

# MRD and High Risk Myeloma

Gareth Morgan

Little Rock

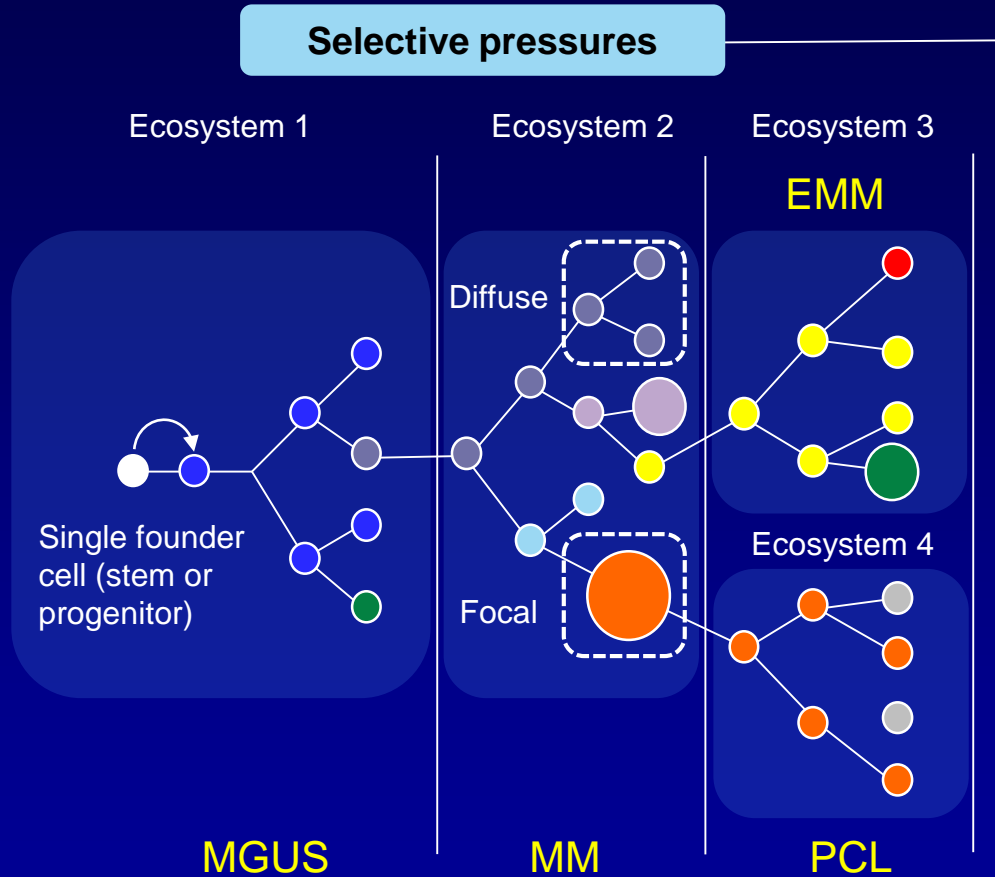
Arkansas

MRD is an effective endpoint, and will enter the clinic, but it requires careful use and interpretation and trial design.

Depth of response and  
biology are independent  
prognostic factors.

# Clonal evolution of myeloma

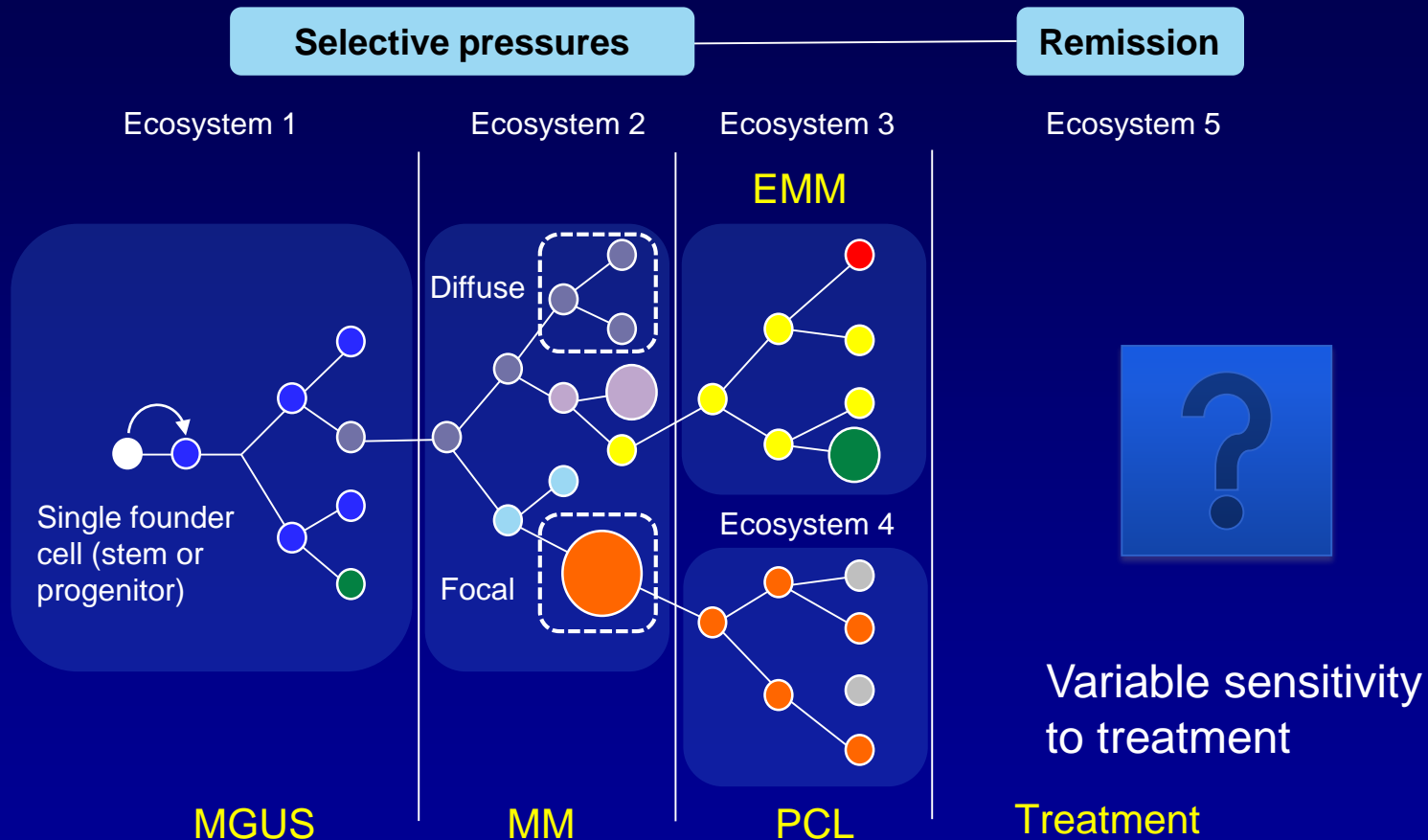
Impact of treatment on clonal composition in remission



● ● ● Subclones with unique genotype/"driver" mutations

# Clonal evolution of myeloma

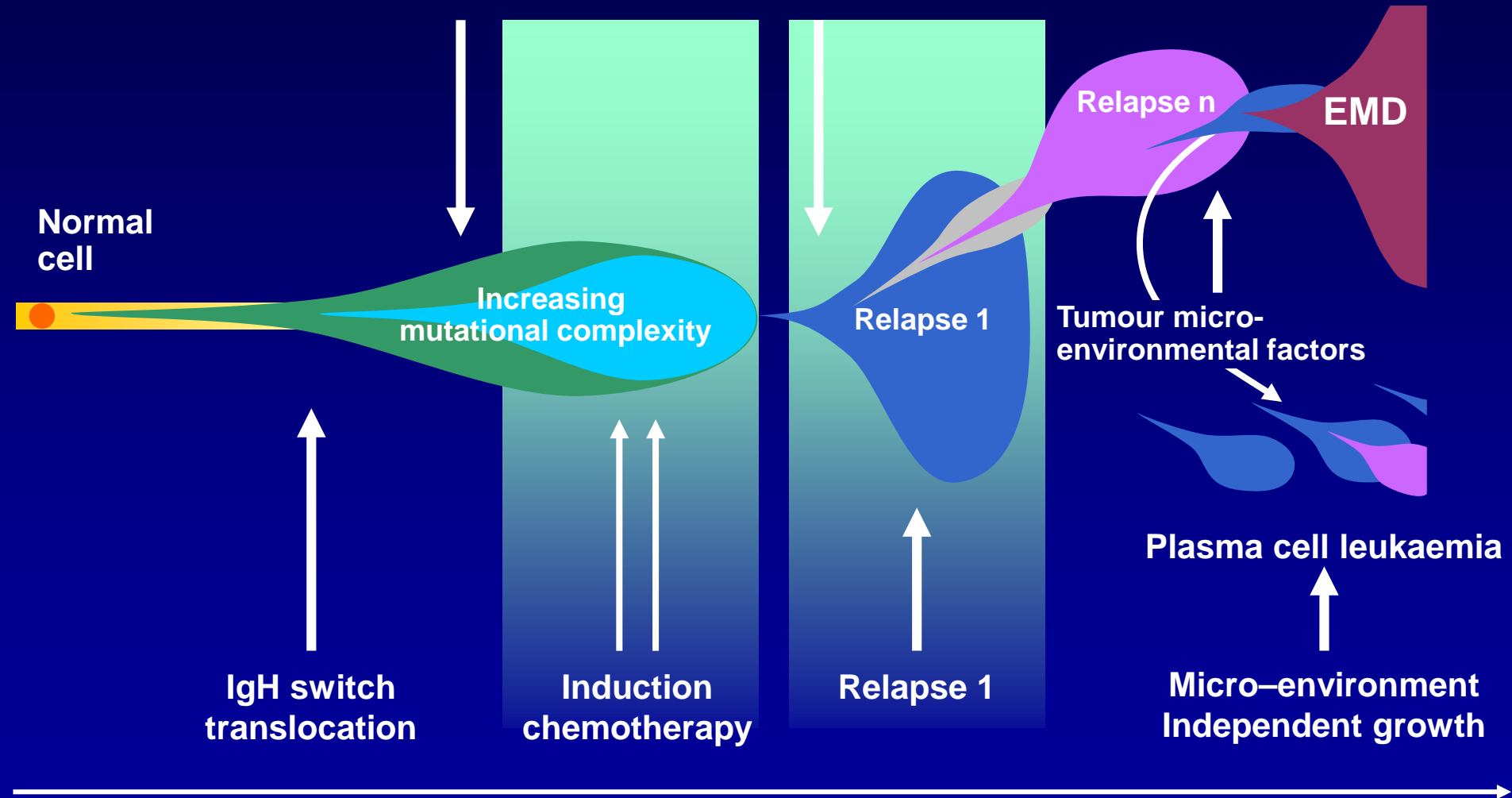
Impact of treatment on clonal composition in remission

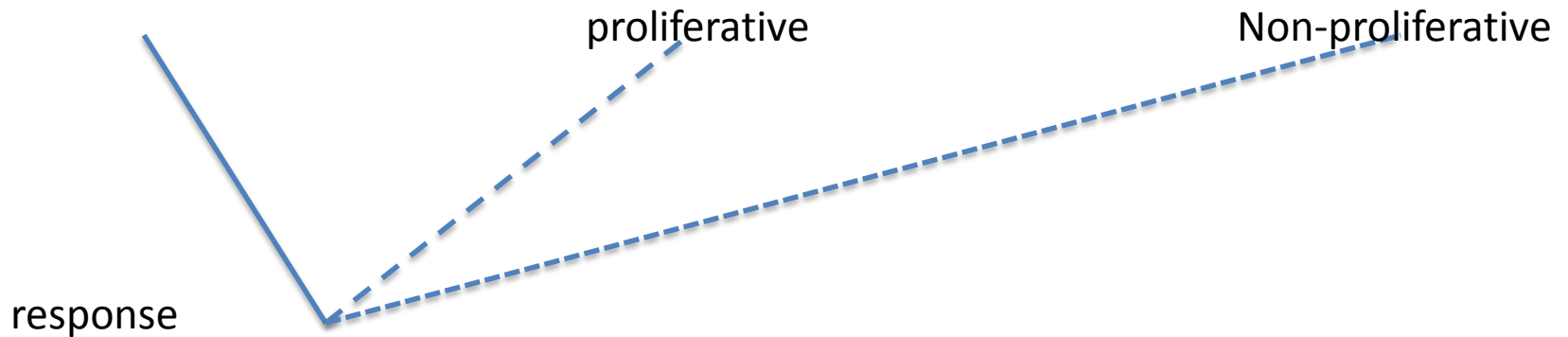


● ● ● Subclones with unique genotype/"driver" mutations

# The micro-environment and the myeloma stem cell

## Micro-environmental factors and angiogenesis

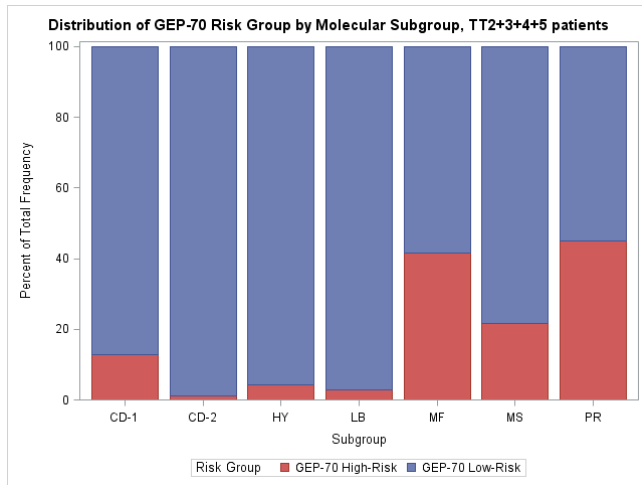




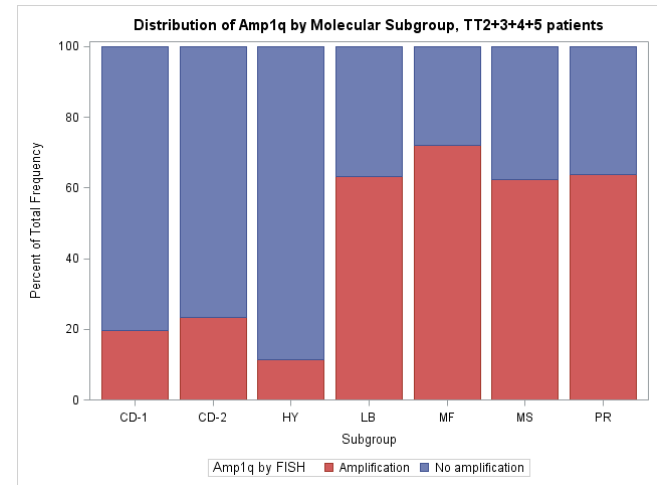
- What is high risk
  - Definitions GEP70, iFISH, adding iFISH lesions
  - Traditional response rates are the same in HR and LR but outcomes are different
- Don't confuse drug resistance with HR
- Can't separate response from biology
- Sensitivity and specificity
  - Predictability of outcome
- When should MRD be measured
  - What is impact of maintenance
- Disease subtype
  - Differences in time to response
- Trial design

# Distribution of molecular features across subtypes

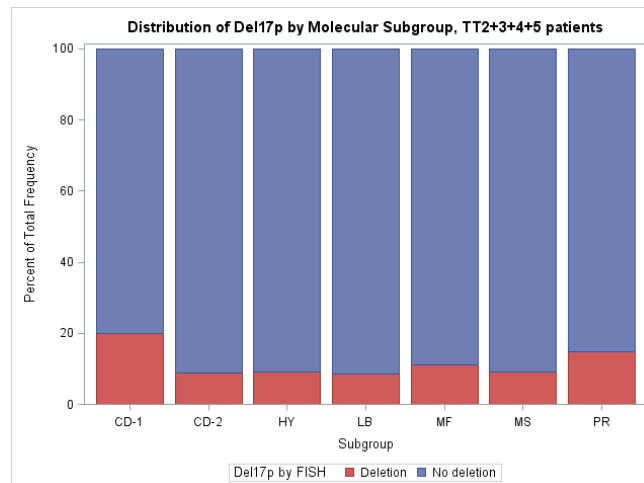
HiR



amp1q

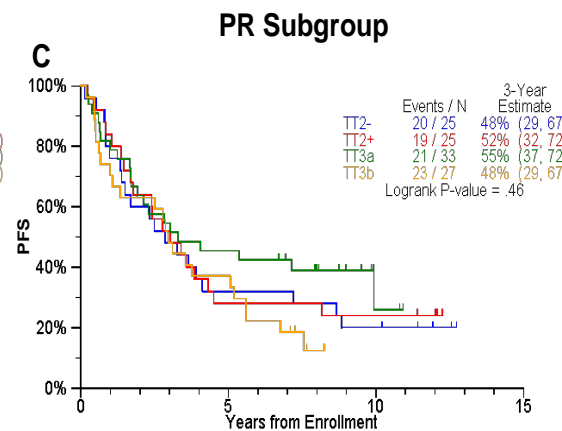
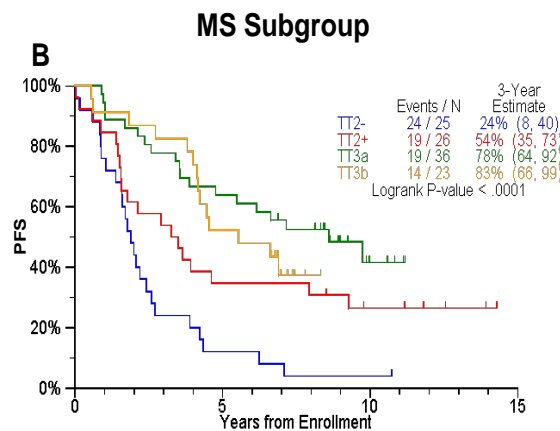
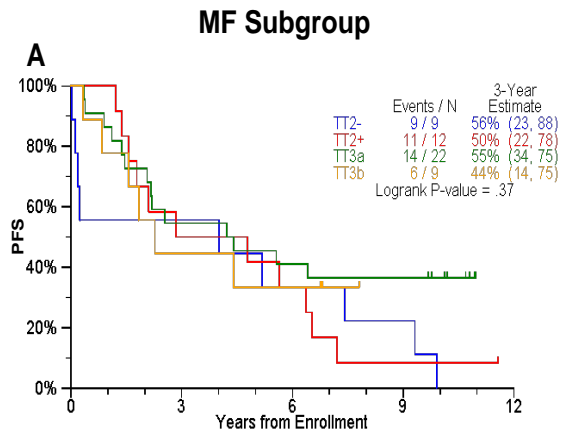
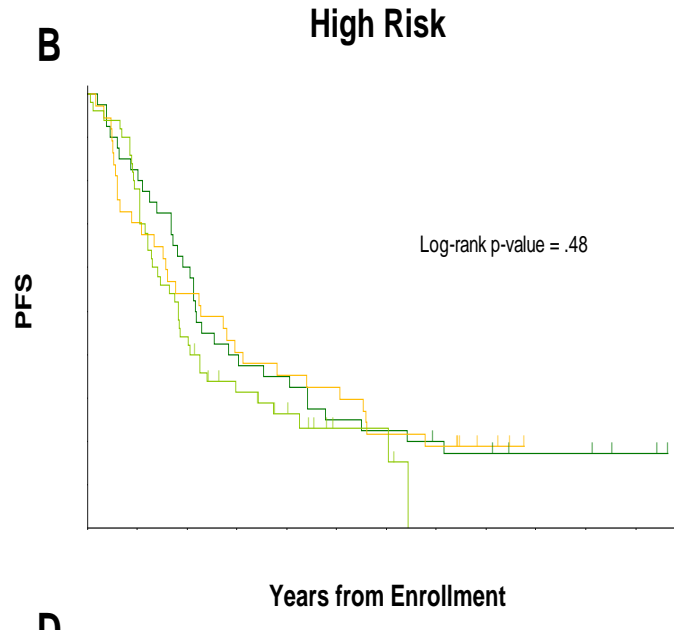
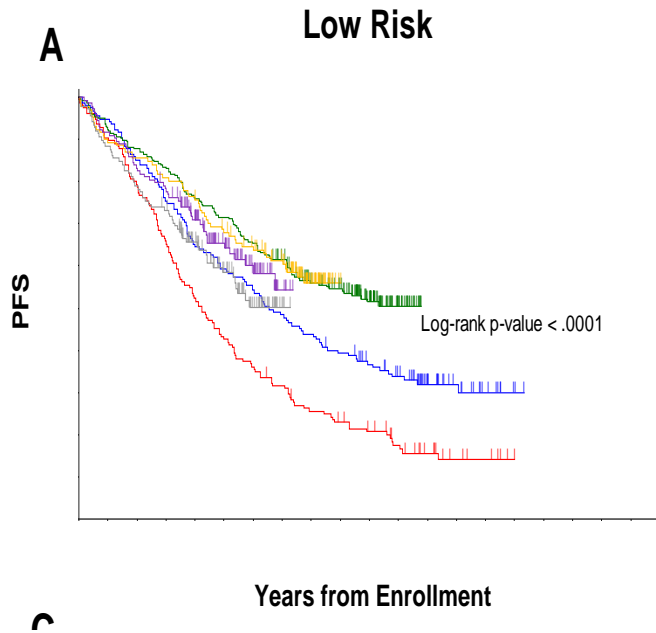


17p-





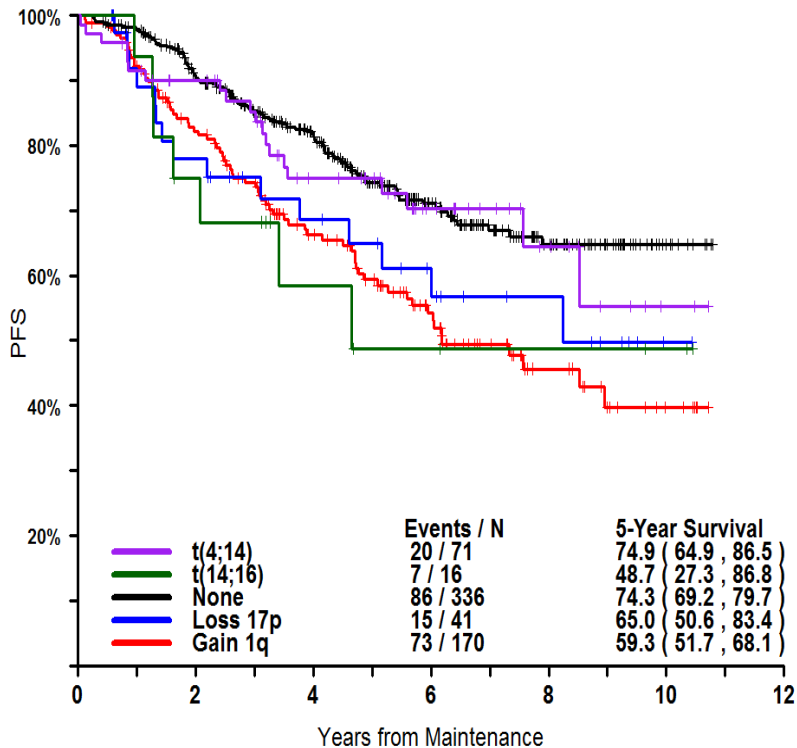
# MM is not a single disease but has different clinical behavior and survival improvement over time



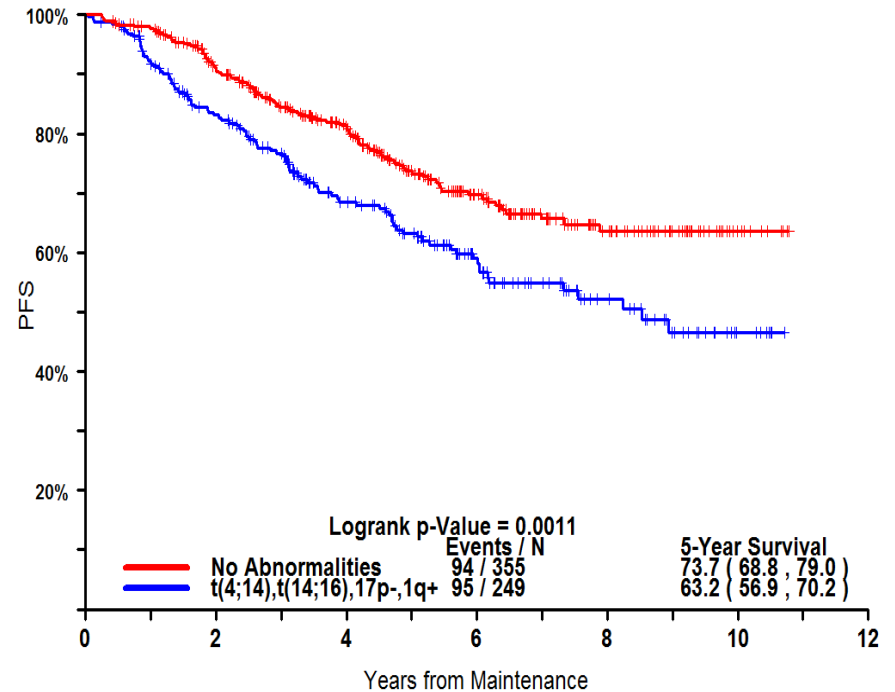
# HR within GEP70 LR

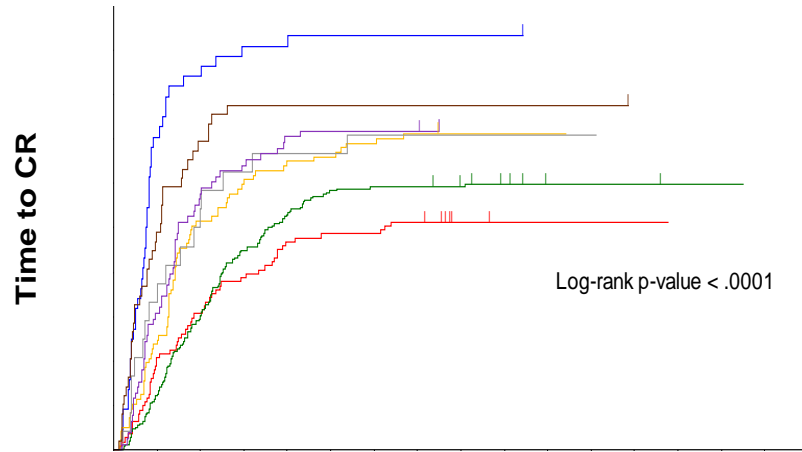
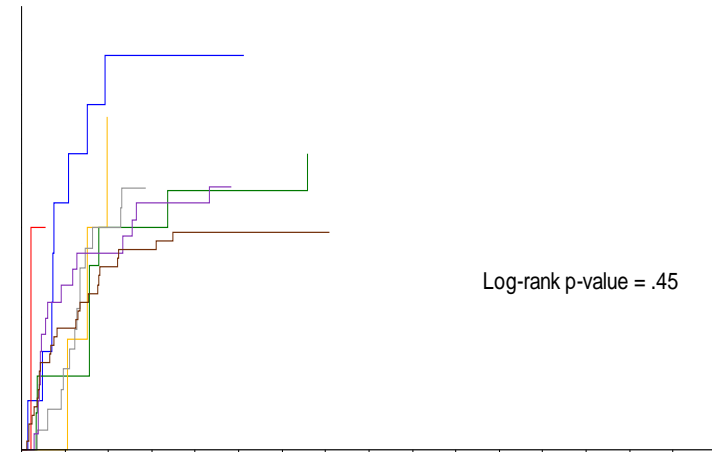
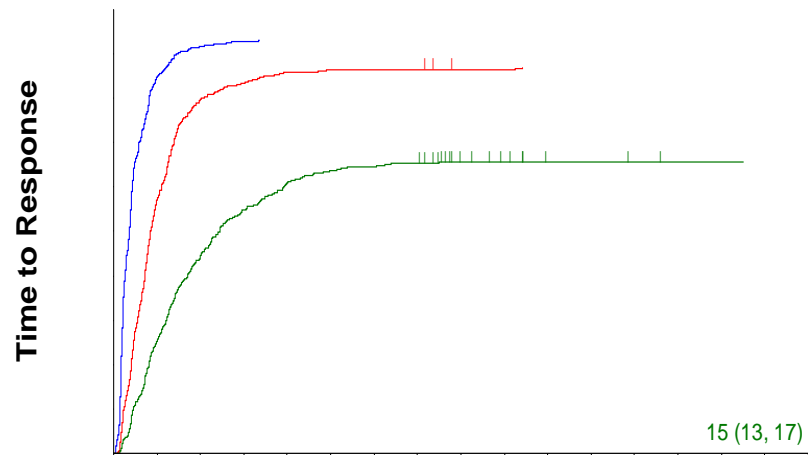
Survival from maintenance

**A** LoRMM Patients by Cytogenetic Subgroup



**B** Pooled LoRMM Patients by Cytogenetic Subgroup



**A****GEP-70 Low-Risk Patients****B****GEP-70 High-Risk Patients****C****GEP-70 Low-Risk Patients****D****GEP-70 High-Risk Patients**

## **Current knowledge of MRD**

- Patients that are in CR and MRD negative have best clinical outcome
- HR patients that do not achieve MRD negativity do very poorly
- The better the sensitivity of MRD assessment, the better prognostication

## **Unanswered questions**

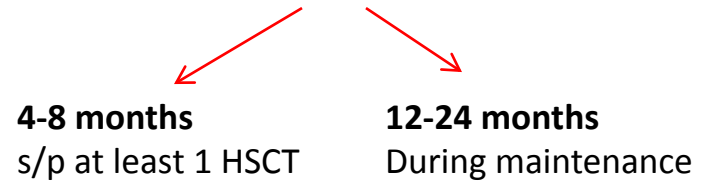
- MRD assessment in most previous studies was done 100 days post Auto SCT -> impact of maintenance is not accounted for
- Impact of MRD assessment on risk groups and different molecular subgroups still needs to be determined.

# Prognostic Value of Adaptive MRD assessment

Protocols- TT3b- TT6, n= 591

Patient required to be in  $\geq$  VGPR

Available Buffycoats at Baseline (for identification of clones) and MRD assessment



-> Next generation sequencing (NGS) by Adaptive Biotechnologies, which is sensitive to 1 MM cell in  $10^6$  normal cells.

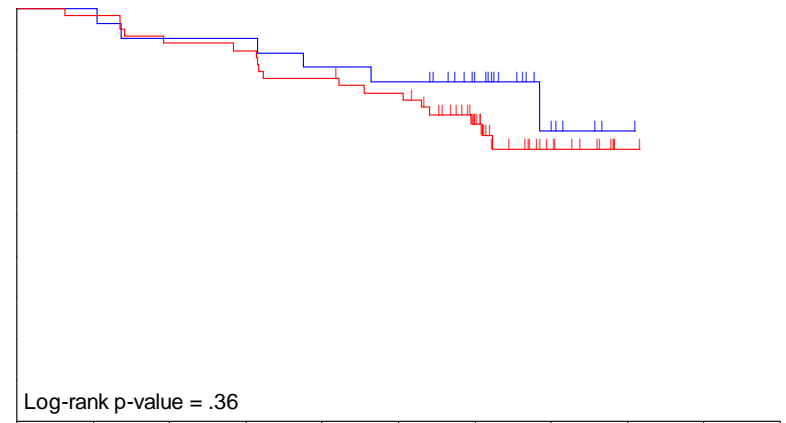
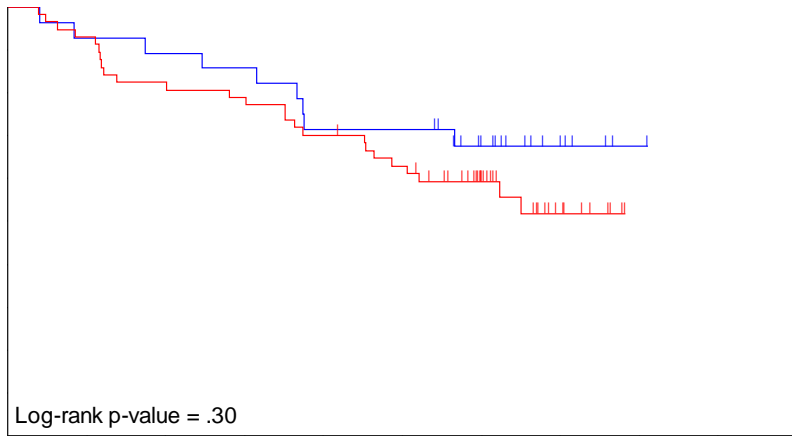
# Overall Results- PFS/OS by MRD status ( $10^{-5}$ and $10^{-6}$ )

4-8 months

n=87

PFS

OS

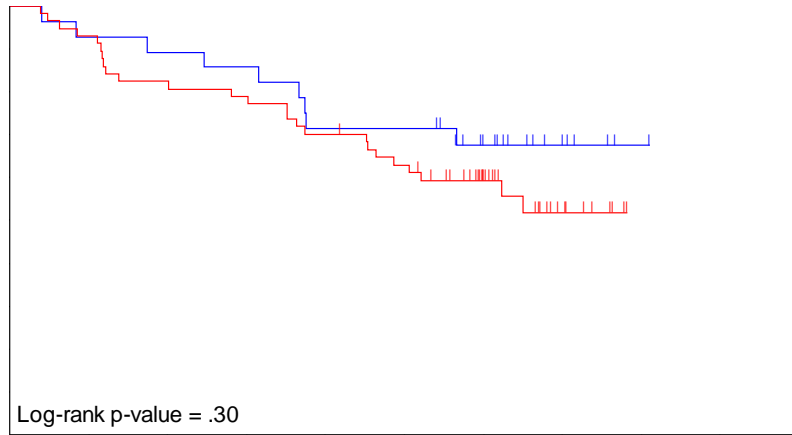


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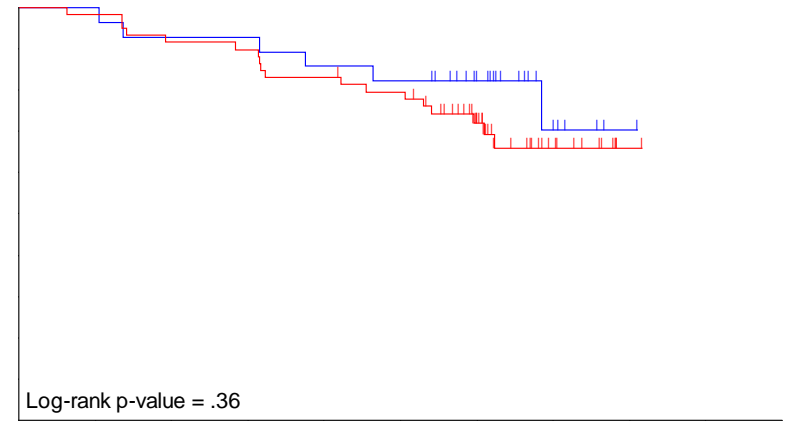
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PFS



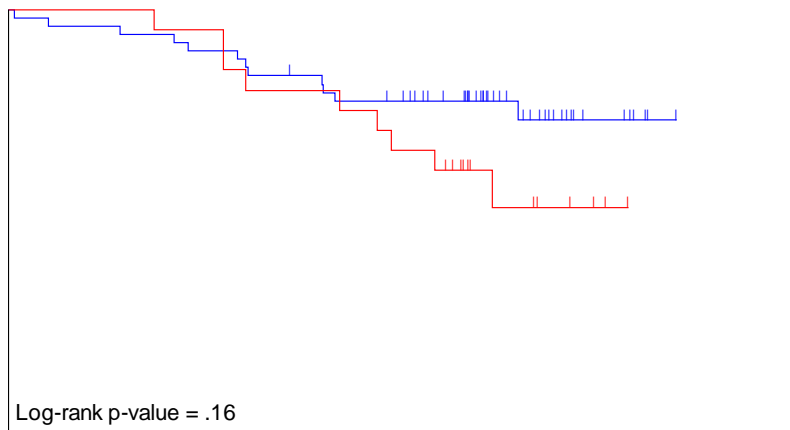
OS



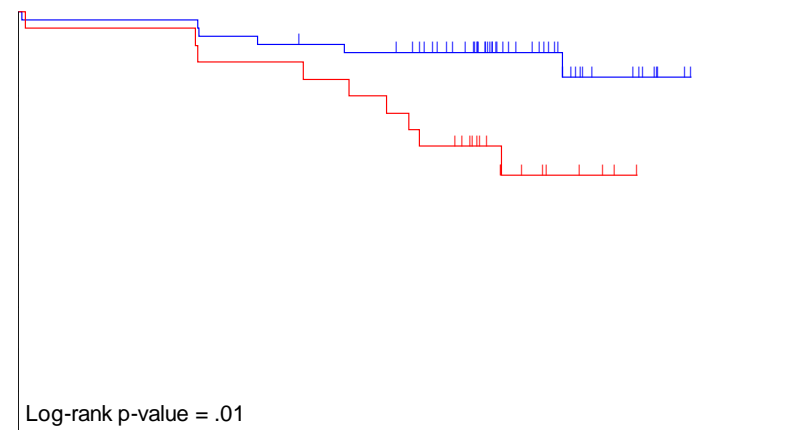
## 12-24 months

n=77

PFS



OS



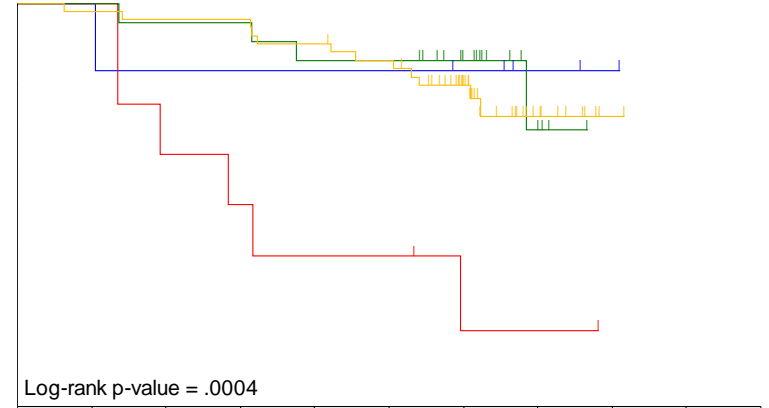
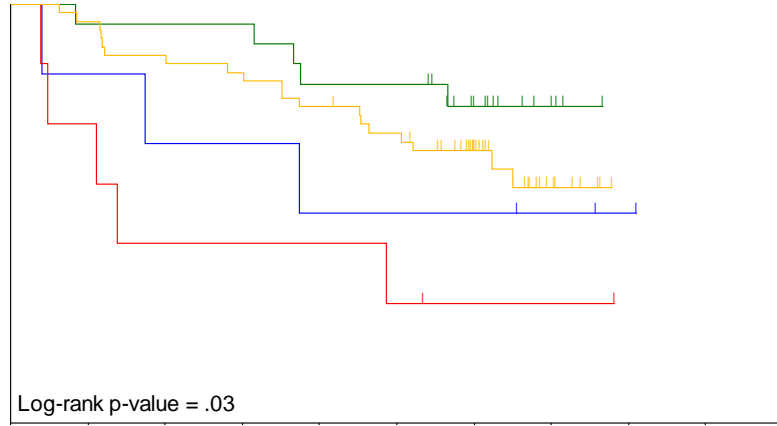
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4-8 months

n=87

PFS

OS





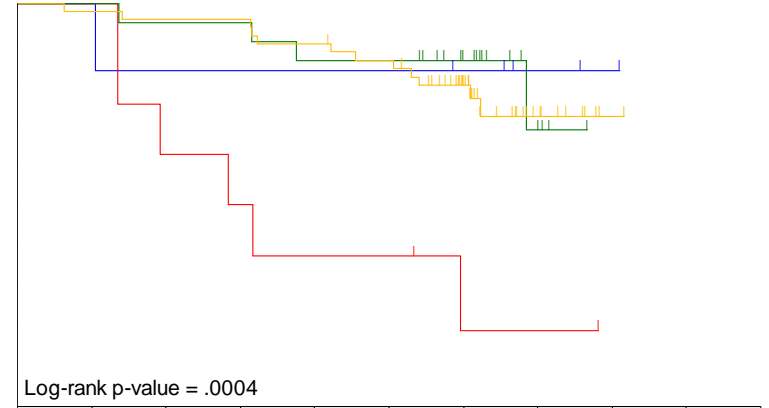
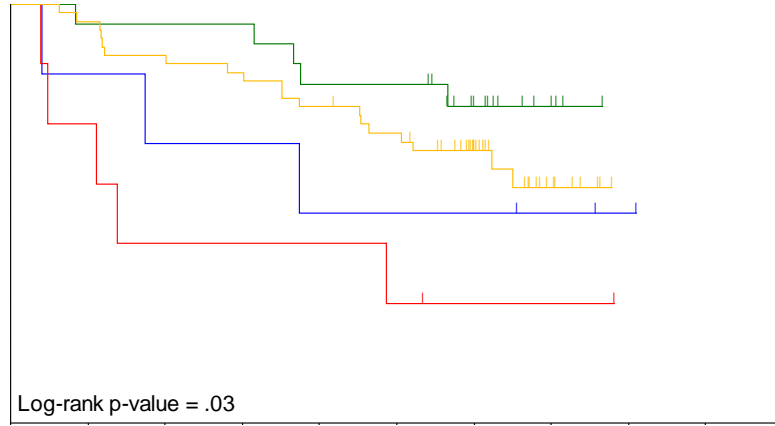
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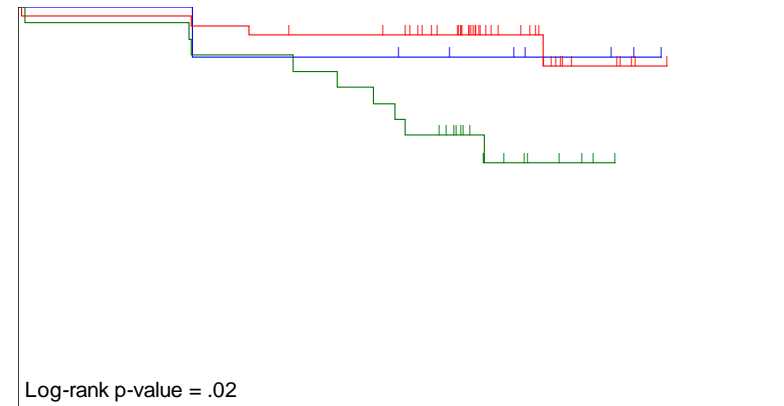
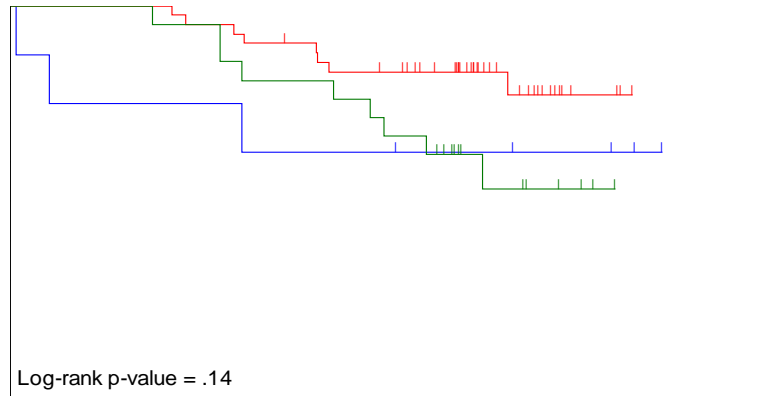


## 12-24 months

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PFS

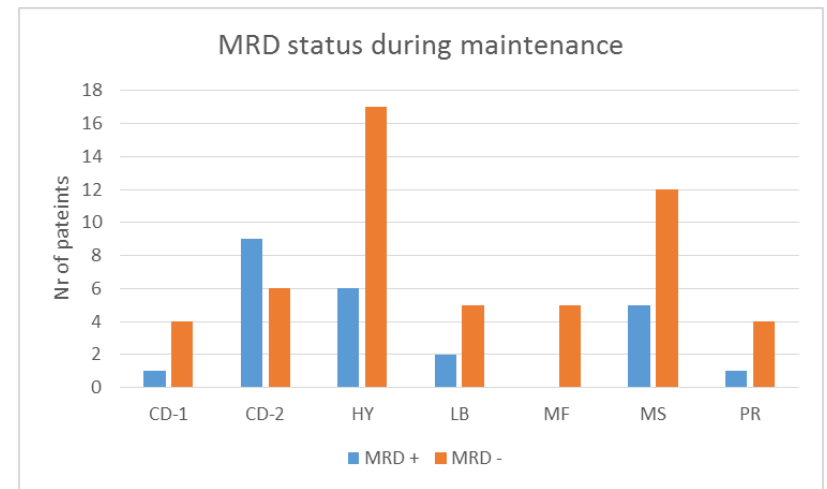
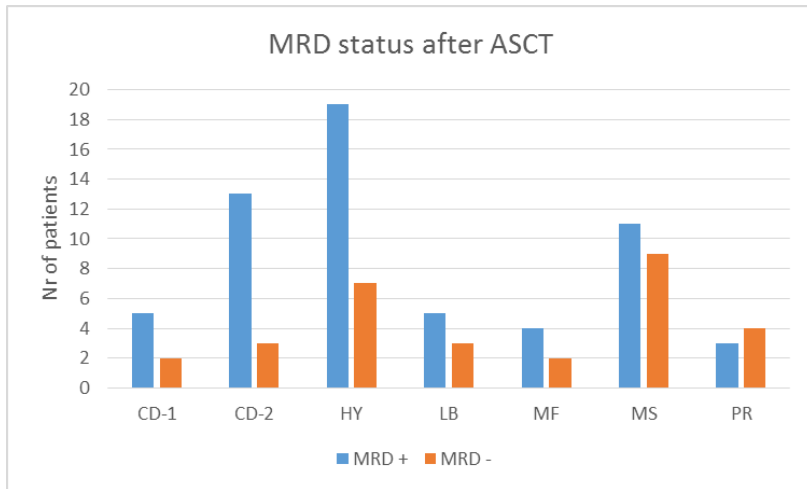
OS



# Results by molecular subgroup

4-8 months

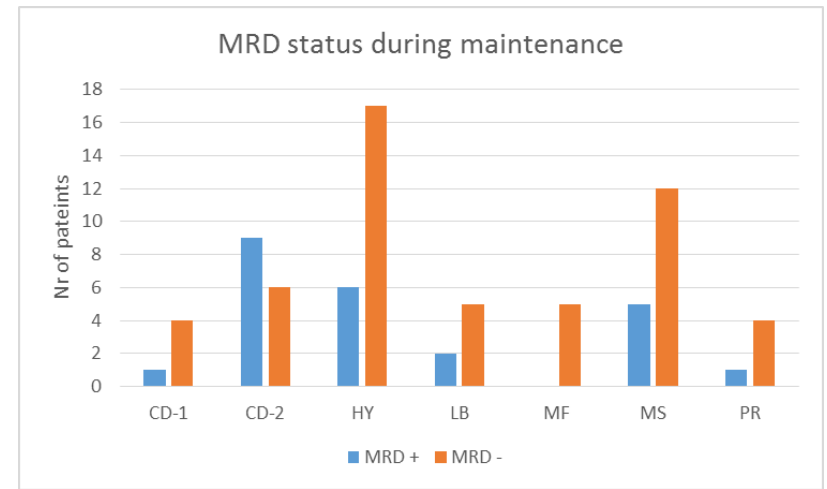
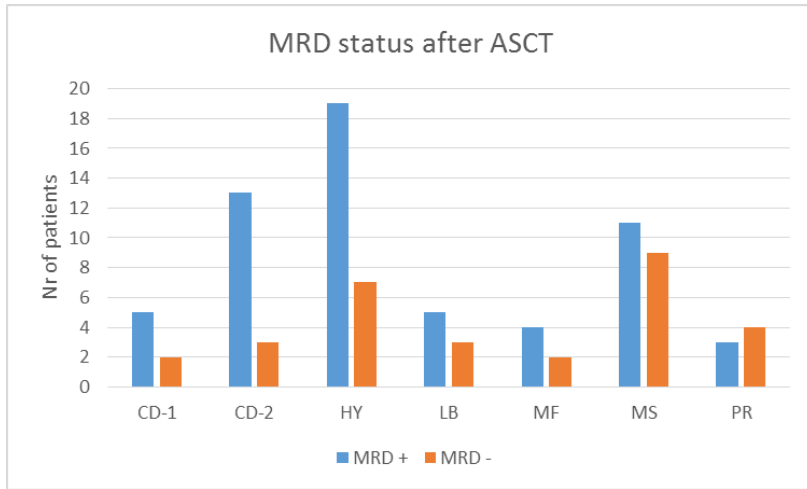
12-24 months



# Results by molecular subgroup

4-8 months

12-24 months

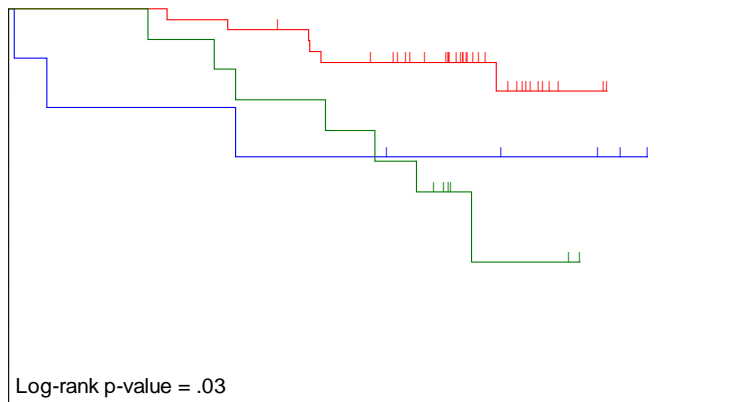


**PFS/OS for patients not including CD2 subgroup by GEP70 and MRD status ( $10^{-5}$  and  $10^{-6}$ )**

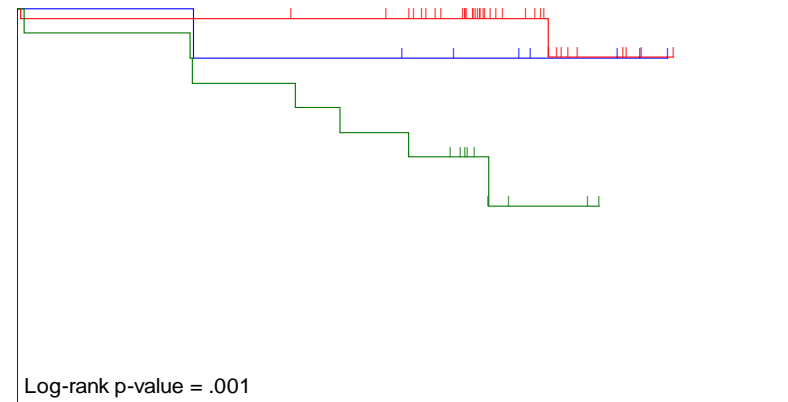
**12-24 months**

n=62

PFS



OS

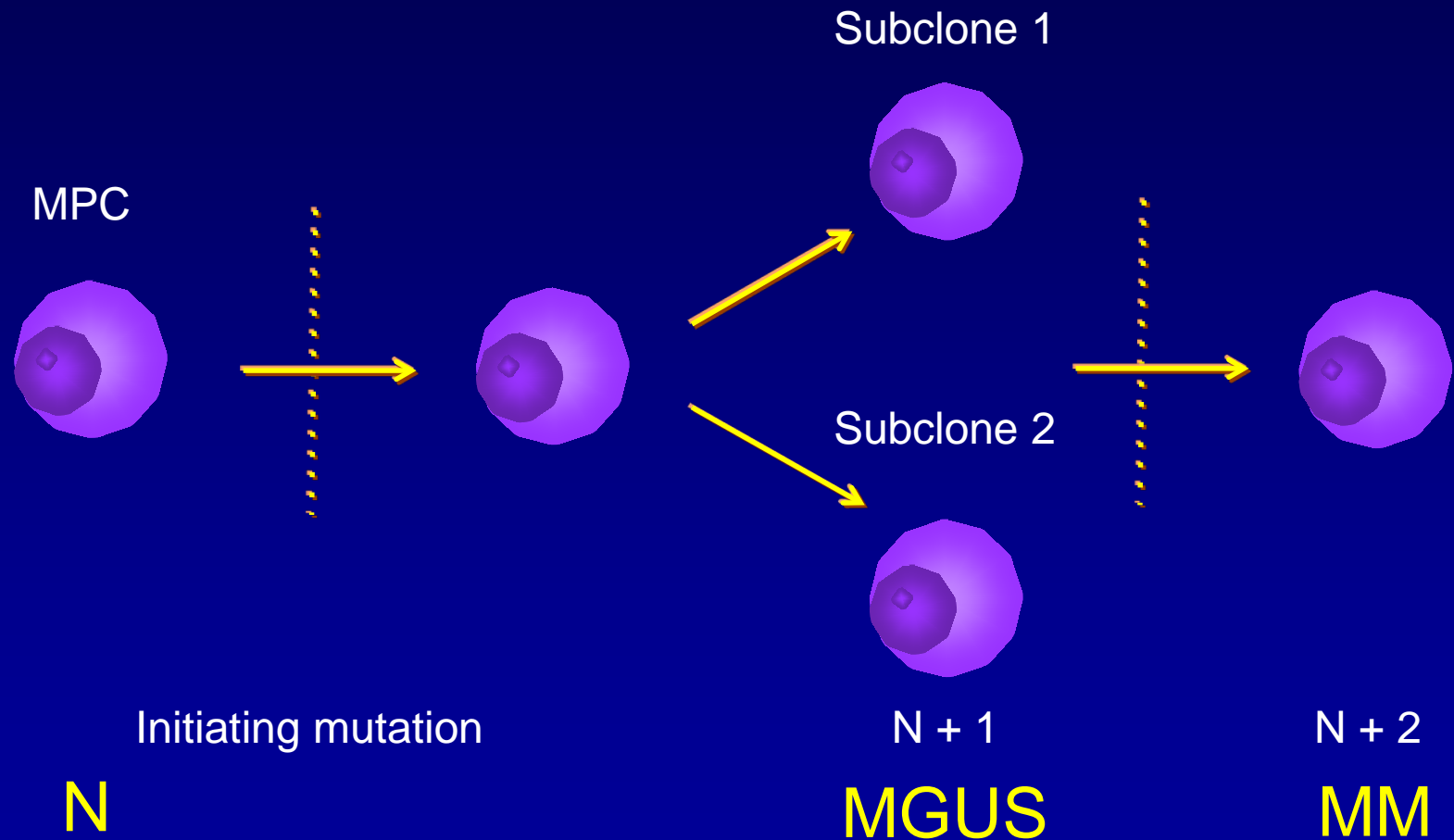


The End

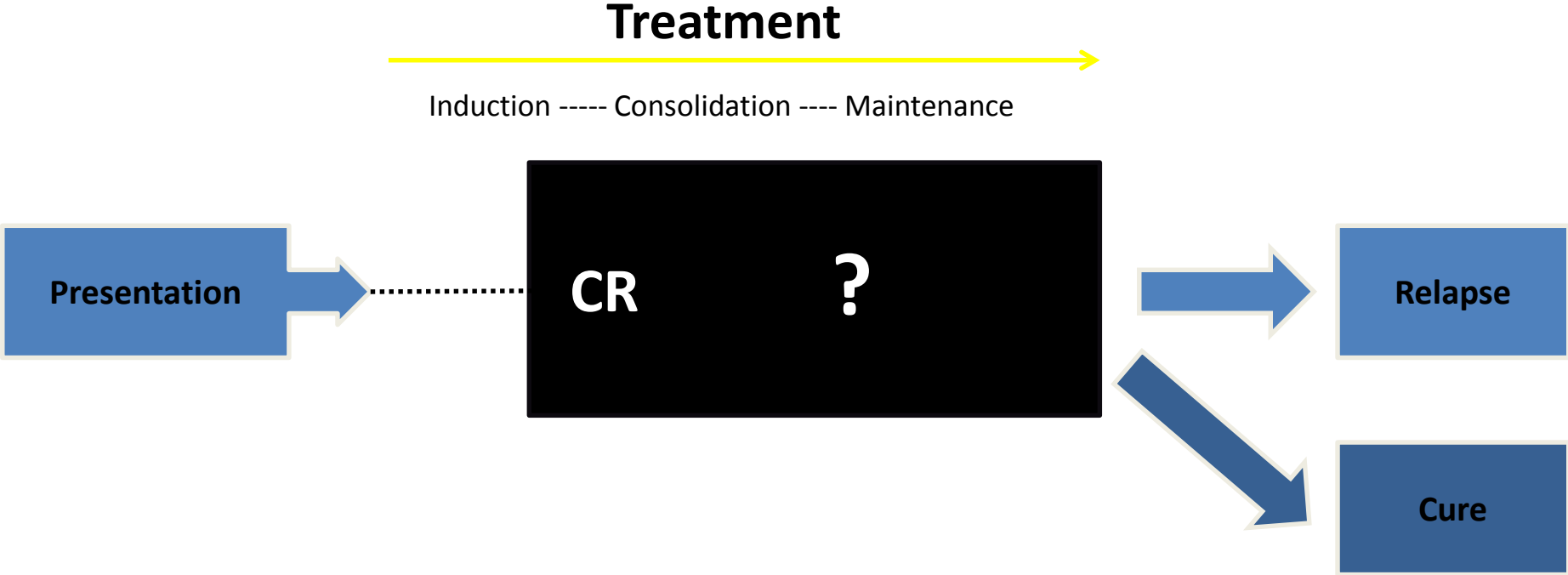
# Mutation and stem cell units

Expansion

Diversification

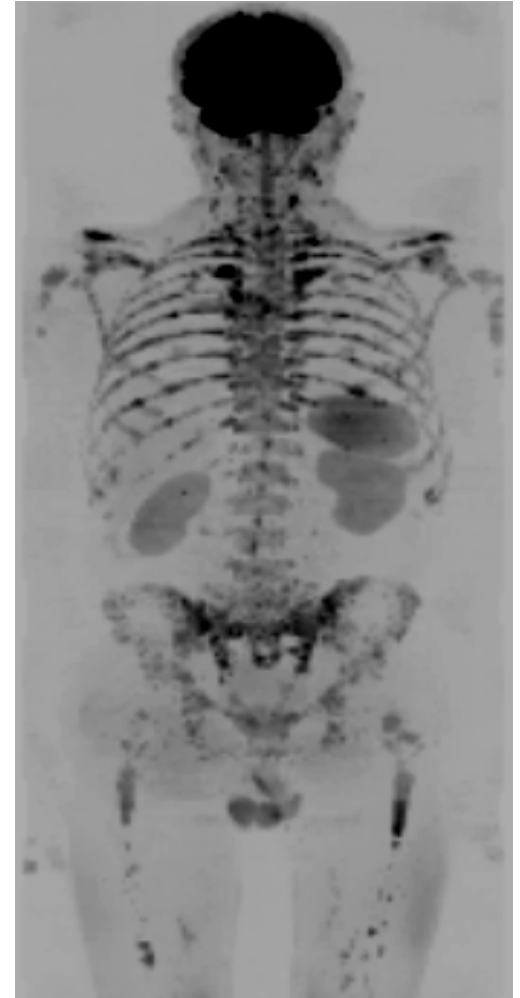


# Minimal Residual Disease Biology



# The clinical relevance of intra clonal heterogeneity

- **Tumour diversity supports the evolutionary fitness of the tumour cells**
- **Tumour adaptation and drug resistance**
  - Drug resistance Metastasis
- **Sites of disease evolve independently**
  - Sampling site bias
  - Different biopsy sites may give different results
- **Clonal dominance can change**
- **Actionable mutations?**
  - Mutations may be present at one site but not another
  - Differential responses



# What drives HiR

- Adverse translocations
  - t(4;14), t(14;16), t(14;20), TxMYC
- Adverse copy number
  - 1p- (CDKN2C, FAF1), 1q+ (CKS1b), 17p- (TP53)
- Adverse mutations
  - ZFH4, ATM/ATR/P53, CCND1
- GEP70 and EMC92 both contain an over-representation of genes on 1q and 1p.
- Proliferation

