Supplemental Methods

Dose-limiting toxicity (DLT) definition for phase 1b pirtobrutinib combinations

The safety of patients enrolled to phase 1b combinations were reviewed at each meeting of the Safety Review Committee (SRC). The DLT assessment period was from C2D1 to C3D8 for both combination regimens. Dose-limiting toxicity (DLT) definitions are outlined below.

1) Any ≥ Grade 3 nonhematologic toxicity except for:
    - First occurrence of Grade 3 electrolyte abnormalities and/or creatinine clearance decrease resolving to Grade 2 (or baseline if baseline is ≥ Grade 2) within 72 hours with supportive treatment or Grade 3. LTLS defined by Howard et al. 2011[1] without evidence of clinical TLS
    - Grade 3 fatigue, nausea, vomiting, diarrhea, or other manageable constitutional symptom that is responsive to supportive therapy
    - Grade 3 infection responding to appropriate antibiotic/antiviral therapy
2) Any ≥ Grade 3 hematologic toxicity will be considered a DLT except for:
    - Grade 3 neutropenia without fever
    - Grade 4 neutropenia without fever lasting 7 days or less
    - Grade 3 thrombocytopenia that does not result in bleeding or transfusion
    - Grade 3 or 4 lymphopenia/lymphocytosis
    - Grade 3 or 4 leukopenia/leukocytosis
3) Any toxicity regardless of the NCI CTCAE v5.0 grade, resulting in discontinuation, dose reduction, or treatment with less than 75% of planned doses of pirtobrutinib or venetoclax will be reviewed by the SRC and will be considered a DLT unless the SRC determines the toxicity is clearly unrelated to study treatment (i.e., related to the patient's underlying disease, other medical condition, or concomitant medications).

Supplemental Results

TLS case report

One PV patient developed grade 4 TLS during cycle 2 dose escalation to venetoclax 400 mg. This patient did not have baseline renal insufficiency reported. Out of 6 lymph node target lesions at screening, the patient had two lymph nodes that were ≥5 cm (6.9 x 4.1 and 5.9 x 4.1). At cycle 1 day 1, the patient's ALC was 13.5 x 10^9/L and at cycle 2 day 1 (i.e., the time of venetoclax initiation) the ALC was 100.54 x 10^9/L. The investigator attributed TLS to venetoclax, and the patient was hospitalized for 3 days and underwent dialysis for refractory hyperkalemia. The venetoclax dose was interrupted for 13 days, and subsequently dose ramp up was resumed. The patient reached the 400mg QD dosing by cycle 3 day 1.

Supplemental Tables

Supplemental Table 1: Patients who discontinued treatment early (n=8)*

		Reason for discontinuation							
Patient	**Treatment**	**Treatment-related AE**	**Death**	**PD**	**Other**	**Time treatment stopped**	**Best response**	**uMRD** ($<10^{-4}$)	**Death (causality)**
1**	PV	-	-	Yes	-	Cycle 24	CR at Cycle16	Cycle 5	-
2***	PV	-	-	Yes	-	Cycle 10	PR at Cycle 5	-	Death attributed to PD ~1 month after last dose
3	PVR	Grade 4, Neutrophil count decrease	-	-	-	Cycle 19	PR at Cycle 3	Cycle 5	-
4	PVR	Grade 3, Urinary tract infection	-	-	-	Cycle 13	PR at Cycle 3	-	Investigator attributed death to grade 5 Covid-19 pneumonia, which occurred ~3 weeks after last dose
5	PVR	-	Grade 5, Cardiac failure	-	-	Cycle 8	PR at Cycle 3	Cycle 5	Investigator attributed death to grade 5 cardiac failure while on treatment, though cardiac failure was not considered related to treatment. Autopsy revealed severe coronary atherosclerosis. This patient met all eligibility criteria as stipulated in the protocol. Only patients requiring therapeutic anticoagulation with warfarin were excluded. At screening, the patient's coagulation panel was normal, and the patient was treated with concomitant medications, including enoxaparin (preventive), Lipitor, and lisinopril.

6	PV	-	-	-	The patient stopped study treatment to begin treatment for metastatic squamous cell carcinoma.	Cycle 19	PR at Cycle 3	Cycle 7	-
7	PV	-	-	-	Upon achieving CR, patient expressed their desire to discontinue treatment	Cycle 13	CR at Cycle 13	Cycle 5	-
8	PV	-	-	-	Protocol violation	Cycle 7	SD at Cycle 3	Not assessed	-

* One patient who completed therapy died due to sepsis >4 months after stopping treatment. **This patient achieved a complete response, had TP53-postive CLL, and 2 prior lines of therapy with chemoimmunotherapy and the covalent BTK inhibitor zanubrutinib. ***This patient had ZAP-70-positive CLL and 2 prior lines of therapy with chemoimmunotherapy and the PI3Kδ inhibitor zandelisib.

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; PV, pirtobrutinib and venetoclax; PVR, pirtobrutinib, venetoclax, and rituximab; uMRD, undetectable minimal residual disease

Supplemental Table 2: Venetoclax pharmacokinetic parameters

Parameter	Pirtobrutinib and Venetoclax	Pirtobrutinib, Venetoclax, and Rituximab
Cycle 3 Day 8		
C_{max} (ng/mL)	3730 (37.3)	1600 (49.7)
T_{max} (h)	7.74 (6.97 – 8.00)	7.57 (4.07 – 8.00)
$AUC_{0\text{-}tlast}$ (hr*ng/mL)	17200 (52.4)	8220 (31.4)
N	12	9
Cycle 4 Day 1		
C_{max} (ng/mL)	2540 (66.3)	1780 (89.9)
T_{max} (h)	7.56 (1.90 – 7.78)	7.52 (1.75 – 8.00)
$AUC_{0\text{-}tlast}$ (hr*ng/mL)	12700 (68.2)	10500 (84.6)
N	12	10

Geometric mean (CV%) presented for C_{max} and AUC; Median and Range presented for T_{max}.

Abbreviations: AUC, area under the curve; C_{max}, maximum concentration; CV, coefficient of variation; T_{max}, time to peak drug concentration;

Supplemental Table 3: Pirtobrutinib pharmacokinetic parameters

Parameter	Pirtobrutinib and Venetoclax	Pirtobrutinib, Venetoclax, and Rituximab
Cycle 1 Day 8 (Pirtobrutinib Alone)		
C_{max} (ng/mL)	5300 (28.3)	5690 (34.1)
T_{max} (h)	2.08 (0.783 – 3.90)	2.11 (0.783 – 4.00)
$AUC_{0\text{-}tlast}$ (hr*ng/mL)	31200 (33.2)	33400 (30.8)
N	13	10
Cycle 2 Day 8 (during Venetoclax and Rituximab escalation)		
C_{max} (ng/mL)	5210 (23.4)	5200 (57.2)
T_{max} (h)	2.00 (0.00 – 4.00)	2.01 (0.00 – 3.83)
AUC0-tlast (hr*ng/mL)	31400 (21.8)	31100 (64.5)
N	14	10
Cycle 3 Day 8		
C_{max} (ng/mL)	5490 (26.3)	5460 (31.3)
T_{max} (h)	2.18 (0.133 – 7.50)	1.95 (0.933 – 7.73)
$AUC_{0\text{-}tlast}$ (hr*ng/mL)	34800 (23.8)	32400 (28.8)
N	13	9
Cycle 4 Day 1		
C_{max} (ng/mL)	3790 (114)	5570 (38.7)
T_{max} (h)	1.97 (0.00 – 4.15)	2.93 (0.833 – 7.53)
$AUC_{0\text{-}tlast}$ (hr*ng/mL)	29600 (33.7)	32500 (41.9)
N	13	10

Geometric mean (CV%) presented for C_{max} and AUC; Median and Range presented for T_{max}.

References

1. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. *N Engl J Med*. 2011;364(19):1844-1854.