A Phase 1b/3 Global Randomized, Double-blind, Placebo-controlled Study of Tazemetostat in Combination with Doxorubicin as Frontline Therapy for Advanced Epithelioid Sarcoma

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BACKGROUND
Epithelioid sarcoma (ES) is a rare and aggressive subtype of soft tissue sarcoma (STS) that can originate in any anatomic location. It predominantly affects young adults (median age 36 years) and is characterized by frequent local recurrences and distant metastasis.

• Tazemetostat is a selective, oral, small molecule inhibitor of EZH2, a catalytic subunit of the polycomb repressive complex 2 (PRC2), to repress cell differentiation and promote tumor growth.

• The loss of INI1 may allow enhancer of zeste homolog 2 (EZH2), a catalytic subunit of PRC2, to repress cell differentiation and promote tumorigenesis via increased transcription of histone H3 at lysine 27 (H3K27).

• Early clinical trials have shown a high percentage of responders in patients with ES.

• Epizyme, Inc. (Amherst, MA) and Epizyme Europe SA (Geneva, Switzerland) have announced the initiation of a Phase 1b/3 Global Randomized, Double-blind, Placebo-controlled Study of Tazemetostat in Combination with Doxorubicin as Frontline Therapy for Advanced Epithelioid Sarcoma (EZH-301). This study is designed to evaluate the safety and efficacy of Tazemetostat + doxorubicin in frontline therapy for patients with ES not eligible for resection (Figure 1).

• Enrolled patients will receive either blinded tazemetostat (100 mg, 250 mg, 400 mg, or 800 mg BID) + doxorubicin or blinded placebo + doxorubicin in 21-day cycles (Figure 2).

• Patients will continue treatment with blinded tazemetostat (100 mg, 250 mg, 400 mg, or 800 mg BID) until disease progression or intolerable toxicity.

• Patients will continue treatment with blinded doxorubicin intravenously on day 1 of each cycle for up to 6 cycles.

• Enrollment of the 1st dose level was completed in March 2018 and the Safety Review Board approved advancement to the 2nd dose level.

• Patients will continue treatment with blinded tazemetostat (100 mg BID, 250 mg BID, or 400 mg BID) + doxorubicin or blinded placebo + doxorubicin in 21-day cycles until disease progression or intolerable toxicity.

• The maximum tolerated dose (MTD) will be identified as the highest dose level at which no patients experience dose-limiting toxicity.

• The study design is summarized in Figure 1.

• All patients reported an improvement in their overall health and quality of life that was sustained through the length of the study.

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STUDY DESIGN

• A phase 1b/3 study is initiation, randomization, and combination with doxorubicin.

• Phase 1b/3: Tazemetostat was being dosed at level 3 (400 mg BID) in combination with doxorubicin.

• Patients will continue treatment with blinded tazemetostat (100 mg, 250 mg, 400 mg, or 800 mg BID) + doxorubicin or blinded placebo + doxorubicin in 21-day cycles until disease progression or intolerable toxicity.

• The maximum tolerated dose (MTD) will be identified as the highest dose level at which no patients experience dose-limiting toxicity.

• The study design is summarized in Figure 1.

• The primary objective of the current study is to evaluate the safety and efficacy of Tazemetostat + doxorubicin as frontline therapy for patients with ES not eligible for resection (Figure 3).

• Key preliminary results are presented in Table 1.

• Tazemetostat was well tolerated and associated with a 15% objective response rate (ORR), with 1 patient achieving a confirmed complete response (CR) and 3 patients achieving a partial response (PR).

• Median duration of response (DOR) was 10.7 months.

• Median overall survival (OS) was 35.8 months.

• Median progression-free survival (PFS) was 9.7 months.

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