



NEWS RELEASE

# Natera Enrolls First Patients in SIGNAL-ER 101, a Prospective, Interventional Study Evaluating MRD-Guided Therapy in Breast Cancer

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Signatera™ will be used to identify patients who may be able to delay or defer adjuvant CDK4/6 inhibitor therapy in intermediate-risk HR+/HER2- breast cancer

SIGNAL is a new group of Natera-sponsored interventional trials designed to establish the clinical utility of MRD-guided treatment de-escalation strategies across multiple cancer types

AUSTIN, Texas--(BUSINESS WIRE)-- **Natera, Inc.** (NASDAQ: NTRA), a global leader in cell-free DNA and precision medicine, today announced enrollment of the first patients in **Signatera-Guided iNterventionAL (SIGNAL)-ER 101**, a prospective, single-arm, multi-center study evaluating Signatera MRD-guided de-escalation in early-stage breast cancer.

The current standard of care recommends two or three years of an adjuvant CDK4/6 inhibitor in combination with endocrine therapy for patients with intermediate-risk, hormone receptor (HR) positive, HER2 negative, early stage breast cancer. This is despite the fact that only ~3% of eligible patients derive benefit, over 60% of patients experience serious adverse events,1-2 and the U.S. retail costs can be over \$400,000 for a full course of treatment. Meanwhile, data presented at SABCS 2025 from the PALLAS trial show that HR+ breast cancer patients who tested MRD-negative with Signatera had excellent long-term outcomes, with >95% distant recurrence-free interval at 5 years. This suggests that MRD-negative patients can safely defer CDK4/6 inhibition with no impact to clinical outcomes, with the provision that it be added if and when MRD is detected on serial testing using a TOMR (Treatment on MRD) approach.



SIGNAL-ER 101 plans to enroll approximately 725 patients across 50 sites in the United States. Patients who test MRD-positive will receive endocrine therapy plus CDK4/6 inhibitors, while those who test MRD-negative (the vast majority of patients) will receive endocrine therapy alone with quarterly Signatera monitoring. Patients who become MRD-positive during surveillance will be eligible to initiate CDK4/6 inhibition at that time, consistent with the TOMR approach.

“Many women with this type and stage of breast cancer are overtreated, which can have a profound impact on their quality of life,” said Minetta Liu, M.D., chief medical officer, oncology and early cancer detection at Natera. “SIGNAL-ER 101 is a key part of our evidence generation roadmap, to support Signatera-guided treatment optimization without compromising the survival benefit from CDK4/6 inhibitors. This approach also allows patients to get the most effective treatment when Signatera shows it is necessary.”

SIGNAL-ER 101 is the first in a series of innovative Natera-sponsored SIGNAL trials across multiple cancer types, designed to demonstrate that MRD-negative patients may be able to delay or defer treatment. There are many instances of overtreatment in cancer. This concept has already been studied in the IMvigor011 trial where MRD-negative patients with muscle-invasive bladder cancer achieved 97% overall survival at 2 years without any adjuvant therapy, and in the GALAXY and CALGB/SWOG 80702 trials, where MRD-negative patients with colorectal cancer saw no clinical benefit from adjuvant chemotherapy and celecoxib, respectively.

## References

1. Johnston SRD, Toi M, O’Shaughnessy J, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *The Lancet Oncology*. 2023;24(1):77-90. doi:10.1016/S1473-0245(22)00694-5.
2. Slamon DJ, Lipatov O, Nowecki Z, et al. Ribociclib plus endocrine therapy in early breast cancer. *New England Journal of Medicine*. 2024;390(12):1080-1091. doi:10.1056/NEJMoa2305488.

## About Natera

Natera™ is a global leader in cell-free DNA and precision medicine, 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 supported by more than 400 peer-reviewed publications that demonstrate excellent performance. Natera operates ISO 13485-certified and CAP-accredited laboratories certified under the Clinical Laboratory Improvement Amendments (CLIA) in Austin, Texas, and San Carlos, California, and through Foresight Diagnostics, its subsidiary, operates an ISO 27001-certified and CAP-accredited laboratory certified under CLIA in Boulder, Colorado. For more

information, visit [www.natera.com](http://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 our efforts to develop and commercialize new product offerings, 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](http://www.natera.com/investors) and [www.sec.gov](http://www.sec.gov).

Investor Relations: Mike Brophy, CFO, Natera, Inc., [investor@natera.com](mailto:investor@natera.com)

Media: Lesley Bogdanow, VP of Corporate Communications, Natera, Inc., [pr@natera.com](mailto:pr@natera.com)

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