UK MYELOMA RESEARCH ALLIANCE

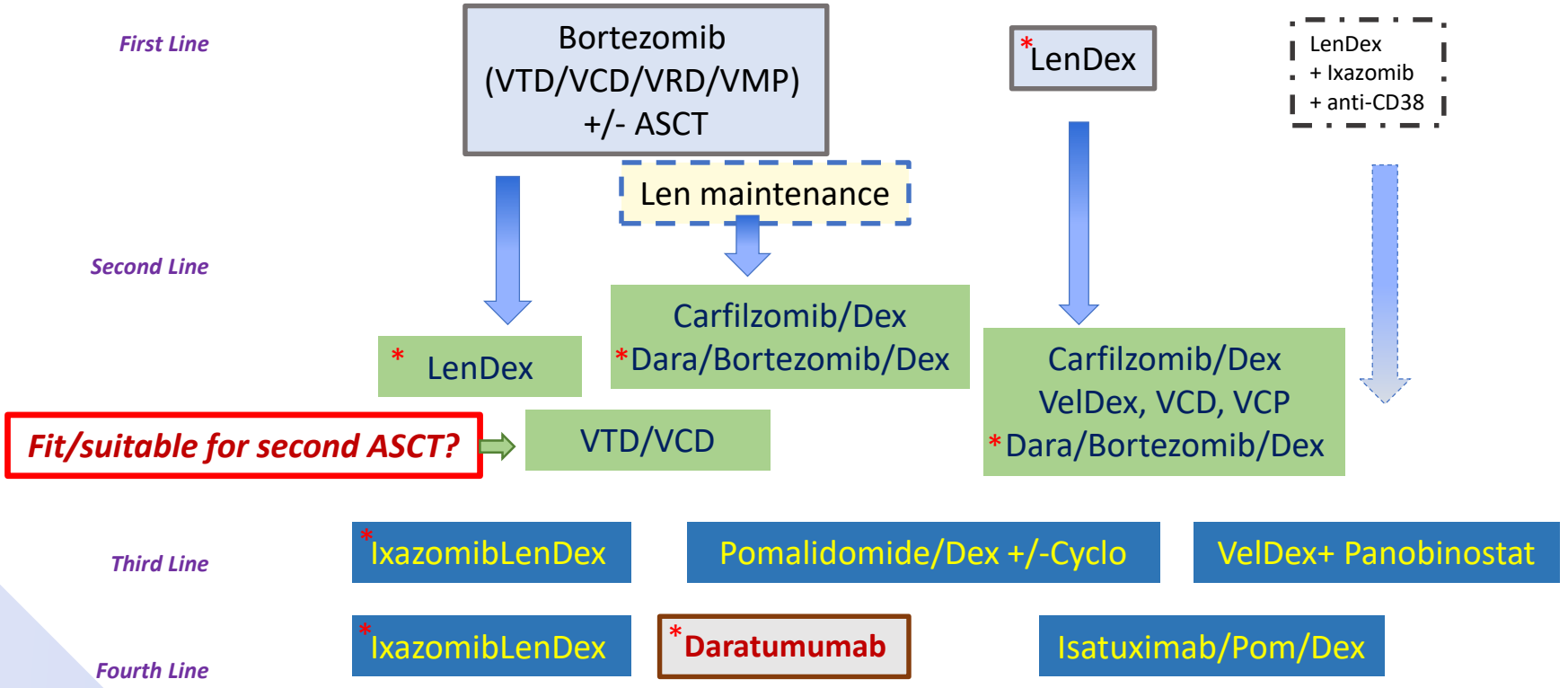
Update on clinical trials in myeloma

Kwee Yong

UCL

January 2020

Current NICE approved pathway



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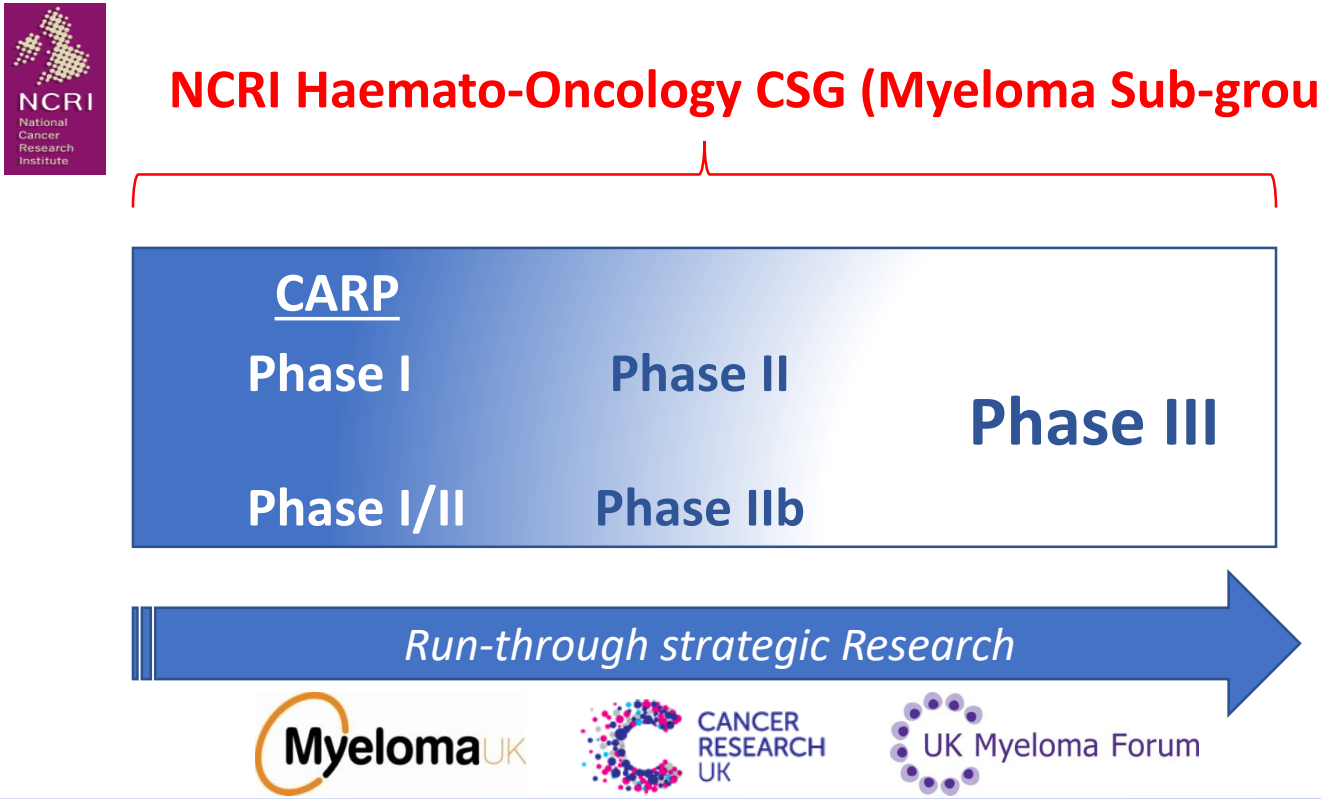


Overview of MRA studies

MGUS/ Smouldering myeloma	Newly diagnosed MM	First Relapse	Later Relapses
Observational study (CRUK Early Detection programme)	**MUKnine**	**Myeloma XII ACCORD**	**MUK 7 MUK 8 MUK11**
DEFENSE Anti-RANK-ligand Ab vs placebo	**CARDAMON**		*CARP programme: PROMISS*
	Myeloma XIV		
	Myeloma XV		

Supportive Care and Special patient populations	
Antibiotic prophylaxis	TEAMM (TEAMM2)
Supportive care	ENCOMPASS
Plasma cell leukemia	EMN Study
Renal impairment	

Trials in newly diagnosed patients:

:A new paradigm of risk stratification

What is the most important risk in older patients?

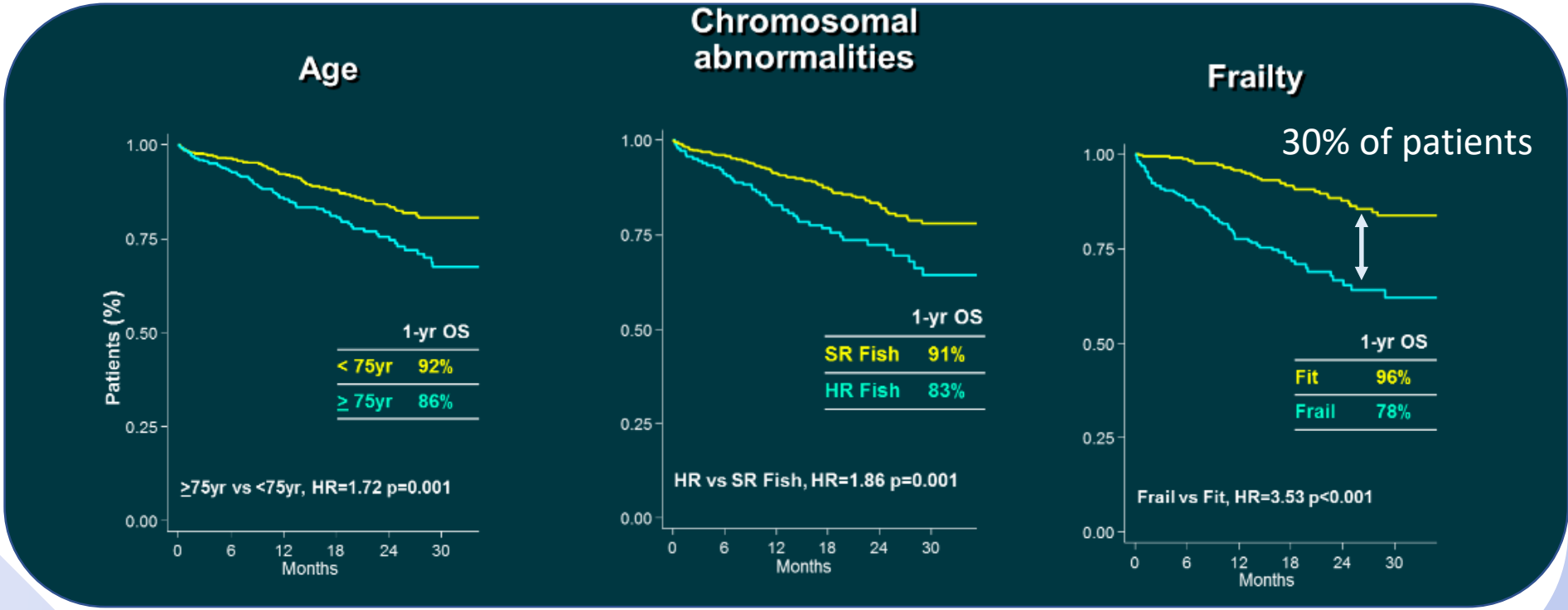
IMWG Frailty score – the gold standard

- 869 patients from 3 international EMN trials
  - All novel agents – bortezomib, lenalidomide or carfilzomib

- Geriatric assessments
  - Age
  - Katz's Activity of Daily Living and Instrumental ADL
  - Charlson Comorbidity Index

- Multivariate analysis, including ISS, chromosomal abnormalities and treatment

IMWG Frailty score – the gold standard in MM?



IMWG Frailty score

FIT

Age ≤75 years, ADL >4, IADL >5, *and* CCI ≤1

ASCT eligibility:
cardiac function (LVEF >40%)
liver function (bilirubin <1.5 ULN, AST/ALT <2.5 ULN)
pulmonary function (DLCO/FEV1 >40-80%)

ASCT

MEL200 mg/m^2 if:
- age ≤70 years
- no renal impairment
- rMCI 1-3
- performance status ≥90% (not related to MM)

MEL100-140 mg/m^2 if:
- age >70 years
- and/or renal impairment
- and/or rMCI 4-6
- and/or performance status <90% (not related to MM)

No ASCT

Dara-VMP
Dara-Rd
VRd
VCd
VMP*
Rd*

INTERMEDIATE-FIT

Age 76-80 years
or ADL ≤ 4
or IADL ≤ 5
or CCI ≥ 2

Reduced-intensity regimens

Weekly VMP
Weekly VCd
Vd
Rd
Rd-R
vrd lite°

FRAIL

Age >80 years regardless of ADL, IADL, CCI
or Age 76-80 years and either ADL ≤ 4, IADL ≤5, CCI ≥2
or Age ≤75 years and at least two of the following: ADL ≤4, IADL ≤5, CCI ≥2

Dose-adjusted regimens

rd°
vd°

Palliation and supportive care

UKMRA Myeloma Risk Profile (MRP)

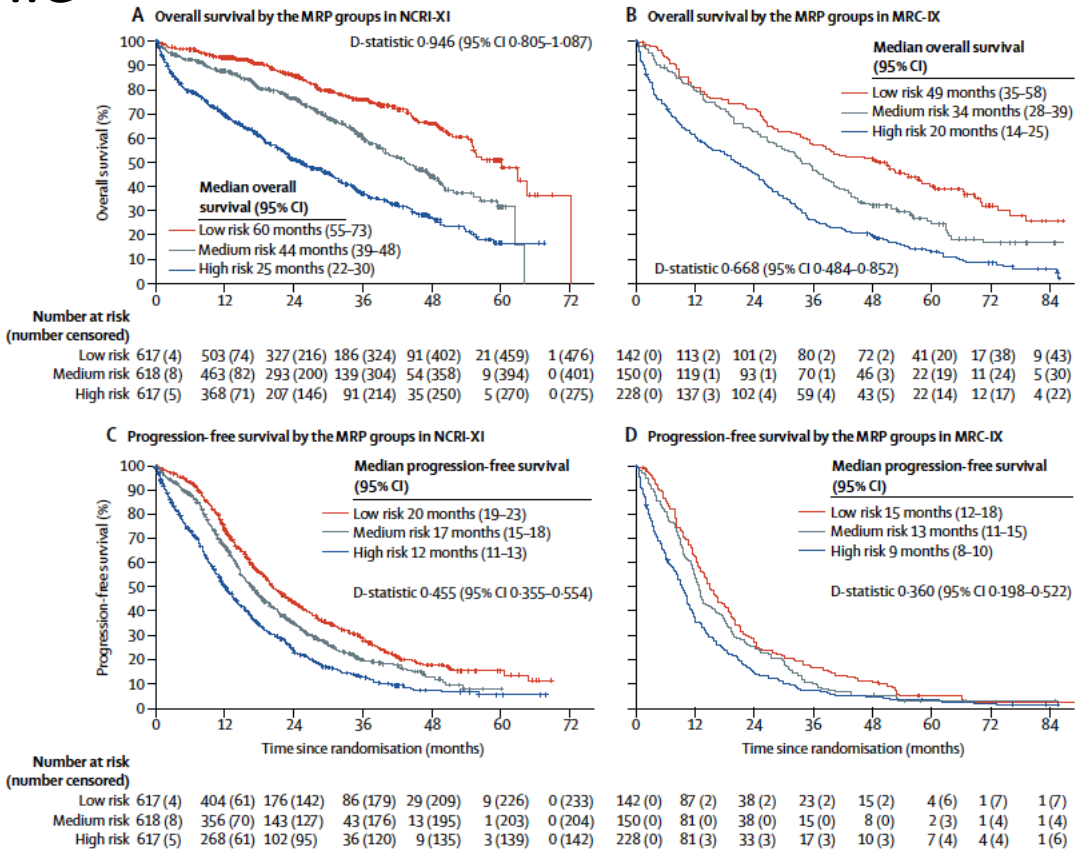
A clinical prediction model for outcome and therapy delivery in transplant-ineligible patients with myeloma (UK Myeloma Research Alliance Risk Profile): a development and validation study

Gordon Cook, Kara-Louise Royle, Charlotte Pawlyn, Anna Hockaday, Vallari Shah, Martin F Kaiser, Sarah R Brown, Walter M Gregory, J Anthony Child, Faith E Davies, Gareth J Morgan, David A Cairns, Graham H Jackson

Variables
WHO Performance Status
Age
ISS
CRP

n=1852

n=849



Cook et al, Lancet Haem, 2019

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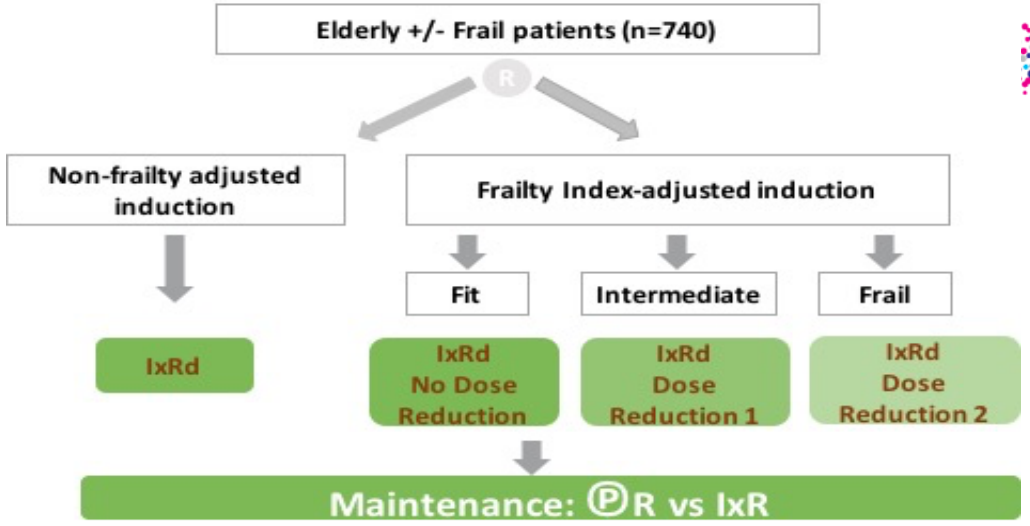
UKMRA Myeloma XIV *FITNEsS*

Frailty-adjusted therapy In Transplant Non-Eligible patientS with Symptomatic myeloma

FiTNEss
UK-MRA Myeloma XIV



	Reactive	FIT	UNFIT	FRAIL
Lenalidomide	25mg D1-21	25mg D1-21	15mg D1-21	10mg D1-21
Ixazomib	4mg weekly	4mg weekly	4mg weekly	4mg weekly
Dexamethasone	20mg weekly	20mg weekly	10mg weekly	10mg weekly

PI: Prof Gordon Cook & Prof Graham Jackson

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Objectives

FiTNEss
UK-MRA Myeloma XIV

Clinical

Primary

The primary objectives are to compare:

- Impact of treatment dose delivery of frailty index adjusted up-front dose reductions vs standard up-front toxicity-dependent reactive dose-modifications during induction therapy, at randomisation 1 (R1).
- PFS of maintenance treatment with lenalidomide (R) vs lenalidomide and ixazomib (IR).

Secondary

- ORR, sCR/CR rate
- Early mortality (<60 days), safety and tolerability
- MRD negativity rate
- Overall survival
- Impact of treatment interventions on outcomes in molecular high-risk disease
- Assess the utility of the UKMRA MRP

Exploratory

Patient Reported Outcomes

- Patients will be asked to complete:
  - EORTC QLQ-C30
  - myeloma specific module, EORTC QLQ-MY20, at key time points.

Frailty Biomarker Discovery

- Cellular senescence and DNA damage markers
  - Immune component quantification
  - Proteomics: SASP, IL-6 (CRP), TNFα, IL-1Rα, sVCAM
  - DNA damage: Telomere length, $p16^{INK4a}$,
- Immuno-genomic & Inheritable variance in expressed genes (SNPs) biomarker discovery
- Imaging biomarkers

Tumour Genome

- MLPA, GWAS, mutational analysis

MRD

- NGF vs NGS

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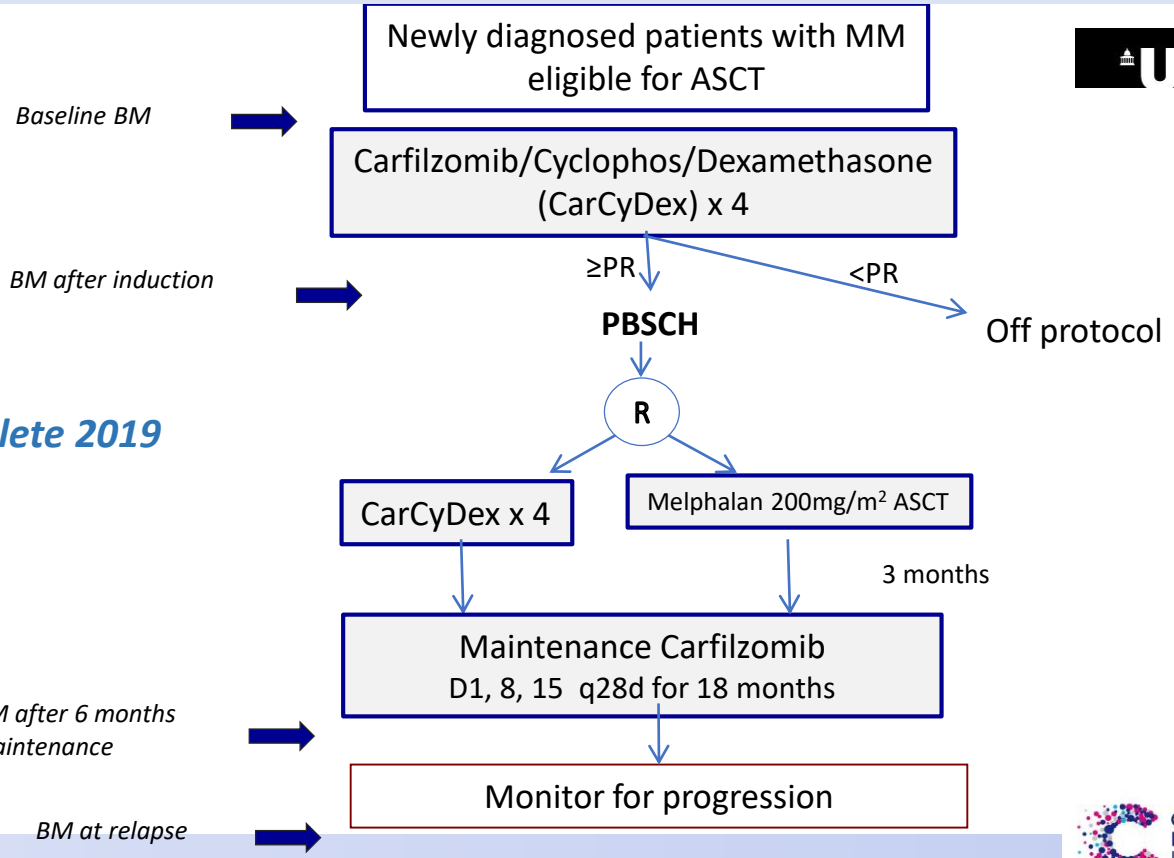
Early or late ASCT – who needs upfront ASCT?

CARDAMON: Carfilzomib/Cyclophosphamide/Dexamethasone with maintenance carfilzomib in untreated transplant-eligible patients with symptomatic MM to evaluate the benefit of upfront ASCT

CI: Kwee Yong

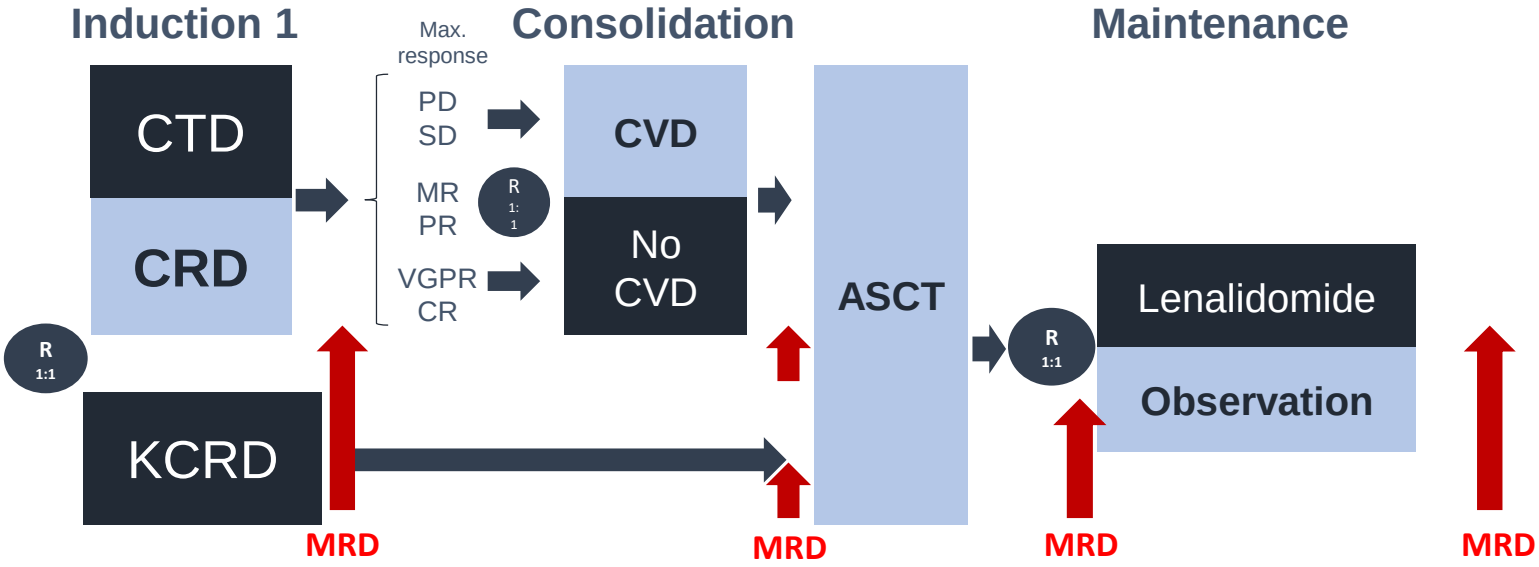


Recruitment complete 2019

Stratifying according to risk factors in younger patients

- ***Genetic risk?***
- ***Response to therapy?***

Myeloma XI – TE pathway

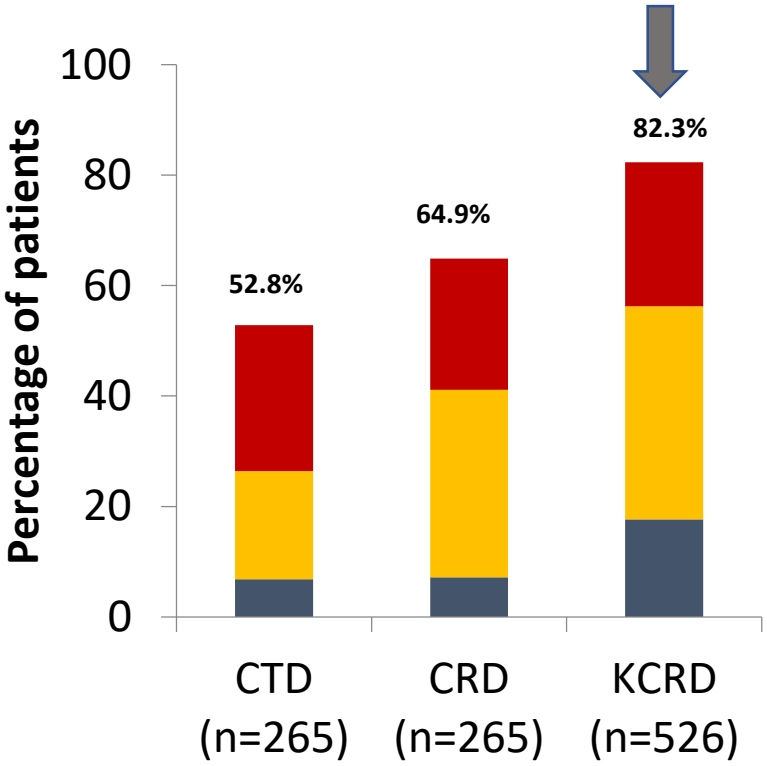


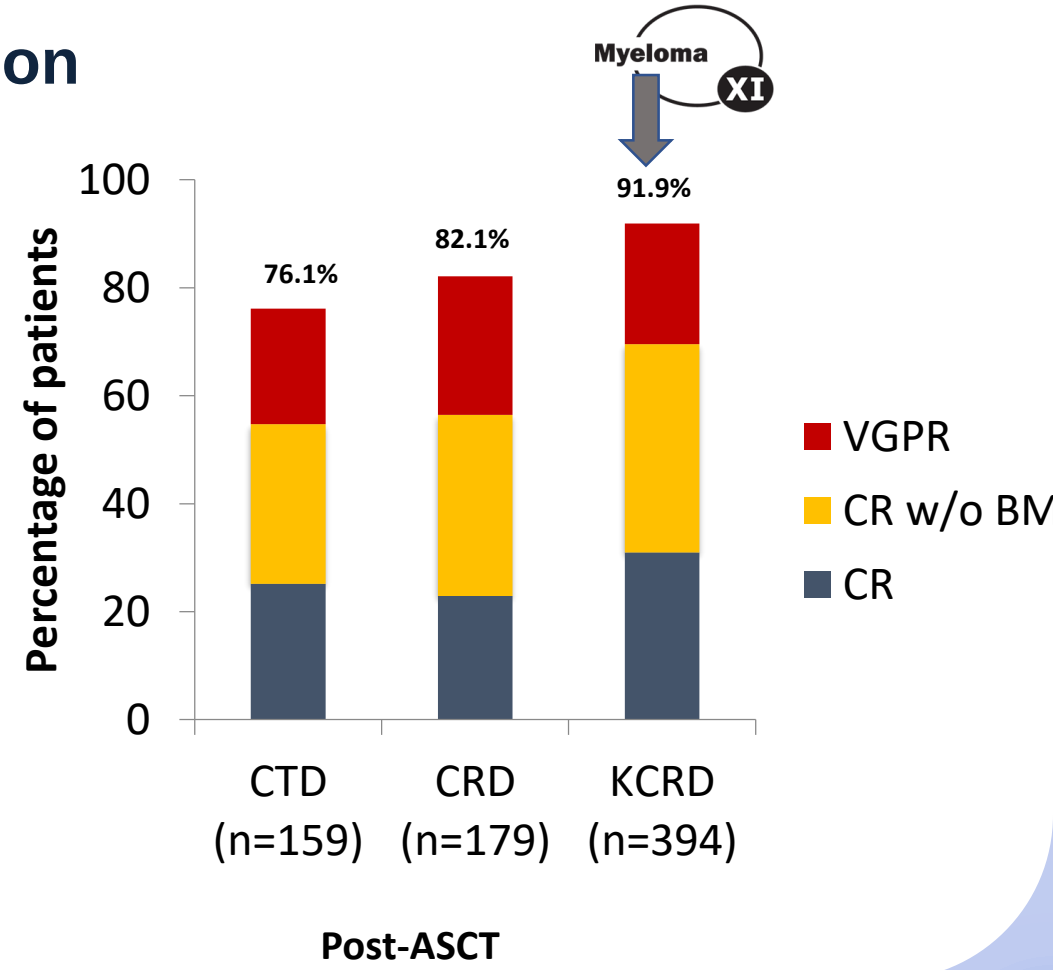
- Primary endpoints: PFS and OS for each randomization
- Median follow up 34.5 months

- Data cut off for this analysis 16th April 2018 and includes contemporaneously randomized patients only

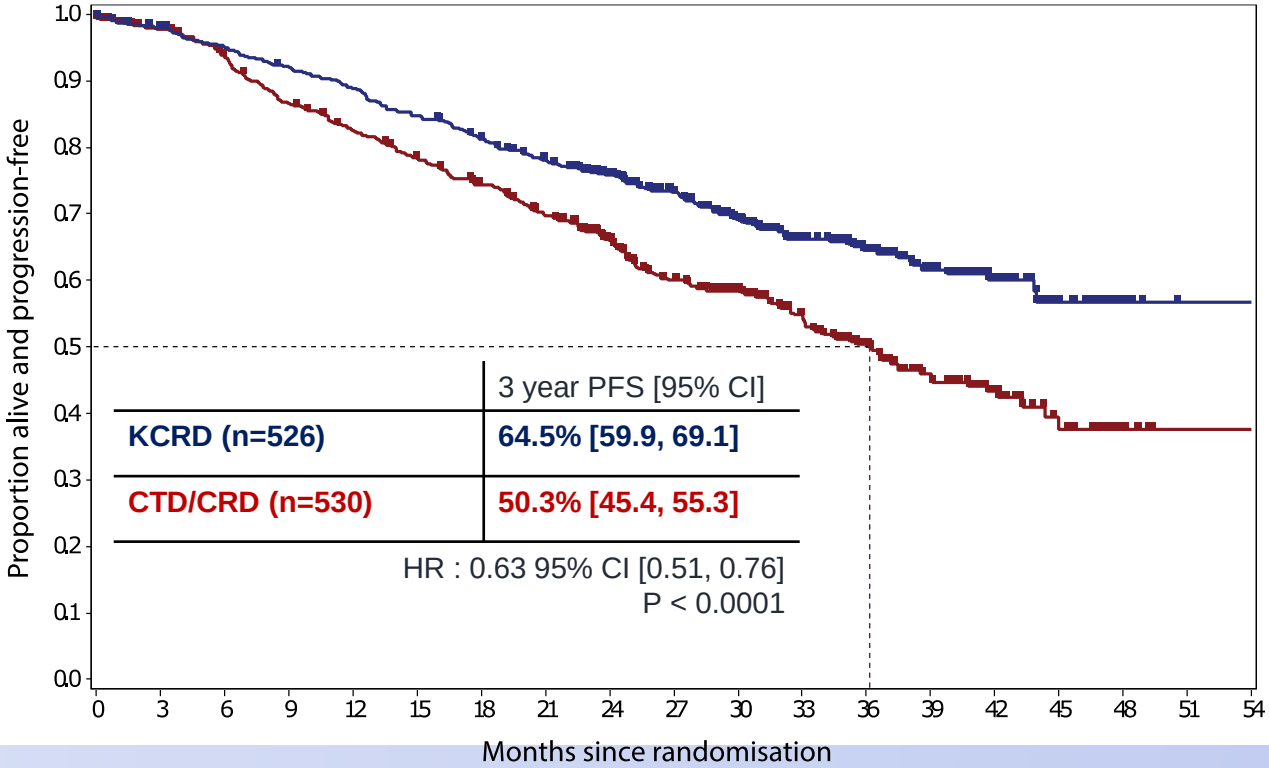
Patients were ineligible for the CVD randomisation if they had achieved a CR or VGPR to induction (went straight to ASCT if eligible or maintenance if not) or had PD or SD to induction (all primary refractory received CVD). Patients were ineligible for the maintenance randomisation if they failed to respond to lenalidomide as their induction IMiD or failed to respond to all trial induction treatment, had PD or had previous or concurrent active malignancies. Dose adjustments for renal impairment and following AEs were permitted.

Response to initial induction





Progression-free survival



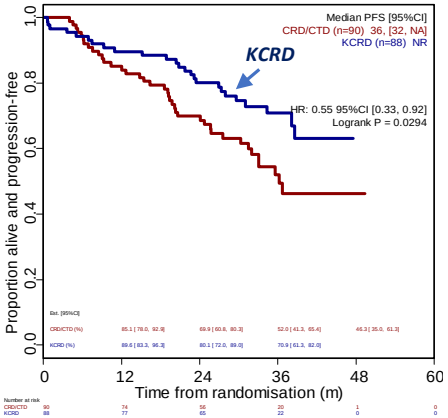
Number at Risk

CTD/CRD	530	501	475	438	412	389	364	335	286	240	198	153	111	80	50	22	7	0
KCRD	526	499	484	468	451	430	410	386	337	298	237	181	129	98	62	26	5	0

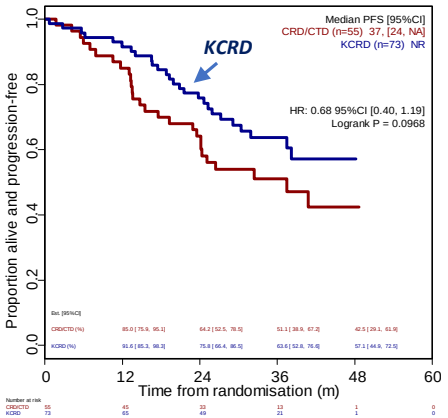
Progression-free survival by risk

KCRD improved PFS compared to triplets in all risk groups

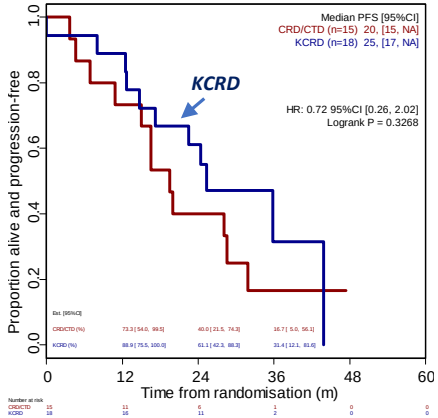
Standard risk: HR 0.55



High risk: HR 0.68



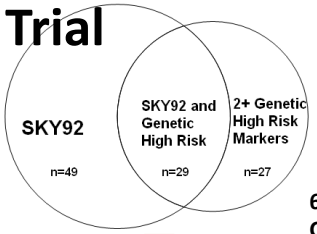
Ultra-high risk: HR 0.72



- Standard risk (SR) - absence of any high risk lesions.
- High risk (HiR) - presence of any one of t(4;14), t(14;16), t(14;20), del(17p), or gain(1q).
- Ultra-high risk (UHiR) - presence of more than one lesion.

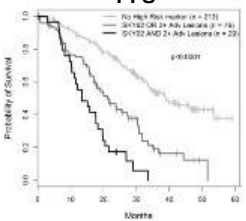
Stratifying treatment according to risk: MUK9b: OPTIMUM Trial

CIs: Dr Martin Kaiser & Dr Matt Jenner



620 patients
Central screening at ICR

Molecularly & clinically matched High Risk group Myeloma XI/XI+

Induction	**CVRDd**	D: Dara d: Dexa	**CTD/CRD/ CCRD**
Single Vel-augmented ASCT	**Velcade-HD-MEL+ASCT**	**PFS + PFS2 comparison**	**HD-MEL+ASCT**
Consolidation 1: 6 cycles	**VRDd**	**PFS** 	**R maintenance**
Consolidation 2: 12 cycles	**VRD**		
Maintenance until progression	**RD**	MRD Imaging	

Objectives

MUK9b

Primary

To assess whether molecular risk-defining investigations can be turned around within 8 weeks

Secondary

In a real world front line therapy setting

1. To assess the feasibility of a phase III trial in this setting in terms of recruitment rates.

2. To summarise progression-free survival, second progression-free survival (PFS2) and overall survival in this setting

3. To summarise anti-myeloma treatment received first and second-line in this setting, including reasons for stopping treatment

4. To summarise response to anti-myeloma treatment received first and second-line in this setting

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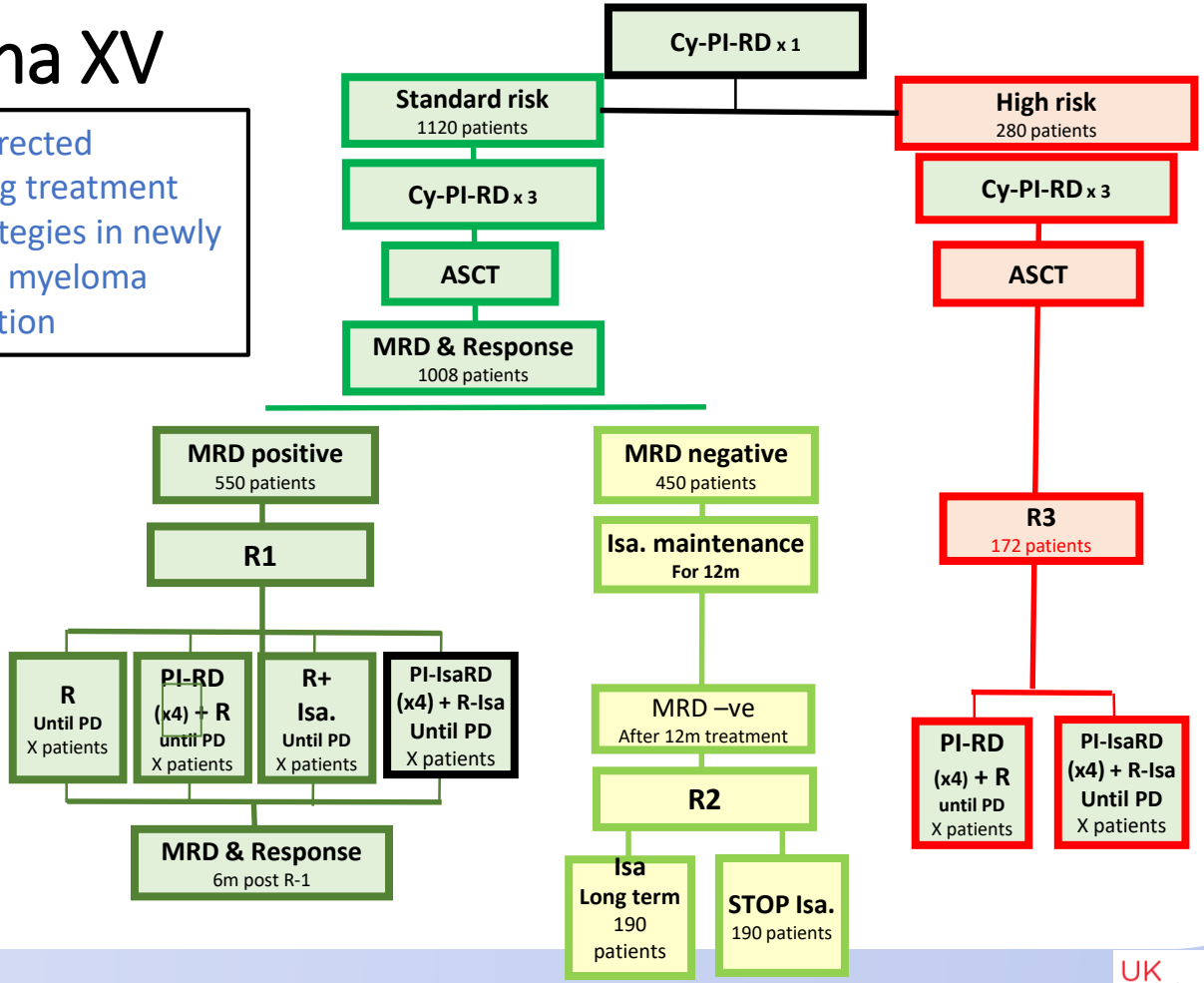
UKMRA Myeloma XV

RADAR: Risk **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



Myeloma XV (RADAR): Primary endpoints

Standard risk patients

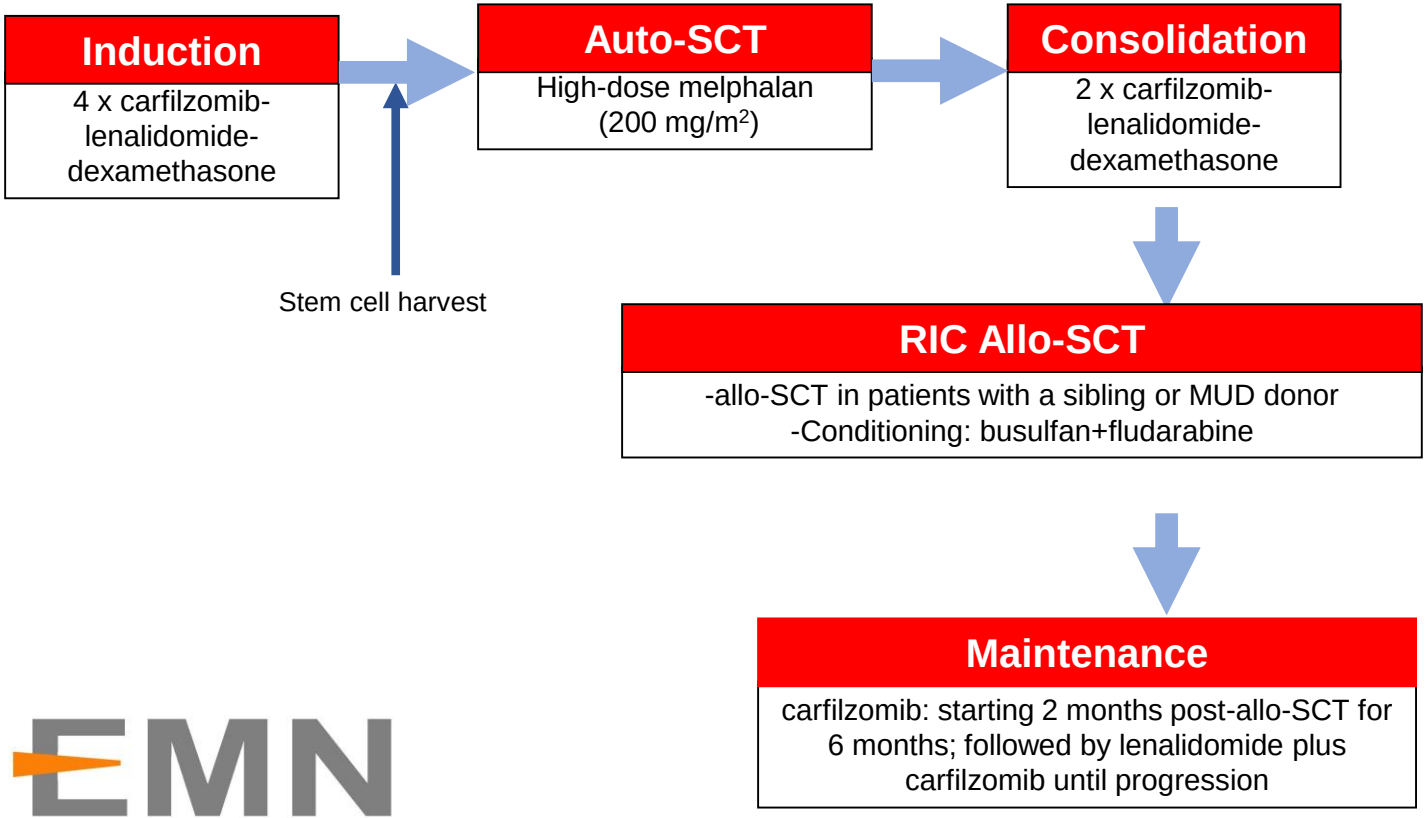
- MRD positive patients: C**onversion of MRD positive to MRD negative disease,** comparing activity and efficacy of post-ASCT consolidation + maintenance strategies using lenalidomide vs lenalidomide-PI +/- **isatuximab**
- MRD negative patients: **Progression-free survival**, comparing continuous isatuximab treatment with **ceasing isatuximab after 12 months** (non-inferiority)

High risk patients

- **Progression-free survival**, evaluating the benefit of adding **isatuximab** to lenalidomide-PI in post-ASCT consolidation + maintenance

Trials in special patient groups

EMN12 Phase 2 study in primary plasma cell leukemia: Younger patients



EMN TRIAL GROUP

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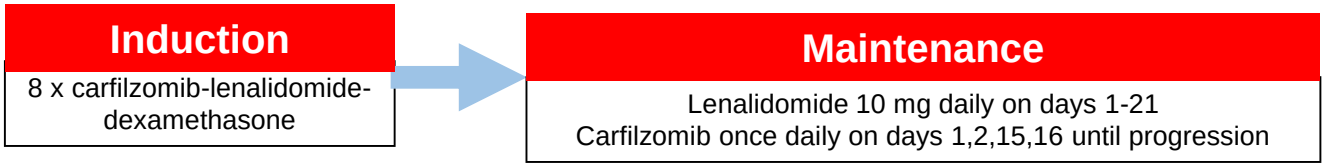
EMN12: Elderly patients: ≥65 years



Trials in relapsed patients:

What are the important questions, what are our aims?

- What is the best regimen?
- Should we stratify? – if so, how?
- How do we get our patients access to the newest compounds?
- What is the place of the new immuno-therapies?
- What is the role of next generation drugs?
  - do patients failing one CD38 antibody respond to re-challenge?
  - What about IMiDs? Do patients failing Pomalidomide response to Iberdomide?
- - Is there a role for CAR-T cell therapy?

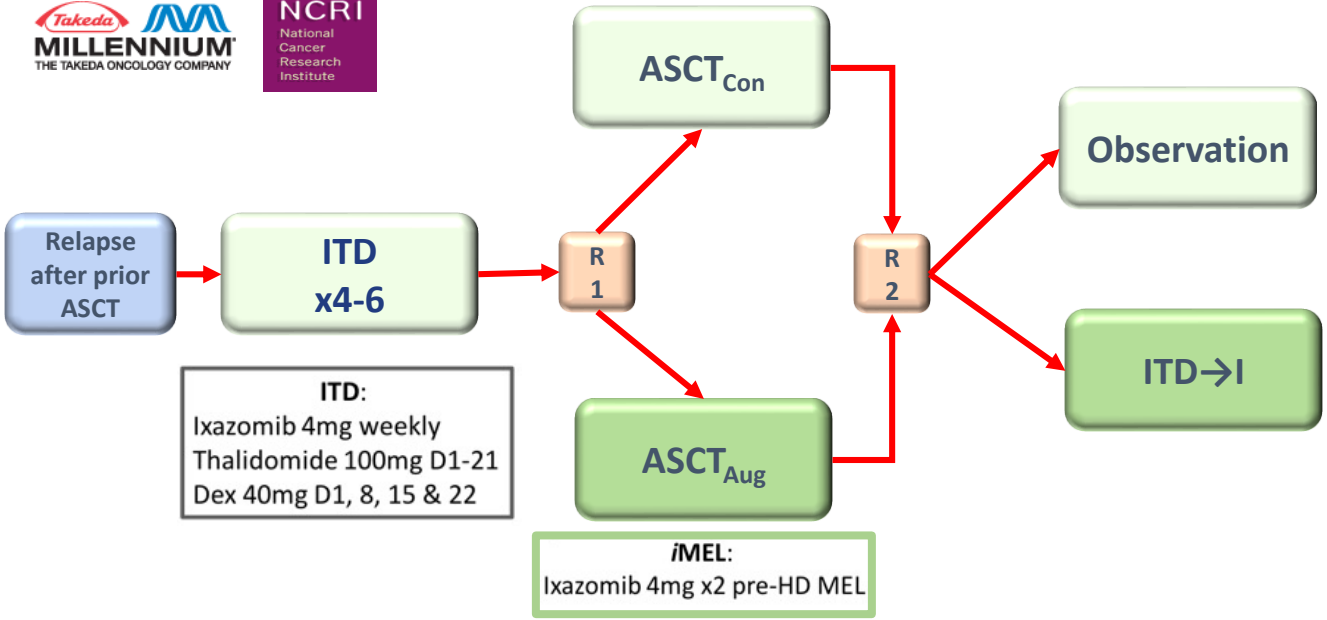
How to optimise treatment of patients eligible for second (salvage) ASCT?

ACCoRD

UK Myeloma Research Alliance Myeloma XII

Augmented Conditioning & Consolidation in Relapsed Disease

CI: Prof Gordon Cook



Total Recruitment Target: 406 first relapse patients

Objectives

Primary

R1

- Depth of Response (DoR: <VGPR vs. ≥VGPR) with augmented ASCT

R2

- The influence of a consolidation and maintenance strategy on the Durability of Response (DuR: PFS)

Secondary

R1 & R2

- Overall survival
- Time to disease progression
- The overall response rate following ixazomib, thalidomide and dexamethasone (ITD) re-induction
- Duration of Response (DoR), Time to next treatment (TtNT) & Progression-free survival 2 (PFS2)
- $MRD^{negative}$ rate post re-induction, post-ASCT and conversion after ITD consolidation
- Engraftment kinetics
- Toxicity, safety & Quality of life (QoL)

Key Study Inclusion & Exclusion Criteria

ACCoRd Myeloma XII

Inclusion criteria

- Diagnosed with relapsed MM previously treated with ASCT with 1st progression requiring treatment >12 months from ASCT .
- ECOG Performance Status 0-2.
- Aged at least 18 years.
- Adequate haematological function:
  - *Absolute neutrophil count (ANC) ≥1x10^9/L*
  - *Platelet count ≥75x10^9/L. If the participant has ≥50% bone marrow infiltration a platelet count of ≥50x10^9/L is allowed.*
- Adequate renal function (Creatinine clearance ≥30ml/min)
- Adequate hepatobiliary function
- Adequate pulmonary function (KCO/DLCO ≥50%).
- Adequate cardiac function (LVEF ≥40%)
- Able to provide written informed consent.

Exclusion criteria

- Received prior second line therapy for their relapsed disease
- ≥Grade 2 peripheral neuropathy
- Known HIV or Hepatitis B/C seropositivity.
- Known resistance, intolerance or sensitivity to any component of the planned therapies.
- Any medical or psychiatric condition which, contraindicates the participant's participation in this study.
- Previous or concurrent malignancies at other sites
- Pregnant, lactating or breast feeding female participants.
- Central nervous system involvement with myeloma.
- Patients that have previously been treated with ixazomib

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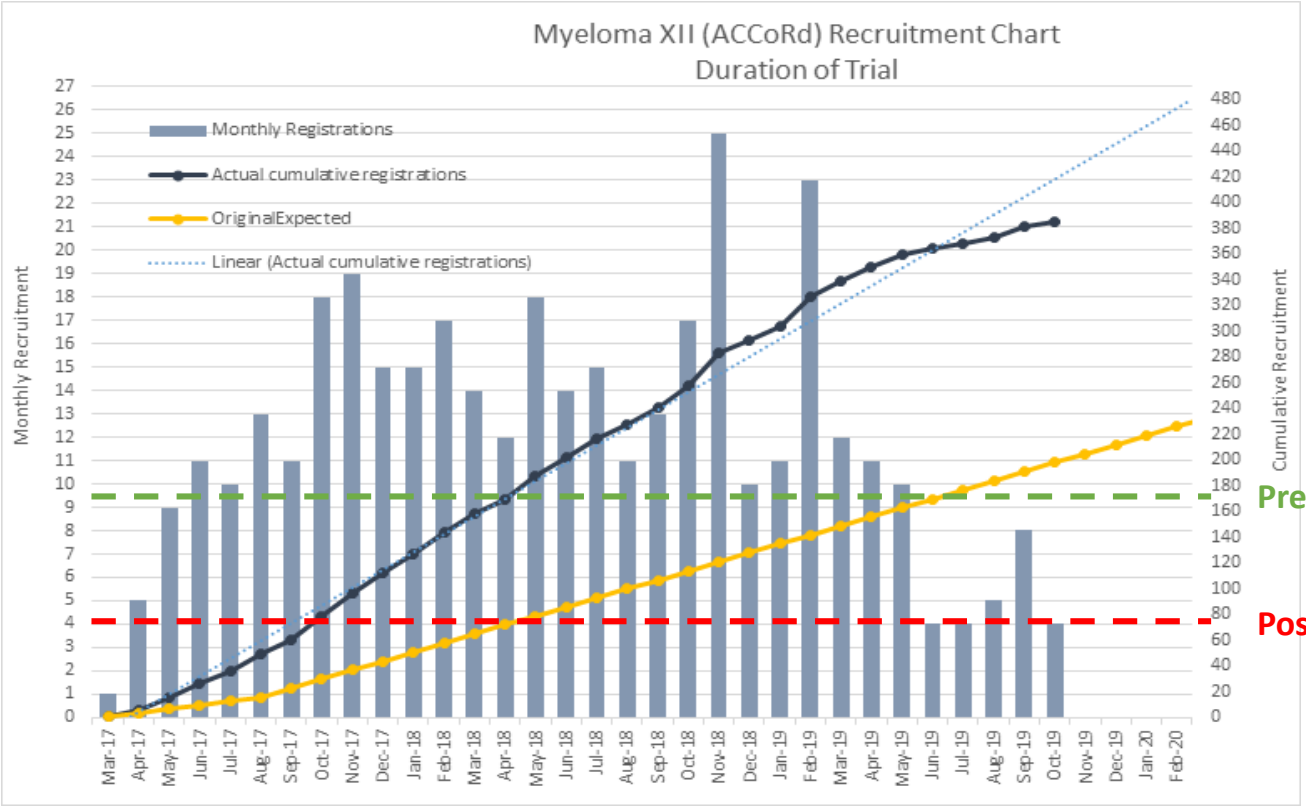
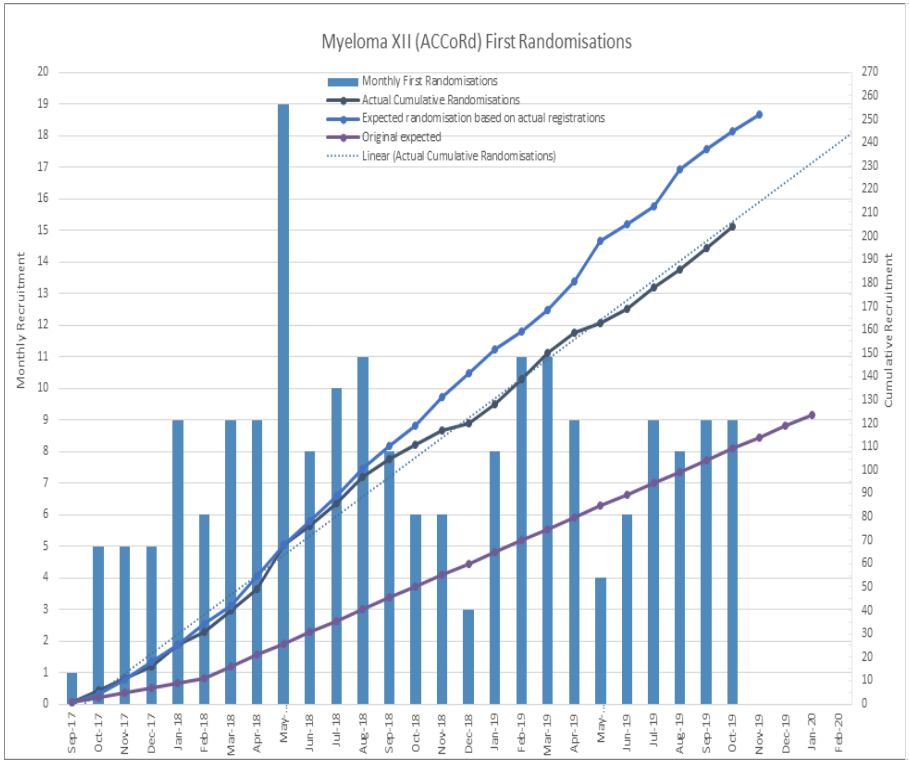
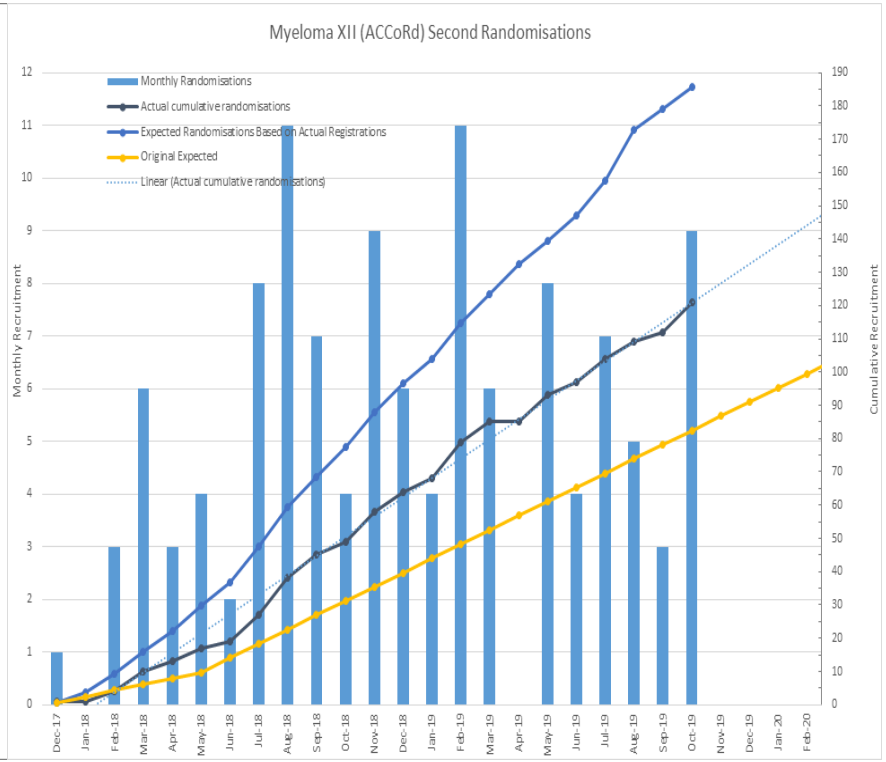
Recruitment



Randomization progress



R1



R2

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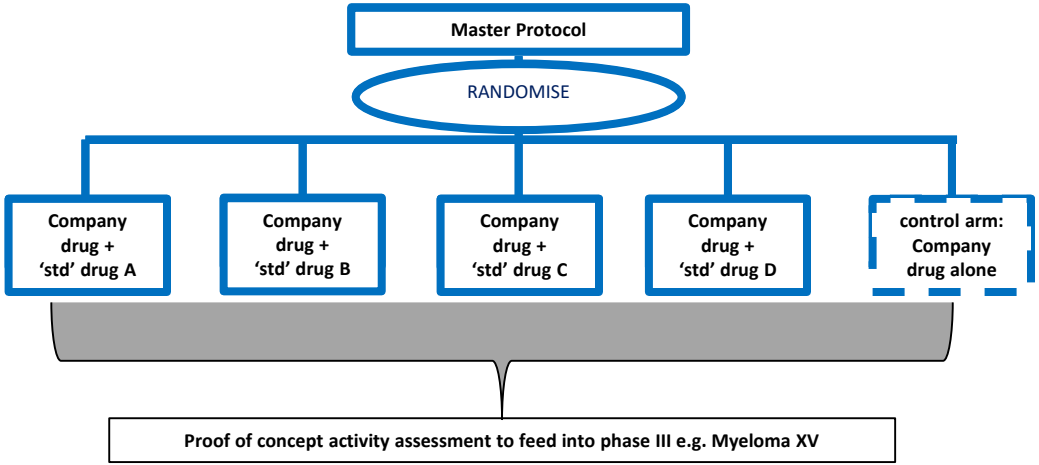
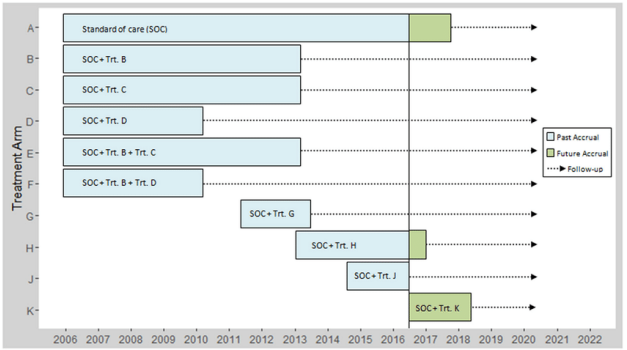
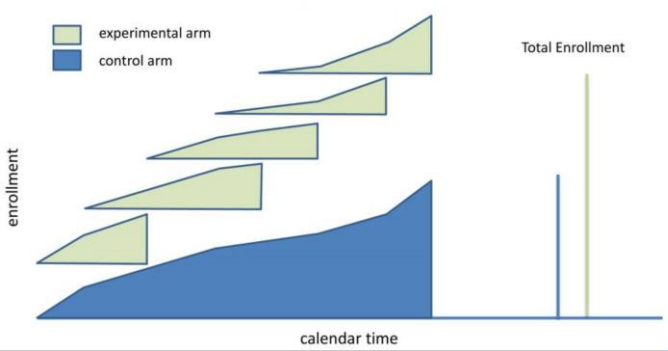
Upcoming studies with new (pipeline) agents, innovative trial designs

- Platform studies with one pharma agent in several different combinations
- Innovative strategy in special patient group
  - EMN study in Primary Plasma Cell Leukemia
- ENCOMPASS study covering several aspects of supportive care

Platform studies with Single industry partner

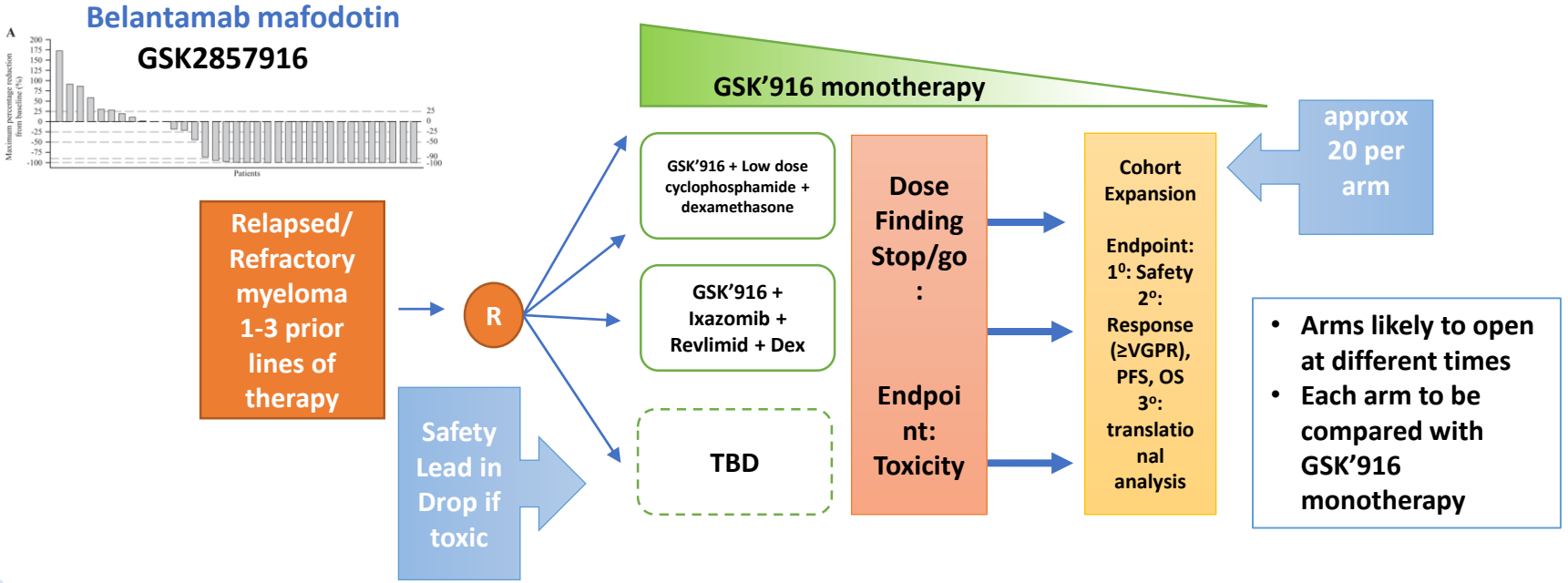






ProMMise (CARP 2019/001)

A Platform trial for Relapsed patients to evaluate Ongoing novel therapies in Multiple Myeloma In combination with Standard of care therapies



CI: Dr Rakesh Popat

Biomarker studies

Biomarker	Studies	PI
Tumour genome	Myeloma XI, Myeloma XIV, MUK7, MUK8, MUK9, MUK11	Martin Kaiser, ICR, London
MRD (MFC, NGS)	Myeloma X, Myeloma XI, Myeloma XII, Myeloma XIV, Myeloma XV, MUK9	Roger Owen, HMDS, Leeds
Immune Biomarkers	Myeloma X, Myeloma XII, Myeloma XIV, MUK8, MUK11	Gordon Cook, University of Leeds
Frailty Biomarkers	Myeloma XIV, MUK8	Gordon Cook, University of Leeds
Marrow environment immune profiling	Myeloma XV	Kwee Yong, UCL, London
Imaging	**Studies**	**PI**
DW MRI	MUK9	Martin Kaiser, ICR, London

UK MRA - Acknowledgments

NCRI National Cancer Research Institute

Chair
(*Prof Gordon Cook*)

Vice-Chair
(*Prof Mark Cook*)

UK Myeloma Forum

PPI: Alan Chant

Governance Lead
(*Prof Kwee Yong*)

Industry Lead
(*Dr Rakesh Popat*)

Translational Lead
(*Dr Martin Kaiser*)

Trial Design Lead
(*Dr Sarah Brown*)

John Ashcroft, Maria Atta, Holger Auner, Supratik Basu, Reuben Benjamin, Jenny Bird, Stella Bowcock, Kevin Boyd, Ceri Bygrave, David Cairns, Jamie Cavenagh, Andy Chantry, Mike Chapman, Rups Chouduri, Charles Crawley, Kirtsy Cuthill, Mark Drayson, Inas El-Najjar, Louise Flanagan, Rachel Hall, Andrew Hall, Anna Hockaday, Hannah Hunter, Graham Jackson, Matt Jenner, Kamar Karunanithi, Bhuvan Kishore, Mariell Lamacchia, Sally Moore, Guy Pratt, Charlotte Pawlyn, Kim Orchard, Roger Owen,Chris Parrish, Neil Rabin, Karthik Ramasamy, Simon Ridley, Alberto Rocci, Jonathan Sive, Dean Smith Matt Streetly, Richard Soutar, Jane Tighe

CANCER RESEARCH UK

Patients & Staff

MyelomaUK

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