# Abstract # 369: 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

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## Background

- ATOR-1015 is a first-in-class tumor-localizing CTLA-4 x OX40 bispecific antibody, developed for improved efficacy and tolerability
- CTLA-4, a checkpoint receptor expressed on regulatory T cells (Tregs) and OX40, a co-stimulatory receptor on T cells, are highly upregulated in the tumor environment
- The mode-of-action of ATOR-1015 is to induce activation of T cells and depletion of Tregs

*Ref: Månsson Kvarnhammar et al. Journal for Immunotherapy of Cancer (2019) 7:103*

## Methods

This is a first-in-human dose escalation study of ATOR-1015 dosed intravenously every 2 weeks until confirmed progression, unacceptable toxicity or withdrawal of consent. Patients with advanced and/or refractory solid malignancies after standard of care therapy are included. The study started with single patient cohorts followed by a modified 3+3 design. Intra-patient dose escalation is allowed.

### Primary objectives

- Assess safety and tolerability of ATOR-1015
- Determine the dose-limiting toxicities, the maximum tolerated dose, and/or the recommended phase 2 dose

### Secondary objectives

- Characterize the pharmacokinetic (PK) profile and immunogenicity of ATOR-1015
- Assess clinical efficacy assessed by response evaluation criteria in solid tumors (iRECIST)

### Exploratory objectives

- Assess the pharmacodynamic (PD) activity of ATOR-1015 in tumors and peripheral blood

## Results

- As of 13 October, 27 patients have been exposed to ATOR-1015. Median age is 54 years (range 40-72)
- Median prior lines of therapy are 5 (1-16)
- Median time on study is 8 weeks (range 3-34) (**Figure 1**)
- Adverse events have been reported in 25 of the 27 patients and 15 of the patients have had at least one drug-related adverse events (**Table 1**)
- Preliminary PK data show dose proportional kinetics (**Figure 2**)
- Anti-drug antibodies (ADA) have been detected, further analyses are ongoing
- Best response by iRECIST has been stable disease (for 34 weeks)
- Preliminary PD data show that ATOR-1015 induces up-regulation of Ki67, ICOS and Eomes on CD4$^+$ and CD8$^+$ T cells in peripheral blood (**Figure 3**)
- ATOR-1015 does not affect serum cytokines or the number of CD4$^+$ and CD8$^+$ T cells, Tregs, NK cells or B cells (data not shown)
- Tumor biopsies before and after ATOR-1015 treatment are currently being evaluated

**Figure 1.** Duration of treatment per dose level (from first dose to off study)

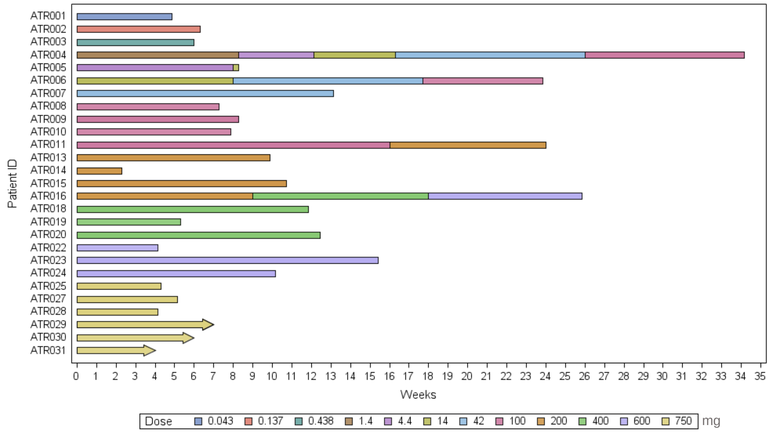


**Table 1.** Summary of drug-related adverse events

| Preferred term | Number of patients (%) | Preferred term | Number of patients (%) |
|---|---|---|---|
| Infusion related reactions | 12 (44.4) | Back pain | 1 (3.7) |
| Pyrexia | 3 (11.1) | Cortisol increased | 1 (3.7) |
| Rash | 3 (11.1) | Thyroxine free increased | 1 (3.7) |
| Fatigue | 2 (7.4) | Flushing | 1 (3.7) |
| Myalgia | 2 (7.4) | Hypotension | 1 (3.7) |
| Dizziness | 2 (7.4) | Headache | 1 (3.7) |
| Vitiligo | 1 (3.7) | Cough | 1 (3.7) |
| Chest discomfort | 1 (3.7) | Throat irritation | 1 (3.7) |
| Chills | 1 (3.7) | Abdominal pain | 1 (3.7) |
| Non-cardiac chest pain | 1 (3.7) | Dry eye | 1 (3.7) |
| Arthralgia | 1 (3.7) | Hypokalaemia | 1 (3.7) |

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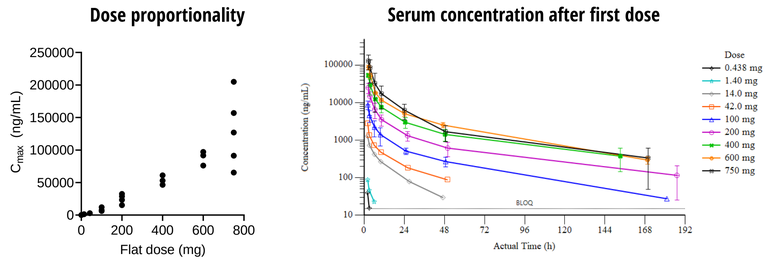
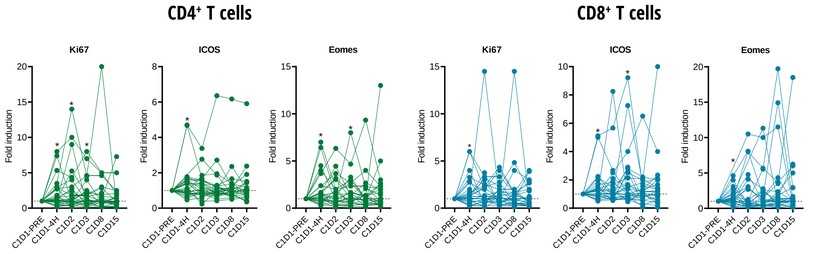
**Figure 2.** Preliminary PK profile of ATOR-1015 from phase 1 dose escalation




- Generally, dose proportional kinetics seen at doses from 0.438 to 750 mg
- The mean terminal elimination half-life is 31 hours based on dose cohorts 100-750 mg
- No accumulation following repeat dosing every 2 weeks

**Figure 3.** Preliminary PD data of ATOR-1015 in peripheral blood during the first cycle




- Significant increases in Ki67, ICOS and Eomes on CD4$^+$ and CD8$^+$ T cells (Wilcoxon matched-pairs signed rank test. *, $p < 0.05$)
- No clear dose-response relationship has been observed

## Summary

- ATOR-1015 is currently evaluated at a flat dose of 750 mg, which is the highest dose to be evaluated in the study
- One dose limiting toxicity (infusion related reaction) has been observed at 750 mg
- No severe immune-related adverse events have been reported
- Essentially dose-proportional kinetics
- Increased expression of Ki67, ICOS and Eomes on CD4$^+$ and CD8$^+$ T cells
- Best response is stable disease