SAFETY AND PHARMACODYNAMIC ACTIVITY OF ATOR-1015, A CTLA-4 X OX40 BISPECIFIC ANTIBODY, IN A PHASE 1 DOSE ESCALATION STUDY OF PATIENTS WITH ADVANCED SOLID MALIGNANCIES

Background ATOR-1015 is a human CTLA-4 x OX40 bispecific antibody developed as a first in class tumor-localizing CTLA-4 antibody for improved efficacy and reduced toxicity.

Methods The study (NCT03782467) is a first-in-human dose escalation study followed by an expansion part. In the dose escalation patients with refractory solid malignancies are enrolled and the expansion part will enroll patients with cutaneous or mucosal malignant melanoma. Patients receive ATOR-1015 intravenously Q2W as a single agent until confirmed progressive disease, unacceptable toxicity or withdrawal of consent. Intra-patient dose escalation is allowed. The primary objective is to assess the safety and tolerability of ATOR-1015. Secondary objectives include pharmacokinetics, immunogenicity, pharmacodynamics, and clinical efficacy as assessed by iRECIST. Pharmacodynamic analyses include serum cytokines, immunophenotyping of peripheral blood mononuclear cells. Tumor biopsies before and after ATOR-1015 will be analyzed.

Results As of June 26, 2020, 23 patients have been exposed to ATOR-1015. The median age of the patients is 54 years (range 40–72). Patients have received a median of 5 prior lines of therapy (range 1–16). Most common cancer type is colorectal cancer. Dose levels from 0.043 mg to 600 mg have been evaluated and declared safe. Dose escalation is ongoing, and currently two patients have been enrolled at 750 mg dose level. The median time on study was 8.4 weeks (range 0.1–34.3). Five patients are on study and 18 patients have discontinued. Reasons for discontinuation included clinical deterioration (n=10), disease progression (n=5), death due to disease progression (n=2), and investigator’s decision (n=1). Twelve of the 23 patients experienced a drug-related adverse event (AE). Two patients experienced a grade 3 drug-related AE, for all other patients AEs were grade 1 or 2. Infusion-related reactions (IRR) were reported in nine patients. Predominant symptoms of the IRR were chills, rash and pain. Potentially immune-related AEs grade 1 were reported in three patients: one patient had rash, one vitiligo, and one exanthema and eczema. No dose-limiting toxicities have occurred. Best response is stable disease. Pharmacokinetic data show dose proportional kinetics up to 600 mg. Preliminary biomarker analysis shows pharmacodynamic activity of ATOR-1015.

Conclusions ATOR-1015 has been safe and well-tolerated up to 600 mg. Currently 750 mg is under evaluation. Best response is stable disease. Following the dose escalation phase, an expansion cohort for patients with advanced malignant melanoma will be initiated.

Ethics Approval The study is approved by the institutional review board of each participating site.

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PHARMACODYNAMIC ASSESSMENT OF A NOVEL FAP-TARGETED 4-1BB AGONIST, ADMINISTERED AS SINGLE AGENT AND IN COMBINATION WITH ATEZOLIZUMAB TO PATIENTS WITH ADVANCED SOLID TUMORS

Background RO7122290 (RO) is a bispecific antibody-like fusion protein that simultaneously targets FAP, abundantly expressed by cancer-associated fibroblasts in most solid tumors, and 4-1BB, transiently expressed on activated T cells. Pre-clinical experiments revealed strong intra-tumoral CD8+ T cells infiltration in FAP-positive tumors, cytokines induction and significant anti-tumor activity mediated by RO (signal 2 of T cell activation), upon TCR/CD3 engagement (signal 1) or in combination with atezolizumab (ATZ). In this first-in-human study, the pharmacodynamic (PD) effects of RO were assessed, both as single agent (SA) (Part A) and in combination with ATZ (Part B).

Methods Pts with advanced and/or metastatic solid tumors were eligible for this ongoing Phase 1/ib trial (EUDRACT 2017-003961-83). RO was administered intravenously, weekly (QW) at escalating dose levels (DLs). In Part A, 62 pts were treated at 13 DLs of RO, dose range 5–2000 mg. In Part B, 39 pts were treated at 8 DLs of RO, dose range 45–2000 mg, with ATZ 1200 mg Q3W. Secondary biomarker objective was characterization of PD effects in tumor tissue and blood. The endpoints were change from baseline in intra-tumoral density (cell/mm²) and proliferation (Ki67) of CD8+ T cells measured by immunohistochemistry (IHC), and change in

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