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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

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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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Background

- More effective treatments for patients with *PIK3CA*-mutated, HR+, HER2- ABC are needed[1]
- PI3Kα inhibitors to date have faced challenges with safety and tolerability[2,3]
- Inavolisib is a highly potent and selective PI3Kα inhibitor that also promotes the degradation of mutant p110α, which may improve the therapeutic window[4,5]
- 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[4,6,7]
- 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[6]
- 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

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2- ABC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**

- **No prior therapy for ABC**
- **Fasting glucose <126 mg/dL and HbA_{1C} <6.0%**

Enrolment period: December 2019 to September 2023

N=325

R 1:1

Inavolisib (9 mg QD PO) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Placebo (PO QD) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Until PD or toxicity

SURVIVAL FOLLOW-UP

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.

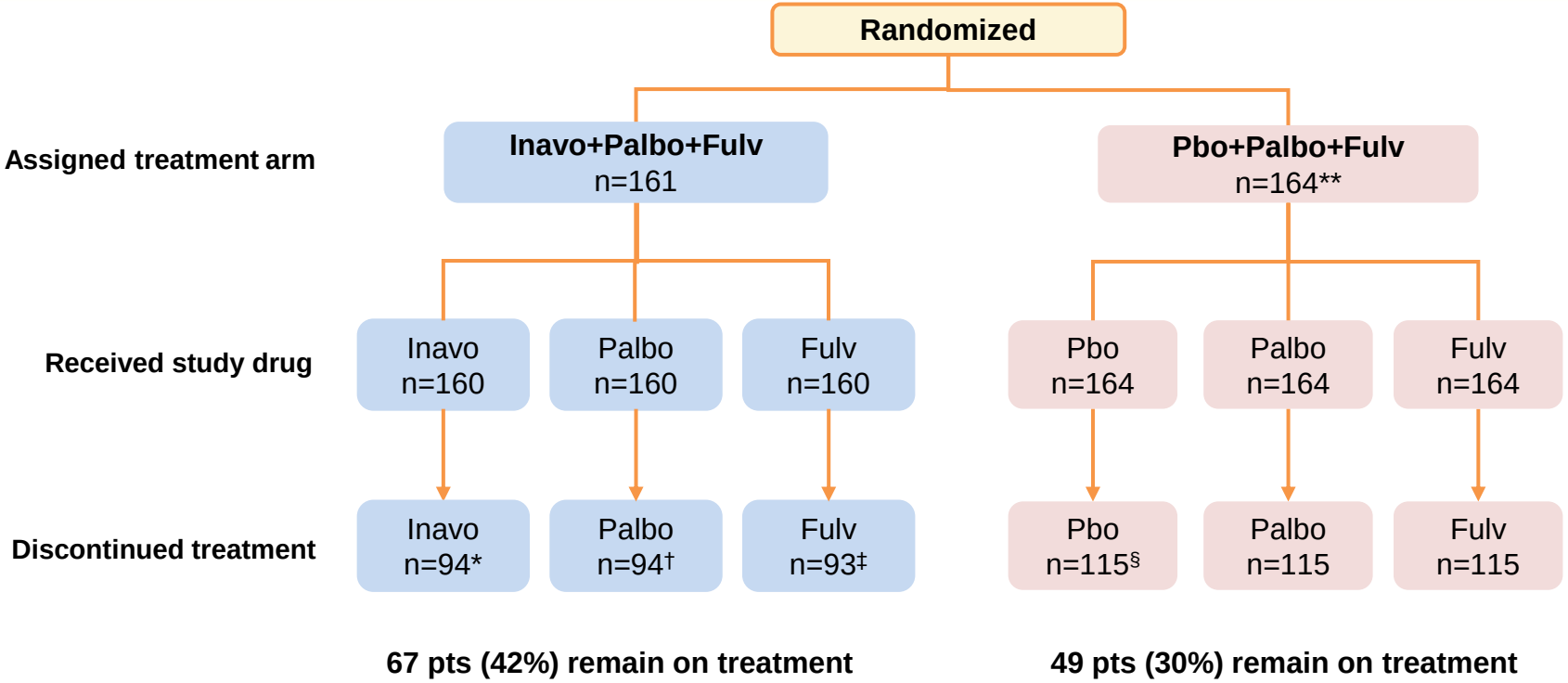
1. Cardoso F, *et al. Ann Oncol* 2018;**29:**1634–1657.

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.

Patient disposition



CCOD: 29th September 2023 * n=11 due to AEs; † n=8 due to AEs; ‡ n=5 due to AEs; § n=1 due to AEs; ** 2 patients received at least one dose of inavolisib meaning that for the safety population n=162.
AE, adverse event; Fulv, fulvestrant; Inavo, inavolisib; ITT, intention-to-treat; Palbo, palbociclib; Pbo, placebo.

Demographics and baseline disease characteristics

	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Age (year)		
Median	53.0	54.5
Min–Max	27–77	29–79
Sex, n (%)		
Female	156 (96.9)	163 (99.4)
Race, n (%)		
Asian	61 (37.9)	63 (38.4)
Black or African American	1 (0.6)	1 (0.6)
White	94 (58.4)	97 (59.1)
ECOG PS, n (%)		
0	100 (62.1)	106 (64.6)
1	60 (37.3)	58 (35.4)
Menopausal status at randomization, n (%)		
Premenopausal	65 (40.4)	59 (36.0)
Postmenopausal	91 (56.5)	104 (63.4)

	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Number of organ sites, n (%)		
1	21 (13.0)	32 (19.5)
2	59 (36.6)	46 (28.0)
≥3	81 (50.3)	86 (52.4)
Visceral disease, n (%)*	132 (82.0)	128 (78.0)
Liver	77 (47.8)	91 (55.5)
Lung	66 (41.0)	66 (40.2)
Bone only†	5 (3.1)	6 (3.7)
ER‡ and PgR status, n (%)		
ER+/PgR+	113 (70.2)	113 (68.9)
ER+/PgR-	45 (28.0)	45 (27.4)
Endocrine resistance, n (%)**		
Primary	53 (32.9)	58 (35.4)
Secondary	108 (67.1)	105 (64.0)

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

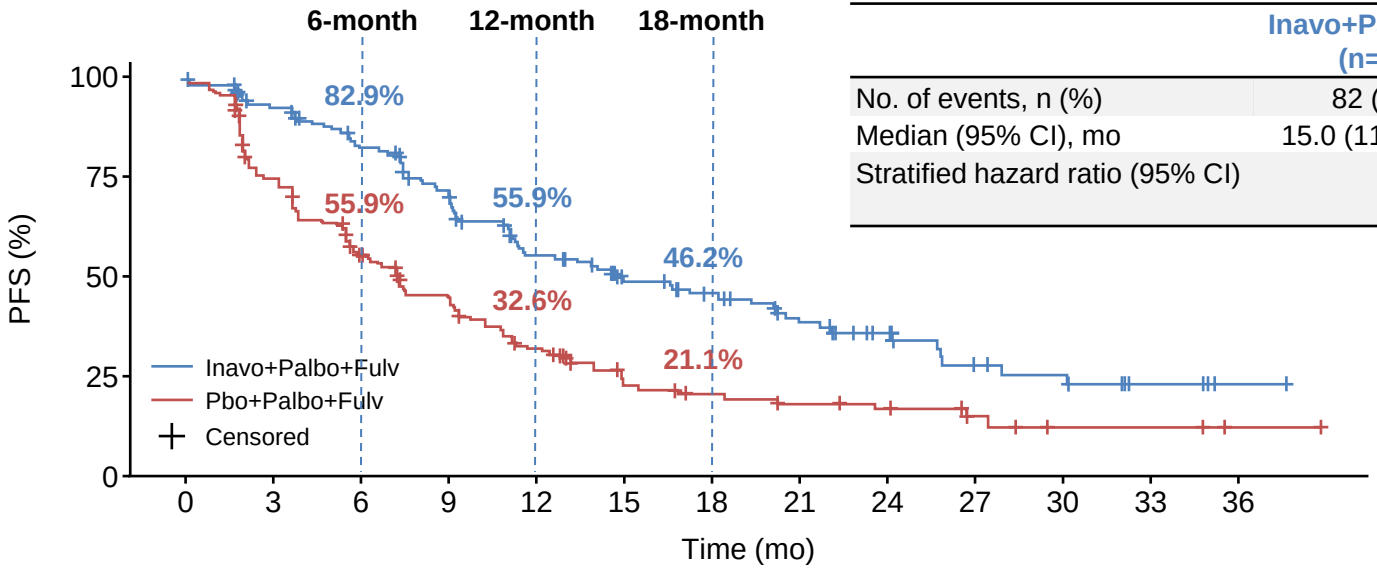
* "Visceral" (yes/no) refers to lung, liver, brain, pleural, and peritoneal involvement; † Patients with evaluable bone-only disease were not eligible; patients with disease limited to the bone but with lytic or mixed lytic/blastic lesions, and at least one measurable soft-tissue component per RECIST 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)
Prior (neo)adjuvant chemotherapy, n (%)		
Yes	132 (82.0)	137 (83.5)
Prior (neo)adjuvant endocrine therapy, n (%)		
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)
Prior adjuvant CDK4/6 inhibitor, n (%)		
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)



	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**	

Patients at risk:

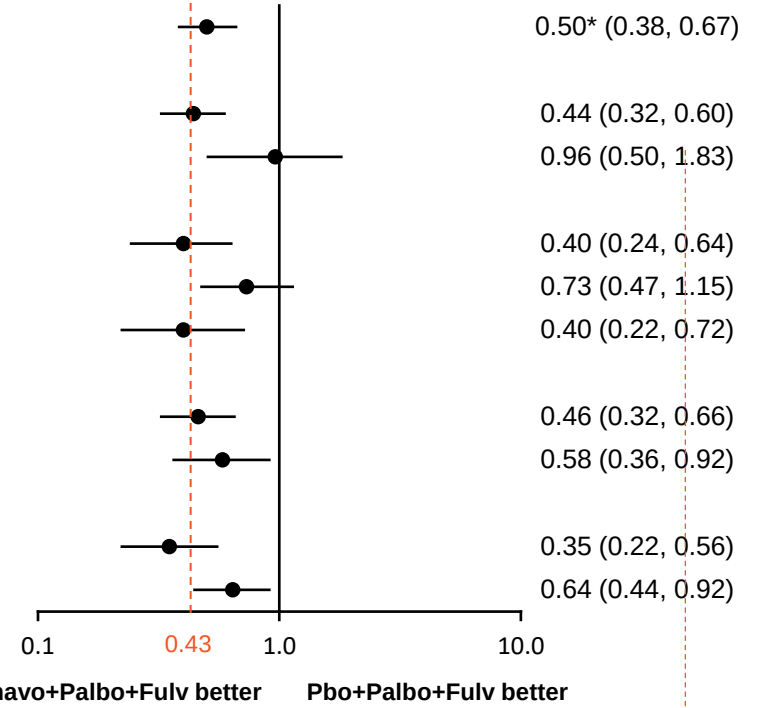
Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

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

	Inavo+Palbo+Fulv		Pbo+Palbo+Fulv		Hazard ratio (95% CI)
	n	Median (mo)	n	Median (mo)	
All patients	161	15.0	164	7.3	0.50* (0.38, 0.67)
Age, years					
<65	136	16.6	130	7.2	0.44 (0.32, 0.60)
≥65	25	9.3	34	10.7	0.96 (0.50, 1.83)
Region					
Asia	56	14.6	58	5.8	0.40 (0.24, 0.64)
North America/Western Europe	63	13.8	64	9.3	0.73 (0.47, 1.15)
Other	42	21.0	42	5.6	0.40 (0.22, 0.72)
ECOG PS at baseline					
0	100	16.6	106	7.4	0.46 (0.32, 0.66)
1	60	11.4	58	5.6	0.58 (0.36, 0.92)
Menopausal status at randomization					
Premenopausal	65	20.1	59	6.5	0.35 (0.22, 0.56)
Post-menopausal	91	13.4	104	7.5	0.64 (0.44, 0.92)

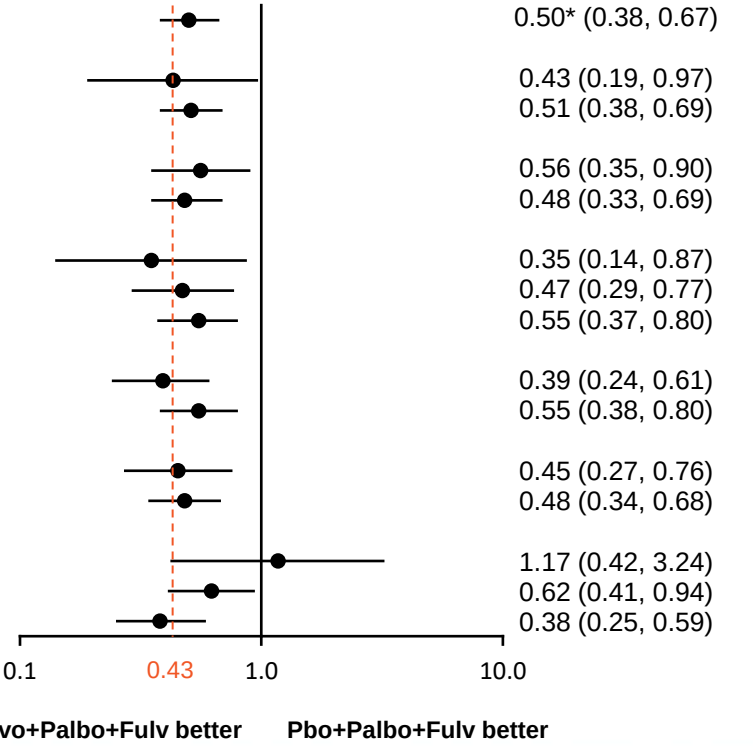


* Sample size is relatively small for many groups therefore the analysis is unstratified including for 'all patients' hence the difference in the HR relative to that for the stratified ITT analysis.

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

	Inavo+Palbo+Fulv		Pbo+Palbo+Fulv		Hazard ratio (95% CI)
	n	Median (mo)	n	Median (mo)	
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)

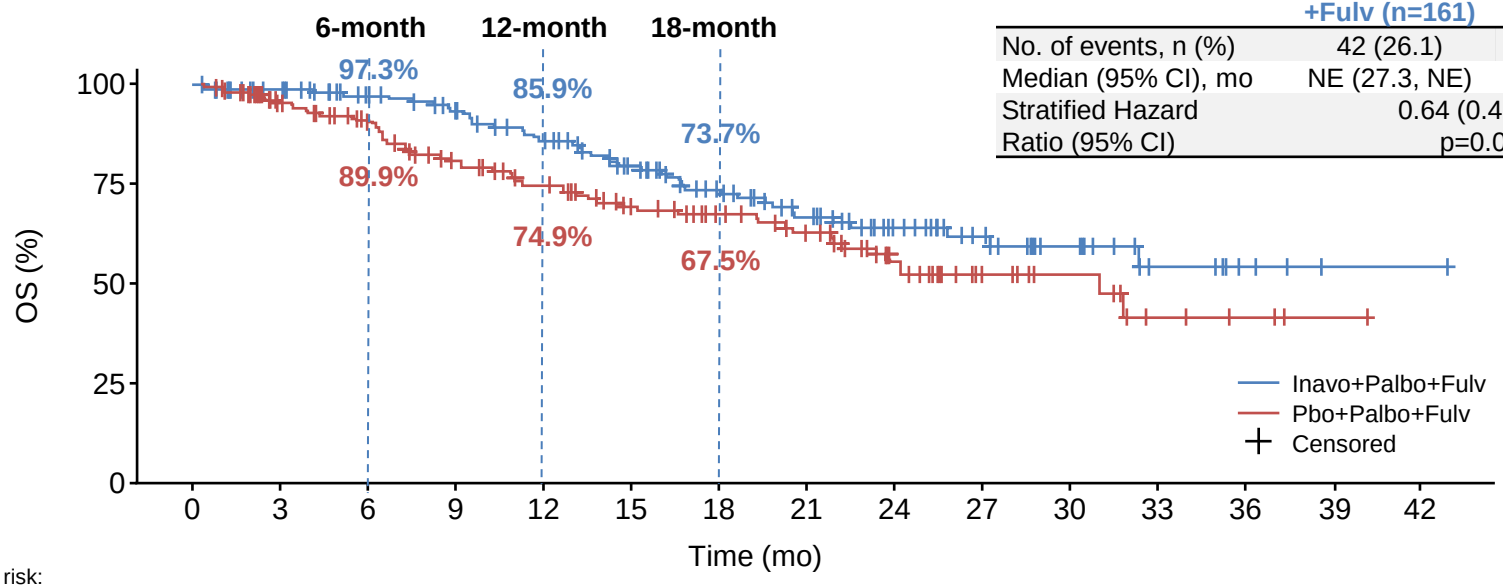


* Sample size is relatively small for many groups therefore the analysis is unstratified including for 'all patients' hence the difference in the HR relative to that for the stratified ITT analysis.

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

Key secondary endpoint: Overall survival (interim analysis)

	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	



Patients at risk:

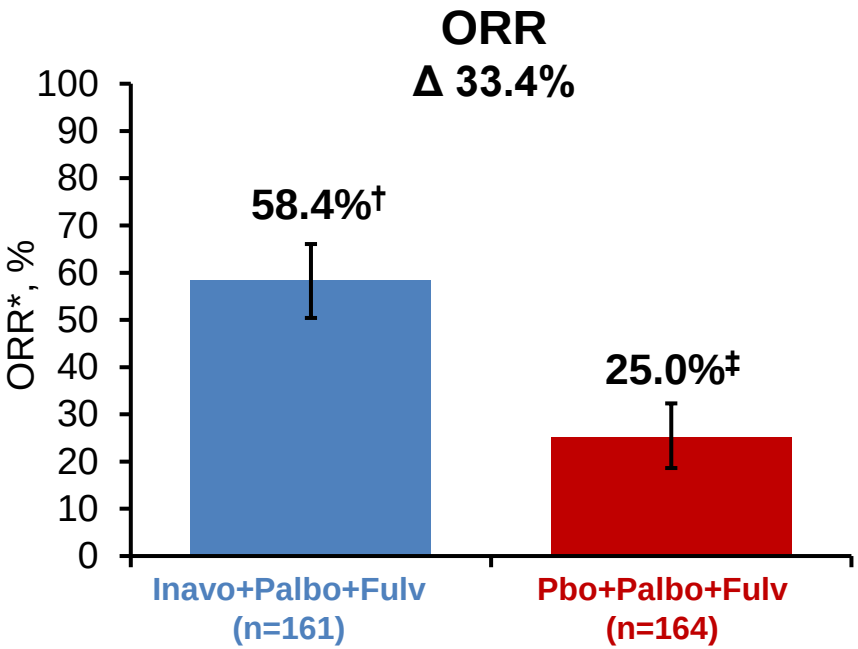
Inavo+Palbo+Fulv	161	143	127	114	101	85	69	56	38	26	17	8	4	1	1
Pbo+Palbo+Fulv	164	139	120	98	87	72	61	52	33	19	11	5	3	1	0

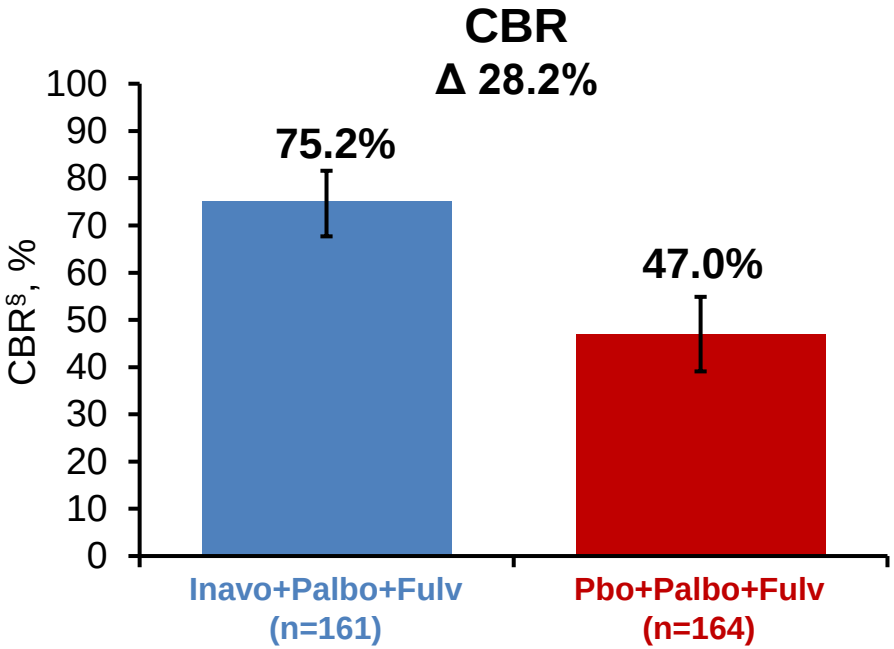
Median follow-up: **21.3 months**

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.

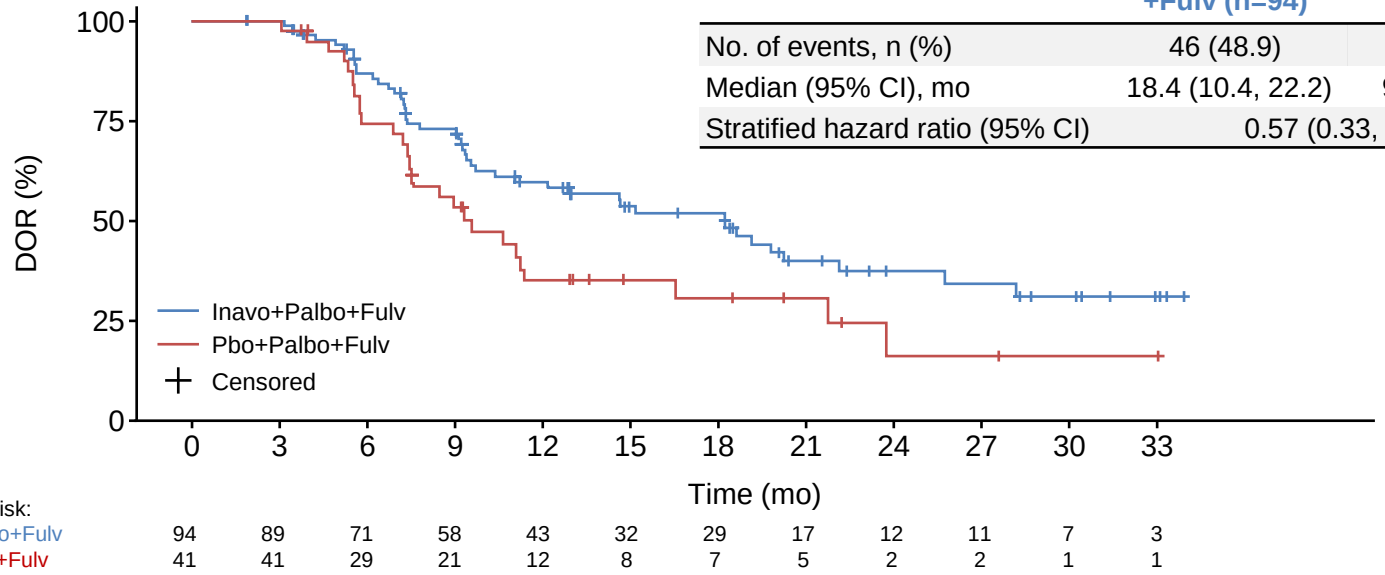
Secondary endpoints: ORR and CBR (investigator-assessed)





* Patients with a CR or PR on two consecutive occasions ≥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 ≥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.

Secondary endpoint: DOR (investigator-assessed)



	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)	

Patients at risk:

Inavo+Palbo+Fulv	94	89	71	58	43	32	29	17	12	11	7	3
Pbo+Palbo+Fulv	41	41	29	21	12	8	7	5	2	2	1	1

Median follow-up:
21.3 months

CI, confidence interval; DOR, duration of response; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo.

Adverse events with any grade AEs ≥ 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
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**
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.

Thank you

To all the patients who participated in INAVO120, along with their families, with special acknowledgment to those on the control arm

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