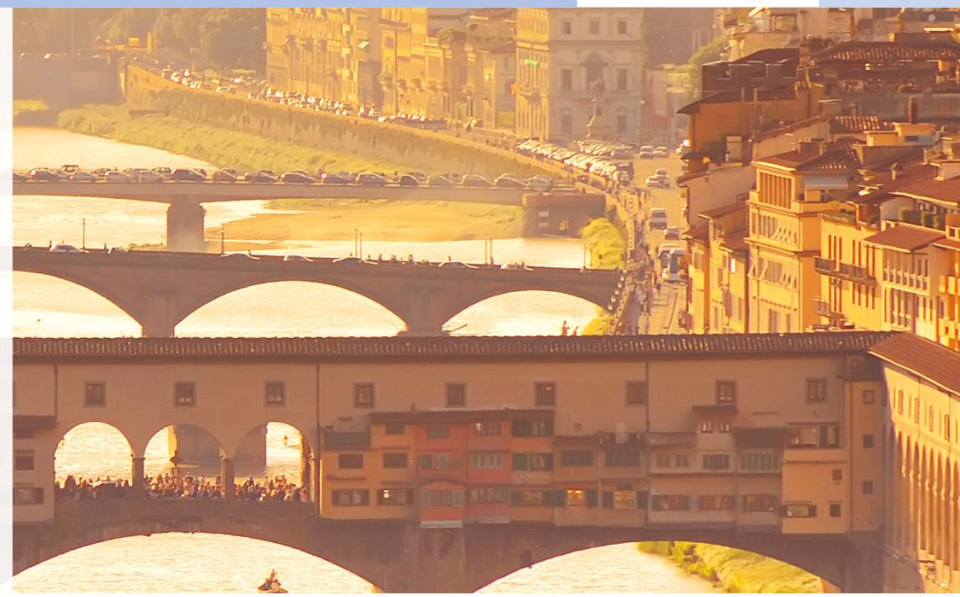
8° WORKSHOP IN EMATOLOGIA TRASLAZIONALE

DELLA SOCIETÀ ITALIANA DI EMATOLOGIA SPERIMENTALE

Firenze - Auditorium CTO - A.O.U. Careggi, 22-23 giugno 2023



Il futuro della terapia del mieloma ad alto rischio

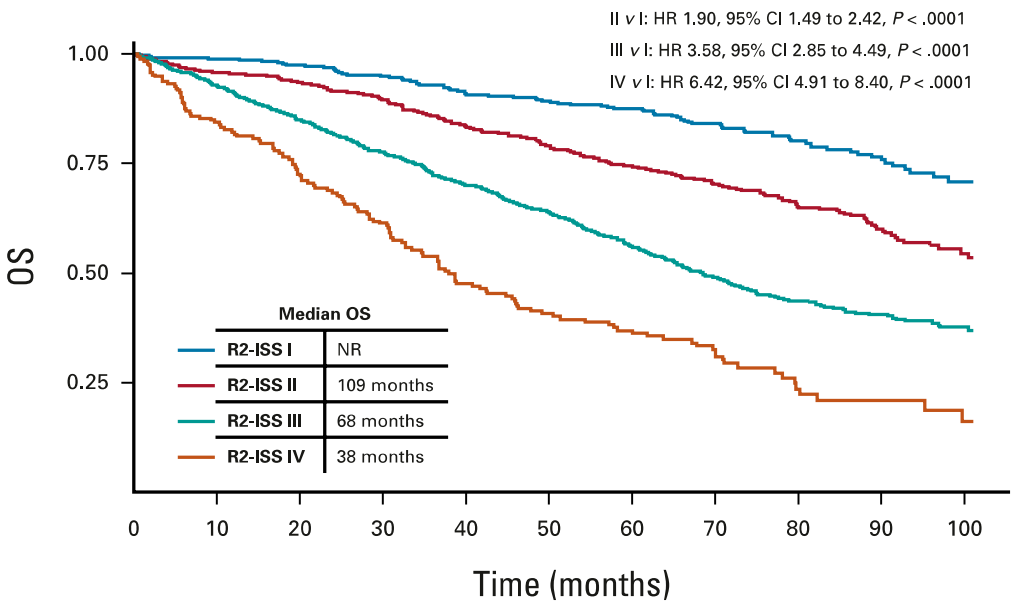
Niccolò Bolli

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen					X		
GSK					X		
Pfizer					X	X	
Janssen					X	X	
Jazz					X		

Risk stratification according to R2-ISS

TE



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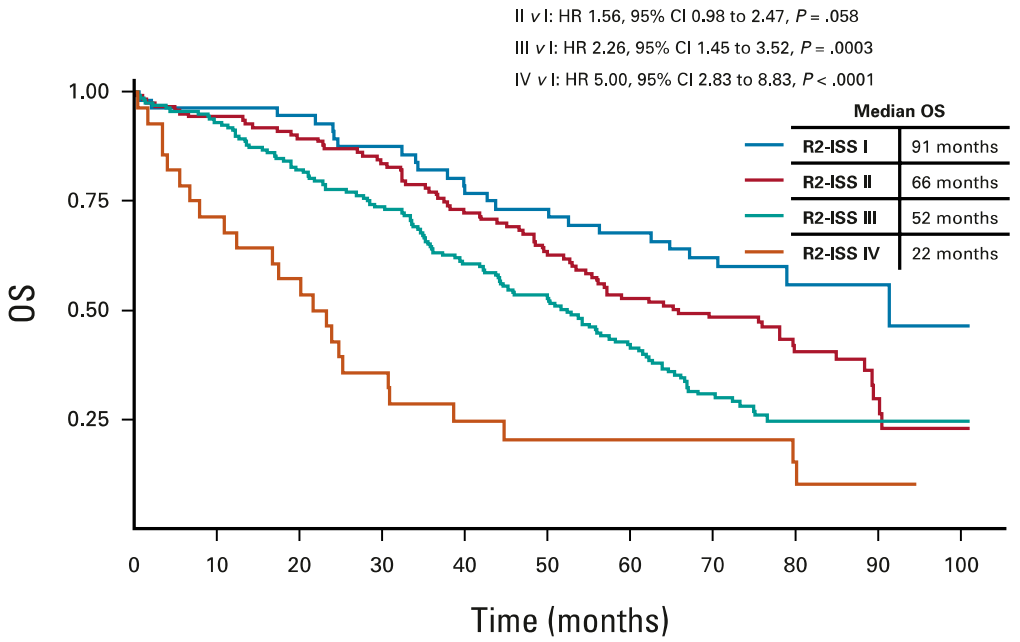


Risk Feature	OS HR (95% CI)	PFS HR (95% CI)	Score Value[a]
ISS II	1.75 (1.49 to 2.05)	1.43 (1.28 to 1.61)	1
ISS III	2.53 (2.13 to 3.01)	1.76 (1.54 to 2.01)	1.5
del(17p)	1.82 (1.53 to 2.17)	1.43 (1.23 to 1.65)	1
LDH high	1.60 (1.36 to 1.88)	1.37 (1.20 to 1.57)	1
t(4;14)	1.53 (1.29 to 1.81)	1.40 (1.21 to 1.62)	1
1q+	1.47 (1.29 to 1.68)	1.33 (1.20 to 1.48)	0.5

Group	No. (%)	Total Additive Score
Low (I)	428 (19)	0
Low-intermediate (II)	686 (31)	0.5-1
Intermediate-high (III)	917 (41)	1.5-2.5
High (IV)	195 (9)	3-5

D'Agostino et al, JCO 2022

Different strategies of risk stratification

	Serum features	Genomic features	Proposed clinical definition of high risk:	% defined as high risk	Definition of high risk	Outcomes based on risk	Additional important notes
ISS [3]	Serum β2-microglobulin Serum albumin	None	NA[a]	33.6%	ISS stage III: Serum β2-microglobulin >5.5 mg/L	Median OS (months) • Stage I: 62 • Stage II: 45 • Stage III: 29	B2-microglobulin: indicative of increased tumor burden and declining renal function Serum albumin: driven by inflammatory cytokines such as IL-6 and the bone marrow microenvironment
R-ISS [2]	LDH Serum β2-microglobulin Serum albumin	del(17p)[b] t(4;14) t(14;16)	NA[c]	10%	ISS stage III and either high-risk CA by iFISH or high LDH	5-year OS: • Stage 1: 82% • Stage 2: 62% • Stage 3: 40%	Stage 3 patients have a median PFS of 29 months and median OS of 37 months [54]
IMWG [5]	Serum β2-microglobulin Serum albumin	del(17p)[b] t(4;14) +1q21	Median OS <2 years	20%	ISS II/III and t(4;14) or 17p13 del by iFISH	Median OS: • Low risk: >10 years • Standard risk: 7 years • High risk: 2 years	High-risk group with a 4-year PFS of 12% and OS of just 35% Low-risk group consists of ISS I/II and absence of t(4;14), 17p13 del or +1q21 and age <55 years
mSMART [55]	LDH Serum β2-microglobulin Serum albumin	Ploidy status t(4;14) t(14;16) t(14;20) t(11;14) t(6/14) del(17p) and p53 deletion deletion 13 gain 1q GEP	NA[d]	20%	High-risk genetic Abnormalities • t(14;16); t(14;20); • Del17p or p53 mutation GEP: high-risk signature	Median OS: • High risk: 3 years • Intermediate risk: 4–5 years • Standard risk: 8–10 years	• Trisomies may ameliorate high-risk genetic abnormalities • High plasma cell S-phase also defines high risk: cutoffs vary • Standard risk includes all others including trisomies, t(11;14), and t(6;14) • t(4;14): re-classified as intermediate risk
EMC92/SYK92 –MMprofiler [30]	None	High-risk survival signature of 92 genes[e]	Median OS <2 years	18–20%	Two-tiered system of high and standard risk	Reduced OS with HR of 2.06 to 5.23 in validation cohorts amongst the TT2, TT3, APEX, and MRC-IX studies	In multivariate analyses, the signature was proven to be independent of the currently used prognostic factors
UAMS GEP70 or MyPRS [28]	None	High-risk survival signature of 70 genes[e]	"early disease-related death"	13–14%	Two-tiered system of high and standard risk	HR for high v standard-risk GEP: • EFS: 3.41 ($P = 0.002$) • OS: 4.75 ($P<0.001$)	Standard-risk patients with a 5-year continuous complete remission of 60% vs. 3-year rate of only 20% in those with a high-risk "Early disease-related death" definition not clear in the primary literature
CoMMpass [19]	LDH	[f]TP53 mutation λ-chain translocation IGLL5 mutation	Time to progression (TTP) of < 18 months	20.6%	TTP < 18 months: high-risk TTP >18 months: low risk	Median OS in months: • High risk: 32.8 • ISS III: 54 • Baseline high-risk CA: 65	TTP 18-month cutoff chosen because time to ASCT was ~6 months and many MM studies define early PD as relapse within 12 months from ASCT
	Serum features	**Genomic features**	**Proposed clinical definition of high risk:**	**% defined as high risk**	**Definition of high risk**	**Outcomes based on risk**	**Additional important notes**
Myeloma Genome Project [6, 17]	Serum β2-microglobulin Serum albumin	TP53 inactivation +1q amp	NA[g]	6.1%	Biallelic TP53 inactivation or amp of CKS1B (1q21) on the background of ISS stage III	High risk: • Median PFS: 15.4 months • Median OS: 20.7 months	1q amplification considered ≥ 4 copies LDH values were not universally available preventing the calculation of R-ISS thus ISS and IMWG risk criteria were used
Cytogenetics Prognostic Index [9]	None	del(17p) t(4;14) del(1p32) 1q21 gain trisomies 3, 5, and 21	NA	11–18%	Prognostic Index >1 defined high risk[h]	5-year survival: • High risk: <50% • Int risk: 50–75% • Low risk: >75%	The main objective was to develop and validate a prognostic model based on the seven cytogenetic abnormalities

Hagen et al, Blood Canc J. 2022

Consensus is lacking for the definition of HR myeloma

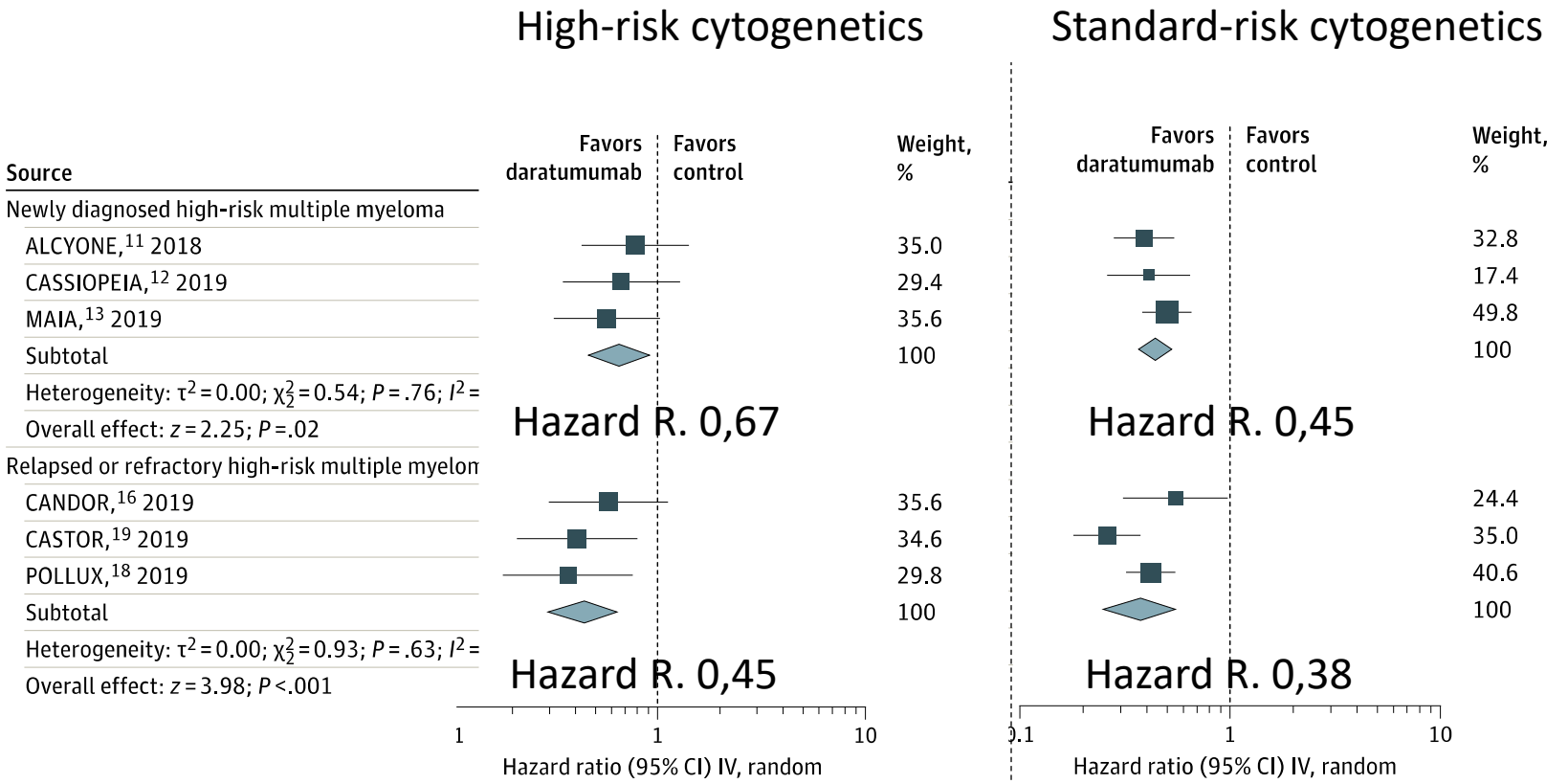
1st take home message

But, are current drugs helping HR patients?

Dara-based induction is significantly better for HR patients but *size effect* is smaller in HR vs standard risk

HR myeloma patients benefit from Dara, but less than standard risk

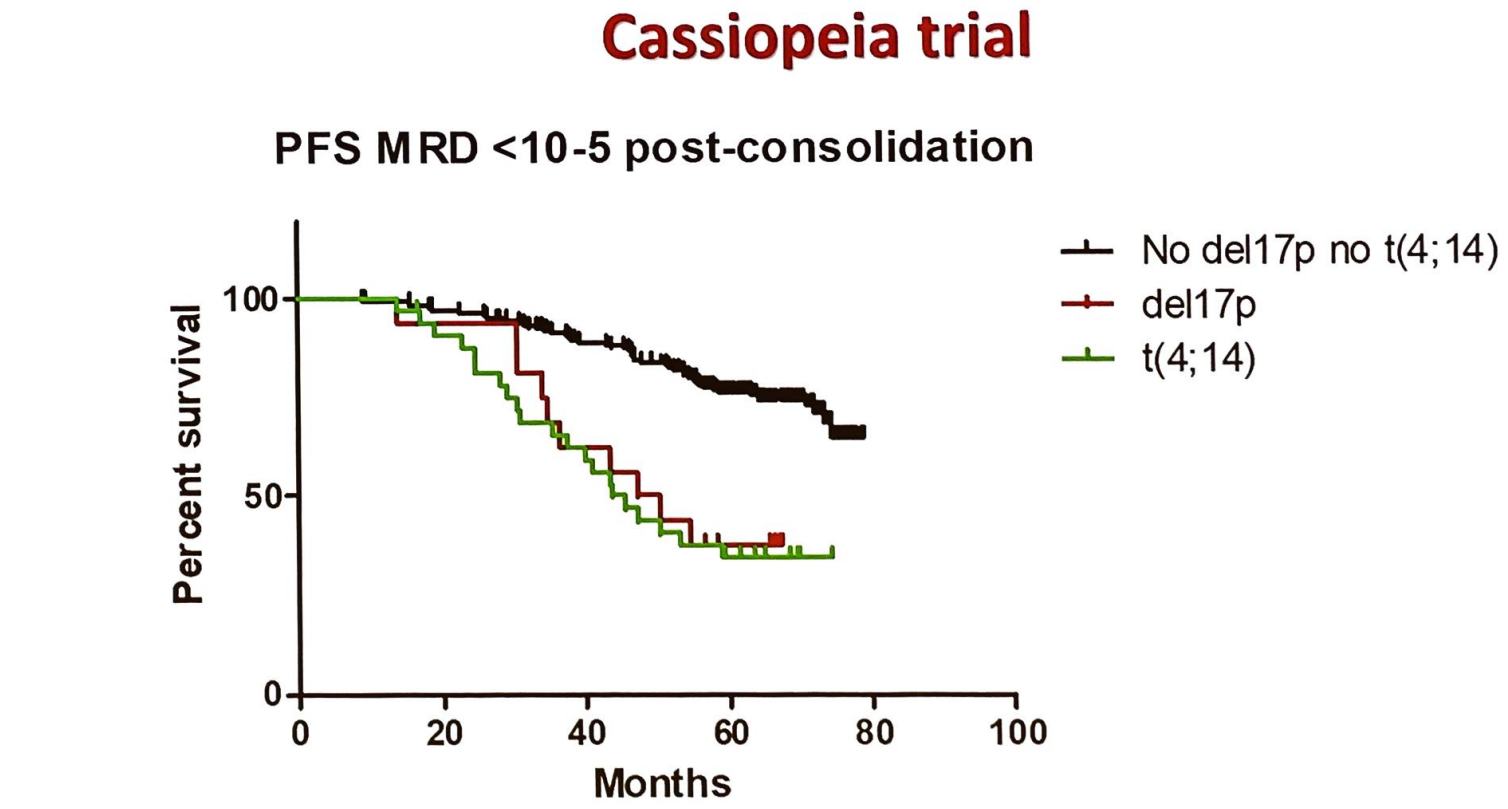
PFS



HR: t(4;14), t(14;16), or del(17p).

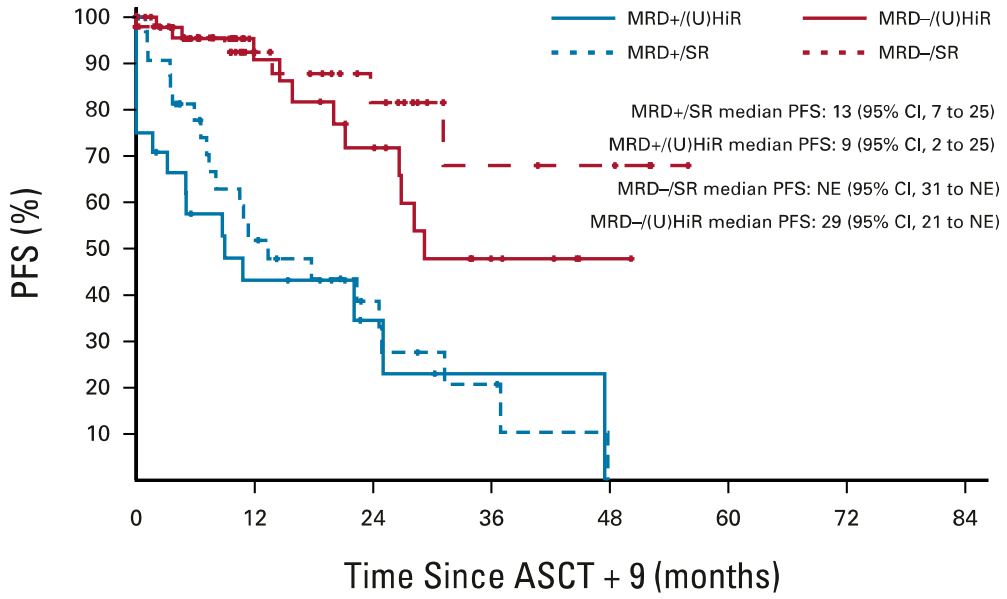
Giri et al, JAMA oncol 2020

Even in the context of high-quality induction AND MRD negativity HR cases show poor PFS



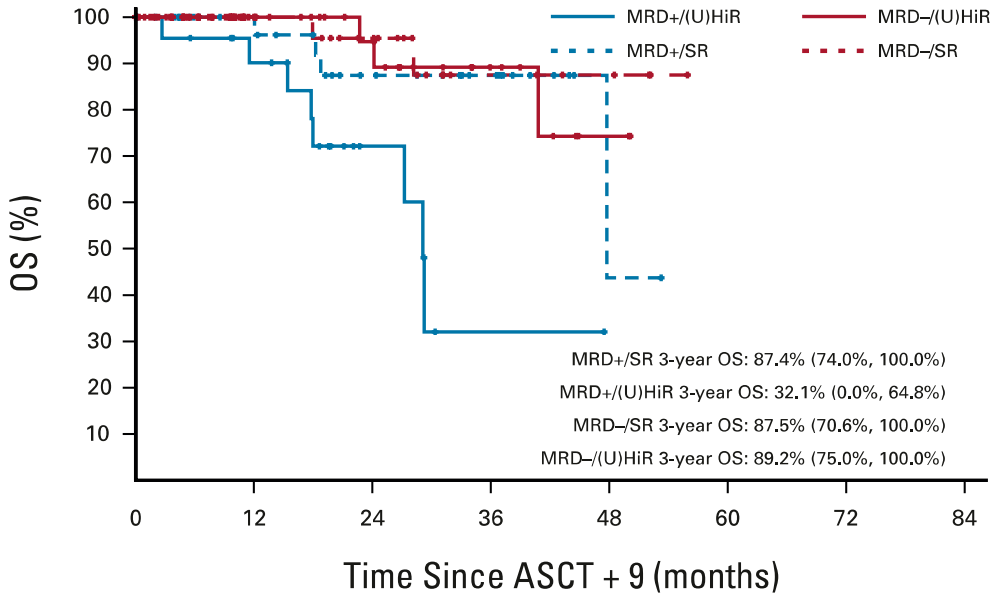
Avet Loiseau et al, IMWG 2022

HR cases have shorter PFR than SR even on Len maintenance (Myeloma XI)



No. at risk (No. censored):

MRD+/(U)HiR	24 (0)	9 (2)	3 (7)	1 (8)	0 (8)	
MRD+/SR	34 (1)	14 (6)	7 (10)	3 (11)	0 (12)	
MRD–/(U)HiR	52 (5)	20 (29)	14 (31)	5 (36)	1 (40)	0 (41)
MRD–/SR	49 (4)	21 (25)	13 (31)	5 (38)	4 (39)	0 (43)



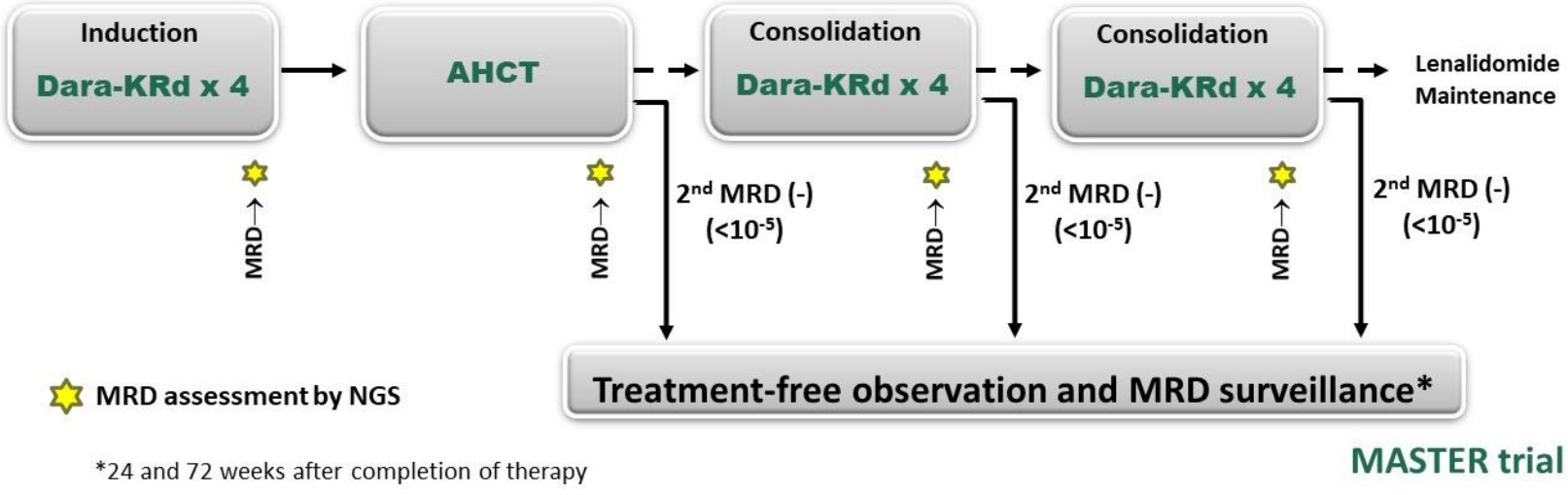
No. at risk (No. censored):

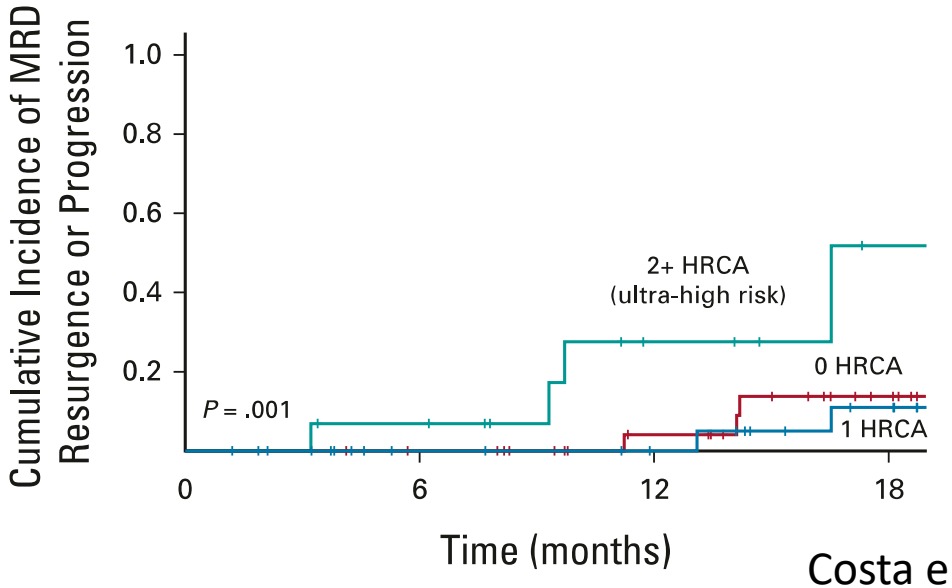
MRD+/(U)HiR	24 (1)	17 (5)	6 (13)	1(15)	0 (16)	
MRD+/SR	34 (0)	26 (8)	16 (15)	10 (21)	1 (29)	0 (30)
MRD–/(U)HiR	52 (5)	22 (30)	18 (33)	8 (42)	2 (47)	0 (49)
MRD–/SR	49 (3)	27 (22)	17 (31)	6 (41)	4 (43)	0 (47)

HR: 4;14, 14;16, 14;20, gain(1q), del(17p). UHR: 2+ HR lesions

De Tute et al, JCO 2022

MRDneg HR cases will relapse quickly at maintenance cessation





HR: 4;14, 14;16, 14;20, gain(1q), del(17p).
UHR: 2+ HR lesions

Costa el at, JCO 2022

HR remains HR even in the context of novel agents, after deep responses with or w/o maintenance, and with effective 2nd lines

2nd take home message

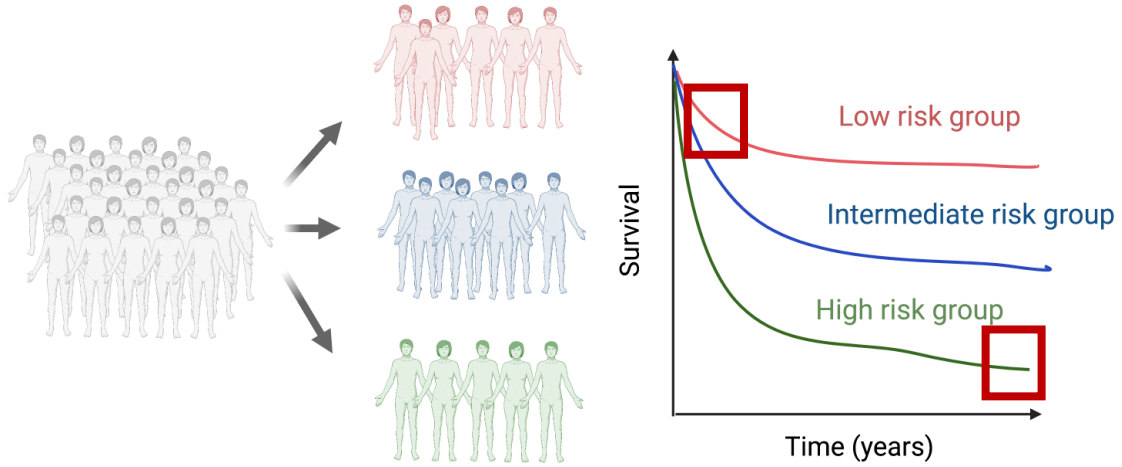
Limitations of all HR scores: they are based on a non-existent *average* patient

ISS
- B2M
- Albumin

R-ISS*
- B2M
- Albumin
- LDH
- t(4;14)
- del17p

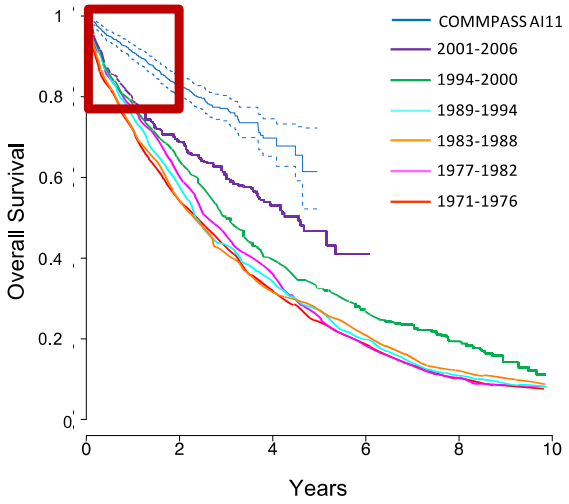
R2-ISS#
- B2M
- Albumin
- LDH
- t(4;14)
- Del17p
- 1q gain

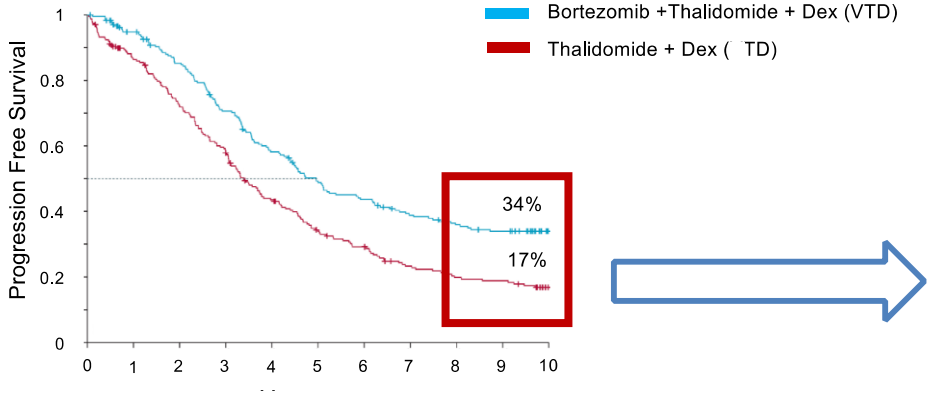
RELATIVE RISK



Not useful for developing patient-specific tailored therapeutic decisions

Functional definition of high-risk and low-risk myeloma





The advent of novel drugs in patients with newly diagnosed and relapsed/refractory multiple myeloma has resulted in improved overall survival

However, a subset of newly diagnosed multiple myeloma patients have not benefited from newer therapies, reflected in persisting poor clinical outcomes

Conversely, another subset of multiple myeloma patients have excellent outcomes despite limited therapy

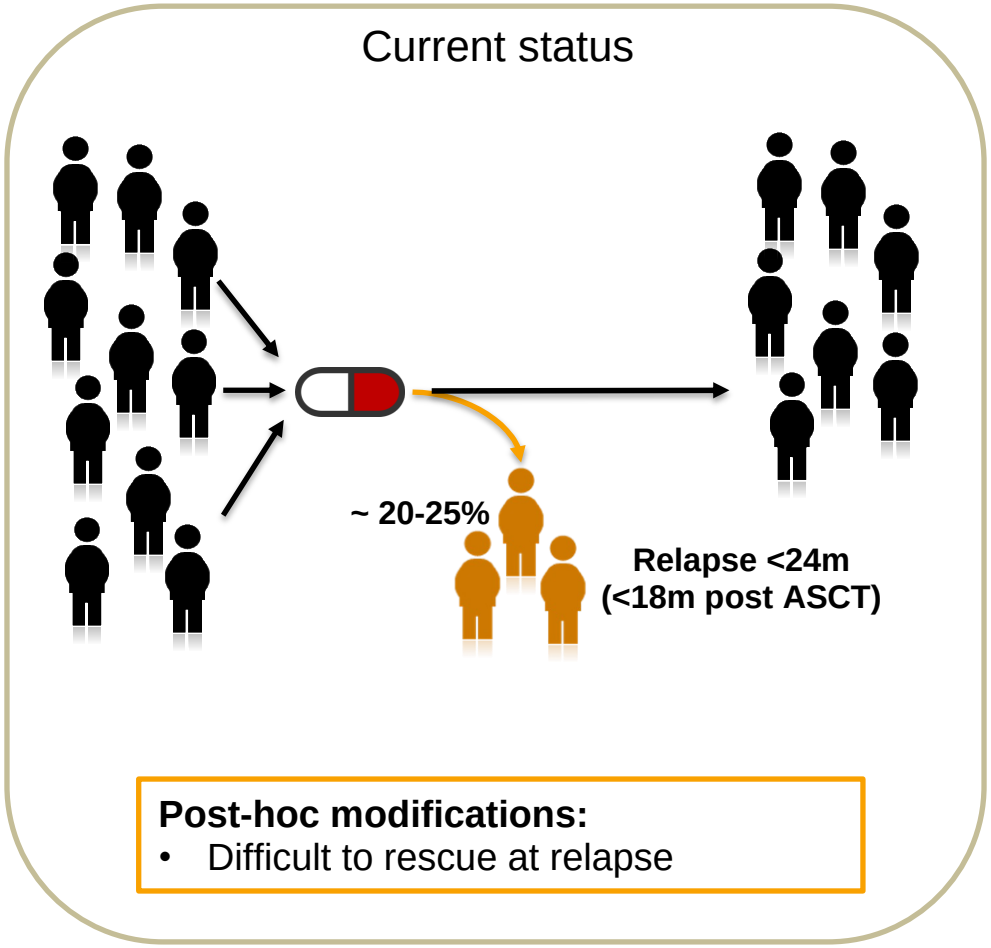
A) Adapted from: Kumar et al. Leukemia 2014 B) Tacchetti et al. Lancet Hem 2020

Absolute prediction of HR risk is not possible today. Sometimes we only know *ex post*

3rd take home message

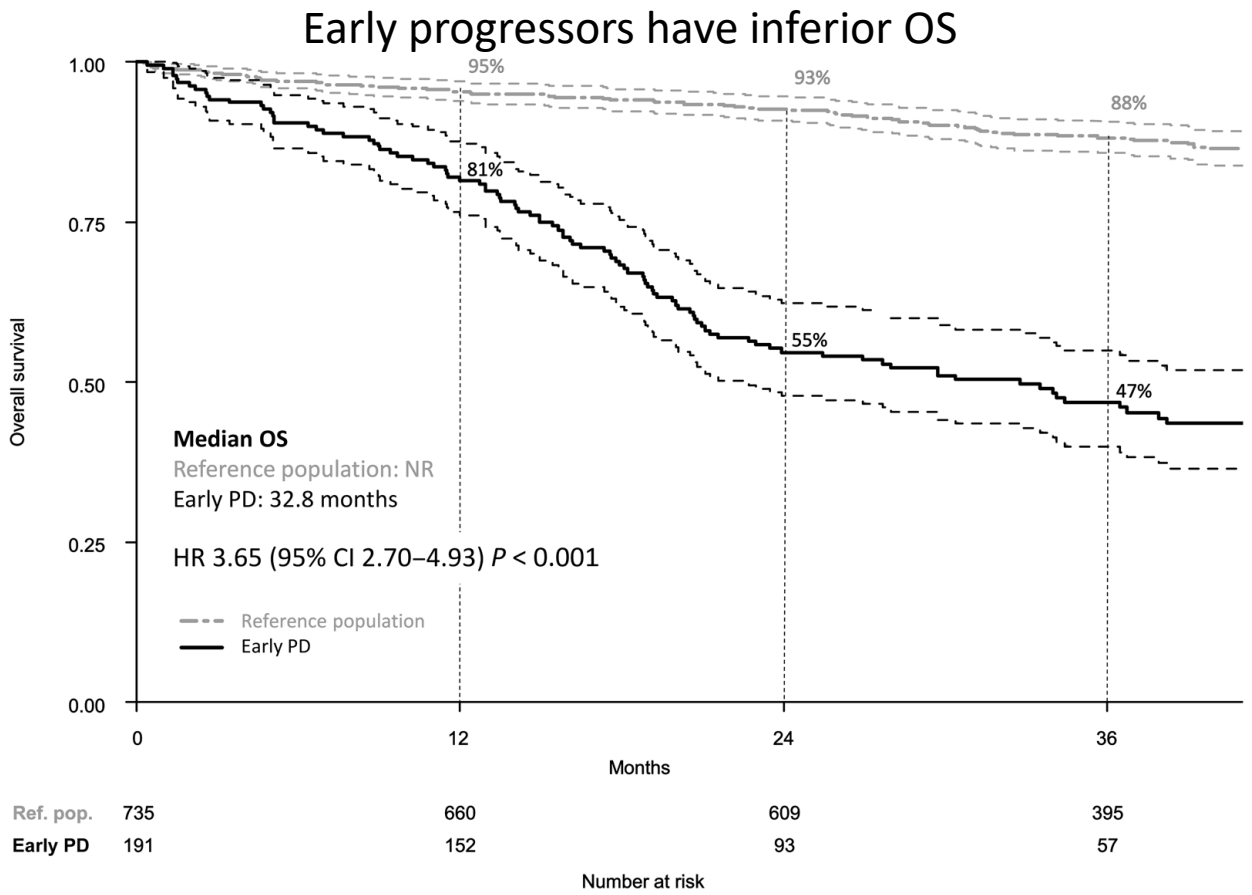
How do we deal with HR disease?

- 1st approach: we deal with it ex-post



ASCT = autologous stem cell transplantation

Courtesy of M. Kaiser

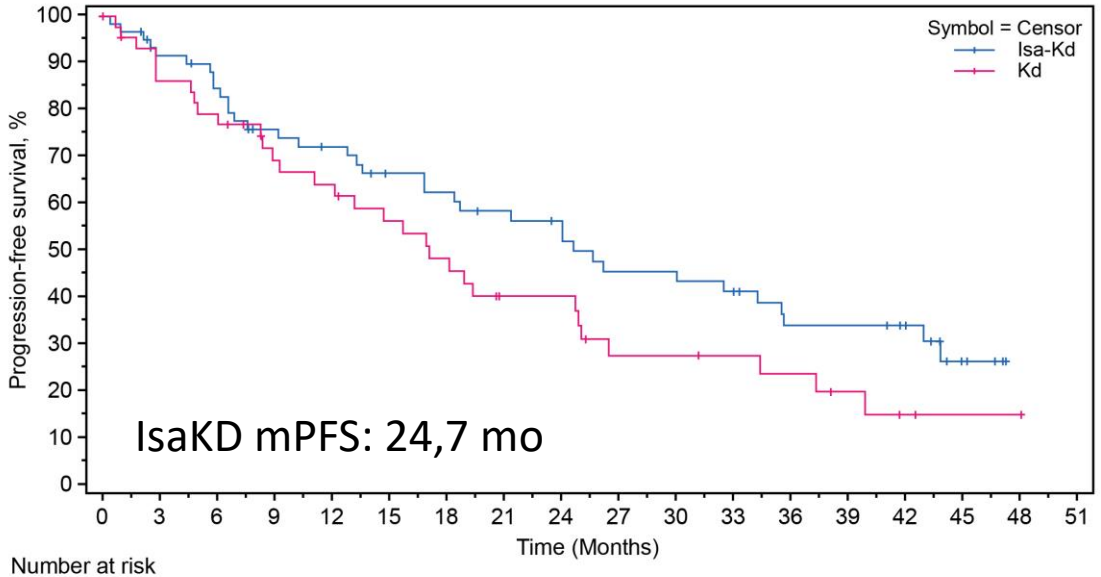


D'Agostino et al., CCR 2020

Impact of early relapse (functional HR) on IKEMA outcomes

EARLY

Figure 1. Kaplan-Meier estimate of progression-free survival for early relapse patients



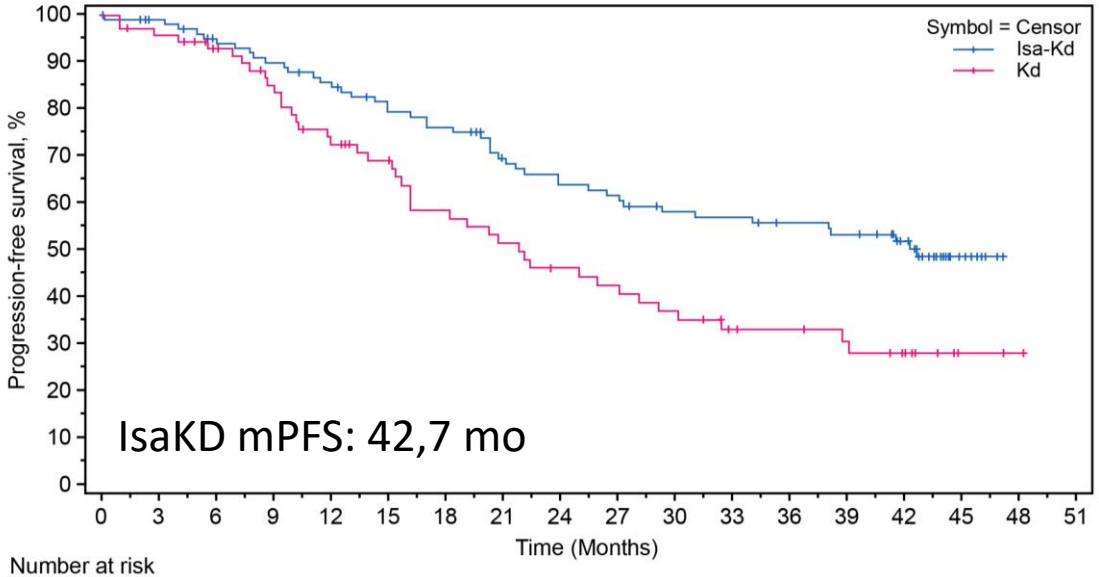
Number at risk

Isa-Kd	61	53	48	41	38	33	31	28	26	21	21	19	14	14	11	5	0
Kd	46	37	34	27	25	21	18	13	13	8	8	7	6	4	2	1	1	0

d, dexamethasone; Isa, isatuximab; K, carfilzomib. Cut-off date: January 14, 2022. Median follow-up time: 44.19 months.

LATE

Figure 2. Kaplan-Meier estimate of progression-free survival for late relapse patients



Number at risk

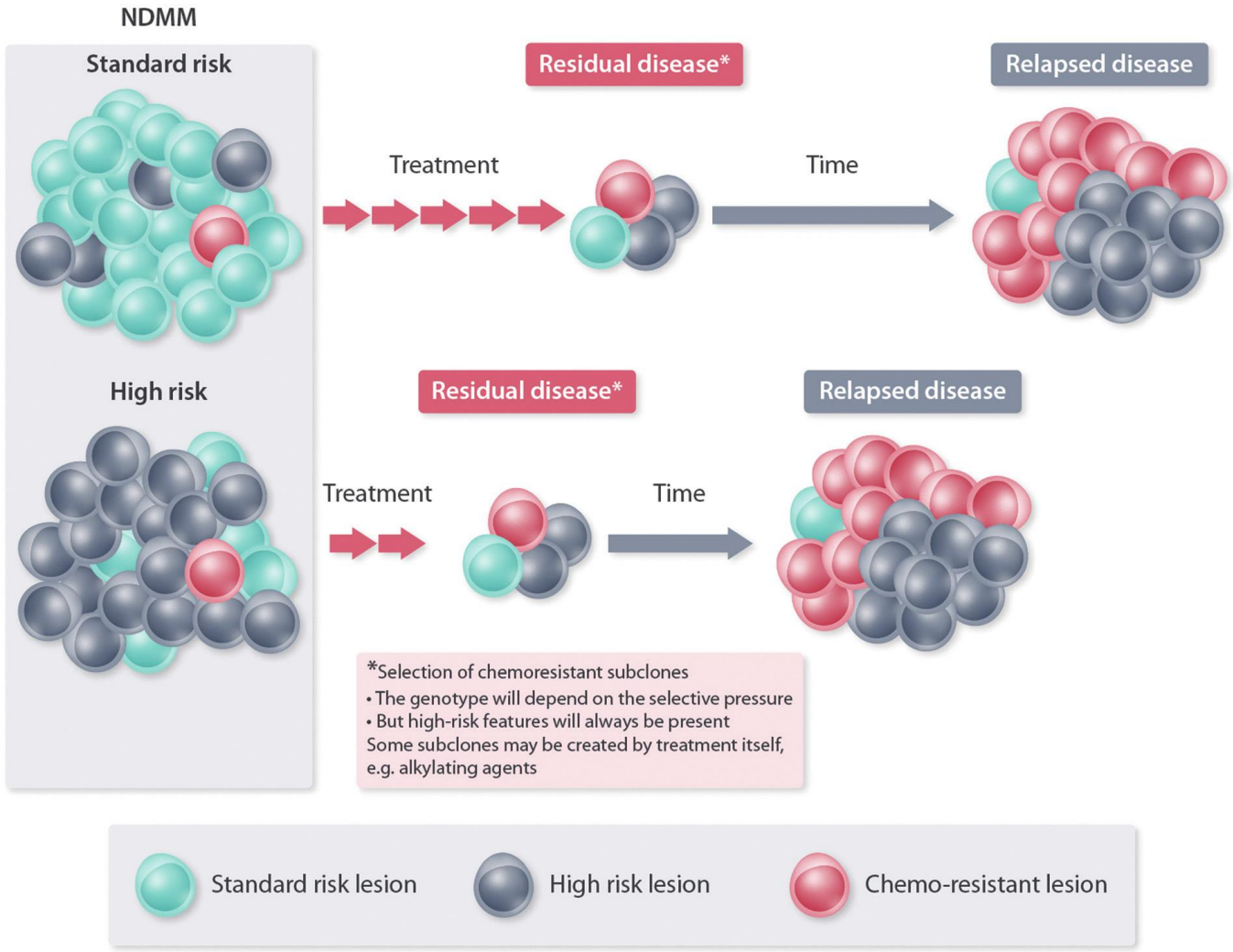
Isa-Kd	104	99	92	87	82	74	71	61	56	54	49	48	45	43	34	12	0
Kd	72	67	61	54	45	40	33	29	25	23	20	15	14	12	8	2	1	0

d, dexamethasone; Isa, isatuximab; K, carfilzomib. Cut-off date: January 14, 2022. Median follow-up time: 43.83 months.

Early relapse: <12 mo from initiation of the most recent LOT for pts with ≥2 prior LOT, <18 mo for pts with 1 prior LOT, and <12 mo from autologous stem-cell transplantation (ASCT).

Facon et al, ASH 2022

Evolutionary-convergent view of risk in myeloma



Da Vià et al, Hemasphere, 2020

“One-size fits all approach” does not work for HR myeloma

4th take home message

Corollary: a truly “personalized” approach should abrogate the negative effect of HR lesions - this therapy does not exist so far

What is the future of treating HR MM?

1st: use novel agents to rescue patients

CARTITUDE-2 Cohort B: Introduction

- In CARTITUDE-2 (NCT04133636), a multicohort phase 2 study, cilta-cel is being evaluated in patients with MM in various patient populations, including in earlier-line settings
- CARTITUDE-2 cohort B consists of patients with early relapse after initial therapy with a PI and IMiD, defined as progression within 12 months after ASCT or from the start of anti-MM therapy for patients who have not had ASCT
  - Previous analysis at median 13.4 months follow-up demonstrated an ORR of 100%, with 90% of patients achieving CR or better and 95% achieving VGPR or better[1]

Objective: To report updated CARTITUDE-2 cohort B efficacy and safety results, along with CAR+ T cell analyses, after a median follow-up of 18 months

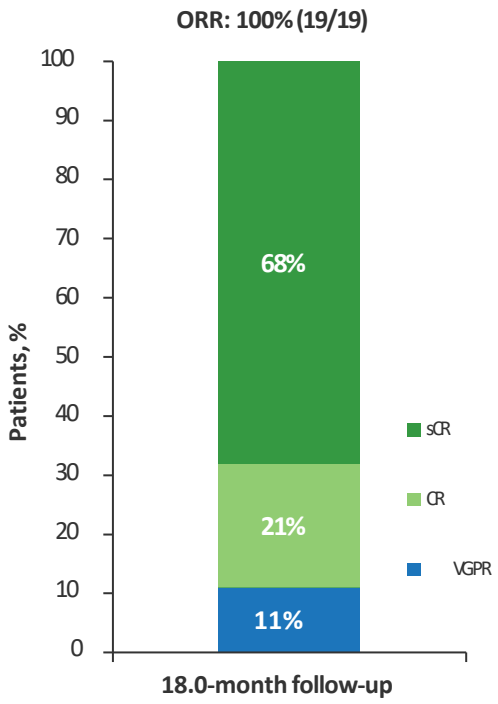
ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CR, complete response; IMiD, immunomodulatory drug; MM, multiple myeloma; ORR, overall response rate; PI, proteasome inhibitor; VGPR, very good partial response.

1. van de Donk NWCJ, et al. Presented at 2022 American Society of Clinical Oncology (ASCO) Annual Meeting; June 3–7 2022; Chicago, IL, USA.

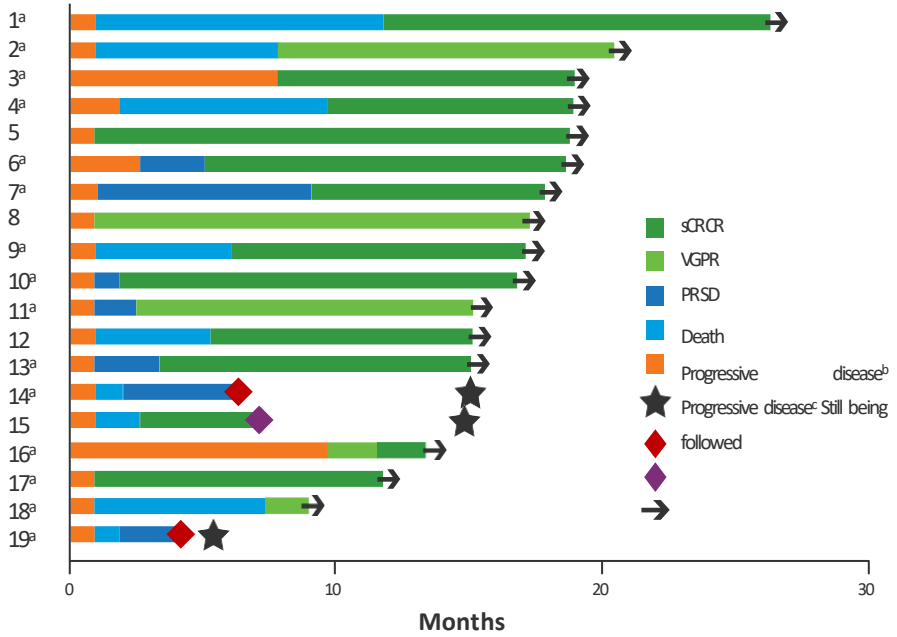
CARTITUDE-2 Cohort B: Efficacy

- ORR was 100% (95% CI, 82.4–100.0) and responses deepened at this longer follow-up
  - 90% (95% CI, 66.9–98.7) achieved ≥CR
  - 100% (95% CI, 82.4–100.0) achieved ≥VGPR
- Median time to first response: 0.95 months (range, 0.9–9.7)
- Median time to best response: 5.09 months (range, 0.9–11.8)
- Median DOR was not reached
- Median PFS and OS at 18-month median follow-up were not reached
  - 18-month PFS rate was 83% (95% CI, 55.9–94.3)
  - 18-month OS rate was 83% (95% CI, 55.7–94.2)
- Of 15 patients with MRD-evaluable samples at 10^{-5} threshold, 14 (93.3%) were MRD negative
  - Of 3 patients with high-risk cytogenetics, 2 (66.7%) were MRD negative at 10^{-5} threshold

Overall response rate



Response and DOR in responders



[a]Patients who received autologous stem cell transplant. [b]PD per International Myeloma Working Group criteria. [c]PD per investigator assessment based on a light chain escape.
CR, complete response; DOR, duration of response; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent CR; SD, stable disease; VGPR, very good partial response.

Ide-cel: KarMMa phase 2 trial

Efficacy Results in cohort 2a

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES | NOVEMBER 15, 2022

KarMMa-2 Cohort 2a: Efficacy and Safety of Idecabtagene Vicleucel in Clinical High-Risk Multiple Myeloma Patients with Early Relapse after Frontline Autologous Stem Cell Transplantation

Saad Usmani, Krina Patel, Parameswaran Hari, Jesus Berdeja, Melissa Alsina, Ravi Vij, Noopur Raje, Xavier Leleu, Madhav Dhodapkar, Ran Reshef, Anna Truppel-Hartmann, Debashree Basudhar, Ethan Thompson, Xirong Zheng, Revathi Ananthakrishnan, Chiara Greggio, Linda Favre-Kontula, Lars Sternas, Jesús San-Miguel

Blood (2022) 140 (Supplement 1): 875–877.

https://doi.org/10.1182/blood-2022-162469

ORR 83%
12m PFS 48%
24m PFS 26%

Usmani et al, ASH 2022

Table 1. Efficacy and safety outcomes following ide-cel.

Efficacy outcome	**N = 37**	
Best overall response		
ORR, n	31	
ORR, % (95% CI[a])	83.8 (68.0–93.8)	
CRR, n	17	
CRR, % (95% CI[a])	45.9 (29.5–63.1)	
Stringent CR, n (%)	14 (37.8)	
CR, n (%)	3 (8.1)	
Very good PR, n (%)	8 (21.6)	
PR, n (%)	6 (16.2)	
Minimal response	2 (5.4)	
Stable disease	4 (10.8)	
Progressive disease	0	
Time to event rates		
12 mo DOR rate, % (SE) 24 mo DOR rate, % (SE)	54.0 (9.07) 31.3 (8.83)	
12 mo PFS rate, % (SE) 24 mo PFS rate, % (SE)	47.9 (8.30) 26.2 (7.63)	
12 mo OS rate, % (SE) 24 mo OS rate, % (SE)	88.0 (5.64) 84.7 (6.31)	
AEs of special interest	**N = 37**	
	CRS	NT
Number of pts with at least one event of any grade, n (%)	31 (83.8)	8 (21.6)
Number of pts with at least one grade 3/4 event, n (%)	1 (2.7)	0
Time to first onset, median, days (range)	2.0 (1–15)	3.0 (1–12)
Duration of event, median, days (range)	3.0 (1–11)	3.5 (2–7)

CI, confidence interval; CR, complete response; CRR, complete response rate; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SE, standard error.
[a]Clopper-Pearson confidence interval.

Table 2. Summary of pharmacokinetic parameters.[a]

Pharmacokinetic parameter	**Evaluable pts (n = 36)**	**Evaluable pts with ≥CR (n = 16)**	**Evaluable pts with <CR (n = 20)**
C_{max}, copies/µg (% geometric CV)[b]	286,462 (136)	404,171 (70)	217,505 (178)
$AUC_{0\text{-}28days}$, days*copies/µg (% geometric CV)[b]	3,360,086 (170)	4,745,793 (102)	2,549,081 (219)
T_{max}, median, days (range)	11 (7–23)	11 (9–17)	11 (7–23)

$AUC_{0\text{-}28days}$, area under the curve of the transgene level from time of dose to 28 days post-infusion; C_{max}, peak serum concentration; CV, coefficient of variation; T_{max}, time to peak concentration.
[a]At 15 Jan 2022 cutoff date. [b]Data are presented as geometric mean.

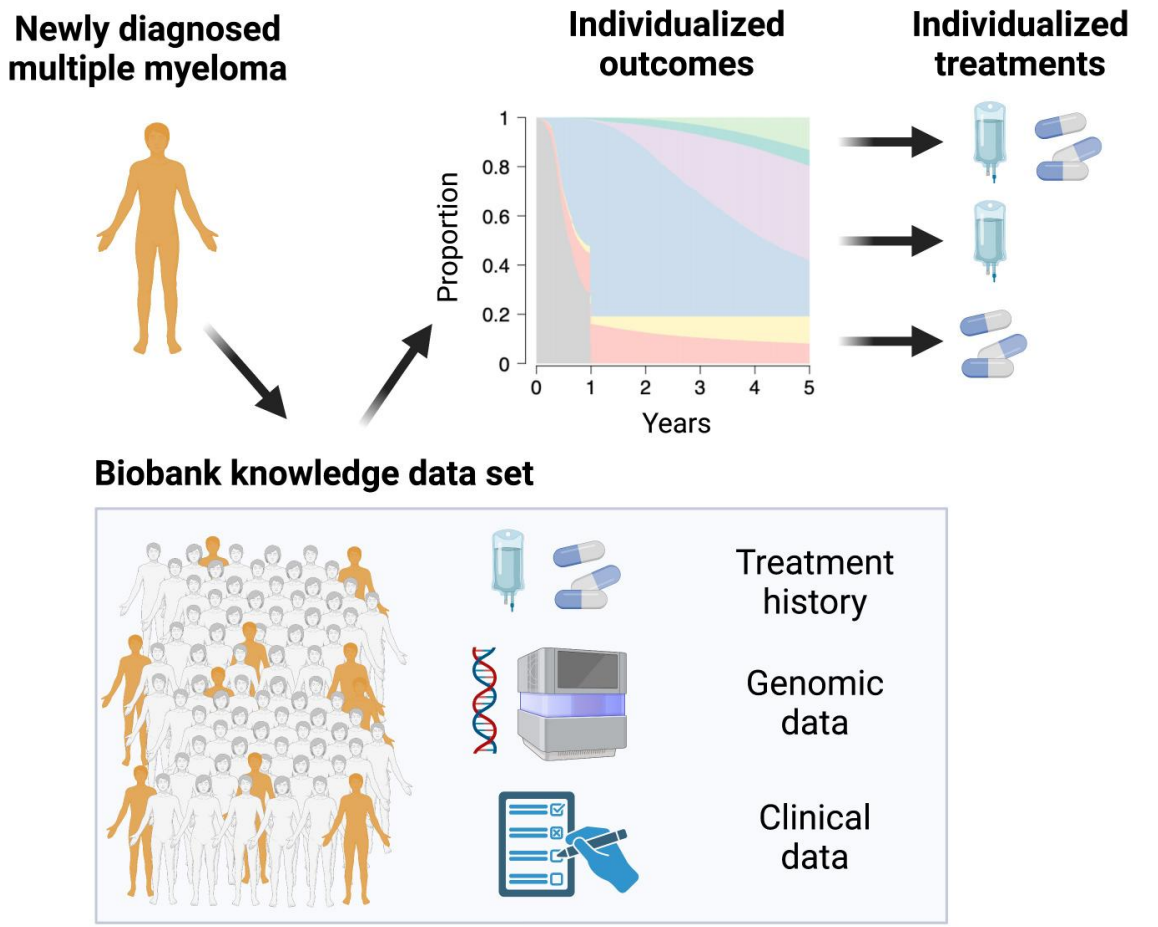
What is the future of treating HR MM?

2nd: identify truly HR patients

Individualized Risk Model for Myeloma (IRMM)

- MMRF, N=1062
- Moffitt, N=177
- MPG, N=492
- MSKCC, N=109
- UAMS, N=93

- Clinical
- Demographic
- Ethnic
- Treatment
- Genomics (WES/WGS)



Model is driven by Deep Neural Networks

Arjun Raj Rajanna

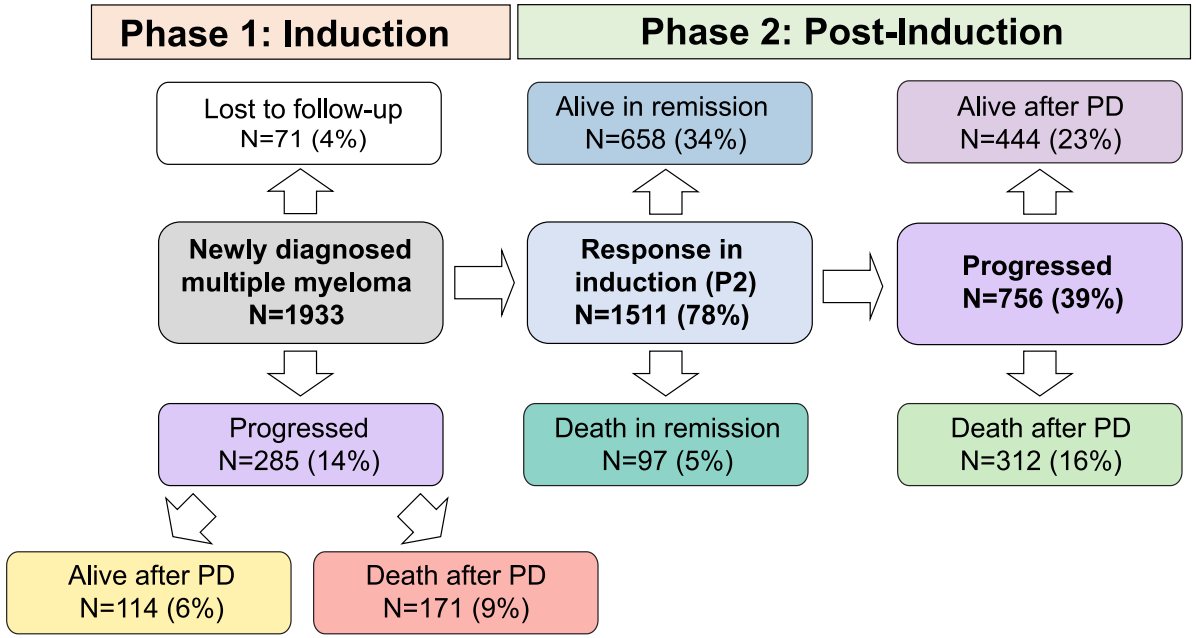
Andriy Derkach

Bachisio Ziccheddu

Courtesy of Francesco Maura (U. of Miami)

Personalized survival prediction in MM

A



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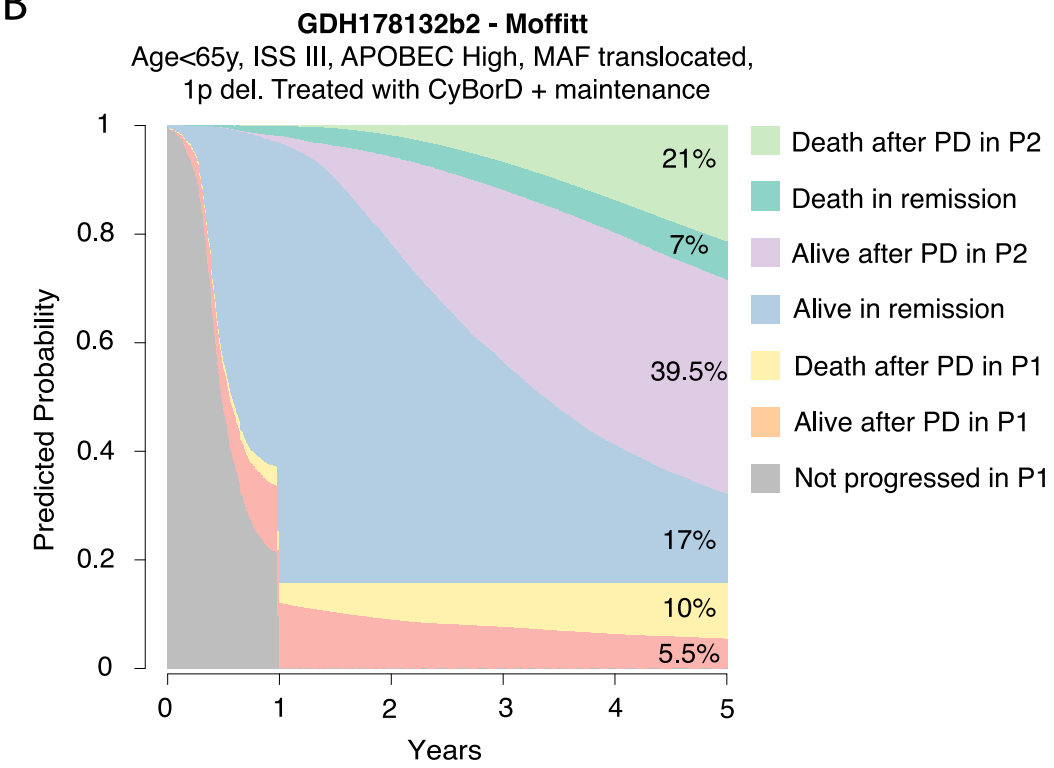
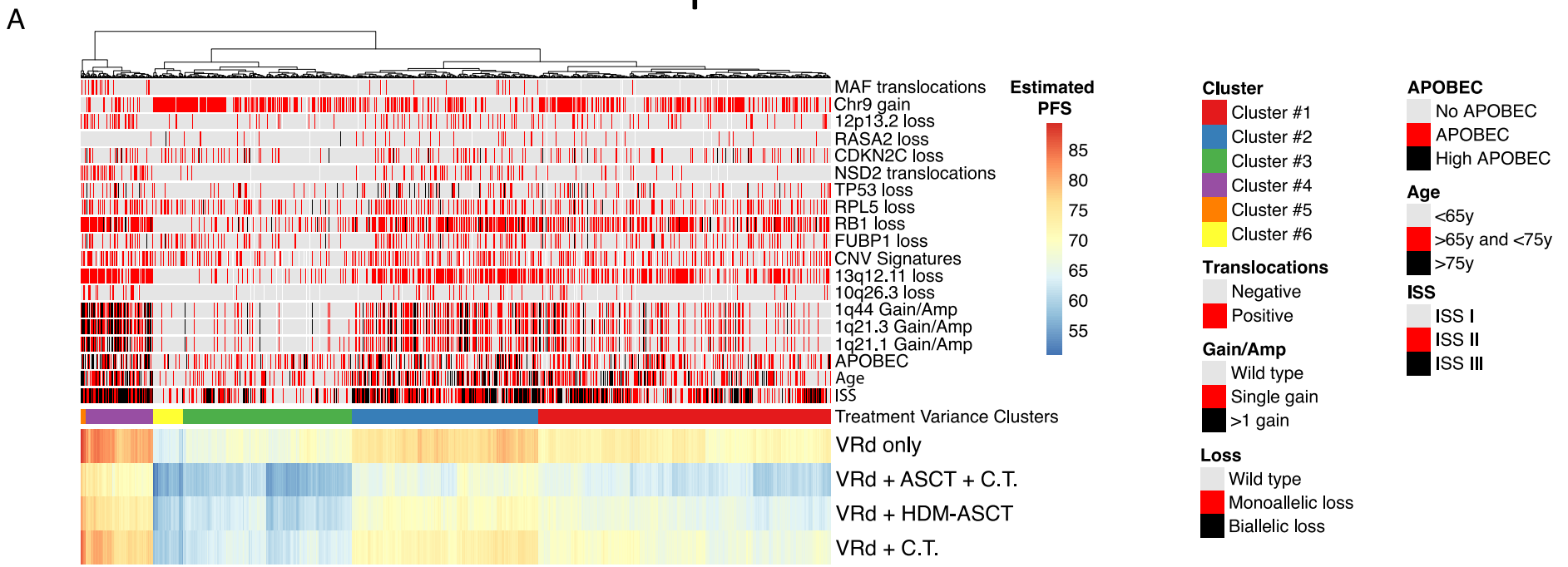
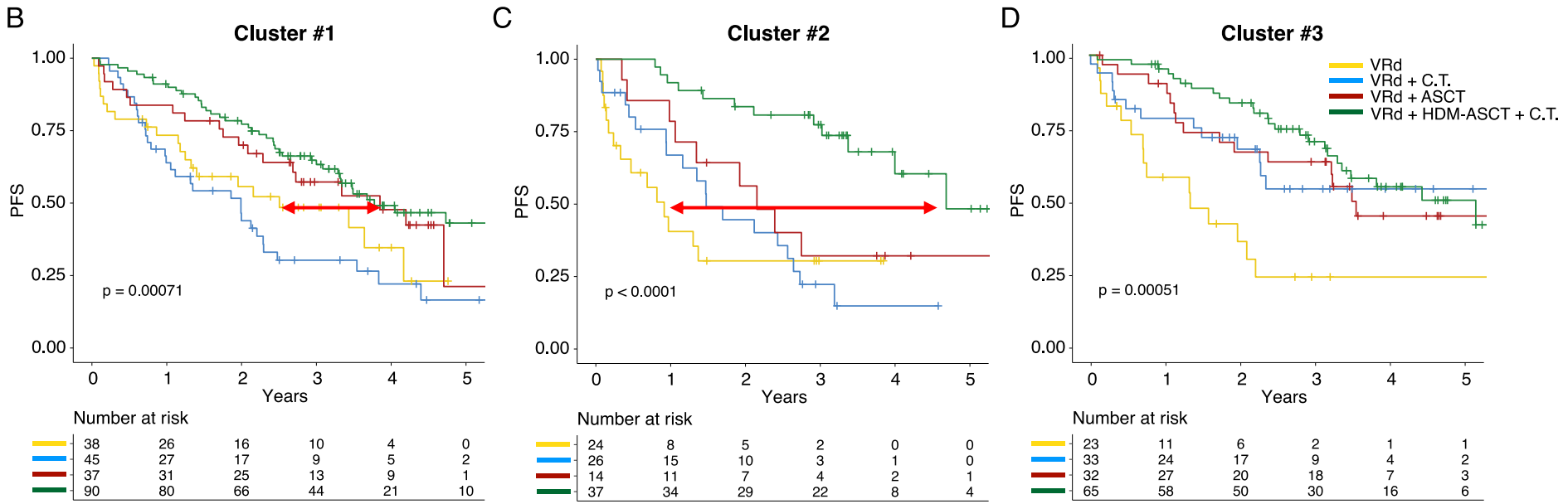


Maura et al, 2023 submitted

Personalized survival prediction and treatment variance





VRd+ASCT+maint vs VRd

Cluster 1: PFS 1.5x

Cluster 2: PFS 4.7x

Maura et al, 2023 submitted

Predicting impact of autologous transplant (ASCT)

at the single patient level

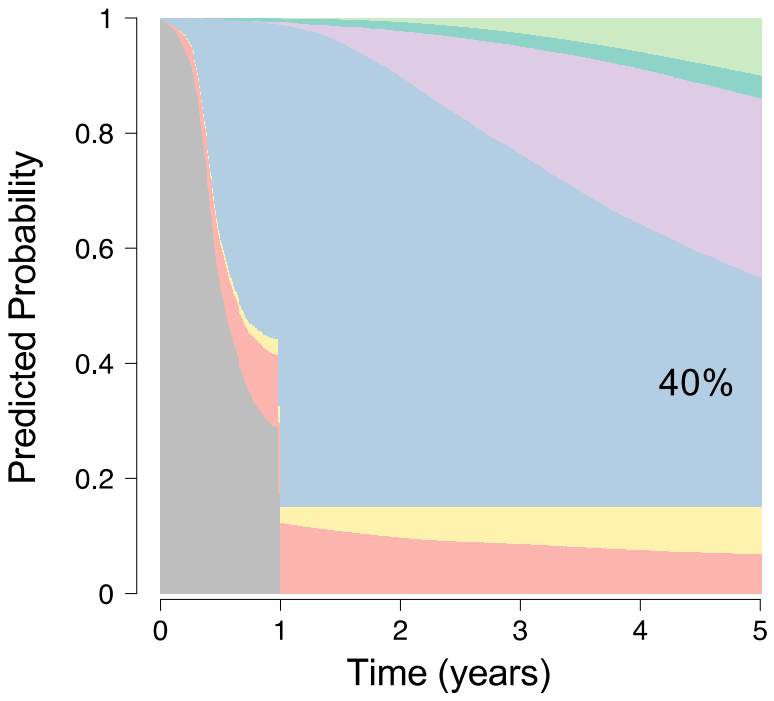
GDH9daaa6d8 – Moffitt

Age<65y, Male, ISS I, APOBEC neg, 1q gain neg, 1p loss

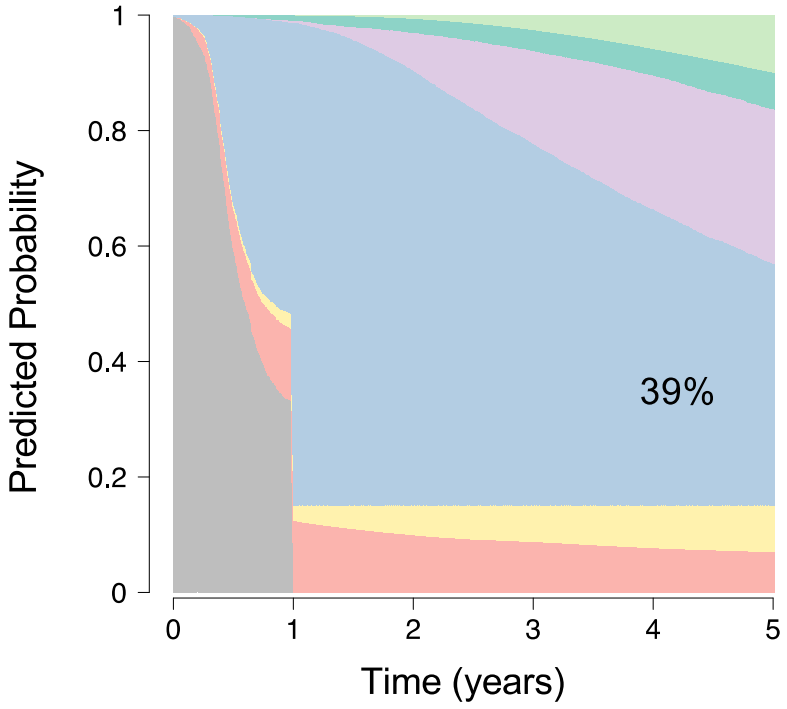
Treated with CyBorD + ASCT + maintenance

Outcomes: Alive in remission at 4.6 years

CyBorD + ASCT + Cont.



CyBorD + Cont.

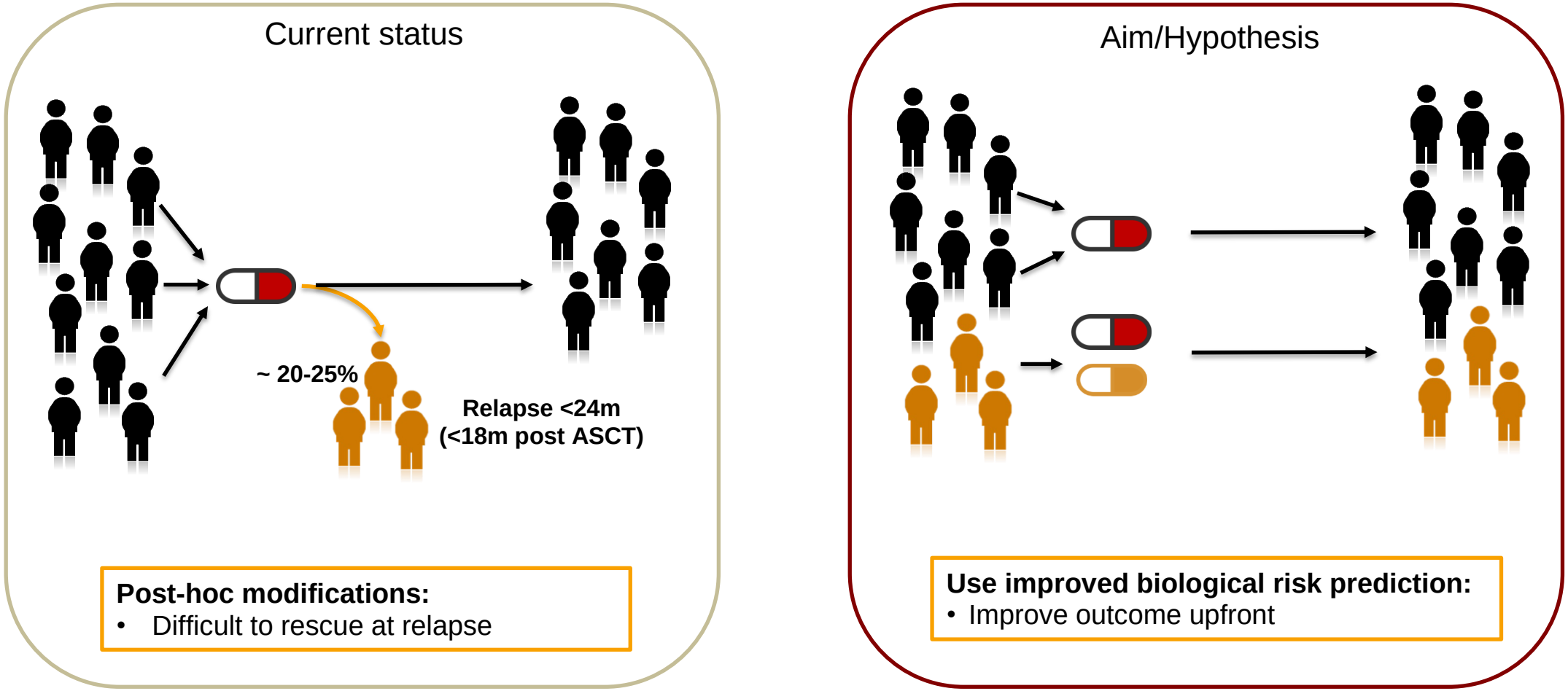


Courtesy of Francesco Maura (U. of Miami)

What is the future of treating HR MM?

3rd: treat HR effectively upfront

High-Risk MM - the unmet need

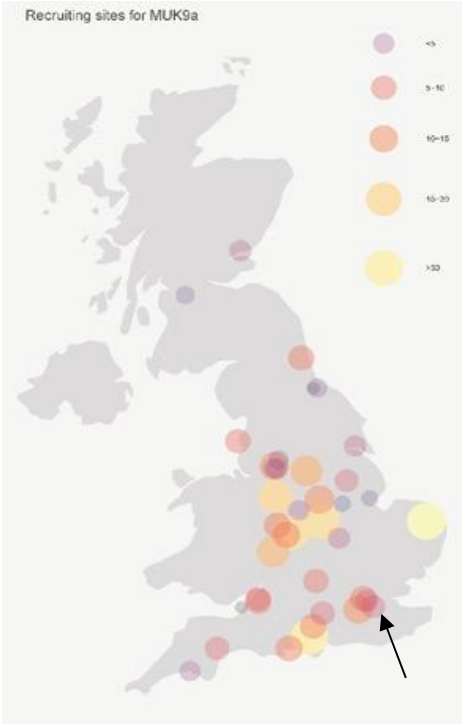


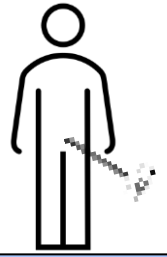
ASCT = autologous stem cell transplantation

Currently no uniform treatment standard

UK multi-centre phase 2 trial for UHiR MM and PCL - Screening protocol

39 NHS hospitals
Mostly community (DGH)
Sep 2017 – Jul 2019





Suspected or confirmed NDMM/PCL
Recruited to OPTIMUM Screening (n=472)

Enrollment

Did not have a symptomatic Multiple Myeloma or PCL diagnosis (n=60)
- Asymptomatic Myeloma (n=22)
- MGUS (n=14)
- Other (n=16)
- No confirmed diagnosis (n=8)

Central sample

Multiple Myeloma or PCL diagnosis (n=412)

Genetic & GEP Risk screening

87% complete screening result

Risk screening result (n=412)
- **Ultra High risk (n=138)**
- Non-high risk (n=221)
- Partial result (n=24)
- Missing risk result (n=29)

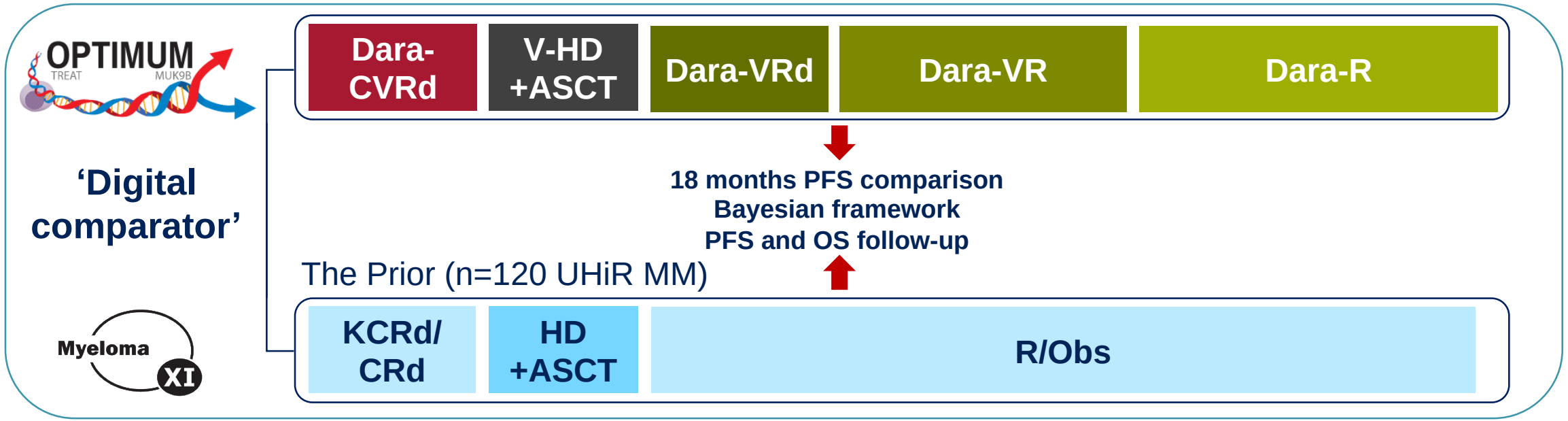
Recruitment 10 months ahead of projection

Remained in OPTIMUM Screening
(n=305; including 30 high risk patients)
- Standard of Care therapy – Data collection

Registered and eligible for OPTIMUM Treatment Trial (n=107)

Presented by: **Martin Kaiser, MD, FRCP, FRCPath**
@MyMKaiser

Clinical UHiR context – digital comparator trial



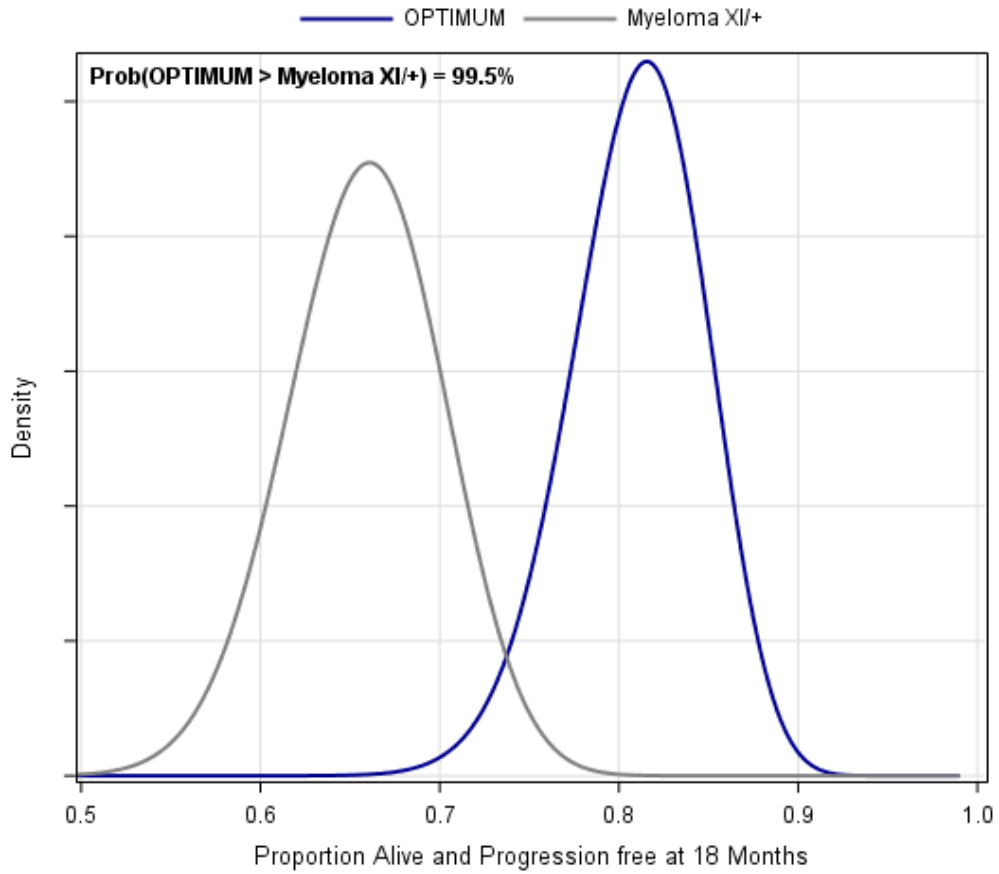
OPTIMUM design (appraisal framework for external comparator trials (Thorlund et al., 2020))**:**

- **Currently no treatment standard for UHiR group – UK standard at design: VTD, single ASCT, observation**
- **Mirrored molecular UHiR criteria** (Double hit and/or SKY92 risk signature)
- **Contemporaneous external dataset: most recent UK phase 3 Myeloma XI trial for NDMM**
  - KCRd (carfilzomib, cyclophosphamide, lenalidomide, dexamethasone) or CRd induction
    At time of design randomisation result not yet available
- **Recruitment in same healthcare system**
  - Same NHS hospitals/geography, virtually identical trial entry criteria

Presented by: **Martin Kaiser, MD, FRCP, FRCPath**
@MyMKaiser

Brown S, et al., BMJ Open 2020
Jackson G., et al., PLOS Med 2021

OPTIMUM primary endpoint result
18 months PFS comparison against Myeloma XI Prior



99.5% chance
OPTIMUM is **superior**
to Myeloma XI Prior
(>85% pre-specified as efficacious)

Follow-up limited:
6 cycles Consolidation 1

Median Follow-up 27.1 months (95% CI 25.1-29.3)

Conclusions

- Consensus on HR disease definition is lacking
  - 2 HR lesions, 1 + HR transcriptome, CTCs etc?
- Current risk prediction strategies are are imperfect for
  - Accuracy
  - Prediction of Tx effect
- Even novel drugs do not abrogate the HR status of patients
  - CAR-T? BsAbs? Earlier use?
- Promise of large knowledge banks
- Need for ad-hoc studies in HR even as we learn how to define and predict HR

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