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NEWS RELEASE

Agenus Announces Nature Medicine Publication of Multicenter UNICORN Phase 2 Trial Demonstrating Deep Responses with Neoadjuvant BOT+BAL in Resectable Colon Cancer

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- In pMMR/MSS colon cancer, neoadjuvant BOT+BAL met the trial's primary endpoint with a 36% major pathologic response rate, including 29% pathologic complete response, within an overall 71% pathologic response rate after one BOT dose and two BAL doses
- No patients treated with BOT+BAL had their cancer return, with median follow-up of 19.2 months in MSS disease and 16.7 months in MSI-H disease; 12-month event-free survival was 100% in both combination cohorts.
- Independent, multicenter UNICORN findings reinforce the NEST peer-reviewed neoadjuvant evidence supporting Agenus' planned Phase 3 ROBBIN trial in curative-intent MSS/pMMR colon cancer

LEXINGTON, Mass.--(BUSINESS WIRE)-- **Agenus** Inc. (Nasdaq: AGEN), a leader in immuno-oncology innovation, today announced the peer-reviewed publication of results from the investigator-sponsored, multicenter Phase 2 UNICORN trial evaluating short-course preoperative, or neoadjuvant, botensilimab (BOT), Agenus' multifunctional, Fc-enhanced anti-CTLA-4 antibody, alone or in combination with balstilimab (BAL), Agenus' anti-PD-1 antibody, in patients with resectable, locally advanced colon cancer. The manuscript, titled "Preoperative botensilimab with or without balstilimab for patients with resectable, locally advanced pMMR or dMMR colon cancer: the UNICORN trial by GONO," was published in Nature Medicine and is available at **DOI 10.1038/s41591-026-04710-1**.

The UNICORN trial enrolled 56 patients in four non-randomized cohorts of 14, evaluating BOT alone or BOT+BAL in mismatch repair proficient/microsatellite stable (pMMR/MSS) and mismatch repair deficient/microsatellite

instability-high (dMMR/MSI-H) colon cancer. The study assessed pathologic response, event-free survival, circulating tumor DNA (ctDNA) and biological changes in tissue samples before and after treatment.

UNICORN clinical findings

Among the 14 patients with pMMR/MSS colon cancer treated with BOT+BAL, 36% achieved a major pathologic response (MPR), defined as 10% or less viable tumor remaining at surgery, and 29% achieved a pathologic complete response (pCR), meaning no viable tumor remained in the primary tumor or lymph nodes. Overall, 71% of patients had a pathologic response, defined as at least 50% tumor reduction.

For historical context, first-generation CTLA-4/PD-1 combination immunotherapy has demonstrated an MPR rate of approximately 20% while neoadjuvant chemotherapy has demonstrated an MPR rate of 8% in previously reported studies of pMMR colon cancer[i,ii].

In the separate pMMR/MSS BOT monotherapy cohort, 43% experienced partial tumor regression, but no patients achieved an MPR or pCR. The findings suggest BOT can initiate anti-tumor activity in a subset of pMMR tumors, while the deeper major and complete responses emerged with the addition of BAL and PD-1 blockade.

In dMMR/MSI-H disease, all 14 patients (100%) in the BOT+BAL treatment cohort achieved an MPR, including 13 (93%) with a pCR, compared with 36% and 29%, respectively, with BOT alone.

The responses with BOT+BAL were durable. At the February 9, 2026, data cutoff, no patients treated with BOT+BAL had their cancer return, with median follow-up of 19.2 months in pMMR/MSS disease and 16.7 months in dMMR/MSI-H disease. Twelve-month event-free survival was 100% in both combination cohorts.

Planned surgical timing was preserved in 98% of patients, and all 56 patients underwent surgical resection. One patient experienced a 10-day surgical delay associated with Grade 3 hyperthyroidism. Grade 3 or 4 immune-related adverse events occurred in 2% of patients.

Translational Findings

- ctDNA clearance tracked with response: All five evaluable pMMR/MSS patients who achieved an MPR cleared ctDNA before surgery. No patients who achieved ctDNA clearance had their cancer return at the data cutoff.
- Biological findings aligned with BOT's Fc-enhanced design: Paired tumor samples collected before treatment and at surgery identified immune changes associated with response that were consistent with BOT’s Fc-enhanced mechanism and its ability to remodel the tumor immune environment, including reductions in immunosuppressive regulatory T-cell signatures and increased immune-cell infiltration.

The UNICORN publication follows the recent peer-reviewed **publication of the independent Phase 2 NEST** study evaluating neoadjuvant BOT+BAL. With NEST and UNICORN now both peer reviewed, the two studies provide complementary and clinical evidence across single-center and multicenter settings, with consistent deep pathologic responses, ctDNA clearance, preserved surgical feasibility and maturing longer term follow-up. While the studies differed in design, the consistency of findings across independently conducted trials strengthens the clinical foundation for evaluating BOT+BAL earlier in the course of colon cancer.

This is particularly relevant in MSS colon cancer, which represents approximately 85% of early-stage colorectal cancers and has historically derived limited benefit from conventional immunotherapy[iii,iv]. In the curative-intent setting, treatment before surgery creates an opportunity to activate the immune system while the primary tumor and surrounding immune environment remain intact, with the goal of eliminating residual disease and preventing recurrence so that more patients may ultimately be cured.

“UNICORN delivers compelling, independent evidence that BOT+BAL can produce deep responses in MSS colon cancer, a disease historically resistant to conventional immunotherapy,” said Steven O’Day, M.D., Chief Medical Officer of Agenus. “With no recurrences observed to date, these findings reinforce the promise of treating earlier. Together with NEST, they provide a strong foundation for our planned Phase 3 ROBBIN trial and our ambition to change how MSS colon cancer is treated in the curative-intent setting.”

Agenus is advancing ROBBIN, the planned global randomized Phase 3 trial evaluating neoadjuvant BOT+BAL followed by standard of care versus standard of care alone in previously untreated patients with high-risk Stage II or Stage III MSS/pMMR colon cancer. Event-free survival is the planned primary endpoint.

“UNICORN gave us a rare opportunity to look beyond whether a tumor responded and examine what was changing biologically during a very short period before surgery,” said Filippo Ghelardi, M.D., first author and Medical Oncology Fellow of Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy. “The alignment we observed between deep pathologic responses, clearance of circulating tumor DNA and changes within the tumor immune environment provides multiple signals of treatment activity. For MSS colon cancer, where immunotherapy has historically had limited impact, these findings give us important new insight into what may be possible when treatment is introduced earlier in the course of disease.”

“For many years, MSS colon cancer has largely been considered resistant to immunotherapy. The UNICORN study challenges that assumption in the curative-intent setting,” said Filippo Pietrantonio, M.D., senior author, study principal investigator and Head of the Gastrointestinal Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy. “The purpose of moving treatment earlier is not simply to shrink

the tumor before surgery. It is to prevent the disease from returning and ultimately increase the number of patients who may be cured. Seeing deep responses after only a short course of treatment, with patients able to proceed to planned surgery and no recurrences observed to date in the combination cohorts, provides a strong rationale to test that objective in a larger randomized trial."

About the UNICORN Study

UNICORN (NCT05845450) is an ongoing multicenter, non-randomized, open-label Phase 2 window-of-opportunity platform trial sponsored by Fondazione GONO. The study evaluates short-course preoperative therapies in molecularly selected patients with resectable colorectal cancer.

The analysis reported in Nature Medicine evaluated Cohorts 4 through 7, comprising 56 patients with pMMR/MSS or dMMR/MSI-H colon cancer treated with BOT alone or BOT+BAL prior to curative-intent surgery. Patients receiving BOT monotherapy received botensilimab 1 mg/kg on Day 1. Patients receiving BOT+BAL received botensilimab 1 mg/kg on Day 1 and balstilimab 3 mg/kg on Days 1 and 15. Surgery was planned for Day 35 ± 5 days. The primary endpoint was centrally assessed major pathologic response, defined as 10% or less residual viable tumor. Secondary and exploratory analyses included safety, quality of life, longitudinal ctDNA, spatial transcriptomics, peripheral immune-cell dynamics, genomic correlates and microbiome analyses. The study was supported by GONO and other research funding sources. Agenus supplied BOT and BAL.

About Agenus

Agenus is a leading immuno-oncology company targeting cancer with a comprehensive pipeline of immunological agents. The company was founded in 1994 with a mission to expand patient populations benefiting from cancer immunotherapy through combination approaches, using a broad repertoire of antibody therapeutics, adoptive cell therapies (through MiNK Therapeutics) and adjuvants. Agenus has robust end-to-end development capabilities, across commercial and clinical cGMP manufacturing facilities, research and discovery, and a global clinical operations footprint. Agenus is headquartered in Lexington, MA. For more information, visit **www.agenusbio.com** or @agenus_bio. Information that may be important to investors will be routinely posted on our website and social media channels.

About Botensilimab (BOT)

Botensilimab (BOT) is a human multifunctional, Fc-enhanced anti-CTLA-4 antibody designed to boost both innate and adaptive anti-tumor immune responses. Its novel design leverages mechanisms of action to extend immunotherapy benefits to "cold" tumors which generally respond poorly to standard of care or are refractory to conventional PD-1/CTLA-4 therapies and investigational therapies. BOT augments immune responses across a wide range of tumor types by priming and activating T cells, reducing intratumoral regulatory T cells, activating myeloid

cells and inducing durable memory responses.

BOT+ balstilimab (BAL) has been studied in over 1,500 patients across more than nine tumor types, spanning late-line refractory disease and early-stage neoadjuvant settings. The combination is being developed to expand immunotherapy benefit to more patients, including those with microsatellite stable (MSS) disease and tumors considered immunologically “cold” or resistant to existing immunotherapies.

For more information about botensilimab trials, visit **www.clinicaltrials.gov**.

About Balstilimab (BAL)

Balstilimab is a novel, fully human monoclonal immunoglobulin G4 (IgG4) designed to block PD-1 (programmed cell death protein 1) from interacting with its ligands PD-L1 and PD-L2. It has been evaluated in more than 900 patients to date and has demonstrated clinical activity and a favorable tolerability profile in several tumor types.

Forward-Looking Statements

This press release contains forward-looking statements that are made pursuant to the safe harbor provisions of the federal securities laws, including statements regarding its botensilimab and balstilimab programs, expected regulatory timelines and filings, and any other statements containing the words "may," "believes," "expects," "anticipates," "hopes," "intends," "plans," "forecasts," "estimates," "will," “establish,” “potential,” “superiority,” “best in class,” and similar expressions are intended to identify forward-looking statements. These forward-looking statements are subject to risks and uncertainties that could cause actual results to differ materially. These risks and uncertainties include, among others, the factors described under the Risk Factors section of our most recent Annual Report on Form 10-K for 2025, and subsequent Quarterly Reports on Form 10-Q filed with the Securities and Exchange Commission. Agenus cautions investors not to place considerable reliance on the forward-looking statements contained in this release. These statements speak only as of the date of this press release, and Agenus undertakes no obligation to update or revise the statements, other than to the extent required by law. All forward-looking statements are expressly qualified in their entirety by this cautionary statement.

References

[i.] Tan PB, Verschoor YL, Van Den Berg JG, et al. Neoadjuvant immunotherapy in mismatch-repair-proficient colon cancers. Nature. Published online October 20, 2025. doi:10.1038/s41586-025-09679-4.
[ii.] Morton D, Seymour M, Magill L, et al. Preoperative Chemotherapy for Operable Colon Cancer: Mature Results of an International Randomized Controlled Trial. J Clin Oncol. 2023;41(8):1541-1552. doi:10.1200/JCO.22.00046.
[iii.] Buchler T. Front Oncol. 2022;12:888181.

[iv.] Guven DC, et al. Oncologist. 2024;29(5):e580-e600.

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