How I treat a patient eligible for high-dose therapy and autotransplantion?

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CRITERIA TO IDENTIFY A MYELOMA PATIENT WHO IS ELIGIBLE FOR AUTOTRANSPLANTATION

- **Patient's chronological age**
  - **Traditionally, although not appropriately, used**
  - **Variable age cut-off**
    - **In EU: up to 65 (70) years of age**
    - **In US: up to 75 years of age (and higher) in selected, medically-fit individuals**

Cavo M et al, Blood 2011 Mar 29 [Epub ahead of print]

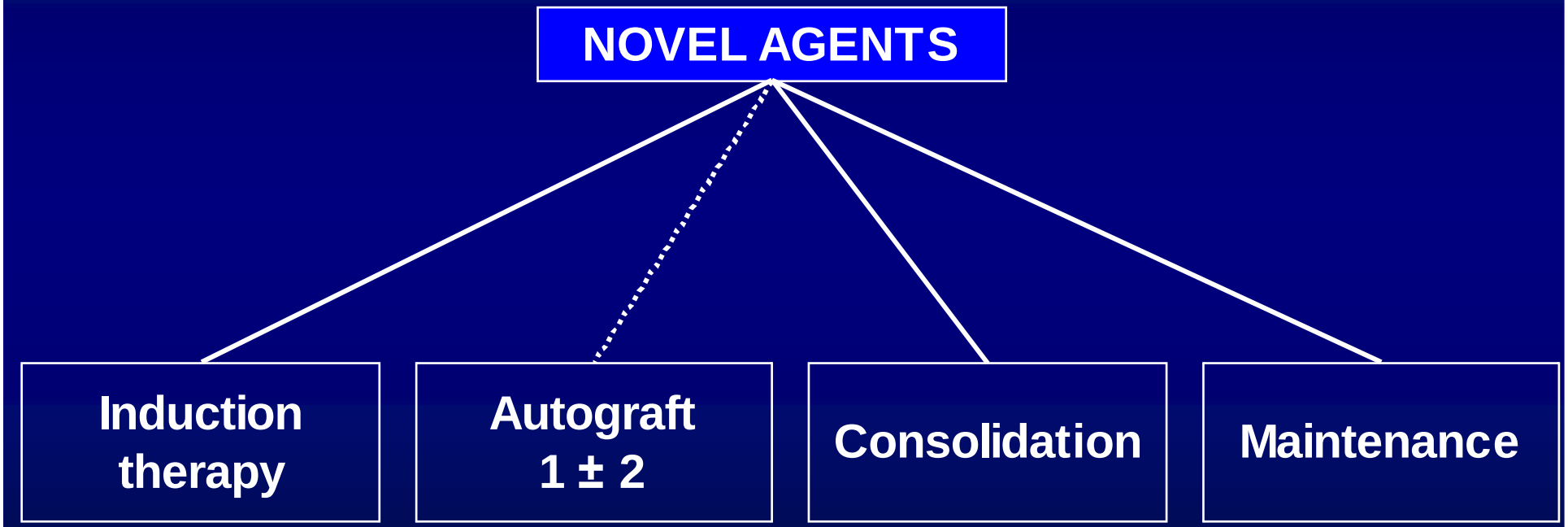
CRITERIA TO IDENTIFY A MYELOMA PATIENT WHO IS ELIGIBLE FOR AUTOTRANSPLANTATION

- Patient's chronological age
- Patient's physiological age
- Absence of comorbidities
- Normal organ function

Renal failure does not preclude ASCT to support reduced-dose melphalan

Cavo M et al, Blood 2011 Mar 29 [Epub ahead of print]

NEW TREATMENT PARADIGM FOR PATIENTS WHO ARE ELIGIBLE FOR AUTOTRANSPLANTATION (ASCT)



GOALS OF NOVEL-AGENT-BASED INDUCTION THERAPIES

- To maximize the speedy and degree of tumor reduction up to the VGPR, nCR and CR level
- To quickly reverse disease-related complications, such as hypercalcemia, renal failure and anemia
- To ameliorate patient's symptoms
- To enable successful collection of PBSCs
- To minimize toxicities precluding subsequent ASCT

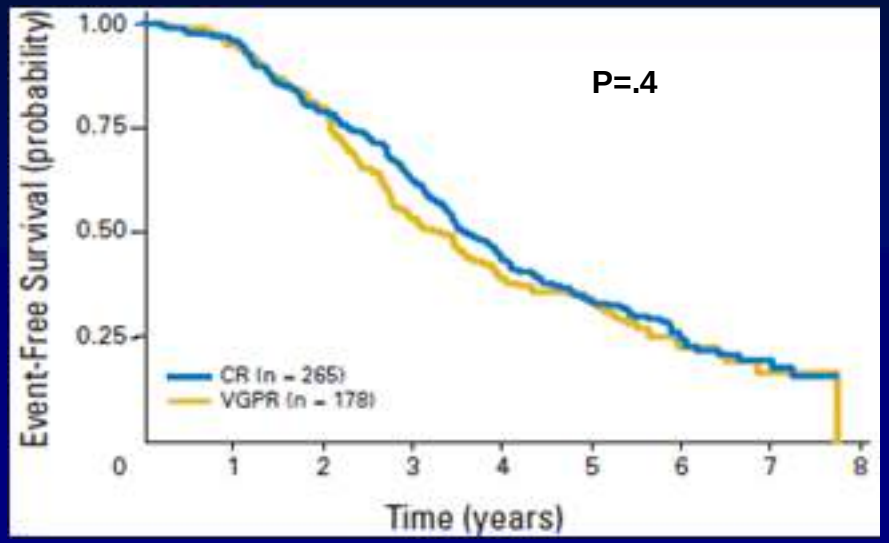
LATER GOALS OF SUBSEQUENT NOVEL-AGENT-BASED TREATMENT PHASES

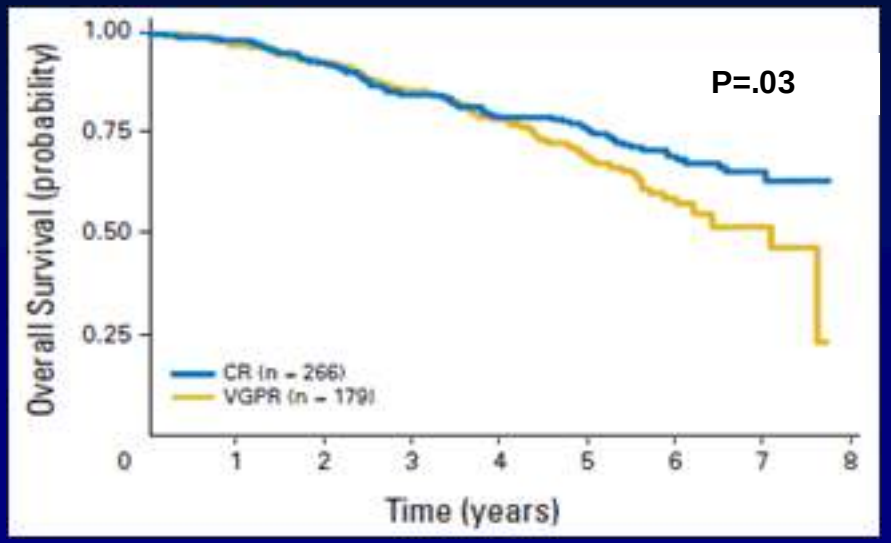
- To furtherly enhance tumor reduction and increase the rate of CR
  - ASCT, either single or double
  - Post-ASCT consolidation therapy
- To reduce the risk of relapse and sustain durable CR
  - Post-ASCT maintenance therapy

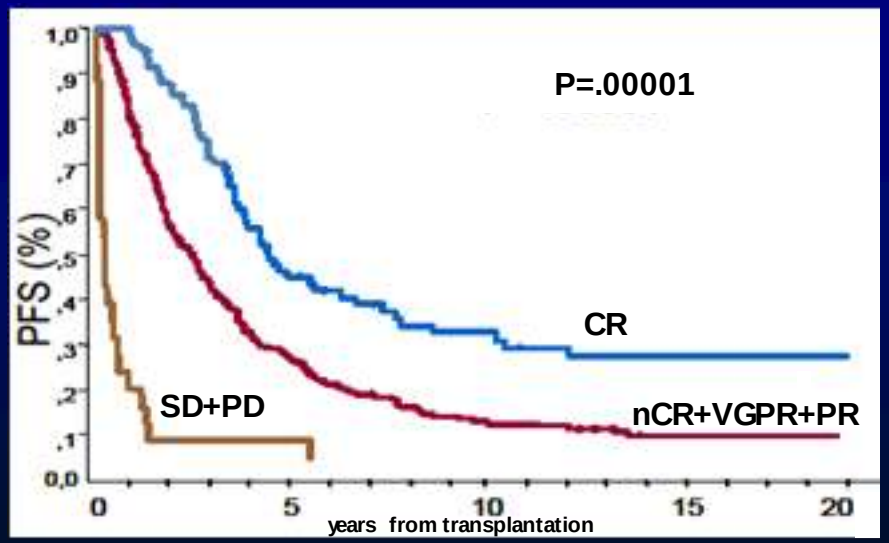
⇩

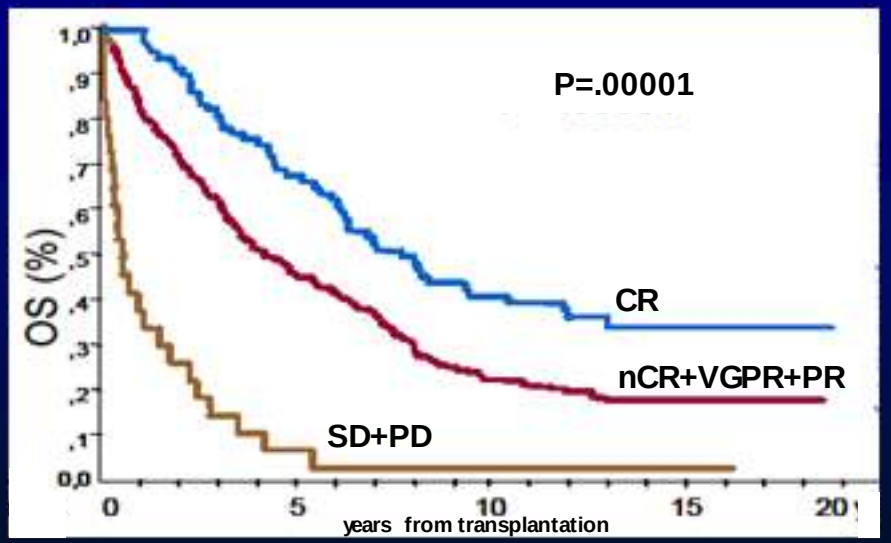
To extend PFS and OS

POST-ASCT HIGH-QUALITY RESPONSES PROGNOSTICATE FOR IMPROVED LONG-TERM OUTCOMES





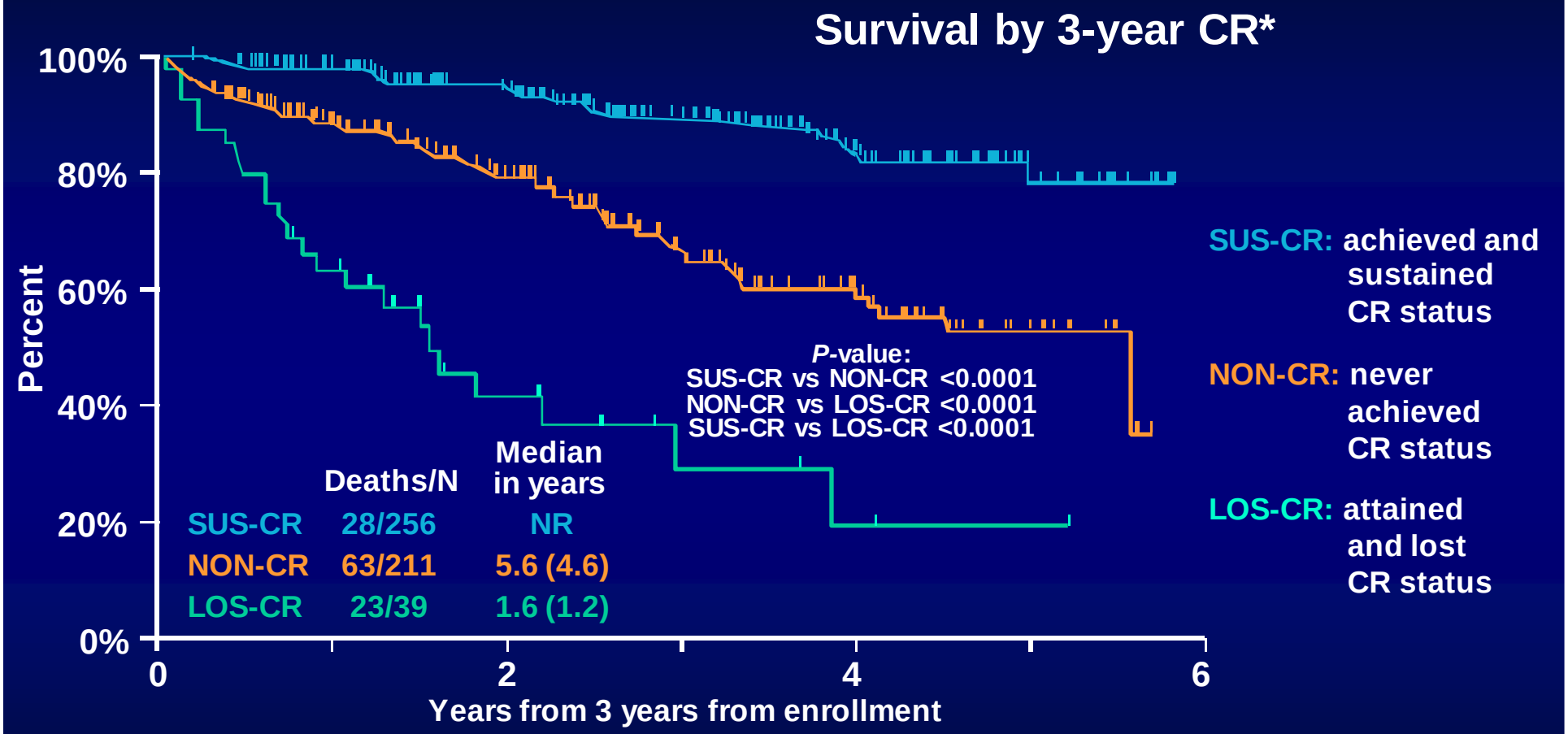




Harousseau et al, J Clin Oncol 2009;27:5720-5726

Martinez-Lopez et al, Blood 2011 Apr 11 [Epub ahead of print]

PROGNOSTIC RELEVANCE OF DURABLE COMPLETE RESPONSE



*Total therapy 2 regimen (TT2)

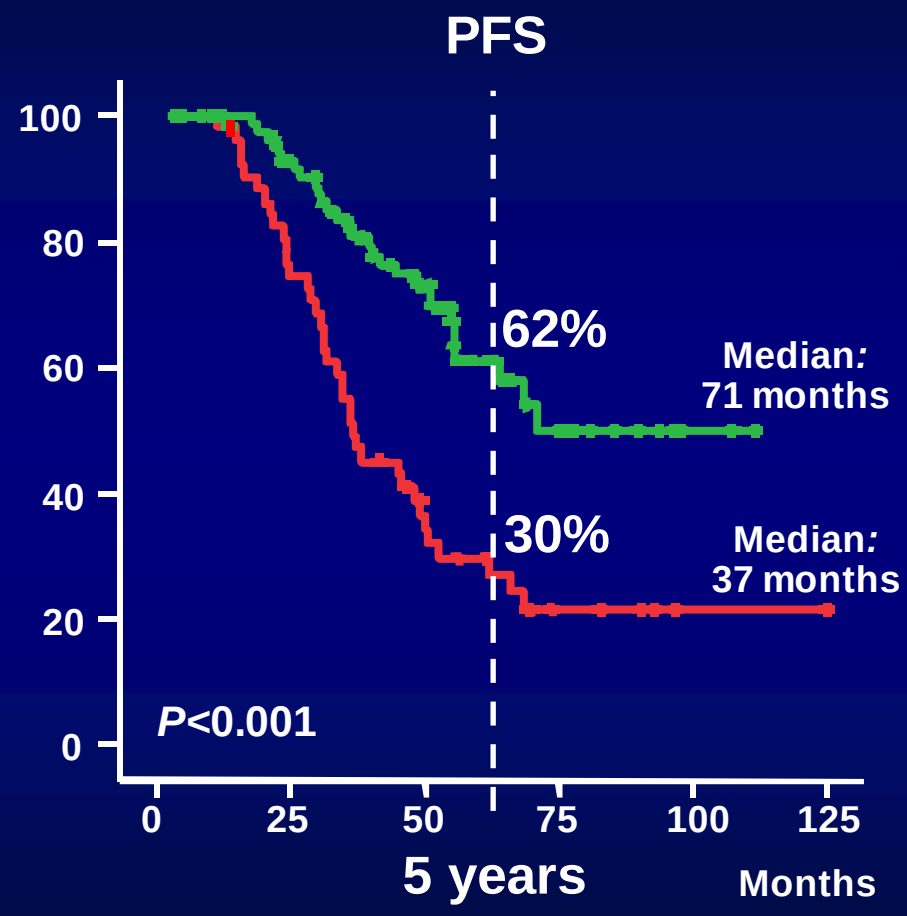
Barlogie et al. Cancer 2008;113:355–359

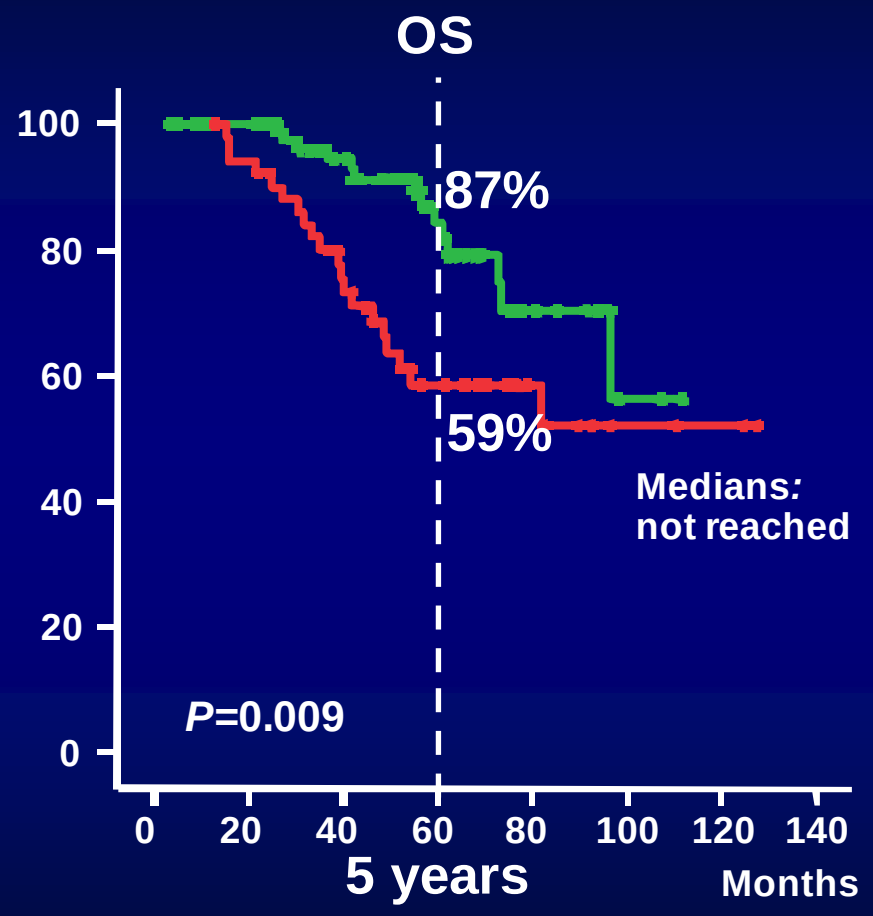
MORE SENSITIVE TECHNIQUES ARE REQUIRED TO DETECT THE DEPTH OF RESPONSE BEYOND THE LEVEL OF CR

- **Bone marrow level**
  - **Clonality of PC and k:λ FLC ratio → STRINGENT CR (sCR)** [1]
  - **Multiparametric flow cytometry → IMMUNOPHENOTYPIC CR** [2]
  - **Qualitative and quantitative RT-PCR → MOLECULAR CR** [3,4]
- **Outside bone marrow**
  - **MRI** [5]
  - **PET-CT** [6]

1. Durie et al, Leukemia 2006;20:1467-1473
2. Paiva et al, Blood 2008;112:4017-4023
3. Terragna et al, Blood 2010;116(21). Abstract 861
4. Ladetto et al, J Clin Oncol 2010;28:2077-2084
5. Barlogie, Blood 2006; 108:2134
6. Zamagni et al, Blood 2010;116(21). Abstract 369

IMPACT ON CLINICAL OUTCOMES OF POST-ASCT MRD DETECTED BY FLOW CYTOMETRY



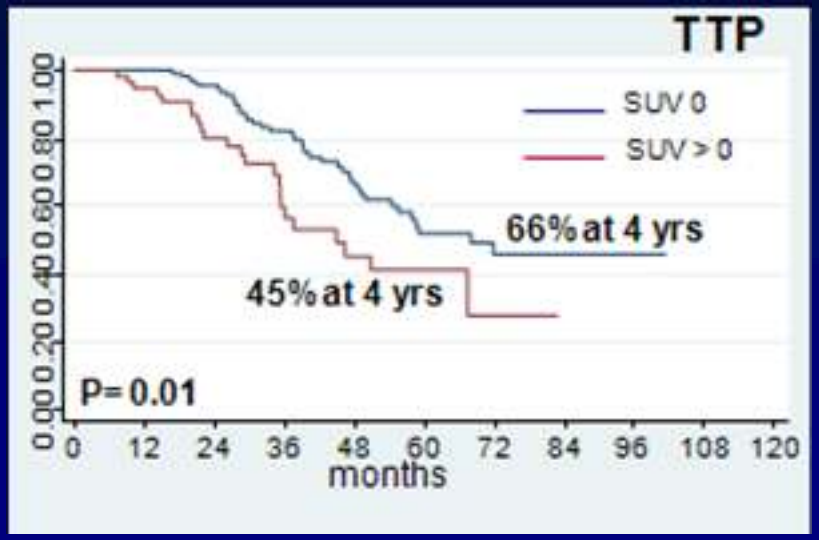


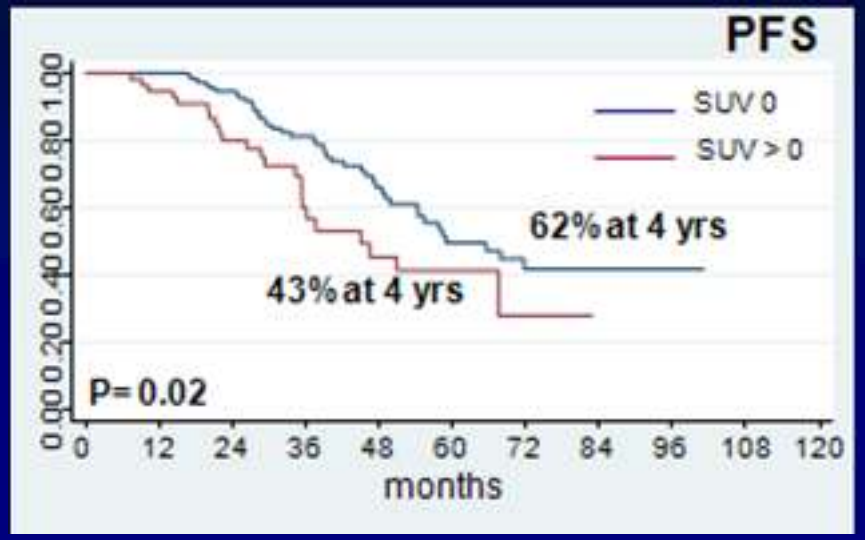
MRD negative (n=94)

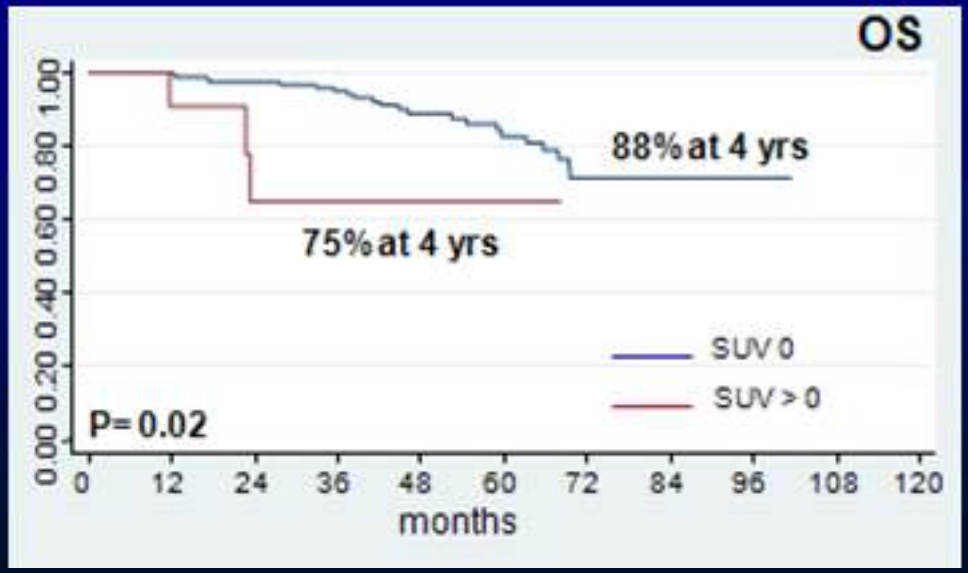
MRD positive (n=53)

Paiva et al. Blood. 2008;112:4017–4023

IMPACT ON CLINICAL OUTCOMES OF POST-ASCT PET-CT NEGATIVITY







Zamagni et al, Plenary Abstract Session II, May 6

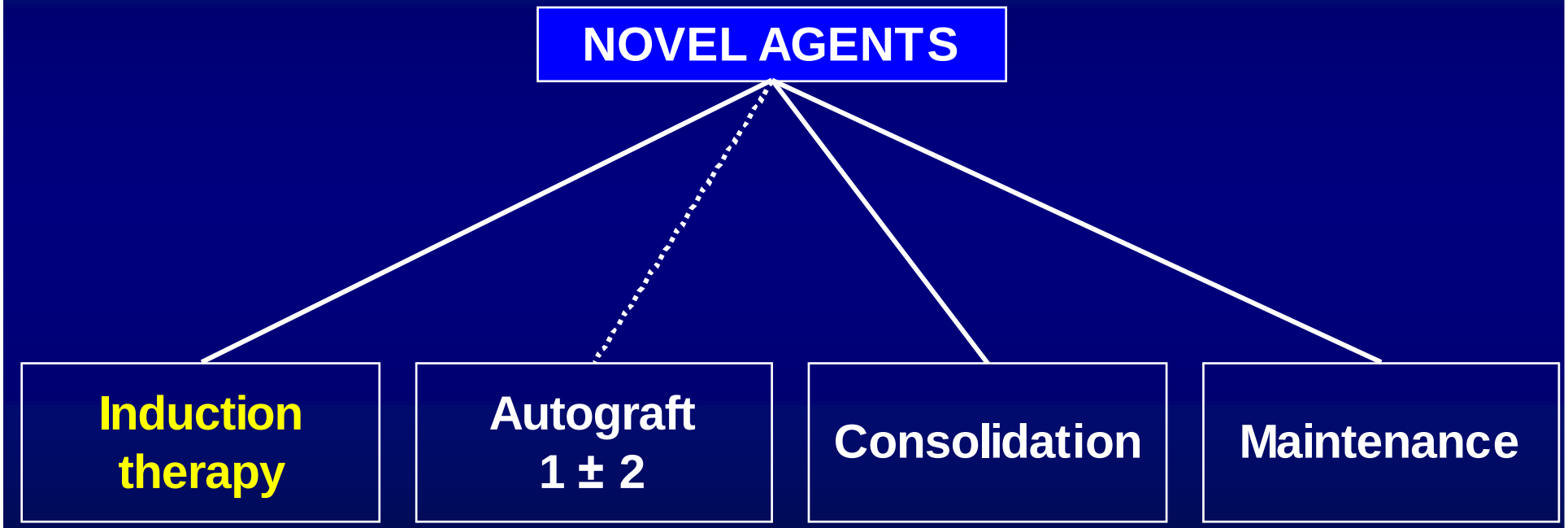
LATER GOALS OF SUBSEQUENT NOVEL-AGENT-BASED TREATMENT PHASES

- To furtherly enhance tumor reduction and increase the rate of CR
  - ASCT, either single or double
  - Post-ASCT consolidation therapy
- To achieve the deepest response
  - Immunophenotypic CR
  - Molecular CR
- To reduce the risk of relapse and substain the duration of CR
  - Post-ASCT maintenance therapy

⇩

To extend PFS and OS

NEW TREATMENT PARADIGM FOR PATIENTS WHO ARE ELIGIBLE FOR AUTOTRANSPLANTATION (ASCT)



NOVEL-AGENT-BASED INDUCTION THERAPIES

	THAL-BASED	LEN-BASED	BORT-BASED	BORT-IMiD-BASED
2-DRUG	• TD	• RD • Rd	• VD	
3-DRUG	• TAD • CTD	• RAD • RCD • BiRD	• PAD • VCD	• VTD • RVD
4-DRUG				• VTDC • RVDC

PHASE 3 STUDIES OF NOVEL AGENTS INCORPORATED INTO AUTOTRANSPLANTATION

	% INDUCTION		% ASCT			
REGIMEN	CR	≥ VGPR	CR	≥ VGPR	PFS	OS
TT2 + Thal vs	NR	NR	59 (3-yr)*	NR	56% (5-yr)*	67% (5-yr)*
TT2 no Thal [1]	NR	NR	42 (3-yr)*	NR	45% (5-yr)*	65% (5-yr)*
TAD + Thal vs	3	37*	14	54*	34 mo*	73 mo
VAD + IFN [2]	2	18*	12	44*	22 mo*	60 mo
VD+Len±Len vs	6	38*	16*	54*	36	81% (3-yr)
VAD+Len±Len [3]	1*	15*	9*	37*	30	77% (3-yr)
PAD+Bort vs	NR	42*	NR	61*	36 mo*	HR = 0.73*
VAD+Thal [4]	NR	15*	NR	36*	27 mo*	Not reach.

1.Barlogie et al. N Engl J Med. 2006;354(10):1021-1030.
2.Lokhorst et al. Blood 2010;115(6):1113-1120.
3.Harousseau et al. J Clin Oncol. 2010;28(30):4621-4629.
4.Sonneveld et al. Blood 2010;116(21). Abstract 40

* P value statistically significant

PHASE 3 STUDIES OF NOVEL AGENTS INCORPORATED INTO AUTOTRANSPLANTATION

REGIMEN	% INDUCTION CR	% INDUCTION ≥ VGPR	% ASCT CR	% ASCT ≥ VGPR	PFS	OS
TT2 + Thal vs	NR	NR	59 (3-yr)*	NR	56% (5-yr)*	67% (5-yr)*
TT2 no Thal [1]	NR	NR	42 (3-yr)*	NR	45% (5-yr)*	65% (5-yr)*
TAD + Thal vs	3	37*	14	54*	34 mo*	73 mo
VAD + IFN [2]	2	18*	12	44*	22 mo*	60 mo
VD+ Len ± Len vs	6	38*	16*	54*	36	81% (3-yr)
VAD+ Len ± Len [3]	1*	15*	9*	37*	30	77% (3-yr)
PAD + Bort vs	NR	42*	NR	61*	36 mo*	HR = 0.73*
VAD + Thal [4]	NR	15*	NR	36*	27 mo*	Not reach.
VTD + VTD vs	19*	62*	42*	82*	68% (3-yr)*	86% (3-yr)*
TD + TD [5]	5*	28*	30*	64*	56% (3-yr)*	84% (3-yr)*
VTD vs	35*	60*	46*	65*	Not reach.*	Not reach.
TD [6]	14*	29*	24*	40*	27 mo*	Not reach.
vTD vs	13*	51*	30*	61*	Not reach.	Not reach.
TD [7]	12*	35*	33*	54*	Not reach.	Not reach.

1.Barlogie et al. N Engl J Med. 2006;354(10):1021-1030.
2.Lokhorst et al. Blood 2010;115(6):1113-1120.
3.Harousseau et al. J Clin Oncol. 2010;28(30):4621-4629.
4.Sonneveld et al. Blood 2010;116(21). Abstract 40
5.Cavo et al. Lancet 2010;379(9758):2075-2085.
6.Rosiñol et al. Blood 2010;116(21). Abstract 307.
7. Harousseau et al. Blood 2009;114(22). Abstract 354.

* P value statistically significant

LENALIDOMIDE-BASED REGIMENS ± AUTOTRANSPLANTATION

	4 cycles				Best response			
REGIMEN	CR (%)	≥ VGPR (%)	AEs grade ≥ 3 (%)	EARLY DEATH (%)	CR (%)	≥ VGPR (%)	PFS	OS
RD vs	NR	42*	52*	5*	13	46	NR	87% (2-yr)
Rd [1]	NR	24*	35*	1*	10	36	NR	75% (2-yr)

1.Rajkumar et al. J Clin Oncol. 2006;24(3):431-436.
2.Richardson et al. Blood 2010;116(5):679-686.

* P value statistically significant

LENALIDOMIDE-BASED REGIMENS ± AUTOTRANSPLANTATION

	4 cycles				Best response			
REGIMEN	CR (%)	≥ VGPR (%)	AEs grade ≥ 3 (%)	EARLY DEATH (%)	CR (%)	≥ VGPR (%)	PFS	OS
RD vs	NR	42*	52*	5*	13	46	NR	87% (2-yr)
Rd [1]	NR	24*	35*	1*	10	36	NR	75% (2-yr)
RVD [2]	NR	11	NR	NR	29	67	75% (18 mo)	97% (18 mo)

1.Rajkumar et al. J Clin Oncol. 2006;24(3):431-436.
2.Richardson et al. Blood 2010;116(5):679-686.

* P value statistically significant

PATIENTS' TOLERANCE TO NOVEL-AGENT-BASED INDUCTION THERAPIES

REGIMEN	COMPLETED INDUCTION (%)	EARLY DEATH (%)	RECEIVED ASCT (%)
TAD vs	88	4	82
VAD [1]	90	3	82
VD vs	95	0	88
VAD [2]	92	3	84
PAD vs	91	NR	85
VAD [3]	90	NR	83
VTD vs	96	0	89
TD (GIMEMA) [4]	92	0	82
VTD vs	NR	2	85
TD (PETHEMA) [5]	NR	2	70

1.Lokhorst et al. Blood 2010;115(6):1113-1120.
2.Harousseau et al. J Clin Oncol. 2010;28(30):4621-4629.
3.Sonneveld et al. Blood 2010;116(21). Abstract 40.
4.Cavo et al. Lancet 2010;379(9758):2075-2085.
5.Rosiñol et al. Blood 2010;116(21). Abstract 307.

EFFECT OF NOVEL AGENTS ON STEM CELL COLLECTION

Thalidomide

- Adequate collection of stem cells [1,2]

Bortezomib

- Not cytotoxic to bone marrow
- Successful mobilization and adequate collection of PBSC with variety of induction regimens [3-5]

REGIMEN	Priming therapy	Collected CD34+ (x10^6/kg)
VD[4]	G-CSF	6.8
VTD[5]	CTX + G-CSF	9.7

1. Breitkreutz et al. Leukemia 2007;21:1294–1299
2. Cavo et al. Blood 2005;106:35-39
3. Kumar et al. Blood 2009;114:1729-1735
4. Moreau et al. Leukemia 2010;24:1233-1235
5. Cavo et al. Lancet 2010;376:2075-2085

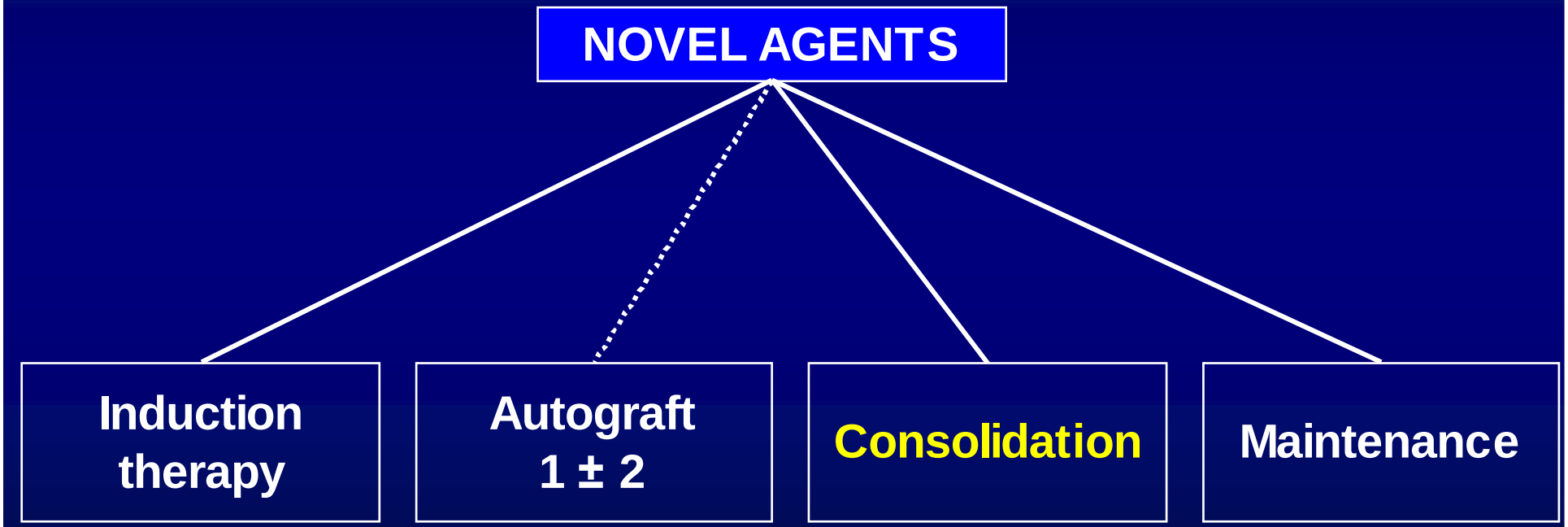
EFFECT OF NOVEL AGENTS ON STEM CELL COLLECTION

Lenalidomide

- Cytotoxic effect on bone marrow
- Evidence of decreased stem cell yield after lenalidomide exposure
- Recommendation:
  - Collection of PBSC within 4 months of initiation of therapy
  - Mobilization with G-CSF + cyclophosphamide after 4 months of therapy and/or in patients aged ≥ 65 years

Kumar et al. Blood 2009;114:1729-1735

NEW TREATMENT PARADIGM FOR PATIENTS WHO ARE ELIGIBLE FOR AUTOTRANSPLANTATION (ASCT)



NOVEL-AGENT-BASED CONSOLIDATION THERAPY

AGENT / REGIMEN	N° CYCLES	PROBABILITY TO UPGRADE RESPONSE (%)	PFS	OS
Bortezomib vs	6	≥ VGPR*: 31	Updated @ IMW 2011	Updated @ IMW 2011
no consolidation [1]	/	≥ VGPR*: 19	Updated @ IMW 2011	Updated @ IMW 2011
VTD [2]	4	CR: 34	60 mo (median)	89% (3-yr)
		molecular CR: 15	> PFS	> OS

1.Mellqvist et al. Haematologica 2011; 96(suppl 1). Abstract 011
2.Ladetto et al, J Clin Oncol 2010;28:2077-2084.
3.Attal et al. Blood 2009;114(22). Abstract 529.
4.Cavo et al. Blood 2010;116(21). Abstract 42.
4.Terragna et al. Blood 2010;116(21). Abstract 861.

* P value statistically significant

NOVEL-AGENT-BASED CONSOLIDATION THERAPY

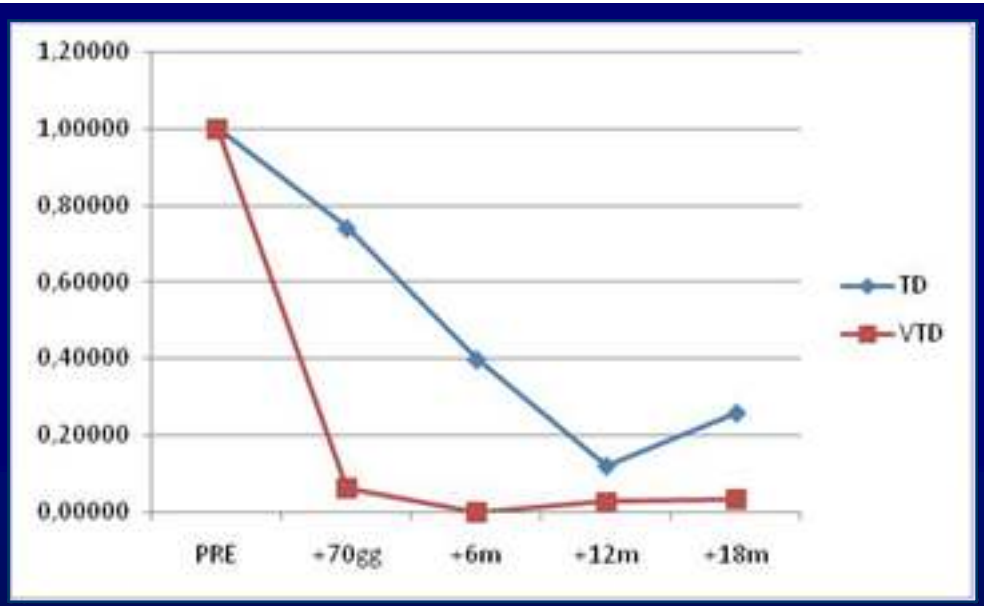
AGENT / REGIMEN	N° CYCLES	PROBABILITY TO UPGRADE RESPONSE (%)	PFS	OS
Bortezomib vs	6	≥ VGPR*: 31	Updated @ IMW 2011	Updated @ IMW 2011
no consolidation [1]	/	≥ VGPR*: 19	Updated @ IMW 2011	Updated @ IMW 2011
VTD [2]	4	CR: 34	60 mo (median)	89% (3-yr)
		molecular CR: 15	> PFS	> OS
Lenalidomide [3]	2	CR: 6	not eval.	not eval.
		≥ VGPR: 10	not eval.	not eval.
VTD [4]	2	CR: 11	not eval.	not eval.
		molecular CR: 25	> PFS	> OS

1.Mellqvist et al. Haematologica 2011; 96(suppl 1). Abstract 011
2.Ladetto et al, J Clin Oncol 2010;28:2077-2084.
3.Attal et al. Blood 2009;114(22). Abstract 529.
4.Cavo et al. Blood 2010;116(21). Abstract 42.
4.Terragna et al. Blood 2010;116(21). Abstract 861.

* P value statistically significant

VTD CONSOLIDATION: PCR (patient-specific) QUALITATIVE AND QUANTITATIVE ANALYSES OF MOLECULAR REMISSION

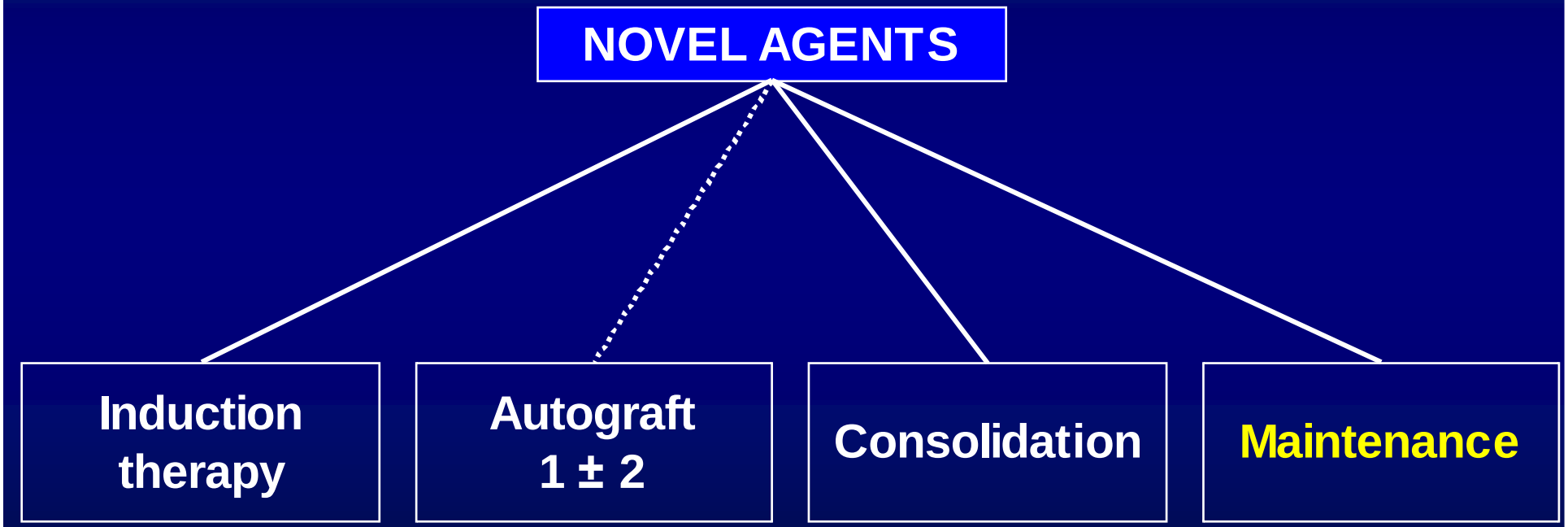
Efficacy	VTD
Pre-consolidation (day 0) PCR neg	39%
Post-consolidation (day +70) PCR neg	64%
P-value (McNemar Test)	0.0078



- VTD consolidation following double ASCT significantly increased the rate of molecular remissions up to the 64% value.
- In comparison with TD, VTD consolidation effected more profound reduction in residual tumor burden (1 log vs 5 log reduction).

Terragna et al. Blood 2010; 116(21). Abstract 861

NEW TREATMENT PARADIGM FOR PATIENTS WHO ARE ELIGIBLE FOR AUTOTRANSPLANTATION (ASCT)



PHASE 3 STUDIES OF THALIDOMIDE MAINTENANCE

	Treatment		
	Induction with thal	ASCT	Maintenance duration
Thal+pamidronate vs Pamidronate vs None [1]	No	Double ASCT	until PD
Thal + pred vs Pred[2]	No	Single ASCT	12 months
Thal vs No Thal[3]	Yes	Double ASCT	until PD
Thal vs IFN [4]	Yes	Single or double ASCT	until PD
Thal vs None [5]	Yes	Single ASCT/ Non-intensive Tx	until PD
Thal+pred vs None [6]	Yes	Single ASCT	until PD

1.Attal et al. Blood 2006;108:3289–3294
2.Spencer et al. J Clin Oncol 2009;27:1788–1793
3.Barlogie et al. N Engl J Med 2006;354:1021–1030; Blood 2008;112:3115–3121; J Clin Oncol 2010;28:1209–1214
4.Lokhorst et al. Blood 2010;115:1113–20
5.Morgan et al. Blood 2010; 116(21). Abstract 623
6.Stewart et al. Blood 2010; 116(21). Abstract 39

PHASE 3 STUDIES OF THALIDOMIDE MAINTENANCE

Induct with Thal	Improved PFS	Improved OS	Survival after relapse
NO [1]	Yes	Yes @ 39 m, Not @ 5.7 yr	Similar in all groups
NO [2]	Yes	Yes (3 yrs follow up)	Similar in all groups
YES [3]	Yes	Yes (7.2 yrs follow-up)	Reduced OS after thal exposure
YES [4]	Yes	No	Reduced OS after thal exposure
YES [5]	Yes	No	Reduced OS after thal exposure
YES [6]	Yes	No	Reduced OS after thal exposure

1.Attal et al. Blood 2006;108:3289–3294
2.Spencer et al. J Clin Oncol 2009;27:1788–1793
3.Barlogie et al. N Engl J Med 2006;354:1021–1030; Blood 2008;112:3115–3121; J Clin Oncol 2010;28:1209–1214
4.Lokhorst et al. Blood 2010;115:1113–20
5.Morgan et al. Blood 2010; 116(21). Abstract 623
6.Stewart et al. Blood 2010; 116(21). Abstract 39

THALIDOMIDE MAINTENANCE STUDIES CAVEATS

In ASCT setting, benefit with thal maintenance seen in terms of PFS but not always of OS [1]

- Toxicity , particularly neurological, leading to discontinuation rates up to 60% [2]
- Shorter survival following relapse in patients with prior exposure to thal
  - Selection of resistant clones?
- No benefit in patients with del(13q) and worse outcome in patients with del(17p) [2,3]

1. Cavo et al. J Clin Oncol 2009; 27(32): e186-187
2. Attal et al. Blood 2006;108:3289–3294
3. Morgan et al. Blood 2010; 116(21). Abstract 623

PHASE 3 STUDIES OF LENALIDOMIDE MAINTENANCE

Study	Treatment	Median follow-up	PFS / TTP	OS	OS after relapse
IFM 2005-02[1]	Len consolid - R → Len	34 mo	42 mo	No significant difference	No significant difference
	Len consolid - R → Placebo		24 mo ($P<10^{-8}$)		
CALGB 100104[2]	R → Len	17.5 mo	42.3 mo	No significant difference	NR
	R → Placebo		21.8 mo ($P<0.0001$)		

1.Attal et al. Blood 2010; 116(21). Abstract 310

2.McCarthy et al. Blood 2010; 116(21). Abstract 37

PHASE 3 STUDIES OF LENALIDOMIDE MAINTENANCE

Study	Adverse events			
	≥ grade 3 neutropenia (%)	≥ grade 3 febrile neutropenia (%)	Secondary malignancies (%)	Discontinuation (%)
IFM 2005-02[1]	43	1	5.5	Due to SAEs, 8
CALGB 100104[2]	44	6	6.5	Due to AEs, 12 other reasons, 13

1.Attal et al. Blood 2010; 116(21). Abstract 310

2.McCarthy et al. Blood 2010; 116(21). Abstract 37

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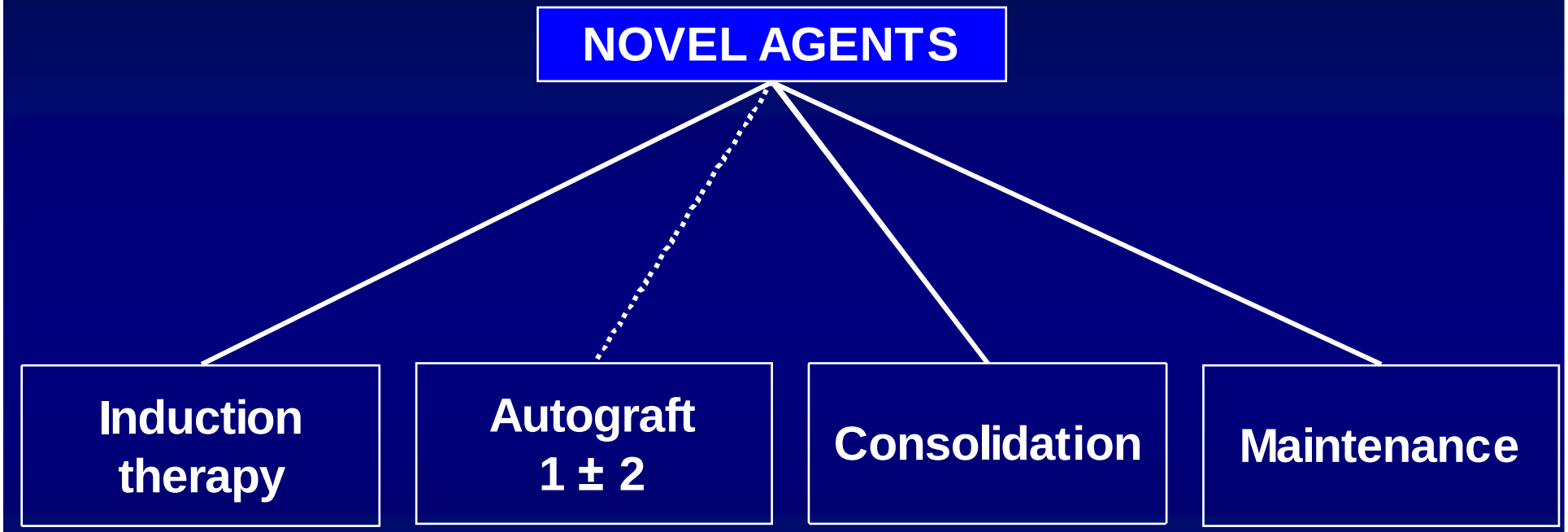

- Have novel agents incorporated into ASCT opened the doors for a risk-adapted strategy?

IMPACT OF BORTEZOMIB INCORPORATED INTO ASCT ON PFS ACCORDING TO CYTOGENETIC ABNORMALITIES

REGIMEN	PROGRESSION-FREE SURVIVAL			
	overall	del (13q)	t (4;14)	del (17p)
VD+ Len ± Len	36 mos (median)	NR	28 mos (median)	14 mos (median)
vs				
VAD+ Len ± Len [1]	30 mos (median)	NR	16 mos (median)	NR
PAD + Bort	48% (at 3-yr)	40% (at 3-yr)	28% (at 3-yr)	22% (at 3-yr)
vs				
VAD + Thal [2]	40% (at 3-yr)	29% (at 3-yr)	20% (at 3-yr)	16% (at 3-yr)
VTD + VTD	68% (at 3-yr)	62% (at 3-yr)	69% (at 3-yr)	NR
vs				
TD + TD [3]	56% (at 3-yr)	46% (at 3-yr)	37% (at 3-yr)	NR

1.Avet-Loiseau et al. Clin Oncol. 2010;28(30):4630-4634.
2.Sonneveld et al. Blood 2010;116(21) Abstract 40.
3.Cavo et al. Lancet 2010;379(9758):2075-2085.

(PERSONAL) CONCLUSION

- **INDUCTION THERAPY**
  - A triplet bortezomib-based regimen is the standard of care
  - 3-4 cycles represent a reasonable balance between efficacy and toxicity
  - BiPN will be significantly reduced by introduction of s.c. bortezomib into daily clinical practice

- **ASCT**
  - Outside clinical trials comparing early vs late ASCT, the preferred approach should continue to be ASCT up-front
  - High-dose therapy further enhance tumor reduction even in face of high CR rates affected by novel-agent-based induction regimens

(PERSONAL) CONCLUSION

- **CONSOLIDATION THERAPY**
  - Provides an incremental improvement in the rate of high-quality responses, up to the deepest level of molecular remission
  - Its impact on long-term clinical outcomes needs to be confirmed in prospective, randomized trials

- **MAINTENANCE THERAPY**
  - Lenalidomide reduces the risk of progression (60% range) and significantly prolongs TTP/PFS
  - Benefits with lenalidomide are seen regardless of β2 m, prior exposure to any of the novel agents, disease status at randomization, del (13q)
  - Does lenalidomide prolong OS?