Allogeneic stem cell transplant in HR-AML

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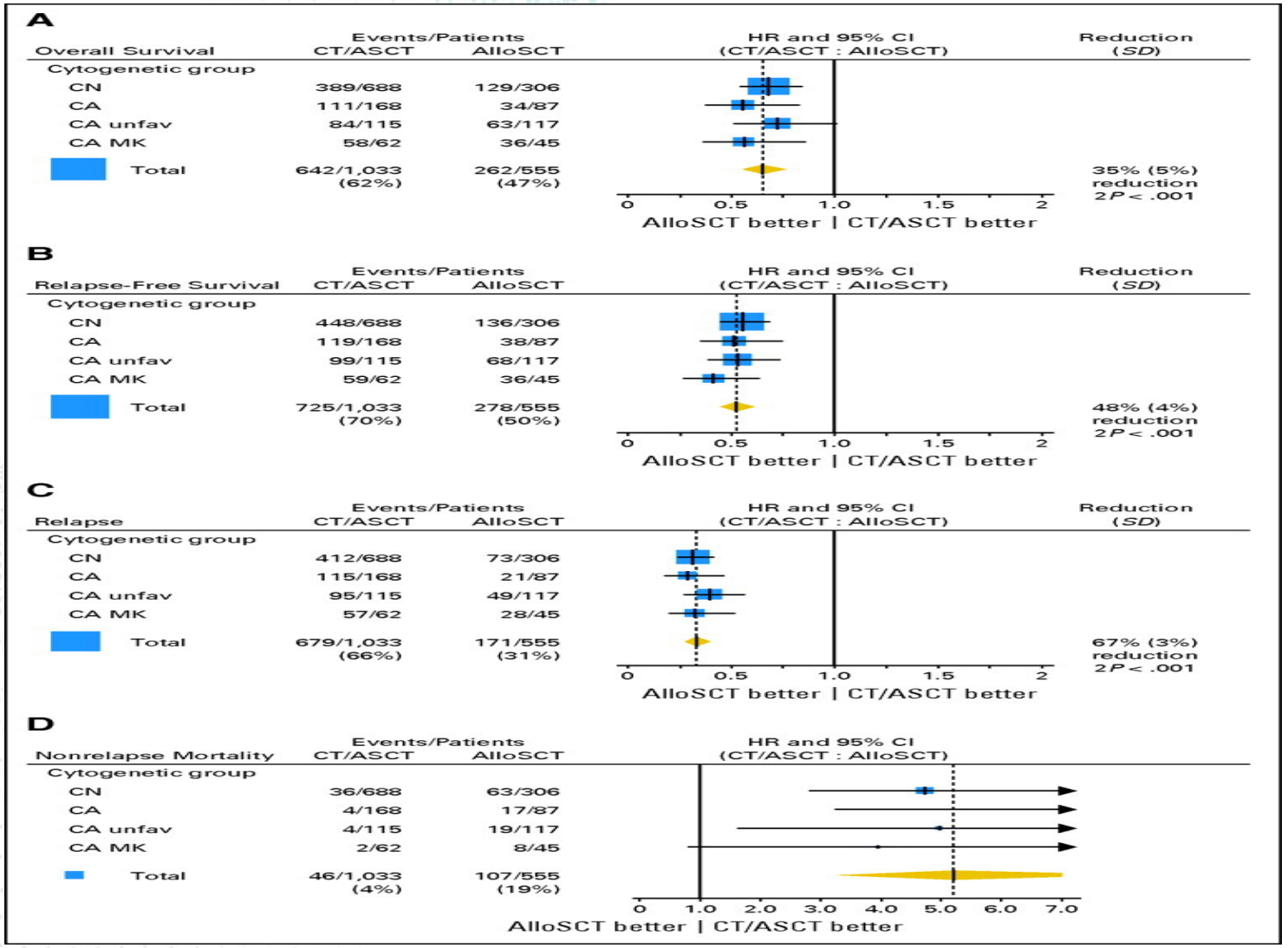
Disclosures:

Company Name	Research Support	Employee	Consultant	Stockholder	Speaker Bureau	Advisory Capacity	Other
Abbvie	No	No	Yes	No	Yes	Yes	No
Janssen	No	No	Yes	No	Yes	Yes	No
KITE	Yes	No	Yes	No	No	No	No
Novartis	No	No	Yes	No	Yes	Yes	No
Roche	No	No	Yes	No	Yes	No	No
Jazz	Yes	No	Yes	No	No	No	No
BMS	No	No	Yes	No	Yes	Yes	No
Pfizer	No	No	Yes	No	Yes	Yes	No
Astellas	No	No	Yes	No	Yes	Yes	No
Daiichi Sankyo	No	No	Yes	No	Yes	Yes	No
Eurocept	No	No	Yes	No	Yes	Yes	No

Structure of Talk

- Refining patient selection for allograft
- Transplant outcomes in older patients
- Emerging strategies to improve outcome in adults allografted for AML in CR1
  - ➢ Novel induction regimens
  - ➢ Improved GVHD prophylaxis
  - ➢ Is there an optimal Reduced Intensity Conditioning regimen?

Allo-SCT reduces relapse risk in AML CR1- regardless of disease biology



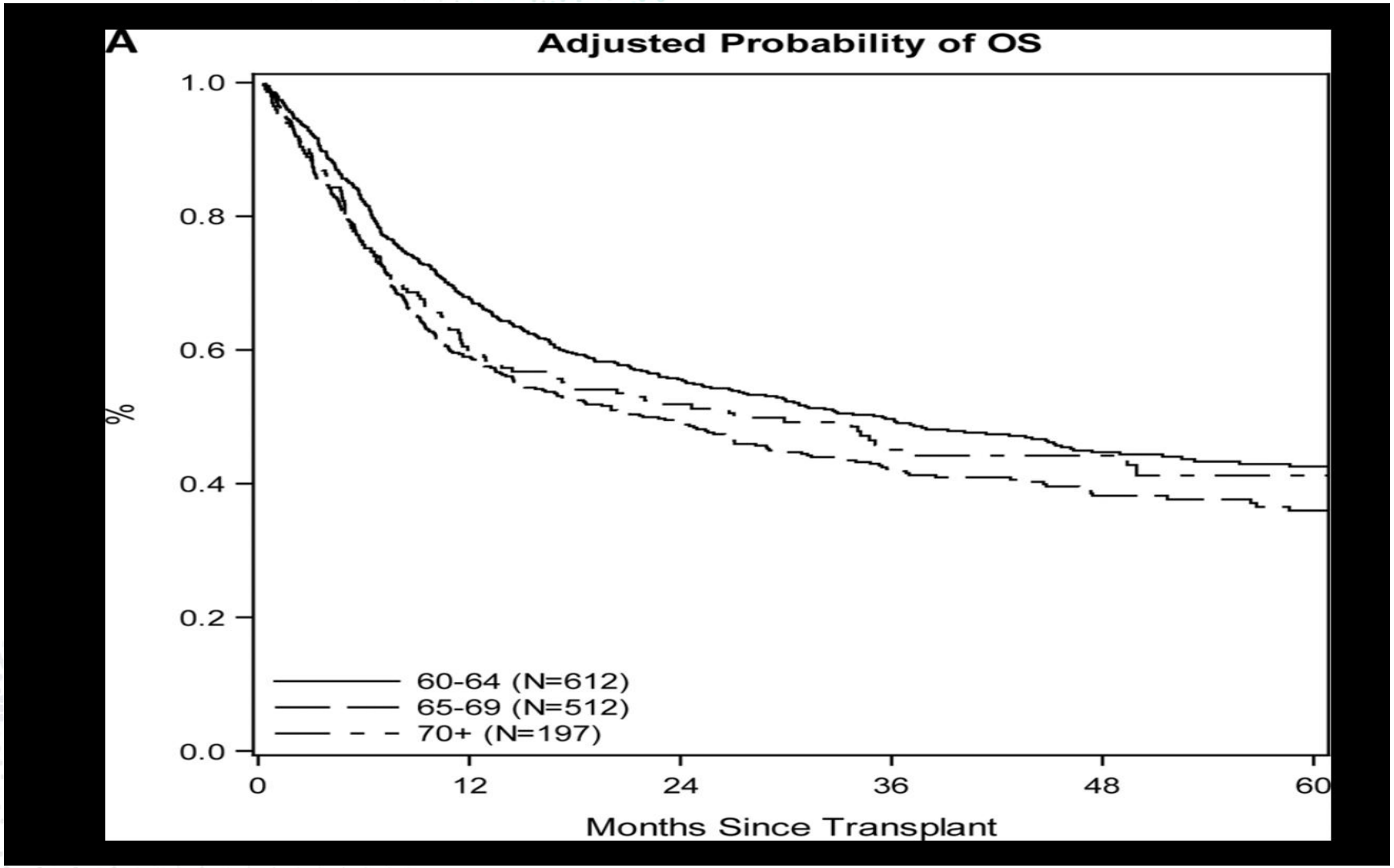
Cornelissen, et al. J Clin Oncol. 2012

In which patients with AML in CR1 should a transplant be considered?

2017 ELN risk stratification by genetics	MRD after cycle 2 chemotherapy	Estimated risk of relapse based on consolidation with:		Maximal tolerated NRM prognostic scores for allo-SCT to be beneficial	
		Chemotherapy alone (%)	Allo-SCT (%)	HCT-CI score	NRM risk (%)
Favourable	Negative	25–35	15–20	N/A (<1)	5
	Positive	70–80	30–40	≤3–4	<30
Intermediate	Negative	50–60	25–30	≤2	<20
	Positive	70–80	30–40	≤3–4	<30
Adverse	N/A	>90	45–55	<5	<35

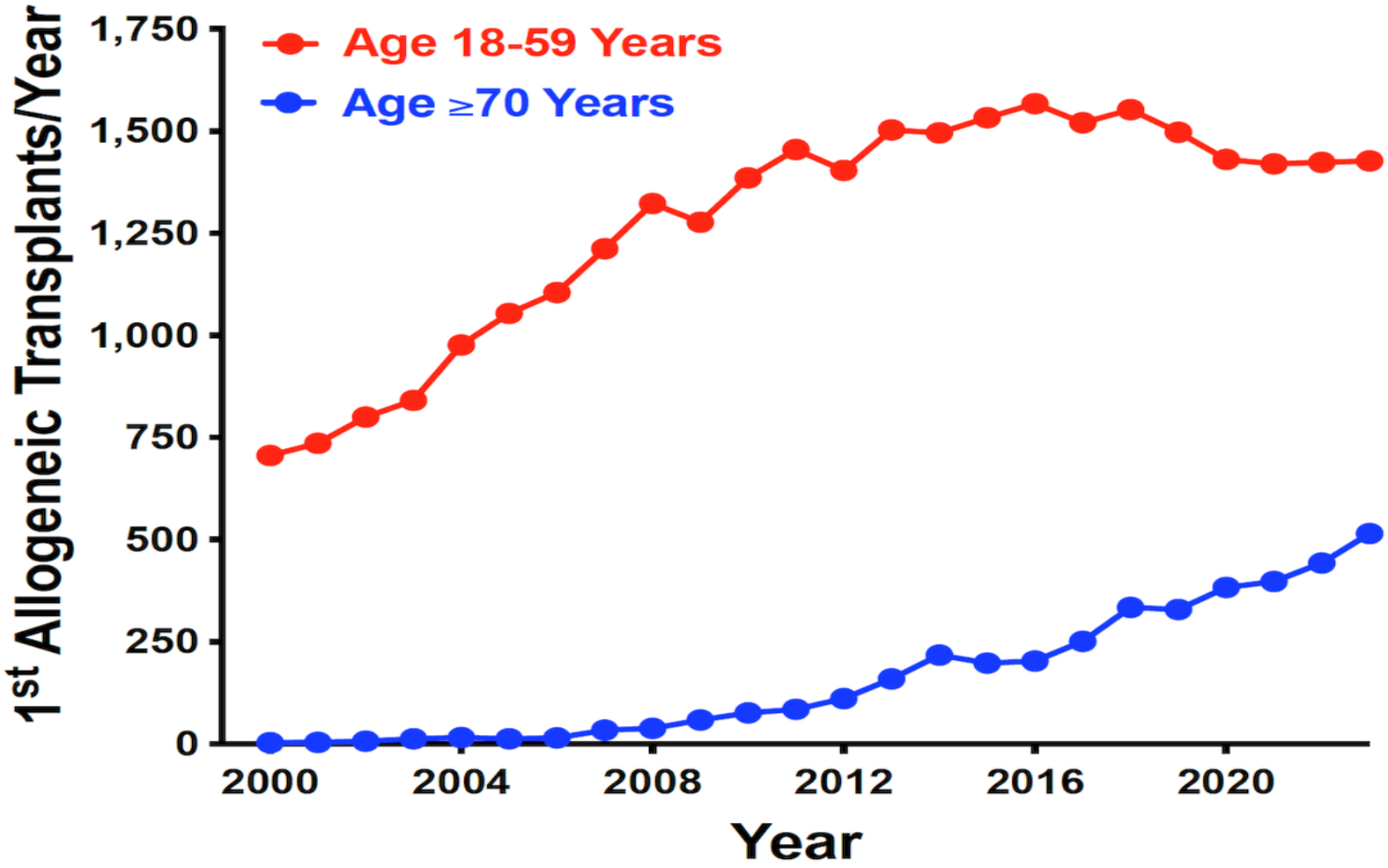
Loke J, et al. *Br J Haematol* 2022

Survival after allo-SCT in AML CR1 according to patient age



Maakaron et al BMT 2022

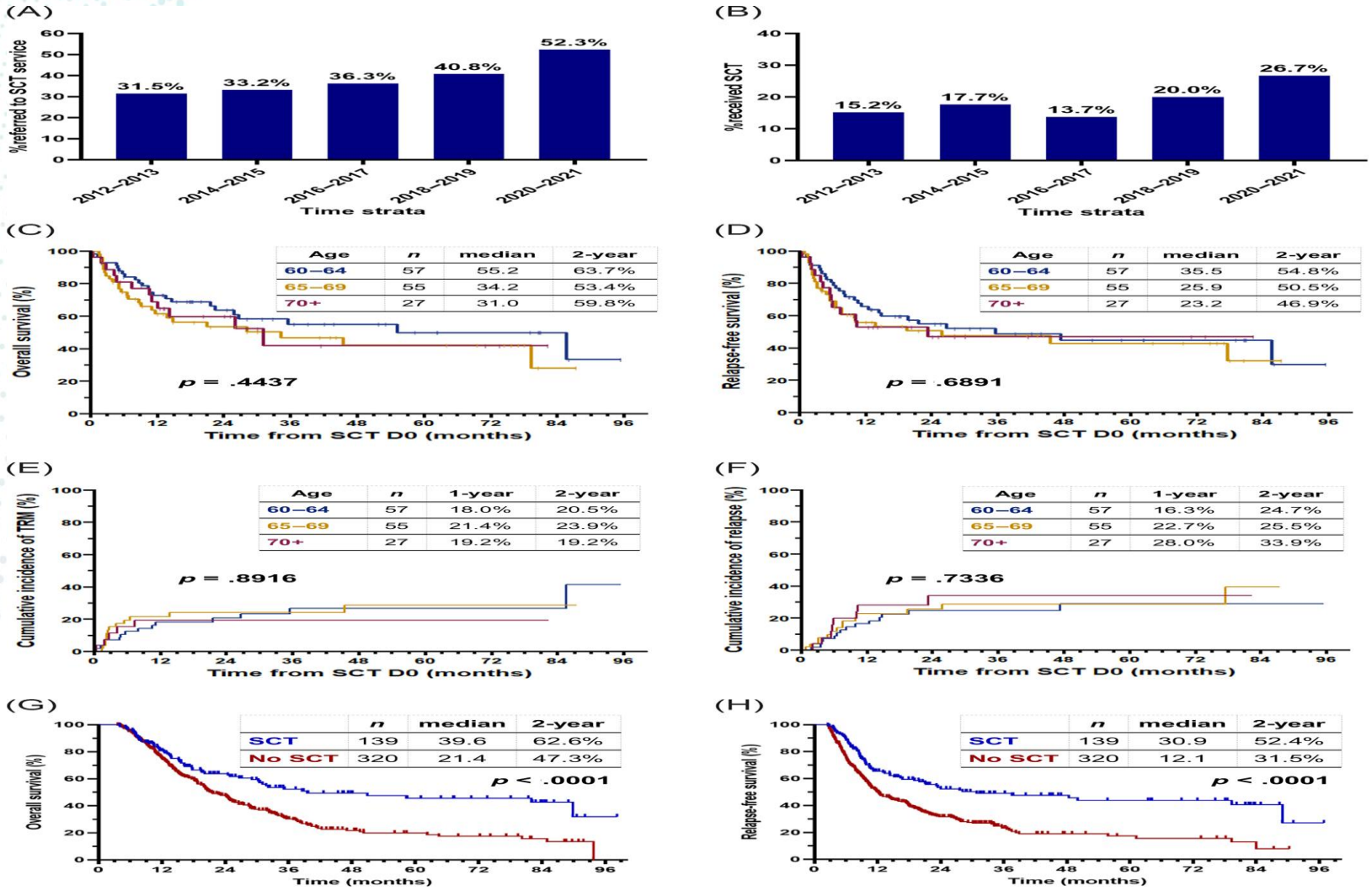
Increasing transplant activity in patients with AML over 70 years of age



Walter et al 2024 Blood

Increased utilization of allo-SCT in older adults with AML

- 1073 patients with newly diagnosed AML > age 60
- Median age 71 years
- 198 (18%) proceded to transplant
- 19% 2 year TRM in patients >70
- Improved OS in allografted patients



Bazinet et al Am J Hematol 2023

Which patients with AML over 60 should NOT receive a transplant in CR1?

2017 ELN risk stratification by genetics	MRD after cycle 2 chemotherapy	Estimated risk of relapse based on consolidation with:		Maximal tolerated NRM prognostic scores for allo-SCT to be beneficial	
		Chemotherapy alone (%)	Allo-SCT (%	HCT-CI score	NRM risk (%)
Favourable	Negative	25–35	15–20	N/A (<1)	5
	Positive	70–80	30–40	≤3–4	<30
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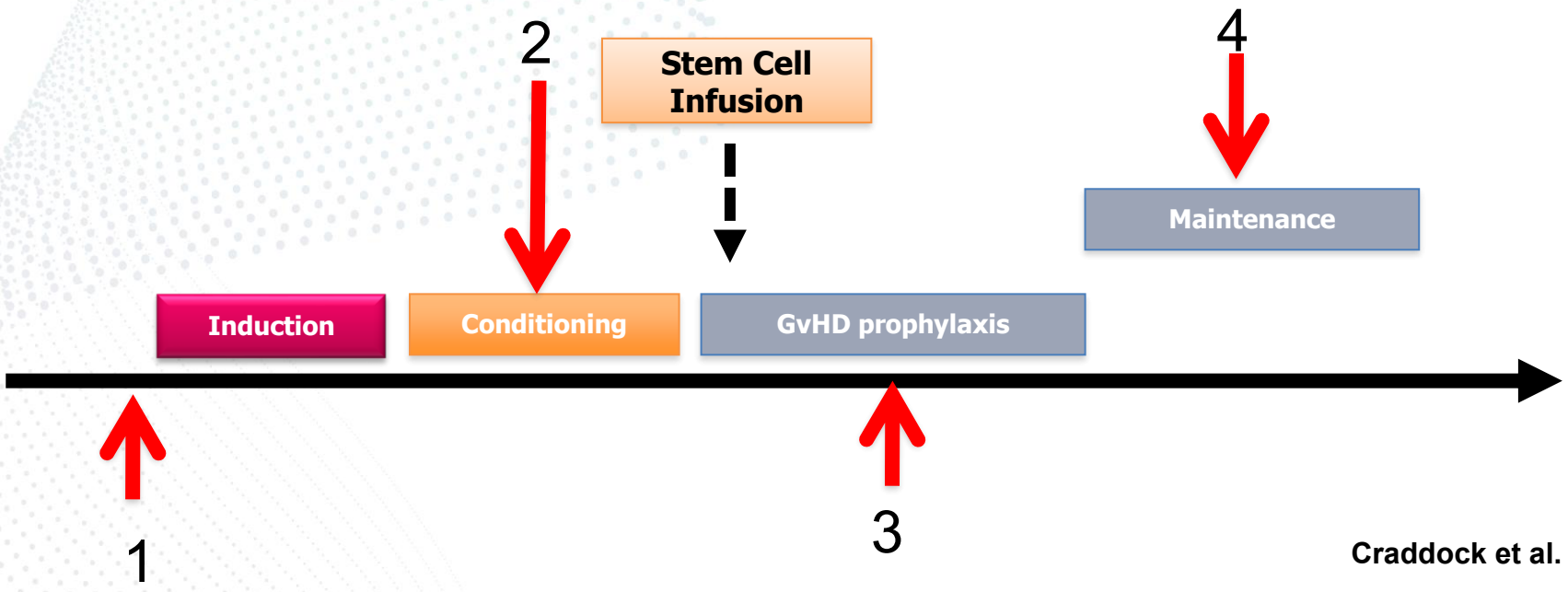
Loke J, et al. Br J Haematol 2022

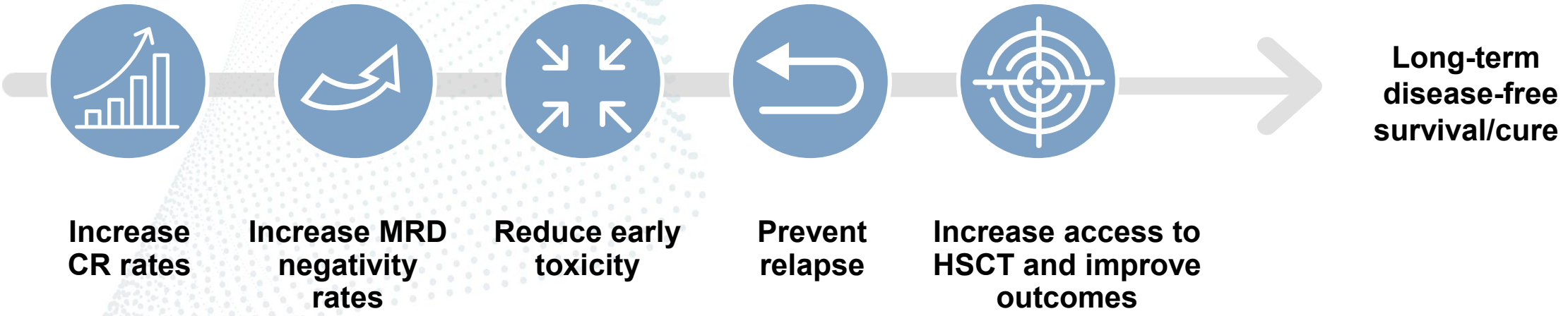
Strategies to improve outcome in patients allografted for AML: optimising the induction regimen

1. Optimising the induction regimen
2. Augmenting conditioning regimen anti-tumour activity without increasing toxicity
3. Improved GVHD prophylaxis
4. Maintenance drug or cellular therapies



Craddock et al. *Bone Marrow Transplant.* 2019

Induction chemotherapy and transplant represent an integrated curative package in high risk AML



Rethinking the optimal induction regimen in fit adults with high-risk AML

- Current induction strategies in fit patients with high risk AML are not fit for purpose and fail to optimise the curative potential of allo-SCT which is now in principle deliverable to almost all patients with high-risk AML
- The optimal induction regimen should:

  be associated with minimal treatment related mortality

  result in a high CR rate

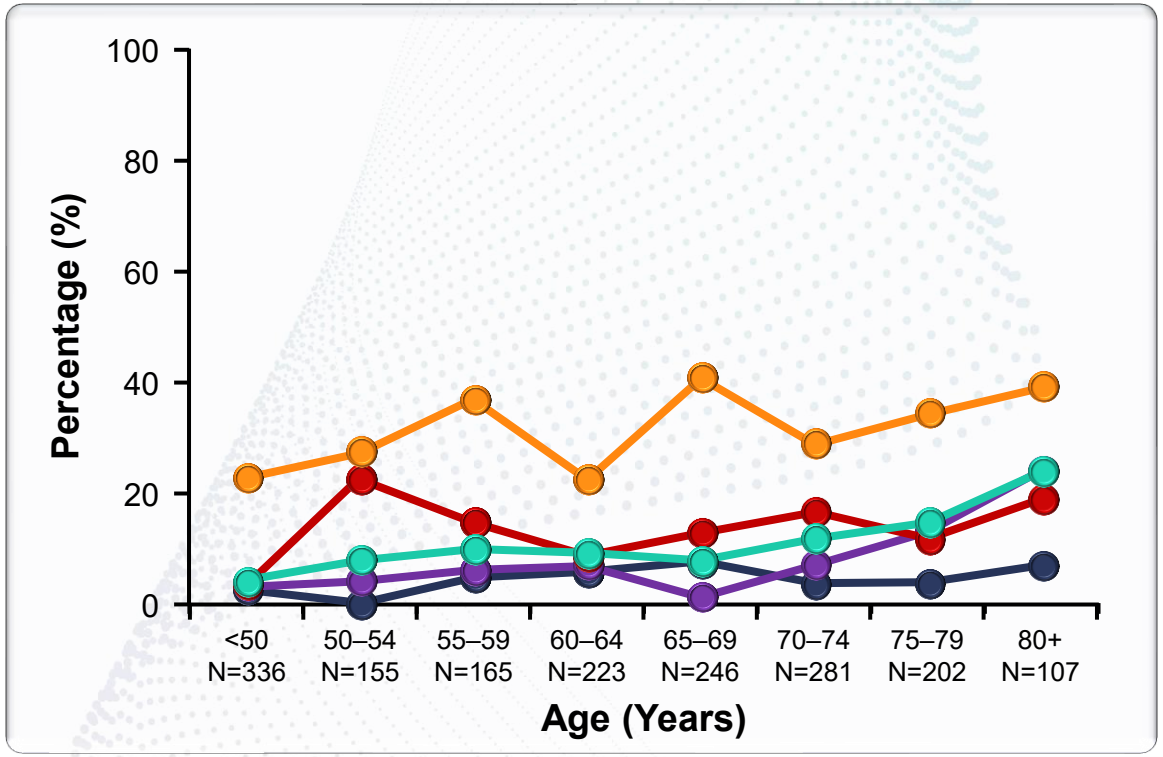
  deliver high rates of MRD negativity pre-transplant

  contribute to a reduced TRM compared with intensive chemotherapy

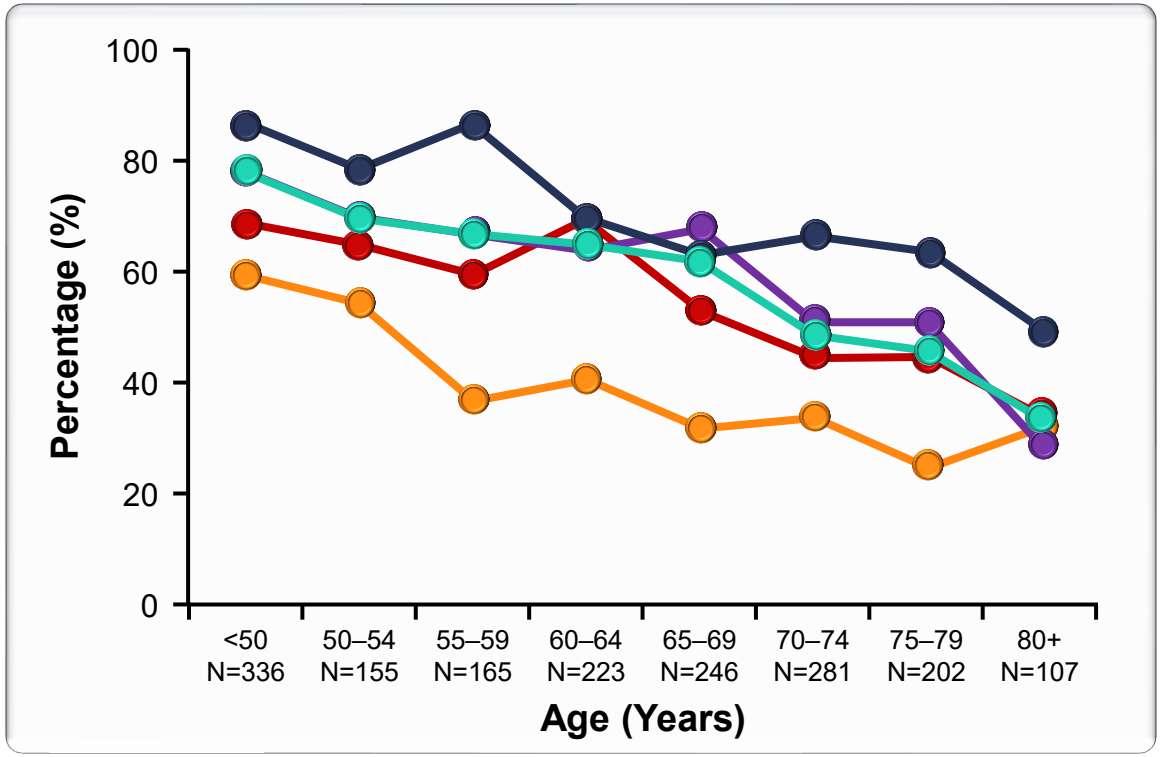
Outcomes after Induction Chemotherapy Vary According to Patient Age and PS

Real-World Data from 2,767 Patients with AML from the Swedish Acute Leukemia Registry

Early Death Rates (%)* with Intensive Therapy, According to Age and Performance Status



CR Rates (%) with Intensive Therapy, According to Age and Performance Status

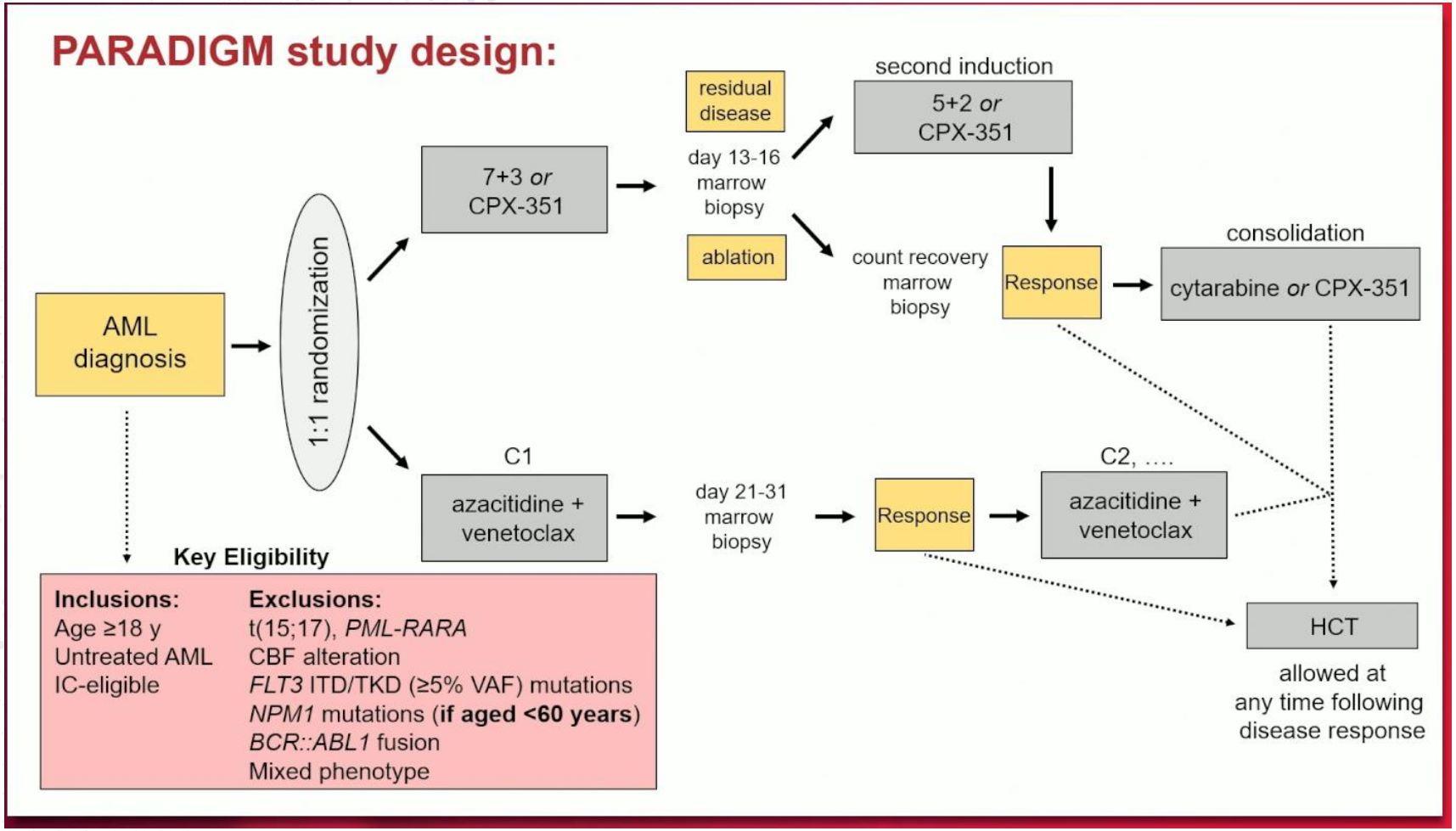


WHO 0 WHO I WHO II WHO III–IV All

* Within 30 days from diagnosis.

Juliusson G, *et al. Blood* 2009; **113:**4179–4187.

PARADIGM trial



Fathi et al ASH 2025

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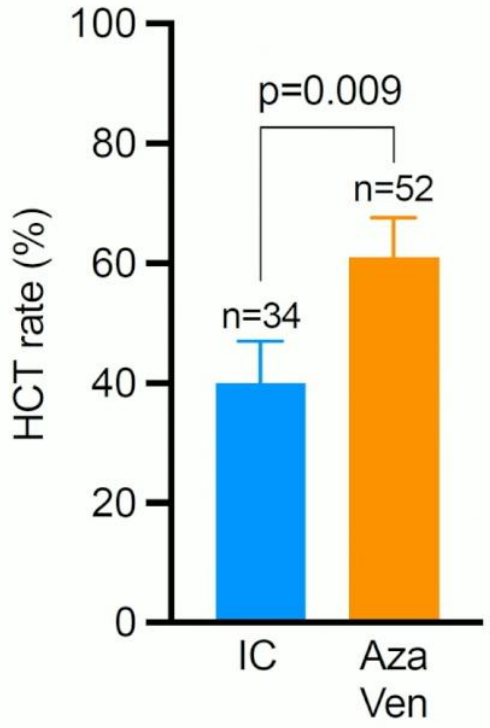
PARADIGM trial

Transplant



- Transplant had a significant protective effect for EFS.
- After adjustment for HCT in univariable and multivariable models for EFS, effect of Aza-Ven remained protective (HR:0.67; P=0.0302).

Fathi et al ASH 2025

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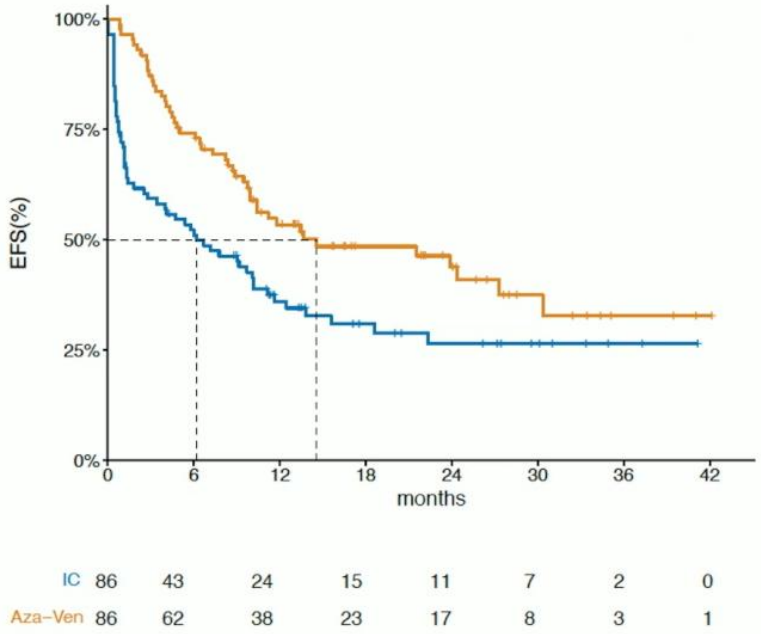
PARADIGM trial

Event-Free Survival



- Median EFS of 14.6 for Aza-Ven vs 6.15 months for IC (P=0.0021).
- One-year EFS was 53.4% for Aza-Ven vs 36.0% for IC.
- The HR for a univariate Cox model was 0.57 (P=0.0022).
- After adjustment for variables in a multivariable model, the effect of Aza-Ven remained protective for EFS (HR:0.66; P=0.0231).

Fathi et al ASH 2025

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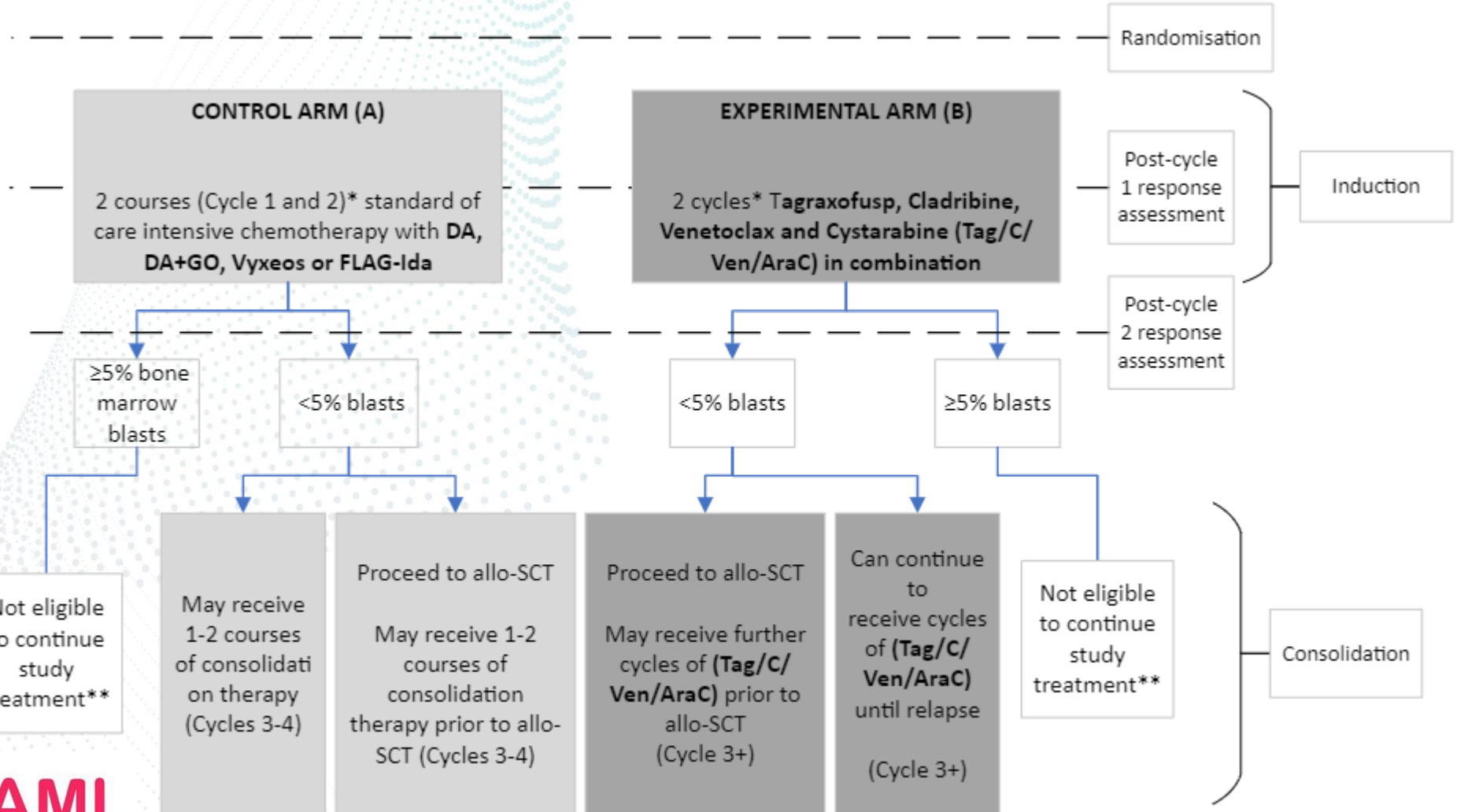
Cladribine/Venetoclax/AraC*- a novel induction regimen in allo-mandatory AML

Characteristic	N = 60; No. (%)
CRc rate (CR plus CRi)	56/60 (93)
Best response	
CR	48/60 (80)
CRi	8/60 (13)
NR	3/60 (5.0)
Died	1/60 (1.7)
Patients requiring reinduction cycle	4/57 (7)
MRD at response assessment (by flow)	
Negative	43/51 (84)
Positive	8/51 (16)
Total No. of course given, median (IQR)	3.0 [2.0-5.0]
Responders who received alloSCT	19/56 (34)
Mortality rate at 4 weeks	1/60 (1.7)
Mortality rate at 8 weeks	4/60 (6.7)

*Off-Label

Kadia et al *J Clin Oncol* 2022

UK AMLRN Randomized trial of TAG/ Cladribine/Venetoclax* Induction in Fit Adults with High Risk AML



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QUIZZICAL

CONTROL ARM
2 courses (Cycle 1 and 2)* SoC IC with **DA and quizartinib**

EXPERIMENTAL ARM
2 cycles **quizartinib/venetoclax/azacitdine combination**

≥5% bone marrow blasts

Not eligible to continue study treatment

End of Study treatment visit

30-day safety visit

<5% bone marrow blasts

Transplant candidate

Proceed to allo-HCT at discretion of Investigator

May receive 1–2 courses of consolidation therapy prior to alloHCT (Cycles 3–4)

End of study treatment visit

Allo-HCT

Not a transplant candidate

Control: May receive 1–2 courses of consolidation therapy (Cycles 3–4)

OR

Experimental arm: Continue quizartinib/ venetoclax/azacitdine for 12 cycles, then QUIZ maintenance

End of study treatment visit

30-day safety visit

Long-term follow-up

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Strategies to improve outcome in patients allografted for AML: optimising the conditioning regimen

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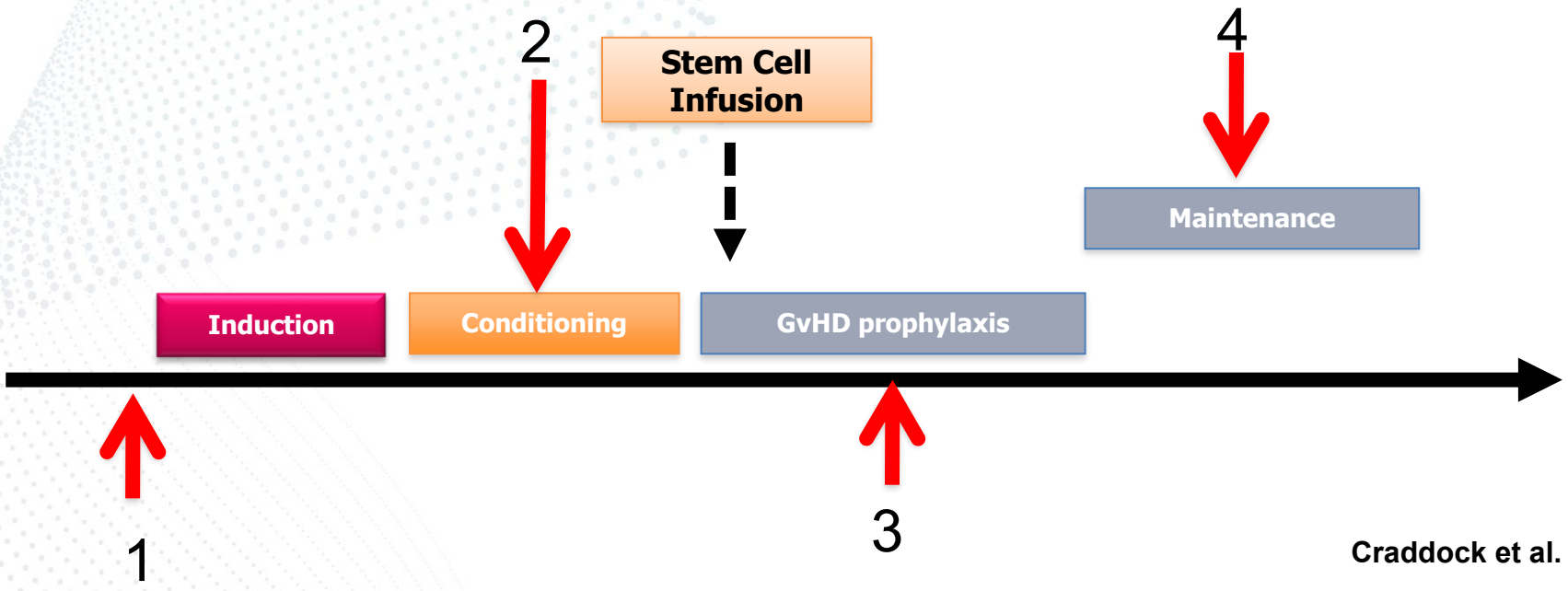
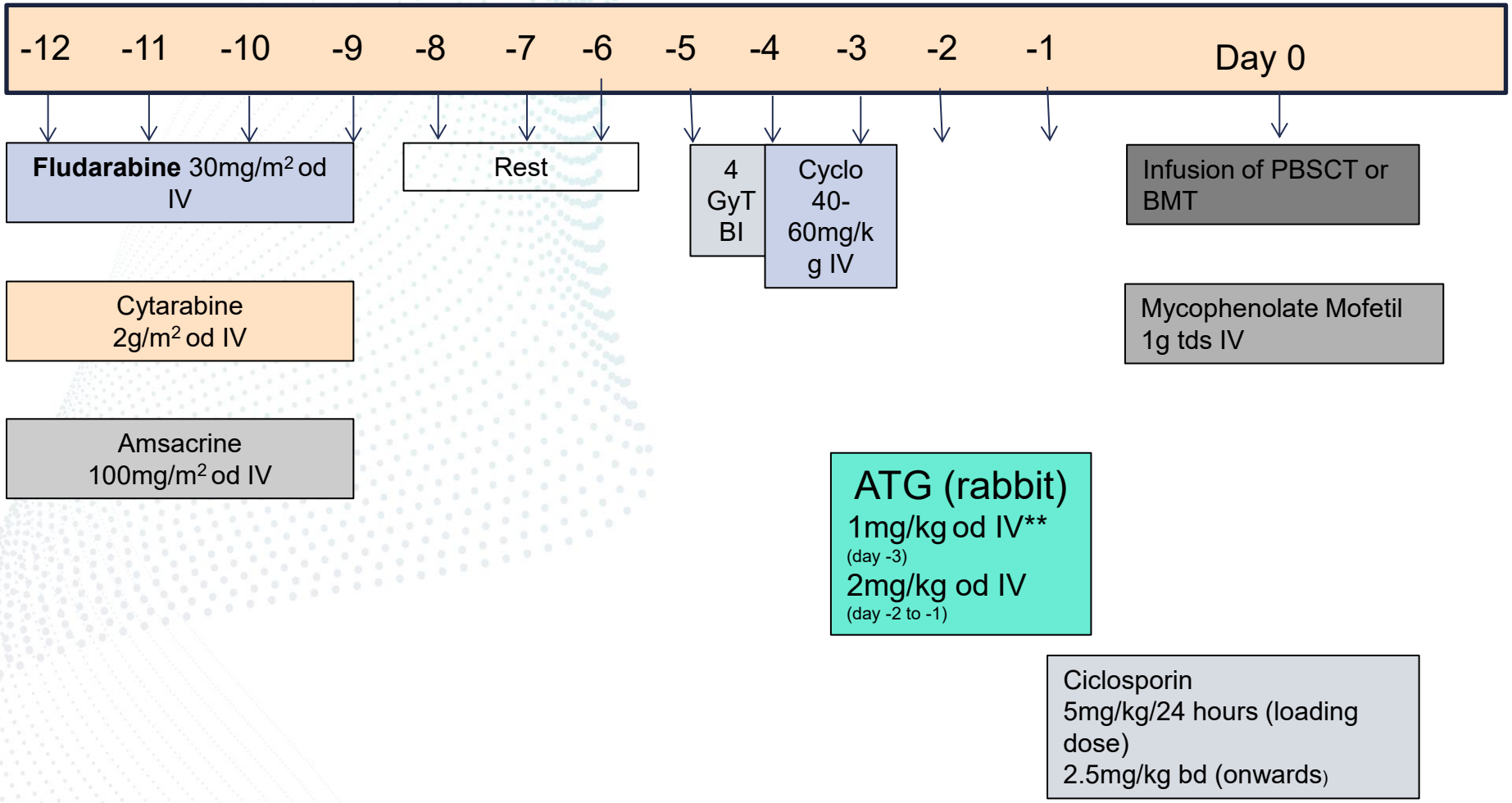
2. Augmenting conditioning regimen anti-tumour activity without increasing toxicity
3. Improved GVHD prophylaxis
4. Maintenance drug or cellular therapies



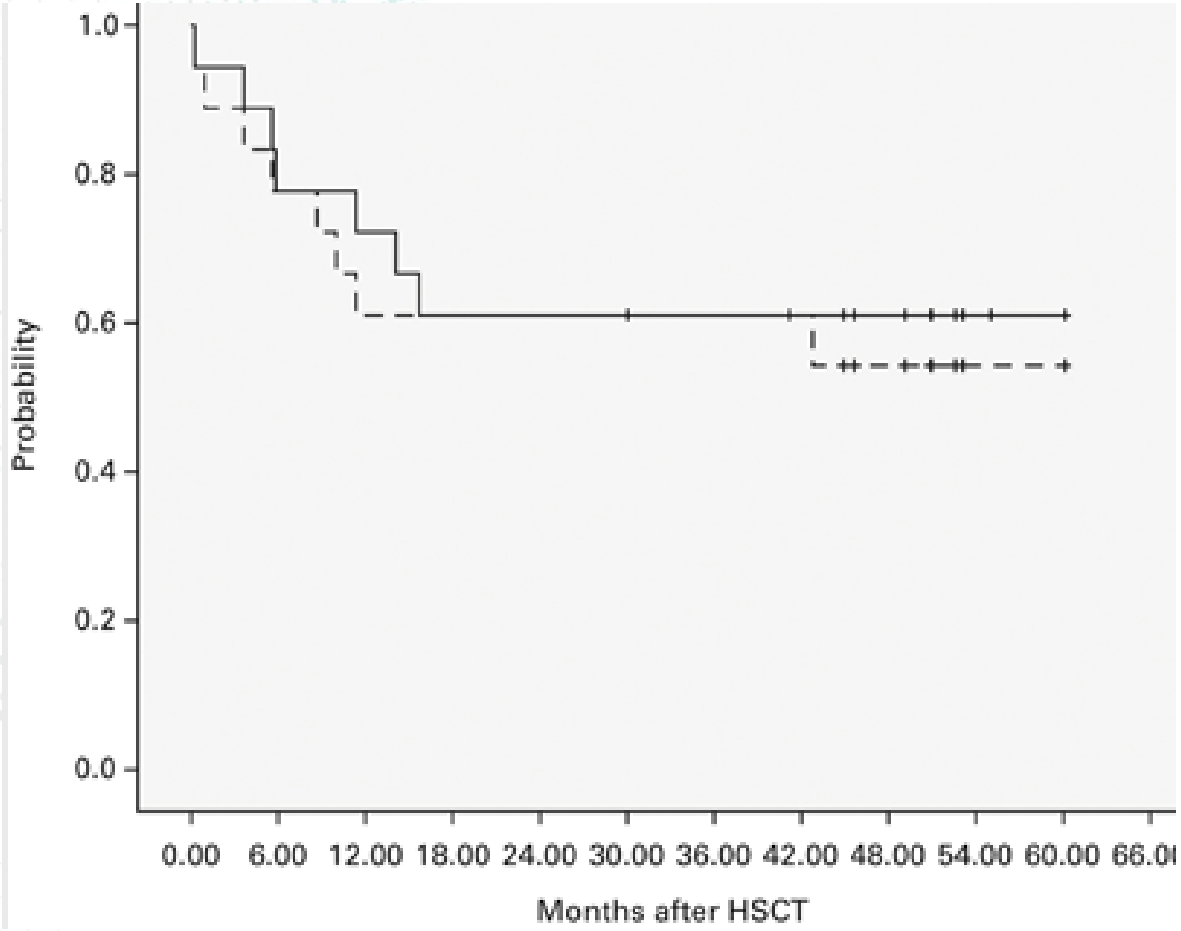
Craddock et al. *Bone Marrow Transplant.* 2019

FLAMSA Conditioning Regimen



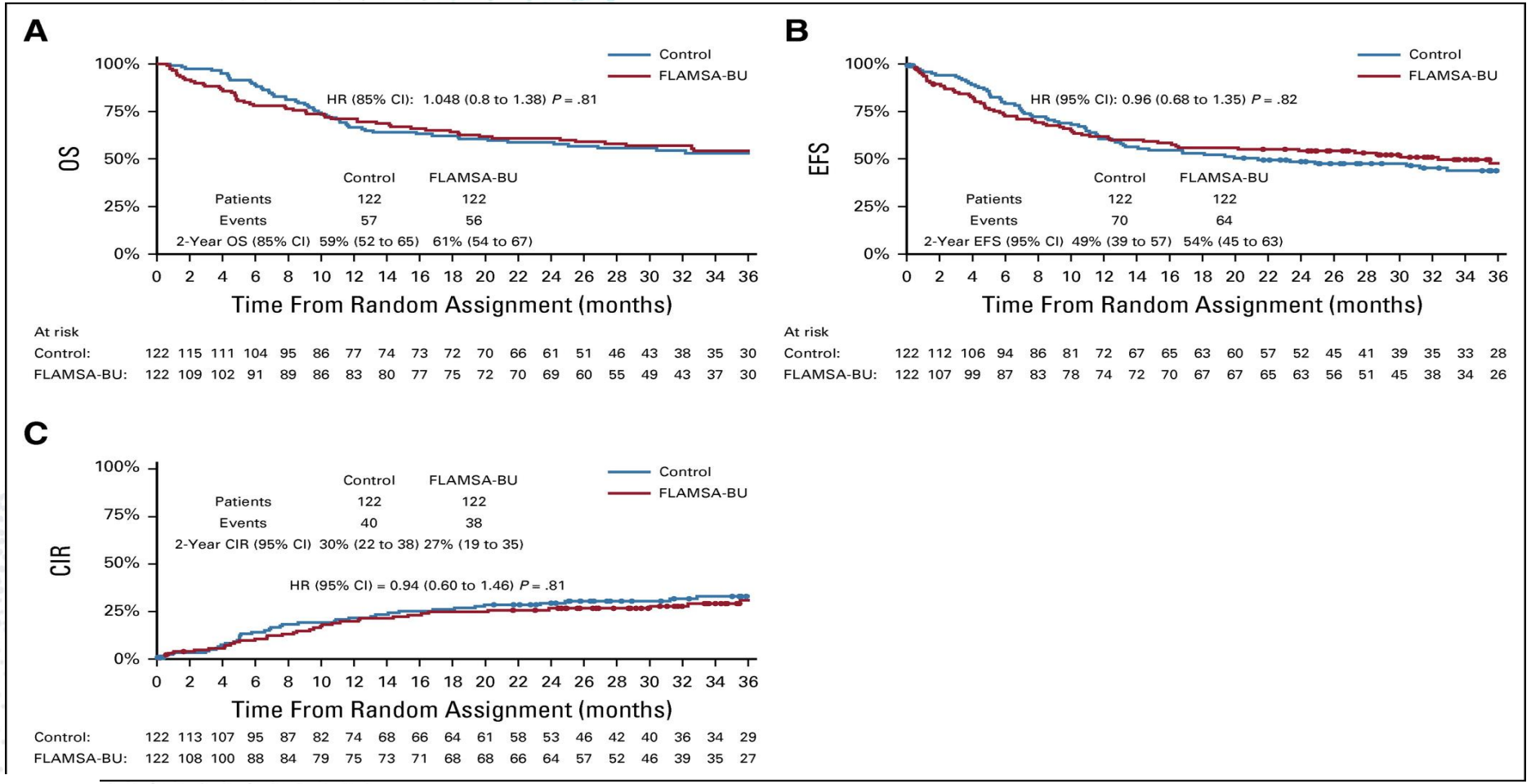
After Schmid et al Blood. 2006;108:1092-9.

Outcome after FLAMSA RIC Allograft in Patients with Adverse Risk Karyotype AML



Schmid et al. Bone Marrow Transplant. 2012: 47:46-53

Impact of FLAMSA-Bu Regimen on Transplant Outcome in High Risk AML: FIGARO



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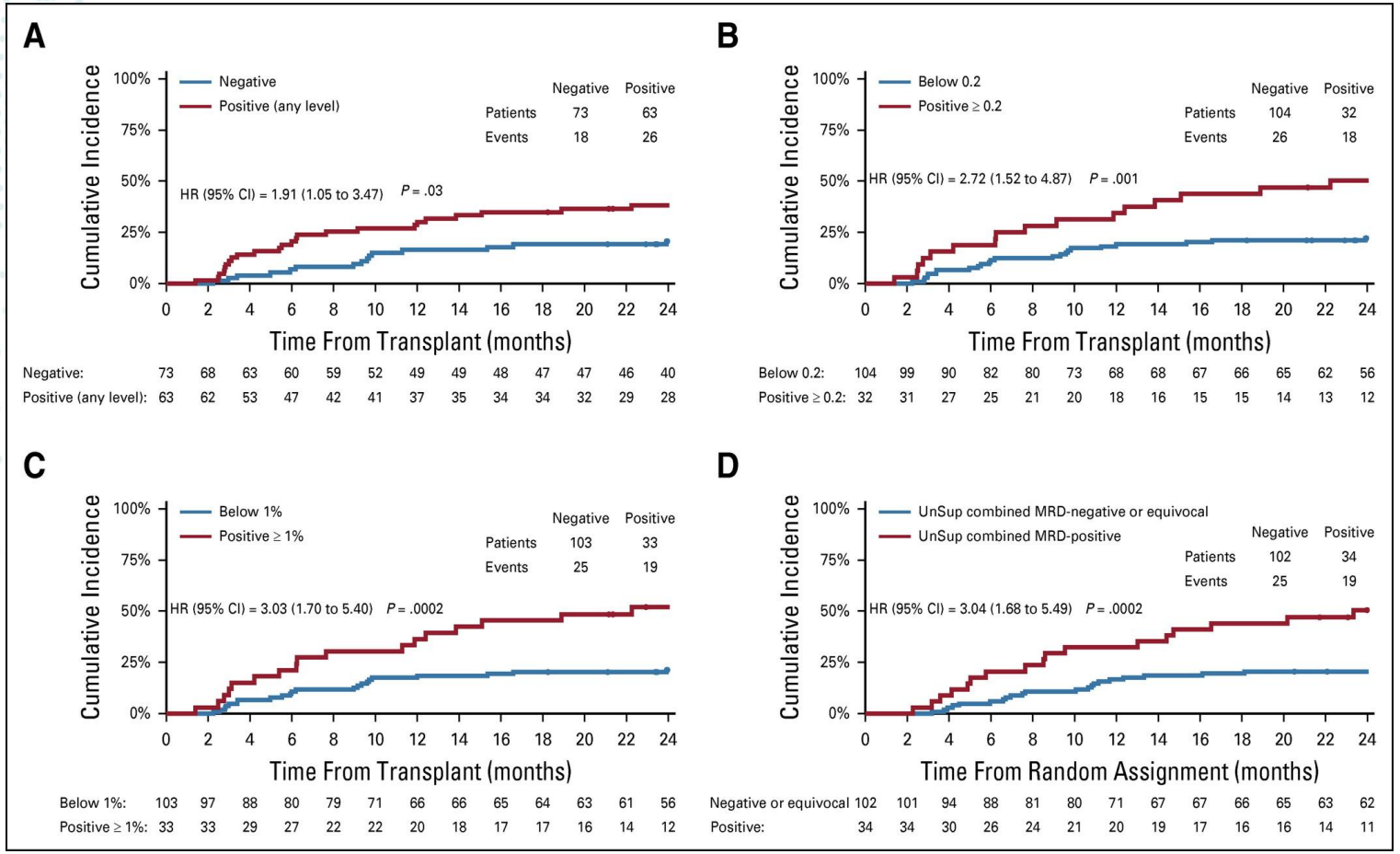
Craddock, et al. *J Clin Oncol.* 2020

Impact of Pre-transplant MRD on Relapse Incidence in Patients Allografted on FIGARO trial

No interaction between MRD status and conditioning regimen

- CIR MRD –ve 20% p= 0.01
  CIR MRD +ve 41%
- 2 yr OS MRD –ve 70%
  2 yr OS MRD +ve 51% p= 0.05



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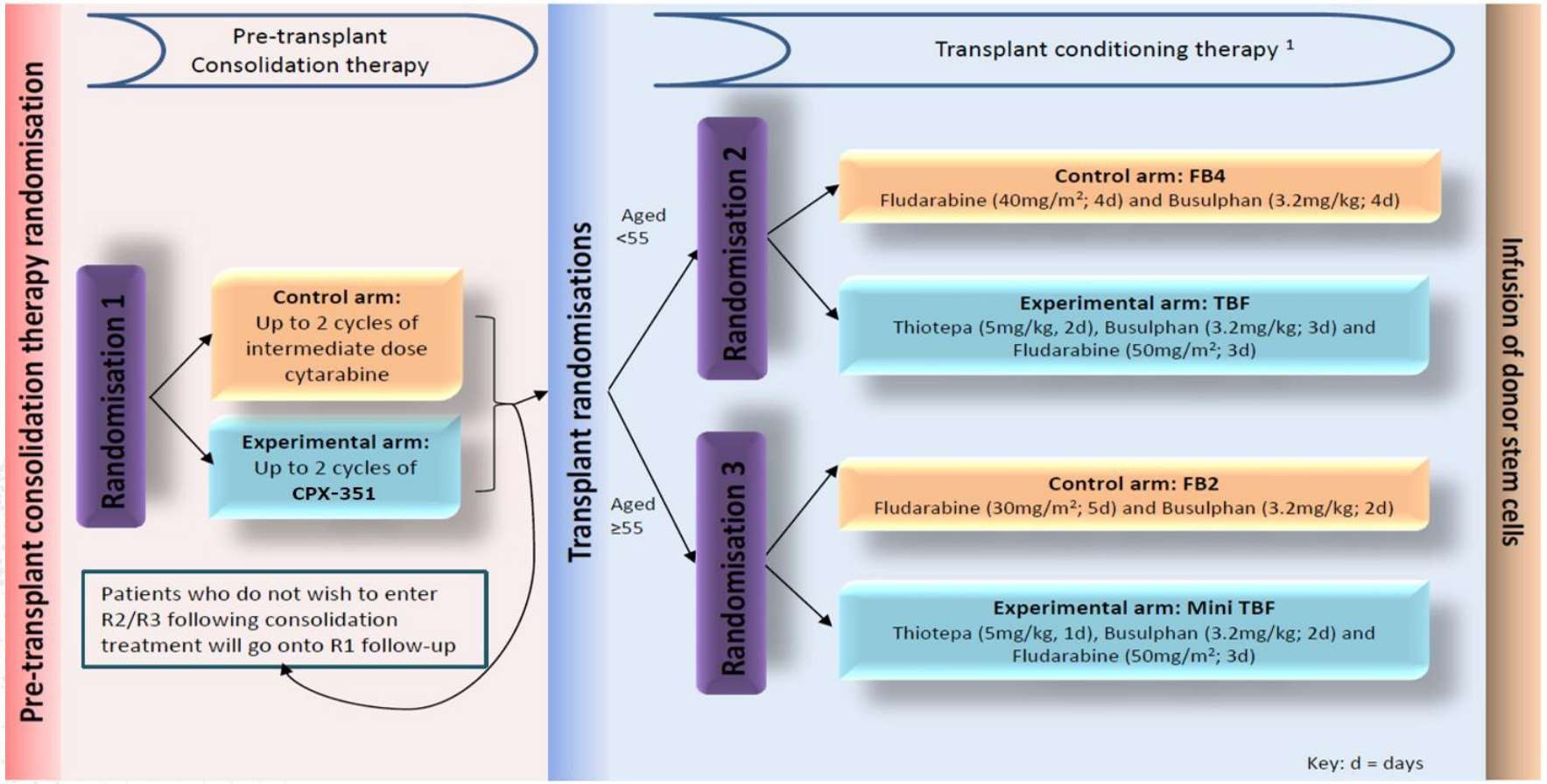
Craddock et al. J Clin Oncol 2020

COSI trial



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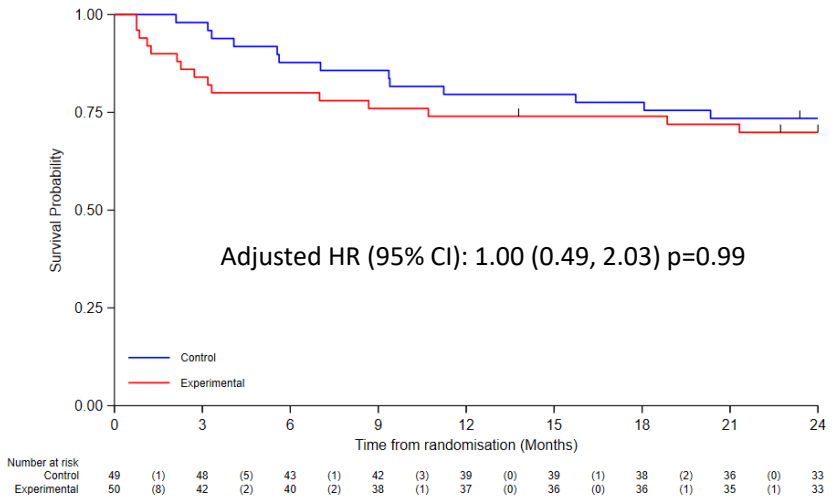
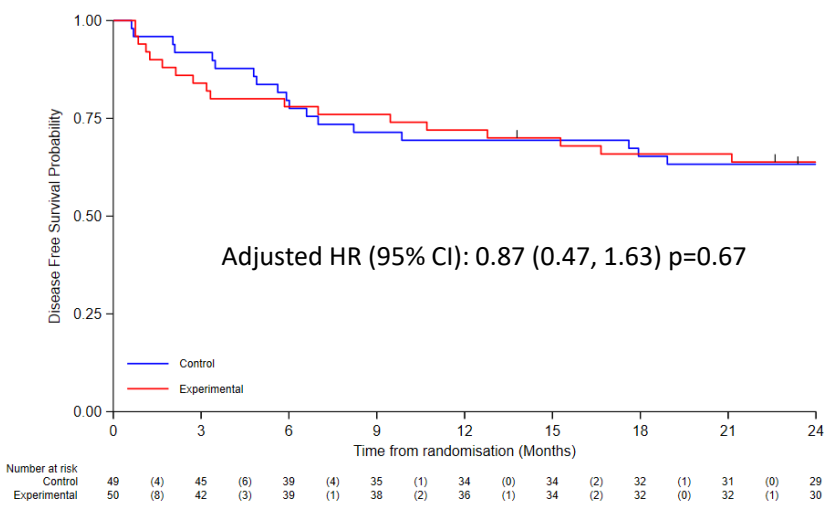
R2: Patient Outcomes According to Conditioning Regimen: FB4 versus TBF

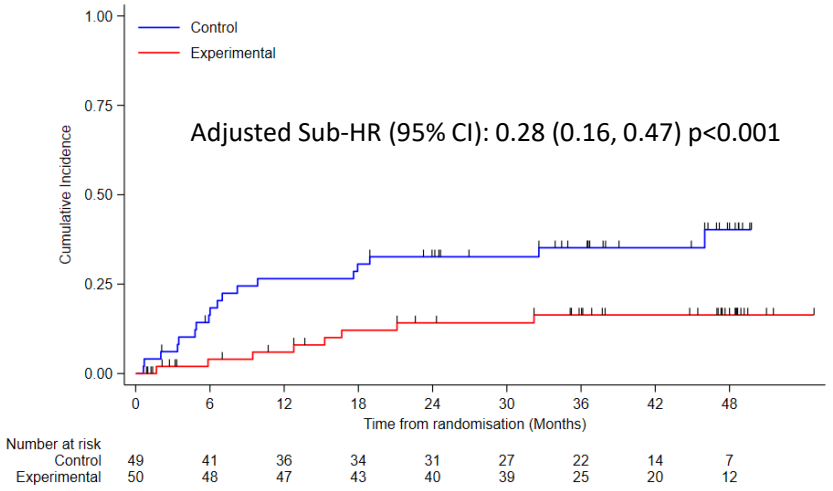
OS



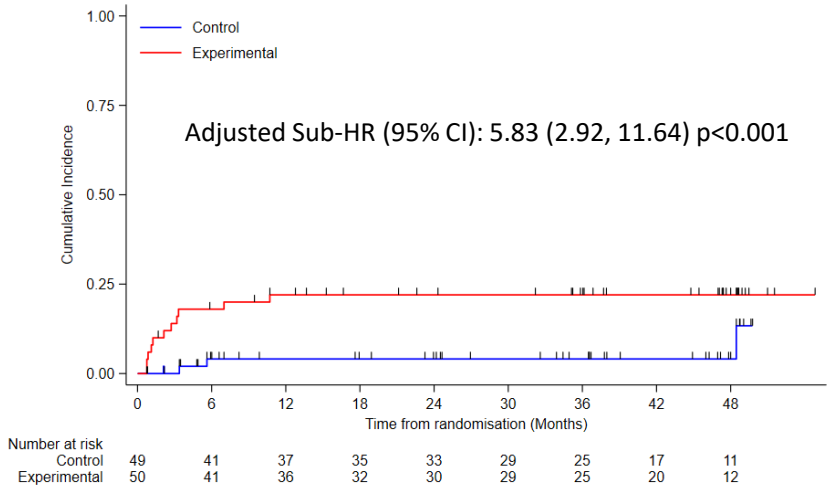
DFS



CIR

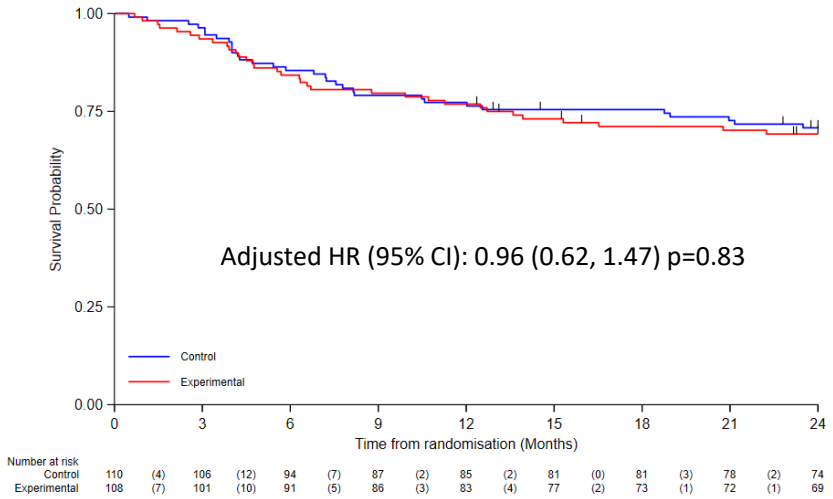


NRM



R3: Patient Outcomes According to RIC Regimen: FB2 versus TBF

OS



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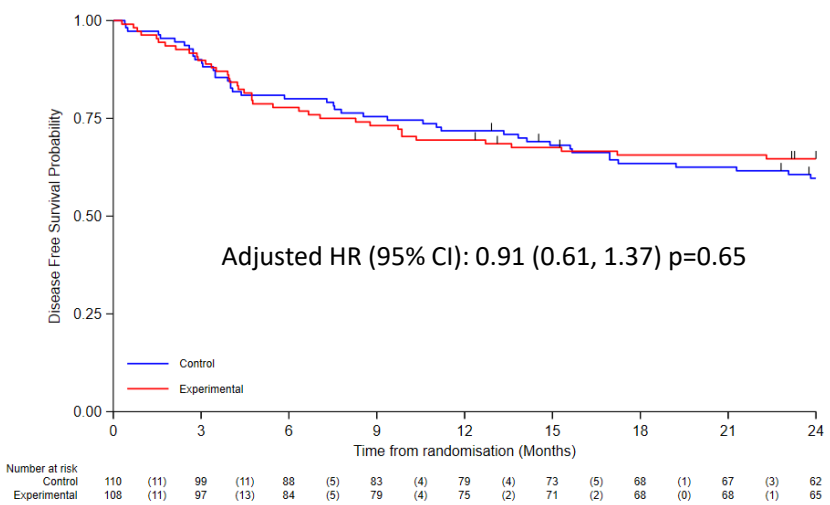

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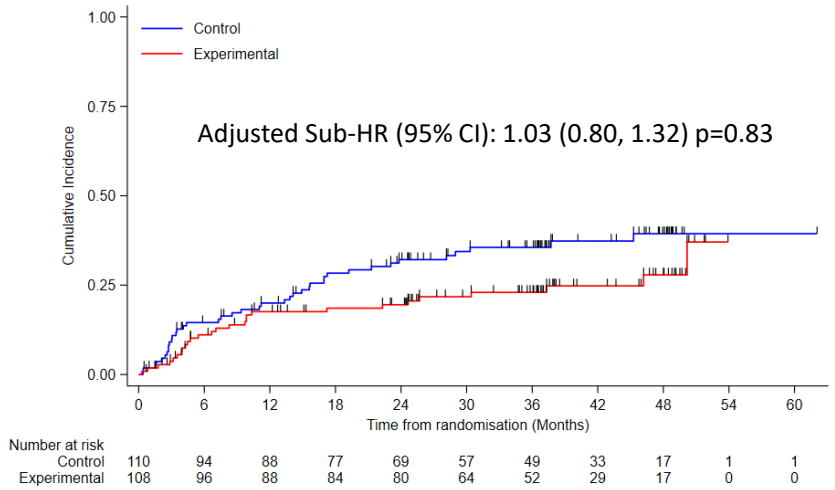
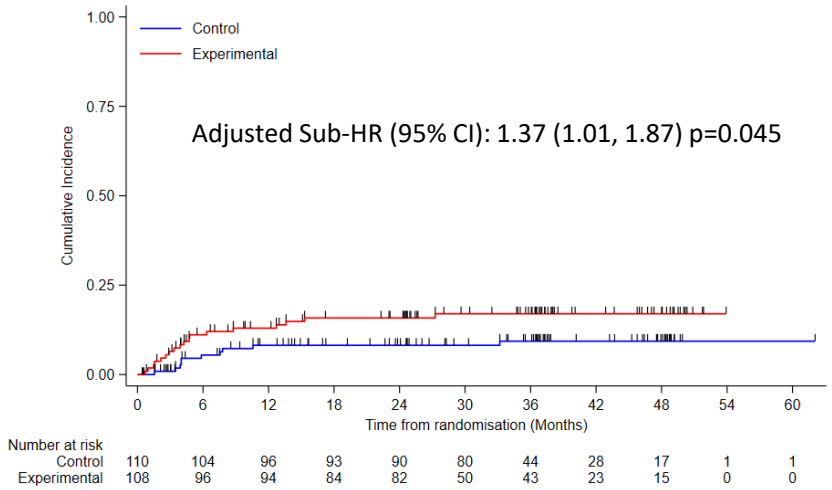
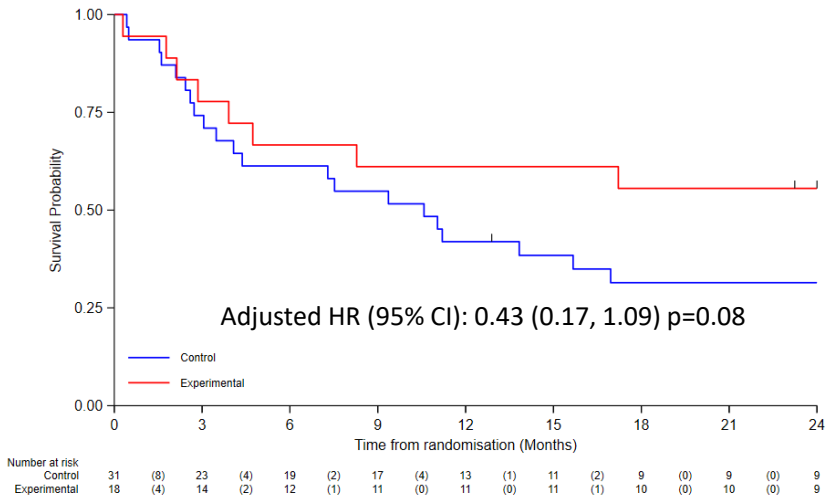


NRM

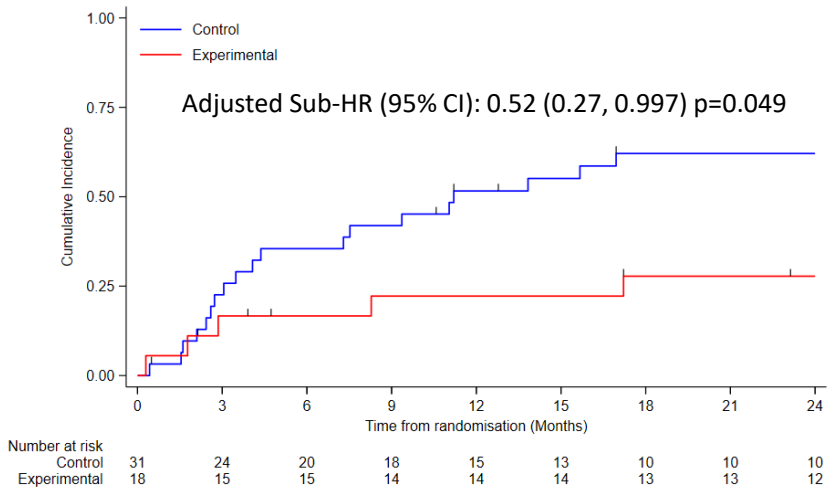


R3: Patient Outcomes According to Pre-Transplant MRD Status ≥ 0.1% Patients

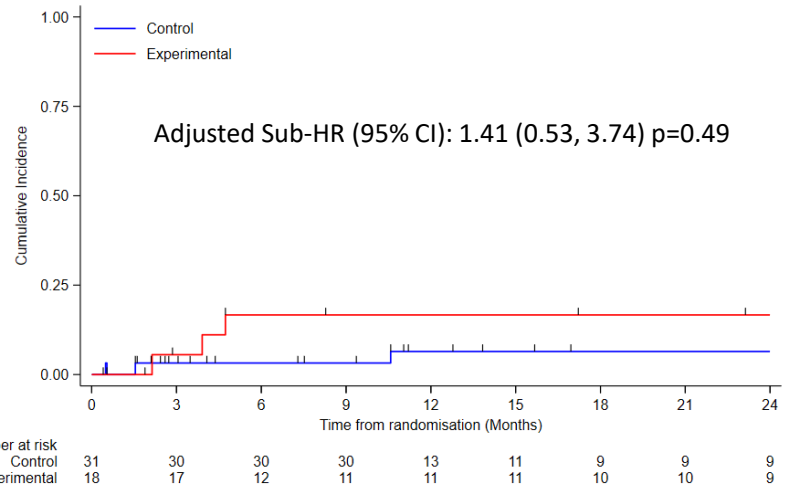
DFS



CIR



NRM



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Strategies to improve outcome in patients allografted for AML: improved GVHD prophylaxis

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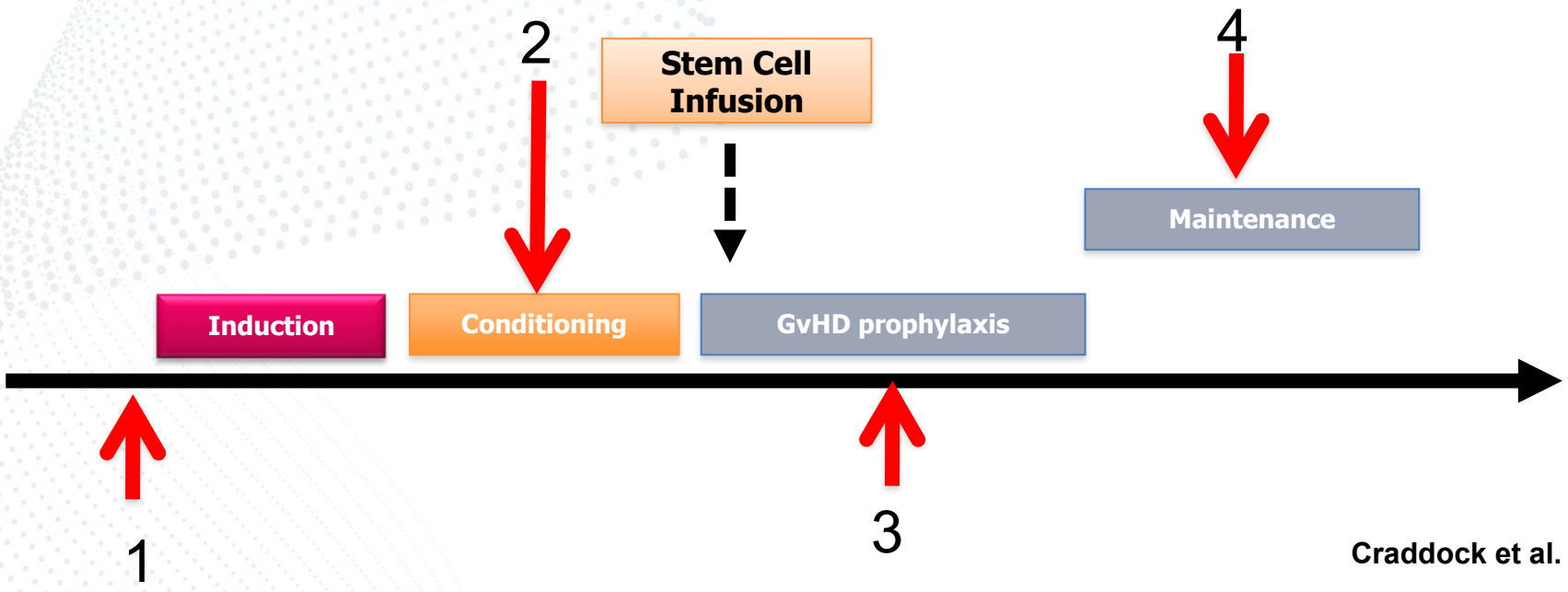


Craddock et al. *Bone Marrow Transplant.* 2019

Post-transplant Cy reduces acute and chronic GVHD after RIC allo-SCT

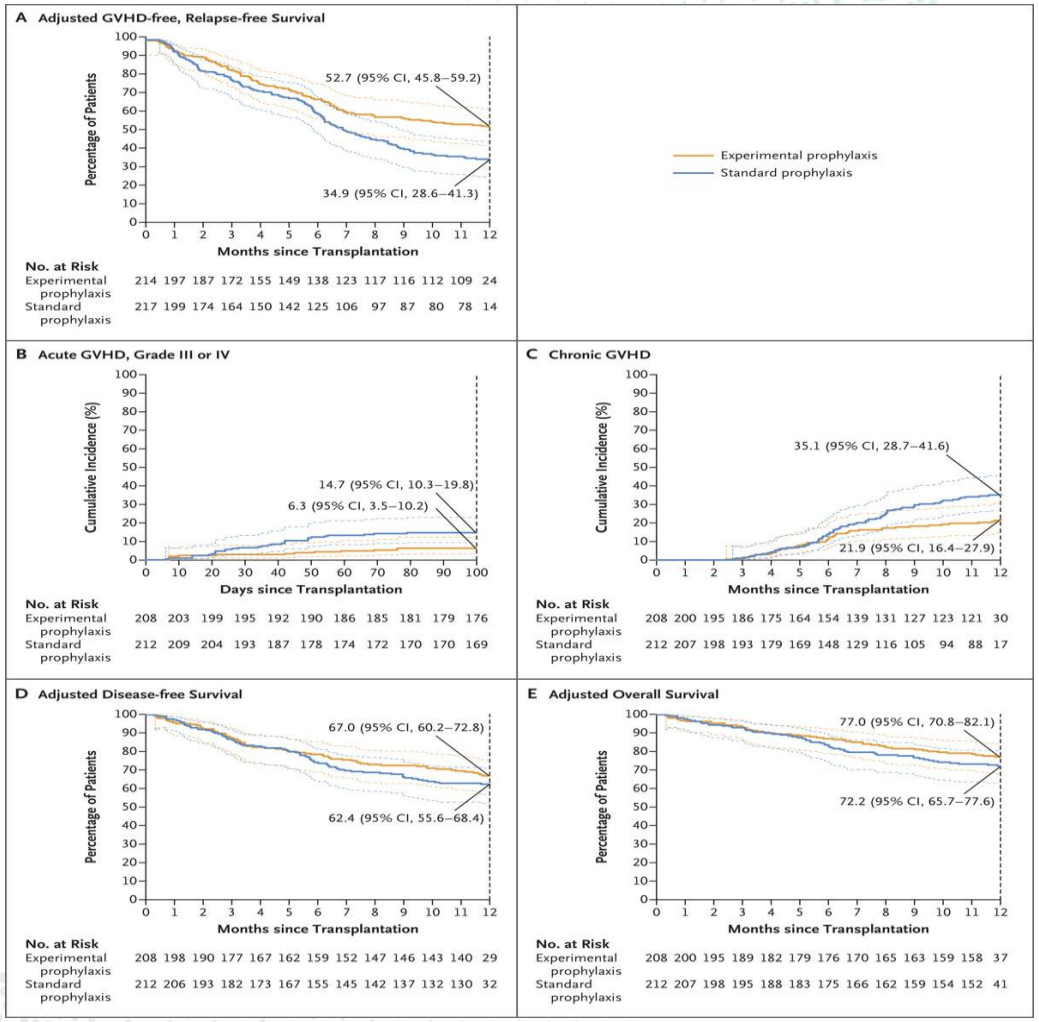


Table 3. Causes of Death in Patients in the Intention-to-Treat Population.

Cause of Death	Experimental-Prophylaxis Group (N=214)	Standard-Prophylaxis Group (N=217)
	number/total number (percent)	
Recurrence or persistence of disease	19/48 (40)	24/56 (43)
Primary graft failure	2/48 (4)	0
Acute GVHD	2/48 (4)	8/56 (14)
Chronic GVHD	0	1/56 (2)
Infection	8/48 (17)	10/56 (18)
Organ failure	11/48 (23)	6/56 (11)
Hemorrhage	3/48 (6)	1/56 (2)
Acute respiratory distress syndrome	0	1/56 (2)
Other*	3/48 (6)	5/56 (9)

* The "other" category includes accident, septic shock, thrombotic microangiopathy, and unknown.

Bolanos-Meade et al *NEJM* 2023

BMT CTN 1703: Conclusions

- In well-matched RIC PBSCT, PTCy/Tac/MMF produces:
  - Superior GRFS owing to reduced severe acute and chronic GVHD
  - No increase in relapse/progression
  - Slightly delayed hematopoietic recovery
  - More grade 2 but not grade 3 infections, mostly in first month
- Extended follow-up required: potential increased toxicity in older patients
- How does PTCy compare to ATG based GVHD prophylaxis?
- Awaiting results of rapidly recruiting MoTD trial which incorporates ATG in control arm

Method of T cell Depletion (MoTD) trial

ELIGIBILITY

9/10 or 10/10 MUD
PBSC
RIC[1]
Blood cancer[2]

Age 18-70
Adequate organ function
Life expectancy>8 weeks
Negative pregnancy test

R

PTCy +3/4
+CNI /MMF

PTCy +3/4
+Siro /MMF

ATG
+CNI/MMF

d+360

1º endpoint

1-year % GFRS

2º endpoints

Incidence/ severity of GVHD
Toxicity and non-relapse mortality
OS and PFS
Immune suppression-free survival
Engraftment and chimerism
Incidence PTLD/Rituximab use
Biological endpoints

[1]RIC protocols

Fludarabine-Melphalan
BEAM or LEAM
Fludarabine-Busulphan

[2]Blood cancers

AML in CR
ALL in CR
CMML or MDS <10% blasts
NHL in CR/PR
HL in CR/PR
MM in CR/PR
CLL in CR/PR
CML in 1st or 2nd chronic phase

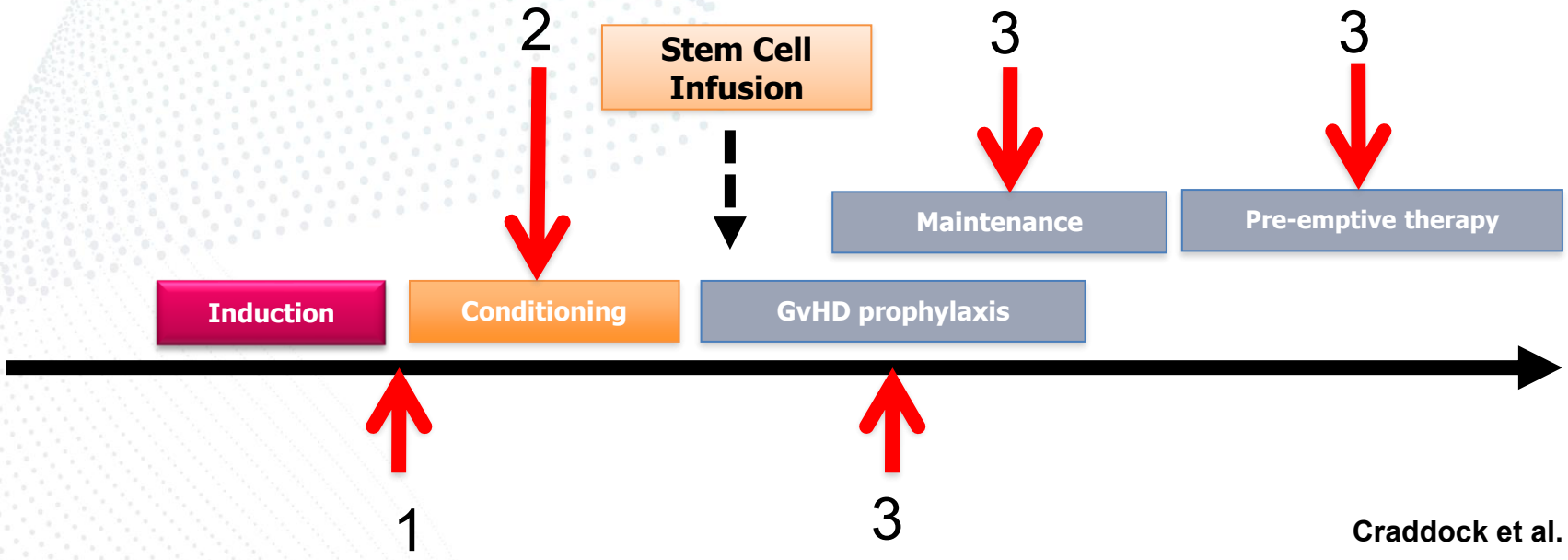
NCT04888741

THE JON MOULTON CHARITY TRUST

IMPACT THE UK'S STEM CELL TRANSPLANT CLINICAL TRIALS PLATFORM

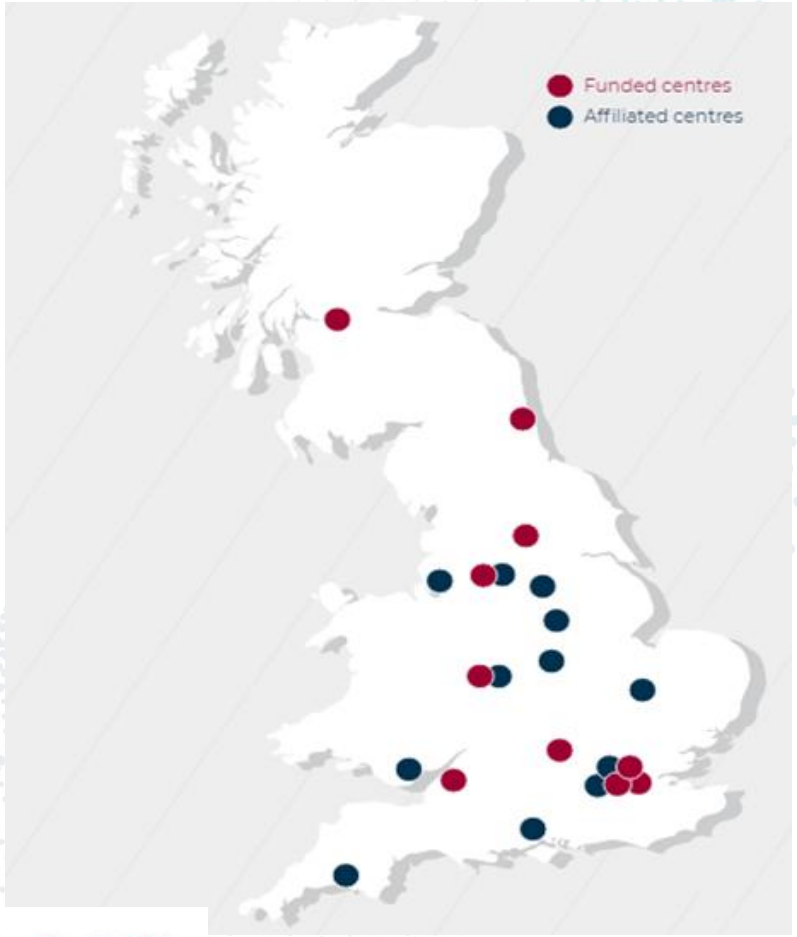
Strategies to improve outcome in patients allografted for AML: the role of post-transplant maintenance

- Optimising the induction regimen
- Augmenting conditioning regimen anti-tumour activity without increasing toxicity
- Maintenance drug or cellular therapies which:
  - Target residual leukaemic stem/progenitors
  - Optimise a GvL effect



Craddock et al. *Bone Marrow Transplant.* 2019

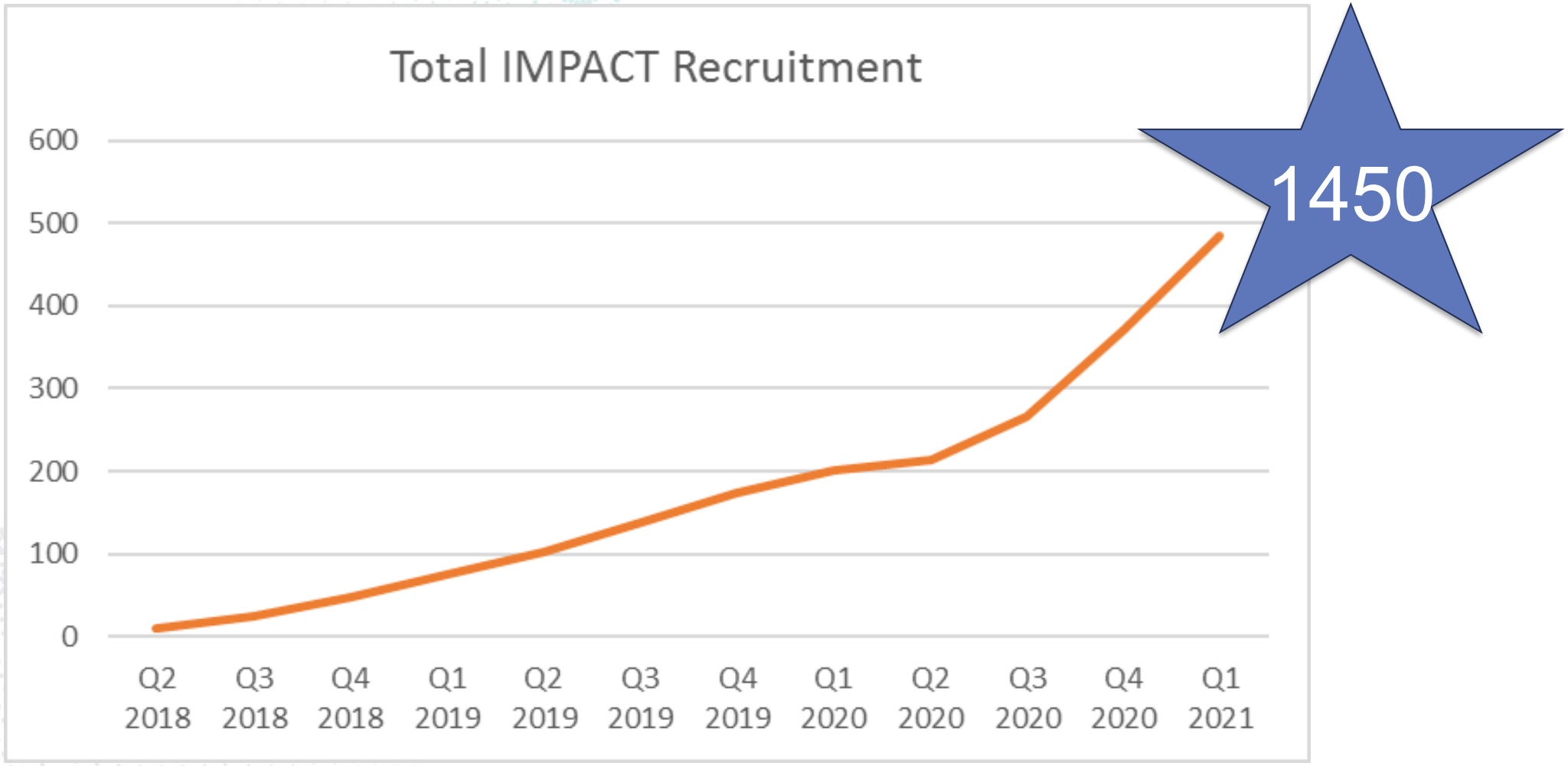
IMPACT Structure: a Trials Delivery HUB linked with a National Research Nurse Network



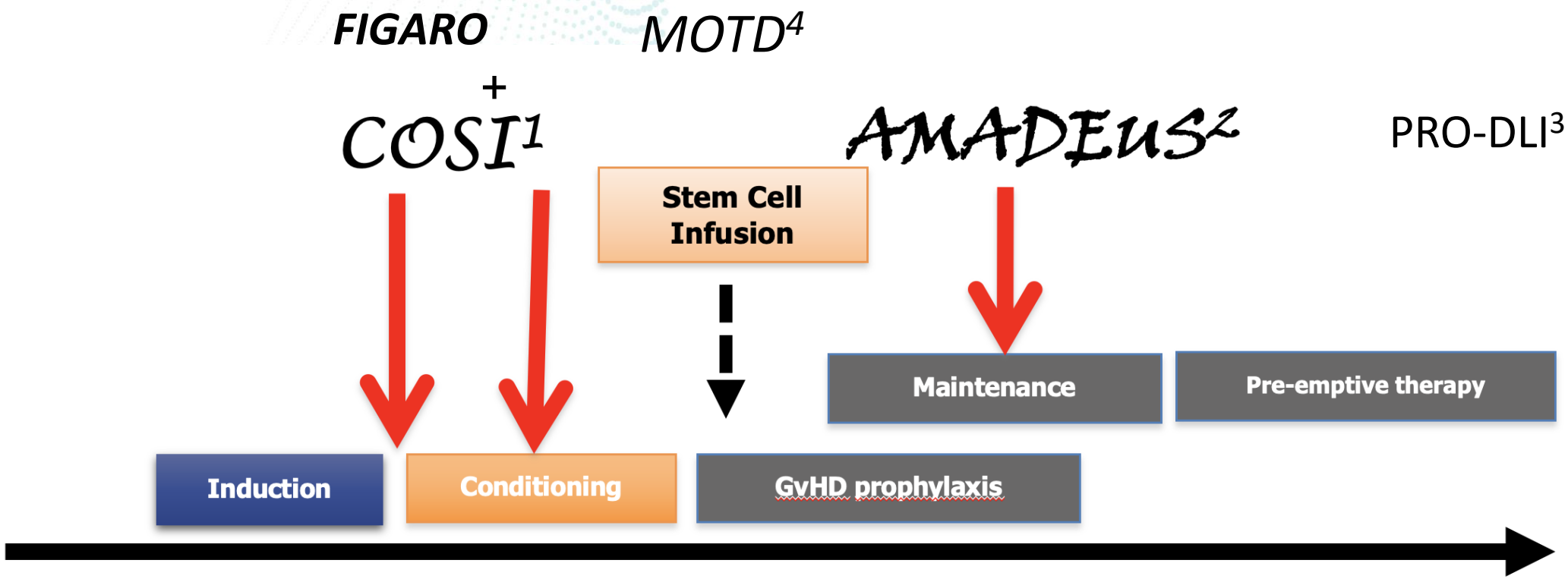
- ✓ Central Hub: responsible for trial design, setup, management and publication
- ✓ 11 funded transplant centres able to recruit to IMPACT studies
- ✓ 11 affiliated transplant centres able to recruit to IMPACT studies

UK AML Research Network

IMPACT Recruitment



IMPACT Trials Designed to Optimise Outcomes in Patients Allografted for AML



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Conclusions (i)

- Allografting is a potent and manipulable anti-leukemic strategy in increasing numbers of older adults with AML in CR1
- Novel induction regimens have the potential to transform transplant outcomes
- Older adults who are MRD+ can still achieve good post-transplant outcomes with a RIC regimen but novel conditioning/post-transplant strategies are required
- There is no evidence that transplant should be deferred in patients who are in morphological CR but have detectable flow based MRD
- No benefit of FLAMSA-BU in AML CR1
- In fit adults under 55 a MAC regimen is to be preferred- especially in patients who are MRD+

Conclusions (ii)

- Randomized trials of novel maintenance strategies eg menin inhibitors, DLI should be prioritized in patients at high risk of relapse post-allograft
- Stratification of post-transplant relapse risk will be critical in rationale use of maintenance
- Strategies to optimise a GVL effect should be studied:

✓ Early taper of immunosuppression

✓ Prophylactic DLI

- Randomized trials of novel maintenance strategies eg menin inhibitors, DLI should be prioritized in patients at high risk of relapse post-allograft