Effects of Itraconazole and Rifampin on Tazemetostat Pharmacokinetics in Patients With Advanced Malignancies

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Background

- Epigenetic dysregulation, such as aberrant histone modifications, has been observed in many cancer types; it contributes to inappropriate activation of oncogenes and inactivation of tumor suppressors[1]
- Overexpression of EZH2, a histone methyltransferase involved in the regulation of gene expression, has been observed in a variety of solid and hematologic cancers[2,3]
- Tazemetostat (TAZ) is an oral, methyltransferase inhibitor of EZH2 a the first-in-class epigenetic therapy approved by the FDA for patients with follicular lymphoma and epithelioid sarcoma[4]
- *In vitro*, TAZ is mainly metabolized by CYP3A to form inactive metabolites[4]
- Itraconazole (ITZ) is a strong CYP3A inhibitor, and rifampin (RIF) is a strong CYP3A inducer[5,6]

Objective

This drug-interaction study (EZH-108; NCT04537715) evaluated the effect of CYP3A inhibition by ITZ and CYP3A induction by RIF on the PK and safety profile of TAZ in patients with advanced malignancies

Methods

Study population

Metastatic or unresectable solid tumor who had progressed on treatment or no standard therapies available

or

Hematologic malignancy who were R/R following ≥2 systemic therapies or no standard therapies available

and:

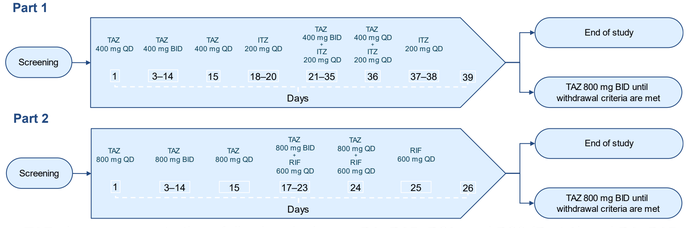
ECOG PS 0–2

Life expectancy >3 months

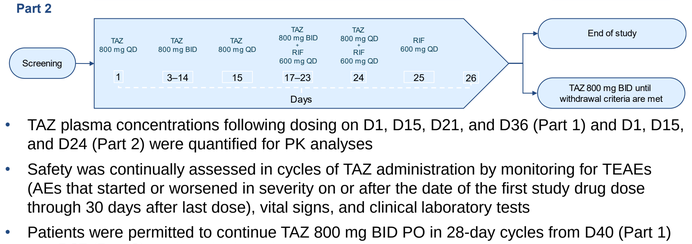
Normal hepatic, hematologic, and renal function

Dosing schedule and analyses

Part 1



Part 2

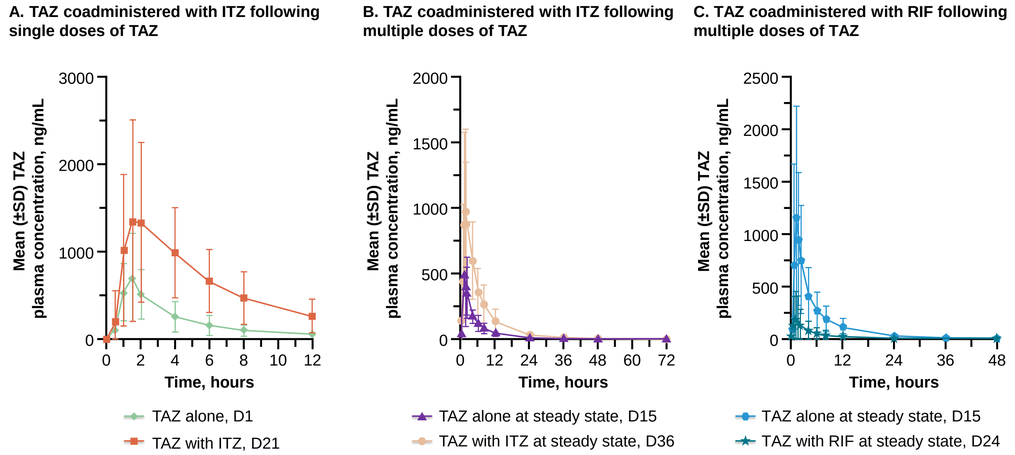


- TAZ plasma concentrations following dosing on D1, D15, D21, and D36 (Part 1) and D1, D15, and D24 (Part 2) were quantified for PK analyses
- Safety was continually assessed in cycles of TAZ administration by monitoring for TEAEs (AEs that started or worsened in severity on or after the date of the first study drug dose through 30 days after last dose), vital signs, and clinical laboratory tests
- Patients were permitted to continue TAZ 800 mg BID PO in 28-day cycles from D40 (Part 1) and D27 (Part 2), until a withdrawal criteria were met

TAKE-HOME MESSAGES

- **Coadministration of TAZ with ITZ increases TAZ exposure by 2–3 fold**
- **Coadministration of TAZ with RIF decreases TAZ exposure by ~84%**
- **Coadministration with strong CYP3A inhibitors or inducers should be avoided**

Figure 1. TAZ plasma concentrations following coadministration with ITZ in Part 1 (A, B) and RIF in Part 2 (C)



CONCLUSIONS

- Coadministration of ITZ (a strong CYP3A inhibitor) with TAZ 400 mg BID increased TAZ exposure by 2–3-fold, indicating that concomitant administration of strong CYP3A inhibitors with TAZ should be avoided
  - The TAZ exposure increase was expected
  - The magnitude of the increase was significantly lower than expected, which may be a result of opposing effects: induction by TAZ itself (time-dependent PK) and CYP3A inhibition by ITZ
- Coadministration of RIF (a strong CYP3A inducer) with TAZ 800 mg BID in patients decreased TAZ exposure by 84%, and coadministration of strong CYP3A inducers with TAZ should be avoided
- Across both study parts and treatment cycles, the nature and severity of TEAEs experienced were consistent with the known safety profile of TAZ

Results

Baseline demographics and disease characteristics

	PK evaluable/ enrolled	Male	Median age	White	ECOG PS 0	ECOG PS 1	Solid tumor
Part 1	16/21 patients	61.9%	62 years	85.7%	52.4%	47.6%	95.2%
Part 2	16/21 patients	38.1%	64 years	57.1%	66.7%	33.3%	100%

Effect of ITZ and RIF on TAZ PK

- For single doses, ITZ increased TAZ mean C_{max} and $AUC_{0–12}$ by 2.00-fold (90% CI 1.60–2.48) and 3.12-fold (90% CI 2.44–3.99), respectively
- For multiple doses, steady-state ITZ increased steady-state TAZ mean C_{max} and $AUC_{0–12}$ by 1.86-fold (90% CI 1.49–2.31) and 2.47-fold (90% CI 2.02–3.02), respectively
- TAZ steady-state exposure decreased by approximately 84% when coadministered with steady-state RIF (Table 1, Figure 1)
  - The geoLSM ratios (90% CI) for C_{max} and $AUC_{0–12}$ were 0.164 (0.122–0.219) and 0.163 (0.128–0.208), respectively

Table 1. Summary of TAZ PK, coadministered with ITZ or RIF

PK assessment	Part 1				Part 2		
	TAZ QD	TAZ BID	TAZ QD with ITZ	TAZ BID with RIF	TAZ QD	TAZ BID	TAZ BID with RIF
Median T_{max}, hours	1.44	1.27	1.53	1.49	1.04	1.00	1.01
C_{max}, ng/mL	704 (56.5)	543 (63.3)	1400 (67.3)	1010 (76.3)	1330 (67.4)	1100 (78.7)	181 (71.7)
AUC_{last}, h*ng/mL	2640 (68.9)	2200 (37.1)	6720 (73.4)	5750 (59.9)	5200 (89.5)	4270 (74.0)	676 (72.5)
AUC_{0-12}, h*ng/mL	2180 (55.3)	1830 (37.6)	6790 (73.2)	4530 (64.5)	4420 (83.2)	3610 (70.3)	588 (65.2)
$t_{1/2}$, hours	5.97 (25.6)	8.01 (39.3)	2.86 (28.9)	11.9 (43.8)	6.22 (35.6)	7.55 (20.3)	4.86 (31.7)
AUC_{0-12} ratio, geoLSM (90% CI)	NA	NA	3.12 (2.44–3.99)[a]	2.47 (2.02–3.02)[b]	NA	NA	0.163 (0.128–0.208)[c]
C_{max} ratio, geoLSM (90% CI)	NA	NA	2.00 (1.60–2.48)[a]	1.86 (1.49–2.31)[b]	NA	NA	0.164 (0.122–0.219)[c]
RacAUC, geoLSM (90% CI)	NA	0.842 (0.726–0.976)[d]	NA	NA	NA	0.816 (0.638– 1.04)[d]	NA
$RacC_{max}$, geoLSM (90% CI)	NA	0.771 (0.662–0.897)[d]	NA	NA	NA	0.828 (0.635–1.08)[d]	NA

Geometric mean (CV%) unless stated otherwise. [a]D21 vs D1. [b]D36 vs D15. [c]D24 vs D15. [d]D15 vs D1.

Safety

- TR-TEAEs occurred in 13 patients (61.9%) in Part 1 and 18 patients (85.7%) in Part 2
- TAZ-related TEAEs occurred in 12 patients (57.1%; Part 1) and 16 patients (76.2%; Part 2); ITZ- and RIF-related TEAEs were reported by eight patients (38.1%) each
  - Part 1: Grade 3/4 TR-TEAEs were anemia (n=2) and hyponatremia (n=1)
  - Part 2: Grade 3/4 TR-TEAEs were diarrhea, ALT increased, AST increased, syncope, acute kidney injury, hypertension (n=1 for each event), anemia, and decreased lymphocyte count (n=2 for each event)

Abbreviations **AE:** adverse event; **ALT:** alanine aminotransferase; **AST:** aspartate aminotransferase; **AUC_{0-12}:** the area under the concentration–time curve over the dosing interval from 0 to 12 hours post-dose; **AUC_{last}:** the area under the concentration-time curve from the last time of dosing to last measurable concentration; **BID:** twice daily; **C_{max}:** maximum observed plasma concentration; **CV:** coefficient of variation; **CYP3A:** cytochrome P450, family 3, subfamily A; **D:** Day; **ECOG PS:** Eastern Cooperative Oncology Group Performance Status; **EZH2:** enhancer of zeste homolog 2; **FDA:** U.S. Food and Drug Administration; **geoLSM:** least squares geometric mean; **ITZ:** itraconazole; **NA:** not applicable; **PK:** pharmacokinetic(s); **PO:** orally; **QD:** once daily; **RacAUC:** area under the concentration–time curve accumulation ratio; **$RacC_{max}$:** maximum observed plasma concentration accumulation ratio; **RIF:** rifampin; **R/R:** relapsed/refractory; **SD:** standard deviation; **$t_{1/2}$:** terminal elimination half-life; **TAZ:** tazemetostat; **TEAE:** treatment-emergent adverse event; **T_{max}:** time to maximum plasma concentration; **TR-TEAE:** treatment-related treatment-emergent adverse event.

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Disclosures **YC**, **RB**, **AS**, **AK**, and **JO** are employees of, and may own stock/stock options in Ipsen. **RT** is an employee of CareCeutics LLC, contracted by Ipsen. **DM** has received research funding from Amgen, Merck, Oncolytics, and Rafael; participated in a scientific advisory board for Actuate, Qurient, and an advisory/speaker bureau for Amgen, BMS, Eisai, and Exelixis; has received funding paid to their institution from Acepodia, Actuate Therapeutics, ADC Therapeutics, Amgen, AVEO, Bayer, Blueprint Medicines, BMS, BioNTech, Dialectic Therapeutics, Epizyme, Fujifilm, ImmuneSensor, Immune-Onc Therapeutics, Leap Therapeutics, Lycera Corp, Merck, Millennium, MiNA Alpha, NGM Biopharmaceuticals, Novartis, Oncolytics, Orano Med, Puma, Qurient, Rafael, Repare Therapeutics, Triumvira Immunologics, Vigeo Therapeutics, and Werewolf Therapeutics.

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