19P Circulating tumor DNA (ctDNA) dynamics predict clinical recurrence in liver-limited metastatic colorectal cancer (mCRC) patients resected after first-line systemic treatment

Vittorio Studiale, Roberto Moretto, Marco Germani, Martina Carullo, Farahnaz Islam, Guglielmo Vetere, Veronica Conca, Victoria Chiou, Christine Lo, Seung Won Hyun, Ada Taravella, Matteo Landi, Filippo Ghelardi, Chithra Sangli, Kate Sasser, Sabina Murgioni, Michele Prisciandaro, Riccardo Cerantola, Halla Nimeiri, Chiara Cremolini

Disclosure statement: V.S. has nothing to disclose

BACKGROUND

Liver-limited disease (LLD) occurs in 20-30% of mCRC patients. While liver resection offers a long-term survival benefit in 20-30% of those patients, most relapse within two years. ctDNA is a promising tool for detecting minimal residual disease (MRD) after surgical resection and may predict recurrence in mCRC patients undergoing liver resection after first-line (1L) treatment.

METHODS

mCRC patients (N=116) with initially unresectable LLD and R0/R1 resected after upfront chemotherapy were selected from three Italian academic centers. Blood samples were collected prospectively at baseline (T_0), pre-surgery (T_{PrS}) and post-surgery (T_{PoS}). T_0 samples were evaluable for 82 patients, T_{PrS} for 116 and T_{PoS} for 60. T_{PoS} samples were collected between 0-4 months post-surgery. Biobanked plasma samples were analyzed with the Tempus xM MRD assay (xM), a tumor-naïve ctDNA MRD assay that integrates methylation and genomic variant classifiers to deliver a binary MRD call blinded to clinical outcomes. Relapse-free survival (RFS) is assessed, defined as the time from the index date (date of resection of liver metastases for pre-surgery MRD status or date of T_{PoS} sample collection for post-surgery MRD status) to the date of recurrence or death from any cause within 24 months. A patient is classified as censored if they do not have a recurrence, or are still alive after 24 months, or lost to follow-up. Reported p-values were obtained using the Wald test, applying a one-sided significance level of 5%.

Figure 1. Workflow

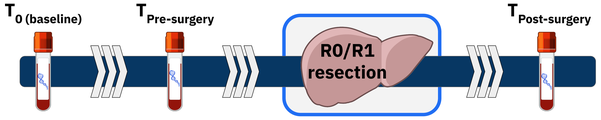


Table 1. Cohort Characteristics

	Overall, n=60	MRD status at T_{PoS}	
		MRD+, n=22	MRD-, n=38
Age at enrollment			
Mean (SD)	58.22 (11.09)	61.64 (11.19)	56.24 (10.69)
Median	59	59.5	57
IQR	53.00 - 65.25	55.00 - 72.25	50.25 - 64.50
Min / Max	29 / 79	39 / 79	29 / 76
Sex			
Female	25 (41.7%)	9 (40.9%)	16 (42.1%)
Male	35 (58.3%)	13 (59.1%)	22 (57.9%)
MSI-High status			
Positive	1 (1.7%)	0 (0.0%)	1 (2.6%)
Negative	57 (95.0%)	21 (95.5%)	36 (94.7%)
RAS status			
Positive	16 (26.7%)	4 (18.2%)	12 (31.6%)
Negative	44 (73.3%)	18 (81.8%)	26 (68.4%)
BRAF mutation status			
Positive	1 (1.7%)	1 (4.5%)	0 (0.0%)
Negative	59 (98.3%)	21 (95.5%)	38 (100.0%)
Adjuvant chemotherapy			
No	24 (40.0%)	12 (54.5%)	12 (31.6%)
Yes	36 (60.0%)	10 (45.5%)	26 (68.4%)
Median follow-up (in months)	11.3	7.3	18.8

RESULTS

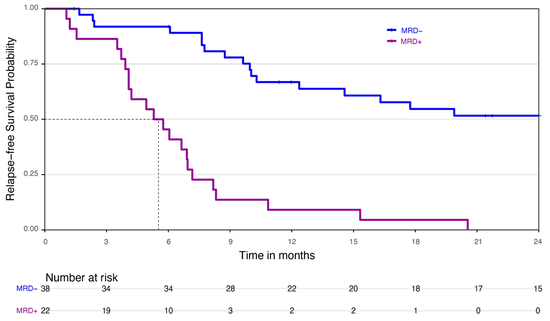
Table 2. Post-surgery (T_{PoS}) clinical performance

	Recurrent	Non-Recurrent	Total
MRD+	22	0	22
MRD-	17	21	38
Total	39	21	60

Sensitivity	56.4% (95% CI: 39.6%, 72.2%)
Specificity	100% (95% CI: 83.9%, 100%)
PPV	100% (95% CI: 84.6%, 100%)
NPV	55.3% (95% CI: 38.3%, 71.4%)

The xM assay demonstrated a clinical sensitivity of 56.4% and a clinical specificity of 100% in post-surgery patients (n=60).

Figure 2. Association between MRD status and RFS at T_{PoS}

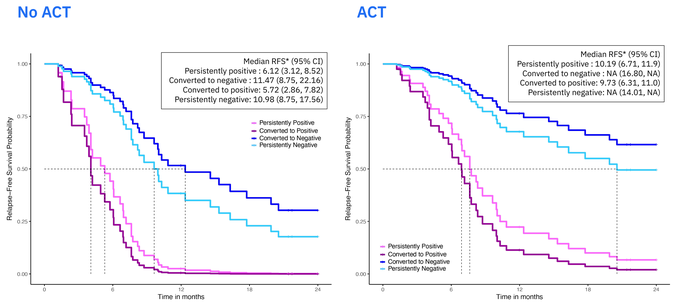


	MRD-, n = 38	MRD+, n = 22
Median RFS*, in months (95% CI)	NA (10.29, NA)	5.52 (3.91, 6.94)
HR[a] (95% CI), MRD+ vs MRD- (Ref.)	6.66 (3.31, 13.39)	

*Median RFS unadjusted for treatment with ACT
[a] HR after adjusting for ACT status

T_{PoS} MRD status was associated with RFS with the MRD- group experiencing longer median RFS (mRFS) than MRD+ (HR = 6.7, mRFS >24 months vs. 5.5 months, p<0.001), adjusting for ACT status. Overall n=60.

Figure 3. Prognostic impact of ctDNA dynamics (MRD status change) on RFS from T_{PrS} to T_{PoS}



MRD Status Change	N	HR [b] (95% CI)	Median RFS* (95% CI)
Persistently positive	9	Reference	5.29 (3.91, 15.32)
Converted to negative	13	0.18 (-0.54, 0.9)	NA (9.63, NA)
Converted to positive	12	1.45 (0.77, 2.14)	5.90 (1.55, 8.19)
Persistently negative	20	0.26 (0.02, 0.5)	16.31 (7.63, NA)

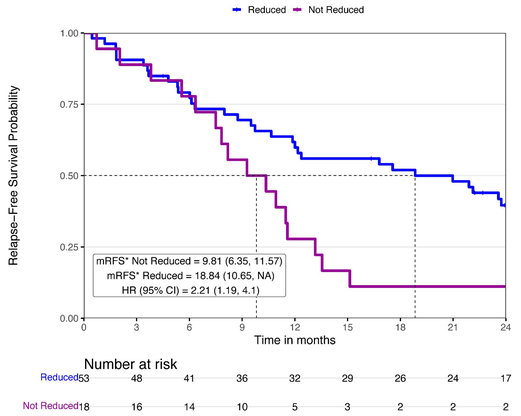
[b]adjusting for ACT status
*Median RFS unadjusted for treatment with ACT

Patients who were persistently positive by methylation calls (n=20) or converted to negative (n=13) from T_{PrS} to T_{PoS} experienced longer RFS (mRFS 16.3 months and >24 months respectively). Those who remained persistently positive (n=9) or converted to positive (n=12) had a mRFS of 5.3 and 5.9 months respectively. Overall n=54.

Plots show comparisons of mRFS* in patients without adjuvant chemotherapy (ACT; left) versus with ACT (right).

*mRFS is the median RFS unadjusted for treatment with ACT

Figure 4. Impact of ctDNA dynamics (reduction in VAF) between baseline and pre-surgery in terms of RFS



Patients with variant allele fraction (VAF) reduction of ≥50% from T0 to TPrS (N=53) experienced longer RFS than those who had <50% reduction or increase in VAF (N=18) (HR 2.21, mRFS 18.8 mos vs. 9.8 mos, p=0.012). Overall n = 71

*mRFS is the median relapse-free survival time unadjusted for treatment with ACT

SUMMARY

- xM demonstrates remarkable performance in predicting clinical recurrence and correlation to RFS at T_{PoS} in LLD mCRC patients resected after upfront systemic therapy
- Patients with a ≥ 50% VAF reduction over baseline experience longer relapse-free survival (RFS) following surgery