Note to File 2

Official Title: A Phase III, Open label, Randomized, Multi-center Study of the Effects of Leukocyte Interleukin, Injection [Multikine] Plus Standard of Care (Surgery + Radiotherapy or Surgery + Concurrent Chemoradiotherapy) in Subjects with Advanced Primary Squamous Cell Carcinoma of the Oral Cavity / Soft Palate Versus Standard of Care Only

NCT Number: NCT01265849

Date: 12 January 2021

Note to File #2
Statistical Analysis Plan
12-Jan-2021

Rationale:

The final SAP signed 27-November-2020 states that OS, PFS, and LRC analyses will be performed for patients alive at the Month 36 milestone visit. Blinded data review confirmed that the LAFU Form sufficiently addressed survival follow-up with >90% of all patients last alive with a follow-up date in 2020. It was further noticed that there were only 9 cases with progression noted as a SAE beyond the Month 36 milestone visit, so additional follow-up efforts to collect PFS and LRC status beyond Month 36 for patients last alive will be needed in order to perform PFS and LRC analyses beyond Month 36 in accordance with the SAP which cites that analyses will be performed for TCI D (Month 36 to Study Exit).

Thus, further follow-up is immediately required to complete pre-planned analyses. This follow-up is constrained by sites still open vs being closed. Only the open sites can be contacted.

Also, if so many patients are indeed disease-free post Month 36, then an additional analysis of lymph node involvement at study entry and following surgery may help explain outcomes.

This Note to File addresses these two points.

To Be Conducted:

Item 1: Perform Additional Follow-up

The open sites will be contacted by Ergomed medical personnel. ICON plc has generated a list of patients last reported to be alive at the Month 36 milestone visit. All parties remain blinded to eliminate any bias.

Item 1 Solution:

Dr. Dusan Markovic (Head Study Physician, Ergomed) will organize calling sites still open to advise and request the following from open sites:

- Identify open sites
- Identify patients last reported to be alive at the Month 36 milestone visit at these sites
- Compile the last survival, progression, and LRC status with corresponding dates
- Advise/remind sites regarding the last survival status per patient including date last alive.
- Ask sites when the patient had their last progression evaluation
    - Ask if it included a progression evaluation of both local and distal disease

- Update new Progression Form to collect progression and local progression status and date from which to conduct the TCI D based analyses.

Item 2: Perform Prediction Modeling

The TNM stage and lymph node status at study entry as well as the surgical margin and lymph node status after surgery (all independent variables) will be cross-tabulated against being alive and progression-free at Months 36, 48, and 60 (dependent variables), separately for each treatment group (independent variables). Differences between treatment groups will be analyzed using a logistic regression analysis separately by time for each of the ITT, eITT, and ePP populations.

Item 2 Solution:

Add the following tables:

- Table 14.2.8.1: Baseline TNM vs Months 36, 48, and 60 Alive and Progression-free
- Table 14.2.8.2: Baseline lymph node status (positive, negative) vs Months 36, 48, and 60 Alive and Progression-free
- Table 14.2.8.3: Post-surgery TNM vs Months 36, 48, and 60 Alive and Progression-free
- Table 14.2.8.4: Post-surgery lymph node status (positive, negative) vs Months 36, 48, and 60 Alive and Progression-free
- Table 14.2.8.5: Post-surgery margin (positive, negative) vs Months 36, 48, and 60 Alive and Progression-free.

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