Multiple Myeloma: Is It Time for Biomarker-Driven Therapy?

Saad Usmani, MD FACP

Director, Plasma Cell Disorders

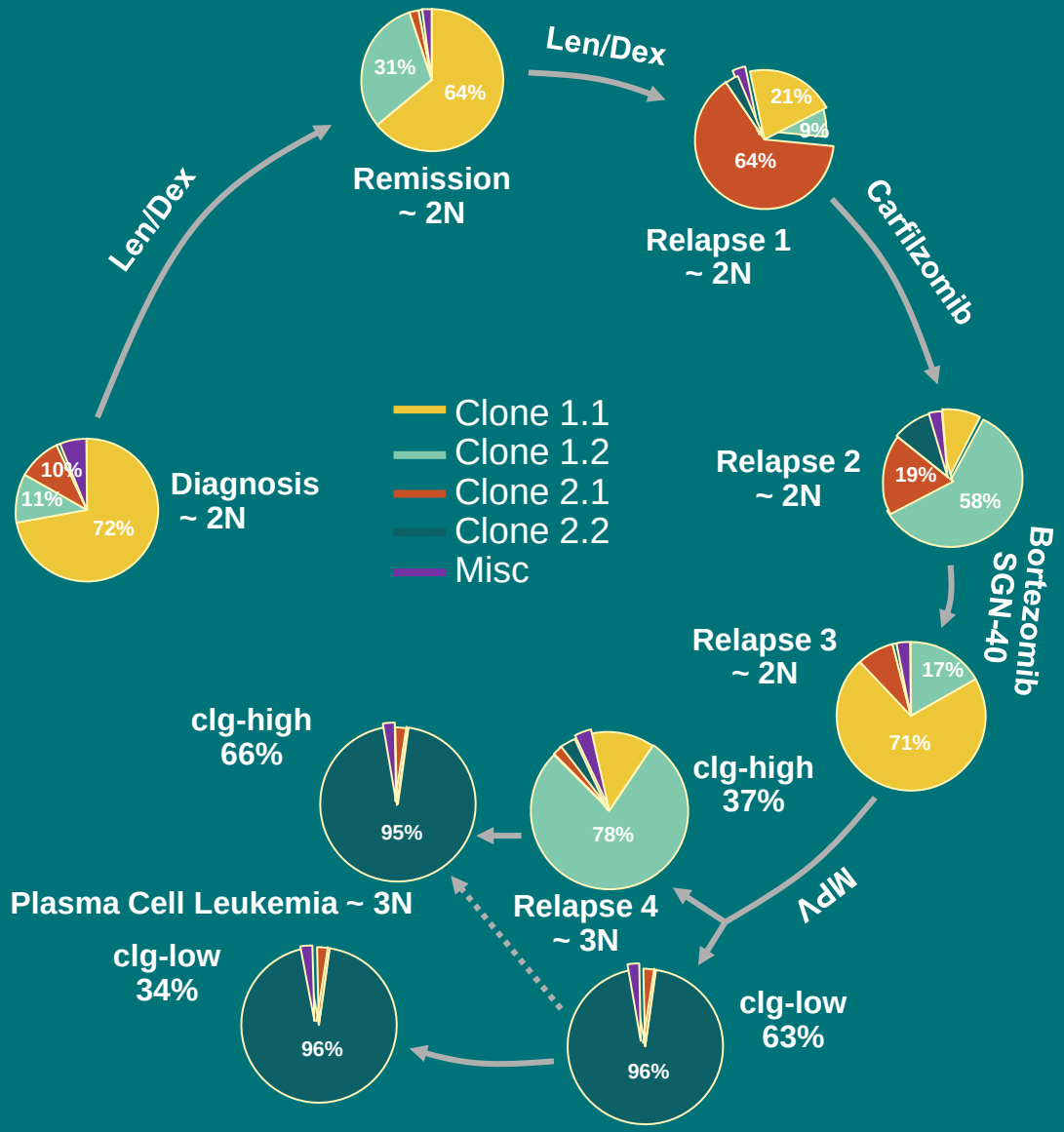
Director, Clinical Research in Hematologic Malignancies

Levine Cancer Institute

Multiple Myeloma(MM): Not One Disease

- MGUS to Active MM transition period is different among patients.
- Diagnosis is made at variable time-points during the transition, so degree of end organ damage is different.
- Management strategies are focusing on changing myeloma in to a chronic illness for majority of patients, probably curative for a subset. [Martinez-Lopez J et al Blood 2011;Usmani et al Leukemia 2012
- Advances in understanding myeloma biology has led to new therapeutic targets.

Multiple MM Clones Exist In the Same Patient



Keats JJ, et al. *Blood*. 2012;120:1067-1076.

Multiple MM Clones Exist In the Same Patient

- Multiple clones may be present at the time of diagnosis. The predominant clone may change over time, especially after sequential treatment rounds

- Hypothesis: effective treatment reduces or eliminates the dominant clone; however, other clones can still exist

- **Relapse can occur when:**
  - Existing clone no longer has to compete for space with the formerly dominant clone
  - Acquires additional mutation(s) providing a growth and/or survival advantage
- Speaks in favor of combination chemotherapy!

Keats JJ, et al. *Blood*. 2012;120:1067-1076.

Treated the same way, MM patients have different outcomes

	GRADE 1 Low-Risk	GRADE 2 Standard-Risk	GRADE 3 High-Risk
Parameters	ISS I/II low LDH No t(4;14), Del17p +1q21	Others	ISS II/III high LDH t(4;14)* Del 17p +1q21 GEP High Risk
Median OS	>10 years	7 years	2 years
% Patients	20%	60%	20%

Chng et al Leukemia 2013: IMWG Consensus on Risk Stratification

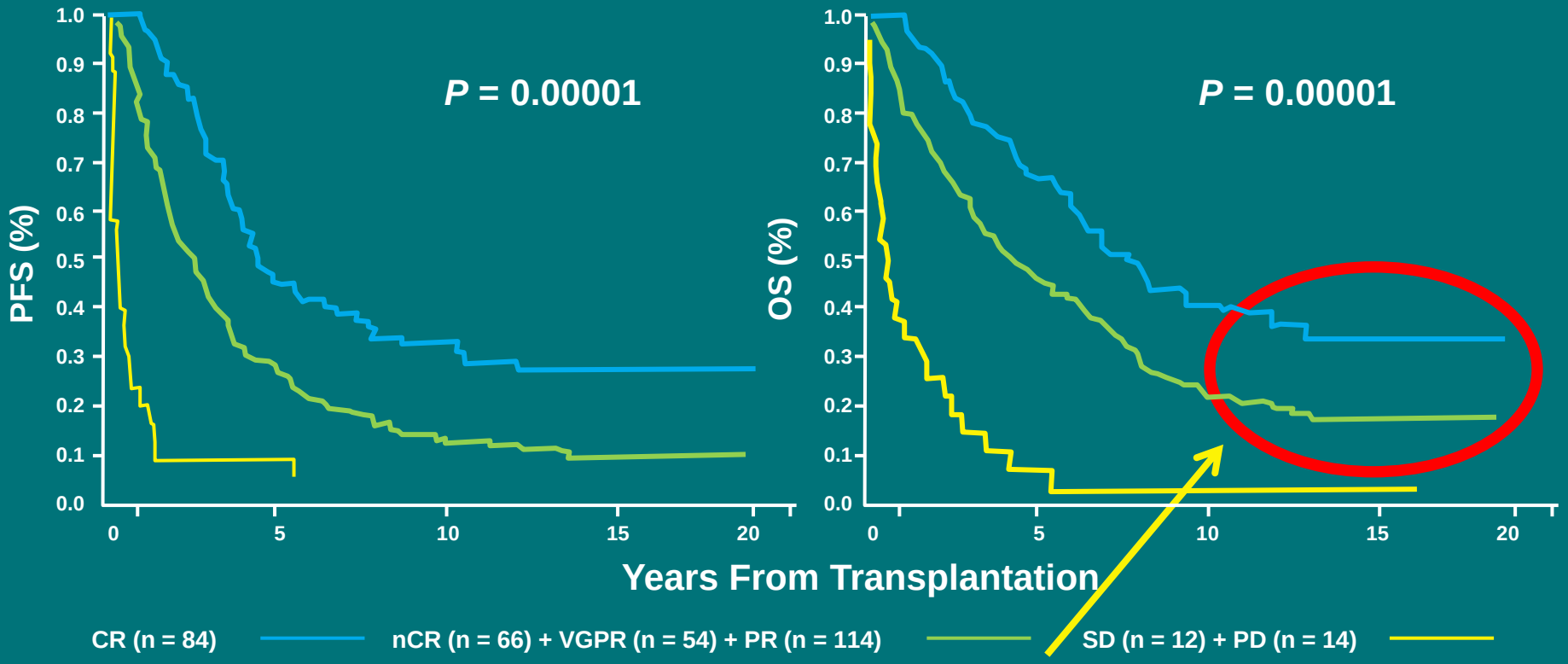
What is a Biomarker?

- Any characteristic (e.g., gene, protein, clinicopathologic variable, imaging feature) that can be objectively and reproducibly measured to serve as an indicator of:
  - Disease (diagnostic)
  - Biology (prognostic)
  - Response to a therapeutic intervention (predictive)

Current Biomarkers in MM

- Almost all biomarkers in MM are either diagnostic or prognostic:
  - Monoclonal protein markers: serum or urine monoclonal proteins, serum free light chains.
  - ISS: Serum beta-2 microglubulin and albumin
  - Cytogentics/FISH

Deeper Response = Better Outcome



Functional Cure?

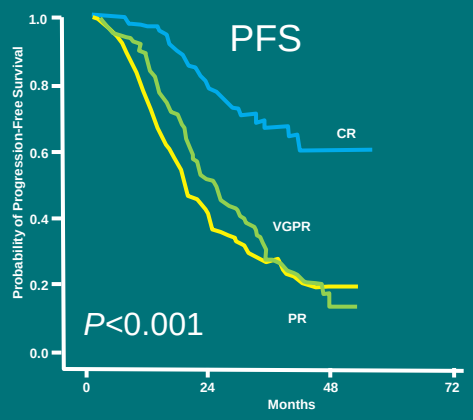
CR = complete response; nCR = near CR; PD = progressive disease; PETHEMA = Programa Espãnol de Tratamientos en Hematologia; PR = partial response; SD = stable disease; VGPR = very good partial response.
Martinez-Lopez J et al. *Blood*. 2011;118:529-534.

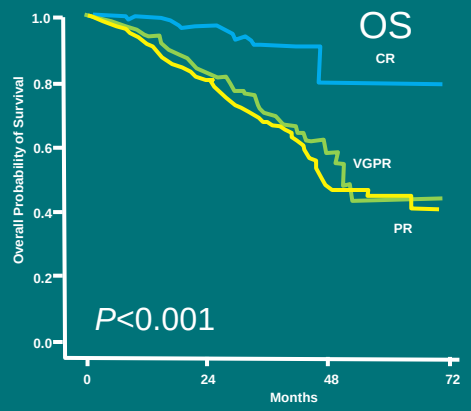
Deeper Response = Better Outcome

Retrospective Analysis: 3 Randomized Trials of GIMEMA and HOVON (N = 1175)

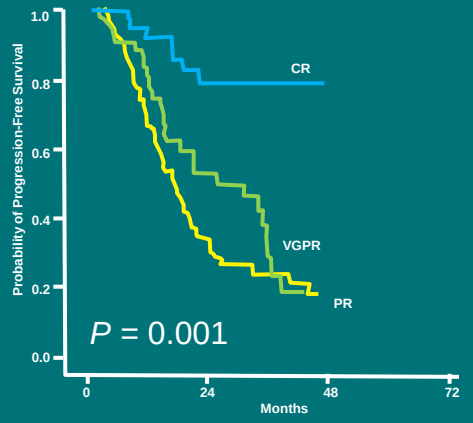
First-line treatment: MP (n = 332), MPT (n = 332), VMP (n = 257), VMPT-VT (n = 254)

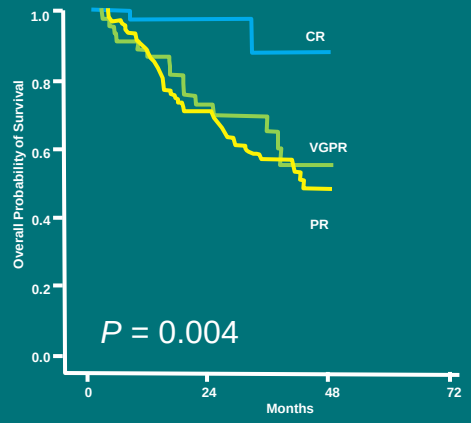
All patients





Patients >75 years





MP = melphalan-prednisone; MPT = melphalan-prednisone-thalidomide; VMP = melphalan-prednisone-bortezomib; VMPT = melphalan-prednisone-bortezomib followed by bortezomib-thalidomide maintenance. Gay F et al. *Blood.* 2011;117:3025-3031.

New Prognostic Biomarkers

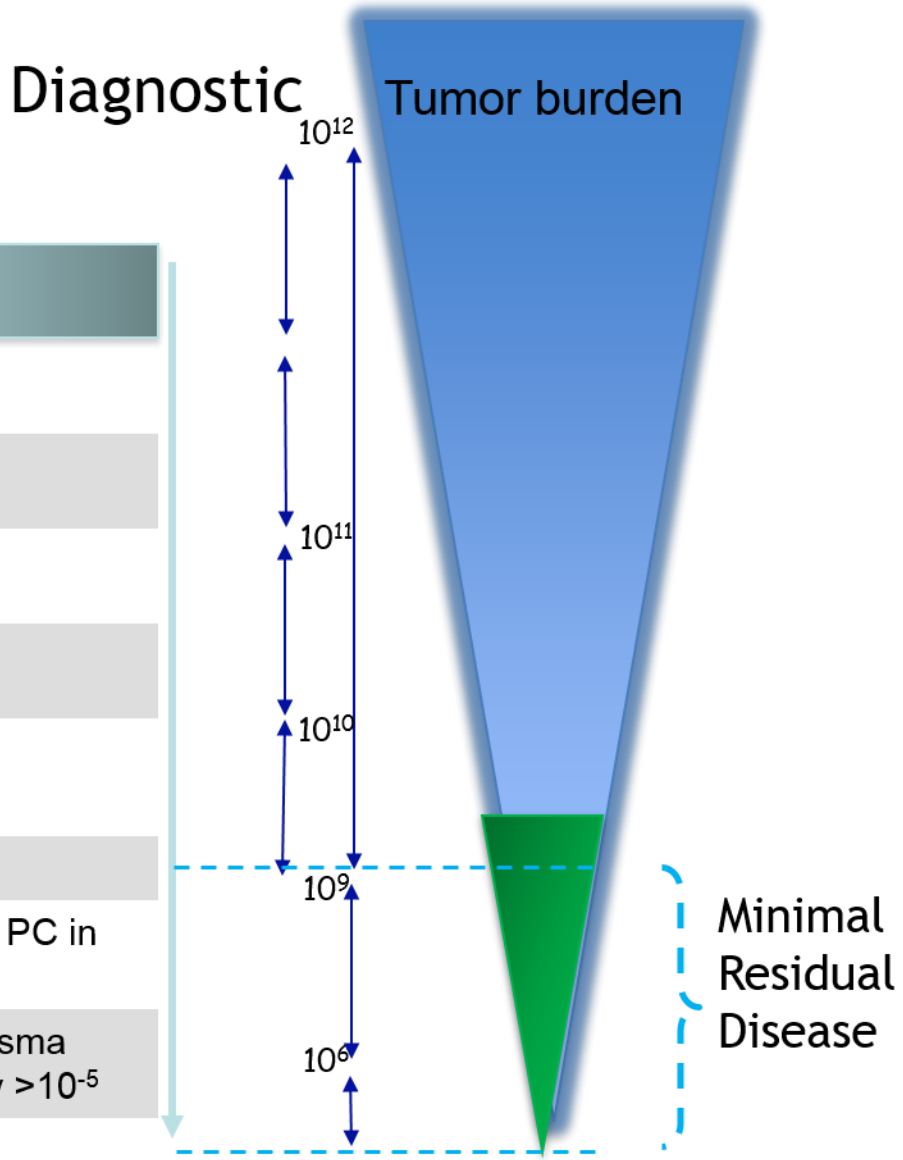
- Disease Burden based:
  - Minimal Residual Disease
    - Flow Cytometry
    - DNA Sequencing
    - Imaging : PET/CT, MRI

- Disease Biology based:
  - Gene expression profiling: UAMS70, EMC-92
    - Identify ~15-20% newly diagnosed MM with high risk of relapse
    - May be replaced with RNA Sequencing in the near future

Why Consider MRD As A Biomarker?

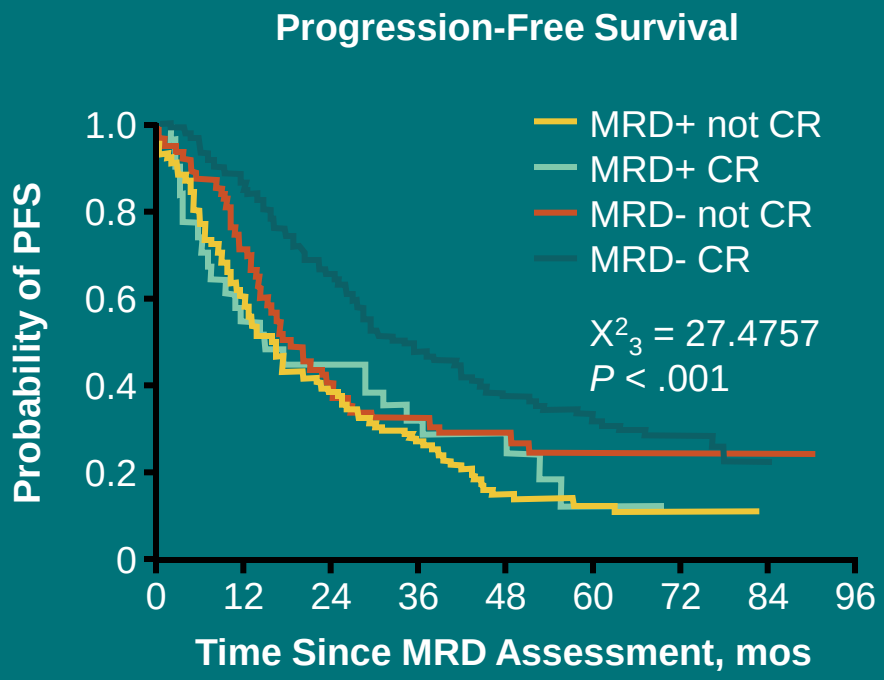
RESPONSE

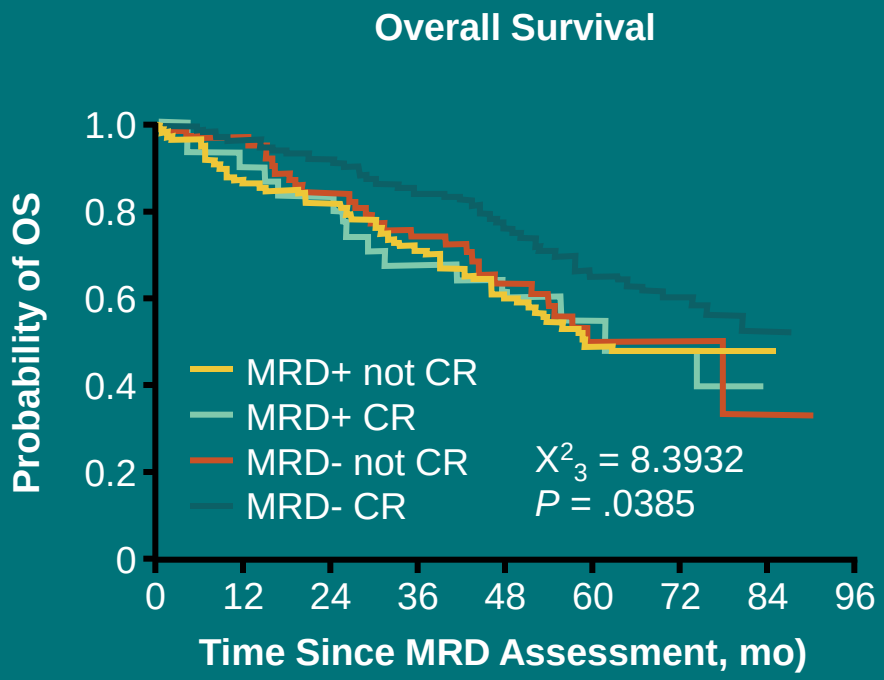
Category	Level of detection
SD	
PR	MC <50%
VGPR	MC <90%
nCR	MC 0.1 – 0.5 g/dl
CR	MC ≤ 0,5g/dl PC in BM<5%
Stringent CR	CMC ≤ 0.01g/dl
Immunophenotypic CR	sCR+ non aberrant PC in 1,000,000 cells
Molecular CR	CR+ non clonal plasma cells with sensitivity $>10^{-5}$



Rajkumar SV et al Blood 2011; Durie B et al Leukemia 2006; Blade J et al BJH 1998

MRD Flow Cytometry Helps Predict Outcomes Post Transplant

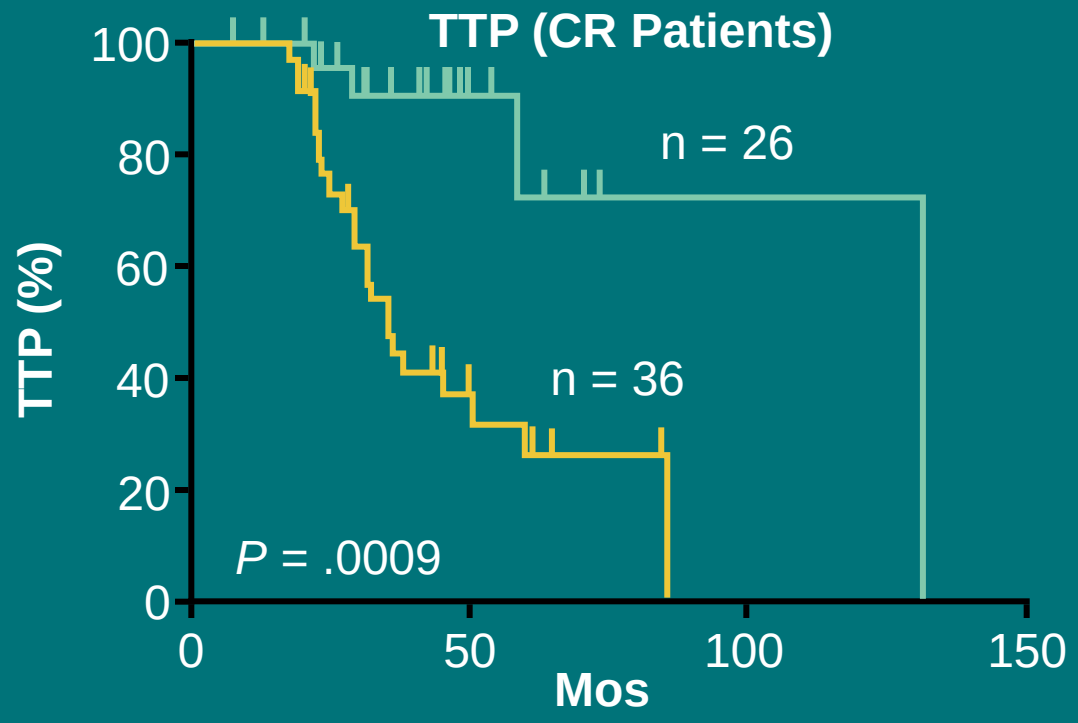




Rawstron AC, et al. J Clin Oncol. 2013;31:2540-2547.

MRD by High-Throughput Sequencing Predicts Prognosis in Patients With CR

- Quantitative; with amplification and sequencing of immunoglobulin gene segments using consensus primers for: immunoglobulin heavy-chain locus complete (IGH-VDJH), IGH incomplete (IGH-DJH), and immunoglobulin κ locus (IGK)



MRD negative
MRD positive
Threshold: 10^{-5}

MRD stratifies the CR population into 2 groups with strikingly different prognosis

Martinez-Lopez, et al. Blood. 2014;123:3073-3079.

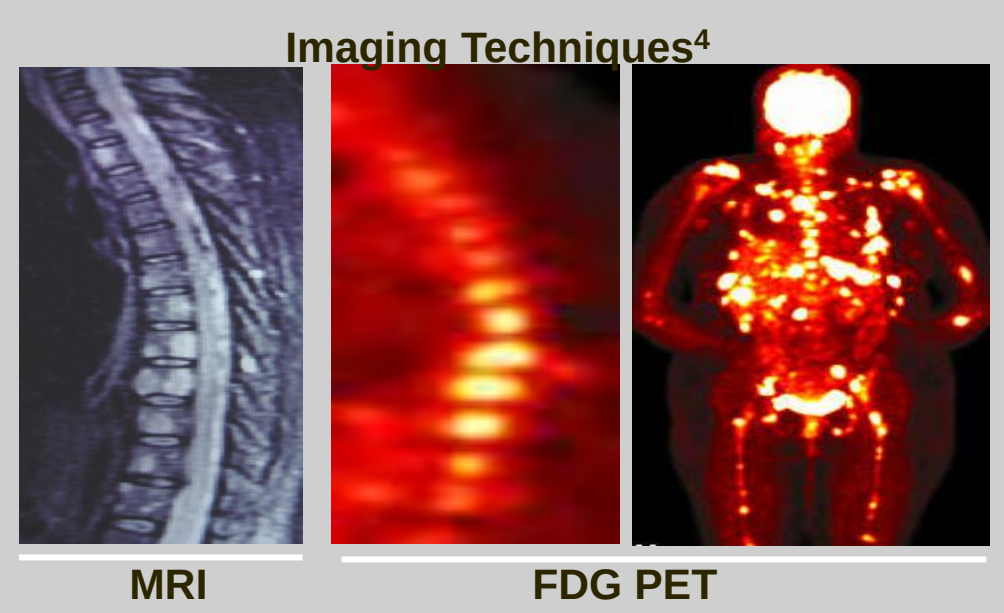
Why The Need for Imaging Biomarkers in MM?

- Current assumption: Pelvic bone marrow aspirates give adequate representation of disease burden, biology and response to therapy
  - Drawback: Biopsy proven PET and MRI Positivity in CR patients

- PET/MRI may provide:
  - Better quantification of burden of disease with potential impact on prognostication at time of diagnosis.
  - Early assessment of therapeutic efficacy.
  - Help determine duration of maintenance.

MRI and FDG-PET in Multiple Myeloma

- Predictors of shorter PFS and OS: > 3 focal lesions or SUV > 4.2 at diagnosis[1]
- 65% of pts PET/CT negative 3 mos after ASCT with longer PFS and OS vs PET positive[1]
- Complete FDG suppression predicts durable disease control and prolonged OS[1]



- Skeletal survey recommended in cases of plasmacytoma, extramedullary disease, suspected spinal cord compression, new symptoms, or progression[2]
- MRI and/or PET/CT indicated when symptomatic areas show no abnormality on radiograph[3]

1. Zamagni E, et al. Blood. 2011;118:5989-5995. 2. Ludwig H, et al. Leukemia. 2014;28:981-992.
3. Usmani et al. 2013;121:1819-23. 4. Boota M, et al. Novel prognostic modalities in multiple myeloma. 2013.

Gene-Expression Profiling – The First Global Biologic Tool for MM

- Identified 7 molecular disease subgroups that have distinct clinical behavior and survival outcomes.
- Identified the ‘high risk’ subgroup that does not benefit from current standard of care therapy.
- Not a predictive tool at present.

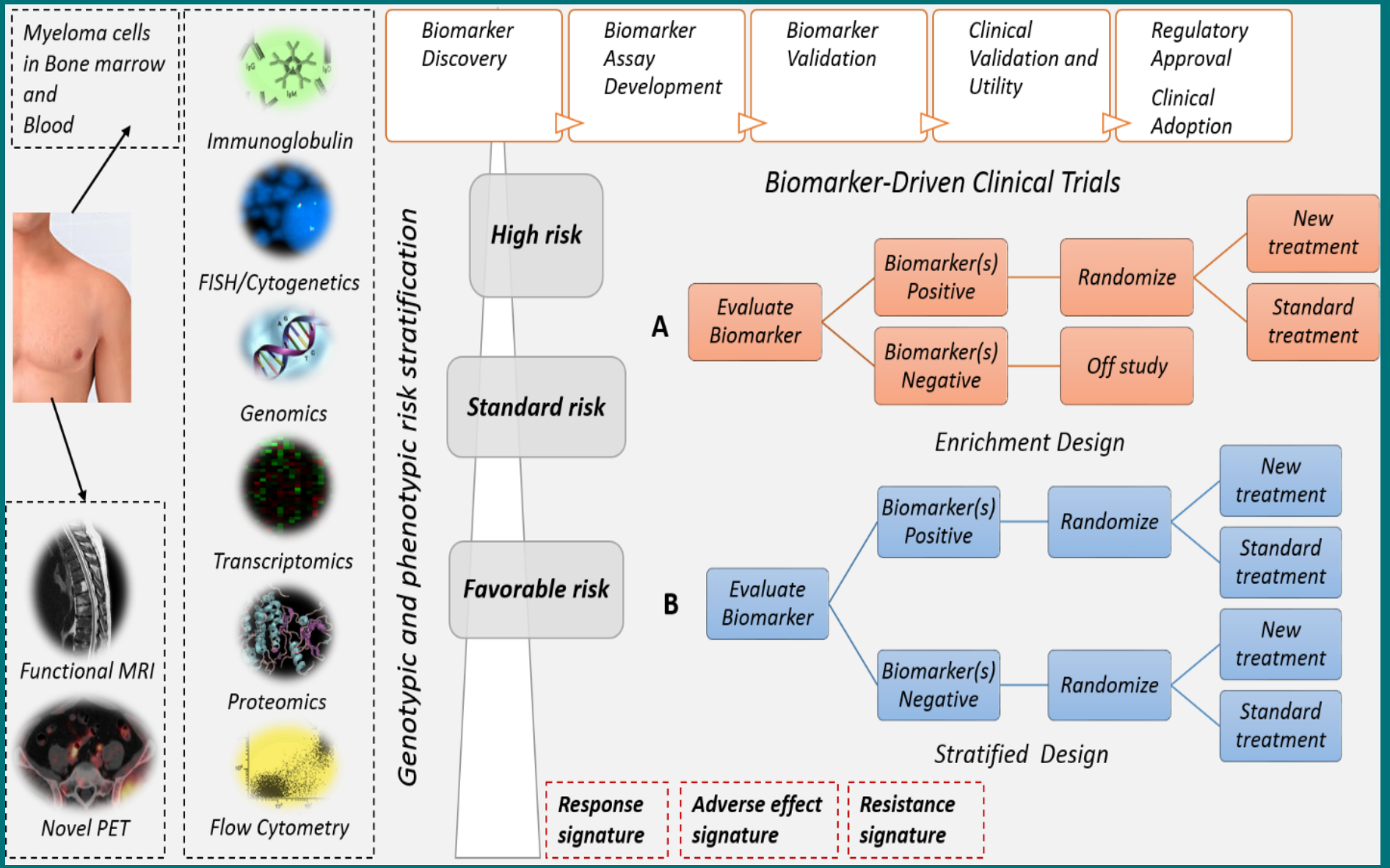
Future of Biomarker Development – Has to Include Predictive Tools

- Need to recognize MM is not one disease.
- Need to recognize the goals of care are different for different patients
  - Fit/young patient versus old/frail patient
- Need to recognize all MM clones at diagnosis for optimal disease control and/or eradication.

Future Predictive Biomarkers

Alterations	Target/Biomarker	Prevalence	Prognosis	Targeted Drug
t(4;14) FGFR3/MMSET	FGFR3 tyrosine kinase receptor	10-15%	Intermediate	PRO-001, CHIR 258, PKC412
t(14;16) c-MAF t(14;20) MAFB	MAF overexpression	5-10%	Poor	MEK inhibitors
t(11;14) CCND1 t(6;14) CCND3	Cyclins	19%	Standard	Cyclin D inhibitors
8q24 translocations c-MYC	c-MYC		Poor	Bromodomain inhibitors such as JQ1
+1q CKS1B, PDZK1 and BCL9	STAT3 and MEK/ERK signaling	39%	Poor	STAT3 and MEK inhibitors
Deletion of 1p FAF1 and CDKN2C	-	11%	Poor	
Deletion of 13q RB1	-	45% by iFISH 19% by conventional cytogenetics	Earlier studies showed poor survival	Mutant RB1 inhibitor
Deletion of 17p TP53, MDM2	Mutant or WT TP53	10%	Poor	nutlin PRIMA-1 CHK inhibitors and Filanesib (target G2M)
Proliferative myeloma GEP- PR subtype	Ki67		Poor	Spindle kinase inhibitors, Aurora kinase inhibitors
NF-κB pathway, multiple genes e.g. NFKB2, NFKB1, CYLD, TACI, NIK, TRAF2, TRAF3, BIRC2, BIRC3, VWOX and CD40	Gene expression signature		Poor	MLN120B (an inhibitor of IKKβ)
JAK/STAT pathway CCND2	Cyclins	50%		JAK inhibitors, atimprimod, AZD1480, TG101209 and INCB16562
MAPK/RAS pathway	RAS mutations (20-35%) BRAF mutations (4%)	20-35%	Poor	Farnesyl transferase inhibitors: perillic acid, FTI-277 and tipifarnib. MEK inhibitors: AZD6244 and AS703026. BRAF kinase inhibitors
PI3 Kinase pathway	Cyclins			P13K inhibitors: SF1126, pichromene and CAL-101 AKT inhibitor: Perifosine mTOR inhibitor: Rapamycin, Temsirolimus
Epigenetic changes	histone methyltransferase activity of MMSET	15%		HDAC6 inhibitor, ACY-1215 DNA methyltransferase inhibitors such as 5-azacytidine, 5-aza-2'deoxycytidine

Roadmap To Biomarkers Utility in MM



Thank you for your attention!