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ORIGINAL ARTICLE

Phase I study of BNC105P, carboplatin and gemcitabine in partially platinum-sensitive ovarian cancer patients in first or second relapse (ANZGOG-1103)

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Abstract

Purpose The primary objective of this study was to determine the recommended dose of the vascular disrupting agent, BNC105P, in combination with gemcitabine and carboplatin in patients with ovarian cancer in first or second relapse with a minimum 4 month progression-free interval after last platinum.

Methods Patients received carboplatin AUC4 on day 1 in combination with escalating doses of 800 or 1000 mg/m^2 gemcitabine on days 1 and 8 and escalating doses of 12 or 16 mg/m^2 BNC105P on days 2 and 9 every 21 days for a maximum for six cycles. Maintenance treatment with 16 mg/m^2 BNC105P treatment continued for a maximum of six additional cycles. Patients were followed for safety and anti-tumor activity.

Results Fifteen patients were enrolled in the study. Adverse events were most commonly of hematological origin. Dose-limiting toxicities (thrombocytopenia and neutropenia) occurred in two patients at the dose level of 800 mg/m^2 gemcitabine, carboplatin AUC4 and 16 mg/m^2 BNC105P. No dose-limiting toxicities were observed at a dose level of gemcitabine 1000 mg/m^2, carboplatin AUC4 and BNC105P 12 mg/m^2. BNC105P as a single agent was well tolerated at a dose of 16 mg/m^2 in maintenance treatment. Ten patients (67%) achieved a complete or partial response according to CA125 and/or RECIST response criteria, four of 13 (31%) responded by RECIST alone. The median progression-free survival was 5.9 months.

Conclusions We have established that BNC105P 12 mg/m^2 with gemcitabine 1000 mg/m^2 and carboplatin AUC4 is the recommended dose level and has an acceptable toxicity profile. Further exploration of BNC105P in the ovarian cancer setting is planned.

Keywords BNC105P · Vascular disrupting agent (VDA) · Ovarian cancer · Phase I · Gemcitabine · Carboplatin

Introduction

Ovarian cancer is the leading cause of death of all gynecological malignancies in the western world. Despite modest improvements in outcomes due to surgery and chemotherapy over recent decades, the great majority of women relapse and eventually die. One of the most important treatment targets in ovarian cancer is the vascular endothelium [1]. Various agents that target tumor angiogenesis, such as bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF) [2], aflibercept (VEGF Trap), a fusion protein that binds all isoforms of VEGF [3–5] and multi-targeted antiangiogenic tyrosine kinase inhibitors such as cediranib [6] and pazopanib [7] have shown significant anti-tumor activity in patients with ovarian cancer, as first-line treatment and also in patients with recurrent disease.

In contrast to anti-angiogenic agents, vascular disruptive agents (VDAs) are designed to disrupt the vasculature of a tumor by binding to proliferating endothelial cells leading to selective occlusion of tumor vessels [8, 9]. VDAs produce

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a characteristic pattern of necrosis after administration to mice and rats with solid tumors [10–13]. As viable tumor cells have been shown to survive at the periphery of the tumor, the combination of anti-vascular and anti-proliferative effects may be a particularly promising therapeutic approach. The VDA combretastatin A-4 phosphate (CA4P) has been studied in combination with carboplatin and paclitaxel in patients classified as having platinum-resistant ovarian cancer. A promising response rate of 29% was reported, but the responses occurred predominantly in patients with progression-free intervals of 4–6 months after last platinum, rather than in patients with shorter progression-free intervals and more definite platinum resistance [14].

BNC105 is a small molecule tubulin polymerization inhibitor that exhibits a high degree of selectivity for tumor endothelial cells, and has both vascular disrupting and anti-proliferative effects. BNC105P is the phosphate ester prodrug of BNC105 and is rapidly converted to the active form by non-specific phosphatases. BNC105P has been tested as single agent in a phase I study with a recommended dose of 16 mg/m^2, day 1 and 8 in a cycle of 21 days [15] without any grade 3 or 4 toxicities at doses $\leq$ 16 mg/m^2. At doses $\leq$ 16 mg/m^2, the drug had an acceptable cardiovascular profile (with one grade 1 CPK-MB increase, and one grade 2 LVEF decrease) and no haematologic toxicity. Preclinical data indicate favorable activity of BNC105P when combined with platinum or with gemcitabine [16].

The aim of this phase I study was to determine the recommended dose and tolerability of BNC105P given in combination with gemcitabine and carboplatin in patients with recurrent ovarian cancer in first or second relapse, with a minimum 4 month progression-free interval after last platinum-based regimen. The regimen of carboplatin with gemcitabine was chosen, as it is a standard regimen for patients with potentially platinum-sensitive relapsed ovarian cancer. A secondary objective of this trial was to assess the effect of combining these drugs on the pharmacokinetics of BNC105P.

Methods

Eligibility criteria

The major eligibility criteria included females with histologically or cytologically confirmed diagnosis of epithelial ovarian cancer, primary peritoneal or fallopian tube cancer, including all histological subtypes, and progression-free interval of $\geq$ 4 months after first or second line platinum-based chemotherapy. Age at baseline had to be $\geq$ 18 years with a WHO performance status of 0–1. Adequate hematologic, renal and hepatic function, defined as follows, was required: absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, creatinine clearance $\geq$ 55 mL/min according to Cockcroft–Gault formula, bilirubin $\leq 1.5 \times$ upper normal limits (UNL), ALT $\leq 2.5 \times$ UNL and normal left ventricular ejection fraction. Patients needed to be assessable for response based on GCIG CA125 [17] and/or RECIST criteria. Exclusion criteria were: symptomatic brain metastases, a history of other primary malignancies except for carcinoma in situ of the cervix and basal cell carcinoma of the skin, any prior chemotherapy for other cancers, persistent toxic effects of previous chemotherapy (including peripheral neuropathy of > grade 1 severity (NCIC CTCAE v4) [18]), a history of significant cardiac disease such as uncontrolled or untreated cardiovascular conditions and/or symptomatic cardiac dysfunction or cardiac ventricular arrhythmias; recent cerebrovascular accident or transient ischemic attack; poorly controlled hypertension; recent thromboembolism, arterial thrombosis, arterial embolism; receiving therapeutic anticoagulants; serious uncontrolled medical illness or psychiatric disorder which might prevent management according to the protocol; significant infections including active hepatitis B, hepatitis C with abnormal liver function tests or HIV, and major surgical procedure within 28 days prior to randomization.

Screening evaluations were performed within 21 days prior to the drug administration.

Ethics

The study was designed and carried out in accordance with Good Clinical Practice, the Declaration of Helsinki and national laws. Institutional ethics committees of each participating center approved the study. All patients provided written informed consent before study entry.

Drug administration, dose escalation and dose modifications

This was a multi-center, open label, phase I study to identify the recommended dose of the combination of BNC105P given with gemcitabine and carboplatin. The trial used a standard 3 + 3 design for allocating participants to a starting dose level. Chemotherapy cycles including carboplatin, gemcitabine and the study drug BNC105P were administered for a maximum of six cycles followed by a maximum of six cycles of BNC105P maintenance treatment. Carboplatin was given intravenously on day 1 over 60 min. Gemcitabine was given intravenously on days 1 and 8 over 30 min. BNCP105P was given intravenously over 10 min on days 2 and 9, 24 h after gemcitabine in combination treatment, and on days 1 and 8 of each 21-day cycle during the maintenance monotherapy treatment.

Patients were enrolled in cohorts of three patients until a dose-limiting toxicity (DLT) was observed. DLT was

defined as any of the following occurring during treatment Cycle 1: grade ≥ 3 neutropenia associated with fever (38.0 °C); grade 4 neutropenia persisting ≥ 7 days; grade 3 thrombocytopenia with bleeding or grade 4 thrombocytopenia (platelets < 25,000 μL); nausea, vomiting or diarrhea grade ≥ 3 despite the use of adequate/maximal medical intervention and/or prophylaxis; any grade ≥ 3 non-hematological toxicity attributable to the study drugs except: (1) alopecia, (2) nausea, vomiting, diarrhea, as defined above and (3) any non-hematologic grade 3 laboratory adverse event that is asymptomatic and rapidly reversible; grade 2–4 neurotoxicity or a delay of cycle 2 of ≥ 15 days. Omission of day 8 gemcitabine was initially included as DLT. However, as such omissions are not uncommon with the carboplatin and gemcitabine regimen, the protocol was amended after completion of dose level 1 and this event was no longer considered a DLT. If one patient experienced a DLT, a total of six patients were enrolled at that dose level. If a second DLT was observed, recruitment to that dose level stopped. The recommended phase II dose was defined as the highest dose with no more than one DLT in six participants.

The starting doses were BNC105P 12 mg/m^2 and gemcitabine 800 mg/m^2. Carboplatin dose was AUC4 on all dose levels. Dose level 2a for BNC105P was 16 mg/m^2, and gemcitabine 800 mg/m^2. Dose level 2b was BNC105P 12 mg/m^2, and gemcitabine 1000 mg/m^2. Dose level 2a and 2b were opened at the same time. A third dose level (dose level 3) with BNC105P 16 mg/m^2 and gemcitabine 1000 mg/m^2 was planned to only open if both dose levels 2a and 2b were deemed to have acceptable toxicity. After concomitant administration, BNC105P was given as single agent at a dose of 16 mg/m^2 BNC105P for a maximum of six additional cycles.

Treatment was withheld during adverse events of severity grade 3–4, and not restarted until the adverse event had resolved to grade 0–1. Day 1 treatment could be delayed for a maximum of 14 days. If the adverse event had not resolved to grade 0–1 after delaying day 1 treatment for 14 days, then study treatment was discontinued. Dose reductions were allowed depending on predefined levels of hematologic or non-hematologic toxicity. Dose reduction levels were as follows: carboplatin 75% (level-1 and -2), gemcitabine 75% (level-1) and omission of day 8 (level-2). For BNC105P, doses were reduced to 75% (level-1) and 50% (level-2). When gemcitabine was to be reduced, both day 1 and day 8 doses were to be reduced. For BNC105P, both day 2 and day 9 doses were to be reduced. Dose escalations or dose re-escalations after reductions for adverse events were prohibited.

Safety and efficacy assessments

Adverse events were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events v.4 and recorded after each treatment cycle. Vital signs, hematology and blood chemistry were monitored prior to registration and before every treatment cycle. Gated Heart Pool scans or echocardiogram were performed prior to registration and after every three cycles. All patients underwent imaging with computed tomography (CT) every 6 weeks for 24 weeks and every 12 weeks thereafter. CA125 was measured before every cycle, 4 weeks after the last cycle, and every 12 weeks until progression. Tumor response was evaluated according to RECIST v1.1 [19] and/or GCIG CA125 criteria [17]. Progression-free survival (PFS) was defined as the interval from date of registration to the date of first evidence of disease progression or death, whichever occurs first. Disease progression was defined according to RECIST v1.1.

Pharmacokinetics

Plasma was collected to assess BNC105 and BNC105P pharmacokinetics on day 2 and 9 of cycle 1 only. Reported PK parameters included the maximum observed concentration (C_{max}), time to C_{max} (T_{max}), the area under the plasma curve concentration–time curve (AUC) from 0 to last quantifiable sampling point post-dose ($AUC_{0–last}$), the AUC extrapolated to infinity ($AUC_{0–inf}$), the elimination half-($t_{1/2}$), and systemic clearance (CL).

Blood-based biomarkers

Blood samples were collected at baseline and 4 h post BNC105P dosing at day 2 and day 9 to study potential pharmacodynamic biomarkers associated with BNC105 biological action in previous trials. The evaluation of samples from ovarian patients was performed using a Myriad Custom Multi Analyte Panel (MAP, Myriad RBM, Austin TX, USA) that utilizes multiplex immunoassay technology to measure 41 analytes (Table 1, supplement).

Statistical analysis

Baseline summary statistics are presented as mean and standard deviation or median and range for continuous variables and number and percent for categorical variables. Percentages given in the summary tables are rounded and may not always add up to exactly 100%.

Progression free survival (PFS) is defined as the interval from date of registration to the date of first evidence of disease progression or death, whichever occurs first. If the patient proceeds to non-protocol therapy without clear

evidence of disease progression, the date when non-protocol therapy commences is deemed the date of disease progression. Progression free survival is summarized using a Kaplan Meier methodology, curves with medians and 95% confidence intervals are reported.

Analyses were carried out using the SAS (Statistical Analysis System, Version 9.3, SAS Institute, North Carolina, USA) software.

All individual analyte data was analyzed using a one-way ANOVA with repeated measures accounting for multiple comparisons followed by Bonferroni multiple comparison tests on selected groups. Data from patients with complete data sets ($n = 13$) were analyzed. No separation was made based on dose level of treatments.

Results

Study population

From July 2012 to May 2013, a total of 15 women from 5 institutions were enrolled in the study. The baseline characteristics of the study population are outlined in Table 1.

Drug exposure

The median number of chemotherapy cycles received was 6 (range 4–6), which was the maximum permitted. The median number of cycles BNC105P received was 10 (range 4–12) in total, with a median of 4 (0–6) cycles given in maintenance treatment.

Safety and tolerability

Six patients were treated on dose level 1, 3 on dose level 2a and 6 on dose level 2b (Table 2). There was one DLT observed on dose level 1 during cycle 1, which was omission of day 8 of gemcitabine in one patient. This dose level was expanded to six patients with no further DLTs occurring. Dose levels 2a and 2b were opened simultaneously. On dose level 2a, DLTs were observed in two patients and accrual to this cohort was ceased after three patients. Both of these patients experienced grade 4 thrombocytopenia, and one of them also experiencing grade 4 neutropenia persisting > 7 days. There were no DLTs in the six patients treated on dose level 2b. The recommended dose of BNC105P given with gemcitabine 1000 mg/m^2 and carboplatin AUC4 is therefore defined as the 12 mg/m^2 dose administered in cohort 2b.

During the course of treatment (all cycles) all patients, independent of dose level cohort, required at least one dose level reduction and one dose delay, predominantly due to hematological toxicity. Hematological toxicities are listed

Table 1 Baseline characteristics

	$N = 15$ (%)
Mean age, years (range)	57 (34–73)
ECOG PS[a]	
0	10 (71)
1	4 (29)
Cancer type	
Epithelial ovarian cancer	14 (93)
Primary peritoneal cancer	1 (7)
Histologic type	
Serous	12 (80)
Endometroid	1 (7)
Adenocarcinoma NOS	1 (7)
Unspecified	1 (7)
Grade of differentiation	
G1	1 (7)
G2	1 (7)
G3	9 (60)
Undifferentiated	1 (7)
Unknown	3 (20)
Cancer sites at baseline	
Ascites	4 (27)
Liver	6 (40)
Lung	2 (13)
Pelvis	9 (60)
Peritoneum	12 (80)
Pleural effusion	1 (7)
Other	5 (33)
Prior lines of chemotherapy	
1	9 (60)
2	6 (40)
Progression-free interval since last platinum (months)	
4–6	2 (13)
7–12	4 (27)
13–24	2 (13)
> 24	7 (47)
Median CA-125 at baseline (range)	2007 (42–18,210)

[a]One patient missing ECOG PS status

Table 2 Starting dose levels and dose limiting toxicities

	Dose level 1	Dose level 2a	Dose Level 2b
BNC105P	12 mg/m^2	16 mg/m^2	12 mg/m^2
Gemcitabine	800 mg/m^2	800 mg/m^2	1000 mg/m^2
Carboplatin	AUC4	AUC 4	AUC 4
No. registered	6	3	6
Patients with DLTs	1	2	0

Table 3 Haematological toxicities—worst toxicity grade reached on treatment, by dose level (all cycles)

	Grade	Dose level 1 $N=6$	Dose level 2a $N=3$	Dose level 2b $N=6$	All patients $N=15$
Anemia	1	1	2	2	5
	2	3	1	1	5
	3	0	0	1	1
Neutropenia	1	0	0	1	1
	2	0	0	0	0
	3	2	2	4	8
	4	3	1	1	5
Thrombocytopenia	1	0	0	0	0
	2	2	1	0	3
	3	0	0	2	2
	4	0	2	0	2

in Table 3. The most common event was neutropenia, with grade 3–4 occurring in five out of six patients at dose level 1 and 2b, and in all 3 patients at dose level 2a (Table 3). Grade 3–4 thrombocytopenia occurred in two out of three patients in cohort 2a (both grade 4) and two out of six in cohort 2b (both grade 3, with no bleeding). Non-hematological toxicities are listed in Table 4. Grade 3–4 non-hematological toxicities were grade 3 hypertension, grade 3 vomiting each in one patient on dose level 1 and grade 3 GGT increase and ALT increase in one patient, respectively, on dose level 2b. There was one patient with carboplatin hypersensitivity reaction grade 3 on dose level 2a. All grade 3 and 4 toxicities, apart from one patient with grade 3 hypertension and one patient with grade 4 neutropenia, occurred in the study phase when BNC105 was administered in combination with chemotherapy.

Table 4 Non-Haematological toxicities—worst toxicity grade reached on treatment, by dose level (all cycles)

	Grade	Dose level 1 $N=6$	Dose level 2a $N=3$	Dose level 2b $N=6$	All patients $N=15$
ALT increases	1	1	2	2	5
	2	0	0	0	0
	3	0	0	1	1
GGT increased	1	1	2	3	6
	2	0	0	0	0
	3	0	0	1	1
AST increased	1	0	2	1	3
	1	0	0	1	1
Creatinine increased	1	0	1	0	1
Anorexia	1	1	0	0	1
	2	0	1	1	2
Nausea	1	3	1	4	8
	2	3	1	0	4
Vomiting	1	3	0	1	4
	2	1	0	0	1
	3	1	0	0	1
Diarrhoea	1	3	0	0	3
	2	1	0	0	1
Constipation	1	3	1	2	6
Mucositis oral	1	0	0	1	1
Weight loss	1	0	1	0	1
Fatigue	1	4	1	2	7
	2	1	2	3	6
Peripheral sensory neuropathy	1	1	0	1	2
Hypertension	1	0	0	1	1
	3	1	0	0	1
Thromboembolic event	2	0	0	1	1
Other	1	1	0	1	2
	2	5	1	4	10
	3	0	1	0	1

Pharmacokinetics of BNC105 and BNC105P

PK profiles generated in this study were similar to when BNC105P was given in previous published studies as a monotherapy (BNC105P.001) [15] or in combination with everolimus (GU09-145) [20] (Fig. 1; Table 2, supplement). There were two patients with high BNC105P Cmax (one at dose level 1—12 mg/m^2 and one at dose level 2a—16 mg/m^2) that were outliers. These two patients experienced omission of day 8 gemcitabine due to grade 3 neutropenia. However, there was no obvious association with toxicity as the two patients that experienced grade 4 hematologic toxicity on dose level 2a had PK parameters that were nine and fourfold lower than the third patient on this dose level.

Efficacy

Of the 15 patients enrolled in the study, 12 stopped treatment due to progressive disease and 3 completed the protocol treatment. The objective response rate by RECIST and /or GCIG CA 125 criteria for all cohorts was 67% (10/15). Ten out of 14 (71%) patients evaluable for response by GCIG CA125 criteria achieved a CA125 response. The median duration of response was 5.5 months (2.5–7.6 months). Four out of the 13 (31%) patients evaluable by RECIST, achieved a partial response. Responses were observed in five out of seven patients with a progression free interval (PFI) after last platinum-based chemotherapy of > 24 months, one out of two with a PFI of 13–24 months, three out of four with a PFI of 7–12 months and one out of two with a PFI of 4–6 months. After median follow-up of 15.9 months (2.8–19.0 months), all 15 patients (100%) had progressed. The median progression-free survival was 5.9 months (Fig. 1).

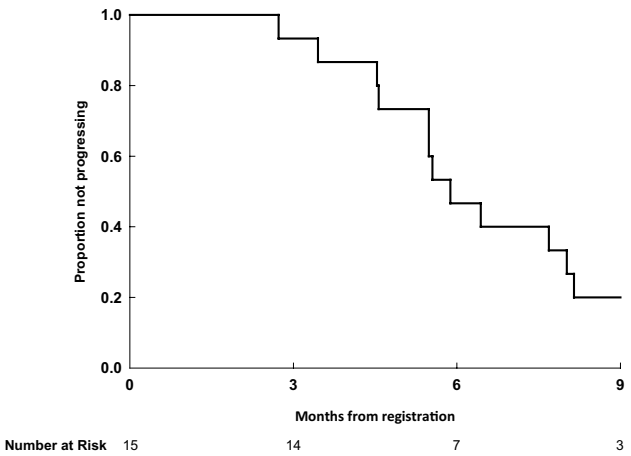

Fig. 1 Progression free survival over all cohorts

Blood-based biomarkers

A number of parameters showed statistically significant changes following doses of BNC105P on both day 2 and 9, indicative that these are reproducible changes that occur following administration of BNC105P. These analytes were ferritin, IL-10 (interleukin-10), IL-8, MIP1B (macrophage inflammatory protein-1b) and TNFR2 (tumor necrosis factor receptor 2) (Table 3, supplement). None of these markers increased after carboplatin and gemcitabine. All other analytes showed changes after only one of the doses, non-significant changes or were below the lower level of quantification (Fig. 1).

Discussion

This is the first study of the VDA BNC105P in combination with chemotherapy. The recommended dose level is 12 mg/m^2 in combination with 1000 mg/m^2 gemcitabine and carboplatin AUC4. This trial also confirmed the good safety profile of single agent BNC105P at a dose of 16 mg/m^2 administered as maintenance treatment. The response rate as assessed by RECIST and /or GCIG CA 125 criteria appeared promising. However, the response rate according to RECIST alone, and the PFS, were not better than what has been reported with carboplatin and gemcitabine [21].

The combination treatment was generally well tolerated, but when 16 mg/m^2 BNC105P was administered in combination with gemcitabine 800 mg/m^2 at dose level 2a, patients experienced an unexpectedly high grade of myelotoxicity. Despite study of several VDAs in pre-clinical models and in clinical trials we still have little understanding of the optimal sequence when combining VDAs with chemotherapy. A decrease in renal perfusion following CA4P administration changes carboplatin pharmacokinetics by increasing the AUC [22]. This may explain the increased myelotoxicity when CA4P was given 1 h after carboplatin administration. Pharmacodynamic analysis of tumor and normal tissue perfusion has shown that it may take up to 24 h before kidney perfusion returned to pre-treatment levels after the administration of CA4P [23]. This is in line with less myelotoxicity when carboplatin was given at least 20 h after CA4P [24] and no significant pharmacological interaction between carboplatin and CA4P were observed.

We opted to administer BNC105P 24 h after carboplatin and gemcitabine on day 2 and after gemcitabine on day 9. This was done with the rationale of avoiding interference with delivery, albeit less likely with BNC105P than CA4P, and initial intra-tumoral distribution of the cytotoxic agents. This schedule is consistent with the sequence used in xenograft models in combination with cisplatin [25]. However, this schedule is clearly inconvenient for patients with four

intravenous treatment days each cycle. Further studies are required to determine the optimal sequencing of chemotherapy and BNC105P.

The observed blood-based biomarker changes suggest that BNC105P at the dose levels used reach plasma concentrations that are sufficient for eliciting a pharmacodynamic response. These observed changes were consistent with those seen in the clinical study of BNC105P as a single agent in mesothelioma [26] and in combination with everolimus in renal cell carcinoma patients [20] and were demonstrated for the first time in this study, at a dose level of 12 mg/m^2. These effects were consistent with those expected for a VDA causing endothelial stress and an acute inflammatory response.

With the caveat of small numbers, and despite the lack of hematologic toxicity observed with single agent BNC105P in previous trials, the higher dose of BNC105P given on dose level 2a may have enhanced the hematologic toxicity of the carboplatin-gemcitabine regimen. BNC105 and BNC105P PK profiles generated in this study were comparable to results in previous published studies when given as monotherapy [15] or in combination with everolimus [20]. Without carboplatin or gemcitabine pharmacokinetic data, we cannot exclude a pharmacokinetic interaction, though the study was designed to minimize any such interaction with a 24-h separation between these drugs and BNC105P.

Although the carboplatin/gemcitabine regimen is generally well tolerated, the considerable myelosuppression induced by the doublet makes it difficult to add any additional drug that increases hematologic toxicity. Furthermore, in many countries carboplatin in combination with gemcitabine is now less frequently administered in the setting of first potentially platinum-sensitive relapse. Carboplatin with pegylated liposomal doxorubicin is increasingly used as first choice for patients with first potentially platinum-sensitive relapse, based on superiority in progression-free survival over carboplatin/paclitaxel with a more favorable toxicity profile [27].

Despite the recognition that VDAs are unlikely to be sufficiently active as single agents, studies of the combination with cytotoxic drugs have been limited by clear signals about optimal sequencing and a lack of biomarkers that are predictive of benefit. There have also been attempts to combine BNC105P with other agents such as the mTOR inhibitor everolimus. However, even though biomarker analysis may reveal a subpopulation with higher response rates, the results in the overall population were limited [20]. The treatment with VDAs has been challenged by the survival of viable tumor cells in the periphery of the tumor contributing to subsequent progression. This may in part be due to putative cancer stem cells, which are typically slow dividing and capable of giving rise to later metastases, being present in perivascular niches near the tumor host interface [28, 29]. The combination with bevacizumab, a VEGF inhibitor, seems to hinder tumor vascular recovery after BNC105 treatment and increased tumor growth inhibition achieved by VDA alone, and may warrant clinical evaluation [30]. Progress in combining VDAs and chemotherapy will likely require a better understanding of mechanisms of interaction, optimal sequencing, determination of the best drugs to combine with VDAs, and identification of the most susceptible cancers and predictive biomarkers.

We have established the recommended doses for this triple combination. With the caveat of low patient numbers, the efficacy was similar to previous reports for the carboplatin/gemcitabine doublet. Further exploration of BNC105P in ovarian cancer is planned but in combination with bevacizumab and/or an immune checkpoint inhibitor rather than with chemotherapy.

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Compliance with ethical standards

Conflict of interest Dr. Lindemann, Dr. Veillard, Dr. Espinoza. Dr. Sommeijer, Dr. Rossi, Dr. Simpson, Dr. Tenney, Dr. Goh and Dr. Vaughan declare that they have nothing to disclose. Dr. Lavranos, Ms. Doolin, Ms. Leske and Dr. Kremmidiotis report salary/stakeholder from Bionomics Limited, outside the submitted work. Dr. Iglesias reports salary from Bionomics Limited, outside the submitted work and has a patent on BNC105 pending. Dr. Martyn reports Grants and non-financial support from Bionomics, during the conduct of the study. Dr. Beale reports personal fees from Roche, personal fees from Astra Zeneca, Grants from Roche, outside the submitted work. Dr. Rischin reports a Grant from Bionomics to ANZGOG for the research costs of the study; in addition, Dr. Rischin has a patent B55 (US) BNC105 Triple Combination Patent Application pending and trial steering/scientific advisory committees—Bionomics, Merck, Amgen, Regeneron, Bristol-Myers—all uncompensated. Dr. Stockler reports Grants from Bionomics, during the conduct of the study; Grants from Bayer, Grants from BMS, Grants from Astra Zeneca, Grants from Specialised Therapeutics, Grants from Amgen, Grants from Astellas, Grants from Merck, outside the submitted work.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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