2. H8K-MC-JZAO Synopsis

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Clinical Study Report Synopsis: Study H8K-MC-JZAO

Title of Study: SUMMIT-1: A Randomized Phase 3 Study of Tasisulam Administered as an Intravenous Infusion on Day 1 of a 28-Day Cycle vs. Paclitaxel as Second-Line Treatment in Patients with Metastatic Melanoma	
Number of Investigators: This multicenter study included 98 principal investigators.	
Study Centers: This study was conducted at 92 study centers in 16 countries.	
Publication(s) Based on the Study: None at this time.	
Length of Study: Date of first patient enrolled: 16 December 2009 Date of last patient completed entire study: 22 March 2011	**Phase of Development:** 3

Objectives: The primary objective of this study was to compare the overall survival (OS) of patients who had received 1 prior regimen of dacarbazine- or temozolomide-based chemotherapy for metastatic melanoma when treated with either tasisulam or paclitaxel.

The secondary objectives of the study were:

--To compare the following between treatment arms:

- time-to-event efficacy variables, including:
  - progression-free survival (PFS)
  - duration of response (DoR)
  - Deterioration in the Functional Assessment of Cancer Therapy – Melanoma (FACT-M) trial outcome index (TOI) score
- objective tumor response rate
- therapeutic benefit rate (TBR)
- measures of relative safety, including quantitative and qualitative laboratory and nonlaboratory toxicities
- health outcome measures, including time to worsening of health related quality of life and measures of the patient's well-being and symptoms

--Translational Research:

- to evaluate the treatment-specific and treatment-independent effects of BRAF and c-Kit mutational status on measures of clinical efficacy, including OS, PFS, DoR, and response
- to evaluate the treatment-specific effects of genetic markers, including but not limited to DMET genes such as CYP2C19 and CYP2C9, on measures of clinical efficacy and toxicity
- to assess other exploratory biomarkers relevant to tasisulam and paclitaxel
- to assess other exploratory biomarkers relevant to the disease state of melanoma
- to assess the association between other exploratory biomarkers and clinical outcome

Study Design: This was a Phase 3, global, multicenter, 2-arm, randomized, open-label investigation of tasisulam versus paclitaxel administered after 1 prior systemic treatment regimen containing either dacarbazine or temozolomide for metastatic melanoma. Tasisulam was administered as a 2-hour intravenous (IV) infusion on Day 1 of a 28-day cycle. Paclitaxel was administered as a 1-hour IV infusion on Days 1, 8, and 15 of a 28-day cycle. Eight hundred patients were to be enrolled into the study worldwide and the study was to remain open until 600 events (deaths from any cause) were observed. Patients were randomized 1:1 to either tasisulam or paclitaxel treatment. Appropriate efficacy measures were recorded every other cycle until progression, and upon discontinuation of treatment, with the exception of physically-assessed lesion measurements, which were repeated every cycle before tasisulam or paclitaxel administration and at discontinuation of treatment, as appropriate.

Protocol Amendment (b) was approved 19 January 2011 and was implemented to change the conduct and analysis of the study after identification of a potential safety risk. A temporary hold was placed on randomization and study drug treatment. All patients on treatment who were randomized to tasisulam treatment (Arm A) and had received only 1 dose of treatment (Cycle 1) as of 23 November 2010 were discontinued from study drug. Subsequently, all patients who were on study drug as of 10 December 2010 were discontinued from treatment. An interim futility test was carried out based on an analysis of PFS.

Number of Patients:

Planned: 400 per treatment arm
Randomized: 168 tasisulam, 168 paclitaxel
Treated (at least 1 dose): 164 tasisulam, 161 paclitaxel
Completed: 141 tasisulam, 126 paclitaxel (completed is defined as not discontinued due to sponsor decision)

Diagnosis and Main Criteria for Inclusion:

Inclusion: histologic and/or cytologic diagnosis of malignant melanoma that is metastatic (Stage IV); measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.0); at least 18 years of age; performance status of 0 to 1 on the Eastern Cooperative Oncology Group (ECOG) Scale; have progressed after 1 previous systemic treatment containing dacarbazine or temozolomide for metastatic melanoma; have discontinued all previous therapies for cancer, including chemotherapy, radiotherapy, immunotherapy, or other investigational therapy for at least 30 days (6 weeks for mitomycin-C or nitrosoureas) before study enrollment and recovered from the acute effects of therapy (except alopecia).

Exclusion: have received ≥2 previous cytotoxic-based treatment regimens for metastatic melanoma; immunotherapy or antibody-based regimen [including vaccination-based treatments], or single-agent treatment with a targeted agent (for example, BRAF or c-Kit inhibitor), are not counted as a prior treatment regimen for determining study eligibility unless either was combined with a chemotherapeutic drug; have documented active central nervous system or leptomeningeal metastasis (brain metastasis) at the time of study entry; were currently receiving warfarin; have primary ocular or mucosal melanoma; any previous treatment with paclitaxel or a paclitaxel-containing regimen for metastatic melanoma.

Test Product, Dose and Mode of Administration:

Tasisulam, administered as a 2-hour IV infusion on Day 1 of every 28-day cycle at a dose that was either equivalent to or lower than the target maximum concentration (C_{max}) dose of 420 µg/mL, as dictated by their precycle albumin.

Reference Therapy, Dose and Mode of Administration: Paclitaxel, 80 mg/m^2, given on Days 1, 8, and 15 of every 28-day cycle as a 1-hour IV infusion.

Duration of Treatment:

Treatment period: until disease progression, unacceptable toxicity, or patient or physician decision
Observation period: until death from any cause, or until the patient is lost to follow-up

- treatment period: until progression
- washout period: 30 days
- observation period: until death

Variables:

Efficacy: OS, PFS, DoR, deterioration in the FACT-M TOI score, objective tumor response rate, TBR

Safety: Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 grades for laboratory and nonlaboratory adverse events, treatment-emergent adverse events, dose adjustments and treatment compliance

Bioanalytical: A validated liquid chromatography/tandem mass spectrometry method (LC/MS/MS) was used to measure plasma concentrations of tasisulam

Health Outcomes: FACT-M, EuroQol-5D (EQ-5D), frequency of resource utilization; treatment complications, transfusions, treatment-related hospitalizations, and concomitant medications

Statistical or Other Evaluation Methods:

The primary objective of this study was to compare the OS of patients who had received 1 prior course of chemotherapy for metastatic malignant melanoma when treated with tasisulam or paclitaxel. A sample size of 800 randomized patients (approximately 400 per arm) was planned, with final analysis conducted after 600 deaths were observed among randomized patients (approximately 25% censoring). A single interim analysis for futility based on the primary objective was planned to occur after 150 deaths were observed. Based on 150 events for the interim analysis, 600 events for the final analysis, a 7.28-month (222-day) median survival in the paclitaxel group and a 2.43-month (74-day) improvement in median OS in the tasisulam group (overall survival hazard ratio [OSHR] = 0.75), this design had 80% power to achieve statistical significance at a 1-sided alpha level of 0.025.

Consistent with the principles of an intent–to-treat (ITT) analysis, the primary analysis population for all endpoints consisted of all patients randomized to a treatment.

Efficacy: OS was calculated from the date of randomization to the date of death from any cause. Patients not known to have died as of the data cutoff date were censored at the last contact date.

For the purpose of the statistical design, the OSHR of tasisulam over paclitaxel was assumed to be approximately constant over the period from randomization to death. A 1-sided log-rank test was used to compare OS between treatment arms as part of the primary analysis. PFS was calculated from the date of randomization to the date of (objectively determined) disease progression or death from any cause if the patient died without observed disease progression. DoR was calculated for patients having an objective response of partial response (PR) or complete response (CR) from the date of their first assessment meeting either CR or PR criteria to the date of objectively determined disease progression or death from any cause. Objective tumor response rate was estimated as the proportion of patients randomized to treatment having a best overall response of either CR or PR. TBR was estimated as the proportion of patients randomized to treatment with a CR or PR plus patients with a best response of stable disease with a reduction from baseline in the sum of target lesion measurements among all patients who received at least 1 dose of study drug.

Safety: Safety analyses include summaries of laboratory and nonlaboratory CTCAE by grade, incidence of Grade 3 or 4 laboratory and nonlaboratory CTCAE, treatment-emergent adverse events, dose adjustments, and study drug compliance. Differences in rates between treatment arms were tested without adjustments for multiple comparisons.

Pharmacokinetics: A population pharmacokinetic (PK) analysis was performed on all patients who received tasisulam for whom PK data were available. This analysis explored the relationship between tasisulam PK and toxicity.

Health Outcomes: Health outcomes analyses included mixed-model, repeated-measures analyses of FACT-M and EQ-5D scores across time by treatment. The primary analysis included only records with complete questionnaire information. Resources used were compared using frequency of at least 1 event.

Conclusions:

- On 22 November 2010, enrollment in the study was temporarily suspended due to an imbalance in possibly study drug related deaths following the occurrence of tasisulam-related myelosuppression, particularly fever and neutropenia, infection, and/or sepsis occurring at a higher frequency than expected for this patient population. At the time of the temporary suspension, the possibly-related deaths on study had occurred during the first 2 cycles.
- As additional safety measures were being implemented, 2 additional deaths in Cycle 3 occurred in the tasisulam arm, and the study was placed on full clinical hold on 10 December 2010.
- Results of the interim analysis of PFS and OS for futility indicated that tasisulam would be unlikely to be superior to paclitaxel if all the patients were followed until progression or death, and the study was permanently closed.
- In the tasisulam arm, 13 deaths due to AEs were possibly related to study drug and none of the 3 deaths due to AEs in the paclitaxel arm were possibly related to study drug.
- The most common possibly-related AE associated with death on study in the tasisulam arm was a septic event, which occurred in 5 subjects.
- SAEs possibly related to study drug treatment in the tasisulam arm occurred in 38 patients (23.2%), and consisted primarily of thrombocytopenia, neutropenia/leukopenia, septic events, anemia, and febrile neutropenia.
- The observed percentage of patients with albumin-corrected exposures (AUCalb) in the intended target range in Cycle 1 was consistent with predictions based on prior tasisulam PK, and was associated with an acceptable rate of Grade 4 hematological toxicity. However, the percentage of patients with an AUCalb above the intended target range in Cycle 2 was higher than predicted, and was associated with an unacceptable rate of Grade 4/5 hematologic toxicity.
- Low tasisulam clearance in a subsection of the study population, leading to drug accumulation and high AUCalb explained the majority of Grade 4 hematological toxicity and possibly-related deaths observed in Cycle 2.
- Univariate analyses indicated that concomitant usage of PPIs, age, and CYP2C19 poor metabolizer status were associated with a higher risk of tasisulam-related Grade 4 hematological toxicity, although none of these alone explained the majority of the events.
- CYP2C19 functional status is also associated with unbound tasisulam clearance, with low unbound clearance being associated with poor metabolizer status. These findings are consistent with results of in vitro studies indicating that tasisulam is metabolized by CYP2C19.
- Stepwise logistic regressions revealed that low clearance of tasisulam, defined as a Cycle 1 Day 15 tasisulam concentration greater than 130 µg/mL was the best predictor of Grade 4 hematologic toxicity in Cycle 2, likely because this variable encompassed multiple factors that could affect tasisulam clearance. These findings are consistent with the results of the PK analysis that identified the 130 µg/mL concentrations and support the use of the dosage adjustment based on Cycle 1 Day 15 concentration.
- Based on the safety findings in this study, strong or moderate CYP2C19 inhibitor drugs have been excluded from other tasisulam studies, and the tasisulam dosing calculator has been revised to decrease the chronic dose of patients with low clearance of tasisulam based on individual Cycle 1 Day 15 PK values.