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Original Research

A phase I study of SAR405838, a novel human double minute 2 (HDM2) antagonist, in patients with solid tumours☆

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Abstract ***Purpose:*** In tumours with wild-type *TP53*, the tumour-suppressive function of p53 is frequently inhibited by HDM2. This phase I, dose-escalating study investigated the maximum tolerated dose (MTD), safety, pharmacokinetics and pharmacodynamics of SAR405838, an HDM2 inhibitor, in patients with advanced solid tumours (NCT01636479). ***Methods:*** In dose escalation, patients with any locally advanced/metastatic solid tumour with *TP53* mutation prevalence below 40%, or documented as *TP53* wild-type, were eligible. In the MTD expansion cohort, only patients with de-differentiated liposarcoma were included. Primary end-points were MTD and efficacy in the MTD

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expansion cohort. Secondary end-points included safety, pharmacokinetics and pharmacodynamics biomarkers.

Results: Seventy-four patients were treated with SAR405838 (50–800 mg once daily [QD], 800–1800 mg weekly and 1800 mg twice weekly). Two patients treated with SAR405838 400 mg QD had thrombocytopaenia as a dose-limiting toxicity (DLT). The MTD for the QD schedule of SAR405838 was 300 mg QD. No DLTs were observed with the weekly schedule; one patient had a DLT of nausea with the 1800 mg twice-weekly dose. Treatment with SAR405838 was associated with increased plasma MIC-1, reflecting p53 pathway activation. In the de-differentiated liposarcoma MTD cohort, 89% of the patients had *HDM2* amplification at baseline and no *TP53* mutations were observed; best response was stable disease in 56% and progression-free rate at 3 months was 32%.

Conclusion: SAR405838 had an acceptable safety profile with limited activity in patients with advanced solid tumours. The MTD of SAR405838 was 300 mg QD; MTD was not reached with the weekly schedule.

1. Introduction

Loss of the tumour-suppressive function of p53 is an important step in tumourigenesis. While loss of p53 is often due to somatic *TP53* mutations, some tumours still harbour wild-type *TP53* [1]. In these cases, biological function of p53 is frequently inhibited by the mouse double minute 2 protein (MDM2; HDM2 in humans) [2–4]. HDM2 inhibits activation of p53 target genes by binding to the transactivation domain of p53 and promoting its degradation. The HDM2 gene is amplified and/or its gene product is overexpressed in several tumour types, including de-differentiated liposarcoma (DDLPS) [5,6]. Disrupting the interaction between HDM2 and p53 using small-molecule antagonists, leading to reactivation of p53, has shown encouraging antitumour activity *in vitro* and *in vivo* [7,8]. Therefore, there is rationale for investigating treatment with HDM2 inhibitors in patients with p53 wild-type tumours.

SAR405838 is an oral spirooxindole derivative antagonist of HDM2, which binds selectively to HDM2 with an inhibitory constant (Ki) value of 0.88 nM [8]. Preclinical data have shown that SAR405838 treatment results in robust p53 pathway activation, leading to p53-dependent cell-cycle arrest and apoptosis *in vitro* and *in vivo* [8]. SAR405838 treatment resulted in tumour regression or complete tumour growth inhibition in multiple mouse xenograft tumour models. In addition, SAR405838 treatment in HDM2-amplified osteosarcoma xenograft models resulted in complete tumour regression.

This phase I, first-in-human study was conducted to determine the maximum tolerated dose (MTD), safety, pharmacokinetics (PK), and pharmacodynamics (PD) of SAR405838 in patients with solid tumours, including an MTD expansion cohort of patients with DDLPS (NCT01636479).

2. Methods

2.1. Study design

This was a phase I, open-label, dose-ranging, dose-escalating, safety, PK and PD study of SAR405838 administered orally in adult patients with advanced solid tumours. Once-daily (QD), once-weekly (QW) and twice-weekly (BIW) oral administration schedules of SAR405838 were evaluated. The primary end-points were MTD and efficacy in the MTD cohort (including progression-free rate [PFR] at 3 months). Secondary end-points included safety, PK, PD (change in macrophage inhibitory cytokine-1 [MIC-1] levels in plasma) and tumour genetics status (including baseline tumour *TP53* mutation and *HDM2* gene copy number status) in tumour samples and plasma.

The protocol was approved by all involved Independent Ethics Committees and Institutional Review Boards. The clinical trial was conducted in compliance with all applicable international and national laws and regulations and adhered to the principles outlined in the Helsinki declaration. Written, informed consent was obtained from each patient before study participation.

2.2. Patient population

Eligible patients were aged ≥18 years with a histologically or cytologically confirmed solid tumour for whom no further effective standard treatment was available. Eligible patients had disease that was locally advanced or metastatic, and measurable as defined by Response Evaluation Criteria in Solid Tumors version 1.1 [9]. For dose escalation, patients with any solid tumour having a reported *TP53* mutation prevalence below 40% [10], or documented as *TP53* wild-type, were eligible. For the MTD expansion cohort, only patients with DDLPS were included. Patients were required to have an Eastern