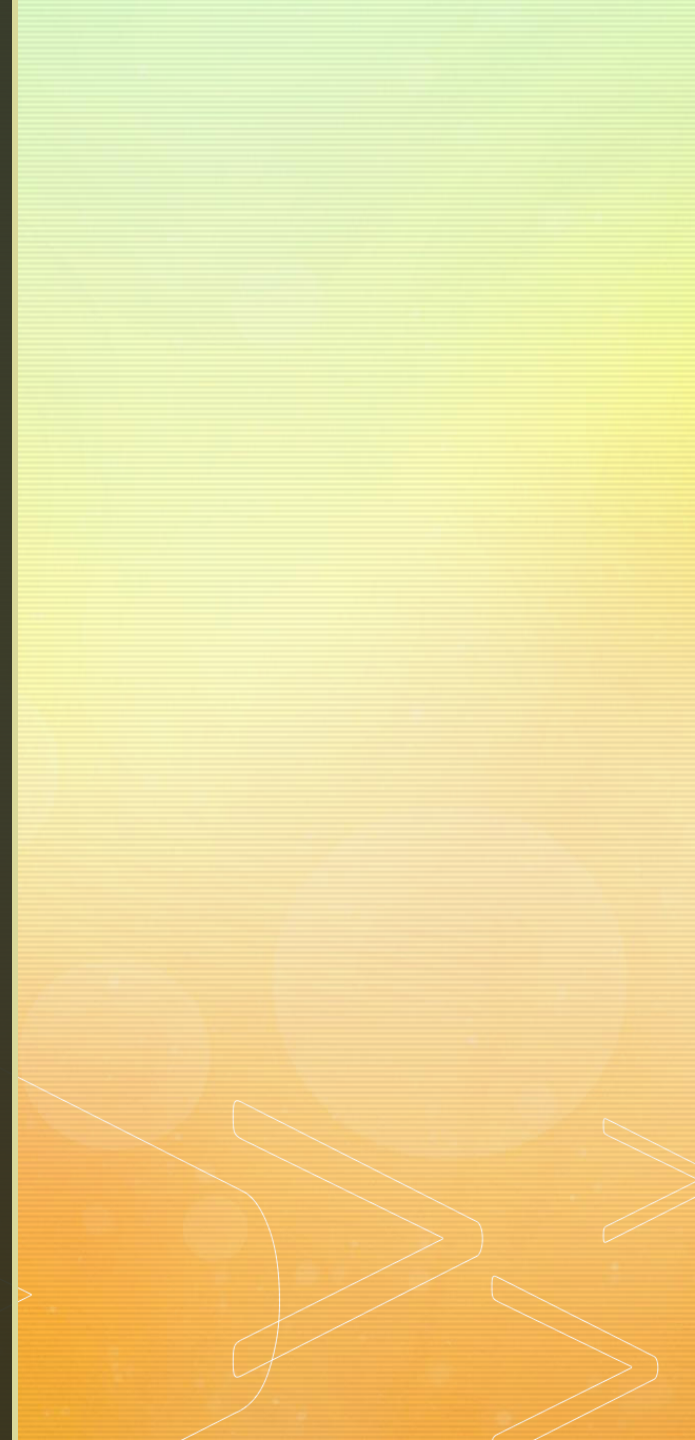


# RRMM: New Drugs and Combinations



ASH UPDATES 2024





American Society of Hematology

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## Lisaftoclax (APG-2575) Combined with Novel Therapeutic Regimens in Patients (Pts) with Relapsed or Refractory Multiple Myeloma (R/RMM) or Immunoglobulin Light-Chain (AL) Amyloidosis

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Presenting author: Dr. Ailawadhi

# Study Design

Phase 1/2 clinical trial of lisaftoclax in R/RMM and R/R AL amyloidosis

נכללו במחקר גם מטופלים ללא t(11,14)

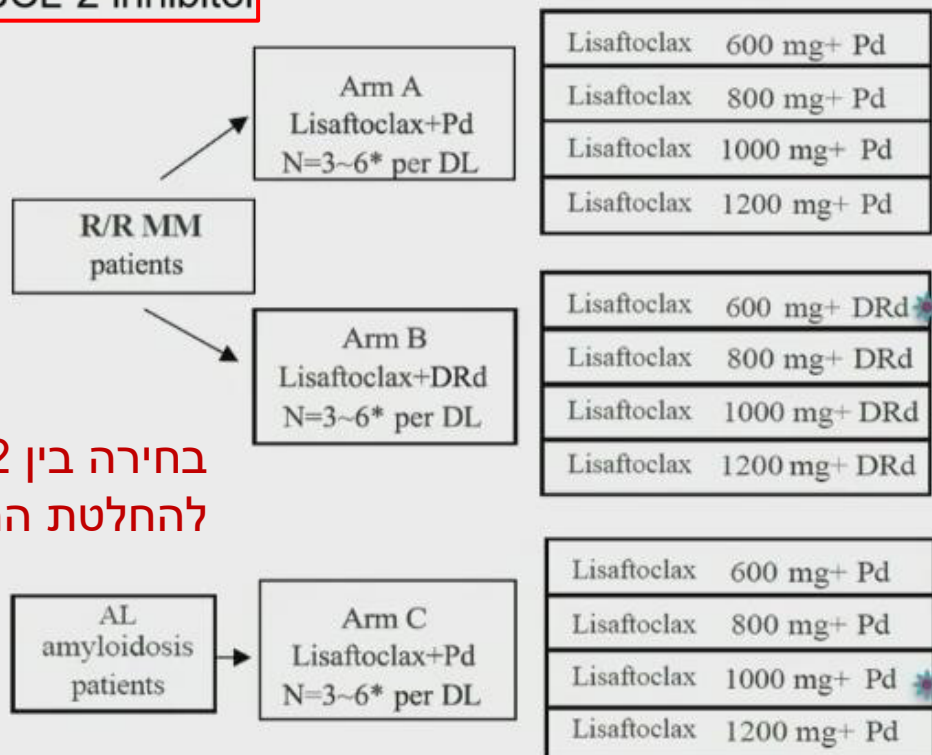
Lisaftoclax, a novel, investigational BCL-2 inhibitor

28 days/cycle  
Lisaftoclax orally once daily

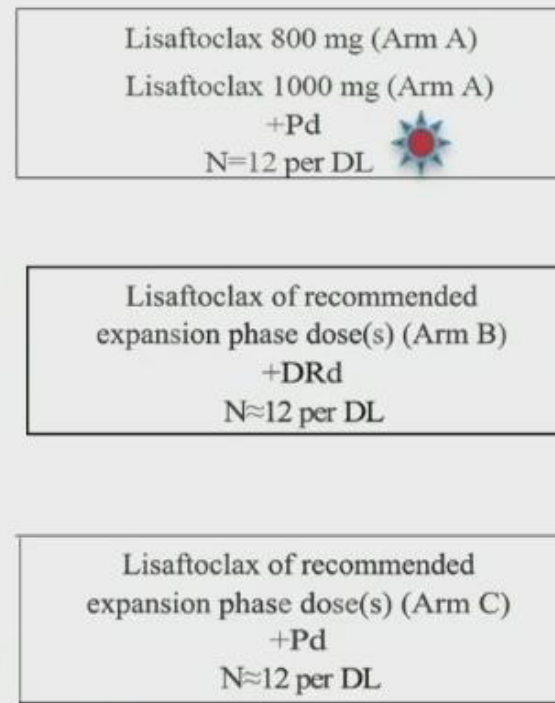
בחירה בין 2 הזרועות לא רנדומלית- להחלטת הרופא המטפל

מטרות המחקר- בטיחות ויעילות

Lisaftoclax (APG-2575) dose escalation phase  
3+3 design



Lisaftoclax (APG-2575) dose expansion phase



Current status

- DRd, daratumumab, lenalidomide, and dexamethasone; Pd, pomalidomide and dexamethasone; DL, dose level.
- Dexamethasone: 40 mg for patients aged ≤ 75 years and 20 mg for patients > 75 years on Days 1, 8, 15, and 22
- Pomalidomide, daratumumab, and lenalidomide were administered according to manufacturer labelling.

Data cutoff date: November 5, 2024



## מאפייני החולים

|                                 | R/R MM<br>(n = 48) |                   | R/R AL amyloidosis<br>(n = 10) |
|---------------------------------|--------------------|-------------------|--------------------------------|
|                                 | Lisaftoclax + Pd   | Lisaftoclax + DRd | Lisaftoclax + Pd               |
| Population                      | 41                 | 7                 | 10                             |
| No. of prior systemic therapies |                    |                   |                                |
| Mean (SD)                       | 4.5 (3.38)         | 4.4 (3.78)        | 2.0 (0.47)                     |
| Median (range)                  | 3.0 (1-19)         | 3.0 (1-12)        | 2.0 (1-3)                      |

רוב המטופלים בזרוע A קיבלו PI (100%), IMiDs (95%), ant-CD38 (85%) לפני

# Efficacy: Responses in 36 R/RMM Patients Treated with Lisaftoclax+Pd

40% קיבלו פומלידומיד בעבר, אין כאן מידע על הבדל בתגובה, מאמינים שיש אפקט סינרגיסטי לשילוב

רק 4/36 היו עם t(11,14) – מנסים להעשיר כמות חולים אלו  
t(11;14) MM

|                         | Dose, mg | Best response | Cycle         |
|-------------------------|----------|---------------|---------------|
| 1201-002                | 400      | VGPR          | 37            |
| 1201-004                | 400      | SD            | 7 (withdrawn) |
| 1201-020                | 800      | PR            | 15            |
| 1201-034                | 1000     | PR            | 4             |
| ORR (PR or better): 75% |          |               |               |

| Hematologic responses        | Lisaftoclax dose combined with Pd |                 |                 |                  |                  | Total (N = 36)   |
|------------------------------|-----------------------------------|-----------------|-----------------|------------------|------------------|------------------|
|                              | 400 mg (n = 3)                    | 600 mg (n = 4)  | 800 mg (n = 14) | 1,000 mg (n = 9) | 1,200 mg (n = 6) |                  |
| Best overall response, n (%) |                                   |                 |                 |                  |                  |                  |
| CR                           | 0 (0.0)                           | 0 (0.0)         | 1 (7.1)         | 1 (11.1)         | 1 (16.7)         | 3 (8.3)          |
| VGPR                         | 1 (33.3)                          | 1 (25.0)        | 2 (14.3)        | 2 (22.2)         | 2 (33.3)         | 8 (22.2)         |
| PR                           | 0 (0.0)                           | 2 (50.0)        | 5 (35.7)        | 5 (55.6)         | 0 (0.0)          | 12 (33.3)        |
| MR                           | 0 (0.0)                           | 0 (0.0)         | 3 (21.4)        | 0 (0.0)          | 0 (0.0)          | 3 (8.3)          |
| SD                           | 2 (66.7)                          | 1 (25.0)        | 2 (14.3)        | 1 (11.1)         | 3 (50.0)         | 9 (25.0)         |
| PD                           | 0 (0.0)                           | 0 (0.0)         | 1 (7.1)         | 0 (0.0)          | 0 (0.0)          | 1 (2.8)          |
| <b>VGPR or better</b>        | <b>1 (33.3)</b>                   | <b>1 (25.0)</b> | <b>3 (21.4)</b> | <b>3 (33.3)</b>  | <b>3 (50.0)</b>  | <b>11 (30.6)</b> |
| 95% CI                       | (0.8-90.6)                        | (0.6-80.6)      | (4.7-50.8)      | (7.5-70.1)       | (11.8-88.2)      | (16.3-48.1)      |
| <b>ORR (PR or better)</b>    | <b>1 (33.3)</b>                   | <b>3 (75.0)</b> | <b>8 (57.1)</b> | <b>8 (88.9)</b>  | <b>3 (50.0)</b>  | <b>23 (63.9)</b> |
| 95% CI                       | (0.8-90.6)                        | (19.4-99.4)     | (28.9-82.3)     | (51.8-99.7)      | (11.8-88.2)      | (46.2-79.2)      |

# Efficacy: PFS in 36 R/RMM Patients Treated with Lisaftoclastax+Pd\*

|                                      | Lisافتoclastax dose combined with Pd, mg |                       |                       |                        |                     |                       |
|--------------------------------------|--|-----------------------|-----------------------|------------------------|---------------------|-----------------------|
|                                      | 400<br>(n = 3)                           | 600<br>(n = 4)        | 800<br>(n = 14)       | 1,000<br>(n = 9)       | 1,200<br>(n = 6)    | Total<br>(N = 36)     |
| No. of patients with an event, n (%) | 0 (0.0)                                  | 4 (100.0)             | 11 (78.6)             | 4 (44.4)               | 4 (66.7)            | 23 (63.9)             |
| No. of patients censored, n (%)      | 3 (100.0)                                | 0 (0.0)               | 3 (21.4)              | 5 (55.6)               | 2 (33.3)            | 13 (36.1)             |
| PFS, mo.                             |  |                       |                       |                        |                     |                       |
| 25th percentile (95% CI)             | NE (NE-NE)                               | 3.7 (2.2-7.7)         | 3.7 (1.4-7.4)         | 2.8 (1.2-15.2)         | 2.6 (2.5-10.2)      | 3.7 (2.2-6.7)         |
| <b>Median (95% CI)</b>               | <b>NE (NE-NE)</b>                        | <b>6.5 (2.2-17.4)</b> | <b>7.4 (3.0-12.9)</b> | <b>11.1 (1.2-15.2)</b> | <b>7.0 (2.5-NE)</b> | <b>9.7 (4.7-12.9)</b> |
| 75th percentile (95% CI)             | NE (NE-NE)                               | 12.5 (2.2-17.4)       | 12.9 (7.4-13.7)       | 15.2 (11.1-15.2)       | NE (2.6-NE)         | 13.7 (10.2-NE)        |

\*Median follow-up: 9.2 months. Abbreviations: CI, confidence interval; mo., months; no., number.



# Efficacy: Responses in 32 R/RMM Patients Pretreated with anti-CD38 MoAb

| Hematologic responses        | Lisafloclax dose combined with Pd, mg |                 |                 |                  |                  | Total<br>(N = 32) |
|------------------------------|---------------------------------------|-----------------|-----------------|------------------|------------------|-------------------|
|                              | 400<br>(n = 3)                        | 600<br>(n = 3)  | 800<br>(n = 14) | 1,000<br>(n = 8) | 1,200<br>(n = 4) |                   |
| Best overall response, n (%) |                                       |                 |                 |                  |                  |                   |
| CR                           | 0 (0.0)                               | 0 (0.0)         | 1 (7.1)         | 1 (12.5)         | 0 (0.0)          | 2 (6.3)           |
| VGPR                         | 1 (33.3)                              | 1 (33.3)        | 2 (14.3)        | 2 (25.0)         | 2 (50.0)         | 8 (25.0)          |
| PR                           | 0 (0.0)                               | 1 (33.3)        | 5 (35.7)        | 4 (50.0)         | 0 (0.0)          | 10 (31.3)         |
| MR                           | 0 (0.0)                               | 0 (0.0)         | 3 (21.4)        | 0 (0.0)          | 0 (0.0)          | 3 (9.4)           |
| SD                           | 2 (66.7)                              | 1 (33.3)        | 2 (14.3)        | 1 (12.5)         | 2 (50.0)         | 8 (25.0)          |
| PD                           | 0 (0.0)                               | 0 (0.0)         | 1 (7.1)         | 0 (0.0)          | 0 (0.0)          | 1 (3.1)           |
| VGPR or better               | 1 (33.3)                              | 1 (33.3)        | 3 (21.4)        | 3 (37.5)         | 2 (50.0)         | 10 (31.3)         |
| 95% CI                       | (0.8-90.6)                            | (0.8-90.6)      | (4.7-50.8)      | (8.5-75.5)       | (6.8-93.2)       | (16.1-50.0)       |
| <b>ORR (PR or better)</b>    | <b>1 (33.3)</b>                       | <b>2 (66.7)</b> | <b>8 (57.1)</b> | <b>7 (87.5)</b>  | <b>2 (50.0)</b>  | <b>20 (62.5)</b>  |
| 95% CI                       | (0.8-90.6)                            | (9.4-99.2)      | (28.9-82.3)     | (47.3-99.7)      | (6.8-93.2)       | (43.7-78.9)       |

Abbreviations: CI, confidence interval; CR, complete response; MR, minimal response; ORR, overall response rate; PD, progressive disease; SD, stable disease; VGPR, very good partial response.



# Efficacy: Responses in 32 R/RMM Patients Pretreated with anti-CD38 MoAb

|                                      | Lisafoclax dose combined with Pd, mg |                       |                       |                        |                       | Total (N = 32)        |
|--------------------------------------|--------------------------------------|-----------------------|-----------------------|------------------------|-----------------------|-----------------------|
|                                      | 400 (n = 3)                          | 600 (n = 3)           | 800 (n = 14)          | 1,000 (n = 8)          | 1,200 (n = 4)         |                       |
| No. of patients with an event, n (%) | 0 (0.0)                              | 3 (100.0)             | 11 (78.6)             | 4 (50.0)               | 3 (75.0)              | 21 (65.6)             |
| No. of patients censored, n (%)      | 3 (100.0)                            | 0 (0.0)               | 3 (21.4)              | 4 (50.0)               | 1 (25.0)              | 11 (34.4)             |
| PFS, mo.                             |                                      |                       |                       |                        |                       |                       |
| 25th percentile (95% CI)             | NE (NE-NE)                           | 2.2 (2.2-17.4)        | 3.7 (1.4-7.4)         | 2.8 (1.2-15.2)         | 3.2 (2.5-10.2)        | 3.7 (1.9-7.4)         |
| <b>Median (95% CI)</b>               | <b>NE (NE-NE)</b>                    | <b>7.7 (2.2-17.4)</b> | <b>7.4 (3.0-12.9)</b> | <b>11.1 (1.2-15.2)</b> | <b>7.0 (2.5-10.2)</b> | <b>9.7 (4.7-12.9)</b> |
| 75th percentile (95% CI)             | NE (NE-NE)                           | 17.4 (2.2-17.4)       | 12.9 (7.4-13.7)       | 15.2 (11.1-15.2)       | 10.2 (2.5-10.2)       | 13.7 (10.2-NE)        |

# Efficacy: Responses in Cohort C R/R Amyloidosis

| Hematologic responses        | Lisafctoclax dose combined with Pd, mg |                  |                  |                  |                 |
|------------------------------|--|------------------|------------------|------------------|-----------------|
|                              | 400 (n = 1)                            | 600 (n = 4)      | 800 (n = 2)      | 1,000 (n = 2)    | Overall (N = 9) |
| Best overall response, n (%) |  |                  |                  |                  |                 |
| sCR                          | 0 (0.0)                                | 1 (25.0)         | 0 (0.0)          | 0 (0.0)          | 1 (11.1)        |
| Unconfirmed sCR              | 0 (0.0)                                | 1 (25.0)         | 0 (0.0)          | 0 (0.0)          | 1 (11.1)        |
| VGPR                         | 0 (0.0)                                | 2 (50.0)         | 2 (100.0)        | 2 (100.0)        | 6 (66.7)        |
| SD                           | 1 (100.0)                              | 0 (0.0)          | 0 (0.0)          | 0 (0.0)          | 1 (11.1)        |
| VGPR or better               | 0 (0.0)                                | 4 (100.0)        | 2 (100.0)        | 2 (100.0)        | 8 (88.9)        |
| 95% CI                       | (0.0-97.5)                             | (39.8-100.0)     | (15.8-100.0)     | (15.8-100.0)     | (51.8-99.7)     |
| <b>ORR (PR or better)</b>    | <b>0 (0.0)</b>                         | <b>4 (100.0)</b> | <b>2 (100.0)</b> | <b>2 (100.0)</b> | <b>8 (88.9)</b> |
| 95% CI                       | (0.0-97.5)                             | (39.8-100.0)     | (15.8-100.0)     | (15.8-100.0)     | (51.8-99.7)     |

CI, confidence interval; ORR, overall response rate; Pd, pomalidomide and dexamethasone; PR, partial response; R/R, relapsed or refractory; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response



זמן לתגובה פחות מחודש, טרם מידע על organ

response אבל יודעים שהיו organ response

- Because AL amyloidosis incidence is low, the current lisafctoclax dose of 1,000 mg was determined at the dose-escalation stage



## Conclusions

- LISAFTOCLAX+Pd has demonstrated an impressive safety profile, even at a relatively high dose to promote longer treatment duration.
- In heavily treated R/RMM, lisaftoclax in combination with Pd has shown improved ORR and extended DoR, noted despite refractoriness to anti-CD38 monoclonal antibodies.
- For R/R AL amyloidosis, lisaftoclax could accelerate the time to hematologic responses.
- Enrollment is ongoing to confirm the efficacy and safety of lisaftoclax in combination with Pd, to explore an optimal dosage for R/RMM (**ClinicalTrials.gov identifier: NCT04942067**).

מינון שימשיכו איתו- נראה 800-1000 מכ

- היסטורית -שילוב ונטוקלקס-פומלידמויד- דקס- רק 8 מקרים דווחו- מינונים גבוהים גרמו רעילות
- לא הייתה בעיית רעילות במינונים גבוהים
- גם ב-10 חולים עם עמילואיד פרופיל בטיחות טוב

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

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CANCER  
RESEARCH  
UK

**Abstract 1023**

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



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

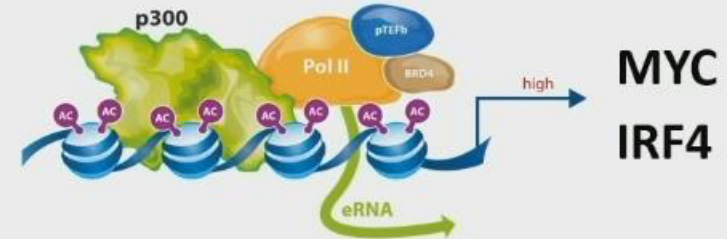
- selective displacement of p300/CBP from 10% of binding sites<sup>1</sup>
- inhibition of key oncogenic drivers IRF4 and MYC
- exquisite synergy with IMiDs<sup>2</sup>

Clinical activity has been observed in patients with relapsed and refractory myeloma when given as a monotherapy (ORR 25%)<sup>3</sup>

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

<sup>3</sup>Searle E et al presented at ASH 2023

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



## Cancer Cell

Article

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

<sup>1</sup>Nicosia et al, *Cancer Cell* 2023

## RESEARCH ARTICLE

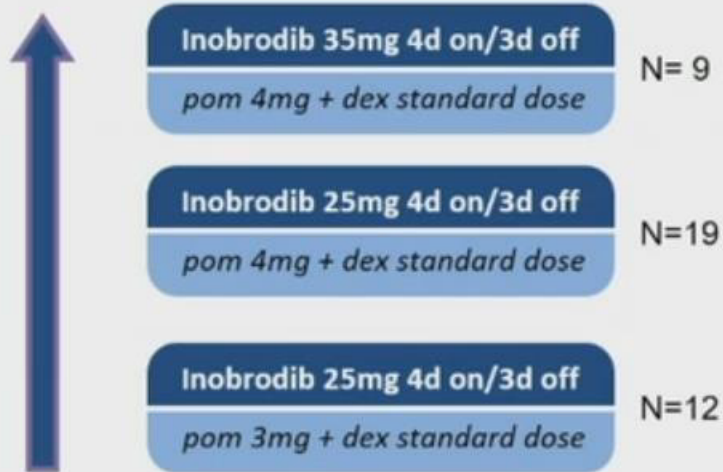
Transcriptional Heterogeneity Overcomes Super-Enhancer Disrupting Drug Combinations in Multiple Myeloma 🧑🏻

<sup>2</sup>Welsh et al, *Blood Cancer Discovery* 2024

# 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

## Prior therapies and refractory status

| Prior therapy n=40                 | Total n (%)              |
|------------------------------------|--------------------------|
| <b>Prior lines; median (range)</b> | 5 (2-9)                  |
| Prior stem cell transplantation    |                          |
| 1                                  | 18 (45%) inc. 1 allo SCT |
| 2                                  | 9 (22.5%)                |
| Triple-class exposed               | 40 (100%)                |
| <b>Refractory</b>                  |                          |
| 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

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

\*Percentage of evaluable patients/data missing

# Safety profile of InoPd: TEAEs irrespective of causality

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

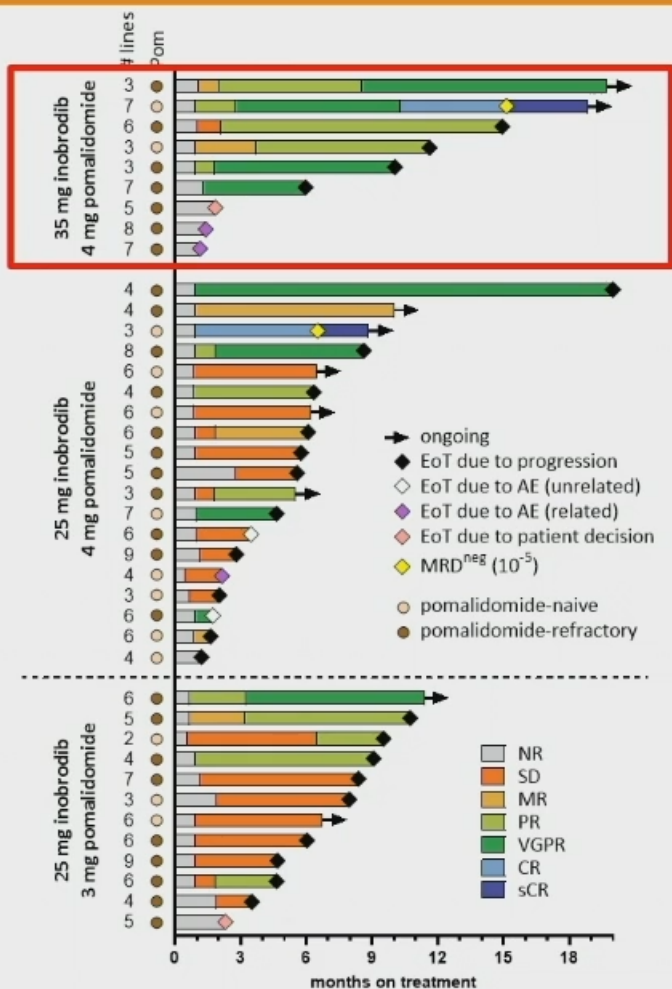
**No new safety signals identified**

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



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

Highest dose cohort: 75% ORR, mDOR 9.7 months

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

\* Among evaluable patients

# Conclusions

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- 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)**

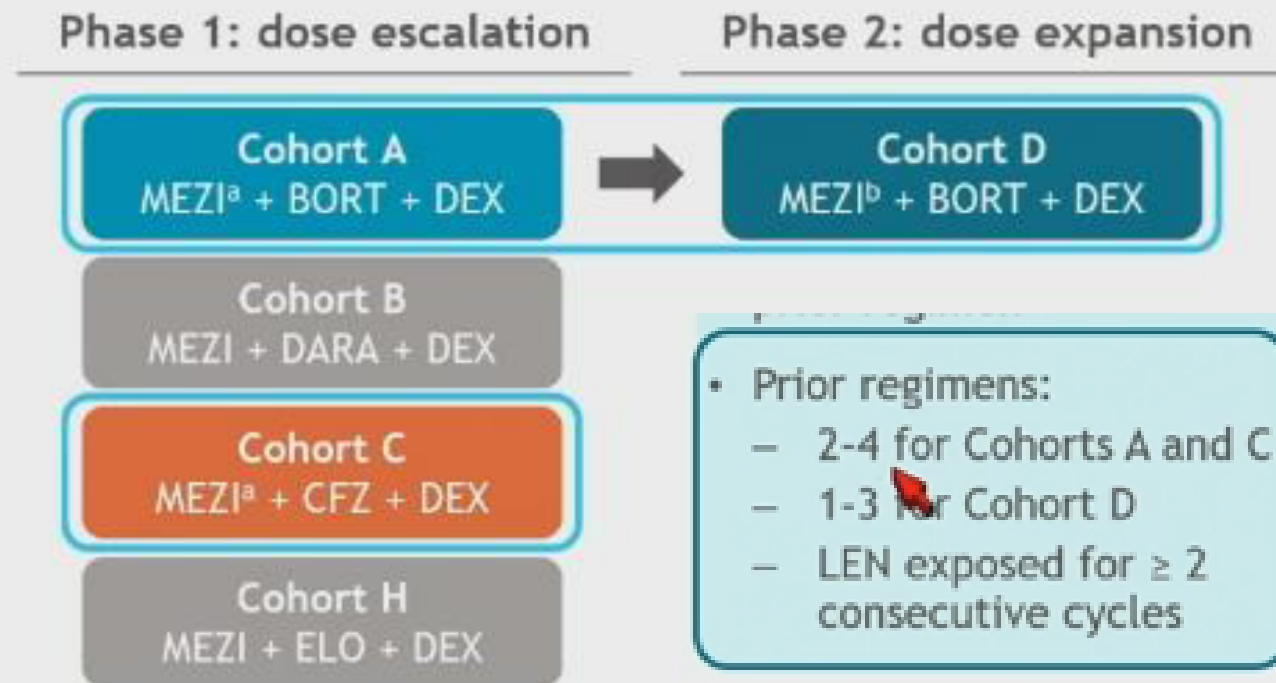


# Mezigdomide plus dexamethasone and bortezomib or carfilzomib in patients with relapsed/refractory multiple myeloma: updated results from the CC-92480-MM-002 trial

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# CC-92480-MM-002 study design

Open-label, multicenter, phase 1/2 dose-finding and dose-expansion clinical trial evaluating MEZI + DEX in combination with different treatments in patients with MM<sup>1,2</sup>

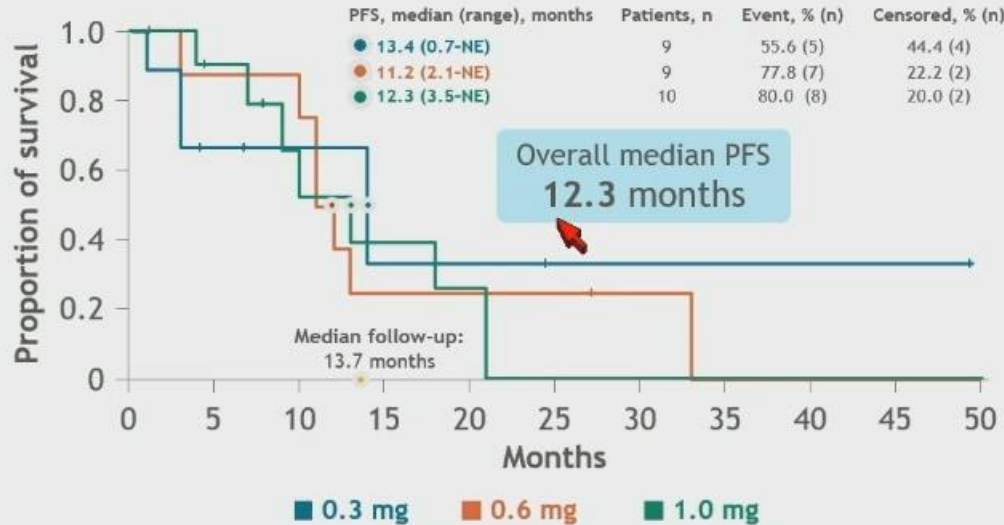


This study reports updated results with longer follow-up from the phase 1/2 CC-92480-MM-002 trial (NCT03989414)<sup>6-8</sup> from the MEZI + DEX + BORT (MeziVd) and MEZI + DEX + CFZ (MeziKd) dose-escalation cohorts (A and C) and the MeziVd dose-expansion cohort (D)

# PFS in dose-escalation Cohort A and dose-expansion Cohort D (MeziVd)

## PFS<sup>a</sup> - Cohort A

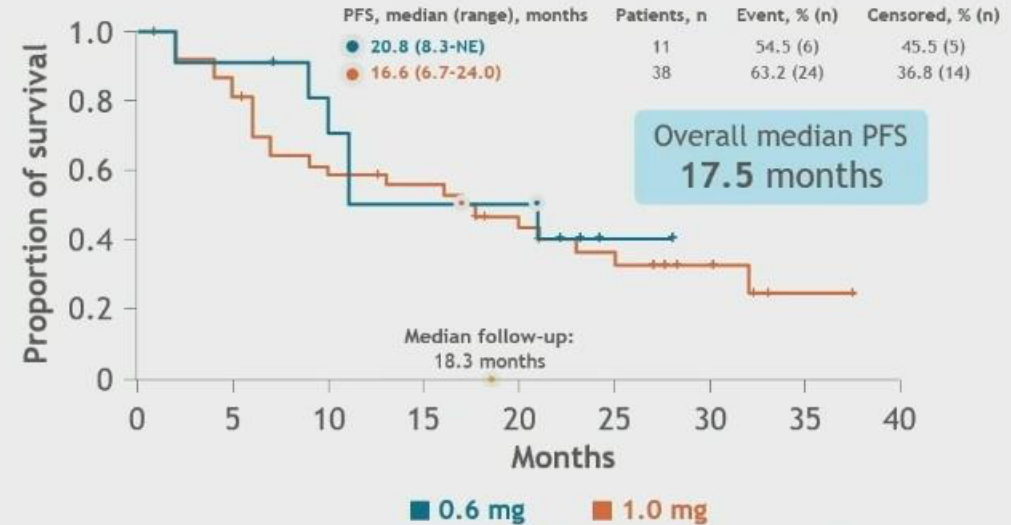
Median number of prior therapies = 3



|                              | All doses        | 1.0 mg           |
|------------------------------|------------------|------------------|
| ORR, <sup>b</sup> % (95% CI) | 75.0 (55.1-89.3) | 60.0 (55.1-89.3) |
| DOR, median (95% CI), months | 10.9 (8.8-18.7)  | 11.6 (5.3-NA)    |

## PFS<sup>a</sup> - Cohort D

Median number of prior therapies = 1



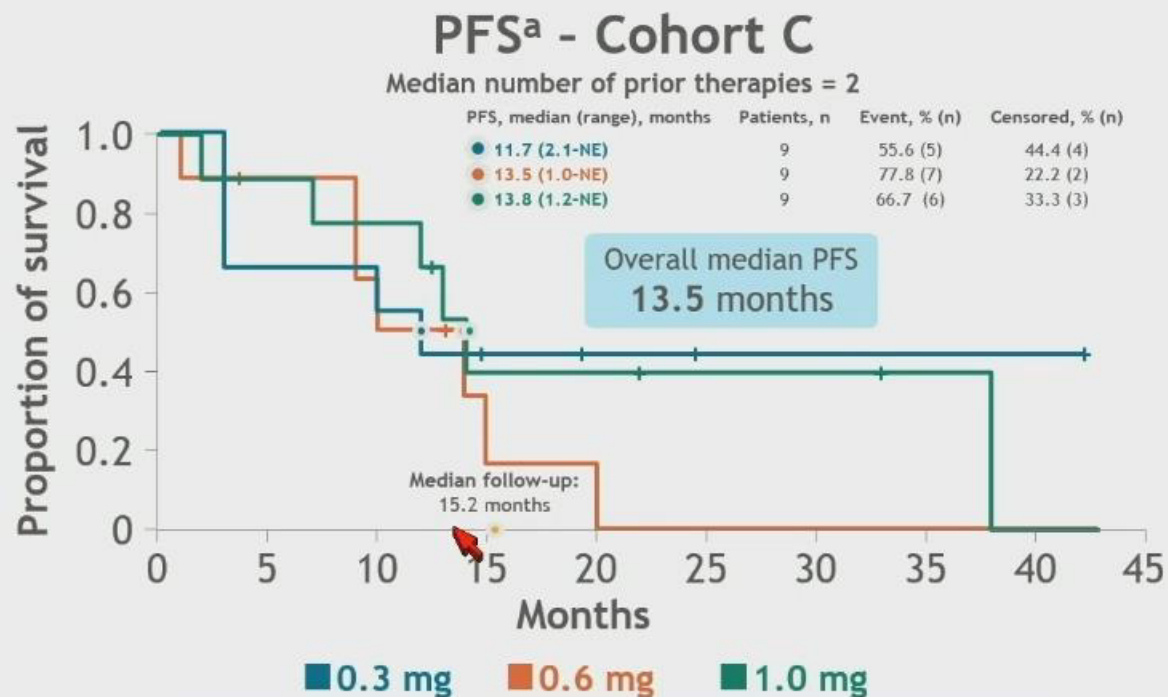
|                              | All doses        | 1.0 mg           |
|------------------------------|------------------|------------------|
| ORR, <sup>b</sup> % (95% CI) | 85.7 (72.8-94.1) | 84.2 (68.7-94.0) |
| DOR, median (95% CI), months | 19.4 (9.7-NA)    | 19.4 (7.0-NA)    |

MeziVd showed durable efficacy at all dose levels tested with an overall median PFS > 1 year (17.5 months in Cohort D)

<sup>a</sup>Data cutoff: June 28, 2024; <sup>b</sup>ORR refractory to LEN and anti-CD38 mAbs (data cutoff: May 9, 2024): Cohort A = 69.2%, Cohort D = 75.0%. CI, confidence interval; DOR, duration of response; NA, not applicable; PFS, progression-free survival.



# PFS in dose-escalation Cohort C (MeziKd)



|                              | All doses        | 1.0 mg           |
|------------------------------|------------------|------------------|
| ORR, <sup>b</sup> % (95% CI) | 85.2 (66.3-95.8) | 77.8 (40.0-97.2) |
| DOR, median (95% CI), months | 11.9 (6.4-35.9)  | 11.9 (0.2-NA)    |

MeziKd showed efficacy at all dose levels tested with an overall median PFS of 13.5 months

<sup>a</sup>Data cutoff: June 28, 2024; <sup>b</sup>ORR refractory to LEN and anti-CD38 mAbs (data cutoff: May 9, 2024): Cohort C = 82.4%.



# Conclusions and future directions

- MEZI is a novel, oral CELMoD agent that induces rapid, potent, and deep degradation of Ikaros and Aiolos, resulting in enhanced cytotoxic effects in myeloma cells and direct T-cell and NK-cell immune-stimulatory activities<sup>1</sup>
- Proteasome inhibition does not abrogate the substrate degradation induced by MEZI
- MEZI demonstrated dose-dependent linear pharmacokinetics, with no difference in exposure between Cohorts A, D, or C<sup>2</sup>
- MeziVd and MeziKd in RRMM confirmed promising efficacy at all dose levels tested, including at the 1.0-mg dose, in patients with RRMM previously exposed to IMiD agents, PI, and anti-CD38 mAbs
  - Responses were deep and durable (ORR Cohort A: 75.0%; Cohort D: 85.7%; Cohort C: 85.2%), with median PFS of  $\geq 1$  year in all cohorts (Cohort A: 12.3 months; Cohort D: 17.5 months; Cohort C: 13.5 months)
  - PFS was longer in the MeziVd dose-expansion cohort (Cohort D) with 1 median prior line of therapy than in the dose-escalation cohort (Cohort A) with 3 median prior lines of therapy
- Among all cohorts, MEZI demonstrated a manageable safety profile with no cumulative toxicity
  - Neutropenia was the most common grade 3/4 TEAE, occurred infrequently with grade 3/4 infections, and was manageable with G-CSF and dose interruption/reduction
  - Non-hematologic grade 3/4 TEAEs were uncommon

**These results support the investigation of MEZI in the phase 3 trials  
SUCCESSOR-1<sup>a</sup> (MeziVd vs PVd) and SUCCESSOR-2<sup>b</sup> (MeziKd vs Kd) in RRMM**

Kd, CFZ + DEX; PVd, POM + BORT + DEX. <sup>a</sup>NCT05519085; eligible patients had MM and measurable disease, received 1-3 antimyeloma regimens, and achieved  $\geq$  MR to  $\geq 1$  therapy. <sup>b</sup>NCT05552976; eligible patients had MM and measurable disease with documented disease progression after the last myeloma regimen, received  $\geq 1$  prior anti-myeloma therapy, received prior LEN treatment and  $\geq 2$  cycles of an anti-CD38 mAb, and achieved  $\geq$  MR to  $\geq 1$  therapy. 1. Richardson PG, et al. *N Engl J Med* 2023;389:1009-1022; 2. BMS. Data on file.

