GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	An open Phase I Study of immunization with the recNY-ESO-1 + AS15 Antigen-Specific Cancer Immunotherapeutic in patients with NY-ESO-1-positive unresectable and progressive metastatic cutaneous melanoma
eTrack study number and Abbreviated Title	112406 (NYESO1-AS15-MEL-001 (MET))
Scope:	All data pertaining to the above study, with the exception of translational research analyses
Date of Statistical Analysis Plan	Final 05-Apr-2018
Co-ordinating author:	PPD
Reviewed by:	PPD (Clinical Research and Development Lead) PPD (SERM safety physician) PPD (SERM Scientist), PPD (Scientific writer) PPD (Lead Scientific writer) PPD (Lead statistical analyst) PPD (Public disclosure representative)
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APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AS	GSK proprietary Adjuvant System (ex. AS01B, AS02B, AS07A…)
ASCI	Antigen Specific Cancer Immunotherapeutic
AST	Aspartate Aminotransferase
ATP	According-To-Protocol
CD4	Cluster Differentiation marker-4 expressed by helper T-cells
CD8	Cluster Differentiation marker-8 expressed by cytotoxic T-cells
CI	Confidence Interval
CR	Complete Response
CMI	Cellular Mediated Immunization
CTC	Common Toxicity Criteria
CTCAE	Common Terminological Criteria for Adverse Events
DSMC	Data Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-linked immunosorbent assay
GGT	Gamma Glutamyl Transferase
GMC	Geometric Mean antibody Concentration
GSK	GlaxoSmithKline
MedDRA	Medical Dictionary for Regulatory Activities
NE	Non Evaluable
NSCLC	Non-Small Cell Lung Cancer
PD	Progressive Disease

PFS	Progression Free Survival
PR	Partial Response
SAE	Serious Adverse Event
NY-ESO-1	Cancer-Testis gene: New York-ESOphageal cancer-1
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
TFL	Tables Figures and Listing template annexed to SAP
TNM	Tumor, Node, Metastasis (staging system for NSCLC)
TTF	Time to Treatment Failure
TTP	Total Treated Population
USA	United States of America

1. DOCUMENT HISTORY

The SAP is divided into 2 parts: the first part detailing the analyses to be performed (current document) and a second part, annex (-es) (called TFL's) describing the flow and format of tables, figures and listings to be annexed to the SR

Date	Version	Description	Protocol Version
05-APR-2018	Final version	Final analysis	Amendment 3 03-SEP-2014

2. STUDY DESIGN

See protocol

The following group name will be used for the statistical analyses:

Group order in tables	Group label in tables	Group definition for footnote
1	Gr.1	recNY-ESO-1 + AS15 ASCI

3. OBJECTIVES

3.1. Co-primary objectives

The two co-primary objectives of this study are to document and to characterize the severe toxicity and clinical activity of the recNY-ESO-1 + AS15 ASCI in patients with NY-ESO-1-positive metastatic cutaneous melanoma.

3.2. Secondary objectives

Note that, as of Amendment 3, the decision was taken not to perform further testing on biological samples already collected in this study by default, except if a scientific rationale remains relevant. No further blood samples for protocol research purposes will be collected.

The secondary objectives of this study are to document and characterize:

1. Additional clinical indicators of clinical activity in the overall population and in the population of patients who present the predictive MAGE-A3 gene signature*.
2. Additional indicators of safety.
3. The specific humoral and cellular immune response* induced by recNY-ESO-1 + AS15 ASCI.

   * changed from protocol (see section 9)

4. ENDPOINTS

4.1. Co-primary endpoints

4.1.1. Safety endpoint

- Occurrence of severe toxicities during the study treatment phase and follow-up.

4.1.2. Clinical activity endpoint

- The induction of objective clinical response (CR or PR).

4.2. Secondary endpoints

4.2.1. Safety endpoints

- Occurrence of AEs and SAEs during the study treatment period and ending 30 days after the last study treatment administration.

4.2.2. Clinical activity endpoints

- Occurrence of stable disease (SD).
- Occurrence of mixed response (MR).
- Time to Treatment Failure (TTF).
- Progression-free survival (PFS).
- Overall survival (OS).
- The duration of response for patients with CR, PR or SD status.

4.2.3. Immunogenicity endpoints

- The anti-NY-ESO-1 humoral antibody concentration and response.
- ~~The anti-NY-ESO-1 specific cellular (T-cell) response.~~ *

5. STUDY POPULATION

5.1. Total treated population (TTP)

The total treated population will include all enrolled patients who have received at least one ASCI dose injection.

5.2. According-to-protocol (ATP) population for analysis of immunogenicity

Due to decision from ITx closure to prepare an abridged annex report, only TTP will be analyzed at final analysis. The ATP population for analysis of immunogenicity will thus be not applicable.

6. STATISTICAL METHODS

All statistical analyses will be performed using SAS version 9.3 under SAS Drug Development (SDD) version 4.3.

Unless otherwise specified, the different characteristics will be tabulated and analyzed by appropriate descriptive statistics:

- Frequency tables will be generated for categorical variables such as center.
- Mean, median, standard error will be provided for continuous data such as age.

6.1. Screening

The following summaries will be presented on the total screened population:

- Number of patients who are NY-ESO-1 positive screening failures and reasons of screening failure
- NY-ESO-1 expression test results: positive, negative, non-conclusive, missing
- NY-ESO-1 quantitative expression

6.2. Analysis of demographics/baseline characteristics

The following demographic (age, gender, etc.) and other baseline characteristics will be presented:

- Number of patients by country and by center
- Demographic characteristics: age, gender, geographic ancestry
- Disease characteristics: T, N, M categories, stage
- Primary tumor characteristics

6.3. Treatment exposure and compliance

The following summaries will be presented on the total treated population:

- Number and percentage of patients who received study treatment doses
- Reason for premature treatment discontinuation
- Listings of (serious) adverse events leading to treatment discontinuation and to study discontinuation
- Number of patients still on treatment at each planned visit of the treatment phase and list of withdrawn patients
- Reason for premature study discontinuation
- Number of patients still on study at each planned visit and list of withdrawn patients

6.4. Analysis of safety

The following summaries will be presented on the total treated population:

- List of patients with at least one severe toxicity as assessed by the investigator, and details of related AE/SAE
- Summary of all adverse events, by MedDRA System Organ Class and Preferred Term and by worst grade (within 31 days post treatment and all)
- Summary of all adverse events that are causally related to treatment administration, by MedDRA System Organ Class and Preferred Term and by worst grade
- Summary of (potential) immune-mediated disorders by worst grade
- Summary of (potential) immune-mediated disorders that are causally related to treatment administration, by worst grade
- Summary of all serious adverse events, by MedDRA System Organ Class and Preferred Term and by worst grade
- Summary of all serious adverse events that are causally related to treatment administration, by MedDRA System Organ Class and Preferred Term and by worst grade
- Listings of all SAEs
- Summary of on-study laboratory data by worst grade versus baseline grade
- Performance status: worst value on study versus baseline

6.5. Analysis of immunogenicity

The analyses will only be produced on the total treated population.

The following summaries will be presented:

- Anti- NY-ESO-1 antibody seropositivity rates and geometric mean concentration with 95% CIs by timepoint.
- Anti- NY-ESO-1 responses by timepoint .
- Reverse Cumulative Curve of anti- NY-ESO-1 antibody concentration at visit 5, 11 and 15
- Individual patient kinetic: anti- NY-ESO-1 antibody concentration (log scale) versus elapsed time since first dose
- Graph of the anti- NY-ESO-1 GMCs by timepoints.

6.6. Analysis of clinical activity

The following summaries will be presented on the total treated population:

- Best overall response per patient (categories: CR, PR, SD, SD/PR, PD, NE) :number and proportion of subjects falling into each category
- Overall clinical response rate: number of patients whose best overall response is PR or CR, divided by the total number of patients.
- Disease control rate: number of patients whose best overall response is: any CR, PR, SD or SD/PR, divided by the total number of patients.
- Proportion of patients who present a slow progressive disease and mixed response during the course of treatment
- Kaplan-Meier curves for Follow-up duration: time from the date of first ASCI to the date the patient was last known to be alive. Patients who died during the study will be censored on the date of death.
- Kaplan-Meier curves for TTF: time from the date of first ASCI to the date of last treatment administration for patients who discontinued the treatment prematurely, regardless of the reason for study treatment discontinuation. Patients who completed their full treatment phase or who are still on treatment at the time of analysis will be censored on their last study treatment administration date.
- Kaplan-Meier curves for PFS: time from the date of first ASCI to either the date of progressive disease (PD) or the date of death (regardless of the reason), whichever occurs first. Patients who were still alive at the time of analysis and without any documented disease progression are censored at the date of their last tumor assessment.

- Kaplan-Meier curves for OS: time from the date of first ASCI to the date of death (regardless of the reason). Patients who were still alive at the time of analysis are censored at the last known alive date.

7. STATISTICAL CALCULATIONS

7.1. Derived and transformed data

7.1.1. Compliance

Permitted deviations from the stipulated date of visit (due, e.g. to week-ends or public holidays) are as follows:

- Cycle 1 (Doses 1 to 6): ± 3 calendar days
- Cycle 2 (Doses 7 to 12): ± 3 calendar days
- Cycle 3 (Doses 13 to 16): ± 4 calendar days
- Cycle 4 (Doses 17 to 24): ± 7 calendar days

7.1.2. Coding and Grading of Adverse events

- Adverse events and serious adverse events are coded according to the MedDRA dictionary (at the level of System Organ Class and Preferred Term) based on the verbatim reports. This coding is made by a medically qualified person experienced in the company-specific coding conventions. The latest available dictionary version at the time of analysis will be used.
- Adverse events and laboratory tests are graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
- Patients who did not report any particular event will be considered as patients not experiencing this event.

7.1.3. Humoral immune response to the administered recNY-ESO-1 + AS15 ASCI

- Anti-NY-ESO-1 antibody ELISA assay cut-off: 179 ELU/mL.
- A seropositive patient is a patient whose anti-NY-ESO-1 antibody titer is greater than or equal to the cut-off value.
- Seroconversion in a patient is defined by the increase in anti-NY-ESO-1 antibodies from a titer below the cut-off level before the treatment to a titer above the cut-off level following treatment.

- A humoral response is defined as:

  For an initially seronegative patient: an increase in the anti-NY-ESO-1 antibody titer to above the cut-off level (i.e seroconversion).

  For an initially seropositive patient: an increase in anti-NY-ESO-1 antibody titer to a level at least two times higher than the pre-treatment titer.

- The geometric mean concentration (GMC) is calculated by taking the anti-logarithm of the mean of the log10 concentration transformations. Antibody concentration below the assay cut-off will be given an arbitrary value of half of the cut-off for the purpose of the calculation.
- For a given patient and given immunogenicity measurement, results of missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude patients with missing or non-evaluable measurements.
- For the analysis performed on the total treated population, patients without immunogenicity measurements after ASCI treatment will be treated as non-responders.

7.1.4. Time-to-event calculation

The baseline reference date is defined as the date of first treatment.

In instances where periods between two dates are to be calculated (time-to-event endpoints), the convention to be used is as follows:

[later date] – [earlier date] + 1 day.

Should the result of this calculation be lower than 1, the time-to-event value will be re-set to 1 (event on Day 1) for the purpose of including the patient in the analysis.

When converting a number of days to other units, the following conversion factors will be used:

1 year = 365.25 days

1 month = 30.4375 days.

7.1.5. Last known alive date

For each patient who is still alive at the time of analysis, a date the patient was last known to be alive (Last Known Alive - LKA - date) will be determined.

The date the patient was last known to be alive will be derived as the latest of the following dates: dates of visits/vaccinations, last contact dates, phone contact dates, laboratory assessment dates, tumor assessment dates, (S)AEs onset/resolution dates.

7.2. Methodology for computing CI

- The 95% CI for GMC is obtained by first computing the 95% CI for the mean of log10-transformed concentration assuming that they are normally distributed with unknown variance. The 95% CI for the GMC is then obtained by applying the reverse operation (10x) on the 95% CI for the mean of log10-transformed concentration.
- The exact 95% CIs of the seropositivity and response rates are calculated using Clopper-Pearson's exact method.
- Two-sided 95% confidence intervals for the median Time to Event will be computed by the Brookmeyer and Crowley method.

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Description	Analysis ID	Disclosure Purpose (CTRS=public posting, SR=study report, internal)	Dry run review needed (Y/N)	Study Headline Summary (SHS)requiring expedited communication to upper management (Yes/No)	Reference for TFL
Final analysis	E1_01	Abridged CSR and CTRS	N	N	TFL FA E1_01

8.2. Statistical considerations for interim analyses

Not applicable.

9. CHANGES FROM PLANNED ANALYSES

- Following MAGRIT study (A double-blind, randomized, placebo-controlled Phase III study to assess the efficacy of recMAGE-A3 + AS15 Antigen-Specific Cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive Non-Small Cell Lung Cancer) showed the absence of treatment effect in any of the primary, secondary, or exploratory analyses, clinical activity will not be reported within the population of patients who present the predictive MAGE-A3 gene signature.
- Cellular (T-cell) response will not be summarized as results only available for few patients
- Due to decision from ITx closure to prepare an abridged annex report, only TTP will be analyzed at final analysis.

10. REFERENCES

Brookmeyer, R., and Crowley, J. A Confidence Interval for the Median Survival Time. *Biometrics*, 38, 29–41, 1982.

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