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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CANCER RESEARCH UK

Abstract 1023

Presented by E Searle at ASH 2024; December 7–10, 2024; San Diego

MANCHESTER 1824
The University of Manchester

Background

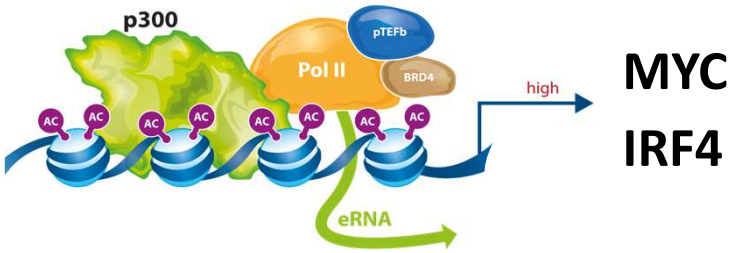
Inobrodib: First-in-class, oral, potent and specific bromodomain inhibitor of p300/CBP, two transcriptional coactivators with key roles in hematological cancers

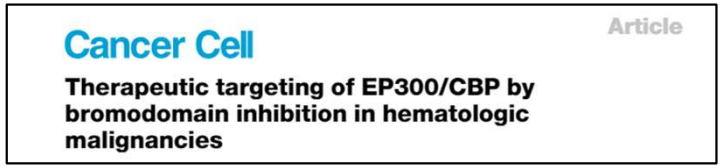
Strong scientific rationale for targeting p300/CBP in myeloma

- selective displacement of p300/CBP from 10% of binding sites[1]
- inhibition of key oncogenic drivers IRF4 and MYC
- exquisite synergy with IMiDs[2]

Clinical activity has been observed in patients with relapsed and refractory myeloma when given as a monotherapy (ORR 25%)[3]

We report on the combination of inobrodib (INO), pomalidomide (POM) and dexamethasone (DEX) in the ongoing Phase I/IIa trial (NCT04068597).

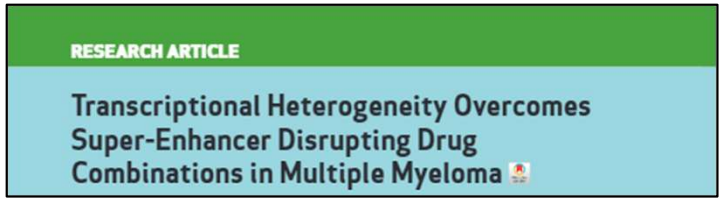



Cancer Cell

Article

Therapeutic targeting of EP300/CBP by bromodomain inhibition in hematologic malignancies

[1]*Nicosia et al, Cancer Cell 2023*


RESEARCH ARTICLE

Transcriptional Heterogeneity Overcomes Super-Enhancer Disrupting Drug Combinations in Multiple Myeloma

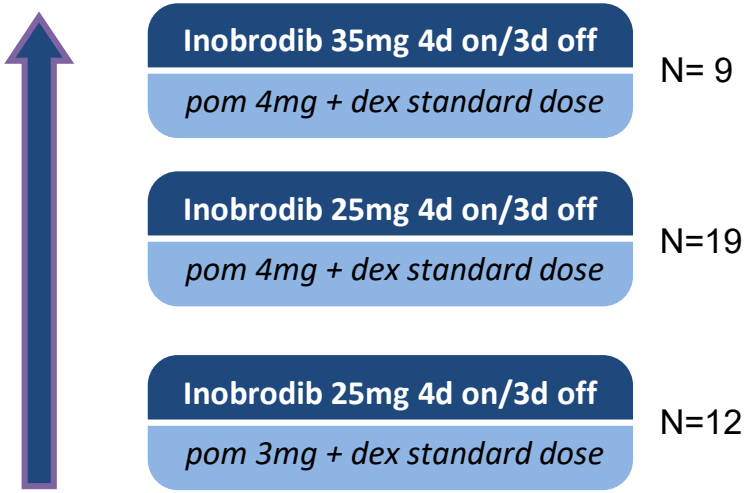
[2]*Welsh et al, Blood Cancer Discovery 2024*

[3]Searle E et al presented at ASH 2023

Study design

PI/IIa of Inobrodib in patients with advanced haematologic malignancies

Myeloma combination cohorts N =40



Three dose escalation cohorts

Inobrodib 4 day on 3 days off, 28-day cycles

Pomalidomide Days 1-21 of each 28-day cycle

Dexamethasone 20mg/ 40mg weekly

Primary objective

Establish safety profile and select doses for expansion cohorts

Secondary objectives

Characterise inobrodib pharmacokinetics

Assess anti-myeloma efficacy (IMWG criteria)

Exploratory objectives

Explore PD biomarker profiling (e.g. IRF4,MYC) in paired BM and serial PBMC samples

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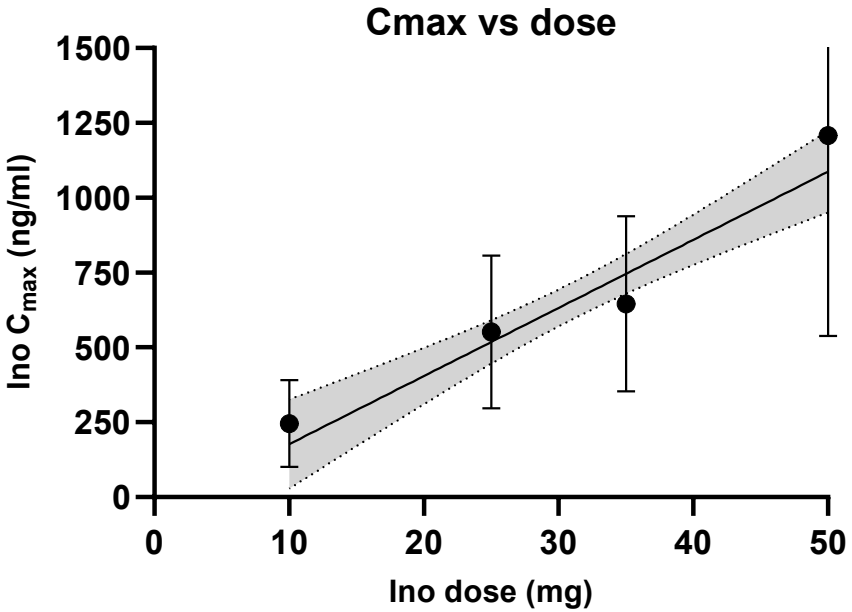
Pharmacokinetic data



Ino dose (mg)	median Cmax (ng/ml)	median AUC (ng*hr/ml)	median Tmax (hr)
10	265	1079	1.5
25	581.5	2301	1
35	714	2825	1.5
50	1180	4315	1

Key Observations

- Dose proportional linear pharmacokinetics
- Rapid absorption
- Short half-life ~ 4-6 hrs supporting BID dosing

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Background characteristics

Demographic / disease n=40	Total n (%)
Age median (range) yrs	68.5 (41-82)
Male sex	24 (60%)
White race	38 (95%)
ECOG PS 0 1 2	 13 (32.5%) 23 (57.5%) 4 (10%)
Disease characteristics	
≥1 plasmacytoma*	4 (10%)
BM involvement ≥50%	17 (42.5%)
ISS stage at baseline/ study entry ** I II or III	 6/25 (24%) 19/25 (76%)
Elevated LDH	15/40 (37.5%)
Cytogenetics	Data pending / analysis in progress

* No mandated MRI/ PET-CT

**Percentage of evaluable patients/data missing

Data cut 04 Nov 2024

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Prior therapies and refractory status

Prior therapy n=40	Total n (%)
Prior lines; median (range)	5 (2-9)
Prior stem cell transplantation 1 2	 18 (45%) inc. 1 allo SCT 9 (22.5%)
Triple-class exposed	40 (100%)
Refractory	
Lenalidomide *	31/38 (82%)
Pomalidomide *	28/40 (70%)
Triple-class *	28/37 (76%)
Penta-drug *	8/39 (20.5%)
aBCMA/TCE	12/40 (30%)
To last line	40 (100%)

Most patients were heavily pre-treated & triple class refractory, 30% had received an anti-BCMA and/or T cell engagers

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Patient disposition and exposure

Treatment Disposition	Total (N = 40)	25mg Ino/ 3mg Pom (N = 12)	25mg Ino / 4mg Pom (N = 19)	35mg Ino / 4mg Pom (N = 9)
Follow-up median (range), months	**14.5 (6 – 25)**	11.8 (6.8 – 15.4)	12.5 (5.5 – 24.7)	19.1 (16.5 – 20.8)
Ongoing, n (%)	**9 (23%)**	2 (17%)	5 (26%)	2 (22%)
Discontinued, n (%) Progressive disease TEAE Patient withdrawal	**31 (77%)** **24 (60%)** **5 (13%)** **2 (5%)**	10 (83%) 9 (75%) 0 (0%) 1 (8%)	14 (74%) 11 (58%) 3 (16%) 0 (0%)	7 (78%) 4 (44%) 3 (22%) 1 (11%)
Exposure	**Total (N = 40)**	**25mg Ino/ 3mg Pom (N = 12)**	**25mg Ino / 4mg Pom (N = 19)**	**35mg Ino / 4mg Pom (N = 9)**
Duration of InoP treatment, median (range), months	**6.1 (1.0 – 21.0)**	7.4 (2.3 – 11.4)	5.5 (1.2 – 21.2)	10.0 (1.2 – 19.8)
Dose reductions of Ino, n (%)	**8 (20)**	3 (25)	4 (21)	1 (11)
Evaluable for ORR [#]	**35**	**8**	**18**	**9**

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[#] Pts evaluable for response assessment excluded 2 who discontinued due to patient decision and 3 who did not have IMWG measurable disease

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Safety profile of InoPd: TEAEs irrespective of causality

TEAEs	All Grades n (%)	Grade ≥3
Thrombocytopenia **Bleeding**	**18 (45)** **5 (12.5)**	13 (32.5) 1 (2.5)
Anaemia	**16 (40)**	7 (17.5)
Neutropenia **Febrile neutropenia**	**15 (37.5)** **2 (5)**	14 (35) 2 (5)
Fatigue	**25 (62.5)**	
Diarrhoea	**18 (45)**	1 (2.5)
Pyrexia	**15 (37.5)**	1 (2.5)
Constipation	**12 (30)**	
Pneumonia	**12 (30)**	8 (20)
UTI	**12 (30)**	3 (7.5)
Muscle spasms	**12 (30)**	
Myocardial ischaemia*	**1 (2.5)**	1 (2.5)
Discontinued due to TEAE	**5 (12.5%)**	

Key Observations

InoPomDex combination had a tolerable safety profile

- Most common TEAEs were cytopenias & fatigue
- Most TEAEs were mild/moderate and did not impact compliance
- No differences between cohorts

Thrombocytopenia, the main anticipated overlapping toxicity was manageable

- Limited (mostly G1) bleeding events

Low treatment discontinuation due to AEs

No new safety signals identified

Most frequent ≥25% (TEAEs) plus *1 patient with Grade 5 event (MI: not related to inobrodib)

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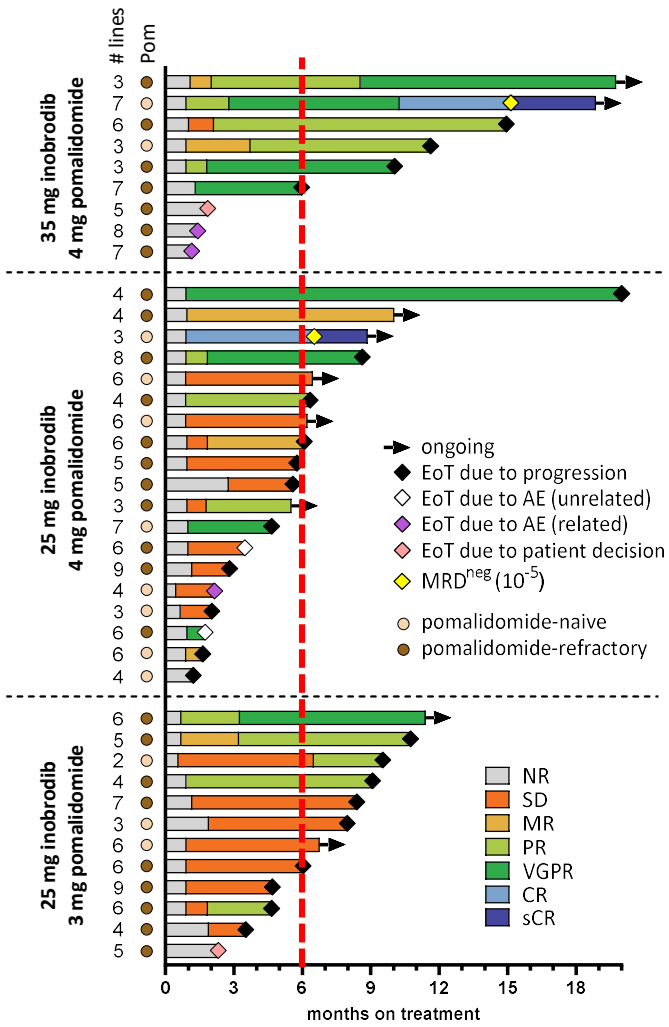
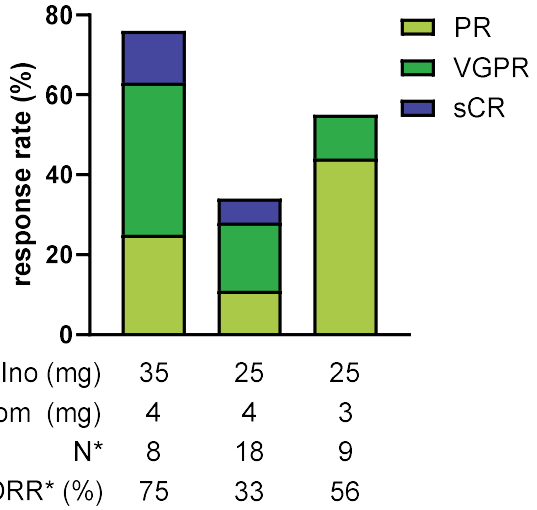
InoPd efficacy in relapsed refractory multiple myeloma





Ino (mg)	35	25	25
Pom (mg)	4	4	3
N*	8	18	9
ORR* (%)	75	33	56

Across all cohorts: 49% ORR, mDOR 6.3 months , 63% of pts ≥ 6 mo.

* Among evaluable patients

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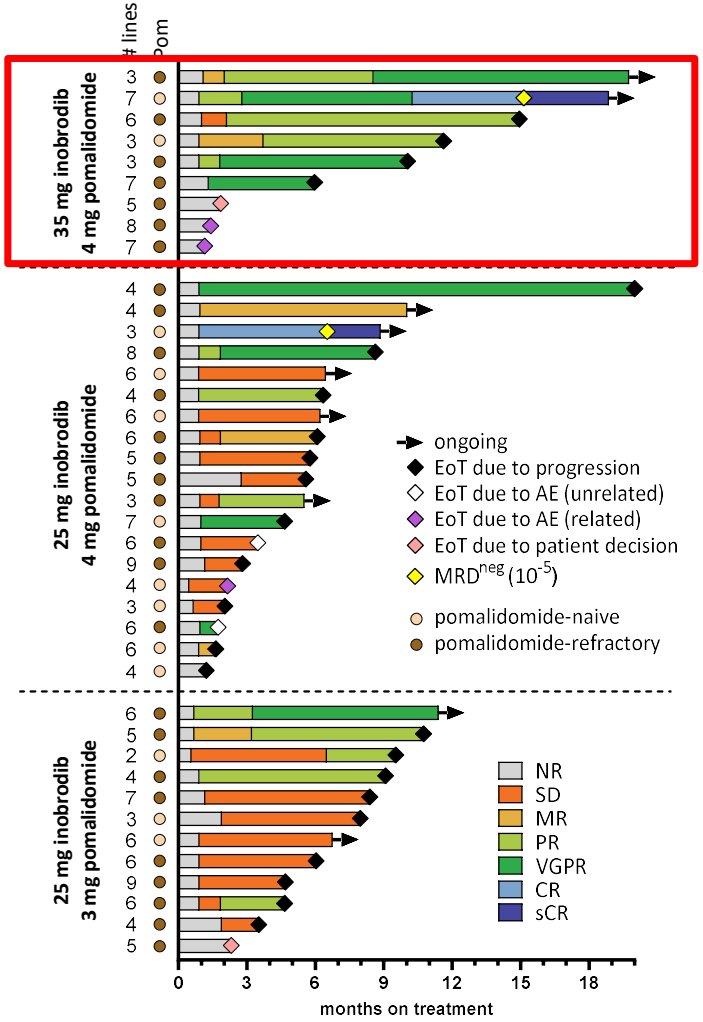

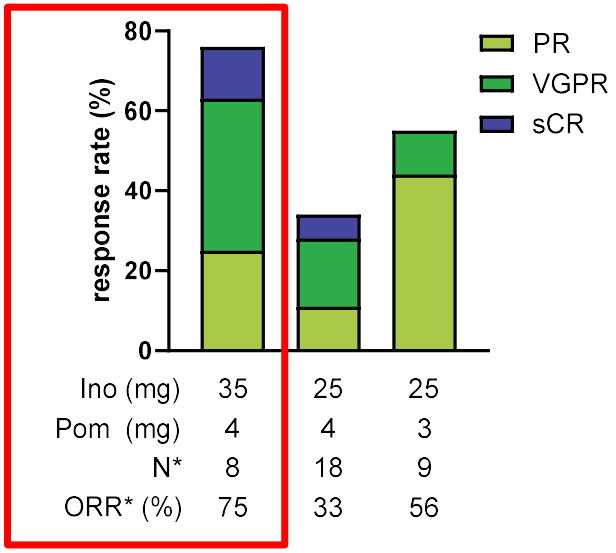

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Highest dose cohort: 75% ORR, mDOR 9.7 months

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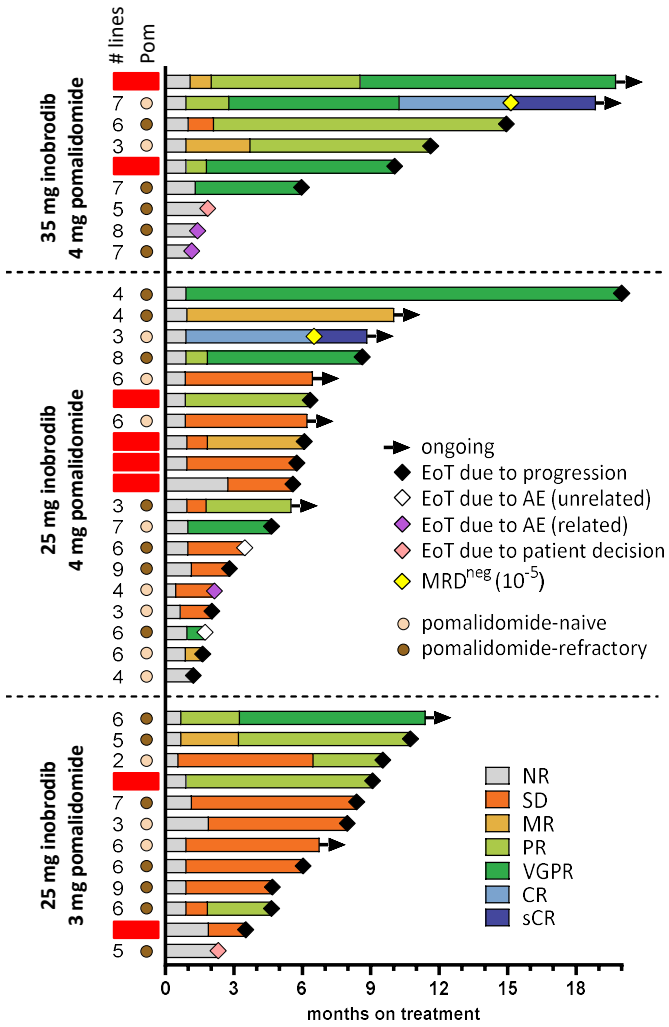

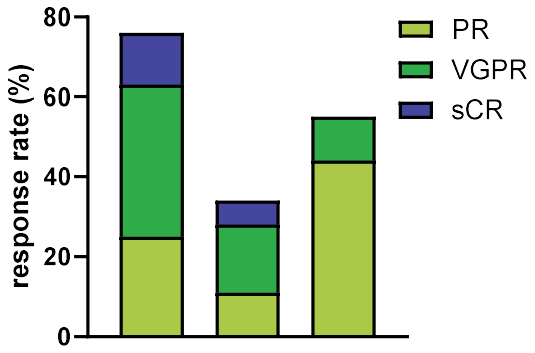

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Pom-refractory patients (last line): 4/8 pts responded ≥PR, + 1 MR

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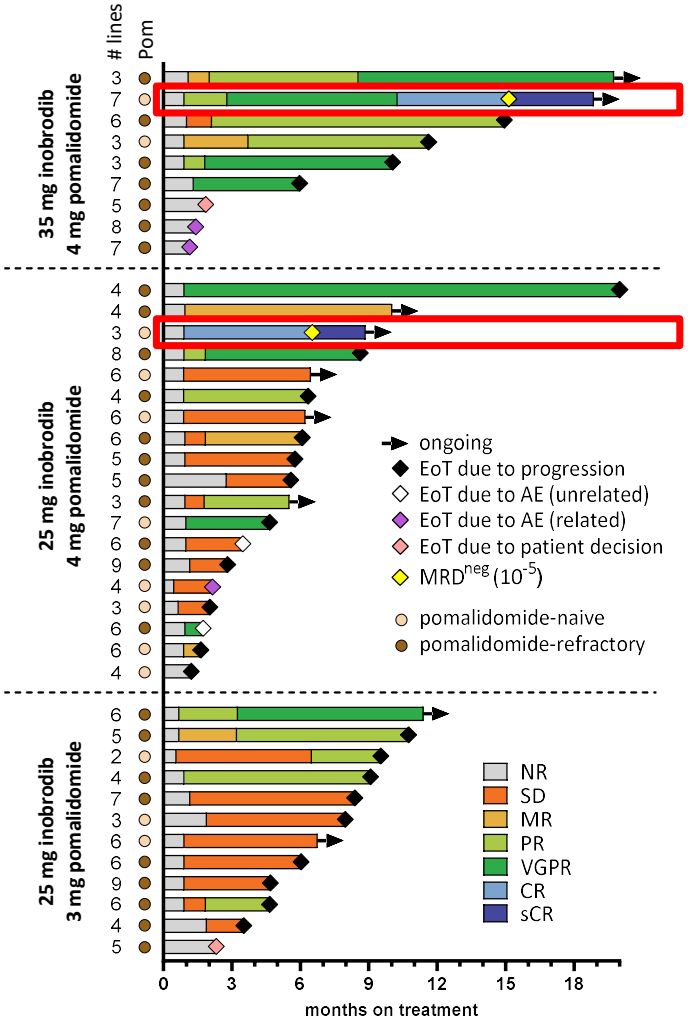

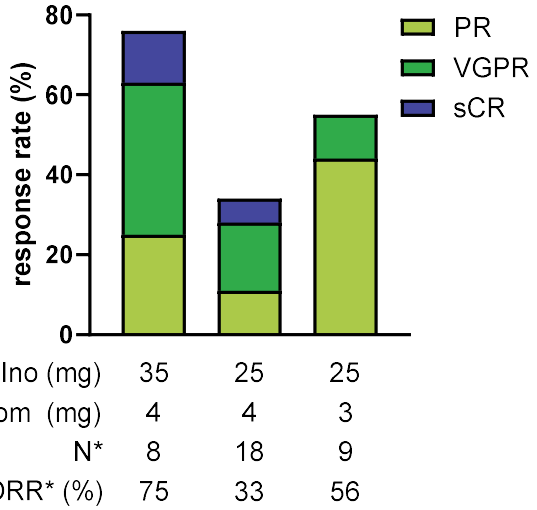

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Pom naïve pts: 2/12 achieved MRD negative sCR

* Among evaluable patients

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Case studies

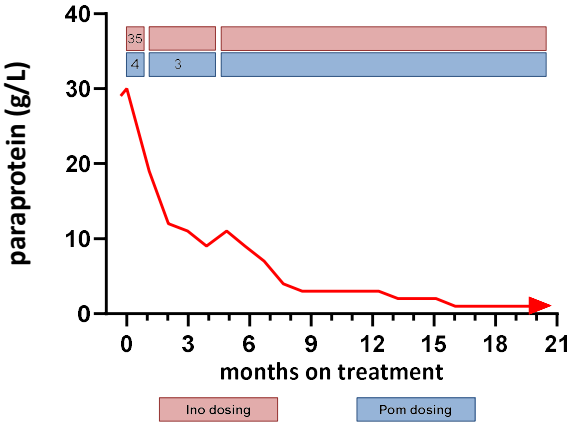
Pom-Refractory

61 yrs, F, ECOG PS 1

3 prior lines in 10m (DVTd, KRd, Isa**P**d)

Penta-drug refractory/pom last line

VGPR; ongoing 19.8m on InoPd (35mg)



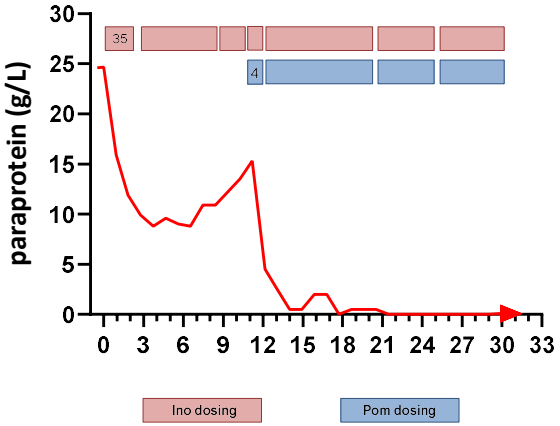
Pom-Naive

63 yrs, F, ECOG PS 1

7 prior lines (VTD,CTD,Vd, Dara, ASCT, Rd, VelPanoDex, Melphalan+ Pred)

Started study on Ino monotherapy

sCR & **MRD^{neg}** (10^{-5}); ongoing 18.9m on InoPd (35mg)



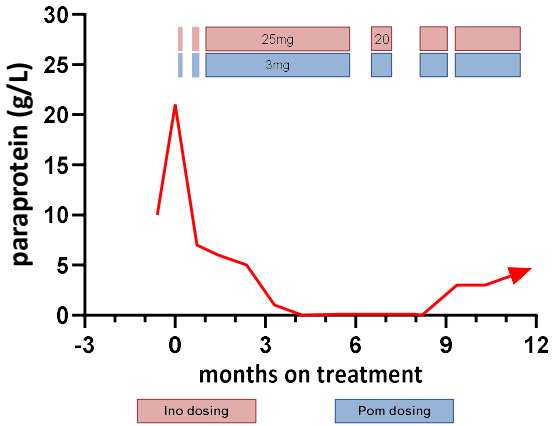
Post BCMA / TCE

64 yrs, m, ECOG PS 0

6 prior lines (VTD,DTPACE,ASCT+Len, DVd, K**P**d, **Elranatamab, Belantamab mafodotin**, Benda/Thal/Methylpred)

Penta-drug, αBCMA / TCE refractory

VGPR; 11.2 m on 25mg Ino / 3mg pom



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Conclusions

- Inobrodib in combination with pomalidomide and dexamethasone (**InoPd**) shows a manageable safety profile, favorable pharmacokinetics and promising efficacy in heavily pre-treated RRMM

- The highest efficacy was seen at doses of 35mg BD (4 days on/3 days off) with 4mg pomalidomide (21 days) and dexamethasone **with a 75% ORR** and activity seen across all dosing levels
  - Two pomalidomide-naïve patients achieved an MRD negative sCR
  - Efficacy was observed in pomalidomide refractory and BCMA-TCE refractory patients

- **No new safety signals were identified across the 3 dosing cohorts**
  - Thrombocytopenia was the most frequent grade 3 /4 TEAE overall which was manageable, and bleeding events were infrequent
  - Neutropenia was the second most common TEAE, but febrile neutropenia was rare

- **A randomized expansion evaluating three doses of Inobrodib with pom/dex is currently recruiting (NCT04068597)**

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Acknowledgements

The patients, their families and carers who made this study possible

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  - Western General Hospital, Edinburgh
  - The Royal Marsden Hospital/Institute of Cancer Research, London
  - University Hospital of Wales, Cardiff
  - The Churchill Hospital, Oxford
  - University College London Hospitals
  - University Hospital Southampton NHS Foundation Trust

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