DRUG DEVELOPMENT TOOL
LETTER OF SUPPORT
DDT-BMQ-000139

June 6, 2023

Nordic Bioscience A/S
Attention: Daniel Guldager Kring Rasmussen
Herlev Hovedgade 205-207
DK-2730 Herlev
Denmark

Dear Dr. Rasmussen:

We are issuing this Letter of Support to encourage the further study and use of the biomarker PRO-C3 as a proposed prognostic biomarker[1] of risk of survival outcomes in clinical trials of patients with solid tumors. PRO-C3 is representative of a specific peptide fragment released to the bloodstream during formation of type III collagen and associates with activity of cancer associated fibroblasts and hence tumor fibrosis. Tumor fibrosis is a common denominator in a proportion of patients across solid tumor types and is associated with a more aggressive tumor progression and poor overall survival. Published and non-published information submitted to FDA suggest that the PRO-C3 biomarker may be linked to fibrosis.

The current standard for assessing tumor fibrosis in patients diagnosed with solid tumors is by use of Sirius red or trichrome staining of total collagen content in tissue biopsies, or by staining for collagens with antibodies for more detailed immunohistochemical assessments. A blood-based biomarker such as PRO-C3 for evaluating tumor fibrosis may provide a novel and clinically applicable tool for patient selection and risk assessments that is non-invasive and potentially more accessible than the standard tumor biopsy based approach.

We support further exploration of the requestor's proposed use of PRO-C3 as a prognostic enrichment biomarker to be used to stratify patients in clinical trials according to their likelihood of experiencing an outcome. Data from several clinical studies suggest that PRO-C3 is associated with the outcome of overall survival. Further work is required to investigate in various cohorts of patients with different solid tumor types and treated with different types of treatment including immunotherapy, the clinical utility of PRO-C3 as a prognostic enrichment biomarker.

[1] A prognostic biomarker, as defined by the BEST Resource, is "used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest." BEST is located at https://www.ncbi.nlm.nih.gov/books/NBK338448/.

The proposed use of the PRO-C3 biomarker for prognostic enrichment is consistent with the FDA's guidance document "Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products"[2]. The ability to identify patients at greater risk for events, can reduce the sample sizes needed to show an effect in outcome studies.

We encourage exploration of the biomarker PRO-C3 as a prognostic enrichment biomarker for patients with solid tumors who are more likely to experience adverse outcomes. If sponsors intend to include analyses of this biomarker to support regulatory decision making for a given IND drug development program, they should prospectively discuss the approach to these analyses with the appropriate CDER review division.

Any groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Daniel Guldager Kring Rasmussen (dgr@nordicbio.com) or view Nordic Bioscience's webpage (www.nordicbioscience.com).

Sincere Regards,

Jeffrey N. Siegel -S

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Jeffrey Siegel, M.D.,
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[2] https://www.fda.gov/media/121320/download.