Note to File 1

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: 28 December 2020

Note to File
Statistical Analysis Plan
28-Dec-2020

Rationale:

The final SAP signed 27-November-2020 states the following; Note: SAP items 5.2 (2) and (3) and 5.4 (2) and (3) need to be fixed (inadvertent text transposition):

To Be Corrected:

Item 1: Swapped Text (Sections 5.2 and 5.4)

5.2 Secondary Hypotheses

The following secondary comparisons are also planned:

(2) **LRC** for Multikine + CIZ + SOC vs. SOC controlling for pre-planned covariates

H_0: $h_{\text{Multikine + CIZ+ SOC}} / h_{\text{SOC}} = 1$ vs.
H_a: $h_{\text{Multikine + SOC}} / h_{\text{SOC}} < 1$,

where $h_{\text{Multikine + CIZ+ SOC}}$ is the active (Multikine + CIZ + SOC) hazard rate and
h_{SOC} is the control (SOC) hazard rate for **progression free survival** time.
TCI E (see Section 4.0) is the main interval of interest.

(3) **PFS** for Multikine + CIZ + SOC vs. SOC controlling for pre-planned covariates

H_0: $h_{\text{Multikine + CIZ+ SOC}} / h_{\text{SOC}} = 1$ vs.
H_a: $h_{\text{Multikine + SOC}} / h_{\text{SOC}} < 1$,

where $h_{\text{Multikine + CIZ+ SOC}}$ is the active (Multikine + CIZ + SOC) hazard rate and
h_{SOC} is the control (SOC) hazard rate for **LRC** (loco-regional control) failure time.
TCI E (see Section 4.0) is the main interval of interest.

5.4 Other Hypotheses

(2) **LRC** for Multikine + CIZ + SOC vs. SOC controlling for pre-planned covariates including histopathology markers

H_0: $h_{\text{Multikine + CIZ+ SOC}} / h_{\text{SOC}} = 1$ vs.
H_a: $h_{\text{Multikine + SOC}} / h_{\text{SOC}} < 1$,

where $h_{\text{Multikine + CIZ+ SOC}}$ is the active (Multikine + CIZ + SOC) hazard rate and
h_{SOC} is the control (SOC) hazard rate for **PFS**.
TCI E (see Section 4.0) is the main interval of interest.

(3) **PFS** for Multikine + CIZ + SOC vs. SOC controlling for pre-planned covariates including histopathology markers

H_0: $h_{\text{Multikine + CIZ+ SOC}} / h_{\text{SOC}} = 1$ vs.
H_a: $h_{\text{Multikine + SOC}} / h_{\text{SOC}} < 1$,

where $h_{\text{Multikine + CIZ+ SOC}}$ is the active (Multikine + CIZ + SOC) hazard rate and
h_{SOC} is the control (SOC) hazard rate for **LRC**.
TCI E (see Section 4.0) is the main interval of interest.

Item 1 Solution:

5.2 Secondary Hypotheses

The following secondary comparisons are also planned:

(2) **LRC** for Multikine + CIZ + SOC vs. SOC controlling for pre-planned covariates

H_0: $h_{\text{Multikine + CIZ+ SOC}} / h_{\text{SOC}} = 1$ vs.
H_a: $h_{\text{Multikine + SOC}} / h_{\text{SOC}} < 1$,
where $h_{\text{Multikine + CIZ+ SOC}}$ is the active (Multikine + CIZ + SOC) hazard rate and
h_{SOC} is the control (SOC) hazard rate for **LRC** (loco-regional control) time.
TCI E (see Section 4.0) is the main interval of interest.

(3) **PFS** for Multikine + CIZ + SOC vs. SOC controlling for pre-planned covariates

H_0: $h_{\text{Multikine + CIZ+ SOC}} / h_{\text{SOC}} = 1$ vs.
H_a: $h_{\text{Multikine + SOC}} / h_{\text{SOC}} < 1$,
where $h_{\text{Multikine + CIZ+ SOC}}$ is the active (Multikine + CIZ + SOC) hazard rate and
h_{SOC} is the control (SOC) hazard rate for **PFS** (progression-free survival) time.
TCI E (see Section 4.0) is the main interval of interest.

5.4 Other Hypotheses

(2) **LRC** for Multikine + CIZ + SOC vs. SOC controlling for pre-planned covariates including histopathology markers

H_0: $h_{\text{Multikine + CIZ+ SOC}} / h_{\text{SOC}} = 1$ vs.
H_a: $h_{\text{Multikine + SOC}} / h_{\text{SOC}} < 1$,

where $h_{\text{Multikine + CIZ+ SOC}}$ is the active (Multikine + CIZ + SOC) hazard rate and
h_{SOC} is the control (SOC) hazard rate for **LRC**.
TCI E (see Section 4.0) is the main interval of interest.

(3) **PFS** for Multikine + CIZ + SOC vs. SOC controlling for pre-planned covariates including histopathology markers

H_0: $h_{\text{Multikine + CIZ+ SOC}} / h_{\text{SOC}} = 1$ vs.

H_a: $h_{\text{Multikine + SOC}} / h_{\text{SOC}} < 1$,

where $h_{\text{Multikine + CIZ+ SOC}}$ is the active (Multikine + CIZ + SOC) hazard rate and h_{SOC} is the control (SOC) hazard rate for **PFS**.
TCI E (see Section 4.0) is the main interval of interest.

Item 2: Infeasible DDT Response Analyses (Section 11.1)

In this study, given the disease stage (III and IVa), a blinded review indicated that >90% of study subjects had surgery and that >90% did not have measurable or evaluable disease following surgery. Thus, there will not be sufficient numbers of subjects to be able to be assessed for partial or complete response following subsequent disease-directed treatment (DDT) with which to conduct such analyses, based on the limited capacity of residual disease to be assessed by either measurement or imaging.

Item 2 Solution:

Drop the following table and figure series involving DDT response stratification:

- Table Series 14.2.1.1.7
- Table Series 14.2.2.1.5
- Table Series 14.2.3.1.5
- Figure Series 14.2.1.1.8.

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