Four decades of myeloma

Ken Romeril
Wellington Blood and Cancer Centre

The first recorded case
Sarah Newbury - 1844

Sarah's Treatment at Barts in 1844

- Hospitalised with multiple fracture of clavicles and right humerus and radius
- Given wine and arrowroot, a mutton chop and a pint of porter daily
- Also treated with a rhubarb pill, an infusion of orange peel and an opiate
- Died suddenly and autopsy revealed that the sternum was replaced by a red substance similar to that seen in Mr McBean (a grocer treated by Dr Bence-Jones)

Move forward to 1974

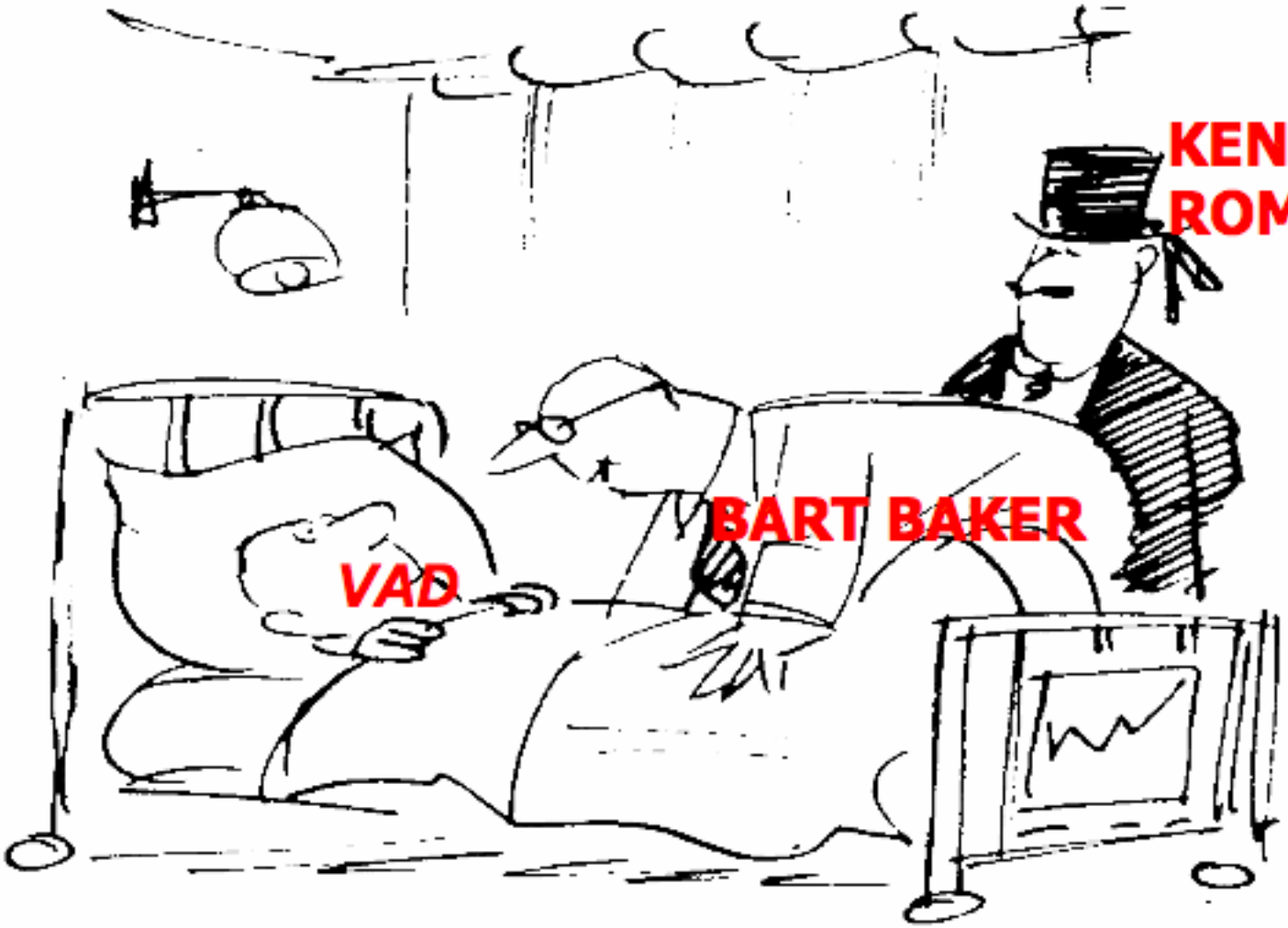
- Dr Milan Brych ran Auckland Cancer Ward
- We treated myeloma with Melphalan and Pred
- Average survival about 2 years
- Patients with myeloma and renal failure were not treated (at least not in ChCh)

Autologous transplant history

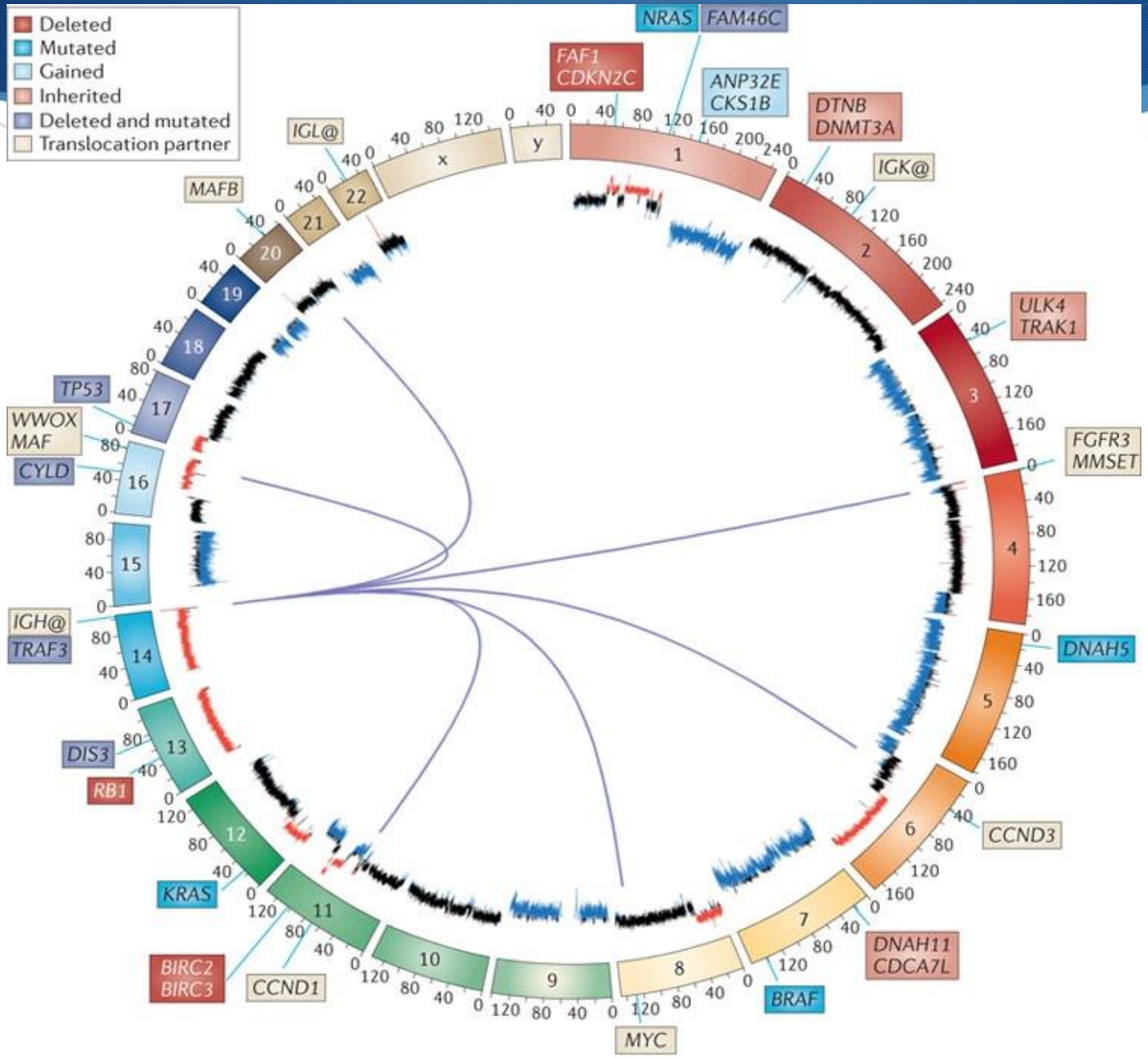
- 1983 – McElwain and Powles (Marsden) pioneered approach using HDM 140 mg/m2
- 1987- Treated 6 patients at Wellington but HDM given with no stem cell rescue and some patients did not recover their marrows. This approach abandoned until next decade because of excessive toxicity and advent of new technology.

Move forward to 1994
Success at last !

- Autologous transplantation for myeloma commenced at Wellington Hospital mainly because of new Kobe cell separator and the discovery of the mobilisation of peripheral blood stem cells using growth factors
- Still using melphalan and cyclophosphamide plus prednisone but VAD induction to preserve stem cells



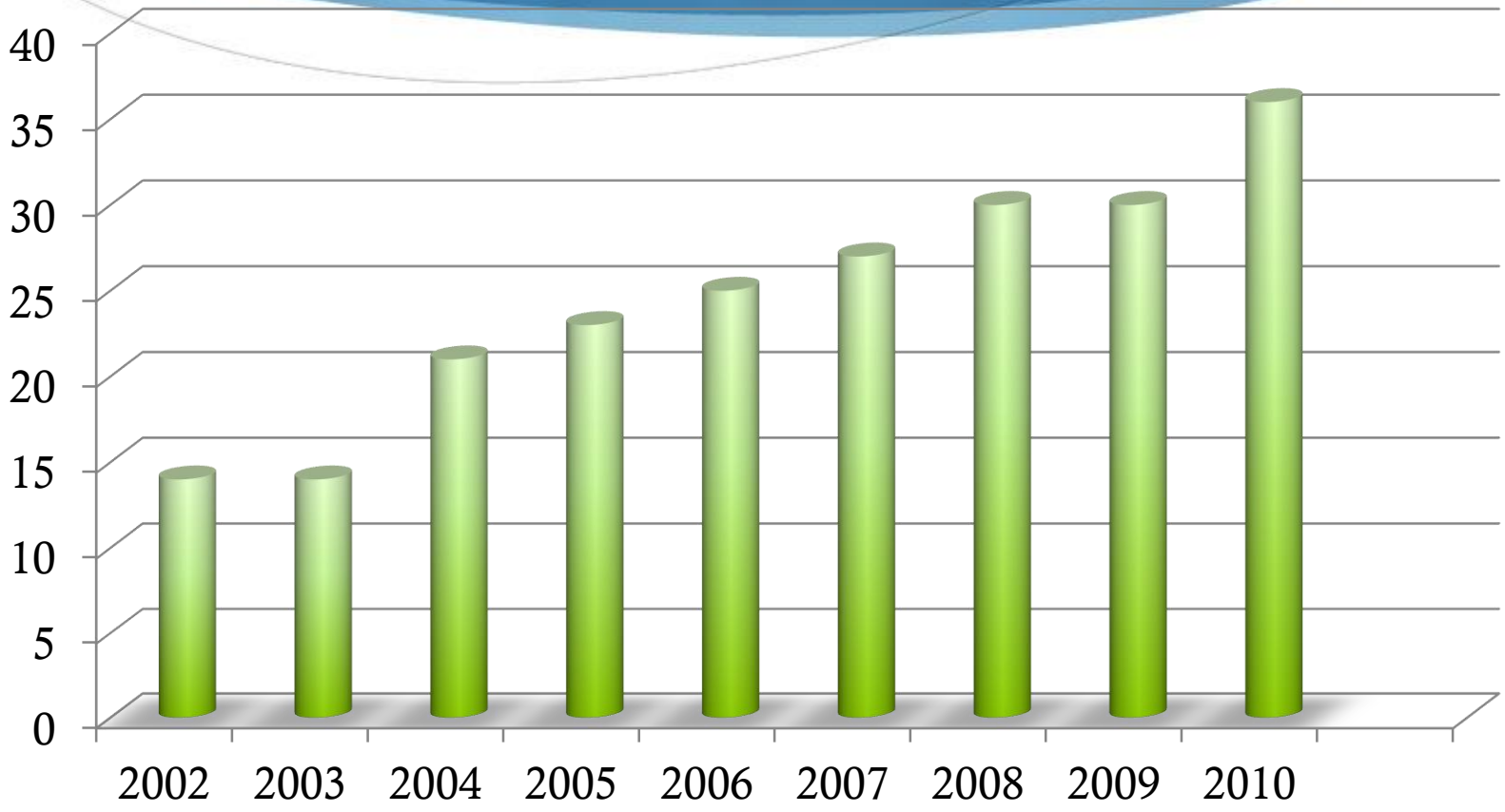
"If its alright with you Mr. VAD ...
I like a second opinion."



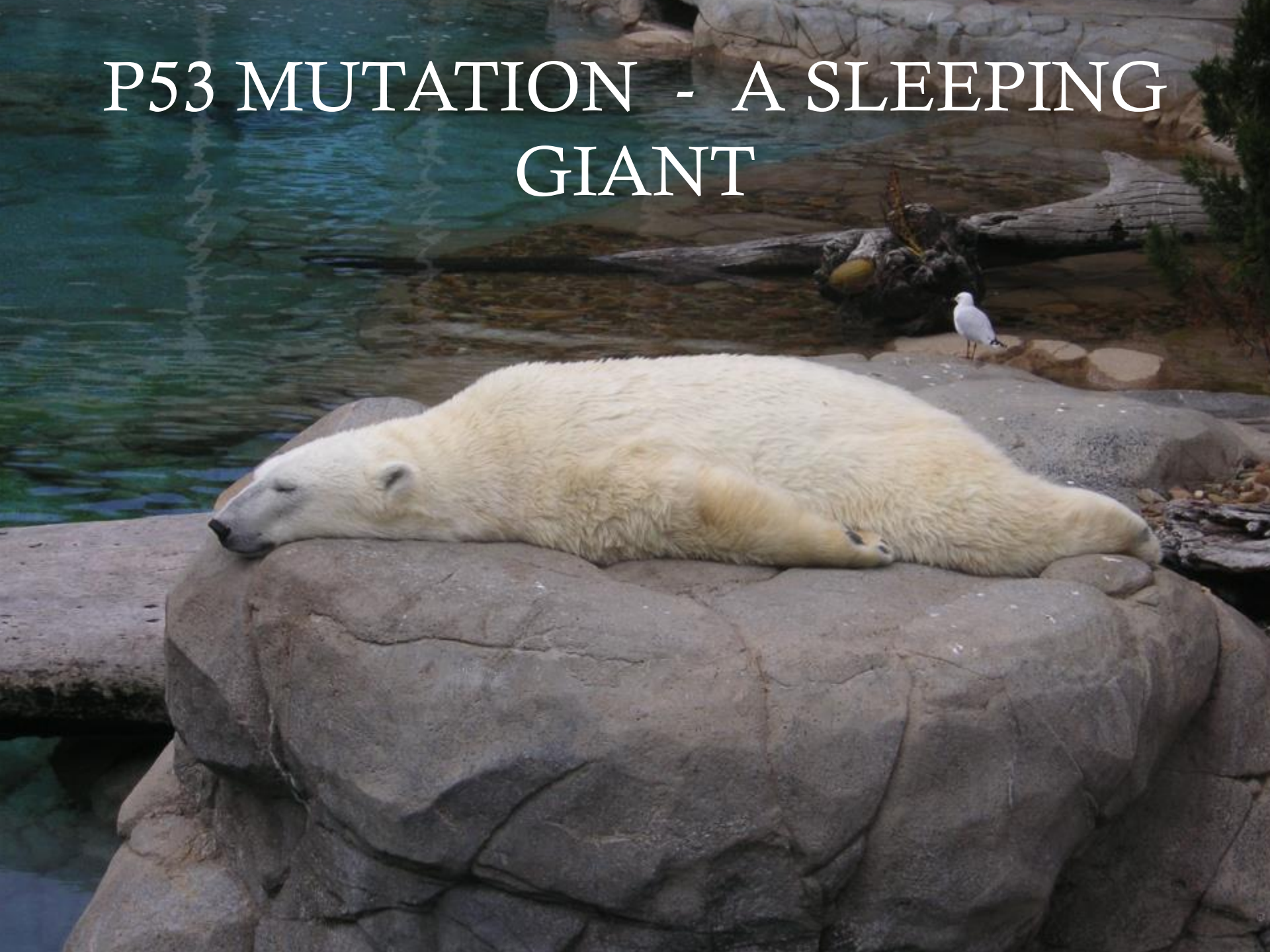
CIRCOS PLOT GENOME

Nature Reviews | Cancer

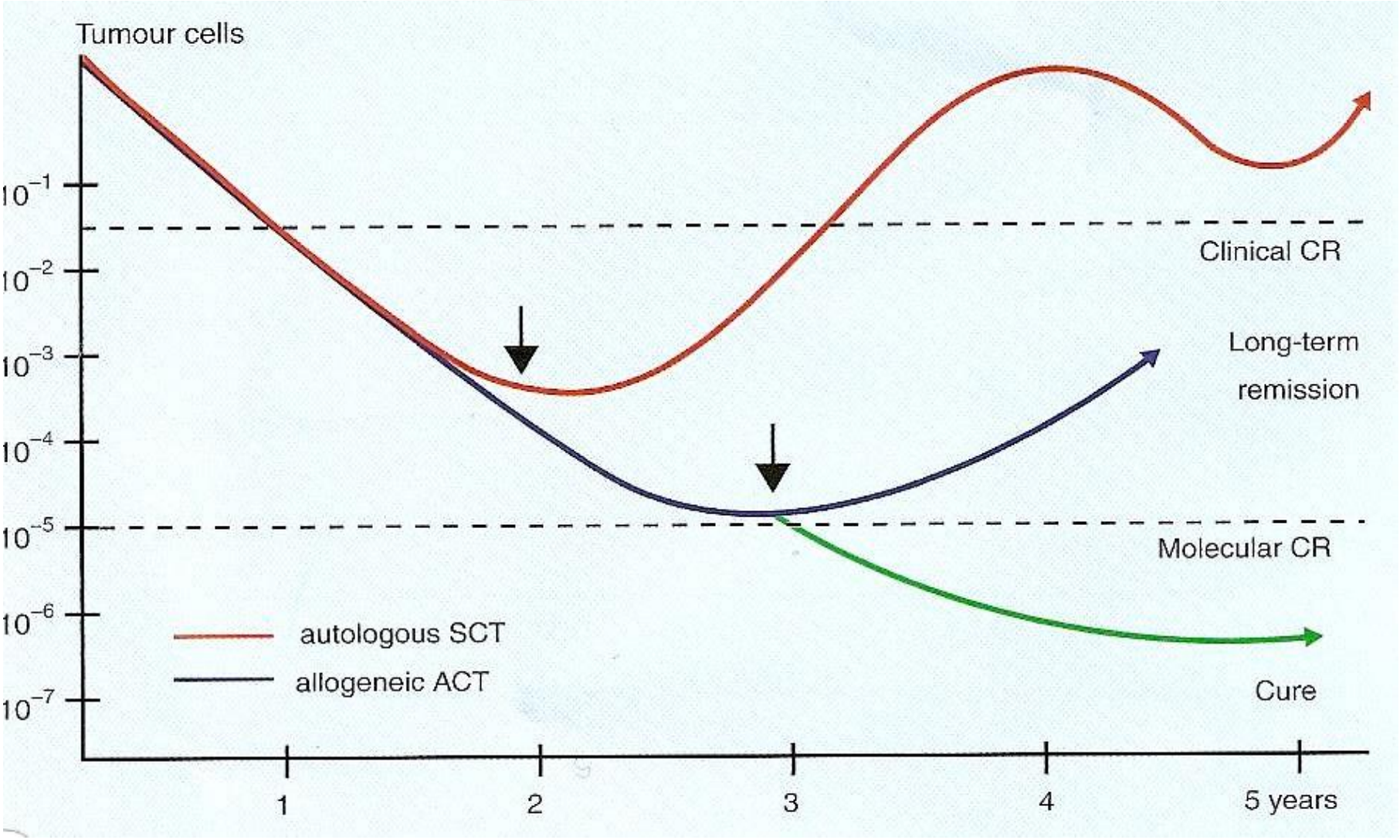
Wellington Myeloma Incidence



P53 MUTATION - A SLEEPING GIANT



Depths of remission in MM



INTERNATIONAL MYELOMA WORKING GROUP RECOMMENDATIONS FOR GLOBAL MYELOMA CARE

H Ludwig,JS Miiguel, MA Dimopoulos,A Palumbo,R Garcia Zanz, R Powles,S Lentzsch,W Ming Chen,J Hou, K Romeril et al

"cytogenetic testing is desirable but not mandatory"

LEUKAEMIA 2014 28, 981-992

mSMART : Classification of Active MM

High-Risk (25%)

FISH
- Del 17p
- t(4;14)*
- t(14;16)

Cytogenetic Deletion 13

Cytogenetic Hypodiploidy

PCLI ≥3%

Standard-Risk (75%) *

All others including:
- Hyperdiploid
- t(11;14)
- t(6;14)

*Patients with t(4;14), β2M<4 mg/l and Hb≥10g/dl may have intermediate risk disease

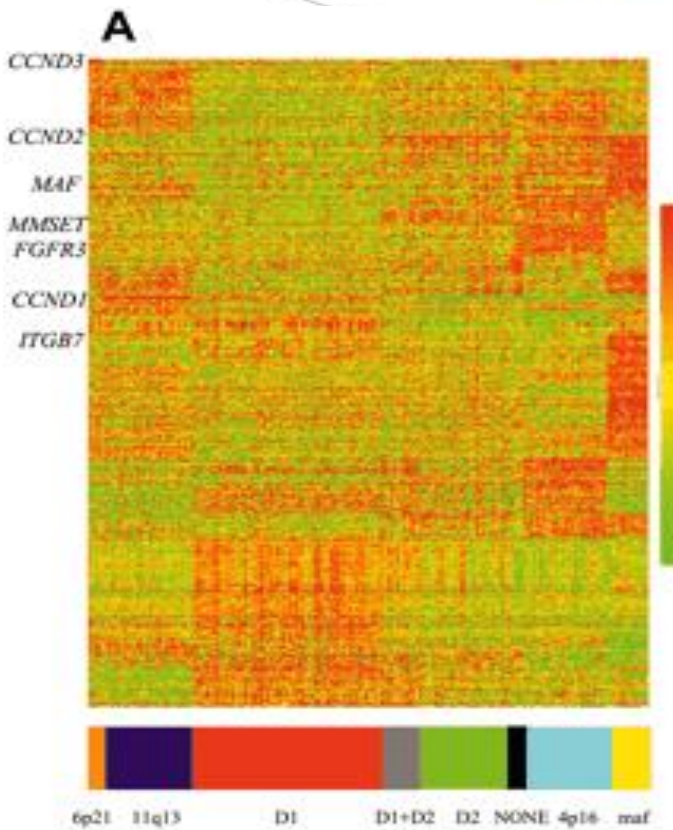
Version 2. January 2008

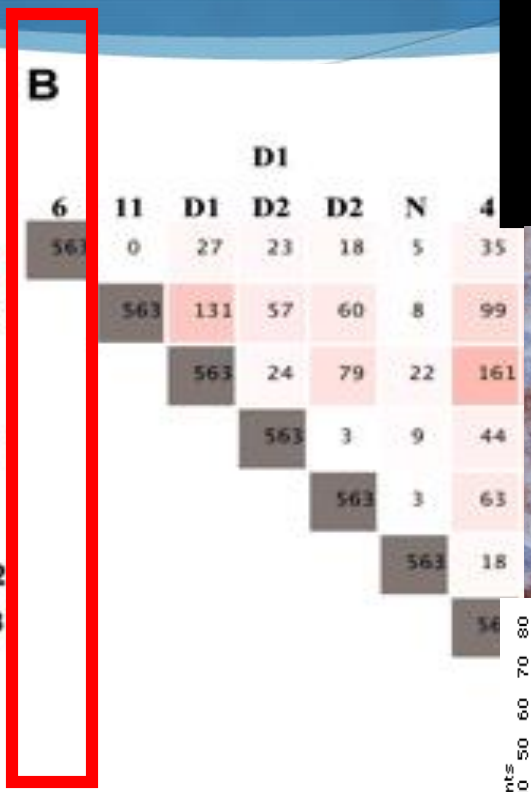
ASH abstract 5371 in 2013

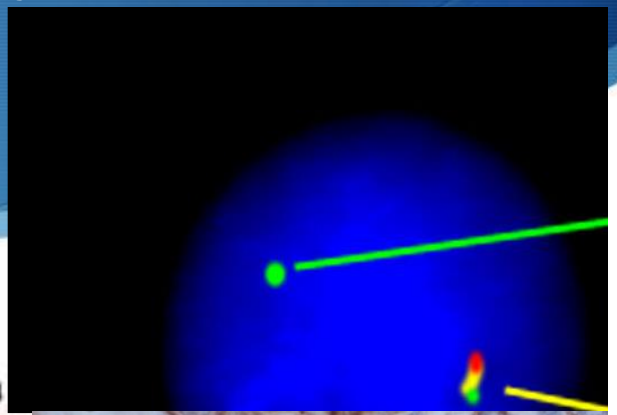
- A High-Risk Genetic signature is predictive for poor outcome in auto-transplant eligible multiple myeloma patients even with use of novel agents. A single institution study.
- Looked at 140 patients on basis of cytogenetics and FISH and analysed their OS
- K. Romeril, H Buyck, R Parfitt, C Wood, A d'Souza and R Weinkove

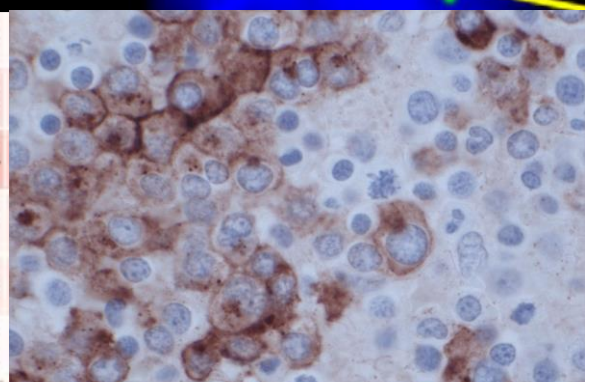
T(4 ;14) MYELOMA

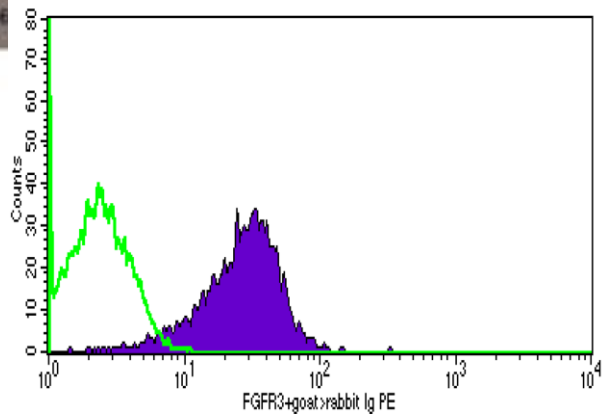
t(4;14) - 15% of myeloma



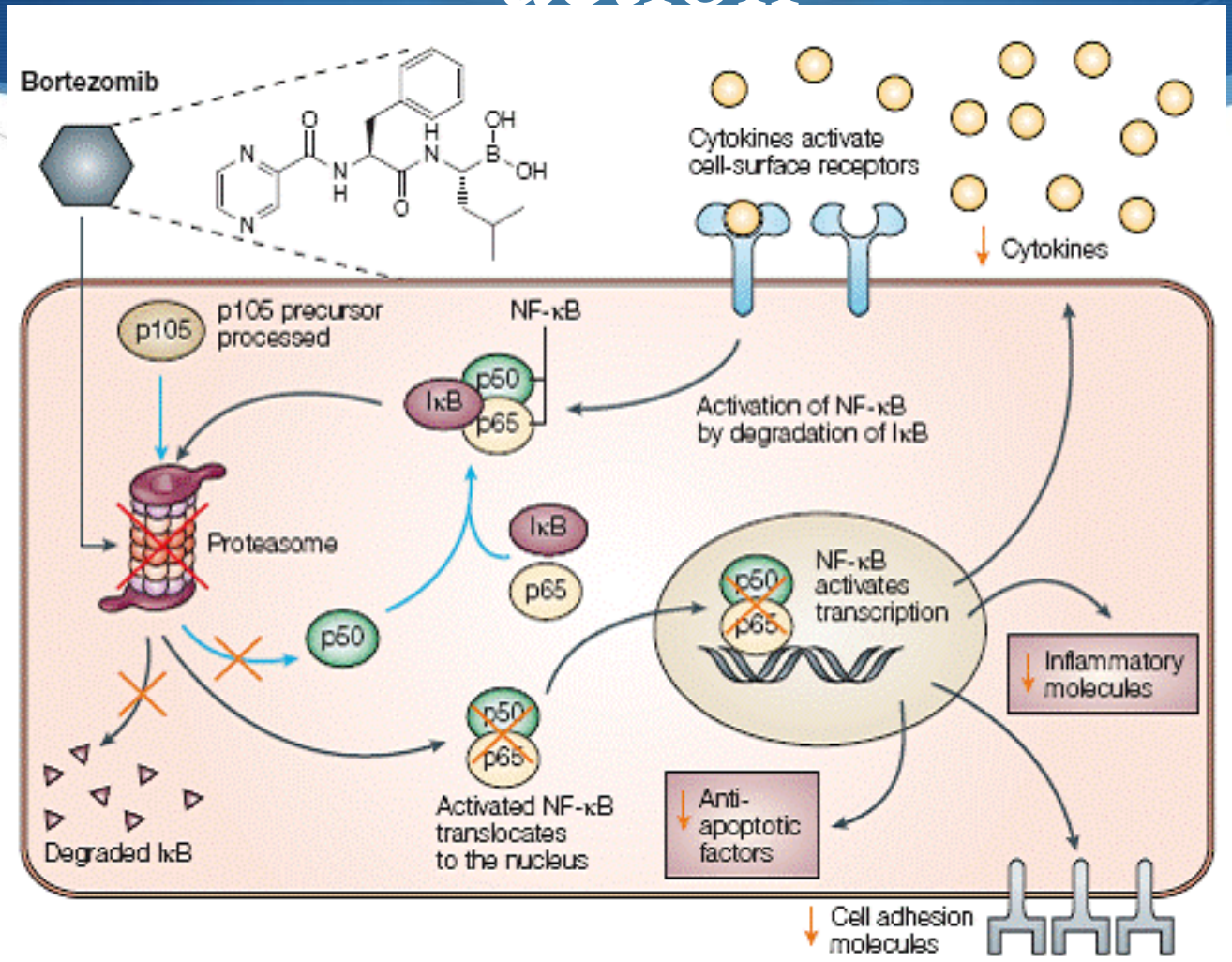








Bortezomib mechanisms of action



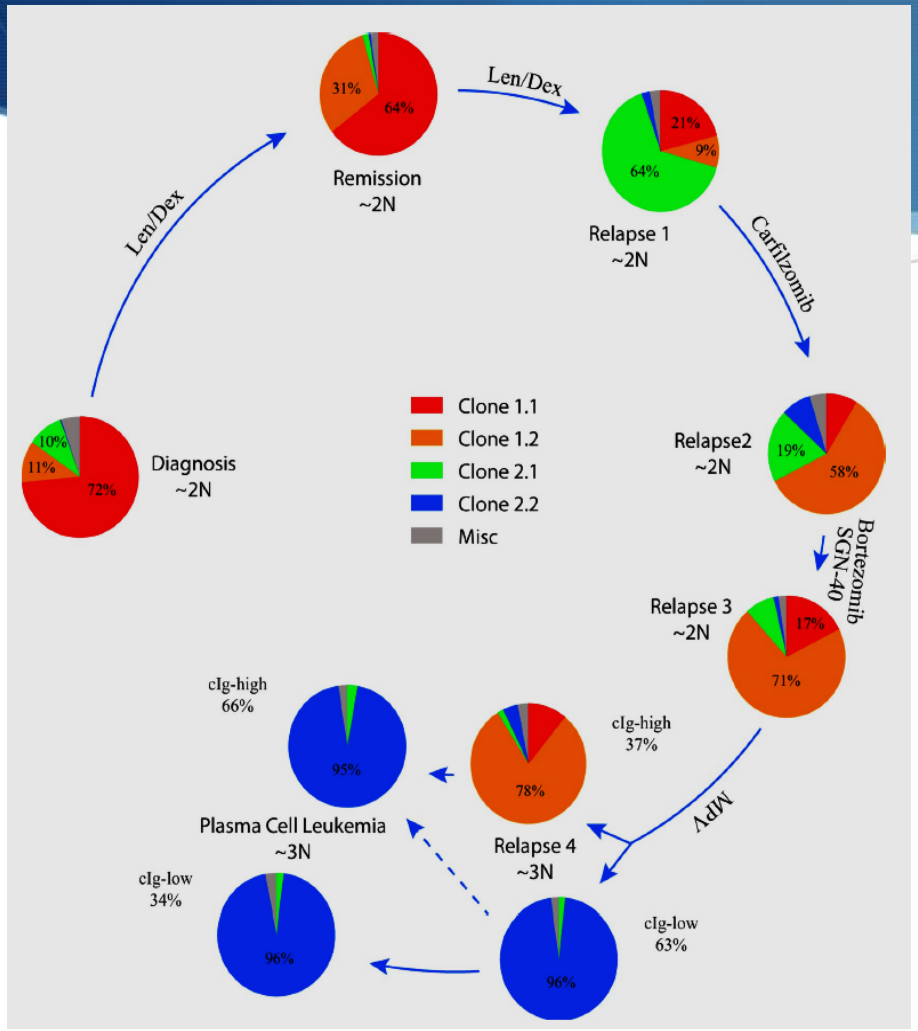
http://www2.cch.org.tw/tumor/images/drug/durg23圖一.gif

Journal of Clinical Oncology July 2010

- Bortezomib plus dexamethasone induction improves outcome of patients with t(4;14) myeloma

Avet-Loiseau et al

How can we achieve cure in Myeloma?



To eradicate the tumor clone: *to achieve and mantain the best*

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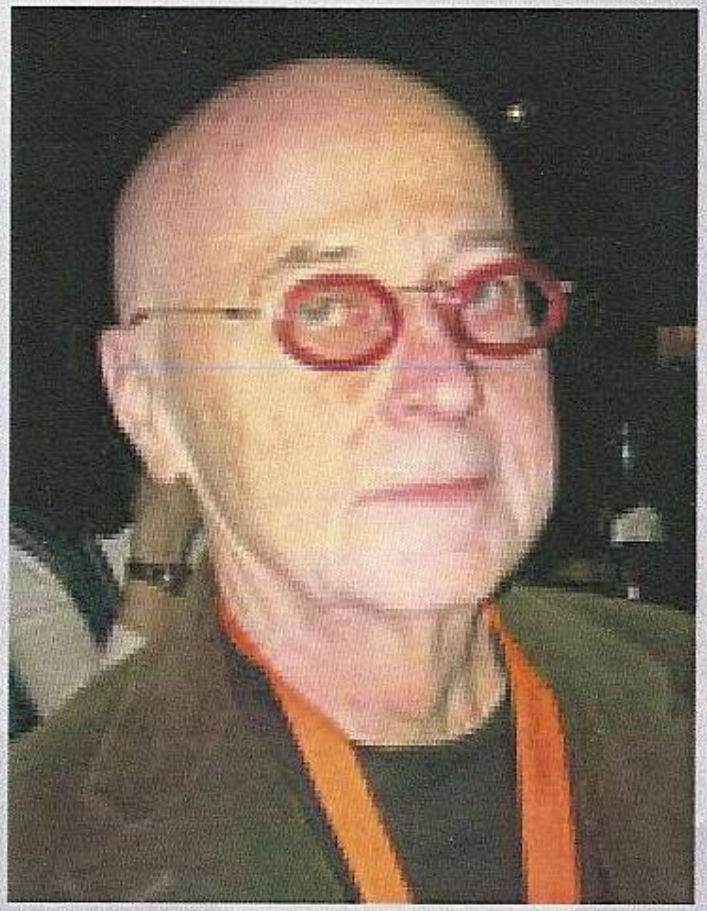
-
-

The Red Baron?



Motto: Hit Him With Everything

http://www.nbbd.com/festivals/warbird/2006/RedBaronDemoTeam.jpg

Current Wellington approach

Transplant eligible

- Induce with 4 cycles of CyBorDex
- Auto-transplant
- Consider consolidation with 4-5 cycles of VTD consolidation

Transplant ineligible > 65 years

- Induction with 9 cycles of either CyBorDex or 9 cycles of VMP as in modified Vista protocol
- Relapsed patients get similar (if Velcade naïve)
- Consider clinical trial novel agents

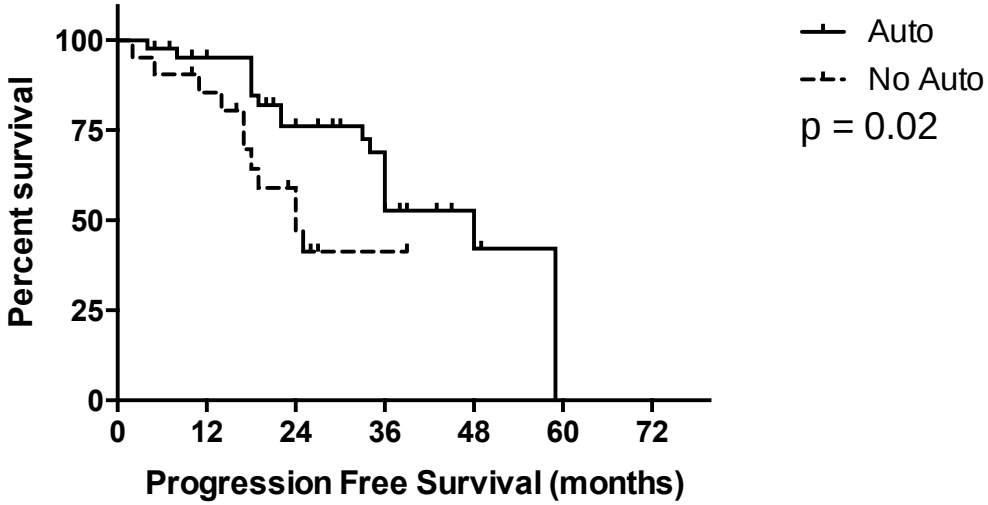
Study outline

- All new MM auto eligible patients treated in a standard approach with 4 CyBorD cycles
- Diagnostic marrow with FISH and flow studies using 8 colour flow.CD38,138,56,20,19 L.C.
- Stem cell mobilisation with Cyclo – Peg and stored
- A HDM of 200 mg/m2 was performed
- Day 100 marrow for MRD analysis and all patients offered 5 cycles VTD consolidation

Response post 4 cycles

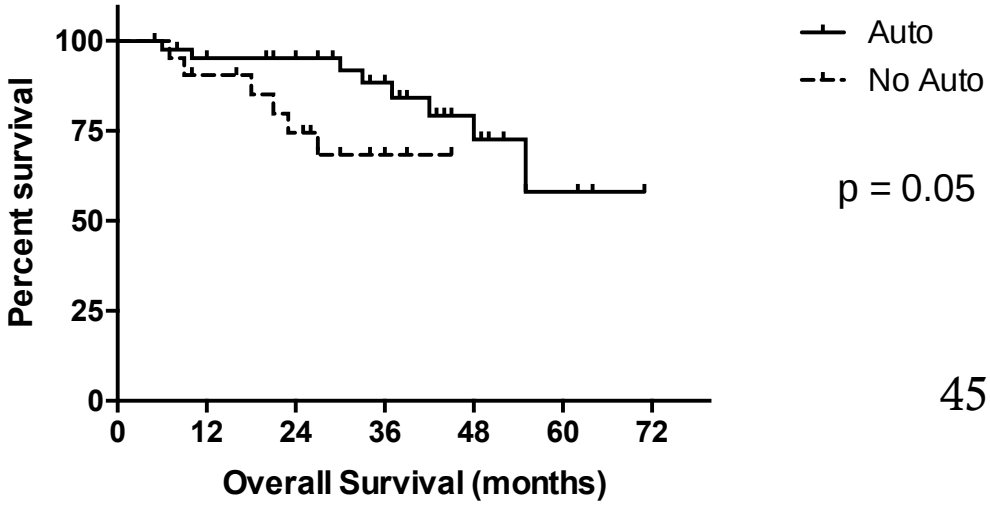
RESPONSE	PERCENTAGE
CR/nCR	46 %
>VGPR	23%
PR	23%
SD progressive	6%

Progression Free Survival
AutoSCT vs. No AutoSCT



p = 0.02

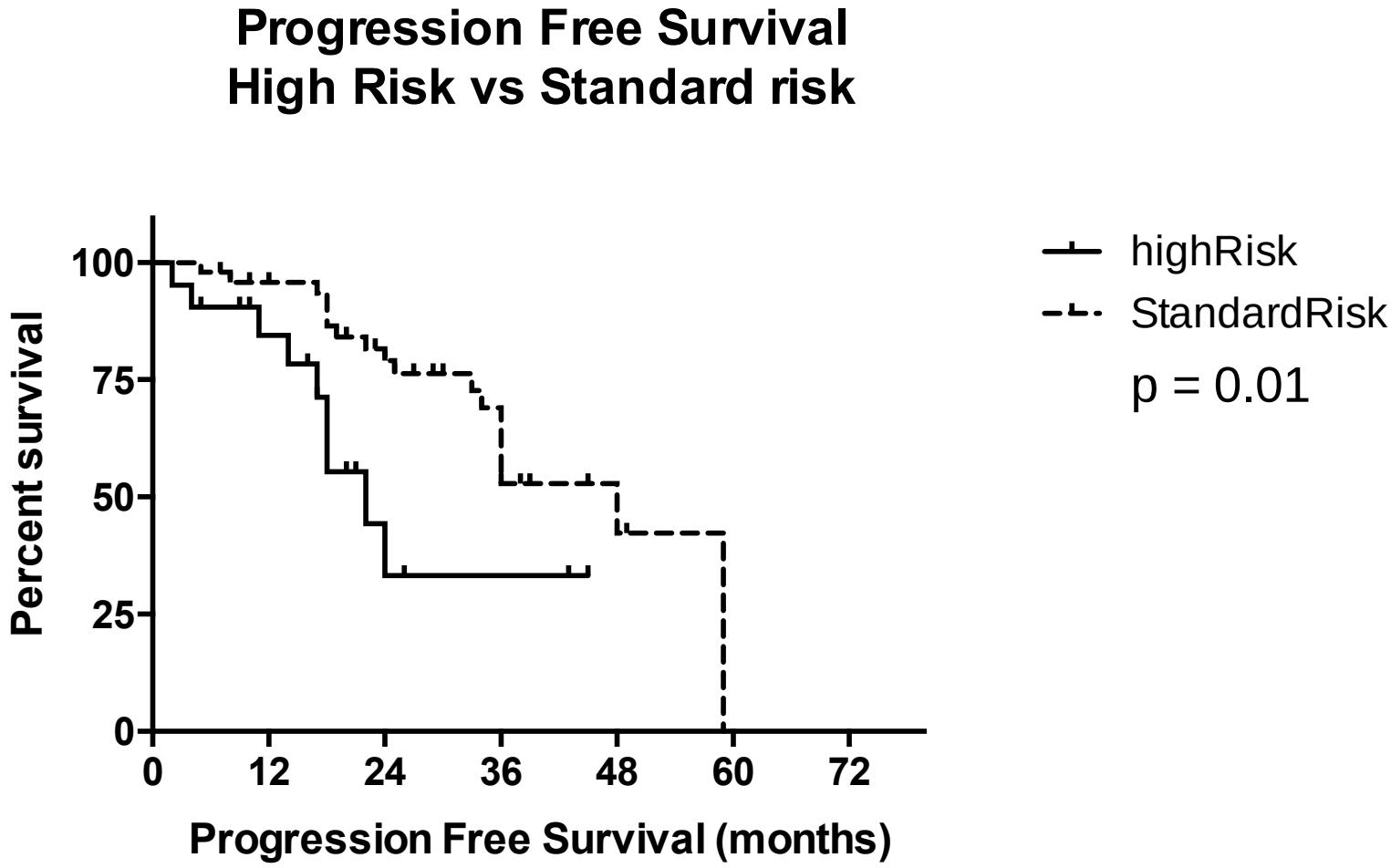
Overall Survival
Auto SCT vs. No Auto SCT

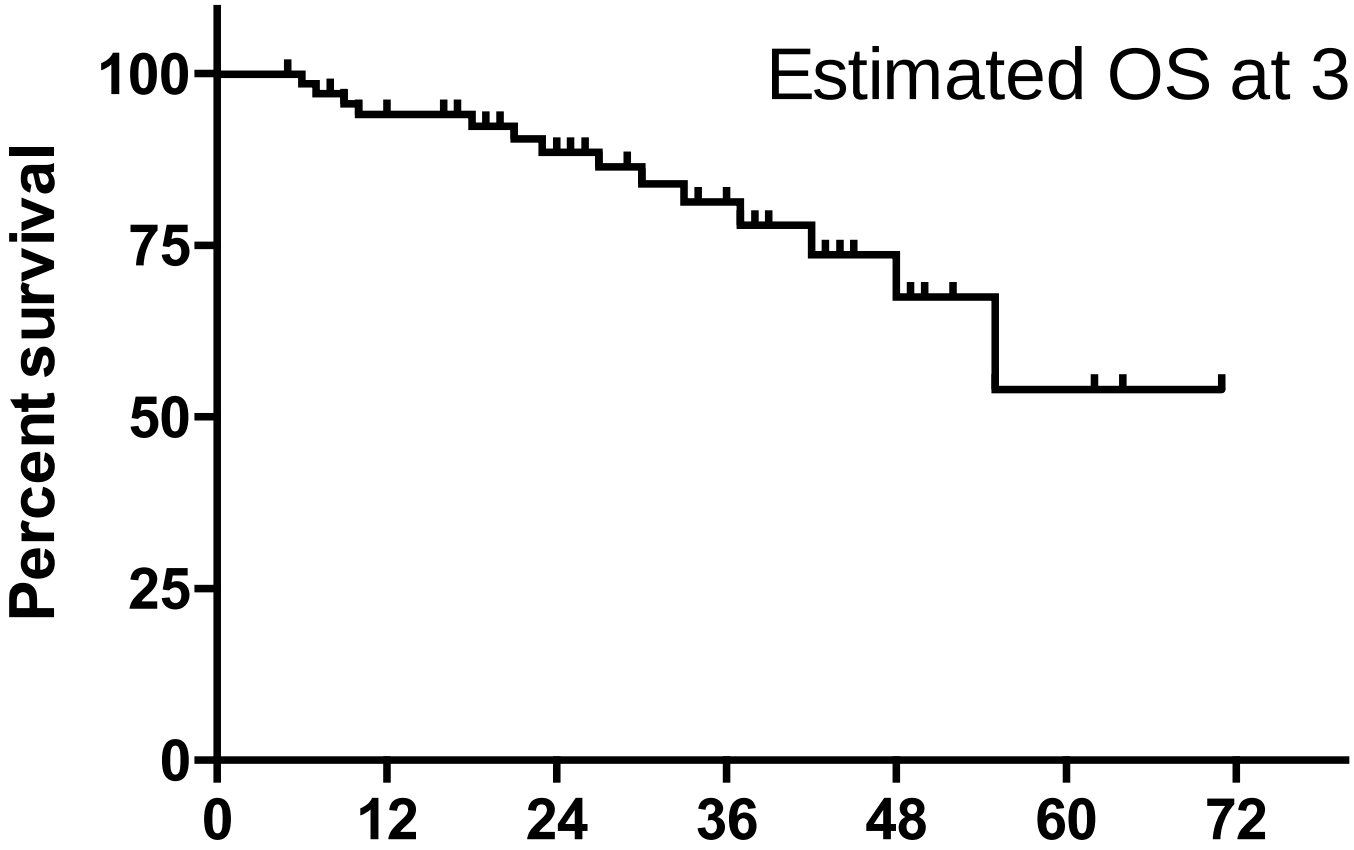


p = 0.05

45 Auto cases

PFS according to genetic risk




Estimated OS at 36m = 81%
Percent survival
100
75
50
25
0
0
12
24
36
48
60
72

TRIPLE HIT or ULTRA HR

- These are co- segregated adverse FISH lesions
- Include an IgH such as t(4;14) or t(14:16) case
- Also a P53 deletion
- Also a 1Q gain and a 1P deletion
- Confers median survival of 9 months.
- Found 3 cases in our series of 200 auto-transplant cases

Conclusions

- CyBOrD induction yields very good CR rates
- Allows adequate stem cell harvests
- Extra post auto therapy with either VTD consolidation or 5 more cycles of CyBorD will confer excellent OS figures
- Once weekly bortezomib schedule has low neuropathy rates and low thrombosis risk
- Can overcome some high risk genetics but not double and triple hits and some t (14;16) cases

Monoclonal antibodies

- Now several agents that target various CD sites
- Daratumamab targets CD38, transmembrane glycoprotein
- Has been used in the CASTOR and POLLUX studies in the relapsed /refractory setting
- Also Elotuzamab which targets SLAMF7 ,universal site
- ELOQUENT-2 study shows benefit of a MAB +chemo.

Other approaches

- Use of oral PI ‘s such as in TOURMALINE study
- Check point inhibitors such as Pembrolizamab
- Panbinostat
- CAR-T cell therapy was very promising in a recent paper

Acknowledgements

- To the clinical and nursing staff at the Wellington Blood and Cancer Centre
- Flow laboratory at Wellington Hospital
- Richard Parfitt in cytogenetics and Brown
- Dr Anup George for help with data analysis
- The apheresis unit for stem cell collection
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