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NEWS RELEASE

Agenus Announces Publication of Phase 1b Botensilimab and Balstilimab Data in Post-Immunotherapy Hepatocellular Carcinoma in Liver Cancer

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- Published prospective cohort showed durable responses and manageable safety in patients with HCC following prior immunotherapy
- Median overall survival of 12.3 months in a heavily pretreated population with poor prognostic features, including ALBI grade 2 liver function

LEXINGTON, Mass.--(BUSINESS WIRE)-- **Agenus** Inc. (Nasdaq: AGEN), a leader in immuno-oncology innovation, today announced the publication of Phase 1b data evaluating botensilimab (BOT), an Fc-enhanced anti-CTLA-4 antibody, in combination with balstilimab (BAL), an anti-PD-1 antibody, in patients with treatment-refractory hepatocellular carcinoma (HCC) who had progressed following prior immunotherapy. The manuscript, titled "A phase 1b study of botensilimab and balstilimab in treatment-refractory hepatocellular carcinoma," was published in **Liver Cancer** and is available at DOI: 10.1159/000551630.

The publication reports results from an expansion cohort of the Phase 1b C-800-01 study in 19 patients with HCC who had progressed on or after prior immunotherapy. The cohort represents a difficult-to-treat population for which prospective data remain limited, including 47% of patients with albumin-bilirubin (ALBI) grade 2 liver function, a marker of poorer liver reserve and prognosis in HCC. In published HCC studies, ALBI grade 2 liver function has been linked to a 4- to 10-month decrement in median overall survival compared with ALBI grade 1, underscoring the poor prognosis and reduced responsiveness typically observed in this population.[i]

Among 18 efficacy-evaluable patients, BOT+BAL demonstrated an objective response rate (ORR) of 17%, including

one complete response and two partial responses. The 18-week clinical benefit rate (CBR) was 50%. Median duration of response (mDOR) was not reached, median progression-free survival (mPFS) was 4.4 months, and median overall survival (mOS) was 12.3 months. All patients had received prior anti-PD-(L)1 therapy, 68% had received prior tyrosine kinase inhibitors, and 58% had received prior atezolizumab/bevacizumab. One patient experienced stable disease for 66 weeks, supporting the conclusion that benefit with BOT+BAL was not confined to RECIST response alone.

Treatment options after immune checkpoint inhibitor (ICI) therapy in advanced HCC remain limited, and available systemic therapies have generally shown modest activity. Published studies evaluating lenvatinib, cabozantinib and regorafenib after ICI-based therapy have reported objective response rates of 6–14%, median progression-free survival of approximately 4–5 months and median overall survival of ≤10.5 months.[ii] The BOT+BAL results therefore, provide early prospective evidence of activity in a post-ICI HCC population that included patients with adverse prognostic features often underrepresented in later-line studies.

“This publication adds to a consistent body of clinical evidence showing BOT plus BAL activity across difficult-to-treat, late-line solid tumors,” said Steven O’Day, MD, Chief Medical Officer of Agenus. “In HCC, where tumor biology and underlying liver function both shape treatment outcomes, these data further support the rationale for botensilimab’s Fc-enhanced CTLA-4 design and its potential to drive immune activity in settings where conventional checkpoint approaches have had limited impact.”

“Patients with advanced HCC who progress after immunotherapy have limited treatment options, and outcomes can be especially poor when liver function is compromised,” said Anthony B. El-Khoueiry, MD, Chief of Section of Developmental Therapeutics and Associate Director for Clinical Research at USC Norris Comprehensive Cancer Center, part of Keck Medicine of USC, and principal investigator of the study. “In this exploratory cohort, seeing objective responses, prolonged disease control and a median overall survival of 12.3 months is encouraging and supports continued study of BOT plus BAL in this post-immunotherapy setting.”

The safety profile of BOT+BAL in the HCC cohort was consistent with prior reports across the broader Phase 1b program. There were no treatment-related deaths and no new class safety signals. Immune-mediated treatment-related adverse events occurred in 68% of patients, with grade 3 events in 37%. The most common immune-mediated treatment-related adverse events were diarrhea/colitis, hepatitis and dermatologic events. No grade 4 or higher immune-mediated treatment-related adverse events were reported. All immune-mediated hepatitis events resolved to grade 1 or lower.

HCC is the most common form of liver cancer and is often diagnosed at an advanced stage. Immune checkpoint

inhibitor combinations have improved outcomes in the frontline setting, but patients who progress after immunotherapy have limited prospective evidence to guide subsequent treatment. In the published manuscript, the authors concluded that BOT+BAL demonstrated promising efficacy and manageable safety in previously treated HCC, including patients who progressed after frontline immunotherapy, and that these findings warrant further investigation.

About the C-800-01 Study

C-800-01 (NCT03860272) is an open-label, multicenter Phase 1b clinical trial evaluating botensilimab in combination with or without balstilimab in patients with advanced solid tumors. The trial enrolled over 400 patients with refractory disease and included tumor types with limited or no responsiveness to prior checkpoint inhibitors.

The HCC expansion cohort enrolled 19 patients between March 2021 and September 2023 across six U.S. sites. Patients received botensilimab at 1 mg/kg or 2 mg/kg once every six weeks plus balstilimab 3 mg/kg once every two weeks. The safety analysis included all 19 patients who received at least one dose of study drug, and the efficacy-evaluable analysis included 18 patients with at least one post-baseline imaging scan.

About Agenus

Agenus is a clinical-stage immuno-oncology company advancing a pipeline of antibody-based programs designed to activate innate and adaptive immunity, overcome tumor immune evasion, and expand the population of patients who may benefit from immunotherapy. Founded in 1994, Agenus' lead program is botensilimab plus balstilimab (BOT+BAL), a next-generation Fc-enhanced CTLA-4 plus PD-1 combination. BOT alone or in combination with BAL has been evaluated in approximately 1,300 patients across more than nine tumor types. The global Phase 3 BATTMAN trial, conducted with the Canadian Cancer Trials Group, is evaluating BOT+BAL in refractory MSS/pMMR metastatic colorectal cancer. BOT/BAL is also available to eligible patients through regulatory-authorized access pathways in select countries, including France's national Autorisation d'Accès Compassionnel framework. Agenus also holds an equity investment in MiNK Therapeutics, Inc. (Nasdaq: INKT), a clinical-stage developer of allogeneic invariant natural killer T cell therapies, and a majority interest in SaponiQx, Inc., a vaccine adjuvant business. Agenus is headquartered in Lexington, Massachusetts. For more information, visit **www.agenusbio.com** or @agenus_bio. Information that may be important to investors will be routinely posted on the Company's website and social media channels.

About Botensilimab (BOT)

Botensilimab (BOT) is a human Fc enhanced multifunctional 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. Botensilimab augments immune responses across a wide range of tumor types by priming and activating T cells, downregulating intratumoral regulatory T cells, activating myeloid cells and inducing long-term memory responses.

Approximately 1,300 patients have been treated with botensilimab and/or balstilimab in phase 1 and phase 2 clinical trials. Botensilimab alone, or in combination with Agenus’ investigational PD-1 antibody, balstilimab, has shown clinical responses across nine metastatic, late-line cancers. 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

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[i] Feng D, Wang M, Hu J, Li S, Zhao S, Li H, et al. Prognostic value of the albumin-bilirubin grade in patients with hepatocellular carcinoma and other liver diseases. Ann Transl Med. 2020;8(8):553; Chan SL, Ryoo BY, Mo F, Chan LL, Cheon J, Li L, et al. Multicentre phase II trial of cabozantinib in patients with hepatocellular carcinoma after immune checkpoint inhibitor treatment. J Hepatol. 2024;81(2):258-264.

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Agenus Investors: 917-362-1370 | **investor@agenusbio.com**

Agenus Media: 781-674-4422 | **communications@agenusbio.com**

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