A first-in-human, multicenter, open-label, phase 1 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.

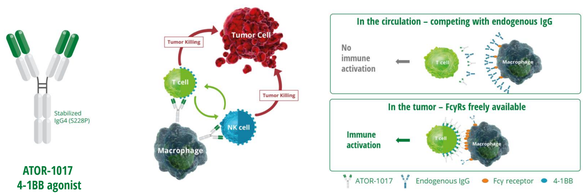

Figure 1. ATOR-1017 4-1BB antibody agonist and mechanism of action

ATOR-1017 is designed for superior efficacy and safety

- ATOR-1017 is a monoclonal antibody (IgG4) dependent on FcγR-mediated crosslinking for its activity.
- Co-localized expression of 4-1BB and FcγRs in tumors results in tumor-directed immune activation, hence less risk of systemic toxicity.
- ATOR-1017 blocks endogenous 4-1BB ligand by binding to the same domain thereby potentially reducing the risk of exaggerated pharmacology.
- No safety concerns were demonstrated in non-human primate toxicity studies.

OBJECTIVES

- The primary objective of this Ph1 trial includes characterization of the safety and tolerability of ATOR-1017 and determination of maximum tolerated dose (MTD).
- Secondary objectives include the establishment of a pharmacokinetic profile, evaluation of immunogenicity and anti-tumor activity of ATOR-1017.
- Exploratory objectives include the assessment of potential pharmacodynamic biomarkers.

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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 2), 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.
- First patient was dosed Dec 2019. Dose level at data cut-off (March 31st, 2021) was 200 mg and the study is still ongoing.
- Efficacy was assessed by computed tomography (CT) 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 SoC with no further therapeutic options.
- ECOG performance status of 0 or 1
- Measurable disease according to RECIST 1.1 criteria

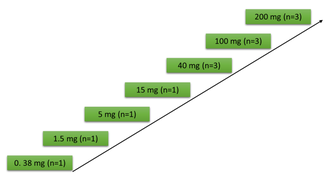

Figure 2. Trial design (dose escalation)

RESULTS

Patient characteristics and disposition

- As of data cut-off March 31st, 2021, a total of 13 patients have been enrolled and treatment is ongoing in 4 (30.8 %) patients (Table 1).
- The study is ongoing and MTD has not been reached.

Table 1. Baseline demographics and clinical characteristics

	Overall
Number of patients	13
Median (range) age, years	49 (39-63)
Age Group, n (%) 18 – 64 65 +	 10 (76.9) 3 (23.1)
Previous SoC therapies, median (range), n	2 (1-6)
ECOG Performance status, n (%) 1 0	 5 (38.5) 8 (61.5)

Efficacy

- As of data cut-off March 31st, 2021, 4 patients (30.8 %) remain on treatment, 3 of whom (23 %) have confirmed stable disease for a period of 3.5-12.5 months (Figure 3).
- One patient, 17-002, has received 5 increasing dose levels and has been on the study for 60 weeks.
- 5 patients (38.5 %) have confirmed disease progression and have discontinued treatment.

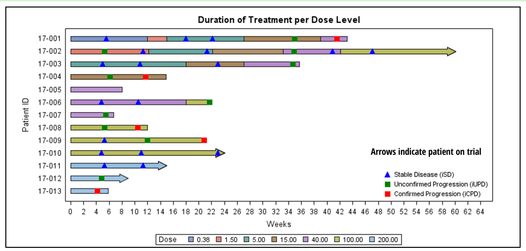

Figure 3. Swimmers plot for dose escalation trial of ATOR-1017

Pharmacokinetics

- Single dose IV infusion shows dose dependent linear clearance (Figure 4).
- Repeat dosing (Q3W) demonstrates stable elimination and no apparent accumulation (Figure 5).

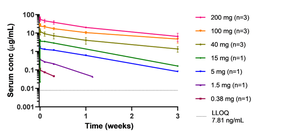

Figure 4. Single dose PK profile for ATOR-1017

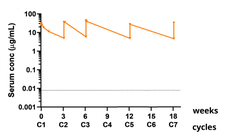

Figure 5. Repeat dose PK profile for ATOR-1017; representative graph from patient 17-010, 100 mg for the first 7 cycles

Pharmacodynamics

- Induction of target-mediated immune modulation by ATOR-1017 was observed in the periphery at doses above 40 mg.
- A 4-1BB-mediated proof of mechanism was demonstrated by increased numbers of activated proliferating (Ki67+) CD8+ T cells, effector memory CD8+ T cells and (ICOS+) CD8+ T cells (Figure 6).

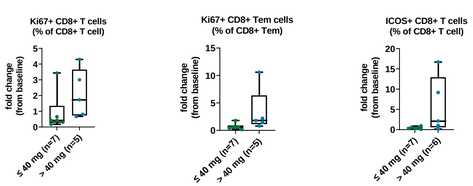

Figure 6. Modulation of peripheral CD8+ T cell proliferation and activation

Safety

- Treatment-emergent adverse events (TEAEs) occurred in 11 (84.6 %) patients. Most TEAEs were Grade 1-2, with Grade 3 being experienced by 3 (27.3 %) patients and Grade 4 by 1 (9.1 %) patient. No patient experienced a Grade 5 TEAE (Table 2).
- Treatment-related adverse events (TRAEs) occurred in 7 (53.8 %) patients. Grade 3 TRAEs were experienced by 1 (14.3 %) patient and Grade 4 TRAEs by 1 patient (14.3 %). No patient experienced a Grade 5 TRAE (Table 2).
- Adverse events of special interest (AESI) include infusion-related reactions, cytokine release syndrome, immune-related adverse events, liver enzyme and bilirubin elevation. Transient neutropenia and transaminase elevations were experienced by 2 (15.4 %) patients (Table 2).
- No dose-limiting toxicity (DLT) was observed at the time of data cut-off March 31st, 2021.

Table 2. Overall summary of treatment-emergent adverse events

	ATOR-1017 dose level (mg)				
	0.38 - 15	40	100	200	Overall
Number of patients	4	3	3	3	13
Patients with any TEAEs, n (%)	4 (100)	3 (100)	3 (100)	1 (33.3)	11 (84.6)
TEAEs of severity Grade 3 or 4, n (%)	1 (25)	2 (66.7)	0	1 (33.3)	4 (36.4)
Patients with any TRAEs, n (%)	2 (50)	3 (100)	1 (33.3)	1 (33.3)	7 (53.8)
TRAEs of severity Grade 3 or 4, n (%)	0	1 (33.3)	0	1 (33.3)	2 (28.6)
Patients with any AESI, n (%)	0	1 (33.3)	0	1 (33.3)	2 (15.4)

CONCLUSIONS

- ATOR-1017 has been dosed up to 200 mg and demonstrates an encouraging safety profile.
- No DLTs were observed.
- Most TRAEs were mild to moderate (one transient Grade 4 and no Grade 5 observed).
- ATOR-1017 exhibits a favorable PK profile with linear elimination and no accumulation at all doses tested.
- Activation of T cells in the circulation was observed across active dose levels of ATOR-1017 demonstrating biological activity and proof of mechanism.
- The study is still ongoing; no MTD reached.

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- DISCLOSURES: None