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Title: Phase IB Dose-Escalation and Expansion Study of AKT inhibitor Afuresertib with Carboplatin and Paclitaxel in Recurrent Platinum-Resistant Ovarian Cancer

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- **Conflicts of Interest:** Authors MdS and PG are employees of Novartis Pharmaceuticals Corporation. HG is now an employee of Astra Zeneca and ES is an employee of GlaxoSmithKline. The other authors have no conflicts of interest.

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Translational Relevance:

Overcoming platinum resistance in ovarian cancer (PROC) is an unmet medical need. There is preclinical evidence showing that platinum resistance is AKT kinase - mediated. In this Phase IB study, the AKT kinase inhibitor afuresertib was combined with 3-weekly paclitaxel and carboplatin in patients with PROC. The combination was tolerable with rash defining the maximum tolerated dose of 125 mg/day of afuresertib. An overall RECIST (v1.1) response rate of 32% with a progression free survival of 7.1 months was observed. This compares favorably to a historical response rate of <15% when patients with platinum-resistance are re-exposed to platinum-containing treatments. Our findings indicate that the combination of an AKT kinase inhibitor with platinum-based chemotherapy is effective and durable and support the preclinical hypothesis that AKT kinase contributes to platinum resistance. Further clinical evaluation of this combination is warranted.

Abstract

Purpose: Preclinically, AKT kinase inhibition restores drug sensitivity in platinum-resistant tumors. Here the pan-AKT kinase inhibitor afuresertib was given in combination with paclitaxel and carboplatin (PC) in patients with recurrent platinum-resistant epithelial ovarian cancer (PROC) and primary platinum refractory ovarian cancer (PPROC).

Experimental Design: Part I was a combination 3+3 dose-escalation study for recurrent ovarian cancer. Patients received daily continuous oral afuresertib at 50–150 mg/day with three-weekly intravenous paclitaxel (175 mg/m^2) and carboplatin (AUC5) for 6 cycles followed by maintenance afuresertib at 125mg/day until progression or toxicity. Part II was a single arm evaluation of the clinical activity of this combination in recurrent PROC (Cohort A) or PPROC (Cohort B). Patients received oral afuresertib at the maximum tolerated dose (MTD) defined in Part I in combination with PC for 6 cycles, followed by maintenance afuresertib. Primary endpoints were safety and tolerability of afuresertib in combination with PC (Part I, dose-escalation), and investigator-assessed overall response rate (ORR) as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Part II).

Results: Twenty-nine patients enrolled into Part I, and 30 into Part II. Three dose-limiting toxicities (DLTs) of grade 3 rash were observed, one at 125mg and two at 150mg afuresertib. The MTD of afuresertib in combination with PC was therefore identified as 125 mg/day. The most common (≥ 50%) drug-related adverse events observed in Part I of the study were nausea, diarrhea, vomiting, alopecia, fatigue and neutropenia and, in Part II, were diarrhea, fatigue, nausea and alopecia. The Part II ORR in the intention to treat (ITT) patients was 32% (95% CI: 15.9–52.4) by RECIST

1.1 and 52% (95% CI: 31.3–72.2) by GCIG CA125 criteria. Median progression-free survival was 7.1 months (95% CI: 6.3–9.0 months).

Conclusion: Afuresertib plus PC demonstrated efficacy in recurrent PROC with the MTD of afuresertib defined as 125 mg/day.

Introduction

The genetic and molecular mechanisms that determine resistance to platinum-based chemotherapy in epithelial ovarian cancer (EOC) have yet to be fully expounded. Nonetheless, analysis of the molecular pathways represented in sub-clones of resistant ovarian cancer cells reveals significant molecular signalling alterations compared to chemotherapy-naïve disease [1]. In high-grade serous EOC, over-expression and copy number alterations in components of the phosphoinositide 3-kinase (PI3K)/ Protein kinase B (AKT)/mammalian target of rapamycin complex 1 (mTORC1) pathway are common (~46%) but the cascade is also a driver of treatment-resistance [2,3]. In resistant cells, exposure to DNA damaging agents has been shown to activate AKT and anti-apoptotic signaling. Various hypotheses have been proposed to explain the role played by AKT in resistance, including its phosphorylation and activation by the non-homologous end joining repair protein DNA-dependent protein kinase, catalytic subunit (DNA-PKcs/PRKDC) [4]. Inhibitors of the upstream kinase mTORC1 have been shown to reverse resistance, but the effect is short-lived due to feedback upregulation of AKT [5]. Following xenograft evidence that inhibition of AKT restores platinum sensitivity in clinically-acquired platinum-resistant tumor cells, a small study of a pan-AKT inhibitor in patients with gynecologic cancers yielded encouraging results [6].

Afuresertib (GSK2110183, ASB183) is an orally bioavailable, low-nanomolar, ATP-competitive, reversible inhibitor of all three AKT kinase isoforms (AKT1–3) that induces significant growth delay in human tumor xenograft models. When given as monotherapy in a first-in-human hematologic study afuresertib displayed evidence of clinical activity and an MTD was defined (following two dose-limiting toxicities of hepatotoxicity) at 125 mg/day [7].

The overall aim of our study was to determine whether the preclinically-demonstrated outcome of platinum resensitization could be reproduced in the clinical setting. We explored the safety and efficacy of afuresertib given in combination with paclitaxel and carboplatin (PC) in patients with PROC and PPROC and whether response could be maintained on continuous afuresertib. Part I was a dose-escalation to identify the maximum tolerated dose (MTD) of afuresertib given orally in combination with PC administered as a 3-weekly intravenous regimen for six cycles. Part II was a dose-expansion to confirm the safety and antitumor activity of PC given with afuresertib at the MTD defined in Part I. In both parts of the study, upon completion of combination treatment, patients remained on maintenance afuresertib at a dose of 125mg/day until disease progression or the emergence of unacceptable toxicity.

Trial registration: Clinicaltrials.gov registry number NCT01653912.

Patients and Methods

This open-label, multicenter escalation/ expansion study was conducted at 10 clinical centers across 3 countries (United Kingdom, Australia, and Russia). This study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The protocol was approved by Institutional Review Boards within each country, and all patients provided written informed consent before undergoing any study procedures.

The primary objectives of the Part I /dose escalation were to determine the safety and tolerability of afuresertib administered in combination with PC in patients with recurrent PROC (to define the MTD), and to identify the optimal combination dosing regimen to be evaluated in the expansion phase. In the Part II expansion, the primary objective was to confirm safety and evaluate any clinical efficacy signal (investigator-assessed ORR as per RECIST v1.1) of afuresertib given at the MTD in relapsed PROC or PPROC EOC [8]. Secondary endpoints were clinical efficacy, defined as response rate by Gynecological Cancer Intergroup (GCIG) cancer antigen 125 (CA125) criteria [9] and progression free survival (PFS) per RECIST v1.1.

Eligible patients were aged ≥18 years with Eastern Cooperative Oncology Group (ECOG) performance score 0-2, histologically or cytologically confirmed serous epithelial ovarian, fallopian tube or primary peritoneal cancer (here collectively termed “ovarian cancer” or EOC), adequate organ function, no peripheral neuropathy ≥ grade 2 and no history of type I (or recent diagnosis of type II) diabetes. Patients must have had (RECIST v1.1 or GCIG CA125 criteria-defined) disease progression following prior platinum-based treatment. There was no limit on the prior number of lines of therapy but patients were not to have had non-platinum treatments immediately prior to commencing the study. For Part II (dose expansion) of the study, patients were also

required to have RECIST v1.1 measurable disease (with at least one measurable lesion). Those in Cohort A were required to have PROC, defined as RECIST v1.1 or GCIG CA125 progression-free interval of greater than 1 month and up to 6 months since last line of platinum-containing treatment, and have responded to at least one prior platinum-based therapy. Cohort B was strictly confined to patients with recurrent PPROC, defined as RECIST1.1 or GCIG CA125 progression whilst receiving platinum or within 4 weeks of last platinum dose and without response to any prior therapy [10].

Afuresertib was administered orally once daily (at doses of 50–150 mg/day in ascending dose levels by cohort) with intravenous paclitaxel (175 mg/m^2) and carboplatin (AUC 5) given in combination every three weeks for 6 cycles (according to the dosing schedule in Table 1). The 50 mg/day starting dose of afuresertib was 40% of the MTD (125 mg) identified in the afuresertib single agent first-in-human study [7]. Following 6 cycles of the combination regimen, patients were switched to maintenance afuresertib monotherapy (at 125 mg/day) until progression or unacceptable toxicity.

Computed tomography (CT)- based tumor assessments were conducted according to RECIST v1.1 at screening, Week 9, 18, 27 while receiving combination treatment and thereafter every 12 weeks. Serum CA125 was measured at baseline and at day 1 of every treatment cycle. Safety assessments were carried out based on all adverse events (AEs; graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, 2009 (NCI-CTCAE v 4.0)), clinical laboratory data, and physical examinations. Blood samples were collected for pharmacokinetic (PK) analyses throughout the study including at Cycle 2 Day 1, Cycle 3 and/or Cycle 4, prior to and at the end of paclitaxel infusion.

The dose-limiting toxicity (DLT) evaluation period was defined as the first 3 weeks after commencing therapy. A DLT was defined as any of the following occurring during the

DLT-evaluation period and at least possibly related to study treatment: grade 3 or 4 non-hematologic toxicity (with the exception of grade 3 electrolyte disturbances that responded to correction within 24 hours; or grade 3 rash, diarrhea, nausea, vomiting and mucositis that responded to standard medical supportive care within 48 hours); grade 4 anemia or thrombocytopenia; grade 4 neutropenia lasting ≥ 5 days or febrile neutropenia; grade 3 thrombocytopenia with bleeding; alanine aminotransferase (ALT) > 3x upper limit of normal (ULN) with bilirubin > 2x ULN or any toxicity that was unresolved after a treatment delay of >14 days.

Phase I Design

A 3+3 design was used in Phase I. The primary objective was to determine the safety and tolerability (MTD) of afuresertib administered in combination with carboplatin and paclitaxel in subjects with recurrent ovarian cancer and to identify the dosing regimen to be evaluated in Phase II. The first three subjects were enrolled in Cohort 1 (50 mg of afuresertib, AUC5 of carboplatin and 175 mg/m^2 of paclitaxel). Evaluation of available safety data from at least three subjects that had completed 3 weeks on study was required prior to defining a new dose and starting the next cohort. The MTD was defined as the highest dose at which 1 or fewer of up to 6 subjects experience a DLT during the first 3 weeks of combination therapy. The MTD was considered exceeded if 2 or more subjects in a cohort of up to 6 subjects experienced a DLT.

Phase II Design

Sample size considerations for Phase II were driven primarily by clinical feasibility. It was anticipated that up to 23 evaluable subjects in each Cohort could be enrolled (due to difficulty in enrolling subjects into cohort B, enrollment was stopped prior to reaching the target number of patients).

In Cohort A, the hypothesis that the ORR was at least 40% was assessed. A Bayesian sequential analysis of efficacy data was utilized to assess the primary objective to allow for stopping early for success or failure [11]. Sequential analysis was facilitated by the size of the eligible population. The prior density for ORR was assumed to be a beta distribution with parameters (1.65, 4.05) and the posterior probability cut off values were a function of the number of subjects evaluated. The sequential decision rule was defined by predictive probabilities for stopping rule decisions.

Efficacy and Safety Analyses

ORR with exact binomial 95% confidence intervals (CIs) and Kaplan-Meier estimates for PFS (based on clinical symptoms and/or RECIST v1.1 progression) are presented; safety analyses were descriptive. The Intention to Treat (ITT) population, defined as all patients receiving at least one dose of study treatment, was used for all analyses of safety and efficacy. For efficacy analyses only, the RECIST-measurable disease population was defined as the subset of the ITT population whereby only patients with measurable disease at baseline were included. The CA125-measurable disease population was defined as the subset of ITT patients with a CA125 value greater than twice the upper limit of normal within 14 days prior to starting treatment.

Pharmacokinetics

Analysis was performed using solid phase extraction followed by high pressure liquid chromatography tandem mass spectroscopy (HPLC).

Results

The study enrolled 59 patients between 13 November 2012 and 1 July 2015. Of these 59 patients, 29 were enrolled into Part I (dose escalation) and 30 into Part II (dose expansion) of the study. In Part I, 28 patients had PROC with platinum-free intervals (PFI) of 6 months or less and 1 had a PFI of 7 months. In Part II, 28 patients were enrolled into Cohort A (with recurrent PROC) and 2 into Cohort B (with recurrent PPROC) (Table 2). Due to difficulties in identifying eligible patients, enrollment into Cohort B was halted after 2 patients had been recruited. The final analysis cut-off date was 24 November 2015.

All but two patients had serous histology (Table 2). All received at least 1 dose of study treatment. The median duration of exposure to afuresertib was 5.7 months in Part I and 6.55 months in Part II (Supplemental Table 1). Overall, 19/59 (32%) patients required ≥1 afuresertib dose reduction. A total of 18/59 (31%) and 23/59 (39%) patients required 1 dose reduction of PC, in Parts I and II respectively. At the time of data cut-off all patients had discontinued treatment; 35/59 (59%) due to disease progression (59% and 60% of patients in Parts I and II) and 10/59 (17%) due to adverse events (AEs; 14% and 20% of patients in Parts I and II) (Supplemental Table S2).

In Part I, three DLTs were reported: grade 3 rash in 1/12 patients treated at 125 mg and grade 3 maculopapular rash in 2/3 patients treated at 150 mg. An MTD of 125 mg afuresertib in combination with carboplatin (AUC 5) and paclitaxel (175 mg/m^2) was defined in Part I, and this dose was subsequently utilized for Part II.

Across both parts of the study, all patients reported at least one AE of any grade suspected to be treatment related, with grade 3–4 AEs reported in 45 (76%) patients

(Table 3). Across Parts I and II, all patients had at least one AE regardless of causality (Supplemental Table S3). AEs of interest were those associated with PI3K/mTOR axis inhibition and those seen previously with afuresertib [12,7]. These included diarrhea, dyspepsia/gastroesophageal reflux, hyperglycemia and rash. In addition, dose-limiting hepatoxicity was described in the afuresertib first-in-human trial at the 150mg dose level [7]. In our study, most (73%) patients experienced at least one event of diarrhea, mainly grade 1–2 and manageable with concomitant medications. Dyspepsia (including gastroesophageal reflux disease) was reported at least once in 30 (51%) of patients, mainly grade 1–2 and was managed with immediate commencement of supportive medications. Grade 1–3 hyperglycemia was reported at least once in 6 (10%) patients, but none led to treatment discontinuation. Rash (including maculopapular rash) was reported at least once in 32 (54%) of patients; this was grade 3 in 20% of cases, and was managed with dose adjustment. These events occurred early and during combination treatment (at a median of 6, 13, 54 and 11 days for diarrhea, dyspepsia, hyperglycemia and rash respectively). Hepatotoxicity was reported at least once in 2 (3%) patients in the 125mg afuresertib cohort (Part II). In one patient, grade 2 elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was observed and resolved without discontinuation or reduction of the study drugs. The second patient experienced grade 3 transaminitis and hyperbilirubinemia necessitating their discontinuation from the study. Of note, this patient had grade 1 elevated AST, ALT and alkaline phosphatase (ALP) at study entry.

No fatal AEs were reported; one death on study was attributed to complications of progressive EOC. A total of 10 patients (17%) reported AEs that led to discontinuation of afuresertib, most commonly diarrhea (5%), and abdominal pain, nausea, vomiting, decreased appetite, and dehydration (all $\leq$3%) (Table 3).

Pharmacokinetics

For the majority of 49 study patients, paclitaxel levels were in the range 1060 ng/mL – 9850 ng/mL. For afuresertib, there were no noteworthy (extremely low or high) concentration values observed and concentrations (sparse [pre- and post-paclitaxel infusion] or serial samples) were similar to those seen in the first-in-human study [7]. Paclitaxel concentrations at the end of the infusion (C_{max}) in this study were similar to reported values with similar doses and schedules [13], suggesting that co-administration of PC and afuresertib did not affect exposure to paclitaxel.

Efficacy

In Part I, the confirmed ORR was 24% (95% CI: 10.3–43.5) in the ITT population (n=29), and 26% (95% CI: 11.1–46.3) in the RECIST v1.1-measurable population (n=27) with partial response being the best response observed. The ORR per GCIG CA125 in CA 125-measurable patients (n=25) was 40% (95% CI: 21.1–61.3) (Table 4).

In Part II, the confirmed ORR per RECIST v1.1 in the ITT population was 32% (95% CI: 15.9–52.4; Table 4). There were two unconfirmed responses in patients who failed to undergo a subsequent, confirmatory CT scan as per protocol schedule– one patient with best response of stable disease (SD) who discontinued due to clinical deterioration and another with best response of partial response (PR) who discontinued study participation for unspecified reasons. The confirmed ORR per GCIG CA125 in 25 evaluable (CA125 measurable) PROC patients was 52% (95% CI: 31.3–72.2; Table 4). The best percentage change from baseline in tumor measurement (RECIST v1.1) for individual PROC patients in Cohort A (n=28) is shown

in Figure 1 and change from baseline in CA125 levels by GCIG CA125-confirmed response in the Part II Cohort A (n=25) in Figure 2. Kaplan-Meier estimated median PFS for the 28 PROC patients in Cohort A was 7.1 months (95% CI: 6.3–9.0) by RECIST v1.1.

Discussion

To address the preclinical evidence that pan-AKT kinase inhibitors are capable of overcoming platinum-resistance, we gave afuresertib with PC chemotherapy at a dose and schedule (175mg/m^2 paclitaxel and AUC5 carboplatin, given 3-weekly for 6 cycles) used for the front-line management of EOC. This chemotherapy schedule was selected as a backbone for afuresertib so it could be later evaluated in the upfront setting. Rash defined the MTD of afuresertib as 125mg/day, the same MTD dose as was derived in the first-in-human hematologic study [7]. There was a higher toxicity burden in our combination study than was described in the first-in-human afuresertib trial, with all patients experiencing at least one AE. Some side effects such as alopecia, neutropenia, neuropathy and arthralgia were likely to be have been caused by the PC chemotherapy backbone, particularly the paclitaxel component. However, the combination was generally well-tolerated with approximately two-thirds of patients completing the six-cycle course of treatment and remaining on study for a median duration that exceeded 6 months.

Although there are no reference studies in which 3-weekly PC has been used in PROC, in one study of patients of a similar age and median platinum-free interval, RECIST response rates of approximately 13% were observed on re-exposure to platinum-based treatment [13]. Here, we demonstrated a confirmed ORR of 32% by RECIST v1.1 and 52% by CA125 criteria respectively. This is significantly better than would be expected in this resistant population of patients particularly within the context of the imaging schedule we utilized; although it should be noted that our hypothesized ORR of 40% was not achieved. We saw a clinical benefit rate (sum of CR, PR and SD) of 71% and responses were durable with a median PFS of 7.1 months. However, it is important to caution that this study was small and response ranges were wide,

suggesting that the combination treatment was more effective in some patients than others.

Our study had limitations. A larger dose expansion cohort would have more clearly characterized disease response. PPROC comprises a small subset (~10%) of EOC patients with a dismal survival outcome [14]. The scarcity of these patients meant that the PPROC-only cohort failed to recruit and was eventually closed. However, it is noteworthy that, with the addition of a patient in Part I, there were 3 patients with PPROC recruited to this study and, among them, one partial response was observed.

In accordance with standard of care, tumor assessments were scheduled after every 9 weeks or 3 cycles of treatment. A RECIST response is only confirmed if it is maintained for 2 consecutive scans timed at least 4 weeks apart [8]. In this study, the scan interval was longer than in comparable chemotherapy studies, in which imaging was conducted every 6–8 weeks [15,16]. Therefore, our reported rates of confirmed ORR and PFS are probably conservative.

As encouraging activity signals had been observed in an earlier monotherapy study of a similar AKT kinase inhibitor [6], our study patients were maintained on afuresertib after combination treatment. However, we noted that responses achieved on the combination were sustained rather than achieved on maintenance afuresertib. This suggests that, in the context of PROC, afuresertib is most effective when administered concurrent with chemotherapy.

At the time of this study, BRCA1/2 gene testing was only approved for EOC patients with an indicative familial or personal cancer history and was therefore unknown for the majority of our trial participants. As recent *in vitro* work has shown that levels of AKT kinase are upregulated in BRCA-mutant ovarian cancer cells and AKT kinase

inhibition enhances cisplatin-induced DNA damage repair [17], it is possible that some of the efficacy signal observed in our study was in patients with impaired germline or somatic BRCA function. The lack of pharmacodynamic endpoints meant that we missed an opportunity to retrospectively assess BRCA or identify molecular markers of activity (such as changes in tumor AKT kinase) that could be used for future patient selection.

As emerging in vitro data support the role of AKT kinase in mediating platinum resistance, our findings would warrant further investigation. The high rate of responses observed in the platinum-resistant patients supports the hypothesis that AKT kinase inhibitors could overcome chemotherapy resistance. Overall this study presents intriguing evidence that AKT kinase inhibition in combination with chemotherapy could be effective in the treatment of platinum-resistant ovarian cancer.

Acknowledgments

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Figures

Figure 1: Best Percentage Change from Baseline in Tumor Measurement (RECIST v1.1) for Platinum-resistant Patients (Part II ITT Population; n=26†).

Figure 2: Best Percentage Change from Baseline in CA125 Levels by CA125 Confirmed Response – Part II Cohort A (ITT population; n=25*).

Table 1: Doses of afuresertib evaluated by cohort in Study Parts I and II

Dose Levels	Afuresertib (once daily)	Carboplatin (every 3 weeks)	Paclitaxel (every 3 weeks)	Maintenance Afuresertib (once daily)
Part I				
1	50mg	AUC5	175mg/m^2	125mg
1.5	75mg	AUC5	175mg/m^2	125mg
2	100mg	AUC5	175mg/m^2	125mg
3	125mg	AUC5	175mg/m^2	125mg
4	150mg	AUC5	175mg/m^2	125mg
Part II (expansion)				
Cohorts A and B (at dose level 3)	125mg	AUC5	175mg/m^2	125mg

Table 2. Patient demographics and disease characteristics (ITT population).

Number of patients, n (%)	**All Patients N=59**	**Part I N=29**	**Part II N=30**
Age, years, n (%)			
Median	60.8	59.2	62.3
Range	35–82	35–76	42–82
Race, n (%)			
Asian	4 (7)	2 (7)	2 (7)
Black/African American	1 (2)	0	1 (3)
Caucasian	51 (86)	25 (86)	26 (87)
Other	2 (3)	1 (3)	1 (3)
ECOG PS, n (%)			
0	16 (27)	11 (38)	5 (17)
1	39 (66)	16 (55)	23 (77)
2	4 (7)	2 (7)	2 (7)
Number of prior systemic regimens (per patient)			
Median	3.6	3.4	3.8
Range	1–10	1–8	1–10
Prior PARP inhibitor[†], n (%)	1 (2)	1 (3)	0

Prior angiogenesis inhibitor‡, n (%)	14 (23.7)	8 (27.6)	6 (20)
Platinum-free interval (months)*			
Median	4.0	5.2	4.2
Mean [SD]	3.43 [2.21]	3.4 [2.23]	3.8 [2.22]
Range	0–7**	1–7	0-6
Histology, n (%)			
Serous	57 (97)	28 (97)	29 (97)
Mixed Epithelial	2 (3)	1 (3)	1 (3)
Endometrioid	1 (2)	1 (3)	0
Other/unknown	1 (2)	0	1 (3)
Grade			
I	2 (3)	1 (3)	1 (3)
II	1 (2)	1 (3)	0
III	54 (92)	26 (90)	28 (93)
Unknown	2 (3)	1 (3)	1 (3)

† Rucaparib. ‡In part I: 3 received AMG386, 3 received cediranib, 1 received pazopanib and 1 bevacizumab; In part II: 6 received bevacizumab. *Platinum free interval was derived as the time (months) between the date of last dose of the most recent prior platinum-based therapy and the date of first dose of carboplatin study treatment. **One patient had a PFI of 7 months.

Table 3. Adverse events (all grades [occurring in ≥10% subjects], suspected to be related to study treatment) by treatment group.

Preferred Term	All Patients, n (%) N=59		Part I, n (%) N=29		Part II, n (%) N=30	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Patients with ≥1 AE	59 (100)	45 (76)	29 (100)	22 (76)	30 (100)	23 (77)
Gastrointestinal						
Diarrhea	38 (64)	7 (12)	20 (69)	1 (3)	18 (60)	6 (20)
Nausea	38 (64)	4 (7)	22 (76)	3 (10)	16 (53)	1 (3)
Vomiting	30 (51)	5 (8)	18 (62)	2 (7)	12 (40)	3 (10)
Gastroesophageal reflux disease	18 (31)	0	14 (48)	0	4 (13)	0
Constipation	11 (19)	0	4 (14)	0	7 (23)	0
Stomatitis	10 (17)	0	7 (24)	0	3 (10)	0
Abdominal pain	8 (14)	1 (2)	6 (21)	0	2 (7)	1 (3)
Dyspepsia	8 (14)	0	2 (7)	0	6 (20)	0
Mouth ulceration	6 (10)	0	0	0	6 (20)	0
Skin and Subcutaneous Tissue						
Alopecia	31 (53)	1 (2)	16 (55)	0	15 (50)	1 (3)
Rash	16 (27)	5 (8)	11 (38)	2 (7)	5 (17)	3 (10)
Rash Maculopapular	15 (25)	7 (12)	3 (10)	2 (7)	12 (40)	5 (17)
Pruritus	13 (22)	0	4 (14)	0	9 (30)	0
General						

Fatigue	34 (58)	5 (8)	16 (55)	1 (3)	18 (60)	4 (13)
Mucosal inflammation	7 (12)	0	5 (17)	0	2 (7)	0
Nervous System						
Peripheral neuropathy	11 (19)	0	5 (17)	0	6 (20)	0
Peripheral sensory neuropathy	10 (17)	1 (2)	8 (28)	0	2 (7)	1 (3)
Headache	6 (10)	0	5 (17)	0	1 (3)	0
Dysgeusia	6 (10)	0	2 (7)	0	4 (13)	0
Metabolism and Nutrition						
Decreased appetite	23 (39)	1 (2)	13 (45)	1 (3)	10 (33)	0
Hypomagnesemia	15 (25)	7 (12)	8 (28)	5 (17)	7 (23)	2 (7)
Hematologic						
Neutropenia	19 (32)	13 (22)	15 (52)	12 (41)	4 (13)	1 (3)
Anemia	14 (24)	5 (8)	4 (14)	2 (7)	10 (33)	3 (10)
Thrombocytopenia	13 (22)	4 (7)	6 (21)	2 (7)	7 (23)	2 (7)
Musculoskeletal and Connective Tissue						
Arthralgia	14 (24)	0	8 (28)	0	6 (20)	0
Myalgia	11 (19)	0	8 (28)	0	3 (10)	0
Respiratory						
Dyspnea	6 (10)	1 (2)	5 (17)	0	1 (3)	1 (3)
Allergy						
Drug hypersensitivity	6 (10)	0	4 (17)	0	2 (7)	0
Hypersensitivity	6 (10)	1 (2)	2 (7)	1 (3)	4 (13)	0

Table 4. Confirmed overall response (RECIST-confirmed and CA125; investigator assessed).

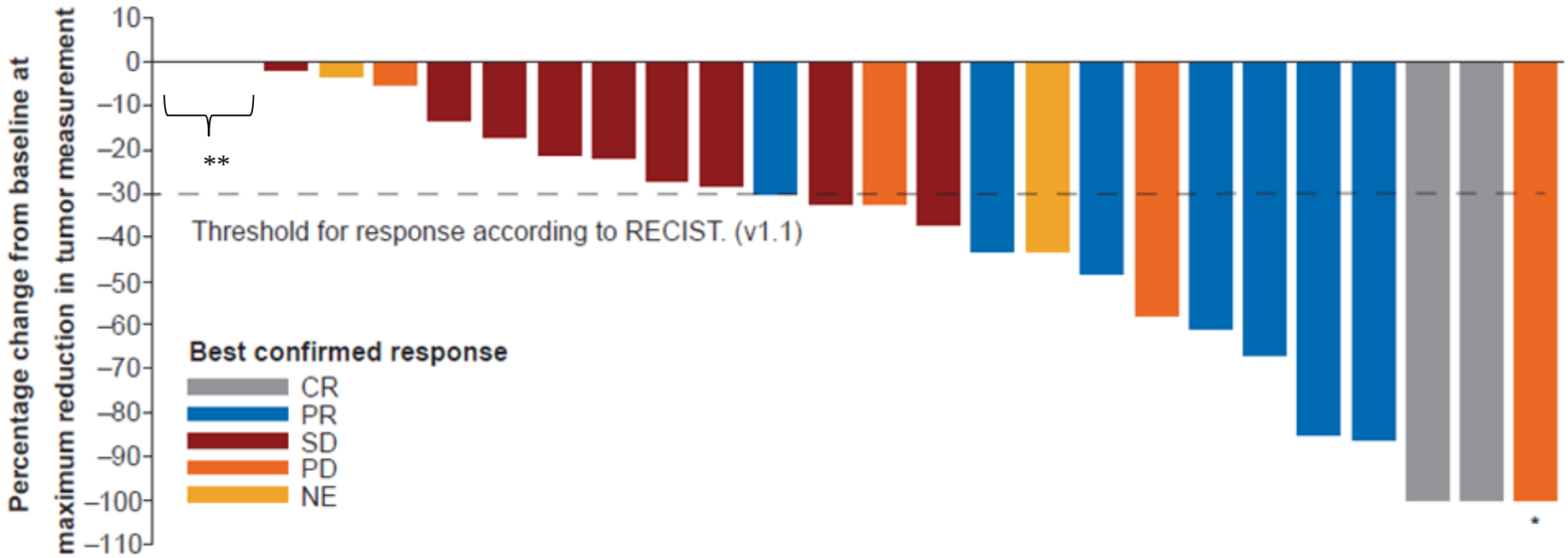
	Part I			Part II	
	RECIST		GCIG CA125	RECIST	GCIG CA125
Overall response, n (%)	**ITT N=29**	**RECIST Measurable N=27**	**CA125 Measurable* N=25**	**ITT Cohort A N=28**	**CA125 Measurable* Cohort A N=25**
Complete response	0	0	2 (8)	2 (7)	5 (20)
Partial response	7 (24)	7 (26)	8 (32)	7 (25)	8 (32)
Stable disease†	13 (45)	12 (44)	11 (44)	11 (39)	9 (36)
Progressive disease	6 (21)	6 (22)	0	4 (14)	0
Not evaluable	3 (10)	2 (7)	4 (16)	4 (14)	3 (12)
ORR	**7 (24)**	**7 (26)**	**10 (40)**	**9 (32)**	**13 (52)**
95% CI	10.3–43.5	11.1–46.3	21.1–61.3	15.9–52.4	31.3–72.2

*Patients included in the CA125 measurable disease population had a CA125 >2 x the ULN within 14 days prior to treatment.

†Stable disease for ≥63 days.

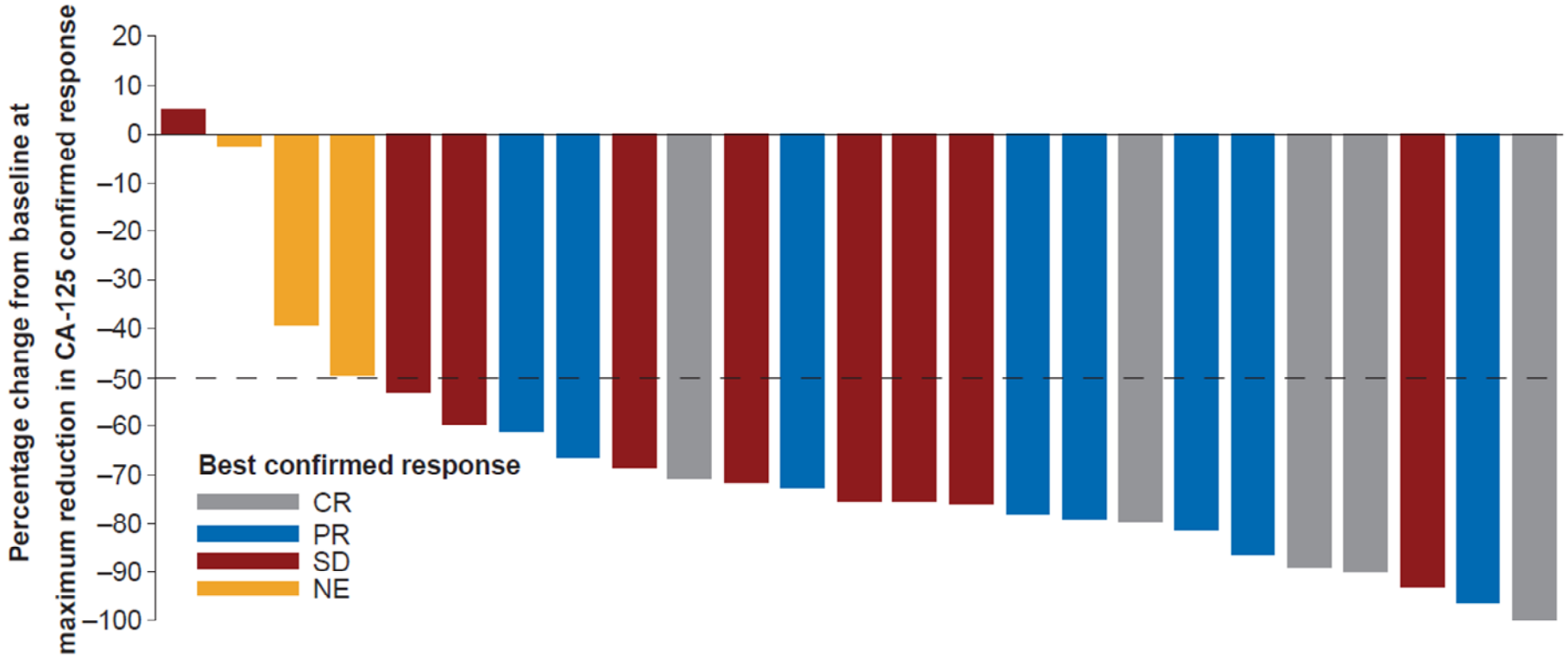
ITT, all treated patients; CR, complete response; GCIC, Gynecological Cancer Intergroup; PR, partial response.

Figure 1.



[†]A total of 26/28 patients (ITT population) are included, who had at least one post-baseline disease assessment. *Patient had 100% reduction in sum of longest diameter (SLD) of target lesions but had new non-target disease and was therefore defined as PD. ** Two patients had a best response of no change in SLD. NE = non evaluable; did not have a repeat CT scan to confirm best response

Figure 2.



*A total of 25/28 patients (ITT population) are included, for whom both baseline and post-baseline CA125 levels were available (CA 125-measurable).