Improving outcomes in multiple myeloma with new treatment targets

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Expert panel

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Agenda

Which novel targets are currently being investigated in relapsed/refractory multiple myeloma?
Presenter: Joseph Mikhael
Panel discussion: Cristina Gasparetto and Elena Zamagni, moderated by Joseph Mikhael

How can we best manage the adverse events associated with these treatments?
Presenter: Joseph Mikhael
Panel discussion: Cristina Gasparetto and Elena Zamagni, moderated by Joseph Mikhael

Could agents with novel targets be used earlier in the multiple myeloma treatment pathway?
Presenter: Joseph Mikhael
Panel discussion: Cristina Gasparetto and Elena Zamagni, moderated by Joseph Mikhael

Which novel targets are currently being investigated in relapsed/refractory multiple myeloma?

Prof. Joseph Mikhael

Professor in Applied Cancer Research and Drug Discovery Division
Translational Genomics Research Institute, Phoenix, AZ, USA

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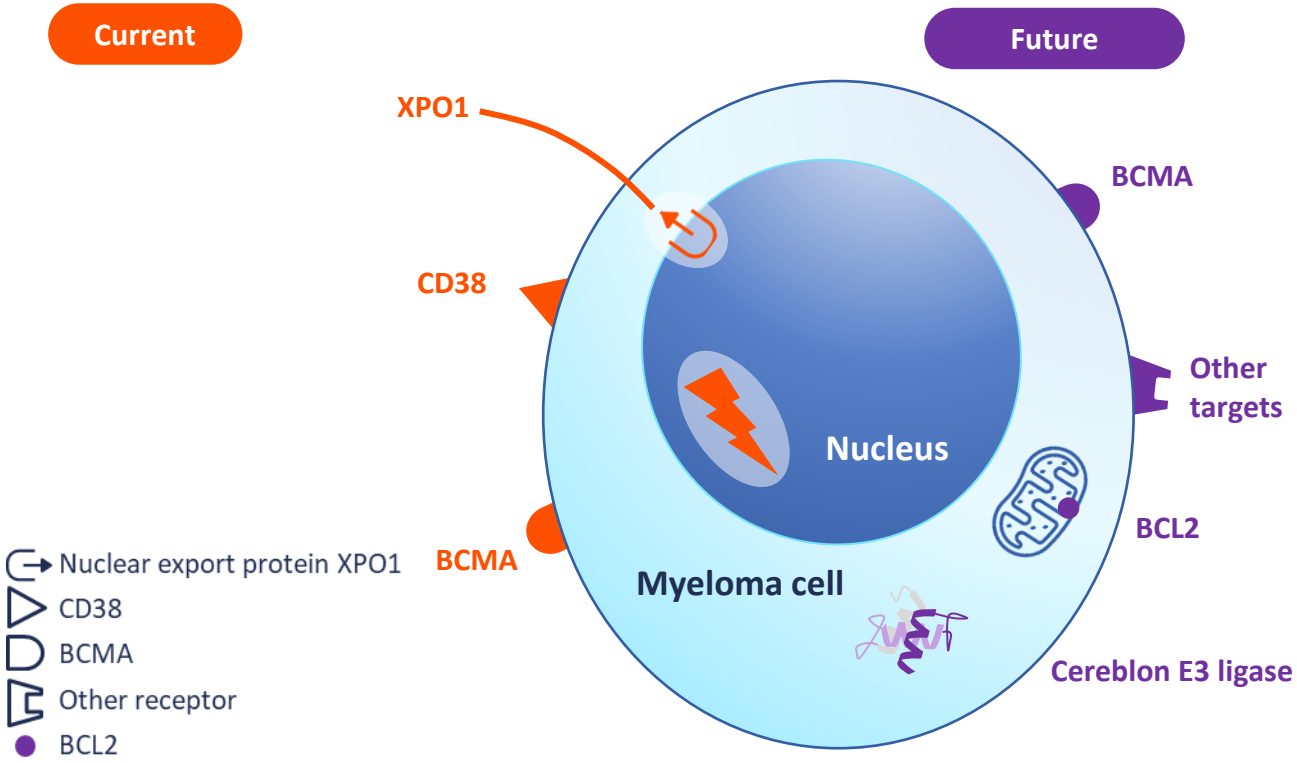
Plasma cell targets in R/R multiple myeloma



BCL2, B-cell lymphoma 2; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T-cell; R/R, relapsed/refractory; XPO1, exportin 1.
Sourced from: www.clinicaltrials.gov (accessed February 2021).

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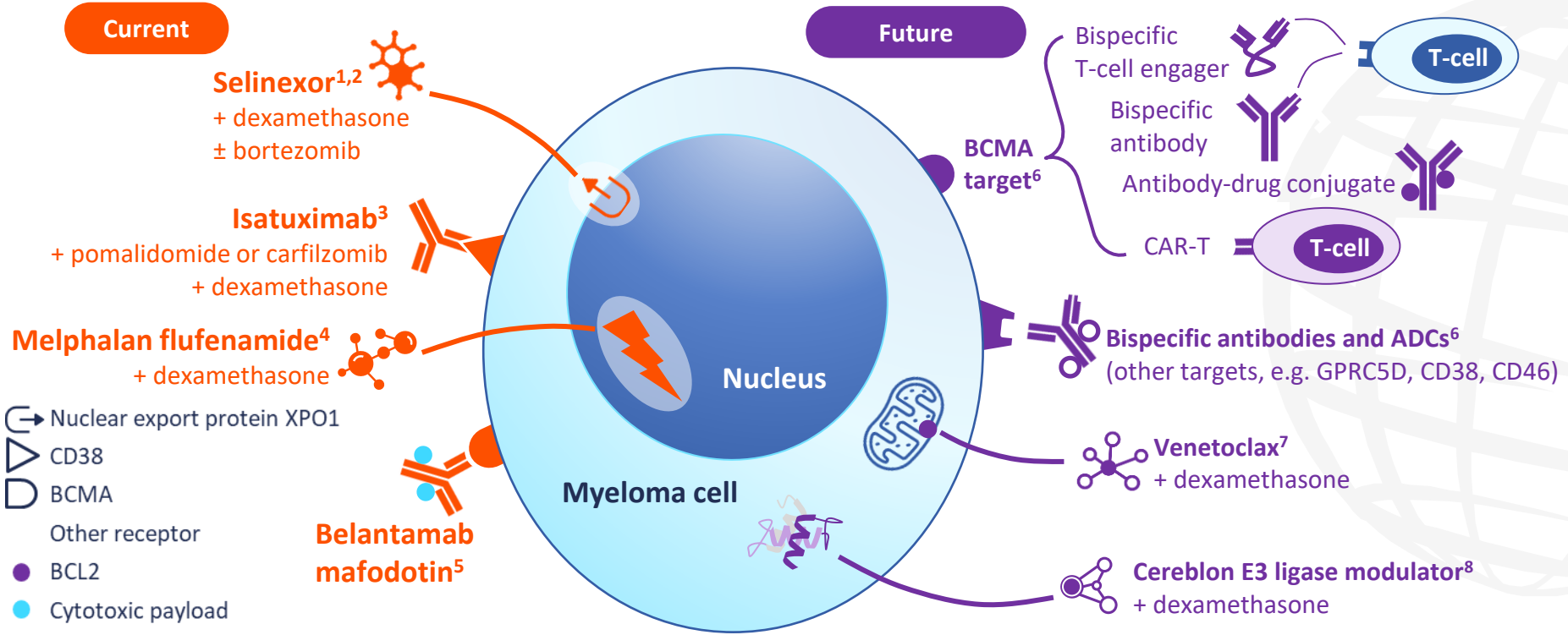
Plasma cell targets in R/R multiple myeloma



ADC, antibody drug conjugate; BCL2, B-cell lymphoma 2; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T-cell; R/R, relapsed/refractory; XPO1, exportin 1.

1. Chari A, et al. *New Engl J Med*. 2019;381:727–38; 2. Dimopoulos MA, et al. *J Clin Oncol*. 2020;38(Suppl):abstract 8501; 3. Richardson PG, et al. *Exp Opin Biol Ther*. 2020;20:1395–404; 4. Richardson PG, et al. *J Clin Oncol*. 2021;39:757–67; 5. Lonial S, et al. *Lancet Oncol*. 2020;21:207–21; 6. Barilà G, et al. *Pharmaceuticals.* 2021;14:40; 7. Kaufman JL, et al. *Am J Hematol*. 2020; doi: 10.1002/ajh.26083; 8. Rajkumar SV, et al. *Blood Cancer J.* 2020;10:94.

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Ongoing development of novel agents

	Phase III	Phase II	Phase I and I/II
Selinexor	+ Vd 1–3 prior lines	+ Vd 1 prior line, triple-refractory + VDd ≥3 prior lines + d ≥4 prior lines, penta-refractory	+ backbone treatments + melp 1–3 prior lines, then ASCT + dox + d ≥2 prior lines + Kd ≥2 prior lines
Isatuximab	+ KRd NDMM, transplant-eligible + VRd NDMM, transplant-ineligible + Kd 1–3 prior lines	+ KRd NDMM, transplant-eligible + KRd NDMM, high-risk + KPd 2–3 prior lines	+ ben + p triple-refractory + cem ≥3 prior lines + d + pom/aTGFβ ≥3 prior lines
Belantamab mafodotin	+ Vd ≥1 prior line + Pd ≥1 prior line Mono ≥2 prior lines	+ R/V+ d ≥1 prior line + pembro ≥3 prior lines + inv ≥3 prior lines	+ standard of care NDMM
Melphalan flufenamide	+ Dd ≥3 prior lines + d 2–4 prior lines, R-refractory	+ d ≥2 prior lines	
BCMA CAR-T	(1 agent) 1–3 prior lines	(2 agents) ≥3 prior lines	(3 agents) ≥2/3 prior lines
Venetoclax	+ d ≥2 lines, t(11;14)+		+ MAPKi ± atez 3–5 prior lines

ADCs
1 x BCMA-targeted
1 x CD46-targeted
≥3 prior lines

Cereblon E3 ligase modulator
+ d ≥3 lines
+ d + V/D/K any prior lines

Bispecific antibodies
5 x BCMA-targeted
1 x CD38-targeted
1 x GPRC5d-targeted
≥2–3 prior lines
alone or + CPI or IMiD or D

Bispecific T-cell engager
≥3 prior lines

ADC, antibody frug conjugate; ASCT, autologous stem cell transplant; atez, atezolizumab; aTGFβ, anti-transforming growth factor beta antibody; BCMA, B-cell maturation antigen; ben, bendamustine; CAR-T, chimeric antigen receptor T-cell; cem, cemiplimab; CPI, checkpoint inhibitor; d, dexamethasone; D, daratumumab; dox, liposomal doxorubicin; IMiD, immunomodulatory imide drug; inv, investigational therapies; K, carfilzomib; MAPKi, mitogen-activated protein kinase inhibitor; melp, melphalan; mono, monotherapy; NDMM, newly diagnosed multiple myeloma; p, prednisone; P, pomalidomide; pembro, pembrolizumab; R, lenalidomide; V, bortezomib.
Sourced from: www.clinicaltrials.gov (accessed February 2021).

How can we best manage the adverse events associated with these treatments?

Prof. Joseph Mikhael

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Common adverse events with MM therapies

Selinexor[1]

- Nausea, vomiting, diarrhoea
- Thrombocytopenia, anaemia, neutropenia
- Fatigue, decreased appetite, hyponatraemia, weight loss

Isatuximab[2]

- IRRs
- Fatigue
- Nausea
- Lymphopenia, neutropenia, anaemia, thrombocytopenia

Belantamab mafodotin[3]

- Keratopathy
- Thrombocytopenia, anaemia

Melphalan flufenamide[4]

- Nausea, diarrhoea
- Pneumonia, fatigue, asthenia, pyrexia
- Neutropenia, anaemia, thrombocytopenia

CAR-T[5]

- CRS
- Neurotoxicity
- Cytopenias

CAR-T, chimeric antigen receptor T-cell; CRS, cytokine release syndrome; IRR, infusion-related reaction; MM, multiple myeloma.

1. Mikhael J, et al. *Clin Lymphoma Myeloma Leuk.* 2020;20:351–7; 2. Richardson PG, et al. *Exp Opin Biol Ther*. 2020;20:1395–404; 3. Lonial S, et al. *Lancet Oncol*. 2020;21:207–21; 4. Richardson PG, et al. *J Clin Oncol*. 2021;39:757–67; 5. Zhou X, et al. *Front Immunol.* 2020;11:620312.

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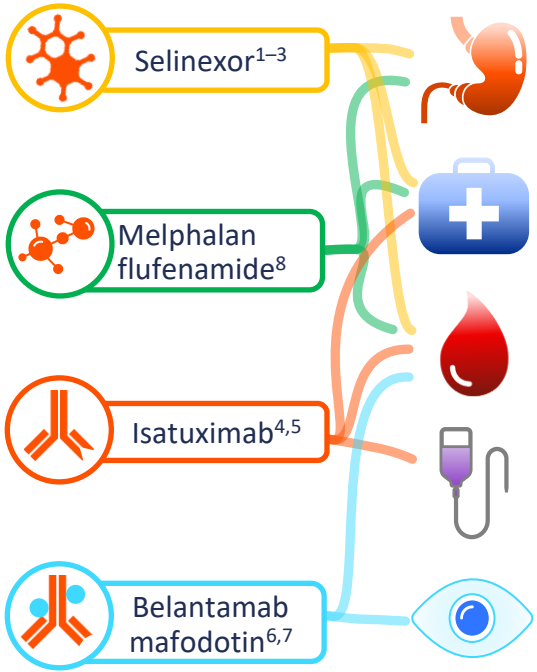
Adverse event management with approved therapies

PROPHYLACTIC AND SUPPORTIVE MEASURES



Nausea/ vomiting	Prophylactic 5-HT3 antagonists, NK1 antagonists, olanzapine, dronabinol
Diarrhoea	Hydration, loperamide, bismuth subsalicylate
Fatigue	Methylphenidate
Low appetite	Megestrol, cannabinoids, olanzapine
Hyponatraemia	Sodium replacement
Cytopenias	GCSF, platelet transfusions, thrombopoietin receptor agonists
Infections	Antibiotic/antiviral prophylaxis
Infusion reactions	Paracetamol, diphenhydramine, corticosteroids
Dry eye	Lubricant eye drops
Keratopathy	Regular monitoring

See specific consensus recommendations for selinexor[3]

DOSE MODIFICATION AND INTERRUPTION
Reduce dose
Change schedule
Drug holidays

GCSF, granulocyte colony stimulating factor; MM, multiple myeloma; NK1, neurokinin 1.; PI, prescribing information.

1. Gavriatopolou M, et al. *Leukemia.* 2020;34:2430–40; 2. Chen C, et al. *Blood.* 2018;131:855–63; 3. Mikhael J, et al. *Clin Lymph Myeloma Leuk.* 2020;20:351–7; 4. Richardson PG, et al. *Expert Opin Biol Ther*. 2020;20:1395–403; 5. Sarclisa PI. 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/761113s000lbl.pdf (accessed 12 March 2021); 6. Lassiter G, et al. *Curr Oncol.* 2021;28:640–60; 7. Blenrep PI. 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/761158s000lbl.pdf (accessed 12 March2021); 8. Richardson PG, et al. *J Clin Oncol*. 2021;39:757–67.

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Could agents with novel targets be used earlier in the multiple myeloma treatment pathway?

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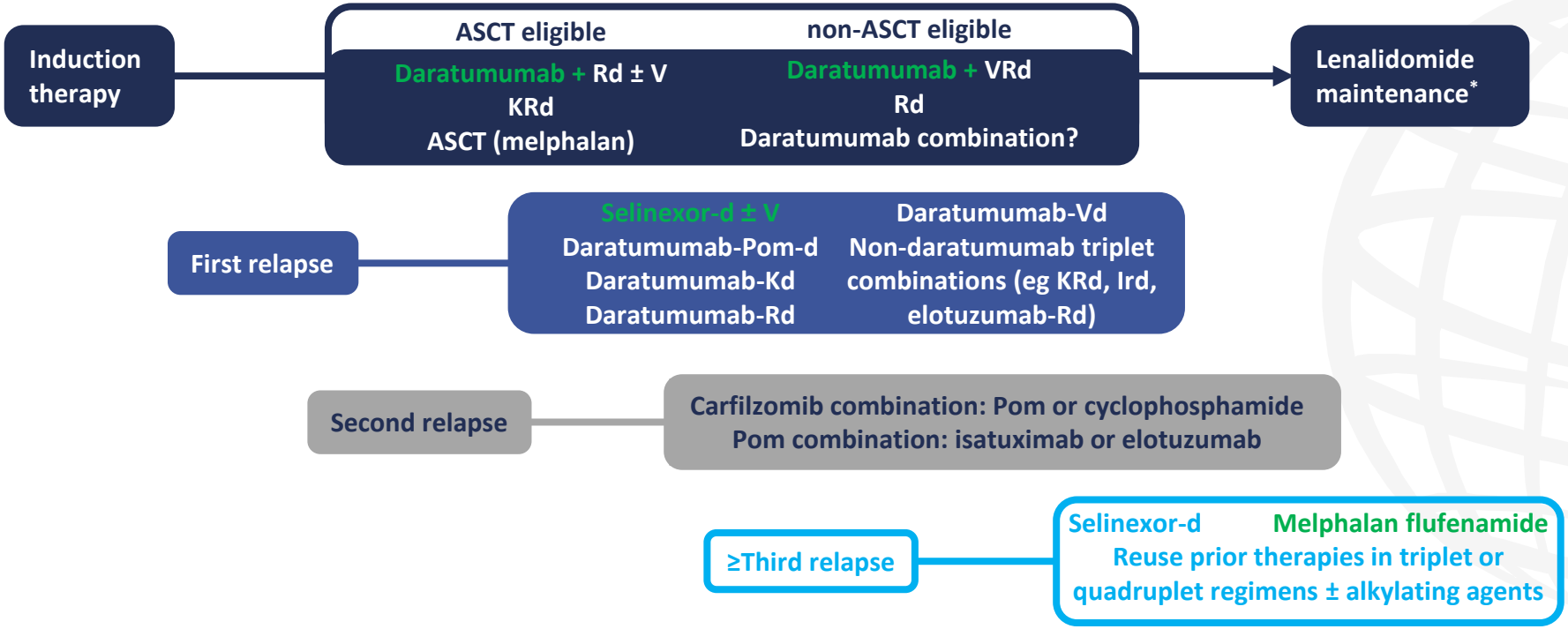
Efficacy data for approved therapies

	Selinexor[1,2]		Isatuximab[3,4]		Belantamab mafodotin[5,6]	Melphalan flufenamide[7]
Setting	≥4 prior therapies (STORM)	1–3 prior therapies (BOSTON)	≥2 prior therapies (ICARIA-MM)	1–3 prior therapies (IKEMA)	≥3 prior therapies (DREAMM-2)	≥2 prior therapies and ref to P + anti-CD38
Regimen	Selinexor + d	Selinexor + Vd	Isatuximab + Pd	Isatuximab + Kd	Belantamab mafodotin + Vd	Melphalan flufenamide
ORR	26.3%	76.4%	60.4%	86.6%	31.0%	29.0%
mPFS	3.7 months	13.93 months	11.53 months	NR	mDOR 2.9 months[6]	4.2 months

d, dexamethasone; DOR, duration of response; K, carfilzomib; m, median; MM, multiple myeloma; NR, not reached; ORR, overall response rate; P, pomalidomide; PFS, progression-free survival; PI, prescribing information; ref, refractory; V, bortezomib.

1. Chari A, et al. *N Engl J Med.* 2019;381:727–38; 2. Dimopoulos MA, et al. *J Clin Oncol.* 2020;38(Suppl):abstract 8501; 3. Sarclisa PI. 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/761113s000lbl.pdf (accessed 12 March 2021); 4. Moreau P. et al. EHA25 2020;abstract LB2603; 5. Blenrep PI. 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/761158s000lbl.pdf (accessed 12 March 2021); 6. Lonial S, et al. *Lancet Oncol.* 2020;21:207–21; 7. Richardson PG, et al. *J Clin Oncol.* 2021;39:757–67.

Developing the treatment paradigm in MM



Agents in green are newly approved in this setting.

*V-based consolidation or maintenance therapy has been used off label after the initial treatment of MM for those with high-risk disease.

ASCT, autologous stem cell transplant; d, dexamethasone; I, ixazomib; K, carfilzomib; MM, multiple myeloma; Pom, pomalidomide; R, lenalidomide; V, bortezomib.

Adapted from: Kumar SK, et al. *J Natl Compr Canc Netw.* 2020;18:1685–717; Rajkumar SV and Kumar S. *Blood Cancer J.* 2020;10:94.

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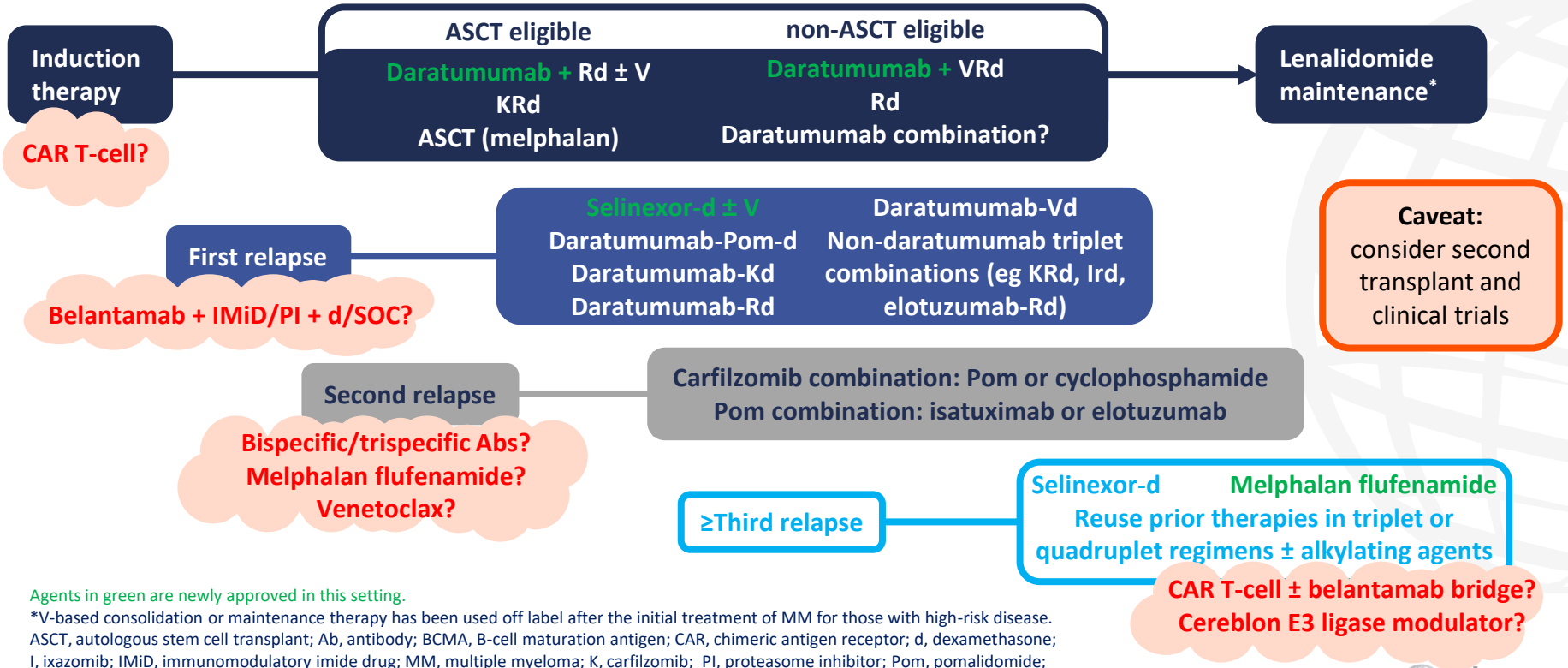
Developing the treatment paradigm in MM



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Summary

The discovery of new targets has resulted in novel therapies for multiple myeloma

- Ongoing trials will be important to determine depth and duration of response

Novel targeted agents have different safety profiles and risks

- Important to monitor patients for toxicities and manage adverse events proactively

Multiple myeloma is a highly heterogeneous disease

- Opportunities to personalize treatment using novel combinations with the potential to improve long-term outcomes