SAN ANTONIO BREAST CANCER SYMPOSIUM®
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AFT-38 PATINA

A Randomized, Open-Label, Phase III Trial to Evaluate the Efficacy and Safety of Palbociclib + Anti-HER2 Therapy + Endocrine Therapy vs Anti-HER2 Therapy + Endocrine Therapy After Induction Treatment for Hormone Receptor Positive (HR+)/HER2-Positive Metastatic Breast Cancer

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Disclosures

Otto Metzger, MD

I have no financial relationships to disclose

Background

- Approximately 15%-20% of breast cancers overexpress HER2
  - Half of HER2+ tumors also co-express estrogen receptors

- Anti-HER2 therapies have significantly improved survival outcomes
  - Resistance to therapy remains inevitable in advanced HER2+ breast cancer

- Rationale for blocking CDK4/6 in HER2+ disease

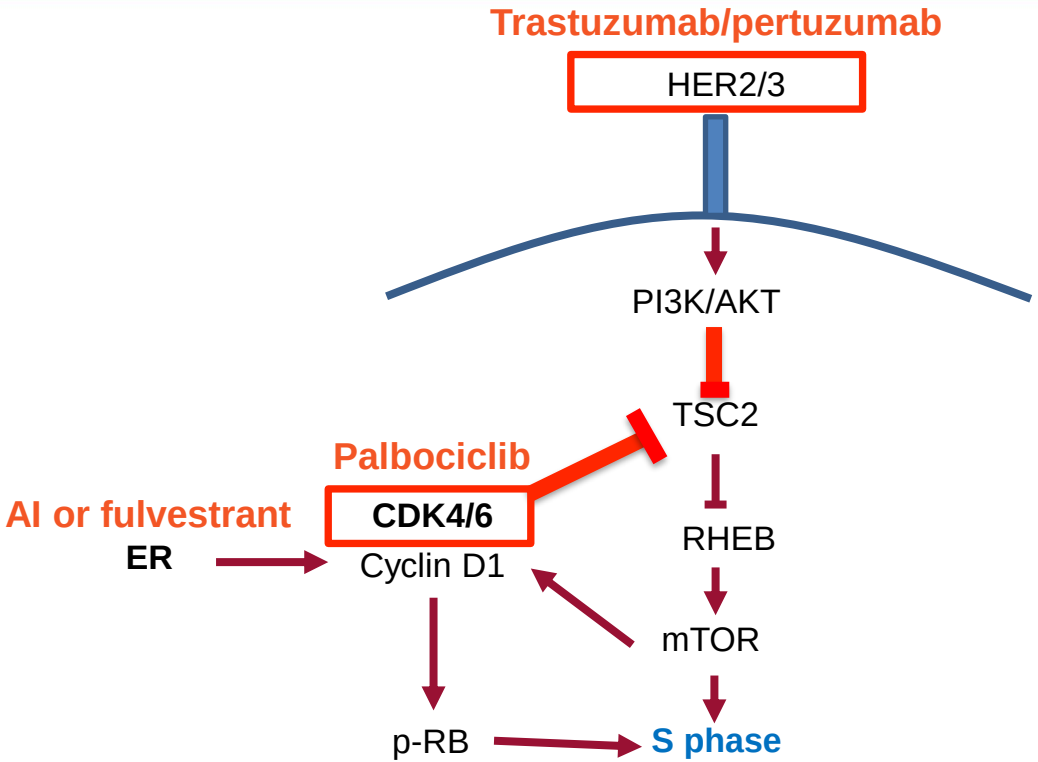
  - The cyclin D1-CDK4 axis is essential for the initiation and maintenance of growth of *ErbB2*-driven mammary carcinomas[1-3]
  - Persistent cyclin D1-CDK4 activity drives resistance to the HER2 pathway blockade[4]
  - Combined CDK4/6 and HER2 inhibition shows synergistic anti-tumor activity in preclinical models of HER2+ breast cancer[4]

- Palbociclib is an approved CDK4/6 inhibitor associated with a clinically meaningful improvement in progression-free survival in HR+,HER2- breast cancer

CDK4=cyclin-dependent kinase 4; CDK4/6=cyclin-dependent kinase 4/6; *ErbB2*=v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2; HER2=human epidermal growth factor receptor 2; HR=hormone receptor.

1. Yu Q, et al. *Nature*. 2001;411(6841):1017-1021.
2. Yu Q, et al. *Cancer Cell.* 2006;9(1):23-32.
3. Choi YJ, et al. *Cancer Cell*. 2012;22(4):438-451.
4. Goel S, et al. *Cancer Cell.* 2016;29(3):255-269.

Background:
Rationale for Blocking HER2 and CDK4/6 Pathways



The HER2 and CDK4/6 pathways converge at the tumor suppressor protein TSC2

When CDK4/6 and HER2 inhibitors are combined, potent suppression of RB phosphorylation and mTORC1 activity, enhancing anti-proliferative effects in tumor cells

AI=aromatase inhibitor; AKT=protein kinase B; CDK4/6=cyclin-dependent kinase 4/6; HER2=human epidermal growth factor receptor 2; HER3=human epidermal growth factor receptor 3; CDK4/6=cyclin-dependent kinase 4/6; ER=estrogen receptor; mTOR=mammalian target of rapamycin; mTORC1=mammalian target of rapamycin complex 1; PI3K=phosphoinositide 3-kinase; p-RB=retinoblastoma protein; RHEB=ras homolog enriched in brain; S phase=synthesis phase; TSC2=tuberous sclerosis complex 2.

Goel S, et al. *Cancer Cell*. 2016;29(3):255-269.

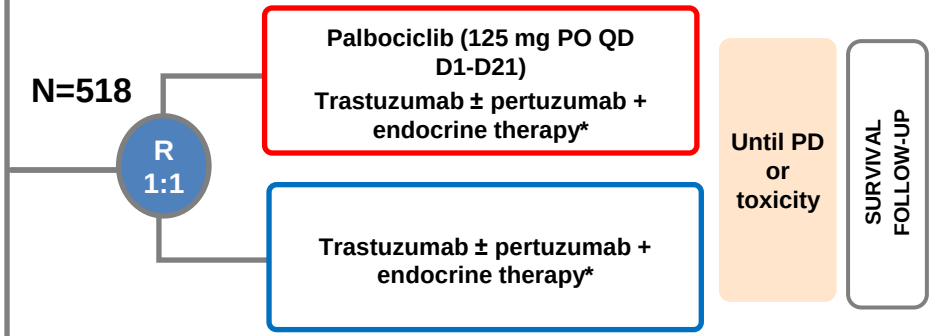
AFT-38 PATINA Study Design

Registration

- Histologically confirmed HR+,HER2+ mBC
- No prior treatment in the advanced setting beyond induction treatment
- 6-8 cycles of treatment, including trastuzumab ± pertuzumab and taxane/vinorelbine

Key eligibility criteria

- Completion of induction chemotherapy and no evidence of disease progression (i.e., CR, PR, or SD)



Stratification factors

- Pertuzumab use (yes vs no)
  - The non-pertuzumab option is limited to up to 20% of the population
- Prior anti-HER2 therapy in the (neo)adjuvant setting (yes vs no, including de novo)†
- Response to induction therapy (CR or PR vs SD) by investigator assessment†
- Type of endocrine therapy (fulvestrant vs aromatase inhibitor)

*Trastuzumab and pertuzumab were administered per SOC. Endocrine therapy options include an aromatase inhibitor or fulvestrant. †Factors used in stratified analyses.
CR=complete response; D=day; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; mBC=metastatic breast cancer; PD=progressive disease; PO=orally; PR=partial response; QD=once a day; R=randomization; SD=stable disease; SOC=standard of care.

Statistical Analysis

Primary endpoint (investigator-assessed PFS)

- 90% power for a minimum detectable hazard ratio of 0.667
- One-sided log-rank test at the 0.025 level of significance
- Final analysis planned after 269 events
  - Two planned interim analyses at 50% and 60% of PFS events

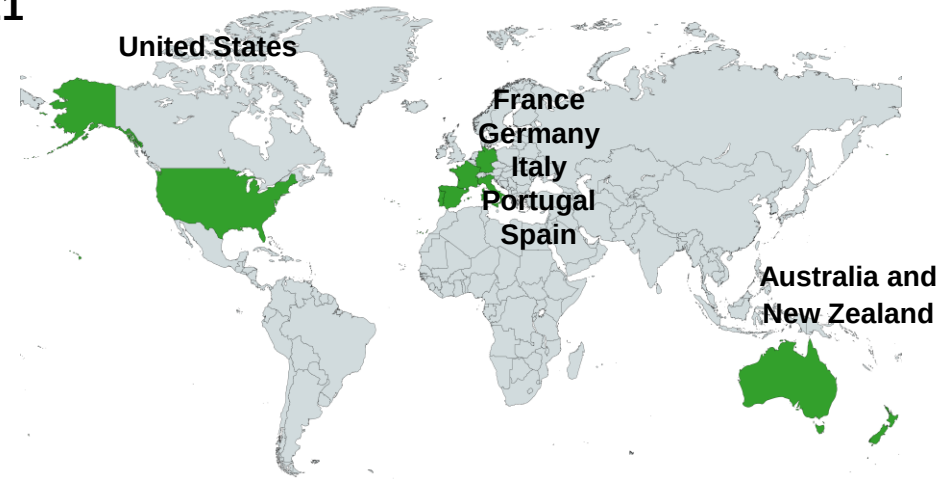
Key secondary objective (OS)

- OS is hierarchically tested at the interim and final PFS analysis
  - Pre-specified boundary (α=0.0002, and 0.025, 1-sided)
- Final OS analysis planned after 247 events
  - 80% power to detect a hazard ratio of 0.70
  - One-sided log-rank test at the 0.05 level of significance

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

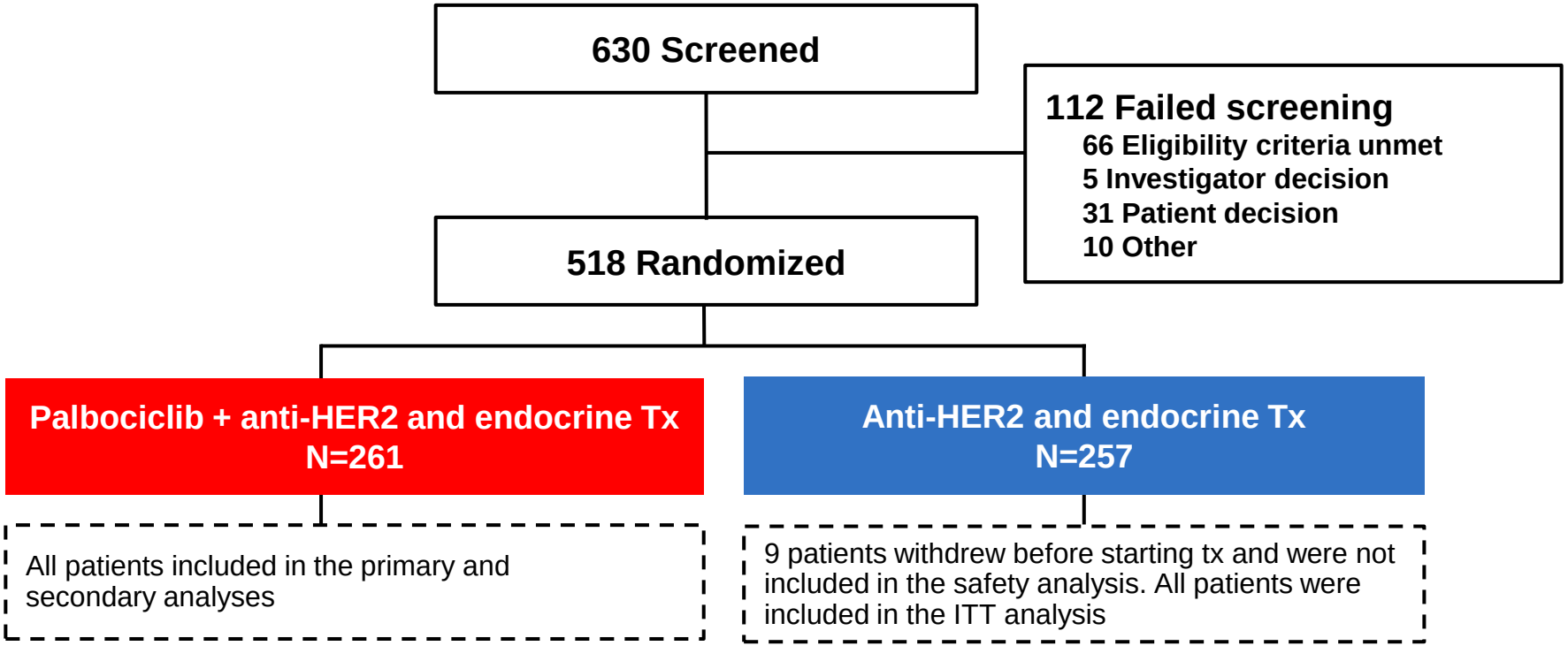
Study Enrollment and Analysis

- Enrollment Period: **June 2017 until July 2021**
  - Target accrual of 496 participants
  - Final accrual of 518 participants
- Date of data cutoff for final PFS analysis: **October 15, 2024**
- DSMB recommendation to release of Study Data: **December 02, 2024**



DSMB=Data and Safety Monitoring Board; PFS=progression-free survival.

CONSORT Diagram



HER2=human epidermal growth factor receptor 2; ITT=intent-to-treat; Tx=treatment.

Patient Demographic and Key Characteristics

	Palbociclib + anti-HER2 and ET (N=261)	Anti-HER2 therapy and ET (N=257)	Total (N=518)
Age (years)			
Median (IQR)	53.5 (43.6, 60.4)	53.0 (45.1, 62.8)	53.4 (44.2, 61.4)
Race, n (%)			
White	205 (91.9)	192 (91.4)	397 (91.7)
Asian Indian + Chinese + other Asian	8 (3.1)	3 (1.2)	11 (2.1)
Black or African American	4 (1.8)	11 (5.2)	15 (3.5)
Other	6 (2.3)	4 (1.6)	10 (1.9)
Gender, n (%)			
Female	259 (99.2)	256 (99.6)	515 (99.4)
Male	2 (0.8)	1 (0.4)	3 (0.6)
Number of cycles of induction Tx			
Median (range)	6 (4-8)	6 (4-8)	

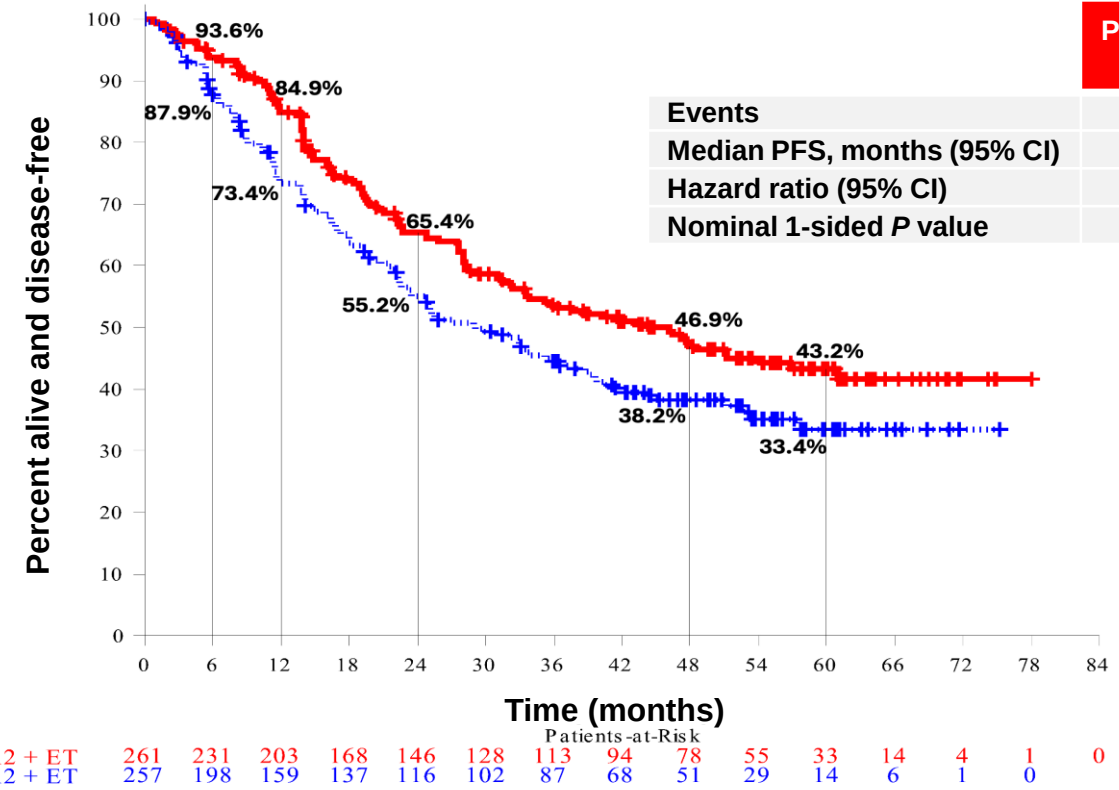
HER2=human epidermal growth factor receptor 2; ET=endocrine therapy; IQR=interquartile range; Tx=treatment.

Patient Demographic and Key Characteristics (cont.)

	Palbociclib + anti-HER2 and ET (N=261)	Anti-HER2 therapy and ET (N=257)	Total (N=518)
Pertuzumab use, n (%)			
No	8 (3.1)	6 (2.3)	14 (2.7)
Yes	253 (96.9)	251 (97.7)	504 (97.3)
Type of endocrine therapy, n (%)			
Aromatase inhibitor	237 (90.8)	234 (91.1)	471 (90.9)
Fulvestrant	24 (9.2)	23 (8.9)	47 (9.1)
Prior anti-HER2 therapy in the (neo)adjuvant setting,* n (%)			
No	71 (27.2)	75 (29.2)	146 (28.2)
Yes	190 (72.8)	182 (70.8)	372 (71.8)
Best response to induction therapy by investigator assessment,* n (%)			
CR or PR	179 (68.6)	176 (68.5)	355 (68.5)
SD	82 (31.4)	81 (31.5)	163 (31.5)

*Factors used in stratified analyses.
CR=complete response; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; PR=partial response; SD=stable disease.

Primary Endpoint: PFS (Investigator-Assessed)



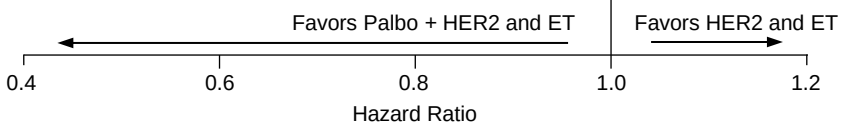
	Palbo + anti-HER2 and ET	Anti-HER2 and ET
Events	126/261	136/257
Median PFS, months (95% CI)	**44.3** (32.4-60.9)	**29.1** (23.3-38.6)
Hazard ratio (95% CI)	0.74 (0.58-0.94)	
Nominal 1-sided *P* value	0.0074	

Median follow-up on patients who are alive and disease-free, 52.6 months

CI=confidence interval; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; palbo=palbociclib.

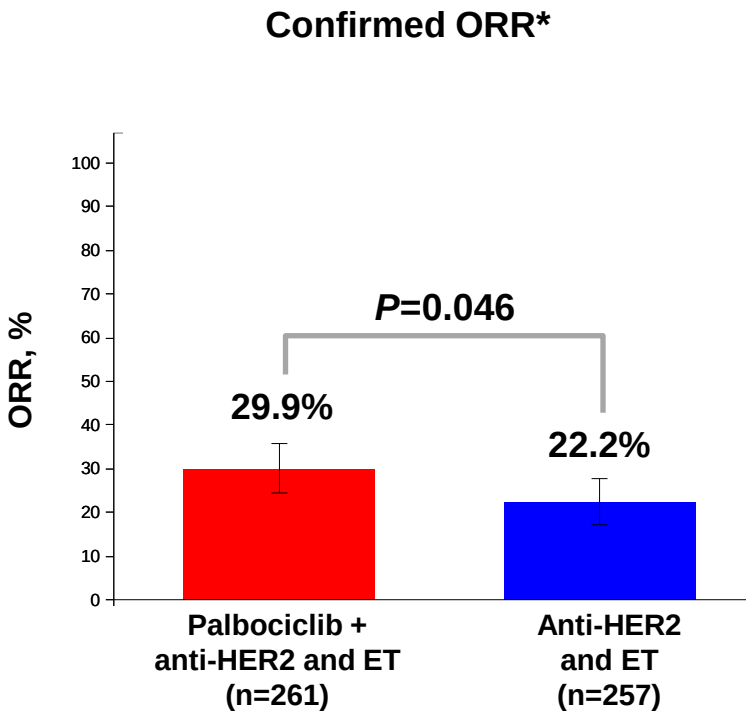
PFS by Stratification Subgroups

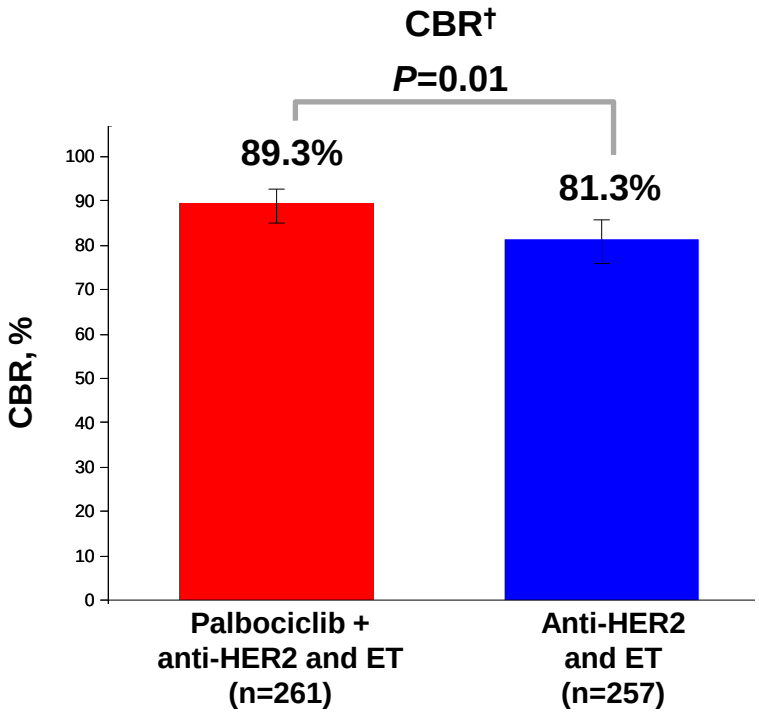
	Events/Total	Hazard Ratio (95% CI)
Overall	262/518	0.74 (0.58-0.94)
Prior anti-HER2 therapy	186/372	0.76 (0.57-1.01)
No prior anti-HER2 therapy	76/146	0.68 (0.543-1.07)
Best response to induction (CR* or PR*)	182/355	0.76 (0.57-1.02)
Best response to induction (SD*)	80/163	0.72 (0.47-1.12)



*Factors used in stratified analyses.
CR=Complete Response; Palbo=palbociclib; PR=Partial Response; SD=Stable Disease

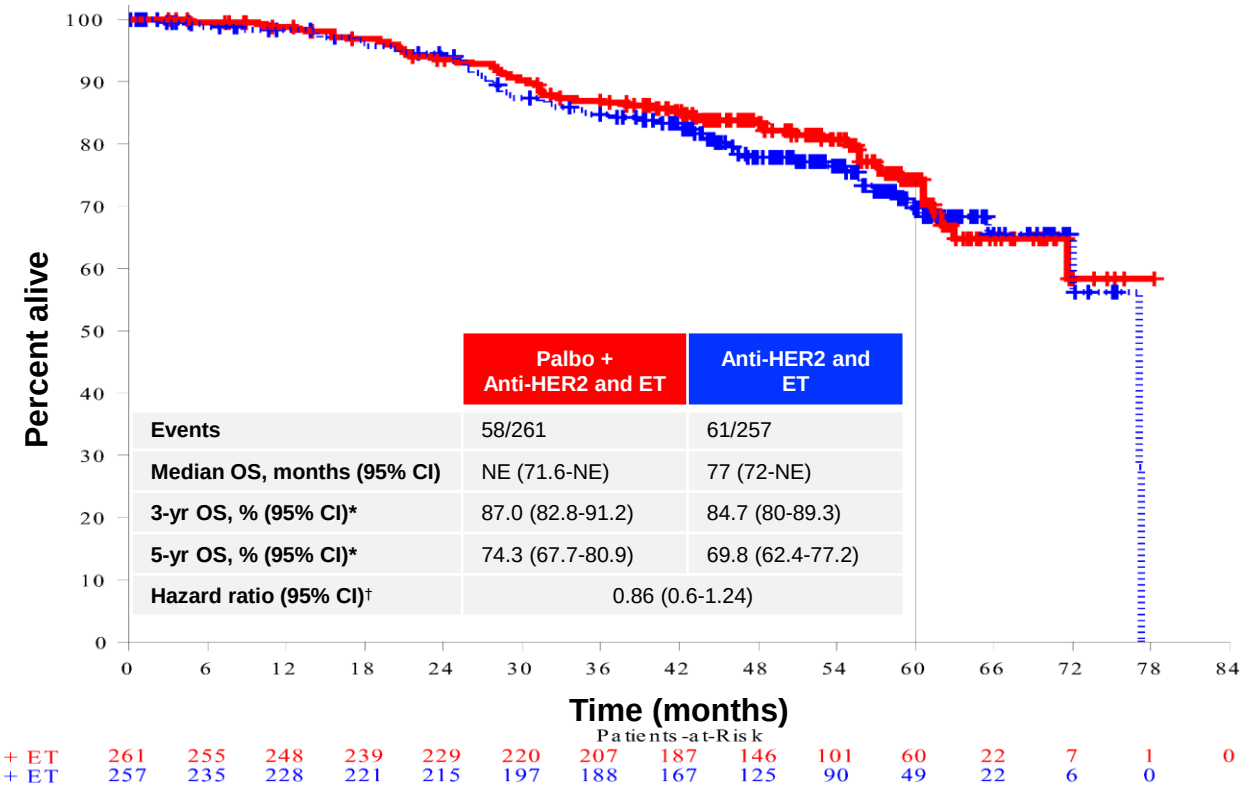
Secondary Endpoints: ORR and CBR (Investigator-Assessed)





*Patients with a CR or PR on at least 2 consecutive reporting periods according to RECIST v.1.1 definitions. †Patients with a CR, PR, and/or SD for ≥24 weeks per RECIST v1.1.
CBR=clinical benefit rate; CR=complete response; ET=endocrine therapy; ORR=objective response rate; PR=partial response; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, version 1.1; SD=stable disease.

Secondary Endpoint: Overall Survival (Interim Analysis)



	Palbo + Anti-HER2 and ET	Anti-HER2 and ET
Events	58/261	61/257
Median OS, months (95% CI)	NE (71.6-NE)	77 (72-NE)
3-yr OS, % (95% CI)*	87.0 (82.8-91.2)	84.7 (80-89.3)
5-yr OS, % (95% CI)*	74.3 (67.7-80.9)	69.8 (62.4-77.2)
Hazard ratio (95% CI)†	0.86 (0.6-1.24)	

*Kaplan-Meier method.
†Unstratified Cox model.
CI=confidence interval; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; NE=not evaluable; OS=overall survival; palbo=palbociclib.

Adverse Events (Grade ≥2 in ≥10% of Patients)

Adverse Events, n (%)*	**Palbociclib + anti-HER2 and ET (N=261)**			**Anti-HER2 and ET (N=248)**		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Neutropenia	52 (19.9)	165 (63.2)	12 (4.6)	10 (4.0)	11 (4.4)	0 (0.0)
White blood cell count decreased	30 (11.5)	30 (11.5)	1 (0.4)	2 (0.8)	0 (0.0)	0 (0.0)
Fatigue	60 (22.9)	14 (5.4)	0 (0.0)	32 (12.9)	0 (0.0)	0 (0.0)
Stomatitis	45 (17.2)	11 (4.2)	0 (0.0)	3 (1.2)	0 (0.0)	0 (0.0)
Diarrhea	69 (26.4)	29 (11.1)	0 (0.0)	26 (10.5)	4 (1.6)	0 (0.0)
Upper respiratory tract infection	30 (11.5)	1 (0.4)	0 (0.0)	16 (6.5)	0 (0.0)	0 (0.0)
Urinary tract infection	26 (10.0)	2 (0.8)	0 (0.0)	19 (7.7)	1 (0.4)	0 (0.0)
Arthralgia	23 (8.8)	4 (1.5)	0 (0.0)	44 (17.7)	3 (1.2)	0 (0.0)
Ejection fraction decreased	22 (8.4)	1 (0.4)	0 (0.0)	21 (8.5)	8 (3.2)	0 (0.0)
Cardiac heart failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)

- The incidence of grade ≥4 adverse events regardless of treatment attribution was similar across study arms (12.3% vs 8.9% for palbociclib-containing arm vs control; *P*=0.21)
- Treatment discontinuation due to AEs were reported in 14 (7.5%) of patients in the palbociclib arm
- No treatment-related deaths were reported in either arm of the study

*Adverse events were assessed per Common Terminology Criteria for Adverse Events, version 4.0 regardless of treatment attribution. Stomatitis, mouth ulceration, mucosal inflammation, and mucositis were assessed as medical concepts using grouped terms. Fatigue and asthenia were assessed as medical concepts using grouped terms. Cardiac safety data were also included in the table above. AE=adverse events.

Conclusions

- Our results reinforce the strong scientific rationale for overcoming resistance to anti-HER2 therapy and endocrine therapy by adding CDK4/6 inhibition

- The addition of palbociclib to anti-HER2 and endocrine therapy demonstrated a statistically significant improvement in PFS in patients diagnosed with HR+,HER2+ advanced breast cancer in the first-line metastatic setting

- Palbociclib added to anti-HER2 and endocrine therapy had a manageable toxicity profile and without new safety signals

CDK4/6=cyclin-dependent kinase 4/6; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; PFS=progression-free survival.

Implications to Clinical Practice

- The AFT-38 PATINA phase III study demonstrates a **clinically meaningful** improvement in PFS among patients diagnosed with HR+,HER2+ breast cancer
  - Median PFS increased from 29.1 to 44.3 months (Δ15.2 months)
  - Manageable toxicity

Palbociclib added to anti-HER2 and endocrine therapy may represent a new standard of care for patients diagnosed with HR+,HER2+ advanced breast cancer

HER2=human epidermal growth factor receptor 2; HR=hormone receptor; PFS=progression-free survival.

Acknowledgments

- All patients and their families who participated in this study
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