Phase 1b Trial Combining Rapid Determination of Drug-Drug Interaction (DDI) Followed by a Dose Finding Period to Assess Safety and Preliminary Efficacy of Fimepinostat Plus Venetoclax in Patients with Aggressive B-Cell Lymphoma

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Background: Fimepinostat (F), a dual inhibitor of PI3K (α, β, δ) and HDAC class 1/2, causes suppression of MYC levels (*Shulman DS et al., JCO 2017; 35:15*). A pooled analysis of diffuse large B-cell lymphoma (DLBCL) pts treated with F in two Ph 1/2 trials revealed an objective response rate (ORR) in evaluable/ITT MYC-altered DLBCL patients of 29%/23%, respectively (*Landsburg D et al., Blood 2018; 132:4184*). Venetoclax (V) had 18% ORR in 34 patients of R/R DLBCL (*Davids MS et al., JCO 2017; 35:826*). Based on preclinical synergistic efficacy of F combined with BCL-2 inhibitor venetoclax , we initiated a Ph 1b/2 study of F + V in patients with relapsed or refractory (R/R) DLBCL or high-grade B-cell lymphoma (HGBL), with or without MYC alteration. V is primarily metabolized by CYP3A4. F may inhibit CYP3A4 (IC of 13.58 and 0.28 μM for midazolam and testosterone), suggesting F could cause DDI with V.

Study Design: In the Phase 1 Dose-Escalation period, F + V was studied in patients with R/R DLBCL or HGBL with ≥1 prior treatment.

Methods: Cohorts of patients received increasing dose levels of Fimepinostat (F) administered on a 5-days-on/2-days-off (5/2) schedule in combination with daily venetoclax (V) in cycles (Cohort 1: F 30 mg QD 5/2 + V 400 mg QD; Cohort 2: F 60 mg QD, 5/2 + V 400 mg QD; Cohort 3: F 60 mg QD 5/2 + V 800 mg QD (was not opened).

- A potential DDI was assessed during Cycle 0 (Table 1), where PK for V (10 mg) monotherapy was compared to that for V (10 mg) in the presence of F.
- Patient PK samples were collected, analyzed and reviewed in < 10 days to determine the final ramp-up dose level of V.

Table 1

Cycle 0											Cycle 1
Day	1	2-5	6-7	8	9-10	11-14	15	16	17	18	19 End of Evaluation	1-2
V dose mg:	10			10		10	20	50	100	(100 - 200)	Continue to target dose	400
F			x	x			x	x	x	x		x
PK	x	x		x			x	x	x	x		x

PK: No significant DDI was observed.
Safety: F + V is safe and well tolerated at projected clinically active dose levels.
Efficacy: Subtherapeutic doses/schedule at Cycle 0 (due to thorough DDI evaluation) and slow V ramp-up at Cycle 2 were suboptimal for efficacy in these aggressive NHLs: early PD.

Results

Pharmacokinetics: Absence of significant DDI

- As of 1-Feb-2020, 16 patients were enrolled in 2 dose cohorts.
- Intensive PK analysis of 13 patients showed only mild (≤ 2-fold) to no increase in V exposure in the presence of F.
- In Cohort 1 (n = 6), the mean AUC increased 1.6-fold, and mean Cmax by 1.5-fold. In Cohort 2 (n = 7), no increase in mean AUC (0.9-fold) or Cmax (1.0-fold) was observed.
- V was ramped up to 100% of the target dose (400 mg) upon entering Cycle 1; rapid escalation of V was well tolerated in all patients.

Safety: DL1 was well tolerated. At DL2 , 3 DLTs occurred (Gr 3 diarrhea; Gr. 4 neutropenia, thrombocytopenia) (Table 2). AEs were manageable, even in 6/18 patients with prior CAR-T-cell + ASCT. The F dose intensity was then reduced to 60 mg Days 4/3. Eleven patients (69%) had SAEs; 4 pts. (25%) had F or V related SAEs.

Preliminary Efficacy: Efficacy evaluation was hampered by the fact that the DDI evaluation in Cycle 0 was done with reduced F dose intensity and only subtherapeutic V test doses for safety reasons. This led to early progression of highly aggressive tumors which were already resistant / refractory to extensive pre-treatments. No CR/PR were seen, but SD and clinical benefits were observed.

Table 2

Adverse Events	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total (n=14) n (%)
Neutrophil count decreased	2 (14)	3 (21)	2 (14)	7 (50)
Diarrhea	9 (64)	2 (14)	0 (0)	11 (79)
Platelet count decreased	0 (0)	4 (29)	1 (7)	5 (36)
Fatigue	4 (29)	0 (0)	0 (0)	4 (29)
Decreased appetite	2 (14)	0 (0)	0 (0)	2 (14)
Nausea	2 (14)	0 (0)	0 (0)	2 (14)
Hypokalemia	2 (14)	0 (0)	0 (0)	2 (14)
Hypomagnesaemia	2 (14)	0 (0)	0 (0)	2 (14)

Conclusions:

The trial enrolled 18 patients, most with highly aggressive tumors and heavy pretreatments. There was limited DDI between F and V. Treatment with F 30 mg D5/7 + V 400 mg QD was well tolerated, but DLT was seen at F 60 mg D5/7 and V 400 mg QD. The trial accrual was stopped for further in-depth evaluations, which could guide future optimization of patient selection, drug combination, dose and administration schedule. NCT01742988.

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