First-in-Human Phase 1b Study of ATRC-101, a Patient-Derived Antibody with a Tumor-Specific Target, as Monotherapy or in Combination with Pembrolizumab, in Patients with Solid Tumors

Jonathan E. Benjamin[1], Nicholas Higgins[1], Carl Millward[1], Jeff DeFalco[1], Amy Manning-Bog[1], Shaun M. Lippow[1], Alexander Scholz[1], Iraz T. Aydin[1], Cathrin Czupalla[1], Danhui Zhang[1], Yvonne Leung[1], Nikhil Vad[1], Judy Lugar-Sapugay[1], Yanhong Zhu[1], Anna Sedello[1], Zane Rogers[1], Ish Dhawan[1], Daniel Emerling[1], William H. Robinson[2], Tito A. Serafini[1], Norman Greenberg[1]

1. Atreca, Inc, South San Francisco, CA. 2. Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA.

Abstract No: CT203

Background and Rationale

ATRC-101 is a fully human, engineered IgG1 version of an antibody discovered through a target-agnostic process designed to identify patient-derived, tumor-targeting antibodies. The parental antibody of ATRC-101 was discovered from a patient with metastatic non-small cell lung cancer (NSCLC) mounting an immune response while receiving a checkpoint inhibitor. ATRC-101 binds selectively to malignant cells across a range of tumor types, including those that are candidates for anti–PD-1 therapy (Figure 1).

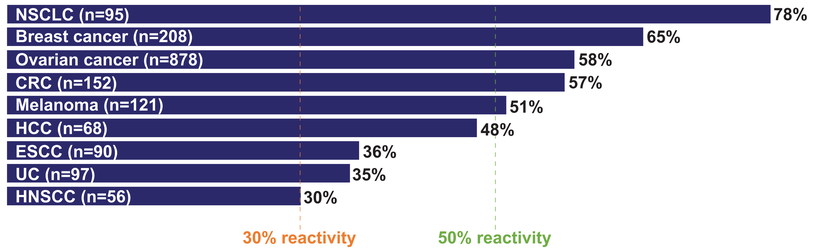


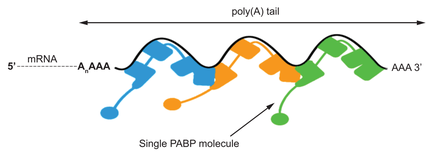
FIGURE 1 – ATRC-101 immunoreactivity in human samples across tumor types

Immunofluorescent staining with mATRC-101* was used to assess immunoreactivity within predominantly treatment-naïve tumors. Reactivity was defined as "moderate or greater" on a four-point scale with at least 40% of malignant cells estimated to be positive. Reactivity has also been observed in several other tumor types and in samples from patients treated with anti-cancer agents. Reactivity cut-offs of 30% and 50% were used to select the tumor types included in the ATRC-101-A01 phase 1b trial (Figure 7).

FIGURE 2 – ATRC-101 binds a tumor-associated RNP complex that includes polyadenylate binding protein (PABP) family members

PABP family members:

- Are ubiquitously expressed
- Are phylogenetically conserved
- Bind mRNA 3' poly(A) tails
- Are involved in mRNA metabolism and translational regulation



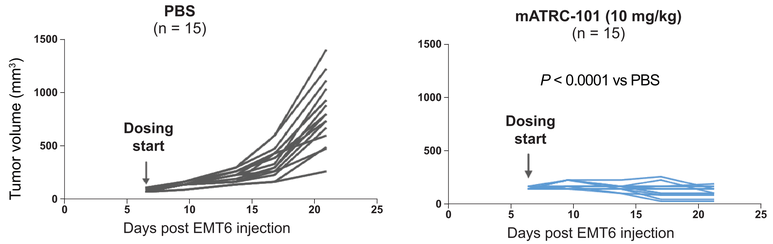


FIGURE 3 – mATRC-101 has single-agent activity in syngeneic mouse models

Anti-tumor activity of mATRC-101, a mouse IgG2a isotype of ATRC-101, has been observed in syngeneic mouse cancer models, including the EMT6 breast tumor model (shown above), with no impact on clinical safety signs, such as body weight (DeFalco et al. 2018).

*ATRC-101 is the clinical candidate with an engineered Fv and human Fc. mATRC-101 designates an antibody comprised of the mouse Fc (IgG2a) region.

CRC, colorectal cancer; dMMR, deficient in mismatch repair; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; H&E, hematoxylin and eosin; HNSCC, head and neck squamous cell carcinoma; IgG, immunoglobulin G; IV, intravenous; MSI-H, microsatellite instability high; NSCLC, non-small cell lung cancer; PBS, phosphate buffered saline; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PK, pharmacokinetic; q2w, every 2 weeks; q3w, every 3 weeks; RNASeq, RNA sequencing; UC, urothelial carcinoma.

Background and Rationale (continued)

FIGURE 4 – Tumor microenvironment infiltration of cytotoxic T cells after mATRC-101 treatment

- An apparent increase of cytotoxic T cell infiltration from the periphery to the tumor core at Day 12 was observed in EMT6 tumors in mice treated with mATRC-101 vs PBS (bottom panel)
- Semi-quantitative cell profile estimation confirmed a significant increase in $CD3^+CD8^+$ cytotoxic T cells by Day 11 with mATRC-101 vs vehicle control in EMT6 tumors (data shown previously)
- Depletion of $CD8^+$ T cells abrogates anti-tumor activity of mATRC-101 in EMT6 tumor-bearing mice (data shown previously)
- These data support the idea that ATRC-101 triggers an adaptive immune response via the innate immune response (data shown previously)

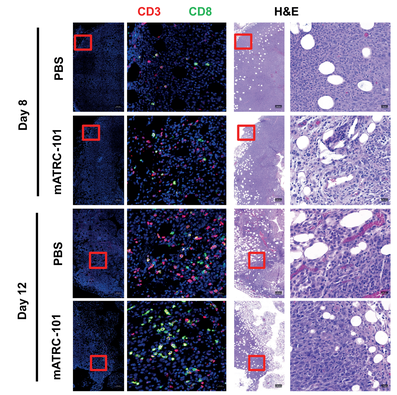
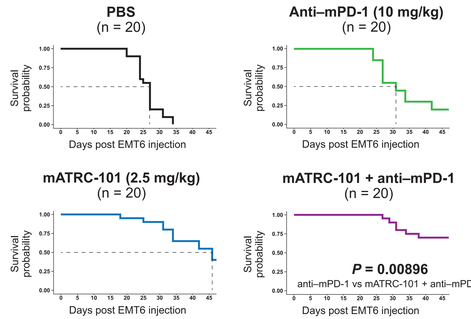


FIGURE 5 – mATRC-101 plus anti–mPD-1 show enhanced anti-tumor activity in EMT6 mice

Suboptimal doses of mATRC-101 in combination with an anti–mPD-1 antibody yield enhanced anti-tumor activity in an EMT6 mouse model, which displays a T cell-excluded microenvironment and in which PD-1/PD-L1 inhibitors exhibit limited activity. The statistical comparison of survival was made using a one-sided log-rank test.



Anti–mPD-1: Dosing twice per week for 2 weeks (last dose Day 21).
mATRC-101 antibody: Dosing twice per week for 3.5 weeks (last dose Day 28).

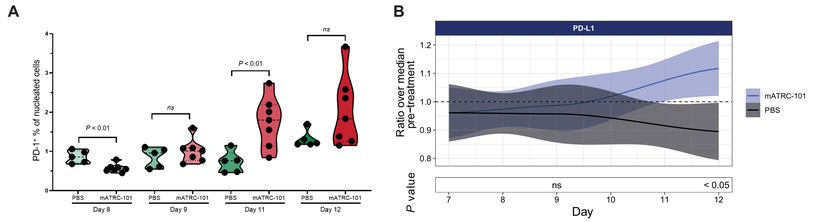


FIGURE 6 – Increase in PD-1/PD-L1 axis markers in the tumor microenvironment of EMT6 mice after treatment with mATRC-101

A: Immunofluorescence analyses revealed a significant increase in the mean percentage of PD-1–reactive T cells within the EMT6 tumor microenvironment at Day 11 following mATRC-101 administration.

B: Elevated transcripts for PD-L1 measured using RNASeq were detected by Day 12 in tumors from EMT6 tumor-bearing mice administered mATRC-101 compared with vehicle control vs baseline.

Study Design

FIGURE 7 – ATRC-101-A01 trial design

- ATRC-101-A01 (NCT04244552) is an open-label, 3+3, dose-escalation phase 1b safety study
- Expansion cohorts of ≤12 patients may be enrolled at doses and frequencies at which biological activity is observed
- Patients will receive treatment for up to 24 months or until unacceptable toxicity or disease progression

Study objectives

Primary
- Characterize safety and tolerability

Secondary
- Define the recommended dose and schedule for expansion
- Characterize PK
- Assess immunogenicity
- Measure anti-tumor activity
- Characterize tumor lymphocytic infiltration

ATRC-101 monotherapy arm (n ≈ 100)

Patients with advanced solid tumors that demonstrated ≥ 50% reactivity to ATRC-101 in preclinical studies, including:
- Non-small cell lung cancer
- Breast cancer
- Ovarian cancer
- Colorectal cancer
- Acral melanoma

ATRC-101 IV q2w* or q3w

*The q2w cohort will likely begin at a dose of 3 mg/kg.

30 mg/kg dose
10 mg/kg dose
3 mg/kg dose
1 mg/kg dose
0.3 mg/kg dose

DOSE EXPANSION (n ≤ 12)

Other dose levels may also be expanded.

ATRC-101 plus pembrolizumab combination arm (n ≈ 60)

Patients† with advanced solid tumors that demonstrated ≥ 30% reactivity to ATRC-101 in preclinical studies,including:
- Non-small cell lung cancer
- Colorectal cancer (MSI-H/dMMR)
- Melanoma
- Hepatocellular cancer
- Esophageal squamous cell cancer
- Urothelial cancer
- Head and neck squamous cell cancer

ATRC-101 IV q3w

30 mg/kg dose
10 mg/kg dose
3 mg/kg dose
1 mg/kg dose

Pembrolizumab 200 mg IV q3w or 400 mg IV q6w

†Patients with disease progression while receiving prior pembrolizumab treatment or those with stable disease who were deemed by their physician to potentially benefit from the addition of ATRC-101 to improve or maintain their response.

Trial Progress

- The q3w monotherapy cohort is currently accruing patients at the 10 mg/kg dose
- The 3 mg/kg monotherapy q3w dose was selected for dose expansion; other doses may also be expanded in the future
- The q2w and combination cohorts will begin at an ATRC-101 dose one level below the most recent cleared q3w monotherapy dose

Acknowledgments

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