Aims of induction therapy in fit myeloma patients

Kwee Yong
Professor of Haematology
UCL

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Disclosures

	Sanofi	Janssen	Amgen	Takeda	Pfizer	BMS
Consultancy	X	X				
Speaker fees	X		X	X	X	
Honoraria	X	X	X	X	X	
Research funding	X	X	X	X		X

Maximize disease free survival, minimize treatment burden

- Highly effective induction regimens
- Longest PFS reported now >80 months
  - Cassiopeia 82m, Perseus 84m, Determination 68m

- What unanswered questions remain? How can we do better?
  - What is the cost: to payers, to the patients
  - Is this benefit seen in all patients?
  - Are we meeting patient goals?

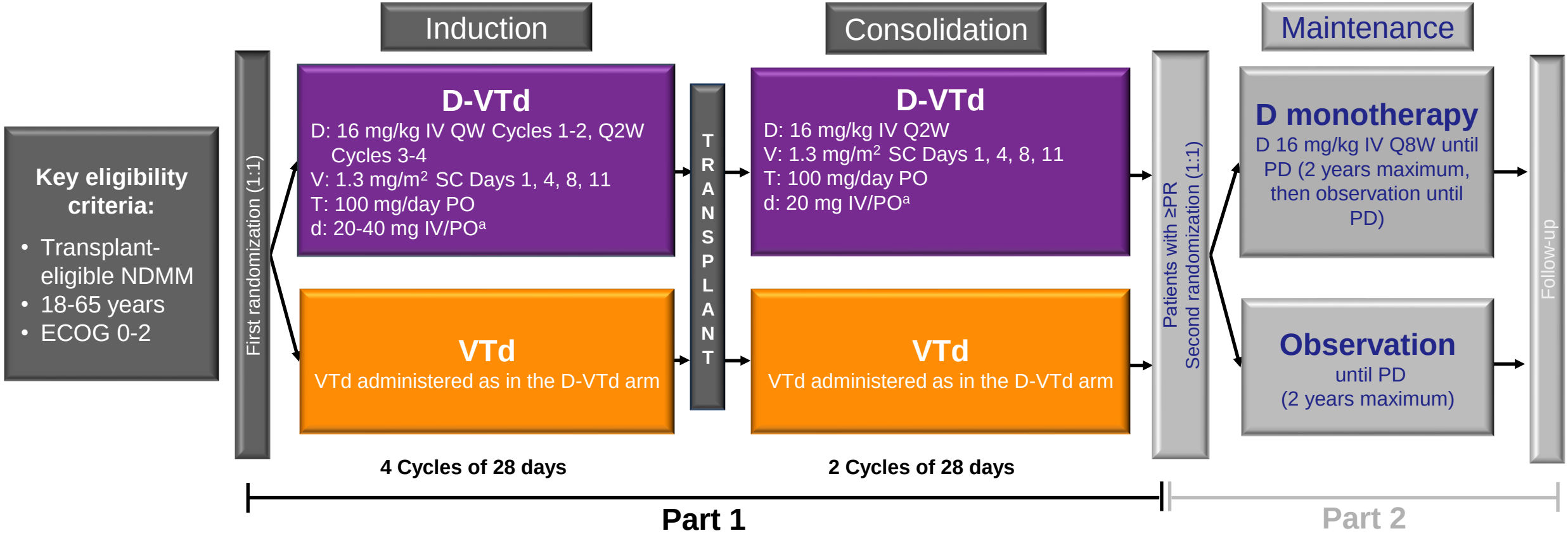
Tailoring and individualizing therapy

Talk outline: what are the key questions?

- CD38 antibody regimens: one size fits all?
- ASCT: one size fits all?
- Maintenance therapy: what is the future?
- Risk adapted therapy: how best to do this
- High risk disease: what is the best approach?
- Is the future immune therapies
  - Belantamab
  - BsAB
  - CAR-T

CASSIOPEIA Study Design

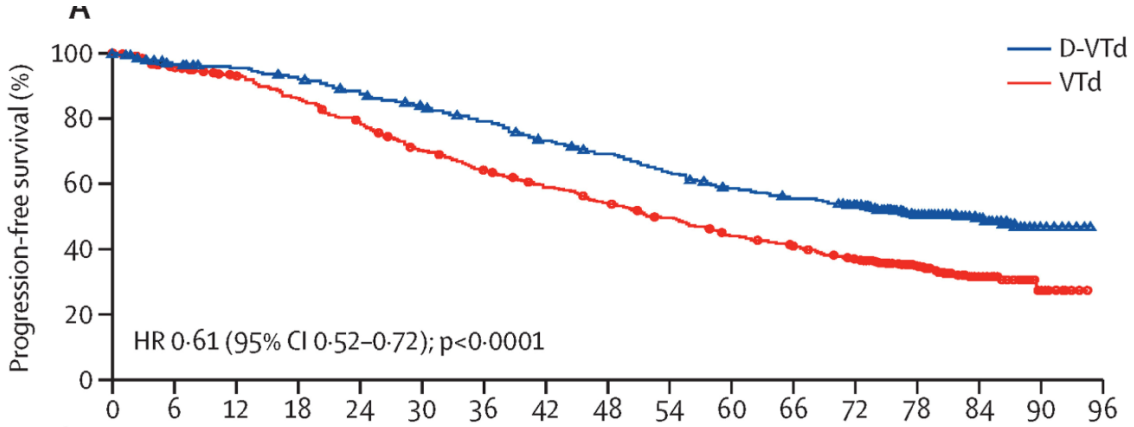
- Phase 3 study of D-VTd versus VTd in transplant-eligible NDMM (N = 1,085), 111 sites from 9/2015 to 8/2017



Moreau et al. The Lancet, 2019
D-VTd, daratumumab/bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; QW, weekly; Q2W, every 2 weeks;
SC, subcutaneous; PO, oral; PR, partial response; Q8W, every 8 weeks; PD, progressive disease.
[a]Dexamethasone 40 mg on Days 1, 2, 8, 9, 15, 16, 22, 23 of Cycles 1-2 and Days 1 & 2 of Cycles 3-4; 20 mg on Days 8, 9, 15, 16 of Cycles 3-4; 20 mg on Days 1, 2, 8, 9, 15, 16 of Cycles 5-6.

CASSIOPEIA study: Dara-VTd versus VTd

PFS Dara-VTd 83·7 months cf. VTd

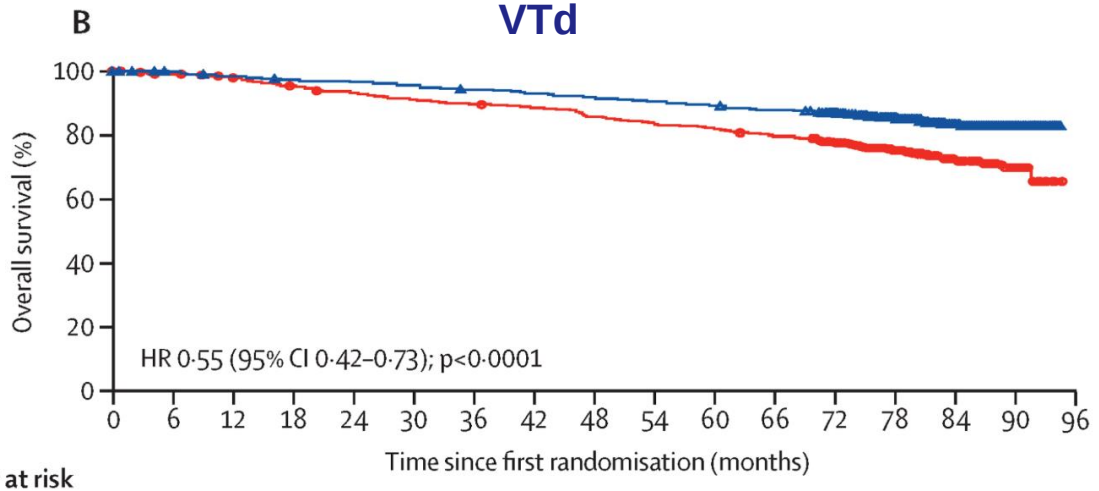


Number at risk (number censored)

VTd	542	504	477	441	400	354	324	293	268	243	214	197	171	103	49	13	0
	(0)	(16)	(29)	(30)	(32)	(35)	(36)	(40)	(41)	(44)	(46)	(49)	(56)	(115)	(161)	(194)	(207)
D-VTd	543	512	500	484	459	434	408	375	352	323	296	278	260	158	82	17	0
	(0)	(13)	(19)	(20)	(22)	(25)	(27)	(29)	(32)	(32)	(35)	(36)	(46)	(135)	(209)	(271)	(288)

PFS in Dara-VTd arm 83·7 months [95% CI 70·2–not estimable (NE)]) cf. VTd (52·8 months [47·5–58·7]

OS at 72m 86% for Dara-VTd cf. 77.7% VTd



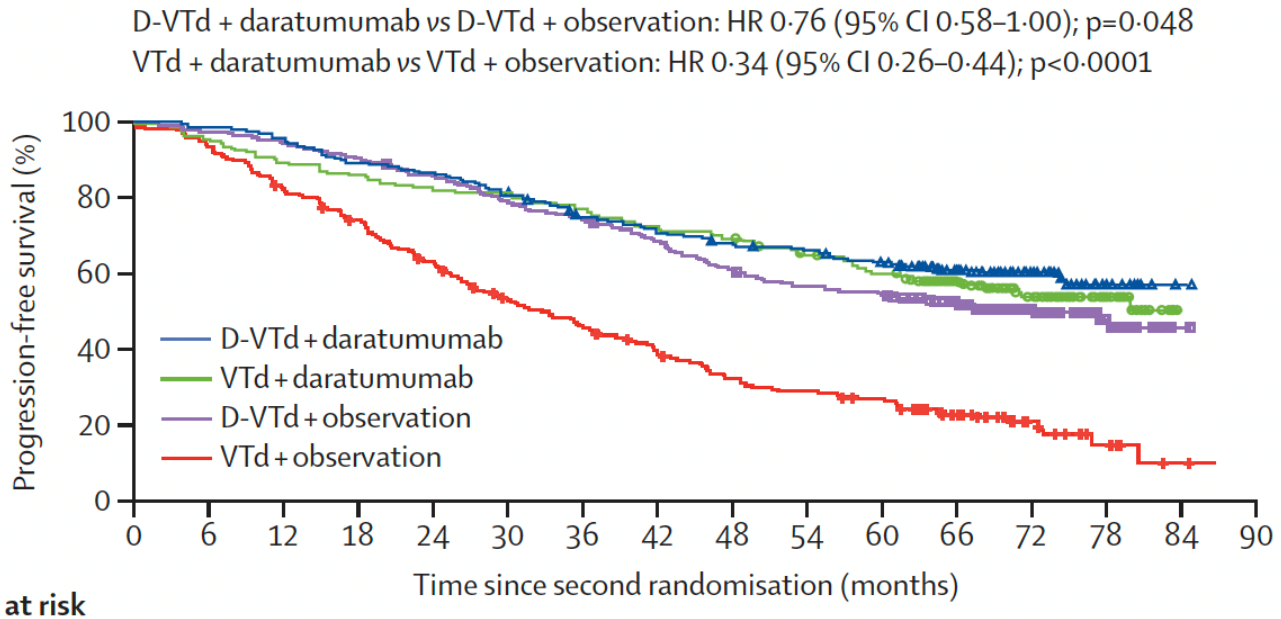
Number at risk (number censored)

VTd	542	531	521	505	494	481	475	467	453	441	433	419	396	242	115	33	0
	(0)	(5)	(9)	(11)	(12)	(12)	(12)	(13)	(13)	(13)	(13)	(14)	(28)	(171)	(292)	(371)	(403)
D-VTd	543	535	526	520	517	511	503	496	490	482	476	467	452	285	147	29	0
	(0)	(6)	(7)	(8)	(8)	(8)	(9)	(9)	(9)	(9)	(9)	(10)	(20)	(180)	(314)	(431)	(460)

72-month overall survival rates were 86·7% (95% CI 83·5–89·3) for the D-VTd group and 77·7% (73·9–81·0) for the VTd group

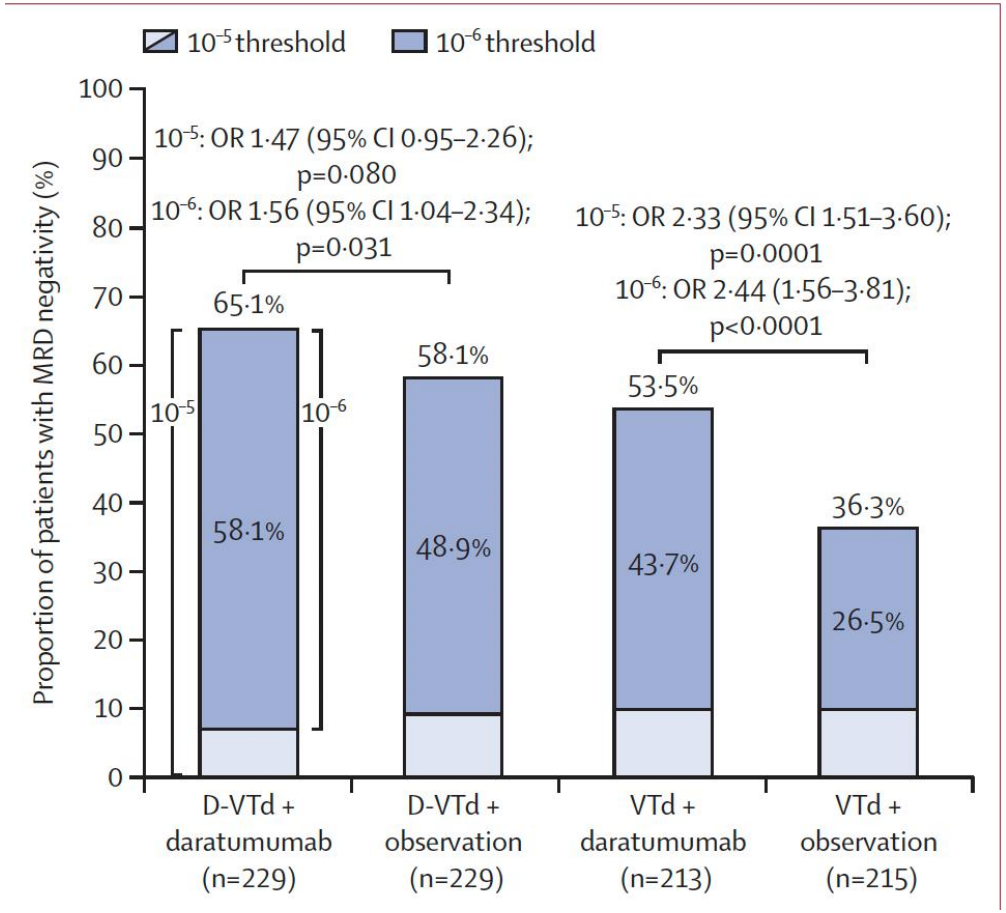
Benefit of daratumumab either as pre- or post-ASCT therapy

PFS according to induction and maintenance



Number at risk (number censored)																
VTd + observation	215	201	176	156	132	107	92	77	63	56	50	32	13	5	1	0
	(0)	(0)	(1)	(3)	(4)	(8)	(8)	(10)	(11)	(11)	(13)	(24)	(41)	(46)	(49)	(50)
VTd + daratumumab	213	203	190	183	175	172	164	153	147	135	123	92	48	23	0	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(5)	(32)	(71)	(96)	(118)	(118)
D-VTd + observation	229	223	216	207	195	179	169	155	138	127	122	90	55	22	1	0
	(0)	(0)	(0)	(0)	(1)	(1)	(1)	(2)	(2)	(3)	(3)	(31)	(63)	(94)	(114)	(115)
D-VTd + daratumumab	229	226	217	204	198	187	168	158	151	146	137	106	51	19	1	0
	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(4)	(5)	(6)	(8)	(35)	(89)	(119)	(137)	(138)

CR and MRD negative rate at any point after consolidation

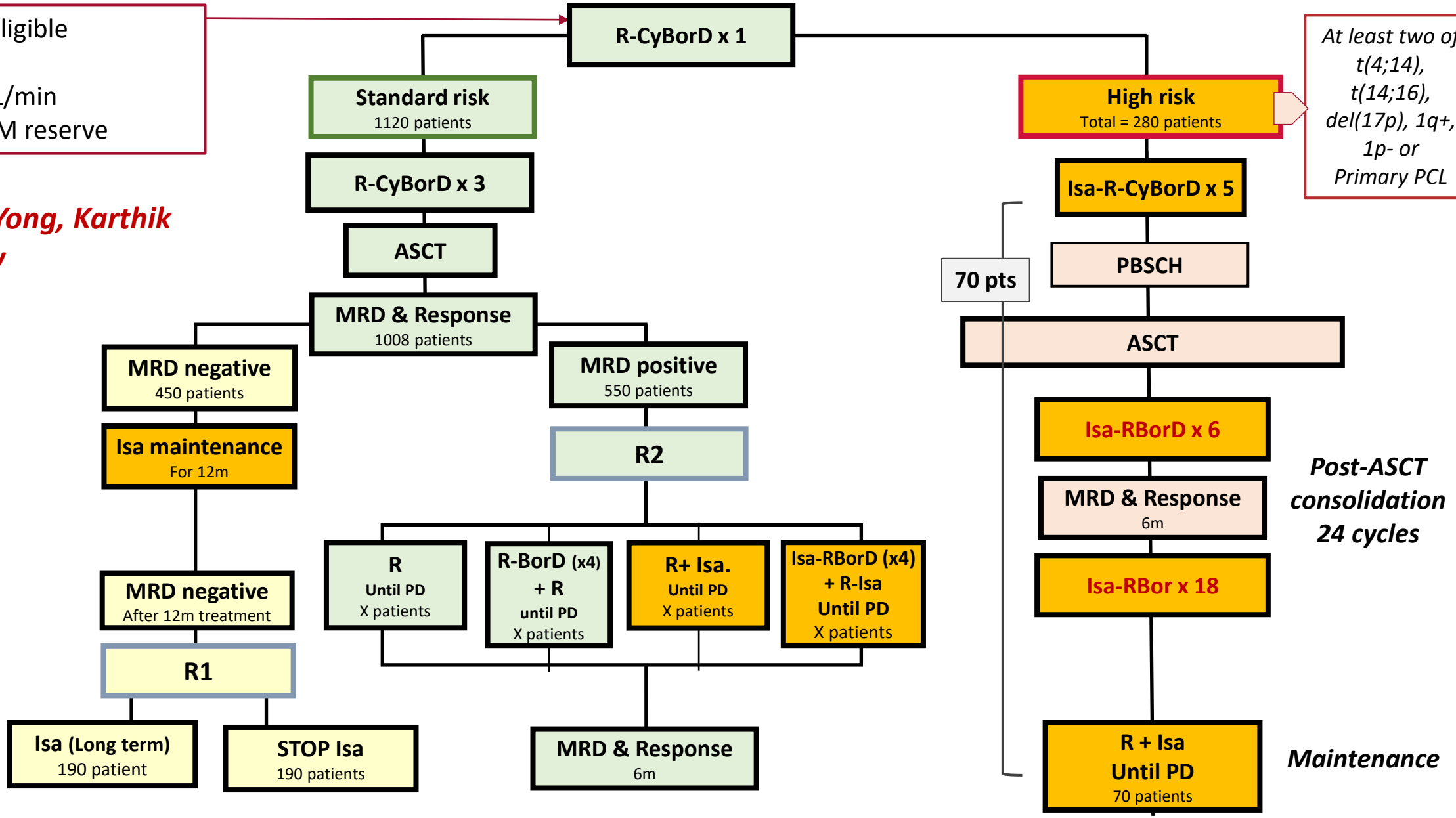


Moreau et al, Lancer Oncology 2024; 25:1004.

RADAR protocol 7.0: Extended induction and post-ASCT consolidation in HR arm

Transplant eligible
ECOG 0-2
GFR ≥ 30 mL/min
Adequate BM reserve

PIs: Kwee Yong, Karthik Ramasamy



All patients are tested for MRD at 12 and 24 months

Risk adapted therapy?

- Induction according to genetic / biological risk
  - **Dedicated high risk trials**
- Adapted according to
  - quality / depth of response
  - Toxicity and tolerability
- What do patients think?

Trial therapy

Bridging
Max
2 cycles

SOC (VTD CVD)

Induction
Max 6 cycles
(incl bridging)

Dara-CVRd

Daratumumab iv 16 mg/kg
Cycle 1&2: Days 1, 8, 15
Cycle 3+: Day 1
Cyclophosphamide po 500 mg
Days 1, 8
Bortezomib sc 1.3 mg/m^2
Days 1, 4, 8, 11*
Lenalidomide po 25 mg
Days 1-14
Dexamethasone po 40 mg†
Days 1, 4, 8, 11

21d cycles

Stem Cell Mobilisation

V-HD-MEL +ASCT

Melphalan iv 200 mg/m^2
Day -1
Autologous Stem Cell Translantation
Day 0

Bortezomib 1.3 mg/m^2
Days -1, +5, +14,*
Weekly after haematopoietic recovery

Consolidation 1
6 Cycles
Start 100-120d post ASCT

Dara-VRd

Daratumumab sc
1800 mg Day 1
Bortezomib sc 1.3 mg/m^2
Days 1, 8, 15, 22*
Lenalidomide po 25 mg
Days 1-21
Dexamethasone po 40 mg †
Day 1, 8, 15, 22

28d cycles

Consolidation 2
12 Cycles

Dara-VR

Daratumumab sc
1800 mg Day 1
Bortezomib sc 1.3 mg/m^2
Days 1, 8, 15*
Lenalidomide po 25 mg
Days 1-21

28d cycles

Maintenance
Until progression

Dara-R

Daratumumab sc
1800 mg Day 1
Lenalidomide po 25 mg
Days 1-21

28d cycles

Central Response, Birmingham University (HydraShift)

*Permissive bortezomib dose reduction schedule
†20mg for elderly/frailer

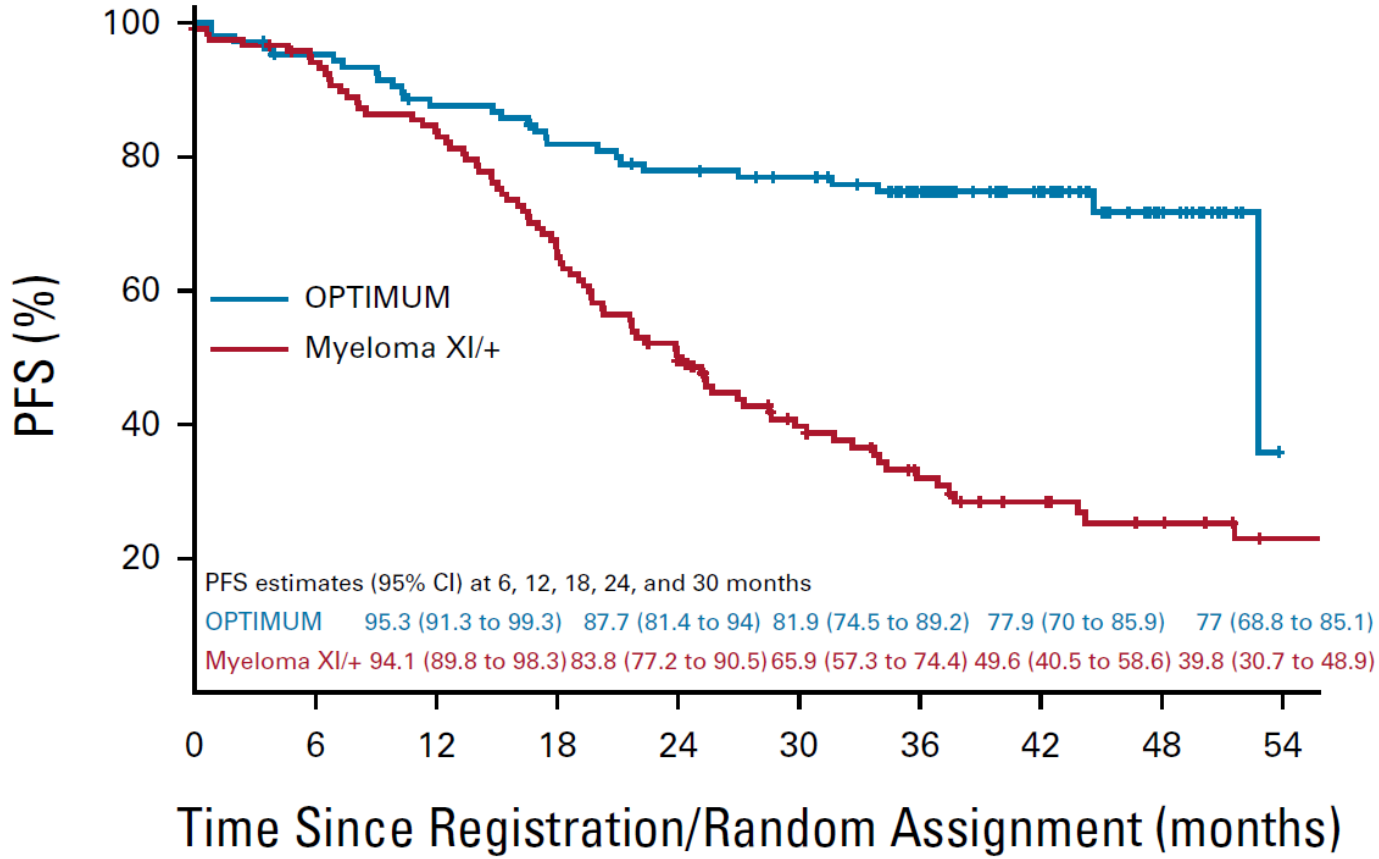
Day 100-120 post-ASCT

Central MRD, HMDS Leeds (Flow cytometry, 10^{-5} sensitivity)

Brown S, et al., BMJ Open 2021

Kaiser et al., J Clin Oncol 2023

PFS for OPTIMUM and the MMXI comparator data set with PFS estimates at 6, 12, 18, 24, and 30 months

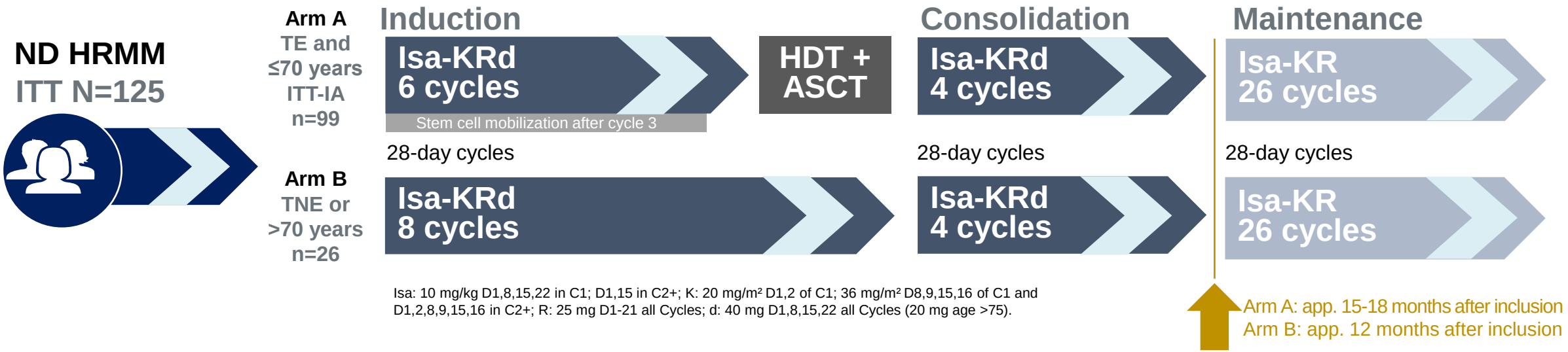


No. at risk (No. censored):

OPTIMUM	107 (0)	100 (2)	91 (3)	84 (4)	79 (5)	75 (8)	59 (22)	37 (44)	13 (67)	0 (79)
Myeloma XI/+	120 (1)	110 (3)	98 (3)	77 (3)	56 (5)	38 (13)	27 (17)	20 (21)	15 (24)	9 (29)

Kaiser et al., J Clin Oncol 2023

GMMG-CONCEPT trial Design



HRMM criteria: ISS stage II or III **PLUS** ≥1 of: del(17p), t(4;14), t(14;16) and/or >3 copies 1q21 (amp1q21)
Primary objective: MRD negativity after consolidation (NGF, 10^{-5})
Secondary objective: PFS; Key tertiary objectives: ORR, OS, safety

Footnotes

Leypoldt, JCO 2023

IFM 2018-04 Study design

Key inclusion criteria:

- Age < 66
- **Newly diagnosed multiple myeloma**
- **Transplant-eligible**
- **High-risk FISH :** t(4;14), 17p Del, t(14;16)
- ECOG 0-2

Objectives:

- **Primary Objective :** Feasability
  primary endpoint : >70% patients receiving 2nd transplant

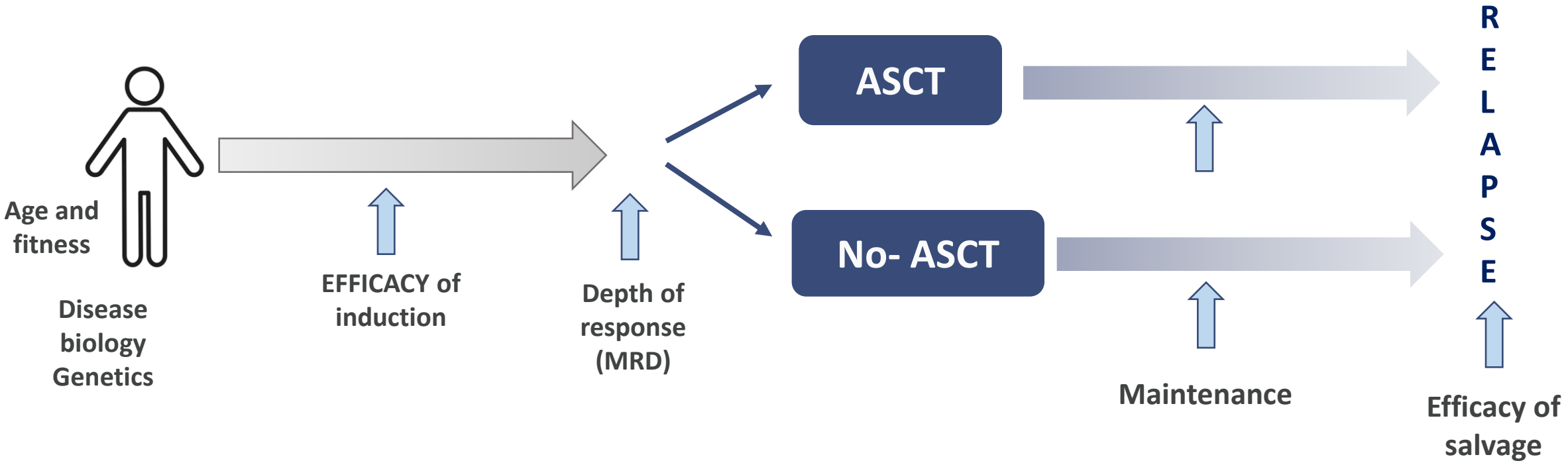
- **Secondary Objectives:** Safety, ORR, PFS, OS, stem-cell collection

Induction Dara-KRd x 6 → Stem cell collection → **ASCT#1** → **Consolidation** Dara KRd x 4 → **ASCT#2** → **Maintenance** Dara Len 2 years

Induction	Stem cell collection	ASCT#1	Consolidation	ASCT#2	Maintenance
Dara : 16 mg/kg IV D1,8,15,22 (cycle 1 and 2) D1 D15 (Cycle 3 to 6) **K : (20)36 mg/m2 IV** D1-2, 8-9, 15-16 **Len : 25 mg** D1-21 **Dex : 20 mg** D1-2, 8-9, 15-16, 22-23 **28-day cycle**	Cyclo GCSF +/- Plerix	**Mel 200**	**Dara : 16 mg/kg IV** D1 D15 **K : 56 mg/m2 IV** D1, 8, 15 **Len : 15 mg** D1-21 **Dex : 40 mg** D1, 8, 15, 22 **28-day cycle**	**Mel 200**	**Dara :** 16 mg/kg IV every 8 weeks **Len :** 10 mg 21/28

Touzeau et al., Abstract 207- ASH 2023

Benefit of frontline ASCT: Does one size fit all?



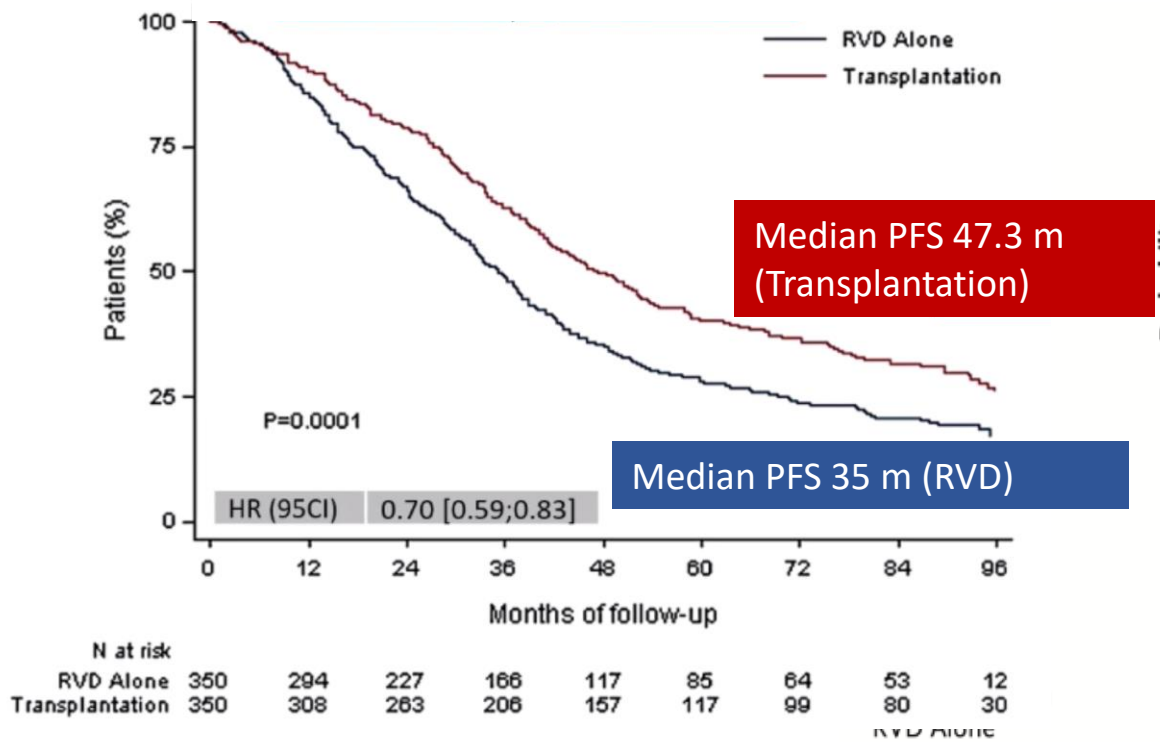
HDM-ASCT vs VRd: progression-free survival

IFM 2009

Median follow up 89.8m

1 1 year len maintenance

N=700



Median PFS 47.3 m (Transplantation)

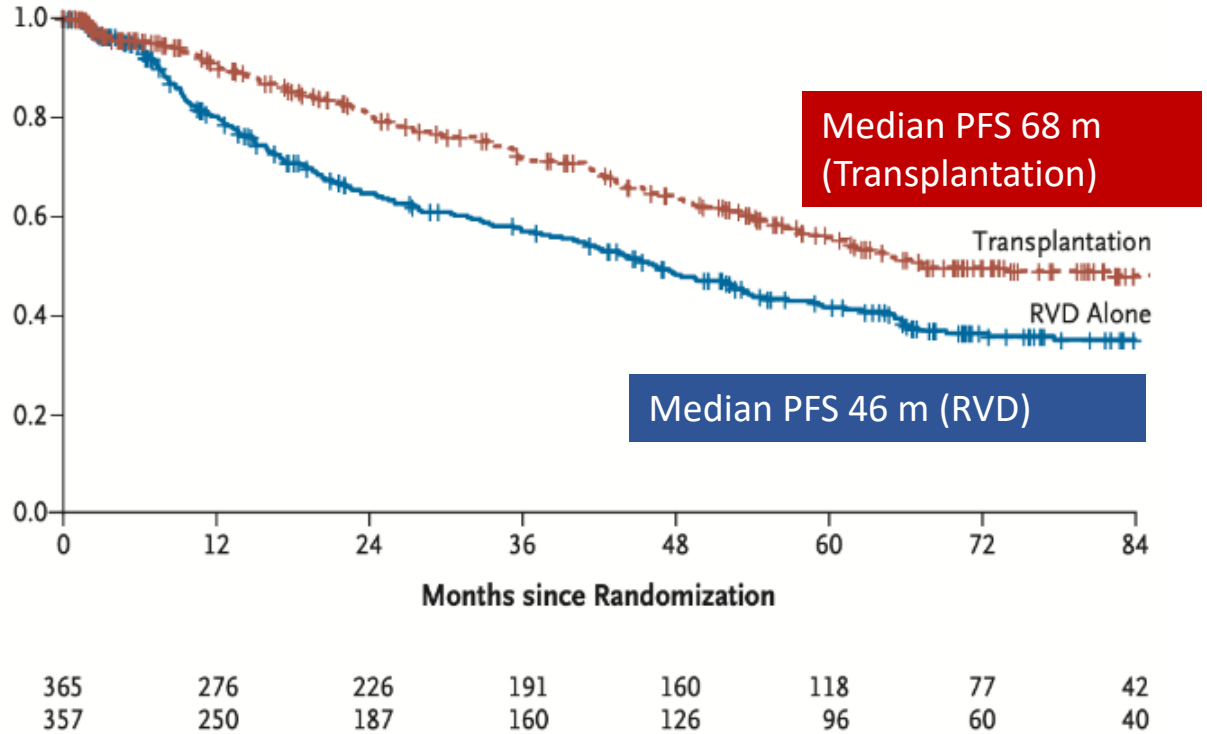
Median PFS 35 m (RVD)

DETERMINATION

Median follow up 76m

Len maintenance until PD

N=722



Median PFS 68 m (Transplantation)

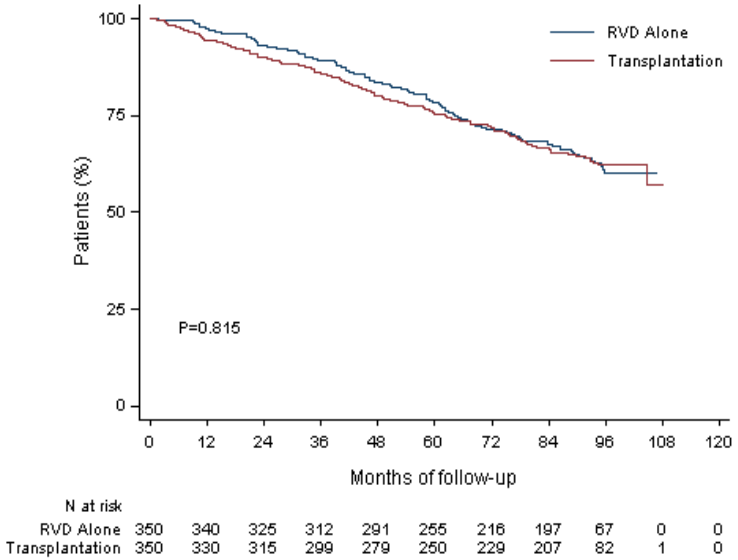
Median PFS 46 m (RVD)

HDM, high-dose melphalan; ASCT, autologous stem-cell transplantation; R, randomization; V, bortezomib; R, lenalidomide; d, dexamethasone; HR, hazard ratio; CI, confidence interval; P, p-value.

Perrot A et al. Blood. 2020; 136(s1):39 [Abstract #143, ASH 2020];
Richardson PG et al. N Engl J Med. 2022 Jun 5.

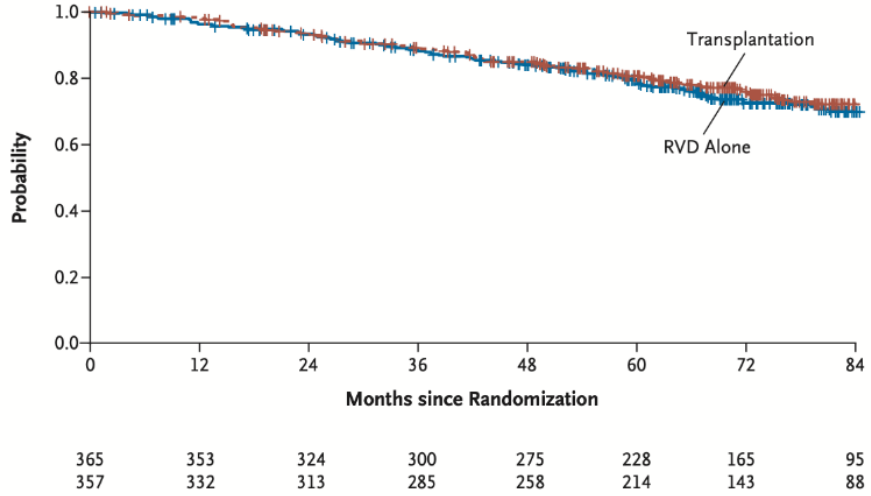
HDM-ASCT vs. VRd: OS in IFM 2009 and DETERMINATION

IFM 2009
8-year overall survival
62% vs. 60%



77% of relapsed patients in the RVd alone arm received salvage ASCT

DETERMINATION
5-year overall survival
81% vs. 79%



28% of relapsed patients in the RVd alone arm received salvage ASCT

No difference in OS despite varying proportion of patients in RVd arm receiving salvage ASCT

HDM, high-dose melphalan; ASCT, autologous stem-cell transplantation; R, lenalidomide; V, bortezomib; d, dexamethasone; P, p-value.

Perrot A et al. Blood. 2020; 136(s1):39 [Abstract #143, ASH 2020];
Richardson PG et al. N Engl J Med. 2022 Jun 5. doi: 10.1056/NEJMoa2204925.

DETERMINATION study: PFS by MRD status and randomization arm

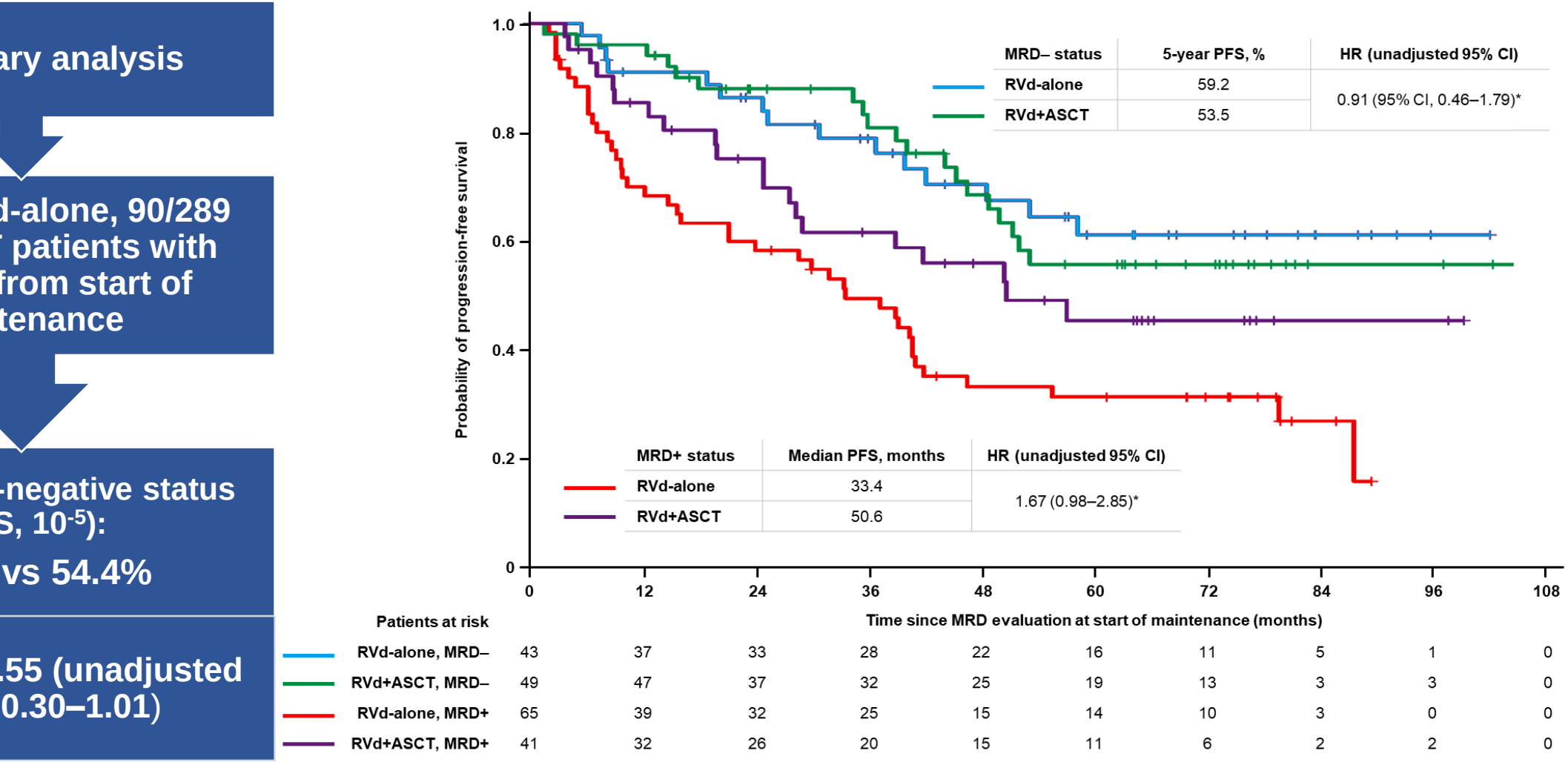
Preliminary analysis

108/291 RVd-alone, 90/289 RVd+ASCT patients with samples from start of maintenance

Rate of MRD-negative status (NGS, 10^{-5}):

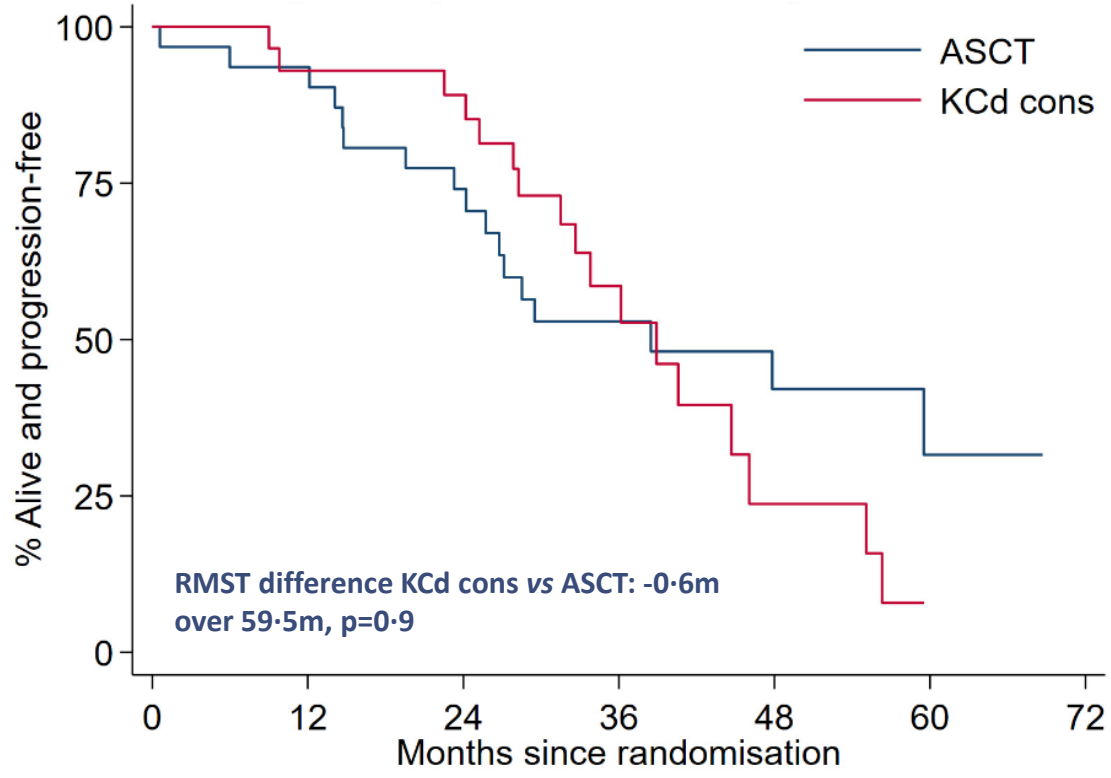
39.8% vs 54.4%

Odds ratio 0.55 (unadjusted 95% CI 0.30–1.01)



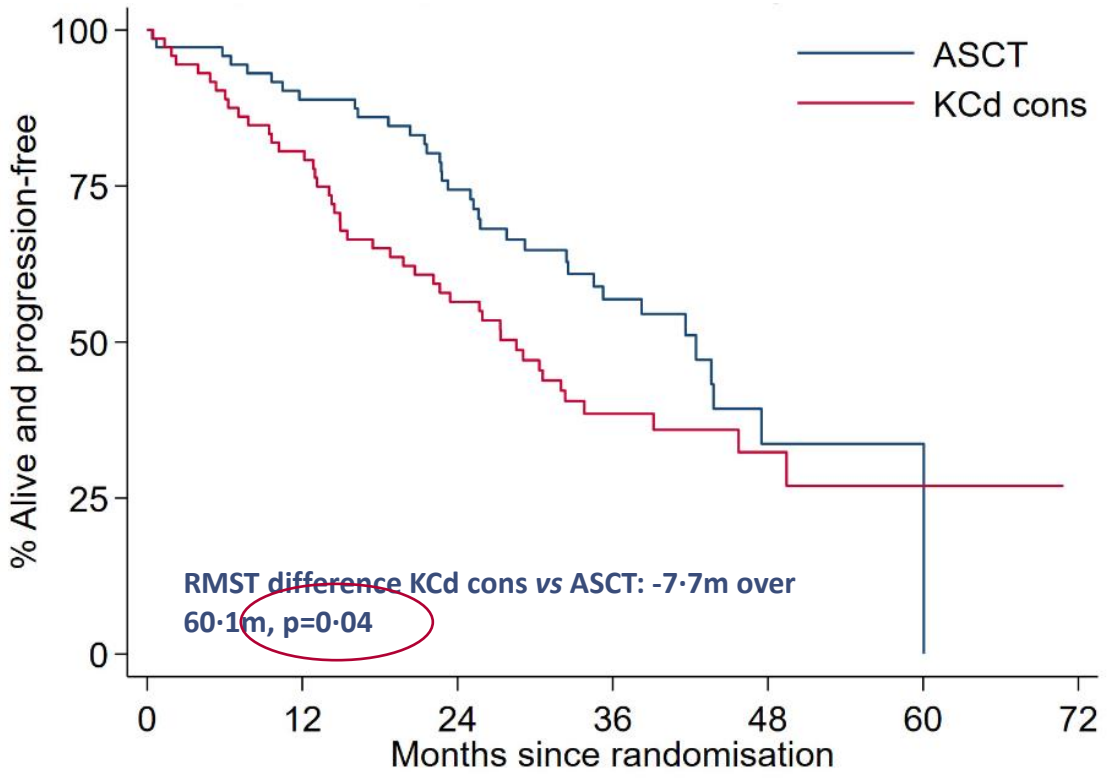
CARDAMON Study: Post-hoc analysis by MRD status post induction

(A) MRD negative



In follow-up							
ASCT	31	29	21	12	7	3	0
KCd cons	30	26	23	10	3	0	0

(B) MRD positive



In follow-up							
ASCT	72	63	50	27	6	1	0
KCd cons	73	57	39	17	6	2	0

ASCT may be of greater benefit to patients who remained MRD positive post-KCd induction (B)

IsaKRd vs ASCT

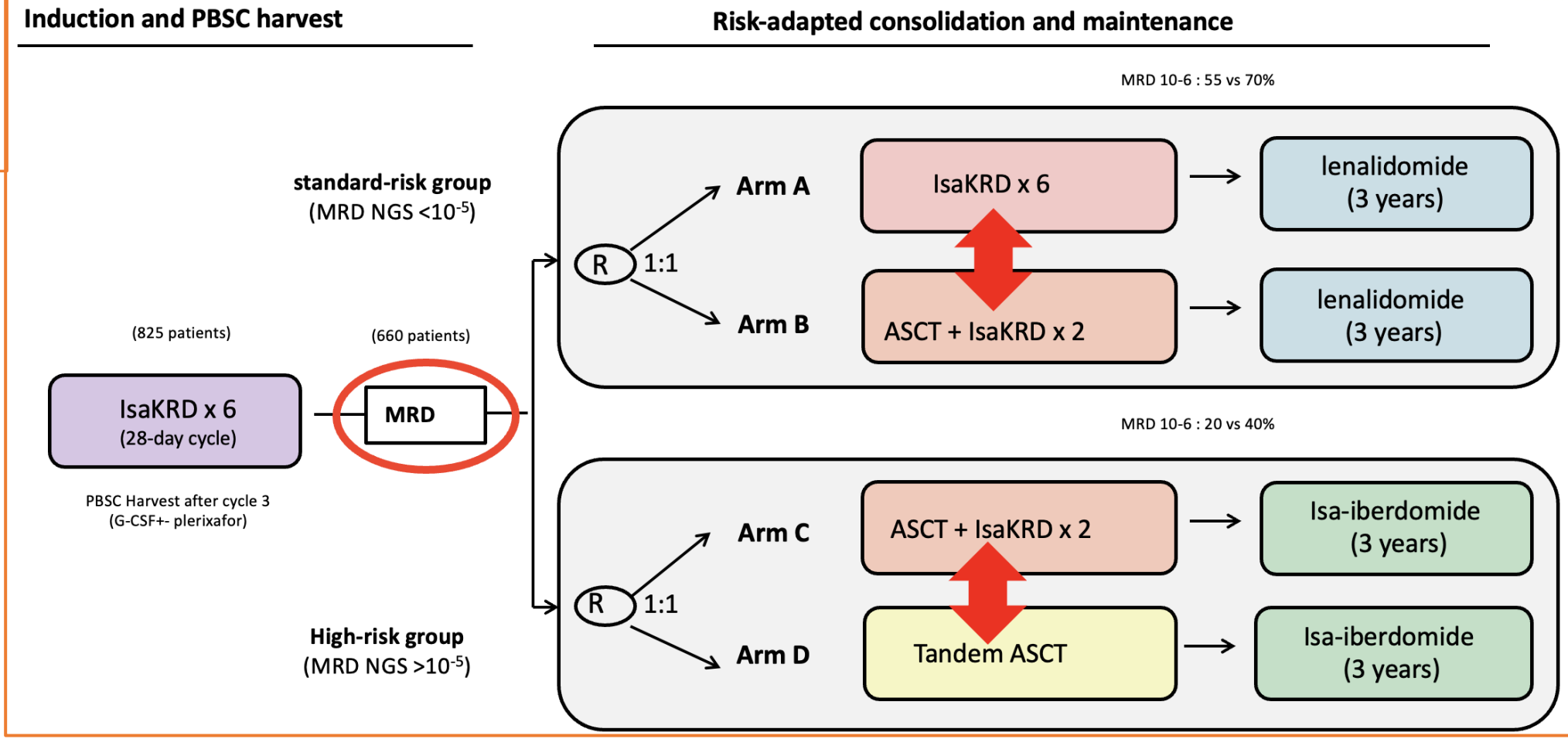
- **IsaKRd backbone**
- **IsaKRd as SOC following EMN24?**

MRD ADAPTED DESIGN

- **If MRD negative, do we still need ASCT?**
- **If MRD positive Tandem-ASCT?**

IFM Trial

MIDAS study : MInimal residual Disease Adapted Strategy



EMN- CARTITUDE 6

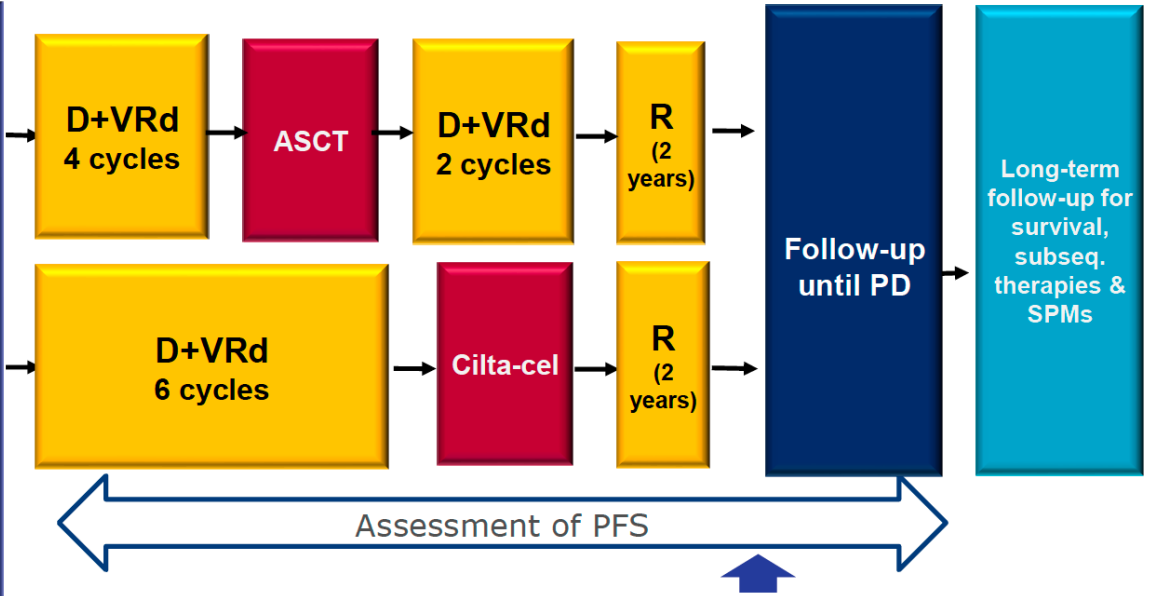
Dual primary endpoints:

Sustained MRD-neg CR and PFS

Stratification factors
a) **ISS staging**
b) **Cytogenetics**
c) **Age**

Key eligibility criteria:
- Newly diagnosed Patients
  - Eligible for initial ASCT
- All risk cytogenetics
- **Sample Size: ~750**

1:1 Randomization



MRD (BM aspirate) time-points:
- Within 7 days prior to melphalan conditioning.
- After D+VRd consolidation, prior to initiating lenalidomide maintenance therapy.
- At time of suspected CR or sCR.
- After initial CR or sCR is confirmed, then once 3 months after, then every 6 months (+1 month) for 5y, then yearly until PD for participants that are in CR or sCR.

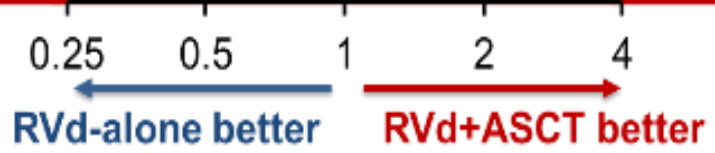
MRD by PET/CT (optional, if locally available): At time of BM MRD-negative CR and every 12 months in BM MRD-negative participants.

Dara, daratumumab; V, bortezomib; R, lenalidomide; d, dexamethasone; ASCT, autologous stem-cell transplantation; PFS, progression-free survival; MRD, minimal residual disease; CR, complete response; sCR, stringent complete response; ISS, International Staging System; SPM, second primary malignancy; PD, progressive disease; BM, bone marrow.

DETERMINATION : differential benefit of ASCT in specific subgroups

ASH 2023:[5] Subgroup analysis of PFS by race and BMI or sex suggest similar PFS, EFS, and OS with RVd-alone and RVd+ASCT in African American patients

Subgroup	AA patients			HR (95% CI)	White patients		
	RVd-alone	RVd+ASCT	HR	RVd-alone vs RVd+ASCT	RVd-alone	RVd+ASCT	HR
All	NR	61.4	1.07		44.3	67.2	1.67
BMI ≥30	NR	58.6	0.74		41.1	64.4	1.58
BMI <30	66.4	NR	1.86		45.3	82.3	1.78
Female	NR	58.6	0.90		42.0	NR	1.85
Male	66.4	NR	1.28		46.2	64.3	1.47

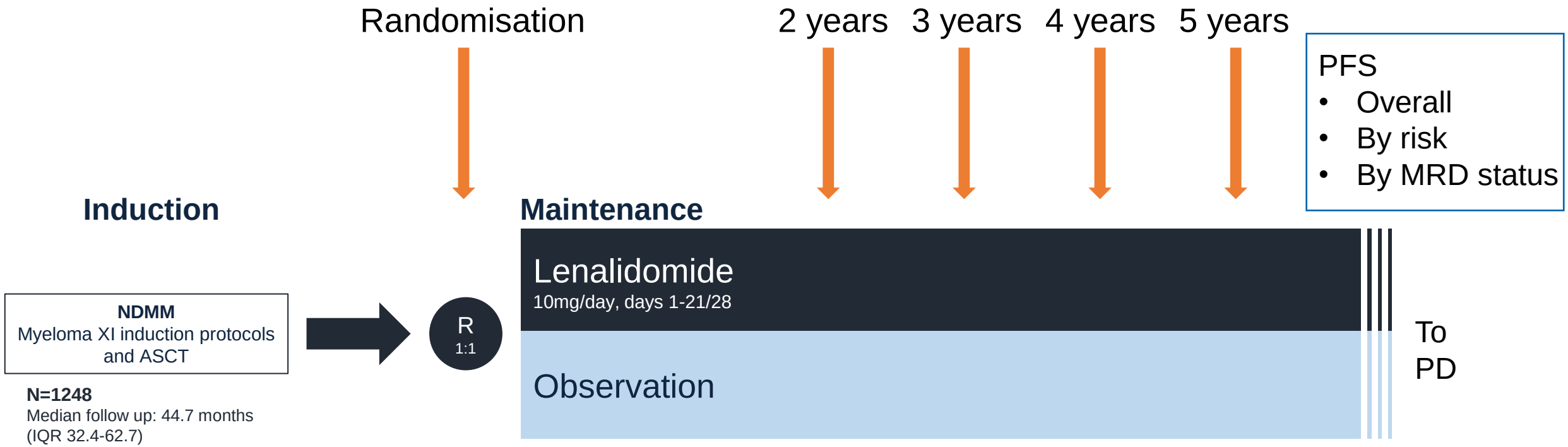


Zonder JA, et al. Blood 2023;142(Supplement 1):4762.

Maintenance: what are the key questions?

- How long?
- Newer agents and regimens
- Risk adapted approaches

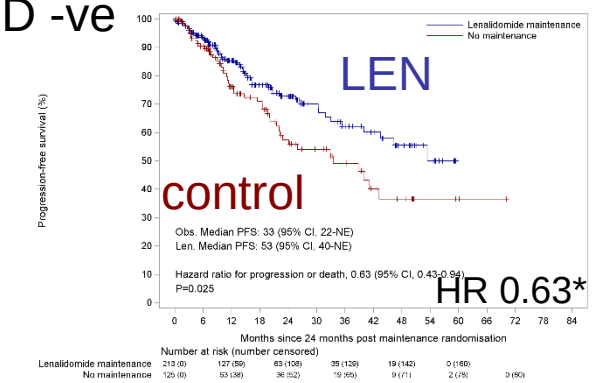
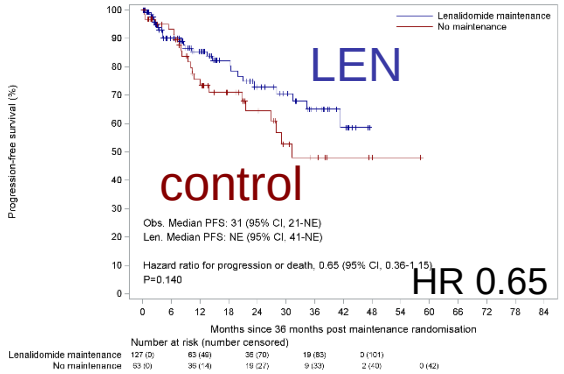
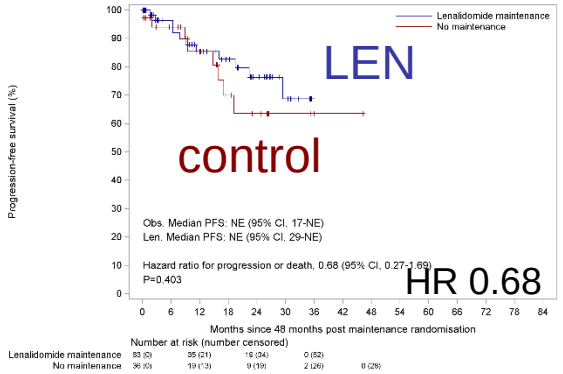
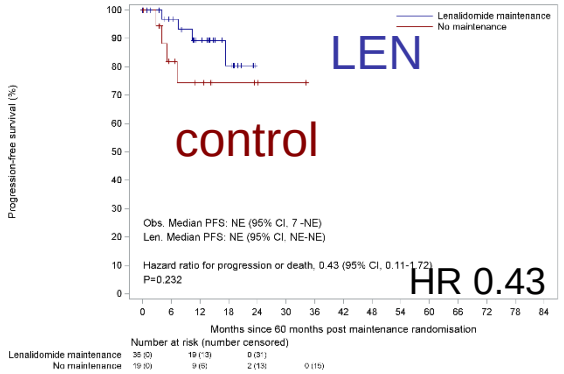
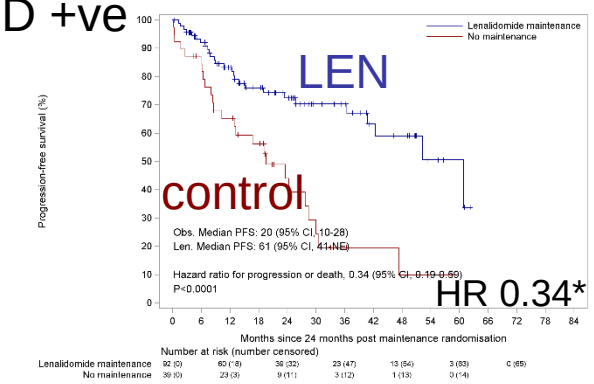
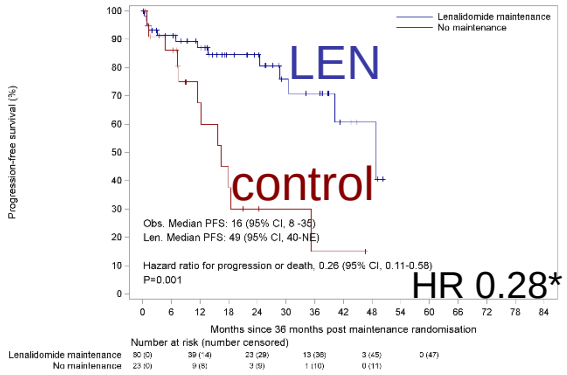
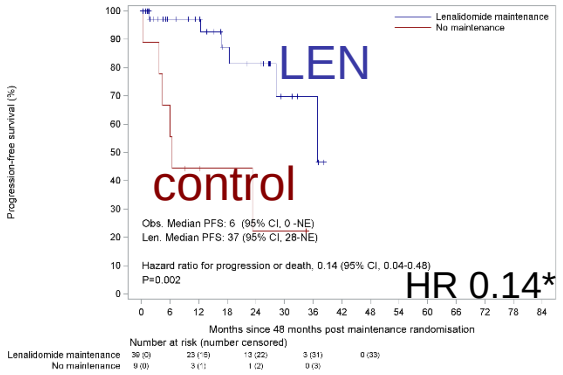
Multiple landmark analyses in Myeloma XI



Median duration of lenalidomide therapy 28 cycles (range 1-96)

- Patients still on therapy 330/730 (45%)

What is the optimum duration of treatment for (1) MRD –ve (2) MRD +ve patients?

	2 years	3 years	4 years	5 years
MRD -ve				
MRD +ve				

*p<0.05

Charlotte Pawlyn, ASH 2022

Maintenance: newer agents and combinations

- CD38 antibody
  - Cassiopeia study (Daratumumab), RADAR (Isatuximab)
- Lenalidomide plus proteasome inhibitor
  - Ixa-R (FiTNEss), carfilzomib-R (FORTE)
- Lenalidomide plus CD38 antibody
  - PERSEUS (Dara-R), RADAR (Isa-R)

Personalizing therapy for myeloma patients

We need to understand

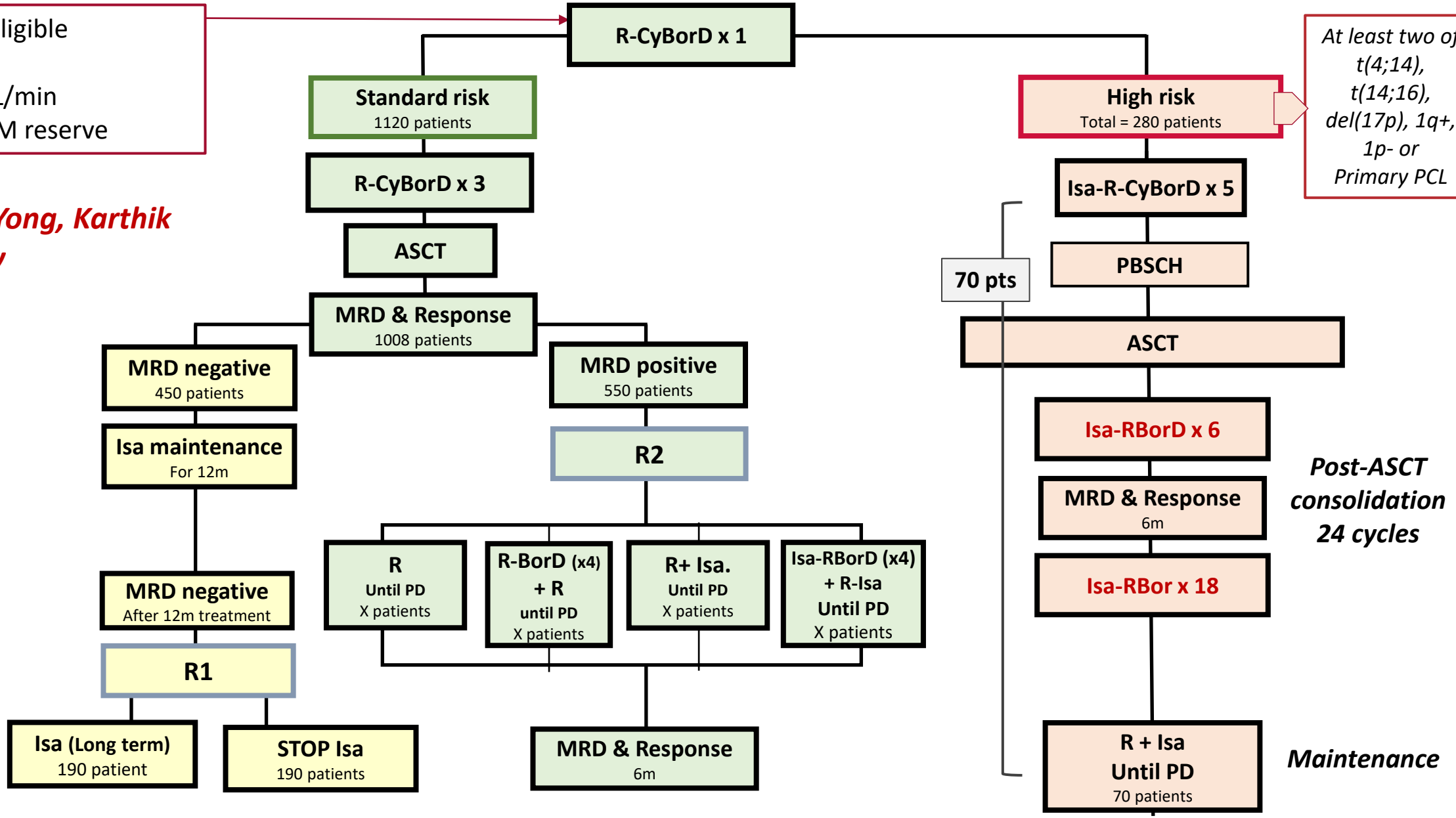
- Disease and host biology
- Molecular and population basis for heterogeneity
- Effects of our therapies on disease and host features

- We need to run studies that are translationally rich, so we can design better studies based on disease biology

RADAR protocol 7.0: Extended induction and post-ASCT consolidation in HR arm

Transplant eligible
ECOG 0-2
GFR ≥ 30 mL/min
Adequate BM reserve

PIs: Kwee Yong, Karthik Ramasamy

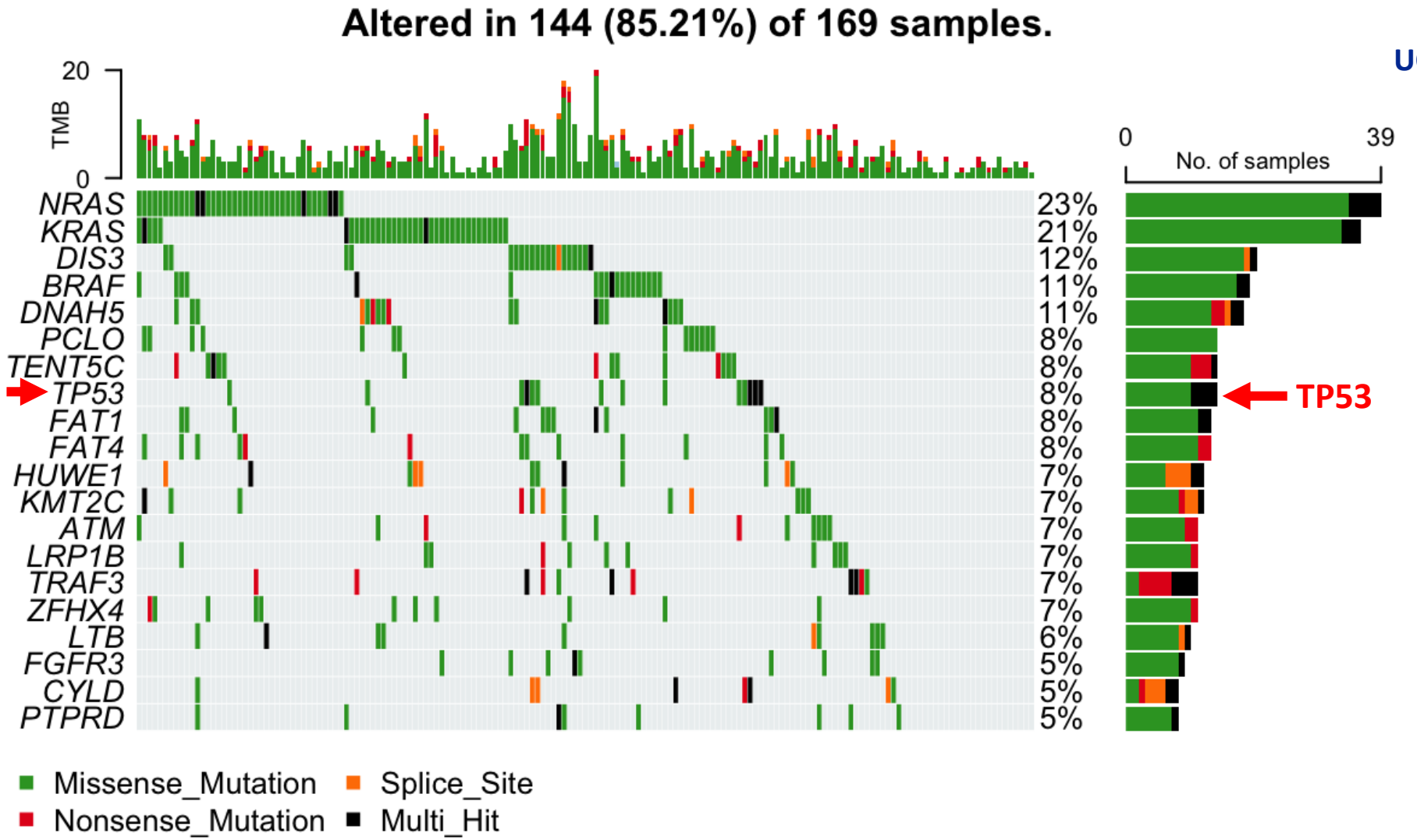


All patients are tested for MRD at 12 and 24 months

Targeted sequencing of tumour samples from RADAR

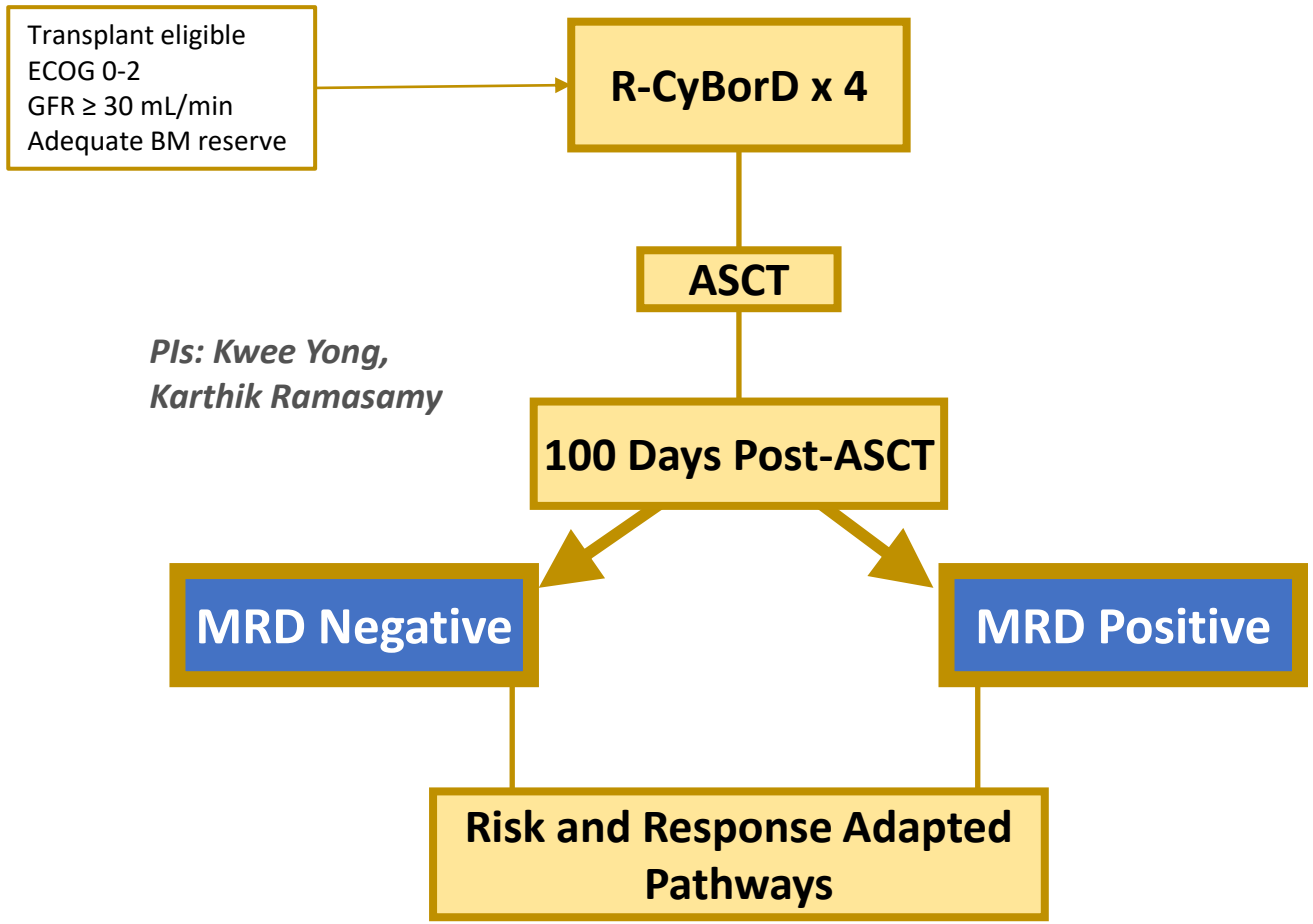
Sarah Gooding, Oxford
Eileen Boyle
Amatta Mirandari
Ines Fethi
UCL Myeloma lab

Genetic variants detected in top 20 myeloma driver genes



85.21% have at least one mutation in these 20 selected genes

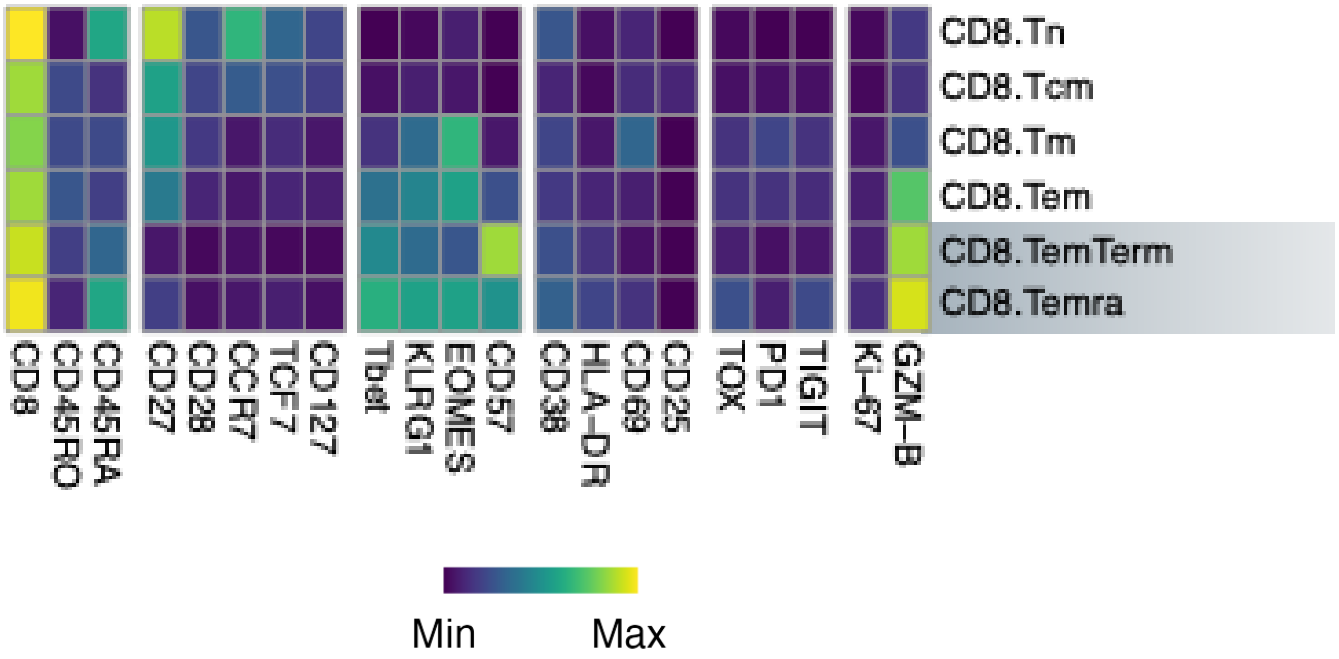
UKMRA RADAR Trial

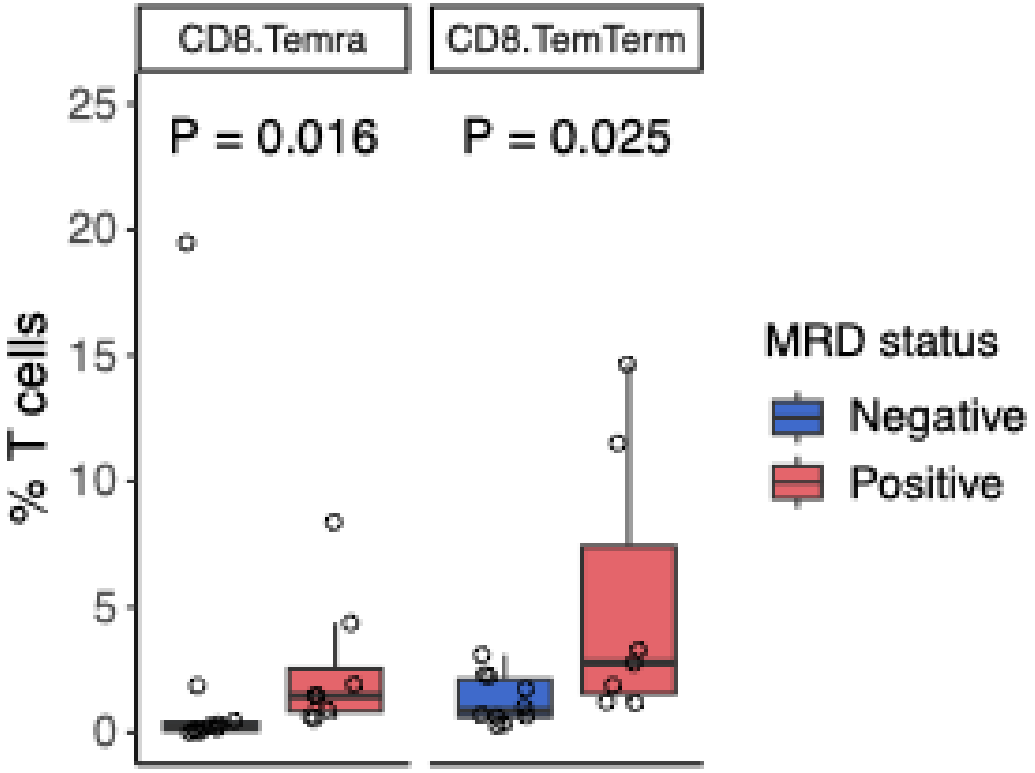


PIs: Kwee Yong, Karthik Ramasamy

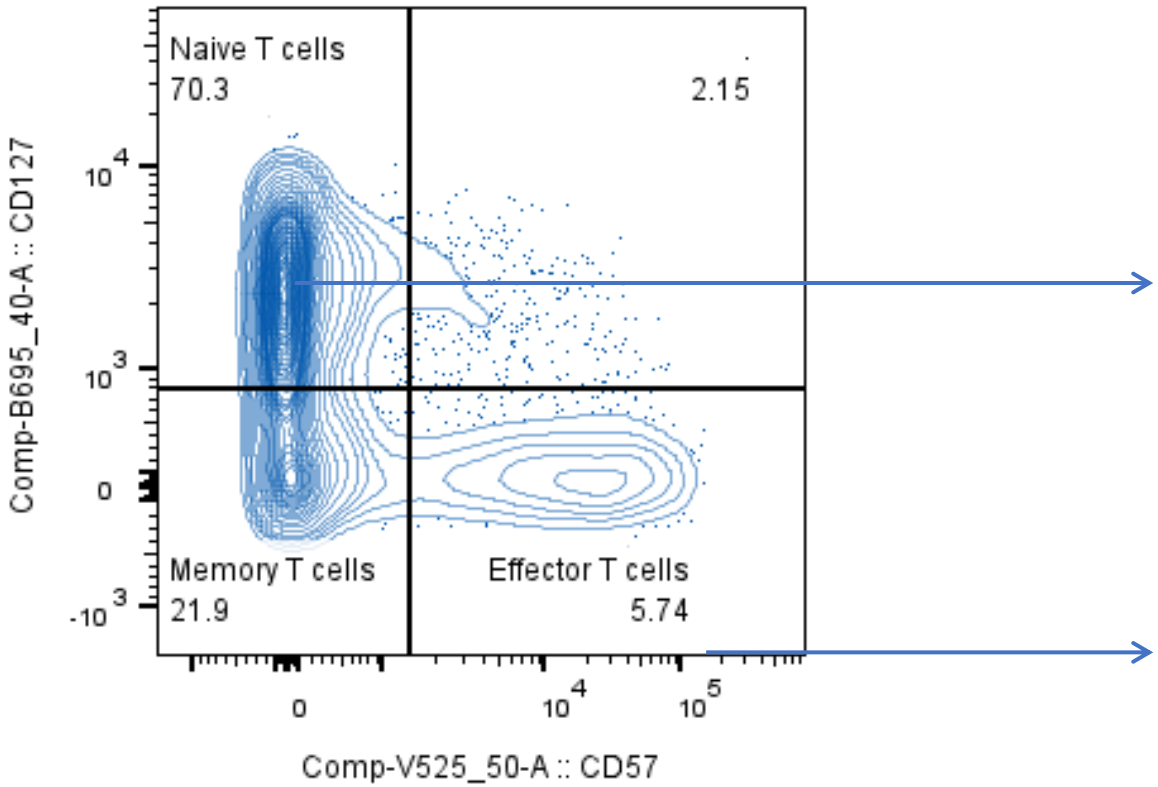
Terminally differentiated CD8+ T-cells enriched in MRD+ patients

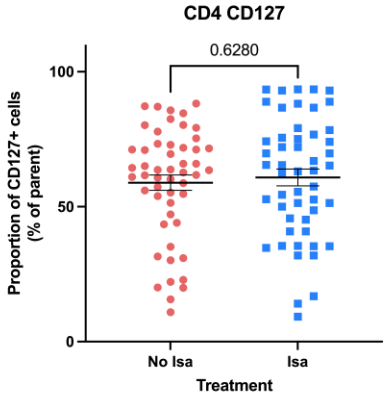
CD8+T_{EM}terminal, **CD8+T_{EMRA}**
Late differentiated (GZM-B+CD57+, CD45RA+/–)

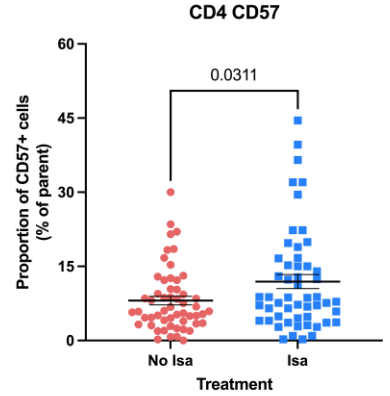




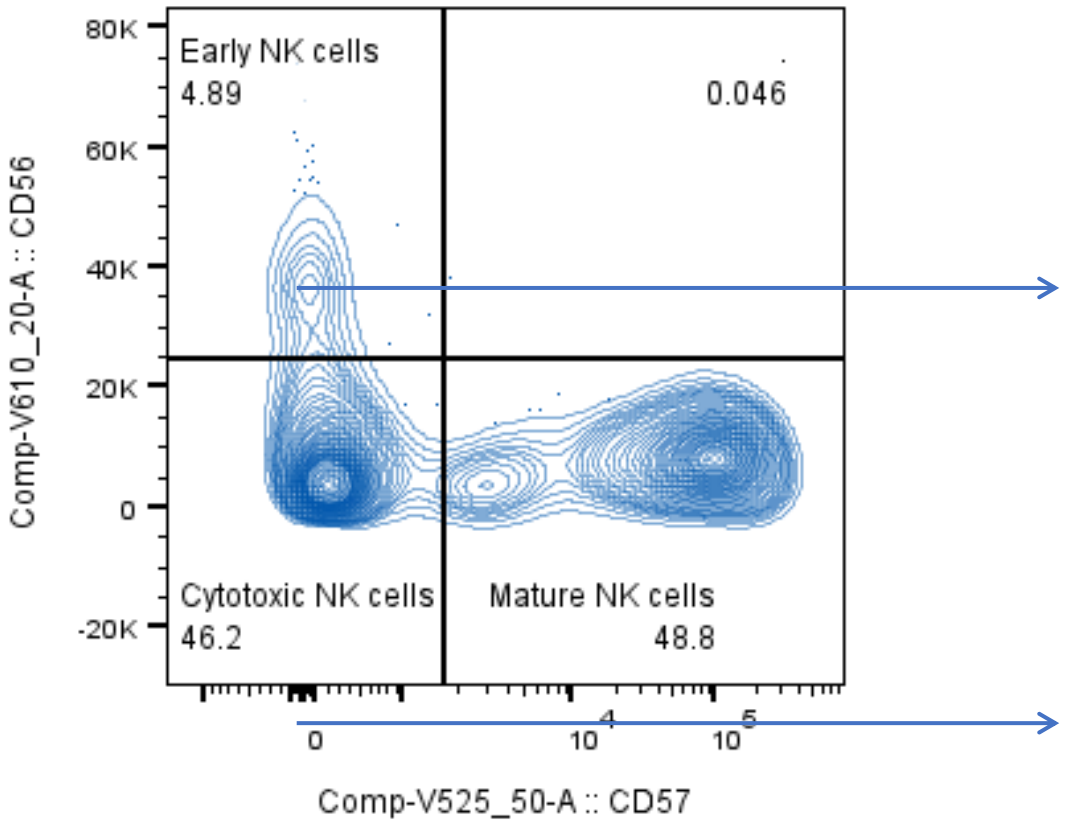
Isatuximab given post-ASCT increases effector T cells without impacting naïve subsets

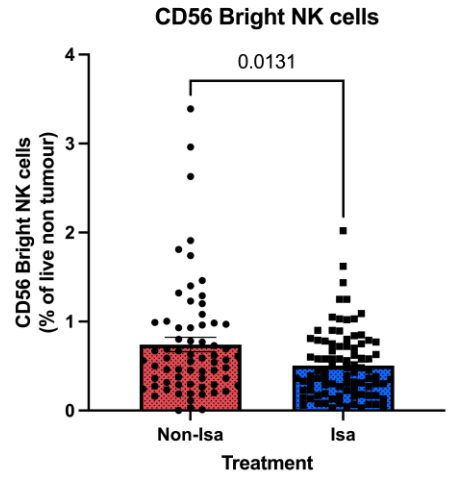


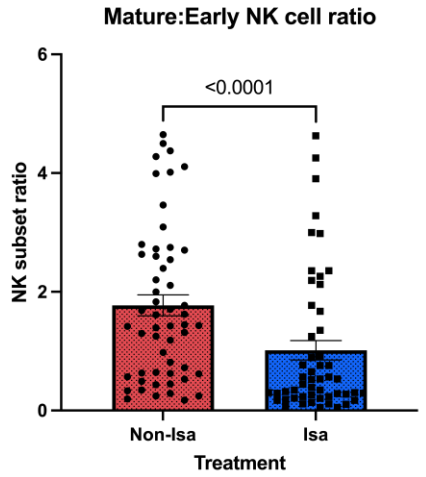


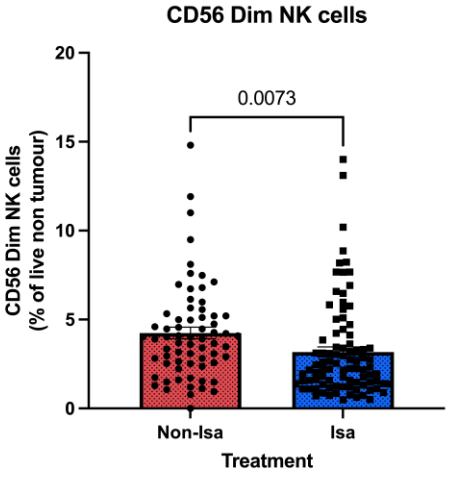


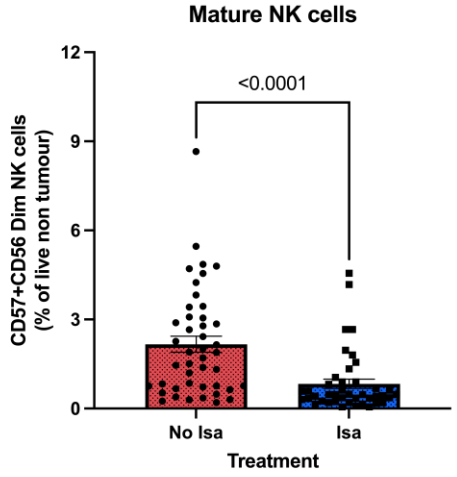
Isatuximab therapy results in preferential loss of mature late differentiated NK cell subsets





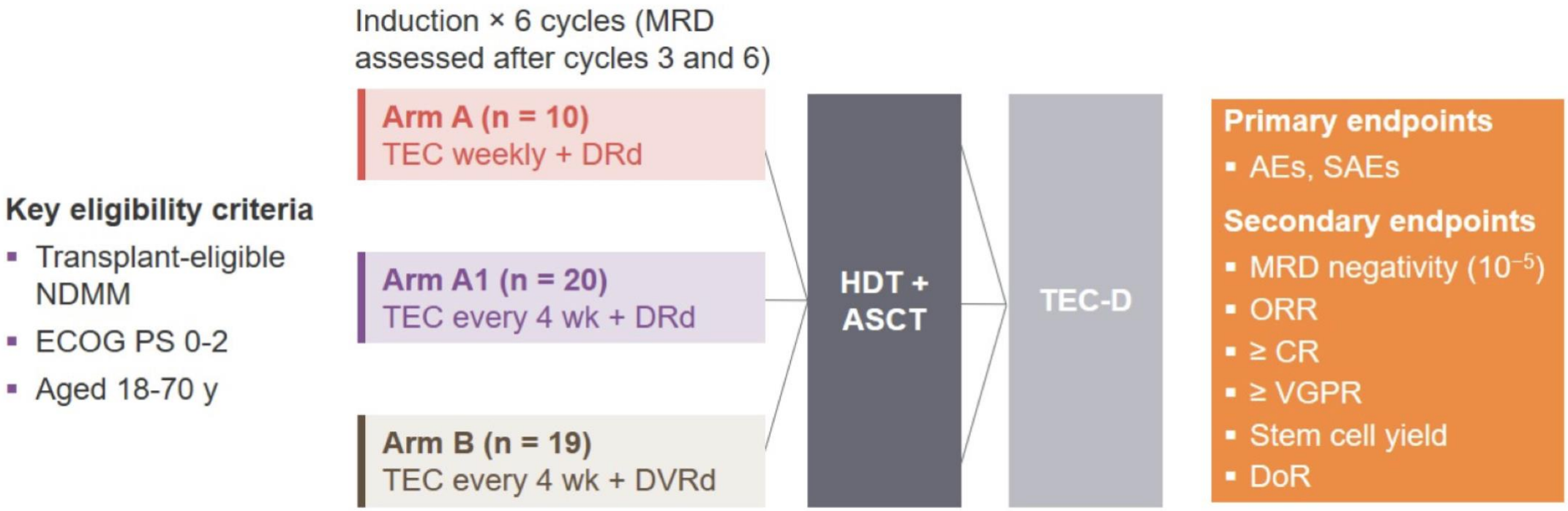






Is the future immunotherapy?

GMMG-HD10/DSMM-XX/MajesTEC-5 study design



Summary

- Highly effective induction regimens extending disease free and overall survival, *but*
- How do we personalize therapy for our newly diagnosed patients?
- Specific subgroups for whom outcomes can be improved
- Continue to scrutinize the benefit of ASCT
- Treating all until progression reflects an un-enlightened approach
- Have we asked our patients?

- Carry out careful translational studies alongside our clinical trials in order to truly advance treatment and improve outcomes

Acknowledgments

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UK-MRA Myeloma XV

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MyelomaUK

ACED INTERNATIONAL ALLIANCE FOR CANCER EARLY DETECTION