Evolving Treatment Approaches in Transplantation-Eligible Myeloma Patients

J.F. San Miguel

University of Salamanca, Spain

Department of Haematology

University of Salamanca

Cancer Research Centre

What Should Be the Treatment Goal in MM Patients?

To search for an appropriate balance between treatment efficacy, toxicity, and costs

- In fit elderly patients (65-80y) and young ones with severe co-morbidities ……
  treatment goal should be to prolong survival and ensure QoL

- In very elderly patients (> 80-85y) …….
  to ensure QoL and avoid additional costs of expensive treatments

- In young patients (< 65y) …In reference centers and large cooperative groups
  ……*to investigate therapeutic schemes with a cure on the horizon*

Long-term Follow-up of IFM, TT and SWOG Trials

- **Median OS**
  - IFM 99-02: NR
  - TT3: NR
  - TT2: 9.0 years
  - TT1: 5.7 years
  - IFM 90: 4.5 years
  - IFM 94: 4.3 years
  - S9321: 4.0 years
  - IFM 99-04: 3.9 years
- **Median EFS**
  - TT3: NR
  - TT2: 4.6 years
  - IFM 99-02: 3.4 years
  - TT1: 2.6 years
  - IFM 90: 2.5 years
  - IFM 94: 2.3 years
  - IFM 99-04: 2.0 years
  - S9321: 1.9 years

Improvement in 10-year OS estimates, from 20% to 30% in IFM90, IFM99, S9321, and TT1 and up to 50% in TT2.

Barlogie B, et al. J Clin Oncol. 2010;28:1209-1214.

For a 52-yr-old patient: is death at the age of 62-65 desirable?

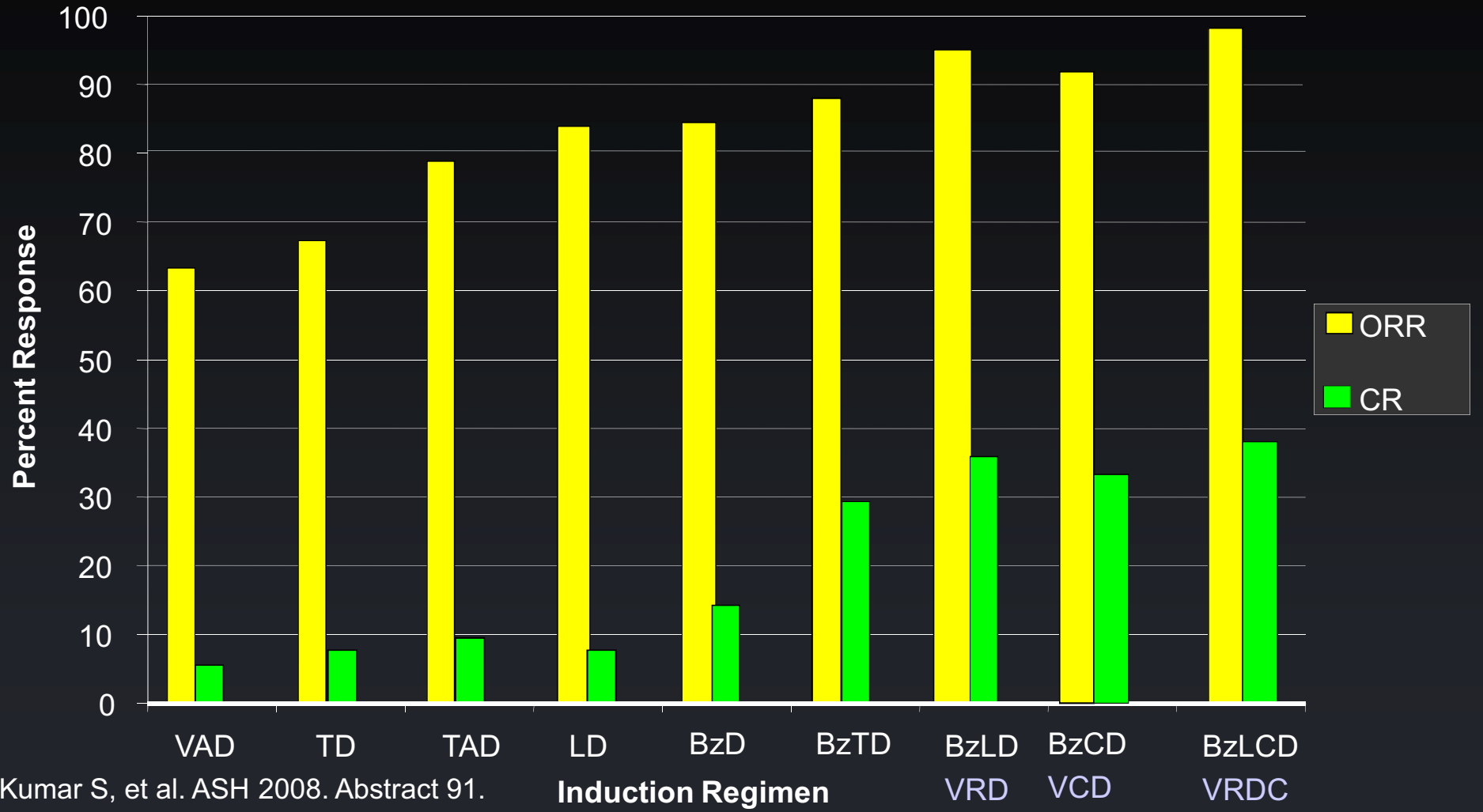
IFM94 (2/1 Trx), IFM99-04 (High risk.Tandem+IL6), S9321 (Trx/Chem), IFM99-02 (Stand.Risk: Tandem+Maint Thal/Pami), TT1 (Tandem+Ifn maint) TT2 (Tandem+Maint: Thal/nothing), TT3 (Tandem + VTD monthly 1y+ TD 2y)

Treatment of Young MM Patients

Controversial Issues

- What is the optimal induction treatment?
- Is there a role for HDT/ASCT?
- What is the value of maintenance treatment?
- Treatment stratification according to risk factors?
- Is there any role for allogeneic transplant?

Do We Have Something Better Than VAD or TD?: Response obtained with novel induction regimens



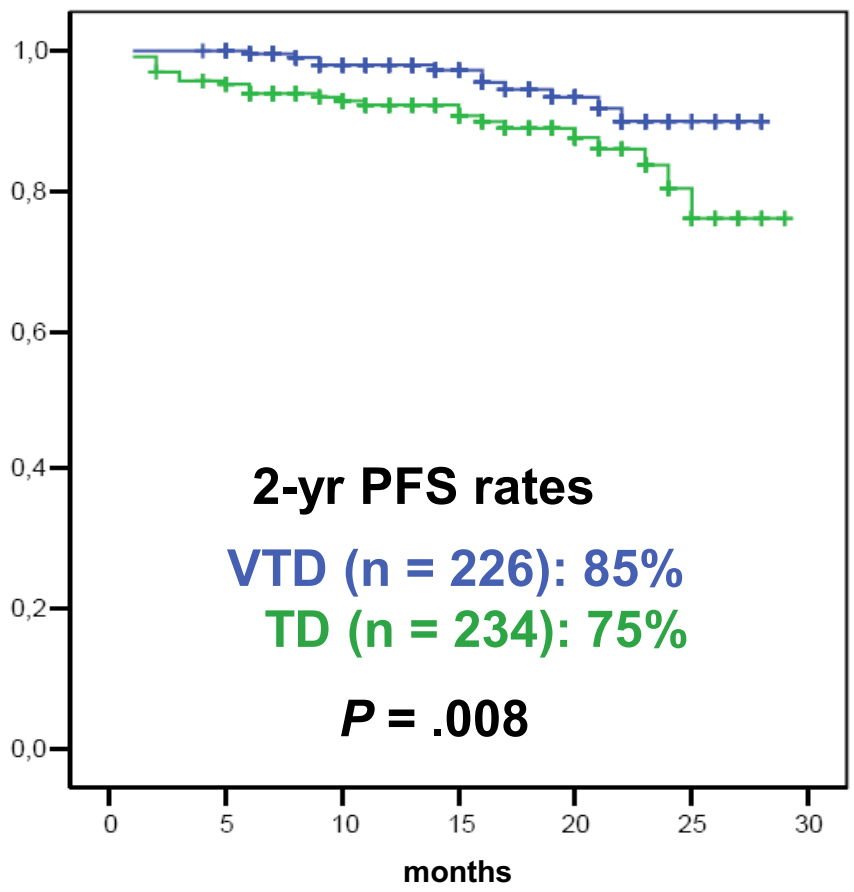
- Kumar S, et al. ASH 2008. Abstract 91.
- Stewart A, et al. EHA 2008. Abstract 205.
- Richardson P, et al. ASCO 2008. Abstract 8520.
- Kumar S, et al. ASH 2008. Abstract 93.
- Kumar S, et al. ASH 2009. Abstract 127: VRD, VCD, VRCD
- Einsel H, et al. ASH 2009. Abstract 131: VCD x 3 cycles
- Jakubowiak A, et al. ASH 2009. Abstract 132: VRDoxD

Bort/Dex vs VAD

- **Median EFS (*P* = .06)**
  - Bortezomib/dex: 36 months
  - VAD: 30 months

Harousseau JL, et al. J Clin Oncol. 2010;28:4621-4629.

VTD vs TD



Cavo M, et al. ASH 2009. Abstract 351.

VTD > TD in PFS (*P* = .01) Rosiñol L, et al. ASH 2009. Abstract 130.

Treatment of Young MM Patients

Controversial Issues

- What is the optimal induction treatment?
- **Is there a role for HDT/ASCT?**
- What is the value of maintenance treatment?
- Treatment stratification according to risk factors?
- Is there any role for allogeneic transplant?

Does ASCT Upgrade the Responses Obtained With Novel Agents?

	% Complete Responses and nCR		Reference
	Pre-ASCT	Post-ASCT (1st)	
. TD	14	40	Rosiñol L, et al. ASH 2009. 130.
. TAD	4	16	Lokhorst HM. Hematologica. 2008.
. CTD	21	65	Morgan G, et al. ASH 2009. 352.
. BzDx	21	35	Harousseau JL. ASH 2009. 353.
. BzTD	36	57	Cavo M, et al. ASH 2009. 351.
. BzTD	29	59	Rosiñol L, et al. ASH 2009. 130.

- ASCT is associated with long treament-free interval and good QoL

Induction regimens using novel agents followed by HDT/SCT are complementary, rather than alternative, treatment approaches

How to Improve the Efficacy of Conditioning Regimens

- **Melphalan 200 mg/m^2……** *the gold standard*

- **Melphalan + Bortezomib ……..** 70% ≥ VGPR (35% CR)[1]

  (1 mg/m^2 D -6, -3, +1 +4)

- **Melphalan + Bortezomib……** 51% ≥ VGPR[2]

  (1.3 mg/m^2 D-1 or +1)

- **Melphalan + Busulphan……** *may be superior*[3]

1. Roussel M, et al (IFM) Blood. 2010;115:32-37: superior CR vs matched patients conditioned with MEL only (35% vs 11%).
2. Lonial S, et al. Clin Cancer Res. 2010;16:5079-5086.
3. Lahuerta JJ, et al. Hematologica. 2010;Jul 27:[E-pub ahead of print].

ASCT upfront or at relapse IFM-DFCI 2009

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 oposite: Mel200 after long term esposure to novel agents*

The answer to this debate will come from the ramdomized trials comparing early vs late transplant

Treatment of Young MM Patients

Controversial Issues

- What is the optimal induction treatment?
- Is there a role for HDT/ASCT?
- **What is the value of maintenance treatment?**
- Treatment stratification according to risk factors?
- Is there any role for allogeneic transplant?

Maintenance Treatment With Thalidomide*

- Attal M, et al. Blood. 2006;108:3289-3294. **Thal > Pamidronate or nothing …… > EFS & OS**
- Spencer B, et al. J Clin Oncol. 2008;26:3735-3742. **Thal**(1y) **+ Pred > Prednisone…….. > EFS & OS**
- Barlogie B,et al. NEJM 2006;354:1021-1030. **Continous Thal…….. > EFS but not OS**
- Morgan G, et al. ASH 2009. Abstract 656. **cThal ……. > EFS but not OS**
- Lokhorst HM, et al. Blood. 2010;115:1113-1120. **cThal > IFN……. > EFS but not OS**

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

***Is lenalidomide the ideal maintenance agent?** IFM 2005-002. Attal M, et al. ASH 2009. Abstract 529; CALGB

Lenalidomide Maintenance After ASCT: CALGB 100104

568 pts: induction therapy plus ASCT

Maintenance	Len 10-15 mg	Placebo	
Median TTP	Not reached	25.5 months	
Number of events	29	58	*P* < .0001

Estimated HR: 0.42, indicating a 58% reduction in event risk in the len arm

Delay in TTP in len arm regardless of B-2M, prior thal or len therapy

Median f/u: 12 months

McCarthy PL, et al. ASCO 2010. Abstract 8017.

To Maintain the Response: Eradicate or Control the Residual Tumor Load

IFM 2005-02 -- Maintenance: Lenalidomide vs Placebo after ASCT

3-yr PFS from randomization (± 4 yrs from diagnosis): 68% for lenalidomide vs 34% for placebo

Attal M, et al. ASH 2009. Abstract 529.

Treatment of Young MM Patients

Controversial issues

- What is the optimal induction treatment?
- Is there a role for HDT/ASCT?
- What is the value of maintenance treatment?
- **Treatment stratification according to risk factors?**
- Is there any role for allogeneic transplant?

Bortezomib maintenance after ASCT

HOVON 65 & GMMG-HD4 (613 patients)

	Arm A	Arm B
Induction x3	**VAD**	**PAD**
ASCT 1 or 2	**ASCT**	**ASCT**
Maintenace x 2y	**Thal** 50mg d	**Btz** / 2w

-Btz achieves high nCR/CR during induction,

-**Btz maintenance** is well tolerated *(9% vs 31% discontinuations AEs)* **and is associated with additional responses.**

- Btz achieves superior PFS at 3y *(48 vs 42%, p= 0.04)* **and results in an improvement of survival** *(78 vs 71%)*, **particularly in patients with high risk cytogenetics and high B2m**

Median f/u: 40 months

Sonneveld et al ASH 2010, abstr 40

Treatment of Young MM Patients

Controversial issues

- What is the optimal induction treatment?
- Is there a role for HDT/ASCT?
- What is the value of maintenance treatment?
- **Treatment stratification according to risk factors?**
- Is there any role for allogeneic transplant?

Total Therapy: Toward the Cure

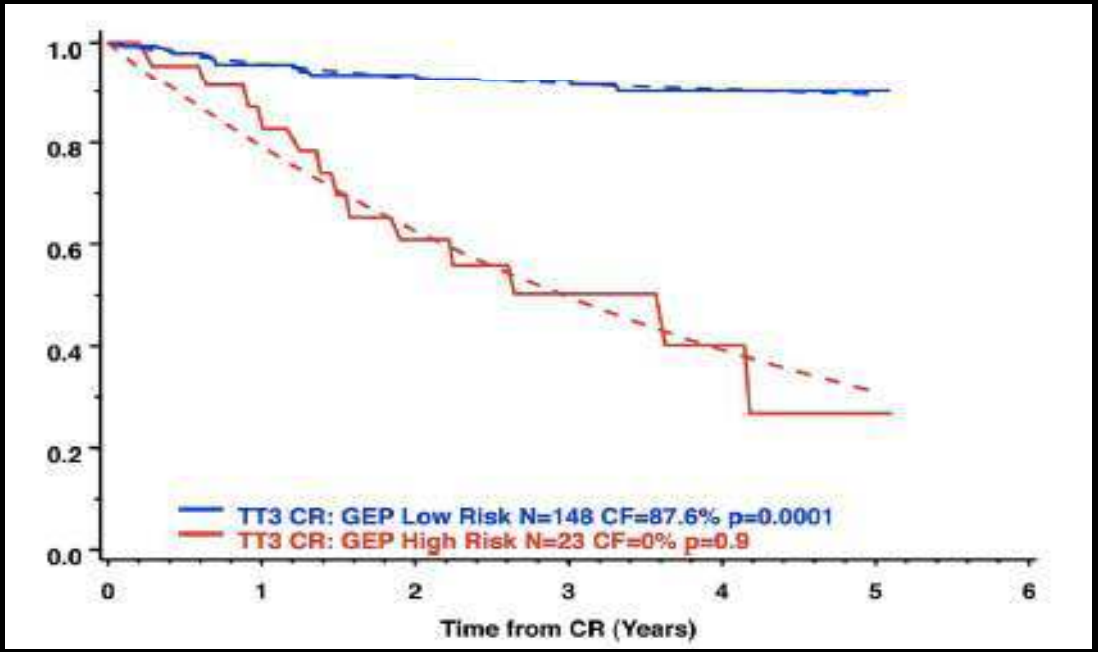
All active treatment tools through induction, consolidation and maintenance

Total Therapy 3 (303 pts) : VTD-PACE (x2)→ASCT (x2)→VTD-PACE (x2)→VTD (monthly during 1 y)→TD (2 y)

- CR & nCR: 63% & 86% **- EFS & OS at 4y: 71% & 78%**

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

Mathematical model of duration of CR in low-risk myeloma patients was able to predict a 55% cure fraction



Increase EFS from 52% (TT2) to 69% (TT3)

Nair B, et al. Blood. 2010;115:4168-4173.

Consolidate the Response: *Bortezomib + Thalidomide + Dex in patients that are already in ≥VGPR after ASCT*

- Patients (n=39) with CR or VGPR following ASCT Treatment : 4 consolidation cycles of Btz-Thal- Dex

- Results
  - IF-CR increased from 15% after ASCT to 49%
  - **Molecular Remissions** from 3% after ASCT to 18% after VTD

    -- **11 progressions occurred: *all among PCR+ patients***

Ladetto *et al JCO 2010, 28: 2077-84*

Consolidation

- with vTD: improved the response rate in 39% of patients (*Roussel et al ASH 2010, abstr 3041)*

-VTD vs TD : improved RR in 55% vs 37% of patients; CR: 60% vs 44% (*Cavo et al ASH 2010, abstr 42)*

- VTD vs TD : 5 vs 1 log reduction in tumor burden by RQ PCR (*Terragna et al ASH 2010 (Abstr 861)*

Intensive vs Gentle Approaches

Arguments in favor of intensive up-front treatment in young patients

- The patient is more fit to tolerate intensive and repeated therapies
- ASCT is associated with long treament-free interval and good QoL
- Relapses after MEL200 are sensitive to novel agents…… *but we don't know the long-term efficacy of the opposite (Mel200 after long-term exposure to novel agents)*

Gentle approach an option for low-risk patients ?

Consolidate the Response: *Bortezomib + Thalidomide + Dex in patients who are already in ≥ VGPR after ASCT*

- Patients (N = 39) with CR or VGPR following ASCT
- Treatment: 4 consolidation cycles of Btz-Thal-Dex
- Results
  - IF-CR increased from 15% after ASCT to 49% after VTD
  - **Molecular remissions** increased from 3% after ASCT to 18% after VTD

3y-OS: 89%

Median PFS: 60 mo

11 progressions occurred: *all among PCR-positive patients*

Median f/u:42m

Ladetto M, et al. J Clin Oncol. 2010;28:2077-2084.

Lenalidomide Maintenance After ASCT (IFM 2005-02)

PFS according to response to pre-consolidation superior with lenalidomide vs placebo

PR or SD

HR: 0.37; 95% CI: 0.25-0.58 ($P < 10^{-5}$)

VGPR or CR

HR: 0.54; 95% CI: 0.37-0.78 ($P = .001$)

Attal M, et al. ASH 2009. Abstract 529.

Treatment stratification according to Risk factors

If cure is the goal, the risk of under-treating low-risk patients may be a wrong philosophical approach, since they should be the first group of patients to achieve cure *(the ALL model)*

Actions to Achieve Cure

Use appropriate tools for evaluating treatment efficacy:

- CR > VGPR > PR > SD (Lahuerta JJ, et al. J Clin Oncol. 2008;26:5775-5782. Harousseau JL, et al. J Clin Oncol. 2009;27:5720-5726.)

- but….serological responses are insufficient

"The deeper the response, the longer the survival" (CML model)

- Evaluate MRD - BM level…...molecular and immunophenotyping
  - Outside the BM….. imaging techniques
- The use of sensitive techniques will avoid under- and overtreatment

In CML and ALL, these techniques have shown the need for prolonged treatment to eradicate MRD…....gain in survival

Impact on Survival of the Depth of Response After Induction Therapy (GEM 2005 Trial; N = 153)

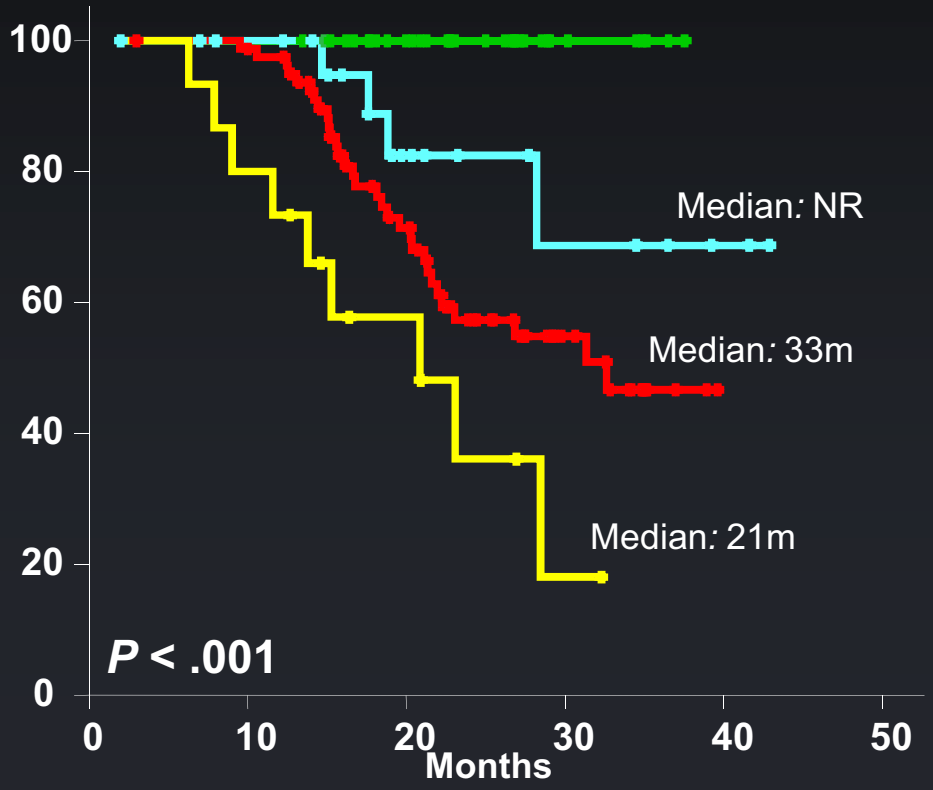
Immunophenotypic remission (n=33)

CR (IFx negative) (n=23)

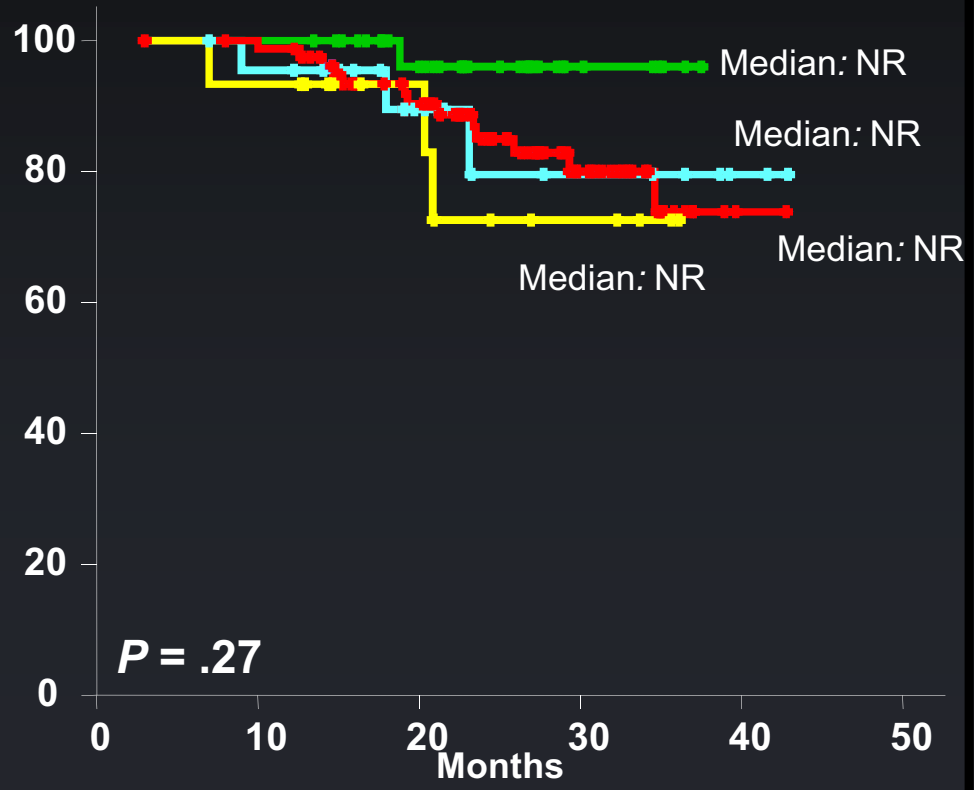
nCR + PR (n=82)

< PR (n=15)

TTP



OS



Mateos MV, et al. ASH 2009. Abstract 3.

Treatment Stratification According to Risk Factors

If cure is the goal, the risk of undertreating low-risk patients may be a wrong philosophical approach, since they should be the first group of patients to achieve cure *(the ALL model)*

Treatment stratification according to Risk factors

If cure is the goal, the risk of under-treating low-risk patients may be a wrong philosophical approach, since they should be the first group of patients to achieve cure *(the ALL model)*

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

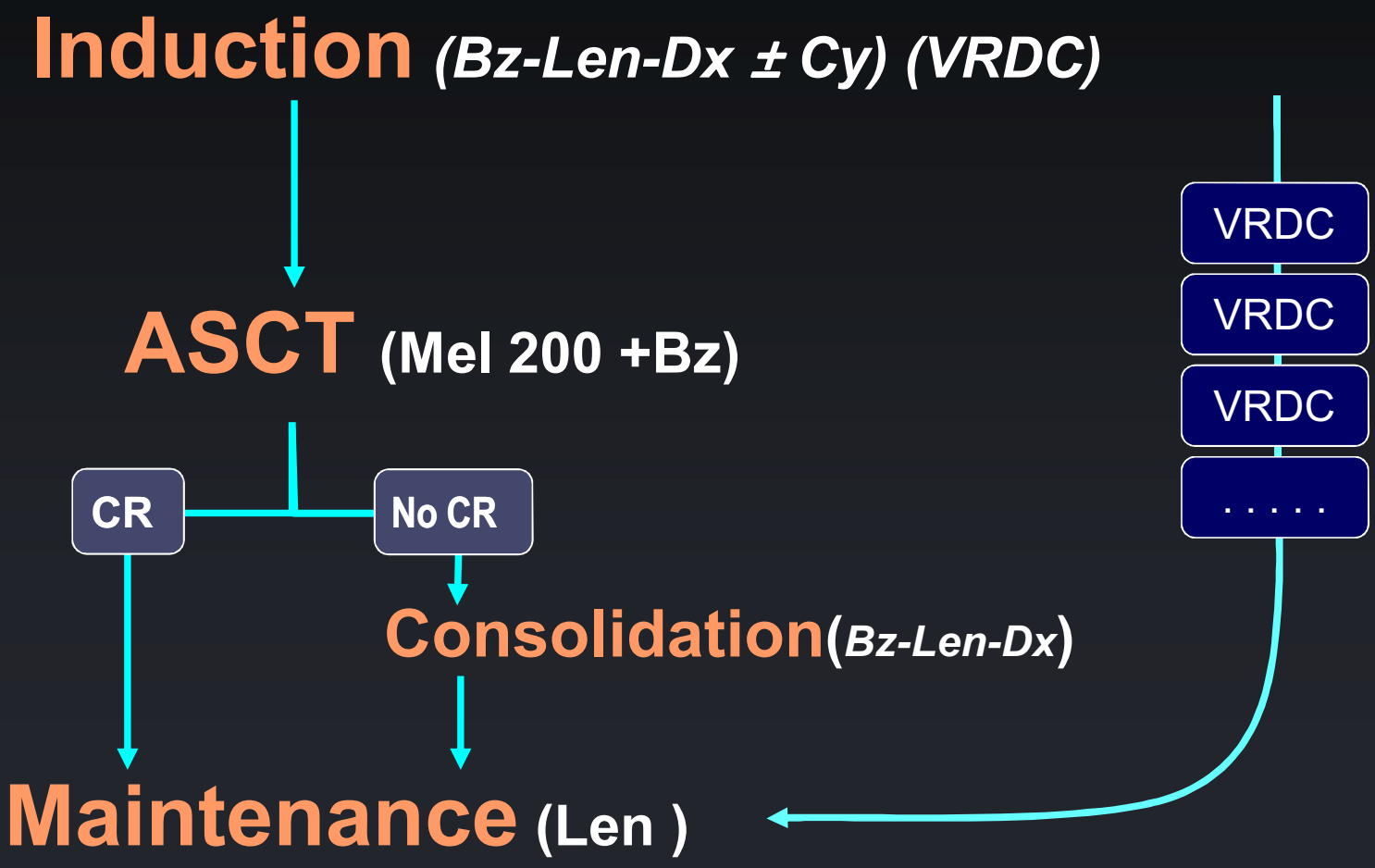
- Premature to mandate specific therapies based on cytogenetics. Moreover, the more intensive therapies selected for high-risk patients may be of even greater benefit to standard-risk cases

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

---

Effective treatment may be not a matter of dose intensity…… but of dose density

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.