Response-related Prognostic Factors:
The Molecular Response

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The amount of BCR-ABL transcripts roughly mirrors the number of residual BCR-ABL positive cells.

Amount of BCR-ABL in the PB after 3 months of imatinib therapy in the different cytogenetic-response groups
Survival Without AP/BC by Level of CyR at 12 Months on First-line Imatinib

Response at 12 months:
- CCyR
- PCyR
- No MCyR

Estimated rate at 54 months:
- CCyR: n=350, 97%
- PCyR: n=86, 95%
- No MCyR: n=73, 81%

p<0.001 p=0.20
Survival Without AP/BC by Molecular Response at 12 Months on First-line Imatinib

Estimated rate at 54 months:
- CCyR with $\geq 3$ log red: 100% (n=136)
- CCyR with $< 3$ log red: 95% (n=94)
- No CCyR: 89% (n=138)

p < 0.001, p = 0.007
Possible explanation:
• the molecular analysis is more precise in discriminating between response subgroups than cytogenetic analysis

Consequence:
• The patient must be followed not only by cytogenetics but also by RQ PCR
Question

Once reached, is MMR stable over time?
PFS by Molecular Response at 12 Months on First-line Imatinib

Although very small, a risk of losing MMR exists!
% BCR-ABL log reduction in 124 CCyR pts at 1 and 4 years: IRIS Trial

- Year 1: 53%
  - >= 4 log reduction: 22
  - 3 - < 4 log reduction: 31
  - 2 - < 3 log reduction: 39
  - < 2 log reduction: 8

- Year 4: 80%
  - >= 4 log reduction: 41
  - 3 - < 4 log reduction: 39
  - 2 - < 3 log reduction: 12
  - < 2 log reduction: 8
Question

Are all molecular remissions the same?
Molecular response at 12 months by Sokal risk category

The probability to achieve MMR correlates to the Sokal risk
However, when a high or intermediate risk patient achieves a Major Molecular Remission, the risk of subsequent progression is as small as that of low risk patients.

(Goldman J et al., ASH 2005)
Question

Is the time to reach MMR relevant in terms of prognosis?
IRIS Q-PCR Study: Overall Estimated Log Reduction of *bcr-abl* with First-line Imatinib

Association of early and late cytogenetic response with progression-free (A) and overall (B) survival

RISE in BCR-ABL

- A rise in BCR-ABL of more than 2-fold identifies patients at high risk to become imatinib resistant
- In 60% of these cases, presence BCR-ABL mutations
- Mutation detection can be important
Question
Which increase in BCR-ABL transcript level must trigger search for mutation?

Still an open question!

- 2 fold rise (Branford et al., Blood 2004)

- consecutive rises (Wang et al., Haematologica 2006)
- **RQ PCR during the first year:**
  - To assess the response

- **RQ PCR on PB every 3 months after the first year:**
  - to identify the late responders (continuously decreasing BCR/ABL%)
  - to detect a possible rise in BCR-ABL