Progress and challenges in the use of endpoints in cancer development:
the example of multiple myeloma

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Disclosures

Name of Company	Research support	Employee	Consultant	Major Stockholder	Speakers' Bureau	Scientific AdBoard	Honoraria
Adaptive							X
Amgen	X						X
Beigene	X						
Becton Dickinson	X						X
Bristol-Myers Squibb	X		X			X	X
GlaxoSmithKline	X		X			X	X
Janssen			X			X	X
Roche	X		X			X	X
Sanofi	X		X			X	X
Takeda	X		X				X
The Binding Site							X

State of the art in some mature B-cell neoplasms

- The overarching aim of treatment is optimally cure: enduring complete clinical remission regardless of the presence of late sequelae of treatments, for the duration of the patient's nature life span
  - On vs off treatment?

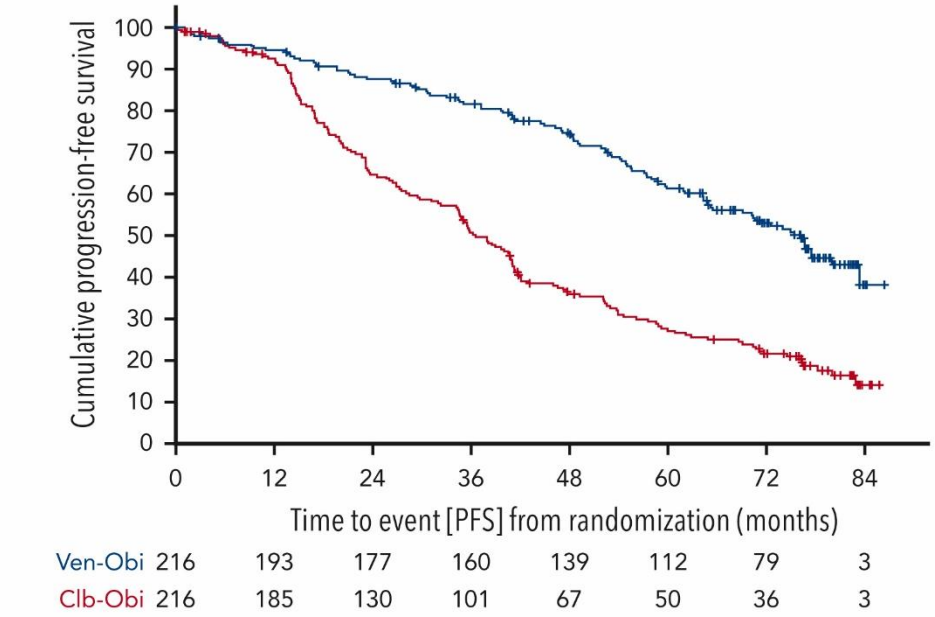
- Overall survival (OS) is considered the most important endpoint in clinical trials

- OS has shifted from primary to secondary endpoint in many clinical trials due to the often very long observation periods required (10 years or longer)
  - Some patients may be cured but not all
  - Unmet clinical needs that must be solved in a reasonable amount of time

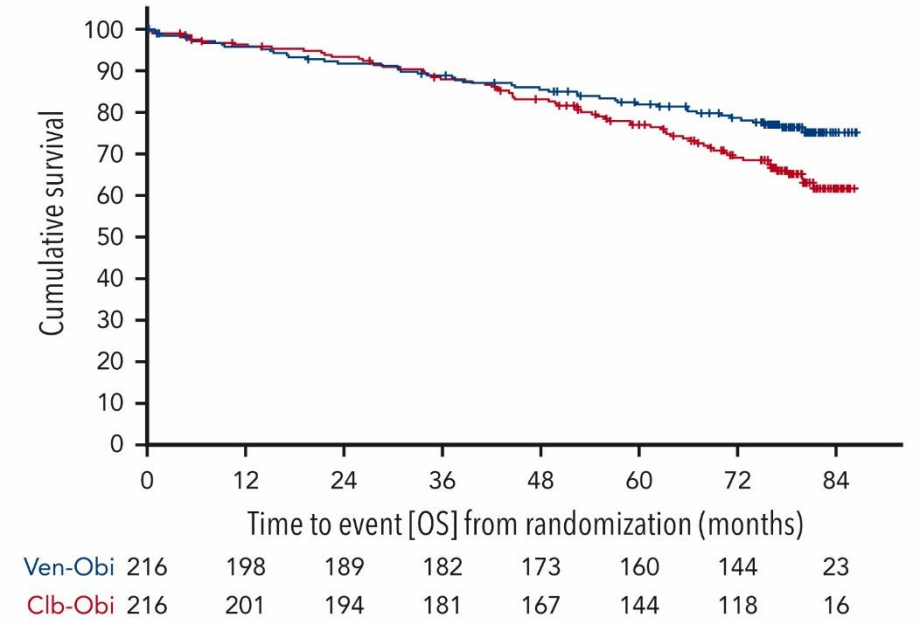
- Prolongation of progression-free survival (PFS) usually results in a prolongation of OS, particularly in the frontline setting
  - Even PFS differences will become increasingly difficult to capture
  - Longer PFS is not always a reliable surrogate of OS due to the increasing number and efficacy of options for salvage treatments, as well as due to patient crossover.

Venetoclax-obinutuzumab for previously untreated CLL: 6-year results of the randomized phase 3 CLL14 study

PFS



OS

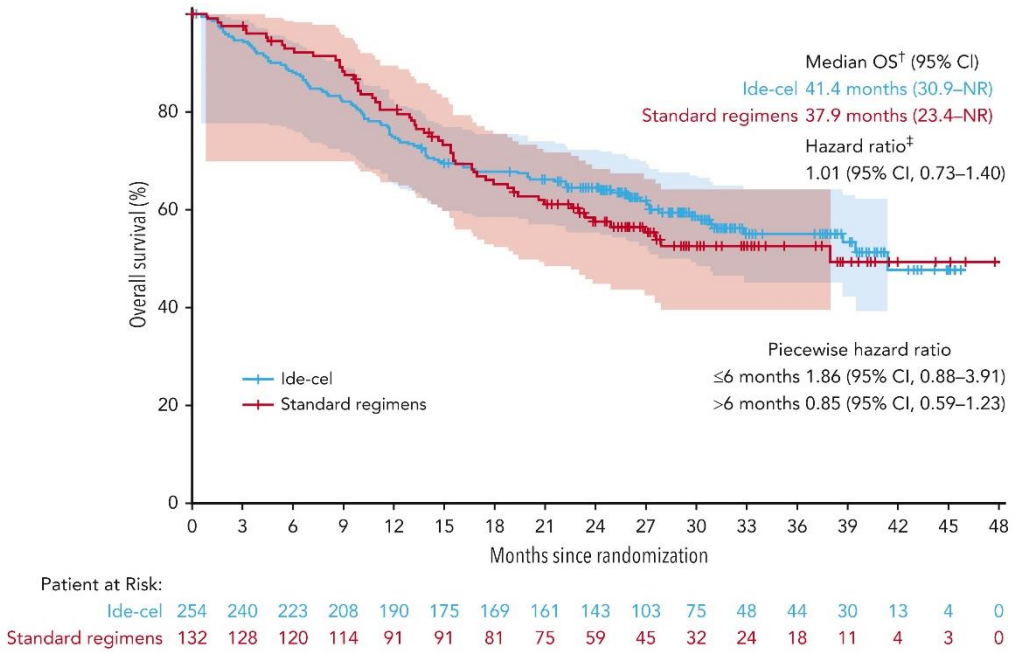


Al-Sawaf O, et al. Blood. 2024 Oct 31;144(18):1924-1935.

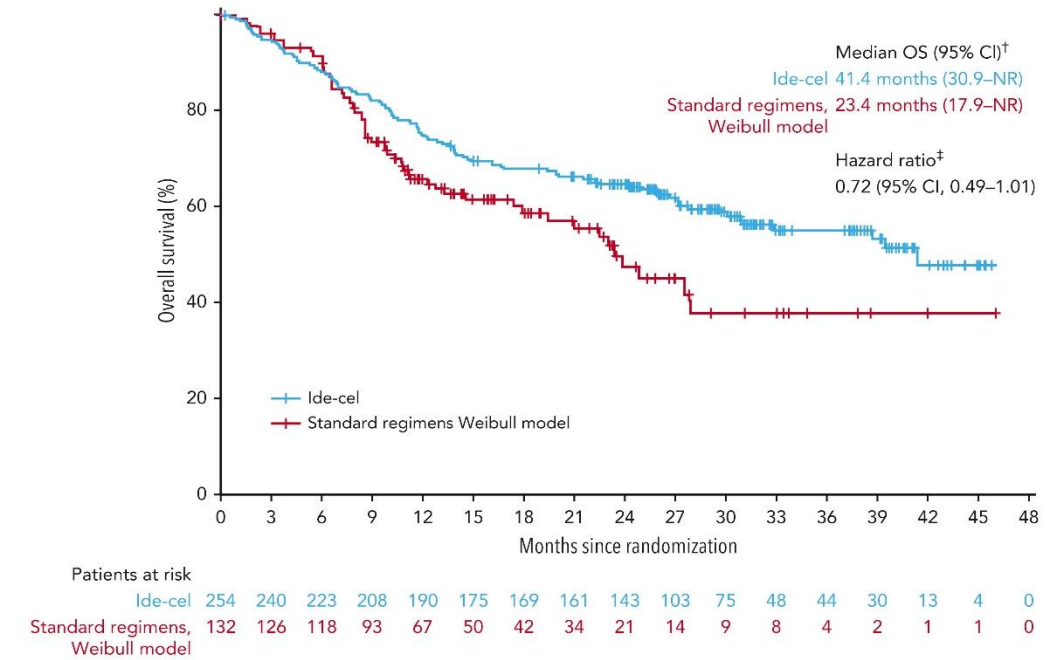
KarMMa-3: Ide-cel vs SOC in triple-class–exposed RRMM

PFS (primary end point) 13.3 vs 4.4 months; HR: 0.49, P < .0001

ITT population

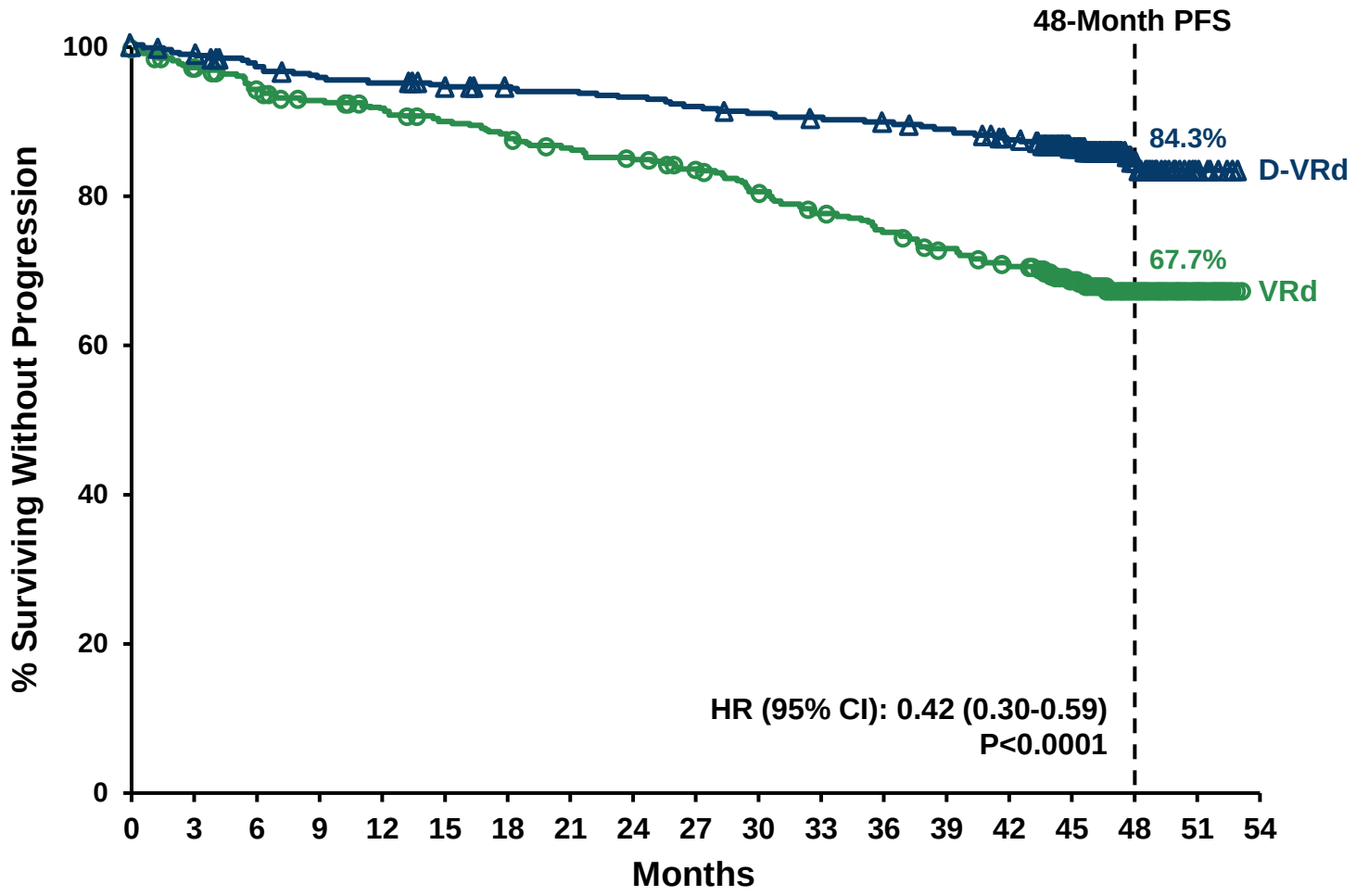


Adjusted for crossover



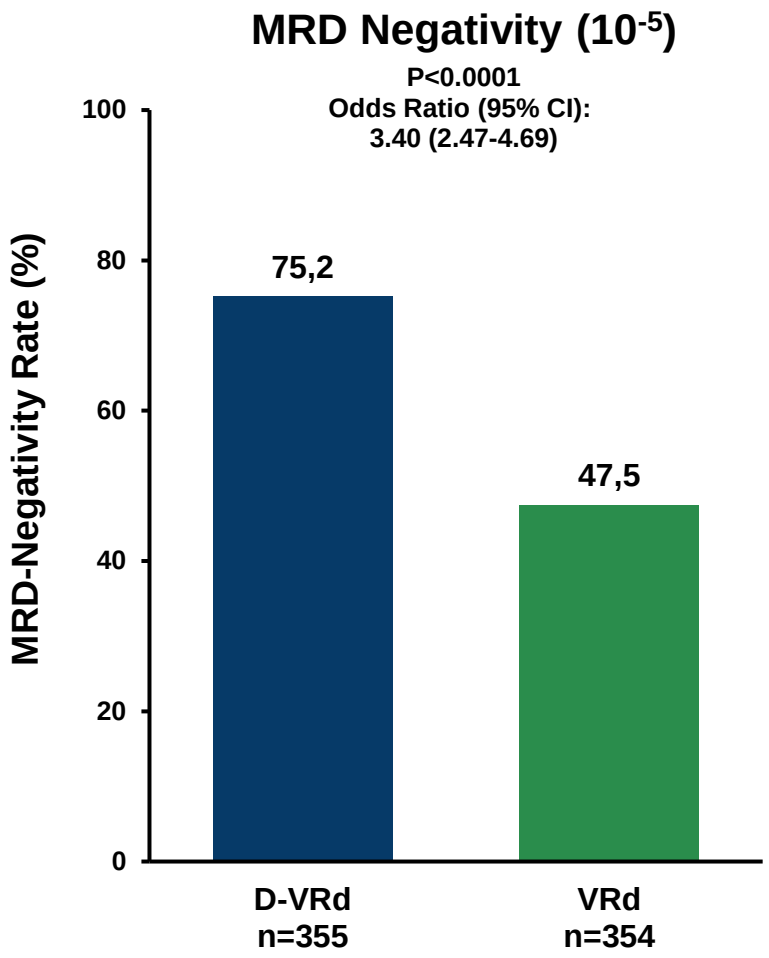
Ailawadhi S, et al. Blood. 2024 Dec 5;144(23):2389-2401.

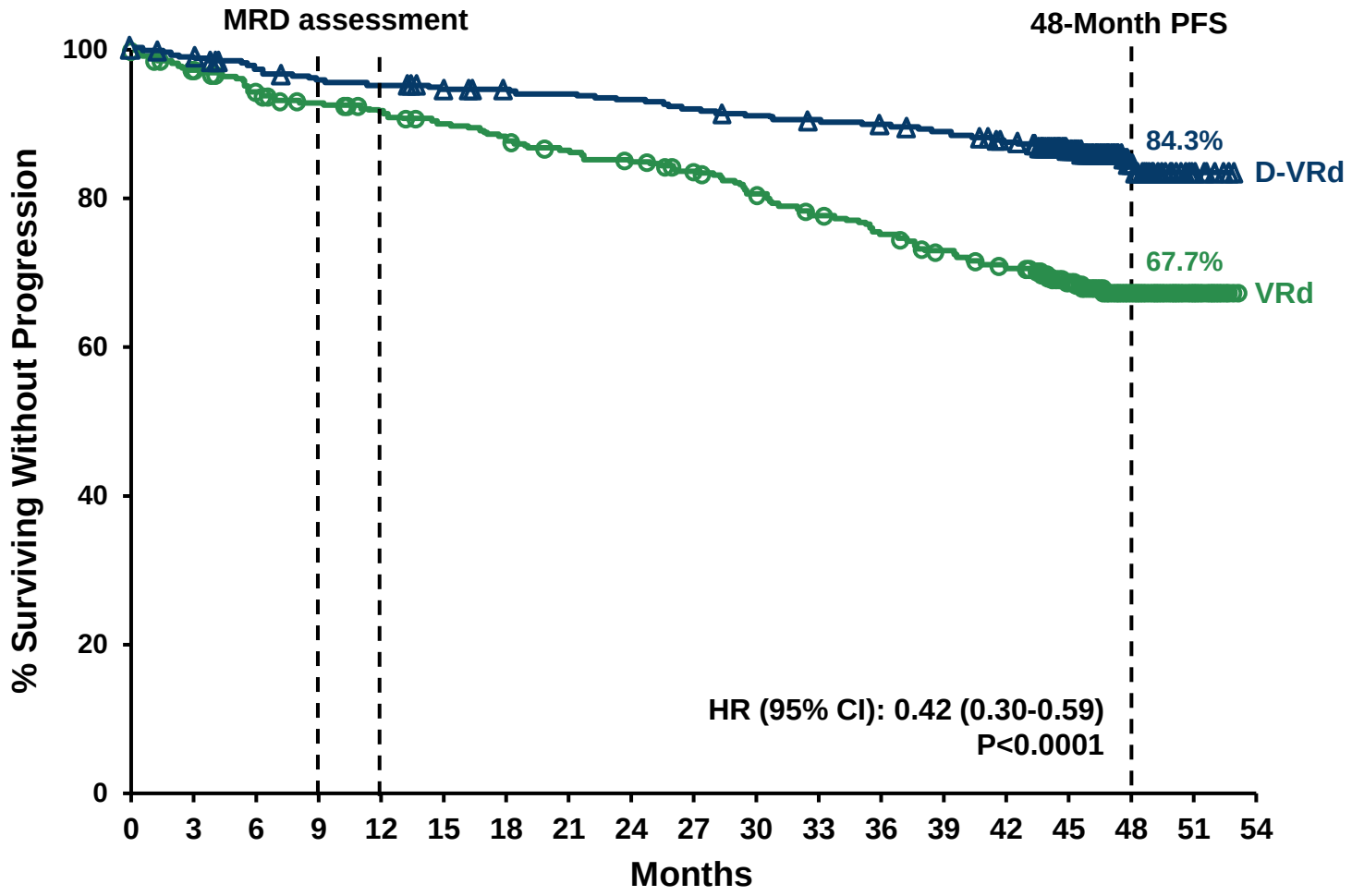
Median PFS in newly-diagnosed transplant-eligible MM patients may surpass 10 years (e.g., PERSEUS)



Sonneveld P, et al. N Engl J Med. 2024 Jan 25;390(4):301-313.

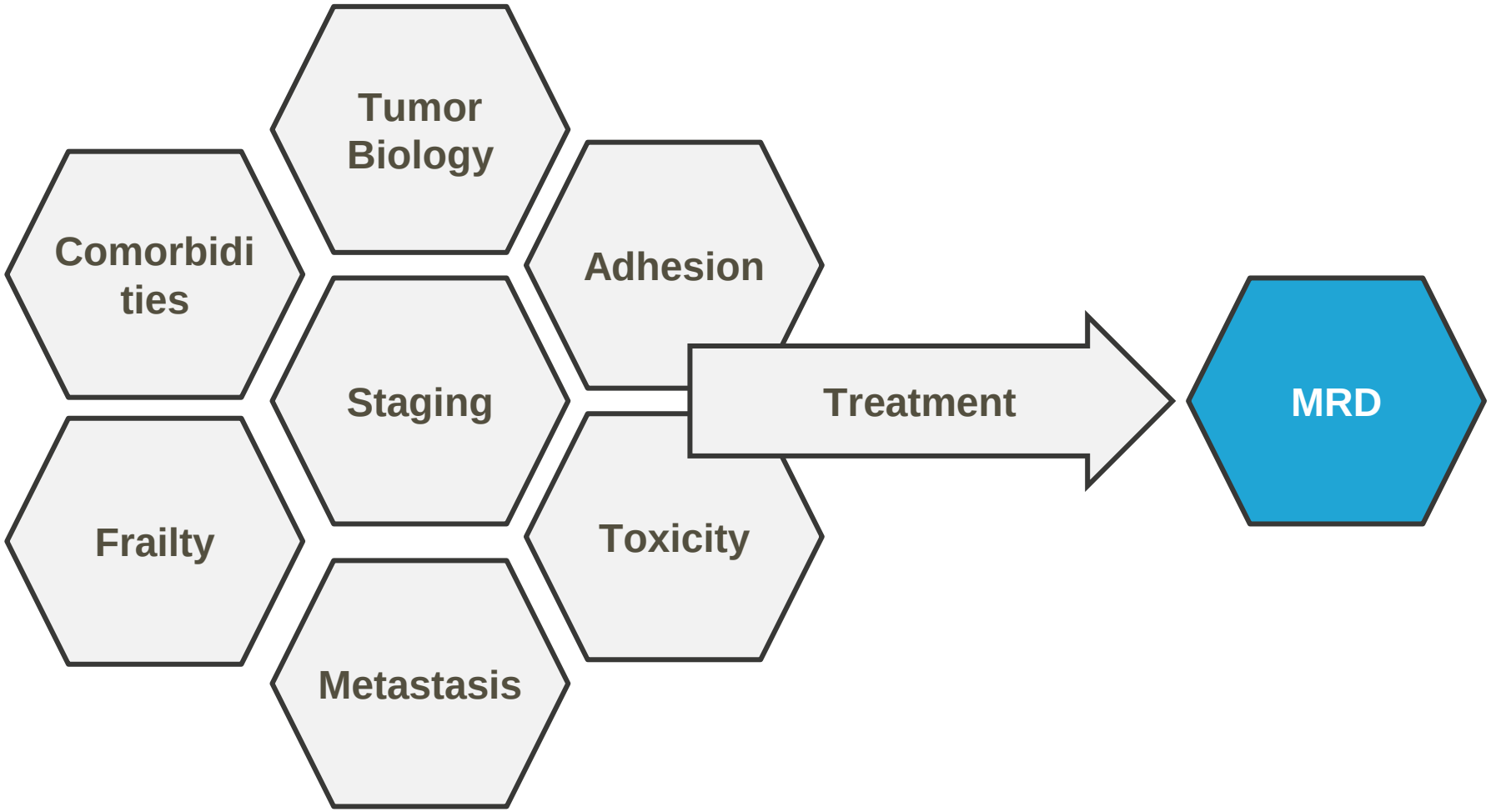
Median PFS in newly-diagnosed transplant-eligible MM patients may surpass 10 years (e.g., PERSEUS)





Sonneveld P, et al. N Engl J Med. 2024 Jan 25;390(4):301-313.

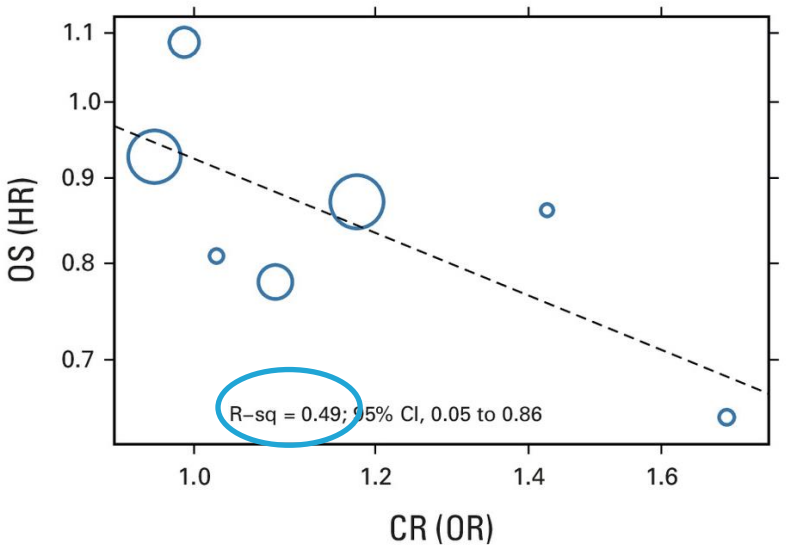
Why MRD?


Tumor Biology
Comorbidities
Adhesion
Staging
Frailty
Toxicity
Metastasis
Treatment
MRD

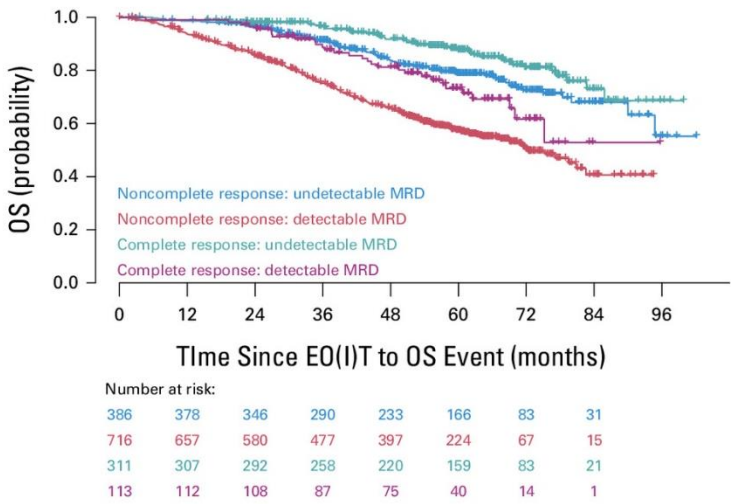
Why not CR?

MRD negativity is the new CR

AML[1]



CLL[2]



MM[3]

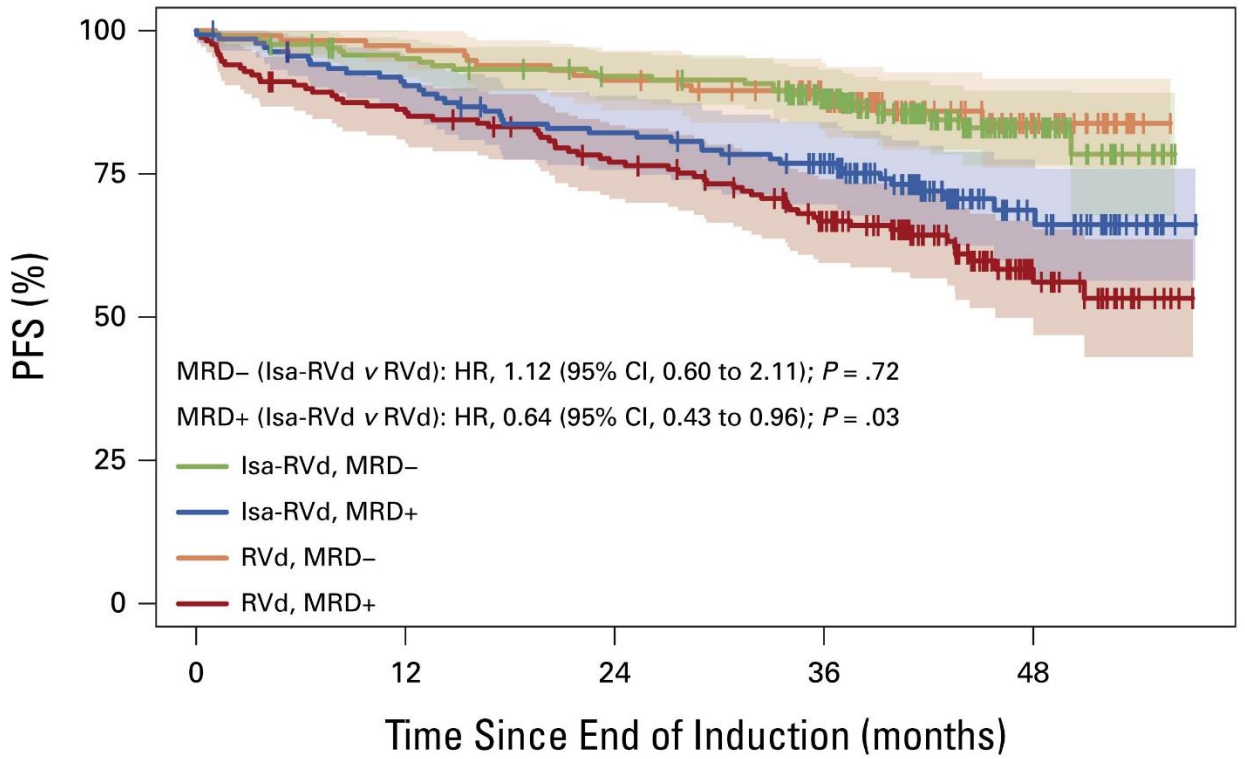
CR rates in GMMG-HD7 trial (secondary endpoint)

Isa-VRD vs VRD: 24% vs 22%

FL: the exception[4]

1. Norsworthy KJ, et al. J Clin Oncol. 2022 Mar 10;40(8):847-854.
2. Simon F, et al. J Clin Oncol. 2025 Feb;43(4):381-391.
3. Goldschmidt H, et al. Lancet Haematol. 2022 Nov;9(11):e810-e821.
4. Shi Q, et al. J Clin Oncol. 2017 Feb 10;35(5):552-560.

Impact of MRD status on PFS in the GMMG-HD7 trial



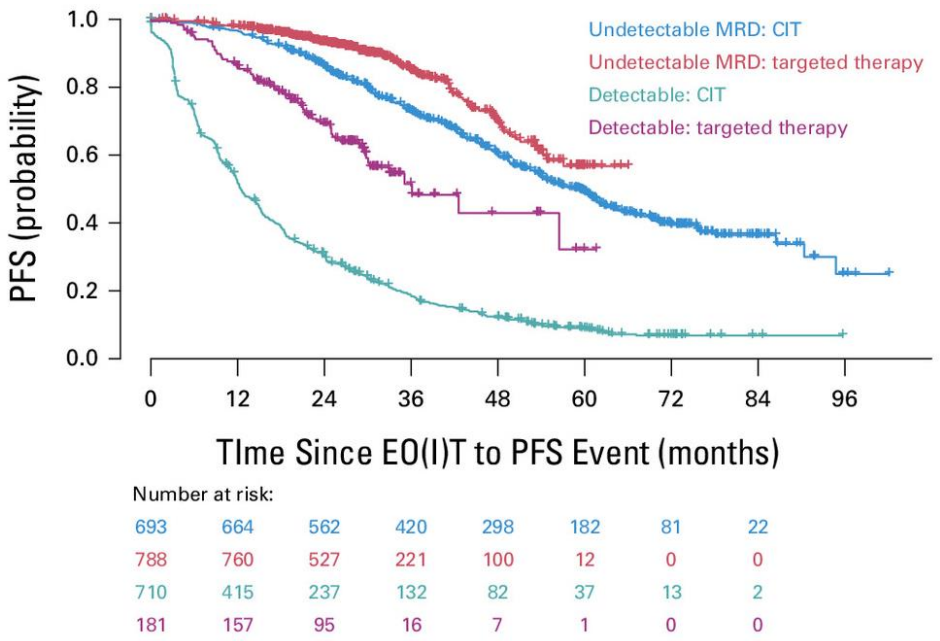
Number at risk (censored):						
Isa-RVd, MRD–	166 (0)	154 (4)	145 (4)	123 (16)	36 (82)	0 (35)
Isa-RVd, MRD+	136 (0)	122 (1)	109 (2)	95 (7)	27 (61)	0 (26)
RVd, MRD–	116 (0)	112 (1)	105 (0)	87 (15)	26 (58)	0 (26)
RVd, MRD+	168 (0)	142 (2)	124 (4)	98 (10)	26 (64)	0 (24)

Mai EK, et al. J Clin Oncol. 2024 Dec 9:JCO2402266.

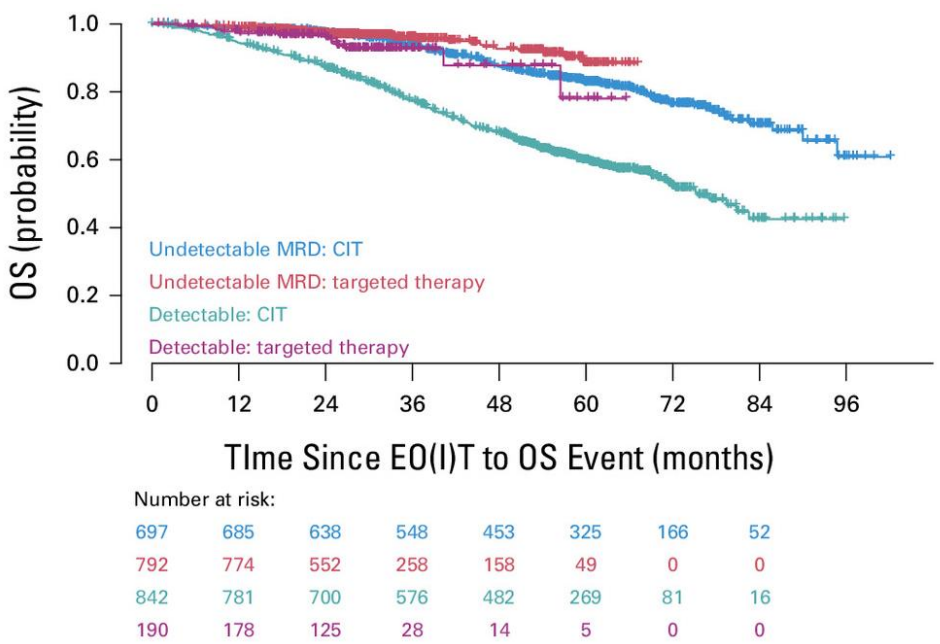
End Point Surrogacy in First-Line CLL

PFS HR of 4.74 // OS HR of 3.0

PFS



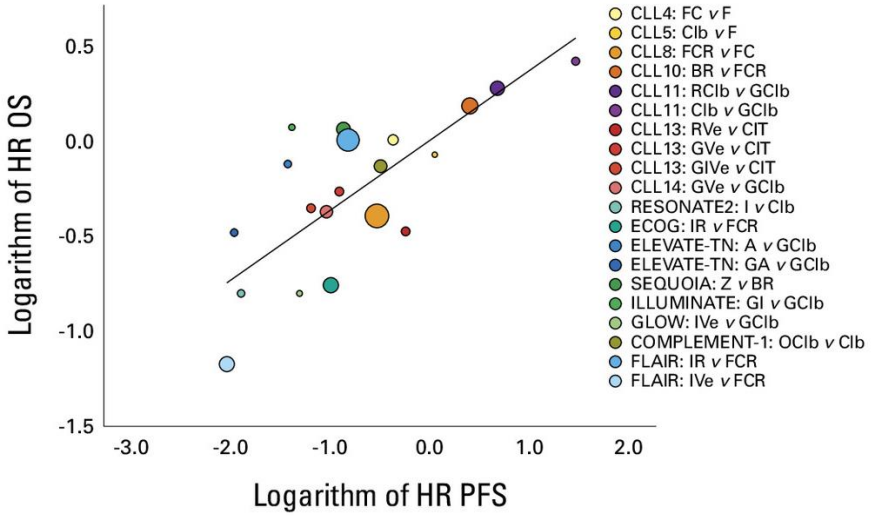
OS



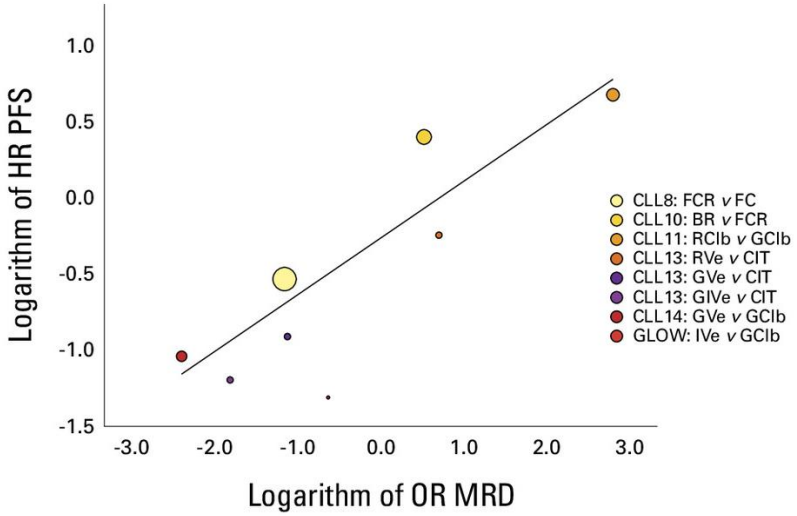
Simon F, et al. J Clin Oncol. 2025 Feb;43(4):381-391.

End Point Surrogacy in First-Line CLL

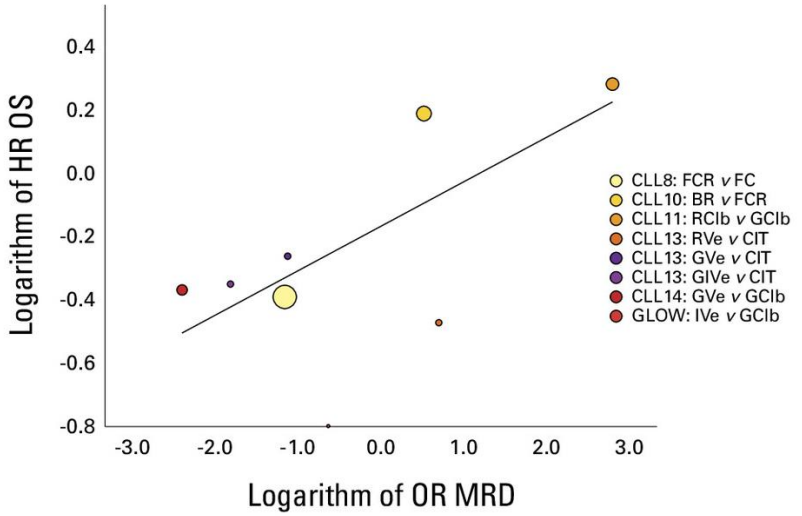
$R^2 = 0.56$



$R^2 = 0.78$

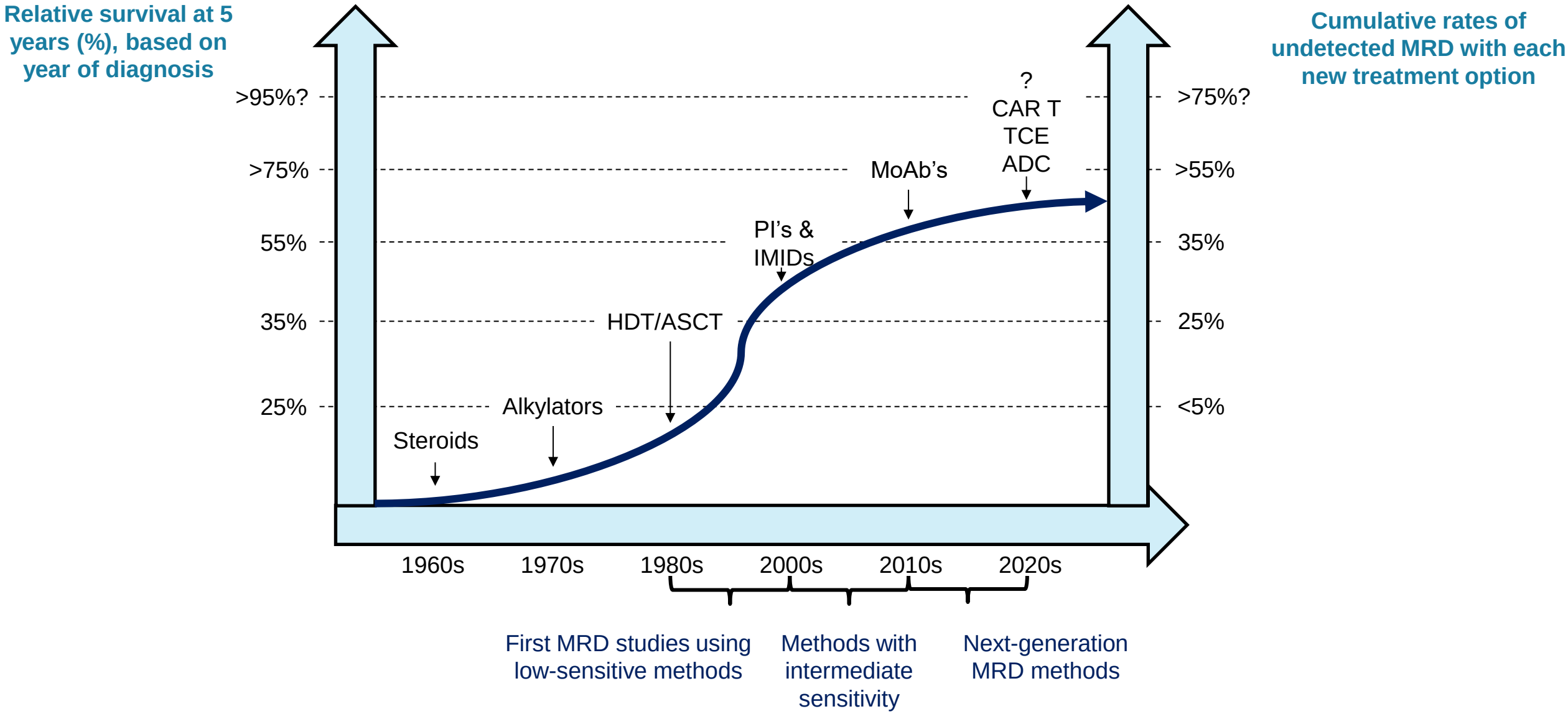


$R^2 = 0.5$



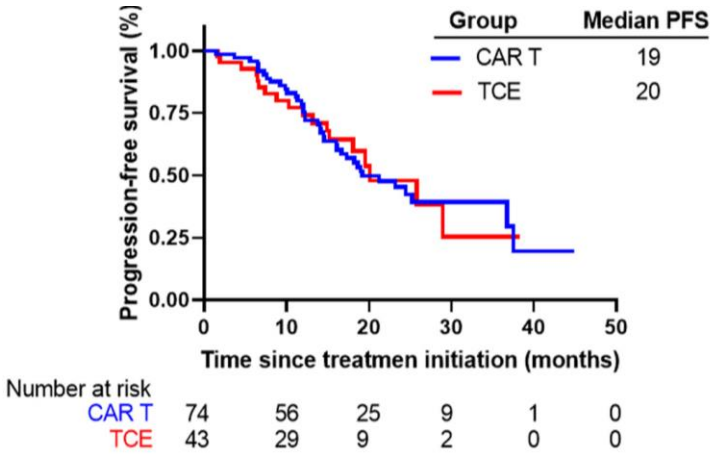
Simon F, et al. J Clin Oncol. 2025 Feb;43(4):381-391.

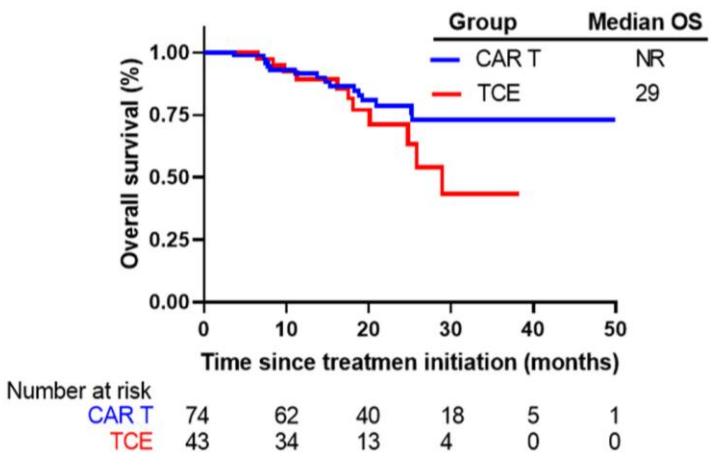
The efficacy of new regimens, deeper and durable MRD responses and prolonged survival are interconnected



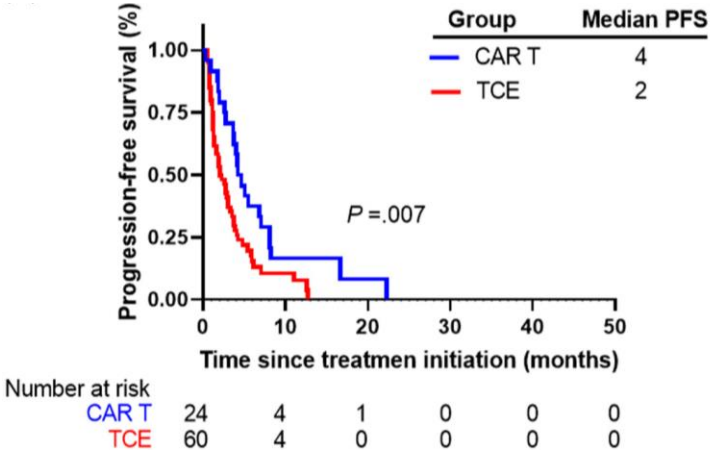
MRD negativity after T-cell redirecting immunotherapy is associated with longer survival

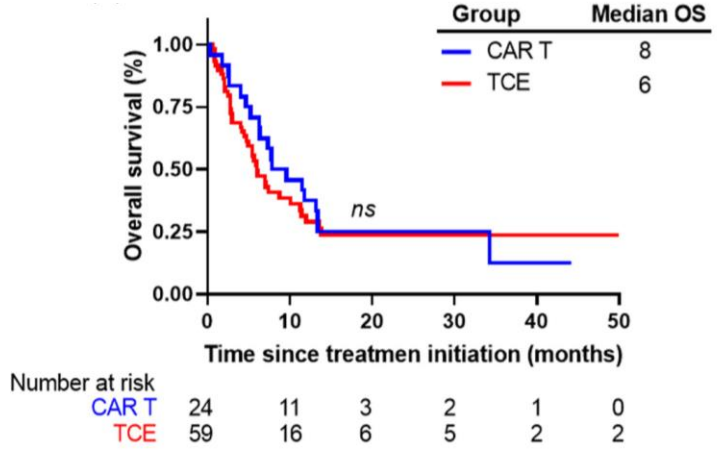
MRD Negative





MRD Positive





Zabaleta, A, et al. Am J Hematol. 2025 Jan;100(1):93-102.

Unique time in progress of myeloma therapy

19 drugs
approved in
the last 20 years

→ **Significant prolongation**
of survival outcomes

↓

Multiple new drugs and combinations
under evaluation

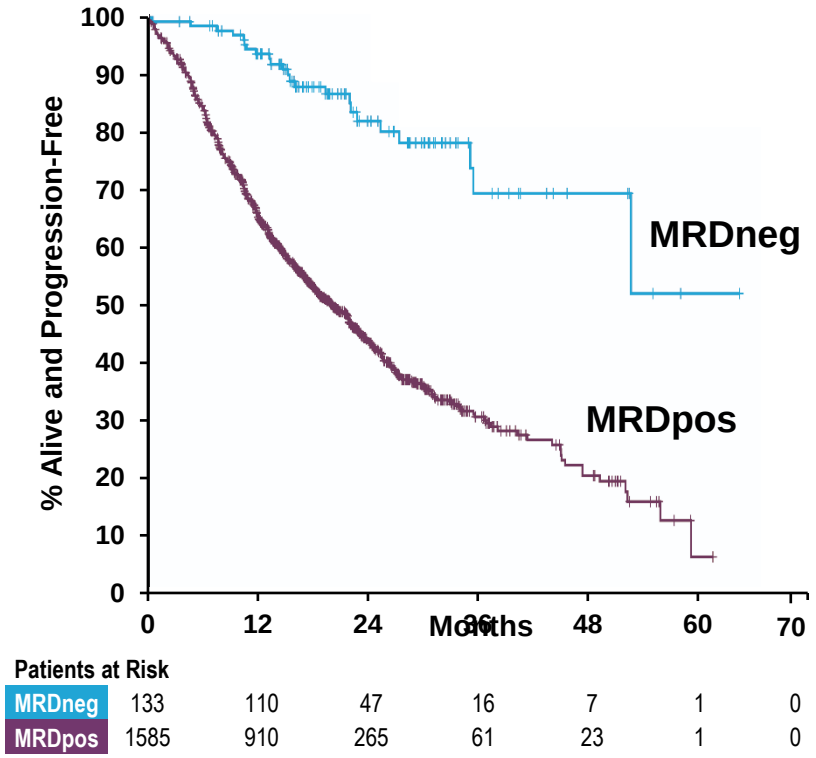
→ **Patients will have to wait for longer and longer periods**
for documented PFS benefit

↓

MRD negative CR 9-12 months
as an intermediate endpoint for accelerated approval of new treatments

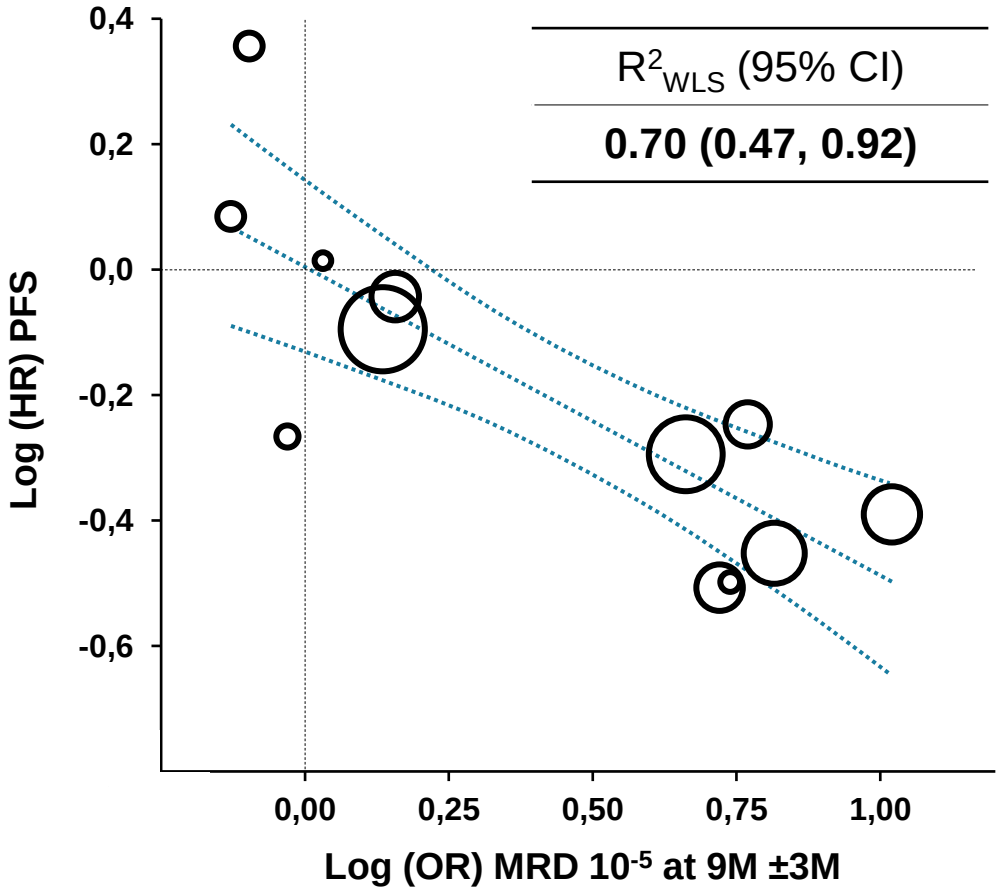
MRD negative CR as an early endpoint for accelerated drug approval in multiple myeloma

Individual-Patient-Level Correlation



HR=0.24 (0.16-0.36); P-value < 0.0001

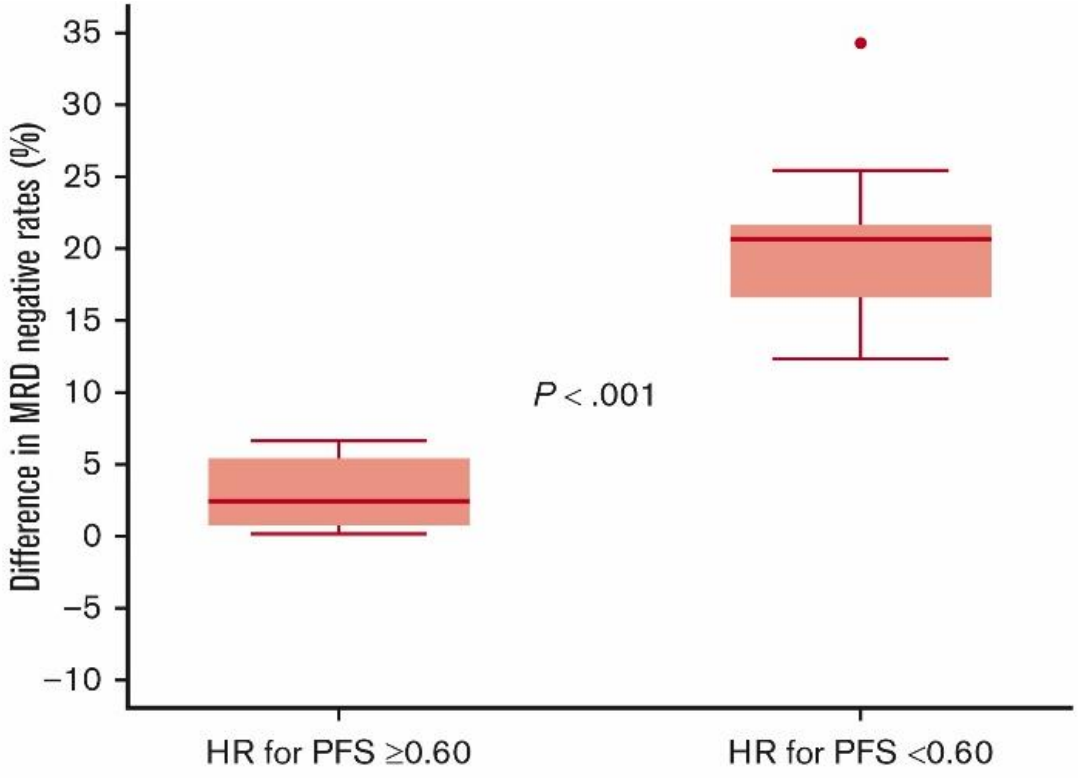
Trial-Level Correlation



Shi Q, et al. *Manuscript accepted in J Clin Oncol*

Difference in MRD negative rates ≥15% predict clinically meaningful improvement in PFS

Difference in MRD negative rates between experimental vs control arms in clinical trials demonstrating with an HR < vs ≥ 0.60



Paiva B, et al. Blood Adv. 2024 Jan 9;8(1):219-223.

MRD negative rates predict clinical benefit in phase 3 trials investigating anti-CD38 antibodies

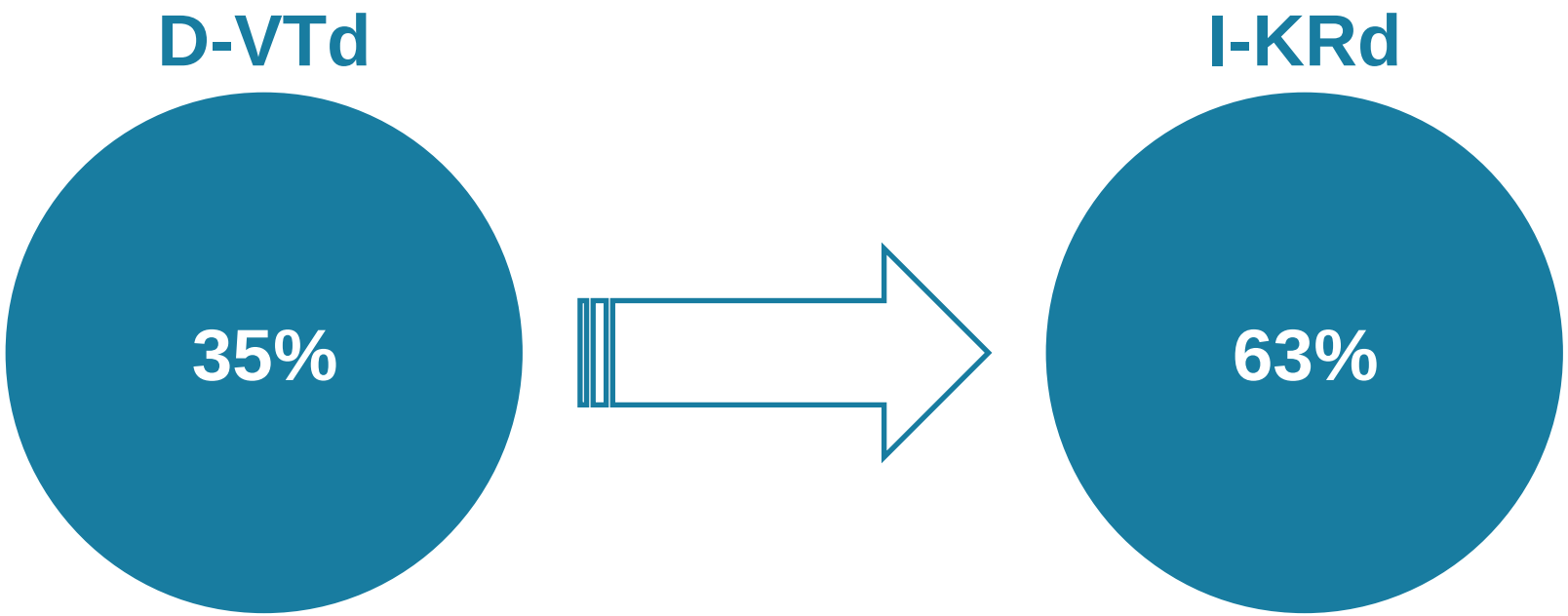
Clinical Trial	Disease Setting	Randomization	Approval
CASSIOPEIA[1]	NDTE	D-VTD vs VTD	D-VTD
PERSEUS[2]	NDTE	D-VRD vs VRD	D-VRD
GMMG-HD7[3]	NDTE	I-VRD vs VRD	-
AURIGA[4]	NDTE	DR vs R	-
ALCYONE[5]	NDTinE	D-VMP vs VMP	D-VMP
MAIA[6]	NDTinE	D-Rd vs Rd	D-Rd
IMROZ[7]	NDTinE	I-VRd vs VRd	-
CEPHEUS[8]	NDTinE	D-VRd vs VRd	-
CASTOR[9]	RRMM	D-Vd vs Vd	D-Vd
IKEMA[10]	RRMM	I-Kd vs Kd	I-Kd
POLLUX[11]	RRMM	D-Rd vs Rd	D-Rd

Significantly higher MRD negative rates preceded significant differences in PFS

1. Moreau P, et al. Lancet. 2019 Jul 6;394(10192):29-38.
2. Sonneveld P, et al. N Engl J Med. 2024 Jan 25;390(4):301-313.
3. Mai EK, et al. J Clin Oncol. 2024 Dec 9:JCO2402266.
4. Badros A, et al. Blood. 2025 Jan 16;145(3):300-310.
5. Mateos MV, et al. Lancet. 2020 Jan 11;395(10218):132-141.
6. Facon T, et al. Lancet Oncol. 2021 Nov;22(11):1582-1596.
7. Facon T, et al. N Engl J Med. 2024 Oct 31;391(17):1597-1609.
8. Zweegman S, et al. Blood 2024; 144 (Supplement 1): 362
9. Mateos MV, et al. Clin Lymphoma Myeloma Leuk. 2020 Aug;20(8):509-518.
10. Moreau P, et al. Lancet. 2021 Jun 19;397(10292):2361-2371.
11. Bahlis NJ, et al. Leukemia. 2020 Jul;34(7):1875-1884.

MRD analysis in the CASSIOPEIA[1] and MIDAS[2] trial

MRD rates on the ITT population, 10^{-5}



1. Corre J, et al. Presented at the IMS 2024
2. Perrot A, et al. Blood. 2025 Jan 22:blood.2024026230.

Subgroup analysis of MRD negativity in the MIDAS trial

On the ITT population, 10^{-5}

Cytogenetic alteration	t(4;14)	t(11;14)	del(17p)	Standard risk	High risk
MRD negative rate (%)	81%	40%	48%	63%	62%

Perrot A, et al. Blood. 2025 Jan 22:blood.2024026230.

Looking into the future (1)

- If 4-year PFS for standard of care in NDMM is assumed to be ~85% and the target hazard ratio for PFS for a new therapy versus standard of care is 0.70, then a 2-arm trial would require 331 total PFS events to have 90% power at its final analysis, and would require a sample size of 960 patients to read out at as early as 7 years (not-fully-powered interim analysis) to 12 years (fully powered final analysis)

- At a typical trial accrual rate of 30 patients per month, the total study accrual duration would be 2.7 years. Adding 12 months to obtain MRD negative CR results for the last subject enrolled, results would become available in 3.7 years from trial initiation to data cut off for analyses of MRD negative CR (benefit) and safety (risk)

- This is >3 years earlier considering that an interim analysis of PFS having any real chance of success would be ~7 years or more, and final PFS would be expected at ~12 years

- **Of note, the trial in this example would provide nearly 4 years of safety data in some study participants**

Looking into the future (2)

- Knowing as soon as possible that two different therapies produce the same benefit in terms of MRD negative CR rates is equally important, since it would **avoid false-expectations and reduce development costs of unsuccessful therapeutic approaches**

- One possible application is the design of studies looking at **improving patients' quality of life** (e.g., with less intensive or fixed duration strategies) relying on non-inferior MRD negative CR rates and expected similar PFS in the long-term

- **Patient crossover:** having MRD negative CR as a primary endpoint could be used to establish the efficacy of investigational vs standard therapies, and facilitate access to the former the earliest as possible without penalizing patients and study promoters

Points of discussion

- There can be no doubts on how the efficacy of new regimens, deeper and durable MRD responses and prolonged survival are interconnected (e.g., MM)
- Have not focused on methodological aspects of MRD assessment (opportunity for improvement rather than barriers)
- Even if only moderate correlations are achieved, PFS or MRD and their impact on patients' QoL should not be underestimated, especially when a long-lasting remission is achieved through a well-tolerated time-limited treatment