Phase 1/2 Study of Vilastobart (XTX101), a Tumor-Activated, Fc-enhanced Anti-CTLA-4 Monoclonal Antibody, in Combination with Atezolizumab in Patients with Advanced Solid Tumors and in MSS CRC

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BACKGROUND

Vilastobart (XTX101): Tumor-Activated, High Affinity Binding, Fc-Enhanced Anti-CTLA-4

- Vilastobart is an investigational tumor-activated, high affinity, Fc-enhanced anti-CTLA-4 antibody designed to focus activity toward the tumor and minimize systemic adverse events
- Vilastobart incorporates protease-cleavable masking peptides designed to block CTLA-4 binding when in the inactive state and dissociate upon activation by tumor-associated proteases
- Vilastobart is designed to block CTLA-4 checkpoint and drive ADCC against regulatory T-cells (Tregs) that highly express CTLA-4
- Vilastobart was 10-fold more potent than ipilimumab in *in vivo* studies[1]
- Fc-enhancement augments FcγR co-engagement on antigen presenting cells and has been linked with efficacy of anti-CTLA-4 combinations in patients with "cold tumors," including MSS CRC[2]

Study Design for First-In-Human Clinical Trial of Vilastobart (XTX101) in Advanced Solid Tumors and in MSS CRC (NCT04896697)

Phase 1A/B
Monotherapy Dose-Escalation and Expansion
Advanced Solid Tumors
(n=39)
Enrollment Completed

→

Phase 1C
Vilastobart + Atezolizumab
Dose-Escalation
Advanced Solid Tumors
(n=21)
Enrollment Ongoing

→

Phase 2
Vilastobart + Atezolizumab
(n = ~40)
Metastatic MSS CRC, Including Patients With and Without Liver Metastases
Enrollment Ongoing

Key Phase 2 Eligibility

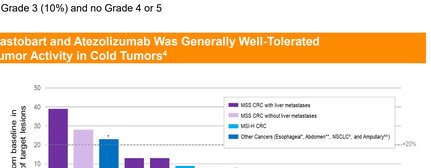
- At least 1 prior chemotherapy regimen for metastatic CRC
- No prior checkpoint inhibitors
- Must be assessed for MSI-H or dMMR status – patients with MSI-H/dMMR tumors are excluded

Vilastobart (XTX101) at the Monotherapy RP2D (150 mg Q6W) in Phase 1A/B Was Generally Well-Tolerated and Demonstrated Evidence of Anti-Tumor Activity [3]

- Phase 1A/B evaluated vilastobart monotherapy. Thirty-nine heavily pre-treated patients with advanced solid tumors were enrolled at dose levels ranging from 7 to 180 mg Q3W or 150 mg Q6W (RP2D) administered intravenously
- Evidence of tumor activation of vilastobart was observed (73-96% activation in n=2 on-treatment biopsies, including a biopsy from MSS CRC liver metastasis), compared to limited peripheral activation (~13%)
- Monotherapy activity with deep and durable confirmed PR seen in PD-L1 negative NSCLC patient (52% reduction of target lesions sum of diameters from baseline and full resolution of liver metastases)
- Vilastobart monotherapy was observed to be generally well-tolerated:
  - No endocrine irAEs and limited skin irAEs
  - At the RP2D, colitis of any grade was reported in 3 patients (14%): 2 patients with Grade 3 (10%) and no Grade 4 or 5
  - No Grade 4 or 5 TRAEs were reported with vilastobart at the monotherapy RP2D

In Phase 1C Dose-Escalation, the Combination of Vilastobart and Atezolizumab Was Generally Well-Tolerated and Demonstrated Anti-Tumor Activity in Cold Tumors[4]

- The combination of vilastobart and atezolizumab showed initial evidence of anti-tumor activity in cold tumors, including:
  - PR (confirmed) in patient with MSS CRC, including resolution of liver metastasis
  - PR (unconfirmed) in patient with ampullary carcinoma
- Vilastobart monotherapy and combination of vilastobart with atezolizumab showed dose-dependent increases in Ki67+ CD4 and CD8 T cells, with minimal impact on Tregs in periphery
- Intratumoral Treg depletion observed in a tumor biopsy from a MSS CRC patient was consistent with the intended mechanism of action of vilastobart
- Dose level of vilastobart 100 mg Q6W in combination with atezolizumab (1200 mg Q3W) was declared the initial RP2D
  - Across all vilastobart dose levels (75-150 mg), minimal irAEs observed, colitis of any grade was experienced in 5% of patients (1 patient with Grade 3)
  - No Grade 4 or 5 TRAEs at any dose level in Phase 1C



RESULTS OF PHASE 2
Combination of Vilastobart (100 mg Q6W) and Atezolizumab (1200 mg Q3W)

Phase 2 Enrolled Heavily Pre-Treated MSS Colorectal Cancer Patients With and Without Liver Metastases

Patient Characteristics	Total (N=40)
Demographics	
Age, median (range)	55 (25-82)
Female	20 (50%)
ECOG PS 0	17 (43%)
ECOG PS 1	23 (58%)

Tumor Types	
MSS CRC	40
Patients with liver metastases	16
Patients without liver metastases	24

Patient Characteristics	Total (N=40)
Prior Lines of Anti-Cancer Treatment	**Median 4 (range 1-10)**
unknown	2 (5%)
1	5 (13%)
2	5 (13%)
3	7 (18%)
4	6 (15%)
5	7 (18%)
6 or more	8 (20%)

70% of patients had 3 or more prior lines of treatment

Treatment Status	Total (N=40)
Continuing on Treatment	**23**
Discontinued Treatment	**17**
Disease Progression	6
Clinical Progression	8
Adverse Events	3

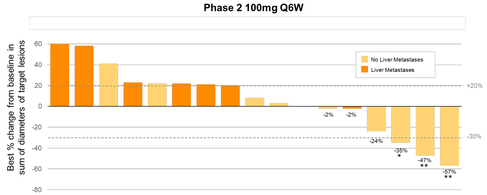
CONCLUSIONS

- Vilastobart (XTX101) is a novel tumor-activated, high affinity binding, Fc-enhanced anti-CTLA-4 mAb that is designed to focus activity toward the tumor and minimize the potential for adverse events
- Clinical data to date suggest that vilastobart has a differentiated safety profile from systemically active anti-CTLA-4, consistent with tumor-selective activation
- In Phase 1C, one patient with MSS CRC has an ongoing PR (confirmed) with resolution of liver metastases
- The combination of vilastobart and atezolizumab showed anti-tumor activity in MSS CRC where previously PD(L)-1 inhibitors and first generation anti-CTLA-4 have not demonstrated efficacy (0-3% ORR historically[5]):
  - 3 PRs (2 confirmed, 1 pending confirmation) in patients with MSS CRC without liver metastases:
    - 1 ongoing response with normalization of CEA accompanied by undetectable ctDNA following treatment
    - 2 ongoing responses with substantial decrease in ctDNA
  - An additional MSS CRC patient without liver metastases had a 24% tumor reduction at their initial 9-week assessment and is ongoing on therapy
  - 27% ORR reported in Phase 2 response-evaluable patients without liver metastases
- In Phase 2, the combination of vilastobart (100 mg Q6W) and atezolizumab (1200 mg Q3W) has been observed to be generally well-tolerated in patients with metastatic MSS colorectal cancer
  - Low incidence of irAEs, with only 2 out of 40 patients (5%) experiencing colitis
- Pharmacodynamic changes consistent with the intended mechanism of action
- These initial data support the further development of the combination of vilastobart and atezolizumab in patients with MSS CRC

RESULTS OF PHASE 2
Combination for Vilastobart (100 mg Q6W) and Atezolizumab (1200 mg Q3W)

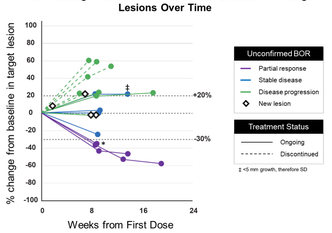
Combination of Vilastobart (XTX101) and Atezolizumab Demonstrated Anti-Tumor Activity in MSS CRC Patients

Phase 2 100mg Q6W



Note: one patient was found to have new brain metastases (progressive disease per RECIST) but did not yet undergo imaging of target lesions. This patient is evaluable for response but not included in the waterfall and spider plot.
* Initial assessment of unconfirmed PR (35%) by investigator at 9 weeks (official radiology assessment pending) (see Patient C vignette).
** Confirmed PR (see Patient A and B vignettes).

Percent Change from Baseline of Sum of Diameters in Target Lesions Over Time



27% ORR in Patients With MSS CRC Without Liver Metastases‡

- 40 patients with MSS CRC enrolled in ongoing Phase 2
- 18 patients response-evaluable with at least 1 scan reported

Best Response	Without Liver Metastases *(n = 11 response-evaluable)*	With Liver Metastases *(n = 7 response-evaluable)*
PR	**3‡**	**0**
SD	**3**	**1**
ORR	**27%‡**	**0%**
DCR*	**55%**	**14%**

‡ Includes 2 confirmed PRs (see Patient A and Patient B vignettes) and 1 unconfirmed PR (pending confirmation, see Patient C vignette).
* DCR is defined as PR or SD through the first on treatment imaging scan as defined by the protocol (~9 weeks)

Combination of Vilastobart (XTX101) and Atezolizumab Was Generally Well-Tolerated in Phase 2

- 6 patients experienced Grade 3/4 TRAEs (related to vilastobart or atezolizumab)
- Only 2 Grade 4 TRAEs (thrombocytopenia and neutropenia, 1 each)
- No Grade 5 TRAEs

AE Category / Term *All TRAEs with ≥10% incidence or Grade 3/4 TRAE with ≥ 5%*	All Phase 2 Patients (n = 40) Any	Grade 3
Fatigue	12 (30%)	0
Diarrhea	8 (20%)	0
Infusion related reactions	5 (13%)	0
Related to vilastobart	3 (8%)	0
Related to atezolizumab	2 (5%)	0
Pyrexia	4 (10%)	0
ALT increased	4 (10%)	0
AST increased	4 (10%)	1 (3%)
Colitis	2 (5%)	2 (5%)
Vilastobart dose reduction due to AE*		0
Treatment discontinuation due to TRAE^		3

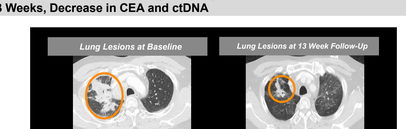
TRAEs are related to vilastobart or atezolizumab
*Dose reduction of atezolizumab is not permitted per protocol
^Reflects discontinuation of both vilastobart and atezolizumab

Non-laboratory Grade 3 TRAEs not included in the table above consisted of: maculopapular rash and febrile neutropenia in 1 patient; lower gastrointestinal hemorrhage in 1 patient with thrombocytopenia; and 1 patient with Triple M overlap syndrome (myocarditis, myositis and myasthenia gravis).

RESULTS OF PHASE 2
Patient Vignettes

PR (Confirmed) in Patient with MSS CRC Without Liver Metastases (Patient A) 47% Reduction in Target Lesions at 13 Weeks, Decrease in CEA and ctDNA

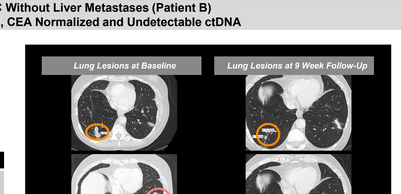
- 50 year-old male
- 4 prior lines of therapy:
  - FOLFOXIRI + bevacizumab
  - FOLFIRI + panitumumab
  - FOLFOX + bevacizumab
  - Regorafenib
- PR (confirmed) with a 47% decrease in target lesions SOD, accompanied by:
  - Carcinoembryonic antigen (CEA) serum tumor marker decrease from 17.7 (C1D1) to 10.7 (C3D1)
  - Multi-log fold decrease in ctDNA
  - Improvement of symptoms, such as cough



PR (Confirmed) in Patient with MSS CRC Without Liver Metastases (Patient B) 57% Reduction in Target Lesions at 18 Weeks, CEA Normalized and Undetectable ctDNA

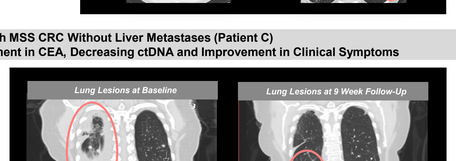
- 63 year-old female
- 2 prior lines of therapy:
  - FOLFOX
  - 5FU and irinotecan
- PR (confirmed) with a 57% reduction in target lesions SOD, accompanied by:
  - 100% ctDNA reduction while on treatment (multi-log fold change to non-detectable)
  - Significant decrease in serum tumor marker CEA

	Screening	C3	C4	C5	C7
CEA value (ng/ml)	192.9	23.6		3.5 (normal)	1.9 (normal)
Target lesions SOD	74 mm		47 mm	35 mm	32 mm



PR (Unconfirmed) in Patient with MSS CRC Without Liver Metastases (Patient C) 35% Reduction in Target Lesions at 9 weeks, Improvement in CEA, Decreasing ctDNA and Improvement in Clinical Symptoms

- 67 year-old female
- 6 prior lines of therapy:
  - FOLFOX
  - Capecitabine + bevacizumab
  - 5FU + bevacizumab
  - 5FU + panitumumab
  - FOLFIRI + panitumumab
  - 5FU + panitumumab
- PR (pending confirmation)* with a 35% reduction in target lesions SOD accompanied by:
  - Substantial decreases in ctDNA CEA serum tumor marker decrease from 7.95 (C1D1) to a normal value 2.8 (C3D1)
  - Improvement of symptoms, such as cough

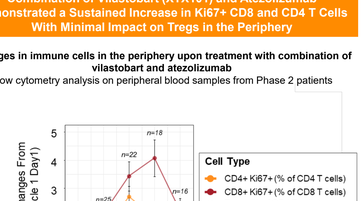


* Initial assessment of unconfirmed PR by investigator at 9 weeks (official radiology assessment pending)

Combination of Vilastobart (XTX101) and Atezolizumab Demonstrated a Sustained Increase in Ki67+ CD8 and CD4 T Cells With Minimal Impact on Tregs in the Periphery

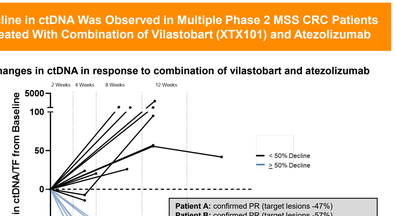
Changes in immune cells in the periphery upon treatment with combination of vilastobart and atezolizumab

Flow cytometry analysis on peripheral blood samples from Phase 2 patients



Decline in ctDNA Was Observed in Multiple Phase 2 MSS CRC Patients Treated With Combination of Vilastobart (XTX101) and Atezolizumab

Changes in ctDNA in response to combination of vilastobart and atezolizumab



Available blood plasma samples (baseline and on-treatment) were analyzed with an analytically validated next generation sequencing ctDNA assay, Guardant Infinity - a multi-omic assay that identifies somatic alterations across >750 cancer-related genes and measuring thousands of differentially methylated regions to produce a TF score at each timepoint. A negative 100% indicates ctDNA negative status.

Data cutoff date: January 13, 2025

Abbreviations: ADCC: antibody-dependent cell-mediated cytotoxicity; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BOR: best overall response; C#D#: Cycle # Day #; CEA: Carcinoembryonic Antigen; CRC: colorectal cancer; ctDNA: Circulating Tumor DNA; CTLA-4: cytotoxic T-Lymphocyte Associated Protein 4; DCR: disease control rate; dMMR: deficient mismatch repair; ECOG PS: Eastern Cooperative Oncology Group Performance Status; Fc: fraction crystallizable; FcγR: fraction crystallizable gamma receptor; irAE: immune-related adverse event; mAb: monoclonal antibody; MMP: matrix metalloprotease; MSI-H: microsatellite instability-high; MSS: microsatellite stable; NSCLC: non-small cell lung cancer; ORR: objective response rate; PD-L1: programmed death receptor ligand 1; PR: partial response; Q3W: every 3 weeks; Q6W: every 6 weeks; SOD: sum of diameters; (i)RECIST: (immune) Response Evaluation Criteria in Solid Tumors; RP2D: recommended phase 2 dose; SD: stable disease; TF: tumor fraction; TRAE: treatment related adverse event: Treg: regulatory T-cell.

References:
1. Jenkins et al., *J Immunother Cancer* 2023 Dec 12;11(12):e007785
2. Bullock et al. ESMO GI 2023
3. Davar et al. ESMO IO 2023
4. Davar et al. SITC 2024, data updated as of Jan 6th, 2025
5. Sahin et al, 2022 ASCO Educational Book

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