NEWS RELEASE

Successful Readout of Prospective Phase 2 SINERGY Trial Supports SignateraTM MRD-Guided Treatment in Head and Neck Cancer

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Interventional trial validates adaptive Signatera-guided treatment approach, achieving strong 63% response rate while reducing chemotherapy exposure in 74% of patients

Results selected for oral plenary at 2026 Multidisciplinary Head and Neck Cancers Symposium (MHNCS)

AUSTIN, Texas--(BUSINESS WIRE)-- **Natera, Inc.** (NASDAQ: NTRA), a global leader in cell-free DNA and precision medicine, today announced results from the SINERGY trial, a Phase 2 study in recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC). Data was recently presented in an oral plenary at the 2026 MHNCS.

Approximately 73K patients are diagnosed with head and neck cancer in the U.S. annually.1 The current standard of care for R/M HNSCC patients, based on the registrational KEYNOTE-048 trial, is immune checkpoint inhibition (ICI) either alone, or combined with chemotherapy; however, these regimens are suboptimal with efficacy and toxicity concerns. To help address these issues, SINERGY (NCT05420948) investigated whether personalized circulating tumor DNA (ctDNA) monitoring with Signatera can provide an early signal of treatment efficacy, enabling adaptive escalation or de-escalation of chemotherapy without reducing therapeutic benefit.

In the trial, 27 patients received initial treatment of either immunotherapy alone or in combination with chemotherapy. Based on Signatera ctDNA dynamics during treatment (ctDNA levels rising or falling), chemotherapy was either escalated or de-escalated.

The study met its primary endpoint (objective response rate), with the following key highlights:

- 74% of patients (20/27) were de-escalated from chemo-immunotherapy to immunotherapy alone, resulting in a median of 2 chemotherapy cycles across the full cohort, a substantial two-thirds reduction from the current standard of care (6 cycles).
- Objective response rate (ORR) was strong at 63% (17/27; 95% CI: 42.4–80.6), comparing favorably to the 36% and 19% ORRs from KEYNOTE-048 patients receiving ICI with and without chemotherapy, respectively.
- Severe toxicity of grade ≥3 was 48.1% (13/27), substantially lower than the 85% and 55% from KEYNOTE-048 patients receiving ICI with and without chemotherapy, respectively.

“The SINERGY trial is unique in that it adapted chemo-immunotherapy treatment guided by ctDNA dynamics. The trial demonstrated a promising response rate and survival, with roughly three-quarters of patients experiencing treatment de-escalation guided by ctDNA dynamics,” said Ari J. Rosenberg, M.D., associate professor of medicine at the University of Chicago and presenting author of the study. “This led to a reduction in the number of chemotherapy cycles along with lower rates of high-grade toxicity compared with historical controls. With these results, there is great potential for ctDNA dynamics to optimize treatment in R/M HNSCC.”

“This trial was designed to address an urgent need for treatment personalization that mitigates unnecessary toxicity while improving survival for patients with recurrent or metastatic head and neck cancer,” said Alexey Aleshin, M.D., general manager of oncology and corporate chief medical officer at Natera. “We saw remarkable results that Signatera can inform therapeutic decision-making in real-time for this aggressive and difficult-to-treat cancer, laying the groundwork for changes in the standard of care.”

References

1. National cancer institute SEER (surveillance, epidemiology, and end results) estimate.

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 350 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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