Optimizing Therapy for Patients with Hormone Receptor-Positive Metastatic Breast Cancer Harboring PI3K/AKT/PTEN Pathway Abnormalities

A CME/MOC-Accredited Live Webinar

Thursday, October 31, 2024
5:00 PM – 6:00 PM ET

Faculty

Komal Jhaveri, MD, FACP
Hope S Rugo, MD

Moderator

Neil Love, MD

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Faculty

Komal Jhaveri, MD, FACP
Patricia and James Cayne Chair for Junior Faculty
Associate Attending Physician
Breast Medicine Service and Early Drug Development Service
Section Head, Endocrine Therapy Research Program
Clinical Director, Early Drug Development Service
Department of Medicine
Memorial Sloan Kettering Cancer Center
Associate Professor of Medicine
Weill Cornell College of Medicine
New York, New York

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Hope S Rugo, MD
Professor of Medicine
Winterhof Family Professor of Breast Cancer
Director, Breast Oncology and Clinical Trials Education
Medical Director, Cancer Infusion Services
University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center
San Francisco, California

Commercial Support

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Dr Love — Disclosures

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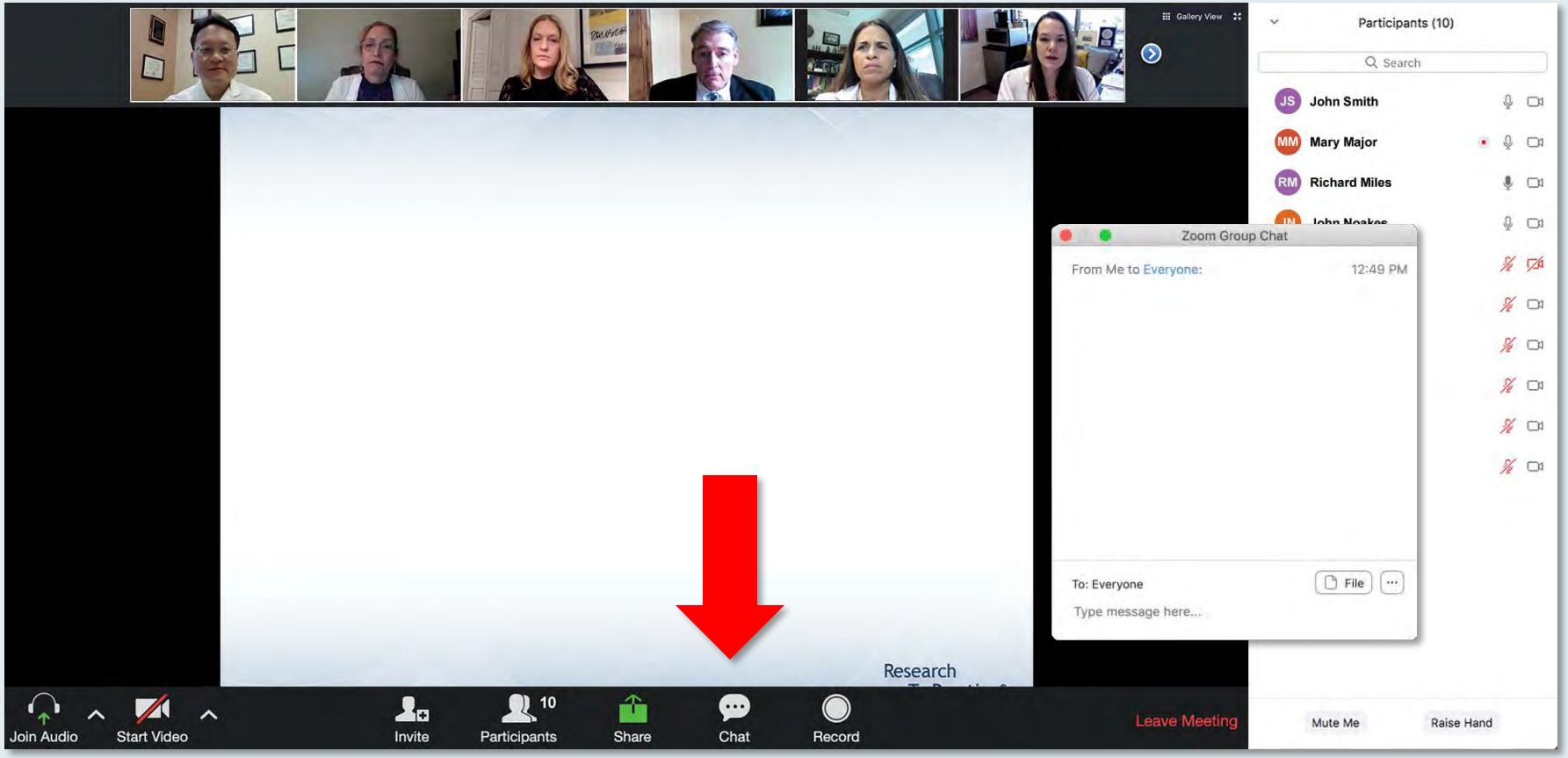

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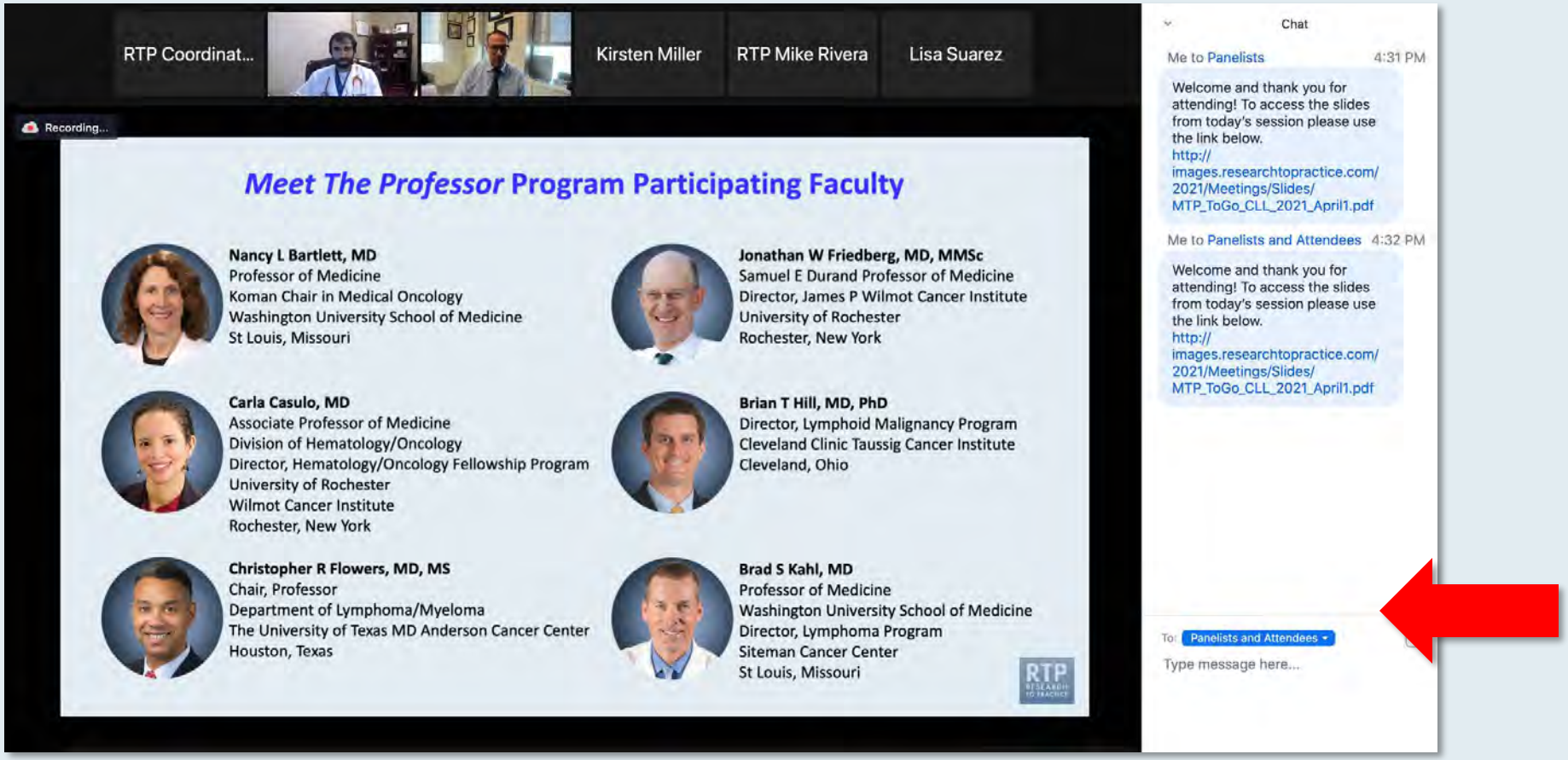

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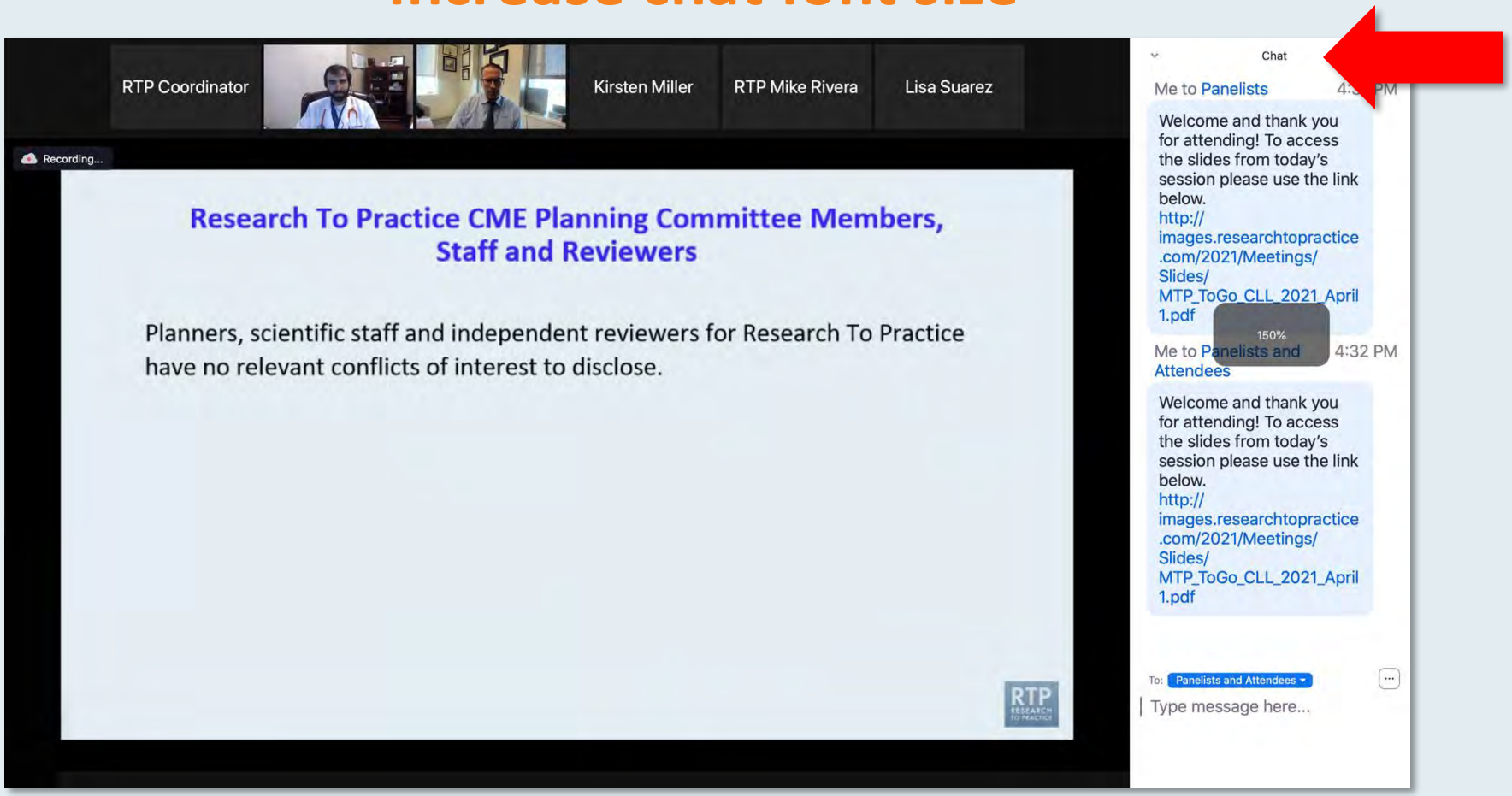

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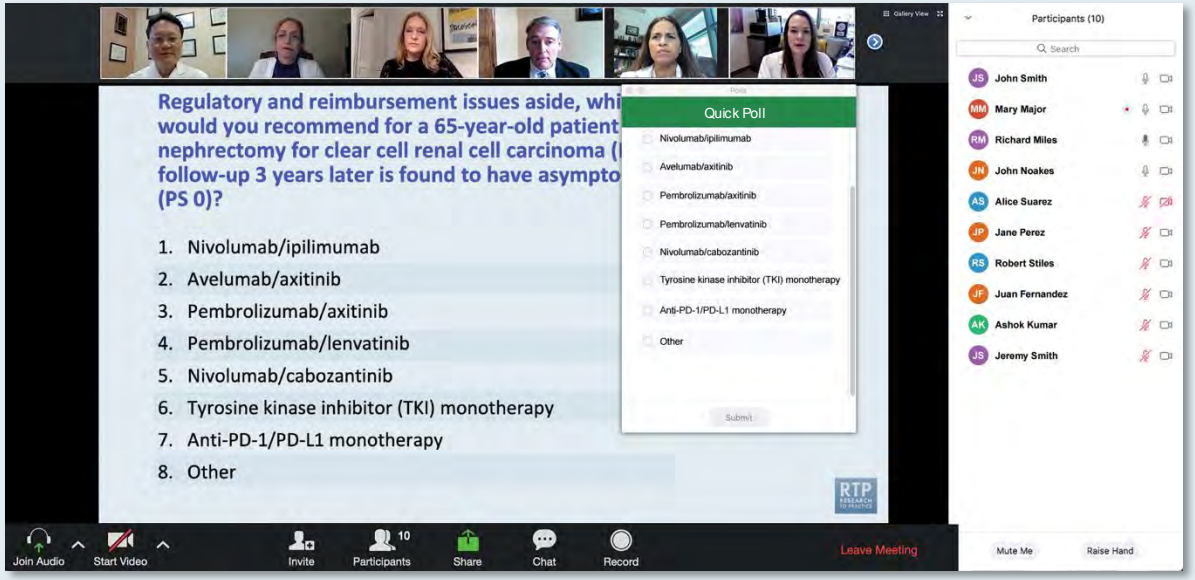

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WITH DR NEIL LOVE

Potential Role of PROTAC ER Degraders in Therapy for HR-Positive Metastatic Breast Cancer

DR ERIKA HAMILTON

SARAH CANNON RESEARCH INSTITUTE

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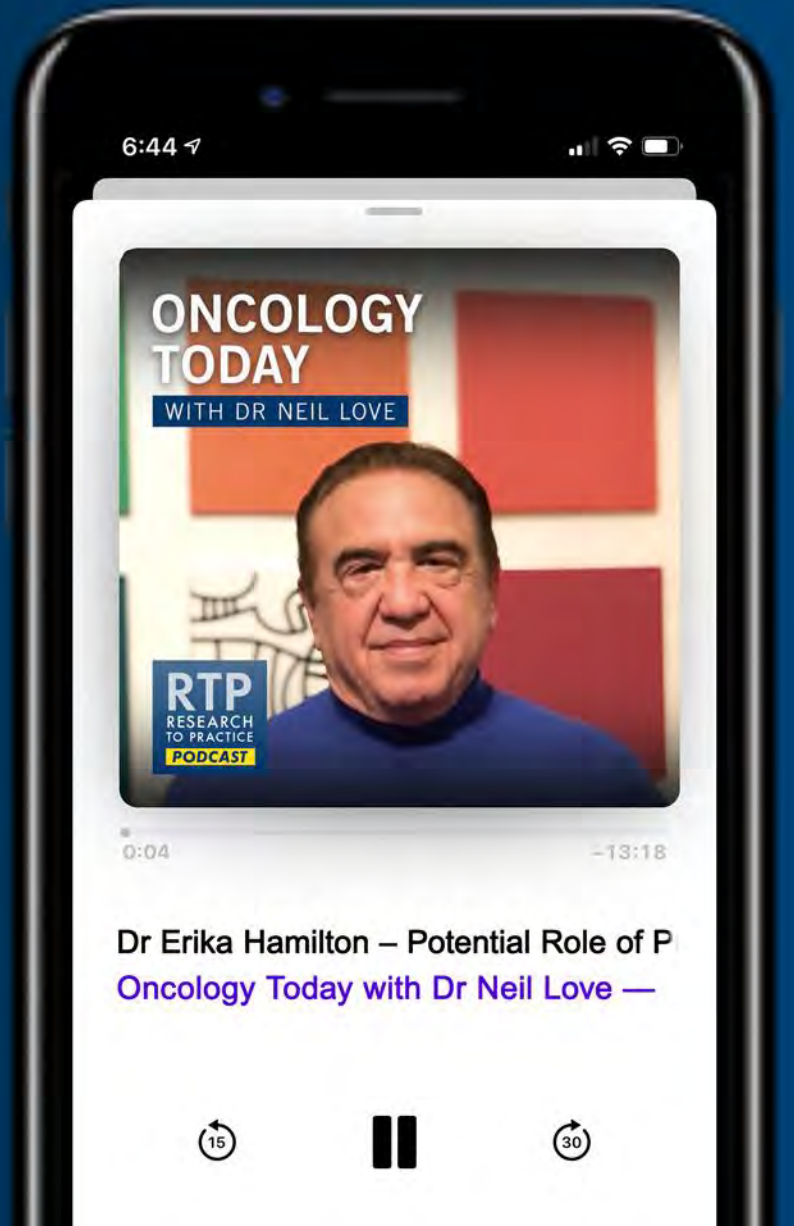

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A Live Webinar for Patients, Developed in Partnership with the Triple Negative Breast Cancer Foundation

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Lung Cancer Update: Antibody-Drug Conjugates and New Approaches

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Patricia and James Cayne Chair for Junior Faculty
Associate Attending Physician
Breast Medicine Service and Early Drug Development Service
Section Head, Endocrine Therapy Research Program
Clinical Director, Early Drug Development Service
Department of Medicine
Memorial Sloan Kettering Cancer Center
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Hope S Rugo, MD
Professor of Medicine
Winterhof Family Professor of Breast Cancer
Director, Breast Oncology and Clinical Trials Education
Medical Director, Cancer Infusion Services
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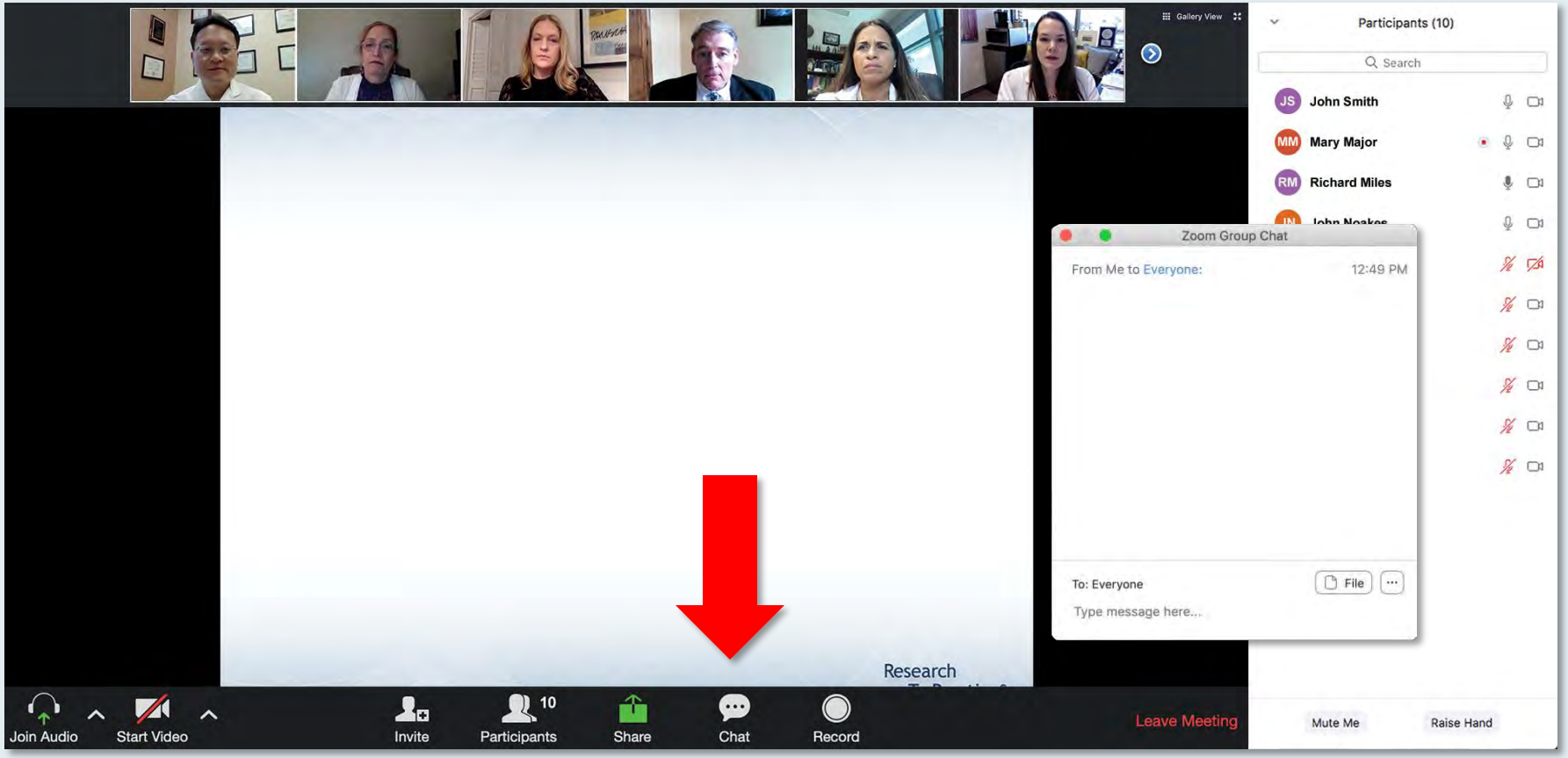

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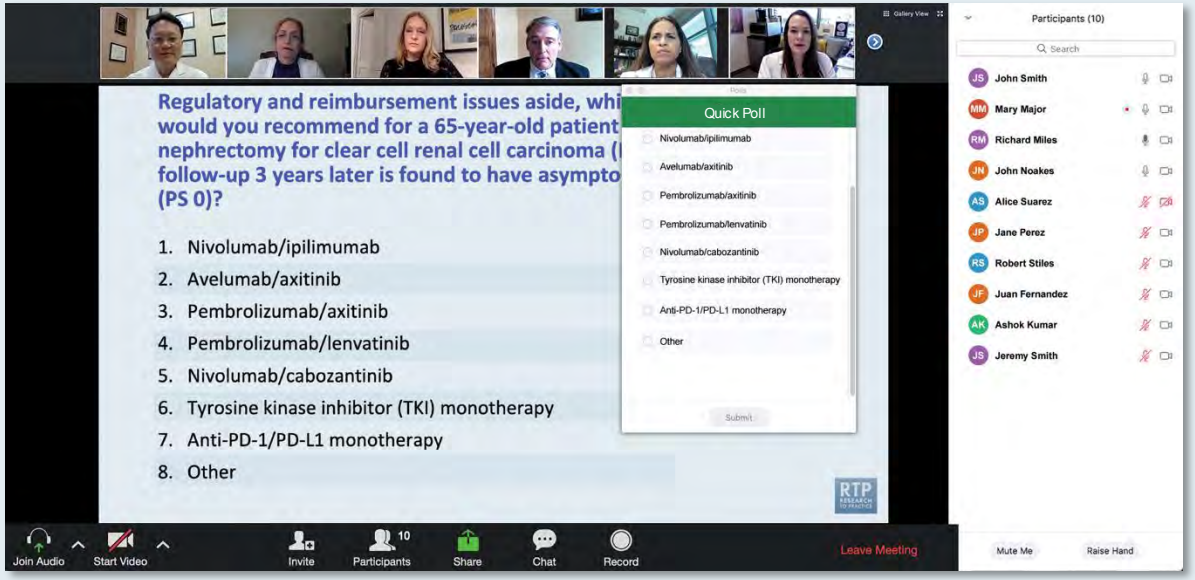

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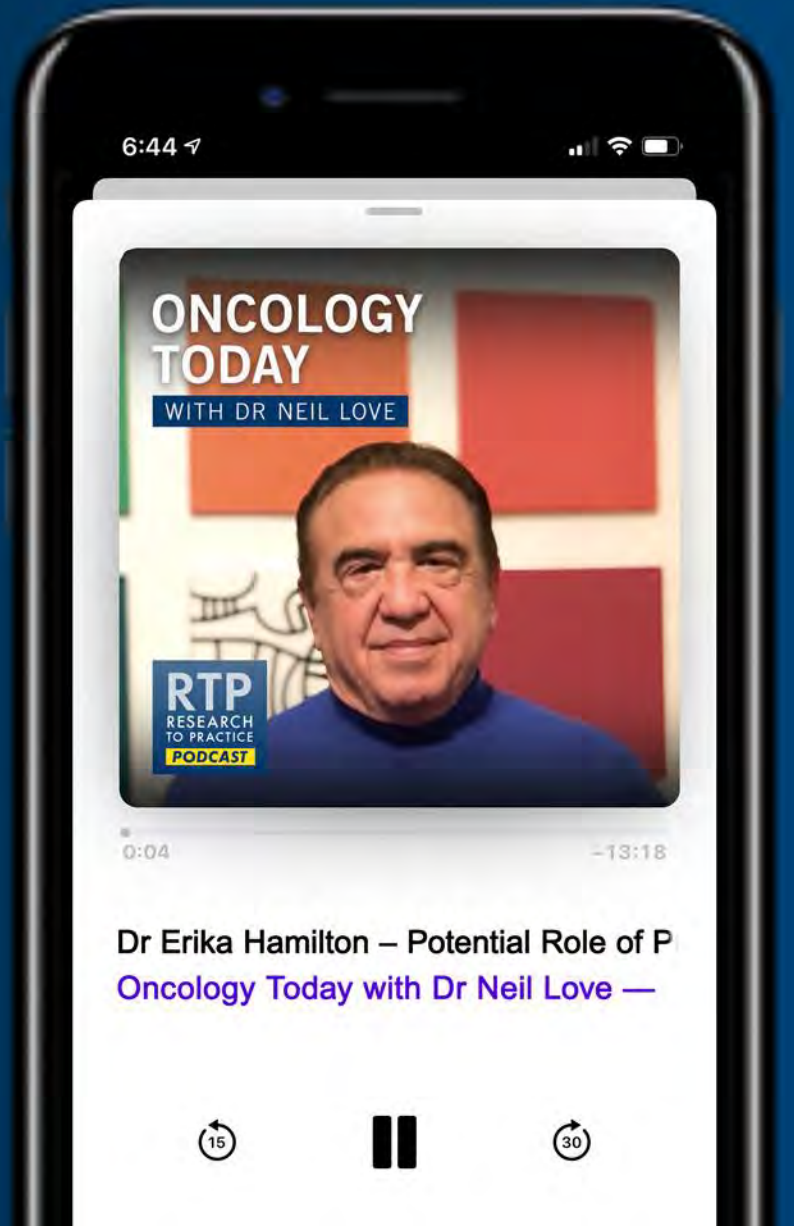

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Breast Cancer Survey Respondents

Aditya Bardia, MD, MPH
Virginia F Borges, MD, MMSc
Adam M Brufsky, MD, PhD
Harold J Burstein, MD, PhD
Karen A Gelmon, MD
Stephanie L Graff, MD, FACP
Sara A Hurvitz, MD, FACP
Komal Jhaveri, MD, FACP
Virginia Kaklamani, MD, DSc
Kevin M Kalinsky, MD, MS
Ian E Krop, Md, PhD
Erica Mayer, MD, MPH, FASCO
Kathy D Miller, MD
Ruth O'Regan, MD
Joyce A O'Shaughnessy, MD
Lajos Pusztai, MD, DPhil, FASCO
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Paolo Tarantino, MD
Sara M Tolaney, MD, MPH
Seth Wander, MD, PhD

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Agenda

Introduction: PI3K/AKT/PTEN Pathway and Resistance to Endocrine Therapy

Module 1: First-Line Therapy for HR-Positive Metastatic Breast Cancer (mBC) Harboring PI3K/AKT/PTEN Mutations

Module 2: Treatment Options for Recurrent mBC with PI3K/AKT/PTEN Mutations

Module 3: Beyond the Guidelines Survey

Module 4: Faculty Case Presentations

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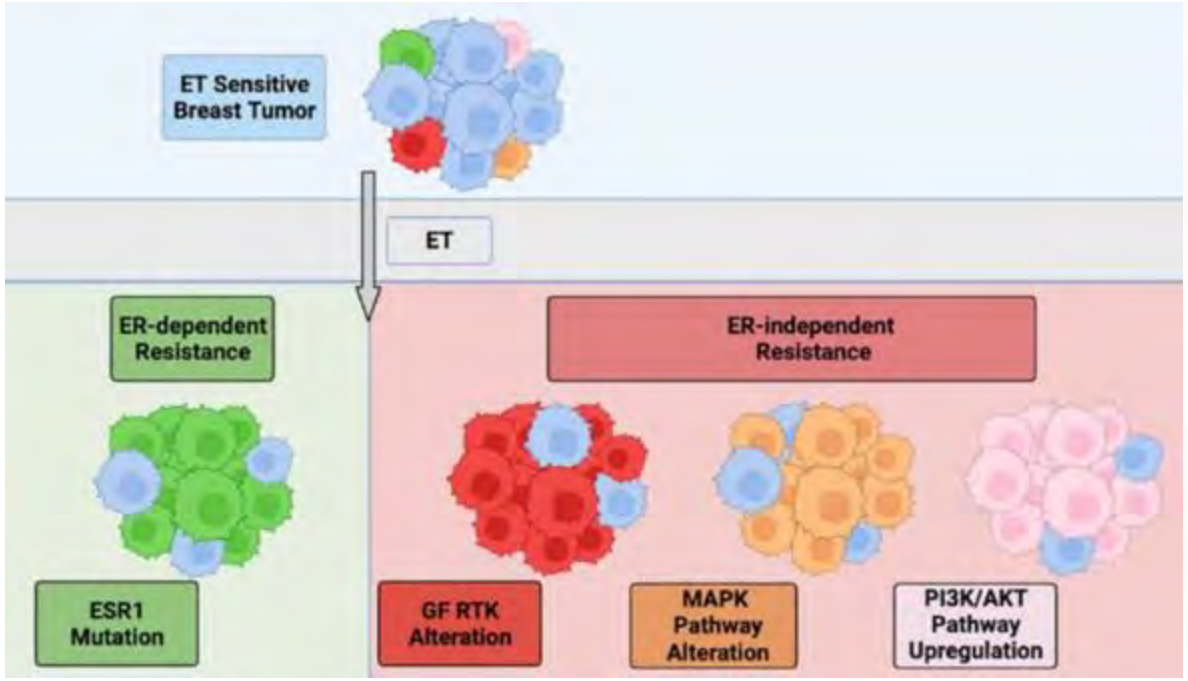
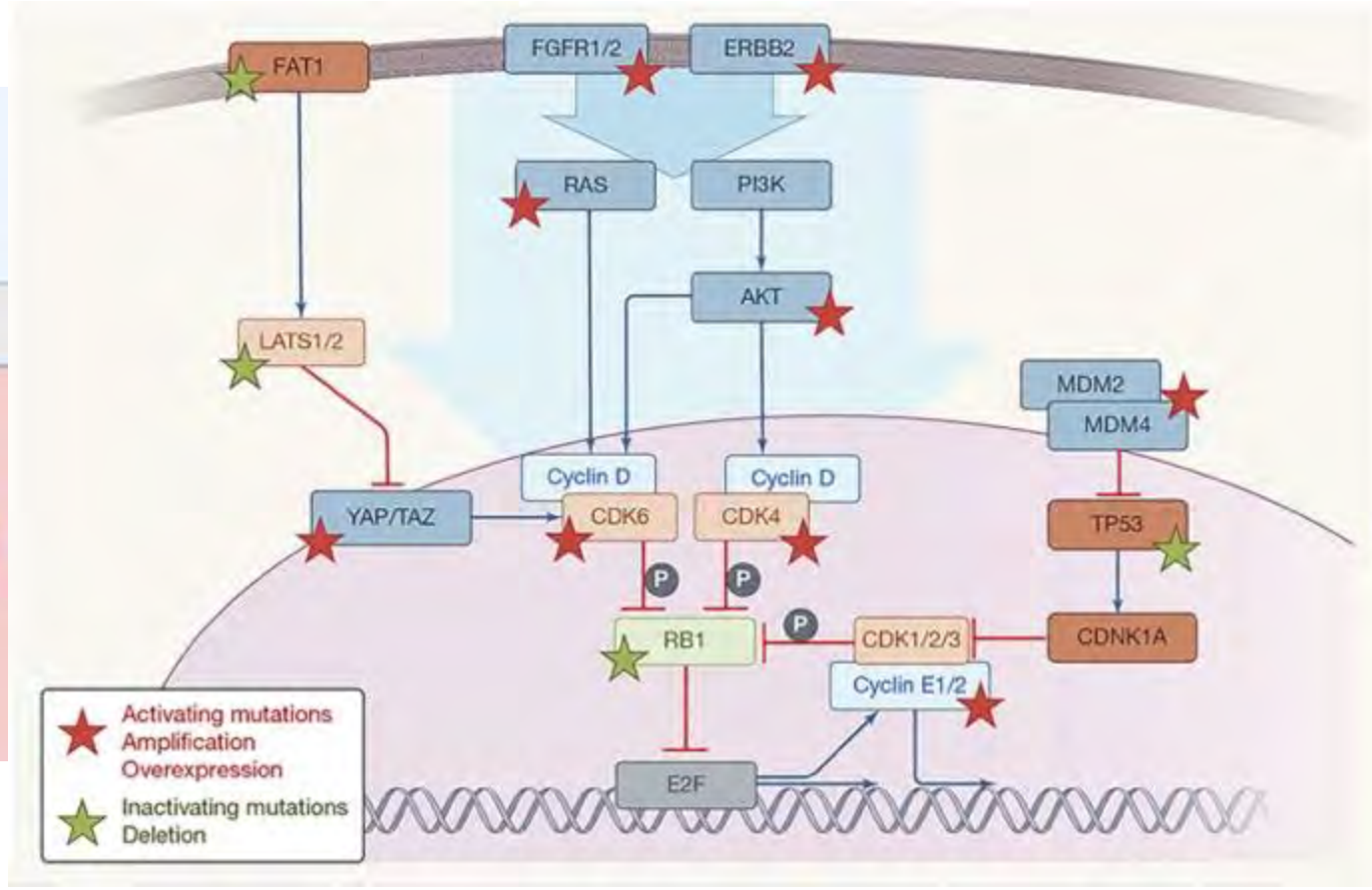
Resistance to ET + CDK4/6i: Remains a High Unmet Need



ER dependent and independent mechanism of resistance



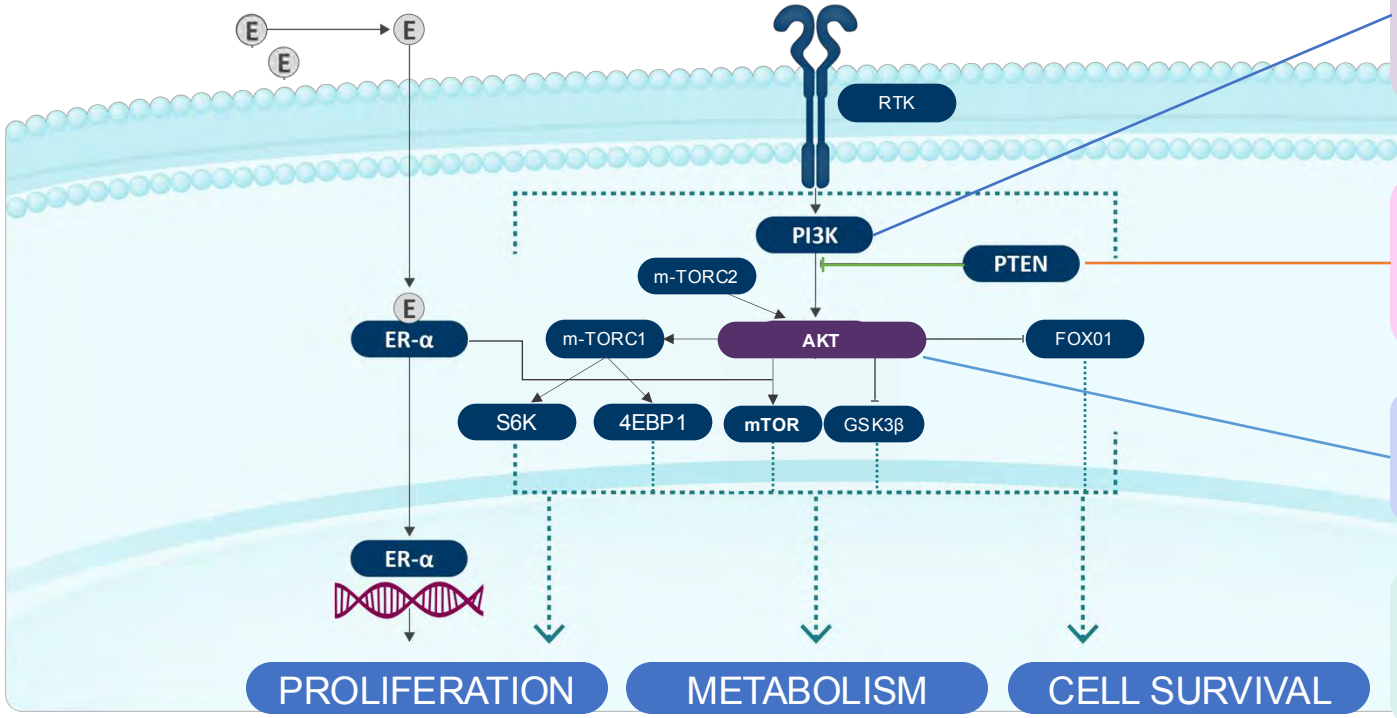
Major Mechanisms of Resistance to CDK4/6 Inhibitors

Lloyd MR, et al. *Ther Adv Med Oncol* 2022, Vol. 14: 1–25
Álvarez-Fernández M, Malumbres M. *Cancer Cell*. 2020;37:514-529.

Courtesy of Hope S Rugo, MD

Genes within the PI3K/AKT pathway are frequently altered in BC resulting in pathway overactivation, leading to tumor growth and treatment resistance[1,2]

The ER and PI3K/AKT pathways in BC[1–4]



***PIK3CA* mutations: ~40%**
Promote cell multiplication, resistance to apoptosis and BC treatment resistance (including ET and ChT)[1,5]

***PTEN* alterations: ~5%**
Result in a loss of tumor-suppressor functions (decreased apoptosis and cell growth control)[5,6]

***AKT1* mutations: ~5%**
Promote tumour progression and resistance to ChT[5,7]

AKT is a key node within the PI3K/AKT pathway. Inhibition of this protein disrupts pathway overactivation driven by alterations in *PIK3CA*, *AKT1* and/or *PTEN*[2,8,9]

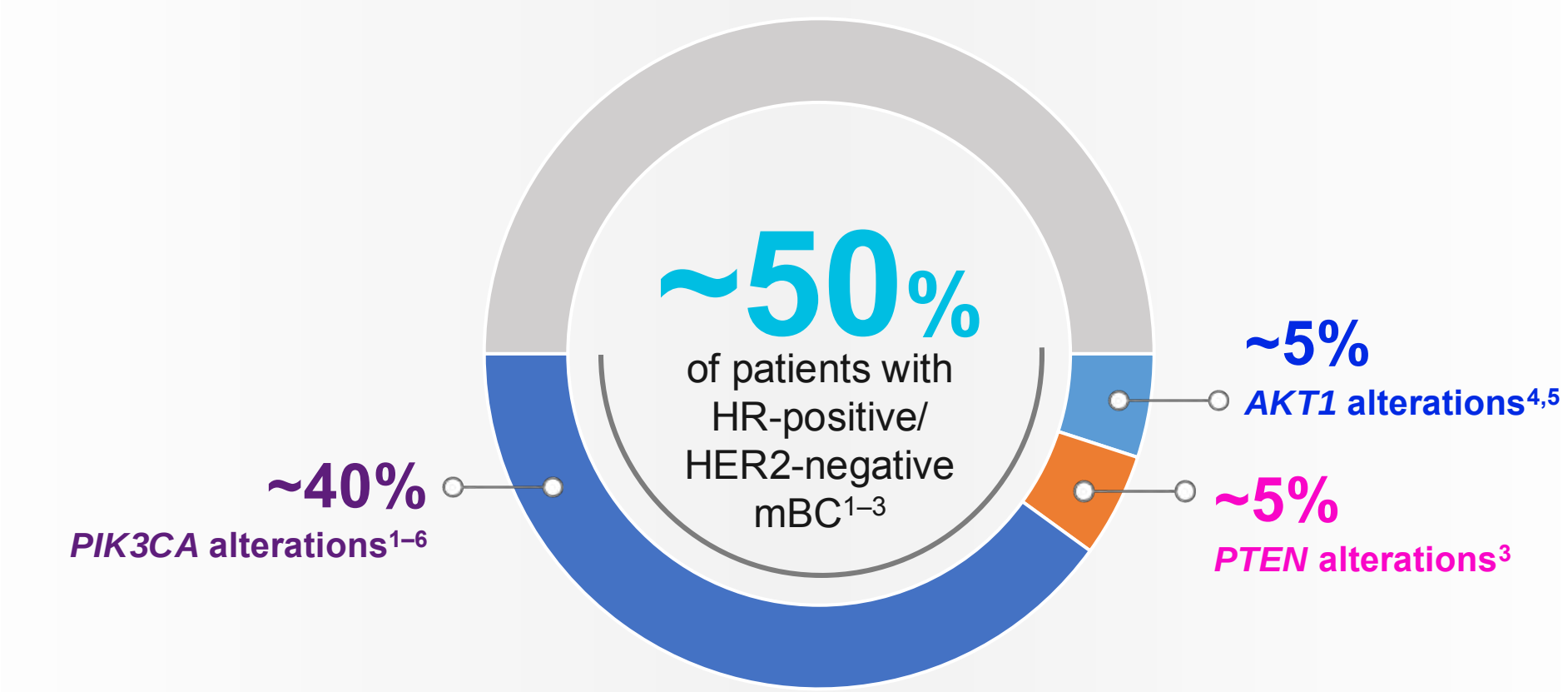
Adapted from: Alves CL and Ditzel HJ. 2023.[1]

4EBP1=eukaryotic translation initiation factor 4E-binding protein 1; AKT(1)=AKT serine/threonine kinase (1); BC=breast cancer; ChT=chemotherapy; E=oestrogen; ER-α=oestrogen receptor-alpha subunit; ET=endocrine therapy; FOXO1=forkhead box protein O1; GSK3β=glycogen synthase kinase 3β; mTOR=mechanistic target of rapamycin; m-TORC1/2=mammalian target of rapamycin complex 1/2; PI3K=phosphatidylinositol-4,5-bisphosphate 3-kinase; *PIK3CA*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN=phosphatase and tensin homologue; S6K=ribosomal S6 kinase.

1. Alves CL and Ditzel HJ. *Int J Mol Sci.* 2023;24:4522; 2. Miller TW, et al. *Breast Cancer Res*. 2011;13:224; 3. du Rusquec P, et al. *Ther Adv Med Oncol*. 2020;12:1–12; 4. Ebrahimnezhad M, et al. *Biomed Pharmacother* 2023:169:115900; 5. Rascio F, et al. *Cancers (Basel).* 2021;13:3949; 6. Mery B, et al. *Int J Mol Sci*. 2021;22:13512; 7. Hua H, et al. *J Hematol Oncol*. 2021;14:128; 8. Miricescu D, et al. *Int J Mol Sci*. 2020;22:173; 9. Davies BR, et al. *Mol Cancer Ther*. 2012;11:873–887.

Courtesy of Hope S Rugo, MD

Genomic alterations within the PI3K/AKT pathway are present in ~50% of patients with HR-positive, HER2-negative mBC



PIK3CA alterations are the most prevalent, with similar rates of *AKT1* and *PTEN* alterations observed in patients with HR-positive, HER2-negative mBC

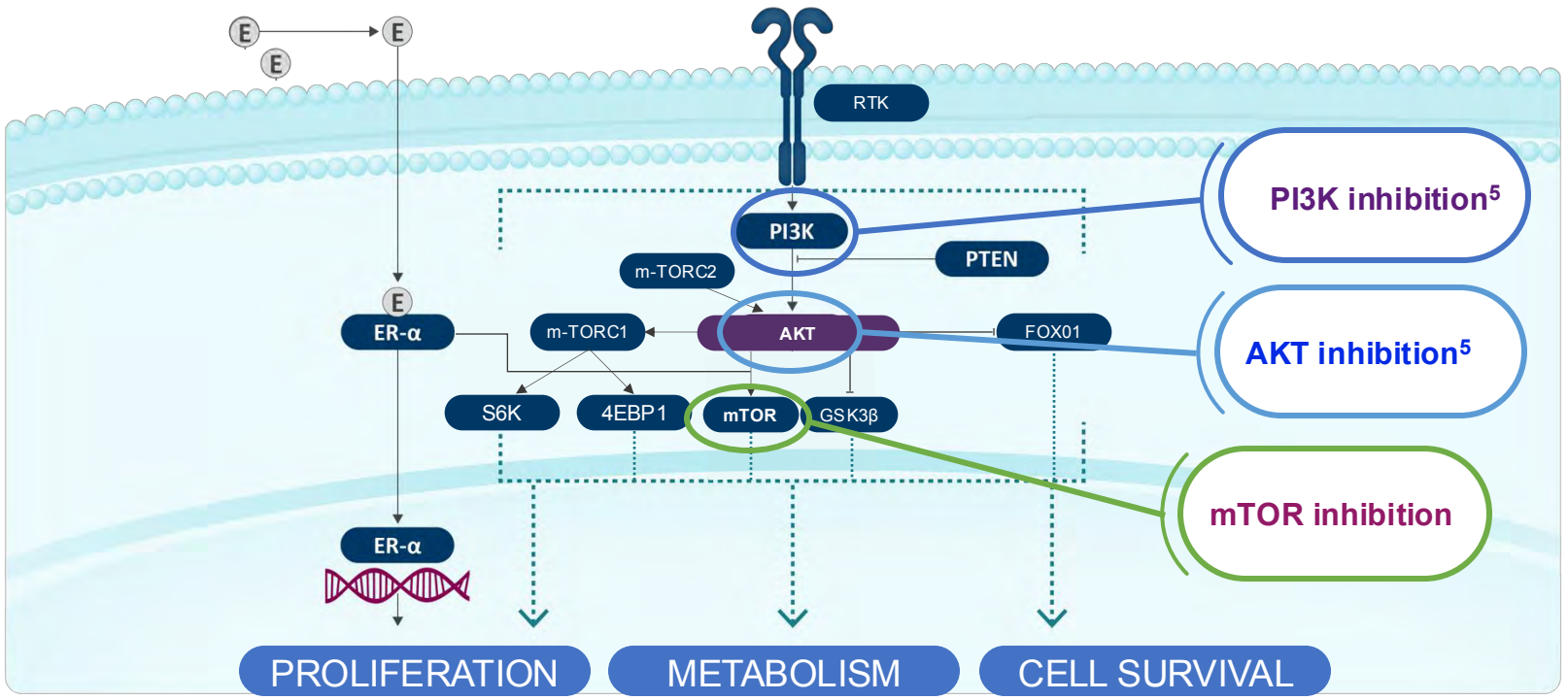
2L=second-line; AKT(1)=AKT serine/threonine kinase (1); HR=hormone receptor; HER2=human epidermal growth factor receptor 2; m=mutation; mBC=metastatic breast cancer; PI3K=phosphatidylinositol-4,5-bisphosphate 3-kinase; *PIK3CA*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*=phosphatase and tensin homologue.

1. Cancer Genome Atlas Network. *Nature*. 2012;490:61–70; 2. Martorana F, et al. *Front Pharmacol*. 2021;12:662232; 3. Park L, et al. Presented at ASCO Annual Congress 2024, May 31–June 4. Chicago, USA. Poster #1041; 4. Miricescu D, et al. *Int J Mol Sci*. 2020;22:173; 5. Smyth LM, et al. *Cancer Discov*. 2020;10:526–535; 6. Paplomata E and O'Regan R. *Ther Adv Med Oncol*. 2014;6:154–166.

Courtesy of Hope S Rugo, MD

There are several targets in the PI3K/AKT signalling pathway that inhibitors can act against[1,5–8]

The ER and PI3K/AKT pathways in BC[1–4]



mTOR is often described as being in the same pathway as PI3K/AKT[1]

Adapted from: Alves CL and Ditzel HJ. 2023.[1]

4EBP1=eukaryotic translation initiation factor 4E-binding protein 1; AKT=AKT serine/threonine kinase; BC=breast cancer; E=oestrogen; ER-α=oestrogen receptor-alpha subunit; FOXO1=forkhead box protein O1; GSK3β=glycogen synthase kinase 3β; mTOR=mechanistic target of rapamycin; m-TORC1/2=mammalian target of rapamycin complex 1/2; PI3K=phosphatidylinositol-4,5-bisphosphate 3-kinase; PTEN=phosphatase and tensin homologue; RTK=receptor tyrosine kinase; S6K=ribosomal S6 kinase.

1. Alves CL and Ditzel HJ. *Int J Mol Sci.* 2023;24:4522; 2. Miller TW, et al. *Breast Cancer Res*. 2011;13:224; 3. du Rusquec P, et al. *Ther Adv Med Oncol*. 2020;12:1–12; 4. Ebrahimnezhad M, et al. *Biomed Pharmacother* 2023:169:115900; 5. ASCO Post. Available at: https://ascopost.com/issues/april-25-2023/emerging-success-with-novel-targeted-therapies-in-endocrine-resistant-metastatic-breast-cancer/ (Accessed September 2024).

Courtesy of Hope S Rugo, MD

Agenda

Introduction: PI3K/AKT/PTEN Pathway and Resistance to Endocrine Therapy

Module 1: First-Line Therapy for HR-Positive Metastatic Breast Cancer (mBC) Harboring PI3K/AKT/PTEN Mutations

Module 2: Treatment Options for Recurrent mBC with PI3K/AKT/PTEN Mutations

Module 3: Beyond the Guidelines Survey

Module 4: Faculty Case Presentations

October 10, 2024

FDA approves inavolisib with palbociclib and fulvestrant for endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, advanced breast cancer

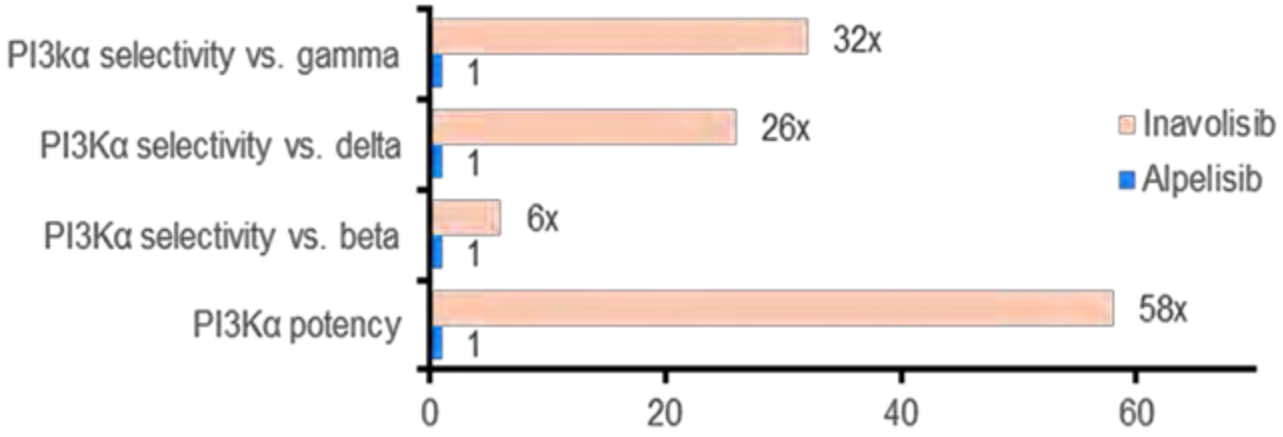
FDA also approved the FoundationOne Liquid CDx assay as a companion diagnostic device to identify patients with breast cancer for treatment with inavolisib with palbociclib and fulvestrant.

Courtesy of Hope S Rugo, MD

Inavolisib: Highly Potent & Selective PI3Kα Inhibitor that Facilitates Specific Degradation of Mutated PI3Kα

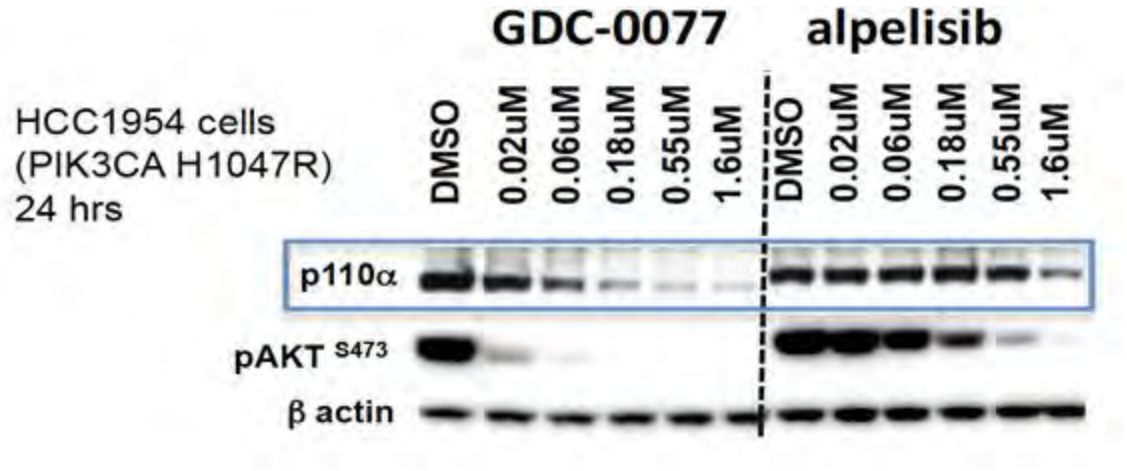
High potency and specificity for PI3Kα

Inavolisib has higher potency and selectivity for PI3Kα inhibition compared to alpelisib*



Mutant-specific degradation of PI3Kα

Inavolisib (GDC-0077) facilitates mutant PI3Kα degradation that leads to sustained pathway inhibition

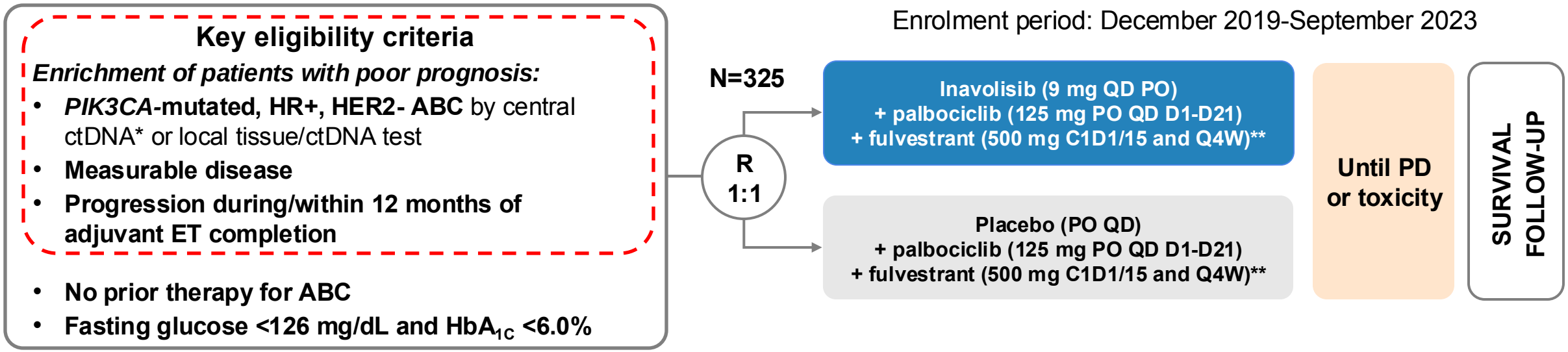


Inavolisib potently inhibits mutant PI3K pathway signaling and cell viability through unique HER2-dependent mutant p110a degradation resulting in prolonged pathway suppression.

* Adapted from Song et al, Cancer Discovery 2022; Edgar et al, AACR 2017

Courtesy of Hope S Rugo, MD

INAVO120 study design



Stratification factors:
- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

Endpoints
- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

* Central testing for *PIK3CA* mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu). † Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.[1] Primary: relapse while on the first 2 years of adjuvant ET; Secondary: relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET. ‡ OS testing only if PFS is positive; interim OS analysis at primary PFS analysis; **Pre-menopausal women received ovarian suppression. ctDNA, circulating tumor DNA; R, randomized. 1. Cardoso F, *et al. Ann Oncol* 2018;**29:**1634–1657.

Jhaveri et al, SABCS 2023

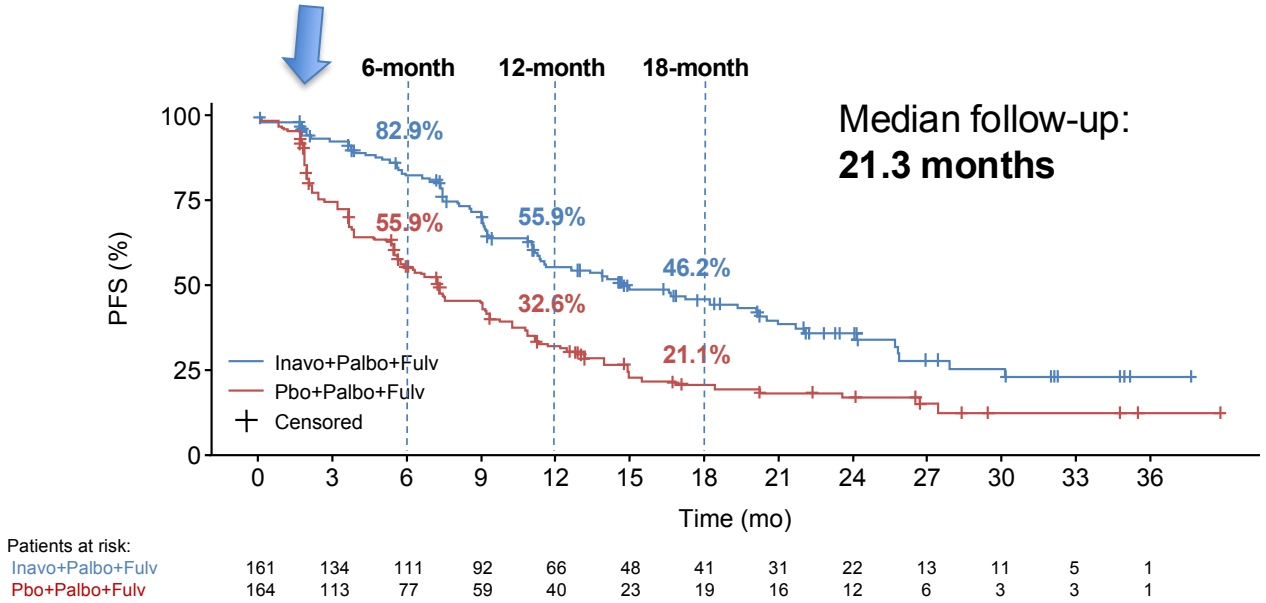
Courtesy of Hope S Rugo, MD

INAVO120: Phase III trial evaluating the addition of inavolisib to a fulvestrant and palbociclib backbone as first-line therapy for mPIK3CA HR+/HER2- MBC

- Trial population (n=325) selected for endocrine resistance
  - ~34% primary endocrine resistance
  - ~66% secondary endocrine resistance
- Additional high-risk features
  - 48% premenopausal
  - 80% visceral mets, 50% liver involvement
- Other
  - 38% Asian
  - 48% adjuvant tamoxifen only
  - Most central ctDNA testing
  - Last patient entered on study: 9/29/23

PFS	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59)** **p<0.0001**	

Overcomes primary resistance

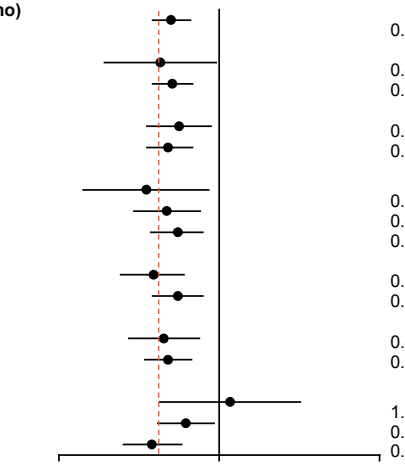


Courtesy of Hope S Rugo, MD

Additional Endpoints

PFS (Investigator assessed) in key subgroups 2/2

	Inavo+Palbo+Fulv n	Inavo+Palbo+Fulv Median (mo)	Pbo+Palbo+Fulv n	Pbo+Palbo+Fulv Median (mo)	Hazard ratio (95% CI)
All patients	161	15.0	164	7.3	0.50 (0.38, 0.67)
Visceral disease					
No	29	25.8	36	7.4	0.43 (0.19, 0.97)
Yes	132	13.8	128	7.2	0.51 (0.38, 0.69)
Liver metastasis at enrollment					
No	84	24.2	73	11.3	0.56 (0.35, 0.90)
Yes	77	11.0	91	5.6	0.48 (0.33, 0.69)
Number of metastatic organs at enrollment					
1	21	20.2	32	7.4	0.35 (0.14, 0.87)
2	59	18.2	46	7.4	0.47 (0.29, 0.77)
≥3	81	14.1	86	7.3	0.55 (0.37, 0.80)
Endocrine resistance					
Primary	53	11.4	58	3.7	0.39 (0.24, 0.61)
Secondary	108	18.2	105	9.7	0.55 (0.38, 0.80)
HR status					
ER+/PgR–	45	11.1	45	5.6	0.45 (0.27, 0.76)
ER+/PgR+	113	18.2	113	7.4	0.48 (0.34, 0.68)
Prior (neo)adjuvant endocrine therapy					
Aromatase inhibitor and tamoxifen	18	11.0	19	12.9	1.17 (0.42, 3.24)
Aromatase inhibitor only	60	10.9	71	5.8	0.62 (0.41, 0.94)
Tamoxifen only	82	21.0	73	7.4	0.38 (0.25, 0.59)



CI, confidence interval; ER, estrogen receptor; Fulv, fulvestrant; HR, hormone receptor; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival; PgR, progesterone receptor.

ORR superior

DOR	Inavo+Palbo +Fulv (n=94)	Pbo+Palbo+Fulv (n=41)
No. of events, n (%)	46 (48.9)	27 (65.9)
Median (95% CI), mo	18.4 (10.4, 22.2)	9.6 (7.4, 16.6)
Stratified hazard ratio (95% CI)	0.57 (0.33, 0.99)	

Safety

- Low treatment discontinuation rates for AE: 6.8%
- Dose reduction/interruption common in both arms

OS early but encouraging

	Inavo+Palbo +Fulv (n=161)	Pbo+Palbo +Fulv (n=164)
No. of events, n (%)	42 (26.1)	55 (33.5)
Median (95% CI), mo	NE (27.3, NE)	31.1 (22.3, NE)
Stratified Hazard Ratio (95% CI)	0.64 (0.43, 0.97) p=0.0338	

Adverse Events	Inavo+Palbo+Fulv (N=162)		Pbo+Palbo+Fulv (N=162)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Neutropenia	**144 (88.9%)**	**130 (80.2%)**	**147 (90.7%)**	**127 (78.4%)**
Thrombocytopenia	78 (48.1%)	23 (14.2%)	73 (45.1%)	7 (4.3%)
Stomatitis/Mucosal inflammation	**83 (51.2%)**	**9 (5.6%)**	**43 (26.5%)**	**0**
Anemia	60 (37.0%)	10 (6.2%)	59 (36.4%)	3 (1.9%)
Hyperglycemia	**95 (58.6%)**	**9 (5.6%)**	**14 (8.6%)**	**0**
Diarrhea	**78 (48.1%)**	**6 (3.7%)**	**26 (16.0%)**	**0**
Nausea	**45 (27.8%)**	**1 (0.6%)**	**27 (16.7%)**	**0**
Rash	**41 (25.3%)**	**0**	**28 (17.3%)**	**0**

Courtesy of Hope S Rugo, MD

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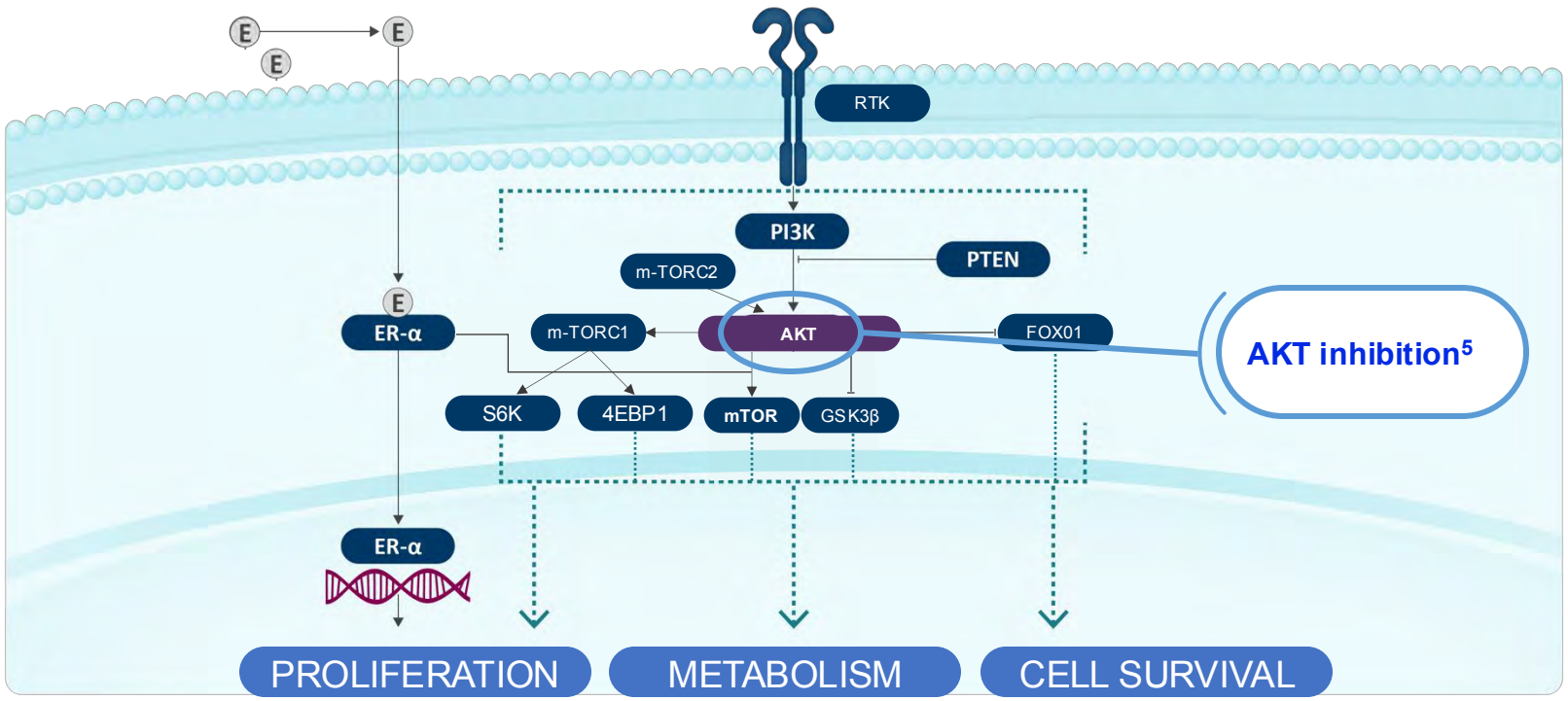
Capivasertib is a potent, selective inhibitor of AKT

The ER and PI3K/AKT pathways in BC[1–4]



Potent inhibition of AKT broadens actionable biomarkers beyond *PIK3CA* alterations to include *AKT1* and *PTEN* alterations[6–8]

Adapted from: Alves CL and Ditzel HJ. 2023.[1]

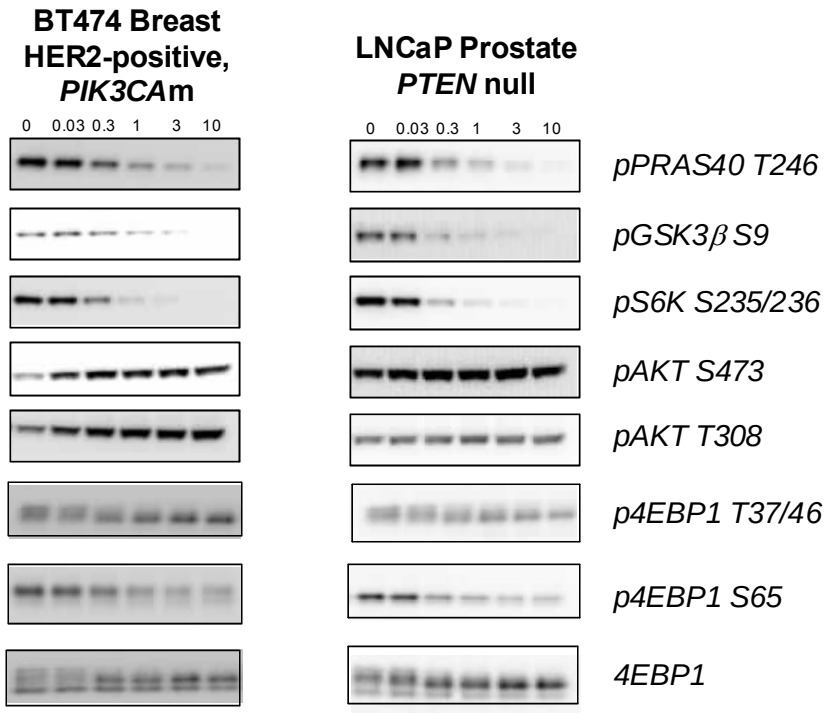
4EBP1=eukaryotic translation initiation factor 4E-binding protein 1; AKT(1)=AKT serine/threonine kinase (1); BC=breast cancer; E=oestrogen; ER-α=oestrogen receptor-alpha subunit; FOXO1=forkhead box protein O1; GSK3β=glycogen synthase kinase 3β; mTOR=mechanistic target of rapamycin; m-TORC1/2=mammalian target of rapamycin complex 1/2; PI3K=phosphatidylinositol-4,5-bisphosphate 3-kinase; *PIK3CA*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN=phosphatase and tensin homologue; RTK=receptor tyrosine kinase; S6K=ribosomal S6 kinase.

1. Alves CL and Ditzel HJ. *Int J Mol Sci.* 2023;24:4522; 2. Miller TW, et al. *Breast Cancer Res*. 2011;13:224; 3. du Rusquec P, et al. *Ther Adv Med Oncol*. 2020;12:1–12; 4. Ebrahimnezhad M, et al. *Biomed Pharmacother* 2023:169:115900; 5. ASCO Post. Available at: https://ascopost.com/issues/april-25-2023/emerging-success-with-novel-targeted-therapies-in-endocrine-resistant-metastatic-breast-cancer/ (Accessed September 2024);
6. Turner N, et al. *N Engl J Med*. 2023;388:2058–2070; 7. Smyth LM, et al. *Clin Cancer Res*. 2020;26:3947–3957; 8. AstraZeneca. Capivasertib Prescribing Information. November 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/218197s000lbl.pdf. (Accessed September 2024).

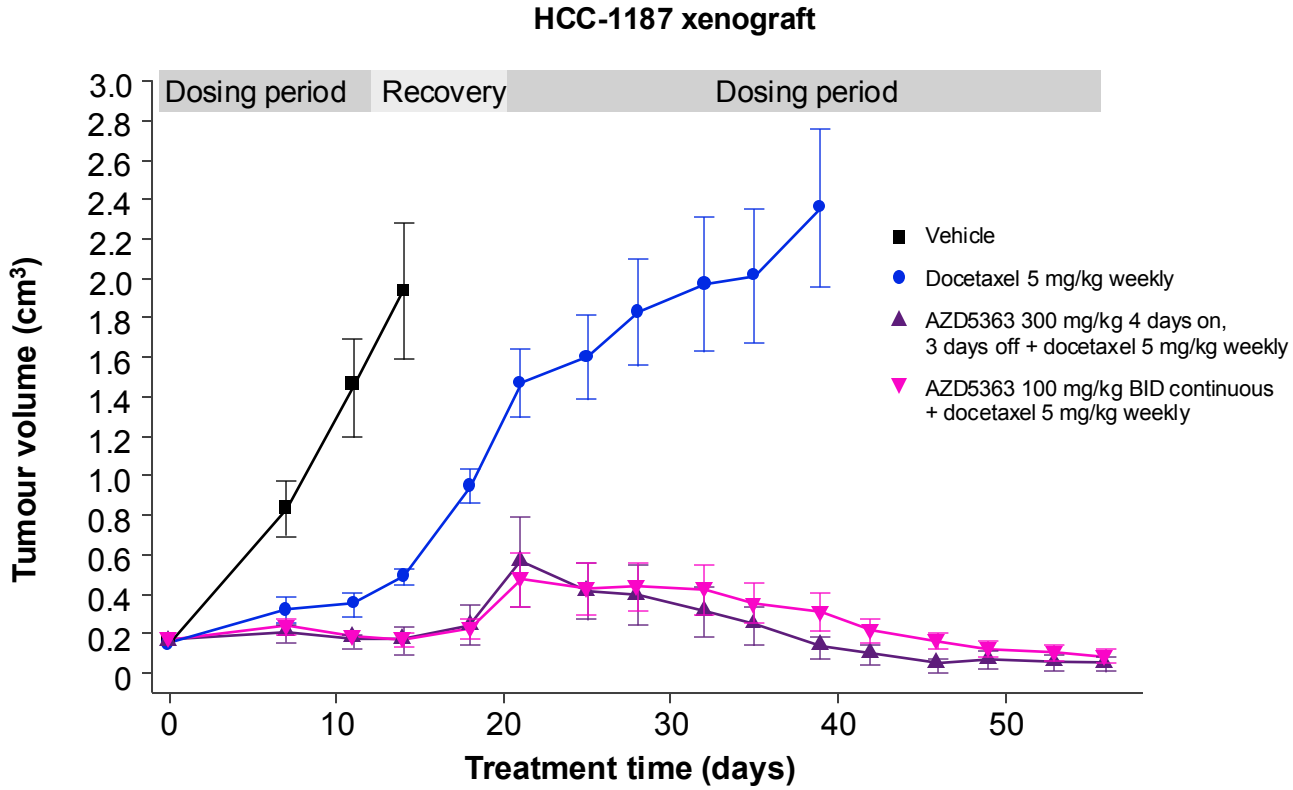
Courtesy of Hope S Rugo, MD

Capivasertib inhibits the phosphorylation of AKT substrates and its downstream pathway proteins

Dose-dependent inhibition of cellular AKT substrates was observed following increasing concentrations of capivasertib



AZD5363 synergizes with docetaxel *in vivo*



4EBP1=eukaryotic translation initiation factor 4E-binding protein 1; AKT=AKT serine/threonine kinase; ER=oestrogen receptor; ET=endocrine therapy; GSK3β=glycogen synthase kinase 3β; HER2=human epidermal growth factor receptor 2; p=phosphylated; PI3K=phosphoinositide 3-kinase; *PIK3CAm*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene mutation; *PTEN*=phosphatase and tensin homologue; PRAS40=proline-rich AKT substrate of 40 kDa; S6K=ribosomal S6 kinase.

1. Courtesy of Prof Turner (August 2024); 2. Davies BR, et al. *Mol Cancer Ther*. 2012;11:873–887.

Courtesy of Hope S Rugo, MD

CAPItello-291:

Phase III, randomized, double-blind, placebo-controlled study

Patients with HR+/HER2– ABC

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

R1:1 (N=708)

Capivasertib — 400 mg twice daily, 4 days on, 3 days off
43.7% altered
Fulvestrant — 500 mg: cycle 1, days 1 & 15; then every 4 weeks

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

Placebo — Twice daily, 4 days on, 3 days off
37% altered
Fulvestrant — 500 mg: cycle 1, days 1 & 15; then every 4 weeks

Dual primary endpoints

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

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

Summary of Demographics

- Median age ~59
- Asian 26%, Black 1%
- Primary ET resistance ~38%
- Visceral mets ~68%
- One line of prior ET for MBC ~75%
- Prior CDK4/6i for MBC ~70%
- Chemotherapy for ABC ~18%

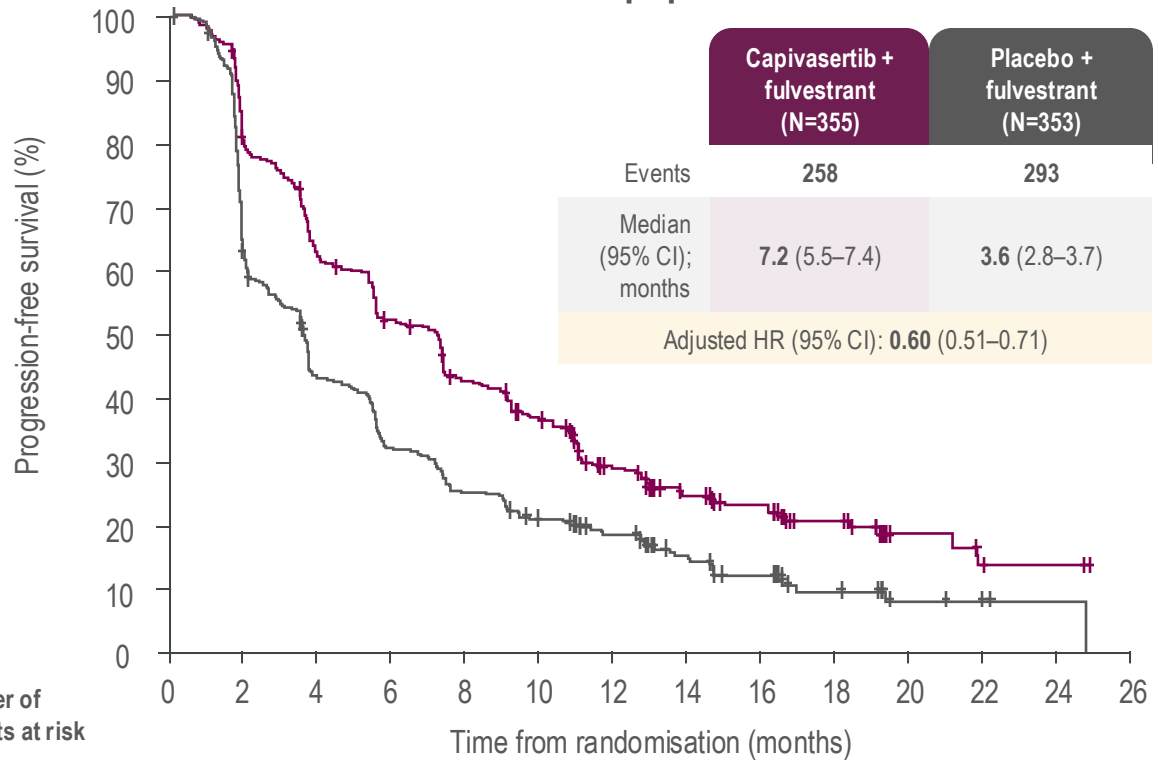
Courtesy of Hope S Rugo, MD

Turner et al, NEJM 2023;388(22):2058-2070.

Dual primary endpoints: PFS in overall and AKT pathway-altered populations[1]

Capivasertib plus fulvestrant provides a statistically significant and clinically meaningful improvement in PFS in the overall and the AKT pathway-altered populations

Overall population

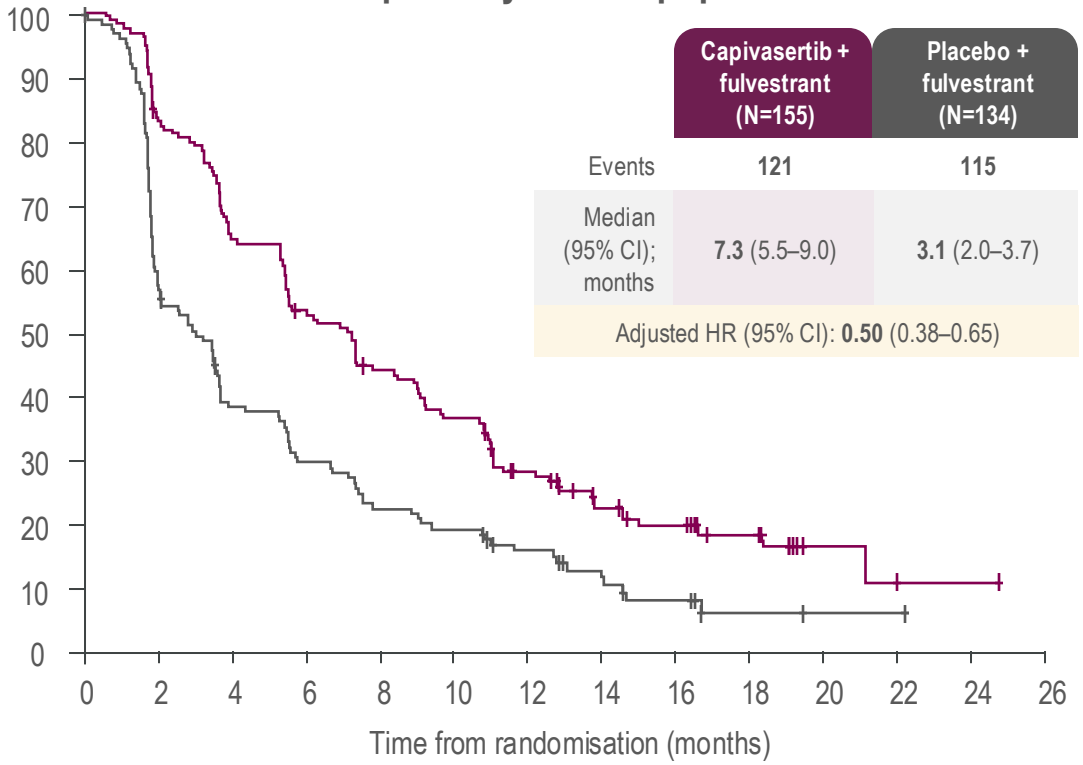


	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Events	258	293
Median (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI): **0.60** (0.51–0.71)		

Number of patients at risk

Capivasertib + fulvestrant	355	226	207	172	138	115	78	55	43	25	8	5	2	0
Placebo + fulvestrant	353	207	142	106	83	66	51	33	23	11	4	3	1	0

AKT pathway-altered population



	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Events	121	115
Median (95% CI); months	**7.3** (5.5–9.0)	**3.1** (2.0–3.7)
Adjusted HR (95% CI): **0.50** (0.38–0.65)		

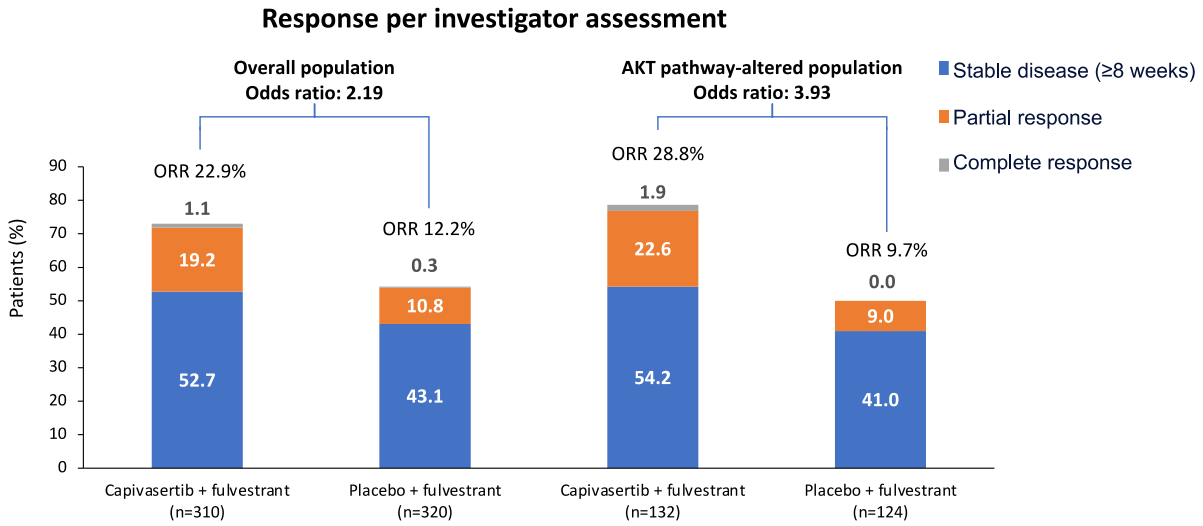
Capivasertib + fulvestrant	155	127	99	80	65	54	38	26	21	12	3	2	1	0
Placebo + fulvestrant	134	77	48	37	28	24	17	11	6	2	1	1	0	0

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

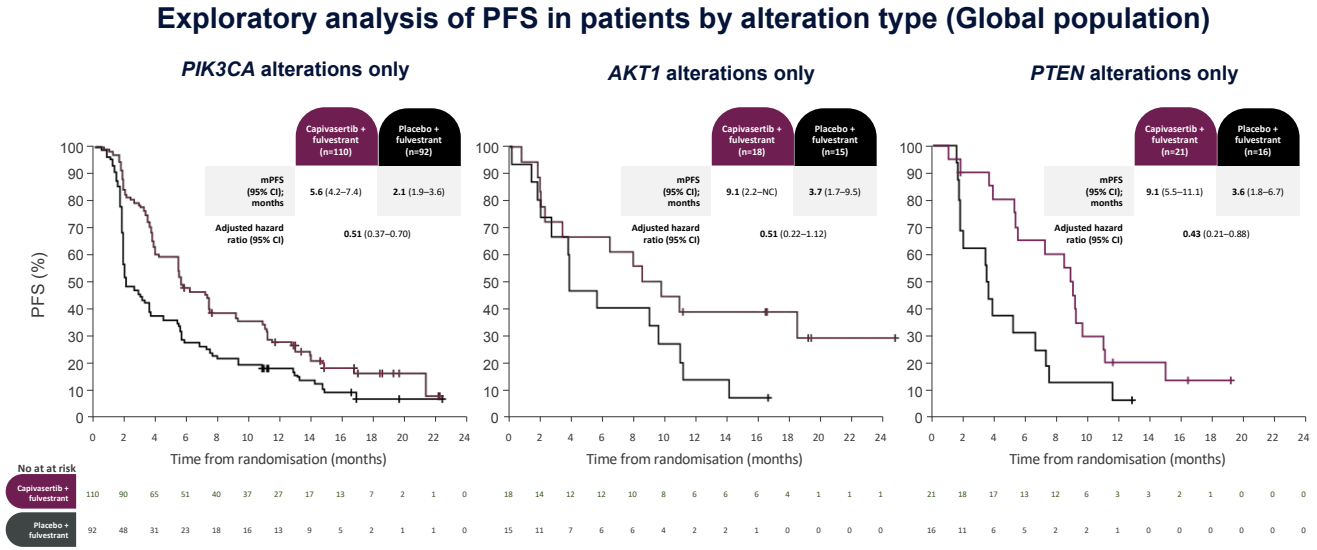
Courtesy of Hope S Rugo, MD

Turner et al, NEJM 2023;388(22):2058-2070

In the overall and *PIK3CA/AKT1/PTEN*-altered populations, response rates were high with the addition of capivasertib to fulvestrant



Observed PFS benefit was consistent across **gene alterations**



DCO August 2022. + indicates a censored observation. Hazard ratio for *PIK3CA* alteration was estimated using the Cox proportional hazard model stratified by presence of liver metastases and prior use of CKD4/6i. Hazard ratios for *ATK1* and *PTEN* alterations were estimated using an unstratified Cox proportional hazard model.

AKT1=AKT serine/threonine kinase 1; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; CI=confidence interval; DCO=data cut-off; NC=not calculable; (m)PFS=(median) progression-free survival; *PIK3CA*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*=phosphatase and tensin homologue.

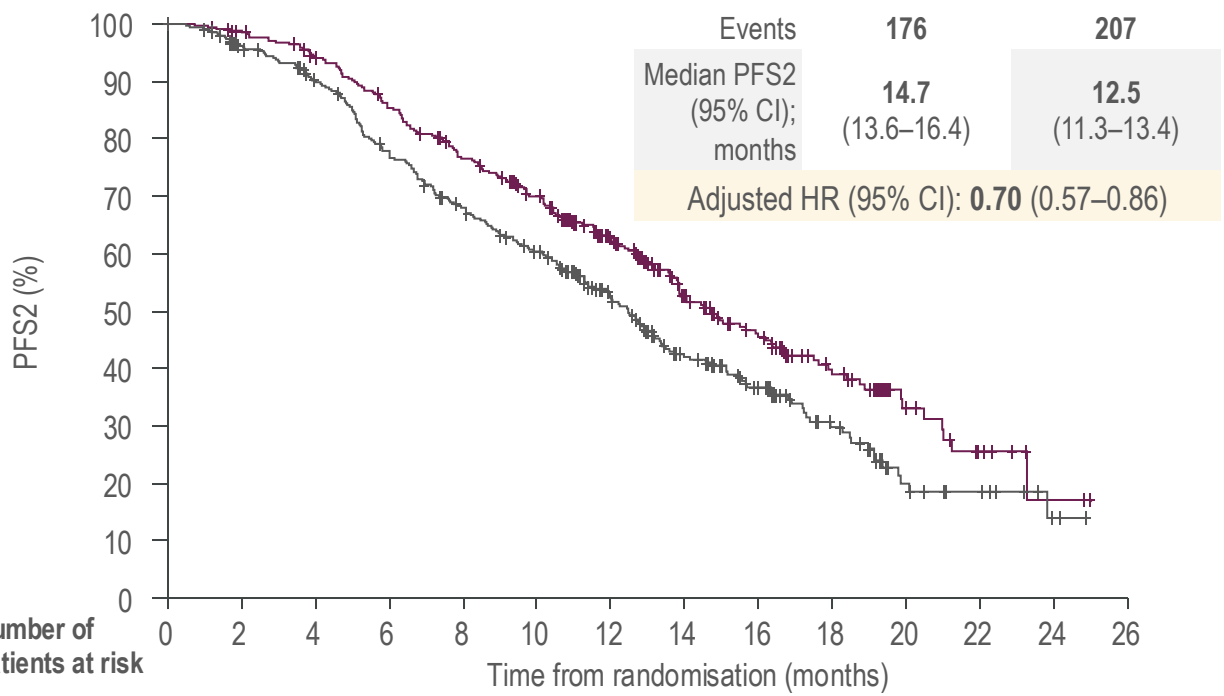
Howell SJ, et al. Presented at SABCS Annual Meeting 2023, December 5–9. San Antonio, US. Abstract #PS17-03.

Courtesy of Hope S Rugo, MD

Progression-free survival 2 (PFS2)

Extended treatment benefit (PFS2) with capivasertib-fulvestrant observed in the overall and the *PIK3CA*/*AKT1*/*PTEN*-altered populations

Overall population

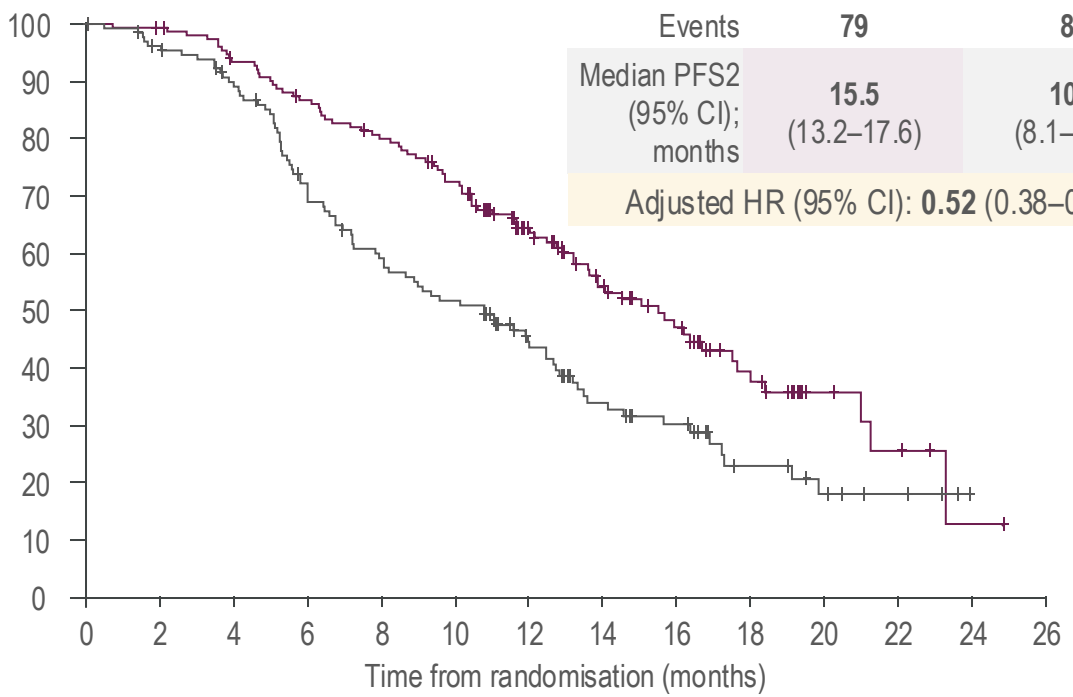


	Capivasertib-fulvestrant (N=355)	Placebo-fulvestrant (N=353)
Events	176	207
Median PFS2 (95% CI); months	14.7 (13.6–16.4)	12.5 (11.3–13.4)
Adjusted HR (95% CI): **0.70** (0.57–0.86)		

Number of patients at risk

Capivasertib-fulvestrant	355	334	315	283	248	218	164	108	78	48	20	11	2	0
Placebo-fulvestrant	353	321	294	252	216	185	137	88	63	33	14	9	2	0

PIK3CA/*AKT1*/*PTEN*-altered population



	Capivasertib-fulvestrant (N=155)	Placebo-fulvestrant (N=134)
Events	79	87
Median PFS2 (95% CI); months	15.5 (13.2–17.6)	10.8 (8.1–12.7)
Adjusted HR (95% CI): **0.52** (0.38–0.71)		

	155	151	140	129	118	105	76	53	38	22	8	5	1	0
	134	124	113	89	72	63	45	29	22	11	7	4	0	0

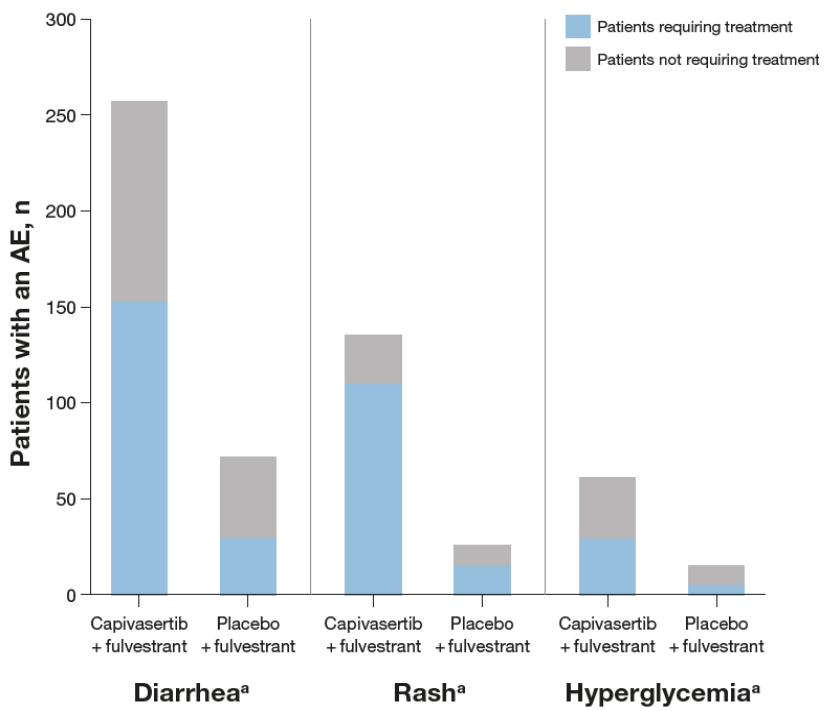
PFS2 defined as the time from randomisation to second progression (i.e. the earliest of either death or a progression event following treatment start after first progression).
HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region.

Rugo et al, ESMO Breast 2024

Courtesy of Hope S Rugo, MD

CAPItello-291: Safety Analysis

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[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
Rash[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
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[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
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



AEs leading to:

- Discontinuation capi/pla: 9.3 vs 0.6%
- Interruption capi/pla: 34.9 vs 10.3%
- Dose reduction capi/pla: 19.7 vs 1.7%

Median time to onset, Days

- Diarrhea: 8 (2-22)
- Rash: 12 (10-15)
- Hyperglycemia: 15 (1-51)

AEs leading to discontinuation

- Diarrhea: 2%
- Rash 4.5%
- Hyperglycemia: 0.3%

Rugo et al, ASCO 2023; ESMO Open 2024

Courtesy of Hope S Rugo, MD

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Invasive Breast Cancer

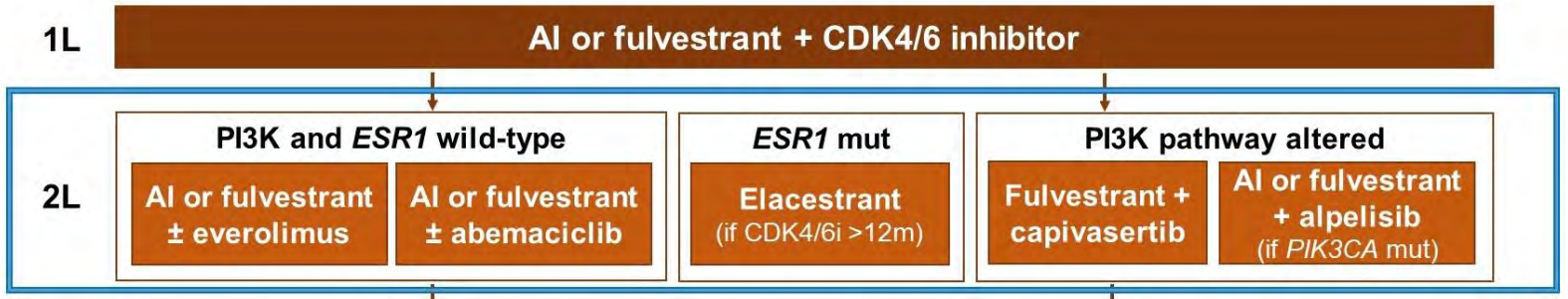
NCCN Guidelines Index
Table of Contents
Discussion

TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
HR-positive/ HER2-negative[w]	*PIK3CA* activating mutation	NGS, PCR (Blood or tumor tissue if blood negative)	Alpelisib + fulvestrant[x]	Category 1	Preferred second- or subsequent-line therapy
HR-positive/ HER2-negative[y]	*PIK3CA or AKT1* activating mutations or *PTEN* alterations	NGS, (Blood or tumor tissue if blood negative)	Capivasertib + fulvestrant[y]	Category 1	Preferred second- or subsequent-line therapy in select patients[y]
HR-positive/ HER2-negative[z]	*ESR1* mutation	NGS, PCR (Tumor tissue or blood)	Elacestrant[z]	Category 2A	Other recommended regimen
Any	Germline *BRCA1* or *BRCA2* mutation	Germline sequencing	Olaparib Talazoparib	Category 1	Preferred
Any	*NTRK* fusion	FISH, NGS, PCR (Tumor tissue or blood)	Larotrectinib[aa] Entrectinib[aa]	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, NGS, PCR, (Tumor tissue)	Pembrolizumab[bb,cc] Dostarlimab-gxly[dd]	Category 2A	
Any	TMB-H (≥10 mut/Mb)	NGS (Tumor tissue or blood)	Pembrolizumab[bb,cc]	Category 2A	
Any	*RET*-fusion	NGS (Tumor tissue or blood)	Selpercatinib[ee]	Category 2A	

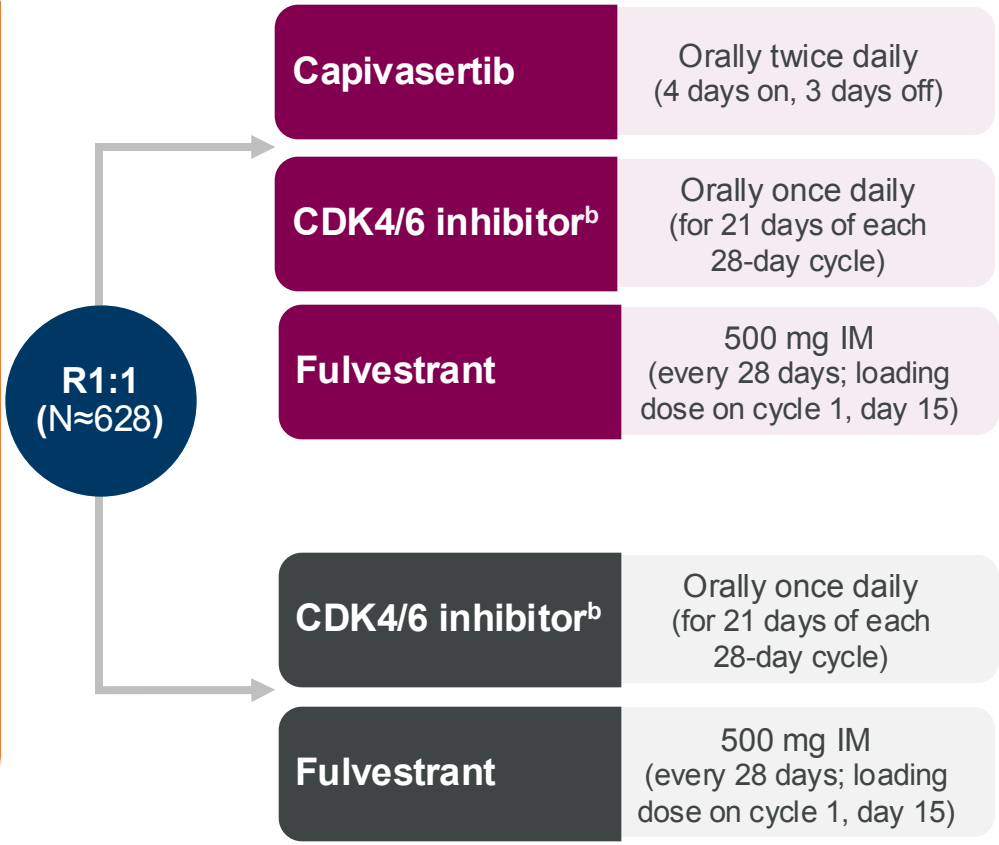
Treatment Algorithm for HR+/HER2- MBC



Courtesy Ana Garrido-Castro

Phase 3 CAPItello-292 (NCT04862663) Study Overview

- Adults ≥18 years of age with metastatic or locally ABC
- Histologically confirmed HR-positive/HER2-negative
- Disease relapse while on, or within 12 months of the end of (neo)adjuvant endocrine therapy[a]
- No prior endocrine therapy for ABC
- No prior CDK4/6 inhibitor for ABC
- No more than one line of chemotherapy for ABC
- No prior or concurrent treatment with systemic AKT, PI3K, and/or mTOR inhibitors



Primary

- **PFS** by BICR

Secondary

- **OS**
- **PFS** in patients with *PIK3CA*, *AKT1*, and/or *PTEN* alterations in their tumors
- **PFS2**, **ORR**, **DoR**, **CBR** at 24 weeks
- **HRQoL**

Safety and tolerability

The inclusion of ribociclib as an investigator's choice of CDK4/6 inhibitor in Phase 3 will be initiated after the combination RP3D has been established in Phase 1b.

Clinical Study Protocol version 5.0

[a]Prior treatment with a (neo)adjuvant endocrine therapy (ET; single agent or in combination) and radiologic evidence of breast cancer recurrence or progression while on, or within 12 months of the end of, (neo)adjuvant ET (tamoxifen, AI, or oral SERD); [b]Investigator's choice of CDK4/6 inhibitor: palbociclib or ribociclib.

HER2-negative is defined as IHC 0, or 1+ or IHC2+/ISH–; ABC, advanced breast cancer; BICR, blinded independent central review; HRQoL, health-related quality of life; RP3D, recommended Phase 3 dose

Courtesy of Hope S Rugo, MD

Rugo et al, SABCS 2023 TIP: PO2-19-10

Agenda

Introduction: PI3K/AKT/PTEN Pathway and Resistance to Endocrine Therapy

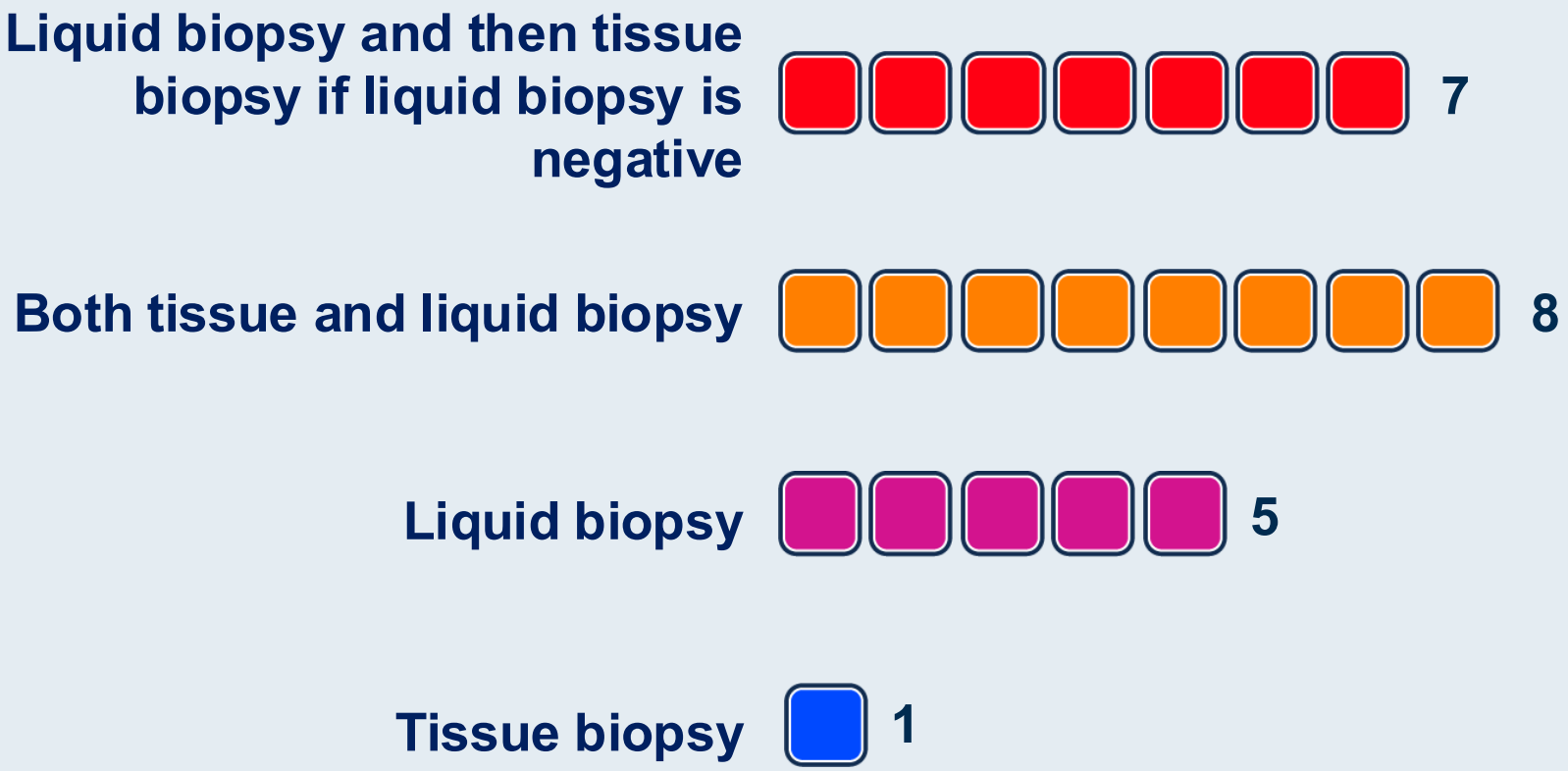
Module 1: First-Line Therapy for HR-Positive Metastatic Breast Cancer (mBC) Harboring PI3K/AKT/PTEN Mutations

Module 2: Treatment Options for Recurrent mBC with PI3K/AKT/PTEN Mutations

Module 3: Beyond the Guidelines Survey

Module 4: Faculty Case Presentations

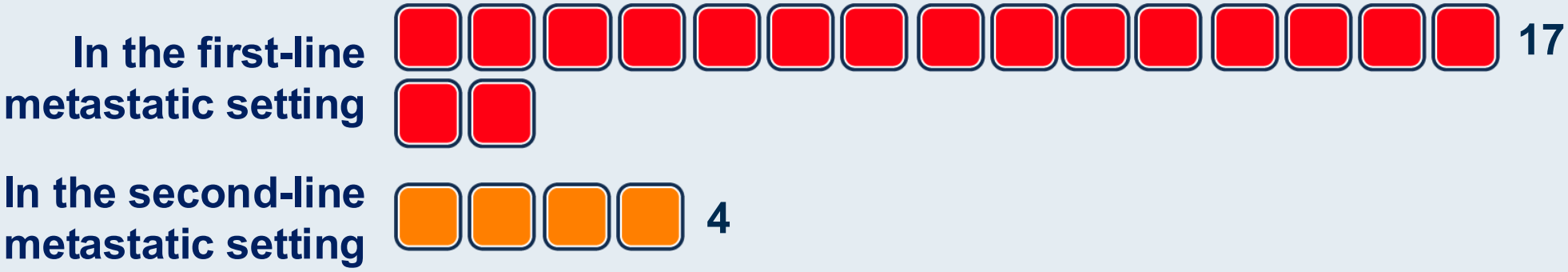
Which method for PI3K/AKT/PTEN mutation testing do you usually use for patients with hormone receptor (HR)-positive metastatic breast cancer (mBC)?



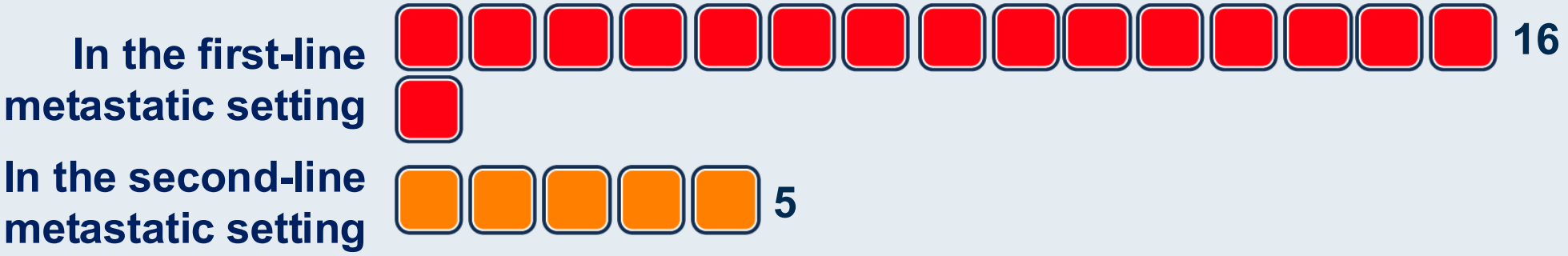
Survey of 21 US-based breast cancer clinical investigators, October 2024

At what point in a patient's treatment course do you usually first assess the mutation status of …?

PIK3CA



AKT/PTEN

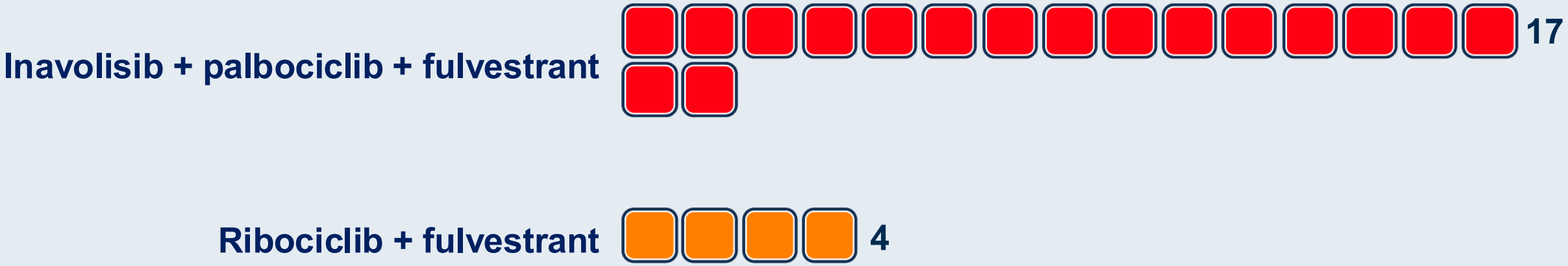


Survey of 21 US-based breast cancer clinical investigators, October 2024

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-positive, HER2-negative (HER2 IHC 0), node-negative breast cancer has developed multiple metastases 9 months after starting adjuvant anastrozole.

ESR1 mutation-negative | **PIK3CA mutation-positive** | **AKT1 and PTEN mutation-negative**



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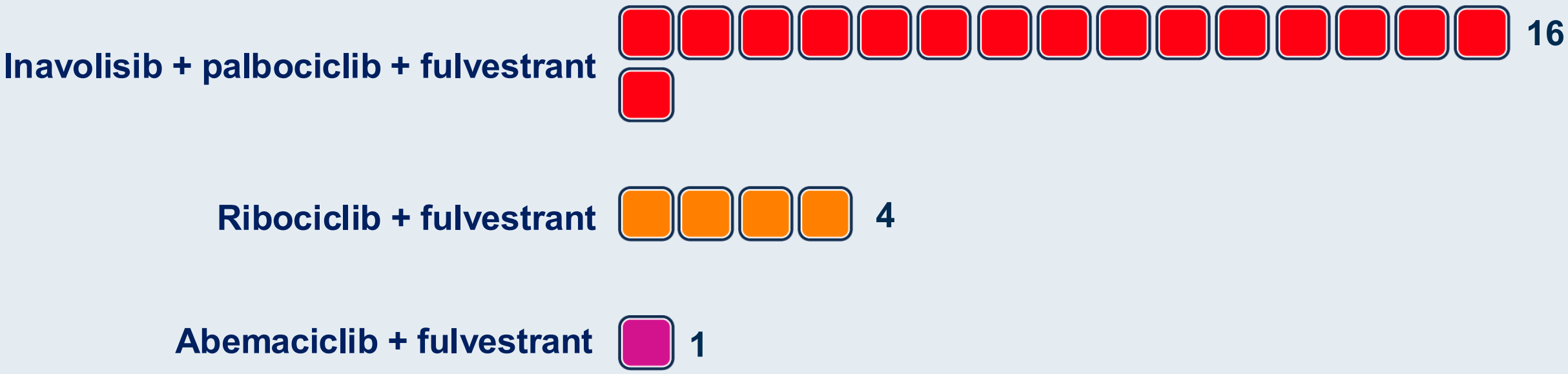
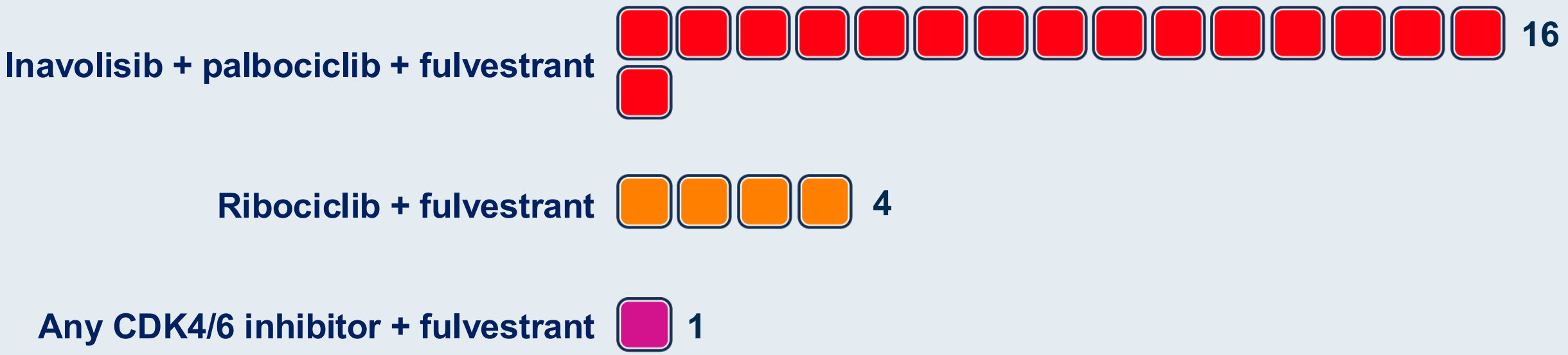


Survey of 21 US-based breast cancer clinical investigators, October 2024

A 65-year-old woman with ER-positive, HER2-negative (HER2 IHC 0), node-negative breast cancer has developed multiple metastases 2 years after starting adjuvant anastrozole.

ESR1 mutation-negative | **PIK3CA mutation-positive** | **AKT and PTEN mutation-negative**



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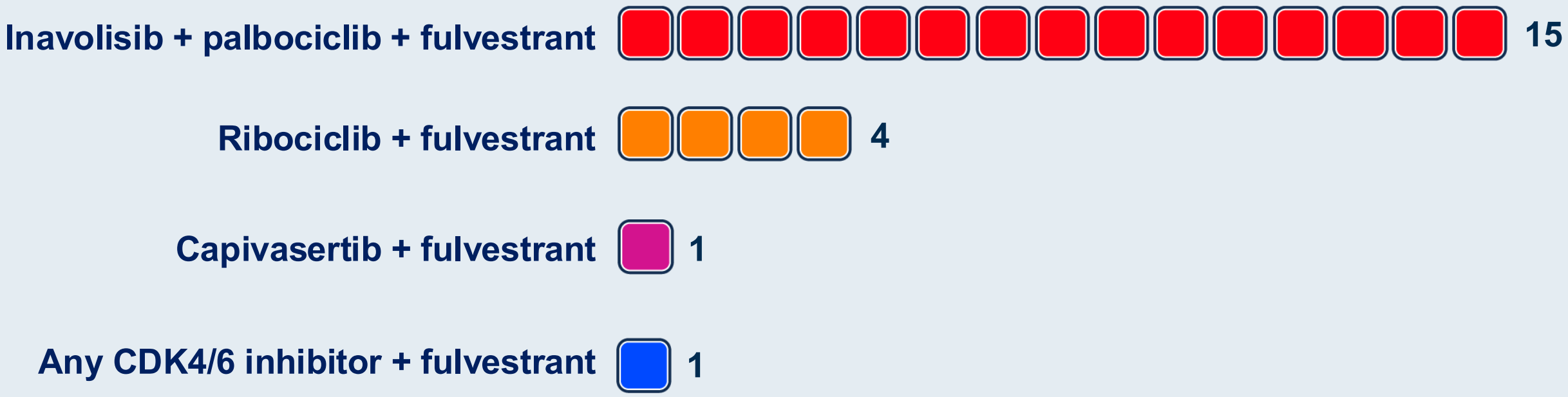
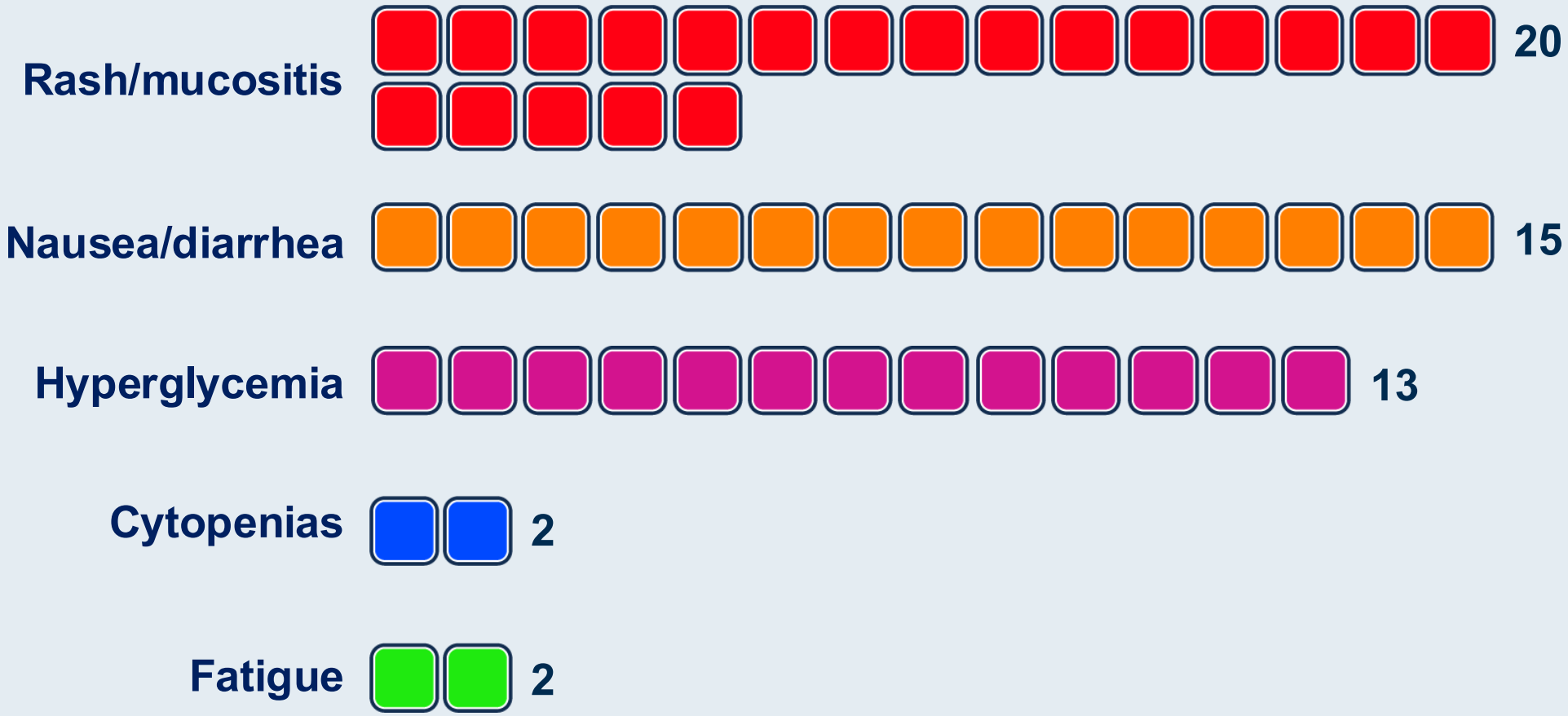


Survey of 21 US-based breast cancer clinical investigators, October 2024

RTP RESEARCH TO PRACTICE

Based on your clinical experience and knowledge of available data, what are the top 3 side effects patients experience when receiving inavolisib?

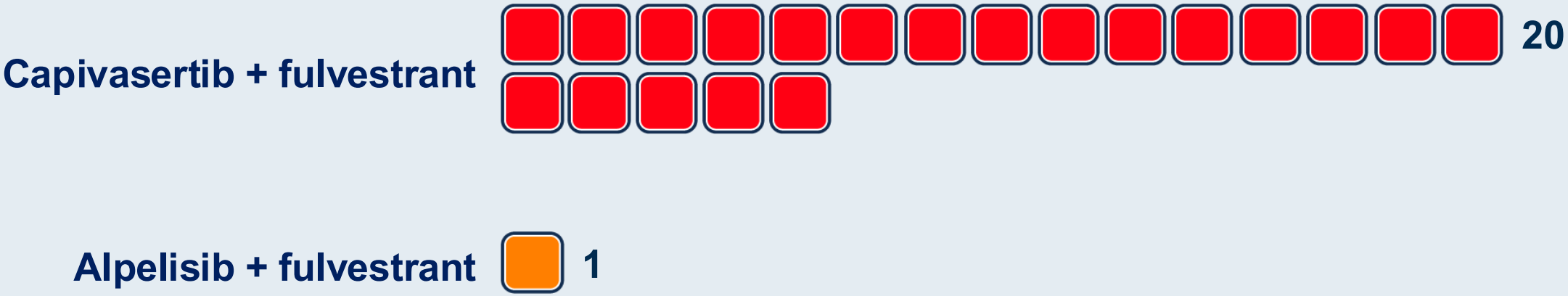


Survey of 21 US-based breast cancer clinical investigators, October 2024

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-positive, HER2-negative (HER2 IHC 0), node-negative mBC receives a CDK4/6 inhibitor with an AI and initially responds but then experiences disease progression 18 months later.

ESR1 mutation-negative | **PIK3CA mutation-positive** | **AKT1 and PTEN mutation-negative**



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ESR1 mutation-negative | **PIK3CA mutation-negative** | **AKT1 or PTEN mutation-positive**

Capivasertib + fulvestrant

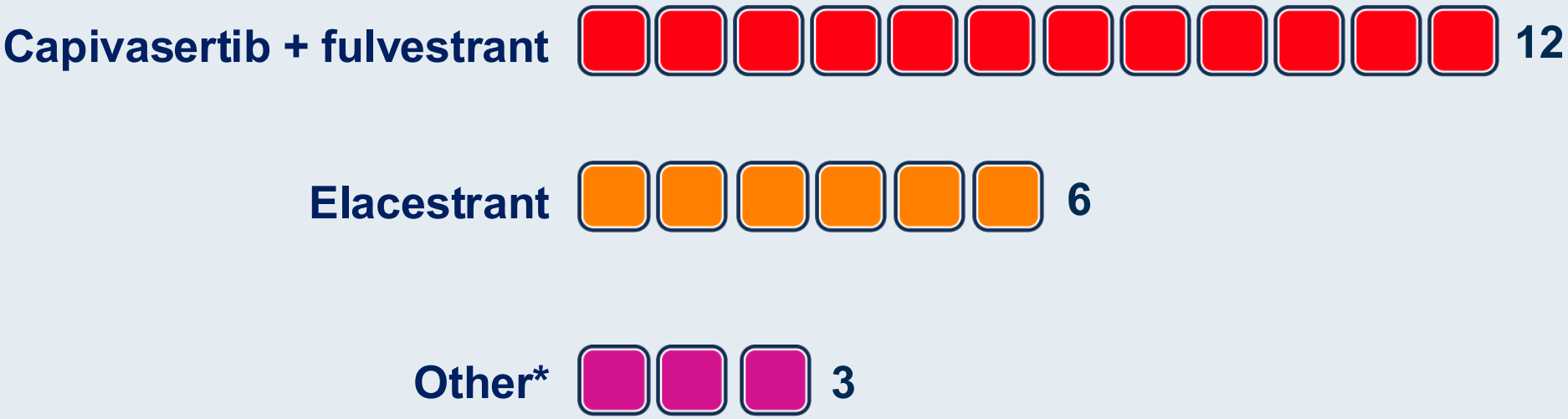
21

Survey of 21 US-based breast cancer clinical investigators, October 2024

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-positive, HER2-negative (HER2 IHC 0), node-negative mBC receives a CDK4/6 inhibitor with an AI and initially responds but then experiences disease progression 18 months later.

ESR1 mutation-positive | **PIK3CA mutation-positive** | **AKT1 and PTEN mutation-negative**

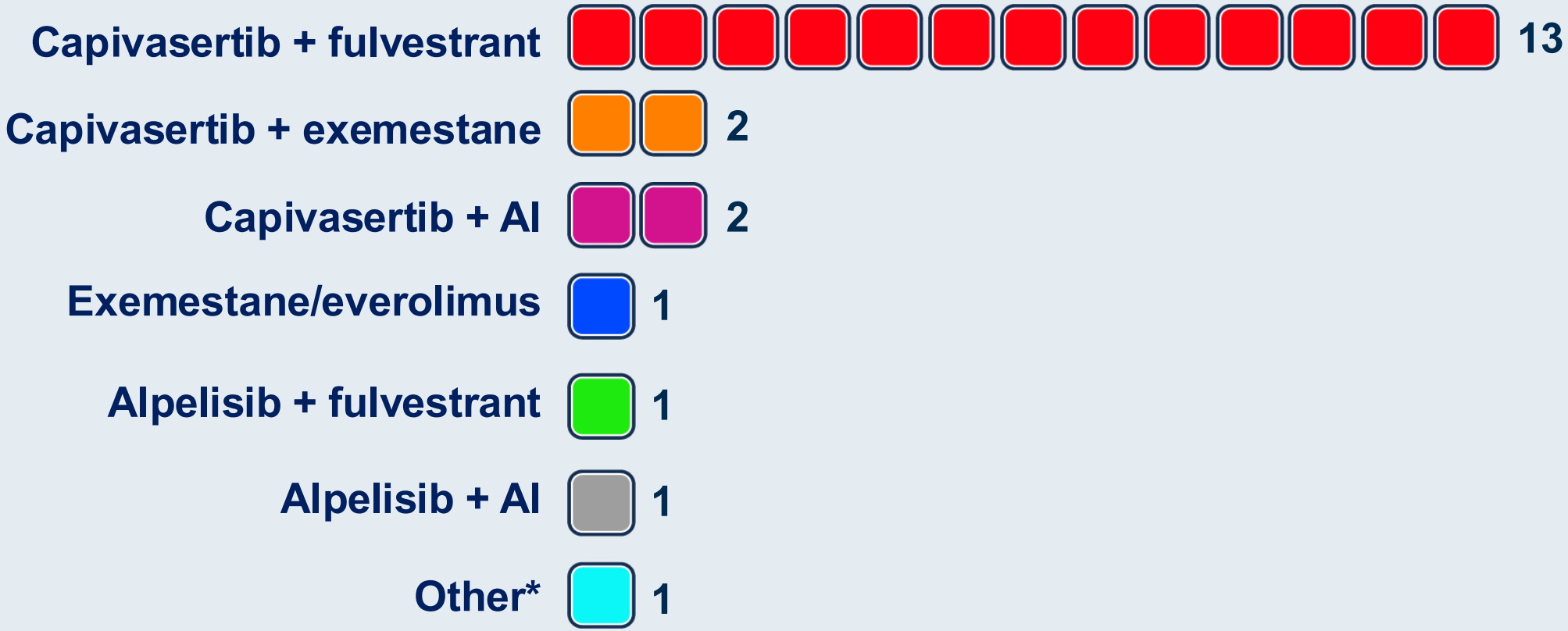


* Depends on extent of progression: Elacestrant if progression is less aggressive/asymptomatic, capivasertib + fulvestrant or combined with ET if progression is more aggressive/asymptomatic

Survey of 21 US-based breast cancer clinical investigators, October 2024

A 65-year-old woman with ER-positive, HER2-negative (HER2 IHC 0), node-negative mBC receives a CDK4/6 inhibitor with fulvestrant and initially responds but then experiences disease progression 18 months later.

ESR1 mutation-negative | **PIK3CA mutation-positive** | **AKT1 and PTEN mutation-negative**



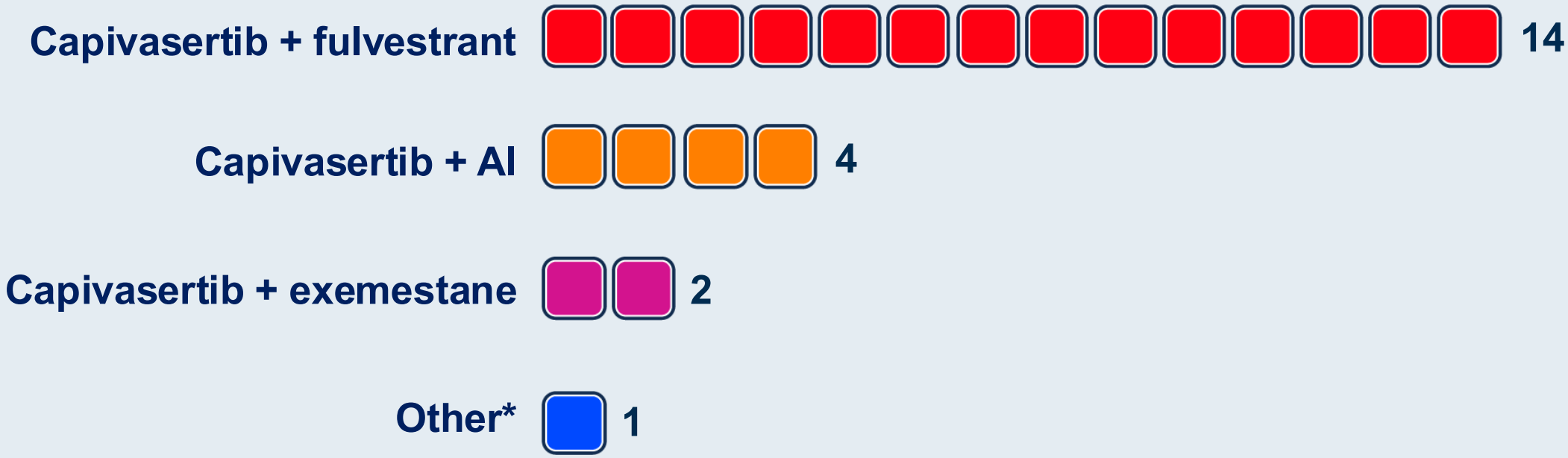
* Capivasertib + fulvestrant or capecitabine/paclitaxel, based on tumor burden

Survey of 21 US-based breast cancer clinical investigators, October 2024

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-positive, HER2-negative (HER2 IHC 0), node-negative mBC receives a CDK4/6 inhibitor with fulvestrant and initially responds but then experiences disease progression 18 months later.

ESR1 mutation-negative | **PIK3CA mutation-negative** | **AKT1 or PTEN mutation-positive**



* Capivasertib + fulvestrant or capecitabine/paclitaxel, based on tumor burden

Survey of 21 US-based breast cancer clinical investigators, October 2024

A 65-year-old woman with ER-positive, HER2-negative (HER2 IHC 0), node-negative mBC receives a CDK4/6 inhibitor with fulvestrant and initially responds but then experiences disease progression 18 months later.

ESR1 mutation-positive | **PIK3CA mutation-positive** | **AKT1 and PTEN mutation-negative**

* Chemotherapy based on tumor burden or fulvestrant + capivasertib

Survey of 21 US-based breast cancer clinical investigators, October 2024

RTP RESEARCH TO PRACTICE

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Case Presentation – Dr Jhaveri: 59-Year-Old Woman with ER-Positive, HER2-Negative mBC with a PI3K Mutation Experiences Disease Progression on Adjuvant Endocrine Therapy

59-year-old postmenopausal female with stage III breast cancer, Invasive ductal s/p mastectomy on the right that revealed a 3.8 cm grade 3 tumor with 4/13 LN, ER+ PR+ HER2 IHC 1+ s/p adjuvant ACT and radiation on letrozole X 3 years, now with back pain

Staging showed liver and bone metastases

Liver biopsy confirmed MBC ER+ PR+ HER2 IHC 0

Tissue NGS: PIK31047R mutation, no other alterations

Genetics: negative

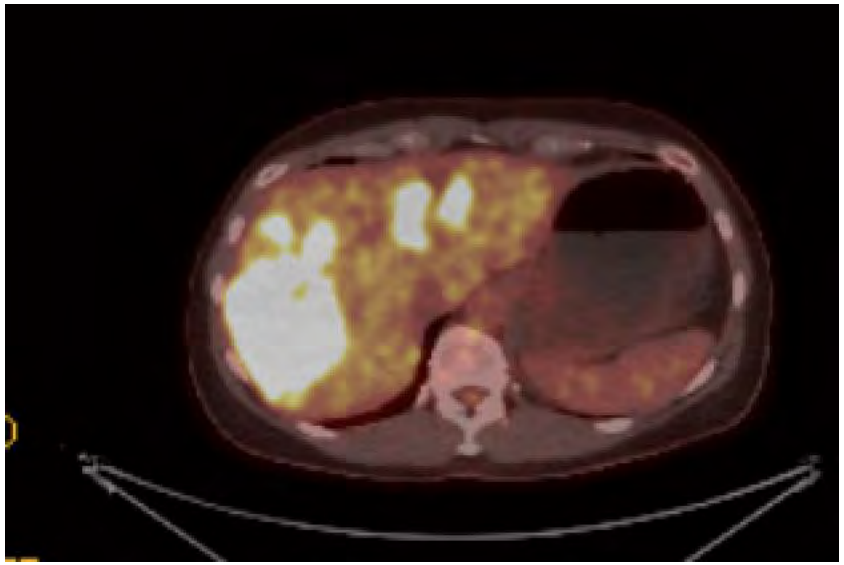
Currently receiving: Inavolisib plus palbo plus fulvestrant - on trial

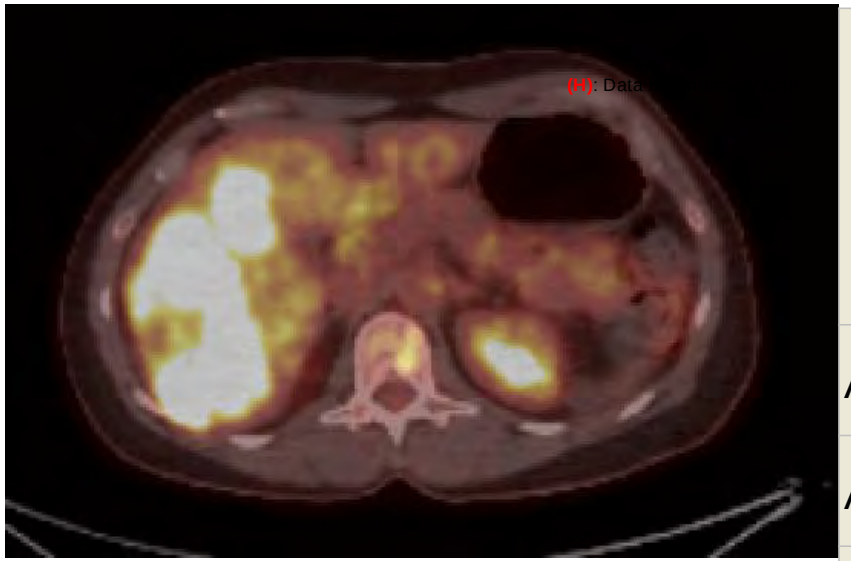
Case Presentation – Dr Rugo: 54-Year-Old Woman with Metastatic Progression of ER-Positive, HER2-Negative Breast Cancer 10 Months After Stopping Tamoxifen (PIK3CA and AKT1 Mutations)

- 50 yo premenopausal woman
  - 2019
    - 6 mm invasive mucinous carcinoma of the right breast, 0/2 axillary nodes
    - ER/PR strongly positive, HER2 IHC 0, Ki67 10-20%
    - Treatment
      - Radiation therapy
      - Tamoxifen until 2022, then stopped due to feeling she had had enough treatment for her small tumor
  - 2023 (10 months after stopping tamoxifen, now 54)
    - Abdominal pain led to US showing multiple liver lesions
  - PET/CT: Widespread metastatic malignancy including lung, liver and bone. Largest liver mass is 5 cm, largest lung nodule 1 cm, lytic bone lesions
    - 3/24/2023 Liver Bx: Grade 2 adenocarcinoma consistent with breast primary. ER+ (95%), PR- (0%), HER2- (0 IHC). Ki-67 35%.
    - ctDNA: PIK3CA E454K mutation, FGFR1 amplification, AKT1 E17K mutation, and multiple others

Case Presentation – Dr Rugo: 54-Year-Old Woman with Metastatic Progression of ER-Positive, HER2-Negative Breast Cancer 10 Months After Stopping Tamoxifen (PIK3CA and AKT1 Mutations) (Continued)

What would you do?





- No respiratory symptoms or bone pain
- Abdominal pain resolved

	Latest Reference Range & Units	03/29/23 15:42
ALT 10 - 61 U/L	**72 (H)**	
AST 5 - 44 U/L	**60 (H)**	
Alkaline Phosphatase 38 - 108 U/L	**139 (H)**	
Bilirubin, Total 0.2 - 1.2 mg/dL	0.4	

Case Presentation – Dr Rugo: 54-Year-Old Woman with Metastatic Progression of ER-Positive, HER2-Negative Breast Cancer 10 Months After Stopping Tamoxifen (PIK3CA and AKT1 Mutations) (Continued)

- She started on letrozole and palbociclib (insurance required)
  - Excellent response and rapid normalization of liver enzymes
  - Progression of disease after 8 months, modest increase in liver lesions
    - Largest lesion 9.8 cm, partially calcified
- 1/2024: Started on a clinical trial (TACTIVE-U) with ARV-471 (vepdegestrant) and ribociclib
  - As of 9/12/24, stable to minimally decreased lung and liver lesions, no new bone lesions
  - Tolerating therapy well

Case Presentation – Dr Jhaveri: 51-Year-Old Woman with ER-Positive, HER2-Negative Recurrent mBC with a PIK3CA Mutation

51-year-old patient, 7 years ago was diagnosed with stage 2 IDC ER/PR+ and HER2 IHC 2+ FISH negative. S/p lumpectomy and SLN that revealed a 2.6 cm grade 2 focus, node negative, Onco*type* DX® 20, S/P TC and leuprolide + letrozole X 3 years followed by tamoxifen X 2 years. 2 years after stopping endocrine therapy (at age 48) was diagnosed with metastatic disease to the bones, biopsy proven ER+ PR+ HER2 1+, on ribociclib + leuprolide + exemestane, s/p BSO, progressed in bones and liver on exemestane plus ribociclib after 26 months. Plasma NGS revealed a PIK3CA E545K mutation, no other alterations, genetics negative

Currently receiving: Capi plus fulvestrant SOC

Case Presentation – Dr Rugo: A Woman with ER-Positive, HER2-Negative Recurrent mBC with a PIK3CA Mutation

- 1999: 44 yo woman presented with a right breast mass and enlarged right axillary node
  - Biopsy of right breast mass and axillary node: Adenocarcinoma, ER+ 50%, PR+ 5%, HER2 FISH not amplified
  - Neoadjuvant chemotherapy with AC x 4
  - Right mastectomy, AXLND: 0.6 cm grade 2 IDC, 3/22 nodes +
  - Adjuvant treatment
    - Paclitaxel x 4
    - RT to CW and nodes
    - 1/2000 - 11/2004: tamoxifen
    - 11/2004 - 1/2010: letrozole and leuprolide
- 2016: worsening back pain playing tennis, shortness of breath after hot tub use
  - MRI L-spine: 5 cm lytic sacral lesion
  - PET/CT: Multiple FDG avid bone lesions in pelvis, sacrum, acetabulum, sternum with LUL consolidation with mediastinal adenopathy
    - Sacral biopsy: adenocarcinoma c/w breast origin, ER 95-100%, PR 20%, HER2 negative
    - Antibiotics: clearance of pulmonary findings and symptoms

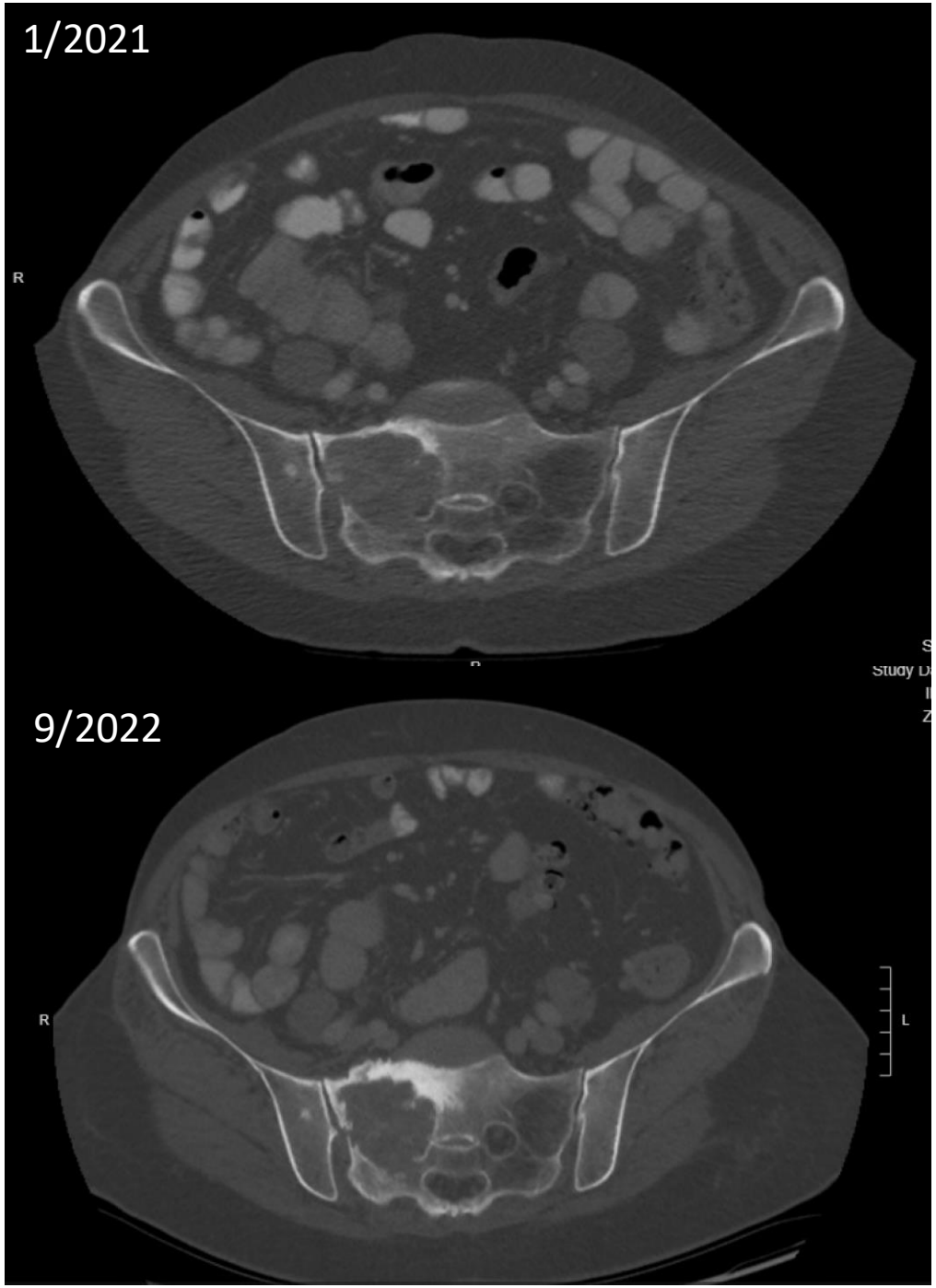
Case Presentation – Dr Rugo: A Woman with ER-Positive, HER2-Negative Recurrent mBC with a PIK3CA Mutation (Continued)

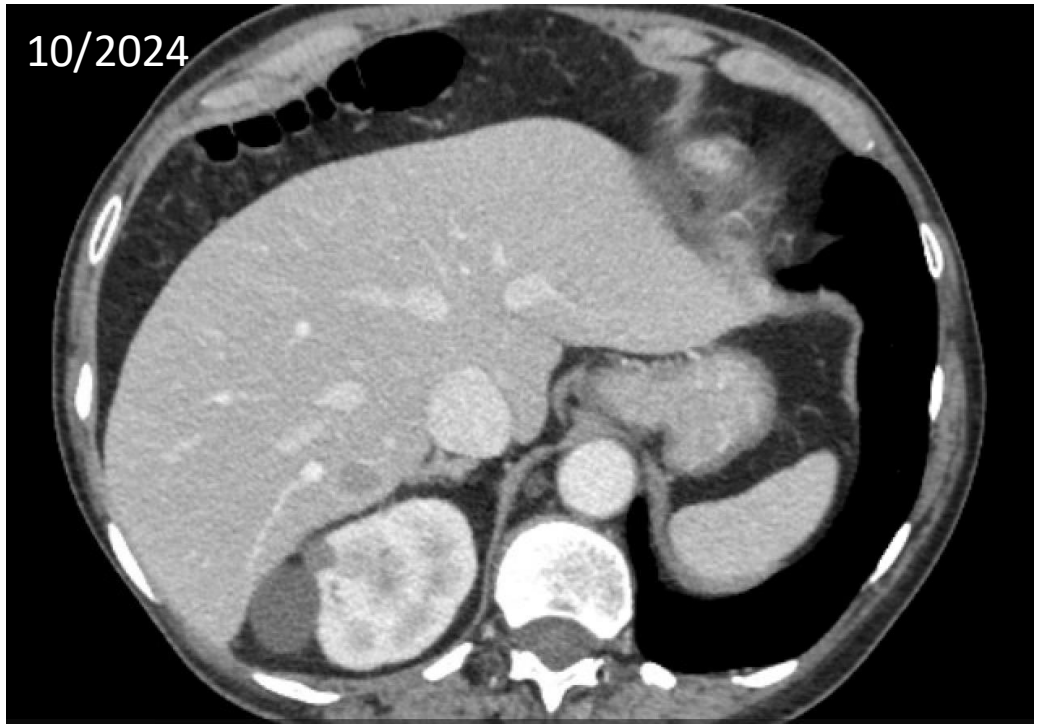
- Treatment
  - 2016 – 2021 letrozole and palbociclib, denosumab
  - Due to risk of fracture, SBRT to right superior pelvic ramus and right sacrum
- 11/19/20 MRI pelvis: increase in size of right sacral ala mass up to 5.0 cm. Invasion with obliteration of the right S1-S3 neural foramen. 4.5 cm mass in the right superior pubic ramus with extension into the right anterior acetabulum, 3.1 cm mass in the left posterior acetabulum unchanged.
  - Biopsy left sacral ala: metastatic carcinoma, ER 95%, PR negative, HER2 1+ negative
  - Guardant360®: PIK3CA H1047R mutation
- 1/2021 CT scan: increasing soft tissue around sacral lesion
  - Increased pain
- What would you do?

Case Presentation – Dr Rugo: A Woman with ER-Positive, HER2-Negative Recurrent mBC with a PIK3CA Mutation (Continued)

- What happened?
- Treatment
  - 2/10/21 fulvestrant and capivasertib on a clinical trial
    - Intermittent diarrhea, grade 1
    - Scattered rash in the first two months resolved over time
    - Mild fatigue
- 10/7/2024
  - New 1.4 cm liver lesion
  - No significant change in bone lesions

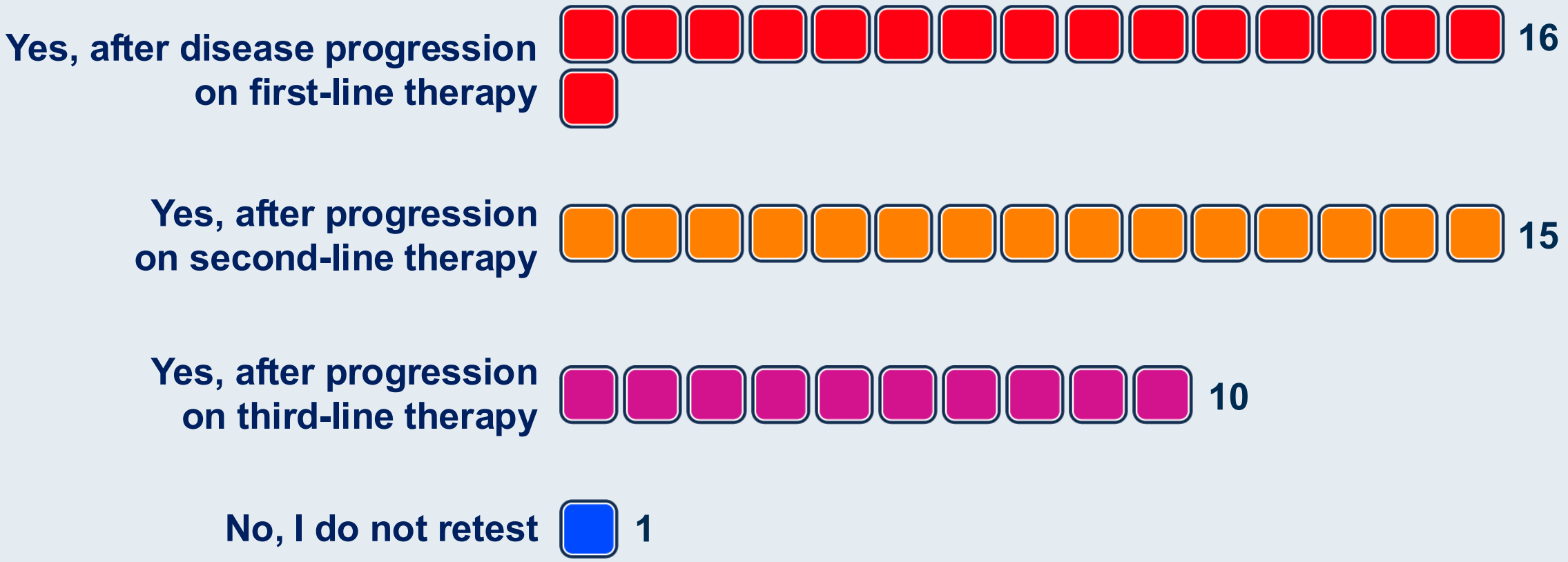
Case Presentation – Dr Rugo: A Woman with ER-Positive, HER2-Negative Recurrent mBC with a PIK3CA Mutation (Continued)





APPENDIX

Do you retest for PI3K/AKT/PTEN pathway alterations along with other genetic alterations at multiple points in a patient's treatment course?

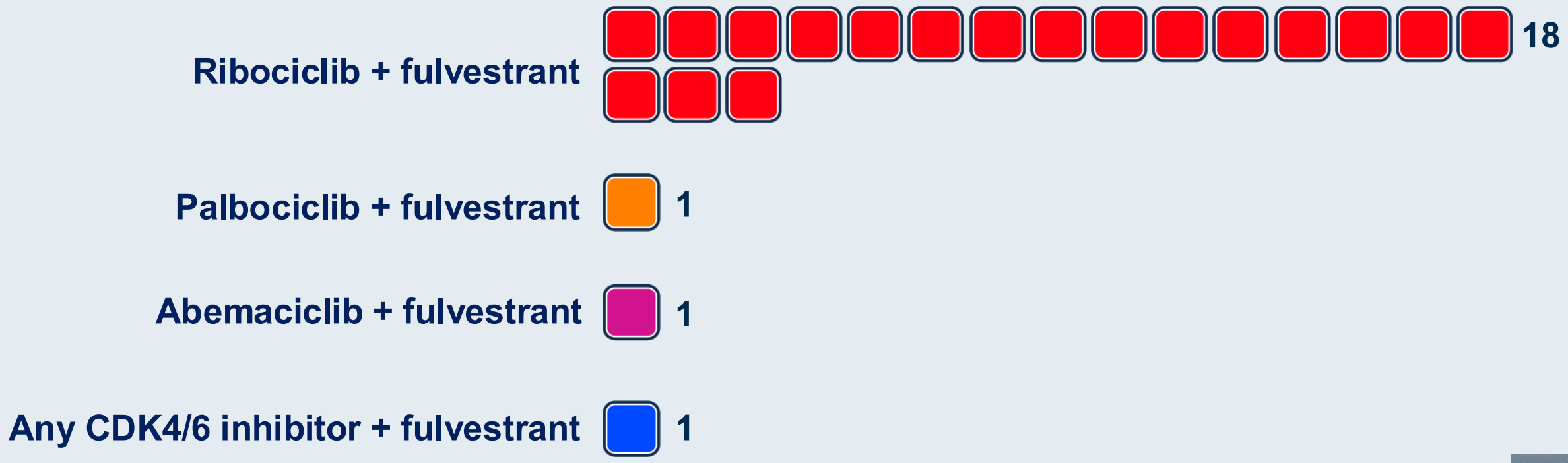


Survey of 21 US-based breast cancer clinical investigators, October 2024

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-positive, HER2-negative (HER2 IHC 0), node-negative breast cancer has developed multiple metastases 9 months after starting adjuvant anastrozole.

ESR1 mutation-negative	PIK3CA mutation-negative	AKT1 and PTEN mutation-negative



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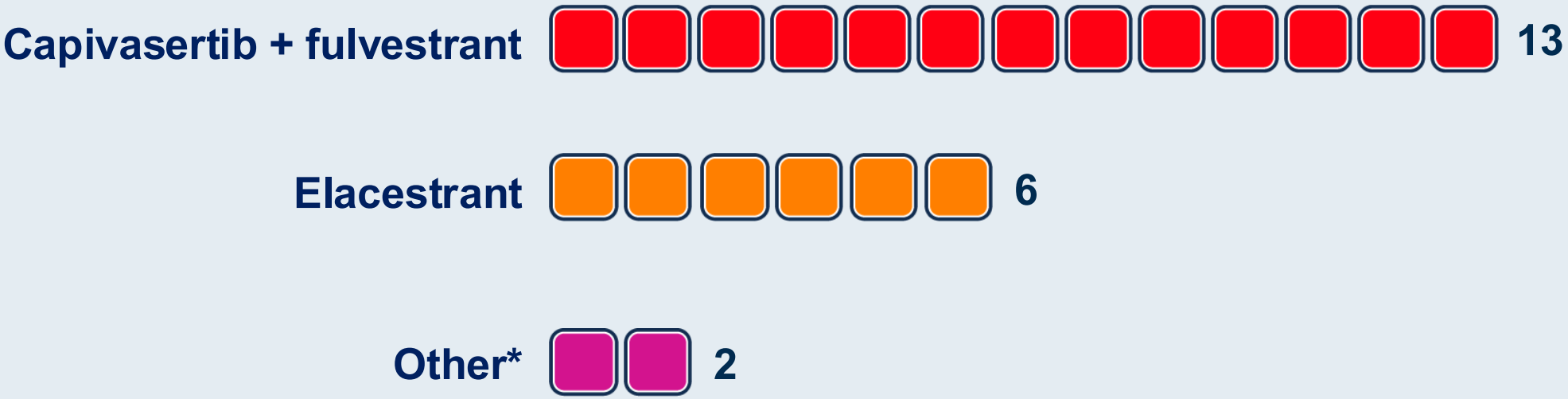
A 65-year-old woman with ER-positive, HER2-negative (HER2 IHC 0), node-negative mBC receives a CDK4/6 inhibitor with an AI and initially responds but then experiences disease progression 18 months later.

ESR1 mutation-positive | **PIK3CA mutation-negative** | **AKT1 or PTEN mutation-positive**



* Elacestrant if asymptomatic and little progression, capivasertib + endocrine therapy if symptomatic and/or greater disease burden; elacestrant for ER-sensitive disease, capivasertib + fulvestrant for more aggresive disease

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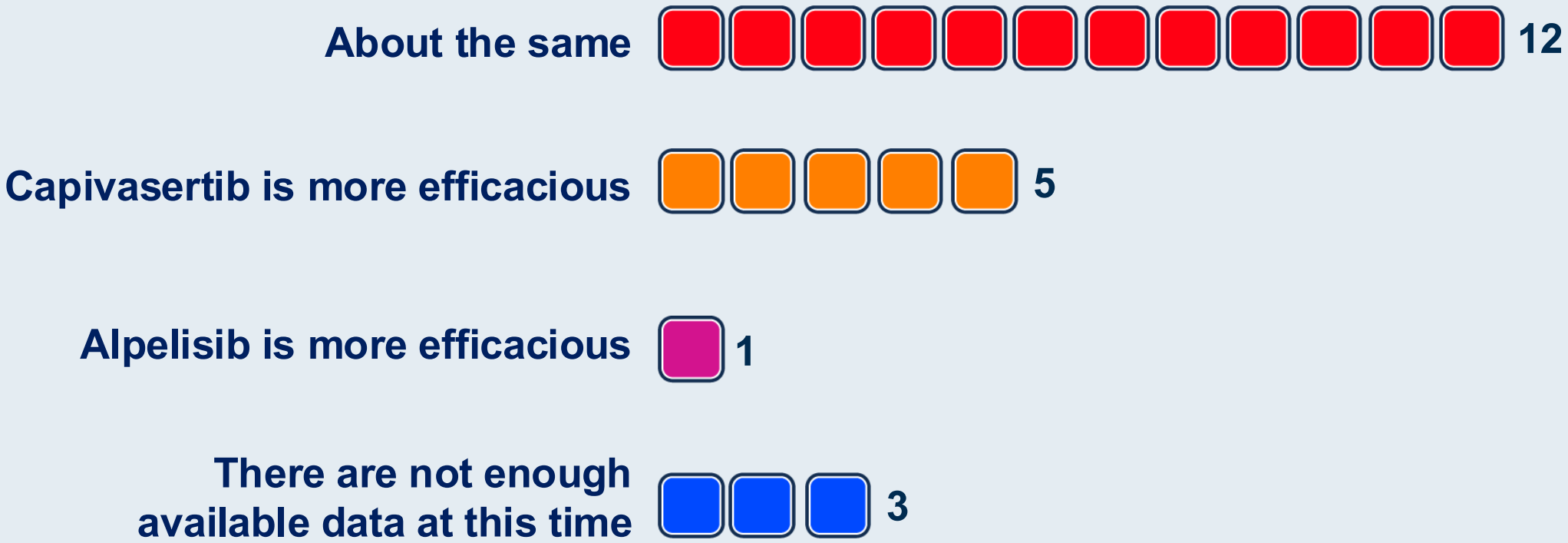
Based on current clinical trial data and/or your personal experience, how would you indirectly compare the global efficacy of capivasertib to that of alpelisib for HR-positive, HER2-negative (HER2 IHC 0) mBC with a PIK3CA mutation?



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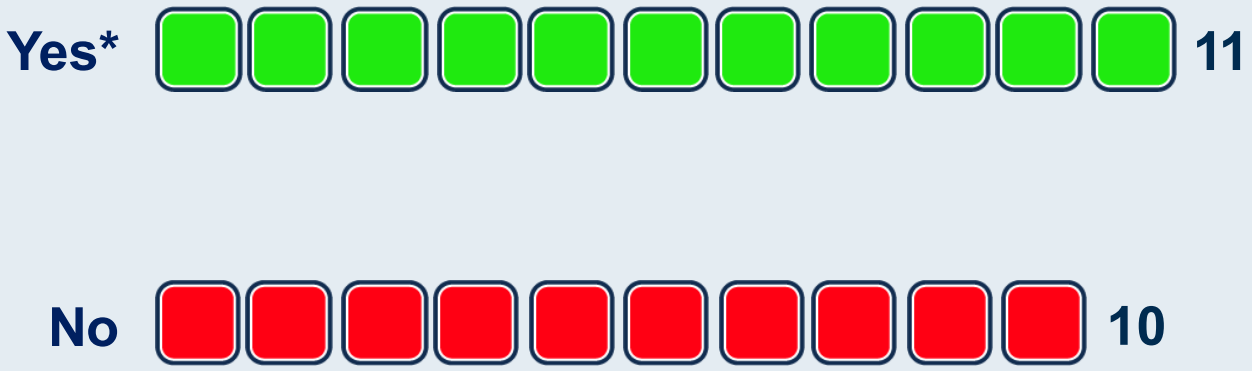
For patients about to receive capivasertib, do you take any prophylactic measures to prevent cutaneous reactions?



* Antihistamines

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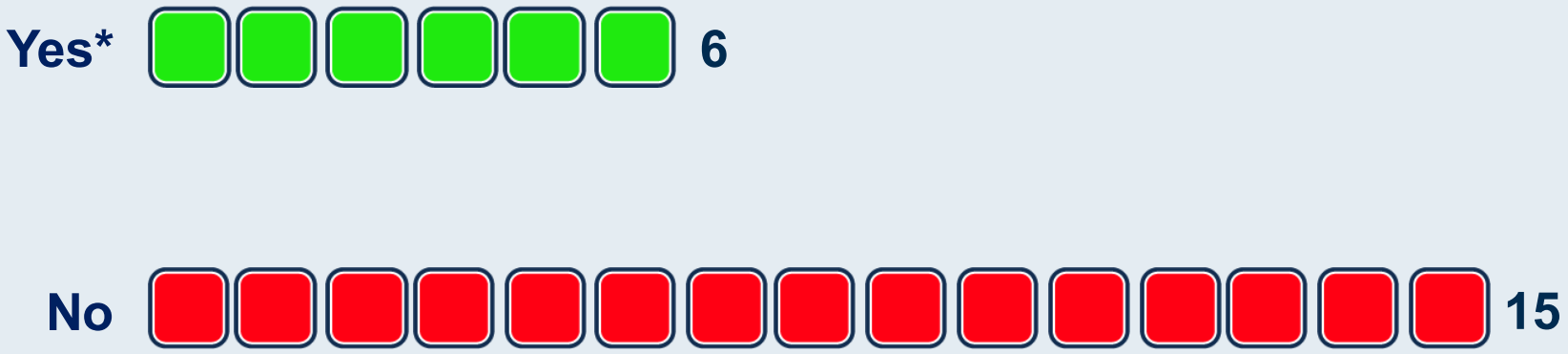
For patients about to receive capivasertib, do you take any prophylactic measures to prevent gastrointestinal toxicity?



* Loperamide/antidiarrheal agents

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Meet The Professor

Optimizing the Management of Chronic Lymphocytic Leukemia

Tuesday, November 5, 2024
5:00 PM – 6:00 PM ET

Faculty

Nicole Lamanna, MD

Moderator

Neil Love, MD

RTP
RESEARCH TO PRACTICE

Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open for 5 minutes after the meeting ends.

Information on how to obtain CME, ABIM MOC and ABS credit is provided in the Zoom chat room. Attendees will also receive an email in 1 to 3 business days with these instructions.