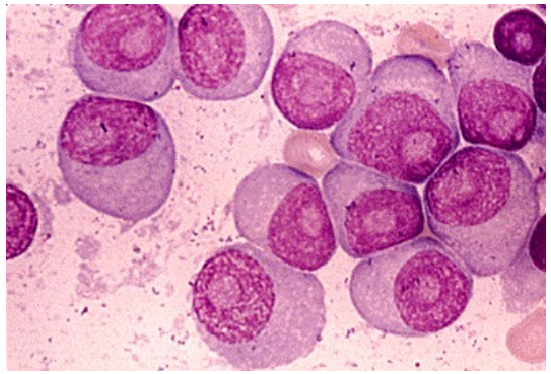
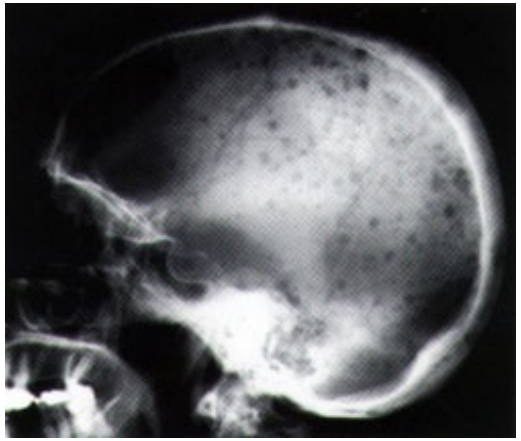
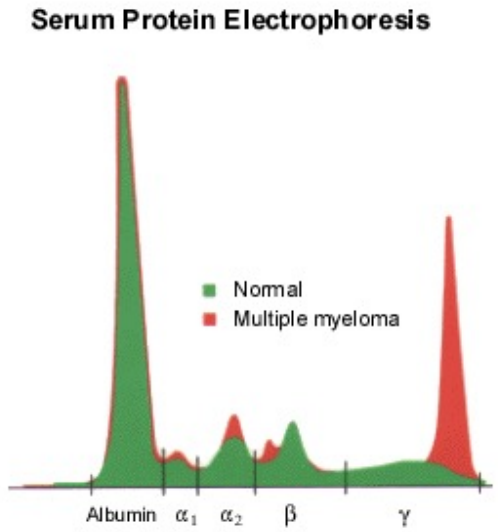
What's the future of CarT cells?







Mario Boccadoro

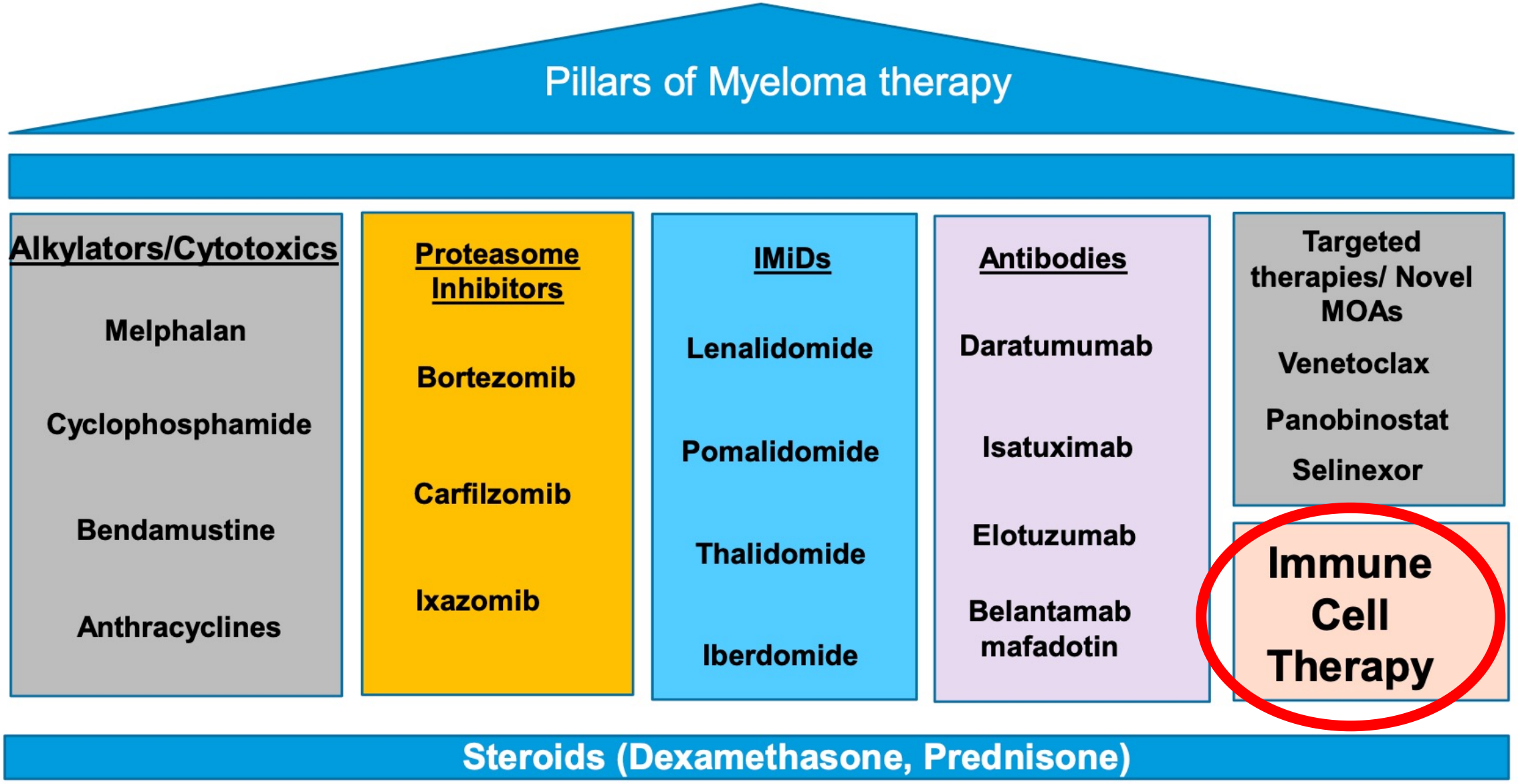
Torino 3-3-23

EMN

Disclosures for Mario Boccadoro, MD

Research Support/P.I.	
Employee	No relevant conflicts of interest to declare
Consultant	No relevant conflicts of interest to declare
Major Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	No relevant conflicts of interest to declare
Honoraria	Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol-Myers Squibb, and AbbVie
Scientific Advisory Board	No relevant conflicts of interest to declare
Research Funding	Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol-Myers Squibb, and Mundipharma

Presentation includes discussion of the off-label use of a drug or drugs

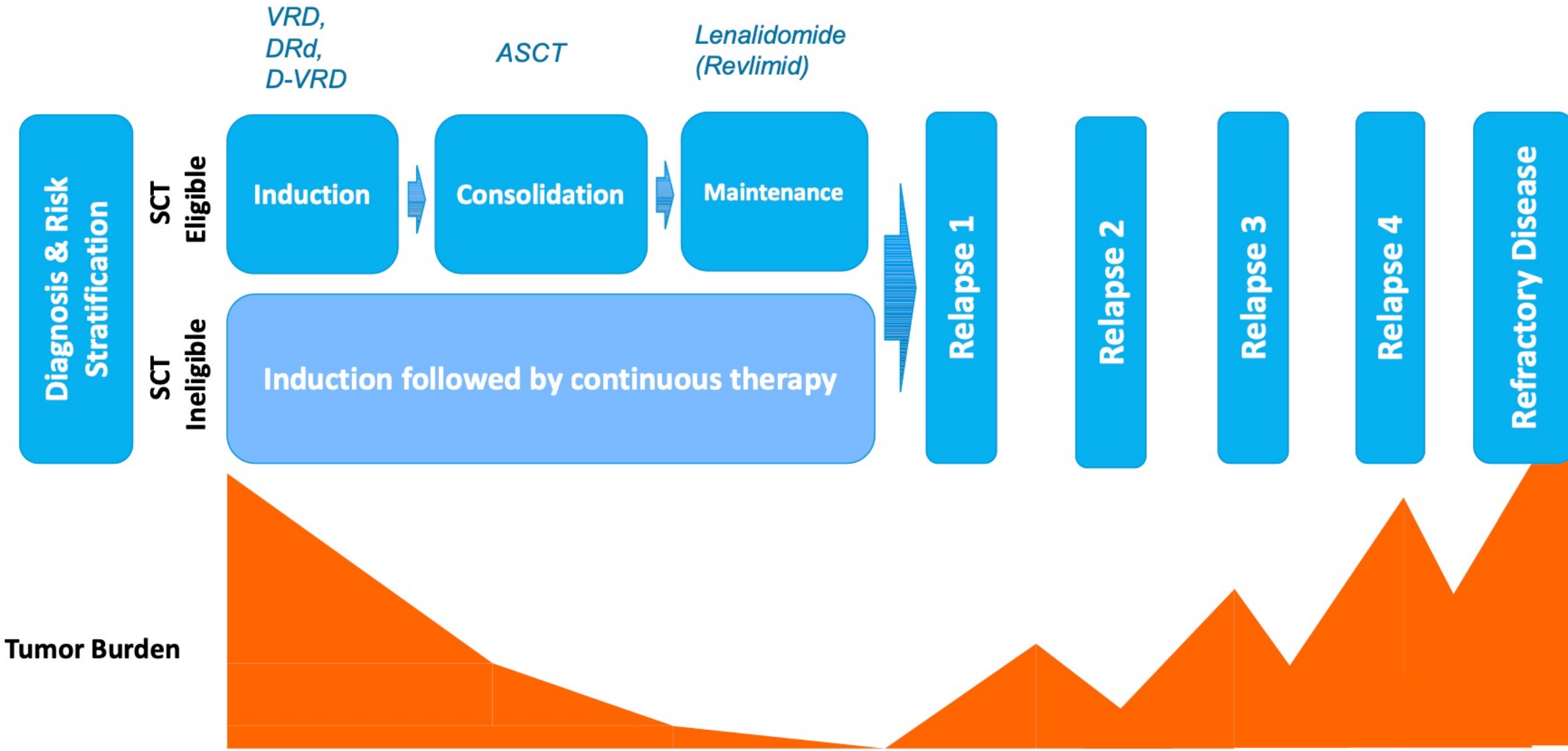

Pillars of Myeloma therapy
Alkylators/Cytotoxics
Melphalan
Cyclophosphamide
Bendamustine
Anthracyclines
Proteasome Inhibitors
Bortezomib
Carfilzomib
Ixazomib
IMiDs
Lenalidomide
Pomalidomide
Thalidomide
Iberdomide
Antibodies
Daratumumab
Isatuximab
Elotuzumab
Belantamab mafadotin
Targeted therapies/ Novel MOAs
Venetoclax
Panobinostat
Selinexor
Immune Cell Therapy
Steroids (Dexamethasone, Prednisone)

Future of CAR T-cell Therapy

- **Several reserches aim to improve the therapy:**
  - obtaining T cells earlier in the disease
  - Obtain T cells from ealthy donors
  - Use other target than BCMA
  - Optimize manufactoring to espedite production
  - Allogeneic CarT
  - ……

  - **General overview of the CAR T positioning**
    (personal point of view)

5. MYELOMA TREATMENT PARADIGM



first-line treatment

Mr. Carl Smith

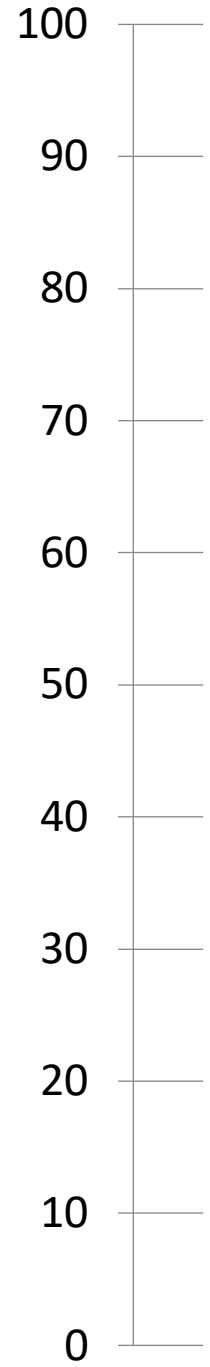
64-year-old male

Initially presents with baseline pain and fatigue

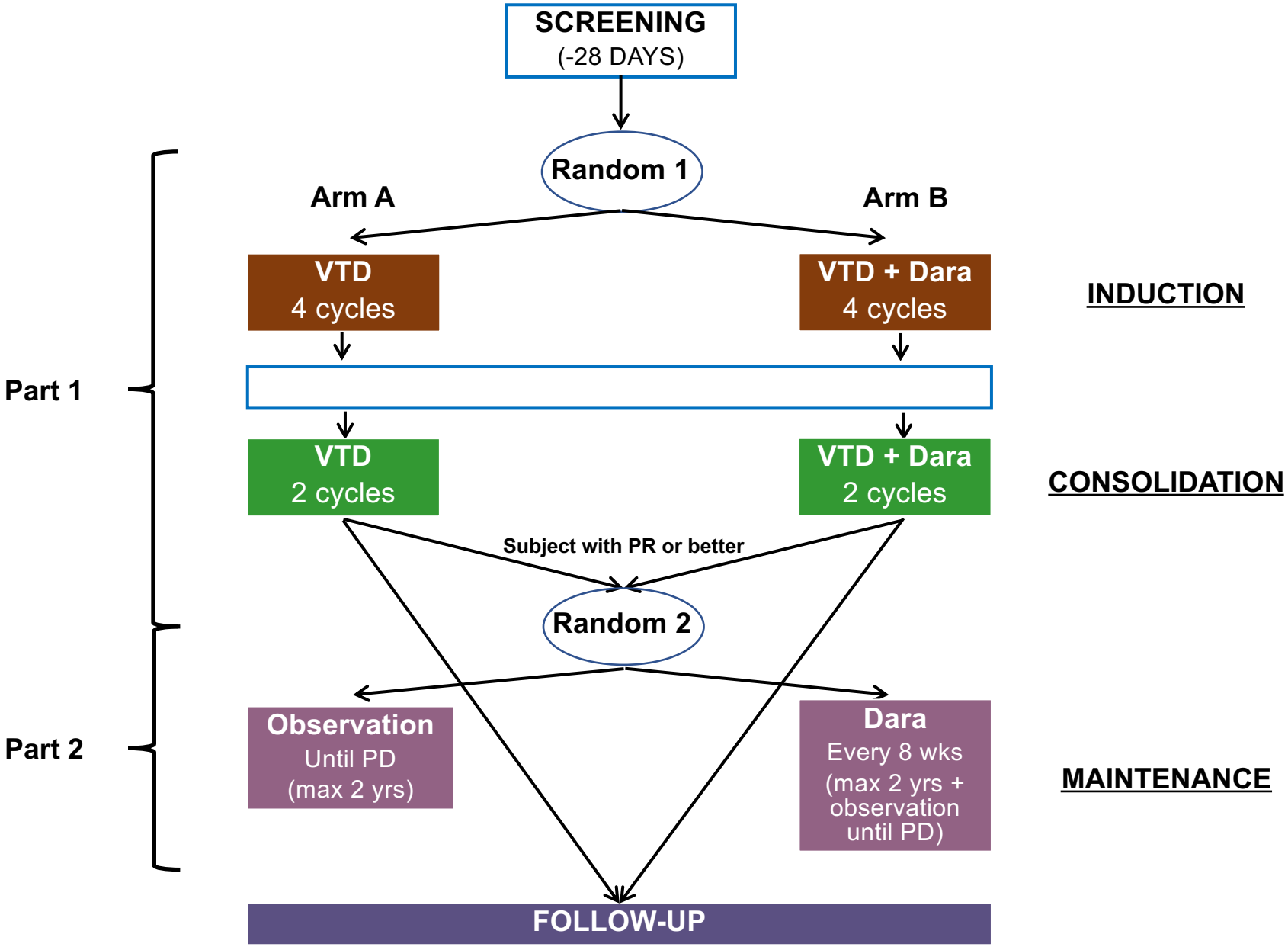
Diagnosis of multiple myeloma with osteolytic bone lesions

Testing revealed high-risk cytogenetics

Hypothetical case study
March 2023

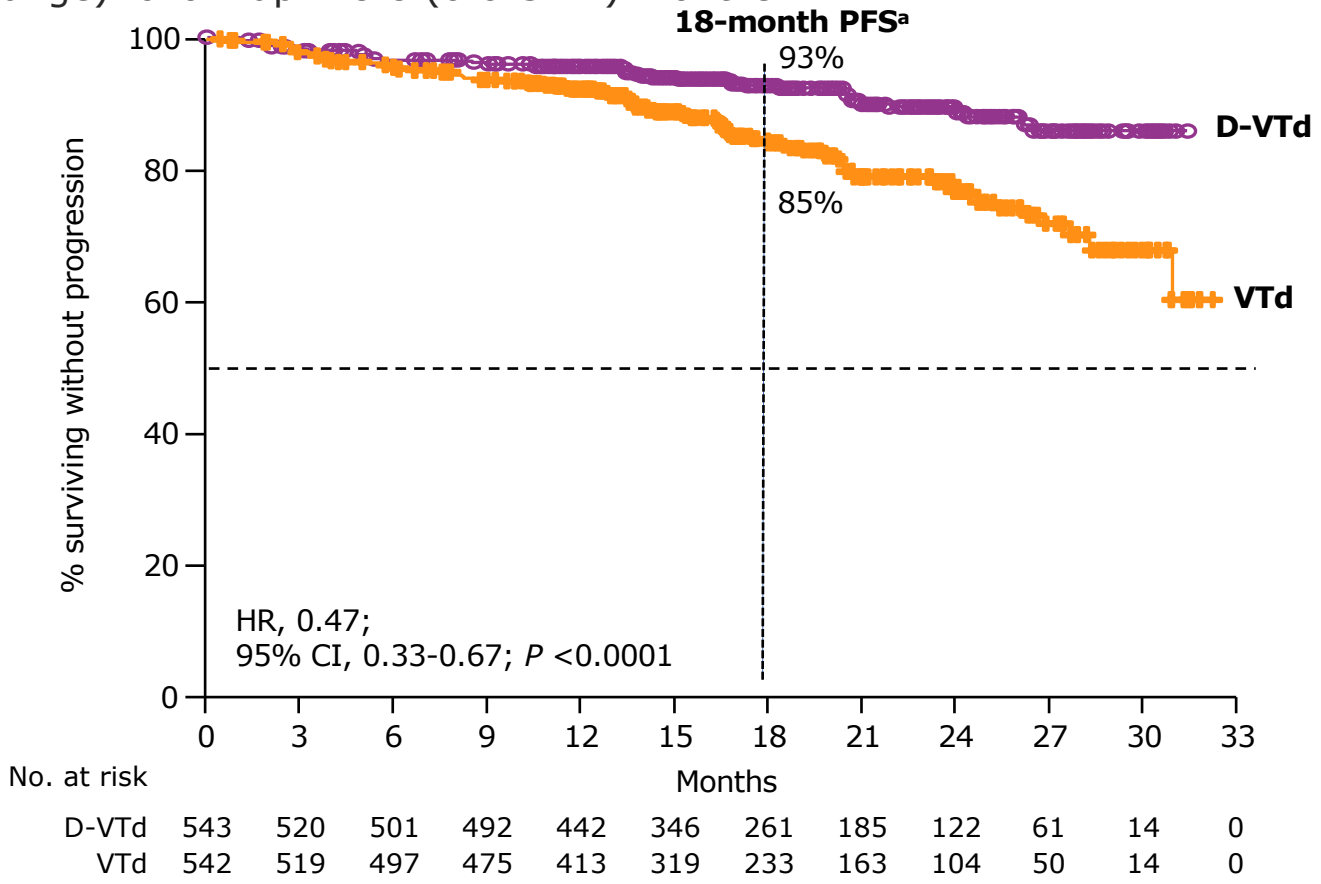


Daratumumab in Transplant Eligible Participants With Previously Untreated Multiple Myeloma (Cassiopeia)



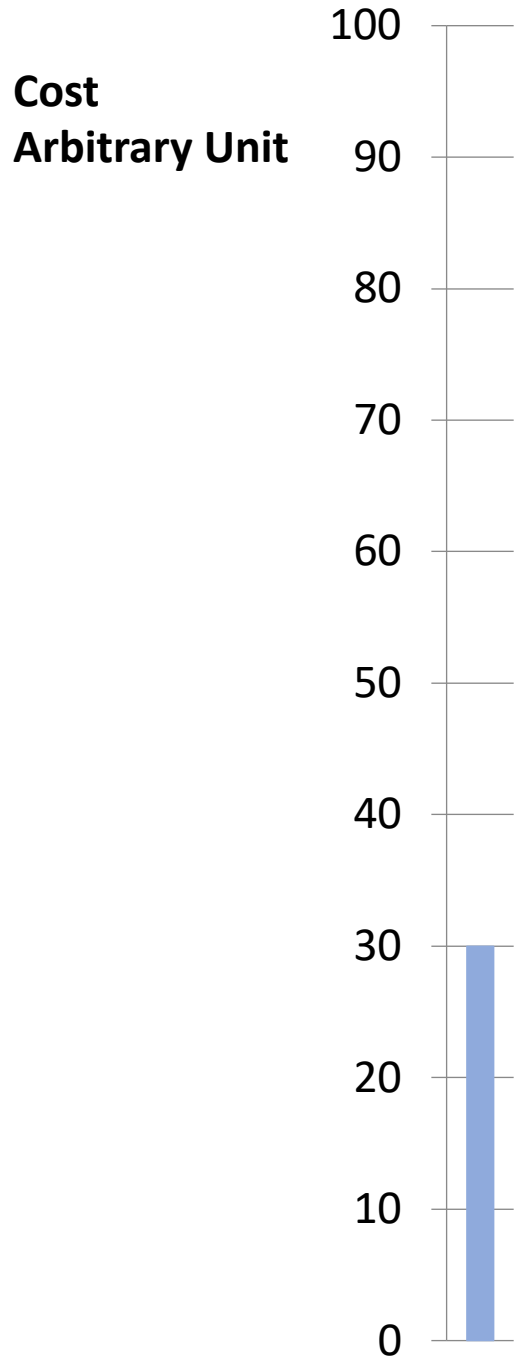
CASSIOPEIA: Daratumumab-VTd vs VTd before and after transplant in NDMM

- Median (range) follow-up: 18.8 (0.0-32.2) months

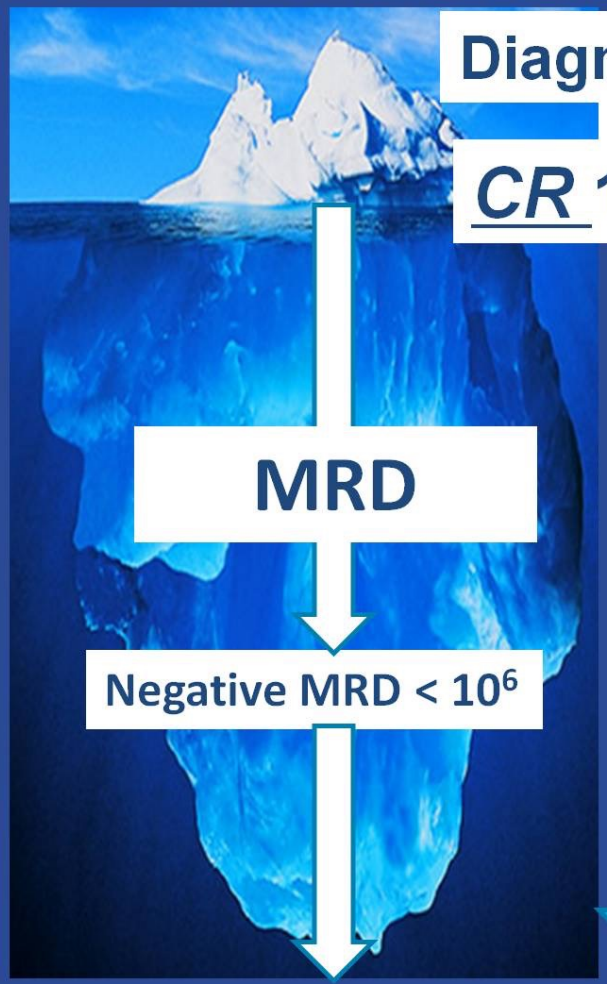


53% reduction in the risk of progression or death in patients receiving D-VTd

Treated Anti-CD38+IMID+PI for 6 months + Auto



Minimal Residual Disease, MRD



Diagnosis 10^{12}

CR 10^{10}

MRD

Negative MRD < 10^{6}

CR

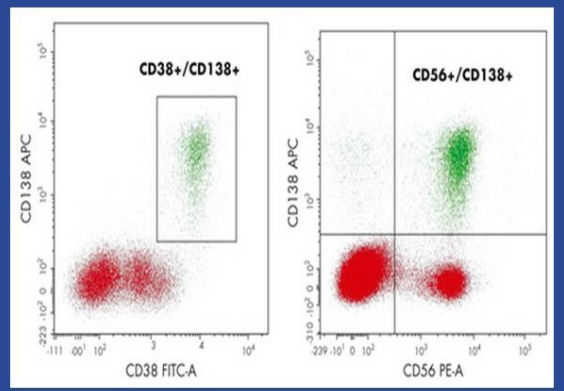
sCR

iCR

mCR

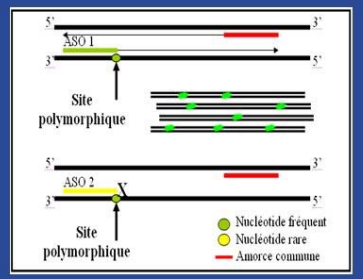
Immunophenotypic CR.

CMF (Sensibilité de 10^{-4} à 10^{-8} selon le nombre de couleurs (2 à 10 couleurs))



Molecular CR.

ASO-PCR (Se 10^{-5}), NGS

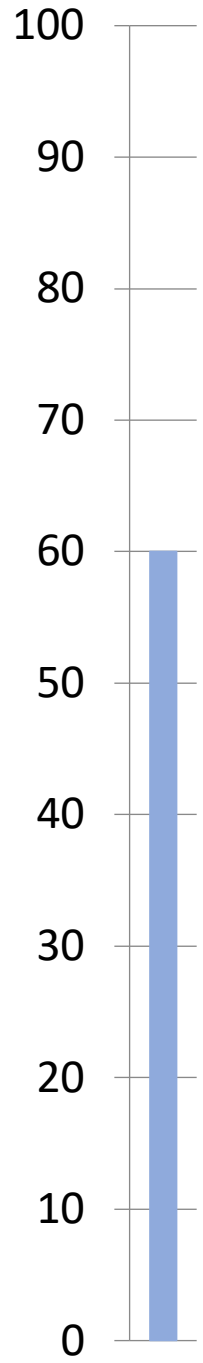


Treated with Exp1+Exp2+D+MoAb for 6 months + Auto

MRD, NGS, NGF, MRI, PET

Treated with Exp1+Exp2+D+MoAb for 6 months + Auto

Maintenance oral IMID or PI

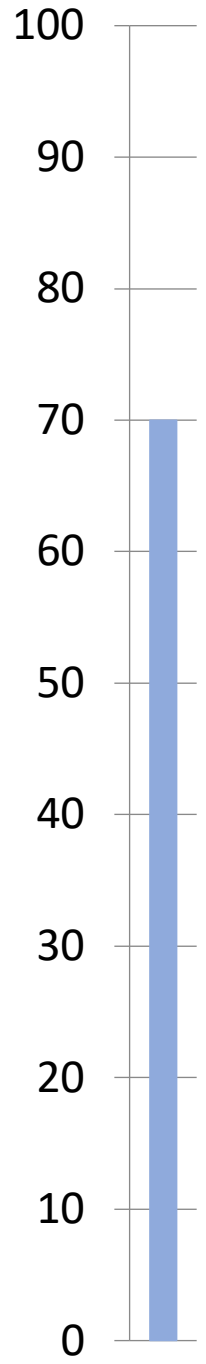


Treated with Exp1+Exp2+D+MoAb for 6 months + Auto

Maintenance oral IMID or PI

First Relapse

Novel IMID + MoAb



Treated with Exp1+Exp2+D+MoAb for 6 months + Auto

Maintenance oral IMID or PI

Second Relapse

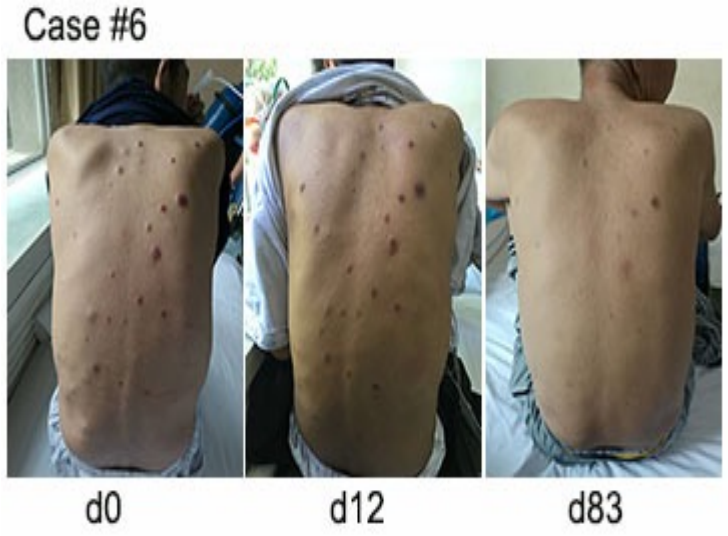
Belantamab/Selinexor

100
90
80
70
60
50
40
30
20
10
0

PHASE I, OPEN-LABEL TRIAL OF ANTI-BCMA CHIMERIC ANTIGEN RECEPTOR T CELLS IN PATIENTS WITH RELAPSED/ REFRACTORY MULTIPLE MYELOMA

Author(s): Wanggang Zhang

EHA Learning Center. Zhang W. Jun 23, 2017; 181390

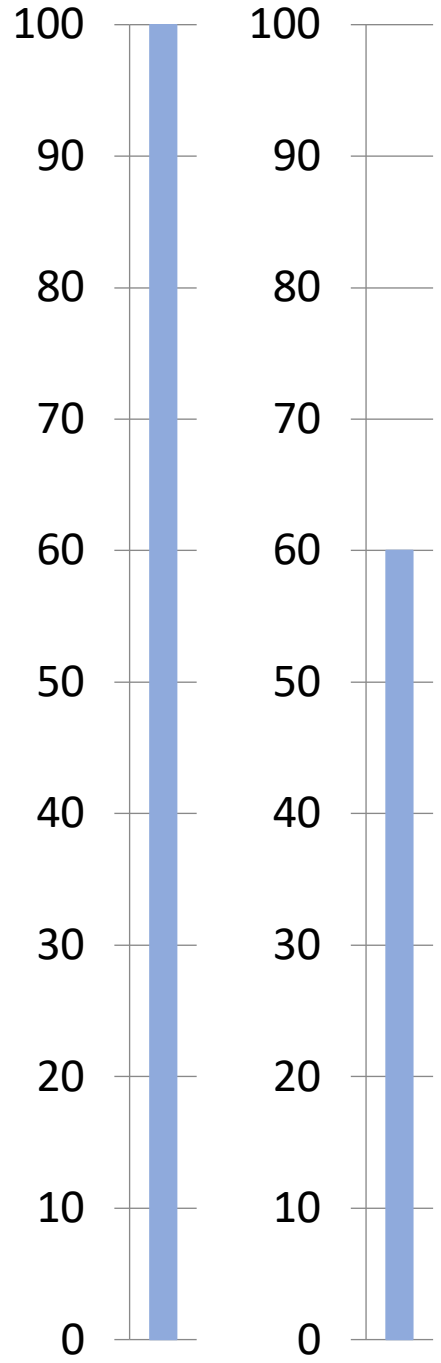


Treated with Exp1+Exp2+D+MoAb for 6 months + Auto

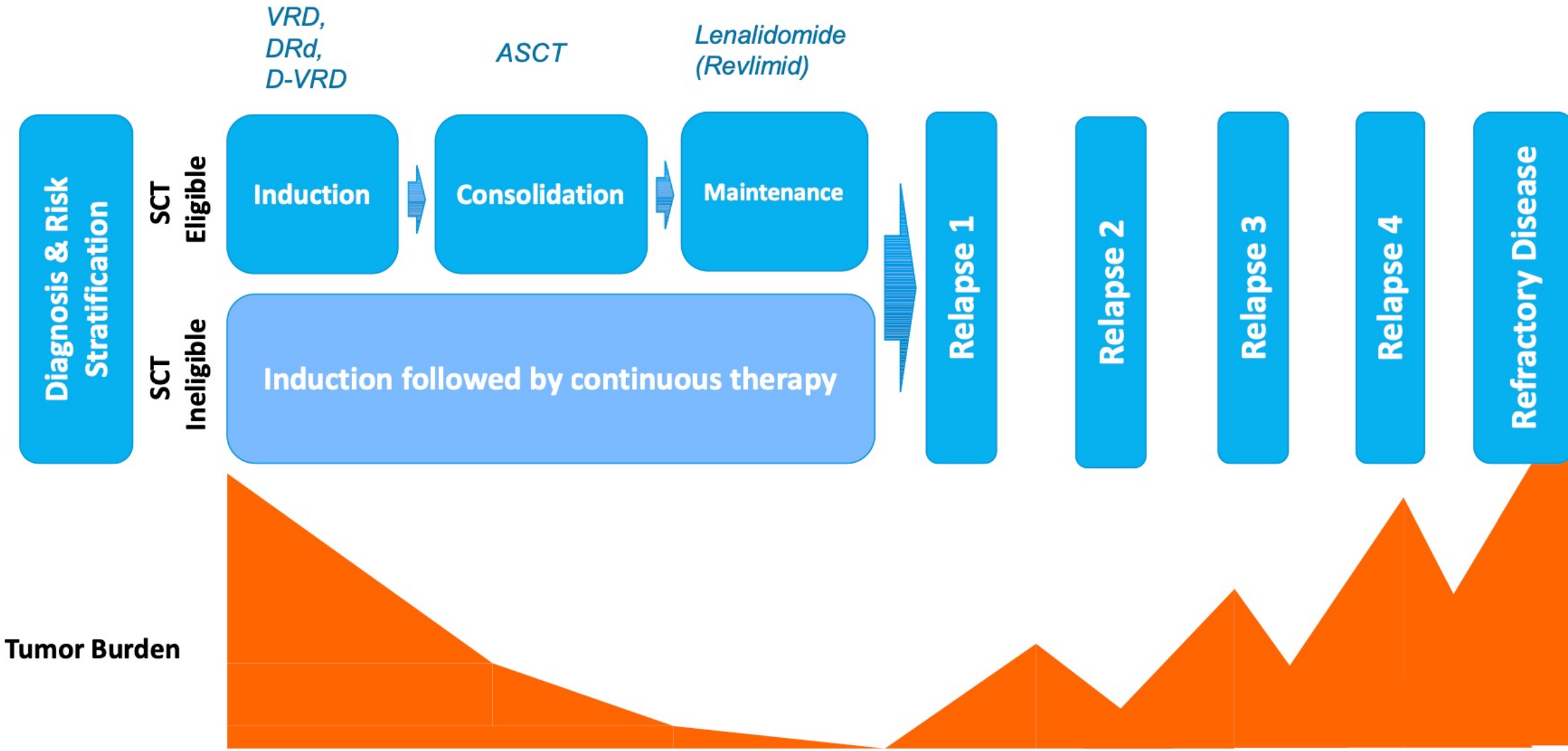
Maintenance oral IMID or PI

Third Relapse

Byspecific/CAR T



5. MYELOMA TREATMENT PARADIGM



Future of CAR T-cell Therapy

- Non realistic to plan 5-6 lines of therapy with innovative drugs
  - Economic reasons
  - Limited number of line of therapy in real word

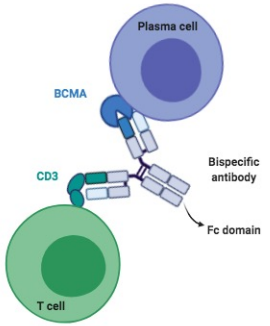
→ New strategies are needed

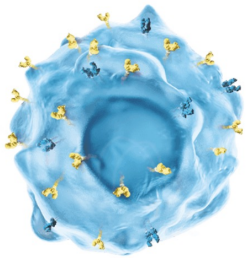
Induction Therapy

First options
quadruplets

antiCD38-VTD
antiCD38-VRD
antiCD38-KRD

New drugs available





CAR T Cell

Strategy

Additive to all Patients

Quadruplets

+Bispecific MoAb

+ Conjugated MoAb

+ Car T

Risk Adapted

New Risk Factors

- 1q gain/amp
- Circulating Plasma Cells (CPC)

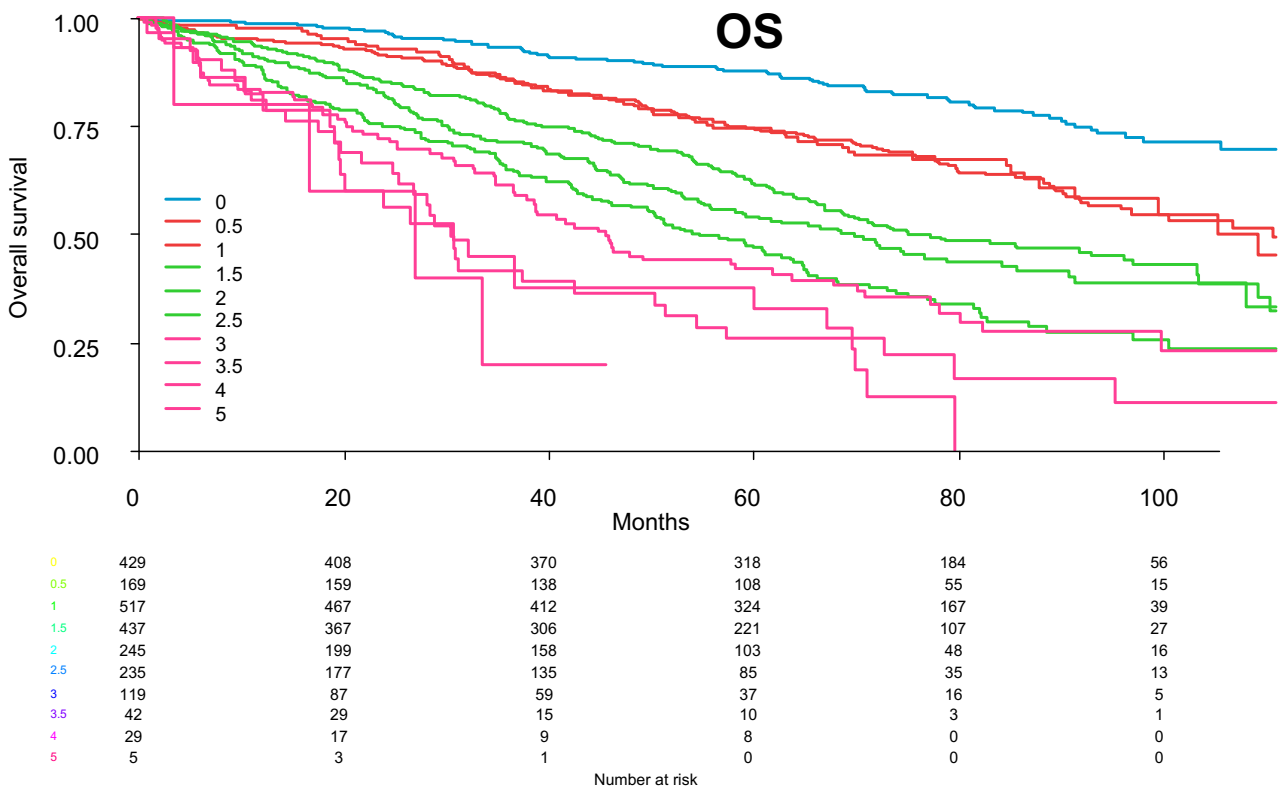
New dynamic Risk Factors

- MRD
- Sustained MRD

Score definition: R2-ISS

Patients with complete data for all risk features in the training set (n=2227)

Risk feature	OS hazard ratio	PFS hazard ratio	Score value*
ISS II	1.75	1.44	**1**
ISS III	2.54	1.76	**1.5**
Deletion 17p	1.82	1.43	**1**
High LDH	1.60	1.37	**1**
Translocation 4;14	1.53	1.40	**1**
1q+	1.47	1.33	**0.5**
Group	**Number of patients (%)**		**Total additive score**
Low (I)	429 (19.3%)		0
Low-Intermediate (II)	686 (30.8%)		0.5-1
Intermediate-High (III)	917 (41.2%)		1.5-2.5
High (IV)	195 (8.8%)		3-5



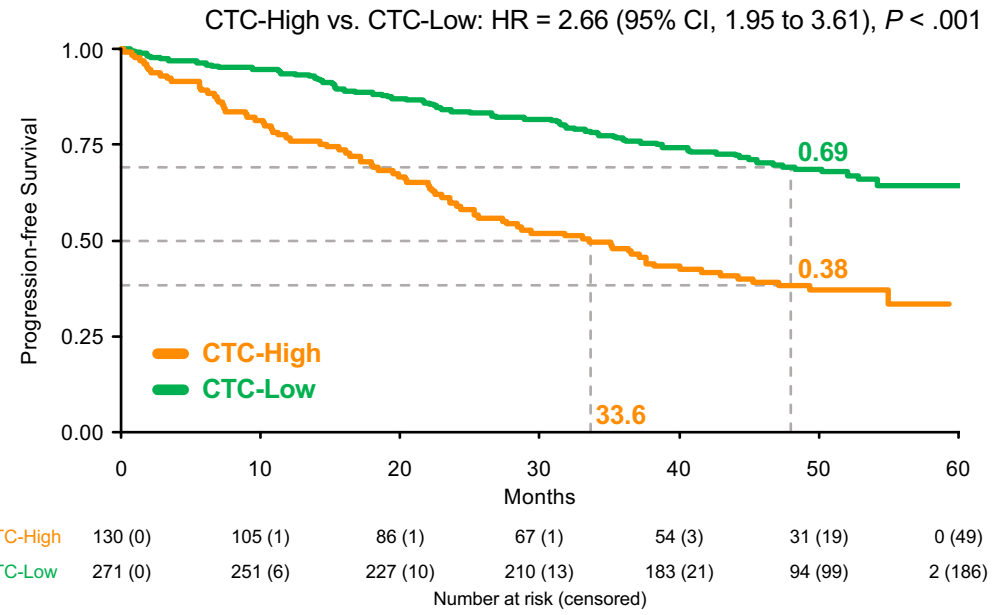
*calculated on the risk of death, value rounded to the nearest 0.5 with ISS II vs I comparison as reference (score = 1).

Abbreviations. R2-ISS: Revision 2 of the International Staging System; ISS: International Staging System stage; LDH: lactate dehydrogenase; OS: overall survival; PFS: progression-free survival.

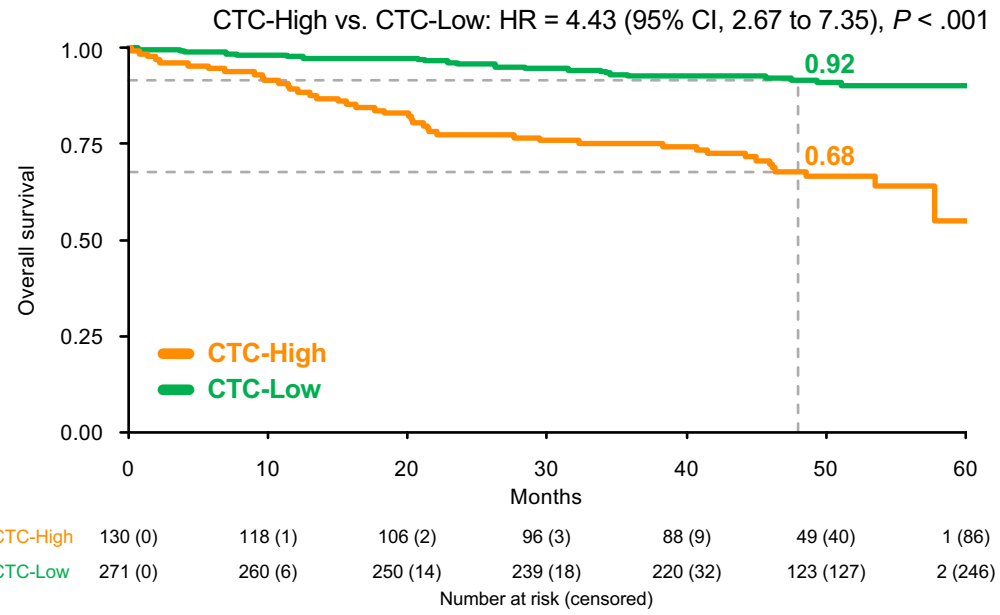
D'Agostino M et Al, J Clin Oncol. 2022;40:3406

CTC impact on PFS and OS

A. Progression-free survival

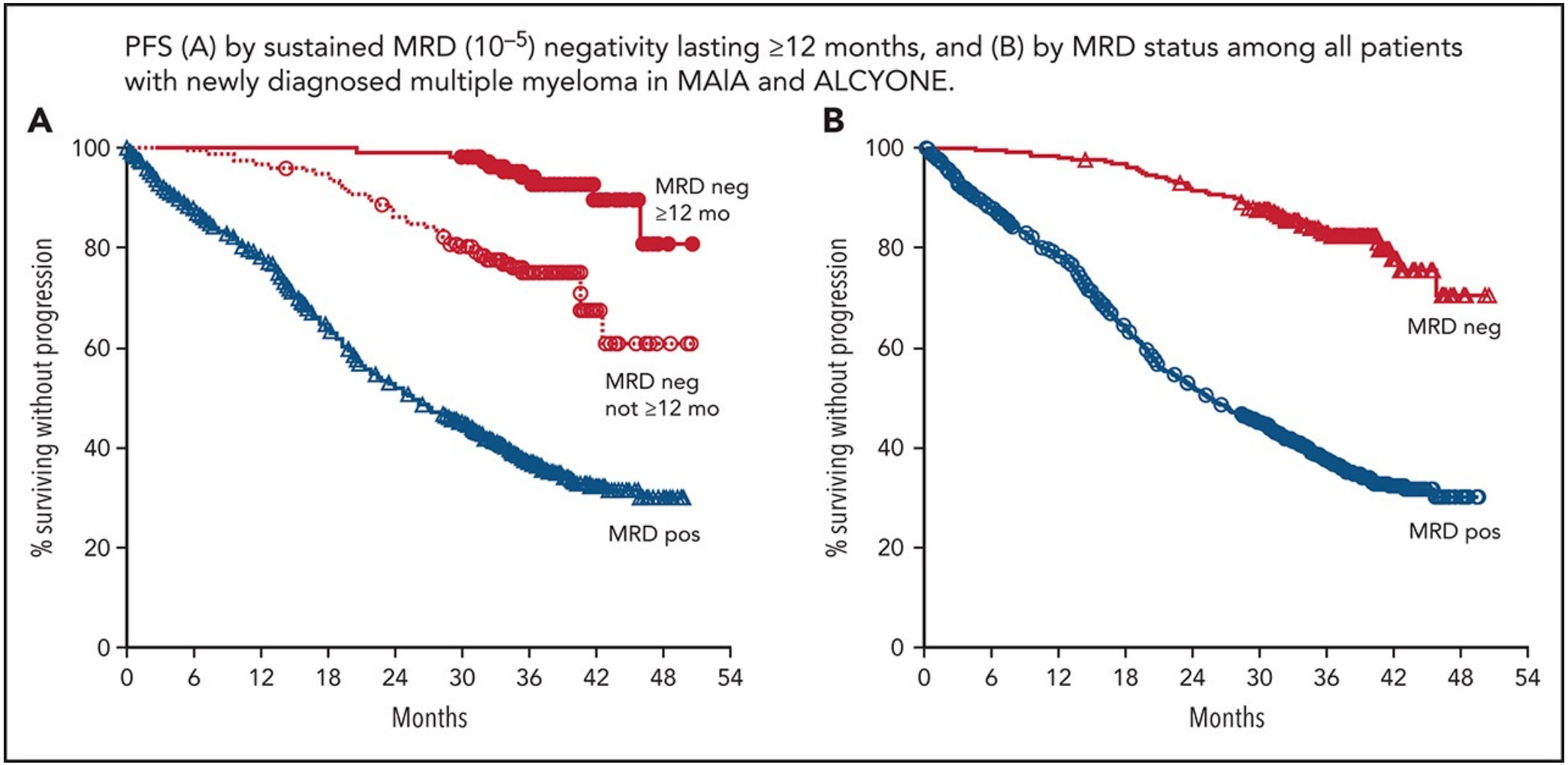


B. Overall survival



Bertamini et Al.:J Clin Oncol. 2022;40:3120

Sustained minimal residual disease negativity in newly diagnosed multiple myeloma and the impact of daratumumab in MAIA and ALCYONE



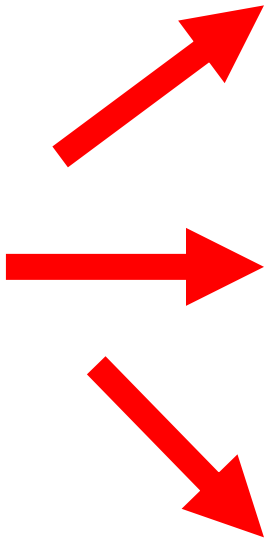
Jesus San-Miguel Blood, 2022,

original reports

Identification of High-Risk Multiple Myeloma With a Plasma Cell Leukemia-Like Transcriptomic Profile

Davine Hofste op Bruinink, MD, MSc[1,2]; Rowan Kuiper, PhD[1,3]; Mark van Duin, PhD[1]; Tom Cupedo, PhD[1]; Vincent H.J. van der Velden, PhD[2]; Remco Hoogenboezem, MSc[1]; Bronno van der Holt, PhD[4]; H. Berna Beverloo, PhD[5]; Erik T. Valent, PhD[3]; Michael Vermeulen, BSc[1]; Francesca Gay, MD, PhD[6]; Annemiek Broijl, MD, PhD[1]; Hervé Avet-Loiseau, MD, PhD[7]; Nikhil C. Munshi, MD, PhD[8]; Pellegrino Musto, MD[9]; Philippe Moreau, MD[10]; Sonja Zweegman, MD, PhD[11]; Niels W.C.J. van de Donk, MD, PhD[11]; and Pieter Sonneveld, MD, PhD[1]

Risk adapted Strategy



Tumor characterics at diagnosis

Cytogenetic, CPC, GEP, transcriptomic profile

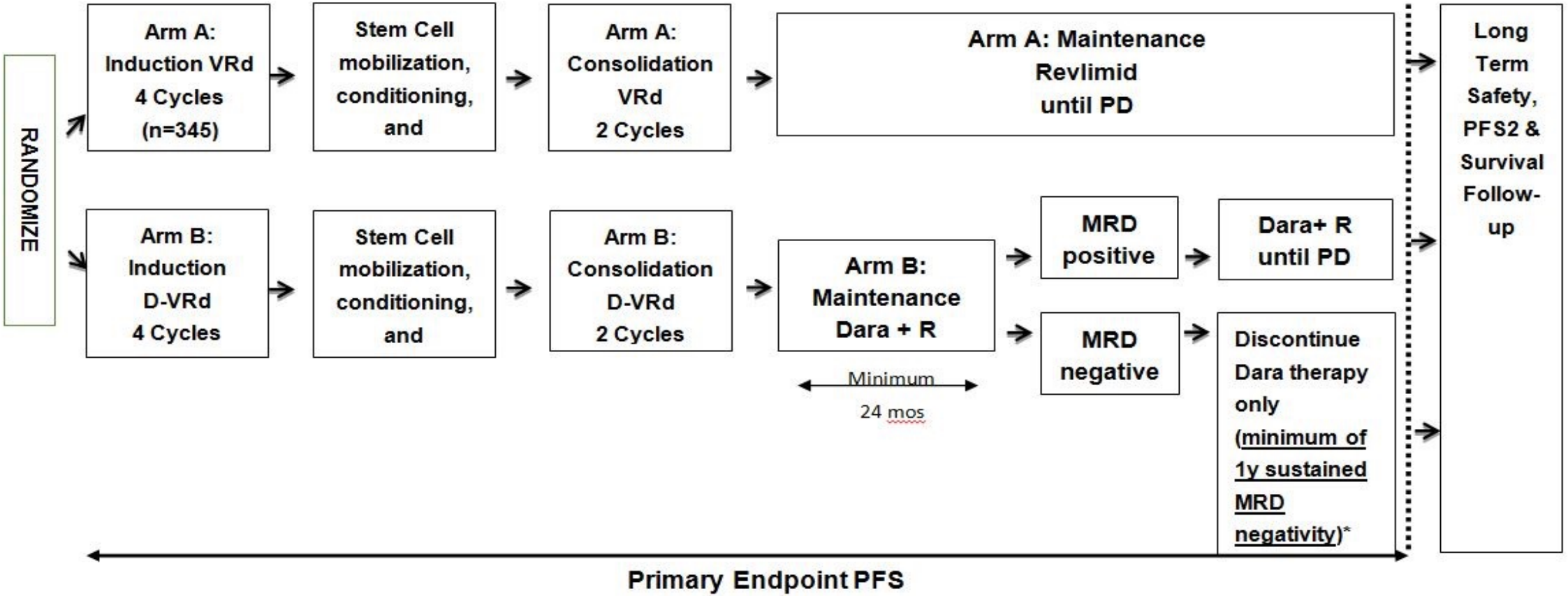
Dynamic response parameters

CR, MRD, sustained MRD

Patients clinical conditions

age, comorbilities

D-VRd vs VRd in TE Myeloma Patients. The Perseus Study (EMN17)

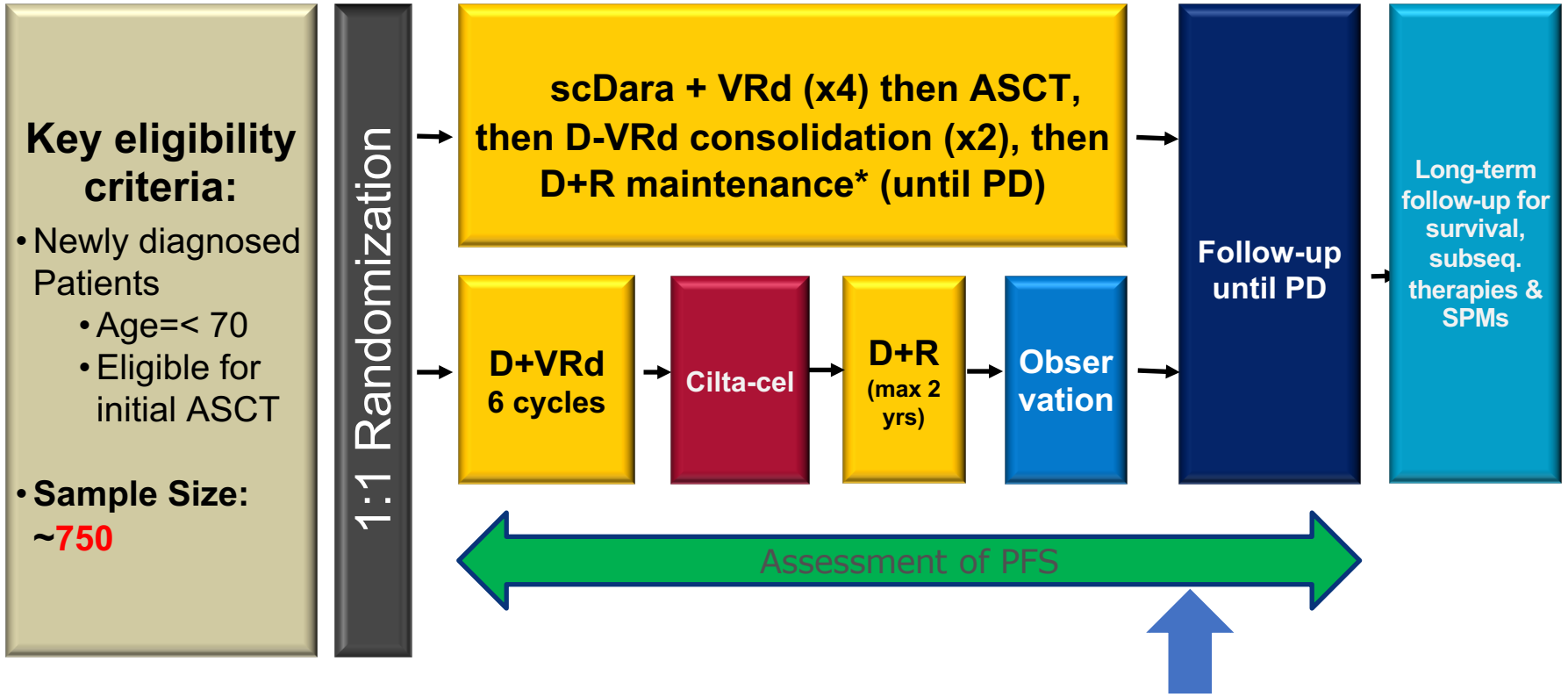


*opportunity to restart therapy upon relapse from CR or loss of MRD status

Key: CR=complete response; Dara=daratumumab; D-VRd=daratumumab in combination with bortezomib, lenalidomide, and dexamethasone; MRD=minimum residual disease; PD=progressive disease; PFS2= progression-free survival on next line of therapy; R=lenalidomide; SPM=second primary malignancy; VRd=bortezomib, lenalidomide, and dexamethasone.

CARTITUDE-6

Randomized Phase 3 study in Newly Diagnosed, Transplant Eligible Patients vs ASCT



Stratification factors:
a) **ISS staging**
b) **Cytogenetics**
c) **Age**

***based on DARA-MMY3014 registration study.** Includes DARA-stopping rules after 2 years for MRD-negativity.

Primary endpoint:
Sustained MRD neg CR
Key Secondary endpoint:
PFS

EMN

Future of CAR T-cell Therapy

- Non realistic to plan 5-6 lines of therapy with innovative drugs
  - Economic reasons
  - Limited number of line of therapy in real word

→ New strategies are needed

→ ***Risk adapted Strategy***

Conclusions:

- Define patients who most benefit from CarT

- New trials will define efficacy/toxicity
  in various patients subgroups