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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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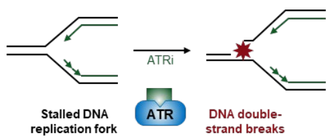
Introduction

- Ataxia telangiectasia and Rad3-related (ATR) is a key mediator of cellular DNA damage response (DDR) that is activated in response to DNA replication stress[1,2]
- Specific genes encoding DNA repair proteins, such as ataxia telangiectasia mutated (ATM), represent synthetic lethal (SL) interactions with ATR[1,2]
  - Perturbation of either SL genes is tolerated, but simultaneous perturbation causes cell death, making ATR inhibition (ATRi) an attractive target for the treatment of patients with specific genetic lesions
- CRISPR-based Synthetic Lethal Interactions for Precision Diagnostics (SNiPDx) screening identifies SL genomic alterations that predict sensitivity to ATRi (STEP[2] genes)
  - *ATM*, *ATRIP*, *BRCA1/2*, *CHEK2*, *CDK12*, *CHTF8*, *FZR1*, *MRE11*, *NBN*, *PALB2*, *RAD17*, *RAD50*, *RAD51B/C/D*, *REV3L*, *RNASEH2A/B*, *SETD2*
- RP-3500 is a potent and highly selective ATRi which has demonstrated efficacy in both pre-clinical xenograft models as well as in early clinical trials[3,4]
- The ongoing TRESR study (NCT04497116) is a phase 1/2a study of patients with advanced cancer whose tumors harbor STEP[2] gene alterations



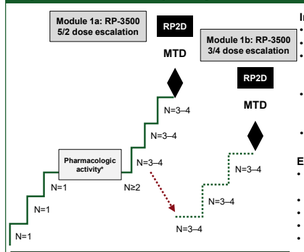
Objective

- The objective of this analysis was to characterize the pharmacokinetic (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, modular, phase 1/2a, first-in-human, multicenter, open-label dose-escalation and dose-expansion study (**Figure 1**)

Figure 1. TRESR study design



Inclusion criteria:
- Male or female patients ≥18 years of age
- ECOG-PS score of 0 or 1
- Histologically confirmed solid tumors resistant or refractory to standard treatment and/or patients who are intolerant to standard therapy
- Existing biomarker profile (tumor tissue or plasma) reported from a local test obtained in a CAP/CLIA, ISO or equivalent lab per institutional guidelines[a]
- Acceptable organ function at screening, as evidenced by laboratory data[b]

Exclusion criteria:
- Chemotherapy, small molecule anticancer or biologic anticancer therapy <14 days prior to first dose of study drug
- Prior therapy with an ATR or DNA-PK inhibitor
- Uncontrolled, symptomatic brain metastases
- Hepatic impairment (ie, Child-Pugh class B or C)
- Current treatment with medications that are well-known to prolong QT interval
- Receiving strong CYP3A inhibitors or inducers, P-glycoprotein inhibitors and/or breast cancer resistant protein inhibitors <14 days prior to first dose of study drug

[a]Documented and confirmed by central review a deleterious genomic alterations for at least 1 of the following genes: *ATM, ATRIP, BRCA1, BRCA2, CDK12, CHTF8, FZR1, MRE11, NBN, PALB2, RAD17, RAD50, RAD51B, REV3L, RNASeH2A, RNAseH2B, SETD2* or other genes decided upon between the sponsor and investigators.
[b]Serum creatinine ≤1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥60 mL/min using the Cockcroft-Gault equation or by 24-hour urine collection; Total bilirubin ≤1.5 × ULN or <3.0 × ULN if known Gilbert's disease; Serum albumin ≥2.5 g/dL; Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN unless liver metastases are present and thought to be a reason for AST/ALT elevation, in which case they must be ≤5 × ULN
ATR, ataxia telangiectasia and Rad3-related; CAP, College of Pathology; CLIA, Clinical Laboratory Improvement Amendments; DNA-PK; DNA-dependent protein kinase; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; ISO, International Organization for Standardization; ULN, upper limit of normal.

- Patients received RP-3500 once daily (QD) or twice daily (BID) on a schedule of 5 days on/2 days off (Module 1a) or 3 days on/4 days off (Module 1b) for a 21-day cycle (**Table 1**)
  - Later cohorts also evaluated a 3 days on/4 days off schedule, 2 out of 3 weeks in a 21-day cycle
  - To evaluate the effect of food (Module 1c) at therapeutically relevant doses, 12 patients received RP-3500 on day -3 with a high fat/calorie meal; the same patients received RP-3500 on day 1 in the fasted state

Table 1. Summary of study modules

Module	Fed/fasted	Day 1 dose
1a: 5 days on/2 days off (N=22)	Fasted	5, 10, 20, 40, 80, 100, 120, or 160 mg QD 40 or 80 mg BID
1b: 3 days on/4 days off (N=86)	Fasted	120, 160, or 200 mg QD 40 or 60 mg BID
1c: Food effect (N=12)	Day -3, high fat meal (~1000 kcal, ~50% fat): day 1, fasted	100, 120, or 160 mg QD

BID, twice daily; QD, once daily.

Study endpoints

- The primary study endpoint was safety and tolerability of RP-3500 and identification of the maximum tolerated dose (MTD) and the recommended phase 2 (RP2D) dose and schedule
- Secondary endpoints included characterization of the PK of RP-3500 as well as investigation of the effect of a high-fat/high-calorie meal on the PK of RP-3500

Study assessments

- PK sampling occurred for 24 hours post dose on cycle 1/day 1, and either cycle 1/day 3 or 5, 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 (Phoenix® WinNonlin® 8.3, Certara USA, Inc., Princeton, NJ)
- PK parameters estimated include half-life ($T_{½}$), time to maximum observed concentration (T_{max}), maximum observed concentration (C_{max}), C_{max}/dose, area under the concentration-time curve from time 0 to last quantifiable concentration (AUC_{last}), AUC_{last}/dose, AUC 0–24 hours post dose ($AUC_{0–24}$), and AUC from time 0 to infinite time (AUC_{inf})
- Descriptive statistics were compiled in Phoenix® WinNonlin® 8.3

Results

Table 2. Baseline characteristics

Characteristic	All subjects (N=120)
Sex, n (%)	
Male	49 (40.8)
Female	71 (59.2)
Age, years	
Mean (SD)	61.3 (10.94)
Median (range)	63.0 (30-77)
Age group, n (%)	
<65 years	66 (55.0)
≥65 years	54 (45.0)
Body mass index*, kg/m²	
Mean (SD)	26.8 (6.15)
Median (range)	26.4 (17-46)
ECOG status, n (%)	
0	57 (47.5)
1	61 (50.8)
Missing	2 (1.7)

*Based on 110 patients
ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

- Within the dose escalation phase of TRESR, 120 patients had sufficient data for which PK parameters could be estimated on cycle 1/day 1
- 323 plasma concentration time profiles were collected over the PK collection period, into cycle 2

PK profile: daily and twice daily dosing

- In general, the PK of RP-3500 exhibited low between-subject variability
- Over the dose range tested (5–200 mg QD), the increases in C_{max} and AUC were approximately linear (**Figure 2, 3; Tables 3–6**)
- The T_{max} of RP-3500 was early; the median T_{max} across dose levels ranged from 1–2 hours (**Figure 2, 3; Tables 3–6**)
- Across the dose range tested, the half-life of RP-3500 was approximately 6 hours with no accumulation after repeat dosing

Figure 2. Daily and twice daily dosing, cycle 1/day 1 , 3, and 5

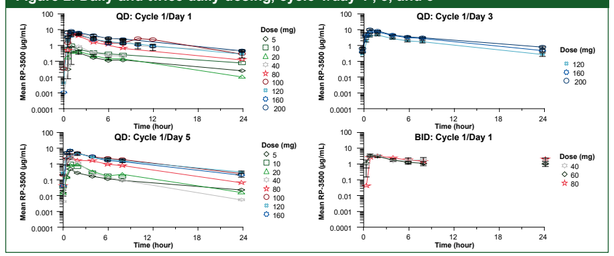


Table 3. PK parameters for daily dosing, cycle 1/day 1

	5 mg (n=1)	10 mg (n=1)	20 mg (n=2)	40 mg (n=1)	80 mg (n=1)	100 mg (n=7)	120 mg (n=31)	160 mg (n=64)	200 mg (n=5)
T_{max}, h*	1	1	1.5	2	1	1	2	1.5	1
C_{max}, µg/mL	0.491	1.05	0.560 (0.338)	0.894	5.66	5.75 (0.974)	5.74 (2.47)	7.64 (2.39)	9.99 (3.65)
C_{max}/dose, µg/mL/mg	0.098	0.105	0.028 (0.019)	0.022	0.071	0.057 (0.010)	0.048 (0.021)	0.048 (0.015)	0.050 (0.018)
AUC_{last}, hr*µg/mL	2.50	6.00	2.33 (1.09)	3.13	22.1	34.3 (17.8)	33.2 (14.7)	48.0 (23.0)	57.7 (13.7)
AUC_{last}/dose, hr*µg/mL/mg	0.499	0.600	0.116 (0.054)	0.078	0.277	0.343 (0.178)	0.276 (0.123)	0.300 (0.114)	0.289 (0.068)
AUC_{inf}, hr*µg/mL	2.77	7.04	2.97 (0.272)	4.65	23.2	37.6 (22.6)	36.8 (16.8)	53.2 (30.6)**	62.5 (16.1)
$T_{½}$, h	7.5	9.1	5.0 (0.4)	4.9	5.9	6.0 (1.8)	6.5 (2.1)	6.3 (2.3)**	6.6 (1.1)

All data presented as mean (SD) unless otherwise noted.
*Data reported as median. **Based on n=61.
AUC, area under the concentration-time curve; AUC_{inf}, AUC from time 0 to infinite time; AUC_{last}, AUC from time 0 to last quantifiable concentration; C_{max}, maximum observed concentration; $T_{½}$, half-life; T_{max}, time to maximum observed concentration.

Table 4. PK parameters for daily dosing, cycle 1/day 3

	5-100 mg (n=0)	120 mg (n=19)	160 mg (n=64)	200 mg (n=4)
T_{max}, h*	NA	2	2	1
C_{max}, µg/mL	NA	5.26 (1.65)	7.68 (2.62)	10.2 (1.79)
C_{max}/dose, µg/mL/mg	NA	0.044 (0.014)	0.048 (0.016)	0.051 (0.009)
AUC_{last}, hr*µg/mL	NA	33.1 (17.7)	50.5 (26.3)	66.3 (9.30)
AUC_{last}/dose, hr*µg/mL/mg	NA	0.276 (0.147)	0.315 (0.164)	0.331 (0.047)
AUC_{inf}, hr*µg/mL	NA	34.7 (21.0)**	57.1 (33.3)***	76.4 (10.8)
$T_{½}$, h	NA	5.6 (1.5)**	6.0 (1.8)***	8.8 (3.1)

All data presented as mean (SD) unless otherwise noted.
*Data reported as median. **Based on n=18. ***Based on n=51.
AUC, area under the concentration-time curve; AUC_{inf}, AUC from time 0 to infinite time; AUC_{last}, AUC from time 0 to last quantifiable concentration; C_{max}, maximum observed concentration; $T_{½}$, half-life; T_{max}, time to maximum observed concentration.

Table 5. PK parameters for daily dosing, cycle 1/day 5

	5 mg (n=1)	10 mg (n=1)	20 mg (n=2)	40 mg (n=1)	80 mg (n=1)	100 mg (n=6)	120 mg (n=4)	160 mg (n=2)	200 mg (n=0)
T_{max}, h*	1	1	1	1	1	1.5	2	1	NA
C_{max}, µg/mL	0.444	0.976	0.439 (0.594)	2.01	2.54	4.73 (1.56)	5.12 (1.25)	6.71 (1.03)	NA
C_{max}/dose, µg/mL/mg	0.089	0.098	0.022 (0.030)	0.050	0.032	0.047 (0.016)	0.043 (0.010)	0.042 (0.006)	NA
AUC_{last}, hr*µg/mL	2.01	3.00	4.10**	4.68	15.0	32.2 (7.80)	31.4 (3.28)	31.6 (1.45)	NA
AUC_{last}/dose, hr*µg/mL/mg	0.401	0.300	0.205**	0.117	0.188	0.322 (0.078)	0.262 (0.027)	0.197 (0.009)	NA
AUC_{inf}, hr*µg/mL	2.23	4.01	4.19**	4.71	15.4	34.1 (8.64)	34.1 (4.30)	33.2 (0.458)	NA
$T_{½}$, h	7.7	4.9	4.6**	3.8	4.5	5.4 (0.7)	6.5 (1.1)	6.0 (1.6)	NA

All data presented as mean (SD) unless otherwise noted.
* Data reported as median. **Based on n=1.

Table 6. PK parameters for twice daily dosing, cycle 1/day 1

	40 mg (n=2)	60 mg (n=4)	80 mg (n=1)
T_{max}, h*	1.5	1.5	2
C_{max}, µg/mL	3.00 (0.608)	3.44 (1.23)	3.01
C_{max}/dose, µg/mL/mg	0.075 (0.015)	0.057 (0.021)	0.038
AUC_{last}, hr*µg/mL	42.0 (19.3)	29.7 (13.8)	42.9
AUC_{last}/dose, hr*µg/mL/mg	1.05 (0.483)	0.495 (0.230)	0.536
AUC_{inf}, hr*µg/mL	605 (716)	80.4 (58.0)	NA**

All data presented as mean (SD) unless otherwise noted.
*Data reported as median. **Based on n=0.
AUC, area under the concentration-time curve; AUC_{inf}, AUC from time 0 to infinite time; AUC_{last}, AUC from time 0 to last quantifiable concentration; C_{max}, maximum observed concentration; T_{max}, time to maximum observed concentration.

PK profile from module 1c, daily dosing

- Median T_{max} was delayed by 3 hours when RP-3500 was administered with a high fat/high calorie meal (**Figure 4**, **Table 7**)
- Mean C_{max} across dose tested was reduced by 45% compared with fasting values (**Figure 4**, **Table 7**)
- On day –3 (fed arm), the mean $AUC_{0–24}$ was 16% lower compared with $AUC_{0–24}$ on day 1 (fasted arm) (**Figure 4**, **Table 7**)

Figure 4a. PK profile of 100 mg QD RP-3500 after a high-fat meal and after a 24-hour fast

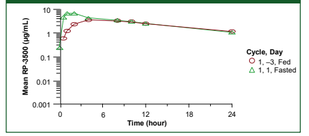


Figure 4b. PK profile of 120 mg QD RP-3500 after a high-fat meal and after a 24-hour fast

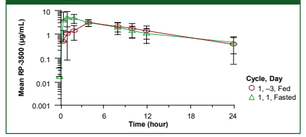


Figure 4c. PK profile of 160 mg QD RP-3500 after a high-fat meal and after a 24-hour fast

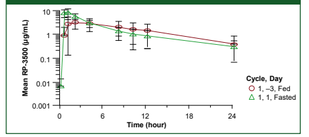


Table 7. PK parameters after a high-fat meal and after a 24-hour fast

	After high-fat meal (cycle 1/day –3)			After 24-hour fast (cycle 1/day 1)		
Dose	100 mg (n=1)	120 mg (n=8)	160 mg (n=3)	100 mg (n=1)	120 mg (n=8)	160 mg (n=3)
T_{max}, h*	4	4	4	2	1	1
C_{max}, µg/mL	3.50	2.91 (0.856)	4.31 (0.904)	6.66	5.75 (3.18)	9.44 (2.95)
C_{max}/dose, µg/mL/mg	0.035	0.024 (0.007)	0.027 (0.006)	0.067	0.048 (0.027)	0.059 (0.018)
AUC_{0-24}, hr*µg/mL	53.6	30.8 (12.3)	35.2 (12.9)	67.9	38.0 (15.5)	39.0 (17.5)
AUC_{inf}, hr*µg/mL	101	36.1 (16.7)	40.2 (18.2)	81.8	43.5 (18.4)	42.6 (20.5)

All data presented as mean (SD) unless otherwise noted.
*Data reported as median.
AUC, area under the concentration-time curve; AUC_{inf}, AUC from time 0 to infinite time; C_{max}, maximum observed concentration; T_{max}, time to maximum observed concentration.

Conclusions

- The safety and tolerability of RP-3500 has been demonstrated previously[4]
  - The RP2D was established as 160 mg daily on a 3 days on/4 days off schedule
- These data demonstrate that both AUC_{last} and C_{max} increase in an approximately dose-proportional manner over the dose range of 5 to 200 mg given once daily
  - The PK profile of RP-3500 was predictable across the dose range and showed low between patient variability
- The PK profile of RP-3500 given twice daily was comparable to that of once daily dosing
- In the patients evaluated as part of the on-going TRESR study, the $T_{½}$ of RP-3500 is approximately 6 hours and generally consistent across dose groups
- The results of the food effect module show that RP-3500 can be administered in both fed or fasted states without affecting the RP-3500 levels and overall PK profile required for efficacy

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