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Clinical Results and Biomarker Analyses of Axitinib and TRC105 versus Axitinib Alone in Patients with Advanced or Metastatic Renal Cell Carcinoma (TRAXAR)

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TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT01806064
- **Sponsor:** TRACON Pharmaceuticals, Inc.

- **Principal Investigator:** Toni K. Choueiri
- **IRB Approved:** Yes

LESSONS LEARNED

- The combination of carotuximab with axitinib did not provide a benefit over axitinib monotherapy in patients with metastatic clear cell renal cell carcinoma who had previously progressed on one or more vascular endothelial growth factor (VEGF)-targeted therapies.
- Exploratory evaluation of pretreatment circulating biomarkers suggested the combination might benefit patients who have low baseline VEGF levels.

ABSTRACT

Background. Endoglin is an angiogenic receptor expressed on proliferating tumor vessels and renal cell carcinoma (RCC) stem cells that is implicated as a mechanism of resistance to vascular endothelial growth factor receptor (VEGFR) inhibitors. This study evaluated an antiendoglin monoclonal antibody (carotuximab, TRC105) combined with axitinib in patients with advanced or metastatic clear cell renal cell carcinoma (mccRCC) who had progressed following one or more prior VEGF inhibitors.
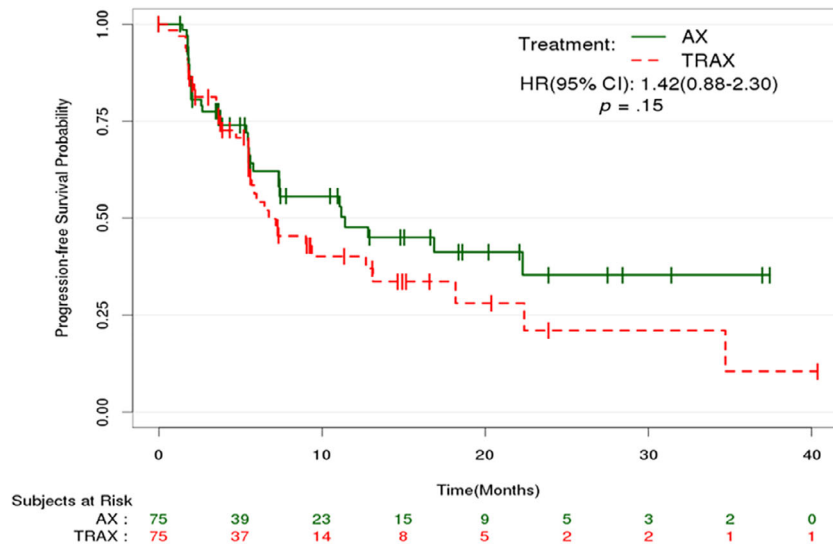
Methods. TRAXAR was a multicenter, international randomized 1:1 (stratified by ECOG, 0 vs. 1), phase II study of carotuximab combined with axitinib versus axitinib alone in mccRCC patients who had progressed following one or more prior VEGF inhibitors. The primary endpoint was progression-free survival (PFS) assessed by independent central review (ICR) per RECIST 1.1

Results. A total of 150 patients were randomized. The combination therapy resulted in shorter median PFS by RECIST 1.1 than axitinib monotherapy (6.7 vs. 11.4 months). The combination was tolerated similarly to axitinib monotherapy, and there were no treatment related deaths. Exploratory evaluation of pretreatment circulating biomarkers suggested the combination might benefit patients who have low baseline VEGF levels.

Figure 1. Kaplan-Meier estimates of progression-free survival by RECIST 1.1 by independent central review. Abbreviations: AX, axitinib monotherapy; CI, confidence interval; HR, hazard ratio; TRAX, TRC105 + axitinib.

Conclusion. The combination of carotuximab with axitinib did not demonstrate additional efficacy over single agent axitinib in patients with mccRCC who progressed following one or more prior VEGF inhibitor treatment. ***The Oncologist*** 2021;26:560–e1103

DISCUSSION

The analysis of the primary endpoint of PFS, performed following 69 events of progression by ICR or death, did not show any benefit for adding carotuximab to axitinib. This combination resulted in numerically shorter median PFS by RECIST 1.1 compared with axitinib alone (Fig. 1).

Both drugs could be administered at their recommended single-agent doses without increasing the toxicities of the individual drugs (Table 1); however, dose escalation to the maximum recommended dose of axitinib was less commonly achieved in the combination arm. Adverse events were rarely a reason for study discontinuation.

We explored whether any pretreatment circulating angiogenic biomarkers could help identifying which patients benefitted most from the combination therapy. Biomarkers were modeled as continuous measures, and each was tested for a prognostic association with PFS using Cox proportional hazards models. Interaction p values (P_{Intx}) for predictive analyses were not subjected to multiple testing correction. We observed that patients with low baseline VEGF levels exhibited longer median PFS in arm TRC105 + axitinib (TRAX) compared with arm axitinib monotherapy (AX) (22.4 vs. 16.9 months, P_{Intx} = .004; Fig. 2). Increased expression of VEGF and VEGFR have previously been associated with clinical responses and improved PFS on sunitinib. Lower VEGF levels might indicate an overall diminished VEGF signaling and perhaps a greater role for drugs targeting angiogenesis through non-VEGF related mechanisms, such as carotuximab.
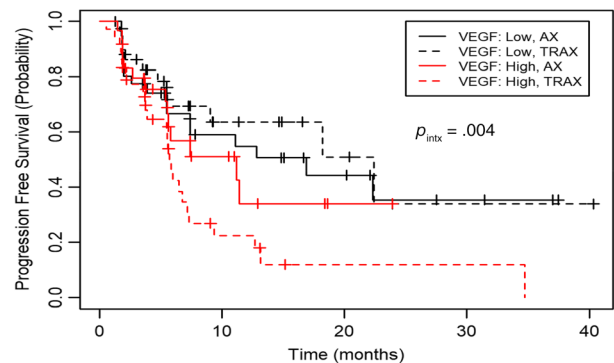
Figure 2. Kaplan-Meier estimate of progression-free survival by RECIST 1.1 by independent central review according to baseline median VEGF levels stratified by treatment arm. Abbreviations: AX, axitinib monotherapy; TRAX, TRC105 + axitinib; VEGF, vascular endothelial growth factor.

Lack of PFS benefit in the TRAX arm when compared with the AX arm led to termination of further development of carotuximab. It is critical to establish solid safety and efficacy signals in a phase Ib study prior to committing patients, investigators, and resources on a larger randomized clinical trial. Despite the favorable efficacy of the combination of axitinib and carotuximab found in a phase Ib study with 18 patients with mRCC [1], another randomized clinical trial in which carotuximab was added to bevacizumab in 59 patients with mRCC failed to improve PFS [2]. Much still remains to be learned in how best to use antiangiogenic therapies in mRCC and whether any biomarker can guide selection of patients. Indeed, the observation of improved PFS in the subpopulation of patients with mRCC with lower than median VEGF emphasizes the value of patient preselection using predictive biomarkers to improve clinical outcomes.

TRIAL INFORMATION

Disease	Renal cell carcinoma – clear cell
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	1 prior regimen
Type of Study	Phase II, randomized
Primary Endpoint	Progression-free survival

Additional Details of Endpoints or Study Design

The analysis of the primary endpoint of PFS compared arm AX and arm TRAX using a log-rank test stratified by performance status (0 or 1). A hazard ratio of 0.67 was considered to be clinically relevant. Based on 1:1 randomization and the use of a one-sided log-rank test at the α = 0.10 level of significance, 115 events were required to have 80% power to detect a hazard ratio of 0.67. The expected PFS of patients treated with axitinib who had progressed following first-line treatment with a VEGF inhibitor was assumed to be 4.8 months. Based on a planned accrual period of 12 months, and a minimum follow-up period of 4.3 months, approximately 150 patients were recruited. Statistical analyses were done using R. The trial population for safety included all patients who received a dose of either study drug according to treatment actually received. An interim analysis for futility was planned following 55 events that defined the PFS endpoint but was not done at the recommendation of the data monitoring committee because of the rate of accrual exceeding the rate of expected events defining PFS.

PK/PD data were previously reported in the phase I study: https://pubmed.ncbi.nlm.nih.gov/30190302/

Investigator's Analysis	Level of activity did not meet planned endpoint

DRUG INFORMATION: TRAX ARM

Axitinib

Generic Name	Axitinib
Trade Name	Inlyta
Company Name	Pfizer
Drug Type	Small molecule
Drug Class	VEGFR
Dose	5 mg per flat dose
Route	oral (po)
Schedule of Administration	5 mg twice daily (b.i.d.), which was escalated to a maximum dose of 10 mg b.i.d. in the absence of hypertension or other significant toxicity.

Carotuximab/TRC105

Generic Name	Carotuximab/TRC105
Company Name	TRACON Pharmaceuticals Inc.
Drug Type	Antibody
Drug Class	Endoglin
Dose	10 mg/kg
Route	IV
Schedule of Administration	Patients randomized to the combination arm received carotuximab 10 mg/kg intravenously (with appropriate premedication) every week, with the initial dose divided over 2 days. Premedication included acetaminophen 650 mg, diphenhydramine 50 mg (or similar H1 receptor antagonist), famotidine 20 mg (or similar H2 receptor antagonist), and methylprednisolone 50 mg. Methyl-prednisolone was tapered and discontinued within the first weeks of dosing. Dose modifications of carotuximab and axitinib were allowed per patient tolerance.

DRUG INFORMATION: AX ARM

Axitinib

Generic Name	Axitinib
Trade Name	Inlyta
Company Name	Pfizer
Drug Type	Small molecule

Drug Class	VEGFR
Dose	5 mg per flat dose
Route	oral (po)
Schedule of Administration	5 mg twice daily (b.i.d.), which was escalated to a maximum dose of 10 mg b.i.d. in the absence of hypertension or other significant toxicity.

PATIENT CHARACTERISTICS: TRAX ARM

Number of Patients, Male	49
Number of Patients, Female	26
Stage	metastatic/advanced
Age	Median: 63 years
Number of Prior Systemic Therapies	Median: 1 or more
Performance Status: ECOG	0 — 39 1 — 36 2 — 0 3 — 0 Unknown — 0
Cancer Types or Histologic Subtypes	Clear cell renal cell carcinoma, 75

PATIENT CHARACTERISTICS: AX ARM

Number of Patients, Male	57
Number of Patients, Female	18
Stage	metastatic/advanced
Age	Median: 65 years
Number of Prior Systemic Therapies	Median: 1 or more
Performance Status: ECOG	0 — 38 1 — 37 2 — 0 3 — 0 Unknown — 0
Cancer Types or Histologic Subtypes	Clear cell renal cell carcinoma 75

PRIMARY ASSESSMENT METHOD: TRAX ARM

Title	PFS
Number of Patients Screened	75
Number of Patients Enrolled	75
Number of Patients Evaluable for Toxicity	73
Number of Patients Evaluated for Efficacy	75
Evaluation Method	RECIST 1.1
(Median) Duration Assessments PFS	6.7 Months, CI: 5.6–13.1

PRIMARY ASSESSMENT METHOD: AX ARM

Title	PFS
Number of Patients Screened	75
Number of Patients Enrolled	75
Number of Patients Evaluable for Toxicity	74
Number of Patients Evaluated for Efficacy	75
Evaluation Method	RECIST 1.1
(Median) Duration Assessments PFS	11.4 Months, CI: 5.8–NE

ADVERSE EVENTS

Table 1. Most common (*n* > 1) and all grade 3 and above AEs by arm

Safety	TRAX (*n* = 73), *n* (%)			AX (*n* = 74), *n* (%)			TRAX-AX, All, %
	All	Grade 3	Grade 4	All	Grade 3	Grade 4	
Headache	48 (65.8)	5 (6.9)	0	12 (16.2)	0	0	49.6
Epistaxis	47 (64.4)	0	0	6 (8.1)	1 (1.34)	0	56.3
Diarrhea	44 (60.3)	10 (13.7)	0	44 (59.5)	7 (9.5)	0	0.8
Fatigue	42 (57.5)	7 (9.6)	0	40 (54.1)	2 (2.7)	0	3.4
Nausea	38 (52.1)	2 (2.7)	0	27 (36.5)	2 (2.7)	0	15.6
Vomiting	30 (41.1)	1 (1.4)	0	15 (20.3)	1 (1.4)	0	20.8
Hypertension	26 (35.6)	11 (15.1)	0	34 (46.0)	17 (23.0)	1 (1.4)	-10.4
Weight loss	25 (34.3)	3 (4.1)	0	17 (23.0)	1 (1.4)	0	11.3
Gingival bleeding	25 (34.3)	0	0	3 (4.1)	0	0	30.2
Decreased appetite	21 (28.8)	2 (2.7)	0	25 (33.8)	1 (1.4)	0	-5.0
Anemia	21 (28.8)	11 (15.1)	0	12 (16.2)	2 (2.7)	0	12.6
Constipation	20 (27.4)	0	0	13 (17.6)	0	0	9.8
Infusion related reaction	19 (26.0)	2 (2.7)	0	0	0	0	26.0
Palmar-plantar erythrodysaesthesia syndrome	18 (24.7)	1 (1.4)	0	14 (18.9)	5 (6.8)	0	5.8
Stomatitis	18 (24.7)	2 (2.7)	0	8 (10.8)	0	0	13.9
Hypothyroidism	16 (21.9)	0	0	20 (27.0)	1 (1.4)	0	-5.1
Back pain	9 (12.3)	3 (4.1)	1 (1.4)	17 (23.0)	2 (2.7)	0	-10.7
proteinuria	3 (4.1)	1 (1.4)	0	15 (20.3)	8 (10.8)	0	-16.2

AEs were coded by using MedDRA dictionary version 14.1. If more than one event was recorded for a patient, the patient was counted only once at the highest grade.
Abbreviations: AE, adverse event; AX, axitinib monotherapy; TRAX, TRC105 + axitinib.

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion	Study completed
Investigator's Assessment	Level of activity did not meet planned endpoint

Angiogenesis is a complex process that is regulated by multiple pathways [3]. Antiangiogenic drugs such as axitinib, sorafenib, sunitinib, pazopanib, and cabozantinib primarily target the vascular endothelial growth factor (VEGF) pathway and have revolutionized the treatment of renal cell carcinoma (RCC) [4]. Axitinib, a selective VEGF receptor (VEGFR)-1, -2, and -3 inhibitor, has been compared with sorafenib in the phase III AXIS trial [5] as a second-line therapy for patients with RCC after progression on sunitinib or cytokine therapy. Axitinib significantly increased median progression-free survival (PFS) over sorafenib (6.7 vs. 4.7 months; hazard ratio, 0.67; *p* = .0001), but without significant improvement in overall survival.

Inhibition of complementary, non-VEGF driven angiogenic pathways is an alternative strategy that may improve antitumor activity and limit resistance to VEGF inhibitors. Beyond the VEGF axis, angiogenesis depends upon multiple growth factors and stromal elements [3]. Upregulated non-VEGF pathways may include the interleukin-6, transforming growth factor (TGF)-β, PDGF, bFGF, c-Met, and angiopoietin axes. In particular, the TGF-β axis, including the soluble bone morphogenic proteins (BMPs) and the endoglin and

ALK1 receptors, may provide an escape pathway for tumor angiogenesis. Endoglin (CD105) is a homodimeric TGF-β co-eceptor expressed on proliferating vascular endothelium in solid tumors [4, 6] and is upregulated by hypoxia through the induction of hypoxia inducible factor 1α [4, 7]. Endoglin is essential for normal vascular development [8], and loss of endoglin expression is associated with the Osler-Weber-Rendu syndrome, a disease characterized by abnormal blood vessel formation that is associated with improved cancer survival, suggesting that targeting endoglin may have beneficial clinical effects [9, 10]. The introduction of the endoglin heterozygous genotype resensitizes spontaneous tumors to VEGF inhibitors, as does the conditional deletion of the endoglin gene in endothelium [9]. In patients with solid tumors, including RCC, high tumor microvessel density is correlated with poor prognosis [11–23]. Furthermore, endoglin expression has been demonstrated on human renal cancer stem cells isolated from nephrectomy specimens and is associated with a tumor initiating function [24].

Carotuximab (TRC105) is a chimeric immunoglobulin G1 antibody that binds human endoglin with high avidity, competitively inhibits BMP ligand binding required for

endothelial signal transduction, induces antibody-dependent cellular cytotoxicity of proliferating human vascular endothelial cells and endoglin-expressing tumor cells, and inhibits angiogenesis stimulated by VEGF and fibroblast growth factor [25]. Carotuximab potentiates VEGF inhibitors in preclinical models of angiogenesis and in tumor xenografts, and was well tolerated at 10 mg/kg every week and 15 mg/kg every 2 weeks as a single agent in a phase I trial, where it demonstrated a safety profile that was distinct from that of VEGF inhibitors, including lack of hypertension and proteinuria [26]. These preclinical and early phase I clinical data set the stage for our randomized phase II clinical trial TRAXAR reported here.

Unfortunately, carotuximab did not demonstrate additional activity when combined with axitinib in patients with metastatic clear cell RCC that progressed following prior VEGF inhibitor treatment. These data are consistent with a randomized trial of bevacizumab and carotuximab in patients with all types of RCC histology (which included 22% nonclear cell) that failed to demonstrate a survival advantage over single agent bevacizumab [2].

Carotuximab was administered at doses that achieved pharmacodynamic effects, as telangiectasia and associated epistaxis or gingival bleeding were observed routinely in patients on the combination arm. These reversible signs and symptoms are expected pharmacologic effects of carotuximab binding to the endoglin receptor to interrupt BMP9 binding and resemble the characteristics of Osler-Weber-Rendu syndrome. Epistaxis or gingival bleeding are observed routinely in trials of carotuximab given as a single agent or concurrently with VEGF inhibitors and provide confirmation that patients have been administered carotuximab doses required to inhibit BMP binding to endoglin.

Dalantercept, a ligand trap for BMP9, also reported negative data in a trial of clear cell RCC in combination with axitinib, although in this trial only a minority of patients demonstrated signs or symptoms of telangiectasia [27], indicating that most patients may have received a subtherapeutic drug exposure required for pharmacologic inhibition of the endoglin pathway.

Across all patients, no PFS advantage was noted in the TRAX arm when compared with the AX arm. We explored whether any circulating angiogenic biomarkers could help identifying which patients benefitted most from the combination therapy. We observed that patients who had low baseline VEGF levels demonstrated greater benefit from the combination than single agent axitinib, using independent central review–defined PFS by RECIST. Increased baseline expression of VEGF and VEGFR have previously been associated with clinical responses and improved PFS in patients with metastatic urothelial carcinoma on sunitinib [28]. It is therefore reasonable to speculate that lower VEGF levels indicate an overall diminished VEGF signaling, and perhaps a greater role for drugs targeting angiogenesis through non-VEGF related mechanisms such as carotuximab. Across multiple preclinical models, synergistic effects have been reported using antiendoglin and anti-VEGF agents to simultaneously block both pathways [29].

In conclusion, the finding of a biomarker selected population that might benefit from the combination of carotuximab and axitinib was not robust enough to merit further clinical development of this therapy. Hopefully the lessons of this trial will guide more effective therapeutic development for patients with advanced RCC that has progressed on VEGF-targeted therapy.

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