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The rationale for protein degradation and immunomodulation in RRMM: Highlighting the latest data and available clinical trials

Practice aid for relapsed/refractory multiple myeloma

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Protein degradation and immunomodulatory approaches in multiple myeloma

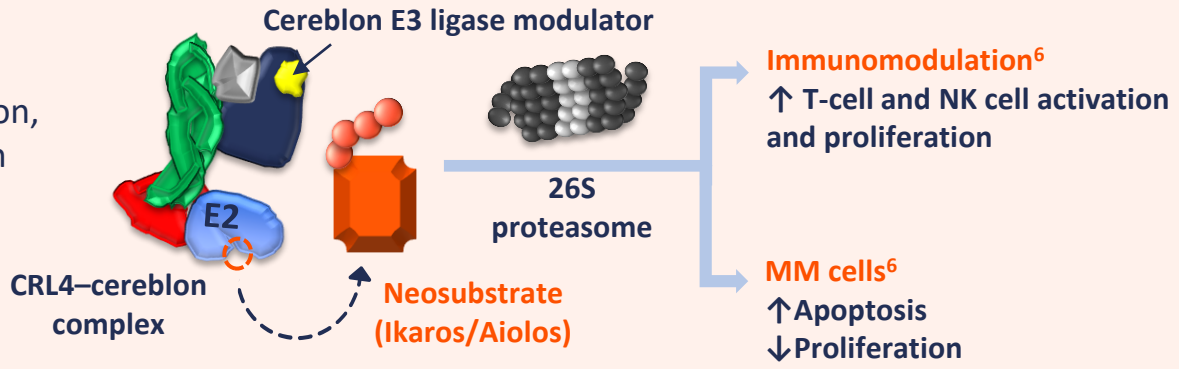
Why target cereblon in the treatment of RRMM?

- Cereblon is a component of the functional E3 ubiquitin ligase complex[1]
- It acts as a substrate receptor and targets proteins for degradation through the UPS[1]
- Neosubstrates of cereblon include Ikaros (IKZF1) and Aiolos (IKZF3), which sustain MM growth and survival[1–3]

Mechanisms of action of emerging therapies

Cereblon E3 ligase modulators

- Bind to a shallow hydrophobic pocket on the surface of cereblon, changing its conformation, to promote interaction with and degradation of target substrates[4,5]
- Investigational agents include iberdomide[6] and mezigdomide[7]



Degradation-activating compounds

- **Proteolysis-targeting chimera** act as a bridge between the E3 ligase and target protein to induce its polyubiquitination and proteasome-mediated degradation[8]
- **Monofunctional degraders** bind to the E3 ligase and modulate the surface to increase interaction with the target protein of interest;[9] investigational agents include CFT7455[10]

Latest data and ongoing clinical trials with iberdomide in RRMM

Data from phase I/II CC-220-MM-001 trial (NCT02773030)[11]

Phase I **dose escalation** (n=90) after ≥2 prior lines of therapy including lenalidomide/pomalidomide + a PI

- **RP2D: 1.6 mg**

Phase II **dose expansion** (n=107) following ≥3 prior lines of therapy and with triple-class refractory disease

- **ORR:** 26% (36.8% in patients exposed to BCMA-targeting therapy [n=38][12])

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

Ongoing clinical trials[13]

Phase III EXCALIBER-RRMM trial (NCT04975997)

Ongoing phase III study comparing iberDd versus DVd

Key inclusion criteria:

- Disease progression during or after last anti-myeloma regimen
- Received one or two prior lines of anti-myeloma therapy
- ECOG PS 0–2

Primary endpoint: PFS

Trial identifier	Phase	Study treatments
NCT05560399	I	Iber + elotuzumab + dexamethasone
NCT05896228	II	Iber-KDd for ~ 8 months, followed by iber monotherapy in absence of disease progression
NCT05354557	II	Iber as maintenance therapy after AHCT
NCT05583617 PLYCOM	I/II	Cevostamab + iber
NCT05289492	I/II	EOS884448 alone or with iber +/- dexamethasone

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Latest data and ongoing clinical trials with mezigdomide in RRMM

Data from phase I/II CC-92480-MM-001 trial (NCT03374085)[14]

Phase I **dose escalation** (n=77) following ≥3 prior lines of therapy, and disease progression on/within 60 days of last myeloma therapy

- **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) in patients with triple-class refractory disease (30% previous anti-BCMA therapy and 40% plasmacytomas)

- **ORR:** 41%
- **Median DOR**: 7.6 months
- **Median PFS**: 4.4 months

Grade ≥3/4 TEAEs (≥30% in dose escalation and expansion cohorts): Neutropenia, infection and anaemia

Data from phase I/II CC-92480-MM-002 trial (NCT03989414)[15]

Patients had received 2–4 prior lines of therapy, with minimal response or better to ≥1 prior regimen and disease progression during or after last therapy

MeziDd (n=56)	MeziEd (n=20)
ORR: 78%*	ORR: 45%

Most common grade 3/4 TEAEs (≥20% in any subcohort): Neutropenia, anaemia and infections

Low non-haematological **grade 3/4 TEAEs**

Ongoing clinical trials[13]

Phase III SUCCESSOR-1 trial (NCT05519085): MeziVd vs PVd

Key inclusion criteria:

- Received 1–3 prior lines of anti-myeloma therapy
- MR or better to ≥1 prior anti-myeloma therapy

Phase III SUCCESSOR-2 trial (NCT05519085): MeziKd vs Kd

Key inclusion criteria:

- ≥1 prior line of anti-myeloma therapy
- Prior treatment with lenalidomide and ≥2 cycles of an anti-CD38 mAb
- MR or better to ≥1 prior anti-myeloma therapy
- Documented disease progression during or after their last antimyeloma regimen

Trial identifier	Phase	Study treatments
NCT03989414	I/II	Mezi + standard treatment
NCT05981209	Ib	Mezi + elotuzumab and dexamethasone
NCT06050512	I/II	Mezi + ixazomib and dexamethasone
NCT06048250	I	Mezi and dexamethasone post idecabtagene vicleucel
NCT05372354	Ib/IIa	Mezi in novel therapeutic combinations

* Combined ORR for the three subcohorts.

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Latest data and ongoing clinical trials with CFT7455 in RRMM

CFT7455 trial study design (NCT04756726)[13]

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

Key inclusion criteria:

- Documented diagnosis of MM and measurable disease at enrolment
- ≥3 prior anti-myeloma regimens, including ≥2 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

Now enrolling: phase I dose escalation at 62.5 µg and phase I dose expansion cohort at 37.5 µg[16]

Phase I dose escalation study preliminary results[16]

CFT7455 monotherapy (n=22; completed)	CFT7455 + DEXA (n=9; currently recruiting)
➢ 14 days on/14 days off schedule ➢ 75 µg was maximum administered dose ➢ Most common* grade ≥3 AE was neutropenia; no DLT results in discontinuations ➢ All patients receiving 75 µg achieved stable disease or better (n=4)	➢ 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 ➢ Shows promising results at low doses, including best responses in patients who are refractory to BCMA-targeted therapies

Clinical trial entry: Key considerations

NCCN encourages any patient with cancer to participate in a clinical trial[17]

Patient eligibility

Limitation to enrolment: advanced age and comorbidities, especially RI and CVD[18]

Patient circumstances

- Distance from clinic[19,20]
- Support network[21]
- Ability to travel[21]
- Frequency of appointments[20]

Additional considerations:

- Timing for considering a patient for a clinical trial[21]
- Ensuring patients provide informed consent[22]
- Tackling enrolment disparities[23,24]

*≥20%

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Abbreviations and references

Abbreviations

↓, decrease; ↑, increase; AE, adverse event; AHCT, autologous haematopoietic cell transplantation; BCMA, B-cell maturation antigen; CD, cluster of differentiation; CVD, cardiovascular disease; Dd, daratumumab and DEXA; DEXA, dexamethasone; DLT, dose-limiting toxicity; DOR, duration of response; DVd, daratumumab, bortezomib and DEXA; ECOG PS, Eastern Cooperative Oncology Group performance status; iber, ibderdomide; IKZF1/3, IKAROS family zinc finger 1/3; Kd, carfilzomib and DEXA; KDd, carfilzomib, daratumumab and DEXA; mAb, monoclonal antibody; mezi, mezigdomide; meziDd, mezi, daratumumab and DEXA; meziEd, mezi, elotuzumab and DEXA; MeziKd, mezi, carfilzomib and DEXA; MeziVd, mezi, bortezomib and DEXA; MM, multiple myeloma; MR, minimal response; MWF, Monday, Wednesday, Friday; NCCN, National Comprehensive Cancer Network; NHL, non-Hodgkin's lymphoma; ORR, overall response rate; PFS, progression-free survival; PI, proteasome inhibitor; PVd, pomalidomide, bortezomib and DEXA; QD, once daily; QW, once weekly; RI, renal impairment; RP2D, recommended phase II dose; RR, relapsed or refractory; TEAE, treatment-emergent AE; UPS, ubiquitin-proteasome system.

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