Clinicopathologic Characteristics of Patients with Metastatic Colorectal Cancer with Molecular Responses Following Treatment with an Individualized Neoantigen Vaccine Regimen

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Abstract

Background : Individualized neoantigen cancer vaccines aim to benefit patients by generating strong, durable neoantigen-specific CD8 T cells. Previous data showed extended overall survival (OS) in patients with metastatic colorectal cancer (CRC) who achieved a molecular response (MR) versus those who did not after individualized neoantigen vaccination in combination with nivolumab and ipilimumab (Catenacci et al ESMO 2021). We report updated OS and exploratory analysis of clinicopathologic features of patients achieving a MR.

Methods: Patients with solid tumors who had received routine chemotherapy were treated in a Phase 1/2 first-in-human study (NCT03639714). The vaccine regimen consisted of sequential administrations of chimpanzee adenovirus and self-amplifying mRNA (samRNA) vectors encoding 20 patient-specific neoantigens in combination with nivolumab (IV 480 mg Q4W) and ipilimumab (SC 30 mg).

Results: Thirteen of 29 patients treated had MSS-CRC. Six of these 13 had stable disease (SD) and 7 had progressive disease (PD) per RECIST v1.1. Six patients achieved a MR defined as ≥ -30% reduction in ctDNA. Patients with a MR had prolonged OS compared to patients without a MR (see Table 1). MR was not associated with primary tumor location, liver metastases or KRAS mutations and patients with a MR were not enriched for higher tumor mutation burden (TMB), PD-L1, or T cell inflamed gene expression profiles (GEP) and had similar baseline ctDNA values based on variant allele frequency (VAF) (p-value=0.204) (see Table 1).

Phase 1: Dose Escalation (N=14)

	Dose Level 1 N=3	Dose Level 2 N=3	Dose Level 3 N=2	Dose Level 4 N=6
Prime ChAd	10^{12} viral particles	→	→	→
Boost samRNA	30 μg	100 μg	100 μg	300 μg
Ipilimumab (SC)	-	-	30 mg	30 mg
Nivolumab (IV)	480 mg	→	→	→

Phase 2: Tumor-Specific Expansion Cohorts

MSS-CRC GEA NSCLC

Demographics and Safety

Demographics and Tumor Types	n=29
Age: mean (range)	**60 (38-77)**
Gender: Female/Male	**11/18**
Tumor Types	
Microsatellite-stable (MSS) Colorectal Cancer	13
Median number of prior therapies (range)	2 (2-3)
Gastroesophageal adenocarcinoma (GEA)	13
Median number of prior therapies (range)	1 (1-2)
Non-small cell lung cancer	3
Median number of prior therapies (range)	2 (2)
Prior anti-PD(L)1 therapy	3

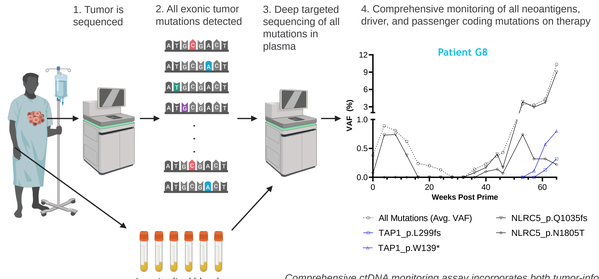
- No DLTs
- 1 patient discontinued due to a TRAE

Safety	n = 29*	
	Grade 1/2	Grade 3/4
Treatment-related adverse events ≥ 10%		
Fever/pyrexia	13	-
Fatigue	10	-
Injection site pain	8	-
Diarrhoea	7	-
Musculoskeletal pain	4	-
Chills	4	-
Decreased appetite	4	
Rash	3	-

* All patients treated with concurrent nivolumab

Date cut-off: 31 Aug 2022

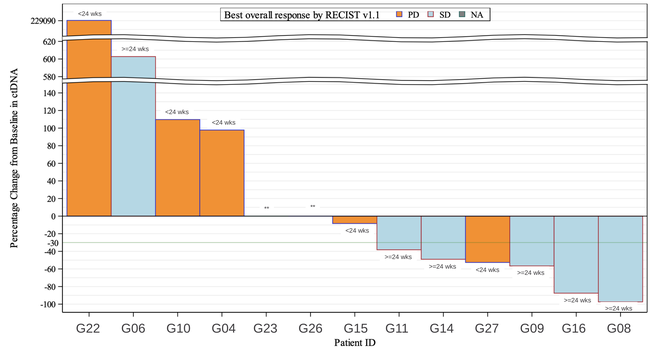
Tumor-informed ctDNA monitoring for all variants on a per patient basis



Attribute	Description
Assay Type	Tumor-informed with tumor-naive regions
Sample type	cfDNA Fragmented (enzymatic or mechanical), high-quality DNA from PBMCs, cells, or tissue
Sample input	≥5ng; For optimal sensitivity ~30ng input (9,000 haploid genomes)
UMI	Duplex
Enrichment	Hybrid capture
Limit of Detection	Analytical validation ongoing; ≈0.1%
Mean number of variants targeted for ctDNA monitoring in patients with MSS-CRC (range)	106 (67, 259)

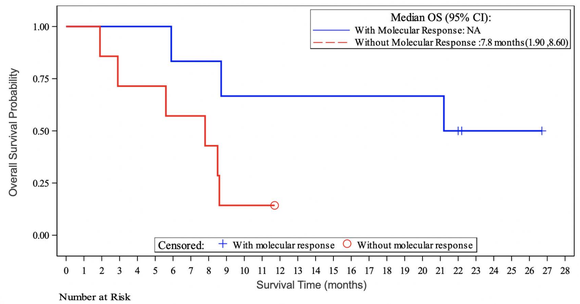
Comprehensive ctDNA monitoring assay incorporates both tumor-informed and naïve design to capture all coding variants from patient tumors identified in neoantigen selection process and includes a static panel to monitor known drivers and genes involved in immunotherapy resistance.

Figure 1. Multiple patients with MSS-CRC have a molecular response and this is associated with clinical benefit.



*Molecular response defined as a reduction of at least 30% in mean variant allele frequency (VAF) relative to baseline at any time following initiation of study treatment. Duration of treatment annotated as < or >= 24 weeks per patient. ** ctDNA data is not available*

Figure 2. Patients with molecular response have prolonged overall survival compared to those without molecular response.



OS in patients with MSS-CRC	Reduction in Mean VAF to define molecular response	
	30% cut-off	50% cut-off
Median OS (95% CI)		
With MR	NR (5.90, NA)	NR (5.90, NA)
Without MR	7.8 (1.90, 8.60)	8.5 (1.90, 21.20)
OS rate at 12 mo		
With MR	67%	50%
Without MR	NA	33%
OS rate at 18 mo		
With MR	67%	50%
Without MR	NA	33%

NA = not achievable; NR = not reached

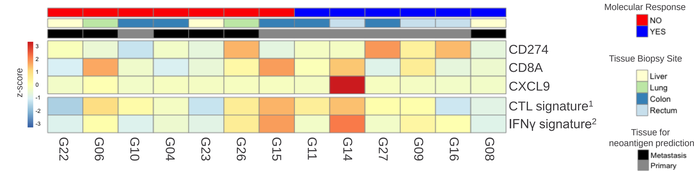
Date cut-off: 31 Aug 2022

Table 1. No clinical or pathologic features associate with patients who have molecular response and prolonged overall survival.

	Overall Survival (median in months)	Primary Tumor Location (# patients)	Presence of liver lesions (# patients)	Median TMB (mutations per megabase, range)	PD-L1 (# patients)	Baseline ctDNA (mean VAF, range)	SD per RECISTv1.1 (# patients)
MR (n=6)	Median: NR 12-mo rate: 67%	Colon: 2 Rectum: 3 Both: 1	4	2.9 (2.1-6.6)	<1%: 4 NE: 2	3.2% (0.0–10.1)	5
Without MR (n=7)	Median: 7.8 12-mo rate: NA	Colon: 5 Rectum: 1 Both: 1	6	3.6 (2.5-17.6)	<1%: 5 NE: 2	7.7% (0.0–17.3)	1

MR = molecular response; NA = not achievable; NE = not evaluable; NR = not reached; SD = stable disease; VAF = variant allele frequency

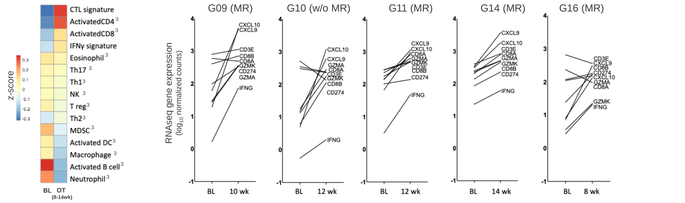
Figure 3. Patients with a molecular response do not have inflamed tumors prior to vaccination.



Heatmap of RNAseq expression of immune related genes and gene signatures from manufacturing biopsies from MSS-CRC patients. CD274, CD8A and CXCL9 expression represented as z-scores and CTL and IFNγ signatures derived from average z-scores of gene sets. RNAseq expression was derived from DEseq2 normalized RSEM expected counts.

[1]CTL – cytotoxic T lymphocyte gene expression signature (PMID: 30127393)
[2]IFNγ – interferon gene expression signature (PMID: 28650338)

Figure 4. Induction of IFNγ–related genes in MSS-CRC tumors indicative of increased immune reactivity following vaccination.



Left- Immune cell type and activation signatures from 5 patients with available paired pre and post vaccine biopsies (average z-score values). Right – Normalized RSEM expected counts of individual IFNγ –related genes from the same 5 patient paired biopsies (right).

[3]Immune subtype signatures (PMID: 29628290)

Conclusion

- Patients who achieved MR had extended OS compared with those patients without MR.
- Patients with a MR were not enriched based on primary tumor location, presence of liver metastases, or known correlates of response to checkpoint inhibitors.
- Vaccination induced IFNγ-related genes reflecting increased immune activation within the tumor microenvironment.
- A randomized, controlled Phase 2/3 trial of this individualized neoantigen immunotherapy is underway in patients with metastatic CRC in the 1L maintenance setting to confirm these preliminary observations (NCT05141721, GRANITE-CRC-1L).