A Phase Ib study of xentuzumab plus abemaciclib and fulvestrant in patients with advanced HR+, HER2-negative breast cancer with visceral or non-visceral disease

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Introduction

- CDK4 & 6 inhibitors, such as abemaciclib, in combination with ET are standard of care for advanced HR+ BC[1]
- Activation of the IGF-1R results in increased cyclin D1 expression,[2] providing a rationale for combining IGF and CDK4 & 6 inhibition
- Xentuzumab is an IGF ligand-neutralizing antibody.[3] Xentuzumab plus exemestane and everolimus has shown PFS benefit in a subgroup of patients with advanced HR+ BC and non-visceral disease[4]

Objectives

- NCT03099174 is a prospective, open-label study investigating xentuzumab + abemaciclib ± ET. In dose-finding cohorts, the RP2D was determined as xentuzumab 1000 mg weekly + abemaciclib 150 mg Q12h ± ET[5]
- We present interim secondary endpoint data from expansion cohorts in patients with advanced HR+ BC and visceral or non-visceral disease

BC, breast cancer; CDK, cyclin-dependent kinase; ET, endocrine therapy; HR+, hormone receptor-positive; IGF, insulin-like growth factor; IGF-1R, IGF 1 receptor; PFS, progression-free survival; Q12h, every 12 hours; RP2D, recommended phase 2 dose.

1. Cardoso F, et al. Ann Oncol 2020;31:1623–49; 2. Tang L, et al. Int J Clin Exp Pathol 2017;10:11652–58; 3. Friedbichler K, et al. Mol Cancer Ther 2014;13:399–409; 4. Schmid P, et al. Breast Cancer Res 2021;23:8; 5. Yee D, et al. Cancer Res 2019;80 (4 Suppl) P3-11-05

Methods

<table>
<tr><th colspan="2">Expansion cohorts in patients with advanced HR+/HER2– breast cancer
Xentuzumab 1000 mg i.v. weekly + abemaciclib 150 mg p.o. Q12h +
fulvestrant 500 mg per label</th></tr>
<tr><td>Cohort D1</td><td>Cohort D2</td></tr>
<tr><td>≥1 documented visceral metastasis*</td><td>No visceral metastases</td></tr>
<tr><td colspan="2">Progression on or after ET (including adjuvant ET)</td></tr>
<tr><td colspan="2">No prior CDK4 & 6 inhibitor therapy</td></tr>
<tr><td colspan="2">No more than one line of prior endocrine-based therapy or any CT for advanced
or metastatic disease</td></tr>
<tr><td colspan="2">Primary endpoint: PFS rate at 18 months (data currently immature)
Secondary endpoints: DCR (CR, PR or SD ≥ Week 24), OR (CR or PR), time to OR,
duration of OR and DCR, PFS</td></tr>
</table>

*Includes lung, liver, pleural and peritoneal metastases, malignant pleural effusion and malignant peritoneal effusion involvement.
CDK, cyclin-dependent kinase; CR, complete response; CT, chemotherapy; DCR, disease control rate; ET, endocrine therapy;
HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; i.v., intravenously; OR, overall response; PFS, progression-free survival; p.o., orally;
PR, partial response; Q12h, every 12 hours; SD, stable disease

Patients and treatment

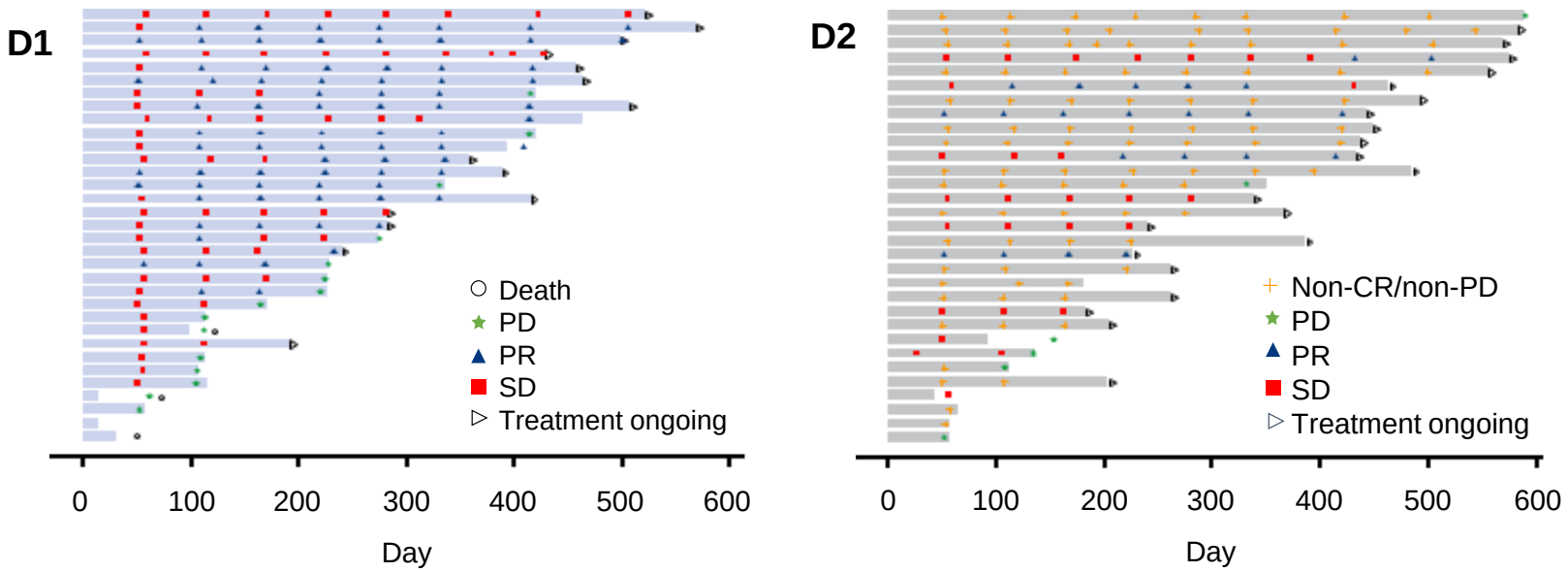
- 33/31 patients were treated in Cohorts D1/D2, respectively; at data cut-off (March 31, 2021*), 14/21 remain on treatment
- 19 patients had discontinued treatment in D1 (14 due to PD) and 10 had discontinued in D2 (6 due to PD)
- In Cohort D2, 20 patients had bone-only, non-measurable disease; other characteristics are shown below

	D1 (N=33)	D2 (N=31)
Female, n (%)	33 (100)	31 (100)
Median age, years (range)	60.0 (36–78)	53.0 (36–80)
Menopausal status (pre/peri/post), n (%)†	2 (6.1) / 4 (12.1) / 27 (81.8)	9 (29.0) / 2 (6.5) / 20 (64.5)
Median time since first metastasis/recurrence, months (range)	1.9 (0.1–208.8)	2.1 (0.7–90.5)
Prior adjuvant CT, n (%)	23 (69.7)	24 (77.4)
Prior ET, n (%)	32 (97.0)	27 (87.1)

*Updated versus abstract; †all pre/perimenopausal patients had chemical/surgical/radiation-induced postmenopausal status.
CT, chemotherapy; ET, endocrine therapy; PD, progressive disease

Interim efficacy

	D1 (N=33)	D2 (N=31)
DCR, n (%)	**22 (66.7)**	**23 (74.2)**
PR	18 (54.5)	5 (16.1)*
Non-CR/non-PD ≥ Week 24	–	15 (48.4)
SD ≥ Week 24	4 (12.1)	3 (9.7)
Median duration of disease control, months (range)	**12.2 (7.2–16.6)**	**12.9 (5.3–19.4)**



*In the non-visceral cohort, 20 patients had non-measurable disease.
CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; SD, stable disease

Safety

Patients with:*	D1 (N=33)		D2 (N=31)	
	All	Grade ≥3	All	Grade ≥3
Any AE	33 (100)	27 (81.8)	31 (100)	27 (87.1)
Diarrhea	29 (87.9)	1 (3.0)	28 (90.3)	4 (12.9)
Nausea	21 (63.6)	0	20 (64.5)	2 (6.5)
Neutrophil count decreased	18 (54.5)	12 (36.4)	15 (48.4)	11 (35.5)
Anemia	13 (39.4)	1 (3.0)	11 (35.5)	1 (3.2)
Asthenia	12 (36.4)	0	9 (29.0)	1 (3.2)
Muscle spasms	12 (36.4)	0	5 (16.1)	0
Platelet count decreased	10 (30.3)	0	13 (41.9)	1 (3.2)
Headache	10 (30.3)	0	12 (38.7)	0
Vomiting	9 (27.3)	0	13 (41.9)	2 (6.5)

*Any-cause AEs with incidence >35% in either cohort shown; there was one grade 5 AE (respiratory syncytial virus infection in Cohort D1)

Patients with AEs leading to:	D1 (N=33)	D2 (N=31)
Dose reduction/discontinuation of xentuzumab	0 / 4 (12.1)	10 (32.3) / 4 (12.9)
Dose reduction/discontinuation of abemaciclib	19 (57.6) / 5 (15.2)	21 (67.7) / 8 (25.8)

- No AEs of hyper/hypoglycemia were reported
- One patient had grade 2 interstitial lung disease/pneumonitis in Cohort D2
- There was one grade 2 infusion-related reaction in Cohort D2

AE, adverse event

Key findings and conclusions

- Xentuzumab plus abemaciclib and fulvestrant demonstrated encouraging disease control in patients with advanced HR+ BC with visceral and non-visceral disease
  - DCR was 66.7% in patients with visceral metastases and 74.2% in those without
- The safety profile was manageable and consistent with the known profiles of the three agents
- The triplet combination will be further evaluated in patients with advanced HR+ BC without visceral metastases that has progressed on aromatase inhibitor and CDK4 & 6 inhibitor therapy (excluding abemaciclib; currently recruiting ~20 patients)

BC, breast cancer; CDK, cyclin-dependent kinase; DCR, disease control rate; HR+, hormone receptor-positive