# Best Upfront Treatment Strategy for Multiple Myeloma: Cure vs. Control?

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# MM: Goals of Treatment !
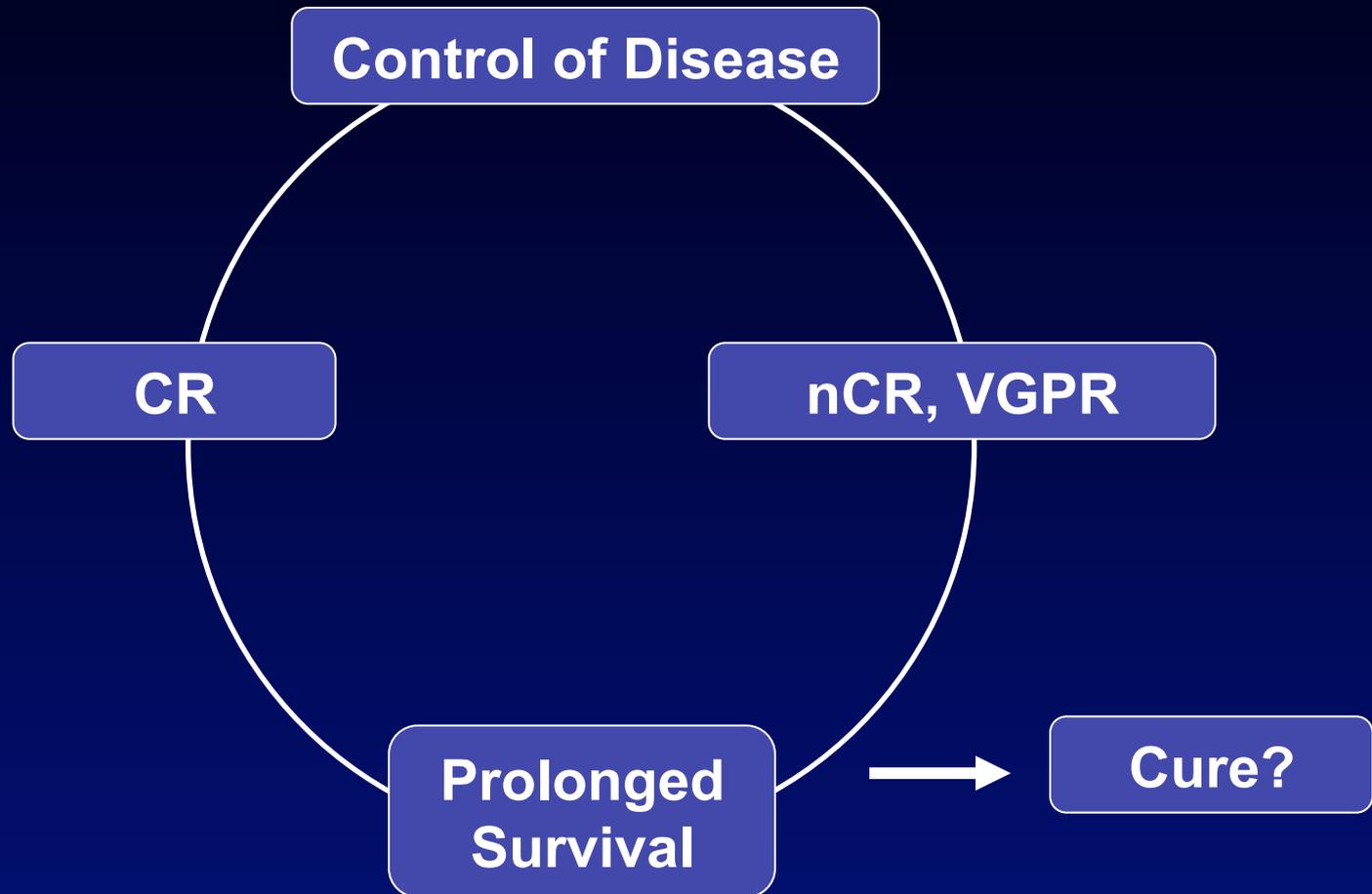
# Multiple Myeloma : Treatment Summary

Induction therapy

Consolidation (ASCT)

Maintenance therapy

# Treatment Algorithm

**Age ≤65 Yrs**
**Candidates for transplant**
**Induction therapy 4-6 cycles**

Response evaluation

CR/VGPR → Stem cell Transplant

PR → 2 more cycles → CR/VGPR

No /min → 2nd line Tt → Good response → Transplant
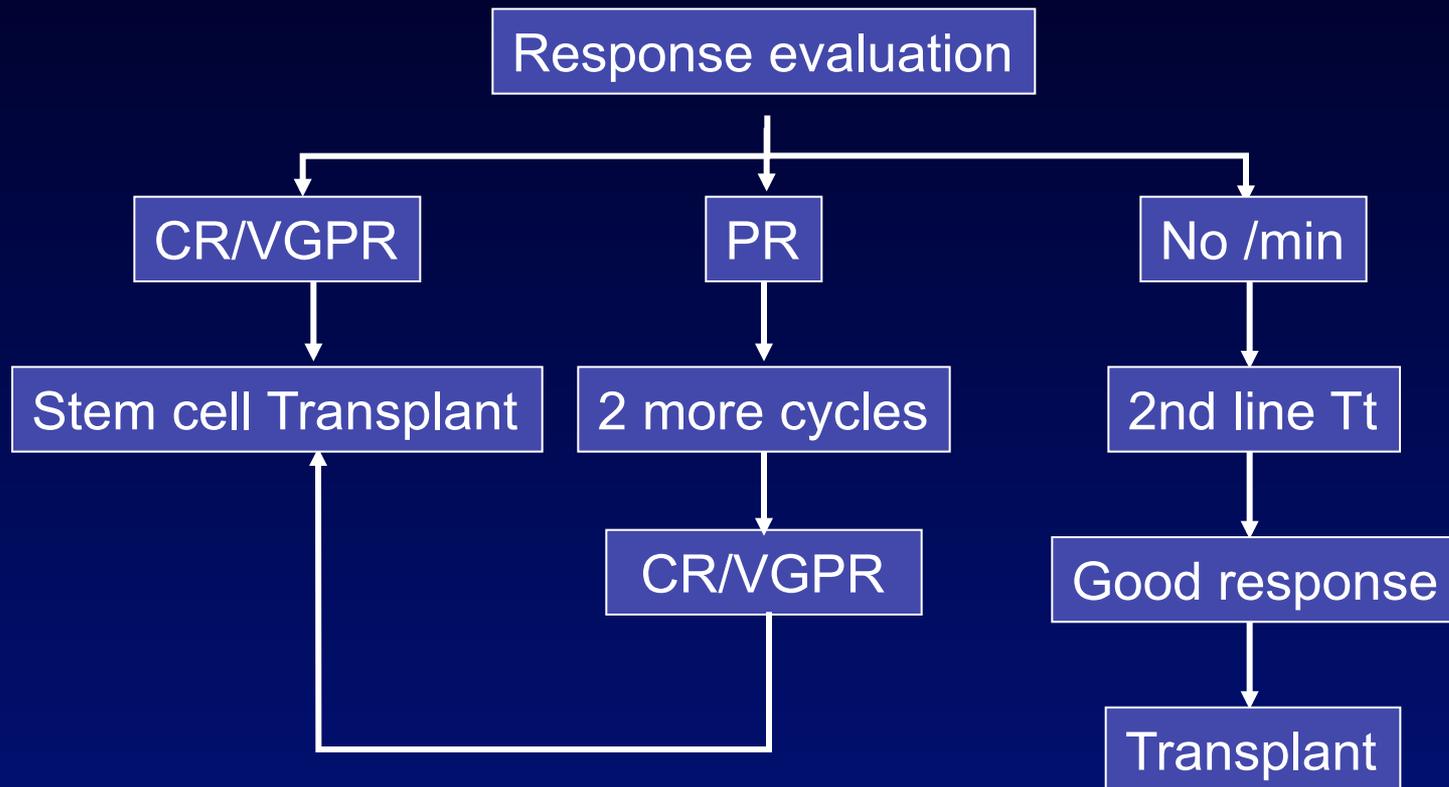
# Induction Therapy

| Regimen | # Pts | ≥PR (%) | ≥VGPR (%) | PFS | OS |
|---|---|---|---|---|---|
| Thal/dex | 235 | 63 | 43.8 | 14.9 mon | 68% @2 Y |
| Len/dex | 34 | 91 | 38 | 74% @ 2 Y | 91% @2 Y |
| Bort-dex | 52 | 66 | 31 | ng | ng |
| PAD | 65 | 97.1 | 50 | 83% @ 2Y | 92% @ 2Y |

Palumbo & Rajkumar, Leukemia 2009, JCO 2008,Blood 2005,Blood 2008,Hemtologica, 2006, Blood 2007

# Induction regimen prior to ASCT : Phase III studies

| Study | n | Regimen | Response | | | | OS (%) |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | | | Post induction (%) | | Post ASCT (%) | | |
| | | | nCR | VGPR | nCR | VGPR | |
| IFM (2010) | 240 | Vel-D | 14.8 | 37.7 | 35 | 54.3 | 81.4@3 Y |
| | 242 | VAD | 8 | 15.1 | 18.4 | 37.2 | 77.4@3Y |
| Cavo (2010) | 236 | VTD | 31.1 | 62 | 55 | 82 | 86@3Y |
| | 238 | TD | 1.0 | 28 | 41 | 64 | 84@3Y |
| Lokhorst (2008) | 201 | TAD | 3 | 33 | 16 | 49 | NR |
| | 201 | VAD | 2 | 15 | 11 | 32 | NR |
| Rajkumar (2010) | 214 | RD | 18 | 50 | NR | NR | 75@2Y |
| | 208 | Rd | 14 | 40 | NR | NR | 87@2Y |

JCO,2010; Lancet,2010;Hematologica,2008;Lancet Onclogy,2010

# Induction regimen prior to ASCT : Phase III studies

| study | n | Regimen | Response | | PFS |
|---|---|---|---|---|---|
| | | | Post induction (%) | Post ASCT (%) | |
| | | | CR | CR | |
| Pathema Group (2012) | 130 127 129 | VTD TD VBMCP/ VBAD/B | 35 14, P<001, 21,p<.01 | 46 24 38 | 56.2 mon 28.2 mon, p<.004 35.5 mon |

# Treatment for elderly patients
## Not a candidate for transplant!

| | MPT<br>n = 129 | MP<br>n = 126 | *P value* |
|---|---|---|---|
| CR | 15.6% | 3.7% | < 0.001 |
| VGPR | 29.3% | 11.0% | < 0.001 |
| PR | 68.9% | 47.6% | < 0.001 |
| Median TTP | 24.7 mo | 15.0 mo | < 0.001 |
| Median PFS | 21.8 mo | 14.5 mo | 0.004 |
| Median OS | 45.0 mo | 47.6 mo | 0.79 |

Palumbo A, et al. *Blood*. 2008;112:3107-3114.

# Treatment for elderly(2)

| Combination | Response rate (%) | CR rate (%) |
|---|---|---|
| Bortezomib +Mel +Pred | 70 | 30 |
| Len +Mel+Pred | 81 | 23.8 |
| Mel + Pred + Thal | 76 | 28 |

Lancet 2006;367:825-31, NEJM 2008;359:906-17,JCO 2007;25:4459-65

# Thal-dexa vs Len-dexa: a phase 3 study

|  | CR + VGPR (%) | PR(%) | NR/Prog. dis |
|---|---|---|---|
| Thal/dexa (n=34) | 32.4 | 38.2 | 29.3 |
| Len/dexa (n=35) | 37.2 | 40.0 | 22.8 |

Mukherjee et al,  ASH,2011

# Thal-dexa vs Len-dexa: a phase 3 study
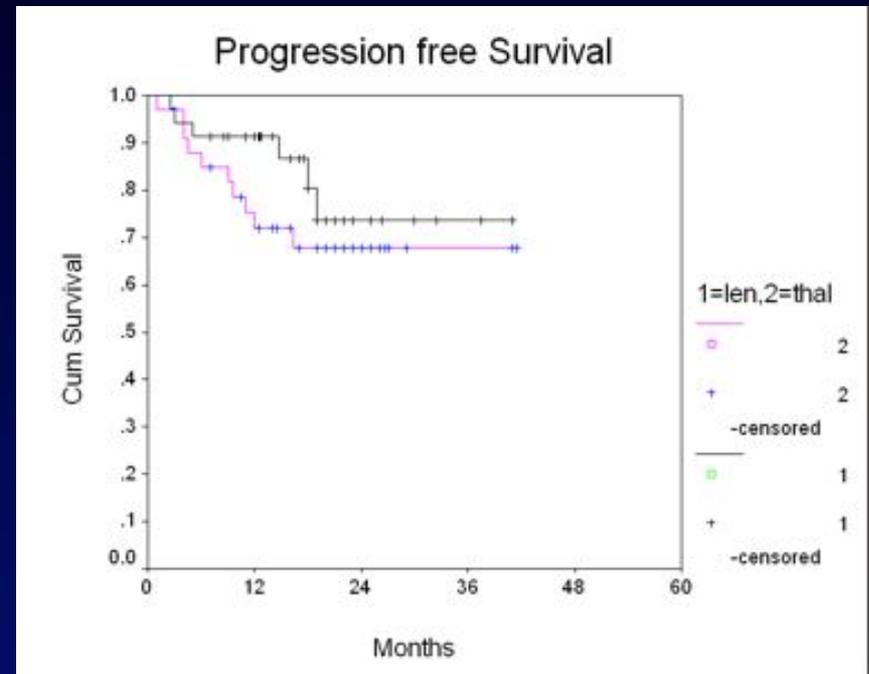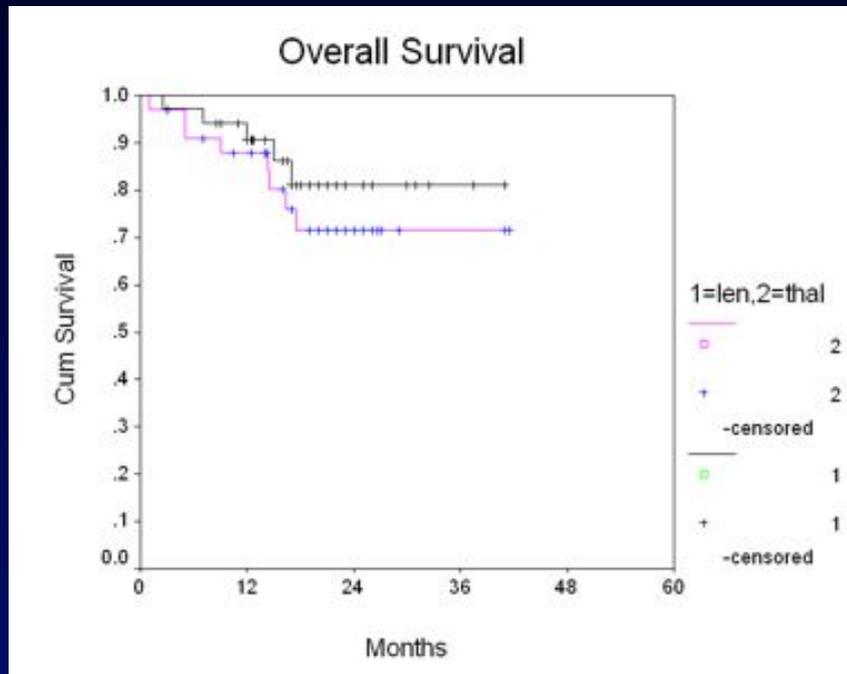


Mukherjee et al.  ASH2011

# Induction therapy : Summary

- No of drugs : 2 vs 3 vs 4 drugs
  - Response rates higher with more drugs
  - Higher PFS
  - Overall survival : ? Generally not different
  - Toxicity : higher with more drugs
- Suggestion
  - Risk based approach
  - Patients Preference

# Myeloma : Cytogenetics

| Risk Group | Cytogenetics | Median OS |
|---|---|---|
| Poor (25%) | t (4;14)<br>t (14;16)<br>-17p13 | 24.7 months |
| Intermediate(17%) | -13q14 | 42.3 months |
| Good (58%) | All others | 50.5 months |

Hyperdiploidy - Good, hypodiploidy - poor risk

Fonesca et al. Blood 2003;101:4569-75

# Risk score model for multiple myeloma: prediction of outcome

| Risk category (del13q14+ ISS) | n (%) | OS | P value | EFS | P | Response (CR+VGPR +PR) | P value |
|---|---|---|---|---|---|---|---|
| Low Risk (score ≥1) | 41 (58%) | 79% | | 55% | | 39 | |
| High Risk (score >1.0) | 30 (42%) | 53% | 0.004 | 29% | 0.002 | 19 | 0.001 |

Sensitivity: 73.5%; Specificity: 75%; Positive predictive value: 90%

# CR : Predictor of Survival (n=170)



AIIMS
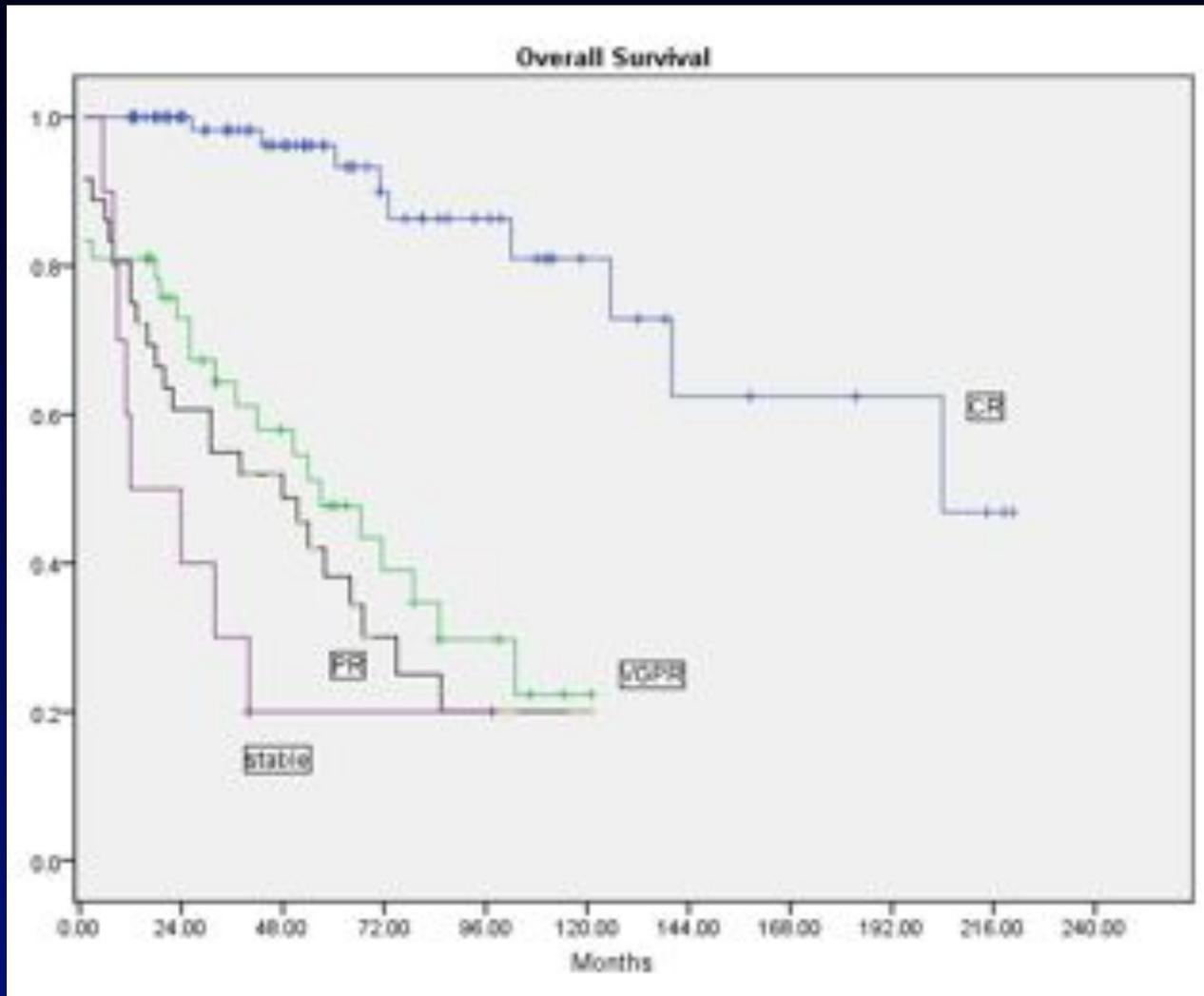
# CR : Predictor of Survival (n=170)

# Treatment Approach

| CR | |
|---|---|
| Yes | VGPR/PR |

| | |
|---|---|
| Maintenance | Consolidation with ASCT |

| | |
|---|---|
| Early relapse ASCT | Maintenance |
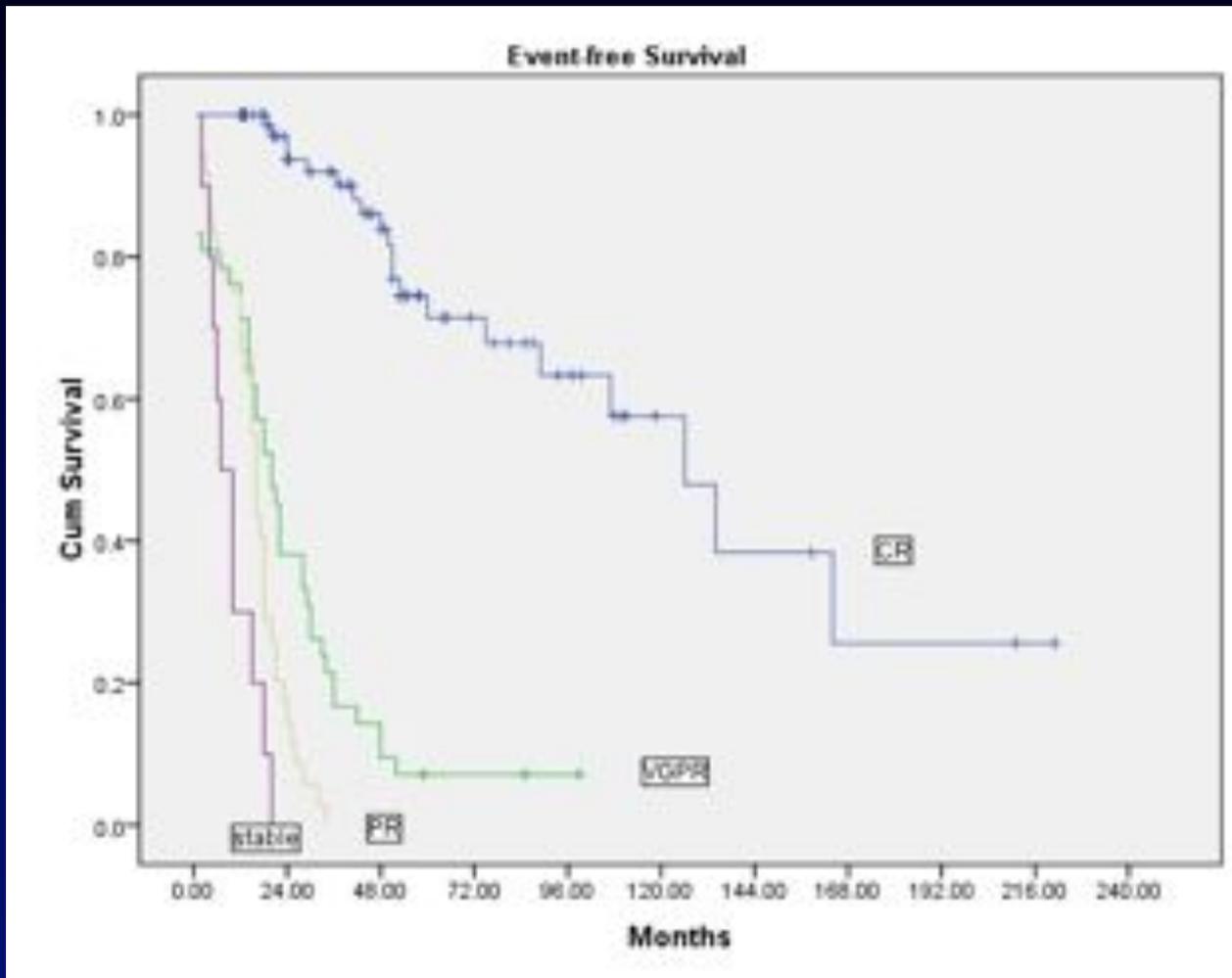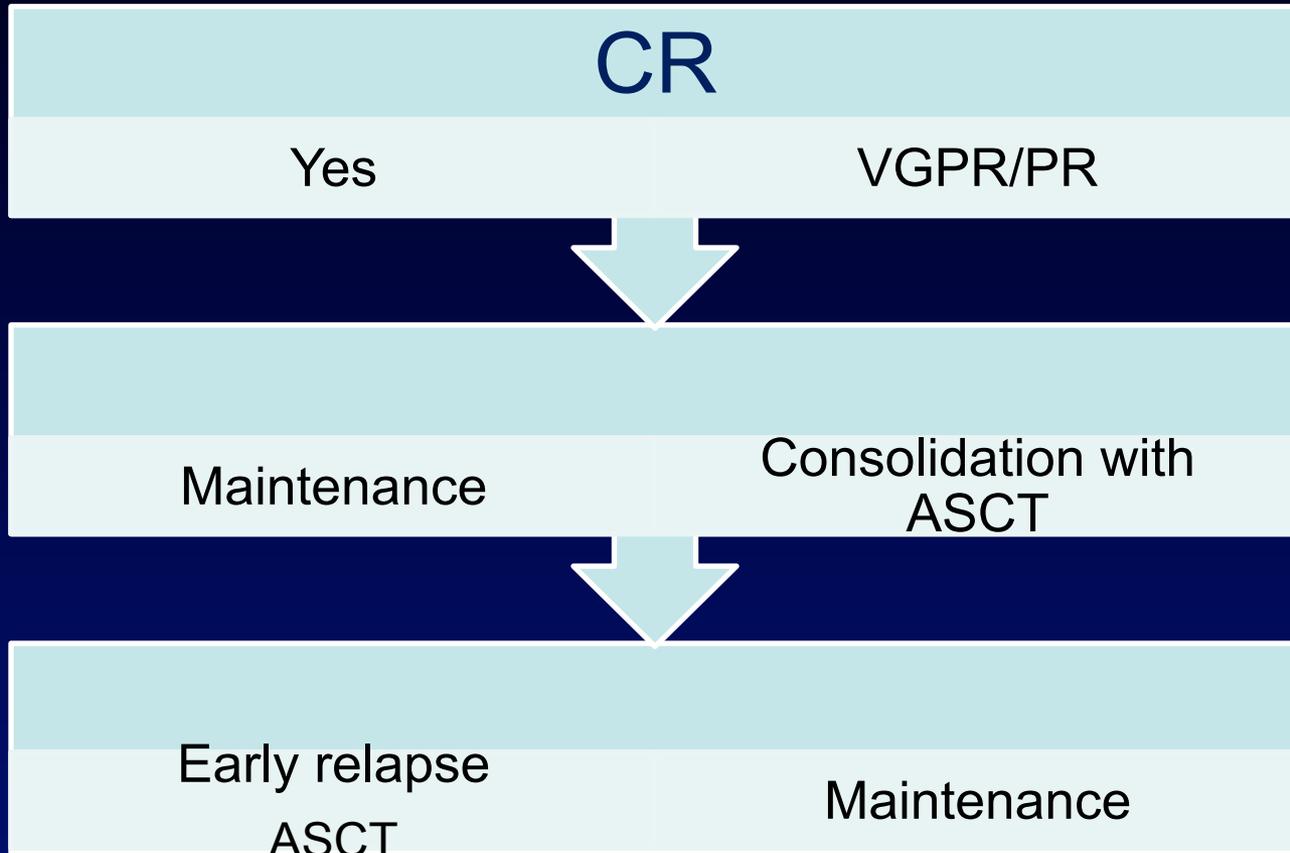
# Summary : Treatment approach

| Cure | Control |
| --- | --- |
| **Maximize Response Multidrug induction** | **VGPR/nCR/CR Regimens to keep disease under control** |
| **ASCT : Single/Double Morbidity/mortality** | **ASCT at relapse** |
| **Allogeneic Stem cell Tx Morbidity/mortality** | **-** |
| **Impaired QOL** | **QOL : maintained** |

# Impact of High-Risk Cytogenetic Risk Status on Outcome

| | High Risk | Standard Risk |
|---|---|---|
| > PR | 81% | 89% |
| CR + VGPR | 38% | 45% |
| PFS (mo) | 18.5 | 37 |
| TTP (mo) | 18.5 | 36.5 |
| OS | 92% | 92% |
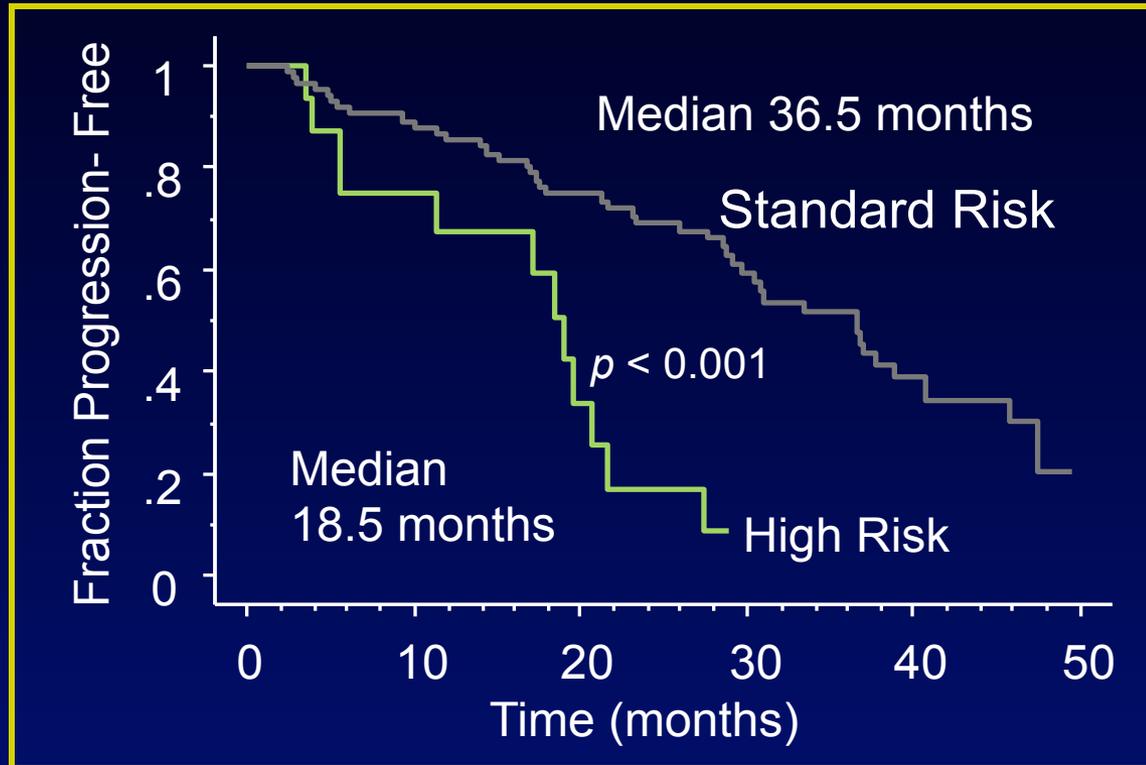


Kapoor MD, et al. *Blood*. 2008:112(11). Abstract 95.

# Outcomes for VMP Patients by Cytogenetic Risk*



**Event Free Survival**

Patients Without Event (%)

- Standard risk
- High risk

Time (months)

**Overall Survival**

Proportion Surviving

- Standard risk
- High risk

Time (months)
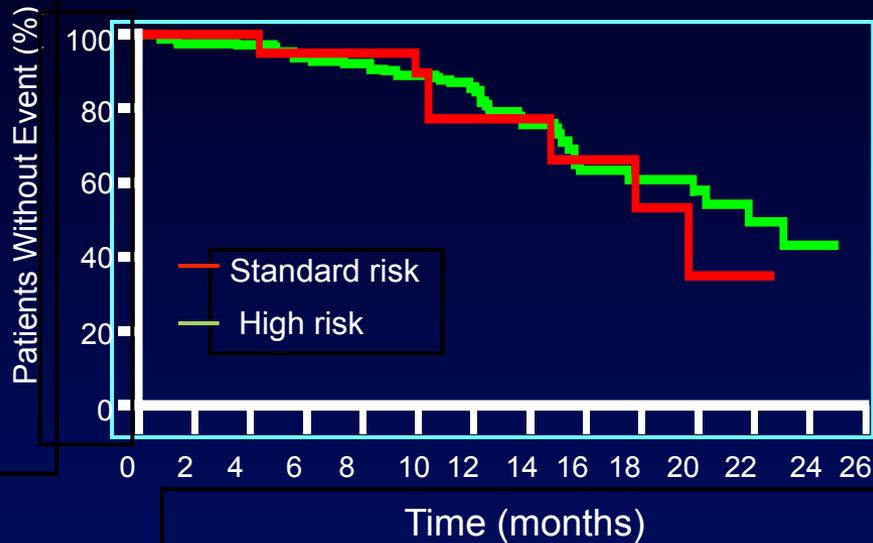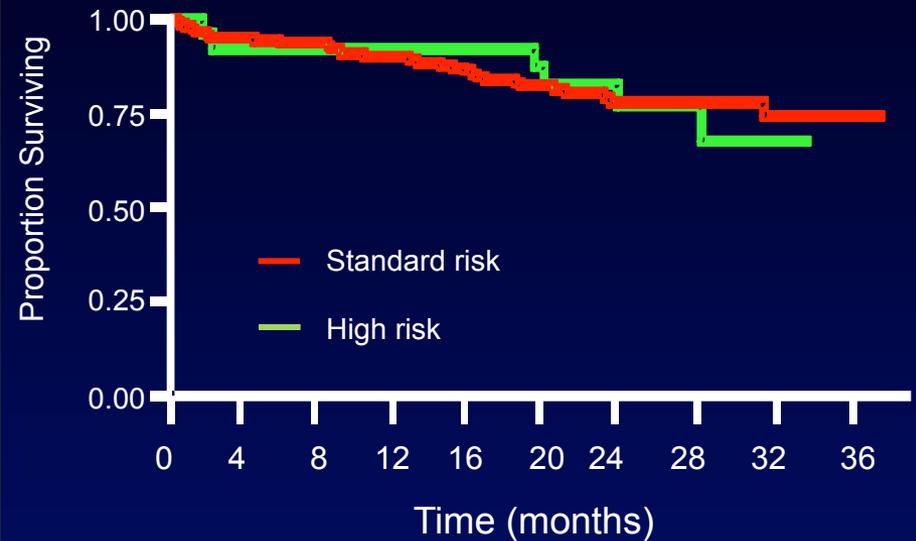
*Cytogenetics by FISH. High-risk: t(4;14), t(14;16), del(17p).

San Miguel JF, *et al. Blood*. 2008;112(11). Abstract 650.
Dimopoulos, et al. *Blood*. 2008;112. Abstract 1727.
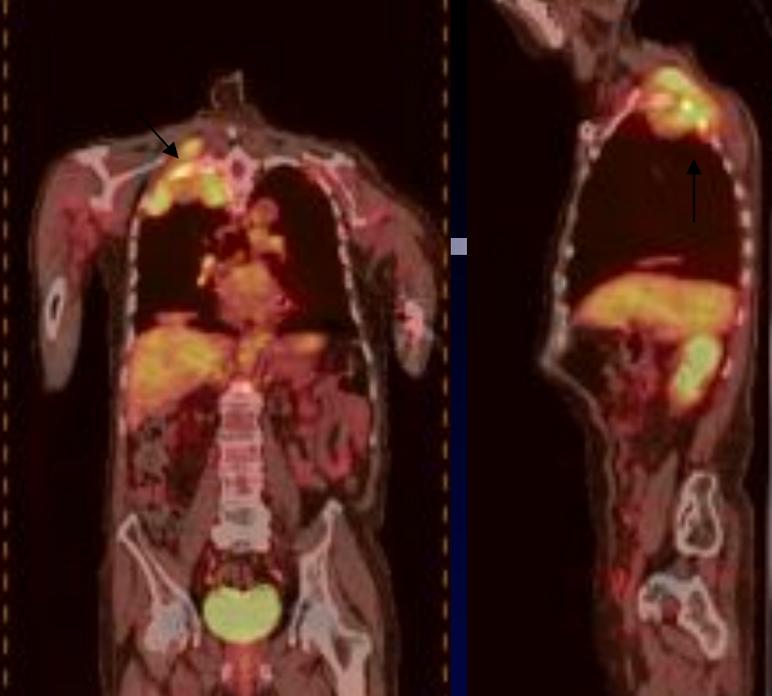
**Pre-treatment**
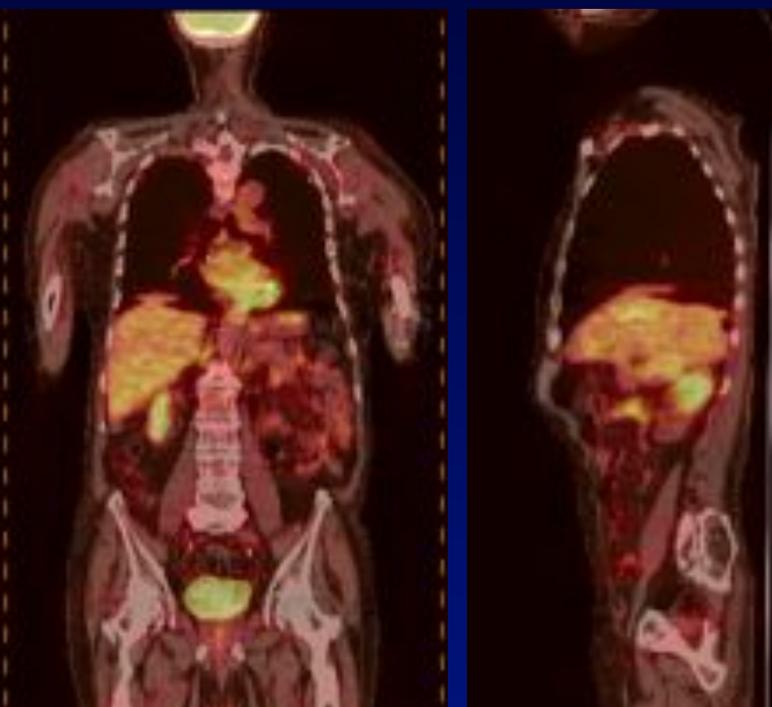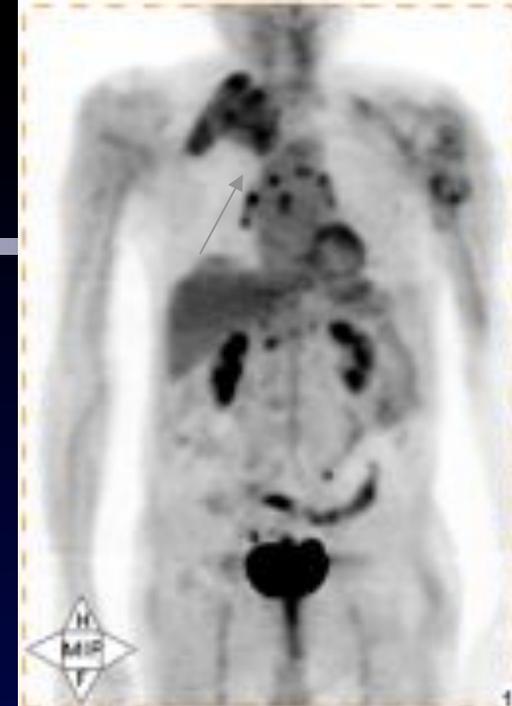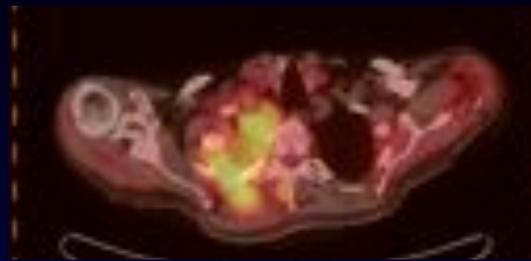
**Post Rx**

**Post treatment**
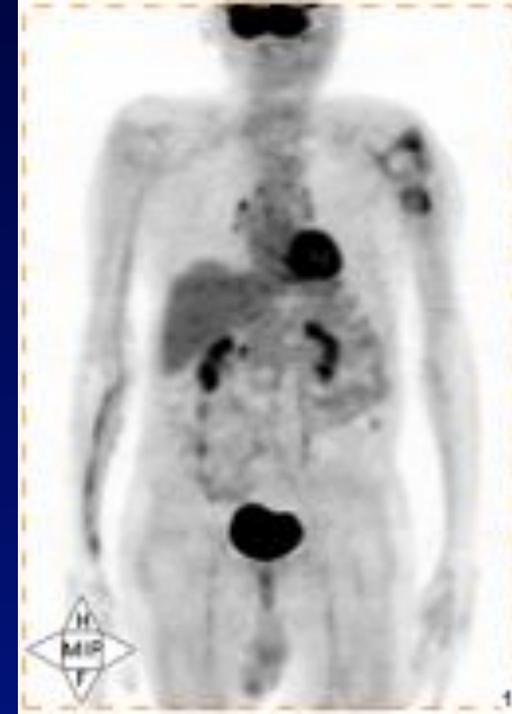
# Newer Agents in Clinical Trials

- **Proteasome inhibitors**
  - **Carfilzomib**
- **Immunomodulators**
  - **Pomalidomide**
- **HDAC inhibitors**
  - **Vorinostat with bortezomib**
- **Monoclonal antibodies**
  - **CNTO 328 (a-IL6) with bortezomib**
- **AKT inhibitor**
  - **Perifosine with bortezomib and dex**

# Free light chain (FLC) assay

|  | Normal values |
|---|---|
| Serum free kappa levels | 3.3 to 19.4 mg/dl |
| Serum free lambda levels | 5.7 to 26.3 mg/dl |
| k/λ ratio | 0.26 to 1.65 |
| k/λ Ratio <0.26 | Free Lambda chain |
| Ratio of 1.65 | Free kappa chain |

# Survival