Longitudinal clinical performance of a novel tumor-naïve minimal residual disease assay in resected stage II and III colorectal cancer patients: A subset analysis from the GALAXY study in CIRCULATE-Japan

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Published Abstract Number: **3618**

INTRODUCTION

The presence of circulating tumor DNA (ctDNA) can identify patients at higher risk of disease recurrence. Longitudinal surveillance of ctDNA may enable early identification of patients who are likely to relapse and presents a window of opportunity for early interventions to improve outcomes. A tumor-naïve plasma-only approach for minimal residual disease (MRD) assessment accelerates turnaround time, enabling rapid adjuvant chemotherapy (ACT) treatment decisions and ongoing molecular surveillance.

METHODS

Patients with pre-specified eligibility criteria (n=80) were randomly selected from GALAXY in the CIRCULATE-Japan study. Patients were selected for recurrence to 50% while maintaining the stage II:III recurrent/non-recurrent ratio observed in GALAXY. There were 69 evaluable patients for landmark timepoint (LMT) analysis and 74 for longitudinal analysis. LMT was defined as 4 weeks after surgery in pathological stage II or III colorectal cancer (CRC).

Residual plasma samples were analyzed with the Tempus xM MRD assay (xM), a tumor-naïve ctDNA assay for MRD that integrates methylation and genomic variant data to deliver a binary MRD call. Calls were blinded to clinical outcomes.

Longitudinal sensitivity and specificity were assessed based on the LMT sample and all the evaluable longitudinal samples (every 3 months after surgery until recurrence, death, or 24 months follow-up was reached, whichever occurred first).

All blood samples, including those at LMT, were analyzed using an improved analytical pipeline performance relative to previously presented work*. Longitudinal samples (post LMT) were analyzed using the methylation pipeline only.

Figure 1. Methyl and variant pipelines

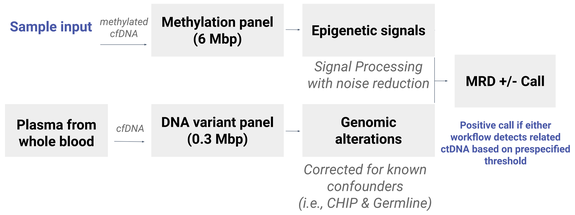


Figure 1. Dual workflow was used at LMT. The methylation workflow alone was used for all subsequent timepoints.

SUMMARY

- xM is a rapid, tumor-naïve MRD assay that demonstrates robust clinical surveillance performance with longitudinal clinical sensitivity of 83.3% (increased from 61% at LMT) and longitudinal specificity of 89.5%.
- xM ctDNA status is a stronger prognostic biomarker to DFS compared to standard of care CEA (Adj. HR 9.69 vs. 2.13).
- xM has an overall mean lead time of 4.66 months & a lead time of 5.62 months for surgery-only patients prior to recurrence.

RESULTS

Figure 2. Clinical follow-up

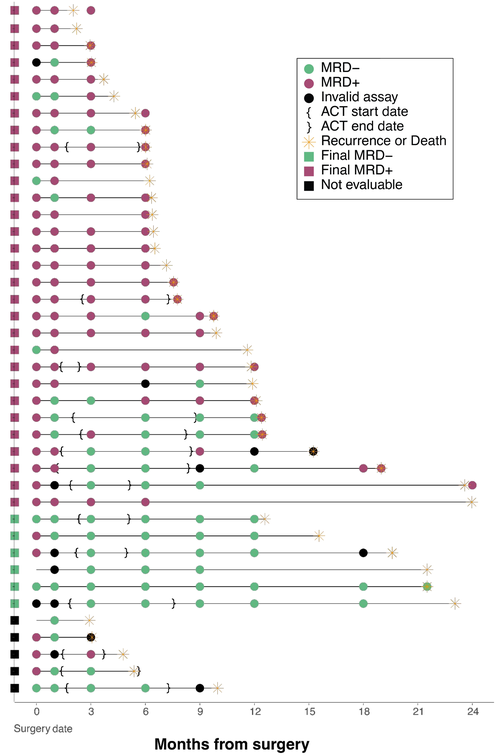


Figure 2. Swimmer plot of recurrent patients (n=41) showing follow-up time, recurrence status, timing of ACT and xM MRD status at baseline, LMT, and longitudinal timepoints. Recurrence includes death events.

Figure 3. Clinical sensitivity and specificity

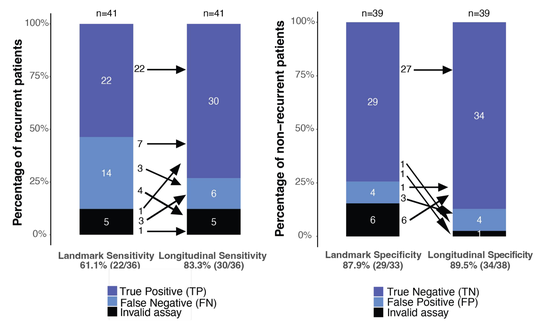
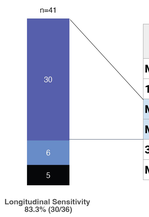


Figure 3. Sensitivity at landmark (61.1%) and longitudinal (83.3%) timepoints in recurrent patients (**left**). Specificity at landmark (87.9%) and longitudinal (89.5%) timepoints in non-recurrent patients (**right**). Arrows show patients who switched MRD status between landmark and longitudinal timepoints.

Table 1. First MRD+ lead time to recurrence or death



	Total (n=30)	Surgery Only (n=22)
Minimum	0.00	0.02
1st Quantile	1.00	2.14
Median	4.77	5.30
Mean	4.66	5.62
3rd Quantile	6.22	6.45
Maximum	22.97	22.97

Table 1. Distribution of lead time (time from first MRD+ call to date of recurrence or death) for TP (n=30) patients. Overall mean lead time defined from first MRD+ to recurrence is 4.66 months. For patients with surgery only treatment, the mean lead time is 5.62 months.

Table 2. Clinical performance by pathological stage

Landmark	Overall	Stage II	Stage III
Sensitivity	61.1% (43.5%, 76.9%)	64.3% (35.1%, 87.2%)	59.1% (36.4%, 79.3%)
Specificity	87.9% (71.8%, 96.6%)	93.3% (68.1%, 99.8%)	83.3% (58.6%, 96.4%)
Adj PPV*	61.4%	75.3%	52.8%
Adj NPV*	87.7%	89.2%	86.6%
Adj HR* (MRD+/MRD-)	7.28	12.25	5.21

Longitudinal	Overall	Stage II	Stage III
Sensitivity	83.3% (67.2%, 93.6%)	91.7% (61.5%, 99.8%)	79.2% (57.8%, 92.9%)
Specificity	89.5% (75.2%, 97.1%)	88.2% (63.6%, 98.5%)	90.5% (69.6%, 98.8%)
Adj PPV*	71.4%	71.1%	72.4%
Adj NPV*	94.4%	97.1%	93.2%
Adj HR* (MRD+/MRD-)	21.9	42.24	18.35

Table 2. Clinical landmark performance **(top)**. Clinical longitudinal performance **(bottom)**. Adj PPV*, Adj NPV*, and Adj HR* are the estimates based on the anticipated true recurrence rate of 24% observed in GALAXY.

Figure 4. 12-week CEA & MRD status & Disease-Free Survival

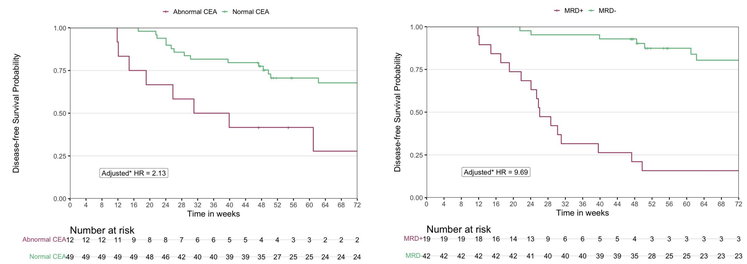


Figure 4. Adjusted hazard ratio (HR) for xM MRD is nearly 5-fold higher compared to carcinoembryonic antigen (CEA) testing at 12 weeks post surgery. Adjusted HR* is the hazard ratio adjusted by anticipated true recurrence rate (24%). The adjusted median DFS time for MRD+ is 25.1 weeks (6.3 months) vs. not reached within 72 weeks (18 months) for MRD-.

***REFERENCE**
Nakamura *et al*, ASCO GI 2024, doi.org/10.1200/JCO.2024.42.3_suppl.21

ACKNOWLEDGMENTS
We thank Dana DeSantis and Adam Hockenberry from the Tempus Science Communications team for poster development.

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