The rationale for protein degradation and immunomodulation in relapsed/refractory multiple myeloma: Highlighting the latest data and available clinical trials

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What are the critical unmet treatment needs in patients with relapsed/refractory multiple myeloma?

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How prevalent is multiple myeloma today, and what is the outlook for patients?

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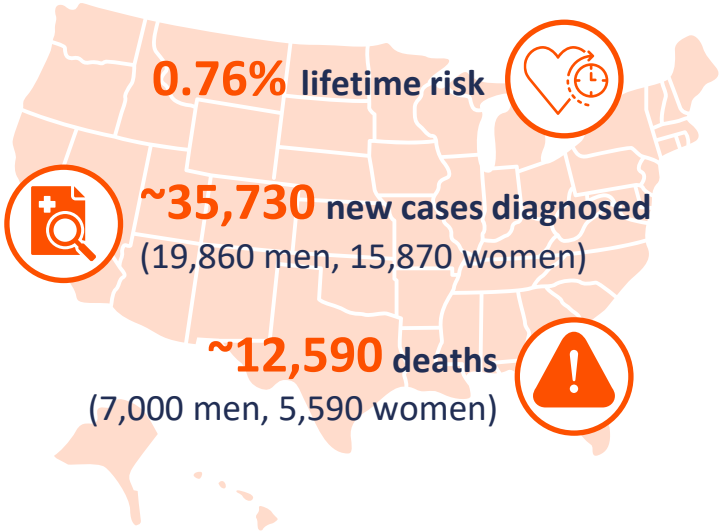
The burden of multiple myeloma

Estimates for multiple myeloma in the USA for 2023[1]



0.76% lifetime risk

~35,730 new cases diagnosed
(19,860 men, 15,870 women)

~12,590 deaths
(7,000 men, 5,590 women)

5-year relative survival*[2]

*Based on data from SEER 22 (excluding IL/MA) 2013–2019. SEER, Surveillance, Epidemiology, and End Results Program.

1. American Cancer Society. Available at: https://cancerstatisticscenter.cancer.org (accessed 22 September 2023);
2. NIH National Cancer Institute. Available at: https://seer.cancer.gov/statfacts/html/mulmy.html (accessed 25 September 2023).

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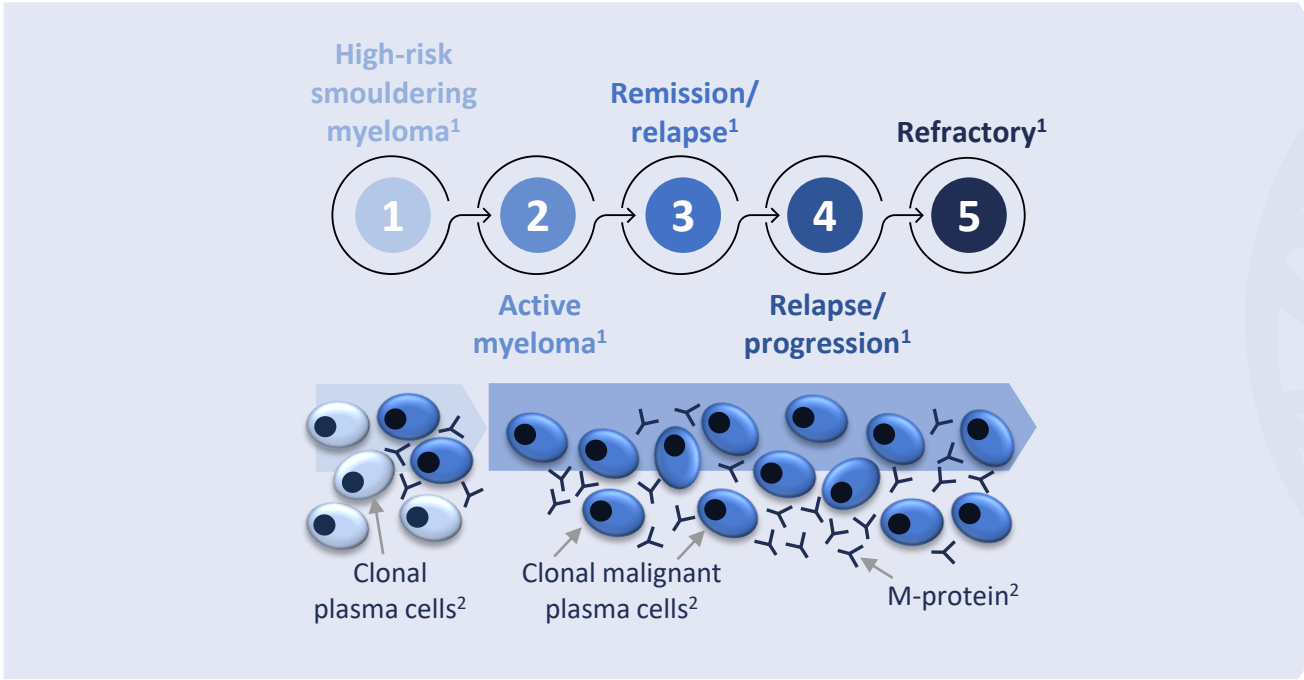
Natural history of multiple myeloma



1. Fernandez de Larrea C, et al. *Adv Cell Gene Ther*. 2020;3:e72; 2. Neumeister P, et al. *Int J Mol Sci*. 2022;23:7627.

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How has the treatment landscape for relapsed/refractory multiple myeloma evolved over time?

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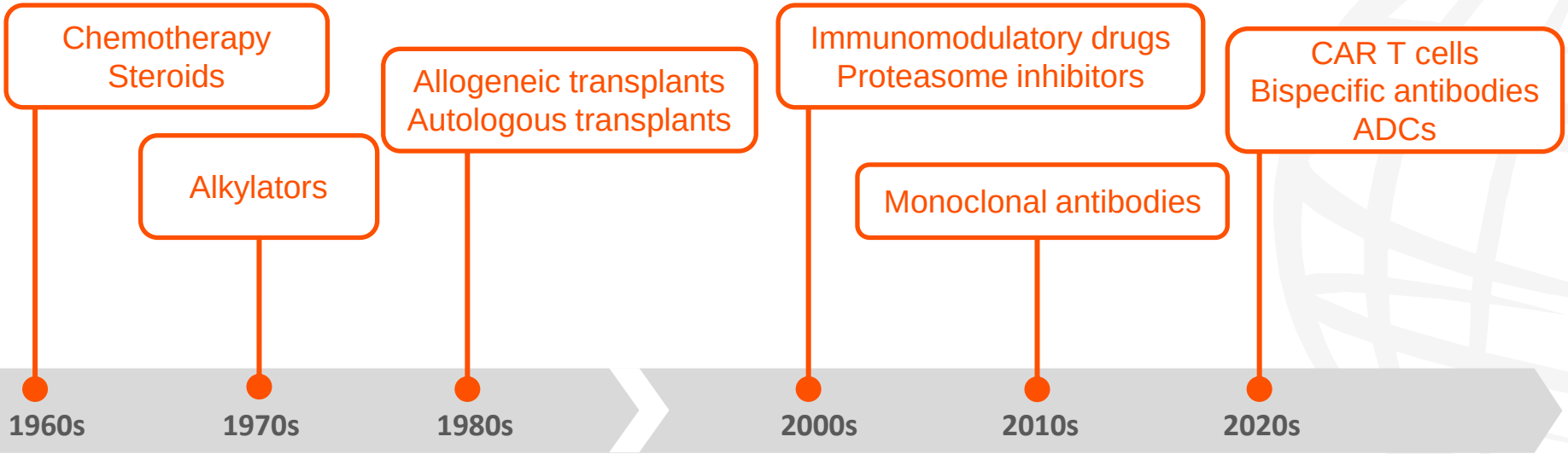
The evolving therapy landscape in multiple myeloma[1,2]



ADC, antibody–drug conjugate; CAR, chimeric antigen receptor.

1. Shah UA, Mailankody S. *Br Med J.* 2020;370:m3176; 2. Ribatti D. *Eur J Haematol.* 2018;100:221–8.

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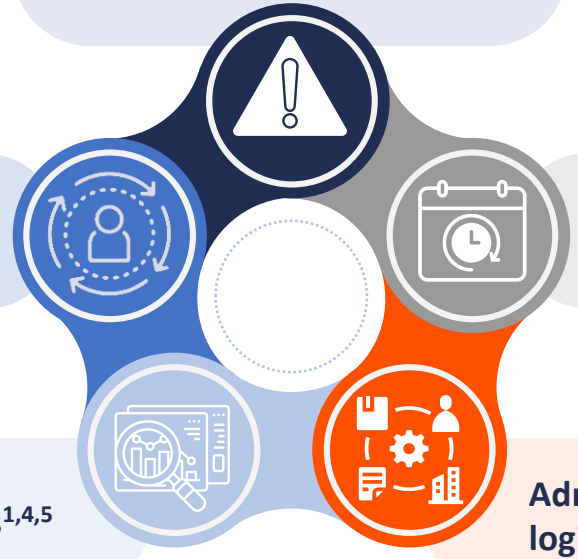
What are the limitations of current therapies for the treatment of relapsed/refractory multiple myeloma?

Limitations of current treatment regimens for patients with RRMM

Toxicity-related complications[1]

QoL is negatively impacted and decreases with increasing lines of therapy[2,3]



Increasingly rapid disease progression with each line of therapy[1,4]

Low OS and PFS rates[1,4,5]

Administration and logistical burdens[6]

OS, overall survival; PFS, progression-free survival; QoL, quality of life; RRMM, relapsed/refractory multiple myeloma.

1. Wang PF, et al. *Leuk Lymphoma.* 2023;64:398–406; 2. Engelhardt M, et al. *Clin Lymphoma Myeloma Leuk*. 2021;21:e160–75; 3. Lee HC, et al. *Clin Lymphoma Myeloma Leuk*. 2023;23:112–22; 4. Bruno AS, et al. *Expert Rev Hematol*. 2020;13:1017–25; 5. Gandhi UH, et al. *Leukemia*. 2019;33:2266–75; 6. Shah N, et al. *Leukemia*. 2020;34:985–1005.

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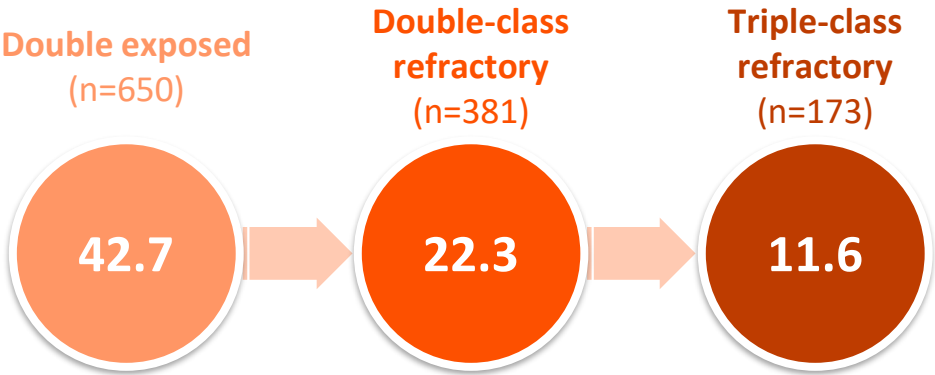
Real-world survival outcomes for patients with double- and triple-class refractory RRMM

A US electronic health record database study[1]



Median OS by treatment status (months)

LocoMMotion: Prospective, non-interventional, multinational study[2]

Outcomes in patients who were triple-class refractory at baseline treated with SOC (n=183):

- ORR: 25.1%
- Median DOR: 4.5 months
- Median PFS: 3.9 months
- Median OS: 11.1 months

DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma; SOC, standard of care.

1. Wang PF, et al. *Leuk Lymphoma.* 2023;64:398–406; 2. Mateos M-V, et al. *Leukemia.* 2022;36:1371–6.

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What do you think are the remaining unmet needs surrounding treatment options in relapsed/refractory multiple myeloma?

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Why are protein degradation and immunomodulatory approaches being trialled in multiple myeloma?

Prof. Sagar Lonial

Professor and Chief Medical Officer
Winship Cancer Institute
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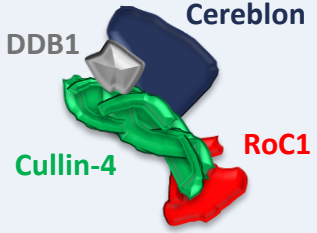
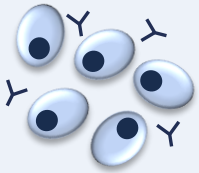
Why are protein degradation and immunomodulatory approaches being trialled in multiple myeloma?

Cereblon as a treatment target

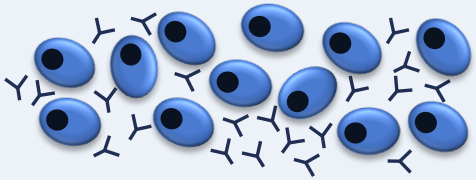


Cereblon interacts with the DDB1, Cullin-4 and RoC1 to form the functional E3 ubiquitin ligase complex[1]

Cereblon functions as a substrate receptor and **targets proteins for degradation** through the UPS[1]



Neosubstrates of cereblon include **Ikaros** (IKZF1) and **Aiolos** (IKZF3), members of the B-cell transcription factors family **critical for plasma cell development and proliferation**, and activation of the immune system[1,2]



Ikaros and Aiolos **sustain MM growth and survival**.[3]

DDB1, DNA damage-binding protein-1; IKZF1/3, IKAROS family zinc finger 1/3; MM, multiple myeloma; RoC1, regulator of Cullins-1; UPS, ubiquitin–proteasome system.

1. Shi Q, Chen L. *J Immunol Res.* 2017;2017:9130608; 2. Huang PA, et al. *Sci Rep.* 2019;9:14884; 3. Cippitelli M, et al. *Int J Mol Sci.* 2021;22:1103.

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What is the rationale for using degradation-activating compounds in the treatment of multiple myeloma?

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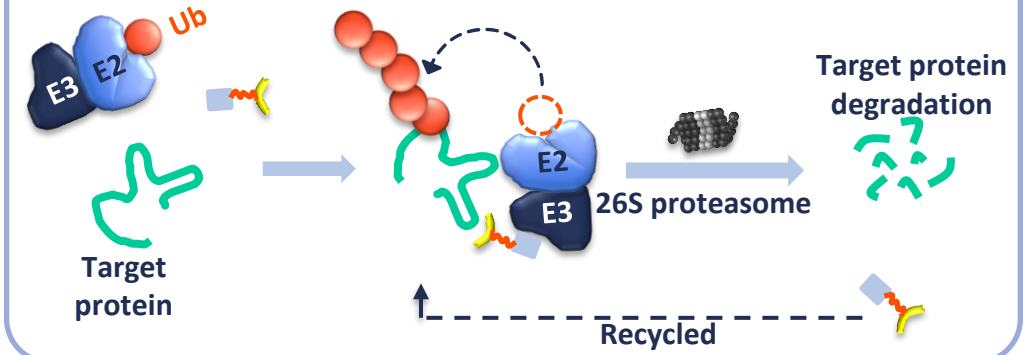
Degradation-activating compounds

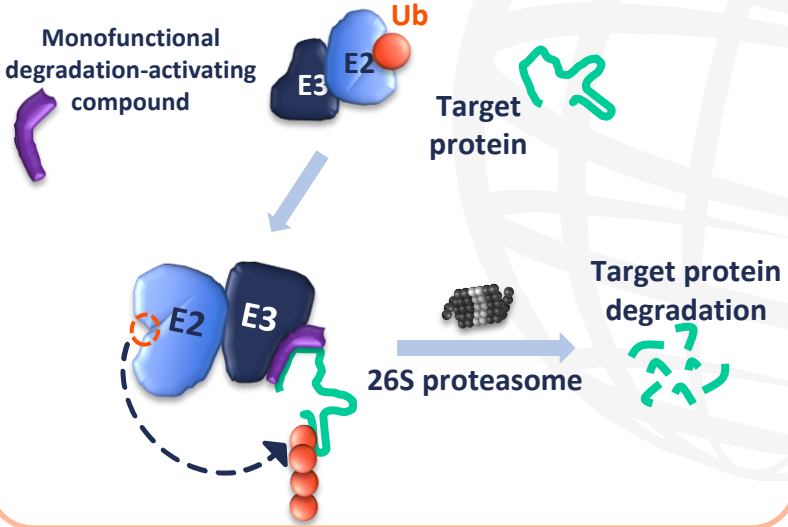
Proteolysis-targeting chimera[1]

Acts as a bridge between the E3 ligase and target protein to induce its polyubiquitination and proteasome-mediated degradation



Monofunctional degrader ("molecular glue")[2,3]

Binds to cereblon E3 ligase and modulates the surface to increase interaction with target protein of interest[2] (e.g. CFT7455 with transcription factors IKZF1/3[4])



E2, ubiquitin-conjugating enzyme; IKZF1/3, IKAROS family zinc finger 1/3; Ub, ubiquitin.

1. Fang Y, et al. *Trends Pharmacol Sci*. 2023;44:303–17; 2. Berdeja JG, et al. Presented at: 63rd ASH Annual Meeting and Exposition, Atlanta, GA, USA. 11–14 December 2021. Poster 1675; 3. Sasso JM, et al. *Biochemistry*. 2023;62:601–23; 4. Lonial S, et al. Presented at: AACR Annual Meeting 2022, New Orleans, LA, USA. 8–13 April 2022. Poster CT186.

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How do cereblon E3 ligase modulators target protein degradation in multiple myeloma?

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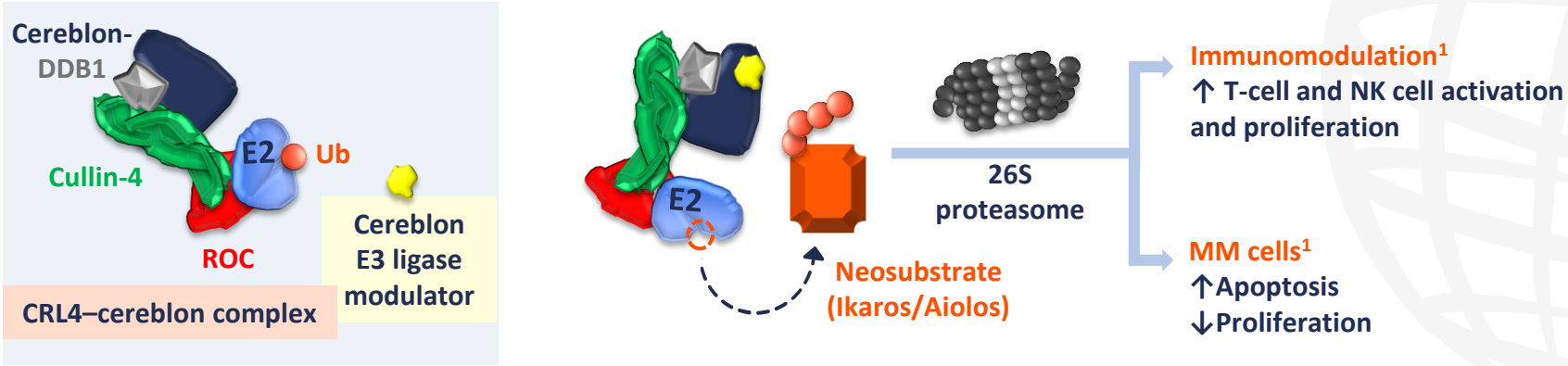
Cereblon E3 ligase modulators

- Work in a similar way to current immunomodulatory drugs, but are more potent[1] and include Ikaros family of zinc finger transcription factors as substrates[2]
- Bind to a shallow hydrophobic pocket on the surface of cereblon, changing its conformation, to promote interaction with and degradation of target substrates[2,3]



- Agents in clinical development include iberdomide[1] and mezigdomide[4]

↓, decrease; ↑, increase; CRL4, Cullin-4 RING ligase; DDB1, DNA damage-binding protein-1; E2, ubiquitin-conjugating enzyme; MM, multiple myeloma; NK, natural killer; ROC, regulator of Cullins; Ub, ubiquitin.

1. Thakurta A, et al. *Oncotarget*. 2021;12:1555–63; 2. Chamberlain PP, Cathers BE. *Drug Discov Today Technol*. 2019;31:29–34; 3. Watson ER, et al. *Science*. 2022;378:549–53; 4. Richardson PG, et al. *Blood*. 2022;140 (Suppl. 1):1366–8.

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How do you think protein degradation and immunomodulatory agents in development for patients with multiple myeloma will impact future clinical practice?

Potential future role of cereblon E3 ligase modulators

In combination with or as salvage therapy after **bispecific antibodies/CAR T-cell therapy**[1–3]

In patients with **extramedullary disease** due to good tissue penetration[4] and available clinical trial data in this patient group[3,5]

In patients with **high-risk cytogenetic abnormalities** based on available clinical trial data in this patient group[3,5]

Potential therapy for **frail/elderly patients** due to oral administration route[3,5]

Potential **use in earlier lines** of therapy, e.g. induction therapy, maintenance therapy and in SMM[6]

CAR, chimeric antigen receptor; SMM, smouldering multiple myeloma.

1. Van de Donk NWCJ, et al. *Curr Opin Oncol.* 2023;35:601–11; 2. Barankiewicz J, et al. *Cancers (Basel).* 2022;14:4492; 3. Lonial S, et al. *Lancet Haematol.* 2022;9:e822–32; 4. Ege N, et al. *Cell Chem Biol.* 2021;28:283–99; 5. Richardson PG, et al. *N Engl J Med.* 2023;389:1009–22; 6. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ (accessed December 2023).

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What are the latest clinical trial data for protein degradation and immunomodulatory-based therapies in relapsed/refractory multiple myeloma, and which trials are ongoing?

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What are the latest clinical trial data and ongoing clinical trials for iberdomide?

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CC-220-MM-001 trial (NCT02773030)

Multicohort, open-label, phase Ib/IIa study to determine dose, safety, tolerability, efficacy and drug levels of iberdomide as monotherapy and in combination with other treatments[1]

Phase I: Dose escalation (n=90)[2]

At least two prior lines of therapy including lenalidomide/ pomalidomide + a proteasome inhibitor
ECOG PS 0–2

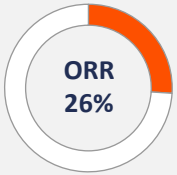
0.3–1.6 mg oral iberdomide on days 1–21/28 + dexamethasone once per week

Primary outcome:
RP2D 1.6 mg

Phase II: Dose expansion (n=107)[2]

At least three prior lines of therapy and had triple-class refractory disease

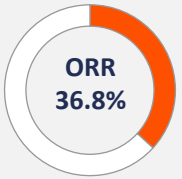
Primary outcome



Grade ≥3 TEAEs (≥20%):
Neutropenia, anaemia, infection, thrombocytopenia and leukopenia

Serious TEAEs in 53% of patients

BCMA-exposed cohort (n=38)[3]



Grade 3/4 TEAEs (≥20%):
Neutropenia, anaemia, leukopenia, thrombocytopenia and infections

BCMA, B-cell maturation antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; RP2D, recommended phase II dose; TEAE, treatment-emergent adverse events.

1. ClinicalTrials.gov. NCT02773030. Available at: https://bit.ly/417FCBm (accessed 29 November 2023); 2. Lonial S, et al. *Lancet Haematol*. 2022;9:e822–32;
3. Lonial S, et al. *Blood*. 2022;140(Suppl. 1):4398–400.

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Ongoing iberdomide clinical trials in patients with MM

Trial identifier	Phase	Study treatments	Primary endpoint(s)	Key inclusion criteria
NCT04975997[1] EXCALIBER-RRMM	Phase III	IberDd vs DVd	PFS	➢ Disease progression during/after last anti-myeloma regimen ➢ Received one or two prior lines of anti-myeloma therapy ➢ ECOG PS 0–2
NCT05560399[2]	Phase I DEC	Iber + elotuzumab + dexamethasone	Iber DLT	➢ Disease progression during or after last anti-myeloma therapy ➢ ECOG PS ≤2 ➢ Received one to three prior lines of therapy, including at least an immunomodulatory drug, a proteosome inhibitor and an anti-CD38 mAb
NCT05896228[3]	Phase II	Iber-KDd for ~ 8 months, followed by iberdomide monotherapy in absence of disease progression	Rate of MRD negativity	➢ Progressive disease during or within 60 days of last regimen ➢ Received one to three prior lines of therapy (inclusive of a lenalidomide-containing regimen); carfilzomib/CD38-directed therapy permitted under certain conditions ➢ Measurable disease and ECOG PS 0–2 within 4 weeks of enrolment

CD, cluster of differentiation; Dd, daratumumab and dexamethasone; DEC, dose expansion cohort; DLT, dose-limiting toxicity; DVd, daratumumab, bortezomib and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; iber, iberdomide; KDd, carfilzomib, daratumumab and dexamethasone; mAb, monoclonal antibody; MM, multiple myeloma; MRD, minimal residual disease; PFS, progression-free survival.

1. ClinicalTrials.gov. NCT04975997; 2. ClinicalTrials.gov. NCT05560399; 3. ClinicalTrials.gov. NCT05896228. All clinical trials available at: https://clinicaltrials.gov/ (accessed 29 November 2023).

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Ongoing iberdomide clinical trials in patients with MM

Trial identifier	Phase	Study treatments	Primary endpoint(s)	Key inclusion criteria
NCT05354557[1]	Phase II	Iber as maintenance therapy after AHCT	CR	**Cohort 1:** ➢ Received a single prior AHCT (within the last 12 months) with melphalan ➢ Have been on lenalidomide maintenance at a dose of ≥5 mg every other day for at least 6 months ➢ Have achieved a VGPR or less to treatment **Cohort 2:** ➢ Received two or three prior lines of systemic anti-myeloma therapy +/- prior AHCT ➢ Received lenalidomide maintenance therapy after a line of treatment prior to salvage AHCT ➢ Undergone salvage AHCT consolidation with a high-dose melphalan-based conditioning regimen within the prior 2–6 months
NCT05583617[2] PLYCOM	Phase I/II	Cevostamab + iber	AEs, response rates, PFS, OS	➢ Previously exposed to at least a PI, an immunomodulatory drug and an anti-CD38 mAb for the treatment of RRMM for whom no suitable SOC therapy options are available
NCT05289492[3]	Phase I/II	EOS884448 alone or with iber +/- dexamethasone	AEs, SAEs, DLT, RP2D, ORR	➢ ECOG PS 0–2 ➢ At least three prior lines of therapy with an immunomodulatory drug, PI and anti-CD38 mAb; progression on last therapy (prior BCMA-targeted therapy allowed)

AE, adverse event; AHCT, autologous haematopoietic cell transplantation; BCMA, B-cell maturation antigen; CD, cluster of differentiation; CR, complete response; DLT, dose-limiting toxicity; ECOG PS, ECOG, Eastern Cooperative Oncology performance status; iber, iberdomide; mAb, monoclonal antibody; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; RP2D, recommended phase II dose; RR, relapsed/refractory; SAE, serious AE; SOC, standard of care; VGPR, very good partial response.

1. ClinicalTrials.gov. NCT05354557; 2. ClinicalTrials.gov. NCT05583617; 3. ClinicalTrials.gov. NCT05289492. All clinical trials available at: https:// clinicaltrials.gov/ (accessed 29 November 2023).

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What are the latest clinical trial data and ongoing trials for mezigdomide?

CC-92480-MM-001 trial (NCT03374085)

Open-label, multicentre, phase I/II study to determine safety, pharmacokinetics and efficacy of mezigdomide as monotherapy and in combination with dexamethasone[1]

Mezigdomide dosing and schedule[2]

n=29; 10/14 days × 2
0.1/0.2/0.3/0.6/1.0 mg QD
n=24; 21/28 days
0.8/1.0 mg QD
n=11; 3/14 days × 2
0.2/0.4/0.8 mg BID
n=13; 7/14 days × 2
0.8 mg BID/1.6/2.0 mg QD

Phase I: Dose escalation (n=77)[2]

ECOG PS 0–2
At least three prior lines of therapy
Disease progression on/within 60 days of last myeloma therapy

Primary outcome

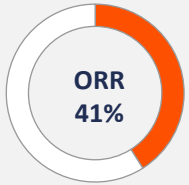
RP2D 1.0 mg QD + dexamethasone for 21 days followed by 7 days off, in each 28-day cycle

Phase II: Dose expansion (n=101)[2]

Triple-class refractory disease
- 30% previous anti-BCMA therapy
- 40% plasmacytomas

1.0 mg mezigdomide QD + dexamethasone for 21 days

Primary outcome



Median DOR: 7.6 months
Median PFS: 4.4 months

Most common grade 3/4 AEs:*
Neutropenia, infection and anaemia

*≥30% in the dose escalation and dose expansion cohort.
AE, adverse event; BCMA, B-cell maturation antigen; BID, twice daily; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; PFS, progression-free survival; QD, once daily; RP2D, recommended phase II dose.
1. ClinicalTrials.gov. NCT05521191. Available at: https://bit.ly/3T2I5L6 (accessed 29 November 2023); 2. Richardson PG, et al. N Engl J *Med*. 2023;389:1009–22.

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CC-92480-MM-002 trial (NCT03989414)

Ongoing phase I/II study to determine safety and preliminary efficacy of mezigdomide in combination with standard treatments[1,2]

Two to four prior lines of therapy

Minimal response or better to at least one prior regimen

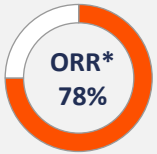
Disease progression during or after last therapy

ECOG PS 0–2

MeziDd (n=56)[2]

Escalating doses in three subcohorts:
B1: on D1–21 per 28-D cycle + DARA1[‡]+DEX
B2: D1–14 per 21-D cycle from C1–8 and D1–21 per 28-D cycle ≥C9 + DARA2[§]+DEX
B3: D1–7 and D15–21 per 28-D cycle C1–6 and D1–21 per 28-D cycle ≥C7 + DARA1[‡]+DEX

Primary outcome

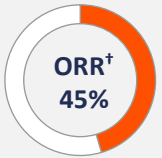


Subcohort B1: 82.6%
Subcohort B2: 61.1%
Subcohort B3: 88.9%

MeziEd (n=20)[2]

Escalating doses of mezi on D1–21 per 28-D cycle + ELO C1–2 weekly (10 mg/kg), ≥C3 monthly (20 mg/kg) + DEX on ELO dosing days + ≥C3 on D8, D15 and D22

Primary outcome



Most common grade 3/4 TEAEs:[‖] Neutropenia, anaemia, infections

Low non-haematological grade 3/4 TEAEs

*Combined ORR; †overall ORR, ‡DARA1, C1–2 weekly, C3–6 biweekly, ≥C7 monthly, §DARA2, C1–3 weekly, C4–8 D1 of each 21-D cycle, ≥C9 D1 of each 28-D cycle; ‖, ≥20% in any subcohort.

C, cycle; D, day; DARA, daratumumab; DEX, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ELO, elotuzumab; mezi, mezigdomide; MeziDd, mezi, DARA and DEX; MeziEd, mezi, ELO and DEX; ORR, overall response rate; TEAE, treatment-emergent adverse event.

1. ClinicalTrials.gov. NCT03989414. Available at: https://bit.ly/3T4cLMj (accessed 30 November 2023); 2. Richardson PG, et al. Presented at: 65th ASH Annual Meeting and Exposition, San Diego, CA, USA. 9–12 December 2023. Abstr 1013.

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Ongoing mezigdomide clinical trials in patients with MM

Trial identifier	Phase	Study treatments	Primary endpoint(s)	Key inclusion criteria
NCT05519085[1] SUCCESSOR-1	Phase III	MeziVd vs PVd	PFS	➢ Received one to three prior lines of antimyeloma therapy ➢ MR or better to at least one prior antimyeloma therapy
NCT05552976[2] SUCCESSOR-2	Phase III	MeziKd vs Kd monoclonal antibody	PFS	➢ At least one prior line of anti-myeloma therapy ➢ Prior treatment with lenalidomide and at least two cycles of an anti-CD38 mAb ➢ MR or better to at least one prior anti-myeloma therapy ➢ Documented disease progression during or after their last antimyeloma regimen
NCT03989414[3]	Phase I/II	Mezi + standard treatment	Recommended dose, regimen measured by DLT, AEs, ORR	➢ Documented disease progression during or after their last antimyeloma regimen ➢ MR or better to at least one prior antimyeloma therapy ➢ ECOG PS 0–2

AE, adverse event; CD, cluster of differentiation; DLT, dose-limiting toxicities; ECOG PS, Eastern Cooperative Oncology Group performance score; Kd, carfilzomib and dexamethasone; mAb, monoclonal antibody; mezi, mezigdomide; MeziKd, mezi, carfilzomib and dexamethasone; MeziVd, mezi, bortezomib and dexamethasone; MM, multiple myeloma; MR, minimal response; ORR, overall response rate; PFS, progression-free survival; PVd, pomalidomide, bortezomib and dexamethasone.

1. ClinicalTrials.gov. NCT05519085; 2. ClinicalTrials.gov. NCT05552976; 3. ClinicalTrials.gov. NCT03989414. All clinical trials available at: https://clinicaltrials.gov/ (accessed 29 November 2023).

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Ongoing mezigdomide clinical trials in patients with MM

Trial identifier	Phase	Study treatments	Primary endpoint(s)	Key inclusion criteria
NCT05981209[1]	Phase Ib	Mezi + elotuzumab and dexamethasone	RP2D, AEs	➢ At least two prior lines of therapy including lenalidomide, a PI, and anti-CD38 mAb and BCMA-targeted therapy ➢ ECOG PS 0–2
NCT06050512[2]	Phase I/II	Mezi + ixazomib and dexamethasone	Phase I: RP2D Phase II: ORR	➢ ECOG PS 0–2 ➢ Received one to three prior lines of therapy and must be exposed to a PI, immunomodulatory drug and an anti-CD38 mAb ➢ Access to ixazomib
NCT06048250[3]	Phase I	Mezi and dexamethasone post idecabtagene vicleucel	AEs	➢ ECOG PS 0–2 ➢ At least four prior lines of therapy, including an immunomodulatory drug, a PI and an anti-CD38 mAb
NCT05372354[4]	Phase Ib/2a	Mezi in novel therapeutic combinations	AEs, RP2D, dosing schedule of each combination for part 2 dose expansion	➢ ECOG PS 0 or 1

AE, adverse event; BCMA, B-cell maturation antigen; CD, cluster of differentiation; ECOG PS, Eastern Cooperative Oncology Group performance score; mAb, monoclonal antibody; mezi, mezigdomide; MM, multiple myeloma; ORR, overall response rate; PI, proteasome inhibitor; RP2D, recommended phase II dose.

1. ClinicalTrials.gov. NCT05981209; 2. ClinicalTrials.gov. NCT06050512; 3. ClinicalTrials.gov. NCT05372354; 4. ClinicalTrials.gov. NCT05981209. All clinical trials available at: https://clinicaltrials.gov/ (accessed 29 November 2023).

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What are the latest clinical trial data and ongoing trials for CFT7455?

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CFT7455 trial study design (NCT04756726)

Ongoing phase I/II study to determine safety and tolerability of CFT7455 monotherapy or in combination with DEXA in RRMM/RRNHL

Phase I

Arm A: CFT7455 at different dosing schedules
Arm B1: Escalating doses of CFT7455 in different dosing schedules
Arm B2: CFT7455 + fixed dose of DEXA in each cohort

Primary outcomes

- Safety and tolerability of CFT7455
- Safety and tolerability of CFT7455 + DEXA
- MTD/RP2D for CFT7455
- MTD/RP2D for CFT7455 + DEXA

Phase II

Arm 1: CFT7455
Arm 2: CFT7455 + DEXA

Primary outcomes

- Antitumor activity of CFT7455 and CFT7455 + DEXA
- ORR based on BOR, DOR, CBR, PFS

Key inclusion criteria:

- Documented diagnosis of MM and measurable disease at enrolment
- At least three prior anti-myeloma regimens including at least two consecutive cycles of lenalidomide, pomalidomide, a PI, a glucocorticoid and an anti-CD38 mAb
- Refractory disease defined as disease that is nonresponsive to therapy or disease progression within 60 days from the last dose of their last myeloma therapy

BOR, best overall response; CBR, clinical benefit rate; CD, cluster of differentiation; DEXA, dexamethasone; DOR, duration of response; mAb, monoclonal antibody; MM, multiple myeloma; MTD, maximum tolerated dose; NHL, non-Hodgkin's lymphoma; ORR, overall response rate; PFS, progression-free survival; PI, proteasome inhibitor; RP2D, recommended phase II dose; RR, relapsed/refractory.

ClinicalTrials.gov. NCT04756726. Available at: https://bit.ly/3uE31hH (accessed 29 November 2023).

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CFT7455 phase I dose escalation data

Preliminary results

CFT7455 monotherapy (n=22; completed)

- 14 days on/14 days off schedule
- 75 µg was maximum administered dose
- Most common* grade ≥3 AE was neutropenia; no dose-limiting toxicities results in discontinuations
- All four patients receiving 75 µg achieved stable disease or better
- Clinical evidence of immune T-cell activation at doses below the maximum administered dose

CFT7455 + dexamethasone (n=9; currently recruiting)

- Dosing and schedules: 50 µg MWF/37.5 µg QD/62.5 µg QD 14 days on/ 14 days off (+ all DEXA 40 mg QW)
- Most common* grade ≥3 AEs were anaemia, neutropenia and febrile neutropenia
- CFT7455 + DEXA shows promising results at low doses including best responses in patients who are refractory to BCMA-targeted therapies
- CFT7455 + DEXA is well tolerated with manageable neutropenia

Now enrolling: phase I dose escalation at 62.5 µg and phase I dose expansion cohort at 37.5 µg

*≥20%.

AE, adverse event; BCMA, B-cell maturation antigen; DEXA, dexamethasone; MWF, Monday, Wednesday, Friday; QD, once daily; QW, once weekly.

C4 Therapeutics. CFT7455 data presentation. Available at: https://bit.ly/3v4gDmd (accessed 13 December 2023).

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What are the key points for clinicians to be aware of when referring patients with relapsed/refractory multiple myeloma to clinical trials?

Clinical trial entry: Key considerations

Patient eligibility

- Limitation to enrolment: advanced age and comorbidities, especially RI and CVD[1]
- 40% of patients with NDMM in the Connect MM registry were ineligible for RCTs[2]
- Up to 72.3% of patients with RRMM in routine care did not meet eligibility criteria for one of the six hallmark RCTs[1]

Patient circumstances

- Distance from clinic[3,4]
- Ability to travel[5]
- Support network[5]
- Frequency of appointments[4]

NCCN encourages any patient with cancer to participate in a clinical trial[6]

Additional considerations:

- Timing for considering a patient for a clinical trial[5]
- Ensuring patients provide informed consent[7]
- Tackling enrolment disparities[8,9]

CVD, cardiovascular disease; MM, multiple myeloma; NCCN, National Comprehensive Cancer Network; NDMM, newly diagnosed MM; RCT, randomized controlled trial; RI, renal impairment; RRMM, relapsed/refractory MM.

1. Chari A, et al. *Clin Lymphoma Myeloma Leuk*. 2020;20:8–17; 2. Shah JJ, et al. *Clin Lymphoma Myeloma Leuk*. 2017;17:575–83; 3. Malave GC, et al. *Blood*. 2019;134(Suppl. 1):5833; 4. Kessel KA, et al. *Clin Transl Radiat Oncol*. 2018;13:44–9; 5. Boquoi A, et al. *Cancers*. 2022;14:2147; 6. NCCN. Multiple myeloma. V2.2024. Available at: myeloma.pdf (nccn.org) (accessed 5 January 2024); 7. Gregersen TA, et al. *Nurs Health Sci*. 2022;24:65–72; 8. Kanapuru B, et al. *Blood*. 2023;142:235–43; 9. Duma N, et al. *Oncologist*. 2018;23:1076–8.

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