Leukemia Research 48 (2016) 92–100

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

A phase I trial of the human double minute 2 inhibitor (MK-8242) in patients with refractory/recurrent acute myelogenous leukemia (AML)

Farhad Ravandi[a,*], Ivana Gojo[b], Mrinal M. Patnaik[c], Mark D. Minden[d], Hagop Kantarjian[a], Amy O. Johnson-Levonas[e], Craig Fancourt[e], Raymond Lam[e], Mary Beth Jones[e], Clayton D. Knox[e], Shelonitda Rose[e], Payal Shah Patel[e], Raoul Tibes[f]

[a] The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[b] Johns Hopkins University, Baltimore, MD, United States
[c] Mayo Clinic, Rochester, MN, United States
[d] Princess Margaret Hospital, Toronto, ON, Canada
[e] Merck & Co., Inc., Kenilworth, NJ, United States
[f] MAYO Clinic Arizona, Scottsdale, AZ, United States

ARTICLE INFO

Article history:
Received 15 March 2016
Received in revised form 6 June 2016
Accepted 21 July 2016
Available online 25 July 2016

Keywords:
Human double minute 2 inhibitor
MK-8242
Acute myelogenous leukemia
p53
Phase I

ABSTRACT

Objective: Evaluate safety/tolerability/efficacy of MK-8242 in subjects with refractory/recurrent AML.
Methods: MK-8242 was dosed p.o. QD (30–250 mg) or BID (120–250 mg) for 7on/7off in 28-day cycle. Dosing was modified to 7on/14off, in 21-day cycle (210 or 300 mg BID).
Results: 26 subjects enrolled (24 evaluable for response); 5/26 discontinued due to AEs. There were 7 deaths; 1 (fungal pneumonia due to marrow aplasia) possibly drug-related. With the 7on/7off regimen, 2 subjects had DLTs in the 250 mg BID group (both bone marrow failure and prolonged cytopenia). With the 7on/14off, no DLTs were observed in 210 mg BID or 300 mg BID (doses >300 mg not tested). Best responses were: 1/24 PR (11 weeks; 120 mg QD, 7on/7off); 1/24 CRi (2 weeks; 210 mg BID, 7on/14off); 1/24 morphologic leukemia-free state (4 weeks; 250 mg BID, 7on/7off). PK on Day7 at 210 mg BID revealed $AUC_{0-12\,h}$ 8.7 μM·h, C_{max} 1.5 μM (n = 5, T_{max}, 2–6 h), $T_{1/2}$ 7.9 h, CL_{ss}/F 28.8 L/h, and V_{ss}/F 317 L.
Conclusions: The 7on/14off regimen showed a more favorable safety profile; no MTD was established. Efficacy was seen using both regimens providing impetus for further study of HDM2 inhibitors in subjects with AML.

1. Introduction

Acute myelogenous leukemia (AML) is the most common form of myeloid leukemia, with an overall incidence rate of approximately 4.0 cases per 100,000 persons and a median age of onset of 67 [1,2]. It is a clonal hematopoietic stem cell disorder with the accumulation of poorly differentiated progenitor cells that fail to respond to the normal regulators of proliferation and differentiation [3]. When left untreated, this uncontrolled hematopoietic proliferation generally leads to rapid death due to cellular infiltration of the bone marrow and organs, leading to bleeding and infection [4,5].

In patients younger than 60 years, treatment of AML typically consists of cytotoxic chemotherapy with a general cure rate of 35–40% depending on the cytogenetic classification [5]. In contrast, standard chemotherapy produces a similar outcome in only 5–15% of older patients, primarily because of their inability to tolerate intensive treatment and their generally higher risk disease features [4,5]. Treatment of older or frail patients usually involves supportive care, low-dose cytarabine and hypomethylating agents; however, no consensus treatment algorithm exists for this difficult to treat population [5,6]. Unfortunately, treatment outcomes in older patients who are unable to receive intensive chemotherapy are extremely poor, with a median survival of 5–10 months [6]. For the majority of treated AML patients who achieve remission, relapse will occur within 3 years of the initial diagnosis [4,7]. In general, the prognosis for AML patients following disease relapse is poor and the treatment options are unsatisfactory [6,8–11]. Therefore an urgent unmet medical need exists for the development of new AML therapies, particularly in older and relapsed patients.

* Corresponding author at: University of Texas – MD Anderson Cancer Center, Unit 428, 1515 Holcombe Boulevard Houston, TX 77030, United States.
E-mail address: fravandi@mdanderson.org (F. Ravandi).

http://dx.doi.org/10.1016/j.leukres.2016.07.004
0145-2126/

The transcription factor p53 is a powerful tumor suppressor that plays a critical role in maintaining genomic stability and protecting against malignant transformation [12]. Nearly 50% of all human cancers harbor loss of function mutations in the p53 gene [13]. However, the frequency of p53 mutations in hematologic cancers is low with only 3–8% of AML cases demonstrating a detectable p53 mutation [14]. Even in the presence of wild type p53, other aberrations can deleteriously influence the function and activity of p53, including over-expression of negative regulators [15]. The interaction of p53 with one such negative regulator, murine double minute 2 (MDM2; sometimes called HDM2 for its human analog), normally plays a central role in controlling the cell cycle by arresting p53 function [16]. HDM2 directly binds to p53 thereby inhibiting its transcriptional activity and mediating its ubiquitination and subsequent degradation [17]. Additionally, inactivation of the p53 pathway by HDM2 overexpression allows cancer cells to avoid p53-driven apoptosis in response to treatment with cytotoxic agents and radiation therapy. In cancer cells, the tight control of the HDM2:p53 protein–protein interaction is disrupted, thereby minimizing the tumor-suppressive activities of HDM2 on p53 and promoting a cell growth advantage [12]. These data collectively support the notion that HDM2 inhibition may hold promise as a potential anti-cancer therapeutic strategy in a wide variety of human malignancies, either alone or in combination with traditional chemotherapy, by restoring normal p53 function [18].

Prior research has shown that HDM2 over-expression, frequently resulting from increased mRNA expression rather than gene amplification, is a signature associated with certain malignancies including AML [19–23]. Furthermore, leukemia cells over-expressing HDM2 are often resistant to conventional therapy resulting in a poor overall prognosis [24]. Taken together, these findings suggest that HDM2 inhibitors may be effective in patients with AML as well as other types of cancer. Indeed, small molecule HDM2 inhibitors have shown significant activity in animal models of leukemia and in preclinical experiments using patient AML cells and leukemic cell lines [25,26]. Given these promising preclinical results, several HDM2 inhibitors have progressed to clinical evaluation in patients with AML and other hematologic malignancies (NCT02319369, NCT02098967, NCT02545283, NCT02319369; NCT02143635) [27].

MK-8242 (otherwise known as SCH 900242) is a potent, orally bioavailable, small-molecule inhibitor of the HDM2:p53 protein–protein interaction. MK-8242 has an IC_{50} value as low as 20 nM resulting in growth arrest and cell death [28]. This report describes the results of a Phase I clinical dose-ranging study designed to establish the recommended phase 2 dose (RP2D) of MK-8242 based on safety, tolerability and pharmacokinetics (PK) in adult patients with refractory or recurrent AML. Other objectives of this study were to determine the complete response (CR) rate, the complete response with incomplete platelet recovery (CRi) [29], and the duration of response following treatment with MK-8242.

2. Methods

2.1. Study design

This was a multi-center, non-randomized, open-label, 2-part (dose escalation and confirmation) study (Study Sponsor: Merck & Co., Inc., Kenilworth, New Jersey; Clinical Protocol MK-8242-005; www.clinicaltrials.gov NCT01451437) conducted between December 2011 and September 2014. The study was terminated in June 2014 by the Sponsor for reasons unrelated to safety (i.e., reprioritization of oncology portfolio) and only the monotherapy cohort (i.e., Arm A, Part 1) was enrolled.

2.2. Treatments

MK-8242 was initially dosed p.o. either QD (30 mg–250 mg) or BID (120 mg–250 mg) for 7 days on/7 days off (7 on/7 off) in a 28-day cycle (Fig. 1A). To improve the safety/tolerability profile of myelosuppression with prolonged cytopenia and infection, the dosing schedule was later modified to 7 on/14 off in a 21-day cycle (210 mg or 300 mg BID) (Fig. 1B).

Subjects were initially enrolled in cohorts of single subjects and treated at accelerated, escalating dose levels of MK-8242 as per Simon et al. [30]. When ≥1 dose-limiting toxicity (DLT) occurred at a particular treatment level, escalation was converted to a modified 3 + 3 design [31]. When ≥1 subject at a given dose level experienced a Grade 2 or greater adverse event (AE) that did not meet DLT criteria and was not clearly attributable to another cause, the level was expanded to 3 subjects. If no additional Grade 2 or greater AEs occurred, escalation continued with the accelerated design. If at any time ≥2 subjects out of 3 experienced a Grade 2 or greater AE that was not clearly attributable to another cause, dose escalation converted to a 3 + 3 design for the remainder of the study. In Part 1, monotherapy escalation continued until a preliminary maximum tolerated dose (MTD) was identified. Patients continued to receive treatment until withdrawal criterion was met or up to 4 cycles of study treatment was received with additional cycles allowed at the Investigator's/Sponsor's discretion.

Each subject provided written informed consent prior to the conduct of any study procedures. The study protocols were approved by the Ethics Review Committees for the individual study centers. The study protocols were conducted in accordance with the guidelines on good clinical practice and with ethical standards for human experimentation established by the Declaration of Helsinki.

2.3. Eligibility criteria

Eligible patients were aged ≥18 years with a diagnosis of refractory or recurrent AML. They had to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 with adequate organ function (creatinine <1.5 upper limit of normal [ULN] or calculated creatinine clearance ≥60 mL/min, total bilirubin <1.5 ULN aspartate aminotransferase/serum glutamic-oxalecetic transaminases(SGOT) and alanine aminotransferase/serum glutamic-pyruvic transaminases (SGPT) <3x ULN) and were ineligible for standard therapy. Subjects enrolled in the 3 + 3 escalation portion of Part 1 were required to have a confirmed WT p53 status (as per Roche Molecular Systems AmpliChip p53 Assay). Significant exclusion criteria included: active malignancy other than AML; history of leptomeningeal leukemia requiring intrathecal therapy; myelodysplasic syndrome (Part 1, only); isolated extramedullary leukemia without meeting bone marrow criteria for AML; diagnosis of AML blast crisis of chronic myelogenous leukemia; bone marrow transplant with active graft-versus-host disease or who received immunosuppressive therapy.

Patients could be withdrawn from the study for failure to comply with the study requirements, pregnancy, disease recurrence or progression, dose delay >2 weeks, intercurrent illness preventing further administration of treatment, unacceptable AEs not manageable by symptomatic therapy, or a serious or life-threatening AE. A subject who discontinued from the study was allowed to be replaced if they did not complete the evaluation period for DLTs in Cycle 1 for reasons other than study treatment-related toxicity.

Dose delays of up to 14 days were allowed for any ≥Grade 3 hematologic AE not clearly attributable to underlying disease. In addition, dose delays were allowed for ≥Grade 3 non-hematologic AE not clearly attributable to underlying disease or another cause, and persist beyond 72 h following maximal supportive care. Subjects were assessed weekly until the AE resolved.