Official Protocol Title:	A Phase IB Trial with OTX015/MK-8628, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, in Patients with Selected Advanced Solid Tumors
NCT number:	NCT02259114
Document Date:	09-February-2017

Statistical Analysis Plan (SAP)

1. INTRODUCTION

This SAP is a companion document to the protocol OTX015_108/MK-8628-003, *A Phase IB Trial with OTX015/MK-8628, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, in Patients with Selected Advanced Solid Tumors*. In addition to the information presented in the protocol statistical considerations section which provides the principal features of analyses for this trial, this SAP provides additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

2. ANALYTICAL AND METHODOLOGICAL DETAILS

2.1 Responsibility for Analyses/In-House Blinding

The statistical analyses of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

The trial is open-label, i.e., subjects, Investigators, and Sponsor personnel will be aware of subject treatment assignment after each subject is enrolled and treatment is assigned. Allocation to treatment will not be randomized.

2.2 Statistical Design and Sample Size

The study is designed to assess the safety of OTX015/MK-8628 in patients with advanced or metastatic solid tumors. The small numbers per cohort are not intended for statistical hypotheses. Treatment decisions will be made by the SMC.

In study part 1, up to 48 patients evaluable for DLT were expected in QD Regimens 1 and 2 (i.e. up to 24 patients per regimen, 6 patients per four dose levels) depending on the number of patients experiencing DLTs.

In study part 2, up to 42 evaluable patients (6-14 per three dose levels) will be included in the BID regimen.

Overall, a total of up to 90 evaluable patients are expected to be accrued in this study. The final sample size will depend on the number of patients experiencing DLTs at each DL and in each regimen, and may be increased if the MTD is not reached and additional DLs are required.

2.3 Study Objectives

Primary Objective

- To determine the Maximal Tolerated Dose (MTD) defined as the recommended phase II dose for three distinct regimens of OTX015/MK-8628 administered orally to patients with selected advanced solid tumors.

Secondary Objectives

- To assess the safety profile of single-agent OTX015/MK-8628
- To characterize pharmacokinetics parameters and pharmacodynamics of OTX015/MK-8628
- To determine the antitumor activity of OTX015/MK-8628 in selected solid tumors

2.4 Study Endpoints

Primary Endpoint

- The number of patients experiencing at least one DLT in cycle 1 (day 1 to 21) for each of the regimens independently

Secondary Endpoints

- *Safety*: Incidence, severity and relationship of AEs, laboratory abnormalities, SAEs, discontinuations due to AEs, dose adaptations due to AEs, and DLT
- *Efficacy*: The number of patients with clinical benefit (defined as complete response, partial response or stable disease) and progressive disease based on the best overall response from tumor evaluations performed every 2 cycles, according to RECIST v1.1 or PCWG2, and tumor marker assessment
- *Pharmacokinetics*: Plasma parameters of OTX015/MK-8628 as appropriate and according to analyses performed (non-compartmental or nonlinear mixed effect modelling)
- *Pharmacodynamics*: Efficacy signal or incidence and severity of AEs along with PK parameters, analyzed in relation to the most pertinent biomarker(s), if any

2.5 Analysis Populations

Evaluable for DLT: Patients who receive at least 85% of the planned dose of study drug (18 days for QD Regimen 1 and the BID regimen, or 6 days for QD Regimen 2) or experience DLT during the first 21-day cycle

Treated population: Patients who receive at least one dose of study drug

Evaluable for efficacy: Patients who receive at least 2 complete cycles (6 weeks) of treatment and have undergone baseline assessment and one on-study tumor assessment, or who discontinue early due to disease progression

2.6 Statistical Methods

The study is designed to assess the safety of OTX015/MK-8628 in patients with solid tumors. The small numbers per cohort are not intended for statistical hypotheses.

Quantitative variables will be summarized using descriptive statistics; continuous variables will be presented as N, mean and/or median, standard deviation, range, and categorical variables will be presented using frequencies and percentage. For CRPC patients, since no response was observed, waterfall plots will not be prepared.

Patient disposition and demographics will be analyzed in all included patients, response will be analyzed in patients evaluable for efficacy, and safety will be analyzed in the treated population with an additional analysis in patients evaluable for DLT.

AEs will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be tabulated by System Organ Class and Preferred Term. Laboratory values outside normal limits will be summarized using the NCI-CTCAE version 4.03. Concomitant medications will be coded according to the WHO Drug Dictionary.

Data will be presented by dose level, regimen, and where appropriate by indication. No imputations for missing data will be made.

Pharmacokinetics and pharmacodynamics will be analyzed and reported separately.

2.7 Interim Analysis

No formal interim analysis is planned.

During the dose escalation phase, regular assessment of data from the most recent cohort of three patients of each regimen evaluable for DLT will be performed by the SMC.