STRATIFICATION BASED ON GENOMICS – IS IT READY FOR PRIMETIME? .................NO

Faith Davies, Clinical Director, Myeloma
Disclosures

• Advisory boards:
  • BMS
  • Celgene
  • GSK
  • Janssen
  • Oncopeptide
  • Sanofi
  • Takeda
Dear Dr. Davies:

The organisers, on behalf of the International Myeloma Society, are pleased to cordially invite you to participate as a faculty member for the 18th International Myeloma Workshop scheduled for September 8-11, 2021 in Vienna, Austria.

You are invited to participate as a faculty member as follows:

Session: Plenary Session - Great Debates in Myeloma
Date: Saturday, September 11, 2021
Session Time: 1:15-3:15pm CET
Faculty Role: Presenter
Talk Name: Stratification based on genomics ready for primetime? (no)
Talk Time: 1:55-2:15pm CET
<table>
<thead>
<tr>
<th>Topic</th>
<th>Participants</th>
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<tbody>
<tr>
<td>Should every transplant eligible NDMM patient receive a transplant?</td>
<td>Sergio Giralt/Morie Gertz</td>
</tr>
<tr>
<td>Are we ready for MRD-guided therapy?</td>
<td>Sundar Jagannath/Ola Landgren</td>
</tr>
<tr>
<td>Is stratification based on genomics ready for primetime?</td>
<td>Gareth Morgan/Faith Davies</td>
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<tr>
<td>Which is the best immune approach to replace ASCT?</td>
<td>Hermann Einsele/Parameswaran Hari</td>
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<td>Can we give our patient treatment free intervals?</td>
<td>Luísano Costa/Phil McCarthy</td>
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<td>Is there a role for alkylator in MM?</td>
<td>Donna Reece/Jeff Wolf</td>
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</table>
Or have they been busy during COVID lockdown?
We have been stratifying patients for years

• Tailoring level of intensive therapy to patient fitness
  • autologous transplantation
  • more recently dose intensity for older/ less fit patients according to frailty score

• Choosing therapy based on side effect profile
  • treatment choices for VTE or neuropathy
Open Questions

1. Do we need to stratify based on genomics?
What do we expect in newly diagnosed patients – huge progress in recent years

Griffin, Voorhees et al Blood 2020

MIAIA, Facon et al NEJM 2019
And what about all of the new agents – their impact is huge in the relapsed setting and will be bigger in earlier lines of therapy
Conclusions of current treatment advances

• These advancements have resulted in improved response rates, progression free and overall survival rates.

• All genetic subgroups seem to benefit – admittedly some more than others but in nearly all studies the subgroups show improvements compared to the control arm

• We should not be withholding treatments from certain subgroups of patients
But what about the microenvironment?
Open Questions ..........

1. Do we need to stratify based on genomics?
2. If we do need to stratify based on genomics, is it ready for primetime?
Targeted therapy

Molecular event → Altered Myeloma Biology → Specific Diagnostic Test → Specific Therapy
Targeted therapy

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Only patients with the target respond
Targeted therapy

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Only patients with the target respond

t(11;14)
Targeted therapy

Molecular event → Altered Myeloma Biology → Specific Diagnostic Test → Specific Therapy

Only patients with the target respond

t(11;14)

smiley faces

(t4;14), (t14;16)

smiley faces
Stratifying for other genetic groups

• Despite advances in therapy there is still a group of patients who perform poorly.

• Clinical trials for High-Risk patients are important and will move the field further dramatically.
Stratifying for other genetic groups

• Despite advances in therapy there is still a group of patients who perform poorly.

• Clinical trials for High-Risk patients are important and will move the field further dramatically.

• I’ll give you a to do job list and when you have completed it - ask me for my opinion again

• I’ll also give you a deadline – 6 Months as the data is there it just needs compiling!
Moving towards consensus

- The variables to include:
  - R-ISS III
  - High risk GEP (GEP70 or SKY-92)
  - Primary plasma cell leukemia
  - Very high LDH
  - Clinical features of high-risk disease
    - Presence of extramedullary disease
    - > 3 focal lesions on F18-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging

  with the addition of 1q+ and TP53 mutation
Refine to include the subtleties of 17P – number and mutation

Incremental CCF change in 17p- was associated with shorter survival (CCF 0.3- 0.8)

A Thakurta et al 2019, J Keats et al MMRF dataset, J Corre Blood et al 2021
Refine to include the subtleties of 1q – gain and amplification

Adding 1q to RISS

Based on Albumin, LDH, FISH for t(4;14), t(14;16), del 17p and 1q+
Including 1q upstaged a number of patients:
97/344 from stage I to stage II
81/1080 from stage II to stage III

N Weinhold et al Haematologica 2021
Moving towards consensus – desperately required for clinical trials and prime time

Conclusions

Response rates, PFS and OS have improved greatly over the last few years – in addition there is lots of exciting research and new drugs coming through.

Response rates for many of the newer agents do not seem to be dependent on genetic subtypes.

Clinical trials for High-Risk patients are important and will move the field further dramatically.
Conclusions

Response rates, PFS and OS have improved greatly over the last few years – in addition there is lots of exciting research and new drugs coming through.

Response rates for many of the newer agents do not seem to be dependent on genetic subtypes.

Clinical trials for High-Risk patients are important and will move the field further dramatically.

Please please stop arguing with me, get off the stage, answer my questions, finish the High Risk position paper and lets get on with it.