**E7389-M001-218**

An Open-Label Single-Arm Multicenter Phase 1b/2 Study to Evaluate the Efficacy and Safety of Eribulin Mesylate in Combination with Pembrolizumab in Subjects with Metastatic Triple Negative Breast Cancer (mTNBC) 三阴性乳腺癌

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**适应症：**

HALAVEN是一种微管抑制剂适用于转移性乳腺癌患者的治疗，患者为转移疾病治疗既往接受至少两种化疗方案。既往治疗应已包括一种蒽环类和一种紫杉烷类或者辅助或转移情况。

**作用机理：**

Eribulin抑制微管的生长阶段，而不会影响缩短相位和螯合微管蛋白进入非生产性聚集体。 Eribulin经由基于微管蛋白抗有丝分裂的机制，导致G2 / M细胞周期阻滞，有丝分裂纺锤体的破坏，以及最终的凋亡细胞死亡延长后有丝分裂阻断发挥其作用。

此外，人乳腺癌细胞的eribulin治疗引起在形态和基因表达的变化，以及在体外迁移和侵袭减小。在人乳腺癌的小鼠异种移植物模型，eribulin治疗与增加血管灌注和渗透性在肿瘤内核相关联，从而导致肿瘤缺氧减少，并且在与在表型的改变相关联的肿瘤标本的基因的表达的变化。

# Study Objectives

In subjects with mTNBC previously treated with

* 0 (Stratum1) or
* 1 to 2 (Stratum 2)

lines of systemic anticancer therapy in the metastatic setting and currently treated with eribulin mesylate in combination with pembrolizumab.

# Primary Objective

* For the Phase 1b part – to determine safety and tolerability of eribulin mesylate in combination with pembrolizumab in all subjects (ie, Stratum 1 and 2).【爬剂量】
* For the Phase 2 part – to evaluate objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by independent imaging review (IIR) in all subjects.【PP要监测的主要目标】
* For the Phase 2 part – to evaluate ORR per RECIST 1.1 by IIR in Stratum 2 subjects and compare with the historical response rate of pembrolizumab monotherapy of 10%.

# Overall Study Design and Plan

Approximately 12 subjects may be enrolled in the Phase 1b part of the study.

Under protocol amendment 1, 107 subjects (including subjects in Phase 1b who are on RP2D level) were enrolled in 2 strata and received the same combination treatment at the RP2D level.

The strata include Stratum 1 and Stratum 2.

Bayesian predictive probability (PP) of response rate was used to monitor the response rate after postbaseline tumor assessments for **at least 38 subjects** were available.

The study could be **stopped early for efficacy or futility** if PP crosses the prespecified boundary.

Hence, efficacy conclusion of the primary efficacy endpoint of ORR could be made on the basis of the predictive probability prior to the full enrollment of 100 evaluable subjects in the study.【在入满100个患者之前，可以提前做出efficacy conclusion，根据PP结果】

There is clinical interest to have a more precise estimation of the efficacy data for **Stratum 2**. Therefore, per protocol amendment 3, additional subjects will be added to Stratum 2 in order to include a total of 80 evaluable subjects in Stratum 2 for final analysis. As a result, approximately 150 subjects in total (145 evaluable with 80 in Stratum 2) will be enrolled.

Per protocol amendment 4, additional subjects will be added to Stratum 2 in order to include a total of at least 100 evaluable subjects in Stratum 2 for final analysis.【protocol amendment 3与4都向Stratum 2增加样本量，在Amendment4时候加到100】

# DETERMINATION OF SAMPLE SIZE

A total of approximately **170 subjects (165 evaluable with 80 in Stratum 2)** will be enrolled.

**Protocol amendment 1**

107 subjects including at least 6 from the Phase 1b part were enrolled in the study.

Bayesian predictive probability was used to monitor the study after response data from the first 38 subjects were available.

Sample size calculation was carried out assuming the **historical response rate of 0.2**. Using simulation, the model parameters (**, , and** ) were calibrated such that

* the **frequentist 1-sided Type I error was 0.0326** when the tumor response rate in the combination regimen was 0.2 (under frequentist’s null hypothesis H0),
* and **the power was 0.9278** when the response rate was 0.35 (under frequentist’s alternative hypothesis Ha).

The expected numbers of subjects needed to reach the decisions were **56 and 61 when p=0.2** (under H0) and 0.35 (under Ha), respectively.

A **vague beta prior distribution for response rate, p**, was specified in PP calculation; that is, . PP was updated for **every 3 new subjects in the simulations**, which mimics the group sequential decision making in a real trial setting. **Without Bayesian interim monitoring, the Type I error was estimated as 0.0358, and power was estimated as 0.9418 in demonstrating posterior probability P(p>0.2|data) ≥0.95.** Five thousand simulations were run to estimate these design characteristics.

**Protocol amendment 3**

Additional subjects will be enrolled to ensure 80 evaluable subjects in Stratum 2. Using binomial exact test, the power is 0.92 with 80 evaluable subjects to demonstrate statistical significance at 1-sided alpha of 0.025 for the assumptions of H0: ORR=0.10 vs. Ha: ORR=0.25. With 80 subjects, the 95% confidence interval for ORR from binomial distribution will be 0.160-0.359 if the observed ORR is 0.25.

**Protocol amendment 4**

Additional subjects will be added to Stratum 2 in order to include a total of at least 100 evaluable subjects in Stratum 2 for final analysis.

# Primary Efficacy Analyses (ORR in All Subjects)

Bayesian predictive probability (PP) design was used in original study design (Yin, 2012). Under original design, in the combined Stratum 1 and 2 subjects, the ORR value per RECIST 1.1 by IIR was assumed to be **0.20** for the historical control (see Table 1 footnote a in protocol amendment 04) and the ORR in this trial was expected to be **0.35**. Under protocol amendment 1, approximately 100 evaluable subjects were expected to be enrolled. Bayesian PP was used to monitor the response rate after postbaseline tumor assessments of at least 38 subjects were available. The calculation of PP was based on the goal of **claiming superiority of the combination therapy at the end of the study** if

where

* was the response rate of the combination therapy,
* 0.2 was the **response rate of historical control** based on single agents pembrolizumab and eribulin in recent trials (Table 1 in Protocol Amendment 4),
* 0.95 was the prespecified target probability (),
* is the posterior probability.

Without any interim analysis, the trial requires the posterior probability of to be at least 0.95 at the end of the trial in order to demonstrate the superiority of combination therapy over historical control.

Since interim monitoring is implemented in the trial, Bayesian predictive probability (PP) is calculated when there are 38 patients in the **Interim Analysis Set (definition in interim analysis section)** to evaluate how likely the trial would complete its full enrollment.

Specifically, on the basis of the accumulated data up to time of data monitor in the study, the probabilities of all possible future outcomes that lead to equation (1) at the end of the study would be added in order to obtain the predictive probability as given in (2) below.

Therefore, early decision of study termination prior to reaching approximately 100 evaluable subjects was possible for claiming the combination therapy is promising when PP is above a prespecified upper threshold () or for claiming futility when PP is below a prespecified lower threshold ().

The **upper and lower cutoff probabilities for decision-making,**  **and , were set as 0.99 and 0.025**. Under the predictive monitoring, the study proceeded as follows:

* If , stop the study and claim the combination therapy promising
* If , stop the study and claim the combination therapy not promising
* Otherwise, continue the study until the number of evaluable subjects reaches to 100

After completion of enrollment under protocol amendment 1, Bayesian PP is no longer used for continuous monitoring of efficacy and futility as the study will not be stopped early for either efficacy or futility.

The Bayesian stopping boundaries are included in table below. During the trial, PP will be calculated with updated response information till the boundary is crossed. **In case continuous PP monitoring is not conducted because of operational and logistic reasons (e.g. delayed TA assessments and fast enrollment) or it is decided to take the trial to full enrollment even is crossed in order to gather more efficacy data, posterior probability in equation (1) will be evaluated to determine the efficacy of the combination regimen after the tumor response status has been collected from the last evaluable subjects.** That is, to claim efficacy if . A two-sided 95% credible interval of ORR based on posterior distribution of will be constructed to aid the interpretation of the results.

Table

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Footnote:

* N=number of subjects included in the predictive probability calculation.
* LB=lower bound (futility boundary crossed if # objective response ).
* UB=upper bound (efficacy boundary crossed if # objective response ).

# Final Analysis

In the evaluable subjects in Stratum 1 and 2 combined, Bayesian posterior probability in equation (1) will be evaluated to determine the efficacy of the combination regimen after the tumor response status has been collected from the last evaluable subjects. That is, to claim efficacy if . A 2-sided 95% credible interval of ORR in the evaluable subjects will be constructed to aid the interpretation of the results.