



Memorial Sloan Kettering  
Cancer Center™

# Clonal heterogeneity and MRD testing in multiple myeloma

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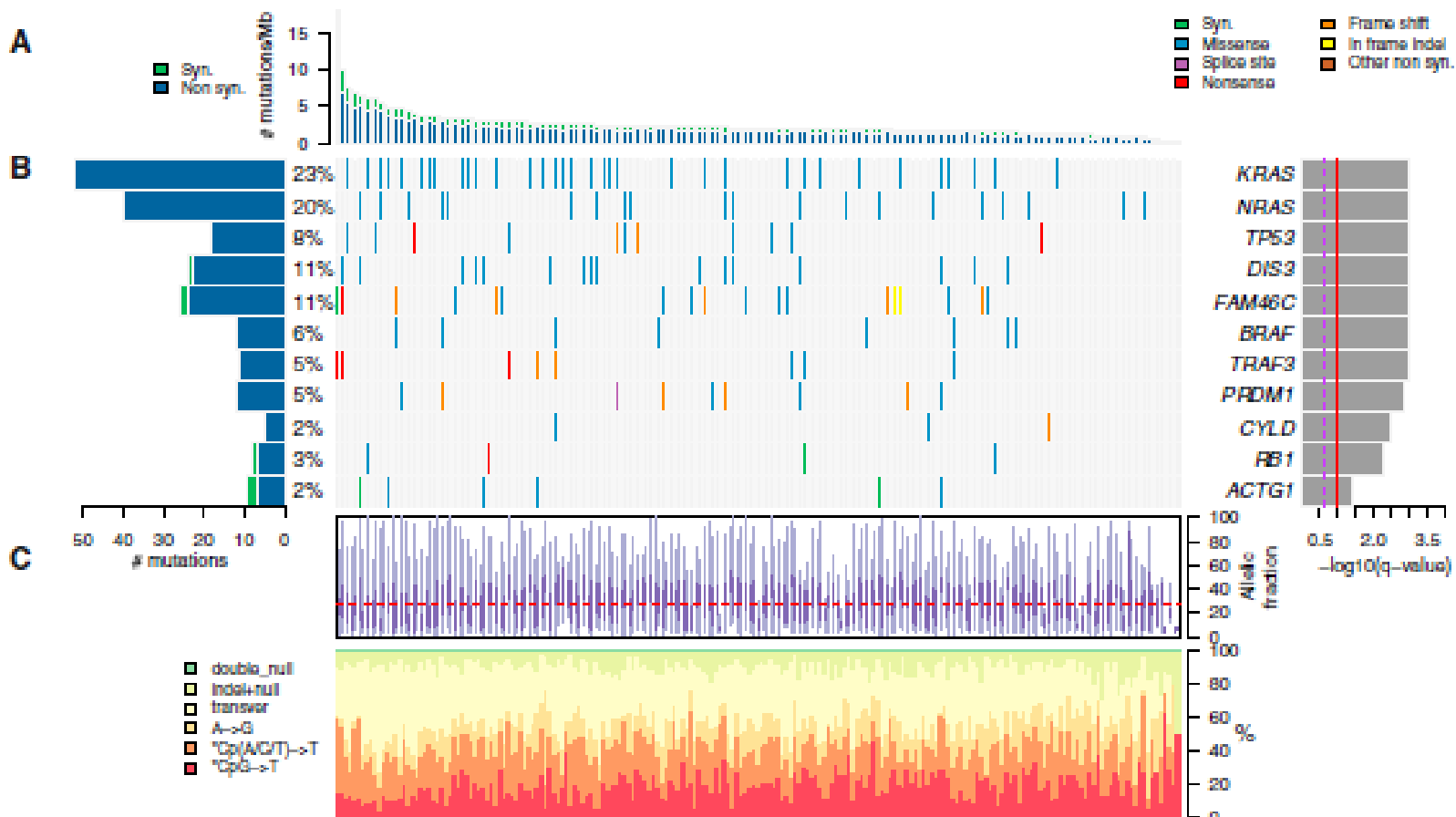
New York

[www.MSKCC.org](http://www.MSKCC.org)



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# Massive genetic heterogeneity in multiple myeloma



Research

Original Investigation

# Treatment With Carfilzomib-Lenalidomide-Dexamethasone With Lenalidomide Extension in Patients With Smoldering or Newly Diagnosed Multiple Myeloma

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# Samples and bioinformatic analysis

- DNA isolated from CD138+ cells and whole exome sequencing on HiSeq2500 sequencers with median target coverage of 125x (range 105-185x)
- Tumor only analysis using TGen JetStream analysis pipeline



# Samples and bioinformatic analysis

- Somatic mutations identified using variant callers Mutect, Seurat and Strelka
- Variants detected by at least two callers are filtered to remove likely germline variants

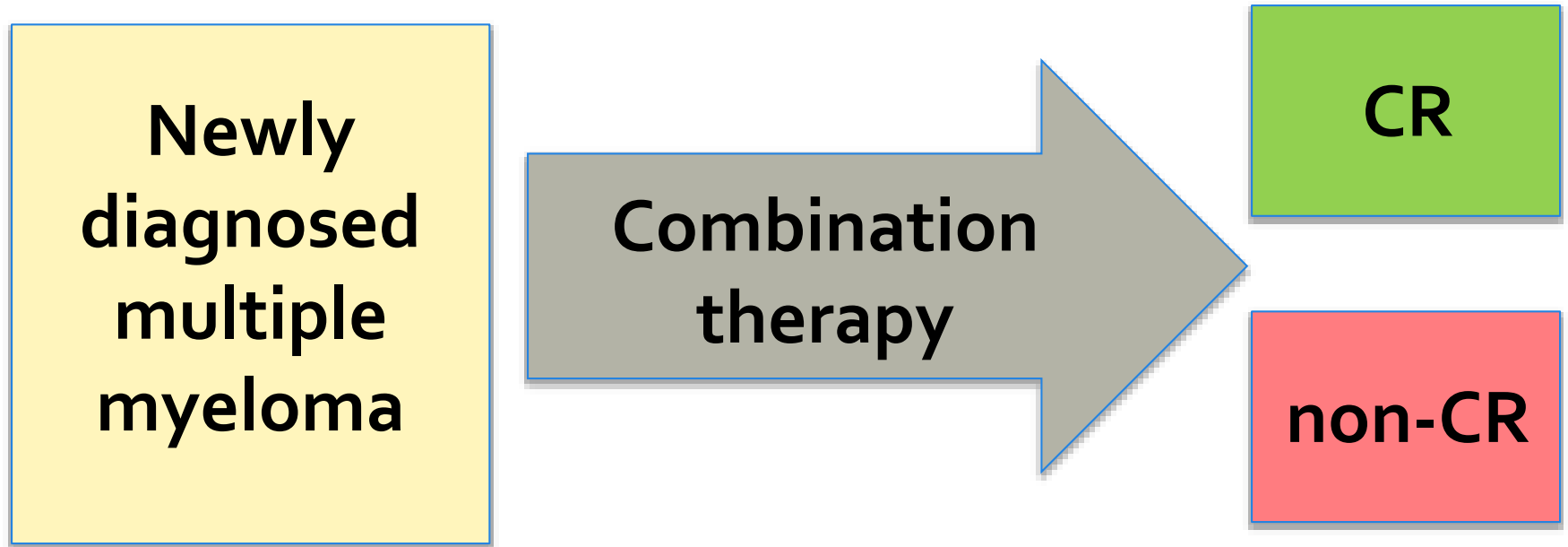
# Significantly recurrent mutations of individual genes in multiple myeloma

- KRAS
- NRAS
- BRAF
- CYLD
- FAM46C
- TRAF3
- DIS3
- IRF4
- HIST1H1E
- ACTG1
- TP53
- LTB
- PRDM1
- RB1
- MAX

1. Lohr JG. et al., *Cancer Cell*, 2014; 25(1):91-101
2. Walker BA. et al., *JCO*, 2015; 33(33): 3911-20
3. Bolli N. et al. *Nature Comm*, 2015 (5): 2997



# Mutational landscape by treatment response?



# Patients and treatment response

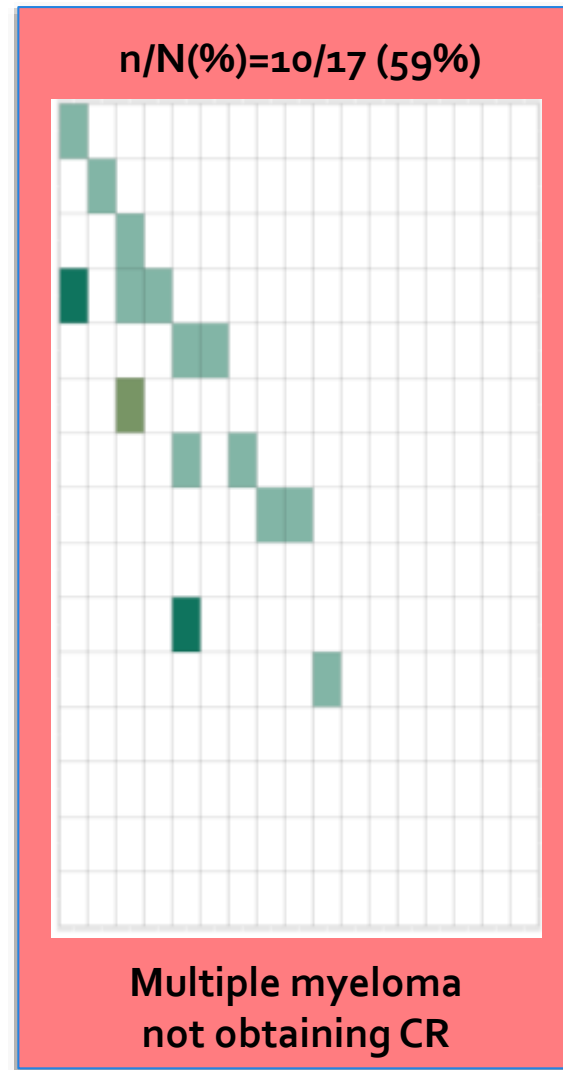
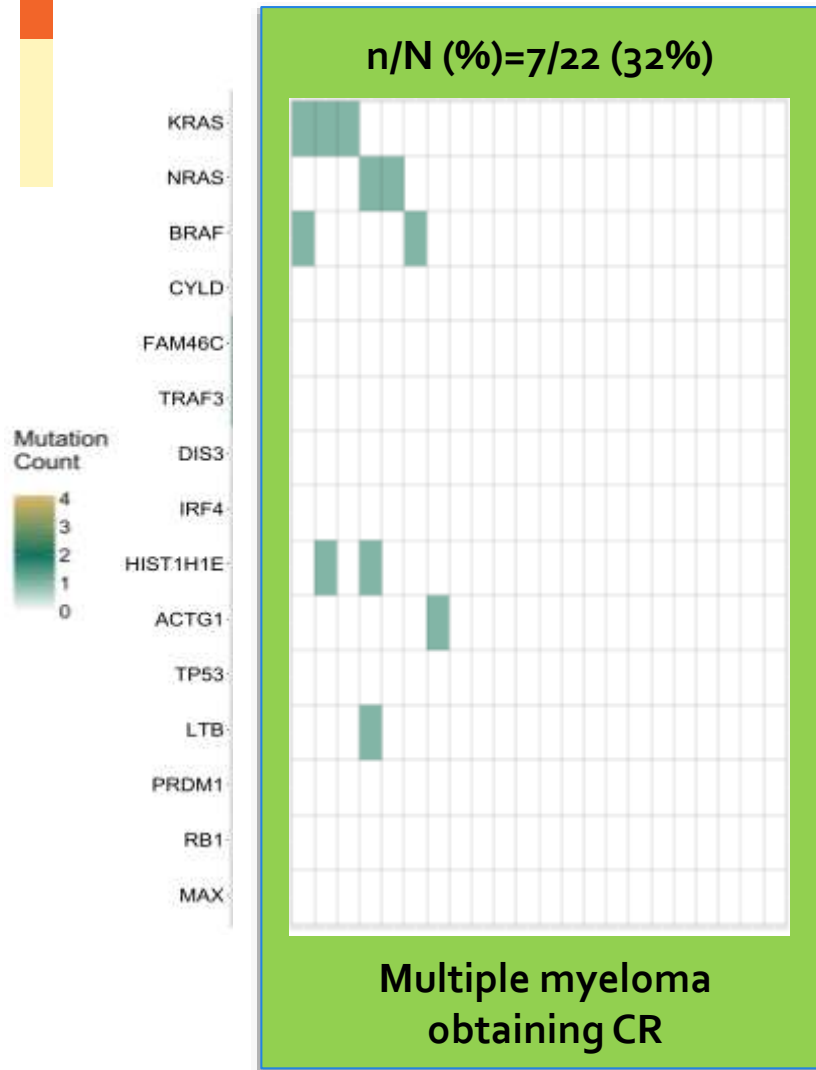
Best treatment response after combination therapy	Newly diagnosed multiple myeloma (N=39)
CR	22 (56%)
non-CR	17 (44%)

CR = complete response

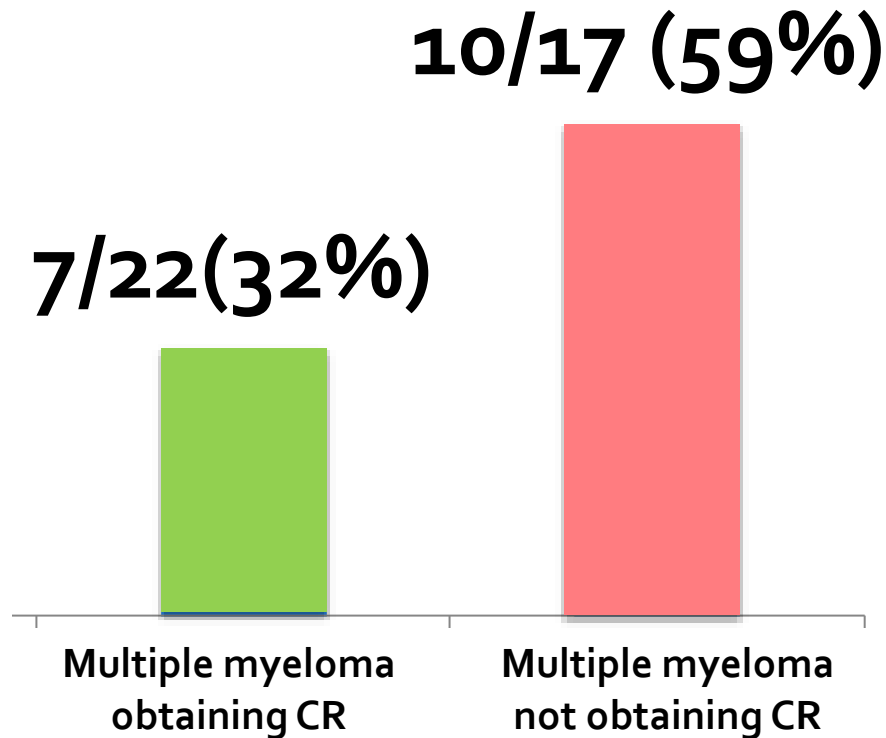




# Mutational landscape by treatment response?



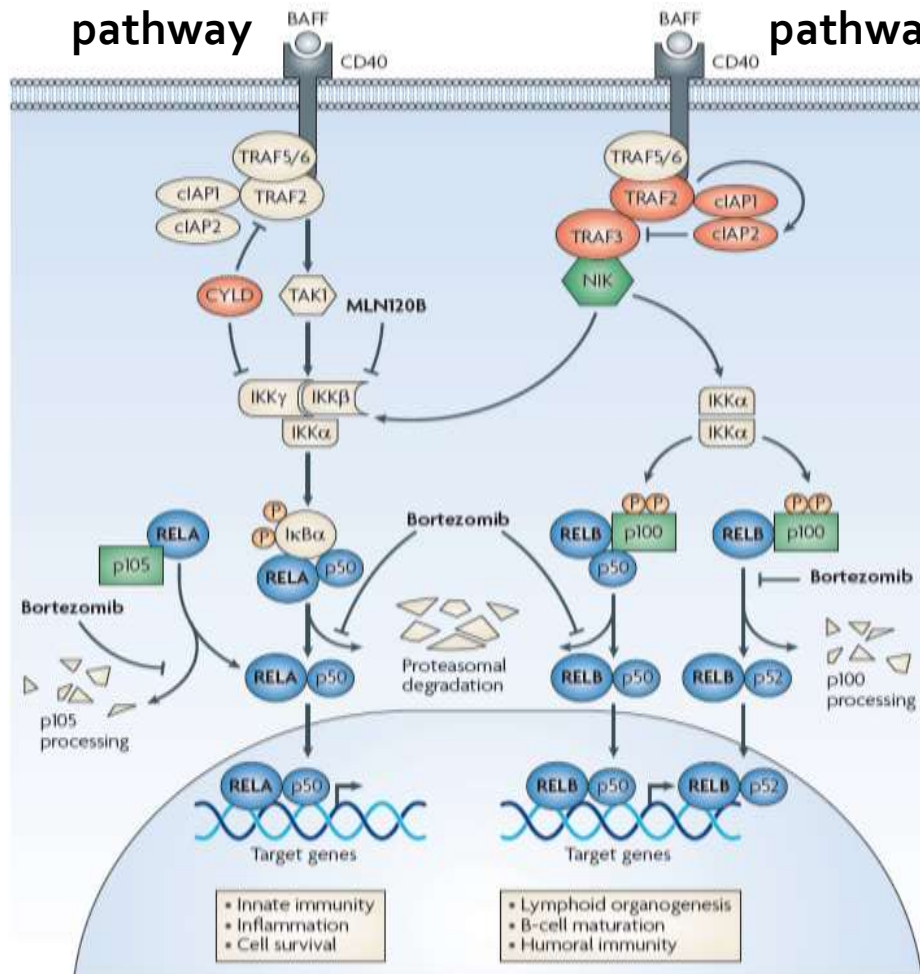
# Patients with significantly recurrent mutations in multiple myeloma genes



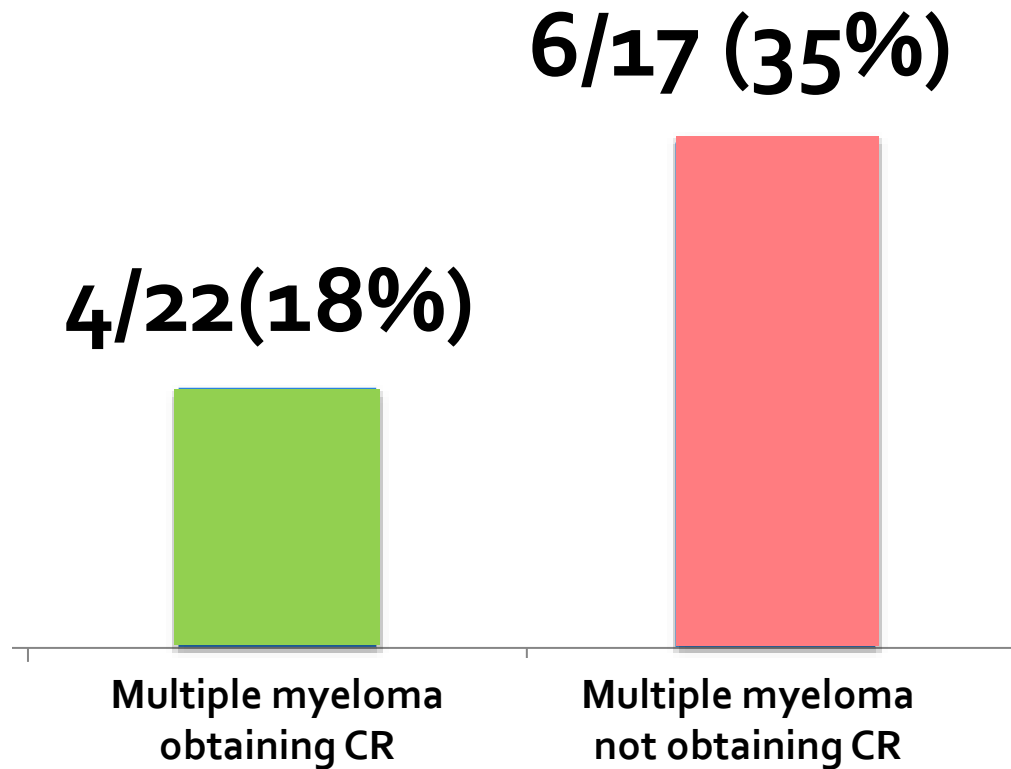
# Recurrent mutations in the NF- $\kappa$ B pathway

## Classical NF- $\kappa$ B pathway

## Alternative NF- $\kappa$ B pathway



# Number of patients with mutations in the NF- $\kappa$ B pathway genes



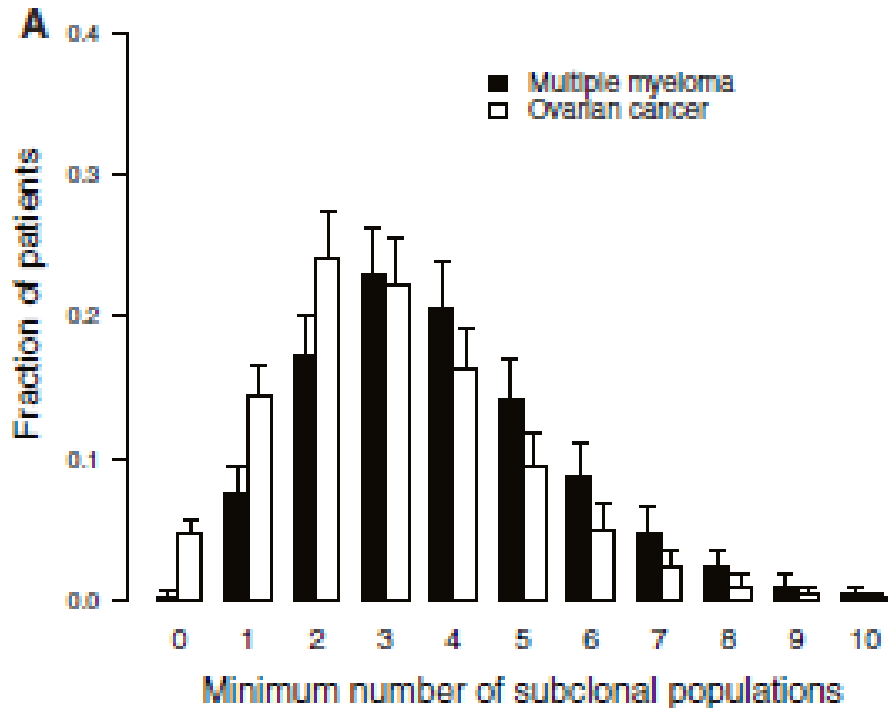


# Summary

- **Modern therapy produces deep and durable response in patients with multiple myeloma**
- **Baseline mutations associated with treatment response**

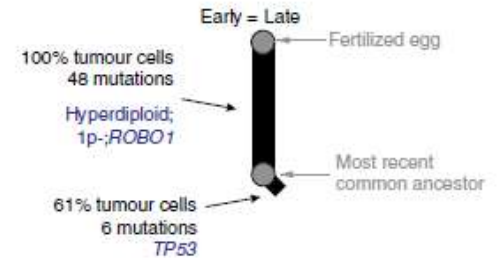
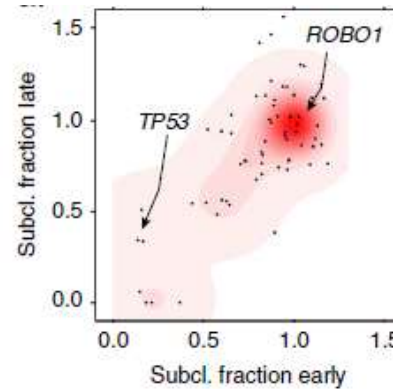
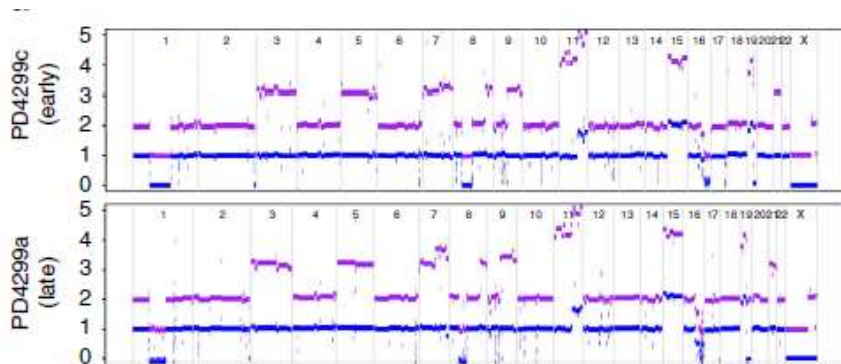


# Clonal heterogeneity in myeloma



# Patterns of clonal evolution

No change

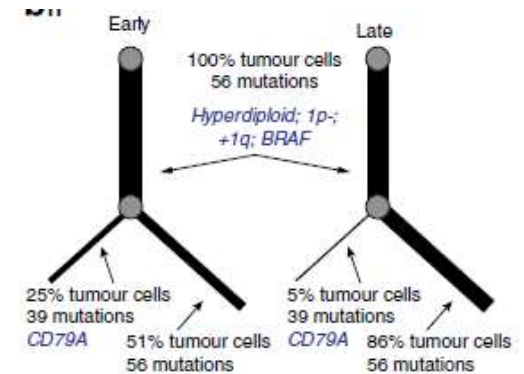
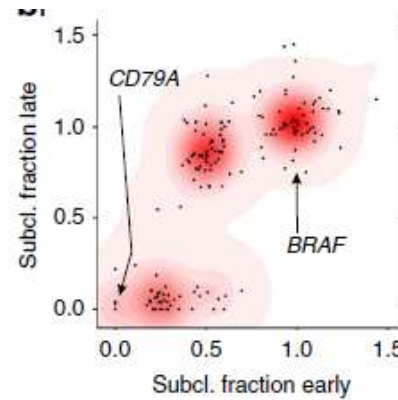
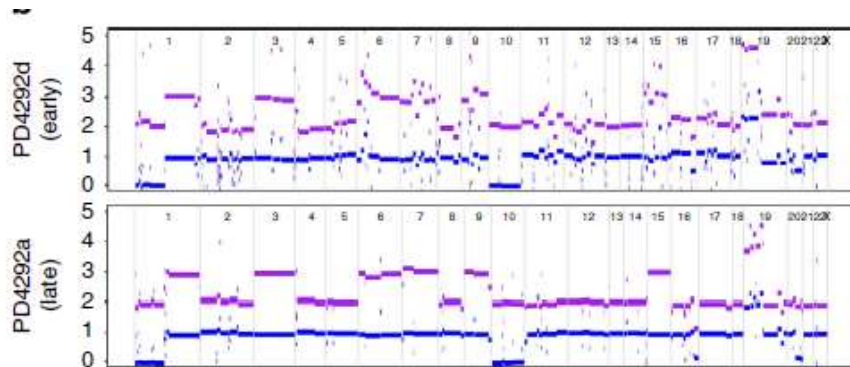


1. *Bolli N. et al. Nature Comm, 2015 (5): 2997*



# Patterns of clonal evolution

## Differential clonal response



1. *Bolli N. et al. Nature Comm, 2015 (5): 2997*



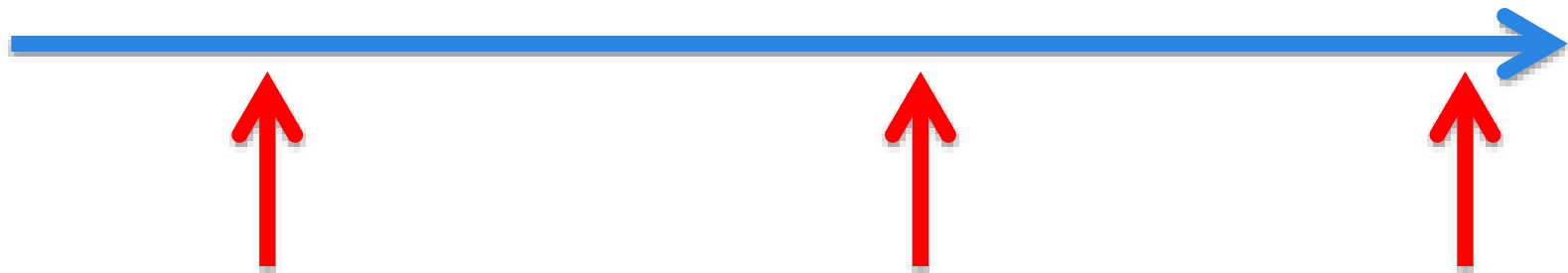


**Average time to CR and MRD negativity  
was 5.5 cycles with KRd therapy**

**5.5 cycles to CR and MRD**

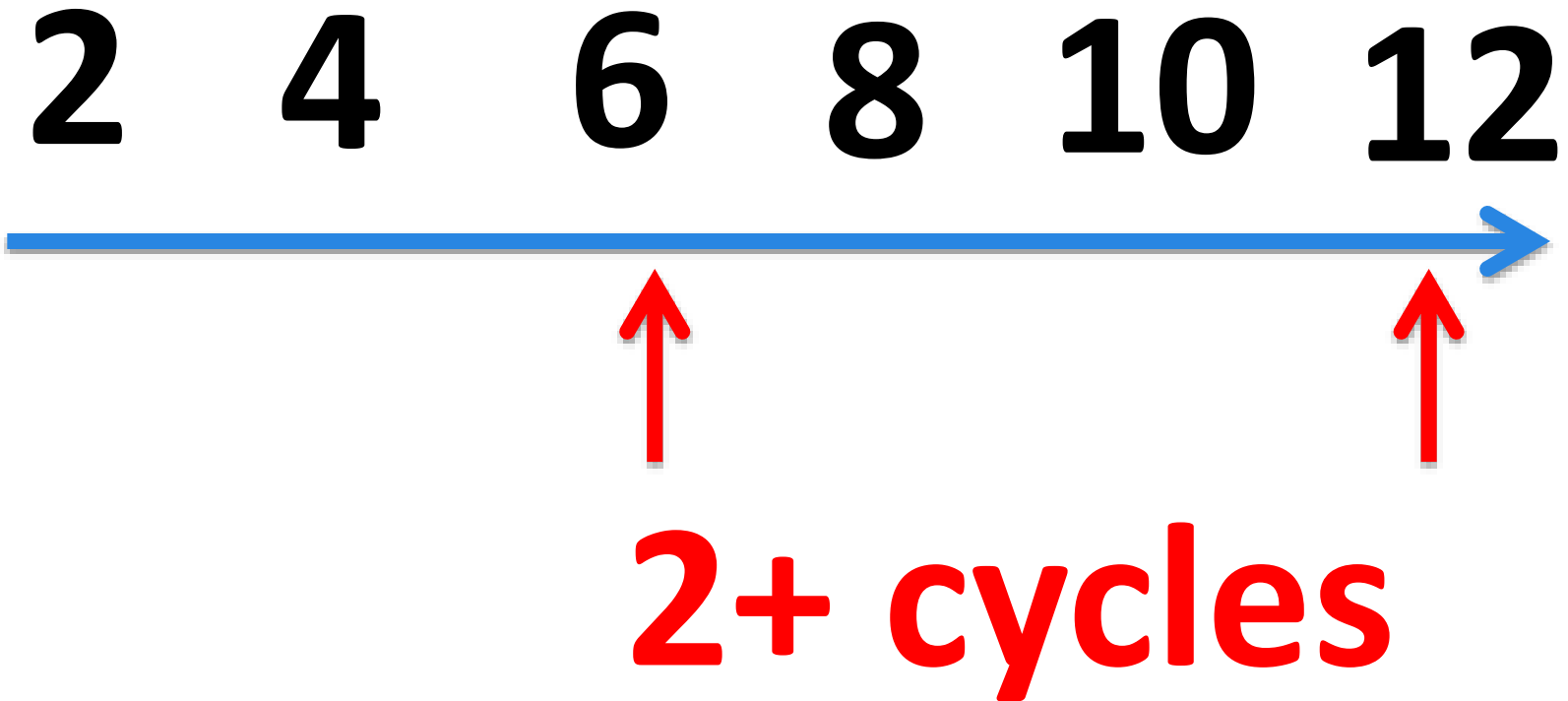
**Average time to CR and MRD negativity  
was 5.5 cycles with KRd therapy**

**2 4 6 8 10 12**



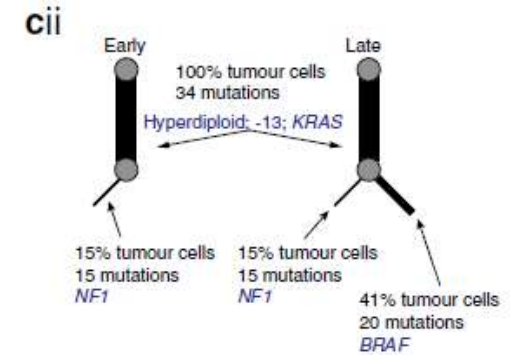
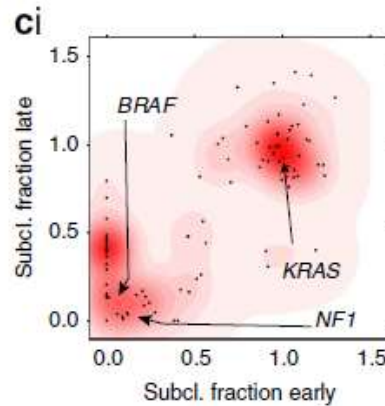
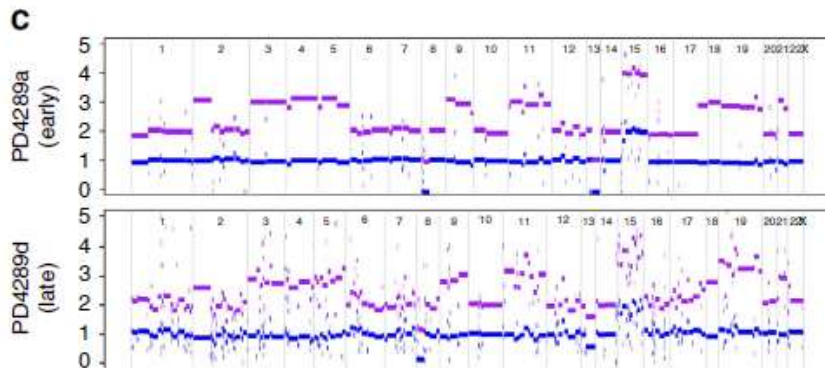
**Determine the number of cycles  
of combination therapy  
by MRD response**

# Number of cycles of highdose KRd defined by MRD negativity



# Patterns of clonal evolution

## Linear evolution

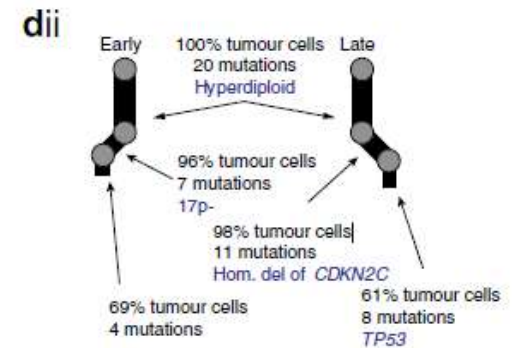
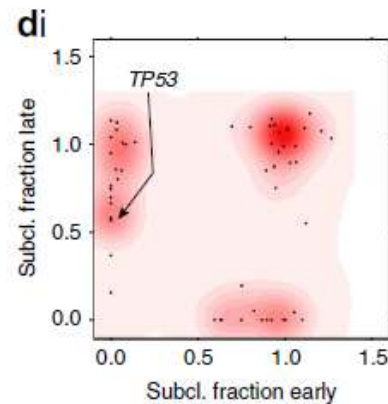
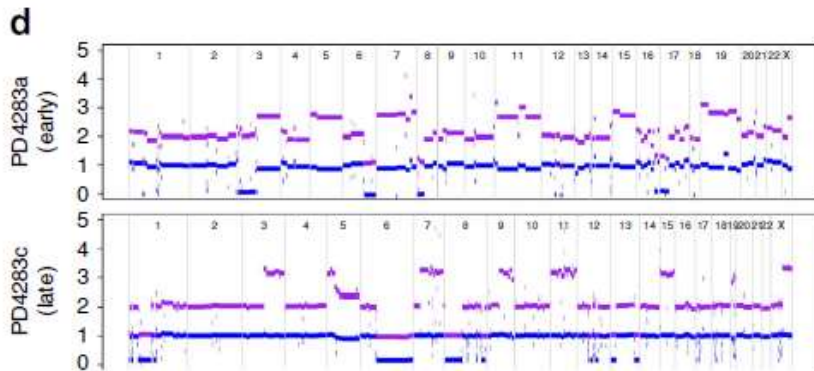


1. *Bolli N. et al. Nature Comm, 2015 (5): 2997*



# Patterns of clonal evolution

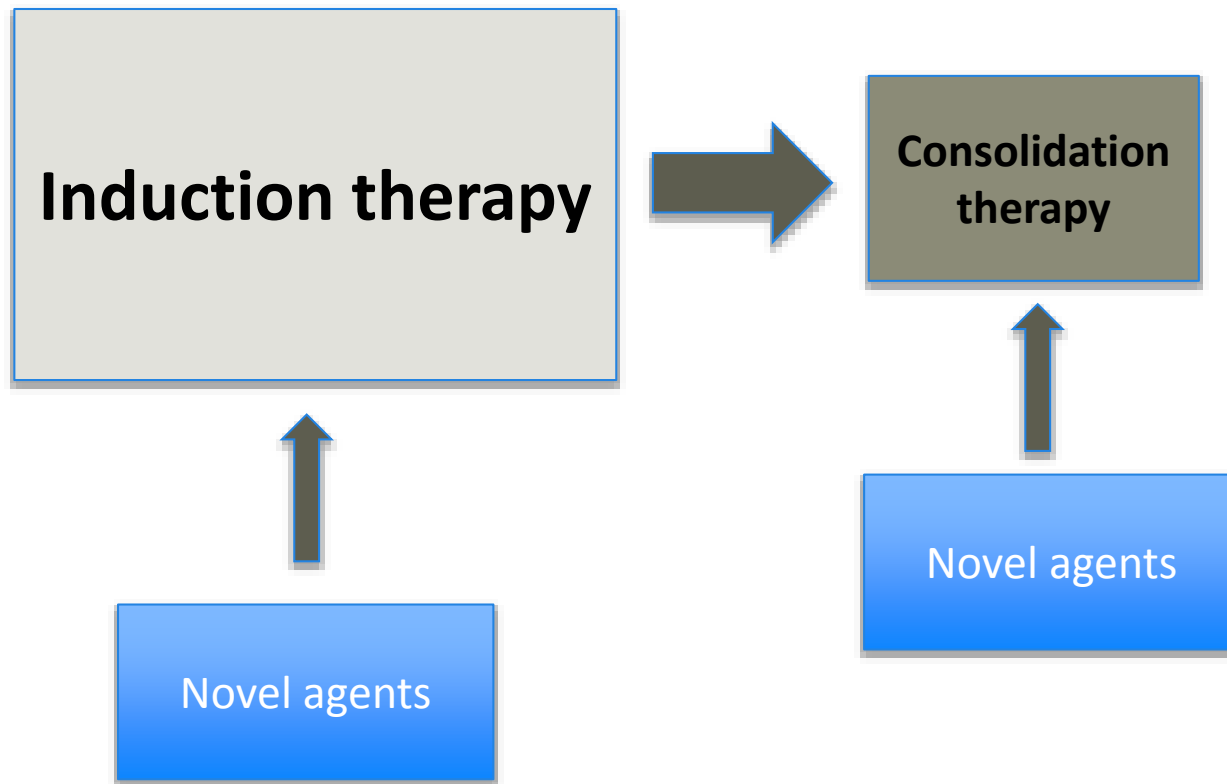
## Branching evolution



1. Bolli N. et al. *Nature Comm*, 2015 (5): 2997



# Adding novel agents to overcome clonal heterogeneity



# Myeloma Program at MSKCC

## Myeloma Service

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Eric Smith, MD, PhD

Sean Devlin, PhD

Sham Mailankody, MD

Ola Landgren, MD, PhD

*and team*

## BM Transplant Service

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Guenther Koehne, MD, PhD

David Chung, MD, PhD

*and team*

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## Hemato Pathology

Ahmet Dogan lab, MD, PhD

## Cellular Therapy

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## Molecular Imaging

Steven Larson lab, MD

Wolfgang Weber lab, MD, PhD

## Immunotherapy

Jedd Wolchok lab, MD



# Collaborators

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*Thank you to our patients!*

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