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Results of TRIO-15, a multicenter, open-label, phase II study of the efficacy and safety of ganitumab in patients with recurrent platinum-sensitive ovarian cancer

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Abstract

Background.—IGF signaling has been implicated in the pathogenesis and progression of ovarian carcinoma (OC). Single agent activity and safety of ganitumab (AMG 479), a fully human

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Author contribution

All authors of this research paper have directly participated in the planning, execution, or analysis of the study. Furthermore, all authors of this paper have read and approved the final version submitted. Details of each contribution is as below:

T. M. Davidson: Formal Analysis, Visualization, Writing – original draft, Writing – review & editing

C. L. Lebreton: Formal Analysis, Visualization, Writing – original draft, Writing – review & editing

A. E. Wahner Hendricksen: Investigation, Supervision, Writing – review & editing

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M. C. Larson: Data curation, Formal Analysis

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G. E. Konecny: Conceptualization, Investigation, Supervision, Writing – original draft, Writing – review & editing

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Declaration of Competing Interest

The authors declare no potential conflicts of interest.

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monoclonal antibody against IGF1R that blocks binding of IGF1 and IGF2, were evaluated in patients with platinum-sensitive recurrent OC.

Methods.—Patients with CA125 progression (GCIG criteria) or measurable disease per RECIST following primary platinum-based therapy received 18 mg/kg of ganitumab q3w. The primary endpoint was objective response rate (ORR) assessed per RECIST 1.1 by an independent radiology review committee (IRC) and/or GCIG CA125 criteria. Secondary endpoints included clinical benefit rate (CBR), progression free survival (PFS) and overall survival (OS).

Results.—61 pts. were accrued. Objective responses were seen in 5/61 patients (ORR 8.2%, 95% CI, 3.1–18.8) with 1 partial response (PR) by RECIST and 2 complete responses (CR) as well as 2 PR by CA125 criteria. CBR was 80.3% (95% CI, 67.8–89.0%). The median PFS according to RECIST by IRC was 2.1 months (95% CI, 2.0–3.1). The median PFS per RECIST IRC and/or CA125 was 2.0 months (95% CI, 1.8–2.2). The median OS was 21 months (95% CI, 19.5-NA). The most common overall adverse events were fatigue (36.1%) and hypertension (34.4%). Grade 1/2 hyperglycemia occurred in 30.4% of patients. Hypertension (11.5%) and hypersensitivity (8.2%) were the most frequent grade 3 adverse events.

Conclusions.—IGF1R inhibition with ganitumab was well-tolerated, however, our results do not support further study of ganitumab as a single agent in unselected OC patients.

Keywords

Ganitumab; AMG 479; IGFR1 inhibitor; Ovarian cancer; Insulin-like growth factor; Targeted therapy

1 Introduction

Ovarian cancer (OC) continues to be the most lethal of all gynecologic malignancies. Despite initial aggressive therapy including surgical cytoreduction [1] and chemotherapy [2] combined with maintenance therapies such as bevacizumab [3,4] and PARP inhibitors [5–7], 50% of patients still relapse after a median of 18–24 months [8]. Advances in the understanding of ovarian cancer molecular pathogenesis coupled with the development of novel targeted therapies are needed to improve patient outcomes. As such, the insulin-like growth factor 1 receptor (IGF1R) pathway is an important regulator of ovarian follicular growth and survival which has been implicated in the pathogenesis of ovarian cancer [9]. It is composed of 3 receptors (IGF1R, IGF2R, insulin receptor), 3 ligands (IGF1, IGF2, insulin) and 6 binding proteins which regulate the IGF signaling by affecting the bio-availability of IGF1 and IGF2 [10]. On ligand activation, IGF1R signals the Ras/mitogen activated protein kinase and phosphatidylinositol 3-kinase/AKT pathways [11] regulating cell proliferation and inhibiting apoptosis [12]. Stimulation of ovarian cancer cell cultures with IGF1 and IGF2 increase cell proliferation and tumorigenesis [13]. These findings suggested at the time that inhibition of the IGF/IGF1R signaling pathway might be a promising approach for the treatment of patients with ovarian cancer. However, complex relationships between the many members of the IGF/IGF1R signaling network may represent barriers to successful treatment using a single-agent anti-receptor antibody, particularly when adjusting for the role of possible compensatory regulatory changes. Despite these potential obstacles, we chose to study Ganitumab (AMG 479) which is a

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fully human monoclonal antibody IgG1 targeting human IGF1R. It inhibits the interaction of IGF1R with its natural ligands, IGF1 and IGF2, both in-vitro and in-vivo ovarian cancer models [14].

In this clinical trial we sought to include patients with a biochemical recurrence or non-measurable disease by RECIST with CA125 elevation. The Gynecologic Cancer Intergroup (GCIG) criteria defines a doubling of CA125 levels from either the upper limit of normal or the nadir as bio-chemical relapse [15]. In many cases, an increase of CA125 levels without symptoms or measurable disease on imaging studies represents a treatment dilemma. Immediate initiation of chemotherapy in this patient population did not show improved overall survival in a randomized clinical trial [16]. Adding to the clinical difficulty, patients without measurable disease are generally not eligible for clinical trials.

Based on ganitumab's pre-clinical results and safety profile [17] the overall aim of this phase II study was to evaluate the safety and efficacy of single agent ganitumab therapy in women diagnosed with recurrent platinum-sensitive OC including patients with non-measurable and/or biochemical recurrence.

2. Patients and methods

2.1. Eligibility criteria

Eligible patients were females >18 years with histologically confirmed epithelial OC (including fallopian tube and primary peritoneal carcinoma) with CA125 progression (as per GCIG criteria) and/or measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) relapsing >6 months after completion of one line of prior platinum-based chemotherapy. Additional inclusion criteria included resolution of any toxic effects of prior therapy (except alopecia) to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0 Grade < 1; baseline laboratory values including adequate hepatic function; adequate coagulation function; serum creatinine ≤1.5 x upper limit of normal; hemoglobin ≥9.0 g/dL, absolute neutrophil count ≥1.5 $\times 10^9$/L, platelet count ≥100 $\times 10^9$/L; HbA1c < 8% and fasting blood glucose <160 mg/dL; Eastern Cooperative Oncology Group (ECOG) performance status ≤1 and a life expectancy >12 weeks. Exclusion criteria included recurrence or progression >24 months after completion of front-line platinum-based chemotherapy; concurrent active secondary malignancy; prior treatment with investigational treatment targeted to IGF axis, anticipation of a need for a major surgical procedure or radiation therapy, significant cardiovascular pathology within the 6 months prior to trial registration, history of brain metastases, spinal cord compression, or carcinomatous meningitis, psychiatric illness, chronic hepatitis B or C, human immunodeficiency virus infection or acquired immunodeficiency syndrome-related illness.

2.2. Study design and treatment plan

TRIO 15 was an investigator initiated multicenter open-label phase II clinical trial run through the Translational Research in Oncology (TRIO) international network and supported by Amgen. The primary objectives were to assess the safety and efficacy of ganitumab

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administrated at 18 mg/kg intravenous (IV) on day 1 of each 21-day cycle, until disease progression or unacceptable toxicity. The study enrolled between February 2009 and April 2010, according to the Declaration of Helsinki and approved by the institutional review boards of each participating institution. All patients were provided written informed consent. The study is registered with http://ClinicalTrials.gov under the identifier NCT00719212.

2.3. Efficacy assessments

Efficacy was assessed with imaging every 9 weeks and physical exams with CA125 assessments at day 1 of every treatment cycle until disease progression. Treatment continued until investigator-determined evidence of progressive disease, unacceptable toxicity, study completion or other withdrawal criteria were met. The primary endpoint was objective response rate (ORR). The secondary endpoints were clinical benefit rate (CBR), progression free survival (PFS) and overall survival (OS). These endpoints were defined as follows. ORR was the percentage of patients who achieve a complete (CR) or partial response (PR) according to RECIST criteria and/or GCIG CA125 response criteria. CBR was defined as the percentage of patients who achieve a CR, PR, or stable disease (SD) for >24 weeks. PFS was defined as the time from registration to first recurrence/progression, last follow-up, or death from ovarian cancer, whichever came first. OS was defined as the time interval between the registration date to death from any cause or last follow-up, whichever came first. Progressive disease was based on either radiological assessment (RECIST 1.1) or CA125 evaluation (GCIG 2005 definition, https://gcigtrials.org/content/ca-125-response-definition). RECIST responses were assessed by the investigator (INV) and an independent radiology review committee (IRC). The IRC determined RECIST was used to determine ORR, CBR, and PFS.

2.4. Assessment of toxicity and quality of life

Safety assessments included physical examination and routine clinical laboratory evaluations during therapy. Adverse events were graded according to the NCI CTCAE 3.0. Interim safety analyses were completed once twelve patients had been followed through one cycle of study treatment. The Functional Assessment of Cancer Therapy in Ovary (FACT-O) questionnaire (version 4.0) was completed by patients for quality-of-life assessment at baseline, at the onset of every cycle in the first year, then every 3 months until disease progression, death or the 36-month visit, whichever came first.

2.5. Molecular analysis

Serum samples were collected at baseline and on day 1 of cycles 1, 2, 4 and 9 prior to treatment for the purpose of measuring circulating levels of IGF1, IGFBP3 and GH. Serum levels were measured using a radioimmunoassay (RIA) for IGF1 (Esoterix, Calabasas, CA) and an immunochemiluminometric assay for IGFBP3 and GH (Esoterix, Calabasas, CA). A sub-study consent form was provided to patients for the collection of tissue (archival paraffin block of the primary tumor) for NanoString gene expression profiling (IGF1, IGF2, IGF1R, IGF2R, IGFBP1, IGFBP2, IGFBP3, IGFBP4, IGFBP5 and IGFBP6).

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2.6. Statistical analyses

An independent data monitoring committee oversaw the trial conduct and the efficacy database resided with TRIO. The primary statistical analysis was initially performed by TRIO and completed by Mayo Clinic Department of Quantitative Sciences statisticians. The sample size was intended to be at least 60 patients which was achieved. The intention to treat population was used for data analysis. ORR and CBS were estimated using descriptive statistics and 95% Clopper–Pearson exact confidence intervals (CIs). Median survival was evaluated using the Kaplan–Meier (KM) method. Serum data for GH, IGF1, and IGFBP3 was visualized via spaghetti plots across cycles. The change from cycle 1 to cycle 2 overall was assessed viaWilcoxon signed rank test and compared between responders (CR/PR) and non-responders (SD/PD) using the Wilcoxon rank sum test. Normalized mRNA expression data was received from Amgen for IGF1, IGF2, IGFBP1, IGFBP2, IGFBP3, IGFBP4, IGFBP5, IGFBP6, IGF1R and IGF2R. Association with change from baseline in CA125 and tumor sizewas assessed using a Spearman correlation and loess smoothers with Bonferonni correction for 10 comparisons. Mean FACT-O scores were calculated. All statistical analyses were performed using Rv4.1.2. A two-sided P value of <0.05 was considered significant.

3. Results

3.1. Patient characteristics

61 patients were accrued and their baseline characteristics are summarized in Table 1. Median age was 62 years (range 35–83 years). Most enrolled patients had an ECOG performance status of 0 (67.2%). The most frequent histology was papillary serous (68.9%). The majority of tumors were poorly differentiated (Grade 3, 73.8%). All patients had received one prior line of chemotherapy. Median time between diagnosis and first relapse was 19 months (IQR, 15–24). Four patients enrolled in the study were later found to have not met eligibility criteria (2 patients had <6 months platinum-free interval and 2 patients had >24 months platinum-free interval) but were included in the present intent to treat analysis. Information on the BRCA status of patients was not routinely collected during study enrollment as this was not yet general practice.

3.2. Efficacy

Objective responses according to RECIST criteria assessed by IRC and/ or CA125 criteria were seen in 5/61 patients (ORR 8.2%, 95% CI, 3.1–18.8%) with 1 partial response (PR) by RECIST and 2 complete responses (CR) as well as 2 PR by CA125 criteria (Table 2). Clinical benefit (CR, PR, or stable disease [SD]) was seen in 49/61 patients (CBR 80.3%, 95% CI, 67.8–89.0%) according to RECIST criteria and/or CA125 values. Treatment duration and changes in the size of target tumor lesions and changes in CA125 levels per patient are shown in Figs. 1 and 2. Median PFS assessed by RECIST criteria was 2.1 months (95% CI, 2.0–3.1) and assessed by RECIST and/or CA125 values was 2.0 months (95% CI, 1.8–2.2) (Fig. 2C). At 2 year follow-up, 19 deaths from ovarian cancer progression were recorded. The median OS was 21 months (95% CI, 19.47-NA) (Fig. 2D).

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3.3. Safety and Quality of Life

Themost common overall adverse events (AE)were fatigue (36.1%) and hypertension (34.4%), with grade 3 hypertension (11.5%) and hypersensitivity (8.2%) being the other most frequent severe adverse events. Grade 1/2 hyperglycemia occurred in 30.4% of patients as well as anemia in 19.7%, neutropenia in 18.0% and thrombocytopenia in 14.8% of the patients (Table 3). One patient died due to cardiac failure which was not deemed to be study drug related by the investigator. In terms of grade 4 events, two patients experienced intestinal obstruction not felt related to ganitumab. Dose reductions were required in 4 patients (1 for hematologic toxicity, 3 for non-hematologic toxicity). Treatment delays were observed in 10 patients and 60% of delays were not related to toxicity and were due to scheduling preferences. No change in quality of life was noted as measured by FACT-O scores in patients during their treatment course (Supplemental Fig. 1).

3.4. Exploratory biomarker analysis

Serum samples were collected in 58 of 61 patients (95%) at baseline and prior to treatment at cycles 1, 2, 4 and 9. We investigated if ganitumab treatment would lead to a change in serum biomarker levels. Blocking IGF1R in hepatocytes has been suggested to lead to a compensatory up regulation of GH [18]. Ganitumab treatment did lead to a statistically significant increase in serum GH, IGF1 and IGFBP3 levels when comparing serum levels between cycle 1 and 2 across the entire study population ($p = 0.049, 0.0036, 0.012$, respectively). However, baseline serum levels of GH, IGF1 or IGFBP3 were not different between patients who responded to ganitumab and those who did not nor was there a difference in change of serum levels between these groups (Fig. 3). Next, we correlated the change of CA125 levels (as a marker of efficacy) with the tumor expression of IGF1, IGF2, IGF1R, IGF2R, and the IGFBPs. We found no statistically significant correlation between CA125 response and the expression of any biomarker assessed using a Bonferonni corrected significance level accounting for multiple testing (Supplemental Fig. 2).

Additional molecular analyses were performed post hoc in a patient with durable disease stabilization for 12 months. This was a 43-year-old woman, with a germline BRCA1 mutation in exon 11 (c.3013 G > T; p.E1005X) who was initially diagnosed with stage IIIB high-grade serous ovarian cancer. Following optimal cytoreductive surgery and 6 cycles of platinum-taxane doublet therapy she recurred 23 months later with peritoneal lesions and an elevated CA125. After 4 cycles of ganitumab on study, her CA125 levels normalized, and CT imaging confirmed stable disease by both INV and IRC assessment. The patient received a total 12 cycles of ganitumab. The local investigator later performed a Comparative Genomic Hybridization assay, and this patient was found to have amplification of the 15q26 gene region which included the region encoding for IGF1R, suggesting that this molecular alteration may have contributed to her treatment response.

4. Discussion

This is the first phase II study evaluating the efficacy of a single agent IGF1R inhibitor in recurrent platinum sensitive OC. When this trial was initiated, IGF1R was of high interest in clinical application based on pre-clinical research into its role in ovarian cancer

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[19]. In fact, there was concurrent enrollment in a phase II multicenter, randomized, placebo-controlled trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-ganitumab in newly diagnosed epithelial ovarian cancer which did not meet its primary endpoint of significantly extending PFS [20]. IGF1R inhibiting antibody therapies including ganitumab, cixutumumab, figitumumab and dalotuzumab have been studied in Phase II and Phase III studies in colorectal, breast, lung, prostate and pancreatic malignancies [21–33]. The majority of studies have shown no significant clinical effect [23–29]. In contrast, a few studies have suggested anti-IGF1R antibodies could shorten OS and/or PFS in lung, colorectal and breast cancers [30–32].Only one study has shown clinical benefit, a randomized study of gemcitabine with or without ganitumab, where ganitumab improved OS in pancreatic cancer [33]. The present study did not demonstrate clinically meaningful activity of ganitumab when given as a single agent in unselected patients diagnosed with recurrent platinumsensitive ovarian cancer. It is possible that the complexity of the IGF signaling pathway may have contributed to this failure as targeting of a single receptormay be too simple an approach for such an intricate system. Six IGFBPs can both facilitate or attenuate IGF1R/IR receptor signaling [34,35]. The high sequence homology between IGF1R and the IR allows for the formation of heterodimers which each differ in their ligand binding affinities to IGF1, IGF2 and insulin [36,37].

A well described mechanism of resistance to highly specific inhibitors of IGF1R may involve enhanced IR-A homodimer formation and IGF2 production as resistant cells are able to switch from IGF1/IGF-1R to IGF-2/IRA dependency to maintain sustained activation of AKT and ERK1/2, proliferation, migration and metastasis [37]. Using this adaptation, ovarian cancer cells may be able to continue to proliferate and metastasize despite IGF1R inhibition. There also exists complex downstream pathways such as the HER2, EGFR and estrogen receptors which add to the redundancy in this system [38–41].

In-vivo data [42] and the initial clinical trials of IGF1R inhibitors [43,44] showed increased circulating levels of serum IGF1, IGFBP3 and GH proteins. This effect was believed to be secondary to blocking the negative feedback on IGF1R on GH production. We noted a similar increase in serum IGF1, IGFBP3 and GH levels after ganitumab treatment but saw no difference between responders and non-responders. Increased GH levels cause hyperglycemia in the setting of increased liver gluconeogenesis and insulin resistance [18]. Hyperglycemia was noted in 30% of all study patients.

In the current study, we also saw no correlation between the mRNA expression of IGF1, IGF2, IGF1R, IGF2R, IGFBP1, IGFBP2, IGFBP3, IGFBP4, IGFBP5 and IGFBP6 measured in tumor tissues using NanoString and the change in CA125 levels as an accepted marker of drug activity in ovarian cancer.

We would like to highlight the case of the 43-year-old patient who experienced long term disease stabilization with ganitumab and was discovered later to have amplification of the 15q26 gene region which includes the region encoding for IGF1R. It is unclear if this response is possibly related to the IGF1R amplification or the underlying germline mutation in BRCA1. Unfortunately, at the time of our study BRCA status was not routinely collected so this information is not known for other patients. It is noteworthy, that two patients with

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endometrioid histology had durable responses (Fig. 1), raising a question about differences in biology between high grade serous and endometrioid tumors that might by more susceptible to alterations in IGF pathways. Although the number is small this observation may warrant further exploration of IGFR1 inhibition specifically in endometrioid ovarian cancer or endometrial cancer.

In conclusion, despite the compelling biological rationale for targeting the IGF receptor pathway in ovarian cancer, the study investigating an IGF receptor inhibitor as single agent in low volume platinum sensitive recurrent ovarian cancer did not meet its primary endpoint. IGF1R inhibition with ganitumab was well-tolerated, however, our results do not support further study of ganitumab as a single agent in unselected OC patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Ganitumab is a fully human monoclonal antibody against IGF1R that blocks binding of IGF1 and IGF2
- Ganitumab as a single agent in unselected ovarian cancer patients does not show promising activity
- Ganitumab was well-tolerated in ovarian cancer patients
- The IGF pathway has significant signaling redundancy which causes resistance to single receptor inhibition

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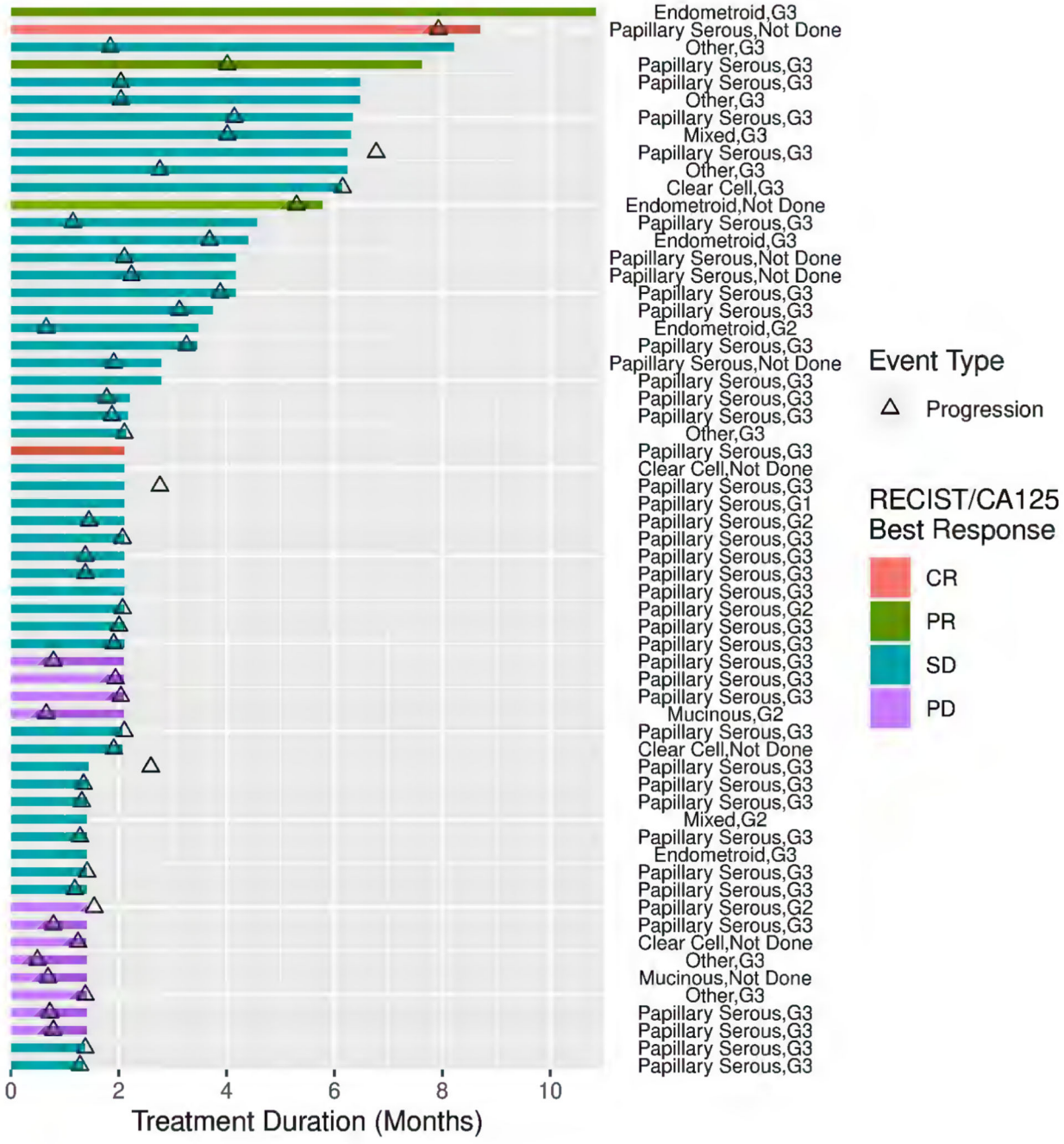

Fig.1.

Treatment duration.

Swimmer plot showing the length treatment duration and timepoint of progression according to CA125 or RECIST criteria. Colored by best response according to CA125 or RECIST criteria. Righthand column includes subject information on tumor histology and grade (N = 61).

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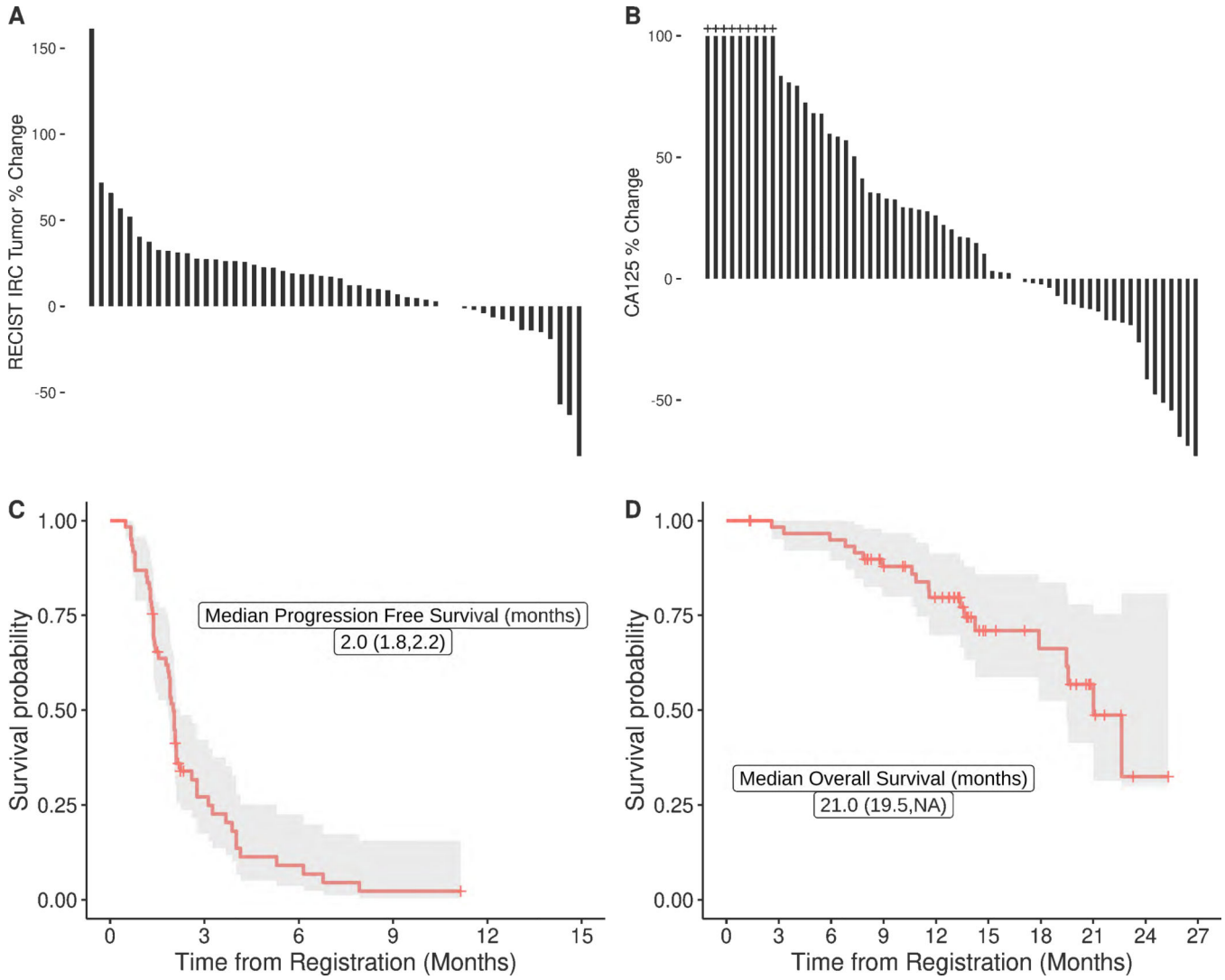

Fig. 2.

Tumor Response.

2A: RECIST Tumor volume percent change from baseline.

Waterfall plot for tumor volume, showing percent change relative to baseline measurement. (*N* = 52; 9 are excluded due to missing RECIST percent tumor change from baseline).

2B: CA125 Percent change from baseline.

Waterfall plot for CA125 level, showing percent change relative to baseline measurement. "+" symbols are used to indicate the percent change goes above 100%. (N = 61).

2C: Progression according to CA125 and/or RECIST criteria.

Kaplan-Meier curves showing time to progression according to CA125 and/or RECIST criteria. (N = 61).

2D: Overall survival according to CA125 and/or RECIST criteria.

Kaplan-Meier curves showing overall survival (N = 61).

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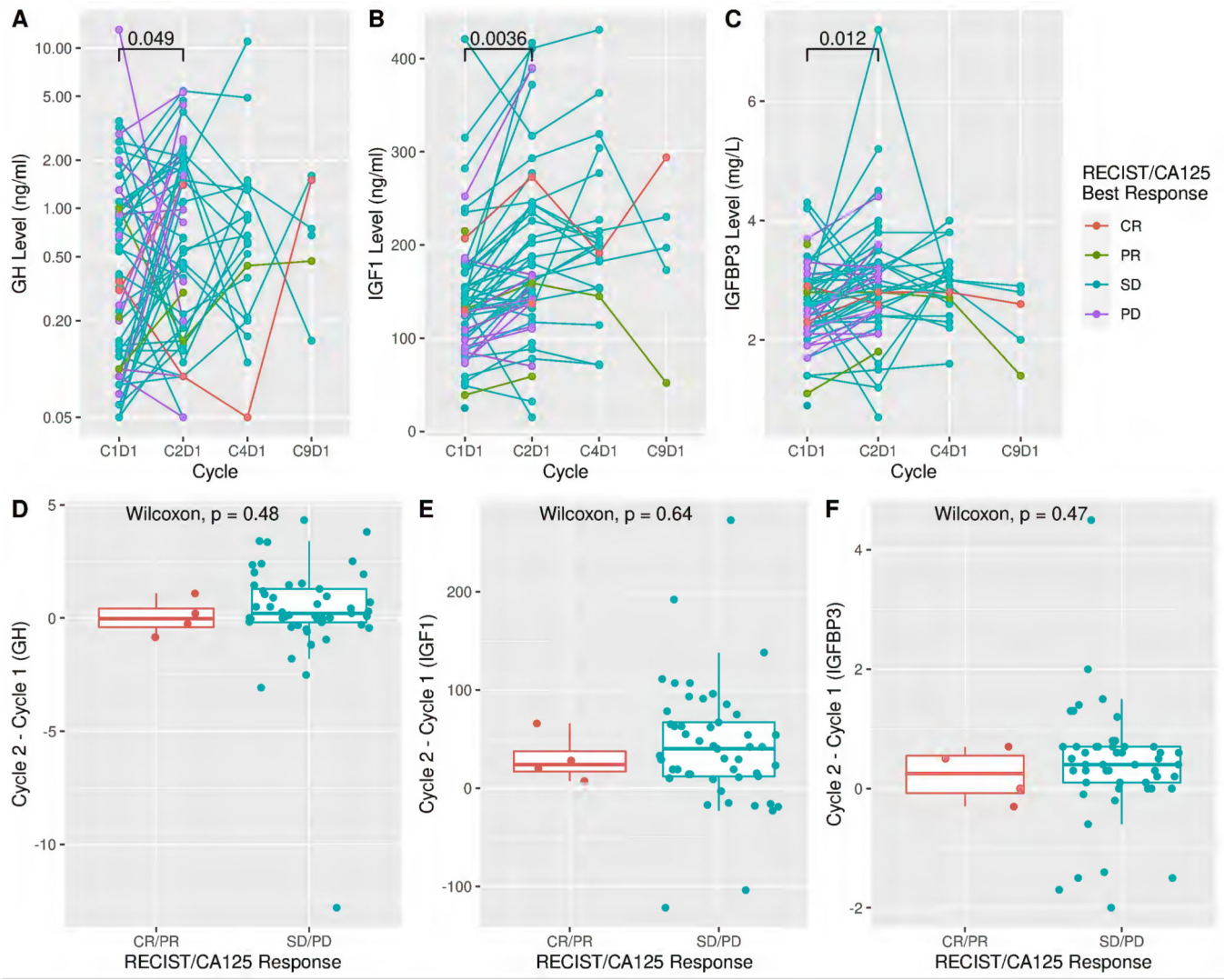

Fig. 3.

Serum concentration levels.

Spaghetti plots showing the change in levels of GH, IGF, and IGFBP3 (A, B, C) on day 1 of cycles 1, 2, 4, and 9. GH is plotted on the natural log scale but labeled on the raw scale. Patients with varying response status are indicated via color according to the legend. The change from cycle 1 to cycle 2 overall was assessed via Wilcoxon signed rank test and compared between responders (CR/PR) and non-responders (SD/PD) using the Wilcoxon rank sum test. The change was displayed using boxplots (D, E, F); the boxes extend from the 25th percentile up to the 75th percentile with middle bar placed at the median, and whisker lines extend above and below the box to the furthest values no >1.5*interquartile range from the 75th or 25th percentile, respectively ($N = 58$).

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Table 1:

Baseline patient and disease characteristics

	Overall (N=61)
Age (years)	
Median	62
Range	35 – 83
ECOG at Baseline	
0	41 (67.2%)
1	20 (32.8%)
Stage at First Diagnosis	
IC	3 (4.9%)
IIA	1 (1.6%)
IIB	2 (3.3%)
IIC	2 (3.3%)
IIIA	1 (1.6%)
IIIB	3 (4.9%)
IIIC	44 (72.1%)
IV	5 (8.2%)
Histopathologic Type	
Clear Cell	4 (6.6%)
Endometroid	5 (8.2%)
Mixed	2 (3.3%)
Mucinous	2 (3.3%)
Papillary Serous	42 (68.9%)
Other	6 (9.8%)
Histologic Grade	
G1	1 (1.6%)
G2	6 (9.8%)
G3	45 (73.8%)
Not Done	9 (14.8%)
CA125 Status at Baseline	
Non-eleavted CA125 + target lesion(s) +/− Non target lesion(s)	8 (13.1%)
Elevated CA125 + Non target lesion(s) only	11 (18.0%)
Elevated CA125 + target lesion(s) +/− Non target lesion(s)	37 (60.7%)
Elevated CA125 only	5 (8.2%)

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TABLE 2:

Efficacy

Response	CA125	IRC RECIST	IRC RECIST and/or CA125
Best Overall Response			
CR	2 (3.3%)	0	2 (3.3%)
PR	2 (3.3%)	1 (1.6%)	3 (4.9%)
SD	39 (64.0%)	23 (38.0%)	44 (72.1%)
PD	10 (16.0%)	33 (54.0%)	12 (19.7%)
NA	8 (13%)	4 (6.6%)	0
Objective Response Rate [95% CI]	4/53 (7.5%) [2.4 – 19.1]	1/57 (1.8%) [0.1 – 10.6]	5/61 (8.2%) [3.1 −18.8]
Clinical Benefit Rate [95% CI]	43/53 (81.1%) [67.6 – 90.1]	24/57 (42.1%) [29.4 – 55.9]	49/61 (80.3%) [67.8 −89.0]

NA Non-Available

NA for Best Overall Response according to RECIST corresponds to patients with no lesion at baseline.

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TABLE 3

Treatment Emergent Adverse Event (TEAE) in the safety population.

TEAE	All Grade (%)	Grade 1 and 2 (%)	Grade 3 or more (%)
Fatigue	22 (36.1%)	21 (34.4%)	1 (1.6%)
Hypertension	21 (34.4%)	14 (23.0%)	7 (11.5%)
Abdominal Pain	20 (32.8%)	18 (29.5%)	2 (3.3%)
Diarrhea	19 (31.1%)	18 (29.5%)	1 (1.6%)
Hyperglycemia*	17 (30.4%)	17 (30.4%)	0 (0.0%)
Nausea	17 (27.9%)	16 (26.2%)	1 (1.6%)
Constipation	14 (23.0%)	14 (23.0%)	0 (0.0%)
Headache	13 (21.3%)	11 (18.0%)	2 (3.3%)
Anemia	12 (19.7%)	12 (19.7%)	0 (0.0%)
Neutropenia	11 (18.0%)	11 (18.0%)	0 (0.0%)
Vomiting	11 (18.0%)	10 (16.4%)	1 (1.6%)
Hypersensitivity	9 (14.8%)	4 (6.6%)	5 (8.2%)
Thrombocytopenia	9 (14.8%)	9 (14.8%)	0 (0.0%)
Chills	9 (14.8%)	9 (14.8%)	0 (0.0%)
Abdominal distension	7 (11.5%)	6 (9.8%)	1 (1.6%)
Decreased Appetite	7 (11.5%)	7 (11.5%)	0 (0.0%)

*Missing data for 5 patients.