DRUG DEVELOPMENT TOOL
LETTER OF SUPPORT

Date: November 23, 2021

ATTN: Stephen Y. Lai, M.D., Ph.D., FACS
1515 Holcombe Blvd, Unit 1445
Houston, TX 77030-4009

Dear Dr. Lai:

We are issuing this Letter of Support to the Joint Head and Neck Radiotherapy-MRI Development Cooperative to encourage the further study and use of DCE-MRI quantitative parameters, K_{trans} and V_e, as exploratory *monitoring biomarkers* for assessment of risk, diagnosis, progression, and/or treatment response of osteoradionecrosis (ORN) in at risk patients with head and neck cancer (HNC) treated with radiation therapy.

At present, no well-accepted biomarkers exist for monitoring of onset, progression, and treatment response of ORN. Consequently, there remains inconsistencies in the definition, diagnosis, and staging of ORN as well as limitations in objective monitoring of disease progression and/or treatment response. Thus, use of an imaging biomarker with quantifiable parameters, DCE-MRI K_{trans} (representing the volume transfer constant for a contrast agent from blood plasma to extravascular extracellular space, or EES) and V_e (representing the fractional volume of the EES in a tissue), may improve early identification of patients at risk, identify early stages of boney change suggestive of ORN, and provide ability to objectively evaluate treatment response or disease progression of boney change suggestive of ORN.

We support the Joint Head and Neck Radiotherapy-MRI Development Cooperative's use of DCE-MRI, K_{trans} and V_e, for monitoring of mandibular injury/ORN in at risk patients with HNC treated with radiation therapy. Use of DCE-MRI K_{trans} and V_e for ORN surveillance allows for the kinetic analysis of physiologic parameters describing microcirculatory perfusion in various tissues of interest. Physiologic parameters derived from DCE-MRI K_{trans} and V_e have been reported in recent years for HNC outcome prediction with promising results.

Given the group's preliminary evidence of establishing DCE-MRI K_{trans} and V_e as a measure of ORN, more experience with the use of this biomarker for the HNC population post-radiation would be useful to confirm its utility for mandibular injury and ORN monitoring. The Joint Head and Neck Radiotherapy-MRI Development Cooperative is proposing to work on 1) prospective qualification and validation of DCE-MRI K_{trans} and V_e as quantitative imaging *monitoring biomarkers* of radiation induced mandibular injury/ORN, and 2) standardization/harmonization of image acquisition and open source computational/analytic methods for DCE-MRI as a potential component of FDA biomarker qualification for mandibular bone injury/ORN.

Strong emphasis on applying good scientific, laboratory, and software development practices for quality control and validation of DCE-MRI K_{trans} and V_e as a monitoring biomarker for radiation-attributable bone injury and subsequent development of ORN is imperative. Specific aspects of monitoring, i.e. risk

assessments, diagnosis, progression, and/or treatment response and other Contexts Of Use for this biomarker, such as a potential early endpoint, will be evaluated when appropriate evidence and biological rationale are presented.

We encourage exploration of DCE-MRI parameters, K_{trans} and $V_{e,}$ for monitoring of radiation induced mandibular injury/ORN risk, onset, treatment response, and progression in at risk patients with HNC treated with radiation. We will consider data collection on this biomarker to be exploratory in nature. We believe data sharing and integrating data across trials can foster an accelerated path for ORN drug development programs. 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 Office of Oncologic Diseases in CDER.

Any groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Dr. Stephen Lai (SYLai@mdanderson.org).

Sincerely,

Jeffrey N. Siegel -S

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Jeffrey Siegel, M.D.
Director,
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