# Bevacizumab (Bev) Alone or in Combination with the CD105 antibody TRC105 for Metastatic Renal Cell Cancer (mRCC): A California Cancer Consortium clinical trial

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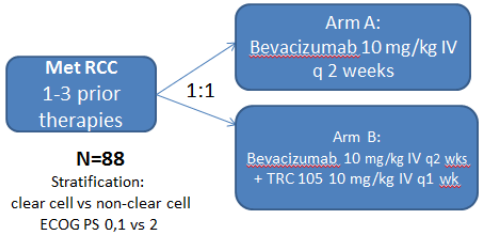
Abstract #4542

## Background

Inhibition of the vascular endothelial growth factor (VEGF) pathway is effective in mRCC, but resistance inevitably develops. CD105 (endoglin) is highly expressed on endothelial cells and has been shown in preclinical models to mediate resistance to VEGF pathway inhibitors, in part due to TGF-beta signaling. In vitro the combination was significantly more effective at inhibiting HUVEC polygon formation[1]. TRC105 is a monoclonal antibody against CD105 which has been shown to be tolerable in combination with Bev at full doses and 5/19 subjects showing radiographic regression [2].

## Methods

Eligible mRCC patients (pts) with any histologic subtype may have received 1-4 prior systemic therapies, including cytokines, VEGF, or mTOR targeted agents. Bev was administered at 10 mg/kg IV on day 1 and 15 of 28-day cycles as a single agent (Arm A) or with TRC105 10 mg/kg IV on days 1, 8, 15, and 22 (Arm B). Primary endpoint was progression-free survival (PFS). A total of 88 pts were to be randomized to detect a halving of PFS with 80% power and α=0.1. An interim analysis for futility was conducted after 44 pts had PFS evaluated.




**Primary Endpoint:** PFS at 12 and 24 weeks
**Secondary Endpoints:** toxicity, RECIST response
**Correlative studies:** tissue: CD105, TGFβrII, ACVRL1
serum: sCD105 baseline, change

## Results

Enrollment began Nov. 2012 and was halted for futility Sept. 2014 after interim analysis identified futility, with 59 pts on therapy, 40 evaluated. PFS on Arm B was lagging Arm A such that the continuation criterion (one sided p <0.43 at 44 evalutaions) was unachievable. Characteristics of the study population are summarized in Table 1. Median age was 60 (24-83). 20 (32%) of pts had received 3 or more prior lines of therapy.

Table 1. Baseline and demographic characteristics.

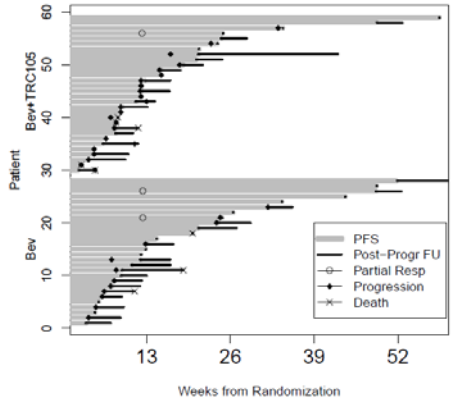
| Characteristic | | Arm A Bev alone n=28 | Arm B Bev + TRC105 n=31 |
|---|---|---|---|
| Age: median (range) | | 58 (25-83) | 65 (24-79) |
| Gender: number (%) | | | |
| Male | | 20 (71%) | 24 (77%) |
| Female | | 8 (29%) | 7 (23%) |
| Ethnicity: number (%) | | | |
| Hispanic | | 6 (21%) | 4 (13%) |
| Asian | | 3 (11%) | 0 |
| Black | | 2 ( 7%) | 2 ( 6%) |
| Caucasian | | 17 (61%) | 25 (81%) |
| Prior nephrectomy: # (%) | | 25 (89%) | 30 (97%) |
| Prior lines of therapy: | 0 | 4 (14%) | 4 (13%) |
| | 1 | 9 (32%) | 9 (29%) |
| | 2 | 9 (32%) | 9 (29%) |
| | 3 | 6 (21%) | 7 (23%) |
| | 4 | 0 | 2 ( 6%) |

One subject on each arm had a confirmed PR (3%) and 2 patients on each arm had stable disease lasting ≥9 cycles (Figure 1). For the 56 evaluable pts, the PFS at 12 weeks was 0.69 (95% CI 0.53, 0.9) on Bev compared to 0.56 (0.41, 0.77) on Bev + TRC105 (p=0.074). 24 week PFS was 0.53 (0.35, 0.79) for Bev and 0.24 (0.12, 0.47) for Bev +TRC105. Survival did not differ significantly (p=0.5) between arms, being 81% at 24 weeks for both arms (Figure 2). Toxicities are summarized in Table 2.

Table 2. Grade 3 and higher toxicities, by treatment arm

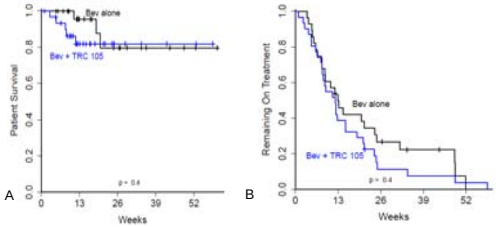
| Toxicity | CTC AE Grade | Arm A Bev alone n=28 | Arm B Bev + TRC105 n=31 |
|---|---|---|---|
| Anemia | 3 | 2 ( 7%) | 5 ( 16%) |
| Cardiovascular | 3 | 3 ( 11%) | 0 |
| Hemorrhage | 3, 5 | 2 ( 7%) | 0 |
| Hyperkalemia | 3 | 0 | 1 ( 3%) |
| Hypertension | 3 | 5 ( 18%) | 4 (13%) |
| Hyponatremia | 3,4 | 0 | 2 ( 6%) |
| Infusion Reaction | 3,4 | 0 | 2 ( 6%) |
| Nausea/Vomiting | 3,4 | 0 | 3 (10%) |
| Proteinuria | 3 | 2 ( 7%) | 0 |

Figure 1. Duration of disease control in patients with met RCC treated with Bevacizumab alone or with TRC105




## Results

Figure 2. Kaplan-Meier Curves depicting (A) overall survival and (B) time to treatment failure for the study arms. TTF was chosen to eliminate the effect of post-treatment follow-up of non-progressed patients




## Conclusions

- TRC105 failed to prolong PFS or OS when added to Bev.
- Grade ≥ 3 toxicities were more common in Arm B, except for hemorrhage, hypertension, and proteinuria which were more common in Arm A.
- Further analysis will examine biomarkers for association with disease control, exploring differences between arms.
- TRC105 is being studied in combination with VEGF receptor tyrosine kinase inhibitors in mRCC to determine whether there is an additive effect on PFS (NCT01806064).

## Acknowledgements

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## References

1. Liu Y et al. Effects of the combination of TRC105 and bevacizumab on endothelial cell biology. Invest New Drugs 2014;32:851
2. Rosen LS et al. A phase Ib dose-escalation study of TRC105 (anti-endoglin antibody) in combination with bevacizumab (BEV) for advanced solid tumors. J Clin Oncol 2013; 31:abstr3059