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Trial Registration NCT02973789

Ethics Approval The study was approved by participating centers’ Institution’s Ethics Boards, NCT02973789

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REFERENCE

1. N/A

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Tumor treating fields (TTFields, 150 kHz) concurrent with standard of care treatment for stage 4 non-small cell lung cancer (NSCLC) in phase 3 LUNAR study

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Background Tumor Treating Fields (TTFields) are a non-invasive, anti-mitotic treatment that disrupts the formation of the mitotic spindle and dislocation of intracellular constituents. TTFields plus temozolomide significantly extended survival in newly diagnosed glioblastoma. Efficacy of TTFields in NSCLC has been shown in preclinical models as well as safety in combination with pemetrexed in a pilot study. In the Phase 3 LUNAR study [NCT02973789], we investigated if the addition of TTFields to immune checkpoint inhibitors or docetaxel increases overall survival (OS).

Methods Patients (N=534), with squamous or non-squamous NSCLC, are stratified by their selected standard therapy (immune checkpoint inhibitors or docetaxel), histology and geographical region. Key inclusion criteria are disease progression, ECOG 0–2, no electronic medical devices in the upper torso, and absence of brain metastasis. TTFields (150 kHz) are applied to the upper torso for at >18 hours/day until progression in the thorax and/or liver. The primary endpoint is superiority in OS between patients treated with TTFields in combination with the standard of care treatments versus standard of care treatments alone. Key secondary endpoints compare the OS in patients treated with TTFields and docetaxel versus docetaxel alone, and patients treated with TTFields and immune checkpoint inhibitors vs those treated with immune checkpoint inhibitors alone. An exploratory analysis will test non-inferiority of TTFields with docetaxel compared to checkpoint inhibitors alone. Secondary endpoints include progression-free survival, radiological response rate, quality of life based on the EORTC QLQ C30 questionnaire. The sample size is powered to detect a HR of 0.75 in TTFields-treated patients versus control group. In March 2020, an independent Data Monitoring Committee (DMC) performed a review of the LUNAR trial data collected to that point. The DMC concluded that no unexpected safety issues could be found in patients treated with the combination of immune checkpoint inhibitors and TTFields, and recommended to continue the LUNAR study as planned.

Results N/A

Conclusions N/A

A randomized double-blind placebo-controlled phase III study evaluating perioperative toripalimab combined with platinum-based doublet chemotherapy in resectable stage III NSCLC

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Background Surgery remains the mainstay of treatment for resectable stage III non-small cell lung cancer (NSCLC). The preliminary results from some pilot trials have shown that neoadjuvant immunotherapy in NSCLC is safe and tolerable.1 Hypothesizing that neoadjuvant toripalimab (a humanized anti-PD-1 antibody) plus chemotherapy can improve the outcome in resectable NSCLC, we are conducting a randomized, double-blind, placebo-controlled, phase III study to evaluate the efficacy and safety of toripalimab plus platinum-based doublet chemotherapy as neoadjuvant/adjuvant therapy for patients with resectable stage III NSCLC.

Methods This ongoing study enrolls patients aged 18–70 years with treatment-naïve, histopathologically confirmed resectable stage III NSCLC without EGFR mutation or ALK translocation, ECOG PS 0–1, and adequate organ function. Eligible subjects are randomized (1:1) into experimental or control group, to receive perioperative toripalimab 240 mg or placebo combined with chemotherapy for 4 cycle in total (Docetaxel 60–75 mg/m² or Paclitaxel 175 mg/m² with platinum [squamous histology] or Pemetrexed 500 mg/m² with platinum [non-squamous histology]) every 3 weeks for three cycles followed by surgery, and one more cycle after surgery, then monotherapy of toripalimab 240 mg or placebo every 3 weeks up to 13 cycles is delivered. Adjuvant radiotherapy is allowed. Randomization is stratified by tumor stage (IIIA vs IIIB), pathological type (squamous vs non-squamous), PD-L1 expression (PD-L1 >1% vs <1% or not evaluable) and planned surgical procedure (pneumonectomy vs lobectomy). Radiographic response is assessed within 4–6 weeks after last dose of neoadjuvant therapy, at 30 days after surgery and every 12 weeks thereafter. Primary endpoints are major pathologic response (pCR) rate evaluated by blind independent central pathology review (BIPR-MPR) and event-free survival evaluated by investigator (INV-EFS). Secondary endpoints include pathologic complete response (pCR) rate evaluated by BIPR and investigators (BIPR-pCR and INV-pCR), disease-free survival (DFS), 2–3 years OS rate, OS, safety, and feasibility of surgery.
Exploratory endpoints are potential correlations between biomarkers and efficacy. A stratified Cochran Mantel Haenszel method will be used to assess binary endpoints. A Kaplan-Meier method, a stratified log-rank test and a stratified Cox proportional hazards model will be used to assess survival endpoints. Planned enrollment is 406 patients. The study is actively enrolling at 52 Chinese sites.

Results

Conclusions

Acknowledgements

Trial Registration

The Clinical trials. gov no NCT04158440

Ethics Approval

This study was approved by the Ethics Board of all the involved sites; Approval number of Shanghai Chest Hospital: LS1936

Consent

N/A

REFERENCES


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A PHASE 1/1B DOSE-ESCALATION STUDY OF INTRAVENOUSLY ADMINISTERED SB 11285 ALONE AND IN COMBINATION WITH ATEZOZILUMAB IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background Activation of the Stimulator of Interferon Genes (STING) pathway within immune and tumor cells of the tumor microenvironment (TME) results in durable anti-tumor effects via induction of innate and adaptive immunity. SB 11285 is a next-generation immunotherapeutic cyclic dinucleotide that activates the STING pathway leading to stimulation of tumor-resident APCs, NK cells and priming of tumor antigen specific CD8+ T cells. In preclinical studies using multiple tumor-derived cell lines, SB 11285 induced cytokines, such as IFN-α and -β, TNF-α and others consistent with engagement of TBK1 downstream of STING activation. Exposure of SB 11285 directly to tumor also induces cell death by STING-mediated apoptosis. SB 11285 reduced tumor volumes in multiple rodent tumor models when administered intravenously, intraperitoneally or intratumorally, as monotherapy and with amplified effect in combination with CTLA-4 or PD-1 antibodies. The novel properties of SB 11285 facilitate systemic administration which may facilitate trafficking of newly activated CD8+ T cells from the periphery into the TME.

Methods This open-label, multicenter phase 1/1b clinical trial (NCT04096638) will enroll approximately 110 patients in the dose escalation (Part 1) and expansion cohorts (Part 2). Part 1 will include parallel dose escalations evaluating ascending doses of intravenously administered SB 11285 via 3+3 design with respect to dose-limiting toxicities, maximum tolerated dose, recommended phase 2 dose (RP2D) and the pharmacokinetic/pharmacodynamic profile. Part 2 Expansion Cohorts of the study will explore initial efficacy via overall response rate in pre-specified tumor types (such as Melanoma, Head and Neck Squamous Cell Carcinoma) at the RP2D in combination with atezolizumab. SB 11285 will be administered as monotherapy weekly on Days 1, 8, 15, and 22 of repeated 28-day cycles in escalating doses and in combination with atezolizumab administered Q4W. Biological effects of SB 11285 will be evaluated via changes in immune cell types, serum cytokines, and gene expression patterns indicative of activation of the peripheral and TME immune compartments.

Results

Conclusions

N/A

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368 REVEAL: PHASE 1 DOSE-ESCALATION STUDY OF NKTR-262, A NOVEL TLR7/8 AGONIST, PLUS BEMPEGALDESLEUKIN: LOCAL INNATE IMMUNE ACTIVATION AND SYSTEMIC ADAPTIVE IMMUNE EXPANSION FOR TREATING SOLID TUMORS

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Background NKTR-262 is a small-molecule agonist of toll-like receptors (TLR) 7/8. Given by intratumoral (IT) injection, NKTR-262 is retained within the tumor microenvironment (TME) and promotes an immunostimulatory milieu and tumor antigen release. Bempegaldesleukin (BEMPEG) is a CD122-preferential IL-2 pathway agonist, which increases proliferation and tumor infiltration of CD8+ T cells and natural killer (NK) cells. Preclinically, NKTR-262 plus BEMPEG combined innate immune signaling and enhanced antigen presentation, with sustained T-cell activation, resulting in tumor growth inhibition of treated and abscopal lesions.

Methods This phase 1 dose-escalation study enrolled patients with relapsed/refractory, advanced/metastatic solid tumors (REVEAL; NCT03435640). Patients received escalating doses of NKTR-262 (0.03 mg to 3.84 mg IT) followed 3 weeks later by BEMPEG (0.006 mg/kg IV) q3wk utilizing a 3+3 design. The primary endpoint was safety and tolerability, including definition of the recommended phase 2 dose (RP2D). Other endpoints included antitumor activity, pharmacodynamics, and pharmacokinetics.

Results As of June 15, 2020, 36 patients were enrolled. One dose-limiting toxicity, transient transaminase elevation, was observed at the highest NKTR-262 dose (3.84 mg). The most frequent treatment-related adverse events were flu-like symptoms, fatigue, nausea, and pruritus, consistent with the known profile of BEMPEG. Early evidence of clinical activity was observed in patients with metastatic melanoma, with a disease control rate (partial response [PR] + stable disease) of 41.2% (7/17 patients), including two patients with PRs after progression on two prior immunotherapy regimens. Preliminary analyses showed dose-dependent induction of CXCL10 and type 1 interferon genes, consistent with TLR7/8 engagement. CD11c+ target cells were significantly more abundant in baseline melanoma biopsies than other tumor types (p<0.001). Induction