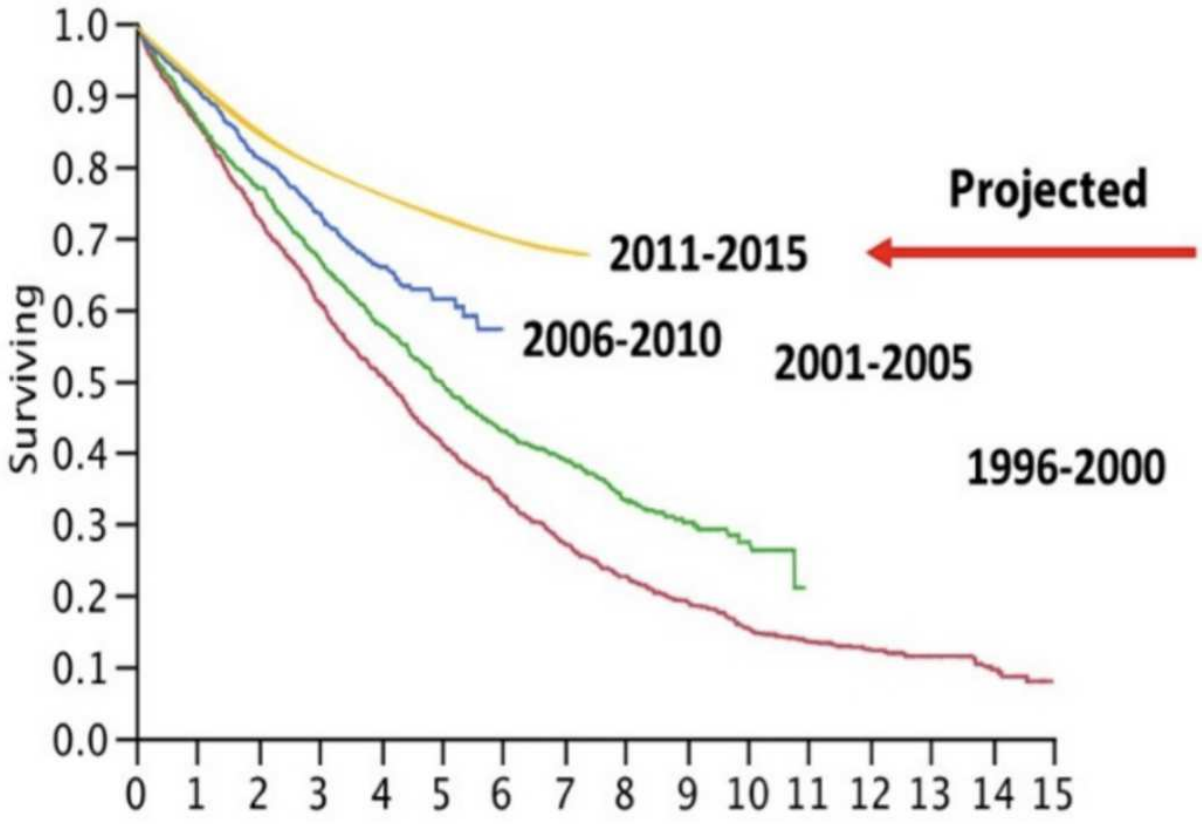
Treatment strategy for R/R multiple myeloma

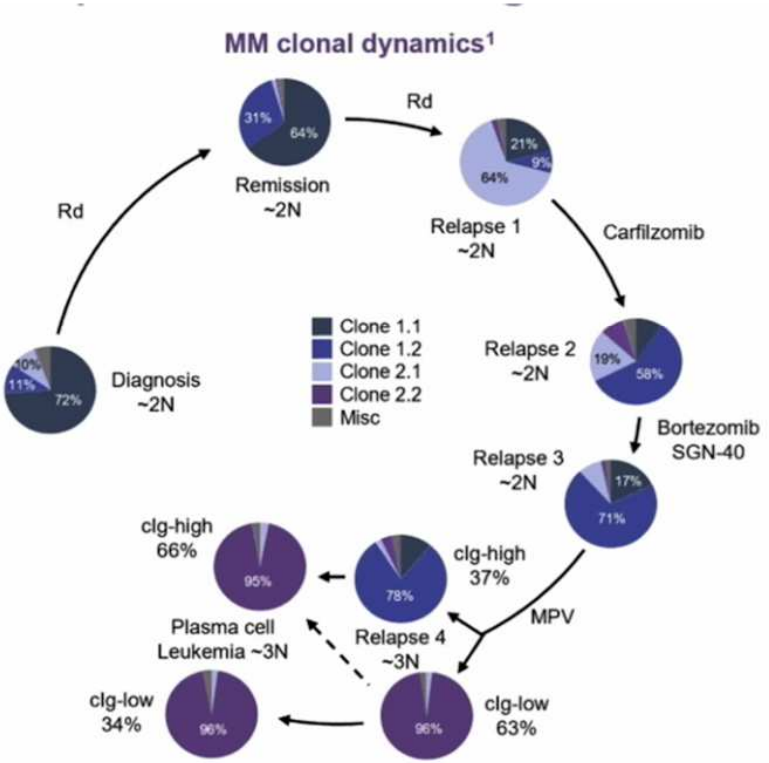
林精湛

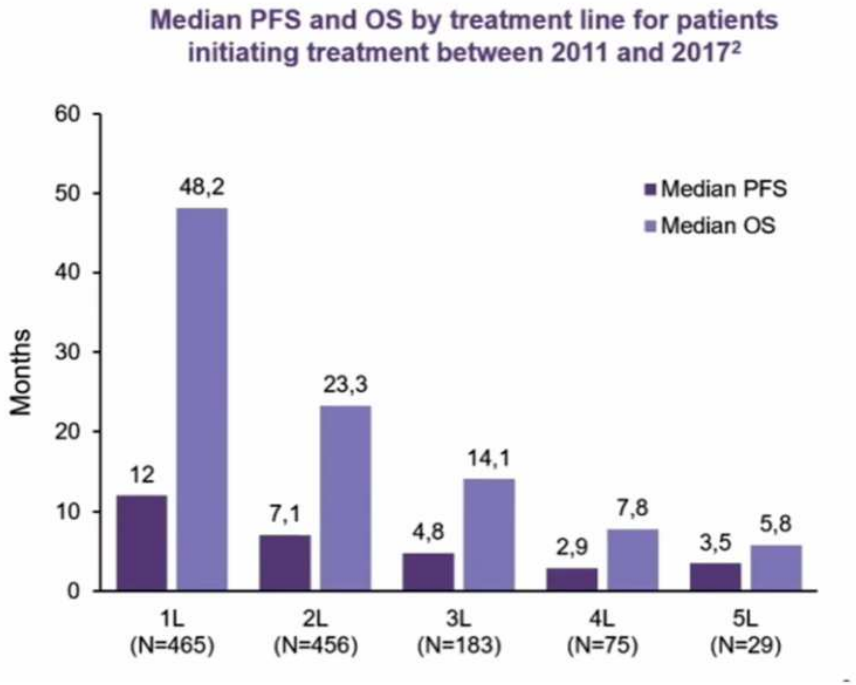
Projected survival for MM



Kumar S. Blood 2008;111: 2516 – 2520; Kumar S. Leukemia (2014) 28, 1122–1128.

Eventually relapse after transplant; responses declining with each subsequent relapse



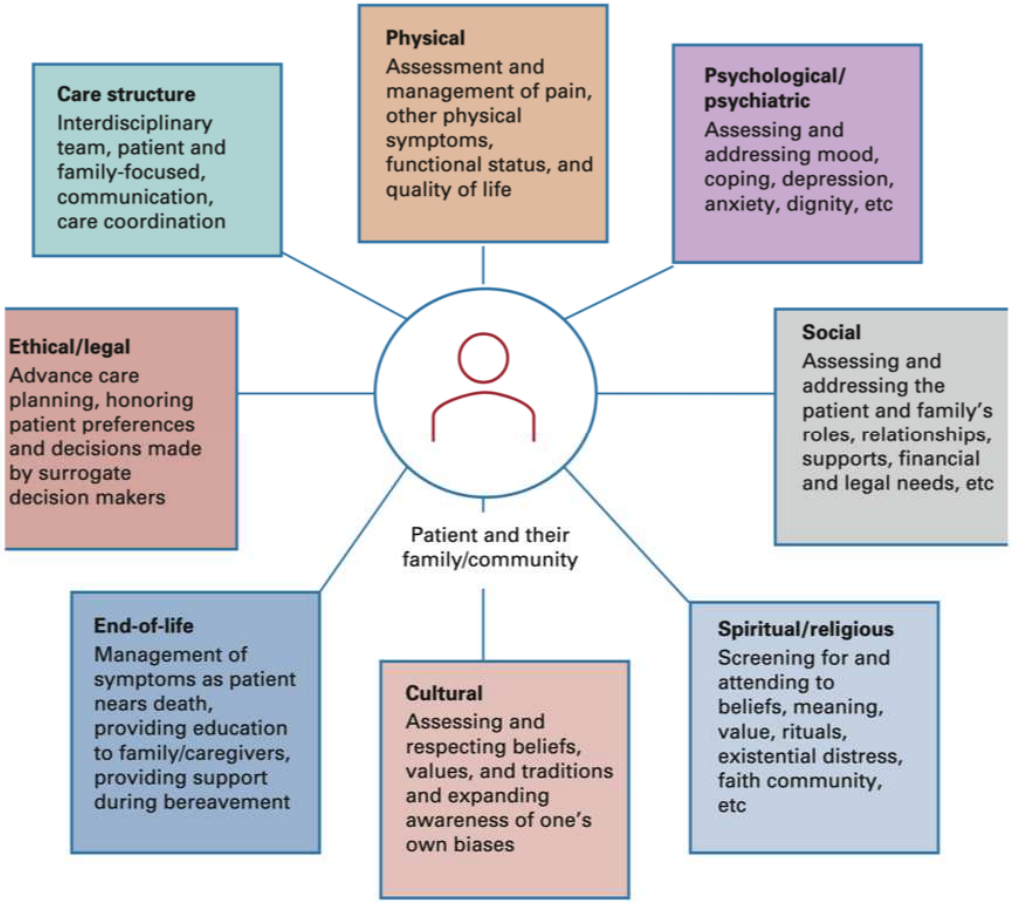


For advanced–stage disease, multiple comorbidities, or older age, cutting–edge cancer therapeutics are not enough

Domains of high quality palliative care

To help patients live better and, in some care, longer with evidence base

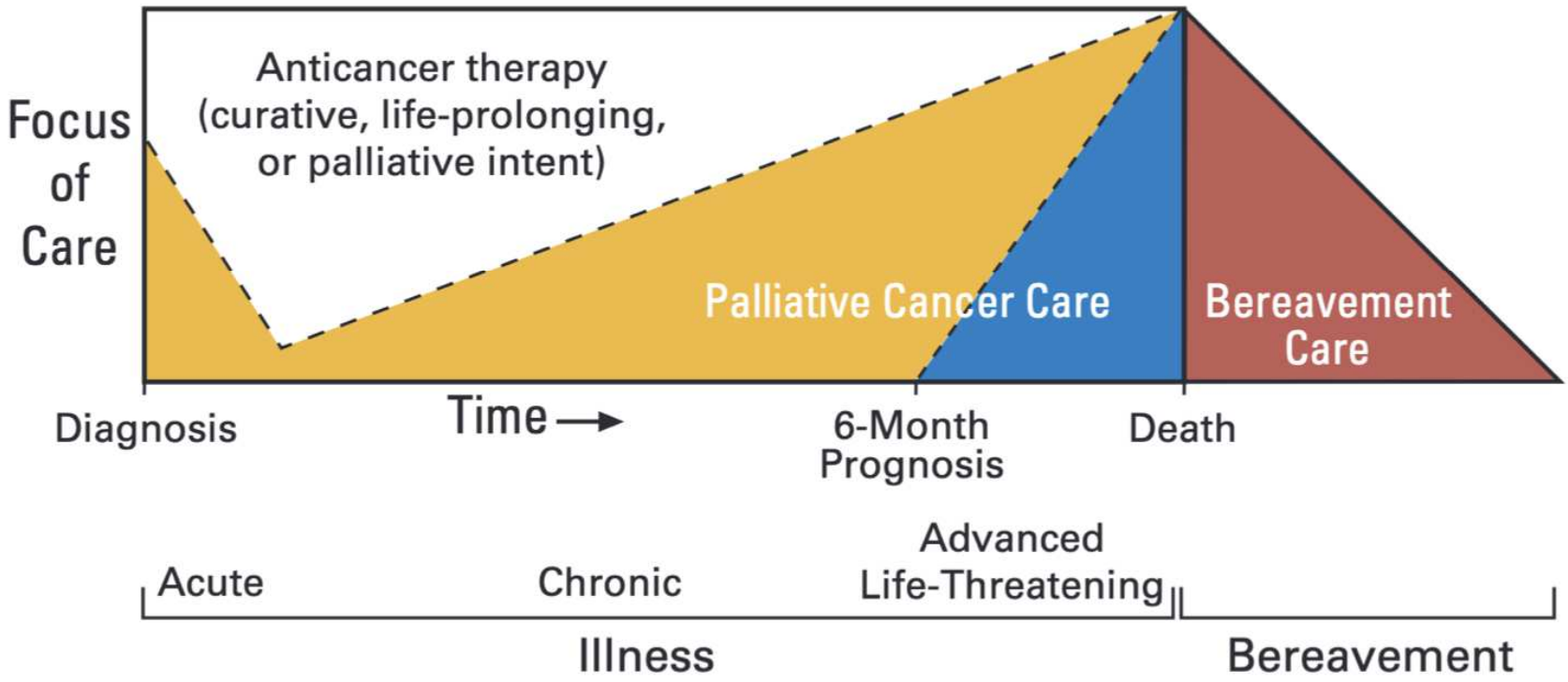
An essential element of high-quality cancer care



Daubman B-R, Rosenberg LB, Meier DE. Beyond the Fight: Why President Biden's Cancer Moonshot Must Include Palliative Care. J Clin Oncol 2023;41(6):1189–92.

Model of palliative cares

ASCO described "the oncologists' responsibility to care for their patients in a continuum that extends from the moment of diagnosis throughout the course



Ferris FD, Bruera E, Cherny N, et al. Palliative Cancer Care a Decade Later: Accomplishments, the Need, Next Steps—From the American Society of Clinical Oncology. J Clin Oncol 2009;27(18):3052–8.

Model of palliative care

An interdisciplinary team is required

Symptom

↓

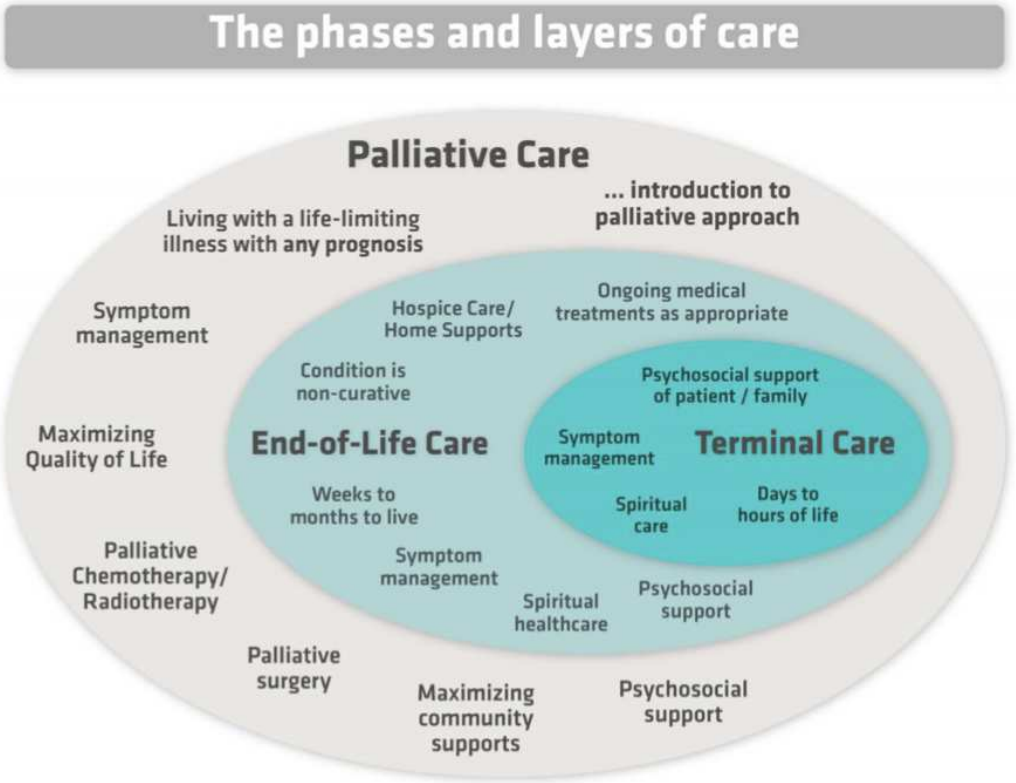
Assessment

↓

Decision-sharing management

Evidence_based medicine

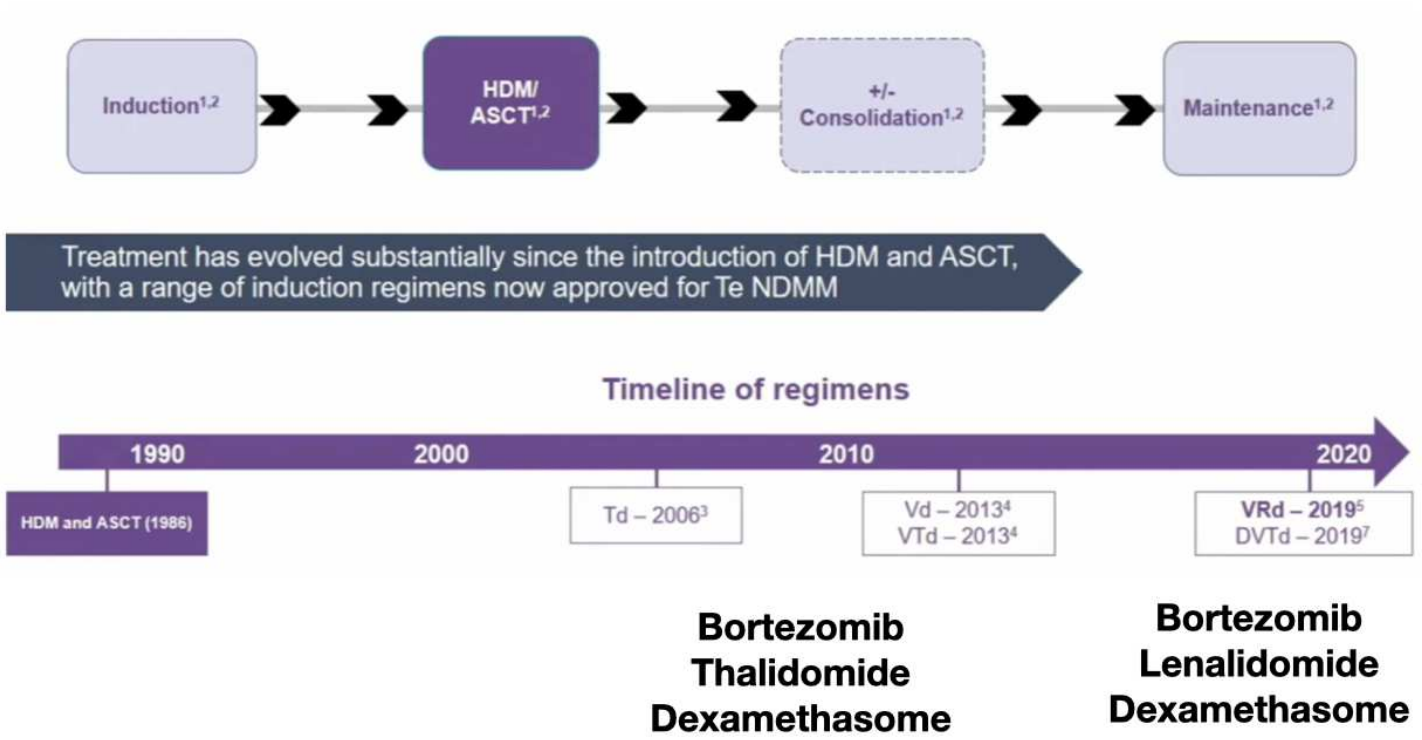
***Determination of capacity**
***Discussion goals of care**
***Requests for withdrawing therapy**
***Advanced care planning**
***Surrogate decision-making**
***Conflict resolution**



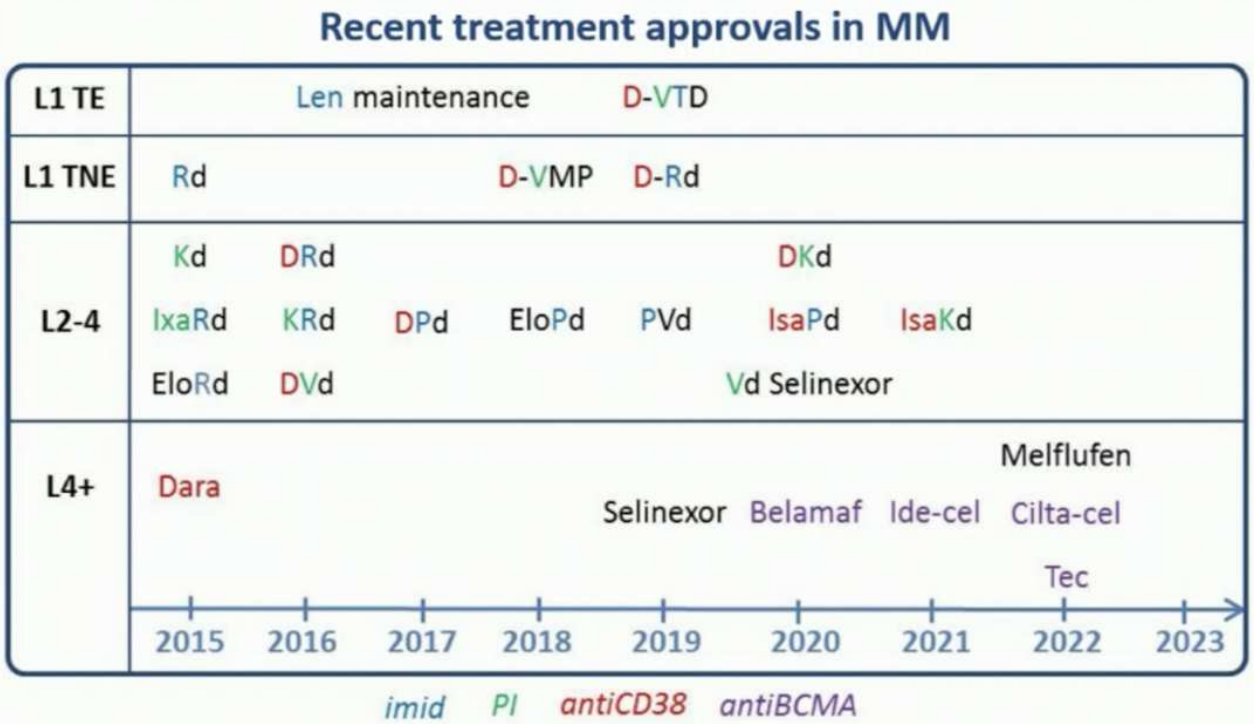
https://hpc.providencehealthcare.org/about/what-palliative-care

Reference

MM treatment algorithm



The treatment landscape is moving very fast



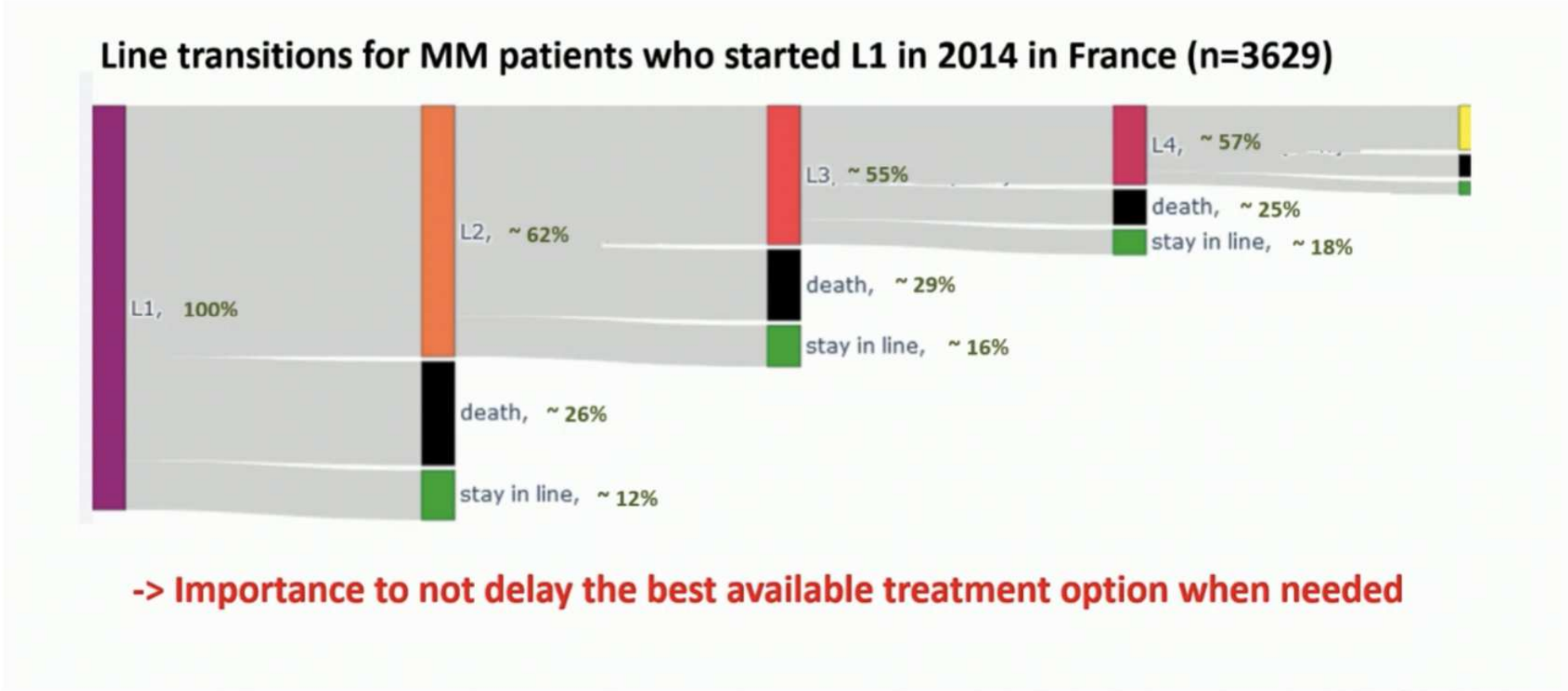
Since 2015,
25 new options approved !
for the treatment of MM

-> Define optimal sequence of treatment in multiple myeloma is challenging

Reference

EHA 2023

Line transitions and attrition rate in MM



-> Importance to not delay the best available treatment option when needed

Reference

EHA 2023

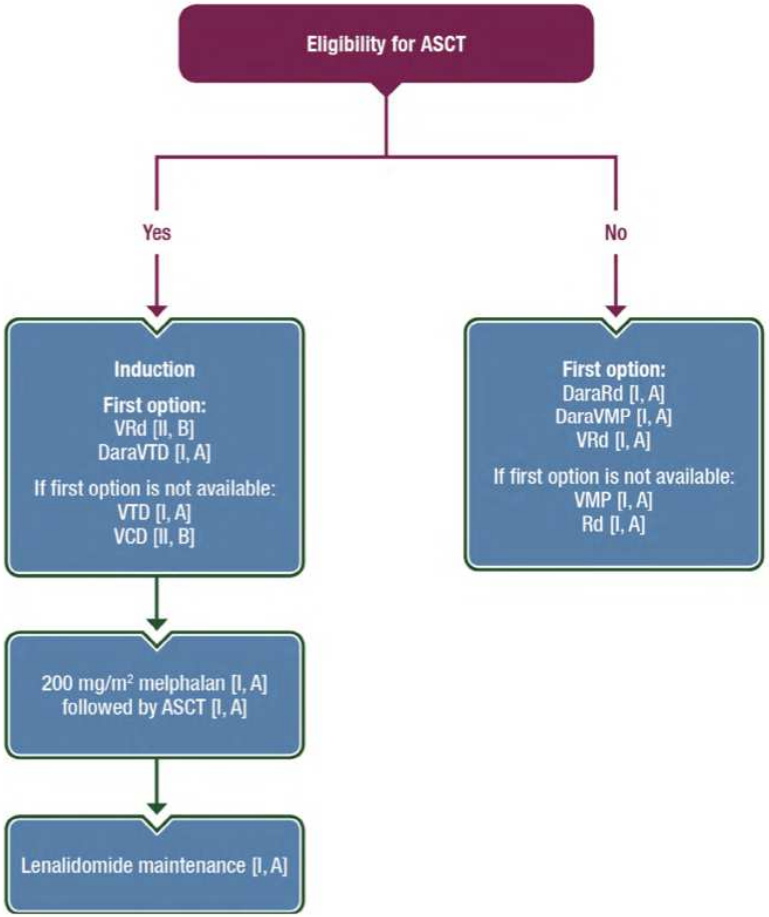
Frontline treatment for transplant-eligible patients

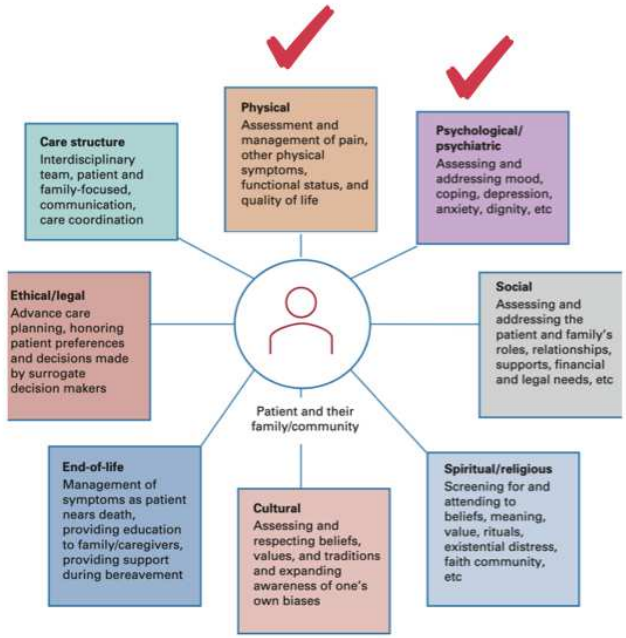
Triplet therapy:
- **VTD** (bortezomib, thalidomide, dexamethasone)
- **VRD** (bortezomib, lenalidomide, dexamethasone)

Covered by reimbursement

Quadruplet therapy:
- **Triplet therapy+ anti-CD38 antibodies**

In Taiwan, thalidomide maintenance or without maintenance

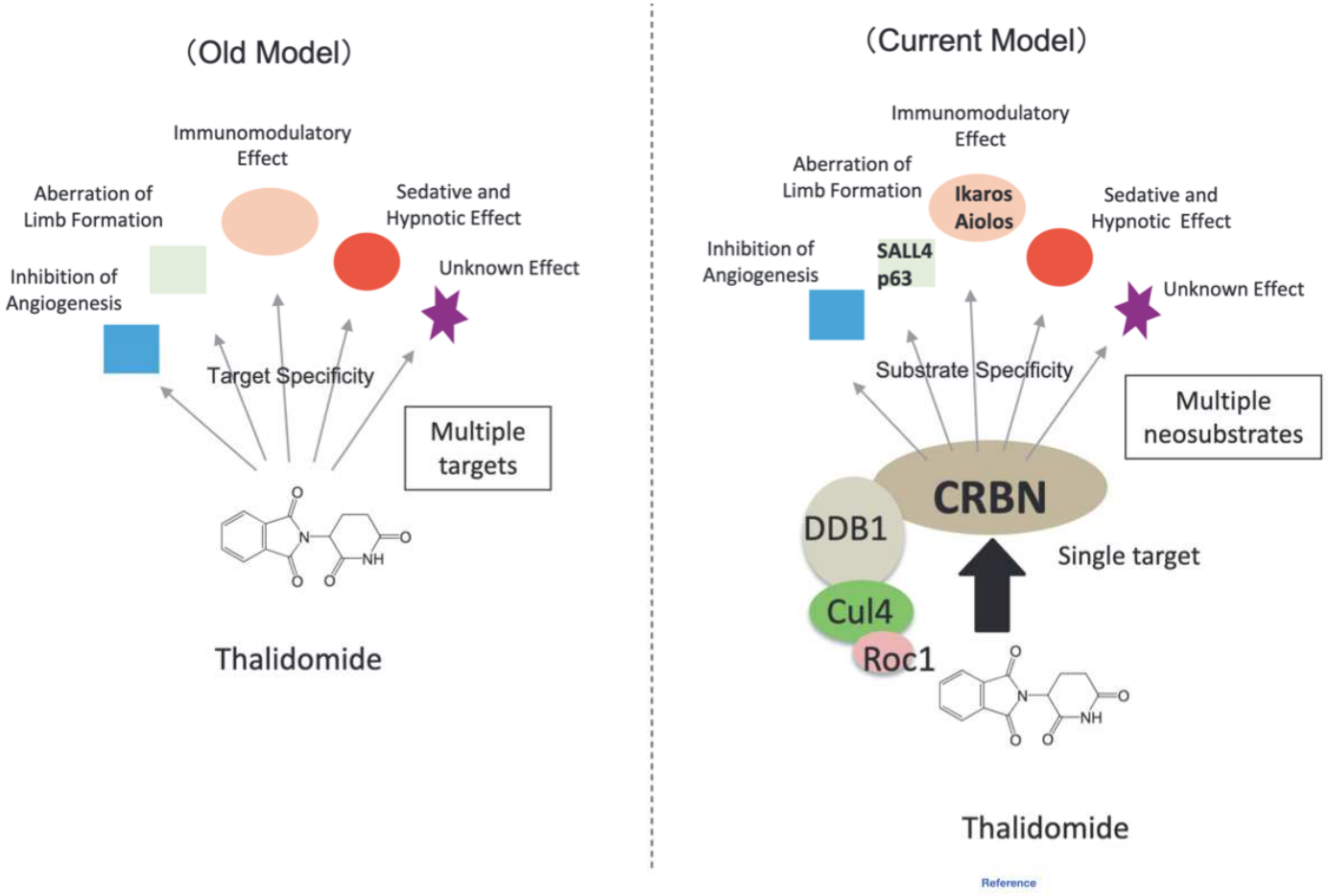




Reference

Dimopoulos MA, Moreau P, Terpos E, et al. Multiple Myeloma: EHA-ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. HemaSphere 2021;5(2):e528.

The proteasomal degradation of specific neosubstrate proteins underlies the clinical efficacy of thalidomide analogues

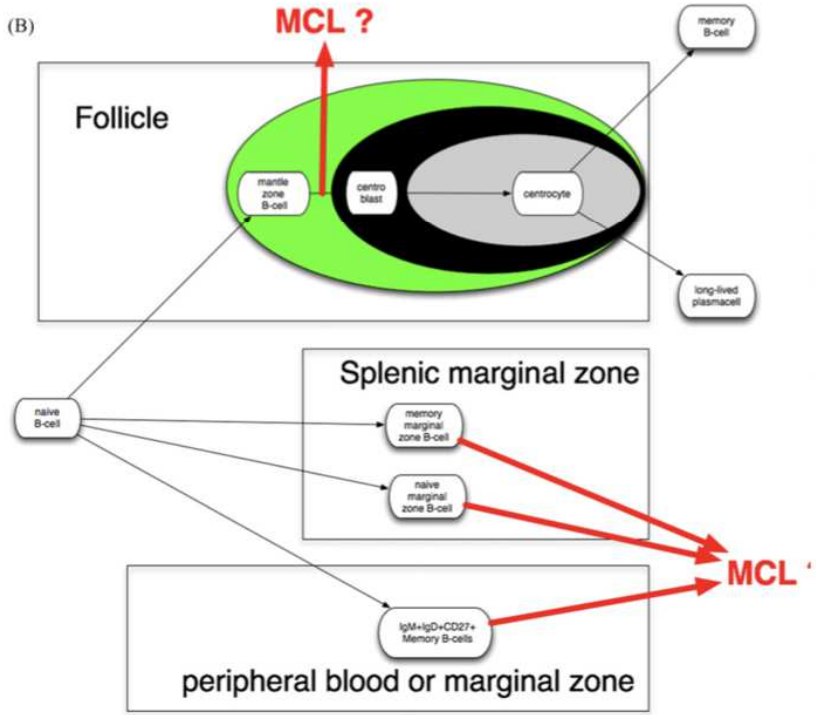


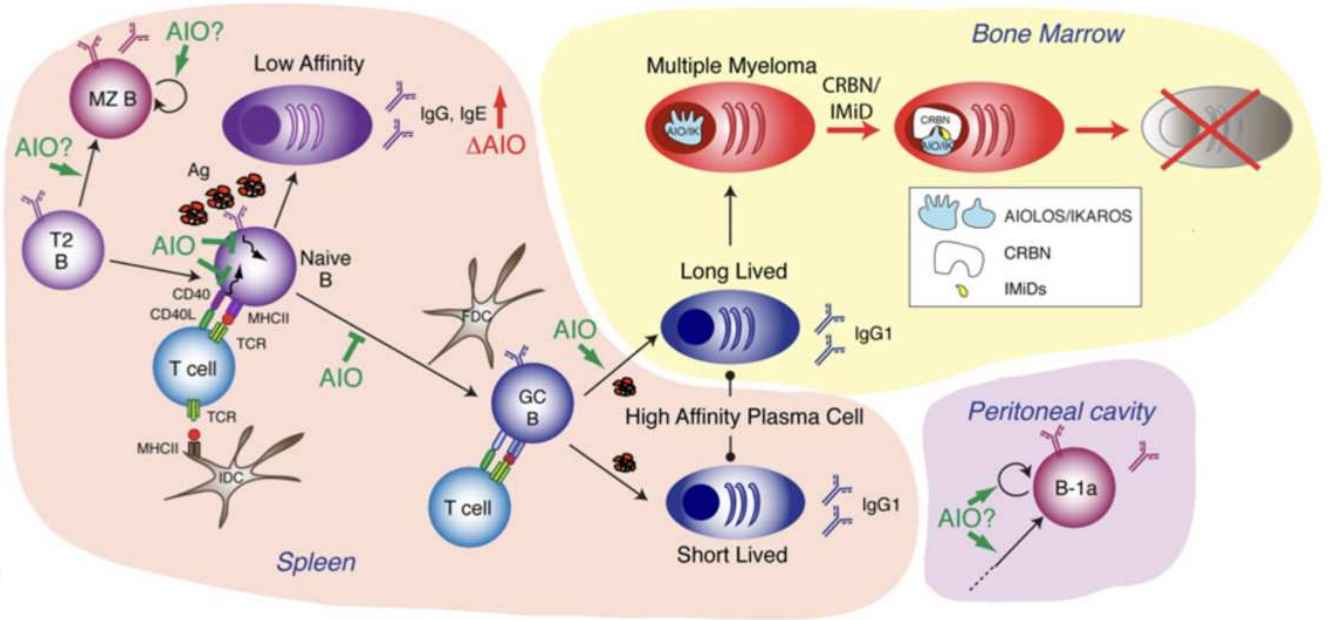
Reference

ITO T, HANDA H. Molecular mechanisms of thalidomide and its derivatives. Proc Jpn Acad, Ser B 2020;96(6):189–203. 10.2183/pjab.96.016

IKAROS regulated mature lymphocytic antigenic response and sustained long-lived plasma cells

The IKAROS family is critical for maintenance of terminally differentiated B cells

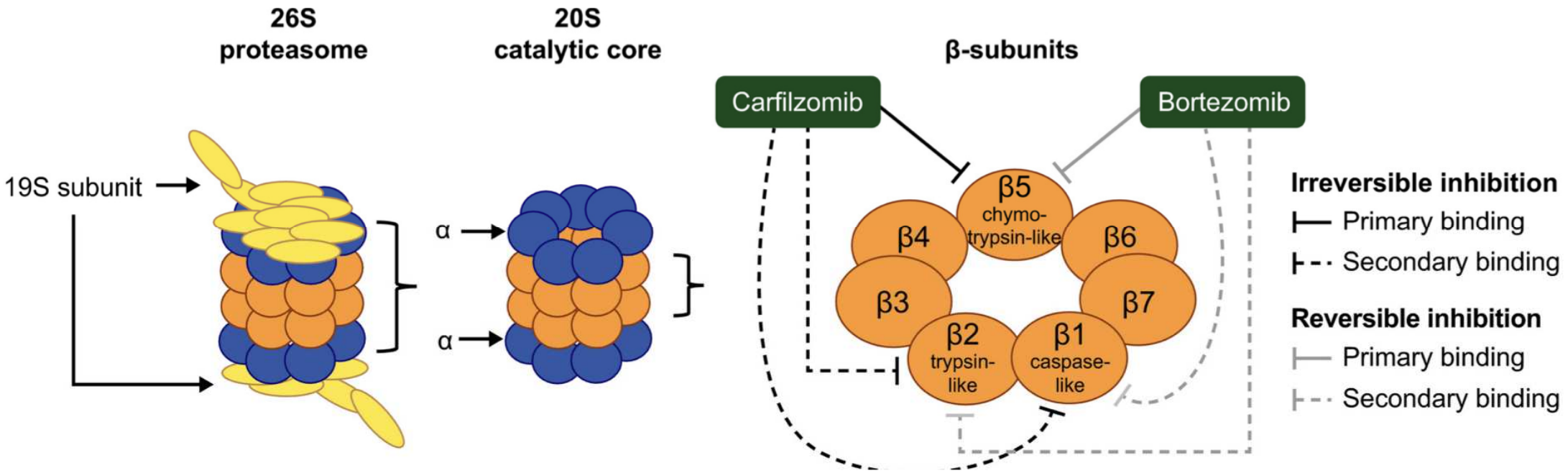




Bertoni F, Ponzoni M. The cellular origin of mantle cell lymphoma. Int J Biochem Cell Biol 2007;39(10):1747–53

Georgopoulos K. The making of a lymphocyte: the choice among disparate cell fates and the IKAROS enigma. Genes Dev 2017;31(5):439–50.

Proteasome inhibition

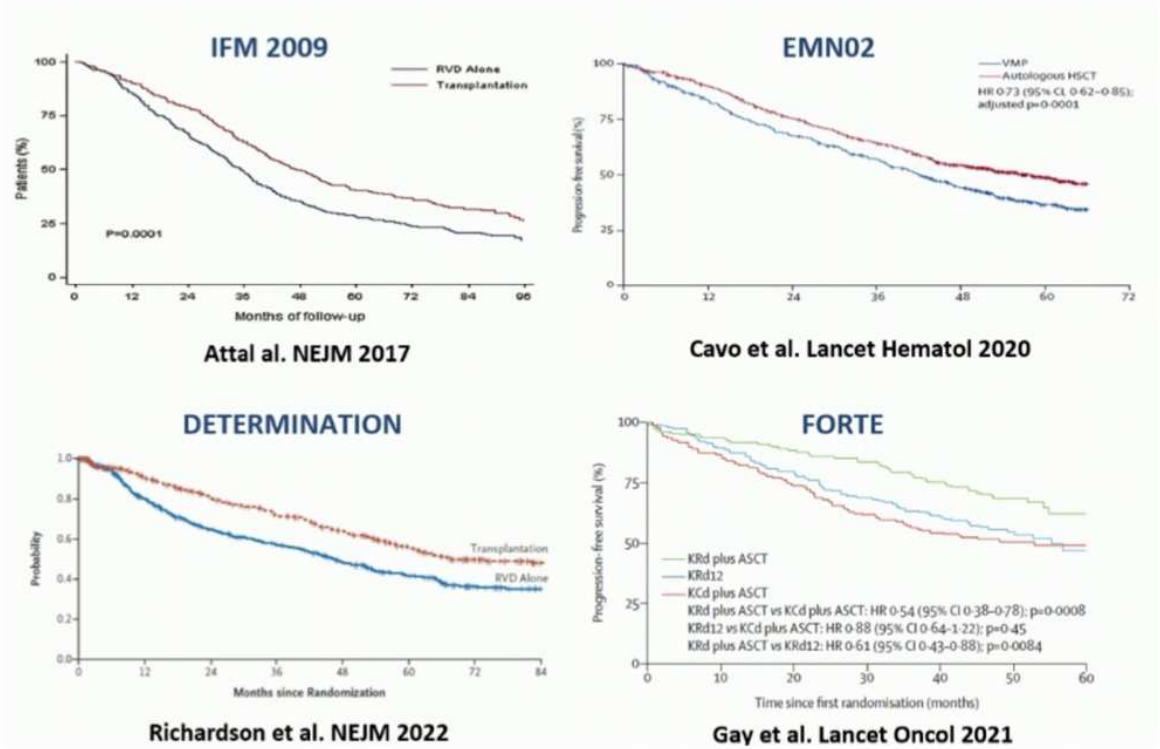


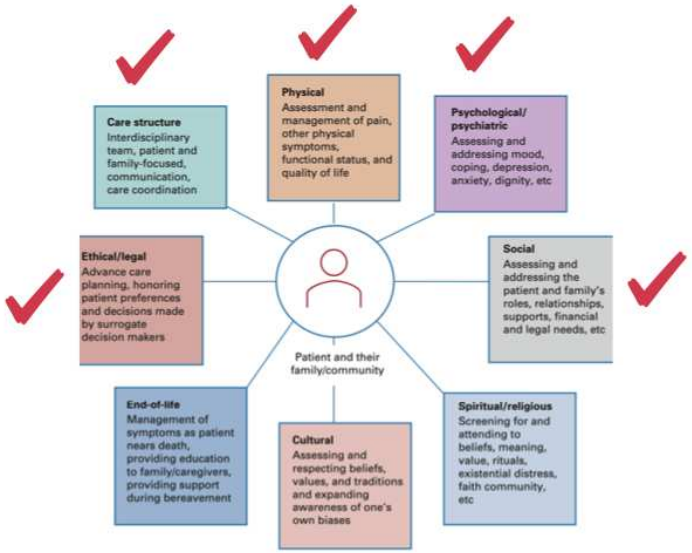
Yong K, Gonzalez-McQuire S, Szabo Z, Schoen P, Hajek R. The start of a new wave: Developments in proteasome inhibition in multiple myeloma. Eur J Haematol 2018;101(2):220–36.

Reference

Transplantation for transplant-eligible patients: PFS benefits, safe treatment, and cost-effective

PFS benefits confirmed by 4 randomized trials in the era of novel agents





- **Transplantation for patients more than 65 y/o is feasible**
- **Lack of a geriatric assessment of multiple domains and support**

説明

Reference

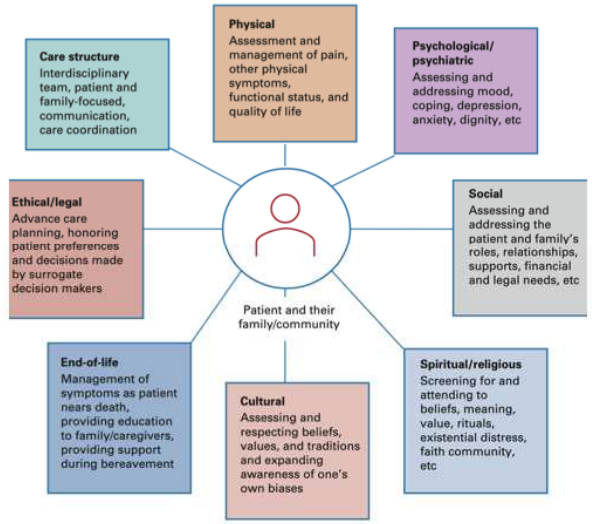
Reference

Factors involved in choosing treatment regimen for relapsed MM

Disease-related	1. Progression pace
	2. Feature of aggressive disease
	3. Plasma cell leukemia
	4. Presence or absence of end-organ damage
	5. Bone marrow reserve at the time of relapse
	6. Time to relapse from ASCT
	7.Cytogenetic profile
Treatment related	1. Induction regimen used
	2. Duration and depth of response to prior therapy
	3. ASCT status
	4. Adverse reactions to prior treatment and any residual toxicities
	5. Duration since last effective induction treatment
	6. Availability of novel agents and accessibility
Patient related	1. Functional age of the patient
	2. Performance status/frailty
	3.Medical comorbidities
	4.Socioeconomic factor
	5.Patient's health care related goals and preferences

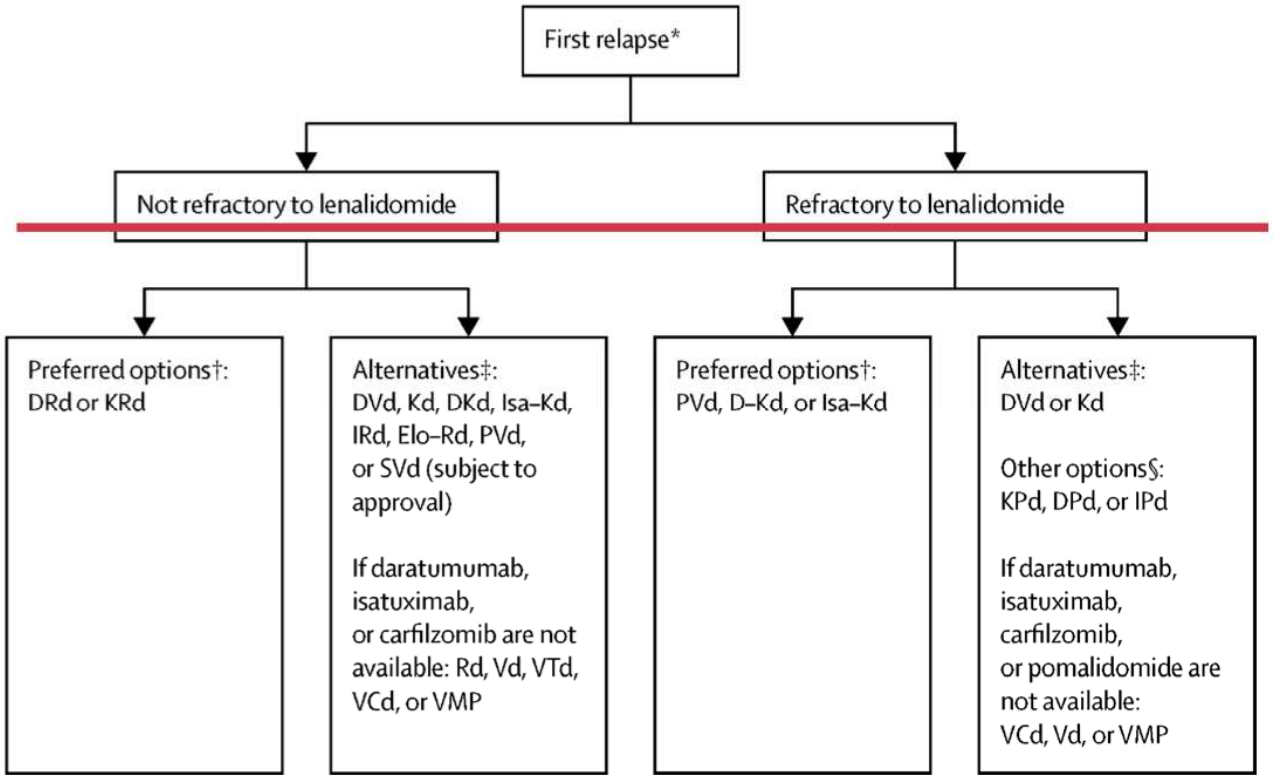
For a physician, the lack of a objective assessment

No assessment, no data, no optimal management



Devarakonda S, Sharma N, Efebera Y. The first relapse in multiple myeloma: how to pick the next best thing. Hematology 2022;2022(1):560–8

First relapse

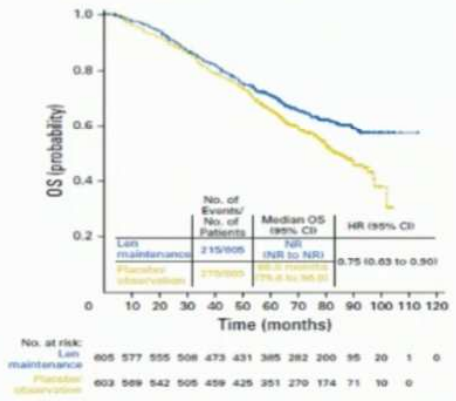


Moreau P, Kumar SK, Miguel JS, et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. Lancet Oncol 2021;22(3):e105–18.
Reference

Patient refractory to lenalidomide

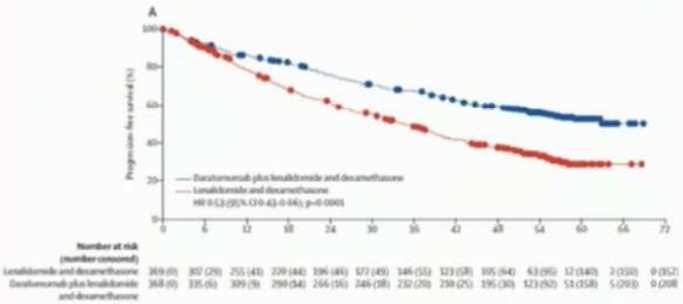
Len given until disease progression in both TE and TNE NDMM patients

Post ASCT maintenance



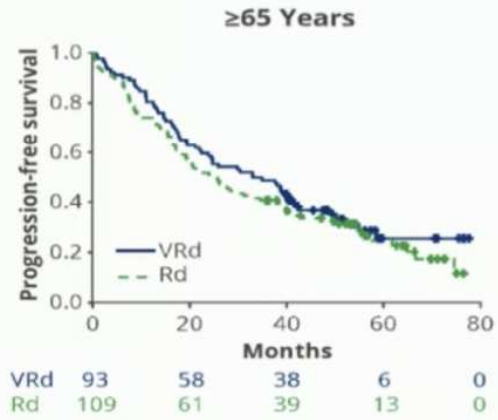
Mc Carthy et al. J Clin Oncol 2017

DRd



Facon et al. Lancet Oncol 2021

VRd



Durie B et al. ASH 2022

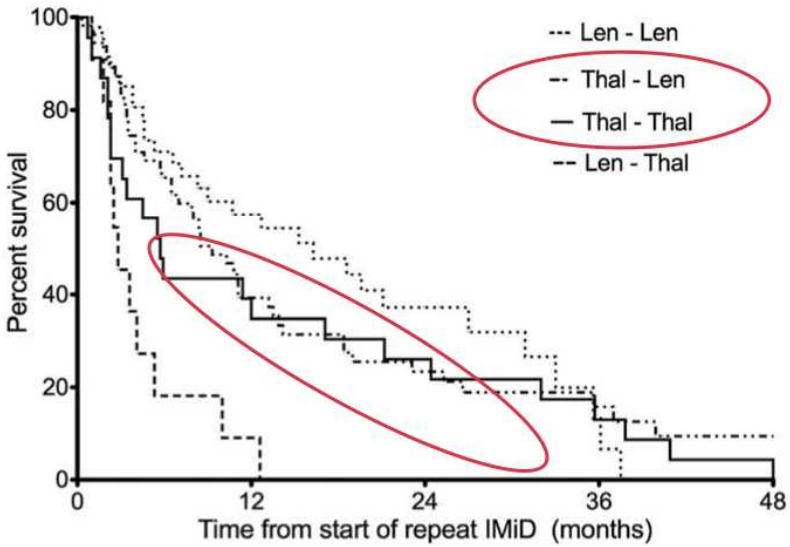
-> The majority of patients are becoming len refractory at first relapse

Reference

The efficacy of lenalidomide after thalidomide maintenance

Thalidomide maintenance was used in Taiwan

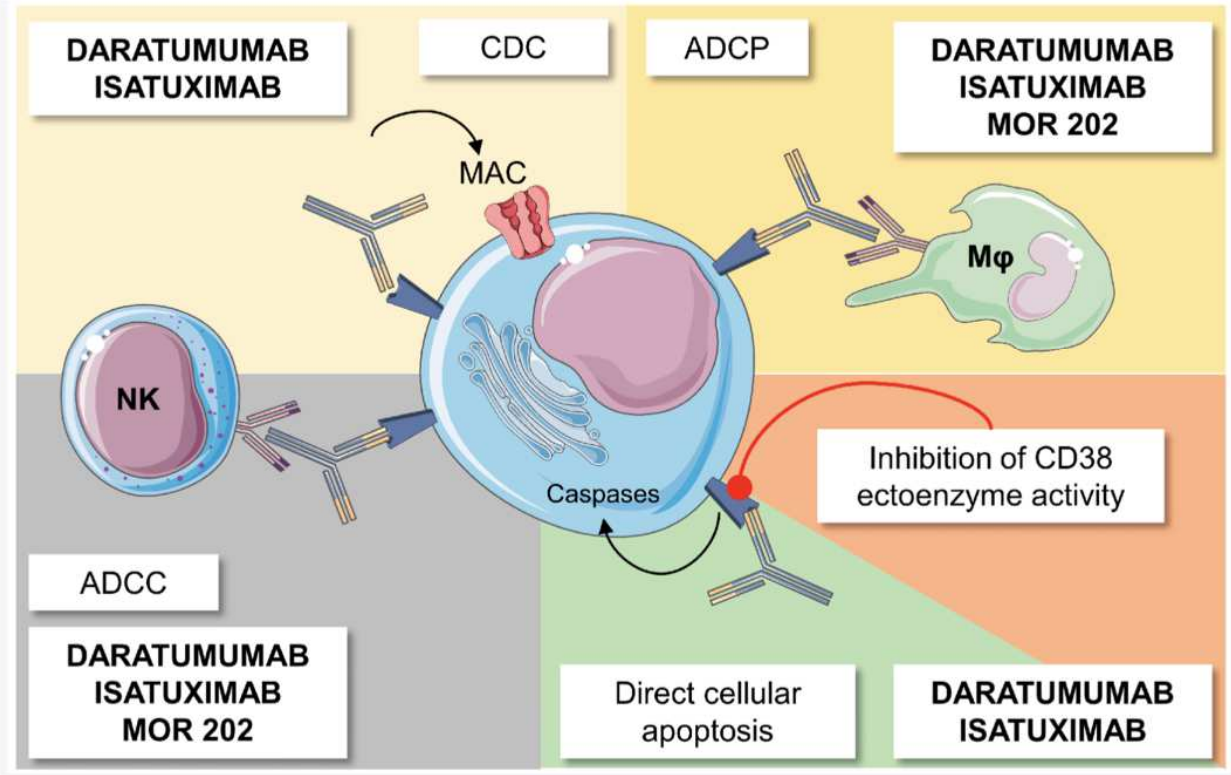
	Len→Len* n = 48	Len→Thal* n = 11	Thal→Len* n = 58	Thal→Thal* n = 23
Median age, y (range)	63 (29-78)	58 (33-72)	60 (38-77)	57 (38-71)
Males, %	58	55	62	74
High-risk MM, n (%)	6 (13)	2 (18)	12 (21)	3 (13)
Median no. of prior treatments	2	1	2	2
SCT before repeat IMiD, %	79	55	71	87
Dex plus repeat IMiD, %	92	100	86	87
Median duration of first IMiD, mo (IQR)	4 (4-6)	5 (4-8)	4 (3-6)	4 (3-5)
Median time from diagnosis to repeat IMiD, mo (IQR)	26 (18-38)	13 (4-23)	31 (23-49)	23 (18-36)
Median duration of second IMiD, mo (IQR)	7 (3-18)	3 (2-4)	7 (3-14)	6 (2-18)
Response to first-line IMiD†				
≥ VGPR(%)†	5 ≥ VGPR (45) 3 PR (27) 3 < PR (27)	1 PR (33) 2 < PR (67)	2 ≥ VGPR (33) 1 PR (17) 3 < PR (50)	1 PR (25) 3 < PR (75)
PR (%)†	4 ≥ VGPR (18) 7 PR (32) 11 < PR (50)	1 ≥ VGPR (25) 3 < PR (75)	2 ≥ VGPR (8) 7 PR (29) 15 < PR (63)	5 PR (45) 6 < PR (55)
< PR (%)‡	2 ≥ VGPR (33) 4 < PR (67)	3 < PR (100)	1 ≥ VGPR (7) 8 PR (57) 5 < PR (36)	5 < PR (100)
ORR (> PR)‡ (n = 140), %	54	20	48	30
N§	44 (92%)	7 (64%)	50 (86%)	22 (96%)
RR§ (n = 123; 88%)‡, %	57	17	47	32
N‖	4 (8%)	4 (36%)	8 (14%)	1 (4%)
RR‖ (n = 17; 12%)‡, %	25	25	50	0



Personal opinion: cross-resistance exists between thalidomide and lenalidomide

Madan S, Lacy MQ, Dispenzieri A, et al. Efficacy of retreatment with immunomodulatory drugs (IMiDs) in patients receiving IMiDs for initial therapy of newly diagnosed multiple myeloma. Blood 2011;118(7):1763–5

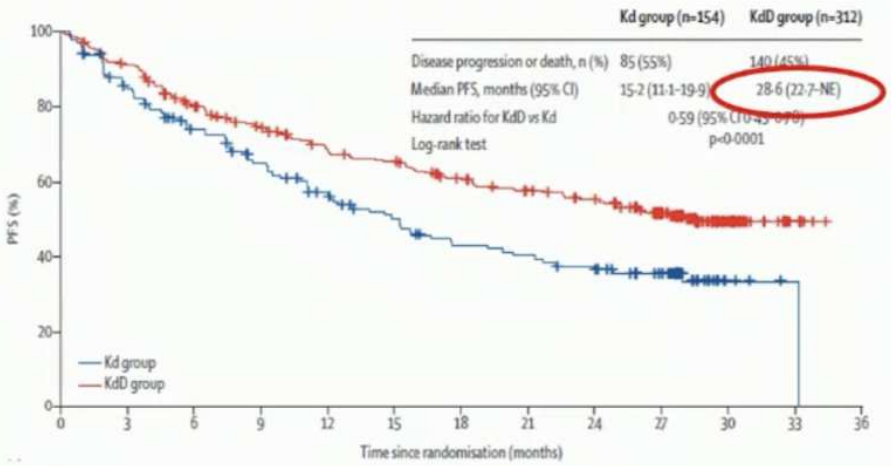
Mechanisms of action of anti-CD38 agents



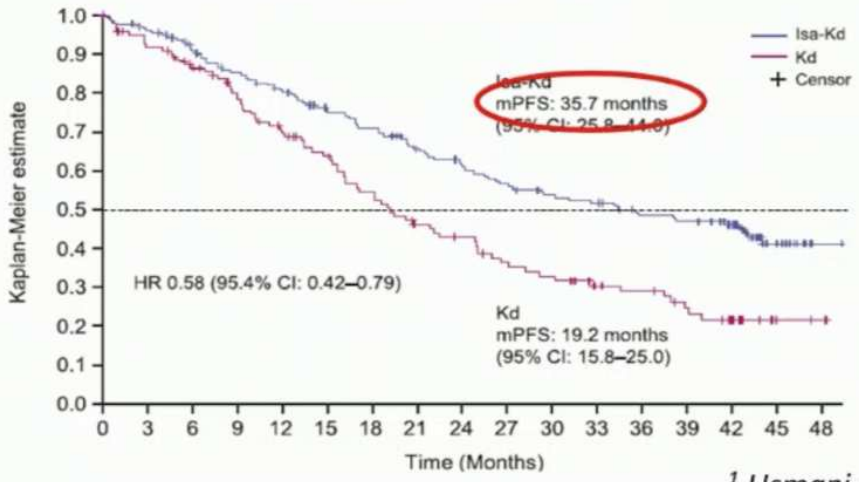
Novellis DD, Fontana R, Giudice V, Serio B, Selleri C. Innovative Anti-CD38 and Anti-BCMA Targeted Therapies in Multiple Myeloma: Mechanisms of Action and Resistance. Int J Mol Sci 2022;24(1):645.

L2-patients refractory to lenalidomide

Dara Kd
CANDOR trial[1]

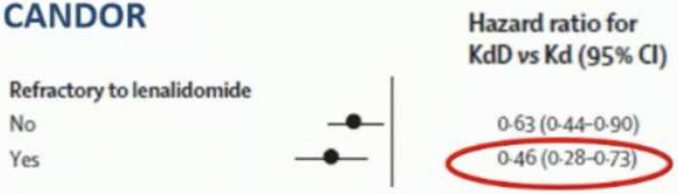


Isa Kd
IKEMA trial[2]



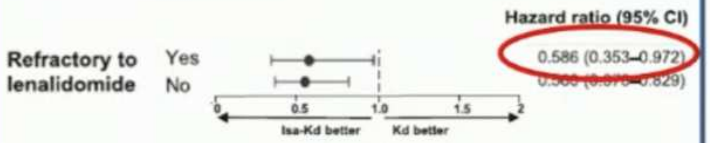
PFS benefit in Len ref. patients

CANDOR



mPFS DKd : 28 months
(Kd=11.1 months)

IKEMA

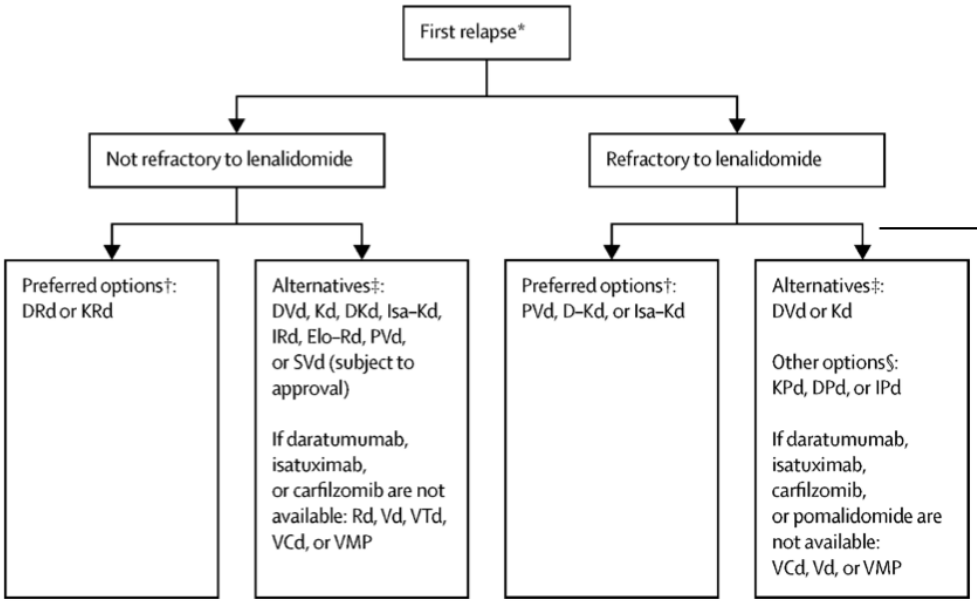


mPFS IsaKd : nearly 26 months
(Kd : 15.7 months)

[1] *Usmani et al. Lancet Oncol 2022* [2] *Martin et al. Blood Cancer J 2023*

L3:patient refractory to lenalidomide

In the next future, most elderly patients will present with len+ antiCD38 refractory disease at first relapse



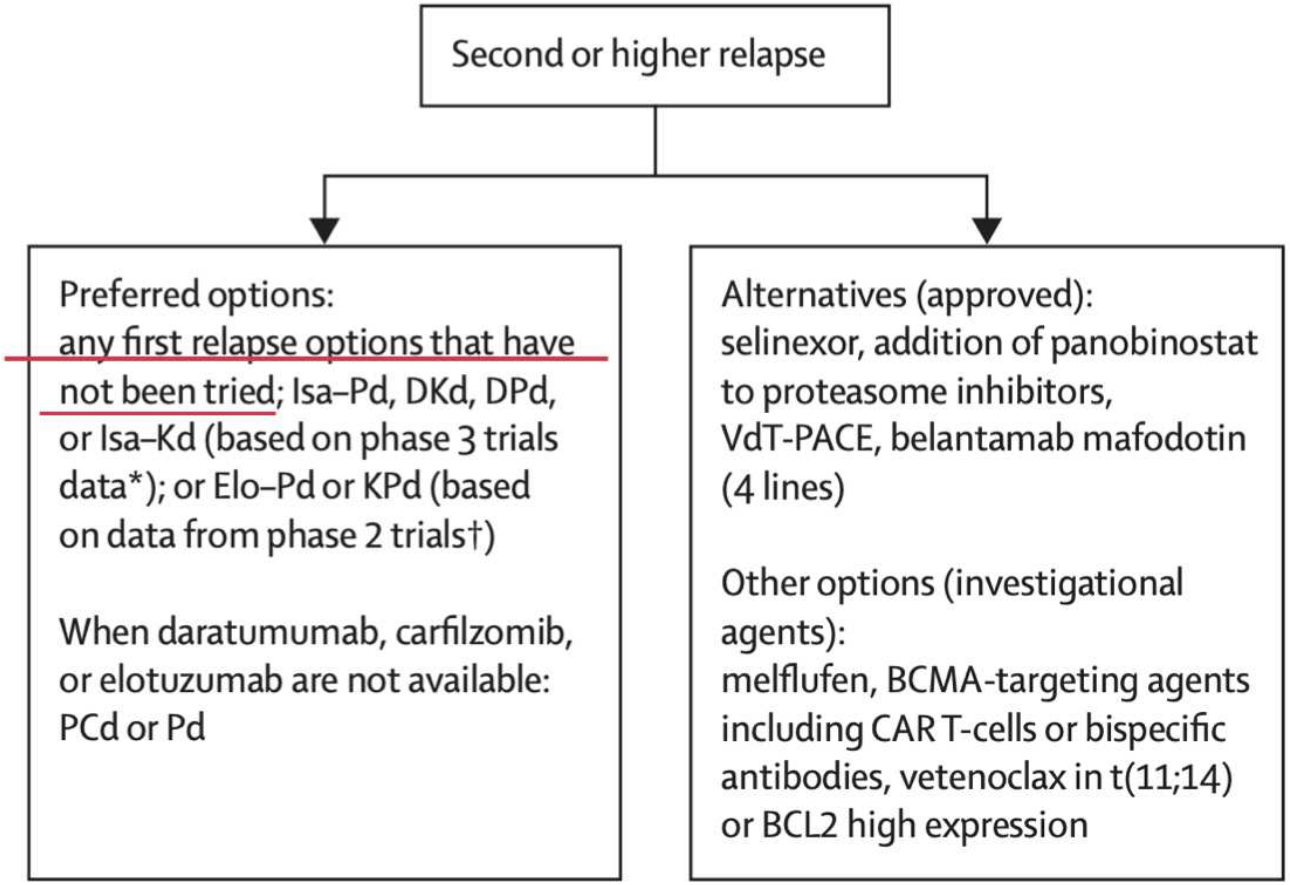
Median age=79, potential frailty

Refractory to len and anti CD38

PVd
Kd
VCd
VMP
....

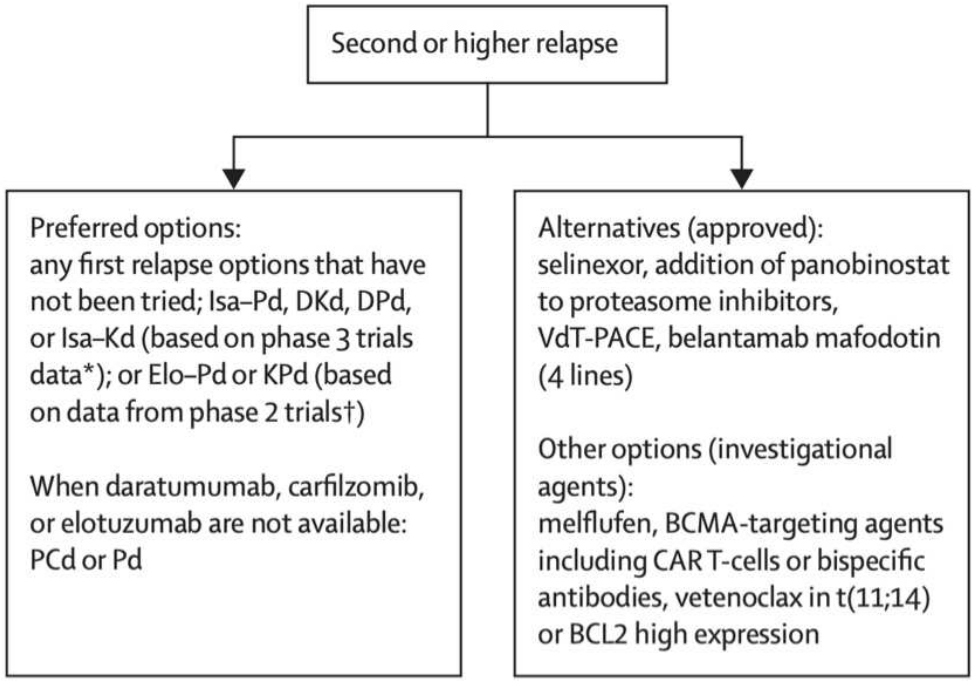
Moreau P, Kumar SK, Miguel JS, et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. Lancet Oncol 2021;22(3):e105–18.

L3(second relapse)



Moreau P, Kumar SK, Miguel JS, et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. Lancet Oncol 2021;22(3):e105–18.

Triple-class refractory

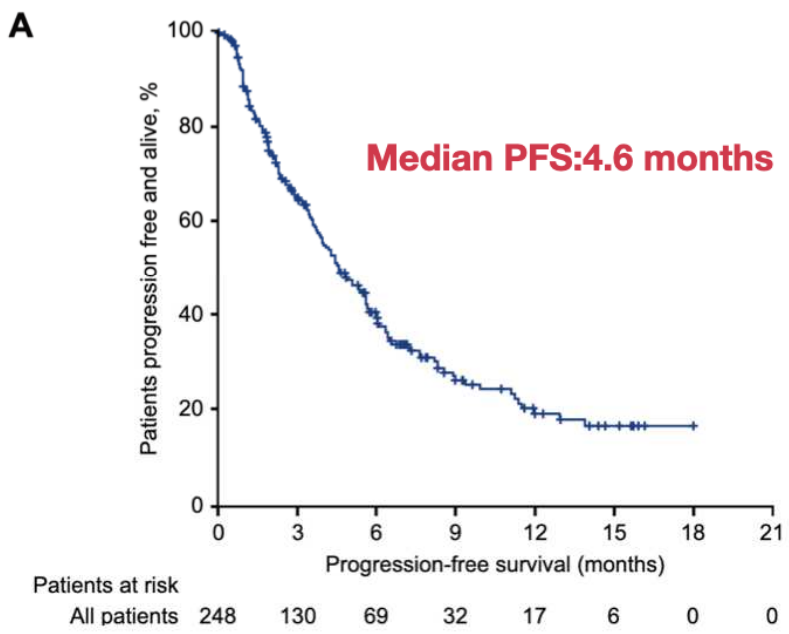


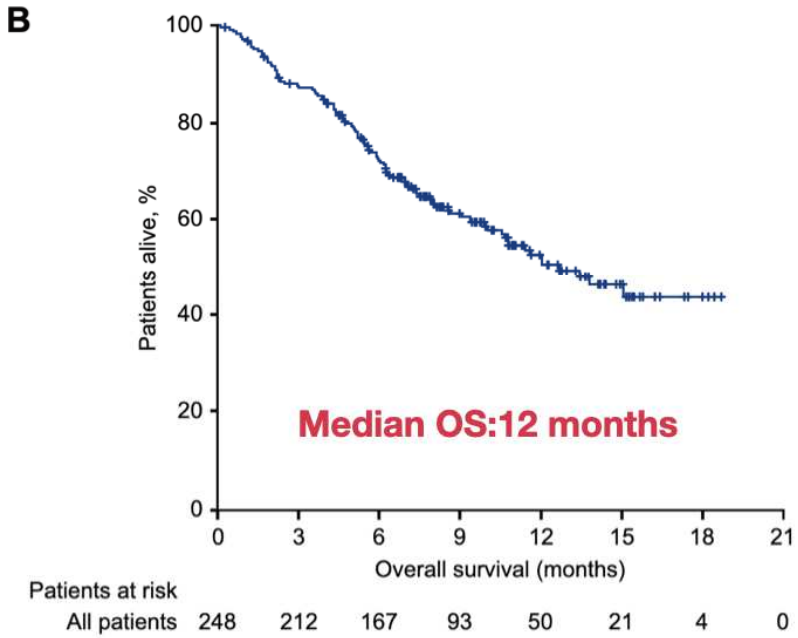
The majority of patients are becoming triple-class (PI+IMid+CD38) refractory

Moreau P, Kumar SK, Miguel JS, et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. Lancet Oncol 2021;22(3):e105–18.

≥ 3 line: triple class exposed

LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma

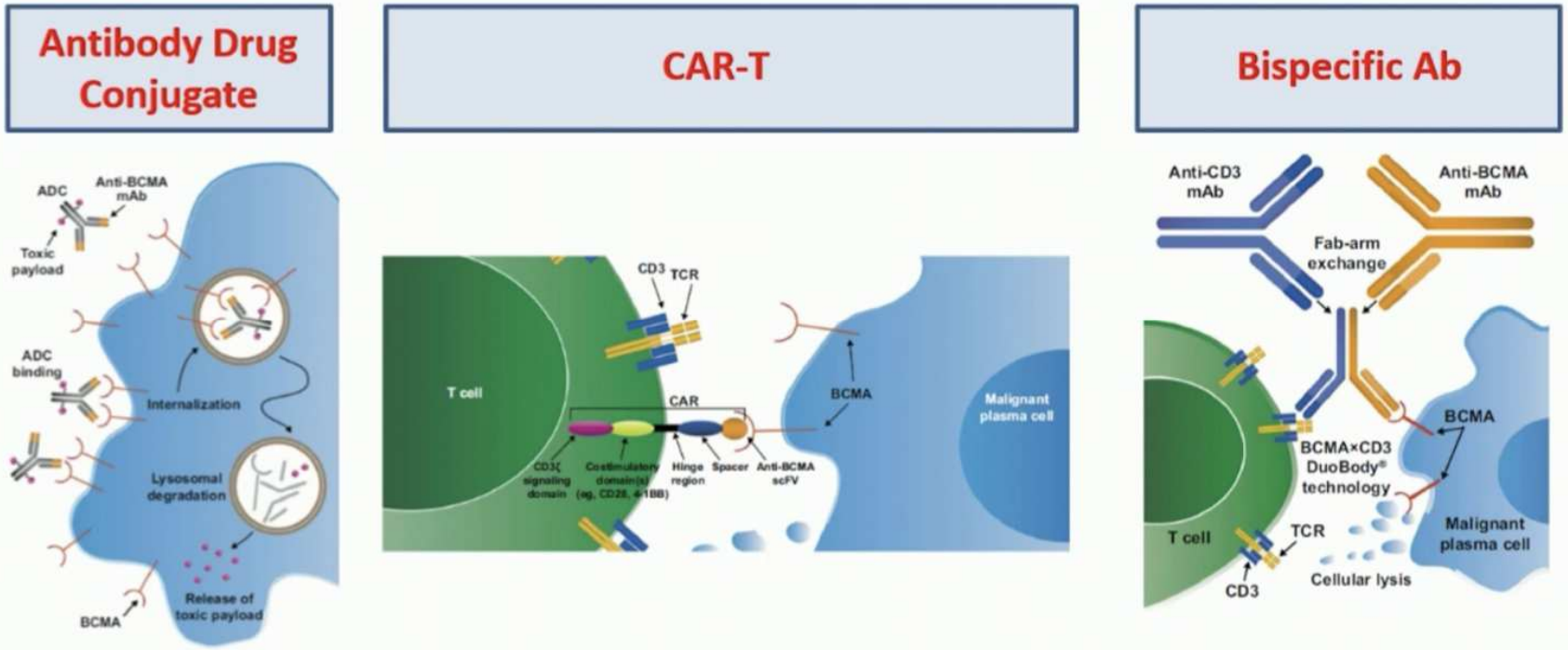




Reference

Mateos M-V, Weisel K, Stefano VD, et al. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. Leukemia 2022;36(5):1371–6.

Approved anti-BCMA agents in advanced triple-class exposed patients



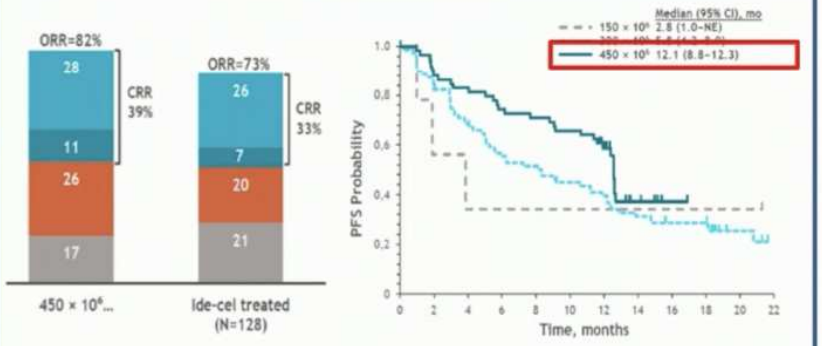
To date, cellular and non-cellular BCMA targeted therapies represent the best option approved for TCE myeloma after ≥3 prior lines

N Shah et al. Leukemia 2020

Approved anti-BCMA agents in advanced triple-class exposed patients

Antibody Drug Conjugate | **CAR-T** | Bispecific Ab

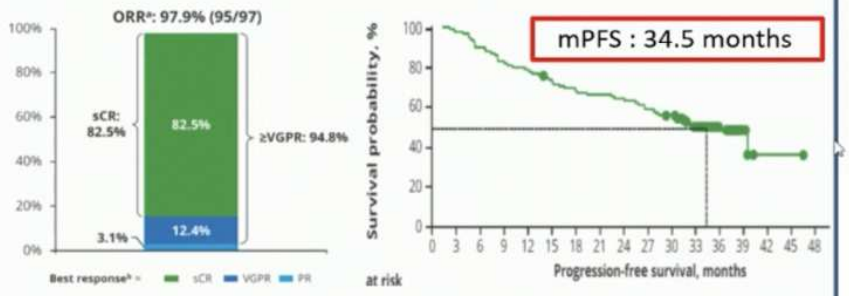
ide-cel (KARMMA)



Key non-hem. toxicity : CRS, ICAN

Munshi et al. NEJM 2021

cilta-cel (CARTITUDE-1)



Key non-hem. toxicity : CRS, ICAN

Lin et al. ASCO 2023 (update from Martin et al. J Clin Oncol 2022)

Reference

Other small molecules in MM

Belantamab mafodotin	Melflufen	Selinexor	Venetoclax	Iberdomide Mezigdomide
DREAMM-9 trial	ANCHOR trial	SELIBORDARA trial	M15-538 trial	CC220MM001 CC92480MM002 trials
Belantamab+VRD	Melflufen+dex With biz or Dara	Selinexor+dex Btz and dara	Venetoclax+Cfz+dex	Iber+btz+dex Dara+Iber+dex
NTE NDMM setting	Early RRMM	Early RRMM	t(11;14) MM	NTE NDM

Reference

More than half of patients never received specialist palliative care access

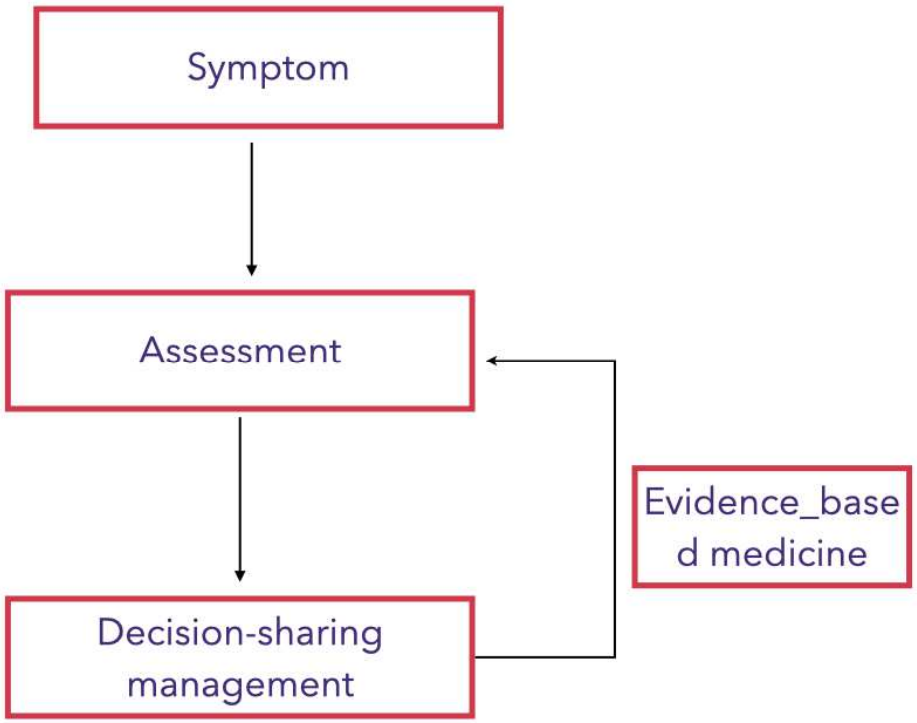
Patient characteristics	Entire population (%) $N = 456$	SPC access (inpatient only) $N = 110$	SPC access (outpatient or inpatient and outpatient) $N = 97$	No specialist palliative care access $N = 249$	SPC seen greater than 6 months prior to death $N = 42$
Median age at diagnosis (years)	65	63	65	66	58
Median age at death (years)	69	66	68	71	66
Male	252 (55.3%)	62 (56.3%)	46 (47.4%)	144 (57.8%)	16 (38.1%)
Caucasian	361 (79.2%)	73 (66.4%)	72 (74.2%)	216 (86.7%)	28 (66.7%)
African American	71 (15.6%)	30 (27.2%)	22 (22.7%)	19 (7.6%)	14 (33.3%)
Median number of hospitalizations in year prior to death	2, range 0–12	4, range 0–12	3, range 0–19	1, range 0–10	2.5 (range 1–7)
Death within a year of diagnosis	97 (21.3%)	34 (30.9%)	14 (14.4%)	49 (19.7%)	4 (9.5%)
Death in acute care setting (amongst 351 where place recorded)	117 (33.3%)	38 (39.6%)	22 (27.2%)	57 (32.8%)	10 (31.3%)
Receipt of active myeloma treatment in month prior to death	153 (33.6%)	49 (44.5%)	30 (30.9%)	74 (29.7%)	8 (19.0%)

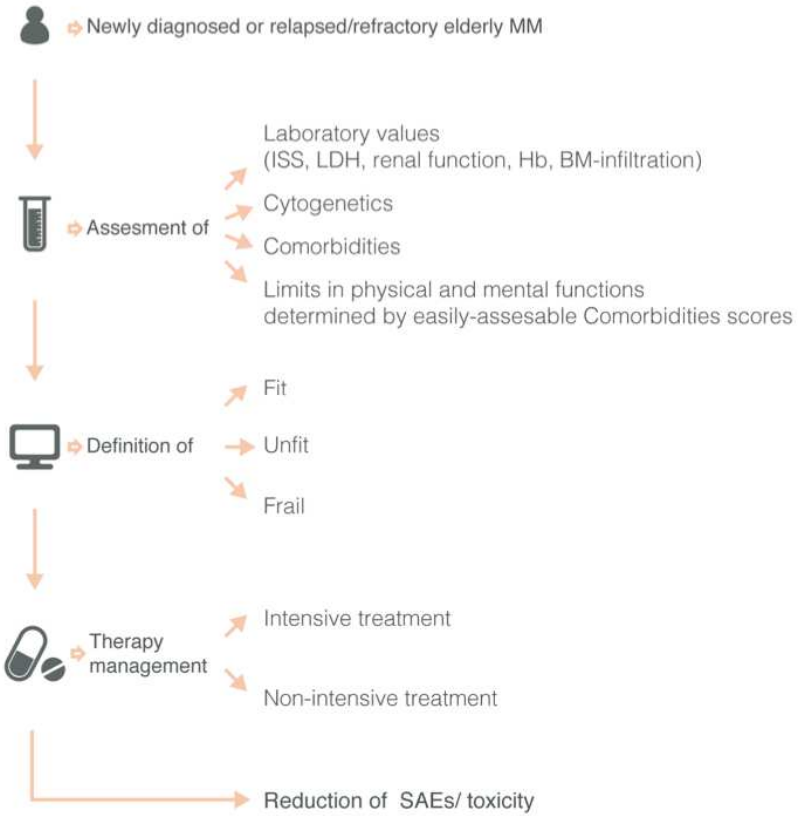
Abbreviation: SPC, palliative care.

1. McInturf G, Younger K, Sanchez C, et al. Palliative care utilization, transfusion burden, and end-of-life care for patients with multiple myeloma. Eur J Haematol 2022;109(5):559–65.

Reference

Early introduction of palliative care in elderly MM patients





Reference

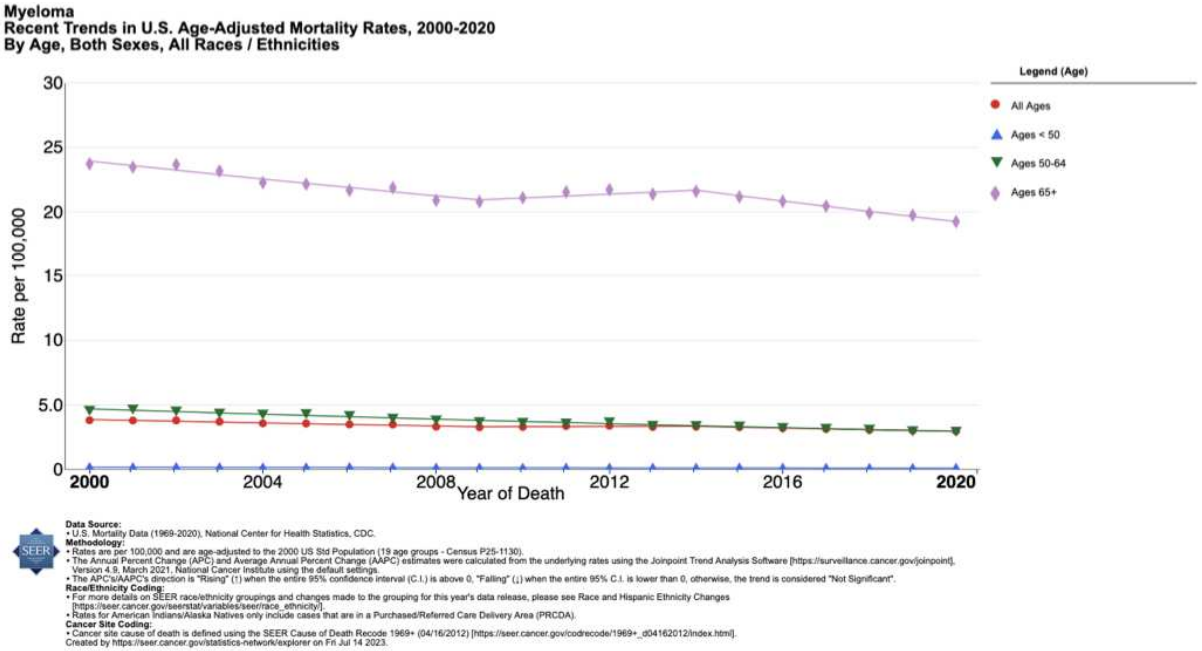
Terpos E, Kleber M, Engelhardt M, et al. European Myeloma Network Guidelines for the Management of Multiple Myeloma-related Complications. Haematologica 2015;100(10):1254–66.

Age-related disparities in early and overall mortality rate in myeloma

Median age:70 years

8.3% died within 6 months of diagnosis

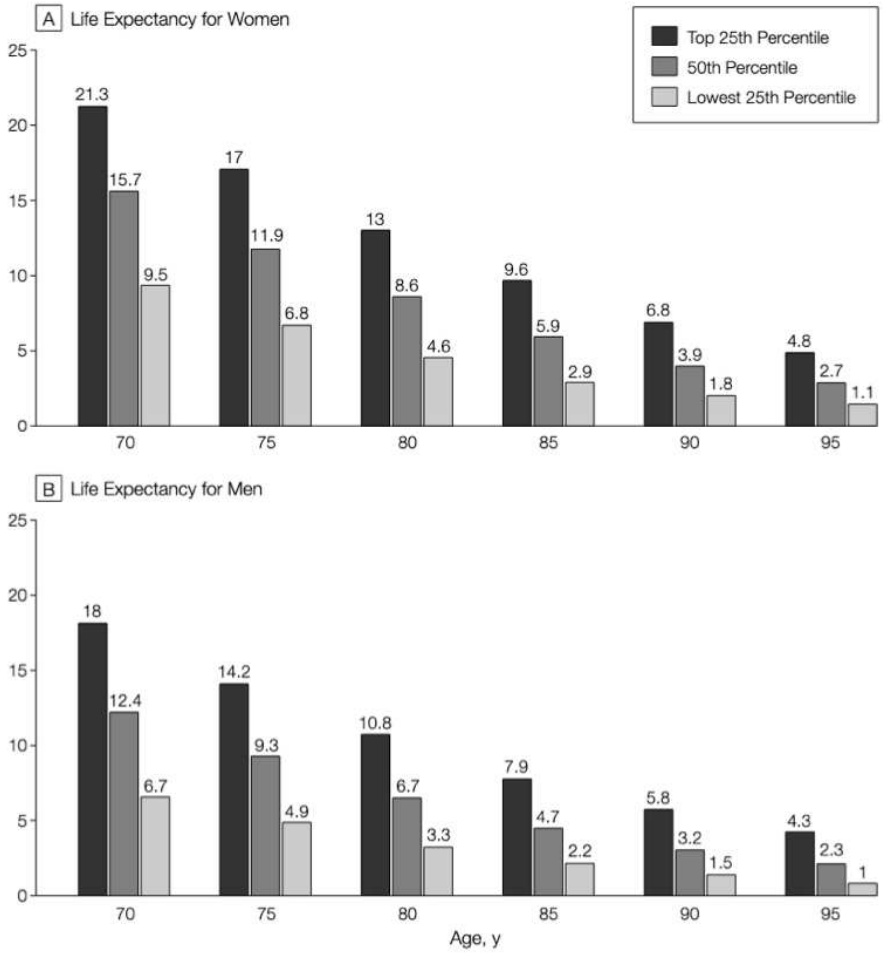
73% of dearly deaths occurred in those aged 70+



Grant SJ et al. A real-world data analysis of predictors of early mortality after a diagnosis of multiple myeloma. Cancer 2023, Mar 29

Reference

Calendar age ≠ Biological age



Fit

Frail

Reference

Walter LC, Covinsky KE. Cancer Screening in Elderly Patients: A Framework for Individualized Decision Making. JAMA 2001;285(21):2750–6.

Multiple myeloma specific frailty score

Frailty Score	International Myeloma Working Group[1]	Revised Myeloma Comorbidity Index[2]	Facon Frailty Score[3]
Domains Measured	1. ADLS 2. IADLS 3. Charlson Comorbidity Index 4. Age	1. Fried frailty 2. Karnofsky performance status 3. Lung function 4. Renal function **5.** Age	1. Charlson Comorbidity Index 2. ECOG performance status **3.** Age
Scoring	0-2	0-9	0-2
Interpretation	1. 0 (fit) 2. 1 (intermediate-fit) 3. 2 (frail)	1. 0-3 (fit) 2. 4-6 (intermediate- fit) 3. 7-9 (frail)	1. 0-1 (non-frail) 2. ≥ 2 (frail)
Researcher/Clinician Administered or Patient-Reported	Researcher, Clinician or Patient	Researcher or Clinician	Researcher, Clinician or Patient
Application in clinical practice	Predicts grade ≥ 3 toxicities and aids prognostication Risk-adapted treatment approaches	Predicts grade ≥ 3 toxicities and aids prognostication Risk-adapted treatment approaches	Predicts grade ≥ 3 toxicities and aids prognostication

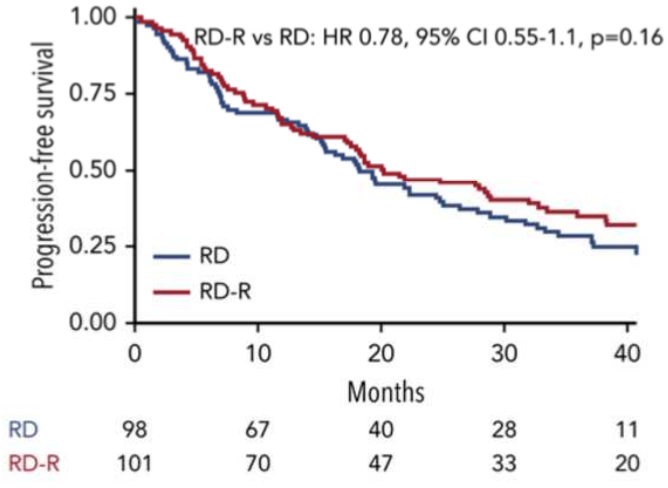
[1]Palumbo et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. Blood. 2015 Mar 26;125(13):2068-74
[2]Engelhardt et al. A concise revised Myeloma Comorbidity Index as a valid prognostic instrument in a large cohort of 801 multiple myeloma patients. Haematologica. 2017 May;102(5):910-921.
[3]Facon et al. A simplified frailty scale predicts outcomes in transplant-ineligible patients with newly diagnosed multiple myeloma treated in the FIRST (MM-020) trial. Leukemia. 2020 Jan;34(1):224-233

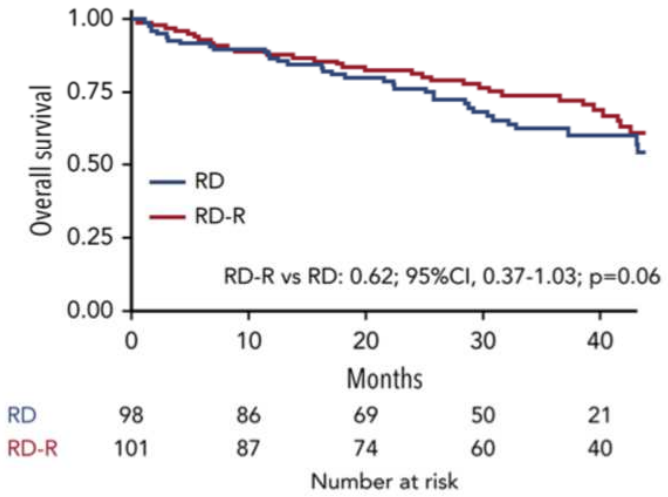
From ASCO 2023
Reference

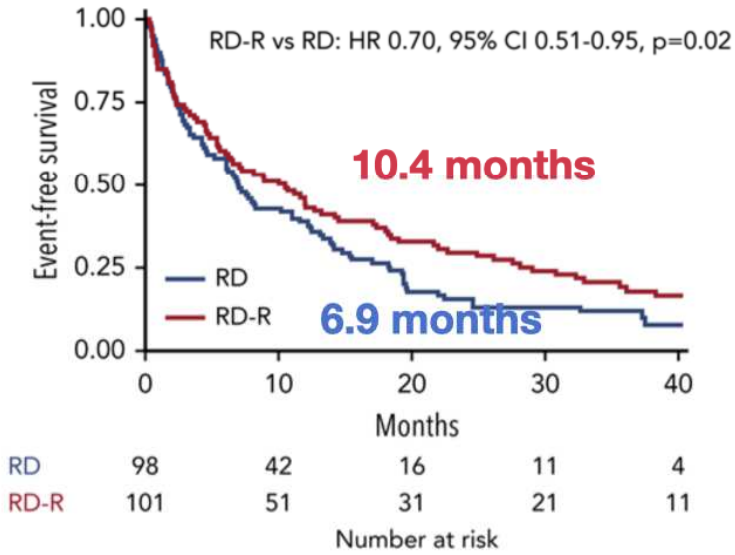
RD versus RD-R in intermediate fit patients based on IMWG-FI

Randomized phase III

EFS:death, progression, discontinuation of lenalidomide, grade IV hematologic toxicity, grade III/IV toxicity



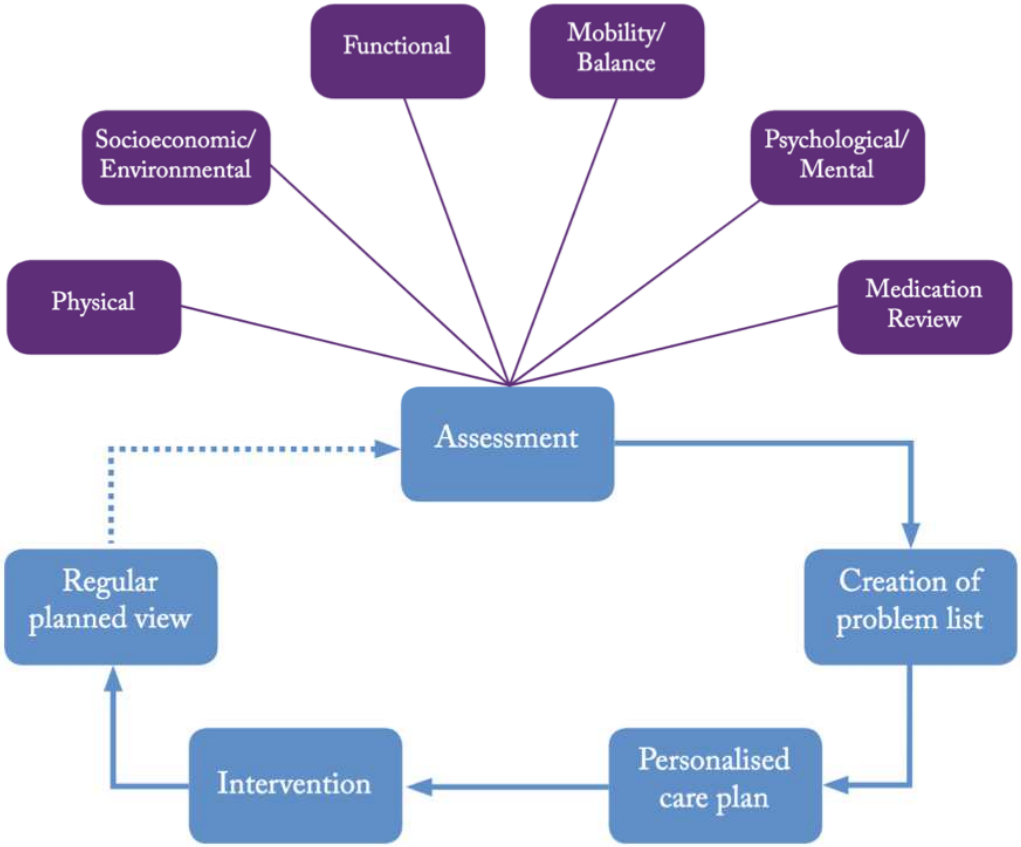




Larocca A, Bonello F, Gaidano G, et al. Dose/schedule-adjusted Rd-R vs continuous Rd for elderly, intermediate-fit patients with newly diagnosed multiple myeloma. Blood 2021;137(22):3027–36.

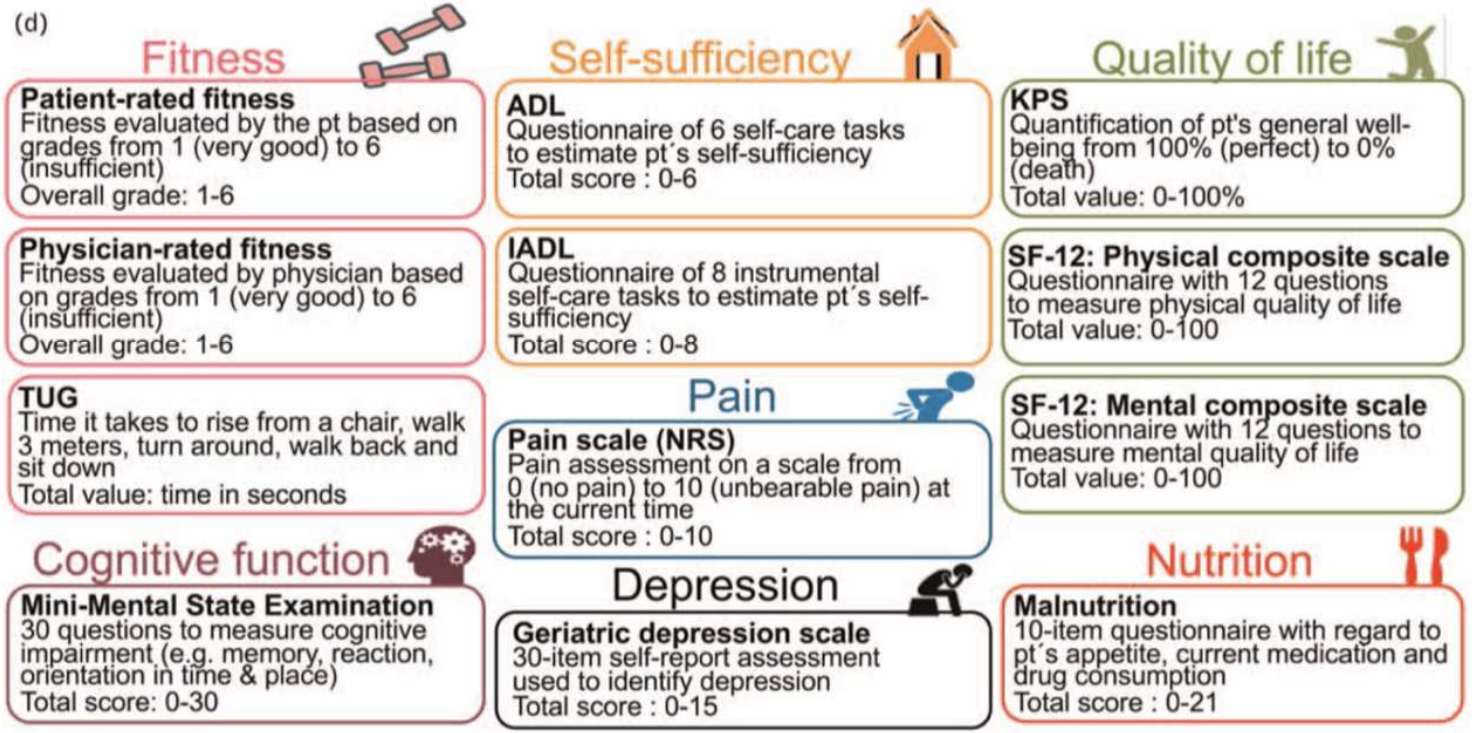
Reference

Comprehensive geriatric assessment



British Geriatric Society

Geriatric assessment: multidimensional functional tests



Möller M-D, Gengenbach L, Graziani G, Greil C, Wäsch R, Engelhardt M. Geriatric assessments and frailty scores in multiple myeloma patients: a needed tool for individualized treatment? Curr Opin Oncol 2021;33(6):648–57.

Reference

What next steps should be considered?

- Conduct a **comprehensive geriatric assessment** (CGA)
- Use **myeloma-specific frailty scores** to predict toxicity risk and guide treatment discussions
- Implement **GA-guided interventions** for identified deficits
- Assess and intervene **on healthcare access barriers**
- Encourage **shared-decision making** regarding treatment options and incorporate patient preferences

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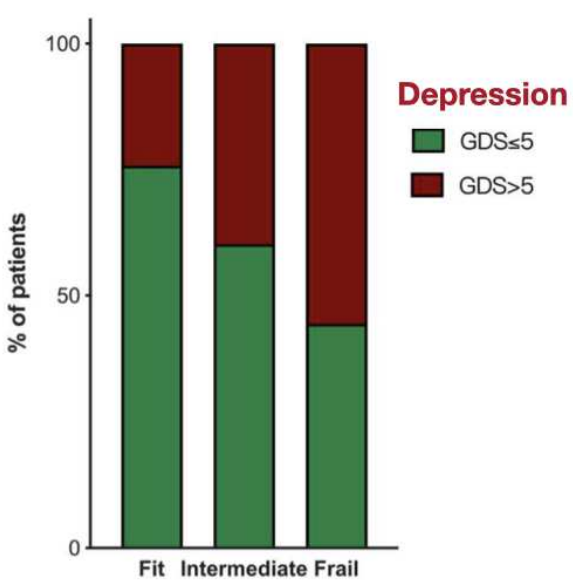
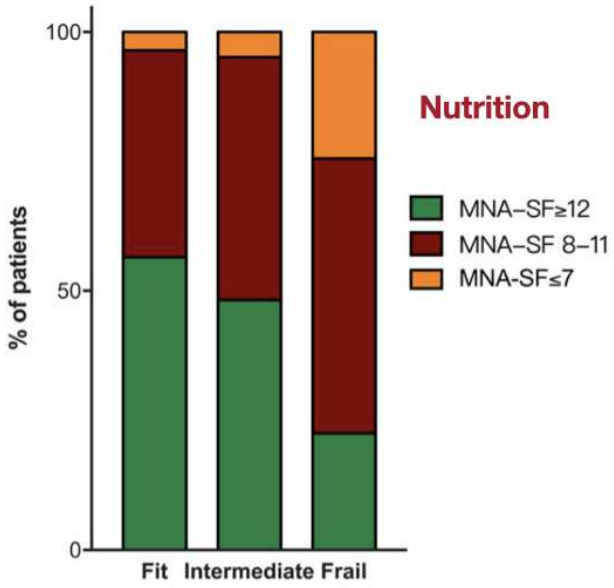
@ShakiraG_MBBS

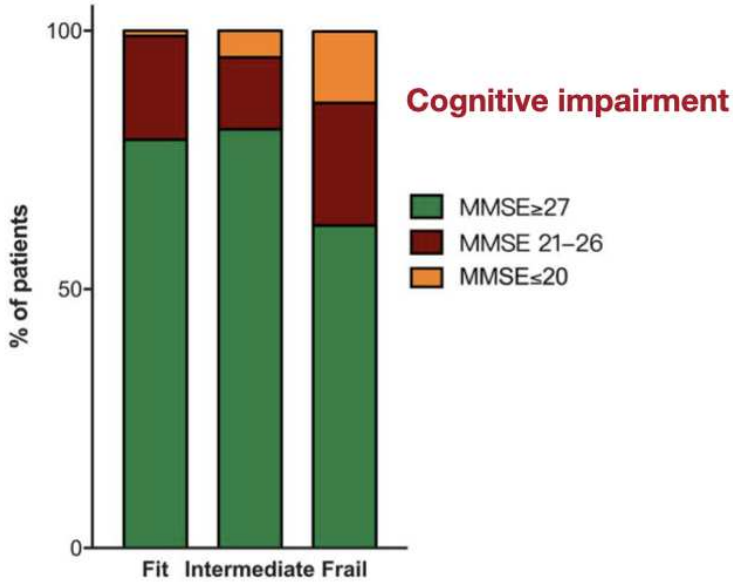
Comprehensive geriatric assessment included more frail patients

A multi-center, prospective, non-interventional trial

349 patients, all can compete geriatric assessment







IMWG-GA assessment

Reference

Yao Y, Sui W-W, Liao A-J, et al. Comprehensive geriatric assessment in newly diagnosed older myeloma patients: a multicentre, prospective, non-interventional study. Age Ageing 2021;51(1).

The Role of the Community in Reducing the Burden of Health Disparities in Multiple Myeloma

Identifying community-based resources to address healthcare access barriers

Fostering partnerships with academic institutions

Raising awareness and education about multiple myeloma

Leading advocacy and policy initiatives e.g., addressing drug costs

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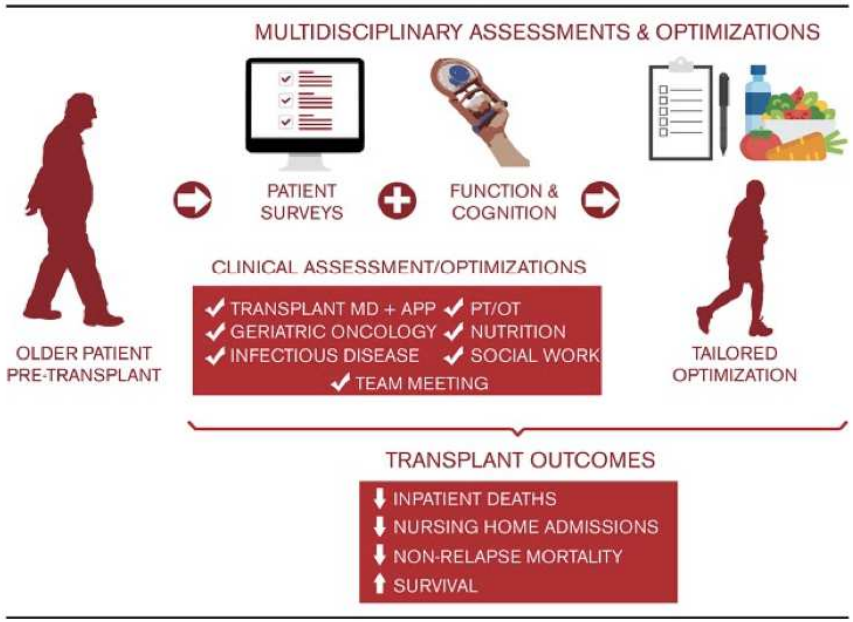
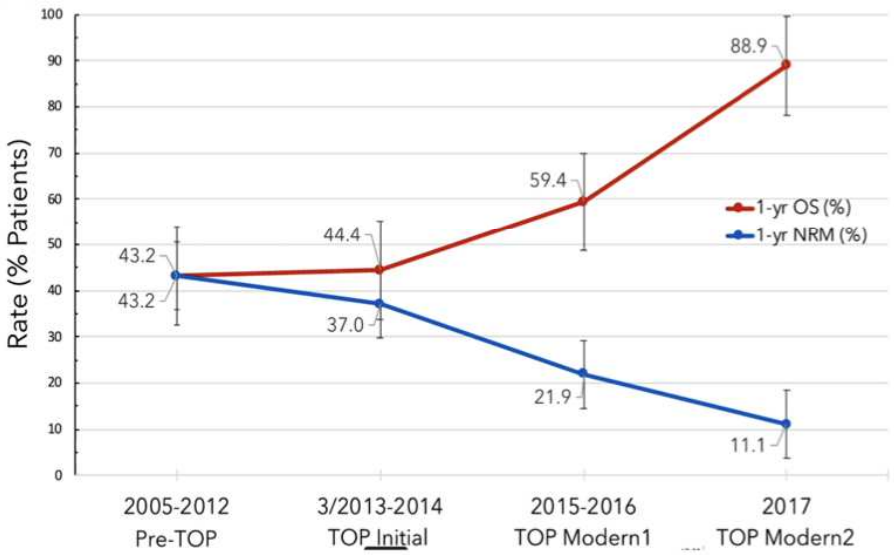
A multidisciplinary clinic guided by geriatric assessment before stem cell transplantation in older adults

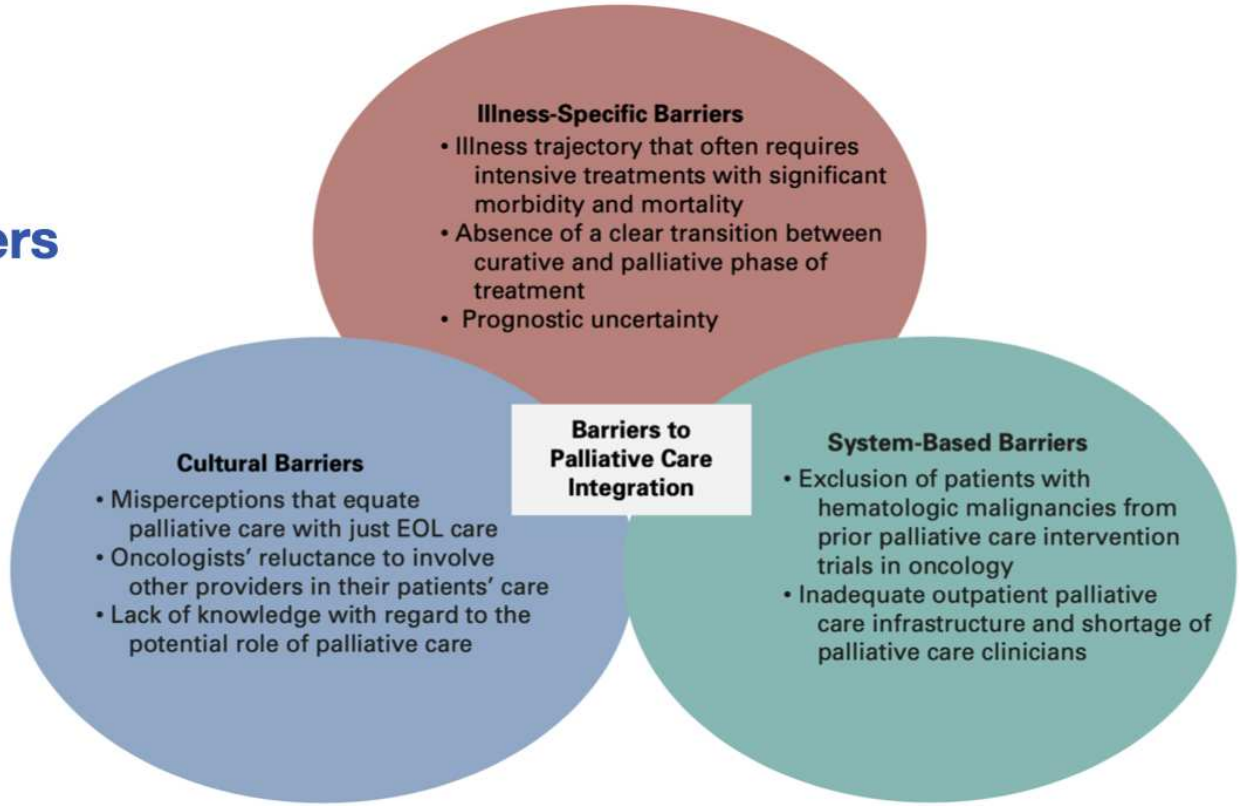




Reference

Conclusion: early palliative care is needed in MM patient care

But many barriers



El-Jawahri A, Nelson AM, Gray TF, Lee SJ, LeBlanc TW. Palliative and End-of-Life Care for Patients With Hematologic Malignancies. J Clin Oncol 2020;38(9):944–53.

Reference

Thank you