

A PHASE 1, OPEN-LABEL, DOSE FINDING STUDY OF NI-1801, A BISPECIFIC MESOTHELIN X CD47 ENGAGING ANTIBODY, IN PATIENTS WITH MESOTHELIN EXPRESSING SOLID CANCERS

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Background Mesothelin (MSLN) is highly expressed in many solid tumors while expression in normal tissue is limited, thus representing an attractive target for immunotherapeutic approaches. NI-1801 is a fully human IgG1 bispecific antibody based on the kl-body format.^{1,2} NI-1801 targets MSLN with a high-affinity arm coupled to a low affinity-optimized CD47-blocking arm. This unbalanced affinity enables the selective CD47-blockade on MSLN-expressing cells. Additionally, NI-1801 contains an unmodified IgG1 Fc and can therefore mediate effector functions. *In vitro*, NI-1801 induces antibody-dependent cellular phagocytosis (ADCP) and antibody-dependent cell-mediated cytotoxicity of MSLN-positive cancer cells. ADCP is negligible or unaffected by a CD47-sink effect mimicked by CD47-expressing red blood cells. NI-1801 does not induce *in vitro* hemagglutination or platelet aggregation. *In vivo*, NI-1801 inhibits tumor growth in xenograft models. NI-1801 was well tolerated and demonstrated favorable PK in multiple non-human primate studies.

Methods Study LCB-1801-001 (NCT05403554) is a first-in-human clinical trial of NI-1801 in patients with MSLN-expressing solid malignancies. Part A (dose escalation) evaluates the safety and tolerability of NI-1801, to determine the maximum tolerated dose (MTD) and the non-tolerated toxic dose. The decision to include additional patients as well as dose escalation decisions are made at the discretion of the Safety Review Committee (SRC). Inpatient dose escalation is permitted by SRC approval. Part B (cohort expansion) will further evaluate the safety and efficacy in up to 20 additional subjects to determine the recommended Phase 2 dose. Expansion may occur at the MTD established in Part A, or at an alternative tolerable dosing schedule, based on review of safety and PK/PD data by the SRC. Treatments are administered intravenously in 28-day cycles for up to 6 months until disease progression, unacceptable toxicity, or investigator/patient decision to withdraw. Treatment can extend for patients without disease progression. The starting dose is 15 mg (fixed dose). Subsequent doses are given QW in Cycles 1/2 and Q2W in Cycles 3-6. LCB-1801-001 study enrolls patients since April 2022 and is ongoing in France and Italy. Adverse events are assessed according to CTCAE v5, tumor response is determined according to RECIST 1.1. Key inclusion criteria include (1) histologically or cytologically confirmed diagnosis of epithelial ovarian cancer (high-grade serous or endometrioid), triple-negative breast cancer, or non-squamous non-small cell lung cancer, (2) advanced, metastatic, or recurrent disease, and (3) MSLN expression with staining intensity of $\geq 2+$ as per immunohistochemistry in $\geq 60\%$ of tumor cells.

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Ethics Approval Ethics approval was obtained from corresponding ethics committees (Committee for Protection of Persons for Sud Méditerranée III, MEDAECPP-2021-09-0021 _ 2021-003808-40; Comitato Etico Degli IRCCS Istituto Europeo Di Oncologia E Centro Cardiologico Monzino, IEO 1632 – RE3604/Em. 001). Participants give informed consent before taking part.

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