Introduction

- Allosteric inhibition of the phosphatase SHP2, a key signaling node in the RAS pathway, is a novel, investigational therapeutic strategy for patients bearing tumors with specific oncogenic mutations in this pathway.
- SHP2 also participates in signal transduction downstream of regulatory immunoreceptors and we have previously shown that inhibition of SHP2 drives anti tumor immunity through modulation of both innate and adaptive mechanisms in preclinical models1.
- Rational combination strategies offer an opportunity to optimize the therapeutic potential of SHP2 inhibitors. For example, we have demonstrated that SHP2 inhibition has combinational anti-tumor effects with a CDK4/6 inhibitor in several RAS-driven human cancer cell-line derived xenograft models. (Fig.1) However, these models use immunocompromised mice, making it impossible to assess the effect of the combination on anti-tumor immunity.

Fig. 1: RMC-4550 combined with CDK4/6 inhibition drives tumor regressions in RAS-driven, human-derived xenograft models.

Aim

- To evaluate the impact of dual SHP2 and CDK4/6 inhibition in a tumor bearing immunocompetent mouse that allows the study of direct inhibition of cancer cell growth with immunomodulation.
- To use a murine model of breast cancer, which is partially sensitive to SHP2 inhibition via both cell intrinsic and immune-mediated mechanisms. RMC-4550, an allosteric inhibitor of SHP2, decreases tumor cell proliferation via inhibition of RAS signaling and increases CD1+ cell infiltration in the core of EMT6 tumors. While monotherapy with either RMC-4550 or CDK4/6 inhibitor results in modest EMT6 tumor growth inhibition, combination treatment leads to complete tumor regressions and induction of immunological memory. RMC-4550 inhibits tumor associated macrophages and increases the frequency of intra-tumoral CD1+ cells. In addition, RMC-4550 or Abemaciclib increases PD1+LAG3+CD8+ T cells, pointing to an increased T cell activation.

Conclusions

- EMT6 is a S051 mutant murine model of breast cancer, which is partially sensitive to SHP2 inhibition via both cell intrinsic and immune-mediated mechanisms. RMC-4550, an allosteric inhibitor of SHP2, decreases tumor cell proliferation via inhibition of RAS signaling and increases CD1+ cell infiltration in the core of EMT6 tumors. While monotherapy with either RMC-4550 or CDK4/6 inhibitor results in modest EMT6 tumor growth inhibition, combination treatment leads to complete tumor regressions and induction of immunological memory. RMC-4550 inhibits tumor associated macrophages and increases the frequency of intra-tumoral CD1+ cells. In addition, RMC-4550 or Abemaciclib increases PD1+LAG3+CD8+ T cells, pointing to an increased T cell activation.

We have previously demonstrated that this combination leads to prolonged suppression of pERK and pHH3, and increased apoptosis in vivo. One-week post last dose of treatment, 100% of mice had complete tumor regressions (Fig. 2).

Fig. 2: RMC-4550 Inhibits Tumor Growth via Both Cell Intrinsic and Immune-mediated Mechanisms in EMT6, a Murine RAS-driven Model of TNBC

Fig. 3: RMC-4550 Combined with CDK4/6 Inhibition Drives Complete Tumor Regressions and Leads to Immunological Memory

Modulation of serum inflammatory cytokines

Abemaciclib 30 mg/kg po qd
RMC-4550 10 mg/kg po qd
Control

Vehicle
Abemaciclib
RMC-4550
Combination

Delay to endpoint
Re-challenge

EMT6 is partially sensitive to checkpoint blockade. Combination of RMC-4550 with Anti-PD1 also drives durable tumor regressions.

Fig. 4: RMC-4550 Increases Tumor Infiltration of Activated PD1+ CD8+ T Cells and Depletes Tumor Macrophages. Changes Maintained in Combination with CDK4/6 Inhibition