Results of a Phase 2 Study of tovecimig (CTX-009), a Novel DLL4-VEGF Bispecific Antibody, as a Monotherapy in Patients with Refractory Metastatic Colorectal Cancer (COMPANION-003)

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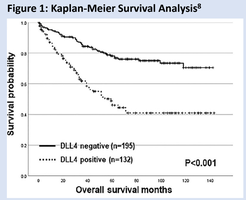
BACKGROUND

Background of Disease

- Patients with unresectable locally advanced and metastatic colorectal cancer (CRC) are sequentially treated with various combinations or single agent courses of cytotoxic chemotherapy, VEGF-A inhibitors, and targeted therapies.[1]
- Despite the approval of multiple new agents in the past two decades, the goals of therapy are generally palliative, and in the cases of patients whose disease has progressed, or who have not tolerated 2 or 3 prior lines of therapy, the expectation for tumor response with the available treatments are less than 5% and the median overall survival is approximately 6 months (for 3rd line therapy) or less (for 4th line therapy).[2, 3]
- The DLL4 pathway has been reported to be a mechanism of acquired resistance for anti-VEGF agents, including through upregulation of DLL4.[4, 5, 6] The expression of DLL4 was observed in the endothelium of 71% of colon cancers by immunohistochemistry (IHC).[7] Patients with positive DLL4 expression showed significantly worse overall survival than that of patients with negative DLL4 expression (HR=2.922; 95% CI 1.976–4.322; p<0.001) **[Figure 1]**.[8]

Figure 1: Kaplan-Meier Survival Analysis[8]



Tovecimig (CTX-009): A Novel DLL4 x VEGF-A Bispecific Antibody

- Tovecimig is a recombinant bispecific antibody that simultaneously blocks the delta-like ligand-4 (DLL4) and vascular endothelial growth factor A (VEGF-A) signaling pathways involved in angiogenesis in the tumor microenvironment. The dual blockade of DLL4-Notch 1 and VEGF-A signaling is synergistic in preclinical models.
- In a Phase 1 study of tovecimig, two patients with metastatic colorectal cancer (CRC) had confirmed partial responses (PRs) prompting the further exploration of tovecimig in patients with CRC treated in the third- or fourth-line setting.

METHODS

- COMPANION-003 (NCT05513742) was a multi-center, single arm Phase 2 study with a Simon Two Stage design.
- Eligible patients had metastatic CRC with primary tumor resection and had progressed after receiving two or three prior systemic therapies, which must have included oxaliplatin, irinotecan, a fluoropyrimidine, an anti-VEGF therapy, and, if indicated, an anti-EGFR therapy.
- Patients with both KRAS wild type and KRAS mutated tumors were eligible.
- Tovecimig was given as a monotherapy intravenously at 10 mg/kg every two weeks, and tumor response was assessed every eight weeks based on RECIST v1.1.
- The primary objective was to assess the objective response rate (ORR) based on RECIST v1.1. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.
- DLL4 expression in tumor tissue from archived biopsy specimens (optional submission) was analyzed by immunohistochemistry (IHC) retrospectively.

BASELINE CHARACTERISTICS

- A total of 68 patients were screened, and 49 patients were enrolled from 8 US medical institutes between January 2023 to April 2024. The main reasons for screen failure were inadequate hepatic and renal function.
- Median age was 57, with 32 Male and 17 Female patients. 36 (73.5%) patients had left-sided CRCs. KRAS mutations were present in 19 (39%) patients, and 9 (18.4%) patients had MSI-high (MSI-H) tumors. Of the patients enrolled, a majority, 32 (65%), received three previous lines of therapy for metastatic disease. **[Table 1]**
- 61.2% of patients had hypertension at baseline. **[Table 2]**
- 57.2% of patients receive ≥2 prior anti-VEGF targeted agents. **[Table 3]**

Table 1: Tumor Characteristics

	Total (n=49)
Anatomic Subsite of Primary Tumor	
Left-sided	27 (55.1)
Right-sided	11 (22.4)
Transverse Colon	2 (4.1)
Rectum	8 (16.3)
Other	1 (2.0)
KRAS Status*	
Mutant	20 (40.8)
Wild Type	26 (53.1)
Unknown	3 (6.1)
MSI Status	
MSI-H	9 (18.4)
Non-MSI-H	40 (81.6)

*assessed locally

Table 2: Medical History (≥20%) by Preferred Term

	Total (n=49)
Preferred Term (PT)	
Hypertension	30 (61.2)
Peripheral sensory neuropathy	17 (34.7)
Gastroesophageal reflux disease	13 (26.5)
Fatigue	12 (24.5)
Anxiety	12 (24.5)
Hyperlipidemia	12 (24.5)
Insomnia	11 (22.4)

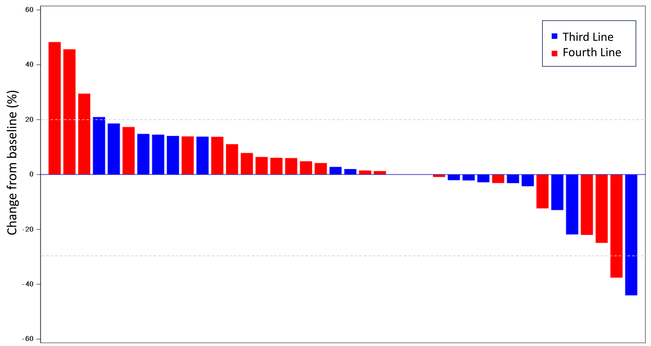
Table 3: Number of Prior Anti-VEGF Agents

	Total (n=49)
1	21 (42.9)
2	21 (42.9)
3	7 (14.3)

RESULTS

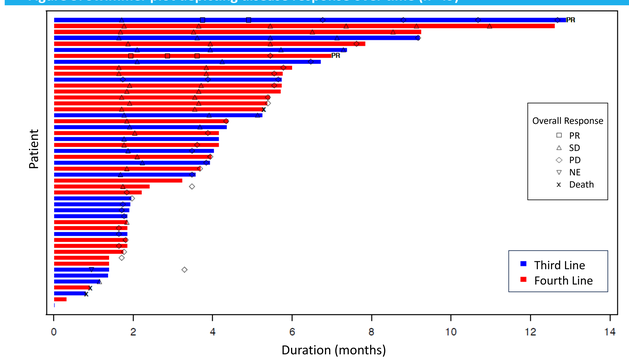
- The response evaluable (RE) population was defined as patients who had measurable disease by RECIST v1.1 and had at least one post-baseline scan at a minimum of 8 weeks from enrollment. Of the 49 patients enrolled in Stage 1 of the study, there were 40 patients included in the RE population.
- 23 out of the 40 RE patients (58%) were treated in the fourth-line setting.
- 16 of the 40 patients (40%) had KRAS mutated tumors.
- In the RE population (n=40), the confirmed BOR by RECIST v1.1 was partial response (PR) in 2 patients with ORR of 5.0% (95% CI: 0.5, 14.0).

Figure 2: Waterfall plot of maximum change in sum of target lesions (n=40)



- Stable disease (SD) was achieved in 25 patients (62.5%), while progressive disease (PD) was reported in 13 patients (32.5%). Results yielded an overall disease control rate (DCR) of 57.1% (28/49) or 67.5% among the response evaluable population. The median duration of response was 14.4 weeks (95% CI: 13.3, NE).

Figure 3: Swimmer plot depicting disease response over time (n=49)



- Thirty-seven patients (75.5%) experienced disease progression, while 12 patients (24.5%) were censored, with a median progression free survival (PFS) of 3.9 months (95% CI: 3.3, 5.4).

Figure 4: Progression Free Survival by Kaplan-Meier Estimation

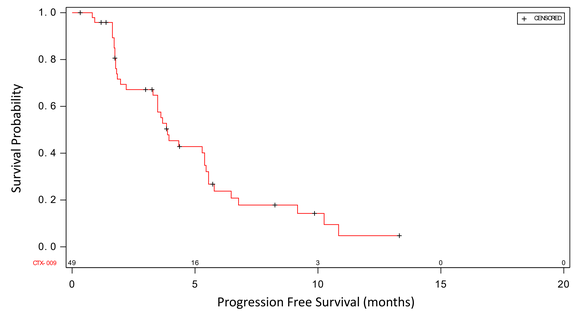
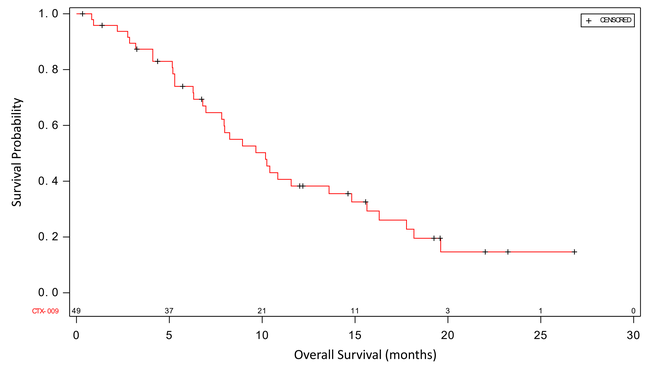


Figure 5: Overall Survival by Kaplan-Meier Estimation

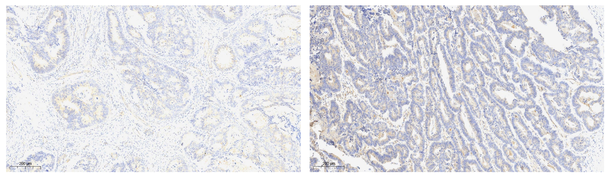


- The median overall survival (OS) was 10.2 months (95% CI: 7.0, 13.6). Landmark survival rates were 38.7% at 12 months, 22.8% at 18 months, and 14.7% at 24 months.

Figures 6 and 7: DLL4 Expression in COMPANION-003 Colorectal Cancer Tumor Samples

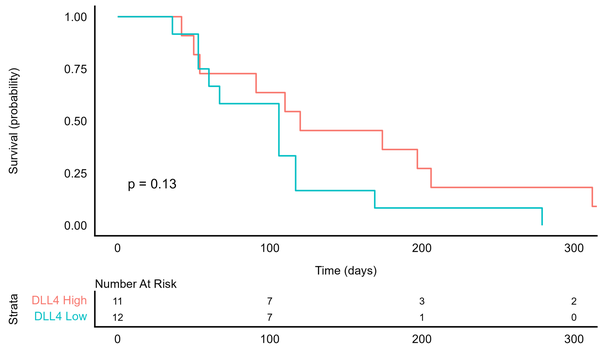
- Formalin fixed and paraffin embedded patient tumor samples were stained for DLL4 expression using an immunohistochemistry method developed by Gnome Sciences (Powell, OH). Baseline tumor tissue samples from 23 patients enrolled were stained for DLL4 expression and an H-score was obtained for each sample.
- Of the two patients with confirmed PRs, one consented to submission of tumor tissue and had the highest vascular H-score for DLL4 expression across all 23 samples analyzed.

Figure 6: Representative DLL4 IHC staining in both tumor cells and tumor vasculature of a baseline tumor sample taken from a patient with low (A) and high (B) vascular DLL4 expression.



(A) Low DLL4 expression (B) High DLL4 expression

Figure 7: Kaplan-Meier curve estimation of tumor vasculature DLL4 using median DLL4 H-score as a cutoff.



- A log rank test showed a trend towards increased PFS for patients whose tumor samples showed DLL4 H-scores higher than the median of all values obtained. The 6-month PFS was 8.3% in the DLL4 low group and 33.6% in the DLL4 high group.

SAFETY

- Treatment emergent AEs (TEAEs), regardless of attribution to tovecimig, were reported in 98.0% of patients and treatment related AEs (TRAEs) were reported in 83.7% of patients.
- Most common reported TEAEs and TRAEs of any grade were hypertension, proteinuria, nausea, fatigue, and headache.
- The most common Grade ≥3 TRAEs were hypertension and proteinuria.
- All patients with a reported AE of Hypertension at any Grade had a documented history of Hypertension at baseline. Hypertension led to treatment modification or interruption in 15 patients (30.6%) and discontinuation in 2 (4.1%).

Table 4: Adverse Events

Overall AEs, n (%)	
Any TEAE (Treatment Emergent AE)	48 (98.0)
Treatment-Related AE	41 (83.7)
Serious AE	14 (28.6)
Serious Related AE	4 (8.2)
Treatment-Related AE leading to Discontinuation	12 (24.5)

Common TRAEs (≥ 15%) by Preferred Term, n(%)	**Any Grade**	**Grade ≥ 3**
Hypertension	19 (38.8)	13 (26.5)
Proteinuria	16 (32.7)	3 (6.1)
Nausea	10 (20.4)	0
Fatigue	9 (18.4)	0
Headache	8 (16.3)	0

SUMMARY

- In a predominantly fourth line patient population (n=40), 2 patients achieved confirmed partial responses, resulting in an ORR of 5.0%.
- Stable disease was reported in 53.1% (26/49) of all patients, yielding an overall disease control rate (DCR) of 57.1% (28/49) or 67.5% among the response evaluable population.
- Median progression-free survival (PFS) was 3.9 months and median overall survival (OS) was 10.2 months.
- IHC analysis suggested a trend toward longer PFS in patients with DLL4 high tumors compared to patients with DLL4 low tumors.
- The most frequently reported TRAEs were hypertension [19 (38.8%)] and proteinuria [16 (32.7%)].
- Moderate increases in blood pressure were controllable with anti-hypertensive medication and consistent with known class effects.
- No new or unexpected safety signals were identified.

CONCLUSIONS

Overall, tovecimig monotherapy was associated with a manageable safety profile and clinically meaningful anti-tumor activity in patients with advanced, metastatic CRC. Clinical benefit was primarily derived from both disease stabilization and survival benefit. Compared with historical data in this population of patients, tovecimig monotherapy demonstrated durable anti-tumor activity and median OS supporting further development of tovecimig in patients with advanced, mCRC.

Longer PFS in patients with high DLL4 tumors (Fig 7) suggests a potential benefit from the dual blockade of DLL4 and VEGF of tovecimig for patients with DLL4 positive tumors for further exploration.

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