Background

TRC105 is an endoglin-targeting monoclonal antibody, with anti-angiogenic and anti-tumor activity. Clinical administration of TRC105 and bevacizumab (BEV) demonstrated activity in a phase Ib trial.  

Previously, we investigated biomarker expression at baseline and on-treatment change in the phase Ib trial evaluating TRC105 and BEV. TRC105 induced a dose-dependent increase in soluble endoglin levels. Unique biomarker features were observed in patients (pts) benefiting from this drug regimen.

In this study, we expanded our biomarker analysis to 3 different phase II trials, where pts received TRC105 and different VEGF inhibitors to confirm previous observations. In addition to evaluating angiogenic and inflammatory biomarkers, we assessed potential drug effects on multiple TGFβ family members.

Methods

Plasma samples were collected from pts in three phase II trials combining TRC105 with an anti-VEGF agent:

- Axitinib in metastatic renal cell carcinoma (mRCC)
- Pazopanib in advanced soft tissue sarcoma
- Bevacizumab in glioblastoma (GBM)

Samples were processed at individual sites and shipped to the Duke Molecular Reference Laboratory for analysis.

Samples were thawed one time, precipitate removed, aliquotted and re-frozen until assayed. All assays were performed in duplicate.

Baseline and on-treatment change of 22 soluble protein biomarkers were assessed using Axon Biosystems CiraScan protein multiplex arrays (Table 2).

Results

Table 1. Patient characteristics, drug dosing and drug schedules. Biomarker levels were assessed across 3 different clinical trials of TRC105. Patient characteristics, drug dosing/timing and overall response rates are shown. CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

Figure 1. Change in endoglin levels from baseline through EOS. Each line represents an individual patient. Increases in soluble endoglin is dependent on patient population treated with TRC105. Significant increases of endoglin were observed in all 3 patient populations after TRC105 administration. Differences in the timing of endoglin increases are due to the different dosing schedules of TRC105 across the 3 trials (see Table 1).

Response Analysis

Drug activity was observed in two of the trials (Table 1).

- In mRCC, 5 pts exhibited partial response (RECIST1.1 criteria) after treatment with the combination of TRC105 and axitinib.
- In sarcoma, 6 pts exhibited partial response (Chi criteria) after treatment with the combination of TRC105 and pazopanib.

In studies where patients exhibited responses, potential biomarkers differentiating responders versus non-responders were explored. Biomarkers associated with response were identified at both baseline and on-treatment (Figure 3).

Table 2. Biomarker baseline levels. Median and range for all biomarkers at baseline are shown.

Table 3. Modulation of biomarkers in response to TRC105 and VEGF inhibitors. Wilcoxon rank sum analyses are shown above. Significant biomarker modulation was observed in response to co-administration of both drugs. Time points analyzed for each study were:

- mRCC: Baseline to C2D15
- Sarcoma: Baseline to C2D1
- mRCC Sarcoma GBM

Baseline Baseline C2D1

Table 3. Modulation of biomarkers in response to TRC105 and VEGF inhibitors. Wilcoxon rank sum analyses are shown above. Significant biomarker modulation was observed in response to co-administration of both drugs. Time points analyzed for each study were:

- mRCC: Baseline to C2D15
- Sarcoma: Baseline to C2D1
- GBM: Baseline to C2D15

Conclusions

- This report is the first analysis across multiple tumor types evaluating circulating biomarkers from cancer pts treated with TRC105 in combination with a VEGF inhibitor.
  - Baseline levels and on-treatment change for most markers were similar to those observed in the original phase Ib TRC105 + BEV trial.
  - Baseline variation was observed for POAG, PDGFB, VEGF and VEGFR1, possibly reflecting differences in the underlying tumor type and patient population.

- Soluble endoglin consistently increases after TRC105 administration, confirming its role as a pharmacodynamic marker of TRC105 treatment.

- Baseline and on-treatment change analyses identified markers differentiating responders from non-responders. Lower baseline expression of OPN and higher baseline expression of TGFβR3 were associated with better outcomes in mRCC. Lower baseline expression of ICAM1 and TGF-2 in sarcoma pts were associated with better outcomes.

- Significant changes in TGFβ-family members were observed in sarcoma pts, but not in mRCC or GBM pts. The potential prognostic and predictive effects of these markers in sarcoma will be confirmed in the ongoing phase III trial of TRC105 and pazopanib in angiosarcoma (NCT02979859).

References

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