The "AlloHSCT" and prospects for cellular therapy

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NHS Foundation Trust

Disclosures

- Research funding and advisory board of Celgene, Cellectis, Novartis

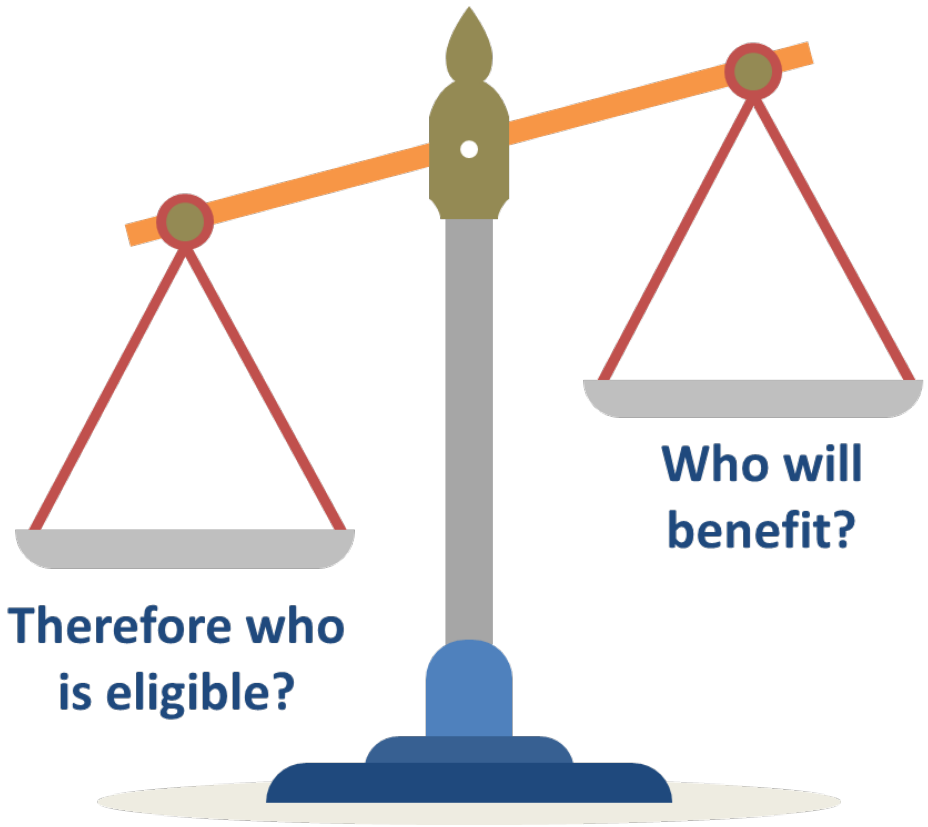
Presentation 7: Recent Advances…

5. **Case Study - Mr X**
   - **Previously fit, 65 year old man with symptoms of anaemia of 6 month duration.**
   - **Bone marrow- hypercellular**
   - **WCC- 1.6x109/l (N=0.3x109/l); Hb- 10.1G/dl; Plts- 21x109/l; Bone marrow blasts- 7%; cytogenetics- 47,XY,+8; Mutation-NRAS(G12A), HCT CI- 1; VUD donor 10/10; CMV -/-**

   Treatment Option

   a. Demethylating agents alone
   b. Demethylating agents followed by alloHSCT
   c. Intensive chemotherapy followed by alloHSCT
   d. AlloHSCT with myeloablative conditioning upfront
   e. Reduced Intensity Conditioning with post-transplant MRD monitoring
   f. a, b & c

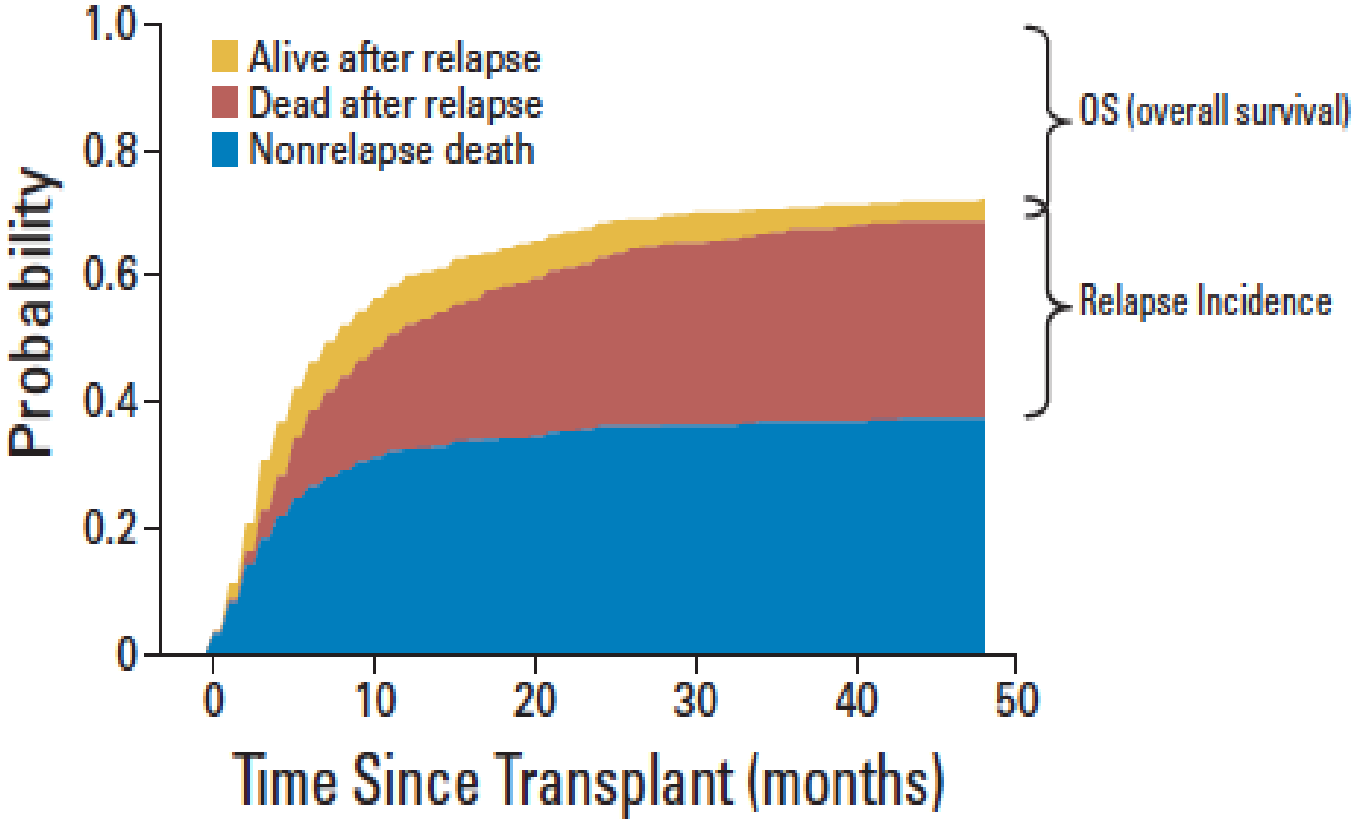
Current treatments for MDS fail to cure MDS & only prolong survival by a few months at best



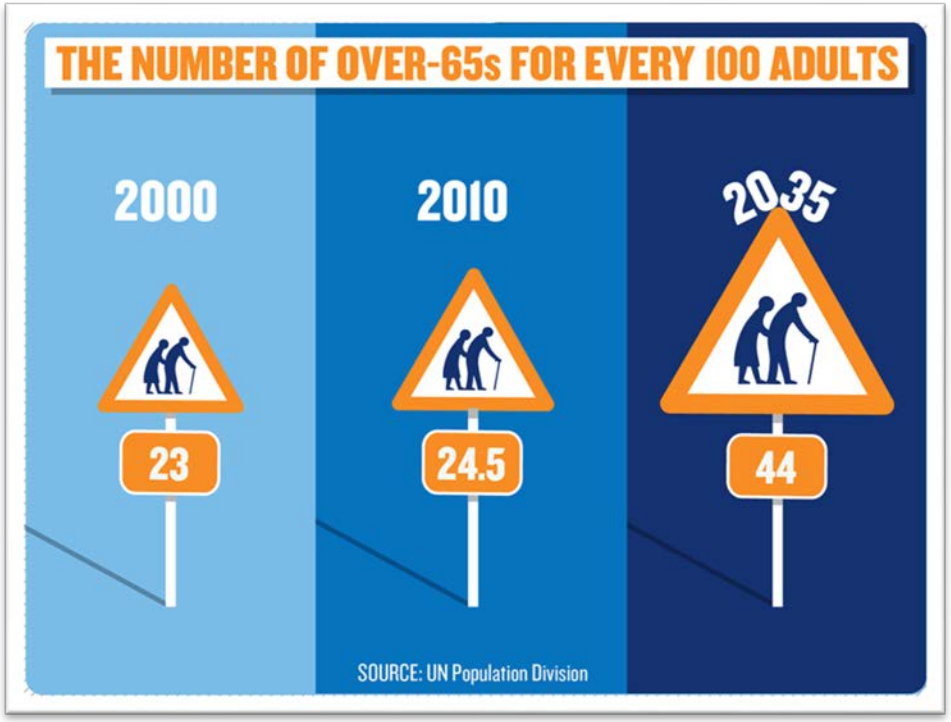
How can benefits of HSCT best be increased in the context of leukaemia specific immunity

Relapse is the leading cause of treatment failure post HSCT

Prevention of relapse post HSCT now the most important challenge in AML/MDS



We have an ageing population



Young and fit

Old and Fit

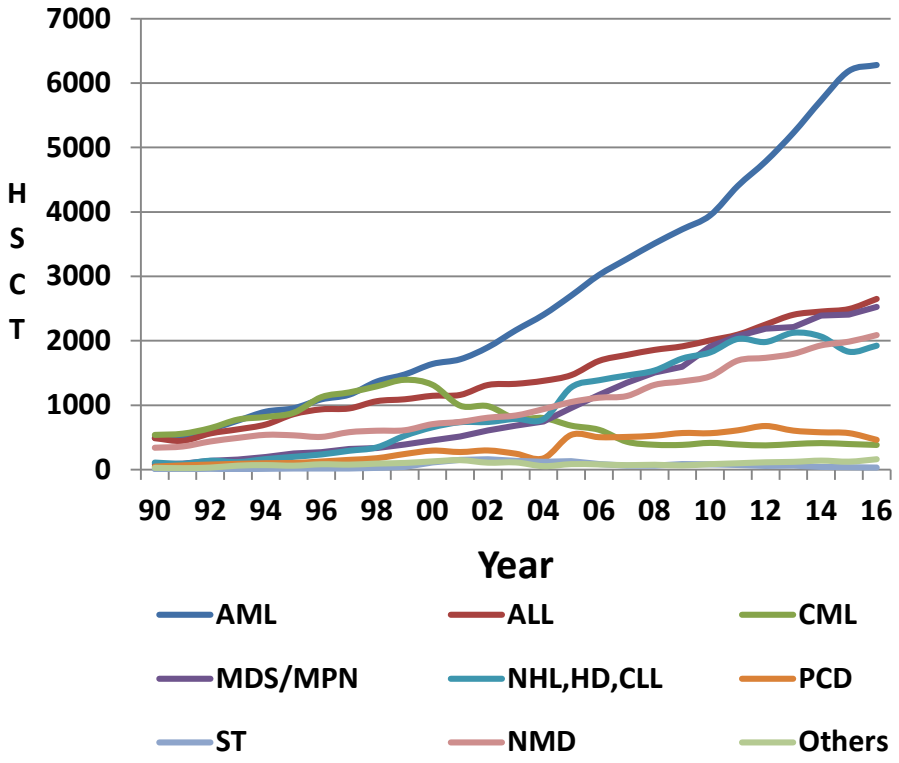
Old and unfit

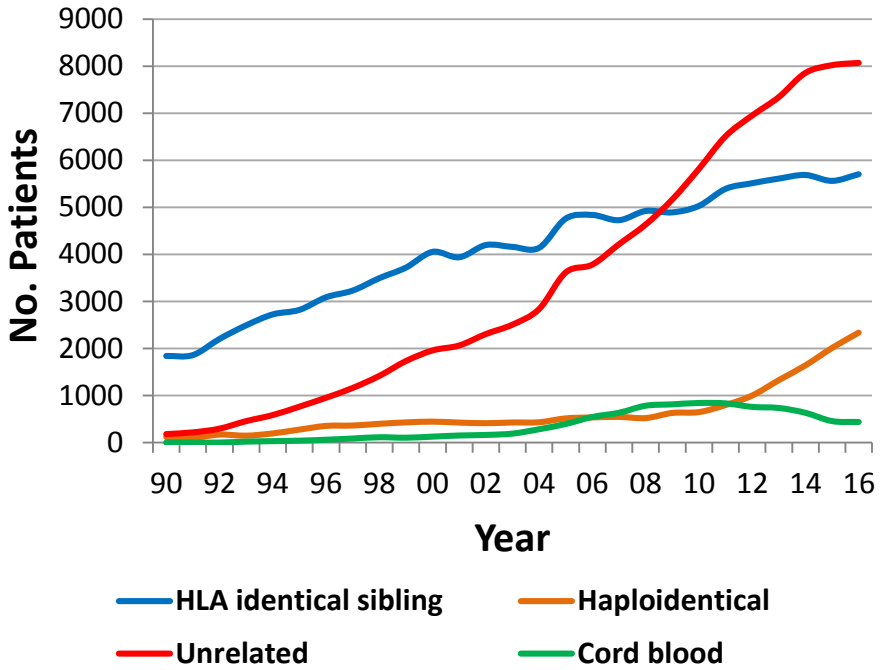
[World Population Prospects: the 2017 Revision]

Number of older people >60 years — In 2017 = 962 million; 2050 = 2.1 billion; 2100 = 3.1 billion.

Patients who are eligible for HSCT are increasing due to a fitter population

HSCT Activity in Europe 1990-2016:
Main indications/donor origin: allogeneic 1st. HSCT





2010 – 2014 activity (12,538)

>70yrs = 1,049 (8%)

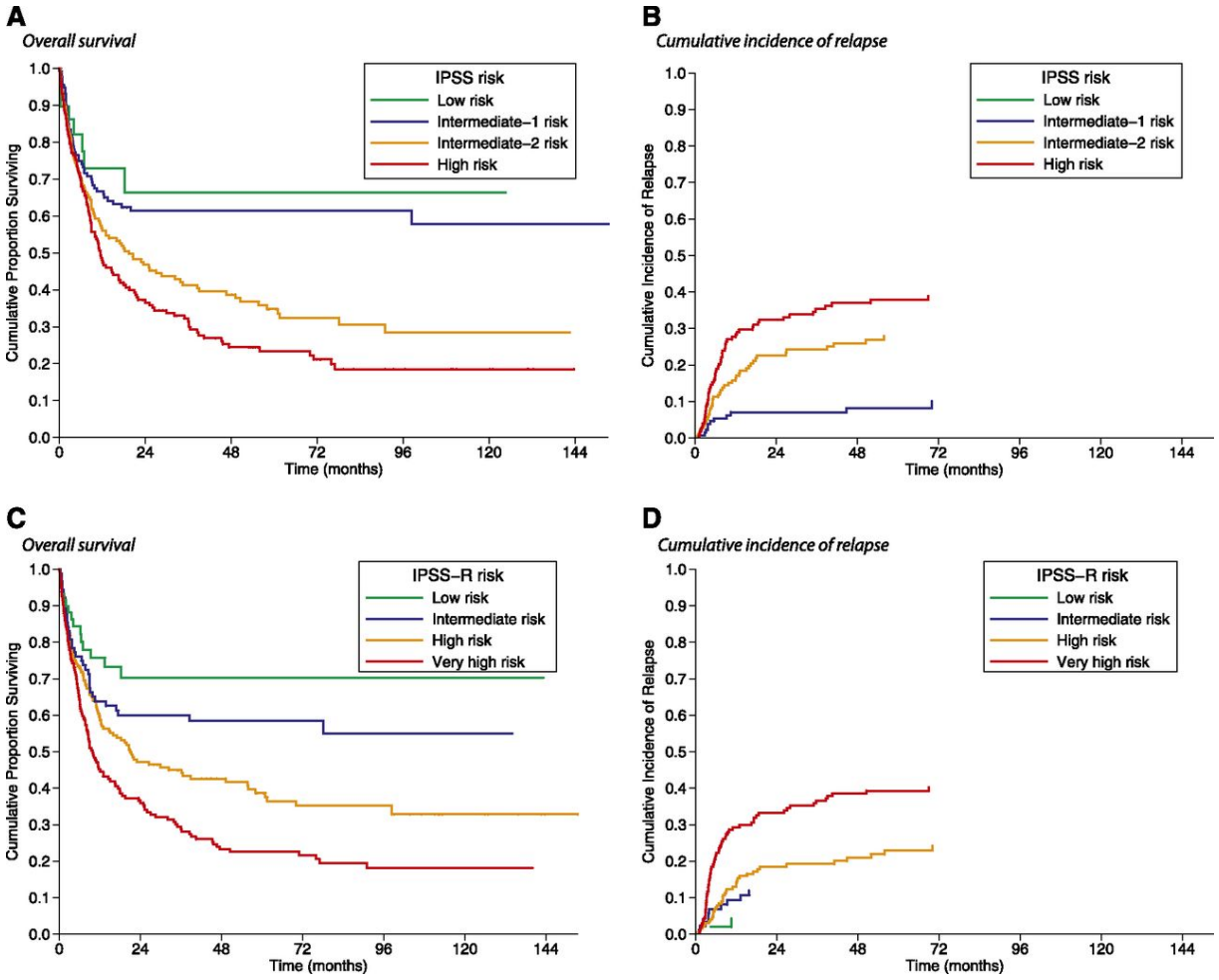
65-70yrs = 4,026 (32%)

60-64yrs = 7,463 (60%)

How best to select for transplant?

1. Disease Subtype & IPSSR
2. Cytogenetic & Molecular
3. HCT-CI PAM
4. Disease status @ Transplant
5. Donor Characteristics
6. Combinations of 1-5

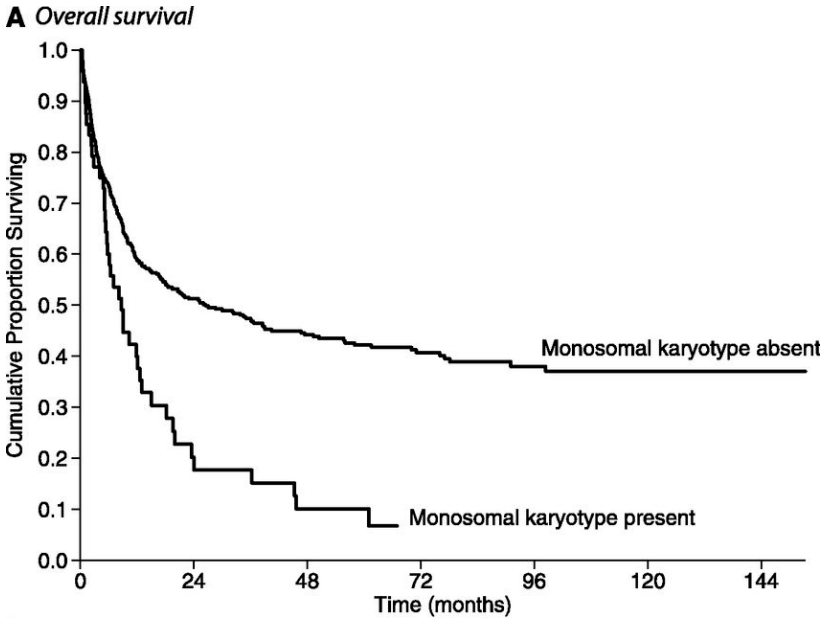
Kaplan-Meier analysis of OS & CIR following allogeneic HSCT in MDS patients stratified on their pre-transplant IPSS or IPSS-R risk

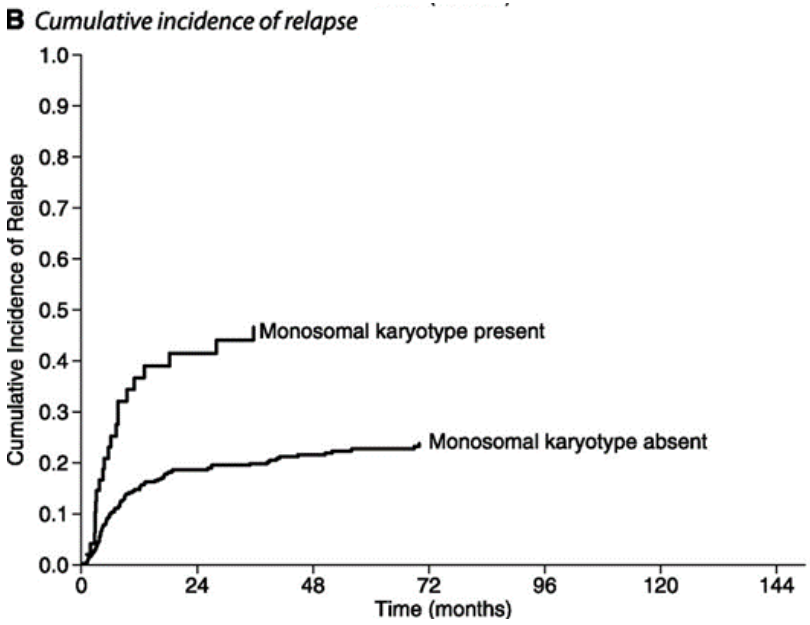


N=519
(2000-2011)

Matteo G. Della Porta et al. Blood 2014

Post-transplant outcome in MDS patients stratified according to the absence or presence of monosomal karyotype

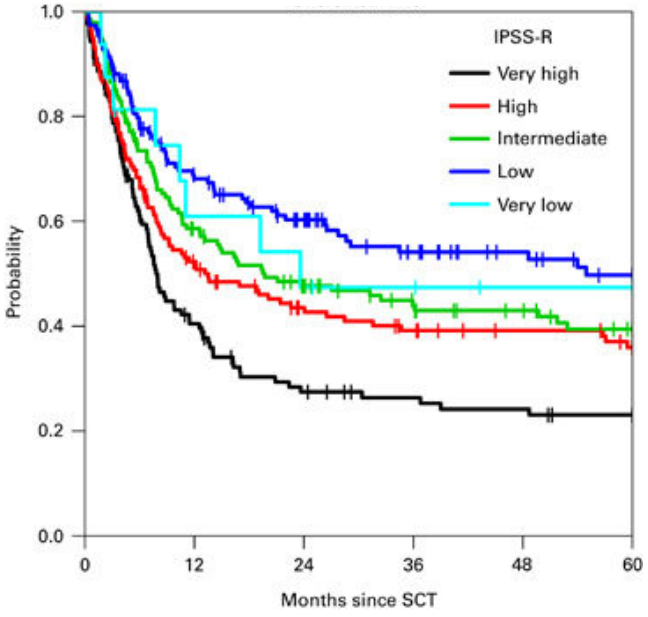




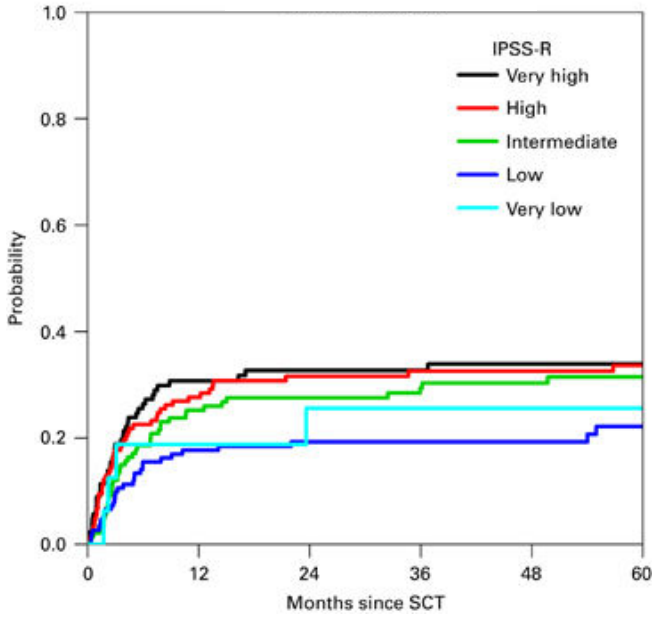
Matteo G. Della Porta et al. Blood 2014

Retrospective EBMT study of 579 patients confirms validity of IPSS-R at HSCT irrespective of prior therapy

Overall Survival



Incidence of NRM



Median OS (months)

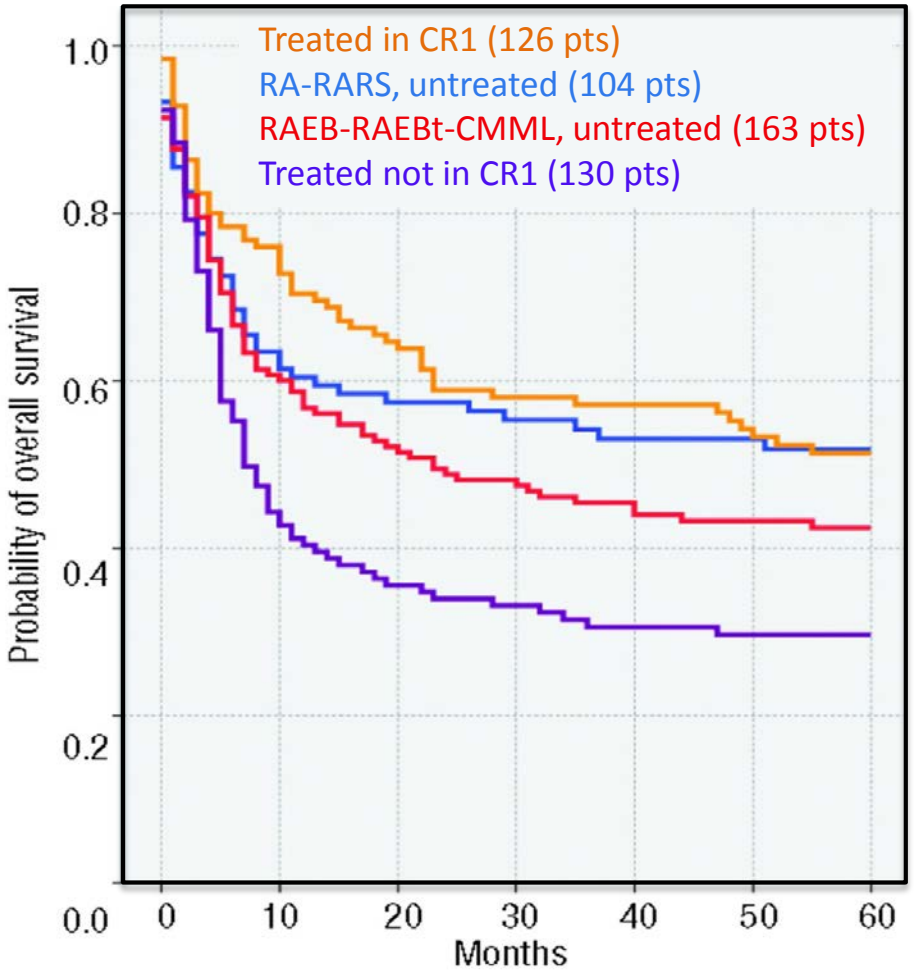
Very low: 23.6; Low: 55; Int: 19.7; High: 13.5; Very high: 7.8

Multivariate Analysis Significant Factors

IPSS-R, graft source, age and prior treatment

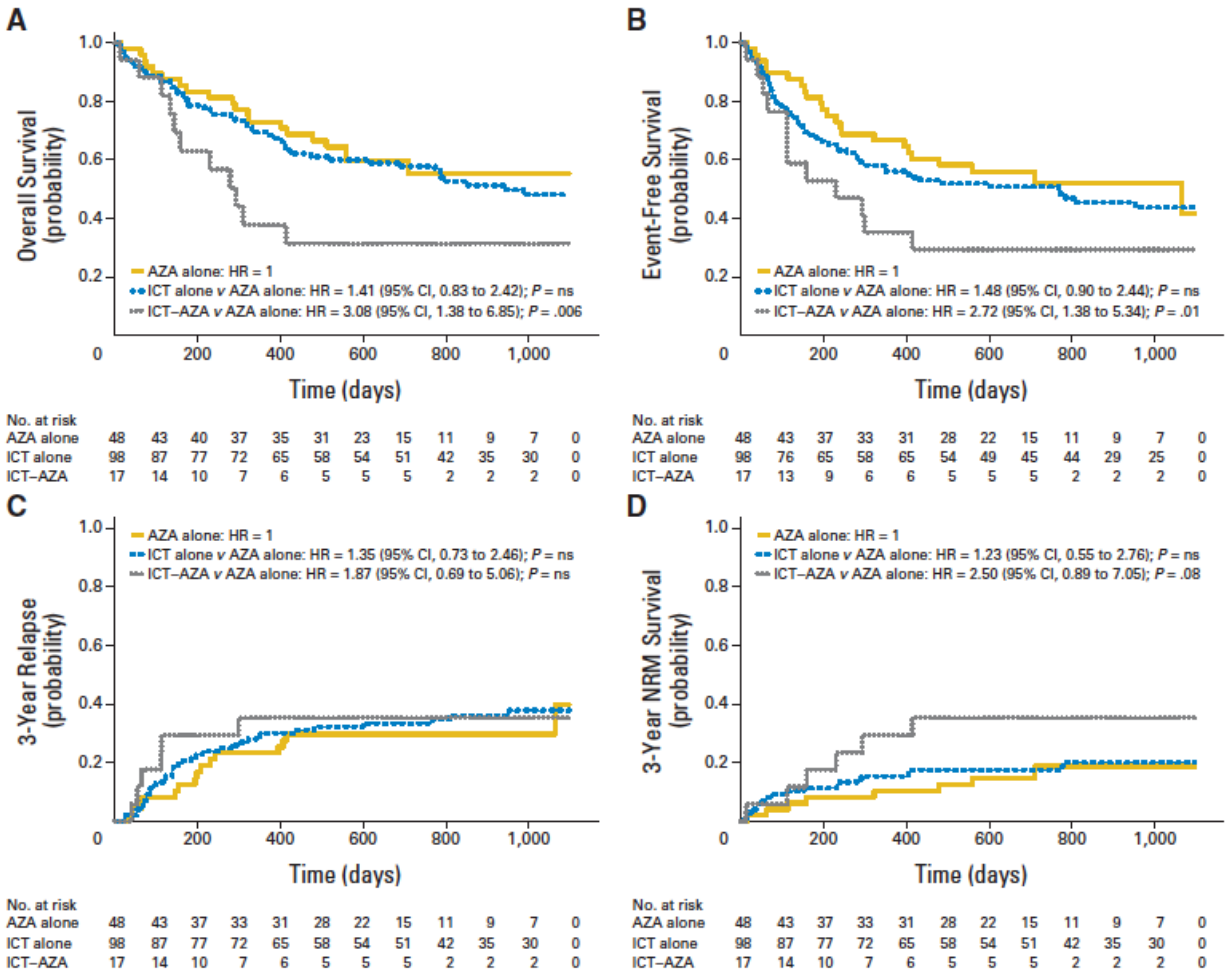
Scheid BMT 2017

Overall survival according to remission status and percentage of marrow blasts



Onida et al. Haematologica 2014

Intensive chemotherapy (ICT) +/- 5-Azacytidine (5-Aza) Cytoreduction pre Allo-HSCT

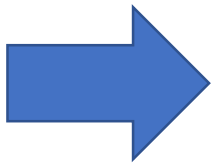


Retrospective study of 265 patients, 163 of whom received cytoreductive therapy prior to transplant. ICT=98, Aza= 48, ICT + AZA = 70, SIB = 75, VUD = 88, MAC = 33, RIC = 130

Damaj et al JCO 2012

Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia

- 145 patients > 65yrs with treatment naïve AML
- Median age 75
- Poor risk cytogenetics in 49%
- Venetoclax (400-1200mg) and azacytidine 75mg/m^2 for 7 days OR Decitabine 20mg/m^2 for 5 days
- Median time on study 8.9 months



- CR + Cri for venetoclax 400mg + HMA cohort was 67%
- Median duration CR+Cri 11.3 months
- Median OS 17.5 months
- Median OS not reached in venetoclax 400mg group

nature medicine ARTICLES
https://doi.org/10.1038/s41591-018-0233-1

Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in patients with acute myeloid leukemia

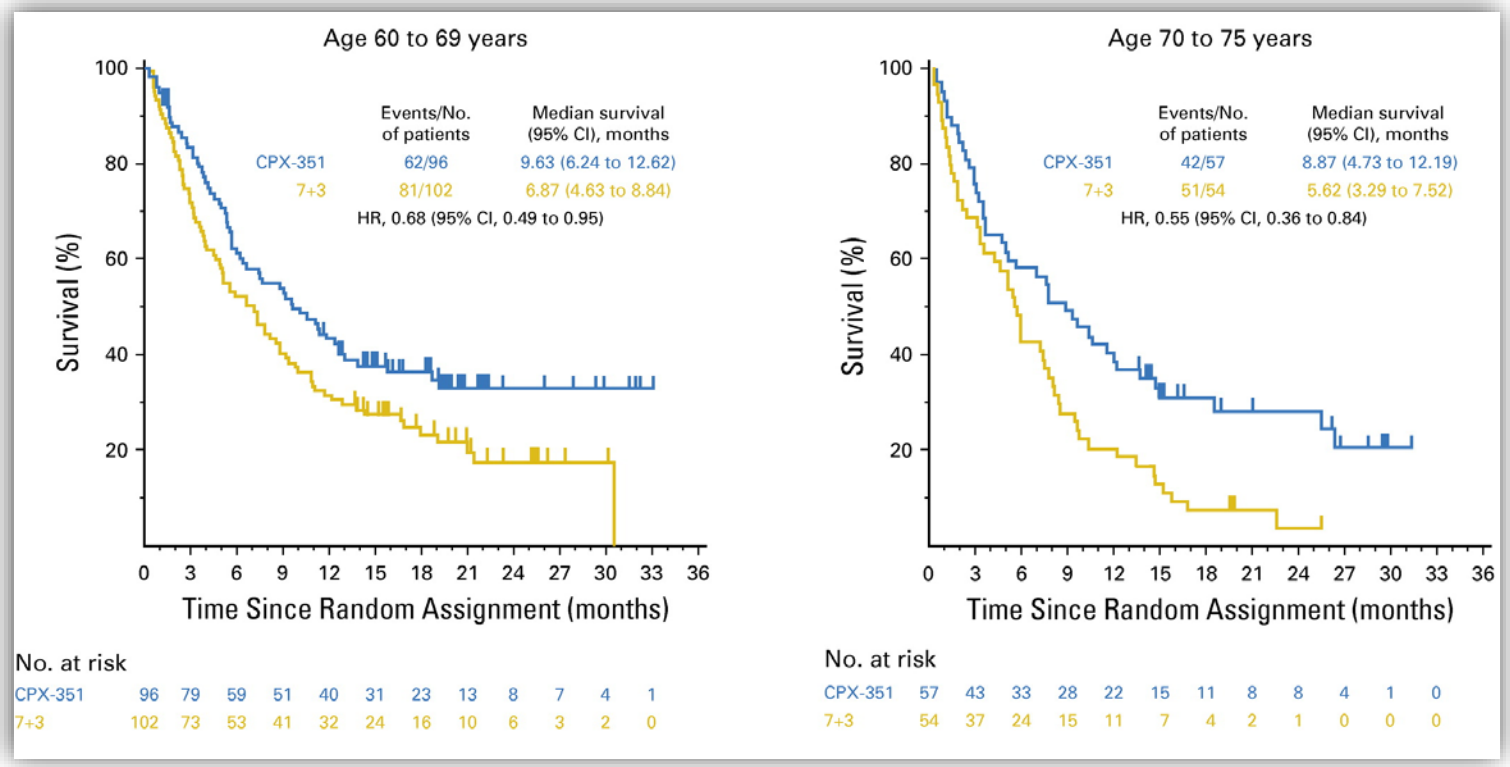
Pollyea et al, Nov 2018

Venetoclax + LD AraC
N=71
CR/CRI Intd Cyto = 76%, Poor Risk = 47%
Responses in all molec subtypes = 60-100%, except Tp53 mut = 44%

Wei et al, Nov 2017

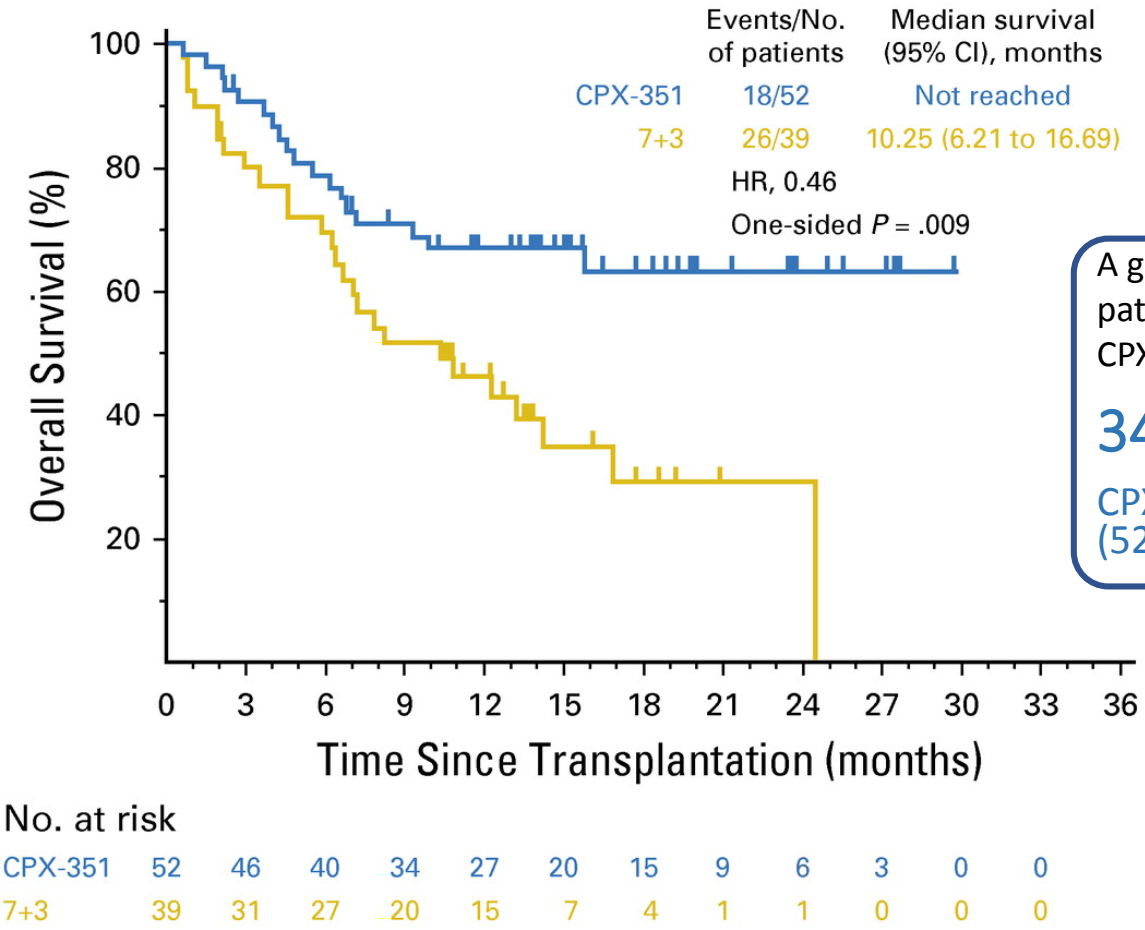
DiNardo et al Blood October 2018

CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia



Lancet JE, Journal of Clinical Oncology. 2018

Post-Hoc Analysis suggests possible improved outcomes in those who received HSCT



A greater proportion of patients receive HSCT with CPX compared with 7+3[2]

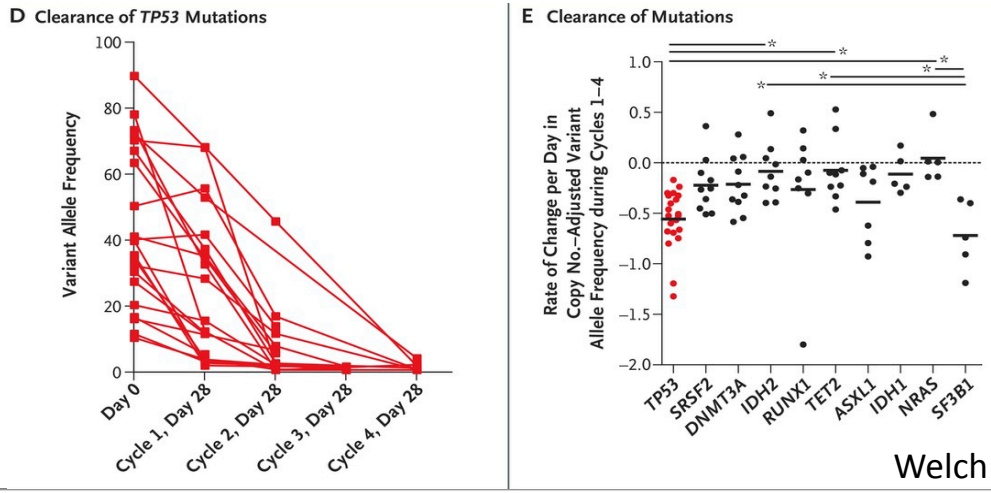
34%	25%
CPX (52/153)	7+3 (39/156)

Lancet JE, Journal of Clinical Oncology. 2018

The NEW ENGLAND JOURNAL of MEDICINE

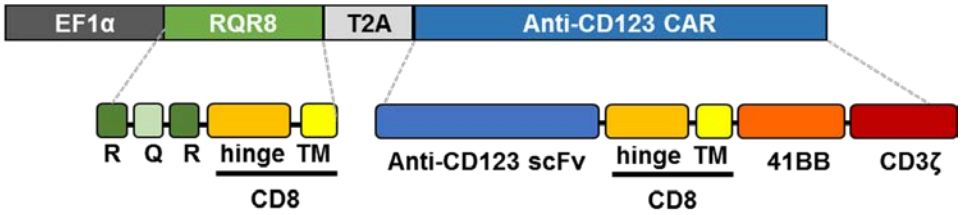
TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes

- Of the 116 patients, 53 (46%) achieved <5% BM blasts.
- Response rates were higher in patients with an unfavourable karyotype than an intermediate-risk or favourable-risk cytogenetic profile (29 of 43 [67%] vs. 24 of 71 [34%], P<0.001)
- Patients with *TP53* mutations had a higher response rate than among patients with wild-type *TP53* (21 of 21 [100%] vs. 32 of 78 [41%], P<0.001).



Welch JS et al. N Engl J Med 2016

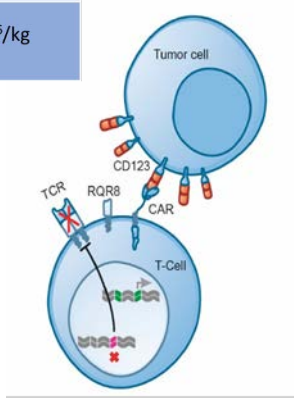
Phase I Trial of Allo-UCART123 in High Risk AML



Cohort number	UCART123 Dose 1	UCART123 Dose 2
-1	$2.5x10^5$/kg	$2.5x10^5$/ kg
1	$6.25x10^5$/kg	$6.25x10^5$/kg
2	$5.05x10^6$/kg	$5.05x10^6$/kg

UCART123 attributes:

- CD123 scFv (Klon43, murine)
- 2nd Generation CAR: CD3ζ + 4-1BB
- RQR8+: CD20 epitope to trigger cell destruction by anti-CD20 antibodies
- TRAC KO: to prevent GvHD



Cytoreduction
Induction
Chemotherapy (DA or FLAG-Ida)

N=18

Residual cytogenetic or morphological disease with blasts <20%

Blasts >20%

Lymphodeplete
FC
UCAR123
Ist Administration

Residual cytogenetic or morphological disease with blast <20%

2nd Cytoreduction
DA
Or FLAG-Ida

Blasts >20%

OFF Study

28 days later → re-assess
28-32 days later
2nd UCART123

MRD by Immunophenotyping (0.1%)

FC
UCAR123
2ndAdministration

28-32 days later

HSCT

cellectis
EDITING LIFE

KING'S College LONDON

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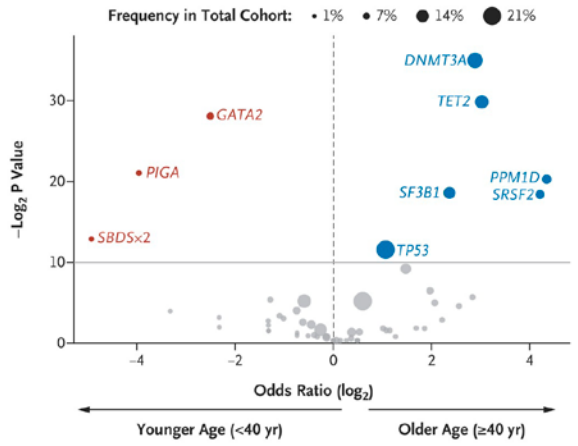
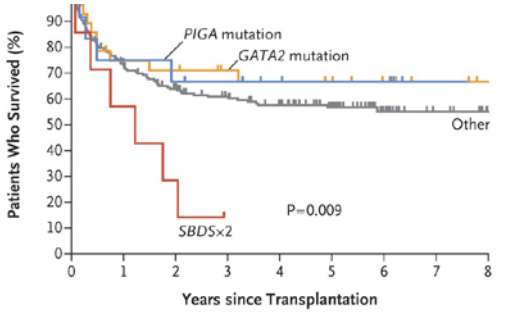
Frequency of Driver Mutations and Age-Independent Association of TP53 Mutations with Poor Overall Survival

Gene Mutation, According to Age of Patient

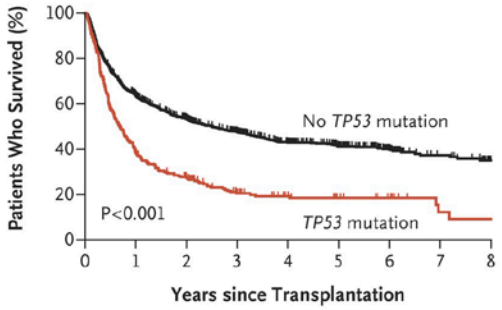


Overall Survival among Patients <40y of Age, According to Mutation Status



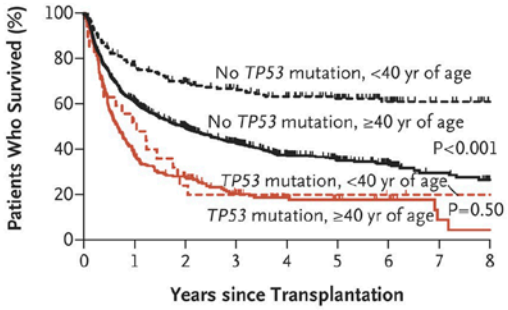
No. at Risk									
PIGA mutation	12	10	9	8	6	5	5	2	1
GATA2 mutation	28	21	20	17	15	13	10	6	5
Other	198	140	111	97	85	66	32	19	11
SBDS×2	7	5	3	1	0	0	0	0	0

Overall Survival, According to *TP53* Mutation Status



No. at Risk									
No *TP53* mutation	1224	757	529	370	261	183	109	53	32
TP53 mutation	289	109	66	39	26	20	14	6	5

Overall Survival, According to *TP53* Mutation Status and Age

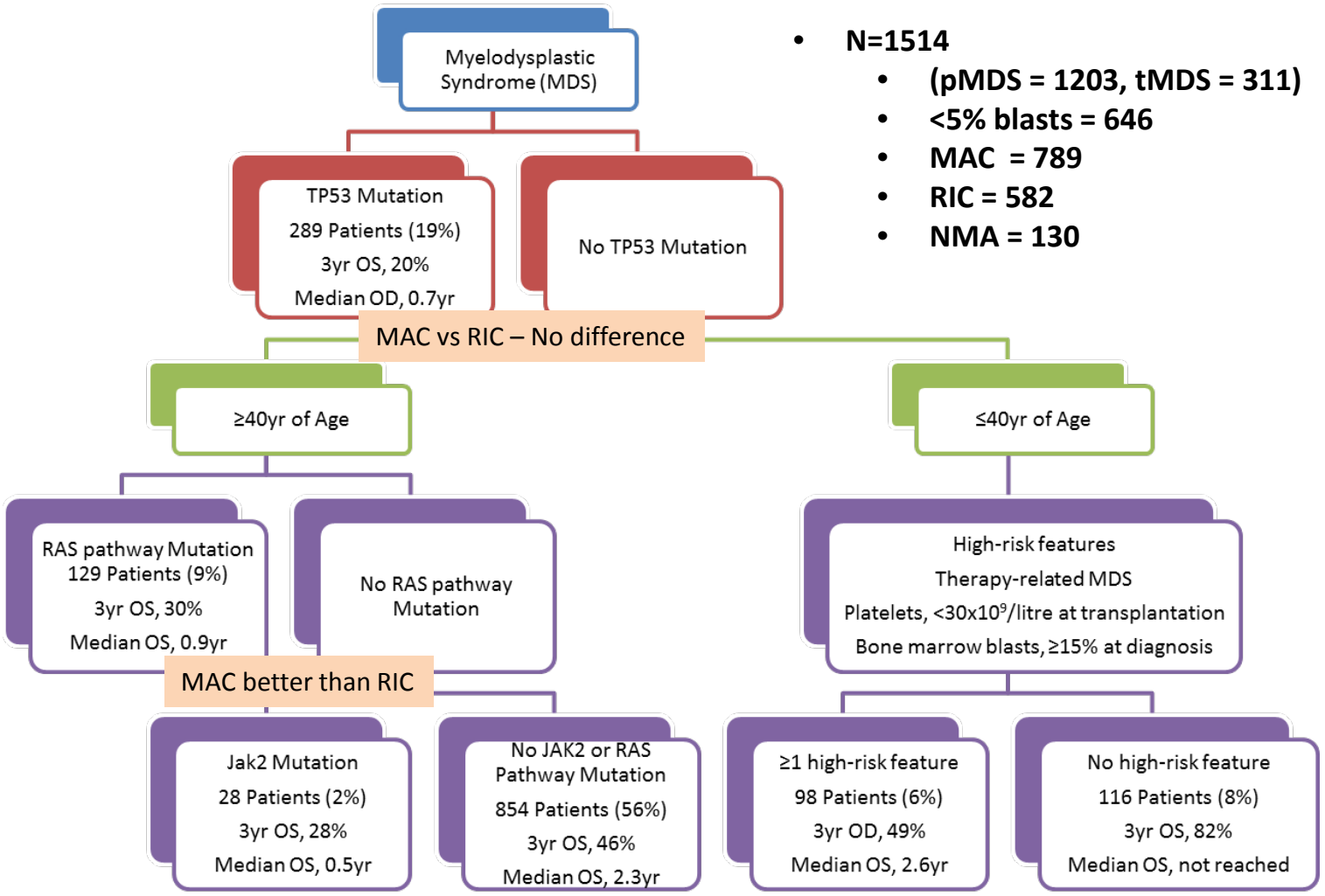


No. at Risk									
No *TP53* mutation									
<40 yr of age	214	159	133	115	100	78	42	23	13
≥40 yr of age	1010	598	396	255	161	105	67	30	19
TP53 mutation									
<40 yr of age	27	14	7	5	5	5	4	4	3
≥40 yr of age	262	95	59	34	21	15	10	3	2

45 patients with truncating *TP53* mutations (16%) had shorter survival than with missense mutations (P=0.005)

Lindsley RC et al. N Engl J Med 2017

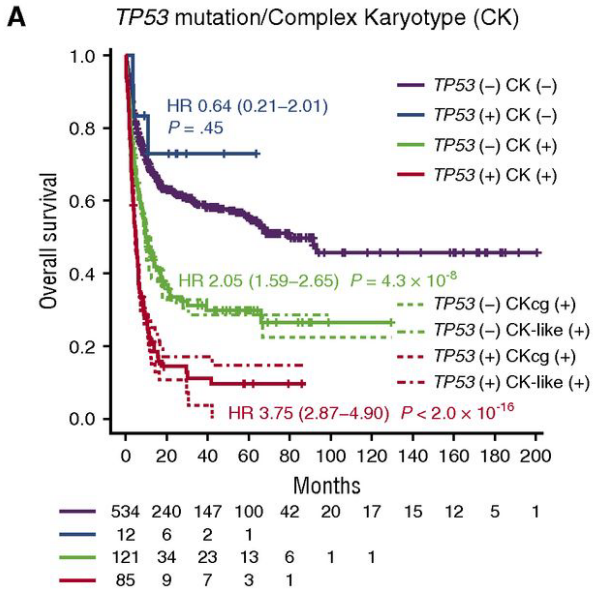
Models for Overall Survival, Including Clinical and Genetic Variables and Effect of Conditioning Intensity

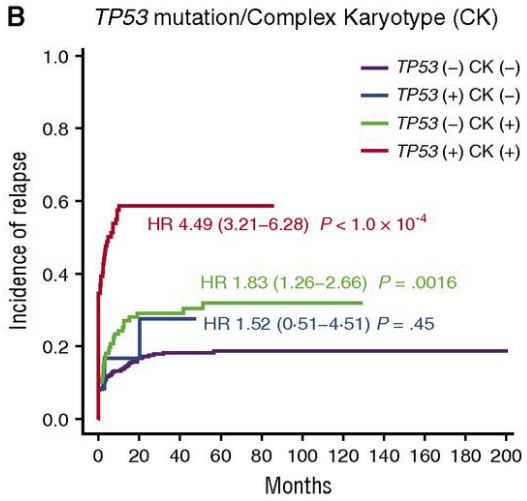


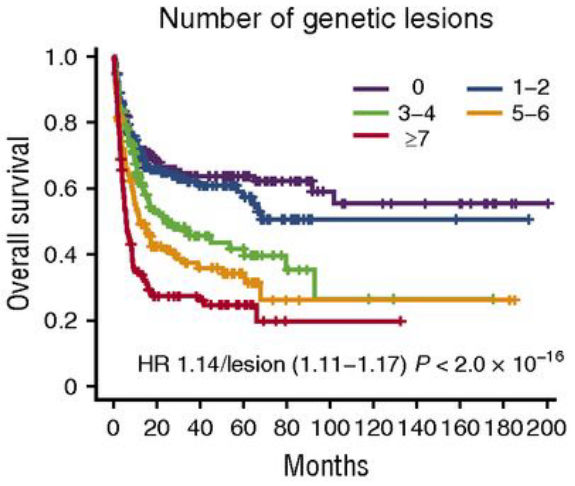
- **N=1514**
  - **(pMDS = 1203, tMDS = 311)**
  - **<5% blasts = 646**
  - **MAC = 789**
  - **RIC = 582**
  - **NMA = 130**

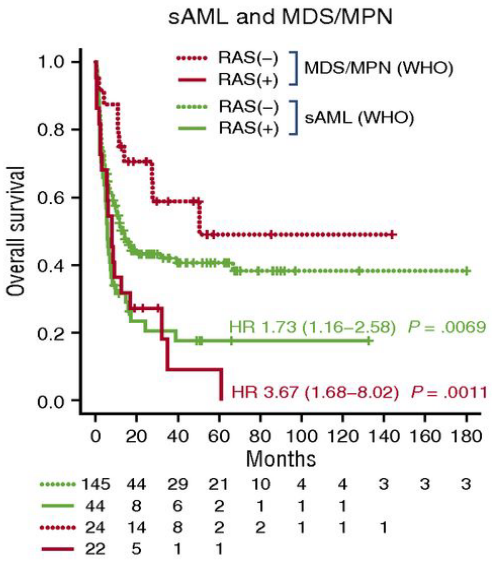
Lindsley RC et al. N Engl J Med 2017

Effects of *TP53*, *RAS* and CK on survival and relapse



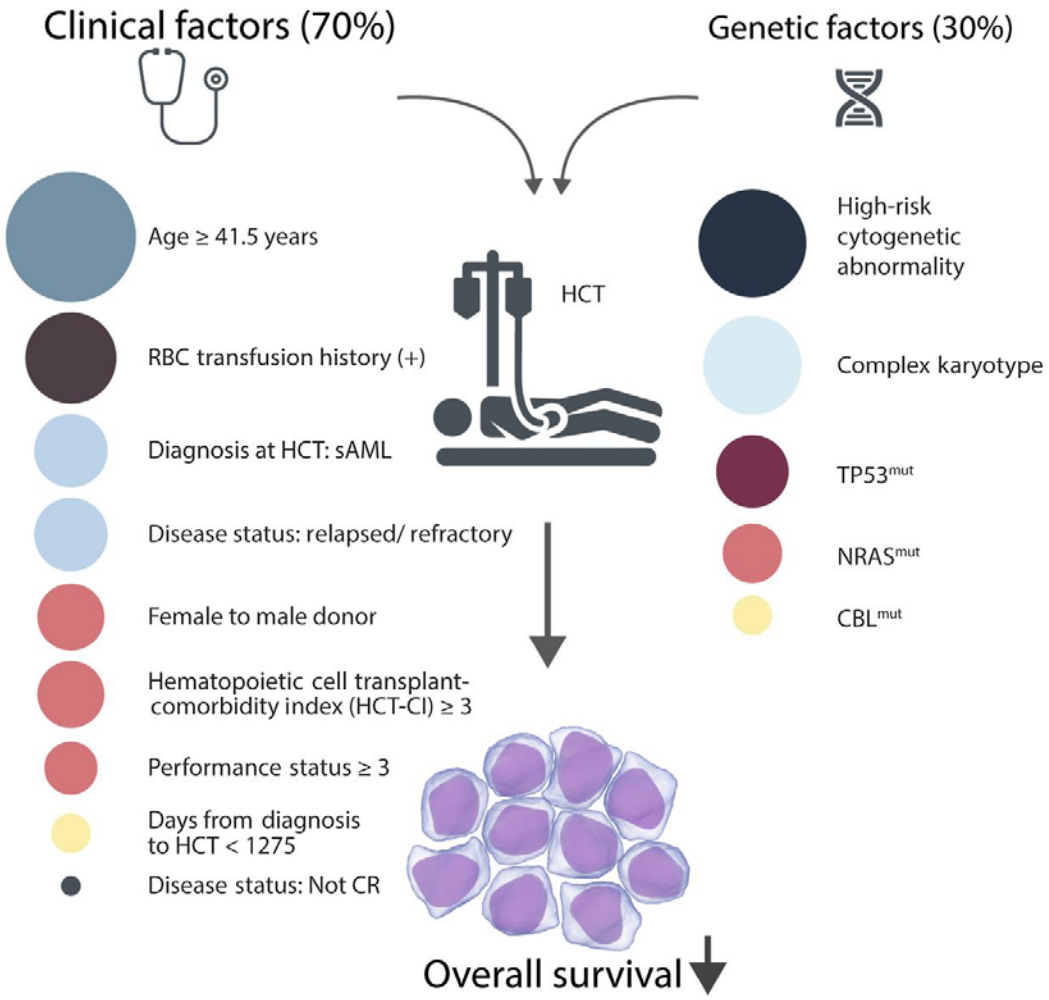






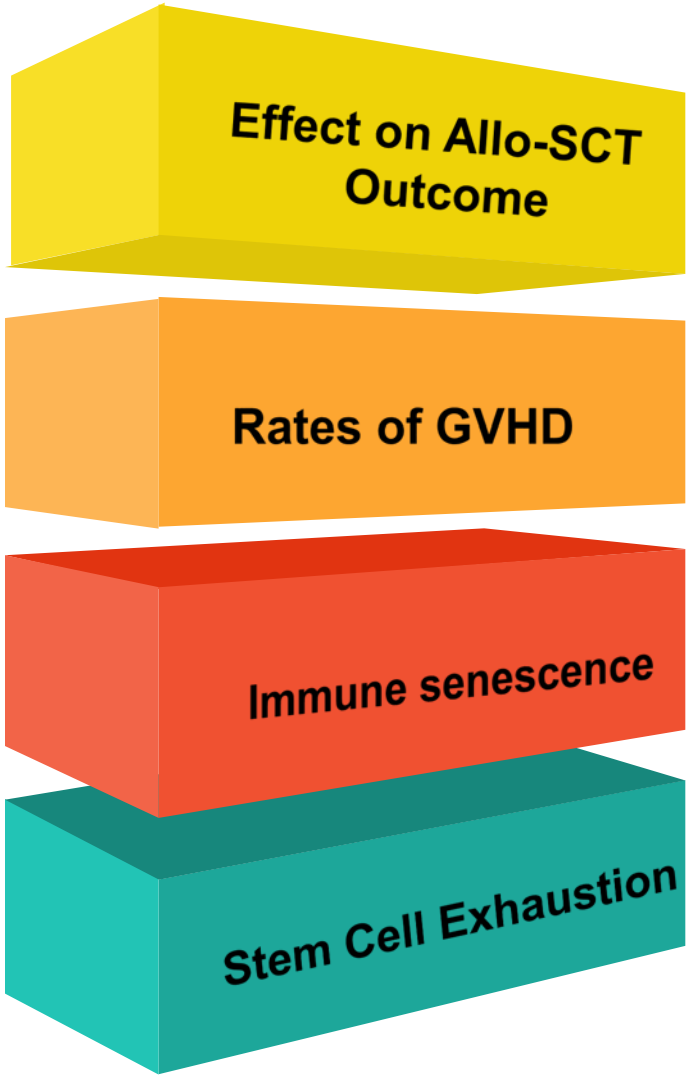
Tetsuichi Yoshizato et al. Blood 2017

Weighted contributions of clinical & genomic factors predicting survival because of leukemic relapse after BMT for MDS and sAML



Noa G. Holtzman, and Aaron P. Rapoport Blood 2017

Choosing an older sibling versus a Volunteer Unrelated Donor?



Conflicting Data

EBMT data: improved survival in older MDS patient with use of young URD compared to MSD (Kroger *et al* 2012). NOT shown in other studies.

Early studies suggested a higher rate of GVHD with aged donors but this has not been consistent and conflicting data has emerged (Kolman et al 2001; Alousi *et al* 2013)

Impaired B cell, T Cell and NK compartments; decreased diversity; chronic inflammation

Stem cell Reserve decreases with ageing. Quality and Regenerative capacity of HSC obtained under GCSF mobilisation from an elderly donor is reduced

Role of donor clonal haematopoeisis in allogenic HSCT

1

- 500 healthy, related HSCT donors (≥55yrs) targeted 66-gene panel sequencing
- (1993 – 2017) Myeloid disease: 19.2 vs 6.3 (p<0.001)

2

92 clonal mutations, median VAF of 5.9% in 80 (16.0%) donors

- DNMT3a = 8%
- TET2 = 2.2% (C→T)
- ASXL1 = 1.4%

3

- Alive patients median follow-up 3.3yr (0.1 - 20.6)
- Higher cumulative incidence of cGVHD; hazard ratio (P=0.003)
- Lower CIR/P (Univariate P =0.027; multivariate P=0.042)
- No effect on non-relapse mortality and OS
- 2 donor leukaemia's & lineage expansion of CHIP clone paralleled the fall in chimerism

CIR/P - cumulative incidence of relapse/progression

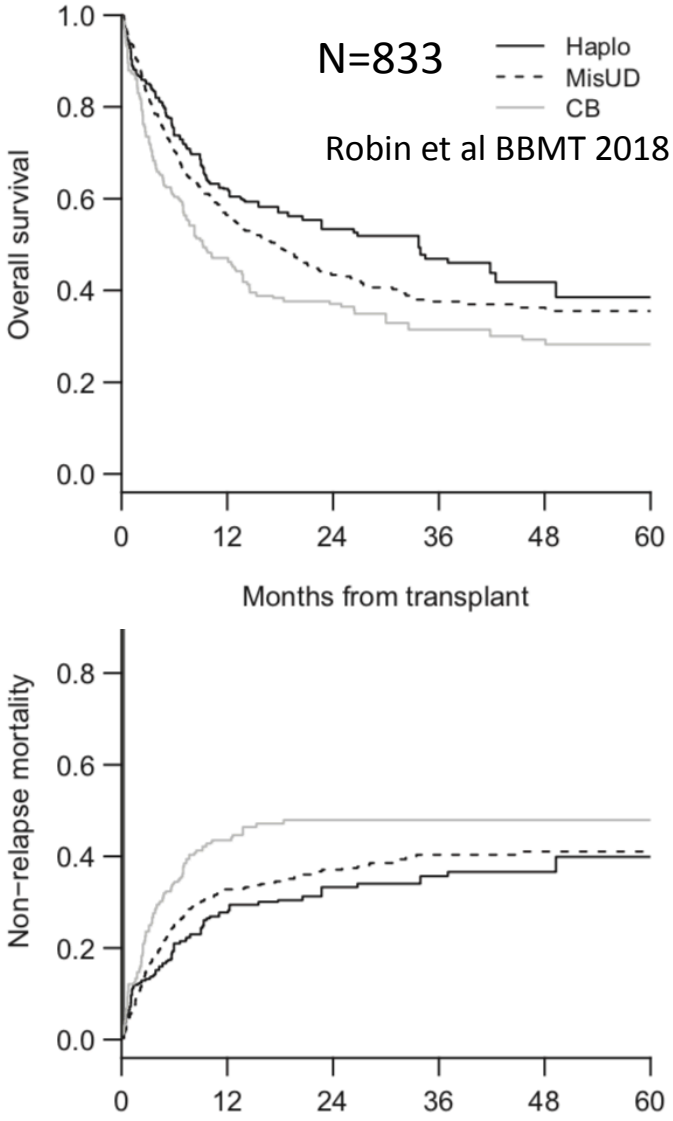
"Allogeneic HSCT from donors with CHIP seems safe and results in similar survival in the setting of older, related donors"

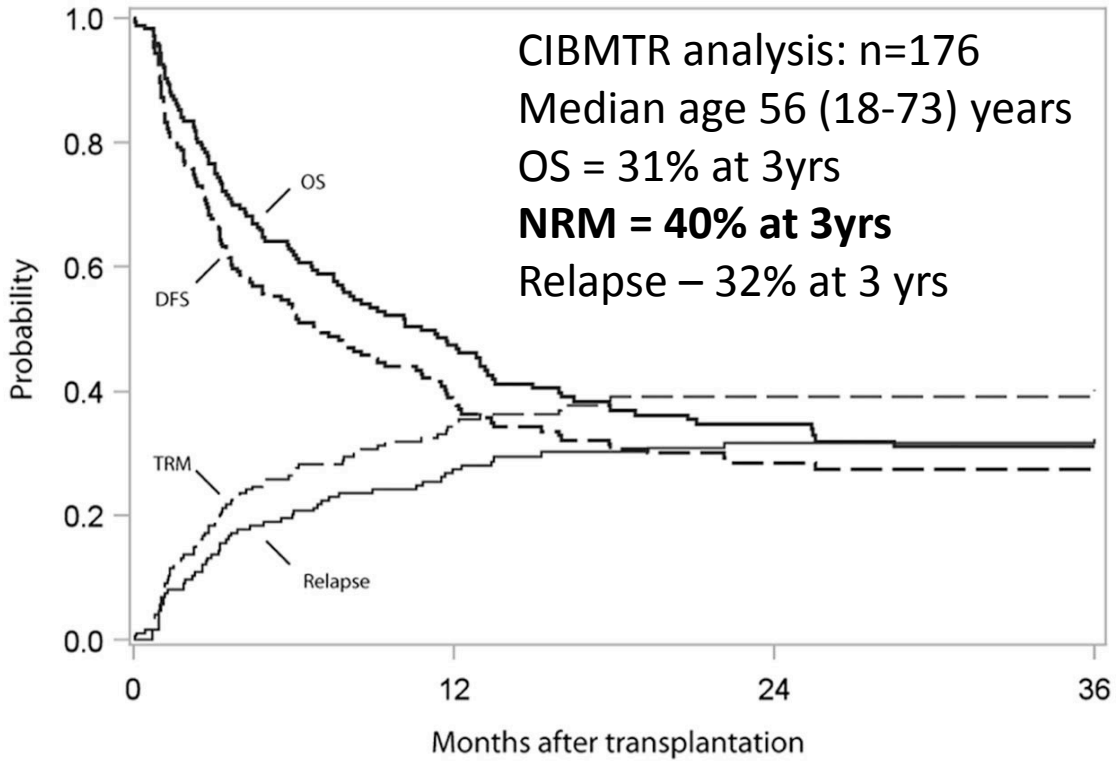
Frick et et al JCO 2018

- CIBMTR (10,000 unrelated donor stem cell transplantation)
- 1999 – 2014 - younger donors are associated with a better transplant outcome

Shaw et al Biol Blood Marrow Transplant. 2018

HLA-Mismatched/Cord Blood Donors in Patients with Myelodysplastic Syndrome: An EBMT Registry Analysis





Outcomes after cord blood transplant are limited by relatively high NRM

Gerds et al BBMT 2017

Dose-Reduced Versus Standard Conditioning Followed by Allogeneic Stem-Cell Transplantation for Patients With Myelodysplastic Syndrome: A Prospective Randomized Phase III Study of the EBMT (RICMAC Trial).

129 patients with MDS and sAML

- Median age = 50
- Matched related (MAC/RIC) = 17/16
- Matched unrelated (MAC/RIC) = 36/38
- MM R/UR (MAC/RIC) = 11/11

- Randomly assigned 1:1
- OS at 2yrs = 76% (RIC), 63% (MAC)
- RFS at 2yrs = 62% (RIC), 58% (MAC)
- No difference in acute or chronic GVHD

RIC (n=65)
- Fludarabine: 150mg/m^2
- Busulphan: 8mg/kg PO or 6.4mg/kg IV

MAC (n=64)
- Busulphan: 16mg/kg PO or 12.8mg/kg IV
- Cyclophosphamide: 120mg/kg

Kroger et al JCO 2017

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Anti-lymphocyte Globulin for Prevention of Chronic Graft-versus-Host Disease

Randomised Phase-3 study patients assigned in a 1:1 ratio to receive ATG or not, with stratification according to center and risk of disease

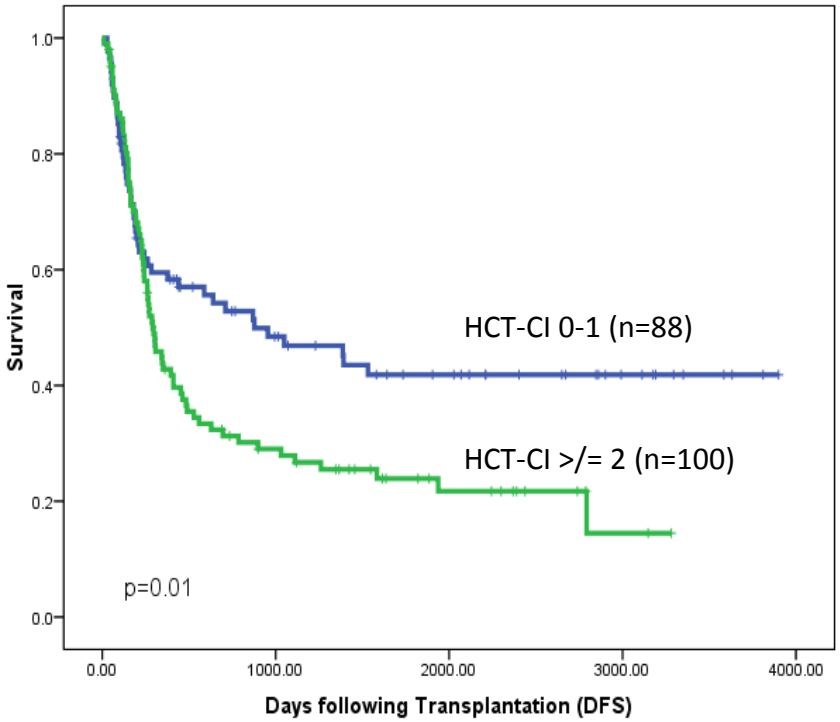
- n=168, median follow-up = 24 months
- Chronic GVHD = 32.2% (with ATG) vs 68.7% (no ATG) ($p<0.001$)
- Chronic GVHD free and Relapse Free Survival at 2yrs = 36.6 (with ATG) vs 16.8 (no ATG) ($p=0.005$)
- Relapse free ($p=0.21$)/Overall survival ($p=0.46$) /Non-relapse mortality ($p=0.6$)

Kröger N et al. N Engl J Med 2016

Kings College Conditioning Regimen: Flu/Bu/Campath RIC Protocol

Cohort Details	
Number=192 (86 F/ 106 M)	
Median Age =56 years (21-72)	
IPSS Low/ Int 1	50(26%)
Int 2/ High	44(23%)
MDS/AML	86 (45%)
URD= 148 (77%)	
MMUD=41 (21%) -9/10	

Cohort Details – Survival at 5yrs
OS = 42%
DFS = 33%
RA/RCMD OS = 63%
MDS-AML OS = 46%
CMML/RAEB OS = 25% and 24%



5-Year DFS
HCTCI 0-1 = 42%
HCTCI >/= 2 = 24%
p=0.01

Potter *et al* BBMT 2014

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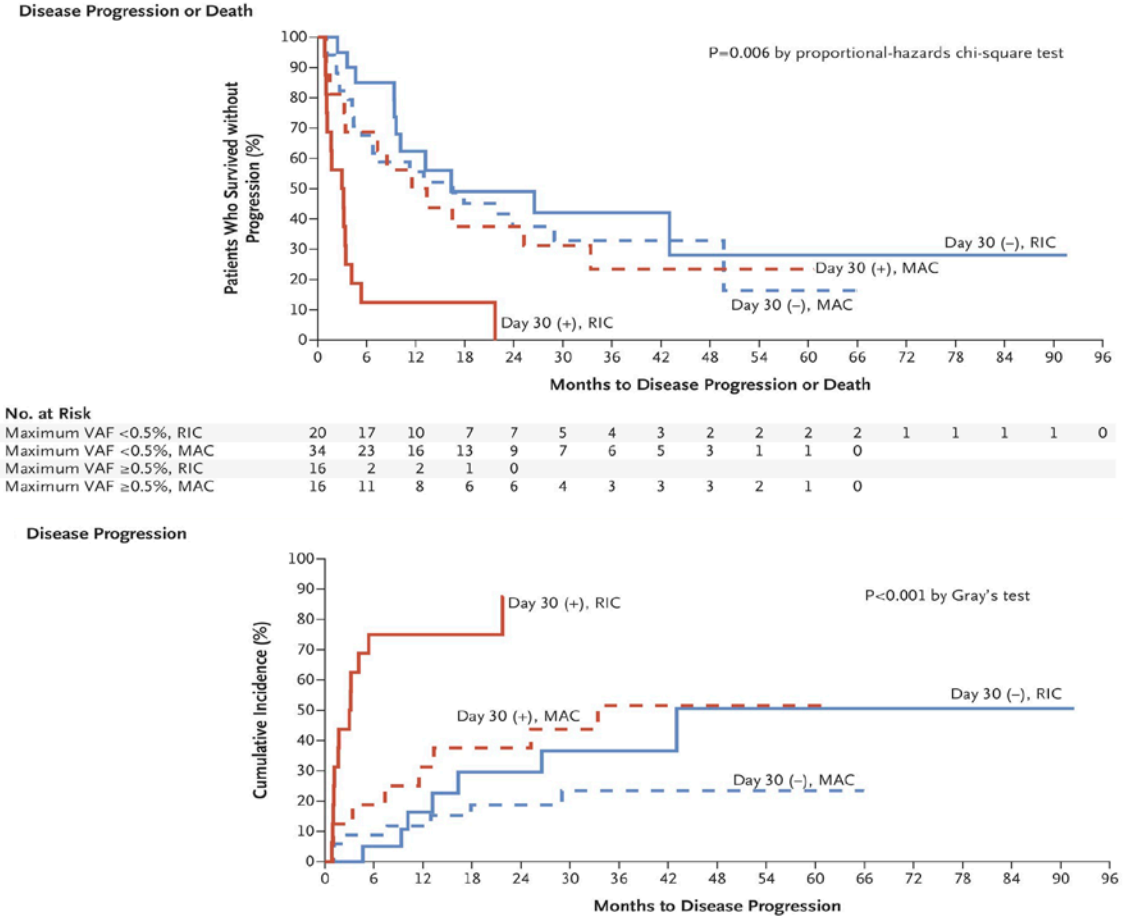
Mutation Clearance after Transplantation for Myelodysplastic Syndrome



- 86 of the 90 patients studies had a mutation
- Multivariate analysis showed that patients with a mutation and a variant allele frequency of at least 0.5% detected at day 30 had a higher risk of progression (P<0.001) and a lower 1-year rate of progression-free survival (P=0.002)

Duncavage et al NEJM 2018

Genetic Trickery — Escape of Leukemia from Immune Attack

Down-regulation of MHC class II genes (*HLA-DPA1*, *HLA-DPB1*, *HLA-DQB1*, and *HLA-DRB1*) at relapse post transplant to levels 3 to 12 times lower than in paired samples obtained at presentation.

In haploidentical transplants at relapse loss of mismatched haplotype leads to the failure of the GVL effect. The remaining minor antigen alloreactions and NK cytotoxicity are insufficient to prevent leukemic proliferation.

Escape from GVL effect and selection of increasingly genomic unstable clones with multiple mutations in stem/progenitor cells

Post-Transplant/Relapse Strategies

Donor Lymphocyte Infusion
- Pre-emptive +/-DLI
- Therapeutic +/-DLI
- +/- Azacitidine +/-DLI
- Chemotherapy +/- DLI

Vaccination Strategies
- B7.1/IL2; WT1; etc

Check Point Inhibitors Therapy
- CTLA4; PD1; PDL1; etc

Neoantigens/Leukemia Associated Antigen Specific T cells

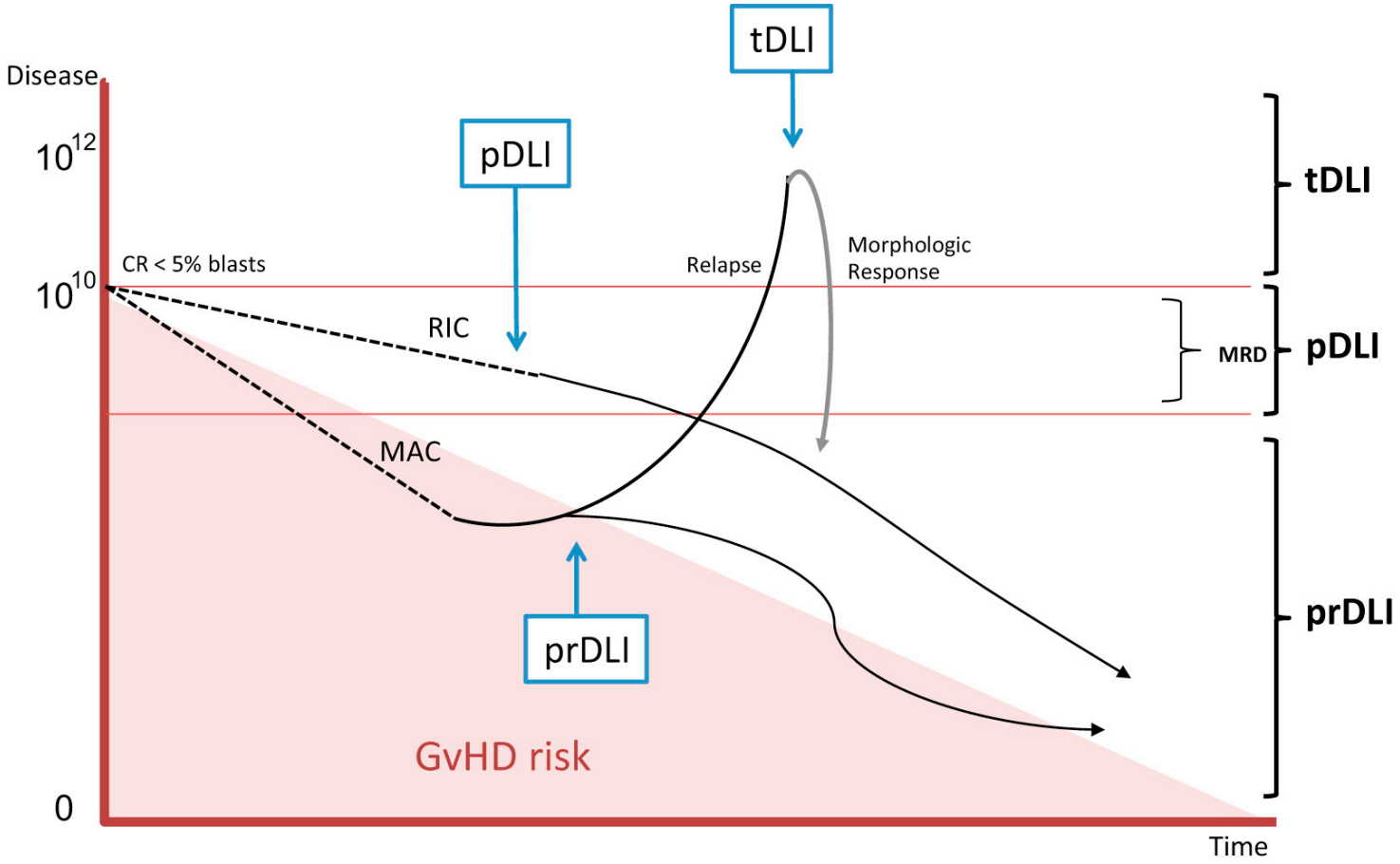
CAR123 Cellular Therapy

NK Mediated Cellular Therapy

Second Transplant

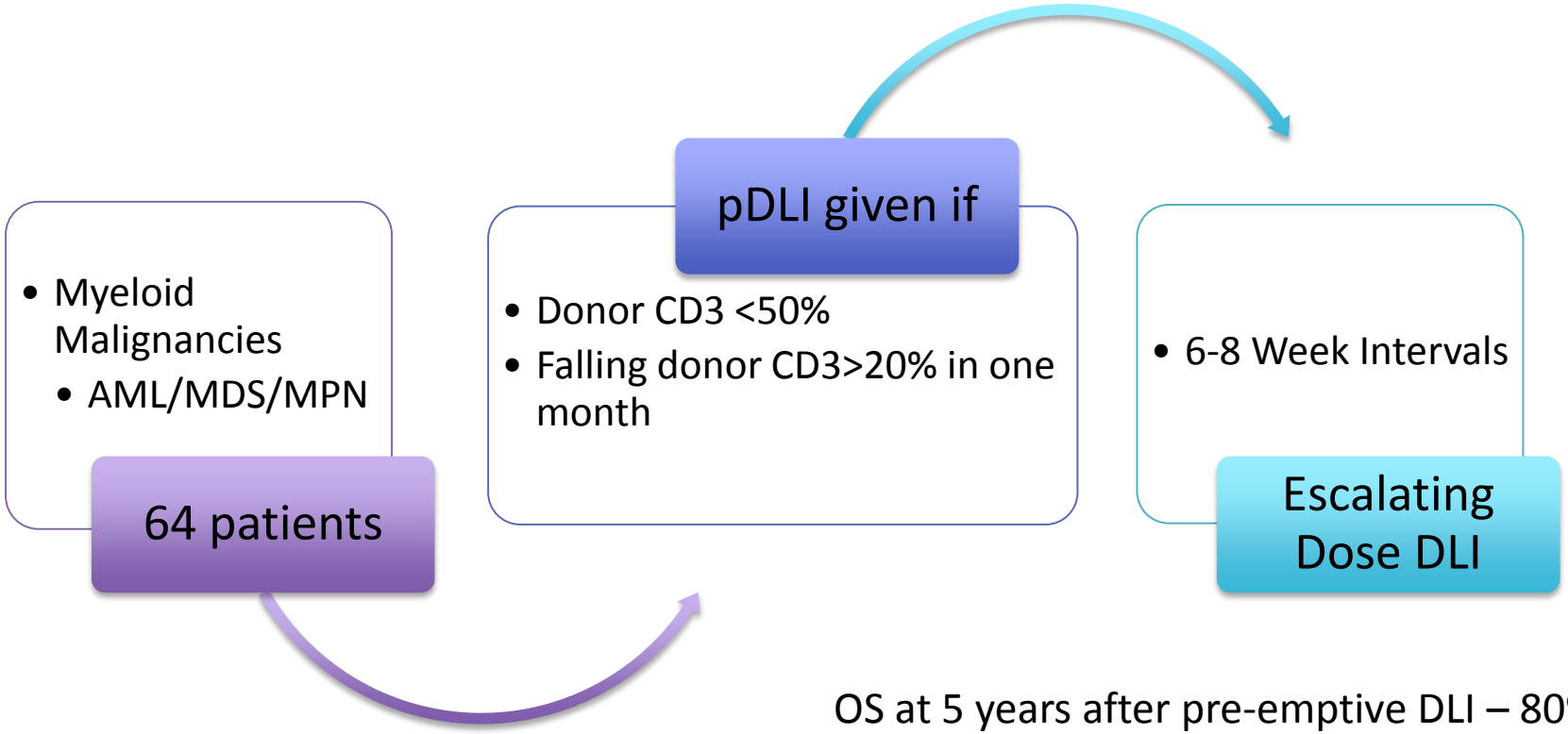
Antibody-based therapeutics (DARTs, BiTEs)
- CD33/CD3; MCLA-117/CD3; CD123/CD3

Different strategies for delivering DLI



Orti et al 2017

Early Administration of Pre-emptive DLI correlates with durable AML/MDS Remission



77% of patients achieved FDC or stable MDC after DLI

- 5yr OS was 91% in these patients

OS at 5 years after pre-emptive DLI – 80%

EFS at 5 years after pre-emptive DLI – 65%

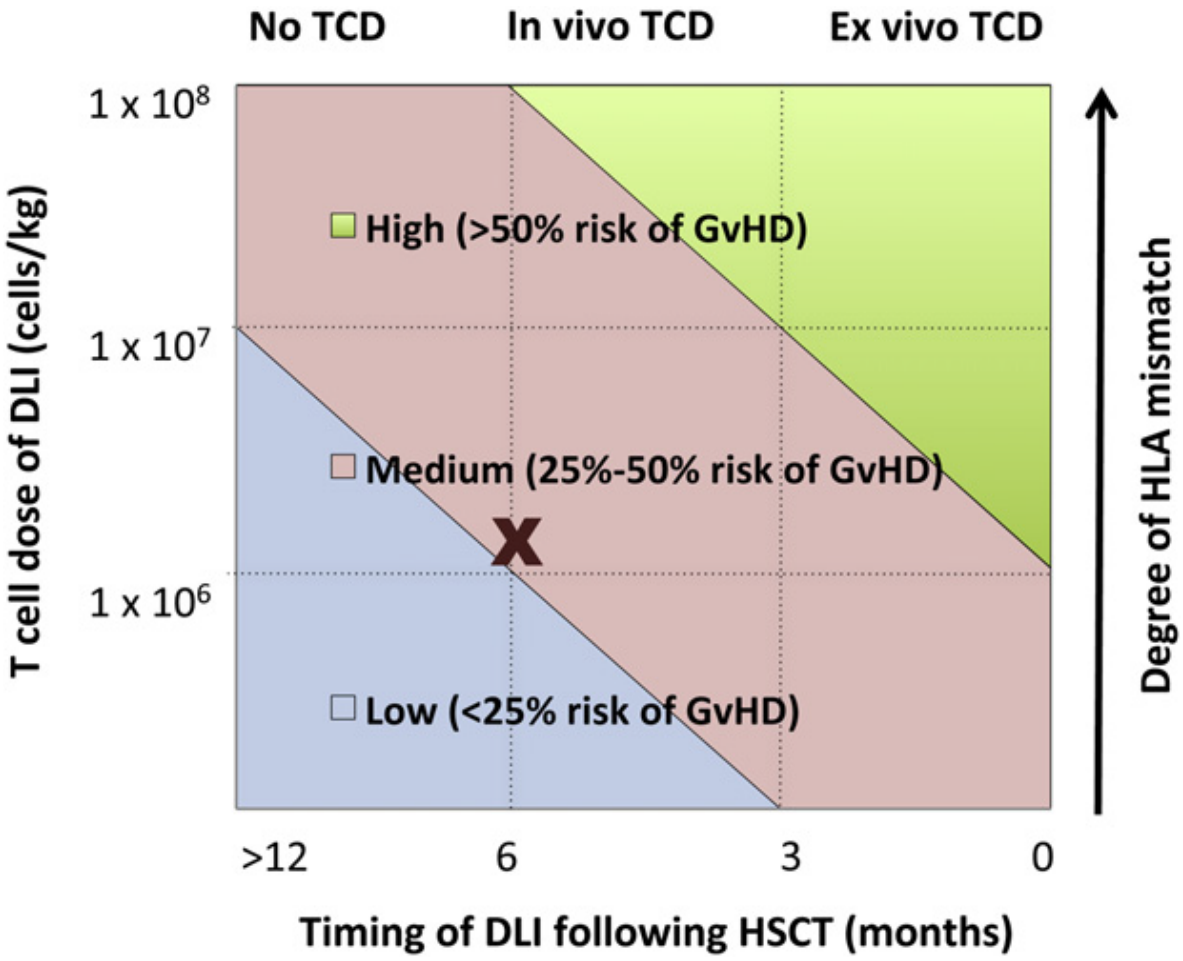
GVHD incidence – 31% (19% chronic extensive) after pre-emptive DLI

Limitations to current data

- Above data ➔ promising results but
  - Retrospective
  - Median time to DLI administration 6 months
  - Varying DLI schedule
  - Varying DLI dose
  - DLI given for mixed CD3 chimerism

  - **No randomised prospective data for DLI in MDS/AML**
  - **No accompanying prospective translational data**
  - **No evidence that pre-emptive or prophylactic DLI influences outcome in MDS/AML despite this being adopted as standard practice by many institutions**

But what is the sweet spot?



Maintenance with 5-Azacytidine for Acute Myeloid Leukemia and Myelodysplastic Syndrome Patients

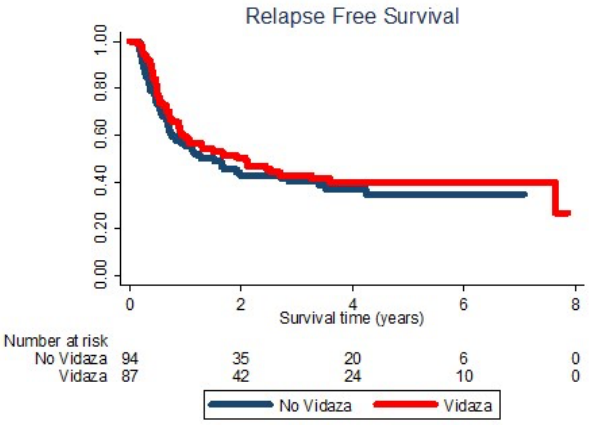
Demographics

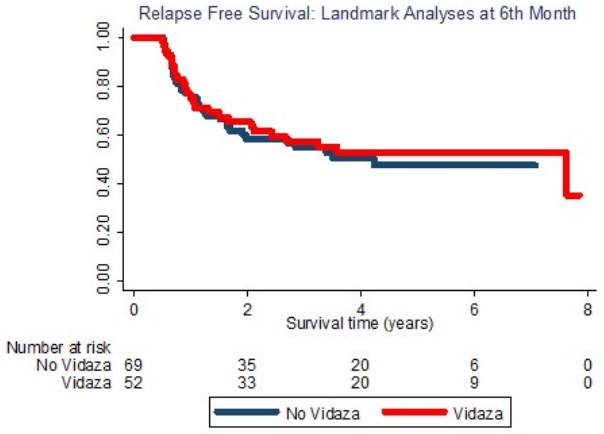
	Observation, N=94	SC Vidaza, N=87	p
Age, median, range	57 (20-75)	57, (19-72)	0.86
Disease, MDS	25 (26.6%)	22 (25.3)	
Disease status, AML			
CR1&2 with count recovery	27 (39.1%)	34 (52.3%)	
CR without count recovery	12 (17.4%)	17 (26.2%)	
Active disease	30 (43.5%)	14 (21.5%)	0.025
Disease status, MDS			
CR	6 (24%)	4 (18.2%)	
Active disease	19 (76%)	18 (81.2%)	0.63
Cytogenetics			
Good	15 (16%)	8 (9.2%)	
Intermediate	42 (44.7%	33 (37.9%)	
Bad	37 (39.4%)	46 (52.9%)	0.14
Hematopoietic stem cell source			
Bone marrow	32 (34%)	31 (35.6%)	
PBSC	60 (63.8%)	55 (63.8%)	
CB	2 (2.1%)	0	0.96
Donor			
MRD	31 (33%)	33 (37.9%)	
MUD	53 (56.4%)	44 (50.6%)	
Mismatched donor	10 (10.6%)	10 (11.5%)	0.7
Conditioning intensity			
Non-myeloablative	18 (19.1%)	14 (16.1%)	0.7
HCT-CI, median, range	2 (	3	
0-1	37 (39.4%)	28 (32.2%)	
2-3	37 (39.4%)	22 (25.3%)	
≥4	20 (21.3%)	37 (42.5%)	0.07

Transplant outcomes

		Median, yrs.	P-value	HR* (95%CI)	P-value*
RFS	Obs.	1.28		Ref.	
	AZA	2.07	0.5	0.77 (0.51-1.14)	0.19
RFS, landmark analysis					
Day 180	Obs.	4.24		Ref	
	AZA	7.64	0.7	0.69 (0.39-1.21)	0.19
Day 270	Obs.	NA		Ref	
	AZA	7.64	0.8	0.70 (0.33-1.46)	0.34
Day 360	Obs.	NA		Ref	
	AZA	7.64	0.19	0.51 (0.19-1.36)	0.18
RFS, stratified analysis					
Group 1	Obs	1.28		Ref	
	AZA, 1-4 cycles	0.54	0.04	1.5 (0.94-4.42)	0.09
Group 2	Obs**	3.40		Ref.	
	AZA, 5-8 cycles	1.06	0.21	0.81 (1.23-0.35)	0.64
Group 3	Obs**	NA		Ref	
	AZA, 9-12 cycles	7.64	0.16	0.47 (0.19-1.17)	0.11

*The results show the Cox-regression analyses adjusted for disease type, cytogenetics, disease status at SCT, conditioning intensity, stem cell source, donor type, HCT-CI and second SCT.
** Obs. included ptsRFS>150
***Obs. included ptsRFs>270

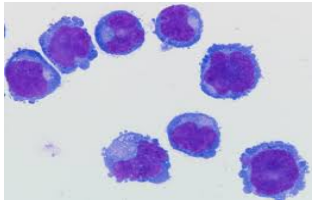


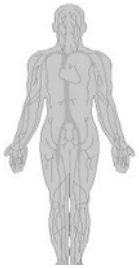


Prospective randomized controlled trial. Most patients did not complete the planned 12 cycles. Study closed early due to slow accrual

Oran et al ASH Abstract 971 Dec 3 5.30pm

Novel therapeutics following Relapse: AZA (= / - DLI)





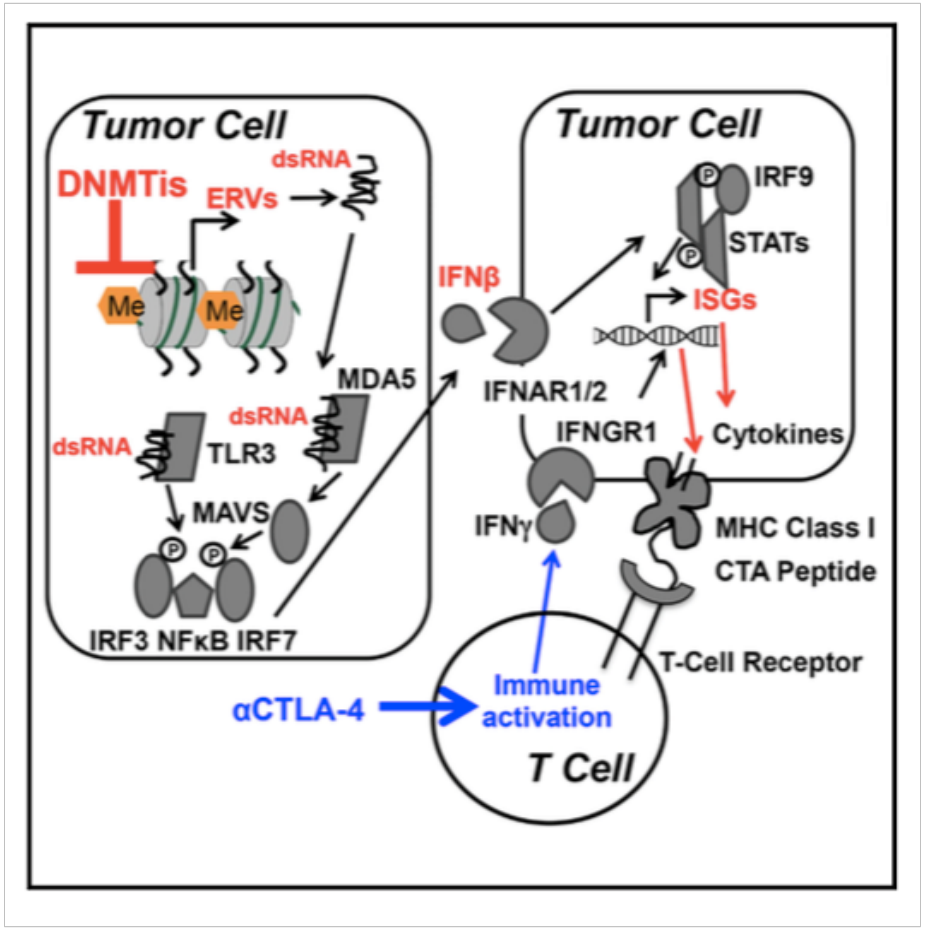
Cancer/testis antigens are upregulated *in vitro* and *in vivo* by these drugs hypothetically sensitizing ("priming") malignant cells to DLIs.

Schroeder *et al* 2015 BBMT: AZA and DLI for relapse

- **154 patients (AML n=24; MDS n=28)**
- **All patients received a median number of 4 courses of Aza (range, 4 to 14)**
- **DLI :105 patients (68%; median DLI, 2; range, 1 to 7).**
- **CR and PR: 27% and 6%, respectively, resulting in an ORR of 33%.**
- **MVA identified molecular only relapse and MDS (as predictors for CR)**
- **OS at 2 years was 29% ± 4%**

(Goodyear et al., Blood 2010, Almstedt et al., Leuk. Res. 2010),

DNMTi Induce Interferon Responses



- DNMTis induce an interferon response in cancer cells by activating dsRNA sensors
- DNMTis induce ERV demethylation and expression helping trigger the dsRNA response
- DNMTi viral defense genes in melanoma track with patient response to immune therapy
- DNMTi treatment sensitizes to anti-CTLA-4 immunotherapy in a melanoma mouse model

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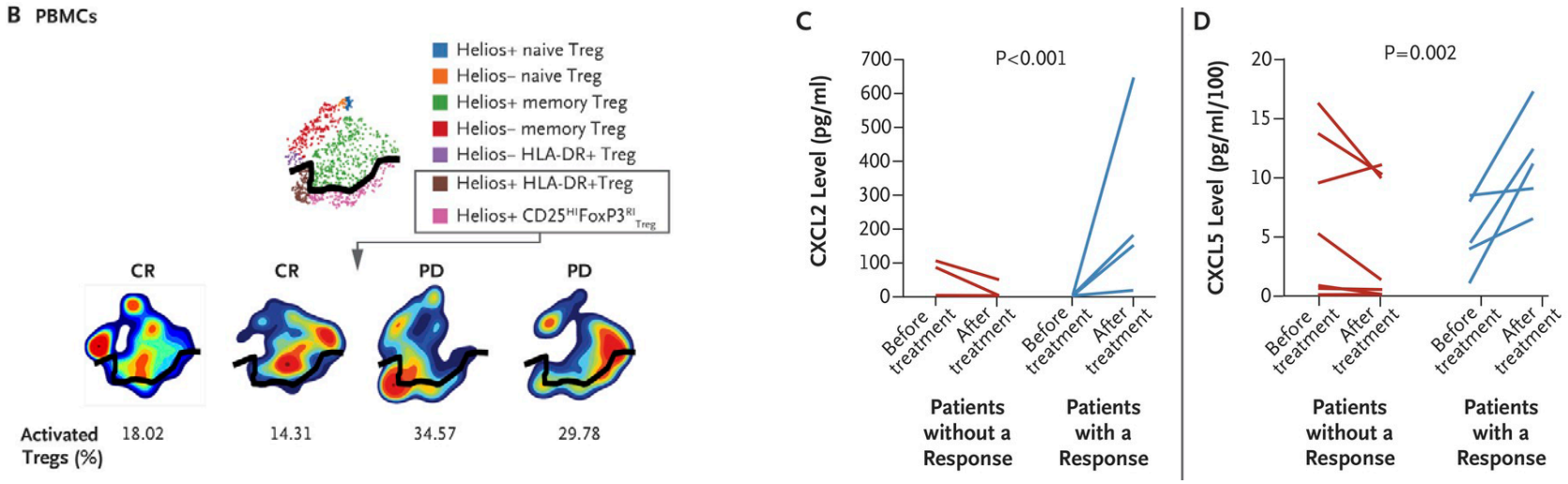
Ipilimumab for Patients with Relapse after Allogeneic Transplantation

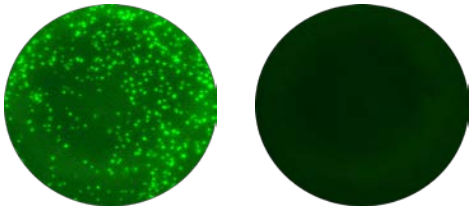


- N=28 (Phase 1/1B)
- AML /MDS = 18
- CR = 5/18 (27%)
- Immune related toxicity = 21%
- GVHD = 14%
- Patients who had a complete response or stable disease had fewer CD4+ Treg cells and more CD4+ Tcon cells than patients with progressive disease.

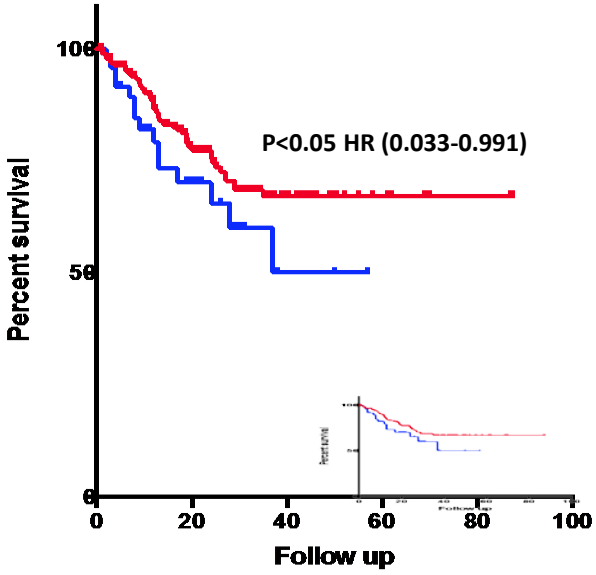
Davids MS et al. N Engl J Med 2016

Impact of Neoantigens on survival in MDS

Characteristics	Patients with neoantigens	Patients with no neoantigens	P value
Number	129	51	
Age in years (median)	68	68	NS
Sex (Male / Female)	86 /43	31 /20	NS
Type of MDS			NS
RARS	10	6	
RCUD	7	1	
RCMD	42	10	
Isolated 5q-	1	2	
RAEB	41	21	
Other	28	11	
IPSS Categories			NS
Low	46	15	
Intermediate-1	55	20	
Intermediate-2	21	12	
High	6	4	
Number of mutations (median)	2.1	1.3	P<0.001
Progression to AML			
Yes	26/129 (20.1%)	8/51 (15.7%)	NS
Vital Status			
Dead	28/129	15/51	NS



IFN-γ



No Neoantigen: Increased expression of CTLA4
(*p <0.05, ** p<0.01

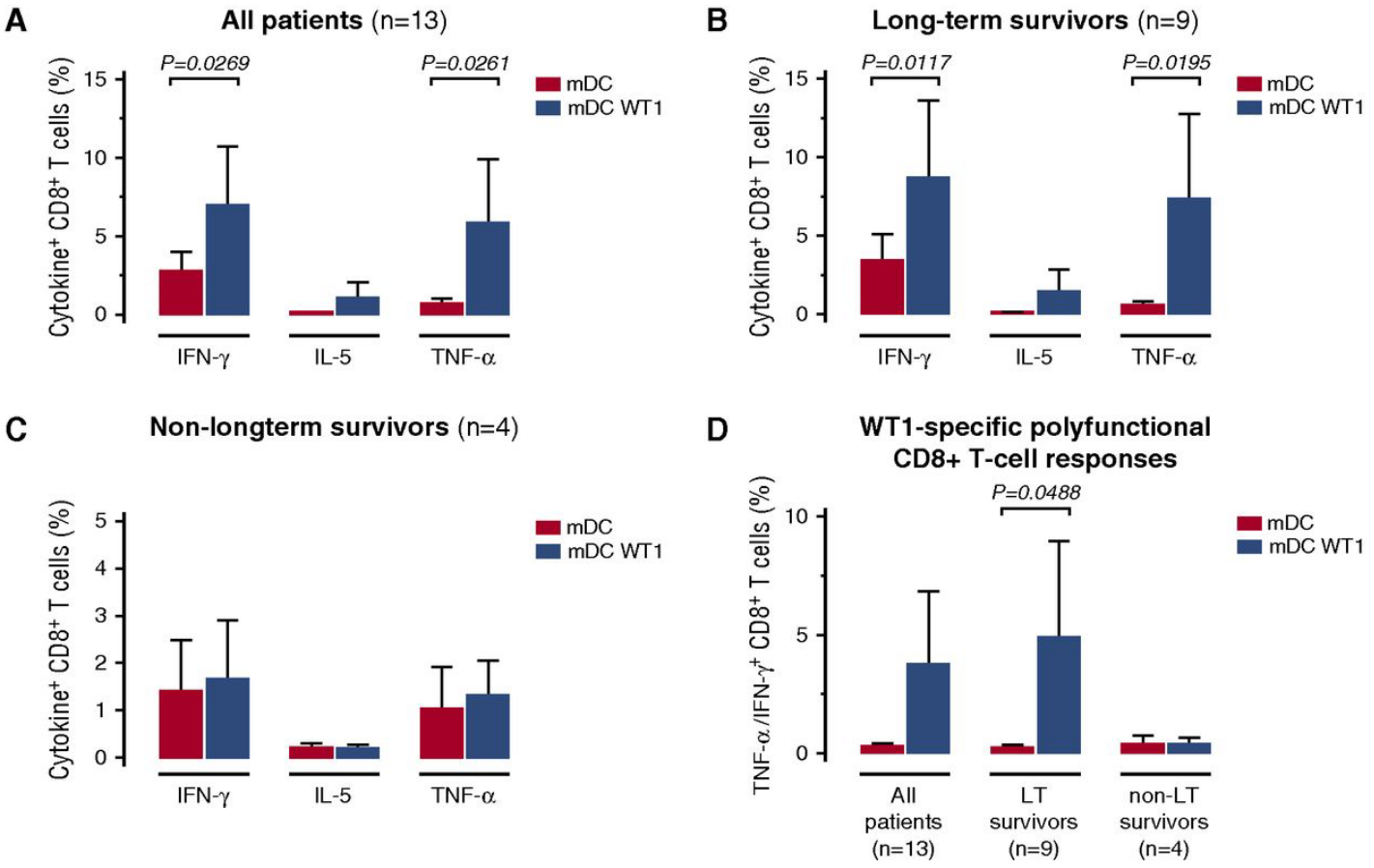
Collaboration with Dresden

Tom Coats, et al 2018

Intracellular cytokine staining of CD8+ DILs after re-stimulation with mature DCs alone or WT1 mRNA-electroporated DCs

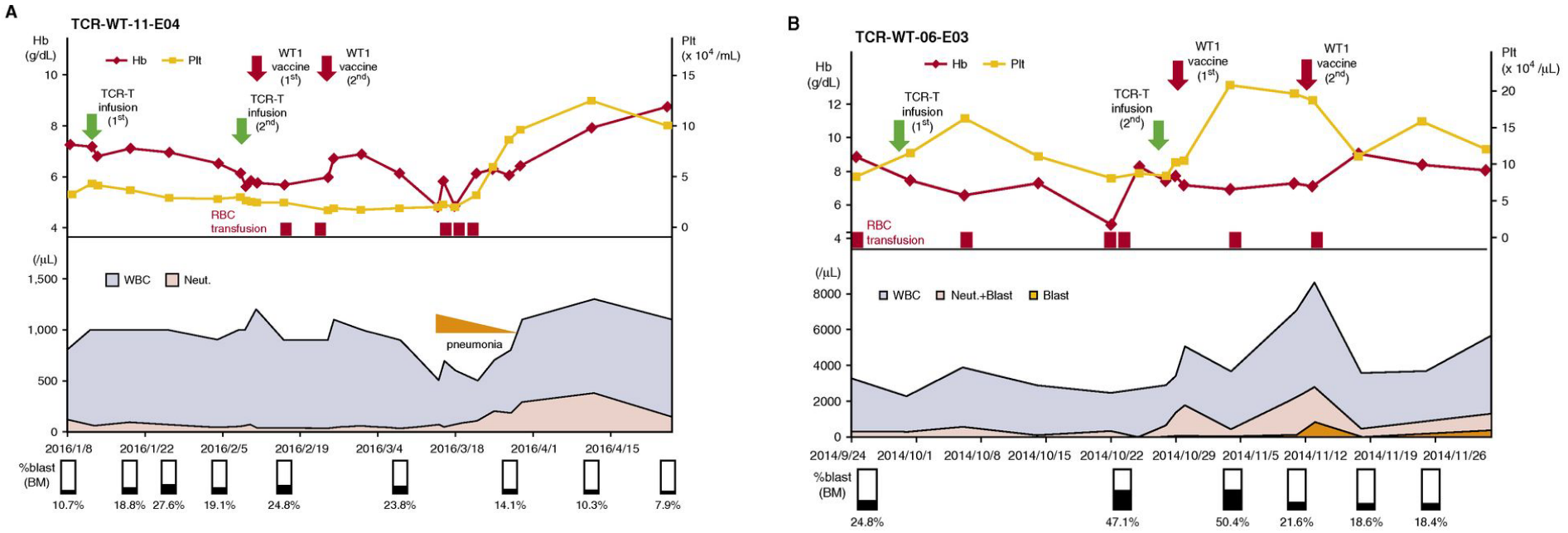
- N=30 High Risk AML
- Anti-leukemic response in 13
- 9/30: sustained CR
- 4/30: Stabilisation of disease

- Polyepitope WT1 specific CD8 response correlated with OS



Sébastien et al Blood 2017

Clinical courses of TCR-WT-11-E04 and TCR-WT-06-E03 after the WT-specific TCR-T cell transfer.



- HLA-A 24:02 restricted WT1 specific TCR redirected T-cells for AML-MDS
- Mutated WT1 peptide with adjuvant
- 16% CD8+ WT1 specific T cells

Isao et al. Blood 2017

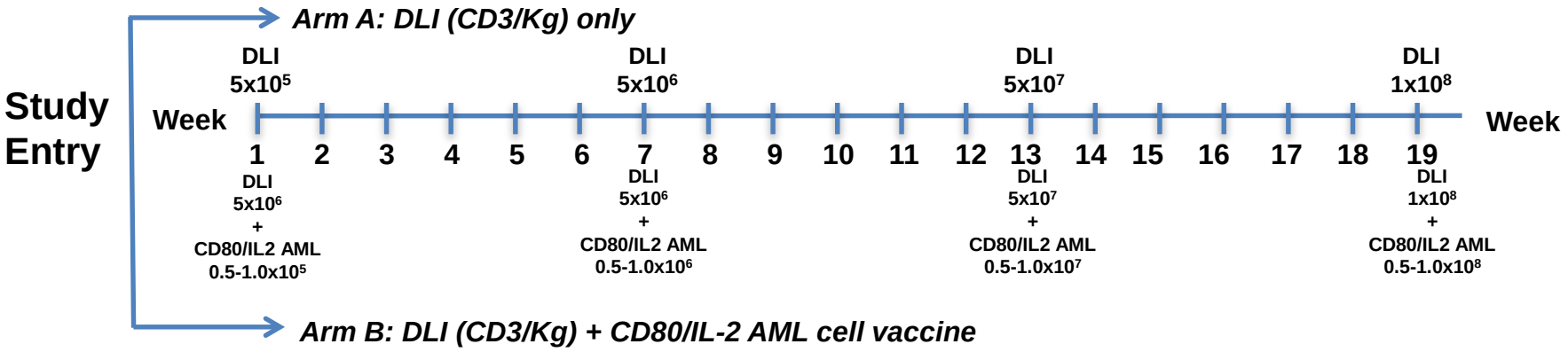
CD80/IL-2 immune gene therapy trials at Kings

- B7.1 is an immune co-stimulatory molecule and IL-2 a cytokine which stimulates an immune response.
- The “AML Cell Vaccine” (ACV) is patient specific, derived from the patients’ own AML cells which are modified ex-vivo to express B7.1 (CD80) and IL-2
- AML cells then g-irradiated and re-administered to the patient as a whole cell vaccine.
- Modification of the AML cells to express B7.1 and IL-2 enhances the efficiency of antigen presentation to the immune system, generating an anti-leukaemia immune response

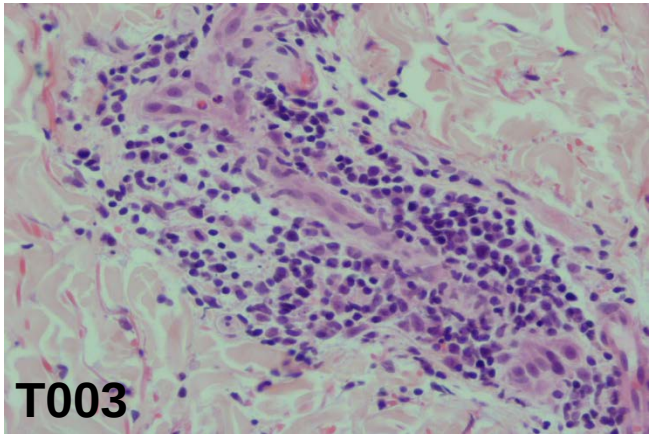
CD80/IL-2 Immune Gene Therapy

Pre-study entry conditions:

- Relapsed AML/MDS, following allogeneic HSCT
- >50% donor CD3 chimerism at relapse
- <5% BM blast following cytoreductive chemotherapy

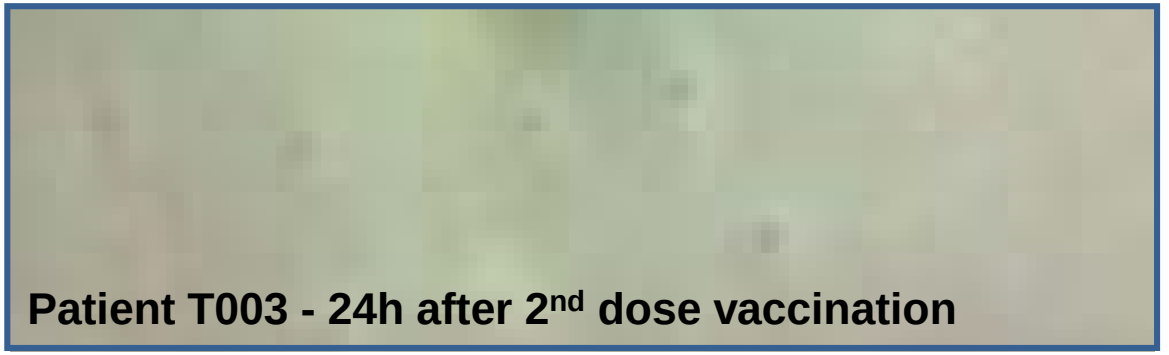


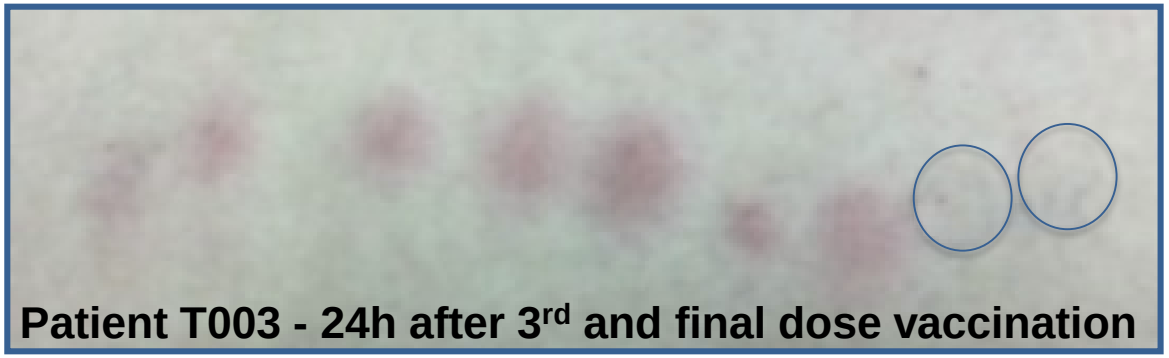
Delayed Type Hypersensitivity (DTH) following DLI + CD80/IL-2 AML cell vaccination



Skin biopsy 76h post 3rd injection

In complete cytogenetic and molecular CR

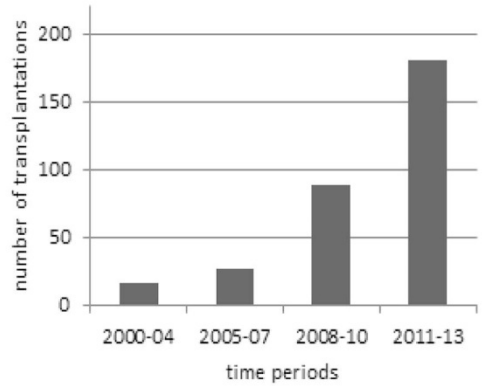




7 Patients enrolled to date:
- Confirmed feasibility
- No acute toxicities / adverse events
- Safety/efficacy studies completely satisfactory

Personalising the transplant for MDS
Optimising opportunities for success

Allogeneic SCT for Patients Age ≥ 70 Years with MDS: A Retrospective Study of the MDS Subcommittee of the Chronic Malignancies Working Party of the EBMT



N=313 Median age 72 (70-78)

MDS = 221, Sec AML = 92

MAC = 52, RIC = 207, Non myeloablative = 54

NRM at 1yr and 3y = 32% and 38%

OS = 34%

Decreasing disease burden pre-transplant

Tailor the treatment according to genetic and MRD profile

Recognise opportunities for excellent long-term outcomes in lower risk cases

Early adaptive immunotherapy and/or post-tx maintenance in high risk cases

Need for prospective randomized trials

Presentation 7: Recent Advances…

5. **Case Study - Mr X**
   - **Previously fit, 65 year old man with symptoms of anaemia of 6 month duration.**
   - **Bone marrow- hypercellular**
   - **WCC- 1.6x109/l (N=0.3x109/l); Hb- 10.1G/dl; Plts- 21x109/l; Bone marrow blasts- 7%; cytogenetics- 47,XY,+8; Mutation-NRAS(G12A), HCT CI- 1; VUD donor 10/10; CMV -/-**

   Treatment Option

   a. Demethylating agents alone
   b. Demethylating agents followed by alloHSCT
   c. Intensive chemotherapy followed by alloHSCT
   d. AlloHSCT with myeloablative conditioning upfront
   e. Reduced Intensity Conditioning with post-transplant MRD monitoring
   f. a, b & c

Acknowledgment

Kings Health Partners Bone Marrow Transplant Team

Dr Victoria Potter

Director of Bone Marrow Transplantation and Immune Effector Cell Therapy Program

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Guy's and St Thomas' NHS Foundation Trust
King's College Hospital NHS Foundation Trust
South London and Maudsley NHS Foundation Trust