TPS3177 Poster Session

IMMUNONET: A multicenter, open-label, proof-of-concept phase II trial evaluating NP137 as add-on therapy in advanced/metastatic solid tumors treated with standard immunotherapies.

Jérôme Fayette, Eve-Marie Neidhardt, Victoria Ferrari, Mona Amini Adle, Jean-Pierre Delord, David Pérol, Gwenaelle Garin, Camille Schiffler, Stephane Depil, Nerea Muñoz Unceta, Elise Georges, Esma Saada; Centre Léon Bérard, Lyon, France; Centre Leon Berard (CLCC), Lyon, France; Centre Antoine Lacassagne, Nice, France; IUCT-Oncopole, Toulouse, France; Hospital Universitario Marques de Valdecilla, Santander, Cantabria, Spain; Netris Pharma, Lyon, France

Background: PD-1/PD-L1 blockade has transformed oncology by offering durable responses in various cancers. However, many patients develop resistance, highlighting the need for novel therapeutic strategies. Epithelial-to-Mesenchymal Transition (EMT) plays a pivotal role in immune checkpoint inhibitor efficacy, with epithelial tumors exhibiting greater immunoreactivity than mesenchymal ones. NP137, a first-in-class anti-Netrin-1 monoclonal antibody, has shown in phase I study the ability to inhibit EMT, potentially overcoming resistance (Cassier et al., *Nature*, 2023). This phase I data demonstrated NP137's ability to shift tumors toward an epithelial phenotype, supporting its combination with immune checkpoint inhibitor to sensitize tumors and alleviate resistance. The goal of IMMUNONET study (NCT05605496) is to evaluate NP137's ability to re-sensitize advanced solid tumors to anti-PD-1/PD-L1 therapy.
Methods: This proof-of-concept study assess NP137 (14 mg/kg, IV, Q3W) as add-on therapy to standard PD-1/PD-L1 inhibitors across three independent cohorts of patients with advanced/metastatic solid tumors of any histological types: Cohort 1 (Stable Disease [SD]): Radiological SD after ≥12 weeks of anti-PD-1/PD-L1 therapy. Cohort 2 (Primary Refractory): Radiological progressive disease (PD) and no response under anti-PD-1/PD-L1 therapy. Cohort 3 (Secondary Refractory): Radiological PD following initial response under anti-PD-1/PD-L1 therapy. Treatment continues until progression, unacceptable toxicity, or consent withdrawal. The primary endpoint is clinical activity: objective response rate (ORR)-12W for cohort 1 and progression-free rate (PFR)-12W for cohorts 2 and 3. Secondary endpoints include ORR-12W (cohorts 2 and 3), Time to Objective Response (ToR), Duration of Response (DoR) and safety for all cohorts. Evolution of EMT, Netrin-1, and receptor expression will be analysed and correlated with clinical outcomes. An adaptive 2-stage design is being used for this study (Lin and Shih, Biometrics 2004). The target levels of clinical activity are set at 20% (relevant) and 25% (high). In stage 1, 18 patients will be enrolled at 1-sided alpha of 5%. Depending on the observed success rate, additional 11 patients (if 1 or 2 successes) or 5 patients (if >2 successes) could be recruited into stage 2. Null hypotheses will be rejected if ≥4 successes are observed in 29 [test $p_0 = 0.05$ vs. 0.20, 80% power] or 23 patients [test $p_0 = 0.05$ vs. 0.25, 90% power], respectively. Current Status: Cohort 1 has been closed due to non-feasibility. Prespecified goals for the first stage were met, stage 2 enrolment is underway. Cohort 2 has enrolled 21 patients, and cohort 3 has enrolled 19 of 23 planned evaluable patients. Clinical trial information: NCT05605496. Research Sponsor: European Innovation Council.