Natera, Inc.

ASCO GI Symposium - data review

January 24, 2022

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We discuss these and other risks and uncertainties in greater detail in the sections entitled “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in our periodic reports on Forms 10-K and 10-Q and in other filings we make with the SEC from time to time. Moreover, we operate in a very competitive and rapidly changing environment. New risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statement. In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed in this presentation may not occur and our actual results could differ materially and adversely from those anticipated or implied. 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Update from ASCO GI Symposium, Jan 2022

ASCO Gastrointestinal Cancers Symposium

- **New predictive data in CRC from CIRCULATE Japan – the largest prospective MRD study**
  - Signatera-positive post surgery: benefit significantly from adjuvant chemo
  - Signatera-negative post surgery: no significant benefit from adjuvant chemo
  - Signatera ctDNA clearance: predictive of treatment efficacy
  - Exceptional sensitivity from single MRD timepoint post surgery
- **Expansion into pancreatic and anal cancers**
- **Implications for the field**

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Why predictive data matters

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- Lack of predictive data has been a barrier to adoption into guidelines and clinical practice
- Unproven until now: are MRD-positive patients destined to relapse, or can treatment help?
- Predictive data changes the way doctors counsel patients about the risk/benefit of chemo

Adjuvant Therapy for Stage II Colon Cancer: ASCO Guideline Update, December 2021

"ctDNA was identified as an emerging potential predictive factor; however, insufficient evidence of predictive value of chemotherapy was available to warrant its inclusion in the list of high-risk features within the main recommendation. The Expert Panel anticipates that data on ctDNA will be forthcoming through prospective clinical trials and included in a future version of this guideline."

https://ascopubs.org/doi/full/10.1200/JCO.21.02538.

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Circulate-IDEA Japan: largest prospective MRD study

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2021: ESMO GI[1]

- ~1200 patients enrolled
- ~800 patients analyzed
- Disease free survival stratified by MRD status:
  - Mean ~ 6 months
  - Max ~10 months

2022: ASCO-GI[2]

- ~3000 patients enrolled
- ~1000 patients analyzed
- Disease free survival stratified by MRD status ***and by treatment status***:
  - Mean ~ 12 months
  - Max ~20 months

Building evidence that could change society practice guidelines

[1] Shirasu H, Taniguchi H, Watanabe J, et al. Monitoring molecular residual disease by circulating tumor DNA in resectable colorectal cancer: Molecular subgroup analyses of a prospective observational study GALAXY in CIRCULATE-Japan. ESMO GI, June 30-July 4, 2021

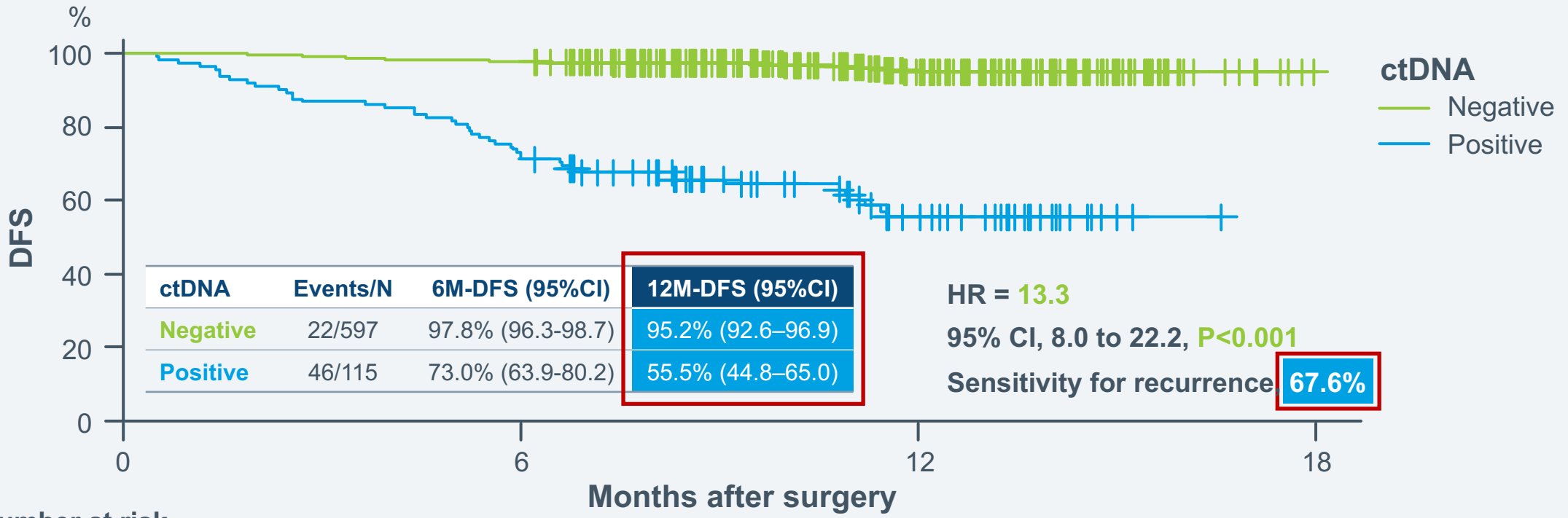
[2] Kotaka et al. Association of circulating tumor DNA dynamics with clinical outcomes in the adjuvant setting for patients with colorectal cancer from an observational GALAXY study in CIRCULATE-Japan. ASCO GI 2022.

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DFS from single timepoint at 4 weeks post surgery (pStage II-III)

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ctDNA	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
Negative	22/597	97.8% (96.3-98.7)	95.2% (92.6–96.9)
Positive	46/115	73.0% (63.9-80.2)	55.5% (44.8–65.0)

Kotaka et al. Association of circulating tumor DNA dynamics with clinical outcomes in the adjuvant setting for patients with colorectal cancer from an observational GALAXY study in CIRCULATE-Japan. ASCO GI 2022.
DFS, disease-free survival; HR, hazard ratio; CI, confidential interval DFS curve was estimated by the Kaplan-Meier method. HR and 95%CI were calculated by the Cox proportional hazard model.

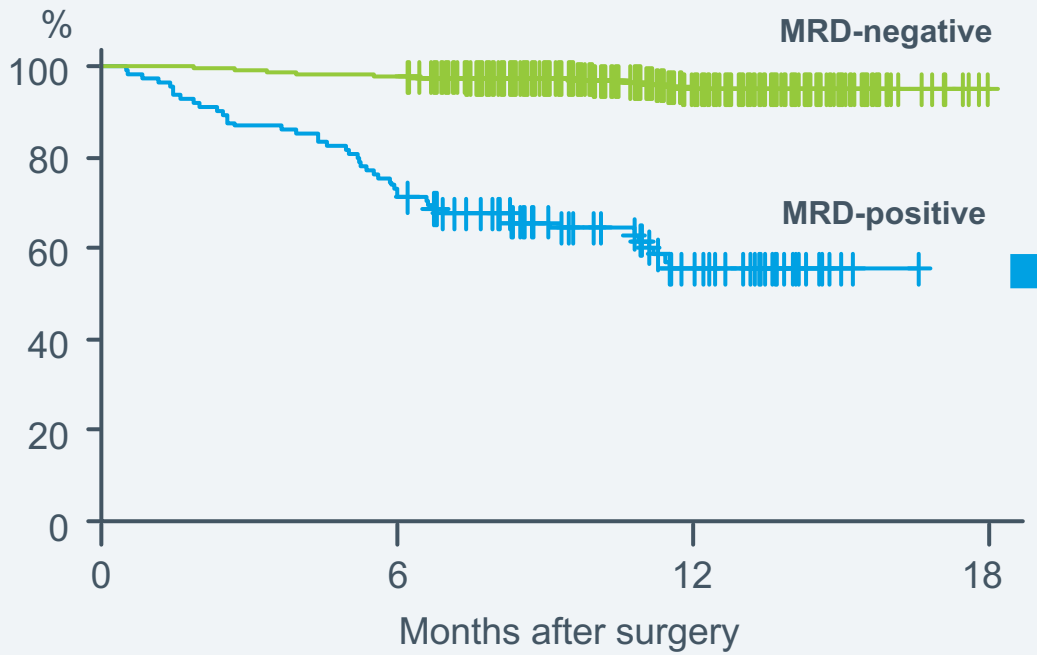
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New predictive data

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Disease-free survival (DFS)



Key questions

Do MRD-positive patients benefit from chemo?

- across all stages of disease?

Kotaka et al. Association of circulating tumor DNA dynamics with clinical outcomes in the adjuvant setting for patients with colorectal cancer from an observational GALAXY study in CIRCULATE-Japan. ASCO GI 2022.

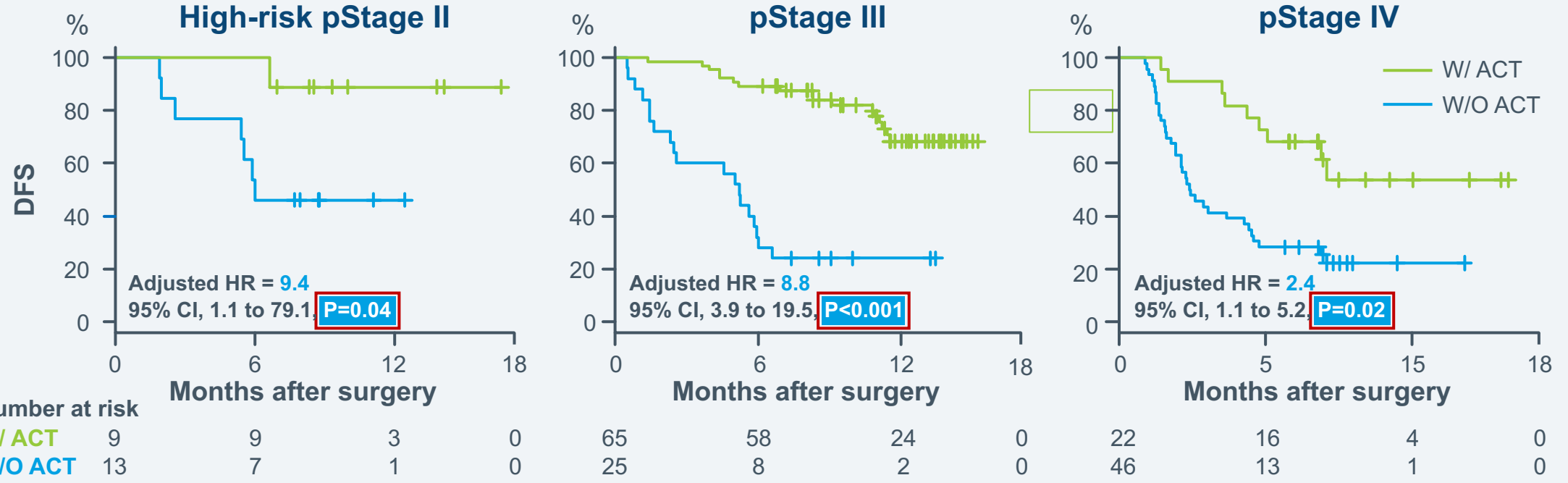
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MRD-positive patients benefit significantly from ACT

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DFS in post-op-4w MRD-positive population



Number at risk

W/ ACT	9	9	3	0
W/O ACT	13	7	1	0

W/ ACT	65	58	24	0
W/O ACT	25	8	2	0

W/ ACT	22	16	4	0
W/O ACT	46	13	1	0

	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	1/9	100% (100–100)	88.9% (43.3–98.4)
W/O ACT	7/13	53.8% (24.8–76.0)	46.2% (19.2–69.6)

	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	17/65	89.2% (78.7–94.7)	68.3% (53.4–79.2)
W/O ACT	19/25	32.0% (15.2–50.2)	24.0% (9.8–41.7)

	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	9/22	72.7% (49.1–86.7)	53.7% (28.4–73.6)
W/O ACT	35/46	28.3% (16.2–41.6)	22.3% (11.2–35.7)

Kotaka et al. Association of circulating tumor DNA dynamics with clinical outcomes in the adjuvant setting for patients with colorectal cancer from an observational GALAXY study in CIRCULATE-Japan. ASCO GI 2022.
HR was adjusted by sex, and performance status. ACT, adjuvant chemotherapy; DFS, disease-free survival; HR, hazard ratio; CI, confidential interval.
DFS curve was estimated by the Kaplan-Meier method. HR and 95%CI were calculated by the Cox proportional hazard model.

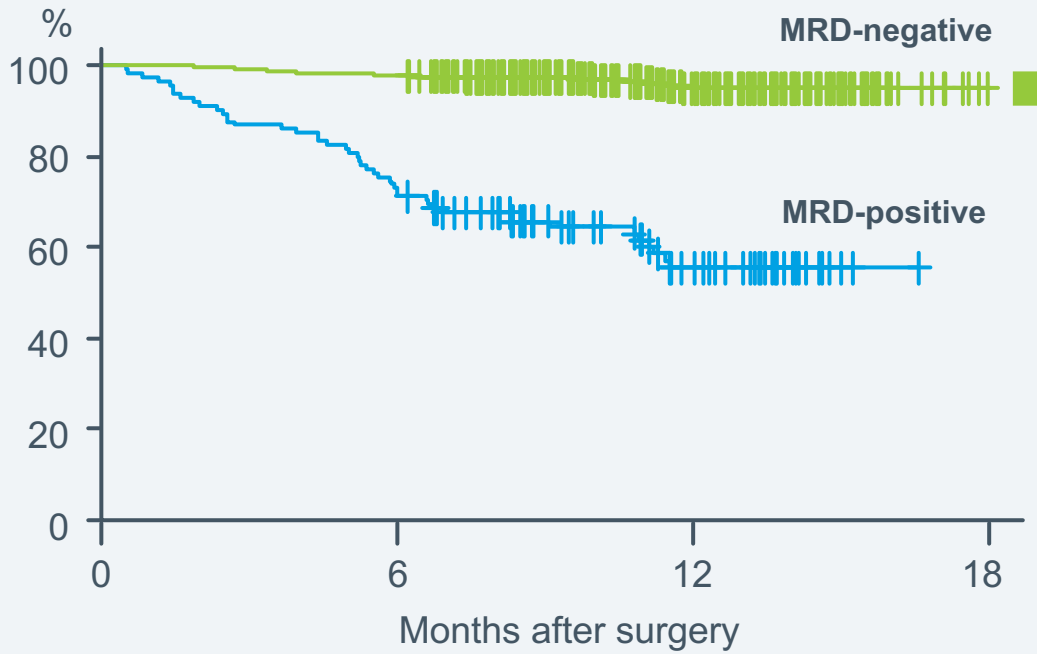
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New predictive data

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Disease-free survival (DFS)



Key questions

Do MRD-negative patients benefit from chemo?

Kotaka et al. Association of circulating tumor DNA dynamics with clinical outcomes in the adjuvant setting for patients with colorectal cancer from an observational GALAXY study in CIRCULATE-Japan. ASCO GI 2022.

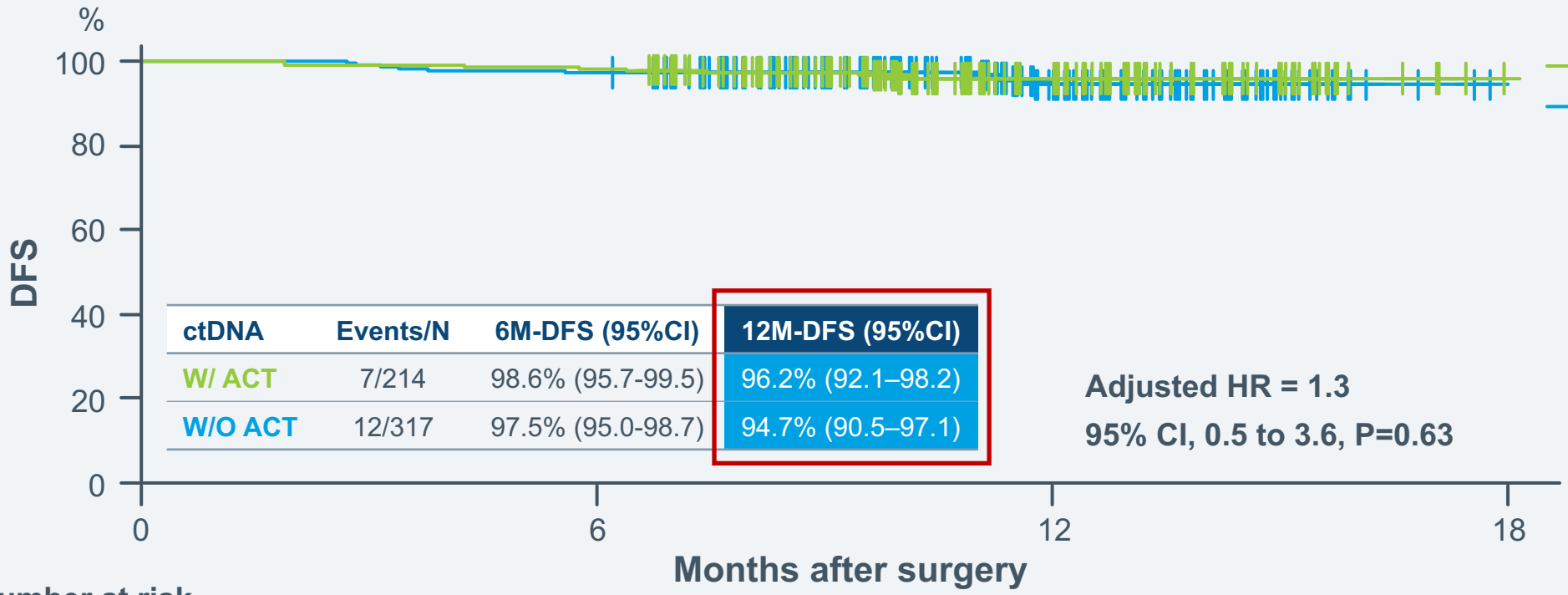
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No significant treatment benefit for MRD-negative patients

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



ctDNA	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	7/214	98.6% (95.7-99.5)	96.2% (92.1–98.2)
W/O ACT	12/317	97.5% (95.0-98.7)	94.7% (90.5–97.1)

Adjusted HR = 1.3

95% CI, 0.5 to 3.6, P=0.63

Number at risk

W/ ACT	214	211	79	0
W/O ACT	317	309	117	0

Median follow-up time: 11.4 months. Data cutoff: Nov 19, 2021

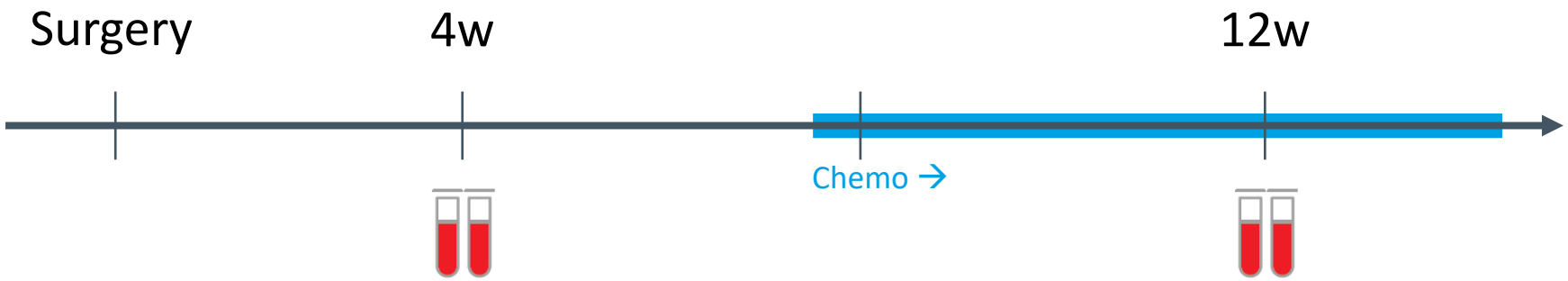
Kotaka et al. Association of circulating tumor DNA dynamics with clinical outcomes in the adjuvant setting for patients with colorectal cancer from an observational GALAXY study in CIRCULATE-Japan. ASCO GI 2022.
HR was adjusted by age, performance status, pStage, and MSI status that are imbalanced between two groups.
ACT, adjuvant chemotherapy; DFS, disease-free survival; HR, hazard ratio; CI, confidential interval.
DFS curve was estimated by the Kaplan-Meier method. HR and 95%CI were calculated by the Cox proportional hazard model.

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Analyzing ctDNA clearance

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- Does the MRD status change between 4w to 12w? (positive/negative)
- Does the change correlate with outcome, and can ctDNA clearance predict treatment benefit? (i.e., surrogate endpoint)

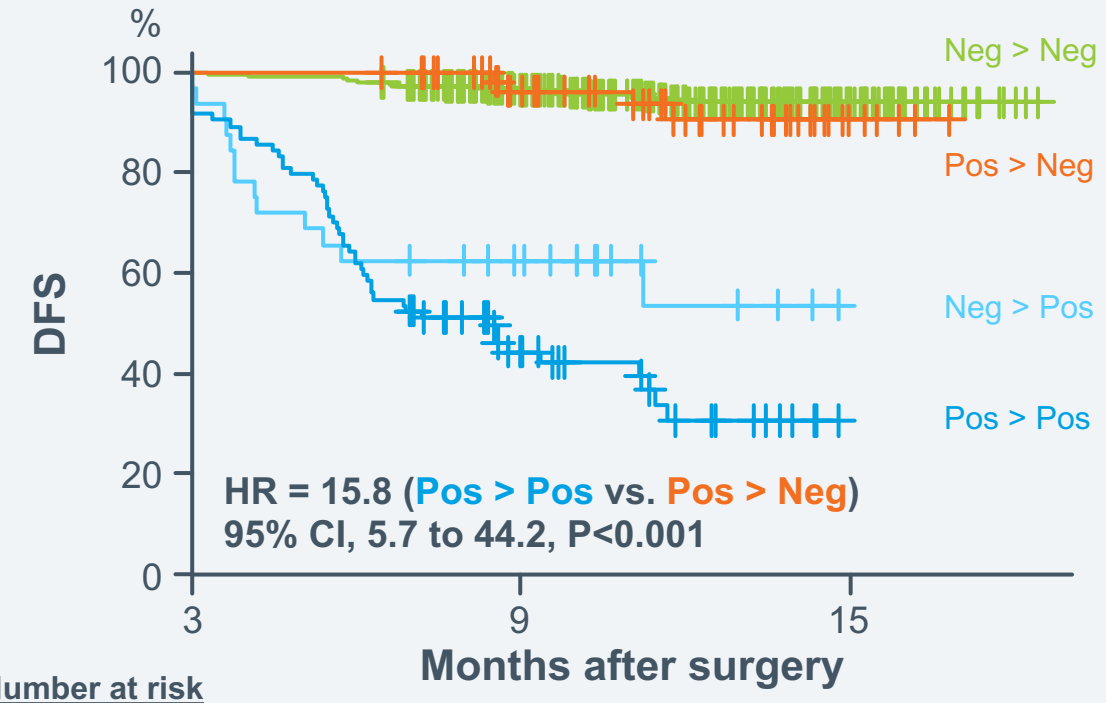
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ctDNA clearance is predictive

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



Number at risk

Neg > Neg	660	490	60
Neg > Pos	32	15	0
Pos > Neg	62	46	5
Pos > Pos	84	23	0

Dynamics	Neg > Neg	Neg > Pos	Pos > Neg	Pos > Pos
Events/N	31/660	13/32	4/62	50/84
6M-DFS	98.0%	62.5%	100%	58.3%
HR	0.8	9.2	Reference	15.8
95%CI	0.27–2.15	3.0–28.4	-	5.7-44.2
P	0.60	<0.001	-	<0.001

Median follow-up time: 11.4 months. Data cutoff: Nov 19, 2021

Kotaka et al. Association of circulating tumor DNA dynamics with clinical outcomes in the adjuvant setting for patients with colorectal cancer from an observational GALAXY study in CIRCULATE-Japan. ASCO GI 2022.
DFS, disease-free survival; HR, hazard ratio; CI, confidential interval DFS curve was estimated by the Kaplan-Meier method. HR and 95%CI were calculated by the Cox proportional hazard model.

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Key takeaways

Prognostic results

Circulate Japan ASCO GI 22[1]

12M-DFS for MRD-positives	55.5%
12M-DFS for MRD-negatives	95.2%
Hazard Ratio (HR) for MRD-positive vs. MRD-negative	13.3
Sensitivity at 4w post-op	67.6%

Predictive results

- Signatera-positive post surgery: benefit significantly from adjuvant chemo (HR 8.8-9.4 in high-risk Stage II or III)
- Signatera-negative post surgery: no significant benefit from adjuvant chemo (Absolute risk reduction of only 1.5% at 12 months DFS)
- Signatera ctDNA clearance: predictive of treatment efficacy (HR 15.8 clearance vs. no clearance)

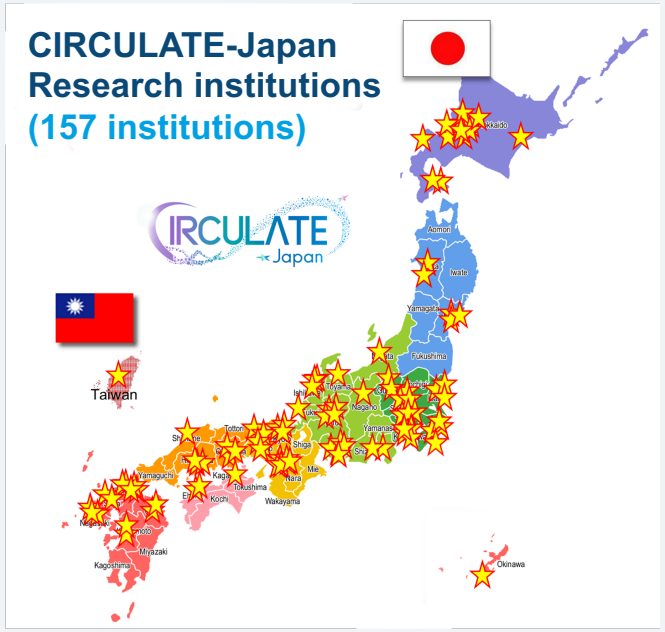
1 Kotaka et al. Association of circulating tumor DNA dynamics with clinical outcomes in the adjuvant setting for patients with colorectal cancer from an observational GALAXY study in CIRCULATE-Japan. ASCO GI 2022.

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Acknowledgements

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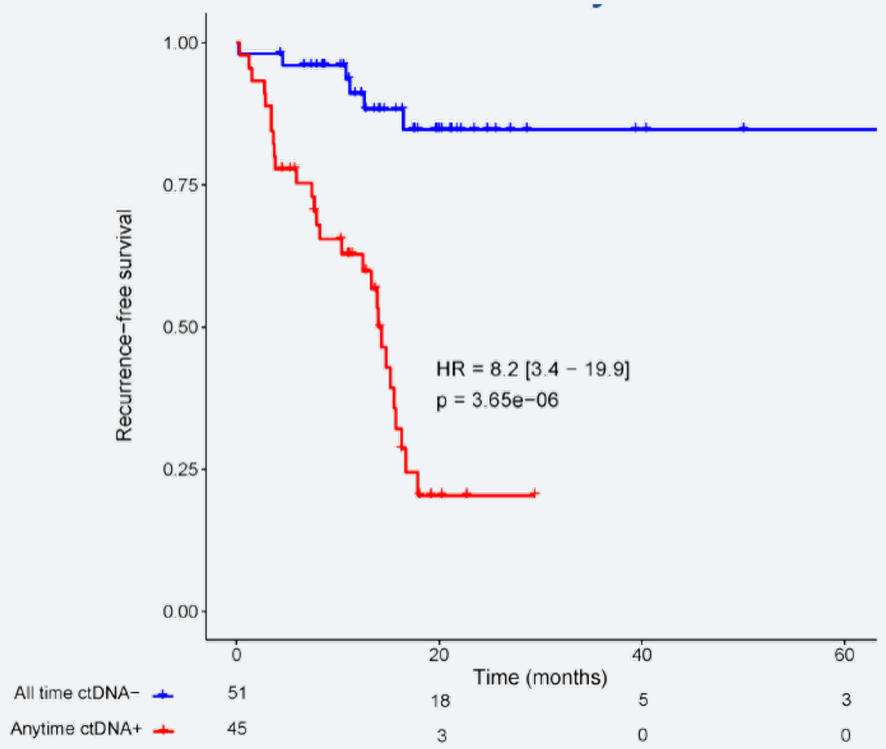
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Announcing expansion: pancreatic cancer

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Stratification by ctDNA



Overview

- ~60K new cases per year, 40-45% early stage[1], 85% recurrence after surgery
- Unmet need: surveillance for early recurrence already recommended by guidelines[2], but CA19-9 lacks sensitivity/specificity. 5-10% don't express CA19-9[3]
- Post surgical MRD+ may influence chemo regimen

Study results[4]

- 116 patients and 450 time points across all stages of PDAC
- Signatera MRD status significantly associated with disease relapse, while CA19-9 was not

[1] SEER Cancer Stat Fact. https://seer.cancer.gov/statfacts.
[2] National Comprehensive Cancer Network (NCCN). NCCN Guidelines for Pancreatic Adenocarcinoma, Version 2.2021. 2021; Available from: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf.
[3] Ballehaninna, U.K. and R.S. Chamberlain, The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence-based appraisal. J Gastrointest Oncol, 2012. 3(2): p. 105-19.
[4] Botta et al. Association of personalized and tumor-informed ctDNA with patient survival outcomes in pancreatic adenocarcinoma. ASCO GI 2022.

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Announcing expansion: anal cancer

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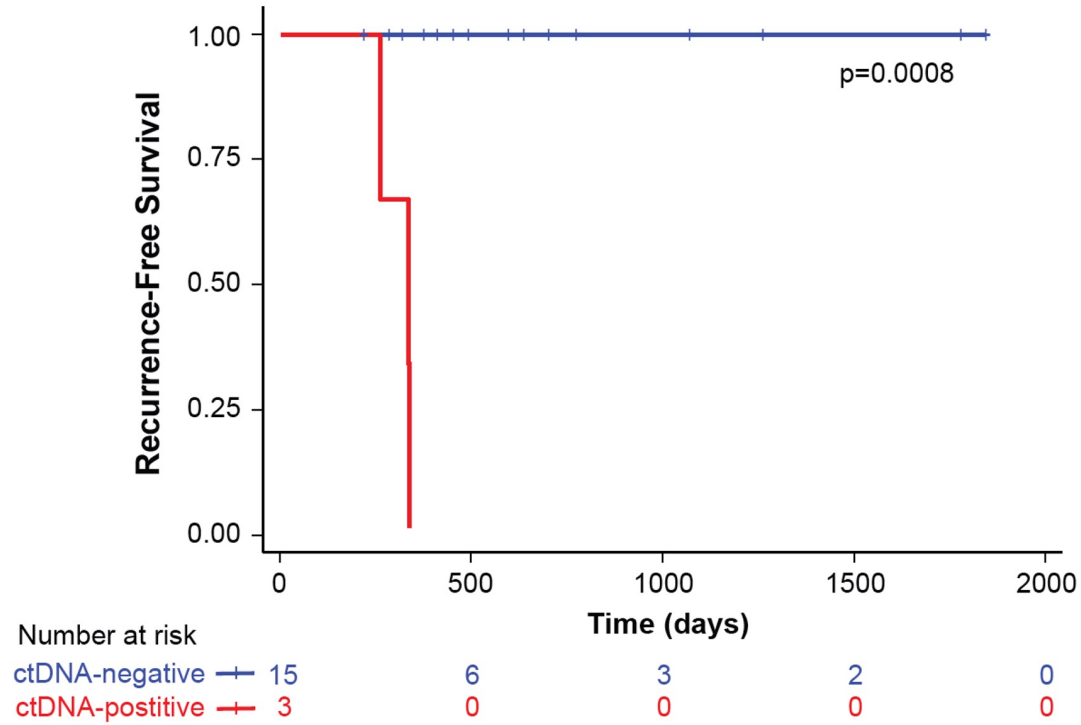
Overview

- 9K new cases per year[1]
- Unmet Need: No established biomarkers, imaging difficult to interpret after definitive treatment, invasive surveillance tools
- 10-30% of patients recur loco-regionally. MRD+ patients post definitive treatment may be candidates for salvage surgery, or possibly metastatic therapy.[2]

Study results[3]

- 25 patients and 141 time points across all stages of anal cancer
- 3 relapses, 100% detected with Signatera
- No relapse in MRD-negative group, stages I-III

Stratification by ctDNA



[1] SEER Cancer Stat Fact. https://seer.cancer.gov/statfacts.
[2] National Comprehensive Cancer Network (NCCN). NCCN Guidelines for Anal Carcinoma Version 2.2021. 2021; Available from: https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf
[3] Azzi et al. Circulating tumor DNA-based molecular residual disease detection and recurrence monitoring in patients with advanced or metastatic anal squamous cell carcinoma. ASCO GI 2022.

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Conclusions

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- Signatera is prognostic *and predictive* of treatment benefit in CRC; with exceptional sensitivity
- Increases likelihood of adoption into guidelines and private payor coverage
- Expands Natera's data leadership in CRC and other GI cancers
- Tumor-informed & personalized approach: great performance, pan-cancer

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Q&A

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2 oral presentations, 4 posters

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Oral presentations

ORAL ABSTRACT SESSION C: Cancers of the Colon, Rectum and Anus

Presenter: Masahito Kotaka, M.D., Ph.D

Association of circulating tumor DNA dynamics with clinical outcomes in the adjuvant setting for patients with colorectal cancer from an observational GALAXY study in CIRCULATE-Japan

ORAL ABSTRACT PRESENTATION: Emerging Roles of ctDNA on the Horizon of GI Cancers

Presenter: Gregory Botta, M.D., Ph.D

Association of personalized and tumor-informed ctDNA with patient survival outcomes in pancreatic adenocarcinoma

Posters

POSTER SESSION C: Cancers of the Colon, Rectum, and Anus

Presenter: Georges Azzi, M.D

Circulating tumor DNA-based molecular residual disease detection and recurrence monitoring in patients with advanced or metastatic anal squamous cell carcinoma

POSTER SESSION C: Cancers of the Colon, Rectum, and Anus

Presenter: RuoBing Xue, M.D.

Prospective study of the correlation of ctDNA with pathologic complete remission (pCR) and other efficacy outcomes in rectal cancer patients undergoing neoadjuvant chemotherapy and radiation

POSTER SESSION C: Cancers of the Colon, Rectum, and Anus

Presenter: Sherise Rogers, M.D., M.P.H

A phase II randomized therapeutic optimization trial for subjects with refractory metastatic colorectal cancer using circulating tumor DNA (ctDNA): Rapid 1 trial

POSTER SESSION C: Cancers of the Colon, Rectum, and Anus

Presenter: Marwan Fakih, M.D.

Exploratory biomarker analyses of the single-arm, phase 2 study of regorafenib plus nivolumab in patients (pts) with mismatch repair-proficient (pMMR)/microsatellite stable (MSS) colorectal cancer (CRC)

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