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# Inavolisib or placebo in combination with palbociclib and fulvestrant in patients with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer: Phase III INAVO120 primary analysis

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## Disclosure information

### Komal Jhaveri

I have the following relevant financial relationships to disclose:

Consultant/advisory board role in Novartis, Pfizer, Taiho Oncology, Genentech, AbbVie, Eisai, Astra Zeneca, Blueprint Medicine, Daiichi Sankyo, Sun Pharma Advanced Research Company Ltd, Menarini/Stemline, Gilead, Scorpion Therapeutics, Lilly/Loxo Oncology, and Zymeworks.

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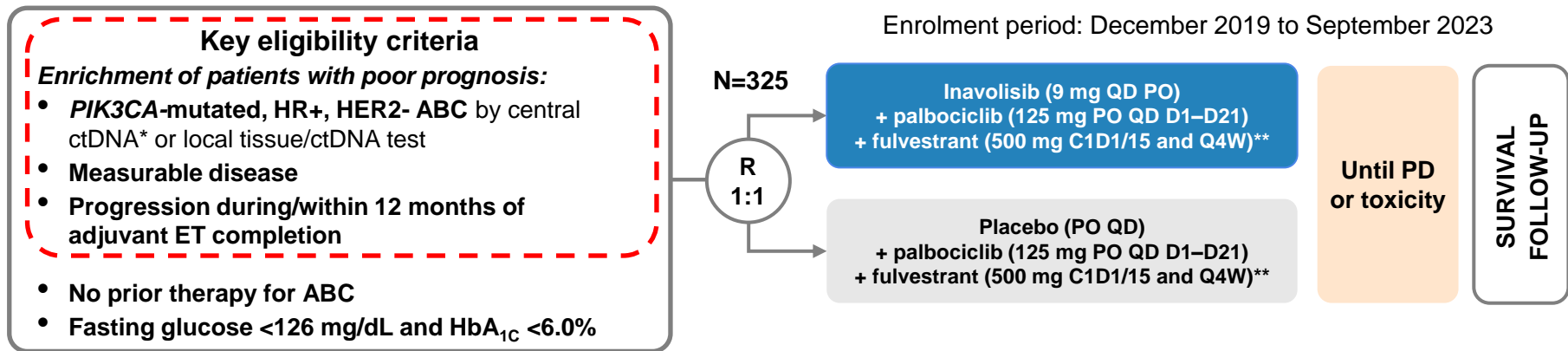
The INAVO120 study is sponsored by F. Hoffmann-La Roche Ltd.

# Background

- More effective treatments for patients with *PIK3CA*-mutated, HR+, HER2- ABC are needed<sup>1</sup>
- PI3K $\alpha$  inhibitors to date have faced challenges with safety and tolerability<sup>2,3</sup>
- Inavolisib is a highly potent and selective PI3K $\alpha$  inhibitor that also promotes the degradation of mutant p110 $\alpha$ , which may improve the therapeutic window<sup>4,5</sup>
- Preclinical data demonstrated substantial synergy between PI3K and CDK4/6 inhibition with ET in *PIK3CA*-mutated xenograft models by deepening responses and blocking routes to resistance<sup>4,6,7</sup>
- Clinically, in a Phase I study (NCT03006172), the triplet of inavolisib, palbociclib and fulvestrant had a manageable safety profile, lacked DDI, and demonstrated promising preliminary antitumor activity in *PIK3CA*-mutated, HR+, HER2- ABC<sup>6</sup>
- INAVO120 (NCT04191499) is a Phase III, randomized, double-blind, placebo-controlled study that assessed inavolisib or placebo with palbociclib + fulvestrant in patients with *PIK3CA*-mutated, HR+, HER2- ABC who recurred on or within 12 months of adjuvant ET

1. Cardoso F, et al. *Ann Oncol* 2020;**31**:1623–1649; 2. André F, et al. *N Eng J Med* 2019;**380**:1929–19:40; 3. Dent S, et al. *Ann Oncol* 2021;**32**:197–207; 4. Hong R, et al. SABCS 2017 (Poster PD4-14); 5. Edgar K, et al. SABCS 2019 (Poster P3-11-23); 6. Herrera-Abreu MT, et al. *Cancer Res* 2016;**76**:2301–2313; 7. Vora SR, et al. *Cancer Cell* 2014;**26**:136–149; 8. Bedard P, et al. SABCS 2020 (Poster PD1-02). ABC, advanced breast cancer; DDI, drug–drug interaction.

# INAVO120 study design



## Stratification factors:

- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)<sup>†</sup>
- Region (North America/Western Europe; Asia; Other)

## Endpoints

- Primary: PFS by Investigator
- Secondary: OS<sup>‡</sup>, 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). <sup>†</sup> Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.<sup>1</sup> 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. <sup>‡</sup> 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.

# Statistical considerations

- **Primary endpoint (investigator-assessed PFS)**
  - Two-sided log-rank test at the 0.05 level of significance
  - Primary analysis was planned after approximately 194 events
  - 85% power to detect a hazard ratio of 0.65
  
- **Key secondary endpoint (OS)**
  - OS is hierarchically tested if PFS is significant
  - Interim analysis of OS was planned at primary PFS analysis (prespecified boundary:  $p=0.0098$ )
  - Final OS analysis is planned after approximately 153 events

OS, overall survival; PFS, progression-free survival.

## Demographics and baseline disease characteristics

	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)		Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
<b>Age (year)</b>			<b>Number of organ sites, n (%)</b>		
Median	53.0	54.5	1	21 (13.0)	32 (19.5)
Min–Max	27–77	29–79	2	59 (36.6)	46 (28.0)
<b>Sex, n (%)</b>			≥3	81 (50.3)	86 (52.4)
Female	156 (96.9)	163 (99.4)	<b>Visceral disease, n (%)*</b>	132 (82.0)	128 (78.0)
<b>Race, n (%)</b>			Liver	77 (47.8)	91 (55.5)
Asian	61 (37.9)	63 (38.4)	Lung	66 (41.0)	66 (40.2)
Black or African American	1 (0.6)	1 (0.6)	Bone only†	5 (3.1)	6 (3.7)
White	94 (58.4)	97 (59.1)	<b>ER‡ and PgR status, n (%)</b>		
<b>ECOG PS, n (%)</b>			ER+/PgR+	113 (70.2)	113 (68.9)
0	100 (62.1)	106 (64.6)	ER+/PgR-	45 (28.0)	45 (27.4)
1	60 (37.3)	58 (35.4)	<b>Endocrine resistance, n (%)**</b>		
<b>Menopausal status at randomization, n (%)</b>			Primary	53 (32.9)	58 (35.4)
Premenopausal	65 (40.4)	59 (36.0)	Secondary	108 (67.1)	105 (64.0)
Postmenopausal	91 (56.5)	104 (63.4)			

301 (92.6%) pts were enrolled per ctDNA testing (284 [94.4%] central, 17 [5.6%] local) and 24 (7.4%) were enrolled per local tissue testing

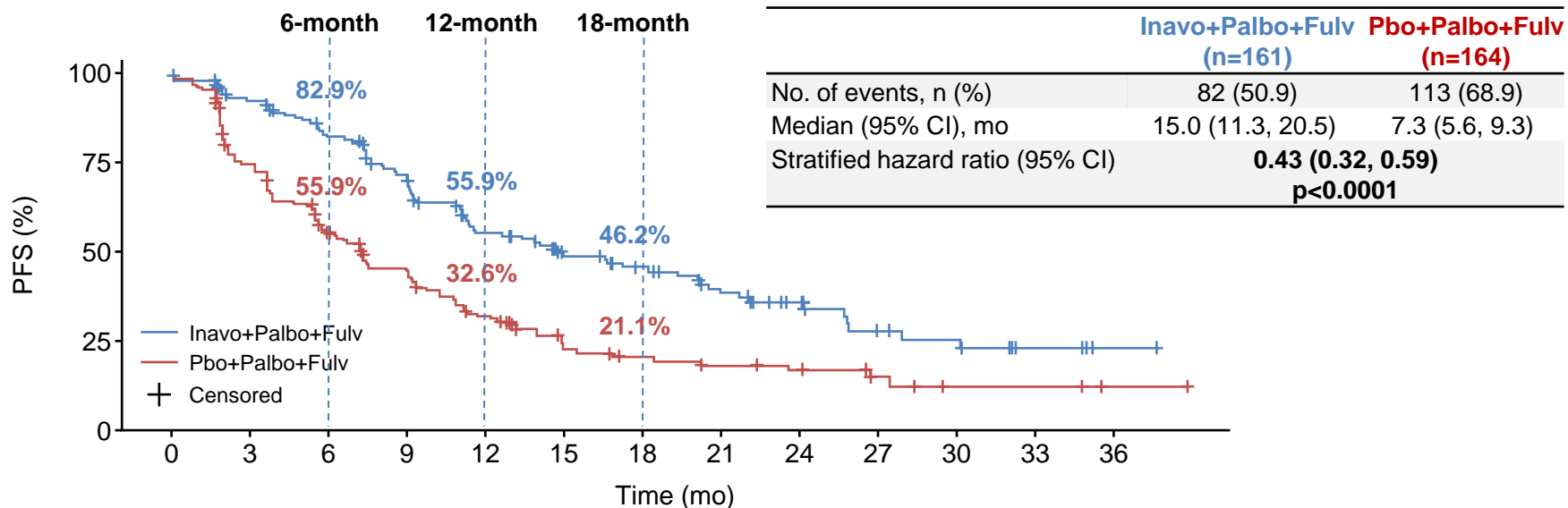
\* "Visceral" (yes/no) refers to lung, liver, brain, pleural, and peritoneal involvement; † Patients with evaluable bone-only disease were not eligible; patients with disease limited to the bone but with lytic or mixed lytic/blastic lesions, and at least one measurable soft-tissue component per RECIST 1.1, may be eligible. ‡ Defined as 10% per ASCO-CAP guidelines. \*\* Endocrine resistance was defined per 4th ESO-[ESMO] International Consensus Guidelines for Advanced Breast Cancer. Primary resistance: Relapse while on the first 2 years of adjuvant endocrine therapy. Secondary resistance: Relapse while on adjuvant endocrine therapy after at least 2 years or relapse within 12 months of completing adjuvant endocrine therapy. ECOG PS, Eastern Cooperative Oncology Group Performance Status; ER, estrogen receptor, Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo; PgR, progesterone receptor; RECIST, Response Evaluation Criteria in Solid Tumors.

## Prior therapy

	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
<b>Prior (neo)adjuvant chemotherapy, n (%)</b>		
Yes	132 (82.0)	137 (83.5)
<b>Prior (neo)adjuvant endocrine therapy, n (%)</b>		
Yes	160 (99.4)	163 (99.4)
Aromatase inhibitor only	60 (37.3)	71 (43.3)
Tamoxifen only	82 (50.9)	73 (44.5)
Aromatase inhibitor and tamoxifen	18 (11.2)	19 (11.6)
<b>Prior adjuvant CDK4/6 inhibitor, n (%)</b>		
Yes	3 (1.9)	1 (0.6)

CDK4/6, cyclin-dependent kinase 4 and 6; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

# Primary endpoint: PFS (investigator-assessed)



Patients at risk:

Inavo+Palbo+Fulv  
Pbo+Palbo+Fulv

161	134	111	92	66	48	41	31	22	13	11	5	1
164	113	77	59	40	23	19	16	12	6	3	3	1

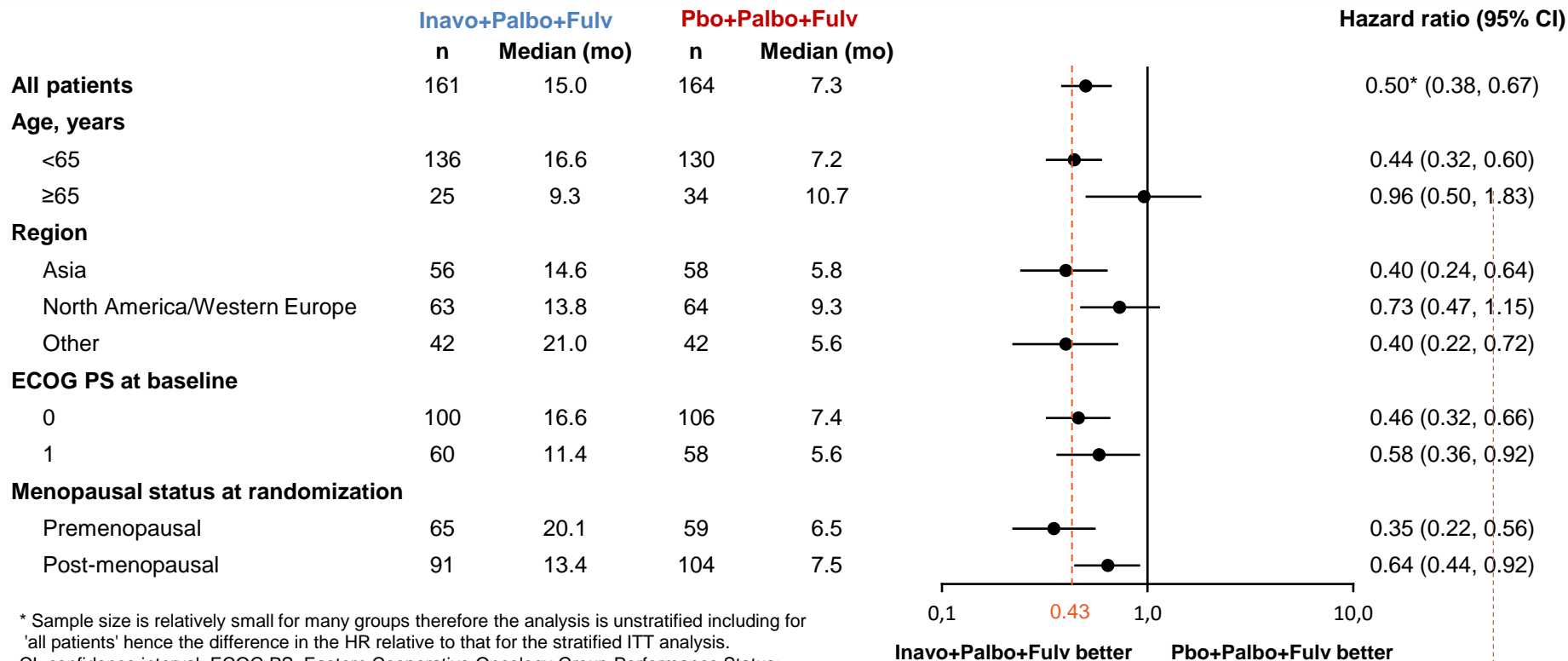
Median follow-up:  
**21.3 months**

CCOD: 29th September 2023

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.



## PFS (investigator-assessed) in key subgroups 1/2

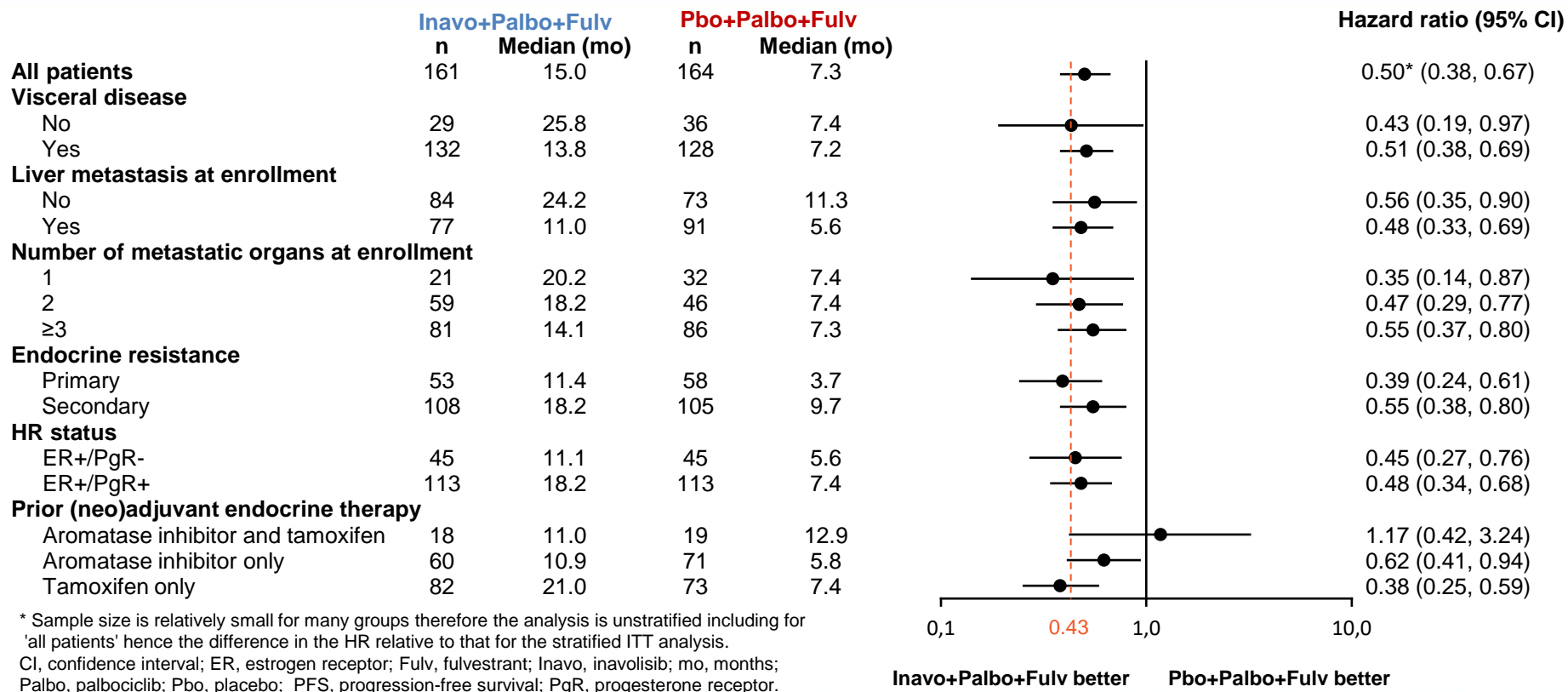


\* Sample size is relatively small for many groups therefore the analysis is unstratified including for 'all patients' hence the difference in the HR relative to that for the stratified ITT analysis.

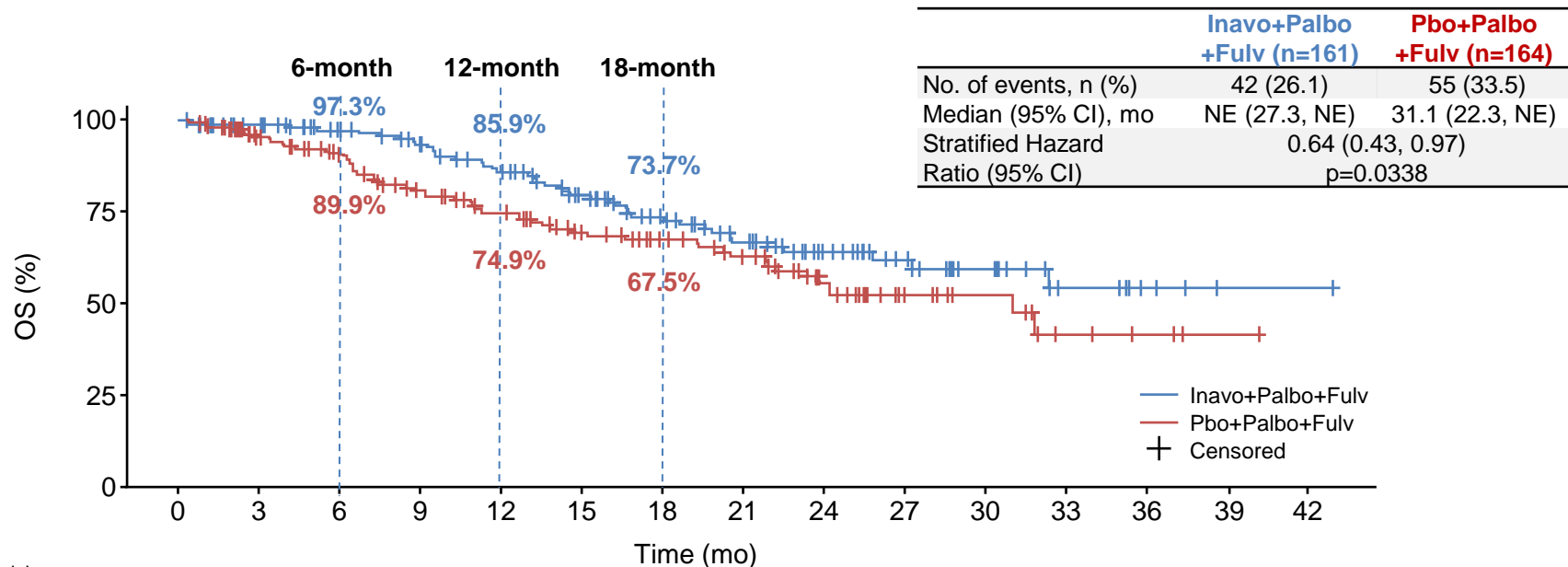
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status;

Fulv, fulvestrant; Inavo, inavolisib; mo, months, Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

## PFS (investigator-assessed) in key subgroups 2/2



## Key secondary endpoint: Overall survival (interim analysis)



Patients at risk:

Inavo+Palbo+Fulv

Pbo+Palbo+Fulv

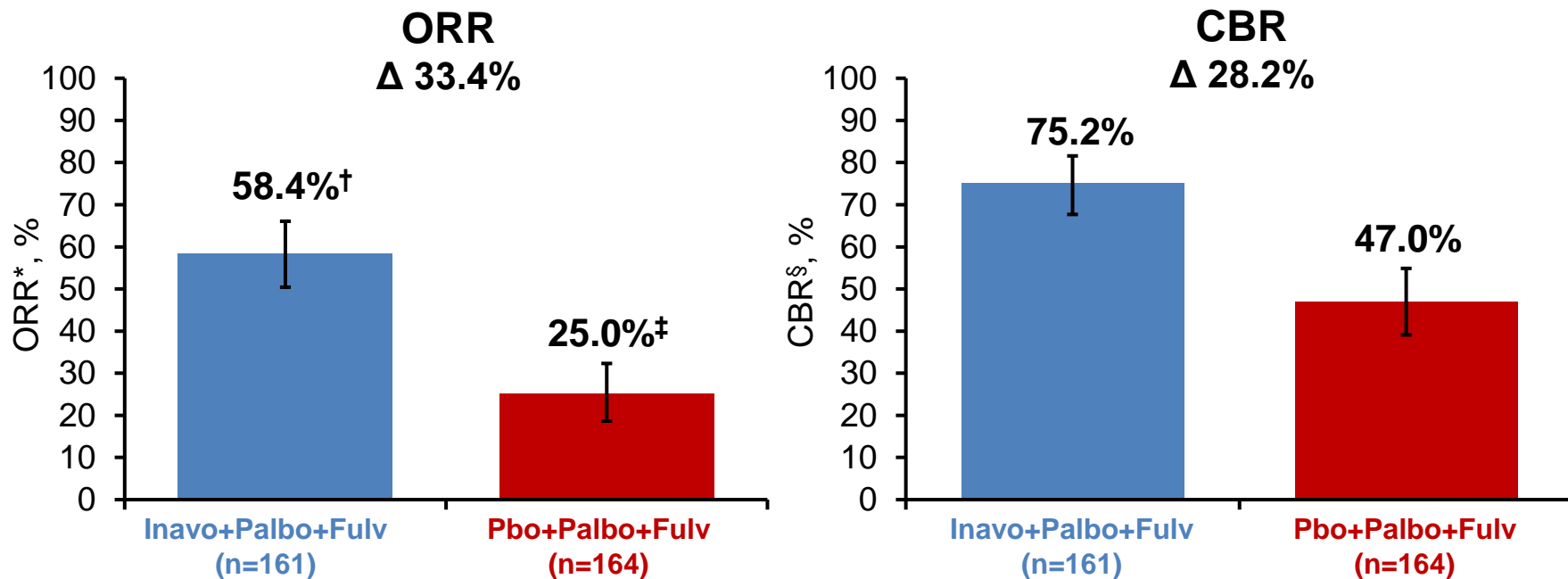
161	143	127	114	101	85	69	56	38	26	17	8	4	1	1
164	139	120	98	87	72	61	52	33	19	11	5	3	1	0

Median follow-up:  
**21.3 months**

The pre-specified boundary for OS (p of 0.0098 or HR of 0.592) was not crossed at this interim analysis

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; NE, not estimable; OS, overall survival; Palbo, palbociclib; Pbo, placebo.

## Secondary endpoints: ORR and CBR (investigator-assessed)



\* Patients with a CR or PR on two consecutive occasions  $\geq 4$  weeks apart per RECIST v1.1. † Seven patients with CR, 87 patients with PR. ‡ One patient with CR, 40 patients with PR, 79 patients with SD, 34 patients with PD, and 10 with missing status. § Patients with a CR, PR, and/or SD for  $\geq 24$  weeks per RECIST v1.1. CBR, clinical benefit rate; CR, complete response; Fulv, fulvestrant; Inavo, inavolisib; ORR, objective response rate; Palbo, palbociclib; Pbo, placebo; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

# Adverse events with any grade AEs $\geq$ 20% incidence in either treatment group

Adverse Events	Inavo+Palbo+Fulv (N=162)		Pbo+Palbo+Fulv (N=162)	
	All Grades	Grade 3–4	All Grades	Grade 3–4
<b>Neutropenia</b>	<b>144 (88.9%)</b>	<b>130 (80.2%)</b>	<b>147 (90.7%)</b>	<b>127 (78.4%)</b>
Thrombocytopenia	78 (48.1%)	23 (14.2%)	73 (45.1%)	7 (4.3%)
<b>Stomatitis/Mucosal inflammation</b>	<b>83 (51.2%)</b>	<b>9 (5.6%)</b>	<b>43 (26.5%)</b>	<b>0</b>
Anemia	60 (37.0%)	10 (6.2%)	59 (36.4%)	3 (1.9%)
<b>Hyperglycemia</b>	<b>95 (58.6%)</b>	<b>9 (5.6%)</b>	<b>14 (8.6%)</b>	<b>0</b>
<b>Diarrhea</b>	<b>78 (48.1%)</b>	<b>6 (3.7%)</b>	<b>26 (16.0%)</b>	<b>0</b>
<b>Nausea</b>	<b>45 (27.8%)</b>	<b>1 (0.6%)</b>	<b>27 (16.7%)</b>	<b>0</b>
<b>Rash</b>	<b>41 (25.3%)</b>	<b>0</b>	<b>28 (17.3%)</b>	<b>0</b>
Decreased Appetite	38 (23.5%)	<2%	14 (8.6%)	<2%
Fatigue	38 (23.5%)	<2%	21 (13.0%)	<2%
COVID-19	37 (22.8%)	<2%	17 (10.5%)	<2%
Headache	34 (21.0%)	<2%	22 (13.6%)	<2%
Leukopenia	28 (17.3%)	11 (6.8%)	40 (24.7%)	17 (10.5%)
Ocular Toxicities	36 (22.2%)	0	21 (13.0%)	0

Key AEs are shown in **bold**. AEs were assessed per CTCAE V5. Neutropenia, thrombocytopenia, stomatitis/mucosal inflammation, anemia, hyperglycemia, diarrhea, nausea and rash were assessed as medical concepts using grouped terms

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

## Overview of adverse events

Patients with ≥1 AE, n (%)	Inavo+Palbo+Fulv (n=162)	Pbo+Palbo+Fulv (n=162)
All, n (%)	160 (98.8%)	162 (100%)
Grade 3–4 AE	143 (88.3%)	133 (82.1%)
Grade 5 AE*	6 (3.7%)	2 (1.2%)
Serious AE	39 (24.1%)	17 (10.5%)
AEs leading to discontinuation of treatment	11 (6.8%)	1 (0.6%)
Inavolisib/Placebo	10 (6.2%)	1 (0.6%)
Palbociclib	8 (4.9%)	0
Fulvestrant	5 (3.1%)	0
AEs leading to dose modification/interruption of treatment	134 (82.7%)	121 (74.7%)
Inavolisib/Placebo	113 (69.8%)	57 (35.2%)
Palbociclib	125 (77.2%)	116 (71.6%)
Fulvestrant	52 (32.1%)	34 (21.0%)

AES were assessed per CTCAE V5

\* None of the grade 5 AEs were reported as related to study treatment by investigators. The grade 5 AEs reported were cerebral hemorrhage; cerebrovascular accident, gastrointestinal hemorrhage, acute coronary syndrome, death and COVID-19 in the inavo+palbo+fulv arm and COVID-19 pneumonia and cardiac arrest in the pbo+palbo+fulv arm.

AE, adverse event; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

## INAVO120 summary and conclusions

- Addition of inavolisib to palbociclib + fulvestrant demonstrated a **statistically significant and clinically meaningful improvement in PFS** in patients with *PIK3CA*-mutated, HR+, HER2- ABC who recurred on or within 12 months of adjuvant ET
  - Median PFS more than doubled from 7.3 to 15.0 mo, with a stratified **hazard ratio of 0.43** (95% CI 0.32, 0.59;  $p < 0.0001$ )
- **OS trend** at this first interim analysis: stratified **hazard ratio 0.64** (95% CI 0.43, 0.97)
- Inavolisib + palbociclib + fulvestrant had a **manageable safety profile**, consistent with the safety profiles of the individual drugs with no new safety signals and with a low discontinuation rate

**Inavolisib in combination with palbociclib and fulvestrant may represent a new standard of care for patients with *PIK3CA*-mutated, HR+, HER2- ABC**

ABC, advanced breast cancer; CI, confidence interval; mo, months; OS, overall survival; PFS, progression-free survival.