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Primary Results From a Phase 2a Study of Zanidatamab in Combination With Palbociclib Plus Fulvestrant in HER2+ HR+ Metastatic Breast Cancer

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Disclosures

- **Consultant for:** AstraZeneca, COR2ED, Daiichi Sankyo, Pierre-Fabre, and Seagen
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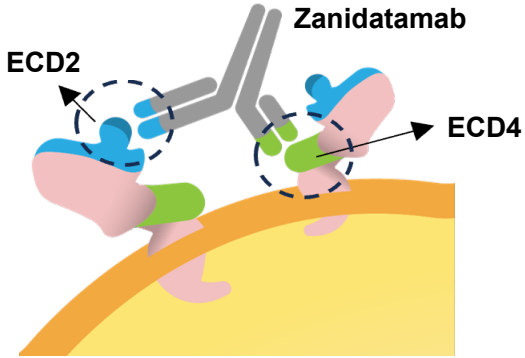
Background and Objective

- Prior studies with a HER2-targeting agent combined with an ER antagonist with or without a CDK 4/6 inhibitor have shown clinical benefit in patients with HER2+ HR+ mBC[1,2]
- Zanidatamab is a bispecific antibody that simultaneously binds two non-overlapping extracellular domains of HER2 (biparatopic binding) leading to[3]:
  - Receptor crosslinking, clustering, internalization, and downregulation
  - Inhibition of tumor cell signaling and proliferation by preventing HER2 dimerization
  - Immune-mediated antitumor effects including antibody-dependent cellular cytotoxicity and phagocytosis, and complement-dependent cytotoxicity

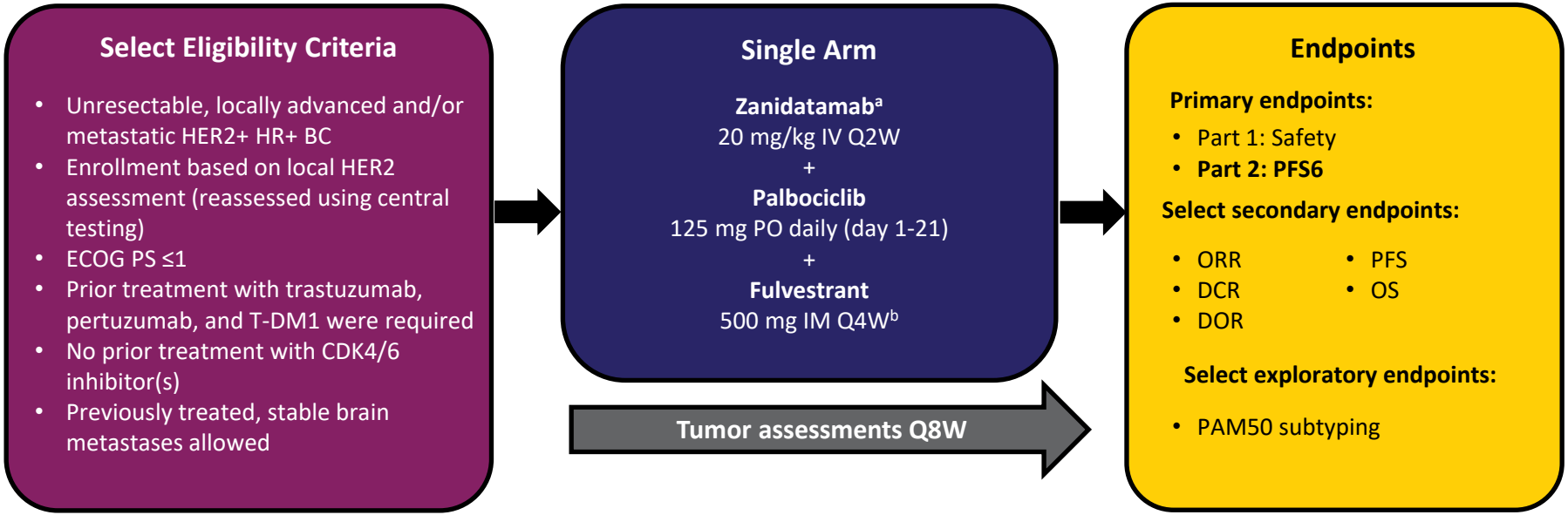
Zanidatamab binding to HER2[3]



Objective: To evaluate the safety and efficacy of zanidatamab in combination with palbociclib (CDK4/6 inhibitor) plus fulvestrant (ER antagonist) in HER2+ HR+ mBC

1. Tolaney SM, et al. *Lancet Oncol*. 2020;21(6):763-775. 2. Ciruelos E, et al. *Clin Cancer Res*. 2020;26(22):5820-5829. 3. Weisser NE, et al. *Nat Commun*. 2023;14(1):1394.

Study Design: Phase 2a study (NCT04224272)



- Part 1 of the study evaluated safety and was previously reported (n=45); no zanidatamab-related DLTs occurred and the RDs for part 2 were identified[1,c]

[a]Mandatory infusion-related reaction prophylaxis (acetaminophen, diphenhydramine, and corticosteroids [hydrocortisone or dexamethasone]). [b]After loading doses of 500 mg IM on days 1, 15, 28. [c]One DLT of grade 4 neutropenia lasting >7 days occurred and was related to palbociclib.

1. Escrivá-de-Romani S, et al. Presented at San Antonio Breast Cancer Symposium 2022. Poster presentation [PD18-10].

Demographics and Baseline Characteristics

- **Enrollment completed November 2022 (data extracted August 2023)**
- HER2 central testing: 32 patients were HER2+ (ccHER2+), 18 HER2− (positive with local assessment), and 1 patient had missing data
- PAM50 subtyping: available for 29 patients (57%) who had adequate tissue samples

	All Patients (N=51)	ccHER2+ (n=32)	non-ccHER2+ (n=19)
Median age (range), years	54 (36-77)	55 (36-75)	54 (39-77)
Female sex, n (%)	49 (96)	31 (97)	18 (95)
Race, n (%)			
White	42 (82)	30 (94)	12 (63)
Asian	2 (4)	1 (3)	1 (5)
Other	7 (14)	1 (3)	6 (32)
ECOG PS, n (%)			
0	25 (49)	18 (56)	7 (37)
1	26 (51)	14 (44)	12 (63)
HER2 and HR status: local testing, n (%)	51 (100)		
HER2+: central testing	32 (63)	32 (100)	0 (0)
HR+: local testing only	51 (100)	32 (100)	19 (100)
Prior history of brain metastases, n (%)	9 (18)	8 (25)	1 (5)
Prior systemic anticancer therapy regimens: metastatic setting, n (%)	51 (100)	32 (100)	19 (100)
Median # of prior regimens (range)	4 (1-12)	4 (1-12)	4 (2-10)

	All Patients (N=51)	ccHER2+ (n=32)	non-ccHER2+ (n=19)
Prior endocrine therapy: metastatic setting, n (%)	37 (73)	21 (66)	16 (84)
Median # of prior regimens (range)	1 (0-5)	1 (0-5)	1 (0-3)
Prior fulvestrant therapy: any setting, n (%)	11 (22)	6 (19)	5 (26)
Prior HER2-targeted therapy: any setting, n (%)	51 (100)	32 (100)	19 (100)
Median (range)	4 (2-6)	4 (1-10)	3 (2-8)
Trastuzumab	51 (100)	32 (100)	19 (100)
T-DM1	50 (98)	31 (97)	19 (100)
Pertuzumab	42 (82)	26 (81)	16 (84)
Lapatinib	14 (27)	9 (28)	5 (26)
Tucatinib	13 (25)	11 (34)	2 (11)
T-DXd	12 (24)	8 (25)	4 (21)
Neratinib	2 (4)	2 (6)	0 (0)
Margetuximab	1 (2)	1 (3)	0 (0)

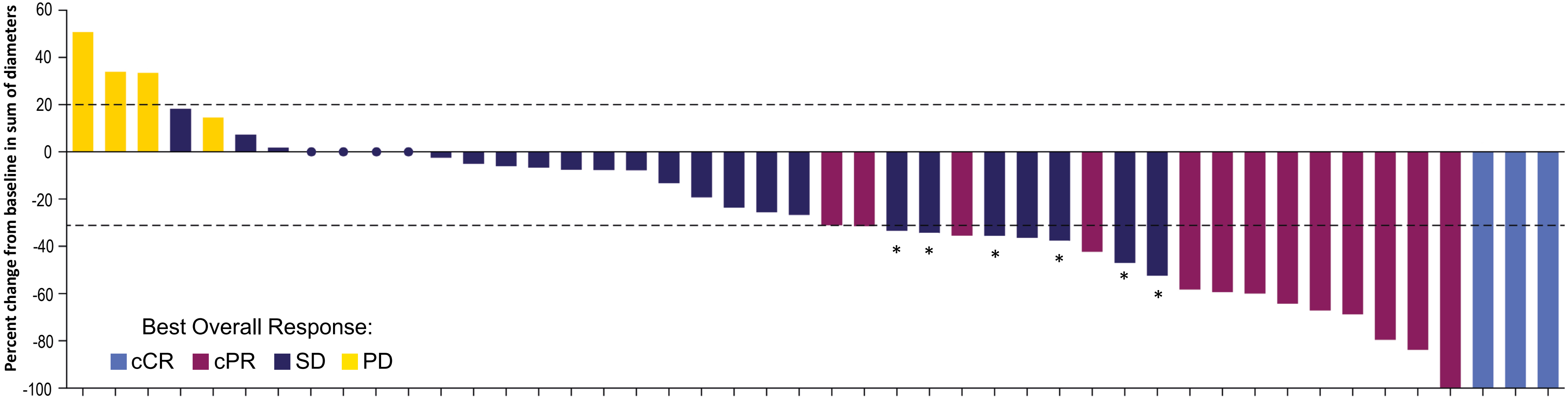
Efficacy and Duration of Treatment

- Median (range) follow-up time: 16 (2-32) months
- Median (range) duration of zanidatamab treatment: 8 (1-30) months

	All Patients (N=51)	ccHER2+ Subset (n=32)	non-ccHER2+ Subset (n=19)
PFS6, n (%) [95% CI]	34 (**67**) [52, 79]	22 (**69**) [50, 84]	12 (**63**) [38, 84]
Median PFS, months (95% CI)	12 (8, 15)	15 (9, 17)	8 (4, 9)
cORR, n (%) [95% CI][a]	16 (35) [21, 50]	14 (48) [29, 68]	2 (10) [1, 33]
cBOR, n (%)[a]			
CR	3 (6)	3 (10)	0 (0)
PR	13 (28)	11 (38)	2 (12)
SD	26 (56)	13 (45)	13 (76)
PD	4 (9)	2 (7)	2 (12)
DCR, n (%) [95% CI]	42 (91) [79, 98]	27 (93) [77, 99]	15 (88) [64, 98]
Median DOR, months (95% CI)[b]	15 (12, 25)	14 (11, 25)	NE (7, NE)[c]

[a]Evaluated in patients with measurable disease (n=46 all patients; n=29 ccHER2+ subset; n=17 non-ccHER2+ subset. [b]Evaluated in patients with a CR or PR (n=16 all patients; n=14 ccHER2+ subset; n=2 non-ccHER2+ subset). [c]Median DOR was 7.1 and 24.1 months for the 2 patients with a response in the non-ccHER2+ subset.

Efficacy of Treatment by Best Overall Response (All Patients With Measurable Disease)



Central IHC	1+	3+	1+	2+	2+	2+	1+	2+	2+	2+		1+	2+	2+	3+	0	1+	2+	2+	3+	1+	1+	2+	2+	3+	0	3+	3+	2+	2+	3+	3+	3+	2+	2+	2+	3+	3+	3+	2+	2+	3+	3+	3+	3+	2+
Central FISH	-	+	-	+	+	+		+	+	-			-	+	+	-	+	+		+	-	-	-	+	+	-	+	+	-	+	+	+	+	+		-	-	+	+	+	+	+	+	+	+	+
PAM50		LB		HE	HE		HE		LB	LB		HE						HE		HE	LB	LB	HE		HE	HE	HE	HE	LB	LB			HE	HE	LB		LB				HE	LB				HE
Prior fulv			Y			Y				Y	Y					Y			Y														Y						Y					Y		
Prior HER2 Trt[a]	DPX	DP CX	DP	DPC	DP CX	DP CX	DPC	DPL	PC LN	DP	DP	DLX	DP	DPC	DL	DPL	DP	DPC	DL	DP	DPC	DP	DP	DP CN	DPL	DPX	DPC	DP CM	DPX	DL	DP	DP	DPL	DLX	D	DP	DPX	DP	DP	DP	DP	DX	D	D	DP	DP

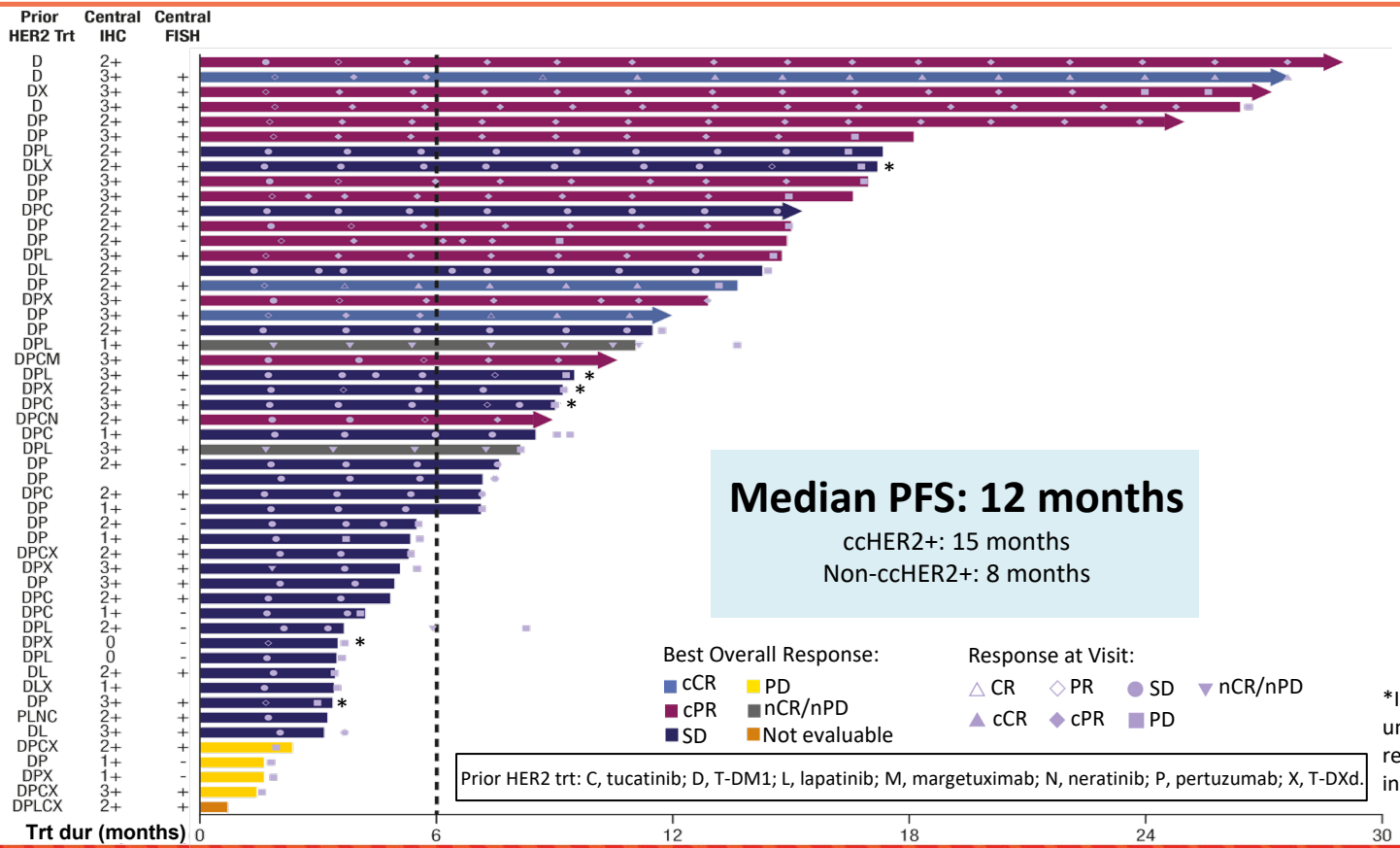
Prior HER2 trt[a]: C, tucatinib; D, T-DM1; L, lapatinib; M, margetuximab; N, neratinib; P, pertuzumab; X, T-DXd.

PAM50 subtype: HE, HER2-enriched; LB, luminal B.

*Indicates patients with unconfirmed partial responses. Dotted lines indicate -30% and +20% change in tumor size.

[a]All patients received prior trastuzumab and taxane.

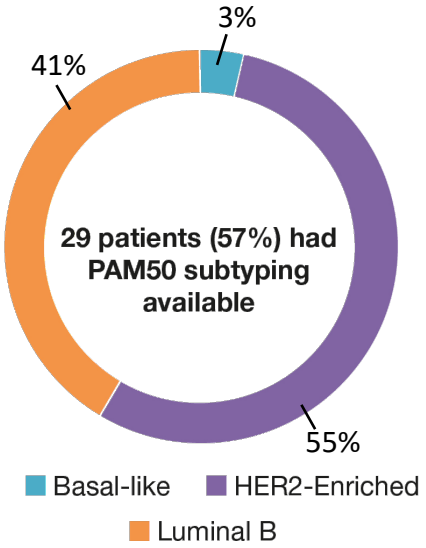
Treatment Duration and PFS



*Indicates patients with unconfirmed partial responses. Dotted line indicates 6 months.

Efficacy of Treatment by PAM50 Subtype

	All Patients With PAM50 Subtyping (n=29)	Basal-Like (n=1)[a]	HER2-Enriched (n=16)	Luminal B (n=12)
PFS6, n (%) [95% CI]	19 (**66**) [46, 82]	1 (**100**) [2, 100]	10 (**62**) [35, 85]	8 (**67**) [35, 90]
Median PFS, months (95% CI)	9 (7, 14)	6 (NE, NE)	9 (4, 15)	12 (3, 24)
cORR, n (%)[b]	7 (28)	0	4 (27)	3 (30)
cBOR, n (%)[b]				
CR	1 (4)	0	1 (7)	0
PR	6 (24)	0	3 (20)	3 (30)
SD	16 (64)	0	10 (67)	6 (60)
PD	2 (8)	0	1 (7)	1 (10)
DCR, n (%) [95% CI][b]	23 (92) [74, 99]	0	14 (93) [68, 100]	9 (90) [56, 100]
Median DOR, months (95% CI)[c]	22 (12, NE)	0	13 (12, NE)	NE (22, NE)



- Compared with HER2-enriched, luminal B mBC was associated with numerically, but not statistically significant, longer median PFS (12 vs 9 months; *P*=0.74) and similar PFS6 (67% vs 62%)
- The cORRs for patients with HER2-enriched or luminal B mBC were numerically similar

[a]This patient did not have measurable disease. [b]Evaluated in patients with measurable disease (n=25 all patients with PAM50 subtyping; n=15 HER2-enriched; n=10 luminal B). [c]Evaluated in patients with CR or PR (n=7 all patients with PAM50 subtyping; n=4 HER2-enriched; n=3 luminal B).

Safety Outcomes Following Treatment (All Patients)

	Patients (N=51)	
	Any Grade	Grade 3 or 4
Any TRAE, n (%)	51 (100)	34 (67)
Serious TRAE, n (%)	1 (2)	1 (2)
TRAE in >20% of patients and/or grade 3 TRAE in ≥2 patients, n (%)		
Diarrhea	41 (80)	7 (14)
Nausea	20 (39)	1 (2)
Stomatitis	19 (37)	1 (2)
Neutrophil count decreased/neutropenia	30 (59)	27 (53)
Anemia	15 (29)	5 (10)
Vomiting	13 (25)	1 (2)
Asthenia	12 (24)	0 (0)
Thrombocytopenia	8 (16)	3 (6)
Hypomagnesemia	5 (10)	2 (4)
Hypokalemia	4 (8)	2 (4)
Treatment-related AESI, n (%)		
Ejection fraction decreased	6 (12)	1 (2)[a]
Infusion-related reaction	2 (4)	0 (0)

AEs requiring discontinuation of drug

- All treatments: 1 patient (grade 1 asthenia)
- Palbociclib treatment: 2 patients (1 had grade 3 diarrhea and 1 had grade 3 transaminases increased)

One serious TRAE (transaminases increased) was reported (event resolved)

AEs led to a dose reduction of zanidatamab in 4 patients

14 deaths (none related to treatment)

- 12 due to disease progression
- 1 due to an unrelated TEAE of COVID-19
- 1 cause unknown (causality pending)

[a]Event ongoing at the time data was extracted.

Conclusions

- Zanidatamab in combination with palbociclib plus fulvestrant demonstrated promising PFS outcomes (PFS6 of 67% and median PFS of 12 months) with durable responses (median DOR of 15 months) in this heavily-pretreated population
  - This trial is ongoing and OS data were not mature at data cutoff
  - There were no statistical differences in efficacy observed between luminal B and HER2-enriched subtypes
- This combination therapy was well tolerated with an easily manageable safety profile in heavily-pretreated patients with HER2+ HR+ mBC
- These results support further development of this novel chemotherapy-free treatment regimen for heavily-pretreated patients with HER2+ HR+ mBC

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