Pharmacokinetic profile and food effect of RP-3500, a highly potent and specific inhibitor of ataxia telangiectasia and Rad3-related protein kinase in patients with cancer

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Introduction

• Ataxia telangiectasia and Rad3-related (ATR) Kinase: Small molecule inhibitors of ATR such as MDC201, are active in responding to replication stress

• Specific gene encoding DNA repair proteins, such as ataxia telangiectasia mutated (ATM), represent synthetic lethality (SL), with ATR

• Replication stress induces DNA damage response mechanisms, which in turn activate ATM

• ATR is a key mediator of cellular activity1,2

• ATM activity* is required for proper DNA repair, and is often inactivated in cancer cells

• ATM mutations (ATM), represent synthetic lethality with ATR inhibition

• MRE11, RAD51, RAD50 and BRCA1/2 are involved in replication and DNA repair, and ATM regulates their activity

• ATM regulates MDC201 activity3

Objective

• The objective of this analysis was to characterize the pharmacokinetics (PK) profile of RP-3500 and assess the impact of food on PK parameters in patients with advanced solid tumors harboring ATR- sensitizing mutations from the dose-escalation portion of TRESR

Methods

• TRESR is an exploratory, open-label, phase 1b, multi-center, open-label dose escalation and dose expansion study (Figure 1)

• Patients received RP-3500 once daily (QD) or twice daily (BID) on a schedule of 5 days on/2 days off, with a high fat challenge meal

Study endpoints

• The primary study endpoint was safety and tolerability of RP-3500 and identification of the maximum tolerated dose (MTD) of RP-3500

• Secondary endpoints included characterization of the PK of RP-3500 as well as assessment of the effect of a high-fat challenge meal on the PK of RP-3500

Study assessments

• PK sampling was performed for 24 hours post dose on cycle 1 Day 1, and either cycle 3 Day 1 or 8, or cycle 2 Day 3 or 5, depending on schedule

• RP-3500 plasma concentrations were measured using a validated LC/MS/MS assay

• The PK parameters of RP-3500 were estimated using noncompartmental methods

• PK parameters estimated include Cmax, time to maximum observed concentration (Tmax), mean observed concentration (C) throughout the dosing interval (C), area under the concentration-time curve from time 0 to last quantifiable concentration (AUC0-t), AUC from time 0 to last quantifiable concentration (AUC0-t), AUC from time 0 to last quantifiable concentration (AUC0-t), AUC from time 0 to last quantifiable concentration (AUC0-t), AUC from time 0 to last quantifiable concentration (AUC0-t), AUC from time 0 to last quantifiable concentration (AUC0-t)

• Descriptive statistics were calculated in Phoenix WinNonlin® 8.3

Results

• Within the dose escalation phase of TRESR, 120 patients had sufficient data for which PK parameters could be estimated on cycle 1 Day 1

• Plasma concentration time profiles were collected over the PK collection period, into cycle 2

• The PK profile of RP-3500 was predictable across the dose range and showed low between patient variability

• The safety and tolerability of RP-3500 has been demonstrated previously4

• The PK profile of RP-3500 given twice daily was comparable to that of once daily dosing

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Conclusions

• The safety and tolerability of RP-3500 has been demonstrated previously

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References