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

Ana Carneiro[1]*, Gustav J. Ullenhag [2], Karin Enell Smith[3], Lena Schultz[3], Tova Landström[3], Peter Ellmark[3], Malin Carlsson[3], Sumeet V. Ambarkhane[3], Jeffrey Yachnin[4]

1 Skåne University Hospital and Lund University, Lund, Sweden; 2 Uppsala University Hospital, Uppsala, Sweden; 3 Alligator Bioscience AB, Lund, Sweden; 4 Karolinska Institutet, Stockholm, Sweden *Corresponding author: ana.carneiro@med.lu.se

SITC 2022
Abstract 714

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 and induces a long-lived memory T cell response that may lead to long-term protection from tumor recurrence.

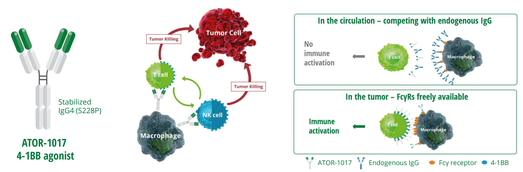


Figure 1. ATOR-1017, a 4-1BB agonistic antibody and its mechanism of action

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].

STUDY DESIGN

- Primary Objective: characterization of the safety and tolerability of ATOR-1017, determination of the Maximum Tolerated Dose (MTD) and/or the recommended phase 2 dose (RP2D).
- Secondary Objectives: Pharmacokinetics (PK), immunogenicity and clinical efficacy of ATOR-1017.
- Exploratory Objectives: Pharmacodynamic (PD) biomarkers of ATOR-1017.

- This is a first-in-human, multicenter, open-label dose-escalating trial of ATOR-1017 conducted in patients with advanced solid malignancies (NCT04144842).
- Patients receive IV infusions every three weeks, flat doses starting at 0.38 mg (see Figure 2).
- Intrapatient dose escalation was 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.
- Efficacy (using iRECIST) was assessed by computed tomography (CT) or magnetic resonance imaging at approximately weeks 6 and 12, 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 all established therapies.
- ECOG performance status of 0 or 1.
- Measurable disease according to RECIST v1.1 criteria.

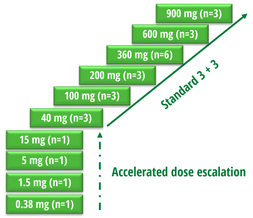


Figure 2. Dose escalation scheme

RESULTS

- Results are based on data cut-off, August 31, 2022.
- Enrolment was complete with a total of 25 patients (Table 1).
- Patients were heavily pretreated: 92.0% of patients had prior chemotherapy, 24% had prior immunotherapy.

Table 1. Summary of Baseline Characteristics

Baseline Characteristics	Overall (n=25)
Age (years), median (range)	57 (34-76)
Age Group, n (%)	
18–64	19 (76.0)
65+	6 (24.0)
Previous therapies, n (%)	
Chemotherapy	23 (92.0)
Immunotherapy	6 (24.0)
Hormonal therapy	2 (8.0)
Monoclonal Antibodies	10 (40.0)
Other Targeted Therapies	6 (24.0)
Radiation	12 (48.0)
Surgery	25 (100.0)
Gender, n (%)	
Female	20 (80.0)
Male	5 (20.0)
ECOG Performance status, n (%)	
0	13 (52.0)
1	12 (48.0)

Safety and tolerability:

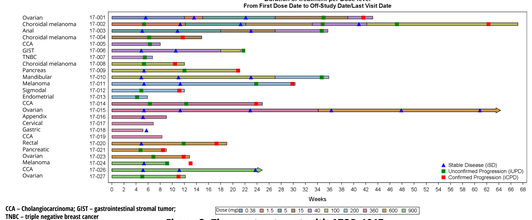
- Treatment-Related Adverse Events (TRAEs) were reported in 13 (52.0%) patients (CTCAE 5.0, Table 2). The most common TRAEs were fatigue and neutropenia (4 [16.0%] and 3 [12.0%] patients respectively), and increased AST/ALT, non-cardiac chest pain, rash and headache (2 patients each; 8.0%).
- Grade 3 TRAEs were febrile neutropenia, leukopenia, thrombocytopenia, AST/ALT elevation and non-cardiac chest pain (4 [16.0%] patients). Grade 4 TRAE was neutropenia (2 [8%] patients)
- One event of Grade 4 Neutropenia in one patient was the only treatment-related serious AE. There were no treatment-related deaths.
- No patient experienced infusion-related reactions, cytokine release syndrome, or immune-related AEs.
- No patient required treatment discontinuation due to AEs.
- No dose-limiting toxicity (DLT) was observed and the MTD was not reached.

Table 2. Summary of treatment-related adverse events

	ATOR-1017 dose level (mg)							
	0.38 - 15	40	100	200	360	600	900	Overall
Number of patients	4	3	3	3	6	3	3	25
Patients with any TRAEs n (%)	2 (50)	3 (100)	1 (33.3)	1 (33.3)	3 (50)	2 (66.7)	1 (33.3)	13 (52.0)
TRAEs of severity Grade 3 or 4 n (%)	0	1 (33.3)	0	1 (33.3)	2 (33.3)	1 (33.3)	0	5 (20.0)

Clinical efficacy:

- Best response was stable disease observed in 13 patients (52.0%), including two ongoing patients at data cut off (Figure 3). No complete or partial response was reported.
- Six patients had durable stable disease lasting >6 months. Their histological subtypes were ovarian carcinoma (high-grade n=1; low-grade n=1); choroidal melanoma (n=1); anal carcinoma (n=1); mandibular adenoid cystic carcinoma (n=1); cutaneous melanoma (n=1).
- One high-grade ovarian carcinoma patient was treated with 5 increasing dose levels, while maintaining disease control for nearly one year.



CCA – Cholangiocarcinoma; GIST – gastrointestinal stromal tumor; TNBC – triple negative breast cancer

Figure 3. Time on treatment with ATOR-1017

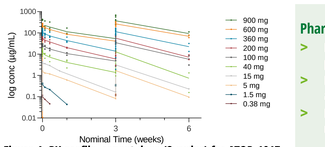


Figure 4. PK profile, repeat dose (2 cycles) for ATOR-1017

Pharmacokinetics:

- Dose dependent and favorable PK profile (Figure 4).
- Dose proportional increase in both Cmax and AUC up to 900 mg.
- No accumulation observed, steady state reached after the initial 2-3 doses.

Case study: Durable SD in a 71 Y female (low grade serous ovarian cancer Stage IIIc)

- Heavily pre-treated with multiple prior chemotherapy combinations; (Table 3); and progressive disease at ATOR-1017 study entry.
- ATOR-1017 treatment resulted in durable SD with ongoing treatment at 62 weeks (Figure 5) with stable CA-125 and stabilization of ascites. ATOR-1017 dose could be escalated from 360 to 600 mg after ~9 mo.
- The patient experienced no SAEs, no Grade ≥3 TRAEs
- PD biomarker modulations reflecting T cell activation (Figure 6).

Table 3. Prior therapies of patient 015

1995	2010	2012	2015	2016	2017-18	2019-20
Surgical resection Cyclophosphamide Carboplatin	Cisplatin	Carboplatin + paclitaxel	Carboplatin + paclitaxel	Carboplatin + caelyx	Bevacizumab + paclitaxel	Paclitaxel

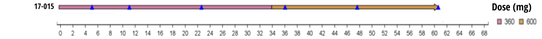


Figure 5. Swimmer's plot indicating stable disease ▲ and dose levels over time

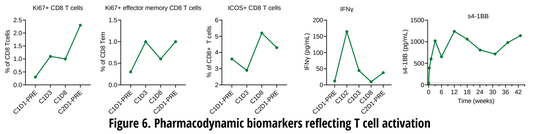


Figure 6. Pharmacodynamic biomarkers reflecting T cell activation

Pharmacodynamics:

- 4-1BB-mediated proof of mechanism was demonstrated in the circulation by increases in proliferating (Ki67+) CD8+ T cells and effector memory CD8+ T cells following treatment vs baseline at doses ≥100 mg (Figure 7 A-B).
- Total levels of soluble 4-1BB (free and bound to ATOR-1017) increased with higher doses of ATOR-1017 (Figure 7C displaying s41BB in cycle 1) and simulated dose response of s4-1BB vs ATOR-1017 (Figure 7D).

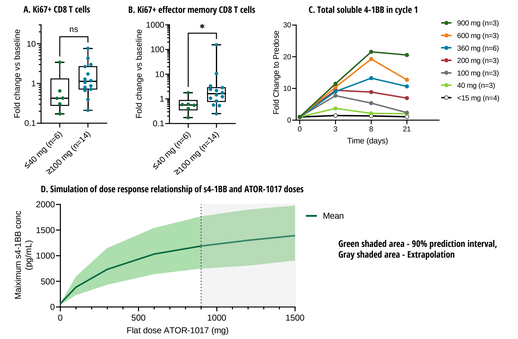


Figure 7. Modulation of peripheral PD markers; (A-B) CD8+ T cell proliferation and (C) total soluble 4-1BB. Data is presented as mean of maximum fold-change from baseline in cycle 1. (D) PK/PD modeling - Simulated dose response of s4-1BB vs ATOR-1017, dosed Q3W for 1 year, 1000 subjects/group.

CONCLUSIONS

- In this FiH study, ATOR-1017, a 4-1BB agonist has been dosed up to 900 mg.
- No DLTs were observed and the MTD has not been reached. Most TRAEs were of severity Grade 1 or 2.
- ATOR-1017 exhibits a favorable PK profile.
- Activation of peripheral T cells and dose-dependent increase in soluble 4-1BB demonstrate biological activity and proof of mechanism at doses 100 mg and above.
- Stable disease was the best response, which was durable (>6 months) in multiple tumor types (ovarian, choroidal & cutaneous melanoma, anal, mandibular adenoid cystic carcinoma) in heavily pretreated patients.
- The promising safety profile and the observed clinical benefit warrants further clinical development of ATOR-1017 as a combination therapy, possibly with other immunotherapy agents such as checkpoint inhibitors.

ACKNOWLEDGEMENTS: All patients and their families. The study investigators and members of the clinical study team. Alligator Bioscience AB, the study sponsor, and the clinical study team at Alligator.

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