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Current Management of Multiple Myeloma

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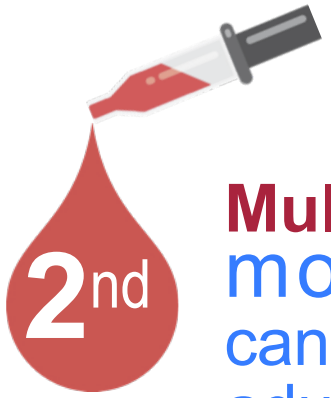
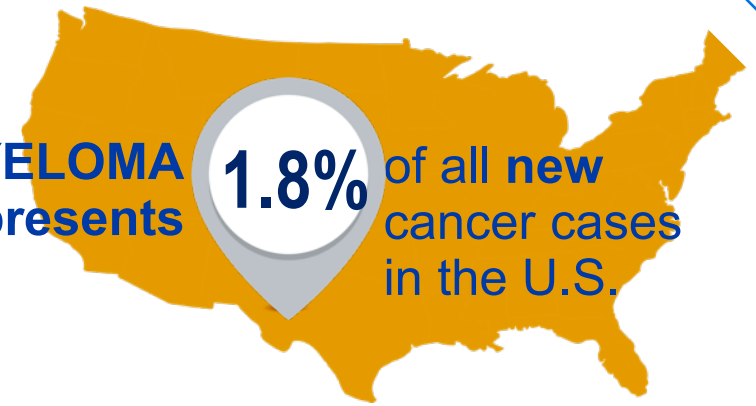
Incidence and Prevalence of Multiple Myeloma



Multiple Myeloma
most common
cancer of the blood in adults

35,730
new cases in 2023

159,787 **living with, or in remission**



Myeloma is most frequently diagnosed among people ages

65-74

Median age at diagnosis **69**

Siegel RL et al. *CA Cancer J Clin.* 2018;68:7; National Cancer Institute. SEER Cancer Stat Facts: Myeloma.

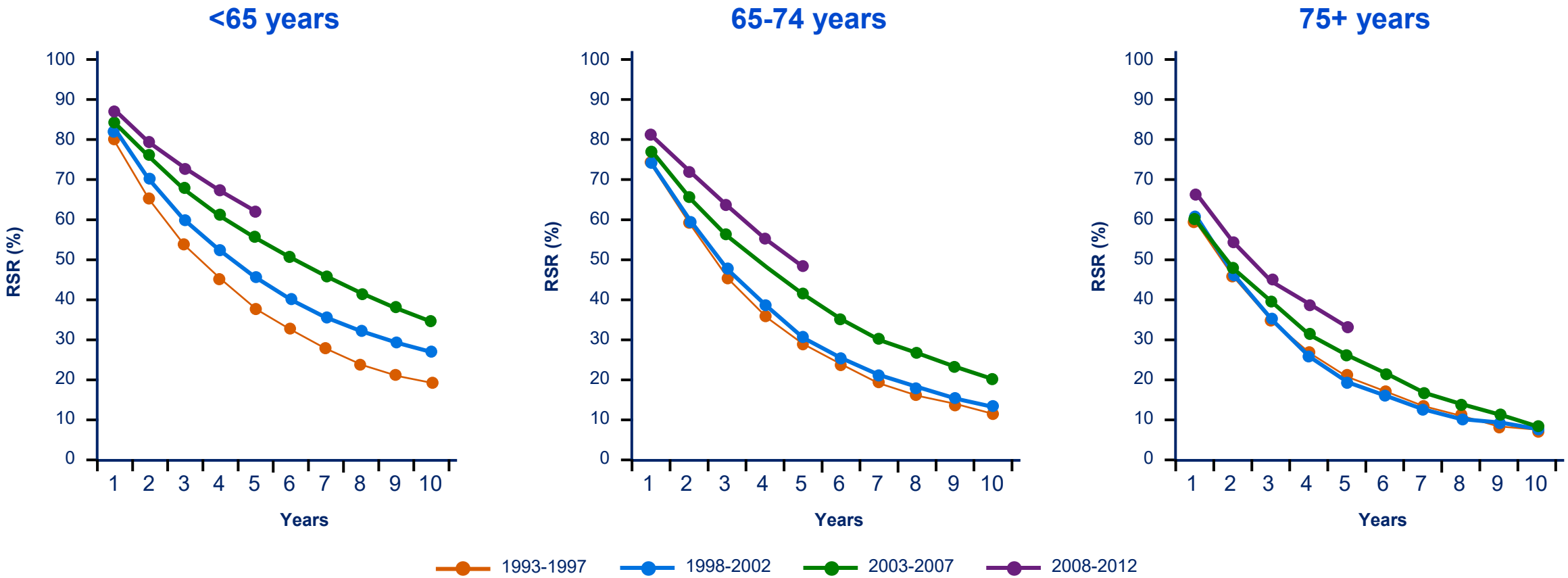
Staging in Multiple Myeloma

Stage[1]	R-ISS[1]
I	Serum albumin ≥3.5 g/dL Serum β2M <3.5 mg/L No high-risk cytogenetics Normal LDH level
II	Not stage I or III
III	Serum β2M >5.5 mg/L High-risk cytogenetics: t(4;14), t(4;16), or del(17p) or elevated LDH

Stage[1]	R2-ISS[3]
I	0 Points (Low Risk, 19% pts)
II	0.5-1 Points (Low-Intermediate Risk, 31% pts)
III	1.5-2.5 Points (Intermediate-High Risk, 41% pts)
IV	3-5 Points (High Risk, 9 % pts)
POINTS: ISS III= 1.5, ISS-II = 1, Del17p =1, elevated LDH =1, Chromosome 1q21+ = 0.5	

Palumbo et al. JCO 2015; D'Agostino et al. JCO 2022

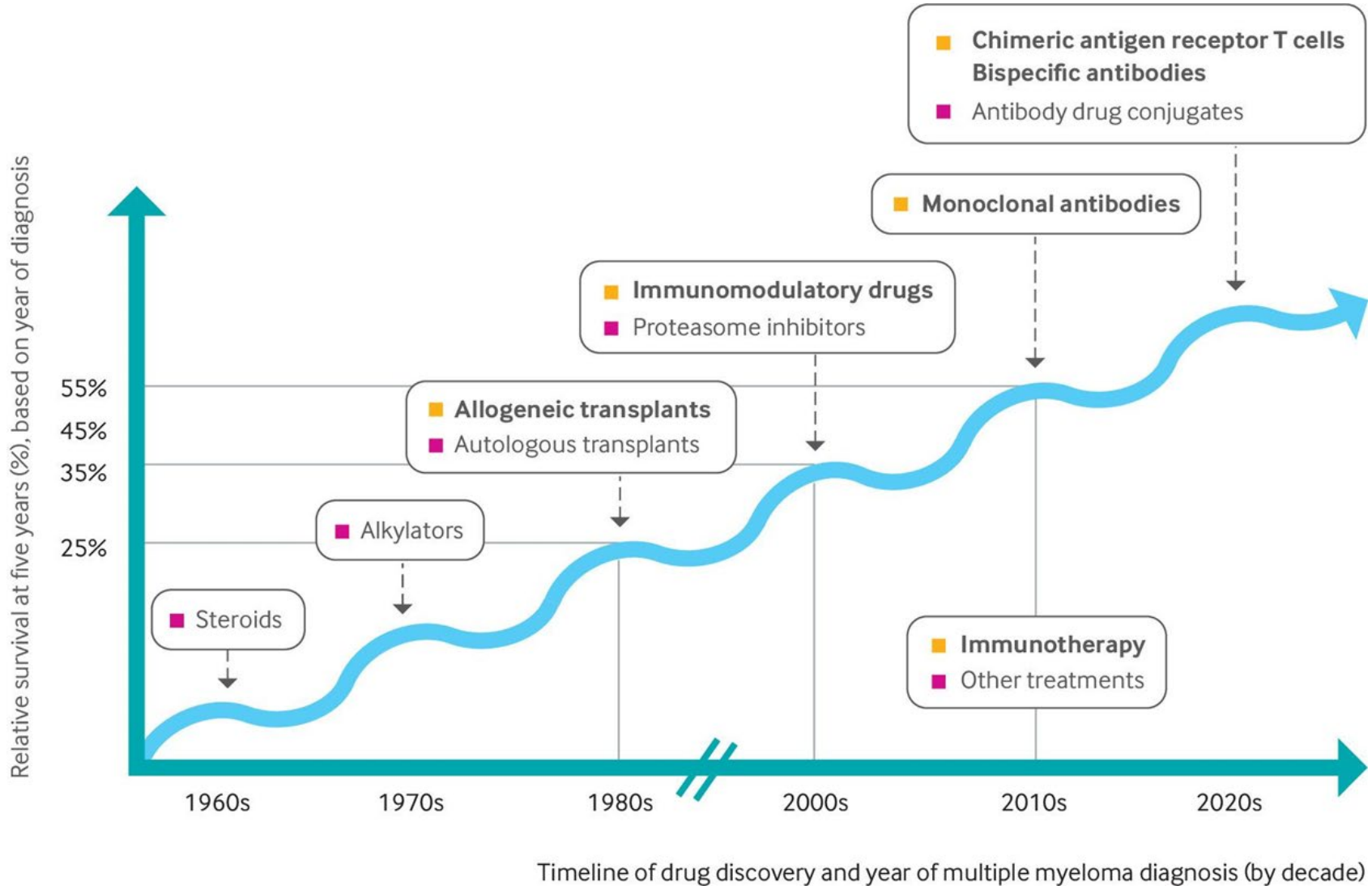
Multiple Myeloma Survival has improved in the last 30 years



In 2023, the average life expectancy may be 10 years or more!

Costa et al. *Blood Adv.* 2017

Six Decades of Drug Discovery in Multiple Myeloma



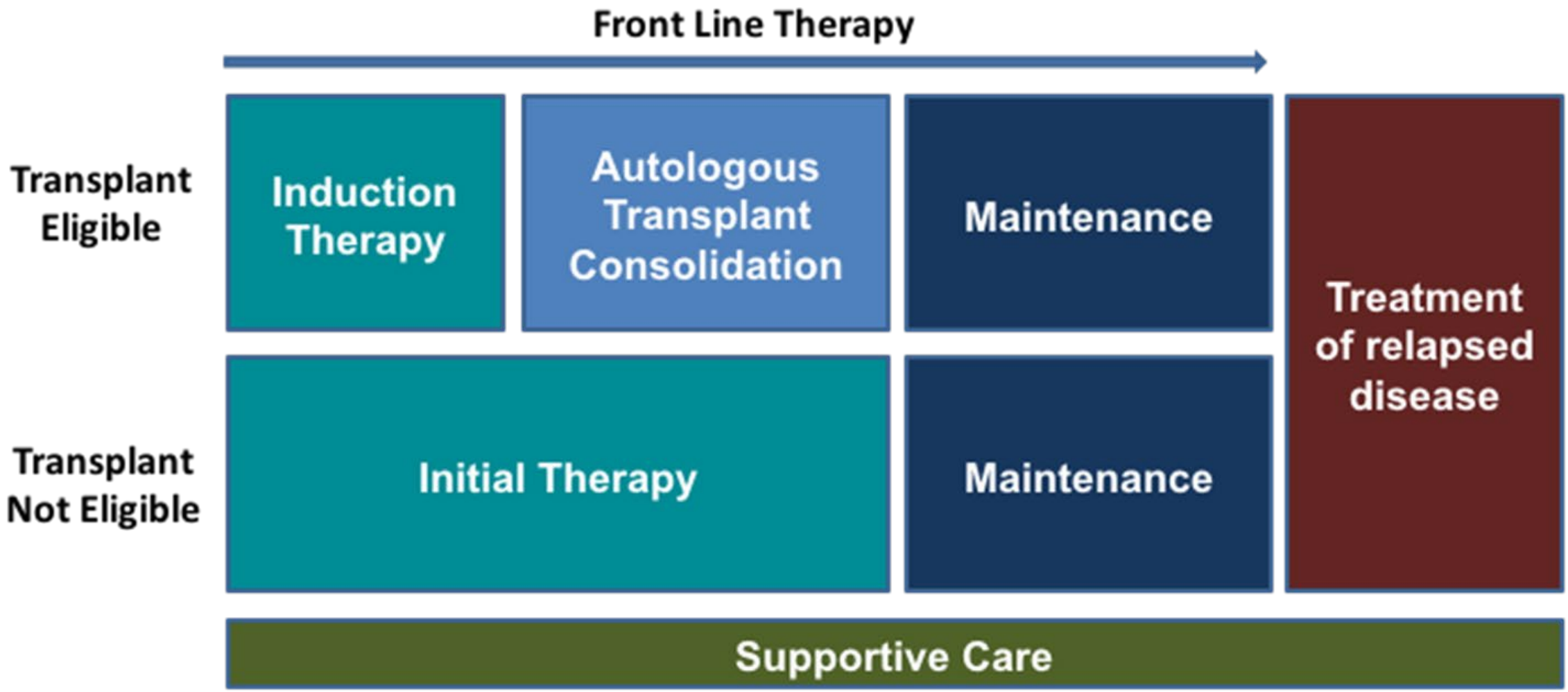
Shah U, Mailankody S. BMJ 2020

Available Therapies for Multiple Myeloma

Proteasome inhibitors	Immunomodulatory drugs	CD38 monoclonal antibodies
Bortezomib (V) Ixazomib (I) Carfilzomib (K)	Thalidomide (T) Lenalidomide (R) Pomalidomide (P)	Daratumumab (D) Isatuximab (Isa)

Other drugs	T cell directed therapies
Cyclophosphamide (C) Selinexor (S) Elotuzumab (E) Melphalan (M) Dexamethasone (D/d)	Idecabtagene Vicleucel Ciltacabtagene Autoleucel Teclistamab Elranatamab Talquetamab

Treatment for Newly Diagnosed Multiple Myeloma



Management of Newly Diagnosed Multiple Myeloma

	SWOG0777		MAIA		ALCYONE		ENDURANCE		CASSIOPEIA		PERSEUS	
Regimens	**RVd**	**Rd**	**DRd**	**Rd**	**D-VMP**	**VMP**	**RVd**	**KRd**	**D-VTd**	**VTd**	**D-RVd**	**RVd**
Transplant	**Not intended**		**Ineligible**		**Ineligible**		**Not Intended**		**Eligible**		**Eligible**	
ORR (%)	82	72	93	82	91	74	84	87	93	90	97	94
≥ CR (%)	16	8	51	30	43	24	15	18	39	26	88	70
Median PFS (months)	43 vs. 30		NR vs. 34.4		36-month PFS: 51 vs. 19%		34.4 vs. 34.6		18-month PFS: 93 vs. 85%		4-year PFS: 84.3 vs. 67.7%	
Median OS (months)	75 vs. 64		NR vs. NR		36-month OS: 78 vs. 68%		NR vs. NR		NR vs. NR		NR vs. NR	

Red indicates results meeting pre-specified statistical significance

- Induction therapy with 3 drugs are generally superior to 2 drugs
- Emerging data for induction with 4 drugs- including a proteasome inhibitor, immunomodulatory drug, and CD38 antibody

Durie et al. Lancet 2017; Facon et al. Lancet Oncology 2021; Mateos et al. Lancet 2020; Kumar et al. Lancet Oncology 2020; Moreau et al. Lancet 2019; Sonneveld et al. NEJM 2024

Role of Consolidative Autologous Stem Cell Transplant (ASCT) and Maintenance Therapy for Multiple Myeloma

CONSOLIDATION	IFM-2009		DETERMINATION	
ASCT	Early	Deferred	Early	Deferred
Induction Therapy	RVd		RVd	
Maintenance Therapy	Lenalidomide for 2 years		Lenalidomide indefinitely	
Median PFS (months)	47.3 vs. 35		67.5 vs. 46.2	
Median OS (months)	8-year OS: 62.2 vs. 60.2%		5-year OS: 80.7 vs. 79.2%	

MAINTENANCE	CALGB100104	IFM 2005-02	GIMEMA	MYELOMA XI
Treatment	R vs. Placebo			
Median PFS (months)	57.3 vs. 28.9*	41 vs. 23	31 vs. 14	39 vs. 20
Median OS (months)	113.8 vs. 84.1	3-year OS: 80 vs. 84%	3-year OS: 70 vs. 62%	3-year OS: 78.6 vs. 75.8%

* Time to progression; Red indicates results meeting pre-specified statistical significance

- ASCT improves PFS but similar OS
- Lenalidomide maintenance improves PFS and OS (in a meta-analysis of the 4 trials)

Attal et al. NEJM 2017; Perrot et al. ASH 2020; Richardson et al. NEJM 2022; Holstein et al. Lancet Hematology 2017; Attal et al. NEJM 2012; Palumbo et al. NEJM 2012; Jackson et al. Lancet 2019.

Newly Diagnosed Multiple Myeloma: Summary

- Standard induction is a combination of 3 or 4 drugs: use of a proteasome inhibitor, immunomodulatory drug and CD38 antibodies upfront increasing
- Role of upfront ASCT is evolving: improved PFS, similar OS → fewer transplant eligible patients receiving upfront ASCT
- Maintenance with lenalidomide is the current standard of care: consistently improves PFS; meta-analysis also shows improved OS
- Median PFS for first line therapy ranges from 4-7 years

Available Therapies for Multiple Myeloma

Proteasome inhibitors	Immunomodulatory drugs	CD38 antibodies
Bortezomib (V) Ixazomib (I) Carfilzomib (K)	Thalidomide (T) Lenalidomide (R) Pomalidomide (P)	Daratumumab (D) Isatuximab (Isa)

Other drugs	T cell directed therapies
Cyclophosphamide (C) Selinexor (S) Elotuzumab (E) Melphalan (M) Dexamethasone (d)	Idecabtagene Vicleucel Ciltacabtagene Autoleucel Teclistamab Elranatamab Talquetamab

Relapsed/Refractory Multiple Myeloma Landscape

1-3 Prior Lines

Len- Sensitive

-KRd
-DRd
-ERd
-IRd

Len-Refractory & Bort-Sensitive

Pom-Based
-DPd
-IsaPd
-PCd
-EPd
-VPd
-KPd

PI-Based
-DVd
-DKd
-IsaKd
-KCd
-CyBorD
-Kd
-VenVd†

Len- and Bort-Refractory

Pom-Based
-DPd
-EPd
-IsaPd
-KPd
-PCd

Carfilzomib-Based
-DKd
-IsaKd
-KCd
-KPd

Other
-Sd
-VTd
-VTd-PACE/VdCEP
-ASCT
-Cyclophosphamide-based regimen

4+ Prior Lines

IMiD Refractory, PI Refractory, Anti-CD38 MoAB Refractory

- Ide-cel
- Cilta-cel
- Teclistamab
- Talquetamab
- Elranatamab
- Sd
- Bendamustine-based regimens
- VTd-PACE/VdCEP
- Cyclophosphamide-based regimen
- Autologous Stem Cell Transplant

ASCT Candidate?

- SCT not performed as part of frontline therapy
- Durable remission after 1st ASCT (≥24 months)

ASCT, autologous stem cell transplant; R-lenalidomide; K-carfilzomib; D-daratumumab; Ixa-ixazomib; P-pomalidomide; V-bortezomib; Isa-Isatuximab; Cy-cyclophosphamide; Seli-selinexor; Ven-venetoclax (not FDA); *Dara monotherapy for frail patients. †Venetoclax only for patients with t(11;14).

Korde, Mailankody, Usmani. Bethesda Handbook of Clinical Hematology. 2023

Management of Relapsed Myeloma: Factors that decide treatment

Factors to Consider when Deciding on Treatment Options

Clinical Nature of the Relapse

-Symptomatic vs Asymptomatic

-Aggressive disease control with high dose chemotherapy

Side Effects and Toxicities

-Peripheral neuropathy

-Cardiovascular/Renal Dysfunction hx

-Blood counts

-Immune recovery

Mechanism of Action

-Response to prior therapies

-Alternate mechanism of action

-Exposure to a class of drug

-Refractoriness to a class of drug

Patient Factors

-Frailty/Fragility

-Distance to center

-Oral vs. infusion

-Trial eligibility

Management of Relapsed Myeloma: Not Lenalidomide-refractory

	POLLUX		ASPIRE		TOURMALINE-MM1		ELOQUENT-2	
	DRd	Rd	KRd	Rd	IRd	Rd	ERd	Rd
Prior Lines of Therapy	1-3		1-3		1-3		1-3	
ORR	93%	76%	87%	67%	78%	72%	79%	66%
≥ CR	43%	19%	32%	9%	14%	8%	4%	7%
PFS (months)	44.5 vs. 17.5		26.3 vs. 17.6		20.6 vs. 14.7		19.4 vs 14.9	
OS (months)	79.7 vs. 67.6		48.3 vs. 40.4		53.6 vs. 51.6		48.3 vs 39.6	

Red indicates results meeting pre-specified statistical significance

- With increasing use of maintenance, most patients are lenalidomide refractory
- 3 drug combinations are consistently better than 2 drugs in this setting

Dimopoulos et al. JCO 2023; Siegel et al. JCO 2018; Richardson et al. JCO 2021; Dimopoulos et al. Blood Cancer Journal 2020

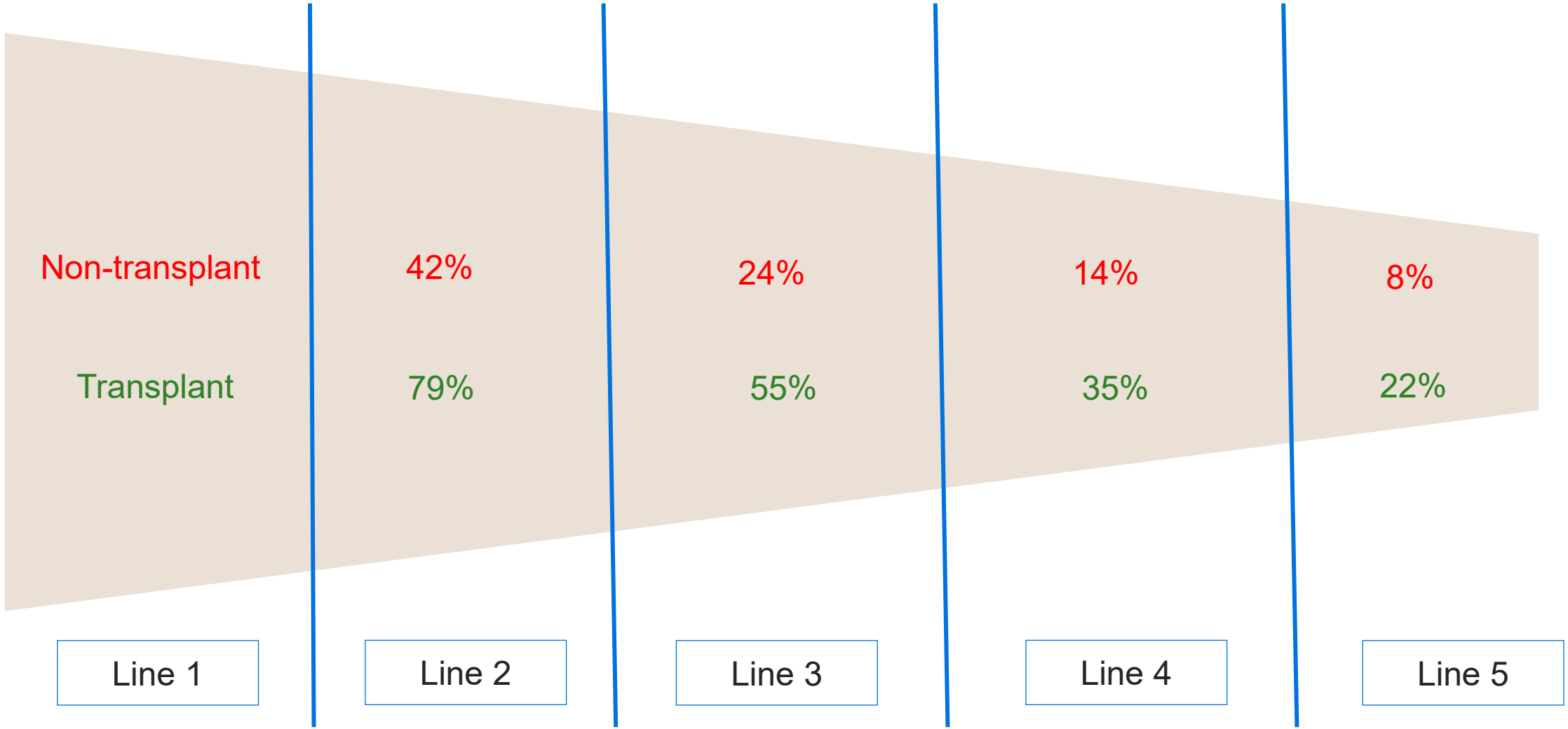
Management of Relapsed Myeloma: Lenalidomide-refractory

	CASTOR		BOSTON		CANDOR		IKEMA		ICARIA		APOLLO		ELOQUENT-3	
	DVd	Vd	SVd	Vd	DKd	Kd	IsaKd	Kd	Isa-Pd	Pd	DPd	Pd	EPd	Pd
Prior Lines of Therapy	2+		1-3		1-3		1-3		2+		2+		2+	
ORR	85%	63%	76%	62%	84%	73%	87%	84%	60%	35%	69%	46%	53%	26%
≥ CR	30%	10%	17%	10%	33%	13%	44.1%	29%	5%	1%	25%	4%	8%	2%
Median PFS (months)	16.7 vs. 7.1		13.9 vs. 9.5		28.4 vs 15.2		35.7 vs. 19.2		11.5 vs 6.5		12.4 vs 6.9		10.3 vs 4.7	
Median OS (months)	49.6 vs 38.5		NR vs 25		50.8 vs 43.6		NR vs. 50.6		24.6 vs 17.7		34.4 vs 23.7		29.8 vs 17.4	

Red indicates results meeting pre-specified statistical significance

Sonneveld et al. JCO 2023; Grosicki et al. Lancet 2020; Usmani et al. Blood Advances 2023; Martin et al. Blood Cancer Journal 2023; Richardson et al. JCO 2021; Dimopoulos et al. Blood 2022; Dimopoulos et al. JCO 2023

Attrition Through Lines of Therapy



Fonseca et al. BMC Cancer 2020

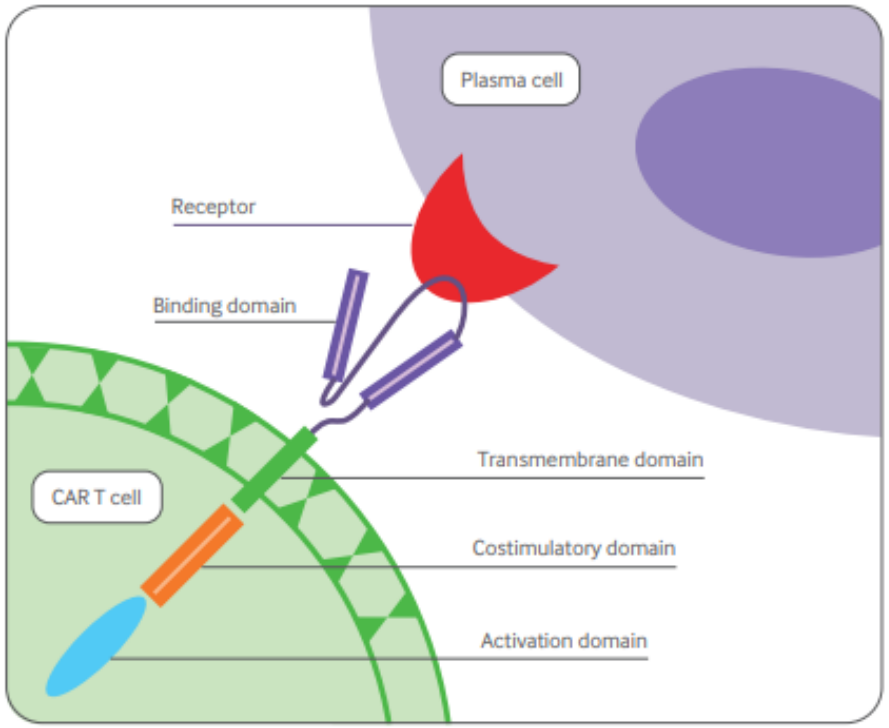
Outcomes for patients with triple class exposed myeloma

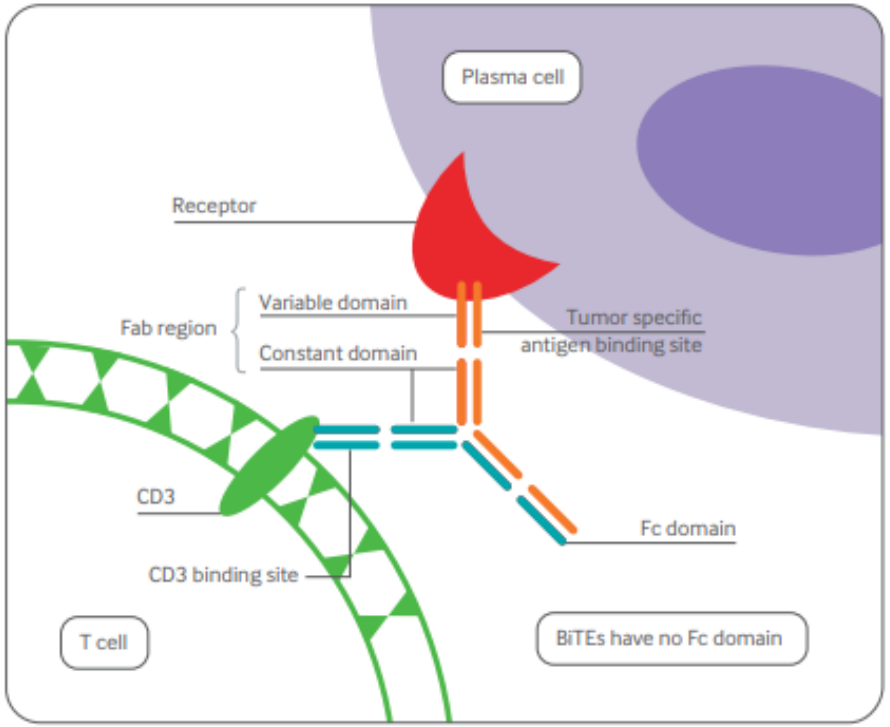
	MAMMOTH	LocoMMotion
Study Type	**Retrospective observational**	**Prospective observational**
Response Rate (%)	31	30
Median PFS (months)	3.4	4.6
Median OS (months)	9.3	12.4

Paucity of prospective long-term data for triple class exposed patients- limited available data suggests response of around 30% and median PFS of less than 6 months

Gandhi et al. Leukemia 2020; Mateos et al. Leukemia 2022

T cell Redirecting Therapies: CAR T Cells and Bispecific Antibodies





Shah U, Mailankody S, BMJ 2020

Immune Therapies for Patients with 4 or More Prior Lines

	Ide-cel	Cilta-cel	Teclistamab	Elranatamab	Talquetamab*
Efficacy					
Median Prior Lines of Therapy	6	6	5	5	6
ORR (%)	73	98	63	61	73
≥ CR (%)	33	83	39	35	NA
Median PFS (months)	8.8	34.9	11.3	NR (15-month estimate: 50.9%)	11.9
Safety					
CRS (%)	84	95	72	58	75
ICANS (%)	18	21	15	3	11
Infections (%)	69	58	76	70	65

* Data presented for Talquetamab 800 µg/kg dosing

Munshi et al. NEJM 2021; Berdeja et al. Lancet 2021; Martin et al. JCO 2022; Moreau et al. NEJM 2022; Lesokhin et al. Nature Medicine 2023; Chari et al. NEJM 2022; Schinke et al. ASCO 2023

Key Adverse Events Associated with T Cell Therapies

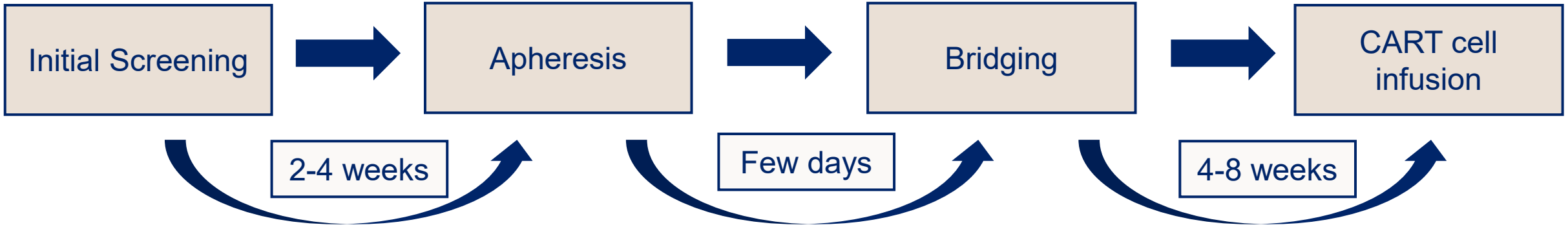
Cytokine Release Syndrome (CRS)

- Symptoms include fever, hypotension, hypoxia
- Any grade CRS in 70-95%; Grade 3 or higher in <5%
- Treatment includes IL6 blocking drugs, steroids
- Some patients with more severe hemophagocytic syndromes

Immune Effector Cell Associated Neurologic Toxicities (ICANS)

- Symptoms include lethargy, confusion, somnolence, seizures
- Any grade CRS in 20-25%; Grade 3 or higher in <5%
- Treatment includes steroids, anakinra
- Some patients with a distinct delayed neurologic syndrome of Parkinson's like features or cranial neuropathies

Logistics of CAR T cell therapies



- Determine eligibility
- Slot availability
- Donor room
- Catheter placement
- Treatment washout

- 60-80% of patients need bridging
- Limited options for bridging
  - Low responses
  - High toxicities
- Treatment washout

- Higher rates of CAR T related toxicities with refractory disease

- Can take 8-12 weeks for eligible patients to get CAR T cell infusion
- Rapid progression and refractory disease, particularly when bridging options are limited is a key challenge
- Bispecific antibodies targeting BCMA maybe preferred in these settings due to ease of access

Challenges with Immune Therapies

	CAR T cell therapies	Bispecific antibodies
Specialized centers	Yes	Maybe
Inpatient/close outpatient	++	+
CRS/ICANS	++	+
Infections	+	++
Availability	More limited	Off-the-shelf
Turn around time	4-8 weeks	NA
Efficacy	++	++
Cost	++	++
Bridging therapy	Yes and often limited options	No

Relapsed or Refractory Multiple Myeloma: Summary

- Multiple available treatment regimens but significant overlap in options
- Cross resistance to drugs and attrition through lines of therapy limits options
- Triple class exposed myeloma is a significant challenge with limited data on long term survival outcomes
    - T cell redirecting therapies (CAR T cells and bispecific antibodies) have high response rates in the triple class exposed setting
    - Limited long term and randomized survival and safety data thus far

Summary

- Substantial progress in the management of myeloma: 19 different FDA approved treatments with most approved in the last 2 decades
- Consistent improvement in survival in clinical trial and population-based studies
- Despite this improvement, most patients with a diagnosis of myeloma will die from the diagnosis

Thank you!

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Thank you to our patients, families and caregivers!

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