26G-ISMS37 **Novel Development of Chemotherapy for Relapsed and Refractory AML Based on the Promising Functional Mechanism of Cytidine Analog, DFP-10917**

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Acute myeloid leukemia (AML) is still progressed disease vigorously challenging to urgently improve a prognosis in patients. At present time, induction-chemotherapy with cytarabine (one of cytidine analog) combined with anthracycline drugs has been frequently conducted for the treatment of AML, and sequential consolidation-chemotherapy with almost same regimen is performed for patients. However there are few suitable treatment options for patients with relapsed and refractory AML.

We developed a new generation of cytidine-type antitumor nucleoside, DFP-10917 and investigated the antitumor efficacy and functional mechanism of this drug in vitro and in vivo using human tumor cells. DFP-10917 showed the most potent antitumor activity on tumor models in mice following its prolonged (14-days) infusion at very low-dose (4.5 mg/kg/day) compared to short injection of DFP-10917 and of other cytidine analog. Under such prolonged dosing schedule, DFP-10917 is converted to its nucleotide form and subsequently incorporated into DNA in tumor cells which cause DNA-strand breaks resulting in G2/M phase-arrest by cellular checkpoint regulators and resultantly formed the ultimate apoptotic cells. In contrast, cytarabine is converted to their nucleoside-triphosphates and then inhibit DNA polymerase activity leading to protection of DNA biosynthesis during the S-phase of the cell cycle.

To evaluate clinical efficacy and toxicity in phase I/II study of DFP-10917, AML patients were treated with continuous infusion (CI) of DFP-10917. In phase I study, low-dose (6 mg/m^2) 14-day CI of DFP-10917 was found to result in a clinical benefit to patients as recommended dose and schedules. In phase II study, total 29 patients were enrolled and the response rate and the median survival time in relapsed/refractory AML patients were 48% and 7.3 months, respectively. No patients discontinued DFP-10917 treatment due to unacceptable drug-related toxicity. Further study of DFP-10917 in a phase III study in AML is planned.