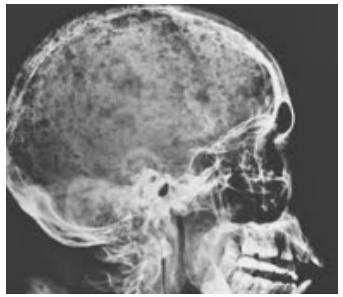
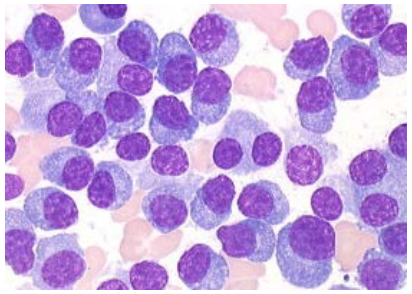
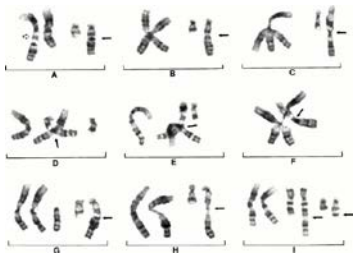
Autologous Stem Cell Transplantation and Cellular Therapy In Multiple Myeloma

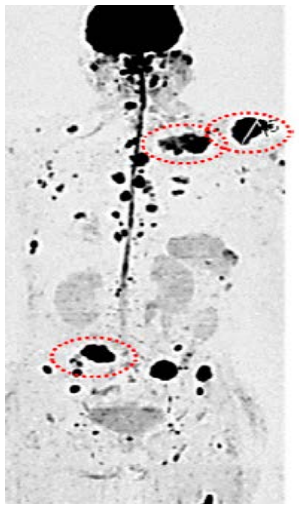
MEERA MOHAN MD, MS
ASSISTANT PROFESSOR OF MEDICINE
MEDICAL COLLEGE OF WISCONSIN, MILWAUKEE

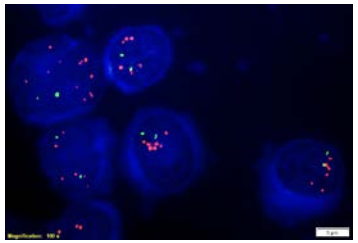
Multiple Myeloma originates from a malignant clone of plasma cells, terminally differentiated B-lymphocytes

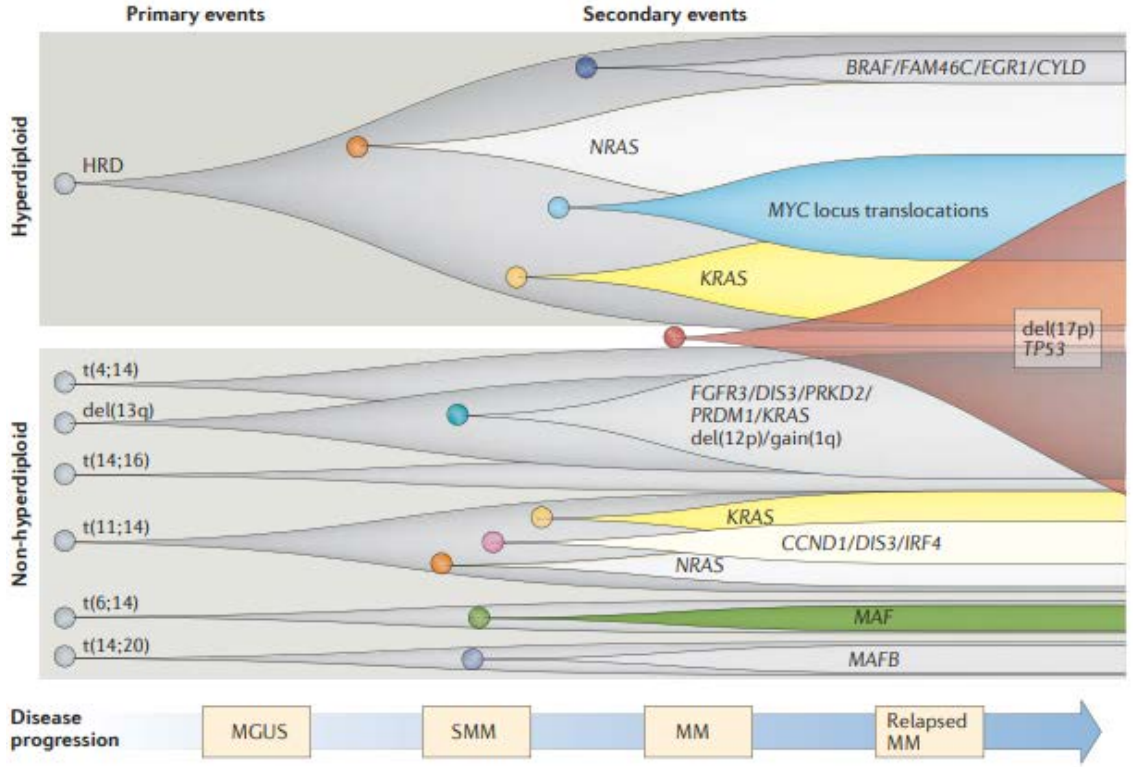






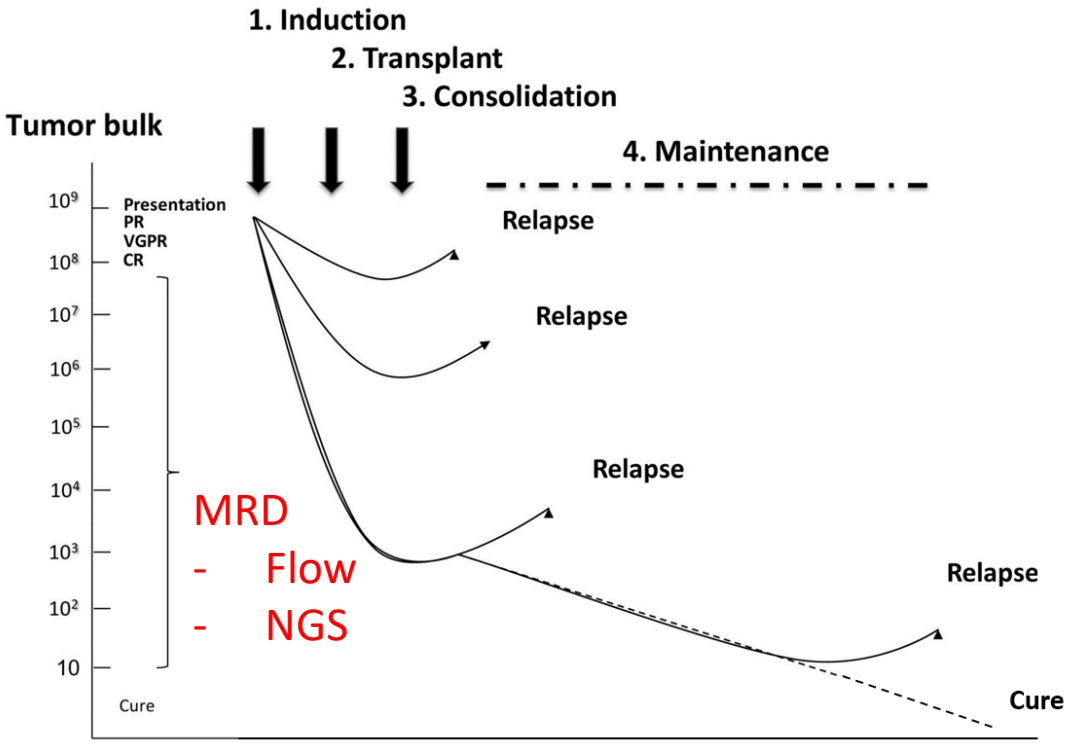


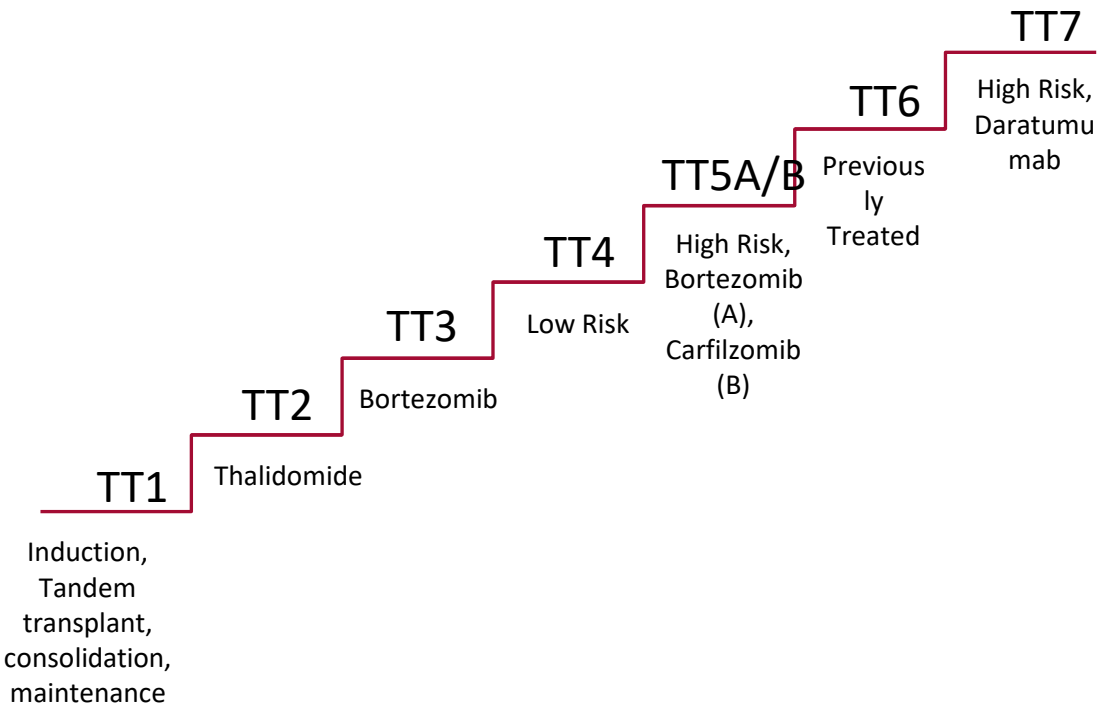




Sawyer, et al. *Blood* 1998;91:1732-1741
Morgan GJ, et al. *Nat Rev Cancer* 2012;12:335-348
Manier S, et al. *Nat Rev Clin Oncol* 2017;14:100-113

Cause of Relapse: Suboptimal Depth of Response





Total Therapy Clinical Trials

Morgan et al. Blood 2003
Nishimura, Barlogie et al.2020,Blood advances
Morgan G, et al.. 2012 Nat Rev Cancer

Role of Upfront Autologous Stem Cell Transplant

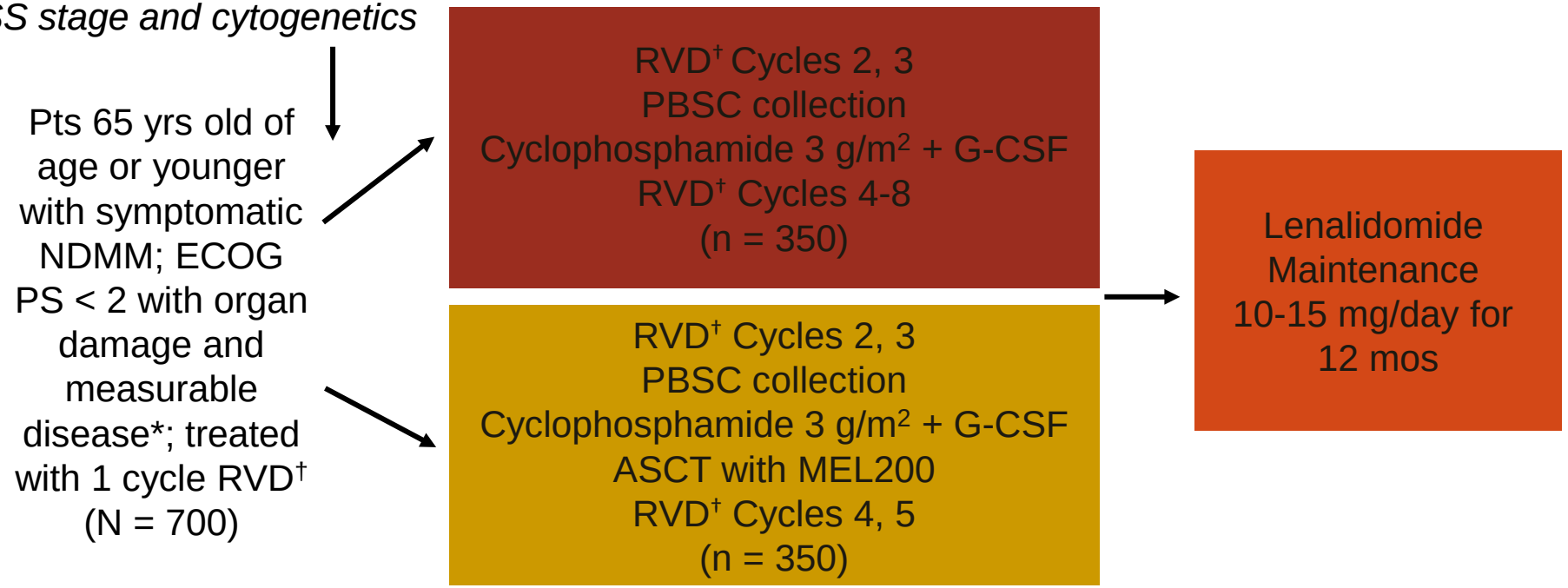
Trials comparing high-dose chemotherapy and ASCT with novel agent–based regimens without ASCT

Trials	Study Design	PFS , Median	OS , Median
RV-MM-209	MPR x 6 cycles vs HDC ASCT x2	43m vs 22 m (p<0.001)	4y 82% vs 65% (p=0.02)
EMN 442	CRD x 6 cycles vs HDC ASCT x2	43 vs 29 m (p<0.001)	4y 86% vs 73% (p=0.004)
EMN02/HO99	VMP x 4 cycles vs HDC ASCT (1 vs 2)	56·7m vs 41·9m (p=0·0001)	5y 75.1% vs 71.6% (p=0.35)
IFM 2009	RVD x 5 cycles vs HDC ASCT x1 + RVD 2 cycles	50m vs 36m (p<0.001)	8y 62.2% (ASCT) % vs 60.2% (RVD) p=NS

Palumbo et al 2014, Gay et al 2015,Cavo 2020, Attal 2017

Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma: IFM 2009

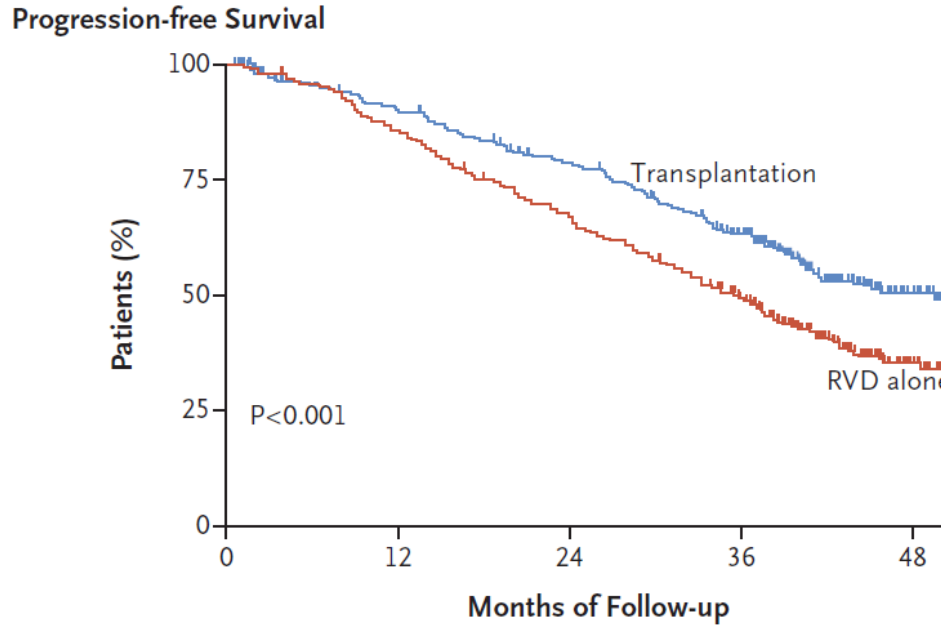
Stratified by ISS stage and cytogenetics



*Serum M-protein > 10 g/L and/or urine M-protein > 200 mg/24 hrs and/or serum FLC > 100 mg/L if serum FLC ratio is abnormal.
†Lenalidomide 25 mg/day on Days 1-14; bortezomib 1.3 mg/m^2 on Days 1, 4, 8, 11; dexamethasone 20 mg/day on Days 1, 2, 4, 5, 8, 9, 11, 12.

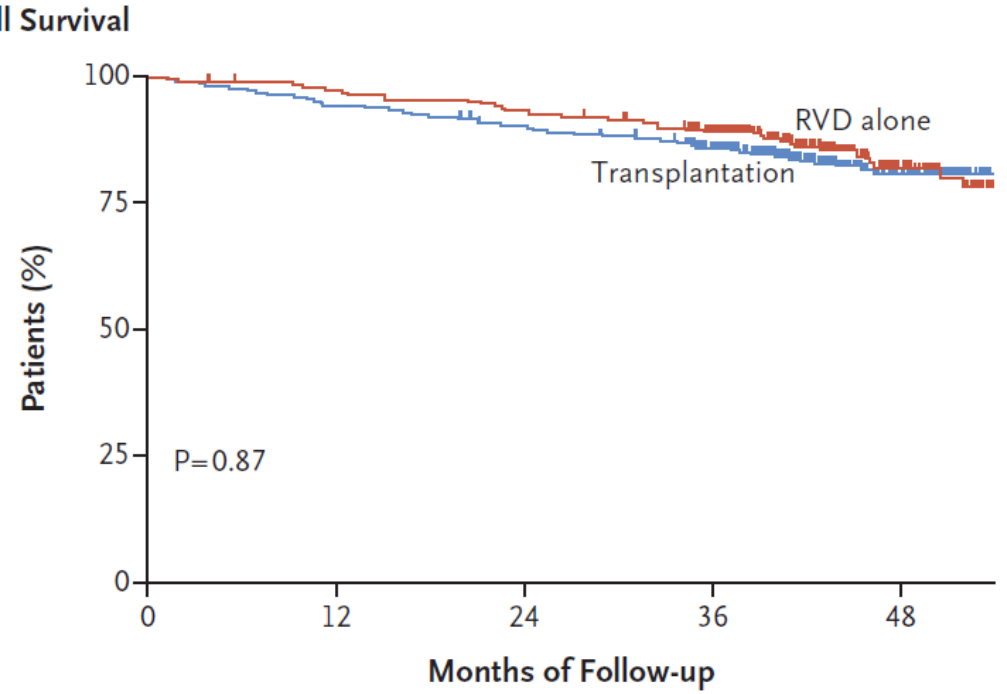
Attal M, et al. NEJM 2017.

High-dose chemotherapy plus transplantation was associated with significantly longer progression free survival



No. at Risk

RVD alone	350	294	228	157	32
Transplantation	350	308	264	196	50



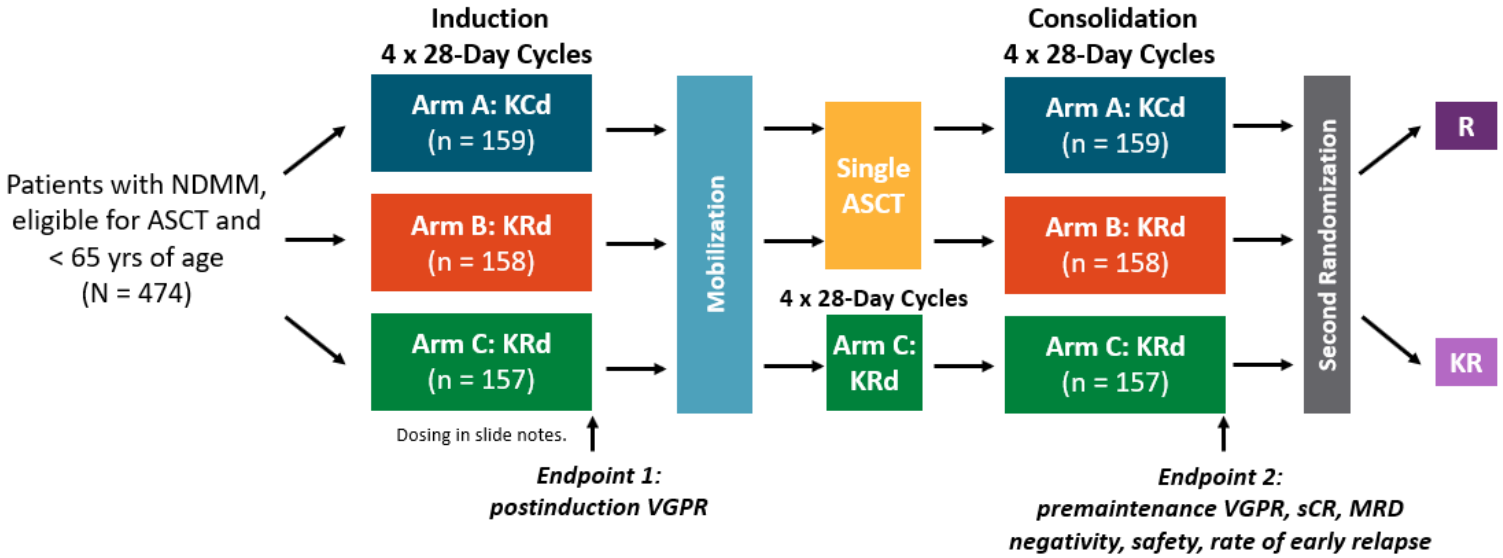
No. at Risk

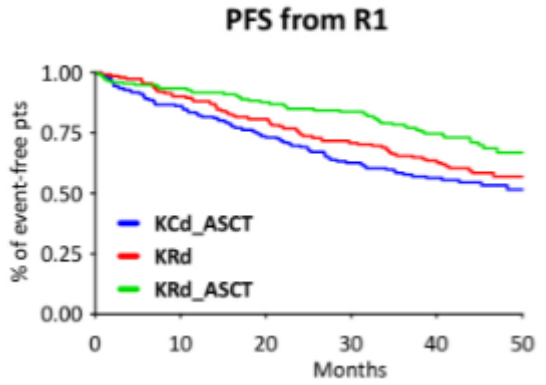
RVD alone	350	339	325	293	95
Transplantation	350	330	313	281	89

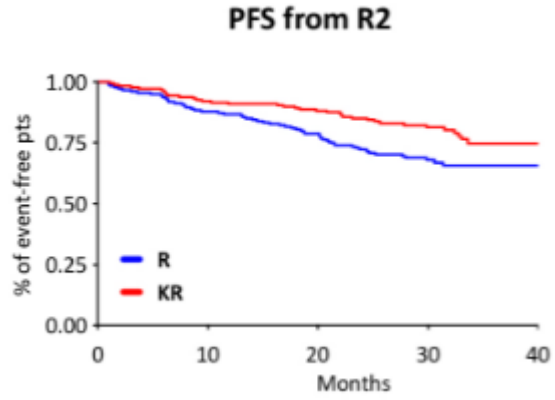
Attal M, et al. NEJM 2017

Carfilzomib-based induction/consolidation with or without autologous transplant (ASCT) followed by lenalidomide (R) or carfilzomib-lenalidomide (KR) maintenance FORTE Trial

- Multicenter, randomized, open-label phase II study





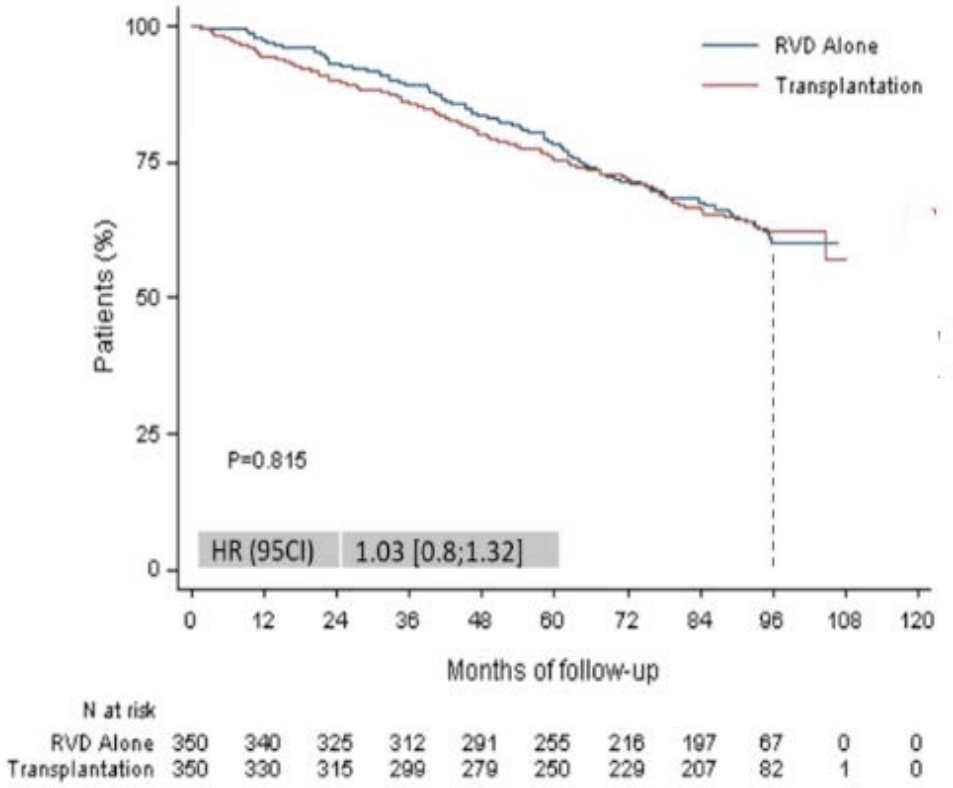


Gay et al ASH 2020

Role of Delayed Autologous Stem Cell Transplant

Early Versus Late Autologous Stem Cell Transplant in Newly Diagnosed Multiple Myeloma: Long-Term Follow-up Analysis of the IFM 2009 Trial

8-year OS 62.2% (ASCT) % vs 60.2% (RVD)



- Transplant significantly reduced the risk of progression or death by 30% compared to RVd alone
- 35% of patients in the transplant arm didn't relapse until after 8 years
- More patients achieved MRD negativity with transplant

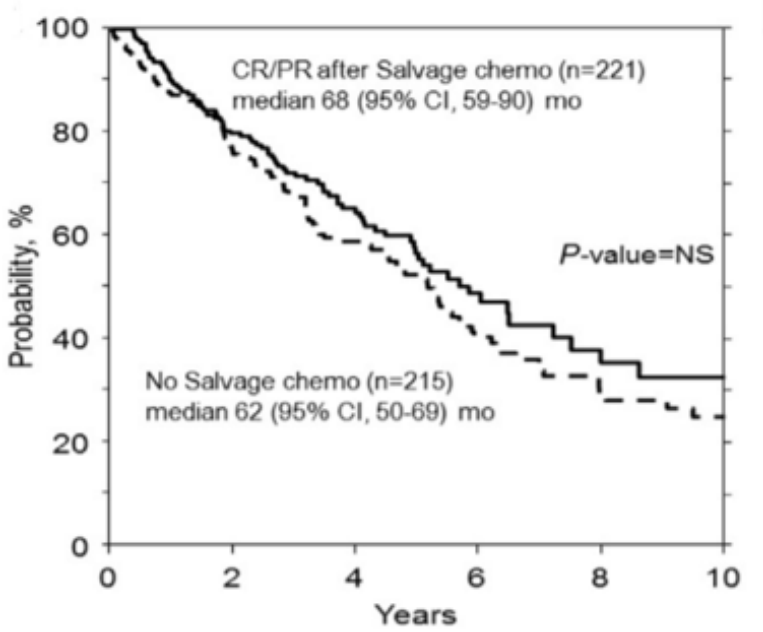
Perrot et al ASH 2020

Early versus Delayed ASCT

Ref.	Year	Study type	Induction regimen (early ASCT vs delayed ASCT)	Response (early vs delayed ASCT)	PFS (early vs delayed ASCT)	OS (early vs delayed ASCT)
Fermand et al	1998	P	VAMP × 3-4 cycles and ASCT vs VMCP until plateau and ASCT at relapse	85.7% vs 55.5%	39 mo vs 13 mo	64.6 mo vs 64 mo (P = .92)
Attal et al	2017	P	VRD × 3 cycles and ASCT + VRD × 2 cycles vs VRD × 8 cycles and ASCT at relapse	CR: 59% vs 48% (P = .03)	50 mo vs 36 mo (P < .01)	4 y: 81% vs 82%
Kumar et al	2012	r	TD or RD × 4-6 cycles followed by early or delayed ASCT		20 mo vs 16 mo (P = NS)	4 y: 73% vs 73% (P = .3)
Dunavin et al	2013	r	T-, R-, or V-based induction followed by early or delayed ASCT	≥VGPR: 77% vs 55% (P < .01)	28 mo vs 18 mo (P = .11)	NR vs 83 mo (P = .45)
Remenyi et al	2016	r	57% in early ASCT and 53.2% in delayed ASCT group received novel therapies	CR: 58.1% vs 46.8% (P = .016)	30.2 mo vs 23.3 mo (P = .036)	97.2 mo vs 99.1 mo (P = .77)

Kumar et al Blood 2018

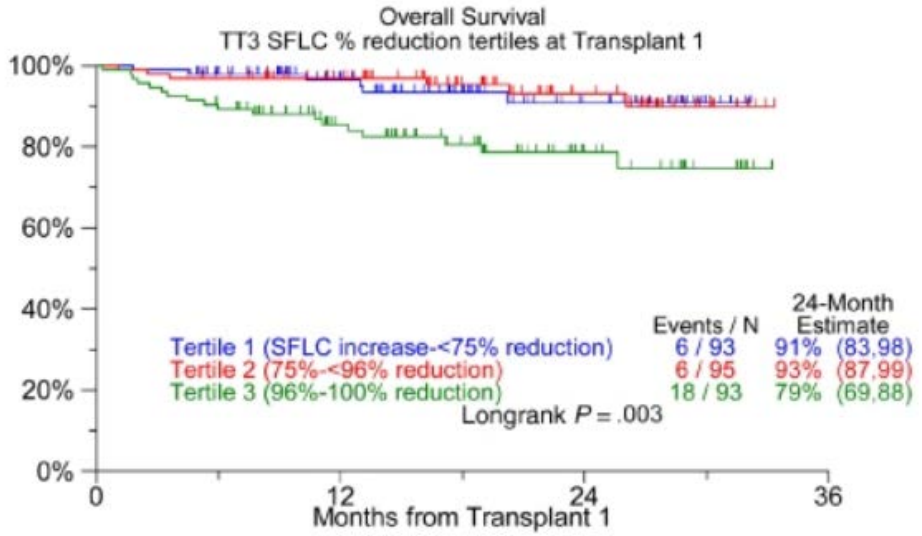
Outcome of patients who have sub-optimal pre ASCT response



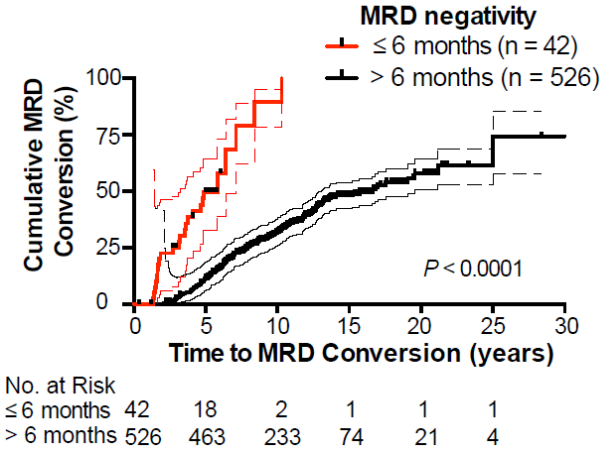
- Additional pretransplant chemotherapy resulted in deepening responses
- There was no impact of pretransplant salvage chemotherapy on treatment-related mortality, risk for relapse, progression-free survival, or overall survival
- Transplant-eligible patients who achieve a suboptimal response to initial induction therapy should move on to planned ASCT

Vij et al Bio Blood marrow Transplant 2015

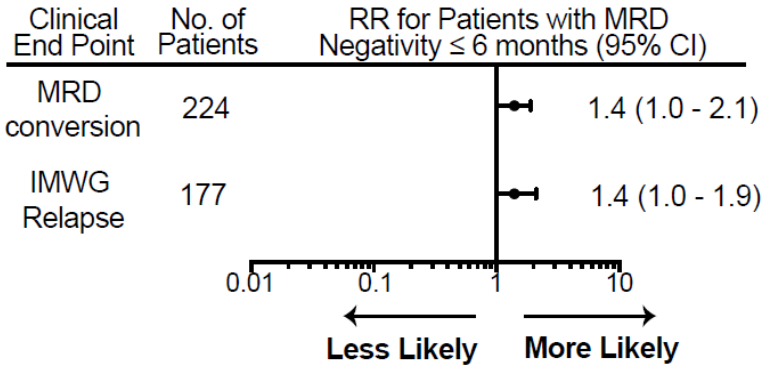
Response Kinetics and Long-term Outcome in MM



OS was inferior among patients with the top-tertile reduction in serum-free light chain compared with the rest of the patients when the response was measured before ASCT
(2-year OS, 79% vs 92%; HR, 3.31; P 5 .001).



Patients with early MRD negativity experienced a shorter time to MRD conversion (*P* <0.0001).



Early attainment of MRD negativity (within 6 months from start of therapy) was associated with a higher risk of MRD conversion (57%, 24/42 *vs.* 38%, 200/526; *P* = 0.02) and IMWG relapse (50%, 21/42 *vs.* 29%, 156/526; *P* = 0.009).

Vanrhee et al Blood 2007
Mohan et al Blood Advances (In press)

Role of Tandem Autologous Stem Cell Transplant

Studies Comparing Single and Double ASCT

Source	Study Design	PFS, Median	OS, Median
Attal 2003	Mel at 140 mg/m^2 + TBI at 8 Gy + ASCT vs Mel at 140 mg/m^2 + ASCT1 → Mel at 140 mg/m^2 + TBI at 8 Gy + ASCT2	25 vs 36 mo	48 vs 58 mo
		P = .03	*P* = .1
Fermand 2003	Mel at 140 mg/m^2 + ASCT vs Mel at 140 mg/m^2 + ASCT1 → Mel at 140 mg/m^2 + VP16 + TBI at 12 Gy + ASCT2	31 vs 33 mo	—
		—	
Cavo 2007	Mel at 200 mg/m^2 + ASCT vs Mel at 200 mg/m^2 ASCT1 → Mel at 140 mg/m^2 + Bu at 1 mg/kg + ASCT2	25 vs 35 mo	65 vs 71 mo
		P = .01	*P* = .9
Mai 2016	Mel at 200 mg/m^2 + ASCT × 1 vs Mel at 200 mg/m^2 + ASCT × 2	25 vs 29 mo	75 vs 79 mo
		P = NS	*P* = NS
Cavo 2016	Mel at 200 mg/m^2 + ASCT × 1 vs Mel at 200 mg/m^2 + ASCT1 × 2	45 mo vs NR	—
		3 y: 60% vs 73%	
		P = .03	
Stadtmauer 2016	Mel at 200 mg/m^2 + ASCT1 → lenalidomide maintenance vs Mel at 200 mg/m^2 + ASCT × 2 → lenalidomide maintenance	38 mo: 57% vs 52%	38 mo: 82% vs 83%
		P = NS	*P* = NS

Abbreviations: ASCT, autologous stem cell transplantation; ASCT1, first autologous stem cell transplantation; ASCT2, second autologous stem cell transplantation; Bu, busulphan; Mel, melphalan; NR, not reported; NS, not significant; OS, overall survival; PFS, progression-free survival; TBI, total body irradiation; VP16, etoposide.

Mina et al 2020

STaMINA : Study Design

Randomized, open-label phase III trial

Stratified by risk group (high vs standard)

ASCT-eligible patients
≤ 70 yrs with symptomatic MM and ≥ 2 cycles systemic tx initiated in past 12 mos; no prior progression; adequate organ function;
(N = 758)

Melphalan
200 mg/m² IV
+ ASCT

ASCT/Maintenance Group
Lenalidomide maintenance until PD
10 mg/day for 3 cycles, then 15 mg/day*
(n = 257)

ASCT/RVD Group
Bortezomib 1.3 mg/m² IV Days 1, 4, 8, 11
Lenalidomide 15 mg Days 1-15
Dexamethasone 40 mg IV Days 1, 8, 15
Four 28-day cycles
(n = 254)

ASCT/ASCT Group
Melphalan 200 mg/m² IV
+ Second ASCT
(n = 247)

Lenalidomide Maintenance until PD
10 mg/day for 3 cycles, then 15 mg/day*

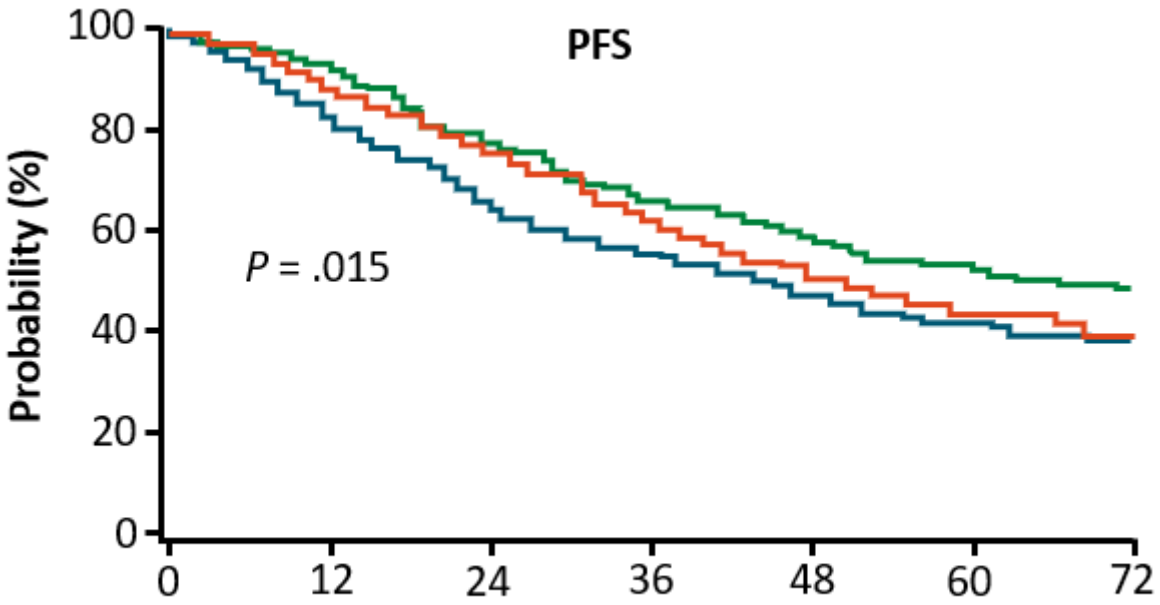
secondary endpoints: OS, ORR, CR conversion rate, safety, infections, tx-related mortality, QoL

Current analysis assessed long-term efficacy, safety in patients with no PD at 38 mos

1. Stadtmauer. ASH 2016. Abstr LBA-1. 2. Stadtmauer. JCO. 2019;37:589. 3. Hari. ASCO 2020. Abstr 8506.

STaMINA Long-term Follow-up: PFS and OS with Tandem ASCT

PFS benefit for ASCT/ASCT cohort, most notably in high-risk group



PFS, % (Range)	ASCT/ASCT (n =170)	ASCT/RVD (n = 222)	ASCT/Maint (n = 361)
5 yrs	53.6 (46-61)	44.1 (37-50)	42.3 (37-47)
6 yrs	49.4 (41-57)	39.7 (33-46)	38.6 (33-43)

5-Yr PFS, % (Range)	ASCT/ASCT	ASCT/RVD	ASCT/Maint	P Value
High risk	43.7 (33-58)	37.3 (26-48)	32 (24-40)	.03
Standard risk	58.1 (48-67)	48.2 (40-56)	47.7 (41-54)	.196

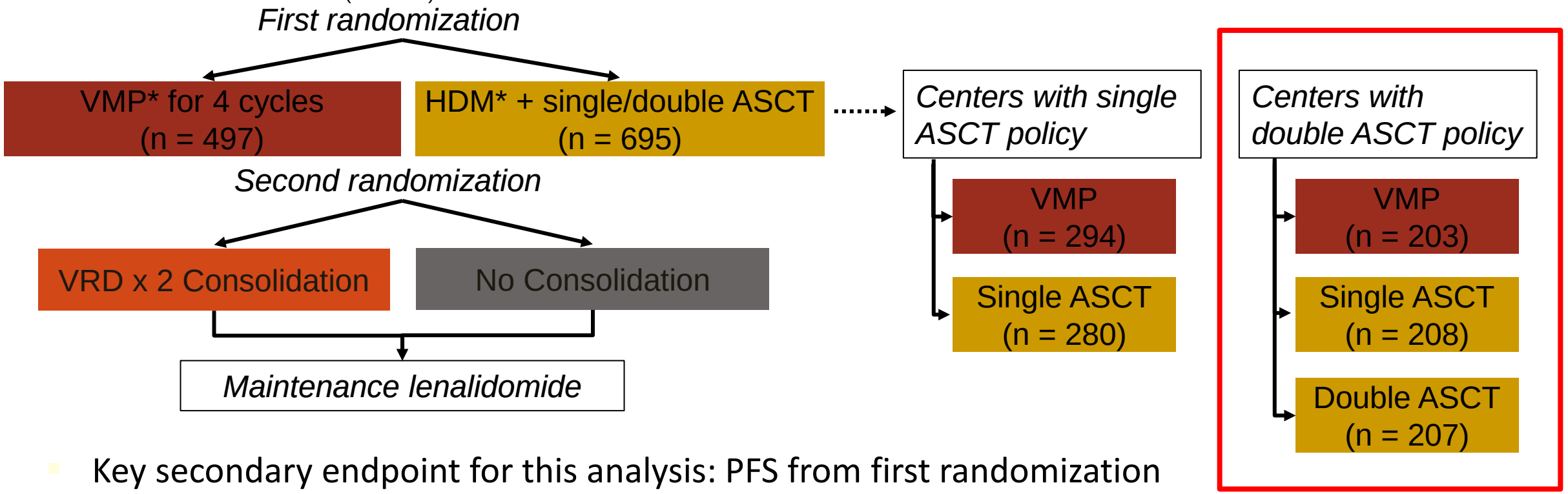
OS difference between treatment groups

Hari. ASCO 2020. Abstr 8506. Reproduced with permission.

Slide credit: clinicaloptions.com

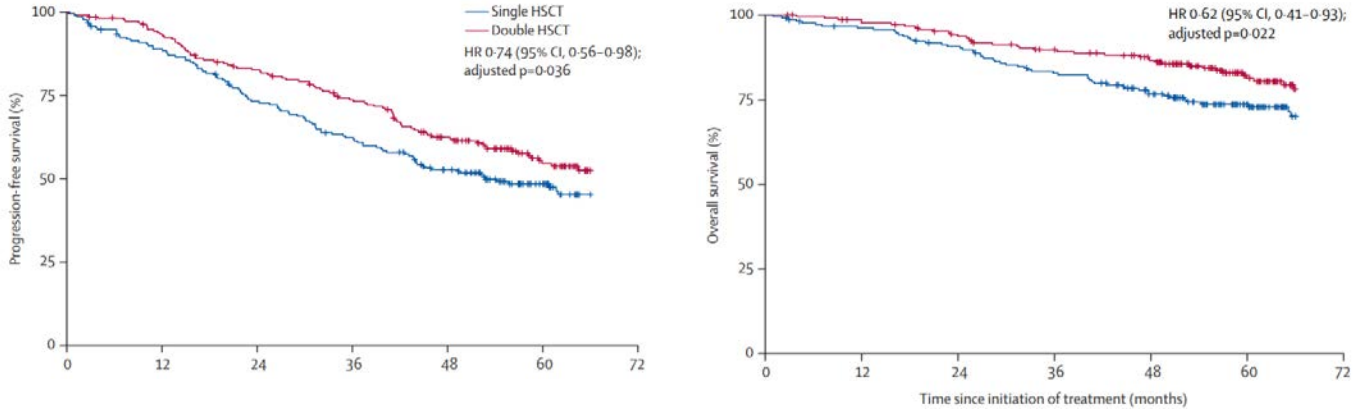
EMN02/HO95

Pts with ND MM who received VCD induction x 3-4 cycles + PBSC collection (N = 1192)

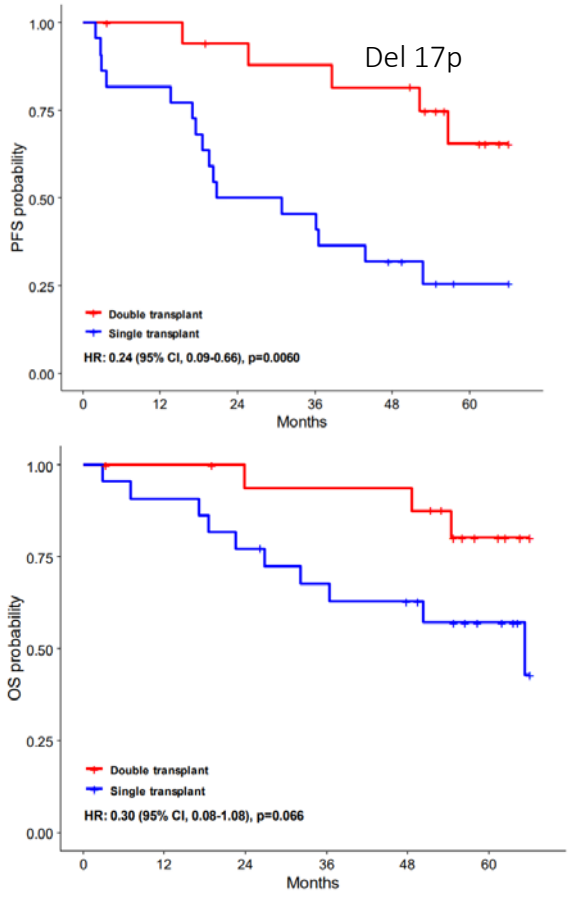


- Key secondary endpoint for this analysis: PFS from first randomization for ASCT-1 vs ASCT-2

Tandem ASCT in high-risk cytogenetics



Double HSCT significantly improved 5-year progression-free survival (53·5%) compared with single HSCT (44·9%; HR 0·74, p=0·036) and 5-year overall survival (80·3% [74·5–86·4]) than single HSCT (72·6% [66·5–79·3]; HR 0·62, 95% CI 0·41–0·93; adjusted p=0·022)



Role of Consolidation therapy

STaMINA : Study Design

Randomized, open-label phase III trial

Stratified by risk group (high vs standard)

ASCT-eligible patients
≤ 70 yrs with symptomatic MM and ≥ 2 cycles systemic tx initiated in past 12 mos; no prior progression; adequate organ function;
(N = 758)

Melphalan
200 mg/m² IV
+ ASCT

ASCT/Maintenance Group
Lenalidomide maintenance until PD
10 mg/day for 3 cycles, then 15 mg/day*
(n = 257)

ASCT/RVD Group
Bortezomib 1.3 mg/m² IV Days 1, 4, 8, 11
Lenalidomide 15 mg Days 1-15
Dexamethasone 40 mg IV Days 1, 8, 15
Four 28-day cycles
(n = 254)

ASCT/ASCT Group
Melphalan 200 mg/m² IV
+ Second ASCT
(n = 247)

Lenalidomide Maintenance until PD
10 mg/day for 3 cycles, then 15 mg/day*

secondary endpoints: OS, ORR, CR conversion rate, safety, infections, tx-related mortality, QoL

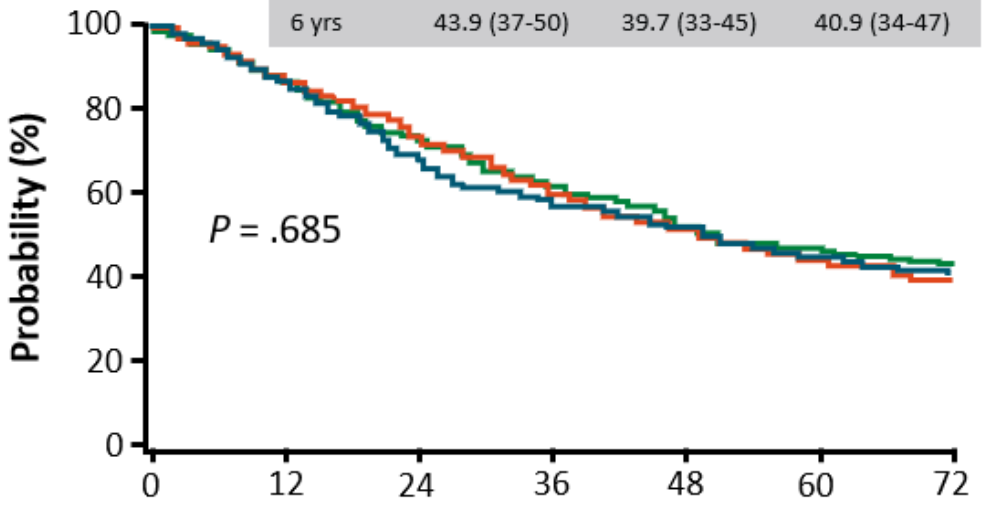
Current analysis assessed long-term efficacy, safety in patients with no PD at 38 mos

1. Stadtmauer. ASH 2016. Abstr LBA-1. 2. Stadtmauer. JCO. 2019;37:589. 3. Hari. ASCO 2020. Abstr 8506.

Autologous Transplantation, Consolidation, and Maintenance Therapy in Multiple Myeloma: Results of the BMT CTN 0702 Trial

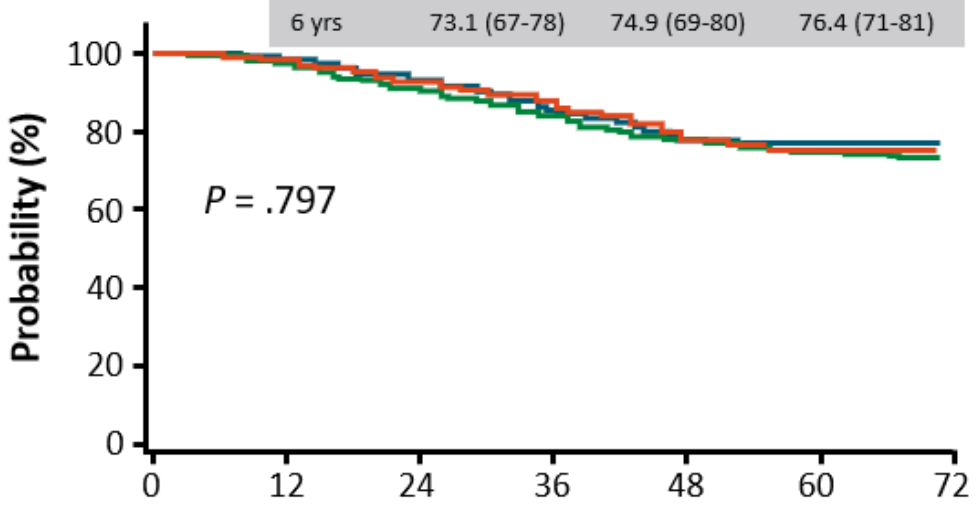
PFS

PFS, % (Range)	ASCT/ASCT	ASCT/RVD	ASCT/Maint
5 yrs	47.4 (41-53)	44.1 (38-50)	45 (38-51)
6 yrs	43.9 (37-50)	39.7 (33-45)	40.9 (34-47)



OS

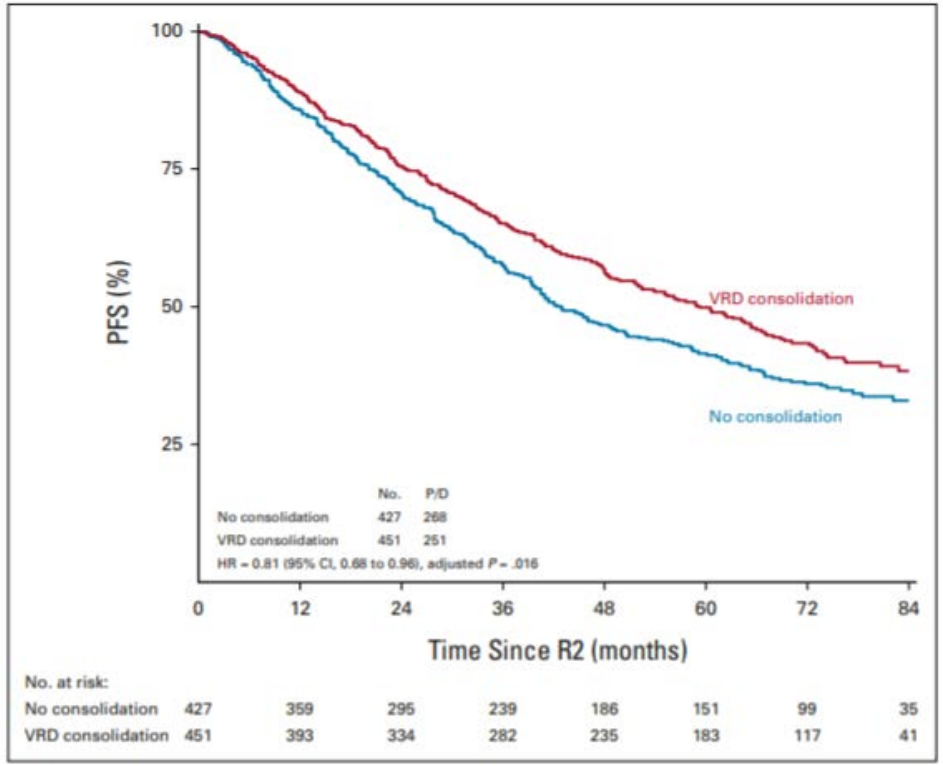
OS, % (Range)	ASCT/ASCT	ASCT/RVD	ASCT/Maint
5 yrs	74.7 (69-80)	75.4 (70-80)	76.4 (71-81)
6 yrs	73.1 (67-78)	74.9 (69-80)	76.4 (71-81)

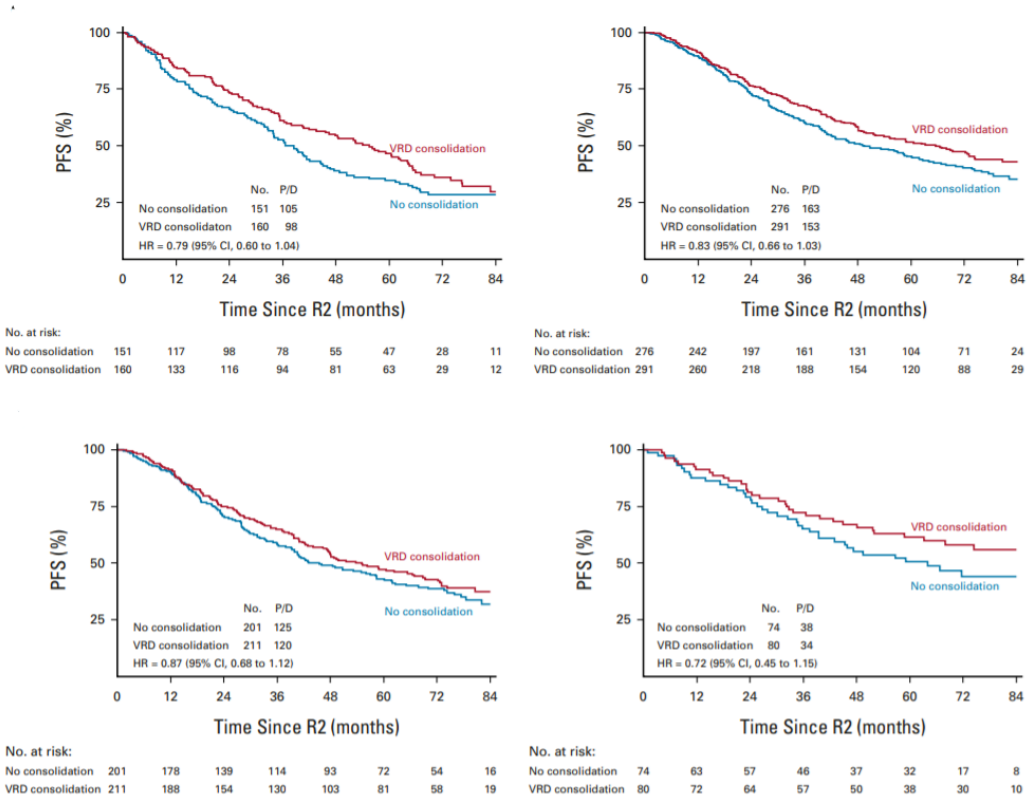


No difference between study arms for PFS and OS

No difference between study arms in incidence of SPM by 6 yrs (*P* = .745); no difference observed between hematologic vs solid cancers between study arms

Role of Consolidation : EMN02/HO95



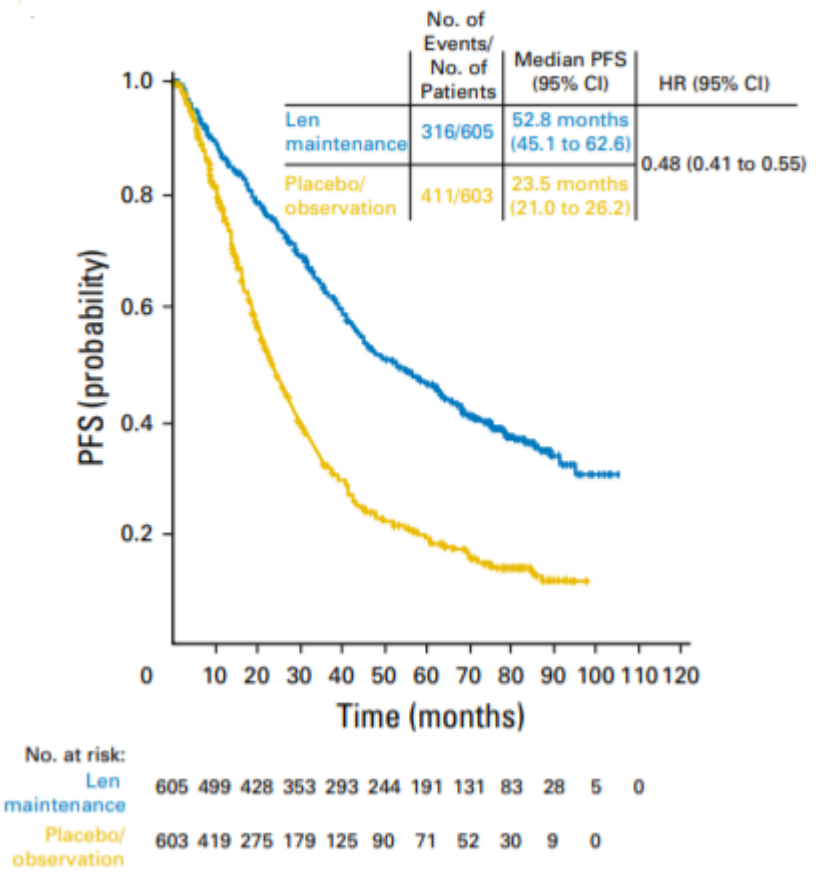


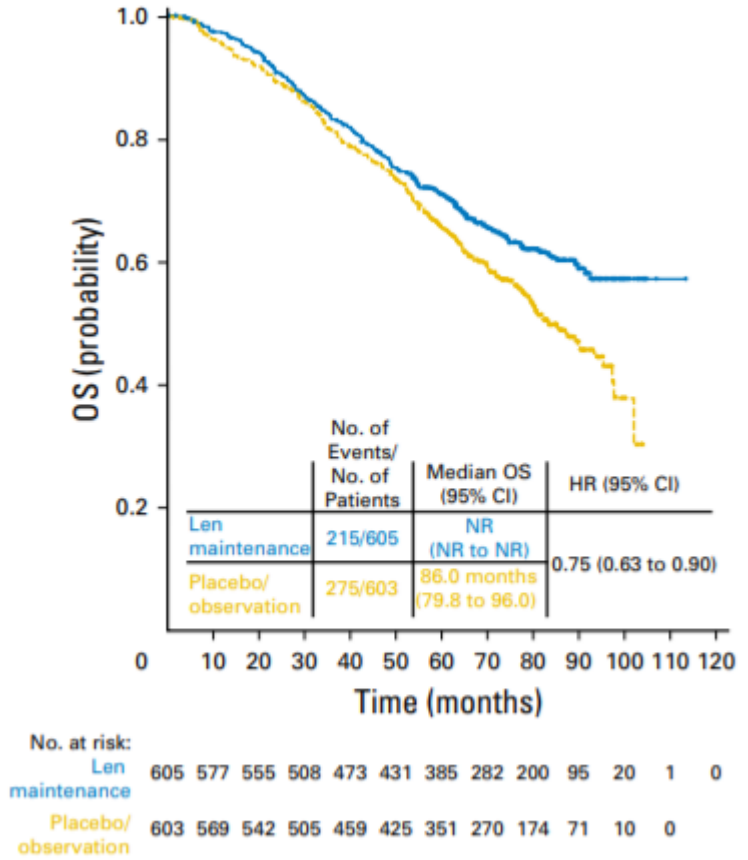
Sonneveld et al JCO 2021

Role of Maintenance therapy

Maintenance Study	Comparison	Planned Length of Maintenance	Progression free survival	Overall survival
McCarthy et al (CALGB 100104)	Lenalidomide vs. placebo	Until progression	Median PFS (46 vs. 27 months; p , .001)	3-year OS (88% vs. 80%; p = .03)
Attal et al (IFM 0502)	Lenalidomide vs. placebo after 2 months lenalidomide consolidation	Until progression, but terminated early for SPM	Median PFS (41 vs. 23 months; p , .001)	4-year OS (73% vs. 75%; p = NS)
Palumbo et al	MPR vs. tandem ASCT followed by lenalidomide vs. placebo	Until progression	Median PFS 41.9 vs. 21.6 months; (p , .001)	3-year OS (88% vs. 79.2%; p = .14)

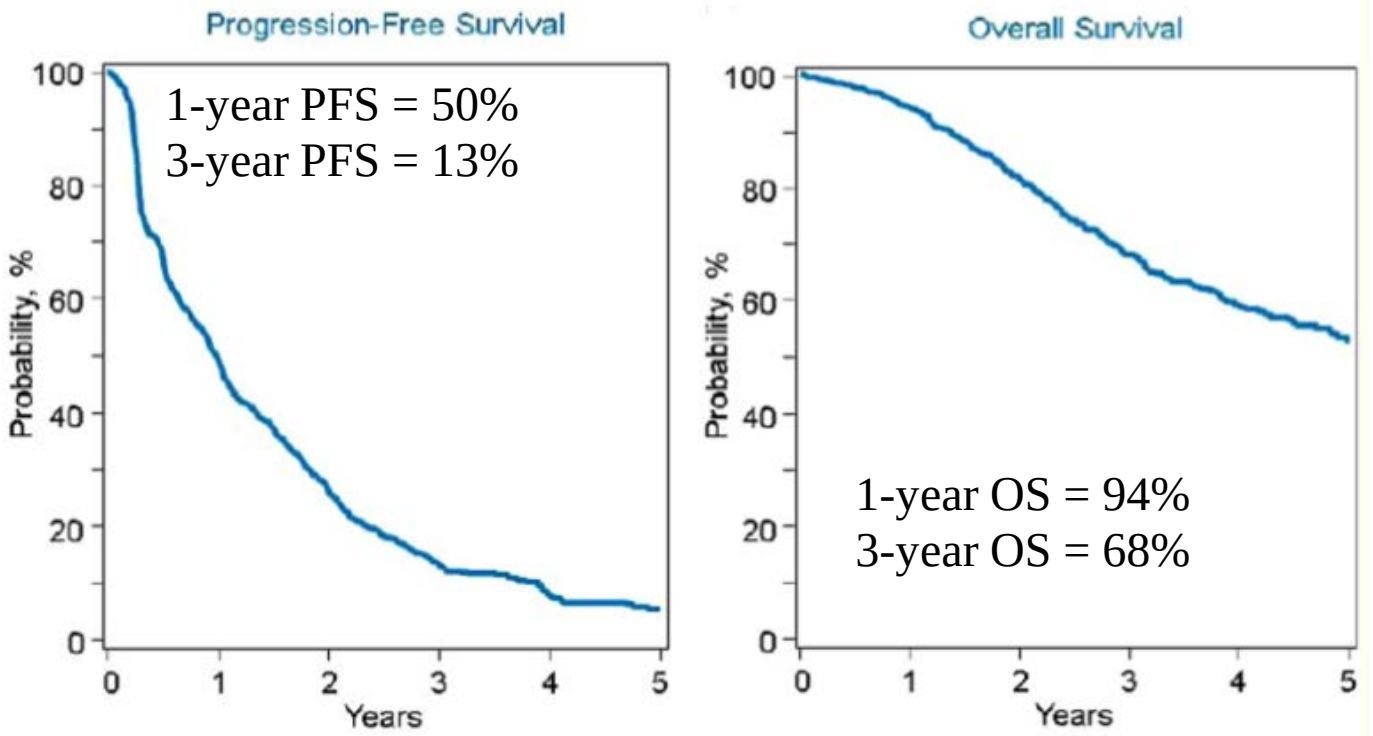
Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis

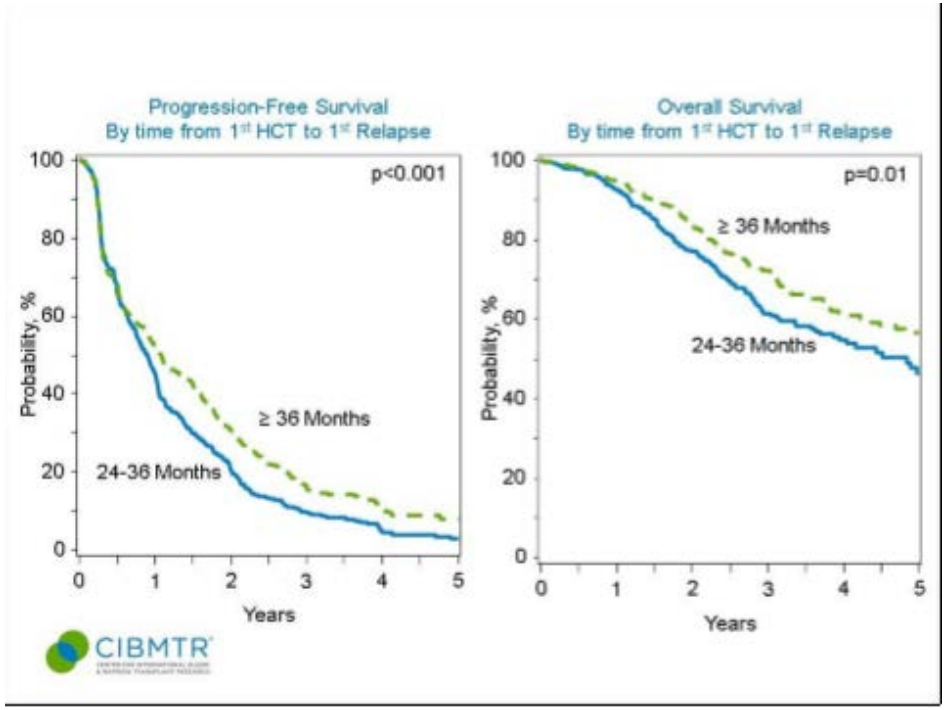




Role of Salvage Autologous Stem Cell Transplant

Salvage Second Transplantation in Relapsed Multiple Myeloma





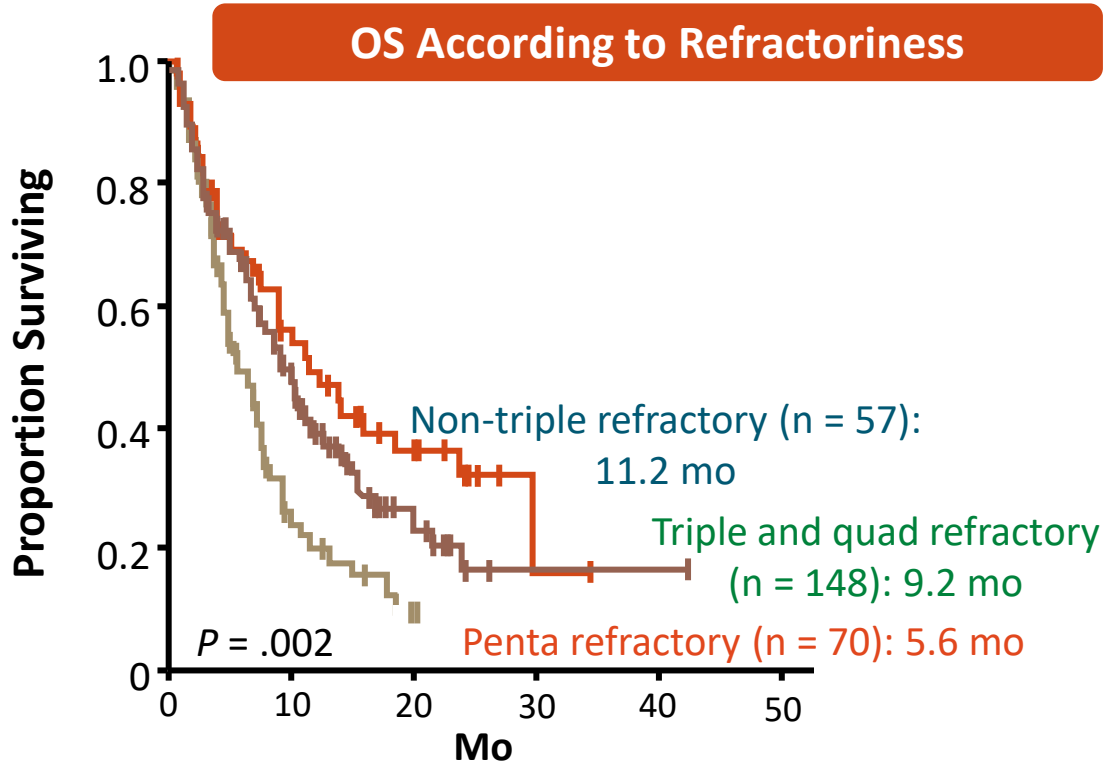
Patients relapsed ≥36 months after first AHCT had significantly better PFS and OS than those relapsing earlier

Dhakal el al Leukemia 2021

Triple class refractory and Penta refractory MM is associated with poor outcome

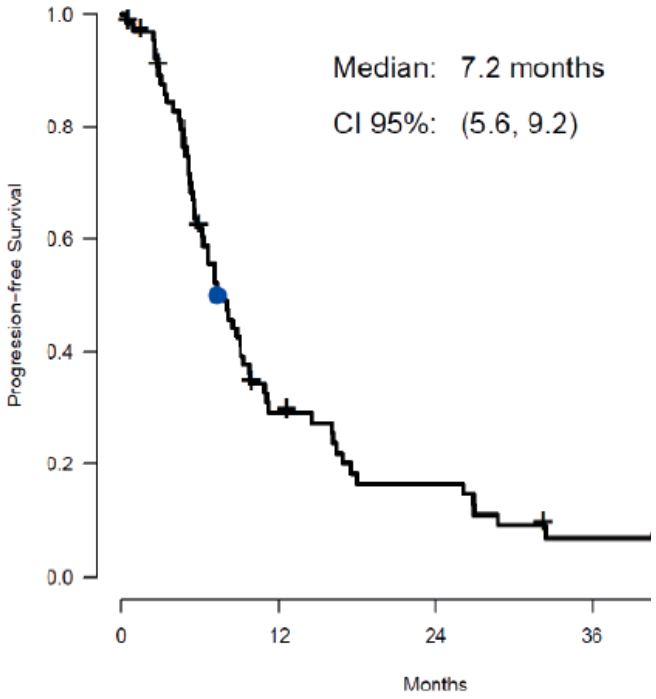
Retrospective study of 275 MM patients refractory to anti-CD38 mAbs

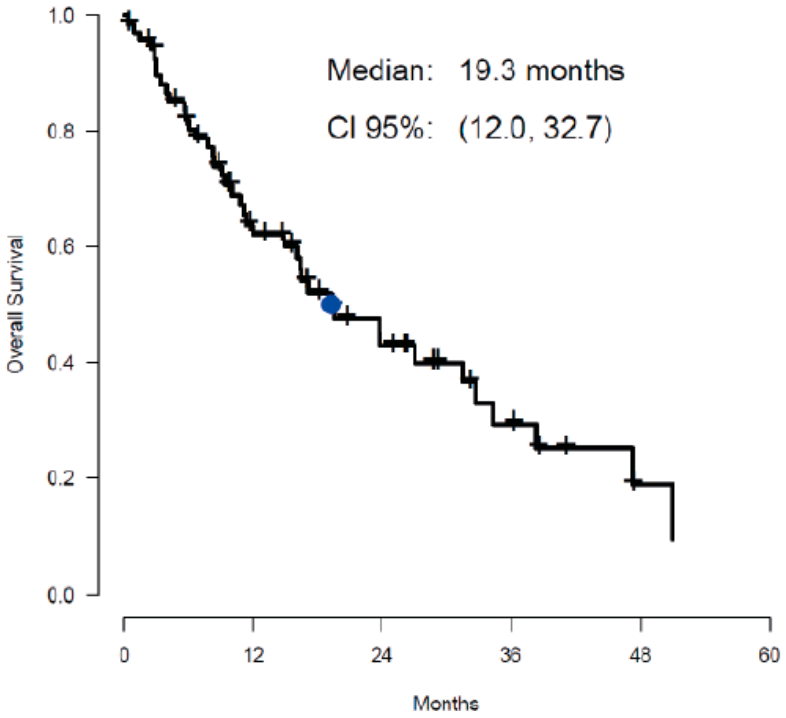
MAMMOTH	Median OS
Triple class refractory (PI, IMiD, anti-CD38)	8.6 months
Penta refractory (2 PIs,2 IMiDs,anti-CD38)	5.6 months



Non-triple refractory: refractory to 1 CD38 mAb, and not both PI and IMiD
Triple and quad refractory: refractory to 1 CD38 mAb + 1 IMiD + 1 PI; or 1 CD38 mAb + 1 PI + 1 or 2 IMiDs; or 1 CD38 mAb + 1 or 2 PIs + 1 IMiD
Penta refractory: refractory to 1 CD38 mAb + 2 PIs + 2 IMiD compounds

What is The Role of Salvage ASCT in Triple Class Refractory MM ?





Factors associated with poor outcome

1.Increasing age
2.Poor performance status
3.High GEP70 risk score at diagnosis

An increased time interval from initial ASCT to salvage ASCT showed an improved outcome but was only significant for PFS

Ide-cel clinical outcomes

Median PFS	**8.8 months**
Median OS	19.4 months

Yarlagadda et al Cancers 2021

BCMA Targeted therapy

BCMA Is Potentially One of the Best Targets in MM, With High Specificity and Expression on MM Cells

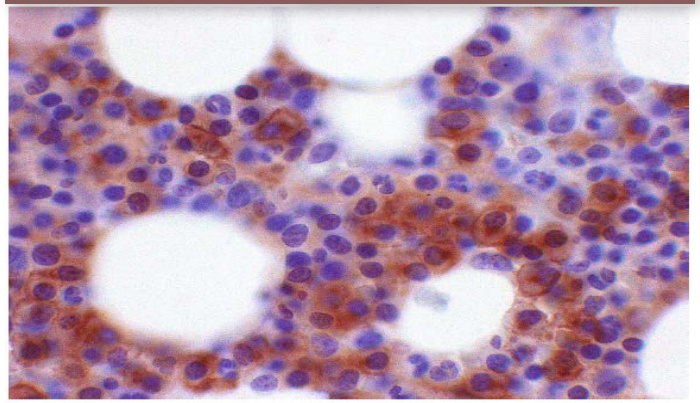
BCMA is member of the TNF receptor superfamily

- Expressed nearly universally on MM cells
- Expression largely restricted to plasma cells and some mature B-cell
- Expression of BCMA increases as disease progresses from MGUS to advanced myeloma

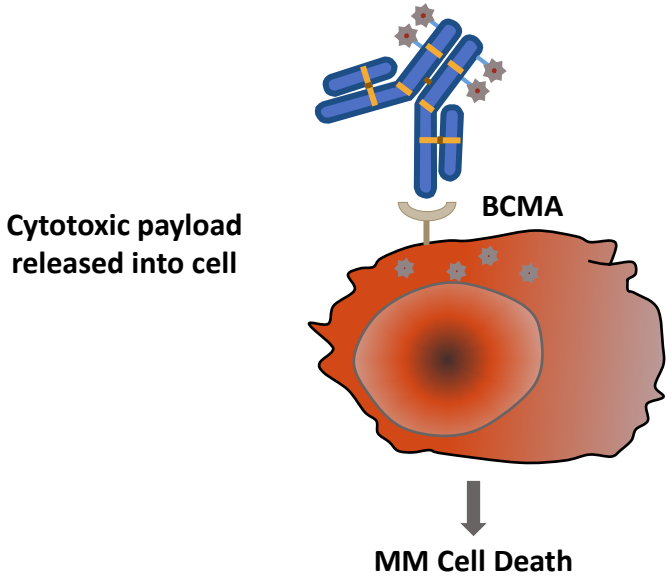
Initial proof of anti-BCMA activity demonstrated (NCI CAR construct)

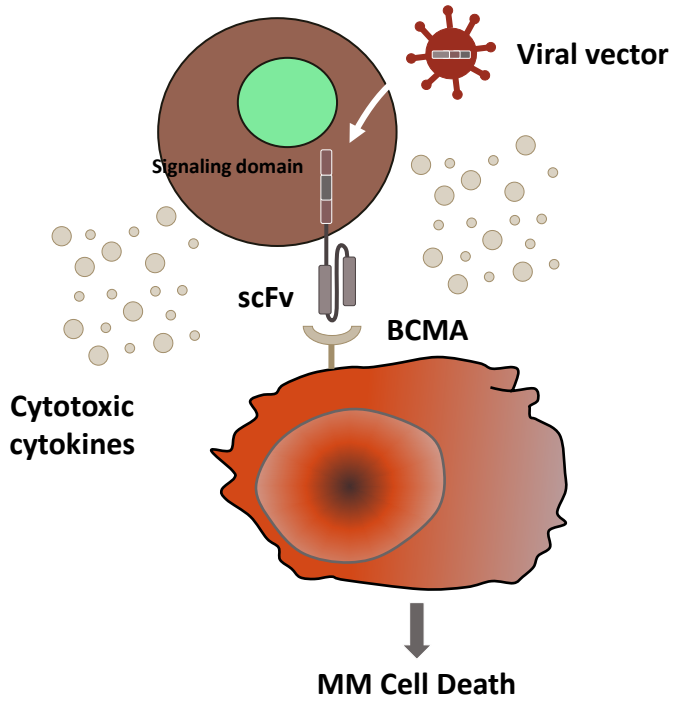
- T-cells transduced with a gamma-retroviral vector encoding anti-BCMA CAR with CD28 costimulatory domain
- Significant CRS occurred in patients with high disease burden treated at highest dose (9 x 10^6 CAR T-cells/kg)
- Deep MM responses (VGPR, sCR) observed at highest dose

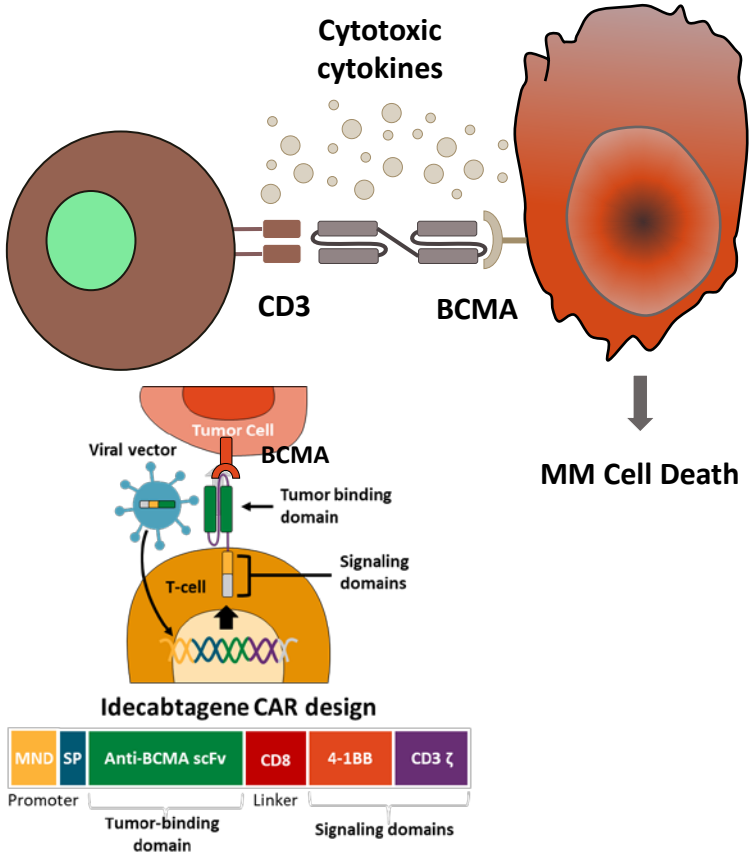
Multiple Myeloma Cells Expressing BCMA



Mechanism of Action for Novel BCMA-Targeted Therapies







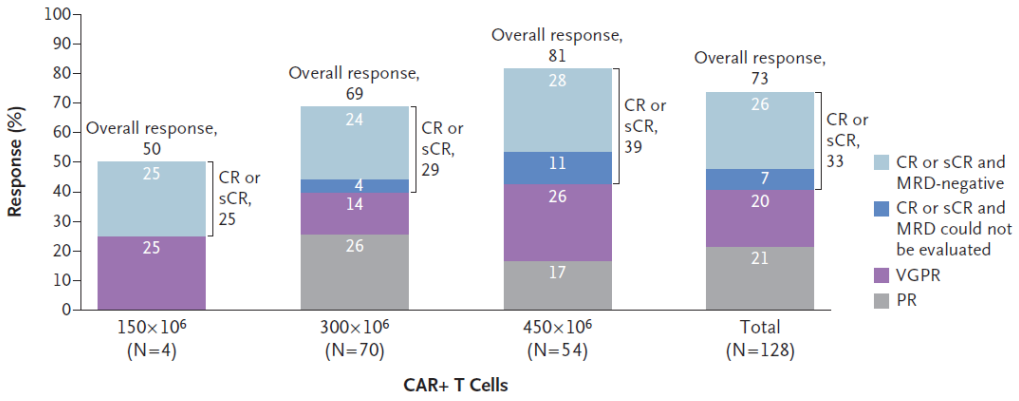
Idecabtagene vicleucel: BCMA-directed genetically modified autologous CAR T-cell therapy

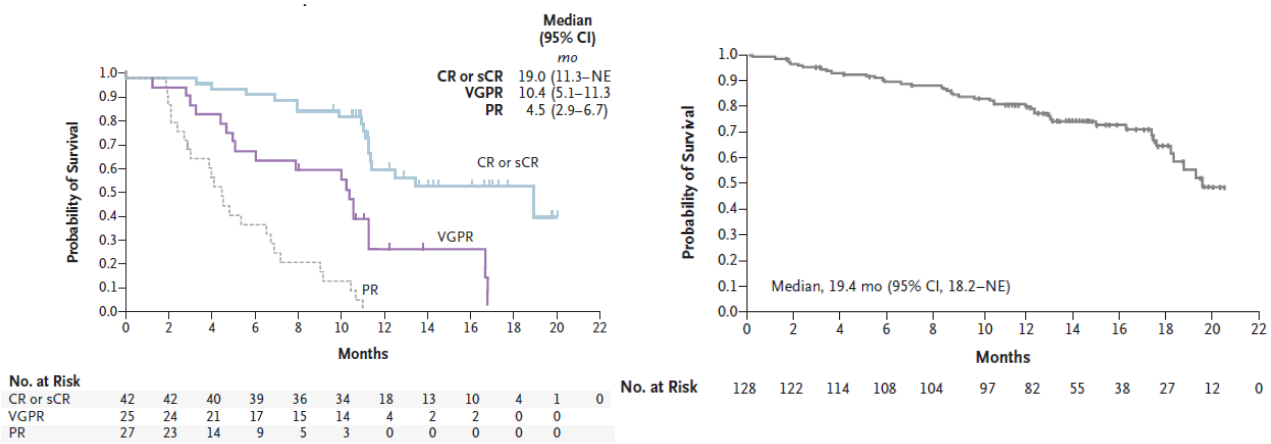
Yu. J Hematol Oncol. 2020;13:1.

Slide credit: clinicaloptions.com

Phase II KarMMa: Pivotal Study of Idecabtagene Vicleucel in Relapsed Refractory MM

Phase II trial of ide-cel in R/R MM; including double- and triple-refractory patients (IMiD, PI, and an anti-CD38 mAb)

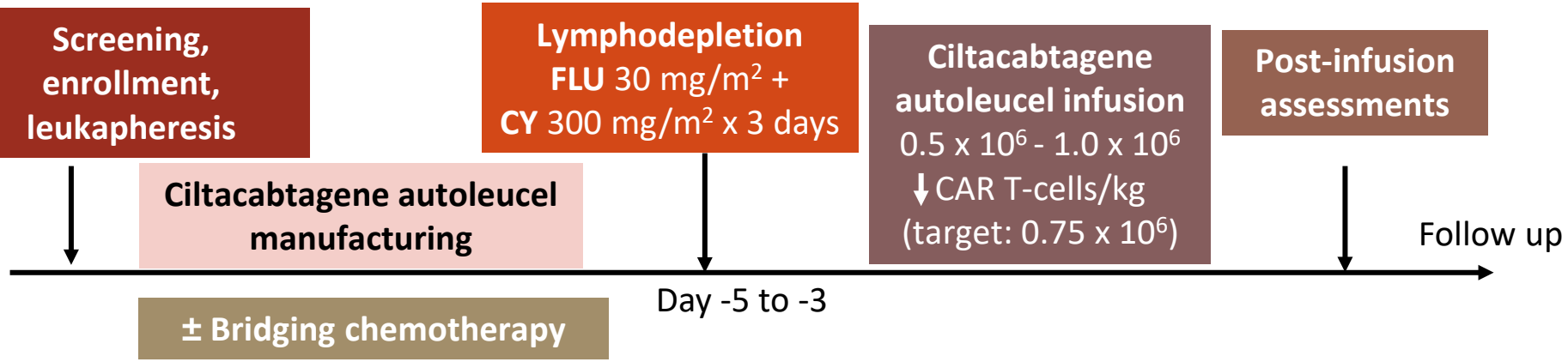


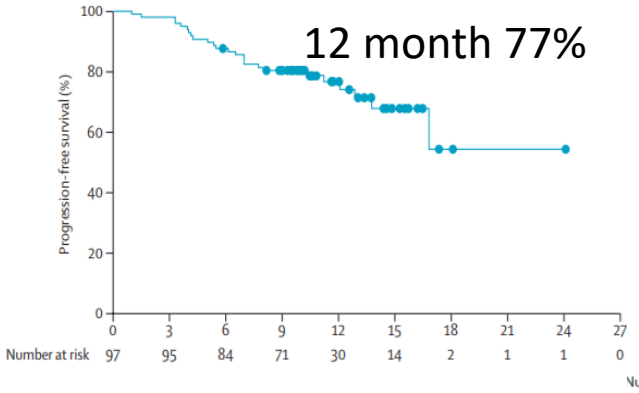


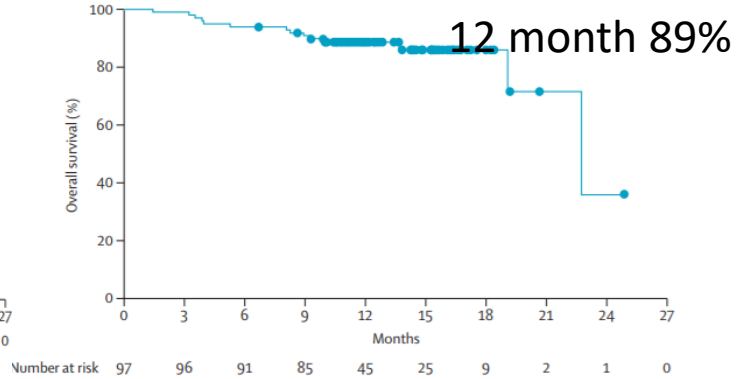
MRD-negative status achieved in 26% of treated patients

Phase Ib/II CARTITUDE-1: Anti-BCMA CAR T-Cell, Ciltacabtagene Autoleucel, in RR MM After ≥3 Prior Tx

Patients with R/R MM, ≥ 3 prior therapies including PI, IMiD, and anti-CD38 therapy, or double refractory to PI and IMiD





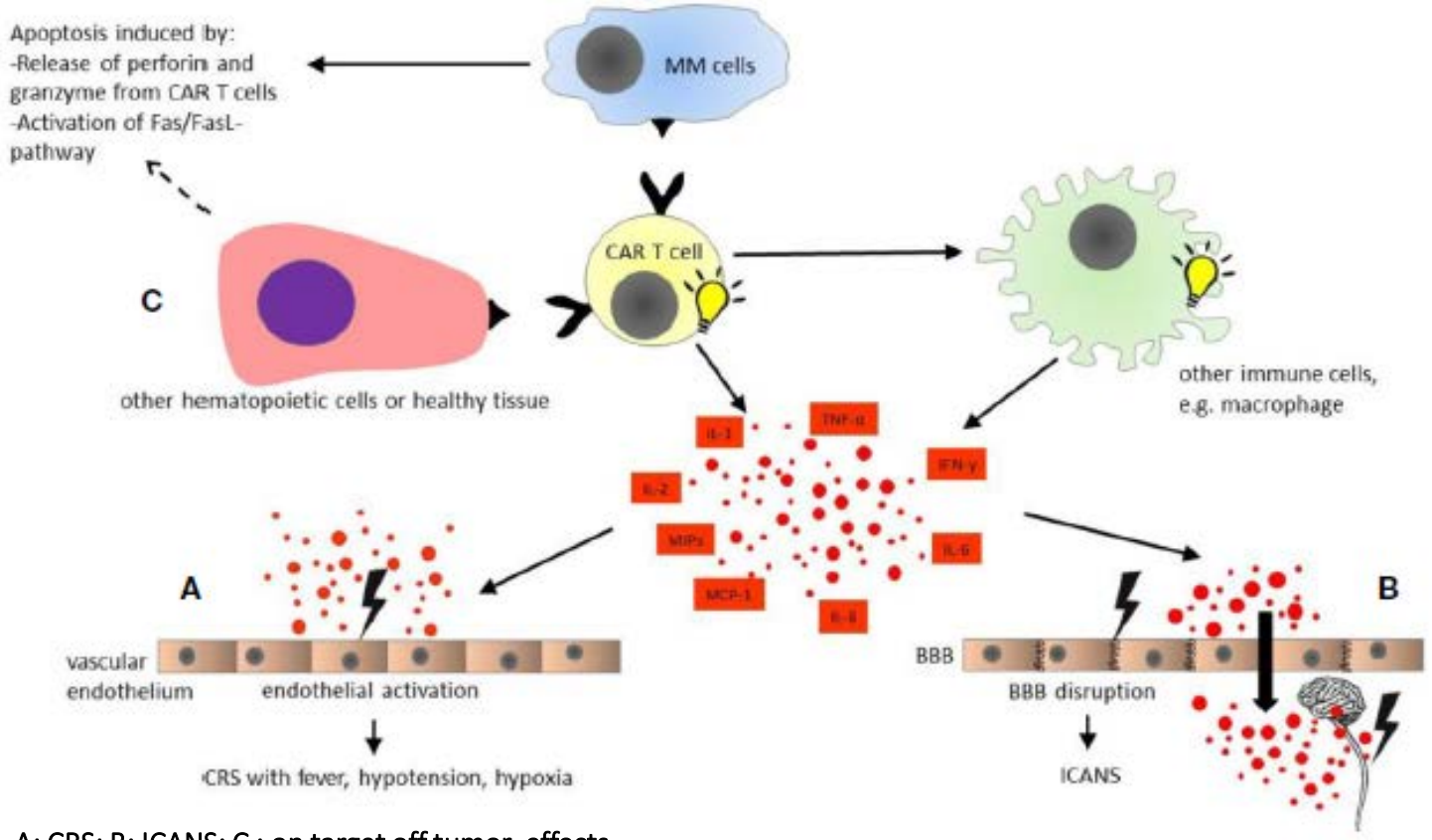


CAR T-Cell Related AEs

AEs of Interest, n (%)	All Patients (N = 97)	
	All Grade	Grade 3/4
CRS	92 (94.8)	4 (4.1)
Neurotoxicity	20 (20.6)	9 (9.3)

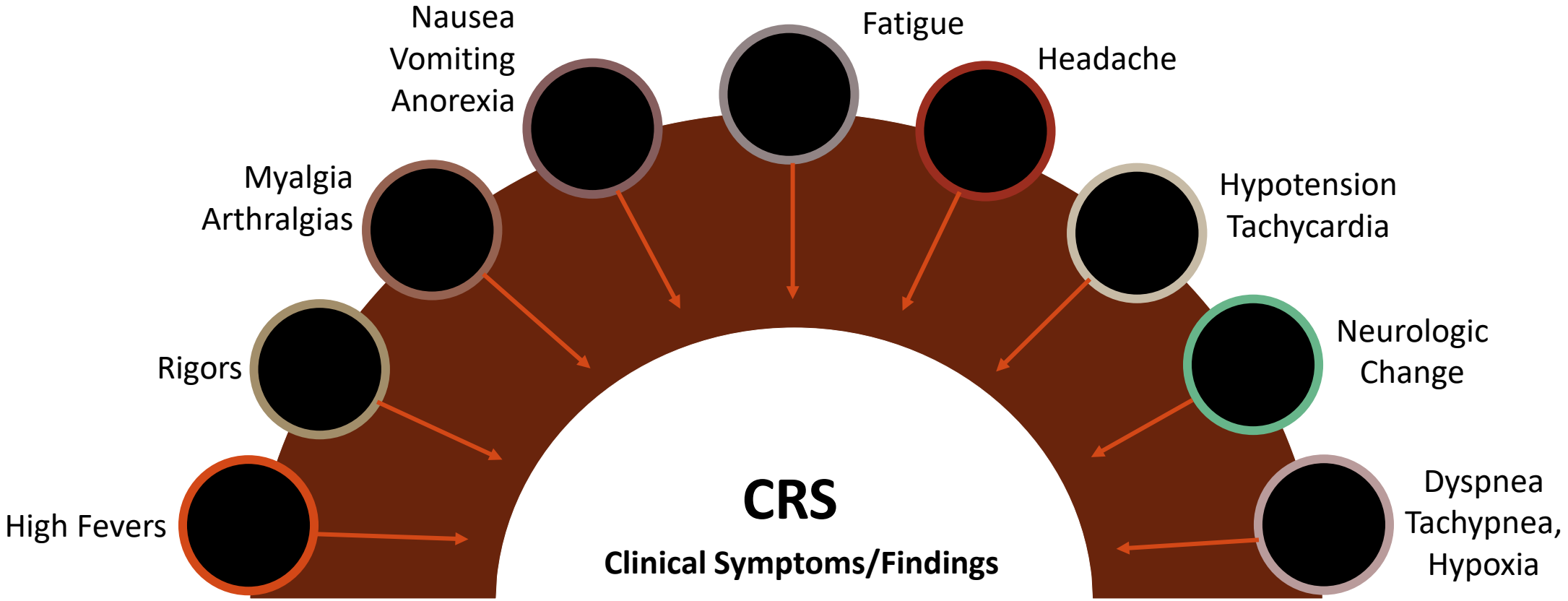
Madduri. ASH 2019. Abstr 577. Madduri. ASH 2020. Abstr 177.

Pathophysiology of CAR T Toxicities

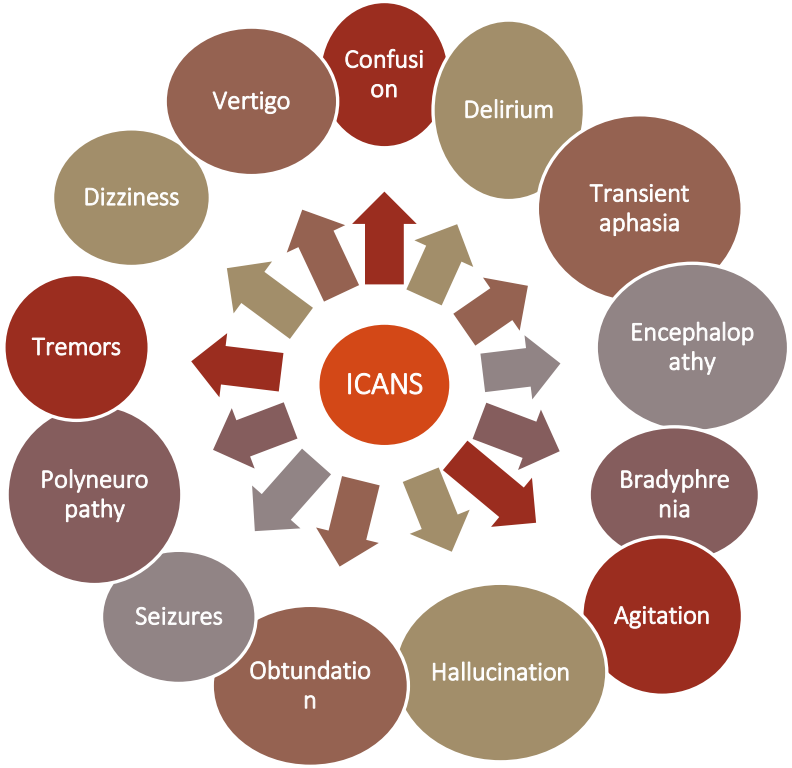


A: CRS; B: ICANS; C : on target off tumor effects

Clinical Manifestations of CRS



Immune effector cell associated neurotoxicity syndrome (ICANS)



Ide-cel

grade 3 parkinsonism

grade 3 myelitis

Cita-cel

Delayed neurotoxicity is a concern

Median onset : 27 (11-108) days

Movement/neurocognitive changes

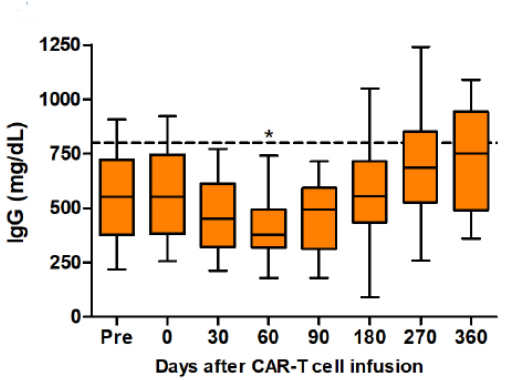
Nerve palsy and peripheral neuropathy

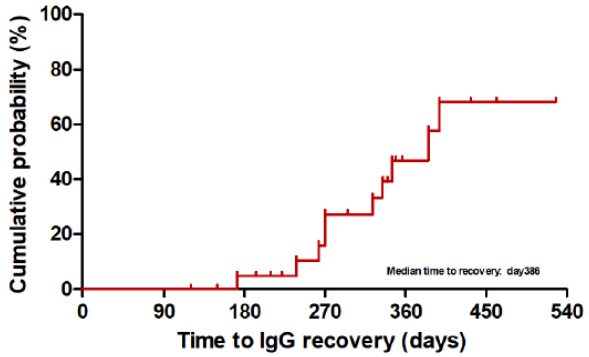
Managing Cytokine-Release Syndrome

Grade	Tocilizumab
1	**Tocilizumab**: Onset ≥72 hr after infusion, treat symptomatically; onset <72 hr after infusion, consider tocilizumab 8 mg/kg IV over 1 hr **Corticosteroids**: Consider dexamethasone 10 mg IV every 24 hr
2-3	**Tocilizumab** 8 mg/kg IV over 1 hr, repeat every 8 hr as needed if not responsive to IV fluids or supplemental O_2 **Corticosteroids**: Dexamethasone 10 mg IV every 12-24 hr If no improvement in 24 hr or rapid progression, repeat tocilizumab and escalate to dexamethasone 20 mg IV every 6-12 hr If no improvement in 24 hr or continued rapid progression, repeat tocilizumab and switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times/day
4 (ICU/critical care required)	**Tocilizumab** 8 mg/kg IV over 1 hr, repeat every 8 hr as needed if not responsive to IV fluids or supplemental O_2 **Corticosteroids**: Dexamethasone 20 mg IV every 6 hr If no improvement in 24 hr, consider methylprednisolone (1-2 g, repeat every 24 hr if needed; taper as clinically indicated) or other anti–T-cell therapies

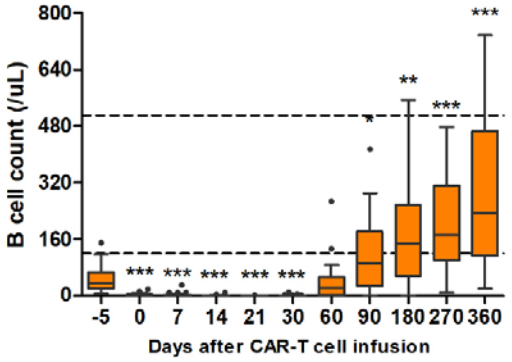
After 2 doses of tocilizumab, consider alternative anticytokine agents; do not exceed 3 doses of tocilizumab in 24 hr, or 4 doses total

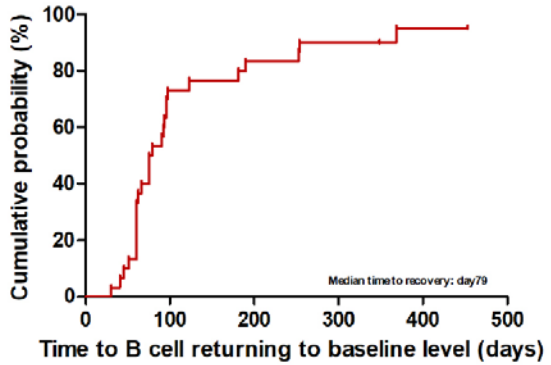
Humoral immune reconstitution after anti-BCMA CAR-T cell therapy in relapse/refractory multiple myeloma





Recovery of serum IgG to normal level was observed in 53.33% patients at 1-year. Median time to IgG recovery was on day 386



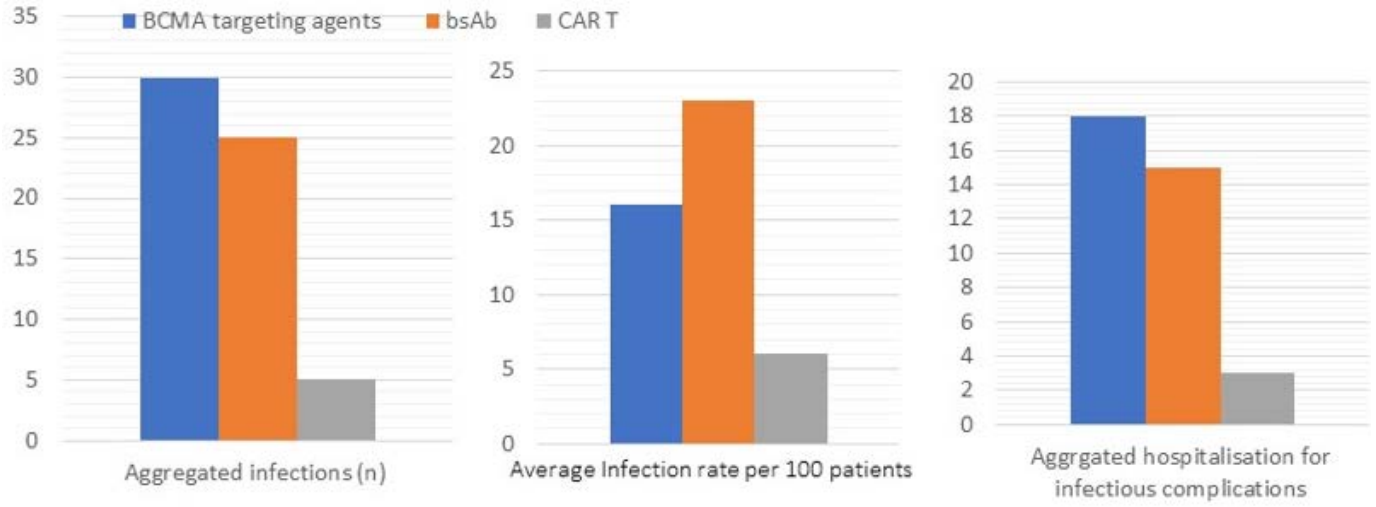


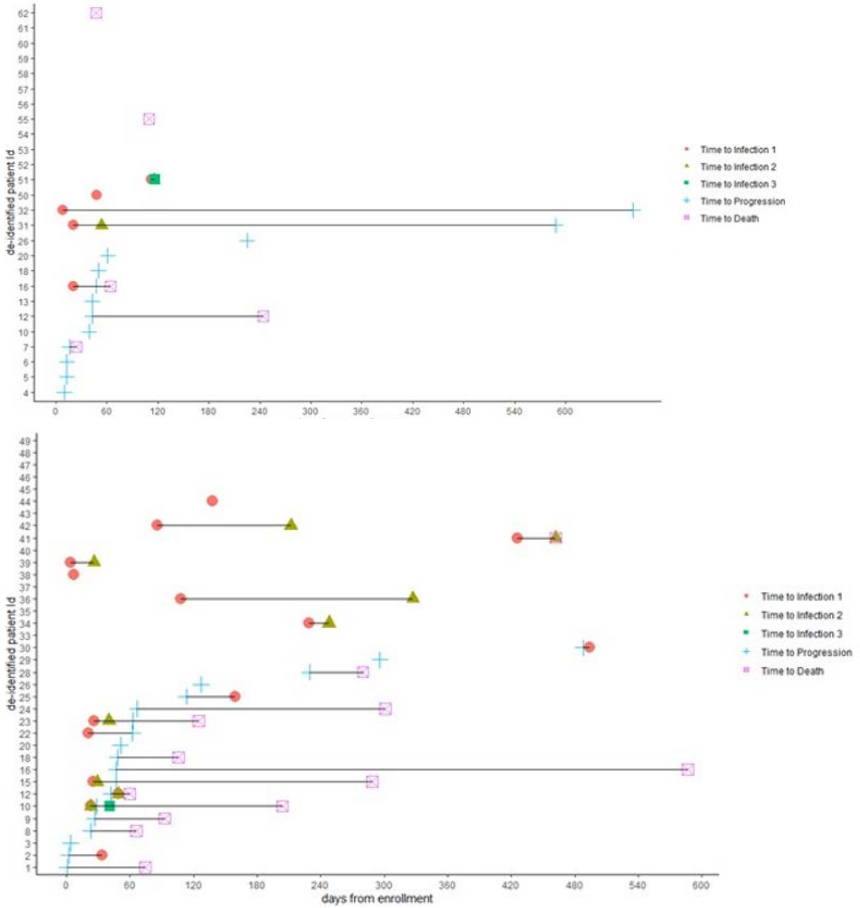
Median times of B cell count returned to baseline level was on day 79 and returned to normal level on day 177 after CAR T infusion

Anti-BCMA CAR-T cells caused a 7-month aplasia of bone marrow normal plasma cells and a longer period of hypogammaglobulinemia.

A prolonged hypogammaglobulinemia suggests a profound and lasting humoral immune deficiency after anti-BCMA CAR-T cell therapy.

Infections with BCMA Targeting T cell therapies





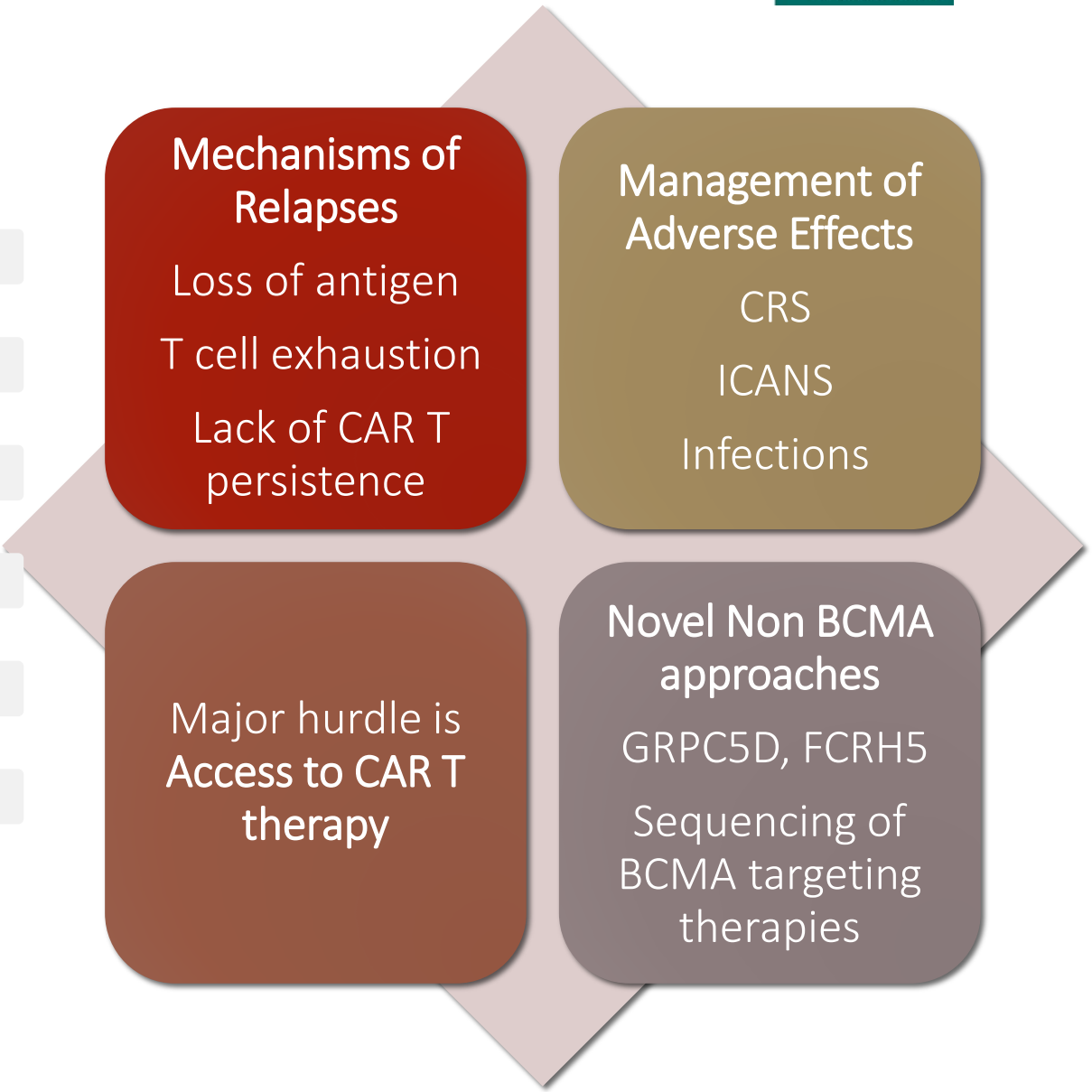
The cumulative incidence of infection with bsAb and CAR-T were 25 and 5 (p=0. 012), respectively, with 41.2% of patients experiencing at least one episode of infection with bsAb and 23.1% with CAR-T (p=0.141)

Mohan et al, ASH 2021
Blood Advances (under review)

Antibody–Drug Conjugate	CAR T-cells	Bispecific Antibody
Off-the-shelf	Personalized	Off the shelf
Targeted cytotoxicity Not dependent on T-cell health Encouraging responses in triple class exposed pts	Targeted immuno-cytotoxicity: Unprecedented ORR incl. MRD-neg in heavily pretreated pts	Targeted immuno-cytotoxicity; rapid and deep responses in ongoing trials
No lymphodepletion No steroids	Single infusion (“one and done”); long “chemo holiday”	No lymphodepletion Minimal steroids
Outpatient administration; Can be given in the community	Potentially persistent	Can be given in the community after 1st cycle (once approved)
Currently requires REMS/close collaboration with Ophthalmology	Manufacturing time makes impractical for pts with rapidly progressive disease	Dosing/schedule/combinations to be determined
Modest ORR and PFS in TCR pts	FACT-accredited center, with required infrastructure	Initial hospitalization required until low CRS risk
Requires continuous treatment until progression or intolerance	CRS and ICANS - hospitalization likely required; Safety in frail elderly?	CRS and neurotoxicity possible but low risk; limited severe cases
	Dependent on T-cell health (manufacturing failures)	Dependent on T-cell health (T-cell exhaustion)
	Requires significant social support – caregiver required	Requires continuous treatment

Concerns with current CAR T data

- No survival plateau so far
- CRS occurs virtually in all patients (grade 3 CRS in 5-10%)
- Neurotoxicity can be seen in up to 20%, delayed neurotoxicity with Cita-cel
- Good renal function (upto 45%) mandated for effective LD chemotherapy
- Multiple Myeloma control is necessary before CAR
- Unknown efficacy in CNS disease and plasma cell leukemia



Conclusions

- ASCT in MM is here to stay
- ASCT is the unbeaten standard of care for every eligible NDMM
- CAR T therapy have unprecedented responses but no plateau
- CRS/ICANS are manageable
- New unmet need “BCMA refractory population”

Acknowledgements

Our Patients and Families

Clinical Faculty: Dr Hari Parameswaran, Dr Anita D'Souza, Dr Saurabh Chabbra, Dr Binod Dhakal

Research faculty : Dr Siegfried Janz, Dr Jing Dong, Dr Sabarinath Venniyil Radhakrishnan

Biostatistical support : Dr Aniko Szabo