Abstract CT058

Ripretinib (DCC-2618) Pharmacokinetics (PK) in a Phase 1 Study in Patients with Gastrointestinal Stromal Tumors (GIST) and other Advanced Malignancies: A Retrospective Evaluation of the PK Effects of Proton Pump Inhibitors (PPIs)

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BACKGROUND

- Ripretinib is an investigational broad spectrum, small molecule KIT and PDGFRα switch control kinase inhibitor. Encouraging clinical benefit has previously been reported from the phase 1 dose escalation and expansion trial, as measured by preliminary ORR (best response), DCR and PFS in 2nd, 3rd, and ≥ 4th line GIST patients with a favorable tolerability profile at doses ≥ 100 mg/day (ESMO 2018, abstract #1603O) (Figure 1)
- Phase 3 trial in ≥4th line, INVICTUS (NCT03353753) is fully enrolled, and data are expected mid-2019
- Phase 3 trial in 2nd line, INTRIGUE (NCT03673501) was initiated December 2018
- More than 40% of GIST patients use acid-reducing agents. PPIs are the most potent acid-reducing agents that may impair the absorption of kinase inhibitors [1,2].
- Ripretinib is a weak base drug with slightly pH-dependent solubility (<2 fold differences between pH 2 and 6.5), leading to the question whether gastric acid suppression by acid-reducing agents would potentially impair ripretinib absorption
- Therefore, a retrospective analysis of the Phase I trial was conducted as preliminary exploration to address this question

OBJECTIVE

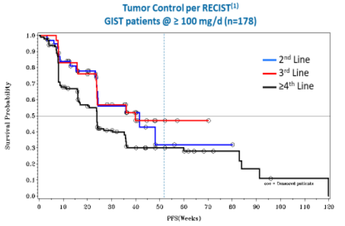
- To evaluate the impact of coadministration of PPIs on ripretinib PK

METHODS

- The analysis assessed the impact of PPIs on the plasma concentration of ripretinib using PK data from the expansion cohort of study DCC-2618-01-001 at the recommended Phase 2 dose of 150 mg QD.
- The plasma concentrations of the active metabolite DP-5439 were also evaluated, as impaired absorption of ripretinib may lead to reduced in vivo formation of the metabolite.
- Plasma concentrations of ripretinib and metabolite DP-5439 were compared on Cycle 1 Day 1 (C1D1, n=106) and Day 15 (C1D15, n=102).
- Log-transformed concentrations were compared using an ANOVA model with PPI use as a fixed effect, and geometric mean ratios were computed with 95% confidence intervals (C.I.).
- In the current analysis, patients using PPIs were defined as those who continuously took PPIs for at least 4 days prior to C1D1 or C1D15.
- Patients who did not use PPIs were defined as those who did not take PPIs or any other acid-reducing agents during the study.
- This retrospective analysis is based on data from patients without a history of gastrectomy.
- The analysis group (N=113) was comprised of 88 GIST (77.9%) patients and 25 non-GIST (22.1%) patients.

Figure 1. Ripretinib: Encouraging background data from Phase 1 in GIST (NCT NCT02571036)

Line of Therapy	mPFS (ripretinib)	Censored Patients
2	42 weeks	22 (58%)
3	40 weeks	15 (52%)
≥4	24 weeks	40 (35%)
2 & 3	40 weeks	37 (55%)



Preliminary mPFS data with ripretinib @ ≥100mg daily exceeds registration trial data for approved 2nd & 3rd line therapies

2nd Line	38	30	21	13	8	2	1	1	1	0	0	0	0
3rd Line	29	24	21	14	8	4	1	1	0	0	0	0	0
≥4th Line	111	71	53	32	20	14	12	6	5	3	1	1	0

Notes: (1) Based on cutoff date of August 31, 2018; RECIST data per investigator assessment

RESULTS

Table 1: Patient Demographics and Baseline Characteristics

Characteristics	Category	Statistic	Patients Using PPIs (N=26)	Patients Not Using PPIs (N=87)	Total (N=113)
Gender	Female	n (%)	8 (30.8)	32 (36.8)	40 (35.4)
	Male	n (%)	18 (69.2)	55 (63.2)	73 (64.6)
Age (years)		N	26	87	113
		Median	62	60	60
		Min , Max	23 , 82	19 , 86	19 , 86
Race	American Indian or Alaska Native	n (%)	0	3 (3.4)	3 (2.7)
	Asian	n (%)	1 (3.8)	5 (5.7)	6 (5.3)
	Black or African American	n (%)	0	4 (4.6)	4 (3.5)
	White	n (%)	23 (88.5)	70 (80.5)	93 (82.3)
	Other	n (%)	2 (7.7)	5 (5.7)	7 (6.2)
Ethnicity	Hispanic or Latino	n (%)	1 (3.8)	7 (8.0)	8 (7.1)
	Not Hispanic or Latino	n (%)	24 (92.3)	76 (87.4)	100 (88.5)
	Not Reported	n (%)	1 (3.8)	4 (4.6)	5 (4.4)
BMI (kg/m^2) [1]		N	26	78	104
		Median	29	26	27
		Min , Max	19 , 40	19 , 54	19 , 54
Diagnosis	GIST	n (%)	17 (65.4)	71 (81.6)	88 (77.9)
	Non-GIST	n (%)	9 (34.6)	16 (18.4)	25 (22.1)

[1] BMI = weight[kg]/height[m]^2.

Table 2. PK Exposure of Ripretinib and Metabolite DP-5439 in Patients Using or not Using PPIs [Arithmetic Mean]

PK Concentrations	Ripretinib in ng/mL [arithmetic mean (CV%)]		DP-5439 in ng/mL [arithmetic mean (CV%)]		Ripretinib + DP-5439 in ng/mL [arithmetic mean (CV%)]	
	Using PPIs	Not using PPIs	Using PPIs	Not using PPIs	Using PPIs	Not using PPIs
C1D1 6 hr	566 (58%) n=24	670 (53%) n=82	302 (64%) n=23	297 (59%) n=82	862 (54%) n=23	975 (48%) n=82
C1D15 pre-dose	364 (79%) n= 24	344 (63%) n=78	960 (80%) n=24	889 (86%) n=78	1350 (72%) n=24	1260 (75%) n=78
C1D15 6 hr	834 (51%) n=24	871 (47%) n=73	1170 (69%) n=24	1060 (67%) n=73	2040 (53%) n=24	1960 (49%) n=73

- Ripretinib and metabolite DP-5439 plasma concentrations (Table 2) were characterized in patients using and not using PPIs, respectively.
- Comparable ripretinib exposure (Table 3, Figures 2) was observed in patients using and not using PPIs.
- Comparable DP-5439 exposure (Table 3, Figures 3) was also confirmed in these two groups.
- In summary, PK profiles were consistent between patients using and not using PPIs, indicating a low likelihood of a clinically significant drug interaction between PPIs and ripretinib.

Table 3. PK Exposure of Ripretinib and Metabolite DP-5439 in Patients Using or not Using PPIs [Geometric Mean Ratios]

PK Concentrations	Ripretinib in ng/mL [geometric mean (CV%)]		Geometric Mean Ratios	95% C.I.	DP-5439 in ng/mL [geometric mean (CV%)]		Geometric Mean Ratios	95% C.I.
	Using PPIs	Not using PPIs			Using PPIs	Not using PPIs		
C1D1 6 hr	460 (87.2%) n=24	587 (56.7%) n=82	0.78	0.60 – 1.02	231 (103.1%) n=23	246 (72.8%) n=82	0.94	0.67 – 1.32
C1D15 pre-dose	280 (85.2) n= 24	269 (89.8) n=78	1.04	0.73 – 1.48	705 (105.0) n=24	622 (121.4) n=78	1.13	0.73 – 1.76
C1D15 6 hr	732 (58.8%) n=24	782 (50.5%) n=73	0.94	0.74 – 1.18	928 (83.6%) n=24	870 (74.0%) n=73	1.07	0.78 – 1.46

Notes: Geometric mean ratios: exposure of patients using PPIs to patients not using PPIs

Boxplots: The solid and dashed lines in the box represent the mean and the median, respectively. Lower end of box – lower 25th percentile, upper end of box – upper 75th percentile. The whiskers represent the minimum or maximum values within 1.5*IQR (interquantile range). The solid black circles (if any) represent the data points beyond 1.5*IQR.

Figure 2: Boxplot of Ripretinib Plasma Concentration in Patients Using vs. Not Using PPIs

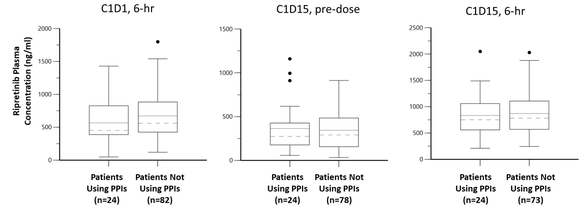
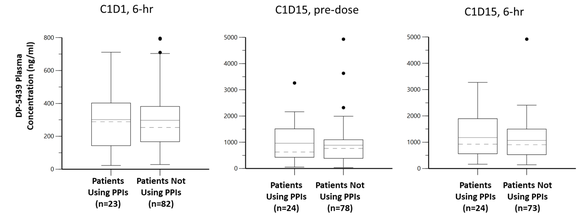


Figure 3: Boxplot of Metabolite DP-5439 Plasma Concentration in Patients Using vs. Not Using PPIs



CONCLUSIONS

- Geometric mean ratios (95% C.I.) between patients using and not using PPIs did not indicate a difference between these groups.
- This preliminary retrospective PK analysis provides supporting evidence that restriction of coadministration of PPIs with ripretinib may not be necessary.
- The use of PPIs is not expected to impact the efficacy of ripretinib
- A dedicated drug interaction study is planned to provide a definitive assessment.

References

1. Smelick et al, Mol. Pharmaceutics 2013, 10, 4055−4062
2. Budha et al, Clin Pharmacol Ther. 2012, 92(2):203-13

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