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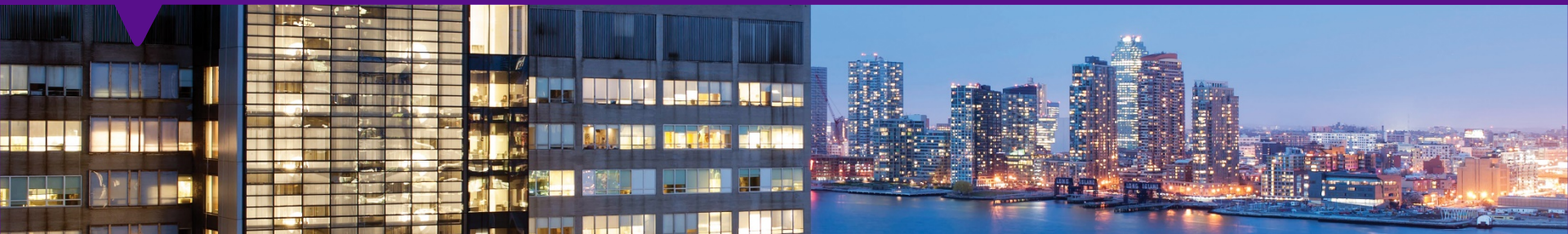
Perlmutter Cancer Center

Multiple Myeloma Research Program

MOLECULAR SEGMENTATION TO IMPROVE OUTCOMES FOR MM: WHY WE SHOULD!

Gareth J Morgan, Director Myeloma Research.



Definition of debate

a formal discussion on a particular matter in a public meeting or legislative assembly, in which opposing arguments are put forward and which usually ends with a vote.

This is a debate!
Analogies, consequences and additional disclosures

Mr. & Mrs. Morgan Davies
Mr. & Mrs. Bergsagel Chiesi
Mr. & Mrs. Bahlis Neri

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It’s a debate!
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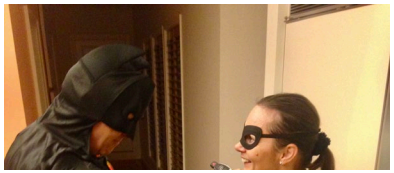
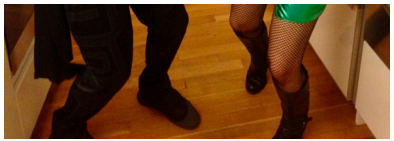
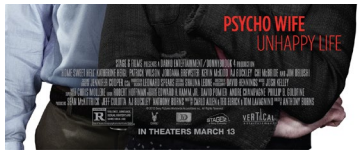


If I win I lose. If lose I win. Compromise!!!





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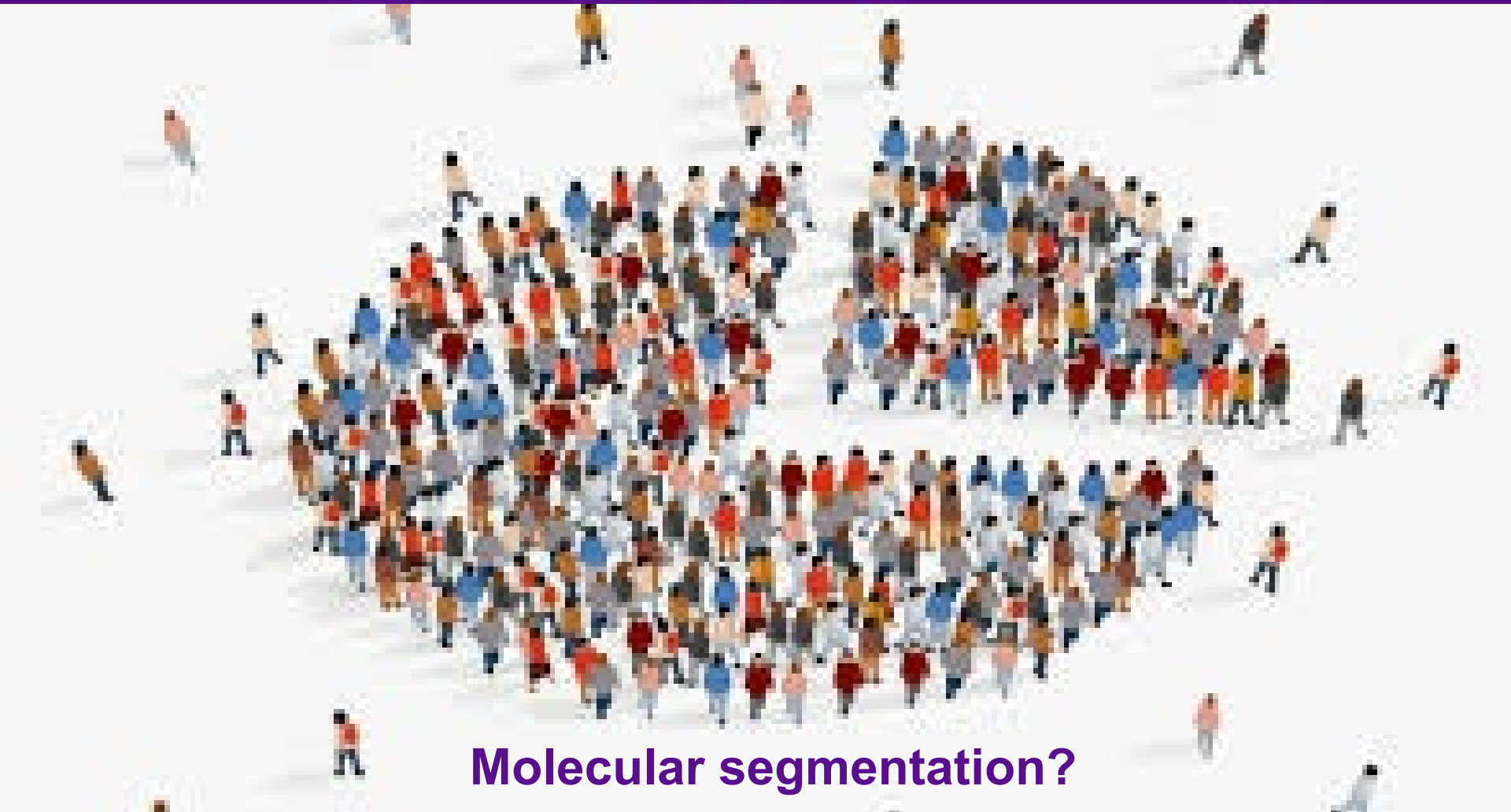
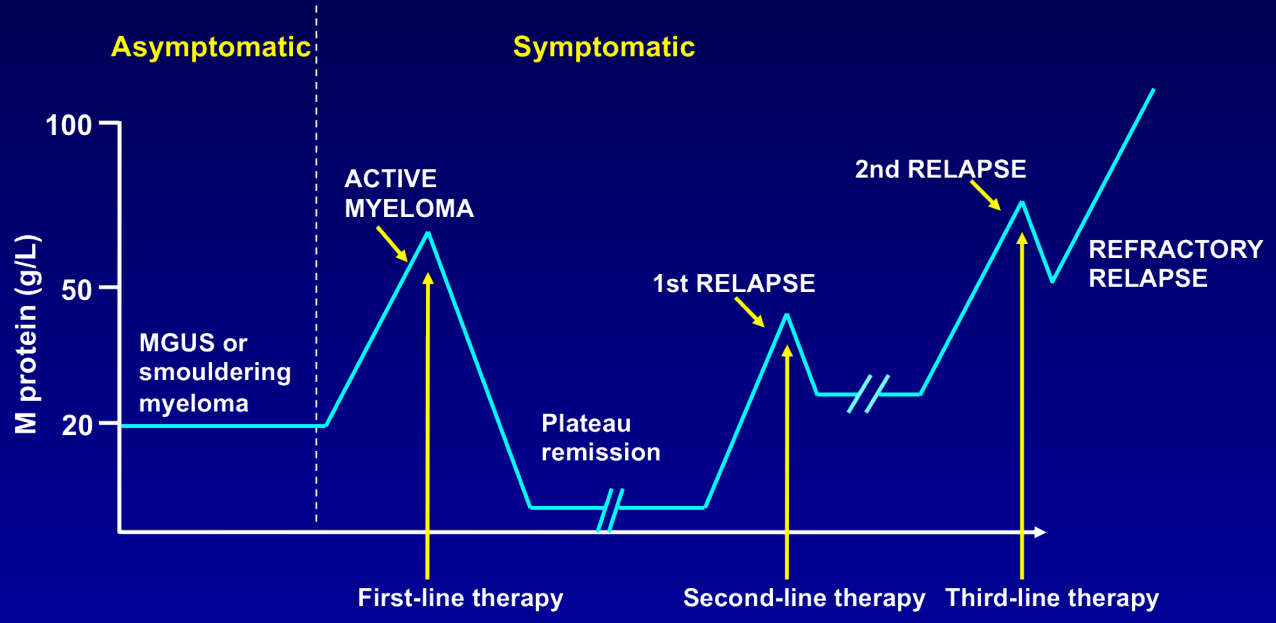


Molecular segmentation?

Why do we need disease segmentation in multiple myeloma

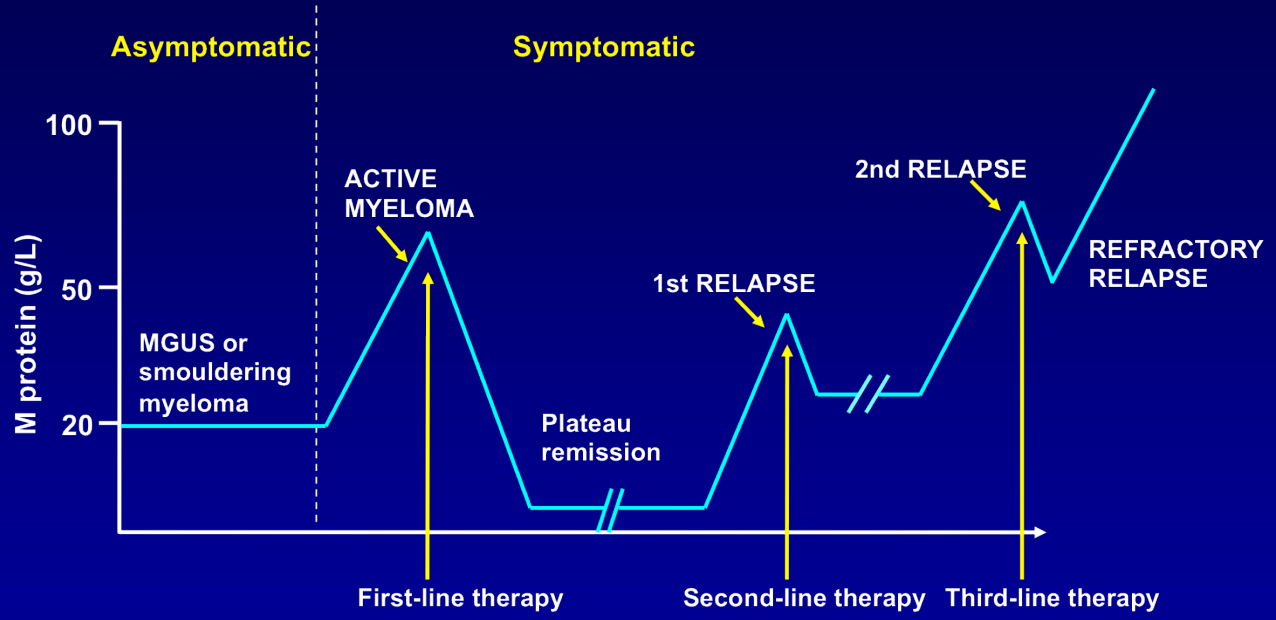


Myeloma remains as incurable disease for most patients

MGUS, monoclonal gammopathy of unknown significance; M protein, myeloma protein.

Durie BGM, ed. Multiple Myeloma Concise Review 2007. International Myeloma Foundation. American Cancer Society. Cancer Facts & Figures, 2008.

Why do we need disease segmentation in multiple myeloma



Myeloma is curable in a significant fraction of patients

MGUS, monoclonal gammopathy of unknown significance; M protein, myeloma protein.

Durie BGM, ed. Multiple Myeloma Concise Review 2007. International Myeloma Foundation. American Cancer Society. Cancer Facts & Figures, 2008.

Molecular segmentation of multiple myeloma

- iFISH and mutational panels are widely available.
- Segmentation is in common use in lung, colon and breast.
- Segmentation is readily applicable in MM.
- Applicable at presentation and relapse.
- Good evidence for use of segmentation.
- We should get on and apply it in the clinic.

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Different considerations operate in older adults where most MM occurs.

Clinical

Patient related
- Frailty
- Chronic illnesses
- Hospitalization
- Psycho-social

Treatment related
- Metabolism
- Drug interaction
- Toxicity profile

Biological

Disease-related
- Genetic
- Epigenetic
- Metabolic

Patient-related
- Aging
- Other

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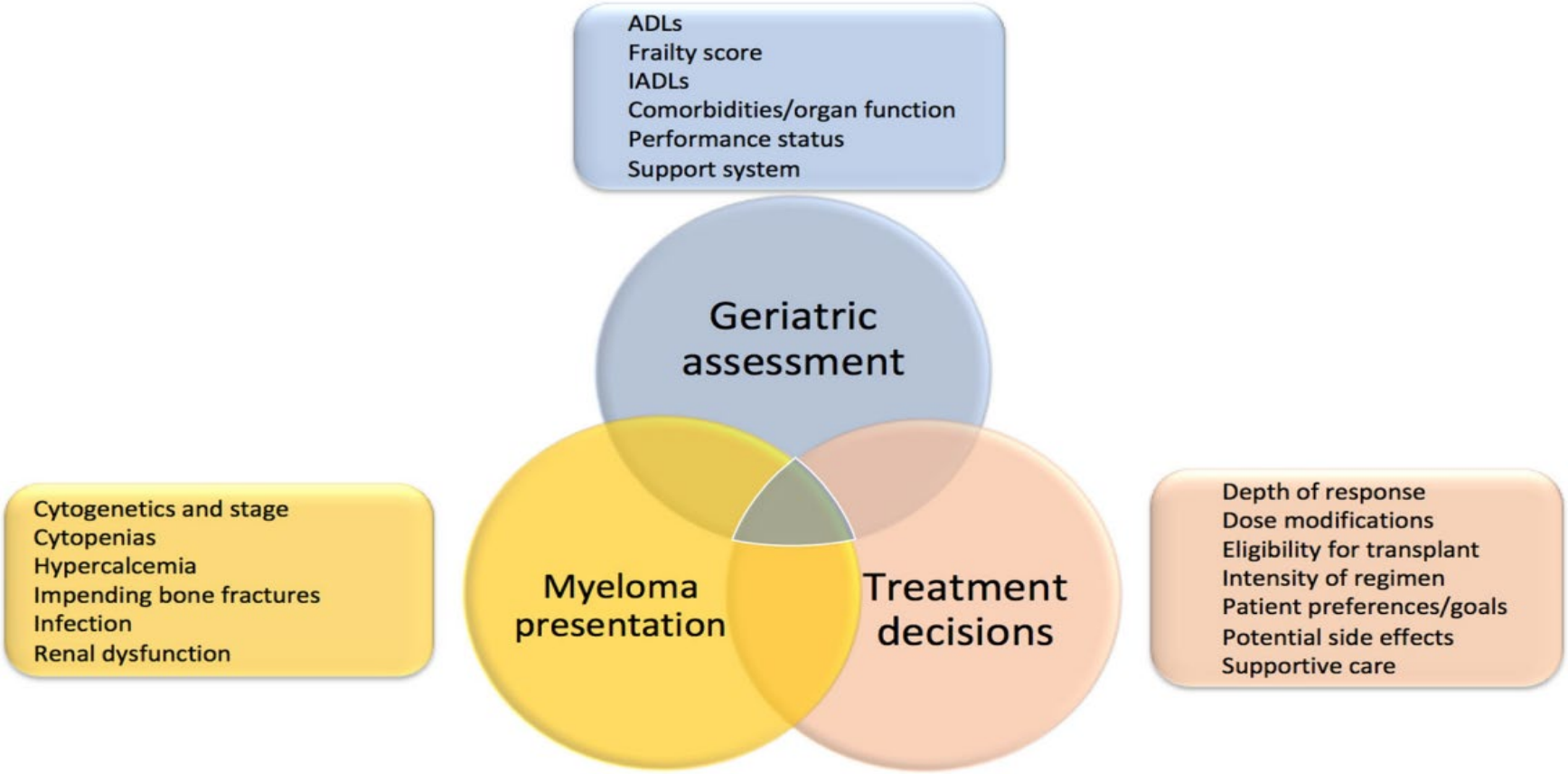
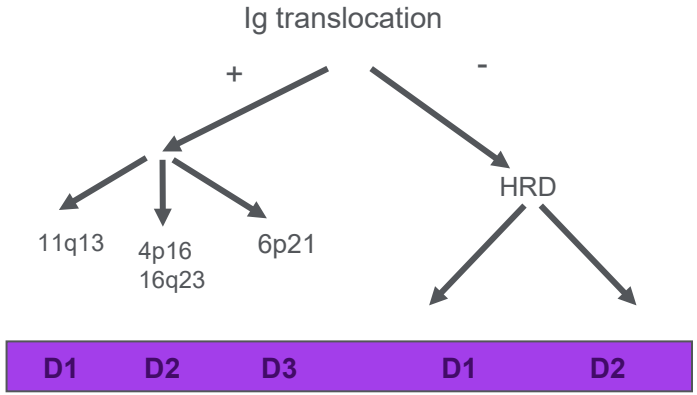
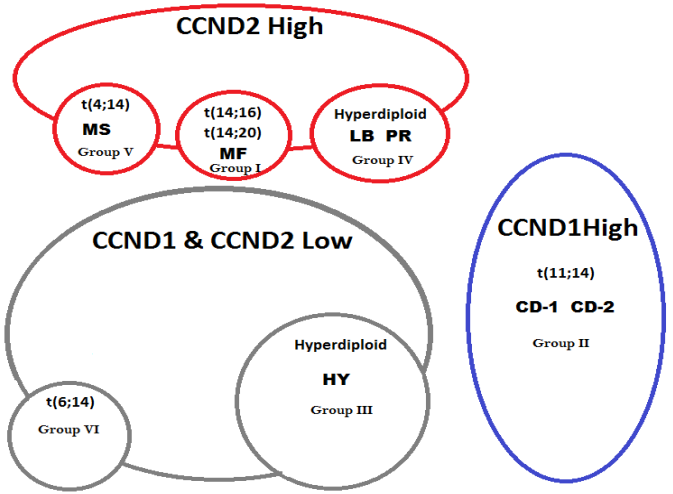
Image: Des Brophy, Slide courtesy of E Boyle

I am arguing for making informed treatment decisions based on data!



Molecular segmentation with iFISH is rather simple!





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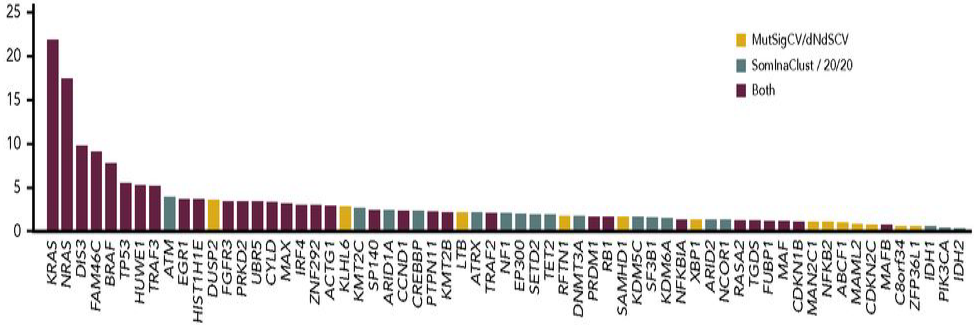
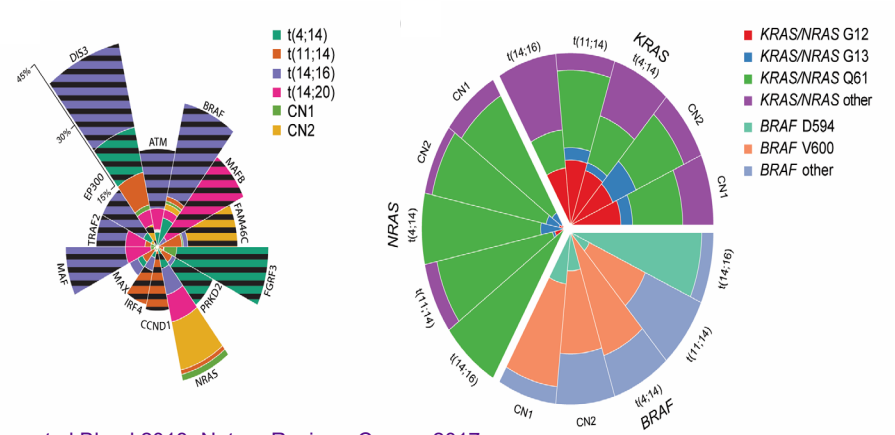
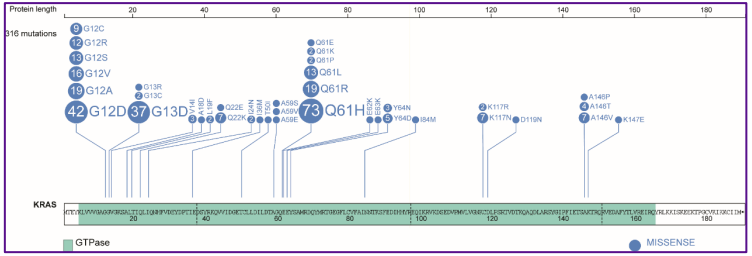
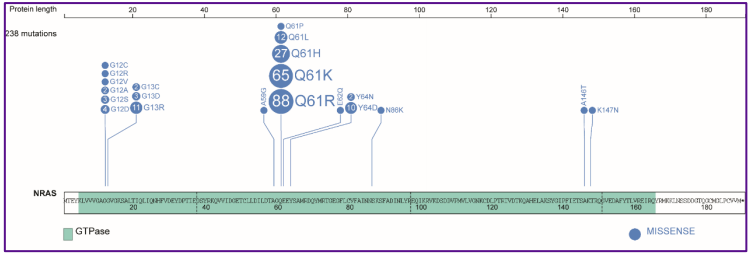
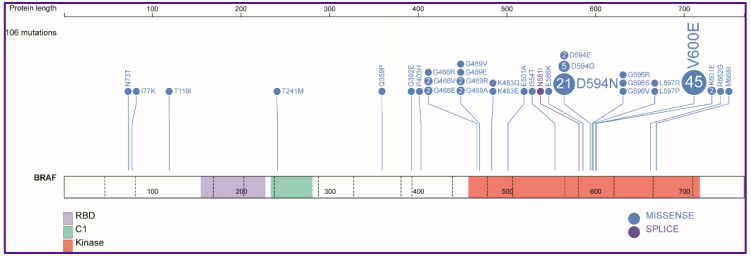
Main mutations are in RAS/MAPK pathway and can be therapeutically targeted





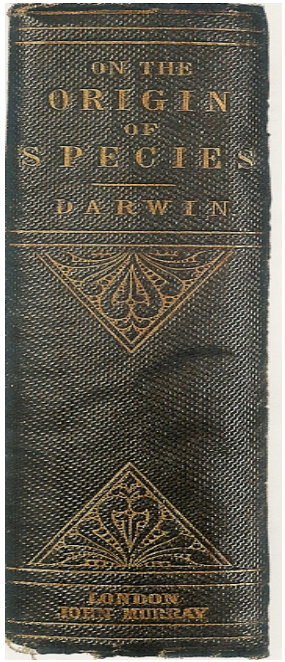


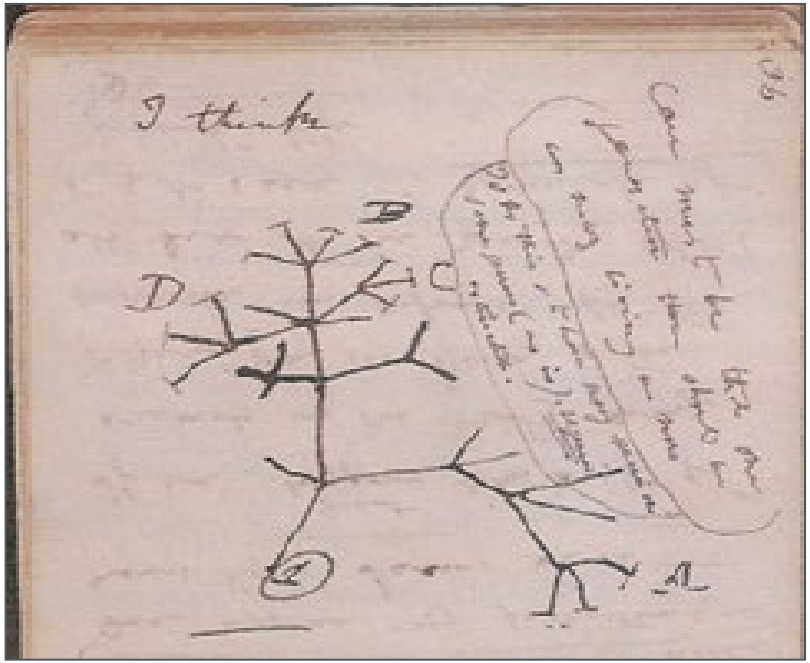


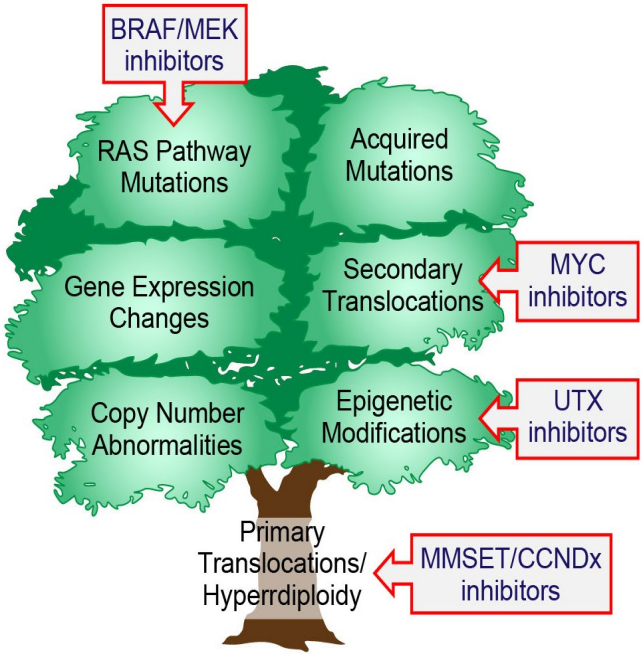


Morgan et al Blood 2018. Nature Reviews Cancer 2017.

Don’t be dissuaded by discussions of evolutionary biology and gardening analogies







Target the trunk not the branches!

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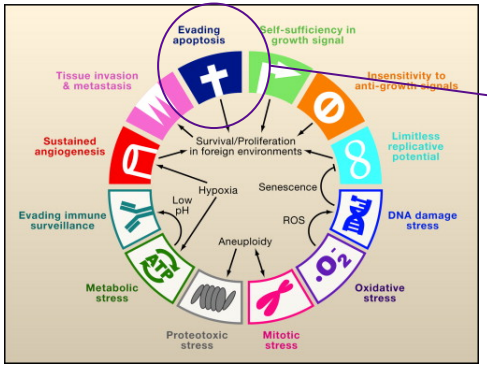
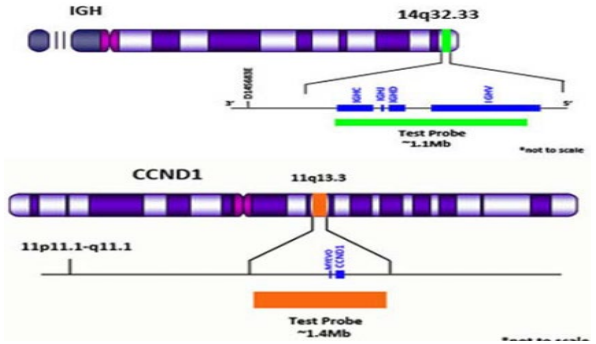
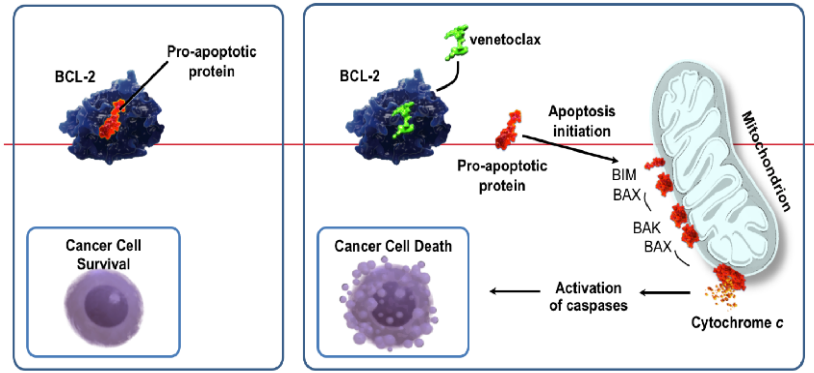
We can target cell death - the t(11;14), bcl2 and venetaclax



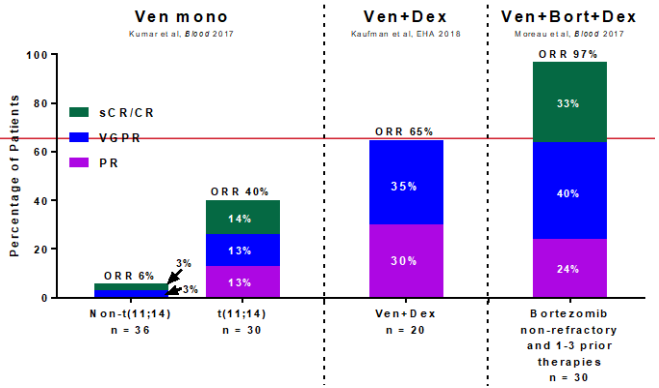
t(11;14)
CCND1





BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.

Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death



Touzeau C et al Leukaemia 2018. Soiuers AJnNat Med 2013.

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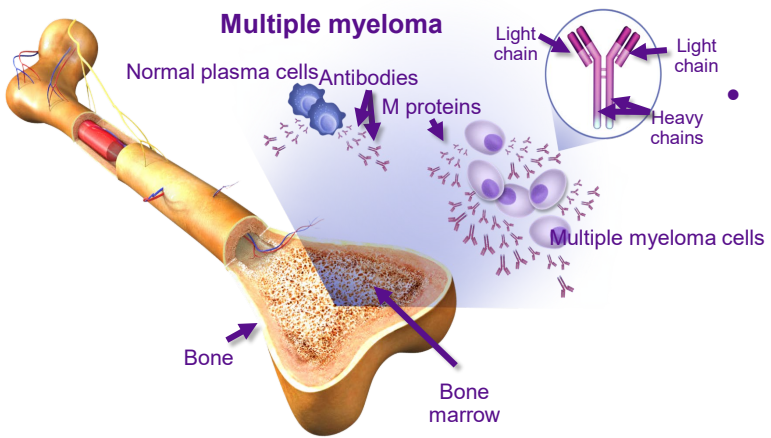
Risk stratified therapy of multiple myeloma?



- **High Risk**
  - Median OS 3 years
  - Behaves like standard risk
- **Ultra High Risk**
  - Median OS 2 years
  - Extramedullary disease
  - Plasma cell leukemia
  - Primary refractory
  - Early relapse post Rx
- **Biology different from standard risk and could be exploited therapeutically.**

IMWG guidance 2014, 2016.

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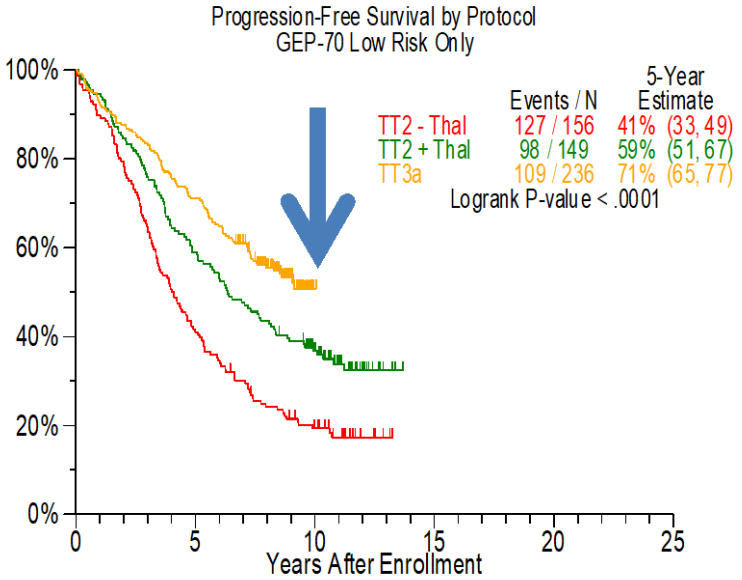
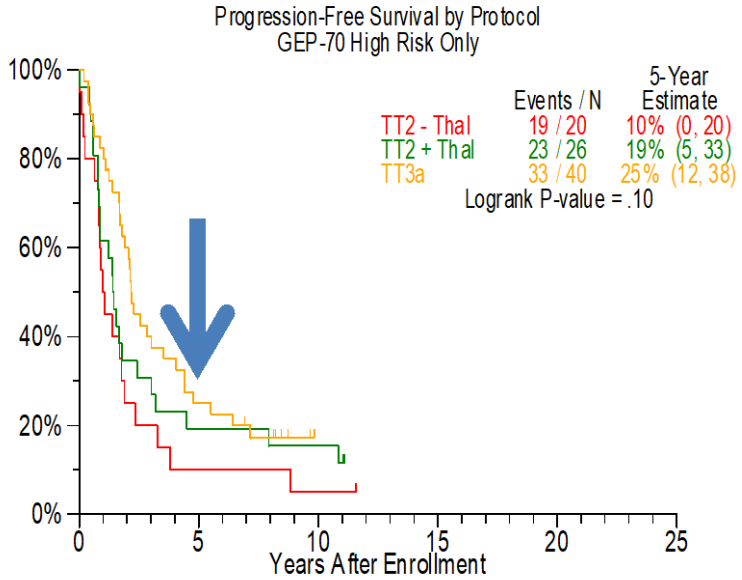
There are good reasons for applying risk stratification





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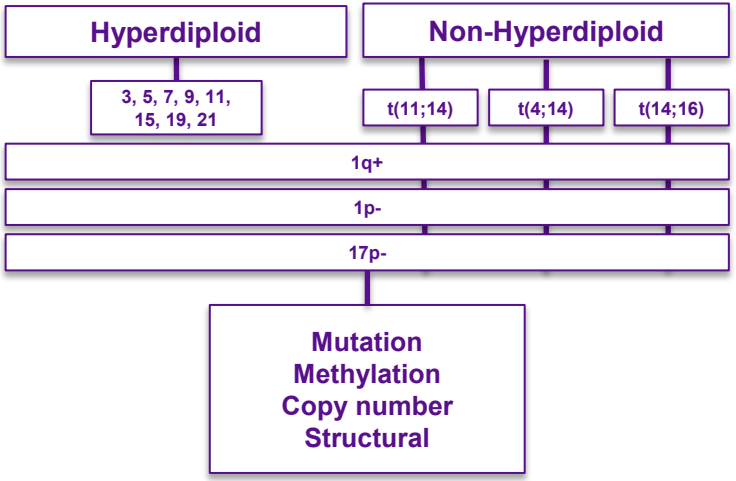
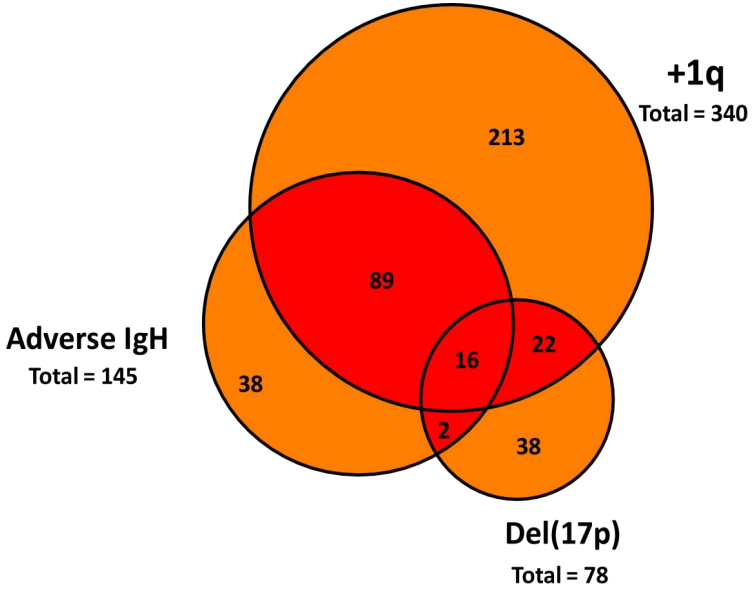
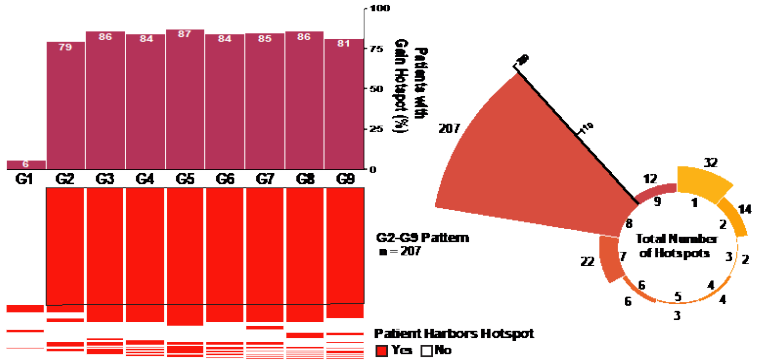
Risk stratification is straightforward and is a standard of care

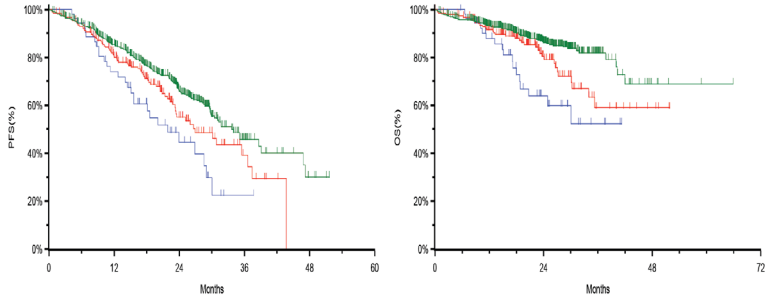




Morgan et al Blood 2018.

Amplification of 1q (10%) not simply gain: We still have things to learn





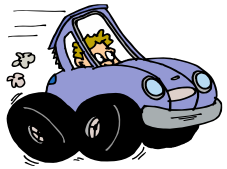
Morgan et al Nature Reviews Cancer 2017. Blood 2018.

Loss of 17p and the role of biallelic TP53 mutations

Normal Brakes

Front ✔

Back ✔



Some Brakes

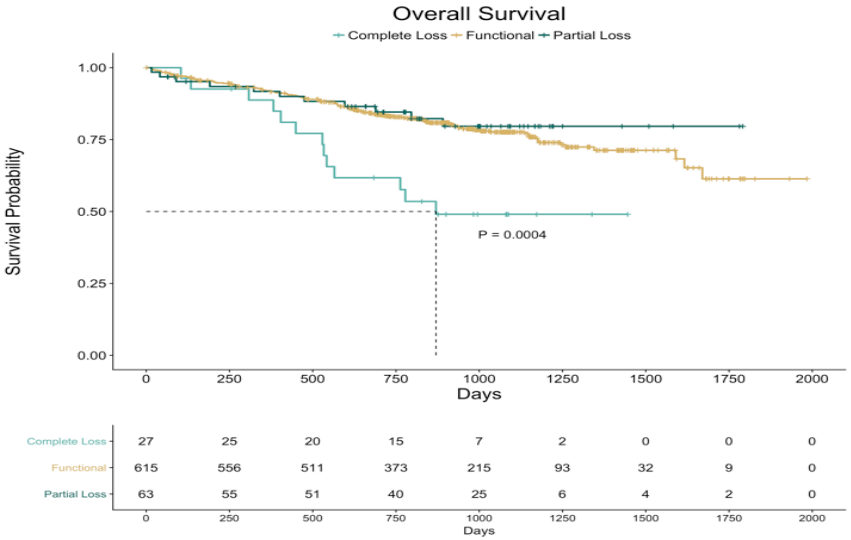
Front ✔

Back ✘

No Brakes

Front ✘

Back ✘



Morgan et al and thanks to J Keats for images.

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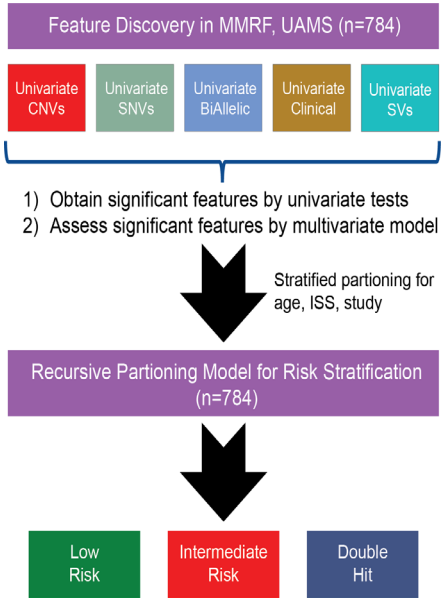
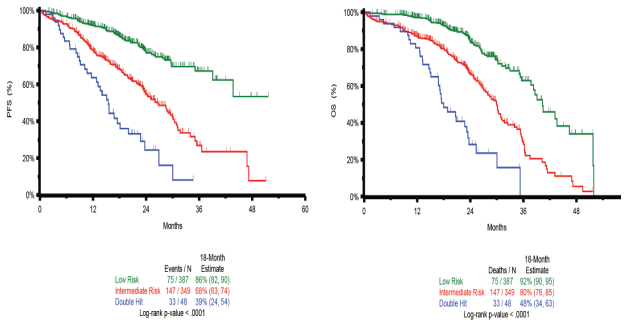
Integrating DNA based data “Double hit”



Biallelic P53
ISS III amp CKS1B
6% NDMM



Double hit MM

- Sensitive.
- Specific.
- Suitable for trial inclusion.

Morgan et al Blood 2018 and Leukaemia 2018.

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There is a general consensus on entry criteria for clinical trials and on the way forward for the treatment of high risk multiple myeloma

PERSPECTIVES ON THE RISK-STRATIFIED TREATMENT OF MULTIPLE MYELOMA

Davies FE, Pawlyn C, Boyle E, Usmani SZ, San Miguel JI, Einsele H, Corre J, Avet Loisseau H, Anderson KA, Auclair D, Lonial S, Sonneveld P, Cho H, Stewart K, Bergsagel L, Kaiser M, Costa L, Weisel K, Ghobrial I, Orlowski R, Landgren O, Gay F, Chari A, Costa L, Walker BW, Bruno B and Morgan GJ.

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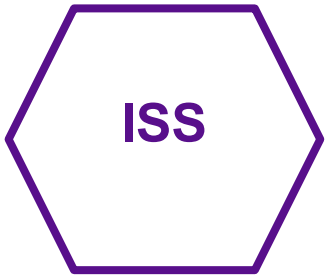

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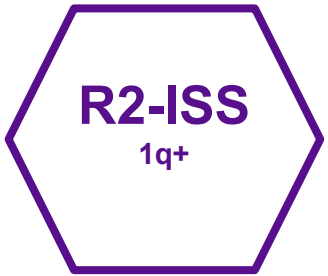

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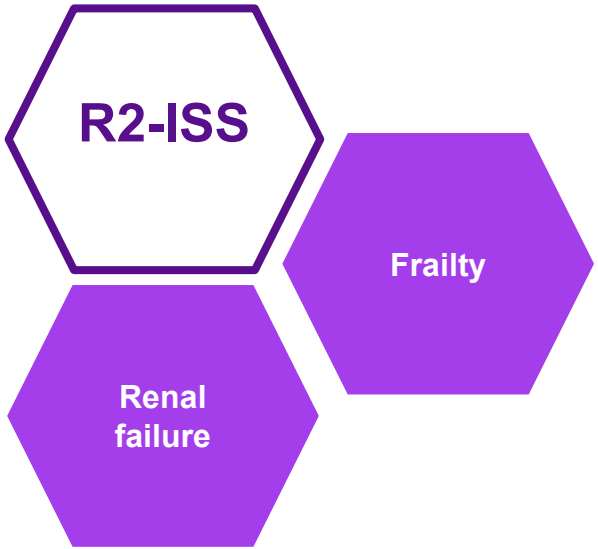

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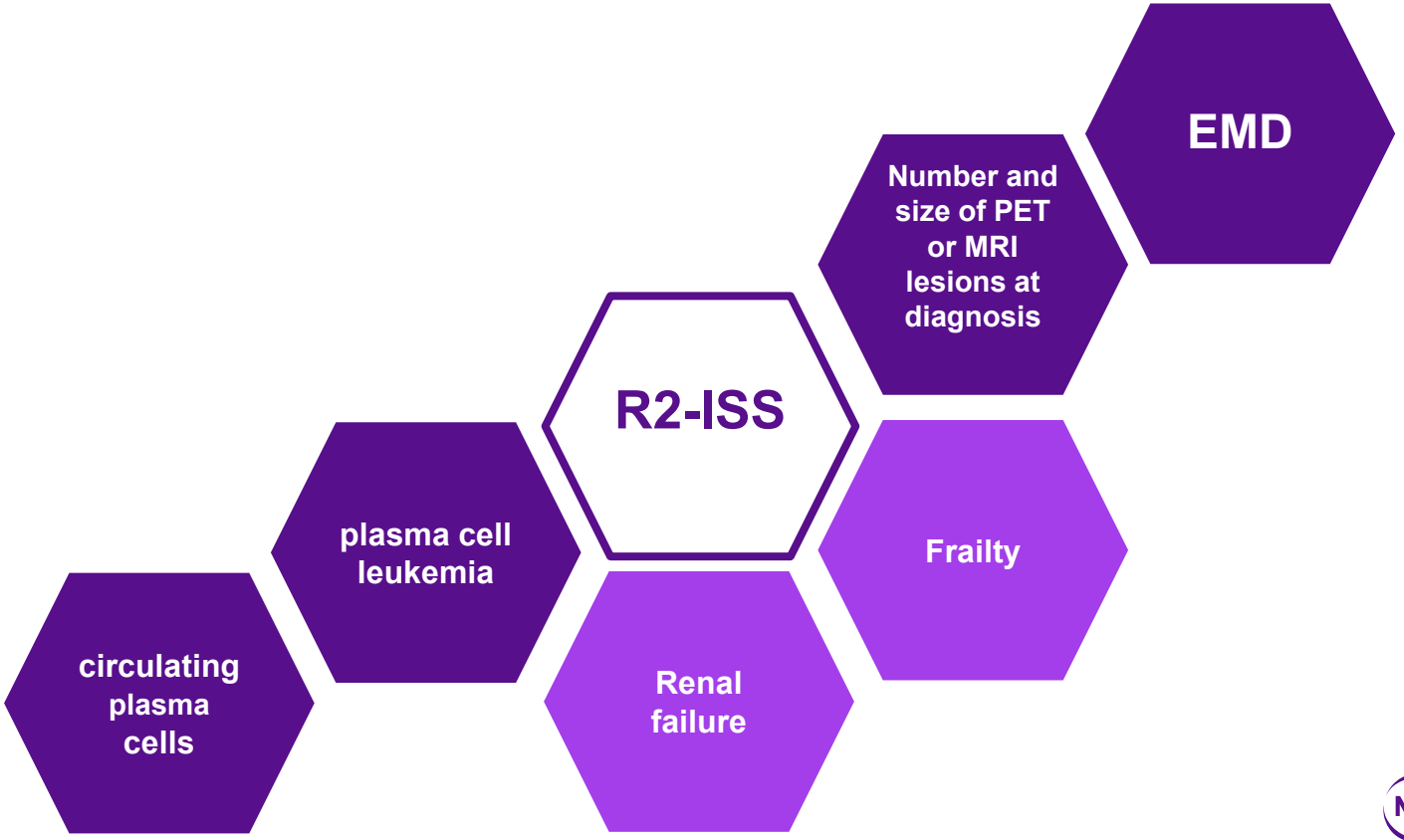

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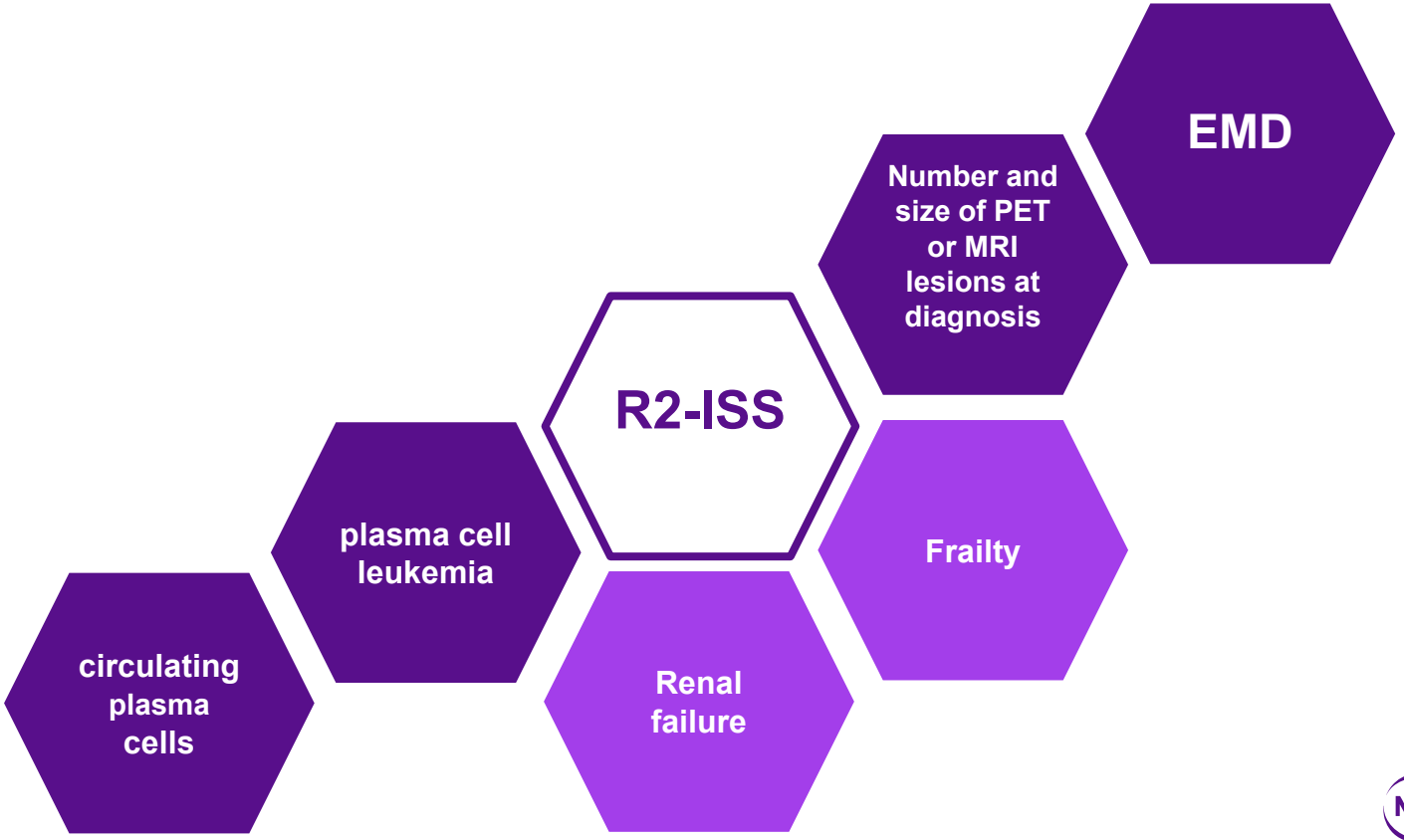

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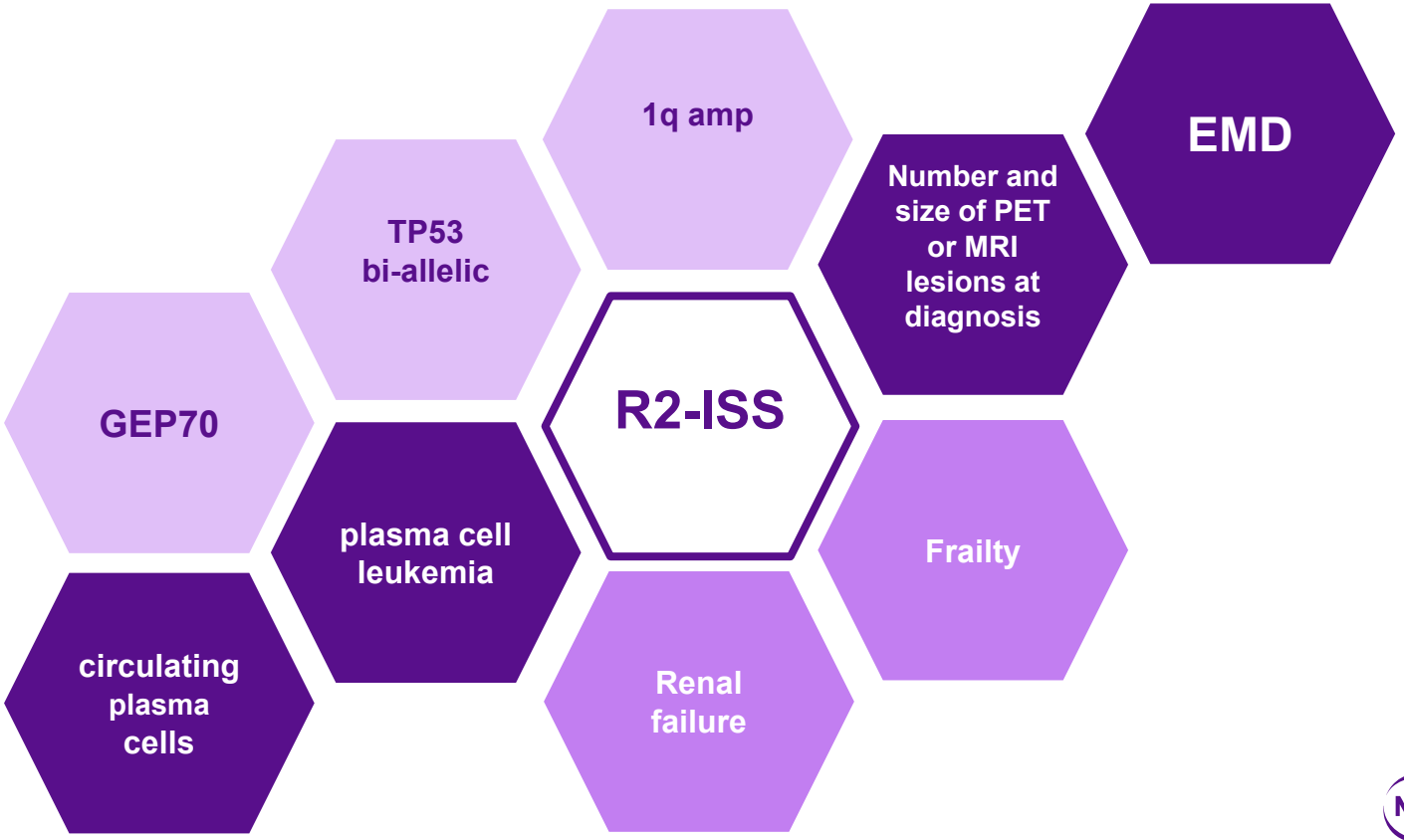

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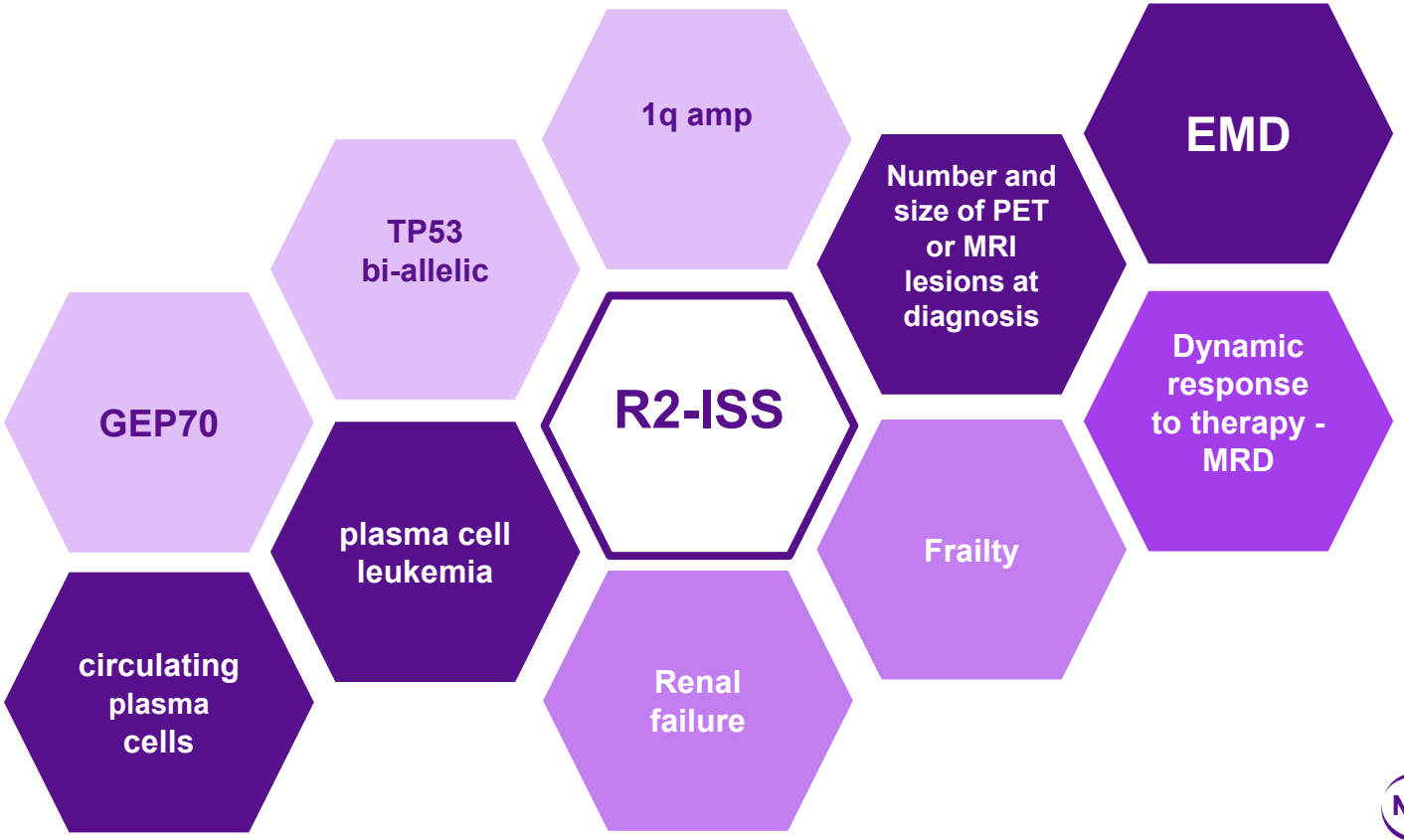

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Expanding therapeutic toolbox

IMiDs	Proteasome	Anthracyclines	Alkylators	Steroids	HDACi	mAbs
Thalomid (thalidomide)	Velcade (bortezomib)	Adriamycin	Cytoxan	Dexamethasone	Farydak (panobinostat)	Empliciti (elotuzumab)
Revlimid (lenalidomide)	Kyprolis (carfilzomib)	Doxil (liposomal doxorubicin)	Bendamustine	Prednisone	Zolinza (vorinostat)	Darzalex (daratumumab)
Pomalyst (pomalidomide)	Ninlaro (ixazomib)		Melphalan		XPOVIO (selinexor)	Sarclisa (isatuximab)
			Melflufen			Blenrep* (belantamab mafodotin)

*Antibody-drug conjugate

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Expanding therapeutic toolbox

Clinical Phase	Novel Agents		Immunotherapies					
	Precision medicine	Novel mechanisms of action	Immuno-modulatory agents	Naked antibodies	Antibody-drug conjugates	Bispecific antibodies and bispecific T-cell engagers	CAR T-cell therapies	Checkpoint inhibitors
Phase 3	Venetoclax*	Melflufen					Idecabtagene vicleucel (ide-cel; bb2121) Ciltacabtagene autoleucel (cilta-cel; JNJ-4528)	Nivolumab
Phase 1, 2	Abemaciclib* Cobimetinib* Dabrafenib Enasidenib* Erdafitinib* Idasanutlin Trametinib Vemurafenib	Selected list: CLR 131 Ibrutinib INCB001158 INCB053914 Molibresib ONC201 Pemigatinib Ruxolitinib	CC-92480 Iberdomide NKTR-255 TAK-573	AO-176 BMS-986016 BMS-986207 CJM112 SAR442085 SEA-BCMA TAK-079 Tiragolumab	CC-99712 FOR46 Lintuzumab-Ac225 MED12228 STRO-001 TAK-169	AMG 420 AMG 701 BFCR4350A CC-93269 CCC-99712 HPN217 ISB 1342 Teclistamab Talquetamab PF-06863135 REGN5458/49 TNB-383B	Selected list: ALLO-715 bb21217 Descartes-08 Descartes-11 JCARH125 JNJ-68284528 NKR-2 P-BCMA-101 UCARTCS1A	Abatacept Avelumab Ipilimumab Pembrolizumab TTI-622

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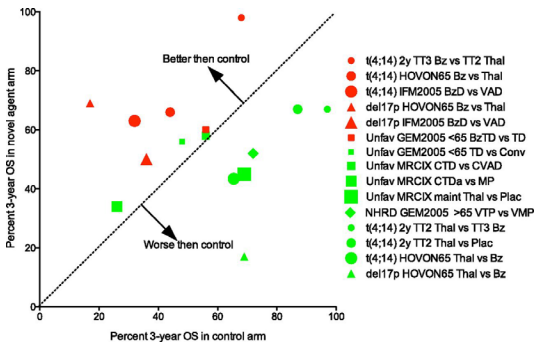
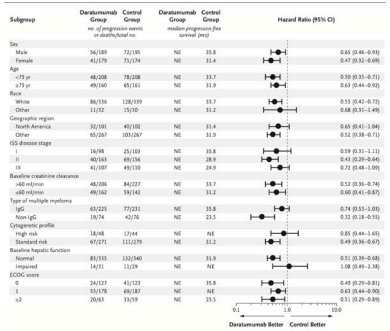
We can optimize the use of current therapies based on risk

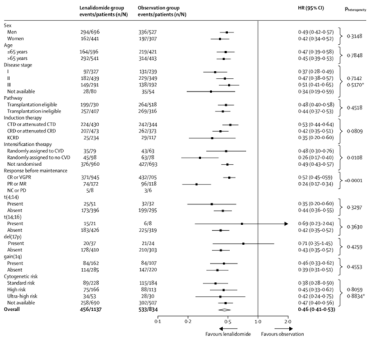
Proteosome inhibitors



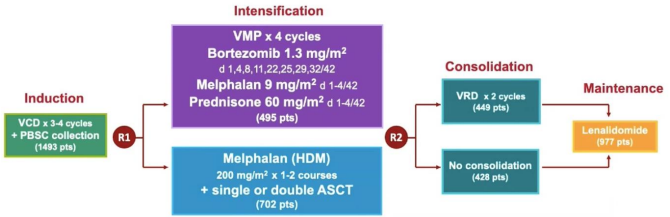
Daratumumab



Revlimid



Tandem ASCT



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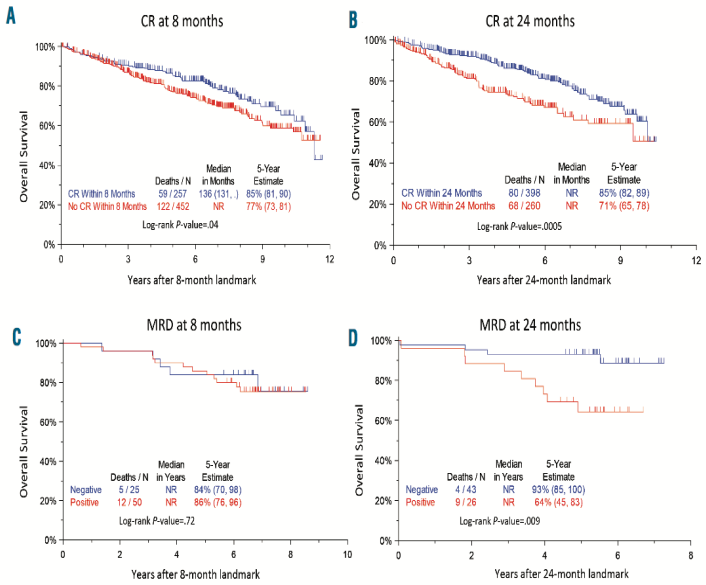
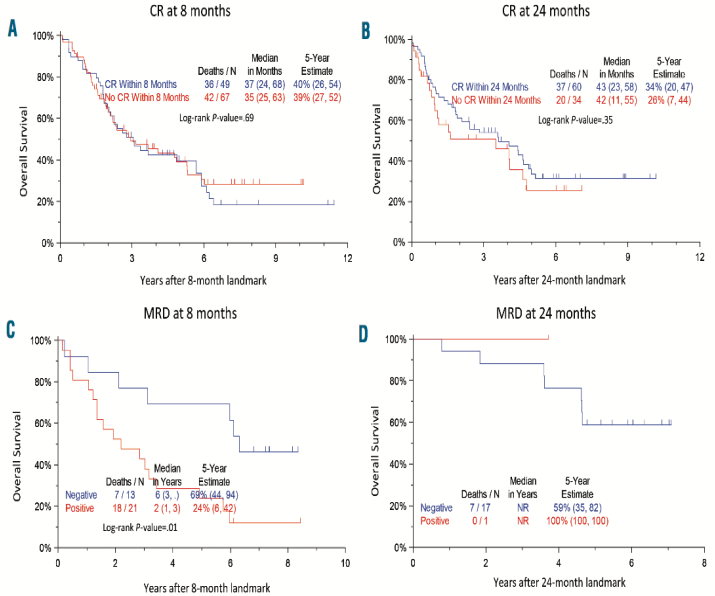
Total therapy and aims of treatment
Achieving MRD- status is critical in high-risk MM



GEP70 low-risk



GEP70 high-risk

Schinke…Morgan, Haematologica 2017

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Guiding Principles for HR therapy

Induction.
4 drug chemo immuntherapy combinations.

Consider double ASCT.

Consolidation.
Assess response risk status and tolerability at day 60-80 and choose appropriate combination

Maintenance.
Based on similar considerations choose appropriate maintenance and duration.

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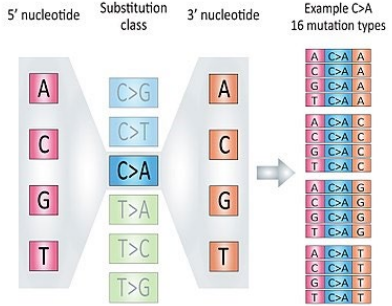
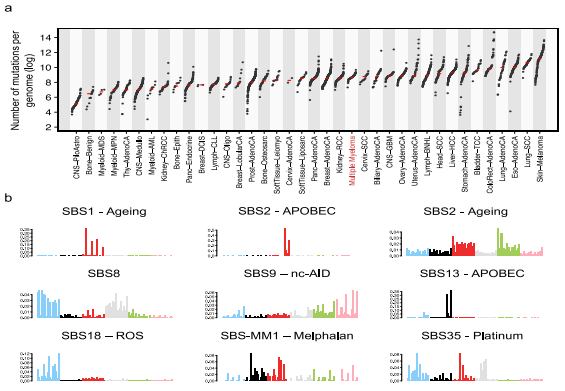
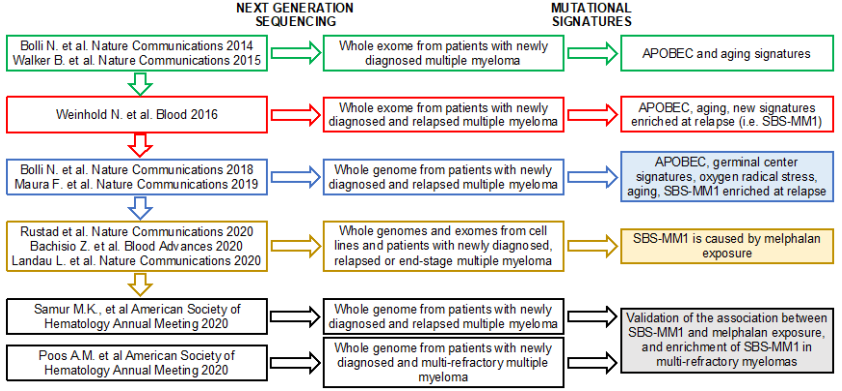
Mutation signatures in multiple myeloma







With increasing potential for long term survival in MM and improved therapies able to induce deep responses the identification of a melphalan signature must make us re-evaluate the role of alkylating agents and high dose melphalan front line in standard risk patients.

Maura F et al 2021.

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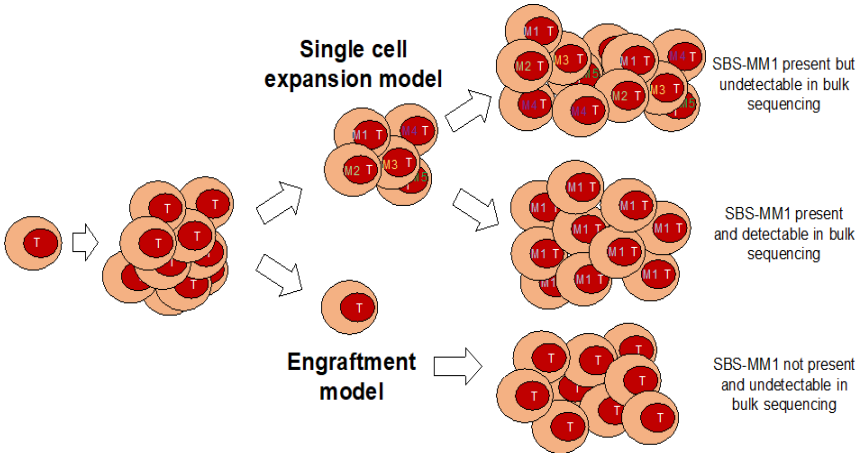
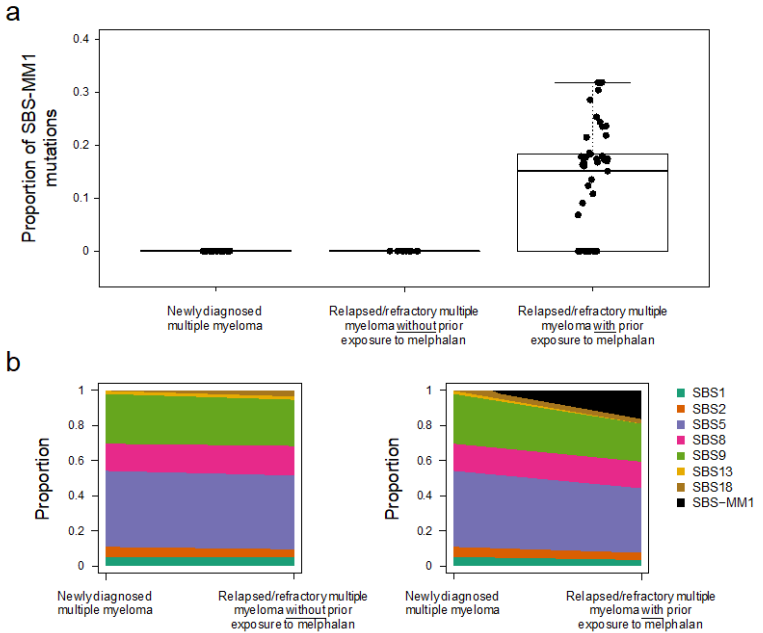
Melphalan can drive clonal outgrowth and relapse





Landau et al 2021

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High-Risk clinical trials in MM

- There is a consensus definition of HR.
- There are multiple trials exploring different therapeutic options for HR planned or in set up.
  - SWOG – 1211 (VRDelo).
  - Optimism (Chemo plus Dara)
  - TT7 (Chemo plus Dara).
  - KarMMA 4 (Abecma).
  - Concept Study (Chemo plus Isa).
  - BMT – CTN SOSS (Car T).
  - HATT trial – (Talqetamab + ASCT).

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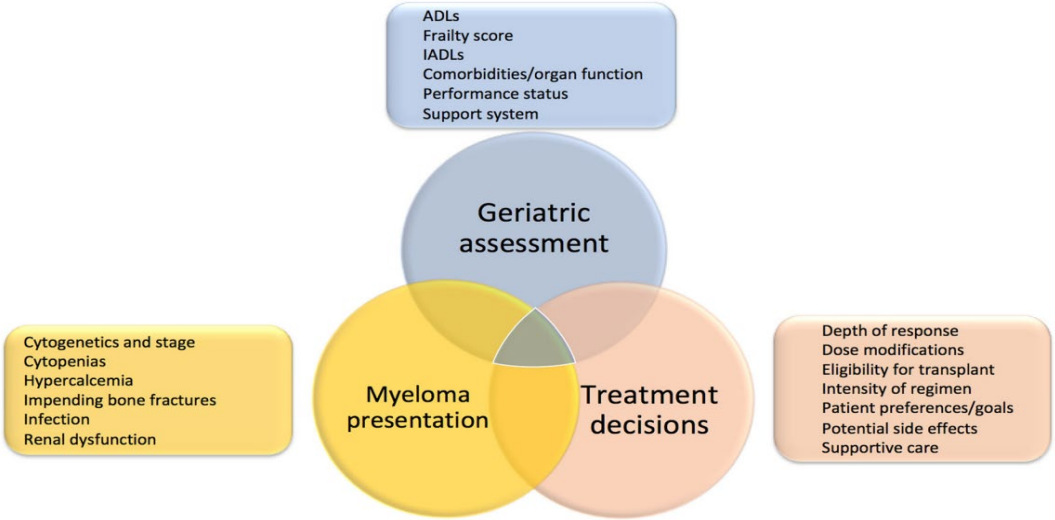
Make informed treatment decisions !

You already do this and disease segmentation is just another component - we can do better going forward!



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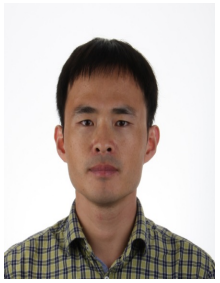

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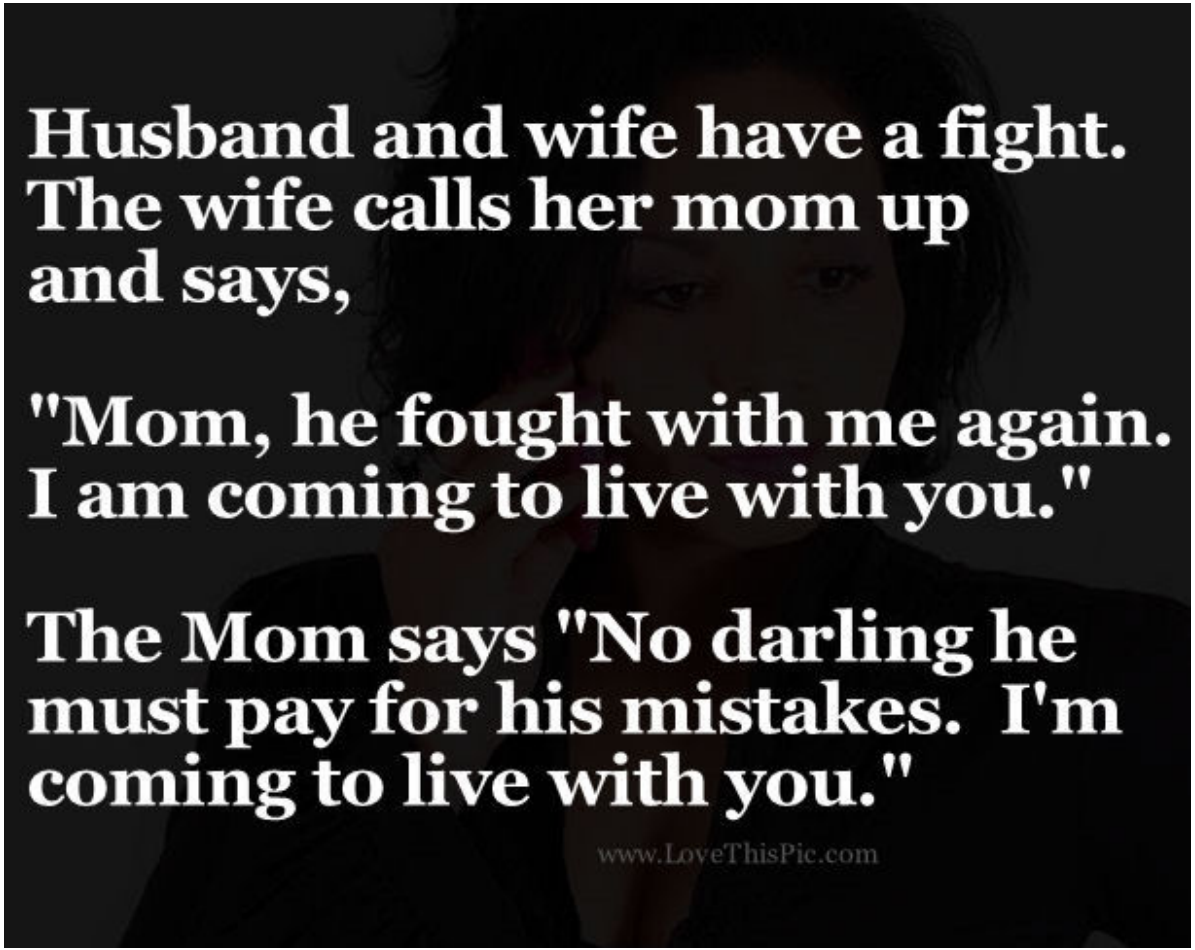

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