Tolerability and clinical activity of novel first in class oral agent, inobrodib (CCS1477), in combination with pomalidomide and dexamethasone in relapsed/refractory multiple myeloma

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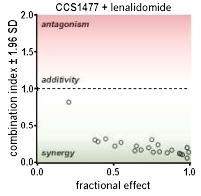
INTRODUCTION

- Inobrodib (Ino) targets the bromodomains of the histone acetyltransferase paralogues, p300 and CBP
  - Orally bioavailable
  - Potent: K_D ~ 1nM
  - Selective: binds p300/CBP >200x stronger than other bromodomains
- Ino inhibits expression of IRF4 and MYC, two potent oncogenes that drive multiple myeloma
- P300 inhibition can reverse resistance to immunomodulatory imide drugs (IMiDs) by inhibiting IRF4/MYC expression (Welsh et al, Cancer Discovery 2023)
- Ino demonstrates synergistic activity with IMiDs *in vitro* and combines well *in vivo*

in vitro



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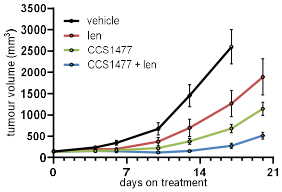


- Ino monotherapy is well tolerated and can elicit objective responses in select RRMM patients (Searle et al, EHA 2023 Congress)
- This poster reports the initial results (data cutoff 31 Oct 2023) exploring the combination of Ino-Pom-dex in late-stage patients with relapsed/refractory myeloma (RRMM) from NCT04068597, an adaptive multi-arm/multi-stage trial exploring Ino 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

Inobrodib dose and schedule: 25/35mg BD; 4 days on / 3 days off

RESULTS

Table 1: Baseline characteristics

Characteristic	25 Ino / 4 Pom n=9 (%)	35 Ino / 4 Pom n=9 (%)	25 Ino / 3 Pom n=3 (%)	Total n=21 (%)
Median age (y)	63	71	72	64
Age range	41-80	61-75	56-82	41-82
Male sex	7 (77.8)	4 (44.4)	2 (66.7)	13 (61.9)
Race				
White	8 (88.9)	9 (100)	2 (66.7)	19 (90.5)
Black/African	1 (11.1)			1 (4.8)
Other			1 (11.1)	1 (4.8)
ECOG performance status				
0	3 (33.3)	1 (11.1)		4 (19)
1	6 (66.7)	7 (77.8)	2 (66.7)	15 (71.4)
2		1 (11.1)	1 (33.3)	2 (9.5)
Prior therapy				
Med. prior lines (range)	5 (4-8)	6 (3-8)	5 (4-5)	5 (3-8)
ASCT	5 (55.6)	6 (66.7)	2 (66.7)	13 (61.9)
Triple class exposed	9 (100)	9 (100)	3 (100)	21 (100)
αBCMA	1 (11.1)	3 (33.3)		4 (19)
Refractory to				
Triple-class	8 (88.9)	8 (88.9)	1 (33.3)	17 (81)
Pom	8 (88.9)	7 (77.8)	3 (100)	18 (85.7)
Last line	9 (100)	9 (100)	3 (100)	21 (100)

Table 2: Treatment-emergent adverse events

TEAE ≥20%	Any Grade n=21 (%)	Grade 3 n=21 (%)	Grade 4 n=21 (%)
Haematological			
Thrombocytopenia	5 (23.8)	3 (14.3)	1 (4.8)
Neutropenia	5 (23.8)	3 (14.3)	2 (9.5)
Other			
Pyrexia	6 (28.6)	1 (4.8)	
Diarrhoea	6 (28.6)		
Constipation	5 (23.8)		
COVID-19	5 (23.8)	1 (4.8)	
Pneumonia	5 (23.8)	4 (19)	
UTI	5 (23.8)		
Insomnia	5 (23.8)		

One patient experienced a fatal unrelated cardiac event at the end of C2

Figure 1: Objective responses and duration

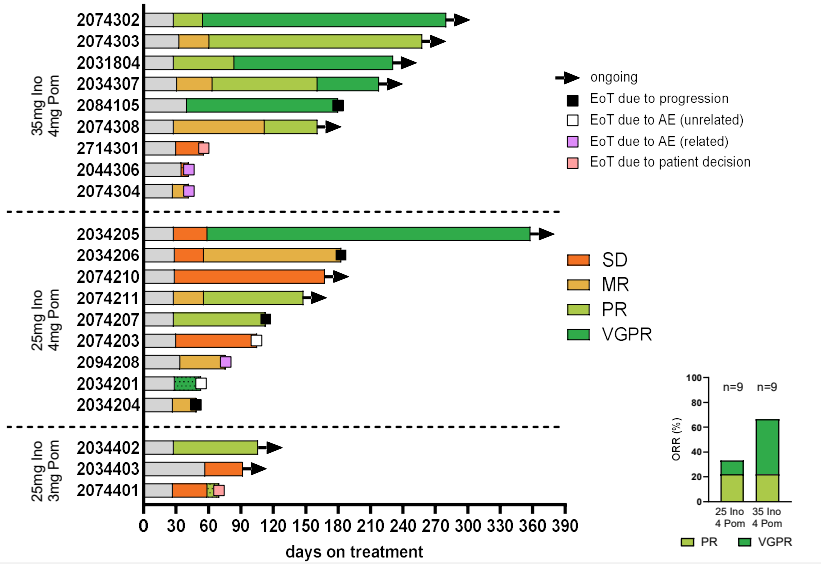
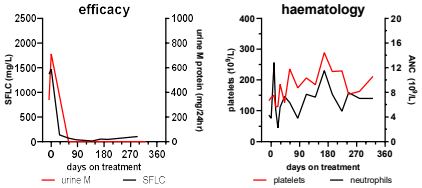


Figure 2: 2034205 case report (VGPR)

- 73 y/o M, ECOG 0, diagnosed Oct 2020, ISS III at diagnosis
- 4 lines of prior therapy; triple-class refractory, including to pomalidomide
- Achieved VGPR after C2 with good haematological tolerability
- Drug holiday between C8-10 (unrelated AE) did not impact efficacy



CONCLUSIONS AND FUTURE DEVELOPMENT

- InoPd is showing promising combination efficacy in heavily pre-treated and pom-refractory RRMM patients (median 5, up to 8 prior lines of therapy)
- All patients demonstrated signs of clinical activity with rapid responses observed and with a number of patients remaining on treatment for > 6 months
- The safety profile is consistent with the individual components of the regimen, with no new safety signals identified
- Dose optimisation is ongoing in order to select two dose levels/regimens for the expansion cohorts in an earlier line (not pom-refractory)
- Additional combinations with PIs and αCD38 are planned within the current study protocol