MRD and High Risk Myeloma

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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

Selective pressures

Ecosystem 1
Single founder cell (stem or progenitor)

Ecosystem 2
Diffuse
Focal

Ecosystem 3
EMM

Ecosystem 4

Ecosystem 5

MGUS
MM
PCL

Subclones with unique genotype/"driver" mutations

Clonal evolution of myeloma
Impact of treatment on clonal composition in remission

The micro-environment and the myeloma stem cell

Micro-environmental factors and angiogenesis

Normal cell
- IgH switch translocation
- Increasing mutational complexity

Induction chemotherapy

Relapse 1
- Tumour micro-environmental factors
- Plasma cell leukaemia
- Micro-environmental growth

EMD

• 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

- **t(4;14)**
- **t(14;16)**
- **None**
- **Loss 17p**
- **Gain 1q**

Events / N: 20 / 71, 7 / 16, 86 / 336, 15 / 41, 73 / 170

5-Year Survival: 74.9 (64.9, 86.5), 48.7 (27.3, 66.8), 74.3 (69.2, 79.7), 65.0 (50.6, 83.4), 59.3 (51.7, 68.1)

Logrank p-Value = 0.0011

- **No Abnormalities**
- **t(4;14), t(14;16), 17p-, 1q+**

Events / N: 94 / 355, 95 / 249

5-Year Survival: 73.7 (68.8, 79.0), 63.2 (56.9, 70.2)
(A) GEP-70 Low-Risk Patients

Time to CR

Log-rank p-value < .0001

(B) GEP-70 High-Risk Patients

Time to CR

Log-rank p-value = .45

(C) GEP-70 Low-Risk Patients

Time to Response

15 (13, 17)

(D) GEP-70 High-Risk Patients

Time to Response

13 (9, .)

Months from Initiation of VDT-PACE
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 ≥ VGPR
Available Buffycoats at Baseline (for identification of clones) and MRD assessment

- 4-8 months s/p at least 1 HSCT
- 12-24 months During maintenance

-> 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

Log-rank p-value = .30

Log-rank p-value = .36
Overall Results - PFS/OS by MRD status (10^-5 and 10^-6)

4-8 months
n=87

Log-rank p-value = .30

12-24 months
n=77

Log-rank p-value = .16

Log-rank p-value = .01
Results by GEP Status - PFS/OS by MRD status \((10^{-5} \text{ and } 10^{-6})\)

4-8 months

n=87

PFS

OS

Log-rank p-value = .03

Log-rank p-value = .0004
Results by GEP Status - PFS/OS by MRD status (10^-5 and 10^-6)

4-8 months
n=87

Log-rank p-value = .03

12-24 months
n=77

Log-rank p-value = .14

Log-rank p-value = .02
Results by molecular subgroup

4-8 months

MRD status after ASCT

12-24 months

MRD status during maintenance
Results by molecular subgroup

4-8 months

12-24 months

MRD status after ASCT

MRD status during maintenance

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

12-24 months

PFS

OS

n=62

Log-rank p-value = .03

Log-rank p-value = .001
The End
Mutation and stem cell units

Expansion

MPC

Initiating mutation

N

Diversification

Subclone 1

Subclone 2

N + 1

MGUS

N + 2

MM
Minimal Residual Disease Biology

Presentation

CR

?  Relapse

Cure

Induction ----- Consolidation ---- Maintenance

Treatment
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
  - ZFHX4, ATM/ATR/P53, CCND1
- GEP70 and EMC92 both contain an over-representation of genes on 1q and 1p.
- Proliferation