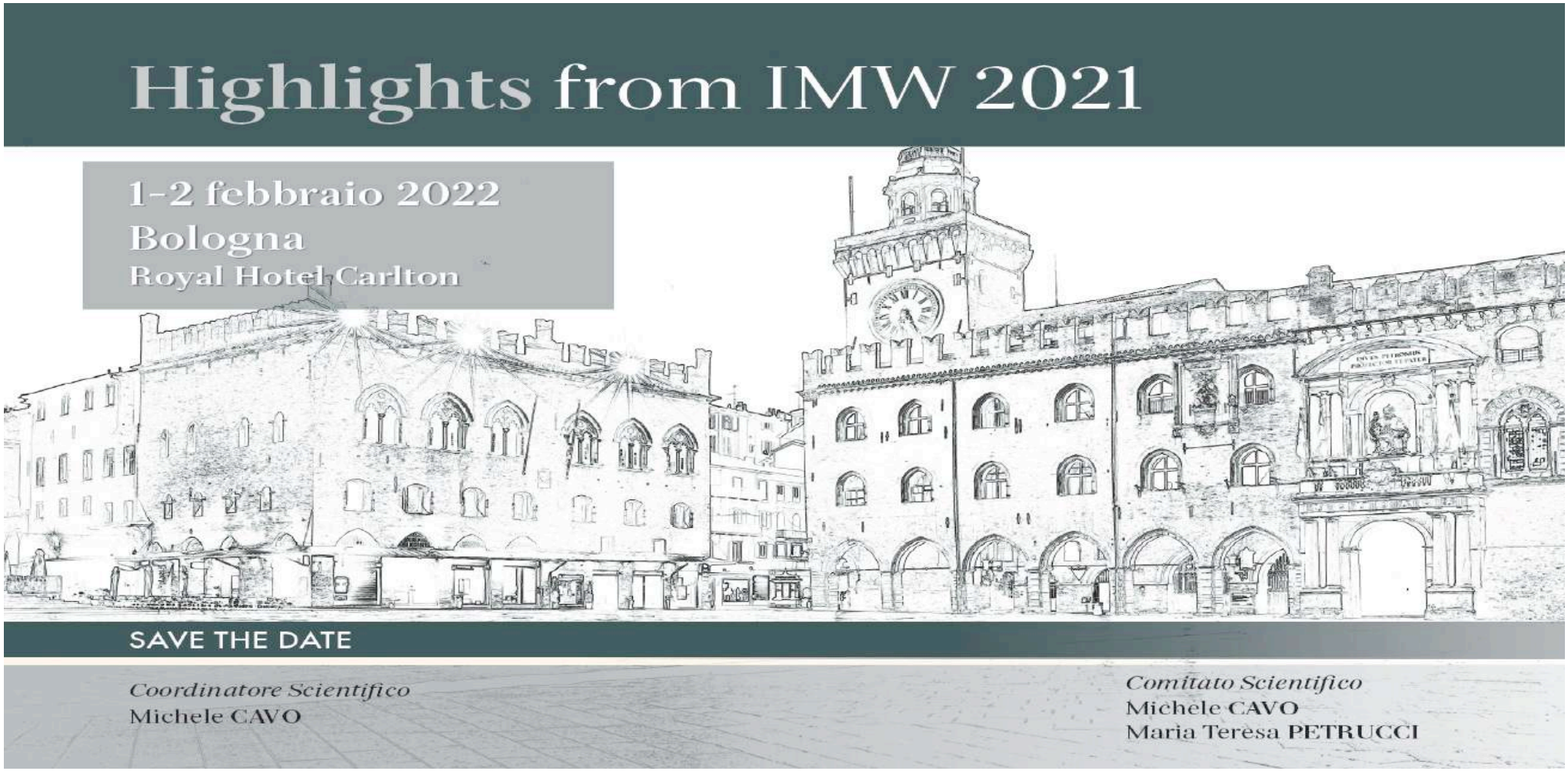


DALLE TERAPIE *ONE-SIZE-FITS-ALL* ALLE TERAPIE GUIDATE DAL RISCHIO PROGNOSTICO

Alessandro Corso
UOC Ematologia
Ospedale di Legnano

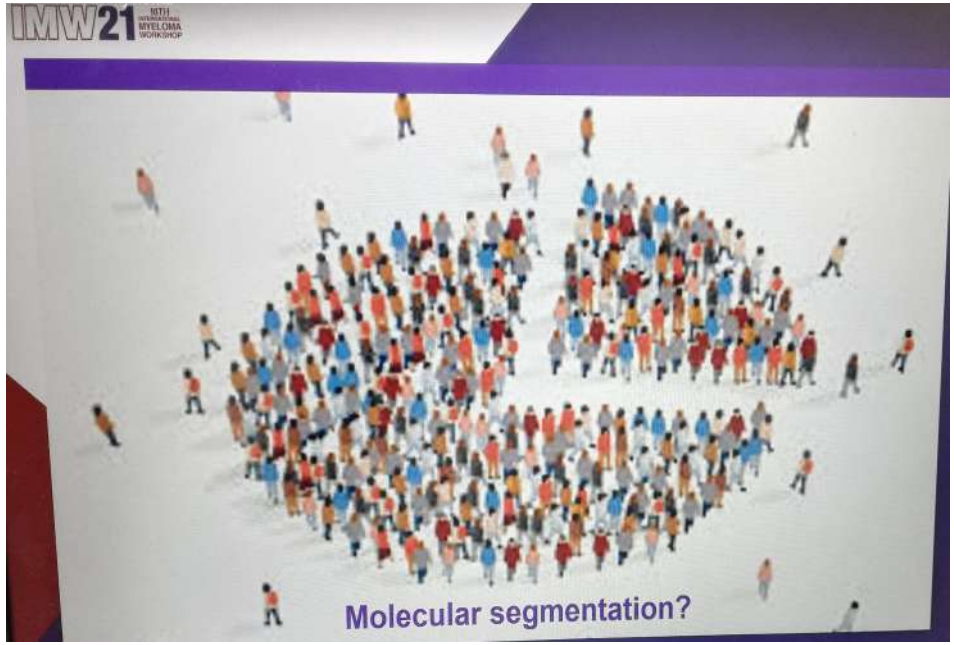
NYU Langone Health

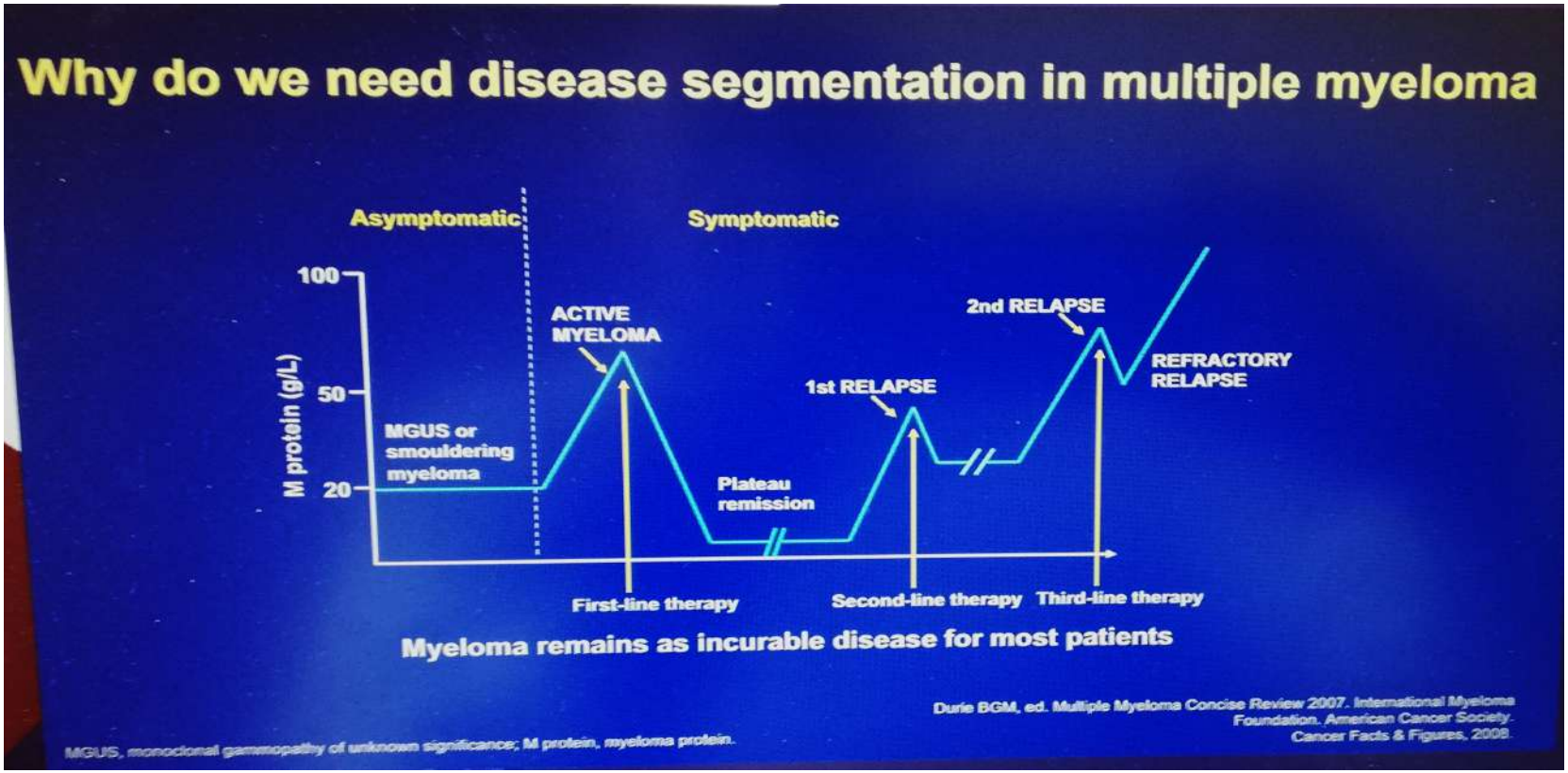
Perlmutter Cancer Center

Multiple Myeloma Research Program

MOLECULAR SEGMENTATION TO IMPROVE OUTCOMES FOR MM: WHY WE SHOULD!

Gareth J Morgan, Director Myeloma Research.





HIGH RISK MM PATIENTS: AN UNMET NEED

Risk factors

- Biological
  - Cytogenetic and FISH risk factors
  - High proliferative PC
  - Circulating PC
  - Elevated LDH
  - Plasmablastic morphology, increased PCLI, increased Ki67
  - Extramedullary disease
- Clinical course (regardless of known cytogenetic and FISH-based risk)
  - Primary refractory disease
  - Trend or frank progressive during evenshort breaks (i.e. between collection of PBSC and transplant)
  - Early relapse post-transplant (<12 mos)

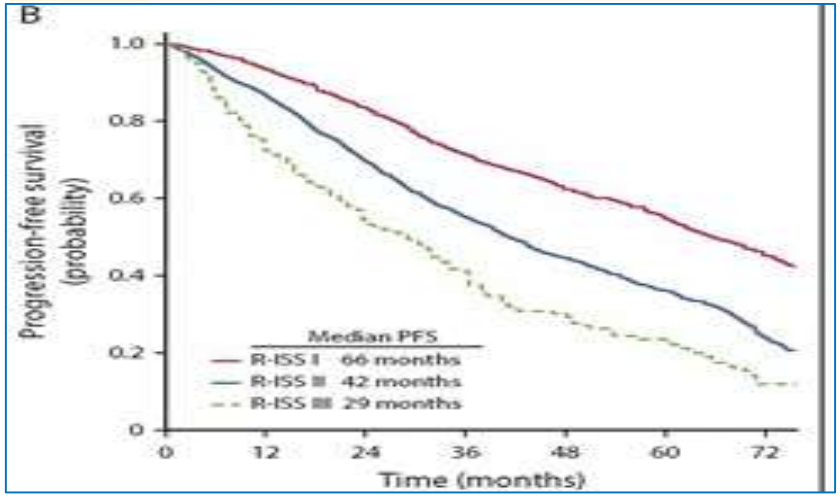
Risk stratification systems and outcome

mSMART 3.0: Classification of Active MM

High-Risk	Standard-Risk[a]
▪High Risk genetic Abnormalities [a,b] ▪t(4;14) ▪ t(14;16) ▪ t(14;20) ▪ Del 17p ▪ p53 mutation ▪ Gain 1q ▪RISS Stage 3 ▪High Plasma Cell S-phase[c] ▪GEP: High risk signature	All others including: ▪ Trisomies ▪ t(11;14)[d] ▪ t(6;14)
▪ Double Hit Myeloma: Any 2 high risk genetic abnormalities ▪ Triple Hit Myeloma: 3 or more high risk genetic abnormalities	

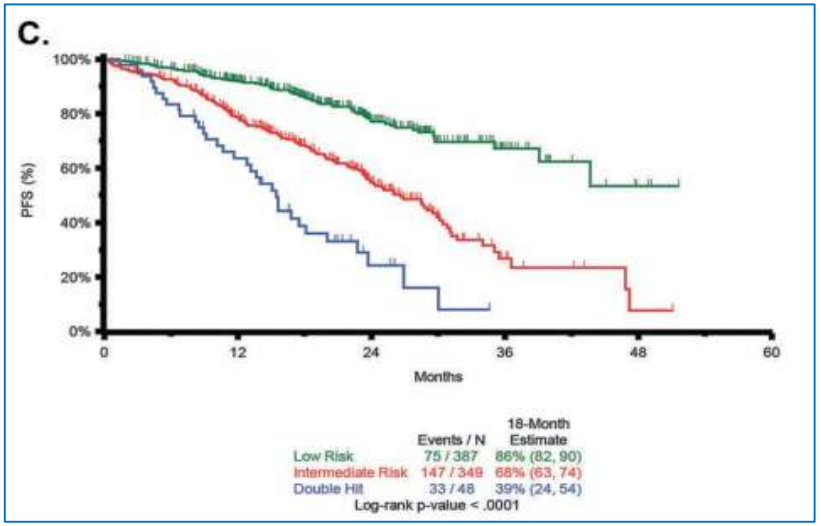
Revised ISS (R-ISS) – NEW 2015

	Parameters	Median Overall Survival
R-ISS Stage I	ISS stage I AND 1) Standard risk cytogenetics AND 2) Normal LDH	Not reached
R-ISS Stage II	Not R-ISS stage I or III	83 months
R-ISS Stage III	ISS stage III AND 1) High-risk cytogenetics OR 2) Elevated LDH	43 months



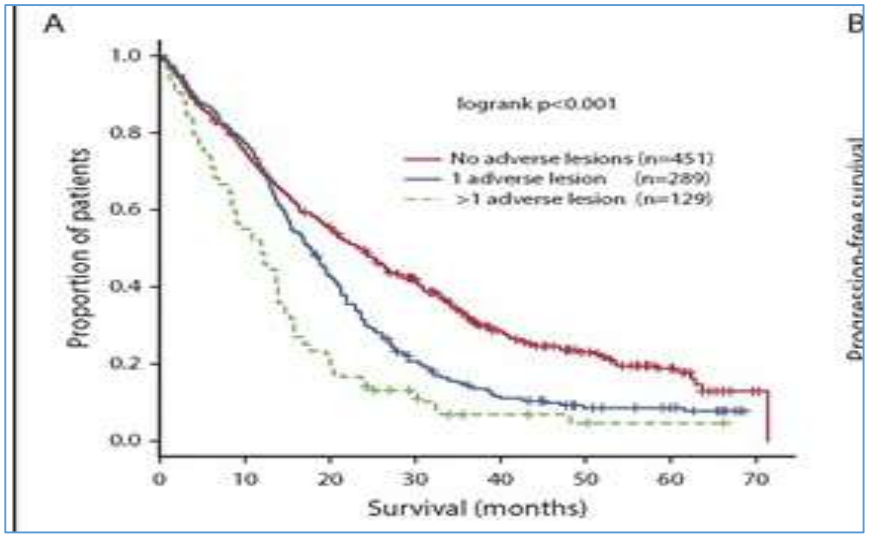
DOUBLE HIT MYELOMA (ultra high risk)

double-hit myeloma (either loss of both alleles of *TP53* [by mutation, deletion or both] or with 2 extra copies of 1q, resulting in amplification rather than a single gain) by incorporating NGS



MRC Myeloma IX trial

Utra high risk defined by the presence of >1 adverse lesion (t(4;14), t(14;16), t(14;20), del(17p), and gain(1q)) in the analysis of 869 cases from the

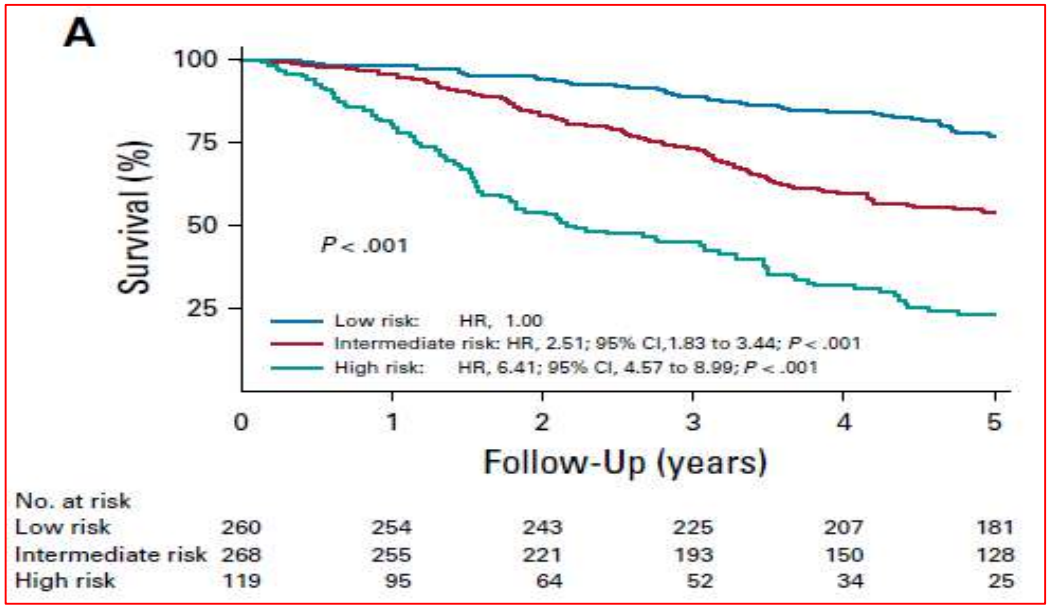


Defining High-Risk Myeloma

6 indipendent variables with a specific score:

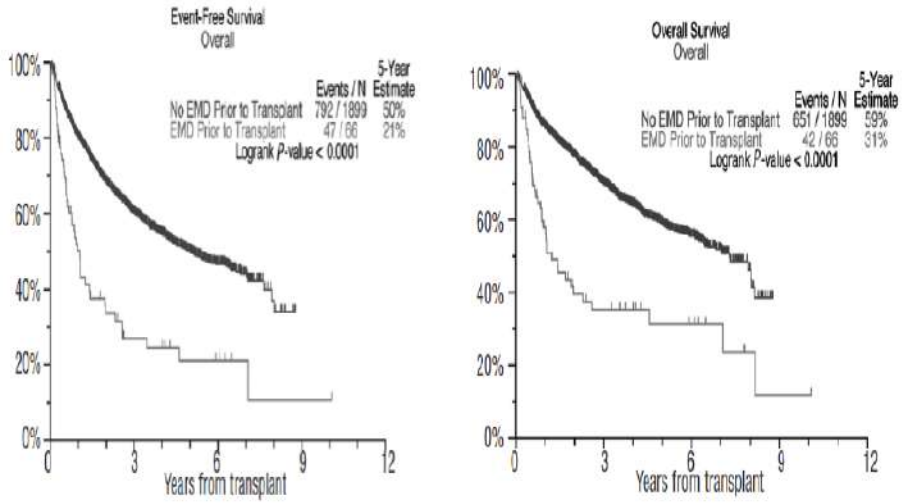
- Trisomy 5 → score -0,3
- Trisomy 21 → score 0,3
- t (4;14) → score 0,4
- 1q gain → score 0,5
- Del (1p32) → score 0,8
- Del (17p) → score 1,2

- **Score ≤ 0: good**
- **Score >0 /<1: intermediate**
- **Score ≥ 1: poor**

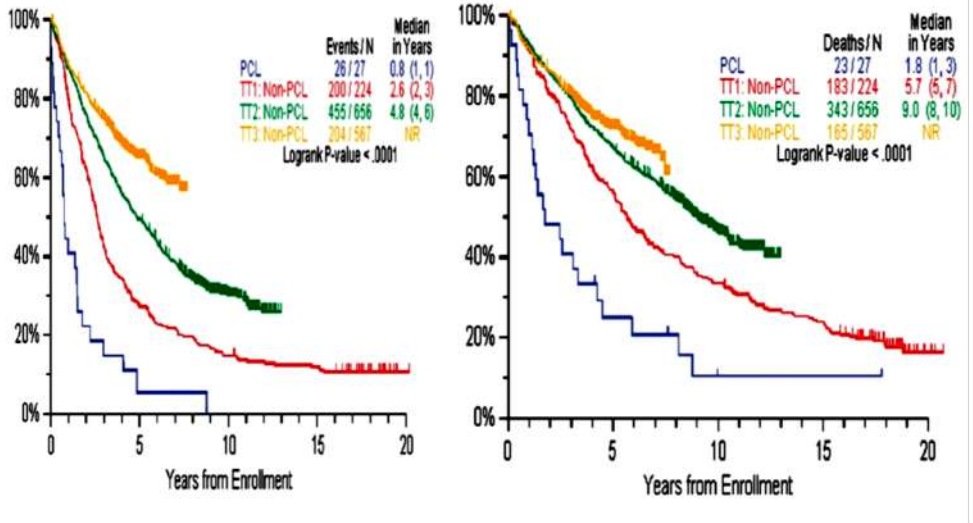


Perrot et al, JCO 2019

Extramedullary disease



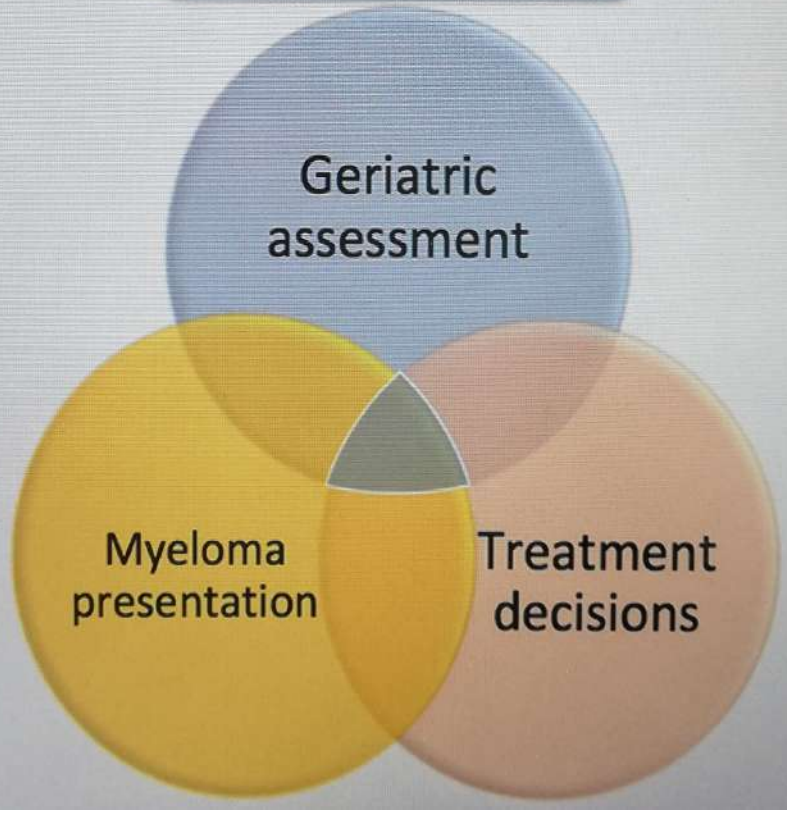
Plasma cell leukemia



Usmani et al, Haematologica 2012

I am arguing for making informed treatment decisions based on data!

ADLs
Frailty score
IADLs
Comorbidities/organ function
Performance status
Support system

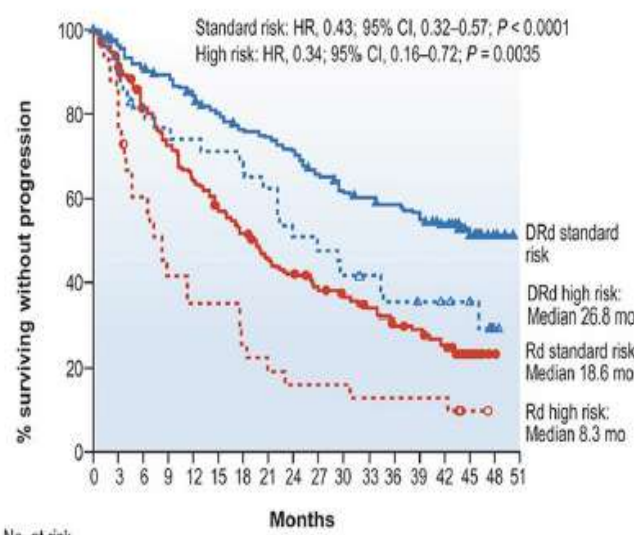


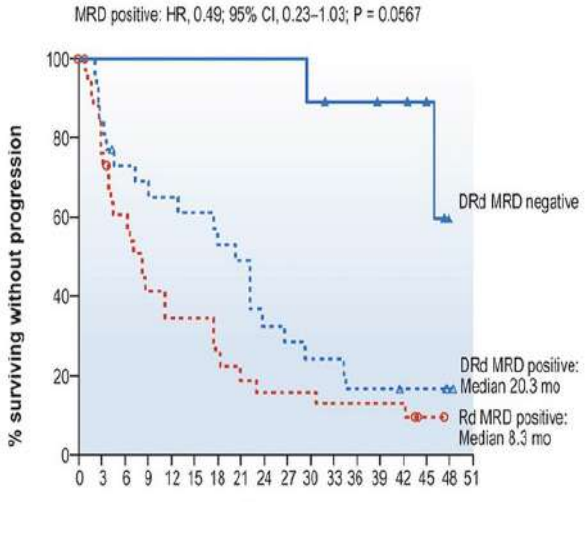
Cytogenetics and stage
Cytopenias
Hypercalcemia
Impending bone fractures
Infection
Renal dysfunction

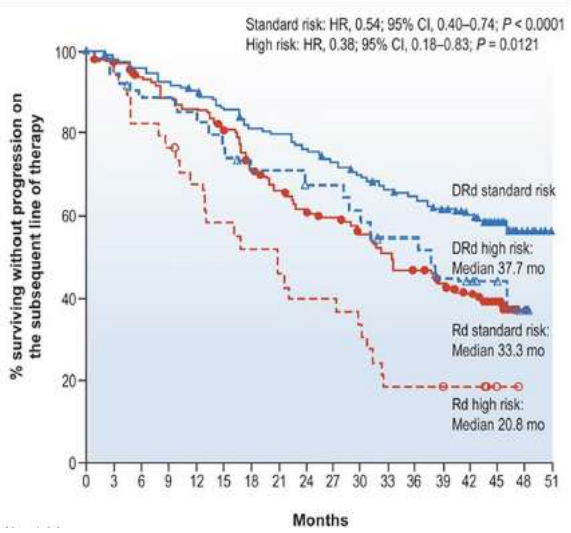
Depth of response
Dose modifications
Eligibility for transplant
Intensity of regimen
Patient preferences/goals
Potential side effects
Supportive care

Treatment of Patients with R/R MM and High-Risk Cytogenetics

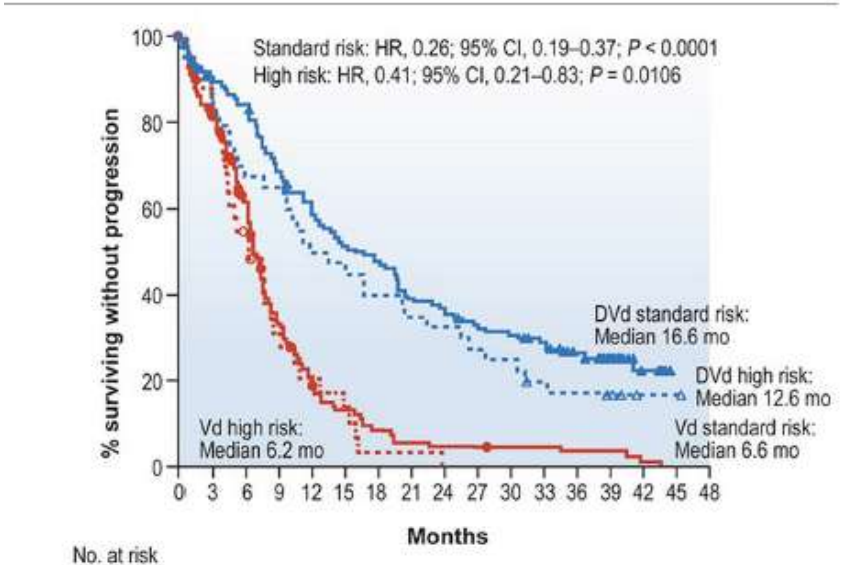
Efficacy and Safety of DRd in R/R MM: Updated Subgroup Analysis of POLLUX Based on Cytogenetic Risk

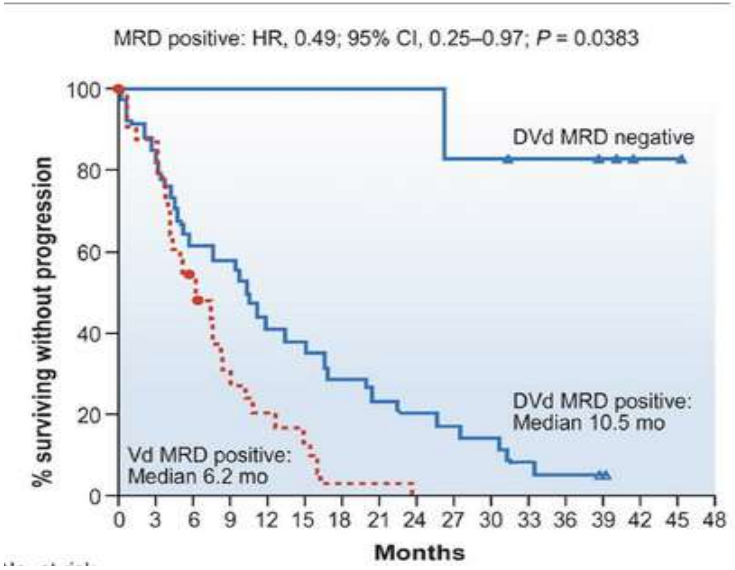






Efficacy and Safety of DVd in R/R MM Based on Cytogenetic Risk: Updated Subgroup Analysis of CASTOR





Oral Abstract Session

IMW 21 18TH INTERNATIONAL MYELOMA WORKSHOP

Daratumumab Improves Depth of Response and Progression-Free Survival in Transplant-Ineligible, High-Risk, Newly Diagnosed Multiple Myeloma*

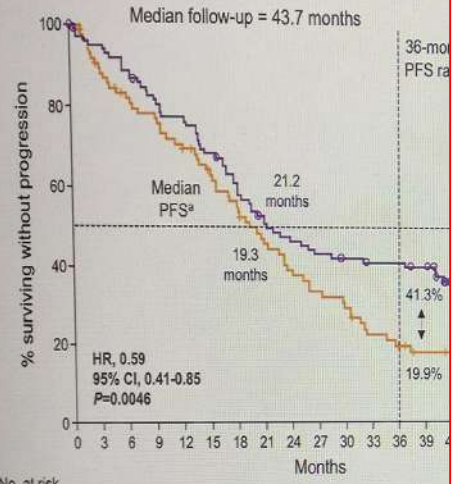
Andrzej J. Jakubowiak,[1] Shaji Kumar,[2] Rohan Medhekar,[3] Huiling Pei,[4] Patrick Lefebvre,[5] Shuchita Kaila,[3] Jianming He,[6] Marie-Hélène Lafeuille,[5] Annelore Cortoos,[3] Anil Londhe,[4] Panagiotis Mavros,[3] Thomas S. Lin,[3] Saad Z. Usmani[7]

[1]University of Chicago Medical Center, Chicago, IL, USA; [2]Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA; [3]Janssen Scientific Affairs, LLC, Horsham, PA, USA; [4]Janssen Research & Development, Raritan, NJ, USA; [5]Analysis Group, Inc., Montreal, QC, Canada; [6]Janssen Global Services, LLC, Raritan, NJ, USA; [7]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA

mPFS :NR D-Rd vs 33.8 m Rd

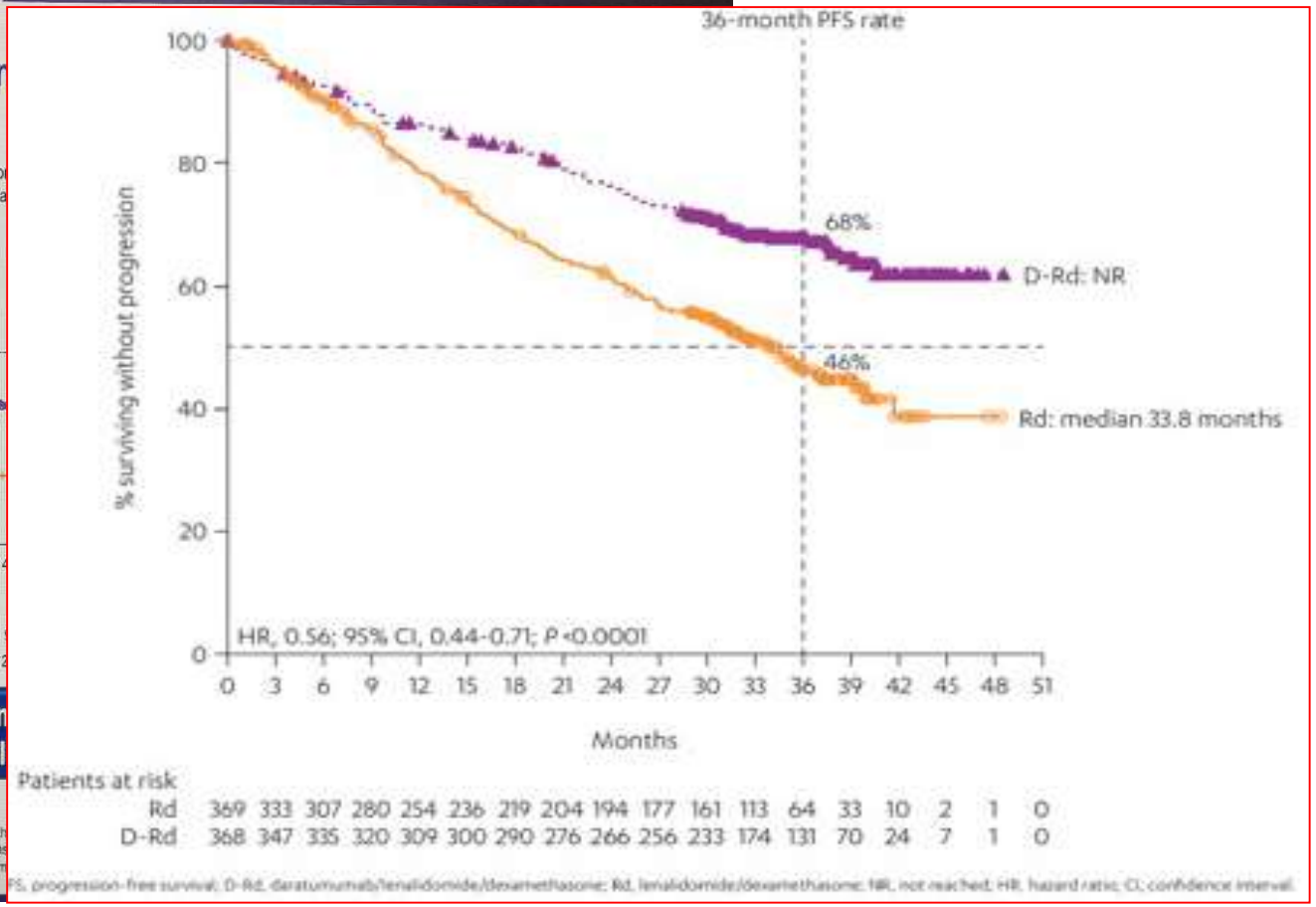
IMW 21 18TH INTERNATIONAL MYELOMA WORKSHOP

PFS Benefit with DARA in Patien



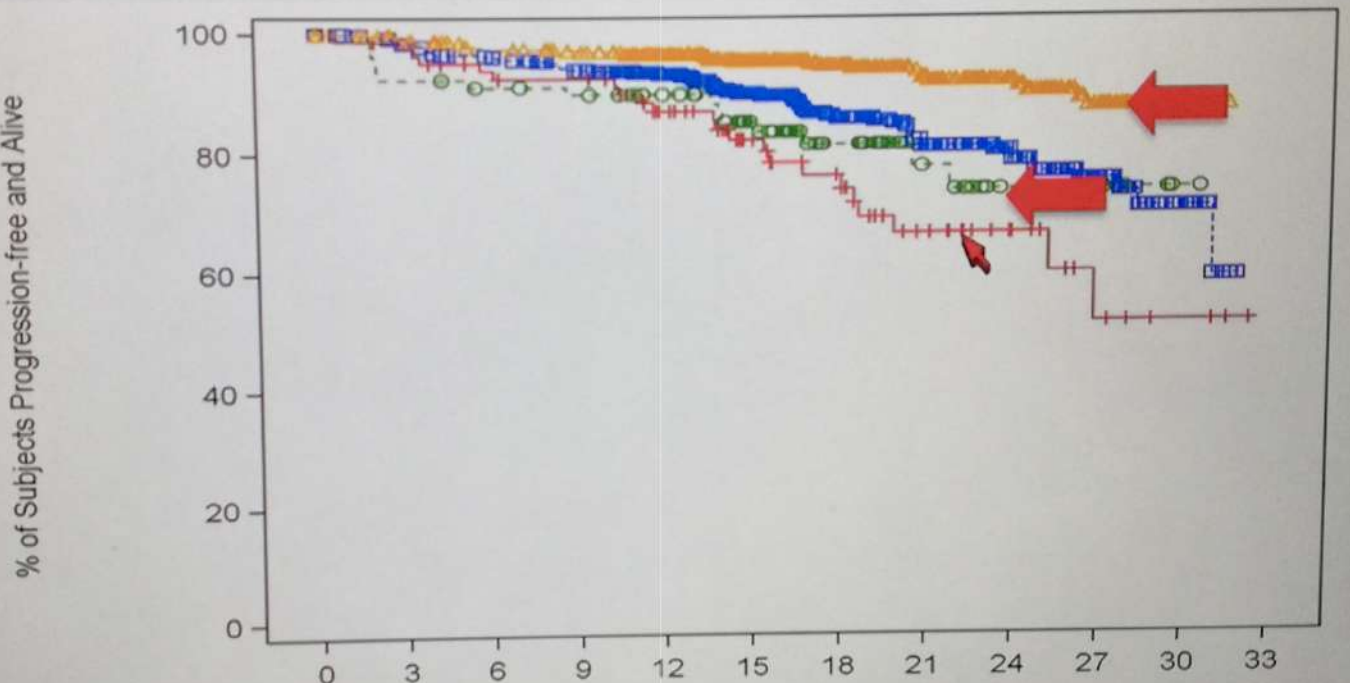
Addition of DARA to Control regin progression or death and a doubl

HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.
Analysis was based on Cox regression stratified by study identifier. Explanatory variables in th baseline renal impairment (ie, baseline creatinine clearance <60 mL/min). PFS was defined as Patients were censored at the date of last disease assessment, initiation of subsequent anti-m A hazard ratio <1 indicates an advantage for DARA + Control.



PFS, progression-free survival; D-Rd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; NR, not reached; HR, hazard ratio; CI, confidence interval.

CASSIOPEIA: PFS According to Risk Status



Subjects at risk												
VTd High risk	86	80	74	72	59	43	35	22	12	6	3	0
DVTd High risk	82	74	71	69	63	49	33	20	11	7	1	0
VTd Standard risk	454	437	421	401	352	274	196	139	91	44	11	0
DVTd Standard risk	460	445	429	422	378	296	227	164	111	54	13	0

VTd High risk
VTd Standard risk
DVTd High risk
DVTd Standard risk

Moreau, Sonneveld, Avet-Loiseau; unpublished data.

Abstract 1066705

Carfilzomib-Based Induction/Consolidation With or Without Autologous Transplant and Lenalidomide (R) or Carfilzomib-Lenalidomide (KR) Maintenance: Efficacy in High-Risk Patients of the FORTE study

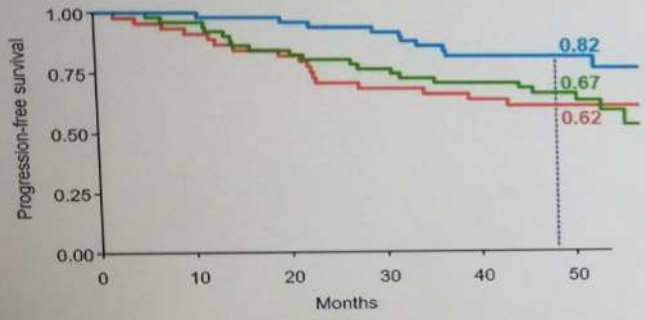
Roberto Mina, MD; Elena Zamagni, MD, PhD; Delia Rota-Scalabrini, MD; Paolo Corradini, MD; Mariella Grasso, MD; Stelvio Ballanti, MD; Nicola Giuliani, MD, PhD; Luca De Rosa, MD; Claudia Cellini, MD, PhD; Iolanda Donatella Vincelli, MD; Cristina Velluti, MSc; Andrea Capra, MScEng; Anna Maria Cafro, MD; Alessandro Gozzetti, MD, PhD; Massimo Gentile, MD; Sara Aquino, MD; Angelo Palmas, MD; Antonio Ledda, MD; Maria Teresa Petrucci, MD; Pellegrino Musto, MD; Mario Boccadoro, MD; Francesca Gay, MD, PhD

Progression-free survival: Random 1

KCd_ASCT vs. KRd_ASCT vs. KRd12

Median follow-up from Random 1: 51 months (IQR 46-55)

Standard risk (N=153)

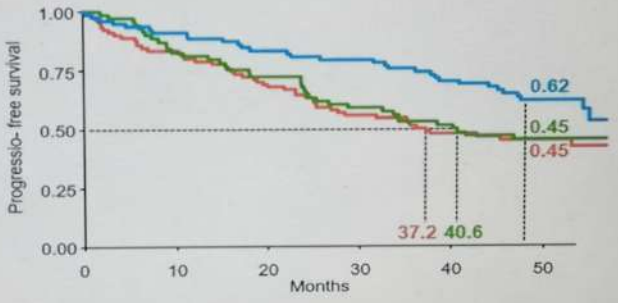


KRd_ASCT vs. KCd_ASCT: HR 0.43, p=0.035

KRd_ASCT vs. KRd12: HR 0.43, p=0.032

KRd12 vs. KCd_ASCT : HR 0.99, p=0.99

High risk (N=243)

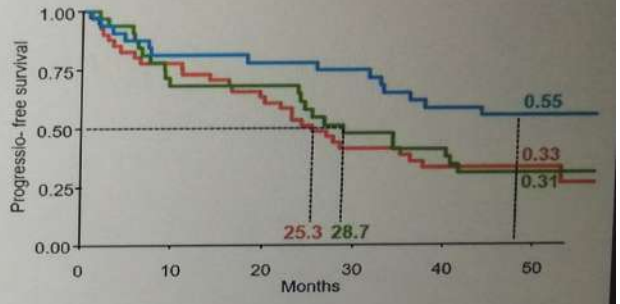


KRd_ASCT vs. KCd_ASCT: HR 0.57, p=0.015

KRd_ASCT vs. KRd12: HR 0.61, p=0.040

KRd12 vs. KCd_ASCT: HR 0.94, p=0.78

Double hit (N=105)



KRd_ASCT vs. KCd_ASCT: HR 0.46, p=0.024

KRd_ASCT vs. KRd12: HR 0.52, p=0.063

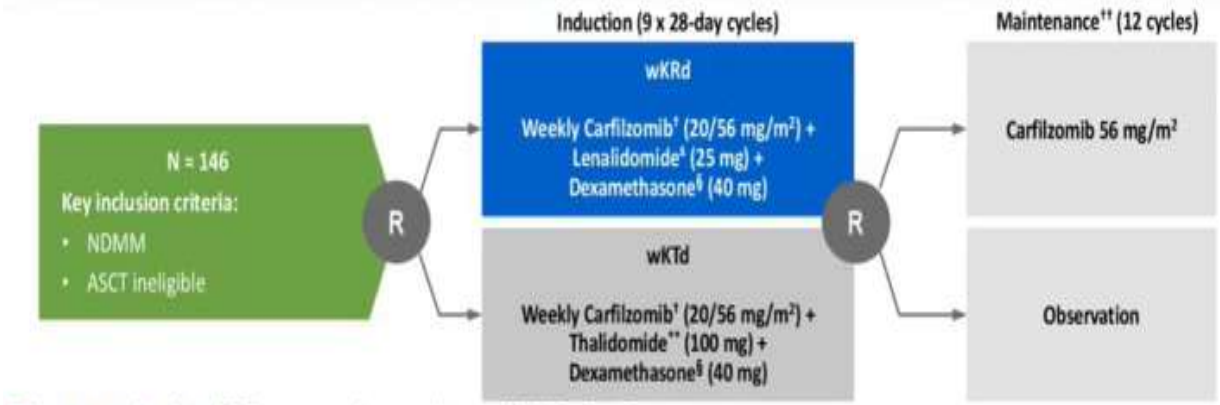
KRd12 vs. KCd_ASCT: HR 0.89, p=0.69

Random 1, first randomization (induction/consolidation treatment); ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; HR, hazard ratio; CI, confidence interval; p, p-value; iQR, interquartile range.

Conclusions

- KRd_ASCT significantly prolonged PFS vs. KRd12 in:
  - SR patients: 4-year PFS → 82% vs. 67%
  - HiR patients: 4-year PFS → 62% vs. 45%
  - DH patients: 4-year PFS → 55% vs. 33%
- KRd_ASCT increased the rate of 1-year sustained MRD negativity vs. Krd12 in patients with both HiR (45% vs 34%) and DH (38% vs 25%) MM.
- KR significantly prolonged PFS from the start of maintenance vs. R alone
  - SR patients: 3-year PFS → 90% vs. 73%
  - HiR patients: 3-year PFS → 69% vs. 59%
  - DH patients: 3-year PFS → 67% vs. 42%
- The benefit of KRd_ASCT vs. KRd12 and KR vs. R was observed in all subgroups: del(17p), gain(1q), del(1p), and t(4;14), except amp(1q).

AGMT MM-02 Study Phase 2 :wKRD vs wKTd NDMM impact of High-Risk Cytogenetics



Primary endpoint: ORR assessed according to IMWG criteria

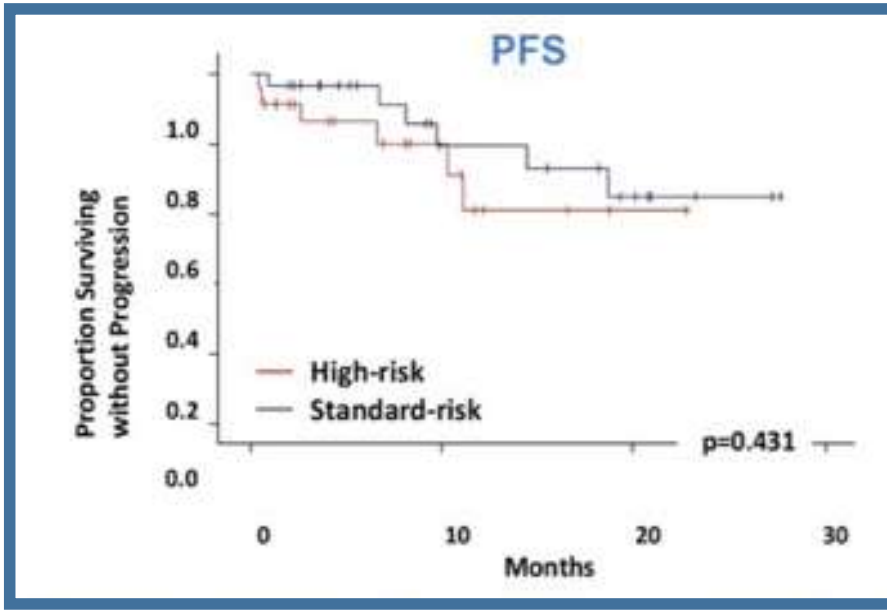
Selected secondary endpoints: Safety, OS, ORR, PFS, MRD negativity rate

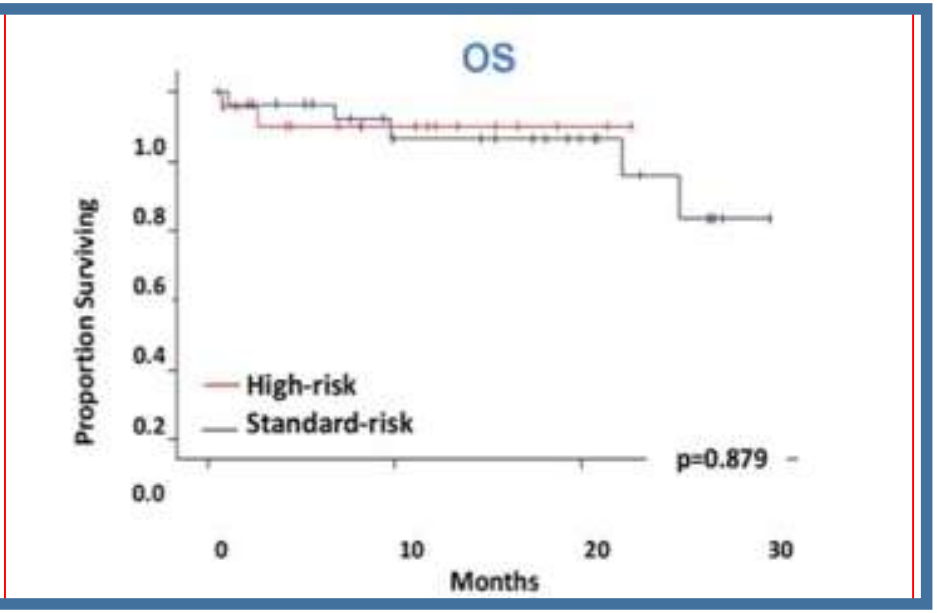
Patient characteristics: Of the 87 patients enrolled to date (ITT), median (range) age is 75 (55–84) years; 76 patients completed ≥ 1 cycle of treatment (PP)

*High-risk cytogenetics were defined by the presence of either t(4;14) and/or del17p and/or amp 1q21;

Conclusions:

- PFS and OS were similar in NDMM patients with high-risk vs standard risk cytogenetics
- Median FU was 11.9 months
- Of the 35 pts elegible for MRD testing :51% of pts achieved MRD negativity





Management of High-Risk Multiple Myeloma Patients

Paula Rodriguez-Otero, Jesús F. San Miguel

Department of Hematology, Clínica Universidad de Navarra, CIMA, IDISNA, CIBERONC, Pamplona, Spain

	NDMM – Non trasplant eligible patients											
	SWOG trial (VRd vs Rd)				ALCYONE (DVMP vs VMP)				MAIA trial (DRd vs Rd)			
	HR		ITT population		HR		ITT population		HR		ITT population	
	VRd	Rd	VRd	Rd	DVMP	VMP	DVMP	VMP	DRd	Rd	DRd	Rd
PFS, m	38	16	43	30	NR	NR	36.4	19.3	NR	29.6	NR	38.8
HR (95% CI)	p-value: 0.19		p-value: 0.0018		0.78 (0.43–1.43)		0.42 (0.34 – 0.51)		0.57 (0.32 – 1.04)		0.56 (0.44 – 0.71)	
CR rate	–	–	16	8	–	–	45	25-	–	–	50	27
MRD neg (%)	–	–	–	–	–	–	28	7	–	–	29	9

The combination of a proteasome inhibitor plus an IMiD (VRD) may yield better PFS but still cannot overcome the adverse prognosis of HR. **KRD may be a preferable option in this setting**

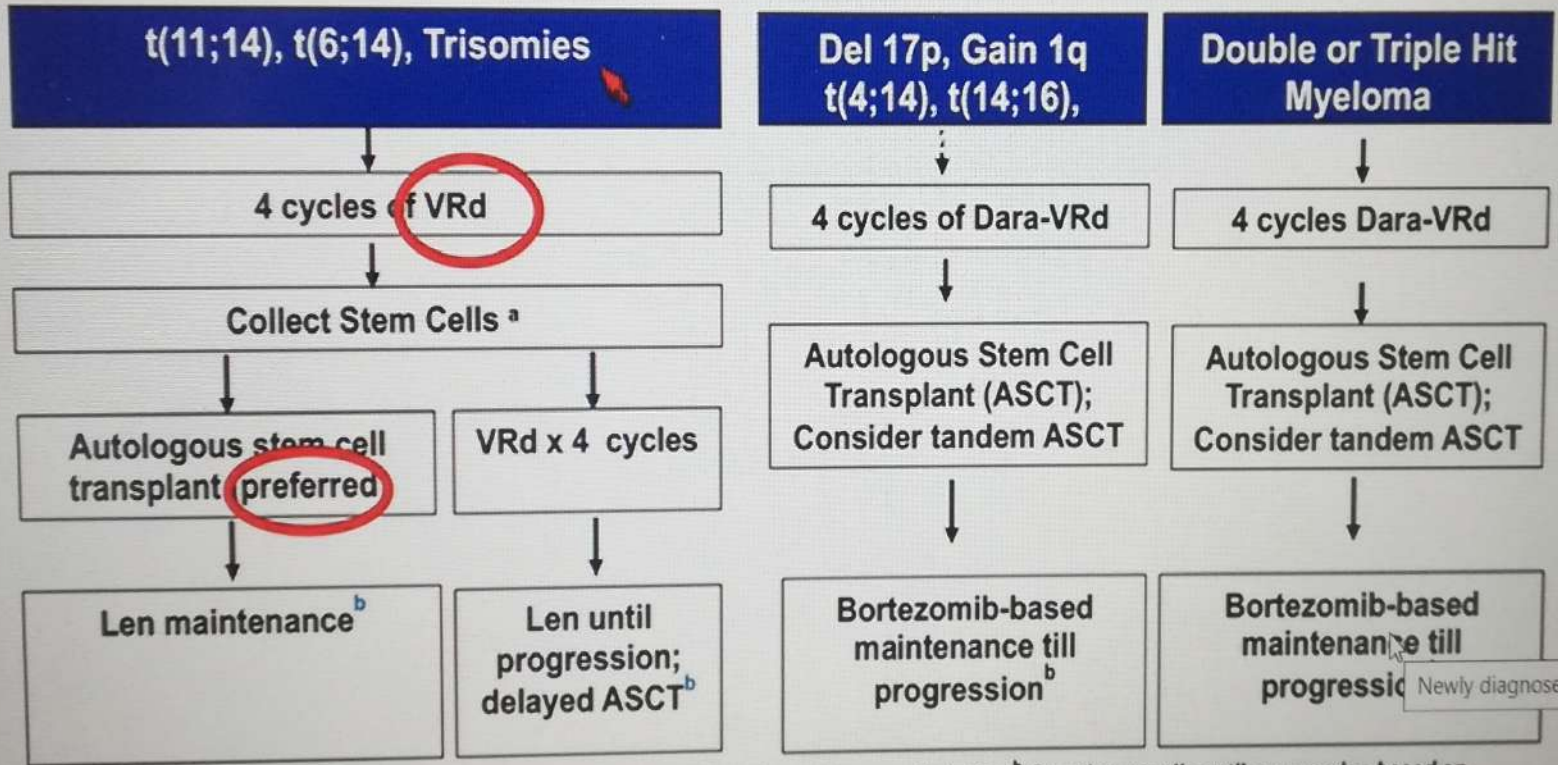
Daratumumab-based trials (Dara-VMP and Dara-Rd) show that the PFS for HR patients is superior to that of the control arms, **but still shorter as compared to SR patients**

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

MAYO CLINIC

mSMART – Off-Study

Transplant Eligible



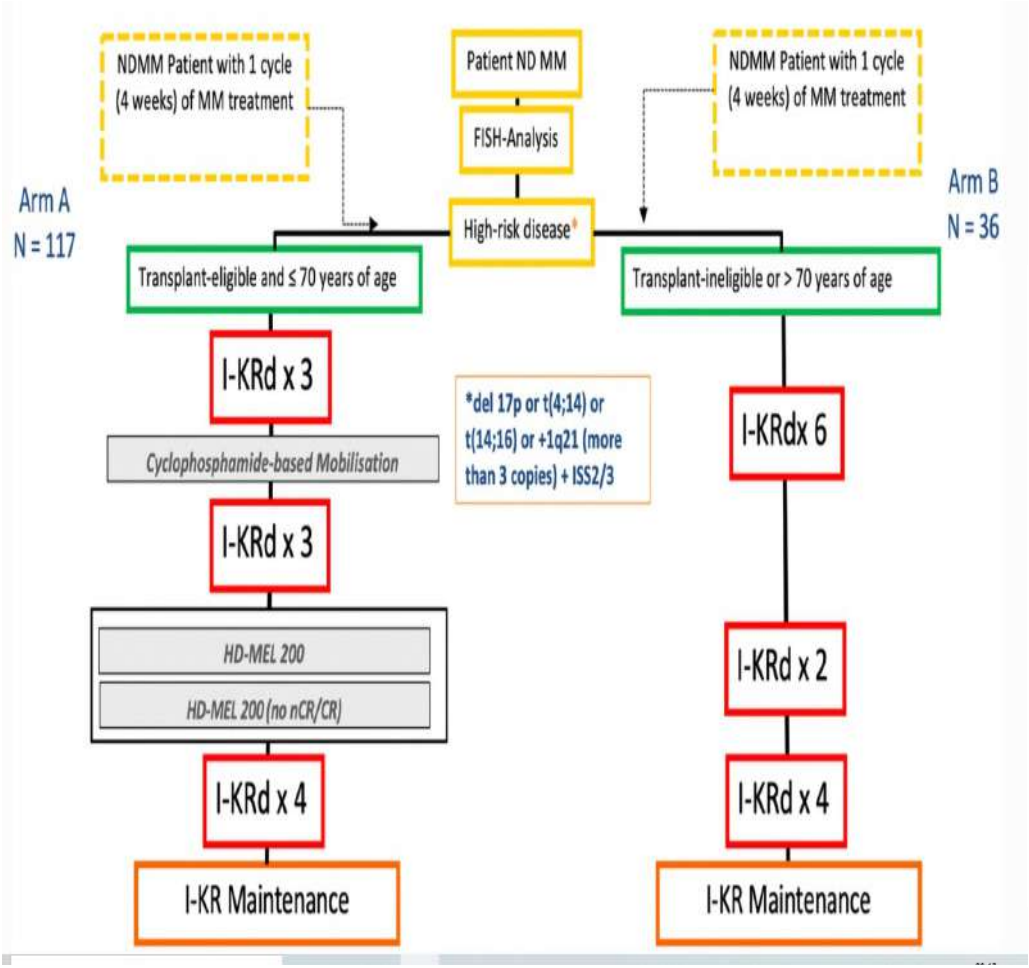
a *If age >65 or > 4 cycles of VRd, consider mobilization with G-CSF plus cytoxan or plerixafor;* b *Duration usually until progression based on tolerance*

VRd, Bortezomib, lenalidomide, dexamethasone; Dara, daratumumab

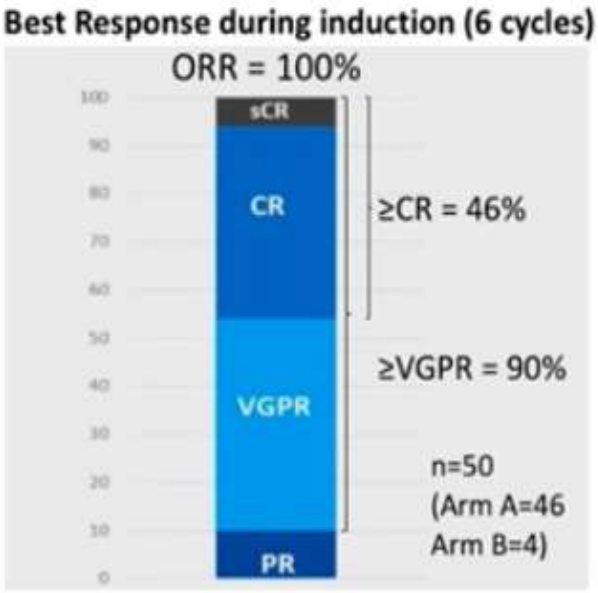
Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v19 //last reviewed Feb 2021

GMMG-CONCEPT Study Phase 2 :interim analysis
Isatuximab+carfilzomib-lenalidomide-dexamethasone in high-risk NDMM

Isa-KRd induction, consolidation and maintenance

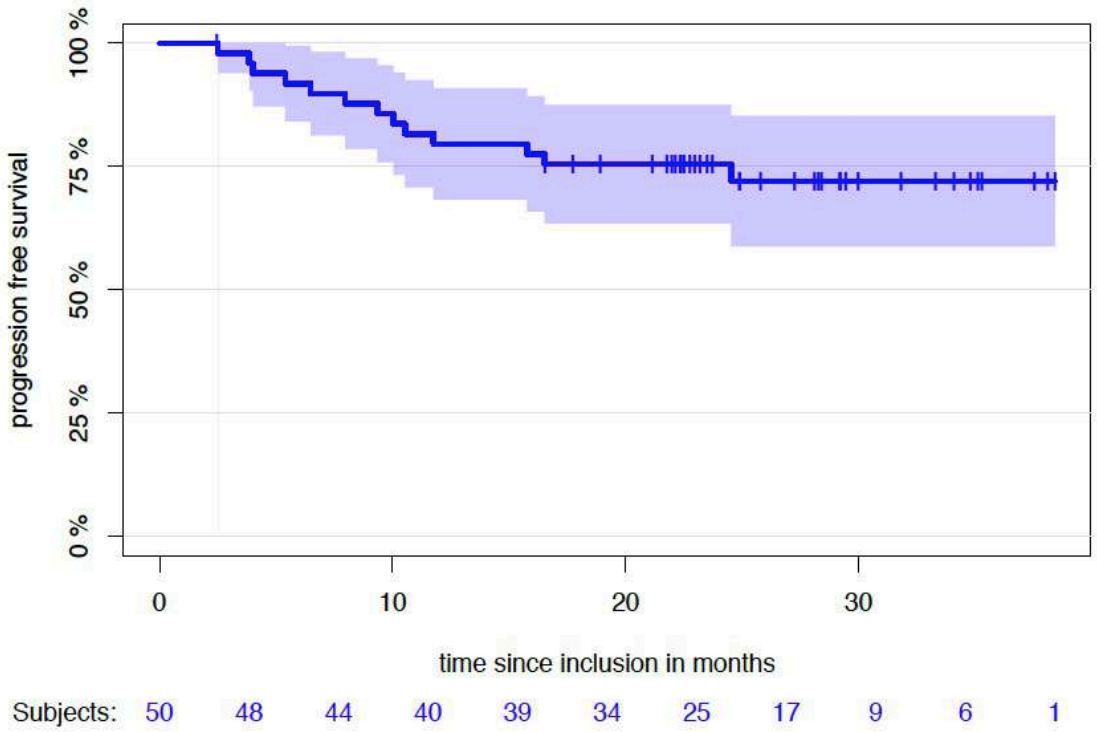


- **High risk** : FISH of the presence of ≥1 of the genetic abnormalities of del(17p), t(4;14), or t(14;16), or >3 copies of 1q21 and International Stage System stage 2 or 3 disease.
- The primary outcome measure for the study **is minimal residual disease** (MRD) negativity measured by flow cytometry.



MRD negative 60% during induction

Progression-free Survival

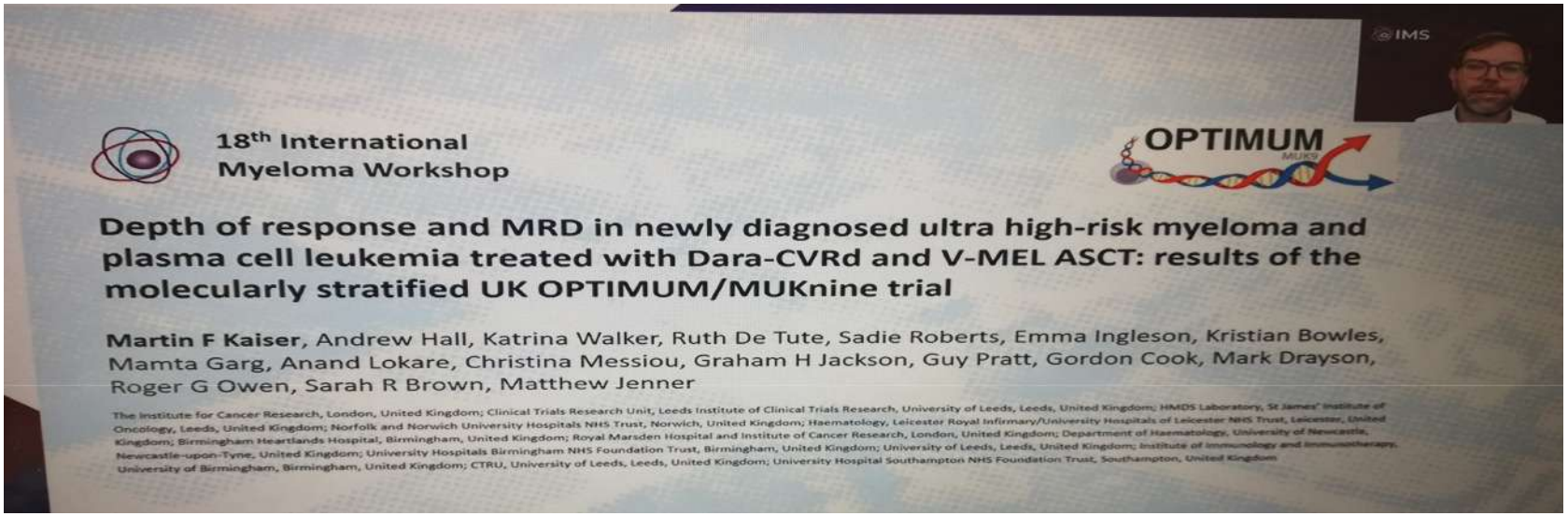


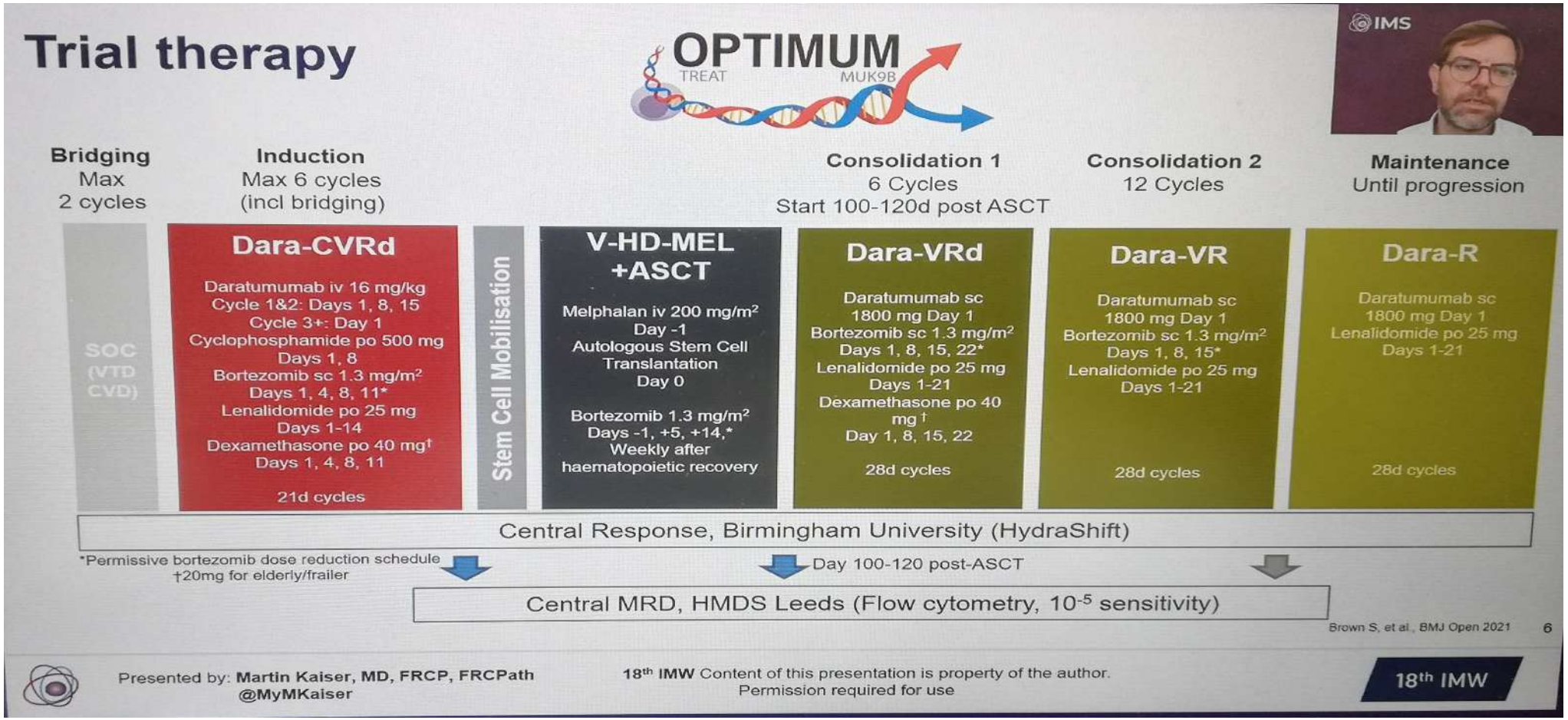
Median follow-up: 24.9 months

- 12-month PFS: 79.6% (68.3%; 90.9%)
- 24-month PFS: 75.5% (63.5%; 87.6%)

Data cut-off: Jan. 26, 2021
(95%-confidence level)

40/50 patients were relapse-free after 1 year


IMS
18th International
Myeloma Workshop
OPTIMUM
MUK9
Depth of response and MRD in newly diagnosed ultra high-risk myeloma and plasma cell leukemia treated with Dara-CVRd and V-MEL ASCT: results of the molecularly stratified UK OPTIMUM/MUKnine trial
Martin F Kaiser, Andrew Hall, Katrina Walker, Ruth De Tute, Sadie Roberts, Emma Ingleson, Kristian Bowles, Mamta Garg, Anand Lokare, Christina Messiou, Graham H Jackson, Guy Pratt, Gordon Cook, Mark Drayson, Roger G Owen, Sarah R Brown, Matthew Jenner
The Institute for Cancer Research, London, United Kingdom; Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, United Kingdom; HMDS Laboratory, St James' Institute of Oncology, Leeds, United Kingdom; Norfolk and Norwich University Hospitals NHS Trust, Norwich, United Kingdom; Haematology, Leicester Royal Infirmary/University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; Birmingham Heartlands Hospital, Birmingham, United Kingdom; Royal Marsden Hospital and Institute of Cancer Research, London, United Kingdom; Department of Haematology, University of Newcastle, Newcastle-upon-Tyne, United Kingdom; University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; University of Leeds, Leeds, United Kingdom; Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, United Kingdom; CTRU, University of Leeds, Leeds, United Kingdom; University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom


Trial therapy
OPTIMUM
TREAT
MUK9B
IMS
Bridging
Max
2 cycles
Induction
Max 6 cycles
(incl bridging)
Consolidation 1
6 Cycles
Start 100-120d post ASCT
Consolidation 2
12 Cycles
Maintenance
Until progression
SOC
(VTD
CVD)
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/m2
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/m2
Day -1
Autologous Stem Cell
Translantation
Day 0
Bortezomib 1.3 mg/m2
Days -1, +5, +14,*
Weekly after
haematopoietic recovery
Dara-VRd
Daratumumab sc
1800 mg Day 1
Bortezomib sc 1.3 mg/m2
Days 1, 8, 15, 22*
Lenalidomide po 25 mg
Days 1-21
Dexamethasone po 40
mg †
Day 1, 8, 15, 22
28d cycles
Dara-VR
Daratumumab sc
1800 mg Day 1
Bortezomib sc 1.3 mg/m2
Days 1, 8, 15*
Lenalidomide po 25 mg
Days 1-21
28d cycles
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
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Presented by: Martin Kaiser, MD, FRCP, FRCPath
@MyMKaiser
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Trial population

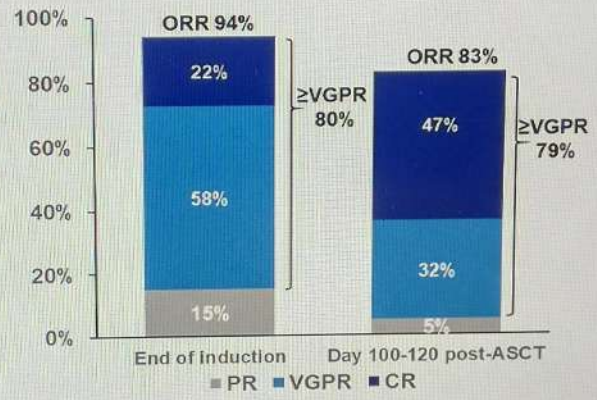
- 472 patients entered OPTIMUM Screen
- Recruitment September 2017 to July 2019
- 39 UK NHS hospitals
- 128 with Ultra High-Risk features
- 10 primary plasma cell leukaemia
- 107 consented and eligible for OPTIMUM Treat

Patient Characteristics	Safety population (n=107)
Median age, yrs (range)	60 (35-78)
Male, n (%)	64 (60%)
ISS Stage 1, n (%)	29 (27%)
Stage 2, n (%)	44 (40%)
Stage 3, n (%)	34 (32%)
missing, n (%)	1 (1%)
ECOG Performance Status	
0, n (%)	51 (48%)
1, n (%)	42 (39%)

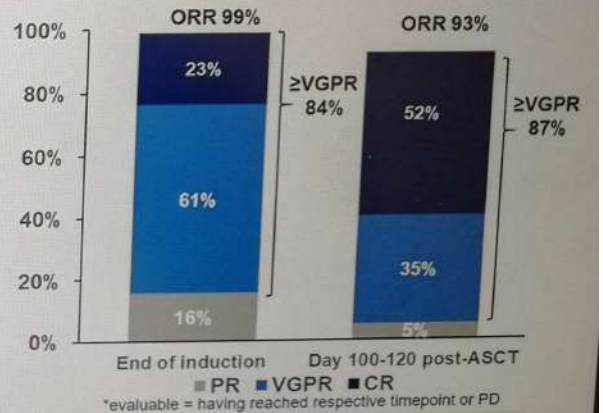
Central response results

Response Safety Population (n=107)	End of induction	100-120 days post-ASCT
CR	23 (21.5%)	50 (46.7%)
VGPR	62 (57.9%)	34 (31.8%)
PR	16 (15.0%)	5 (4.7%)
PD	1 (0.9%)	7 (6.5%)
Timepoint not reached	5 (4.7%)	11 (10.3%)

Safety population (n=107)



Evaluable* population (n=102/n=96)



*evaluable = having reached respective timepoint or PD

pPCL (evaluable D100-120; n=8)

- CR: 2 (25%)
- VGPR: 2 (25%)
- PR: 2 (25%)
- PD: 2 (25%)

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

18th IMW

IMW21 18TH INTERNATIONAL MYELOMA WORKSHOP

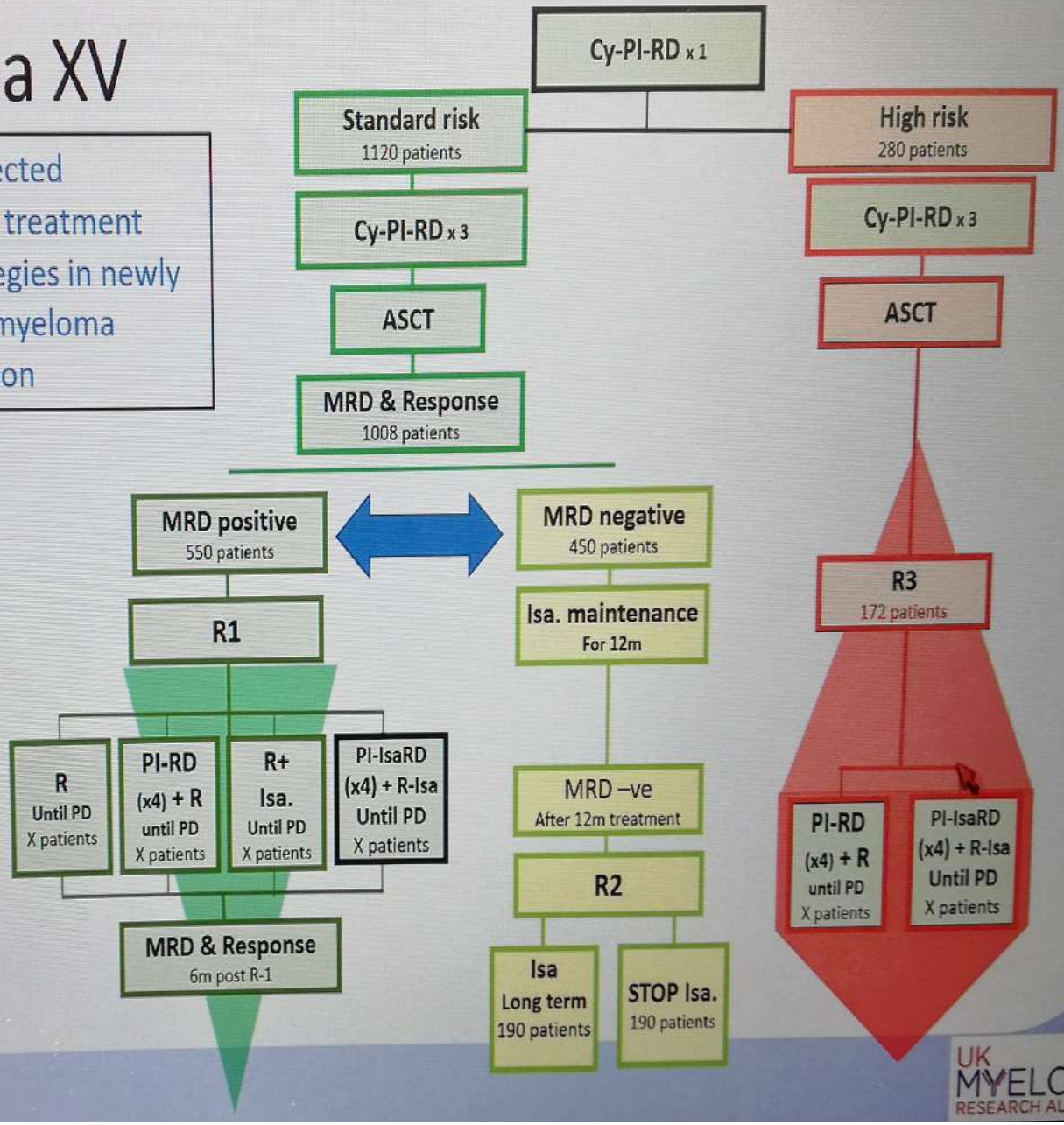
UKMRA Myeloma XV

RADAR: **R**isk **A**dapted therapy **D**irected **A**ccording to **R**esponse comparing treatment escalation and de-escalation strategies in newly diagnosed patients with multiple myeloma suitable for stem cell transplantation

PIs: Kwee Yong, Mark Cook

CANCER RESEARCH UK

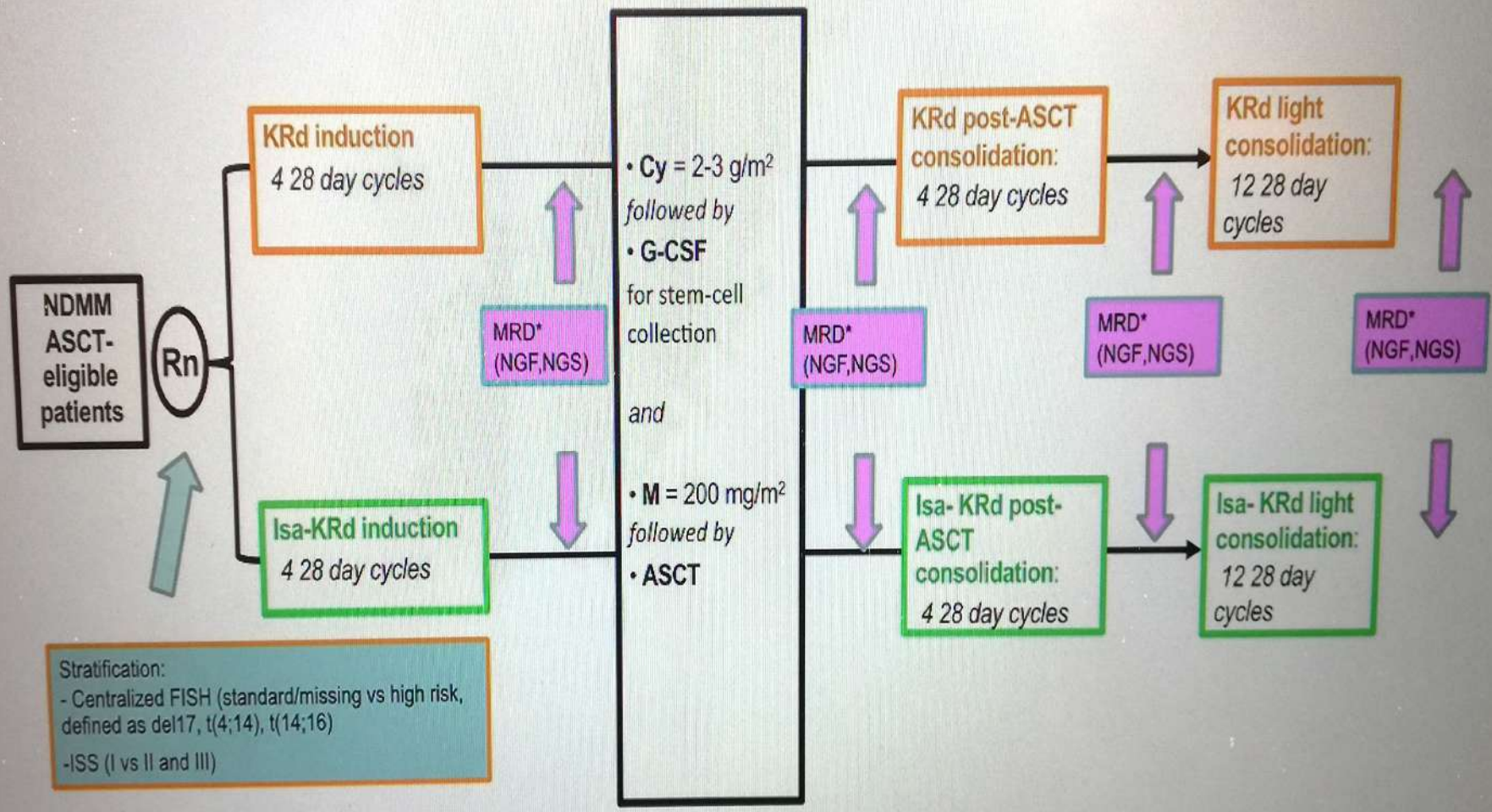
NCRI National Cancer Research Institute



UK MYELOMA RESEARCH ALLIANCE

Phase III EMN24 IsKia study

Isa-KRd vs. KRd in NDMM ASCT-eligible patients

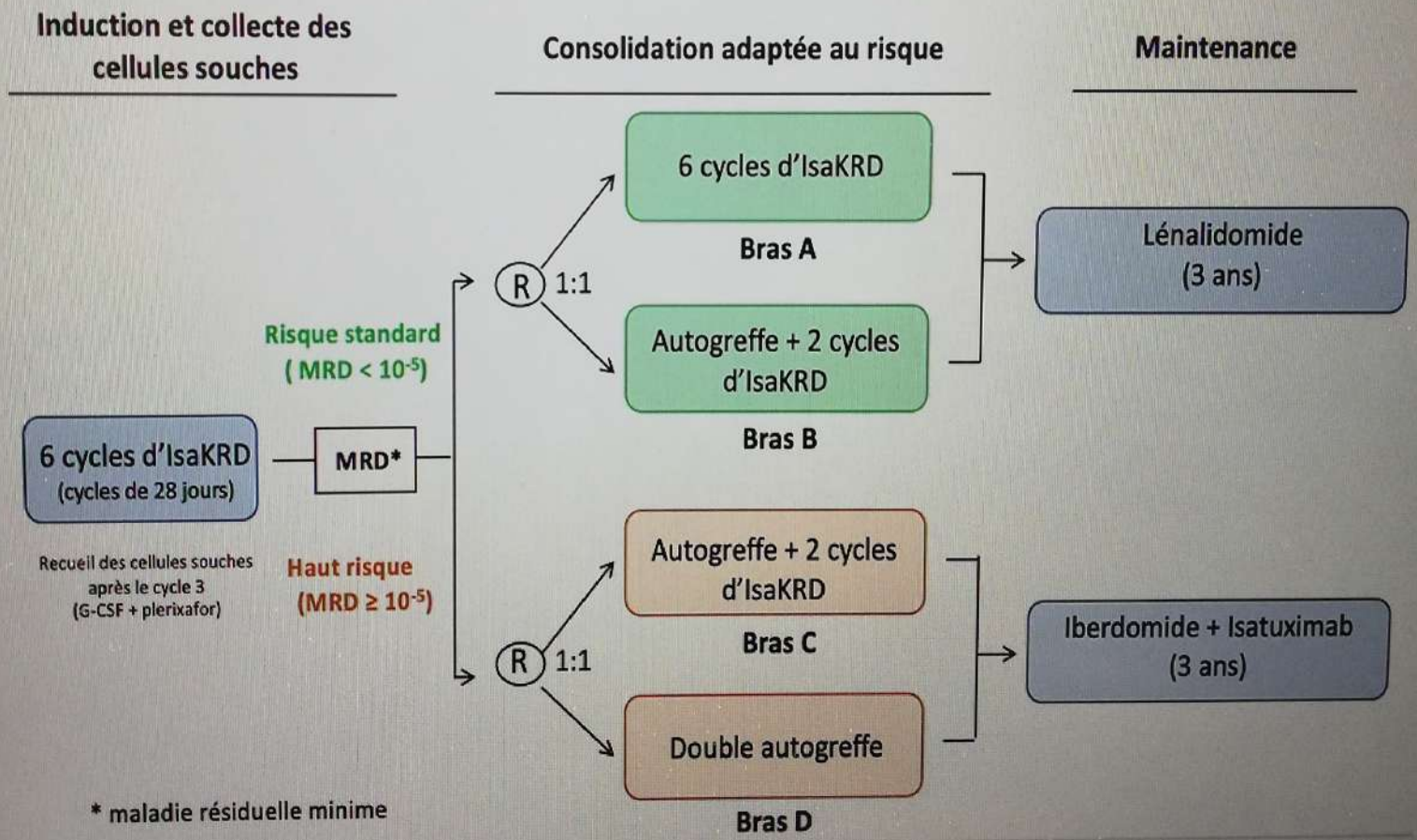


Rn, randomization; Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; Cy, cyclophosphamide; M, melphalan; NDMM, newly diagnosed multiple myeloma; ASCT, autologous stem-cell transplantation; dd, days; cc, cycles; G-CSF, Granulocyte-Colony Stimulating Factor PO, orally; IV, intravenous; ISS International Staging System. *in patients achieving >= VGPR; centralized MRD evaluation

EMN

Perspectives 2021-2022

Response adapted strategy: protocole IFM 2020-02 MIDAS



RRMM

An Immuno-therapeutic salvage strategy for 'functional' high-risk multiple myeloma incorporating Isatuximab, Iberdomide and Dexamethasone (IBIS) – AMaRC 20-02

RRMM
PD <12mths from 1L therapy
n = 50

→

- **Isatuximab: 10mg/kg q1week x 4, then q2weekly**
- **Iberdomide 1.6mg days 1 - 21**
- **Dexamethasone 40mg weekly**

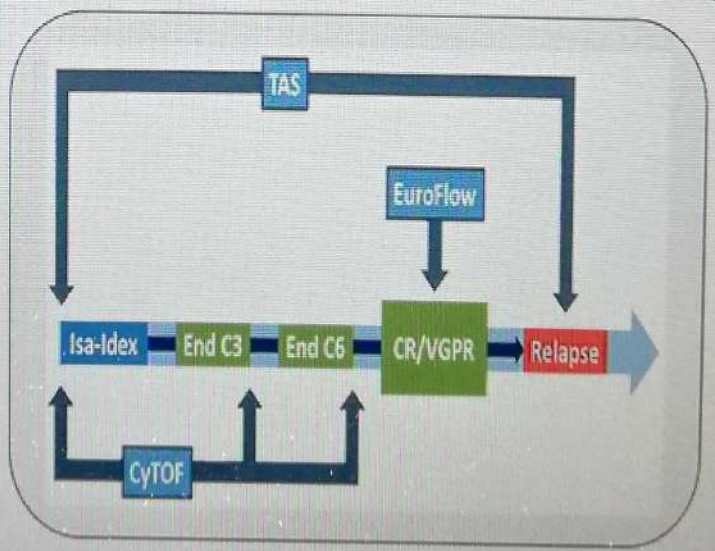
→ **UNTIL PROGRESSION OR TOXICITY**

OBJECTIVES

Primary: ***ORR***

Secondary: **PFS; OS; *MRD; Safety/tolerability***

- Recruitment status: Accrual imminent.



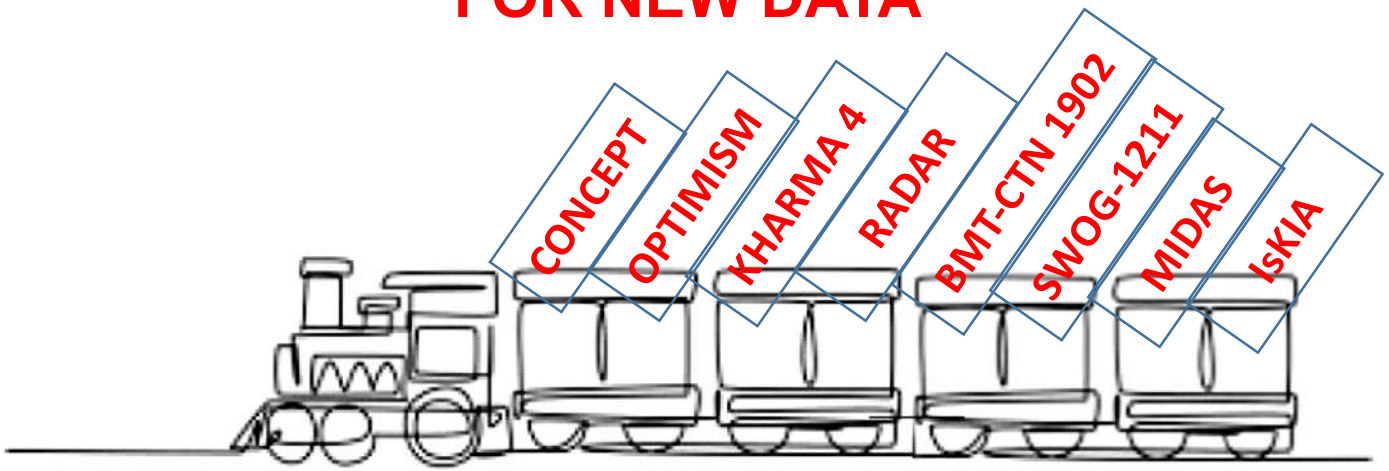
CPI Andrew Spencer

AMaRC
AUSTRALASIAN MYELOMA RESEARCH CONSORTIUM

High-Risk clinical trials in MM

- There is a consensus definition of HR.
- There are multiple trials exploring different therapeutic options for HR planned or in set up.
  - SWOG – 1211 (VRDelo).
  - Optimism (Chemo plus Dara)
  - TT7 (Chemo plus Dara).
  - KarMMA 4 (Abecma).
  - Concept Study (Chemo plus Isa).
  - BMT – CTN SOSS (Car T).
  - HATT trial – (Talqetamab + ASCT).

SERCHING FOR THE RIGHT RISK FACTOR WAITING FOR NEW DATA



RISK ASSESSMENT

Multidimensional Geriatric Assessment

PATIENT RELATED
TREATMENT TOLERANCE
LIFE-EXPECTANCY

CLINICAL DECISION

TAILORED THERAPY

Cancer-risk score

DISEASE RELATED
AGGRESSIVENESS
CHEMOSENSITIVITY
AVAILABILITY DRUGS