natera™ | Signatera™ Residual disease test (MRD)

Does my patient need adjuvant chemotherapy?

Signatera™ is prognostic and predictive of treatment benefit in colorectal cancer

New study published in Nature Medicine demonstrates the ability of Signatera™ MRD test to identify patients with an increased risk of recurrence and likely to benefit from adjuvant chemotherapy (ACT).

Study Overview: GALAXY arm of CIRCULATE-Japan

- Because high risk features alone often don't tell the whole story, risk stratifying colorectal cancer (CRC) patients can pose a challenge especially when determining next steps
- In this analysis, 1,039 patients with stage II-IV resectable CRC were monitored prospectively using Signatera™ with a median follow-up of 16.74 months
- A subset of patients received adjuvant chemotherapy (ACT) at physician's discretion

Prognostic results

***Nature Medicine* 2023**

18M-DFS for MRD-positive patients	38.4%
18M-DFS for MRD-negative patients	90.5%
HR for DFS at 4 weeks post-op	10.0

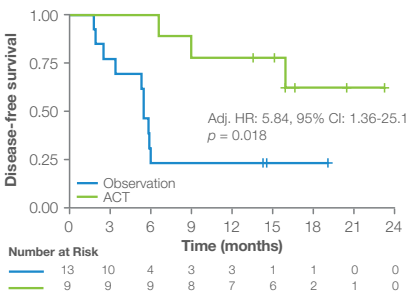
Predictive results

- Signatera™-positive post surgery: significant benefit from adjuvant chemo (HR 6.59 in high-risk Stage II or III)
- Signatera™-negative post surgery: no significant benefit from adjuvant chemo (Absolute risk reduction of only 3.4% at 18 months DFS)
- Signatera™ ctDNA clearance: predictive of treatment efficacy (HR 11 for DFS in ctDNA-positive patients treated with ACT, clearance vs. no clearance)

* DFS = disease free survival

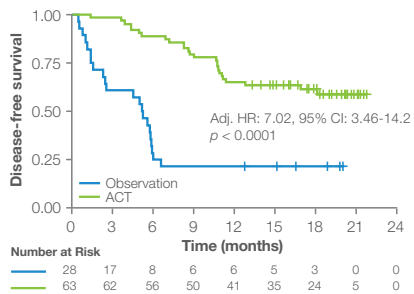
MRD-positive patients benefitted significantly from adjuvant chemotherapy, regardless of stage

High-risk stage II



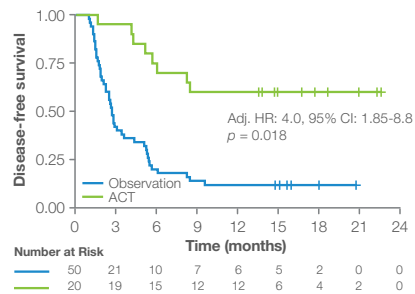
Treatment	Events/N	6M-DFS (95% CI)	12M-DFS (95% CI)	18M-DFS (95% CI)
Observation	10/13	30.8% (9.5-55.4)	23.1% (5.5-47.5)	23.1% (5.5-47.5)
ACT	3/9	100.0% (100.0-100.0)	77.8% (36.5-93.9)	62.2% (21.3-86.4)

Stage III



Treatment	Events/N	6M-DFS (95% CI)	12M-DFS (95% CI)	18M-DFS (95% CI)
Observation	22/28	28.6% (13.5-45.6)	21.4% (8.7-37.8)	21.4% (8.7-37.8)
ACT	25/63	88.9% (78.1-94.5)	65.1% (52.0-75.4)	61.4% (48.0-42.3)

Stage IV

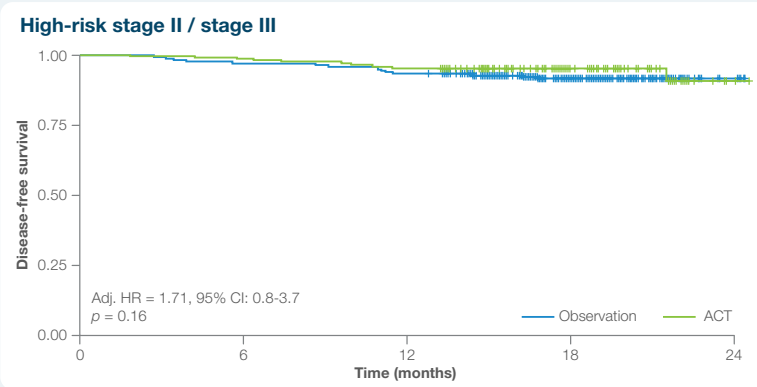


Treatment	Events/N	6M-DFS (95% CI)	12M-DFS (95% CI)	18M-DFS (95% CI)
Observation	44/50	20.0% (10.3-32.0)	12.0% (4.8-22.6)	12.0% (4.8-22.6)
ACT	8/20	75.0% (50.0-88.7)	60.0% (35.7-77.6)	60.0% (35.7-77.6)

No significant treatment benefit trend for MRD-negative patients

DFS in 4 week post-op MRD-negative population (High risk stage II-III)

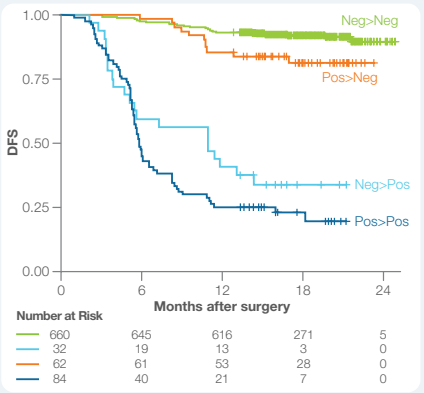
- Patients that were MRD-negative post surgery appeared to derive no significant benefit from ACT (Absolute risk reduction of only 3.4% at 18 months DFS)



ctDNA clearance may serve as a new surrogate end point to predict treatment benefit

DFS by ctDNA dynamics from 4 weeks to 12 weeks post-op

- Patients who were persistently ctDNA-negative had significantly better DFS than patients who did not persistently clear their ctDNA (HR 21)

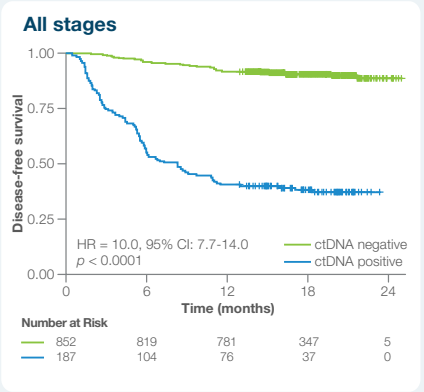


Dynamics	Events/N	18M-DFS	HR	95% CI	P
Neg>Neg	52/660	92.1%	Reference	-	-
Neg>Pos	21/32	33.8%	14.0	8.5-24.0	**<0.001**
Pos>Neg	11/62	81.4%	2.3	1.2-4.4	0.012
Pos>Pos	65/84	22.9%	21.0	14.0-31.0	**<0.001**

ctDNA was a strong prognostic factor in the largest prospective cohort to date

DFS based on ctDNA status at 4 weeks post-surgery

- With a single test at 4w post-op, overall 18M-DFS of 38.4% in the ctDNA-positive group and 90.5% in the ctDNA-negative group, including all treated and non-treated patients



ctDNA	Events/N	6M-DFS (95% CI)	12M-DFS (95% CI)	18M-DFS (95% CI)
ctDNA negative	81/852	96.1% (94.6-97.2)	91.7% (89.6-93.3)	90.5% (88.3-92.3)
ctDNA positive	115/188	55.6% (48.2-62.64)	40.6% (33.6-47.6)	38.4% (31.4-45.5)

Scan to read the publication

Discover more at **natera.com/oncology**

References
1. Kotani D. et al., Molecular residual disease and efficacy of adjuvant chemotherapy in patients with colorectal cancer, *Nature Medicine* v29 Issue 1 Jan 2023

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