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Perlmutter Cancer Center

Myeloma Program

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

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Excitement about IMW invitation – May 2021

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**

Who is my opponent?

	PLENARY SESSION	
11:15-13:15	**Great Debates in Myeloma**	
	Moderators: Ludwig/Goldschmidt/Einsele/Hajek	
	Should every transplant eligible NDMM patient receive a transplant?	Sergio Giralt/Morie Gertz
	Are we ready for MRD-guided therapy?	Sundar Jagannath/ Ola Landgren
	Is stratification based on genomics ready for primetime?	Gareth Morgan/Faith Davies
	Which is the best immune approach to replace ASCT?	Hermann Einsele/ Parameswaran Hari
	Can we give our patient treatment free intervals?	Lu«ano Costa/ Phil McCarthy
	Is there a role for alkylator in MM?	Donna Reece/Jeff Wolf

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Roman

Heinz

Hartmut

Hermann

IMW Vienna's got Talent

Or have they been busy during COVID lockdown?

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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

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Open Questions……

1. Do we need to stratify based on genomics?

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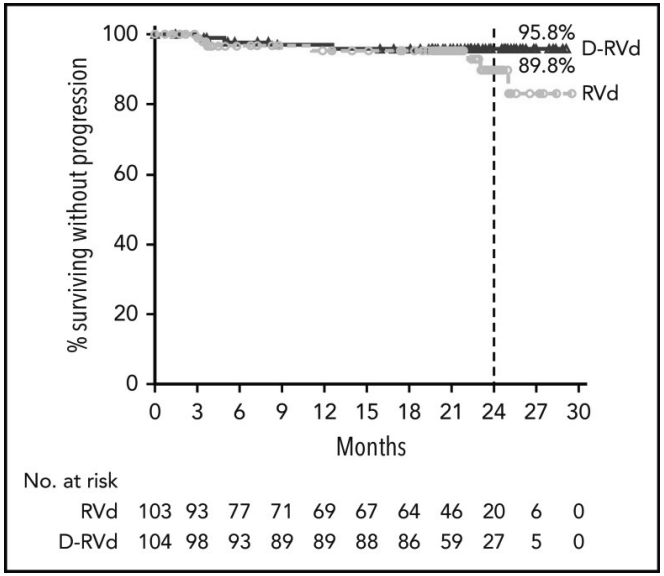
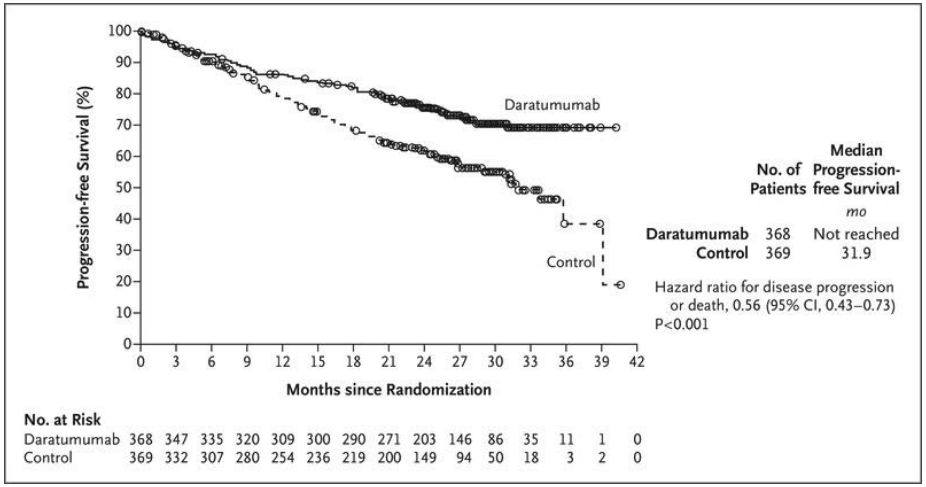
What do we expect in newly diagnosed patients
– huge progress in recent years



Griffin, Voorhees *et al* Blood 2020



MIAIA, Facon *et al* NEJM 2019

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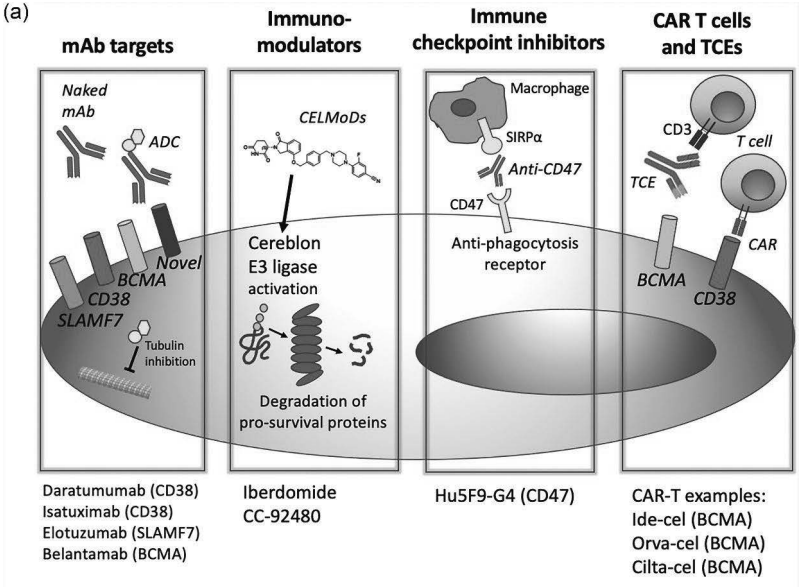
And what about all of the new agents
– their impact is huge in the relapsed setting and will be bigger in earlier lines of therapy



Braunstein, Weltz and Davies, Expert Reviews in Hematology 2021

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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

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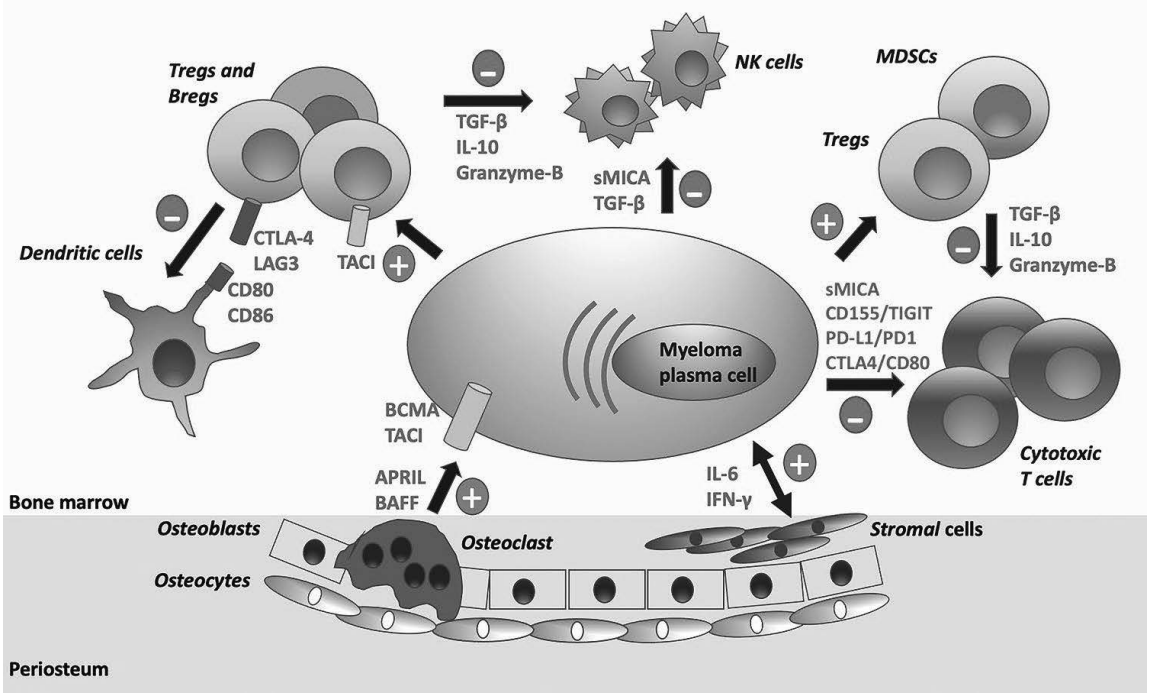
But what about the microenvironment?



Braunstein, Weltz and Davies, Expert Reviews in Hematology 2021

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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?**

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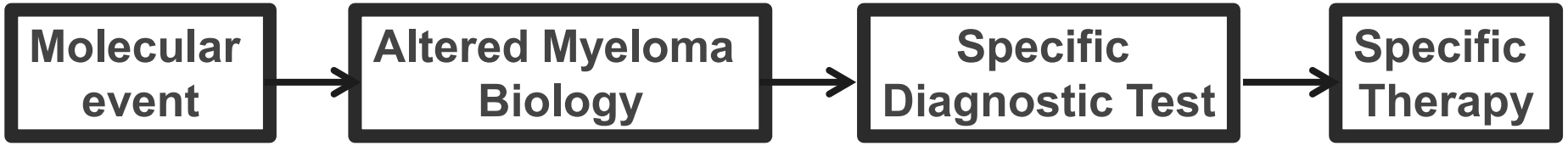
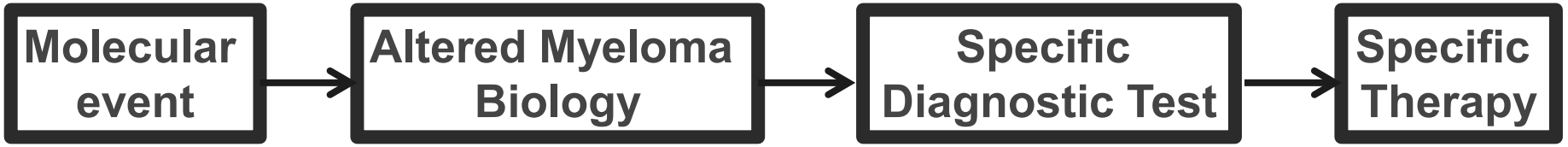
Targeted therapy



Targeted therapy



Only patients with the target respond

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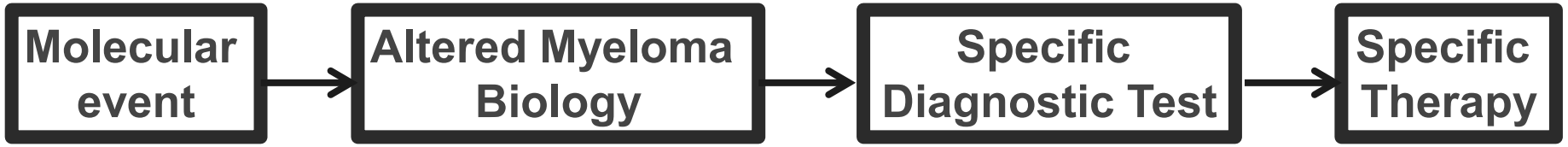
Targeted therapy



Only patients with the target respond

t(11;14)

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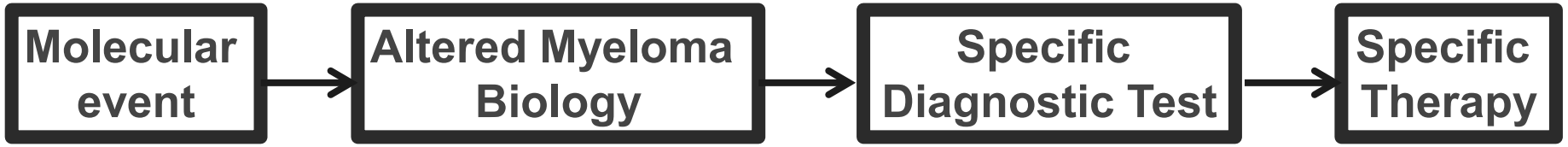
Targeted therapy



Only patients with the target respond

t(11;14)

t(4;14), t(14;16)

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.

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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!

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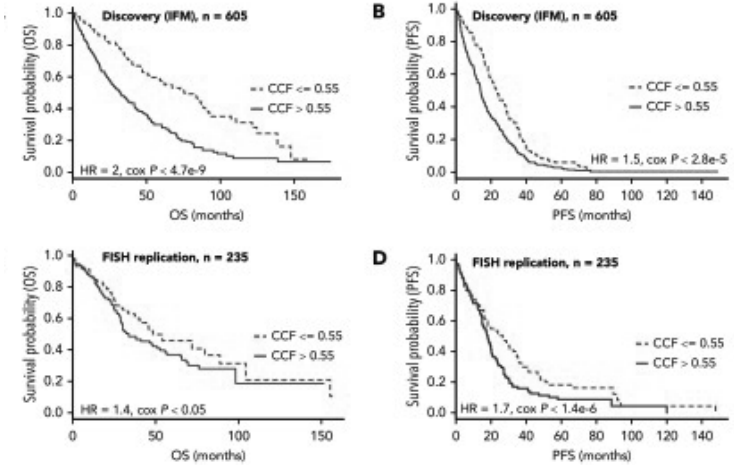
Moving towards consensus

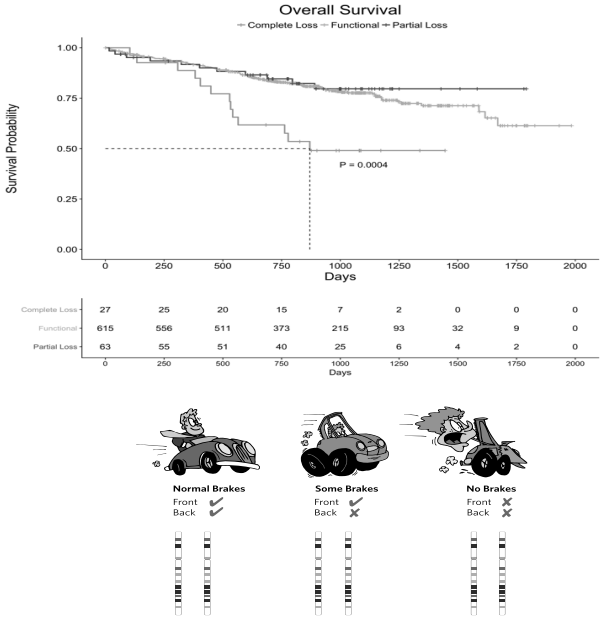
- The variables to include:-
  - R-ISS III
  - High risk GEP (GEP70 or SKY-92)
  - Primary plasma cell leukemia
  - Very high LDH
  - Clinical features of high-risk disease
    - Presence of extramedullary disease
    - > 3 focal lesions on F18-fluorodeoxyglucose positron emission tomography (FDG-PET)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

with the addition of 1q+ and TP53 mutation

Refine to include the subtleties of 17P
– number and mutation



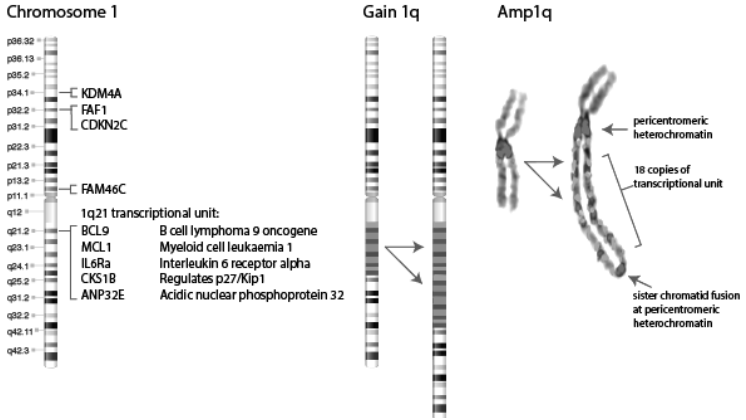
Incremental CCF change in 17p- was associated with shorter survival (CCF 0.3- 0.8)

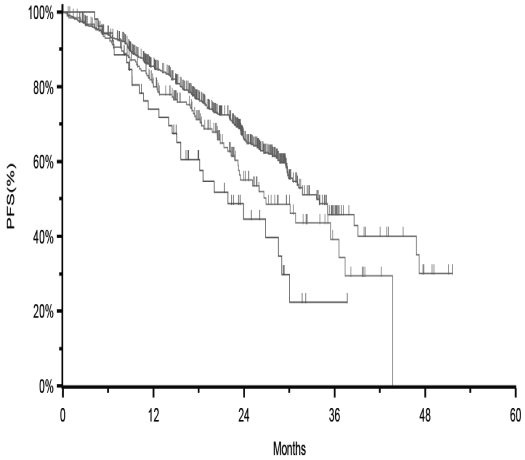


Mutation and deletion effect PFS and OS

A Thakurta et al 2019, J Keats et al MMRF dataset, J Corre Blood et al 2021

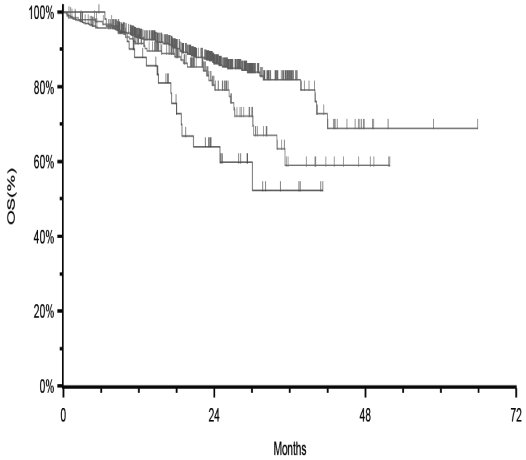
Refine to include the subtleties of 1q
– gain and amplification





	Events / N	18-Month Estimate
CKS1B Amp	28 / 54	60% (46, 74)
CKS1B Gain	72 / 188	71% (64, 78)
CKS1B Normal	195 / 620	77% (73, 80)

Log-rank p-value = .0008

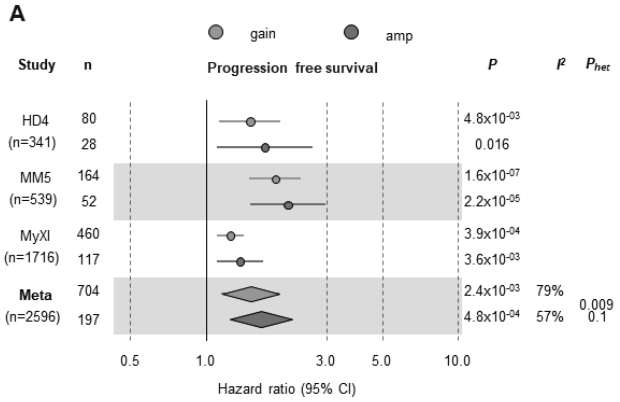


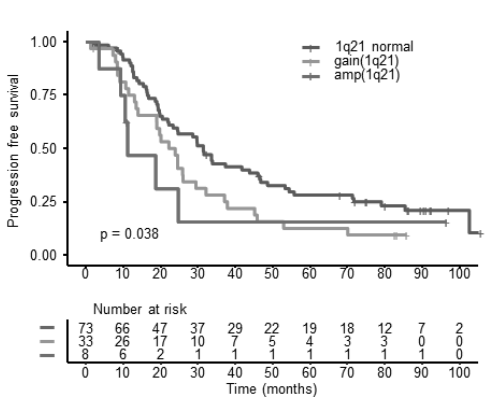
	Deaths / N	18-Month Estimate
CKS1B Amp	17 / 54	73% (59, 86)
CKS1B Gain	36 / 189	88% (83, 93)
CKS1B Normal	80 / 619	90% (88, 93)

Log-rank p-value = .000

B Walker et al Leukemia 2018, J Sawyer et al Blood Cancer J 2019

Adding 1q to RISS





German and UK trial data

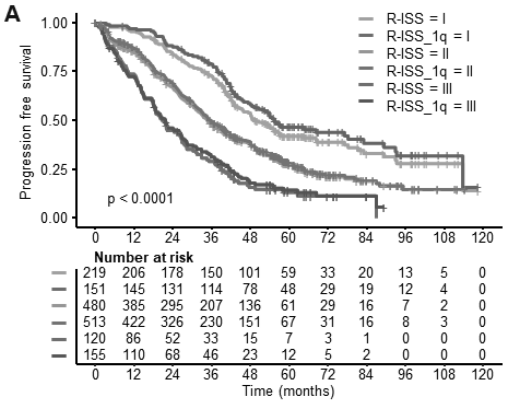
Based on Albumin, LDH, FISH for t(4;14), t(14;16), del 17p and 1q+

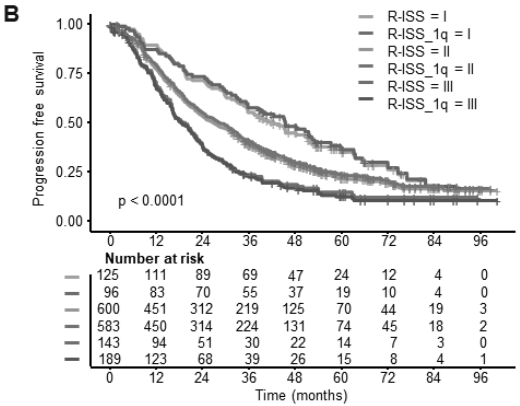
Including 1q upstaged a number of patients:

97/344 from stage I to stage II

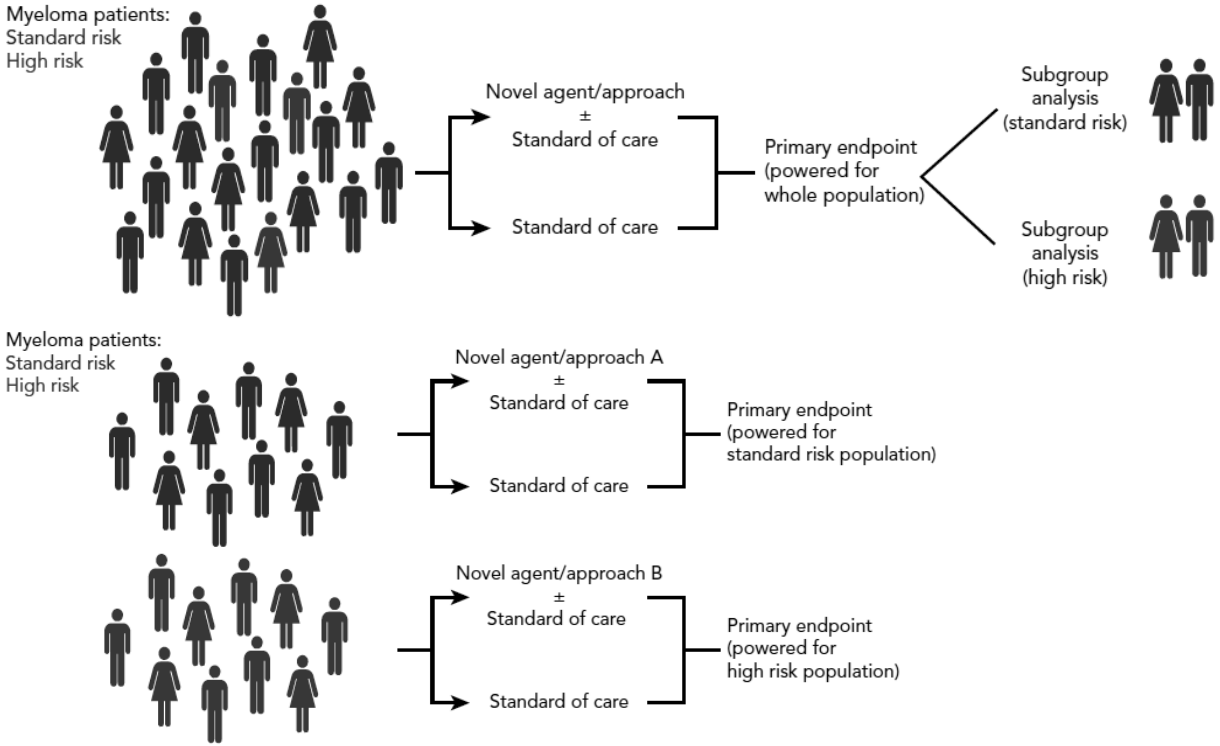
81/1080 from stage II to stage III

N Weinhold *et al* Haematologica 2021





Moving towards consensus – desperately required for clinical trials and prime time



Pawlyn C and Davies FE. *Blood.* 2019. 133(7):660–675

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.

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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

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