

# Individualizing the Selection of First-Line Therapy for Patients with Hormone Receptor-Positive Metastatic Breast Cancer

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Celebrating Women Chair in Breast Cancer Research

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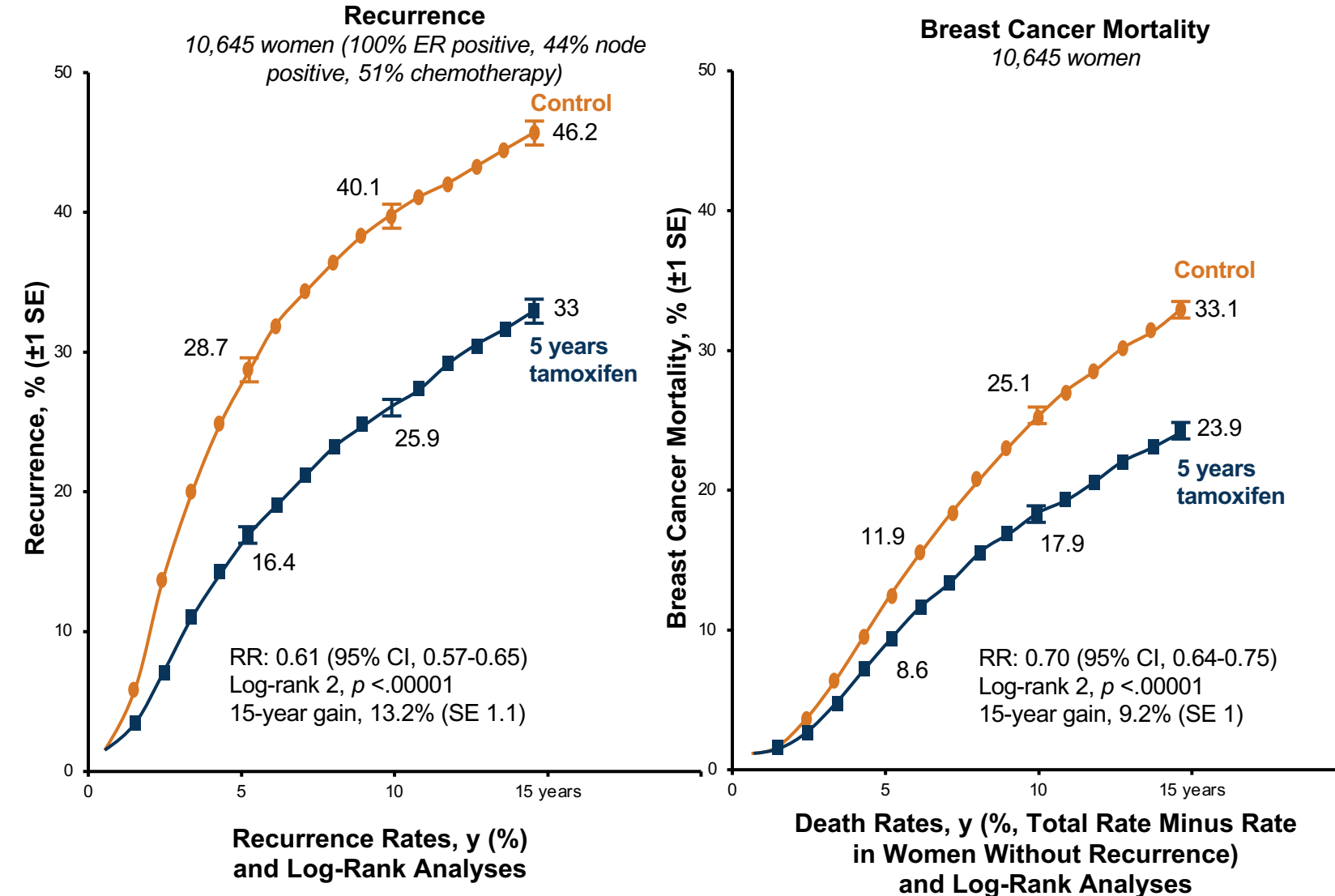
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Dallas TX

# High-Risk HR+/HER2- Early Breast Cancer

- Endocrine therapy resistance is a key feature of high-risk HR+/HER2- EBC that recurs within 5 yrs of diagnosis
- Tumor size, nodal status, and grade impact recurrence risk and improve prognostic accuracy of gene expression signatures
- Higher proliferation and lower ER levels increase risk of recurrence
- Luminal B, HER2 enriched, and basal like are high-risk HR+/HER2- EBCs
- Failure of preoperative ET to suppress Ki-67 predicts poor outcome with adjuvant ET
- Genomic instability and clonal heterogeneity in high-risk HR+/HER2- EBC lead to therapeutic resistance, virulence and metastagenicity

# Despite the Benefits of Adjuvant Chemo- and Endocrine Therapy, Risk of Recurrence Is Still High<sup>1</sup>

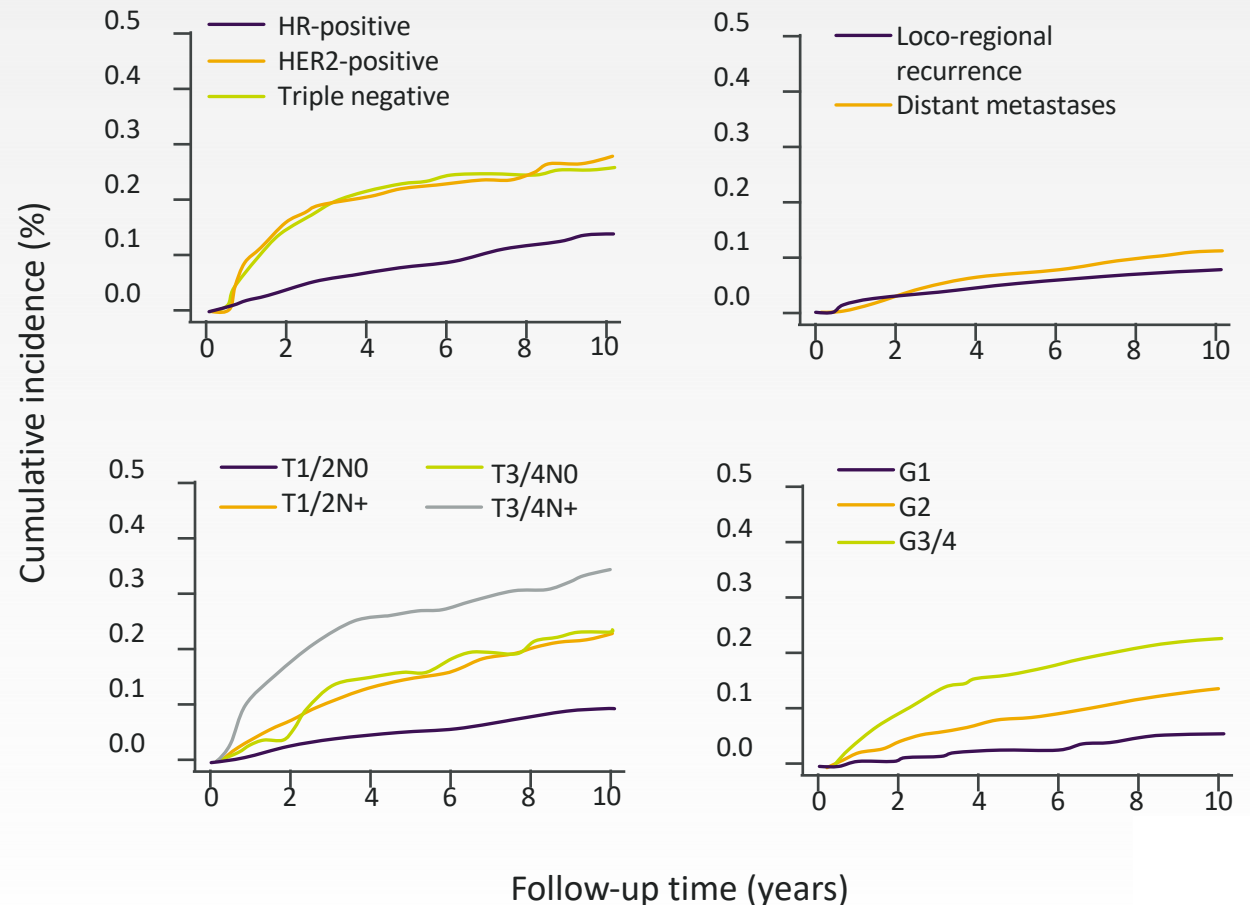


1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet. 2011 Aug 27;378(9793):771-84.

# Many early breast cancer patients experience recurrence, with some groups at higher risk<sup>1,2</sup>

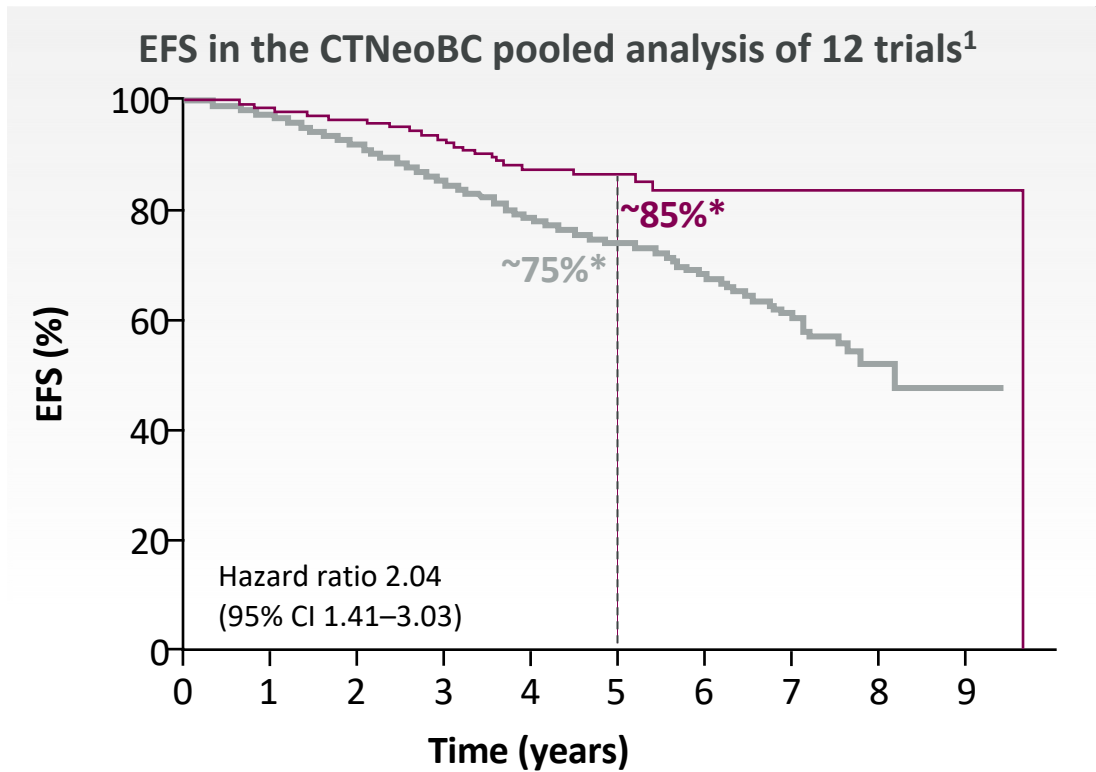
- Up to 30% of early breast cancer patients with high-risk clinical and/or pathologic features may experience distant recurrence within a few years of treatment.<sup>1</sup>
- A number of factors increase the risk of recurrence, including higher tumor/nodal stage, higher tumor grade, and certain histological subtypes.<sup>2</sup>

## 10-year cumulative incidence of cancer recurrence in primary invasive breast cancer<sup>2</sup>



# Failure to achieve a pCR after neoadjuvant chemotherapy increases a patient's risk of recurrence<sup>1,2</sup>

## Outcomes in HR-positive HER2-negative patients according to pCR status after NACT

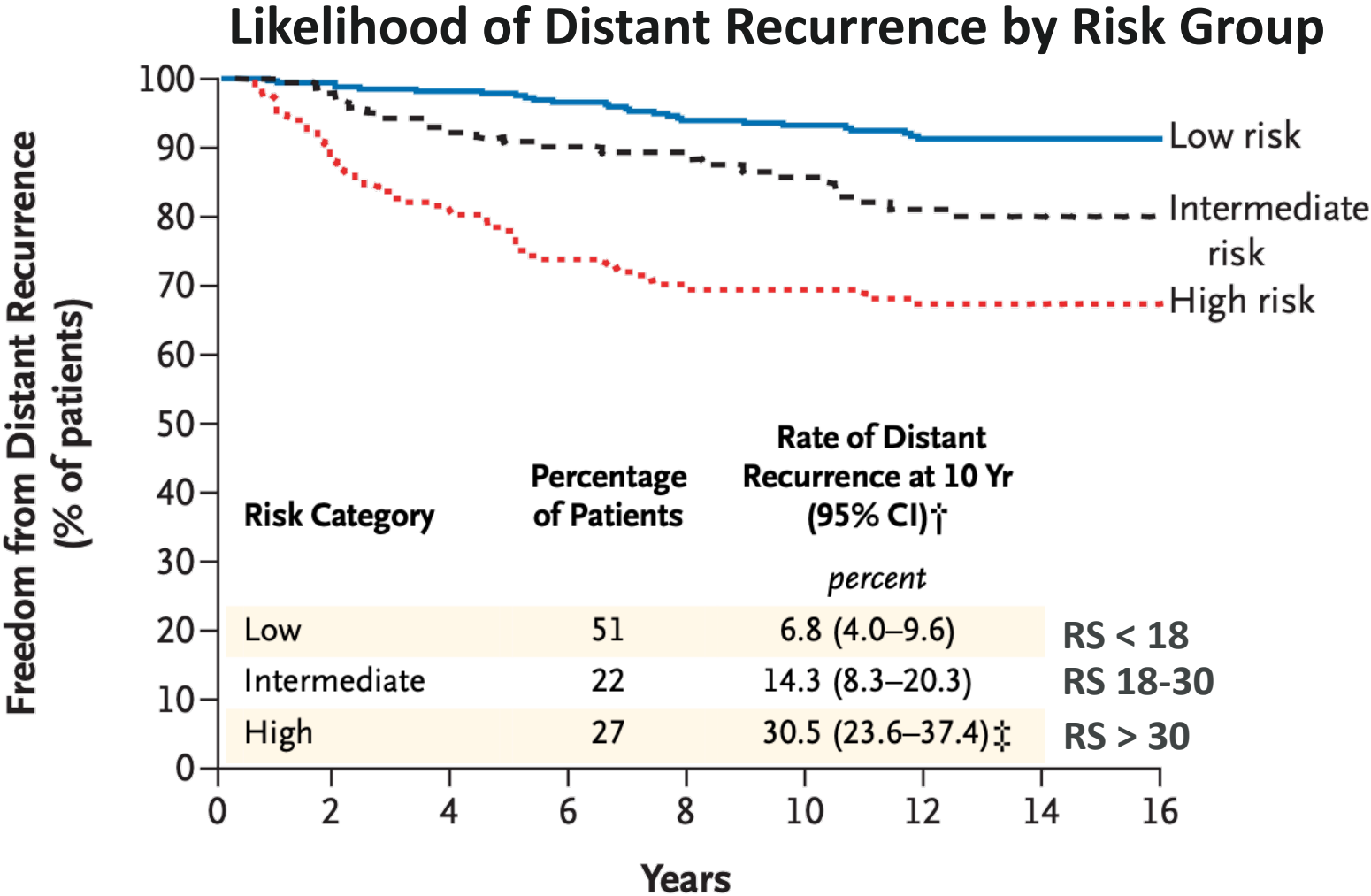
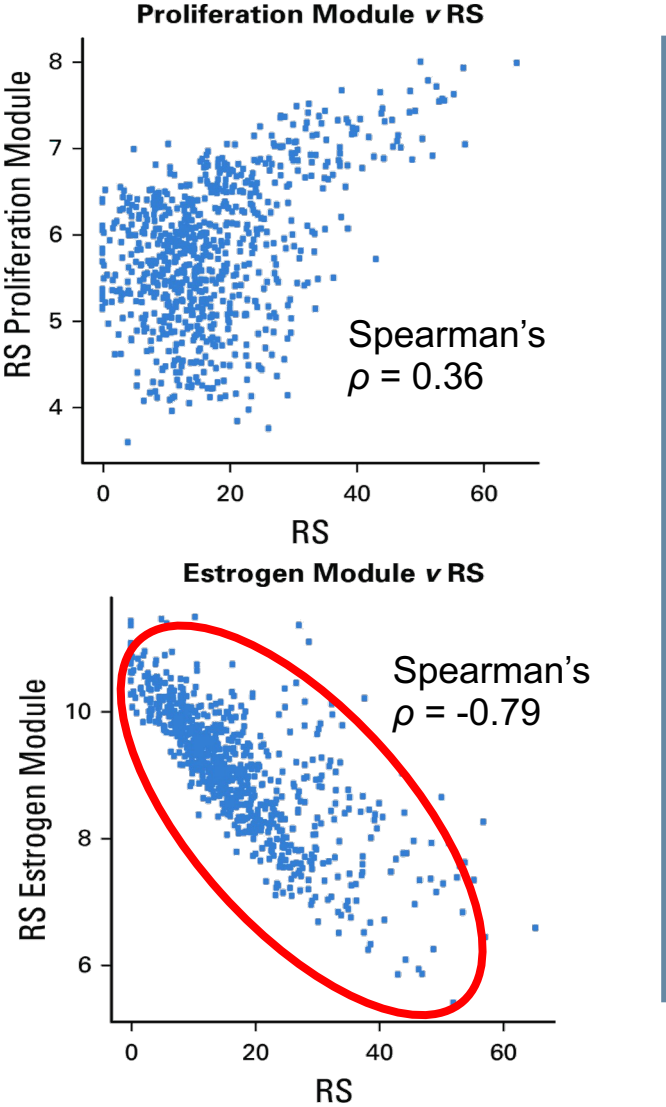


\*Estimated from Kaplan–Meier curve

CI=confidence interval; CTNeoBC=Collaborative Trials in Neoadjuvant Breast Cancer; DFS=disease-free survival; EFS=event-free survival; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; NACT=neoadjuvant chemotherapy; pCR=pathologic complete response; TNBC=triple negative breast cancer

1. Cortazar P, et al. *Lancet*. 2014;384:164–172; 2. Von Minckwitz G, et al. *J Clin Oncol*. 2012;30:1796–1804

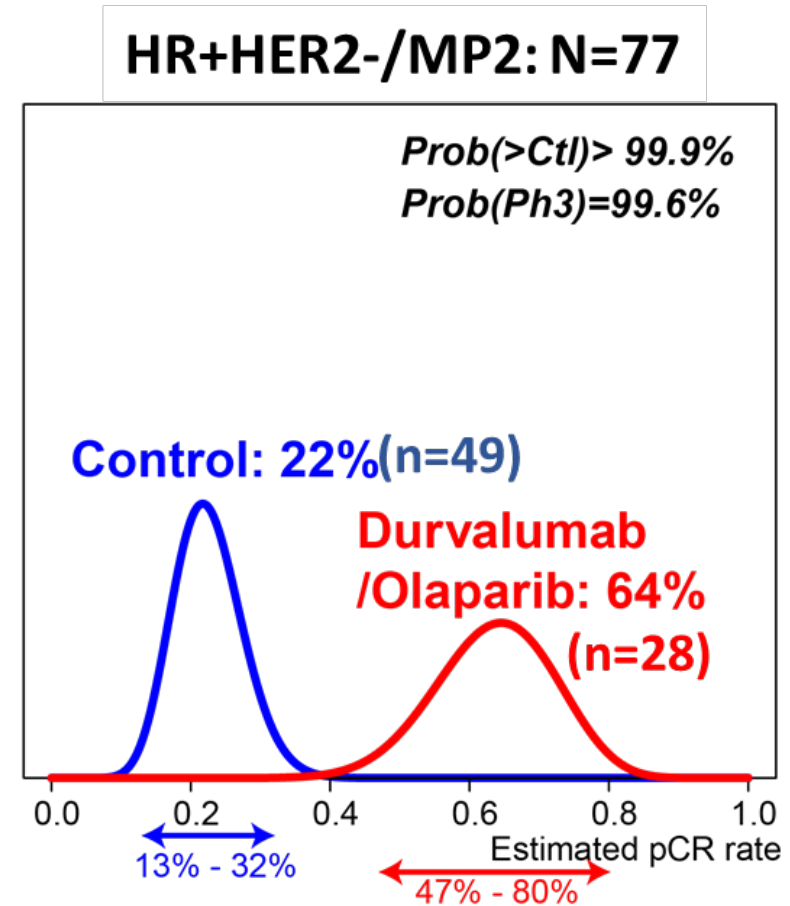
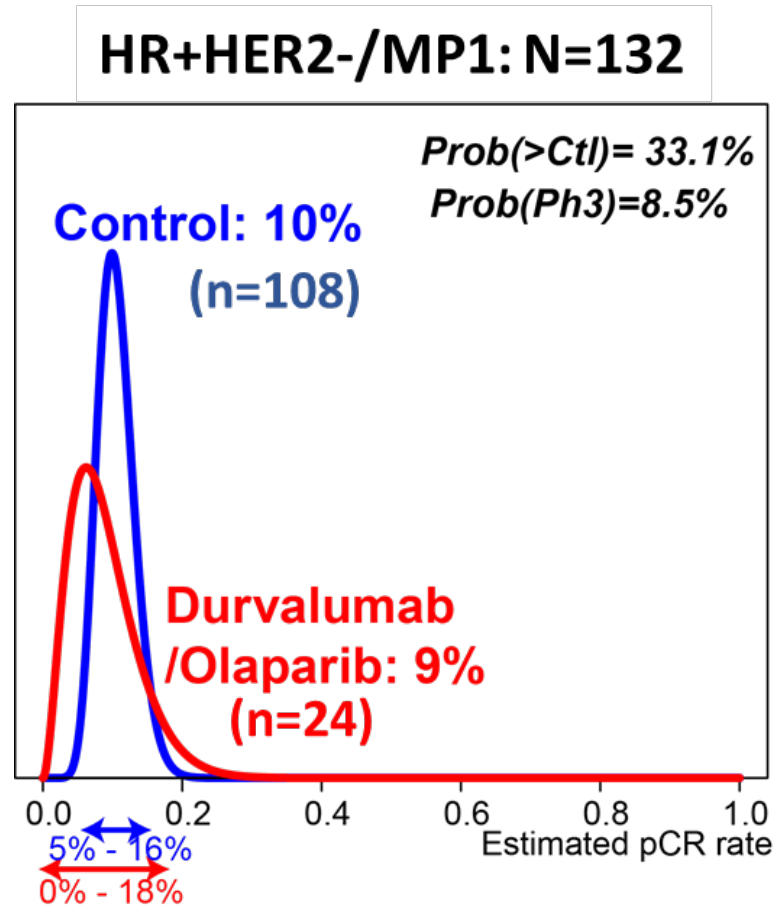
# ET Resistance and Risk of Recurrence in the NSABP B-14 Adjuvant Tamoxifen Trial



1. Buus R et al. J Clin Oncol. 2021;39:126-135.

2. Paik S et al. N Engl J Med. 2004;351:2817-2826.

# HR+ HER2- EBC With “Ultra-High (MP2)” 70-Gene Scores Benefit From Preoperative Paclitaxel + Durvalumab/Olaparib: I-SPY 2 Trial<sup>1</sup>



# Are the Differences Among the CDK4/6 Inhibitors Clinically Significant?<sup>1-3</sup>

All Inhibit CDK4/6 complexes

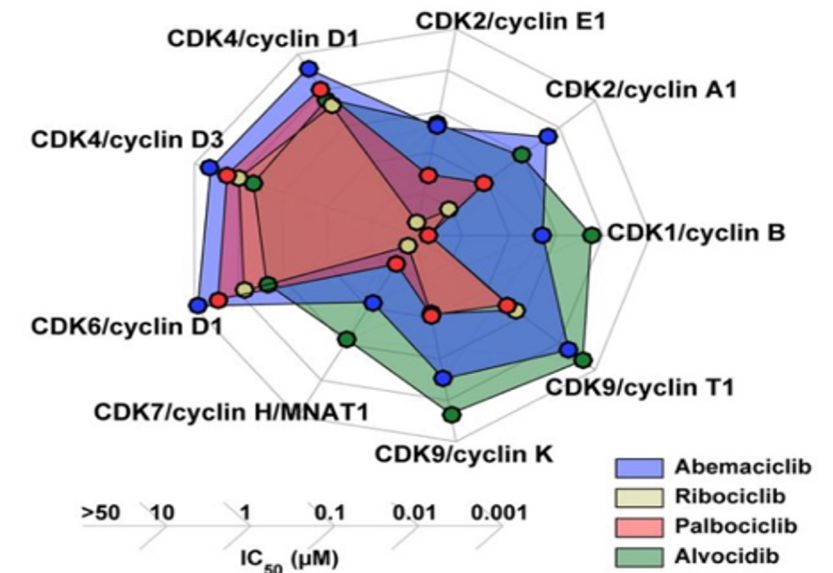
- Ribociclib and abemaciclib are 4 and 5 times more selective toward CDK4 over CDK6
- Abemaciclib has cyclin B–CDK1, cyclin A/E–CDK2, and cyclin T–CDK9 inhibition

**IC<sub>50</sub> Inhibition Values (nmol/L) Against Cyclin-CDK Complexes**

	Cyclin D1-CDK4	Cyclin D1/2/3-CDK4	CDK4:CDK6 Inhibition Ratio	Cyclin B-CDK1	Cyclin A/E-CDK2	Cyclin T-CDK9
Palbociclib	11	16	1:1.5	>10,000	>10,000	NR
Ribociclib	10	39	1:4	113,000	76,000	NR
Abemaciclib	2	10	1:5	1,627	504	57

- Ribociclib and palbociclib dosed intermittently, abemaciclib continuously
- Blood-brain barrier penetration with abemaciclib
- Different acquired resistance mechanisms
- Different toxicity profiles

**Extent of Inhibition of CDK/Cyclin Complexes By Abemaciclib, Palbociclib, or Ribociclib**

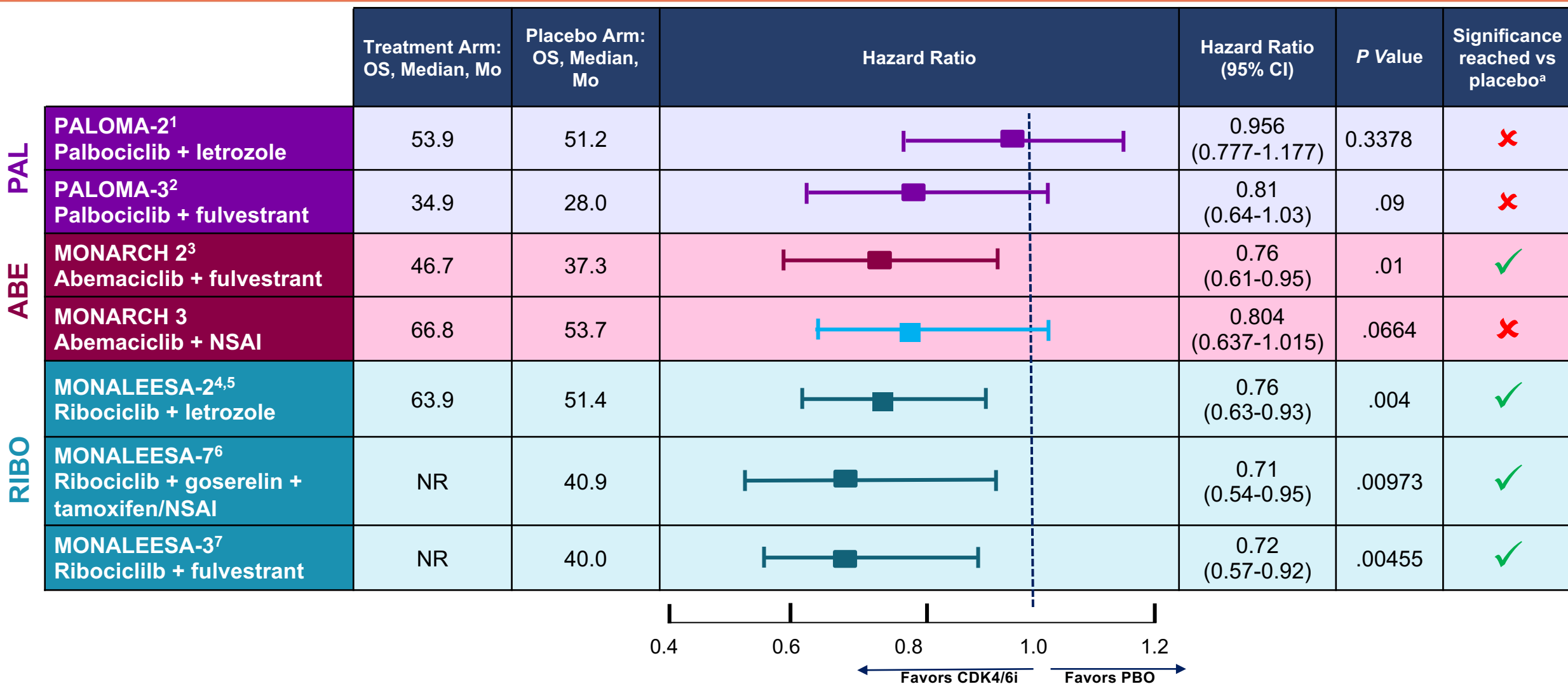


# Phase 3 Trials of CDK4/6 Inhibitors: Consistent PFS Benefit in the First-Line Setting<sup>1-5</sup>

	PALOMA-1	PALOMA-2	MONALEESA-2	MONARCH 3	MONALEESA-3
<b>Design</b>	Phase 2 First line	Phase 3 First line	Phase 3 First line	Phase 3 First line	Phase 3 First and second line
<b>Endocrine Partner</b>	Letrozole	Letrozole	Letrozole	Letrozole or anastrozole	Fulvestrant
<b>CDK4 and 6 Inhibitor</b>	Palbociclib	Palbociclib	Ribociclib	Abemaciclib	Ribociclib
<b>Patients on Study, n</b>	165	666	668	493	367
<b>HR</b>	0.49	0.58	0.56	0.54	0.54
<b>PFS, mo</b>	20.2 vs 10.2	24.8 vs 14.5	25.3 vs 16	28.18 vs 14.76	33.6 vs 19.2

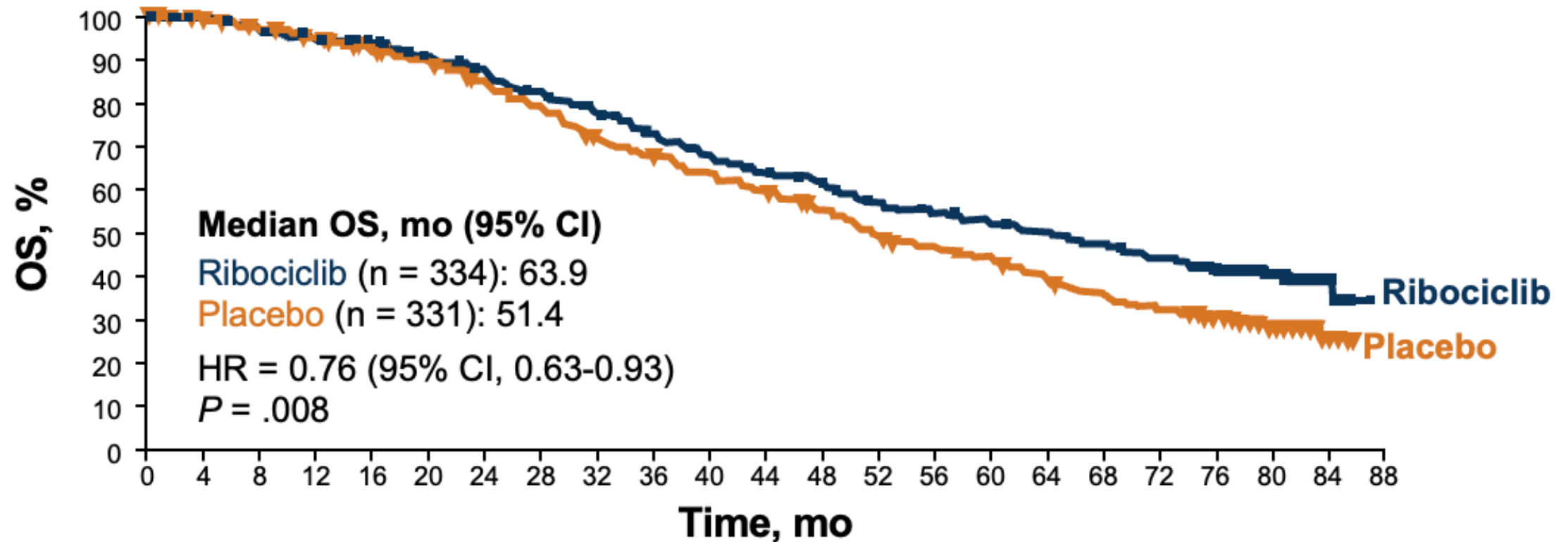
1. Finn RS et al. *Lancet Oncol.* 2015;16:25-35. 2. Finn RS et al. *N Engl J Med.* 2016;375:1925-1936. 3. Hortobagyi GN et al. *Ann Oncol.* 2018;29:1541-1547.  
4. Johnston S et al. *NPJ Breast Cancer.* 2019;5:5. 5. Slamon DJ et al. *N Engl J Med.* 2020;382:514-524.

# Overall Survival in MBC Patients Treated with CDK4/6i



<sup>a</sup> The red ✗ denotes trials that did not report significant median OS compared with placebo. ABC, advanced breast cancer; ABE, abemaciclib; NR, not reached; NSAI, non-steroidal aromatase inhibitor; OS, overall survival; RIBO, ribociclib; PAL, palbociclib. 1. Finn RS, et al. *J Clin Oncol*. 2022; 40 (suppl 17; abstr LBA1003). 2. Turner NC, et al. *N Engl J Med*. 2018;379:1926-1936. 3. Sledge GW, et al. *JAMA Oncol*. 2020;6:116-124. 4. Hortobagyi GN, et al. *N Engl J Med*. 2022;386:942-950. 5. Hortobagyi GN, et al. ESMO 2021. Oral LBA17\_PR. 6. Im SA, et al. *N Engl J Med*. 2019;381:307-316. 7. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524.

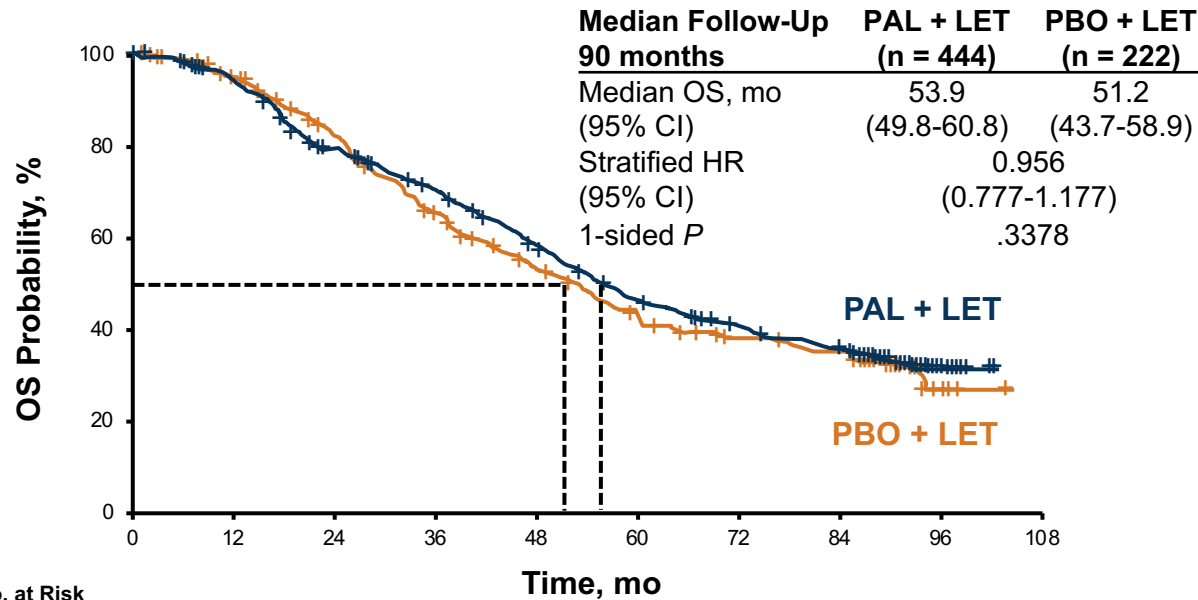
# Phase 3 MONALEESA-2: First-Line AI ± Ribociclib in HR+/HER2- MBC<sup>1</sup>



Ribociclib + letrozole showed a significant OS benefit, with a 1-year improvement over placebo in HR+/HER2- advanced breast cancer → new benchmark for OS in the first-line setting of over 5 years

# PALOMA-2 First-Line Letrozole ± Palbociclib: Overall Survival Analysis<sup>1</sup>

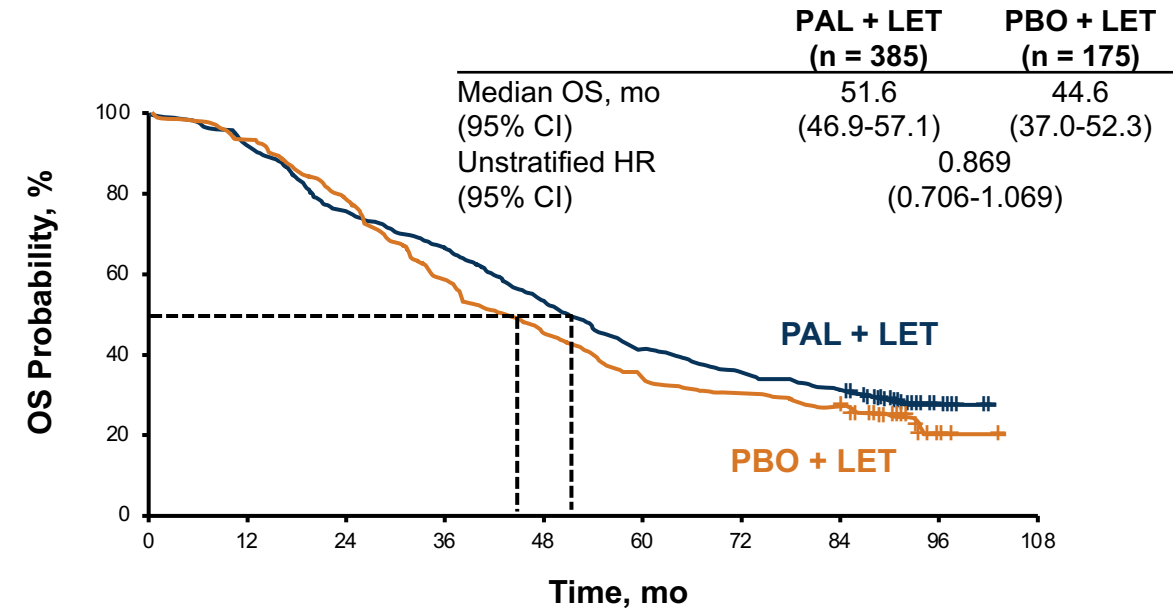
## OS: ITT



No. at Risk

PAL + LET	444	400	325	280	222	174	145	128	13	0
PBO + LET	222	203	168	126	95	72	60	53	4	0

## Post-Hoc Sensitivity Analysis: Excluding Patients With Survival Data Not Available

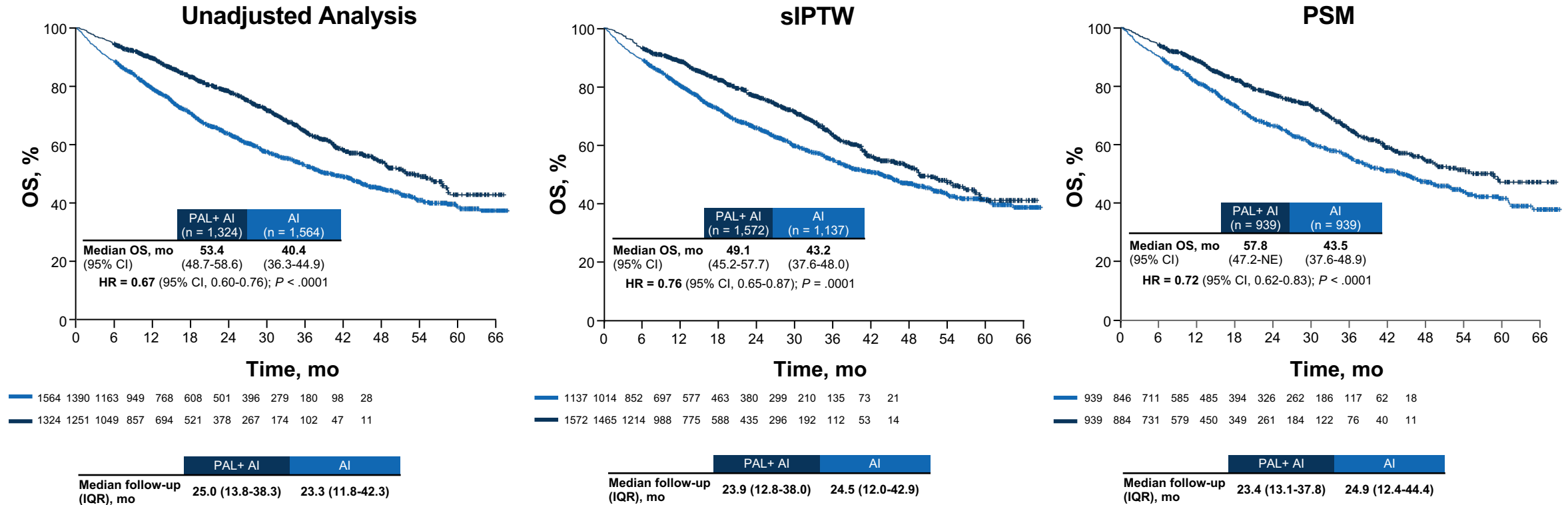


No. at Risk

PAL + LET	385	353	292	257	206	162	140	124	13	0
PBO + LET	175	164	138	103	80	61	54	49	4	0

- Median follow-up: 7.5 years
- Missing survival data: 13% palbociclib + letrozole and 21% control
- More crossover to CDK4/6i in the control arm, 27% vs 12%
- 10% of patients continued on palbociclib and letrozole at 7.5-year follow-up

# Real-World Overall Survival Data for Palbociclib Before and After sIPTW and PSM: P-REALITY X<sup>1</sup>



Median OS<sup>a</sup> was significantly longer among patients who received PAL+ AI vs AI alone before and after sIPTW and PSM

**Note: Observational retrospective analyses are designed to evaluate associations among variables and cannot establish causality; they are not intended for direct comparison with clinical trials.**

<sup>a</sup> OS was defined as the time in months from the index date to death from any cause.

1. Rugo H et al. ESMO BC 2022. Poster 169P.

# MONARCH 3: First-Line AI ± Abemaciclib<sup>1</sup>

- HR+/HER2- advanced BC
- Postmenopausal
- Metastatic or locoregionally recurrent disease with no prior systemic therapy in this setting
- If (neo)adjuvant ET administered, a disease-free interval of >12 months since completion of ET
- ECOG PS 0-1

## Stratified by

- Metastatic site (visceral, bone only, or other)
- Prior ET (AI, no ET, or other)

(N = 493)

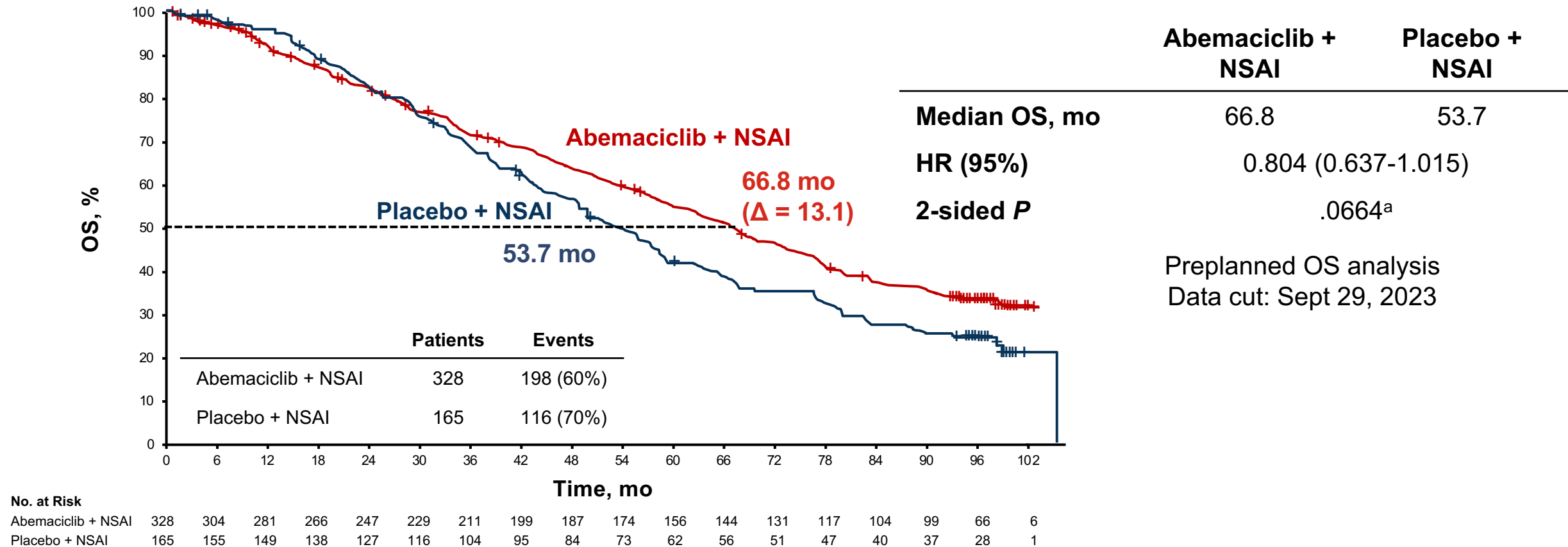
R 2:1

**Abemaciclib 150 mg PO BID +  
anastrozole 1 mg or letrozole 2.5 mg  
PO QD until PD**

**Placebo PO BID + anastrozole 1 mg  
or letrozole 2.5 mg PO QD until PD**

- **Primary endpoint:** investigator-assessed PFS
- **Key secondary endpoints:** OS, response rates, and safety

# MONARCH 3: Final OS in the ITT Population<sup>1</sup>

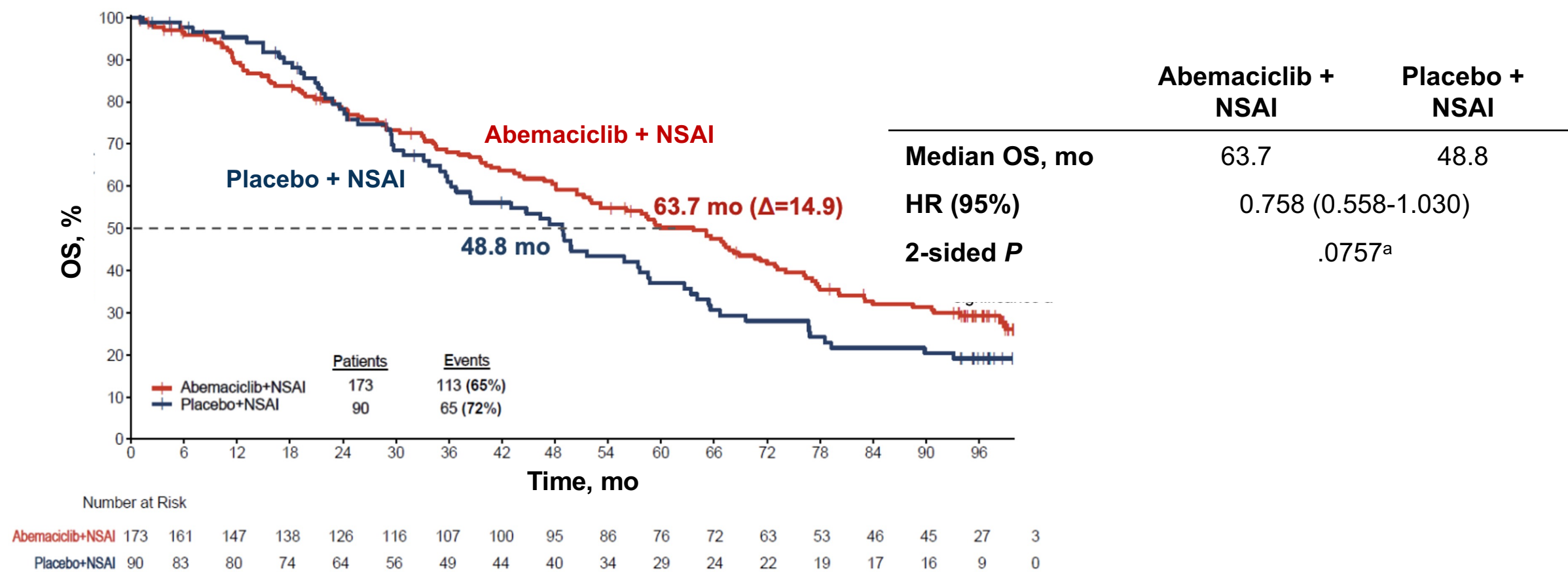


Abemaciclib + NSA resulted in a numerically longer OS vs NSA alone; clinically significant but statistical significance was not reached; the observed improvement in median OS was 13.1 months

<sup>a</sup> Did not reach threshold (0.034) for statistical significance at this final analysis.

1. Goetz MP et al. SABCS 2023. Abstract GS01-12.

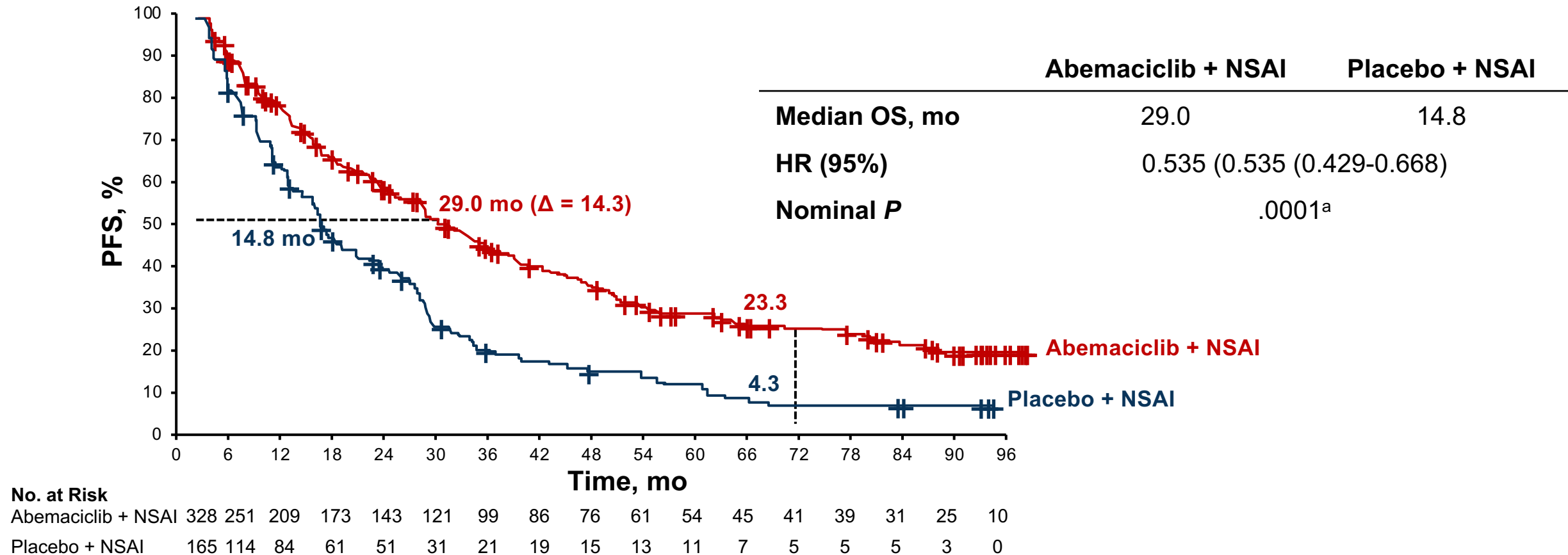
# MONARCH 3: OS in the Subgroup With Visceral Disease<sup>1</sup>



Abemaciclib + NSA resulted in a numerically longer OS compared with NSA alone in the sVD; clinically significant but statistical significance was not reached; the observed improvement in median OS was 14.9 months

<sup>a</sup> Did not reach threshold (0.009) for statistical significance at this final analysis.  
1. Goetz MP et al. SABCS 2023. Abstract GS01-12.

# MONARCH 3: Updated PFS in the ITT Population<sup>1</sup>

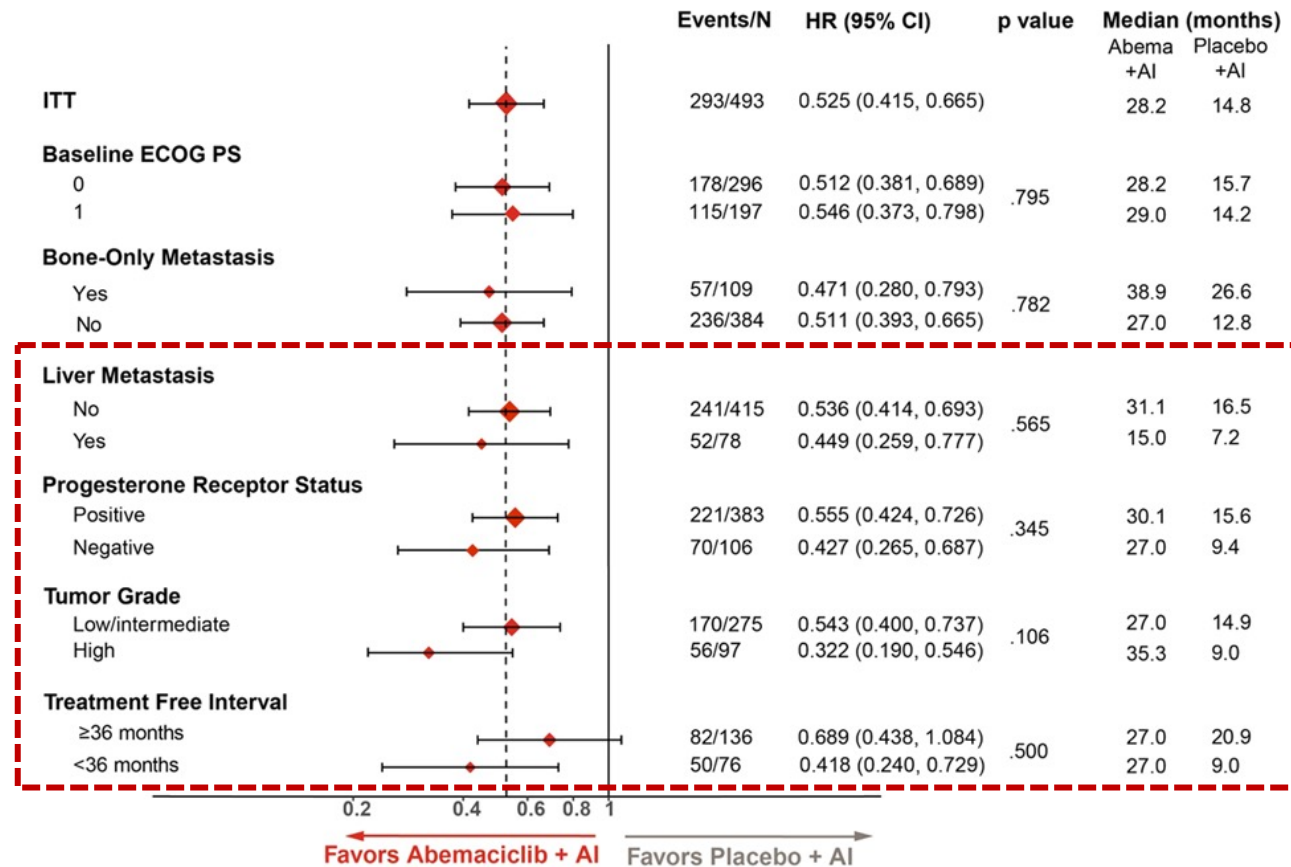


The addition of abemaciclib to NSA resulted in a 14.3-month improvement in median PFS with continued separation of the curves at longer follow-up

<sup>a</sup> Statistical significance was reached at the interim PFS analysis.

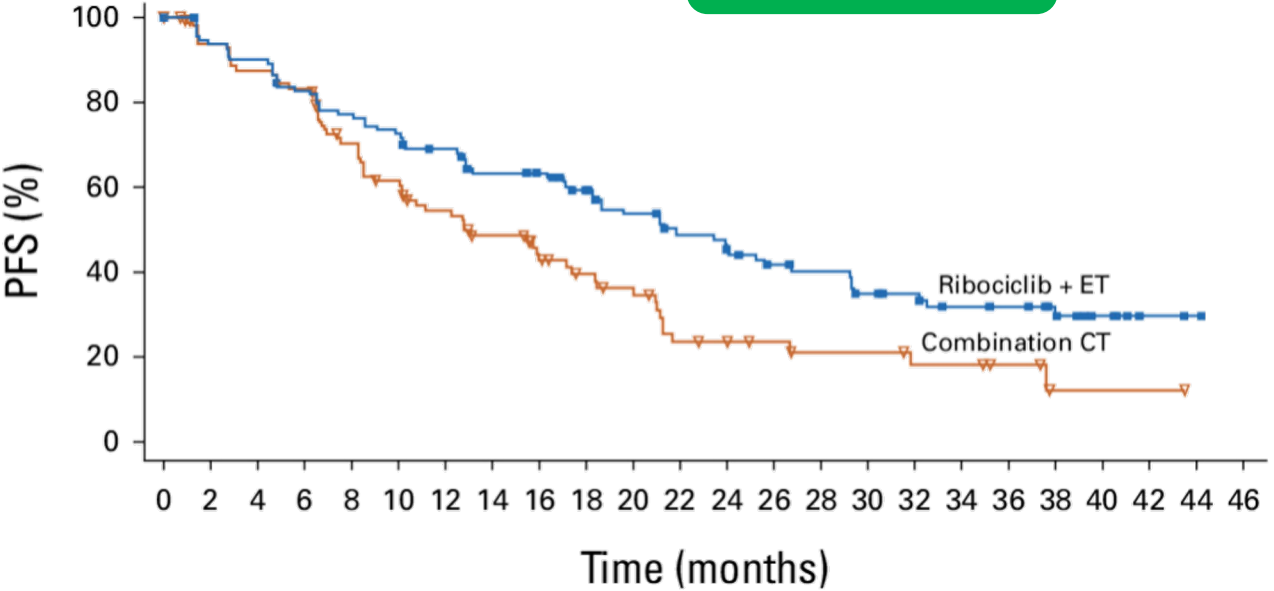
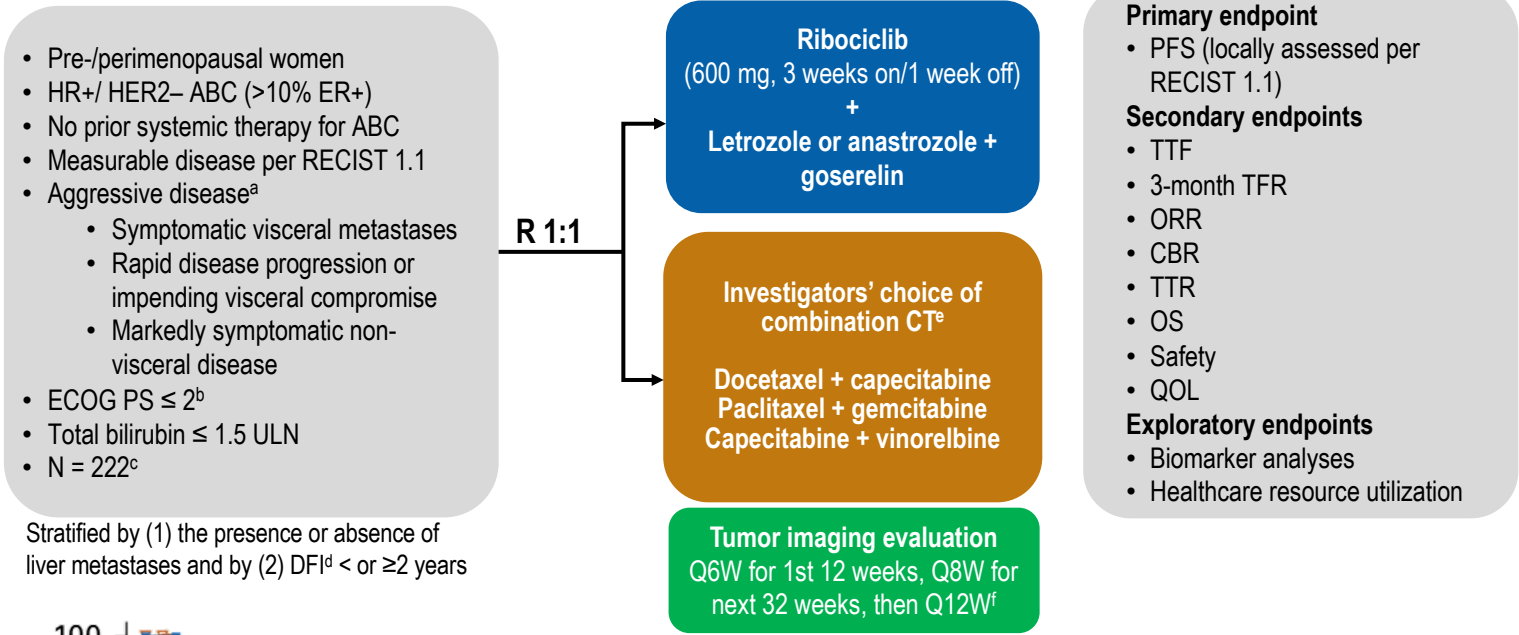
1. Goetz MP et al. SABCS 2023. Abstract GS01-12.

# MONARCH 3: Updated PFS in Subgroups<sup>1</sup>



Treatment benefit was observed across all subgroups, with the largest effects observed in patients with liver metastases, progesterone receptor-negative tumors, high-grade tumors, or TFI < 36 months

# The Phase II RIGHT Choice Trial



## Demographics

- Median age: 44
- De novo MBC: 62.5%
- Visceral mets: 79.5%
- Visceral crisis: 50.9%
- Symptomatic visceral mets: 66.1%

	RIB + ET arm	Combo CT arm
Events/n	67/112	65/110
Median PFS, mo	21.8	12.8
HR (95% CI)	0.611 (0.429-0.870)	
P value	.003	

# CDK4/6 Inhibitors – Toxicity Profiles

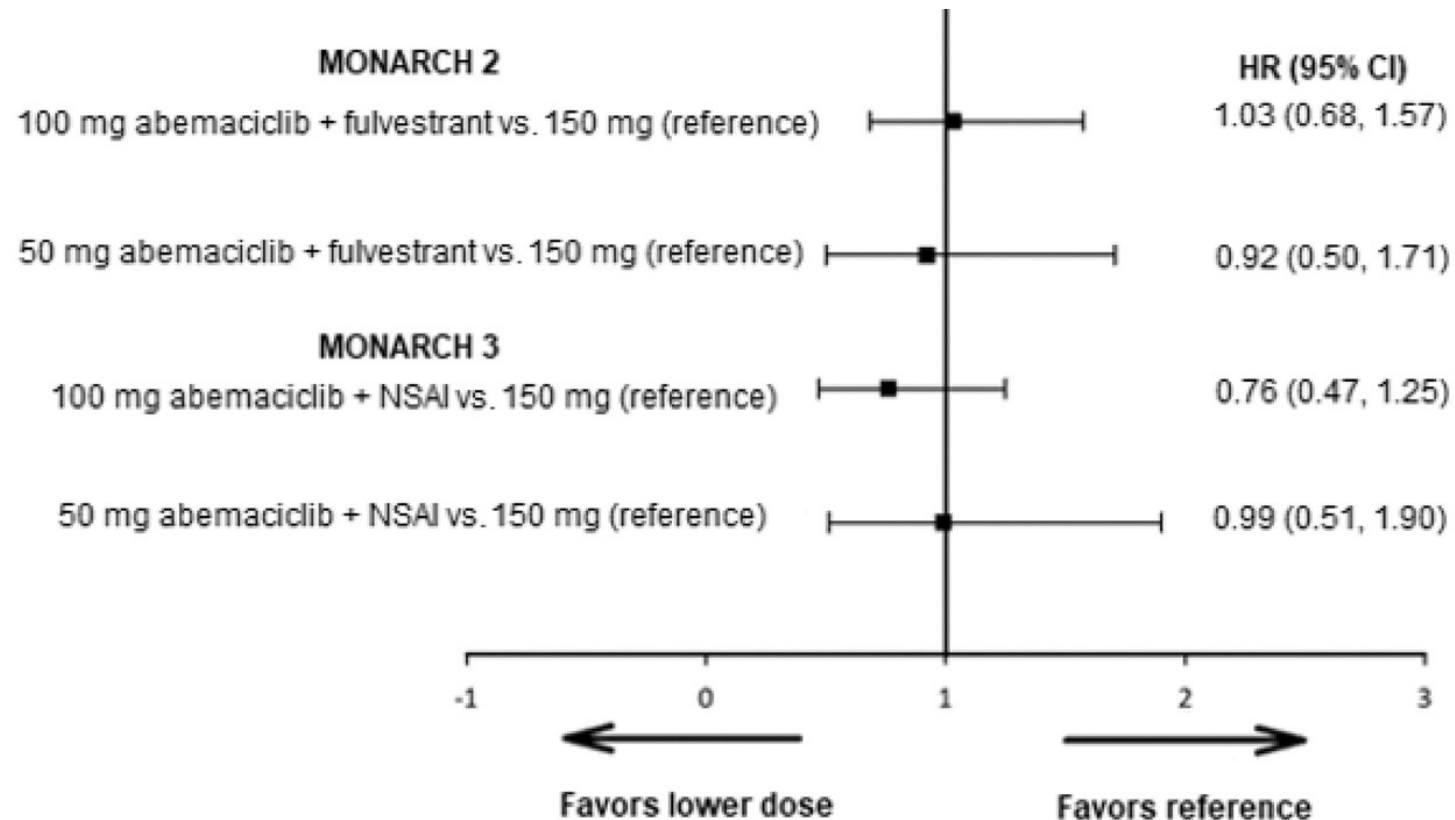
Toxicity in First-Line	Palbociclib	Ribociclib	Abemaciclib
Dosing schedule	3 wks on, one wk off	3 wks on, one wk off	Continuous
≥ Gr 3 neutropenia	66%	59.6%	21.1%
Febrile neutropenia	1.6%	1.5%	< 1%
≥ Gr 3 diarrhea (all grade)	1% (26%)	1.2% (35%)	9.5 (81%)
Gr 2/3 QTc prolongation	-	3/0.3 (with TAM)	-
≥ Gr 3 AST/ALT increase	-	5.7/9.3% All grade ML3 13.7%	3.8/7%
Dose reduction/discontin due to AEs	36% / 9.7%	51% / 7.4%	43.4% / 19.6%
Alopecia	33%	33%	27%
Increased creatinine	-	-	98% (nl fcn)
VTE/PE	0.9 vs 1.4%	NR	4.9 vs 0.6%
ILD/pneumonitis	1%	1.1%	3.3%

# Key AEs With CDK4/6 Inhibitors: Monitoring and Prevention

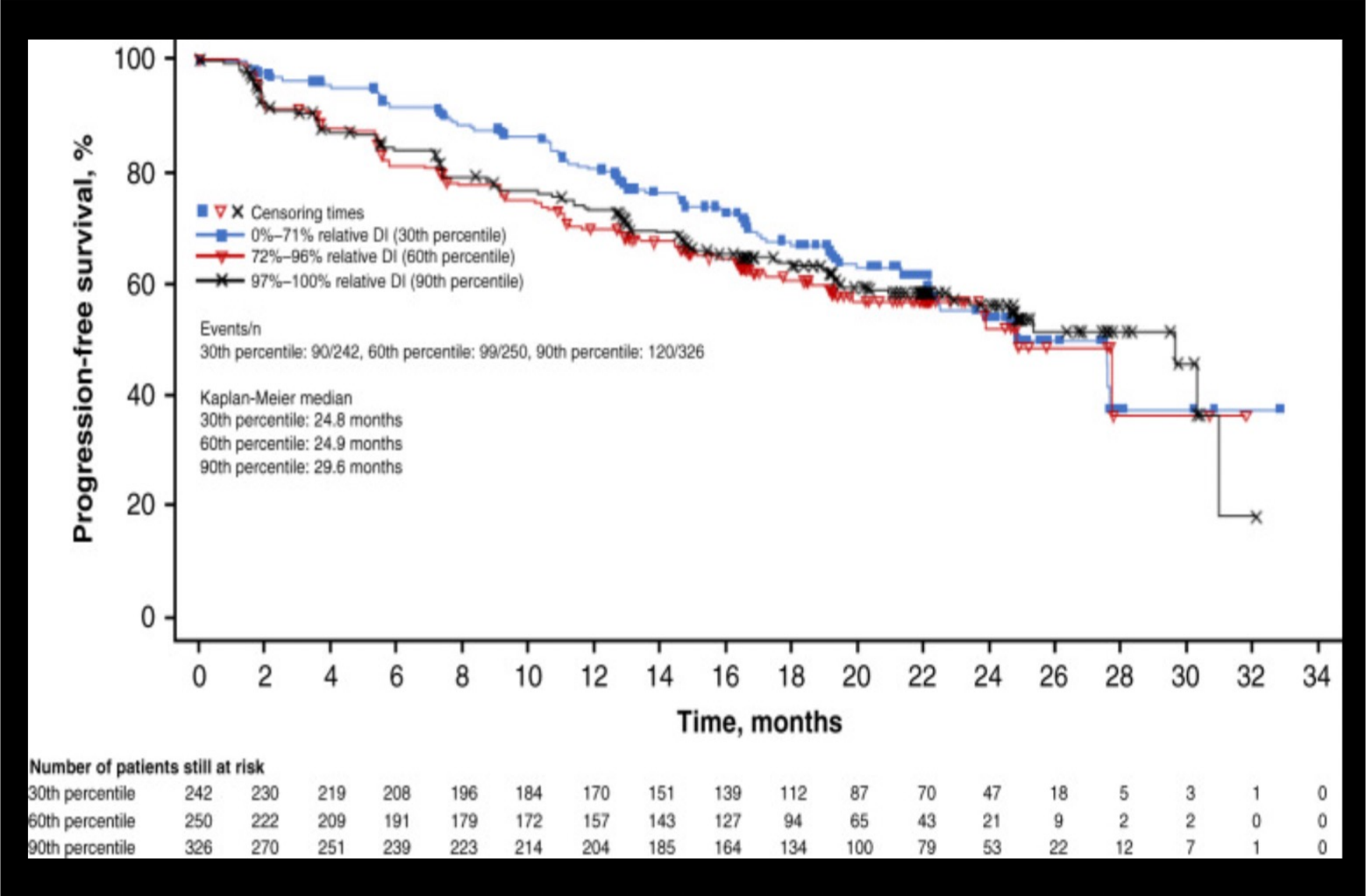
Diarrhea	Hepatobiliary Toxicity	Neutropenia	VTE	ILD/ Pneumonitis
Abemaciclib	Abemaciclib	Abemaciclib	Abemaciclib	Abemaciclib
Palbociclib		Palbociclib	Palbociclib	Palbociclib
Ribociclib	Ribociclib	Ribociclib	Ribociclib	Ribociclib
<p>Antidiarrheal therapy</p> <p>Increase oral hydration</p> <p>Notify healthcare professional</p> <p>Dietary modification</p>	<p>LFTs before starting treatment, Q2W x 2 mo, then:</p> <ul style="list-style-type: none"><li>▪ <i>Abemaciclib</i>, QM x 2 mo, then as indicated</li><li>▪ <i>Ribociclib</i>, at start of cycle x 4 cycles</li></ul>	<p>CBC before starting treatment, then:</p> <ul style="list-style-type: none"><li>▪ <i>Abemaciclib</i>, Q2W x 2 mo, QM x 2 mo, then as indicated</li><li>▪ <i>Palbociclib</i>, D1 and D15 of C1-2, then as indicated</li><li>▪ <i>Ribociclib</i>, Q2W x 2 cycles, start of next 4 cycles, then as indicated</li></ul>	<p>Monitor for signs and symptoms of thrombosis or pulmonary embolism</p>	<p>Monitor for pulmonary symptoms indicative of ILD or pneumonitis (eg, hypoxia, cough, dyspnea)</p>

# MONARCH 2 and 3: Impact of Abemaciclib Dose Reduction on PFS<sup>1</sup>

- In the abemaciclib arms of MONARCH 2 and 3, 189 (42.9%) and 142 (43.4%) patients had dose reductions due to AEs
- Most frequent AEs accounting for  $\geq 10\%$  of dose reductions were grade 2 or 3 diarrhea (14%–19%) and grade  $\geq 3$  neutropenia (10%–13%)
- In both studies, there was no difference in PFS when the dose was reduced to 100 mg, or to 50 mg at any point in the treatment, compared with being treated at the 150-mg dose



# Dose Reductions in MONALEESA-2, -3, -7 Trials and Outcomes



# The “SIMPLE” Approach to Improving Adherence to CDK4/6 Inhibitors<sup>1,2</sup>



# **Oncology Today: Individualizing the Selection of First-Line Therapy for Patients with Hormone Receptor-Positive Metastatic Breast Cancer**

## **Clinical Investigator Survey**

# Participating Breast Cancer Clinical Investigators

Francois-Clement Bidard, MD, PhD

Virginia F Borges, MD, MMSc

Adam M Brufsky, MD, PhD

Harold J Burstein, MD, PhD

Karen A Gelmon, MD

Matthew P Goetz, MD

Stephanie L Graff, MD, FACP

Virginia Kaklamani, MD, DSc

Kevin Kalinsky, MD, MS

Erica Mayer, MD, MPH, FASCO

Kathy D Miller, MD

Rita Nanda, MD

Ruth O'Regan, MD

Joyce O'Shaughnessy, MD

Lajos Pusztai, MD, DPhil, FASCO

Mark E Robson, MD

Paolo Tarantino, MD

Sara M Tolaney, MD, MPH

Tiffany A Traina, MD, FASCO

Seth Wander, MD, PhD

# Survey Outline

## Three base clinical scenarios:

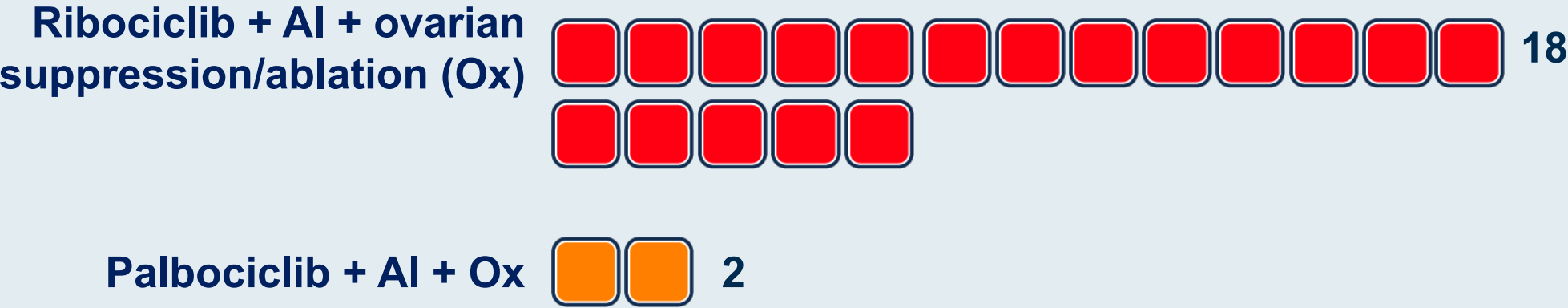
- De novo presentation of metastatic disease
- Development of metastatic disease 2 years after starting an adjuvant aromatase inhibitor (AI)
- Development of metastatic disease 2 years after completing 5 years of an AI

## Additional variables within the 3 base scenarios:

- Age
- Tumor grade
- PR status

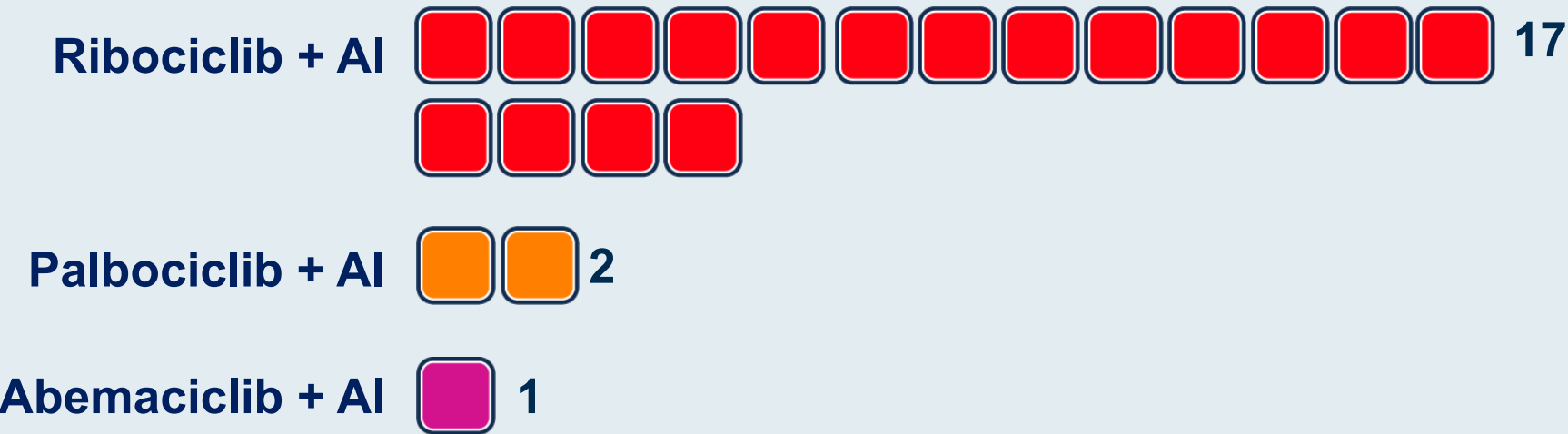
A woman presents with de novo ER-positive, PR-positive, HER2-negative, BRCA wild-type (WT) metastatic breast cancer. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 40 (premenopausal), PS 0  
Asymptomatic bone metastases



A woman presents with de novo ER-positive, PR-positive, HER2-negative, BRCA WT metastatic breast cancer. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0  
Asymptomatic bone metastases



A woman presents with de novo ER-positive, PR-positive, HER2-negative, BRCA WT metastatic breast cancer. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 40 (premenopausal), PS 0

Symptomatic visceral (including liver) metastases

Ribociclib + AI + Ox  13

Abemaciclib + AI + Ox  4

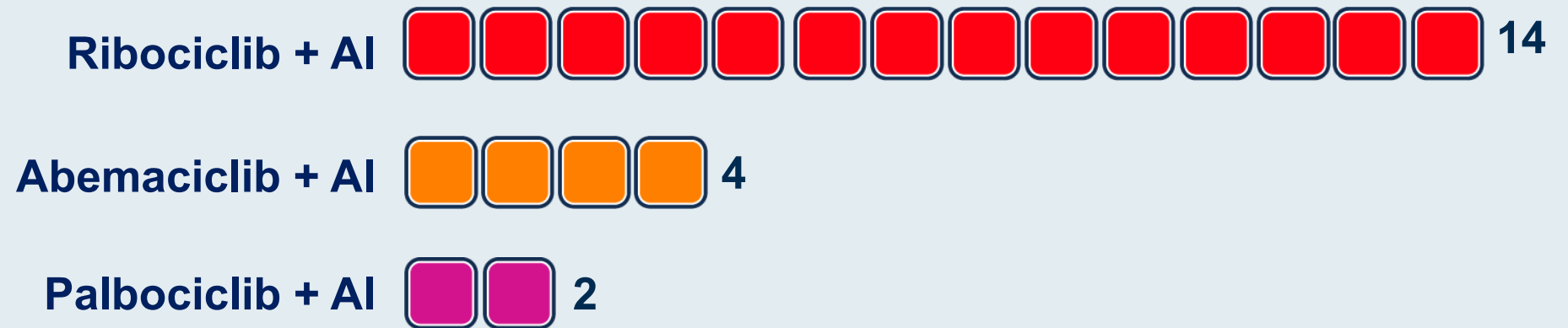
Palbociclib + AI + Ox  1

Ribociclib + fulvestrant + Ox  1

A woman presents with de novo ER-positive, PR-positive, HER2-negative, BRCA WT metastatic breast cancer. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0

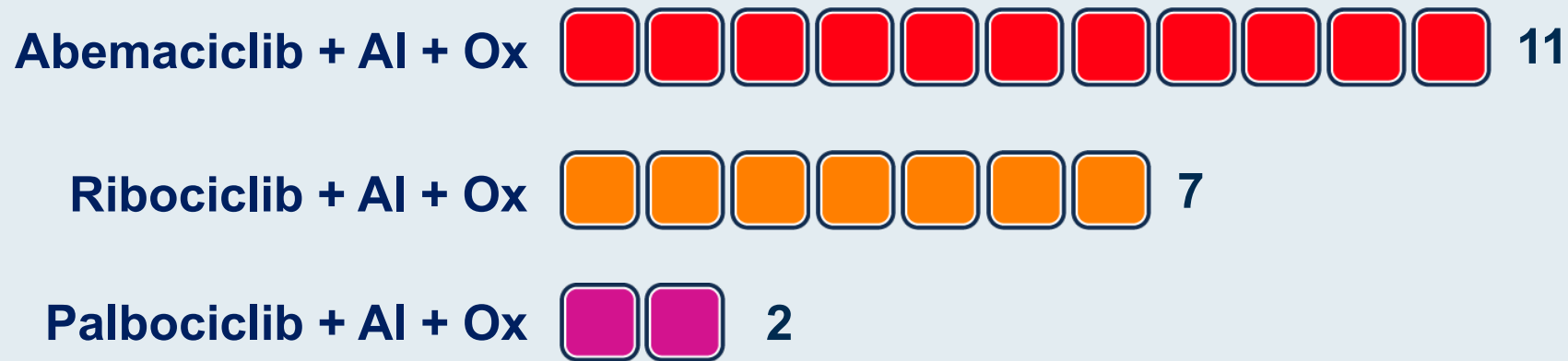
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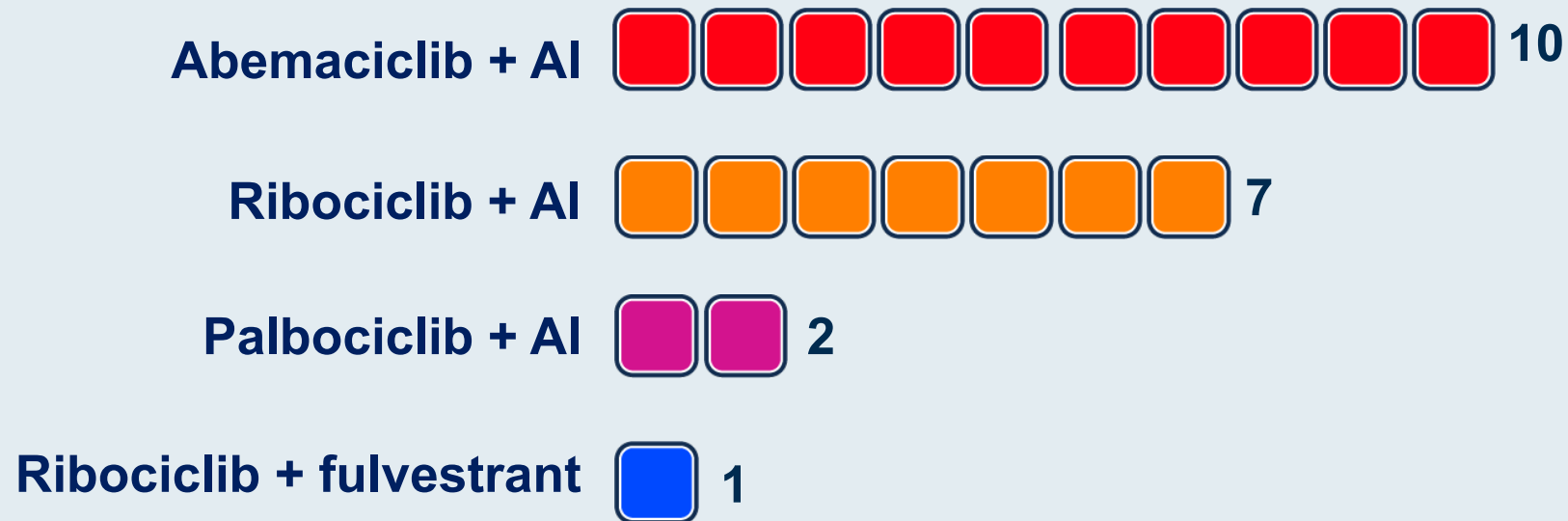
Multiple asymptomatic brain metastases that require whole-brain radiation therapy (WBRT)



A woman presents with de novo ER-positive, PR-positive, HER2-negative, BRCA WT metastatic breast cancer. Which endocrine-based treatment would you most likely recommend for the scenario below?


Age 65, PS 0

Multiple asymptomatic brain metastases that require WBRT



A woman presents with de novo ER-positive, PR-negative, HER2-negative, BRCA WT metastatic breast cancer. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0  
Asymptomatic bone metastases

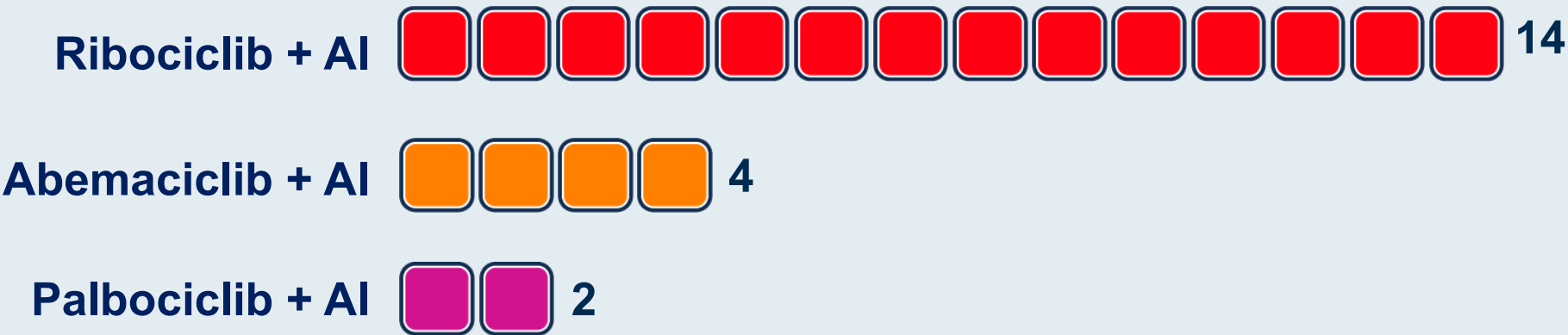
Ribociclib + AI  18

Palbociclib + AI  2

A woman presents with de novo ER-positive, PR-negative, HER2-negative, BRCA WT metastatic breast cancer. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0

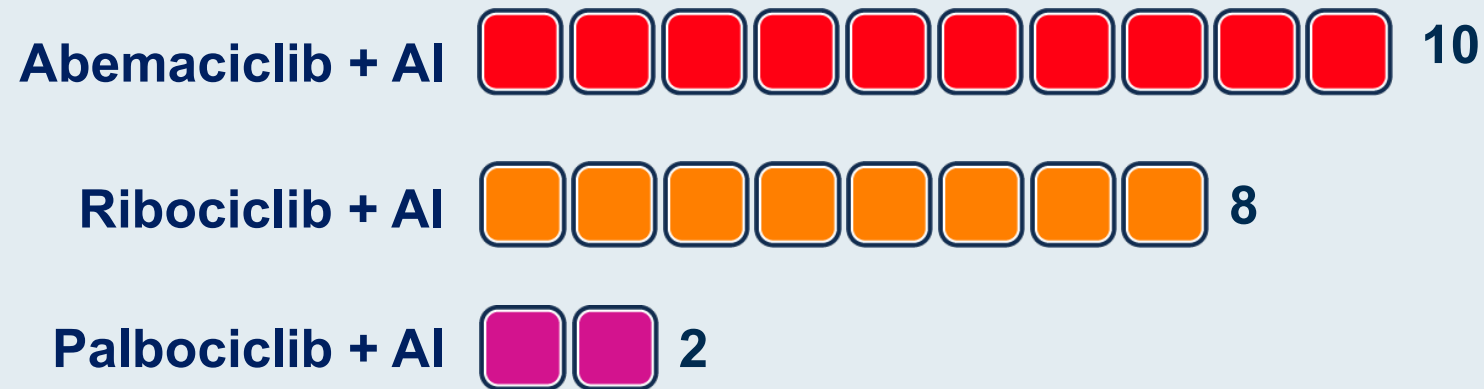
Symptomatic visceral (including liver) metastases



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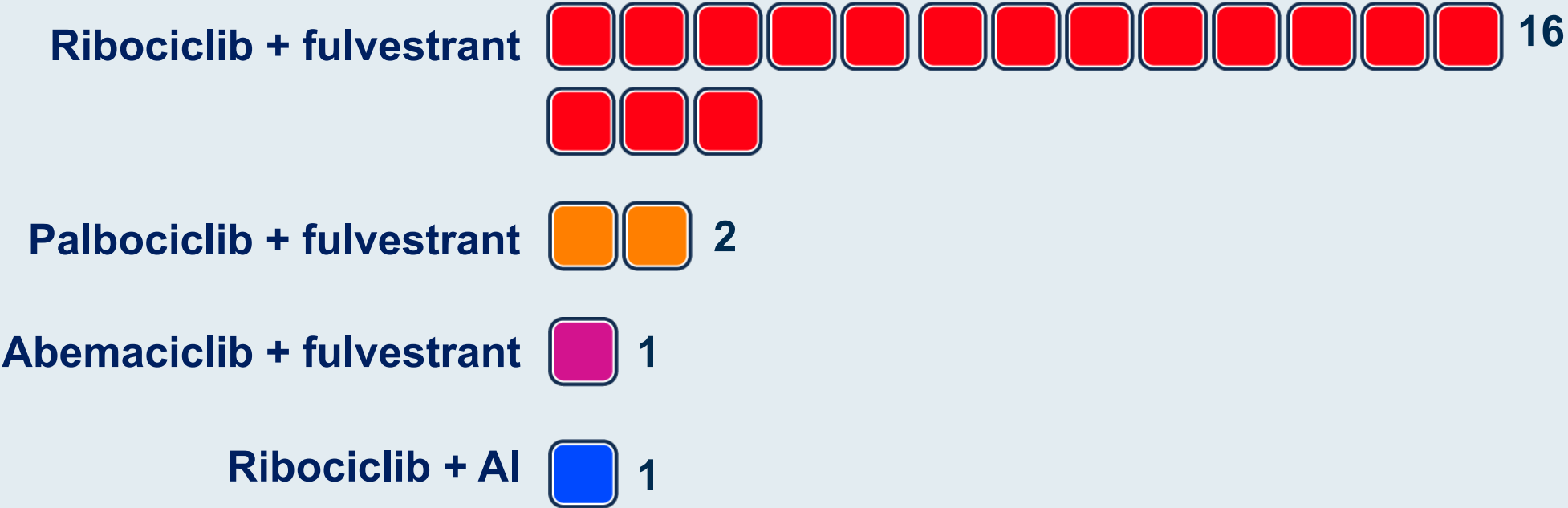
Age 65, PS 0

Multiple asymptomatic brain metastases that require WBRT



A woman who is receiving anastrozole (with ovarian suppression/ablation if needed) for lower-grade ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after starting adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

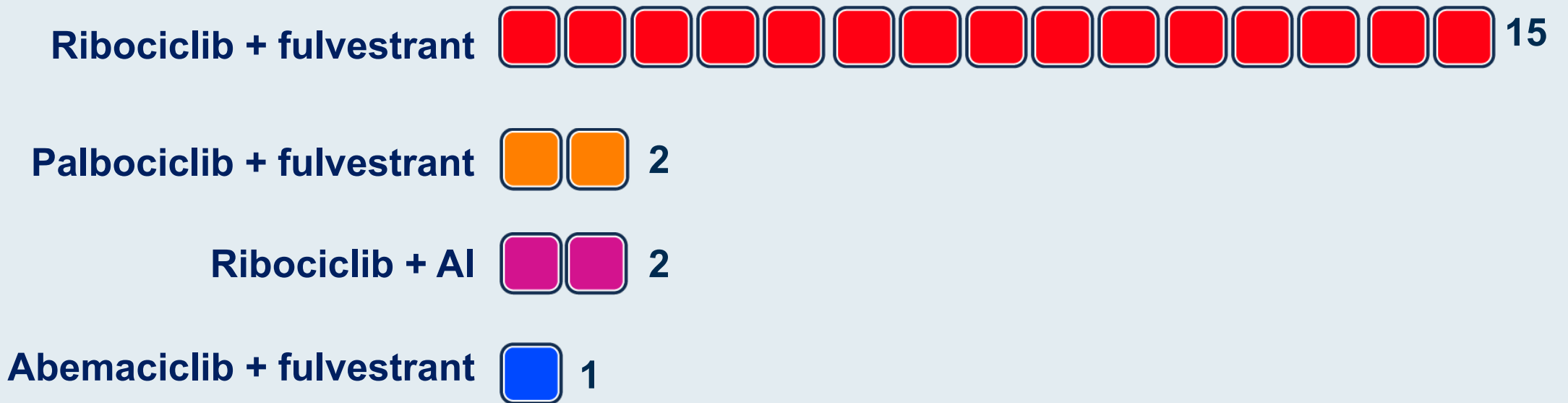
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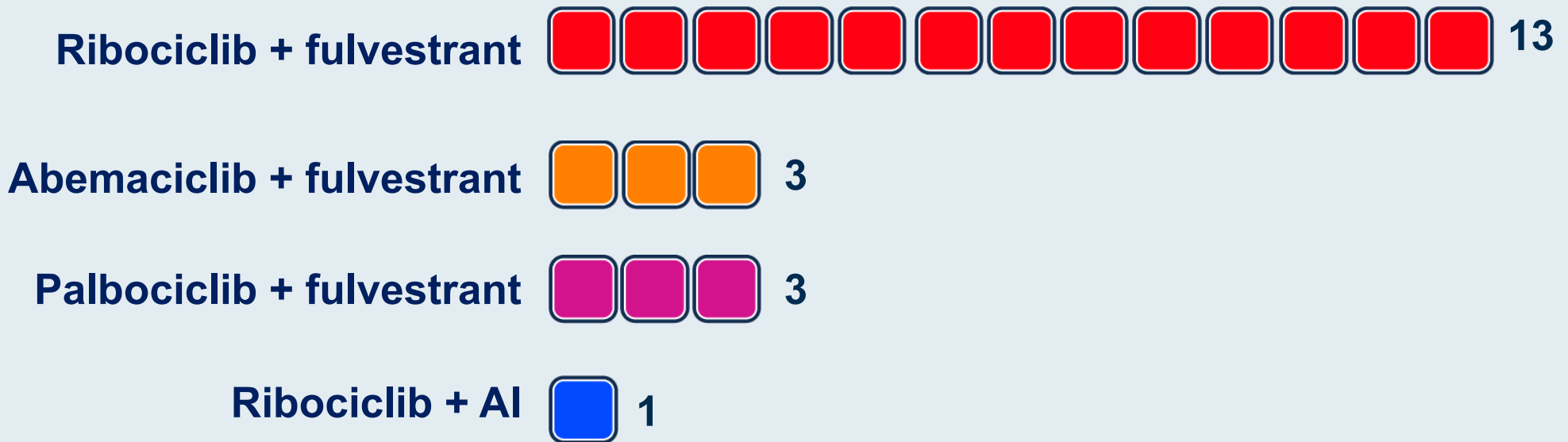
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Multiple asymptomatic brain metastases that require WBRT



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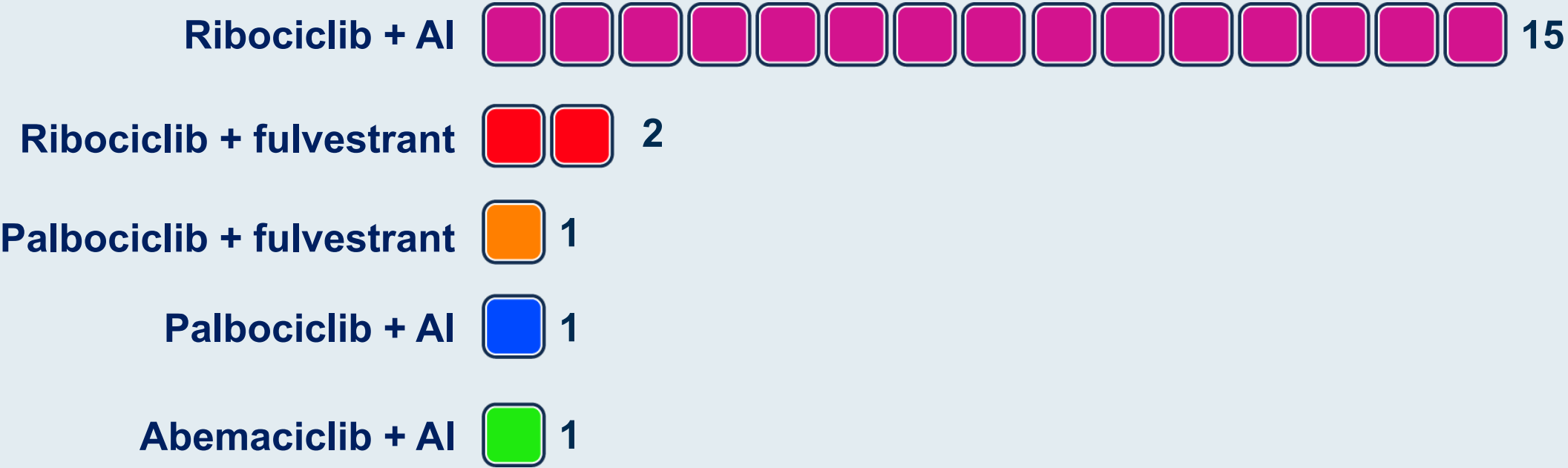
Age 65, PS 0

Multiple asymptomatic brain metastases that require WBRT



A woman who received 5 years of anastrozole (with ovarian suppression/ablation if needed) for high-grade ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after completing adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0  
Asymptomatic bone metastases



A woman who received 5 years of anastrozole (with ovarian suppression/ablation if needed) for high-grade ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after completing adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0

Symptomatic visceral (including liver) metastases



A woman who received 5 years of anastrozole (with ovarian suppression/ablation if needed) for high-grade ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after completing adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0

Multiple asymptomatic brain metastases that require WBRT



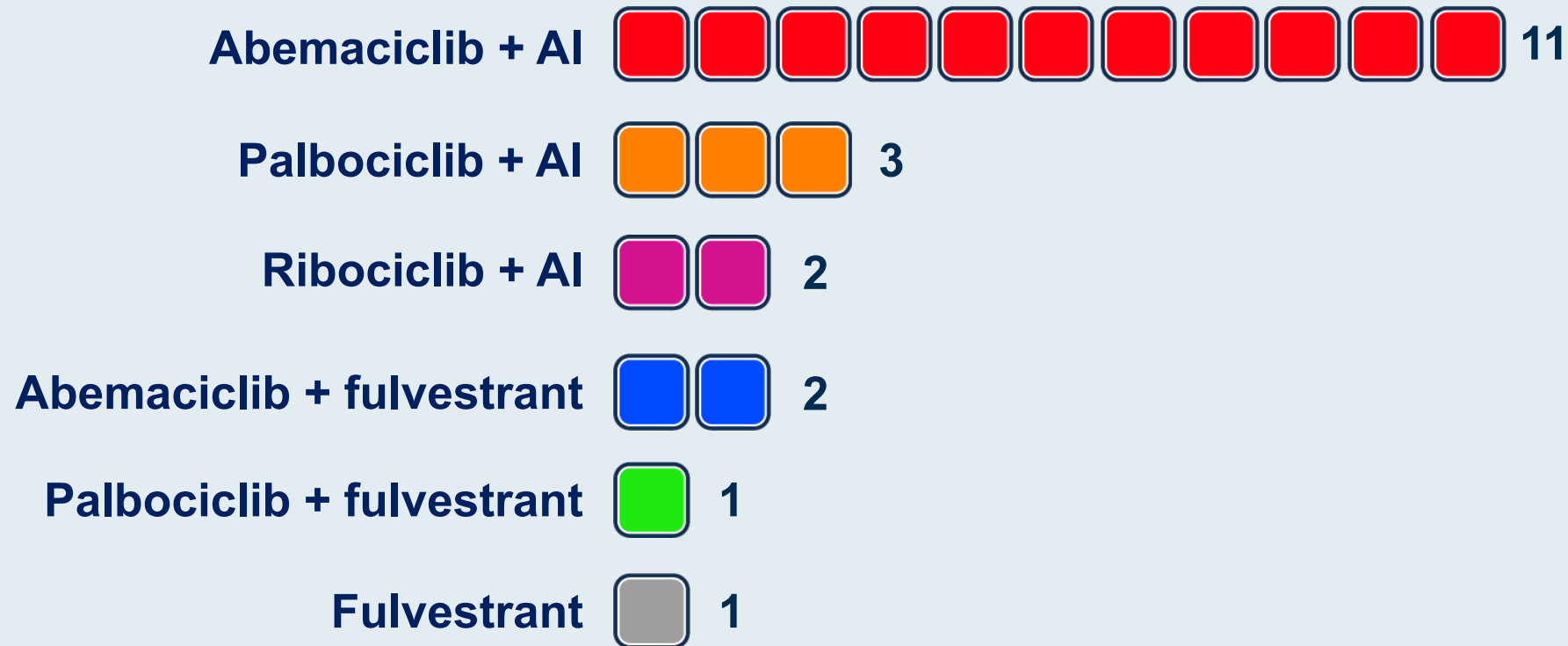
A 65-year-old woman who received 2 years of adjuvant abemaciclib in combination with endocrine therapy for high-risk node-positive, ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer develops visceral metastases 18 months after completing treatment. Which endocrine-based treatment would you most likely recommend?



A 65-year-old woman with a history of congestive heart failure who is currently receiving an ACE inhibitor and a beta blocker and who received 5 years of anastrozole for high-grade ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer develops visceral (including liver) metastases 2 years after completing adjuvant therapy. Which endocrine-based treatment would you most likely recommend?



A 65-year-old woman with a history of systemic lupus erythematosus and asymptomatic moderate neutropenia (ANC = 750/ $\mu$ L) who received 5 years of anastrozole for high-grade ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer develops visceral (including liver) metastases 2 years after completing adjuvant therapy. Which endocrine-based treatment would you most likely recommend in addition to WBRT?



A 65-year-old woman who received 5 years of anastrozole for high-grade ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer develops visceral (including liver) metastases 2 years after completing adjuvant therapy. She presents to the emergency room with symptoms related to her metastatic disease and needs to start therapy immediately. Which endocrine-based treatment would you most likely recommend?



An 85-year-old woman with a history of diabetes, hypertension and hyperlipidemia presents with de novo ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer and symptomatic visceral metastases. Which endocrine-based treatment would you most likely recommend?

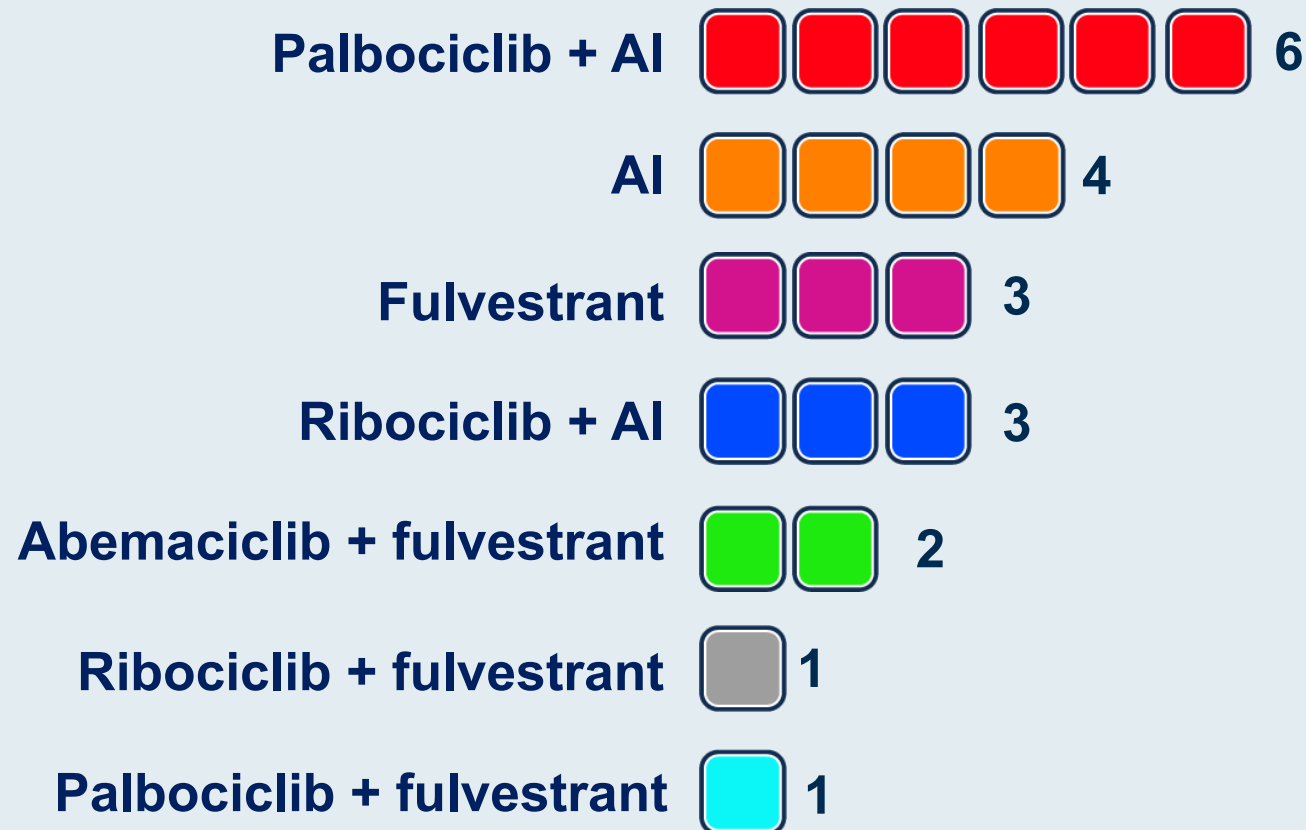
Ribociclib + AI  12

Palbociclib + AI  6

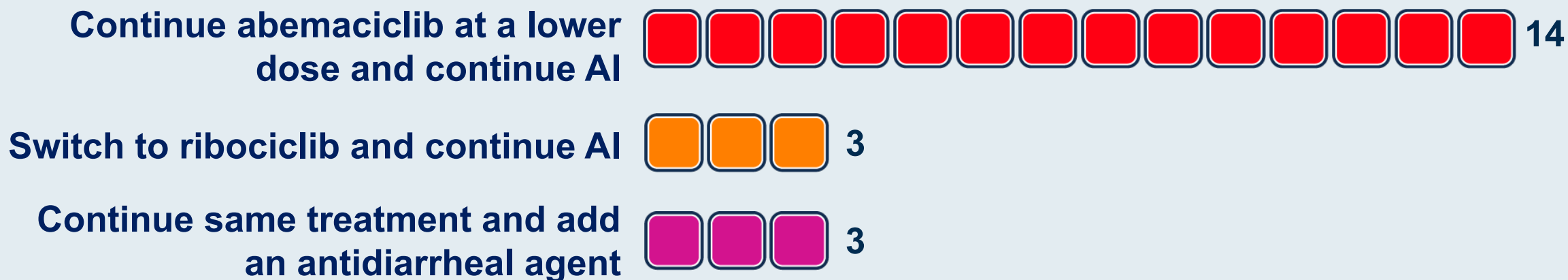
Abemaciclib + AI  1

Palbociclib + fulvestrant  1

An 85-year-old woman with multiple comorbidities who has a difficult time managing polypharmacy presents with de novo ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer and symptomatic visceral metastases. Which endocrine-based treatment would you most likely recommend?



A 65-year-old woman who received 5 years of anastrozole for high-grade ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer with a history of inflammatory bowel disease with constipation develops visceral metastases 2 years after completing adjuvant therapy. She is started on abemaciclib with an AI and develops treatment-related Grade 1 diarrhea. What would be your most likely endocrine-based treatment approach?



**A 65-year-old woman who is receiving ribociclib in combination with an AI for de novo ER-positive, PR-positive, HER2-negative, BRCA WT metastatic breast cancer develops abnormal LFTs 6 months after initiating therapy. What would be your most likely endocrine-based treatment approach?**

**Continue ribociclib at a lower dose and continue AI**  **11**

**Switch to palbociclib and continue AI**  **4**

**Switch to abemaciclib and continue AI**  **2**

**Temporarily hold ribociclib until LFTs resolve; restart at lower dose with AI**  **2**

**A 65-year-old woman who is receiving ribociclib in combination with an AI for de novo ER-positive, PR-positive, HER2-negative, BRCA WT metastatic breast cancer develops QTc interval prolongation 6 months after initiating therapy. What would be your most likely endocrine-based treatment approach?**

**Switch to palbociclib and continue AI**  **7**

**Switch to abemaciclib and continue AI**  **7**

**Continue ribociclib at a lower dose and continue AI**  **3**

**Temporarily hold ribociclib for 1 week; restart at lower dose if improvement**  **1**

# APPENDIX

A woman presents with de novo ER-positive, PR-negative, HER2-negative, BRCA WT metastatic breast cancer. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 40 (premenopausal), PS 0  
Asymptomatic bone metastases

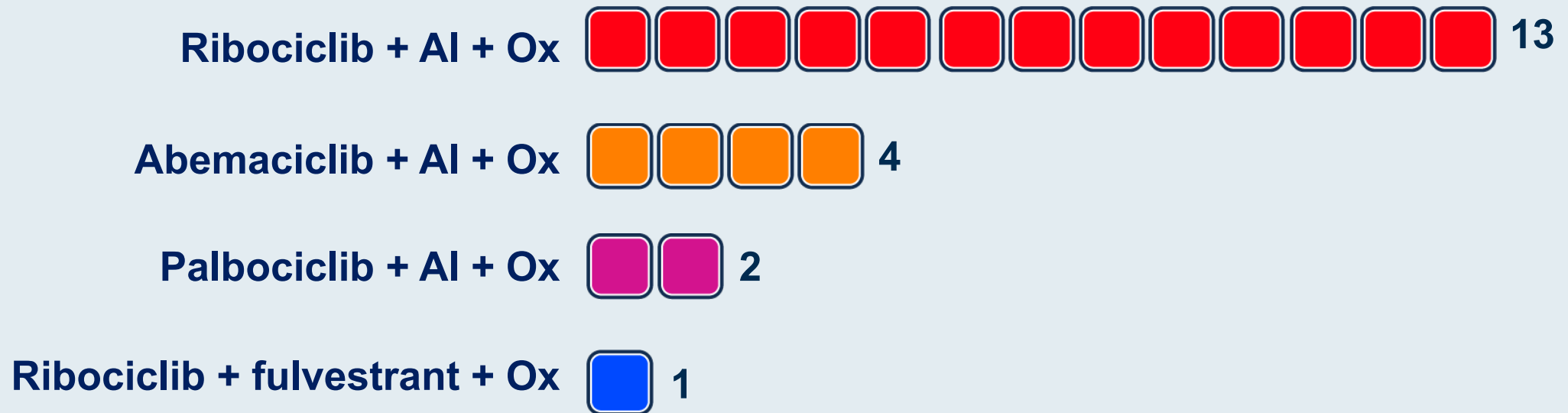
Ribociclib + AI + Ox  18

Palbociclib + AI + Ox  2

A woman presents with de novo ER-positive, PR-negative, HER2-negative, BRCA WT metastatic breast cancer. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 40 (premenopausal), PS 0

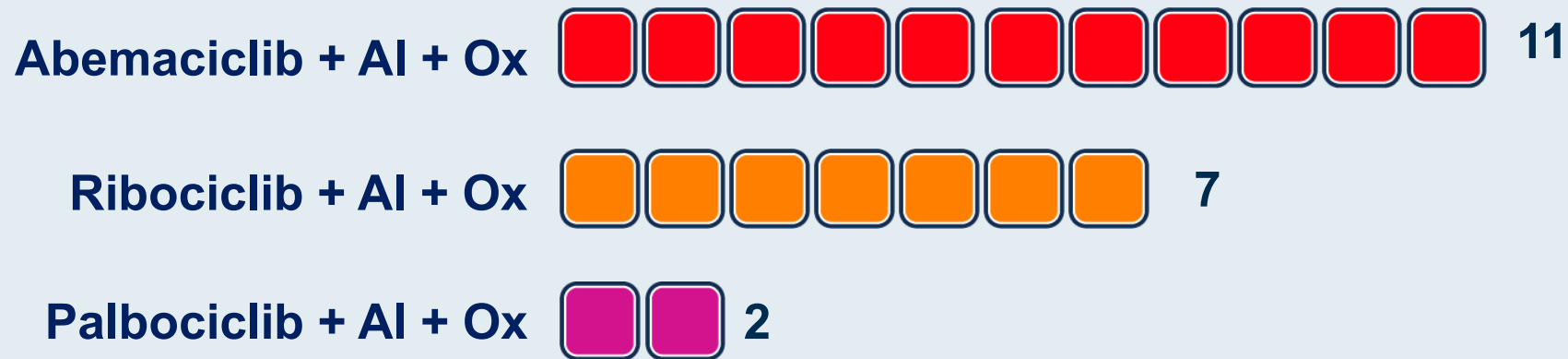
Symptomatic visceral (including liver) metastases



A woman presents with de novo ER-positive, PR-negative, HER2-negative, BRCA WT metastatic breast cancer. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 40 (premenopausal), PS 0

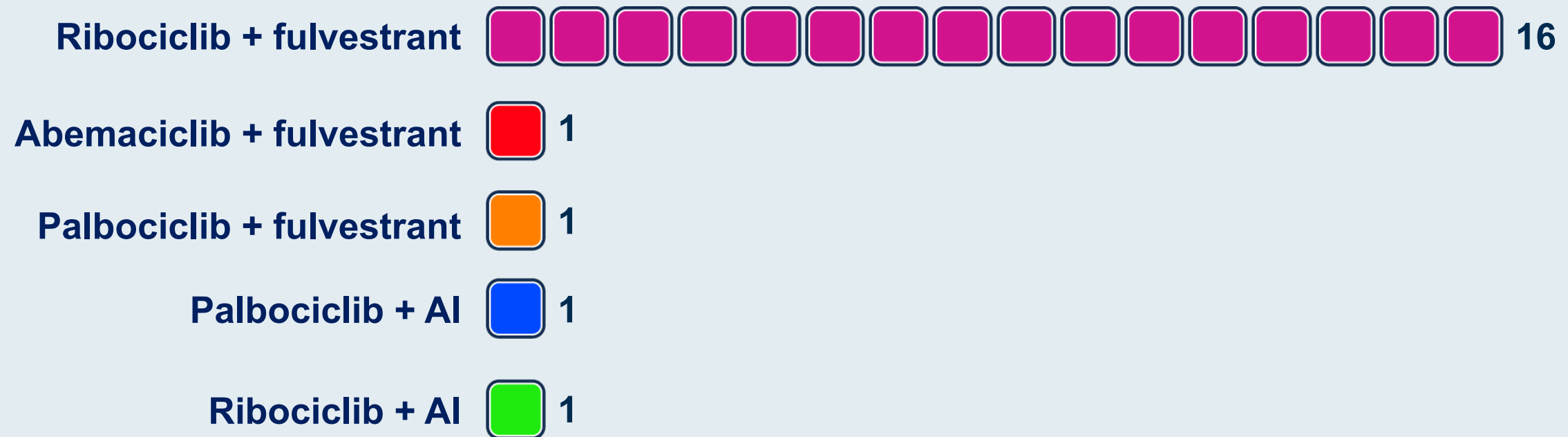
Multiple asymptomatic brain metastases that require WBRT



A woman who is receiving anastrozole (with ovarian suppression/ablation if needed) for lower-grade ER-positive, PR-negative, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after starting adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0

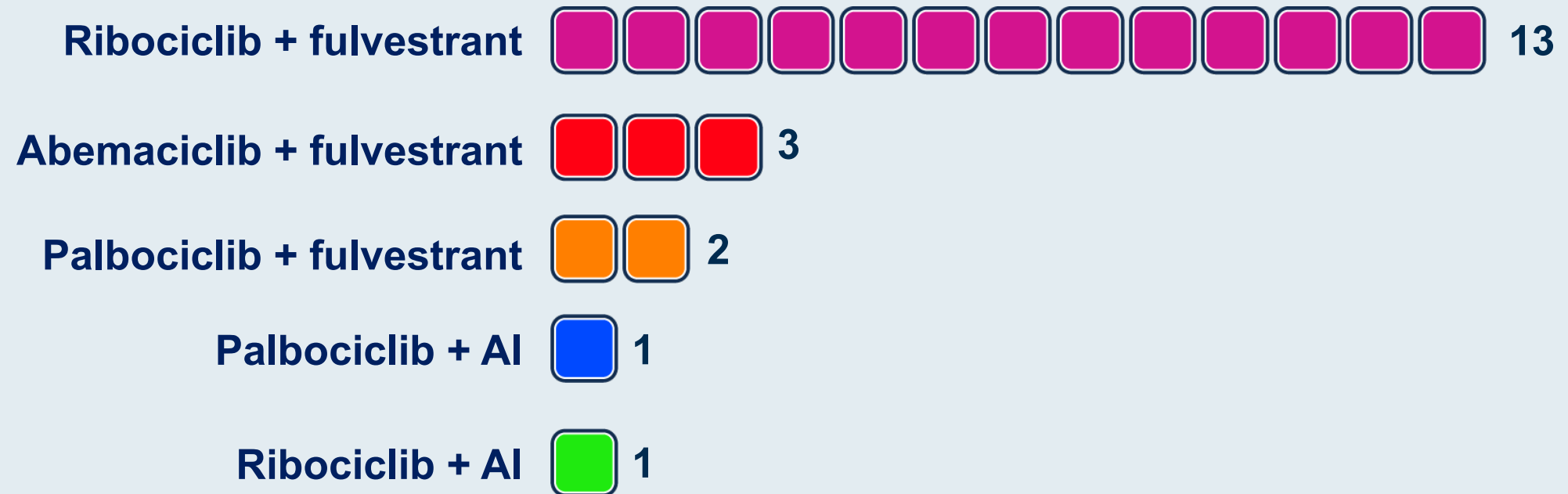
Asymptomatic bone metastases



A woman who is receiving anastrozole (with ovarian suppression/ablation if needed) for lower-grade ER-positive, PR-negative, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after starting adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0

Symptomatic visceral (including liver) metastases



A woman who is receiving anastrozole (with ovarian suppression/ablation if needed) for lower-grade ER-positive, PR-negative, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after starting adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0

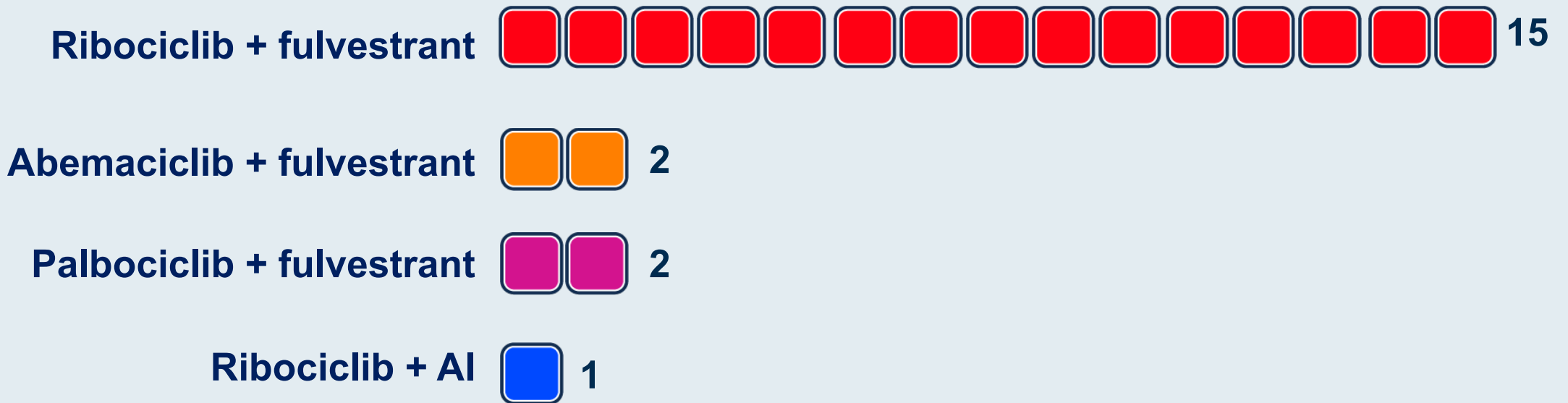
Multiple asymptomatic brain metastases that require WBRT



A woman who is receiving anastrozole (with ovarian suppression/ablation if needed) for high-grade ER-positive, PR-negative, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after starting adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0

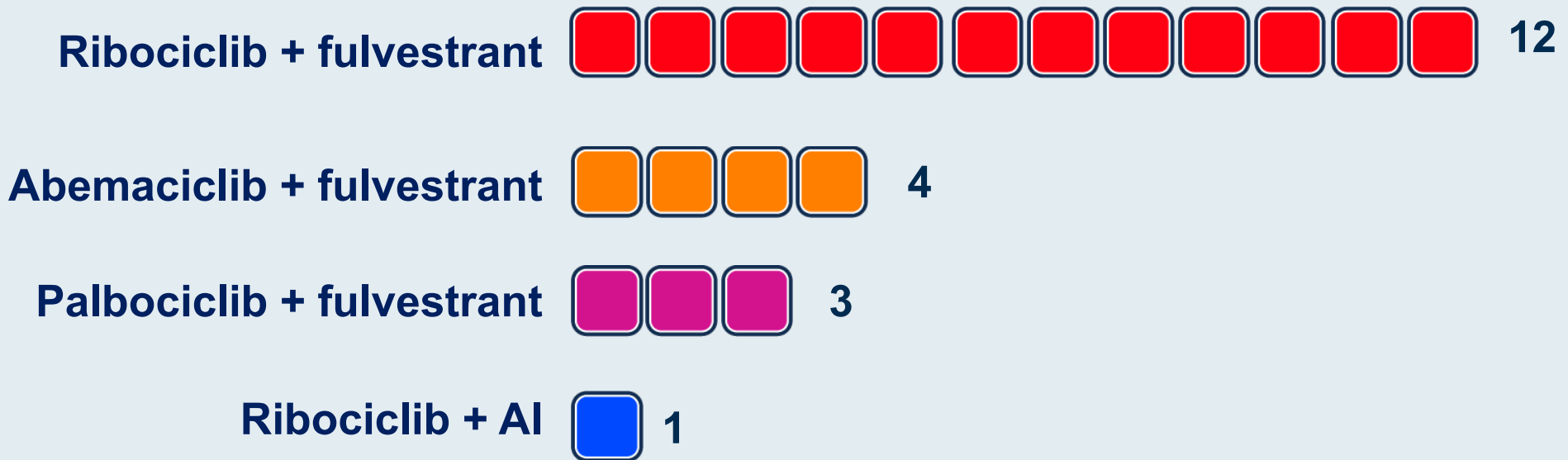
Asymptomatic bone metastases



A woman who is receiving anastrozole (with ovarian suppression/ablation if needed) for high-grade ER-positive, PR-negative, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after starting adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0

Symptomatic visceral (including liver) metastases



A woman who is receiving anastrozole (with ovarian suppression/ablation if needed) for high-grade ER-positive, PR-negative, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after starting adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

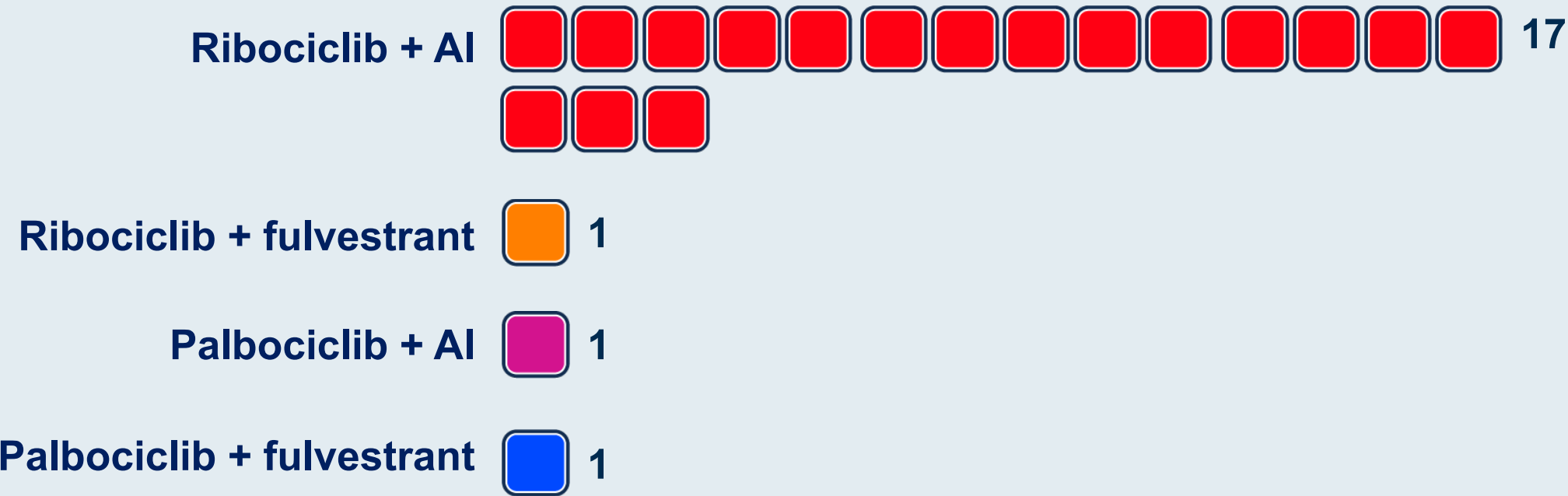
Age 65, PS 0

Multiple asymptomatic brain metastases that require WBRT



A woman who received 5 years of anastrozole (with ovarian suppression/ablation if needed) for lower-grade ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after completing adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0  
Asymptomatic bone metastases



A woman who received 5 years of anastrozole (with ovarian suppression/ablation if needed) for lower-grade ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after completing adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0

Symptomatic visceral (including liver) metastases



A woman who received 5 years of anastrozole (with ovarian suppression/ablation if needed) for lower-grade ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after completing adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

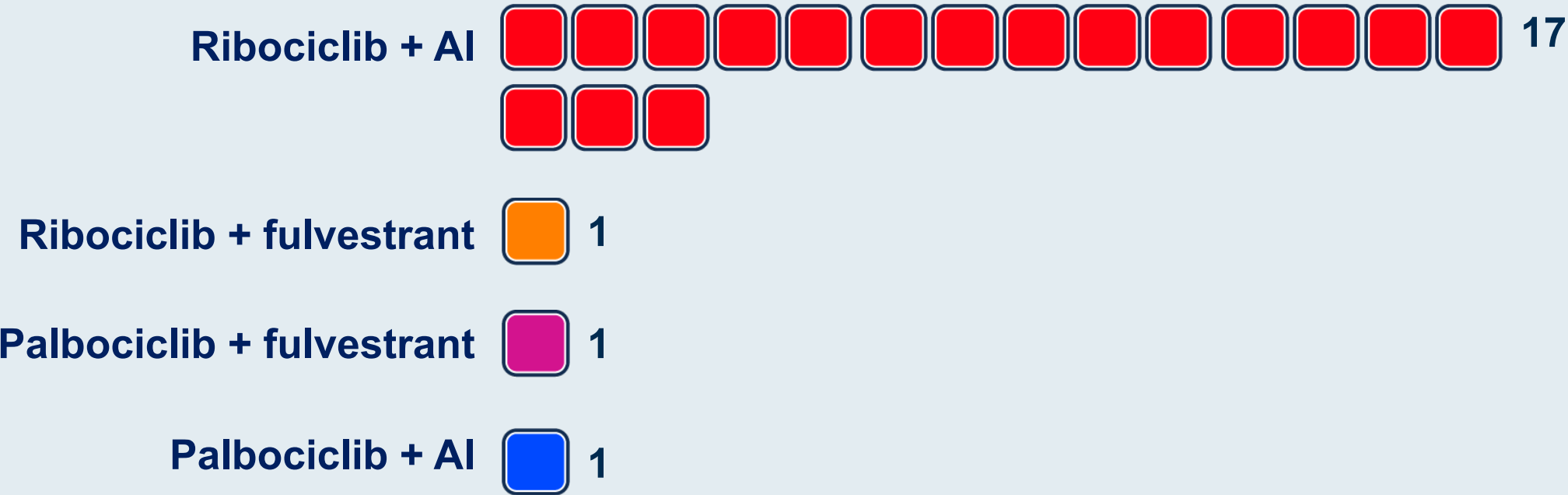
Age 65, PS 0

Multiple asymptomatic brain metastases that require WBRT



A woman who received 5 years of anastrozole (with ovarian suppression/ablation if needed) for lower-grade ER-positive, PR-negative, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after completing adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0  
Asymptomatic bone metastases



A woman who received 5 years of anastrozole (with ovarian suppression/ablation if needed) for lower-grade ER-positive, PR-negative, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after completing adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0

Symptomatic visceral (including liver) metastases



A woman who received 5 years of anastrozole (with ovarian suppression/ablation if needed) for lower-grade ER-positive, PR-negative, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after completing adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

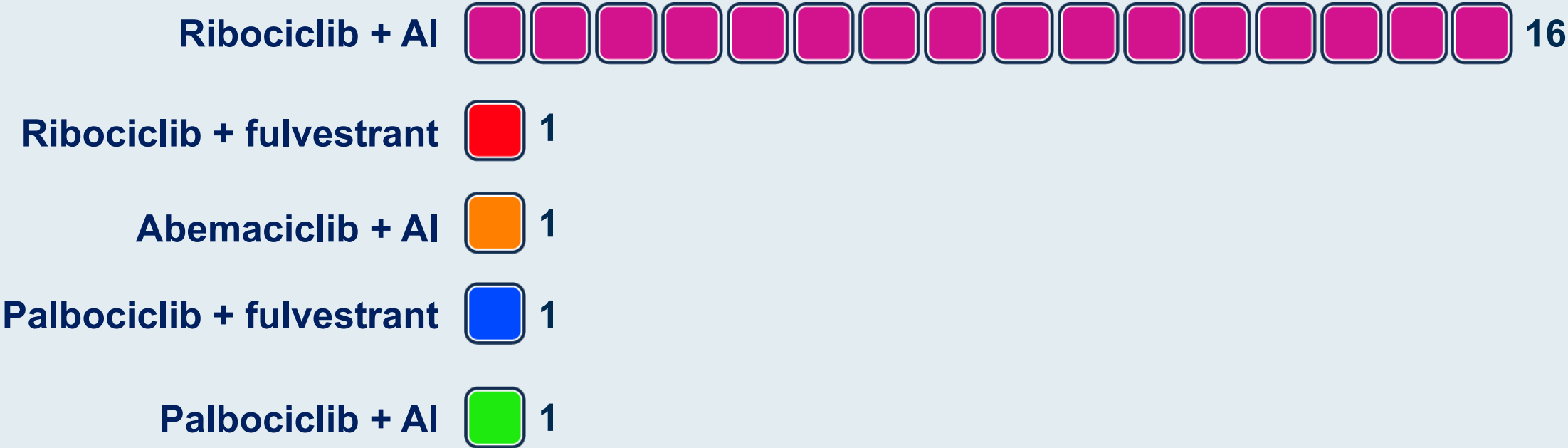
Age 65, PS 0

Multiple asymptomatic brain metastases that require WBRT



A woman who received 5 years of anastrozole (with ovarian suppression/ablation if needed) for high-grade ER-positive, PR-negative, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after completing adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0  
Asymptomatic bone metastases



A woman who received 5 years of anastrozole (with ovarian suppression/ablation if needed) for high-grade ER-positive, PR-negative, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after completing adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0

Symptomatic visceral (including liver) metastases



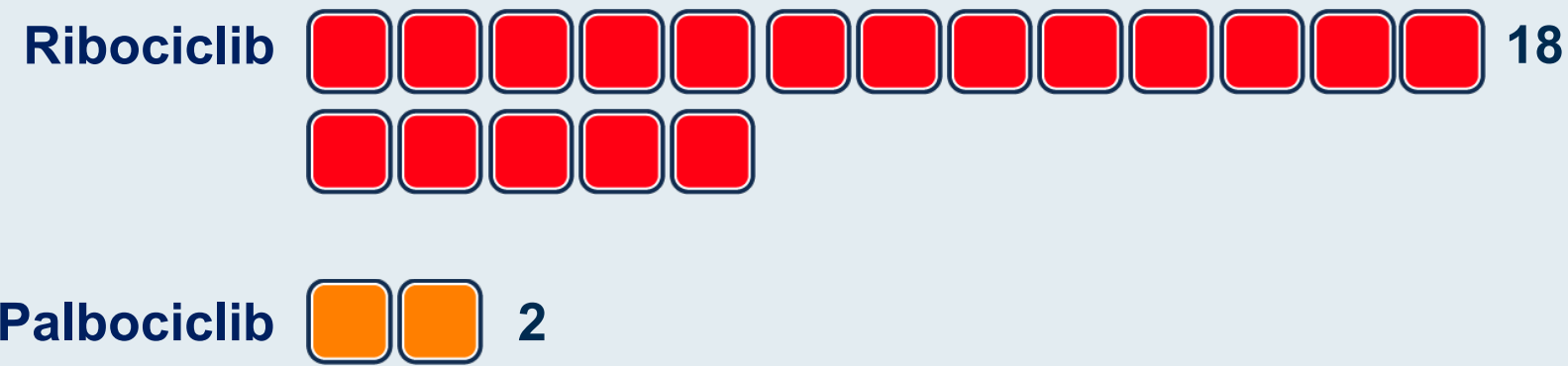
A woman who received 5 years of anastrozole (with ovarian suppression/ablation if needed) for high-grade ER-positive, PR-negative, HER2-negative, BRCA WT breast cancer develops metastatic disease 2 years after completing adjuvant therapy. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0

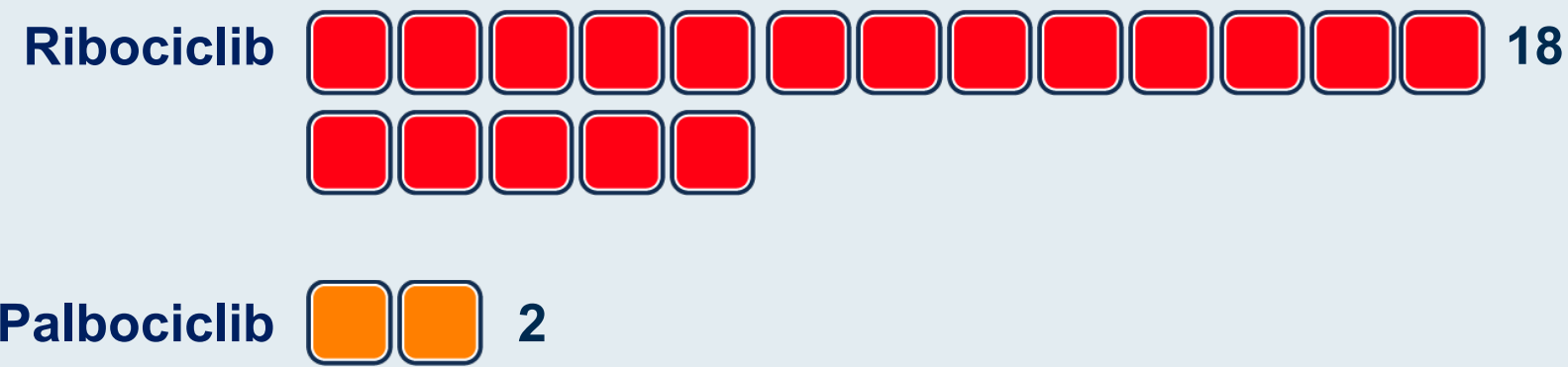
Multiple asymptomatic brain metastases that require WBRT



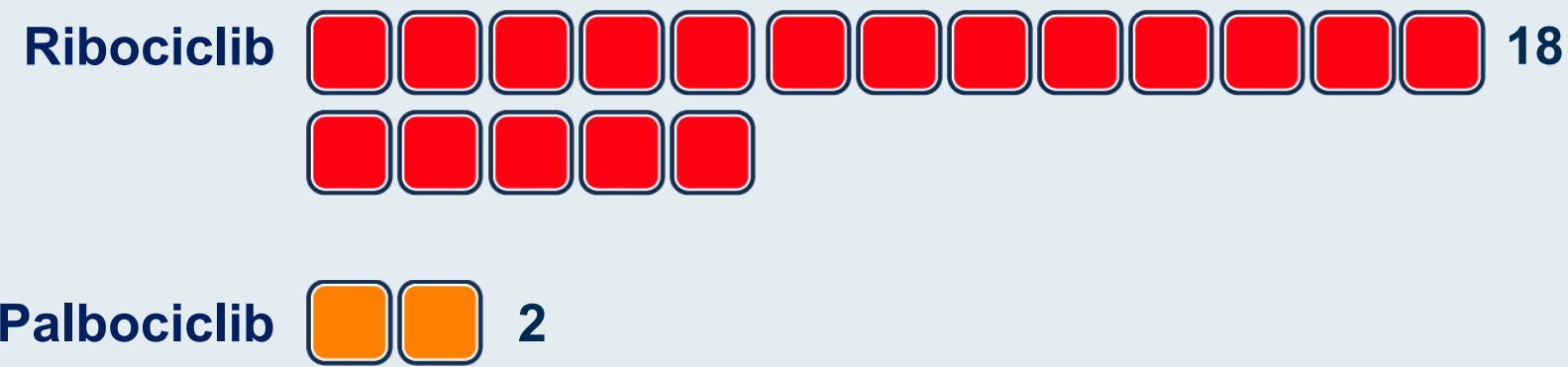
In general, which CDK4/6 inhibitor are you most likely to recommend in combination with endocrine therapy for a premenopausal patient with ER-positive, PR-positive, HER2-negative, BRCA WT metastatic breast cancer?



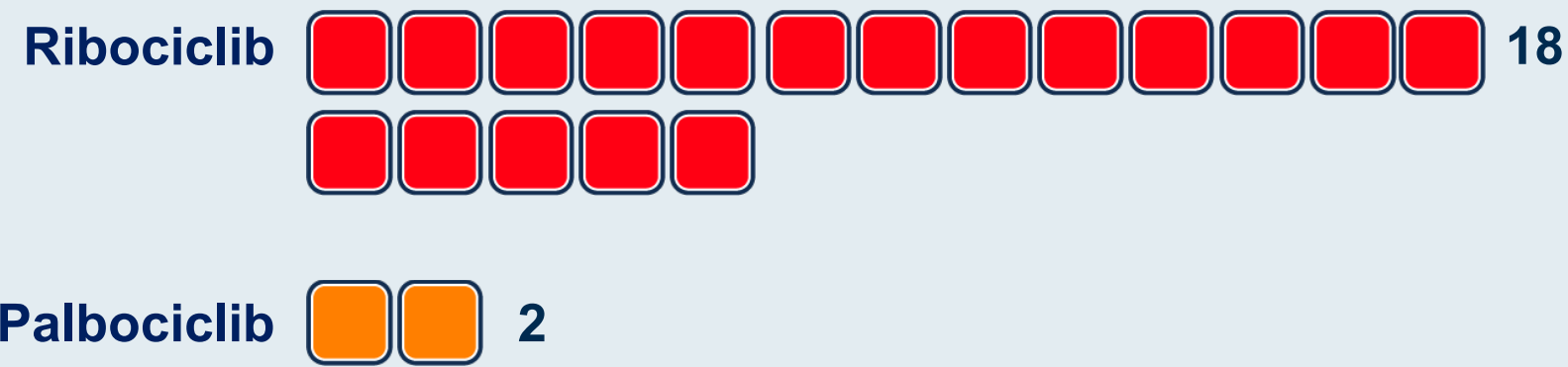
In general, which CDK4/6 inhibitor are you most likely to recommend in combination with endocrine therapy for a premenopausal patient with ER-positive, PR-negative, HER2-negative, BRCA WT metastatic breast cancer?



In general, which CDK4/6 inhibitor are you most likely to recommend in combination with endocrine therapy for a postmenopausal patient with ER-positive, PR-positive, HER2-negative, BRCA WT metastatic breast cancer?



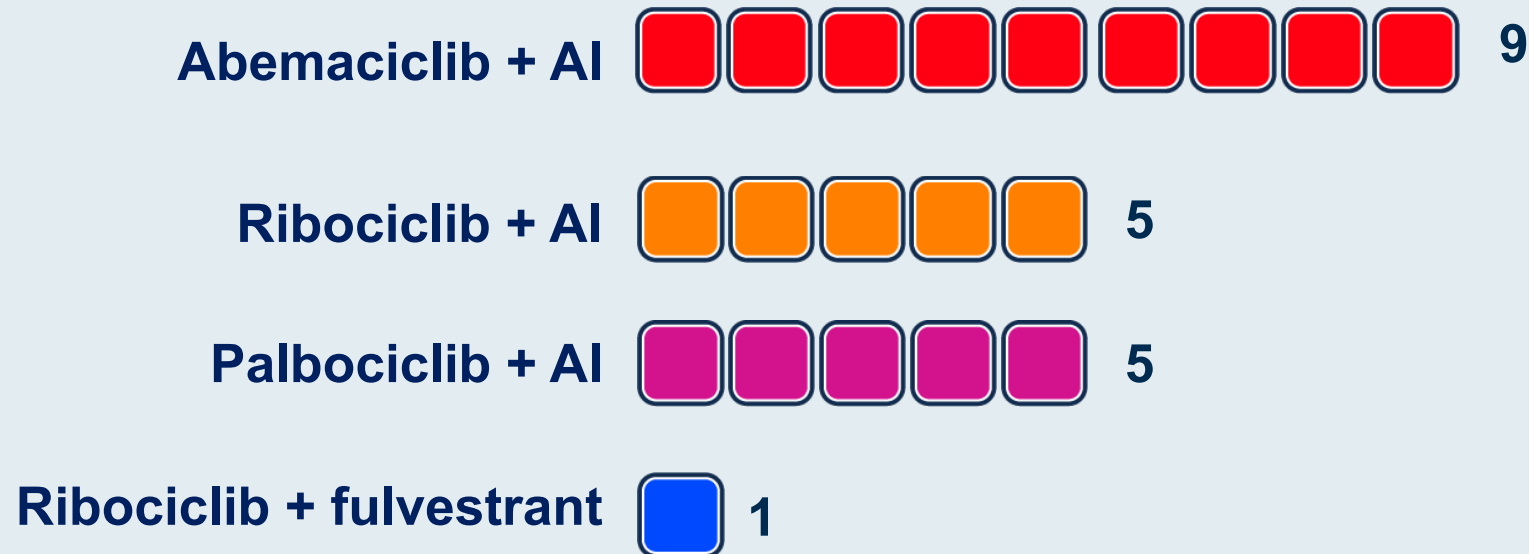
In general, which CDK4/6 inhibitor are you most likely to recommend in combination with endocrine therapy for a postmenopausal patient with ER-positive, PR-negative, HER2-negative, BRCA WT metastatic breast cancer?



A 65-year-old woman with a history of bone marrow suppression due to chronic heavy alcohol use who received 5 years of anastrozole for high-grade ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer develops visceral (including liver) metastases 2 years after completing adjuvant therapy. Which endocrine-based treatment would you most likely recommend?



A 65-year-old woman with a history of myocardial infarction 3 months ago presents with de novo ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer with symptomatic visceral (including liver) metastases. Which endocrine-based treatment would you most likely recommend?



A 65-year-old woman who received 5 years of anastrozole for high-grade ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer with a history of inflammatory bowel disease with constipation develops visceral metastases 2 years after completing adjuvant therapy. Which endocrine-based treatment would you most likely recommend?



**A 65-year-old woman who is receiving ribociclib in combination with an AI for de novo ER-positive, PR-negative, HER2-negative, BRCA WT metastatic breast cancer develops abnormal LFTs 6 months after initiating therapy. What would be your most likely endocrine-based treatment approach?**

**Continue ribociclib at a lower dose and continue AI**  **11**

**Switch to palbociclib and continue AI**  **4**

**Switch to abemaciclib and continue AI**  **2**

**Temporarily hold ribociclib until LFTs resolve; restart at lower dose with AI**  **2**

A 65-year-old woman who received 2 years of adjuvant abemaciclib in combination with endocrine therapy for high-risk node-positive, ER-positive, PR-negative, HER2-negative, BRCA WT breast cancer develops visceral metastases 18 months after completing treatment. Which endocrine-based treatment would you most likely recommend?



**A 65-year-old woman who is receiving ribociclib in combination with an AI for de novo ER-positive, PR-negative, HER2-negative, BRCA WT metastatic breast cancer develops QTc interval prolongation 6 months after initiating therapy. What would be your most likely endocrine-based treatment approach?**

**Switch to palbociclib and continue AI**  **7**

**Switch to abemaciclib and continue AI**  **7**

**Continue ribociclib at a lower dose and continue AI**  **3**

**Temporarily hold ribociclib for 1 week; restart at lower dose if improvement**  **1**

A 65-year-old woman who is receiving ribociclib in combination with an AI for de novo ER-positive, PR-positive, HER2-negative, BRCA WT metastatic breast cancer develops asymptomatic moderate neutropenia (ANC = 750/ $\mu$ L) 6 months after initiating therapy. What would be your most likely endocrine-based treatment approach?

Continue ribociclib at a lower dose and continue AI  15

Continue ribociclib at same dose and continue AI  3

Temporarily hold ribociclib until neutropenia improves; restart at same dose  1

Temporarily hold ribociclib until neutropenia improves; restart at reduced dose  1

A 65-year-old woman who is receiving ribociclib in combination with an AI for de novo ER-positive, PR-negative, HER2-negative, BRCA WT metastatic breast cancer develops asymptomatic moderate neutropenia (ANC = 750/ $\mu$ L) 6 months after initiating therapy. What would be your most likely endocrine-based treatment approach?

Continue ribociclib at a lower dose and continue AI  15

Continue ribociclib at same dose and continue AI  3

Temporarily hold ribociclib until neutropenia improves; restart at same dose  1

Temporarily hold ribociclib until neutropenia improves; restart at reduced dose  1

Approximately what proportion of patients receiving CDK4/6 inhibitors for ER-positive metastatic breast cancer do you anticipate will need treatment to be withheld or discontinued because of toxicity?

CDK4/6 inhibitor	% needing treatment withheld or discontinued Median (range)
Palbociclib	10% (5%-60%)
Abemaciclib	20% (5%-50%)
Ribociclib	15% (5%-5-%)

**Approximately what proportion of patients receiving CDK4/6 inhibitors for ER-positive metastatic breast cancer do you anticipate will require a dose reduction or delay due to toxicity?**

<b>CDK4/6 inhibitor</b>	<b>% needing dose reduction or delay Median (range)</b>
Palbociclib	25% (5%-70%)
Abemaciclib	30% (15%-60%)
Ribociclib	28% (10%-60%)

# **In general, how do you and your team monitor adherence in patients who are receiving a CDK4/6 inhibitor in combination with oral endocrine therapy?**

- **Patient-reported compliance and pharmacy refill record reviewed at each f/u**
- **They are seen and have labs at cycle 1 day 1 and day 14, cycle 2 day 1 and day 14 and then monthly until month 6 to see how it goes. If things go smoothly, then we liberalize the visits**
- **We ask them if they are taking their meds**
- **We see patients every 2 weeks for 2 months then monthly thereafter until patient is very comfortable with safety and efficacy of the ET + CDK 4/6 inhibitor, then we see patient every 2 months thereafter**
- **Very involved outpatient pharmacist**
- **Taking a history and monitoring refill intervals**
- **Through clinical assessment and labs**
- **Question. Pill bottle return**
- **Can assess MCV as a biomarker of whether CDK4/6 inhibitors are being used. For ribociclib and palbociclib, assess neutropenia**

# **In general, how do you and your team monitor adherence in patients who are receiving a CDK4/6 inhibitor in combination with oral endocrine therapy? (Continued)**

- **Generally discuss plans/strategies for adherence up front, and then ask them at f/u visits if they are missing doses**
- **We monitor prescription refills and ask patients**
- **Typically bimonthly visits x 2m with labs; if stable, transition to monthly x ~6m; then continue to see with labs at least every 6-8w once stable long-term**
- **Partner with APP, specialty pharmacy team to confirm dosing/refill schedule/adherence; regular question and follow-up about how taking/if missed doses**
- **Pharmacist monitors**
- **Instruct patients to bring pill bottles to each visit. Ask how many doses missed since last visit**
- **Patient history**
- **Discuss at monthly visit**
- **Monitoring at hospital visits (no monitoring in between, unless the patient asks for it)**
- **Discussion with patients, monitoring of labs, monitoring of rx refills**
- **Ask patient in visits if they are taking medication**