To Transplant or **NOT** When Minimal Residual Disease has been Achieved as Initial Therapy for Multiple Myeloma

20th Annual Indy Review

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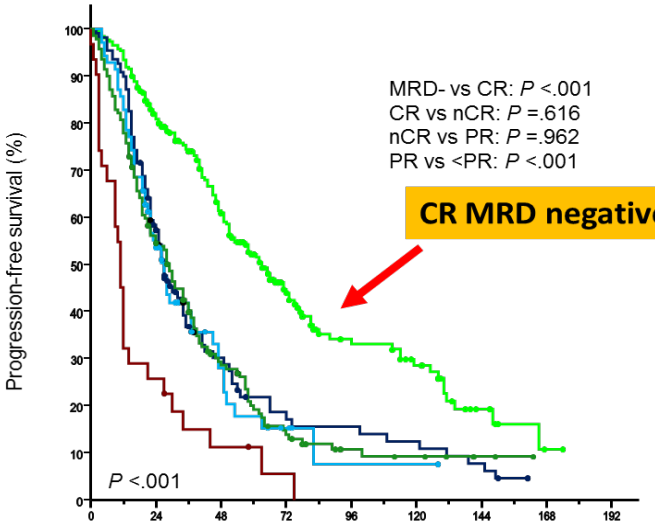
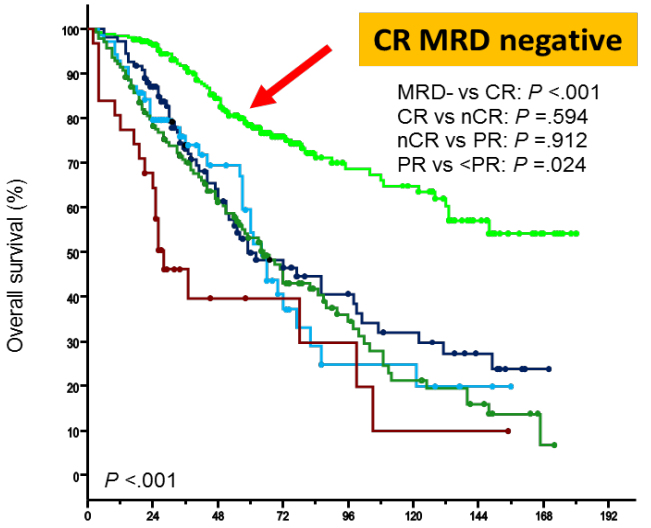
City of Hope Cancer Center

Why you should NOT transplant patients in MRD negativity

1. DEPTH of response generally correlated to DURATION of response
2. Transplant prolongs PFS but not OS
3. Transplant can be delayed – sometimes for a LONG time
4. Transplant is toxic – it should be used carefully
5. MRD negativity can guide de-escalation and stoppage of therapy in some patients
6. Transplant is NOT for everyone
7. The FUTURE is clearly not about transplant…

MRD is Prognostic in Frontline Therapy – Both for PFS and OS





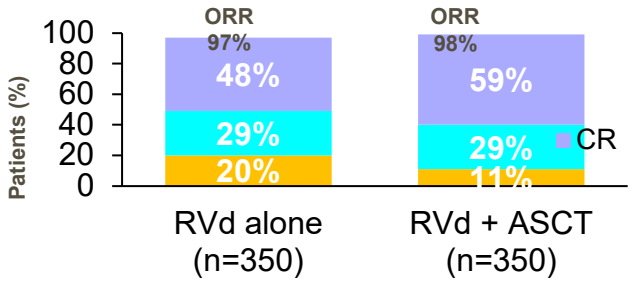
Lahuerta JJ, Paiva B, et al. J Clin Oncol. 2017; 35(25): 2900–2910

2. Transplant prolongs PFS but not OS

IFM 2009: Improved PFS with RVd+ASCT vs RVd-Alone, But No OS Advantage

IFM 2009: RVd+ASCT vs RVD-alone, plus lenalidomide maintenance for 1 year; 76.7% RVd-alone patients received 2nd-line ASCT[1]

Response rates[2]



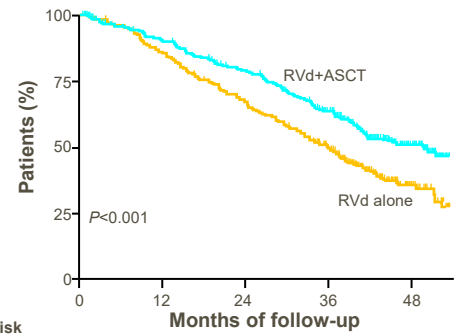
MRD negativity: 20.4% vs 29.8%
A strong predictor of outcome[1]

MRD-neg vs MRD-pos	HR (95%CI)	*P*-value
PFS	0.28 (0.22–0.36)	<0.001
PFS2*	0.27 (0.20–0.37)	<0.001
OS	0.35 (0.25–0.49)	<0.001

Safety[2]

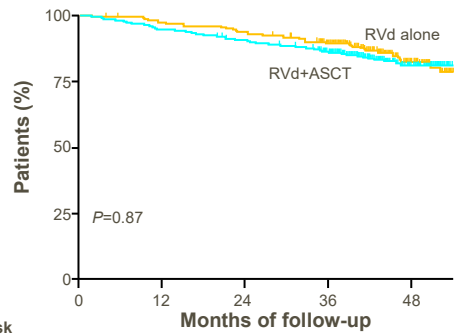
Grade 3/4 AEs, %	RVd alone (n=350)	RVD + ASCT (n=350)
Neutropenia	47%	92%
GI disorders	7%	28%
Infections	9%	20%

PFS[2]



No. at risk					
RVd alone	350	294	228	157	32
RVd+ASCT	350	308	264	196	50

OS[2]



No. at risk					
RVd alone	350	339	325	293	95
RVd+ASCT	350	330	313	281	89

8-year follow-up: similar survival outcomes between RVd alone and RVd + ASCT[1]

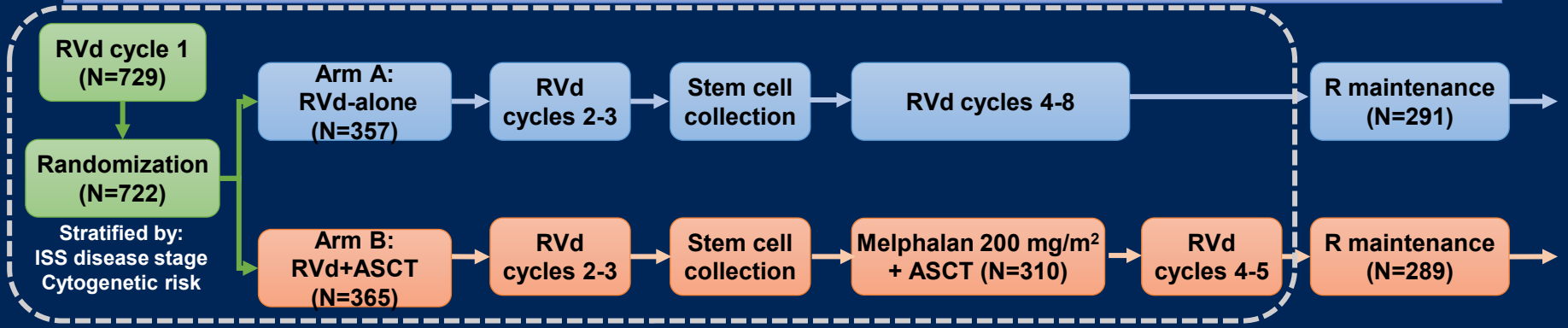
Survival outcomes[1]	RVd alone (n=350)	RVD + ASCT (n=350)	*P*-value
Median PFS (months)	35.0	47.3	<0.001
Median PFS2* (months)	95	NR	0.76
Median second PFS† (months)	36	25	0.003
Median OS (months)	NR	NR	–
8-year OS (%)	60.2	62.2	0.81

Median follow-up was 93 months

1. Perrot A et al. Blood 2020;136(suppl):39. 2. Attal M et al. N Engl J Med 2017;376(14):1311–20.

DETERMINATION: study design and patient disposition

DETERMINATION: Delayed vs Early Transplant with Revlimid Maintenance and Antimyeloma Triple Therapy



Each RVd cycle (21 days):
R 25 mg/day PO, days 1-14
V 1.3 mg/m² IV/SC, days 1, 4, 8, 11
Dex 20/10 mg PO, days 1, 2, 4, 5, 8, 9, 11, 12

Induction ± ASCT + consolidation treatment duration = ~6 months

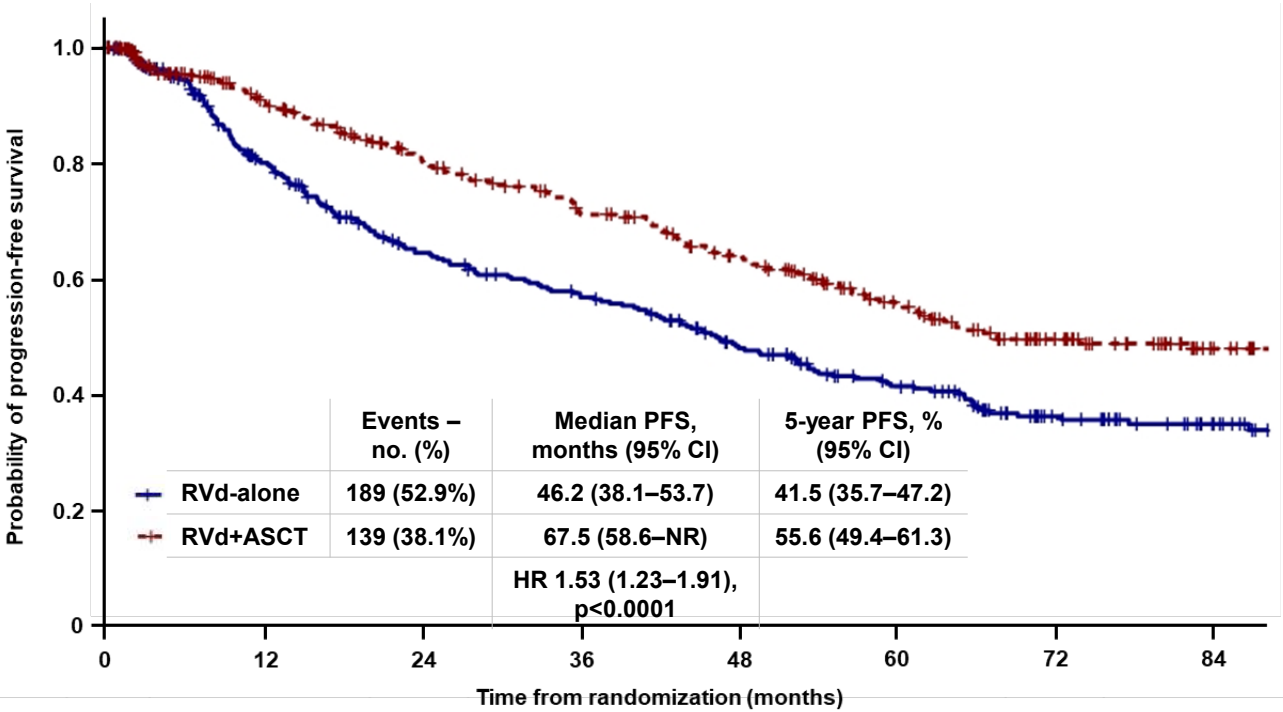
Lenalidomide maintenance
Months 1-3: 10 mg/day
Month 4 onwards: 15 mg/day

Primary endpoint: PFS

Secondary endpoints: response rates; DOR; TTP; OS; QoL; safety

d/Dex, dexamethasone; DOR, duration of response; ISS, International Staging System; IV, intravenous; PO, orally; R, lenalidomide; SC, subcutaneous; TTP, time to progression; V, bortezomib

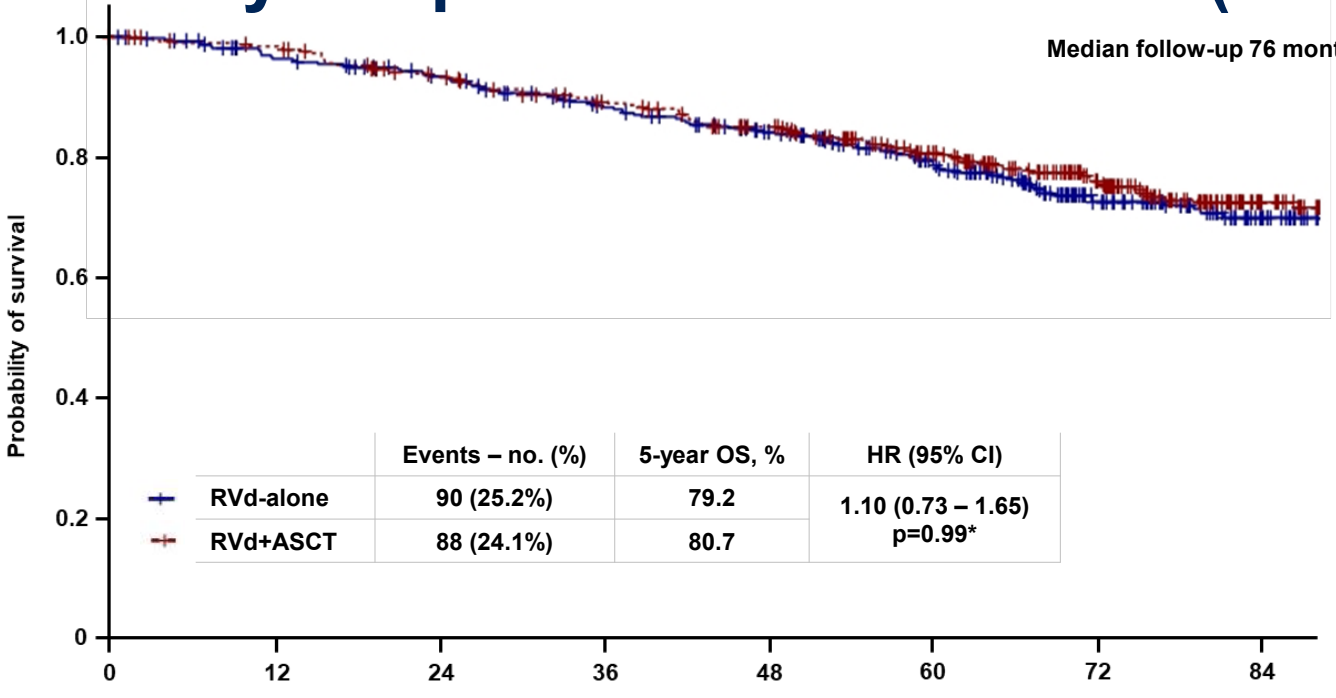
Primary endpoint: Progression-free survival (PFS)



Patients at risk								
RVd-alone	357	250	187	160	126	96	60	40
RVd+ASCT	365	276	226	191	160	118	77	42

CI, confidence interval; HR, hazard ratio; Data cut off: 12/12/21

Key secondary endpoint: Overall survival (OS)



	Events – no. (%)	5-year OS, %	HR (95% CI)
RVd-alone	90 (25.2%)	79.2	1.10 (0.73 – 1.65) p=0.99*
RVd+ASCT	88 (24.1%)	80.7	

Patients at risk								
RVd-alone	357	332	313	285	258	214	143	88
RVd+ASCT	365	353	324	300	275	228	165	95

*p-value adjusted using Bonferroni's correction to control overall family-wise error rate for secondary outcomes

Data cut off:12/12/21

MRD / PFS by MRD status

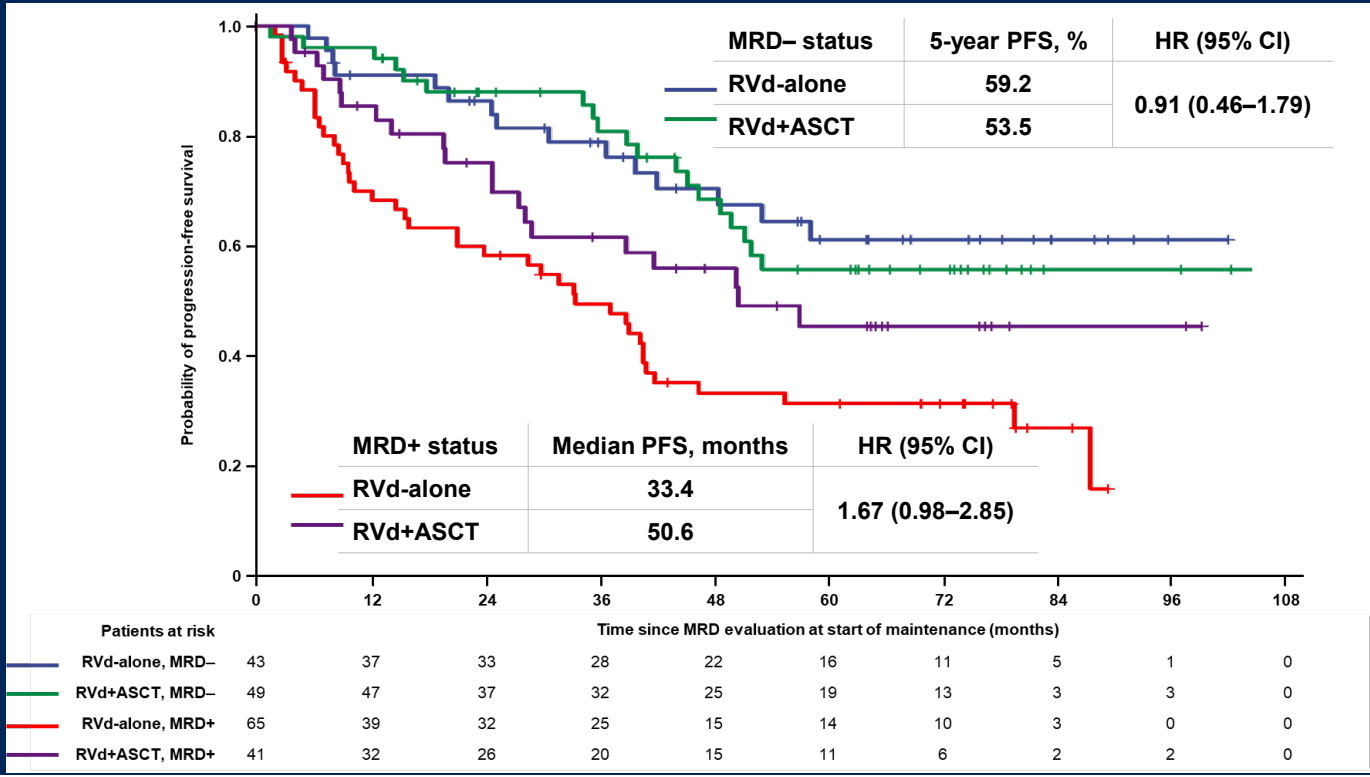
Preliminary analysis

108 RVd-alone, 90 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)



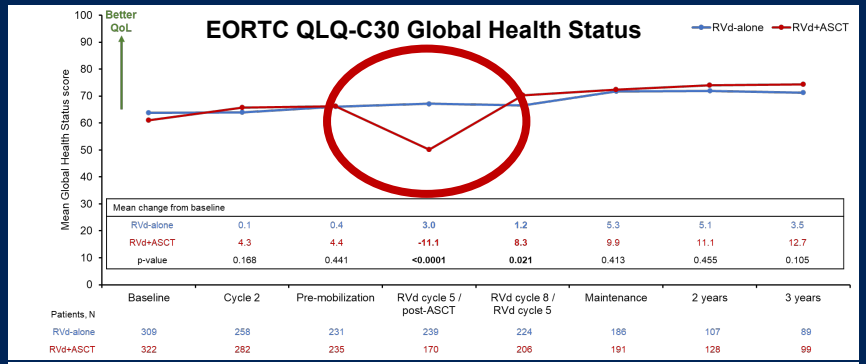
3. Transplant can be delayed – sometimes for a LONG time

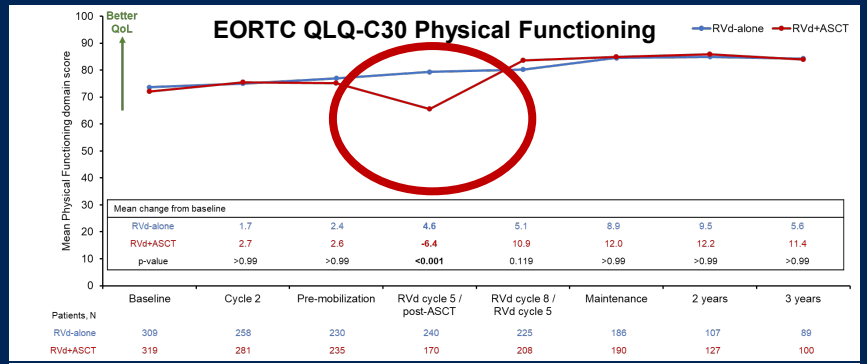
- In IFM 79% of pts in the non ASCT arm had ASCT at first relapse
- In DETERMINATION only 28% of pts in the non ASCT arm had ASCT

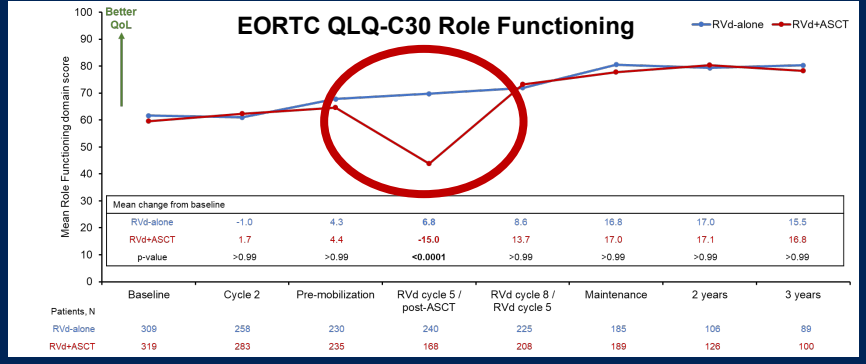
This underscores that outcomes can be the same even WITHOUT a transplant!

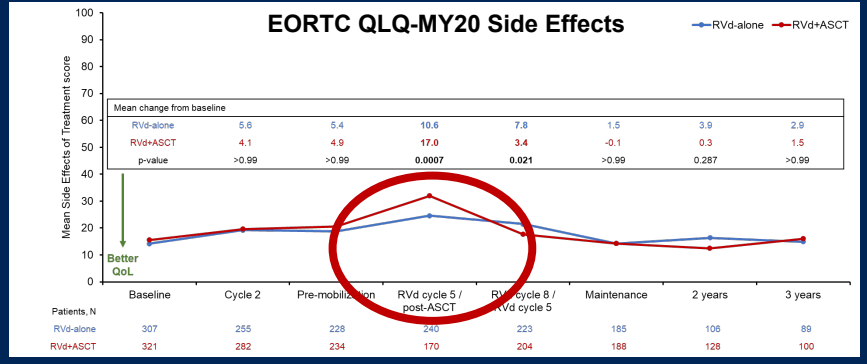
4. Transplant is toxic – it should be used carefully

QoL over the course of treatment with RVd-alone vs RVd+ASCT (n=326 vs 332 at baseline)



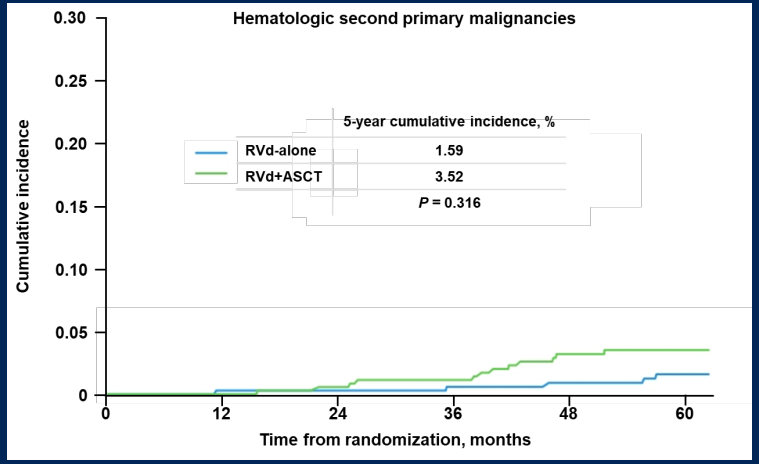






Second primary malignancies

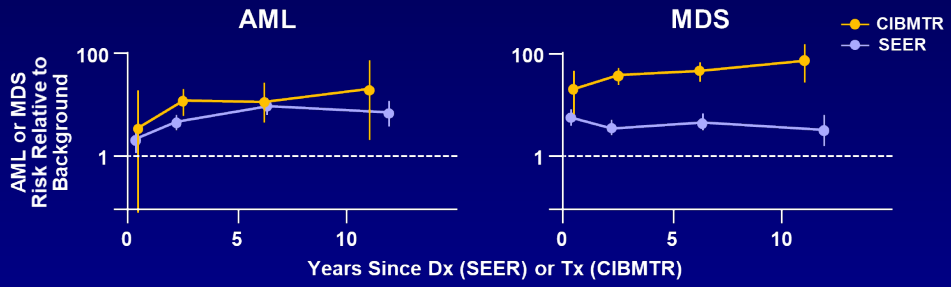
- 5-year cumulative incidence of SPMs (RVd-alone vs RVd+ASCT):
  - All : 9.7% vs 10.8%
  - Invasive: 4.9% vs 6.5%
  - Hematologic: 1.59% vs 3.52%



SPMs, %	RVd-alone (N=357)	RVd+ASCT (N=365)
Any	10.4	10.7
Any invasive SPM	5.3	6.8
Any hematologic SPM	2.5	3.6
ALL, n	7	3
AML/MDS, n	0*	10*
CLL/CML, n	2	0
Any solid tumor SPM	3.4	3.3
Any non-invasive sold tumor SPM	0	0.5
Any non-melanoma skin cancer	5.9	4.1

Risk of AML/MDS and Mutational Burden in MM Cells at Relapse After High-Dose Melphalan + ASCT

Risk of AML/MDS Increased After High-Dose Melphalan + ASCT[1]



SEER data:

- Risks for AML/MDS in MM patients 5–10 times the background rate

CIBMTR data (n=4,566):

- Relative risks 10–50 for AML and ~100 for MDS in the HDM/ASCT cohort

Mutational Burden Significantly Increased After High-Dose Melphalan + ASCT (IFM 2009)[2]

Known mutagenic effect of high-dose melphalan[3]

Paired purified MM cells at diagnosis and at relapse from 68 patients using deep (75×) whole-genome sequencing to identify genomic changes induced by HDM and observed at relapse[2]

Impact on prognosis

	RVd	RVd→HDM+ASCT	*P*-value
Patients, n	45	23	—
Median follow-up, mos	29	31	—
Mutations at diagnosis, n	7137 [IQR=3741]	7230 [IQR=3702]	0.67
Mutations at relapse, n	1745	5686	0.000014
Indels* at relapse, n	360	467	0.02

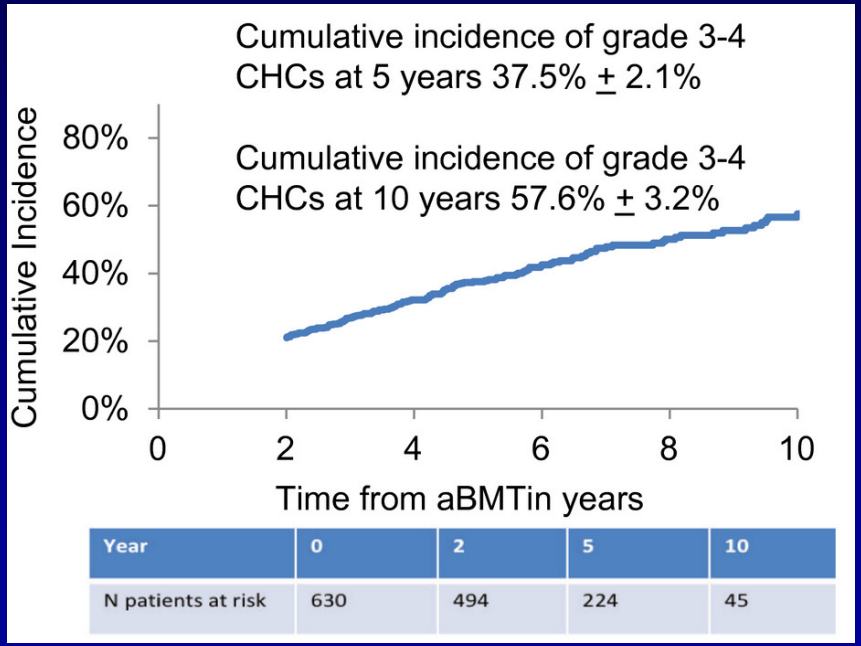
*The insertion or deletion of one or several nucleotides within a sequence

HDM causes a 4.1-fold higher mutation accumulation rate per month than RVd only (158.3 vs 38.3 mutations/month; *P*=0.003)

1. Radivoyevitch T, et al. Leuk Res. 2018;74:130.
2. Samur MK, et al. Blood 2020;136(suppl):abstract 61.
3. Maura F, et al. Leukemia 2021;35:2145–50.

Chronic Health Conditions After High-Dose Melphalan + ASCT

- 630 patients from 3 BMT centers who had survived >2 years after HDM-ASCT
  - 289 nearest-age siblings as controls
- Study on severe and/or life-threatening chronic health conditions (CHCs) and SPMs in MM patients treated with HDM-ASCT
- Compared with sibling controls, MM patients treated with HDM-ASCT had 40% greater odds of developing grade 3-4 CHCs
- 10-year cumulative incidence of any grade 3-4 CHC among MM patients treated with HDM-ASCT was 57.6%



Year	0	2	5	10
N patients at risk	630	494	224	45

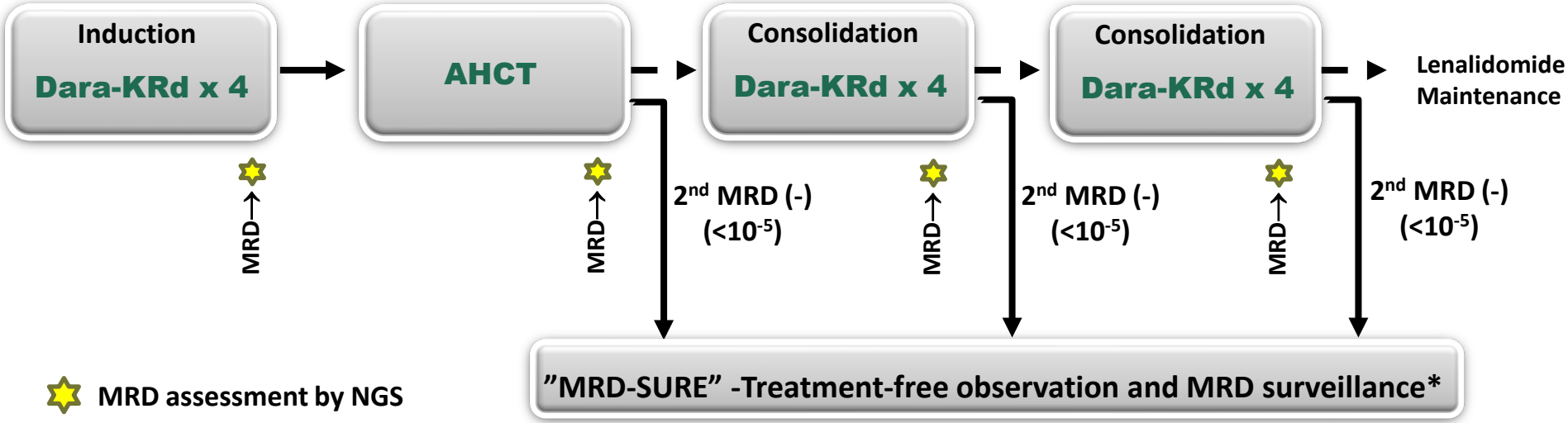
Arora M, et al. Cancer 2020;126(14):3322–9.

5. MRD negativity can guide de-escalation and stoppage of therapy in some patients

MASTER Trial - Treatment

Dara-KRd

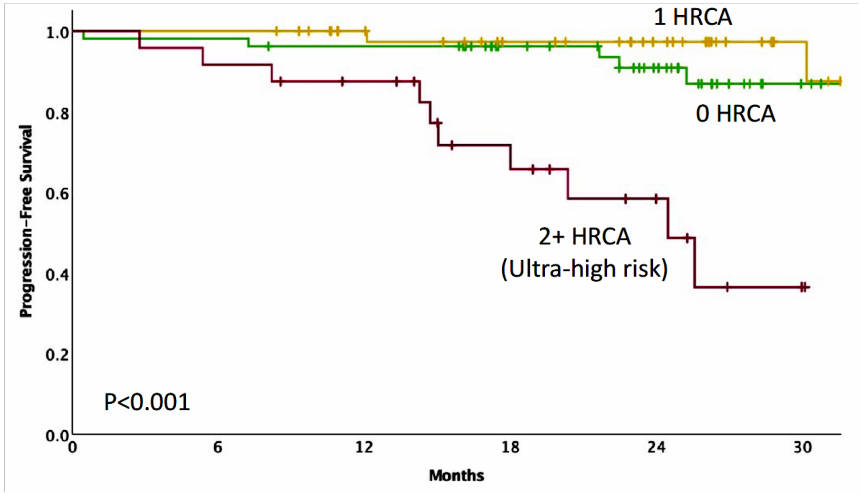
- Daratumumab 16 mg/m^2 days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m^2 Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40mg PO Days 1,8,15,22



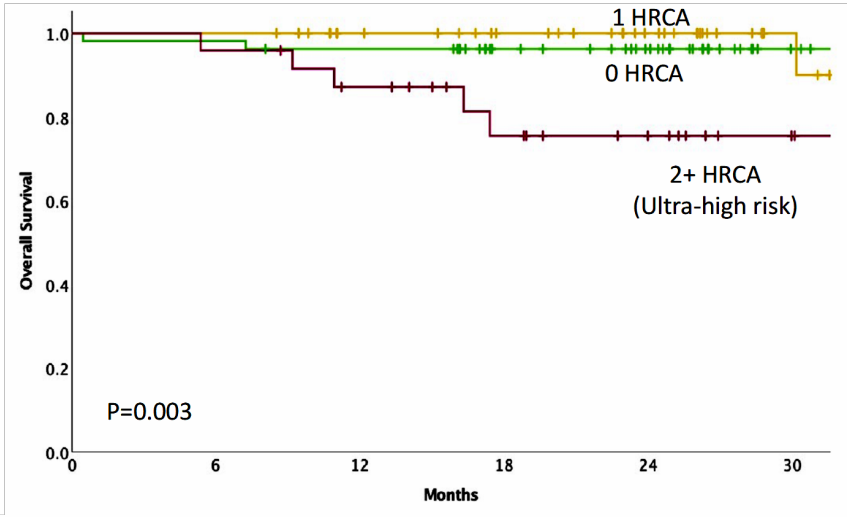
*24 and 72 weeks after completion of therapy

MASTER trial

Progression-Free and Overall Survival



No. at risk:						
0 HRCA	50	49	46	36	27	10
1 HRCA	44	44	36	30	23	9
2+ HRCA	24	22	19	12	7	2



No. at risk:						
0 HRCA	50	49	46	36	29	11
1 HRCA	44	44	36	30	23	9
2+ HRCA	24	23	19	13	9	3

2-year PFS	0 HRCA	91%
	1 HRCA	97%
	2+ HRCA	58%

2-year OS	0 HRCA	96%
	1 HRCA	100%
	2+ HRCA	76%

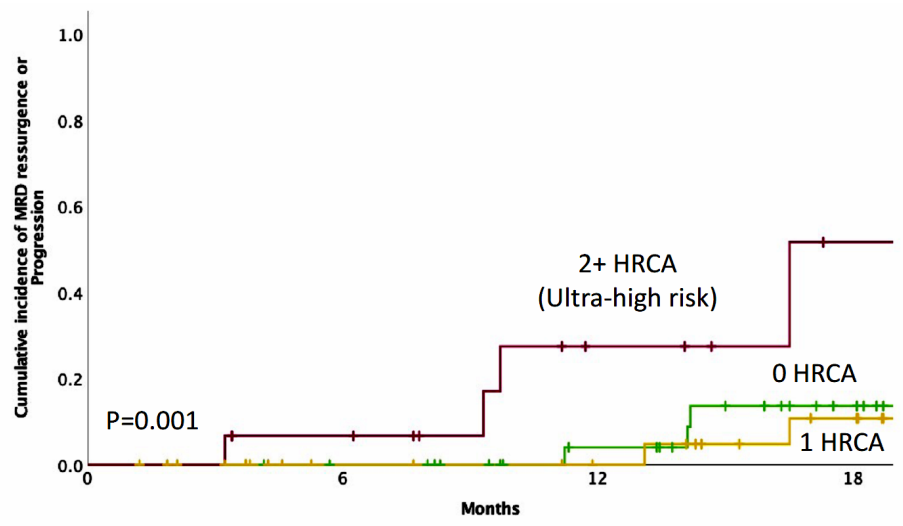
HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

MASTER trial

MRD-SURE

- 84 patients achieved MRD-SURE
  - 0 HRCA – 62%
  - 1 HRCA- 78%
  - 2+ HRCA – 63%
- Median follow up in MRD-SURE: 14.2 mo.
- Risk of MRD resurgence or progression 12 months after treatment cessation
  - 0 HRCA – 4%
  - 1 HRCA- 0%
  - 2+ HRCA – 27%
- **None** of patients entering MRD-SURE died from MM progression

Cumulative incidence of MRD resurgence or progression



No. at risk:				
0 HRCA	33	31	23	12
1 HRCA	36	24	21	14
2+ HRCA	15	23	5	0

HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

MASTER trial

6. Transplant is NOT for everyone

Transplant is simply ANOTHER treatment for MM – transplantamab, transplantamide, transplantimib…

DETERMINATION only included pts 65 years old and younger

7. The FUTURE is clearly not about transplant…

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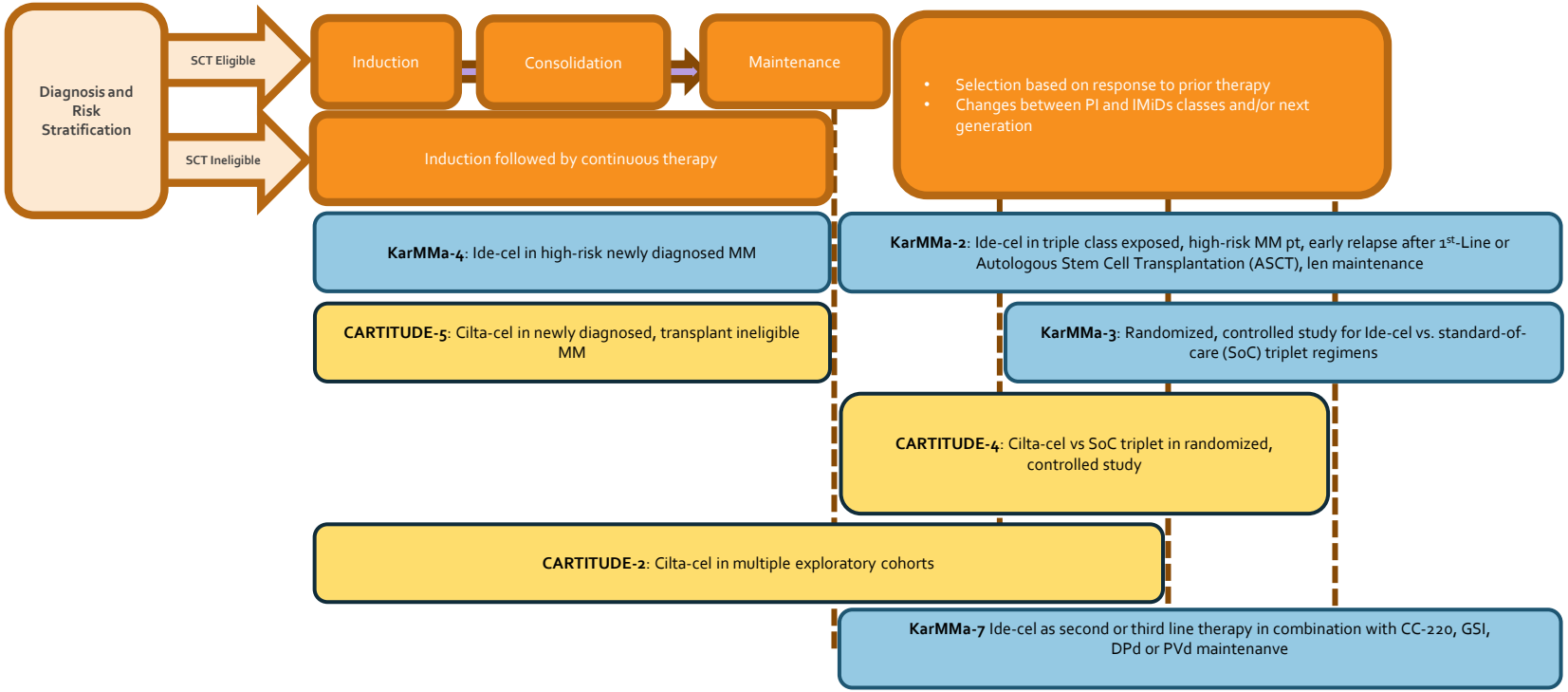
INTERNATIONAL MYELOMA FOUNDATION

Moving CAR-T upfront



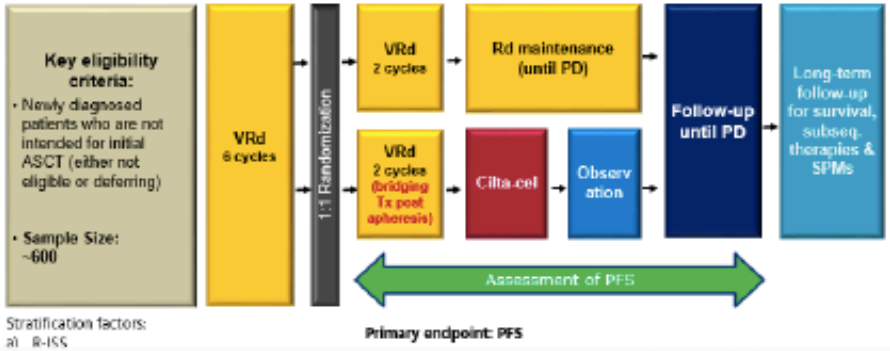
*Graphic adapted from ASCO 2021 Discussion Session – Created and presented by Yi Lin, MD, PhD – Mayo Clinic

CARTITUDE-5

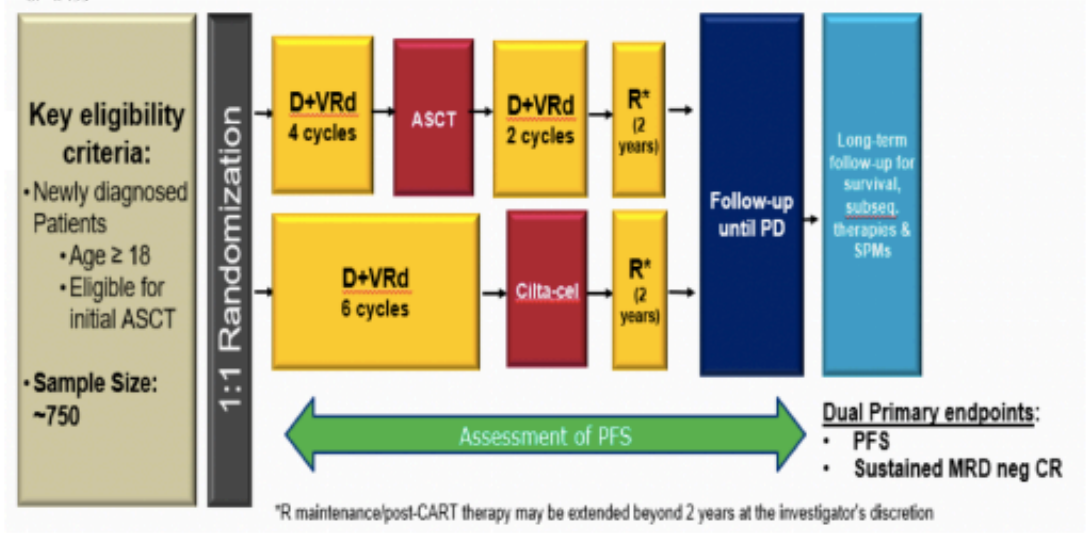
Randomized Phase 3 Study in NDMM, Not Intended for Initial Transplant

CARTITUDE-5 and 6:

- Randomized, ph 3
- NDMM
  - 5 TI
  - 6 TE



CARTITUDE-6



Early MRD will lead to late PFS benefit
- And hopefully early FDA approval

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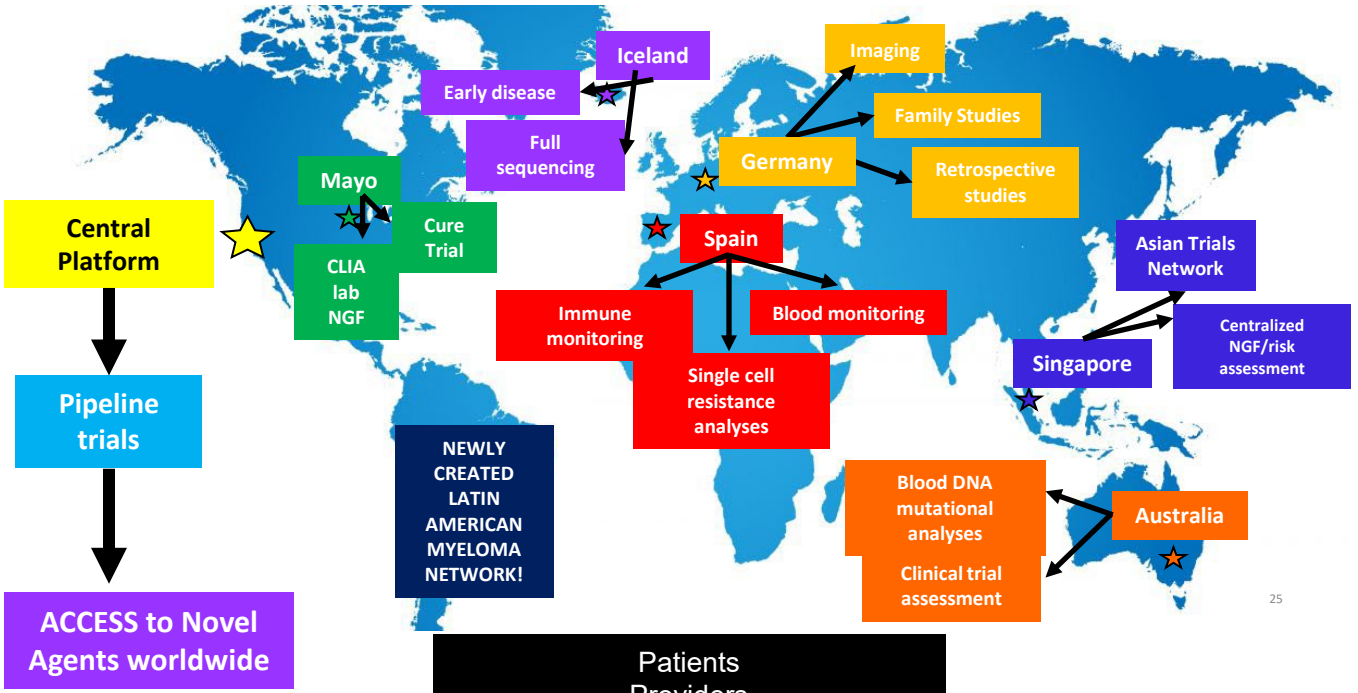
IMF Global Presence

Primary Goal is to cure Myeloma



Patients
Providers
Countries
Industry
Myeloma Community

BLACK SWAN RESEARCH INITIATIVE

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INTERNATIONAL MYELOMA FOUNDATION

THANK YOU!

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