First-line inavolisib/placebo + palbociclib + fulvestrant (Inavo/Pbo+Palbo+Fulv) in patients (pts) with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative locally advanced/metastatic breast cancer who relapsed during/within 12 months (mo) of adjuvant endocrine therapy completion: INAVO120 Phase III randomized trial additional analyses.

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Summary slide

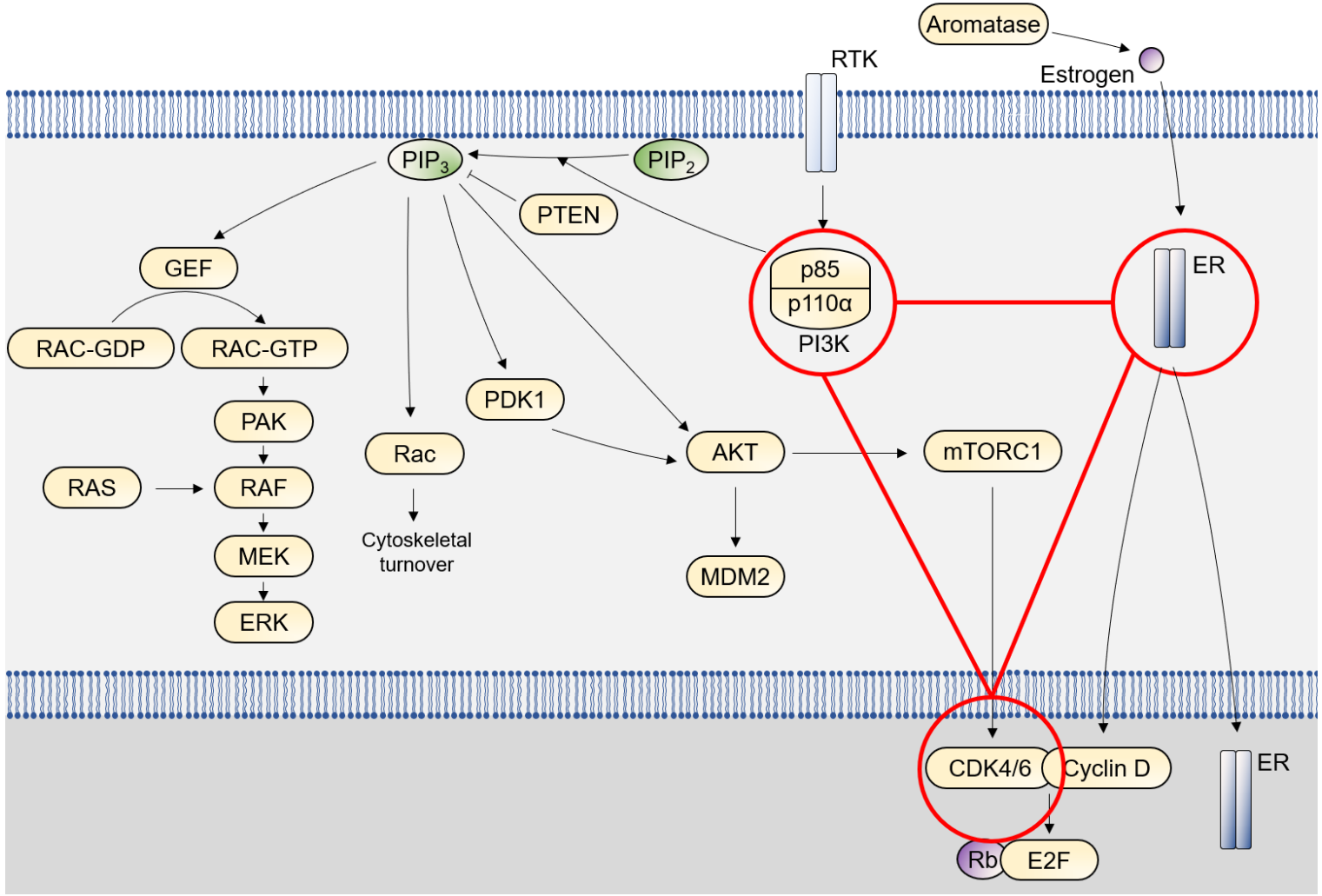
- INAVO120 met its primary endpoint, with a statistically significant and clinically meaningful improvement in PFS (15.0 months versus 7.3 months; hazard ratio, 0.43 [95% CI = 0.32, 0.59]; p<0.0001)[1]
- To allow further characterization of inavolisib-based treatment we report additional efficacy, safety, and patient-reported outcomes
- Data further support inavolisib-based therapy by demonstrating sustained benefit beyond disease progression, a manageable safety and tolerability profile, prolonged time to deterioration in pain severity, and maintained day-to-day functioning and HRQoL
- **Inavolisib with palbociclib and fulvestrant is a promising new treatment option for patients with *PIK3CA*-mutated, HR+, HER2– LA/mBC**

(LA/m)BC, (locally advanced/metastatic) breast cancer; CI, confidence interval; HER2–, HER2-negative; HR+, hormone receptor-positive; HRQoL, health-related quality of life; PFS, progression-free survival.

1. Jhaveri KL, *et al.* SABCS 2023 (Abstract GS03-13).

Background

- More effective and tolerable treatments for patients with *PIK3CA*-mutated, HR+, HER2– advanced BC are needed[1–3]
- Preclinical data demonstrated substantial synergy upon simultaneous inhibition of the PI3K, CDK4/6, and estrogen receptor pathways in *PIK3CA*-mutated xenograft models by deepening responses and blocking routes to resistance[4–7]
- Inavolisib is a highly potent and selective inhibitor of the catalytic alpha isoform subunit (p110α encoded by *PIK3CA*) of the PI3K complex that also promotes the degradation of mutated p110α[7–9]



BC, breast cancer; CDK4/6, cyclin-dependent kinase 4/6; ER, estrogen receptor; HER2–, HER2-negative; HR+, hormone receptor-positive.

1. Cardoso F, *et al. Ann Oncol* 2020;**31:**1623–1649; 2. André F, *et al. N Eng J Med* 2019;**380:**1929–1940; 3. Dent S, *et al. Ann Oncol* 2021;**32:**197–207;
4. Hong R, *et al*. *Cancer Res* 2018;**78(4 Suppl):** Abstract PD4-14; 5. Herrera-Abreu MT, *et al*. *Cancer Res* 2016;**76:**2301–2313; 6. Vora SR, *et al. Cancer Cell* 2014;**26:**136–149.
7. Song KW, *et al. Cancer Discov* 2022;**12:**204–219; 8. Edgar K, *et al*. *Cancer Res* 2020;**80(4 Suppl):** Abstract P3-11-23; 9. Hanan EJ, *et al. J Med Chem* 2022;**65:**16589–16621.

INAVO120 study design[1]

Key eligibility criteria

Enrichment of patients with poor prognosis:

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

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)

Statistical methods

- For efficacy endpoints and TTCD, hazard ratios were estimated using a Cox proportional hazard model with 95% CI and Kaplan–Meier methodology was used to estimate the medians with the Brookmeyer–Crowley method used for the 95% CI

Efficacy endpoints

- PFS by investigator
- OS
- ORR, BOR, CBR, DOR
- **Time from randomization to end or discontinuation of next-line treatment, or death from any cause (proxy for PFS2)**
- **Time from randomization to first subsequent chemotherapy after treatment discontinuation**

Safety endpoints

Key selected AEs (hyperglycemia, diarrhea, rash, and stomatitis/mucosal inflammation)*

Patient-reported outcomes endpoints†

- **BPI-SF: TTCD in worse pain‡§**
- **EORTC QLQ-C30: mean change from baseline in HRQoL, physical functioning, and role functioning‖**
- **PRO-CTCAE: presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptomatic treatment toxicities**
- **An overall bother item: overall bother experienced due to side effects of treatment**

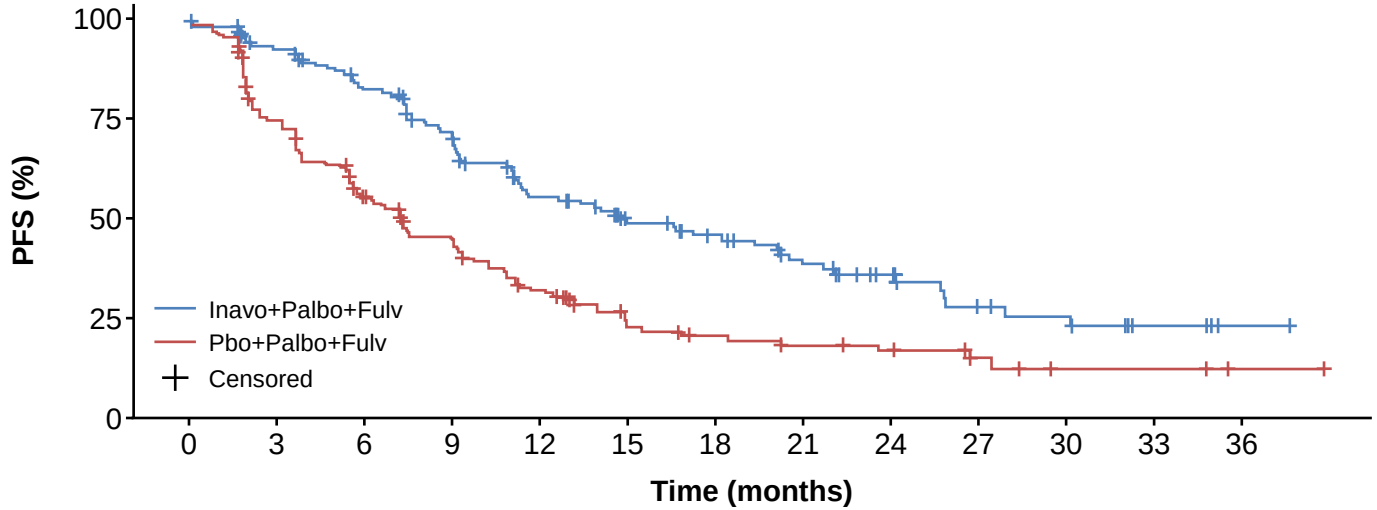
* Assessed using grouped terms; severity reported per National Cancer Institute CTCAE version 5.0. † Assessed at D1 of C1–3 then D1 of every other C thereafter (5, 7, 9, etc.), at treatment discontinuation, and every 3 months during survival follow-up; baseline completion rates in both arms were >90% for all assessments; post-baseline rates in both arms remain >80% through C15; <50% intent-to-treat sample remaining at C9 in the inavolisib arm versus C5 in the placebo arm. ‡ Type I error-controlled; hierarchically tested according to a prespecified fixed order of endpoints. § Defined as the time from randomization to the first documentation of a ≥2-point increase from baseline on the "worst pain" item held for at least two consecutive Cs, or an initial increase followed by death or treatment discontinuation within 3 weeks from the last assessment. ‖ A ≥10-point change was defined as a clinically meaningful difference.

AE, adverse event; (LA/m)BC, (locally advanced/metastatic) breast cancer; BOR, best overall response; BPI-SF, brief pain inventory-short form; C, Cycle; CBR, clinical benefit rate; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; ctDNA, circulating tumor DNA; D, Day; DOR, duration of response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; ET, endocrine therapy; HER2–, HER2-negative; HR+, hormone receptor-positive; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, time from randomization to next progression after discontinuing study treatment for PD, or death from any cause; PO, orally; PRO, patient-reported outcomes; Q4W, every 4 weeks; QD, once daily; R, randomized; TTCD, time to confirmed clinical meaningful deterioration.

1. Jhaveri KL, *et al.* SABCS 2023 (Abstract GS03-13).

INAVO120 primary analysis results

- INAVO120 (NCT04191499) is a Phase III, randomized, double-blind, placebo-controlled study that assessed inavolisib or placebo with palbociclib and fulvestrant in patients with *PIK3CA*-mutated, HR+, HER2– LA/mBC who recurred on or within 12 months of adjuvant endocrine therapy
- INAVO120 met its primary endpoint, with a statistically significant and clinically meaningful improvement in PFS (15.0 months versus 7.3 months; hazard ratio, 0.43 [95% CI = 0.32, 0.59]; p<0.0001)[1]

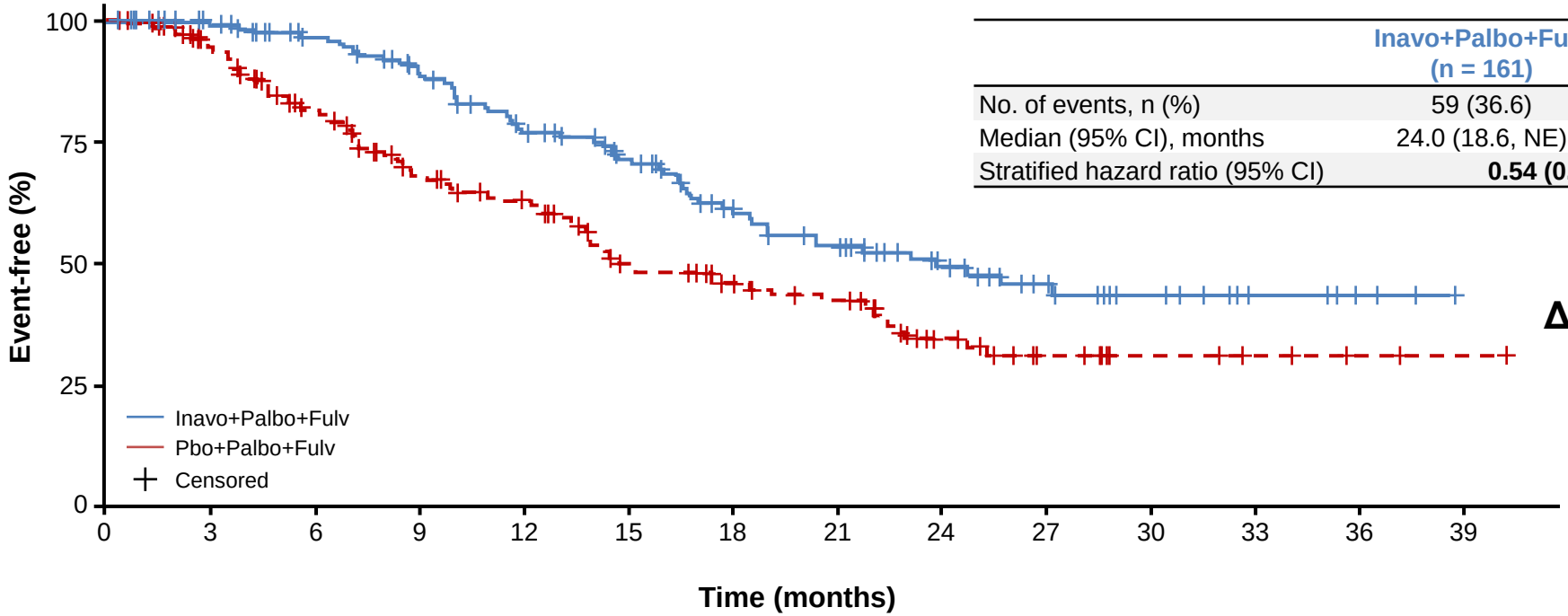


- Here we report additional efficacy, safety, and patient-reported outcomes data from the primary analysis (CCOD: September 29, 2023; median follow-up: 21.3 months)
  - As the prespecified boundary of significance for OS was not met, these analyses are descriptive

CCOD, clinical cutoff date; CI, confidence interval; Fulv, fulvestrant; HER2–, HER2-negative; HR+, hormone receptor-positive; Inavo, inavolisib; LA/mBC, locally advanced/metastatic breast cancer; OS, overall survival; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

1. Jhaveri KL, *et al.* SABCS 2023 (Abstract GS03-13).

Time from randomization to end or discontinuation of next-line treatment, or death from any cause (proxy for PFS2)



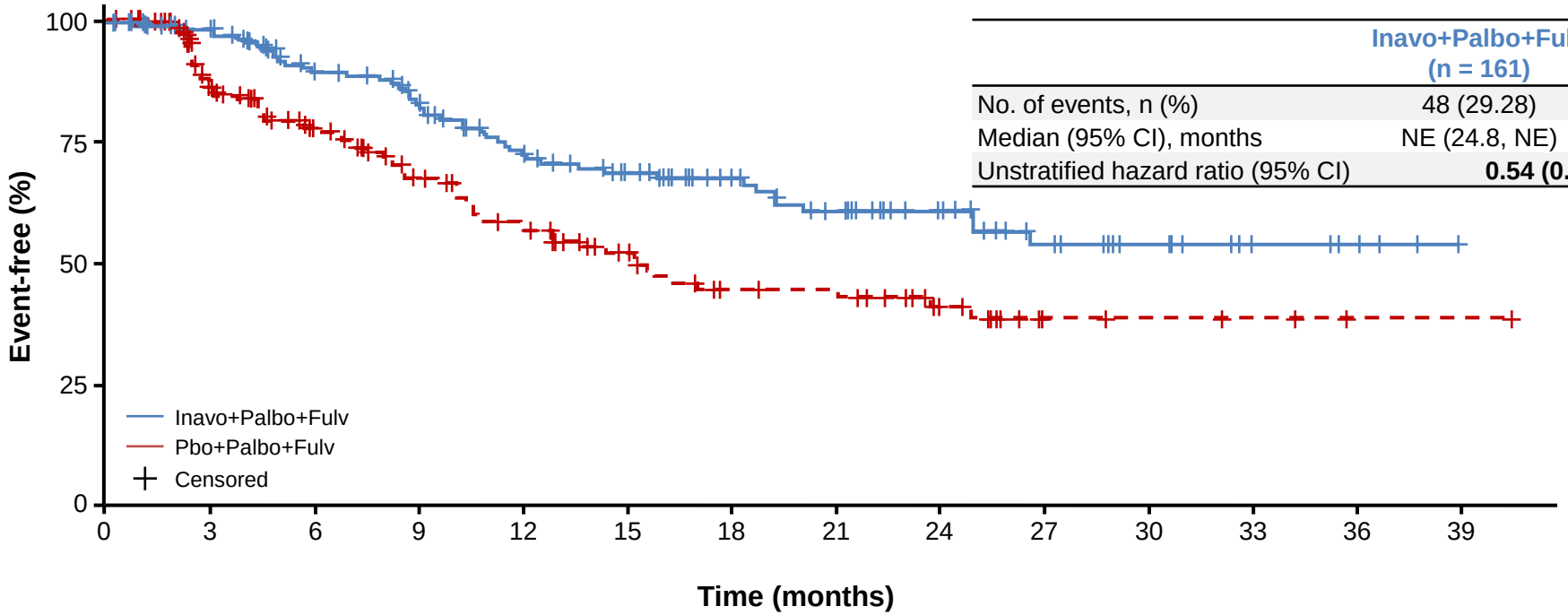
	Inavo+Palbo+Fulv (n = 161)	Pbo+Palbo+Fulv (n = 164)
No. of events, n (%)	59 (36.6)	80 (48.4)
Median (95% CI), months	24.0 (18.6, NE)	15.1 (13.5, 22.3)
Stratified hazard ratio (95% CI)	**0.54 (0.38, 0.77)**	

Δ 8.9 months

Patients at risk:														
Pbo+Palbo+Fulv	164	140	110	84	74	52	43	37	22	12	6	4	2	1
Inavo+Palbo+Fulv	161	143	126	111	92	77	58	48	33	22	14	6	3	0

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; NE, not evaluable; Palbo, palbociclib; Pbo, placebo; PFS2, time from randomization to next progression after discontinuing study treatment for disease progression, or death from any cause.

Time from randomization to first subsequent chemotherapy after treatment discontinuation



	Inavo+Palbo+Fulv (n = 161)	Pbo+Palbo+Fulv (n = 164)
No. of events, n (%)	48 (29.28)	68 (41.5)
Median (95% CI), months	NE (24.8, NE)	15.0 (10.6, 24.8)
Unstratified hazard ratio (95% CI)	**0.54 (0.37, 0.78)**	

Patients at risk:

Pbo+Palbo+Fulv	164	121	94	71	56	41	29	27	18	7	5	4	2	1
Inavo+Palbo+Fulv	161	141	115	98	78	66	51	42	30	20	13	6	3	0

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; NE, not evaluable; Palbo, palbociclib; Pbo, placebo.

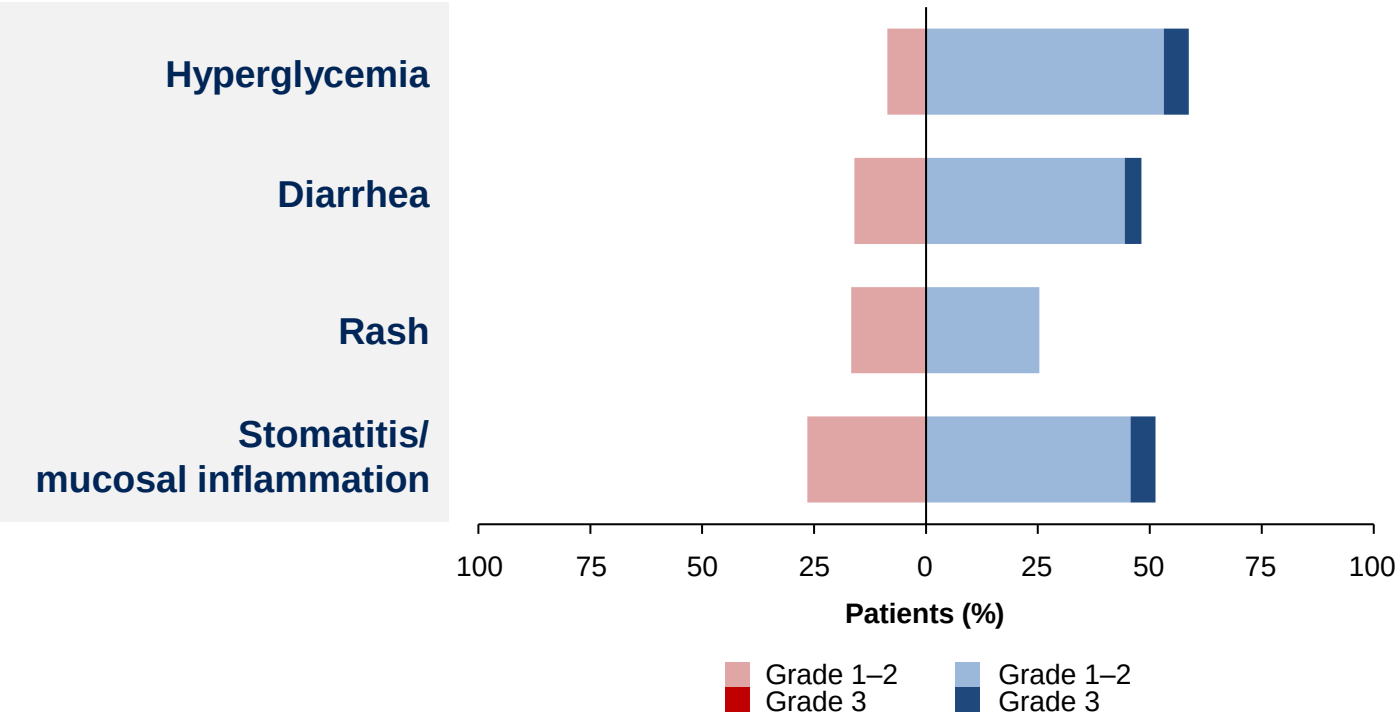
Post-progression therapies

Patients, n/N (%)	Inavo+Palbo+Fulv (n = 161)	Pbo+Palbo+Fulv (n = 164)
Discontinued treatment	93/161 (57.8)	115/164 (70.1)
No subsequent therapy – death	12/161 (7.5)	19/164 (11.6)
Received subsequent therapy*	65/161 (40.4)	82/164 (50.0)
Chemotherapy (any)	40/65 (61.5)	60/82 (73.2)
Capecitabine	21/65 (32.3)	29/82 (35.4)
ADC (any)	0	1/82 (1.2)
PI3K inhibitor (any)	2/65 (3.1)	21/82 (25.6)
Alpelisib	2/65 (3.1)	14/82 (17.1)
mTOR kinase inhibitor (any)	8/65 (12.3)	6/82 (7.3)
Everolimus	8/65 (12.3)	6/82 (7.3)
CDK4/6 inhibitor (any)	8/65 (12.3)	5/82 (6.1)
Ribociclib	1/65 (1.5)	5/82 (6.1)
Abemaciclib	3/65 (4.6)	0
Other (any)†	13/65 (20.0)	10/82 (12.2)

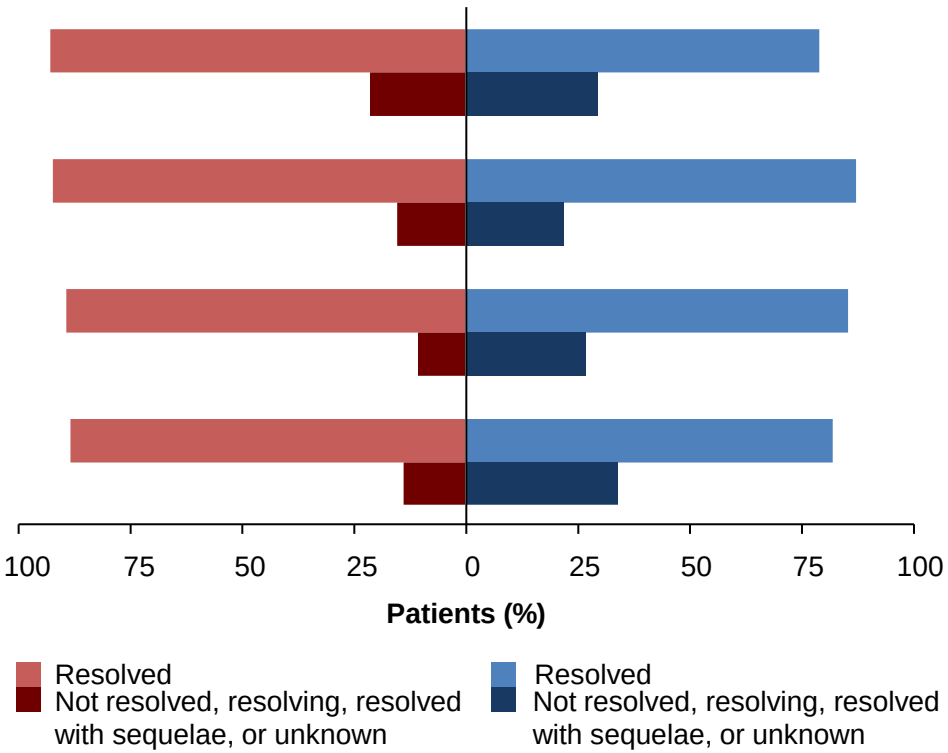
* One patient had a treatment unrelated to breast cancer (cytarabine) in the Pbo arm; † Includes less common HR+ therapies, such as PARP inhibitors and HER2-targeted therapies.
ADC, antibody–drug conjugate; CDK4/6, cyclin-dependent kinase 4/6; Fulv, fulvestrant; HR+, hormone receptor-positive; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

Safety

Key selected AEs



Resolution of key selected AEs*†

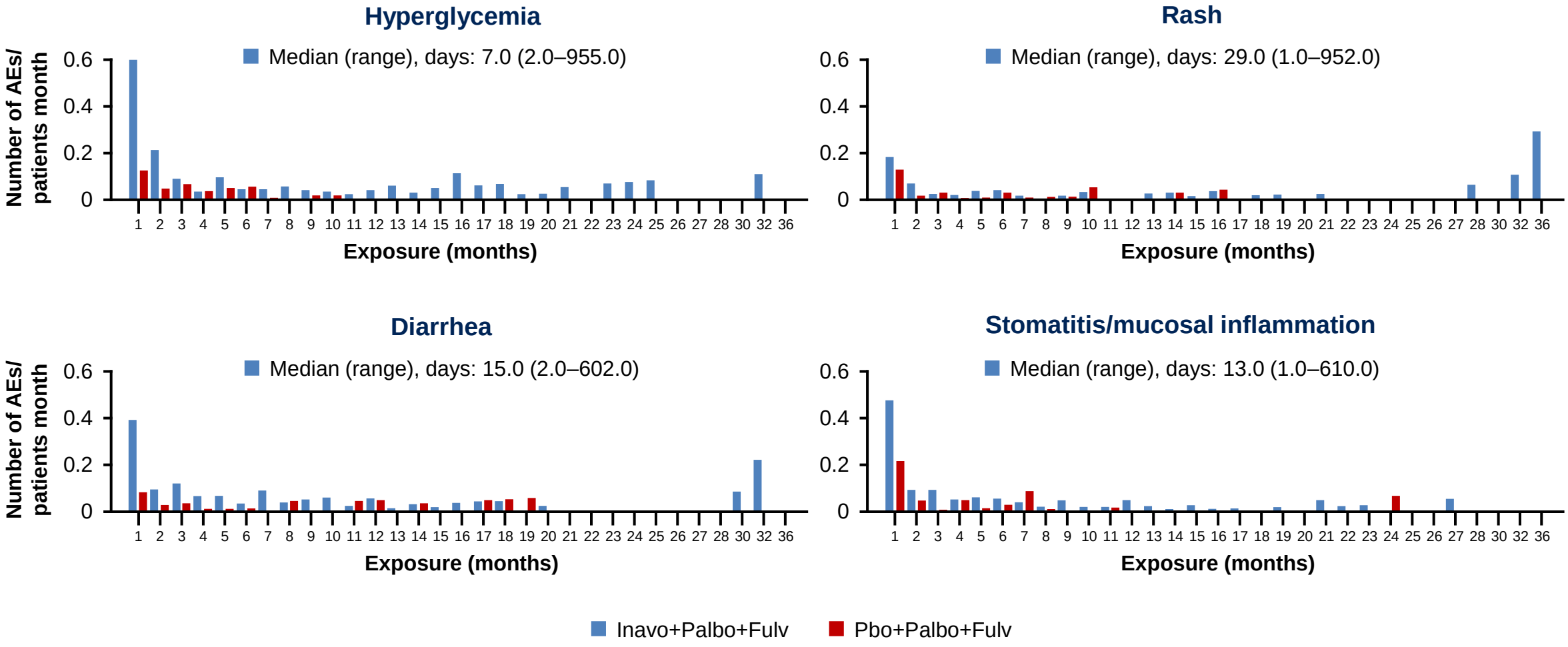


*** Majority of key selected AEs had resolved ('resolution' was per investigator decision) by the CCOD; some patients were enrolled close to the CCOD and AE follow-up is ongoing for these patients.**

† Denominators are patients with at least one AE (hyperglycemia, Inavo+Palbo+Fulv: n = 95, Pbo+Palbo+Fulv: n = 14; diarrhea, Inavo+Palbo+Fulv: n = 78, Pbo+Palbo+Fulv: n = 26; rash, Inavo+Palbo+Fulv: n = 41, Pbo+Palbo+Fulv: n = 28; and stomatitis/mucosal inflammation, Inavo+Palbo+Fulv: n = 83, Pbo+Palbo+Fulv: n = 43).

AE, adverse event; CCOD, clinical cutoff date; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

Time to onset of key selected AEs*



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

Inavolisib treatment interruption, reduction, and discontinuation due to key selected AEs

Discontinuation rate of inavolisib due to any AE was 6.2%[1]

Patients, n (%)	Hyperglycemia	Diarrhea	Rash	Stomatitis/ mucosal inflammation
Inavolisib interruption due to AE	44 (27.2)	11 (6.8)	2 (1.2)	16 (9.9)
Inavolisib reduction due to AE	4 (2.5)	2 (1.2)	1 (0.6)	6 (3.7)
Inavolisib discontinuation due to AE	1 (0.6)*	0	0	1 (0.6)

Data are for the Inavo+Palbo+Fulv arm (n = 162).
* One patient discontinued due to an AE of Type 2 diabetes in the Inavo+Palbo+Fulv arm, which was not captured under hyperglycemia.
AE, adverse event; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib.
1. Jhaveri KL, *et al.* SABCS 2023 (Abstract GS03-13).

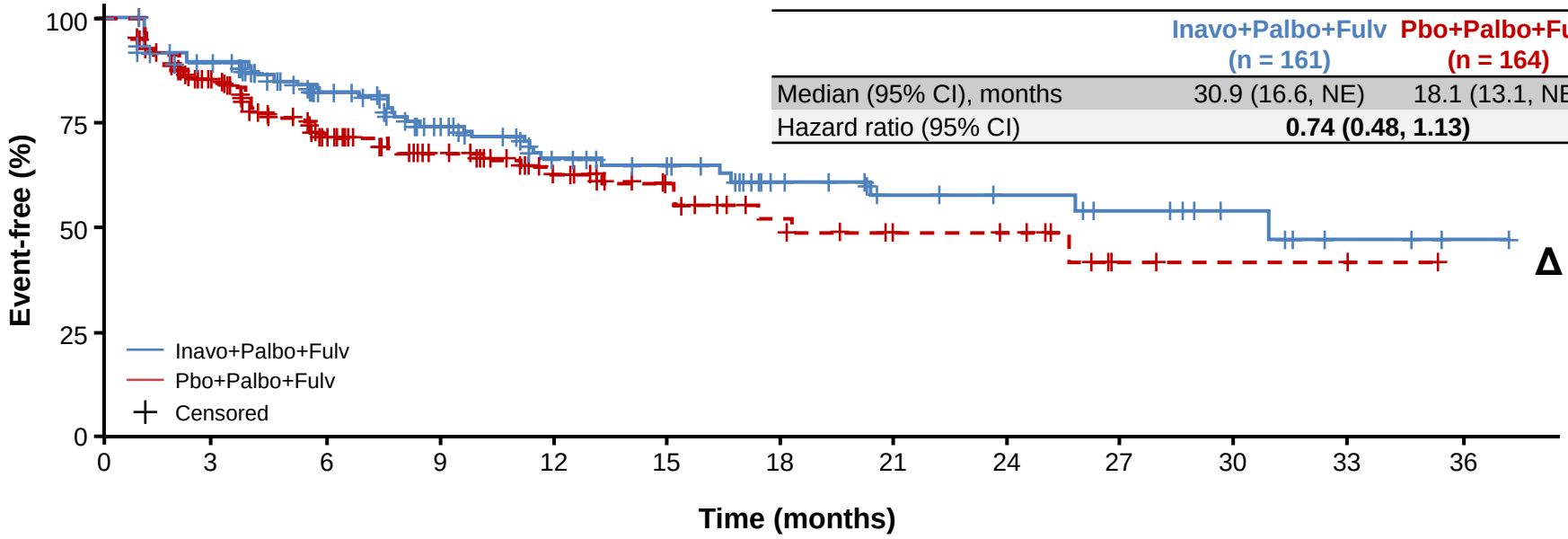
Concomitant medications for key selected AEs

Patients, n/N (%)	Inavo+Palbo+Fulv (n = 162)	Pbo+Palbo+Fulv (n = 162)
Received ≥1 concomitant medication for:		
Hyperglycemia	66/162 (40.7)	1/162 (0.6)
Diarrhea	46/162 (28.4)	6/162 (3.7)
Rash	26/162 (16.0)	19/162 (11.7)
Stomatitis/mucosal inflammation	69/162 (42.6)	26/162 (16.0)
Most common concomitant medications per AE:		
Metformin: hyperglycemia	62/66 (93.9)	1/1 (100)
Loperamide: diarrhea	38/46 (82.6)	6/6 (100)
Hydrocortisone (topical): rash	5/26 (19.2)	3/19 (15.8)
Steroid (mouthwash): stomatitis/mucosal inflammation	42/69 (60.9)	12/26 (46.1)
Prophylactic use	(20)	(14.2)

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

Time to confirmed clinical meaningful deterioration in worst pain severity (BPI-SF)

Patients in the inavolisib arm experienced a longer duration of time without confirmed, clinically meaningful worsening pain severity than patients in the placebo arm



	Inavo+Palbo+Fulv (n = 161)	Pbo+Palbo+Fulv (n = 164)
Median (95% CI), months	30.9 (16.6, NE)	18.1 (13.1, NE)
Hazard ratio (95% CI)	**0.74 (0.48, 1.13)**	

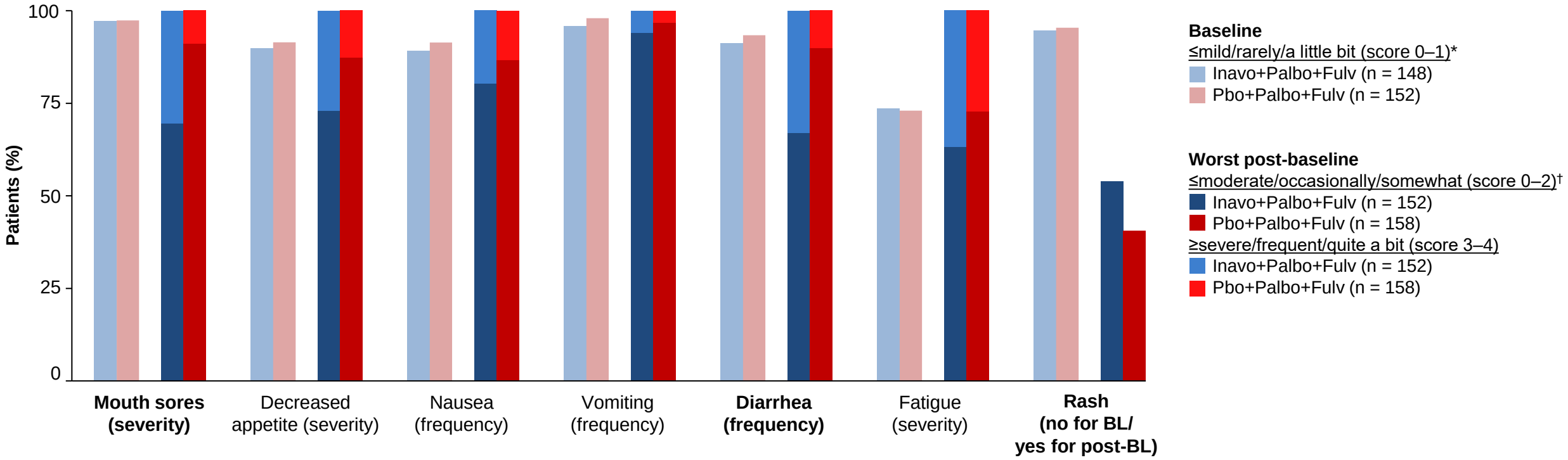
Δ 12.8 months

Patients at risk:													
Pbo+Palbo+Fulv	164	100	66	48	33	23	16	11	10	3	2	2	0
Inavo+Palbo+Fulv	161	120	92	65	46	37	23	18	15	12	8	3	1

BPI-SF, brief pain inventory-short form; CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; NE, not evaluable; Palbo, palbociclib; Pbo, placebo.

Symptomatic toxicities (PRO-CTCAE)

- Most patients reported worst post-baseline symptomatic toxicities at moderate levels or less
- Diarrhea, mouth sores, and rash were experienced at higher (worse) levels by patients in the inavolisib arm than the placebo arm

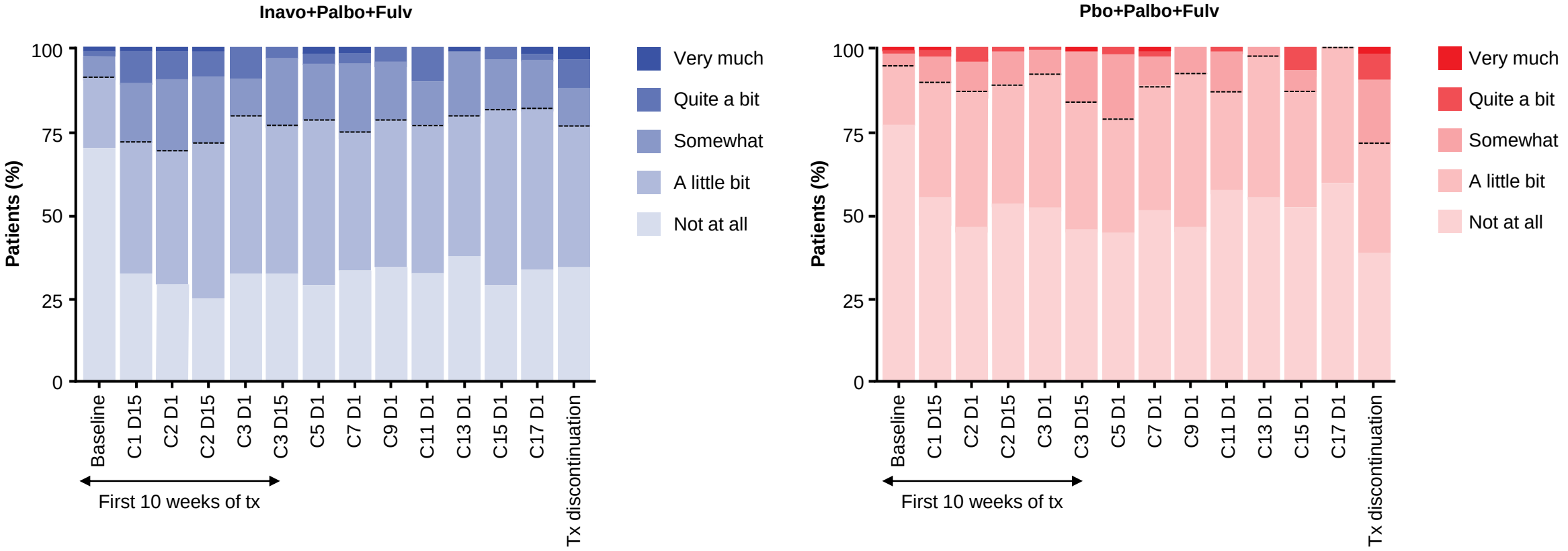


* No for rash.
† Yes for rash.
BL, baseline; CTCAE, Common Terminology Criteria for Adverse Events; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo; PRO, patient-reported outcome.

Overall “bother”

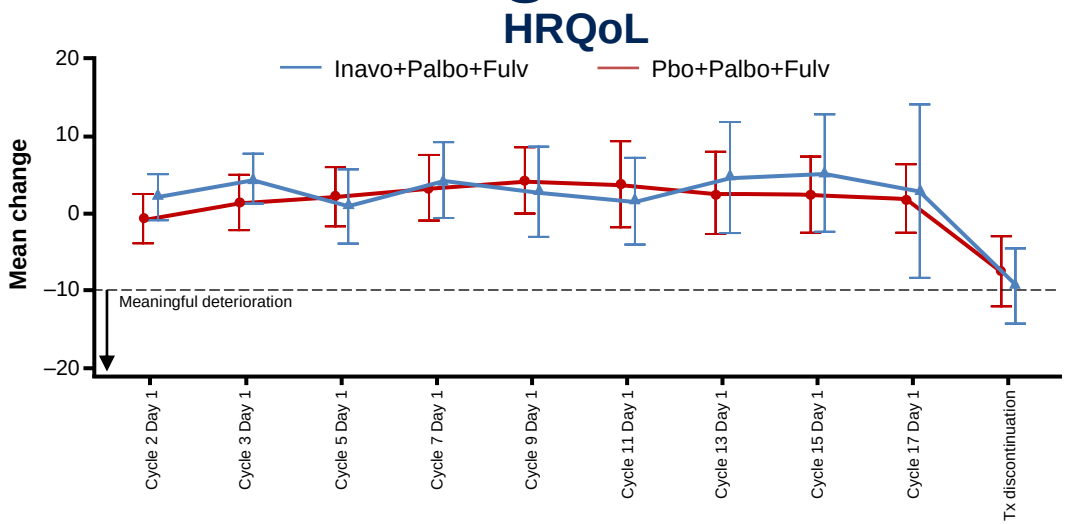
Most patients reported overall “bother” from treatment as “not at all” or “a little bit”

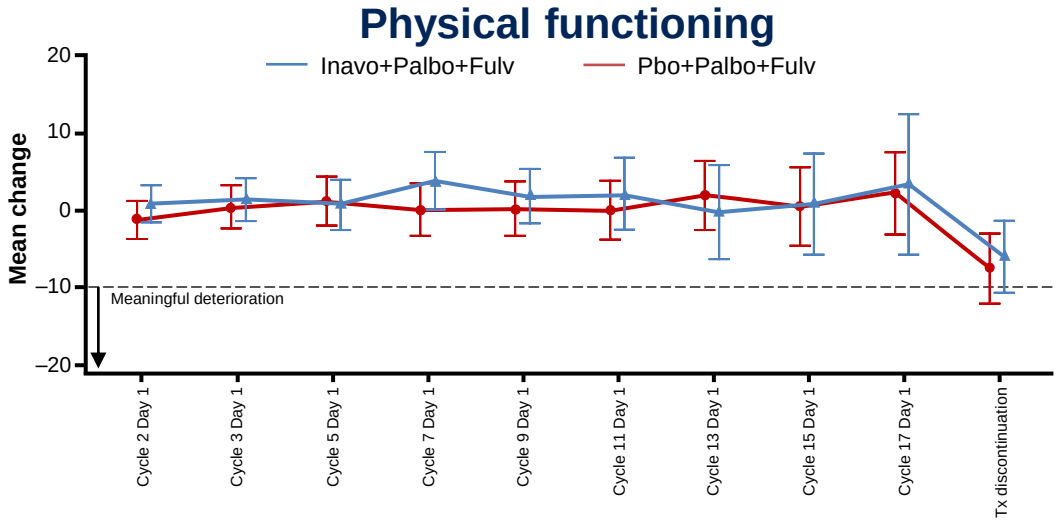
“In the last 7 days, how bothered were you by the side effect(s) of your treatment?”

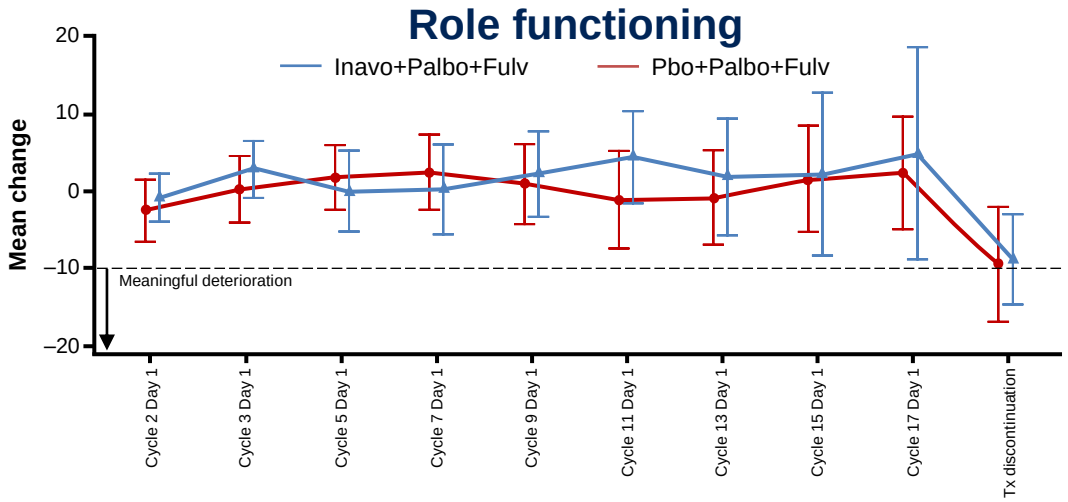


C, cycle; D, day; Fulv, fulvestrant; Inavo, inavolisib; Pbo, placebo; Palbo, palbociclib; Tx, treatment.

Mean change from baseline in EORTC QLQ-C30 scores







- Patients in both arms maintained baseline levels of HRQoL, physical functioning, and role functioning
- Adding inavolisib had no detrimental impact on patients' physical functioning, role functioning, and HRQoL

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; Fulv, fulvestrant; HRQoL, health-related quality of life; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo; Tx, treatment.

Conclusions

- INAVO120 met its primary endpoint, with a statistically significant and clinically meaningful improvement in PFS (15.0 months versus 7.3 months; hazard ratio, 0.43 [95% CI = 0.32, 0.59]; p<0.0001)[1]
- Inavolisib with palbociclib and fulvestrant was associated with sustained benefit beyond disease progression, demonstrating a delayed need for subsequent therapy (Δ 8.9 months), including chemotherapy (NE versus 15.0 months), and supporting the clinical benefit of the inavolisib-based therapy
- Inavolisib discontinuations for hyperglycemia, diarrhea, rash, and stomatitis/mucosal inflammation were low, confirming the manageable safety and tolerability profile of inavolisib
- Patient-reported outcomes data suggest patients receiving inavolisib in addition to fulvestrant and palbociclib experienced a longer median time to deterioration in pain severity (Δ 12.8 months), and maintained day-to-day functioning and HRQoL while on treatment with little increased treatment burden
- **Inavolisib with palbociclib and fulvestrant is a promising new treatment option for patients with *PIK3CA*-mutated, HR+, HER2– LA/mBC**

HER2–, HER2-negative; HR+, hormone receptor-positive; HRQoL, health-related quality of life; LA/mBC, locally advanced/metastatic breast cancer; NE, not evaluable; PFS, progression-free survival.

1. Jhaveri KL, *et al.* SABCS 2023 (Abstract GS03-13).

Lay summary

What is the INAVO120 study?[1]

- INAVO120 is an ongoing Phase III study to test whether a study drug called inavolisib, combined with palbociclib + fulvestrant, is more effective than placebo + palbociclib + fulvestrant
- The study includes people with a type of advanced breast cancer called *PIK3CA*-mutated, hormone receptor-positive, and HER2-negative
- People in this study had been treated with hormonal therapy after surgery, and the hormonal therapy had stopped working during treatment or within 12 months of stopping
- The aims of the study were:
  - To find out whether inavolisib + palbociclib + fulvestrant increases the length of time before people's cancer gets worse*, compared with placebo + palbociclib + fulvestrant
  - To compare any side effects in the two groups of patients

Key results from the INAVO120 study

- Inavolisib + palbociclib + fulvestrant significantly increased the average length of time before people's cancer got worse* compared with placebo + palbociclib + fulvestrant[1]
- Inavolisib + palbociclib + fulvestrant increased the average length of time before people needed additional therapy, including chemotherapy
- Side effects were able to be managed by doctors, and only a small number of people had to stop taking inavolisib because of side effects
- Inavolisib + palbociclib + fulvestrant increased the average time before peoples' pain got worse
- Patients were able to complete daily tasks and maintain their quality of life

* Or until they died.

1. Jhaveri KL, *et al.* SABCS 2023 (Abstract GS03-13).

Acknowledgments

- We thank all the patients who participated in INAVO120, along with their families, as well as the INAVO120 investigators and research staff
- This study was funded by F. Hoffmann-La Roche Ltd
- Research support in the form of third-party writing assistance for this presentation, furnished by Eleanor Porteous, MSc, of Nucleus Global, an Inizio Company, was provided by F. Hoffmann-La Roche Ltd

Thank you