

Impact of Complete Response in Multiple Myeloma

Jean-Luc Harousseau



Intergroupe Francophone du Myélome

BACKGROUND

- Before HDT, it was not possible to demonstrate the prognostic impact of CR achievement since CR was such a rare event with CC
 - < 5% avec MP
 - < 10% avec VAD
- CR even did not exist in response assessment classifications
- The increase of CR rate with HDT and more recently with novel agents has been associated with better outcomes
- However this question remains controversial

• Definition of CR

- Prognostic value of the depth of response
- Is the impact of CR identical in all patients ?
- Which level of CR is clinically relevant ?

EBMT Criteria

J. Blade Br J Haematol 1998

- Mostly Based on serum and urine M-component assessment + BM evaluation and Immunofixation for CR
 - No impact of Bone Disease Assessment
 - Response must be sustained for a minimum of 6 weeks
- CR**
- Negative Immunofixation (B + U)
 - < 5% plasma cells in BM
- PR**
- $\geq 50\%$ reduction in S M-component
 - $\geq 90\%$ (or < 200 mg/24H) reduction of ULC
- MR**
- 25-49% reduction in S M-component
 - 50-89% reduction in U LC

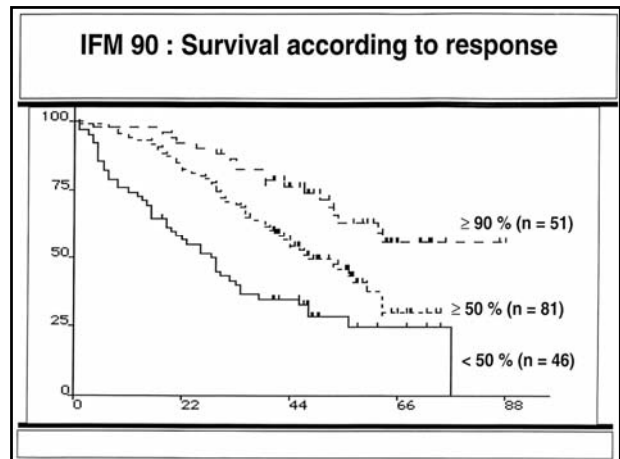
International Uniform Response Criteria - B. Durie Leukemia 2006

Stringent CR	CR + Normal FLC ratio No clonal cells in BM (IHC or IF)
CR	Negative IF (B + U) < 5% plasma cells in BM
VGPR	Positive IF but no M-component (or $\geq 90\%$ reduction) in the blood and U M-protein level < 100 g/24H)
PR	Same as EBMT

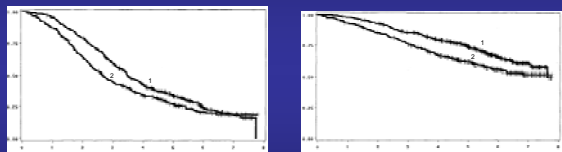
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- **High Dose Therapy**
- **Conventional Dose Therapy**
- **Relapsed MM**



**CR/VGPR vs PR
IFM 99 trials (double ASCT)**

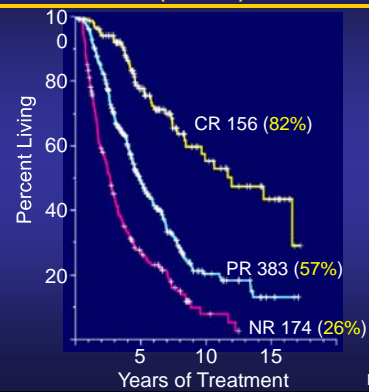


EFS

OS

Harousseau JCO in press

**Survival according to best response
(% ASCT)**



M. Wang Ash 2006

**Correlation between CR after ASCT
and OS/ PFS
Metaanalysis of 21 studies
(Van de Velde H – Haematologica 2007)**

- 10 prospective
 - 11 retrospective
- } 4990 pts
- **Significant correlation between maximal response and outcome**
prospective studies (< 0.00001)
retrospective studies (< 0.00001)

- **High Dose Therapy**
- **Conventional Dose Therapy**
- **Relapsed MM**

ECOG E 9486

- 653 pts treated with conventional chemotherapy
- ± IFN α or HD cyclophosphamide

	CR N = 85	PR N = 335	p. Value
Median OS from the date of objective response	5.1 yr	3.3 yr	< 0.0001
Median OS for pts who survived longer than 2 years	3.6 yr	2.4 yr	0.006

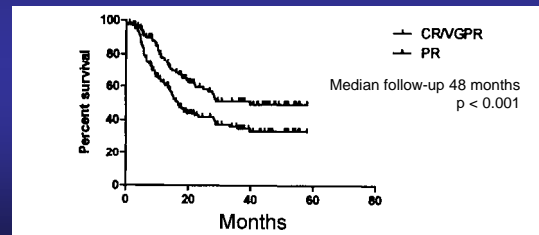
Kyle RA, Cancer 2006

VISTA trial (VMP arm) CR is associated with improved long-term outcomes

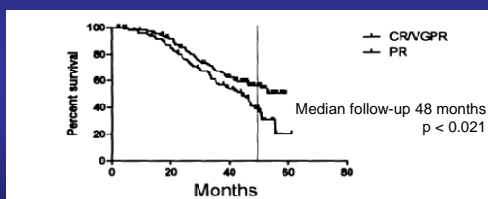
	Hazard ratio, p-value	
	CR vs PR	CR vs <PR
TTP	0.45, p=0.004	0.31, p=0.0001
TNT	0.46, p=0.0004	0.27, p <0.0001
TFI	0.38, p <0.0001	0.21, p <0.0001
OS	0.82, p=0.50	0.41, p= 0.003

- High Dose Therapy
- Conventional Dose Therapy
- Relapsed MM

MM009 – MM010 Lenalidomide arm PFS



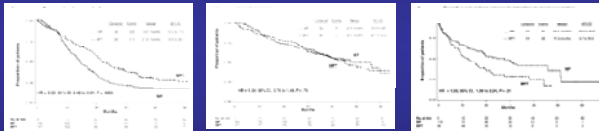
MM009 – MM010 Lenalidomide arm Overall survival



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Impact of CR on OS depends on salvage treatment at relapse MPT (Italian Study)

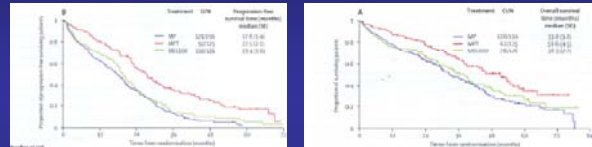
PFS OS OS from relapse



Palumbo Blood 2008

Prognostic impact of CR is related to age Intensive treatment (IFM 99/06 age 65-75)

PFS OS

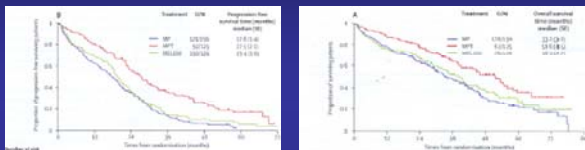


MP N=196 IDM N=126

Best response at 12 months		
CR	2%	17%
CR+VGPR	7%	41%
Median PFS	18 m	19 m
Median OS	33 m	38 m

Impact of CR may depend on age (IFM 99/06 patients aged 65-75)

PFS OS



MP N=196 IDM N=126

Best response at 12 months		
CR	2%	17%
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Prognostic Impact of CR is related to age

- Randomized trial comparing Thal/Dex vs MP in 289 elderly patients (median age 72)

	Thal/Dex	MP	p
RR	68%	50%	0.0023
CR-VGPR	26%	13%	0.0066

Higher toxicity particularly in patients >75 years and with poor PS

Ludwig H Blood 2009

Prognostic Impact of CR is related to age

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	Thal/Dex	MP	p
RR	68%	50%	0.0023
CR-VGPR	26%	13%	0.0066
PFS m	18.7	20.7	0.2
OS m	41.5	49.4	0.024

Higher toxicity particularly in patients >75 years and with poor PS

Ludwig H Blood 2009

Some patients without CR can be long-term survivors

-Pineda-Roman M et al, Br J Haematol 2006

Arkansas TT2 → 668 pts including 56 pts with prior MGUS Smoldering MM or solitary plasmacytoma

	De novo MM N = 612	« Secondary » MM N = 56
CR	48%	22%
4-yr EFS	56%	54%
4-yr OS	70%	65%

→ CR achievement is less important for survival in patients with prior History of « benign » gammopathy

In some patients with poor prognosis CR achievement is not related with better survival

- Some patients with aggressive MM may achieve CR and yet relapse rapidly = t(4;14)
- Prognostic impact of serum free light chains rapid reduction (Van Rhee, Blood 2007)

Baseline Sflc > 75mg/L is associated with

* poor prognosis parameters ($\beta 2m$, LDH, Bm plasmacytosis, creatinine)

* higher CR rate (37% vs 20%)

* but inferior 2-yr EFS (73% vs 90%) and OS (76% vs 91%)

Prognostic impact of CR+VGPR achievement according to ISS (IFM99 trials)

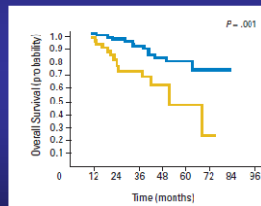
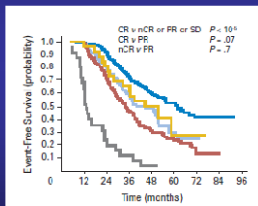
	CR + VGPR	<VGPR	p-value
ISS 1	N=195	N=159	
5-yr EFS	39 %	35 %	0.210
5-yr OS	82 %	75 %	0.280
ISS 2	N=152	N=119	
5-yr EFS	36 %	20 %	0.0009
5-yr OS	76 %	55 %	<0.0001
ISS 3	N=74	N=62	
EFS (median)	2.6y	1.3y	0.009
OS (median)	5.9y	2.6y	0.0065

Prognostic impact of CR+VGPR achievement according to IFM staging system (IFM 99 trials)

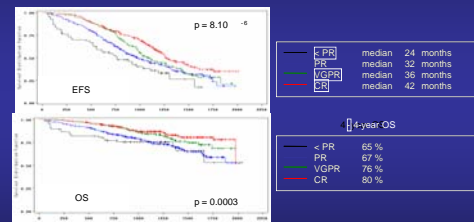
	CR + VGPR	<VGPR	p-value
$\beta 2m < 4mg/L$ no t(4;14) and no del(17p)	N= 121	N= 116	
5-yr EFS	42.5 %	33. %	0.038
5-yr OS	79 %	75 %	0.191
t(4;14) and/or del(17p)	N= 47	N= 50	
5-yr EFS	12.5%	2.2 %	0.0003
5-yr OS	48 %	25.2 %	0.0052

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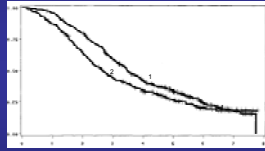
INFLUENCE OF RESPONSE OBTAINED AFTER HIGH-DOSE THERAPY (Pethema)



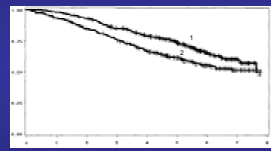
Impact of Overall Response on EFS and OS in IFM 99 trials



CR/VGPR vs PR IFM 99 trials (double ASCT)



EFS



OS

Harousseau JCO in press

Prognostic Impact of CR is related to treatment

- VISTA trial

	MPV n=337	MP n=331
CR	30%	4%
CR duration	24 m	12.8 m

The « quality » of CR is not the same !!

San Miguel NEJM 2008

MOLECULAR REMISSION

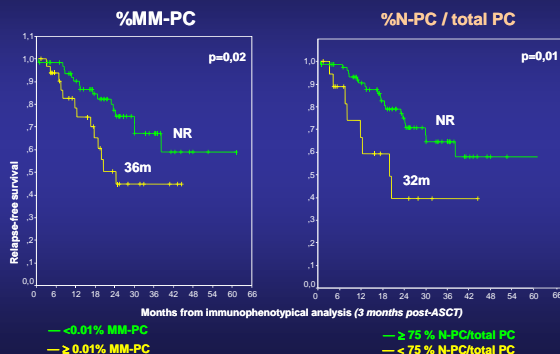
- Oligonucleotide real-time quantitative PCR
- Most sensitive technique to detect MRD
- Excellent correlation with long-term remission (Corradini JCO 1999, Blood 2003; Martinelli JCO 2000)
- Rare event (mostly after allogeneic SCT)
- Expensive and time-consuming

FLOW CYTOMETRY

Comparison with ASO-RQ-PCR (Haematologica 2005)

- Detects MRD at the level of 0.01 %
- Slightly less sensitive and specific
- Applicable in more patients (90% vs 75%)
- Less time-consuming

RFS: Impact of immunophenotyping at 3 months post-ASCT in 99 CR (IF-) patients



MRI

- Detects focal lesions prior to standard Bone Survey
- Has prognostic significance (N/1-7 FL/> 7 FL)
- MRI-CR states confers superior OS specially in patients > 7 FL
- Is a tool for diagnosis staging and monitoring in non secretory MM and plasmacytomas

Walker et al. J Clin Oncol 2007;25:1121-1128

CONCLUSIONS

- **Currently the requested level for CR definition is negative immunofixation**
- **In the near future the upper level (s-CR or MRI+ CR) might be useful due to the better efficacy of treatment (like in CLL)**
- **SFLC assay is necessary for response assessment in non-secretory MM but its role in all MM patients needs further evaluation**
- **Clinical relevance of Flow cytometry or molecular CR needs prospective evaluation**