Should All Patients Who Achieve Complete Response Receive a Transplant?

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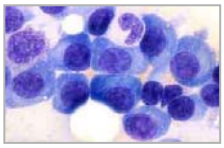


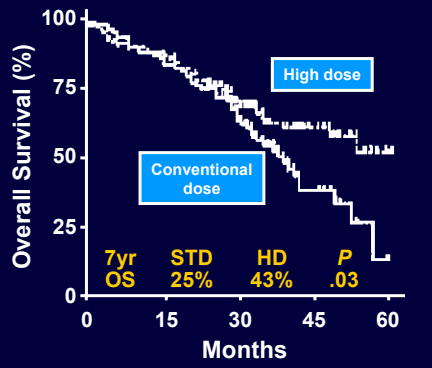
What We Know

- High-dose therapy + auto SCT (ASCT) increases complete response (CR) rates
- CR correlates with survival
- New drugs improve induction CRs → higher CR rates after ASCT
- Tandem ASCT seems to benefit a subgroup of patients
- Post-ASCT maintenance may improve responses, and increase EFS, OS
- Some new drugs can affect stem cell yields
- Reduced-intensity allografting may prolong EFS, OS after ASCT

What We Don't Know

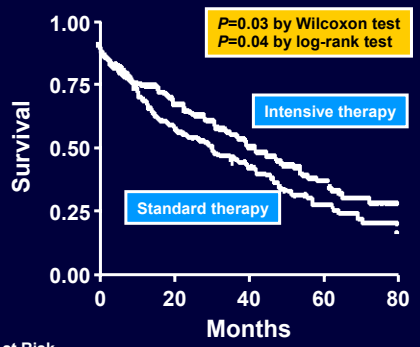
- Do the higher response rates observed after novel-drug combinations + ASCT improve survival?
- Which drug combinations are optimal for patients proceeding to transplant?
- Are tandem ASCTs beneficial after novel induction therapies?
- If your patient achieves a CR after novel induction therapies, is a transplant "optional"?
- Can allografting overcome any of the negative prognostic features?

Conventional Chemotherapy vs ASCT: Survival



Conventional dose	63 (53–73)	35 (22–50)	12 (1–40)
High dose	69 (58–78)	61 (50–71)	52 (36–67)

STD, standard dose; HD, high dose.



No. at Risk					
Intensive therapy	201	148	79	38	8
Standard therapy	200	129	70	30	8

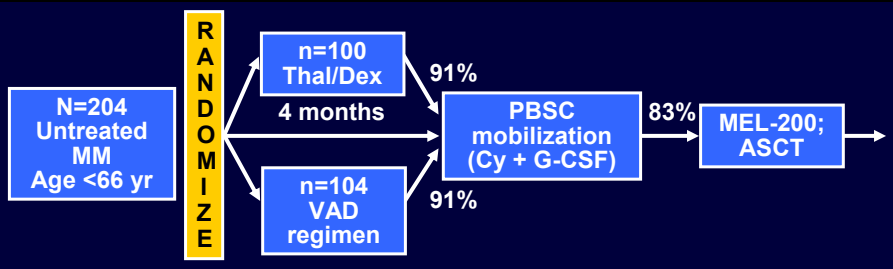
Single vs Double Autografts for MM

- Attainment of CR, near CR, VGPR is important for survival benefit
- Only 1 trial showed overall survival benefit for tandem tx vs single tx
- Patients in CR / near CR / VGPR after 1 autograft do not benefit from a second autograft
  - Confirmed in 2 trials
- Only patients with PR or stable disease (SD) appear to derive benefit from a second autograft

New Induction Therapies Prior to Autologous Transplant

- Thalidomide, dexamethasone
- Bortezomib, dexamethasone
- Bortezomib, thalidomide, dexamethasone
- Lenalidomide, dexamethasone
- Cyclophosphamide, bortezomib, dexamethasone
- Bortezomib, peg-doxorubicin, dexamethasone
- Bortezomib, lenalidomide, dexamethasone

Thal/Dex vs VAD as Induction Treatment in Newly Diagnosed MM Prior to SCT



Parameter	Thal/Dex (n=100)	VAD (n=104)	*P* Value
VGPR before PBSC collection (%)	25	7	.0027
VGPR before MEL-200 (%)	35	13	.002
VGPR 6 mo post-ASCT (%)	44	42	.87 (*NS*)
Mean duration of hospitalization before PBST (all causes)	8.3 days	20 days	.0001

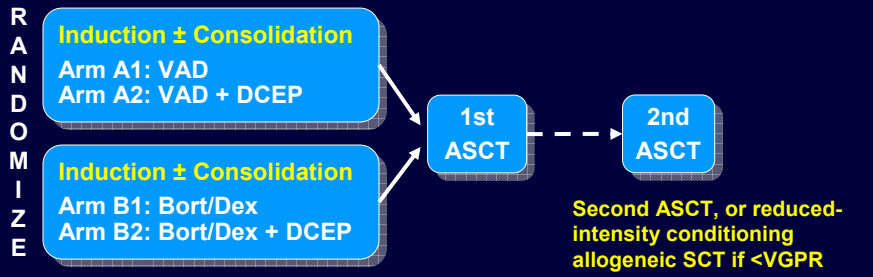
Macro M et al. *Blood*. 2006;108:22a. Abstract 57.

Bort/Dex vs VAD Induction Prior to ASCT
IFM 2005/01 Trial

Updated results: Randomized phase III IFM trial comparing Bort/Dex with VAD induction in MM up to age ≤65 yr

- **End points:** Primary include CRIF-+nCR postinduction; secondary include DCEP consolidation, post-SCT outcomes, overall response rate, safety
- **Patients:** 482 enrolled; previously untreated symptomatic MM with measurable paraprotein in serum/urine; age ≤65 yr

Stratification for β_2 microglobulin and Ch 13 abnormalities



Harousseau JL et al. *J Clin Oncol*. 2008;26: Abstract 8505.

Bort/Dex vs VAD

Response* to Induction

Intention-to-treat analysis	VAD (n=219)	Bort/Dex (n=223)	*P* Value
CR	3%	10%	0.004
CR + nCR	8%	19%	0.0004
≥VGPR	19%	47%	<0.0001
≥PR	66%	83%	<0.0001

Response* to Consolidation

Intention-to-treat analysis	No DCEP A1 + B1 (n=222)	DCEP A2 + B2 (n=220)	*P* Value
CR +nCR	16%	17%	0.73
VGPR	33%	36%	0.47

*Modified EBMT criteria

Harousseau JL et al. *J Clin Oncol.* 2008;26: Abstract 8505.

Bort/Dex vs VAD

Post–First ASCT Response

Intention-to-treat analysis	VAD A1 + A2 (n=219)	Bort/Dex B1 + B2 (n=223)	*P* Value
CR + nCR	23%	35%	0.0063
≥VGPR	44%	63%	<0.0001
≥PR	79%	84.3%	NS

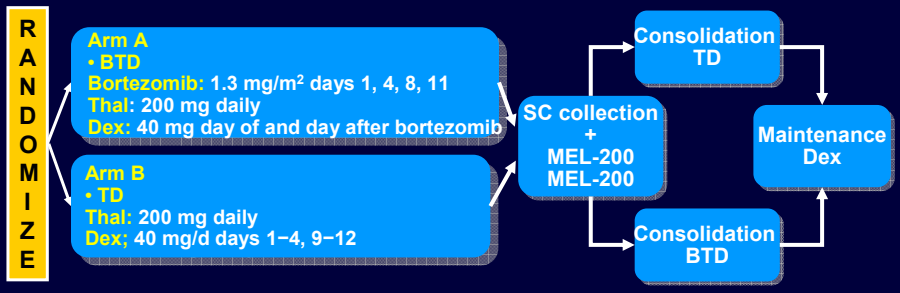
Actual SCT performed	VAD A1 + A1 (n=185)	Bort/Dex B2 + B2 (n=197)	*P* Value
CR + nCR	28%	40%	0.01
≥VGPR	52%	72%	<0.0001
≥PR	94%	95%	NS

Harousseau JL et al. *J Clin Oncol.* 2008;26: Abstract 8505.

Bort/Thal/Dex vs Thal/Dex for SCT Induction

Phase III study: Planned interim analysis

- **End points:** Primary include CR+nCR postinduction; secondary include CR+nCR postconsolidation, time to progression, EFS, OS, stem cell yield, safety
- **Patients:** 450 planned patients: 256 enrolled (Arm A, n=129; Arm B, n=127)
- **Dose:** Three 21-day cycles



- **DVT prophylaxis:** Pts randomized to LMWH (enoxaparin 40 mg/d), aspirin (100 mg/d), or warfarin 1.25 mg/d

Cavo M et al. *Blood.* 2007;110:30a. Abstract 73.

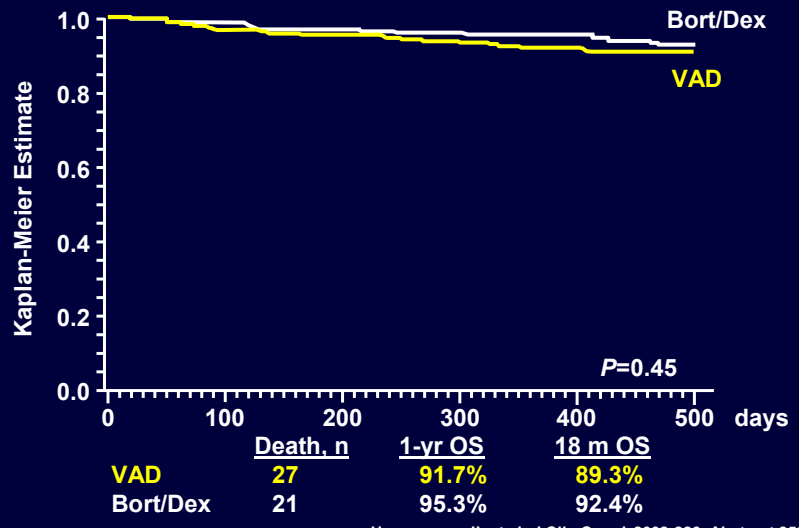
Bort/Thal/Dex vs Thal/Dex for SCT Induction

Response	Induction			Post-SCT #1	
	TD (n=127)	BTD (n=129)	*P* Value	TD (n=79)	BTD (n=74)
CR + nCR	9%	36%	<0.001	28%	57%
≥VGPR	27%	60%	<0.001	54%	77%
PR	53%	33%		—	—

Cavo M et al. *Blood.* 2007;110:30a. Abstract 73.

- Thus: ASCT can improve the response rates after induction with some suboptimal regimens (ie, VAD vs Thal/Dex)
- ASCT can further improve the response rates after induction with more optimal regimens (ie, Bort/Dex vs VAD; Bort/Thal/Dex vs VAD)
- Will this affect survival? (unknown)

Bort/Dex vs VAD Induction Prior to ASCT: IFM 2005/01 Trial *Overall Survival*



	Death, n	1-yr OS	18 m OS
VAD	27	91.7%	89.3%
Bort/Dex	21	95.3%	92.4%

Harousseau JL et al. *J Clin Oncol.* 2008;226. Abstract 8505.

E4A03: Lenalidomide + High-Dose Dexamethasone (RD) vs Lenalidomide + Low-Dose Dexamethasone (Rd) as Primary Induction Therapy for Newly Diagnosed MM

Results of Primary Therapy Beyond 4 Cycles With Rd (Landmark Analysis)

Factor/Result	Primary Rd (N=142)	All Rd Except SCT Group (N=181)	SCT Group (N=85)	ITT Rd Arm (N=222)
Median age, yr	66	64	59	65
>PR @ 4 cycles	86%	74%	70%	69%
1-yr survival	99%	96%	99%	96%
2-yr survival	93%	88%	93%	88%

Rajkumar SV et al. *J Clin Oncol.* 2008;26. Abstract 8504.

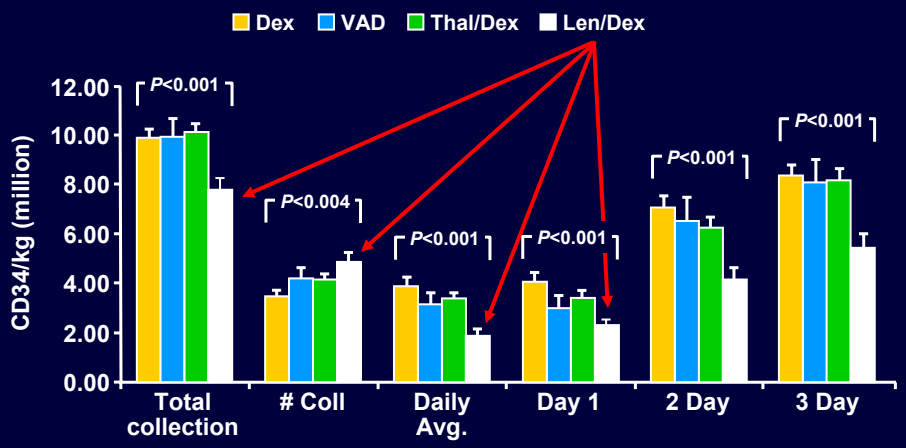
Post-ASCT Maintenance

	N	Thal Dose	CR Rate	PFS (yr)	OS (yr)
Barlogie * *NEJM* 2006	668	400	62% vs 43%	56% vs 44% (5)	ns
Attal *Blood* 2006	597	400	67% vs 55%	52% vs 36% (3)	87% vs 77% (4)
Abdelkefi † *Blood* 2008	195	100	68% vs 54%	85% vs 57% (3)	85% vs 65% (3)
Spencer ASH 2006	243	200 ‡	24% vs 15%	63% vs 36% (2)	90% vs 81% (2)

* Continuous thal.
† Compared with double transplant.
‡ Thal + prednisone vs prednisone.

Barlogie B et al. *N Engl J Med.* 2006;354:1021.
Attal M et al. *Blood.* 2006;108:3289.
Abdelkefi A et al. *Blood.* 2008;111:1805.
Spencer A et al. *Blood.* 2006;108:22a. Abstract 58.

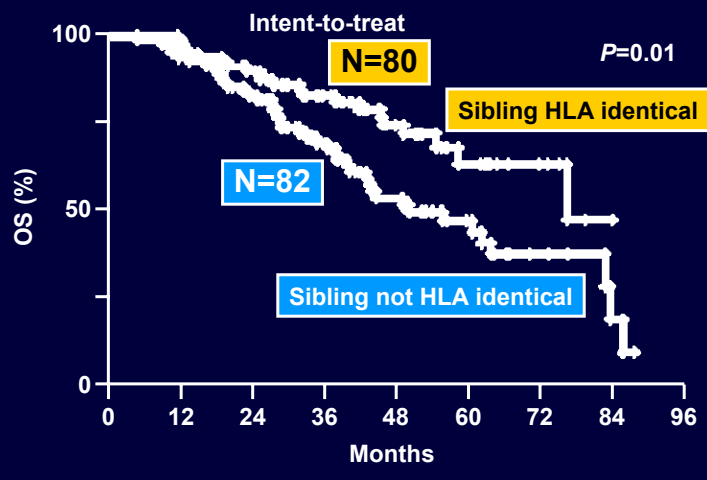
Impact of MM Induction Therapy on Stem Cell Yield: G-CSF Mobilization



CY + GCSF mobilization may overcome this

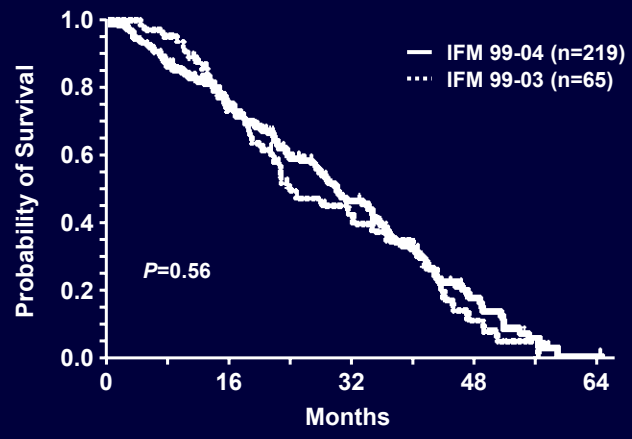
Kumar S et al. *Leukemia*. 2007;21:2035. Reprinted with permission from Macmillan Publishers Ltd: *Leukemia*, ©2007.

Tandem Autologous or Auto→Nonablative Allograft for MM



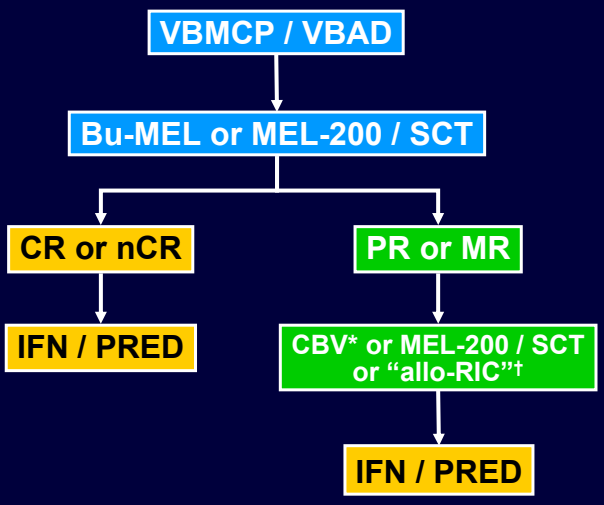
Bruno B et al. *N Engl J Med*. 2007;356:1110.

Tandem Auto vs Auto→Nonablative Allograft for High-Risk MM Patients



Garban F et al. *Blood*. 2006;107:3474.

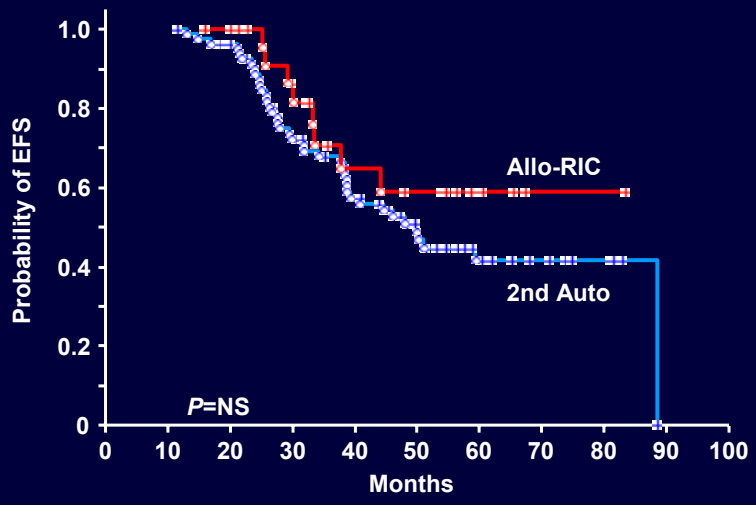
Spanish PETHEMA / GEM-2000 Trial



*Cyclophosphamide, etoposide, BCNU.
†Fludarabine / melphalan-140.

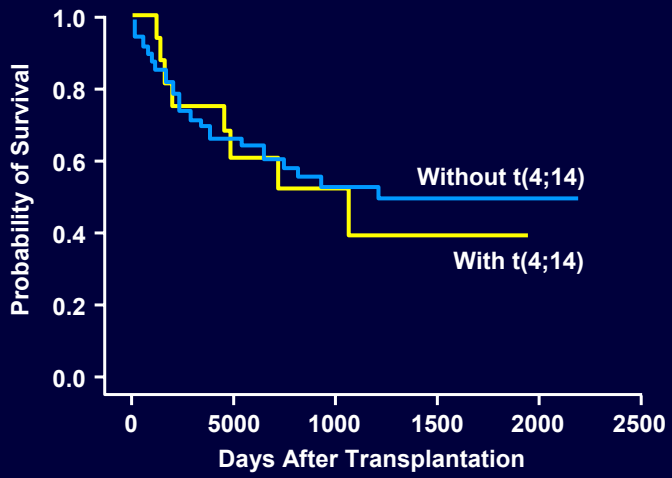
Mateos MV et al. *Blood*. 2007;110:284a. Abstract 937.

2nd Auto vs Allo-RIC: EFS



Mateos MV et al. *Blood*. 2007;110:284a. Abstract 937.

Impact of FISH 4;14 Translocation on Survival After RIC Allograft



Schilling G et al. *Leukemia*. 2008;22:1250. Reprinted with permission from Macmillan Publishers Ltd: *Leukemia*, ©2008.

Should All Patients Who Achieve a Complete Response to Induction Therapy Proceed to Autologous Transplant?

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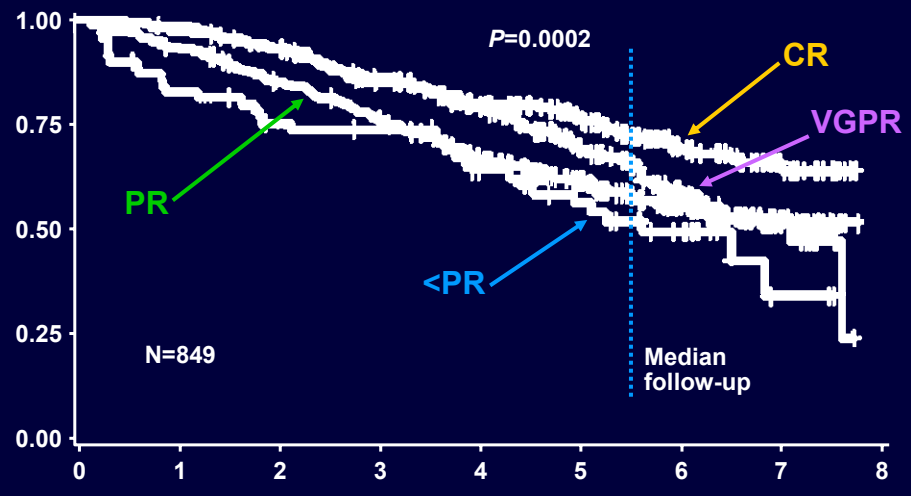
Pro-Transplant (ASCT)

- CR is a marker for survival
- Novel drugs alone may or may not produce a "depth of remission" as good as ASCT
- Novel drugs may eliminate "high-risk" cells that lead to relapse, BUT data are lacking at present that suggest novel drugs without transplant improve survival. THUS, ASCT may further improve remission durability
- Early trials of novel drugs prior to ASCT demonstrate added value of ASCT on response

Impact of Response on Outcome: OS After 1 or 2 Transplants



IFM 99 trials courtesy of JL Harousseau.
Harousseau JL et al. *Blood.* 2006;108:877a. Abstract 3077.

ASCT Improves Responses After Traditional or Novel Induction

	Macro ASH 2006		Harousseau ASCO 2008		Cavo ASH 2007	
	VAD	Thal/D	VAD	Bort/D	Thal/D	Bort/Thal/D
Induction ≥VGPR	7%	25%	19%	47%	27%	60%
Transplant ≥VGPR	42%	44%	44%	63%	54%	77%

Macro M et al. *Blood.* 2006;108:22a. Abstract 57.
Harousseau JL et al. *J Clin Oncol.* 2008;26: Abstract 8505.
Cavo M et al. *Blood.* 2007;110:30a. Abstract 73.

ASCT Improves Responses After Traditional or Novel Induction

	Harousseau ASCO 2008		Cavo ASH 2007	
	VAD	Bort/D	Thal/D	Bort/Thal/D
Induction ≥nCR	8%	19%	9%	36%
Transplant ≥nCR	23%	35%	28%	57%

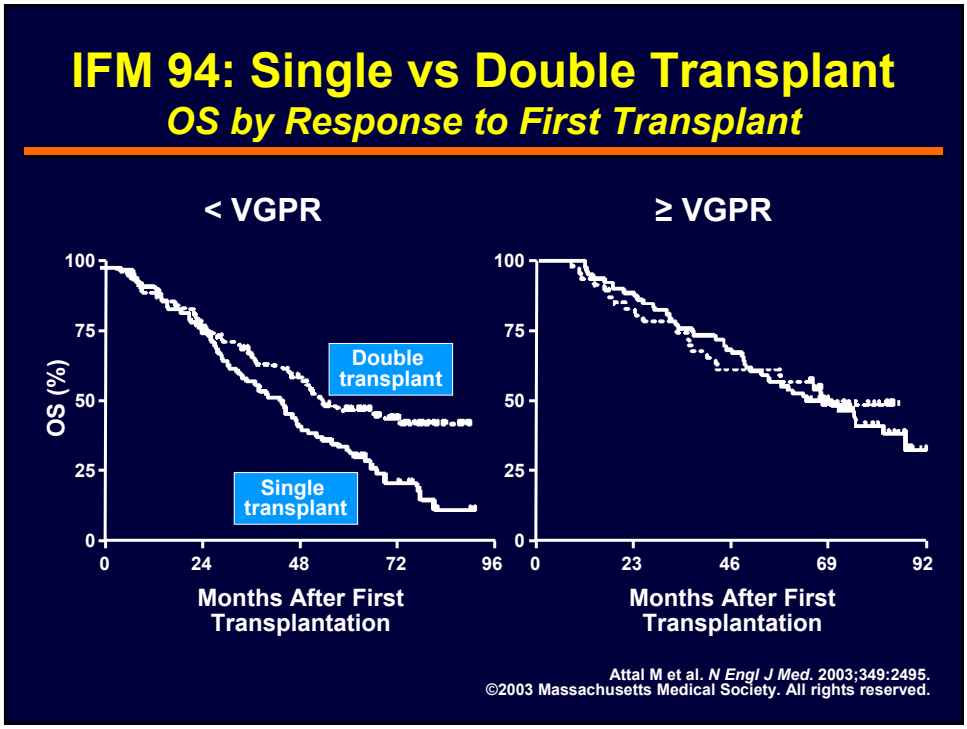
Harousseau JL et al. *J Clin Oncol.* 2008;26: Abstract 8505.
Cavo M et al. *Blood.* 2007;110:30a. Abstract 73.

Con-Transplant (ASCT)

- CR is a marker for survival

  BUT

  - Tandem ASCT does not benefit VGPR or better patients
  - Retrospective studies suggest patients in CR after induction DO NOT BENEFIT from ASCT
- Novel drugs may eliminate "high-risk" cells that lead to relapse, making ASCT superfluous
- "High risk" patients clearly have less benefit from ASCT


IFM 94: Single vs Double Transplant
OS by Response to First Transplant
< VGPR
≥ VGPR
OS (%)
100
75
50
25
0
Double transplant
Single transplant
0
24
48
72
96
23
46
69
92
Months After First Transplantation
Months After First Transplantation
Attal M et al. N Engl J Med. 2003;349:2495.
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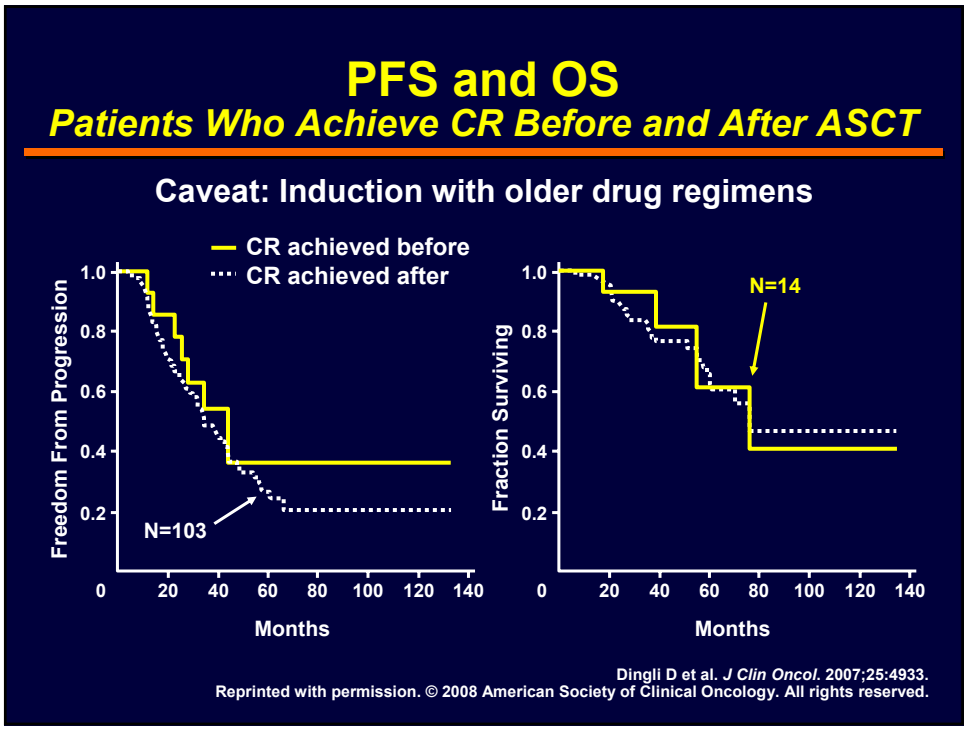
PFS and OS
Patients Who Achieve CR Before and After ASCT
Caveat: Induction with older drug regimens
CR achieved before
CR achieved after
Freedom From Progression
Fraction Surviving
1.0
0.8
0.6
0.4
0.2
0
N=103
N=14
20
40
60
80
100
120
140
Months
Months
Dingli D et al. J Clin Oncol. 2007;25:4933.
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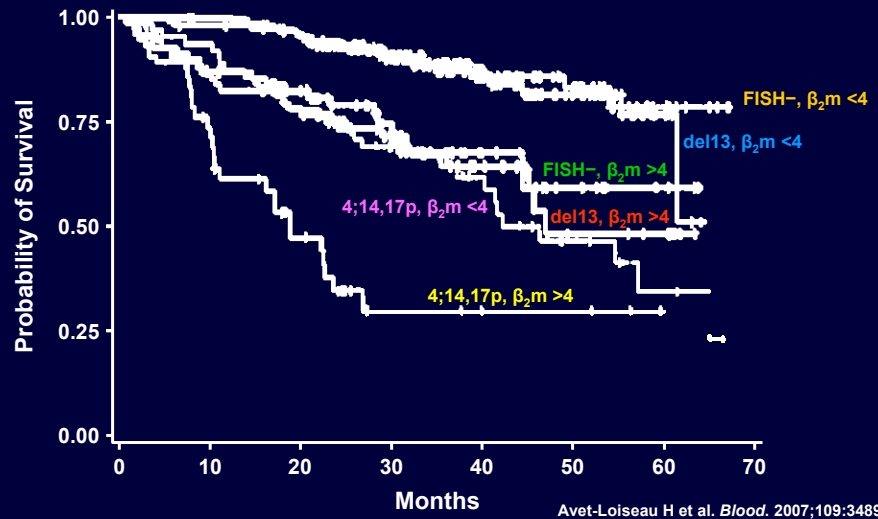
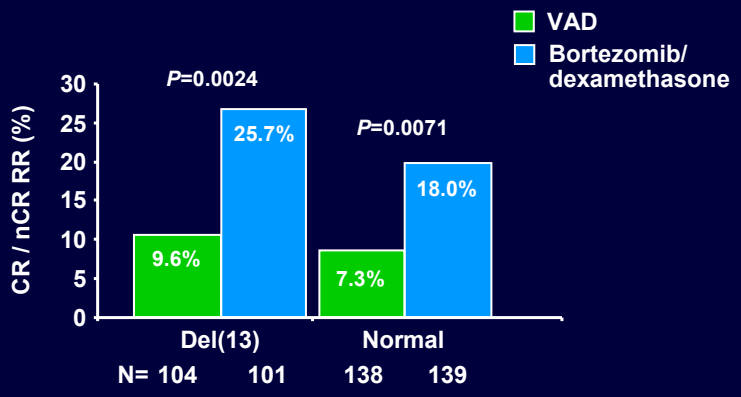
IFM Analysis of Cytogenetics/β_2m
Effect on Survival After Tandem ASCT



Avet-Loiseau H et al. *Blood.* 2007;109:3489.

IFM 2005-01 Trial
RR With Del(13)

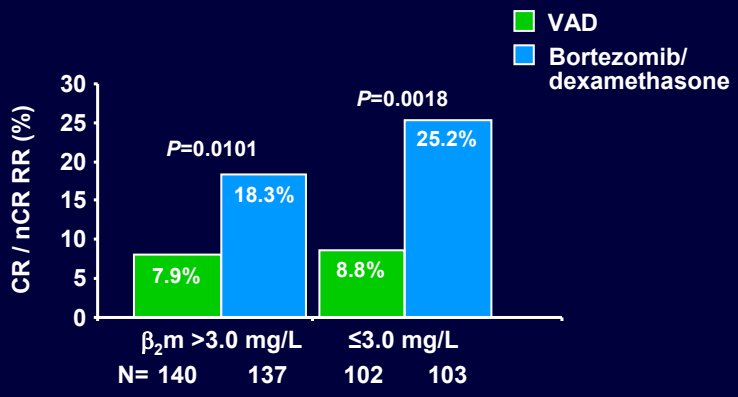
- **Updated analysis of postinduction CR/nCR in VAD vs bortezomib/dexamethasone in untreated MM**



Harousseau JL et al. *Blood.* 2007;110:139a. Abstract 450.

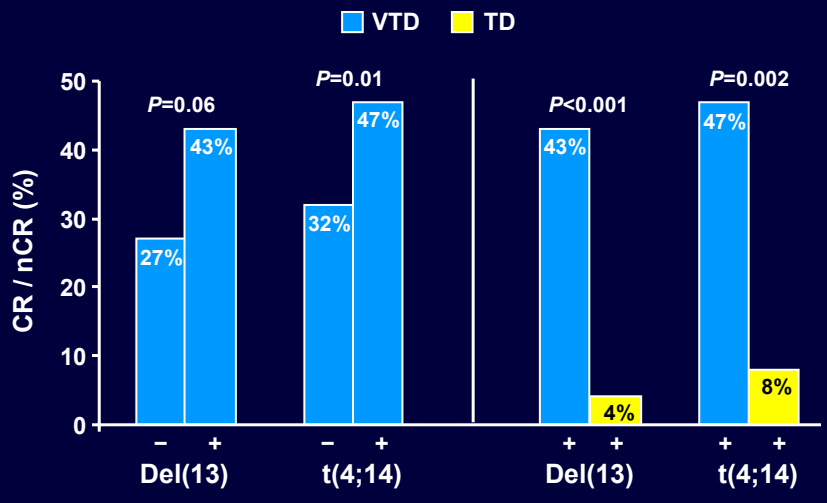
IFM 2005-01 Trial
RR With β_2m

- Updated analysis of postinduction CR/nCR in VAD vs bortezomib/dexamethasone in untreated MM



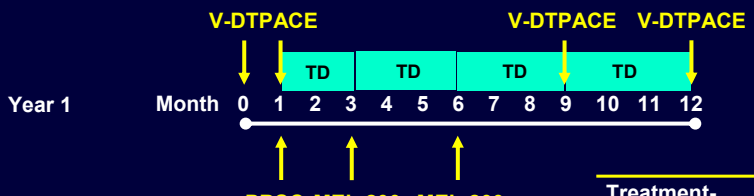
Harousseau JL et al. *Blood.* 2007;110:139a. Abstract 450.

Bort/Thal/Dex vs Thal/Dex as Induction Therapy in MM: Efficacy in High-Risk Groups



Cavo M et al. *Blood.* 2007;110:30a. Abstract 73.

Phase 2 Study: Total Therapy 3 With Bortezomib



Year 2 — Monthly VTD

Years 3−4 — TD

Newly diagnosed patients up to 75 yr, N=303

* Risk defined by gene expression profiling; overrides prognostic implications of t(4;14).

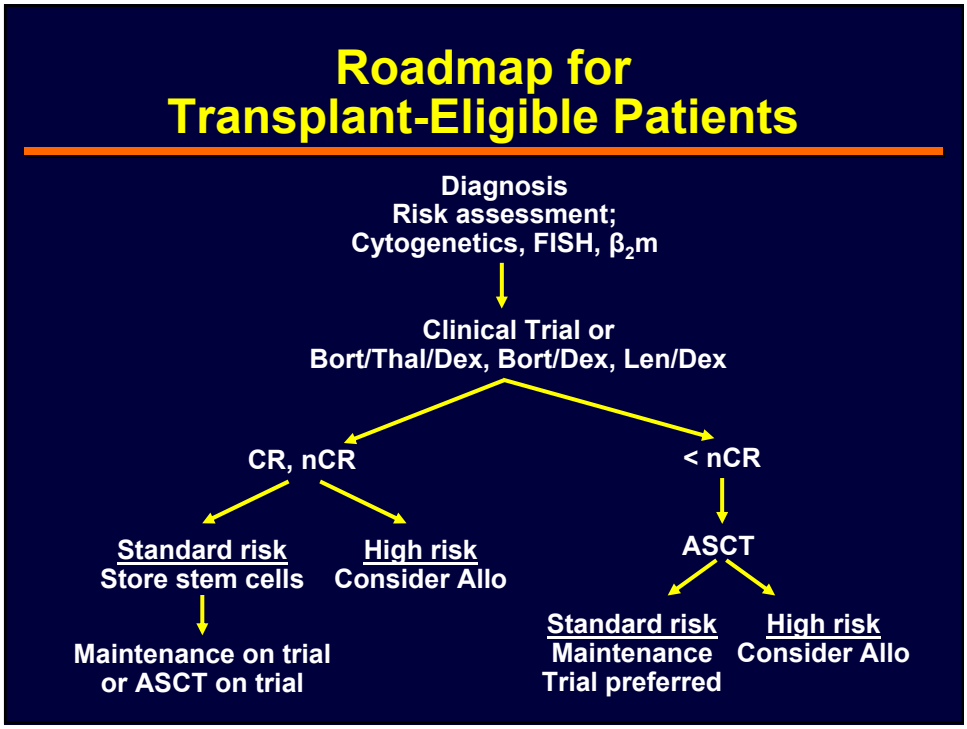
V-DTPACE = bortezomib / dexamethasone / thalidomide/ cisplatin / doxorubicin / cyclophosphamide / etoposide.

Treatment-related mortality	5%
nCR	80%
CR	60%
2-yr OS	87%
Low risk*	91%
High risk	70%
2-yr EFS	84%
Low risk	90%
High risk	58%

Barlogie B et al. *J Clin Oncol.* 2007;25:Abstract 8020.

Conclusions

- ASCT remains as a standard of care, but its relevance with novel drugs is less clear
- Novel-drug combinations for front-line therapy confirm higher rates of ≥VGPR after induction AND after ASCT, but their effect on OS with or without transplant is unknown
- Very few trials compare novel-drug regimens with each other
- Trials are needed to compare outcomes of novel induction regimens ± ASCT
- Maintenance or RIC allografts may improve results


Roadmap for Transplant-Eligible Patients
Diagnosis
Risk assessment;
Cytogenetics, FISH, β2m
Clinical Trial or
Bort/Thal/Dex, Bort/Dex, Len/Dex
CR, nCR
< nCR
Standard risk
Store stem cells
High risk
Consider Allo
ASCT
Maintenance on trial
or ASCT on trial
Standard risk
Maintenance
Trial preferred
High risk
Consider Allo