

714

**ATOR-1017, A 4-1BB ANTIBODY, DEMONSTRATES PROMISING SAFETY AND PROOF OF MECHANISM IN A FIRST-IN-HUMAN STUDY IN PATIENTS WITH ADVANCED SOLID MALIGNANCIES**

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**Background** ATOR-1017 is a human Fcγ-receptor cross-linking dependent IgG4 4-1BB (CD137) agonist. ATOR-1017 activates T cells and natural killer cells in the tumor environment, leading to immune-mediated tumor cell killing.

**Methods** In this first-in-human, dose escalation, multicenter, phase 1 study, adult patients with solid tumors refractory to standard therapy were enrolled in single patient cohorts for doses up to 40 mg, and thereafter in cohorts of 3-6 patients. Intra-patient dose escalation is allowed. ATOR-1017 is administered intravenously as monotherapy (as flat dose) every three weeks until disease progression or unacceptable toxicity. The primary objectives are assessment of safety (maximum tolerated dose (MTD), adverse events (AEs), dose-limiting toxicities (DLT)), and determination of recommended phase 2 dose. Secondary and exploratory objectives include pharmacokinetics (PK), immunogenicity, efficacy (by iRECIST), and Pharmacodynamic (PD) biomarkers.

**Results** At cut off date 14 June 2022, 25 patients (20 females/5 males), with median age 57 years (34-76), median of 3 (1-9) prior lines of chemotherapy and/or median 1 (1-3) lines of immunotherapy, 21 (84%) with disease stage IV at entry had been treated. Ten dose levels were evaluated; 0.38mg, 1.5mg, 5mg, 15mg, 40mg, 100mg, 200mg, 360mg, 600mg, and 900mg. Treatment-related AEs (TRAEs) were reported in 13 patients (52%); most common ( $\geq 10\%$ ) were fatigue (16%) and neutropenia (12%). Five patients experienced a grade 3-4 TRAE; neutropenia (n = 2), febrile neutropenia (n = 1), non-cardiac chest pain (n = 1), increased liver enzymes (n = 1) and leukopenia/thrombocytopenia (n = 1). No patients discontinued due to TRAEs, no DLTs were observed, and MTD has not been reached. Three patients remained on treatment and 22 had discontinued treatment [(confirmed disease progression (n = 12), clinical deterioration (n = 6), withdrawal of consent (n = 1), death due to disease progression (n = 2), investigator's decision (n=1)]. The median time on treatment was 12.1 weeks (range 5.3-67.3). A dose-proportional pharmacokinetics was observed. PD biomarkers demonstrated activation of peripheral CD8 T cells and a dose-dependent increase in soluble 4-1BB confirming biological activity and proof-of-mechanism. Stable disease was observed in 13 patients (52%), which lasted longer than 6 months for 6 (24%) patients (of which 2 had ovarian cancer).

**Conclusions** ATOR-1017 demonstrated excellent safety at doses up to 900 mg, together with a favorable PK profile, confirmation of biologic activity and signs of clinical benefit. These data warrant further development of ATOR-1017, a 4-1BB agonistic antibody, in combination with other therapeutic approaches in solid tumors.

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**Trial Registration** ClinicalTrials.gov Identifier: NCT04144842

**Ethics Approval** Name of the ethics committee(s): Swedish Ethical Review Authority (Etikprövningsmyndigheten)

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All patients provided written informed consent prior to study participation.

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