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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