Plasma Tumor Mutational Burden (pTMB) Enriched for Response to Vilastobart in Combination with Atezolizumab in Patients with Microsatellite Stable (MSS) Metastatic Colorectal Cancer (mCRC)

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Abstract 1315

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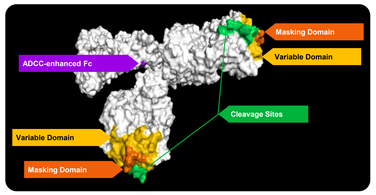
BACKGROUND

MSS mCRC Remains a Significant and Growing Unmet Need

- In the US, CRC is 2nd in cancer mortality and the leading cause of death from cancer in young men (<50 years), often presenting late-stage[1]
  - Only ~5% of mCRC is MSI-H.[2] ICIs are approved in this setting[3,4]
  - Response rates for approved agents in third-line+ mCRC (trifluridine + tipiracil, regorafenib and fruquintinib) are low (0<6%[5-8]), and approved ICIs in MSI-H CRC have minimal efficacy in MSS mCRC (<5% ORR)[9,10]
  - ~95% of mCRC is MSS and ~1/3 of patients do not have liver metastases, representing a population with an unmet medical need[11]
- Next generation anti-CTLA-4 agents in development have activity in MSS mCRC without liver metastases when combined with anti-PD-1/PD-L1.[12-15] However, tolerability is a limitation of systemically active, unmasked agents, including high imAEs and/or discontinuation rates[12]

Vilastobart: Tumor-Activated, Anti-CTLA-4 in Phase 2 Development



- Vilastobart is a tumor-activated, Fc-enhanced high-affinity binding anti-CTLA-4 designed to focus activity toward tumors while minimizing systemic exposure and the potential for AEs
- In a non-biomarker selected population, we previously reported vilastobart in combination with atezolizumab (Tecentriq®) had an ORR of 26%, including 7 PRs (6 confirmed) per RECISTv1.1, in heavily pretreated patients with MSS mCRC without liver metastases together with a differentiated safety profile, consistent with the tumor-activated design of vilastobart[15]

Tissue-Based TMB as a Predictive Biomarker of ICI Response

- High TMB (≥10 mut/Mb, TMB-H) is a biomarker predictive of response to ICI and is an approved tissue-based companion diagnostic for pembrolizumab in a tumor agnostic indication for advanced solid tumors[3]
- Data suggest <10% of patients with MSS mCRC have TMB-H tumors assessed using a tissue-based assay.[16-18] In contrast to other tumor types, tissue TMB did not predict for response to ICI in MSS mCRC:
  - Pembrolizumab response in tissue TMB-H MSS mCRC is <10% ORR[19, 20]
  - Tissue TMB-H was not predictive of response for novel anti-CTLA-4 agents active in MSS mCRC without liver metastases[12]

Newer Plasma-Based TMB May Have Enhanced Predictive Performance

- Plasma-based TMB assays:
  - Capture spatial and temporal tumor heterogeneity, which provides a comprehensive picture of mutational load, while tissue TMB captures mutations from one area in a single-site biopsy specimen and is typically obtained at the time of diagnosis
  - Provide real-time tumor mutational status contemporaneous with treatment without invasive procedures
- In MSS mCRC, studies have indicated plasma TMB may be a predictive biomarker for response to novel ICIs
  - Median plasma TMB was significantly higher than median tissue TMB (15.3 vs 6.5 mut/Mb) with most patients' plasma TMB ≥10 mut/Mb[21]
  - Plasma TMB-H correlated with improved OS for combination tremelimumab and durvalumab compared with best supportive care, while tissue TMB had no predictive value[22]

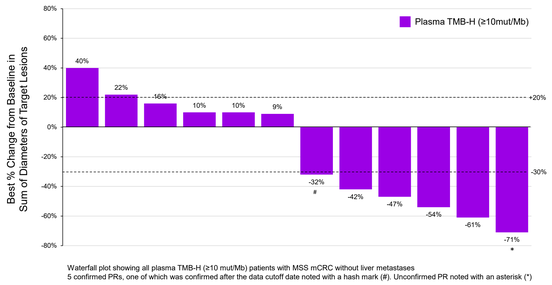
High Prevalence of Plasma TMB-H Demonstrated in a Real-World Dataset of Patients With MSS mCRC

- ~55% of non–MSI-H CRC patients were TMB-H (>10 mut/Mb) in an analysis of the GuardantINFORM real-world clinical-genomic database, based on ~8,000 patients who received the Guardant360 Liquid (Infinity) assay, had MSS disease and had a reportable TMB result

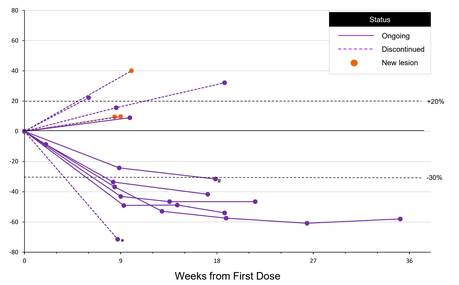
STUDY DESIGN AND METHODS

- This Phase 2 study (NCT04896697) evaluated vilastobart (100mg Q6W) in combination with atezolizumab (1200mg Q3W) in patients with MSS mCRC who had ≥1 prior chemotherapy regimen in the metastatic setting[15]
- In this retrospective analysis, we explored whether plasma TMB could serve as a predictive biomarker in patients with MSS mCRC without liver metastases and enrich for response to treatment with vilastobart in combination with atezolizumab
- Baseline plasma TMB was assessed using the Guardant-Infinity Liquid Assay. We evaluated the relationship between plasma TMB status (plasma TMB-H ≥10 mut/Mb; plasma TMB-L <10 mut/Mb) and best overall response using 2-sided Fisher's Exact Test
- As of May 12, 2025, 44 heavily pretreated patients with MSS mCRC were treated with vilastobart in combination with atezolizumab, including 27 without liver metastases. Of the patients without liver metastases, 24 had sufficient ctDNA at baseline to determine plasma TMB status
- Safety is reported for all 44 patients with MSS mCRC (with and without liver metastases) treated with vilastobart in combination with atezolizumab in the Phase 2 study

40% ORR, DEEP TUMOR REDUCTIONS, AND DURABLE RESPONSES IN PATIENTS WITH MSS mCRC WITHOUT LIVER METASTASES WHO WERE PLASMA TMB-H



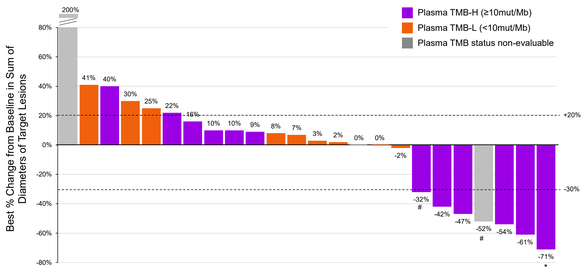
Waterfall plot showing all plasma TMB-H (≥10 mut/Mb) patients with MSS mCRC without liver metastases
5 confirmed PRs, one of which was confirmed after the data cutoff date noted with a hash mark (#). Unconfirmed PR noted with an asterisk (*)



Spider plot showing all plasma TMB-H (≥10 mut/Mb) patients with MSS mCRC without liver metastases
5 confirmed PRs, one of which was confirmed after the data cutoff date noted with a hash mark (#). Unconfirmed PR noted with an asterisk (*)

- In the plasma TMB-H population, ORR was 40% (95% CI:16%, 68%), with 5 of 6 responses confirmed, while ORR in TMB-L patients (n=9) was 0% (p=0.05)
- Responses were deep and durable in patients with MSS mCRC without liver metastases who were plasma TMB-H

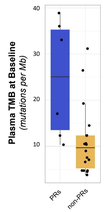
PLASMA TMB SIGNIFICANTLY CORRELATED WITH RESPONSE IN PATIENTS WITH MSS mCRC WITHOUT LIVER METASTASES



Waterfall plot showing plasma TMB status for all patients with MSS mCRC without liver metastases
Of 2 patients with 0% best change, one was TMB-L, and the other was non-evaluable for TMB status
6 confirmed PRs, 2 of which were confirmed after the data cutoff date noted with a hash mark (#). Unconfirmed PR noted with an asterisk (*)

Baseline TMB Threshold ≥10 mut/Mb Captured All TMB-Evaluable Responders

Plasma TMB by Best Overall Response



	MSS mCRC Without Liver Metastases		
	Total n (%) (n=27)	PR (n=7)	Non-PR (n=20)
Plasma TMB evaluable	24	6	18
Plasma TMB-H ≥10 mut/Mb	15 (63%)	6	9
Plasma TMB-L <10 mut/Mb	9 (38%)	0	9
Plasma TMB non-evaluable	3	1	2

2-sided Fisher's Exact, *p=0.05*

Boxplot showing plasma TMB scores at baseline with respect to best overall response (non-PR: includes stable disease and progressive disease)

- Overall, 63% (n=15) of TMB-evaluable patients (n=24) were plasma TMB-H
- 100% (n=6) of TMB-evaluable responders were plasma TMB-H
- Plasma TMB status significantly correlated with response (p=0.05)

VILASTOBART IN COMBINATION WITH ATEZOLIZUMAB WAS GENERALLY WELL-TOLERATED IN HEAVILY PRETREATED PATIENTS

TRAEs ≥ 10% incidence (any Grade) or Grade 3/4 TRAEs with ≥ 5% incidence	Total Safety Population N=44	
	Any Grade n (%)	Grade 3 n (%)
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)
Dose Reduction and Treatment Discontinuation n (%)		
Vilastobart dose reduction due to TRAE+	1 (2)	
Treatment discontinuation due to TRAE‡	2 (5)	

TRAEs are related to vilastobart or atezolizumab
+ Dose reduction of atezolizumab was not permitted per protocol
‡ Reflects discontinuation of both vilastobart and atezolizumab

- No Grade 5 TRAEs and 2 Grade 4 TRAEs (reversible laboratory abnormalities)
- 11 patients (25%) required steroids or other immunosuppression for imAEs
- 3 patients (7%) experienced colitis

CONCLUSIONS

- Vilastobart in combination with atezolizumab demonstrated a 40% ORR in heavily pretreated patients with MSS mCRC without liver metastases who were plasma TMB-H (≥10 mut/Mb). Responses were deep and durable
- Plasma TMB significantly correlated with response (p=0.05) and all responders with known TMB status were plasma TMB-H
- In MSS mCRC, approximately 55% of patients were estimated to be plasma TMB-H, making this a meaningful subset of patients with a high unmet need
- These encouraging data suggest plasma TMB may be a promising predictive biomarker to enrich for response to vilastobart in combination with atezolizumab in MSS mCRC patients without liver metastases

ABBREVIATIONS: AEs: adverse events; ADCC: antibody-dependent cellular cytotoxicity; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CI: confidence interval; CRC: colorectal cancer; ctDNA: circulating tumor DNA; CTLA-4: cytotoxic T-Lymphocyte Associated Protein 4; Fc: fraction crystallizable; ICIs: immune checkpoint inhibitors; imAEs: immune-mediated adverse events; Mb: megabase; mCRC: metastatic colorectal cancer; mut: mutations; MSI-H: microsatellite instability-high; MSS: microsatellite stable; OS: overall survival; ORR: objective response rate; PD-1/PD-L1: programmed cell death (ligand)-1; PR: partial response; pTMB: plasma tumor mutational burden; RECISTv1.1: Response Evaluation Criteria in Solid Tumor version 1.1; TMB: tumor mutational burden; TMB-H: tumor-mutational burden high (≥10 mut/Mb); TMB-L: tumor mutational burden low (<10 mut/Mb); TRAE: treatment-related adverse events; Q3W: every 3 weeks; Q6W: every 6 weeks; WBC: white blood cells.

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