Diabetology for the Medical Oncologist: Managing Hyperglycemia in Patients with Breast Cancer Receiving Agents Targeting the PI3K/AKT/PTEN Pathway

A CME/MOC-Accredited Live Webinar

Thursday, March 5, 2026

5:00 PM – 6:15 PM ET

Faculty

Jamie Carroll, APRN, MSN, CNP
Professor Giuseppe Curigliano, MD, PhD
Marie E McDonnell, MD
Hope S Rugo, MD

Moderator

Neil Love, MD

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Faculty

Jamie Carroll, APRN, MSN, CNP
Assistant Professor, Oncology
Mayo Clinic
Rochester, Minnesota

Professor Giuseppe Curigliano, MD, PhD
Clinical Director
Division of Early Drug Development for Innovative Therapy
Co-Chair, Cancer Experimental Therapeutics Program
Department of Oncology and Hemato-Oncology
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European Institute of Oncology
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Marie E McDonnell, MD
Associate Professor of Medicine
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Brigham and Women's Hospital
Boston, Massachusetts

Hope S Rugo, MD
Director, Women's Cancers Program
Division Chief, Breast Medical Oncology
Professor, Department of Medical Oncology and Therapeutics Research
City of Hope Comprehensive Cancer Center
Duarte, California
Professor Emeritus, UCSF

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

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Dr Love — Disclosures

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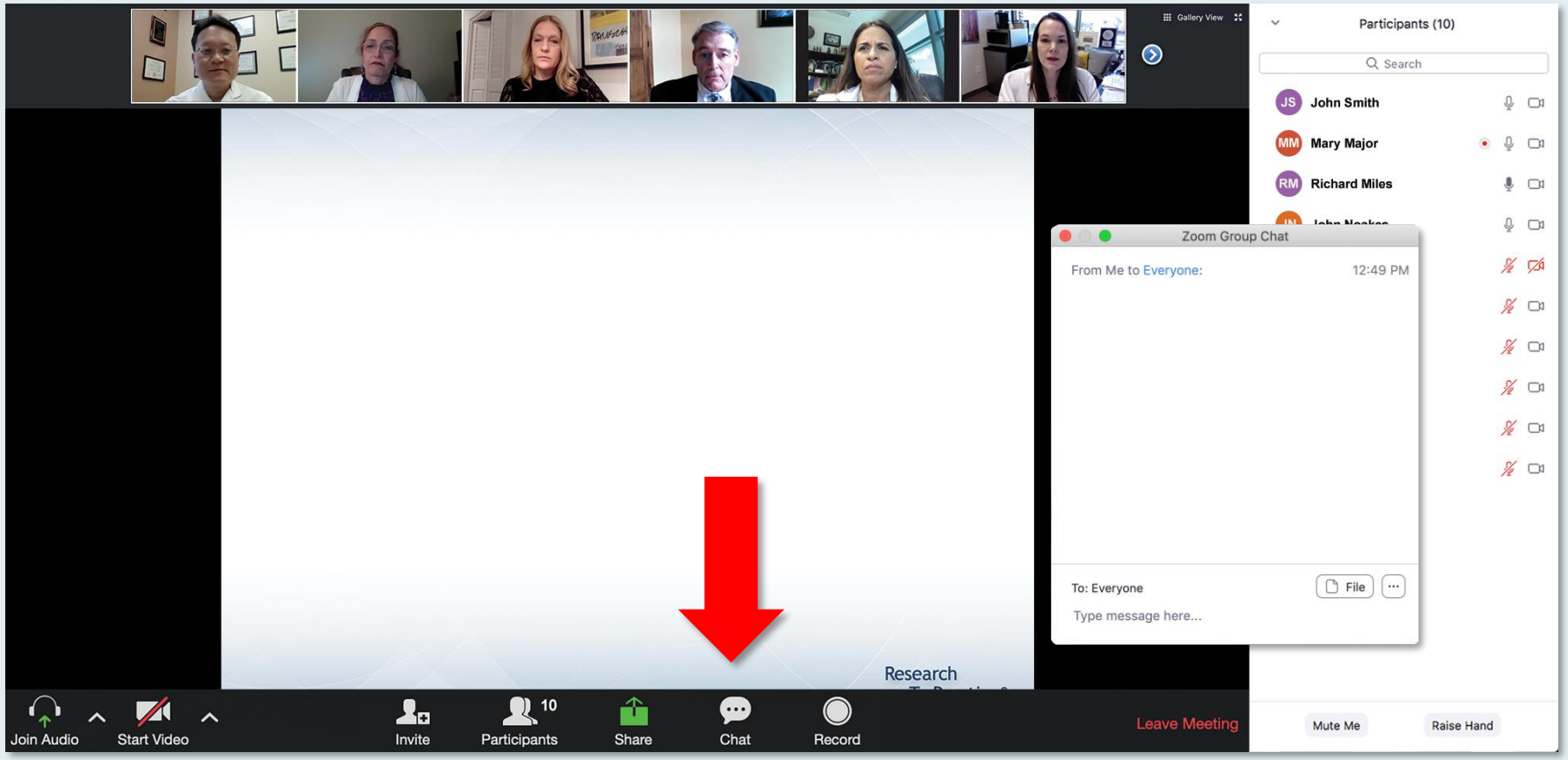

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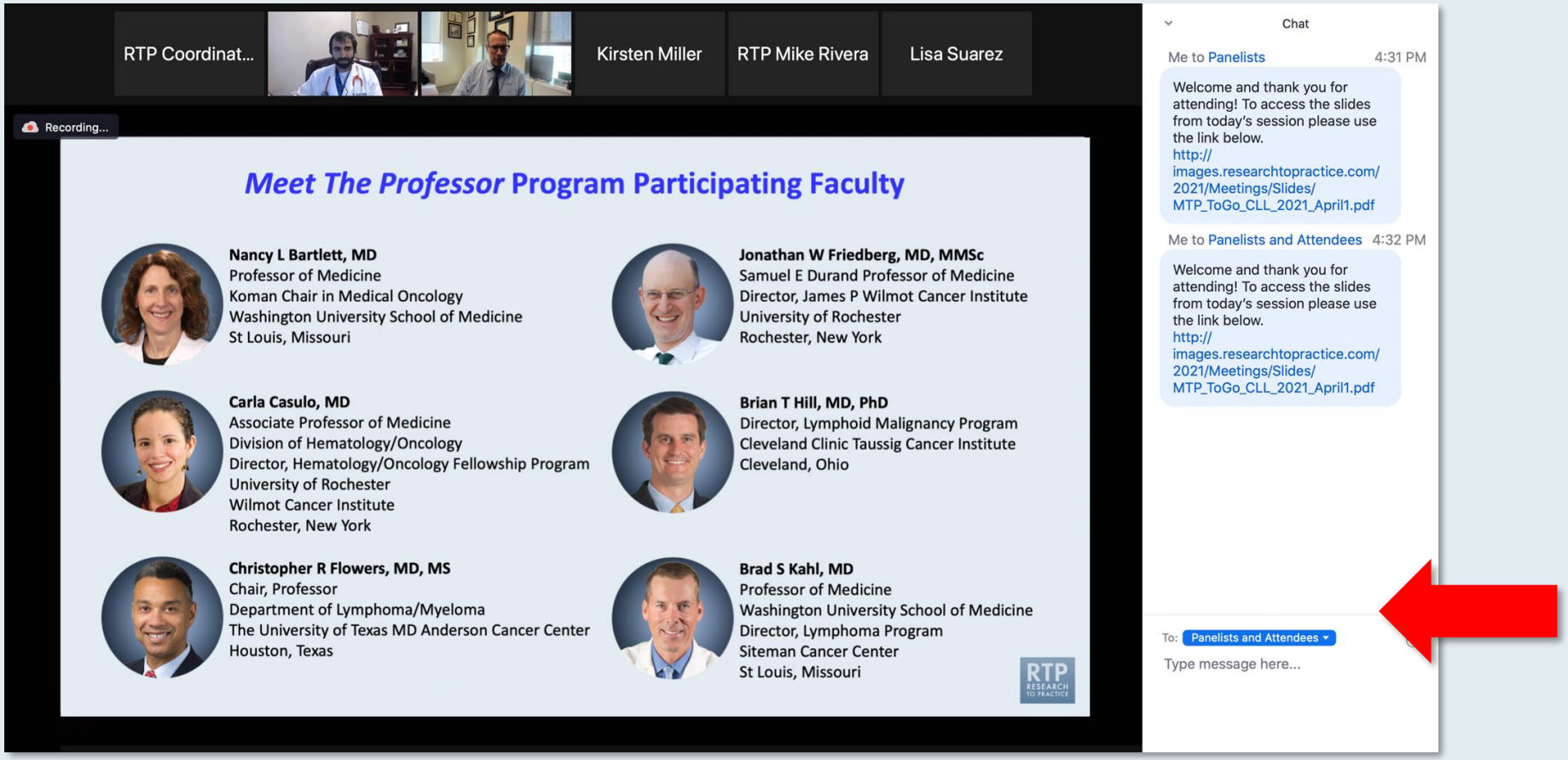

Drag the white line above the submission box up to create more space for your message.

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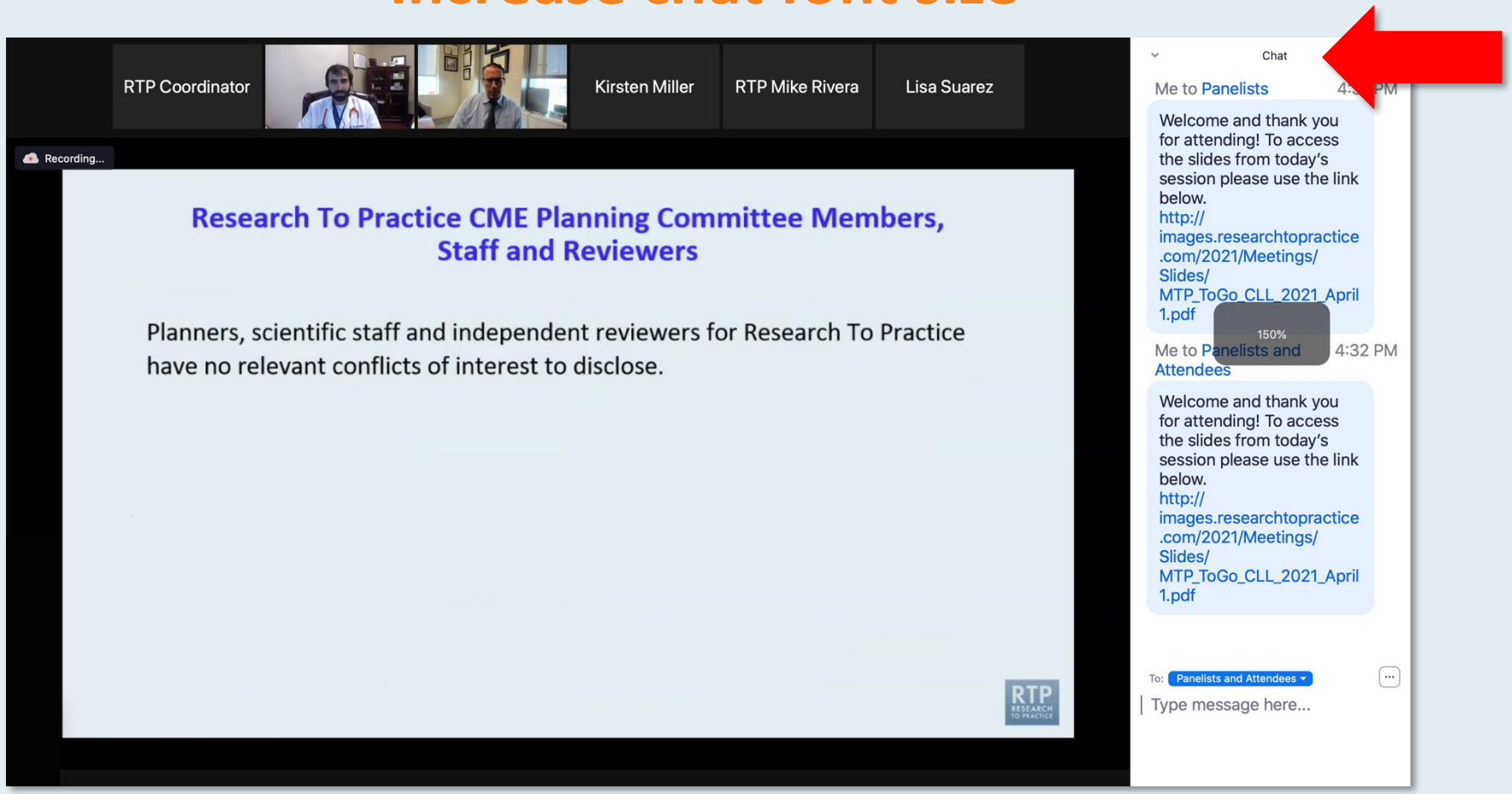

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You may do this as many times as you need for readability.

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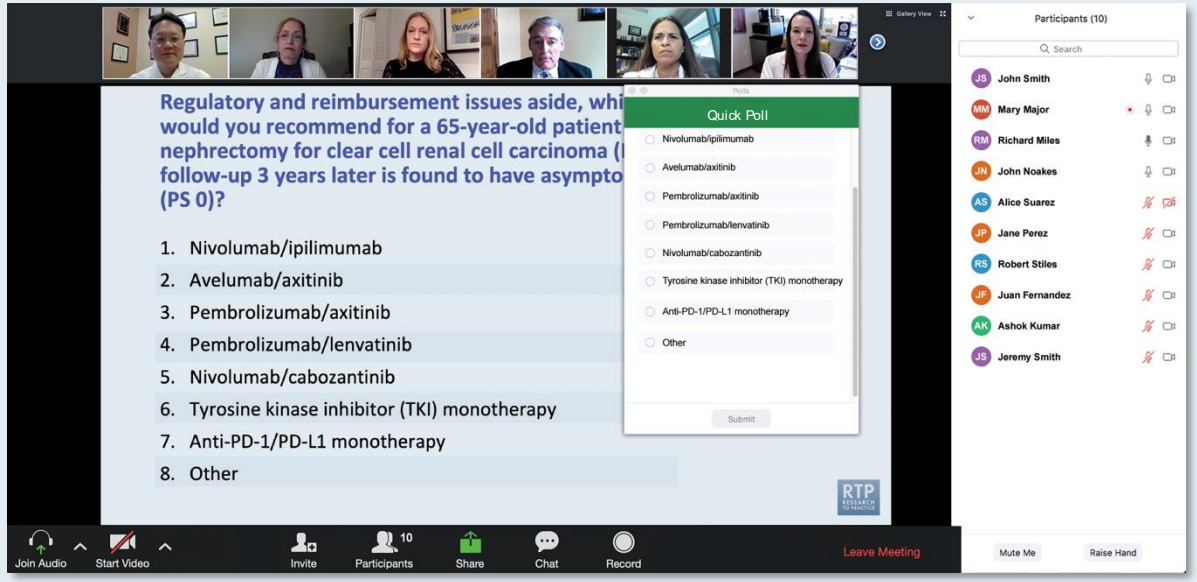


Endocrine-Based Therapy for HR-Positive Breast Cancer — Proceedings from a San Antonio 2025 Symposium Series

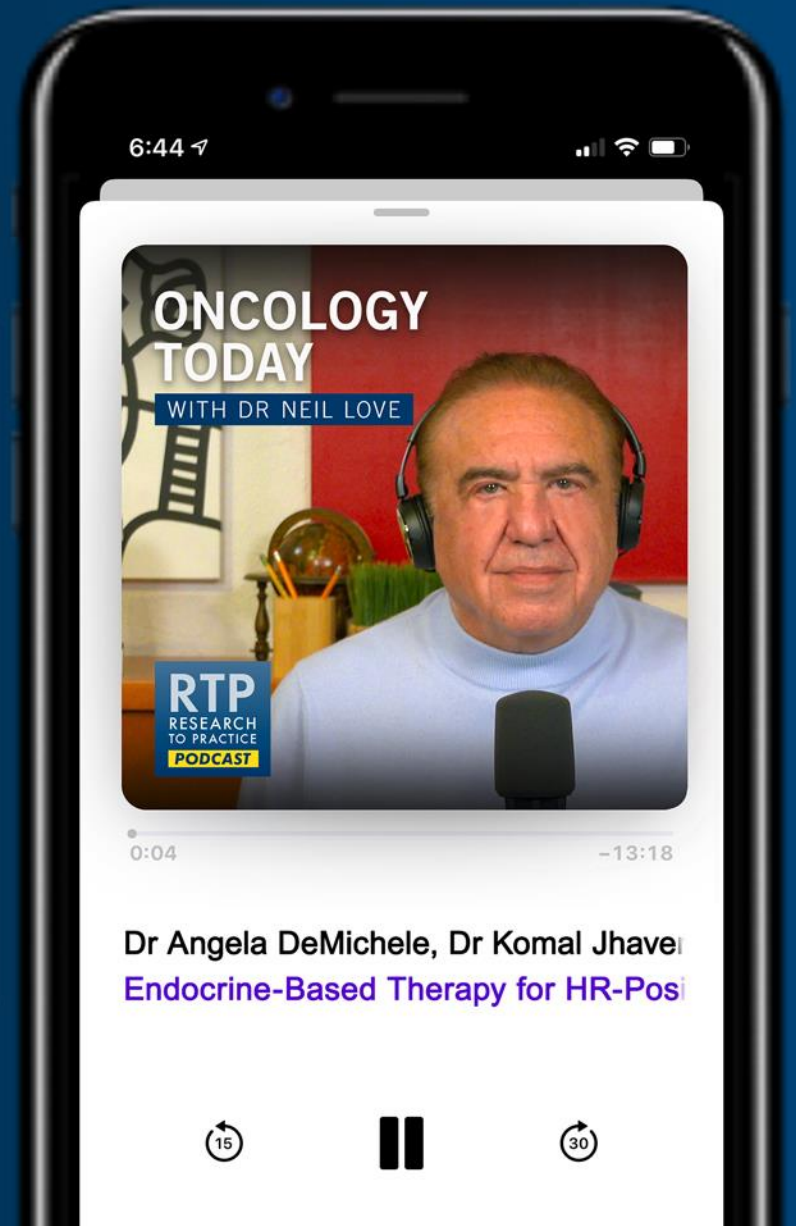
DR ANGELA DEMICHELE
ABRAMSON CANCER CENTER

DR HOPE S RUGO
CITY OF HOPE COMPREHENSIVE CANCER CENTER

DR KOMAL JHAVERI
MEMORIAL SLOAN KETTERING CANCER CENTER

DR SETH WANDER
MASSACHUSETTS GENERAL HOSPITAL

DR ERICA MAYER
DANA-FARBER CANCER INSTITUTE



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Year in Review: Clinical Investigator Perspectives on the Most Relevant New Datasets and Advances in Oncology

Bruton Tyrosine Kinase Inhibitors for Chronic Lymphocytic Leukemia

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Wojciech Jurczak, MD, PhD

Moderator

Neil Love, MD

RTP Year in Review 2026

What Clinicians Want to Know: First-Line and Maintenance Therapy for Patients with ER-Positive, HER2-Positive Metastatic Breast Cancer

A CME/MOC-Accredited Live Webinar

Wednesday, March 18, 2026

5:00 PM – 6:00 PM ET

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Ian E Krop, MD, PhD

Moderator

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Eunice S Wang, MD

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CME/MOC-Accredited Interactive Series

Regional Activities

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Save The Date

Fifth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, April 24 to 26, 2026

The Ritz-Carlton Orlando, Grande Lakes | Orlando, Florida

Moderated by Neil Love, MD

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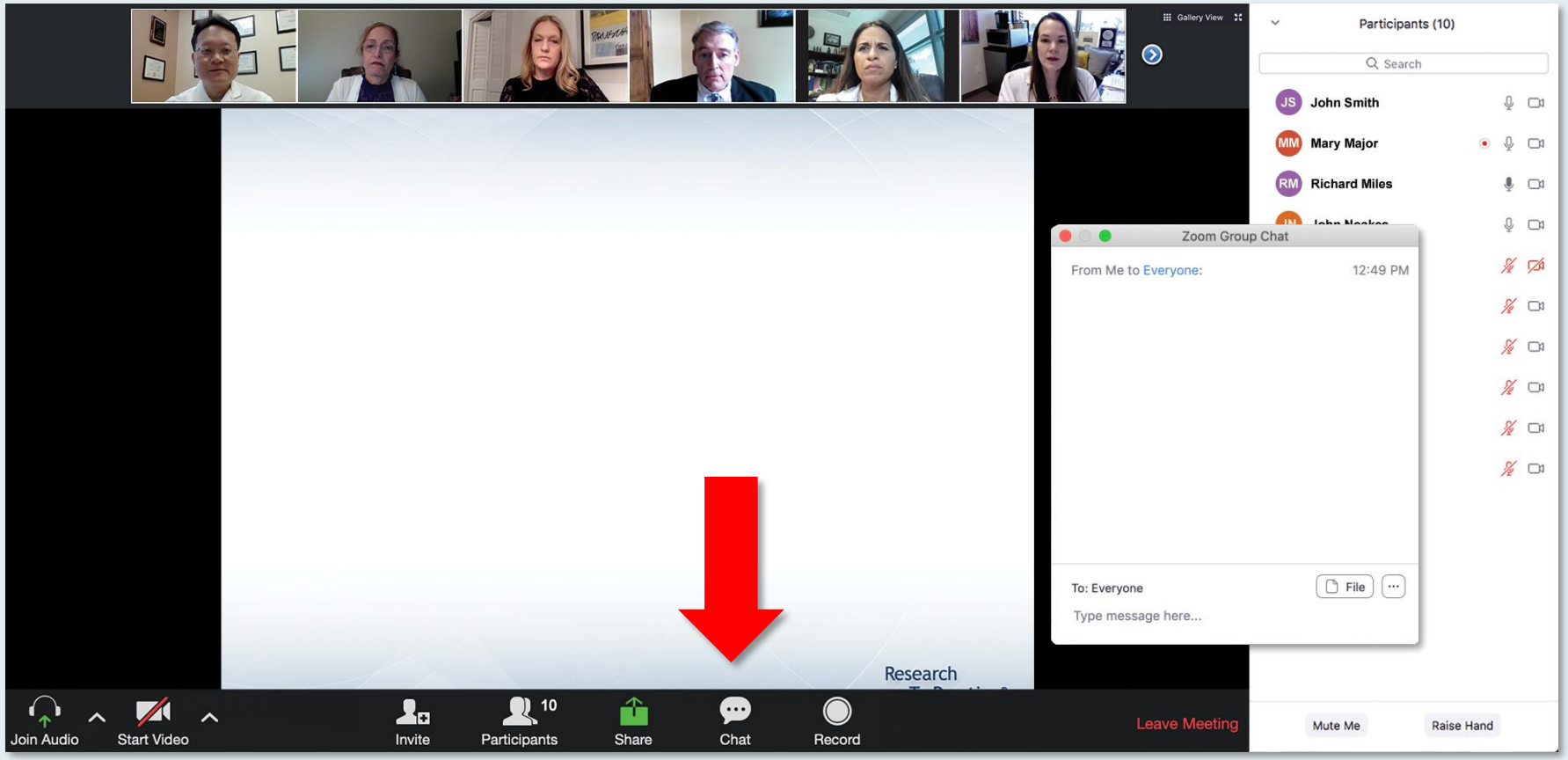

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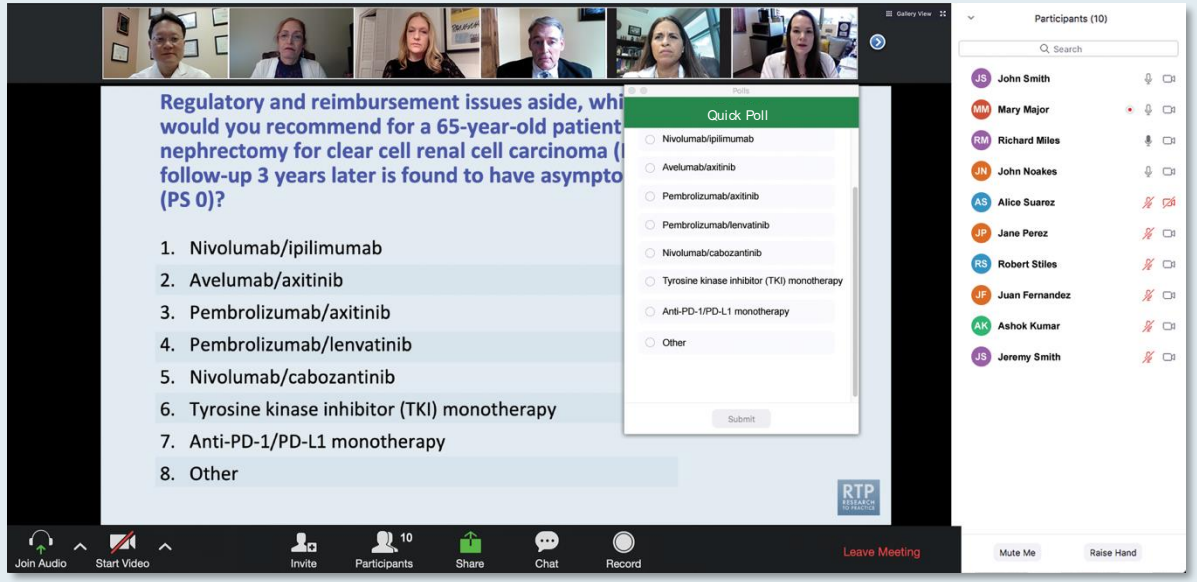

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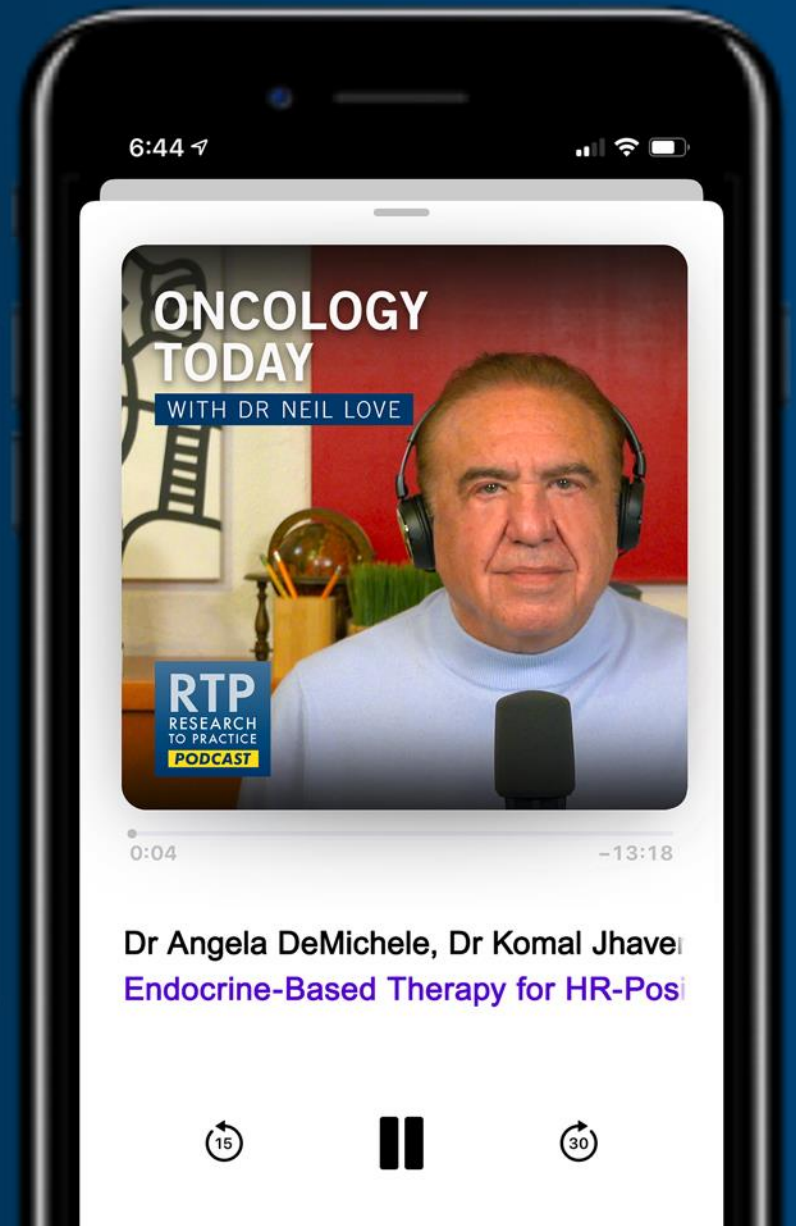

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Agenda

Introduction: Use of On-Body Glucose Monitoring Devices

Module 1: Overview of Breast Cancer and Diabetes

Module 2: PI3K/AKT/mTOR Pathway and Glucose Metabolism

Module 3: Case Presentations — Part 1

Module 4: Current Data with Alpelisib, Capivasertib and Inavolisib

Module 5: Prevention and Management of Hyperglycemia

Module 6: Case Presentations — Part 2

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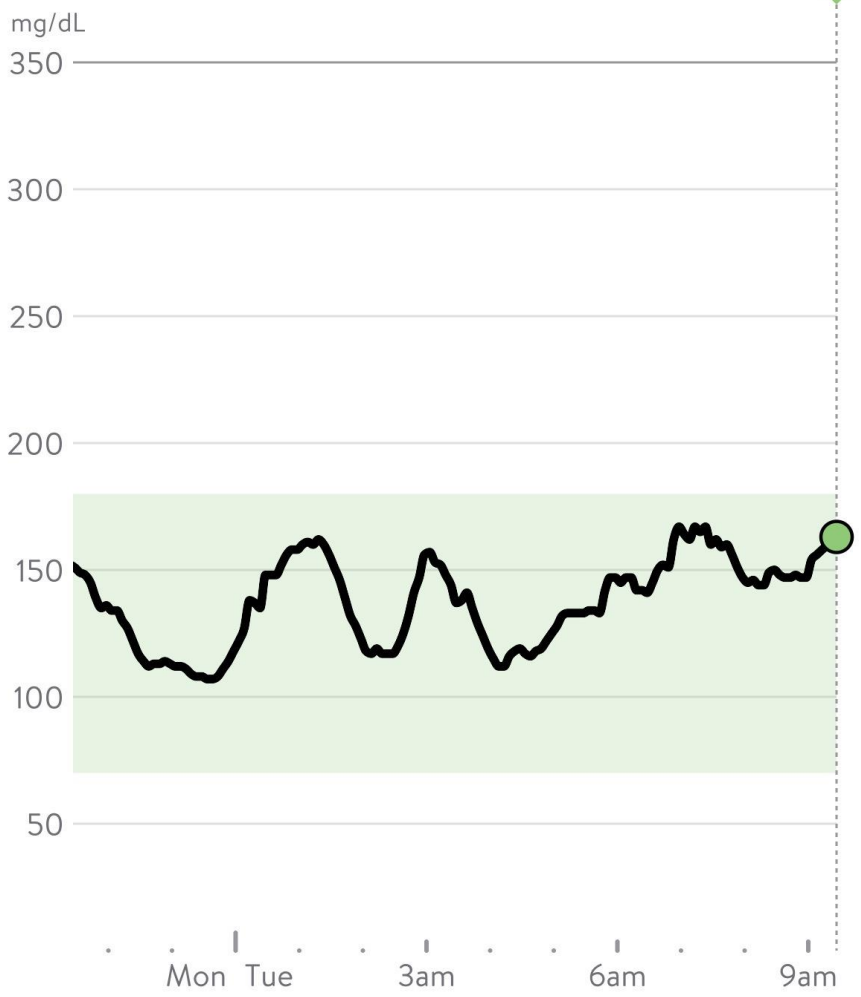
Nuovo sensore in
fase di avvio
59
minuti


OK
124
127
128
127
00:00
12:00
24:00

Glucose In Range

163 → mg/dL



5 Days until Sensor ends

% Glucose Management Indicator (GMI)

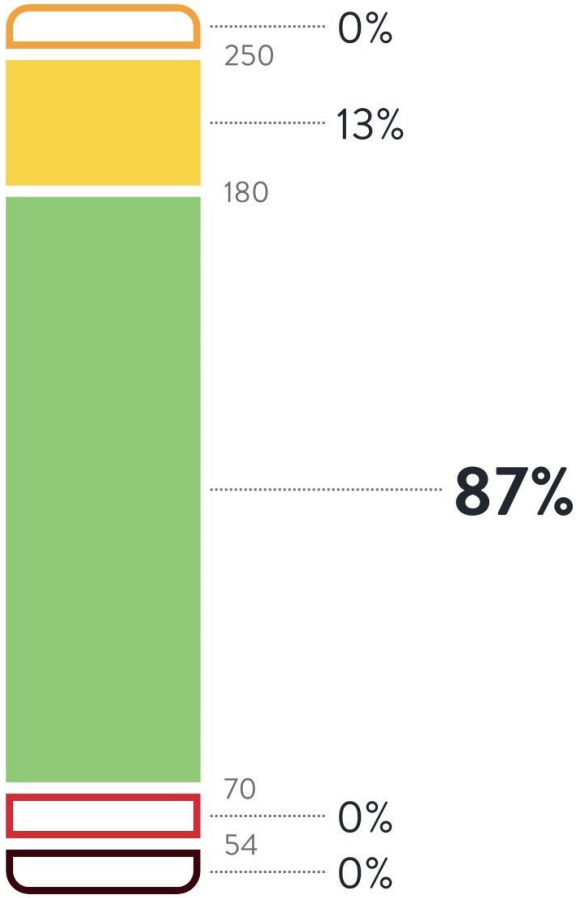
6.8%

(51 mmol/mol)

Learn More

Date range: **Feb 24 - Mar 2**
Data available for: **7 of 7 days**

Time in Range 87 %



Standard | Custom

Standard Target Range

70 - 180 mg/dL

QUESTIONS FOR THE FACULTY

What are the advantages and disadvantages of on-body glucose monitoring systems, and what specific systems are most useful?

Can physicians access the data from on-body glucose monitoring systems directly?

In which situations should an on-body glucose monitoring system be used when starting treatment with a PI3K/AKT inhibitor?

Agenda

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Managing Hyperglycemia associated with agents targeting the PI3K/AKT/mTOR pathway

Marie E. McDonnell, MD
Director, Brigham and Women's Diabetes Program
Chief, Diabetes Section
Division of Endocrinology, Diabetes and Hypertension
Brigham and Women's Hospital
Associate Professor of Medicine
Harvard Medical School

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S
Diabetes Program

HARVARD
MEDICAL SCHOOL

Today's Discussion

- **Brief Background**
- **Review the PI3K/AKT/mTOR pathway** and link to glucose levels
- **The problem of acute hyperglycemia** in people with cancer
- **Explore the available agents targeting the PI3K/AKT/mTOR pathway** : Comparative incidence, severity and timing of onset of hyperglycemia with approved (capivasertib, alpelisib, inavolisib) and investigational (eg, gedatolisib)
- **Discuss current guidelines on optimal monitoring and management** of patients receiving approved AKT and PI3K inhibitors

Brigham & Women's Diabetes program

T1 and T2 Diabetes

Monogenic diabetes

CFRD (Boston Children's Hospital)

Post-pancreatectomy diabetes

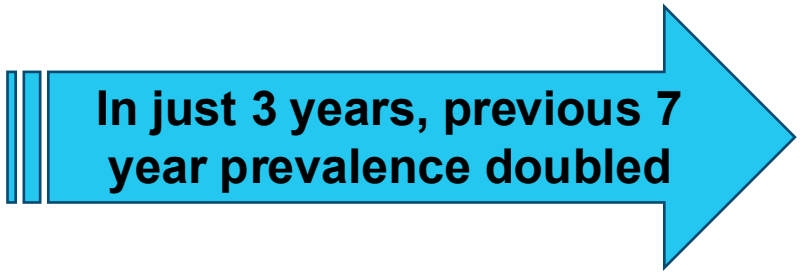
Cancer-related diabetes (Dana Farber Cancer Institute and MGB Cancer Center)

Diabetes in Pregnancy (BWH Maternal Fetal Medicine)

Syndromic diabetes

Secondary diabetes

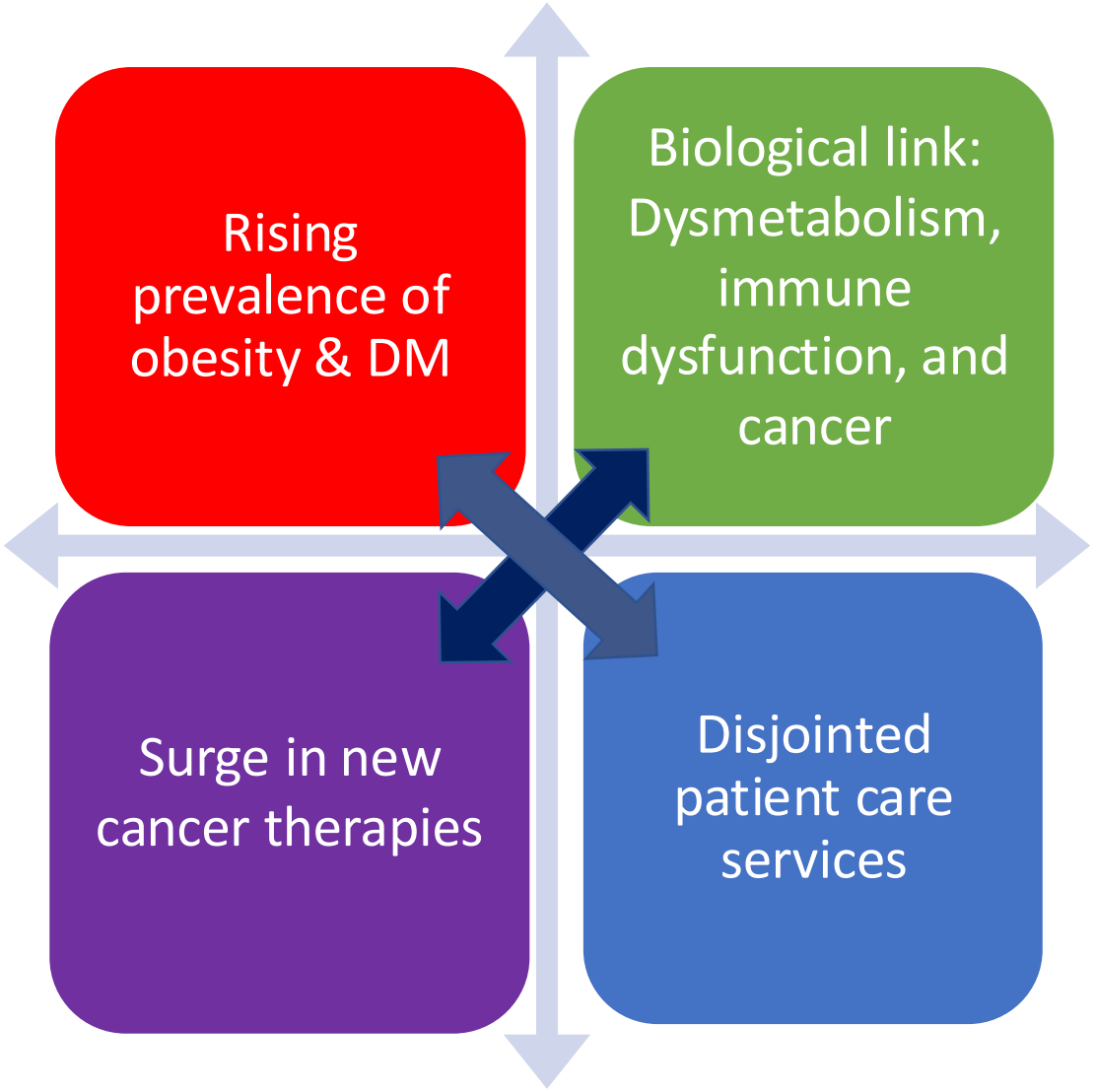
Diabetes among DFCI patients in Boston, MA



	2010 - 2017	2010-2020
Total	1471	2805
A1C < 7	783	1536
A1C > 7	500	1025

Total number of patients with breast cancer and the diagnosis of type 2 diabetes (A1c + medications OR diagnosis code)

Diabetes and cancer: *Multidimensional link*



The breast cancer case

- >20% of women with breast cancer in the US have diabetes (approx. double the prevalence in general adult population)
- Type 2 diabetes is undiagnosed in almost one-third of individuals with the disease: **“surprise” diagnoses are common**
- Breast cancer survivors with type 2 diabetes
  - 38% higher breast cancer-specific mortality; 49% higher all-cause mortality
- For early-stage breast cancer survivors, type 2 diabetes is associated with significantly shorter median disease-free survival (36 vs. 81 months); ***diabetes may be less impactful on metastatic disease survival***

Cheung YM, McDonnell ME, et al. JCEM 107(9), 2022
Eketunde et al, Cureus 12:e8010, 2020
Peairs et al, *J Clin Oncol* 29:40-6, 2011
Wolf et al, *Lancet Onc* 6:103-11, 2005

It’s not only common, it’s complicated

- Diabetes issues can be complex in cancer and usual care leads to issues such as disruption in chemotherapy or suboptimal management
- Patient engagement is challenging because diabetes self-management can be burdensome and may not be prioritized, and >30% of patients express depressive symptoms
- Specialized cancer-diabetes care delivery models have not been formally developed and studied

Srokowski TP et al, *J Clin Oncol* 27:2170-2176, 2009 Rodriguez KM, *Clinical Therapeutics* 35:170-178, 2013 Harrod JC…McDonnell ME. Diabet Med. 2024 Apr;41(4)

Groups are attempting to organize

Current Diabetes Reports (2021) 21: 62
https://doi.org/10.1007/s11892-021-01435-y

HEALTH CARE DELIVERY SYSTEMS AND IMPLEMENTATION IN DIABETES (ME MCDONNELL AND AR SADHU, SECTION EDITOR)

Check for updates

Patient-Centered Diabetes Care of Cancer Patients

Anupam Kotwal[1] · Yee-Ming M. Cheung[2,3] · Grace Cromwell[3] · Andjela Drincic[1] · Houry Leblebjian[4] · Zoe Quandt[5] · Robert J. Rushakoff[5] · Marie E. McDonnell[3]

Cheung YM, McDonnell M, Hamnvik OR. A targeted approach to phosphoinositide-3-kinase/Akt/mammalian target of rapamycin-induced hyperglycemia. Curr Probl Cancer. 2022

Gallagher EJ, Managing hyperglycemia and rash associated with alpelisib: expert consensus recommendations using the Delphi technique. NPJ Breast Cancer. 2024 Jan 31;10(1):12. doi: 10.1038/s41523-024-00613-x.

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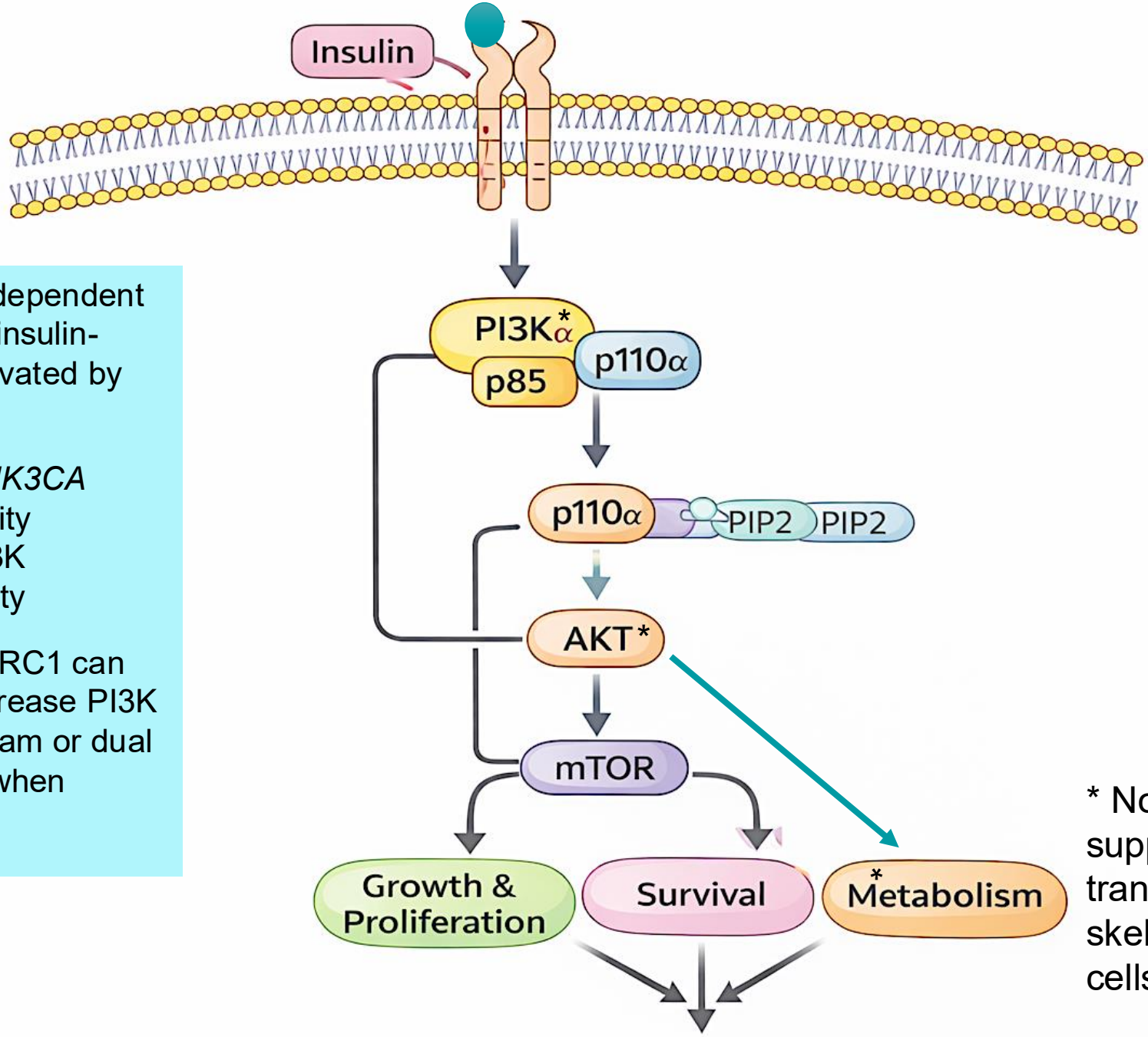
THE PI3K/AKT/MTOR PATHWAY AND LINK TO GLUCOSE LEVELS

Some cancer cells are dependent on growth signals from insulin-mediated pathways activated by mutated oncogenes

In cancer cells with a *PIK3CA* mutation, PIK3K α activity increases. Inhibiting PI3K decreases PI3K α activity

Direct inhibition of mTORC1 can upregulate AKT and increase PI3K activity, so either upstream or dual blockade is necessary when mTOR is inhibited



* Normally PI3Kα supports Glucose transport only into skeletal, adipose cells

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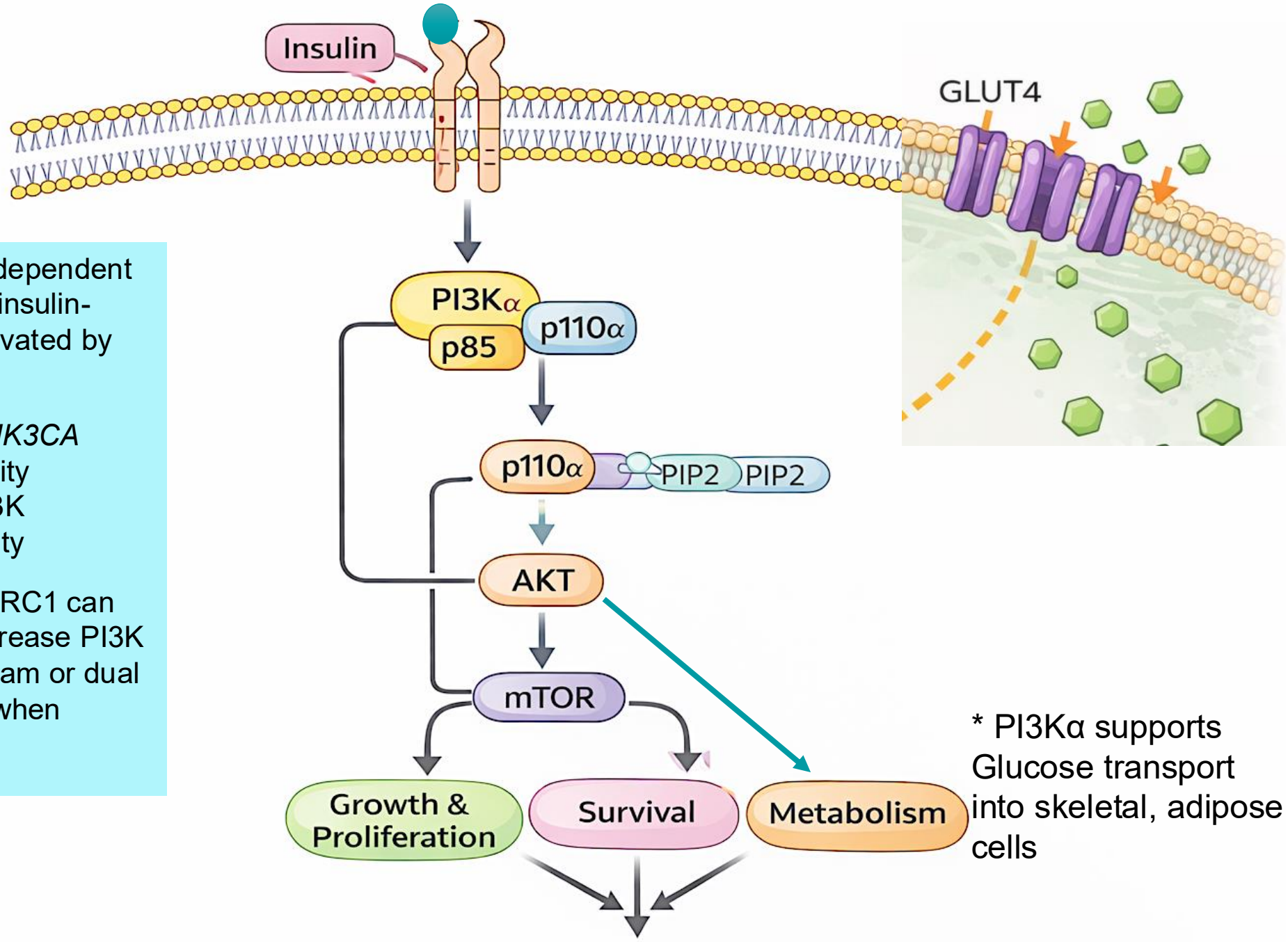


* PI3Kα supports Glucose transport into skeletal, adipose cells

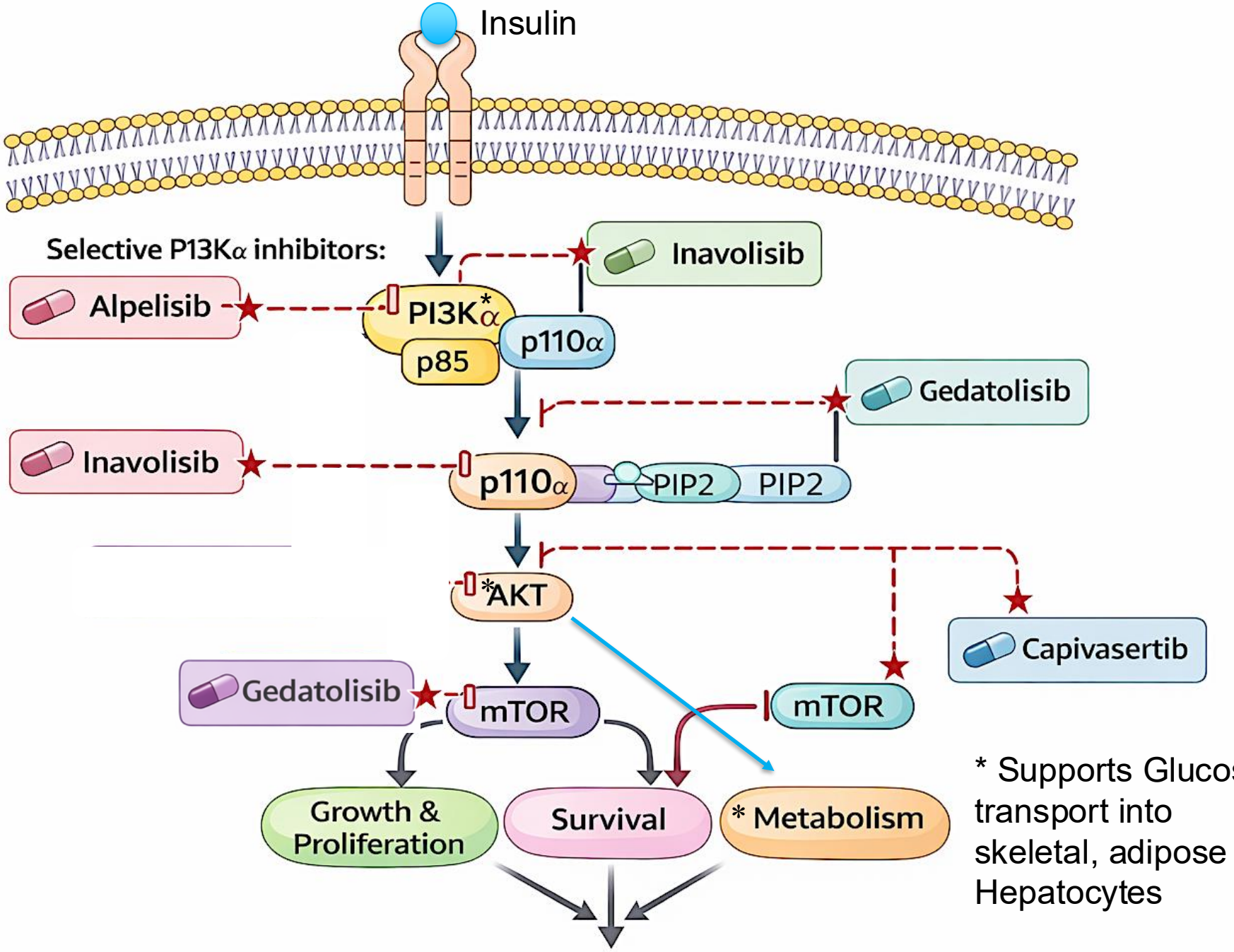
Isoforms matter

- PI3K isoforms are expressed in different tissues and possess specialized functions, hence their inhibition leads to unique adverse effects

- PI3Kα (alpelisib, inavolisib) - specific to uptake of glucose into skeletal and adipose tissues, regulates glucose output from liver

- Other - PI3K (idelalisib, duvelisib) – nonspecific nor potent inhibitors of PI3Kα

Srokowski TP et al, *J Clin Oncol* 27:2170-2176, 2009 Rodriguez KM, *Clinical Therapeutics* 35:170-178, 2013 Harrod JC…McDonnell ME. Diabet Med. 2024 Apr;41(4).C



* Supports Glucose transport into skeletal, adipose and Hepatocytes

Downstream Pan-AKT Inhibition

- Capivasertib targets all 3 AKT isoforms (AKT1/2/3), inhibiting signaling driven by PIK3CA, AKT1 and/or PTEN alterations.
- In combination with fulvestrant, capivasertib is approved in the US for adults with HR-positive, HER2-negative locally advanced or metastatic breast cancer with ≥1 PIK3CA, AKT1 or PTEN alterations, after disease progression on ≥1 endocrine therapy (ET)-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant ET.
- As capivasertib inhibits physiologic PI3K/AKT pathway signaling, it leads to on-target, off-tumor toxicities. The most common adverse events are diarrhea, cutaneous adverse reactions and elevated glucose levels.

Iyengar NM et al. *NPJ Breast Cancer* 2025 December 4;12(1):16.

QUESTIONS FOR THE FACULTY

By what mechanism do PI3K/AKT inhibitors cause hyperglycemia?

By what mechanism do corticosteroids cause hyperglycemia?

Agenda

Introduction: Use of On-Body Glucose Monitoring Devices

Module 1: Overview of Breast Cancer and Diabetes

Module 2: PI3K/AKT/mTOR Pathway and Glucose Metabolism

Module 3: Case Presentations — Part 1

Module 4: Current Data with Alpelisib, Capivasertib and Inavolisib

Module 5: Prevention and Management of Hyperglycemia

Module 6: Case Presentations — Part 2

Dr Rugo Case: 79-year-old woman

HR+/HER2- MBC: Capivasertib and Fulvestrant

- 79 yo woman
  - Left breast ER+/PR- ILD diagnosed in 2001 with 1/14 positive nodes
    - Treated with chemotherapy, surgery, radiation, tamoxifen for 2.5 years, then exemestane for 8 years stopping in 2012
  - 2020 diagnosed with metastatic disease to pleura and bone; ER+/PR-/HER2 1+
    - Treated with letrozole/palbociclib x 2.5 years then letrozole/abemaciclib (due to anemia) for 1.5 years with PD in liver and Tx dependent anemia
  - Liver biopsy ER/PR+/HER2 0; NGS + ESR1 (40%) and PIK3CA (38%) mutations
    - Treated with elacestrant/ribociclib on a clinical trial x one year with slow progression in liver
  - 12/2024 Fulvestrant and capivasertib 400 mg BID
    - Normal fasting glucose and HgbA1c (5.4)

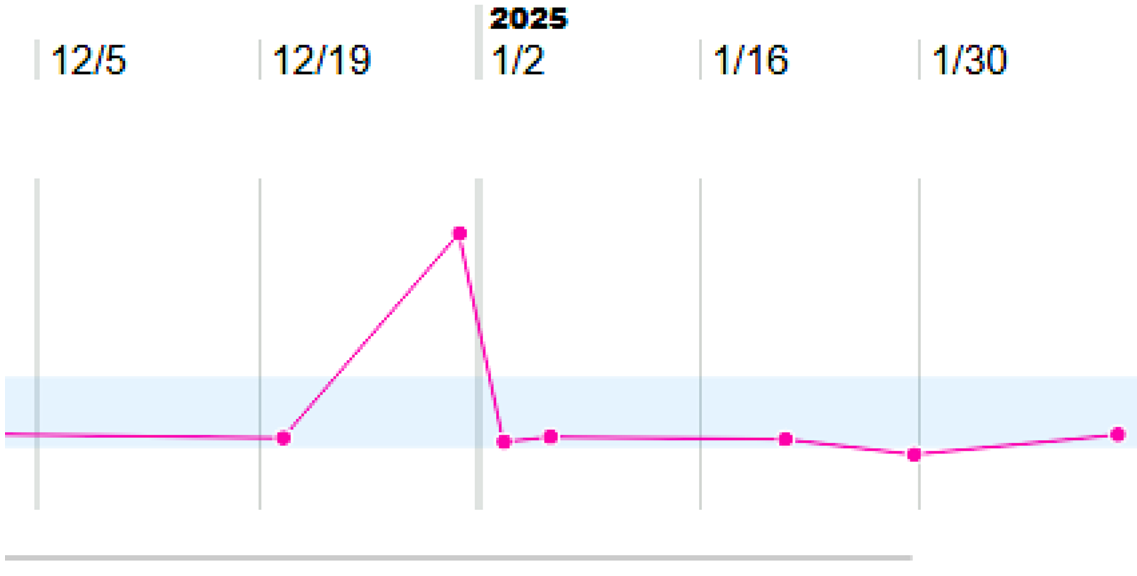
Dr Rugo Case: 79-year-old woman (continued)

Hyperglycemia

- 12/29/24 after visiting with family developed low grade fever, diarrhea
  - 12/30/24 labs: normal glucose
- 12/31/24 fever returned with worsening diarrhea and malaise
  - Sent to ED
  - Glucose 461!
  - Cultures negative, capivasertib held, hydrated and treated with insulin with normalization of labs, resolution of diarrhea
- 1/15/25
  - Restarted capivasertib at 320 mg, and metformin 500 mg BID
  - Tolerated well without further hyperglycemic episodes
  - 12/25 progressive disease with ascites, bowel involvement
    - Started on dose reduced T-DXd

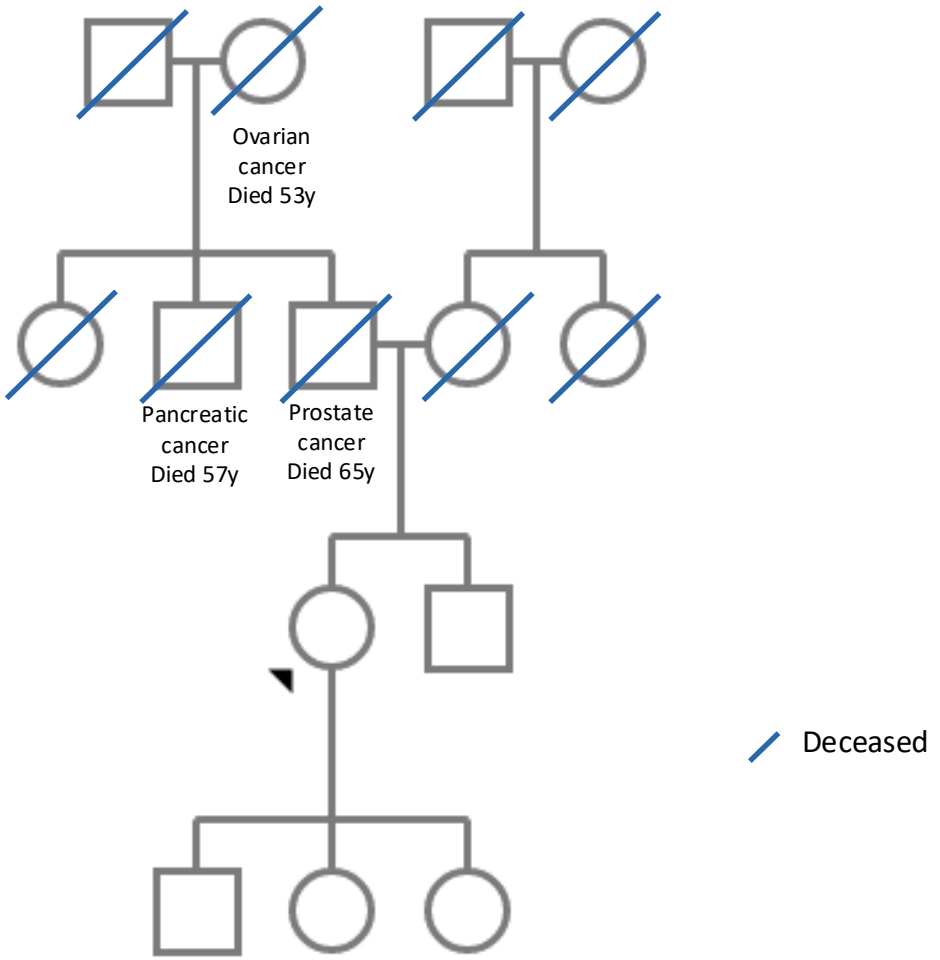
Dr Rugo Case: 79-year-old woman (continued)

CHEM PROFILE	2025 1/6/25 12:04	1/3/25 13:28	12/31/24 17:25	12/20/24 12:40	11/27/24 10:42
Sodium	139	138	134 ↓	138	138
Potassium	4.3	4.1	4.1	4.2	3.8
Chloride	105	103	99 ↓	104	103
CO2	25	25	22	24	28
Anion Gap	9	10	13	10	7
Glucose	89	80	461 ↑	87	96
Glucose, fasting					
Hemoglobin A1c					5.4
Urea Nitrogen, serum/plasma	21	18	41 ↑	16	14
BUN/Creatinine Ratio (External Lab)					
Creatinine	0.99	0.93	1.67 ↑	1.31 ↑	1.01
eGFRcr	58 ↓	63	31 ↓	42 ↓	57 ↓
Cystatin C		1.37 ↑		1.32	1.00
eGFRcys		44 ↓		47 ↓	67
eGFRcr-cys		54 ↓		46 ↓	66
Calcium	8.5	8.7	9.0	9.2	9.5



Prof Curigliano Case: 61-year-old woman

- 61-year-old overweight woman (BMI: 31 kg/m^2) with family history of cancer
- Diagnosed with metastatic ER+/HER2-low BC (germline BRCA2 mutation)
- Receives first-line ribociclib/letrozole
- One year later undergoes bilateral nipple-sparing mastectomies for disease progression
- Genetic testing reveals **PIK3CA E542K mutation**
- Patient receives capivasertib/fulvestrant
- Baseline assessment:
  - Fasting glucose: 126 mg/dL
  - Hemoglobin A1C 5.2%



BMI: Body mass index; y: years

Ms Carroll Case: 79-year-old woman

- 79 yo female, diagnosed in 2020. IDC, Grade III, ER/PR positive, HER2 Negative by FISH s/p bilateral mastectomy (pT2N3a). Adjuvant AC/T, radiation and Anastrozole.

- Presented fall of 2025 with acute SOB. Imaging revealed pleural effusion and cytology from thoracentesis was positive for malignancy, consistent with breast primary.

Ms Carroll Case: 79-year-old woman (continued)

Summary of Genomic & Epigenetic Biomarkers with Associated Treatment Options

✓ Approved in indication ~ Approved in other indication ⊗ Lack of response

DETECTED ALTERATION(S) / BIOMARKER(S)	ASSOCIATED FDA-APPROVED THERAPIES	CLINICAL TRIALS (SEE PAGE 6)	% CFDNA OR COPY NUMBER
PIK3CA E545K	✓ Alpelisib+fulvestrant, Capivasertib+fulvestrant, Inavolisib+palbociclib+fulvestrant	Yes	5.3%
BRAF L485S	~ Trametinib	Yes	0.1%
TP53 M246I	None	Yes	0.2%
TP53 Splice Site SNV	None	Yes	0.1%
ARID1A E2250Rfs*28	None	Yes	9.6%

Variants of uncertain clinical significance listed on following pages.

Ms Carroll Case: 79-year-old woman (continued)

- Started Palbociclib 125 mg, Inavolisib 9 mg and Fulvestrant
- Within 2 weeks, FG 199
- Patient instructed to hold Inavolisib but continue to check BG
- One week later, FG 214
- Two days later, FG 229
- Addit. Two days later, FG 262

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Module 6: Case Presentations — Part 2

Patient Eligibility in Randomized Clinical Trials of Approved PI3K/AKT Inhibitors

Trial	Agent	Eligibility by fasting glucose	Eligibility by HbA1c
SOLAR-1	Alpelisib	≤140 mg/dL	≤6.4%
CAPItello-291	Capivasertib	_	<8%
INAVO120	Inavolisib	<126 mg/dL	<6%

André F et al. *Ann Oncol* 2021;32(2):208-17; Turner NC et al. *N Engl J Med* 2023:388(22):2058-70; Jhaveri KL et al. *N Engl J Med* 2025;393(2):151-61.

Hyperglycemia Grading for Approved PI3K/AKT Inhibitors

Grade 1	Grade 2	Grade 3	Grade 4
FG > 125-150 mg/dL or 6.9 to 8.9 mmol/L or HBA1C > 7%*	FG > 160 to 250 mg/dL or > 8.9 to 13.9 mmol/L	FG > 250 to 500 mg/dL or > 13.9 to 27.8 mmol/L	FG > 500 mg/dL or > 27.8 mmol/L

* Capivasertib only

Alpelisib package insert, July 2025; capivasertib package insert, February 2025; inavolisib package insert, December 2025.

SOLAR-1 Trial: Updated Adverse Events (AEs) with Alpelisib in Combination with Fulvestrant for Advanced Breast Cancer with a PIK3CA Mutation

Most frequent AEs (≥20% in either arm), *n* (%)	Alpelisib + fulvestrant (*n* = 284)[a]			Placebo + fulvestrant (*n* = 287)[a]		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Any AE	282 (99.3)	187 (65.8)	35 (12.3)	267 (93.0)	90 (31.4)	17 (5.9)
Hyperglycemia	184 (64.8)	94 (33.1)	11 (3.9)	27 (9.4)	2 (0.7)	1 (0.3)
Diarrhea	169 (59.5)	20 (7.0)	0	47 (16.4)	2 (0.7)	0
Nausea	133 (46.8)	8 (2.8)	0	65 (22.6)	1 (0.3)	0
Decreased appetite	103 (36.3)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash	103 (36.3)	28 (9.9)	0	20 (7.0)	1 (0.3)	0
Vomiting	81 (28.5)	2 (0.7)	0	29 (10.1)	1 (0.3)	0
Weight decreased	79 (27.8)	15 (5.3)	0	7 (2.4)	0	0
Fatigue	72 (25.4)	10 (3.5)	0	51 (17.8)	3 (1.0)	0
Stomatitis	71 (25.0)	7 (2.5)	0	20 (7.0)	0	0
Asthenia	64 (22.5)	7 (2.5)	0	39 (13.6)	0	0
Alopecia	58 (20.4)	0	0	7 (2.4)	0	0

Safety set ($N = 571$). Numbers (n) represent counts of patients. A patient with multiple severity grades for an AE is only counted under the maximum grade. Medical Dictionary for Regulatory Activities version 23.0, Common Terminology Criteria for Adverse Events version 4.03.

[a] AEs (any grade) leading to discontinuations of one or both treatments in the safety set (both *PIK3CA*-mutant and non-mutant cohorts) occurred in 75 patients (26.4%) in the alpelisib plus fulvestrant arm and 16 patients (5.6%) in the placebo plus fulvestrant arm.[12]

André F et al. *Ann Oncol* 2021;32(2):208-17.

RTP RESEARCH TO PRACTICE

SOLAR-1: Hyperglycemia (≥20% in Either Arm)

Alpelisib + fulvestrant (n = 284)			Placebo + fulvestrant (n = 287)		
All grades	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
184 (64.8)	94 (33.1)	11 (3.9)	27 (9.4)	2 (0.7)	1 (0.3)

n (%)

André F et al. *Ann Oncol* 2021;32(2):208-17.

INAVO120 Trial: Select Adverse Events with Inavolisib

Adverse Event	Inavolisib (N=161)		Placebo (N=163)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Key risks				
Neutropenia	147 (91.3)	133 (82.6)	148 (90.8)	131 (80.4)
Hyperglycemia	102 (63.4)	11 (6.8)	22 (13.5)	0
Stomatitis or mucosal inflammation	89 (55.3)	9 (5.6)	47 (28.8)	0
Diarrhea†	84 (52.2)	6 (3.7)	26 (16.0)	0
Rash	43 (26.7)	0	32 (19.6)	1 (0.6)
Thrombocytopenia	80 (49.7)	22 (13.7)	75 (46.0)	8 (4.9)
Anemia	64 (39.8)	11 (6.8)	62 (38.0)	3 (1.8)
Nausea	47 (29.2)	0	32 (19.6)	0
Ocular toxic effects‡	47 (29.2)	1 (0.6)	26 (16.0)	0
Increased AST or ALT level	34 (21.1)	7 (4.3)	37 (22.7)	4 (2.5)
Vomiting	26 (16.1)	2 (1.2)	10 (6.1)	2 (1.2)
Lymphopenia	6 (3.7)	1 (0.6)	15 (9.2)	3 (1.8)
Pneumonitis	5 (3.1)	1 (0.6)	2 (1.2)	0

* Data are from the safety analysis population, which included all the patients who had received at least one dose of any trial agent. Patients were assessed according to the actual trial agents received. Palbociclib–fulvestrant was included in both the inavolisib and placebo regimens. Grouped terms (i.e., adverse events grouped according to medical concept) were used to assess selected adverse events (defined in the protocol) on the basis of the known safety profile of inavolisib. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

† Grade 2 events, which have a substantial effect on quality of life, occurred in 29 patients (18.0%) in the inavolisib group and 7 patients (4.3%) in the placebo group.

‡ The most common ocular toxic effects that were observed were dry eye (in 14 patients [8.7%] in the inavolisib group and 7 patients [4.3%] in the placebo group) and blurred vision (in 8 [5.0%] and 2 [1.2%], respectively). All were grade 1 or 2 events.

Jhaveri KL et al. *N Engl J Med* 2025;393(2):151-61.

RTP RESEARCH TO PRACTICE

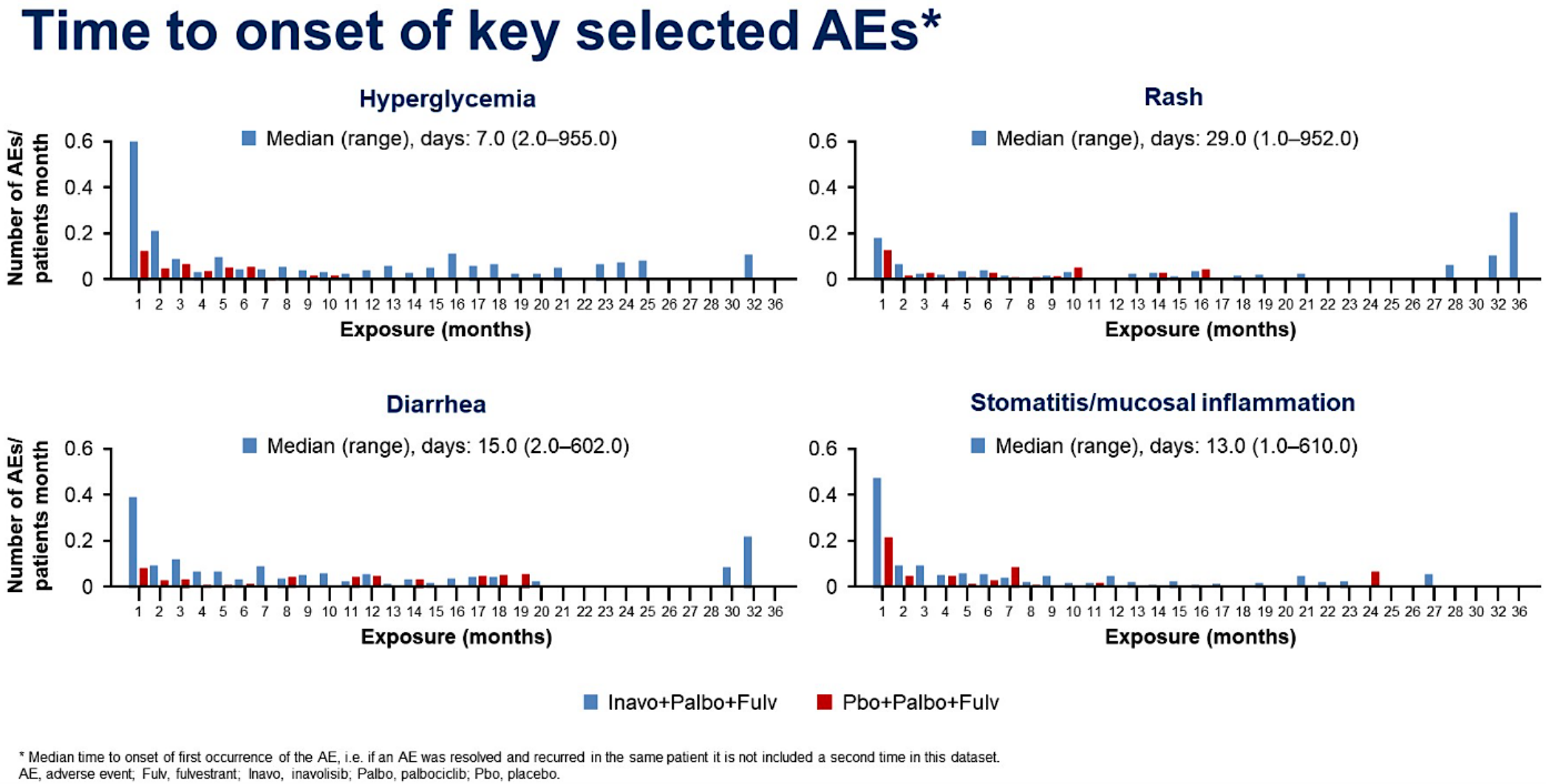
INAVO120: Hyperglycemia

Inavolisib (n = 161)		Placebo (n = 163)	
Any grade	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**
102 (63.4)	11 (6.8)	22 (13.5)	0

n (%)

Jhaveri KL et al. *N Engl J Med* 2025;393(2):151-61.

Hyperglycemia in patients receiving inavolisib



* Median time to onset of first occurrence of the AE, i.e. if an AE was resolved and recurred in the same patient it is not included a second time in this dataset.
AE, adverse event; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

Jhaveri KL et al. N Engl J Med. 2025 Jul 10;393(2):151-161; Juric D et al. ASCO 2024

Courtesy of Prof Giuseppe Curigliano MD, PhD

CAPItello-291 Trial: Most Frequent Adverse Events of Any Grade

AE, *n* (%)	Capivasertib-fulvestrant *n* = 355					Placebo-fulvestrant *n* = 350				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Any AE	343 (96.6)	52 (14.6)	139 (39.2)	139 (39.2)	9 (2.5)	288 (82.3)	115 (32.9)	118 (33.7)	44 (12.6)	10 (2.9)
Diarrhea (group term)[a]	257 (72.4)	164 (46.2)	60 (16.9)	33 (9.3)	0	71 (20.3)	61 (17.4)	9 (2.6)	1 (0.3)	0
Diarrhea	257 (72.4)	164 (46.2)	60 (16.9)	33 (9.3)	0	70 (20.0)	60 (17.1)	9 (2.6)	1 (0.3)	0
Frequent bowel movements	0	0	0	0	0	0	0	0	0	0
Gastrointestinal hypermotility	0	0	0	0	0	1 (0.3)	1 (0.3)	0	0	0
Rash (group term)[a]	135 (38.0)	57 (16.1)	35 (9.9)	43 (12.1)	0	25 (7.1)	19 (5.4)	5 (1.4)	1 (0.3)	0
Rash	78 (22.0)	41 (11.5)	18 (5.1)	19 (5.4)	0	15 (4.3)	10 (2.9)	4 (1.1)	1 (0.3)	0
Rash maculopapular	57 (16.1)	18 (5.1)	17 (4.8)	22 (6.2)	0	9 (2.6)	8 (2.3)	1 (0.3)	0	0
Rash papular	4 (1.1)	1 (0.3)	1 (0.3)	2 (0.6)	0	0	0	0	0	0
Rash pruritic	2 (0.6)	2 (0.6)	0	0	0	1 (0.3)	1 (0.3)	0	0	0
Rash macular	1 (0.3)	1 (0.3)	0	0	0	1 (0.3)	1 (0.3)	0	0	0
Nausea	123 (34.6)	85 (23.9)	35 (9.9)	3 (0.8)	0	54 (15.4)	42 (12.0)	10 (2.9)	2 (0.6)	0
Fatigue	74 (20.8)	49 (13.8)	23 (6.5)	2 (0.6)	0	45 (12.9)	35 (10.0)	8 (2.3)	2 (0.6)	0
Vomiting	73 (20.6)	54 (15.2)	13 (3.7)	6 (1.7)	0	17 (4.9)	10 (2.9)	5 (1.4)	2 (0.6)	0
Headache	60 (16.9)	47 (13.2)	12 (3.4)	1 (0.3)	0	43 (12.3)	33 (9.4)	8 (2.3)	2 (0.6)	0
Hyperglycemia (group term)[a]	60 (16.9)	26 (7.3)	26 (7.3)	7 (2.0)	1 (0.3)	14 (4.0)	8 (2.3)	5 (1.4)	1 (0.3)	0
Hyperglycemia	58 (16.3)	24 (6.8)	26 (7.3)	7 (2.0)	1 (0.3)	13 (3.7)	8 (2.3)	4 (1.1)	1 (0.3)	0
Blood glucose increased	2 (0.6)	2 (0.6)	0	0	0	1 (0.3)	0	1 (0.3)	0	0
Decreased appetite	59 (16.6)	37 (10.4)	21 (5.9)	1 (0.3)	0	22 (6.3)	11 (3.1)	9 (2.6)	2 (0.6)	0
Stomatitis	52 (14.6)	24 (6.8)	21 (5.9)	7 (2.0)	0	17 (4.9)	15 (4.3)	2 (0.6)	0	0
Asthenia	47 (13.2)	29 (8.2)	14 (3.9)	4 (1.1)	0	36 (10.3)	31 (8.9)	3 (0.9)	2 (0.6)	0
Pruritus	44 (12.4)	32 (9.0)	10 (2.8)	2 (0.6)	0	23 (6.6)	19 (5.4)	4 (1.1)	0	0
Anemia	37 (10.4)	15 (4.2)	15 (4.2)	7 (2.0)	0	17 (4.9)	4 (1.1)	9 (2.6)	4 (1.1)	0
Urinary tract infection	36 (10.1)	8 (2.3)	23 (6.5)	5 (1.4)	0	23 (6.6)	2 (0.6)	21 (6.0)	0	0

The listed events were reported in at least 10% of the patients for any grade in the capivasertib-fulvestrant arm. AEs are reported regardless of the relationship to the study drugs.
AE, adverse event.
[a]Group terms (preferred terms): diarrhea (diarrhea, frequent bowel movements, gastrointestinal hypermotility); rash (rash, rash macular, rash maculopapular, rash papular, rash pruritic); hyperglycemia (blood glucose increased, hyperglycemia).

Rugo H et al. *ESMO Open* 2024;9(9):103697.

RTP RESEARCH TO PRACTICE

CAPItello-291: Hyperglycemia

Capivasertib + fulvestrant (n = 355)					Placebo + fulvestrant (n = 350)				
Any grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Any grade**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
60 (16.9)	26 (7.3)	26 (7.3)	7 (2.0)	1 (0.3)	14 (4.0)	8 (2.3)	5 (1.4)	1 (0.3)	0

n (%)

Rugo H et al. *ESMO Open* 2024;9(9):103697.

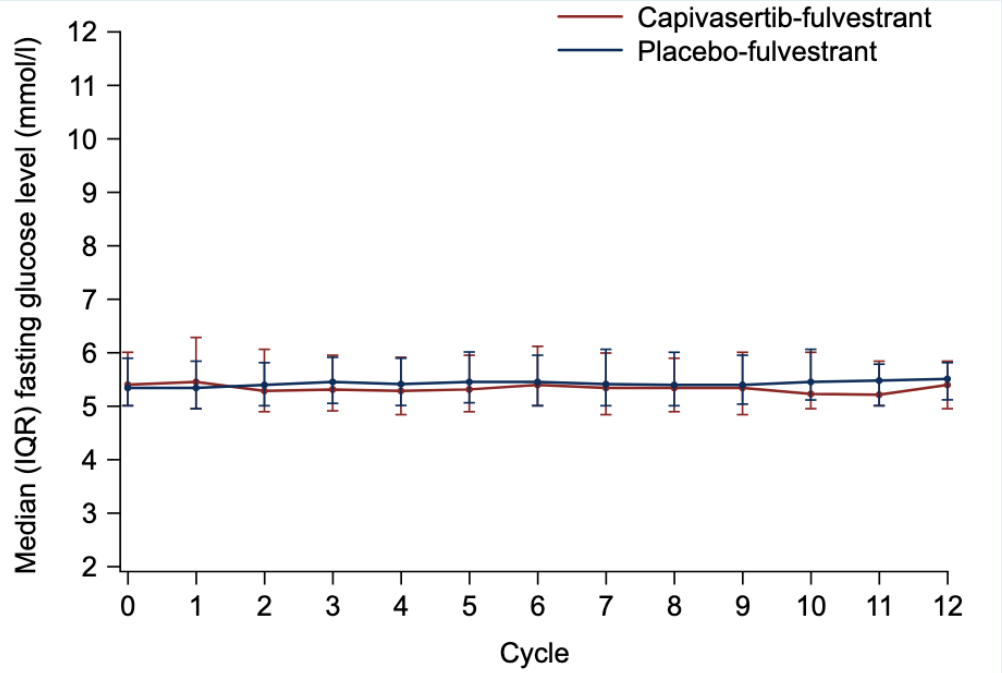
CAPItello-291: Hyperglycemia with Capivasertib/Fulvestrant

	Hyperglycemia[a]	
	Capivasertib-fulvestrant $n = 355$	Placebo-fulvestrant $n = 350$
Any grade	60 (16.9)	14 (4.0)
Grade 1	26 (7.3)	8 (2.3)
Grade 2	26 (7.3)	5 (1.4)
Grade 3	7 (2.0)	1 (0.3)
Grade 4	1 (0.3)	0
Serious AE, *n* (%)	3 (0.8)	0
AEs led to hospitalization, *n* (%)	3 (0.8)	0
Median (IQR) time to onset, days		
All grade	15[b] (1-51)	48 (28-120)
Grade 1	15 (1-29)	62 (23-257)
Grade 2	16 (1-68)	29 (28-56)
Grade 3	18 (8-30)[b]	120 (120-120)
AE leading to capivasertib/placebo dose change, *n* (%)		
Reduction	2 (0.6)	0
Interruption	9 (2.5)	3 (0.9)
Discontinuation	1 (0.3)	1 (0.3)

Rugo H et al. *ESMO Open* 2024;9(9):103697.

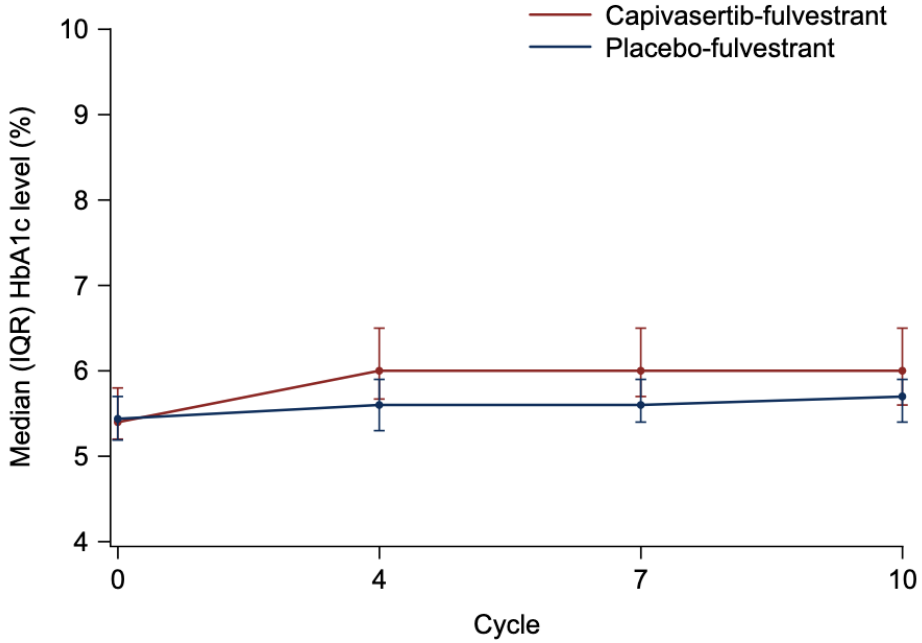
RTP RESEARCH TO PRACTICE

CAPItello-291: Hyperglycemia Markers over Time for Fasting Glucose and HbA1c



Number of patients:

Capivasertib-fulvestrant	353	339	330	310	265	235	198	191	164	164	139	131	113
Placebo-fulvestrant	350	343	332	303	219	182	147	136	115	100	92	82	70



Number of patients:

Capivasertib-fulvestrant	353	286	174	138
Placebo-fulvestrant	350	285	129	92

Rugo H et al. *ESMO Open* 2024;9(9):103697.

Capivasertib Package Insert November 2023

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Capivasertib safely and effectively. See full prescribing information for capivasertib.

Capivasertib tablets, for oral use
Initial U.S. Approval: 2023

---------- INDICATIONS AND USAGE ----------
Capivasertib is a kinase inhibitor indicated, in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN*-alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Select patients for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer with capivasertib based on the presence of one or more of the following genetic alterations in tumor tissue: *PIK3CA/AKT1/PTEN*. (2.1)
- Recommended Dosage: 400 mg orally twice daily, with or without food, for 4 days followed by 3 days off. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------
Tablets: 160 mg and 200 mg (3)

---------- CONTRAINDICATIONS ----------
Severe hypersensitivity to Capivasertib or any of its components. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Hyperglycemia: Evaluate blood glucose levels prior to starting and at regular intervals during treatment. Withhold, reduce dose, or permanently discontinue capivasertib based on severity. (2.2, 2.4, 5.1)
- Diarrhea: Capivasertib caused diarrhea in most patients. Advise patients to increase oral fluids, start antidiarrheal treatment, and consult with a healthcare provider if diarrhea occurs while taking capivasertib. Withhold, reduce dose, or permanently discontinue capivasertib based on severity. (2.4, 5.2)
- Cutaneous Adverse Reactions: Monitor for signs and symptoms of cutaneous adverse reactions. Withhold, reduce dose, or permanently discontinue capivasertib based on severity. (2.4, 5.3)
- Embryo-Fetal Toxicity: Capivasertib can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. Refer to the Full Prescribing Information of fulvestrant for pregnancy and contraception information. (5.4, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence ≥20%), including laboratory abnormalities, were diarrhea, cutaneous adverse reactions, increased random glucose, decreased lymphocytes, decreased hemoglobin, increased fasting glucose, nausea, fatigue, decreased leukocytes, increased triglycerides, decreased neutrophils, increased creatinine, vomiting and stomatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------
- Strong CYP3A Inhibitors: Avoid concomitant use. If concomitant use cannot be avoided, reduce capivasertib dose. (2.5, 7.1)
- Moderate CYP3A Inhibitors: Reduce capivasertib dose. (2.5, 7.1)
- Strong and Moderate CYP3A Inducers: Avoid concomitant use. (7.1)

---------- USE IN SPECIFIC POPULATIONS ----------
Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 11/2023

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/218197s000lbl.pdf

Capivasertib Package Insert February 2025

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use capivasertib safely and effectively. See full prescribing information for capivasertib.

Capivasertib tablets, for oral use
Initial U.S. Approval: 2023

---------- RECENT MAJOR CHANGES ----------
Warnings and Precautions, Hyperglycemia (5.1) 02/2025

---------- INDICATIONS AND USAGE ----------
Capivasertib is a kinase inhibitor indicated in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN*-alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Select patients for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer with capivasertib based on the presence of one or more of the following genetic alterations in tumor tissue: *PIK3CA/AKT1/PTEN*. (2.1)
- Recommended Dosage: 400 mg orally twice daily, with or without food, for 4 days followed by 3 days off. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------
Tablets: 160 mg and 200 mg (3)

---------- CONTRAINDICATIONS ----------
Severe hypersensitivity to capivasertib or any of its components. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Hyperglycemia: Capivasertib can cause hyperglycemia. Evaluate blood glucose levels prior to starting and at regular intervals during treatment. Withhold, reduce dose, or permanently discontinue capivasertib based on severity. (2.2, 2.4, 5.1)
- Diarrhea: capivasertib caused diarrhea in most patients. Advise patients to increase oral fluids, start antidiarrheal treatment, and consult with a healthcare provider if diarrhea occurs while taking capivasertib. Withhold, reduce dose, or permanently discontinue capivasertib based on severity. (2.4, 5.2)
- Cutaneous Adverse Reactions: Monitor for signs and symptoms of cutaneous adverse reactions. Withhold, reduce dose, or permanently discontinue capivasertib based on severity. (2.4, 5.3)
- Embryo-Fetal Toxicity: Capivasertib can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. Refer to the Full Prescribing Information of fulvestrant for pregnancy and contraception information. (5.4, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence ≥20%), including laboratory abnormalities, were diarrhea, cutaneous adverse reactions, increased random glucose, decreased lymphocytes, decreased hemoglobin, increased fasting glucose, nausea, fatigue, decreased leukocytes, increased triglycerides, decreased neutrophils, increased creatinine, vomiting and stomatitis. (6.1)

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- Strong and Moderate CYP3A Inducers: Avoid concomitant use. (7.1)

---------- USE IN SPECIFIC POPULATIONS ----------
Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 02/2025

https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218197s002lbl.pdf

RTP RESEARCH TO PRACTICE

Warnings and Precautions, Hyperglycemia — February 2025

5.1 Hyperglycemia

Severe hyperglycemia, including diabetic ketoacidosis and fatal outcomes, can occur in patients treated with capivasertib.

Increased fasting glucose from baseline occurred in 37% of patients treated with capivasertib, including 11% of patients with Grade 2 (FG > 160 to 250 mg/dL), 2% with Grade 3 (FG > 250 to 500 mg/dL), and 1.1% with Grade 4 (FG > 500 mg/dL) events.

The median time to first occurrence of hyperglycemia was 15 days (range: 1 to 367). Dose reduction for hyperglycemia was required in 0.6% of patients and permanent discontinuation was required in 0.6% of patients.

Diabetic ketoacidosis occurred in 0.3% of patients and diabetic metabolic decompensation in 0.6% of patients.

In CAPItello-291, 12% (43/355) of patients who received capivasertib had an anti-hyperglycemic medication regimen either initiated or changed during the study, including treatment with insulin in 4.8% (17/355) of patients.

The safety of capivasertib has not been established in patients with Type I diabetes or diabetes requiring insulin. Patients with insulin-dependent diabetes were excluded from CAPItello-291.

Before initiating treatment with capivasertib, test fasting glucose levels (FPG or FBG), HbA1C levels, and optimize fasting glucose.

After initiating treatment with capivasertib, monitor or self-monitor fasting glucose levels on Day 3 or 4 of the dosing week during weeks 1, 2, 4, 6 and 8; then monthly while on treatment with capivasertib; and as clinically indicated. Monitor HbA1C levels every 3 months during treatment with capivasertib and as clinically indicated. Patients with a history of well-controlled Type 2 diabetes mellitus may require intensified anti-hyperglycemic treatment and close monitoring of fasting glucose levels.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218197s002lbl.pdf

RTP RESEARCH TO PRACTICE

Recommended Monitoring for Hyperglycemia for Approved PI3K/AKT Inhibitors

Agent	Before treatment	After treatment initiation
Alpelisib	Baseline FG and HbA1c*	FG weekly every 2 weeks then at least once every 4 weeks
Capivasertib	Baseline FG and HbA1c*	FG on day 3 or 4 of the dosing week during weeks 1, 2, 4, 6, then 8, then monthly while on treatment
Inavolisib	Baseline FG and HbA1c*	FG every 3 days week 1; once weekly for next 3 weeks; every 2 weeks for 8 weeks; then monthly

*Obtain HbA1c every 3 months, FG = fasting glucose

Alpelisib package insert, July 2025; capivasertib package insert, February 2025; inavolisib package insert, December 2025.

Recommended Dose Modifications for Approved PI3K/AKT Inhibitors

Agent	Starting dose	First dose reduction	Second dose reduction
Alpelisib	300 mg daily	250 mg daily	200 mg daily
Capivasertib	400 mg BID for 4 days followed by 3 days off	320 mg BID for 4 days followed by 3 days off	200 mg BID for 4 days followed by 3 days off
Inavolisib	9 mg daily	6 mg daily	3 mg daily

BID = twice a day

Alpelisib package insert, July 2025; capivasertib package insert, February 2025; inavolisib package insert, December 2025.

QUESTIONS FOR THE FACULTY

What were the entry criteria for the major trials of PI3K/AKT inhibitors in terms of fasting glucose levels and hemoglobin A1c levels? How were the trials designed?

What specifically has been observed in the in trials of PI3K/AKT inhibitors in terms of the timing of onset and frequency of hyperglycemia and diabetes?

Agenda

Introduction: Use of On-Body Glucose Monitoring Devices

Module 1: Overview of Breast Cancer and Diabetes

Module 2: PI3K/AKT/mTOR Pathway and Glucose Metabolism

Module 3: Case Presentations — Part 1

Module 4: Current Data with Alpelisib, Capivasertib and Inavolisib

Module 5: Prevention and Management of Hyperglycemia

Module 6: Case Presentations — Part 2

RTP
RESEARCH
TO PRACTICE

Second Opinion: Clinical Investigators Provide Perspectives on the Future Role of AKT Inhibition in the Management of Prostate Cancer

A CME Symposium Held Adjunct to the
2026 ASCO® Genitourinary Cancers Symposium

Friday, February 27, 2026
6:00 PM – 7:30 PM PT (9:00 PM – 10:30 PM ET)

Faculty

Professor Karim Fizazi, MD, PhD
Daniel George, MD

Moderator

Elisabeth I Heath, MD

RTP
RESEARCH TO PRACTICE

Second Opinion

Rana R McKay, MD, FASCO

Neil Love, MD

RTP RESEARCH TO PRACTICE

71-year-old obese man with Type 2 diabetes (HbA1c 7.4%) presents with high volume mHSPC, PTEN deficient on NGS

- 71-year-old gentleman who presented with a PSA of 85 ng/mL and bone pain
- Workup showed Gleason 8 prostate cancer
- PSMA PET scan shows widespread bony metastases, retroperitoneal adenopathy
- PTEN deficient on NGS
- Patient has Type 2 diabetes, receiving metformin
  - Last HbA1c was 7.4% and fasting blood sugars are in the 140 to 160 range
  - He is obese (BMI 31)
- GFR ~55 mL/min/1.73 m^2

QUESTIONS FOR THE FACULTY

What issues are likely to occur related to hyperglycemia in patients with prostate cancer receiving abiraterone/prednisone/capivasertib?

2026 American Diabetes Association Diabetes Standards of Care includes *Therapeutic Strategies for Individuals Receiving Cancer Treatment*

9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2026

*American Diabetes Association Professional Practice Committee for Diabetes**

Diabetes Care 2026;49(Suppl. 1):S183–S215 | https://doi.org/10.2337/dc26-S009

Courtesy of Marie McDonnell, MD

2026 AMERICAN DIABETES ASSOCIATION DIABETES STANDARDS OF CARE

THERAPEUTIC STRATEGIES FOR INDIVIDUALS RECEIVING CANCER TREATMENT

Evidence is lacking for strong recommendations on prescreening, prevention and management

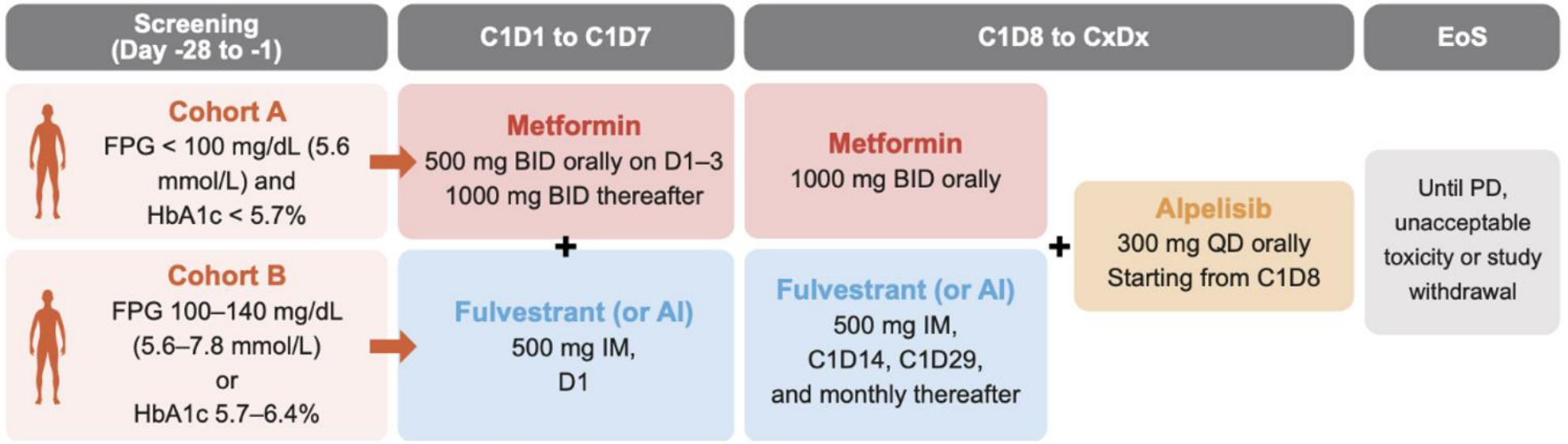
9.34 Consider metformin as the first-line treatment of hyperglycemia due to mTOR inhibitors. **E**

9.35a Consider metformin as the first-line treatment of hyperglycemia due to phosphoinositide 3-kinase (PI3K) inhibitors that affect the α isoform (e.g., alpelisib and inavolisib). **E**

9.35b Use of insulin should be reserved for severe hyperglycemia and hyperglycemic crises due to its potential impact on the efficacy of PI3K inhibitors. **E**

Courtesy of Marie McDonnell, MD

Phase II METALLICA Study: Metformin for Preventing Alpelisib-Associated Hyperglycemia in Hormone Receptor-Positive, HER2-Negative, PIK3CA-Mutated Breast Cancer



Abbreviations: BID: Twice a day; C: Cycle; D: Day; EoS: End of study; FPG: Fasting plasma glucose; HbA1c: Glycosylated hemoglobin; IM: intramuscular injection; PD: Progressive disease; PIK3CAMut: Mutation in *PIK3CA* gene; QD: One a day.

Llombart-Cussac A et al. *EClinicalMedicine* 2024;71:102520.

METALLICA: Hyperglycemia over the First 8 Weeks of Treatment

Hyperglycaemia	Cohort A n (%) N = 48	Cohort B n (%) N = 20	All patients n (%) N = 68
No hyperglycaemia	35 (72.9)	7 (35.0)	42 (61.8)
Grade 1	10 (20.8)	3 (15.0)	13 (19.1)
Grade 2	2 (4.2)	7 (35.0)	9 (13.2)
Grade 3	1 (2.1)	3 (15.0)	4 (5.9)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
Primary endpoint:			
Grade 3–4	1 (2.1)	3 (15.0)	4 (5.9)
95% CI, P-value	(0.5–11.1; P < 0.0001)	(5.6–37.8; P = 0.016)	(2.4–14.4)

At data cutoff, there were no new patients with grade 3–4 hyperglycaemia. Percentages may not total 100% due to rounding. P-values for all patients are not reported, since it was not a predefined primary objective of the protocol. Only the comparison between the study data and historical estimation for cohorts A and B was planned.

Llombart-Cussac A et al. *EClinicalMedicine* 2024;71:102520.

METALLICA: Adverse Events Leading to Discontinuation

Adverse event leading to discontinuation	Grade 1–2 n (%)	Grade 3 n (%)	Grade 4 n (%)
For alpelisib			
Any adverse event, n (%)	4 (5.9)	4 (5.9)	1 (1.5)
Diarrhoea[a]	3 (4.4)	1 (1.5)	0 (0)
Fatigue	2 (2.9)	1 (1.5)	0 (0)
Decreased appetite	1 (1.5)	1 (1.5)	0 (0)
Rash[a]	0 (0.0)	1 (1.5)	0 (0)
Hypovolaemic shock	0 (0.0)	0 (0)	1 (1.5)
Hypertransaminasaemia	0 (0.0)	1 (1.5)	0 (0)
Dysphagia	0 (0.0)	1 (1.5)	0 (0)
Lipase increase	0 (0.0)	1 (1.5)	0 (0)
Odynophagia	0 (0.0)	1 (1.5)	0 (0)
Gastrointestinal pain	1 (1.5)	0 (0)	0 (0)
Pyrexia	1 (1.5)	0 (0)	0 (0)
Stomatitis	1 (1.5)	0 (0)	0 (0)
Vomiting projectile	1 (1.5)	0 (0)	0 (0)
For metformin			
Any adverse event, n (%)	8 (11.8)	0 (0)	0 (0)
Diarrhoea[a]	5 (7.4)	0 (0)	0 (0)
Nausea	2 (2.9)	0 (0)	0 (0)
Vomiting	1 (1.5)	0 (0)	0 (0)
Diabetes mellitus	1 (1.5)	0 (0)	0 (0)

Maximum toxicity grade for each adverse event was reported. Percentages may not total 100% due to rounding. [a]Adverse event of special interest.

Llombart-Cussac A et al. *EClinicalMedicine* 2024;71:102520.

Preferred second line agents to add after metformin

Class	Mechanism of Action	Key Clinical Considerations
Thiazolidinediones (TZDs): Daily pill Pioglitazone	PPAR-γ agonists → ↑ insulin sensitivity in adipose tissue, muscle, and liver	Avoid in **heart failure** (fluid retention, edema risk) *Time for full effect: 4-6 weeks*
SGLT-2 inhibitors: Daily pill Empagliflozin; Dapagliflozin; Canagliflozin	Block renal glucose reabsorption in proximal tubule → ↑ urinary glucose excretion	⚠ Monitor for **DKA** (including euglycemic DKA). Advise increased hydration *Time for effect: 2 days*
GLP-1 receptor agonists Daily pill or weekly injection Semaglutide; Tirzepatide	Enhance glucose-dependent insulin secretion, suppress glucagon, slow gastric emptying, ↑ satiety	⚠ Use only if baseline nausea is controlled. Increases early post-meal insulin secretion but overall insulin dependence is reduced so on balance may have anti-tumor effect *Time for effect: 1 week*
Basal insulin Daily injection Glargine	Provides steady background insulin → suppresses hepatic glucose production	⚠ Requires glucose monitoring and hypoglycemia education
Sulfonylureas Glimepiride, glipizide, glyburide	**Increases endogenous secretion of insulin**	⚠ Requires glucose monitoring and hypoglycemia education

Courtesy of Marie McDonnell, MD

QUESTIONS FOR THE FACULTY

What is the optimal approach to therapy for a patient with preexisting hyperglycemia or diabetes who is a candidate to receive a PI3K/AKT inhibitor?

What preemptive therapies (eg, metformin) should be recommended to patients starting on PI3K/AKT inhibitors?

Which preparation and dosing schedule of metformin is preferred? What side effects and toxicities need to be managed?

QUESTIONS FOR THE FACULTY

What is the role of other agents used to manage hyperglycemia and diabetes, including insulin, for patients with PI3K/AKT inhibitor-associated hyperglycemia?

What is the role of GLP-1 receptor agonists for patients about to receive PI3K/AKT inhibitors?

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

What dietary recommendations do you provide to patients receiving PI3K/AKT inhibitors, and in which situations do you refer patients to see a nutritional counselor or dietician?

What recommendations do you provide to patients receiving PI3K/AKT inhibitors regarding exercise?

Agenda

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RTP
RESEARCH TO PRACTICE

Dr Rugo Case: 69-year-old woman

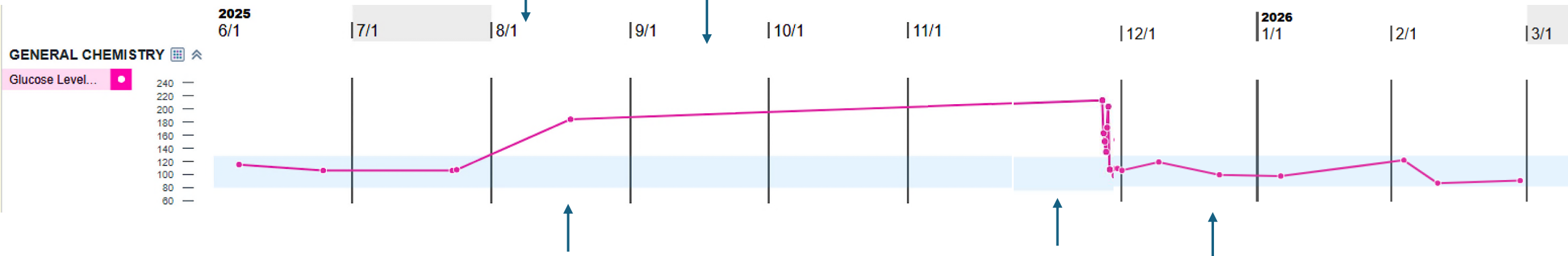
HR+/HER2- MBC: Inavolisib, Palbociclib and Fulvestrant

- 69 yo woman from Mexico
  - 2007 stage II node positive HR+ breast cancer
    - Rx: TAC x 6, tamoxifen to 2014
  - 2021 axillary node recurrence, HR+
    - TC x 1, then paclitaxel x 9 weeks, mastectomy/AXLD
    - 2021 – 2025 exemestane
  - Late 2024: bone pain, then axillary node enlargement
    - 3-5/25 workup: grade II IDC in node, extensive bone metastases
    - Tamoxifen x 3 weeks, then Fulvestrant x 2 with abemaciclib x 5 days (stopped due to toxicity), relocated to U.S. with severe bone pain
  - U.S.
    - PET/CT: extensive disease in left breast, bone, nodes, liver
    - Guardant ctDNA: PIK3CA C420R 9.5%, TMB 9.49
    - Left breast bx: grade 2 IDC, ER 50%, PR 0, HER2 2+/FISH NA, Ki67 25%
    - 7/25 RT: C7-T2, L3-4 x 5 fractions
    - **8/25: Palbociclib 125 mg, inavolisib 9 mg with continued fulvestrant**
      - **HgbA1c: 6.2**
      - **Glucose 107**

Dr Rugo Case: 69-year-old woman (continued)

8/9/25: Palbo 125 mg 21 days on 7 days off and Inavolisib 9 mg daily. Meformin 500 mg BID

9/5/25 Sitagliptin 100 mg/d Meformin 1000 mg BID



8/27/25 Dose reduced inavolisib to 6 mg ANC 0.51, Palbociclib held, resumed at 100 mg

11/25/25 hospitalized for pneumonia, held Inavolisib and Palbociclib

12/23/25 restart inavolisib 3mg and palbociclib 75mg

Dr Rugo Case: 69-year-old woman (continued)

Hyperglycemia

- Bone pain quickly resolved but complicated by diarrhea and hyperglycemia
  - Dose reduced inavolisib (6 mg) and palbociclib (100 mg)
  - Anihyperglycemic medications in consult with endocrinology
- Imaging: dramatic response with resolution of adenopathy, now sclerotic bone lesions, tiny residual liver lesions
- Admitted with fever, hypoxia and diagnosed with pneumonia
  - Palbociclib and inavolisib held
- With recovery, restarted inavolisib at 3 mg and palbociclib

Prof Curigliano Case: 69-year-old woman

- 69-year-old overweight woman (BMI: 29 kg/m^2)
- ER+/HER2-low BC (cT2 (m) cN0 cM0) with **PIK3CA E542K mutation**
- Surgery → adjuvant letrozole
- Approximately 1 year later PD in liver
- Receives inavolisib/fulvestrant
- Baseline assessment:
  - Fasting glucose: 126 mg/dL
  - Hemoglobin A1C 5.2%

Ms Carroll Case: 74-year-old woman

- 74 yo female, initially diagnosed in 1996. Underwent mastectomy, AC/T and completed 5 years of Tamoxifen in 2001.
- 2016: Recurrence to bone, ER/PR positive, HER2 Negative. She started ET. Received several therapies (AI, SERD, Tam, CDK4/6i) over the years.
- 2021: Progression noted in bone, liver and mediastinal LN

Ms Carroll Case: 74-year-old woman (continued)

Summary of Detected Somatic Alterations, Immunotherapy Biomarkers & Associated Treatment Options

KEY ✓ Approved in indication ✓ Approved in other indication ✗ Lack of response

Detected Alteration(s) / Biomarker(s)	Associated FDA-approved therapies	Clinical trial availability (see page 4)	% cfDNA or Amplification
ESR1 D538G	✓ Fulvestrant ✗ Anastrozole, Exemestane, Letrozole	Yes	0.2%
PIK3CA E542K	✓ Alpelisib ✓ Copanlisib	Yes	5.6%
ATM Q2397*	✓ Niraparib, Olaparib, Rucaparib, Talazoparib	Yes	19.0%
ATM G2891D	✓ Niraparib, Olaparib, Rucaparib, Talazoparib	Yes	1.6%
PIK3CA R93Q	✓ Alpelisib, Copanlisib	Yes	0.8%
ATM N6fs	✓ Niraparib, Olaparib, Rucaparib, Talazoparib	Yes	2.1%

Ms Carroll Case: 74-year-old woman (continued)

- Started Alpelisib at 150 mg daily
- 7 days later: FG completed locally but facility did not receive results
- 4 days later: Patient presented to the ED with weakness, obtunded and BG 700
- Stopped Alpelisib and patient declined to restart after hospitalization

Ms Carroll Case: 83-year-old woman

- 83 year old female, initially diagnosed in 2021 with invasive lobular carcinoma, Grade II, ER/PR positive, HER2 Negative. Upfront mastectomy, pT3N1mi, Oncotype 11.
- Recommended radiation, AI with zoledronic acid
- 2024: Presented with SOB. Imaging revealed large pleural effusion, LN and bony involvement. Started 1L CKD4/6i/Fulvestrant. Progression within one year.

Ms Carroll Case: 83-year-old woman (continued)

Summary of Genomic & Epigenetic Biomarkers with Associated Treatment Options

✓ Approved in indication ~ Approved in other indication ⊗ Lack of response

DETECTED ALTERATION(S) / BIOMARKER(S)	ASSOCIATED FDA-APPROVED THERAPIES	CLINICAL TRIALS (SEE PAGE 7)	% CFDNA OR COPY NUMBER
PIK3CA E542K	✓ Alpelisib+fulvestrant, Capivasertib+fulvestrant, Inavolisib+palbocidlib+fulvestrant	Yes	2.8%
PIK3CA E453K	✓ Inavolisib+palbocidlib+fulvestrant ~ Alpelisib+fulvestrant, Capivasertib+fulvestrant	Yes	2.1%
CDH1 C22Mfs*12	None	No	1.3%

Variants of uncertain clinical significance listed on following pages

Additional Biomarkers

Tumor Mutational Burden (TMB)	15.42 mut/Mb	
MSI-High	NOT DETECTED	
Homologous Recombination Deficiency (HRD)	**Genomic Instability Status**	**HRR mutations**
	Not detected	Not detected
Tumor Fraction#	2.5% - Based on 2587 patient-specific biomarkers	

Tumor fraction is defined as the proportion of tumor molecules present in the cfDNA within the submitted specimen and is based on epigenomic signals

Ms Carroll Case: 83-year-old woman (continued)

- Started capivasertib 400 mg BID 4 on/3 off/fulvestrant
- Baseline hemoglobin A1c 5.5
- Patient BG checks on Day 3 of each cycle
- Very diligent about ensuring care team responds to her messages

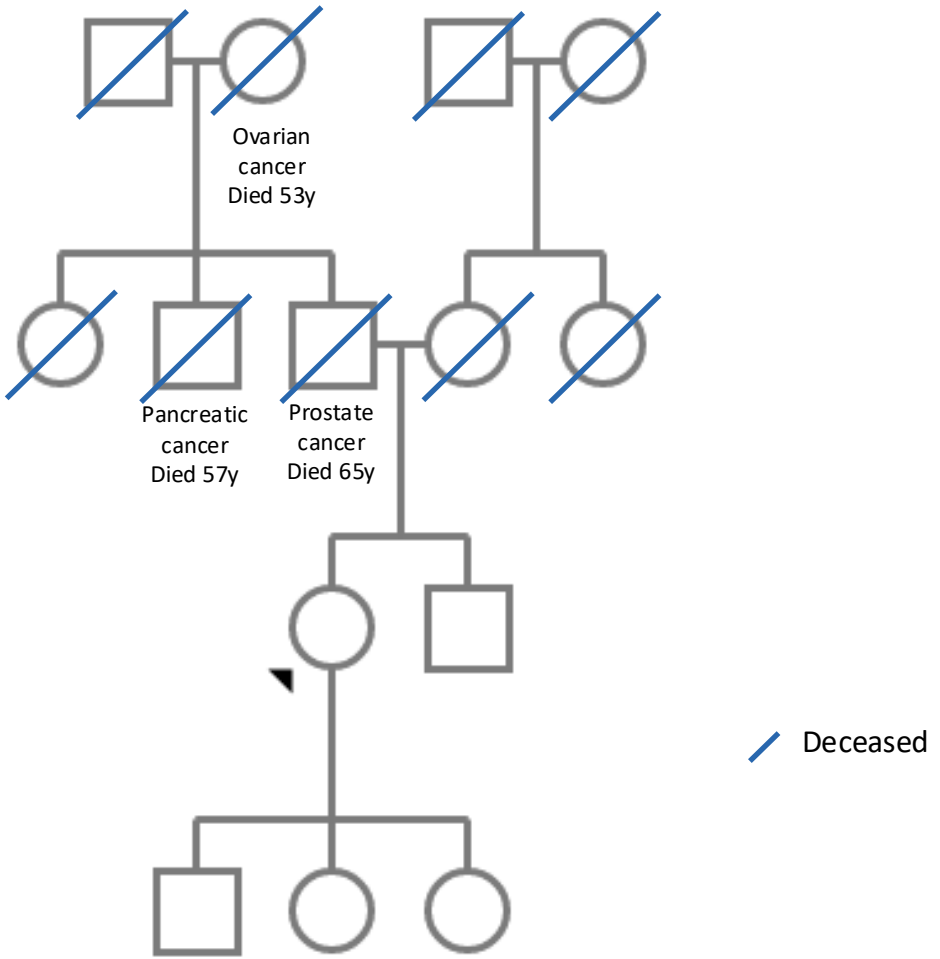
APPENDIX

Prof Curigliano Case: 61-year-old woman

Patient history

Patient profile

- 61-year-old woman
- Caucasian ethnicity
- BMI: 31 kg/sm (overweight)
- G3P3, menopause at 47 y
- Non-smoker, drinks socially
- No relevant major comorbidities
- No allergies
- Family history of cancer:
  - Father deceased for prostate cancer (65 years old)
  - Paternal uncle deceased for pancreatic cancer (57 years old)
  - Paternal grandmother deceased for ovarian cancer (53 years old)



BMI: Body mass index; G: gravidity; P: parity; y: years

Prof Curigliano Case: 61-year-old woman (continued)

Diagnosis of HR+/HER2-low breast cancer

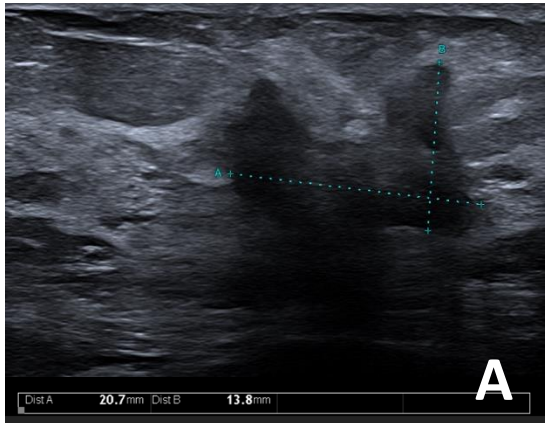
Aug 2024

Timeline

Diagnosis

Initial presentation

- Biannual screening mammography with evidence of new calcifications.
- Breast US: at left breast, two hypoechogenic nodules measuring 21x14 mm (**A**), in the left supero-external quadrant, and 14x9 mm (**B**), in the superior parareolar site. No axillary lymphadenomegalies. BIRADS: 4c.



BIRADS: Breast Imaging-Reporting and Data System; US: ultrasound

Prof Curigliano Case: 61-year-old woman (continued)

Diagnosis of HR+/HER2-low breast cancer

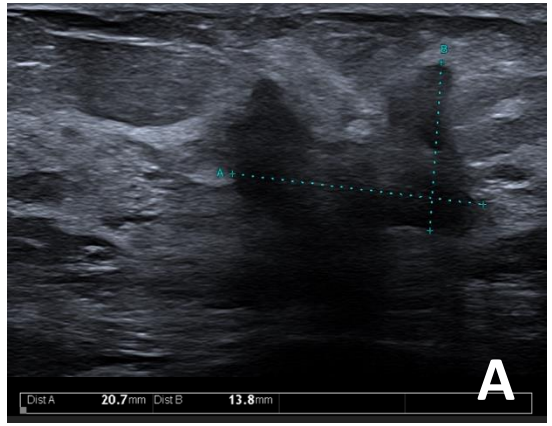
Timeline

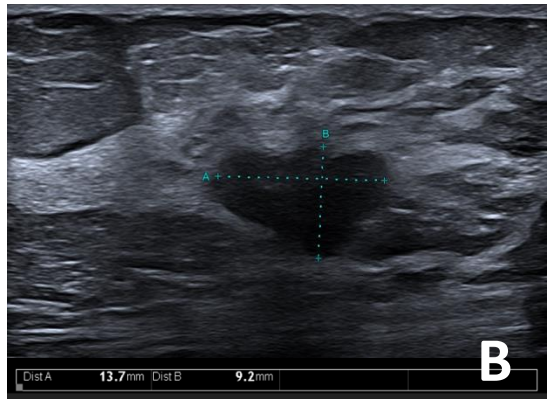
Aug 2024

Diagnosis

Initial presentation

- Biannual screening mammography with evidence of new calcifications.
- Breast US: at left breast, two hypoechogenic nodules measuring 21x14 mm (**A**), in the left supero-external quadrant, and 14x9 mm (**B**), in the superior parareolar site. Axillary lymphadenomegalies. BIRADS: 4c.





Core biopsy (A). Pathology report

- IDC NOS, G2.
- ER (IHC): 65%; PgR (IHC): 5%; Ki67: 40%; HER2 IHC score: 2+
- ISH test: negative.

FNAC (B). Pathology report

- C5

Stage: cT2 (m) cN1 cM0 (II)

BIRADS: Breast Imaging-Reporting and Data System; ER: estrogen receptor; FNAC, fine-needle aspiration cytology; G: grade; HER2: human epidermal growth factor receptor 2; IDC: invasive ductal carcinoma; IHC: immunohistochemistry; ISH: in situ hybridization; NOS: not otherwise specified; PgR: progesterone receptor; TNM, tumour–node–metastasis; US: ultrasound

Prof Curigliano Case: 61-year-old woman (continued)

Diagnosis of HR+/HER2-low breast cancer

Invasive ductal carcinoma G2 of the left breast
ER: 65%; PgR: 5%; Ki67: 40%; HER2-positive
Stage: cT2 (m) cN1 M1 (Liver metastases)
Germline mutation of BRCA2: c.6313delA p.(Ile2105Tyrfs) – class 5

First line treatment with letrozole and ribociclib

+ genetic counseling indicated

ER: estrogen receptor; G: grade; HER2: human epidermal growth factor receptor 2; PgR: progesterone receptor; TNM, tumour–node–metastasis

Prof Curigliano Case: 61-year-old woman (continued)

First line therapy

- Letrozole and ribociclib

Prof Curigliano Case: 61-year-old woman (continued)

First line therapy

- Left and right nipple-sparing mastectomy: 4 confluent lumps measuring more than 2 cm on left breast
- SLND. Frozen section examination: metastasis of carcinoma with extranodal extension in 2/2 sentinel lymph nodes.

Surgery

Axillary dissection

- Bilateral Mastectomy and annessectomy indicated
- 2/2 metastatic lymph nodes
- Extranodal extension
- SOC for >2 N+

ESMO Guidelines 2022; Donker, Lancet Oncol 2014; Sávolt, Eur J Surg Oncol 2017

Prof Curigliano Case: 61-year-old woman (continued)

Surgery

- Left and right nipple-sparing mastectomy: 4 confluent lumps measuring more than 4 cm
- Left axillary lymph node dissection
- Immediate breast reconstruction

Histology

- IDC NOS, G2. pLVI1
- ER (IHC): 65%; PgR (IHC): 5%; Ki67: 40%; HER2 IHC score: 2+; ISH test: negative.
  PIK3CA E542K

Genetic counseling

- Germline mutation of BRCA2: c.6313delA p.(Ile2105Tyrfs) – class 5
- Bilateral prophylactic adnexectomy and right prophylactic mastectomy indicated
- First degree relatives counseling indicated

Stage: pT2 (4.2 cm) pN2a (6/16) cM1 (progressive disease on lung)

ESMO Guidelines 2022; Donker, Lancet Oncol 2014; Sávolt, Eur J Surg Oncol 2017

Prof Curigliano Case: 61-year-old woman (continued)

Surgery

- Which therapy?
- Olaparib?
- Fulvestrant and Capivasertib?
- Fulvestrant and alpelisib?

ESMO Guidelines 2022; Donker, Lancet Oncol 2014; Sávolt, Eur J Surg Oncol 2017

Prof Curigliano Case: 61-year-old woman (continued)

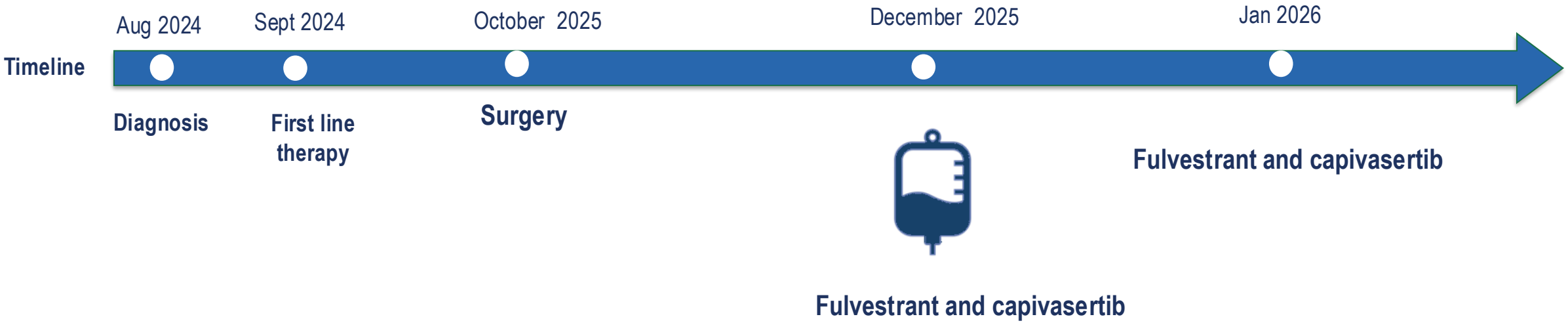
Surgery

Baseline assessment

Fasting glucose: 126 mg/dL; Hemoglobin A1C 5.2.0% at baseline

Prof Curigliano Case: 61-year-old woman (continued)

Surgery



What to do?

Fasting blood glucose of 450 mg/dL

Hyperglycemia in patients receiving capivasertib

Hyperglycemia	Any	Consider consultation with a health care practitioner with expertise in hyperglycemia management. Counsel patients on lifestyle modifications.
	FBG[b] > ULN to 160 mg/dL or FBG > ULN to 8.9 mmol/L or HbA_{1c} >7%	Consider initiation or intensification of oral antidiabetic therapy.
	FBG 161 to 250 mg/dL or	Withhold capivasertib until FBG decreases to ≤160 mg/dL (or ≤8.9 mmol/L).

Capivasertib [Prescribing Information]. 2025; Rugo H et al. ESMO Open. 2024 Sep;9(9):103697.

Hyperglycemia in patients receiving capivasertib

Adverse reaction	Severity	Capivasertib dosage modification[a]
	FBG 9 to 13.9 mmol/L	*Resolution ≤28 days after interruption*: Resume capivasertib at the same dose. *Resolution >28 days after interruption*: Resume capivasertib at one lower dose level.
	FBG 251 to 500 mg/dL or FBG 14 to 27.8 mmol/L	Withhold capivasertib until FBG decreases to ≤160 mg/dL (or ≤8.9 mmol/L). *Resolution ≤28 days after interruption*: Resume capivasertib at one lower dose level. *Resolution >28 days after interruption*: Permanently discontinue capivasertib.
	FBG >500 mg/dL or FBG >27.8 mmol/L or Life-threatening hyperglycemia sequelae at any FBG level	*Withold capivasertib.* *Life-threatening hyperglycemia sequelae or if FBG persists at ≥500 mg/dL after 24 hours:* Permanently discontinue capivasertib. *If FBG is ≤500 mg/dL (or ≤27.8 mmol/L) within 24 hours:* Follow the guidance in this table for the relevant grade.

Capivasertib [Prescribing Information] 2025; Rugo H et al. ESMO Open. 2024 Sep;9(9):103697.

Prof Curigliano Case: 69-year-old woman

Patient history

Patient profile

- 69-year-old woman
- Caucasian ethnicity
- BMI: 29 kg/sm (overweight)
- G1P1, menopause at 47 y
- Non-smoker, drinks socially
- No relevant major comorbidities
- No allergies

BMI: Body mass index; G: gravidity; P: parity; y: years

Prof Curigliano Case: 69-year-old woman (continued)

Diagnosis of HR+/HER2- breast cancer

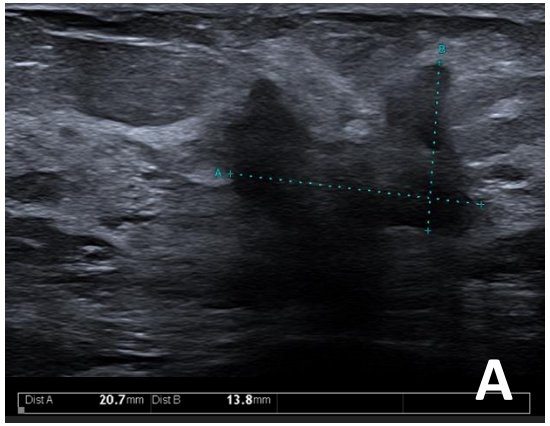
Aug 2024

Timeline

Diagnosis

Initial presentation

- Annual screening mammography with evidence of new calcifications.
- Breast US: at left breast, two hypoechogenic nodules measuring 44x54 mm (**A**), in the left supero-external quadrant, and 24x19 mm (**B**), in the superior parareolar site. Bilateral axillary lymphadenomegalies.
- BIRADS: 4c.



BIRADS: Breast Imaging-Reporting and Data System; US: ultrasound

Prof Curigliano Case: 69-year-old woman (continued)

Diagnosis of HR+/HER2-low breast cancer

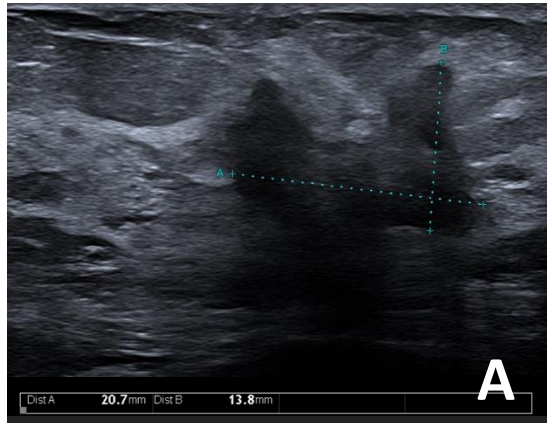
Aug 2024

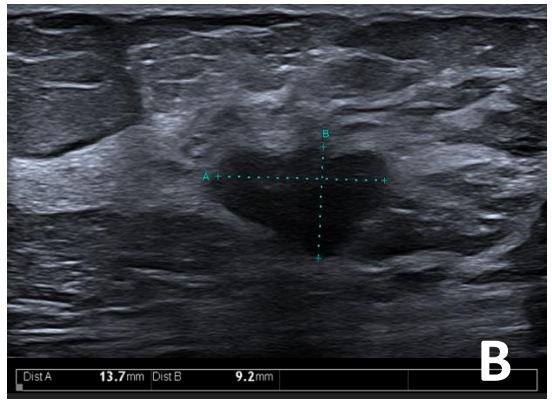
Timeline

Diagnosis

Initial presentation

- Annual screening mammography with evidence of new calcifications.
- Breast US: at left breast, two hypoechogenic nodules measuring 44x54 mm (**A**), in the left supero-external quadrant, and 24x19 mm (**B**), in the superior parareolar site. No axillary lymphadenomegalies.
- BIRADS: 4c.





Core biopsy (A). Pathology report

- IDC NOS, G2.
- ER (IHC): 95%; PgR (IHC): 15%; Ki67: 20%; HER2 IHC score: 1+

Stage: cT2 (m) cN0 cM0

BIRADS: Breast Imaging-Reporting and Data System; ER: estrogen receptor; FNAC, fine-needle aspiration cytology; G: grade; HER2: human epidermal growth factor receptor 2; IDC: invasive ductal carcinoma; IHC: immunohistochemistry; ISH: in situ hybridization; NOS: not otherwise specified; PgR: progesterone receptor; TNM, tumour–node–metastasis; US: ultrasound

Prof Curigliano Case: 69-year-old woman (continued)

Diagnosis of HR+/HER2-low breast cancer

Invasive ductal carcinoma G2 of the left breast
ER: 65%; PgR: 15%; Ki67: 20%; HER2: 1+
Stage: cT2 (m) cN0 M0

Surgery

ER: estrogen receptor; G: grade; HER2: human epidermal growth factor receptor 2; PgR: progesterone receptor; TNM, tumour–node–metastasis

Prof Curigliano Case: 69-year-old woman (continued)

Adjuvant therapy

- Left nipple-sparing mastectomy: 4 confluent lumps measuring more than 4 cm
- Left axillary lymph node biopsy
- Immediate breast reconstruction

Histology

- IDC NOS, G2. pLVI1
- ER (IHC): 95%; PgR (IHC): 95%; Ki67: 10%; HER2 IHC score: 1+. **PIK3CA E542K**

- **Adjuvant letrozole**

Stage: pT2 (2.2 cm) (m) pN0 sent (0/1) cM0

Prof Curigliano Case: 69-year-old woman (continued)

Adjuvant therapy

- Left nipple-sparing mastectomy: 4 confluent lumps measuring more than 4 cm
- Left axillary lymph node biopsy
- Immediate breast reconstruction

Histology

- IDC NOS, G2. pLVI1
- ER (IHC): 95%; PgR (IHC): 95%; Ki67: 10%; HER2 IHC score: 1+. **PIK3CA E542K**

Adjuvant letrozole

Progressive disease in lung and liver

Stage: pT2 (2.2 cm) (m) pN0 sent (0/1) cM0

Prof Curigliano Case: 69-year-old woman (continued)

First line therapy

- Left nipple-sparing mastectomy: 4 confluent lumps measuring more than 4 cm
- Left axillary lymph node biopsy
- Immediate breast reconstruction

Histology

- IDC NOS, G2. pLVI1
- ER (IHC): 95%; PgR (IHC): 95%; Ki67: 10%; HER2 IHC score: 1+. **PIK3CA E542K**

Adjuvant letrozole

Progressive disease in lung and liver

- Which therapy?
- Fulvestrant and Capivasertib?
- Fulvestrant and inavolisib?

Stage: pT2 (2.2 cm) (m) pN0 sent (0/1) cM0

Prof Curigliano Case: 69-year-old woman (continued)

First line therapy

- Left nipple-sparing mastectomy: 4 confluent lumps measuring more than 4 cm
- Left axillary lymph node biopsy
- Immediate breast reconstruction

Histology

- IDC NOS, G2. pLVI1
- ER (IHC): 95%; PgR (IHC): 95%; Ki67: 10%; HER2 IHC score: 1+. **PIK3CA E542K**

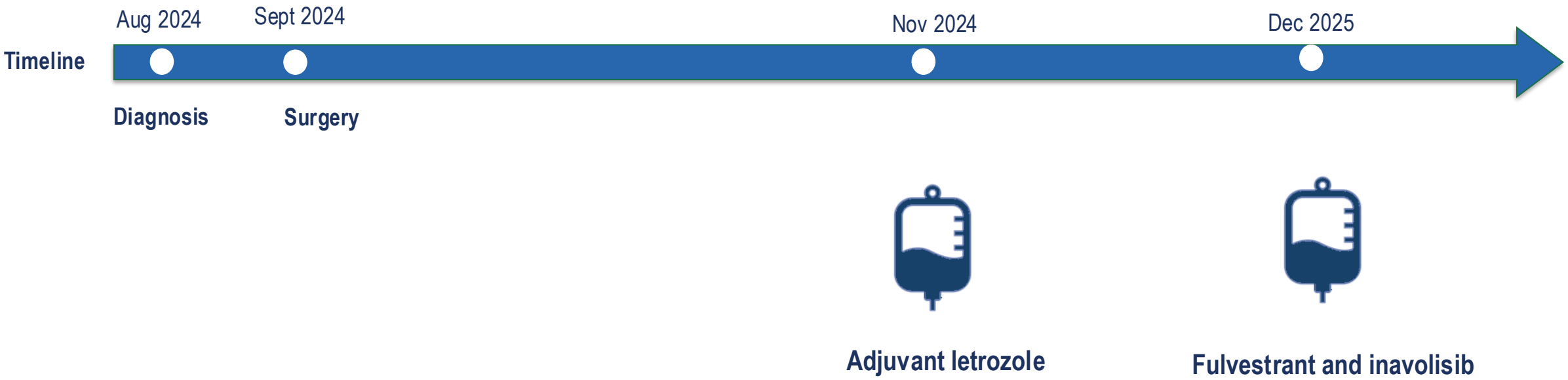
Adjuvant letrozole

Fulvestrant and inavolisib

Stage: pT2 (2.2 cm) (m) pN0 sent (0/1) cM0

Prof Curigliano Case: 69-year-old woman (continued)

First line therapy



Baseline assessment

Fasting glucose: 126 mg/dL; Hemoglobin A1C 5.2.0% at baseline

Prof Curigliano Case: 69-year-old woman (continued)

First line therapy

Assessment after 10 days

Fasting blood glucose of 450 mg/dL

Hyperglycemia in patients receiving inavolisib

High-risk factors for hyperglycemia[1,2]

- >45 years of age
- HbA1c ≥5.7%
  (the cutoff for INAVO120 trial was <6.0%)
- Pre-diabetes
- Family history of diabetes
- BMI ≥30 kg/m^2
- History of gestational diabetes

Any other factor that increases the risk of hyperglycemia

(eg, certain ethnicities such as
African American, South Asian; inactive lifestyle)

Information provided is general guidance from the INAVO120 study protocol and is not advice or recommendations. Treatment decisions are ultimately at the discretion of the treating HCP and per local institutional guidelines.

Patients were advised to report symptoms associated with hyperglycemia such as polydipsia, polyuria, polyphagia, blurry vision, or symptoms associated with acidosis such as rapid or shallow breathing, confusion, fatigue, headache, or drowsiness.

Jhaveri KL et al. N Engl J Med. 2025 Jul 10;393(2):151-161.

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Datasets and Advances in Oncology

Bruton Tyrosine Kinase Inhibitors for Chronic Lymphocytic Leukemia

A CME/MOC-Accredited Live Webinar

Wednesday, March 11, 2026

5:00 PM – 6:00 PM ET

Faculty

Jennifer R Brown, MD, PhD

Wojciech Jurczak, MD, PhD

Moderator

Neil Love, MD

RTP Year in Review 2026

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