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# Randomized Phase II Dose-Optimization Study of Inobrodib (CCS1477) in Combination with Pomalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma (RRMM)


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## BACKGROUND

- Inobrodib (ino; CCS1477) is a first-in-class potent, selective, orally bioavailable inhibitor of the bromodomains of p300 and CBP, two closely-related histone acetyltransferases with oncogenic roles in hematological malignancies[1]
- *In vitro*, combining pomalidomide (pom), an immunomodulatory imide drug (IMiD), with a p300/CBP inhibitor significantly increased apoptosis and myeloma cell death compared with either agent alone[2]
  - Combining pom and ino represents a promising therapeutic strategy for patients with relapsed/refractory multiple myeloma (RRMM)
- Ino is currently being investigated as monotherapy and in combination across several hematological malignancies in an adaptive multi-arm/multi-stage trial (NCT04068597)
  - Preliminary clinical activity and a manageable safety profile were observed in patients with RRMM in the dose-escalation phase, which included two doses of pom (3 mg and 4 mg) and required patients to fast prior to dosing[3,4]
  - Here, we report the results of the randomized dose-expansion phase of ino plus pom and dexamethasone (dex; InoPd) in patients with RRMM, including those who relapsed on prior treatment with T-cell engagers (TCEs); these patients have particularly poor outcomes, with an estimated overall response rate (ORR) of 25–30%, and progression-free survival (PFS) of 3–4 months[5,6]

## METHODS

- Patients with confirmed RRMM and ECOG performance status of 0/1, who had either exhausted standard-of-care options or, if pom-naïve, had received ≥2 prior therapies (including lenalidomide and a proteasome inhibitor), were randomized to one of three dose levels of oral ino (20 mg, 30 mg, or 40 mg) on an intermittent 4 days-on/3 days-off schedule in combination with a standard dosing regimen of pom 4 mg/day (Days 1–21) and dex 20 or 40 mg once weekly (based on age) on a 28-day cycle
  - Randomization was stratified according to pom exposure status
  - For convenience, patients were allowed to take ino with or without food
- The primary objective was to determine the optimal dose for pivotal studies of InoPd in accordance with FDA guidance (Project Optimus),[7] accounting for key aspects of both safety and efficacy
  - Adverse events (AEs) were investigator-assessed per Common Terminology Criteria for Adverse Events v5.0, and responses by International Myeloma Working Group criteria (2016)[8]
- Multiple secondary and exploratory objectives were also assessed, including pharmacodynamic profiling of paired bone marrow and serial peripheral blood mononuclear cell samples (data reported separately)

## RESULTS

### Patients

- At the time of data cut-off (October 6, 2025), of 63 patients randomized, 61 had been treated with ino 20 mg (n=21), 30 mg (n=19), or 40 mg (n=21), with 44 patients evaluable for response
- Baseline patient and disease characteristics are presented in **Table 1**
  - Patients were heavily pretreated with a median 5 lines of prior therapy (range, 2–17)
    - 71% of patients had triple-class refractory disease, 53% were pom-refractory, and 66% had been previously treated with anti-B-cell maturation antigen (BCMA) therapy and/or a TCE
- Cohorts were balanced regarding prior pom (stratification factor), and while some differences in adverse risk characteristics were noted, all cohorts had multiple characteristics consistent with poor prognosis

### Table 1. Baseline characteristics

| Characteristic | InoPd 20 mg (n=21) | InoPd 30 mg (n=19) | InoPd 40 mg (n=21) | Total (N=61) |
|---|---|---|---|---|
| Median age (range), years | 68 (50–80) | 69 (44–83) | 72 (58–81) | 70 (44–83) |
| Male / White | 16 (76) / 17 (81) | 13 (68) / 18 (95) | 12 (57) / 13 (62) | 41 (67) / 48 (79) |
| ECOG PS 0 / 1 | 5 (24) / 16 (76) | 7 (37) / 12 (63) | 1 (5) / 20 (95) | 13 (21) / 48 (79) |
| BM involvement ≥50% | 6 (29) | 6 (32) | 4 (19) | 16 (26) |
| Plasmacytoma | 9 (43) | 4 (21) | 2 (10) | 15 (25) |
| ISS stage I / II / III[a] | 4 (19) / 6 (29) / 3 (14) | 7 (37) / 5 (26) / 2 (11) | 6 (29) / 7 (33) / 3 (14) | 17 (28) / 18 (30) / 8 (13) |
| R-ISS stage I / II / III[a] | 2 (10) / 15 (71) / 1 (5) | 3 (16) / 12 (63) / 2 (11) | 8 (38) / 10 (48) / 2 (10) | 13 (21) / 37 (61) / 5 (8) |
| IMWG CGS[9] standard risk / high risk[a] | 2 (10) / 4 (19) | 2 (11) / 11 (58) | 7 (33) / 7 (33) | 11 (18) / 22 (36) |
| Prior SCT | 11 (52) | 11 (58) | 11 (52) | 33 (54) |
| Median no. of prior lines of therapy (range) | 6 (2–9) | 5 (2–14) | 5.5 (2–17) | 5 (2–17) |
| Triple-class[b] exposed | 20 (95) | 17 (90) | 19 (91) | 56 (92) |
| BCMA/TCE exposed | 15 (71) | 12 (63) | 13 (62) | 40 (66) |
| TCE exposed | 13 (62) | 10 (53) | 12 (57) | 35 (57) |
| Refractory | | | | |
| Pom | 10 (48) | 11 (58) | 11 (52) | 32 (53) |
| Triple-class[b] | 16 (76) | 12 (63) | 15 (71) | 43 (71) |
| Penta-drug[c] | 5 (24) | 6 (32) | 5 (24) | 16 (26) |

Data are n (%) unless otherwise specified.
[a]Total ≠ 100% because of missing data. [b]Exposed/refractory to an IMiD, PI, and an anti-CD38. [c]Refractory to ≥2 IMiDs, 2 different PIs, and an anti-CD38.
BCMA, B-cell maturation antigen; BM, bone marrow; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory imide drug; IMWG CGS, International Myeloma Working Group Consensus Genomic Staging; InoPd, inobrodib, pomalidomide, dexamethasone; PI, proteosome inhibitor; pom, pomalidomide; (R)-ISS, (Revised) International Staging System; SCT, stem cell transplantation; TCE, T-cell engager.

### Safety

- Overall, 95% of patients had a treatment-emergent AE (TEAE) and 80% had an ino-related AE (**Table 2**)

### Table 2. Safety summary

| Patients with TEAE, n (%) | InoPd 20 mg (n=21) | InoPd 30 mg (n=19) | InoPd 40 mg (n=21) | Total (N=61) |
|---|---|---|---|---|
| Any-grade TEAE | 20 (95) | 19 (100) | 19 (91) | 58 (95) |
| Ino-related | 17 (81) | 15 (79) | 17 (81) | 49 (80) |
| Serious TEAE | 9 (43) | 11 (58) | 12 (57) | 32 (53) |
| Ino-related | 7 (33) | 5 (26) | 7 (33) | 19 (31) |
| Grade ≥3 TEAE | 12 (57) | 15 (79) | 16 (76) | 43 (71) |
| Ino-related | 10 (48) | 9 (47) | 13 (62) | 32 (53) |
| Grade 5 TEAE | 1 (5) | 1 (5) | 0 | 2 (3) |
| Ino-related | 0 | 0 | 0 | 0 |

ino, inobrodib; InoPd, inobrodib, pomalidomide, dexamethasone; TEAE, treatment-emergent adverse event.

- In the InoPd 20 mg cohort, of whom almost half were pom-refractory, 33% and 29% of patients had dose interruptions, and 5% and 29% of patients had dose reductions of ino and pom, respectively (**Table 3**)
- One patient had a TEAE that led to discontinuation of ino

### Table 3. Treatment compliance

| Patients, n (%) | InoPd 20 mg (n=21) | InoPd 30 mg (n=19) | InoPd 40 mg (n=21) | Total (N=61) |
|---|---|---|---|---|
| Dose modification | | | | |
| Reduction of ino / pom | 1 (5) / 6 (29) | 3 (16) / 7 (37) | 9 (43) / 6 (29) | 13 (21) / 19 (31) |
| Interruption of ino / pom | 7 (33) / 6 (29) | 9 (47) / 10 (53) | 11 (52) / 12 (57) | 27 (44) / 28 (46) |
| TEAE leading to discontinuation of ino | 1 (5) | 0 | 0 | 1 (2) |
| Ino-related | 0 | 0 | 0 | 0 |

ino, inobrodib; InoPd, inobrodib, pomalidomide, dexamethasone; pom, pomalidomide; TEAE, treatment-emergent adverse event.

- The most common any-grade TEAEs were cytopenias and fatigue (**Table 4**), and the most common grade 3/4 TEAEs were thrombocytopenia (36%), neutropenia (34%), and anemia (20%)
  - The incidence of thrombocytopenia increased with increasing dose of ino; however, in the 20 mg cohort, the rate and severity were similar to those observed with pom/dex in a less heavily pretreated population in the phase 3 DREAMM-3 study[10]
  - Bleeding events (mostly grade 1/2) were reported in 12 patients (20 mg, n=4; 30 mg, n=2; 40 mg, n=6), including two patients with grade 3 bleeding events (both considered unrelated to treatment)
  - Grade 3/4 febrile neutropenia was reported in six patients (20 mg, n=1; 30 mg, n=1; 40 mg, n=4)
  - Non-hematologic TEAEs were mostly grade 1/2

### Table 4. Any-grade all-cause TEAEs reported in ≥15% of patients

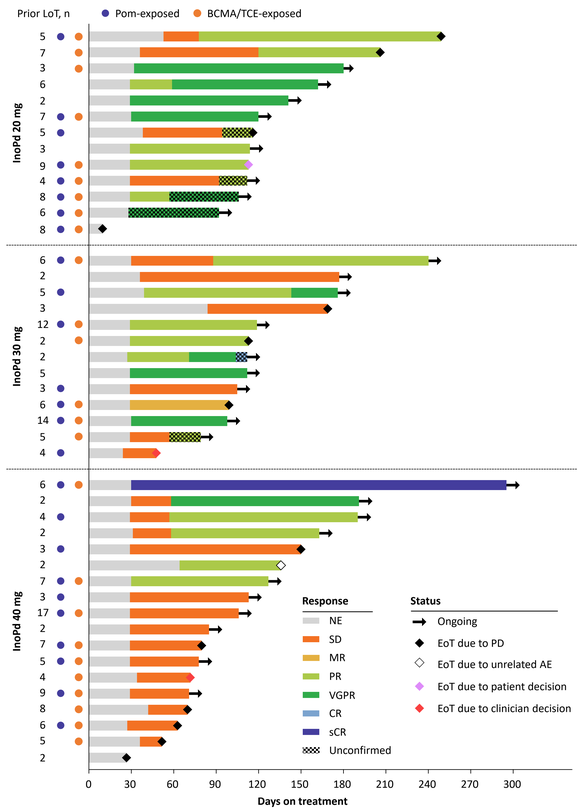
| Patients with TEAE, n (%)[a] | InoPd 20 mg (n=21) | | InoPd 30 mg (n=19) | | InoPd 40 mg (n=21) | | Total (N=61) | |
|---|---|---|---|---|---|---|---|---|
| | Any-grade | Grade 3/4 | Any-grade | Grade 3/4 | Any-grade | Grade 3/4 | Any-grade | Grade 3/4 |
| **Hematologic** | | | | | | | | |
| Thrombocytopenia | 8 (38) | 5 (24) | 10 (53) | 6 (32) | 14 (67) | 11 (52) | 32 (53) | 22 (36) |
| Neutropenia | 8 (38) | 5 (24) | 9 (47) | 8 (42) | 13 (62) | 8 (38) | 30 (49) | 21 (34) |
| Anemia | 8 (38) | 4 (19) | 6 (32) | 4 (21) | 9 (43) | 4 (19) | 23 (38) | 12 (20) |
| Leukopenia | 1 (5) | 1 (5) | 5 (26) | 3 (16) | 11 (52) | 5 (24) | 17 (28) | 9 (15) |
| **Non-hematologic** | | | | | | | | |
| Fatigue | 12 (57) | 2 (10) | 9 (47) | 3 (16) | 8 (38) | 1 (5) | 29 (48) | 6 (10) |
| Diarrhea | 2 (10) | 0 | 4 (21) | 1 (5) | 7 (33) | 2 (10) | 13 (21) | 3 (5) |
| Muscle spasms | 4 (19) | 0 | 6 (32) | 0 | 3 (14) | 0 | 13 (21) | 0 |
| Hyperglycemia | 2 (10) | 0 | 6 (32) | 0 | 4 (19) | 2 (10) | 12 (20) | 2 (3) |
| Hypomagnesemia | 3 (14) | 0 | 1 (5) | 0 | 8 (38) | 0 | 12 (20) | 0 |
| Hyponatremia | 2 (10) | 1 (5) | 4 (21) | 0 | 6 (29) | 0 | 12 (20) | 1 (2) |
| Pyrexia | 4 (19) | 1 (5) | 4 (21) | 1 (5) | 3 (14) | 0 | 11 (18) | 2 (3) |
| Dizziness | 2 (10) | 0 | 4 (21) | 0 | 4 (19) | 0 | 10 (16) | 0 |

[a]Listed in order of frequency of any-grade TEAEs in total population.
InoPd, inobrodib, pomalidomide, dexamethasone; TEAE, treatment-emergent adverse event.

### Efficacy

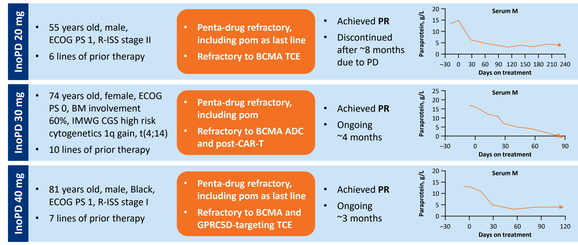
- As of October 6, 2025, median follow-up (range) among all patients was 105 (11–294) days
- Among evaluable patients (n=44) treated with ino 20 mg, 30 mg, and 40 mg, the ORR was 69%, 54%, and 33%, respectively
- High response rates (60% and 75% in the 20 mg and 30 mg cohorts, respectively) were noted in a population of unmet need (heavily pretreated, pom-refractory and post-BCMA/TCE) (**Figures 1–3**), with deep responses developing in pom-naïve patients (previously reported as MRD-negative complete responses[4]) and in heavily-pretreated patients, post-TCE
- Data regarding median duration of response and PFS were immature at the time of analysis, however, several patients remain on treatment for >6 months (longest time on treatment >9 months)

### Figure 1. Efficacy of InoPd in patients with RRMM



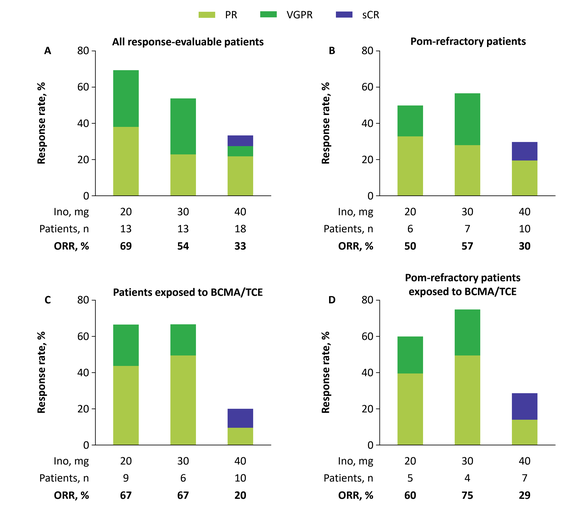

AE, adverse event; BCMA, B-cell maturation antigen; CR, complete response; EoT, end of treatment; InoPd, inobrodib, pomalidomide, dexamethasone; LoT, lines of therapy; MR, minimal response; NE, not evaluable; PD, progressive disease; pom, pomalidomide; PR, partial response; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; SD, stable disease; TCE, T-cell engager; VGPR, very good partial response.

### Figure 2. Illustrative case studies




ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; BM, bone marrow; CAR-T, chimeric antigen receptor T-cell therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; GPRC5D, G protein-coupled receptor 5D; IMWG CGS, International Myeloma Working Group Consensus Genomic Staging; InoPd, inobrodib, pomalidomide, dexamethasone; PR, partial response; R-ISS, Revised International Staging System.

### Figure 3. Overall response rates in (A) all response-evaluable patients, (B) pom-refractory patients, (C) patients exposed to BCMA/TCE and (D) pom-refractory patients exposed to BCMA/TCE




BCMA, B-cell maturation antigen; ino, inobrodib; ORR, overall response rate; pom, pomalidomide; PR, partial response; sCR, stringent complete response; TCE, T-cell engager; VGPR, very good partial response.

## CONCLUSIONS

- The combination of InoPd has promising clinical activity, including in populations of high unmet need (e.g., patients previously treated with TCEs)
  - Observed response rates in this limited dataset (60–75% in the 20 mg and 30 mg cohorts) appear at least two-fold higher than previously published real-world data for a similar population
- Responses among pom-refractory patients, including those who were progressing with pom as the last line of therapy, further confirm previously generated clinical data as well as nonclinical data that show exquisite synergy with IMiDs
- Ino 20 mg appears to have the best benefit/risk profile
  - However, because patient numbers are relatively small and the data are not yet mature, careful interpretation is needed to select the optimal dose for pivotal clinical trials of InoPd
  - The lower ORR with ino 40 mg may reflect the disproportionate number of interruptions of ino and pom in this cohort, particularly compared with the 20 mg cohort
  - The differing benefit/risk profiles between this dataset and the dose-escalation study[4] likely reflect the removal of fasting restrictions leading to increased exposure and the use of standard 4 mg pom dosing with the lowest dose of ino
- This all-oral regimen with a novel mechanism of action has the potential to benefit diverse populations of patients with RRMM, many of whom are treated in the community setting

## REFERENCES


1. Nicosia L, et al. *Cancer Cell*. 2023;41(12):2136–2153.e13.
2. Welsh SJ, et al. *Blood Cancer Discov*. 2024;5(1):34–55.
3. Searle E, et al. Poster presentation at EHA 2023 (P863).
4. Searle E, et al. Oral presentation at ASH 2024 (Abstract #1023).
5. Costa LJ, et al. *Leukemia*. 2025;39(3):543–554.
6. Weisel K, et al. Poster presentation at EHA 2024 (P913).
7. FDA. Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases. Guidance for Industry (August 2024).
8. Kumar S, et al. *Lancet Oncol*. 2016;17(8):e328–e346.
9. Avet-Loiseau H, et al. *J Clin Oncol*. 2025;43(24):2739–51.
10. Dimopoulos MA, et al. *Lancet Haematol*. 2023;10(10):e801–e812.


## ACKNOWLEDGMENTS


We thank the patients, their families, the investigators, and the site staff.
Medical writing support was provided by Fiona Bolland, PhD, CMPP, of Twist Medical, and funded by CellCentric Ltd.
The study is sponsored by CellCentric Ltd, Cambridge, UK.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**Presented at the 67th ASH Annual Meeting and Exposition; Orlando, FL, USA; December 6–9, 2025**