An open-label phase I/IIa study to evaluate the safety and efficacy of inobrodib (CCS1477) as monotherapy in patients with relapsed/refractory multiple myeloma

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INTRODUCTION

- Inobrodib is a potent, selective and orally bioavailable inhibitor of the bromodomains of p300/CBP, two closely related histone acetyl transferases with oncogenic roles in multiple cancer types.
- Inobrodib inhibits expression of IRF4 and MYC, two potent oncogenes that drive multiple myeloma.
- This poster reports the interim results (as of 06 Feb) of the multiple myeloma monotherapy data from NCT04068597, an adaptive multi-arm/multi-stage trial exploring inobrodib as monotherapy or in combination across several haematological malignancies.

METHODS

Eligibility criteria

- Progressing relapsed/refractory MM
- ECOG performance status 0-2
- Must have previously received standard therapy

Primary endpoints

- Adverse events (AEs) assessed per Common Terminology Criteria for AEs (CTCAE) v5.0
- Dose-limiting toxicities (DLTs)

Secondary endpoints

- Objective response rate (IMWG criteria)
- Duration of response
- CCS1477 pharmacokinetics

Table 1: Dose escalation cohorts (MM and NHL)

cohort	inobrodib dose	schedule	DLTs (# enrolled pts)
1	50mg - O	3d on/4d off	No DLTs (5)
2	25mg - O	daily	No DLTs (4)
3	50mg - O	4d on/3d off	G3 Hypotension (2)
4	30mg - M	4d on/3d off	No DLTs (3)
5	50mg - M	4d on/3d off	No DLTs (7)
6	25mg BD - M	4d on/3d off	G3 Nausea and Vomiting (8)
7	50mg - M	10d on/4d off	G3 Thrombocytop. (3)
8	**35mg BD - M**	**4d on/3d off**	**No DLTs (9)**
9	50mg BD - M	4d on/3d off	No DLTs (3)

O = original formulation; M = modified formulation

Recommended phase 2 dose and schedule

RESULTS

Table 2: Baseline characteristics

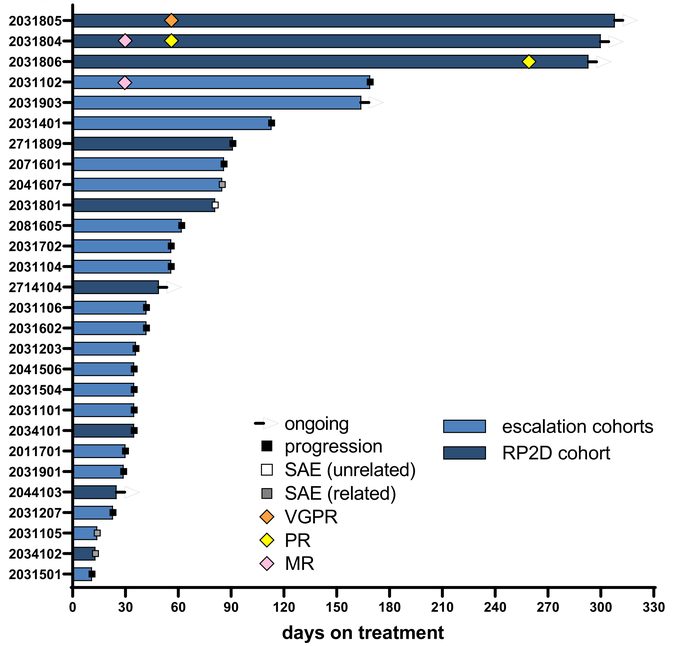
Characteristic	Escalation (Cohorts 1-7 and 9) n=19 (%)	RP2D (cohort 8 + exp) n=9 (%)
Median age	67	62
Age range	50-80	54-90
Male sex	14 (74)	5 (56)
Race		
White	18 (95)	8 (89)
Black African	1 (5)	1 (11)
ISS staging		
stage I	4 (22)	3 (3)
stage II	5 (26)	1 (11)
stage III	5 (26)	3 (33)
unknown	5 (26)	2 (22)
Yr since diagnosis median (range)	7.5 (3.6-18.1)	7.6 (4.9-11.4)
Prior therapy		
Med prior lines (range)	6 (4-8)	6 (3-8)
ASCT	15 (79)	6 (67)
PI	19 (100)	9 (100)
IMiD	19 (100)	9 (100)
αCD38	14 (74)	8 (89)
Refractory to (incomplete dataset)		
PI	15/16	5/6
IMiD	16/16	6/7
αCD38	12/12	6/6

Table 3: Treatment-emergent AE

TEAE	Any Grade n=28 (%)	Grade 3/4 n=28 (%)
Thrombocytopenia	16 (57)	11 (39)
Fatigue	15 (54)	1 (4)
Anaemia	12 (43)	9 (32)
Hypercalcaemia	10 (36)	1 (4)
Diarrhoea	9 (32)	0
Blood creatinine increased	9 (32)	0
Decreased appetite	8 (29)	1 (4)
Pneumonia	7 (25)	6 (21)
Acute kidney injury	3 (11)	3 (11)

any grade: ≥25% and/or grade 3/4: ≥10%

Figure 1: Objective responses and duration



- 1/19 objective response in dose escalation
- 3/9 objective responses at RP2D

Figure 2: 2031805 case report (VGPR)

- 57y/o male, PS1
- ISS-3 at study entry
- 4 lines of prior therapies including 2x ASCT
- Triple class refractory

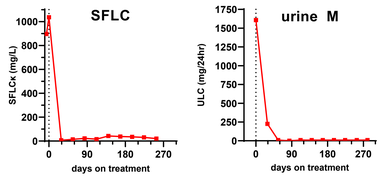


Table 4: Inobrodib pharmacokinetic parameters[1]

	C_{max} (ng/mL)	T_{max} (h)	AUC_{inf} (h*ng/ml)	$T_{1/2}$ (h)
n	12	12	12	12
mean	712		2501	4.19
SD	288		1638	2.07
CV%	40.4		65.5	49.4
min	305	1	683	2.36
median	759	1.25	1866	3.44
max	1260	2	5876	8.70

[1] From all RP2D monotherapy cohorts in NCT04068597

CONCLUSIONS

- Inobrodib dose escalation has completed and the RP2D has been selected for monotherapy.
- The safety profile is in line with preclinical data and inobrodib is well tolerated at the RP2D.
- All inobrodib-associated toxicities are manageable.
- The most common TEAE, thrombocytopenia, was readily reversible.
- In contrast to other agents, inobrodib does not cause neutropenia or neuropathy.
- The inobrodib pharmacokinetic profile is well-characterised with reproducible exposure values.
- Inobrodib monotherapy has encouraging signs of clinical activity against myeloma at the RP2D.

FUTURE DEVELOPMENT

- Inobrodib in combination with pomalidomide and dexamethasone is currently in dose escalation
- The safety profile and scientific rationale supports further combinations with other standard-of-care agents for multiple myeloma
- NCT04068597 is additionally exploring inobrodib monotherapy and combinations in other haem indications
  - AML/higher risk MDS
  - NHL

EHA2023 JUNE 8 - 16 / FRANKFURT & VIRTUAL