Society of Medical Education & Research

2022, Volume 2, Issue 2, Page No: 89-102

ISSN: 3108-4834

Archive of International Journal of Cancer and Allied Science

Phase Ib Trial of Xentuzumab Combined with Abemaciclib in Patients with Advanced Solid Tumors, Including Its Use Alongside Endocrine Therapy in Advanced Breast Cancer

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Abstract

This phase Ib study evaluated the IGF-1/IGF-2-neutralizing antibody xentuzumab combined with abemaciclib, with or without endocrine therapy (ET), in patients with advanced or metastatic solid tumors, particularly hormone receptor (HR)-positive, HER2-negative breast cancer. In the initial dose-escalation phase (cohort A), patients with advanced solid tumors received increasing doses of xentuzumab combined with abemaciclib. Subsequent dose-finding phases (cohorts B–D) enrolled patients with advanced/metastatic HR-positive, HER2-negative breast cancer, who received xentuzumab plus abemaciclib in combination with letrozole, anastrozole, or fulvestrant. Expansion phases evaluated xentuzumab plus abemaciclib and fulvestrant in patients with HR-positive, HER2-negative breast cancer who had progressed on prior ET, focusing on those with visceral metastases (cohort D1), non-visceral disease (cohort D2), or non-visceral disease after prior ET and CDK inhibitor therapy (cohort F). Primary outcomes included maximum tolerated dose (MTD) for cohorts A–D, 18-month progression-free survival (PFS) rate for cohorts D1/D2, and disease control rate for cohort F. Extensive biomarker evaluations were also performed.

Overall, 133 patients received treatment. The MTD was established as xentuzumab 1000 mg weekly plus abemaciclib 150 mg twice daily (cohorts A–D). The most frequent grade ≥3 adverse event was neutropenia. Response rates in cohorts B–D were at least 25%. The 18-month PFS rates were 41.4% in cohort D1 and 78.5% in cohort D2. The disease control rate in cohort F reached 40.0%. Biomarker assessments confirmed target inhibition, with potential prognostic indicators including baseline serum IGF-1 levels, CCND1 expression, and MCL-1 mutations. The combination of xentuzumab with abemaciclib and ET showed acceptable safety and encouraging clinical activity, particularly in breast cancer patients with non-visceral metastases.

Keywords: Hormone receptor-positive breast cancer, Insulin-like growth factor 1 (IGF-1), Insulin-like growth factor 2 (IGF-2), Xentuzumab, Abemaciclib

Introduction

The insulin-like growth factor type 1 receptor (IGF-1R) pathway and the cyclin-dependent kinase (CDK) 4/6-retinoblastoma axis play key roles in tumor development and treatment resistance across various malignancies, notably in hormone receptor (HR)-positive, HER2-negative breast cancer [1-4] and non-small-cell lung cancer (NSCLC) [5, 6]. In advanced HR-positive, HER2-negative breast cancer, the combination of CDK4/6 inhibitors with endocrine therapy (ET) represents the established first-line standard of care [7]. Abemaciclib, an orally administered CDK4/6 inhibitor with continuous dosing, is approved for use alongside an aromatase inhibitor as initial ET, with fulvestrant in patients whose disease has progressed after prior ET, or as single-agent therapy following ET and chemotherapy in the metastatic

Access this article online https://smerpub.com/

Received: 29 May 2022; **Accepted:** 14 September 2022

How to cite this article: Sokolova KI, Petrova EV, Kowalski JM, Wisniewski AP. Phase Ib Trial of Xentuzumab Combined with Abemaciclib in Patients with Advanced Solid Tumors, Including Its Use Alongside Endocrine Therapy in Advanced Breast Cancer. Arch Int J Cancer Allied Sci. 2022;2(2):xx-xx. https://doi.org/10.51847/m2jHDVGQlR

setting [8]. IGF-1R signaling promotes elevated cyclin D1 levels, suggesting that simultaneous blockade of IGF and CDK4/6 pathways may impair tumor cell proliferation by interfering with cell cycle regulation [9]. Multiple approaches to targeting the IGF axis have been explored clinically, including monoclonal antibodies against IGF-1R (e.g., ganitumab, figitumumab, dalotuzumab, cixutumumab) and tyrosine kinase inhibitors (TKIs) directed at IGF-1R. Combinations of IGF-1R antibodies with antiestrogens have generally yielded underwhelming results in breast cancer, possibly owing to incomplete suppression of IGF signaling [10]. Moreover, both IGF-1R antibodies and TKIs frequently provoke hyperglycemia—through increased growth hormone and IGF-binding protein levels or direct inhibition of insulin receptor isoforms A and B, respectively [11].

Xentuzumab is a humanized IgG1 monoclonal antibody that binds IGF-1 and IGF-2 with high affinity, thereby neutralizing the downstream proliferative and anti-apoptotic signals induced by these ligands in cancer cells [12]. This ligand-neutralization strategy distinguishes it from IGF-1R antibodies and TKIs [12]. Xentuzumab prevents both IGF ligands from engaging IGF-1R and, by sequestering IGF-2 (which binds strongly to insulin receptor isoform A), may avert compensatory signaling through IR-A—a mechanism linked to resistance against IGF-1R-directed antibodies [12-16]. In vitro studies showed robust suppression of both IGF-1R and IR-A pathways by xentuzumab, whereas IGF-1R antibodies failed to block IGF-2-mediated IR-A activation and were inferior in inhibiting IGF-1R signaling [12]. In a preclinical model of bone-metastatic prostate cancer, an IGF ligand-neutralizing antibody effectively reduced activation of both receptors and limited tumor progression [17]. Unlike IGF-1R antibodies, xentuzumab does not substantially alter growth hormone regulation [18-21] and seldom causes hyperglycemia [21-24]. Early-phase trials of xentuzumab alone revealed initial signs of antitumor effects in advanced solid malignancies [22]. A phase Ib/II trial combining xentuzumab with everolimus and exemestane in HR-positive, HER2-negative breast cancer indicated good tolerability, with the randomized portion showing improved progression-free survival (PFS) for the triplet versus everolimus/exemestane alone in patients with non-visceral involvement [23]. However, the follow-up randomized phase II XENERA-1 study, focused on similar patients with non-visceral disease [24], found no PFS advantage for the triplet. Notably, few participants in the earlier trial had prior CDK4/6 inhibitor exposure (none in the xentuzumab group), compared with approximately 75% in XENERA-1. Consequently, more than four years after trial initiation, the sponsor halted further oncology development of xentuzumab. Prior to this decision, the present phase Ib study was launched to evaluate the safety and activity of xentuzumab combined with abemaciclib, with or without ET, in individuals with advanced solid tumors, NSCLC, or HR-positive, HER2-negative breast cancer—predominantly the latter group. The trial also incorporated an extensive biomarker program, examining serum markers, tumor genomic alterations, and tumor mRNA expression profiles to pinpoint prognostic indicators linked to PFS in HR-positive, HER2-negative breast cancer patients treated with xentuzumab-containing regimens.

Materials and Methods

Study design and participants

This open-label, non-randomized, prospective phase Ib trial (NCT03099174) with multiple dose-escalation components was structured in three segments. Part 1 (cohort A) focused on establishing the maximum tolerated dose (MTD) or recommended phase II dose (RP2D) of xentuzumab combined with abemaciclib in patients with advanced solid malignancies. Part 2 included dose-finding arms (cohorts B, C, and D) to define the MTD/RP2D of the doublet plus background ET—letrozole (cohort B), anastrozole (cohort C), or fulvestrant (cohort D)—exclusively in postmenopausal women with locally advanced or metastatic HR-positive, HER2-negative breast cancer. Additionally within part 2, cohort E served as a safety, pharmacokinetic, and preliminary efficacy expansion in NSCLC patients receiving xentuzumab plus abemaciclib. Part 3 comprised expansion arms (D1, D2, and F) assessing the triplet (xentuzumab + abemaciclib + fulvestrant) for antitumor effects in locally advanced/metastatic HR-positive breast cancer patients with visceral involvement (defined as disease in lung, liver, pleura, peritoneum, or malignant effusions; cohort D1), non-visceral disease progressing after ET (aromatase inhibitor or selective estrogen receptor modulator; cohort D2), or non-visceral disease progressing after aromatase inhibitor and prior CDK inhibitor therapy (cohort F). The prioritization of non-visceral disease stemmed from observations in a prior phase Ib/II study [23].

The study aimed to include roughly 12 participants in each of cohorts A through D, 20 in cohorts E and F, and 30 in cohorts D1 and D2. Candidates needed to be adults (at least 18 years old, or 20 in Japan), with males and females allowed in cohorts A and E, but only women in the remaining breast cancer-focused groups (B, C, D, D1, D2, F). A performance status of 0 or 1 (per WHO/ECOG scale) was mandatory at enrollment. Further requirements were tailored to individual cohorts.

- Cohort A: Adults with confirmed advanced or metastatic solid malignancies (measurable and unresectable) that were no longer responsive to, unsuitable for, or intolerant of established beneficial treatments; minimum anticipated survival of three months.
- Cohorts B, C, D: Women past menopause with proven locally advanced or metastatic HR-positive, HER2-negative breast cancer (measurable, unresectable), limited to zero to two chemotherapy courses in the metastatic phase (neoadjuvant/adjuvant allowed). Suitability for the assigned hormone treatment was required. Prior fulvestrant or exemestane was acceptable in B and C; non-steroidal aromatase inhibitors or exemestane in D.
- Cohort E: Individuals with stage IV NSCLC (confirmed, RECIST v1.1-measurable) refractory to platinum-containing chemo(immuno)therapy and not candidates for further standard chemotherapy. Patients harboring EGFR mutations or ALK fusions must have exhausted relevant targeted options.
- Cohorts D1, D2, F: Postmenopausal females with verified advanced/metastatic HR-positive, HER2-negative breast cancer (measurable per RECIST v1.1, unresectable).
    - D1 and D2: Progression during/within 12 months of (neo)adjuvant hormone therapy (no additional ET afterward); or recurrence over a year post-adjuvant ET following one metastatic ET line (no chemo); or initial metastatic diagnosis with progression on first-line metastatic ET (no chemo). D1 mandated visceral site involvement; D2 prohibited it.
    - F: Demonstrated lack of response to an aromatase inhibitor combined with a CDK4/6 blocker (not abemaciclib) in advanced disease, without visceral sites. At most one prior hormone regimen; no metastatic chemotherapy.

Notable exclusions encompassed prior CDK inhibitors (except F), any IGF-1R inhibitors, symptomatic/uncontrolled brain lesions, ongoing or prior pneumonitis/interstitial lung issues, significant upper gastrointestinal resection, or chronic inflammatory bowel conditions.

Conduct followed Helsinki Declaration and ICH Good Clinical Practice standards. Site-specific ethics approvals were secured, and informed consent was obtained from every participant.

Regimens

Standard dosing across groups: weekly intravenous xentuzumab 1000 mg plus twice-daily oral abemaciclib 150 mg.

Additional agents:

- Cohort B: daily oral letrozole 2.5 mg.
- Cohort C: daily oral anastrozole 1 mg.
- Cohorts D, D1, D2, F: monthly intramuscular fulvestrant 500 mg, including a loading injection at week 2.

Temporary holds or dose adjustments were allowed for toxicities or serious side effects. Xentuzumab could step down to 750 mg then 500 mg weekly; abemaciclib to 100 mg then 50 mg twice daily. It was permissible to stop one component while maintaining the rest.

Endpoints and evaluations

For cohorts A through D, the main goals were to identify the maximum tolerated dose (MTD) or recommended phase II dose (RP2D) for the combination of xentuzumab and abemaciclib, either alone or alongside endocrine therapy (ET). Dose-limiting toxicities (DLTs) were monitored throughout the initial 28-day cycle to guide these determinations. If no MTD was identified, the RP2D would be selected using overall safety profiles and supporting data. The MTD was specified as the highest level where the probability of exceeding a 33% true DLT rate remained below 25%, guided by a Bayesian Logistic Regression Model (BLRM) incorporating escalation with overdose control principles [25].

In cohort E, the primary focus was objective response rate, including complete or partial responses according to RECIST version 1.1. For cohort F, it was the rate of disease control, encompassing complete response, partial response, confirmed stable disease of at least 24 weeks,

or non-complete response/non-progression lasting ≥24 weeks per RECIST v1.1. Cohorts D1 and D2 targeted the progression-free survival (PFS) rate at 18 months.

Additional endpoints included disease control rates (limited to cohorts D1, D2, and E), time to response, response duration, disease control duration, overall PFS, and objective response rates (for cohorts D1, D2, and F). Biomarker explorations in cohorts D1, D2, and E involved both quantitative and qualitative approaches. Quantitatively, three serum markers related to IGF were measured: total IGF-1, free IGF-1, and dissociable IGF-2. Changes in free IGF-1 levels over time were specifically examined in cohorts D1/D2 and E (selected due to sufficient sample sizes, with >10 patients having baseline and at least one on-treatment assessment). In cohorts D1 and D2, serum samples for total/free IGF-1 and IGF-2 were collected on cycle day 1 (pre-dose) for cycles 1–4 and 6, plus at treatment end (within one week of last dose) and follow-up (42 ± 7 days post-treatment). Validated immunoassays were used for quantification. A comparable timing applied to cohort E, but sampling extended to day 1 of cycles 1–12, 15, and 18.

Furthermore, pretreatment tumor tissue was analyzed for mRNA expression of 48 selected genes. Patients were divided into high- versus low-expression categories for each gene, with thresholds optimized via maximization of partial log-likelihood in a Cox model for 18-month PFS [26]. Tumor DNA sequencing targeted the coding regions of 395 oncology-relevant genes (plus introns from 31 genes) to detect single nucleotide variants, certain fusions, and other mutations, employing a FoundationOne®-adapted T7 hybrid-capture panel [27] at certified Foundation Medicine laboratories. Detected alterations were grouped into pathways such as RAS, DNA repair, PI3K (including PTEN alterations), apoptosis, everolimus-related genes from BOLERO-2 post-hoc findings [28], cell cycle, and various PI3K subclasses, plus specific PIK3CA short variants. Results from mRNA and genomic analyses are reported only for markers with adequate sample quality and quantity.

Statistical approaches

Dose escalation relied on a BLRM with overdose control, applied to binary DLT data to estimate toxicity risks per level and recommend the MTD. Models were updated ongoing as safety information emerged. A dedicated Steering Committee—comprising independent specialists, company representatives, and led by the lead investigator—oversaw escalation decisions, cohort expansions, and final MTD declaration.

Outcomes in expansion arms were summarized descriptively. For biomarkers, Cox proportional hazards models generated hazard ratios (HRs) with 95% confidence intervals for PFS, comparing high/low expression or alteration presence/absence, adjusted for the biomarker dichotomy and baseline visceral disease status. Modeling required at least five patients and three PFS events per subgroup. HRs with confidence intervals excluding 1 (suggesting $P < 0.05$) were highlighted, especially those with values <0.2 or >5.

Results and Discussion

Participant enrollment and exposure

The dose-finding arms (cohorts A–D) ran from May 31, 2017, to November 6, 2020, across 11 sites in France, Japan, Spain, and the United States. Expansion arms (E, F, D1, D2) involved 30 centers in France, Japan, Spain, the United States, Denmark, Finland, and Korea.

As of the data cutoff on March 31, 2022, ongoing participation included 7 patients in cohort F, 8 in D1, and 14 in D2.

A total of 28 individuals joined dose escalation: 6 in cohort A, 7 each in B and C, and 8 in D. Expansion treated 105 more: 26 in E, 15 in F, 33 in D1, and 31 in D2.

Demographics and baseline features are detailed in **Table 1**. The HR-positive, HER2-negative breast cancer subgroup aligned well with typical patient profiles.

Across groups, disease progression was the predominant cause for stopping xentuzumab.

Table 1. Patient demographics and baseline disease features at study entry

Characteristic	Cohort F (n=15)	Cohort E (n=26)	Cohort D2 (n=31)	Cohort D1 (n=33)	Cohort D (n=8)	Cohort C (n=7)	Cohort B (n=7)	Cohort A (n=6)
Median age, years (range)	59.0 (40–76)	64.0 (53–76)	53.0 (36–80)	60.0 (36–78)	49.0 (40–70)	66.0 (35–70)	56.0 (34–64)	60.5 (56–66)

Female sex, n (%)	15 (100)	8 (30.8)	31 (100)	33 (100)	8 (100)	7 (100)	7 (100)	5 (83.3)
Median BMI, kg/m² (range)	26.2 (17.2–35.9)	23.6 (18.9–41.2)	25.4 (17.6–33.3)	24.2 (19.4–38.2)	22.0 (17.3–28.8)	24.8 (17.7–45.7)	22.9 (16.5–26.6)	24.2 (18.6–27.9)
Race, n (%)								
Asian	1 (6.7)	4 (15.4)	7 (22.6)	9 (27.3)	2 (25.0)	1 (14.3)	1 (14.3)	2 (33.3)
Black or African American	0	1 (3.8)	0	0	0	0	0	0
White	8 (53.3)	17 (65.4)	21 (67.7)	21 (63.6)	4 (50.0)	5 (71.4)	5 (71.4)	2 (33.3)
Missing	6 (40.0)	4 (15.4)	3 (9.7)	3 (9.1)	2 (25.0)	1 (14.3)	1 (14.3)	2 (33.3)
ECOG performance status, n (%)								
0	11 (73.3)	7 (26.9)	21 (67.7)	24 (72.7)	6 (75.0)	4 (57.1)	6 (85.7)	2 (33.3)
1	4 (26.7)	19 (73.1)	10 (32.3)	9 (27.3)	2 (25.0)	3 (42.9)	1 (14.3)	4 (66.7)
Tumor type, n (%)								
Breast cancer	15 (100)	0	31 (100)	33 (100)	8 (100)	7 (100)	7 (100)	3 (50.0)
Non-small cell lung cancer	0	26 (100)	0	0	0	0	0	1 (16.7)
Soft tissue/bone sarcoma	0	0	0	0	0	0	0	1 (16.7)
Colorectal cancer	0	0	0	0	0	0	0	1 (16.7)
Median time from initial diagnosis, months (range)	43.1 (6.7–324.6)	29.9 (9.4–56.2)	60.0 (18.7–189.7)	64.7 (13.8–259.6)	67.5 (36.9–246.1)	118.0 (5.3–399.5)	97.9 (12.0–215.5)	53.5 (23.2–128.5)
Disease stage at study entry, n (%)								
I	0	0	0	0	0	0	1 (14.3)	0
II	0	0	1 (3.2)	0	0	0	1 (14.3)	1 (16.7)
III	0	3 (11.5)	0	0	0	0	0	0
IV	14 (93.3)	21 (80.8)	30 (96.8)	33 (100)	8 (100)	5 (71.4)	4 (57.1)	5 (83.3)
Missing	1 (6.7)	2 (7.7)	0	0	0	2 (28.6)	1 (14.3)	0
Number of metastatic sites at entry, n (%)								
1	11 (73.3)	1 (3.8)	26 (83.9)	5 (15.2)	0	0	1 (14.3)	0
2	4 (26.7)	5 (19.2)	4 (12.9)	9 (27.3)	6 (75.0)	4 (57.1)	4 (57.1)	2 (33.3)
3	0	8 (30.8)	1 (3.2)	12 (36.4)	1 (12.5)	2 (28.6)	2 (28.6)	2 (33.3)

4	0	3 (11.5)	0	7 (21.2)	1 (12.5)	1 (14.3)	0	1 (16.7)
≥5	0	9 (34.6)	0	0	0	0	0	1 (16.7)
Visceral metastases at entry, n (%)	0	—	0	32 (97.0)	7 (87.5)	7 (100)	4 (57.1)	6 (100)
Bone metastases at entry, n (%)	14 (93.3)	12 (46.2)	30 (96.8)	23 (69.7)	6 (75.0)	5 (71.4)	6 (85.7)	4 (66.7)
Prior endocrine therapy, n (%)	15 (100)	0	30 (96.8)	33 (100)	7 (87.5)	5 (71.4)	7 (100)	1 (16.7)
Prior neoadjuvant chemotherapy, n (%)	4 (26.7)	1 (3.8)	5 (16.1)	9 (27.3)	3 (37.5)	1 (14.3)	1 (14.3)	2 (33.3)
Prior adjuvant chemotherapy, n (%)	6 (40.0)	7 (26.9)	19 (61.3)	14 (42.4)	4 (50.0)	3 (42.9)	4 (57.1)	3 (50.0)
Prior chemotherapy for metastatic disease, n (%)	1 (6.7)	19 (73.1)	0	0	3 (37.5)	4 (57.1)	3 (42.9)	5 (83.3)

BMI= body mass index; ECOG= Eastern Cooperative Oncology Group.

DLTs and MTD

During the 28-day MTD assessment period, dose-limiting toxicities occurred in two of six evaluable patients in cohort A (both with grade 3 neutropenia), one of six in cohort B (grade 3 neutropenia), one of six in cohort C (grade 4 thrombocytopenia), and one of six in cohort D (grade 3 neutropenia) **(Table 2)**. The maximum tolerated doses were defined as follows: (i) xentuzumab 1000 mg weekly combined with abemaciclib 150 mg twice daily for all cohorts; (ii) cohort B also received letrozole 2.5 mg daily; (iii) cohort C was administered anastrozole 1 mg daily; and (iv) cohort D (including D1, D2, and F) received fulvestrant 500 mg monthly, with an additional 500 mg given two weeks after the first dose.

Table 2. Summary of adverse events and most frequently reported all-cause, any-grade adverse events (occurring in ≥50% of the patients in any cohort)

***n* (%)**	**Cohort A (*n* = 6)**	**Cohort B (*n* = 7)**	**Cohort C (*n* = 7)**	**Cohort D (*n* = 8)**	**Cohort D1 (*n* = 33)**	**Cohort D2 (*n* = 31)**	**Cohort E (*n* = 26)**	**Cohort F (*n* = 15)**
Any AE	6 (100)	7 (100)	7 (100)	8 (100)	33 (100)	31 (100)	26 (100)	15 (100)
Xentuzumab-related AEs	6 (100)	7 (100)	6 (85.7)	7 (87.5)	29 (87.9)	29 (93.5)	16 (61.5)	12 (80.0)
Abemaciclib-related AE	6 (100)	7 (100)	7 (100)	8 (100)	32 (97.0)	31 (100)	24 (92.3)	15 (100)
AEs leading to xentuzumab dose reduction	1 (16.7)	3 (42.9)	1 (14.3)	1 (12.5)	0	10 (32.3)	1 (3.8)	0
AEs leading to abemaciclib dose reduction	2 (33.3)	5 (71.4)	7 (100)	4 (50.0)	21 (63.6)	25 (80.6)	7 (26.9)	7 (46.7)
AEs leading to discontinuation of xentuzumab	0	1 (14.3)	1 (14.3)	0	6 (18.2)	4 (12.9)	3 (11.5)	3 (20.0)
AEs leading to discontinuation of abemaciclib	1 (16.7)	1 (14.3)	0	2 (25.0)	7 (21.2)	5 (16.1)	6 (23.1)	3 (20.0)

DLT (MTD evaluation period)			2 (33.3)[a]		1 (16.7)[b,c]		1 (16.7)[b,d]		1 (16.7)[b,e]		—		—		—	
DLT (on treatment period)			2 (33.3)[a]		3 (42.9)[c,f,g,h,i,j]		1 (14.3)[d]		3 (37.5)[k,l]		—		—		—	
SAEs			0		4 (57.1)		4 (57.1)		3 (37.5)		11 (33.3)		16 (51.6)		13 (50.0)	
Fatal AEs			0		0		0		0		1 (3.0)[m]		1 (3.2)[n]		1 (3.8)[o]	
AE, grade (CTCAE)	**Any**	**≥3**	**Any**	**≥3**	**Any**	**≥3**	**Any**	**≥3**	**Any**	**≥3**	**Any**	**≥3**	**Any**	**≥3**	**Any**	**≥3**
Diarrhea	6 (100)	1 (16.7)	7 (100)	2 (28.6)	6 (85.7)	0	8 (100)	2 (25.0)	30 (90.9)	1 (3.0)	29 (93.5)	4 (12.9)	16 (61.5)	1 (3.8)	14 (93.3)	2 (13.3)
Nausea	3 (50.0)	0	4 (57.1)	0	4 (57.1)	0	6 (75.0)	0	22 (66.7)	0	21 (67.7)	2 (6.5)	16 (61.5)	0	4 (26.7)	0
Anemia	3 (50.0)	0	7 (100)	1 (14.3)	4 (57.1)	2 (28.6)	4 (50.0)	0	14 (42.4)	1 (3.0)	14 (45.2)	3 (9.7)	10 (38.5)	2 (7.7)	4 (26.7)	2 (13.3)
Asthenia	3 (50.0)	0	5 (71.4)	1 (14.3)	5 (71.4)	0	5 (62.5)	1 (12.5)	12 (36.4)	0	10 (32.3)	2 (6.5)	7 (26.9)	3 (11.5)	9 (60.0)	0
Vomiting	4 (66.7)	0	2 (28.6)	0	4 (57.1)	0	3 (37.5)	0	9 (27.3)	0	16 (51.6)	2 (6.5)	11 (42.3)	0	4 (26.7)	0
Decreased appetite	4 (66.7)	0	3 (42.9)	0	4 (57.1)	0	3 (37.5)	0	11 (33.3)	1 (3.0)	10 (32.3)	0	11 (42.3)	0	7 (46.7)	0
Creatinine increased	2 (33.3)	0	3 (42.9)	0	4 (57.1)	0	3 (37.5)	0	8 (24.2)	0	8 (25.8)	0	8 (30.8)	1 (3.8)	2 (13.3)	0
Neutropenia	1 (16.7)	0	6 (85.7)	3 (42.9)	5 (71.4)	3 (42.9)	4 (50.0)	4 (50.0)	8 (24.2)	8 (24.2)	10 (32.3)	7 (22.6)	7 (26.9)	3 (11.5)	5 (33.3)	4 (26.7)
Abdominal pain	2 (33.3)	0	5 (71.4)	0	3 (42.9)	0	3 (37.5)	0	10 (30.3)	0	11 (35.5)	1 (3.2)	4 (15.4)	1 (3.8)	7 (46.7)	0

Neutrophil count decreased	2 (33.3)	2 (33.3)	1 (14.3)	1 (14.3)	2 (28.6)	0	1 (12.5)	1 (12.5)	17 (51.5)	13 (39.4)	16 (51.6)	11 (35.5)	4 (15.4)	0	1 (6.7)	0
Arthralgia	0	0	3 (42.9)	0	4 (57.1)	0	2 (25.0)	0	8 (24.2)	0	11 (35.5)	2 (6.5)	3 (11.5)	0	2 (13.3)	0
AST increased	2 (33.3)	0	6 (85.7)	2 (28.6)	1 (14.3)	0	0	0	7 (21.2)	2 (6.1)	7 (22.6)	2 (6.5)	4 (15.4)	0	3 (20.0)	0
Nasopharyngitis	0	0	1 (14.3)	0	0	0	4 (50.0)	0	2 (6.1)	0	2 (6.5)	0	0	0	0	0

AE, adverse event; AST, aspartate transaminase; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; SAE, serious adverse event.
[a]Grade 3 neutrophil count decreased ×2.
[b]$n = 6$.
[c]Grade 3 neutrophil count decreased.
[d]Grade 4 thrombocytopenia.
[e]Grade 3 neutropenia.
[f]Grade 3 febrile neutropenia.
[g]Grade 4 alanine aminotransferase increased.
[h]Grade 4 aspartate aminotransferase increased.
[i]Grade 3 blood bilirubin increased.
[j]Grade 4 gamma-glutamyltransferase increased.
[k]Grade 3 neutropenia ×2.
[l]Grade 2 decreased appetite.
[m]Respiratory syncytial virus infection/respiratory failure.
[n]Myocardial infarction.
[o]Pulmonary embolism.
[p]Acute respiratory distress syndrome.

Safety and tolerability

An overview of adverse events (AEs), along with dose adjustments and treatment terminations for xentuzumab and abemaciclib in various study groups, is presented in **Table 2**. The proportion of participants needing dose lowering of xentuzumab because of AEs varied from none (in groups D1 and F) to 3 individuals (42.9% in group B). In total, across the entire study population, 17 participants (12.8%) underwent dose modifications. The primary causes for these adjustments included low neutrophil counts or neutropenia (n=10) and low platelet counts or thrombocytopenia (n=3). The role of IGF signaling in supporting healthy blood cell production has been noted previously[29, 30]. Dose adjustments for abemaciclib occurred in proportions ranging from 26.9% (group E) to 100.0% (group C). Treatment cessation of xentuzumab owing to AEs varied from none (groups A and D) to 3 cases (20.0%) in group F (attributed to headache, acute respiratory distress syndrome, and pulmonary embolism in individual patients). Rates of stopping abemaciclib due to AEs ranged from 0 percent (group C) to 25% (group D). Specifically, two individuals halted abemaciclib because of diarrhea, with one case each due to reduced neutrophils and increased aspartate transaminase levels.

Rates of serious AEs differed from 0.0% (group A) to 57.1% (groups B and C). Four deaths related to AEs were recorded: one in group D1 (respiratory failure, potentially linked to abemaciclib but complicated by concurrent respiratory syncytial virus infection), one in group D2

(myocardial infarction, deemed unrelated to study drugs), one in group E (pulmonary embolism, not drug-related), and one in group F (acute respiratory distress syndrome, not drug-related; **(Table 2)**). The AEs most commonly observed across all grades are detailed in **Table 2**. In general, the prevalent AEs of any severity were diarrhea, nausea, anemia, and fatigue; the predominant grade ≥3 event was reduced neutrophil count **(Table 2)**. Mild hyperglycemia linked to xentuzumab was seen in two cases (one each in groups D and D2; both grade 1).

Antitumor activity

Objective response rates (ORRs, based on RECIST v1.1) reached 28.6 percent, 28.6 percent, and 25.0 percent in groups B, C, and D, respectively, accompanied by disease control rates (DCRs) of 57.1 percent, 71.4 percent, and 62.5 percent in those same groups **(Table 3)**. For subgroups D1 and D2, progression-free survival (PFS) rates at eighteen months stood at 41.4 percent and 78.5 percent, with median PFS values of 13.6 months (95 percent CI 7.2–25.9 months) and 33.1 months (95 percent CI 19.4–33.1 months), respectively **(Figure 1)**. The ORR was 60.6 percent in subgroup D1 and 19.4 percent in D2, with corresponding DCRs of 69.7 percent and 77.4 percent; each subgroup included one complete response **(Table 3)**.

Table 3. Summary of efficacy

n (%)[a]	Cohort F (*n* = 15)	Cohort E (*n* = 26)	Cohort D2 (*n* = 31)	Cohort D1 (*n* = 33)	Cohort D (*n* = 8)	Cohort C (*n* = 7)	Cohort B (*n* = 7)	Cohort A (*n* = 6)
CR	0	0	1 (3.2)	1 (3.0)	0	0	0	0
PR	1 (6.7)	1 (3.8)	5 (16.1)	19 (57.6)	2 (25.0)	2 (28.6)	2 (28.6)	1 (16.7)
Non-CR/non-PD	4 (26.7)	0	15 (48.4)	0	0	1 (14.3)	2 (28.6)	0
SD	1 (6.7)	11 (42.3)	3 (9.7)	3 (9.1)	3 (37.5)	2 (28.6)	0	0
PD	6 (40.0)	10 (38.5)	4 (12.9)	8 (24.2)	2 (25.0)	1 (14.3)	2 (28.6)	5 (83.3)
Not evaluable	3 (20.0)	4 (15.4)	3 (9.7)	2 (6.1)	1 (12.5)	1 (14.3)	1 (14.3)	0
Objective response	1 (6.7)	1 (3.8)	6 (19.4)	20 (60.6)	2 (25.0)	2 (28.6)	2 (28.6)	1 (16.7)
Disease control rate	6 (40.0)	12 (46.2)	24 (77.4)	23 (69.7)	5 (62.5)	5 (71.4)	4 (57.1)	1 (16.7)
DoR (months), median (range)	4.6 (4.6-4.6)	5.8 (5.8-5.8)	17.5 (7.9-25.8)	11.1 (0.0-27.2)	5.3 (1.8-8.8)	9.0 (1.9-16.1)	13.4 (7.4-19.4)	5.6 (5.6-5.6)
DDC (months), median (range)	12.4 (9.2-14.0)	5.8 (1.4-25.0)	22.0 (5.5-33.1)	15.0 (7.2-30.7)	12.4 (5.5-21.9)	9.1 (5.6-20.1)	24.0 (9.1-30.4)	7.3 (7.3-7.3)
PFS (months), median (95% CI)	NC (2.3-NC)	2.1 (1.5-5.7)	33.1 (19.4-33.1)	13.6 (7.2-25.9)	12.4 (0.7-21.9)	9.1 (1.8-NC)	18.7 (1.6-30.4)	1.7 (1.0-7.3)

CI= confidence interval; CR= complete response; DDC= duration of disease control; DoR= duration of response; NC, not calculated; PD= progressive disease; PFS= progression-free survival; PR= partial response; RECIST v1.1= Response Evaluation Criteria in Solid Tumours version 1.1; SD= stable disease.

[a]Investigator assessed using RECIST v1.1.

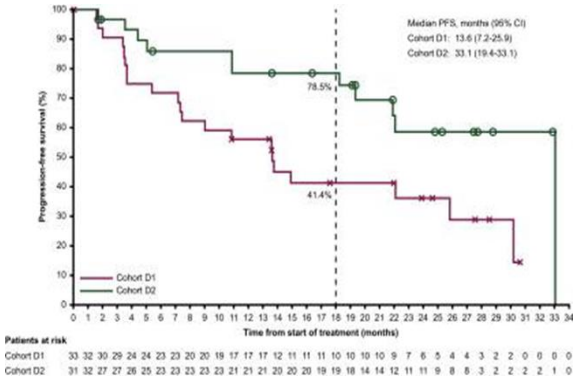
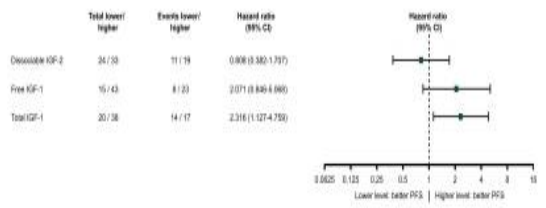


Figure 1. Progression-free survival for subgroups D1 and D2, highlighting the PFS rates at 18 months. CI denotes confidence interval; PFS stands for progression-free survival.

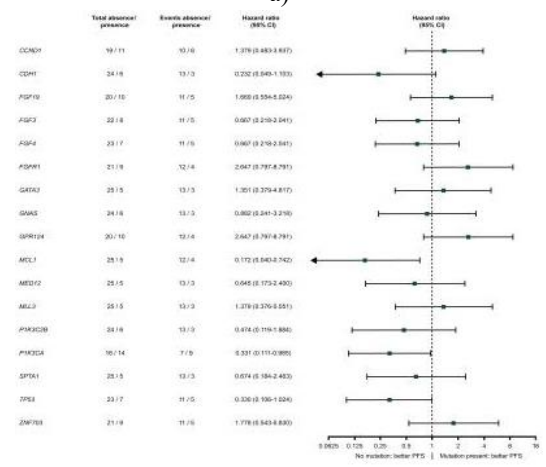
In subgroup E, a single participant (3.8%) achieved an objective response (partial response), resulting in a disease control rate of 46.2% and a median duration of controlled disease of 5.8 months (range 1.4–25.0 months; **(Table 3)**). For subgroup F, the disease control rate reached 40.0 percent, with a median duration of 12.4 months (range 9.2–14.0 months). The objective response rate was 6.7 percent **(Table 3)**.

Biomarkers

Evaluation of the three most substantial groups—D1, D2, and E—revealed a decline in free IGF-1 levels during xentuzumab administration, confirming on-target effects. Comparable patterns emerged in the less populated groups (data not presented). Patients exhibiting elevated baseline total serum IGF-1 levels (>115 U/ml) experienced extended median PFS compared to those with lower levels (31.0 months versus 10.9 months; HR 2.32, 95 percent CI 1.13–4.76, P = 0.022; **(Figure 2a)**). Among 395 genes screened for mutations, MCL-1 emerged as the sole candidate with potential prognostic value for PFS (HR 0.17, 95 percent CI 0.04–0.74, P = 0.0182). Median PFS reached 13.5 months in individuals harboring MCL-1 mutations, in contrast to 25.9 months in those without **(Figure 2b)**. Baseline tumor mRNA quantification, stratified into high and low expression categories, identified elevated levels of five genes associated with favorable PFS outcomes (HR >5.0): CCND1 (encoding cyclin D1; HR 17.27, 95 percent CI 4.18–71.32, P < 0.0001), BCL-2 (HR 11.40, 95 percent CI 3.0–44.0, P = 0.0004), INSR (HR 6.05, 95 percent CI 2.00–18.37, P = 0.0015), MAPK3 (HR 5.69, 95 percent CI 1.93–16.81, P = 0.0016), and ErbB2a (HR 5.50, 95 percent CI 1.86–16.29, P = 0.0021).



a)



b)

Figure 2. Forest plots from biomarker evaluations. This includes quantitative assessments of (a) serum-based markers and (b) mutational analysis in tumor DNA across chosen genes from 10 signaling pathways (limited to genes with successful genotyping in at least five participants and a minimum of three progression-free survival events per subgroup). CI indicates confidence interval; IGF refers to insulin-like growth factor; PFS denotes progression-free survival.

Findings from this investigation indicated that xentuzumab could be safely paired with abemaciclib and administered alongside endocrine agents such as letrozole, anastrozole, or fulvestrant. Instances of adverse events necessitating dose lowering for xentuzumab were more prevalent in the initial dose-finding phase but occurred less often in the subsequent expansion phase. Fewer than one in five participants stopped either xentuzumab or abemaciclib because of adverse events; generally, the frequency of dose adjustments for abemaciclib exceeded that for xentuzumab. Prevalent adverse events linked to the combination of xentuzumab and abemaciclib involved diarrhea, nausea, fatigue/asthenia, and neutropenia/low neutrophil counts. Multiple findings point to a limited role of xentuzumab in contributing to the toxicity profile of the evaluated regimens. First, earlier investigations showed that xentuzumab alone was relatively well tolerated[22]. Second, the pattern of adverse events in groups receiving xentuzumab plus abemaciclib and fulvestrant mirrored that seen with abemaciclib and fulvestrant in the MONARCH-2 study[31]. In particular, mild hyperglycemia attributed to xentuzumab (grade 1) was reported in only two cases, likely due to xentuzumab's preservation of insulin binding to the IR-B receptor isoform. In summary, the tolerability of xentuzumab combined with abemaciclib (with or without endocrine therapy) was acceptable, with adverse events comparable to those reported for abemaciclib (with or without endocrine therapy), though blood cell reductions may have been intensified by the dual therapy[31].

Promising objective response and disease control rates emerged in groups B through D involving the three-drug regimens. In group E (non-small cell lung cancer patients), the objective response rate was low at 3.8%, yet nearly half achieved disease control lasting a median of 5.8 months. Group F showed a 40.0% disease control rate with a meaningful median duration of 12.4 months (range 9.2–14.0 months). Results from subgroups D1 and D2 appeared favorable, yielding median progression-free

survival of 13.6 and 33.1 months, respectively. Notably, progression-free survival in subgroup D2 surpassed that observed with xentuzumab plus everolimus and exemestane in the XENERA-1 study (median 12.7 months) and with abemaciclib plus fulvestrant in MONARCH 2 (median 16.4 months), notwithstanding challenges in direct comparisons across trials, particularly given variations in patient characteristics [24, 32]. For instance, MONARCH 2 included 56% visceral involvement, while subgroup D2 restricted to non-visceral sites. XENERA-1 permitted only one prior CDK4/6 inhibitor line. The modest cohort sizes in the present work also warrant consideration.

This investigation examined prognostic potential of various serum markers, including free and total IGF-1 levels. Aligning with a prior phase Ib/II trial in hormone receptor-positive, HER2-negative breast cancer, treatment with xentuzumab lowered free serum IGF-1, confirming mechanism of action (Boehringer Ingelheim, data on file)[23]. Additionally, elevated total IGF-1 at baseline, and somewhat free IGF-1, indicated prognostic relevance for progression-free survival, mirroring the earlier trial. Baseline IGF-2 levels (dissociable) lacked prognostic significance for progression-free survival.

Absence of a comparator group precluded assessment of whether IGF-1 levels predicted specific benefit from xentuzumab here. However, the prior phase Ib/II suggested potential predictivity, with trends for both free IGF-1 and dissociable IGF-2 toward better progression-free survival on the xentuzumab regimen versus control (Boehringer Ingelheim, data on file). This was not confirmed in XENERA-1. Additional research is needed to explore circulating IGF-1 markers as predictors, potentially selecting patients likely to respond to IGF-1R pathway inhibitors. Supporting this, IGF-1 has shown predictive potential in trials of other IGF-1R agents like dalotuzumab [33] and ganitumab [34]. A recent neoadjuvant breast cancer study linked IGF-1R phosphorylation to ganitumab response [35]. Combining high IGF-1 with tumoral receptor phosphorylation assessment might form a robust predictive composite for this drug class.

Extensive genomic profiling aimed to uncover new markers. Elevated tumoral mRNA for CCND1 stood out with substantial prognostic strength (HR 17.3) compared to low expression. High CCND1 also exhibited strong predictivity for progression-free survival in the prior phase Ib/II (interaction P = 0.0002) but not XENERA-1 (Boehringer Ingelheim, data on file). IGF-1 and cyclin D1 are recognized as central interacting genes in breast atypical hyperplasia pathogenesis [36]. The analysis screened cancer-associated genes for mutational prognostic effects, identifying only MCL-1 (BCL-2 family apoptosis regulator) as potentially relevant. MCL-1 mutations correlated with reduced progression-free survival (P = 0.0182), suggesting impaired apoptosis might hinder xentuzumab efficacy. This was not echoed in the prior phase Ib/II or XENERA-1 analyses (Boehringer Ingelheim, data on file) [23, 24]. Prior reports associate MCL-1 overexpression with advanced tumor grade and worse outcomes in breast cancer [37]. In contrast, high BCL-2 expression here linked to prolonged progression-free survival (HR 11.40, P = 0.0004), reinforcing possible ties between apoptosis dysregulation (BCL-2 family) and diminished xentuzumab effect. Nonetheless, BCL-2 is known as a positive prognostic marker in breast cancer due to its correlation with estrogen receptor positivity [38].

Study constraints include its single-arm, non-blinded design. Given multiple tested variables and limited numbers, biomarker prognostic interpretations require prudence. Without a control, definitive efficacy judgments for regimens were impossible. Early termination following XENERA-1 efficacy shortfall [24] prevented full accrual, restricting group sizes.

Conclusion

Xentuzumab is compatible with abemaciclib and endocrine therapies in individuals with progressed solid malignancies or breast cancer. These regimens exhibited acceptable safety and notable anticancer effects, especially in breast cancer cases without visceral spread. Oncology advancement of xentuzumab ceased, however, owing to absent efficacy gain in the phase II randomized XENERA-1 breast cancer study [24]. Still, this work highlights key distinctions in safety and possible efficacy between ligand-blocking and receptor-directed IGF inhibition approaches.

Acknowledgments: The authors thank the patients and their families, as well as the investigators and staff at the participating sites. The authors also thank Beate Zadow, Laura Schlieker, Maria Kreuzberg, Owen Hudson, Rory Wilson, Ulrich Kunz, Theresia Leo-Kress, and Claudia Bühnemann for their contributions towards biomarker analysis and reporting for this trial. The authors were fully responsible for all content and editorial decisions,

were involved at all stages of manuscript development, and have approved the final version. The authors received no direct compensation related to the development of the manuscript. Medical writing support for the development of this manuscript, under the direction of the authors, was provided by Lynn Pritchard, DPhil, of Ashfield MedComms, an Inizio company, and funded by Boehringer Ingelheim.

Conflict of Interest: MO has received consulting fees from AstraZeneca, Daiichi Sankyo, Eli Lilly, Gilead, iTEOS, Merck Sharp & Dohme (MSD), Pierre Fabre, Relay Therapeutics, Roche, and Seagen; grants or funds from AstraZeneca, Ayala Pharmaceuticals, Boehringer Ingelheim, Genentech, Gilead, GlaxoSmithKline (GSK), Novartis, Roche, Seagen, and Zenith Epigenetics (all to the institution); honoraria from AstraZeneca, Eisai, Eli Lilly, Gilead, Libbs, MSD, Novartis, Pfizer, Roche, and Seagen; and is the head of the SOLTI Breast Cancer Group. RML reports consulting fees from and employment with Boehringer Ingelheim. MCH reports employment with and the ownership of stock/shares in Eli Lilly. AS reports consulting fees from AstraZeneca, Boehringer Ingelheim, Gilead, Novartis, and Seagen; and is a member of GEICAM's executive board. AG has received consulting fees/is on the advisory council or committee on behalf of their institution for AstraZeneca, Gilead, Innate Pharma, MSD, Novartis, and Parexel; and has received travel, accommodation, and meeting registration payments from Menarini, Mylan, and Novartis. HI reports consulting fees from AstraZeneca, Chugai, Daiichi Sankyo, Eli Lilly, Gilead, MSD, and Pfizer; grants from AstraZeneca, Chugai, and Daiichi Sankyo; and honoraria from AstraZeneca, Chugai, Daiichi Sankyo, Eli Lilly, Kyowa Kirin, MSD, Pfizer, and Taiho. YF, NF, and MP report employment with Boehringer Ingelheim. DY reports consulting fees for Martell Diagnostics; and research funding from Boehringer Ingelheim and Fusion Pharmaceuticals. MV reports advisory council or committee work for Adamed, AstraZeneca, Daiichi Sankyo, Pfizer, and Roche; and honoraria from Daiichi Sankyo, Novartis, Pfizer, and Roche. PL reports advisory board work for AbbVie, ABL Bio, Actuate Therapeutics, Agenus, AstraZeneca, Atreca Development, BAKX Therapeutics, Compass BADX, Cullinan, DAiNA, EMD Serono, GSK, I-Mab, imCheck, IQVIA, Kineta, Inc., Kyowa Kirin, MEKanistic, Mersana Therapeutics, Modifi Bio, Molecular Templates, NeuroTrials, Pfizer, Prelude, QED Therapeutics, Qualigen, Quanta Therapeutics, Relay Therapeutics, Scenic Biotech, Schrodinger, Seagen, STCube Pharmaceuticals, Stemline, Takeda, Wells Therapeutics, Zai Lab, Zentalis Pharmaceuticals; consultant fees and independent data monitoring committee (IDMC) for SOTIO; consultant fees for I-Mab and Roivant Sciences; imCORE Alliance for Roche Genentech; participation in the data monitoring committee for Amgen CodeBreak 202; participation in the data safety monitoring board for Dren Bio; and participation in the STING Agonist Global Advisory Board for Boehringer Ingelheim. All other authors have declared no conflicts of interest.

Financial Support: This work was supported by Boehringer Ingelheim (no grant number).

Ethics Statement: None

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