Initial findings from a first-in-human, multicenter, open-label study of ATOR-1017, a 4-1BB antibody, in patients with advanced solid malignancies

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INTRODUCTION

- 4-1BB is a co-stimulatory receptor highly expressed on tumor reactive CD8+ T cells and NK cells infiltrating the tumor.
- 4-1BB co-stimulation activates cytotoxic T cell and NK cell-mediated anti-tumor responses as well as induction of a long-lived memory T cell responses that may lead to long-term protection from tumor recurrence.

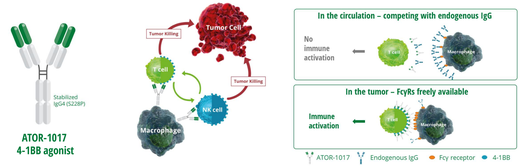

Figure 1. ATOR-1017 4-1BB antibody agonist and mechanism of action

Background:

- ATOR-1017 is a conditional 4-1BB agonist (IgG4) relying on FcγR-mediated crosslinking for its activity.
- Co-localized expression of 4-1BB and FcγRs in tumors results in tumor-directed immune activation (Figure 1), hence less risk of systemic toxicity.
- ATOR-1017 binds to the same domain as the endogenous 4-1BB ligand thereby blocking its binding and potentially reducing the risk of exaggerated biology.
- No safety concerns were demonstrated in non-human primate toxicity studies [1] and preclinical studies demonstrating potent anti-tumor effects support this first-in-human clinical evaluation [2-3].

OBJECTIVES

- The primary objective of this first-in-human trial includes characterization of the safety and tolerability of ATOR-1017, determination of the Maximum Tolerated Dose (MTD) and/or the recommended phase 2 dose.
- Secondary objectives include the evaluation of a pharmacokinetic (PK) profile, immunogenicity and anti-tumor activity of ATOR-1017.
- Exploratory objectives include the assessment of pharmacodynamic biomarkers.

STUDY DESIGN

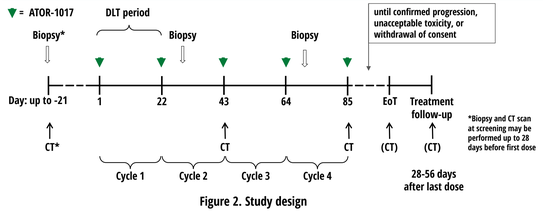

Figure 2. Study design

- This is a first-in-human, multicenter, open-label dose-escalating trial of ATOR-1017 conducted in patients with advanced solid malignancies (NCT04144842).
- Patients received IV infusions every three weeks, flat doses starting at 0.38 mg.
- Dose escalation started with an accelerated phase consisting of single-patient cohorts up to 40 mg, followed by a modified 3+3 design (Figure 3), with at least 6 patients at MTD.
- Intrapatient dose escalation is allowed after the first 2 treatment cycles according to the judgment of the Investigator up to a dose level declared safe by the data review committee.
- The study (patient enrolment and treatment) is ongoing at 900 mg dose level.
- Efficacy (using iRECIST) is assessed by computed tomography (CT) or magnetic resonance imaging at weeks 6 and 12 (-7 days), and thereafter every 12th week until disease progression.

Key inclusion criteria:

- ≥ 18 years of age
- Histologically or cytologically confirmed, metastatic or unresectable advanced and/or refractory solid malignancy. Have received established therapies with no further therapeutic options.
- ECOG performance status of 0 or 1
- Measurable disease according to RECIST v1.1 criteria

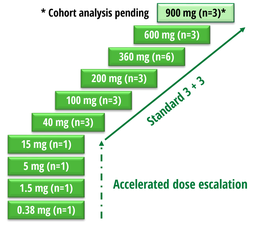

Figure 3. Trial design (dose escalation)

RESULTS

Patient characteristics and disposition

- As of data cut-off, January 18, 2022, a total of 22 patients have been enrolled (Table 1).
- Patients were heavily pretreated; 86.4% of patients had received prior treatment with chemotherapy and 36.4% had received prior immunotherapy.

Table 1. Baseline demographics and clinical characteristics

	Overall
Number of patients	22
Age (years), median (range)	55 (34-76)
Age Group, n (%)	
18–64	17 (77.3)
65+	5 (22.7)
Previous therapies, n (%)	
Chemotherapy	19 (86.4)
Immunotherapy	8 (36.4)
Hormonal therapy	1 (4.5)
Other	10 (45.5)
Radiation	12 (54.5)
Surgery	20 (90.9)
Gender, n (%)	
Female	18 (81.8)
Male	4 (18.2)
ECOG Performance status, n (%)	
0	12 (54.5)
1	10 (45.5)

Safety

- Treatment-Emergent Adverse Events (TEAEs) occurred in 22 (100%) patients, with Grade 3 or 4 being experienced by 12 (54.5%) patients. No patient experienced a Grade 5 TEAE (Table 2).
- Treatment-Related Adverse Events (TRAEs) occurred in 12 (54.5%) patients. The most common (≥10%) TRAEs were fatigue and neutropenia, experienced by 3 patients each (13.6%), and increased AST/ALT, non-cardiac chest pain and headache experienced by 2 patients each (9.1%). Grade 3 TRAEs (febrile neutropenia, leukopenia, thrombocytopenia, AST/ALT elevation and non-cardiac chest pain) were experienced by 4 (18.2%) patients and Grade 4 TRAEs (neutropenia) were experienced by 2 (9%) patients.
- No patient experienced infusion-related reactions, cytokine release syndrome, or immune-related adverse events.
- No dose-limiting toxicity (DLT) was observed.

Table 2. Overall summary of treatment-emergent adverse events

	ATOR-1017 dose level (mg)						
	0.38 - 15	40	100	200	360	600	Overall
Number of patients	4	3	3	3	6	3	22
Patients with any TEAEs n (%)	4 (100)	3 (100)	3 (100)	3 (100)	6 (100)	3 (100)	22 (100)
TEAEs of severity Grade 3 or 4 n (%)	1 (25)	2 (66.7)	0	2 (66.7)	5 (83.3)	2 (66.7)	12 (54.5)
Patients with any TRAEs n (%)	2 (50)	3 (100)	1 (33.3)	1 (33.3)	3 (50)	2 (66.7)	12 (54.5)
TRAEs of severity Grade 3 or 4 n (%)	0	1 (33.3)	0	1 (33.3)	2 (33.3)	1 (33.3)	5 (22.7)

Trial status and efficacy

- At data cut-off, 4 patients (18.2%) remain on treatment, 1 of whom (4.5%) have confirmed stable disease for a period of 4 months (Figure 4).
- Best response was stable disease observed in 10 patients (45.4%).
- One patient, 17-002, was treated with 5 increasing dose levels and experienced stable disease for nearly one year.
- Nine patients (40.9%) had confirmed disease progression and have discontinued treatment.

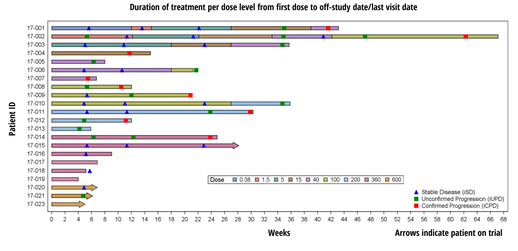

Figure 4. Swimmers plot for dose escalation trial of ATOR-1017

Pharmacokinetics

- Repeat dosing of ATOR-1017 demonstrates dose dependent and favorable PK profile (Figure 5).

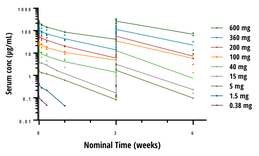

Figure 5. Repeat dose PK profile for ATOR-1017

Pharmacodynamics

- A 4-1BB-mediated proof of mechanism was demonstrated in the circulation by increased numbers of (A) proliferating (Ki67+) CD8+ T cells, (B) effector memory CD8+ T cells, (C) activated (ICOS+) CD8+ T cells, and (D) increased levels of soluble 4-1BB at doses above 40 mg (Figure 6).

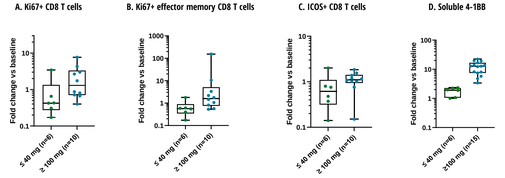

Figure 6. Modulation of peripheral (A-C) CD8+ T cell proliferation and activation and (D) soluble 4-1BB
Data is presented as maximum fold-change from baseline in cycle 1

CONCLUSIONS

- In this FiH study, ATOR-1017 has been dosed up to 600 mg and demonstrates an encouraging safety profile and indications of clinical benefit.
- No DLTs were observed and the MTD has not been reached.
- Most TRAEs were mild to moderate (severity Grade 1 or 2).
- ATOR-1017 exhibits a favorable PK profile.
- Activation of peripheral T cells and increased levels of soluble 4-1BB was observed across active dose levels of ATOR-1017, demonstrating biological activity and proof of mechanism.
- The study is ongoing at the 900 mg dose level.

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1) Dahlén, E., et al. (2019) ATOR-1017: A 4-1BB antibody designed for superior safety/efficacy profile in cancer immunotherapy, Cancer Immunology Research 7 (Suppl 2) A183-A183.
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