

MGUS to Myeloma: Bench to the Bedside

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Disclosures

Advisory Board/Consultant: AbbVie, Adaptive, BMS, C4 Therapeutics, Celgene, Coding.bio, GlaxoSmithKline, IASO, Janssen, Koi, Legend, Novartis, Oncopep, Pfizer, Regeneron, Sanofi, Sebia

Scientific Founder: Oncopep, Koi





Objective

- **Understand the spectrum of plasma cell disorders and their manifestations**
- **Define the molecular and pathophysiologic mechanisms linking the plasma cell clone to disease progression**
- **Review therapeutic advances in plasma cell disorders**
- **Explore the evolving potential for deep, durable remission—and ultimately cure**



Criteria for Diagnosis of Myeloma

MGUS

- <3 g M spike
- <10% PC

Smoldering MM

- ≥ 3 g M spike
- **OR** $\geq 10\%$ PC

AND

NO

Active MM

- $\geq 10\%$ PC
- M spike +

AND

YES

C - High calcium
R - Renal dysfunction
A - Anemia
B - Bone lesions

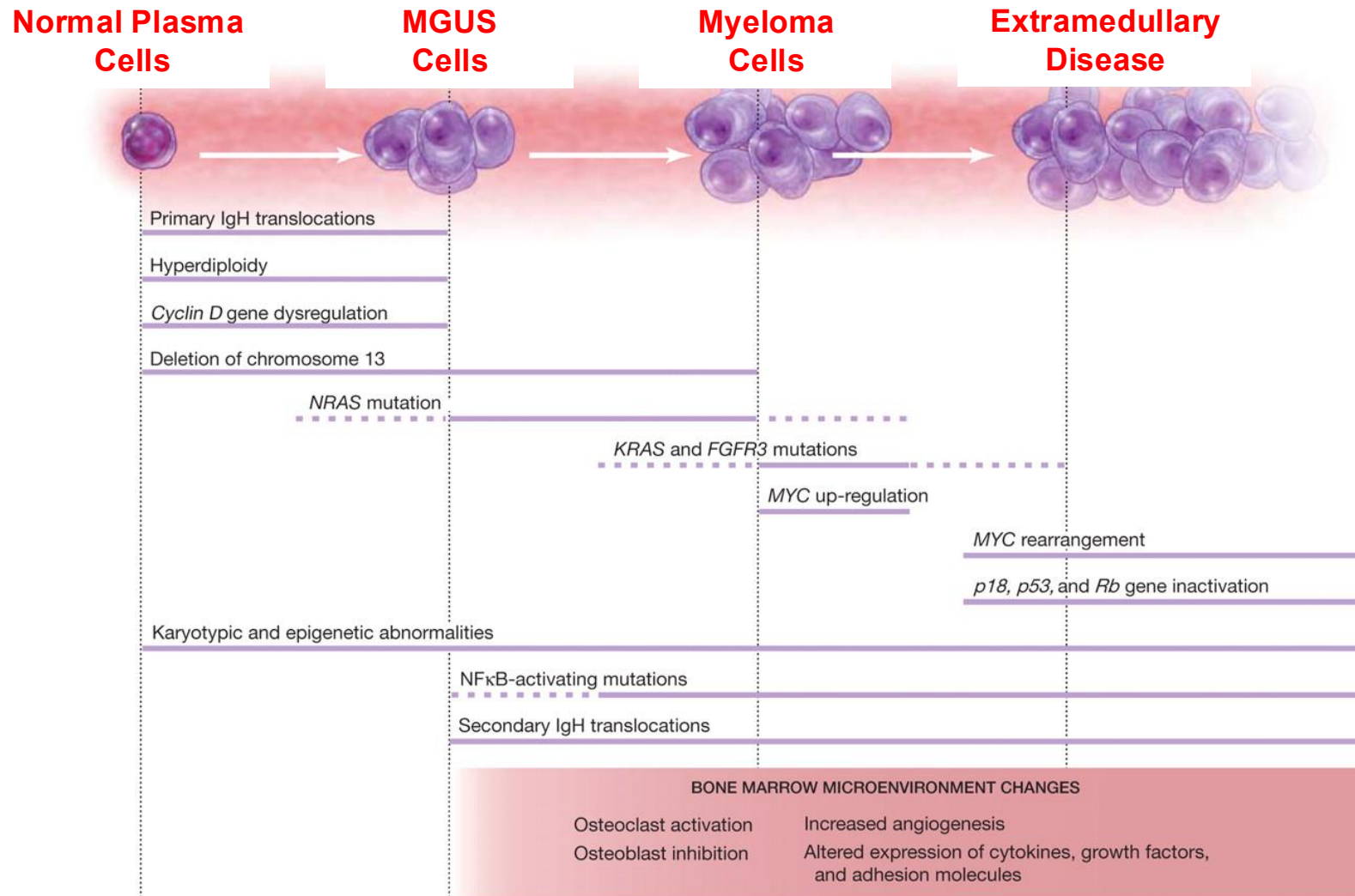
$\geq 60\%$ BMPC
 ≥ 100 FLC ratio
>1 MRI focal lesion

Kyle RA. *N Engl J Med* 2002; 346: 564

- Renal dysfunction:
- ~20–30% of newly diagnosed
- ~40–50% have eGFR <60, and
- >50% will experience renal dysfunction during their disease course.
- About 2–4% require dialysis.

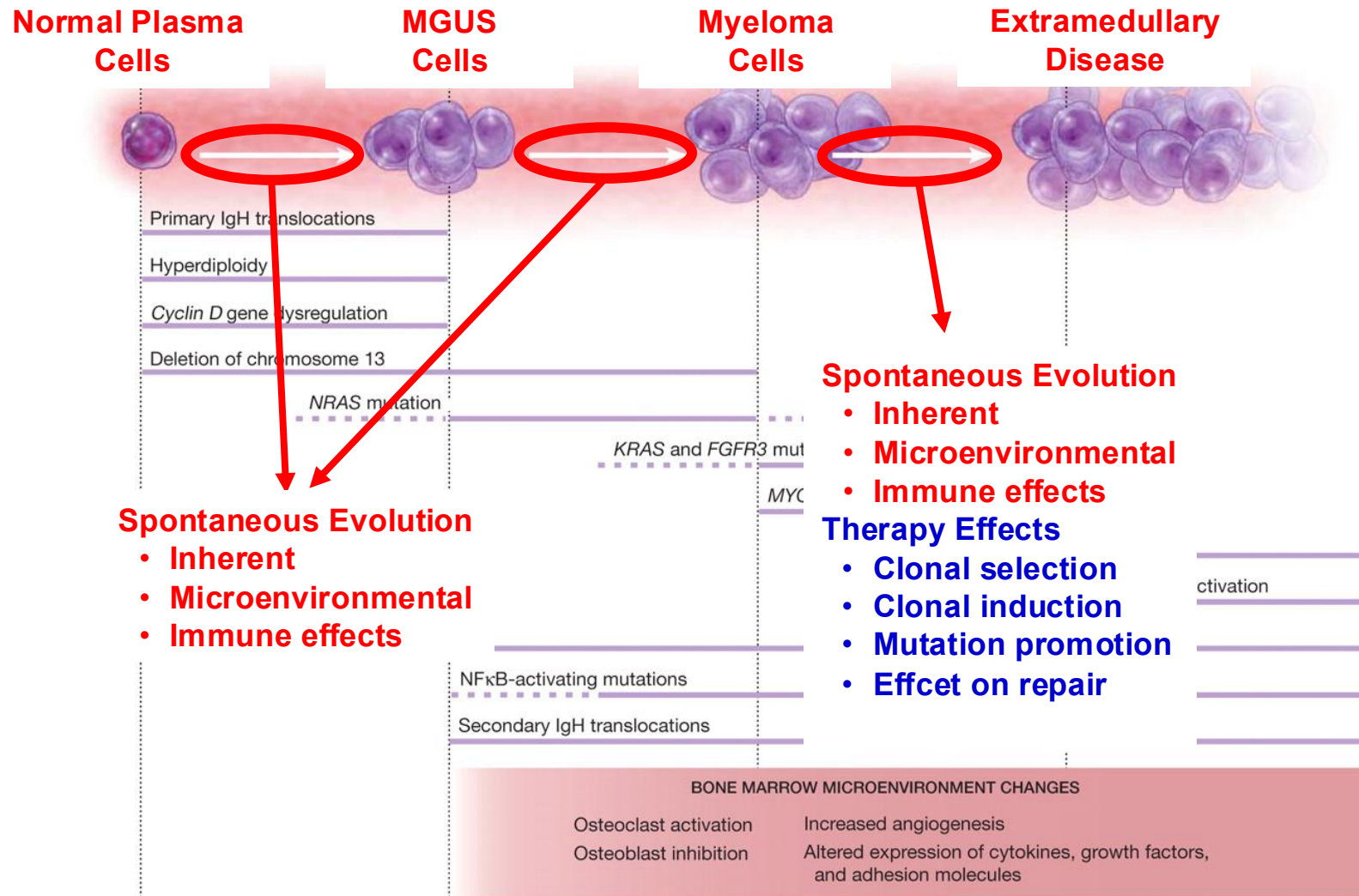
Neha Korde et al. *Blood* 2011;117:5573-5581

Evolution of Multiple Myeloma – Genomic Changes



Neha Korde et al. Blood 2011;117:5573-5581

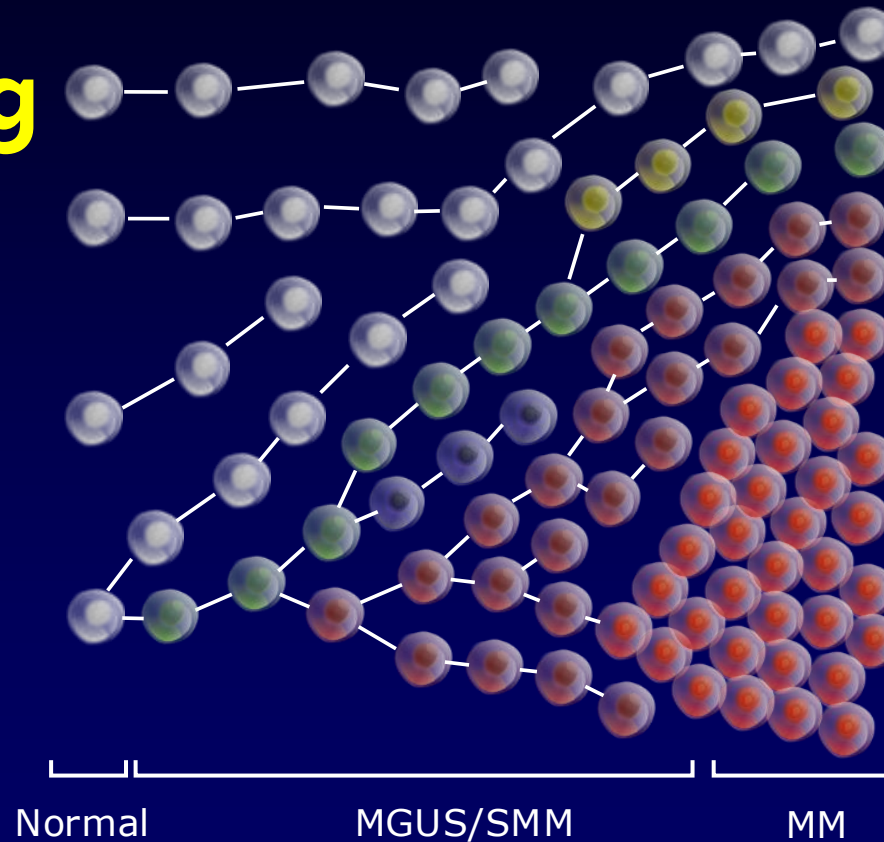
Evolution of Multiple Myeloma – Genomic Changes



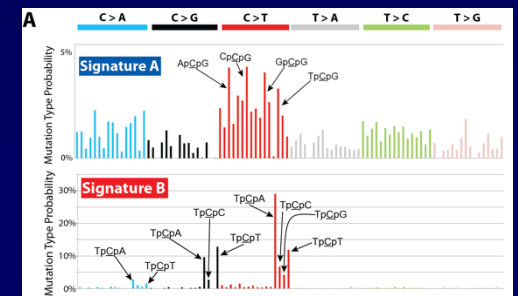
Neha Korde et al. Blood 2011;117:5573-5581

MM is a heterogeneous disease featuring clonal variants

Multiple genetic events drive the MM disease course¹⁻³

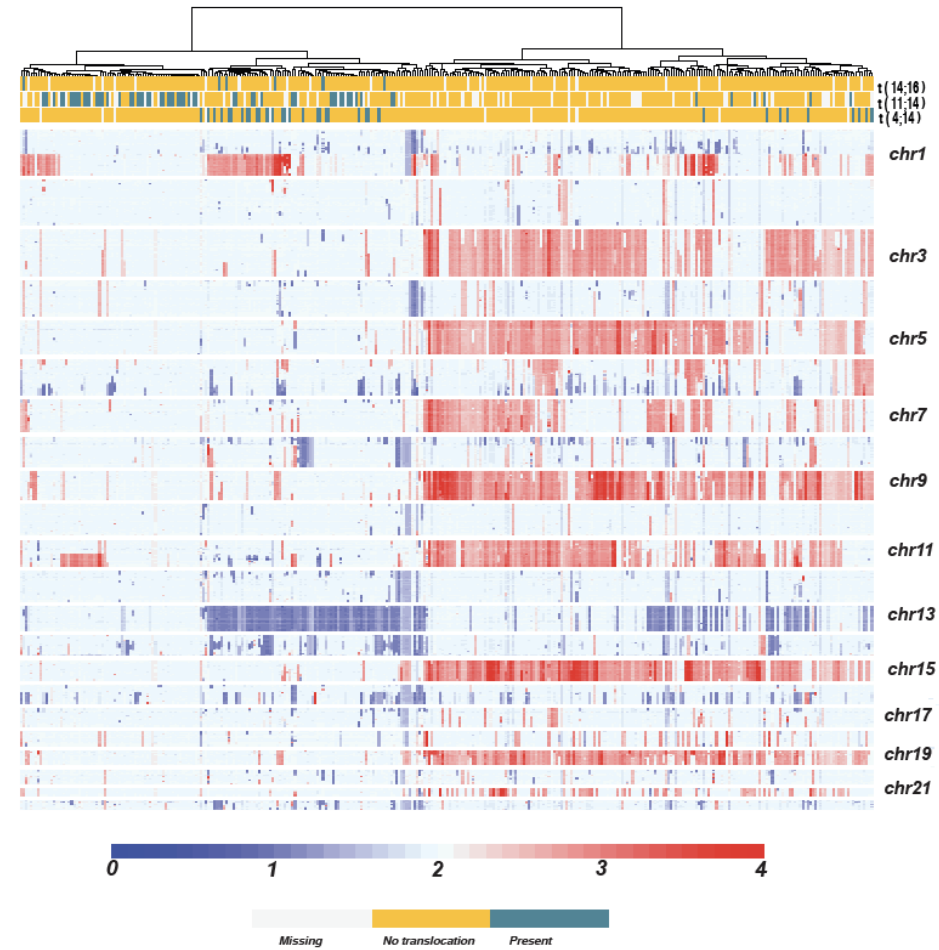


- Present at diagnosis and increase throughout the disease course¹⁻⁴
- Evolve over time due to selective pressures from treatment and microenvironment effects^{1,4}
- Clonal evolution can result in disease progression and treatment resistance⁵



Two Basic Types of Myeloma Based on Genomic Characteristics(N = 336)

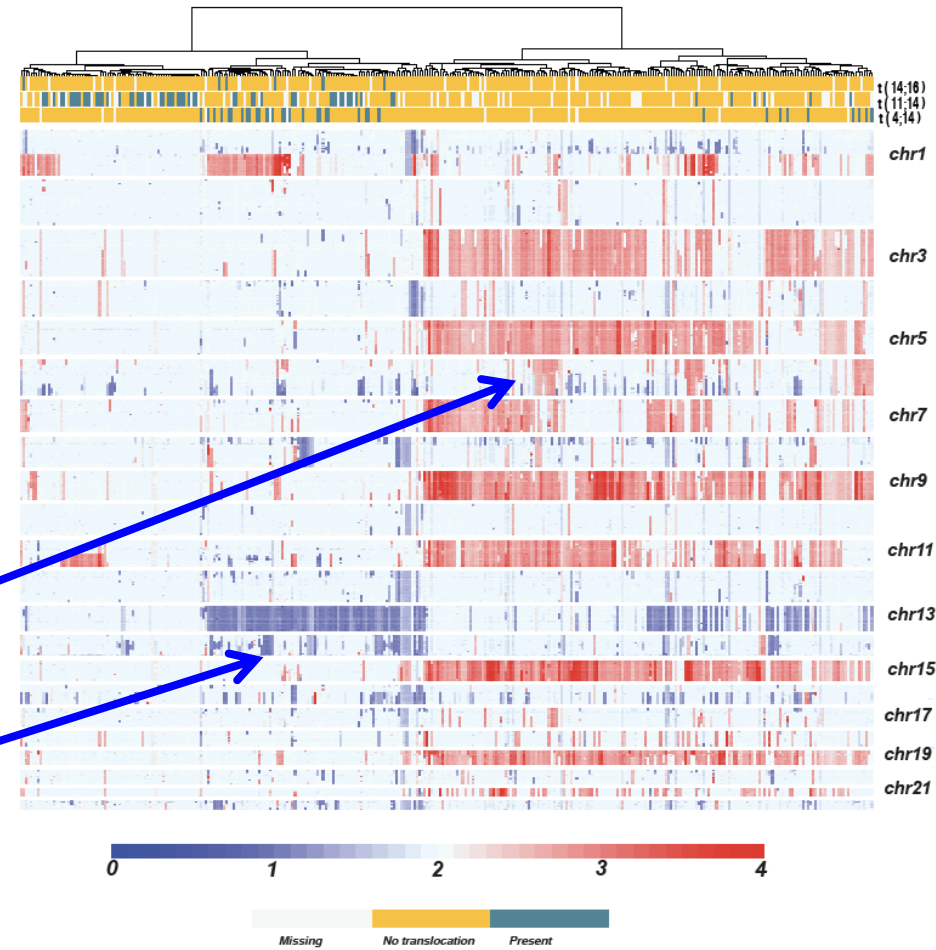
A



Two Basic Types of Myeloma Based on Genomic Characteristics(N = 336)

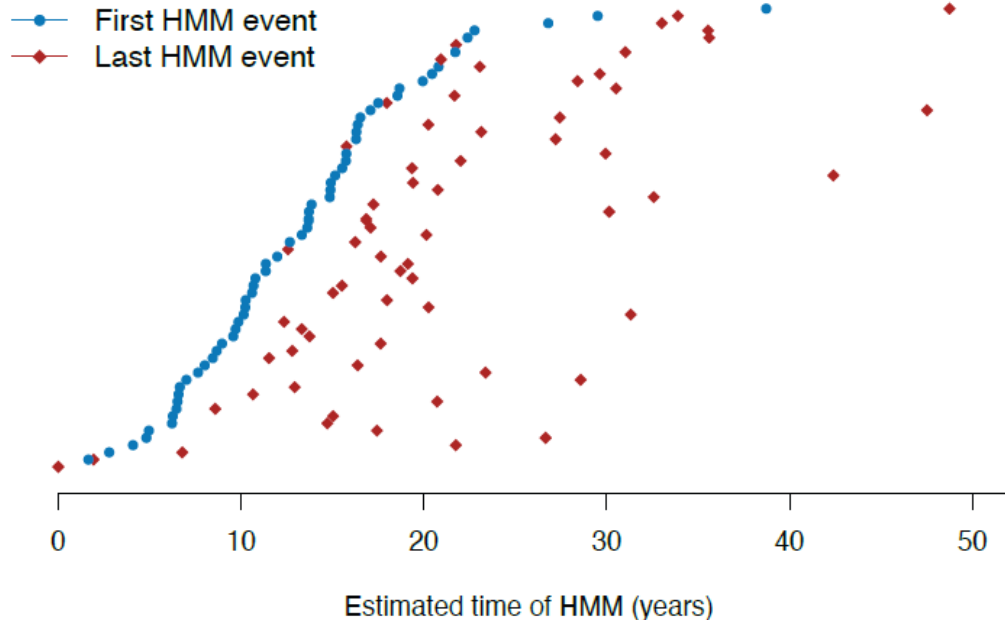
- Most frequent Trisomies involving 3,5,7,9,11, 15,19,21 Hyperdiploid Myeloma (HMM) HMM - 54.5 %;
- Non-HMM (45.5%)

A

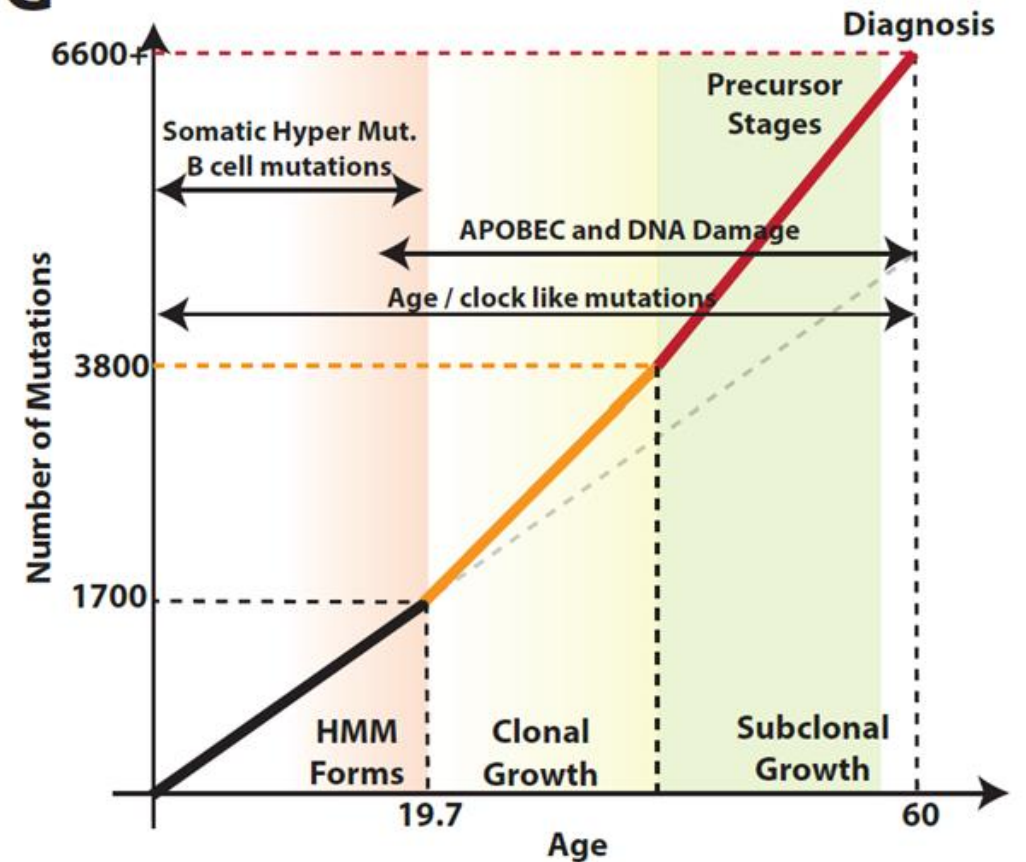


Development of hyperdiploidy starts at an early age (Median 13 years) and takes a decade to complete

A

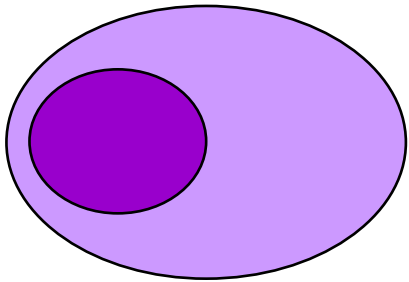


G

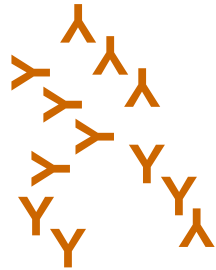


Drivers of MGCS?

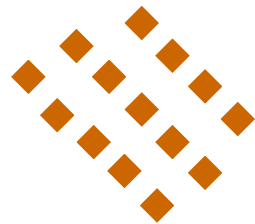
Plasma cell
(or lymphoid clone)



Humoral mediators

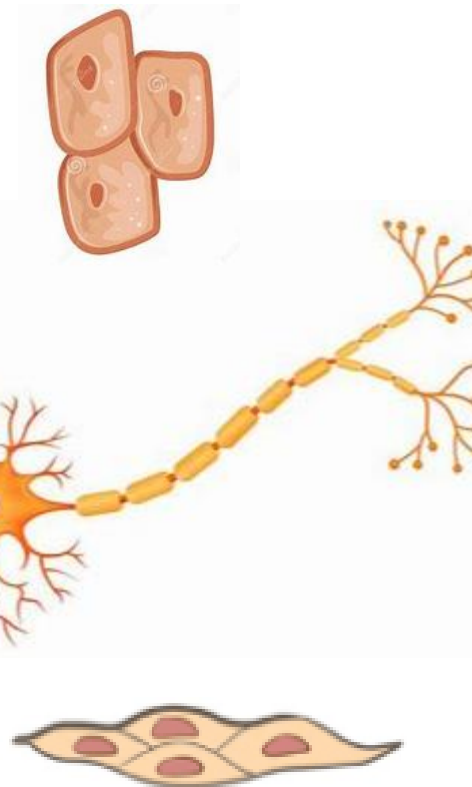


Antibodies

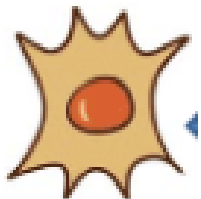
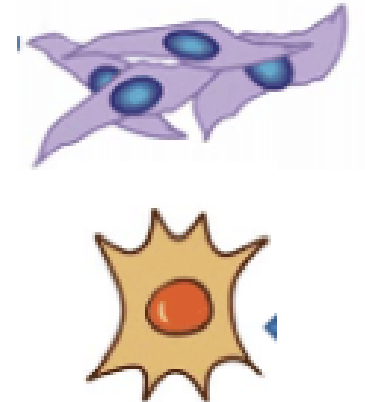


Cytokines or
chemokines

Target tissue
cells

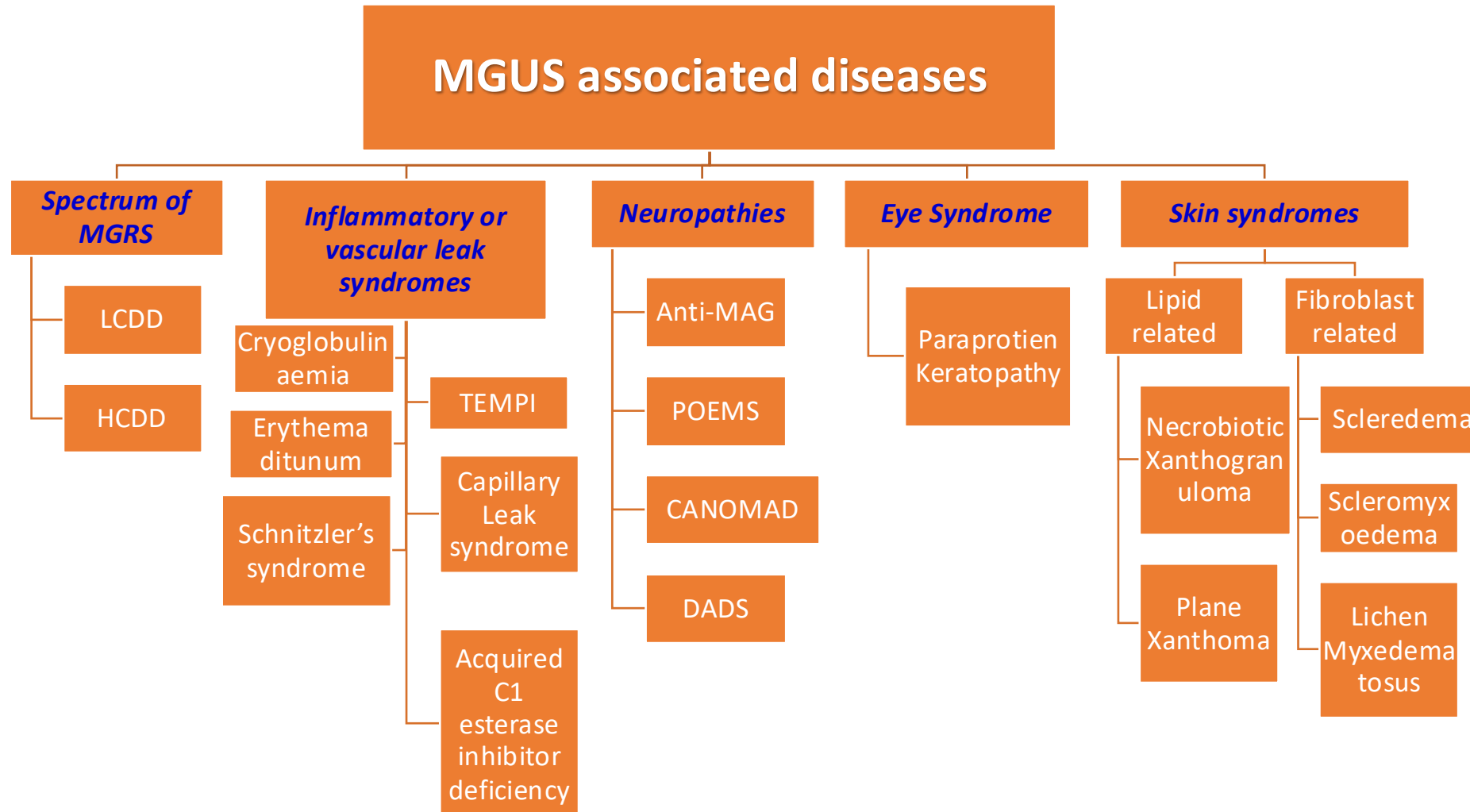


Target tissue
microenvironment

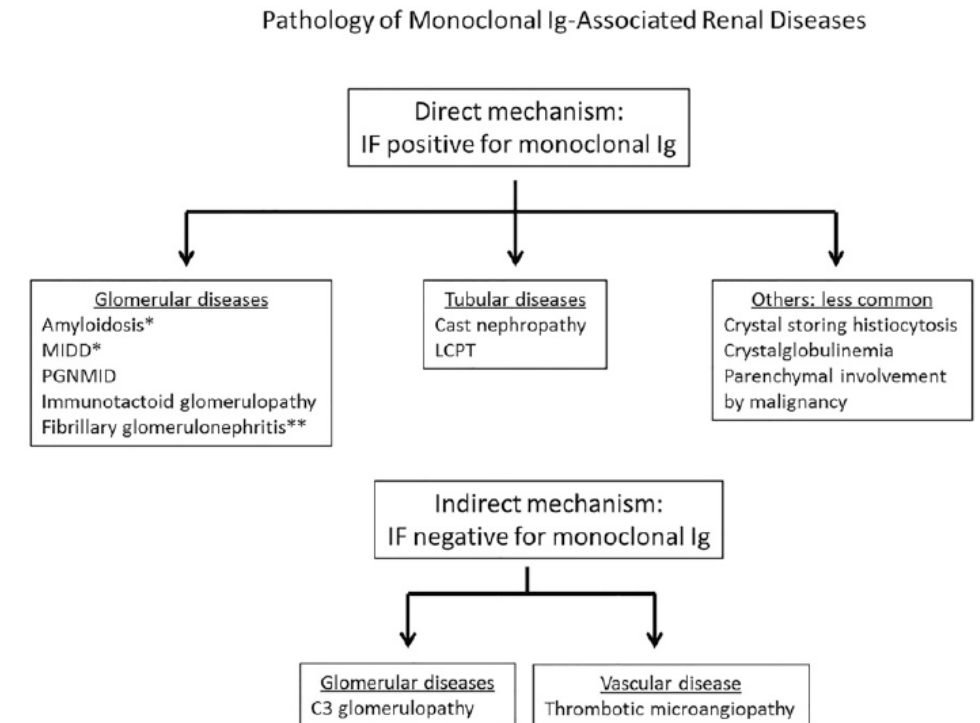
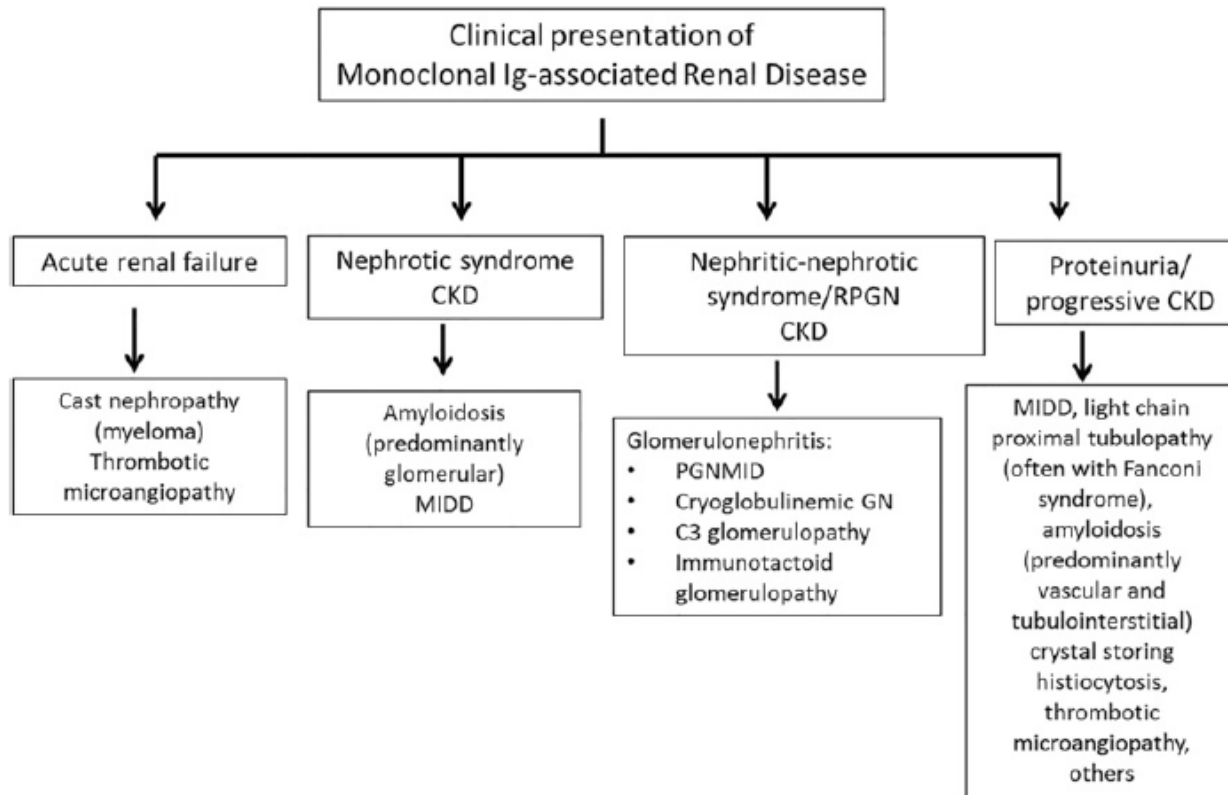


Plasma cell
microenvironment

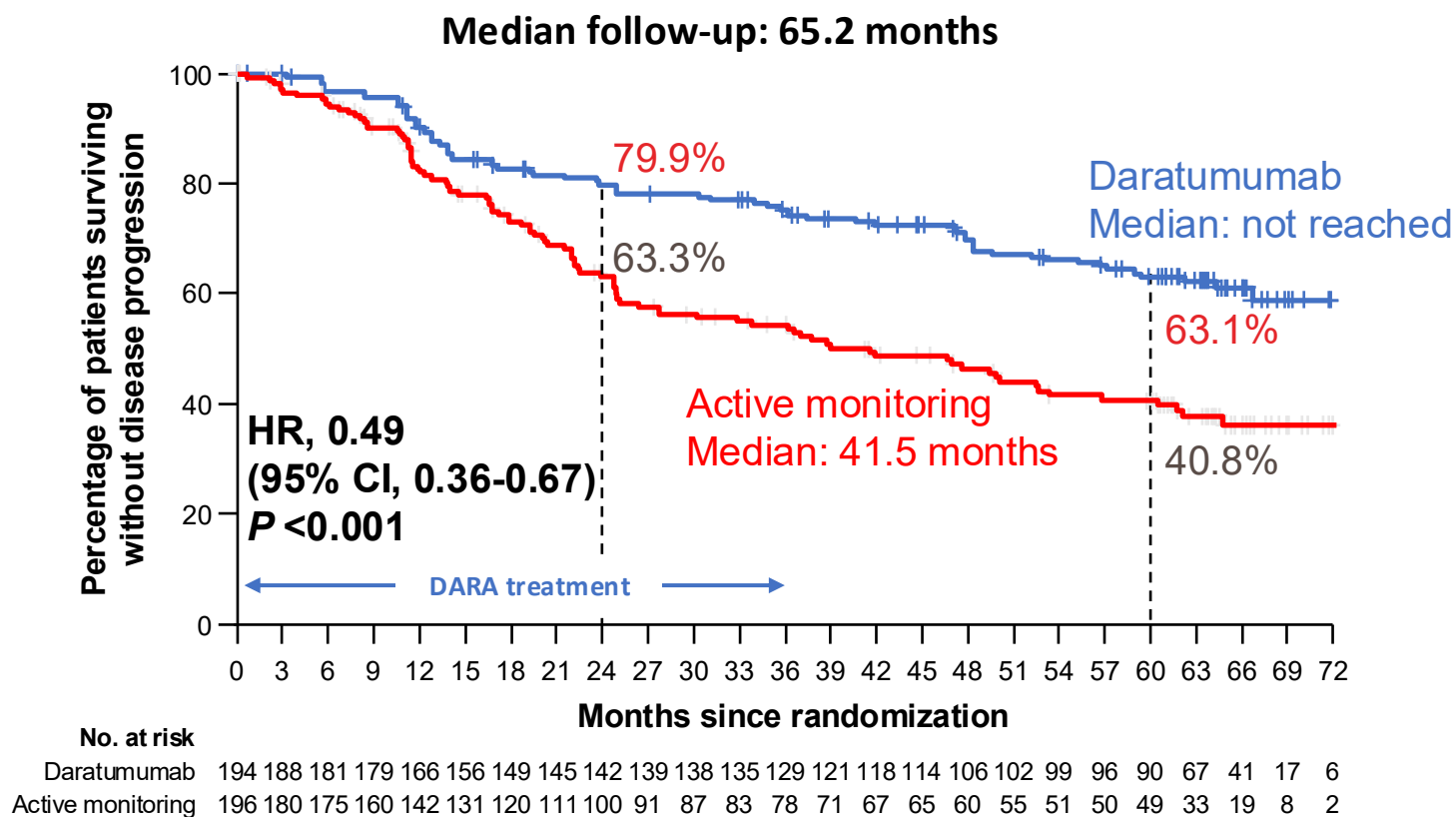
The Spectrum of MGUS associated disorders



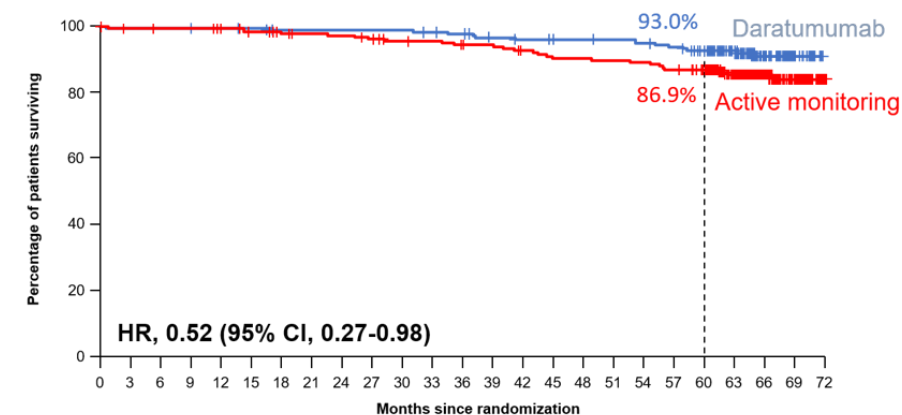
Spectrum of renal disorders



AQUILA: Progression to MM by IMWG SLiM-CRAB Criteria (IRC Assessment)



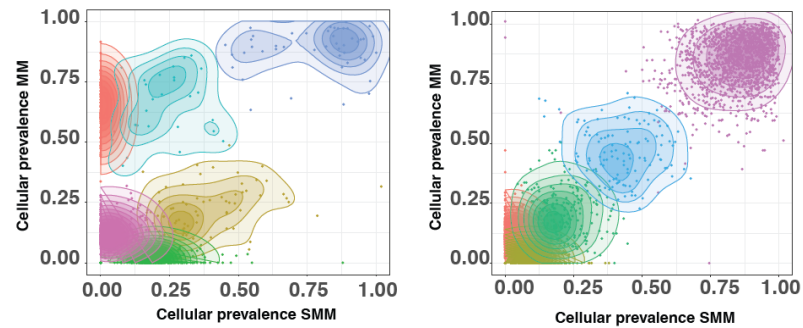
Overall Survival



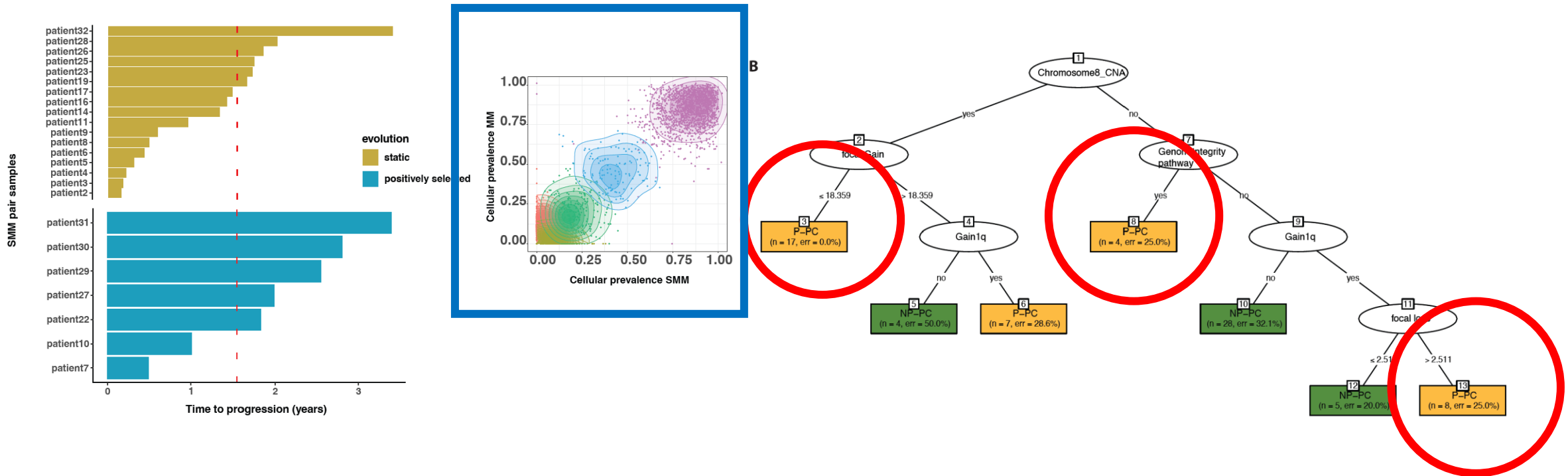
- First-line treatment for MM was initiated by:
 - 33.2% (64/193) in the DARA group
 - 53.6% (105/196) in the active monitoring group

Consideration of early treatment – reduces genomic heterogeneity

A Sub-group of SMM are genomically MM



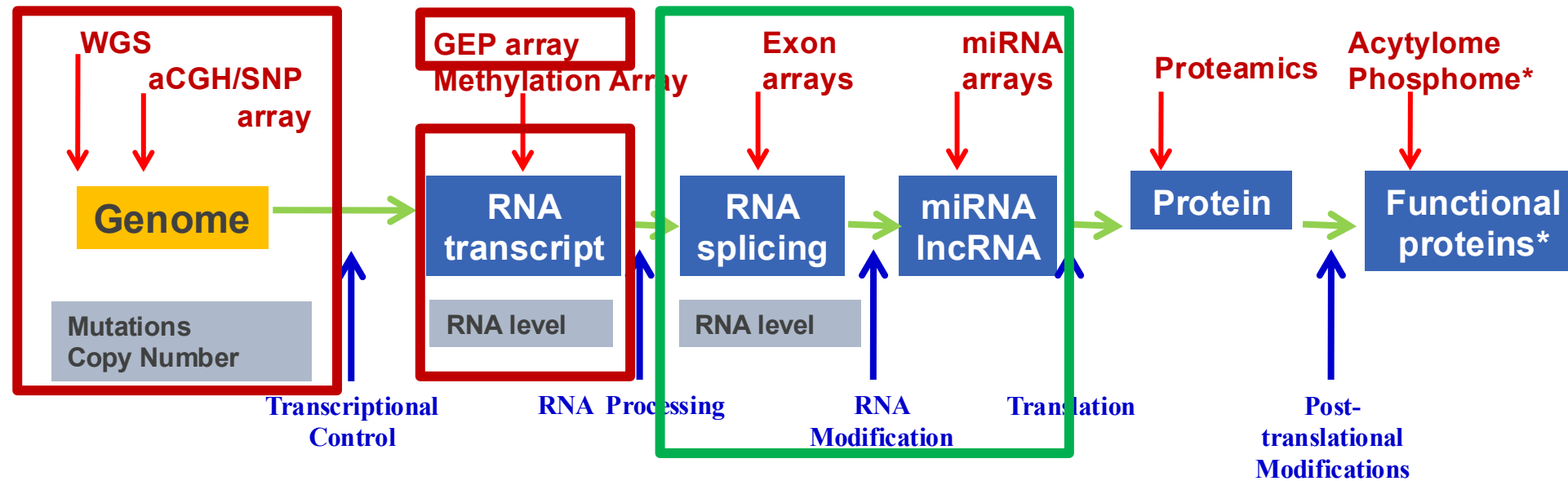
A Sub-group of SMM are genomically MM



Genomics Instability drives progression in both SMM and MM

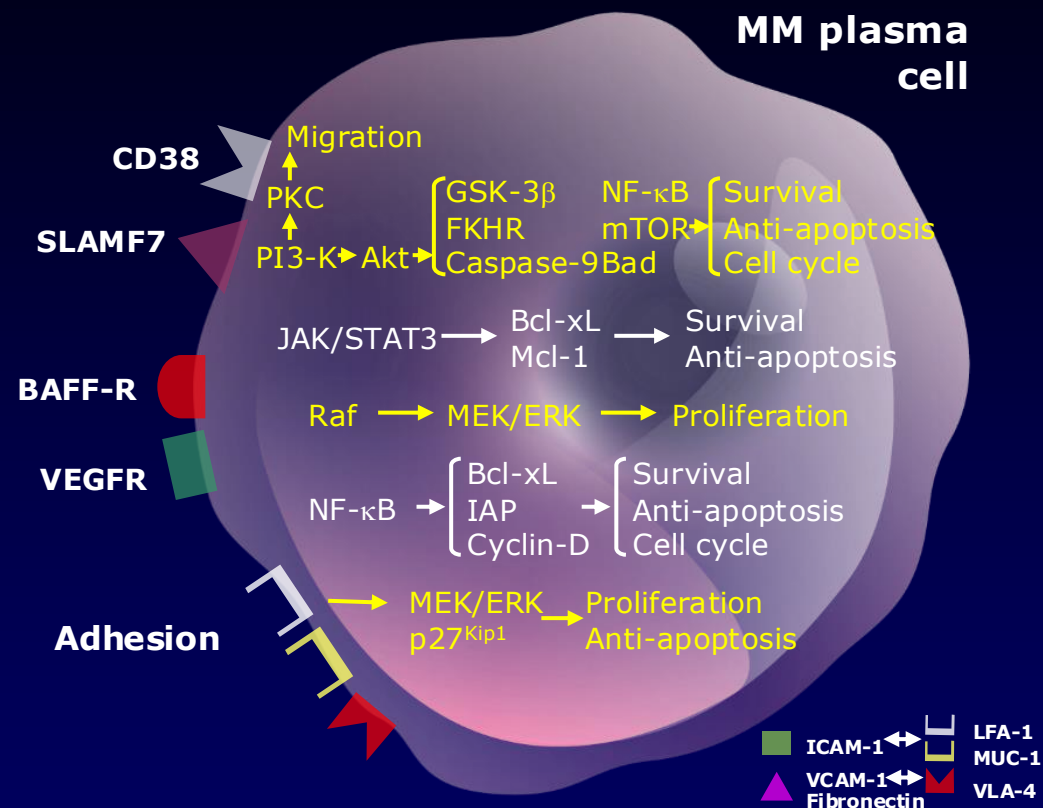
Improved Understanding of The Biology

High-throughput genomic analysis spanning all regulatory checkpoints



- **Intronic PolyA utilization** – Singh et al Nat Comm 2019
- **Alternate splicing** – Anil Samur et al Blood 2023
- **Transcriptional; program** – Samur et al 2020
- **Long-non-coding RNA** – Morelli et al Blood 2023

Growth of MM in the BM Microenvironment



BM, bone marrow.

Figure adapted from Hideshima T, Anderson KC. *Nat Rev Cancer* 2007;7:585–598.

Growth of MM in the BM Microenvironment

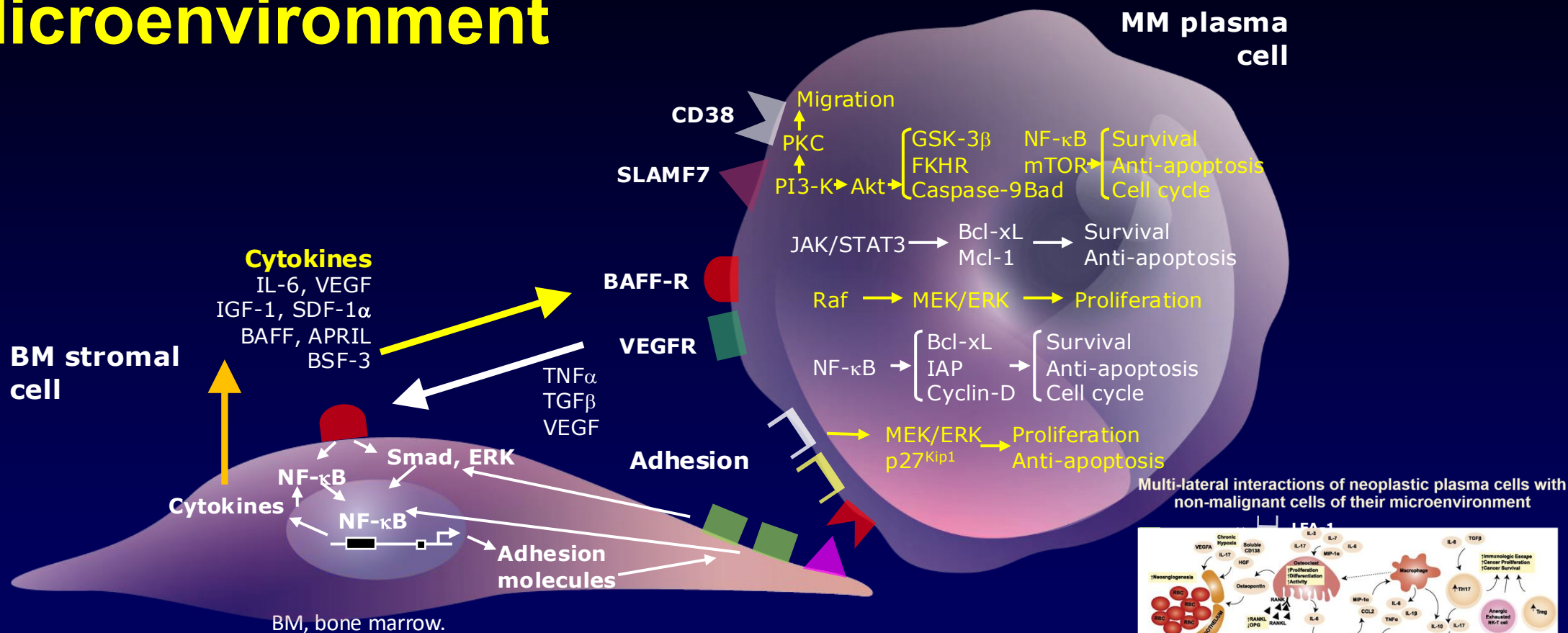
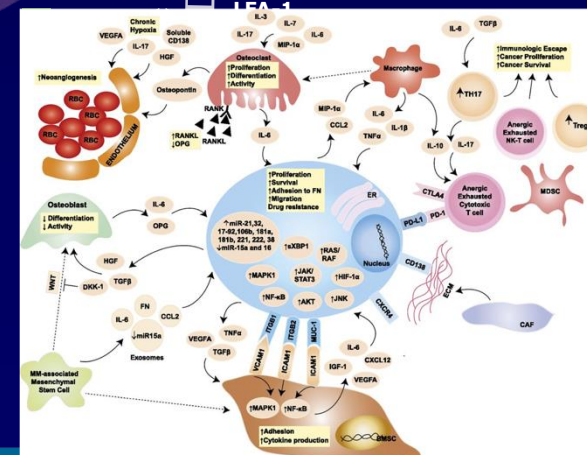
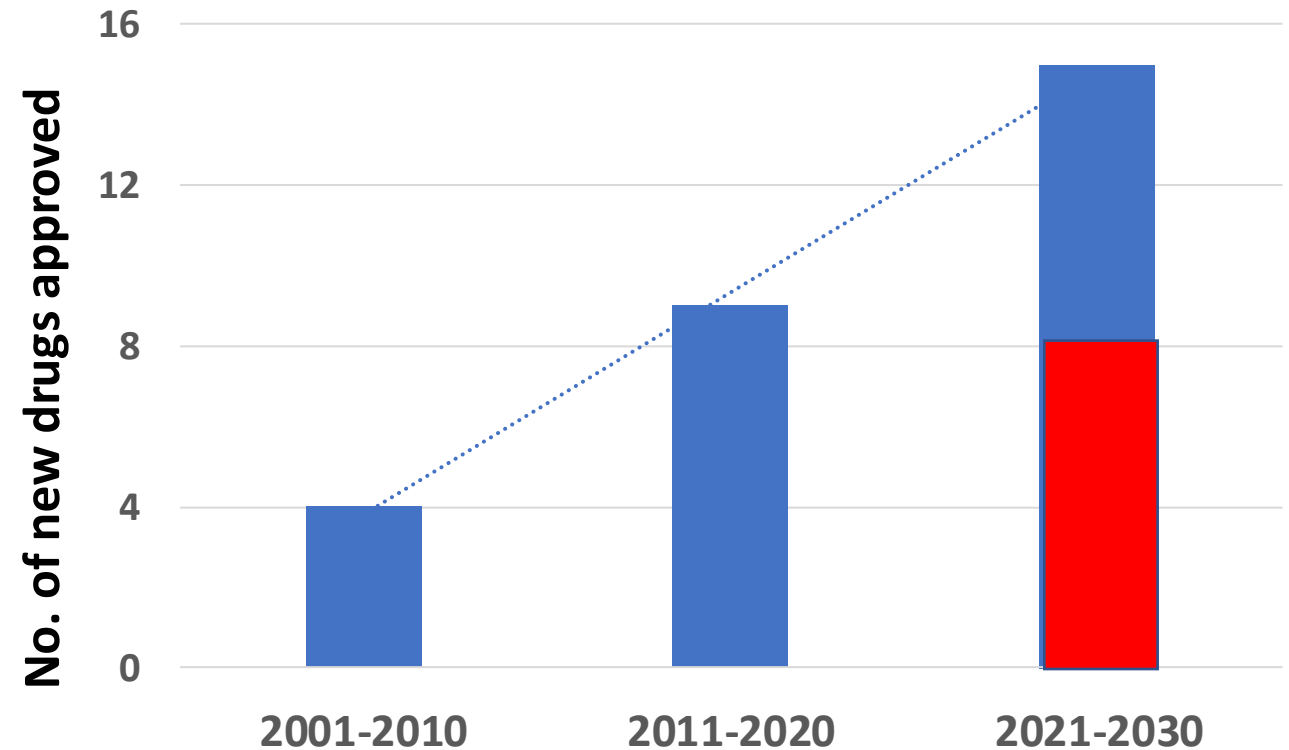


Figure adapted from Hideshima T, Anderson KC. *Nat Rev Cancer* 2007;7:585–598.



Tremendous Progress

New Drug Approval in Myeloma Since 2001



	Drug	Approval
1	Bortezomib	AA (2003)
2	Lenalidomide with dex	Regular (2005)
3	Thalidomide	Regular (2006)
4	Liposomal doxorubicin HCl	Regular (2007)
5	Carfilzomib	AA (2012)
6	Pomalidomide with dex	AA (2013)
7	Panobinostat with Vd ^	AA (2015)
8	Ixazomib with Rd	Regular (2015)
9	Daratumumab-IV	AA (2015)
10	Elotuzumab with Rd	Regular (2015)
11	Selinexor with dex	AA (2019)*
12	Belantamab mafodotin (BCMA)	AA (2020)
13	Isatuximab with Pd	Regular (2020)
14	Melflufan	AA (2021)
15	Idecabtagene vicleucel (BCMA)	Regular (2021)
16	Ciltacabtagene autoleucel (BCMA)	Regular (2022)
17	Taclistimab (BCMA)	AA (2022)
18	Elranatamab (BCMA)	AA (2023)
19	Talquatemab (GPC5D)	AA (2023)
20	Linvoseltimab (BCMA)	AA(2025)
21	Iberdomide	AA – MRD 2026

Quadruplet Combinations for Induction Therapy

High MRD Negative Rates With or Without ASCT

Study	Induction/ Consolidation	ASCT	MRD-neg	PFS	OS
GMMG-HD6 ¹	Elo-RVd x 6*	Yes	NR	3-yr 67.2%	3-yr 89.7%
GMMG-HD7 ⁴	Isa-RVd x 3 [§]	No	50.1%	NR	NR
IFM 2018-01 ⁸	Dara-IRd x 6*	Yes	51%	2-yr 95.2%	NR
IFM 2018-04 ⁹	Dara-KRd x 10*	Pre	62%	NR	NR
GMMG- CONCEPT ¹⁰	Isa-KRd x 6 [‡] (High-risk MM)	No	62.5%	2-yr 75.5%	NR
CASSIOPEIA ⁷	Dara-VTd	Yes	64%	1.5-yr 93%	NR
GRIFFIN ³	Dara-RVd x 6*	Yes	64.4%	3-yr 88.9%	NR
MANHATTAN ¹¹	Dara-KRd x 8 [‡]	No	71%	1-yr 98%	1-yr 100%
MASTER ¹²	Dara-KRd x ≥4 [‡]	Pre/Post	38%/80%	2-yr 87%	2-yr 94%



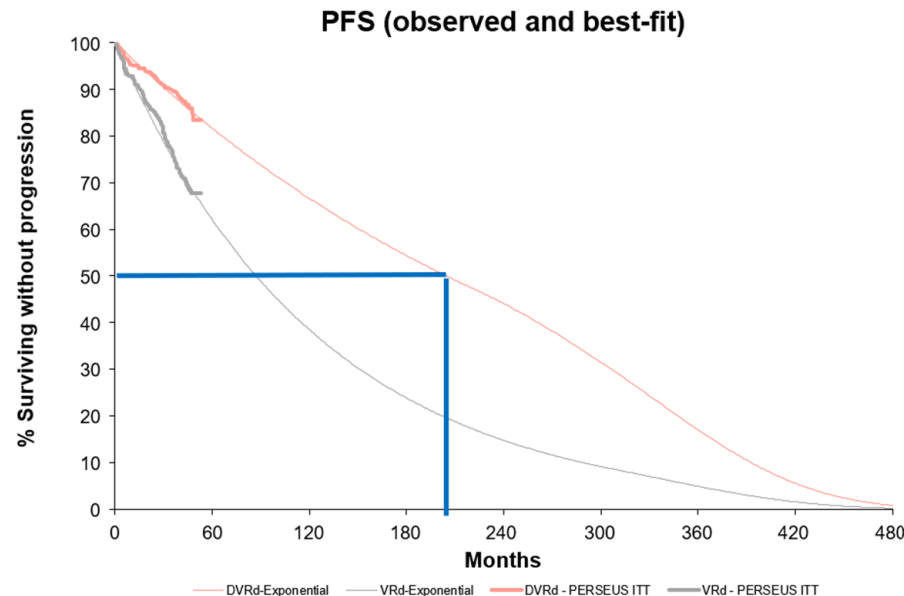
The changing Field

- 9 Drugs/therapies approved as 4-5th line treatments

PERSEUS: Significantly Longer Projected PFS With DVRd TE NDMM

- Median PFS not reached in the ITT population
- Estimated median PFS
 - Range across all distributions:
 - DVRd: 158–255 months
 - VRd: 76–119 months
 - Best-fit:
 - DVRd: 205 months
 - VRd: 87 months

The best-fit projection estimates a 118-month longer PFS benefit with DVRd vs VRd



DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ITT, intent-to-treat; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; TE, transplant-eligible; VRd, bortezomib, lenalidomide, and dexamethasone.

Presented by P. Sonneveld at the 6th European Myeloma Network (EMN) meeting: April 10–12, 2025; Athens, Greece

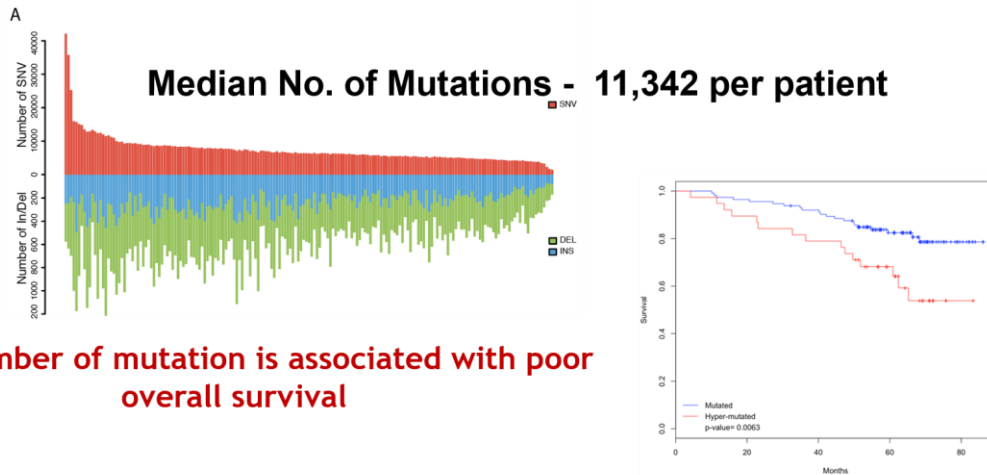
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3 Eras of Progress:

Transplant 1980-; Targeted Therapies 2000-; Immune Therapies 2020-



Heterogeneity of Somatic Mutations

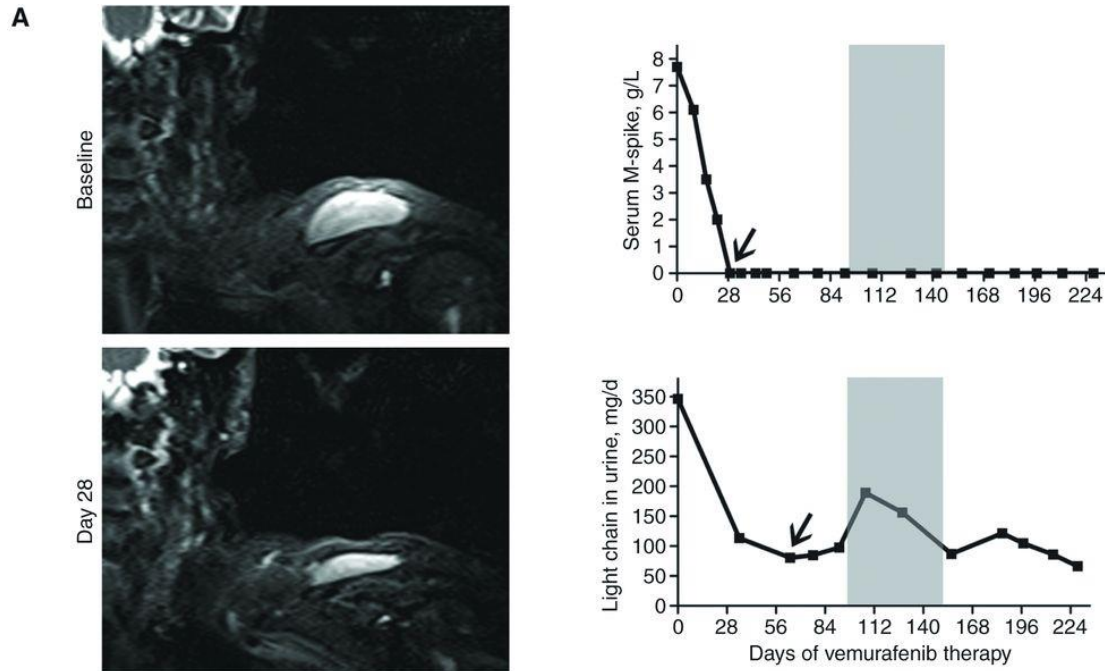


Revised Definition of High-risk Myeloma

Gene	Bolli et al. (n=84 pts)	Lohr et al. (n=203 pts)	Walker et al (n=463)
NRAS	25%	20%	22%
KRAS	25%	23%	20
TP53	15%	8%	3.5%
DIS3	1.5 %	11%	10%
FAM46C	12%	11%	5.4%
BRAF	15% (V600E in 3/10)	6%	8%
SF3B1	3%	1.5%	<2%
CYLD	3%	2.5 %	3%
TRAF3	3%	5.5%	4.1%
ROBO1	7%	2%	<2%
EGR1	6%	3.5%	3.6%
SP140	7%	4.4%	<2%
LTB	4.5%	1%	3%
RASA2	3%	3%	<2%
FAT3	7%	4.4%	3.9%
CCND1	3%	3%	3.5%%

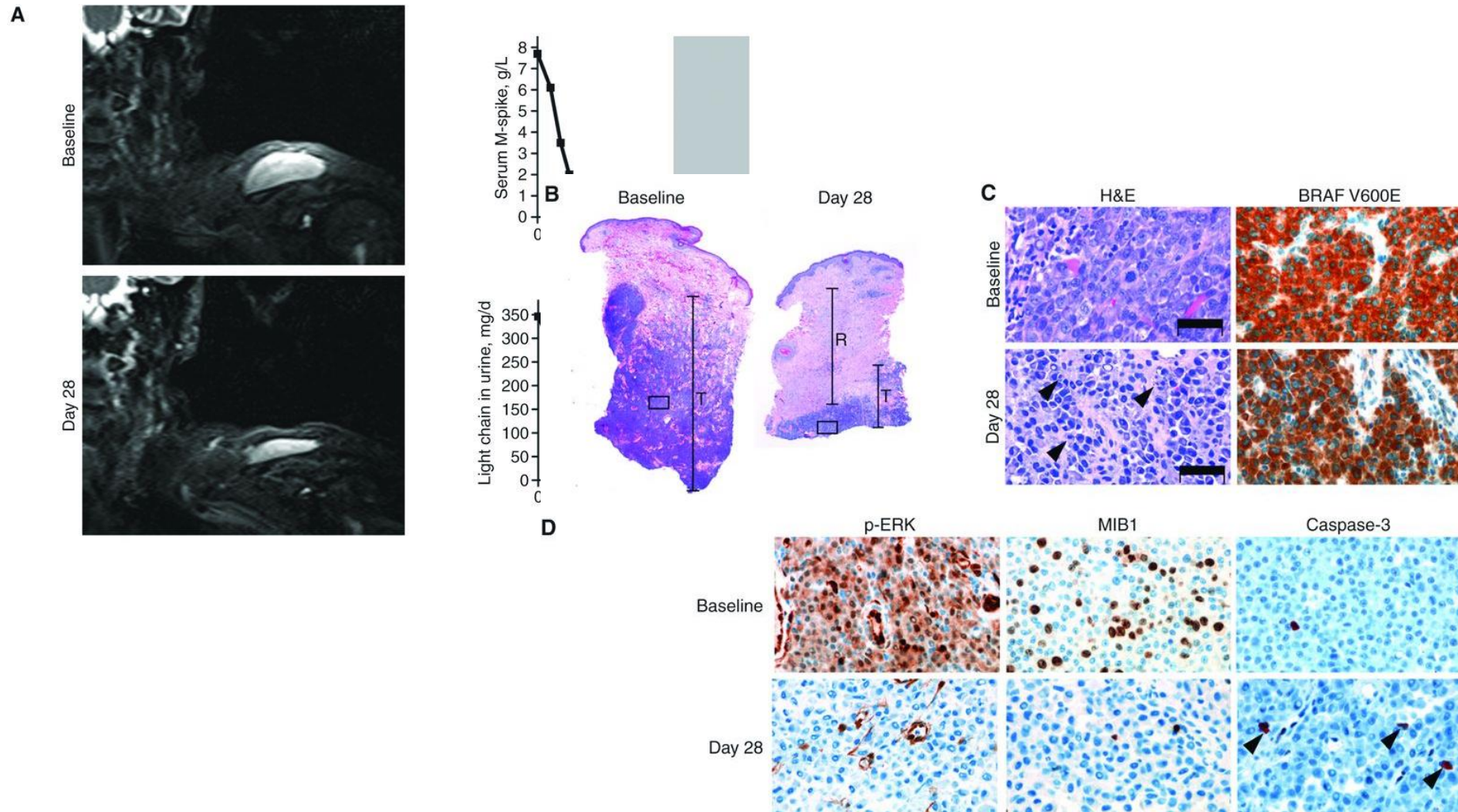


Patient With BRAF V600E - Response to Vemurafenib



Andrulis M et al. Cancer Discovery 2013;3:862-869

Patient With BRAF V600E - Response to Vemurafenib

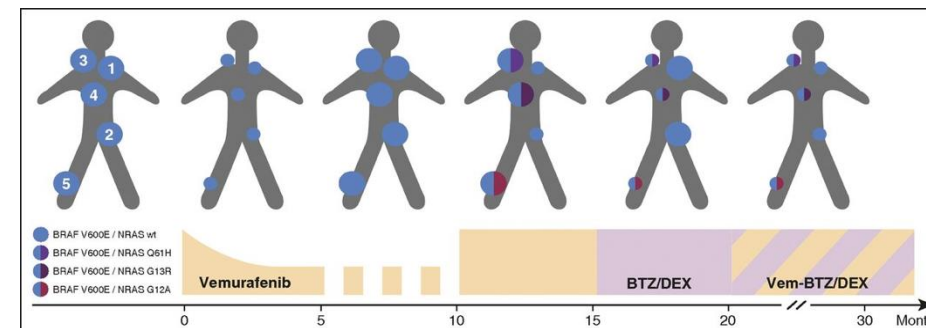
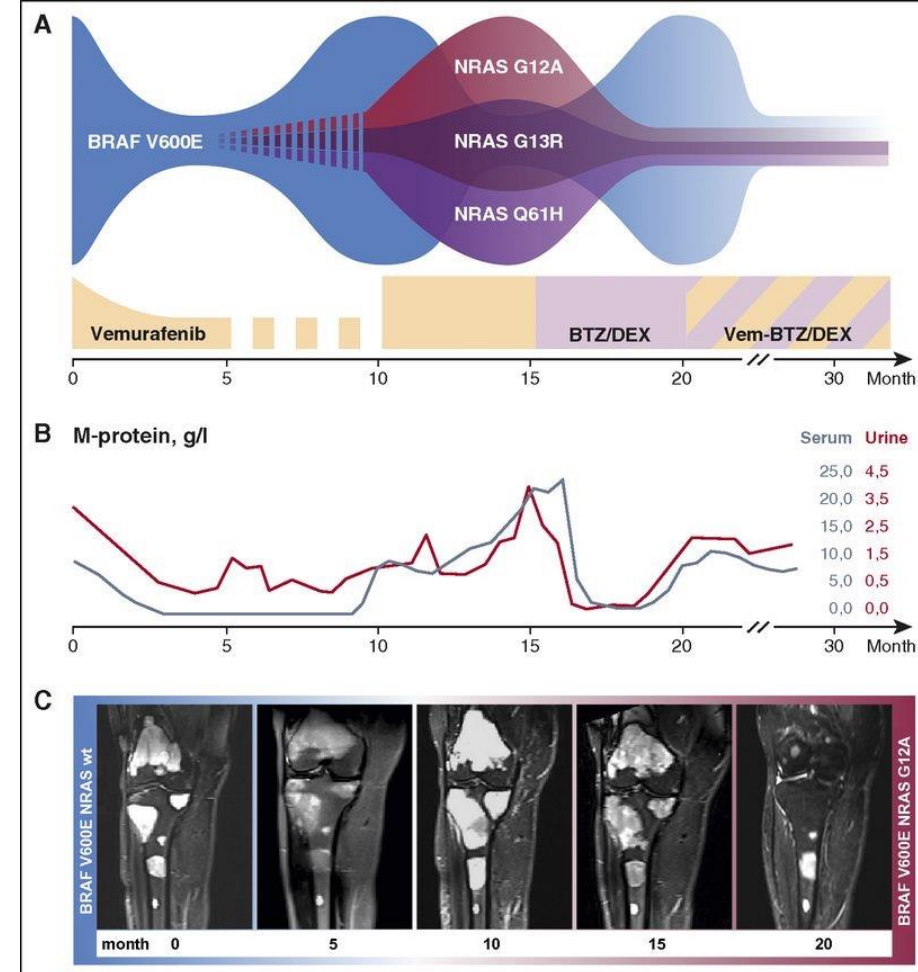


Andrulis M et al. Cancer Discovery 2013;3:862-869

AACR American Association
for Cancer Research



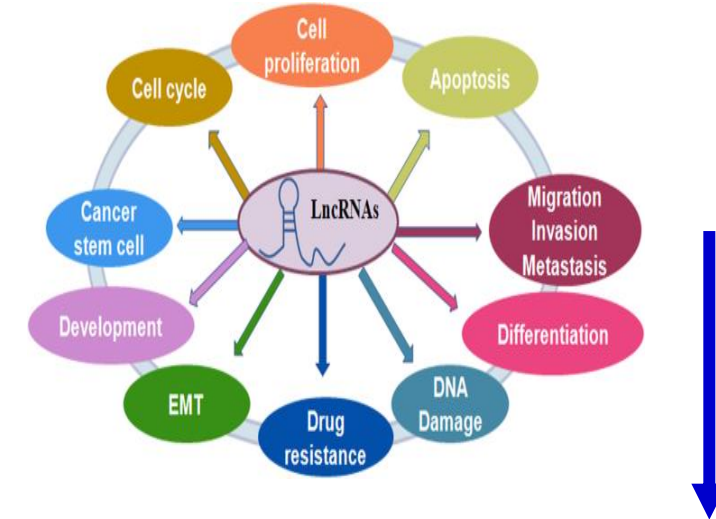
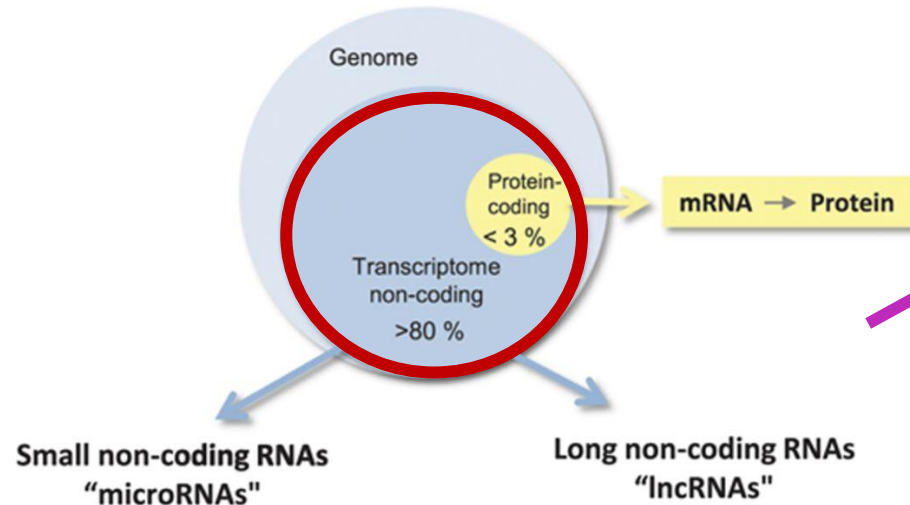
The clinical course and management of a patient with BRAFV600E-mutant MM developing resistance to treatment with vemurafenib.



Long Noncoding RNAs – key players in cancer biology

Most of the human transcriptome is “noncoding” and functionally unexplored

LncRNAs are implicated in all aspects of malignant transformation



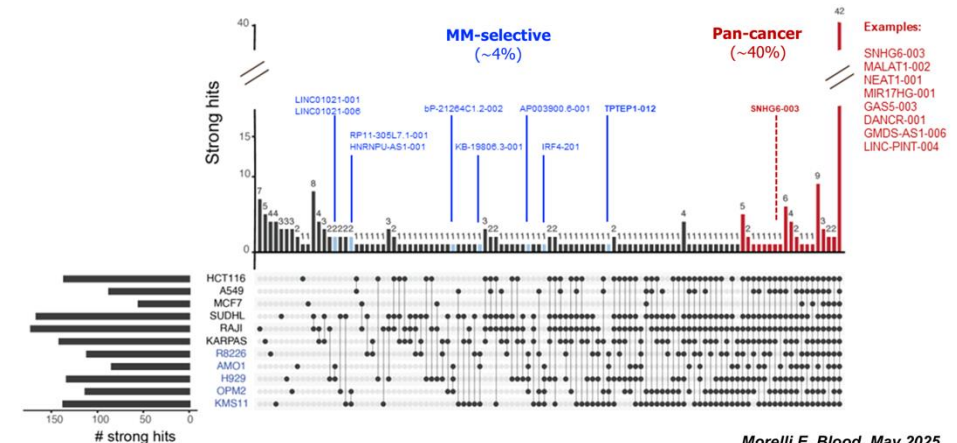
Essential isoforms are either MM-selective or Pan-Cancer

- <200nt
- transcribed by RNA Polymerase II
- endogenously processed by endonucleases
- well conserved

> 2,000 microRNAs

- >200nt
- transcribed by RNA Polymerase II
- mostly 5'-cap, polyadenylated (in part), spliced
- poorly conserved

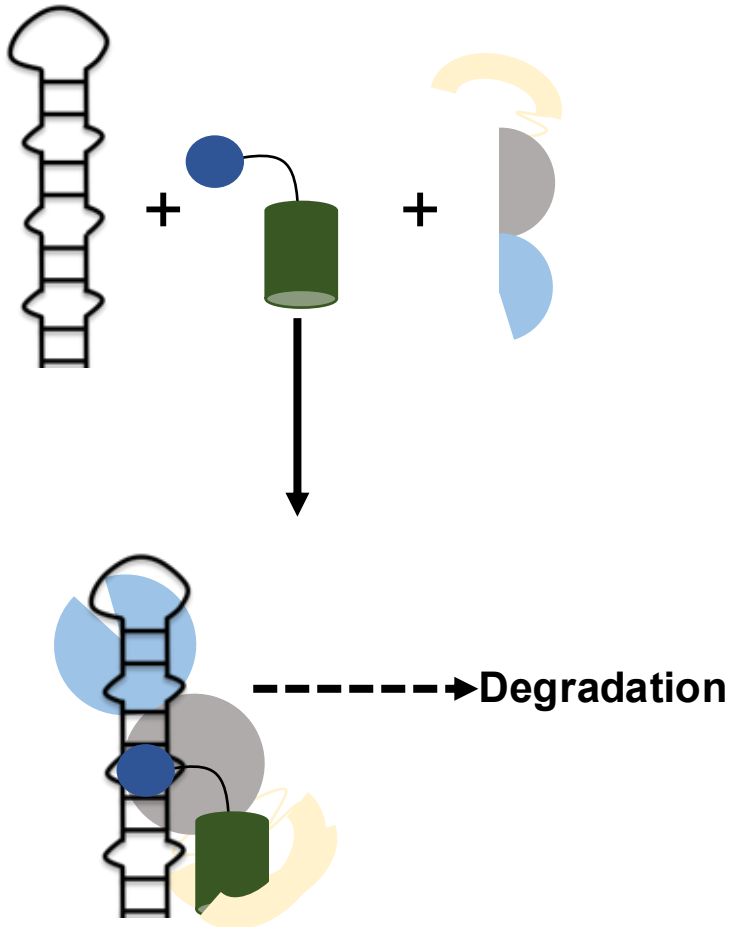
> 30,000 lncRNAs



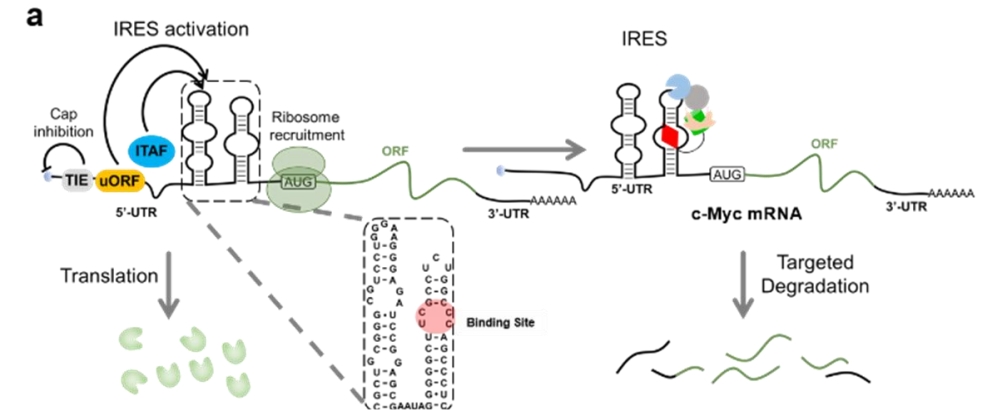
Morelli E, Blood, May 2025

“Small molecule“ approaches to degrade RNA - RiboTec

Induced proximity of a ribonuclease. Costales et al. (2018) JACS, 140, 6741 & Costales et al., PNAS (2020), 117, 2406-2411



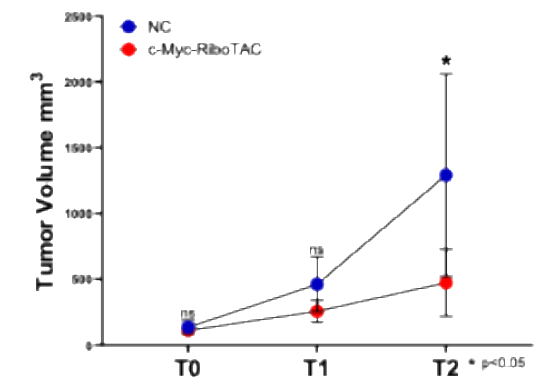
cMYC has a conserved RNA structure at 5' UTR (IRES) that can bind small molecules



cMYC is constitutively and aberrantly expressed in over 70% of human cancers. Many cancer targets have IRESs.

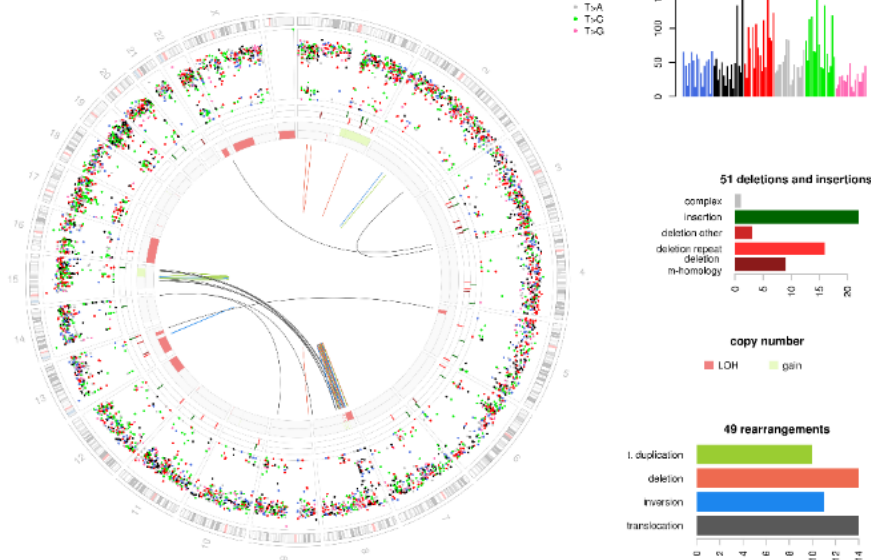
Tong, et al., Nature (2023), 618, 169
D Maisano, et al. Blood (2024), 144, 3268

Compound reduces tumor burden from transplanted human MM in mouse

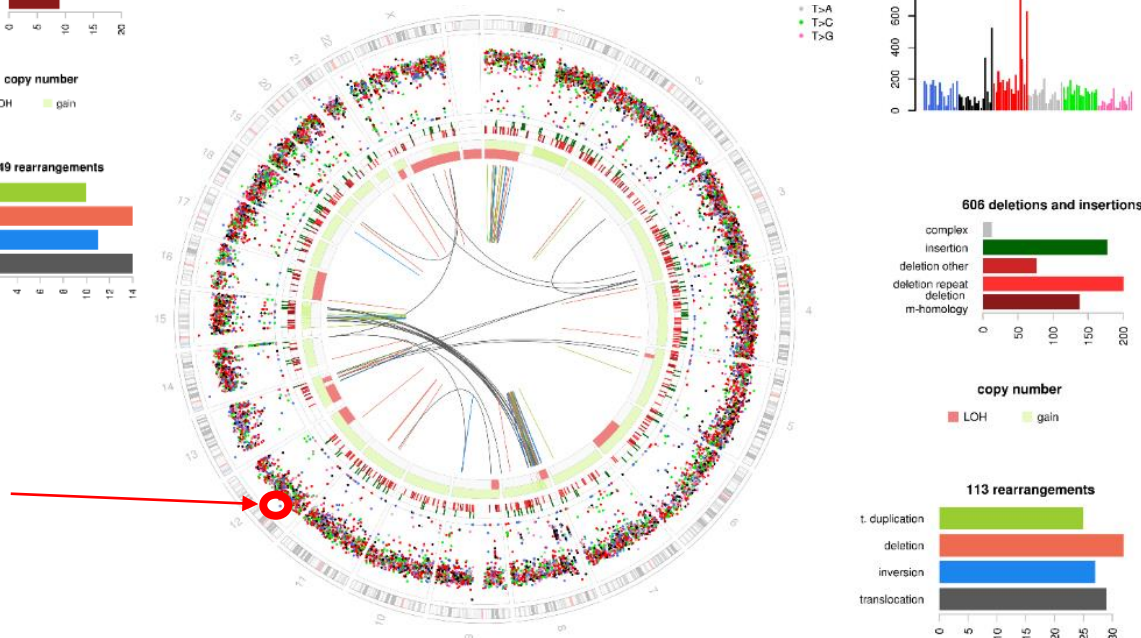


Development of Complex Genome and Resistance

Complex Genomic Changes at Diagnosis



Genomic Complexity Increases at Relapse



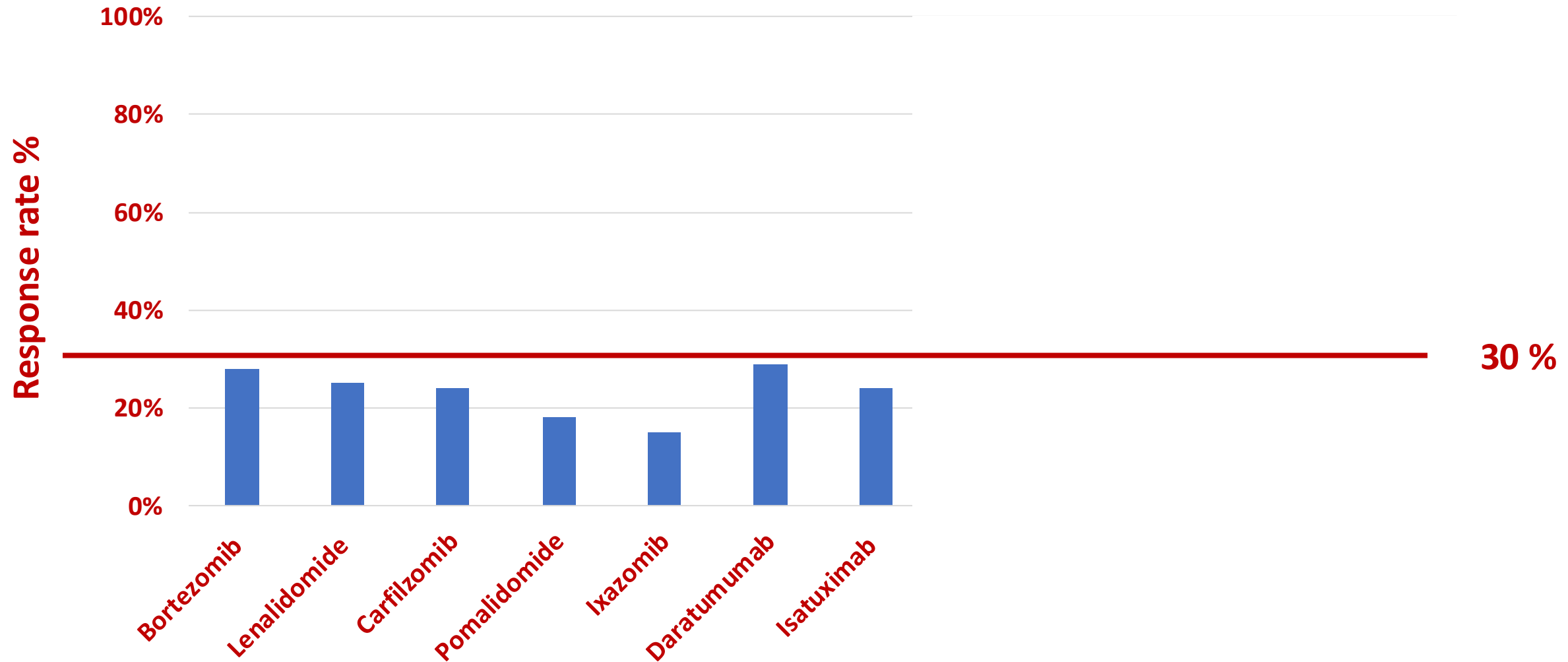
Use the Best Option Early!!
Rise of Immunotherapy



Immunotherapy is in a Different League!

Single Agent Response Rate – Changing Landscape

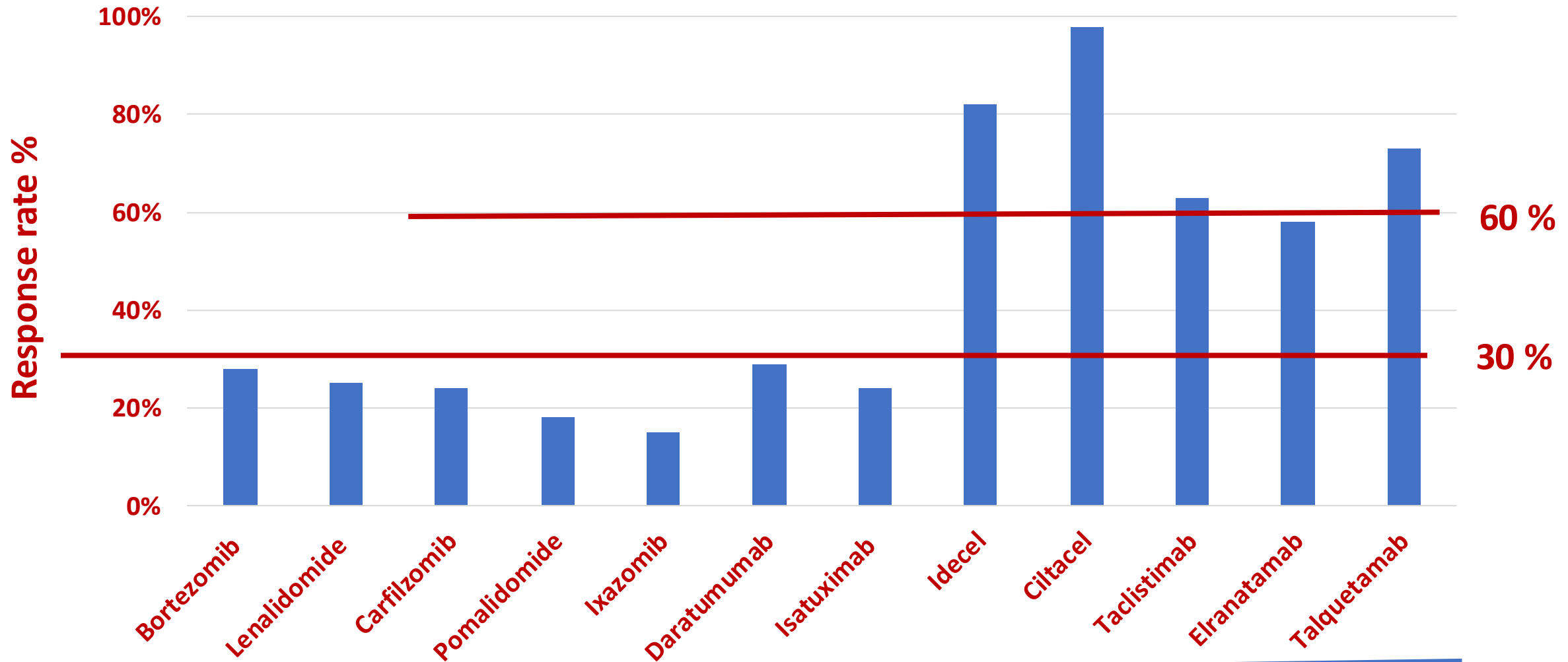
Single Agent Response Rate



Immunotherapy is in a Different League!

Single Agent Response Rate – Changing Landscape

Single Agent Response Rate



2021-23



CAR T Cell Therapy: High Effectiveness

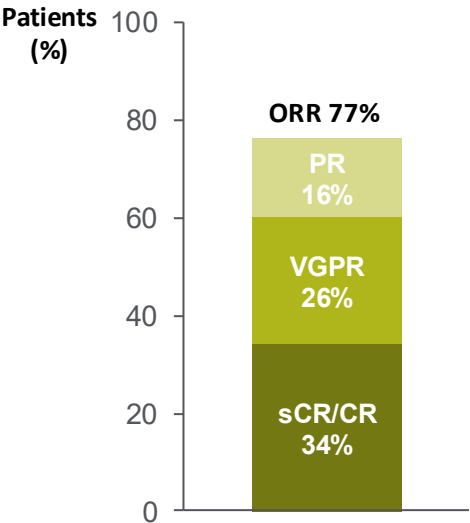
KarMMa¹⁻³ 4L+

mFU: 63.6 months
Open label, single-arm, multicentre, phase 2 study in adult patients with RRMM receiving idecabtagene vicleucel (N=137)

Target antigen:
BCMA

Primary endpoint:
ORR by IMWG criteria

Patient characteristics
Triple-class refractory: 84%
High-risk cytogenetics: 35%
Extramedullary disease: 39%



Safety (n=128) ¹				
CRS (%)	5	84		All grade
Neurotoxic effect (%)	3	18		Grade 3/4

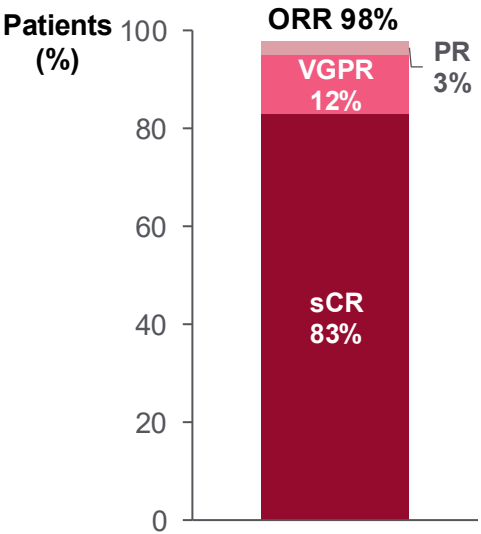
CARTITUDE-1¹⁻³ 4L+

mFU: 61.3 months
Open-label, single-arm, multicentre, phase 1b/2 study in adult patients with RRMM receiving ciltacabtagene autoleucel (N=97)

Target antigen:
BCMA

Primary endpoint:
Phase 2: ORR by IMWG criteria

Patient characteristics
Triple-class refractory: 88%
High-risk cytogenetics: 24%
Extramedullary disease: 13%



Safety ¹				
CRS (%)	4	95		All grade
ICANS (%)	2	17		Grade 3/4
Non-ICANS neurotoxicity (%)	8	12		

High Response Rates and Sustained Survival Seen With All Approved BCMA BsAbs in RRMM

	MajesTEC-1 (Teclistamab) ^{1,2}	MagnetisMM-3 (Elranatamab) ^{3,4}	LINKER-MM1 (Linvoseltamab) ^{5,6}
Median follow-up	30.4 months	33.9 months	21.3 months
ORR	63.0%	61.0%	70.9%
MRD-negativity among MRD-evaluable patients with ≥CR	-	90.3%*	94%**
MRD-negativity among MRD-evaluable patients	85.7%*	-	-
Median DOR	24.0 months	NR	29.4 months
Median PFS	11.4 months	17.2 months	At 18 months: 60.4% (95% CI 17.3-NE)
Median OS	22.2 months	24.6 months	31.4 months

Notes: Linvoseltamab has not been approved by Health Canada; direct cross-trial comparison cannot be performed due to differences in patient populations, study design, and length of follow-up.

*MRD negativity assessed at a sensitivity threshold of 10^{-5} via next-generation sequencing of DNA from bone marrow aspirates using the clonoSEQ MRD assay from Adaptive Biotechnologies.

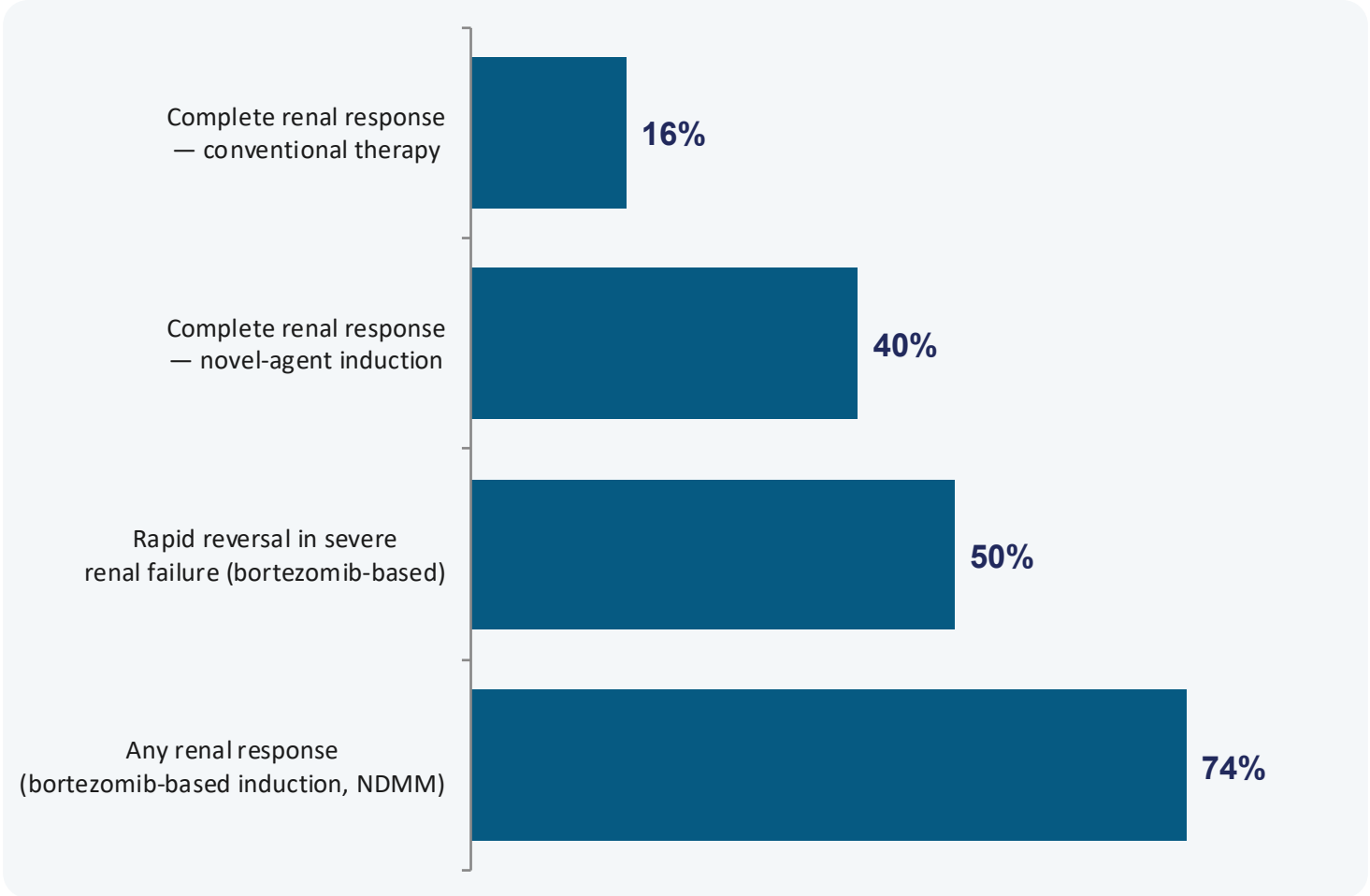
†MRD negativity assessed at a sensitivity threshold of 10^{-5} via next-generation sequencing using the clonoSEQ MRD assay from Adaptive Biotechnologies or next-generation flow cytometry using the EuroFlow assay from Cytognos, now BD Biosciences. BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CR, complete response; DOR, duration of response; MRD, minimal residual disease; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma.

1. Garfall AL et al. ASCO 2024. Abstract 7540 and Presentation. 2. Moreau P et al. N Engl J Med. 2022;387:495-505. 3. Lesokhin AM et al. Nat Med. 2023;29:2259-2257. 4. Prince HM et al. ASH 2024. Abstract 4738. 5. Bumma N et al. J Clin Oncol. 2024;42:2702-2712. 6. Shah MR et al. ASH 2024. Abstract 3369.



What Proportion of Patients Recover Renal Function?

Share of patients reaching a renal response, by treatment scenario



Recovery Tracks With Survival

Never impaired	112 mo
Impaired → recovered	56 mo
Impaired → persists	33 mo

Median overall survival, newly diagnosed myeloma (Mayo Clinic, n=1,135)

Sources: Dimopoulos et al., Eur J Haematol 2010; Leung/Mayo Clinic cohort, Bone Marrow Transplant 2015; prospective NDMM renal-impairment cohort, Am J Blood Res 2022.



Modern Immunotherapy Equally Effective Even With Renal Failure

CAR-T cells, bispecific antibodies, and daratumumab-based regimens were tested with renal-impaired patients excluded — real-world data now show they work just as well when the kidneys don't



67%

achieved a renal response on
daratumumab + bortezomib +
dexamethasone despite SEVERE
baseline renal impairment

*GMMG-DANTE phase 2 trial, relapsed/refractory MM with
severe RI*

Response Rates Hold Up Regardless of Kidney Function

■ Normal renal function

■ Renal impairment

BCMA CAR-T (ide-cel)

real-world cohort, n=189



Bispecific antibody (teclistamab)

real-world cohort, n=384



Across CAR-T and bispecific real-world cohorts, neither moderate nor severe renal impairment reduced response rates or survival — a reversal of the exclusion criteria used in the pivotal registration trials.

Sources: Sidana et al. (ide-cel real-world, TCT 2023); teclistamab real-world renal-impairment cohort (13 US centers, 2024); GMMG-DANTE phase 2 trial (2023).





Concept of Total Immunotherapy

• Induction

- Combinations of Immunomodulator agent with ICD inducing agent

Consolidation

- Anti-BCMA CAR T cell Therapy

Maintenance

- Alternating BCMA and GPRC5D BiTE for 2 years

• MRD Negative





Myeloma Cure Summit:

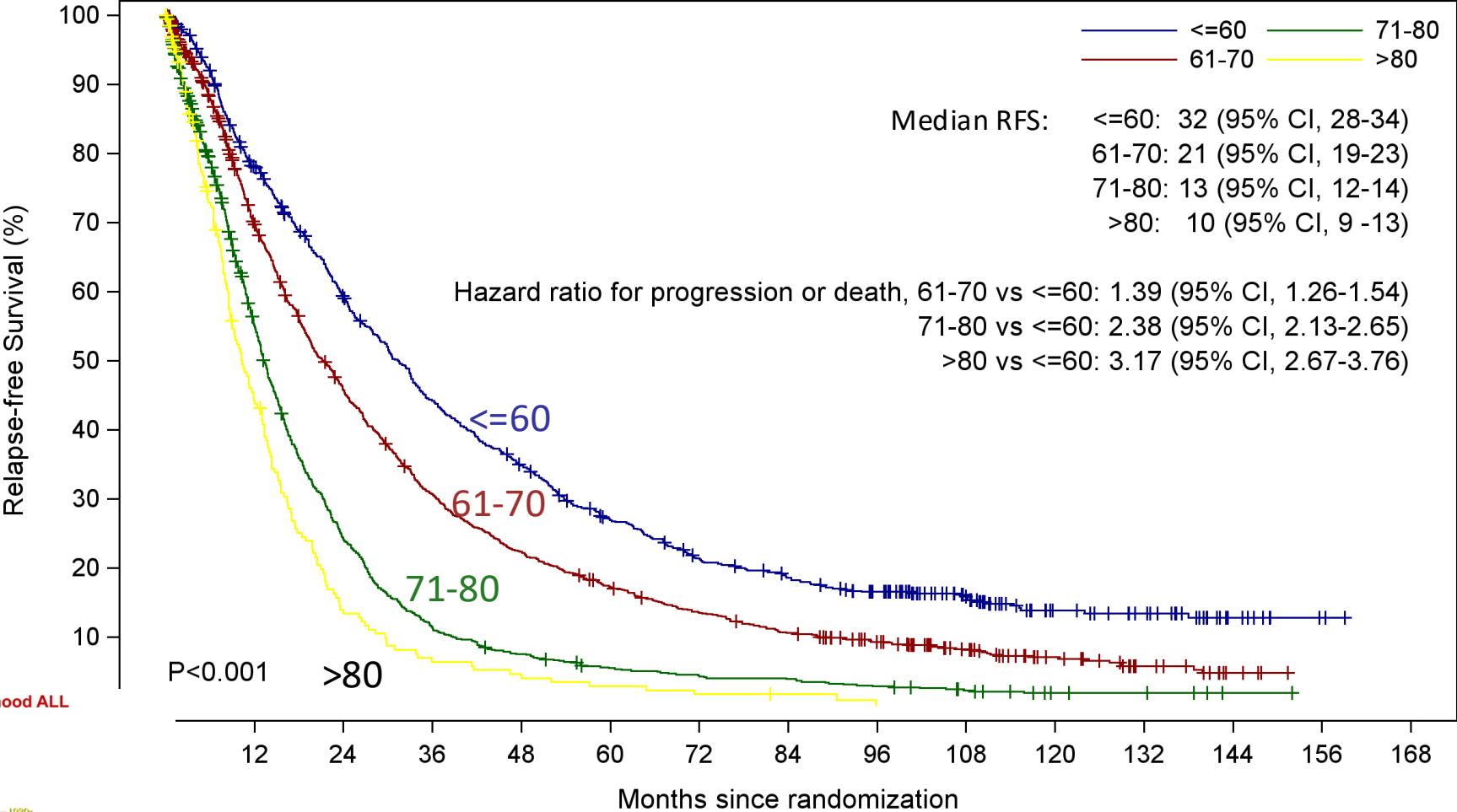
DEFINITIONS, METRICS, AND MILESTONES

FEBRUARY 20-21, 2026 | MIAMI, FL

Nikhil Munshi Vincent Rajkumar and Philippe Moreau



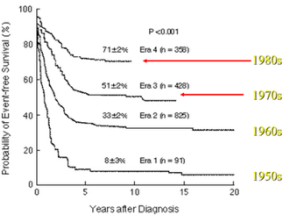
Myeloma XI - RFS for patients off therapy



Cure fraction:

≤ 60	0.16
61-70	0.09
71-80	0.05
>80	0.05

Improvement in EFS in Childhood ALL
A Model for MM



Number at risk (number censored)

(2)	555 (29)	414 (39)	307 (41)	240 (43)	180 (49)	140 (52)	119 (55)	98 (63)	65 (93)	35 (116)	27 (123)	9 (140)	2 (147)	0 (149)
(12)	743 (68)	481 (75)	322 (77)	234 (77)	178 (80)	139 (82)	107 (83)	82 (96)	53 (116)	31 (132)	15 (143)	4 (152)	0 (156)	
(6)	452 (57)	198 (59)	94 (59)	61 (60)	42 (63)	33 (63)	30 (63)	22 (63)	14 (67)	6 (73)	5 (74)	1 (78)	0 (79)	
(0)	76 (25)	23 (26)	11 (26)	8 (26)	5 (26)	3 (26)	2 (27)	0 (27)						

Proposed Definition of Cure

- Patient could be newly-diagnosed or with relapsed myeloma
- Patient in sustained Complete Remission (CR) by standard criteria
- MRD negative at 10^{-6} sensitivity by either NGS or NGF
- MRD negativity Sustained for 5 years **WITHOUT** any therapy. (Irrespective of length of previous sustained MRD negativity on therapy)
 - There should be at least 4 MRD assessments in 5 years, last one being at 5 years; all negative and no positive test in between, if performed.
- Negative by functional imaging (PET/CT or DWI WB MRI)
- **Accumulated data suggests that a cure fraction is observed following various therapies and long-term follow up - Average calculated cure ranges between 5-30%**

Multiple myeloma remains an incurable disease,

Multiple myeloma (MM) is an incurable plasma cell dyscrasia

Although multiple myeloma is sensitive to both chemotherapy and RT, it remains incurable

Multiple myeloma is a malignant tumour of plasma cells that remains incurable for the vast majority

Multiple myeloma (MM) is an incurable malignancy in majority of patients

the disease is still incurable for most patients.

Multiple myeloma (MM) is an incurable hematopoietic cancer

remains an incurable disease.

Multiple myeloma (MM) is an incurable plasma cell malignancy

myeloma is still an incurable disease.

Multiple myeloma (MM) is an incurable blood cancer



Multiple myeloma remains an **incurable** disease,

Multiple myeloma (MM) is an **incurable** plasma cell dyscrasia

Although multiple myeloma is sensitive to both chemotherapy and RT, it remains **incurable**



Mention of Cure and Myeloma in PubMed



multiple myeloma (MM) is an **incurable** hematopoietic cancer

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Multiple myeloma remains an incurable disease,

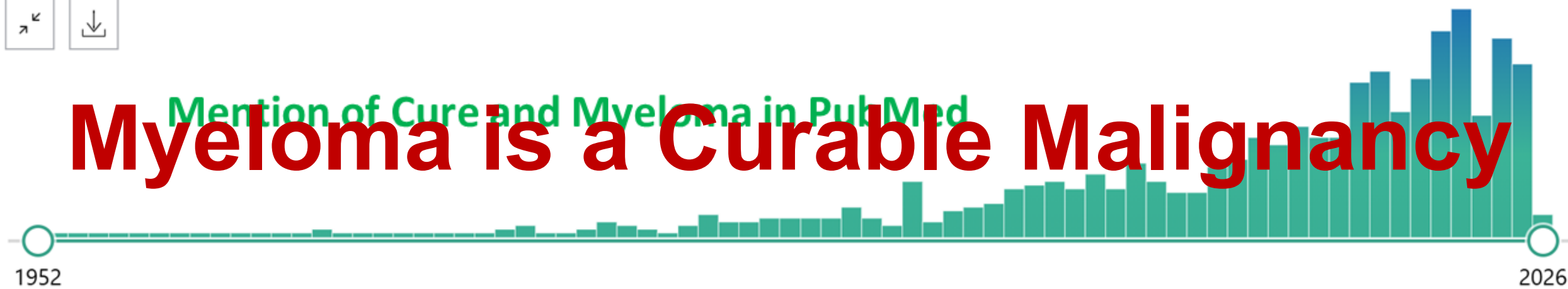
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Myeloma is a Curable Malignancy

Mention of Cure and Myeloma in Pub Med



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Conclusion - The Likely Future!

- **Treat early – define some SMM as MM or treat them as MM**
- **Getting deeper MRD negativity will be THE central focus of any therapy**
- **Innovative immune and biologic therapies used simultaneous and/or sequential will achieve an unprecedented level of responses in all stages of myeloma**
- **Cure means normal life without treatment**

Myeloma is a Curable Malignancy





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