Clinical Trials Summary for out of hours Important Reference

Lancashire Teaching Hospitals NHS Foundation Trust

Acronym study title	**BNT327-01**
Study Details	**Trial title:** A Phase II, multi-site, randomized, open-label, parallel group trial of BNT327 in combination with chemotherapy for participants with untreated extensive-stage small-cell lung cancer and participants with previously treated small-cell lung cancer **Brief lay title:** Safety, preliminary effectiveness of BNT327, an investigational therapy for patients with small-cell lung cancer in combination with chemotherapy **Trial phase:** Phase II **Indication:** Untreated extensive-stage small-cell lung cancer and previously treated small-cell lung cancer Investigational medicinal product (IMP): BNT327 (also referred to as PM8002)
Principal Investigator PI Sub PI's	Principal Investigator: Prof Dennis Hadjiyiannakis FRCP, FRCR Consultant Clinical Oncologist Medical Director of NIHR Lancashire Clinical Research Facility Email: dennis.hadjiyiannakis@lthtr.nhs.uk Tel: 01772 523736 Sub-Investigator: Prof Ruth Board 07842634191 (Sec)
Research Nurse Team	Email: lancashirecrf@lthtr.nhs.uk Tel: 01772 522031

Drug therapy	**Table 1: Overview of treatment groups, populations, and trial treatments** **Cohort / No. of trial participants** | **Population** | **BNT327 dosing** | **Duration/timing of treatment** Cohort 1 Arm 1 / 20 | Participants with ES-SCLC without prior systemic anticancer therapy received in the ES setting. | BNT327 / 20 mg/kg / IV infusion | Participants will initially receive 4 cycles of combination therapy: • BNT327 20 mg/kg on Day 1, Q3W (21-day [3-week] treatment cycle) with IV carboplatin AUC 5 [b] with a total dose ≤750 mg on Day 1, Q3W plus IV etoposide 100 mg/m² once daily on Day 1 to 3, Q3W (Treatment Period). Followed by a Maintenance Period with BNT327 alone 20 mg/kg Q3W, until disease progression, intolerable toxicity, participant withdrawal, trial termination or up to 2 years (whichever occurs first). Cohort 1 Arm 2 / 20 | Participants with ES-SCLC without prior systemic anticancer therapy received in the ES setting. | BNT327 / 30 mg/kg / IV infusion | Participants initially receive 4 cycles of combination therapy: • BNT327 30 mg/kg on Day 1, Q3W (21-day [3-week] treatment cycle) with IV carboplatin AUC 5 [b] with a total dose ≤750 mg on Day 1, Q3W plus IV etoposide 100 mg/m² once daily on Day 1 to 3, Q3W (Treatment Period). Followed by a Maintenance Period with BNT327 alone 30 mg/kg, Q3W, until disease progression intolerable toxicity, participant withdrawal, trial termination or up to 2 years (whichever occurs first). Cohort 2 Arm 1 [a] / 20 | Participants with SCLC who have disease progression/relapse after first-line platinum-based chemotherapy with or without immunotherapy or after first-line platinum-based chemotherapy and one second-line of chemotherapy (not the same chemotherapy agent in the specific arm to be enrolled to) with TTP ≥3 months during second-line treatment. | BNT327 / 20 mg/kg / IV infusion | Participants will initially receive 5 cycles of combination therapy: • BNT327 20 mg/kg on Day 1, Q3W (21-day [3-week] treatment cycle) with IV paclitaxel 175 mg/m² on Day 1 Q3W (Treatment Period). Followed by a Maintenance Period with BNT327 alone 20 mg/kg, Q3W until disease progression, intolerable toxicity, participant withdrawal, trial termination or up to 2 years (whichever occurs first). [a] Cohort 2 Arm 2 [a] / 10 | Participants with SCLC who have disease progression/relapse after first-line platinum-based chemotherapy with or without immunotherapy or after first-line platinum-based chemotherapy and one second-line of chemotherapy (not the same chemotherapy agent in the specific arm to be enrolled to) with TTP ≥3 months during second-line treatment. | BNT327 / 30 mg/kg / IV infusion | Participants will initially receive 5 cycles of combination therapy: • BNT327 30 mg/kg on Day 1, Q3W (21-day [3-week] treatment cycle) with IV paclitaxel 175 mg/m² on Day 1 Q3W (Treatment Period). Followed by a Maintenance Period with BNT327 alone 30 mg/kg, Q3W until disease progression, intolerable toxicity, participant withdrawal, trial termination or up to 2 years (whichever occurs first). [a] **Cohort / No. of trial participants** | **Population** | **BNT327 dosing** | **Duration/timing of treatment** Cohort 3 Arm 1 [a] / 20 | Participants with SCLC who have disease progression/relapse after first-line platinum-based chemotherapy with or without immunotherapy or after first-line platinum-based chemotherapy and one second-line of chemotherapy (not the same chemotherapy agent in the specific arm to be enrolled to) with TTP ≥3 months during second-line treatment. | BNT327 / 20 mg/kg / IV infusion | BNT327 20 mg/kg on Day 1, Q3W (21-day [3-week] treatment cycle) with IV topotecan 1.5 mg/m² or oral topotecan [d] (2.3 mg/m²), once daily on Days 1 to 5 of a Q3W treatment cycle, until disease progression, intolerable toxicity, participant withdrawal, trial termination or up to 2 years (whichever occurs first). [a] Cohort 3 Arm 2 [a] / 20 | Participants with SCLC who have disease progression/relapse after first-line platinum-based chemotherapy with or without immunotherapy or after first-line platinum-based chemotherapy and one second-line of chemotherapy (not the same chemotherapy agent in the specific arm to be enrolled to) with TTP ≥3 months during second-line treatment. | BNT327 / 30 mg/kg / IV infusion | BNT327 30 mg/kg on Day 1, Q3W (21-day [3-week] treatment cycle) with IV topotecan 1.5 mg/m² or oral topotecan [d] (2.3 mg/m²), once daily on Days 1 to 5 of a Q3W treatment cycle, until disease progression, intolerable toxicity, participant withdrawal, trial termination or up to 2 years (whichever occurs first). [a] a. Required dose reductions for paclitaxel and topotecan will be done as stated in the product label. Dose banding m
In the event that a patient	Working Days 9am – 5 pm:Contact: **Principal Investigator**:

calls this hotline for advice

Prof Dennis Hadjiyiannakis FRCP, FRCR
Consultant Clinical Oncologist
Medical Director of NIHR Lancashire Clinical Research Facility

Email: dennis.hadjiyiannakis@lthtr.nhs.uk
Tel: 01772 523736

Sub-Investigator:
Prof Ruth Board 07842634191 (Sec)

Lead Research Nurse:

Email: lancashirecrf@lthtr.nhs.uk
Tel: 01772 522031

Out of Hours: On-Call oncology registrar

IMP Adverse reactions:

PD-L1 associated	VEGF-associated
Immune-related AEs	Hypertension/ Increased blood pressure
	Proteinuria
	Hemorrhage
	Intestinal perforation/ fistula formation
	Reproductive toxicity

Potential risk of clinical significance	Summary of data/Rationale for risk	Mitigation strategy
Trial treatment: IMP		
Hypertension/ Increased BP	Hypertension is one of the most commonly reported adverse reactions for VEGF targeting monoclonal antibodies. Severe hypertension occurred at a higher incidence in patients receiving BNT327 as compared to patients receiving chemotherapy alone. Across clinical trials, the incidence of Grades 3 to 4 hypertension ranged from 5% to 18%. As of 17 NOV 2023, a total of 384 patients have been treated with BNT327. The incidence of TEAEs was 97.7%. The incidence of Grade ≥3 TEAEs was 39.1%. The incidence of hypertension TEAEs was 19.3% with Grade ≥3 hypertension TEAEs reported at <1%.	Inclusion/exclusion criteria: exclude patients with poorly controlled BP. Monitor BP frequently and as needed during treatment with BNT327. Treat with appropriate antihypertensive therapy and monitor BP regularly. Continue to monitor BP at regular intervals in patients with BNT327-induced or -exacerbated hypertension after discontinuing BNT327. Withhold BNT327 in patients with severe hypertension that is not controlled with medical management; resume once controlled with medical management. Discontinue in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria	The incidence and severity of proteinuria was higher in patients receiving VEGF targeting monoclonal antibodies such as bevacizumab as compared to patients receiving chemotherapy. Grade 3 (defined as urine dipstick 4+ or >3.5 g of protein per 24 h) to Grade 4 (defined as nephrotic syndrome) ranged from 0.7% to 7% in clinical trials. As of 17 NOV 2023, a total of 384 patients have been treated with BNT327. The incidence of TEAEs was 97.7%. The incidence of Grade ≥3 TEAEs was 39.1%. The incidence of proteinuria TEAEs was 27.7% with Grade ≥3 proteinuria TEAEs reported was 1.8%.	Inclusion/exclusion criteria: exclude patients with urine protein ≥2+ and 24 h urine protein ≥1 g. Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during BNT327 therapy. Patients with a 2+ or greater urine dipstick reading should undergo further assessment with a 24 h urine collection. Withhold for proteinuria greater than or equal to 2 g per 24 h and resume when less than 2 g per 24 h. Discontinue in patients who develop nephrotic syndrome.

Potential risk of clinical significance	Summary of data/Rationale for risk	Mitigation strategy
Immune-related AEs	The PD-L1 part of BNT327 belongs to a class of drugs that bind to either the PD-1) or the PD-L1, blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. IrARs which may be severe or fatal, can occur in any organ system or tissue and can affect more than one body system simultaneously. IrARs can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies As of 17 NOV 2023, a total of 384 patients have been treated with BNT327. The incidence of TEAEs was 97.7%. The incidence of Grade ≥3 TEAEs was 39.1%. Immune-related AEs were 48.6%. These IrAEs included immune-mediated severe reports of myocarditis and myositis (PM8002-A001 [NCT05918445]).	Based on existing clinical trial dat most irAEs were reversible and c be managed with interruptions of treatment, administration of corticosteroids, and/or other supportive care. For suspected ir ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation Dose modification and toxicity management guidelines for irAEs associated with BNT327 are prov in Section 8.4.9.2.

Hemorrhage	The incidence and severity of hemorrhage was higher in patients receiving VEGF targeting monoclonal antibodies such as bevacizumab as compared to patients receiving chemotherapy. VEGF inhibitors can result in two distinct patterns of bleeding: minor hemorrhage, which is most commonly Grade 1 epistaxis, and serious hemorrhage, which in some cases has been fatal. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving VEGF inhibitors such as bevacizumab compared to patients receiving chemotherapy alone. As of 18 OCT 2023 (Data cut-off date for DSUR), a total of eight cases of Grade 3 and serious adverse reactions of hemorrhage were reported (PM8002-A001 [NCT05918445]).	Inclusion/exclusion criteria: exclud patients with diseases of coagulopathy and significant risk c hemorrhage such as a history of intracranial or intraspinal cord hemorrhage, clinically significant intra-tumor hemorrhage or hemoptysis within 30 days before screening, and tumor lesions inva large vessels. Monitor coagulation parameters a platelets according to the SoA and needed. Avoidance or reduced dose of dru that could increase the risk of hemorrhage as concomitant medications. Close monitoring of pulmonary hemorrhage in patients especially with squamous cell lung cancer. Discontinue BNT327 for Grade 3 a above hemorrhage.
Intestinal perforation/ fistula formation	All VEGF-targeted therapies can cause gastrointestinal perforation and fistula formation, although this complication is best described in patients receiving bevacizumab. The mechanism by which these drugs contribute to gastrointestinal perforation has not been proven, but proposed mechanisms include intestinal wall disruption (ulceration) in areas of tumor necrosis, disturbed platelet-endothelial cell homeostasis causing submucosal inflammation and subsequent ulcer formation, impaired healing of pathologic or surgical bowel injury, and mesenteric ischemia from thrombosis and/or vasoconstriction. As of 18 OCT 2023 (Data cut-off date for DSUR), a total of four cases of serious adverse reactions of Intestinal perforation/fistula formation were reported.	Inclusion/exclusion criteria: exclus of patients with abdominal fistula, tracheoesophageal fistula, gastrointestinal perforation, or abdominal abscess within 6 month before starting trial treatment. Close monitoring of patients with persistent, recurrent, or metastatic cervical cancer for fistula formation between the vagi and any part of the gastrointestina tract (gastrointestinal-vaginal). Treatment discontinuation for pati with Grade ≥3 gastrointestinal perforation.
Reproductive toxicity	BNT327, is a bispecific antibody that acts on both PD-L1 and VEGF-A proteins to relieve immunosuppression in the tumor microenvironment and reduce angiogenesis like bevacizumab. Based on its mechanism of action and findings from animal studies, bevacizumab may cause fetal harm when administered to pregnant women. Congenital malformations were observed with the administration of bevacizumab to pregnant rabbits during organogenesis every 3 days at a dose as low as a clinical dose of 10 mg/kg. Furthermore, animal models link angiogenesis and VEGF and VEGFR2 to critical aspects of female reproduction, embryofetal development, and postnatal development.	Pregnant or lactating women were excluded. Female participants of childbearing potential selected in the inclusion criteria of the trial protocol have a negative serum pregnancy test res within 7 days before the start of tria treatment, and are willing to mainta abstinence or take highly effective medically approved contraceptive measures (such as intrauterine device and condom) from signing t informed consent form to 6 months after the last dose; male participant are willing to remain abstinent from sexual intercourse or to take highly effective medically approved contraceptive measures from signi the informed consent form until 6 months after the last dose, and d not donate sperm during this perio
