Multiple Myeloma

- Multiple myeloma is a neoplastic proliferation of bone marrow plasma cells
- It is characterized by
  - Monoclonal protein in serum and/or urine
  - lytic bone lesions
  - excess plasma cells in the bone marrow

Symptomatic plasma cell myeloma

- Monoclonal protein in serum and/or urine
- Bone marrow clonal plasma cells or plasmacytoma
- Related organ or tissue impairment (CRAB: hypercalcaemia, renal insufficiency, anaemia, bone lesions)

Asymptomatic (smoldering) myeloma

- Monoclonal protein in serum at myeloma levels(>30g/l)

AND/OR

- 10% or more clonal plasma cells in bone marrow
- No related organ or tissue impairment or myeloma-related symptoms

Epidemiology 1

- 1% of all cancers
- 10% of haematological cancers
- About 3,500 new cases of myeloma per year in the UK
- Median survival-

  7 months in pre-chemotherapy era

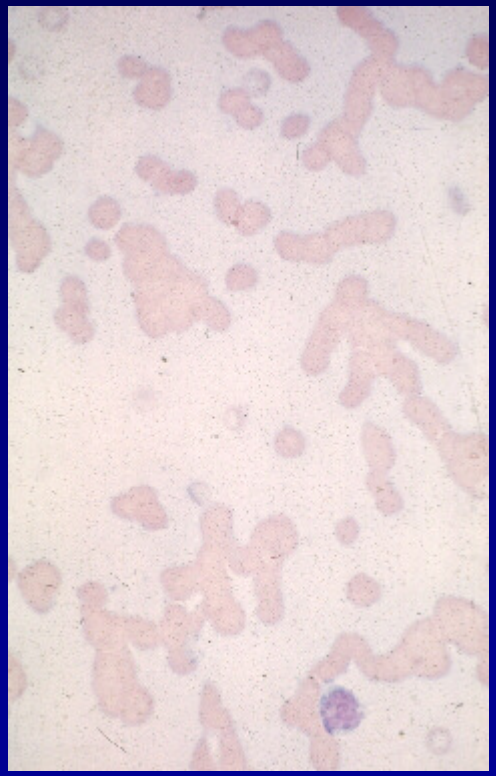
  3 years with conventional chemotherapy

  5 years with autologous stem cell transplantation
- No cure except with allogeneic stem cell transplantation

Epidemiology 2

- More common in men than women (1.4:1)
- More common in blacks than whites (2:1)
- Does not occur in children
- Incidence increases with age.
- Median age at diagnosis is 70
- Slightly increased incidence in individuals with a first degree relative with myeloma

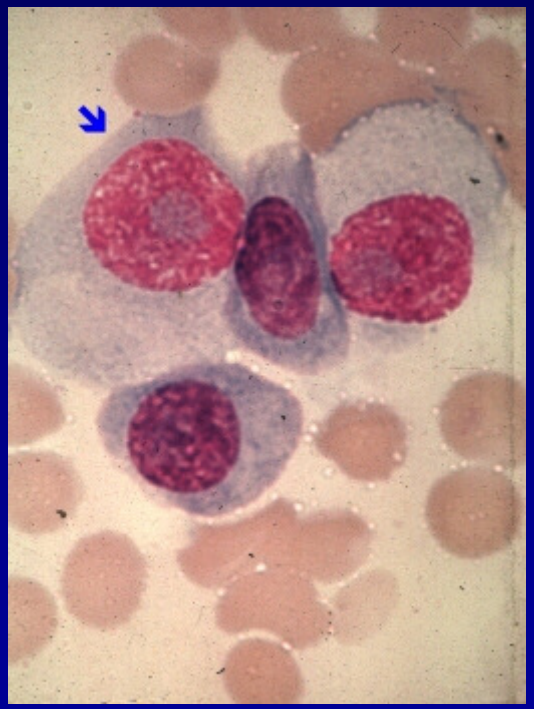
Peripheral blood



Rouleaux formation

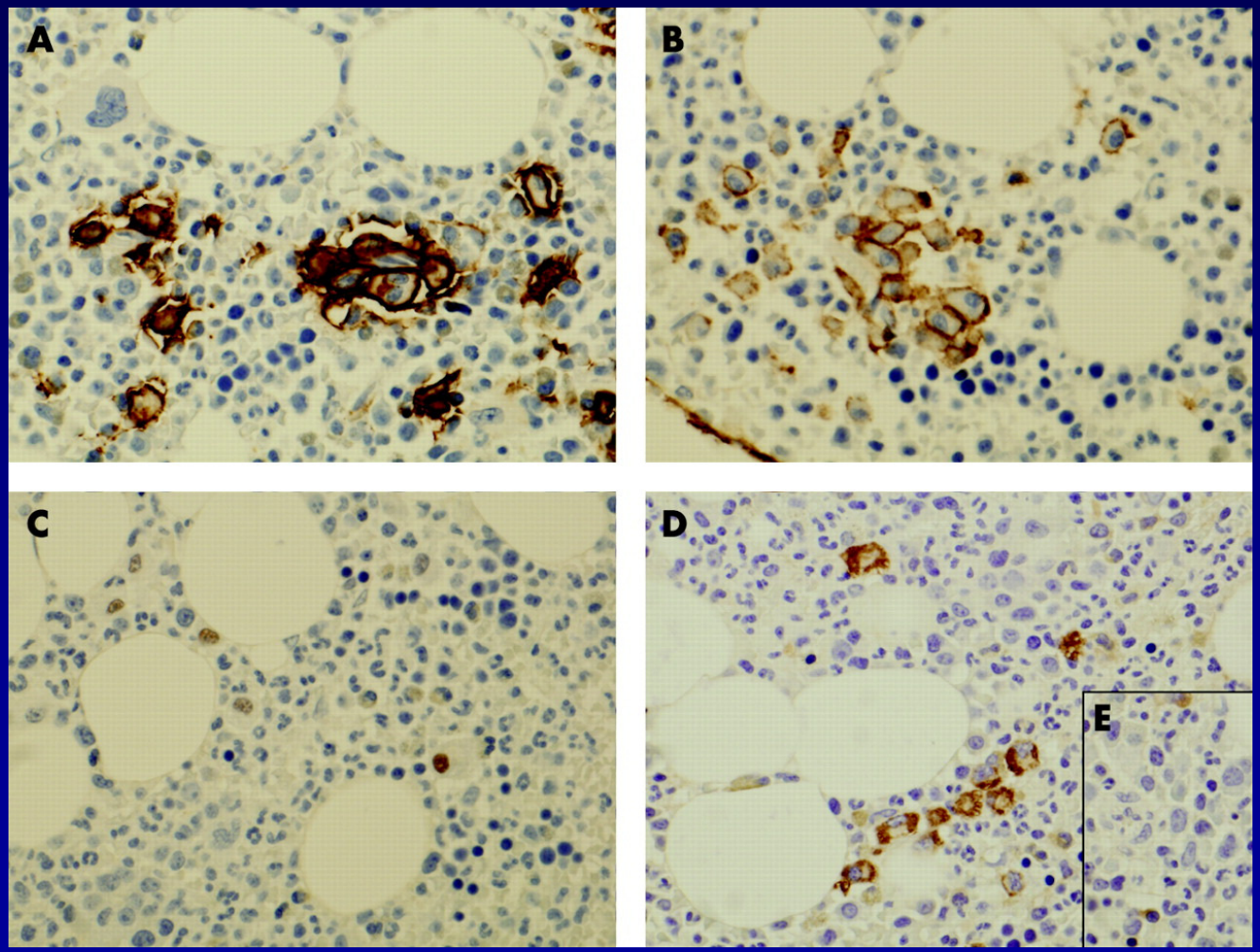
Prof Barbara Bain

Multiple Myeloma



Immuno-histochemistry

CD138



CD56

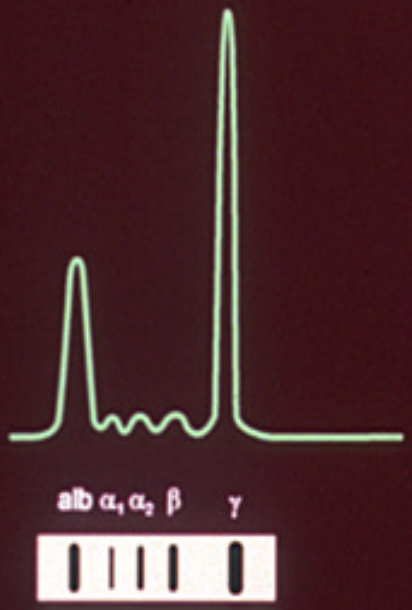
Cyclin D1

kappa

lambda

Joshi, R et al. J Clin Pathol 2008;61:213-216

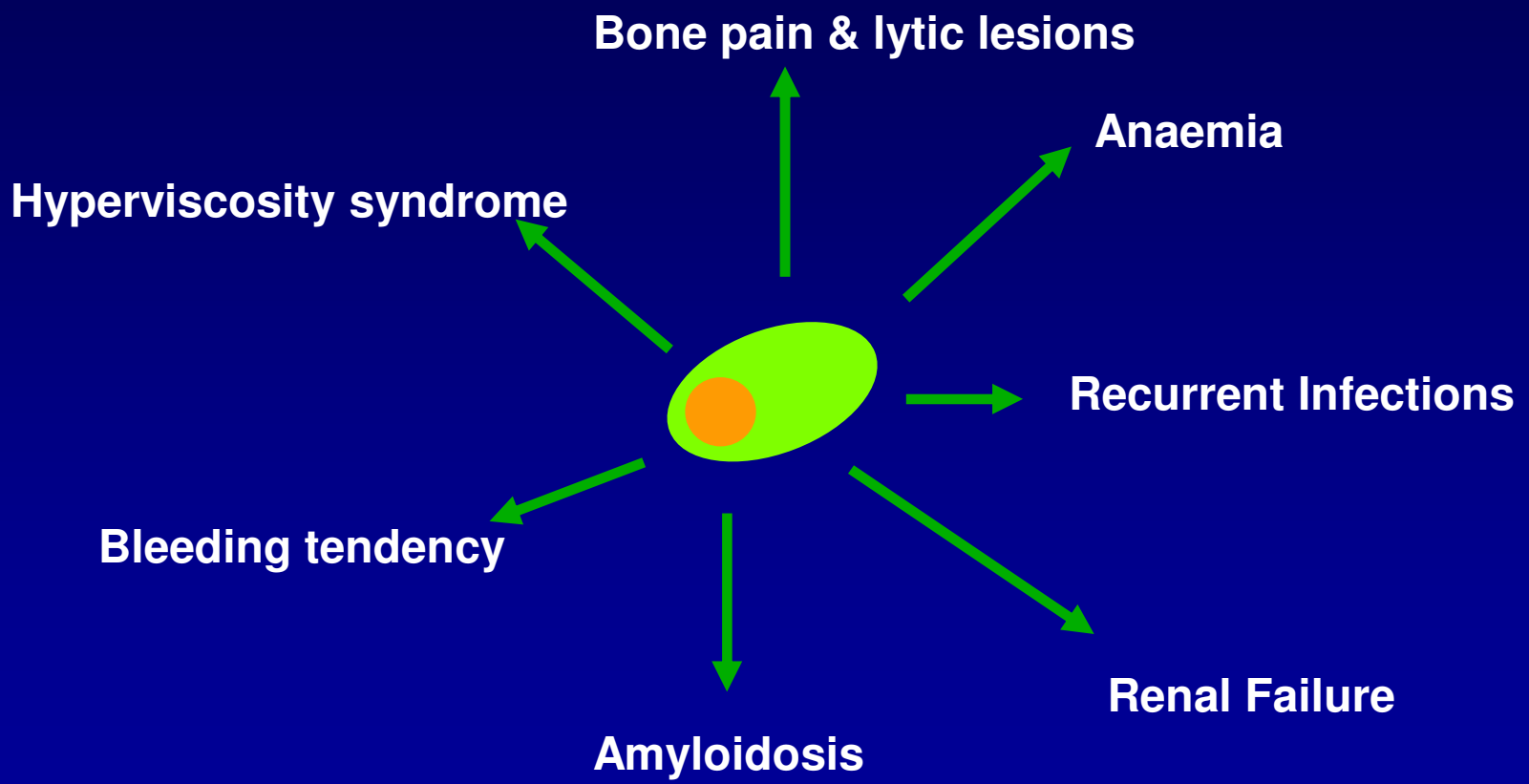
Serum protein electrophoresis



Type of protein	Myeloma patients (%)
IgG	52
IgA	22
IgM (macroglobulinaemia*)	12
IgD	2
IgE	Rare
Light chain (κ or λ)	11
Heavy chain (γ, α, or μ)	Rare
2 or more monoclonal proteins	<1
No monoclonal protein (non-secretory)	1

* Usually classified along with Waldenström's macroglobulinaemia

Clinical features



Bone disease in myeloma

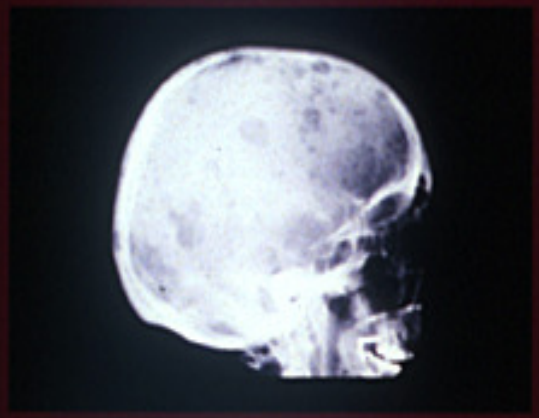


Figure A
Skull — multiple lesions

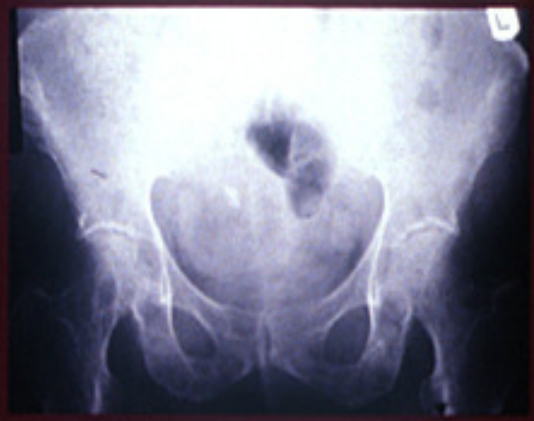


Figure B
Pelvis — multiple lytic lesions

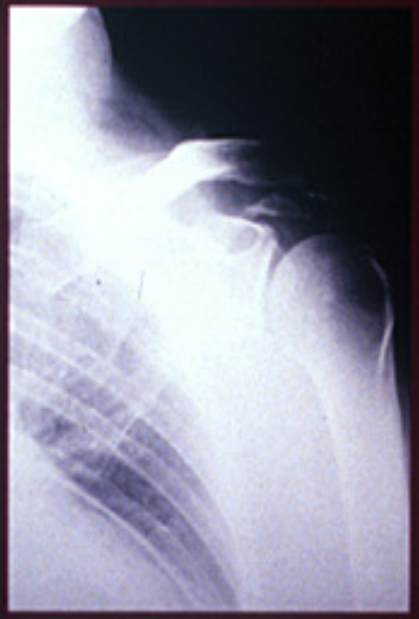


Figure C
Shoulder — solitary plasmacytoma

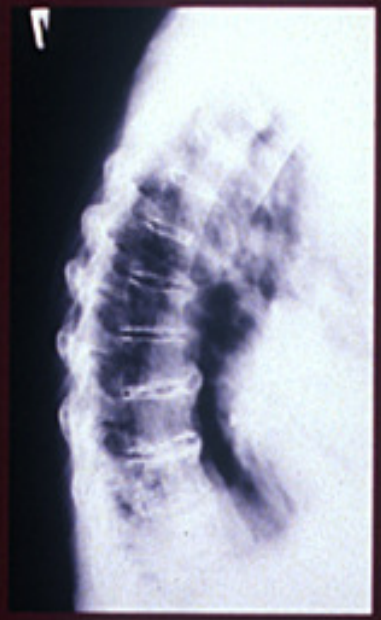


Figure D
Osteopenia and wedge fractures

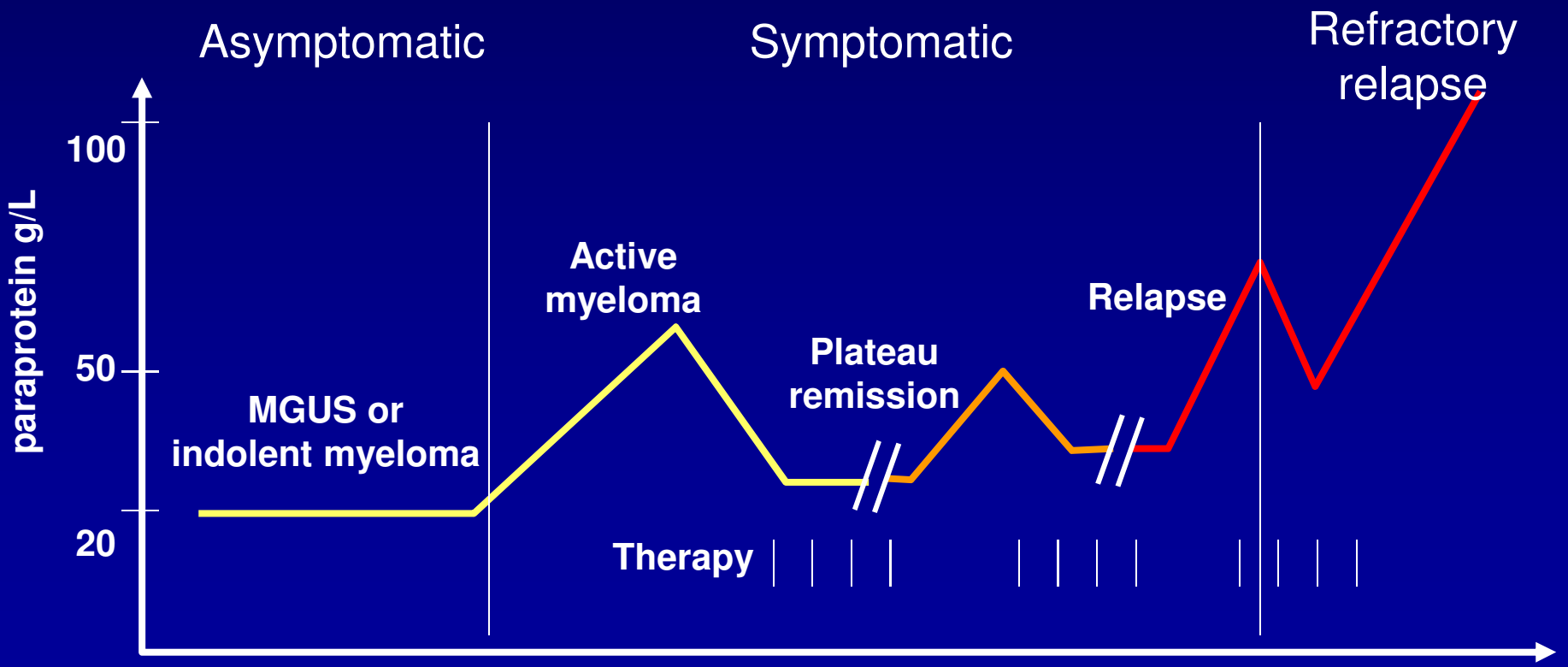
Staging of multiple myeloma (Durie-Salmon)

- Stage I: all of the following
  - Hb > 10g/dl
  - Serum calcium value normal
  - No lytic lesions or solitary plasmacytoma
  - IgG<50g/l IgA<30g/l
  - Urine light chain M-component < 4g/24hrs
- Stage II: fitting neither Stage I nor Stage III
- Stage III: one or more of the following
  - Hb <8.5g/dl
  - Serum calcium>3mmol/l
  - Multiple lytic lesions
  - IgG>70g/l IgA>50g/l
  - Urine light chain M-component >12g/24hrs

The International Staging System (ISS) 2005

- Stage I: β2-microglobulin (β2M) < 3.5 mg/L, albumin>= 35 g/L
- Stage II: β2M < 3.5 and albumin < 35; or β2M >= 3.5 and < 5.5
- Stage III: β2M >= 5.5

Multiple Myeloma
- disease course -



Conventional Chemotherapy

- Melphalan and prednisolone
- VAD
- CTD

Regimens with similar survival outcomes:

- High dose dexamethasone
- Cyclophosphamide and prednisolone
- CVAMP, VBMCP, VMCP/BVAP

Conventional Chemotherapy

- No single alkylating agent superior
- Combination of alkylating agents and Pred similar to MP
- Maintenance interferon α prolongs survival after chemotherapy but not after ASCT
- Bisphosphonates in advanced disease

Treatment of bone disease

- Hypercalcaemia
  - IV fluids
  - Steroids
  - Bisphosphonates
- Pamidronate, Zoledronic acid, clodronate
  - Significant reduction in bone pain and requirement for analgesics
  - Improved quality of life
  - Reduction in development of new pathological fractures
  - Reduced need for radiotherapy
  - Significantly improved survival in patients on salvage therapy

High dose therapy

- Randomized trial- IFM90 -Attal et al 1996
- Conventional chemotherapy vs high-dose therapy + ABMT
- 200 previously untreated patients < 65 yrs
- Durie-Salmon stage II/III
- Chemotherapy- VMCP/BVAP for 1 yr +IFNα
- HDT- 4-6 xVMCP/BVAP

  ABMT (Melphalan 140mg/m^2 + TBI) + IFNα

High dose therapy

- Results:(December 2000)

	CC	HDT
CR + good PR	14%	38%
7 yr EFS	8%	16%
7 yr OS	25%	43%

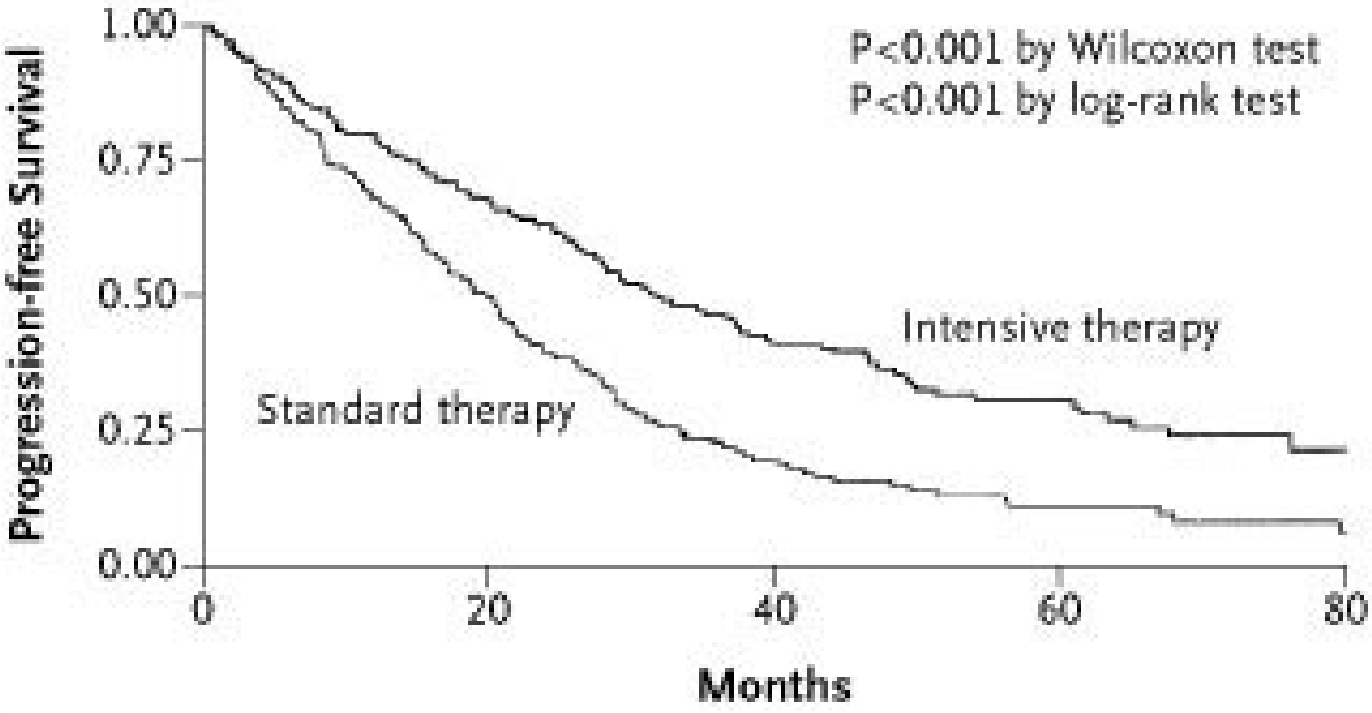
Relapses continue at a constant rate

No cures

Myeloma VII

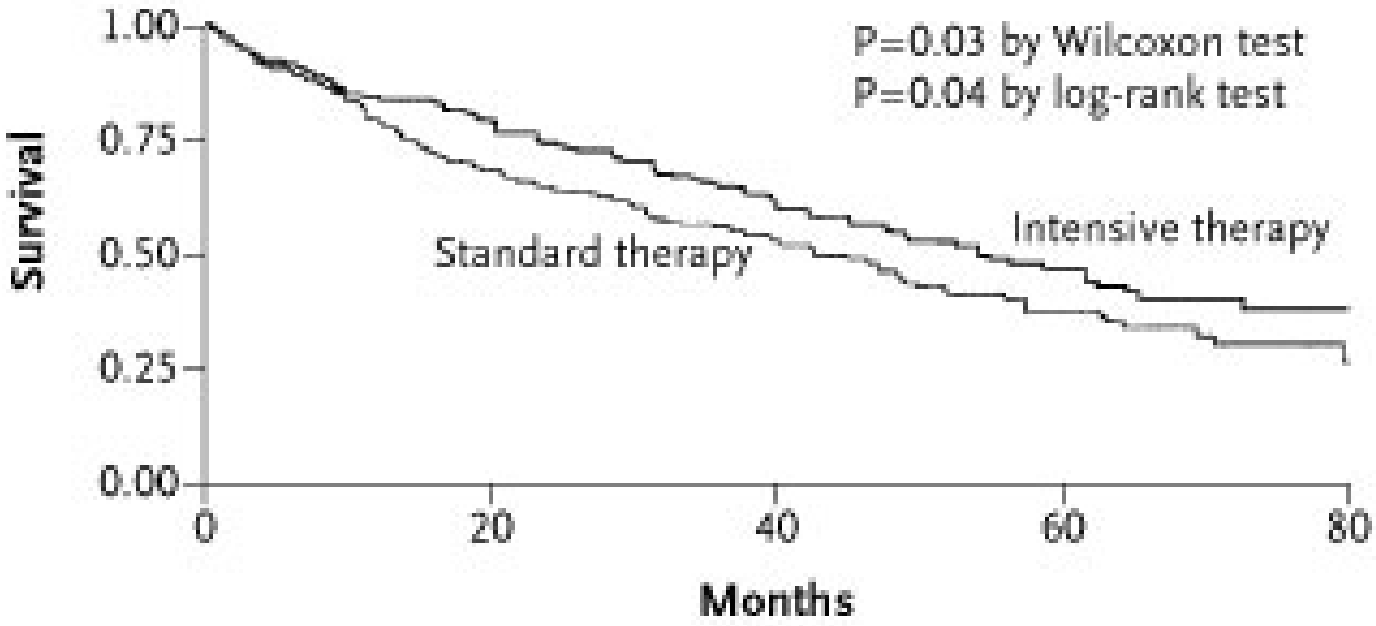
- Child et al. NEJM 2003
- 407 pts < 65 yrs
- Standard – ABCM (Doxorubicin, BCNU, cyclophosphamide and Mel) every 6 wks (4-12 cycles) followed by IFN maintenance
- Intensive – C-VAMP (cyclophosphamide, vincristine, doxorubicin and methyl-pred) until maximal response (at least 3 courses) followed by stem cell mobilization and HDT +IFN maintenance

Myeloma VII- PFS



No. at Risk					
Intensive therapy	199	124	55	27	5
Standard therapy	196	90	25	9	3

Myeloma VII- overall survival



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

Myeloma VII

- Results:

	CC	HDT
CR + good PR	8%	44%
Median OS	42 mths	54mths

How do we improve the results?

Conditioning regimen

- Uncontrolled studies 20-50% vs 70% CR
- IFM95 - HDM 140+TBI vs HDM 200
- followed by PBSCT
- (preliminary analysis of 221 pts)
- No significant difference in outcome
- HDM 200 less toxic-shorter time to haemopoietic recovery, fewer toxic deaths

How do we improve the results?

Tandem transplants

- Largest experience at Little Rock
- 495 patients enrolled 2 x HDM 200
- 95% completed course 1
- 73% completed course 2
- CR after 1 course = 24%
- CR after 2 courses = 43%
- Now over 1000 patients have been treated

How do we improve the results?

Tandem transplants

- IFM94
- 1 transplant (HDM 140 +TBI) vs
- 2 transplants (HDM 140 then HDM140+TBI)
- 405 untreated patients < 60 years
- Initially treated with VAD x 3-4

IFM94 interim analysis

- 402 patients with a median follow-up of 5 years

	1 transplant	2 transplants
CR	32%	35%
5yr EFS	20%	31%
5yr OS	37%	51%

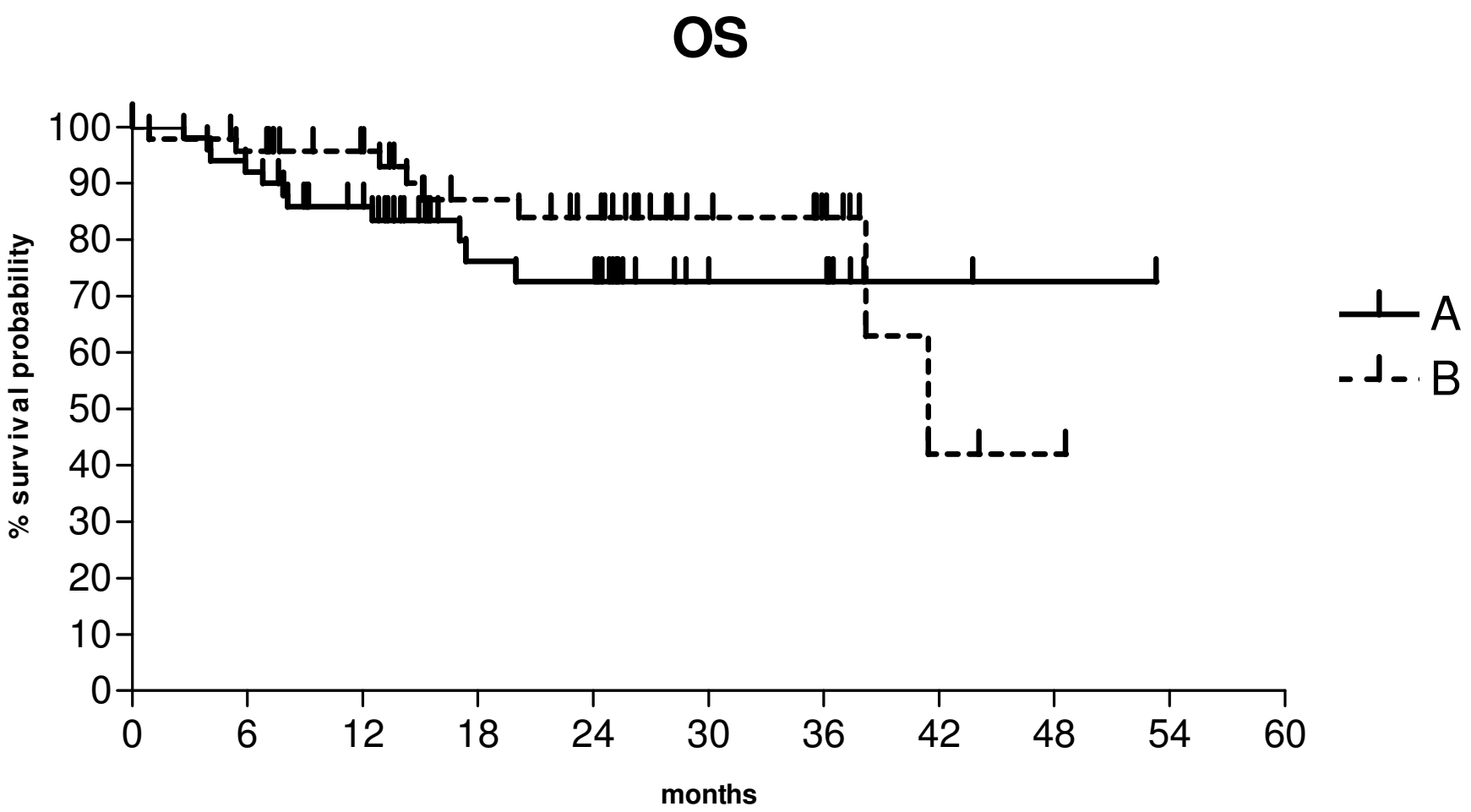
How do we improve the results?

EBMT CD34 selection study (Cellpro)

- 111 pts included
- VAD x 3, Cyclo-mobilization then
- Melphalan 140 and TBI
- CD34-selected vs unselected PBSCT

EBMT CD34 selection results

	CD34-selected (N=56)	Unselected (N=55)
• Neutrophils	10d	10d
• Platelets	11d	9d
• Infections		
(neutropenia)	3.6%	0%
(to day 100)	17.9%	1.8%


OS
% survival probability
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
24
30
36
42
48
54
60
months
A
B

Timing of transplantation

- Fermand et al 1998
- Early ASCT vs late ASCT (rescue for primary resistance or at relapse)
- No significant difference in OS
- Better quality of life for those patients in the early ASCT arm (TWiSTT)

Allogeneic transplant

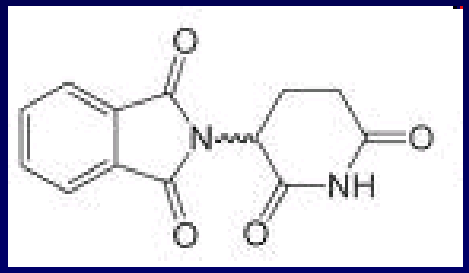
- Suitable for patients <50yrs therefore only a small proportion of patients eligible
- Transplant-related mortality is high
- About 20% of patients remain disease-free at 6 years
- The only genuinely curative treatment
- Favourable prognostic features
  - female gender
  - Stage I disease
  - one previous treatment
  - in CR pre-transplant
- ? Graft vs Myeloma effect

Graft vs Myeloma effect

- Anecdotal evidence that DLI is effective in treating relapsed myeloma after BMT
- Long-term disease free survival in a small number of patients after BMT
- Main problem is GVHD
- Escalating dose DLI may reduce GVHD while maintaining GVM effect

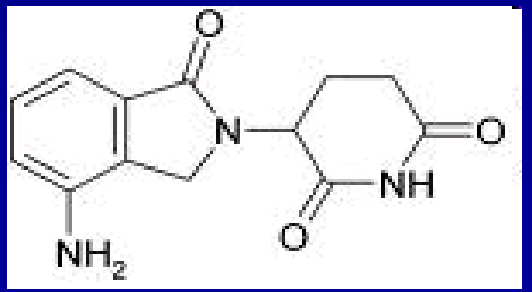
The New Drugs

- thalidomide



- bortezomib (Velcade®)

- lenalidomide (Revlimid®)



Thalidomide

Immunomodulatory effects

- Alters expression of adhesion molecules
- Suppresses production of TNFα
- Increases production of IL10
- Enhances cell-mediated immunity
- Increases B and T cells

Anti-angiogenic

- Inhibits angiogenesis induced by FGF and VEGF in a rabbit and murine cornea assays
- Apoptosis of endothelial cells in established angiogenesis

Thalidomide in Multiple Myeloma

- 169 pts with advanced MM (67% abnormal cytogenetics, 76% previous autograft)
- THAL 200mg/d increased every 2w to 800mg/d

Results:

- 30% of pts had PR (> 50% reduction in pp)
- 14% of pts had CR or nCR
- Response more common in pts with low PCLI and normal cytogenetics
- 2 yr OS 48%
- survival longer in pts with normal cytogenetics, low PCLI and low β2m
- Response rates higher and survival longer in high-risk pts given > 42g THAL in 3 months ?dose-response effect

Barlogie B et al Blood 2001, 98:492

Thalidomide (update Aug 2008)

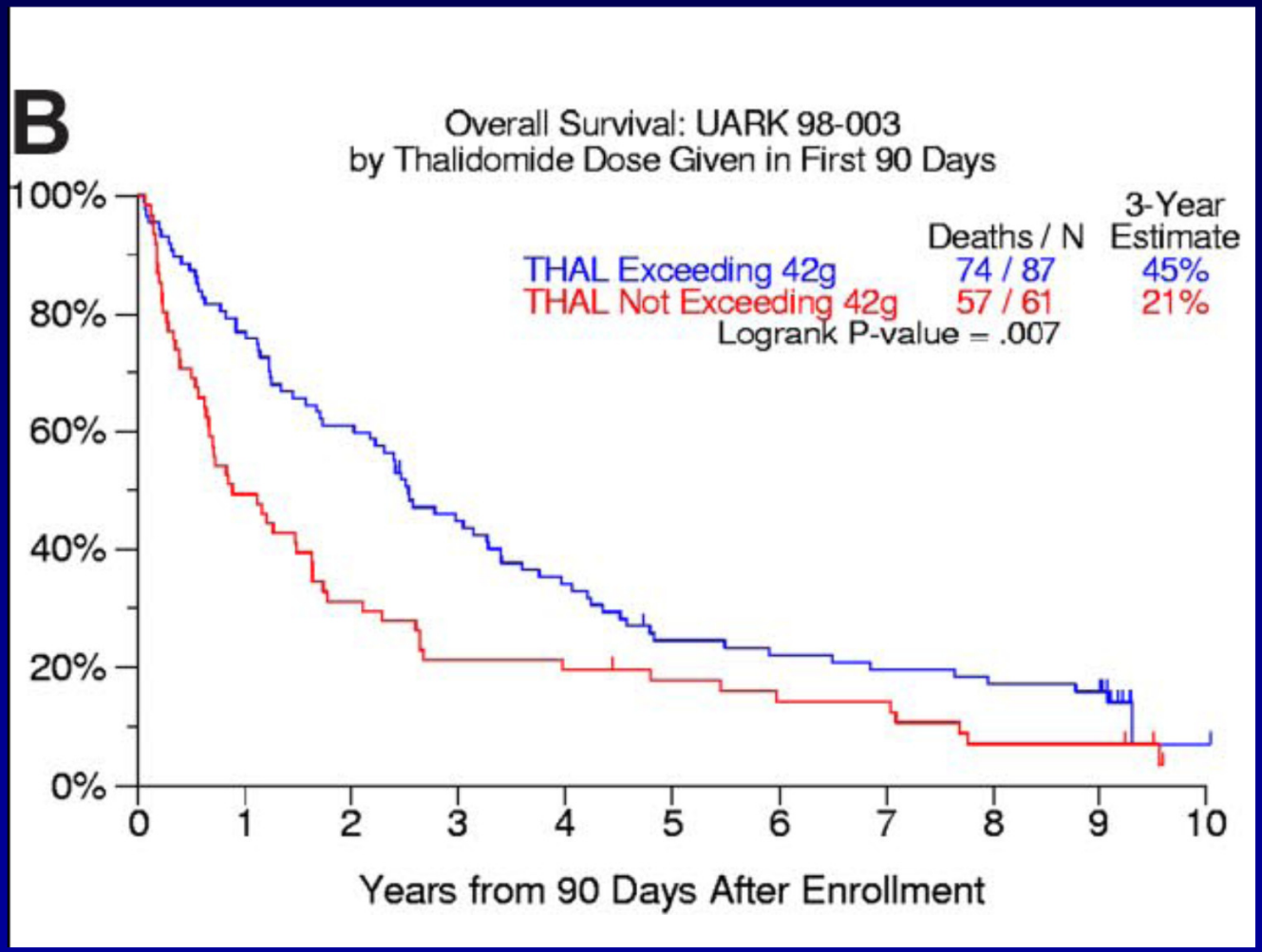
- 169 pts
- Median follow up 9.2 years
- 17 pts alive
- 10 pts event-free

Multivariate analysis

- Cytogenetic abnormalities and λ-light chain expression – poor overall survival

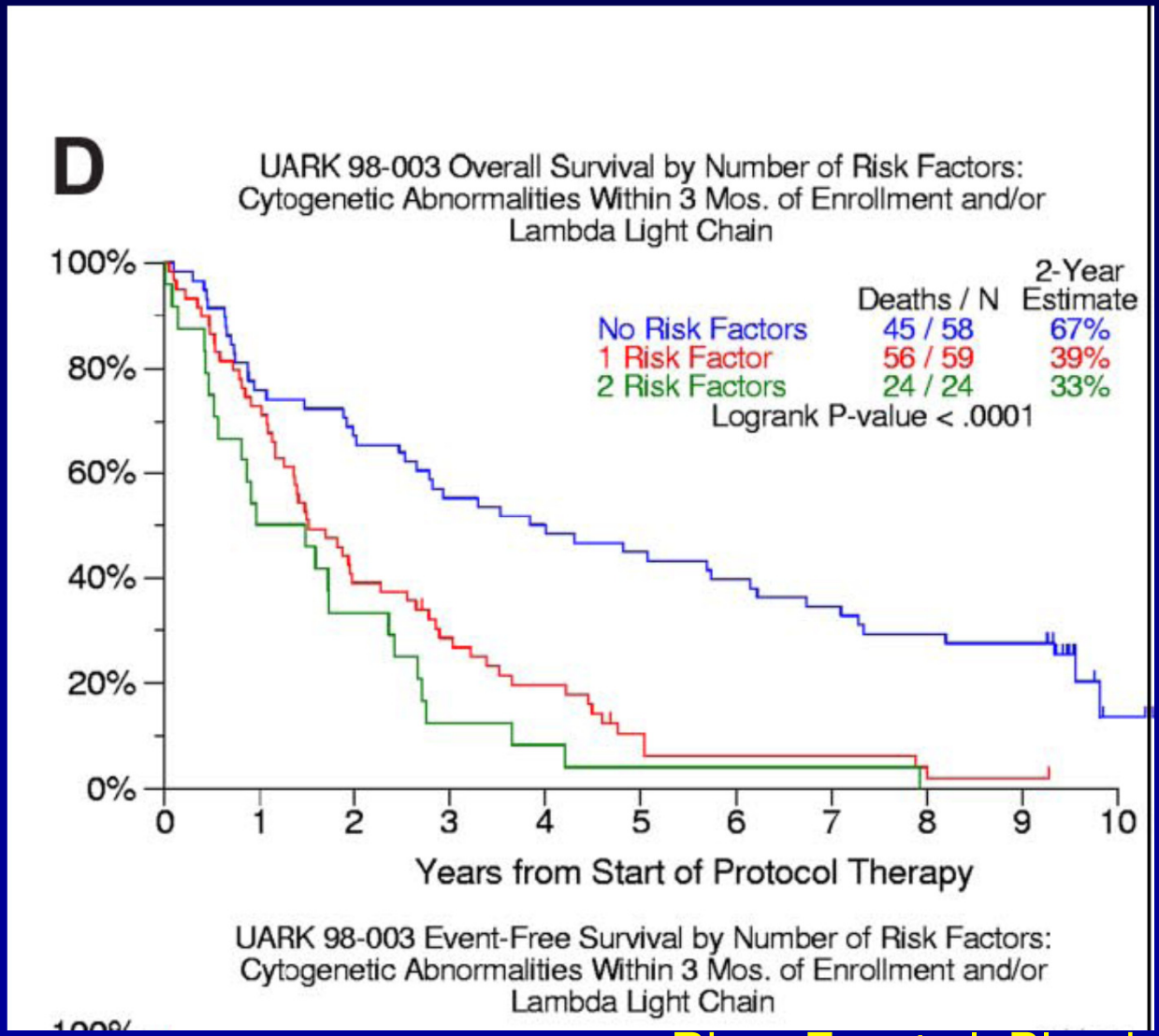
Rhee F v et al. Blood, 2008,112:1035

Thalidomide (update Aug 2008)



Rhee F v et al. Blood, 2008,112:1035

Thalidomide (update Aug 2008)



Rhee F v et al. Blood, 2008,112:1035

Thalidomide and dexamethasone in Multiple Myeloma

- 44 pts with relapsed/refractory myeloma
- THAL 200mg/d increased after 2w to 400mg/d
- Dex 20mg/m^2 (d1-4, 9-12, 17-20) 1st cycle then d1-4 subsequent cycles

Results:

- 55% of pts achieved a PR

Side effects

- constipation
- somnolence
- peripheral neuropathy

Dimopoulos et al Ann Oncol 2001, 12:991

Thalidomide
- advantages and limitations -

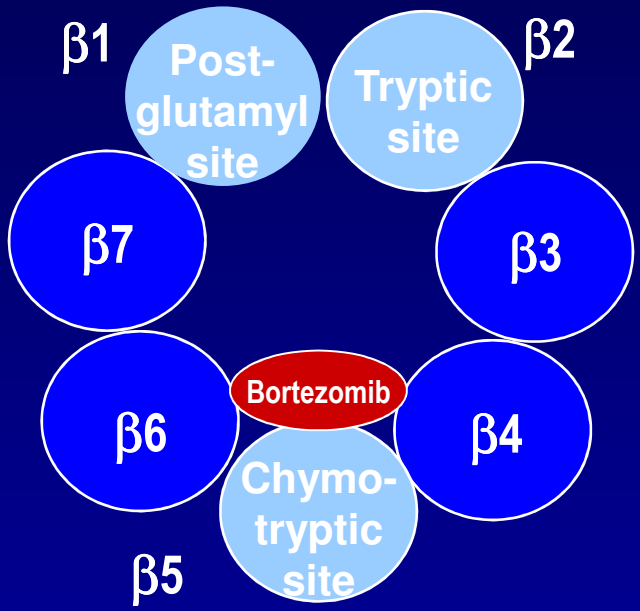
- Advantages:
  - activity:
    - single agent: 30%,
    - activity increases when combined with: steroids (60%), chemotherapy
  - oral drug
  - up to 10 y of experience in relapsed myeloma
  - Affordable

- Limitations:
  - toxicity:
    - dose-limiting
    - side effect profile: neuropathy, VTE, somnolence and constipation

Cross section of β ring of 20S Proteasome

Bortezomib
(Dipeptidyl boronic acid)

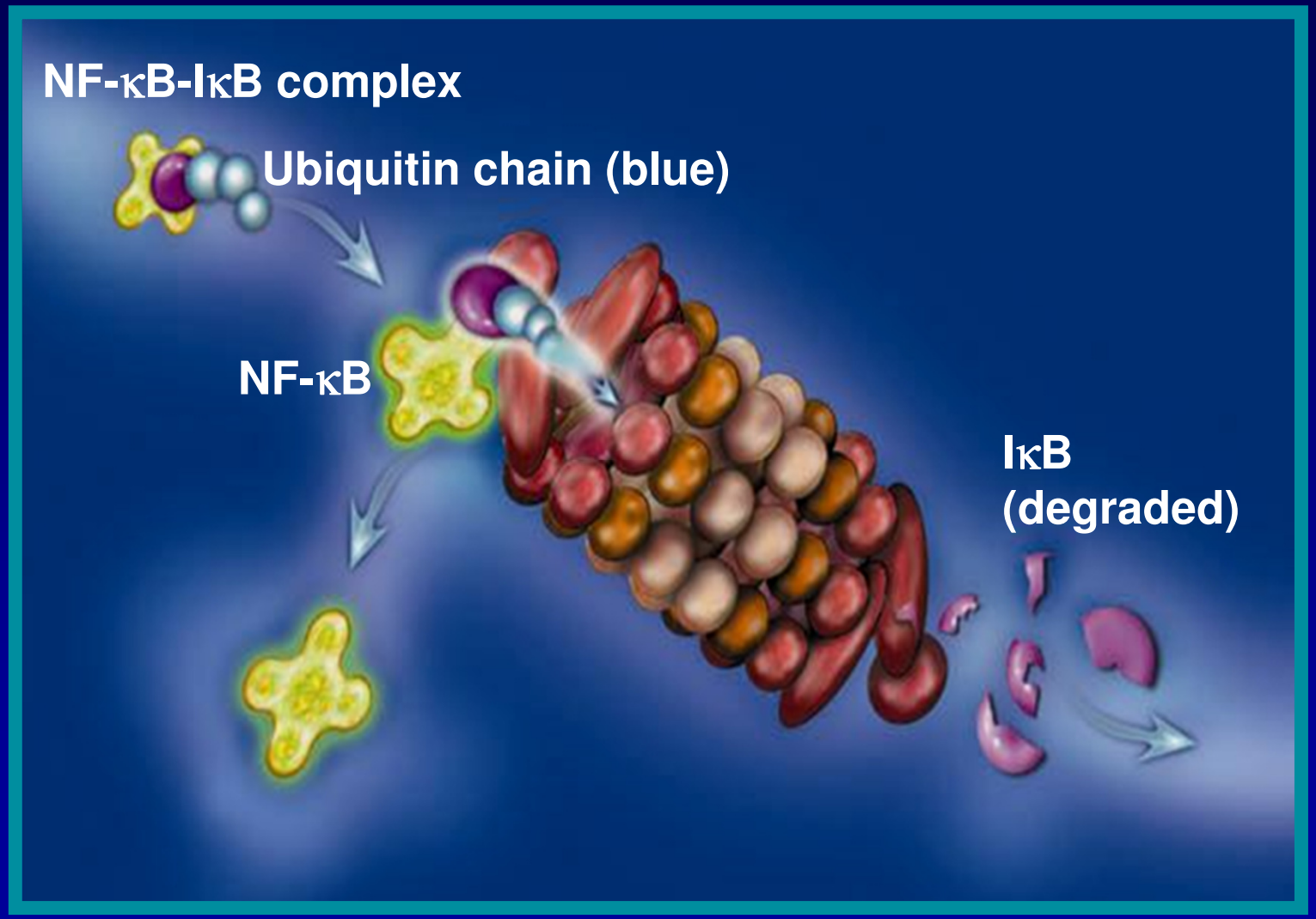
Cross-section of β-ring



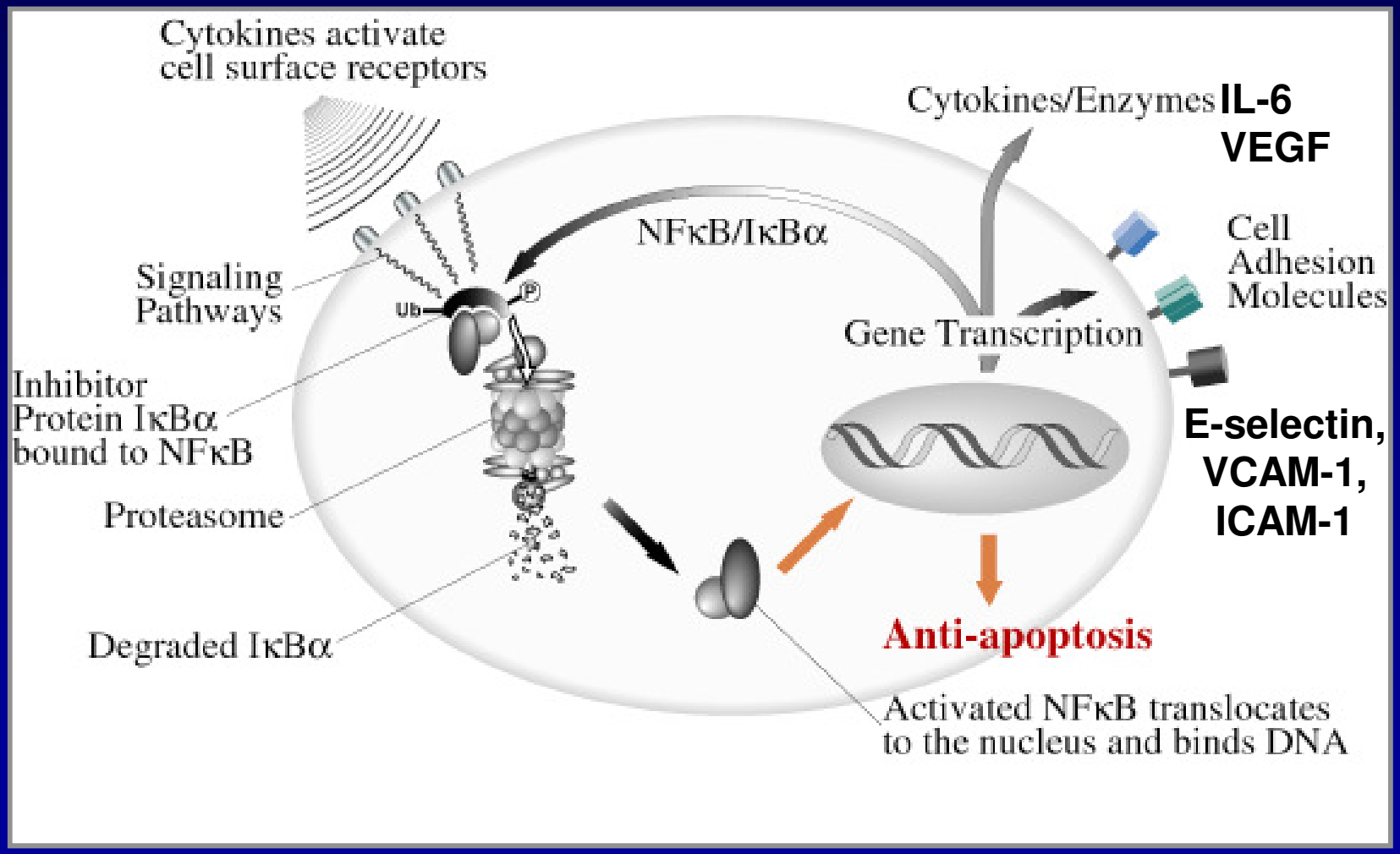
(reversible inhibitor of chymotryptic active site of proteasome β subunit)

DeMartino *et al. J Biol Chem* 1999;274:22123;
Seemuller *et al. Science* 1995;268:579;
Adams *et al. Bioorg Med Chem Lett* 1998;8:333

NF-κB Activation After IκB Degradation by the Proteasome



NF-κB Activation Is Pivotal for Myeloma Growth



APEX- Treatment Plan

Randomization

Bortezomib		Dexamethasone
8 cycles	*Induction*	4 cycles
1.3 mg/m^2 IV push D 1, 4, 8, 11 q 3-wk cycle		40 mg PO D 1–4, 9–12, 17–20 q 5-wk cycle
3 cycles	*Maintenance*	5 cycles
1.3 mg/m^2 IV push D 1, 8, 15, 22 q 5-wk cycle		40 mg PO D 1–4 q 4-wk cycle
273 treatment days		280 treatment days

Richardson PG et al. NEJM 2005, 352:2487

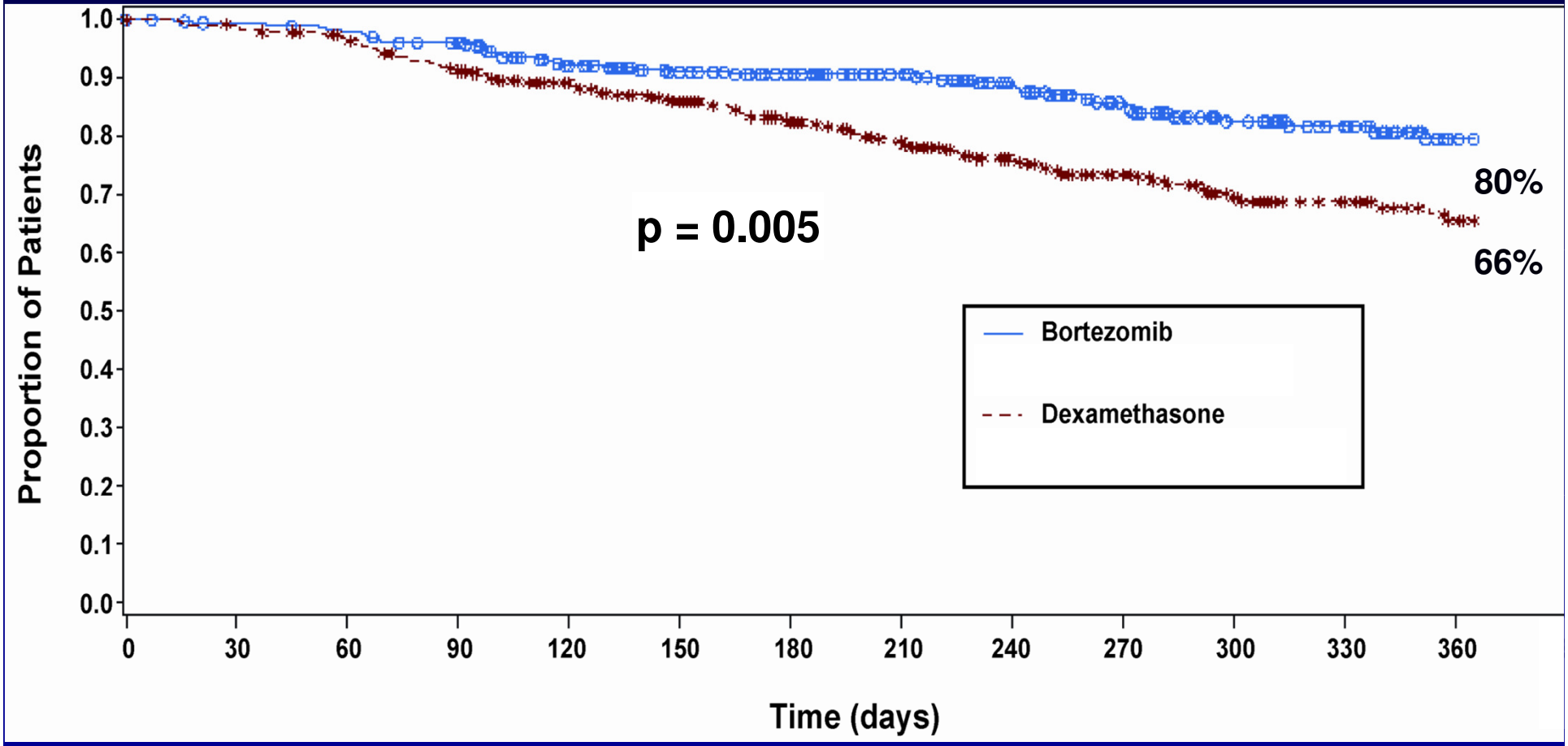
APEX Trial

- 669 pts randomized

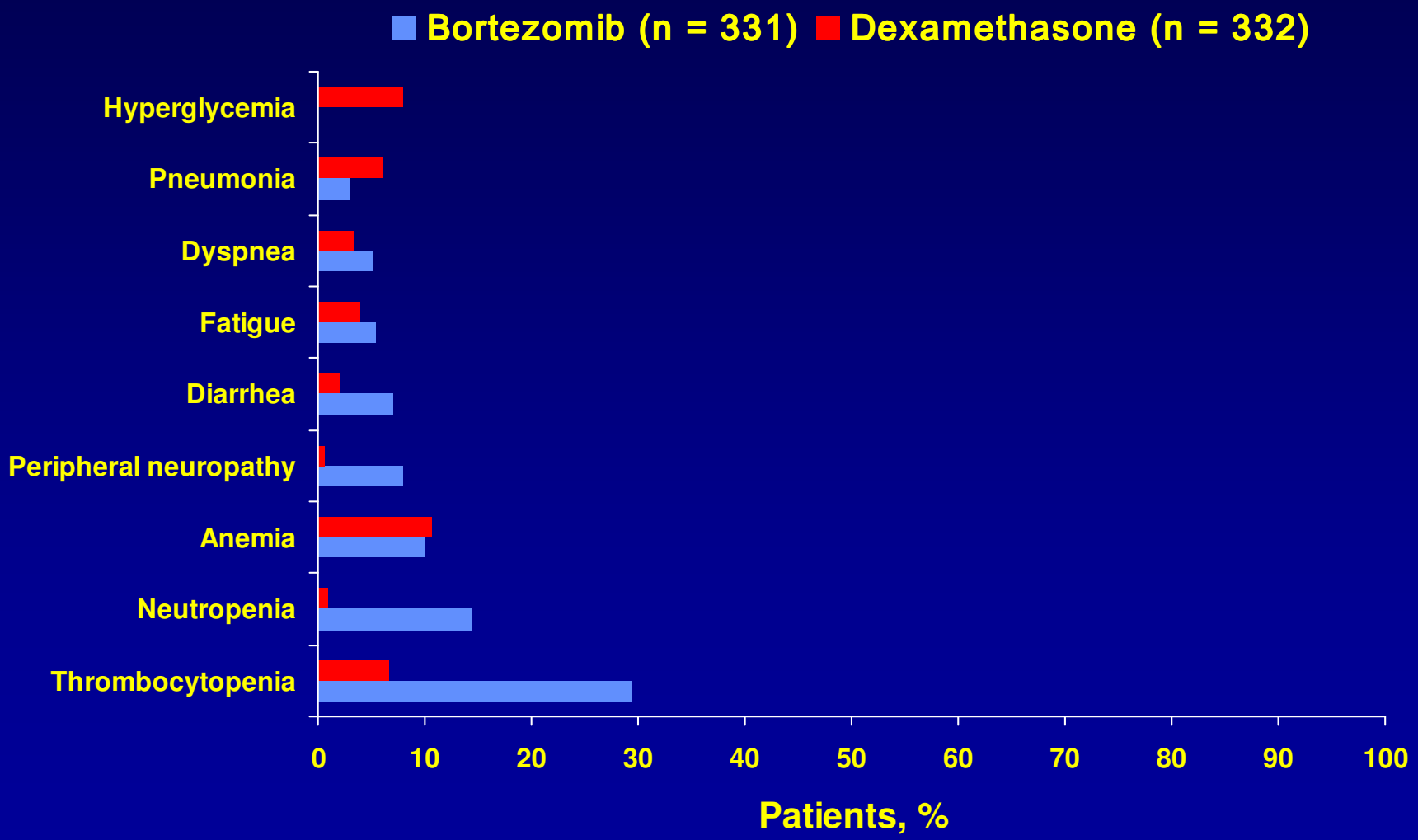
	Bortezomib	Dex
CR+PR	38%	18%
Median TTP	6.2months	3.5months
1 year survival	80%	66%

Richardson PG et al. NEJM 2005, 352:2487

1-Year Survival (N = 669)



Adverse Effects (>G3)



Bortezomib
- advantages and limitations -

- Advantages:
  - activity:
    - ✓ single agent: 35-40%
    - ✓ high and rapid responses, also when combined with other agents (steroids or chemotherapy)
  - Phase III study evidence

- Limitations:
  - high cost
  - toxicity: neuropathy, systemic toxicity
  - IV administration

Lenalidomide+Dex vs Dex in Relapsed Myeloma

- 177 pts randomized to len + dex (len d1-21)
- 176 pts randomized to dex

	Len + Dex	Dex
CR + PR	61%	20%
CR	14%	<1%
TTP	11.1 months	4.7months
Median OS	29.6m	20.2months
Neutropenia	41.2%	4.6%
VTE	14.7%	3.4%

Weber DM et al N Engl J Med. 2007, 357:2123

Lenalidomide+Dex vs Dex in Relapsed Myeloma

- 176 pts randomised to len + dex
- 175 pts randomised to dex

	Len + Dex	Dex
CR + PR	60.2%	24%
CR	15.9%	3.4%
TTP	11.3 months	4.7months
Neutropenia	29.5%	2.3%
Thrombocytopenia	11.4%	5.7%
VTE	11.4%	4.6%

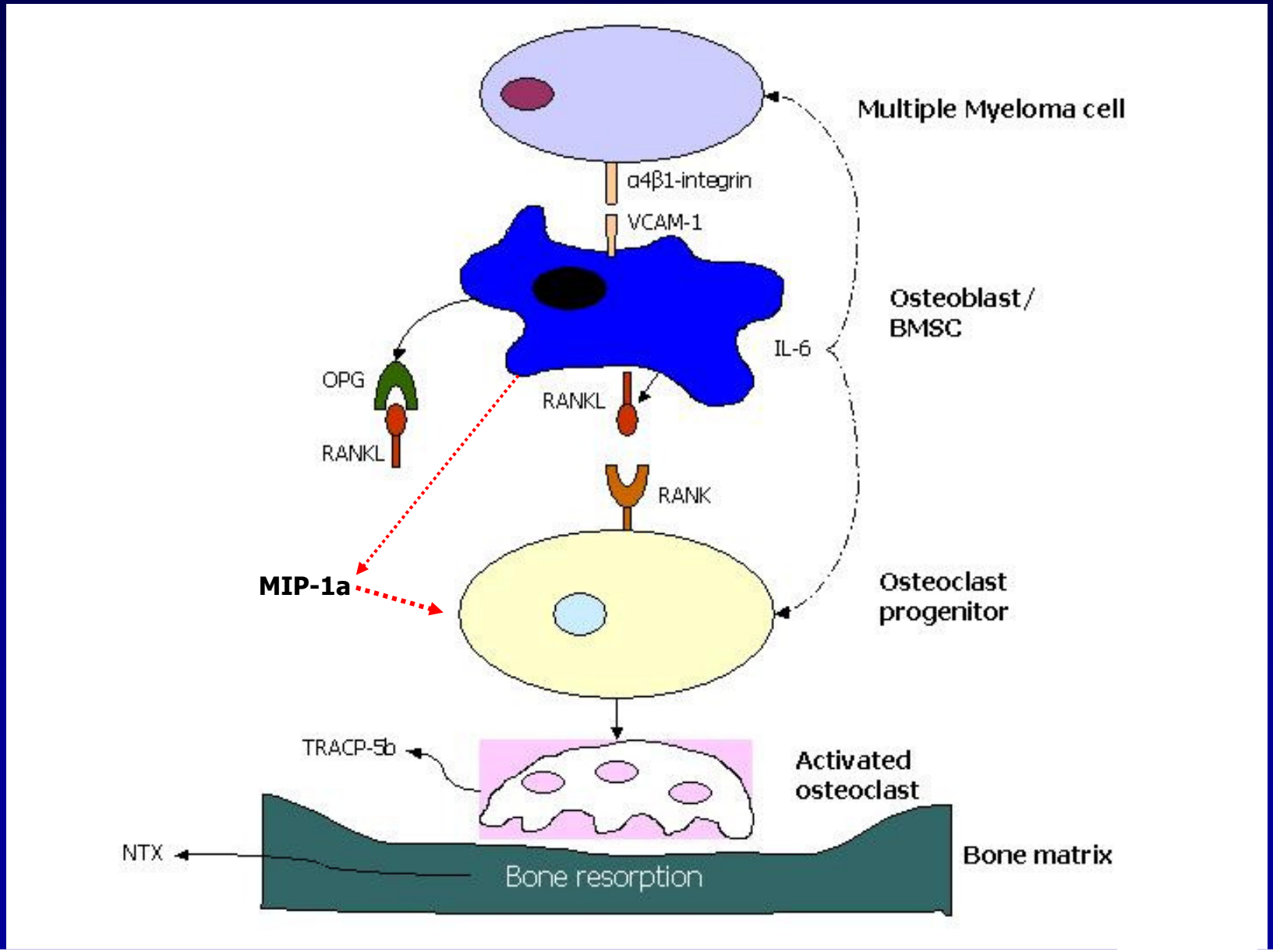
Dimopoulos M et al NEJM 2007, 357:2133

Lenalidomide
- advantages and limitations -

- Advantages:
  - activity:
    - single agent: 25%
    - combined with steroids :60%
  - oral drug
  - evidence from phase III trials

- Limitations:
  - high cost
  - toxicity: particularly hematological
  - need for inclusion in Patient Risk Management Program

RANK – RANKL PATHWAY in MM



Conclusions 1

- Myeloma remains incurable in the majority of patients
- Allogeneic SCT should be considered in pts <50yrs with a matched sibling
- Autologous SCT is the treatment of choice for most patients
- Post-transplant strategies such as RIC SCT, vaccination and ex-vivo T cell manipulation require further evaluation

Conclusions 2

- Thalidomide has anti-myeloma activity but the precise role needs further evaluation
- Many new agents including IMiDs,PS-341, tyrosine kinase inhibitors, RANK-Fc and monoclonal antibody treatment require further evaluation
- Participation in clinical trials should be encouraged

MATT

'There is a side effect with this new drug – the NHS goes bankrupt'