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Should every transplant eligible NDMM patient receive a transplant?.
YES

Sergio Giralt, MD
Melvin Berlin Family Chair in Myeloma Research
Professor of Medicine Weill Cornell Medical College
Deputy Head Division of Hematologic Malignancies
Attending Physician, Adult BMT Service
Memorial Sloan Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College

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Disclosures

- Research Support
  - CELGENE, SANOFI, Johnson & Johnson, Actinuum, Millenium, AMGEN, TAKEDA
- Consulting
  - CELGENE, SANOFI, Johnson & Johnson, Actinuum, Millenium, AMGEN
  - Kite (Gilead), Novartis, BMS, Jazz, Pfizer,
- I am a transplanter

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What will it take to defend the YES position?

- Goal
  - Longest life with the best quality of life with the least burden of therapy
- To justify the YES position I must do one or all of the following
    - Demonstrable survival benefit of high dose melphalan consolidation.
    - Demonstrable progression free survival benefit of high dose melphalan.
    - Demonstrable cost-effective benefit of high dose melphalan consolidation.
    - Equivalent long term QOL.

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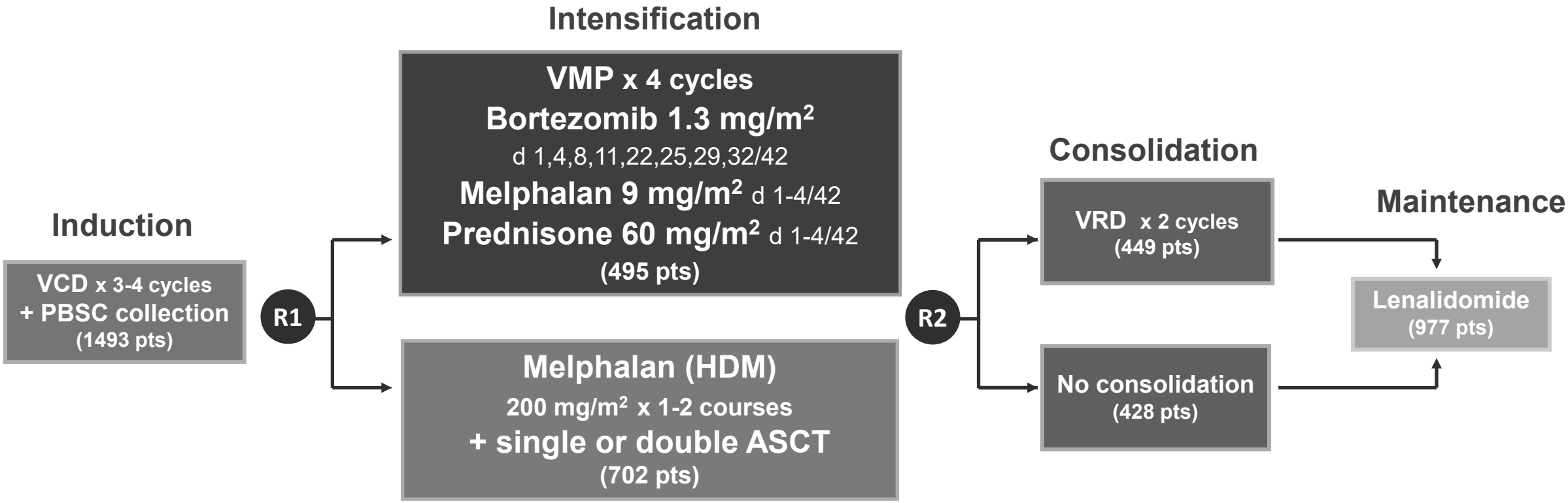
Is high dose melphalan consolidation associated with a survival benefit?

EMN02/HO95 MM study design



Primary endpoints:
- PFS from R1: ASCT *vs* VMP
- PFS from R2: VRD consolidation *vs* no consolidation

Secondary endpoints:
- PFS from R1: HDM-1 *vs* HDM-2
- Rates of response to ASCT or VMP
- OS from R1: ASCT *vs* VMP
- Toxicities with ASCT and VMP

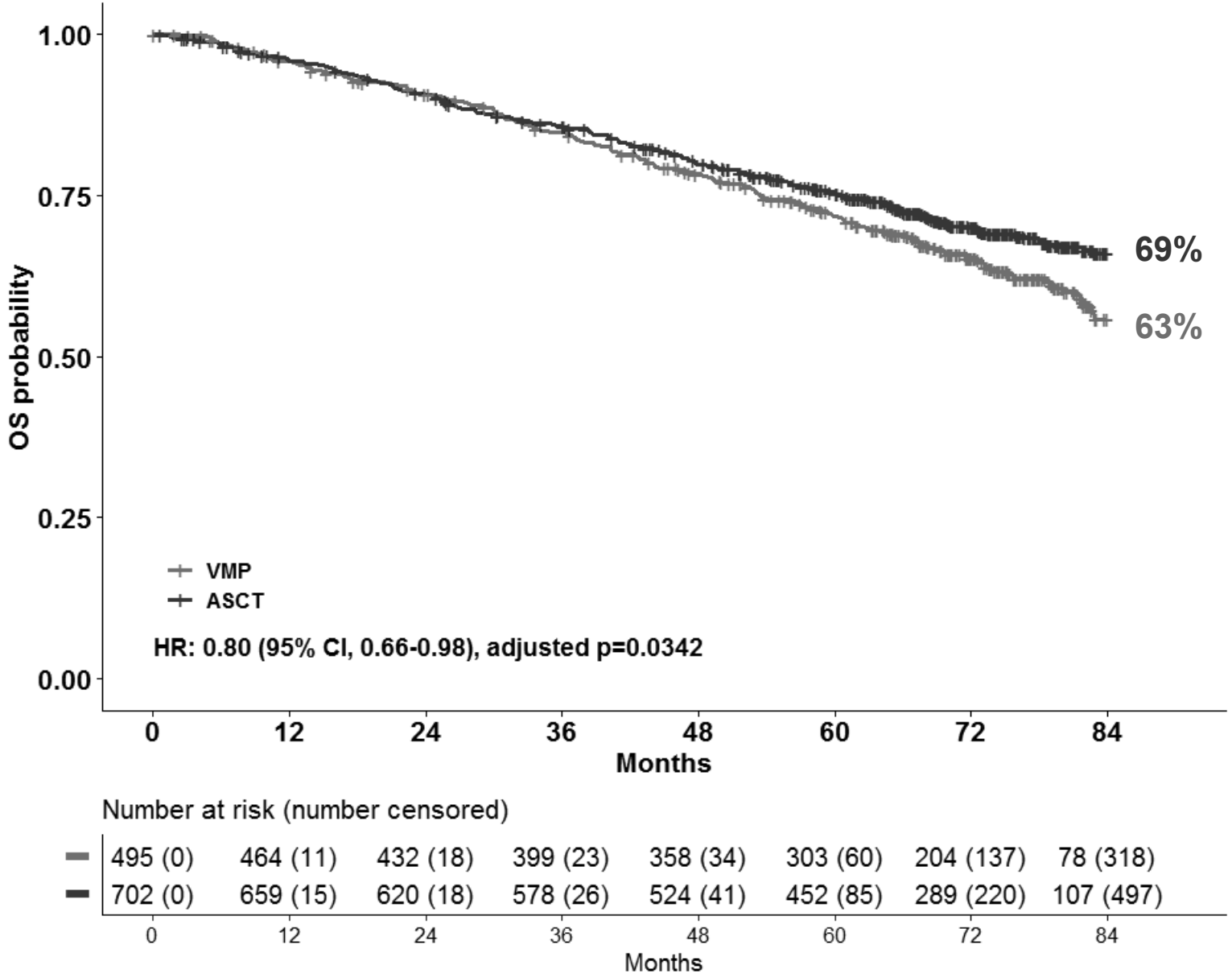
Overall survival (extended follow-up: 75 months)

What will Morie say?

Old data

Who uses VMP today?

6% difference and what access to new agents did they have



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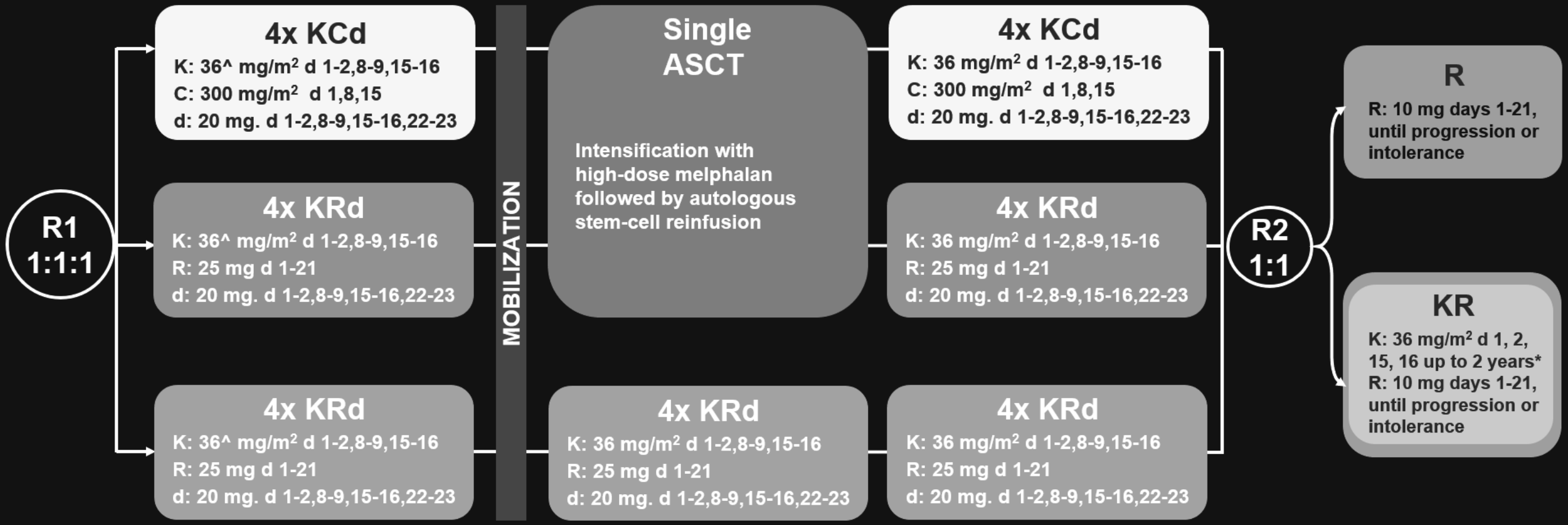
Is there a PFS benefit for high dose melphalan consolidation in the era of modern MM induction?

Trial design

474 NDMM patients, transplant-eligible and younger than 65 years

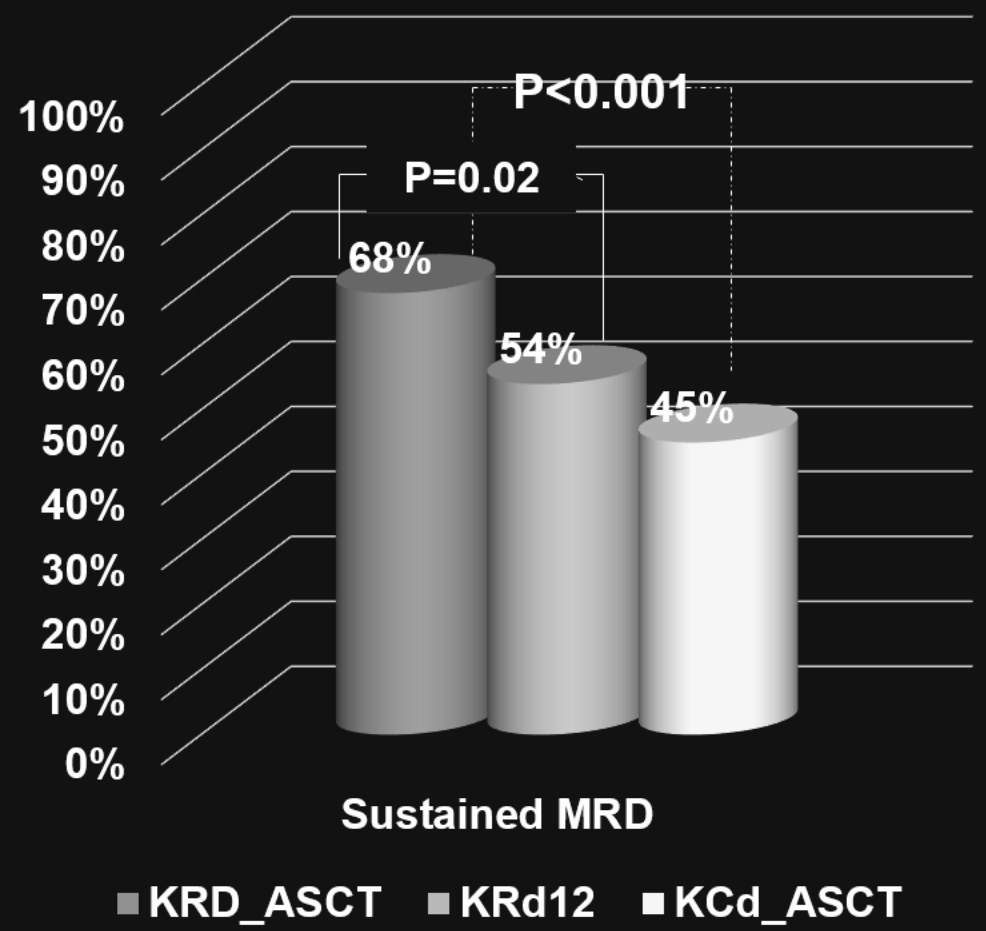


^20 mg/m^2 on days 1-2, cycle 1 only. *Carfilzomib 70 mg/m^2 days 1, 15 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards. NDMM, newly diagnosed multiple myeloma, R1, first randomization (induction/consolidation treatment); R2, second randomization (maintenance treatment); IQR, interquartile range K, carfilzomib; C, cyclophosphamide; R, lenalidomide; d, dexamethasone; d, days; ASCT, autologous stem-cell transplantation.

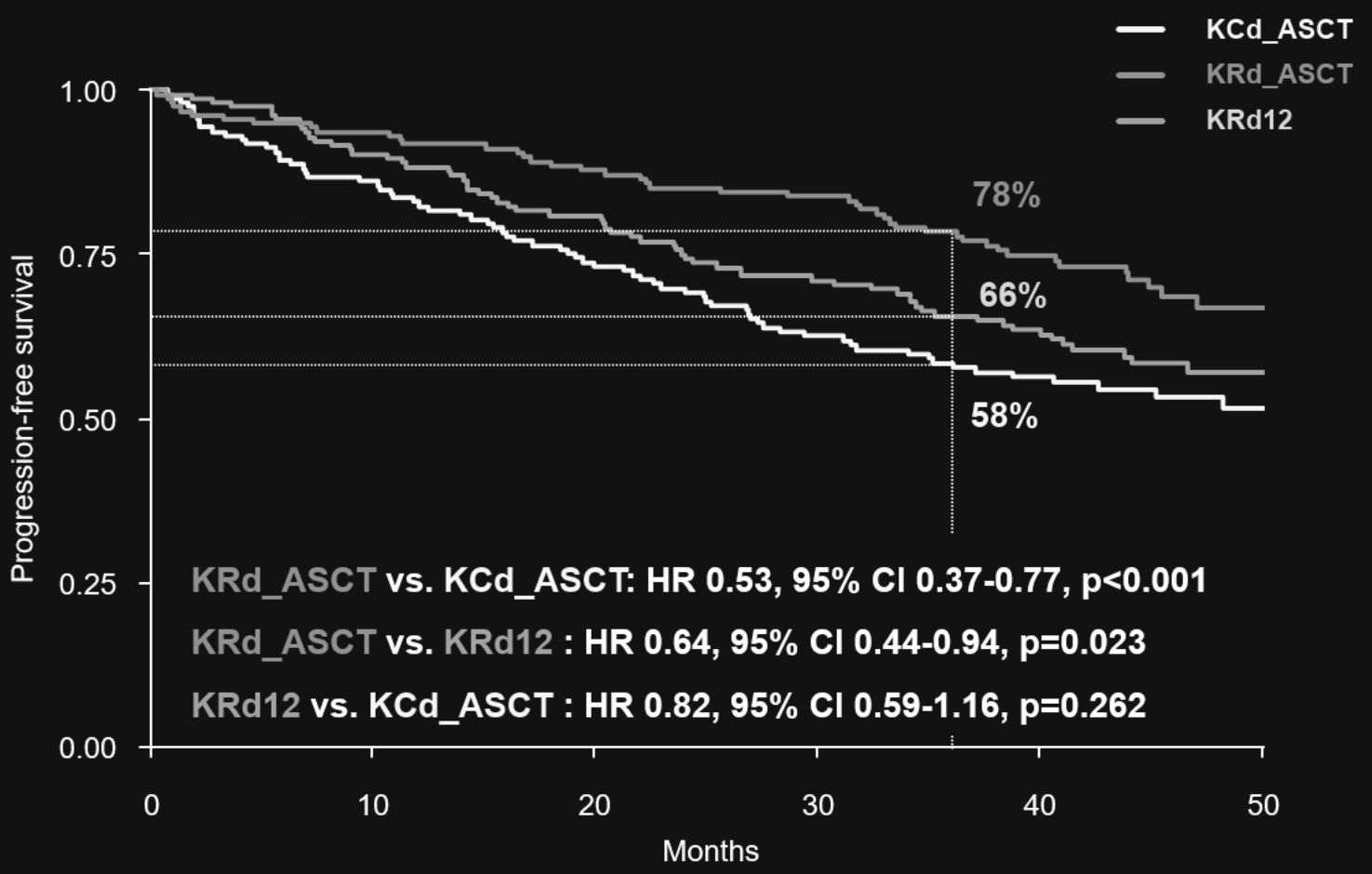
Progression-free survival: Random 1

Median follow-up from Random 1: 45 months (40-49 months)

Rate of sustained MRD MCF 10^{-5}

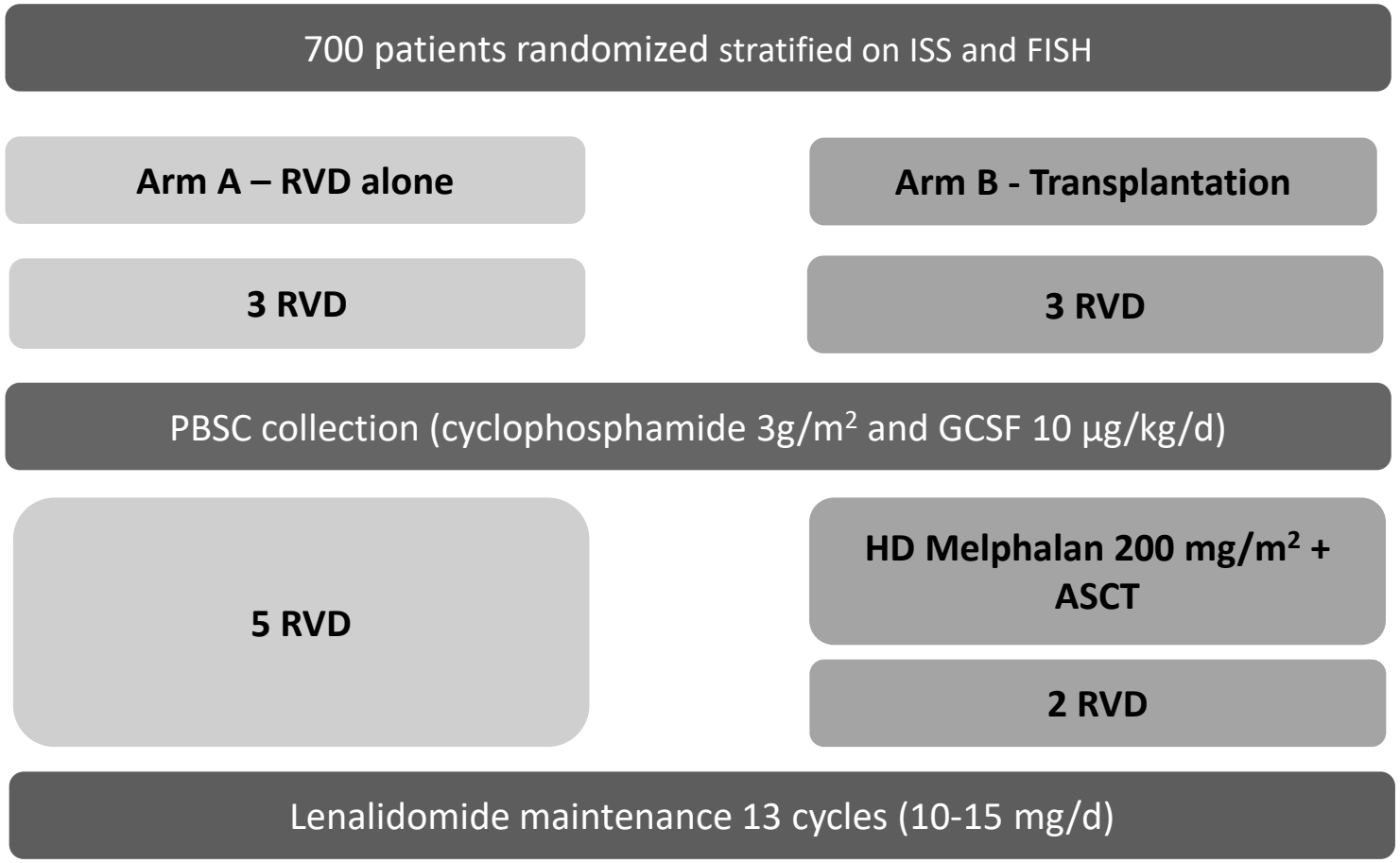


Progression-free survival



Random 1, first randomization (induction/consolidation treatment); ASCT, autologous stem-cell trasplantation; 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; p, p-value; HR, hazard ratio; CI, confidence interval; MRD, minimal residual disease; MFC, multiparameter flow cytometry; 3-year PFS reported in the figure.

IFM 2009 Study design



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RVd 21d cycles
. Lenalidomide 25 mg/d: D1-D14
. Bortezomib 1.3 mg/m^2 D1, D4, D8, D11
. Dexamethasone 20 mg/d: D1, D2, D4, D5, D8, D9, D11, D12

Primary endpoint = PFS

Secondary endpoints
. ORR, MRD
. TTP
. OS
. Toxicity

M Attal et al, N Engl J Med 2017

Updated PFS (primary endpoint)

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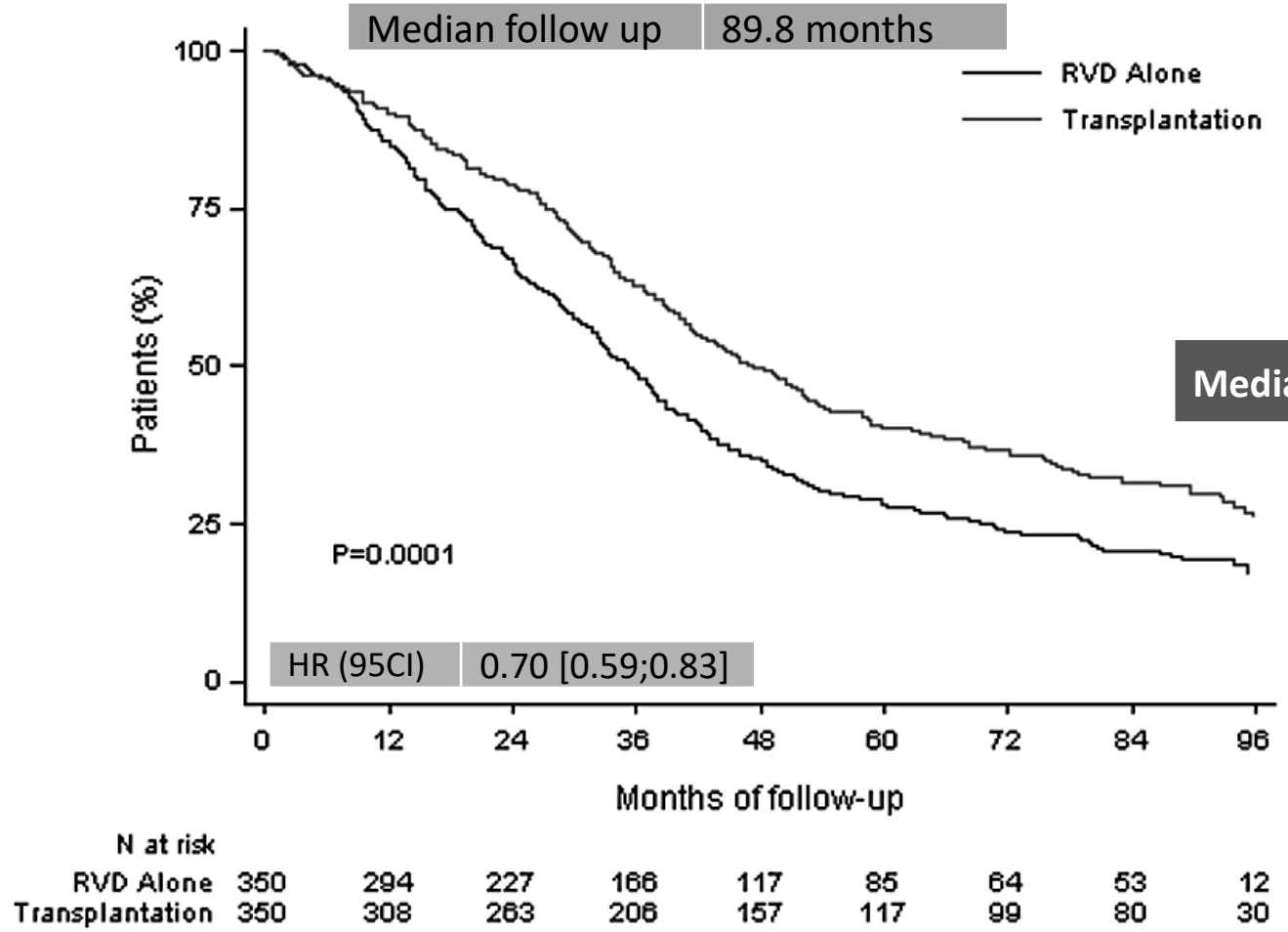


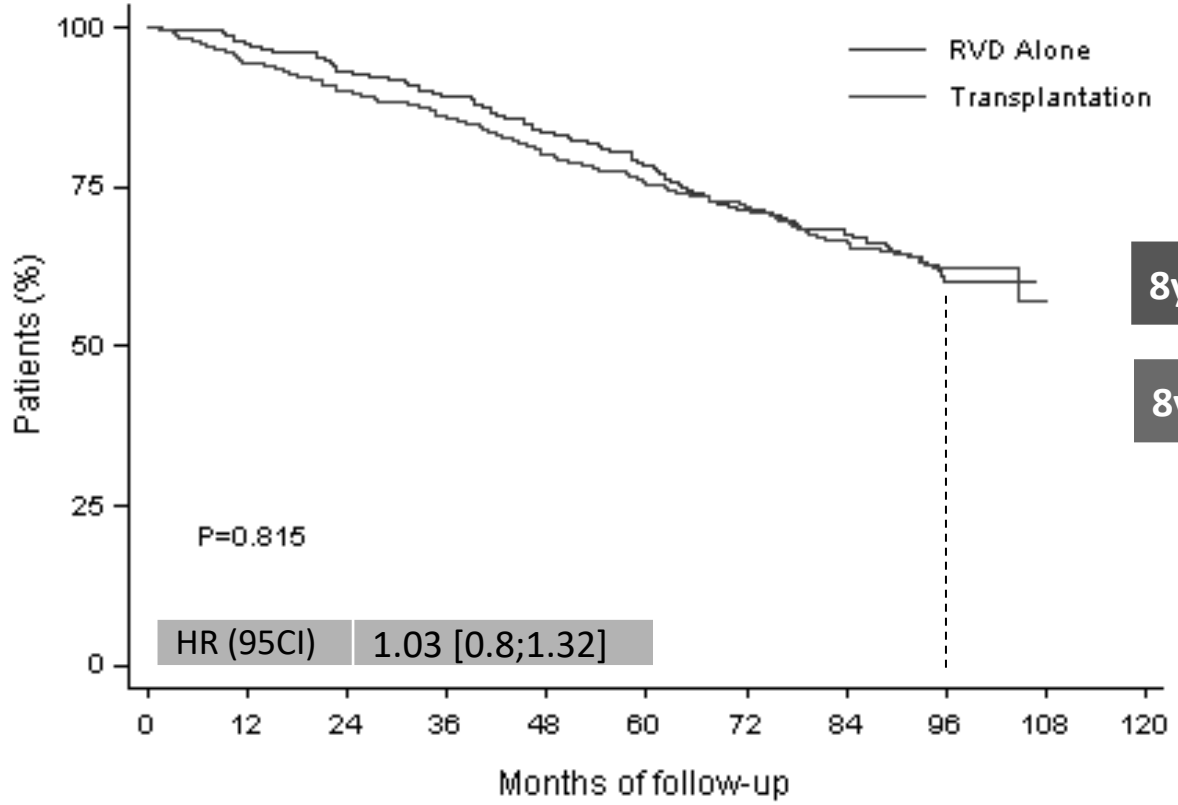
Median PFS 47.3 months (Transplantation, arm B)

Median PFS 35 months (RVD alone, arm A)

30% reduction in the risk of progression or death in patients receiving transplant

OS

Median follow up	89.8 months



N at risk											
RVD Alone	350	340	325	312	291	255	216	197	67	0	0
Transplantation	350	330	315	299	279	250	229	207	82	1	0

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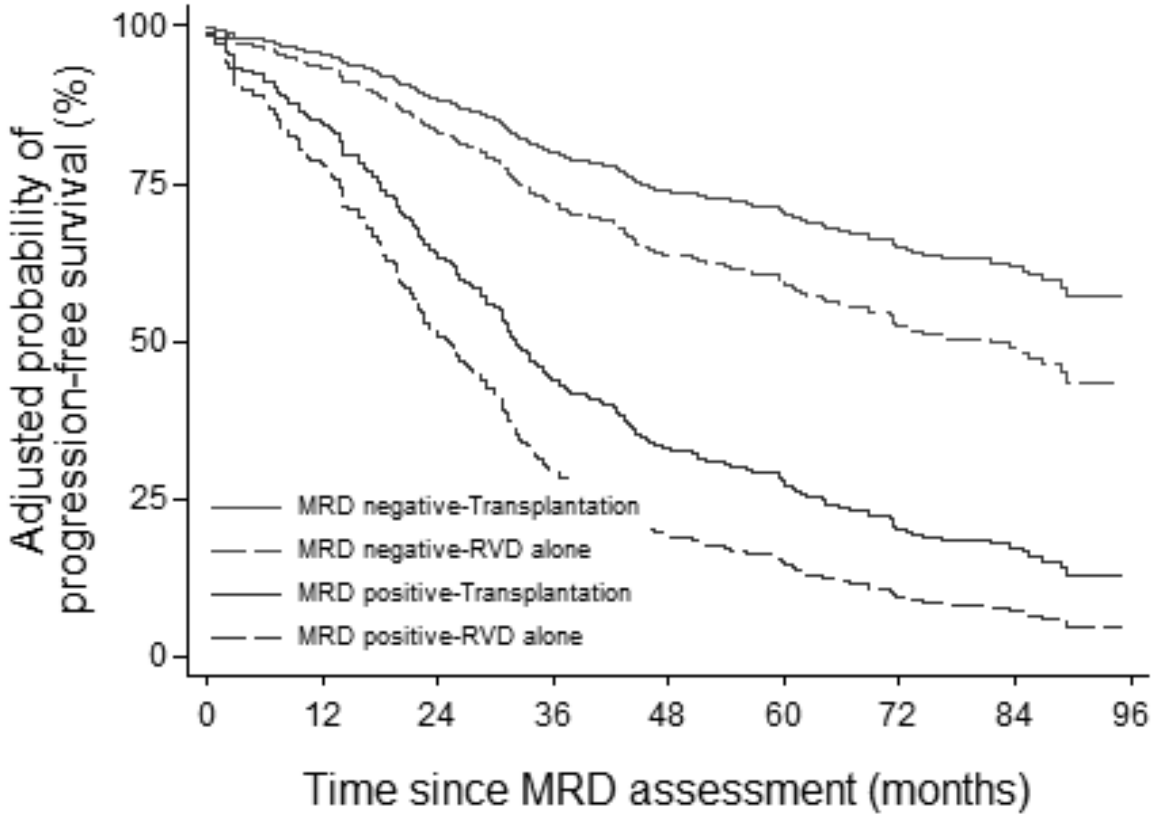
8y-OS 62.2% (Transplantation, arm B)

8y-OS 60.2% (RVD alone, arm A)

More than 60% of the patients in the two arms are alive after 8 years of follow-up

Subgroup analyses

Median follow up	89.8 months



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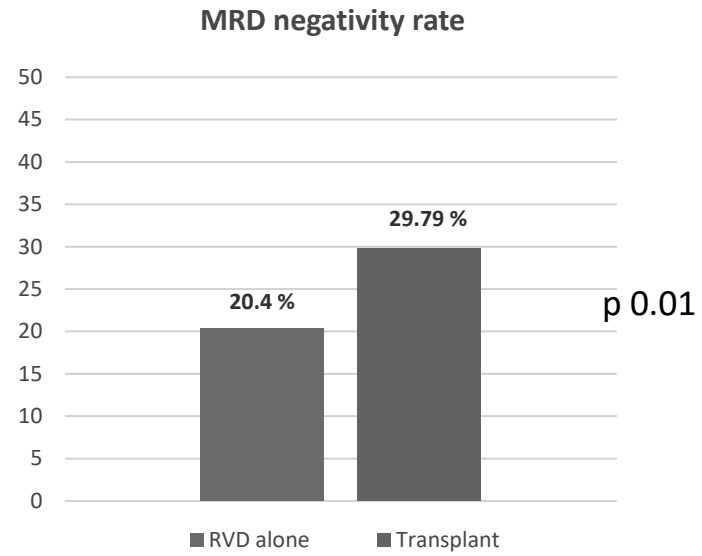

p 0.01

Transplant is superior to VRD alone, even in patients who achieved undetectable MRD at 10^{-6}

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Is there a cost-effective benefit of high dose melphalan consolidation?

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What would Morie say?

- Pandya C, Hashmi S, Khera N, Gertz MA, et al. Cost-effectiveness analysis of early vs. late autologous stem cell transplantation in multiple myeloma Clin Transplant 2014 Oct;28(10):1084-91. doi: 10.1111/ctr.12421. Epub 2014 Aug 18.
  - ***"The Consumer Price Index adjusted 2012 costs of eASCT and dASCT were $249 236 and $262 610, respectively. eASCT cohort had a benefit of 1.96 quality-adjusted life years (QALYs), 0.23 QALYs more than dASCT, implying that eASCT is preferred (dominant) over dASCT. "***
- Fu, S., Wu, CF., Wang, M. et al. Cost Effectiveness of Transplant, Conventional Chemotherapy, and Novel Agents in Multiple Myeloma: A Systematic Review. PharmacoEconomics 37, 1421–1449 (2019). https://doi.org/10.1007/s40273-019-00828
  - ***"Twenty-four publications were included in the systematic review and summarized according to treatment regimen and line. For first-line treatment, transplant was the most cost-effective option for transplant-eligible MM patients [the incremental cost-effectiveness ratio (ICER) was $4053-€45,460 per quality-adjusted life-year (QALY) gained, and $3848-$72,852 per life-year gained (LYG)…"***

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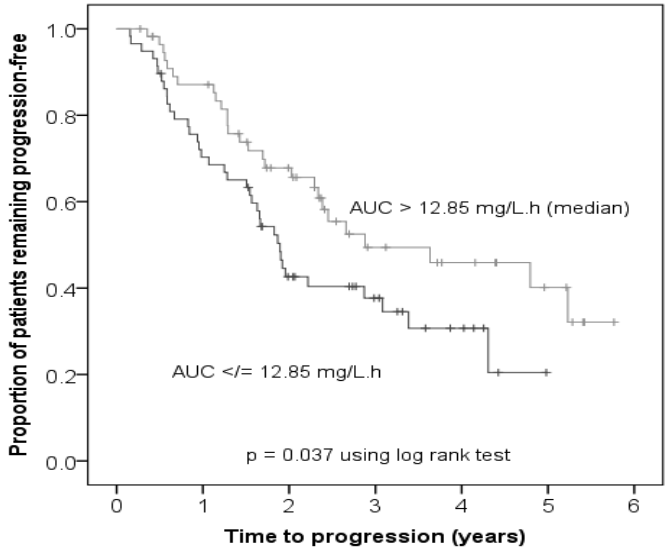
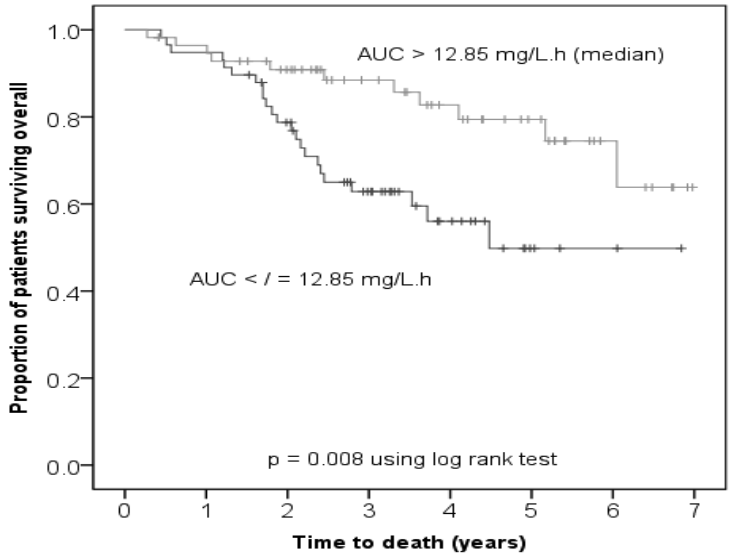
Can we make high dose melphalan better?

Higher Melphalan AUC Predicts Time to Progression, Overall Survival, and Toxicity





- Melphalan median AUC 12.85 mg/L.h
- Mucositis >= Grade 3
  - 12% clinical, 20% functional
  - Multivariate analysis Melphalan AUC (continuous), HR 1.2, p = 0.004

*Shaw BBMT 2012;18(2):S207

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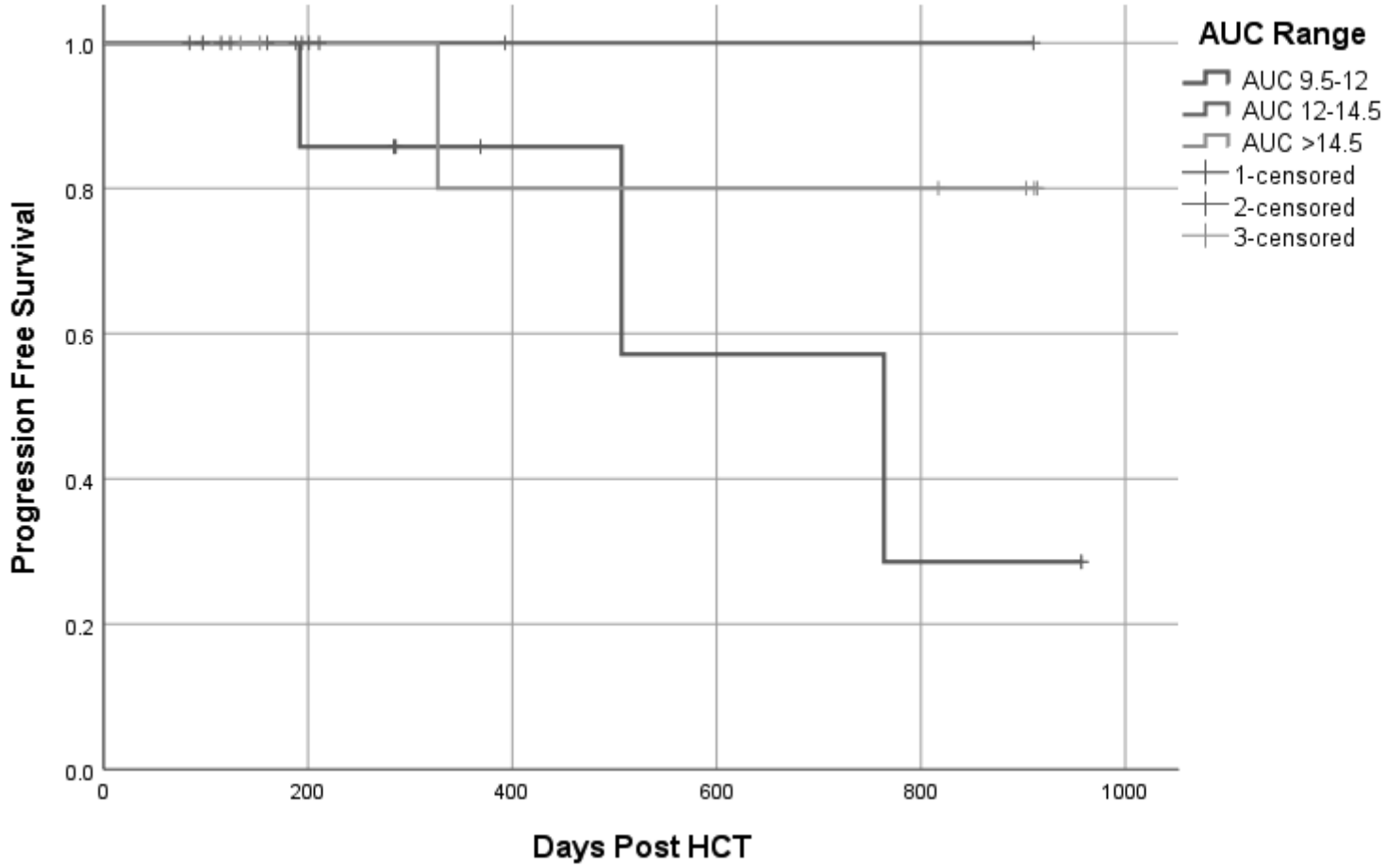
PFS by AUC (n=25)



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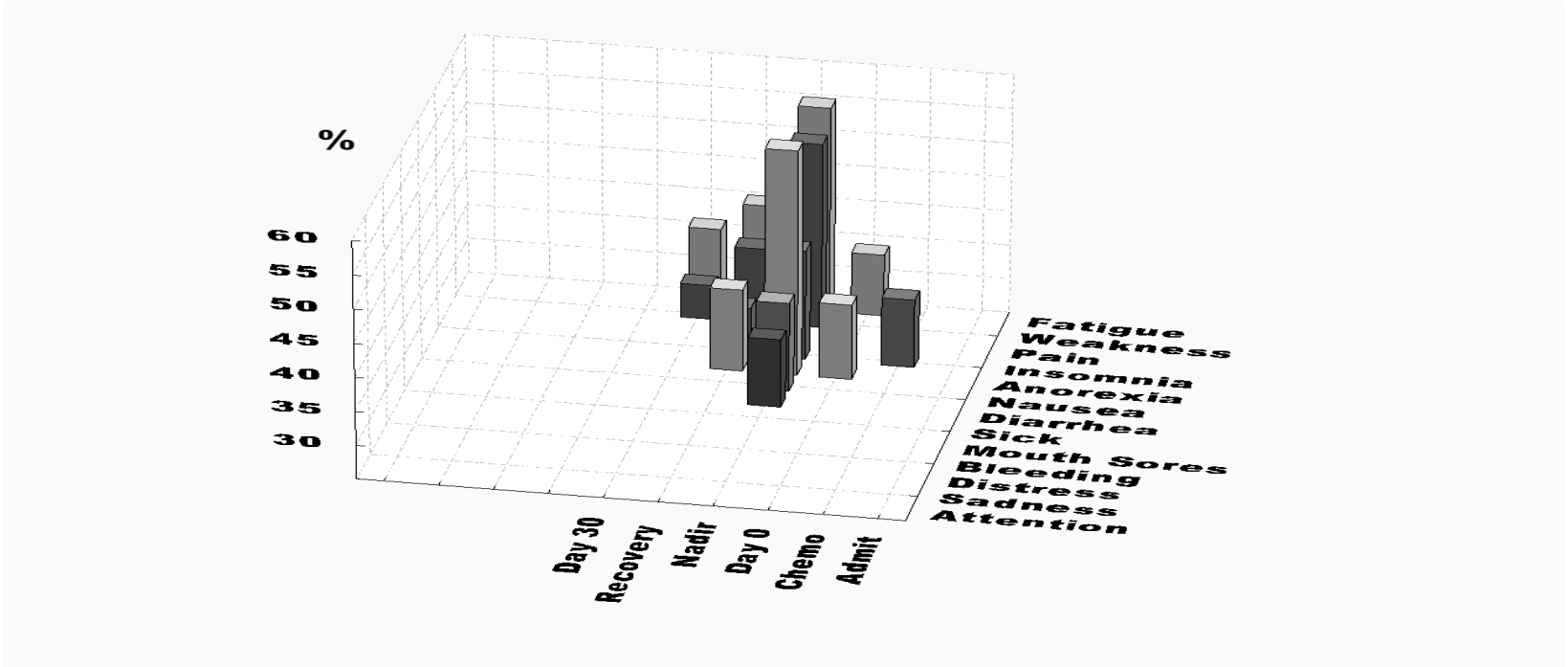
How about QOL?

Incidence of Moderate to Severe Symptoms Post Auto HCT for MM. Anderson et al. BMT



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Can we make high dose melphalan better tolerated?

Interventions

- Nausea/Vomiting
  - 5HT antagonists
- Pain
  - Opiates
- Cytopenias
  - Filgrastim
  - Erythropoietin
- Diarrhea
  - Octreotide
- Mucositis
  - Opiates
  - Palifermin
- Fatigue

Isolated treatment of symptoms

No understanding of the effects of control of one symptom over another

Efficacy of interventions generally measured only in one dimension

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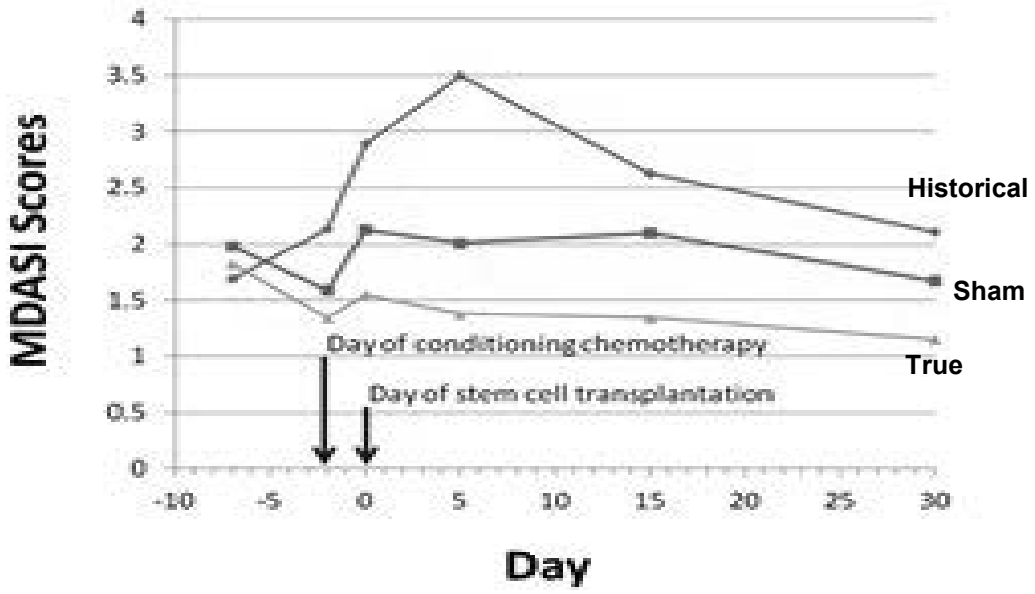
Support Care Cancer (2018) 26:657–665
DOI 10.1007/s00520-017-3881-7

ORIGINAL ARTICLE

Acupuncture for reduction of symptom burden in multiple myeloma patients undergoing autologous hematopoietic stem cell transplantation: a randomized sham-controlled trial

Gary Deng[1] · Sergio Giralt[2] · David J. Chung[2] · Heather Landau[2] · Jonathan Siman[1] · Benjamin Search[1] · Marci Coleton[1] · Emily Vertosick[3] · Nathan Shapiro[3] · Christine Chien[3] · Xin S. Wang[4] · Barrie Cassileth[1] · Jun J. Mao[1]



The Sham Acupuncture group had greater than five times odds of increasing pain medication use from baseline. Deng G et al. Pain Medicine 2020

IL6 is the main cytokine driver of symptoms after auto HCT

Wang et al, J Clin Oncol

Figure 1.

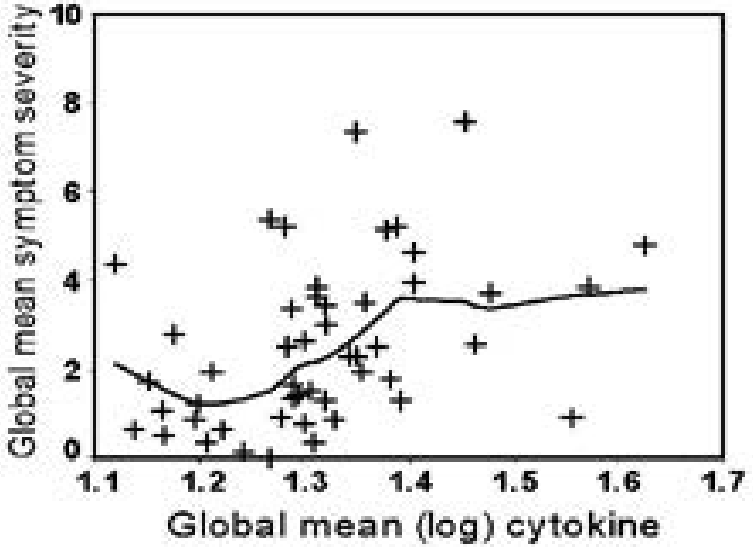
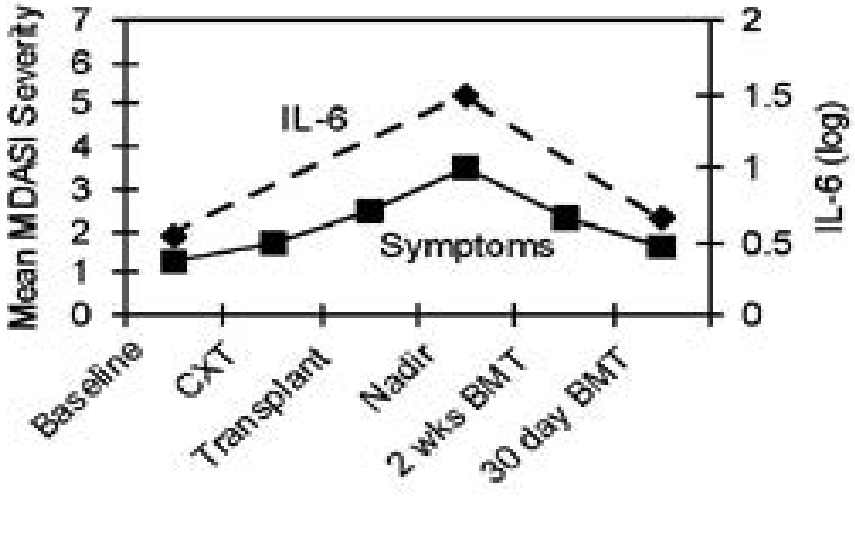
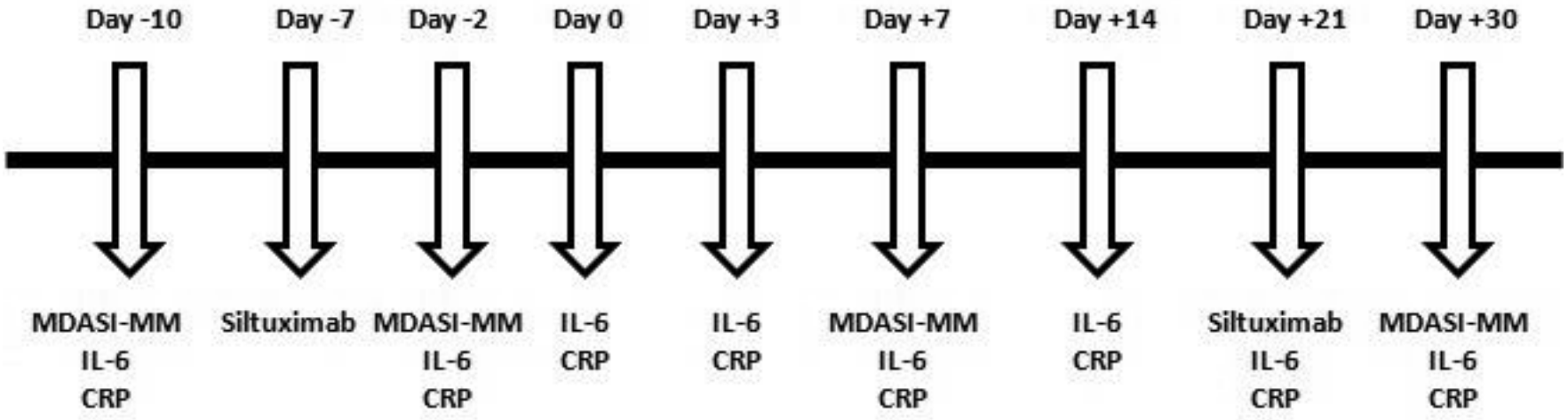


Figure 2.



Cytokine blockade as a potential strategy to reduce symptom burden

Phase II Trial of IL6 Blockade



Siltuximab Treated Patients (N=28)

Historical Control (N=10)

	Question Short	Day -10/Day -7	Day -2	Day +7	Day +30	0:Screen..	1:Day +1	6:Day +6	11:Day +11	30:Day +30
Symptom Severity Symptoms	bone aches	3.000	1.793	1.185	1.560	2.000	1.400	2.600	4.556	2.625
	constipation	1.920	1.357	0.333	0.520	3.600	4.600	3.500	5.889	6.000
	diarrhea (loose stools)	0.957	1.034	2.630	0.560	1.900	3.500	3.600	5.111	4.625
	disturbed sleep	2.593	2.286	2.111	1.769	3.700	5.700	5.500	6.222	6.625
	dry mouth	1.704	1.000	1.741	1.231	2.000	5.000	3.600	4.889	1.625
	fatigue/tiredness	2.889	2.357	3.000	3.038	3.300	3.444	3.667	5.667	4.333
	feeling drowsy (sleepy)	1.741	1.321	2.423	1.923	1.000	2.700	2.100	4.333	3.250
	feeling sad	2.556	1.483	1.815	0.923	5.000	4.556	3.300	3.667	3.625
	feelings of being distressed (upset)	2.370	2.000	1.519	0.923	3.900	2.900	3.100	4.000	4.000
	muscle weakness	1.458	0.862	1.259	2.120	2.200	2.700	3.200	6.667	4.875
	nausea	1.296	1.000	2.074	0.923	1.900	0.900	0.800	1.667	2.125
	numbness or tingling	2.556	1.793	0.852	1.231	2.900	4.100	4.200	6.375	6.125
	pain	2.889	2.310	1.481	1.692	1.800	2.600	1.600	1.889	2.250
	problem remembering things	2.296	1.517	1.333	0.962	1.900	5.200	3.700	5.556	2.500
	problem with lack of appetite	1.296	1.448	2.037	1.962	3.300	5.500	3.800	4.778	3.875
	problem with paying attention (concentrating)	1.280	0.793	1.222	0.280	2.600	5.600	5.100	8.111	5.625
	rash	0.240	0.069	0.074	0.160	3.100	2.600	3.200	4.000	3.375
	shortness of breath	0.741	1.034	0.778	1.231	0.100	2.200	1.500	0.778	0.125
	sore mouth or throat	0.760	0.034	0.370	0.160	2.600	2.778	0.800	2.778	3.000
	vomitting	0.630	0.517	0.615	0.038	2.800	4.700	2.200	1.000	0.750
Symptom Interference REM	enjoyment of life	2.440	2.138	2.407	1.920	2.800	3.100	3.400	4.667	5.750
	mood	2.750	1.690	1.815	1.400	1.700	2.100	2.333	7.556	2.250
	Relations with other people	1.120	0.897	1.000	1.000	1.000	0.000	2.778	2.556	0.375
Symptom Interference WAW	general activity	2.600	1.724	2.808	2.120	1.000	0.700	0.600	1.333	1.625
	Walking	2.800	1.690	2.556	1.960	1.500	1.600	2.800	1.556	2.000
	Work	2.520	1.931	2.308	2.200	2.700	2.500	1.000	3.333	3.000

Score

0.00 10.00

Avg. Score

0.000 8.111

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In Summary

- High dose melphalan with autologous stem cell support as consolidation of initial therapy has been shown in multiple randomized trial to be associated with a significant PFS benefit.
- With long term follow up that PFS benefit can translate into a OS benefit and definitely a reduction in the burden of therapy and the need for new treatments.
- A priori, we cant identify who could benefir from HDM and thus all transplant eligible patients should receive it.
- Even patients with MRD negativity benefit from HDM and thus depth of response to induction should NOT be considered a reason not to proceed.
- POSSIBLE EXCEPTIONS
  - Low risk Stage 1 disease in a older patient (75 or older) MRD negative to induction.
  - Patients beyond one year of induction

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Reminders

- Dose intense therapy was one of the first strategies developed to overcome drug resistance.
- Dose intense therapy can overcome multiple resistance pathways
- High dose melphalan is associated with less than 1% NRM
- 2nd primary malignancies an issue that we need to better understand and address
- Mechanisms of resistance to high dose therapy need to be investigated with the same enthusiasm that we investigate mechanisms of resistance to other immune therapies. Suboptimal dosing could be one of them and is likely the easiest to address
- Most of the newer therapies could enhance outcomes after high dose therapy and should be complementary and not mutually exclusive
- ***REMEMBER TO REGISTER TO THE 5th INTERNATIONAL WORKSHOP ON THE BIOLOGY, PREVENTION AND TREATMENT OF RELAPSE AFTER HEMATOPOIETIC CELL TRANSPLANTATION AND CELLULAR THERAPIES HSCT²***
- ***Join Online or Live in New York City for HSCT² October 8-9, 2021 Sheraton Times Square New York City,***
- ***Register now LINK https://www.relapse-after-hsct.com/***

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Questions?

giralts@mskcc.org

7135045082