



Multiple Myeloma: Stem Cell Transplant and Beyond

Celebrating a Second Chance at Life Survivorship Symposium

April 17- 23, 2021

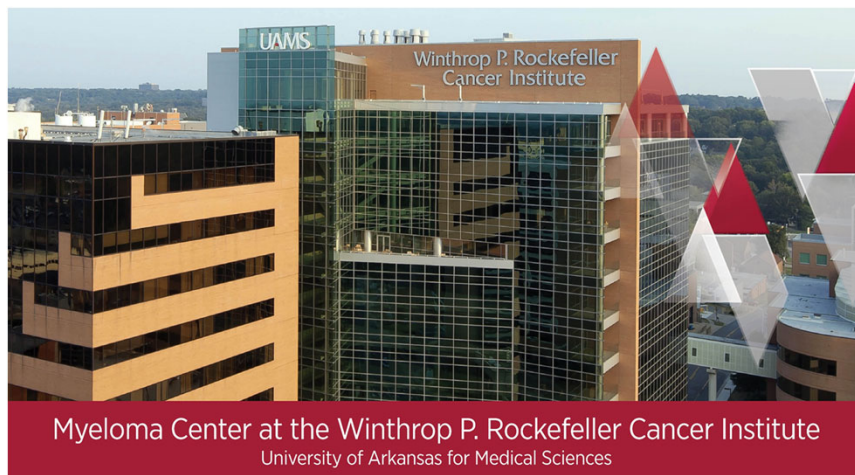


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1

Multiple Myeloma: Stem Cell Transplants and Beyond



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Clinical Director, Professor of Medicine



2

Overview

- Introduction to myeloma
- Who should have a stem cell transplant?
- Stem cell transplantation and new drugs
- Maintenance therapy after transplant
- New immunotherapies for relapsed myeloma



3

How Common is Multiple Myeloma?

- Approximately 30,000 cases per year
- Second most common hematologic malignancy
- Most common cancer of the bone marrow



4

Risk Factors for Multiple Myeloma

- Age: 6th and 7th decades of life
- Gender: Males > Females
- Race: African Americans > Caucasian > Asian
- Exposure to environmental toxins like Agent Orange
- Exposure to radiation
- Immune system disorders
- Cause remains mostly unknown

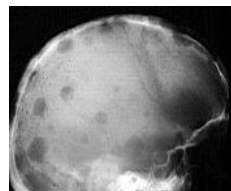
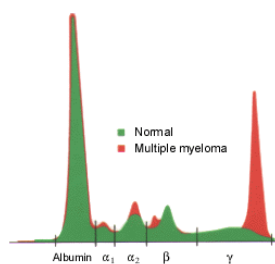


5

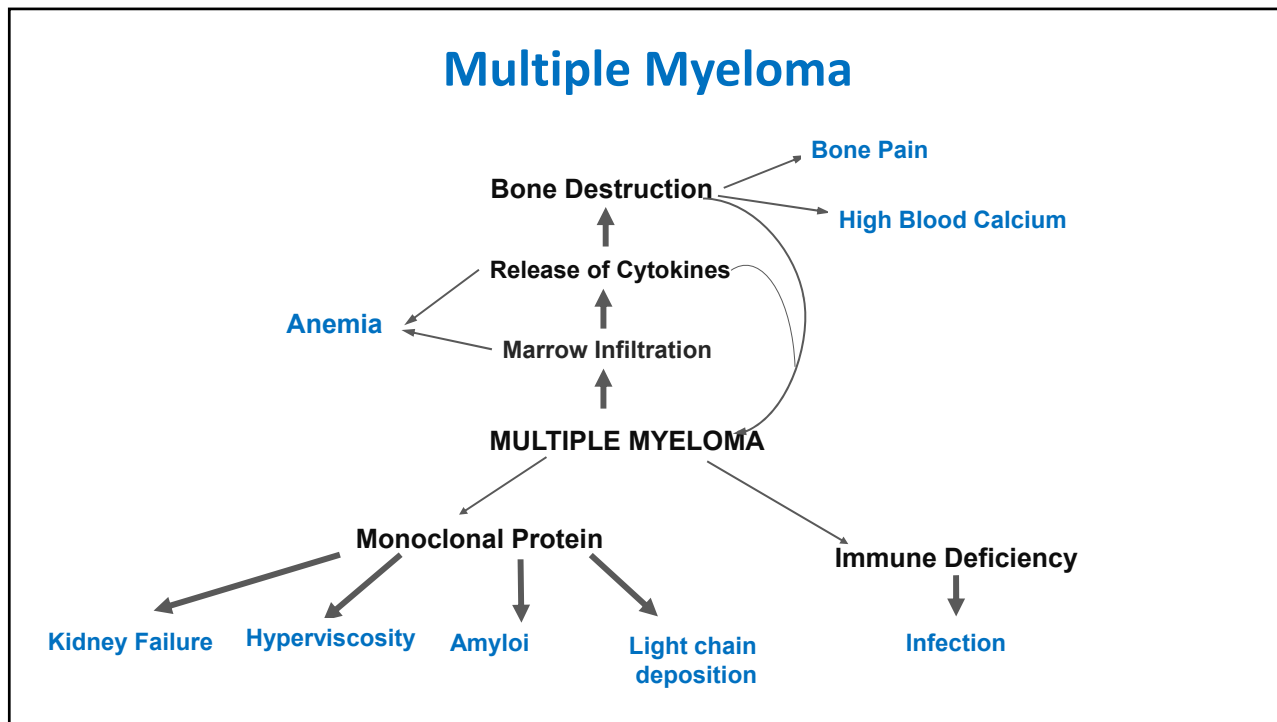
Hallmarks of Multiple Myeloma

- High level of monoclonal immunoglobulin (M-Spike) and/or high free light chains
- Unusually large number of plasma cells in bone marrow (plasmacytosis)
- Cancerous plasma cells (plasmacytomas) on tissue biopsy and/or bone damage (skeletal lesions)

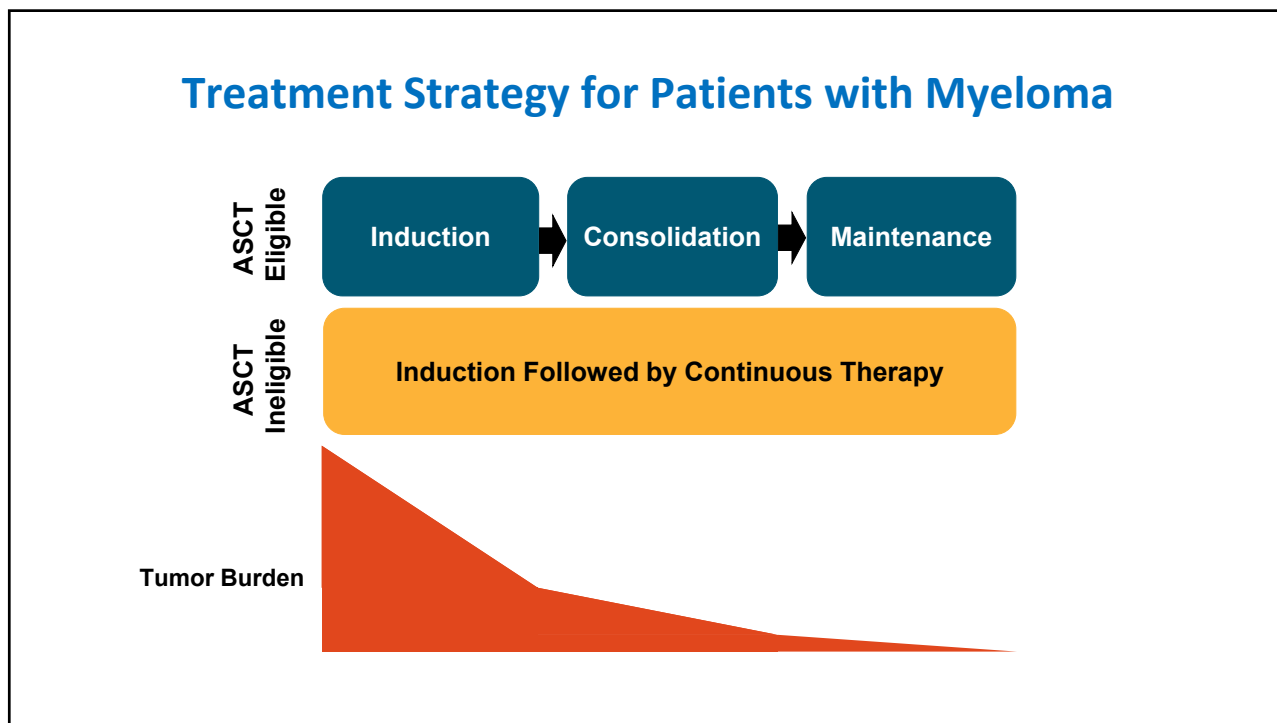
Serum Protein Electrophoresis



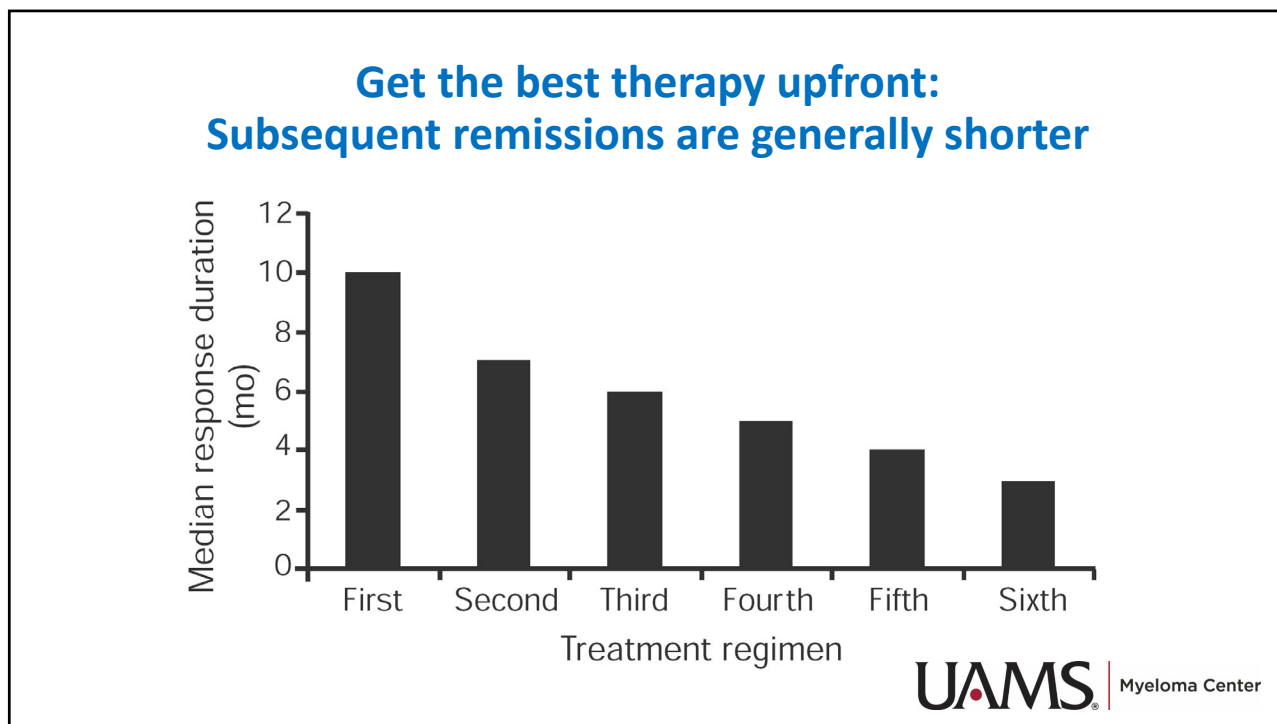
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8



9

- ### To Transplant or Not Transplant: Factors to Consider
- Physiologic Age
 - Elderly patients may be transplant ineligible
 - Older patients more sensitive to toxicity; less physical reserve
 - Performance status
 - Aggressiveness of the Disease
 - Other illnesses
 - Kidney Disease
 - Heart disease
 - Lung disease
 - Liver disease (e.g., chronic hepatitis or cirrhosis)

10

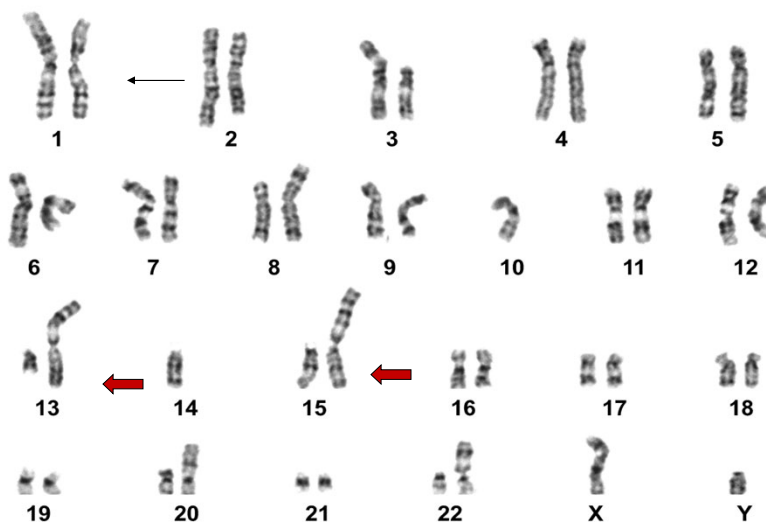
Tests can determine if the myeloma is high-risk or standard-risk disease

- Risk affects Prognosis:
 - how the disease will progress with currently available treatments
- Risk affects Recommended Therapy:
 - Different treatment strategies are appropriate, depending on whether myeloma is standard-risk or high-risk



11

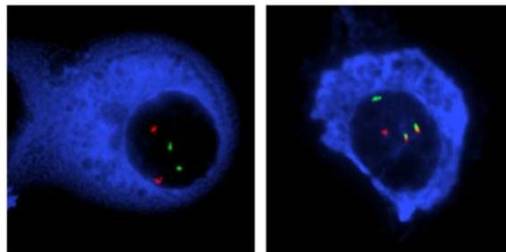
Cytogenetics: Chromosomes under the microscope



12

FISH Detects Chromosome Abnormalities

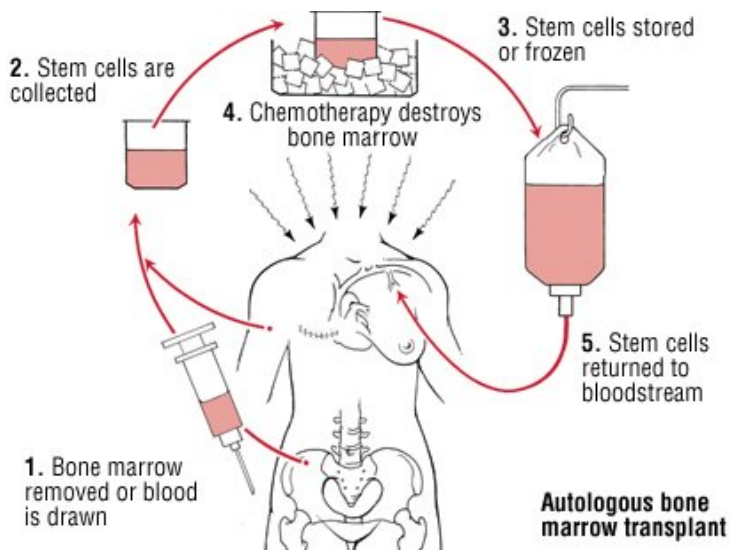
- High-risk
 - t(4;14)
 - t(14;16)
 - del(17p)
 - Amp 1q
- FISH can be done on resting cells and will yield information in all cases
- You will only find what you look for



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13

Stem Cell Transplant Process



<https://www.drugs.com/health-guide/images/205427.jpg>

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14

Stem Cell Transplant Process - General Guidelines

- Collect stem cells after not more than four cycles of induction chemotherapy (VRD, VRD-Dara*)
- Collect extra cells for a rainy day
- Melphalan dose reduced in older patients (>65 yrs) and those with renal disease (Melphalan 140mg/m² rather than 200mg/m²)
- Consider tandem transplant especially for high-risk disease

*VRD = Revlimid® + Velcade® + dexamethasone

VRD-Dara = Revlimid® + Velcade® + dexamethasone + daratumumab

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15

Do we still need to do transplants for myeloma?

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16

Phase III Study IFM/DFCI 2009: VRd ± Autologous Stem Cell Transplant in Newly Diagnosed Multiple Myeloma patients

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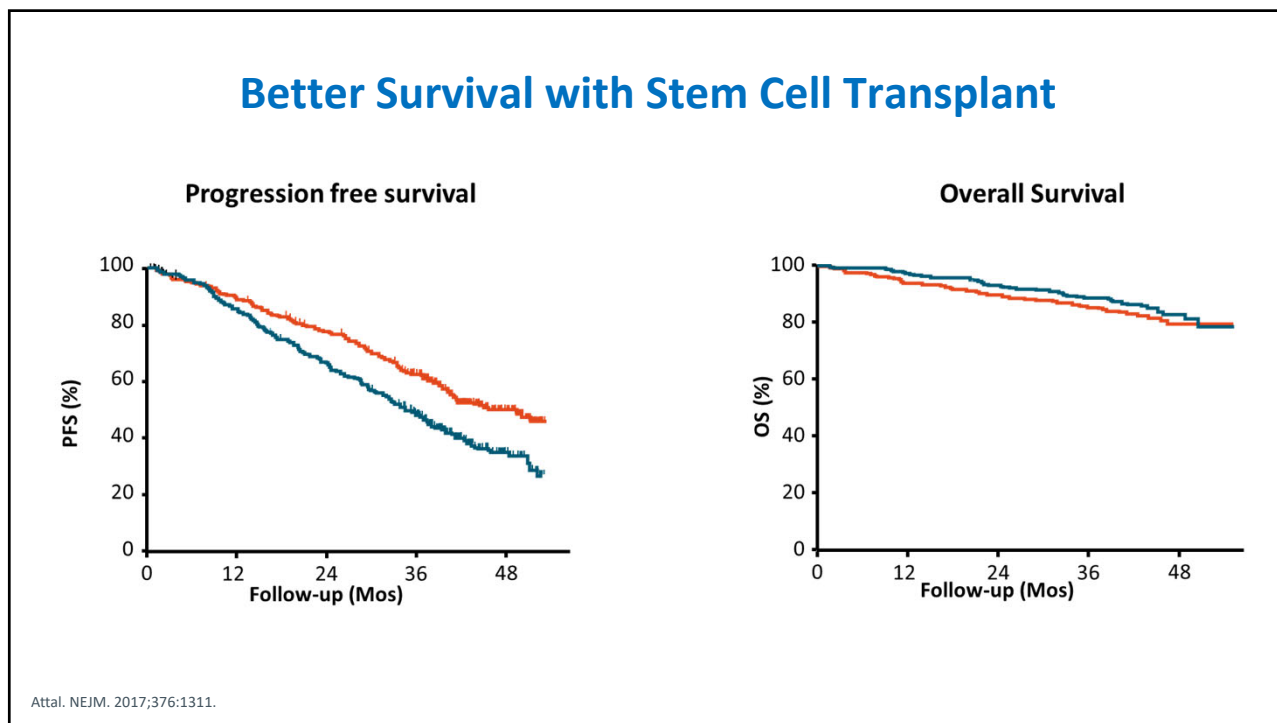
    graph LR
      A[Patients 65 yrs of age or younger with symptomatic ND MM (N = 700)] --> B[VRd*± 8 cycles]
      A --> C[VRd* 3 cycles]
      C --> D[MEL200 ASCT 1 cycle]
      D --> E[VRd* 2 cycles]
      B --> F[Lenalidomide maintenance 12 mos]
      E --> F
    
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Option for delayed transplant in non-transplant arm of the study

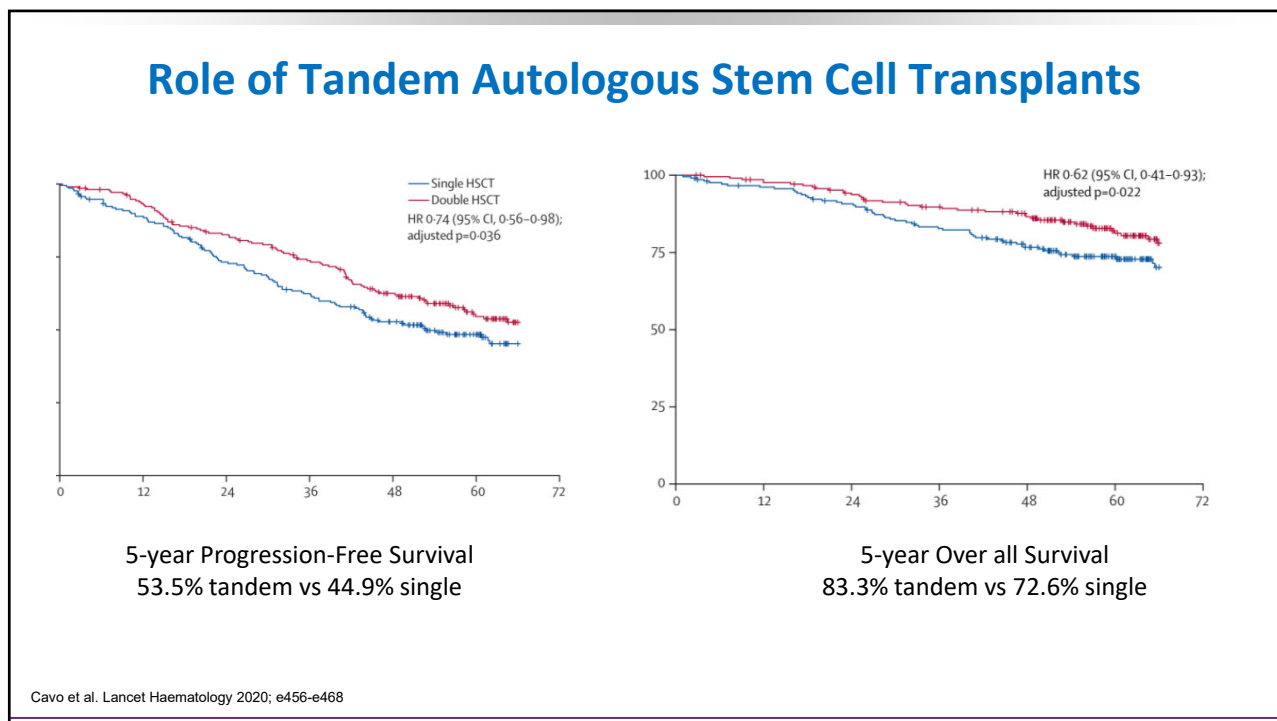
VRd = Revlimid® + Velcade® + dexamethasone
 MEL = Melphalan
 ASCT = Autologous Stem Cell Transplant

Attal. NEJM. 2017;376:1311.

17



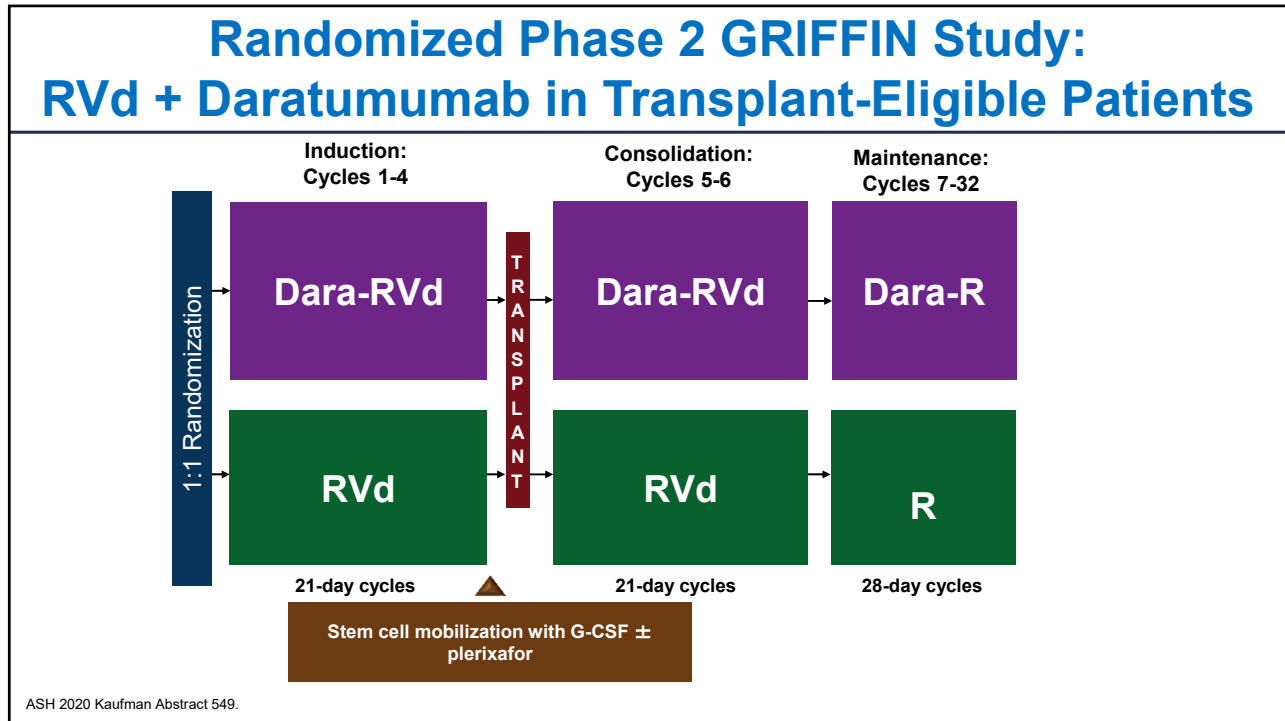
18



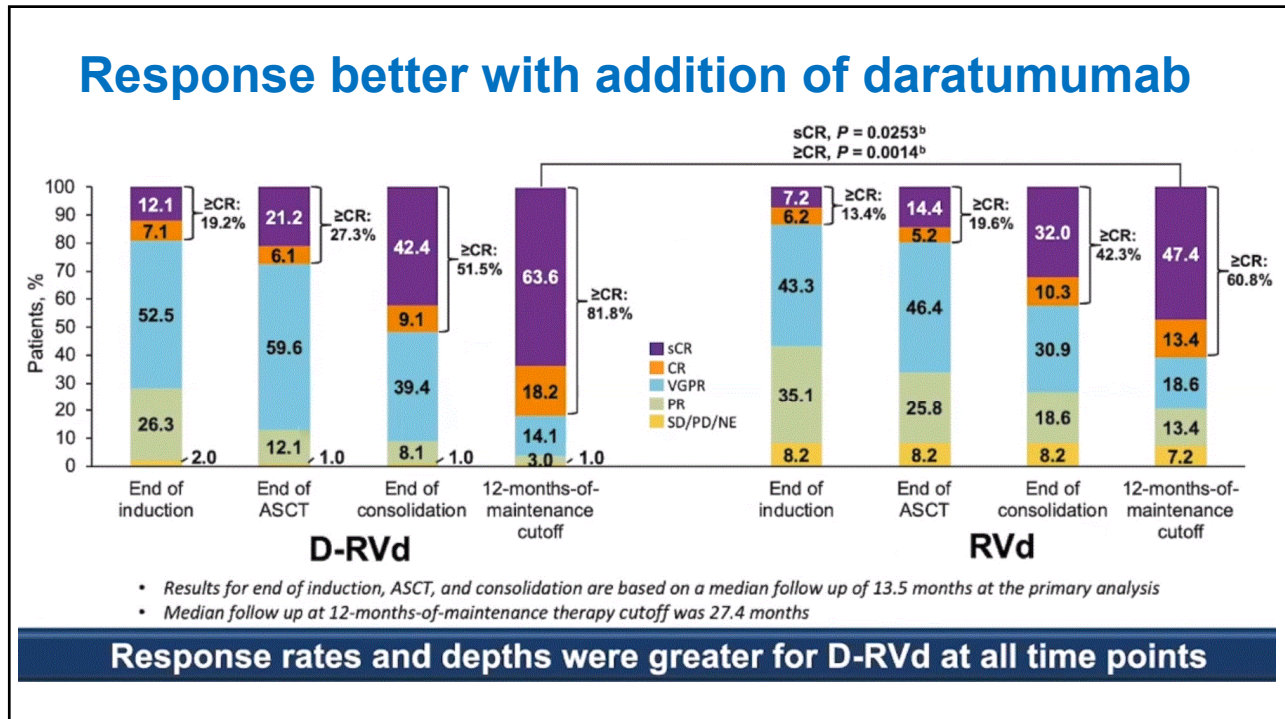
19

Combining stem cell transplantation with new drugs

20



21



22

GRIFFIN Study - Summary

- Dara-VRD better response rate and less residual disease after treatment (MRD negativity)
- However, VRD arm did very well and no difference yet in Progression-Free or Overall Survival
- Dara-VRD seems to have less benefit in high-risk patients
- Some increase in toxicity with Dara
- Underlines need to collect stem cells early

23

Objectives of Maintenance Therapy in Myeloma

- Goal is to prevent relapse
- Acceptable toxicity and quality of life
- Fixed duration or until progression
- In future, likely guided by minimal residual disease testing

24

Options for Maintenance

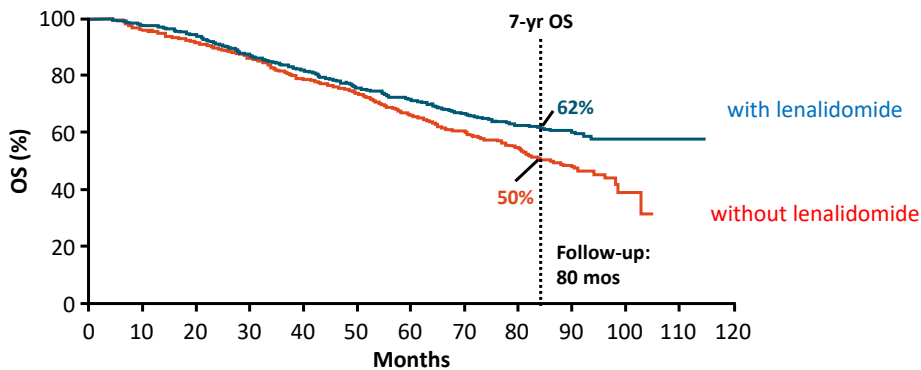
- Lenalidomide (Revlimid®)
- Bortezomib (Velcade®), Ixazomib (Ninlaro®)
- Daratumumab (Darzalex®) in clinical trial
- Drug combinations



25

Survival Post-Transplant Better with Lenalidomide Maintenance (analysis of 3 trials)

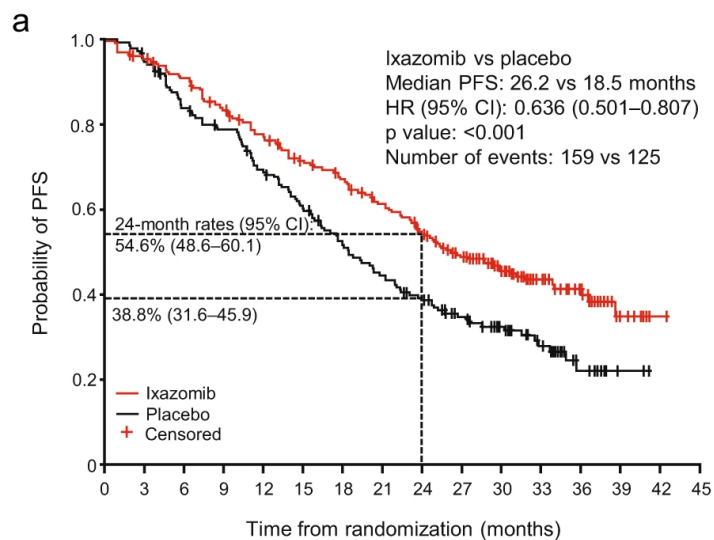
26% reduction in risk of death; estimated 2.5-year increase in survival



McCarthy. J Clin Oncol. 2017;35:3279.

26

Ixazomib Improves Survival after Transplant



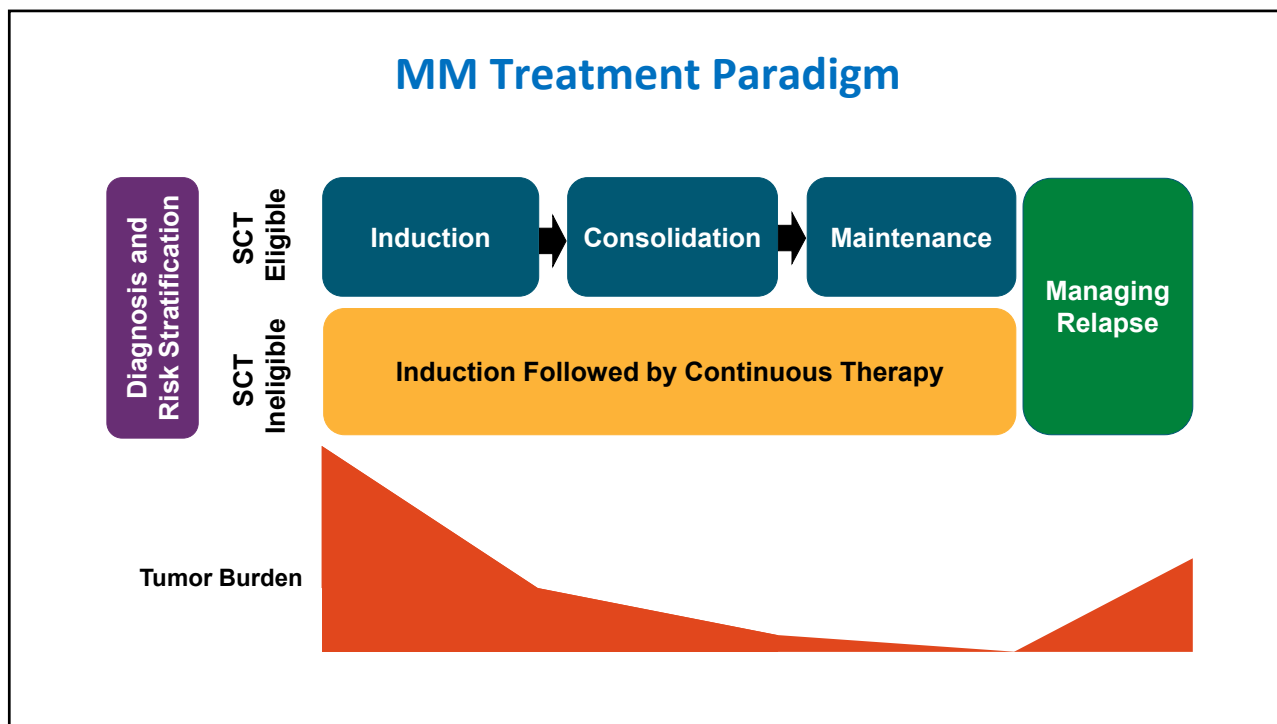
27

Maintenance Therapy in Myeloma

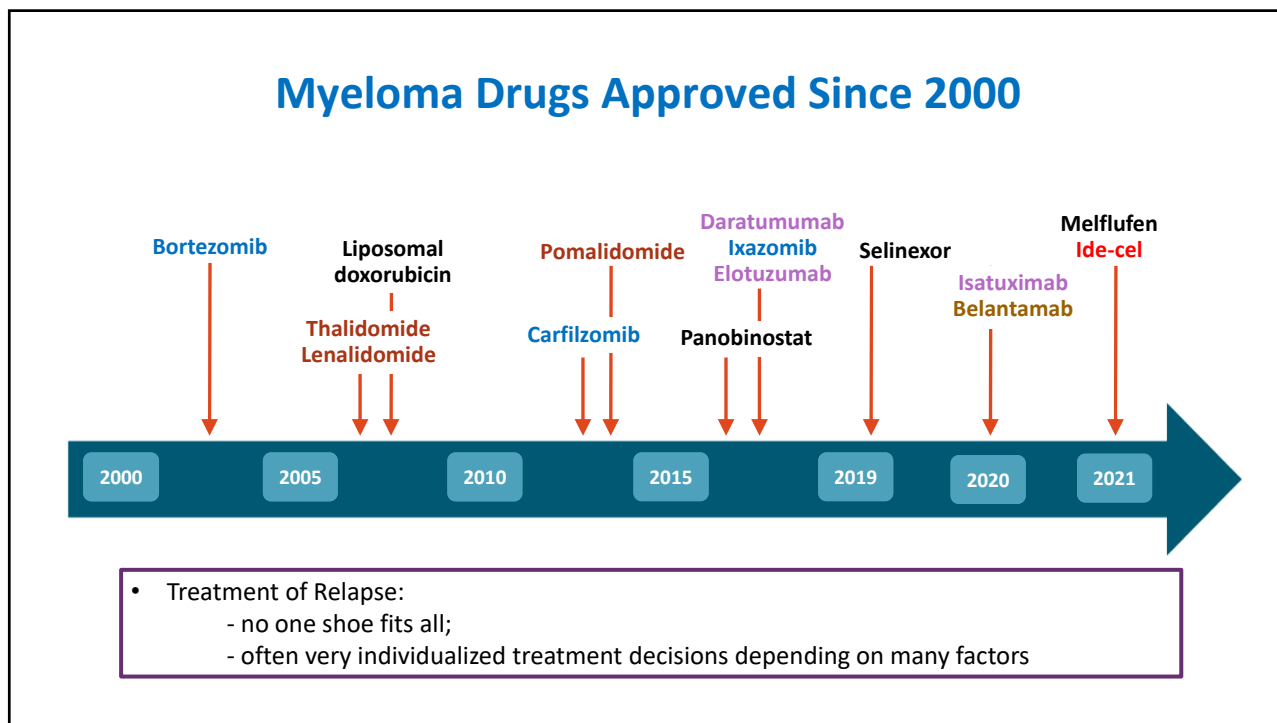
- Improvements in progression-free survival, not always overall survival
- Side effects:
 - risk of second cancers
 - impact of quality of life
 - reduction in blood counts,
- Fixed duration or until progression?
- In future likely guided by minimal residual disease testing

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28



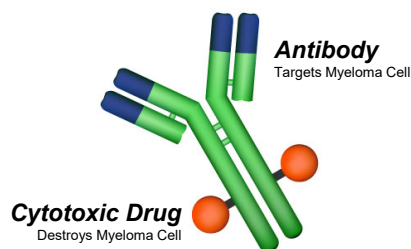
29



30

New Immunotherapy for Relapsed Myeloma

Antibody-Drug Conjugate
Precisely Delivers Cytotoxic Drug to Myeloma Cells

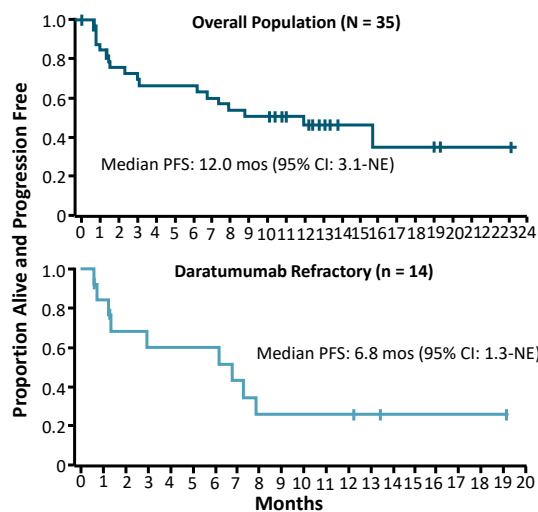


Belantamab (Blenrep)



31

DREAMM-1: Belantamab for relapsed myeloma



Trudel. Lancet Oncol. 2018;19:1641. Trudel. Blood Cancer J. 2019;9:37.

32

Side Effects

- Corneal toxicity (blurred vision)
- Blood count suppression

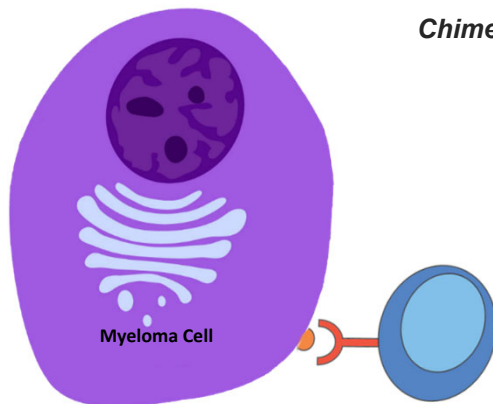
33

DREAMM-1: Corneal Toxicity

- Clinical corneal events reported in 63% of patients (n = 22)
 - 9% with grade 3 events
- Time to onset: 23 days (range: 1-84)
- Time to resolution 30 days (range: 5-224 days)
- Dose reductions: 40%
- Dose interruption/delays: 43%
- No treatment discontinuations due to corneal toxicity

34

New Immunotherapy for Relapsed Myeloma: CAR T-cells



Chimeric Antigen Receptor T-cells

CAR T-Cell

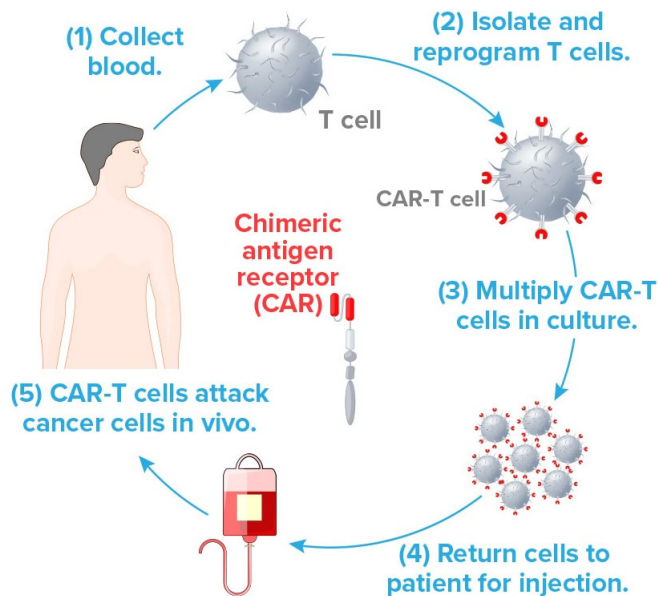
Genetically engineered to target myeloma

Ide-Cel (®Abecma)



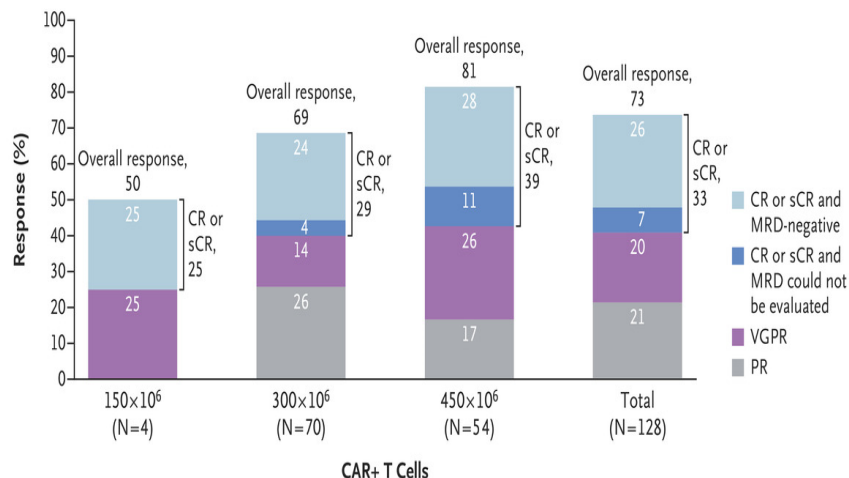
35

CAR T-cell Manufacture Process



36

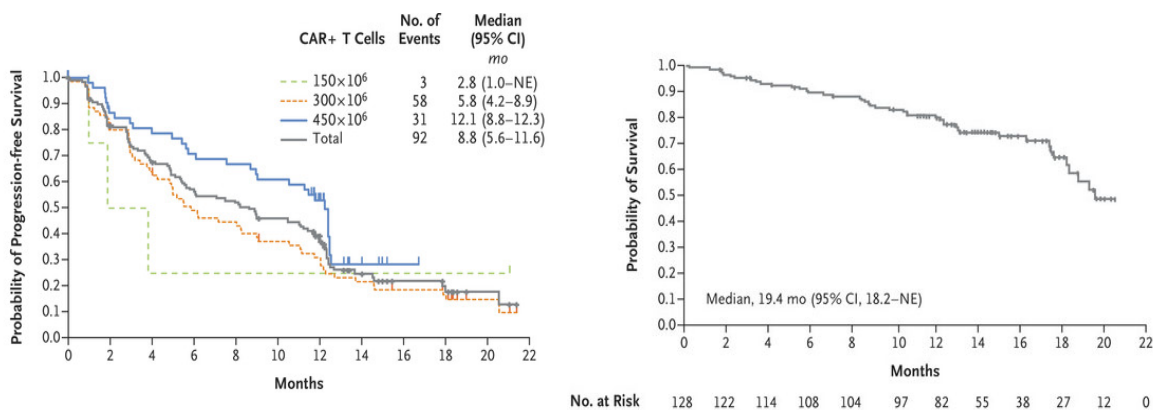
Ide-cel (ABECMA®) Response According to Cell Dose



NC Munshi et al. N Engl J Med 2021;384:705-716.

37

Progression Free Survival by Dose and Overall Survival



NC Munshi et al. N Engl J Med 2021;384:705-716.

38

Side Effects

- Cytokine release syndrome
- Neurological Toxicity
- Blood count suppression



39

Ide-cel Side Effects

	I
Cytokine Release Syndrome	
All Grades	84%
Grade 3 / 4 / 5	4% / <1% / <1%
Median Onset, Days	1 (1 – 12)
Median Duration	5 (1 – 63)
Neurotoxicity	
All grades	18%
Grade 3 / 4 / 5	3% / 0% / 0%
Median Onset, Days	2 (1 – 10)
Median Duration	3 (1 – 26)

Munshi. ASCO 2020. Abstr. 8503

40

CAR T-cell versus Antibody Therapy?

Factor	CAR T-cells	Antibody
Requires Chemotherapy	yes	no
Reasonable blood counts	yes	yes
Depends on patient's own immune system	yes	no
Availability	Community oncologist	Hospital based
Administration	One dose	Multiple doses
Complexity	Manufacturing process	Monitoring by eye-specialist or optometrist
Response Rate	Higher	Lower
Side effects	CRS and neurologic	Vision

41

Immunotherapy

- Exciting new therapy
- Not ready yet to replace existing front line treatment options
- In future, likely to be used earlier in treatment and for some patients upfront

42

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Nurse get on the internet, go to Myeloma.com scroll down and click on the "Are you totally lost?" icon

43



Questions?

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44