of the PI3K/mTOR Pathway as a Cancer Driver

**Lance Laing, PhD**  
Chief Science Officer and Co-Founder

# The PAM Pathway Regulates Critical Cell Functions

PAM – PI3K/AKT/mTOR pathway

**PAM is a “command and control” center of critical cellular processes.**

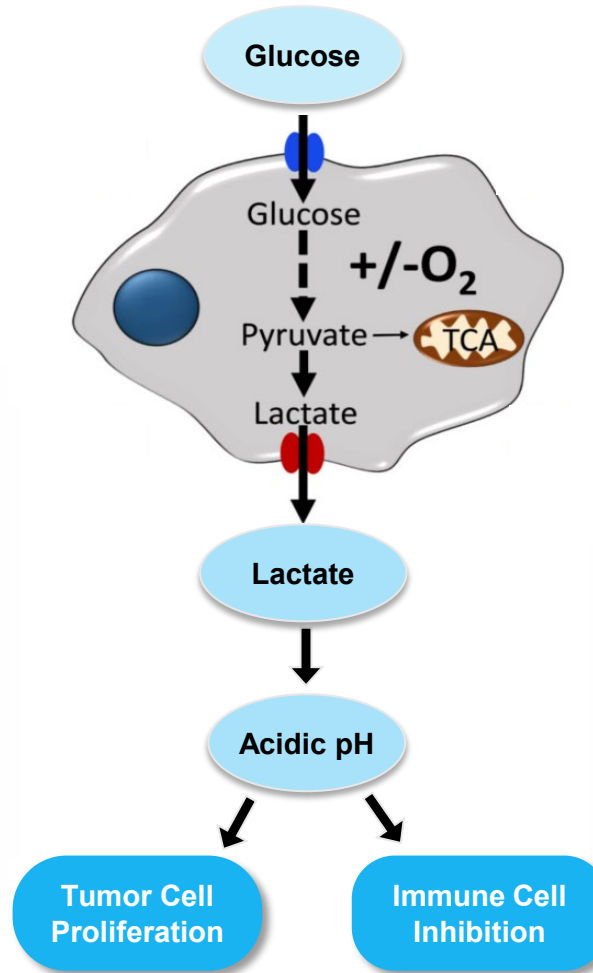


# Tumors Rely on Metabolic Changes Controlled by PAM Pathway

Activity controlled by the PAM pathway creates a pro-tumor microenvironment

Tumor cells require tremendous amounts of glucose relative to normal cells

- **High glucose consumption causes excess** extracellular lactate, low pH, and low oxygen
- Creates a tumor microenvironment **that can promote** tumor cell proliferation and inhibit normal immune cell function



The PAM pathway regulates glucose consumption, which makes it a fundamental tumor driver

- PAM's role as regulator of glucose consumption cells is a feature of all tumor types
- Makes PAM a therapeutic target regardless of a tumor's mutational status

# PAM has Multiple Signaling Nodes that Provide Functional Redundancy

Redundancy ensures pathway function is maintained if a single node becomes disrupted

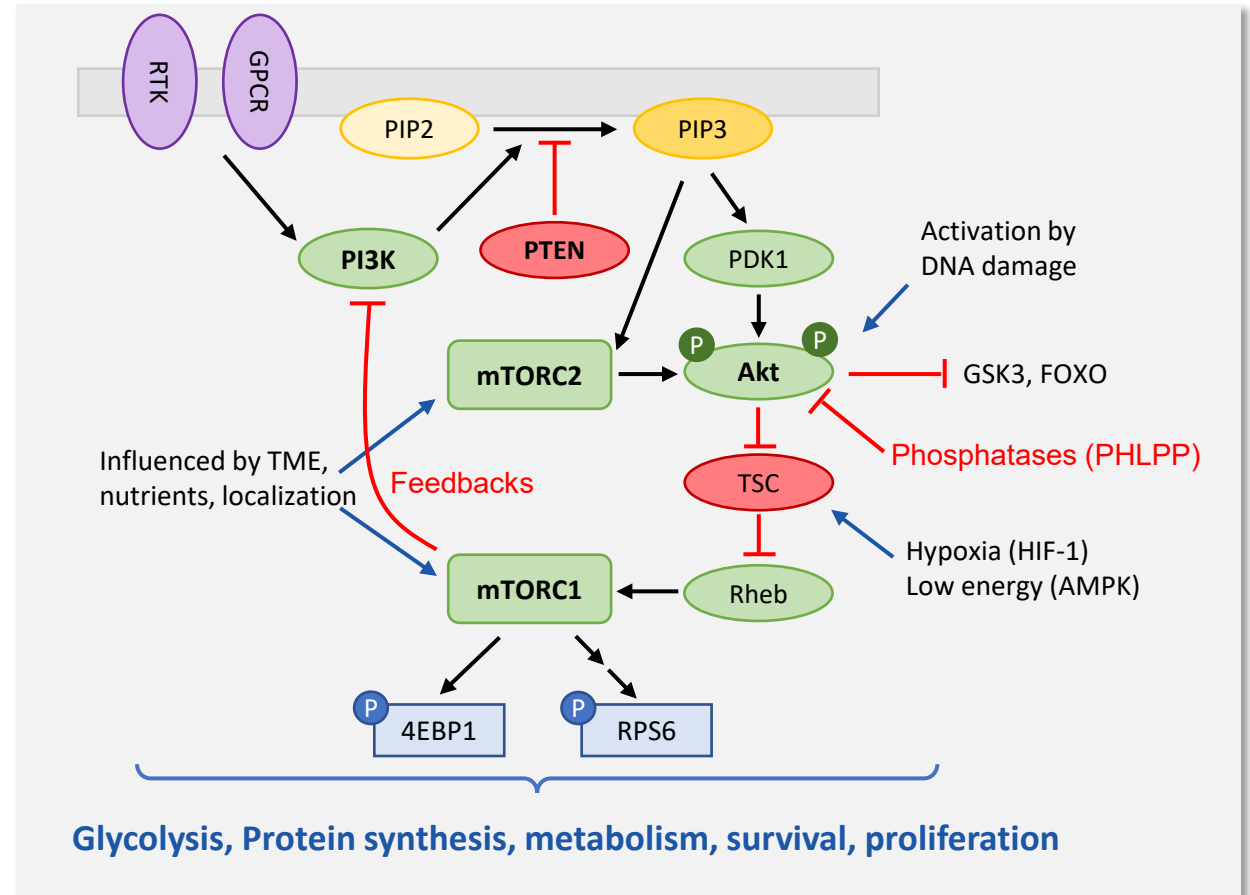
- **PAM pathway primary signaling nodes**

- PTEN
- Class I PI3K isoforms –  $\alpha, \beta, \gamma, \delta$
- mTORC1 and mTORC2
- AKT

- **Redundancy in PAM signaling nodes** ensures tumor can maintain metabolic dysfunction under variety of conditions

- Enables the tumor to be resilient

- To overcome this redundancy, **must target multiple nodes of the PAM pathway**



# Node Redundancy Requires PI3K $\alpha/\beta/\gamma/\delta$ and mTORC1/2 Inhibition

Intrinsic pathway complexity challenges single node control therapeutic approach

- Each PAM node has a critical role in maintaining viability
- Inhibition of individual nodes results in adaptive/resistance signaling
- Partial or imbalanced inhibition results in compensatory resistance
- Feedforward and feedback loops between PI3K isoforms and mTOR cross-activate uninhibited sub-units
- Multiple pathway components must be targeted

## Adaptive response of PAM nodes when a single PAM node inhibited

PI3K $\alpha$ inhibition	➡	Reduces PTEN tumor suppression Increase PI3K $\beta$ activity <sup>1,2,3,4</sup>
PI3K $\beta$ inhibition	➡	Reduces PTEN tumor suppression Increase PI3K $\alpha$ activity <sup>3,4</sup>
AKT inhibition	➡	Activates RTK's <sup>5</sup> and mTOR <sup>6</sup>
mTOR inhibition	➡	Reactivates PAM nodes <sup>7,8</sup>



# Gedatolisib Differentiation

## Nonclinical Data Review

# Gedatolisib Has a Highly Differentiated Mechanism of Action

Inhibits six different PAM nodes to induce comprehensive pathway blockade

Gedatolisib vs PAM Node Inhibitors IC<sub>50</sub> (nM)<sup>1</sup>

## Gedatolisib is Potent Against all Class I PI3K Isoforms and mTORC1/2

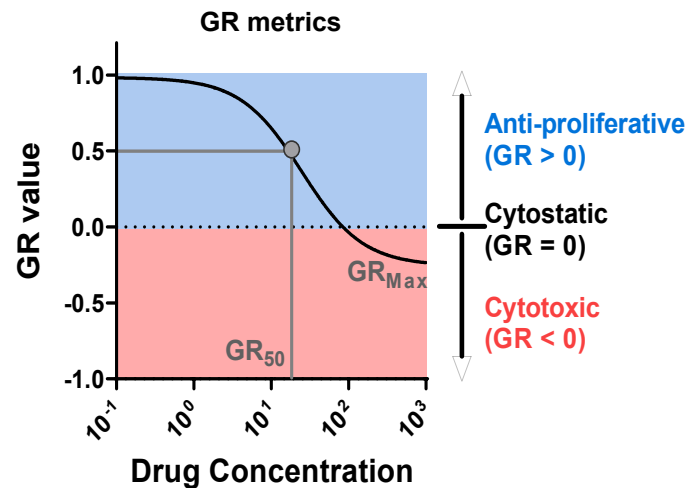
- More potent against these targets than single node inhibitors
- Pan-PI3K/mTOR inhibition limits cross-activation that occurs with node-specific drugs
- MOA creates potential to induce anti-tumor activity independent of PIK3CA status

Node	Gedatolisib <sup>2</sup>	Alpelisib <sup>3</sup>	Everolimus <sup>4</sup>	Capivasertib <sup>5</sup>
PI3K- $\alpha$	0.6	~4.0	-	-
PI3K- $\beta$	6.0	1,156	-	-
PI3K- $\gamma$	5.4	250	-	-
PI3K- $\delta$	6.0	290	-	-
mTORC1	1.6	-	~2.0	-
mTORC2	1.6	-	-	-
AKT	-	-	-	3.0

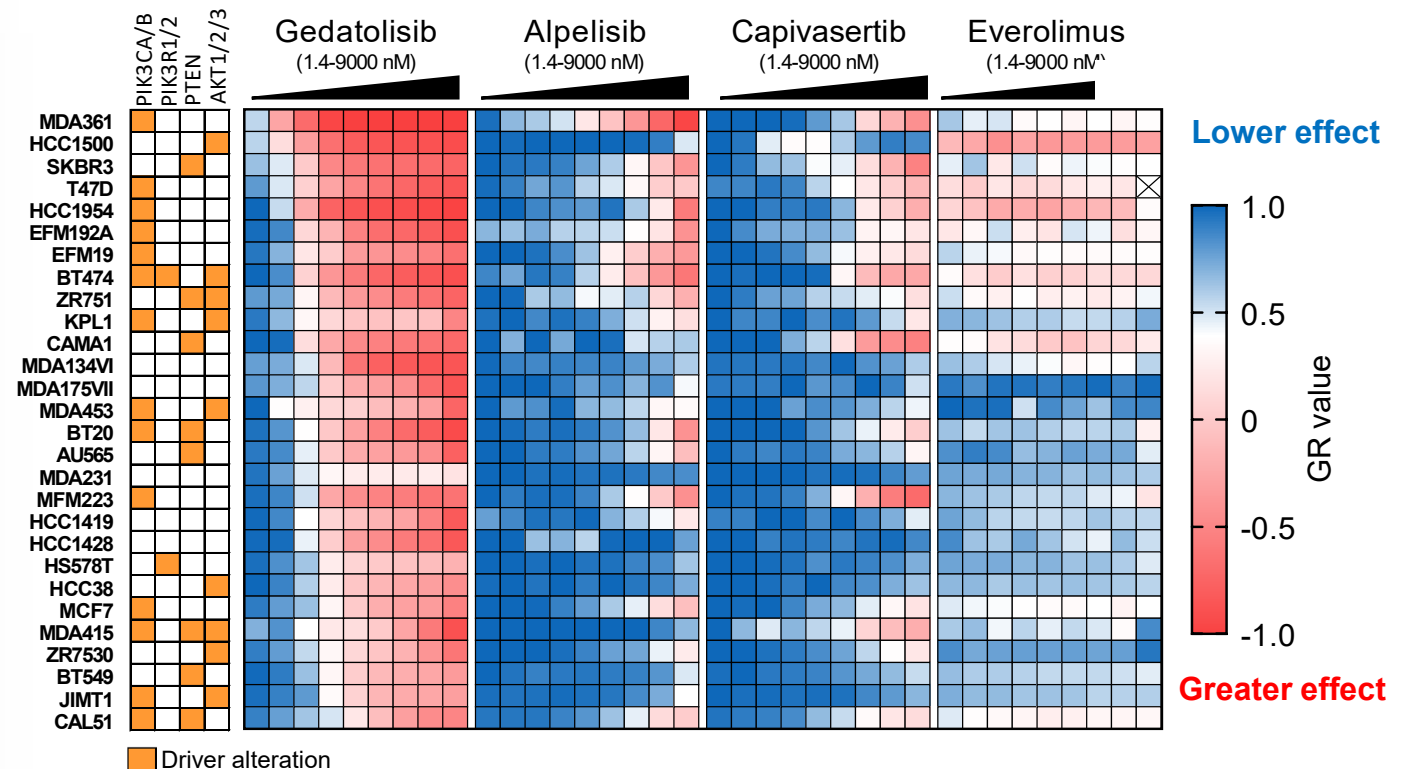
# Breast Cancer Cell Lines: Evaluated Gedatolisib and Node-Specific Inhibitors

Gedatolisib exerts superior cytotoxic effects at all concentrations relative to other PAM inhibitors

- Assessed cytotoxic and cytostatic effects using growth rate metric
- Avoids the confounding effects of individual cell line proliferation rates




## 28 Cell Lines Evaluated



# Breast Cancer Cell Lines: Gedatolisib is >300x more potent, 2X more cytotoxic

## Average Values for 28 Breast Cancer Cell Lines

Potency  
Low  High

Efficacy  
Cytostatic  Cytotoxic  
0-100% 101%-200%

### GR<sub>50</sub> (nM)

Geda	Alpe	Capi	Evero
12	6308	8666	3611
12	2594	2590	1867
12	10308	15209	5501

### Max Cell Growth Inhibition<sup>1</sup>

Geda	Alpe	Capi	Evero
168%	89%	80%	62%
174%	116%	99%	68%
162%	62%	60%	56%

### % Cell Lines Sensitive<sup>2</sup>

Geda	Alpe	Capi	Evero
<100nM	<3000nM	<3000nM	<3000nM
100%	57%	54%	50%
100%	86%	79%	71%
100%	29%	29%	29%

### % High Efficacy in Cell Lines<sup>3</sup>

Geda	Alpe	Capi	Evero
96%	43%	29%	7%
100%	64%	43%	7%
93%	21%	14%	7%

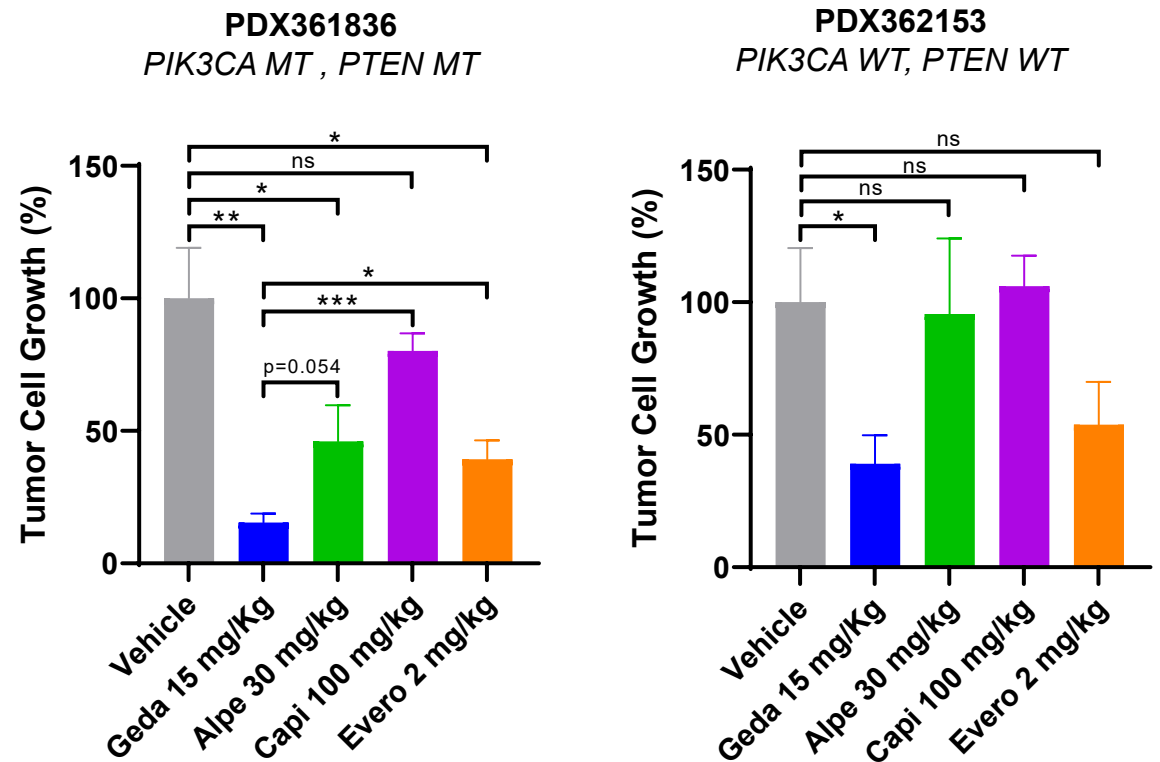
## Gedatolisib vs. Other PAM Inhibitors

- ~ 2x higher in vitro efficacy than other PAM inhibitors
  - Alpelisib, capivasertib, everolimus mostly not cytotoxic
- **More potent** than other PAM inhibitors
  - **> 300X** more potent than alpelisib, capivasertib, & everolimus on average
- Same potency and efficacy regardless of PIK3CA/PTEN status unlike other PAM inhibitors

# Breast Cancer Mini-PDX Models: Compared PAM Inhibitors

Gedatolisib induced higher tumor growth inhibition than node specific inhibitors in PIK3CA WT and MT models

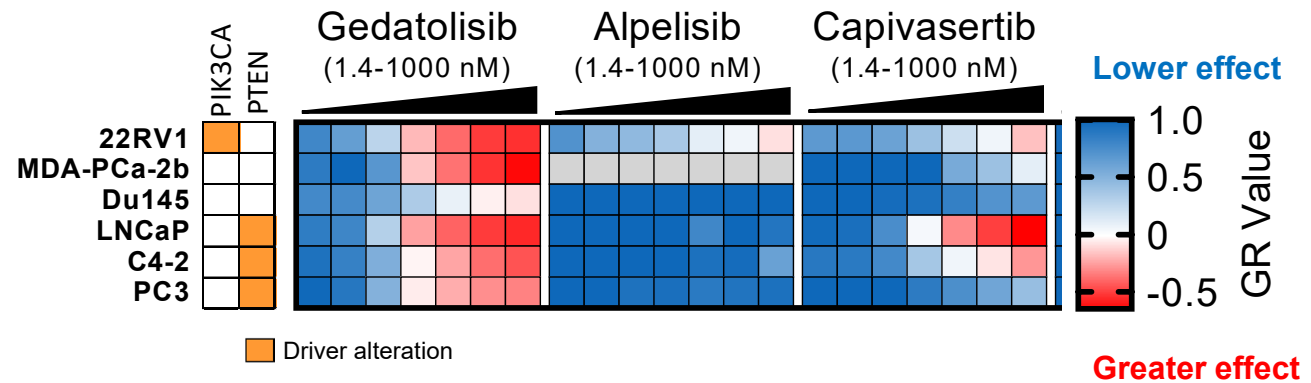
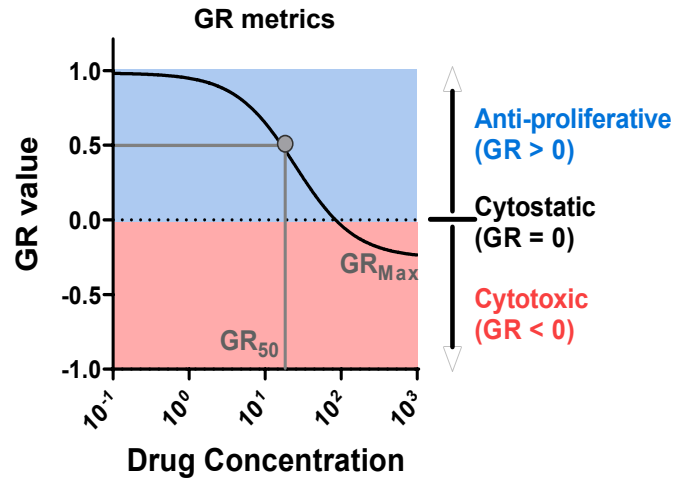
- **Gedatolisib induced significant tumor growth inhibition (TGI) in both wild type and mutant PI3K/PTEN PDX models**
  - Only agent effective in both wild-type and mutant models
- **Results**
  - 85% TGI in PIK3CA/PTEN mutant model
  - 61% TGI in PIK3CA/PTEN wild-type model



# Prostate Cancer Cell Lines: Compared PAM Inhibitors

Gedatolisib exerts superior cytotoxic effects at all concentrations relative to other PAM inhibitors

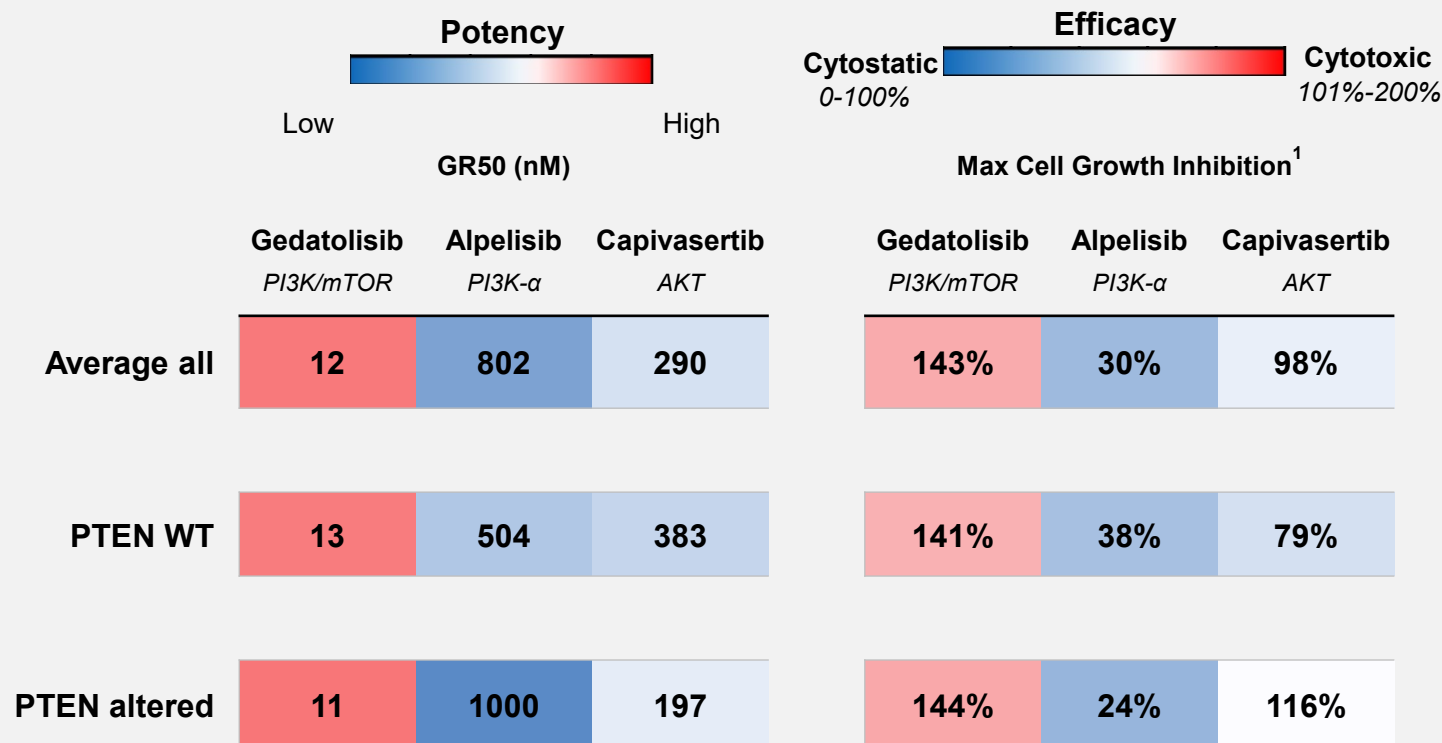
- Assessed cytotoxic and cytostatic effects using growth rate metric
- Avoids the confounding effects of individual cell line proliferation rates





# Prostate Cancer Cell Lines: Gedatolisib is ~20-65x more potent, more cytotoxic

## Average Values for Six Prostate Cancer Cell Lines (22RV1, MDA-PCa-2b, DU145, LNCaP, C4-2, PC3)

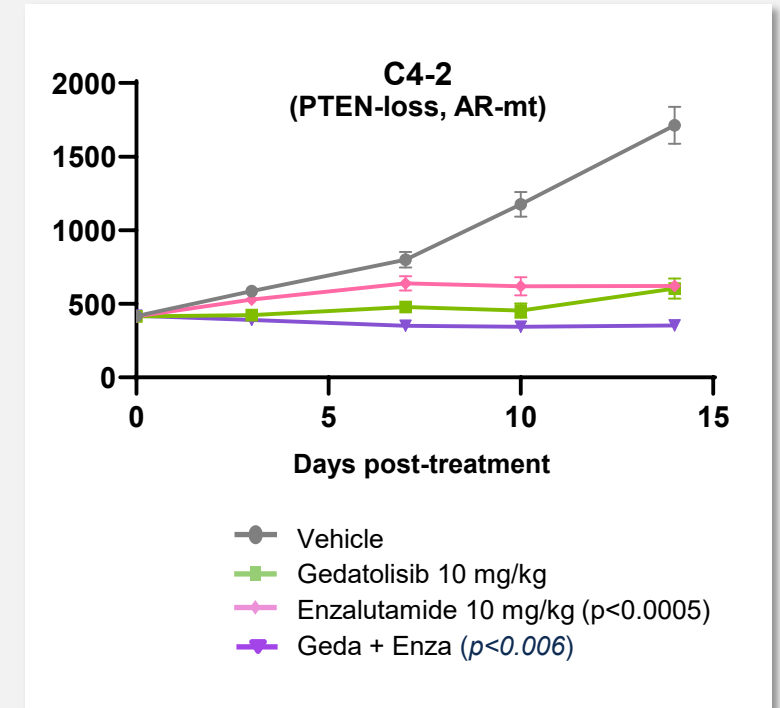
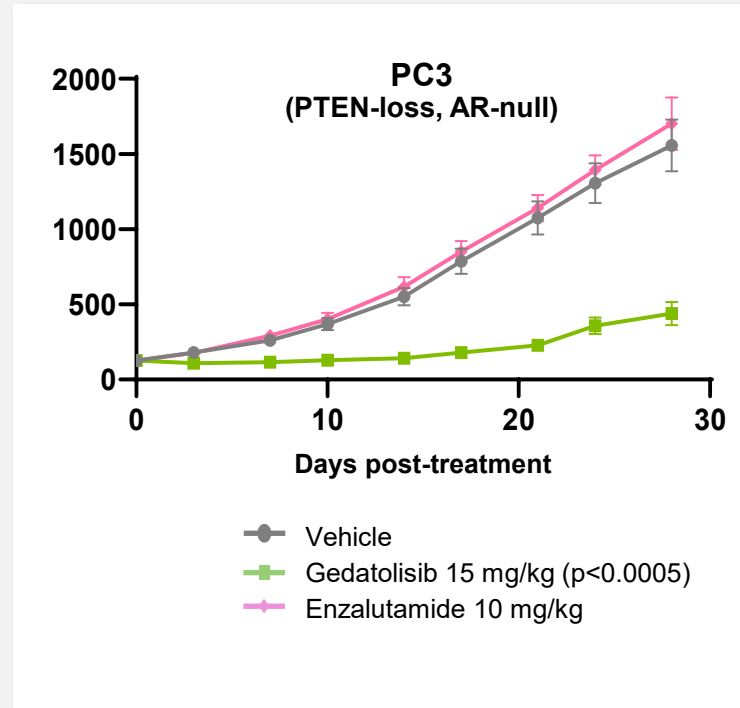
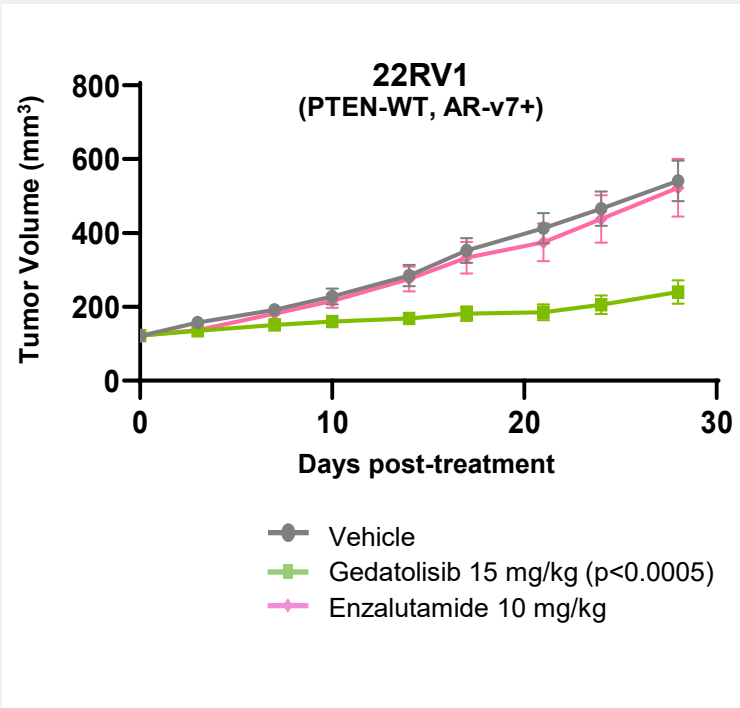


## Gedatolisib vs. Other PAM Inhibitors

- **More cytotoxic** than other PAM inhibitors on average
  - Alpelisib and capivasertib are not cytotoxic
- **More potent** than other PAM inhibitors on average
  - **65x** more potent than alpelisib
  - **24x** more potent than capivasertib
- Gedatolisib has same potency and efficacy regardless of PTEN status unlike other PAM inhibitors.

# In Vivo Activity of Gedatolisib in Prostate Cancer Xenograft Models

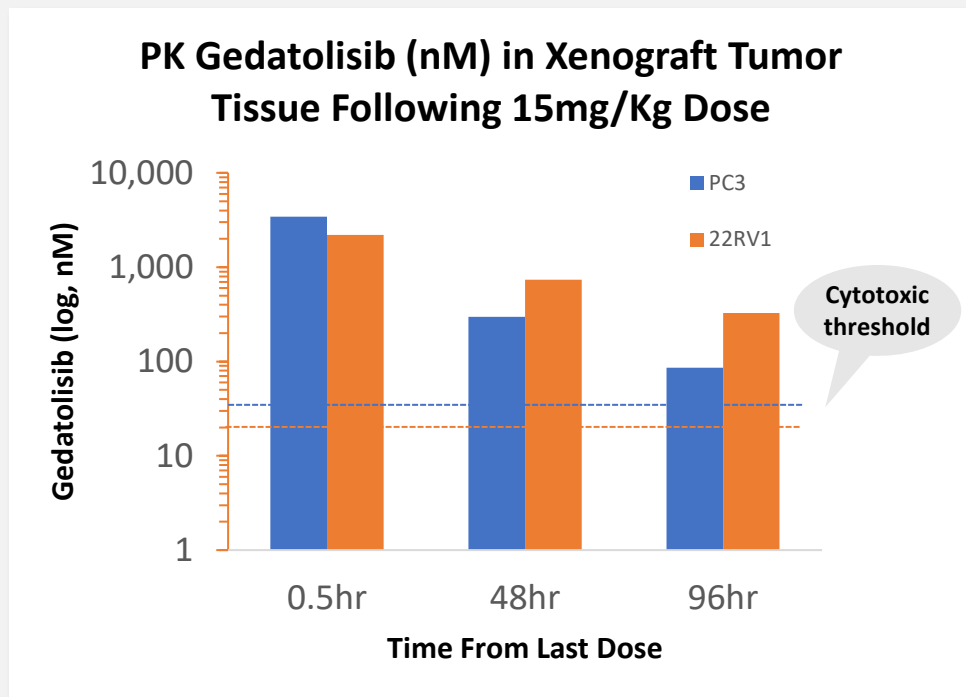
Gedatolisib induced >80% tumor growth inhibition (TGI) regardless of PTEN or AR status



- Robust single-agent TGI in PC xenograft models regardless of sensitivity to enzalutamide (ARi) and PTEN status
- Gedatolisib + enzalutamide induced significantly greater TGI than enzalutamide alone in enzalutamide sensitive model

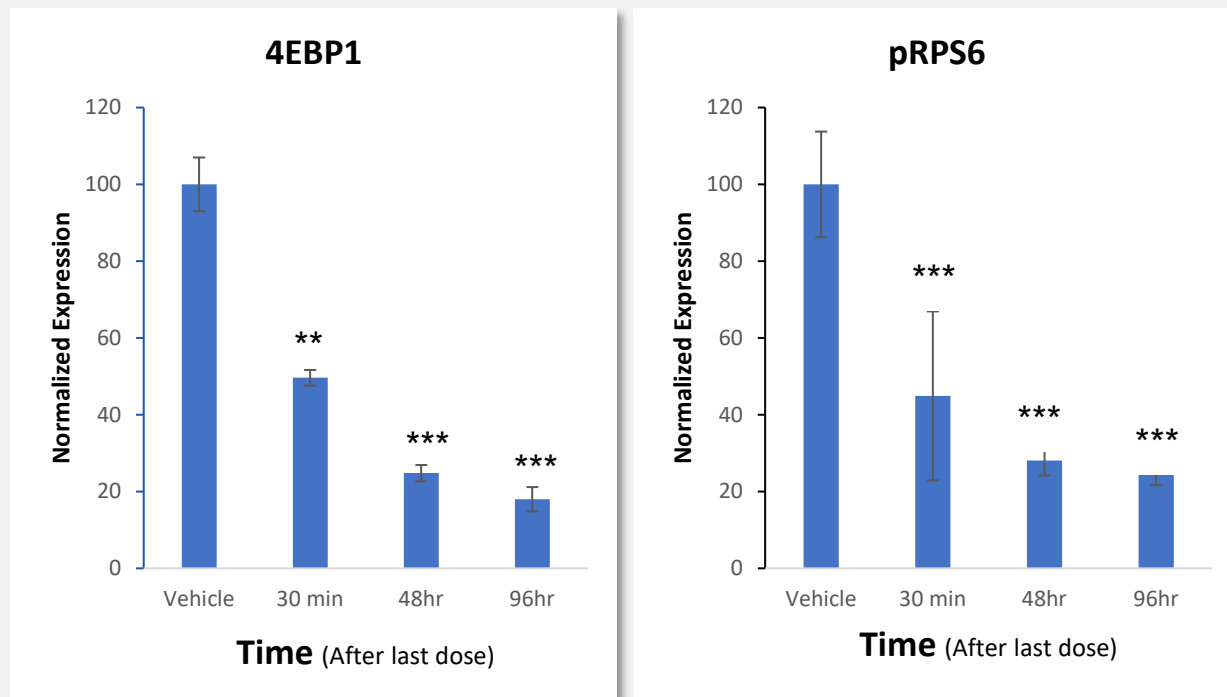
# PK/PD Xenograft Tumor Tissue Analysis During Dosing Interval

Gedatolisib concentration remains above cytotoxic and pathway inhibition threshold during dosing interval



Dosing every 4 days in mice comparable to once per week in patients;  
Cytotoxic threshold equivalent to in vitro  $IC_{80}$  for each cell line

Effect of gedatolisib on PAM pharmacodynamic markers in PC3 xenograft tissue



Total protein production and active translation  
suppressed between doses

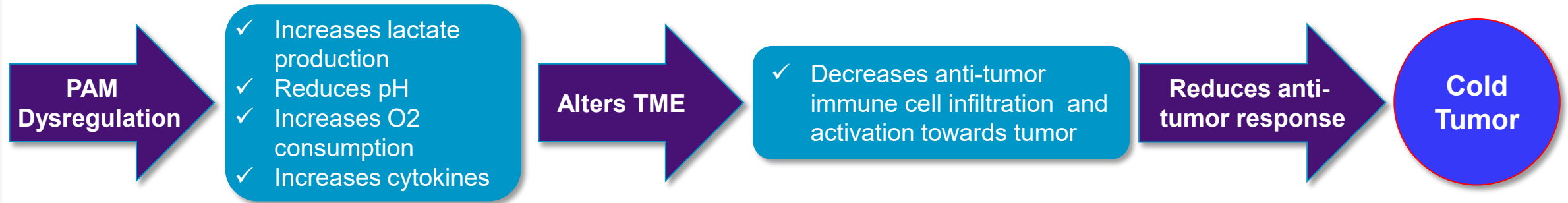
## Pharmacokinetics

- Plasma  $T_{1/2}$  = 4.9 hours mice
- Plasma  $T_{1/2}$  = 37 hours human

# PAM Reduces Immune System Function in Tumors

Causes tumor cells to generate biochemical factors that negatively affect tumor microenvironment (TME)

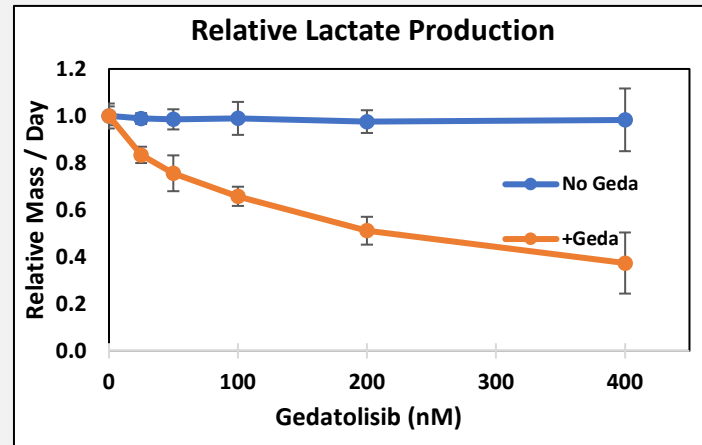
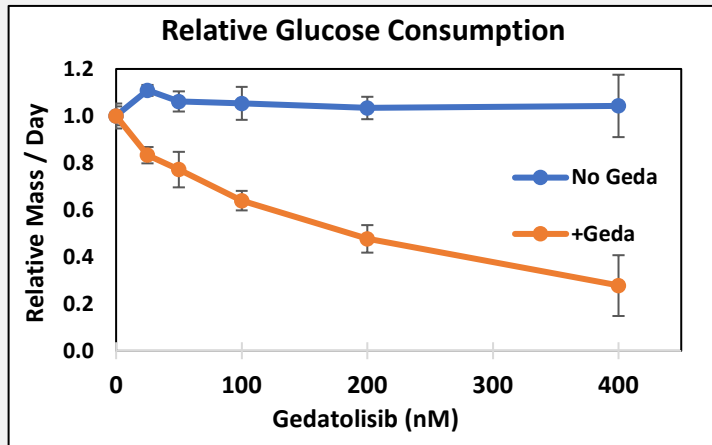
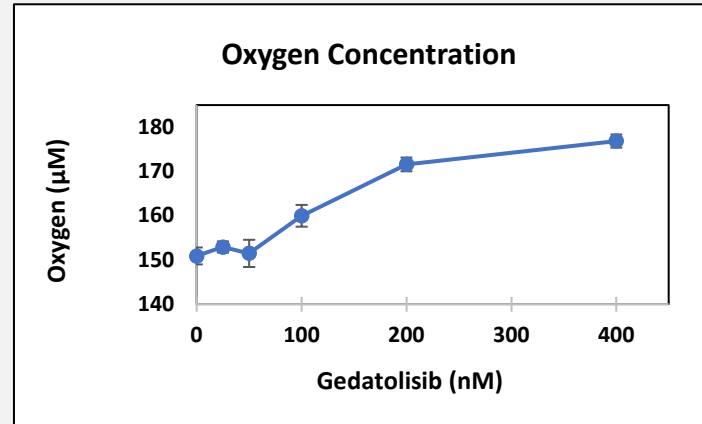
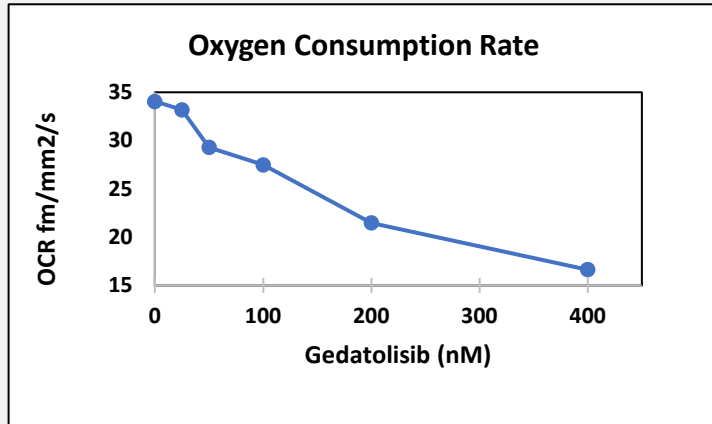
**PAM pathway impact on TME is likely a major factor that causes breast and prostate tumors to be immunologically “cold”**



**Inhibition of PAM improves the TME which can increase anti-tumor immune response**

# Gedatolisib Favorably Impacts Tumor Microenvironment

PAM inhibition decreases O<sub>2</sub> and glucose consumption and lactate production



A TME with low O<sub>2</sub>, low glucose, and high lactate is correlated with immuno-suppression, low anti-tumor activity<sup>1, 2,3,4</sup>

Gedatolisib's dose-dependent reduction of O<sub>2</sub> consumption leads to an increase in O<sub>2</sub> available

Gedatolisib's dose-dependent reduction in glucose consumption leads to decreased lactate production

Data demonstrates Gedatolisib improves TME factors that enable anti-tumor immune function

# Gedatolisib Increases Immune Cell Tumor Infiltration and Activation

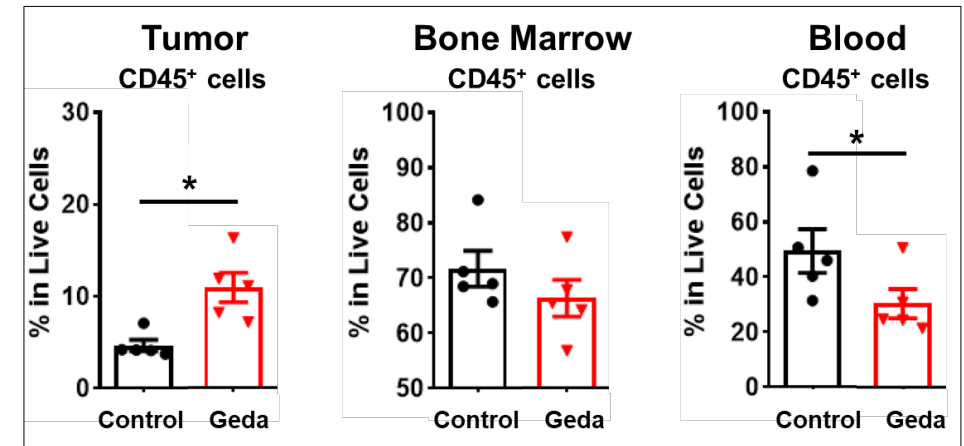
Profiled CD45+ immune cell populations in tumor, bone marrow, peripheral blood

Proportions of CD45+ anti-tumor immune cell subsets in tumor

	Day 10			Day 17		
	Control	Geda	P-Value	Control	Geda	P-Value
% CD45+	4.7	10.9	0.03	-	-	-
% DC (in CD45+)	9.0	15.4	0.0002	2.9	4.0	NA
% CD4+ (in CD45+)	8.6	19.6	0.0002	7.4	19.2	0.014
% CD8+ (in CD45+)	1.7	4.8	NA	13.6	24.5	0.02

## Desired immune cell types infiltrated into the tumor

- Gedatolisib increased CD45+ cells in tumors 2.3 fold vs control
- Gedatolisib induced durable infiltration of key anti-tumor immune cell types - DC, CD4+, CD8+



**Tumor infiltration likely resulted from recruitment of leukocytes from blood circulation into the TME**

## Immune cells that infiltrated are activated

- Gedatolisib induced a 1.5-2 fold increase of activated CD8+ cytotoxic T cells (CD69+) and activated NK cells (CD69+) in tumors at day 10 and day 17



# Key Takeaways: Non-clinical

Gedatolisib is highly potent and cytotoxic; controls factors that induce immunosuppression in TME

## PAM is Complex Pathway

- PAM pathway is an important driver of metabolic activities that support tumor cell proliferation
- Multi-node inhibition is required to address pathway complexity and effectively block PAM activity

## Comprehensive MOA

- Gedatolisib equipotently antagonizes major PAM signaling nodes
- Reduces tumor glucose and oxygen consumption and lactate production

## Superior Potency and Cytotoxicity

- Superior potency and cytotoxicity in vitro and in vivo vs single node PAM inhibitors
- Gedatolisib remains above  $IC_{80}$  threshold throughout dosing interval in PK/PD xenograft studies

## Reduces Immuno-suppression

- Gedatolisib's control of tumor glucose and oxygen reduce TME potential to support tumor cell proliferation
- Data suggests gedatolisib may improve infiltration and activation of anti-tumor immune cells in TME

# PK and Safety Overview of Gedatolisib

**Igor Gorbachevsky, MD**  
Chief Medical Officer

# Gedatolisib's PK and Metabolic Profile

Stable chemical structure leads to optimized PK profile

## PK characteristics in humans

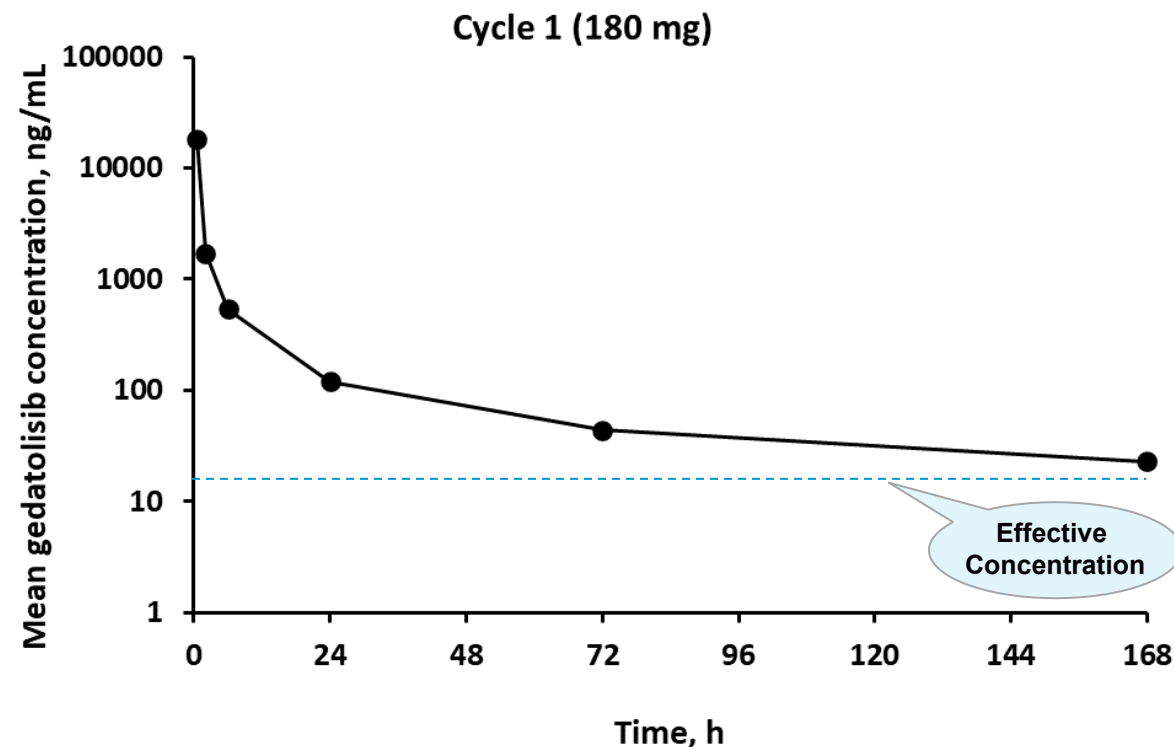
- $T_{1/2} \approx 37$  hours
- Dose-proportional and predictable PK exposure
- No accumulation after multiple doses
- Minimal inter-patient variability in PK parameters

## Metabolism

- Minimal metabolic turnover in in-vitro and in-vivo studies
- No metabolites have been identified (<1%)
- Main route of elimination for unchanged gedatolisib in human: feces and urine

## PK Drug Interactions

- No impact on metabolic clearance of drugs that are substrates of CYP enzymes
- Potentially low or no risk for clinically significant CYP-pathway mediated DDI



**Gedatolisib remains above its effective concentration threshold throughout dosing interval**

# Gedatolisib Key PK Properties and Safety Metrics vs. Approved PI3Ki

Differentiated favorable PK profile leads to lower toxicity

	Gedatolisib <sup>1</sup>	Alpelisib <sup>2,3</sup>	Copanlisib <sup>3</sup>	Duvelisib <sup>3</sup>	Idelalisib <sup>3</sup>
Target(s)	Pan-PI3K mTOR	PI3K- $\alpha$	Pan-PI3K	PI3K- $\delta$	PI3K- $\delta$
Administration	IV	Oral	IV	Oral	Oral
Dosing (mmol/month)	0.88	19.03	0.37	3.22	20.22
Volume of distribution (L)	39	114	871	29	23
Hyperglycemia (G 3/4)	1%	26%	41%	-	-
Treatment related SAE's	2%	10%	26%	65-73%	50-77%
Treatment related (TR) Discontinuations	0%	13%	16%	35%	17-53%

## Gedatolisib vs. PI3K- $\alpha$ and pan-PI3K drugs (single-agents)

- >95% lower rate of Grade 3/4 hyperglycemia
  - Due to gedatolisib's lower liver exposure
  - Alpelisib dosage 22x > gedatolisib
  - Copanlisib 50x > retention liver vs plasma
- >80% lower rate of TR discontinuations
- 3x-20x more balanced distribution

## Gedatolisib vs. PI3K- $\delta$ drugs (single-agents)

- 73%-97% lower dosage (molar/month)
- No direct GI exposure
- Minimal GI, liver, and infection-related AE's

# Gedatolisib Single Agent Safety Profile

Phase 1 Trial: gedatolisib at maximum tolerated dose (MTD) - 154 mg weekly (IV)<sup>1</sup>

- **Limited incidence of Grade 3 adverse events**
- The most frequent AE, stomatitis, is manageable with prophylactic steroidal mouth rinse
  - Stomatitis was not treated prophylactically in this study
  - **Prophylactic treatment may reduce G2 incidence by 90%; G3 by 100%<sup>2</sup>**
  - Phase 3 study will include prophylaxis
- **Low incidence of Grade 3 hyperglycemia (1%)**
- **No treatment related neutropenia**
- No Grade 4 or 5 adverse events

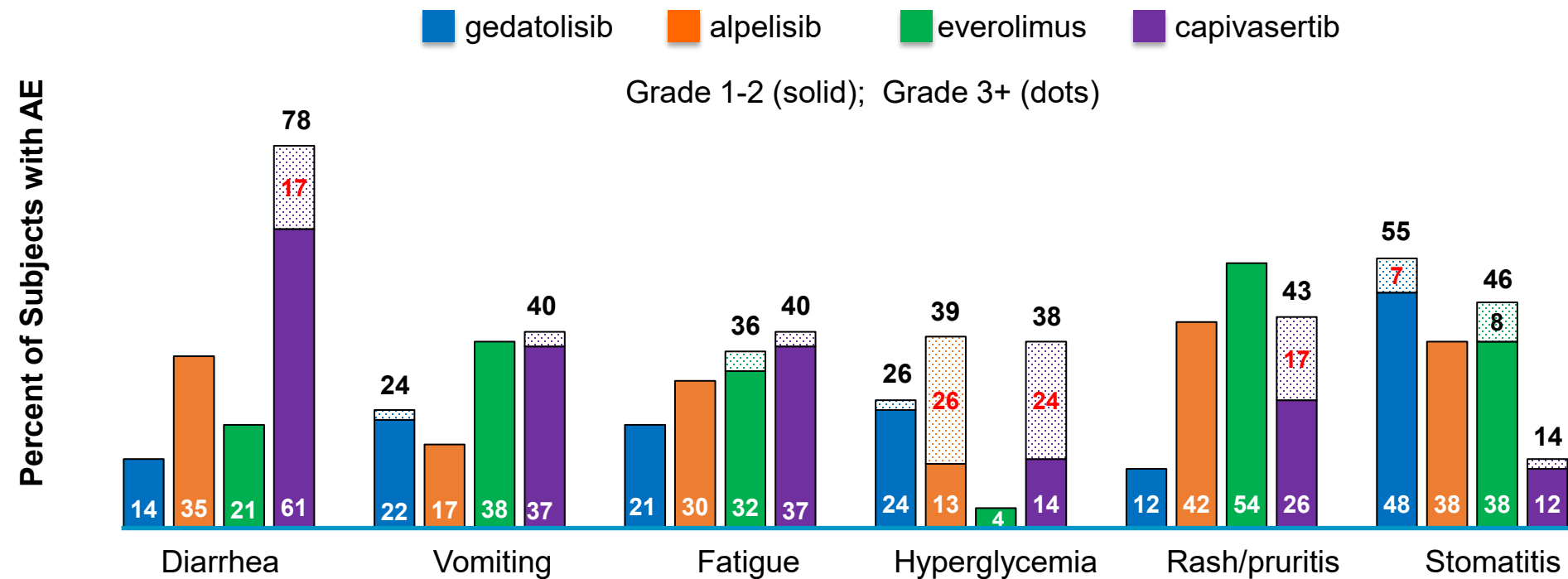
## MTD Arm (n=42)

### Related TEAE's > 20%

	Grade 1	Grade 2	Grade 3/4
Adverse Event	%	%	%
<b>Stomatitis</b>	45	2	7
<b>Nausea</b>	36	2	2
<b>Hyperglycemia</b>	17	7	1
<b>Vomiting</b>	19	2	2
<b>Asthenia</b>	7	12	2
<b>Fatigue</b>	19	2	-
<b>Appetite decrease</b>	14	7	-

# Safety Data for Single-Agent Gedatolisib vs. Single Node PAM Inhibitors

Fewer patients reported AE when treated with gedatolisib as single agent compared to other PAMi





## Prostate Cancer

# Current Standards of Care in mCRPC and Unmet Clinical Needs

**Karim Fizazi, MD, PhD**

Professor of Medicine, University of Paris-Saclay

GETUS President

Head, GU Group, Institute Gustav Roussy

University of Paris Saclay

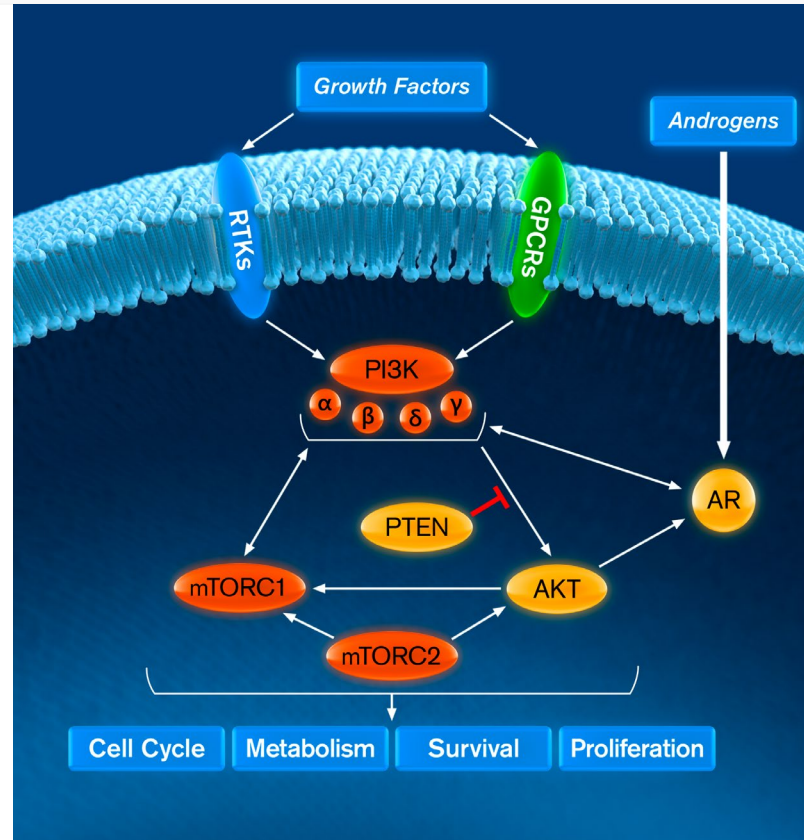


# Androgen Signaling is the Key Driver of Prostate Cancer

The PI3K/AKT/mTOR (PAM) pathway helps promote excessive cell proliferation and resistance to apoptosis

## The AR Pathway is the Primary Therapeutic Target

- The androgen receptor (AR) drives the expression of target genes which promote cancer cell survival and growth
- The androgen signaling pathway is the primary therapeutic target for prostate cancer at all stages of disease
- Androgen deprivation therapies (ADT) are used primarily for localized disease
- Second generation AR inhibitors are used for advanced disease

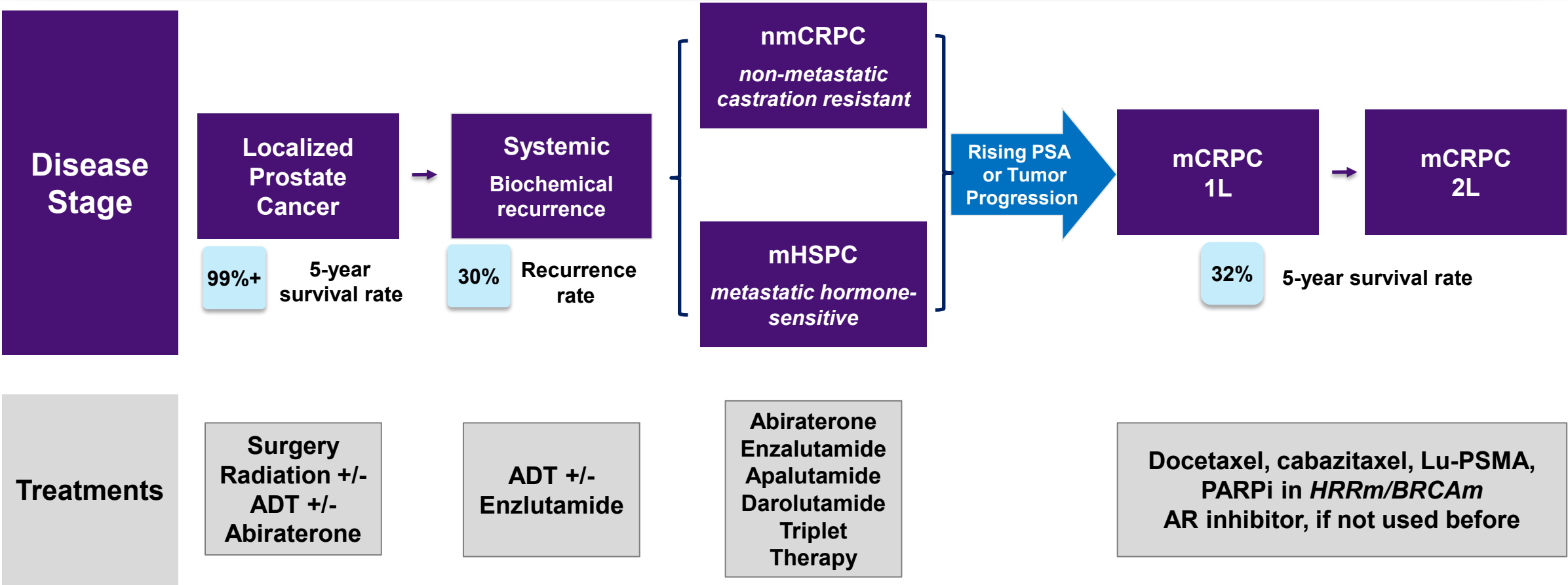


## The PAM Pathway Plays a Key Role in mCRPC

- AR and PI3K-AKT-mTOR pathways cross-regulate each other.
- 70% - 100% of mCRPC tumors have PI3K/AKT/mTOR related pathway alterations.
- Mutations dispersed across PTEN, PI3K, AKT, and mTOR sub-units

# Prostate Cancer Disease and Treatment Landscape<sup>1,2</sup>

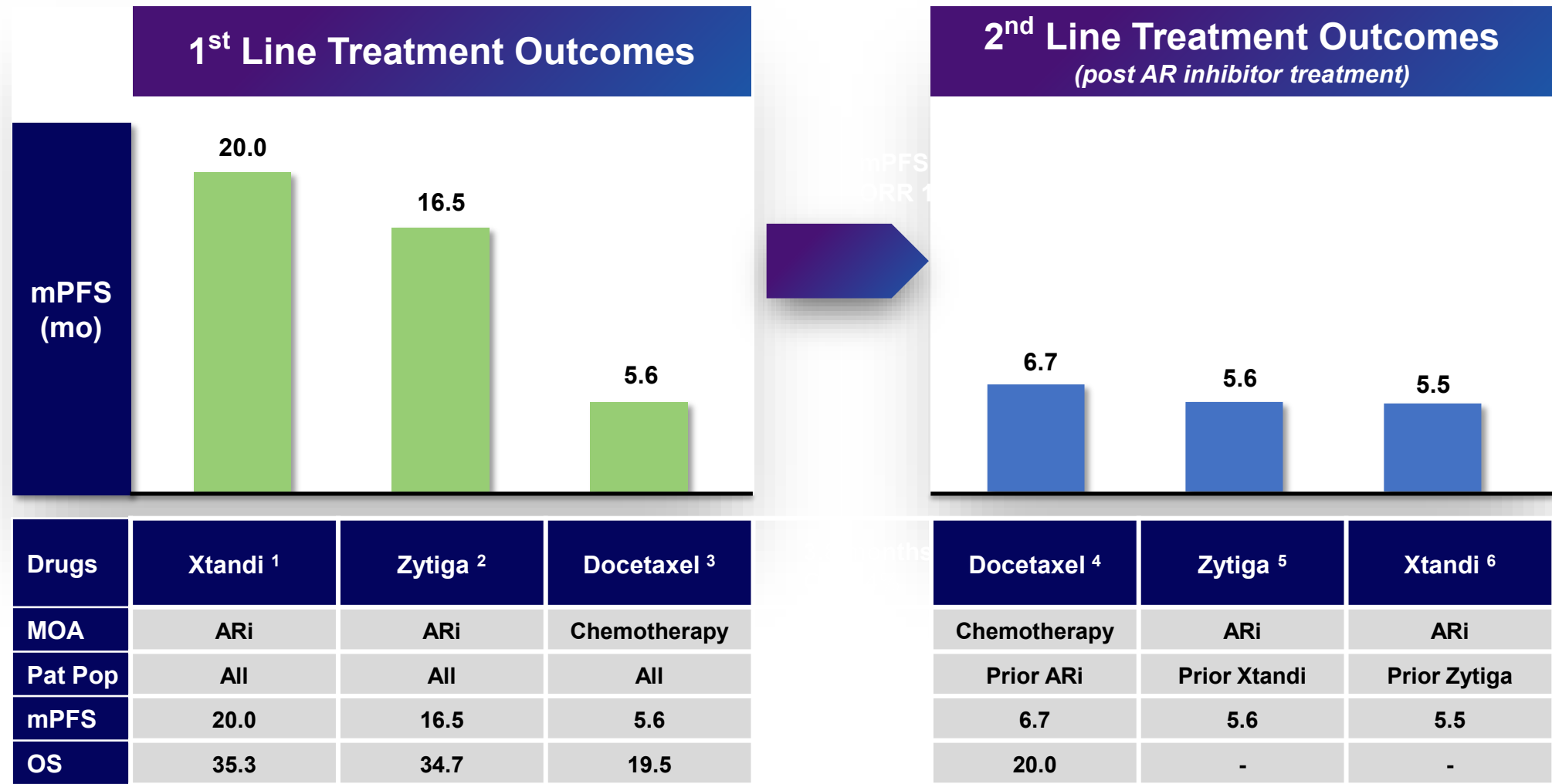
34,700 men in US and 62,400 men in 5EU and Japan die from prostate cancer annually<sup>3,4</sup>



(1) Saad, Prostate Cancer Prostatic Dis. 2021; (2) Scher, Plos One 2015; Leith, A. et al. 2022; George, D. J. et al. 2022; NCCN Guidelines for Prostate Cancer Version 1.2023; (3) American Cancer Society, Cancer Facts & Figures 2023; (4) Wang, Front. Public Health, 2022; Abbreviations: mCRPC = metastatic castration resistant prostate cancer; HRR = homologous recombination repair 1L = first line of therapy; 2L = second line of therapy; ADT = androgen deprivation therapy; AR = androgen receptor

# Limited Benefit for 2L HRR- mCRPC Patients After Treatment with AR Inhibitor

Significant need for better therapeutic options



Karim Fizazi, MD, PhD  
Gustave Roussy

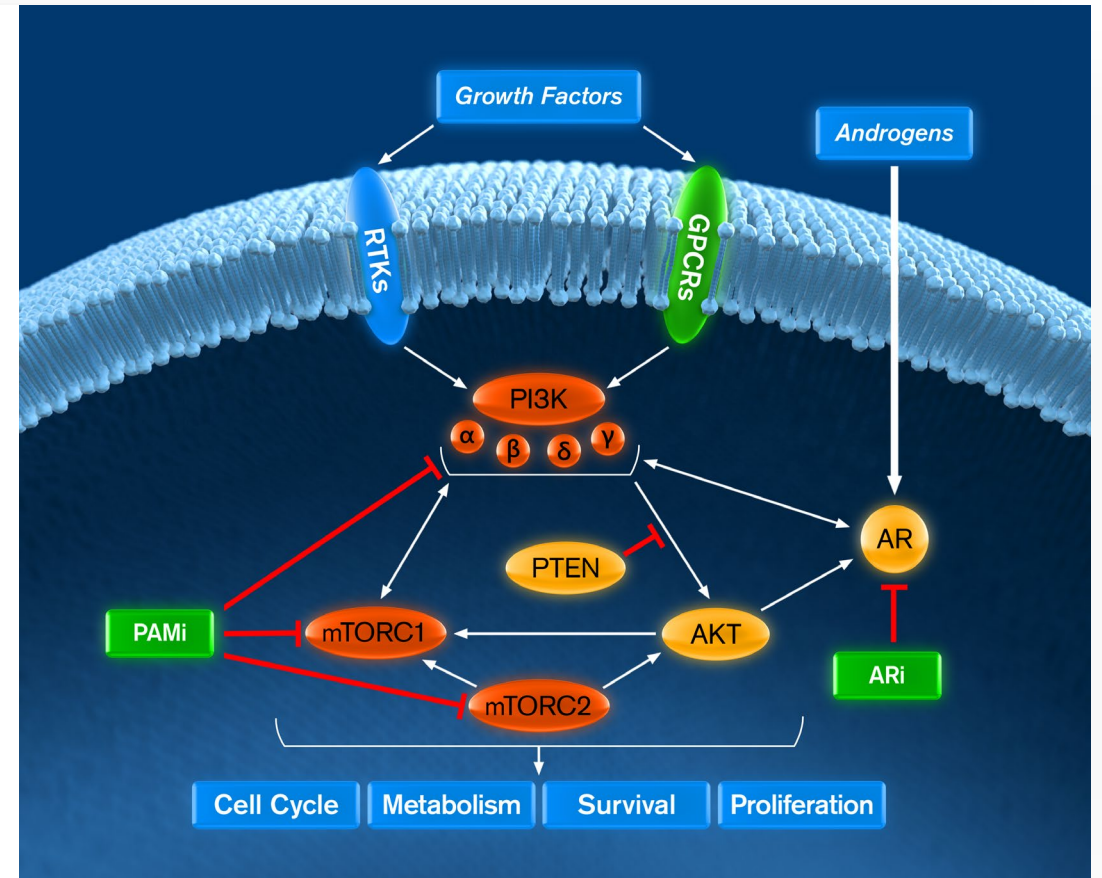
(1) Beer Eur Urol. 2017; (2) Ryan NEJM 2013; Ryan Lancet Oncol 2015 (3) Kellokumpu-Lehtinen Lancet Oncol. 2013, time-to-treatment failure reported; (4) Crabb J Clin Oncol 2021; (5) Attard J Clin Oncol 2018; (6) Sweeny Clin Cancer Res 2022. Abbreviations: HRR = homologous recombination repair; AR = androgen receptor

# Combining a PAM Inhibitor with an AR Inhibitor has Strong Scientific Rationale

Biological parallels between mCRPC and HR+ ABC – PAM and hormonal pathway drive progression <sup>1</sup>

## PI3K/mTOR + AR Inhibition *Treatment Rationale*

- AR inhibition increases PAM pathway signaling <sup>2</sup>
- For patients who progressed on an AR inhibitor, PI3K inhibition may resensitize them to an AR inhibitor
- PI3K inhibition increases AR protein levels and activation <sup>3</sup>
- mTOR inhibition is particularly critical in patients when the tumor suppressor, PTEN, is functional
- Strong rationale to combine an AR inhibitor with a PAM inhibitor in patients who progressed on an AR inhibitor



# PAM Inhibitor Development Efforts for mCRPC Have Focused on AKT

Reflects high incidence of PTEN alterations in mCRPC that AKT inhibition can address

- **The AKT inhibitor, ipatasertib, has been extensively evaluated in prostate cancer**
  - AKT inhibition can lead to reactivation of the PAM pathway through various resistance mechanisms <sup>1,2,3,4</sup>
- **When PTEN is altered**, AKT inhibition can overcome some resistance mechanisms
  - Feedback mechanisms through mTORC1/2 are still functional and likely limit potential effect of AKT inhibition<sup>1,4</sup>
- **When PTEN is not altered, AKT inhibition has limited effect likely due to resistance feedback loops<sup>1,4</sup>**
  - Resistance mechanisms include relief of negative feedback loops between PI3K and mTORC1/2 <sup>4</sup>
- **Signaling feedback loops between PI3K and mTORC1/2 may limit efficacy for AKTi to PTEN loss patients**

(1) Mao 2021. Nat Commun. 2021; (2) Chandarlapaty 2011, Cancer Cell; (3) Bago 2016, EMBO J; (4) Manning 2017, Cell

# Clinical Trial Results for PAM Inhibitors After Progression on AR Therapy

Evidence of PAM pathways involvement and sensitivity to PAM inhibitors in mCRPC

Study Regimens	Line of Therapy	Patient Population	N	Overall Results (Months rPFS)	Comments
<b>Samotolisib</b> (PI3K/mTOR) + Enzalutamide vs. Enzalutamide <sup>1</sup>	2 <sup>nd</sup> Line prior abiraterone	All	129	<b>10.5 vs. 5.5 months</b> (HR = 0.64; P = 0.03)	<ul style="list-style-type: none"> <li>Samotolisib efficacious despite only modest PI3K-α and mTOR potency</li> <li>Results in PTEN wild-type patients reflect benefit of mTOR inhibition</li> <li>Gedatolisib vs. samotolisib <sup>3</sup> <ul style="list-style-type: none"> <li>7X more potent overall; 100x for mTOR</li> <li>More cytotoxic</li> </ul> </li> <li>Drug is not under active development</li> </ul>
		AR-v7-negative	103	<b>13.2 vs. 5.3 months</b> (HR = 0.52; P = 0.03)	
		PTEN wild-type	60	<b>13.2 vs. 3.6 months</b> (HR = 0.49; P = 0.07)	
<b>Ipatasertib (AKT)</b> + Abiraterone vs. Abiraterone <sup>2</sup>	1 <sup>st</sup> Line	All	1101	<b>19.2 vs. 16.6 months</b> (HR = 0.84; P = 0.04 )	<ul style="list-style-type: none"> <li>Efficacy limited to PTEN loss patients</li> <li>Limited response in PTEN functional patients demonstrates role mTOR plays as resistance mechanism to AKT inhibition</li> </ul>
		PTEN loss by NGS	209	<b>19.1 vs. 14.2 months</b> (HR = 0.65; P = 0.02)	

# Key Takeaways

Strong scientific rationale to combine a pan-PI3K/mTOR inhibitor with a next generation AR inhibitor

1

- **Efficacy of current 2L therapies for mCRPC post-ARi is limited; new therapeutic approaches are needed**
- Docetaxel                      mPFS: 6-7 months
- AR inhibitors                mPFS: 5-6 months

2

- **Extensive nonclinical data has characterized the role the PI3K/mTOR pathway plays as a driver of mCRPC**
- The challenge has been finding the right PI3K/mTOR drug to address this disease mechanism

3

- **The limited efficacy gains reported to date for AKT inhibitors in mCRPC suggest more comprehensive blockade of the PAM pathway may be required**

4

- **Evaluating a PAM inhibitor in combination with a next generation AR is an important priority for mCRPC research**



# Clinical Overview of Gedatolisib for mCRPC

**Igor Gorbachevsky, MD**  
Chief Medical Officer



# Strong Scientific Rationale to Evaluate Gedatolisib in mCPRC

Favorable clinical data in mCRPC with PAM inhibitors provides “proof-of-concept” of benefit of combining a PAM and AR inhibitor in 2L setting

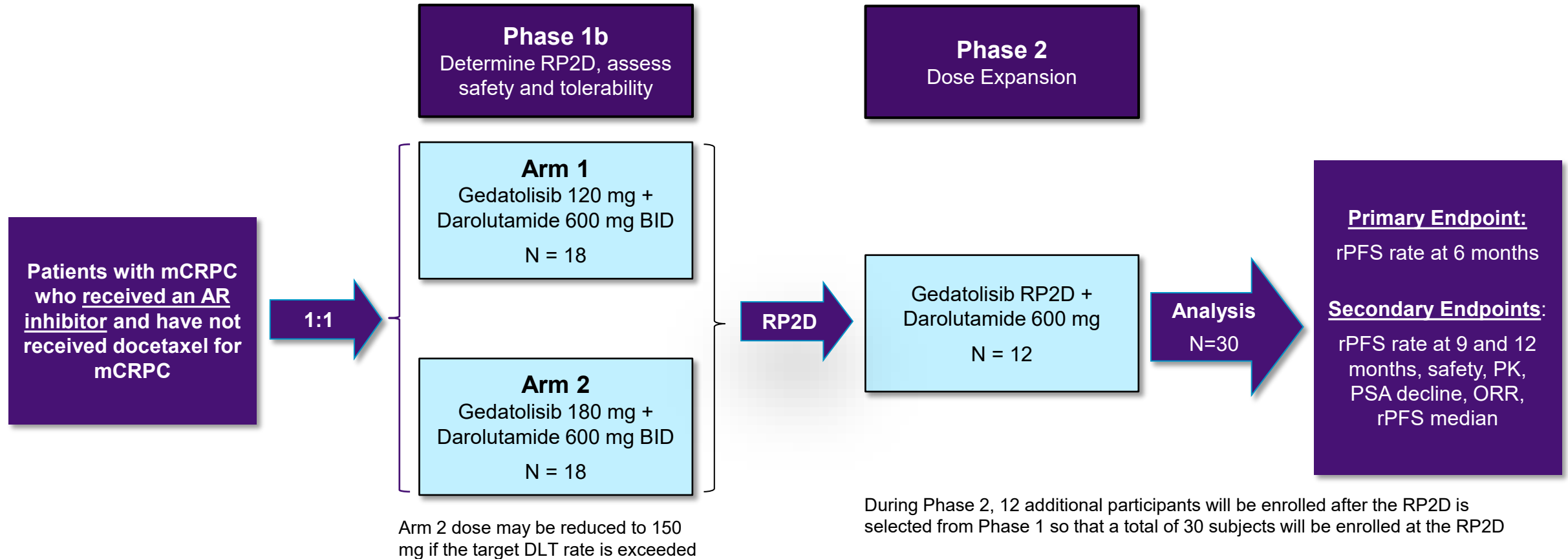
Gedatolisib’s clinical efficacy in breast cancer correlated with strong activity in nonclinical tumor models

Gedatolisib exhibits similar potency and efficacy in prostate cancer cell lines as those reported in breast cancer cell lines

Xenograft data in PR models is consistent with in vivo data – gedatolisib exhibits anti-tumor effects independent of PTEN or AR status

# CELC-G-201: Phase 1b/2 Trial Design Overview

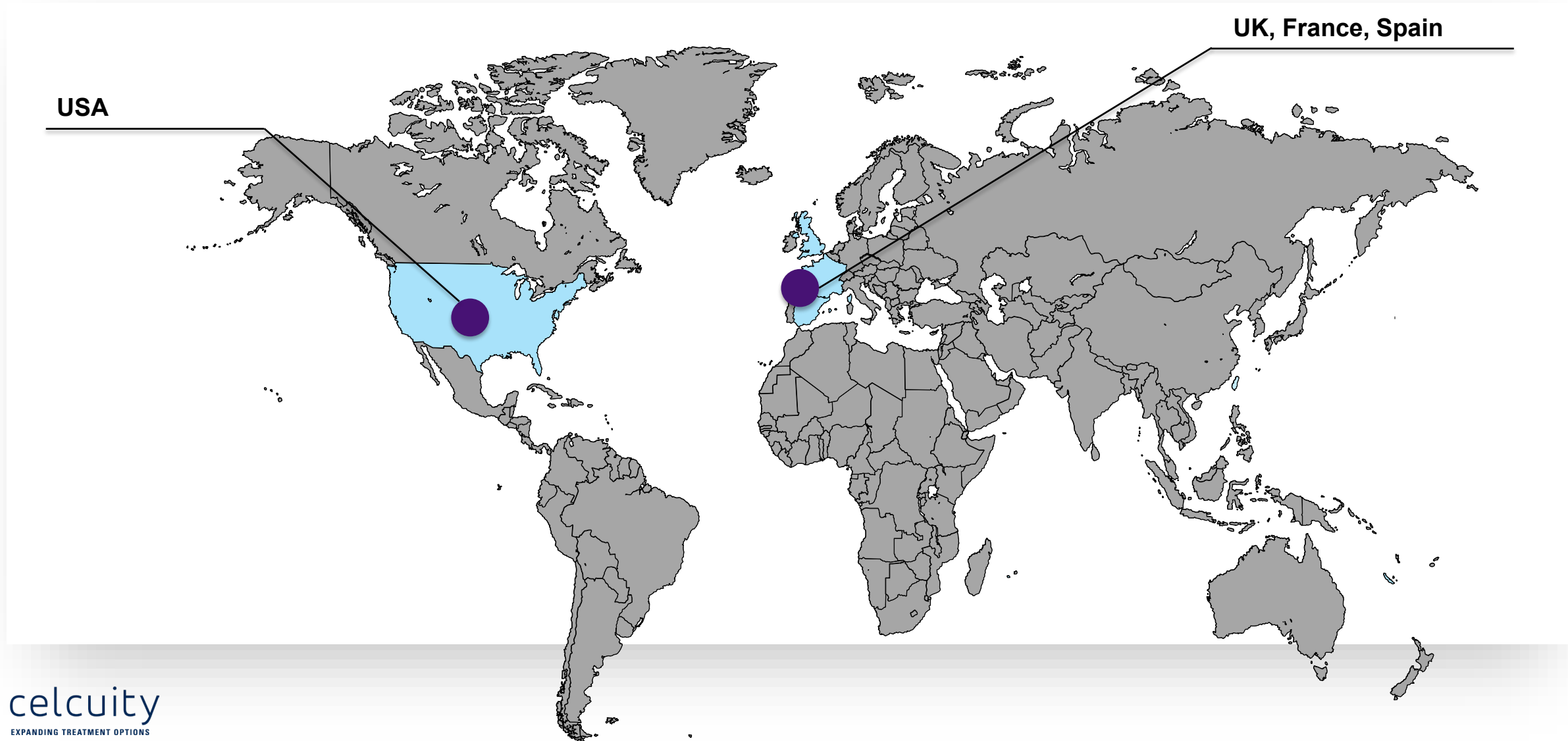
Evaluating gedatolisib combined with darolutamide, a potent next generation androgen receptor inhibitor



Expect to enroll first patient Q1 2024 and announce initial data 1H 2025

# ~12 Sites Across US and Europe

Expect to enroll first patient Q1 2024 and announce initial data 1H 2025



# Darolutamide is More Potent and Better Tolerated than SOC 1L AR Inhibitors

Bayer is collaborating with Celcuity and will supply darolutamide for the trial

	Darolutamide		Abiraterone		Enzalutamide	
Approved Indications	nmCRPC, mHSPC		mCRPC, mHSPC		mCRPC, nmCRPC, mHSPC	
IC <sub>50</sub> <sup>1</sup>	11 nM <sup>2</sup>		72 nM <sup>3</sup>		86 nM <sup>2</sup>	
Most Common AE's (%) <sup>4</sup>	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Fatigue	16	1	39	2	51	9
Pain in extremities	6	0	30	2	21	3
Edema	<2	0	25	0.4	15	1
Constipation	<2	0	23	0.4	<2	0
Diarrhea	<2	0	23	1	22	2
Hot Flush	<2	0	22	0.2	20	0
Hypertension	<2	0	22	4	<2	1
Back Pain	<2	0	<5	0	26	5



## Breast Cancer

# Current Standards of Care in HR+/HER2- Advanced Breast Cancer and Unmet Clinical Needs

**Sara A. Hurvitz, MD, FACP**

Professor of Medicine  
Head, Division of Hematology and Oncology  
Senior Vice President, Clinical Research Division  
Department of Medicine, UW Medicine  
Fred Hutchinson Cancer Center

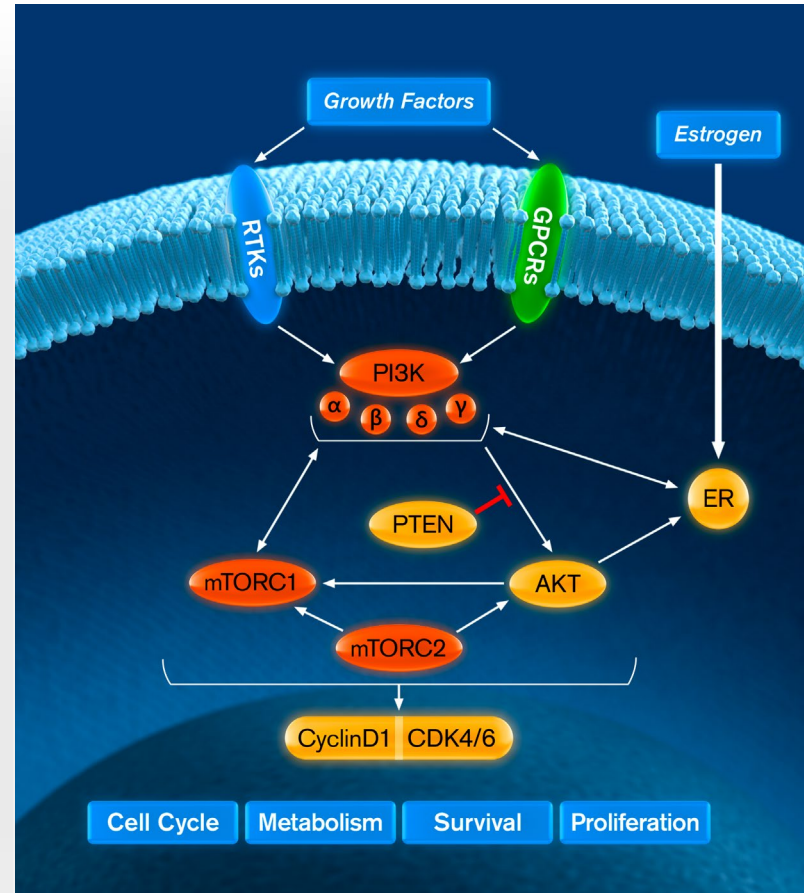


# ER, CDK4/6, & PI3K/mTOR are Interdependent Drivers of HR+/HER2- ABC

Dysregulation of these pathways promotes excessive cell proliferation and resistance to apoptosis

## ER and PI3K/mTOR

- Activation of the PI3K/mTOR pathway induces estrogen independent ER transcriptional activity by mTOR
- Conversely, ER target gene expression activates upstream effectors of the PI3K/mTOR pathway
- ER also activates the PI3K/mTOR pathway by direct binding to PI3K $\alpha$
- PI3K/mTOR inhibition increases ER activity which increases sensitivity to endocrine therapy



## CDK4/6, ER and PI3K/mTOR

- Estrogen promotes cyclin D1 transcription and cyclin D1 can cause estrogen independent transcription
- Provides rationale for simultaneously inhibiting ER and CDK4/6
- CDK4/6 inhibition causes incomplete cell cycle arrest – addition of PI3K/mTOR inhibition enables more complete arrest
- PI3K/mTOR inhibition increases cyclin D1 activity which increases sensitivity to CDK4/6 inhibition

Alves, Int J Mol. Sci. 2023

# Drug Development Activities Reflect Important Role of ER, CDK4/6 and PAM

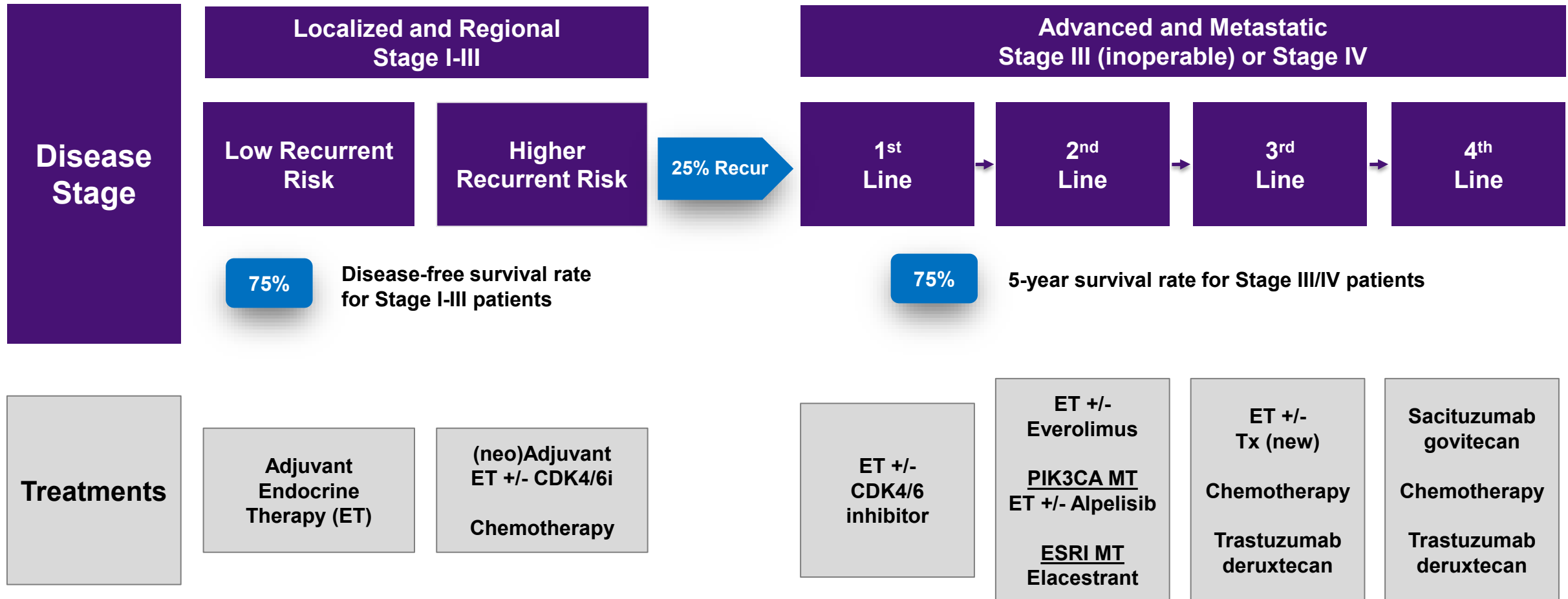
Key targeted therapy approval milestones for HR+/HER2- ABC

		1977	1997	2002	2012	2015	2019	2023
Pathway	ER	SERM Tamoxifen	AI Letrozole	SERD (IM) Fulvestrant				SERD (oral) Elacestrant
	PI3K/mTOR				mTORC1 Everolimus		PI3Kα Alpelisib	
	CDK					CDK4/6 Palbociclib		



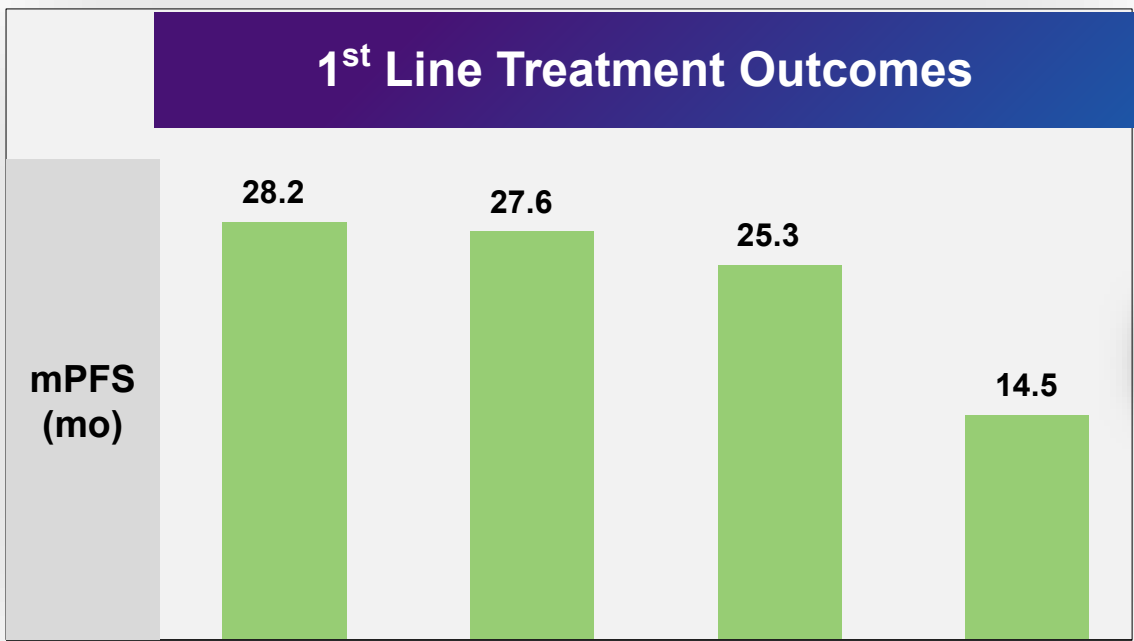
# HR+/HER2- Breast Cancer Treatment Landscape<sup>1</sup>

~30,000 women in US and ~33,000 women in 5EU and Japan die from breast cancer annually<sup>2</sup>

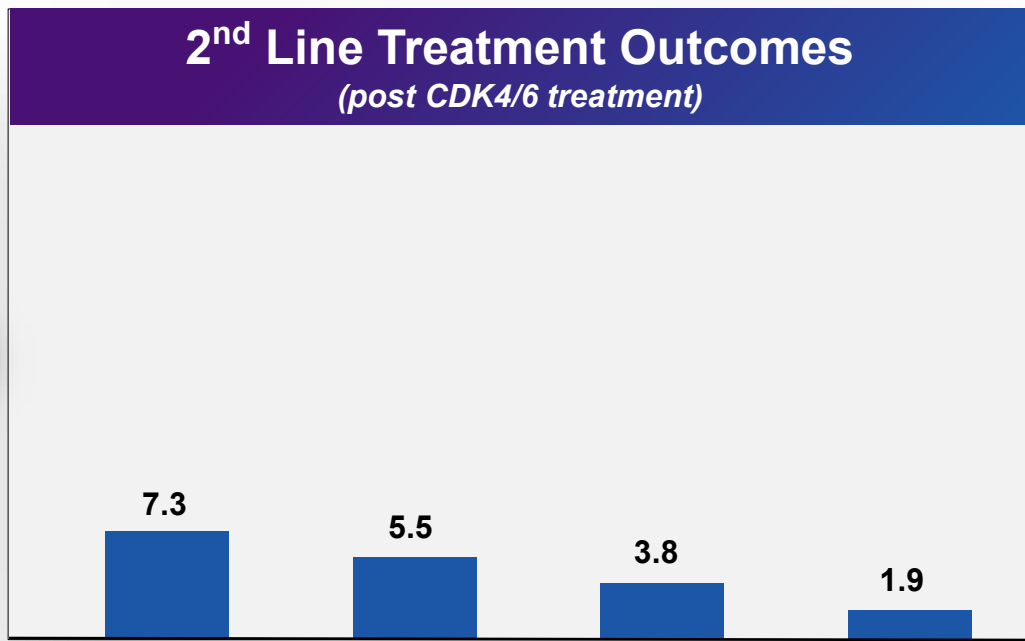


# Limited Benefit for 2nd Line HR+/HER2- ABC Patients Post-CDK4/6 Treatment

Significant need for better therapeutic options



Drugs	Abemaciclib + letrozole <sup>1</sup>	Palbociclib + letrozole <sup>2</sup>	Ribociclib + letrozole <sup>3</sup>	Letrozole <sup>2</sup>
MOA	CDK4/6 + AI	CDK4/6 + AI	CDK4/6 + AI	AI
Pat Pop	All	All	All	All
mPFS	28.2	27.6	25.3	14.5
ORR	55%	55%	53%	44%



Alpelisib + fulvestrant <sup>4</sup>	Capivasertib + fulvestrant <sup>5</sup>	Elacestrant <sup>6</sup>	Fulvestrant <sup>6</sup>
PI3Kα + SERD	AKT + SERD	SERD	SERD
PIK3CA MT	All	ESRI MT	All
7.3	5.5	3.8	1.9
21%	23%	7%	6%

# Key Unmet Needs for Patients with HR+/HER2- ABC

## Key Unmet Needs

- Improve mPFS after progression on CDK4/6 inhibitors
  - PIK3CA WT patients: 2 – 5.5 months
  - PIK3CA MT patients: 5.5 – 7.3 months
- Extend period before patients are treated with chemotherapy and antibody drug conjugates (ADC's)



## Key Questions

- What role can PI3K/mTOR inhibitors play?
- Is retreatment with CDK4/6 inhibitors beneficial?
- What role will new oral SERDs play?
- What role will new ADC's play?

# Initial PAM Drug Development in ABC Focused on PI3K/mTOR Inhibitors

Toxicity, PK, and efficacy limitations resulted in shift towards PAM single-node inhibitors

<div> <div>1<sup>st</sup> Gen</div> <div>PI3K/mTOR</div> <div>➔</div> </div>		<div> <div>2<sup>nd</sup> Gen</div> <div>Pan-PI3K</div> <div>➔</div> </div>		<div> <div>3<sup>rd</sup> Gen</div> <div>Single Node</div> <div>➔</div> </div>		PI3K/mTOR
Programs halted at Phase 1/2		Programs halted at Phase 3		Approved	Phase 3	Phase 3
<b>PF-04691502</b> <b>PKI-402</b> <b>Dactolisib</b> <b>BGT226</b> <b>Apitolisib</b>	<b>Pictlisib</b> <b>Omipalisib</b> <b>GSK01059615</b> <b>Samotolisib</b>	<b>Buparlisib</b>	<b>Taselisib</b>	<b>Everolimus</b> <i>(mTORC1)</i>  <b>Alpelisib</b> <i>(PI3Kα)</i>	<b>Capivasertib</b> <i>(AKT)</i>  <b>Inavolisib</b> <i>(PI3Kα)</i>	<b>Gedatolisib</b>
Orally administered Too toxic to proceed Poor PK properties		Orally administered High toxicity Limited efficacy		Orally administered Limited PFS benefit Tolerable to difficult to tolerate safety profiles		IV administered Promising preliminary PFS Well-tolerated Excellent PK properties

# Clinical Trial Results for PAM Inhibitors After Progression on CDK4/6 Therapy

Evidence of PAM pathways involvement and sensitivity to PAM inhibitors in HR+/HER2- ABC

Therapies	Patient PIK3CA Status	N	ORR	mPFS (months)	Comments
<b>Gedatolisib + Palbociclib + Fulvestrant</b> <sup>1</sup>	WT and MT	27	63%	<b>12.9</b>	<ul style="list-style-type: none"> <li>• Data for pan-PI3K/mTOR, AKT, and mTOR inhibitors suggest efficacy is independent of PIK3CA status</li> <li>• PI3Kα inhibitors have only demonstrated efficacy in patients with PIK3CA MT</li> <li>• ORR was 0% for PIK3CA WT patients treated with alpelisib + fulvestrant in a Phase 1b study<sup>8</sup></li> <li>• Alpelisib is poorly tolerated</li> </ul>
<b>Everolimus + Ribociclib + Exemestane</b> <sup>2</sup>	WT and MT	46	7%	<b>8.0</b>	
<b>Alpelisib + Fulvestrant</b> <sup>3</sup>	MT	127	21%	<b>7.3</b>	
<b>Alpelisib + Letrozole</b> <sup>4</sup>	MT	126	NR	5.7	
<b>Capivasertib + Fulvestrant vs. Fulvestrant</b> <sup>5</sup>	WT and MT	496	NR	5.5 vs. 2.6	
<b>Everolimus + Fulvestrant</b> <sup>6</sup>	WT and MT	25	NR	4.9	

(1) Wesolowski SABCS 2022, Arm D; includes 2 unconfirmed partial responses; (2) Hurvitz JCO 2022, TRINITI-1; Group 1 patients; (3) Rugo Lancet 2021, BYLieve Cohort A; (4) Juric SABCS 2021, BYLieve Cohort B; (5) Oliveira SABCS 2022, CAPItello-292; (6) Nchette ESMO 2020; retrospective analysis; (8) Juric Jama 2019, Phase 1b

Abbreviations: WT, wild-type; MT, mutant; NR, not reported

Note: No head-to-head trials have been conducted; data collected from different trials, in different patient populations and may not be comparable.

# Therapy after Progression on a CDK4/6i

Is there a benefit to retreating with CDK4/6i with a different ET or different CDK4/6i or both?

Therapies (Study)	Patient Population	N	Results	Comments
<b>Ribociclib + Switched ET</b> <b>vs.</b> <b>Switched ET</b> <b>(MAINTAIN) <sup>1</sup></b>	Prior palbociclib	103	<b>5.3 vs. 2.8 months</b> <b>HR = 0.58 (0.38-0.89)</b>	<ul style="list-style-type: none"> <li>• MAINTAIN suggests ribociclib after palbo with a different ET may be beneficial                             <ul style="list-style-type: none"> <li>• Benefit reported is comparable to treatment with a PI3Kai or AKTi + ET</li> </ul> </li> <li>• PACE showed no benefit continuing palbociclib treatment with a different ET after progression on palbociclib                             <ul style="list-style-type: none"> <li>• Sub-group of endocrine resistant patients (25% of total) reported encouraging results</li> </ul> </li> <li>• <b>Unknown whether switching from palbociclib or abemaciclib to a different CDK4/6i is beneficial</b></li> </ul>
	Prior ribociclib	14	2.8 vs. 2.8 months HR = 0.50 (0.15-1.70)	
<b>Palbociclib + fulvestrant</b> <b>vs.</b> <b>Fulvestrant</b> <b>(PACE) <sup>2</sup></b>	Prior palbociclib	154	4.6 vs. 4.8 months HR = 1.15 (0.81-1.63)	
	Endocrine Resistant	42	<b>HR = 0.41 (0.20-0.82)</b>	

# Therapy after Progression on a CDK4/6i

What role should oral SERD's play?

Therapies (Study)	Prior CDK4/6i	Prior Fulvestrant	mPFS ESR1 MT	Comments
<b>Elacestrant vs ET (EMERALD)<sup>1</sup></b>	100%	30%	<b>3.8 vs 1.9 months</b> <b>HR = 0.65, P=0.005</b>	<ul style="list-style-type: none"> <li>• <b>Data to date not as promising as expected when development of this drug class began</b></li> <li>• mPFS benefit of oral SERD's as single agents evaluated to date has been limited to patients with ESR1 mutations                             <ul style="list-style-type: none"> <li>• Magnitude of mPFS benefit ~2 months</li> </ul> </li> <li>• Several studies underway to evaluate oral SERD's with CDK4/6 inhibitors                             <ul style="list-style-type: none"> <li>• Given extended mPFS for current CDK4/6i + ET regimens, an oral SERD must add substantially greater mPFS benefit than 2 months to demonstrate efficacy</li> </ul> </li> </ul>
<b>Camizestrant vs fulvestrant (Serena-2)<sup>2</sup></b>	100% (sub-group)	0%	<b>3.8-5.5 vs 2.1 months</b> <b>HR = 0.49-68</b>	
<b>Giredestrant vs ET (aceIERA)<sup>3</sup></b>	42%	19%	5.3 vs 3.5 months HR = 0.60, P=0.06	
<b>Amcenestrant vs. ET (AMEERA-3)<sup>4</sup></b>	80%	10%	3.7 vs 2.0 months HR = 0.90	

# Therapy after progression on a CDK4/6i

When should an ADC be used?

Therapies (Study)	Patient Population	Prior Therapy	N	mPFS	Comments
<b>Trastuzumab Deruxtecan</b>  <b>(DB-04)</b>	Progressed on prior chemotherapy  HR+ HER2 IHC 1+ or 2+	70% prior CDK4/6i  1-2 prior lines of chemo in ABC (median 1)	480	<b>10.1 vs 5.4 months</b> <b>HR = 0.51; <math>P &lt; 0.001</math></b>	<ul style="list-style-type: none"> <li>• <b>Goal is to utilize endocrine backbone therapy as long as possible</b></li> <li>• <b>ADC's should be used after exhausting endocrine based regimens</b></li> <li>• Adverse event profiles are similar to chemotherapy               <ul style="list-style-type: none"> <li>• Alopecia</li> <li>• Neutropenia</li> <li>• Nausea/vomiting (especially T-DX)</li> <li>• Diarrhea (especially SG)</li> <li>• ILD (especially T-DX)</li> </ul> </li> </ul>
<b>Sacituzumab Govitecan</b>  <b>(TROPiCS-02)</b>	Progressed on prior chemotherapy  HR+/HER2-	99% prior CDK4/6i  2-4 prior lines of chemo in ABC (median 3)	543	<b>5.5 vs 4.0 months</b> <b>HR = 0.66; <math>P = 0.003</math></b>	



# Key Takeaways

A more effective PAM inhibitor may offer best opportunity to improve outcomes for HR+/HER2- ABC

1

- **The PAM pathway is key driver of breast cancer and is linked to ER and CDK4/6 pathways**
  - Approval of multiple PAM inhibitors confirm relevance of pathway

2

- **The two approved PAM therapies and one likely to be approved have shortcomings**
  - Limited efficacy: 5.5 – 7.3 months
  - Suboptimal safety profile in the case of alpelisib; leads to high discontinuation rate and limits utilization

3

- **Oral SERD's offer greater convenience than fulvestrant, but efficacy has not been as significant as was hoped**
  - ~2 months mPFS improvement has only been demonstrated in patients with ESR1 mutants
  - Obtaining approvals in combination with other agents will require greater mPFS improvement

4

- **Developing an effective and well tolerated PAM inhibitor is an important research priority**
  - Gedatolisib's early phase results are promising, and, if replicated in VIKTORIA-1 study, regimen could be new SOC

# Clinical Data for Gedatolisib in Breast Cancer

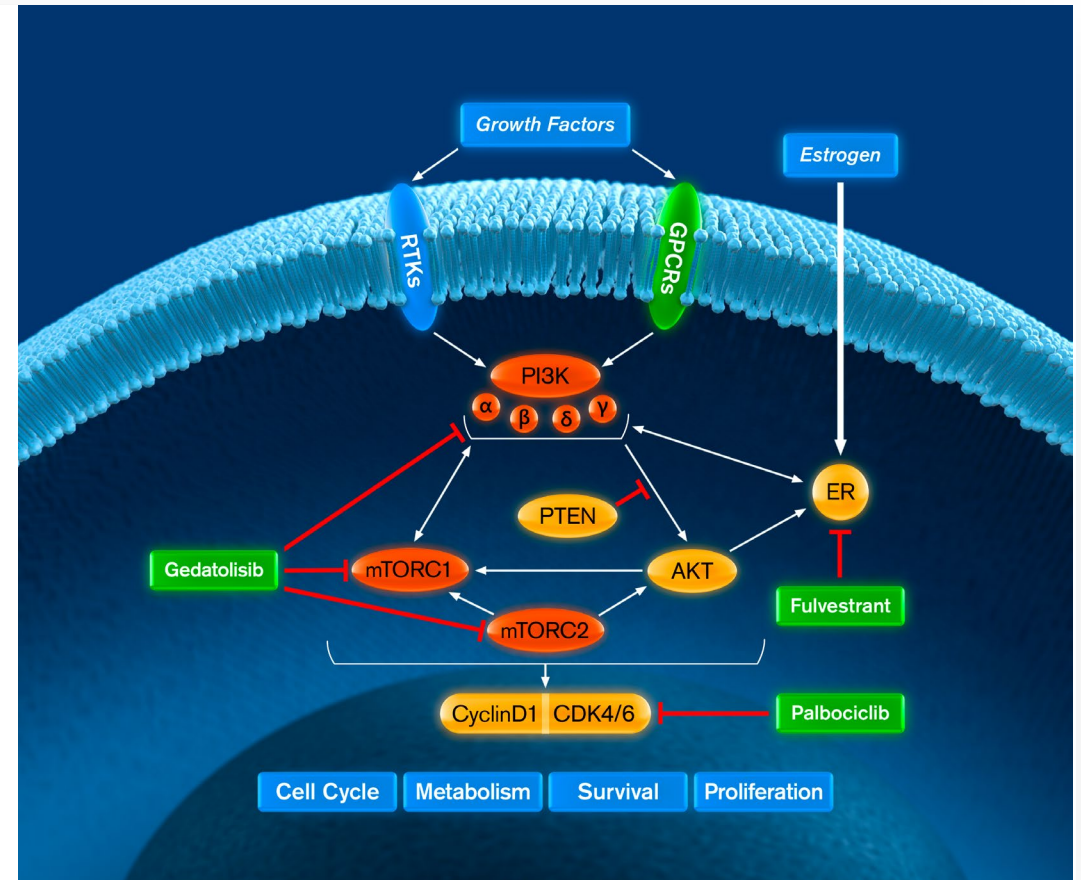
**Igor Gorbachevsky, MD**  
Chief Medical Officer

# PI3K/mTOR, ER, and CDK4/6 are Interdependent Signaling Pathways

PI3K/mTOR is a key resistance mechanism to estrogen and CDK4/6 therapies

## PI3K/mTOR + ER + CDK4/6 Inhibition *Treatment Rationale*

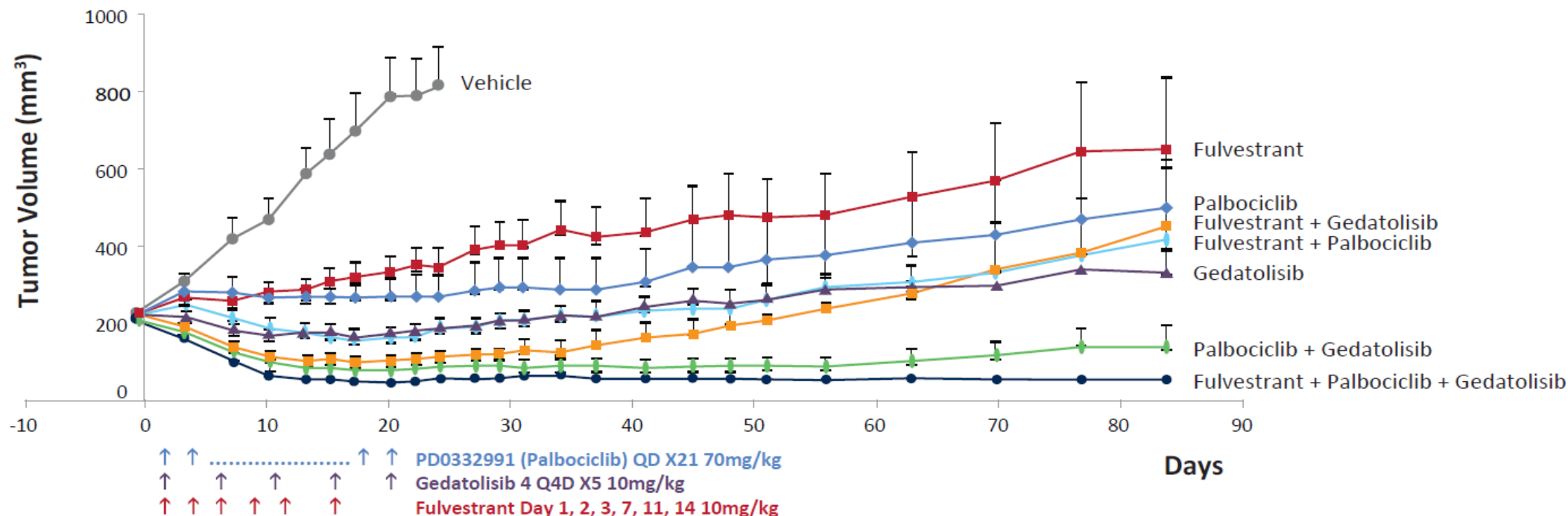
- Simultaneously blocking interdependent ER, PI3K, mTOR & CDK signaling pathways in ER+ breast cancer addresses ER and CDKi resistance mechanisms
- Inhibiting all PI3K isoforms and mTORC1/2 prevents resistance mechanisms that occur when only PI3K- $\alpha$  or mTOR are inhibited
- Leads to improved response rates and duration of response



# Non-Clinical Data Consistent with Treatment Hypothesis

Gedatolisib with palbociclib and fulvestrant in ER+/PIK3CA mutated breast cancer mouse xenograft

Cell Line: MCF7 (ER<sup>+</sup> HER2<sup>-</sup> PI3K<sup>E545K</sup>)



**Tumor Growth Inhibition**  
(during dosing)

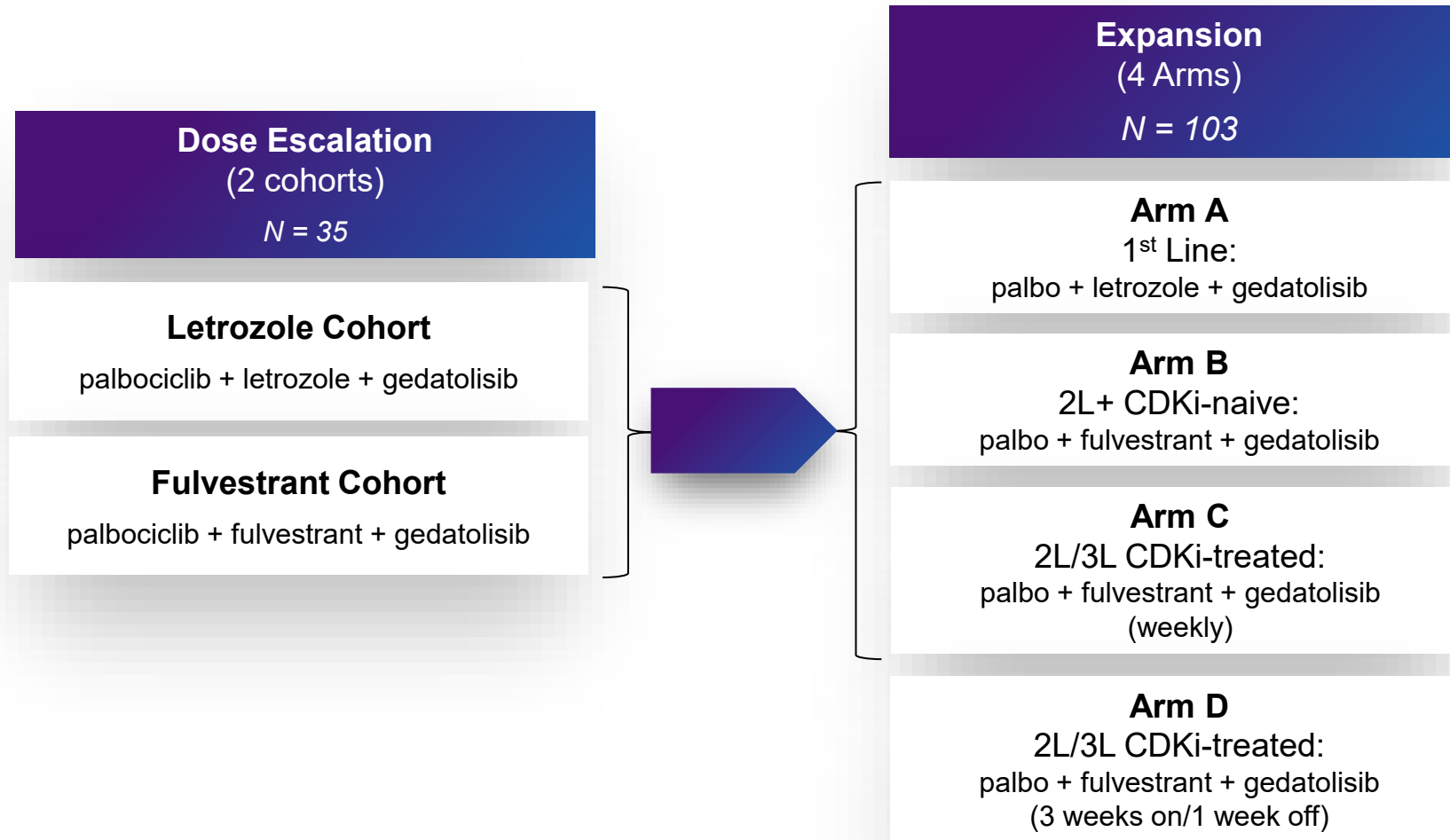
G+P+F, G+P, G+F > 120%

**Maintenance of Tumor Suppression**  
(65 Days post-dosing)

G+P+F and G+P

# B2151009: Phase 1b Study (138 patients)

Provided Data in Treatment Naïve and Prior CDK4/6 Treated Patients with HR+/HER2- ABC



# B2151009 Expansion Arms: Baseline Characteristics

	Arm A (N=31)	Arm B (N=13)	Arm C (N=32)	Arm D (N=27)
<b>Tumor, Node, Metastasis (TNM) Current Stage, n (%)</b>				
<b>Stage IV</b>	31 (100)	13 (100)	32 (100)	27 (100)
<b>Prior therapies for ABC, n (%)</b>				
<b>Prior Chemotherapy</b>	1 (3.2)	4 (30.8)	15 (46.9)	5 (18.5)
<b>Prior Endocrine Therapy<sup>1</sup></b>	0	11 (84.6)	31 (96.9)	26 (96.3)
<b>Prior CDK4/6 inhibitor</b>	0	0	32 (100)	26 (96.3)
<b>Number of prior systemic therapies ABC, n (%)</b>				
<b>0</b>	30 (96.8)	2 (15.4)	0	0
<b>1</b>	1 (3.2)	9 (69.2)	15 (46.9)	18 (66.7)
<b>≥2</b>	0	2 (15.4)	17 (53.2)	9 (33.3)
<b>Metastatic disease site involved</b>				
<b>Liver or Lung</b>	20 (64.5)	12 (92.3)	23 (71.9)	22 (81.5)
<b>Liver</b>	14 (45.2)	10 (76.9)	20 (62.5)	17 (63.0)
<b>Lung</b>	7 (22.6)	3 (23.1)	7 (21.9)	6 (22.2)
<b>Bone</b>	18 (58.1)	11 (84.6)	25 (78.1)	18 (66.7)
<b>Bone only</b>	0	0	0	0

# B2151009 Expansion Arms: Patient Treatment Discontinuation

Reasons for treatment discontinuation, n (%)	Arm A (N=31)	Arm B (N=13)	Arm C (N=32)	Arm D (N=27)
Progression or relapse	12 (38.7)	10 (76.9)	24 (75.0)	20 (74.1)
Global Deterioration	2 (6.5)	0	1 (3.1)	2 (7.4)
Death <sup>a</sup>	0	0	0	1 (3.7)
Adverse Event <sup>b</sup>	3 (9.7)	2 (15.4)	3 (9.4)	1 (3.7)
Protocol Violation	1 (3.2)	0	0	0
No Longer willing to participate in study	4 (12.9)	0	4 (12.5)	0
Study Terminated by sponsor <sup>c</sup>	8 (25.8)	1 (7.7)	0	2 (7.4)
Other <sup>d</sup>	1 (3.2)	0	0	1 (3.7)

a) One subject died of septic shock, which was reported as due to disease in the liver and not related to treatment.

b) Overall discontinuation rate due to AE <10%; stomatitis was the only AE that led to more than one patient discontinuing treatment (4%); no discontinuations due to hyperglycemia

c) Celcuity terminated the study and transitioned subjects who were still receiving study therapy to either expanded access protocol CELC-G-001 or a single subject investigational new drug (IND) to continue therapy.

d) Arm A: new diagnosis of renal cell carcinoma; Arm D: too many missed visits and assessments due to transportation issues/COVID-19 pandemic.

# ORR and PFS in Each Expansion Arm Was Superior to SOC

Results from Arm D - 63% ORR and 12.9 months PFS – provide basis for Phase 3 clinical trial

B2151009 Expansion Arms Efficacy Summary (N=103)								
	Arm A		Arm B		Arm C		Arm D	
Prior Therapy	1L		2L+ CDKi-naïve		2L/3L CDKi-pretreated		2L/3L CDKi-pretreated	
n (Full, response evaluable)	31, 27		13, 13		32, 28		27, 27	
Study Treatment (gedatolisib dosing schedule)	P + L + G (weekly)		P + F + G (weekly)		P + F + G (weekly)		P + F + G (3 weeks on / 1 week off)	
ORR <sup>1</sup> (evaluable)	85%		77%		36%		63%	
mPFS <sup>2</sup> , months (range)	48.4 (16.9, NR)		12.9 (7.6, 38.3)		5.1 (3.3, 7.5)		12.9 (7.4, 16.7)	
PFS % at 12 mos <sup>2</sup>	72%		55%		24%		53%	
PIK3CA Status	WT	MT	WT	MT	WT	MT	WT	MT
	81% <sup>3</sup>	16%	69%	31%	75%	25%	56% <sup>3</sup>	41%
ORR <sup>1</sup> (evaluable)	81%	100%	78%	75%	25%	63%	60%	73%
PFS % at 12 mos <sup>2</sup>	74%	60%	50%	67%	22%	29%	49%	60%



## **2nd Line HR+/HER2- Advanced Breast Cancer**

# B2151009 Arm D: Safety Summary for Phase 3 Dosing

G + P + F was well tolerated overall; < 4% discontinuation rate

- Discontinuation of gedatolisib due to AE - <4%
  - Alpelisib – 25% discontinued <sup>1</sup>
- Most TRAE's were Grade 1 or 2
- Few hyperglycemia adverse events
  - 26% all Grades, 7% Grade 3/4
  - Alpelisib (65% all, 37% Grade 3/4) <sup>2</sup>
- Stomatitis prophylaxis was not utilized in this study
  - **Swish-and-Spit dexamethasone prophylactic mouth rinse reduced Grade 2-4 stomatitis by 90%** <sup>3</sup>
  - Phase 3 study will include prophylaxis
- Neutropenia, leukopenia, and anemia AE incidence is nearly identical to PALOMA-3 (palbociclib + fulvestrant)

Arm D (n=27)  
Gedatolisib + Palbociclib + Fulvestrant  
(180 mg IV, 3 weeks on, one week off)

Related TEAE's > 30%			
	Grade 1	Grade 2	Grade 3/4
Adverse Event	%	%	%
Stomatitis <sup>4</sup>	11	56	22
Neutropenia <sup>5</sup>	-	15	67
Nausea	44	30	-
Fatigue	22	37	7
Dysgeusia	44	7	-
Diarrhea	37	-	4
Rash	19	15	7
Leukopenia <sup>6</sup>	-	19	23
Constipation	30	4	4
Vomiting	22	11	4
Anemia <sup>7</sup>	4	15	15
Hyperglycemia	15	4	7

# Arm C and D Had Significant Differences in Baseline Characteristics

Both arms enrolled patients who had received prior CDK4/6 therapy

Baseline Characteristics That Differed Significantly Between Arm C and D		
	Arm C (N=32)	Arm D (N=27)
Gedatolisib (dosing schedule)	Weekly	3 weeks on / 1 week off
Duration of Immediate Prior Therapy (DIPT)	5.2 months	13.5 months
Prior Chemotherapy (%)	47%	19%
Median Lines of Prior therapy	2	1
Participants with ≥3 metastatic disease site	59.4%	44.4%

- 61% shorter duration on immediate prior therapy in Arm C vs. D
  - 5.2 vs. 13.5 months
  - 2L patients whose prior treatment was 1L CDK4/6 + aromatase inhibitor, would expect DIPT to be 18-22 months
- 2.5 times more patients received prior chemotherapy for ABC in Arm C vs. D
  - 47% vs. 19%
- 2X more median number of prior therapies in Arm C compared to Arm D
  - 2 vs 1
- More metastatic patients with ≥ 3 metastatic sites in Arm C vs. D
  - 59.4% vs. 44.4%

# Analysis of Arm C and D Patients with Similar Prior Treatment Durations

Enables isolation of effect of the different dosing schedules used in each arm

## Duration of Immediate Prior Treatment (DIPT)

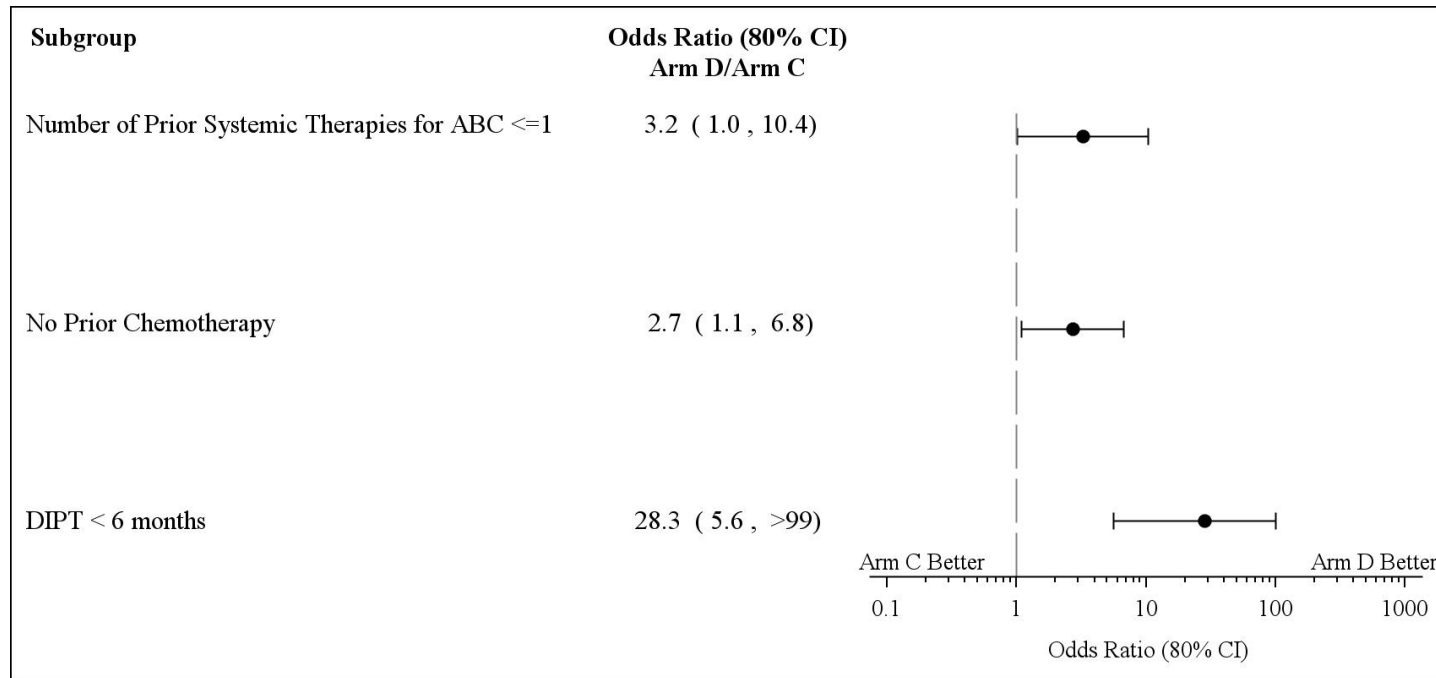
	DIPT <180 Days		DIPT <365 Days	
	Arm C	Arm D	Arm C	Arm D
# Evaluable patients with DIPT <185 or 365 days (% of evaluable)	12 (44%)	7 (27%)	20 (74%)	11 (42%)
Gedatolisib Dosing Schedule	Weekly	3 weeks on / 1 week off*	Weekly	3 weeks on / 1 week off*
Median DIPT (months)	3.2	3.5	4.8	5.1
Median Duration of Study Treatment (DST, months)	2.7	8.9	4.3	9.2
Ratio of median DST vs. DIPT	0.8	2.6	0.9	1.8
ORR (95% CI)	0% (0%-26%)	71% (29%-96%)	15% (3%-38%)	73% (39%-94%)

### Key Finding

Patients remained on gedatolisib 2-3X longer on a 3 weeks on/one week off vs. weekly schedule when they had similar time on their prior therapy

# Forest Plot for Model-Selected Subgroups

Dose schedule effect (Arm D over C) is observed in all critical subgroups selected by a logistic regression model



## Approach

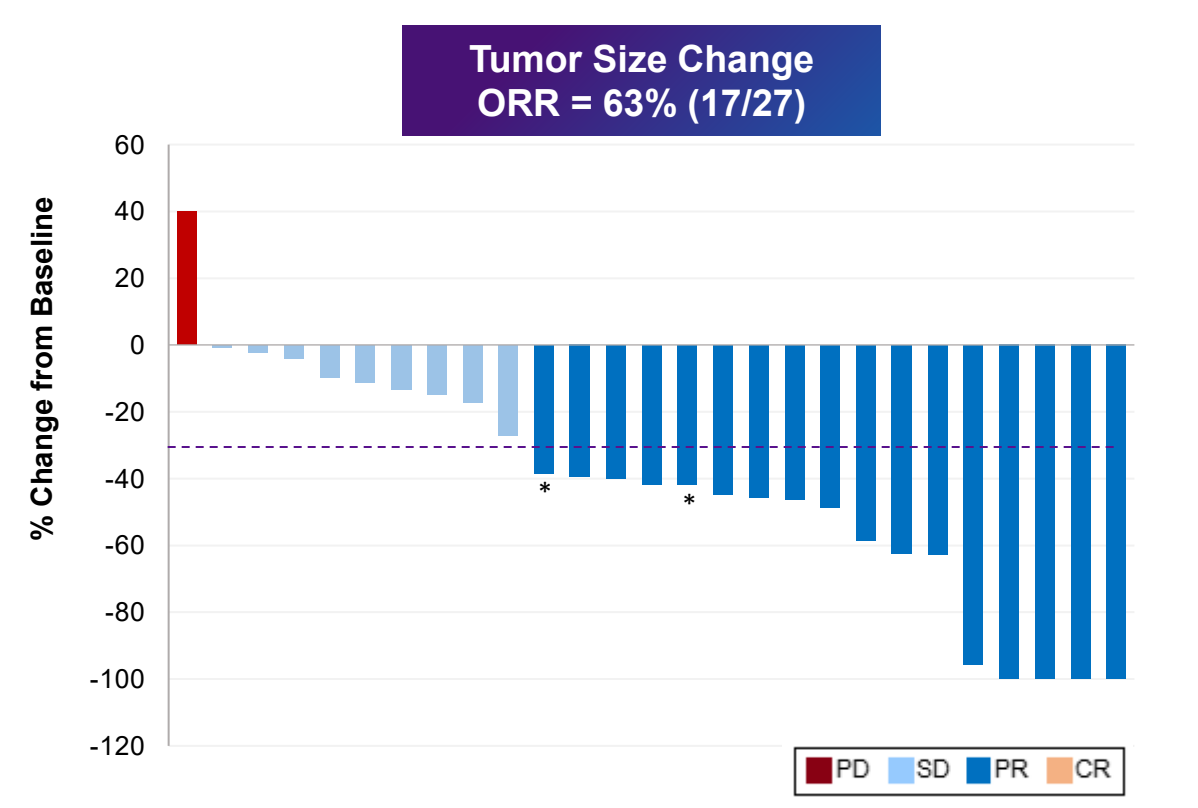
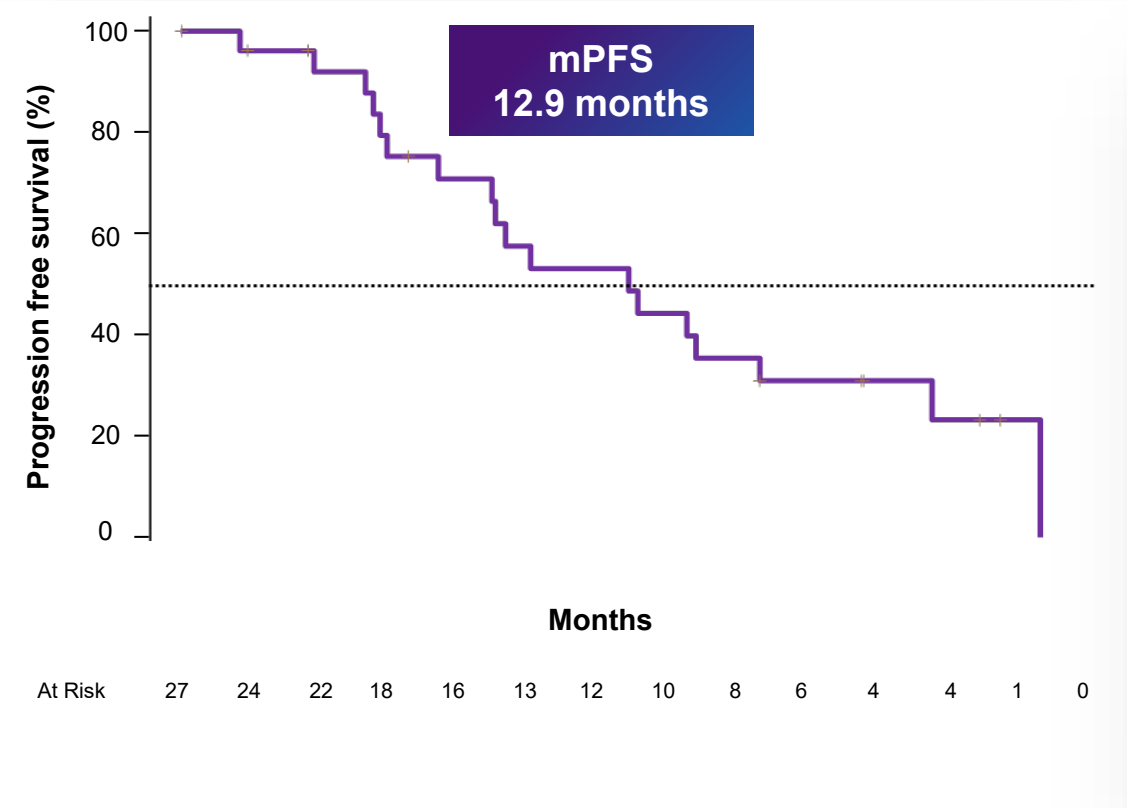
- Tested 8 factors to identify ones affecting ORR
- Of the 8 factors tested, 3 met significance criteria
  - Duration of immediate prior therapy
  - Number of prior therapies
  - Prior chemotherapy (yes or no)

## Conclusions

- Effect of dose schedule on efficacy (ORR) remained robust when controlled for all 3 factors
- Provide strong evidence that intermittent dose schedule is associated with enhanced efficacy

# Gedatolisib + Palbociclib + Fulvestrant in 2<sup>nd</sup>/3<sup>rd</sup> Line HR+/HER2- ABC Patients

Data from Arm D with Phase 3 regimen compares favorably to published data with current SOC



# Gedatolisib Combo vs. SOC for 2L HR+ / HER2- ABC Post-CDKi

Gedatolisib Combo Offers Potential for Superior Efficacy Compared to Alternatives

Patient Population	2 <sup>nd</sup> Line ER+/HER2- ABC	
All	Gedatolisib + Fulvestrant + Palbociclib <sup>1</sup>	mPFS 12.9 months ORR 63%
PIK3CA+	Alpelisib + Fulvestrant <sup>2</sup>	mPFS 7.3 months ORR 17%
PIK3CA+	Alpelisib + Fulvestrant <sup>3</sup>	mPFS 5.6 months ORR 24%
All	Capivasertib + Fulvestrant <sup>4</sup>	mPFS 5.5 months ORR 23%
ESR1+	Elacestrant <sup>5</sup>	3.8 months ORR 4%
All	Fulvestrant <sup>5</sup>	mPFS 1.9 months ORR 6%

# Phase 3 Study Design

## VIKTORIA-1

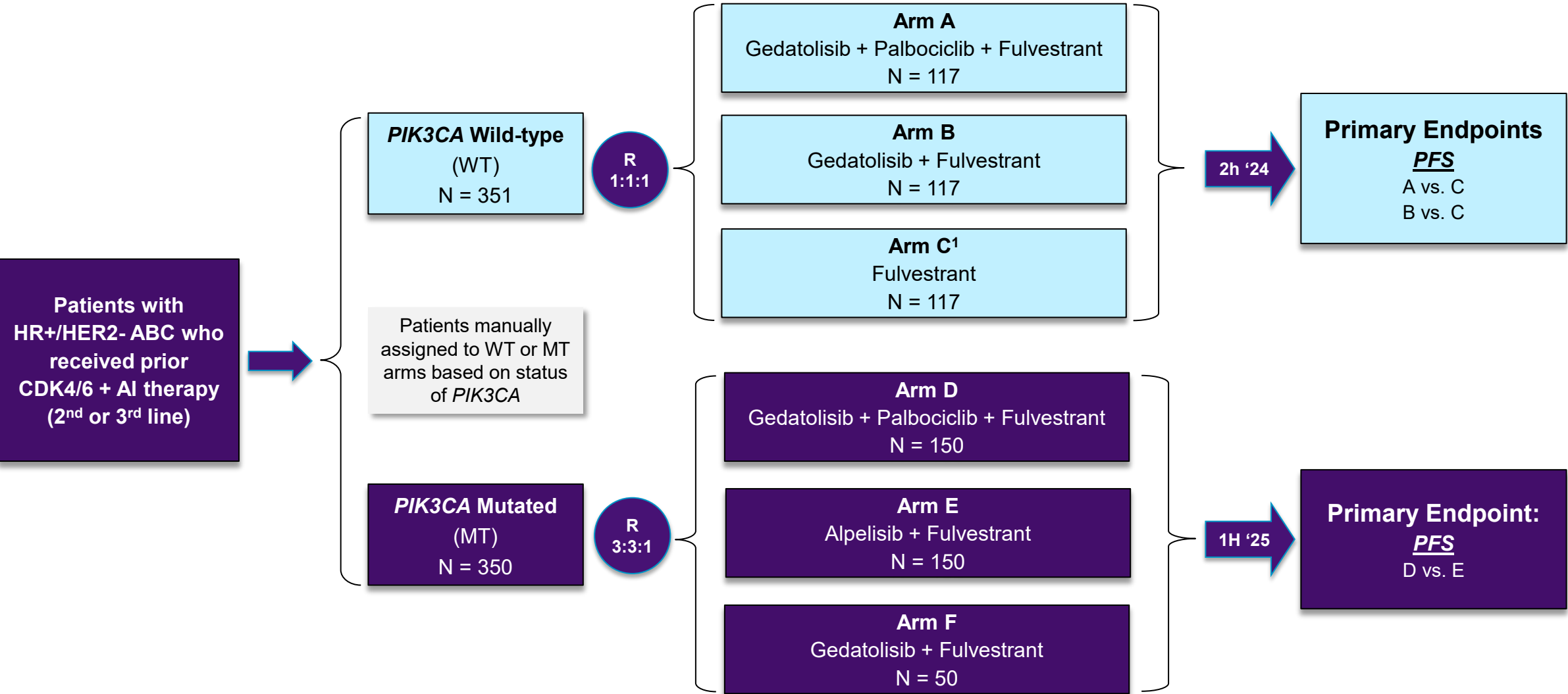


# Pivotal Trial Design Considerations for 2<sup>nd</sup> Line HR+/HER2- ABC

- Standard-of-care 2<sup>nd</sup> line treatment is based on *PIK3CA* status
- ~35% of patients have disease with *PIK3CA* mutations
- PFS is accepted primary end point for randomized studies in ABC

Supports design with multiple  
primary endpoints in different  
sub-groups

# VIKTORIA-1 Pivotal Phase 3 Trial Design Overview



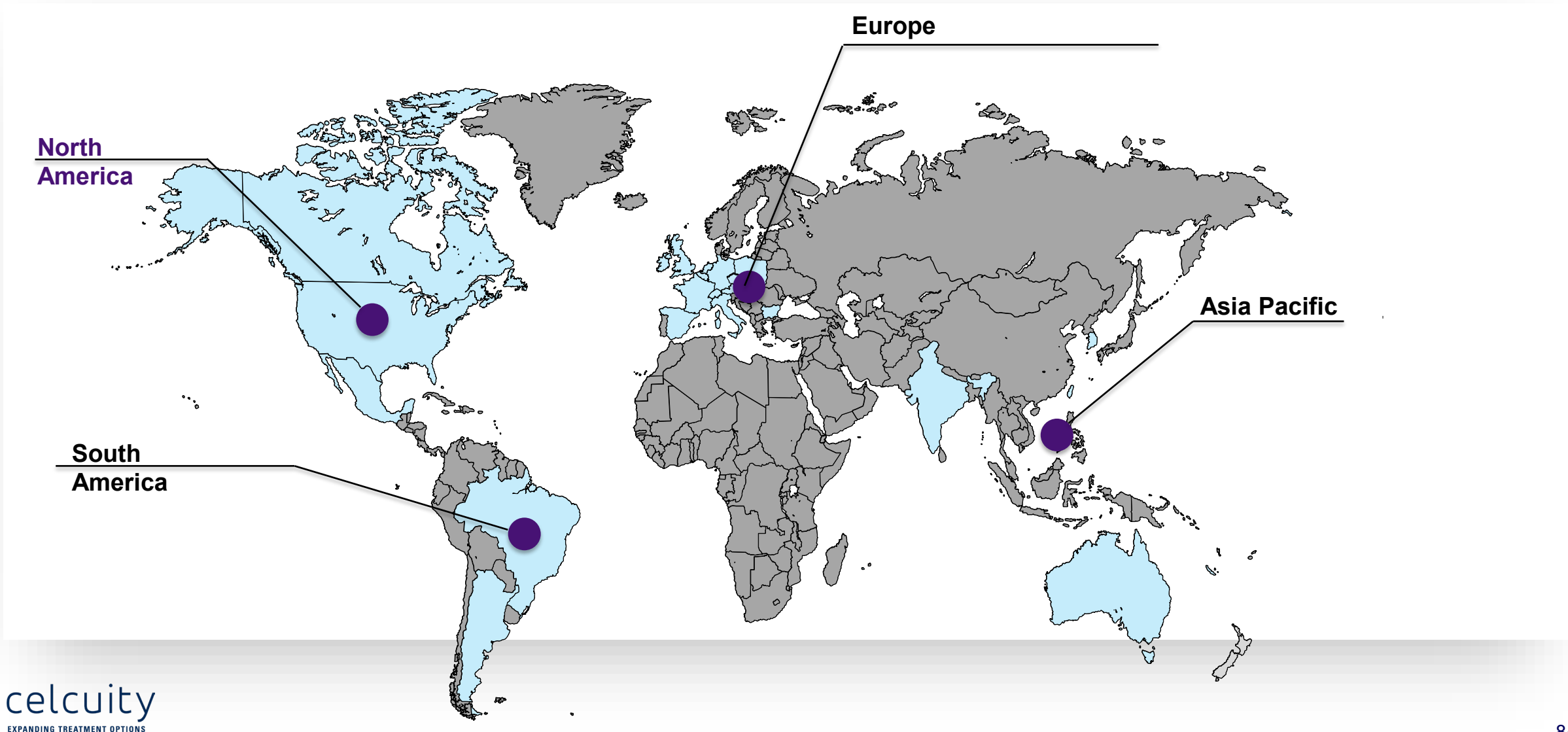
1) Optional Cross-over to Arm A or Arm B upon progressive disease; WT = wild type; MT = mutant; PFS = progression free survival

# VIKTORIA-1 Pivotal Study Features

- **Global open-label randomized study**
- **Key eligibility criteria:**
  - Any *PIK3CA* status
  - Prior CDK4/6i + NSAI
  - Any menopausal status
  - $\leq 2$  prior endocrine therapy
  - No prior chemotherapy for ABC
- **Three primary endpoints could support three separate indications**
  - Two co-primary endpoints (PFS) in *PIK3CA* WT patients
  - One primary endpoint (PFS) in *PIK3CA* MT patients
- **Three-arm design for *PIK3CA* WT and MT patients enables evaluation of two different regimens and shows contribution of gedatolisib**
- **Stratification by geography, prior treatment response ( $\leq$  or  $>$  6 months), presence of liver or lung metastasis (yes/no)**

Supports indications for **gedatolisib and fulvestrant with or without palbociclib as second or third treatment for patients with HR+/HER2-advanced or metastatic breast cancer** who have progressed on prior treatment with a CDK4/6 therapy in combination with AI

# 200+ Sites Across 20 Countries



# Relevant Comparisons in CDK4/6i Pretreated Patients with ABC

B2151009 Study results compared to published data for patients who received prior CDK4/6i

	Gedatolisib + Palbociclib + Fulvestrant N=27 <sup>1,2</sup>	Fulvestrant N=165 <sup>3</sup>	Fulvestrant N=52 <sup>5</sup>	Alpelisib + Fulvestrant N=126 <sup>6</sup>	Alpelisib + Fulvestrant N=121 <sup>7</sup>
<b>PIK3CA Status</b>	WT / M (56% / 41%)	WT	WT / MT (70% / 30%)	M	M
<b>Line of Therapy (% by line)</b>	2L / 3L+ (67% / 33%)	2L / 3L+ (73%/27%) <sup>4</sup>	2L / 3L+ (83% / 17%)	2L / 3L+ (37%/ 63%)	1L / 2L/ 3L+ (12% / 70% / 19%)
<b>mPFS (months)</b>	12.9	1.9	1.9	5.6	7.3
<b>ORR</b>	63% (overall) <sup>2</sup> <u>WT</u> 60% <u>M</u> 73%	NR	6%	22%	17%
<b>PFS % at 12 months</b>	53% (overall) <u>WT</u> 49% <u>M</u> 60%	10%	12%	22%	27%

# 1st Line HR+/HER2- Advanced Breast Cancer

# B2151009 Treatment Naïve Patients: Baseline Characteristics

	Escalation Arm A (n=11)	Expansion Arm A (N=30)	Total Treatment-Naïve (n=41)
Tumor, node, metastasis (TNM) stage, n (%)			
Stage IV	11 (100.0)	30 (100.0)	41 (100.0)
Number of Prior Therapies - Advanced Breast Cancer, n (%)			
0	11 (100.0)	30 (100.0)	41 (100.0)
Disease Site Involved, n (%)			
Liver or Lung	1 (9.1)	20 (66.7)	21 (51.2)
Liver	1 (9.1)	14 (46.7)	15 (36.6)
Lung	0	7 (23.3)	7 (17.1)
Bone	9 (81.8)	17 (56.7)	26 (63.4)
Bone Only	1 (9.1)	0	1 (2.4)
Prior Adjuvant Endocrine Therapy, n (%)			
Yes	2 (18.2)	16 (53.3)	18 (43.9)
No	9 (81.8)	14 (46.7)	23 (56.1)

# B2151009 Treatment Naïve Patients: Treatment Discontinuation

Patients who discontinued treatment, n (%)	Total Treatment-Naïve Patients (n=41)
<b>Reasons other than AE's</b>	36 (87.8)
Progression or relapse	15 (36.6)
Study terminated by sponsor <sup>1</sup>	9 (22.0)
Withdrawal by Subject	6 (14.6)
Global Deterioration	2 (4.9)
Protocol Violation	1 (2.4)
Lost to Follow-up	1 (2.4)
Other <sup>2</sup>	2 (4.9)
<b>Adverse Events <sup>3</sup></b>	
Treatment related	4 (9.8)
Unknown	1 (2.4)

Source: Rugo 2023 ESMO Breast; internal data on file; (1) After study termination, nine pts in this subgroup rolled over to an expanded access protocol (EAP) and continued treatment. As of March 16, 2023, 5 of these pts remain enrolled in the EAP. (2) Other includes: withdrawal by subject, lost to follow up, global deterioration, PI decision, new diagnosis-renal cell carcinoma; (3) Treatment related AEs: 1 each of four different AE's



# Efficacy in Treatment-Naïve Population Superior to SOC

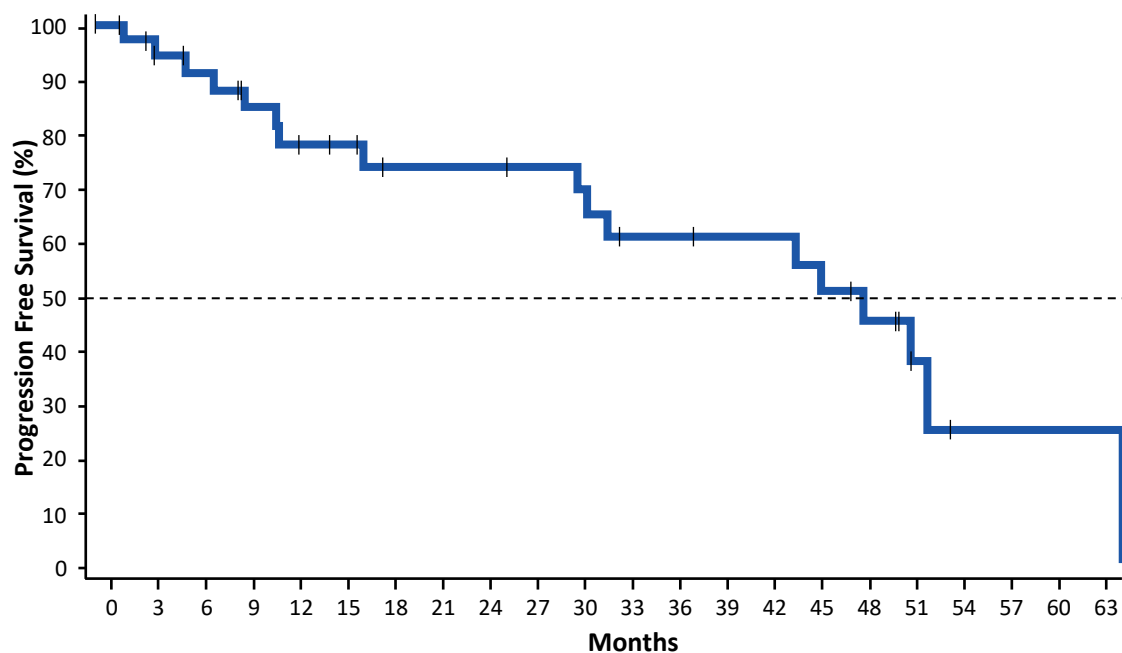
mPFS of 48.6 months, mDOR of 46.9 months, and ORR of 79%

B2151009 Treatment-Naïve Patients (N=41)			
	Escalation Arm A	Expansion Arm A	Total Treatment Naïve
<b>Progression-Free Survival (full analysis set)</b>	n = 11	n = 30	n = 41
Median PFS, mos (95% CI)	<b>45.8</b> (32.3, NR)	<b>48.6</b> (11.6, NR)	<b>48.6</b> (30.4, NR)
<b>Responses (evaluable, measurable disease)<sup>1</sup>, n (%)</b>	n = 7	n = 26	n = 33
CR	0	1 (3.8)	1 (3.0)
PR	4 (57.1)	21 (80.8)	25 (75.8)
SD	3 (42.9)	3 (11.5)	6 (18.2)
Unconfirmed PR	0	0	0
Durable SD (≥24 weeks)	1 (14.3)	2 (7.7)	3 (9.1)
PD	0	1 (3.8)	1 (3.0)
ORR <sup>1</sup>	<b>4 (57.1)</b>	<b>22 (84.6)</b>	<b>26 (78.8)</b>
Median DOR, mos (95% CI) <sup>2</sup>	<b>39.7</b> (30.5, NR)	<b>46.9</b> (11.3, NR)	<b>46.9</b> (24.6, 49.5)

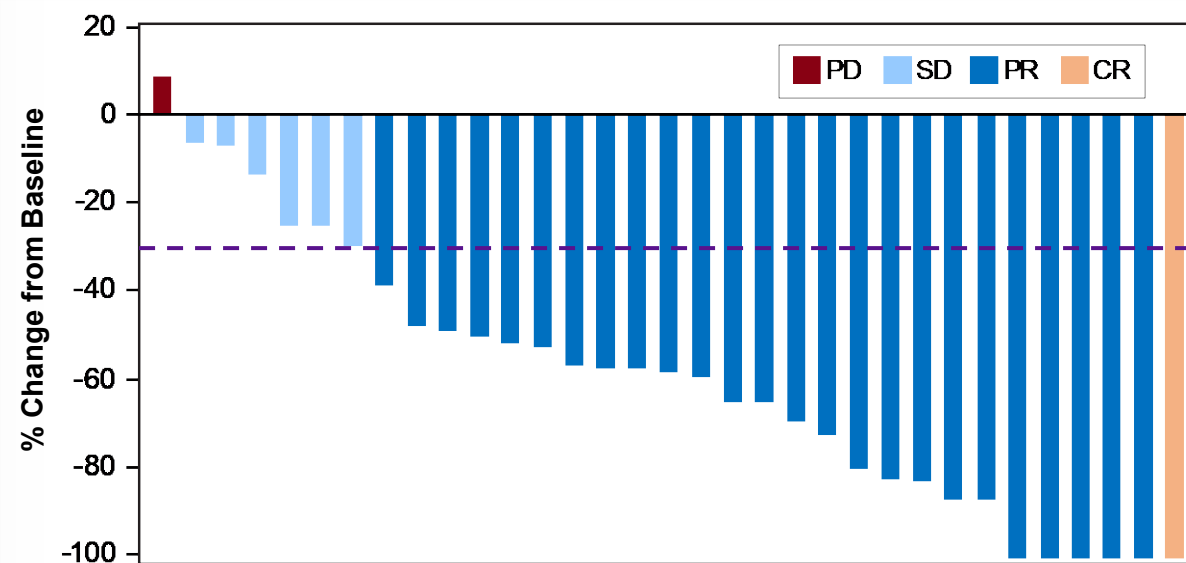
# Gedatolisib + Palbociclib + Letrozole in 1<sup>st</sup> Line HR+/HER2- ABC (N=41)<sup>1</sup>

Combined 1L data from Esc Arm A + Exp Arm A compares favorably to published data for SOC palbociclib + letrozole<sup>2</sup>

mPFS  
48.6 Months

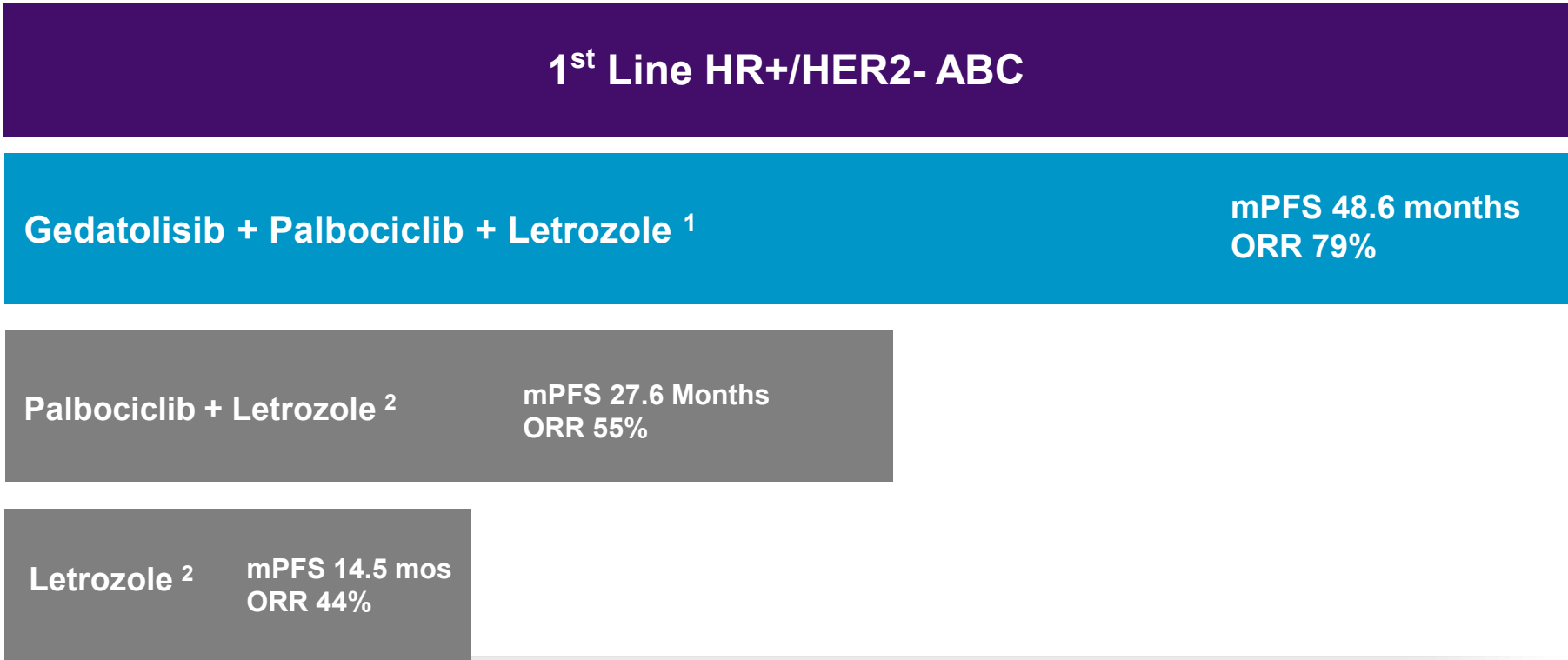


Tumor Size Change  
ORR = 79% (26/33)



# Gedatolisib Combo vs. SOC for 1L HR+ / HER2- ABC

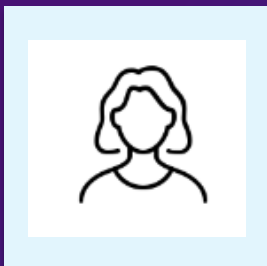
Gedatolisib Combo Offers Potential for Superior Efficacy Compared to SOC



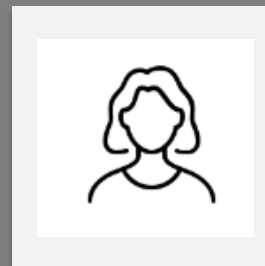
Sources: (1) Rugo 2023 ESMO-Breast. (2) Rugo H, et al. Breast Cancer Res Treat, 2019; Finn 2016. Abbreviations: mPFS = median progression free survival; ORR = objective response rate. SOC = standard of care. Note: No head-to-head trials have been conducted; data collected from different trials, in different patient populations and may not be comparable.

# B2151009: 1L and 3L Patient Overview

1L patient on therapy for 5.1 years; 3L on therapy for 4.3 years; both remain on treatment



- 62-year-old female
- Initial diagnosis of BC: 2008
- Recurrence with Stage 4 (lung metastases) on May 2018
- Start of treatment: May 2018 (Geda + Palbo + Letrozole)
- Best Overall response: PR
- **Remains on treatment**
- **Completed 67 cycles of treatment as of August 2023**



- 61-year-old female
- Initial diagnosis of BC: 2000
- Prior treatment for BC:
  - Radical mastectomy 2000
  - Adjuvant chemotherapy 2000
  - Hormonal therapy: 2001-2006
- Recurrence with stage 4 (metastases in lung) Feb 2016
- Two prior lines of therapy for ABC:
  - Chemotherapy: May - Aug '16
  - Palbociclib + Fulvestrant: Oct '16 - Mar '19
- Start of treatment: March 2019
  - Geda + Palbo + Fulvestrant
- Best Overall response: PR
- **Remains on treatment**
- **Completed 57 cycles of treatment as of August 2023**

# The Celcuity Opportunity

**Don't blame the pathway for limited efficacy and tolerability of PAM inhibitors**

**Blame the drugs**

## **Significant untapped potential to treat PAM pathway involved cancers**

- Failures, limited efficacy, and lack of tolerability of other PAM inhibitors reflect limitations of the drugs, not irrelevance of pathway
  - MOA of single node PAM inhibitors have limited potential to achieve potency or cytotoxicity necessary to optimize efficacy
  - Oral route of administration challenging

# The Celcuity Opportunity

Significant untapped potential to effectively treat PAM pathway involved cancers

1

- Gedatolisib's differentiated MOA and PK profile result in a highly potent and cytotoxic PAM inhibitor

2

- Very compelling data in 1L and 2L patients with HR+/HER2- ABC
- Potential to replace currently available standard-of-care

3

- Strong scientific rationale to develop gedatolisib for prostate cancer indications
- Parallels between breast and prostate cancer – interdependent activity between PAM pathway and hormonal pathways

4

- Uniquely positioned to advance multiple potential blockbuster indications in breast and prostate cancer

# Q&A

## Instructions

- Submit questions using the Q&A feature on the event page

## Participants in Today's Q&A Session



**Brian Sullivan**

*Chief Executive Officer and Co-Founder*



**Lance Laing, PhD**

*Chief Scientific Officer and Co-Founder*



**Igor Gorbachevsky, MD**

*Chief Medical Officer*