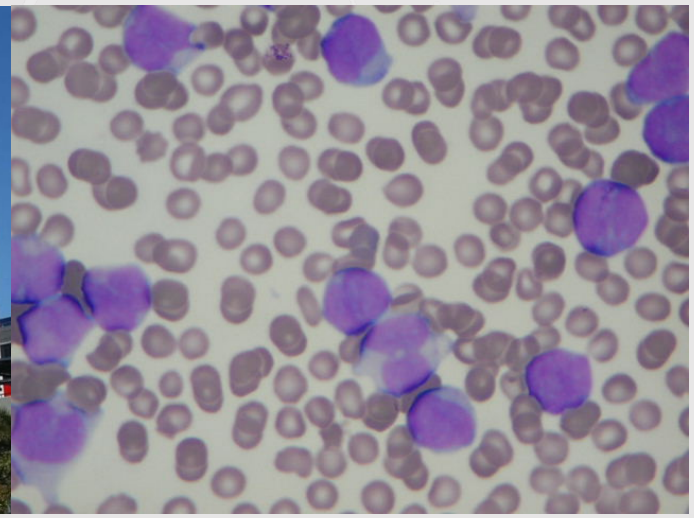


“TRANSPLANTATION IN AML”

Dr Steven Lane

CLINICAL HAEMATOLOGIST, ROYAL BRISBANE AND WOMEN’S HOSPITAL.

GROUP LEADER, GORDON AND JESSIE GILMOUR LEUKAEMIA RESEARCH LABORATORY, QIMR BERGHOFER MRI

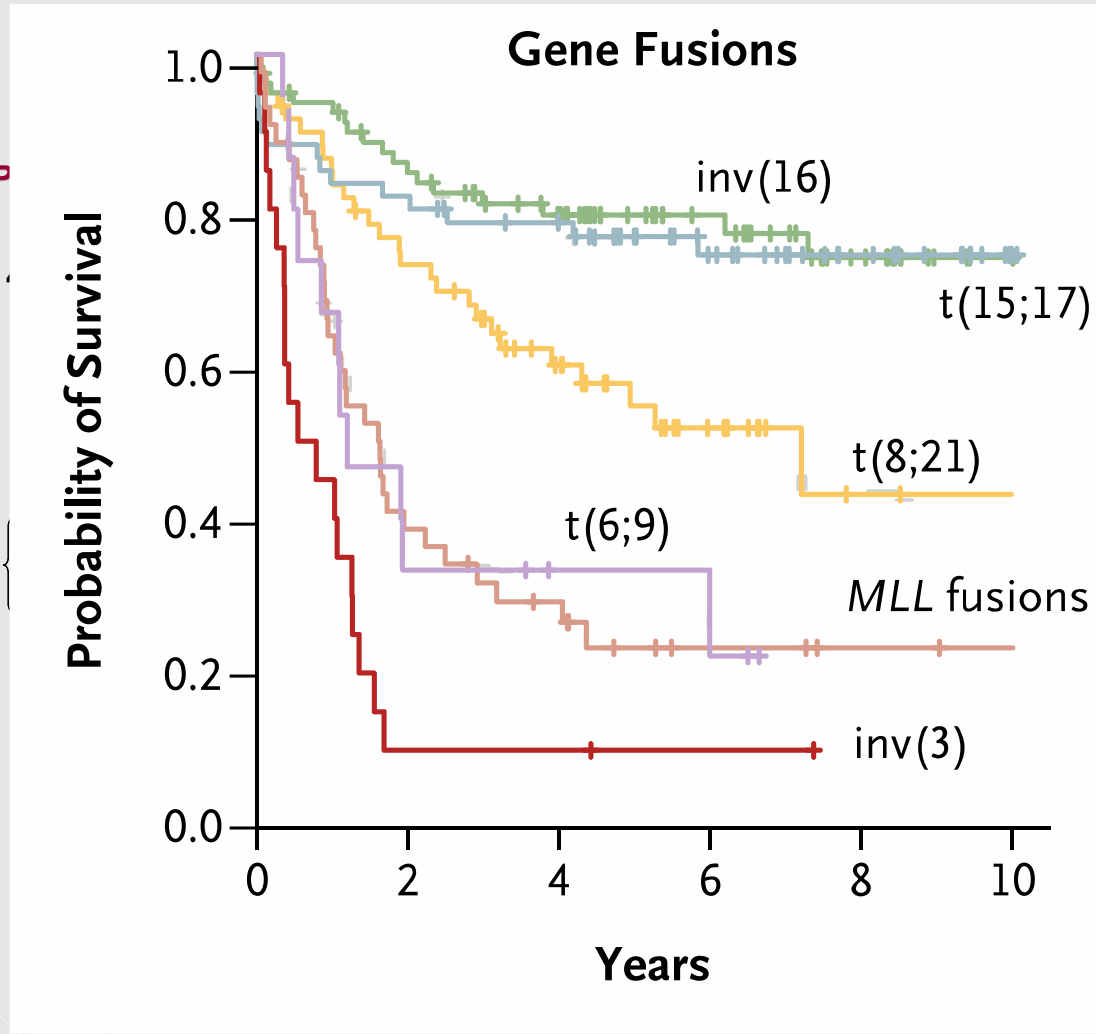
ASSOC. PROF, UNIVERSITY OF QUEENSLAND, AUSTRALIA

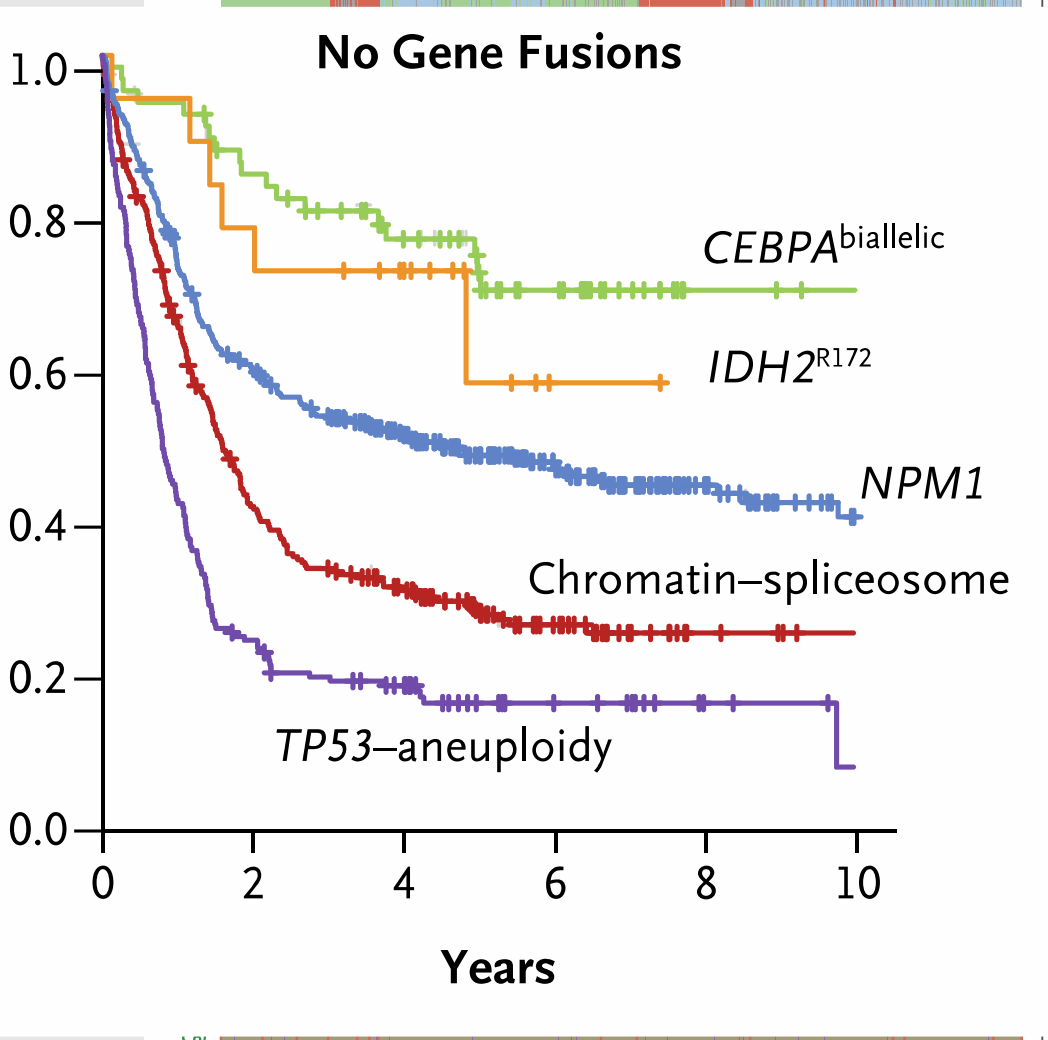
Disclaimer: I am not a Bone Marrow Transplant Physician

Outline of transplantation in AML

- Introduction to AML and genomics
- What are the indications for allogeneic HSC/BM transplantation in AML?
- Factors to consider in the selection of patients for Allo HSCT
- Ongoing discussion points regarding AlloHSCT in AML
  - Role of MRD prior to transplantation
  - Role of $NPM1^{mut}FLT3\text{-}ITD^{low}$ in prognosis of AML
  - Do we still need to transplant in the age of targeted therapies
  - Strategies for relapse post transplantation

AML is a genetically heterogeneous disease.
Relapse and survival after treatment are defined by the tumour genetics



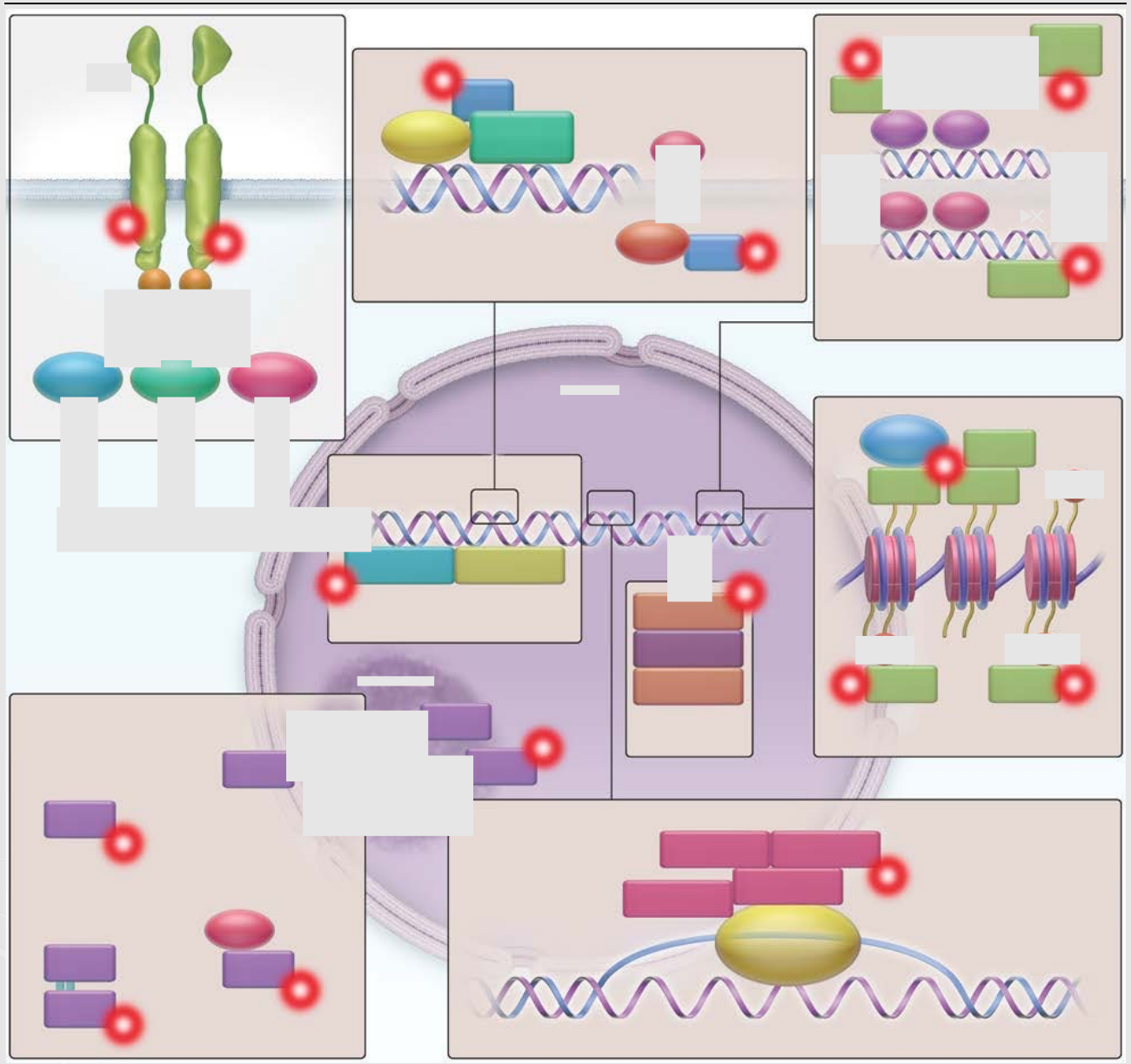


Döhner, Haematologica 2008

Schlenk and Dohner, NEJM 2008

Papaemmanuil et al. NEJM 2016

Discrete classes of mutations in the pathogenesis of AML



1. Signaling activation
2. Transcription factor loss
3. Epigenetic regulators
    1. Chromatin
    2. DNA methylation
4. Nucleophosmin localization
5. Splicing
6. Cohesin and chromosome segregation
7. Tumour suppressors

Döhner et al, NEJM 2015

A complex classification of a complex disease

Myeloid neoplasms with germ line predisposition
Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
▪ AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
▪ AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
▪ APL with *PML-RARA*
▪ AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
▪ AML with t(6;9)(p23;q34.1);*DEK-NUP214*
▪ AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
▪ AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
▪ AML with mutated *NPM1*
▪ AML with biallelic mutations of *CEBPA*
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
▪ AML with minimal differentiation
▪ AML without maturation
▪ AML with maturation
▪ Acute myelomonocytic leukemia
▪ Acute monoblastic/monocytic leukemia
▪ Pure erythroid leukemia
▪ Acute megakaryoblastic leukemia
▪ Acute basophilic leukemia
▪ Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
▪ Transient abnormal myelopoiesis (TAM)
▪ Myeloid leukemia associated with Down syndrome

WHO classification of AML – from Uptodate.com

The European Leukemia Net categorisation is used to predict prognosis and guide treatment in AML

Table 5. 2017 ELN risk stratification by genetics

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Do not transplant in CR1

Consider allo transplant in CR1

Consider allo transplant in CR1

Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2016:blood-2016-08-733196.

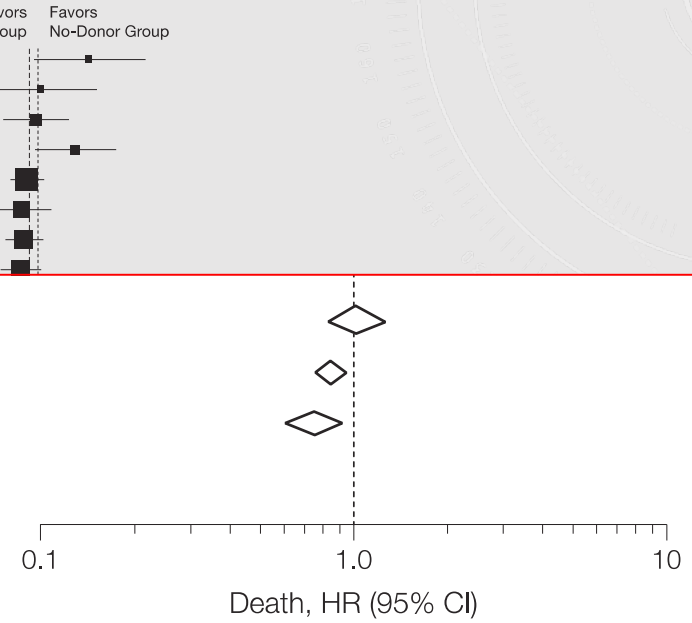
Factors to consider in the selection of patients for Allo HSCT

- Disease – risk, stage
- Age
- Comorbidity index
  - Psychosocial and compliance
- Donor – sibling, matched unrelated, HLA mismatched, Haplo, Cord
- Conditioning regimens
- Availability of other treatments

A meta-analysis of survival post Allo HSCT in AML

Figure 3. Overall Survival Benefit of Allogeneic SCT for AML in First Complete Remission

Source	No. of Patients: Donor Group	No. of Patients: No-Donor Group	No. of Trials	HR (95% CI)
Schiller et al,[11] 1992	28	54		1.91 (0.95-3.84)
Archimbaud et al,[12] 1994	27	31		1.04 (0.52-2.11)
Hewlett et al,[13] 1995	53	110		0.98 (0.65-1.49)
Sierra et al,[14] 1996	47	68		1.60 (0.96-2.65)
Keating et al,[16] 1998	295	377		0.88 (0.72-1.09)
Slovak et al,[17] 2000	89	174		0.82 (0.57-1.18)
Suciu et al,[18] 2003	293	441		0.85 (0.67-1.08)
Jourdan et al[20] 2005	182	290		0.81 (0.63-1.05)
Overall survival benefit by cytogenetic risk				
Good-risk AML	188	359	10	1.07 (0.83-1.38)
Intermediate-risk AML	864	1635	14	0.83 (0.74-0.93)
Poor-risk AML	226	366	14	0.73 (0.59-0.90)
Test for heterogeneity: $\chi^2_2 = 5.29$; $P = .07$; $I^2 = 62.2\%$				



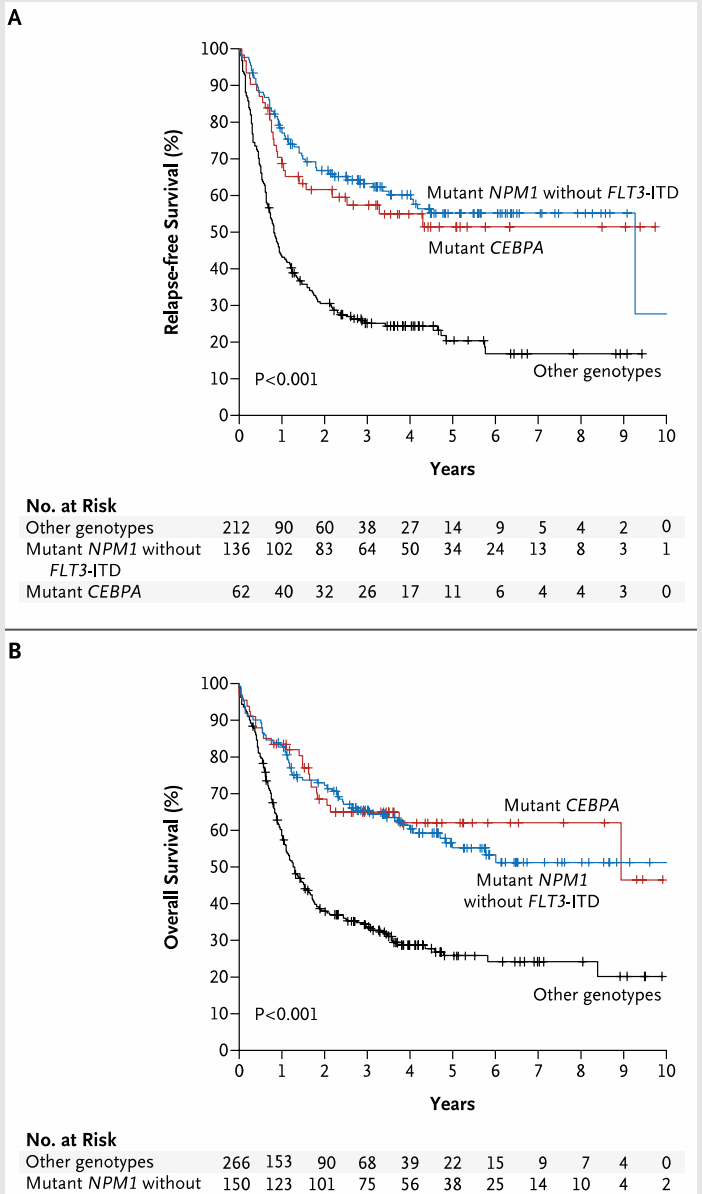
SWOG or MRC classification of CG Risk

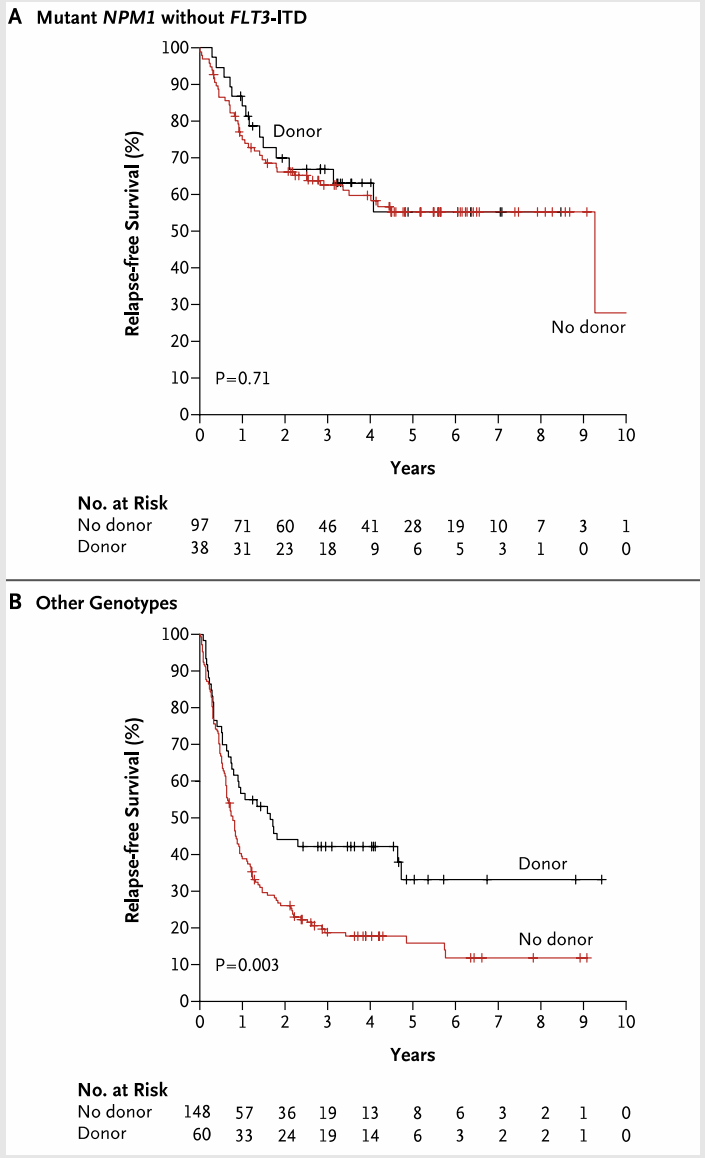
Overall survival benefit by cytogenetic risk
Good-risk AML 188 359 10 1.07 (0.83-1.38)
Intermediate-risk AML 864 1635 14 0.83 (0.74-0.93)
Poor-risk AML 226 366 14 0.73 (0.59-0.90)
Test for heterogeneity: $\chi^2_2 = 5.29$; $P = .07$; $I^2 = 62.2\%$
0.1 1.0 10
Death, HR (95% CI)

Black rectangles indicate summary effects estimates (hazard ratios [HRs]) for individual study reports. Sizes of data markers are proportional to the study weights. Error bars indicate 95% confidence intervals (CIs). AML indicates acute myeloid leukemia.

KORETH, et al. JAMA 2009

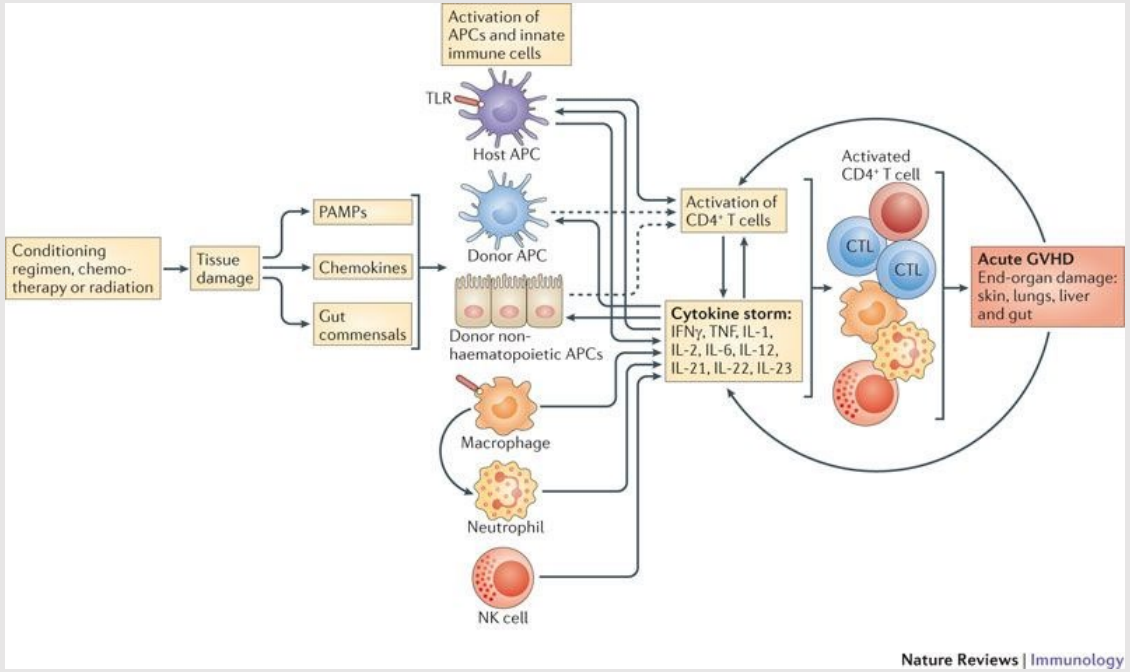
Favourable risk AML ($NPM1^{mut}FLT3ITD^{neg}$) does not benefit from Allo SCT in CR1

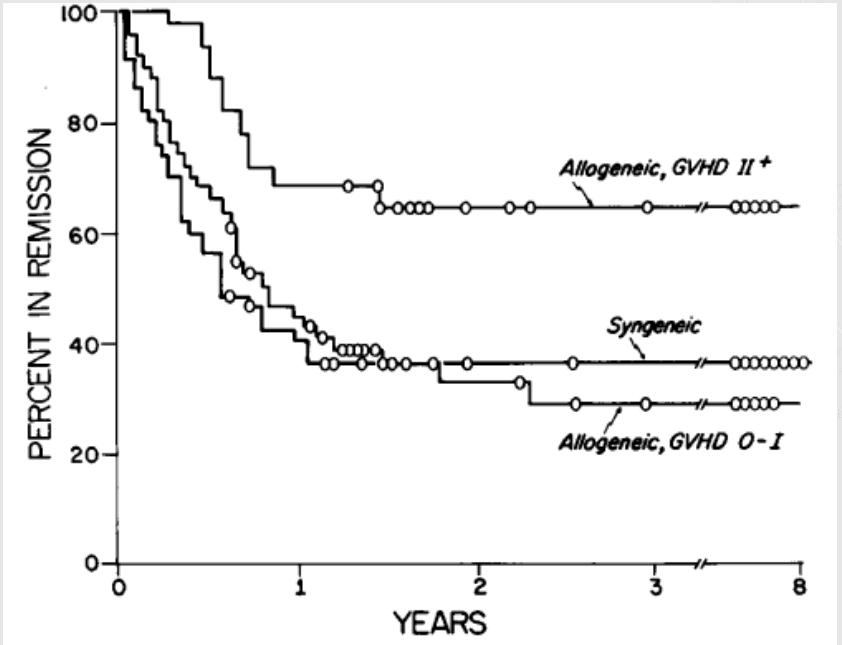


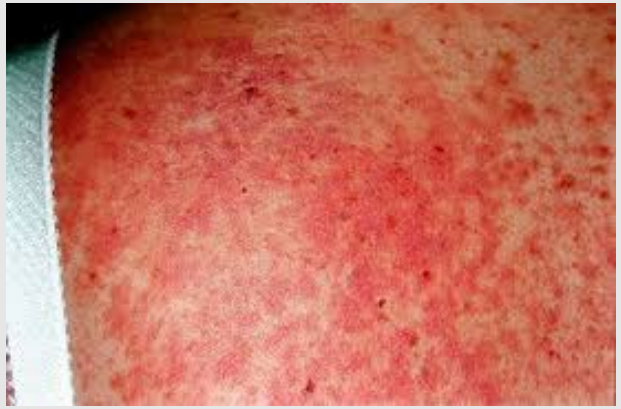


Schlenk et al. NEJM 2008

GVHD is the major toxicity after Allo HSCT, and is linked to GVL effect

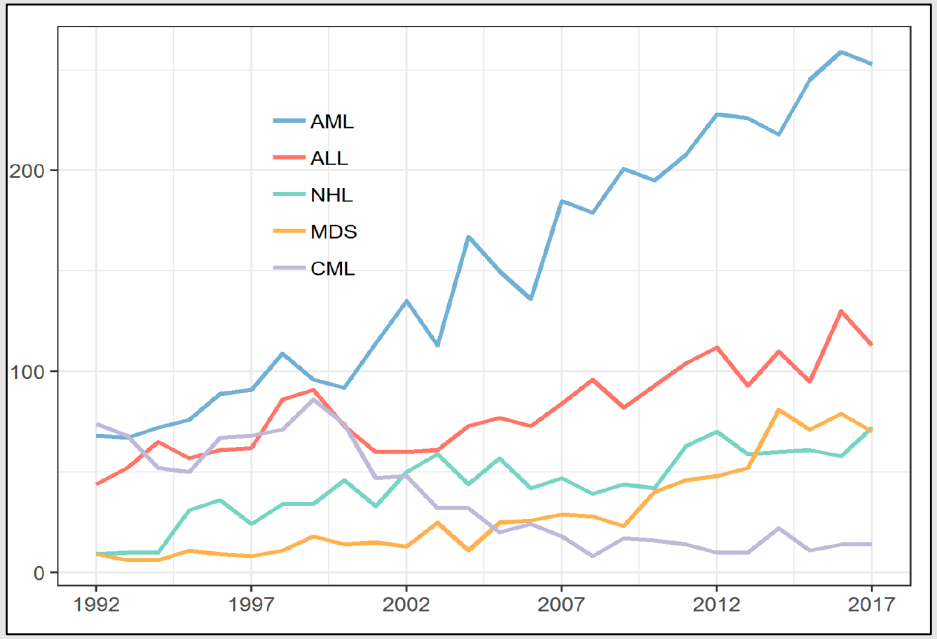




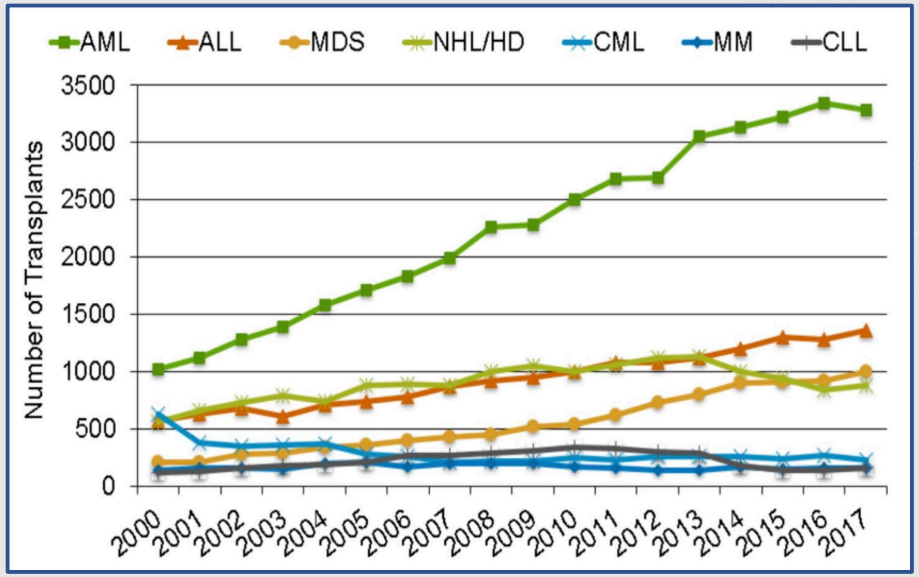


Blazar, et al. Nat Rev Immunol, 2012
Weiden et al. NEJM 1979
Cancer.gov

Who is being transplanted in Australia/ globally?



Australian – ABMTRR



CIBMTR

ABMTRR Annual Data Summary 2017
D'Souza A, Fretham C.: CIBMTR Summary Slides 2018

ABMDR – Slide Courtesy of Ashish Bajel

Disease stage: Outcomes of transplantation beyond CR1 are poor

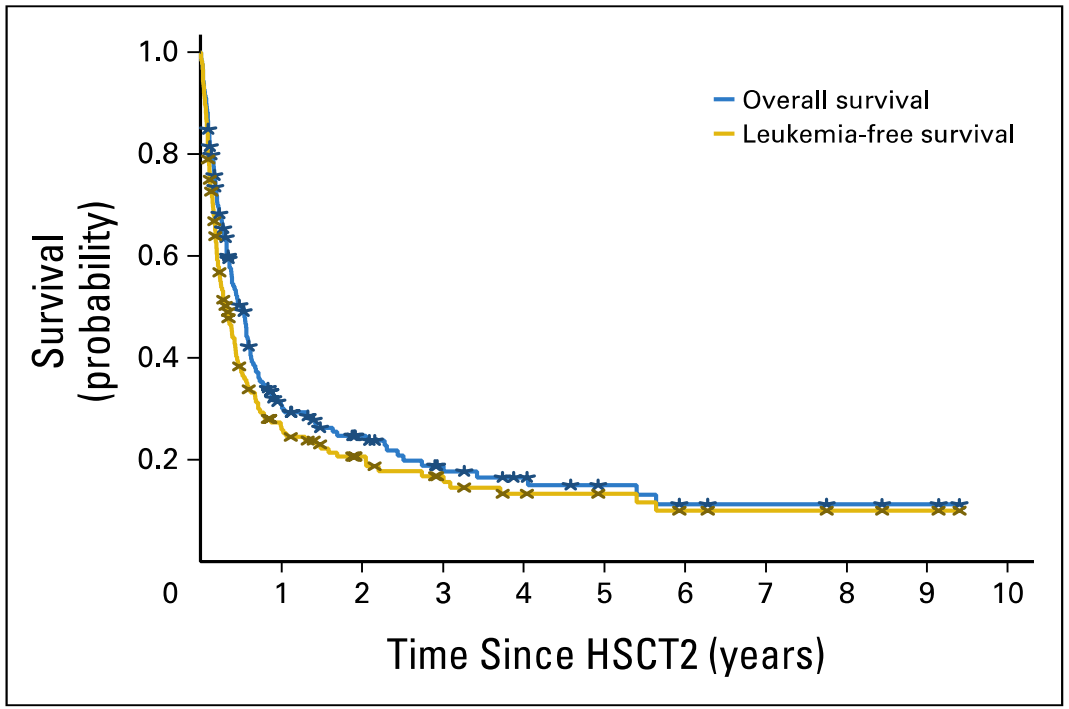


Fig 1. Probabilities of overall survival and leukemia-free survival for the entire cohort (N = 179) were 31% ± 4% and 26% ± 4%, respectively, at 1 year and 25% ± 4% and 21% ± 3%, respectively, at 2 years from second hematopoietic stem-cell transplantation (HSCT2).

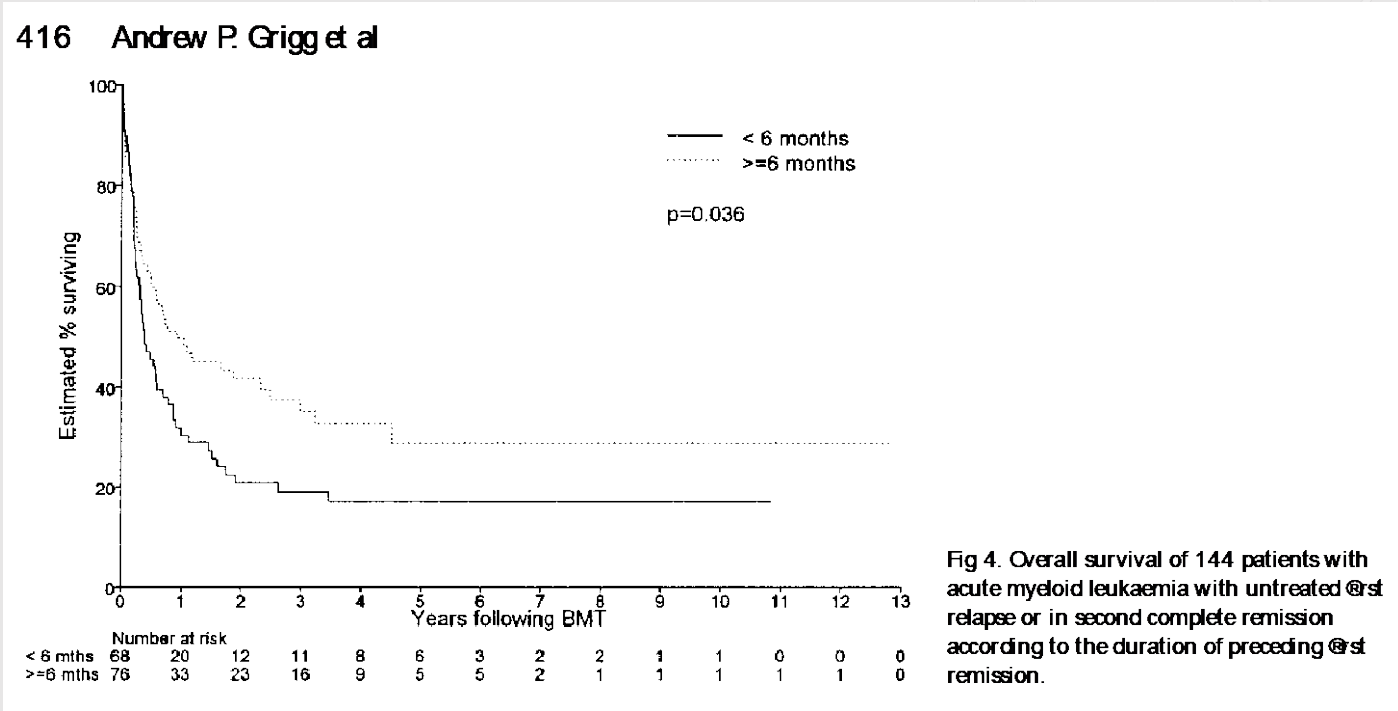


Fig 4. Overall survival of 144 patients with acute myeloid leukaemia with untreated ®rst relapse or in second complete remission according to the duration of preceding ®rst remission.

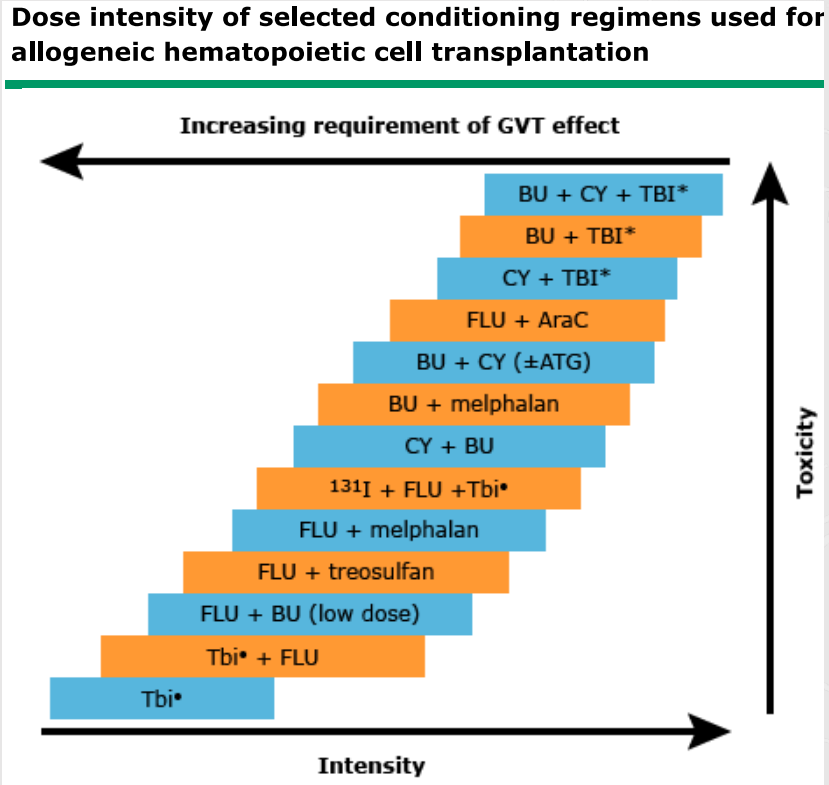
Grigg et al, Br J Haematol 1999
Christopeit, et al. JCO 2013

Patient: Who is fit for Allogeneic transplantation?

Table 1. Selection of patients for transplantation

Good-risk candidates
Young age
No comorbid conditions
No active infections
Lymphohematopoietic disease in remission or responsive to therapy
Good socioeconomic support system
HLA-matched donor
Low risk of posttransplantation relapse
High-risk candidates
Older age
Comorbid conditions present
Refractory/relapsed disease (diagnosis-dependent)
Aggressive prior therapy
High-risk/complex karyotype

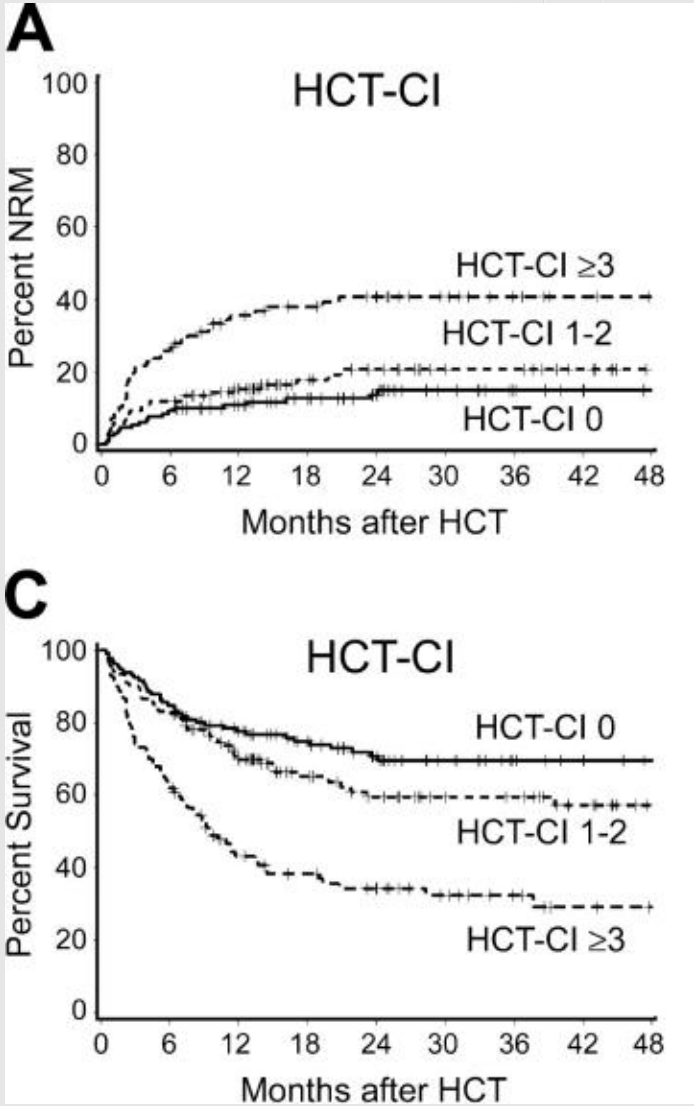
Enhanced access to Allo-HSCT with non-myeloablative conditioning



Deeg et al. Blood 2010

Patient: HCT Comorbidity index

Comorbidity	HCT-CI
Mild pulmonary	Dyspnea on moderate activity or DLco and/or FEV_1 81%-90%
Moderate pulmonary	Dyspnea on slight activity or DLco and/or FEV_1 66%-80%
Severe pulmonary	Dyspnea at rest or requires oxygen or DLco and/or $FEV_1 \leq 65\%$
Cardiac	Includes coronary artery disease,* congestive heart failure, myocardial infarction, or ejection fraction ≤ 50%: one or more acquiring a score of 1
Mild hepatic	Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN
Moderate-severe hepatic	Cirrhosis, fibrosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN
Mild renal	Creatinine 1.2-2 mg/dL
Moderate-severe renal	Creatinine > 2 mg/dL, renal dialysis, or renal transplant
Prior solid tumor	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer

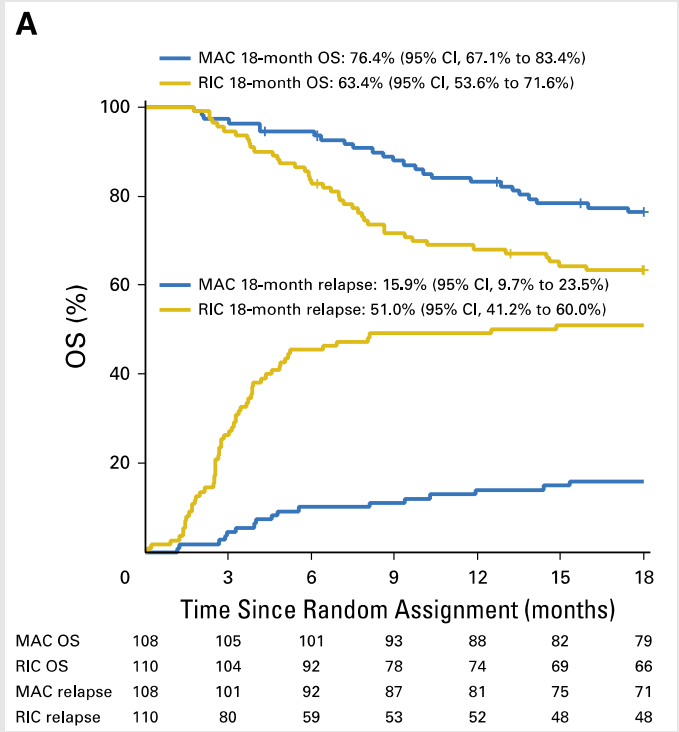


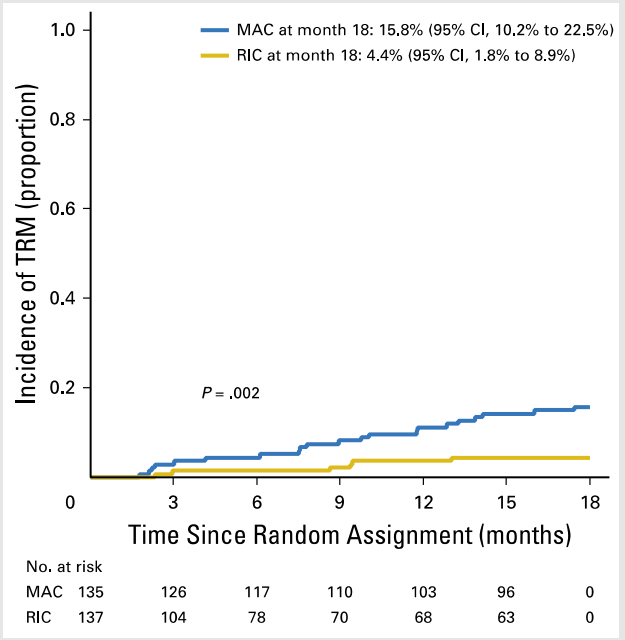
Sorror Blood 2005

Choice of conditioning regimen

Myeloablative Versus Reduced-Intensity Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndromes

Bart L. Scott, Marcelo C. Pasquini, Brent R. Logan, Juan Wu, Steven M. Devine, David L. Porter, Richard T. Maziarz, Erica D. Warlick, Hugo F. Fernandez, Edwin P. Alyea, Mehdi Hamadani, Asad Bashey, Sergio Giralt, Nancy L. Geller, Eric Leifer, Jennifer Le-Rademacher, Adam M. Mendizabal, Mary M. Horowitz, H. Joachim Deeg, and Mitchell E. Horwitz





Randomised data

Caveats:
AML and MDS
Mixed regimens

RIC: Flu/Bu2; Flu/Mel;
MAC: Flu/Cy, Flu/Bu4; CyTBI

Scott et al, JCO 2017

Choice of conditioning regimen – RIC has increased relapse in high risk disease

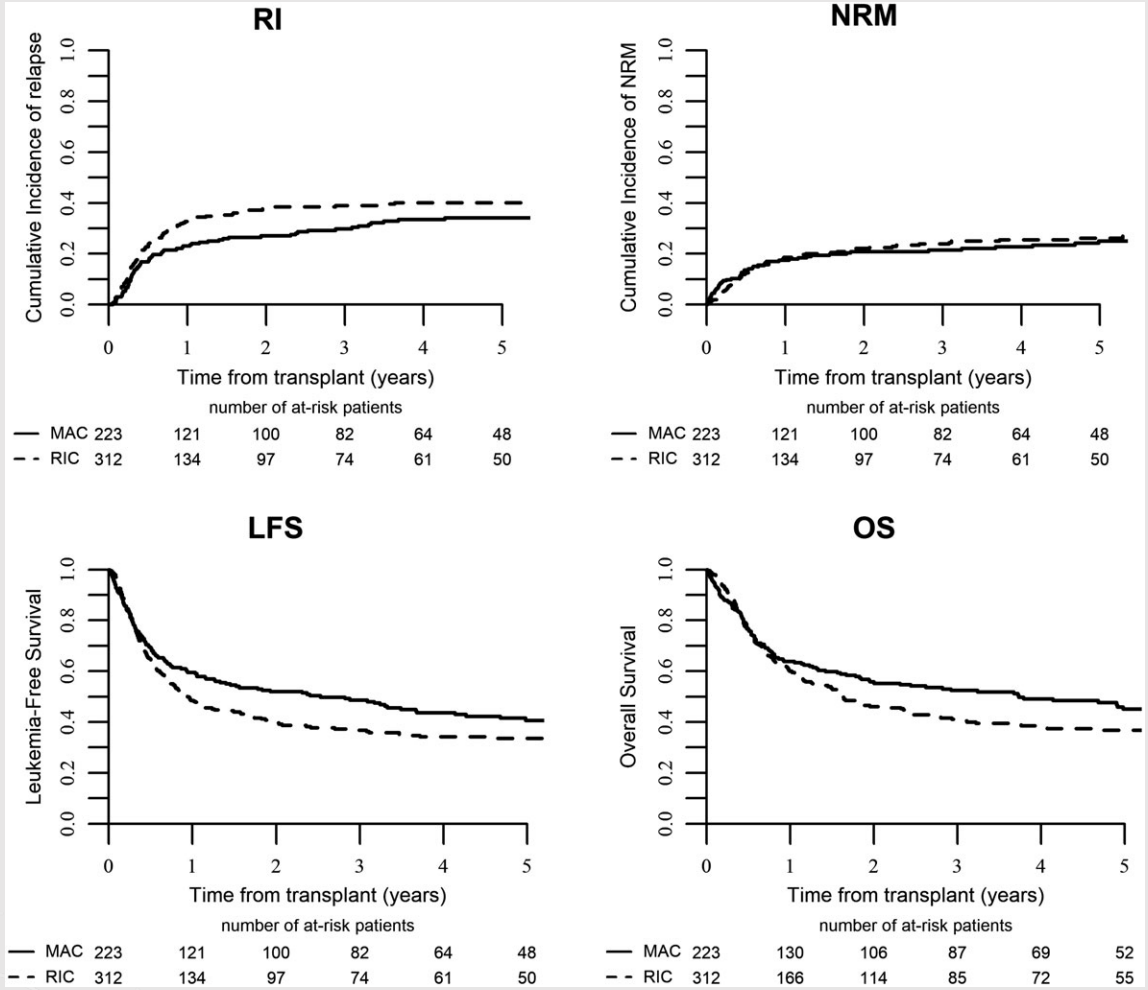


FIGURE 1 Unadjusted cumulative incidence of relapse, NRM, LFS, and OS at 3 years for patients with t-AML receiving a myeloablative or reduced intensity conditioning allogenic HCT

Outcome	Hazard ratio (95% CI)	*P*
NRM		
Conditioning intensity RIC vs MAC	1.49 (0.94-2.37)	0.09
Age (per 10 years)	1.00 (0.82-1.21)	0.98
Cytogenetics Poor vs good	1.01 (0.44-2.35)	0.98
Donor type UD vs MRD	1.91 (1.2-3.05)	0.006
Disease status at transplant Active vs CR1	1.36 (0.82-2.25)	0.24
Donor-recipient sex match Female donor/male recipient	1.99 (1-3.97)	0.05
Relapse		
Conditioning intensity RIC vs MAC	1.52 (1.02-2.26)	0.04
Age (per 10 years)	0.93 (0.79-1.10)	0.39
Cytogenetics Poor vs good	1.87 (0.89-3.91)	0.10
Donor type UD vs MRD	0.59 (0.42-0.84)	0.003
Disease status at transplant Active vs CR1	2.59 (1.79-3.75)	$<10^{-5}$
Time from prior ST to *t*-AML ≤45 months vs >45 months	0.997 (0.994-1)	0.03
LFS		
Conditioning intensity RIC vs MAC	1.52 (1.12–2.05)	0.01
Age (per 10 years)	0.96 (0.84-1.08)	0.47
Cytogenetics Poor vs good	1.46 (0.84-2.53)	0.18
Donor type UD vs MRD	0.93 (0.71-1.22)	0.59
Disease status at transplant Active vs CR1	2.08 (1.55-2.80)	$<10^{-5}$
Time from prior ST to *t*-AML ≤45 months vs >45 months	0.997 (0.995-1)	0.01
OS		
Conditioning intensity RIC vs MAC	1.51 (1.09-2.09)	0.01
Age (per 10 years)	1.01 (0.88-1.15)	0.94
Cytogenetics Poor vs good	1.32 (0.74-2.36)	0.34
Donor type UD vs MRD	1.03 (0.77-1.38)	0.85
Disease status at transplant Active vs CR1	1.98 (1.44-2.71)	2×10^{-05}
Time from prior ST to *t*-AML ≤45 mo vs >45 mo	0.997 (0.995-1)	0.02

Caveats:
Selection bias
Non randomized
Recipient comorbidities

Lee et al. Am J Hematol 2019

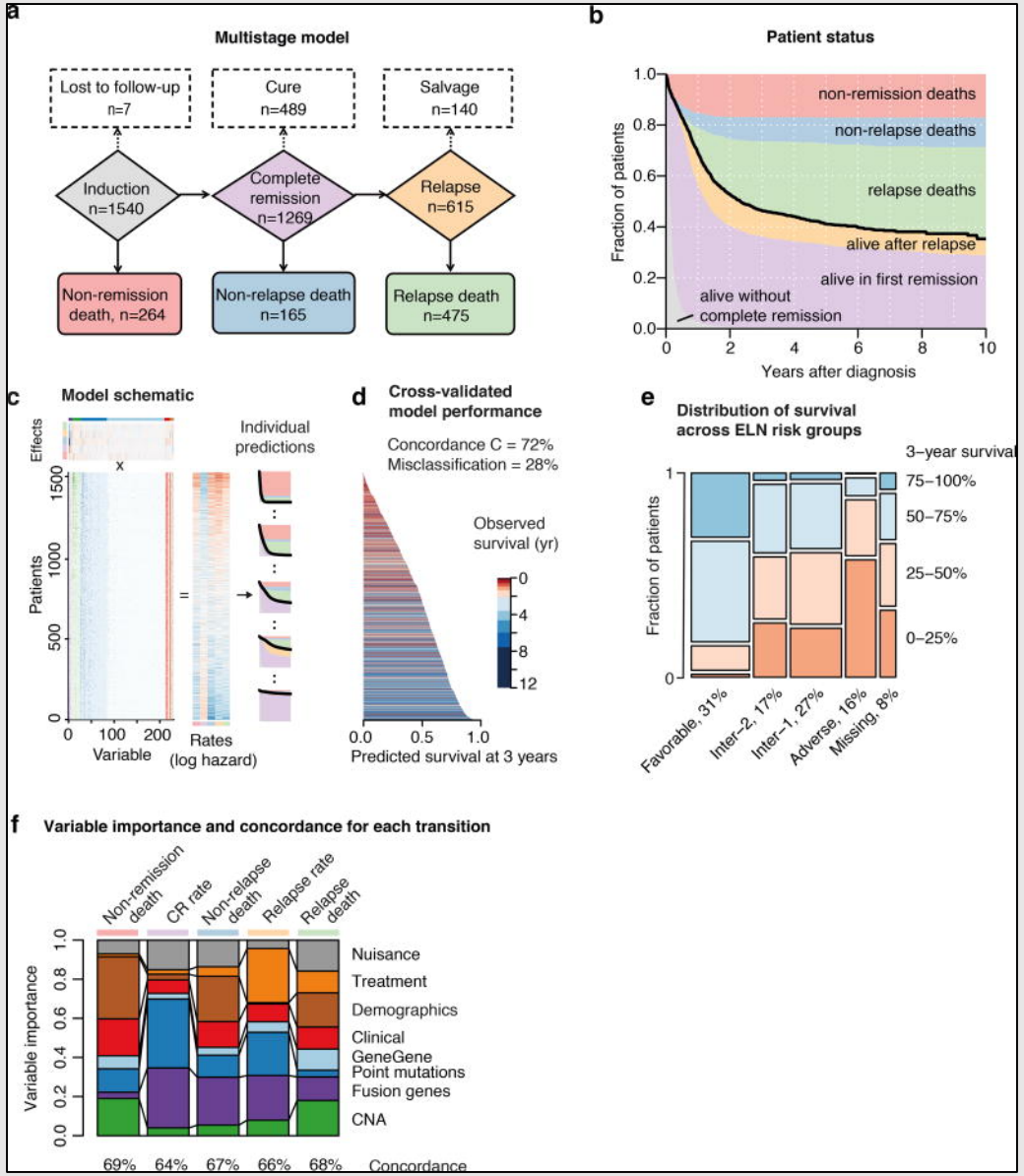
Integrative analysis to provide recommendations for Allo HSCT in CR1

Table 4 | Recommendations for allogeneic HSCT in patients with AML in their first complete remission based on integrated-risk profiles*

AML risk group‡	AML risk assessment§	Risk of relapse following consolidation approach		Prognostic scores for nonrelapse mortality that would indicate allogeneic HSCT as preferred consolidation		
		Chemotherapy or autologous HSCT (%)	Allogeneic HSCT (%)	EBMT score	HCT–CI score	Nonrelapse mortality risk (%)
Good	t(8;21) with WBC ≤20 Inv(16)/t(16;16) Mutated *CEBPA* (double allelic) Mutated NPM1 (No *FLT3*–ITD mutation) Early first complete remission and no MRD	35–40	15–20	NA (≤1)	NA (<1)	10–15
Intermediate	T(8;21) with WBC >20 Cytogenetically normal (or with loss of X and Y chromosomes), WBC count ≤100 and early first complete remission (after first cycle of chemotherapy)	50–55	20–25	≤2	≤2	<20–25
Poor	Otherwise good or intermediate, but no complete remission after first cycle of chemotherapy Cytogenetically normal and WBC >100 Cytogenetically abnormal	70–80	30–40	≤3–4	≤3–4	<30
Very poor	Monosomal karyotype Abn3q26 Enhanced Evi-1 expression	>90	40–50	≤5	≤5	<40

Cornelissen et al. Nat. Rev. Clin. Oncol (2012)

Digital resources to help risk stratify patients for Allo SCT



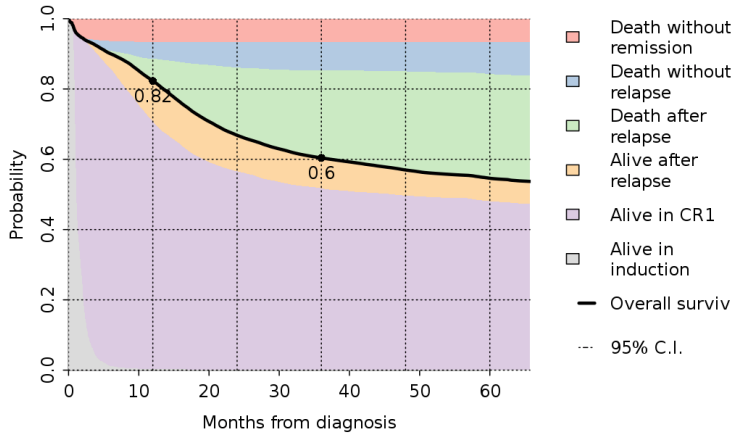
Gerstung et al. Nat Genet 2017

Digital resources to help risk stratify patients for Allo SCT

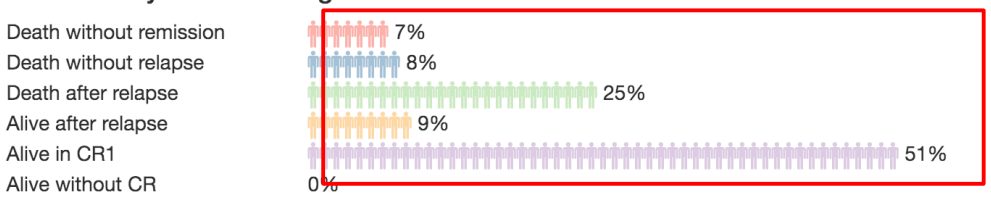
Patient summary

Patient:	50yr old female
Driver mutations:	t(8;21); +8/8q
Blood counts:	80 % Bone marrow blasts, 5 % Peripheral blood blasts, 20 1e-9/l White cell count, 500 units/l Lactic Acid Dehydrogenase, 9 g/dl Hemoglobin, 80 1e-9/l Platelet count
Treatment:	No HSCT

Outcome after diagnosis



Outcome 3 years after diagnosis



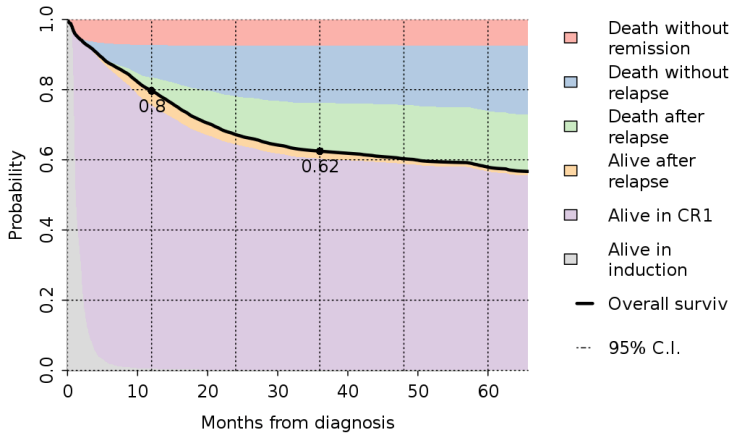
Gerstung et al. Nat Genet 2017

Digital resources to help risk stratify patients for Allo SCT

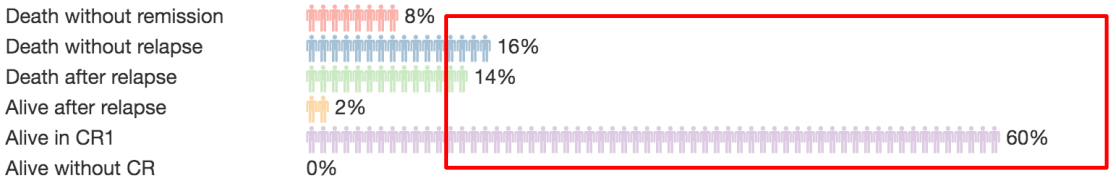
Patient summary

Patient:	50yr old female
Driver mutations:	t(8;21); +8/8q
Blood counts:	80 % Bone marrow blasts, 5 % Peripheral blood blasts, 20 1e-9/l White cell count, 500 units/l Lactic Acid Dehydrogenase, 9 g/dl Hemoglobin, 80 1e-9/l Platelet count
Treatment:	HSCT in CR1

Outcome after diagnosis



Outcome 3 years after diagnosis



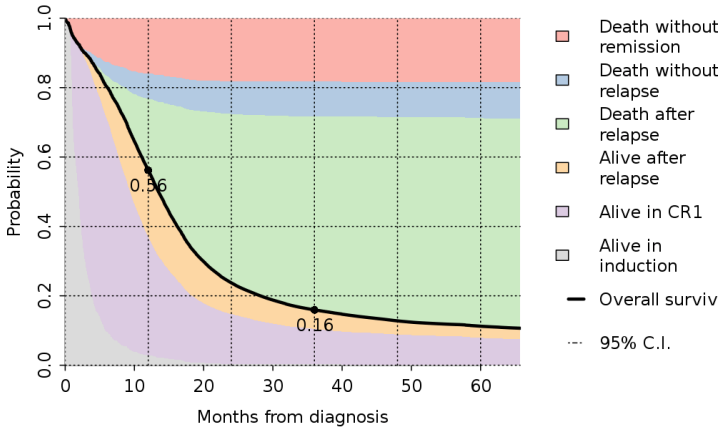
Gerstung et al. Nat Genet 2017

Digital resources to help risk stratify patients for Allo SCT

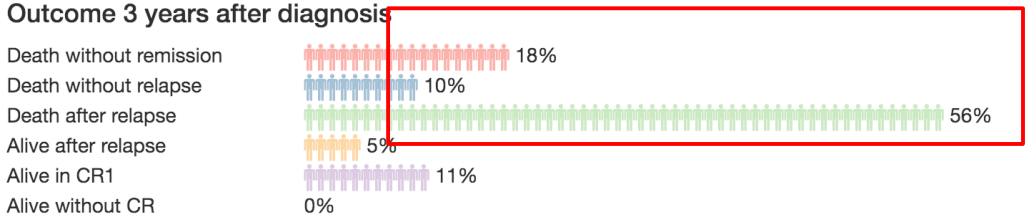
Patient summary

Patient:	30yr old female
Driver mutations:	STAG2, TET2; complex
Blood counts:	100 % Bone marrow blasts, 100 % Peripheral blood blasts, 30 1e-9/l White cell count, 1000 units/l Lactic Acid Dehydrogenase, 10 g/dl Hemoglobin, 45 1e-9/l Platelet count
Treatment:	No HSCT

Outcome after diagnosis



Outcome 3 years after diagnosis



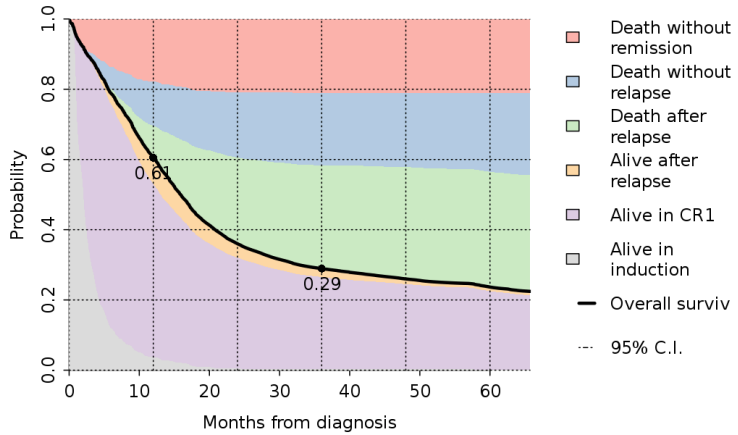
Gerstung et al. Nat Genet 2017

Digital resources to help risk stratify patients for Allo SCT

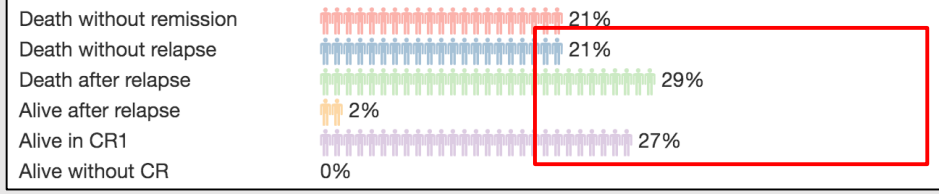
Patient summary

Patient:	30yr old female
Driver mutations:	STAG2, TET2; complex
Blood counts:	100 % Bone marrow blasts, 100 % Peripheral blood blasts, 30 1e-9/l White cell count, 1000 units/l Lactic Acid Dehydrogenase, 10 g/dl Hemoglobin, 45 1e-9/l Platelet count
Treatment:	HSCT in CR1

Outcome after diagnosis



Outcome 3 years after diagnosis



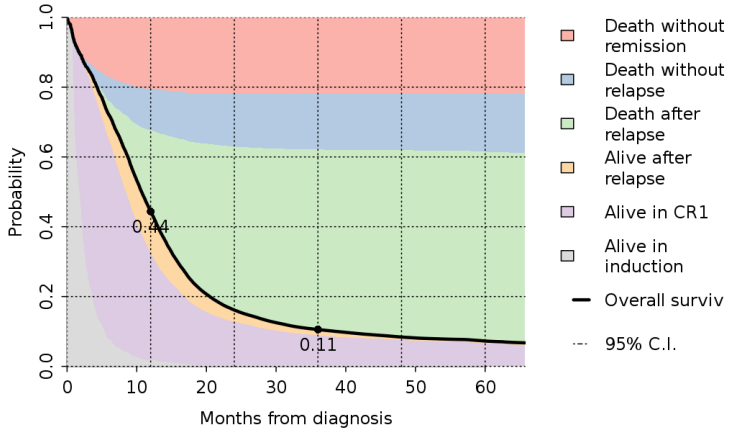
Gerstung et al. Nat Genet 2017

Digital resources to help risk stratify patients for Allo SCT

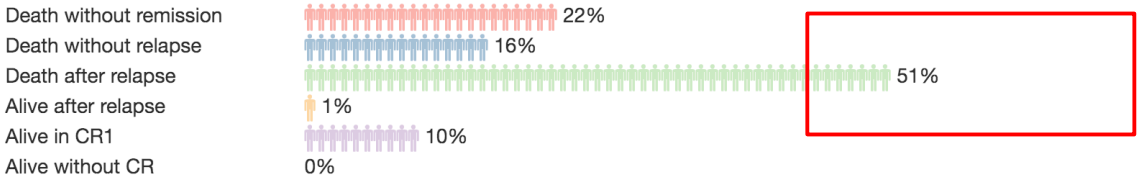
Patient summary

Patient:	68yr old male
Driver mutations:	DNMT3A, NPM1, FLT3 (ITD)
Blood counts:	80 % Bone marrow blasts, 100 % Peripheral blood blasts, 30 1e-9/l White cell count, 500 units/l Lactic Acid Dehydrogenase, 10 g/dl Hemoglobin, 45 1e-9/l Platelet count
Treatment:	No HSCT

Outcome after diagnosis



Outcome 3 years after diagnosis



Gerstung et al. Nat Genet 2017

Digital resources to help risk stratify patients for Allo SCT

Patient summary

Patient:	68yr old male
Driver mutations:	DNMT3A, NPM1, FLT3 (ITD)
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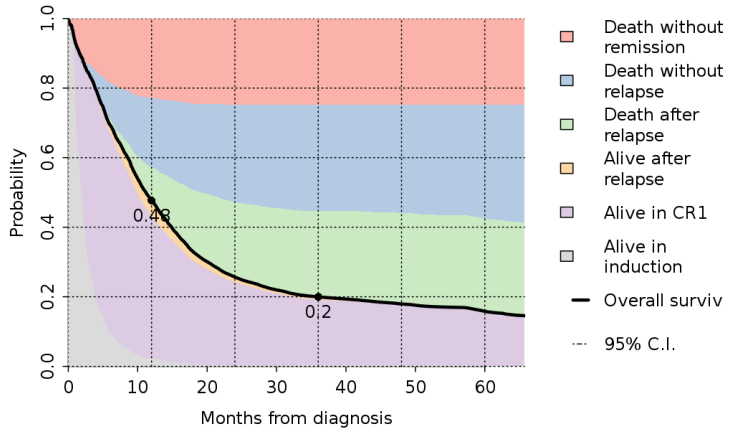
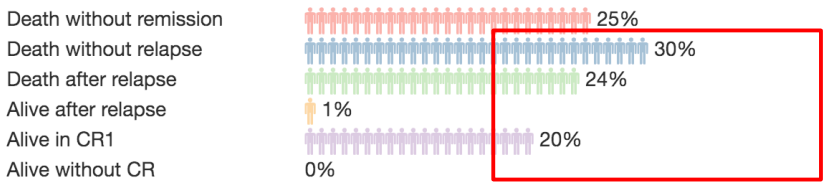
Treatment:	HSCT in CR1

Outcome after diagnosis



Outcome 3 years after diagnosis



Gerstung et al. Nat Genet 2017

Outline of transplantation in AML

- Introduction to AML and genomics
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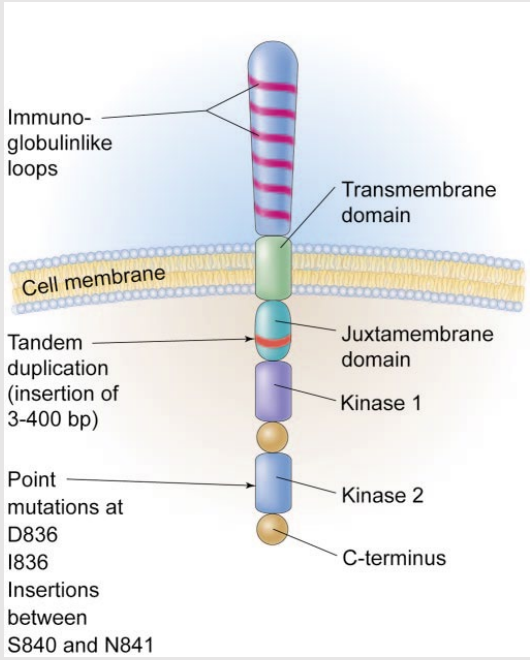
  - **Do we still need to transplant in the age of targeted therapies**
  - **Role of $NPM1^{mut}FLT3ITD^{low}$ in prognosis of AML – should these patients receive AlloSCT**
  - Role of MRD prior to transplantation
  - Strategies for relapse post transplantation

The role of FLT3 in predicting AML prognosis

FLT3^{ITD}

- Tandem duplications in the juxtamembrane (JM) domain
- This interferes with the normal negative regulatory role of JM
- Various length mutations 3-400bp
- Strongly linked to adverse prognosis
- Adverse prognosis may be mitigated with mutated NPM1
- Higher WCC



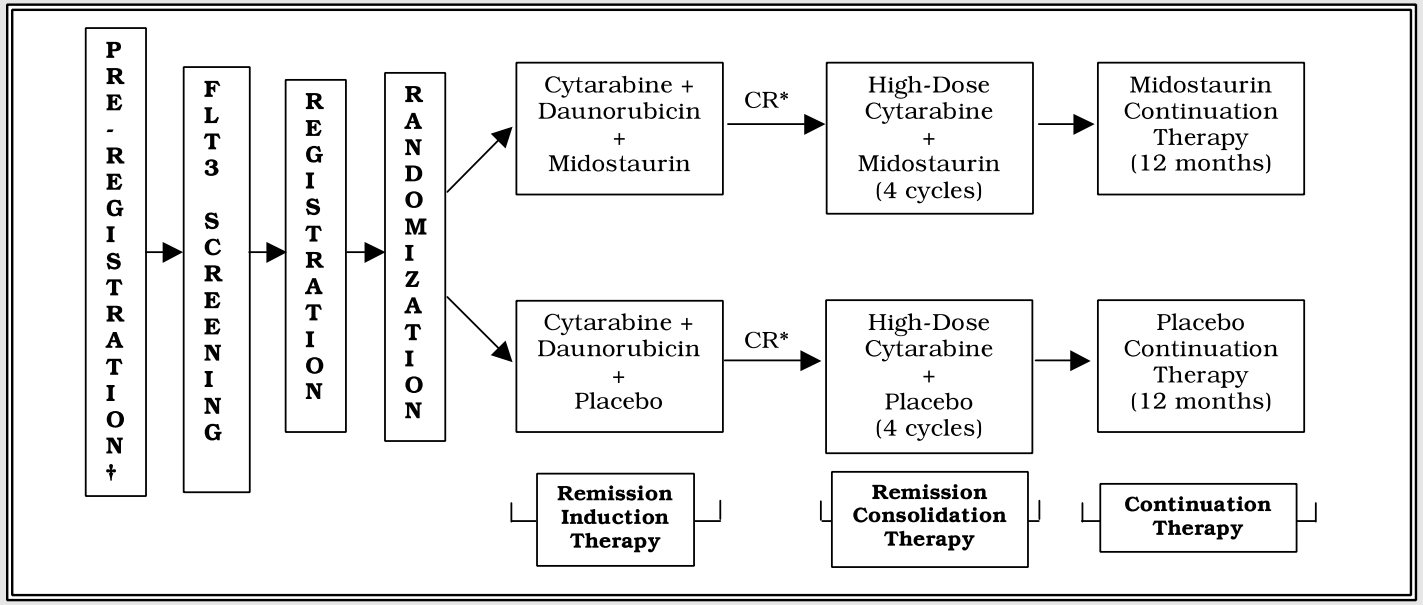
A schematic diagram of the FLT3 receptor tyrosine kinase showing the location of the internal tandem duplication of genes within the juxtamembrane domain and point mutations and gene insertions in the second kinase domain. Illustration by Kenneth Probst.

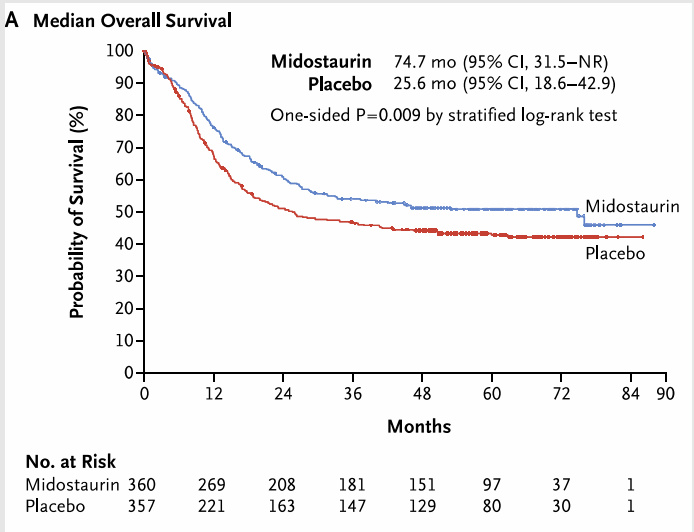
FLT3^{TKD}

- Activating mutations in the intracellular kinase residues
  - Constitutively open ATP binding pocket
- Variable effect on prognosis, negative impact in some series (CBF AML, MLLPTD)
- M5b, M4 and M3v AML
- D835 (89%) and deletions in I836 (10%)
- Frequently lost at time of relapse after chemotherapy (unstable)

Bacher, Schnittger, Blood 2008
Frohling, Dohner, Blood 2002
Litzow, Blood 2005, Pappamanuel, NEJM 2016

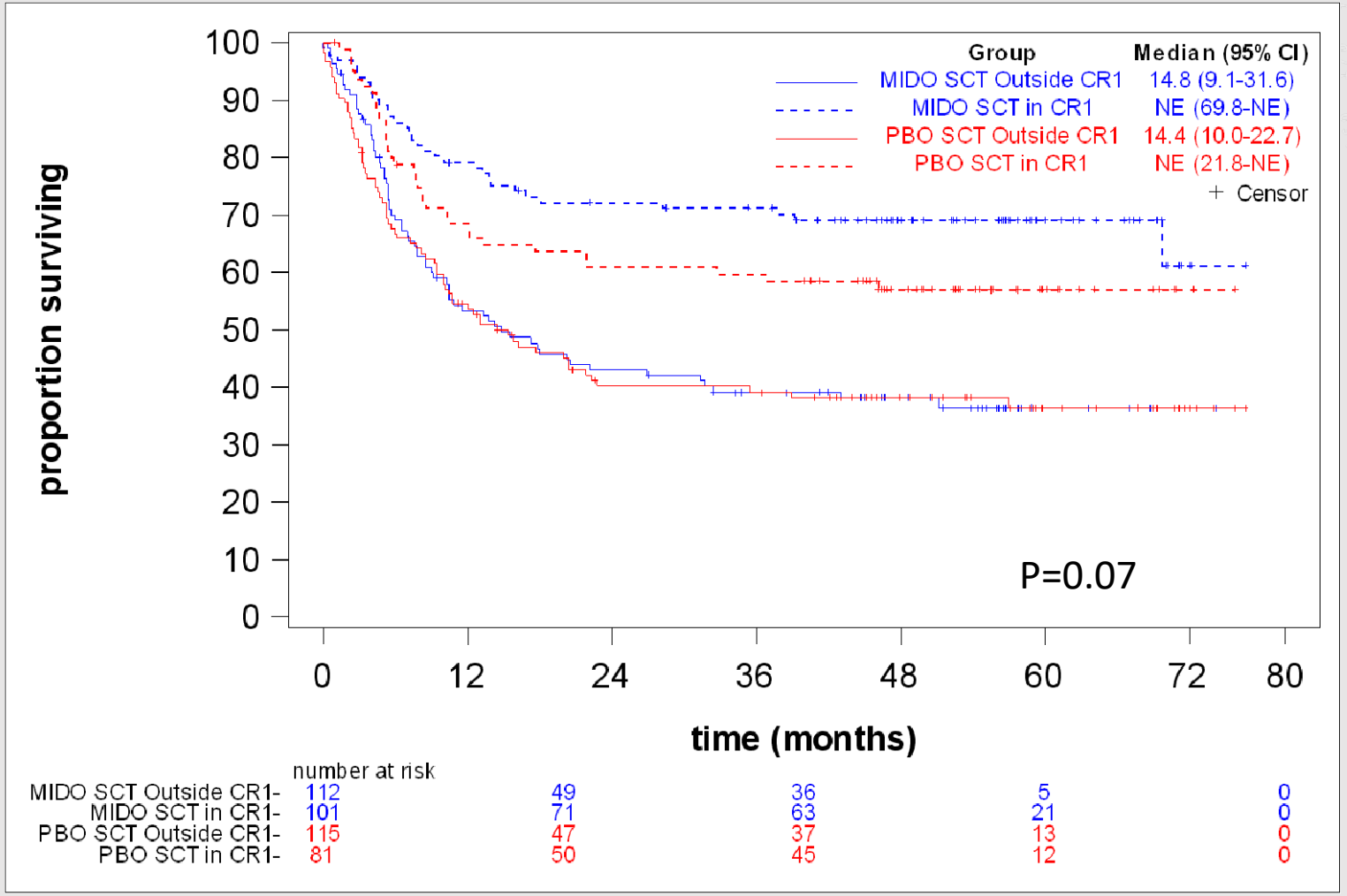
Ratify Study – do we need to transplant in the age of targeted therapy





Stone et al, NEJM 2017

Midostaurine + SCT superior to Placebo + SCT



Stone et al, NEJM 2017

AML is a genetically heterogeneous disease. Relapse and survival after treatment are defined by the tumour genetics

Table 5. 2017 ELN risk stratification by genetics

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Döhner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. 2010;115(3):453-74.

Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2016:blood-2016-08-733196.

Validating the performance of ELN2017

- Aim: to evaluate the performance of ELN2017 in predicting AML prognosis after chemotherapy
- Insufficient patient numbers within Australia to answer these highly relevant genomic questions
  - ~800 Australians are diagnosed with AML each year with heterogeneous treatment regimens
  - ALLG AML M12 trial recruited 442 patients over 7 years

Papaemmanuil et al. 2016, *NEJM*; Cancer Genome Atlas Research Network, 2013, *NEJM*; Farrar et al. 2016, *Cancer Research; ALLG Annual Report 2010*

- Large international consortia have published datasets with genetic information and clinical annotation
- Identified datasets totalling 2409 patients with

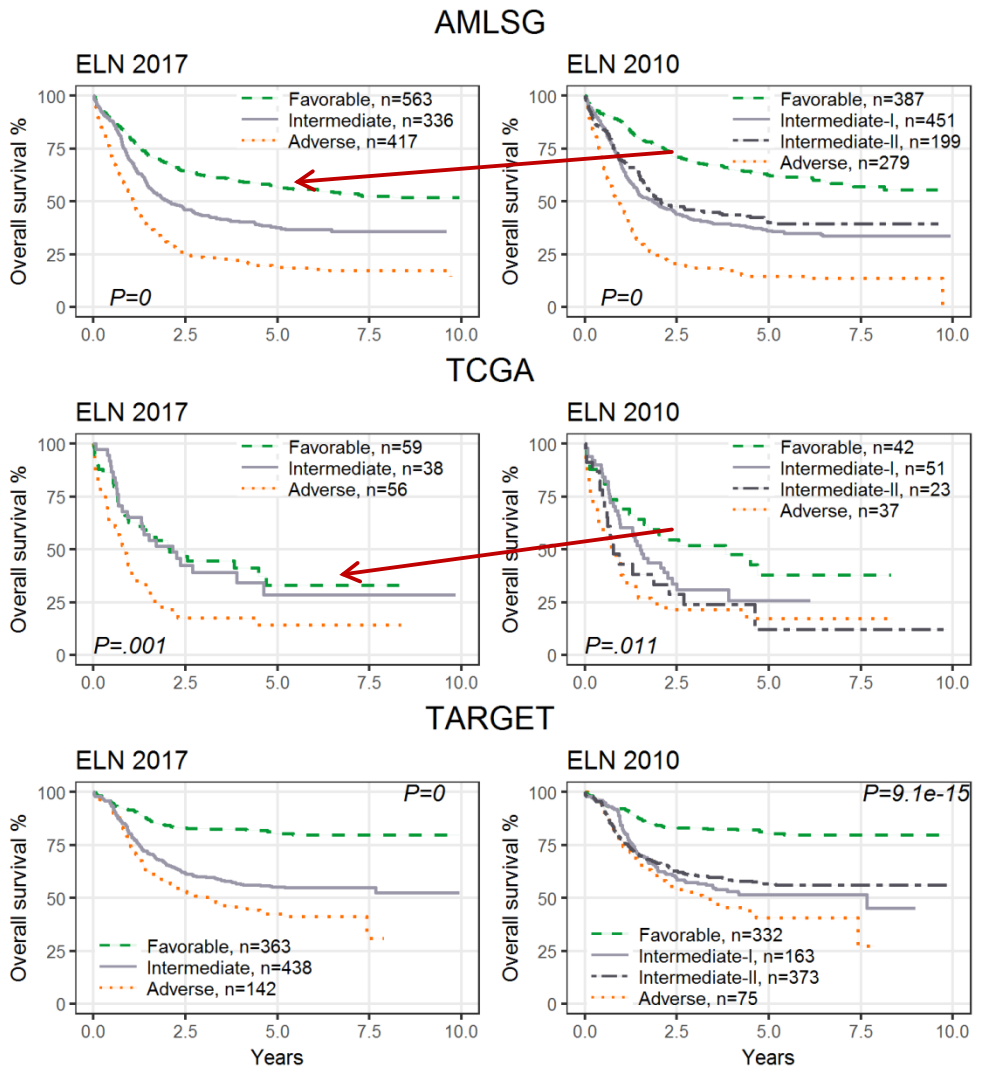
  comprehensive clinical and genomic information

Jasmin Straube

AMLSG	TCGA	TARGET
n=1316	n=150	n=943
Age 18-80	Age 21-82	(paediatric) Age 2-29

Papaemmanuil et al. 2016, *NEJM*; Cancer Genome Atlas Research Network, 2013, *NEJM*;
Farrar et al. 2016, *Cancer Research; ALLG Annual Report 2010*

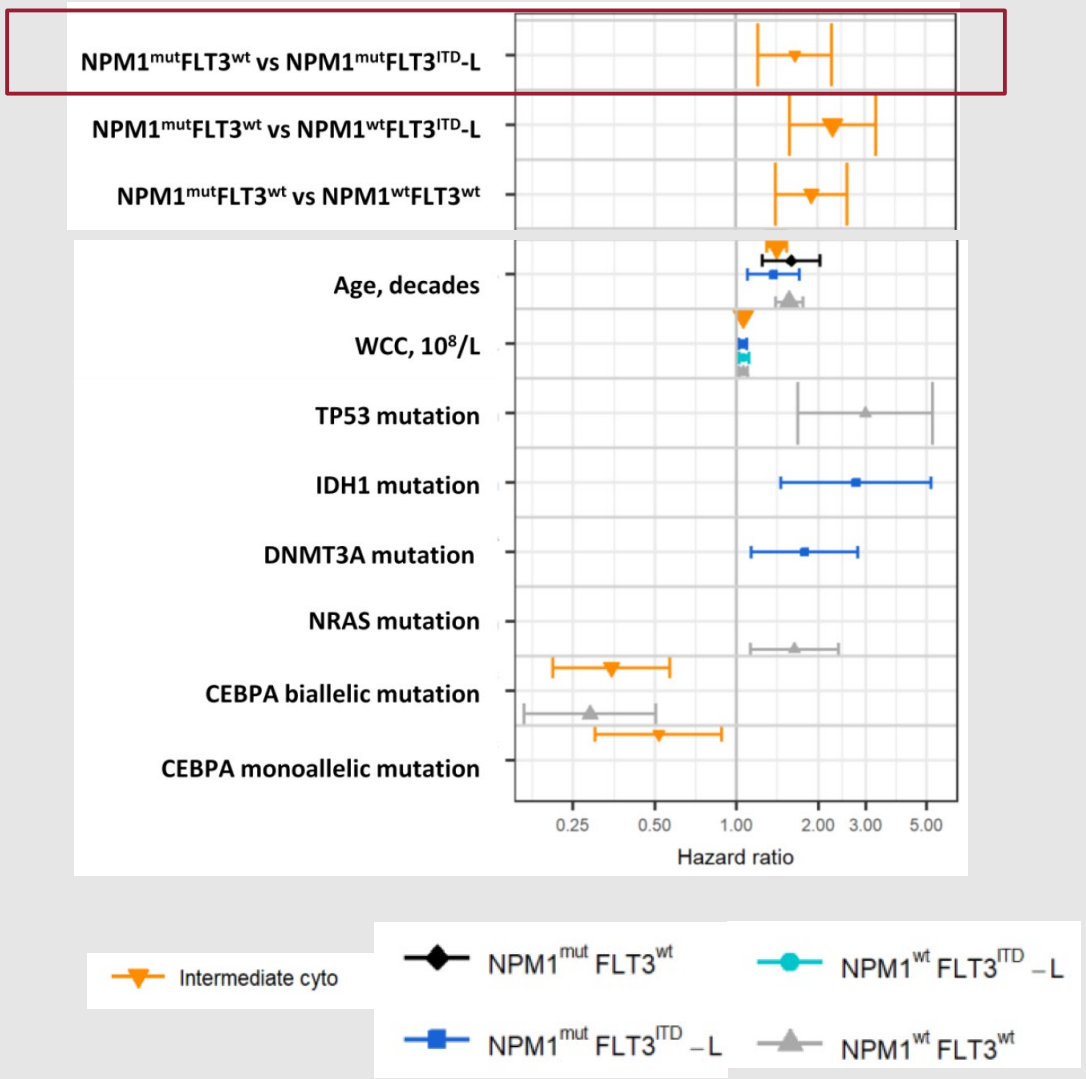
ELN2017 is able to identify prognostic groups in AML cohorts



Favourable/ Intermediate/ Adverse

- ELN 2017 and ELN 2010 identified clinically relevant prognostic groups
- Inferior outcomes are seen in TCGA compared to AMLSG
  - median age 59 vs 50 years
- For adult cohorts, the favourable group had inferior outcomes in ELN2017 compared to ELN2010
  - AMLSG 6% reduction
  - TCGA 5% reduction
- 2017 favourable risk includes $NPM1^{mut}FLT3^{ITD}$–L patients
- Paediatric AML has relatively favourable outcome

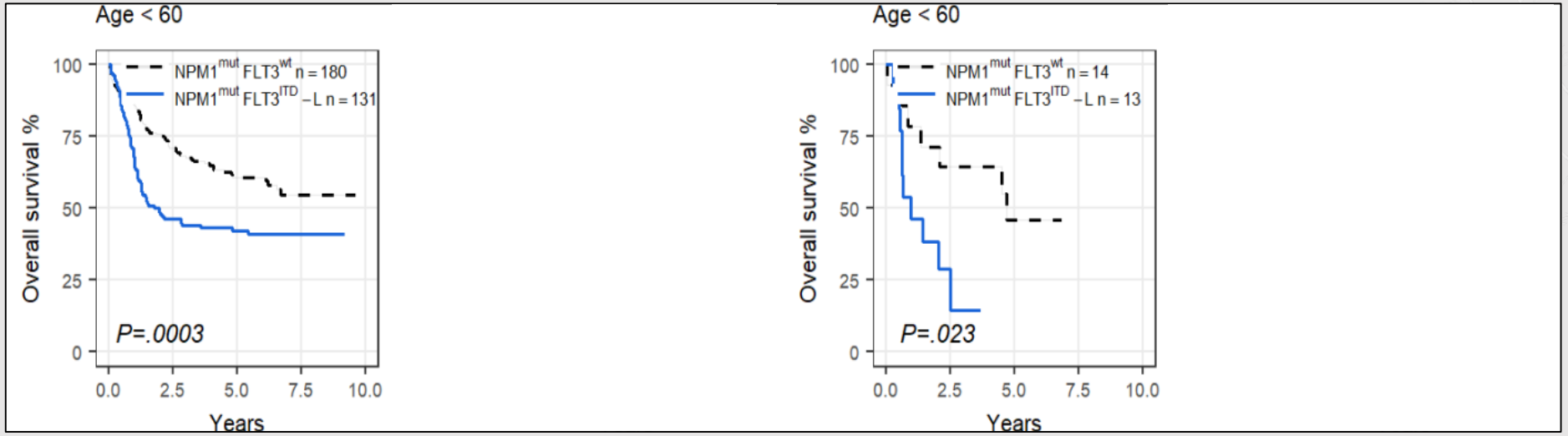
MULTIVARIATE ANALYSIS CONFIRMS ADVERSE PROGNOSIS OF FLT3^{ITD}-L IN NPM1^{MUT} AML



- Adverse prognosis with FLT3^{ITD}-L in NPM1^{mut} AML
  - HR 1.7 (95% CI 1.2-2.3)
- Other key prognostic factors in NPM1^{mut} AML
- Age
- WCC
- Other mutations: DNMT3A, IDH1

Age interacts with NPM1^{mut} and FLT3^{ITD}-L to predict survival

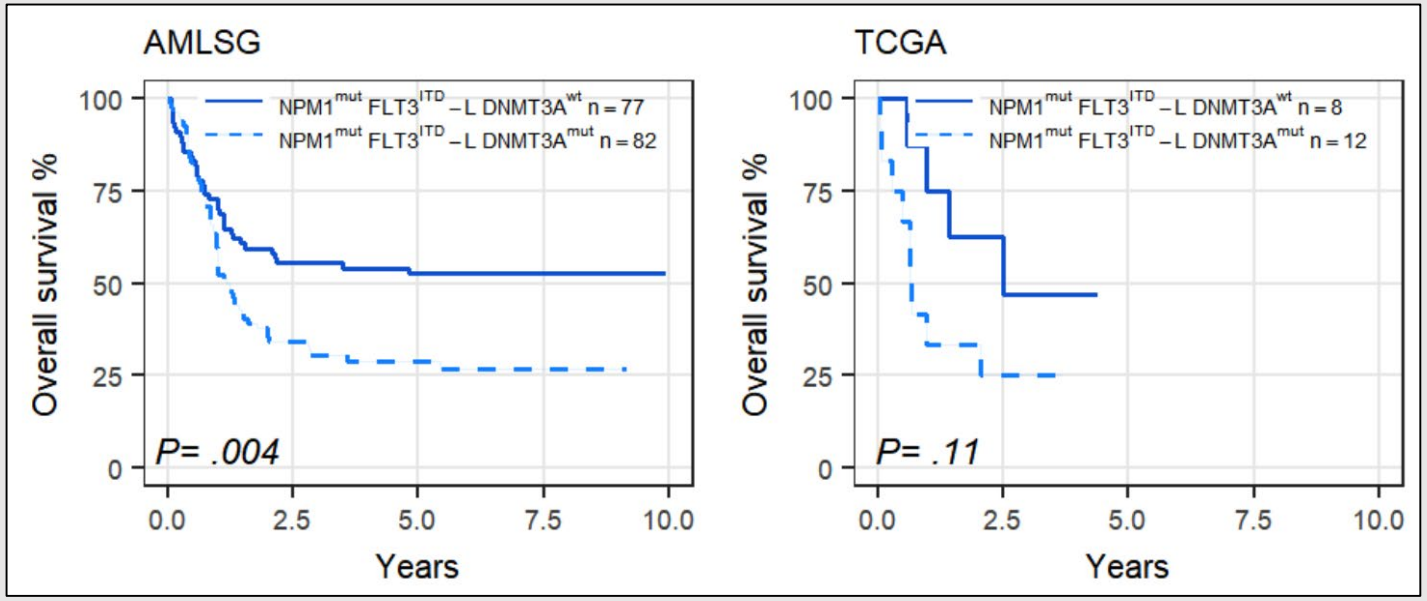
AMLSG



TCGA

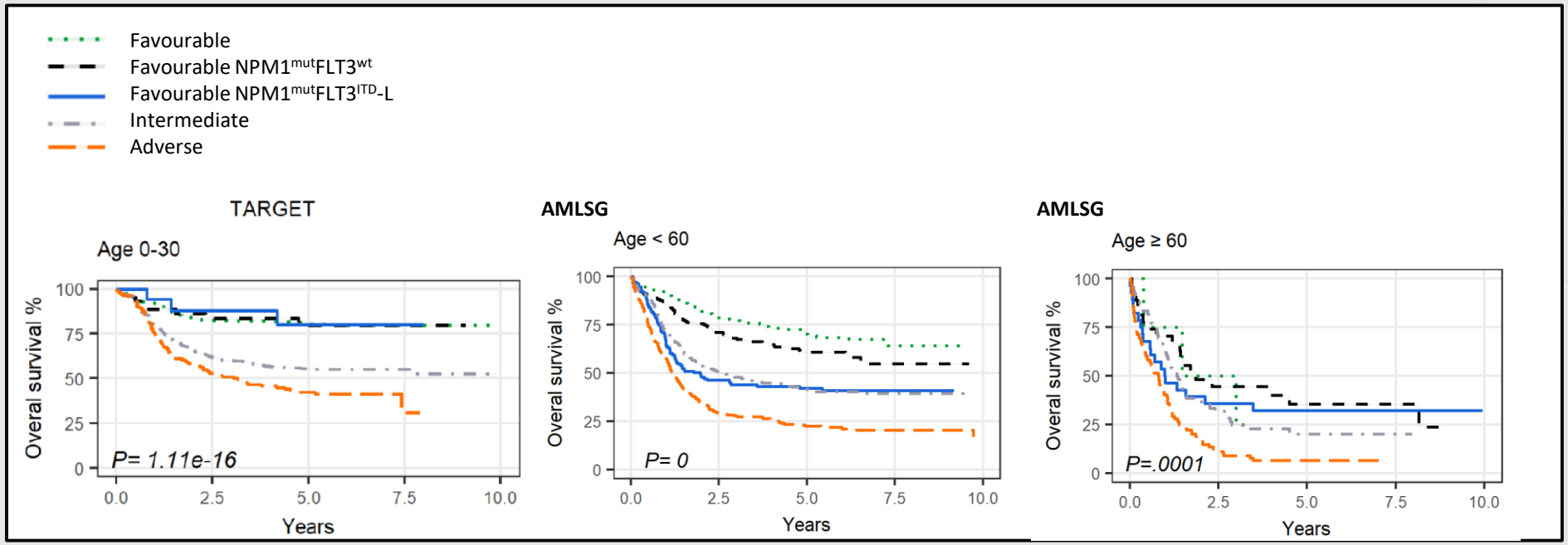
- Dominant effect of age on prognosis in AML
- Absence of a favourable prognostic group in patients >60 yrs

DNMT3A mutation stratifies survival in NPM1^{mut}FLT3^{ITD}-L AML



- Comprehensive molecular genotyping will be essential to develop and apply prognostic algorithms in individuals

Context dependent clinical utility of ELN2017 in AML



- Context dependent clinical utility of ELN 2017 in adult and paediatric AML
- Age is a dominant clinical risk factor
- There is no favourable risk subgroup in elderly patients with AML
- DNMT3A mutations are potent risk modifying alleles

The impact of age, NPM1^{mut}, and FLT3^{ITD} allelic ratio in patients with acute myeloid leukemia

Jasmin Straube,[1] Victoria Y. Ling,[1] Geoffrey R. Hill,[1-3] and Steven W. Lane[1-3]

[1]QIMR Berghofer Medical Research Institute, Herston, QLD, Australia; [2]School of Medicine, University of Queensland, Brisbane, QLD, Australia; and [3]Department of Haematology, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia

Straube, et al. Blood 2018

Absence of a favourable outcome in elderly AML

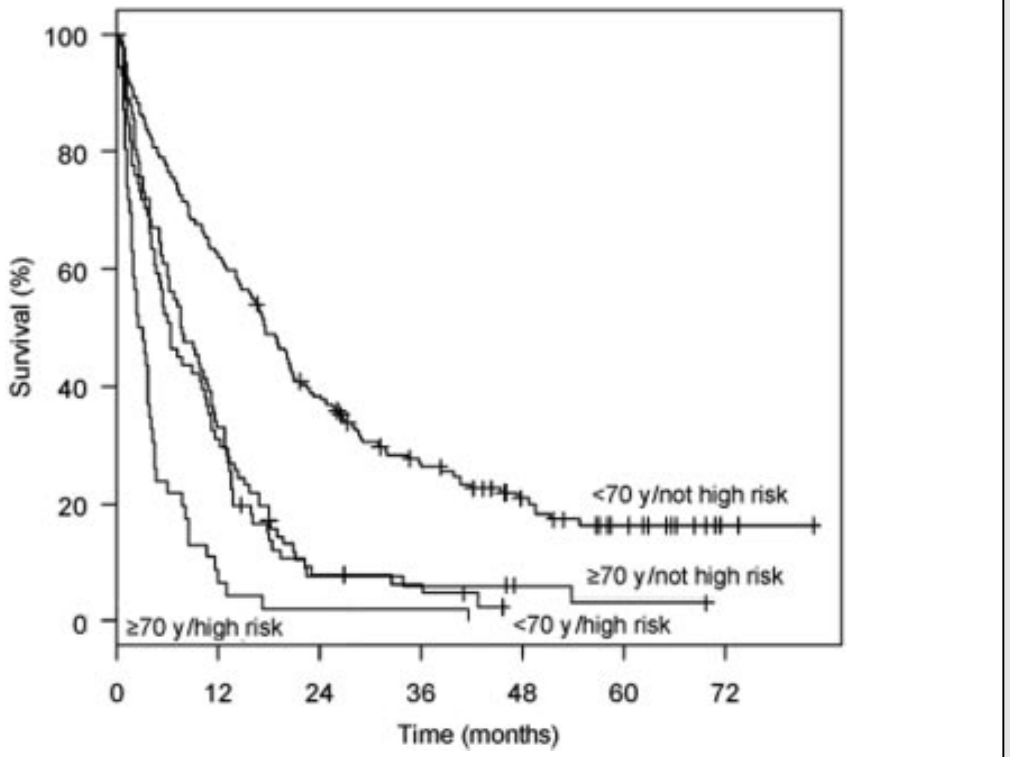


Figure 3. OS based on cytogenetic stratification system and age. OS of 361

- Only patients eligible for intensive induction chemotherapy

Fröhling et al. Blood 2006

Outline of transplantation in AML

- Introduction to AML and genomics
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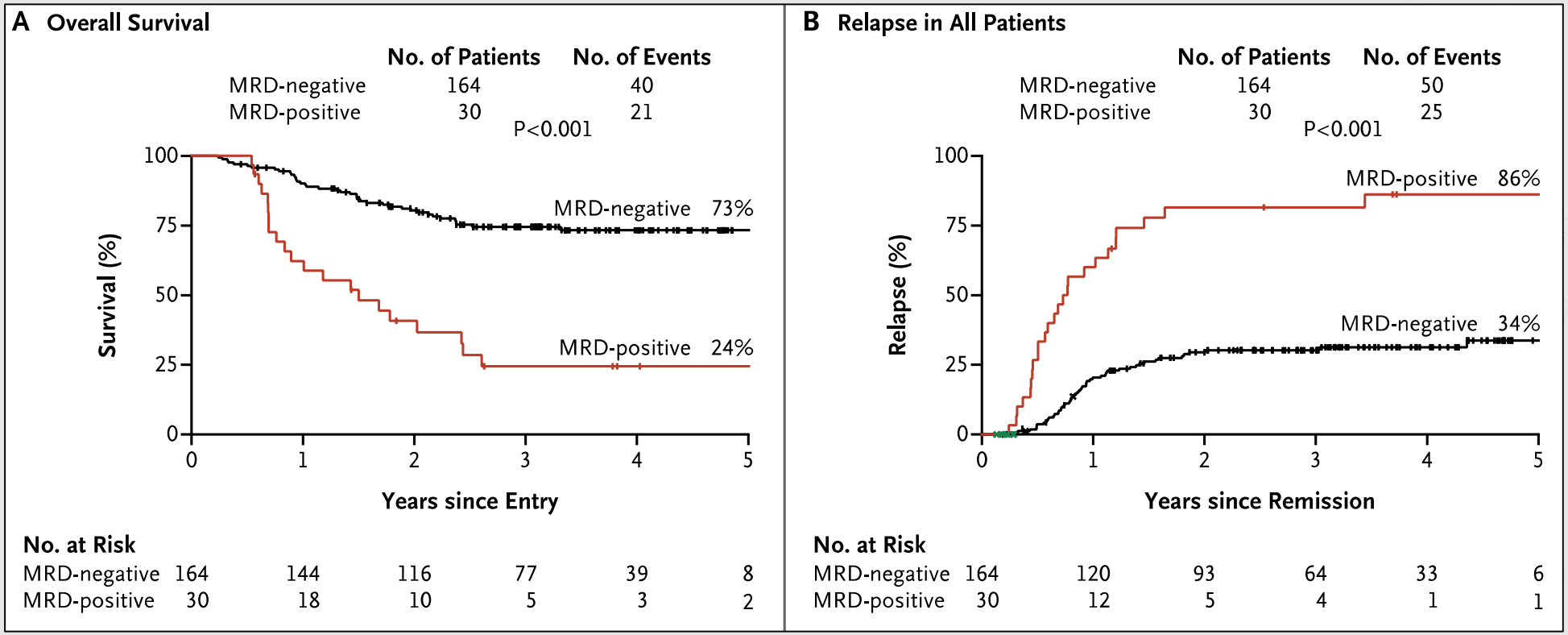
  - Do we still need to transplant in the age of targeted therapies
  - Role of $NPM1^{mut}FLT3ITD^{low}$ in prognosis of AML – should these patients receive AlloSCT
  - **Role of MRD prior to transplantation**
  - Strategies for relapse post transplantation

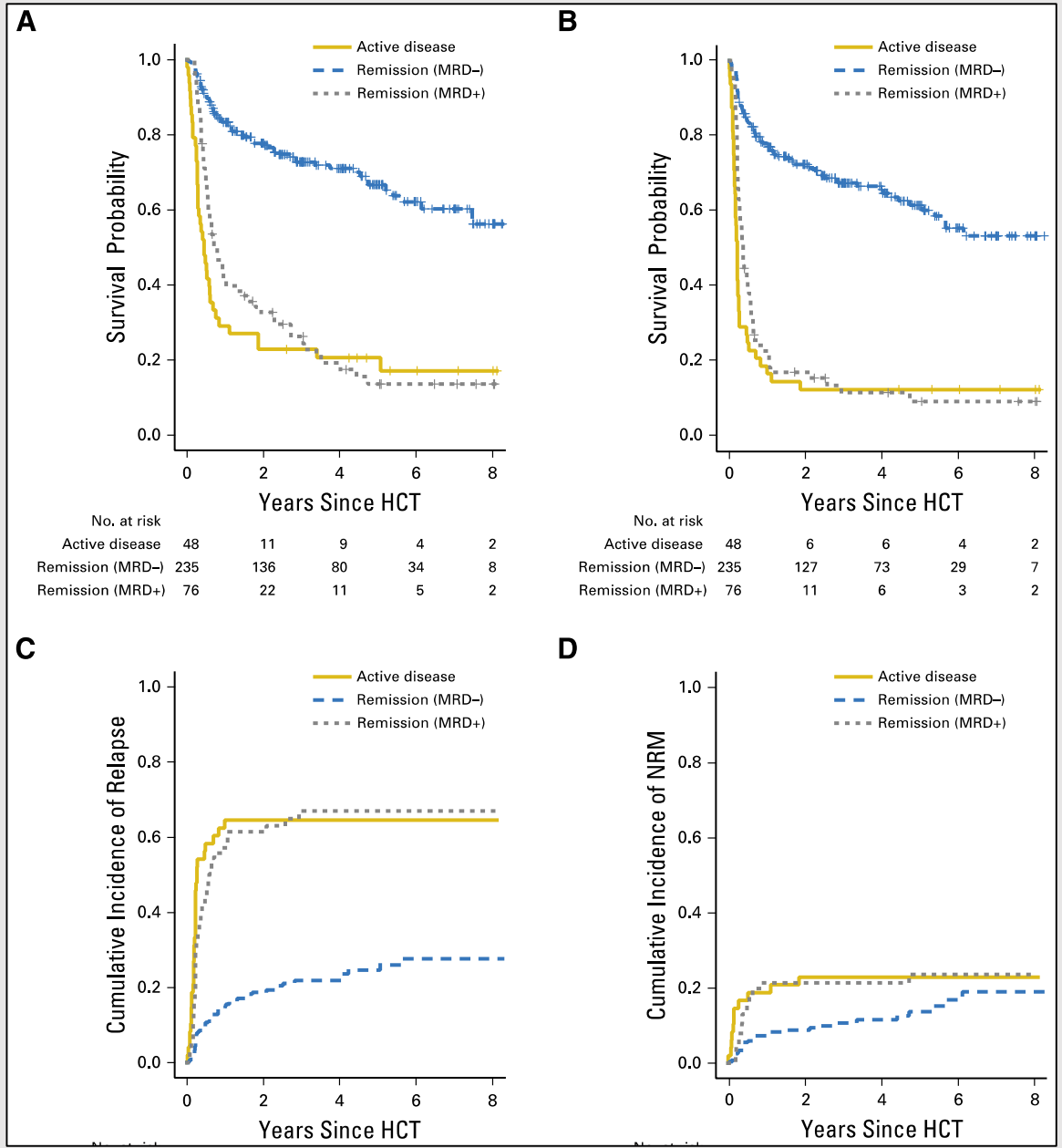
Molecular positive post chemotherapy predicts relapse in AML



Note – this holds true for other AML
MRD positive predicts relapse in CBF AML
Lane, et al. Leuk Lymphoma 2008
Carbacioglu, et al. J Clin Oncol 2010

Ivey, et al. NEJM 2016

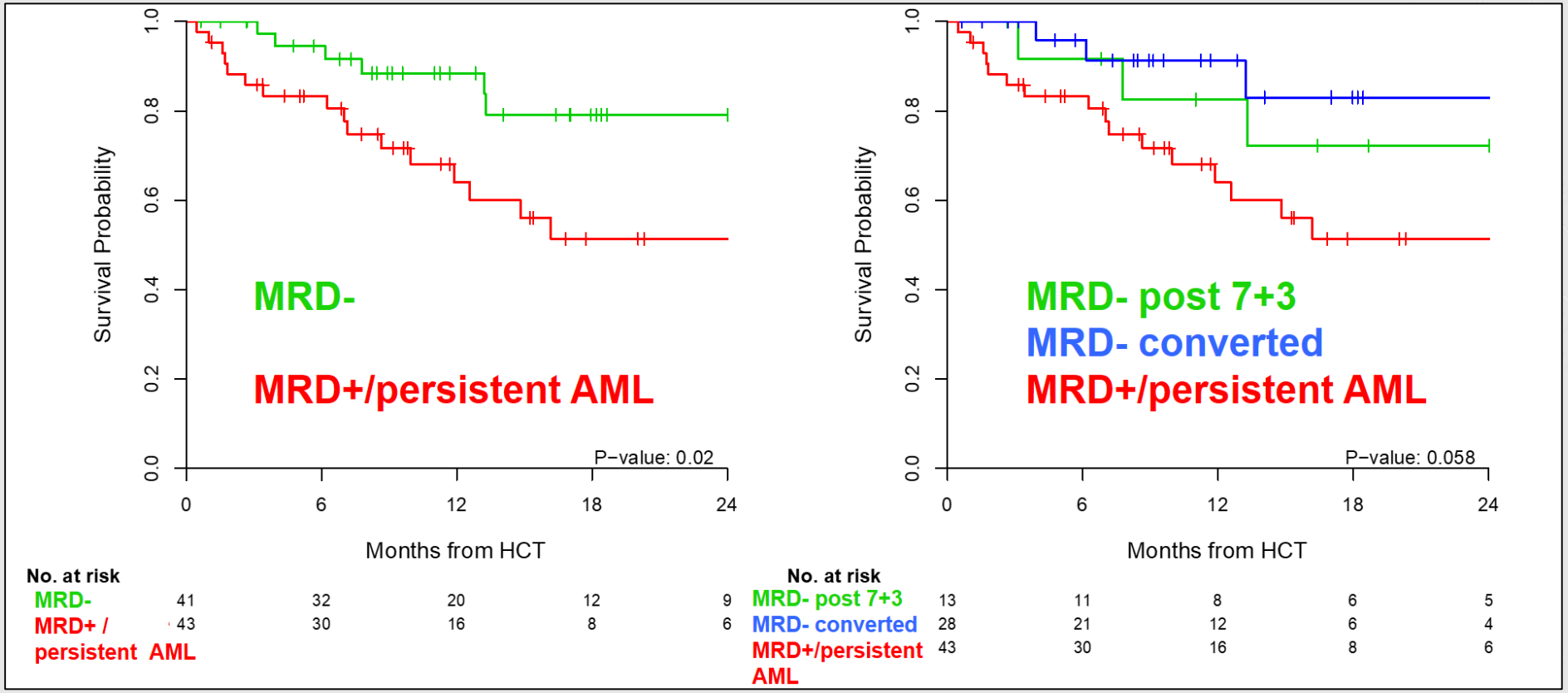
The role of MRD prior to Allo HSCT



Multicolour flow
Sensitivity 0.1% approx

Araki, JCO 2016

NGS based MRD prior to Allo HSCT



Specific mutations were more likely to be positive (RUNX1, SF3B1, TP53).

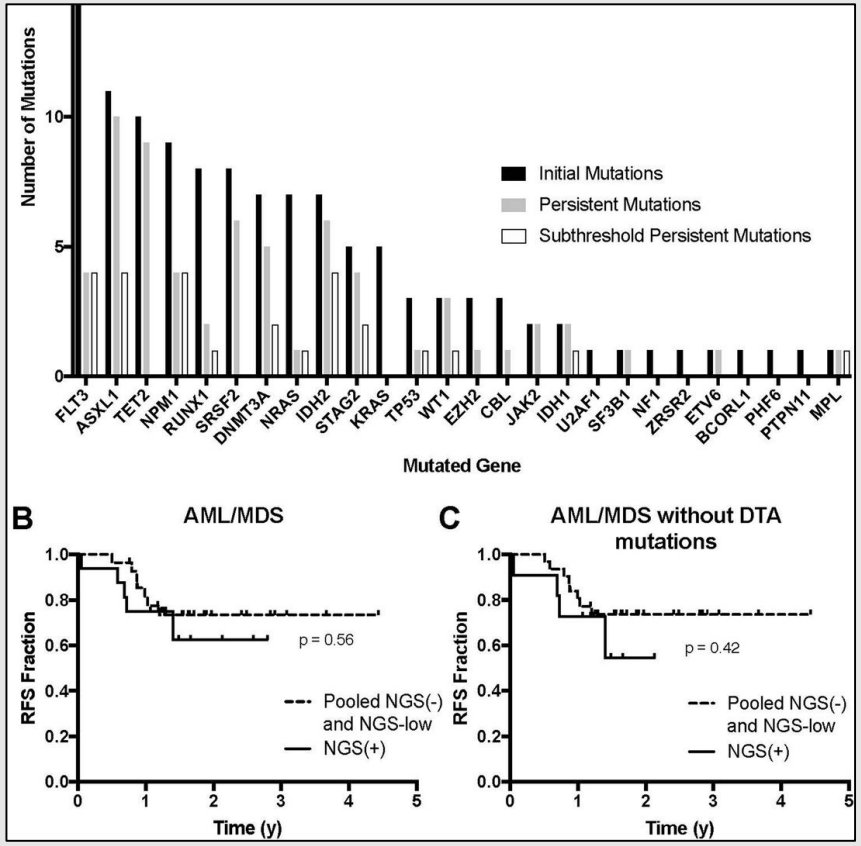
It did not matter how long it took to become MRD negative

Molecular Predictors and Current Management of Minimal Residual Disease (MRD) Following Induction Chemotherapy for Acute Myeloid Leukemia (AML)

Aaron D Goldberg, Christopher Famulare, Sean M Devlin, Noushin Farnoud, Kamal Menghrajani, Minal Patel, Sheng Cai, Andrew Dunbar, Zachary D. Epstein-Peterson, Erin McGovern, Jessica Schulman, Jacob L Glass, Justin Taylor, Aaron D Viny, Bartlomiej Getta, Maria E Arcila, Ross L. Levine, Brian C. Shaffer, Boglarka Gyurkocza, Esperanza B. Papadopoulos, Miguel-Angel Perales, Elli Papaemmanuil, Sergio Giralt, Yanming Zhang, Mikhail Roshal, and Martin S. Tallman

Blood 2018 132:292; doi: https://doi.org/10.1182/blood-2018-99-112938

The role of MRD prior to Allo HSCT

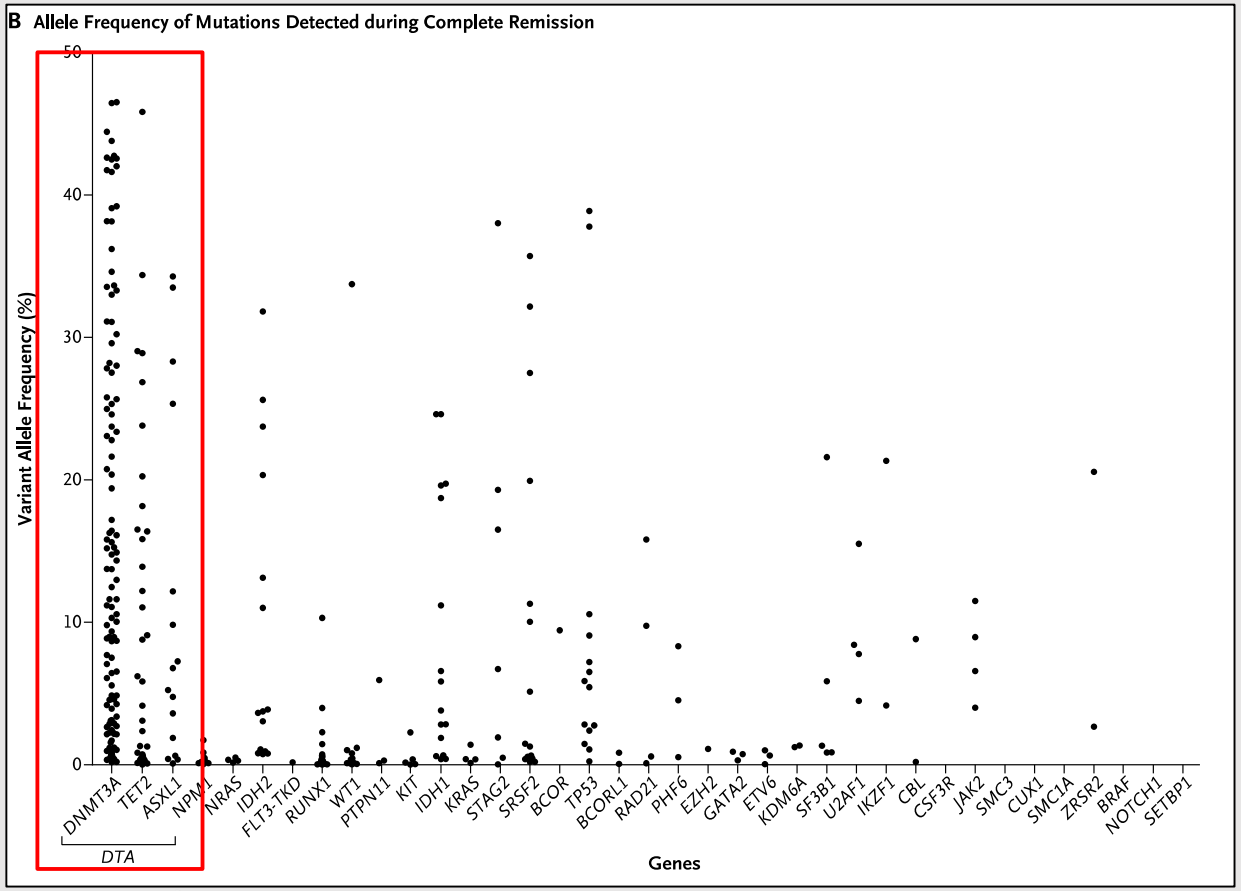


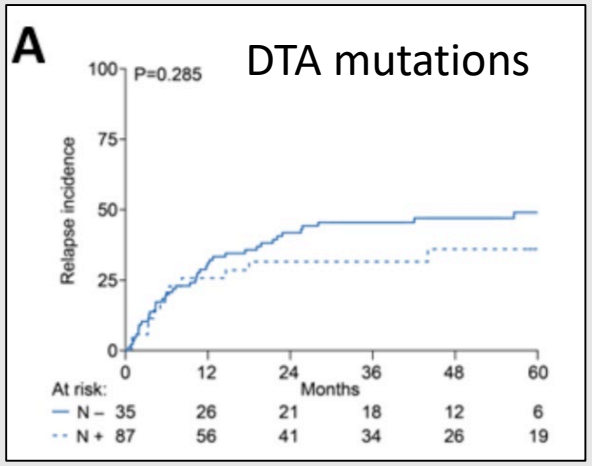
Outcomes of Allogeneic Stem Cell Transplantation for AML and MDS Based on Pre-Transplant MRD Status By Next-Generation Sequencing

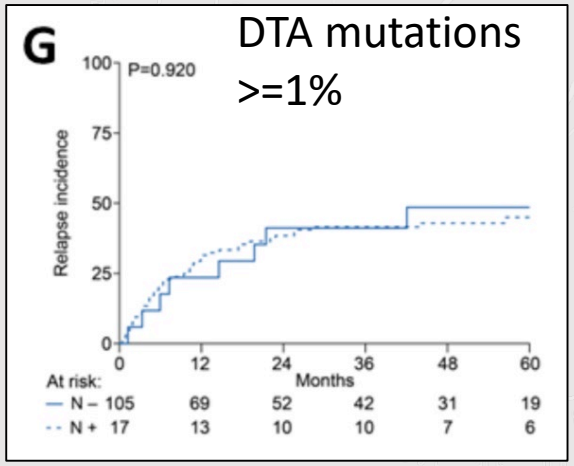
Benjamin M Manning, Robyn T Sussman, Safoora Deihimi, Noelle V. Frey, Elizabeth O. Hexner, Alison W. Loren, Selina Luger, James K. Mangan, Mary Ellen Martin, Shannon R. McCurdy, Jennifer J.D. Morrissette, Alexander E. Perl, Edward A. Stadtmauer, David L. Porter, and Saar I. Gill

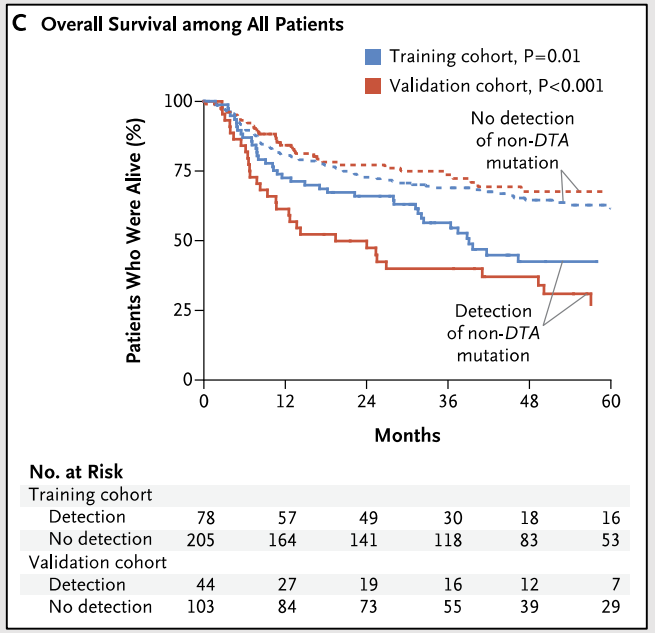
Blood 2018 132:2134; doi: https://doi.org/10.1182/blood-2018-99-117410

Detection of MRD and relapse after chemotherapy – not all MRD is equal









Non-DTA mutations

Jongen-Lavrencic NEJM 2018

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Immunological mechanism of relapse after Allo-HSCT

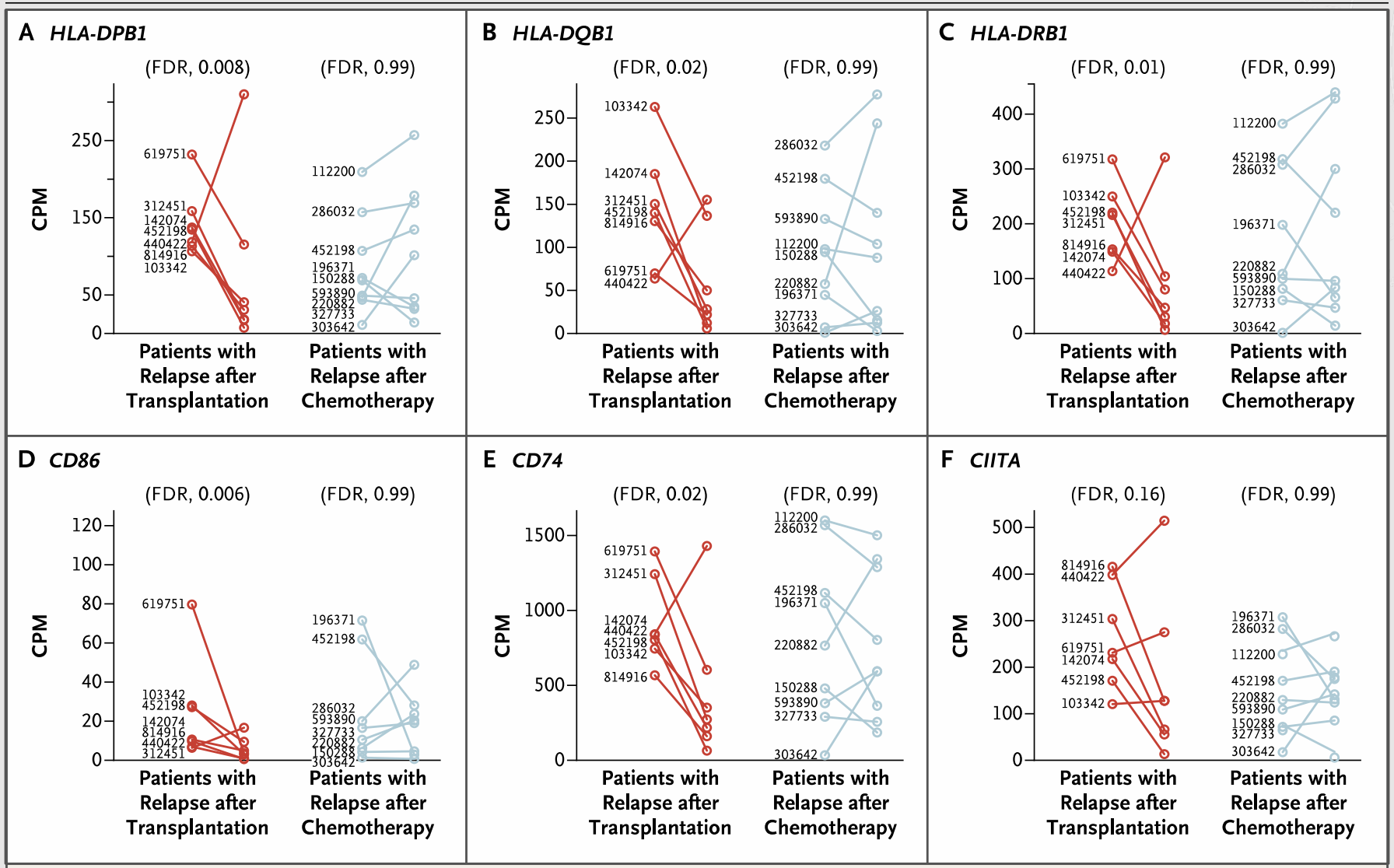
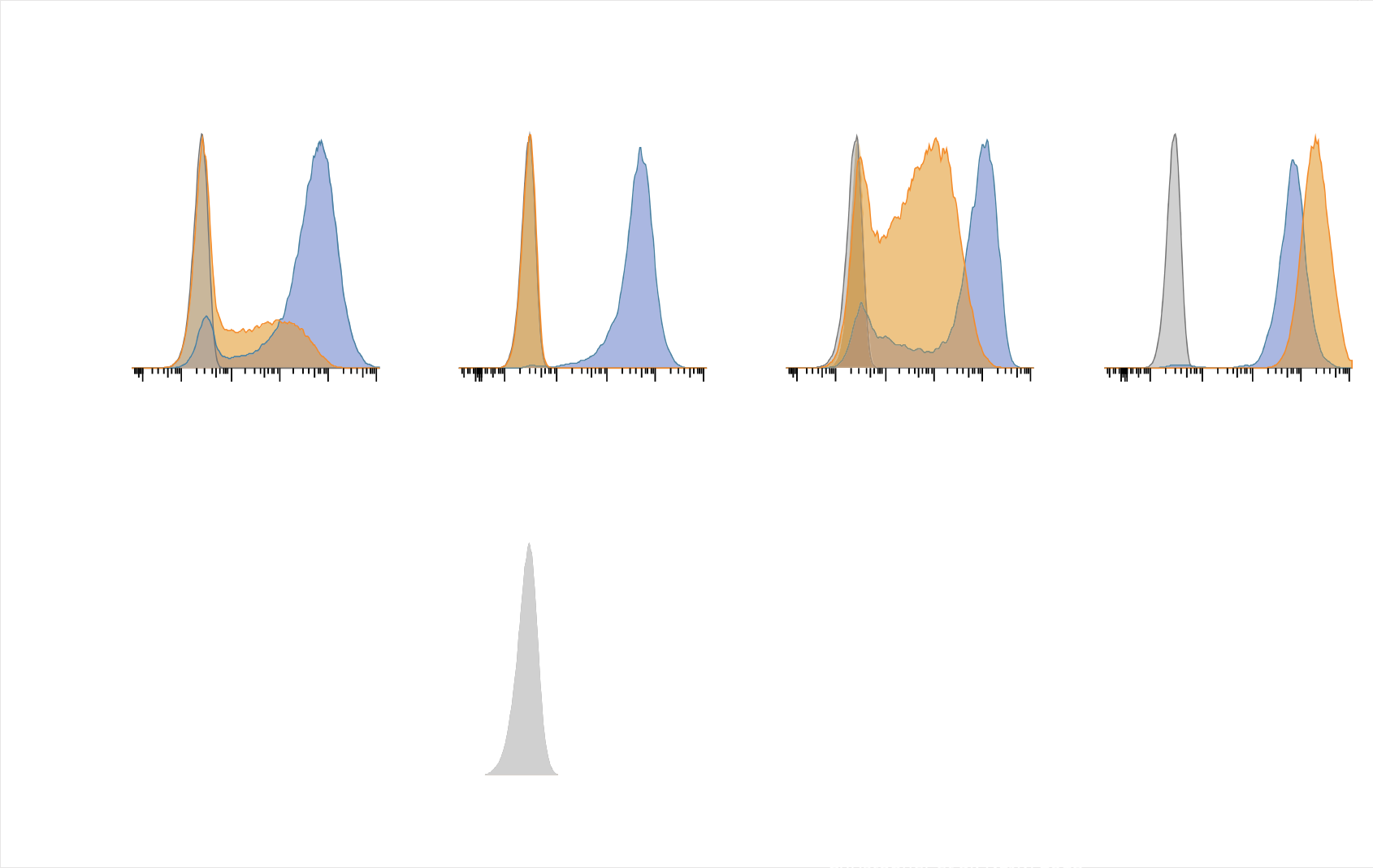


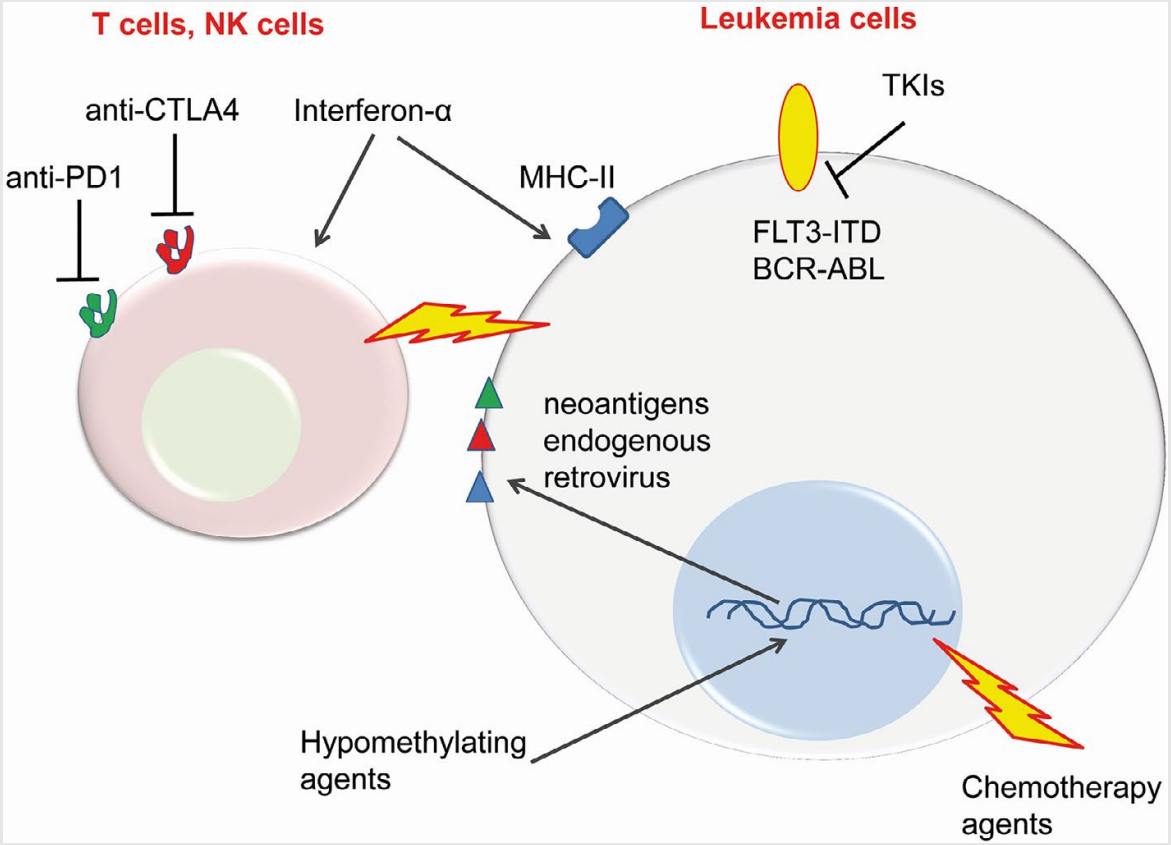
Figure 1. Expression of Immune-Related Genes among Patients with a Relapse of AML.

Down-regulation of HLA-class II molecules in AML relapsing after AlloHSCT



Christopher, et al. NEJM 2018

Strategies to treat relapsed AML after allogeneic stem cell transplantation



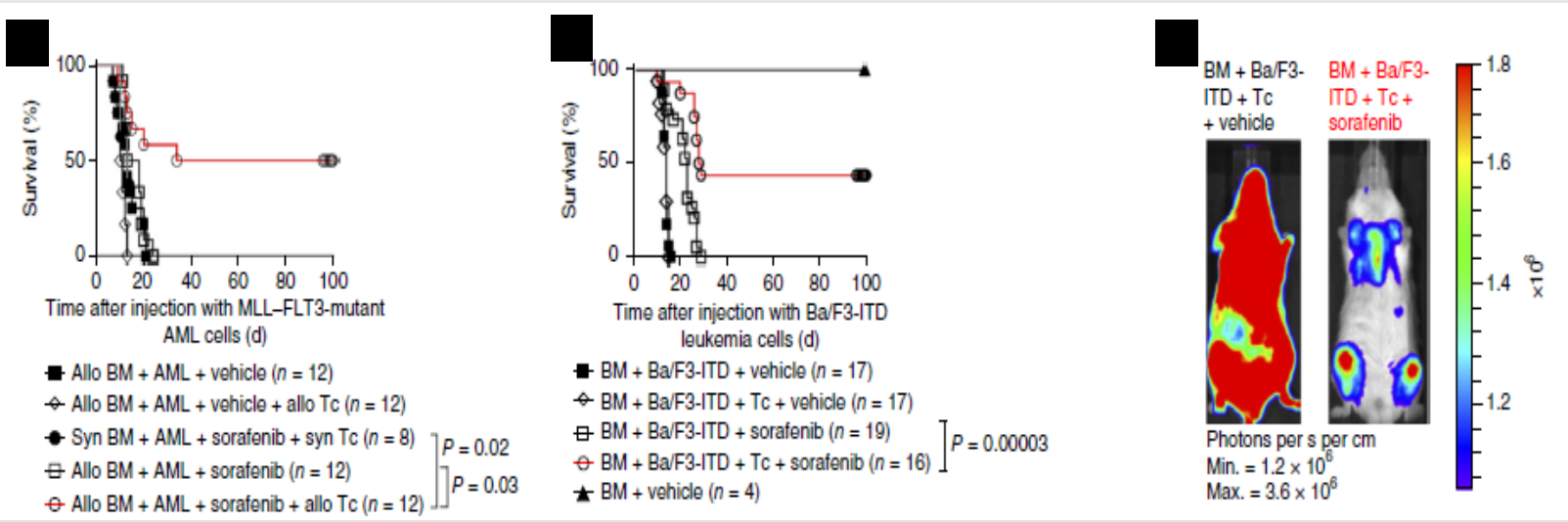
herapy.

Zeiser R, et al. BBMT 2019

FLT3 inhibitors post Allo transplantation?

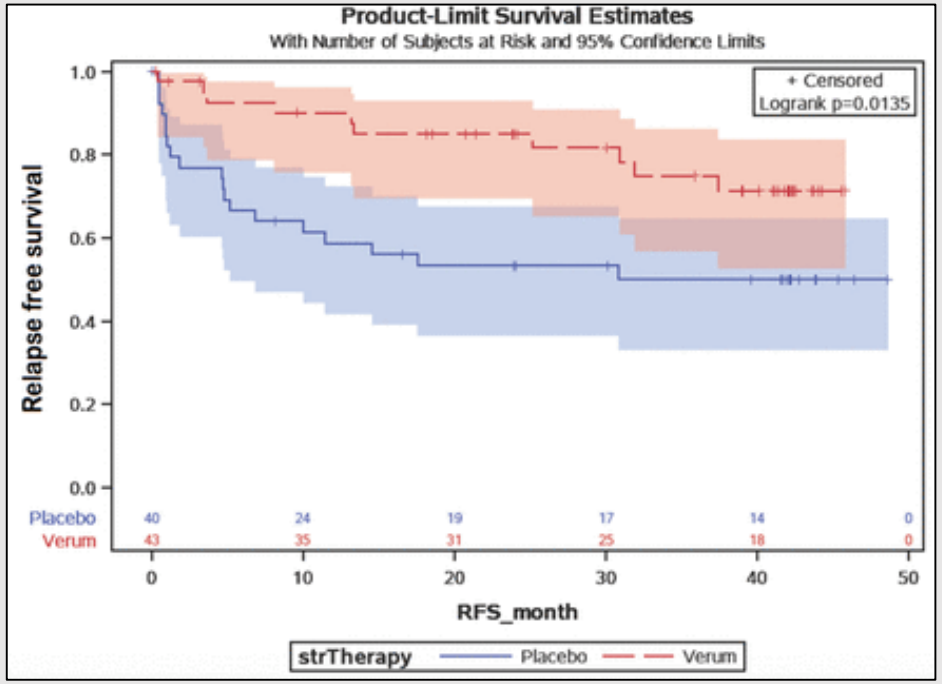
nature medicine

Sorafenib promotes graft-versus-leukemia activity in mice and humans through IL-15 production in FLT3-ITD-mutant leukemia cells



Mathew et al. Nat Med 2018

FLT3 inhibitors post Allo transplantation – more data are needed

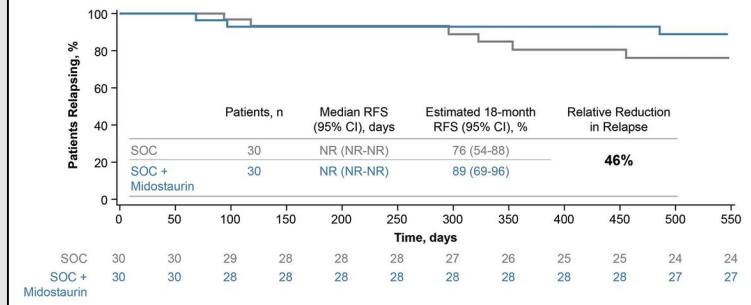


Sorafenib As Maintenance Therapy Post Allogeneic Stem Cell Transplantation for FLT3-ITD Positive AML: Results from the Randomized, Double-Blind, Placebo-Controlled Multicentre Sormain Trial

Andreas Burchert, Gesine Bug, Jürgen Finke, Matthias Stelljes, Christoph Rollig, Ralph Wäsch, Martin Bornhäuser, Tobias Berg, Fabian Lang, Gerhard Ehninger, Hubert Serve, Robert Zeiser, Eva-Maria Wagner, Nicolaus Kroeger, Christine Wolschke, Michael Schleuning, Ahmet Elmaagacli, Katharina S. Götze, Christoph Schmid, Edgar Jost, Dominik Wolf, Alexandra Böhm, Christian Thiede, Torsten Haferlach, Wolfgang Bethge, Susanne Harnisch, Michael Wittenberg, Susanne Rospleszcz, Andreas Neubauer, Markus Brugger, Konstantin Strauch, Carmen Schade-Brittinger, and Stephan K Metzelder

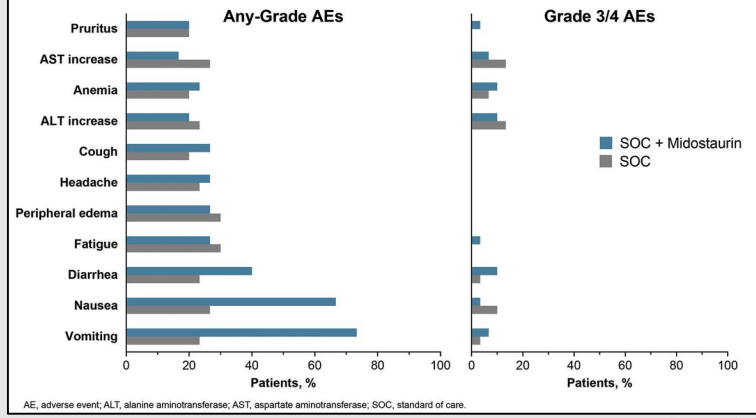
Blood 2018 132:661; doi: https://doi.org/10.1182/blood-2018-99-112614

Figure 1: Kaplan-Meier Plot for Relapse-Free Survival at 18 Months After alloHSCT[a]



alloHSCT, allogeneic hematopoietic stem cell transplant; NR, not reached; RFS, relapse-free survival; SOC, standard of care.
[a]RFS was defined as the time from transplant to relapse or death due to the disease.

Figure 2: Any-Grade and Grade 3/4 AEs (occurring in ≥20% of patients overall)



AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SOC, standard of care.

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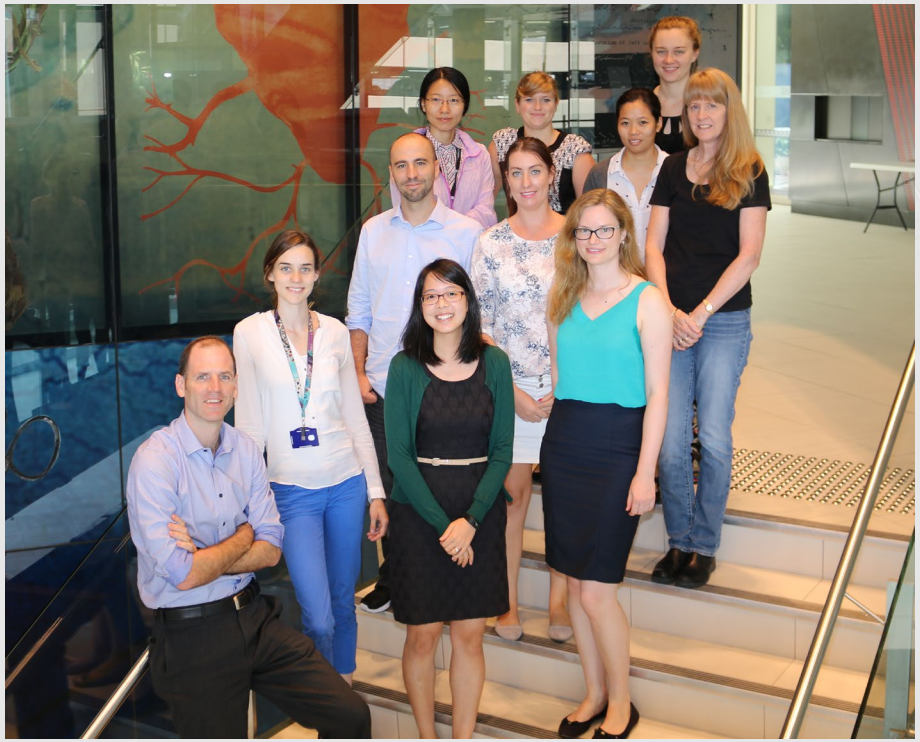

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