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t(4;14) and genomic instability in high-risk myeloma

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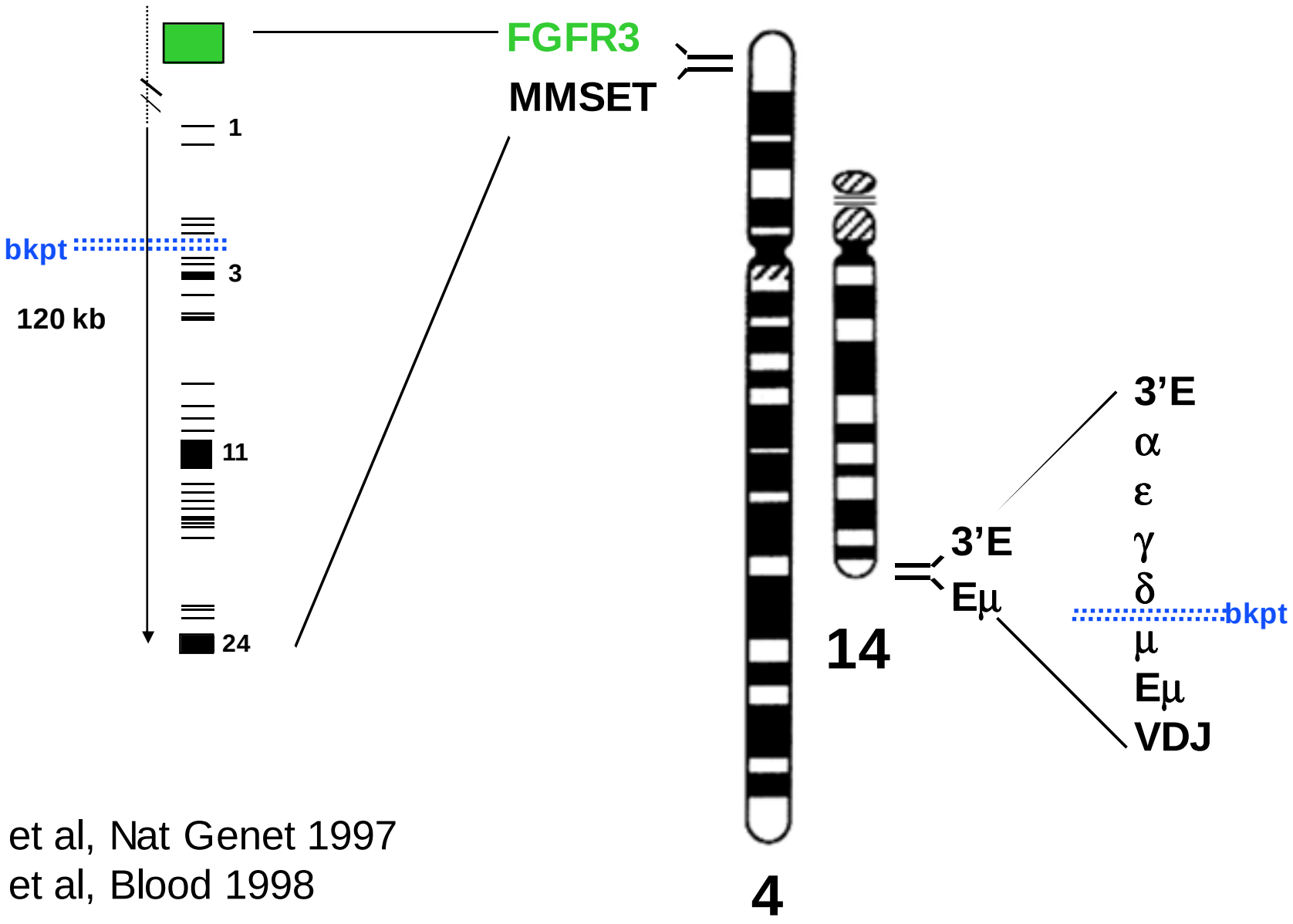
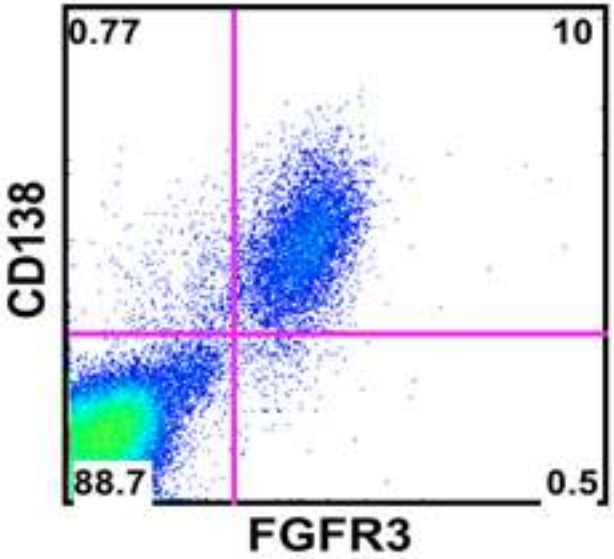
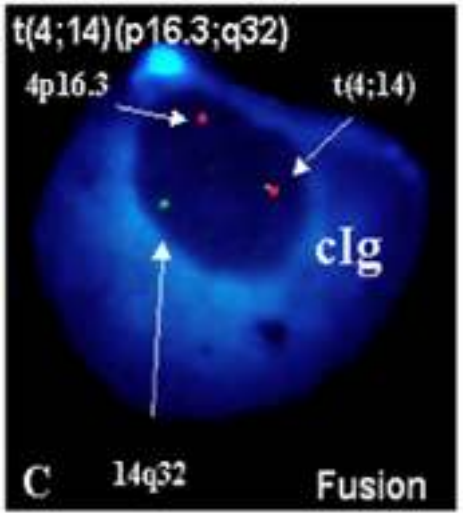
t(4;14) dysregulates MMSET and FGFR3

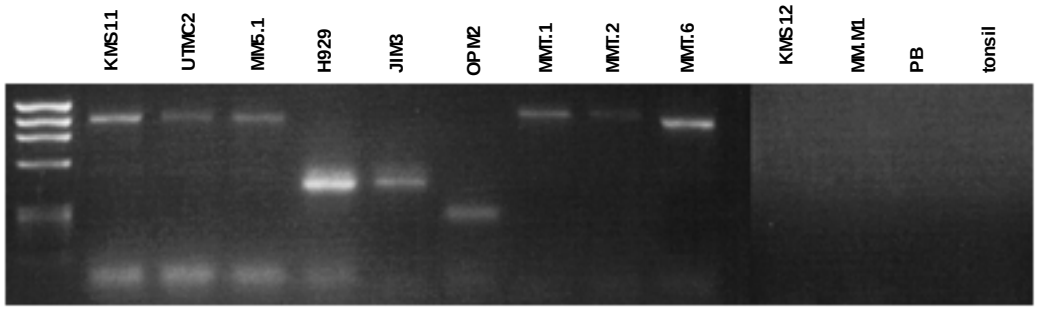


Chesi et al, Nat Genet 1997
Chesi et al, Blood 1998

Clinical detection of t(4;14) in MM Flow, cIg-FISH, RT-PCR

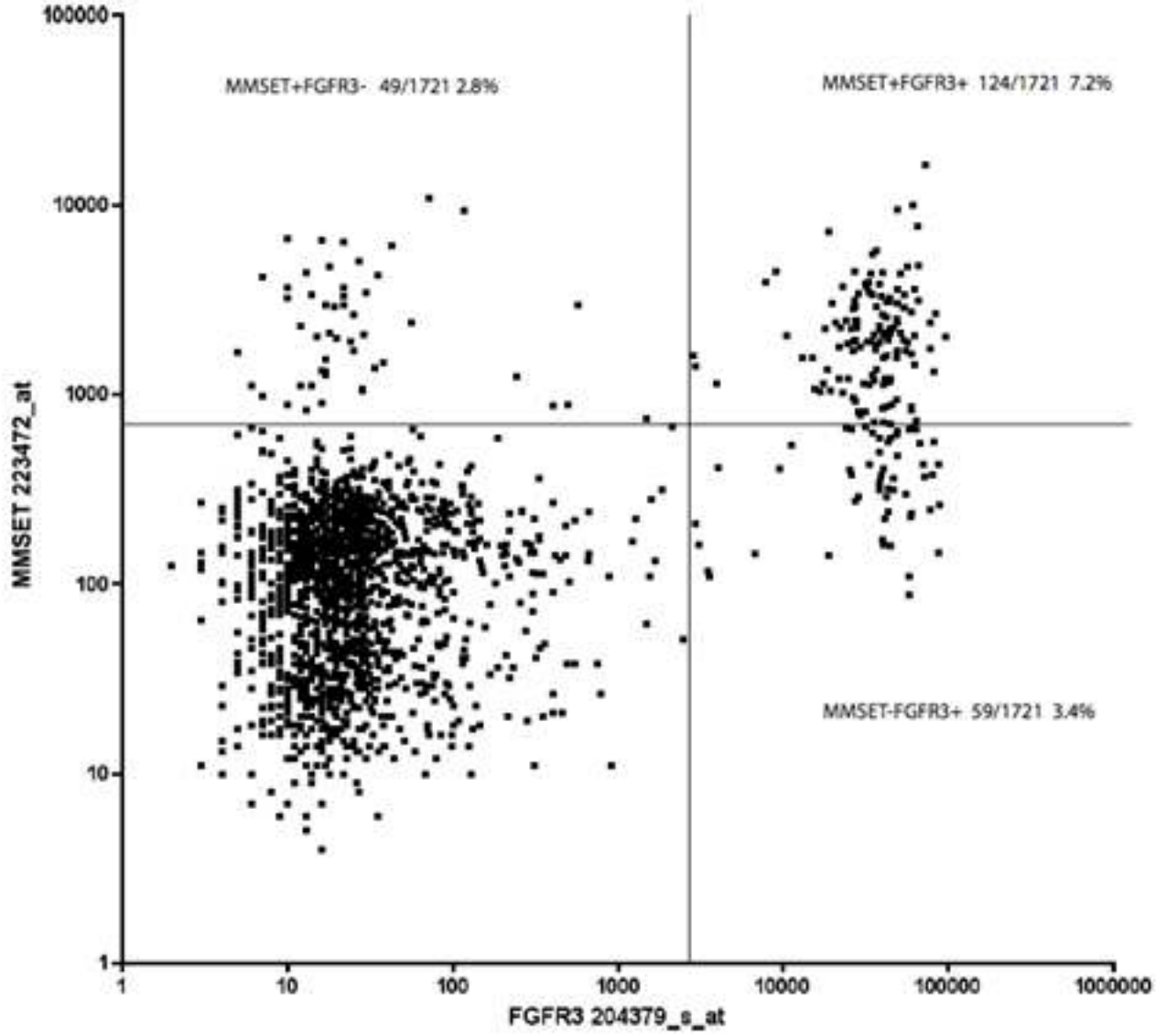




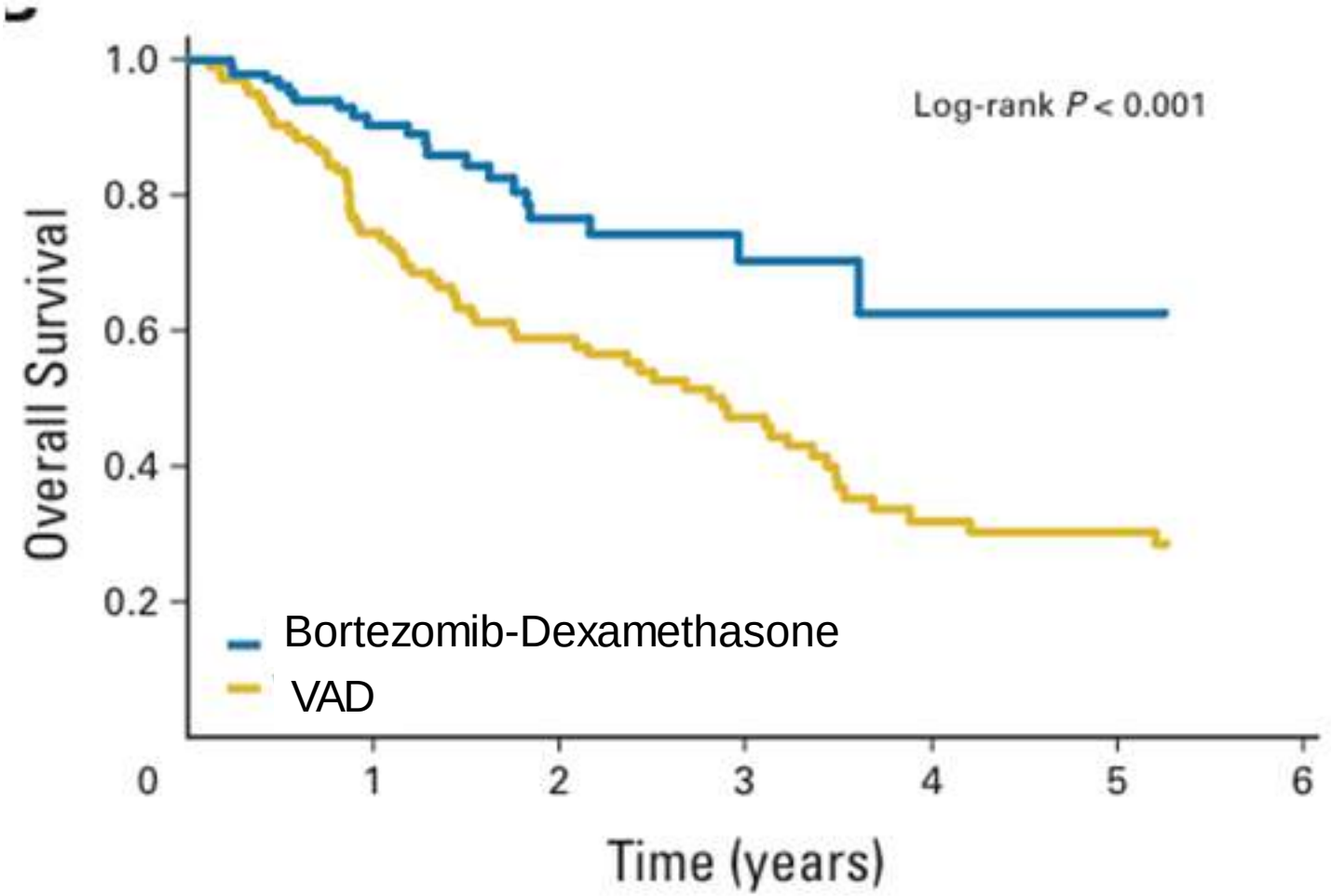


Iμ/JH-MMSET on der(4)

Co-expression of FGFR3 and MMSET in MM patients



Better OS in t(4;14) with bortezomib induction



AVET-LOISEAU, JCO 2010

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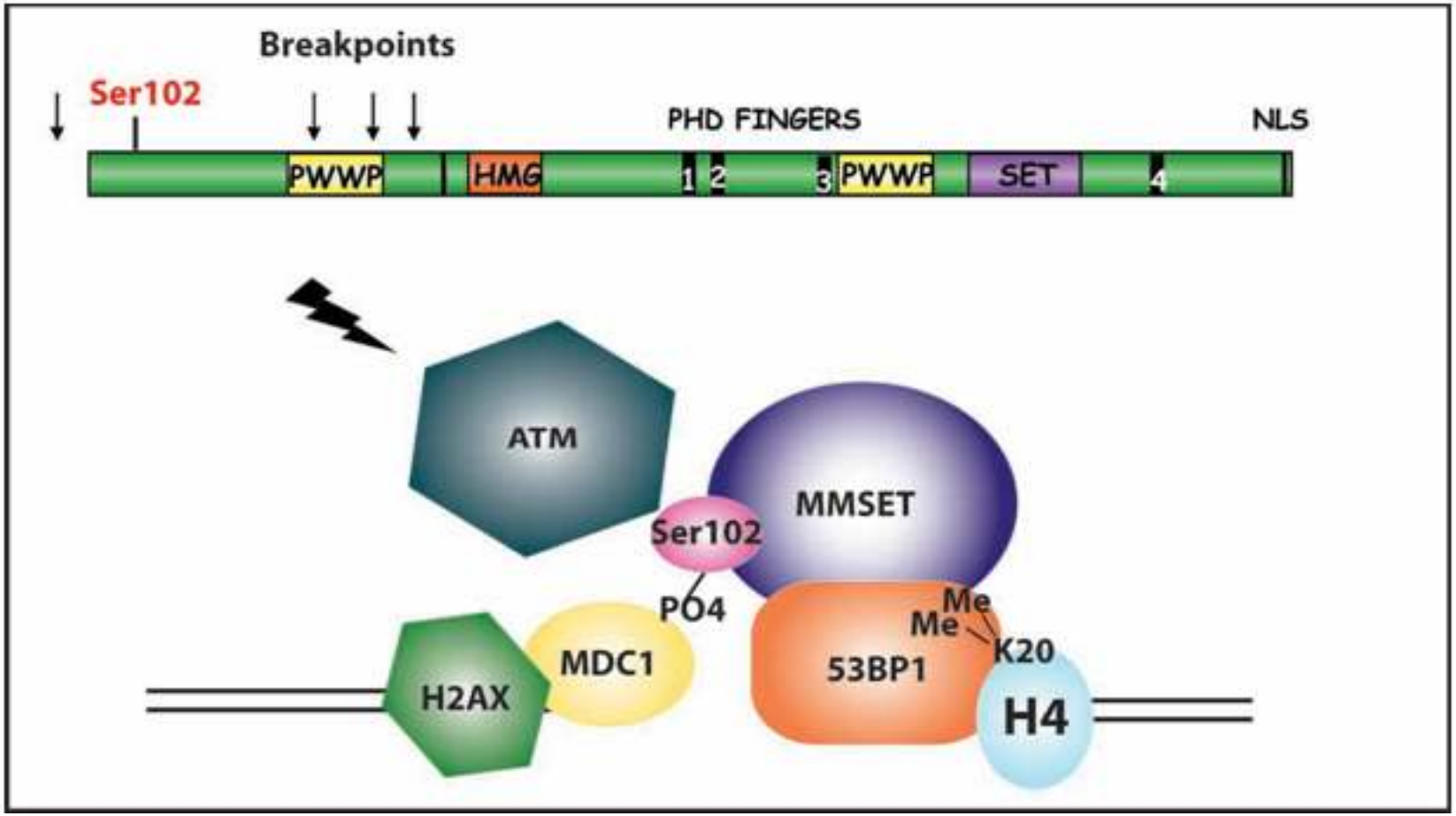
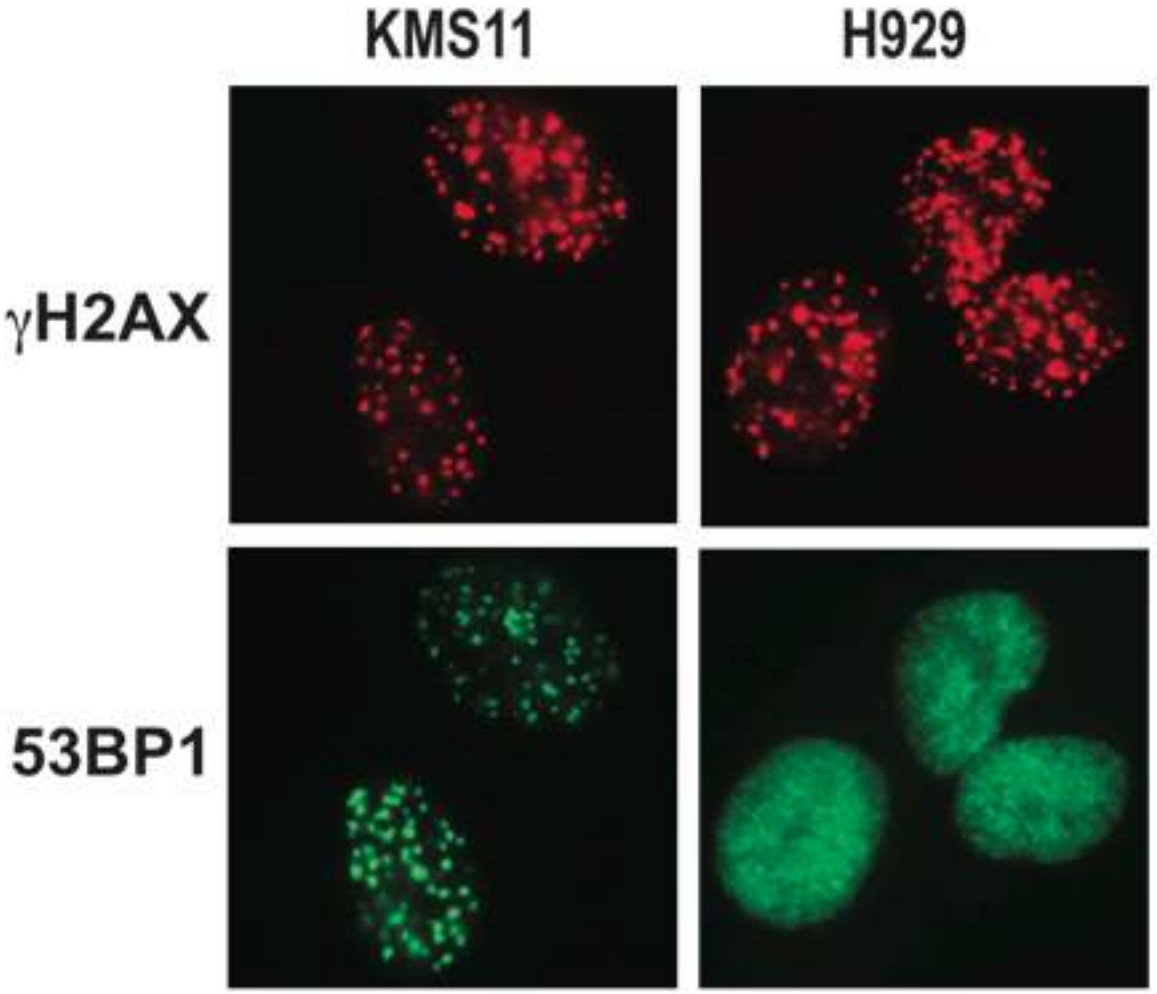
MMSET regulates histone H4K20 methylation and 53BP1 accumulation at DNA damage sites

Huadong Pei[1], Lindsey Zhang[2]*, Kuntian Luo[1]*, Yuxin Qin[3], Marta Chesi[4], Frances Fei[2], P. Leif Bergsagel[4], Liewei Wang[3], Zhongsheng You[2] & Zhenkun Lou[1]

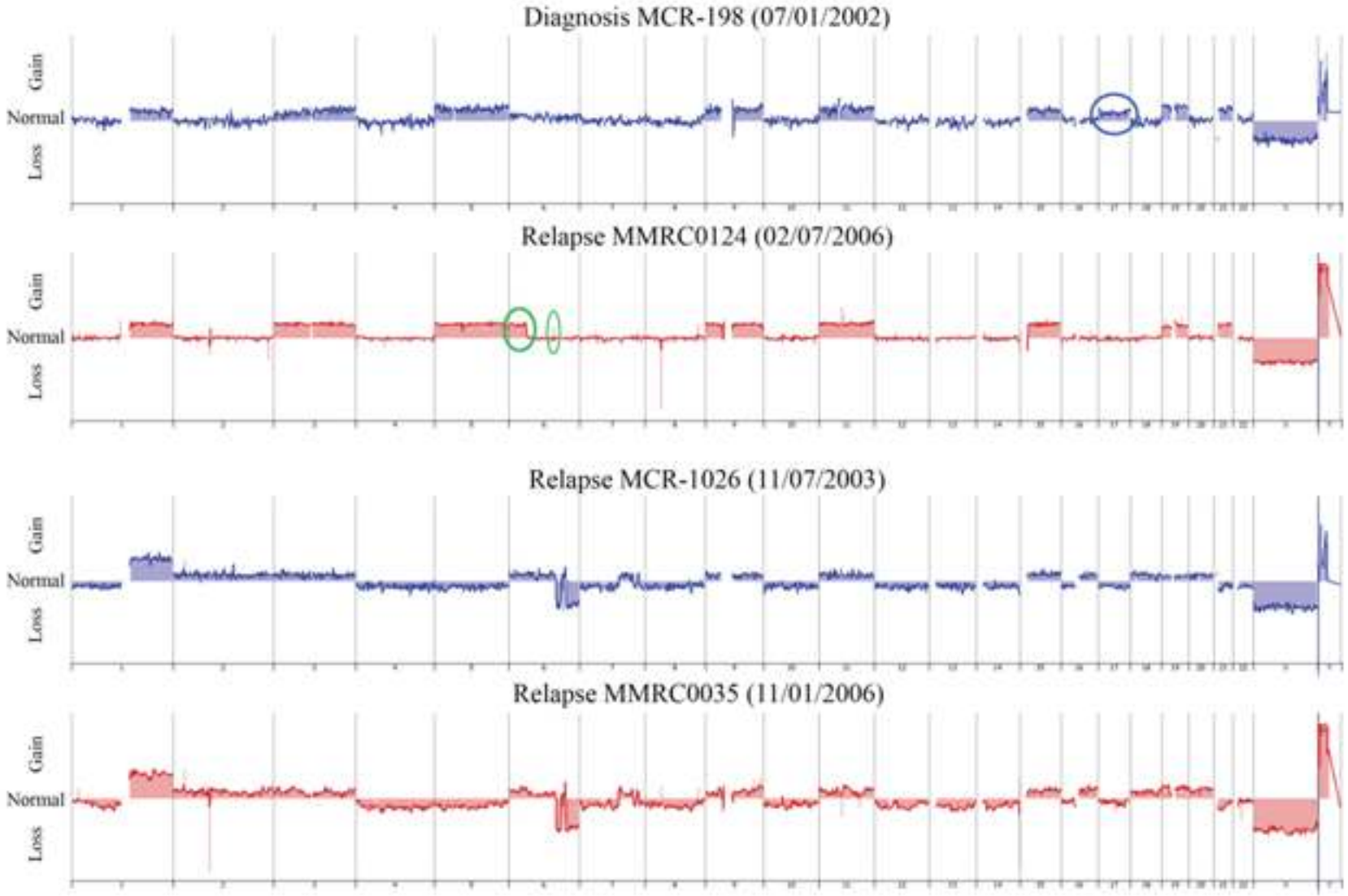


MMSET regulates histone H4K20 methylation and 53BP1 accumulation at DNA damage sites



Pei H, Zhang L, Luo K, Qin Y, Chesi M, Fei F, Bergsagel PL, Wang L, You Z & Lou Z. Nature 2011 (470)124

Patient Tumors are Stable Over Time



Three changes in one patient and no changes in second patient

Keats JJ et al, unpublished

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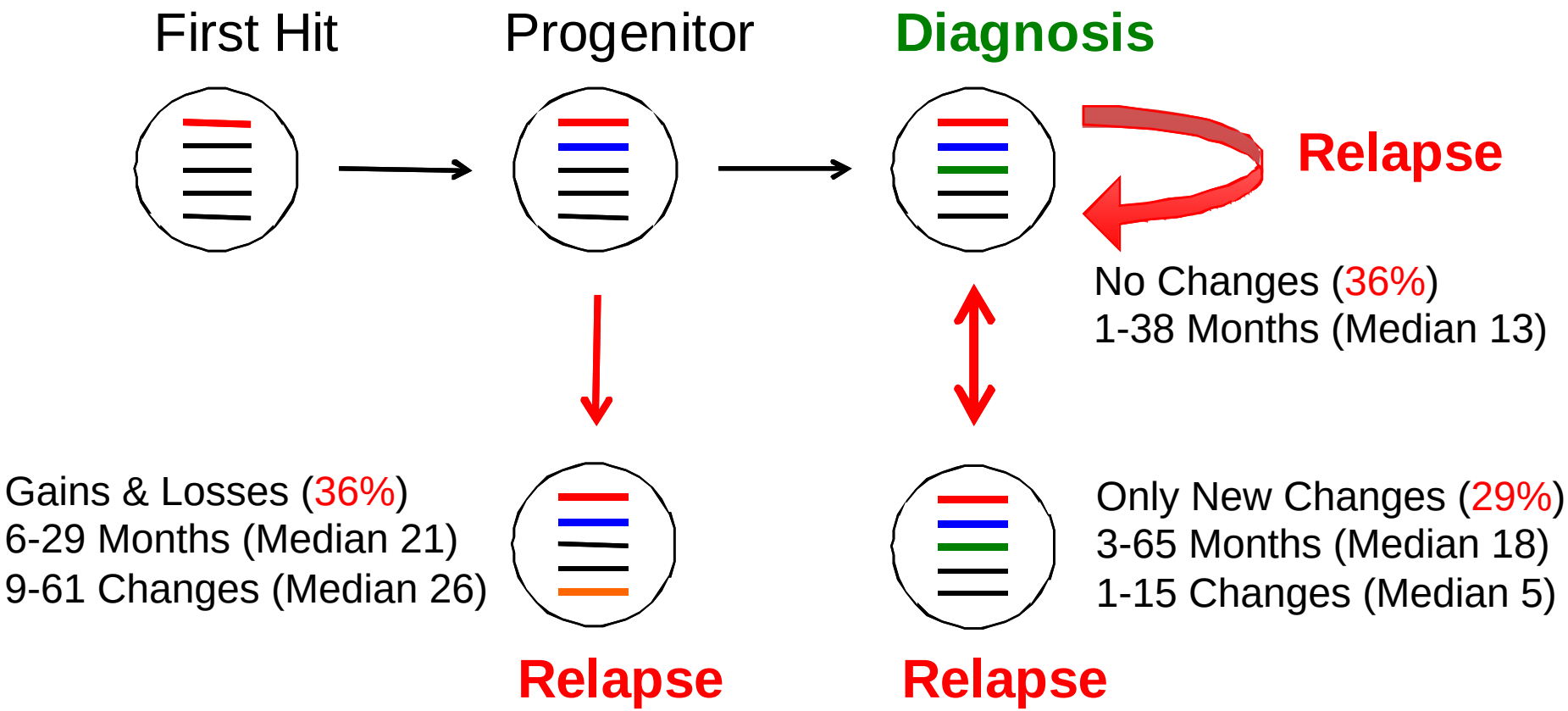
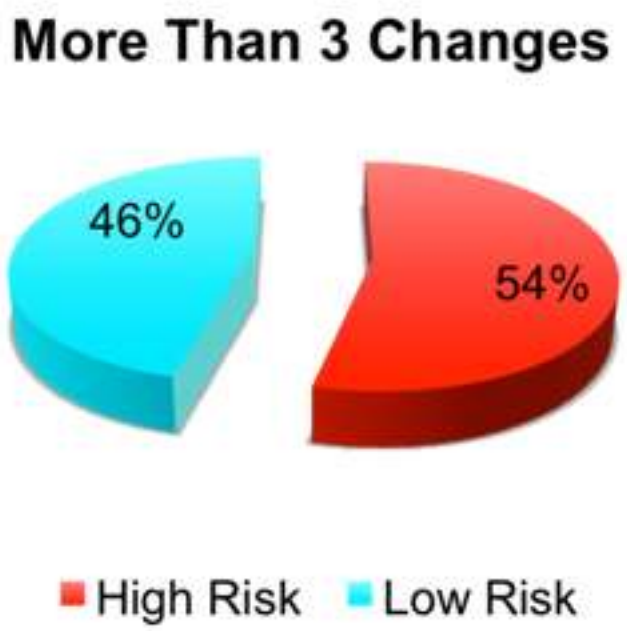
Summary of the Paired Analysis



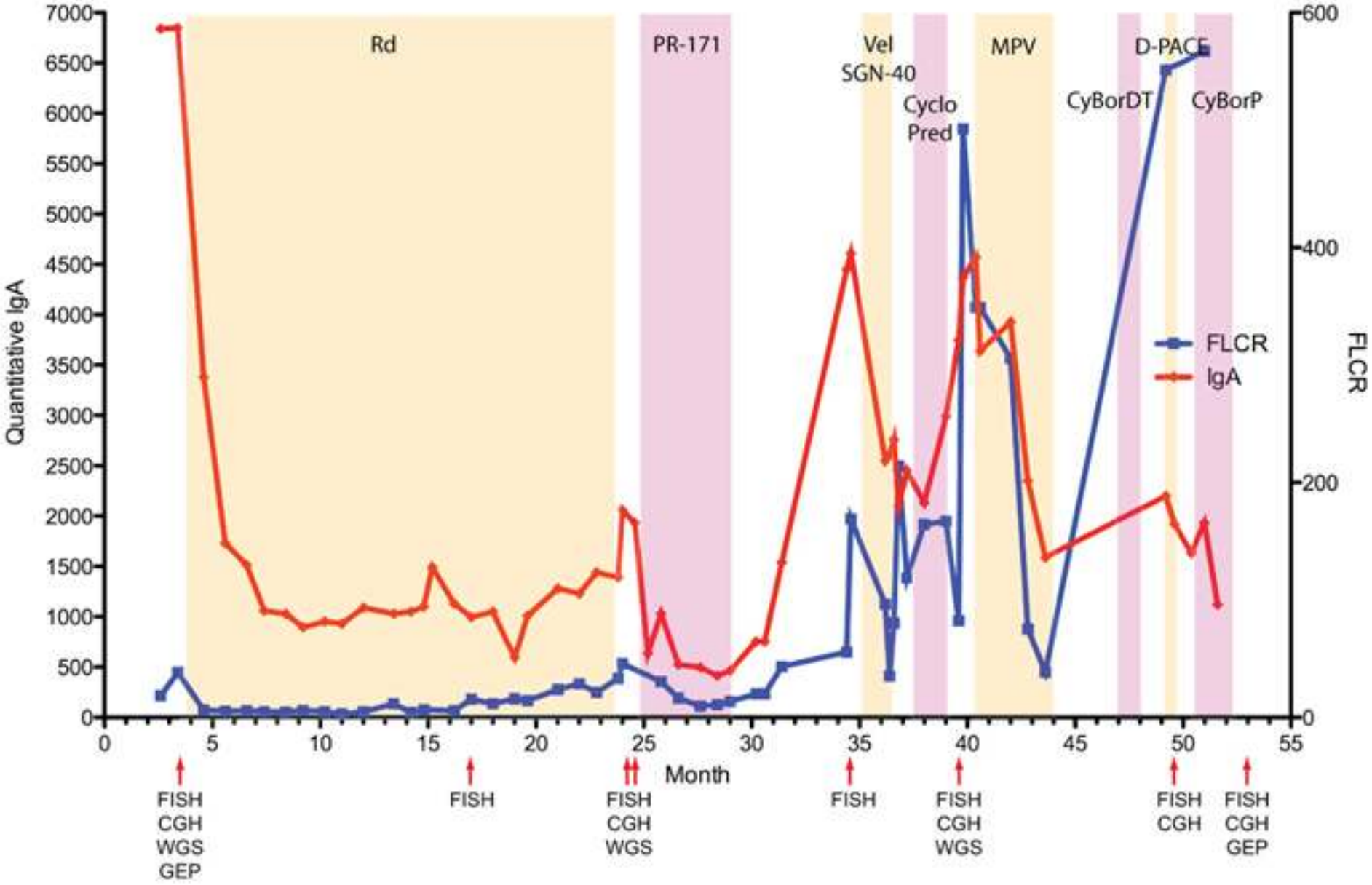
Keats JJ et al, unpublished

Relationship Between Changes and Subtype



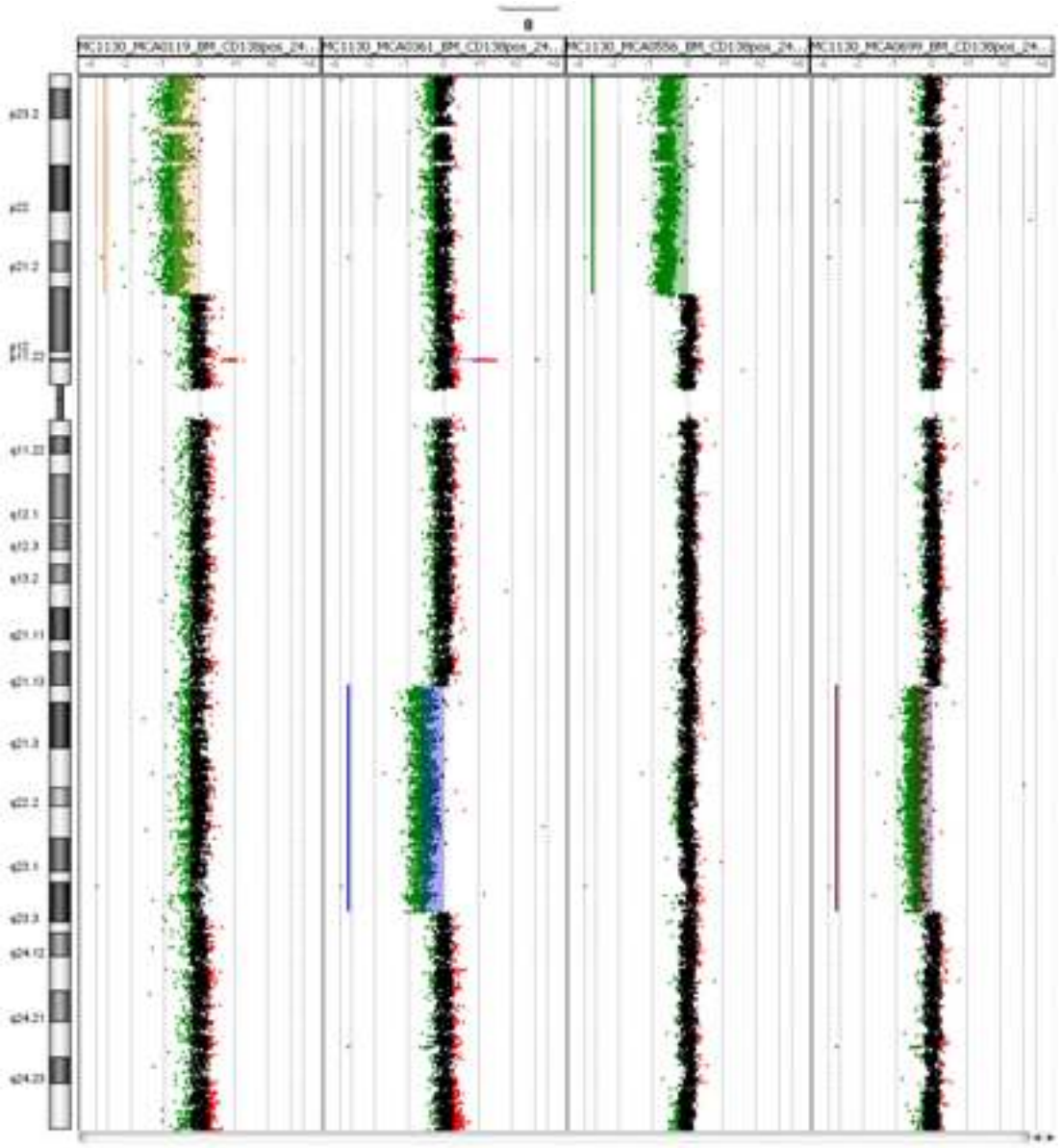
Keats JJ et al, unpublished

Clinical course of a patient with t(4;14) MM

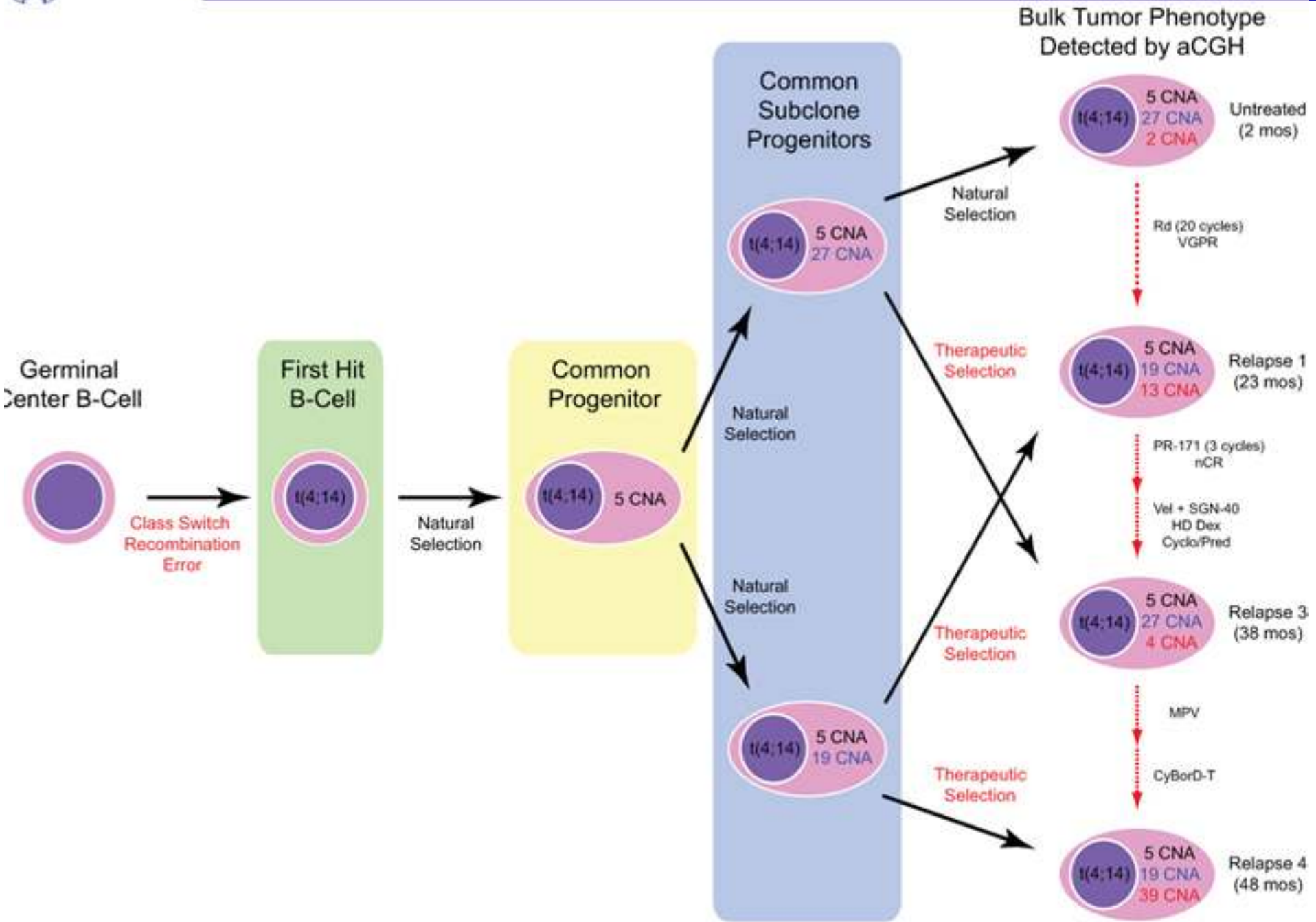


Keats JJ et al, unpublished

Chromosome 8

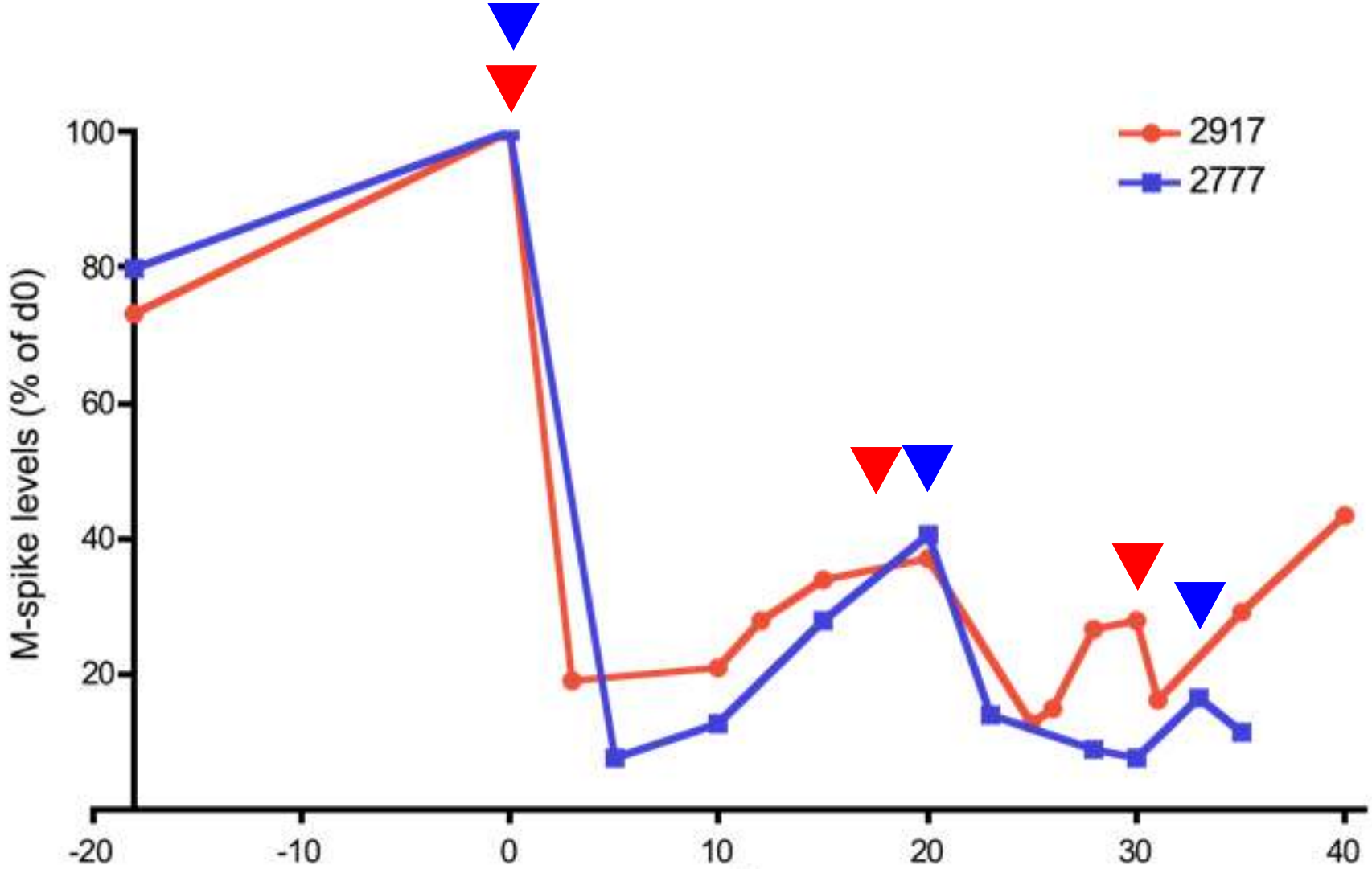


Keats JJ et al, unpublished

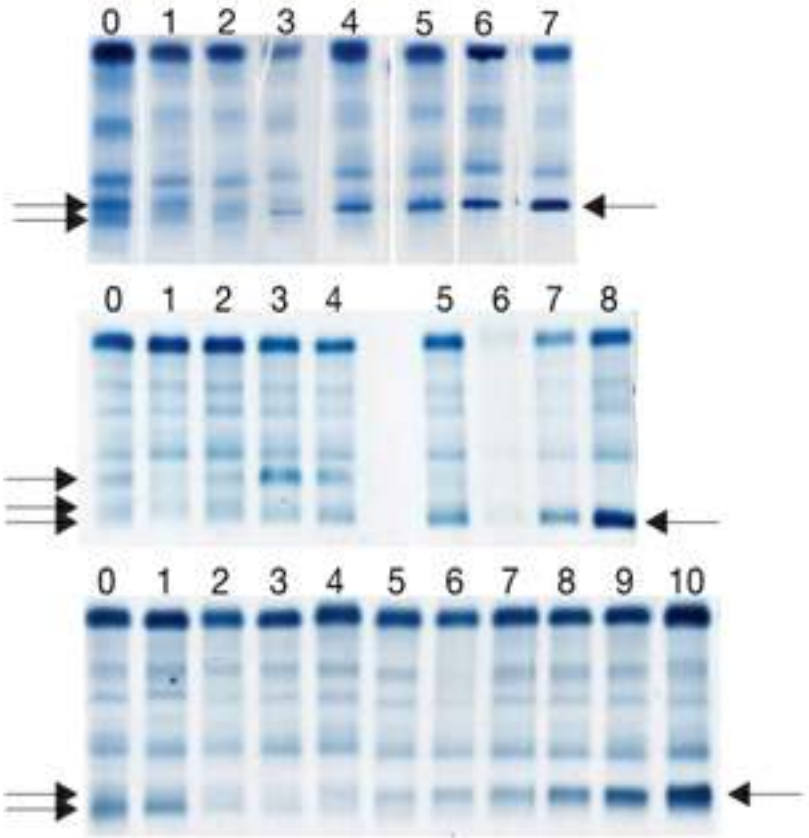


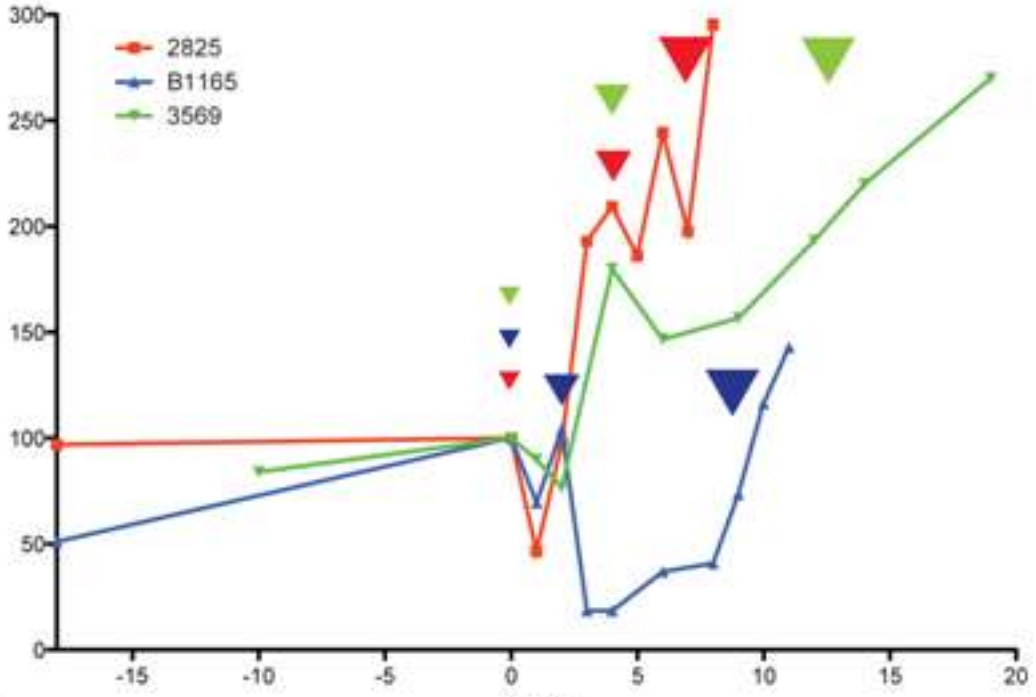
Keats JJ et al, unpublished

Effective re-treatment of MM with full dose bortezomib



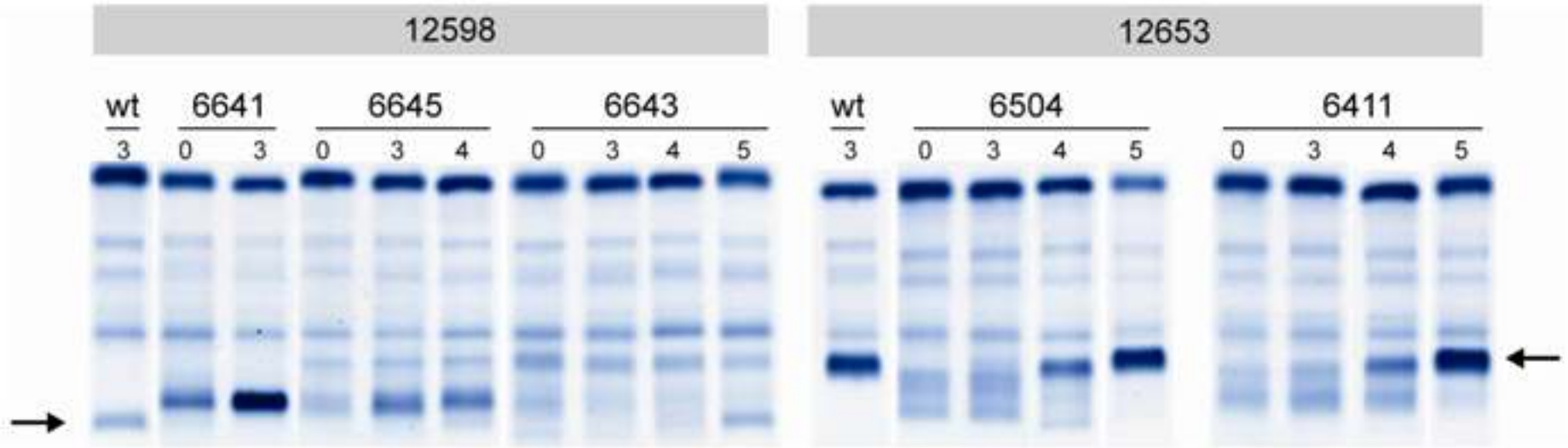
Suboptimal bortezomib treatment alters disease course





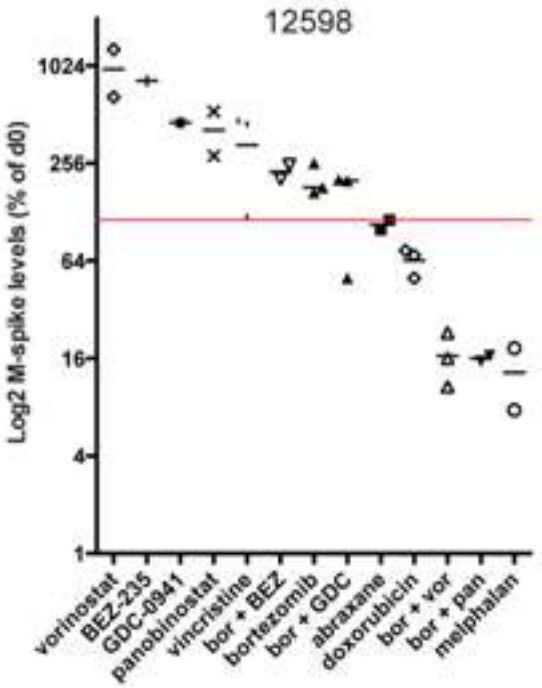
Chesi et al, unpublished

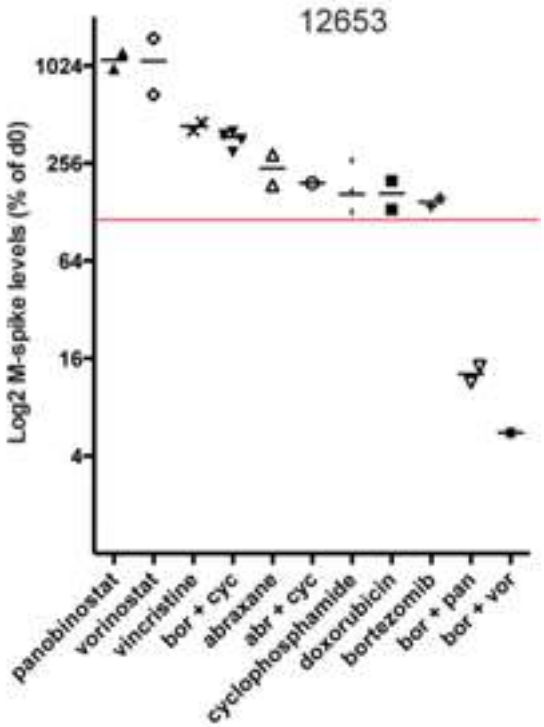
Aggressive MM can stimulate or eradicate indolent MM

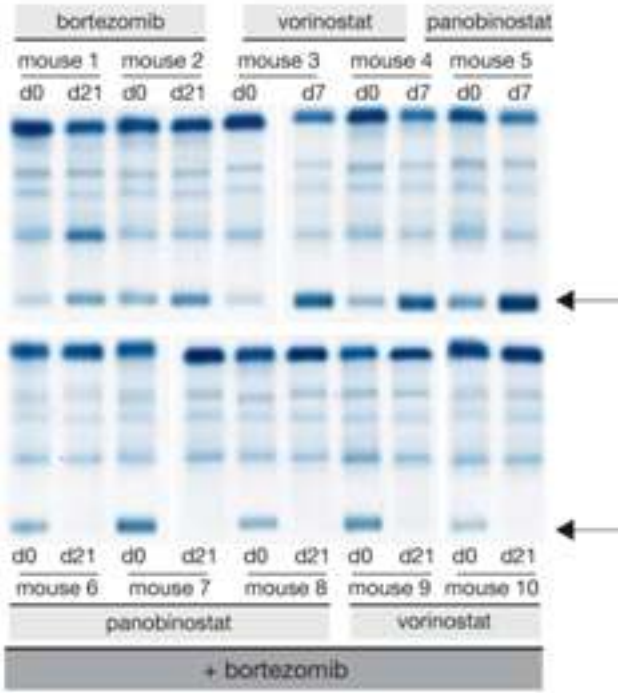


Chesi et al, unpublished

Drug response in transplanted Vk*MYC MM
Remarkable activity of HDACi+Bortezomib







Chesi et al, unpublished

Possible clinical implications of genomic instability and intra-clonal heterogeneity in high-risk MM

- Argues for combination vs sequential therapy (E.g., RVd instead or Rd followed by Vd)
- Selection of pre-existing resistant clones by low-dose maintenance therapy more likely with high-risk MM
- For drugs used in maintenance, the initial exposure should be when the tumor burden is lowest
- There are more genetic changes following relapse from melphalan then from agents that do not target DNA
- Melphalan may be harmful to high-risk MM (that are not in CR)
- Melphalan is best used following a maximal cytoreduction so that the fewest possible MM cells are exposed to its mutagenic effects
- Early treatment (e.g., smoldering MM) may preferentially eradicate “good” myeloma, making room for “bad” myeloma

Collaborators

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