2021 ESMO congress

1521O

A phase II biomarker-driven study evaluating the clinical efficacy of an MDM2 inhibitor, milademetan, in patients with intimal sarcoma, an ultra-rare cancer with highly life-threatening unmet medical needs (NCCH1806/MK004)

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Background

Intimal sarcoma is an ultra-rare, high-grade malignant neoplasm arising in the intima of large blood vessels, most frequently the pulmonary arteries and aorta. As murine double minute 2 (*MDM2*) amplification is found in over 70% of intimal sarcomas, inhibition of MDM2 could provide clinical benefit in this patient population. This study was conducted to evaluate the activity of milademetan, a novel specific small-molecule inhibitor of MDM2 in intimal sarcoma patients as a sub-study under the nationwide large registry for rare cancers in Japan (MASTERKEY Project).

Methods

Between December 2018, and January 2021, we conducted an open-label phase 2 trial in patients with *MDM2* amplified, *TP53* wild type, intimal sarcoma. Patients were eligible if they had an ECOG PS of 0-2, measurable disease, and adequate organ function. Patients received 260 mg of milademetan orally qdx3 every 14 days twice in a 28 days cycle, until disease progression or unacceptable toxicity. Primary endpoint was objective response rate, assessed by central review. Secondary endpoints included safety, PK profile, disease control rate, progression-free survival, and overall survival.

Results

A total of 11 patients, age: 20-72 (median:33.0), were enrolled and treated. One patient was excluded from response assessment due to detection of *TP53* mutation, revealed after enrollment. Median follow-up was 8.2 months (IQR 4.4-18.6). Of the ten evaluable patients, two had partial responses. Response rate and disease control rate were 20% (95% CI 2.5-55.6) and 50% (95% CI 18.7-81.3), respectively. The most common grade 3 and 4 treatment-related adverse events were cytopenic in nature, including: thrombocytopenia (10/11 [90.9%]), neutropenia (8/11 [72.7%]) and luekocytopenia (6/11 [54.5%]). No treatment-related mortality was observed.

Conclusions

Milademetan showed acceptable safety profile with some clinical activity in patients with intimal sarcoma with *MDM2* amplification. These results suggest that MDM2 inhibitor may be a potential promising therapeutic option for this life-threatening unmet medical needs.

Clinical trial identification

JMA-IIA00402.

Legal entity responsible for the study

The authors.

Funding

Daiichi Sankyo.

Disclosure

T. Shimizu: Financial Interests, Personal, Speaker's Bureau: AbbVie; Financial Interests, Personal, Speaker's Bureau: Daiichi-Sankyo; Financial Interests, Personal, Speaker's Bureau: Eisai; Financial Interests, Personal, Speaker's Bureau: Takeda

Oncology; Financial Interests, Personal, Speaker's Bureau: MSD; Financial Interests, Personal, Advisory Board: Daiichi-Sankyo; Financial Interests, Personal, Advisory Board: AbbVie; Financial Interests, Personal, Advisory Board: akeda Oncology; Financial Interests, Institutional, Research Grant: Novartis; Financial Interests, Institutional, Research Grant: AbbVie; Financial Interests, Institutional, Research Grant: Daiichi-Sankyo; Financial Interests, Institutional, Research Grant: Takeda Oncology; Financial Interests, Institutional, Research Grant: Eli Lilly; Financial Interests, Institutional, Research Grant: LOXO Oncology; Financial Interests, Institutional, Research Grant: Bristol-Myers Squibb; Financial Interests, Institutional, Research Grant: Eisai; Financial Interests, Institutional, Research Grant: Incyte; Financial Interests, Institutional, Research Grant: AstraZeneca; Financial Interests, Institutional, Research Grant: Pfizer; Financial Interests, Institutional, Research Grant: Chordia Therapeutics; Financial Interests, Institutional, Research Grant: ymbio Pharmaceuticals; Financial Interests, Institutional, Research Grant: 3D-Medicine; Financial Interests, Institutional, Research Grant: Five Prime; Financial Interests, Institutional, Research Grant: Five Prime; Financial Interests, Institutional, Research Grant: Astellas; Financial Interests, Institutional, Principal Investigator: Novartis; Financial Interests, Institutional, Principal Investigator: AbbVie; Financial Interests, Institutional, Principal Investigator: Daiichi-Sankyo; Financial Interests, Institutional, Principal Investigator: Takeda Oncology; Financial Interests, Institutional, Principal Investigator: Eli Lilly; Financial Interests, Institutional, Principal Investigator: LOXO Oncology; Financial Interests, Institutional, Principal Investigator: Bristol-Myers Squibb; Financial Interests, Institutional, Principal Investigator: Eisai; Financial Interests, Institutional, Principal Investigator: Incyte; Financial Interests, Institutional, Principal Investigator: AstraZeneca; Financial Interests, Institutional, Principal Investigator: Pfizer; Financial Interests, Institutional, Principal Investigator: Chordia Therapeutics; Financial Interests, Institutional, Principal Investigator: Symbio Pharmaceuticals; Financial Interests, Institutional, Principal Investigator: 3D-Medicine; Financial Interests, Institutional, Principal Investigator: Five Prime; Financial Interests, Institutional, Principal Investigator: PharmaMar; Financial Interests, Institutional, Principal Investigator: Astellas. 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