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A phase II clinical trial of the Vascular Disrupting Agent BNC105P as second line chemotherapy for advanced Malignant Pleural Mesothelioma

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ABSTRACT

BNC105P is a tubulin polymerisation inhibitor that selectively disrupts tumour vasculature and suppresses cancer cell proliferation. This agent has exhibited preclinical and phase I activity in Malignant Pleural Mesothelioma (MPM). This phase II, single arm trial investigated the efficacy and safety of BNC105P as second line therapy in MPM. Participants had progressive MPM after first line pemetrexed/platinum chemotherapy, ECOG PS 0–1, adequate organ function, and measurable disease. BNC105P 16 mg/m^2 was administered intravenously on day 1 and 8 every 21 days until progression or undue toxicity. The primary endpoint was centrally reviewed objective response rate (RR). Tumour response was assessed every two cycles using modified RECIST. 30 patients were enrolled in 10 months, predominantly male (90%), ECOG PS 1 (77%), epithelioid histology (67%), and non-metastatic disease (67%). All patients received at least one dose of study drug, with a median of 2 cycles. No significant haematologic, biochemical, or cardiac adverse events (AEs) were observed. Grade 3 or 4 AEs occurred in 10 patients (33%). There were 2 deaths on study: 1 cardiorespiratory, the other to pneumonia. We observed 1 partial response (3%); 13 patients had stable disease (43%). Median progression free survival was 1.5 months (95% CI 1.4–2.4); median overall survival was 8.2 months (95% CI 3.8–11.9). BNC105P was safe and tolerable. The sole response was insufficient to warrant further research as a single agent.

1. Introduction

Malignant Pleural Mesothelioma (MPM) usually presents with advanced disease, commonly several decades after asbestos exposure. Chemotherapy with pemetrexed and cisplatin is the established first line treatment for advanced MPM [1] and improves survival modestly over cisplatin alone. However, patients invariably progress, and to date there is no established second line treatment. There is a clear need for drug development and clinical trials of second-line therapy in this disease.

Targeting the vasculature of tumours represents a promising cancer therapeutic approach. Tumour microvascular density is significantly higher in MPM than in non-neoplastic mesothelium, or in other tumour types [2–4]. Increased tumour microvascular density in MPM is associated with a significantly shorter survival [3]. As a result, tumour blood vessels are a potential target for therapy in MPM. Vascular Disrupting Agents (VDAs) destroy tumour blood vessels and present an attractive proposition for therapy in MPM. The properties of tumour endothelium appear to be sufficiently different from normal endothelial tissue, enabling VDAs to be developed that selectively target tumour blood vessels. These

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agents exert their primary action on the pre-existing blood vessels of solid tumours, in contrast to the anti-angiogenic agents that prevent new blood vessel formation [5].

BNC105P is a pro-drug of BNC105, a small molecule tubulin polymerisation inhibitor that functions as a VDA through selectively shutting down tumour blood vessels without affecting normal vasculature. BNC105 has 80-fold higher potency in inhibiting proliferating as compared with quiescent endothelial cells [6]. Preclinical *in vitro* and *in vivo* cancer models have demonstrated significant tumour growth suppression and regression with BNC105P, with a better therapeutic index compared to other VDAs in development such as the combretastatin CA4P [5]. Phase I data determined a maximum tolerated dose of 16 mg/m^2 on a day 1 and day 8 of a 21 day schedule [7]. This study also demonstrated *in vivo* changes in tumoral blood flow using dynamic contrast enhanced MRI, thus reflecting an expected VDA mechanism of action. A dose–response relationship was seen, with reduced levels of polymerised tubulin detected in peripheral blood mononuclear cells when exposed to higher BNC105P doses. Although the phase I trial did not show any objective responses among 21 patients, the best observed response was stable disease up to week 22 in a patient with MPM who had progressive disease at study entry and received BNC105P at a dose of 8.4 mg/m^2 [7]. Following this signal for potential activity, this single arm phase II clinical trial investigated the efficacy of single agent BNC105P in patients with progressive MPM after pemetrexed and platinum first line chemotherapy. An additional aim was to identify potential biomarkers of response.

2. Materials and methods

2.1. Study design

This prospective, multicentre, non-randomised phase II trial was conducted by the Australasian Lung Cancer Trials Group. The primary endpoint was centrally-reviewed objective tumour response rate (OTRR) as assessed by spiral computed tomography (CT) using the Modified Response Evaluation Criteria In Solid Tumours (RECIST) [8]. Secondary endpoints included progression free survival (PFS), treatment duration, adverse events, and overall survival. Exploratory correlative analysis of serum mesothelin and other potential biomarkers was performed.

2.2. Eligibility criteria

Eligible patients were ≥18 years of age with histologic confirmation of MPM and radiologic evidence of disease progression following first line chemotherapy. Patients had ECOG performance status 0–1, adequate renal, haematologic, and hepatic function, normal left ventricular ejection fraction (defined as ≥50%), and corrected QTc < 470 ms. All patients were required to have measurable disease (≥10 mm) according to modified RECIST for MPM [8]. Exclusion criteria were: uncontrolled cardiac conditions, history of a cerebrovascular event within the prior 12 months, poorly controlled hypertension, prior diagnosis of another malignancy within 5 years, history of a venous or arterial thrombosis within the prior 12 months, or receiving therapeutic anticoagulation doses of warfarin or heparin derivatives. Anti-platelet agents including aspirin ≥325 mg/day, and clopidogrel, ticlopidine, and persantin were required to be discontinued prior to study entry. The study protocol was approved by the institutional ethics committee and all patients provided written informed consent before study entry. Clinical trial registration number was ACTRN12610000093088 (ANZ Clinical Trials Registry).

2.3. Study treatment

BNC105P 16 mg/m^2 was administered intravenously over 10 min on days 1 and 8 of a 21 day cycle. Symptomatic supportive care was given as clinically appropriate; however concomitant cytotoxic therapy, surgery, or investigational anticancer agents were not permitted. Palliative radiation for urgent local complications was allowed but areas irradiated were not included as sites of measurable disease. Patients continued BNC105P until radiologic progression, clinical deterioration in keeping with progressive disease, unacceptable toxicity, or patient wish to discontinue with no maximum number of cycles specified.

Study drug dose modifications were based on treatment day blood counts; treatment could not resume until neutrophil count reached $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and haemoglobin concentration ≥100 g/L. Grade 3 or 4 cardiovascular events and Grade 3 or 4 arterial thromboembolic events necessitated discontinuation of study drug. Grade 3 and 4 venous thromboembolic events were to be treated with therapeutic doses of anticoagulation and did not require a dose reduction. Treatment could be delayed by 14 days until the toxicity returned to Grade 0–1; if toxicities did not resolve during this time period, then study treatment was to be discontinued. No dose escalations were permitted.

2.4. Study assessments

All patients had clinical assessment at baseline, in addition to full blood counts, liver and renal function tests, and LDH. Baseline ECG and assessment of left ventricular ejection fraction (LVEF) was required using a multigated acquisition scan or echocardiogram.

Clinical examination, adverse event recording, haematology and biochemistry, and lung function and Health-related quality of life (HRQL) testing were performed on day 1 of each cycle. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Contrast-enhanced CT scans of the chest and abdomen were performed every 6 weeks for the first 18 weeks, and 12-weekly thereafter, with objective response rates determined according to the modified RECIST criteria for MPM [8] both at the study site and subsequently by a single independent reviewer. ECG was repeated 3 h post-dose following cycle 1 study drug administration only. Assessment of LVEF was performed after every third cycle using the same technique as baseline on each occasion.

2.5. Correlative biomarkers

Serum for mesothelin measurement was collected at baseline, day 1 of every cycle, 30–42 days after the last treatment dose, and then every 12 weeks until progression unless progression was the reason for treatment cessation. Serum mesothelin concentrations were determined using the MESOMARK^{TM} kit (Fujirebio Diagnostics Inc., Malvern, PA) as previously described [9]. Plasma samples were collected at baseline, 3 h following the first dose of drug, and immediately prior to the second dose of study drug (cycle 1 day 8) and used to generate a multi-analyte profile of 62 exploratory correlative biomarkers (Myriad-Rules Based Medicine, Austin, TX).

2.6. Statistical considerations

A Simon's optimal 2-stage design was used, assuming a response rate of 20% to be of interest, with response rate of 5% considered to be of no interest with alpha and beta error rates of 0.05. If one or fewer objective responses were observed in the first 24 evaluable patients, the trial would be closed early. If two or more objective responses occurred, then recruitment would proceed to 55 evaluable patients with a response rate of 6 or more from 55

Table 1
Baseline patient characteristics.

Age (median, range)	64 (41–82)
Gender (*n* (%))	
Male	27 (90)
Histology (*n* (%))	
Epithelial	20 (67)
Mixed/biphasic	3 (10)
Sarcomatoid	2 (7)
Other/unspecified	5 (17)
Disease extent (*n* (%))	
Local disease	27 (90)
Regional nodes	16 (53)
Distant metastases	7 (23)
Prior radiation (*n* (%))	8 (27)
ECOG (*n* (%))	
0	7 (23)
1	23 (77)
Laboratory values (median, range)	
Haemoglobin	133 (87–158)
Platelets	314 (167–489)
LDH	189 (90–921)

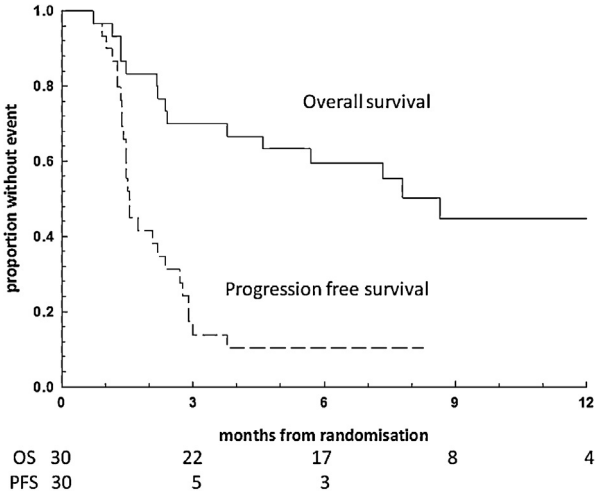

Fig. 2. PFS (median = 1.5 months) and OS (median = 8.7 months); all accrued subjects shown, *N* = 30.

evaluable patients considered to meet the primary endpoint of the trial.

All patients received at least one dose of BNC105P and were included in the analysis. Time-to-event endpoints were calculated from the date of study registration and summarised *via* the Kaplan–Meier method. The method of Brookmeyer and Crowley was used to estimate the 95% confidence interval for the median of the survival distributions [10]. Analysis was performed in SAS (version 9.1). Analyses on the 62 biomarkers were performed using paired *t*-tests of baseline samples with each of the two follow-up time-points. *p*-Values were not adjusted for multiple comparisons. All results are reported.

3. Results

Thirty participants were enrolled between July 2010 and April 2011. The analysis of centrally reviewed tumour responses from the first 24 patients triggered the study to terminate recruitment and results from all 30 patients are reported here with a median follow up of 10.4 months. Patient characteristics are displayed in Table 1. The median time from diagnosis to study enrolment was 13.9 months (range 3.2–51 months).

All patients received at least one dose of study drug. The median treatment duration was 30 days (range 7 days to 13 months) and the median dose intensity was 100%. 17% of patients remained on study drug 3 months from first dose. The majority of patients (87%) stopped study treatment due to progressive disease. One patient required a dose reduction due to an SAE (dyspnoea/anxiety) during the 3rd cycle. Five patients had a day 8 dose omitted for haematological or other adverse events.

All patients had radiologically evaluable disease according to Modified RECIST, and all imaging was reviewed centrally. No complete responses were seen. One of the first 24 patients achieved a partial response (PR); there were no responses in the additional 6 patients accrued before study closure, giving an overall objective response rate of 3% (95% CI 1–17). Stable disease was observed in 13 of 30 patients (43%). A waterfall plot of tumour assessment is shown in Fig. 1. The median PFS was 1.6 months (95% CI 1.4–2.4) and the median OS was 8.2 months (95% CI 3.8–11.9) (Fig. 2).

3.1. Adverse events

All grades of adverse events are shown in Table 2, irrespective of attribution to study drug. Four patients (13%) reported Grade 3 or 4 fatigue. Two patients developed Grade 3 and 4 venous thromboembolic events respectively. Other Grade 3 or 4 events included one incidence each (3%) of febrile neutropenia, oral mucositis, stroke, hypotension, confusion, and colonic obstruction. During the study, nine patients experienced at least one SAE and two patients died. One death, a 65 year old male with multiple cardiovascular risk factors, experienced a stroke (Grade 3) during cycle 5, deemed related. The patient recovered with sequelae, however two days after transfer to a rehabilitation unit, and three weeks after the initial event, he became acutely short of breath and had a respiratory arrest. A Not for Resuscitation Order was in place. The site

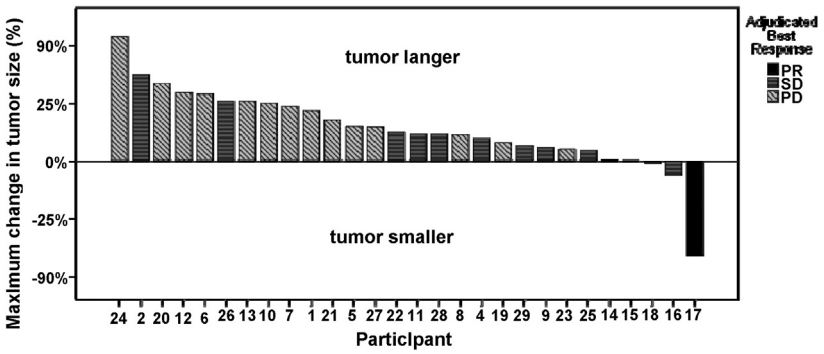

Fig. 1. Waterfall plot demonstrating the best radiological response (largest % decrease or smallest % increase) in each assessable participant as determined by central review (*N* = 28 patients with dual imaging timepoints available, *n* = 2 did not have subsequent imaging).

Table 2
Treatment-emergent toxicities experienced by worst grade, irrespective of attribution.

Adverse event ($N=30$)	Patients with worst grade (n)						Patients with Grade 3/4/5	
	0	1	2	3	4	5	N	(%)
Anorexia	16	9	5	0	0	0	0	(0)
Nausea	18	9	3	0	0	0	0	(0)
Vomiting	26	4	0	0	0	0	0	(0)
Diarrhoea	29	1	0	0	0	0	0	(0)
Constipation	19	9	2	0	0	0	0	(0)
Mucositis oral	27	2	0	1	0	0	1	(3)
Alopecia	30	0	0	0	0	0	0	(0)
Palmar-plantar erythrodysesthesia syndrome	30	0	0	0	0	0	0	(0)
Peripheral motor neuropathy	30	0	0	0	0	0	0	(0)
Peripheral sensory neuropathy	25	5	0	0	0	0	0	(0)
Fatigue	10	7	9	4	0	0	4	(13)
Febrile Neutropenia	29	0	0	1	0	0	1	(3)
Hypertension	27	3	0	0	0	0	0	(0)
Venous thromboembolic events	28	0	0	0	2	0	2	(7)
Other adverse event	3	7	10	7	1	2	10	(33)
Anaemia	19	9	2	0	0	0	0	(0)
Neutrophil count decreased	30	0	0	0	0	0	0	(0)
Platelet count decreased	30	0	0	0	0	0	0	(0)
Alanine aminotransferase increased	25	5	0	0	0	0	0	(0)
Aspartate aminotransferase increased	28	2	0	0	0	0	0	(0)
Blood bilirubin increased	30	0	0	0	0	0	0	(0)
Creatinine increased	28	2	0	0	0	0	0	(0)
GCT increased	24	5	1	0	0	0	0	(0)

investigator and principal investigator assessments were that the events leading to death were not due to extension of stroke, were most likely cardio-respiratory and could not be definitively determined. The second death occurred in a 68 year old male who was admitted to hospital after cycle 2 with left sided pneumonia and died in acute respiratory failure which was considered unrelated. There were no further occurrences of cardiac or thrombotic events.

3.2. Mesothelin levels

At baseline, the median mesothelin level was 4.3 nM (ranging from below detection limits to 62 nM), with 20/30 (67%) having a value above the upper limit of the normal (2.5 nM). Paired samples were available in 27 of 30 patients. One patient had a decrease of 25% or more from baseline after the first cycle of treatment [11]; this was the same patient who achieved a radiological partial response. A further 2 patients with stable disease achieved a mesothelin nadir of 25% or greater reduction from baseline with all others having levels that were stable (within 25% of baseline: 21 patients) or increasing (>125% of baseline: 3 patients) as their best response (Supplementary Figure 1). There was a significant correlation between change in tumour measurement and change in baseline mesothelin concentration on treatment ($r_p = 0.475$; $p = 0.012$).

3.3. Biomarkers

A panel of 62 biomarkers (Supplementary Table 1) was assessed in 19 patients at baseline, 3 h after the first dose of study drug, and just prior to the second dose of study drug. Significant elevations from baseline were observed in the following analytes 3 h following the first study drug administration (p-value): MIP-1beta (0.0023), Ferritin (<0.0001), IL-8 (<0.001), IL-10 (0.002), IL-12 subunit p40 (0.12), TIMP-1 (0.03), TNFR2 (0.0001), Adiponectin (0.04) and IL-16 (0.004). All analytes had returned to baseline levels by day 8 except ferritin which remained elevated.

Supplementary material related to this article found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2013.05.006.

4. Discussion

There remains no accepted second line systemic therapy in MPM. This study of BNC105P in progressive Malignant Pleural Mesothelioma did not meet its primary endpoint, with the majority of patients demonstrating progression shortly after study entry. A single centrally confirmed and prolonged partial response was seen; there were no distinguishing clinical characteristics noted in this patient other than a long period from diagnosis to study entry. This is the first clinical trial to investigate the efficacy of a dual vascular disrupting and anti-proliferative agent in MPM, and adds to a body of literature demonstrating minimal or modest responses to agents targeting the tumour vasculature in this disease, including the anti-VEGF antibody bevacizumab and tyrosine kinase inhibitors targeting VEGF receptor tyrosine kinases [12–15].

It has been argued that VDAs may have a cytostatic mechanism, which may be potentiated in the presence of chemotherapy and/or radiation, and as a therapeutic class VDAs have elicited few objective radiological responses when used as a single agent. Among four phase I trials of single agent VDAs, objective responses were seen in 2/117 patients [7,16–18]. Nevertheless, phase II and III data using VDAs concurrently with chemotherapy have resulted in only modest survival improvements in relapsed ovarian cancer [19], and disappointing phase III results in advanced non-small cell lung cancer [20]. Limited biomarker research to date has not been helpful in pre-selecting patients who may benefit from these agents. This study included an extensive panel of biomarkers, demonstrating immediate post-dose effects consistent with those expected for a VDA causing endothelial stress and an acute inflammatory response. However, where significant effects were seen, they were observed relatively uniformly in all patients, and with only one partial response, there was no clear relationship with drug efficacy.

Further to the safety and efficacy observations reported in this paper, there are a number of points of interest, which are worth highlighting. Firstly, this trial accrued rapidly, confirming the need for effective second line therapies in this disease, and the willingness of the patient group to participate in clinical trials. The study remained open to recruitment while central response was confirmed in the first 24 patients, as only one additional confirmed

response in the first 24 was required to continue the study. The rapid recruitment resulted in an additional 6 participants being enrolled over 4 weeks, and the study was then closed to accrual. The median overall survival of nearly 9 months, suggests that a relatively 'fit' population took part in the study. Secondly, the short median PFS of 1.6 months is effectively identical to the PFS of 1.5 months in the Best Supportive Care (BSC) arm of a randomised clinical trial of pemetrexed with BSC *vs* BSC alone [21]. A number of agents with modest activity have reported PFS or TTP of around three months in the second line setting, and despite many of these studies not meeting their primary efficacy endpoints these agents do show signals for activity [14,21–24]. Finally, this study determined the primary endpoint on the basis of central review of objective tumour response, a prudent measure to ensure the validity of a clinical trial in mesothelioma using response rate as a primary endpoint. Central review was not performed in real time, and a majority of patients had been removed from the study for progression before central review results were available. Central review confirmed the sole response and did not refute any site-determined responses. However, there were a number of instances in which central review altered the time to progression. In five of 28 patients with an evaluable response, the central reviewer placed the date of progression at a different timepoint to the site radiologist. In three of these patients the central reviewer considered the disease stable where the site investigator had removed the patient from study for disease progression. In two patients, the site assessed stable disease while the central reviewer assessed PD; both of these were subsequently assessed as PD at site at the next imaging timepoint.

The study also highlights some points regarding clinical trial design in mesothelioma. The selection of RR or PFS as a primary endpoint is difficult; in this case, RR with central review was considered appropriate and unambiguous for a single agent phase II trial. This study also demonstrates that small phase II trials can eliminate inactive agents from further development more quickly and with fewer patient numbers than a randomised phase II or III trial. The use of RR and a non-randomised design would have been less appropriate in a combination setting.

5. Conclusion

In conclusion, this study adds to the literature reporting the use of BNC105P in patients with advanced cancer, and confirms the tolerability of the drug in this group. However, the results do not support use of BNC105P as a single agent in this disease. Ongoing laboratory work is examining combinations of BNC105P with cytotoxic chemotherapy in murine xenograft models, including MPM. Phase I/II studies of BNC105P in combination with everolimus as second line therapy in renal cell carcinoma, and of BNC105P in combination with gemcitabine/carboplatin and gemcitabine in ovarian cancer progressing within 6–12 months of a first line platinum regimen are currently accruing.

Conflict of interest

Gabriel Kremmidiotis and Annabell F. Leske are employees of Bionomics Ltd. David C. Bibby was an employee of Bionomics Ltd during the conduct and analysis of the study.

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