NEWS RELEASE

First of its Kind Colorectal Cancer Data from Prospective GALAXY Study Released at ESMO; Demonstrates Signatera's Ability to Predict Overall Survival

2024-09-14

Shows nearly 10x advantage in overall survival at 36 months based on ctDNA status and affirms Signatera’s ability to predict chemotherapy benefit

Shows a 50% reduction in risk of death for Signatera-positive patients when treated with ACT

AUSTIN, Texas--(BUSINESS WIRE)-- **Natera, Inc.** (NASDAQ: NTRA), a global leader in cell-free DNA and genetic testing, announced that new data from the GALAXY arm of the ongoing CIRCULATE-Japan trial was released today at the 2024 Congress of the European Society for Medical Oncology (ESMO) in Barcelona, Spain. GALAXY is one of the largest and most comprehensive prospective studies of circulating tumor DNA (ctDNA) testing in resectable colorectal cancer (CRC).

This latest analysis, which will also be published in Nature Medicine on September 16, provides the first evidence of the ability of Signatera-based molecular residual disease (MRD) detection to predict overall survival (OS). The data also demonstrates Signatera’s ability to predict adjuvant chemotherapy (ACT) benefit in resectable CRC, with ctDNA clearance as an indicator of a superior survival benefit compared to no clearance.

In the study, 2,240 patients with stage II–IV CRC were monitored using Signatera after curative-intent surgery with a median follow-up of 23 months. Key takeaways include:

- Signatera status was predictive of overall survival. Signatera-positivity in the post-op MRD window was found to be significantly associated with worse OS compared to Signatera-negative patients (HR: 9.68, p-value < 0.01) with a 36-month OS of 71.80% vs. 96.0%, respectively. This 10x advantage in overall survival compares favorably to all known guideline-recommended biomarkers that have HRs for overall survival in a range of 1-4.
- Signatera status was predictive of an overall survival benefit from adjuvant chemotherapy.
    - High-risk stage II and stage III-IV patients who were Signatera-positive after surgery and received ACT demonstrated superior OS (adjusted HR: 0.53, p-value = 0.05), corresponding to a 50% reduction in the risk of death when treated with ACT. By comparison, the MOSAIC trial 1 , which was the last practice-changing study in adjuvant CRC, demonstrated a 16% reduction in risk of death (HR: 0.84, p-value = 0.05).
    - Signatera-negative patients did not derive an OS benefit from ACT (adjusted HR: 0.53, p-value = 0.13).
- Signatera status remained the most significant predictor of recurrence. Signatera-positivity after surgery was the single most significant prognostic factor associated with inferior DFS (HR 12.08, p-value <0.01) and OS (HR 9.87, p-value <0.01) in a multivariate analysis that included all clinicopathologic risk factors currently in use. This is also reflected by the 36-month DFS difference between Signatera-positive and Signatera-negative patients at 16.7% (95% CI: 12.1–21.9%) versus 83.5% (95% CI: 81.2%–85.6%), respectively. The association of Signatera-positivity with a significantly increased risk for recurrence was observed across all pathologic stages.
- Sustained Signatera clearance after ACT was associated with improved survival. Patients who clear ctDNA and remained Signatera-negative (referred to as “sustained clearance”) had superior survival benefit with 24-month OS of 100%. This compares to patients who cleared ctDNA for a period of time but later become Signatera-positive (referred to as “transient clearance”), with 24-month OS of 82%, and patients who did not achieve ctDNA clearance, with 24-month OS of 61%. This finding further supports the utility of sustained ctDNA clearance as a surrogate endpoint for long-term outcomes.

“We now have compelling prospective evidence from a large trial of more than 2,200 patients that clearly reinforces the link between MRD status and overall survival,” said Yoshiaki Nakamura, MD, PhD, co-author of the paper and principal investigator of the study from the National Cancer Center Hospital East in Kashiwa, Chiba, Japan. “These findings suggest that Signatera can predict post-surgical outcomes for colorectal cancer patients with great precision, redefining the future of personalized medicine and providing the potential to significantly improve outcomes for a greater number of patients.”

“The GALAXY data released today builds on an earlier analysis from the same study **that was published in Nature Medicine** in 2023,” said Minetta Liu, MD, chief medical officer of oncology at Natera. “Introducing 36-month, first-of-its-kind data on overall survival is an important milestone that reinforces the potential to improve outcomes for patients diagnosed with colorectal cancer. The updated data affirms ctDNA status as a critical measure both for

prognosis and for predicting which patients may truly benefit from adjuvant chemotherapy.”

About Signatera

Signatera is a personalized, tumor-informed, molecular residual disease test for patients previously diagnosed with cancer. Custom-built for each individual, Signatera uses circulating tumor DNA to detect and quantify cancer left in the body, identify recurrence earlier than standard of care tools, and help optimize treatment decisions. The test is available for clinical and research use and is covered by Medicare for patients with colorectal cancer, breast cancer, ovarian cancer and muscle invasive bladder cancer, as well as for immunotherapy monitoring of any solid tumor. Signatera has been clinically validated across multiple cancer types and indications, with published evidence in more than 70 peer-reviewed papers.

About Natera

Natera™ is a global leader in cell-free DNA and genetic testing, dedicated to oncology, women’s health, and organ health. We aim to make personalized genetic testing and diagnostics part of the standard of care to protect health, and inform earlier, more targeted interventions that help lead to longer, healthier lives. Natera’s tests are validated by more than 200 peer-reviewed publications that demonstrate high accuracy. Natera operates ISO 13485-certified and CAP-accredited laboratories certified under the Clinical Laboratory Improvement Amendments (CLIA) in Austin, Texas and San Carlos, California. For more information, visit **www.natera.com** .

Forward-Looking Statements

All statements other than statements of historical facts contained in this press release are forward-looking statements and are not a representation that Natera’s plans, estimates, or expectations will be achieved. These forward-looking statements represent Natera’s expectations as of the date of this press release, and Natera disclaims any obligation to update the forward-looking statements. These forward-looking statements are subject to known and unknown risks and uncertainties that may cause actual results to differ materially, including with respect to whether the results of clinical or other studies will support the use of our product offerings, the impact of results of such studies, our expectations of the reliability, accuracy and performance of our tests, or of the benefits of our tests and product offerings to patients, providers and payers. Additional risks and uncertainties are discussed in greater detail in "Risk Factors" in Natera’s recent filings on Forms 10-K and 10-Q and in other filings Natera makes with the SEC from time to time. These documents are available at **www.natera.com/investors** and **www.sec.gov** .

References

1. Thierry André et al., Improved Overall Survival With Oxaliplatin, Fluorouracil, and Leucovorin As Adjuvant Treatment in Stage II or III Colon Cancer in the MOSAIC Trial. JCO 27, 3109-3116(2009). DOI:10.1200/JCO.2008.20.6771

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Source: Natera, Inc.