Vilastobart (XTX101), a Tumor-Activated, Fc-Enhanced Anti–CTLA-4 Monoclonal Antibody, in Combination with Atezolizumab in Patients with MSS Colorectal Cancer

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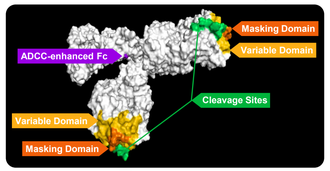
BACKGROUND

Metastatic Microsatellite Stable (MSS) Colorectal Cancer (CRC) Remains a Significant and Growing Unmet Need

- CRC is 2nd in cancer-related deaths in the US and leading cause of cancer-related death in men younger than 50 in the US[1]
- Objective response rates for FDA-approved agents in 3L+ MSS CRC (trifluridine and tipiracil, regorafenib and fruquintinib) range from 0 to 6%[2-5]
- Immune checkpoint inhibitors (pembrolizumab / nivolumab / ipilimumab) approved in MSI-H CRC have no meaningful efficacy in patients with MSS CRC (0-3% ORR)[6]
- Other systemically active anti-CTLA-4 agents in development have reported activity in patients with MSS CRC without liver metastases, but have been associated with toxicity (including a high incidence of immune-mediated AEs and/or discontinuation rates)

Vilastobart: Tumor-Activated, High Affinity Binding, Fc-Enhanced Anti-CTLA-4 in Phase 2 Development

- High affinity binding, 10x potency of ipilimumab in preclinical studies[7]
- Fc mutations for enhanced effector function (ADCC), improved T cell priming and Treg depletion[7]
- On-treatment biopsies in Phase 1 monotherapy demonstrated >70% activated molecule in tumor with <15% activated molecule in periphery[8]
- Generally well-tolerated in Phase 1 as a monotherapy and combination therapy, consistent with tumor-activated design[8,9]
- Confirmed and durable PR observed with monotherapy in Phase 1 in a PD-L1 negative NSCLC patient, including resolution of innumerable liver metastases[8]
- PRs observed with combination of atezolizumab (Tecentriq®) in Phase 1, including a patient with MSS CRC with full resolution of a liver metastasis[9]
  - PR (confirmed) in patient with MSS CRC with liver metastasis – ongoing for 14+ months
  - PR (unconfirmed) in ampullary carcinoma patient



STUDY DESIGN

First-In-Human Phase 1/2 Clinical Trial of Vilastobart in Advanced Solid Tumors and Metastatic MSS CRC (NCT04896697)

PHASE 1A/B
Monotherapy Dose-Escalation and Expansion
Advanced Solid Tumors (n=39)
Vilastobart monotherapy RP2D established as 150 mg Q6W

PHASE 1C
Vilastobart + Atezolizumab Dose-Escalation
Advanced Solid Tumors (n=26)
Vilastobart dose levels up to 150 mg Q6W cleared

PHASE 2
Vilastobart + Atezolizumab
Metastatic MSS CRC (n=44)
Vilastobart 100 mg Q6W + atezolizumab 1200 mg Q3W

Enrollment Completed

KEY PHASE 2 ELIGIBILITY
- At least 1 prior chemotherapy regimen for metastatic CRC
- No prior checkpoint inhibitors
- Must be assessed for MSI-H or dMMR status – patients with MSI-H/dMMR tumors are excluded

RESULTS OF PHASE 2

Phase 2 Enrolled Heavily Pre-Treated Patients With MSS CRC With and Without Liver Metastases, Including Patients With Peritoneal Metastases

Patient Characteristics	Total (n=44)
Age, median (range)	55 (25-82)
Female	22 (50%)
ECOG PS 0	18 (41%)
ECOG PS 1	26 (59%)

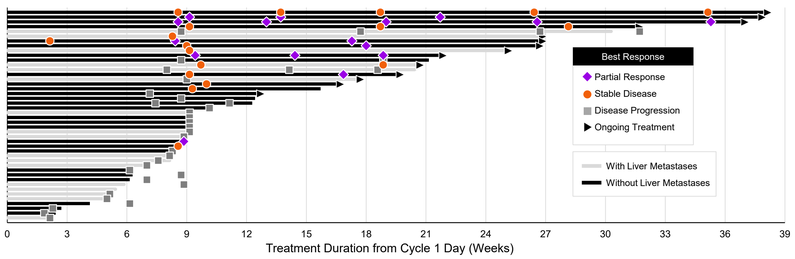
Prior Lines of Anti-Cancer Treatment	
Median	**4 (1-8)**
1	4 (9%)
2	5 (11%)
3	11 (25%)
4	9 (21%)
5	6 (14%)
6 or more	9 (20%)

80% of patients had 3 or more prior lines of treatment

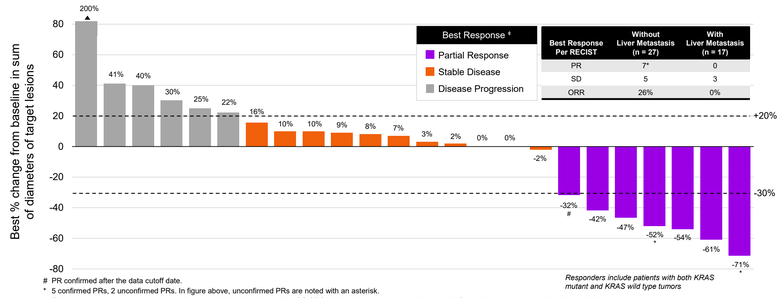
Tumor Types	Total (n=44)
MSS CRC	**44**
with liver metastases	17
without liver metastases	27
with peritoneal metastases	*8*

Treatment Status	Total (n=44)
Continuing on Treatment	**14**
Discontinued Treatment	**30**
Disease Progression	23
Adverse Events	4
Investigator Decision	1
Other	2

Duration of Treatment for Patients With MSS CRC Without and With Liver Metastases



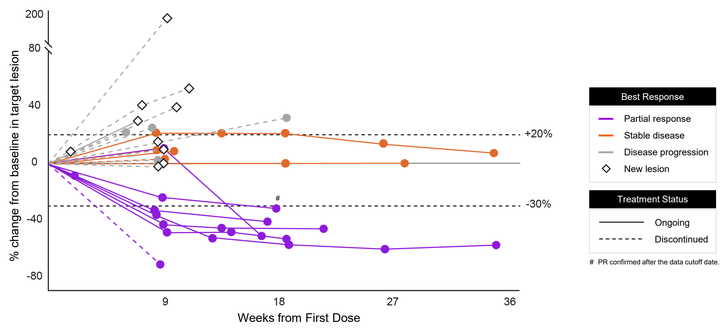
Preliminary 26% ORR Reported in Patients With MSS CRC Without Liver Metastases



Best Response Per RECIST	Without Liver Metastasis (n = 27)	With Liver Metastasis (n = 17)
PR	7*	0
SD	5	3
ORR	26%	0%

\# PR confirmed after the data cutoff date.
* 5 confirmed PRs, 2 unconfirmed PRs. In figure above, unconfirmed PRs are noted with an asterisk.
ǂ Figure above represents best response in target lesions. 3 patients with MSS CRC without liver metastases not included in figure above had progressive disease (patients had new lesions but target lesions were not assessed).

Durable Anti-Tumor Activity Observed in Patients With MSS CRC Without Liver Metastases

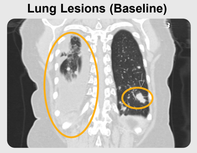


\# PR confirmed after the data cutoff date.

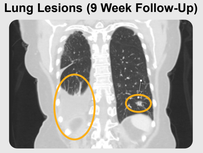
Representative Patients: Significant Reductions in Tumor Burden, Decreases in Tumor Biomarkers and Improvement in Clinical Symptoms Observed in Patients With MSS CRC Without Liver Metastases

- 67-year-old female with 6 prior lines of therapy
- 42% tumor reduction accompanied by substantial decreases in ctDNA and CEA

Lung Lesions (Baseline)

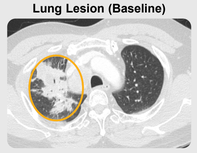


Lung Lesions (9 Week Follow-Up)

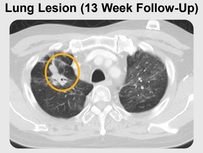


- 50-year-old male with 4 prior lines of therapy
- 47% tumor reduction accompanied by substantial decreases in ctDNA and CEA with improvement of symptoms, such as cough

Lung Lesion (Baseline)

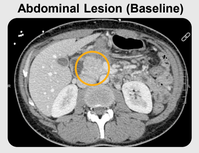


Lung Lesion (13 Week Follow-Up)

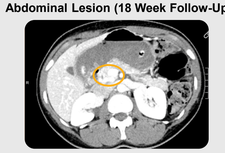


- 35-year-old female with peritoneal lesions and *KRAS* mutant disease
- Prior treatment with FOLFIRI, sotorasib and panitumumab
- 32% tumor reduction accompanied by substantial decreases in ctDNA and CEA

Abdominal Lesion (Baseline)



Abdominal Lesion (18 Week Follow-Up)



Combination of Vilastobart and Atezolizumab Was Generally Well-Tolerated in Heavily Pre-Treated Patients With MSS CRC

TRAEs ≥10% incidence (any Grade) or Grade 3/4 TRAEs with ≥ 5% incidence	Any grade	Grade 3
Fatigue	13 (30%)	0
Infusion related reaction	10 (23%)	2 (5%)
related to vilastobart	9 (21%)	2 (5%)
related to atezolizumab	2 (5%)	0
Diarrhea or colitis	9 (20%)	2 (5%)
Diarrhea	8 (18%)	0
Colitis	3 (7%)	2 (5%)
AST increased	6 (14%)	2 (5%)
ALT increased	5 (11%)	2 (5%)
Pruritus	5 (11%)	0
Pyrexia	5 (11%)	0
WBC decreased	3 (7%)	2 (5%)

TRAEs are related to vilastobart or atezolizumab

Dose Reduction and Treatment Discontinuation	
Vilastobart dose reduction due to TRAE+	1 (2%)
Treatment discontinuation due to TRAE‡	2 (5%)

\+ Dose reduction of atezolizumab is not permitted per protocol
‡ Reflects discontinuation of both vilastobart and atezolizumab

- No Grade 5 TRAEs and only 2 Grade 4 TRAEs (neutropenia and thrombocytopenia, n=1 each, both recovered)
- 11 patients (25%) required steroids or other immunosuppression for imAEs
- 3 patients (7%) experienced colitis
- 2 patients (5%) required treatment discontinuation for TRAEs: 1 patient with Grade 3 maculopapular rash, pruritis and febrile neutropenia; 1 patient with Grade 3 Triple-M overlap syndrome

Radiographic Responses in Patients With MSS CRC Without Liver Metastases Were Accompanied by Meaningful ctDNA Reductions

* Patient with undetectable ctDNA for > 20 weeks

Dodged waterfall plot showing best % change from baseline in the sum of diameters of target lesions (left y-axis; dark gray bars) and best % change from baseline in ctDNA score (right y-axis; light gray bars). Each pair of bars corresponds to the same patient (x-axis).

CONCLUSIONS

Vilastobart is a novel tumor-activated, high affinity binding, Fc-enhanced anti-CTLA-4 mAb that is designed to focus activity toward the tumor while minimizing systemic exposure and minimize the potential for adverse events

Combination of vilastobart and atezolizumab demonstrated promising deep and durable anti-tumor activity in patients with metastatic MSS CRC without liver metastases together with a differentiated safety profile, consistent with tumor-selective activation of vilastobart

26% ORR in Phase 2 in metastatic MSS CRC patients without liver metastasis:
- 7 PRs (5 confirmed, 2 unconfirmed), including 6 responders ongoing on therapy as of the data cutoff date
- Responses were accompanied by decreases in tumor biomarkers (ctDNA and CEA) and improvement in clinical symptoms
- Responses were seen regardless of *KRAS* status

Combination of vilastobart and atezolizumab continued to demonstrate low incidence of imAEs, which have typically limited the potential for anti-CTLA-4 agents:
- 11 patients (25%) required steroids or other immunosuppression for imAEs
- 3 patients (7%) experienced colitis
- 2 patients (5%) discontinued treatment due to a TRAE

In addition, in Phase 1C, a previously reported patient with MSS CRC with a liver metastasis and confirmed PR (including complete resolution of liver metastasis) remains on treatment for 14+ months

These data support further development of vilastobart combinations in MSS CRC as well as other cold tumors previously not responsive to aPD-(L)1 therapy or indications where treatment with anti-CTLA-4 agents have been limited by toxicity

ABBREVIATIONS: 3L: third line; ADCC: antibody-dependent cell-mediated cytotoxicity; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CEA: carcinoembryonic antigen; ctDNA: circulating tumor DNA; CTLA-4: cytotoxic T-Lymphocyte Associated Protein 4; dMMR: deficient mismatch repair; ECOG PS: Eastern Cooperative Oncology Group Performance Status; Fc: fraction crystallizable; imAE: immune-mediated adverse event; KRAS: Kirsten rat sarcoma gene; imAb: monoclonal antibody; MSI-H: microsatellite instability-high; NSCLC: non-small cell lung cancer; ORR: objective response rate; (a)PD-L1: (anti) programmed death receptor ligand 1; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; Q3W: every 3 weeks; Q6W: every 6 weeks; RP2D: recommended phase 2 dose; SD: stable disease; TF: tumor fraction; TRAE: treatment related adverse event: Treg: regulatory T-cell.; WBC: white blood cell.

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