Are we ready for Pragmatic Trials in Multiple Myeloma?

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Disclosures

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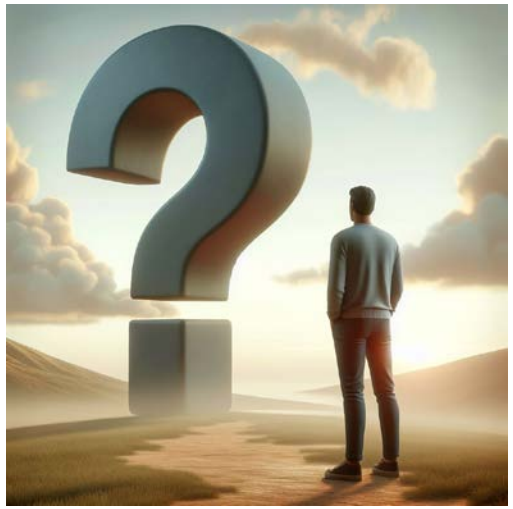
Research Support: BMS, Kite Pharma, Janssen and Novartis

Honoraria: Gilead

Outline

- **What are Pragmatic Trials?**
- Why do pragmatic trials and why in multiple myeloma?
- How to run a pragmatic trial?



Pragmatic Trials – *definition*

…”*Pragmatic trials inform a clinical or policy decision by providing evidence for adoption of (an) intervention(s) into real-world clinical practice”….*

Schwartz, D and Lellouch J, J Chronic Dis, 1967

Pragmatic vs. Classic Explanatory Trials

	Pragmatic Trials	Explanatory Trials
Purpose	Seek to determine whether an intervention works in real-world, everyday practice and to guide decision-making for clinical practice	Aim to understand whether a treatment works under ideal conditions and to discover if there is a difference between treatment
Patient Population	include a wider, more heterogeneous patient population with fewer selection criteria, better reflecting real-world diversity	have strict eligibility criteria to create a homogeneous patient group

Glasziou P et al, Journal of Royal Society of Medicine, 2023

Pragmatic vs. Classic Explanatory Trials

	Pragmatic Trials	Explanatory Trials
Intervention Flexibility	allow for more flexible and complex interventions, accounting for auxiliary treatments and the possibility of withdrawals	typically have strictly defined interventions with little flexibility
Outcome Measures	Focus on outcomes that are relevant to patients, clinicians, and policymakers, including broader considerations like costs	Often use biologically meaningful criteria or surrogate endpoints
Study Conditions	carried out under usual care conditions, reflecting real-world clinical practice	conducted under ideal, tightly controlled conditions

Glasziou P et al, Journal of Royal Society of Medicine, 2023

Pragmatic vs. Classic Explanatory Trials

	Pragmatic Trials	Explanatory Trials
Generalizability	high external validity and generalizability to inform real-world clinical decisions	have limited generalizability due to their ideal conditions and specific patient populations
Analysis Approach	use intention-to-treat analysis, including all randomized participants regardless of adherence	focus on per-protocol analysis, including only patients who adhered to the treatment protocol

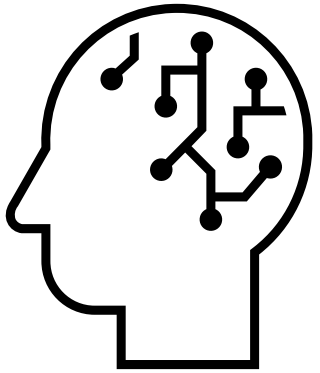
Glasziou P et al, Journal of Royal Society of Medicine, 2023

Table 1. Nine Dimensions for Assessing the Level of Pragmatism in a Trial, as Proposed in the Pragmatic–Explanatory Continuum Indicator Summary 2 (PRECIS-2) Tool.*

Dimension	Assessment of Pragmatism
Recruitment of investigators and participants	
Eligibility	To what extent are the participants in the trial similar to patients who would receive this intervention if it was part of usual care?
Recruitment	How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?
Setting	How different are the settings of the trial from the usual care setting?
The intervention and its delivery within the trial	
Organization	How different are the resources, provider expertise, and organization of care delivery in the intervention group of the trial from those available in usual care?
Flexibility in delivery	How different is the flexibility in how the intervention is delivered from the flexibility anticipated in usual care?
Flexibility in adherence	How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?
The nature of follow-up	
Follow-up	How different is the intensity of measurement and the follow-up of participants in the trial from the typical follow-up in usual care?
The nature, determination, and analysis of outcomes	
Primary outcome	To what extent is the primary outcome of the trial directly relevant to participants?
Primary analysis	To what extent are all data included in the analysis of the primary outcome?

* Information in the table is adapted from Loudon et al.[22]

How Pragmatic is a trial? 9 proposed dimensions



Ford I, Norrie J, NEJM 2016

FDA Project on Pragmatic Trials

- **Project Pragmatica** seeks to introduce functional efficiencies and enhance patient centricity by integrating aspects of clinical trials with real-world routine clinical practice through appropriate use of pragmatic design elements.

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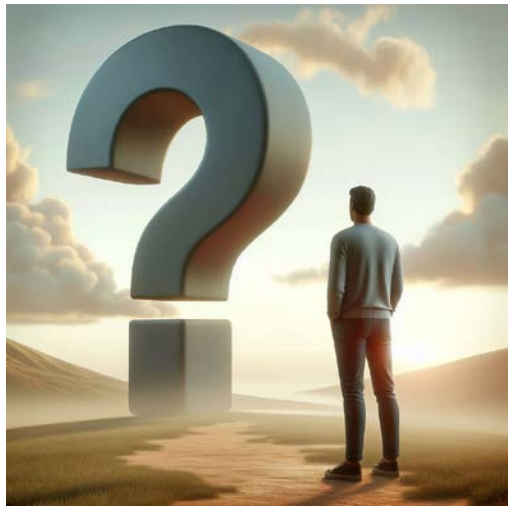
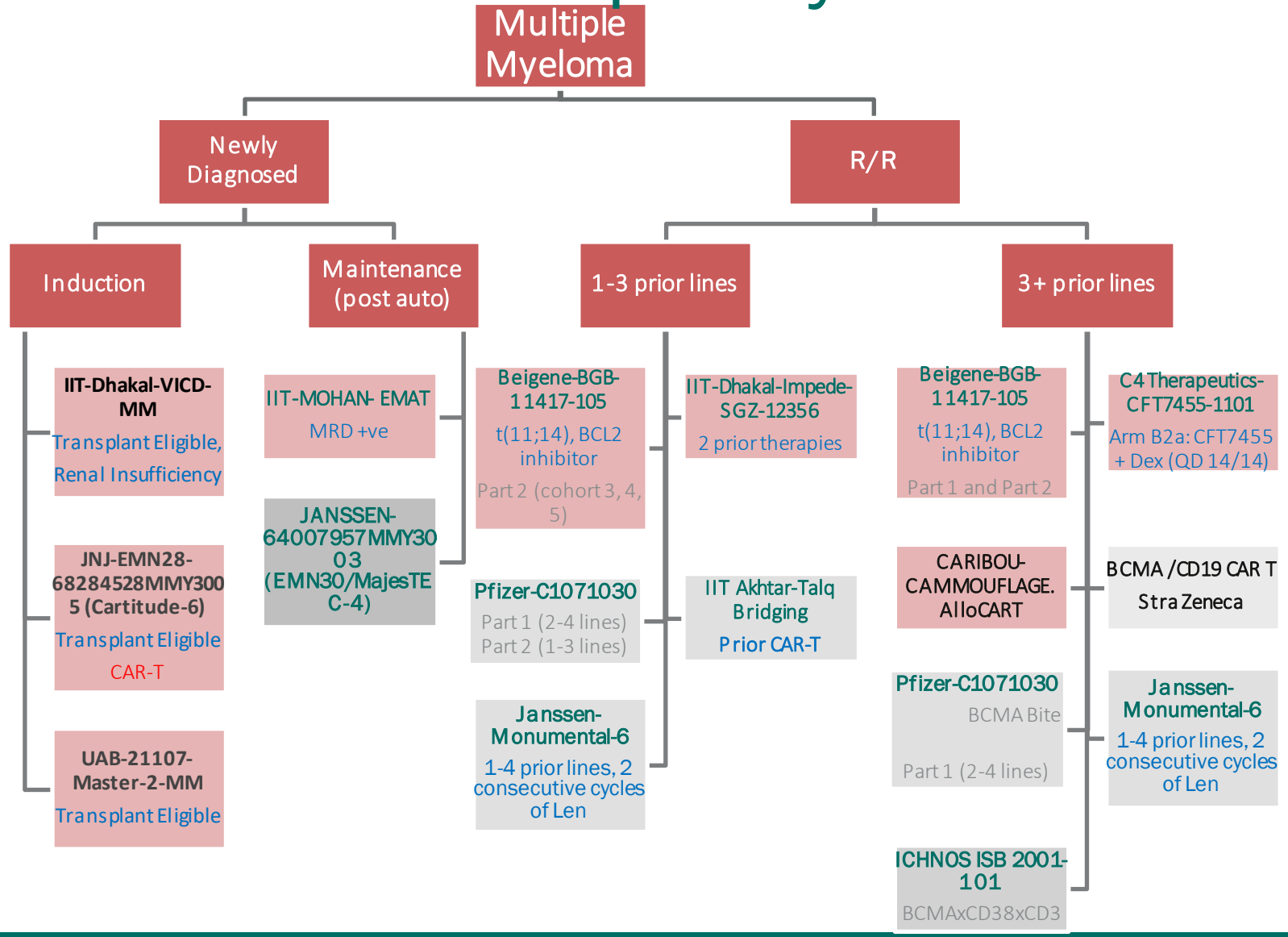


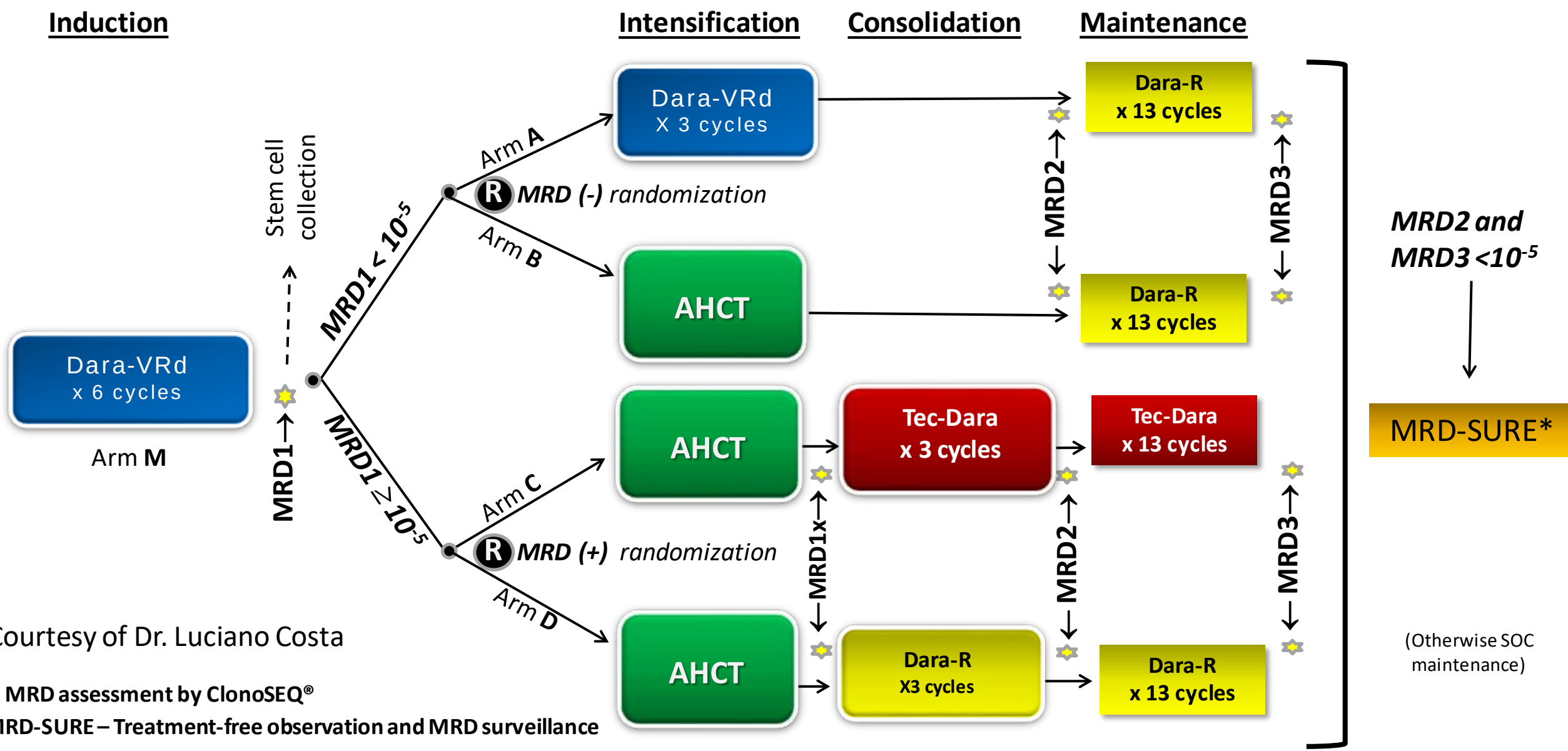
Why Pragmatic trials?

- Explanatory trials have increase in complexity and costs
  - Increase in regulatory stringency in the US which led to comprehensive requirements to ensure quality;
  - High operational standards, requiring state of the art facilities and highly skilled personnel
  - Recruitment challenges due to competing trials and fragmented healthcare system
  - Complexity in trial design
- Explanatory Trials still exclude populations
  - Trials are not available to all groups of patients – *Gaps in between trials*
  - Groups that are ineligible to trials – *Screen failures*

MCW PCD DOT: Multiple Myeloma Trials



MASTER-2 Clinical Trial: Risk- and Response-Adapted Trial

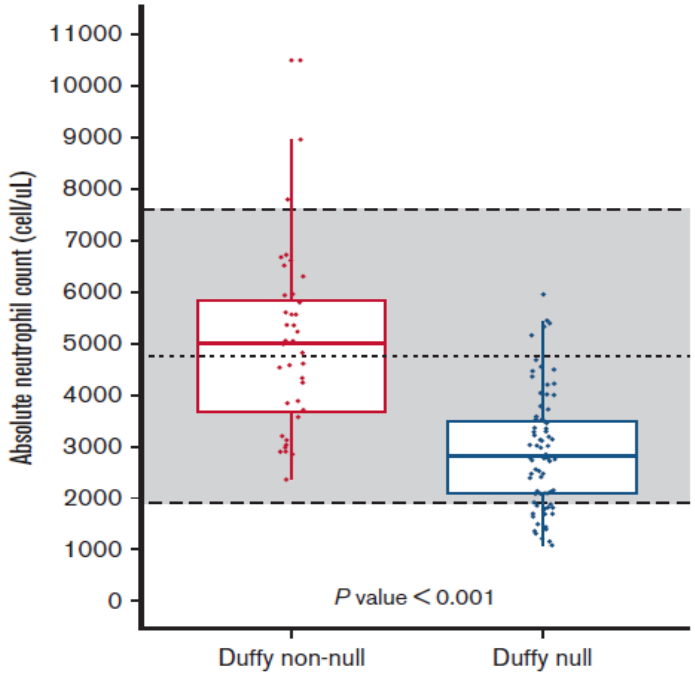


Courtesy of Dr. Luciano Costa

MRD assessment by ClonoSEQ®

*MRD-SURE – Treatment-free observation and MRD surveillance

Duffy Null phenotype: common in clinic; not a pathology



blood® Perspective

When non-Whiteness becomes a condition

Lauren E. Merz[1] and Maureen Achebe[2,3]

[1]Department of Internal Medicine, Brigham and Women's Hospital, Boston, MA; [2]Division of Hematology, Department of Internal Medicine, Brigham and Women's Hospital, Boston, MA; and [3]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

The term "benign ethnic neutropenia" describes the phenotype of having an absolute neutrophil count (ANC) <1500 cells/μL with no increased risk of infection. It is most commonly seen in those of African ancestry. In addition, ANC reference ranges from countries in Africa emphasize that ANC levels <1500 cells/μL are common and harmless. The lower ANC levels are driven by the Duffy null [Fy(a-b-)] phenotype, which is protective against malaria and seen in 80% to 100% of those of sub-Saharan African ancestry and <1% of those of European descent. Benign ethnic neutropenia is clinically insignificant, but the average ANC values differ from what are typically seen in those of European descent. Thus, the predominantly White American medical system has described this as a condition. This labeling implicitly indicates that common phenotypes in non-White populations are abnormal or wrong. We believe that it is important to examine and rectify practices in hematology that contribute to systemic racism. (*Blood*. 2021; 137(1):13-15)

BMT CTN Blood & Marrow Transplant Clinical Trials Network

Courtesy of Dr. Saurabh Chhabra on SWOG 1803 Trial

Merz LE et al. Blood Advances 2022, Blood 2021.

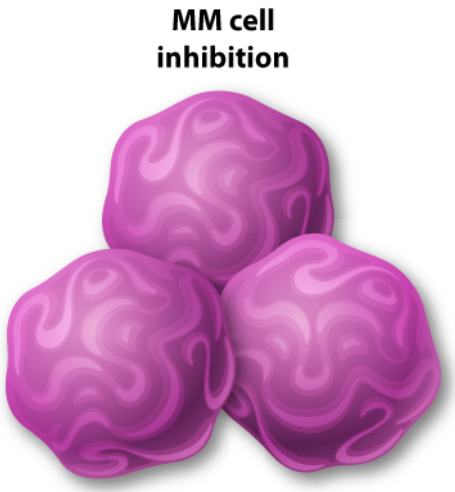
Why Pragmatic trials in MM?

- Large number of approved drugs that compete in its use at the same phases of care:
  - Initial therapy (maintenance), first progression, 4 or more lines of therapy, triple or penta refractory.
- The sequencing of agents are important as the use of one agent or combination may abrogate the use of another agent in the future.
- Different groups who did not enroll on trial and for which the results of an explanatory can only be extrapolated
- Longevity of therapy: most regimens are used until progression but there are many emerging side effects with forever therapies
- When outcomes in clinical trials are excellent, how does this translate to RW

Therapies available for MM: many single agents and multiple combinations

Agents	Frontline → Early RRMM	
IMiD agents	Lenalidomide Thalidomide	Pomalidomide Lenalidomide
Proteasome inhibitors	Bortezomib	Bortezomib Ixazomib Carfilzomib
Corticosteroids	Dexamethasone Prednisone	Dexamethasone
Antibodies	Daratumumab	Daratumumab Elotuzumab Isatuximab
Alkylating agents	Cyclophosphamide Melphalan	Cyclophosphamide
Other agents		Selinexor Venetoclax

Sorontoclax



- CELMoD agents
- Bispecific T-cell engagers targeting:
  - BCMA
  - GPRC5D
  - FcRH5
- ADCs targeting:
  - BCMA
- Car T-cells targeting:
  - BCMA
  - GPRC5D
  - SLAMF7

Raje N et al, Blood Cancer Journal 2023

Front Line MM Regimens

National Comprehensive Cancer Network®

Transplant Candidates

Preferred
RVD
KRD

Other recommended regimens
DaraRVD

Useful in certain circumstances
CyBorD
DoxoBorD
CyKD
DaraTVD
DaraCyBorD
DaraKRD
VTD-PACE
IsaRvd

Non-Transplant Candidates

Preferred
RVD
DaraRD

Other recommended regimens
DaraMelVP
KRD
DaraCyBorD

Useful in certain circumstances
Rd
Vd
CyBorD
RVDlite
CyKD
CyRD

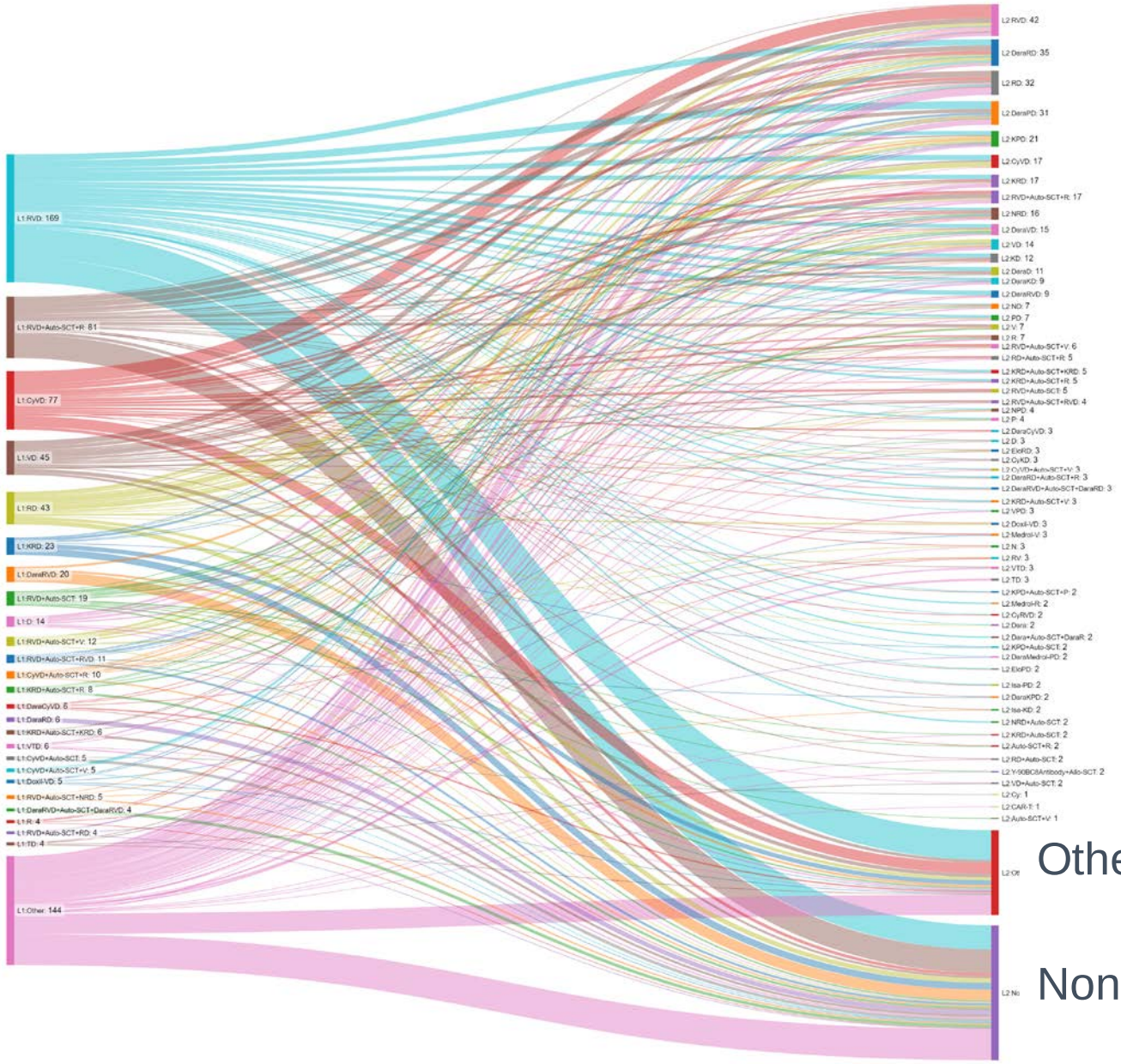
Courtesy of Tony Blau, MD, All4Cure

Every Patient is on a Unique Treatment Path

N = 736

LOT 1

Other



LOT 2

Other

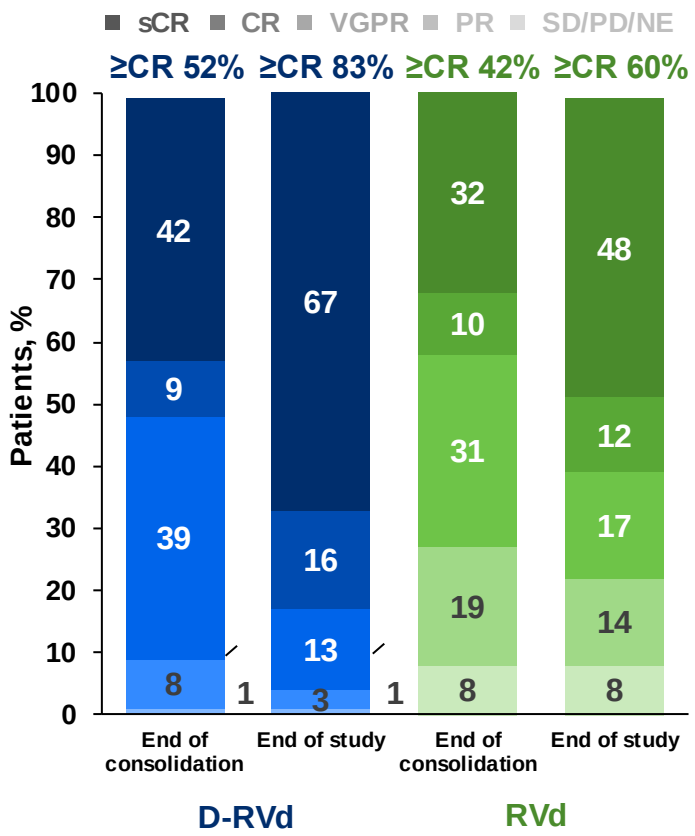
None

Courtesy of Tony Blau, MD, All4Cure

Dara-based quadruplet induction/consolidation + ASCT

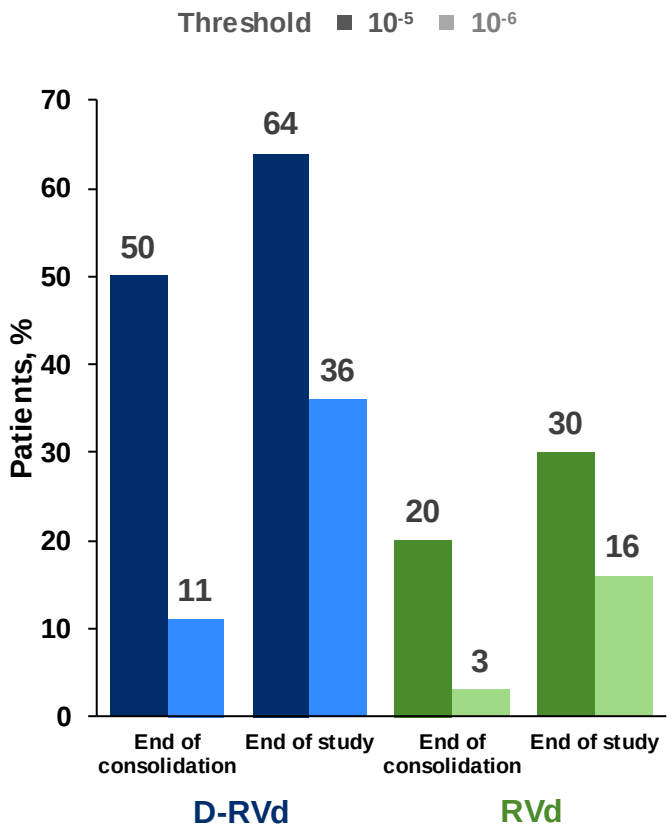
GRIFFIN:[1,2] Dara-RVd vs RVd – prolonged PFS, deepened responses

ORR



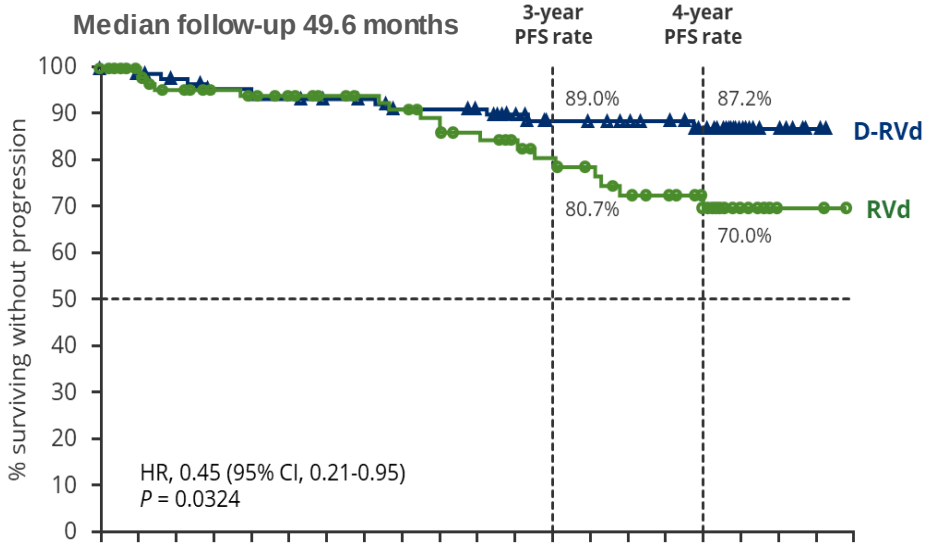
≥CR rates increased over time, with deepest responses at end of study

MRD-neg rate



14% vs 10% of patients converted from MRD-pos at end of consolidation to MRD-neg by end of study

PFS/OS in the ITT population for D-RVd versus RVd



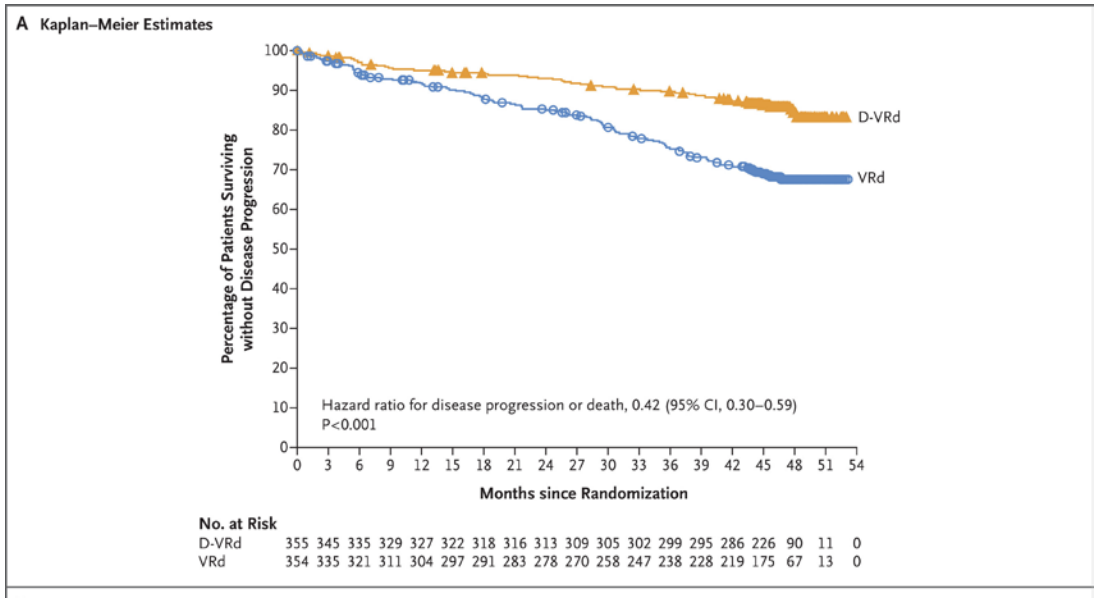
- PFS benefit seen across subgroups, including high-risk cytogenetics[3]
- Median OS not reached in either arm; 4-year OS with D-RVd vs RVd: 92.7% vs 92.2% (HR 0.90)

Safety data

- Hematologic Grade 3/4 AEs with D-RVd vs RVd: neutropenia (46% vs 23%), lymphopenia (23% vs 23%), leukopenia (17% vs 8%), thrombocytopenia (16% vs 9%), anemia (9% vs 6%)
- Non-hematologic Grade 3/4 AEs: PN (7% vs 9%), fatigue (7% vs 6%), diarrhea (7% vs 5%)
- AEs led to discontinuation in 33% vs 31% of patients (due to infections in 2% vs 3%)
- Minimal impact on stem cell mobilization, predictable stem cell harvesting and engraftment in all patients who underwent ASCT[4]

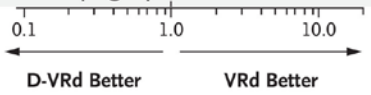
1. Voorhees PM, et al. Blood 2020;136(8):936–45. 2. Voorhees PM, et al. Lancet Haematol 2023;10(10):e825–37.
3. Chari A, et al. Blood Cancer J 2024;14(1):107. 4. Chhabra S, et al. Transplant Cell Ther 2023;29(3):174.e1–10.

Excellent Outcomes with Quadruple induction and Dara-Len Maintenance: PERSEU Study



B Subgroup Analyses

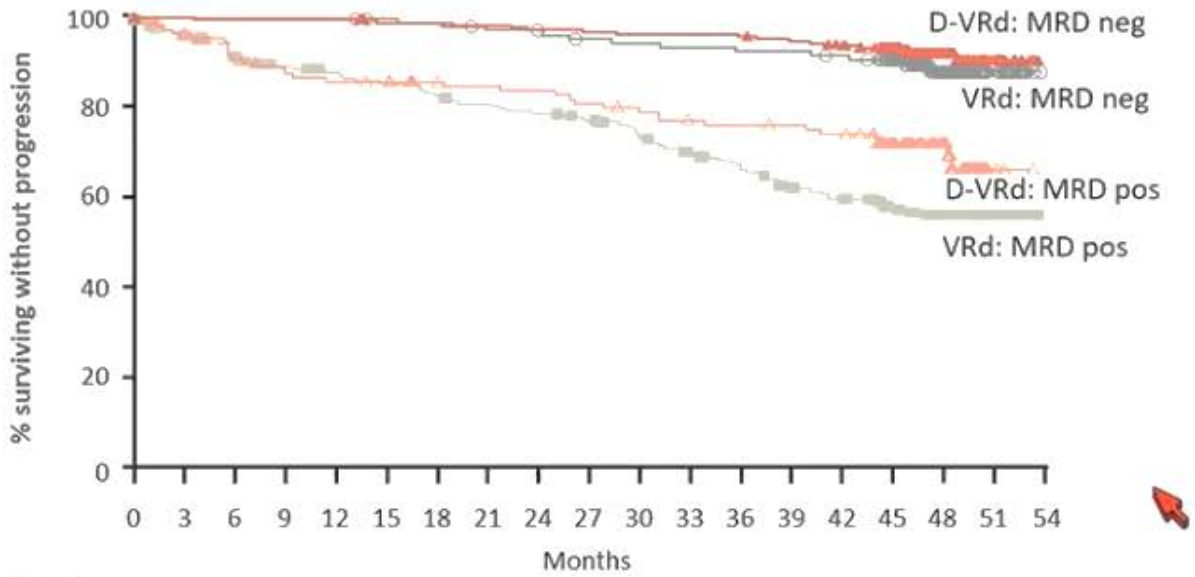
Subgroup	Disease Progression or Death		Median Progression-free Survival		Hazard Ratio for Disease Progression or Death (95% CI)
	D-VRd	VRd	D-VRd	VRd	
	no. of events/total no. of patients		*mo*		
Sex					
Male	36/211	61/205	NE	NE	0.51 (0.34–0.77)
Female	14/144	42/149	NE	NE	0.29 (0.16–0.53)
Age					
<65 yr	30/261	84/267	NE	NE	0.30 (0.20–0.46)
≥65 yr	20/94	19/87	NE	NE	0.97 (0.52–1.81)
Race					
White	47/330	95/323	NE	NE	0.42 (0.30–0.60)
Other	3/25	8/31	NE	NE	0.40 (0.11–1.50)
ISS disease stage					
I	18/186	35/178	NE	NE	0.46 (0.26–0.81)
II	19/114	43/125	NE	NE	0.37 (0.22–0.64)
III	13/55	25/50	NE	41.9	0.42 (0.22–0.83)
Type of multiple myeloma					
IgG	28/204	58/185	NE	NE	0.36 (0.23–0.57)
Non-IgG	13/78	31/96	NE	NE	0.46 (0.24–0.88)
Cytogenetic risk					
Standard	25/264	62/266	NE	NE	0.35 (0.22–0.56)
High	24/76	38/78	NE	44.1	0.59 (0.36–0.99)
Indeterminate	1/15	3/10	NE	NE	0.16 (0.02–1.56)
ECOG performance-status score					
0	28/221	60/230	NE	NE	0.42 (0.27–0.66)
≥1	22/134	43/124	NE	NE	0.41 (0.25–0.69)



Sonneveld P et al, NEJM 2023

PERSEUS: PFS by MRD-negativity Status (10^{-6}; ITT)

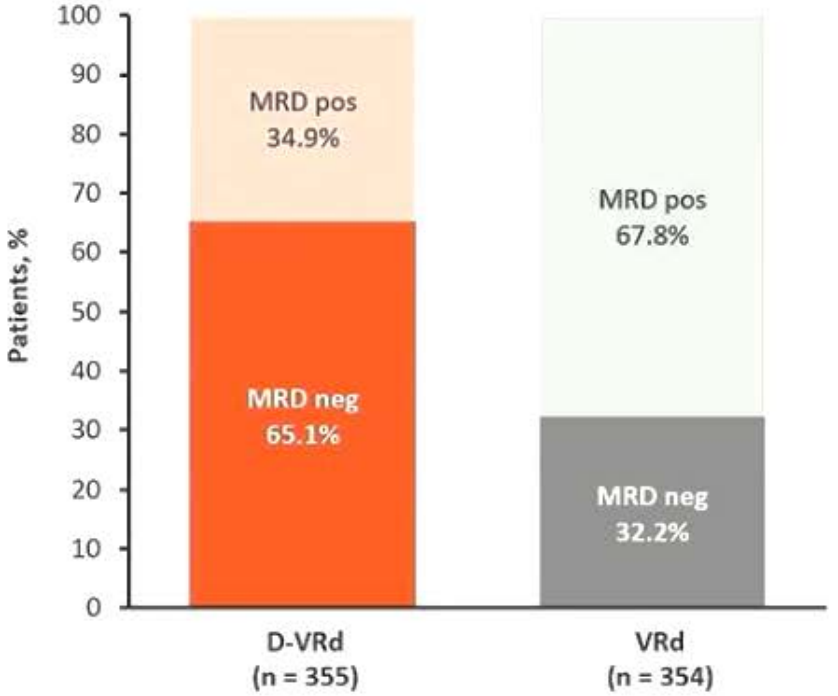
PFS according to MRD status (10^{-6})



No. at risk

VRd: MRD neg	114	114	114	114	114	112	111	108	107	104	103	102	101	101	98	87	34	9	0
D-VRd: MRD neg	231	231	230	230	230	226	226	225	223	222	221	221	219	216	210	169	70	10	0
VRd: MRD pos	240	221	207	197	190	185	180	175	171	166	155	145	137	127	121	88	33	4	0
D-VRd: MRD pos	124	114	105	99	97	96	92	91	90	87	84	81	80	79	76	57	20	1	0

Overall MRD negativity (10^{-6})

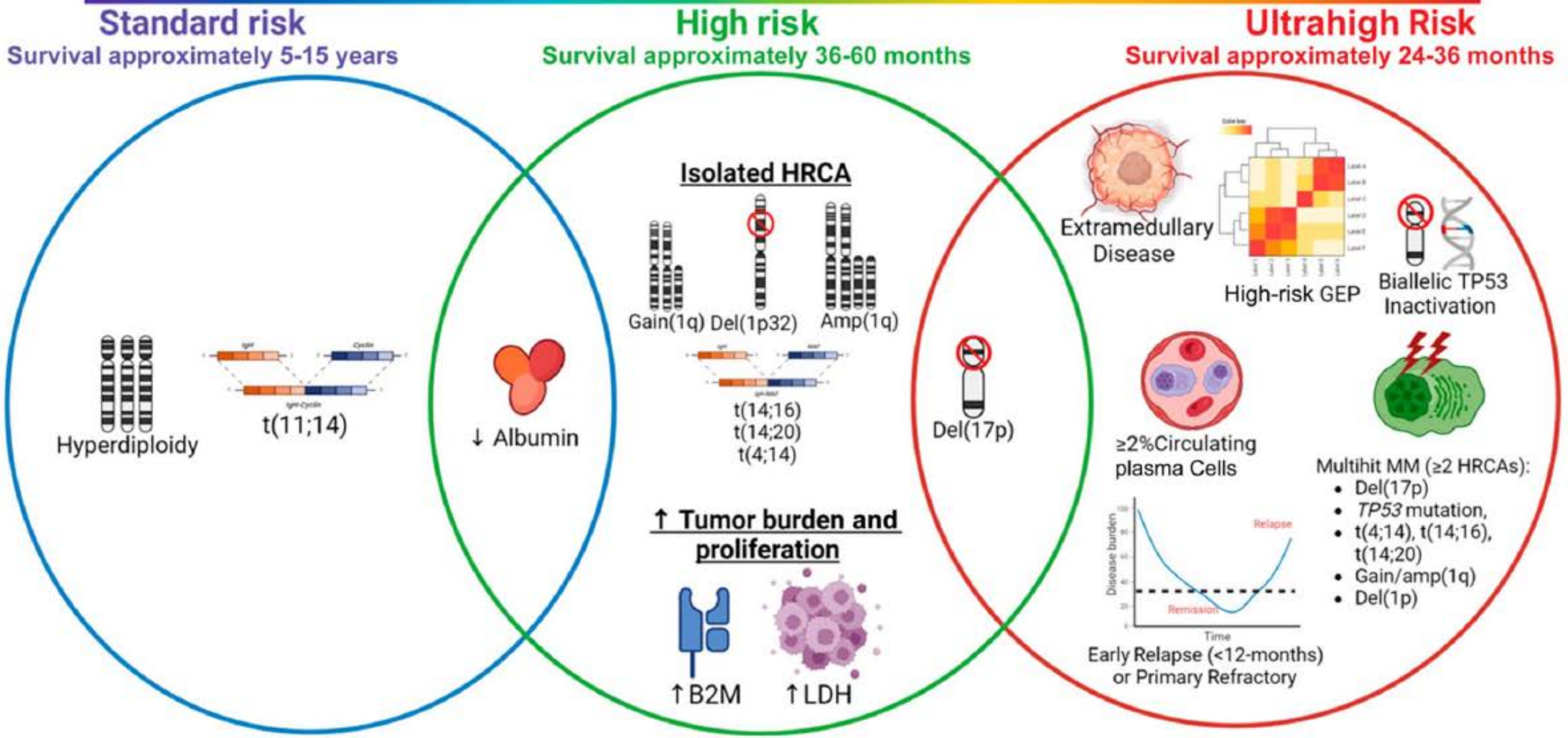


- **MRD negativity at 10^{-6} was associated with improved long-term outcomes**
- **Twice as many patients achieved MRD negativity at 10^{-6} with D-VRd + D-R versus VRd + R**
- **Patients remaining MRD positive had improved PFS with D-R maintenance versus R alone**

MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR in the ITT population. Patients who were not evaluable or had indeterminate results were considered MRD positive.

Presented by P Rodriguez-Otero at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 31-June 4, 2024; Chicago, IL, USA

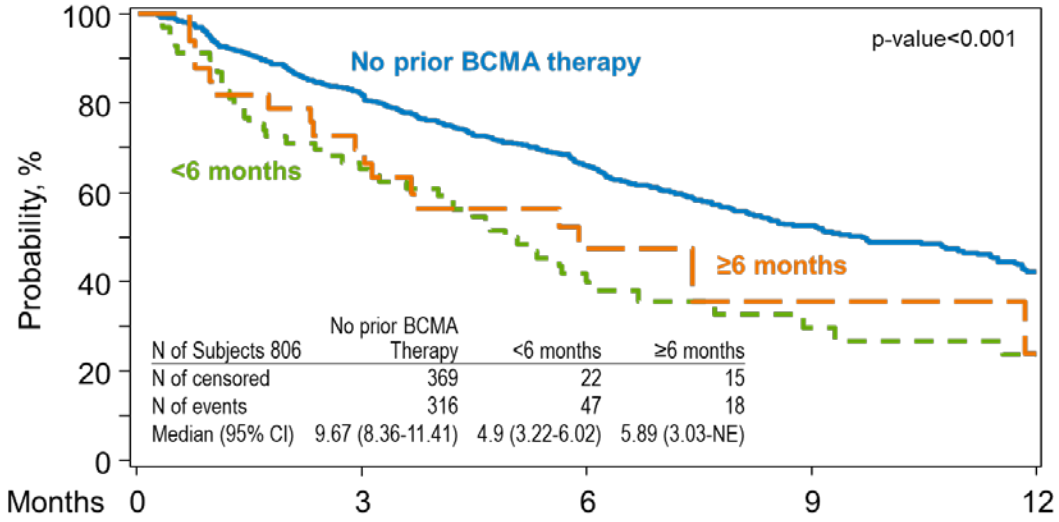
Myeloma Risk



Rees MJ, Am Soc Clin Oncol Educ Book, Vol 44, Issue 3, 2024

Ide-cel (Abecma) for treatment of Relapse Refractory Multiple Myeloma: Prior BCMA directed Therapy

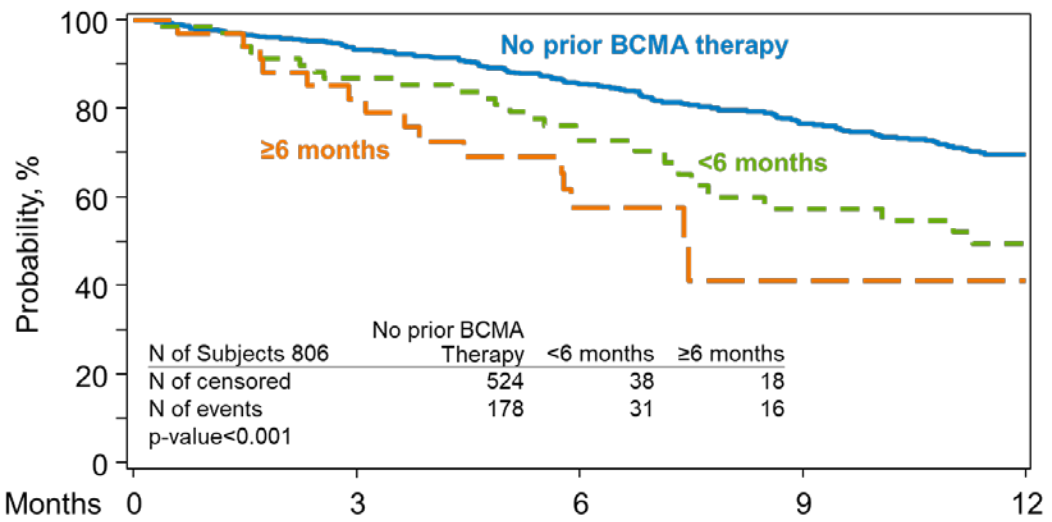
Progression-free Survival



N at Risk

No prior BCMA therapy	685	549	335	186	135
<6 months	69	45	21	10	8
≥6 months	33	22	10	3	2

Overall Survival



N at Risk

No prior BCMA therapy	702	642	451	281	234
<6 months	69	60	41	22	19
≥6 months	34	27	13	5	5

Prior BCMA therapy: Primarily belantamab mafodotin. This analysis excludes prior CAR-T therapy

Sidana S, Akthar O, et al ASH 2023

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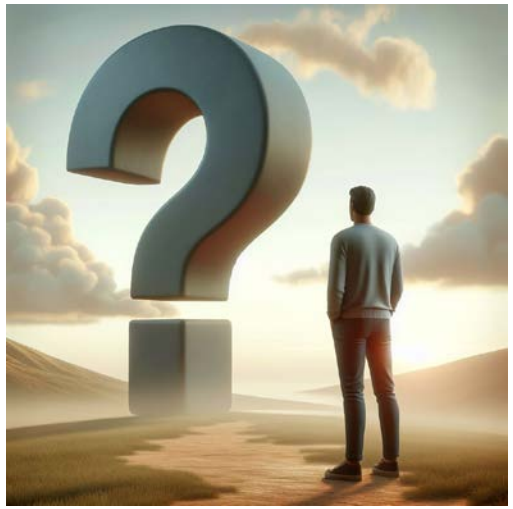
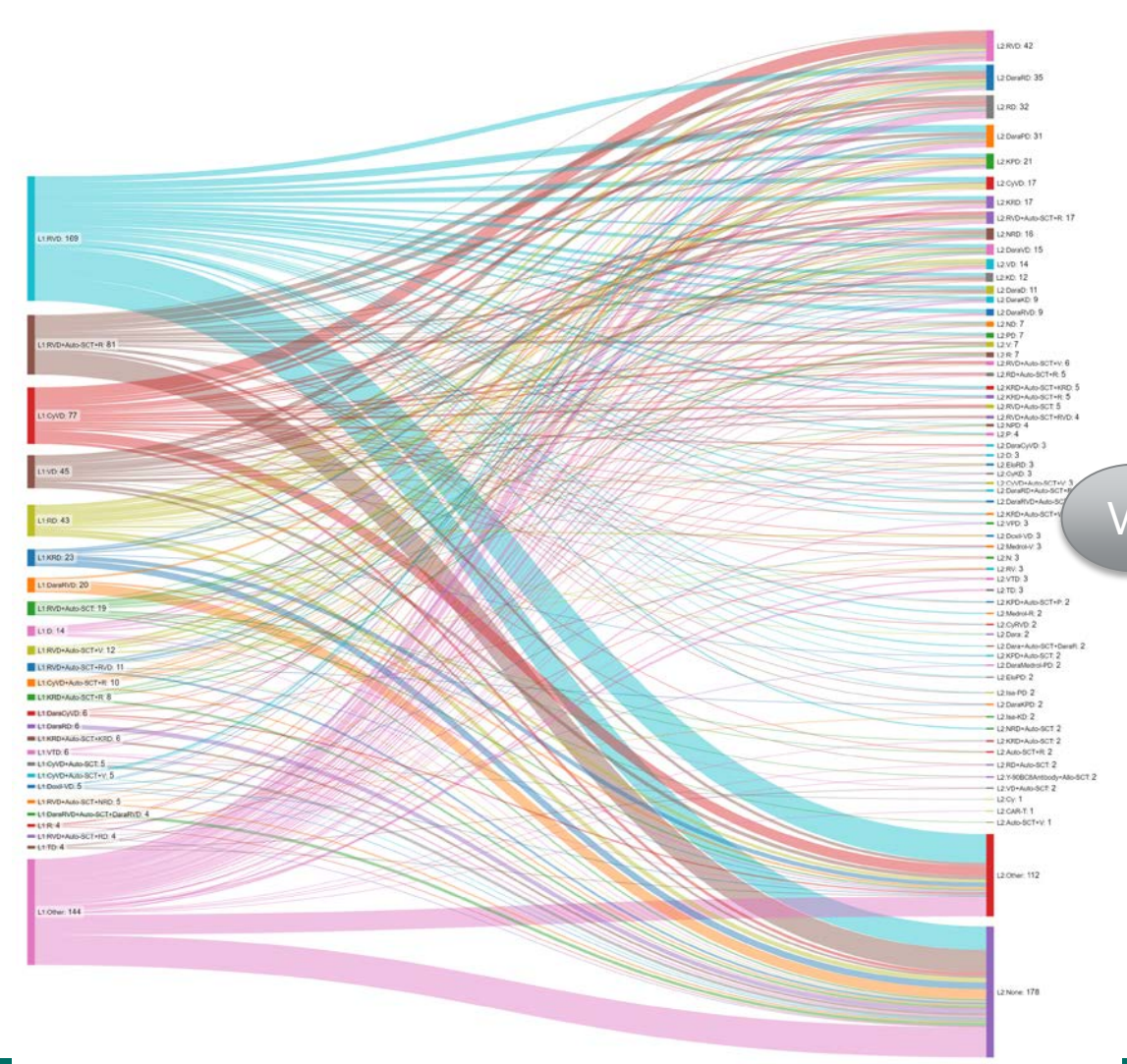


How to implement pragmatic trials?

- Assessment of the current and upcoming trial portfolio?
  - Filling the Gaps
- Should this single-institution, include other institutions or regional (WI)
- Explore the differences in SOC – considerations
  - Patient age, comorbidities, phase of the disease, prior treatment exposure

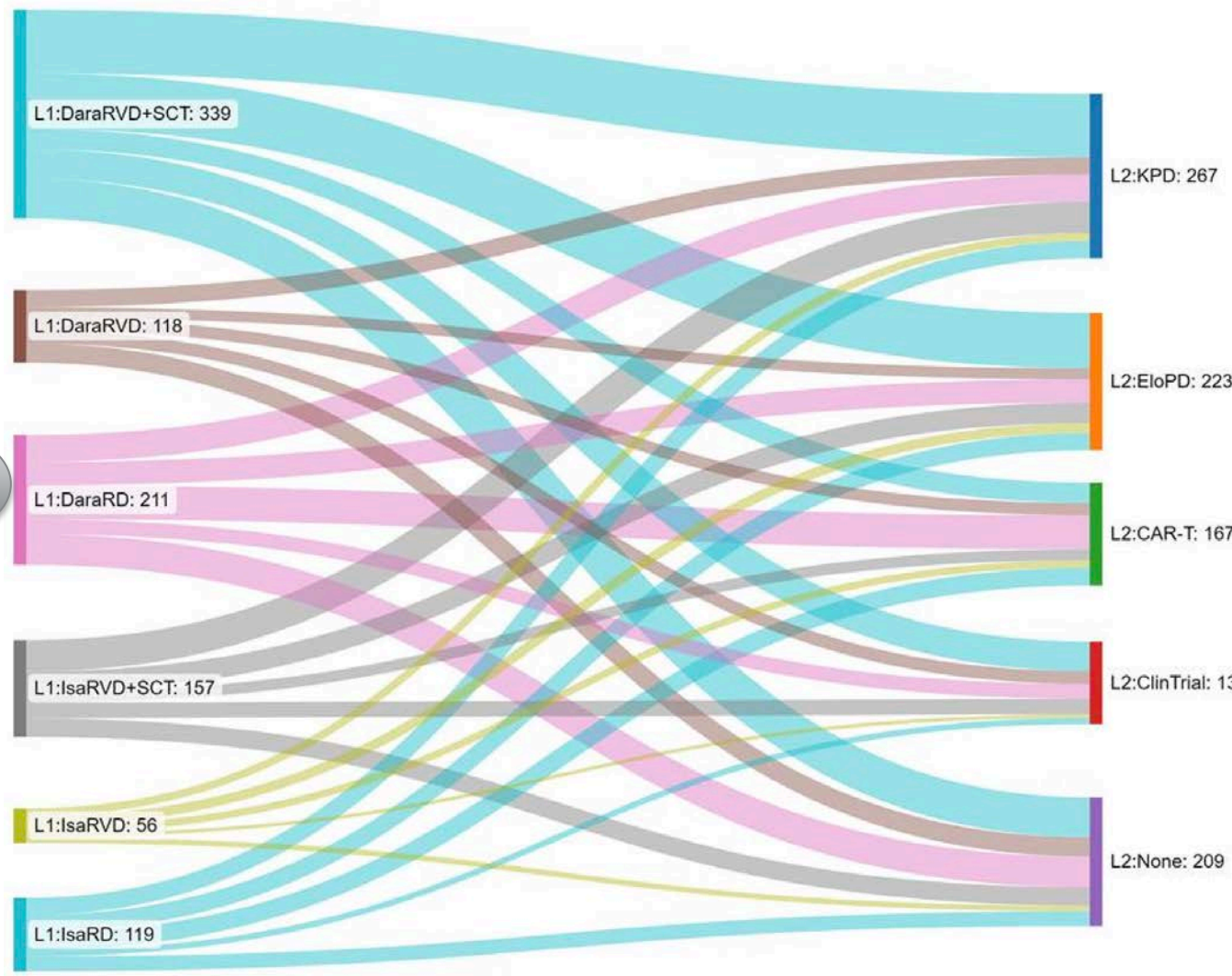
Designing Pragmatic Trials to test Treatment Paths

Current State



VS

New State



Courtesy of Dr. Tony Blau, All4Cure

How to implement pragmatic trials?

- Establish a path of therapy
- Trial ideas:
  - Upfront setting for patients with decrease renal function
  - Sequencing question: CAR T Cell timing
  - Early cessation of maintenance
  - Fixed time or varied schedule of BiteS
  - Incorporate alloHCT in certain situations
- Incorporate patient-centered outcomes
  - Freedom from treatment
  - Second PFS (PFS2)

MCW approach for alloHCT for MM

- Multiple Myeloma:
  - Age ≤ 50
  - High risk disease (Cytogenetic) or Ultra High Risk (≥2 HRCA, EMD, circulating plasma cells)
  - Upfront setting (No prior disease progression)
  - Disease in VGPR or better (ideally CR/MRD neg)
  - Second line: rapid progression (<18 months) from autoHCT
- Primary Plasma cell leukemia:
  - Age ≤ 70 years
  - Upfront setting (No prior disease progression)
  - Disease in VGPR or better
  - No circulating plasma cells

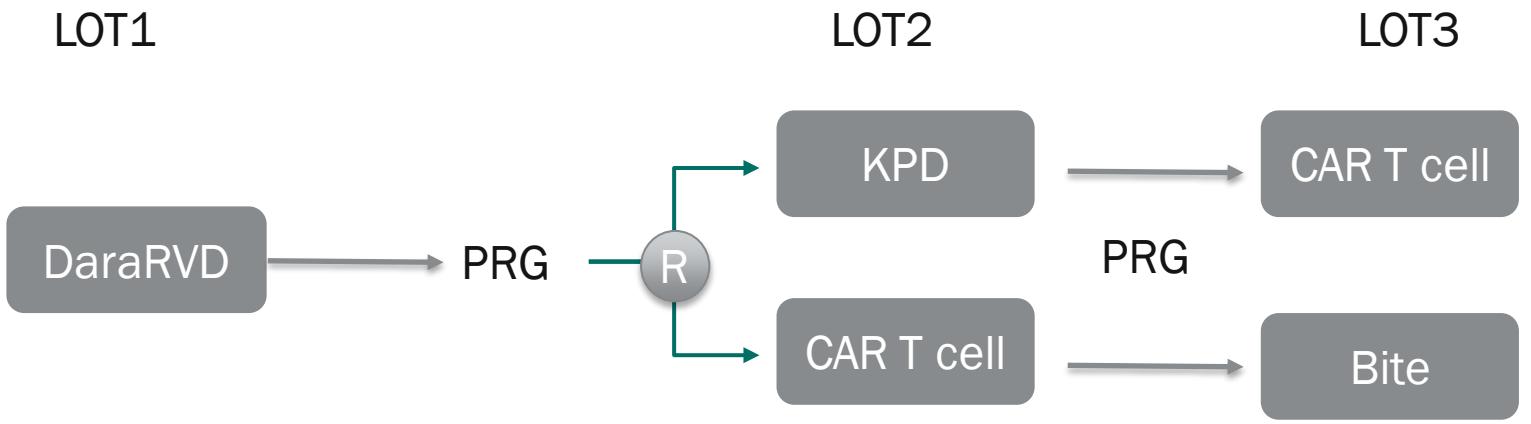
Pragmatic Trial Design

Considerations

- Age
- Commorbidities
- Treatment Era (Doublets, Triplets, Quads)
- Time (response to most recent progression)
- Prior responses
- Patient compliance
- Socio economic factors (insurance, education, rural/urban)

Data collection and approaches:
- EHR integration would be ideal

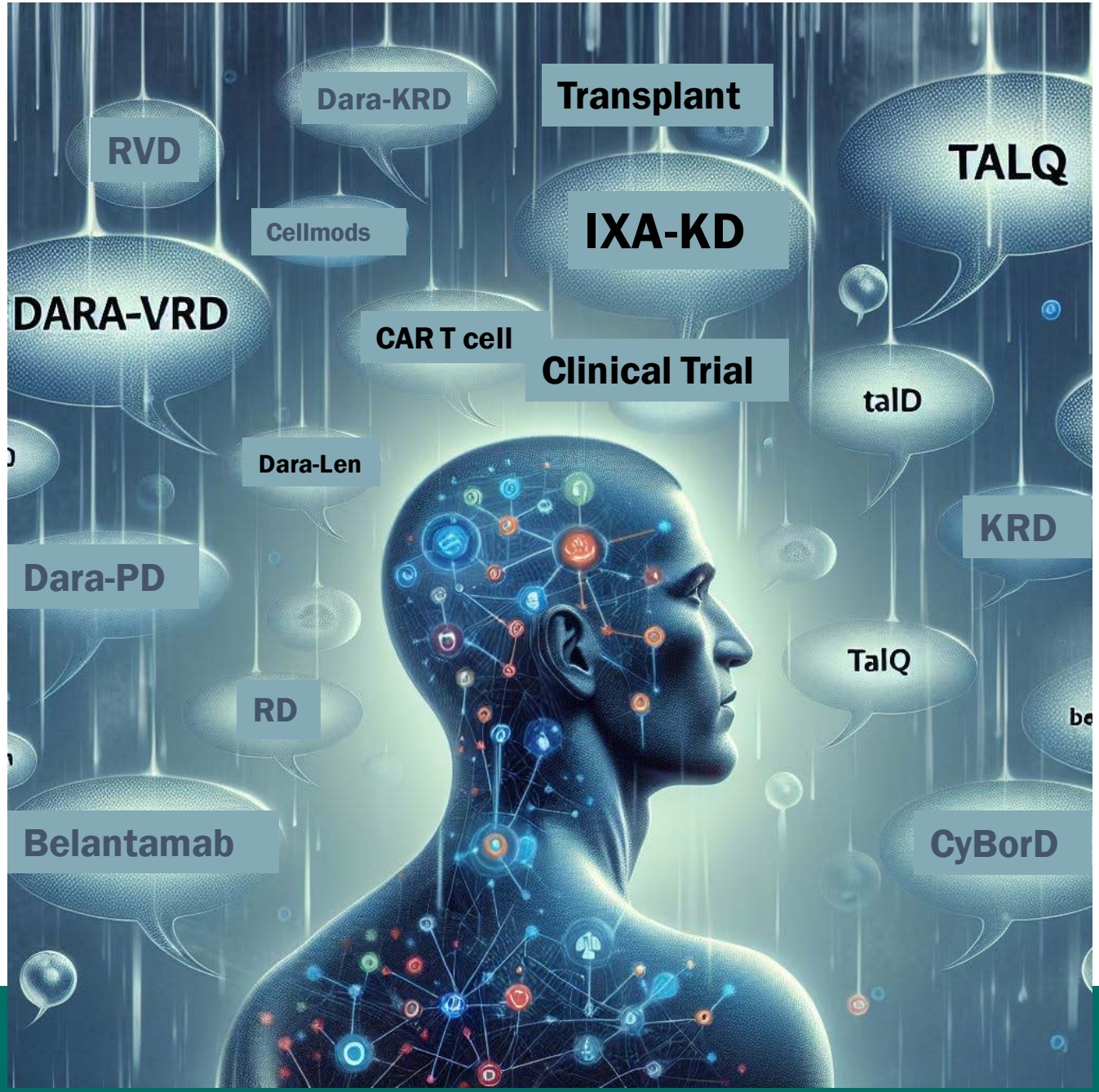
Simplified Scenario



Freedom from Treatment
PFS2
Overall survival

Integration of AI in Therapy Clinical Decision Making

- Pragmatic trials can add another dimension the design of explanatory trials:
  - Improve efficiency: trial simulation and protocol optimization
- Improve predictions of how therapies perform in the real world setting.



Pragmatic Trials in Multiple Myeloma

- Important tool to assess outcomes of patients with multiple myeloma in the real-world setting.
- Variety of treatment options approved with questions on how to sequence them could be tested through a pragmatic trial tool.
- Include all comers and investigate the true impact of certain therapies.
- Foster collaboration across institutions as it helps standardize therapies and recognize gaps in care.

Thank You!