# A Phase 2 biomarker-driven study evaluating the clinical efficacy of MDM2 inhibitor, milademetan, in patients with intimal sarcoma, a disease with a high unmet need

Kan Yonemori[1)2)], Toshio Shimizu[1)], Takafumi Koyama[1)], Yuki Kojima[2)], Naoko Matsui[3)], Hitomi Sumiyoshi Okuma[2)3)], Emi Noguchi[2)], Kazuki Sudo[1)2)], Akihiro Hirakawa[4)], Natsuko Okita[3)], Tamie Sukigara[3)], Kenichi Nakamura[3)], Kenji Tamura[2)], Noboru Yamamoto[1)], Yasuhiro Fujiwara[2)5)]

1) Department of Experimental Therapeutics, National Cancer Center Hospital, Japan, 2) Department of Breast and Medical Oncology, National Cancer Center Hospital, Japan, 3) Clinical Research Support office, National Cancer Center Hospital, Japan, 4) Department of Biostatistics and Bioinformatics, the University of Tokyo, Japan, 5) Pharmaceuticals and Medical Devices Agency

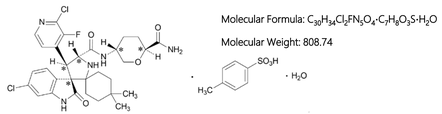
## Background

### Overview of Intimal Sarcoma

- Intimal sarcoma is a very rare disease that originates from large blood vessels throughout the body.
- MDM2 amplification has been reported in approximately 60-70% of intimal sarcomas. MDM2 amplification in sarcoma tend to occur in a mutually exclusive manner with p53 mutations.
- Surgical resection is the first choice in many cases. Standard treatment for cases with difficult resection, recurrence after resection, distant metastasis has not been established.
- In clinical practice, chemotherapy is performed for usual advanced malignant soft tissue sarcomas such as cytotoxic anticancer drug doxorubicin and molecular target drug pazopanib, but none of them can be expected to have anti-tumor effect.
- The prognosis is very poor, and survival time after diagnosis is about 5-9 months for aortic root and about 13-18 months for pulmonary artery.

### Overview of Milademetan

- Milademetan is a novel specific small-molecule inhibitor of MDM2 that disrupts the MDM2-p53 interaction in tumor cells and developed by Daiichi Sankyo.
- A cell-free study using recombinant MDM2 and p53 proteins demonstrated inhibition of MDM2-p53 binding by milademetan with an IC50 value of 5.57 nM.
- Milademetan also inhibited cell growth in a p53 wild-type cell line, but not p53 mutant or null cell lines.
- The safety and efficacy of Milademetan has been investigated in several phase 1 trials for patients with solid tumor or lymphoma (NCT01877382), those with leukemia (NCT02319369), those with multiple myeloma (NCT02579824) and those with solid tumor and lymphoma in Japan (JapicCTI-142693).
- Objective response and durable stable disease are seen in patients with WD/DD LPS and other tumors that harbor MDM2 gene amplification.(TM. Bauer, et. al ASCO 2018)



Molecular Formula: $C_{30}H_{34}Cl_2FN_5O_4 \cdot C_7H_8O_3S \cdot H_2O$

Molecular Weight: 808.74

## Study Design

- A sub-study of our basket trial under the nationwide large registry for rare cancers in Japan (MASTER KEY Project)

**Description of Study Design**

- Phase 2, open-label, 2-part clinical trial (JMACCT ID: JMA-II A00402)
- Study period: December 2018 – November 2022


To evaluate the safety, tolerability, and pharmacokinetics of milademetan

## Objective and endpoints

**Objective**

- The purpose of this study is to evaluate the efficacy and safety of milademetan (DS-3032b) in patients with intimal sarcoma.

**Primary Endpoint**

- Number of patients with objective response (central review) in Parts 1 and 2 who have received milademetan. (Weeks 8, 16, 24, and q 12 weeks thereafter)

**Secondary Endpoints**

- Objective Response Rate (central review, institutional review)
- Disease Control rate (CR+PR+SD) (central review)
- Progression-Free Survival
- Overall Survival
- Safety

## Rationale

**Rationale for Study Design**

- From the epidemiology viewpoint of rare cancers, it is not realistic to have control arm to compare PFS or other endpoints.
- Due to the absence of any effective treatment for intimal sarcoma, at least 1 patient with objective response will be regarded as clinically meaningful.

**Rationale for Dose**

- Schedule of qdx3 every 14 days twice in a 28 days cycle is preferred for future development in solid tumors (TM. Bauer, et. al ASCO 2018)
- 90mg QD 21 on-treatment and 7 off at each cycle (21/28 treatment) has been evaluated as MTD and also considered to be RP2D in Japanese patients (JapicCTI-142693).
- Regimen would be finally determined, considering the conclusion from sponsor study (NCT01877382).

## Population

**Key Inclusion Criteria**

- MDM2 amplification is confirmed by NGS or FISH or IHC
- Wild-type TP53 is confirmed by NGS or FISH or IHC
- Age ≥ 18 years old at the informed consent
- PS=0-2
- Written informed consent
- Has measurable target lesion at the baseline
- Has adequate organ functions as below
  Neutrophil count ≥ 1500 $mm^3$, Platelet count ≥ 100,000 $mm^3$,
  Hb ≥ 8.0g/dL, AST/ALT ≦ 100U/L, Cr ≦ 1.5 mg/dL or CCr ≥ 45mL/min

## Treatment

**Dose and schedule**

- Miladametan 260 mg qdx3 every 14 days twice in a 28 days cycle
- Continue until intolerability or disease progression

Contact information: NCCH1806_1809_office@ml.res.ncc.go.jp, Sponsor information: Daiichi Sankyo Co., Ltd.(Finance and Investigational product)