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A PHASE I/II TRIAL OF INTRACEREBROVENTRICULAR 177LU DTPA OMBURTAMAB RADIOIMMUNOTHERAPY FOR LEPTOMENINGEAL METASTASIS FROM SOLID TUMORS

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Background Leptomeningeal metastasis (LM) from solid tumors may be diagnosed in approximately 10% of patients with metastatic cancer and can occur with virtually all malignant tumors. Median overall survival (OS) is poor and limited to a few months with LM-directed treatment, including available targeted therapy, immunotherapy and radiation therapy. Omburtamab specifically binds to B7-H3 (CD276), a transmembrane glycoprotein of the immunoglobulin superfamily. The limited expression of B7-H3 on normal cells, including normal brain, combined with the broad expression in various types of solid tumors, makes B7-H3 a target for radioimmunotherapy of LM from solid tumors. In this first-in-human trial the safety and efficacy of intracerebroventricular administration of radiolabeled omburtamab, ¹⁷⁷Lu-DTPA-omburtamab, will be evaluated in patients with LM from ductal or lobular breast cancer, non-small cell lung cancer, or melanoma.

Methods This is an open-label phase I/II study. Part 1 is a dose-escalation phase to be conducted at ~4 sites (US/Europe) with a primary objective of identifying the maximum tolerated dose and/or recommended phase II dose for Part 2 (RP2D). It will follow a 3+3 design with pts receiving up to five 5-week cycles of ¹⁷⁷Lu-DTPA-omburtamab. Part 2 is a cohort-expansion phase at ~9 sites (US/Europe) in which a maximum of 48 patients in 3 cohorts (ductal or lobular breast cancer [cohort A], non-small cell lung cancer [cohort B], and melanoma [cohort C]) with up to 16 patients in each will receive up to five 5 week cycles of treatment with intracerebroventricular ¹⁷⁷Lu DTPA omburtamab at the RP2D determined in Part 1. The primary objective of Part 2 is to establish the safety of repeat doses of ¹⁷⁷Lu-omburtamab. Additional objectives of Parts 1/2 include the evaluation of absorbed radiation doses, PK profile, investigator-assessed response, duration of response, progression-free survival, and OS. Key inclusion criteria include diagnosis of either ductal or lobular breast cancer, non-small cell lung cancer, or malignant melanoma and diagnosis of recurrent or refractory LM; prior standard of care treatment of leptomeningeal disease; acceptable hematological, liver and kidney status; and a life expectancy of >2 months. The study has been approved by each institution's ethics board, and patients provided informed consent before taking part.

Trial Registration NCT04315246

Ethics Approval The study has been approved by each institution's ethics board, and patients provided informed consent before taking part.

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