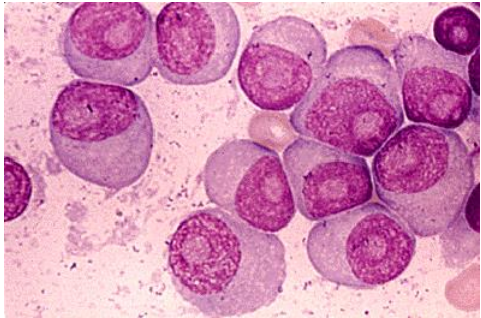
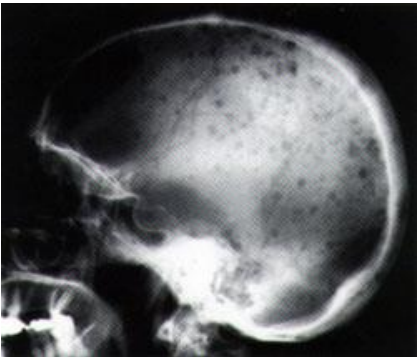
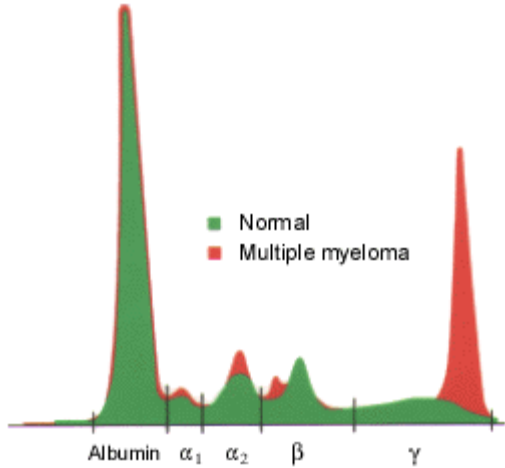


ORGANIZZAZIONE E PROGRAMMAZIONE DI UNA TARGET THERAPY



Serum Protein Electrophoresis



Asiago 19-9-2019

Mario Boccardo

DIVISION OF HEMATOLOGY
UNIVERSITY OF TORINO
AZIENDA OSPEDALIERO-UNIVERSITARIA CITTÀ
DELLA SALUTE E DELLA SCIENZA DI TORINO
TORINO, ITALY



An aerial photograph of a rural landscape. In the center, a prominent, rounded hill covered in dense green forest rises above the surrounding terrain. The landscape is a patchwork of green and golden-brown fields, separated by dark lines representing roads or hedgerows. In the distance, a small town or village is visible, followed by a vast, flat plain that extends to a clear horizon under a blue sky with scattered white clouds. The overall scene is bright and clear, suggesting a sunny day.

Horizon Scanning

Image: John McLinden, via Flickr

Now Available: Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting

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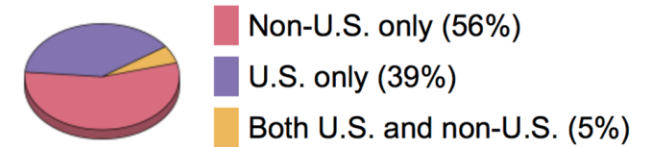
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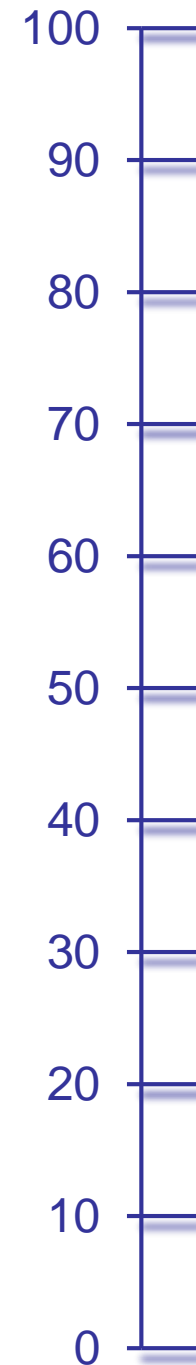
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First-line treatment

Cost
Arbitrary
Unit



Case 1



Mr. Mario Rossi

64-year-old male

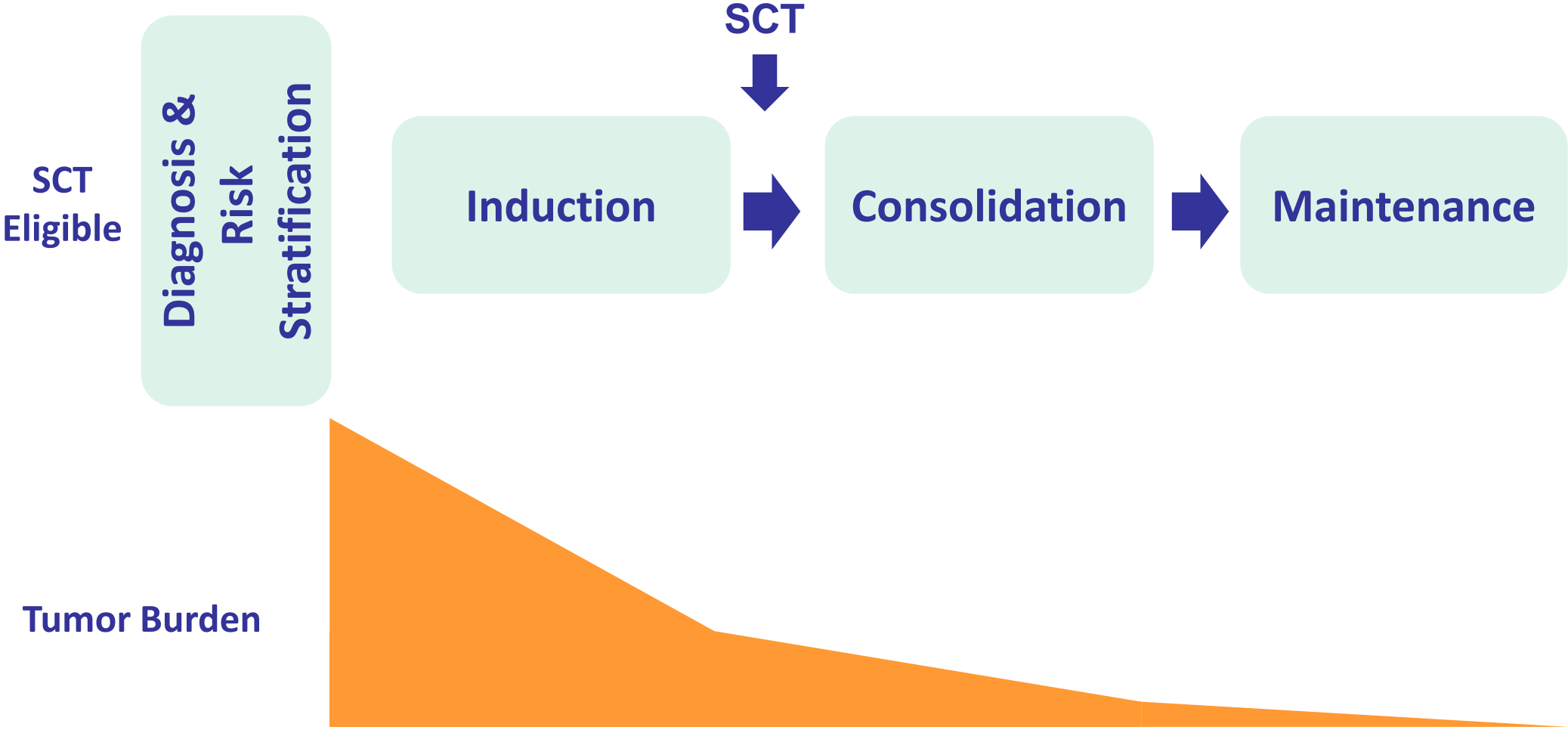
Initially presents with baseline pain and fatigue

Diagnosis of multiple myeloma with osteolytic bone lesions

Testing revealed high-risk cytogenetics

Hypothetical case study
Sept 2019

Myeloma Treatment Paradigm

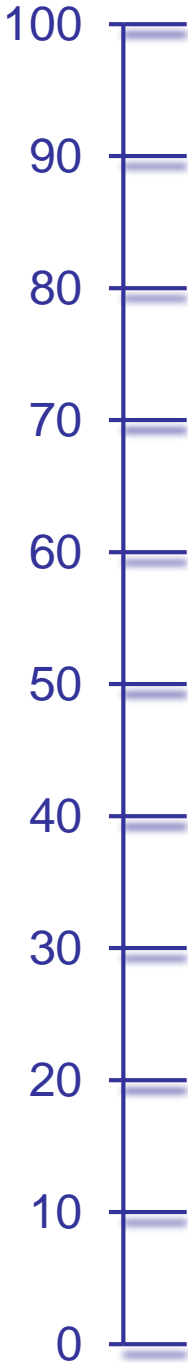


SCT, stem cell transplant

Case 1

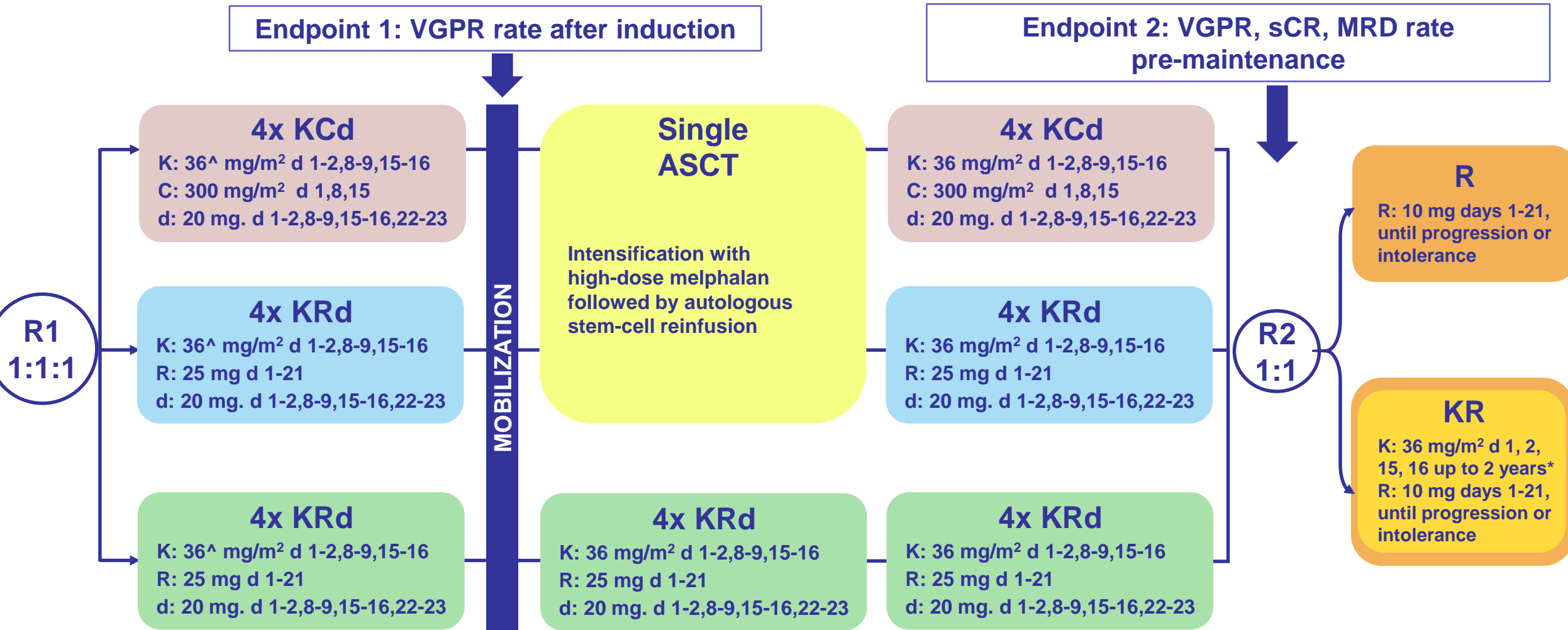


Induction treatment



UNITO-MM-01/FORTE Study

NDMM patients, transplant-eligible and younger than 65 years



Gay F. et al.
ASCO 2019.
Oral pres. #8002

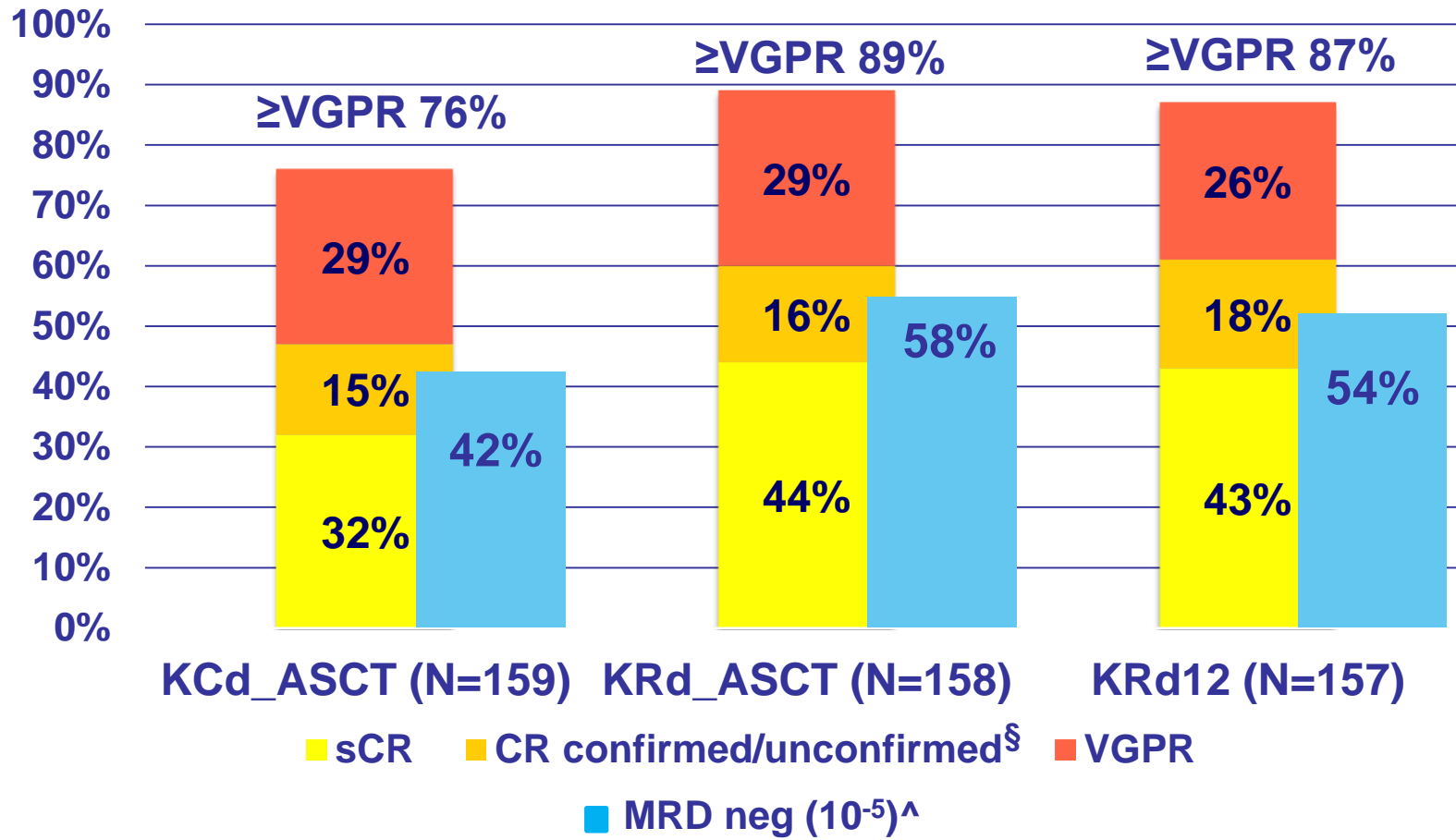
[^]20 mg/m² on days 1-2, cycle 1 only. *Carfilzomib 70 mg/m² days 1, 15 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards.

R1, randomization 1; R2, Randomization 2; IQR, interquartile range K, carfilzomib; C, cyclophosphamide; R, lenalidomide; d, dexamethasone; d, days; ASCT: autologous stem-cell transplantation; R, lenalidomide; KR, carfilzomib, lenalidomide. NDMM, newly diagnosed multiple myeloma; VGPR, very good partial response.

UNITO-MM-01/FORTE study

Pre-maintenance response rate and MRD negativity

ITT analysis

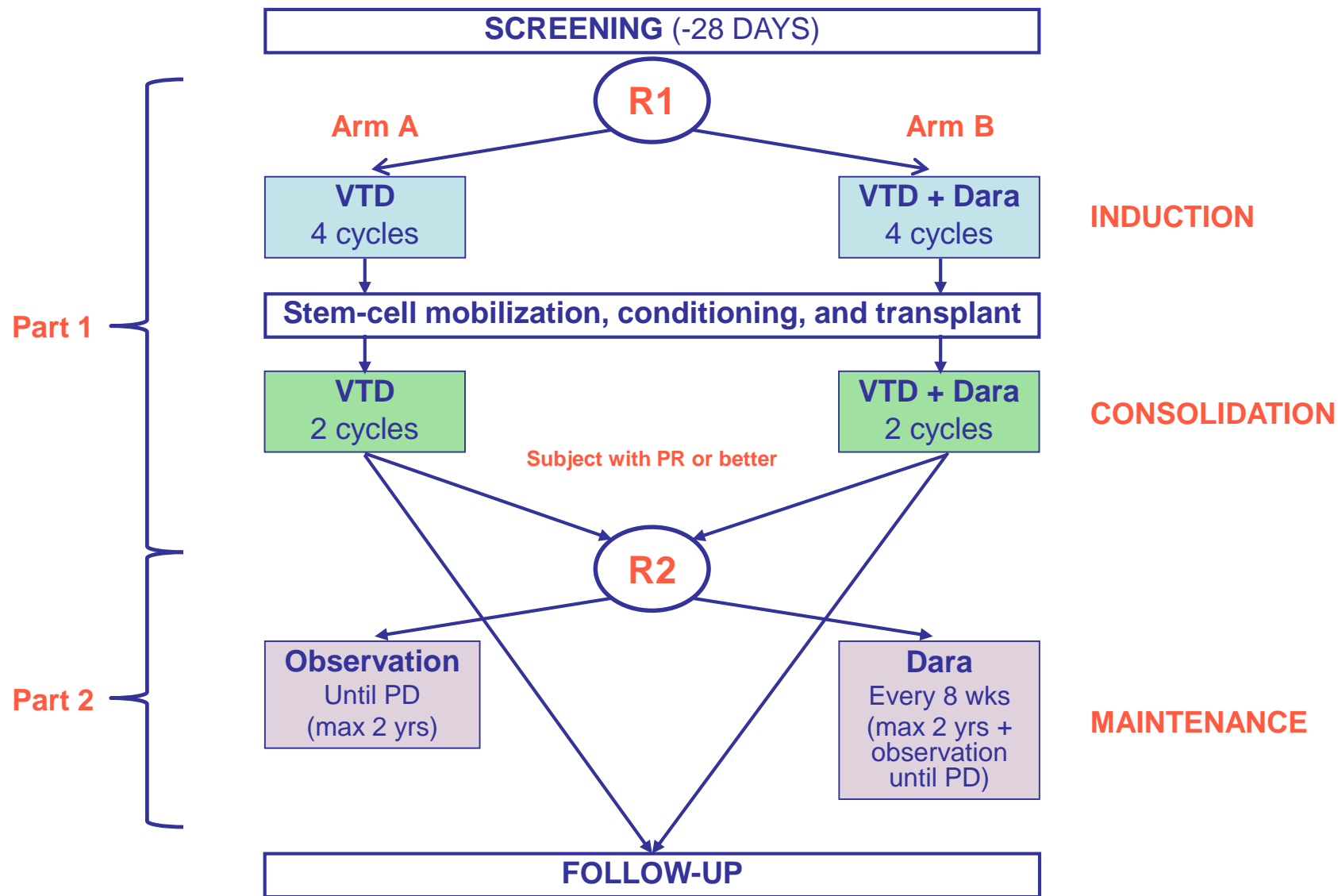


	OR>1	P value*
≥VGPR		
KRd_ASCT vs KCd_ASCT	2.53	0.004
KRd12 vs KCd_ASCT	2.11	0.015
sCR		
KRd_ASCT vs KCd_ASCT	1.65	0.035
KRd12 vs KCd_ASCT	1.60	0.048
MRD neg (10⁻⁵)		
KRd_ASCT vs KCd_ASCT	2.02	0.009
KRd12 vs KCd_ASCT	1.73	0.042

**Gay F. et al.
ASCO 2019.
Oral pres. #8002**

[^]Patients whose samples were not available (~10%) were considered as positive. *Adjusted for ISS, Age, FISH, LDH.
[§]Unconfirmed CR/sCR: patients missing immunofixation/sFLC analysis needed to confirm CR/sCR (6% in KCd_ASCT_KCd; 8% in KRd_ASCT_KRd; 6% KRd_12).
 ASCT, autologous stem-cell transplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; MRD, minimal residual disease; neg, negativity; sCR, stringent complete response; CR: complete response; VGPR: very good partial response; OR: odds ratio; FISH, fluorescence in situ hybridization; LDH, lactate dehydrogenase; FLC, free light chain, ISS, International Staging System.

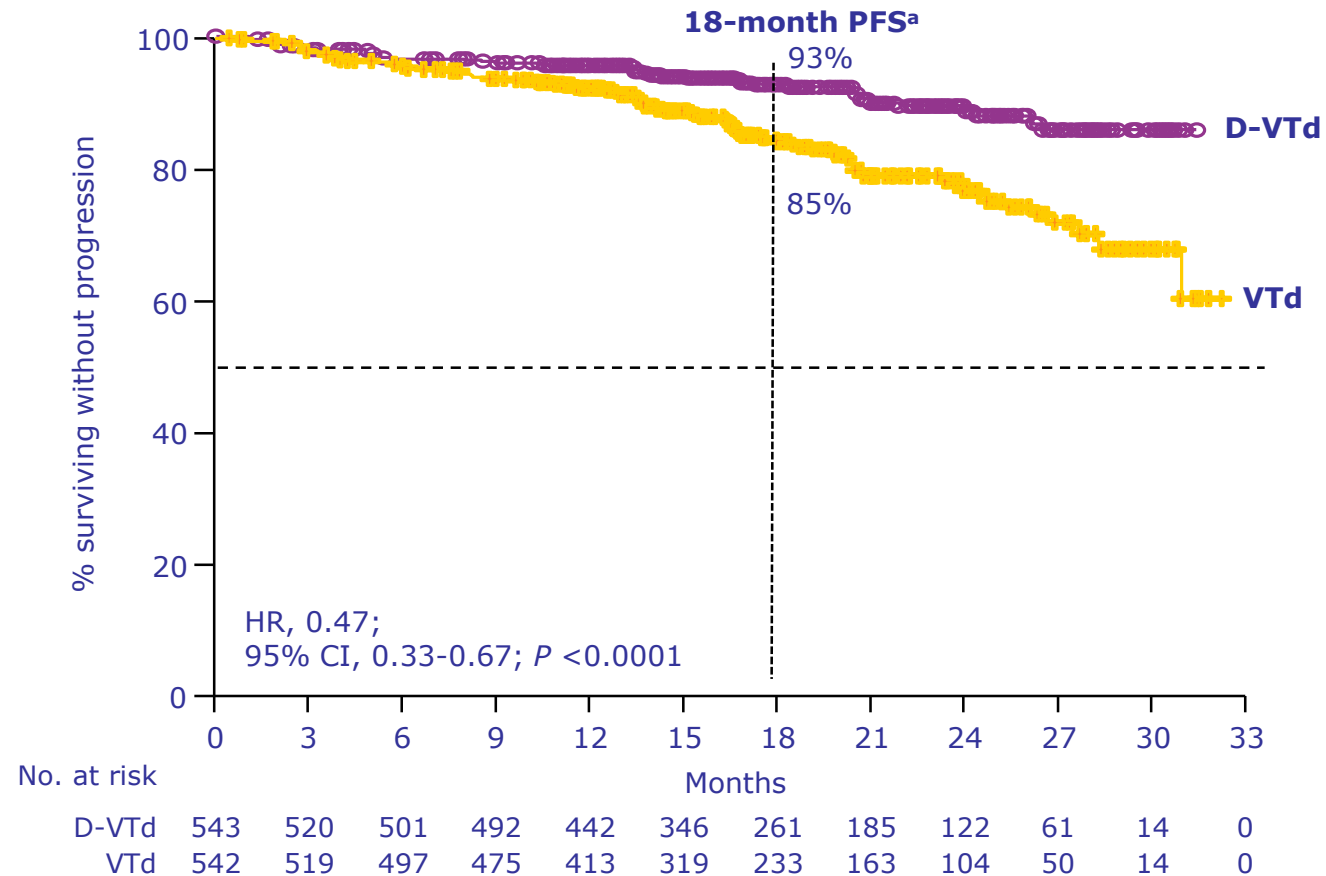
Daratumumab in Transplant-Eligible Participants With Previously Untreated Multiple Myeloma (Cassiopeia)



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

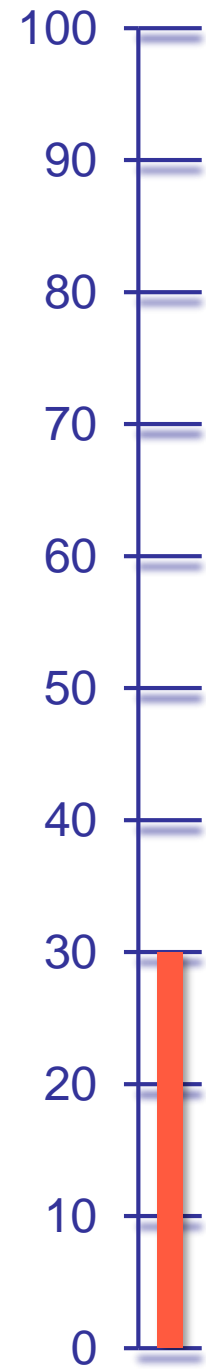
Moreau P. et al.
ASCO 2019.
Oral pres. #8003

a. Kaplan-Meier estimate.
D, daratumumab; V, bortezomib; T, thalidomide; d, dexamethasone; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

Case 1



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



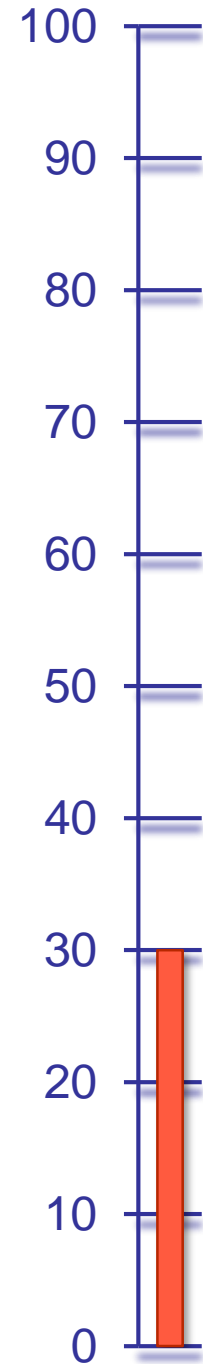
Exp = Expensive drug

Case 1



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

MRD, NGS, NGF, MRI, PET

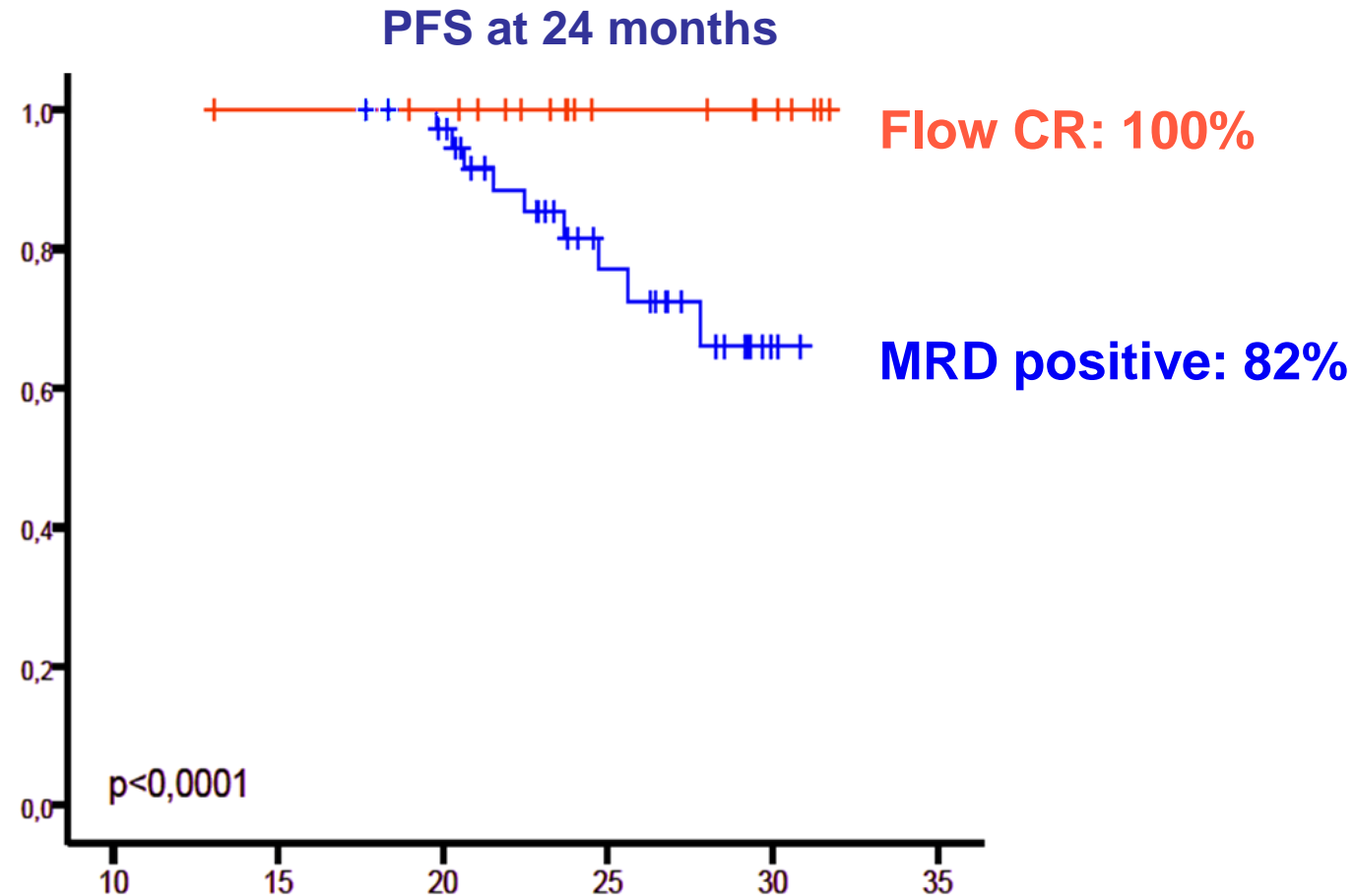


Exp = Expensive drug

D, dexamethasone; MoAb, monoclonal antibody; MRD, minimal residual disease; NGS, next-generation sequencing; NGF, next-generation flow; MRI, magnetic resonance imaging; PET, positron emission tomography.

GEM2010: 8-colors and 10^{-5} (> 2×10^6 leukocytes)

Median follow-up: 20 m (10-32)



No progressions or deaths have been observed in patients who achieved Flow-CR

Mateos MV. et al.
Blood 2013;122:
ASH 2013; oral pres. #403

Techniques available to measure MRD in MM

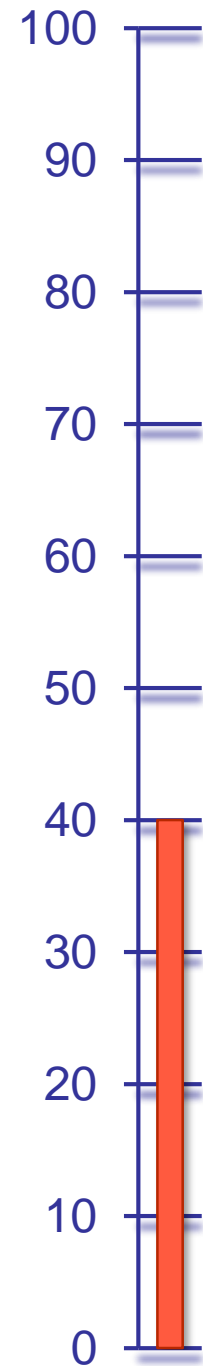
	Multidimensional (≥8-color) FC	Molecular ASO-PCR	High- throughput sequencing	PET-CT
Diagnostic sample	Important but not mandatory	Mandatory	Mandatory	?
Time	2 hours	5 days	7 days	2 hours
Availability	High	Intermediate	?	Intermediate
Cost	~150 euros	~450 euros	??	High
Standardization	Ongoing	Yes (Biomed)	Yes (Sequentia)?	?
Sensitivity	10^{-5}	10^{-5} - 10^{-6}	10^{-6}	High (?)

Case 1



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

MRD, NGS, NGF, MRI, PET



Exp = Expensive drug

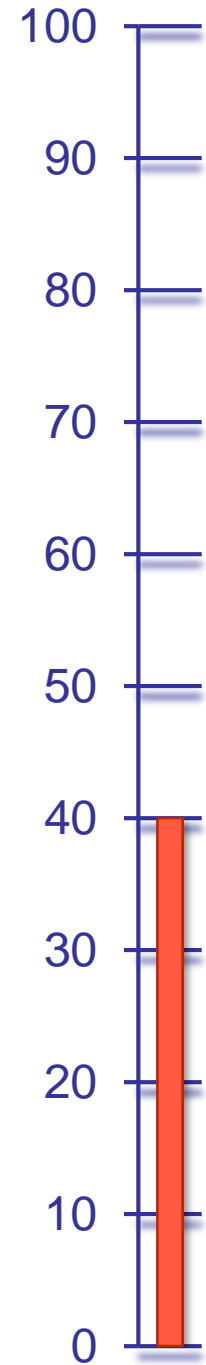
D, dexamethasone; MoAb, monoclonal antibody; MRD, minimal residual disease; NGS, next-generation sequencing; NGF, next-generation flow; MRI, magnetic resonance imaging; PET, positron emission tomography.

Case 1



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

Maintenance



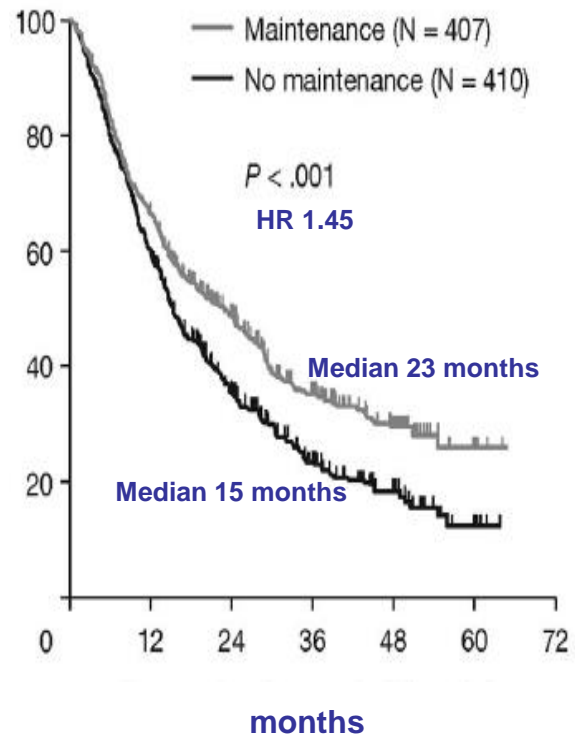
Exp = Expensive drug
D, dexamethasone; MoAb, monoclonal antibody.

Maintenance treatment prolongs PFS

MRC Myeloma IX

Thalidomide maintenance
PFS

IND. T continuous therapy

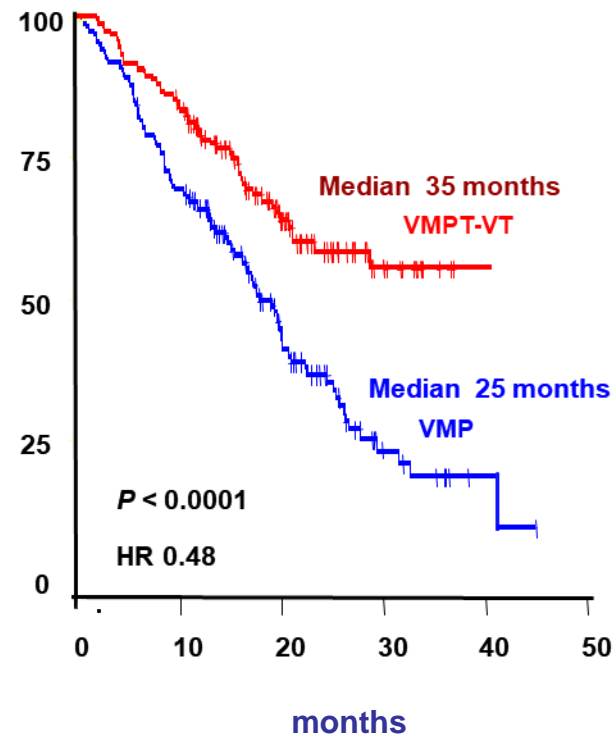


Morgan GJ, et al. Blood 2012;119:7

GIMEMA MM 03 05

Bortezomib-based maintenance
PFS in landmark

VMPT VT continuous therapy

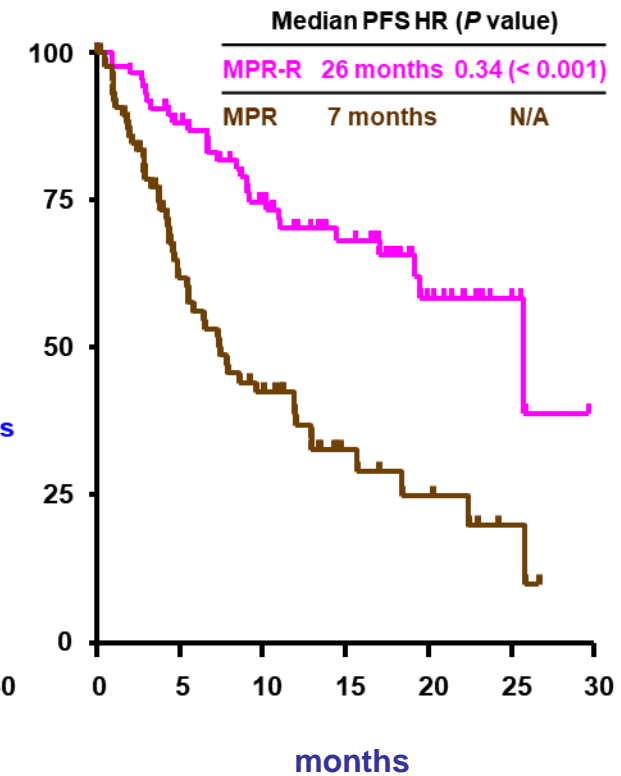


Palumbo A, et al. ASH 2012; Abs.200

MM-015

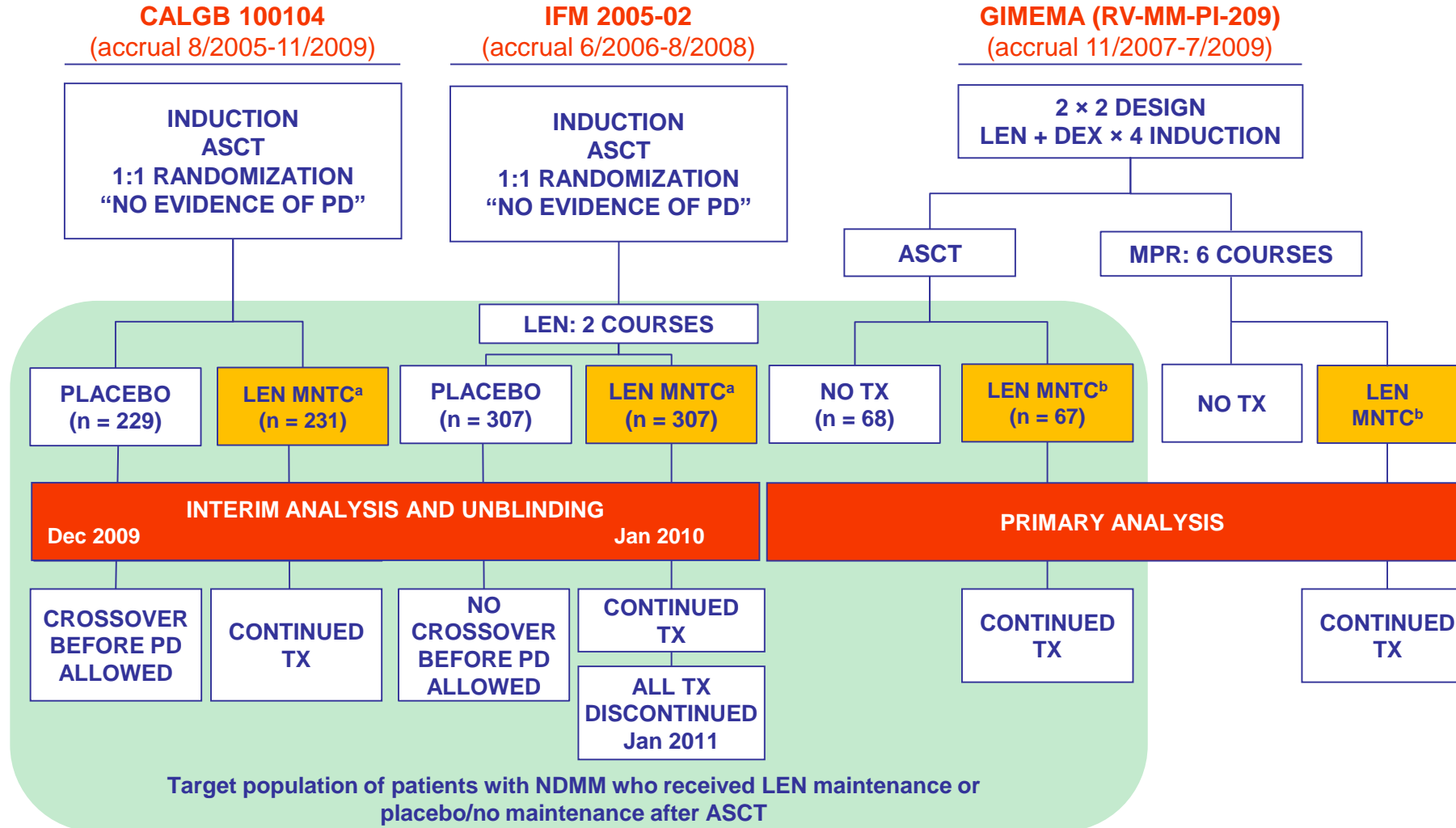
Lenalidomide maintenance
PFS in landmark

MPR R continuous therapy



Palumbo A, et al. NEJM 2012;366:1759

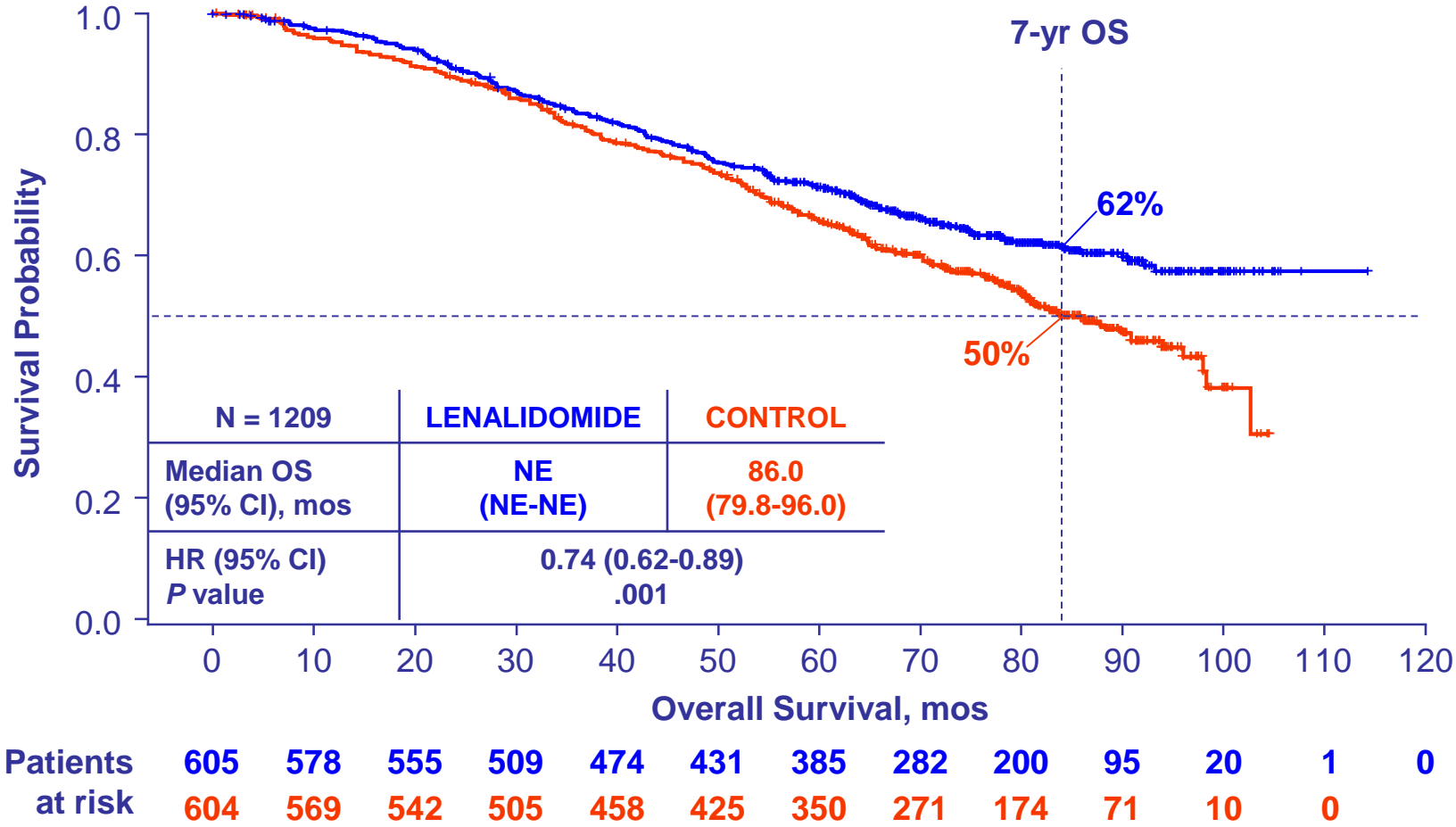
Studies Included in Meta-Analysis



^a Starting dose of 10 mg/day on days 1-28/28 was increased to 15 mg/day if tolerated and continued until PD. ^b Patients received 10 mg/day on days 1-21/28 until PD. ASCT, autologous stem cell transplant; DEX, dexamethasone; LEN, lenalidomide; MNTC, maintenance; MPR, melphalan, prednisone, and lenalidomide; NDMM, newly diagnosed multiple myeloma; PD, progressive disease; Tx, treatment.

Overall Survival: Median Follow-Up of 80 Months

26% reduction in risk of death
2.5-year increase in median overall survival^a



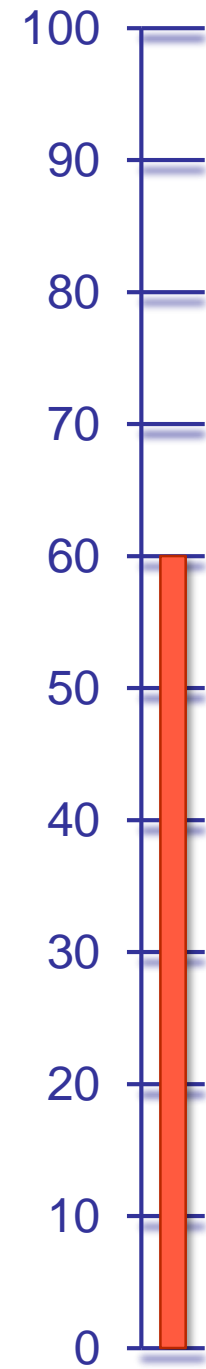
^a Median for lenalidomide treatment arm was extrapolated to be 116 months based on median of the control arm and HR (median, 86 months; HR = 0.74). HR, hazard ratio; NE, not estimable; OS, overall survival.

Case 1



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

Maintenance oral IMiD or PI



Exp = Expensive drug

D, dexamethasone; MoAb, monoclonal antibody; IMiD, immunomodulatory agent; PI, proteasome inhibitor.

Case 1

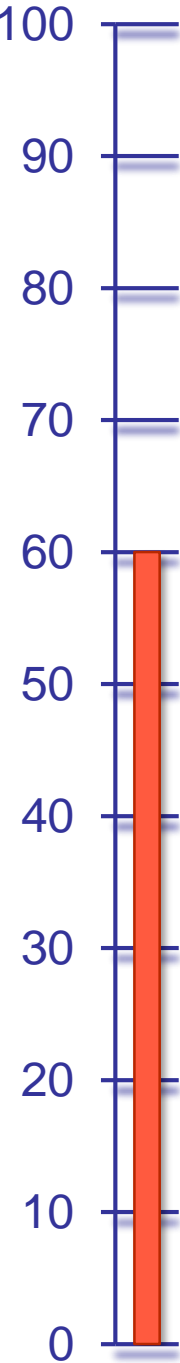


Treated with Exp1+Exp2+D+MoAb
for 6 months + Auto

Maintenance oral IMiD or PI

Relapse & Refractory

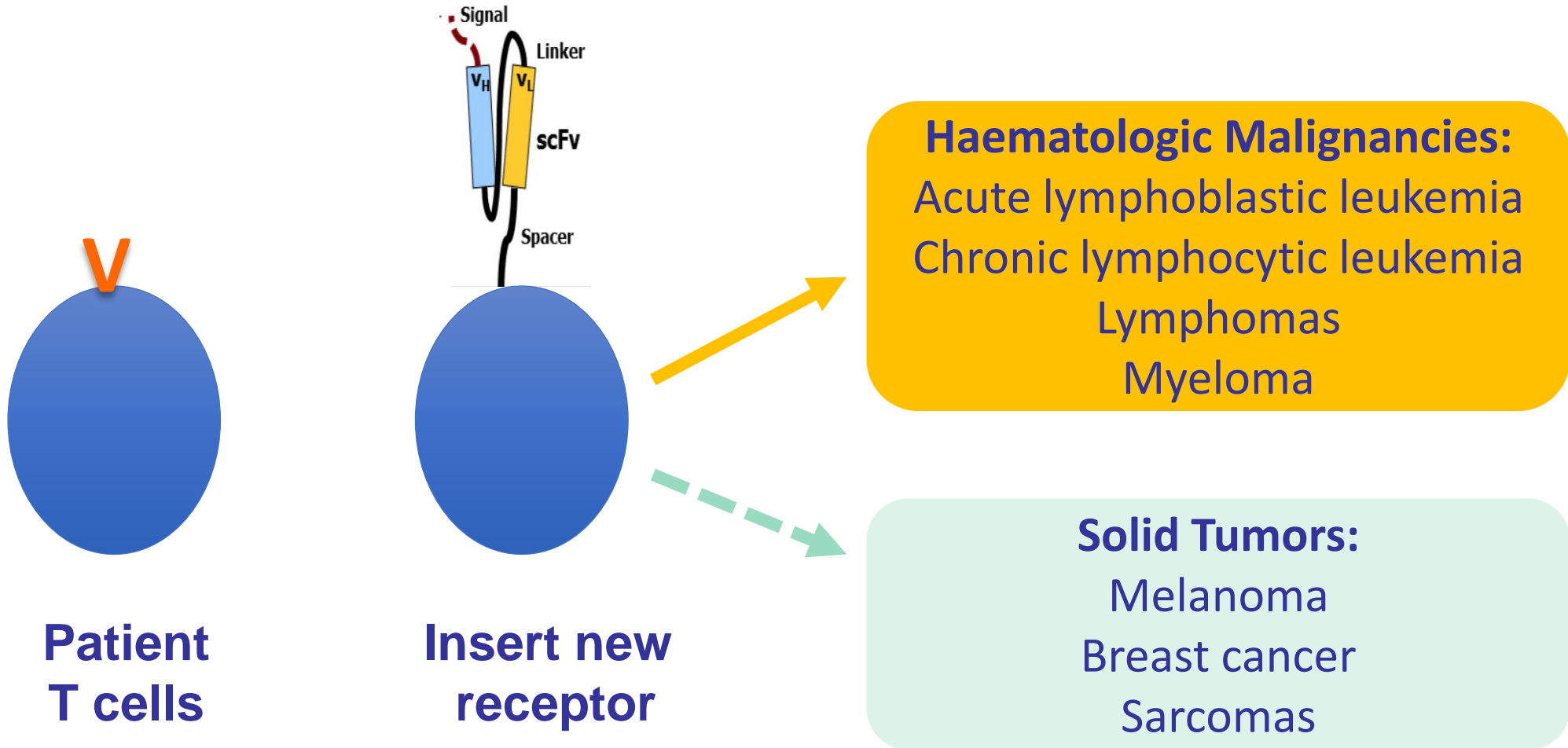
CAR T cells



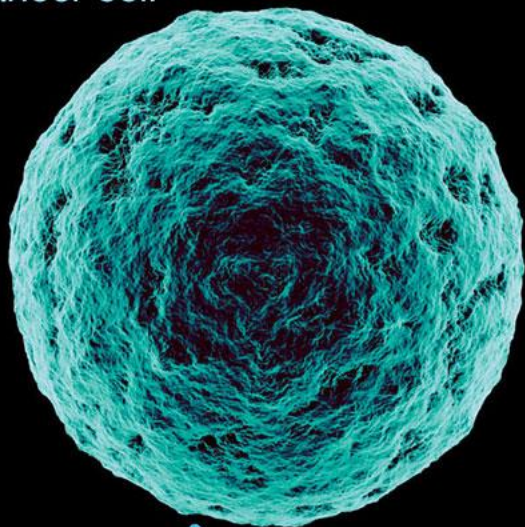
Exp = Expensive drug

D, dexamethasone; MoAb, monoclonal antibody; IMiD, immunomodulatory agent; PI, proteasome inhibitor; CAR T cells, chimeric receptor T cells.

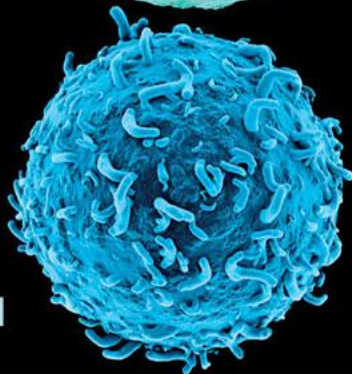
CAR T cells (Chimeric Receptor T cells)



Cancer cell



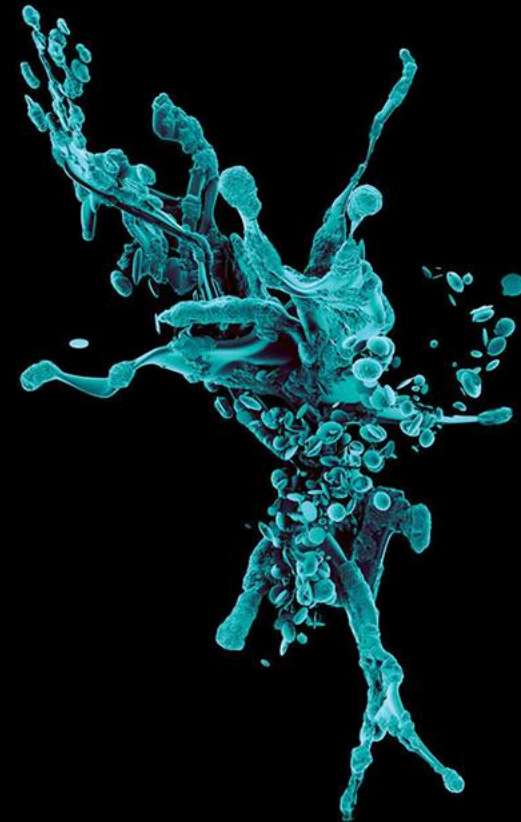
T cell



T cell approaches cancer cell.



T cell attacks cancer cell.



Cancer cell destroyed.

Phase I, Open-label Trial Of Anti-BCMA Chimeric Antigen Receptor T Cells in Patients With Relapsed/ Refractory Multiple Myeloma

Wanggang Zhang et al.

Haematologica 2017; 102(s2): 2 [EHA 2017 22nd Congress, #S103]

Case #6

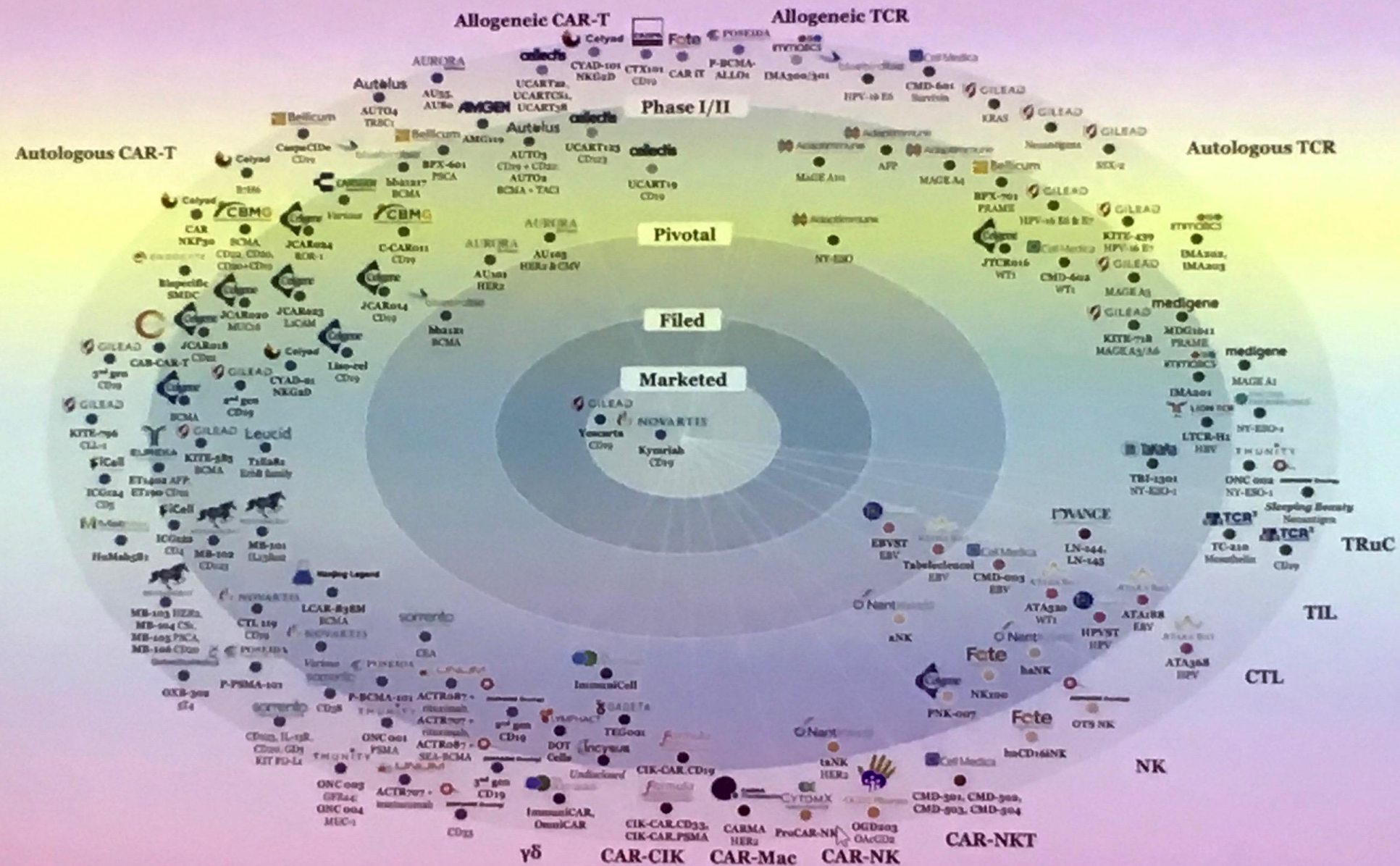


d0

d12

d83

CAR T Success Leads to Massive Investment in Cell Therapy



Source: Aditi Krishnamurthy, Michelle Teicher, Benjamin Leibowitz, Jim Tornatore, Filippo Petti & John Bishai (Wells Fargo)

Case 1

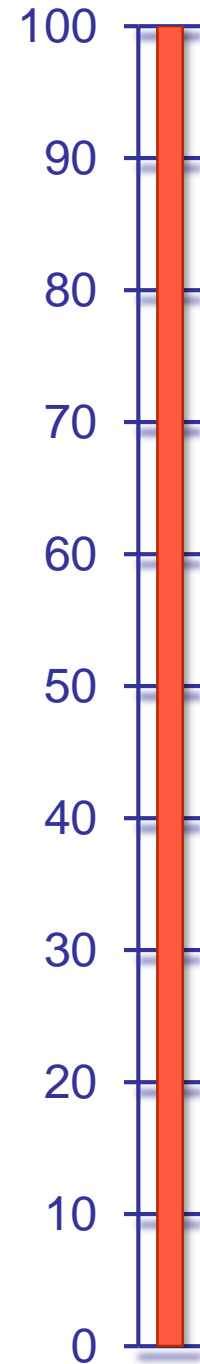


Treated with Exp1+Exp2+D+MoAb
for 6 months + Auto

Maintenance oral IMiD or PI

First relapse

CAR T cells



Exp = Expensive drug

D, dexamethasone; MoAb, monoclonal antibody; IMiD, immunomodulatory agent; PI, proteasome inhibitor; CAR T cells, chimeric receptor T cells.

CONCLUSIONS

EFFICACY



COST



Sustainability??



CarT
Approvazione
regionale



- Ruolo delle regioni
- Coinvolgimento delle società scientifiche
- Scelta dei centri



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