ATRC-101: A First-in-Class Engineered Fully Human Monoclonal Antibody that Targets a Tumor-Restricted Ribonucleoprotein Complex

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Introduction

The checkpoint inhibitor (CPI) class of immunotherapeutic drugs demonstrates a key role for active T cells in anti-tumor immune responses and positive clinical outcomes in cancer treatment. However, the role of B cells and their antibodies in anti-tumor immune responses is less clear. We propose that B cells might aid in tumor control by producing antibodies that target tumor antigens and thereby induce tumor cell lysis or prime anti-tumor T cell responses. To this end we built a proprietary technology called Immune Repertoire Capture® (IRC™) to characterize the active B cell response in patients whose immune systems are responding to disease (DeFalco 2018). We are now using IRC™ to discover antibodies that can identify novel targets and have established a screening and validation platform to identify those antibodies with potential to become next generation therapeutics.

Methods

Atreca's lead program, ATRC-101, was initiated and developed using our IRC™ technology that generates unbiased and virtually error-free, natively paired heavy and light chain sequences of antibodies expressed by individual B cells, specifically plasmablasts, isolated from patient samples. Many antibody lineages in patient repertoires had evidence of progressive affinity maturation and class switching. We used various repertoire, lineage, and sequence analyses to select and recombinantly express monoclonal antibodies from these repertoires and then performed in vitro and in vivo studies to further characterize antibodies and engineered variants, thereof.

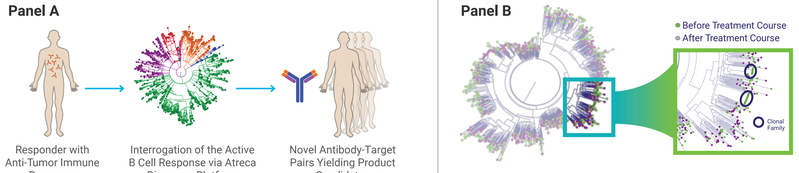
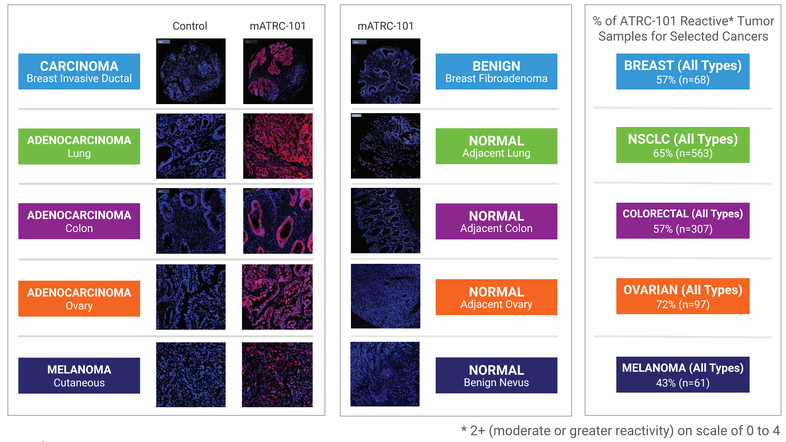


FIGURE 1: The Atreca Ab Discovery Process and Immune Repertoire Capture® from a Cancer Patient Demonstrating a Clinical Response

- Panel A: We isolate single plasmablasts from cancer patients before and after treatment and determine the sequences of the co-expressed antibody genes. We analyze these sequences and select antibodies for expression as recombinant proteins and further evaluation.
- Panel B: An example of a clonal family expansion in a patient that received CPI therapy.

Target



* 2+ (moderate or greater reactivity) on scale of 0 to 4

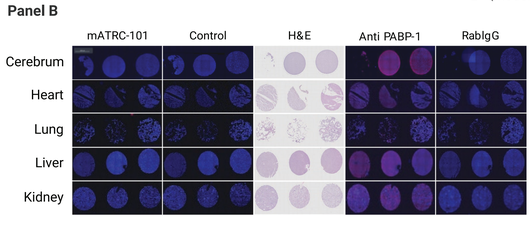


FIGURE 2

ATRC-101 Binds Selectively to Non-Autologous Tumor Tissue

- Panel A displays selective binding to tumor tissue from unrelated patients.
- Panel B shows no appreciable binding to normal human tissues.

Target

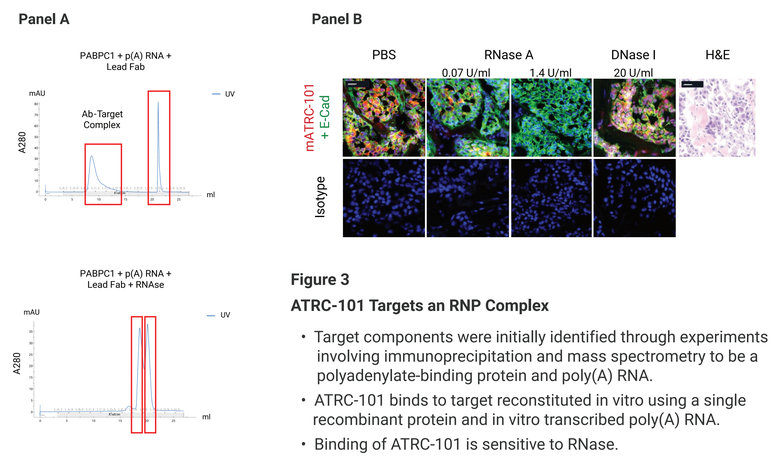
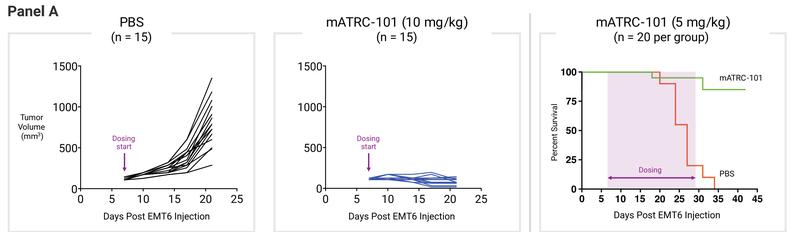


Figure 3

ATRC-101 Targets an RNP Complex

- Target components were initially identified through experiments involving immunoprecipitation and mass spectrometry to be a polyadenylate-binding protein and poly(A) RNA.
- ATRC-101 binds to target reconstituted in vitro using a single recombinant protein and in vitro transcribed poly(A) RNA.
- Binding of ATRC-101 is sensitive to RNase.

Pharmacology



Dosing: 2x per week starting at Day 7 (at randomization)
Last dose: Day 21

Dosing: 2x per week starting at Day 7 (at randomization)
Last dose: Day 29

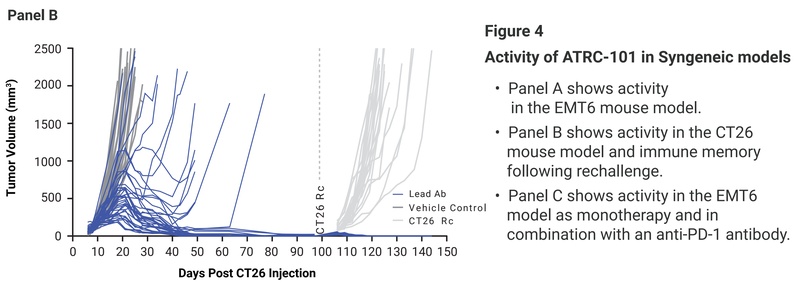
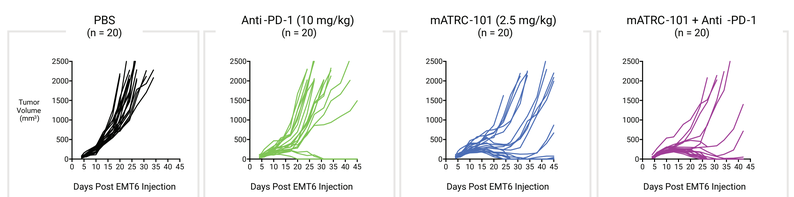


Figure 4

Activity of ATRC-101 in Syngeneic models

- Panel A shows activity in the EMT6 mouse model.
- Panel B shows activity in the CT26 mouse model and immune memory following rechallenge.
- Panel C shows activity in the EMT6 model as monotherapy and in combination with an anti-PD-1 antibody.



Anti-PD-1: Dosing 2x per week x 2 weeks (last dose Day 21)
mATRC-101 Antibody: Dosing 2x per week x 3.5 weeks (last dose Day 28)

Mechanisms of Action

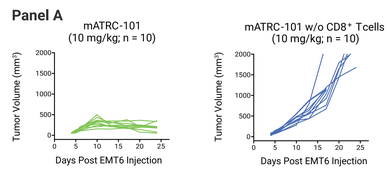
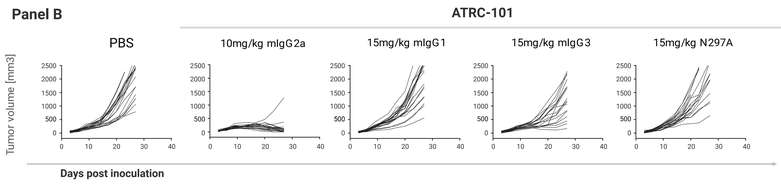
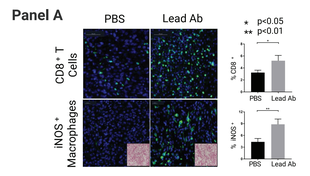


Figure 5: ATRC-101 anti-tumor effect requires CD8+ T Cells and is mediated via Fc interactions

- Activity of ATRC-101 was abrogated when CD8+ T cells were depleted in the EMT6 model.
- ATRC-101 was expressed as mIgG1, mIgG2a, mIgG2a[N297A], and mIgG3 variants and tested in the EMT6 model. Full activity was dependent on the mIgG2a Fc.





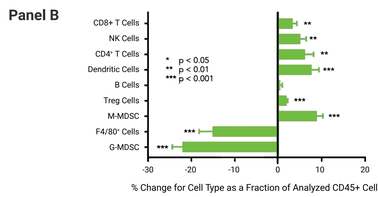


FIGURE 6: ATRC-101 Remodels the Tumor Microenvironment

- In Panel A, dosing with lead antibody causes substantial changes to the immune cell population in the tumor microenvironment. Note the statistically significant increase in CD8+ T cells and M1-polarized macrophages (shown in green) in tumors from treated animals. The presence of both of these cell types indicates a shift to a more anti-tumorigenic tumor microenvironment.
- Panel B shows the relative levels of other immune cells associated with an anti-tumorigenic microenvironment, such as NK cells, CD4+ T cells as a group, and dendritic cells. Note the decreased infiltration of F4/80+ macrophages and granulocytic-MDSC populations, commonly associated with a pro-tumorigenic phenotype.

Safety

- 4-week dose range-finding toxicology study in cynomolgus monkeys
  - » Administration of ATRC-101 via IV infusion once weekly for 4 weeks was well tolerated in cynomolgus monkeys at doses up to 100 mg/kg/week.
- No signal of toxicological significance across a wide range of normal human tissues in sensitive GLP immunohistochemistry study.
- No definitive safety signals observed in normal and tumor-bearing mice.

Clinical Strategy

On Track to File IND in Q4 2019 and Initiate Phase 1b in Early 2020

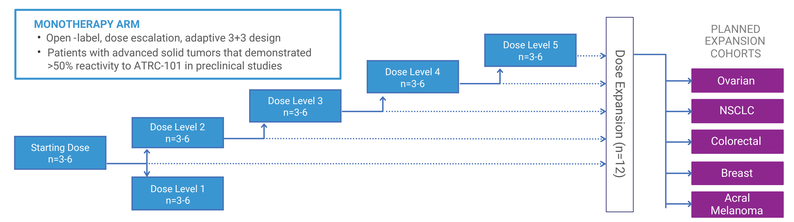


Figure 7: Proposed Clinical Trial Design

- Primary objective of the study is to determine the safety and tolerability of ATRC-101 administered as monotherapy in participants with advanced solid malignancies.
- Secondary and exploratory objectives include PK/PD, dose-finding, preliminary efficacy assessment, biomarker identification, etc.

Conclusion

Based on robust in vitro and in vivo data ATRC 101 is now being advanced to the clinic for evaluation in solid tissue malignancies.

References DeFalco, J., Harbell M., Manning-Bog, A., et al. Non-progressing cancer patients have persistent B cell responses expressing shared antibody paratopes that target public tumor antigens. Clinical Immunology 2018; 187, 37-45

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