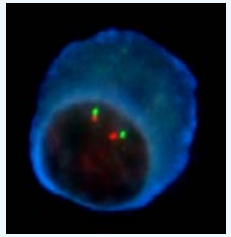
Newly Diagnosed Myeloma



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Newly diagnosed MM subcommittee

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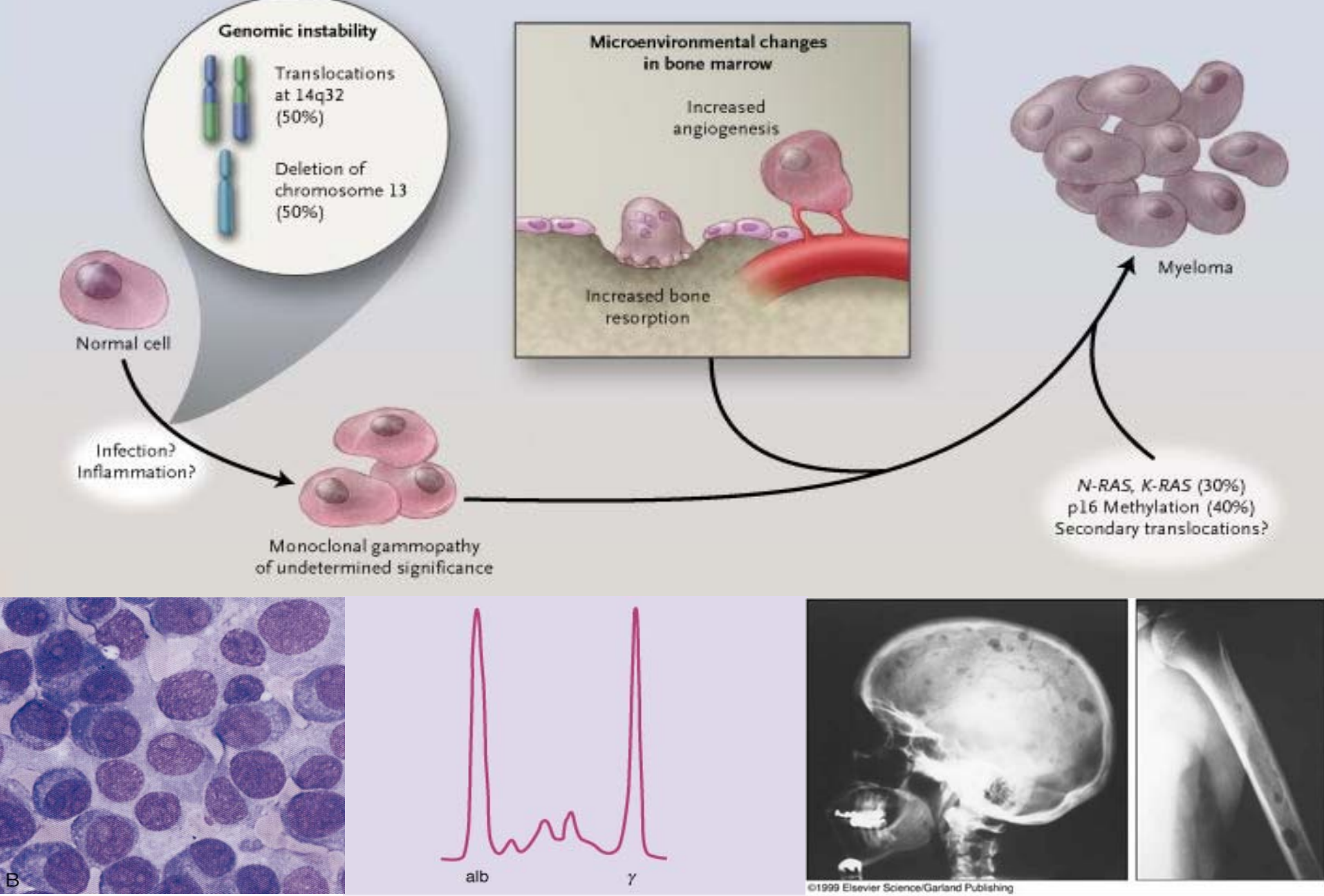
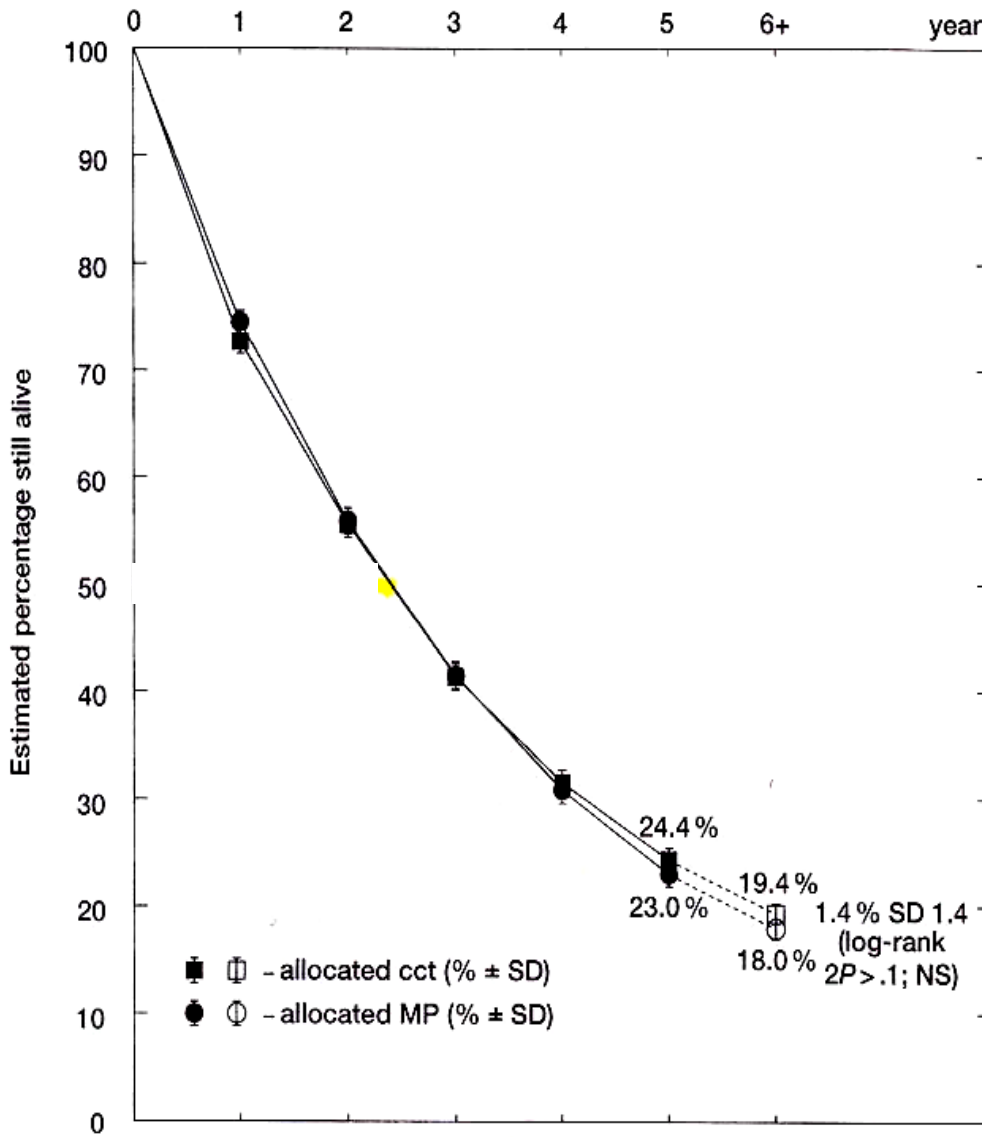
Mario Boccadoro, MD	University of Torino
Sundar Jagannath, MD	St. Vincentõ Comprehensive Cancer Center
Bart Barlogie, MD, PhD	Univ. of Arkansas for Medical Sciences; Myeloma Inst. for Research & Therapy
Kaushikkumar Shastri, MD	US Food and Drug Administration



Kyle RA and Rajkumar SV. Cecil Textbook of Medicine, 22nd Edition, 2004

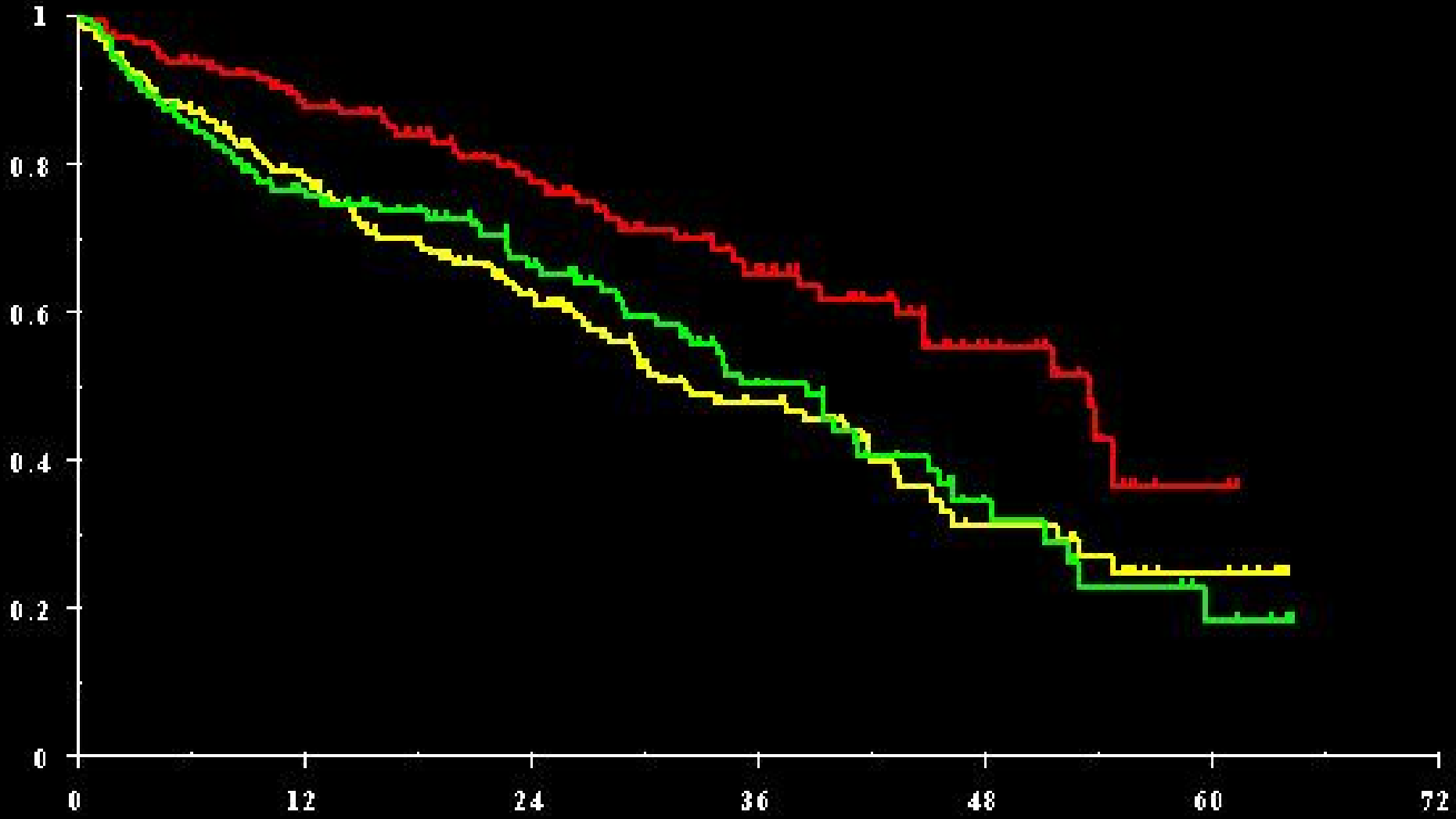
Kyle RA and Rajkumar SV. N Engl J Med 2004;351:1860-73

Treatment of newly diagnosed MM



MTCG. J Clin Oncol 1998; 16:3832

MP vs Mel 100 vs MPT in Newly Diagnosed MM



**Facon, T. ASC0 2006

mSMART

Mayo Stratification for Myeloma And Risk-adapted Therapy

Newly Diagnosed Myeloma

www.msmart.org

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

Issues

- Response criteria
- Alternatives to OS TTP and PFS.

LEADING ARTICLE

International uniform response criteria for multiple myeloma

BGM Durie[1], J-L Harousseau[2], JS Miguel[3], J Bladé[4], B Barlogie[5], K Anderson[6], M Gertz[7], M Dimopoulos[8], J Westin[9], P Sonneveld[10], H Ludwig[11], G Gahrton[12], M Beksac[13], J Crowley[14], A Belch[15], M Boccadaro[16], I Turesson[17], D Joshua[18], D Vesole[19], R Kyle[7], R Alexanian[20], G Tricot[5], M Attal[21], G Merlini[22], R Powles[23], P Richardson[24], K Shimizu[25], P Tosi[26], G Morgan[27] and SV Rajkumar[7] on behalf of the International Myeloma Working Group[29]

[1]Aptium Oncology, Inc., Cedars-Sinai Outpatient Cancer Center, Los Angeles, CA, USA; [2]Institute de Biologie, Nantes, France; [3]University of Salamanca, Salamanca, Spain; [4]Hospital Clinica, Barcelona, Spain; [5]MIRT UAMS, Little Rock, Arkansas, USA; [6]DFCI, Boston, MA, USA; [7]Mayo Clinic, Rochester, MN, USA; [8]Alexandra Hospital, Athens, Greece; [9]University of Gothenberg, Gothenberg, Sweden; [10]Rotterdam, The Netherlands; [11]Wilhelminenspital Der Stat Wien, Vienna, Austria; [12]Karolinska Institutet, Stockholm, Sweden; [13]Ankara University, Turkey; [14]Cancer Research and Biostatistics, Seattle, WA, USA; [15]Cross Cancer Institute, Canada; [16]University of Torino, Torino, Italy; [17]University of Malmo, Malmo, Sweden; [18]Royal Prince Alfred Hospital, Sydney, Australia; [19]St Vincent's Comprehensive Cancer Center, New York, NY, USA; [20]MD Anderson, Houston, TX, USA; [21]Purpan Hospital, Toulouse, France; [22]University of Pavia, Pavia, Italy; [23]The Leukemia and Myeloma Program, Wimbledon, UK; [24]Dana Farber Cancer Institute, Boston, MA, USA; [25]Nagoya City Midori General Hospital, Nagoya, Japan; [26]University of Bologna, Bologna, Italy and [27]Royal Marsden Hospital, London, UK

Leukemia 2006;20:1467-73

Committee Recommendation #1

- Adopt IMWG Uniform Response Criteria for future trials
  - Developed with extensive input
  - Accepted by several major cooperative groups and industry
- Continue to enroll only patients with measurable disease on regulatory studies

IMWG Uniform Response Criteria

- Validated
- Improved detail; less chance for subjectivity
- For definition of progression - *and thus calculation of TTP and PFS*- the criteria remain unchanged from EBMT criteria
- Adds important categories of VGPR and sCR
- CR and PR requirements remain unchanged except for change in confirmation time
- Recommend: Validation of FLC criteria over time in non-regulatory studies

Alternative End-points

- Overall RR
- Toxicity
- CR
- QOL

Overall RR

- Overall response: CR plus PR or better
- Precedent: Thalidomide-Dexamethasone in 2006
- Problems:
  - No superiority in OS with improvement in response rate in many newly diagnosed studies
  - Current overall RR rates in excess of 80-90% will make it difficult to design trials with overall response as an endpoint.

Committee Recommendation #2

- Overall RR not recommended for regulatory purposes

Toxicity

- Improved versions of existing agents with reduced toxicity are likely
- Reduction in one type of toxicity will not address possible increase in another type of toxicity
- Best assessed by formal patient reported QOL analysis

Committee Recommendation #3

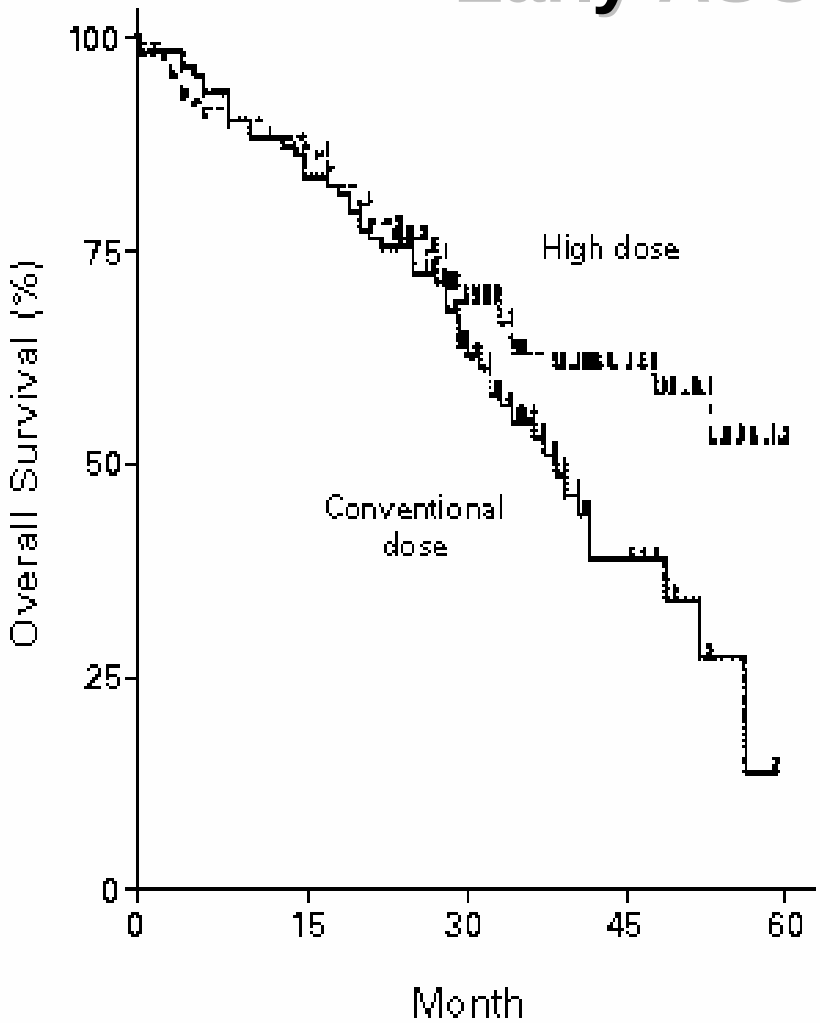
- Reduction in toxicity is not recommended for regulatory purposes

CR

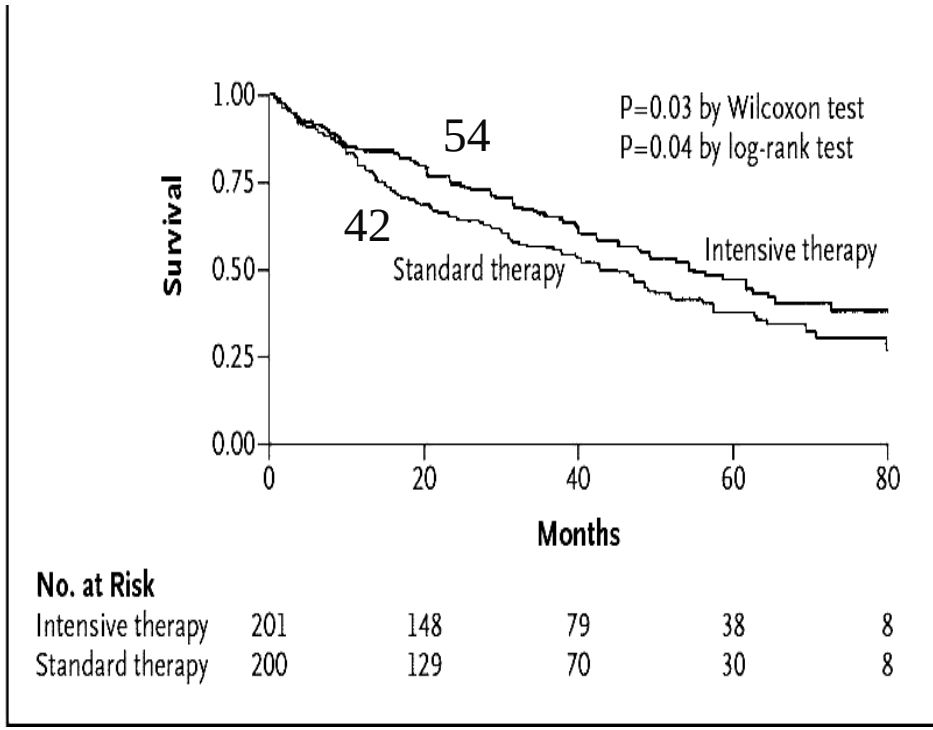
- OS is not a realistic end-point
- TTP/PFS while acceptable will take years to complete

- CR is an important goal of therapy.
- It be reliably defined
- CR rates even with new regimens is less than 30-40%

Early ASCT in Myeloma



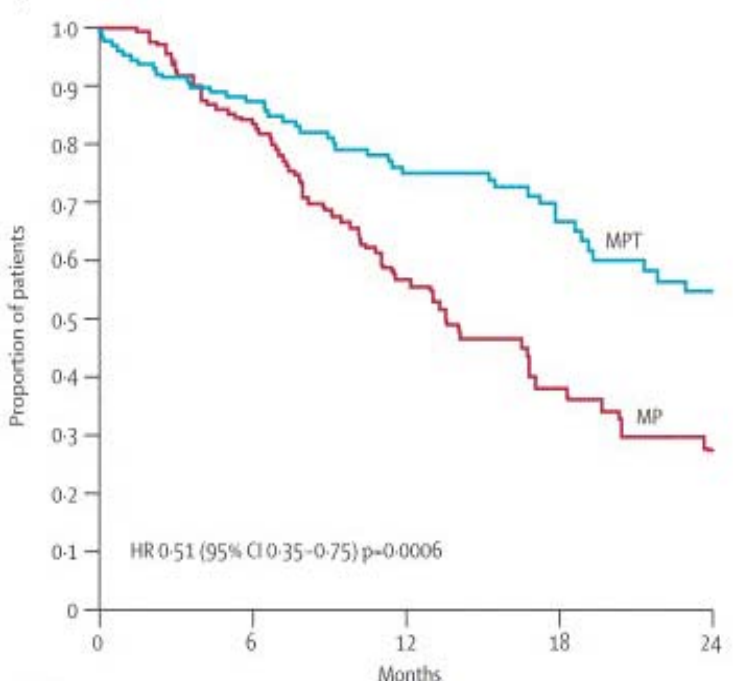
Conventional dose	63 (53–73)	35 (22–50)	12 (1–40)
High dose	69 (58–78)	61 (50–71)	52 (36–67)

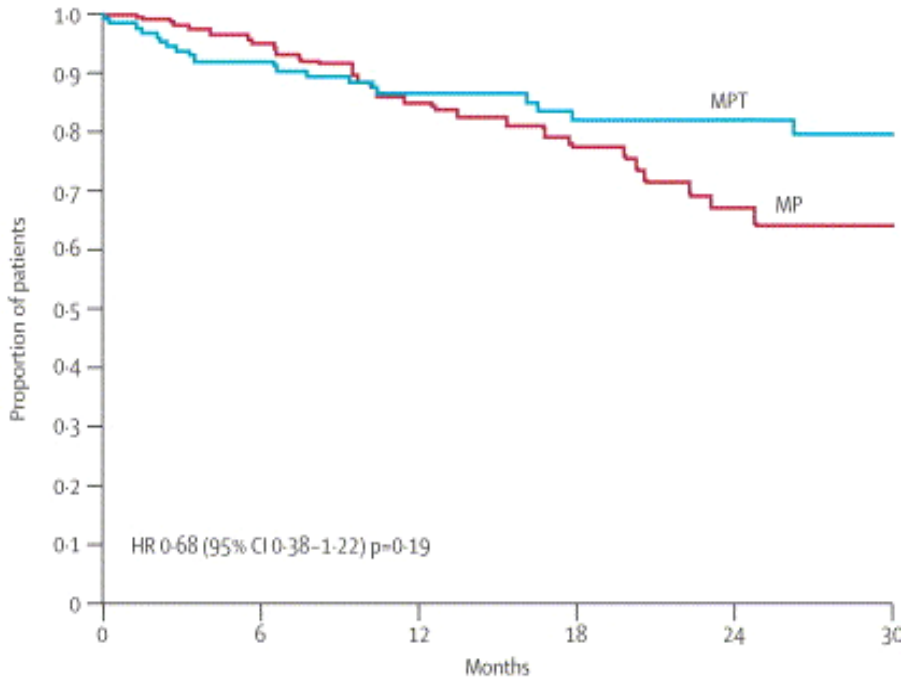


No. at Risk					
Intensive therapy	201	148	79	38	8
Standard therapy	200	129	70	30	8

Attal M. N Engl J Med 1996; 335:97; Child J. N Engl J Med 2003; 348:1875

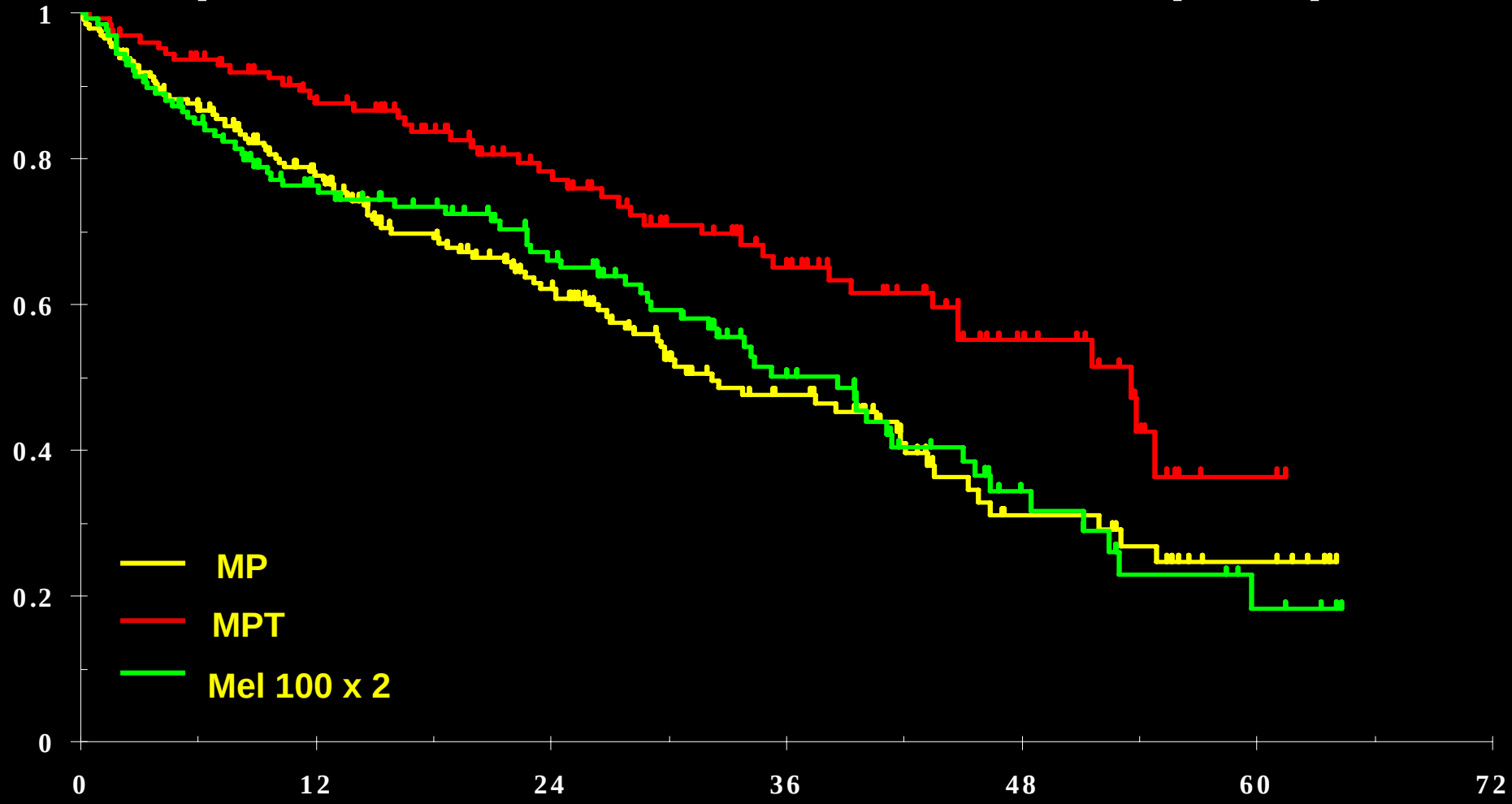
Induction Therapy: Non-Transplant Candidates Melphalan, Prednisone, Thalidomide (MPT)





Palumbo et al. Lancet 2006;367:825-831

Induction Therapy: Non-Transplant Candidates Melphalan, Prednisone, Thalidomide (MPT)



**Facon, T. ASC0 2006

CR

- CR is associated with superior EFS and OS
  - Lahuerta, BJH 2001; Alexanian, BMT 2001
- CR associated with improved survival (using landmark analysis) and quality of CR
  - Kyle, Cancer 2006
- Improved EFS and OS duration with earlier achievement of CR
  - Barlogie, Blood 1999

CR

- sCR needs to be studied and evaluated
- BMT CTN group is planning to study this, as are other groups

CR

Caveats

- Not all studies show association of CR with improved OS; but almost all show strong association with TTP/PFS
- Patients who do not achieve CR are not a homogeneous group

Committee Recommendation #4

- CR is recommended as an appropriate surrogate end-point for regulatory purposes

QOL

- QOL is an important endpoint for regulatory purposes
- Already accepted in some form as a regulatory endpoint
- Achievement of response with MM therapy is associated with improved QOL.
- Improvement in QOL is a major reason for preference of early stem cell transplant in myeloma over delayed transplantation.

QOL

- Will capture important improvements in therapy with regards to lower toxicity compared to existing standard therapies
- Will also capture important improvements in delivery of therapy (eg., oral proteasome inhibitors)

- Main issue: Type of QOL tool and type of analysis

QOL

ECOG: FACT-MM scale

- Input from patients
- *Hypothesis:* FACT-MM will assess the functional and physical well-being of MM patients and correlate with the impact of a specific treatment intervention on PFS etc
- Being validated

FACT-MM

- FACT-G version 4 (14 questions)- addresses the physical (PWB) and functional (FWB) well-being of MM patients.
- FACT-NTX (11 questions), which will evaluate symptoms of neurotoxicity.
- MM specific subscale (14 questions)

Committee Recommendation #5

- QOL assessment is recommended for regulatory purposes
- But details on which instrument, and specific guidelines from FDA on how studies using QOL as endpoint should be designed is needed

Summary Recommendations

- IMWG Uniform Response Criteria
- Do not recommend overall RR
- Do not recommend toxicity reduction
- Recommend CR as a regulatory endpoint in newly diagnosed MM
- Recommend, with input from FDA on specifics, QOL as an endpoint