How to treat a newly diagnosed young patient with multiple myeloma

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Disclosures for Jesús San Miguel

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How to treat a newly diagnosed young MM patient?

- **Young : <65-70 years & No severe co-morbidities***
- **Goal: Long-term survival (>10-20 years) with good QoL……"cure" ****

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* *To endure intensive treatments & to assume "drawbacks"*

** *Erradication or major reduction of tumor cell clone (CR)*

Patient Case

- 53-year-old man
- Diagnosed with symptomatic IgG-K MM in January 2009
  - Hb 9.3 g/dL; kidney function was normal, B2M was 4.6 (ISS stage 2), M component 4.5 g/dL; PCs BM: 32%
  - FISH analysis: Rb deletion and t(4;14)
  - Lytic lesions in skull and femur

Transplant candidate patient:
standard treatment until now

Induction (VAD)

↓

ASCT (Mel 200)

↓

Maintenance (IFN +/- Predn)

Treatment of Young MM Patients

Controversial issues

- What is the optimal induction treatment ?
- The rationale for HDT/ASCT
- Maintenance or consolidation treatment ?
- Will novel agents replace ASCT ?
- Role of Allogeneic Transplant
- Can novel drugs overcome high-risk factors ?

Do we have something better than VAD as debulky regimen?

- *In 5 randomized trials*

Thalidomide (TAD[1,2], CTD[3])..... > VAD

Bortezomib (BzD[4], BzAD[5])..... > VAD

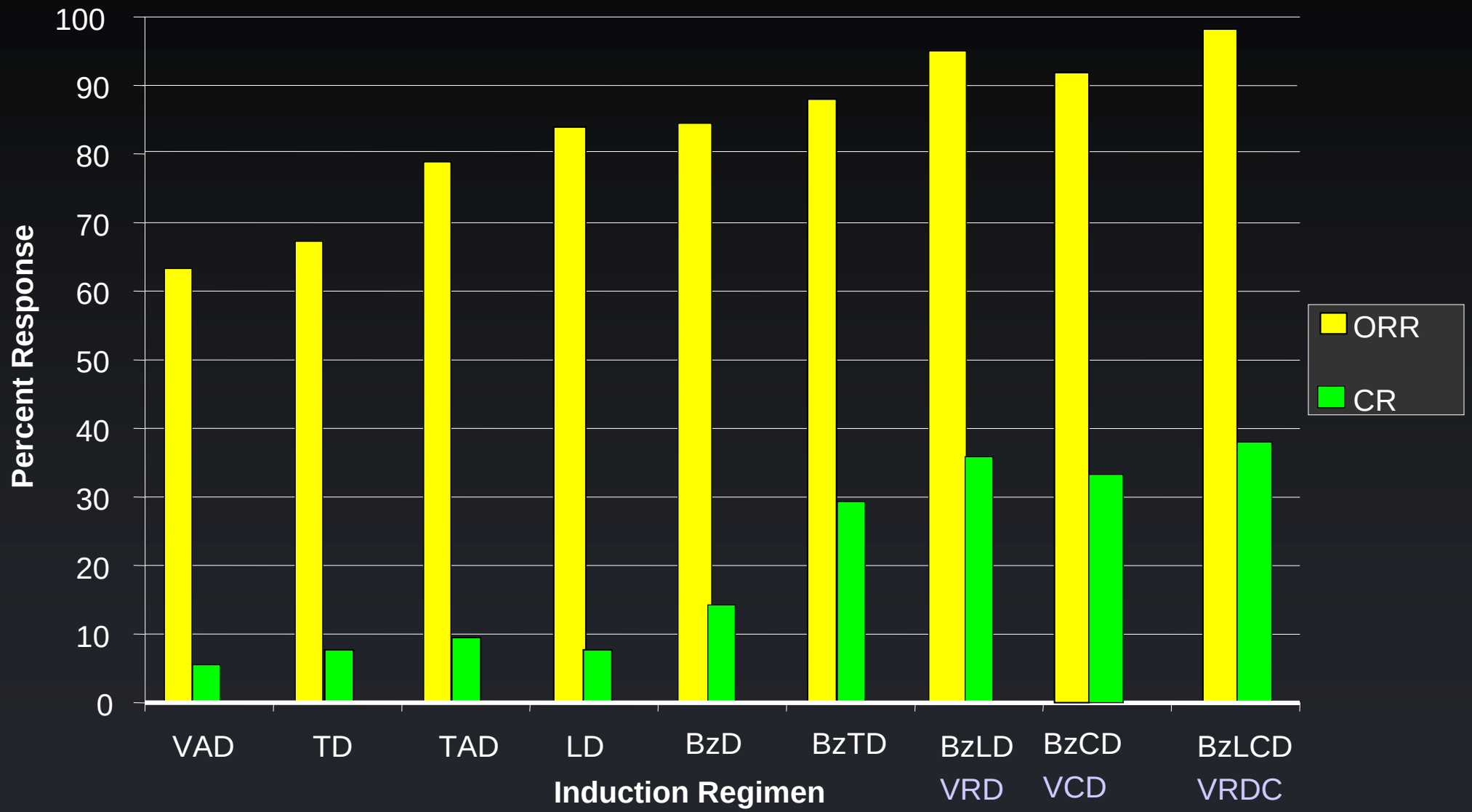
- *In 2 randomized trials*

BzTD[6,7]..... >TD

- In one BzTD bordeline vs BzD[8]

1. *Lokhorst, Blood 2009 ; 2. Zervas Ann Oncol 2007; 3. Morgan ASH 2009 (Abst 352),* 4. *Harousseau ASH 2008-09 (Abst 353);* 5.*Sonnoveld ASH 2008 (abst 653).* 6.*Cavo ASH 2009 (Abst 351);* 7. *Rosiñol ASH 2009 (Abst130) , 8.Harouseau ASH 2009 (abst 354)*

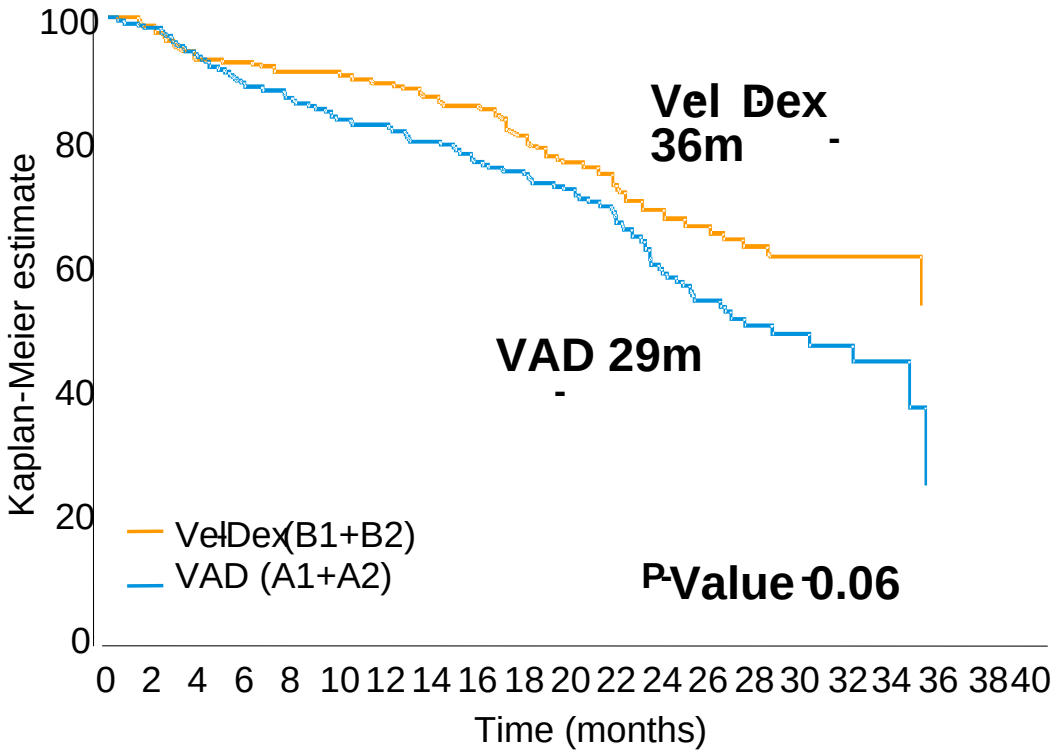
Response obtained with Novel Induction Regimens



1. *Kumar ASH 2008 (Blood 112, 91a)*
2. *Stewart EHA 2008 (Abstr 205)*
3. *Richardson ASCO 2008 (Abstr 8520)*
4. *Kumar ASH 2008 (Blood 112, 93a).*

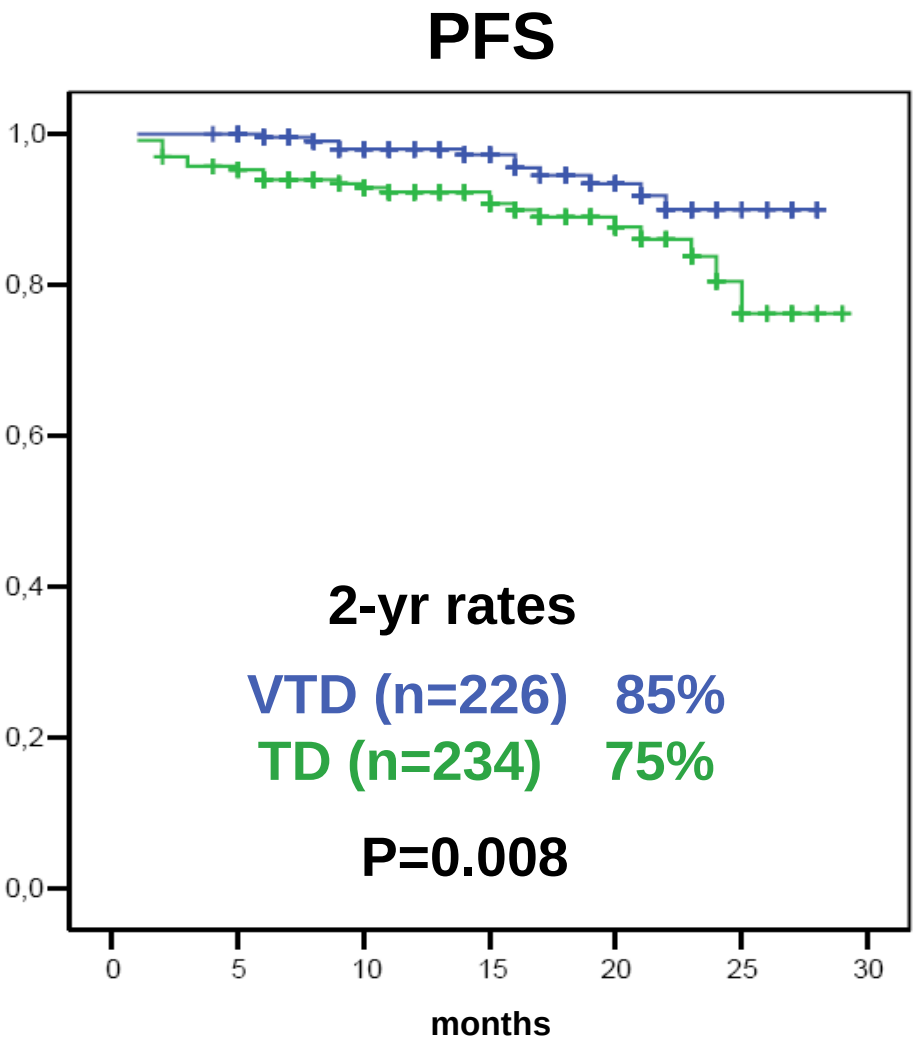
- *Kumar ASH 2009 (Abst 127): VRD, VCD, VRCD*
- *Einsele ASH 2009(Abst 131): VCD x 3 cycles*
- *Jakubowiak ASH 2009 (Abst 132): VRDoxD*

Vel/Dex vs. VAD



Harousseau JL et al. ASH 2009 (Abst 353)

VTD vs. TD



Cavo M et al. ASH 2009 (abst 351)

VTD > TD in PFS (0,01) Rosiñol et al ASH 2009 (Abst 130)

Toxicity profile of novel induction regimens

- **Thal - based :** PN (G3: 2%) (+10%), DVT : 6-15%
- **Lena – based:** No constipation. No somnolence, no PN, but……
  Neutropenia (14%) and DVT (9%)

- **Bortez-based:** G-I symptoms (22%), thrombocytopenia
  PN (G3: 4-7%) (+12% G2)

** Overall toxicity of BzD similar to VAD: SAE (31 vs 25%), Discontinuations (4 vs 6%)**

*Harousseau JL et al. ASH 2008, Joint ASH/ASCO Symposium

Stem cell collection with novel agents

- **Thalidomide- & bortezomib-based regimens do not affect stem cell collection**

- **Lenalidomide: induces lower stem cell yields….but….** ***No problems if PBSC are collected after no more than 4-6 cycles of Len using Cyclophosphamide as mobilizing agent***

Mazumder et al. ASH 2007 (abstract 3612) Kumar et al. Leukemia 2007;21:2035–42, Paripati et al. Leukemia 2008 Jan 24 [Epub ahead of print

Treatment of Young MM patients

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Does ASCT up-grade the responses obtained with Novel Agents?

	% Complete Responses & nCR		Reference
	Pre-ASCT	Post-ASCT (1st)	
. TD	14	40	*Rosiñol ASH 2009 (Abst 130)*
. TAD	4	16	*Lokhorst Hematologica 2008*
. CTD	21	65	*Morgan ASH 2009 (Abst 352*
. BzDx	21	35	*Harousseau ASH 2008-09 (Abst353)*
. BzTD	36	57	*Cavo ASH 2009 (Abst 351)*
. BzTD	29	59	*Rosiñol ASH 2009 (Abst 130)*

- ***Induction with novel agents followed by HDT/SCT are complementary rather than alternative treatment approaches***

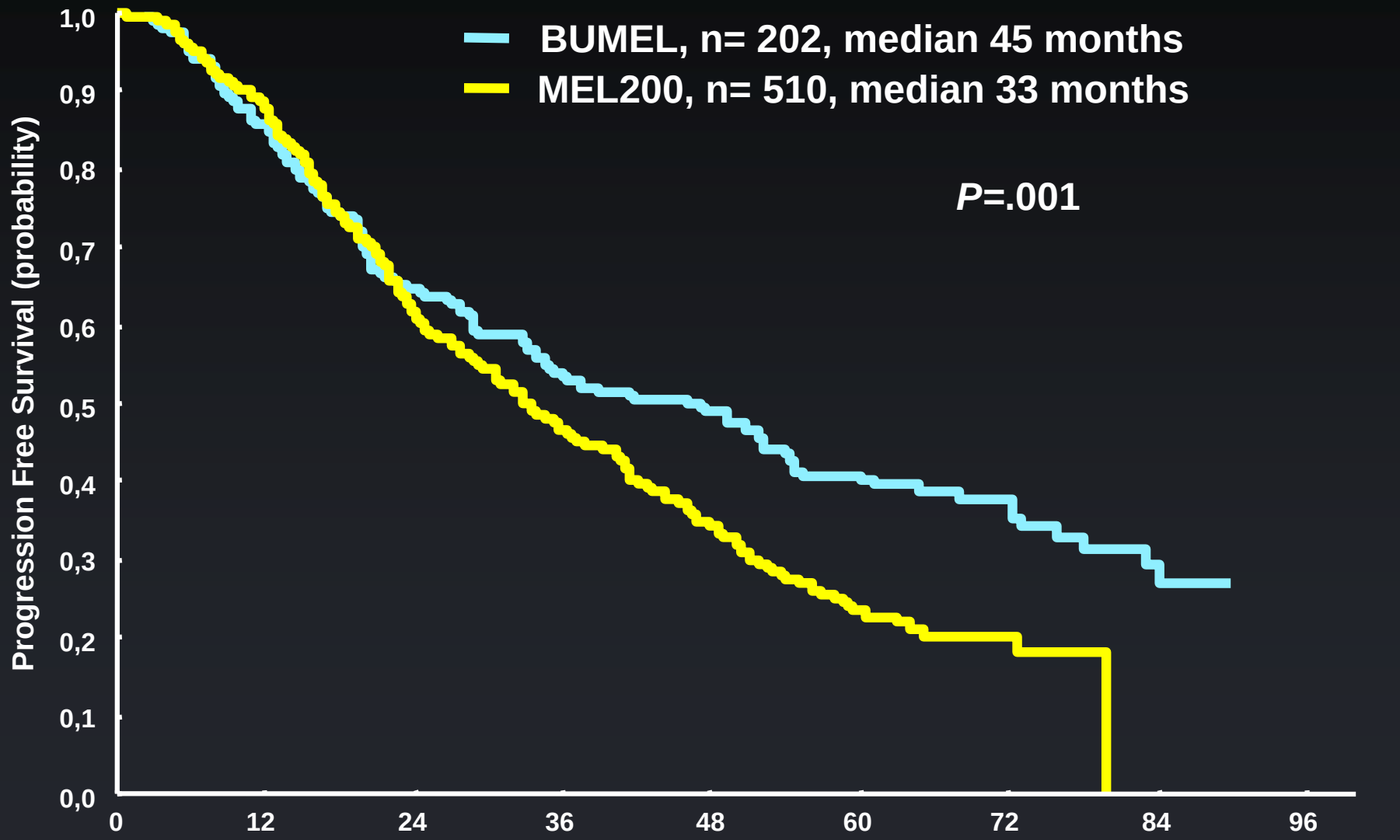
How to improve the efficacy of conditioning regimens

- **Melphalan 200 mg/m2……** *the gold standard*
- **Melphalan + Busulphan……** *may be superior*[1]
- **Melphalan + Bortezomib ……..** 70% ≥ VGPR (35% CR)[2]
  (1 mg/m2 D -6, -3, +1 +4)
- **Melphalan + Bortezomib……..** 53% ≥ VGPR[3]
  (1,3mg/m2 D-1 or +1)

1. *Lahuerta et al (submitted)*
2. *Roussel et al (IFM) Blood 2009 (on line) : superior CR (35 vs 11%) as compared with matched patients conditioned with MEL only*
3. *Kaufman et al IMMW 2009 (abst 364)*

Outcome according to the conditioning regimen

BU-MEL vs MEL200 (PETHEMA/ GEM 2000 trial)



Lahuerta et al (submitted)

One or Two ASCT?

- **3 randomized trials** *: **benefit in EFS** (3-12m) **in all, but OS only in one**

  - **Only patients with <VGPR benefit from 2nd Trx ***
  - **Thalidomide (maintenance) converts PR post-Trx into CR****
  - **The CR rate with Novel drugs + one ASCT = Tandem ASCT**

No Tandem…. ***but… increase use of 2nd ASCT at relapse if EFS > 3y***

** IFM, Italian and HOVON: Attal NEJM 2003 , Cavo JCO 2007, Sonneveld Hematologica 2007;*

*** Attal Blood 2006 & Spencer JCO 2008*

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Maintenance treatment with Thalidomide*

- *Attal (Blood 2006)* **Thal > Pamidronate or nothing …… > EFS & OS**
- *Spencer (JCO 2008)* **Thal**(1y) **+ Pred > Prednisone…….. > EFS & OS**
- *Barlogie (NEJM 2006)* **Continous Thal…….. > EFS but not OS**
- *Morgan (ASH 2009)* **cThal ..... > EFS but not OS**
- *Lokhorst (Blood 2009)* **cThal > IFN..... > EFS but not OS**

Caveats: Role in CR patients, duration of maintenance, outcome after relape

*** Is Lenalidomide the ideal maintenance agent?** *IFM 2005-002 Attal ASH 2009 (Abst 529); CALGB*

Consolidation with Bortezomib + Thalidomide + Dex

- **Patients** (n=40) with CR or VGPR following ASCT
- **Treatment :** 4 consolidation cycles of Btz-Thal- Dex
- **Results**
  - 36% converted from VGPR to CR
  - Six patients (15%) achieved Molecular Remission
  - 12 progressions occurred: *all among PCR-positive patients*

Ladetto *et al*. ASH 2009 (abstract 960)

Treatment of Young MM patients

- What is the optimal induction treatment ?
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Is there an alternative to upfront ASCT?

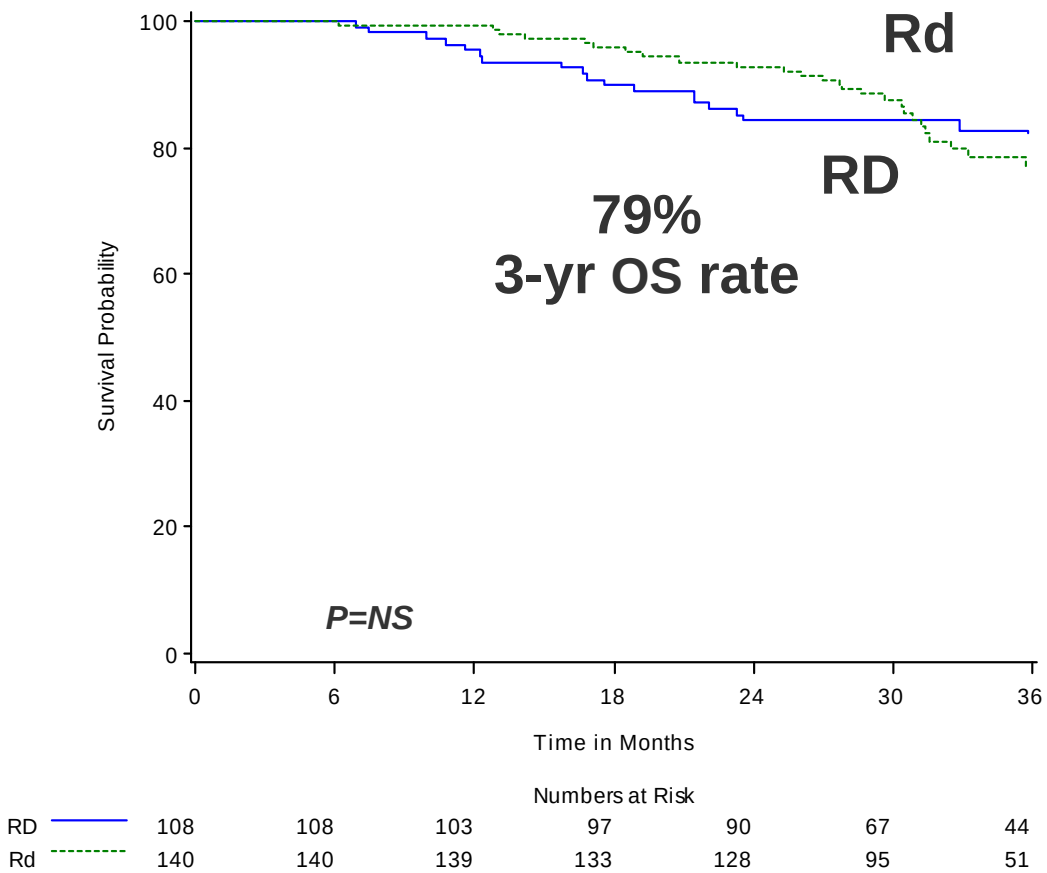
Continuous optimized treatment with novel agents and to postpone ASCT until relapse

Intensive vs. gentle approaches

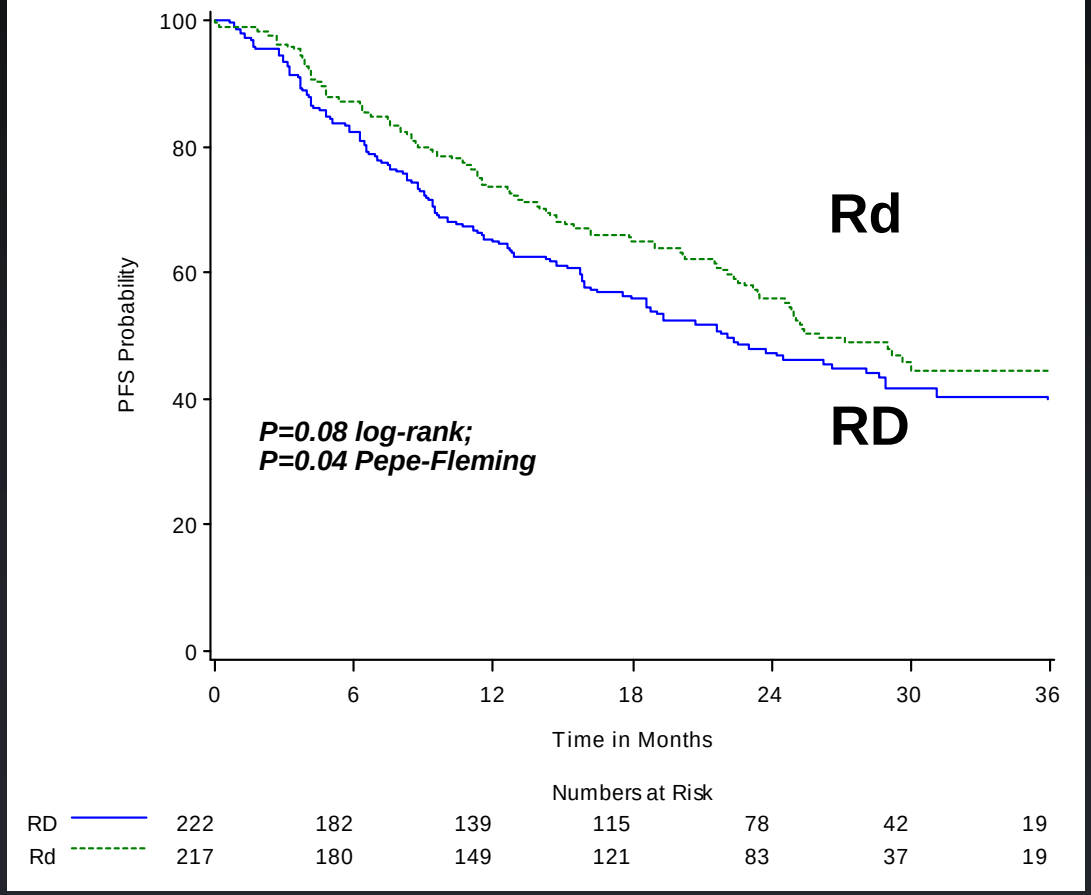
Lenalidomide + high (RD) vs. low-dose dex (Rd)

Phase III ECOG trial :Primary Therapy beyond 4 cycles

OS



PFS



Rajkumar *et al*. ASH 2008 Joing ASH/ASCO symposium

Total Therapy 3 (TT3) 438 patients enrolled

Induction and Mobilization: BzDT-PACE x 2 cycles

↓

MEL 200 mg/m^2 based ASCT x 2 (2-3 months apart)

↓

Consolidation: BzDT-PACE

↓

Maintenance: BzTD → TD

Responses

CR & nCR: 63% & 86% (vs ~60% for TT2)

Efficacy: *after follow-up of 39m*

- EFS & OS at 4y: 71% & 78%
- CR & nCR sustained at 4y (from the onset of response) in 87% & 78% patients

Barlogie et al. ASH 2008 Abstract 162

ASCT upfront or at relapse IFM-DFCI 2009

Kumar et al ASH 2009 (Abstr 956): Similar OS for early vs late Trx (after Thal or Len-Dex)

Intensive vs. gentle approaches:

Arguments in favor of intensive upfront treatment in young patients

- The patient is more fit to tolerate intensive and repetitive therapies
- ASCT is associatted with long treament-free interval & good QoL
- Relapses after MEL200 are sensitive to novel agents…… *but we don´t know the long term effcicacy of the oposite (Mel200 after novel agents)*
- The long-term use of all active agents upfront (i.e: Bz-Len-Dex) may induce more resistant relapses, with few options for rescue treatment

Gentle approach an option for low risk patients ?

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ALLOGENEIC-SCT

ADVANTAGES

- **Stem cells**
  - Non-contaminated
  - No damage (chemo.)
- **GVM effect**

DISADVANTAGES

- **Trx related mortality**
  > 20% - 40%
- **Age & Donor availability**
  10% candidates

High mortality with conventional Allo……. has favored the **Reduced Intensity Conditioning regimens (RIC)……** but TRM is still 10-20%; cGVHD: 35-70% & more relapses (extramedullary) **…..to overcome relapses: "Tandem Auto-Allo" programs**

Auto/Allo-RIC vsTandem Auto

- **3 studies (IFM[1], HOVON[2], PETHEMA[3])…….. No benefit**
- **2 studies (GIMEMA[4], EBMT[5])……Significant benefit (EFS, OS)**

❖ ***Differences in patient characteristics, GVHD prophylaxis, & conditioning regimens may explain these discrepant results***

1.Garban, Blood 2006 and Moreau, Blood 2008; 2. Lokhorst ASH 2008 (Abstr 461);
3.Rosinol, Blood 2008; 4. Bruno, NEJM 2007 (updated EBMT 2009);

5. Gahrton, ASH 2009 (Abst 52)
6. Knop, ASH 2009 (abst 51)……..Higher CR, similar OS but short follow-up

ALLO-Transplant: Can it be recommended?

- **Outside of clinical trials: NOT upfront…. but YES at relapse in high-risk patients** (early relapses/ refractory disease)…… *the patient should go to Trx with low tumor burden*

- **In clinical trials: Integration of Novel Drugs in RIC-Allo programs**

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Thalidomide in newly diagosed MM patients with cytogenetic abnormalities

- **TD**: Lower RR (CR) in del(13), t(4;14), del (17p) [1,2]…… shorter PFS & OS[1].
- **TAD**: Del(13) no influence [3]
- **Total Therapy II** : survival benefit for pts with cytogenetic abnormalities in the thalidomide arm (after 7 years of follow-up) [4]

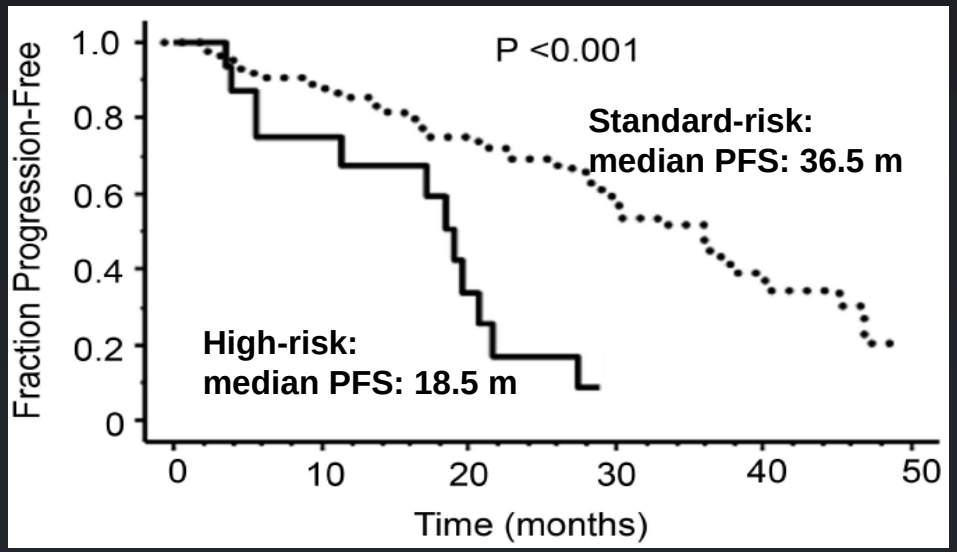
1 Zamagni et al ASH 2009 (abst 349)
2. Rosiñol et al ASH 2009 (abst 130)
3.Lokhorst et al Blood 2009 (on line)
4. Barlogie et al., Blood 2008

Impact of risk stratification on outcome with Lenalidomide/Dex in newly diagnosed MM

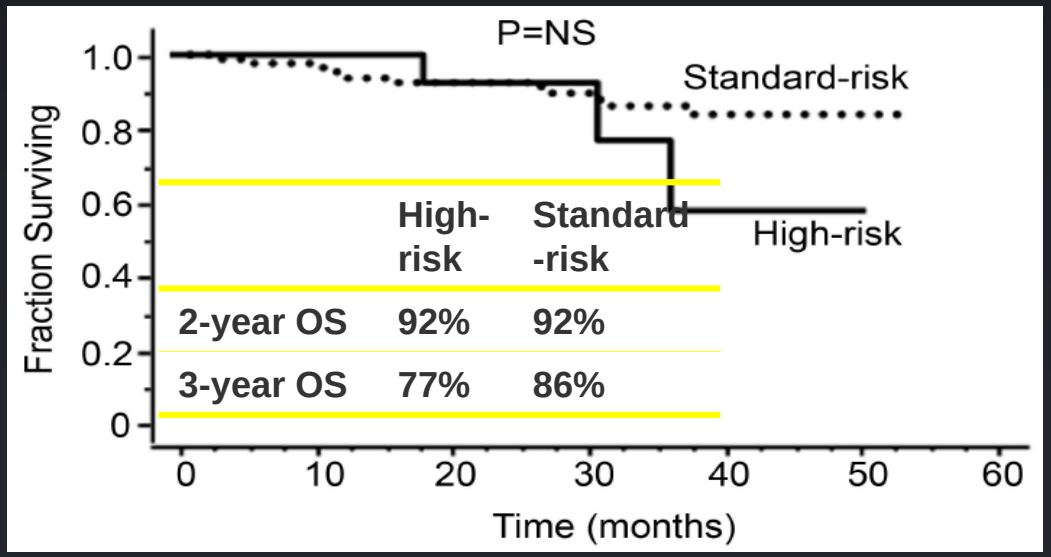
- **Patients** (n=100 newly diagnosed):*16% high-risk* *[hypodiploidy, del(13) (cytogenetics), del p53 , PCLI ≥ 3%, t(4;14), t(14;16)*
- **Treatment: Lenalidomide (25mg/day), days 1-21 of 4-week cycle + Dex**
- **Results** (median follow up: 36 months)

	High-risk	Standard risk	*P*
≥ PR	81%	89%	0.56
≥ VGPR	38%	45%	0.36

PFS



OS



	High-risk	Standard -risk
2-year OS	92%	92%
3-year OS	77%	86%

Kapoor *et al*. Blood. 2009;114:518-521.

Bortezomib (± IMID's) in newly diagnosed MM with high-risk cytogenetics

- **Btz-Dex:** Partially overcome high risk*, *& superior to VAD (CR & PFS)*[1]
- **Btz-TD**: Overcome high risk, *& superior to TD (CR & PFS)* [2,3]
- **Btz-Len-Dex** : high CR[4]
- **TT3:** Overcome del P53 and FGFR3+ particlualry in low risk (GEP)[5]

* No significant differences with Standard Risk…… del (17p) ?

CR: (40%-17%)[1] (58%- 33%)[2] (42-5%)[3]

PFS (33 vs 24 m)[1] (Btz > TD p 0,03)[2]

1. Harousseau et al ASH 2009 (abstr 353); Avet loiseau ASH 2009 (abstr 957)
2. Cavo ASH 2009 (Abst 351)
3. Rosiñol ASH 2009 (Abst 130)
4 Richardson ASH 2008 (Abst 92)
5 Barlogie BJH 2009; 147: 347

Should we recommend stratification according to Risk factors?

- Novel agents can overcome the initial adverse prognosis of high-risk cytogenetics (not so clear for del 17p)……..Nevertheless, limited number of patients and few studies with PFS.

- Premature to mandate specific therapies based on cytogenetics. Moreover, the more intensive therapies selected for high-risk patients may be of even greater benefit to standard-risk cases.

- Large Clinical trials: enrol both high- and standard-risk patients; perform a comprehensive genetic analysis up-front…..to identify patients benefiting most from each treatment.

Potential options for patients with High Risk cytogentics

- Experimental pilot trials:
  - Targeted therapy: In t(4;14) to add a FGFR KI to an efficient scheme (BRD).
  - Combination of experimental drugs with a complementary mechanism of action (e.g., Hsp90 or HDAC inhibitors) plus Prot.Inh and/or IMiD.

- Outside of clinical trials:
  - No VAD + ASCT
  - Schemes based on two novel agents (particularly Btz) plus corticosteroids and/or one alkylating agent….BRD or BRDC +/- ASCT

- The role of ASCT and RIC-Allo should be revisited in the era of novel agents

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Transplant candidate patient:
standard treatment until now

Induction (VAD)

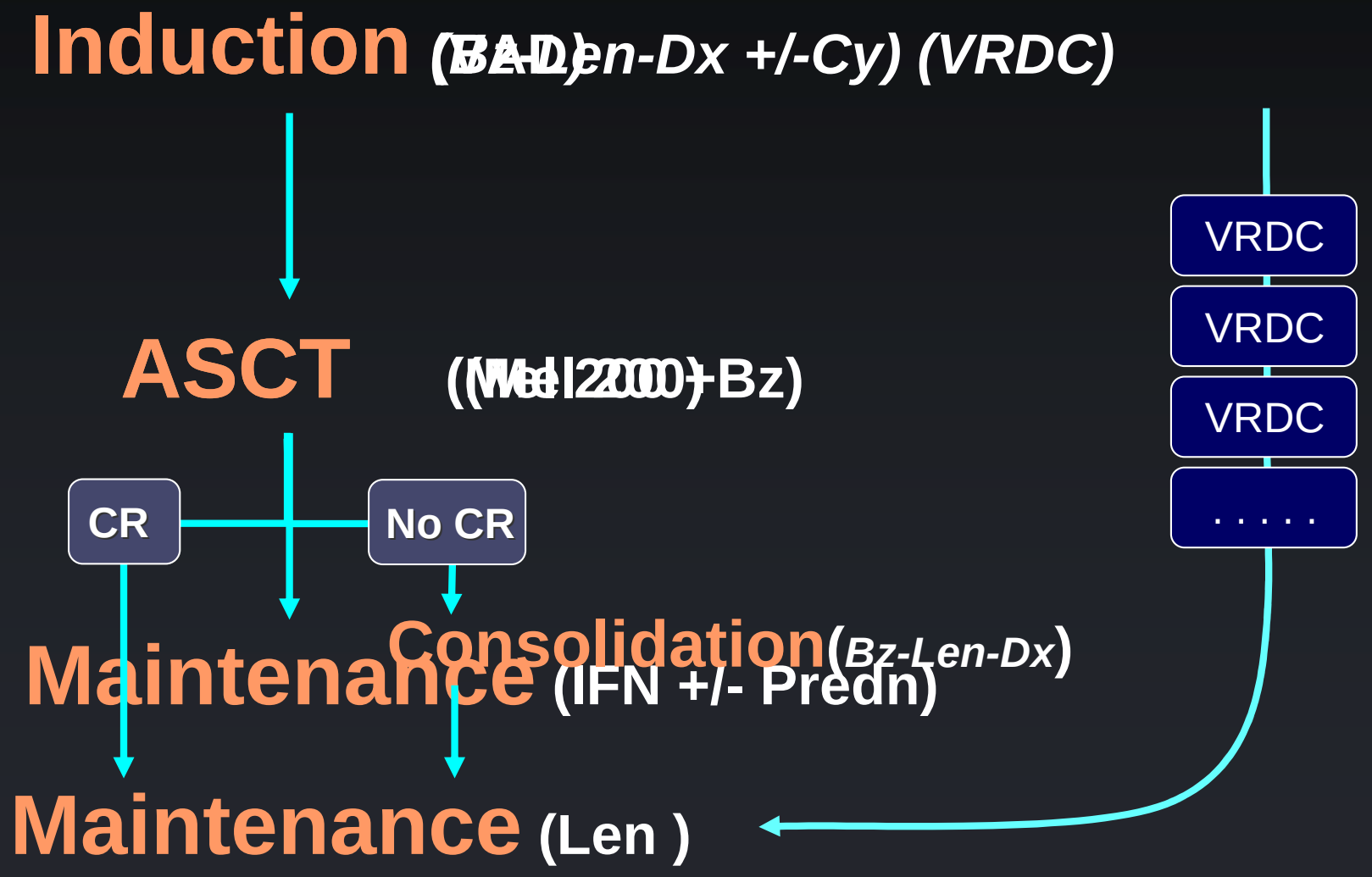
↓

ASCT (Mel 200)

↓

Maintenance (IFN +/- Predn)

Transplant candidate patient:
standard treatment from tomorrow



Final Thoughts and Reflections

- The progress in myeloma survival observed in the last decade has been possible only through the active commitment of the patients and doctors who participated in previous clinical trials.

  These showed a significant survival advantage for patients treated with drugs such as Bortezomib and Lenalidomide and this finally led to the approval of these agents for use in other patients.

- At present, several drugs, *such as histone deacetylase inhibitors, AKT inhibitors, novel IMIDs and proteasome inhibitors,* are looking for their place in the treatment armamentarium of MM, but……..

  only the continuous commitment to clinical research will lead to them being made available to all patients, thus eventually changing this incurable disease into either a chronic one or, let us dare to dream…, a curable disease.