NEWS RELEASE

Phase III PALLAS Study Shows Signatera™ MRD Testing Provides Powerful Post-Surgical Prognostic Information in Patients with High and Intermediate Risk HR+/HER2- Breast Cancer

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MRD status after surgery stratifies patients beyond established clinical and genomic risk tools

AUSTIN, Texas--(BUSINESS WIRE)-- Natera, Inc. (NASDAQ: NTRA), a global leader in cell-free DNA and precision medicine, together with Alliance Foundation Trials, LLC (AFT) and the Austrian Breast and Colorectal Cancer Study Group (ABCSG), today announced initial translational research results from the international randomized Phase III PALLAS study.

Presented today at the San Antonio Breast Cancer Symposium (SABCS), these first data, generated from a U.S. biomarker cohort of 420 patients, show that molecular residual disease (MRD) status, measured by the Signatera Genome test after surgery (and adjuvant chemotherapy +/- radiation if administered), is a highly prognostic biomarker for distant recurrence risk in stage II–III, HR+/HER2- breast cancer. The findings support Natera's strategy to integrate MRD testing into routine post-surgical risk assessment, enabling a more personalized approach to managing early-stage HR+ breast cancer. Data from a parallel ex-US cohort will be presented in conjunction with a treatment subgroup analysis at a later date.

In PALLAS, patients with stage II–III HR+/HER2- breast cancer were randomized to receive two years of palbociclib, a CDK4/6 inhibitor, in combination with endocrine therapy. Signatera MRD assessments were performed after surgery at three key postoperative timepoints: on the first day of protocol-directed experimental therapy (baseline), on-treatment at approximately 6 months (C6D1), and at the end of the 2-year interventional treatment period

(EOT). Key findings from this initial analysis include:

Signatera correctly identified patients with low risk of recurrence.

- At baseline, approximately 92% of patients were MRD-negative and had excellent outcomes, with 5-year distant recurrence-free interval (DRFI) of 93%. Measured starting at EOT, MRD-negative patients had a 5-year DRFI of 95%. This underscored that MRD-negativity after surgery and adjuvant endocrine therapy is associated with an exceptionally low risk of distant recurrence.

MRD-positive patients had very poor outcomes with current therapy.

- Baseline MRD positivity was observed in roughly 8% of this stage II–III HR+/HER2- population. These patients had 5-year DRFI of 28%, corresponding to a markedly elevated hazard of distant recurrence compared with MRD-negative patients (hazard ratio [HR] ~15). At the end of protocol-directed therapy, MRD-positive patients had a 5-year DRFI of 32%, with hazard ratios exceeding 20 versus MRD-negative patients.

There was strong prognostic value across all postoperative timepoints tested in the analysis.

- Signatera ctDNA status at baseline, C6D1 and EOT was consistently and strongly associated with distant recurrence risk, even when accounting for clinical and pathologic features. Across these timepoints, MRD-positive patients had hazard ratios well into the double digits (13.4-21.5) compared with MRD-negative patients, demonstrating much larger risk separation than is typically seen with individual clinicopathologic factors alone.

“ctDNA has emerged as one of the most promising biomarkers in early-stage breast cancer, and the TransPALLAS collaboration gives us a uniquely powerful opportunity to study ctDNA in the adjuvant setting,” said Heather Parsons, M.D., MPH, first author, Trans-PALLAS member, and associate professor of the clinical research division and program head of the breast oncology program at Fred Hutch Cancer Center. “We are excited to share these findings with the breast oncology community and advance a better understanding of recurrence risk for patients with HR+/HER2- disease.”

“The results from this preplanned analysis of the PALLAS trial support Natera’s vision for individualizing the management of early-stage HR+/HER2- breast cancer,” said Minetta Liu, M.D., chief medical officer of oncology and early cancer detection at Natera. “Implementation of longitudinal post-surgical ctDNA testing with Signatera advances us beyond a one-size-fits-all management approach based solely on initial tumor characteristics. Instead, we can start to imagine treatment algorithms where ctDNA-negative patients are spared unnecessary treatment with related toxicity, and ctDNA-positive patients are prioritized for more intensive or novel therapies. It’s a fundamental shift toward truly MRD-informed care.”

About the PALLAS Trial

PALbociclib CoLlaborative Adjuvant Study (PALLAS) (NCT02513394) is a randomized (1:1), prospective, international, multicenter, open-label Phase 3 study comparing the combination of palbociclib in combination with endocrine therapy (ET) versus ET alone for adults with HR+, HER2- Stage II and Stage III EBC, including those at moderate to high risk of recurrence. MRD detection via ctDNA testing was a predefined biomarker analysis to identify patients at highest risk of recurrence. The previously reported trial which did not include MRD analysis, co-sponsored by the ABCSG and the AFT as part of a clinical research collaboration with Pfizer, Breast International Group (BIG), German Breast Group (GBG), National Surgical Adjuvant Breast and Bowel Project (NSABP), and PrECOG, LLC (PrECOG), did not meet its primary endpoint, showing no benefit of palbociclib plus endocrine therapy in the adjuvant setting in patients with histologically confirmed HR+/HER2- invasive EBC. Palbociclib is not approved in EBC.

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 325 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**.

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.

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