# Tolerability and Clinical Activity of Novel First-In-Class Oral Agent, inobrodib (CCS1477), in Combination With Pomalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma

***Emma Searle***[1,2], *Victoria Campbell*[3], *Charlotte Pawlyn*[4,5], *Ceri Bygrave*[6*], *Sarah Gooding*[7], *James Cavet*[1], *Matthew W. Jenner*[8], *Vivek Radhakrishnan*[9], *Steve Knapper*[10], *Dima el-Sharkawi*[5], *Jenny O'Nions*[11*], *Tomasz Knurowski*[12], *Karen Clegg*[12], *Will Henry West*[12], *Debbie Haynes*[12], *Kris Frese*[12] *and Tim Somervaille*[1,2]

[1]*The Christie NHS Foundation Trust, Manchester, United Kingdom,*[2] *University of Manchester, Manchester, United Kingdom,* [3]*Department of Haematology, Western General Hospital, Edinburgh, United Kingdom,* [4]*Institute of Cancer Research, Sutton, United Kingdom,* [5]*The Royal Marsden NHS Foundation Trust, London, United Kingdom,* [6]*Department of Haematology, Cardiff & Vale University Health Board, Cardiff, United Kingdom,* [7]*MRC Molecular Haematology Unit, Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, ENG, United Kingdom,* [8]*University Hospital Southampton, Southampton, United Kingdom,* [9]*University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom,* [10]*Cardiff University School of Medicine, Cardiff, United Kingdom,* [11]*Department of Haematology, University College London Hospital, London, United Kingdom,* [12]*CellCentric Ltd, Cambridge, United Kingdom*

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

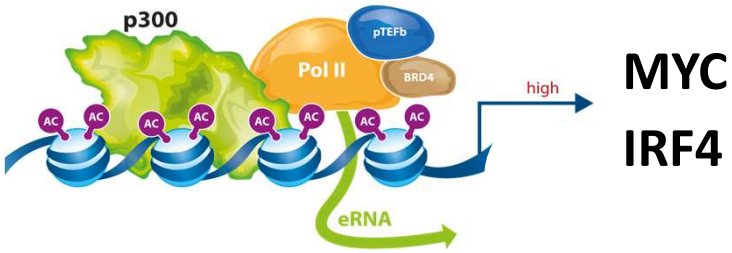
Inobrodib: First-in-class, oral, potent and specific bromodomain inhibitor of p300/CBP, two transcriptional coactivators with key roles in hematological cancers

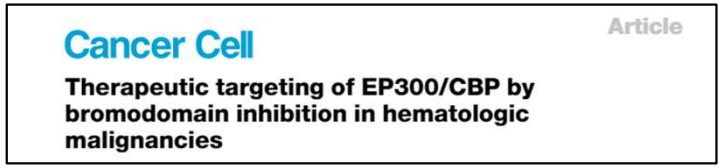
Strong scientific rationale for targeting p300/CBP in myeloma

- 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).

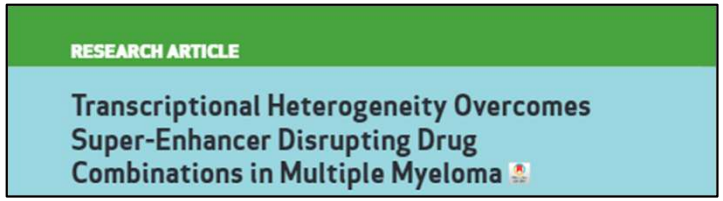




Cancer Cell

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

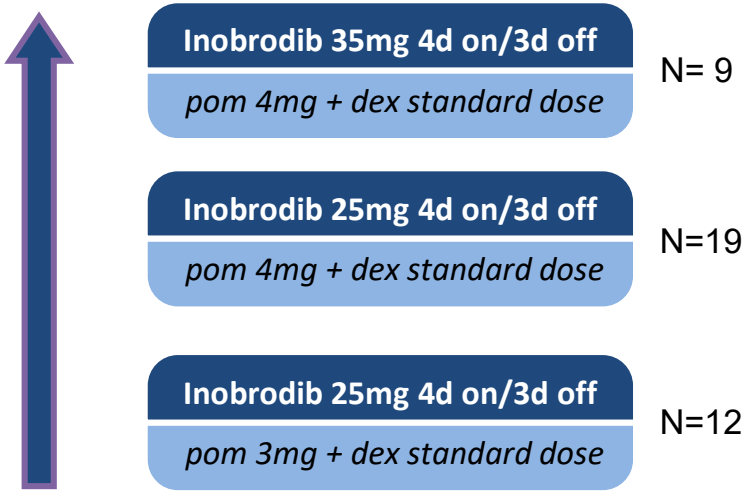
[2]*Welsh et al, Blood Cancer Discovery 2024*

[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

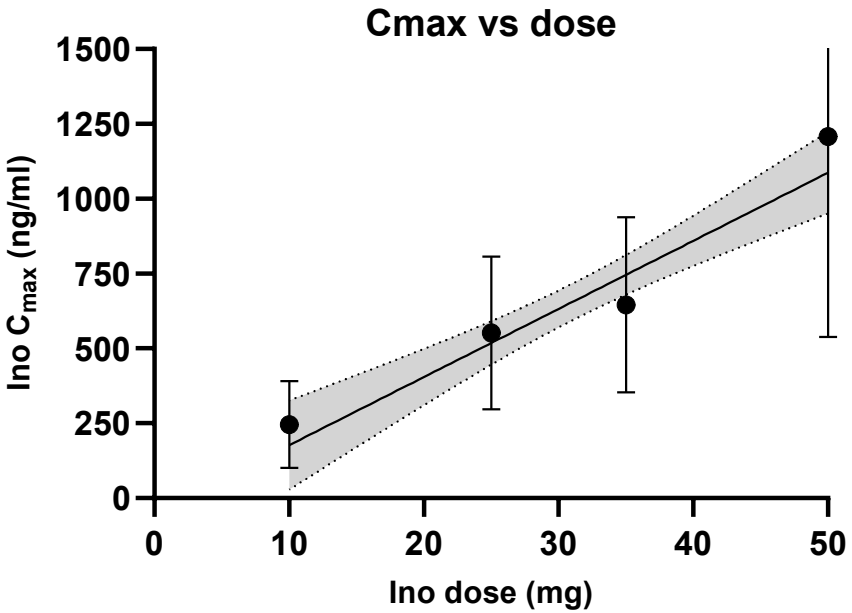
Assess anti-myeloma efficacy (IMWG criteria)

***Exploratory objectives***

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

Searle E, et al. ASH 2024 [Abstract #1023]

# 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

Searle E, et al. ASH 2024 [Abstract #1023]

# 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<br>0<br>1<br>2 | <br>13 (32.5%)<br>23 (57.5%)<br>4 (10%) |
| **Disease characteristics** | |
| ≥1 plasmacytoma* | 4 (10%) |
| BM involvement ≥50% | 17 (42.5%) |
| ISS stage at baseline/ study entry **<br>I<br>II or III | <br>6/25 (24%)<br>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

Searle E, et al. ASH 2024 [Abstract #1023]

# Prior therapies and refractory status

| Prior therapy n=40 | Total n (%) |
|---|---|
| **Prior lines**; median (range) | 5 (2-9) |
| Prior stem cell transplantation<br>1<br>2 | <br>18 (45%) inc. 1 allo SCT<br>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**

Data cut 04 Nov 2024

*Percentage of evaluable patients/data missing

Searle E, et al. ASH 2024 [Abstract #1023]

# 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 (%)<br>Progressive disease<br>TEAE<br>Patient withdrawal | **31 (77%)**<br>**24 (60%)**<br>**5 (13%)**<br>**2 (5%)** | 10 (83%)<br>9 (75%)<br>0 (0%)<br>1 (8%) | 14 (74%)<br>11 (58%)<br>3 (16%)<br>0 (0%) | 7 (78%)<br>4 (44%)<br>3 (22%)<br>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** |

Data cut 04 Nov 2024

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

Searle E, et al. ASH 2024 [Abstract #1023]

# Safety profile of InoPd: TEAEs irrespective of causality

| TEAEs | All Grades n (%) | Grade ≥3 |
|---|---|---|
| **Thrombocytopenia**<br>**Bleeding** | **18 (45)**<br>**5 (12.5)** | 13 (32.5)<br>1 (2.5) |
| **Anaemia** | **16 (40)** | 7 (17.5) |
| **Neutropenia**<br>**Febrile neutropenia** | **15 (37.5)**<br>**2 (5)** | 14 (35)<br>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**

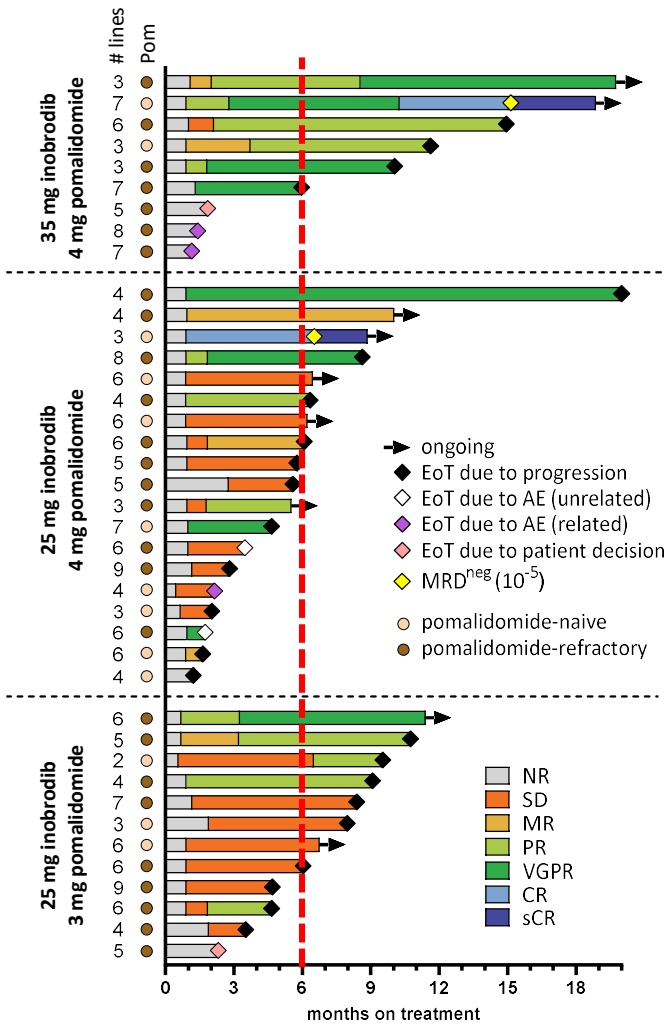
**No new safety signals identified**

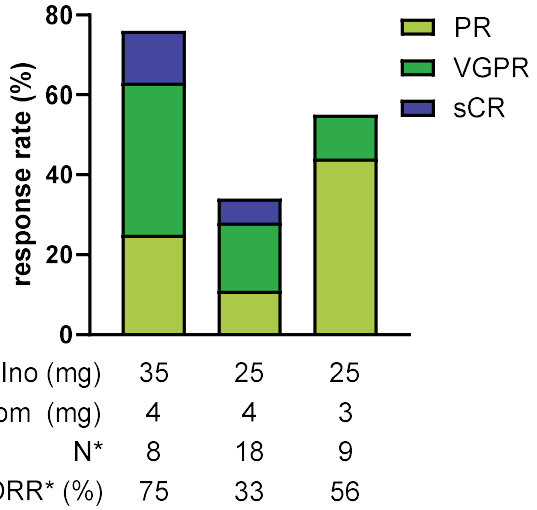
Most frequent ≥25% (TEAEs) plus *1 patient with Grade 5 event (MI: not related to inobrodib)

Data cut 04 Nov 2024

Searle E, et al. ASH 2024 [Abstract #1023]

# InoPd efficacy in relapsed refractory multiple myeloma



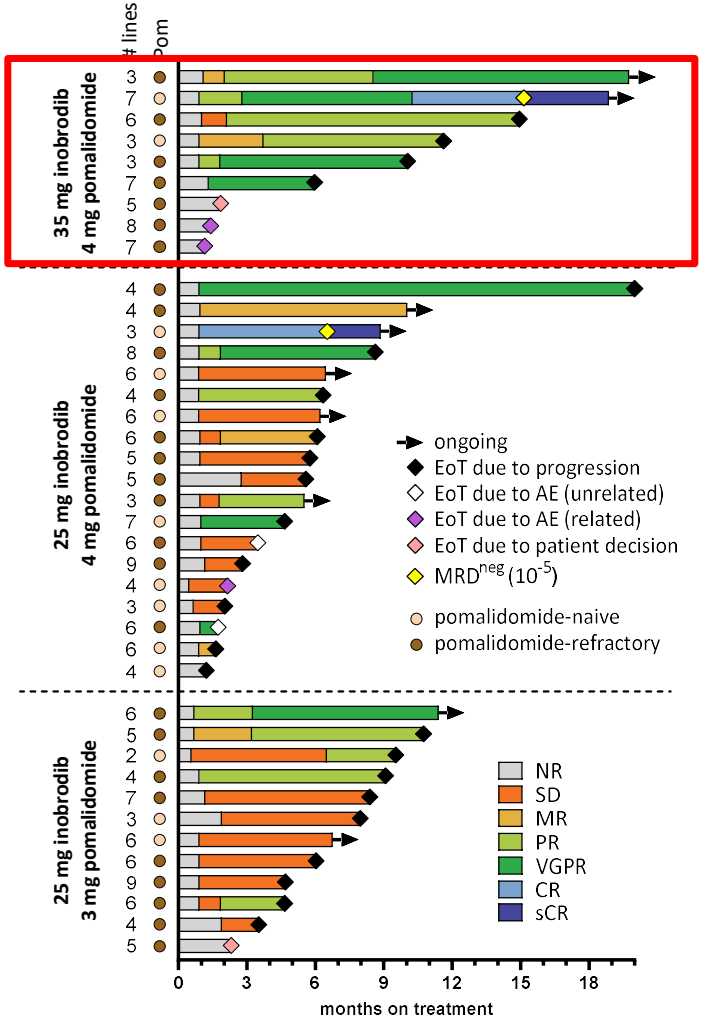

| | | | |
|---|---|---|---|
| Ino (mg) | 35 | 25 | 25 |
| Pom (mg) | 4 | 4 | 3 |
| N* | 8 | 18 | 9 |
| ORR* (%) | 75 | 33 | 56 |

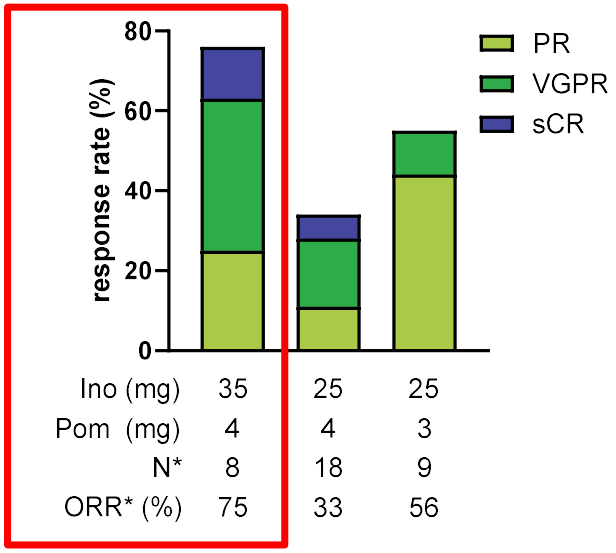
Across all cohorts: 49% ORR, mDOR 6.3 months , 63% of pts ≥ 6 mo.

* Among evaluable patients

Searle E, et al. ASH 2024 [Abstract #1023]

# InoPd efficacy in relapsed refractory multiple myeloma



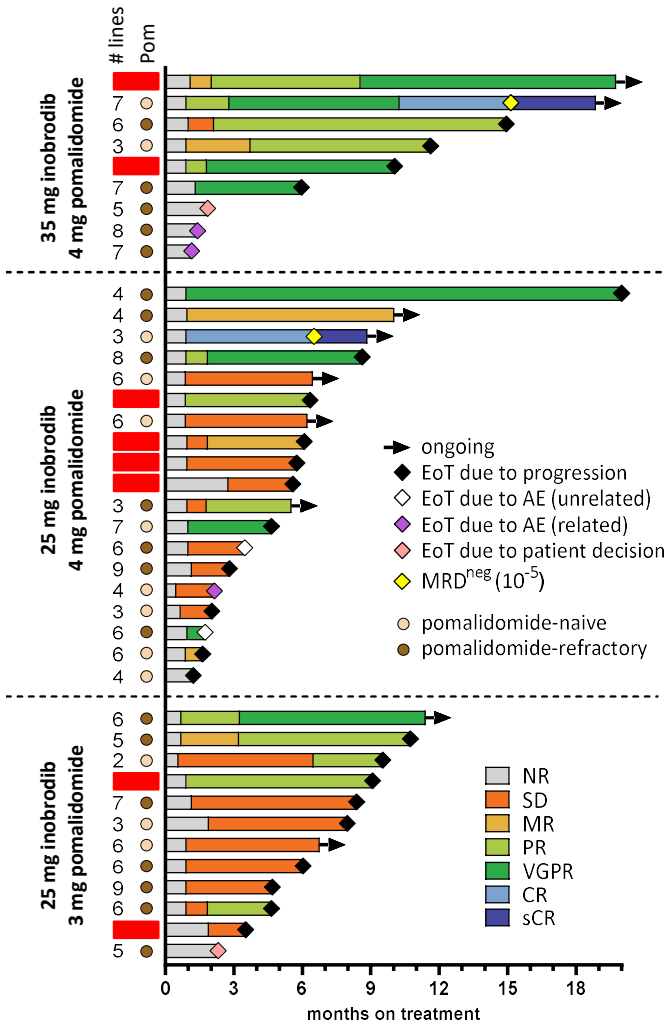

Across all cohorts: 49% ORR, mDOR 6.3 months , 63% of pts ≥ 6 mo.

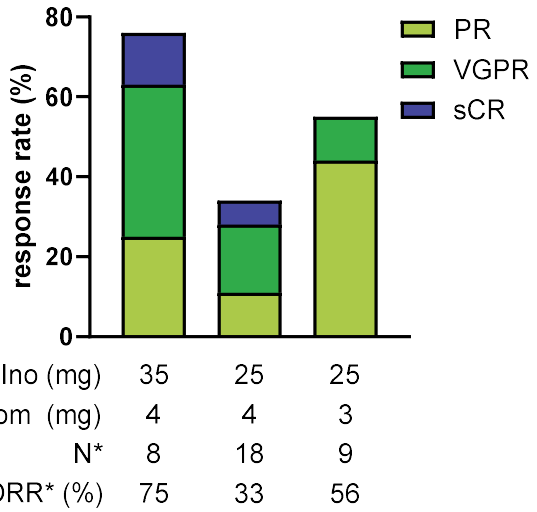
Highlighted dose cohort: 75% ORR, mDOR 9.7 months

* Among evaluable patients

Searle E, et al. ASH 2024 [Abstract #1023]

# 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.

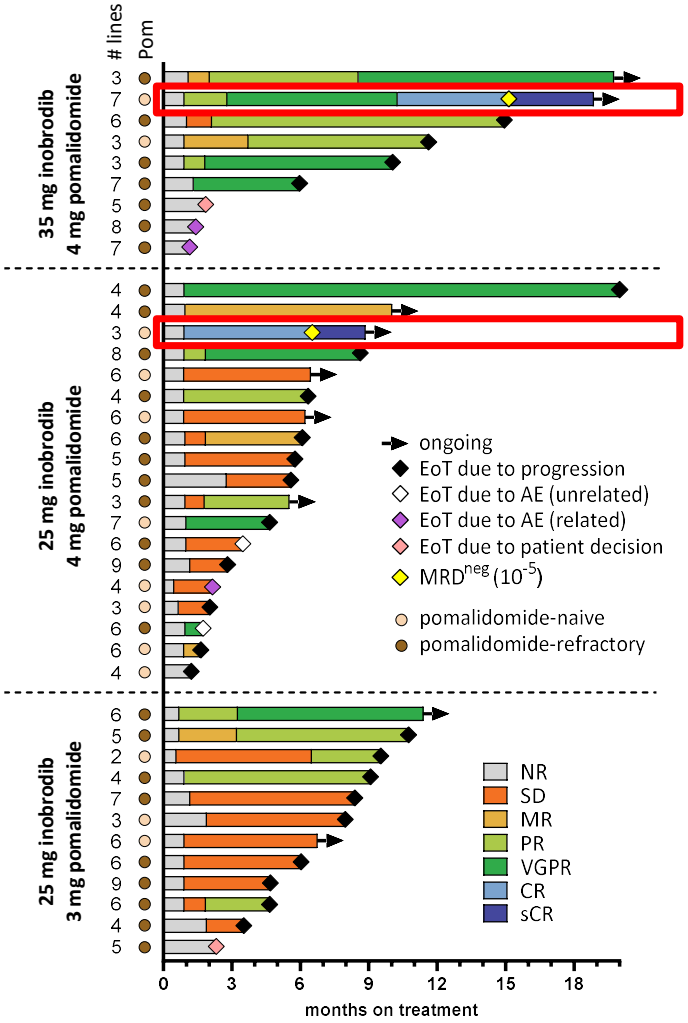
Highest dose cohort: 75% ORR, mDOR 9.7 months

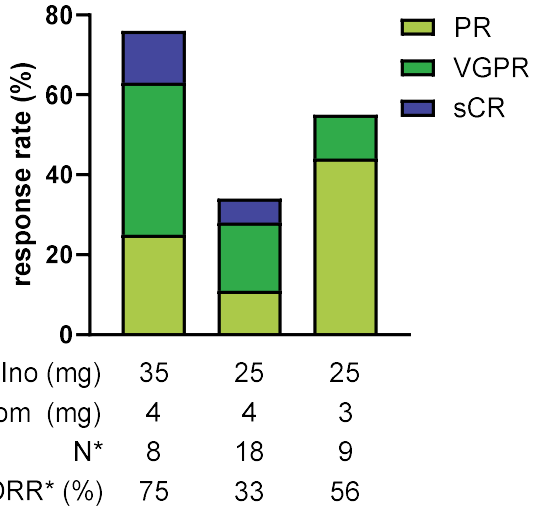
Pom-refractory patients (last line): 4/8 pts responded ≥PR, + 1 MR

* Among evaluable patients

Searle E, et al. ASH 2024 [Abstract #1023]

# 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.

Highest dose cohort: 75% ORR, mDOR 9.7 months

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

Pom naïve pts: 2/12 achieved MRD negative sCR

* Among evaluable patients

Searle E, et al. ASH 2024 [Abstract #1023]

# Case studies

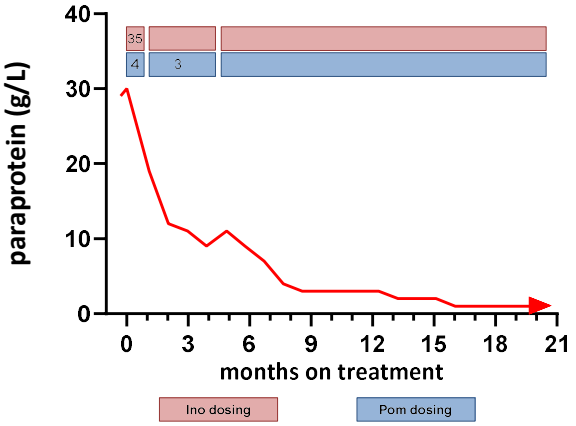
## Pom-Refractory

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)



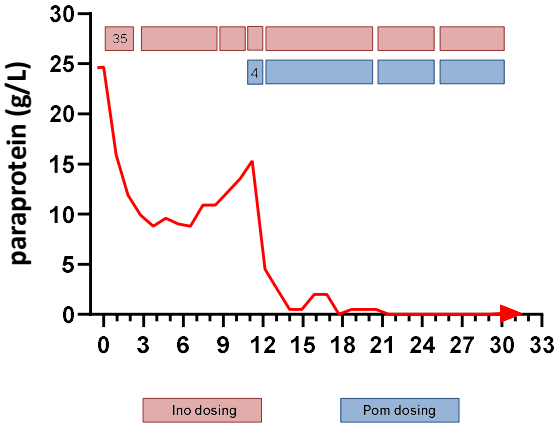

## Pom-Naive

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)



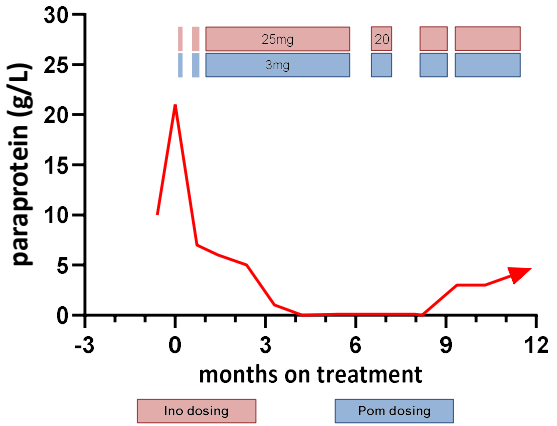

## Post BCMA / TCE

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




Searle E, et al. ASH 2024 [Abstract #1023]

# 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)**

Searle E, et al. ASH 2024 [Abstract #1023]

# Acknowledgements


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

- The physicians, nurses and all staff involved in data collection and analysis
- The study was funded by CellCentric Ltd, UK
- The study sites (myeloma):
  - The Christie Hospital, Manchester
  - 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


Searle E, et al. ASH 2024 [Abstract #1023]

# CCS1477-02 – UK Sites

## Sites Currently Recruiting

| | |
|---|---|
| Christie Manchester | Dr Emma Searle |
| Royal Marsden | Dr Charlotte Pawlyn |
| Oxford | Dr Sarah Gooding |
| Edinburgh | Dr Victoria Campbell |
| Cardiff | Dr Ceri Bygrave |
| Glasgow | Dr Jennifer Travers |
| Southampton | Dr Matthew Jenner |
| UCL | Dr Rakesh Popat |
| Imperial | Dr Aris Chaidos |
| Newcastle | Dr Thomas Creasy |
| Bristol | Dr Sally Moore |
| SCRI at Guy's | Dr Majid Kazmi |

## Future sites (opening soon)

| | |
|---|---|
| Clatterbridge | Dr Gillian Brearton |
| Derby | Dr Firas al Kaisi |
| St Bartholomew's | Dr Heather Oakervee |
| Nottingham | Dr Dean Smith |
| Birmingham | Dr Aung |
| Stoke | Dr Kamaraj Karunanithi |
| Sheffield | Dr Elisa Roldan-Galvan |

## Patient Population

- Pomalidomide refractory (irrespective of prior therapy, inc. of post BCMA)
- Pomalidomide naïve (gap in 3L UK?)