OVERCOMING RESISTANCE TO IMMUNOTHERAPY WITH FGFR INHIBITION IN GU CANCER MODELS

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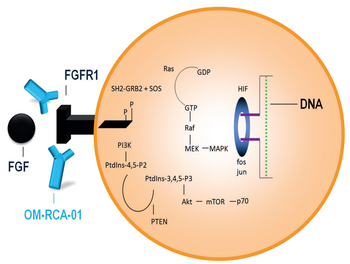
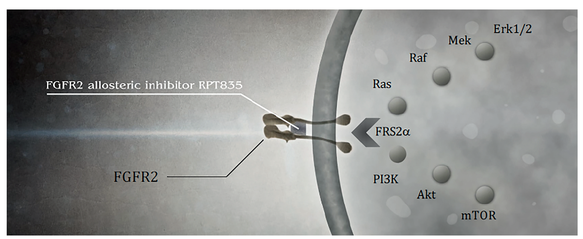
RESISTANCE TO IMMUNOTHERAPY

- Despite the encouraging success of checkpoint inhibitors, approximately 70% of tumors can eventually become resistant over time.
- The tumor microenvironment, in particular cancer-associated fibroblasts (CAFs), is one of the important mechanisms of resistance.
- OM-RCA-01, a FGFR1-blocking antibody, and alofanib, a FGFR2 allosteric inhibitor showed promising results in previous studies.
- Here, we report activity of FGFR-inhibition in immunoresistant tumor models with or without CAFs

OM-RCA-01: A HUMANIZED ANTI-FGFR1 ANTIBODY



ALOFANIB: AN ALLOSTERIC EXTRACELLULAR FGFR2 INHIBITOR

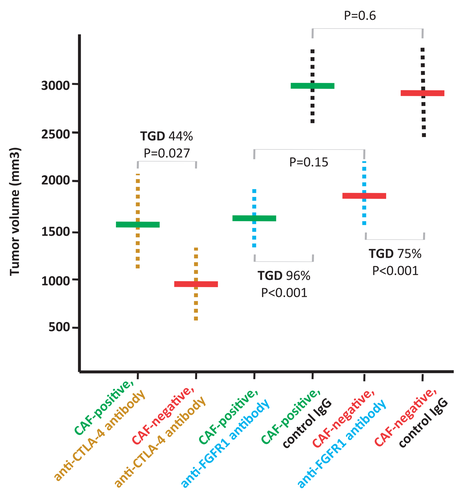


STUDY 1: IMPACT OF CANCER-ASSOCIATED FIBROBLASTS ON EFFICACY OF ANTI-CTLA4 AND SECOND-LINE ANTI-FGFR1 ANTIBODIES

- **CAF-negative group:** Renal cancer cells (Renca; 5×105) were implanted by subcutaneous (sc) injection into C57BL/6 mice (N=20).
- **CAF-positive group:** Renca cells and human kidney CAFs (1.5×106) were premixed in Matrigel and implanted sc in second cohort of C57BL/6 mice (N=20).
- **Treatment with anti-CTLA4** (9H10-CP146 mouse antibody /similar to ipilimumab/, 200 mcl on days 7, 10, and 13) was initiated in both cohorts when tumor volumes reached 70 mm3.
- **Treatment with OM-RCA-01** (pre-humanized mouse clone #56 1A10C11 with Kd 4.6 nM; 30 mg/kg; every 3 days) or IgG2a isotype control was initiated after ipi when tumor volumes reached 1,500 mm3. Tumor growth was monitored by caliper measurement every 3 days.
- Mouse cytokine levels (IFNγ and IL-2) were determined using multiplex immunodetection kits (Millipore) in second-line treatment groups.
- **The primary endpoint** was tumor growth delay (TGD) from the initiation of immunotherapy.

RESULTS

- Significant differences were detected between CAF positive and negative groups treated with anti-CTLA-4 antibody. Tumor growth was faster in the positive group.
- The use of anti-FGFR1 antibody after immunotherapy slowed tumor growth compared to control in both CAF groups.
- IHC showed a significantly lower number of α-SMA/FSP/vimentin-positive CAFs in the OM-RCA-01 cohort.

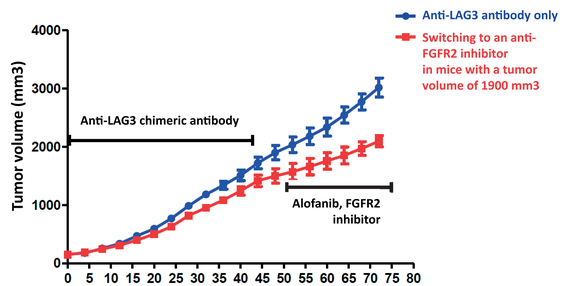


STUDY 2: FGFR2 INHIBITION IN IMMUNOREFRACTORY PROSTATE CANCER MODEL

- Prostate cancer cells (DU-145; 4×106) were implanted sc in female BALB/c mice.
- **Treatment with anti-LAG3 antibody** (1 mg/kg, biweekly) or control was initiated when tumor volumes reached 150 mm3.
- **Treatment with alofanib** (116 mg/kg, iv daily) or control was initiated when tumor volumes reached 1,900 mm3.
- Tumor growth was monitored by caliper measurement every 3 days.
- **The primary endpoint** was tumor growth delay (TGD) from the initiation of immunotherapy.

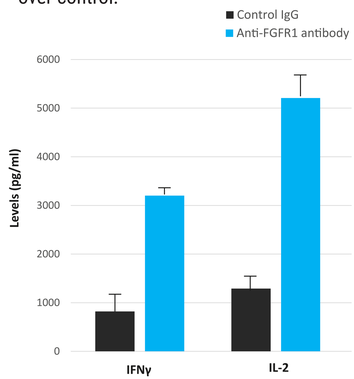
RESULTS

- In this study, prostate cancer initially proved to be almost resistant to the anti-LAG3 antibody.
- Switching from immunotherapy to an FGFR2 inhibitor was accompanied by a statistically significant delay in tumor growth.



RESULTS

- Treatment with OM-RCA-01 resulted in higher levels of IFNγ release by 43% and increased IL-2 secretion by 65% over control.



CONCLUSION

- Inhibition of FGFR1 and FGFR2 following immunotherapy resulted in a twofold suppression of tumor growth, especially in the CAFs+ cohort.

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