Calling All Super Heroes

The Villain Returns: Disease Relapse Following Transplant, MRD Assessment and Treatment Strategies

Philip McCarthy, MD
Roswell Park Comprehensive Cancer Center

Veronika Bachanova, MD, PhD
University of Minnesota Medical Center

November 9, 2018

Disclosures

The following faculty and planning committee staff have the following financial disclosures:

Name	Institution	Disclosure
Alan Howard, PhD	CIBMTR	Jazz Pharmaceuticals, Travel/Lodging, Consultant
Misty Evans, DPN	Vanderbilt	Jazz Pharmaceuticals, Monetary, Speakers Bureau
Veronika Bachanova, MD, PhD	University of Minnesota	None
Philip McCarthy, MD	Roswell Park Comprehensive Cancer Center	Celgene, Honoraria, Advisory Board Karyopharm, Honoraria, Advisory Board Celgene, Institute research Support, Research Medscape, Honoraria, Generating content for online lecture Axis, Honoraria, Generating content for MM lecture

Treating Disease Relapse after Allogeneic Hematopoietic Stem Cell Transplantation

- 1975 NEJM review of BMT - E. Donnall Thomas (BMT pioneer & Nobel Prize laureate) noted that one of the major barriers to the successful application of BMT was: "***Relapse of Disease***".

- State of the Science Symposium – FEB 2014

High Priority Trial Categories

  - ***Prevention of Post-Transplant Relapse***
  - Application of HCT to Selected Non-Malignant Diseases
  - Prevention and Treatment of GVHD
  - Avoidance of HCT Complications

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Learning objectives

- At the conclusion of this session, attendees will be able to:
  - Discover the incidence and continuing challenges of hematopoietic malignancy relapse following allogeneic hematopoietic stem cell transplantation.
  - Compare innovative methodologies to detect pre- and post-HCT minimal residual disease (MRD).
  - Analyze the promise of innovative cellular therapeutic strategies to treat and prevent relapse in HCT patients.
  - Evaluate the strategies employed when utilizing new targeted immunotherapeutic approaches to treat disease relapse.

Philip McCarthy, MD

Professor of Oncology and Internal Medicine
Director, Blood and Marrow Transplant Center,
Department of Medicine
Roswell Park Comprehensive Cancer Center

Minimal Residual Disease (MRD) Testing and Prevention of Relapse in Multiple Myeloma

Veronika Bachanova, MD, PhD

Associate Professor of Medicine
Division of Hematology, Oncology and Transplantation
University of Minnesota

AML and ALL Relapse Following HCT and Treatment Strategies

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Let's go!

Minimal Residual Disease (MRD) Testing and Prevention of Relapse in Multiple Myeloma

Philip McCarthy
Roswell Park Comprehensive Cancer Center
Buffalo, NY
November 2018

Disclosures for Philip McCarthy, MD

The presentation will discuss off-label use of drugs for multiple myeloma treatment	
Research Support/P.I.	Celgene
Employee	No relevant conflicts of interest to declare
Consultant	Bristol-Myers Squibb, Celgene, Janssen, Karyopharm, Takeda, Amgen, Sanofi, The Binding Site, Magenta Therapeutics
Major Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	No relevant conflicts of interest to declare
Honoraria	Bristol-Myers Squibb, Celgene, Janssen, Karyopharm, Takeda, Amgen, Sanofi, The Binding Site
Scientific Advisory Board	No relevant conflicts of interest to declare

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Minimal Residual Disease Testing

- After Primary Therapy
  - Biomarker for prognosis
- At time points during follow-up/maintenance
  - Biomarker for prognosis
  - Endpoint for stopping or continuing therapy?
- Monitor for relapse
- Trial Design
  - Patient Stratification
  - Criterion for randomization to continued therapy or stopping therapy
  - Risk assessment for treatment arm selection
  - Can MRD serve as a surrogate endpoint for PFS/OS?

Treatment for the Transplant Eligible Newly Diagnosed Multiple Myeloma (NDMM) Patient

- Autologous Stem Cell Transplant (ASCT) after induction therapy
  - Standard for NDMM patient even with novel drug availability
- Maintenance +/-consolidation therapies post ASCT
  - Lenalidomide[1-3] (Len) and bortezomib[4] maintenance prolong response and Len maintenance improves overall survival[2,5-7]
- However the majority of patients will have relapse/progression of disease
  - Continue to test new strategies to improve outcome
  - Add to standard maintenance therapy to improve outcome
  - *Early surrogate endpoints for long term outcome (PFS/OS) must be tested in clinical trials so as to prevent studies that must remain open for 10 years or longer especially for an OS endpoint (Examples include Minimal Residual Disease (MRD) testing and Immune Profiling)*

- **1. Palumbo A et al NEJM; 2014, 371:895; 2. McCarthy P et al NEJM; 2012, 366: 1770; 3. Attal M et al NEJM; 2012, 366:1782; 4. Sonneveld P et al JCO; 2012, 30:2946; 5. McCarthy P et al JCO; 2017, 35:3279; 6. Holstein S et al Lancet Haem; 2017: 4:e431; 7. Gay et al JAMA Oncology; 2018, August**

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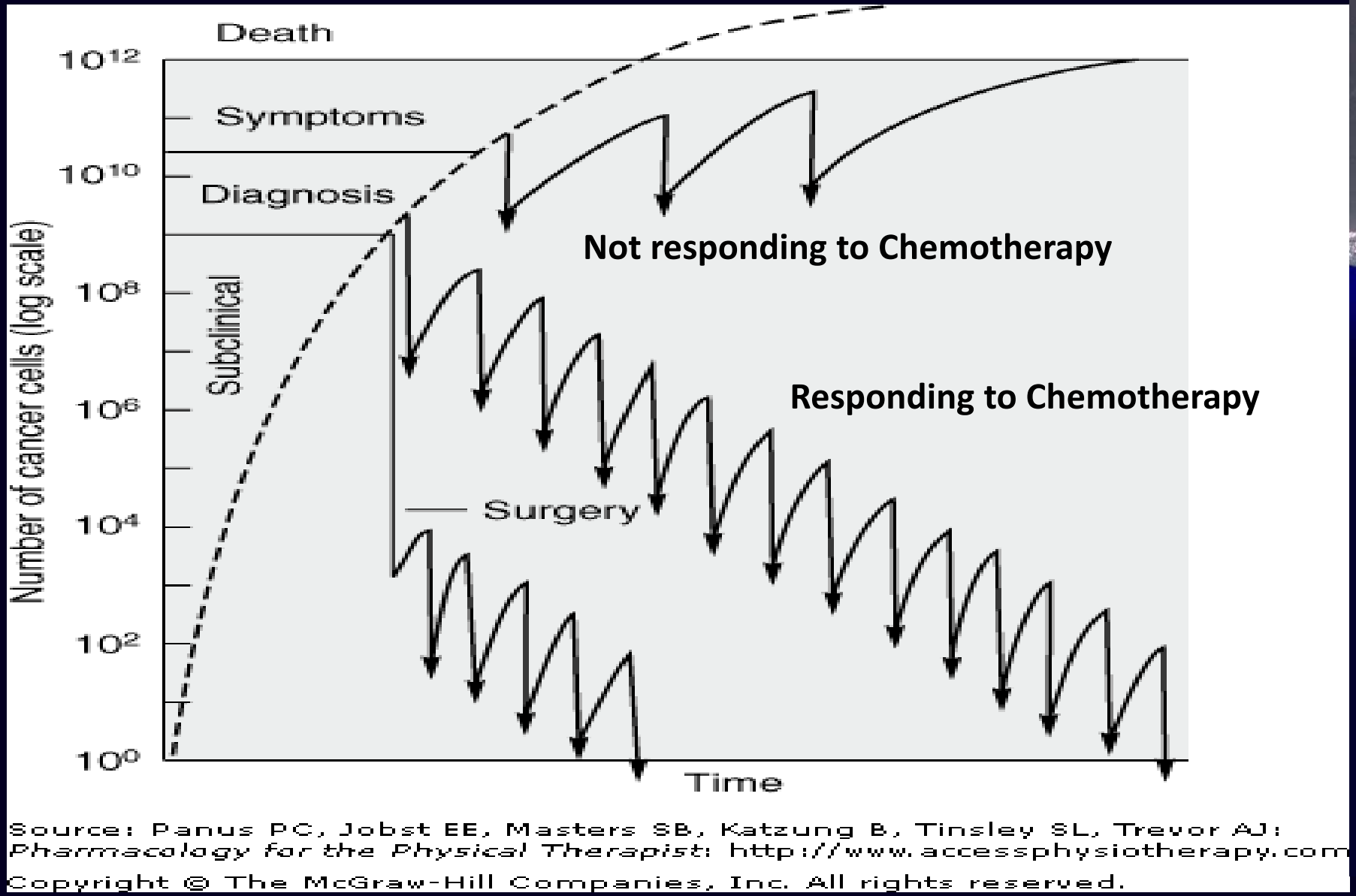
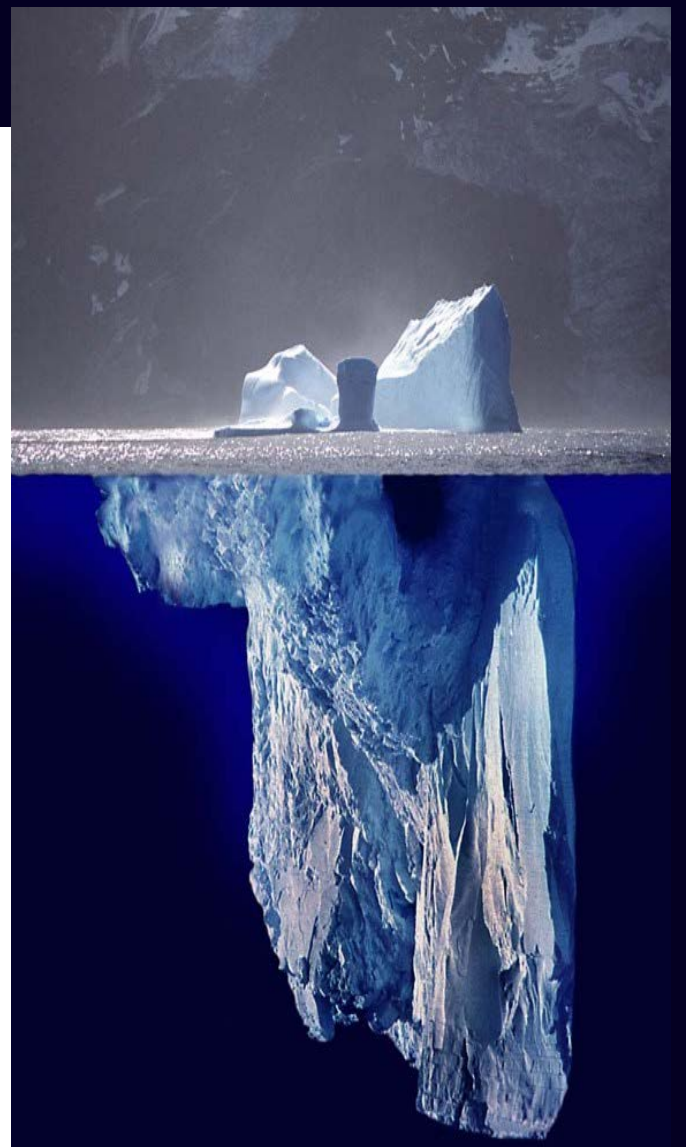
Fractional Cell Kill and the Tip of the Iceberg (10%)



Source: Panus PC, Jobst EE, Masters SB, Katzung B, Tinsley SL, Trevor AJ: *Pharmacology for the Physical Therapist*: http://www.accessphysiotherapy.com



https://commons.wikimedia.org/wiki/File:Iceberg.jpg

https://en.wikipedia.org/wiki/Fractional_kill

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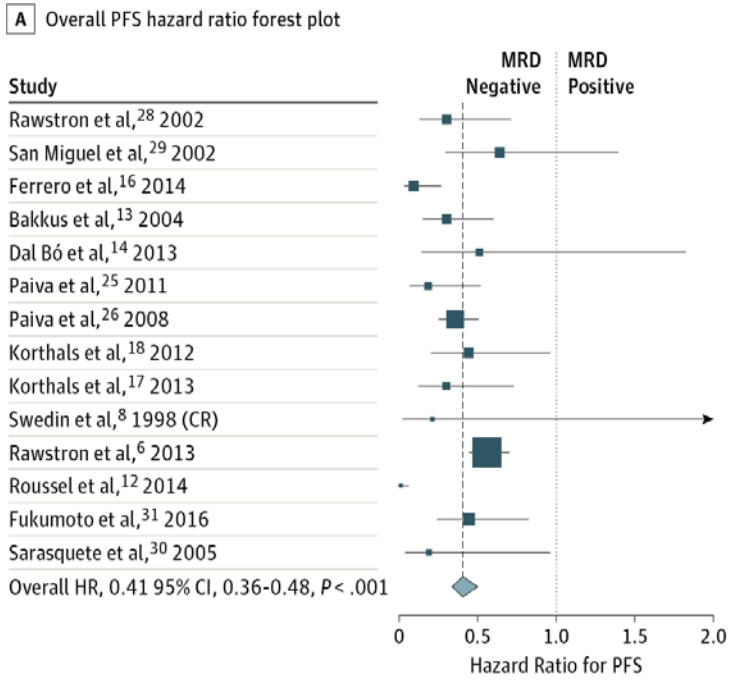

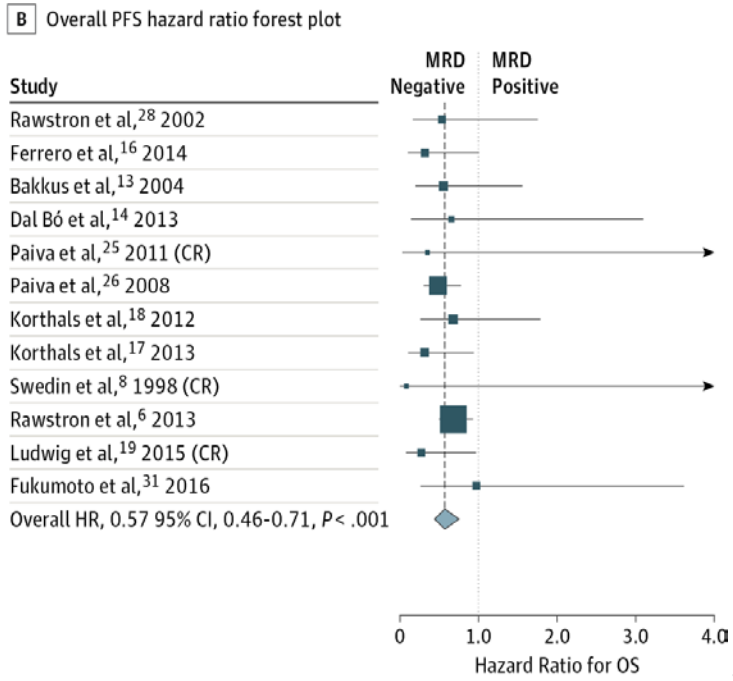

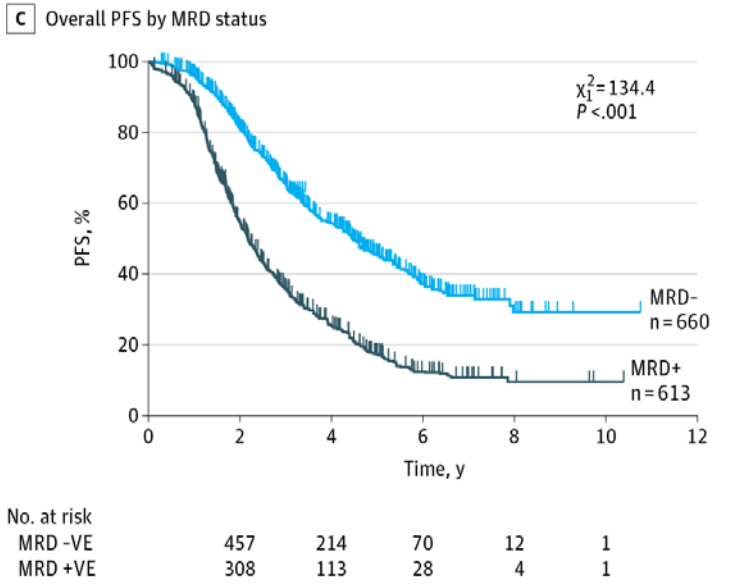

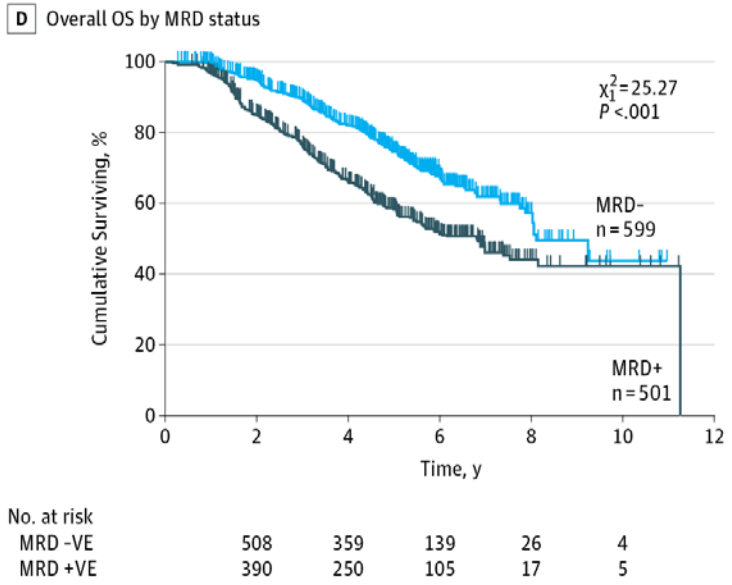

JAMA Oncology | Original Investigation

Association of Minimal Residual Disease With Superior Survival Outcomes in Patients With Multiple Myeloma
A Meta-analysis

Nikhil C. Munshi, MD; Herve Avet-Loiseau, PhD; Andy C. Rawstron, PhD; Roger G. Owen, MD; J. Anthony Child, MD; Anjan Thakurta, PhD; Paul Sherrington, PhD; Mehmet Kemal Samur, PhD; Anna Georgieva, MD, PhD; Kenneth C. Anderson, MD; Walter M. Gregory, PhD

JAMA Oncol. 2017;3(1):28-35. doi:10.1001/jamaoncol.2016.3160
Published online September 15, 2016.

PFS: 14 studies (n=1273) & OS: 12 studies (n=1100) CR analysis: 5 studies (n=574) for PFS & 6 studies (n=616) for OS

PFS:MRD-negative, HR=0.41;95%CI,0.36-0.48;*P*<0.001

OS:MRD negative, HR=0.57;95%CI,0.46-0.71;*P*<0.001

CR/PFS:MRD negative, HR=0.44;95%CI,0.34-0.56; *P*<0.001

CR/OS:MRD negative, HR=0.47;95%CI,0.33-0.67; *P<0.001*

MRD Assays: Multiparameter Flow Cytometry (10^{-4} to 10^{-6}) (n=9), Allele-specific oligonucleotide quantitative Polymerase Chain Reaction (10^{-4} to 10^{-6}) (n=11), Next Generation Sequencing (10^{-6}) (n=1)

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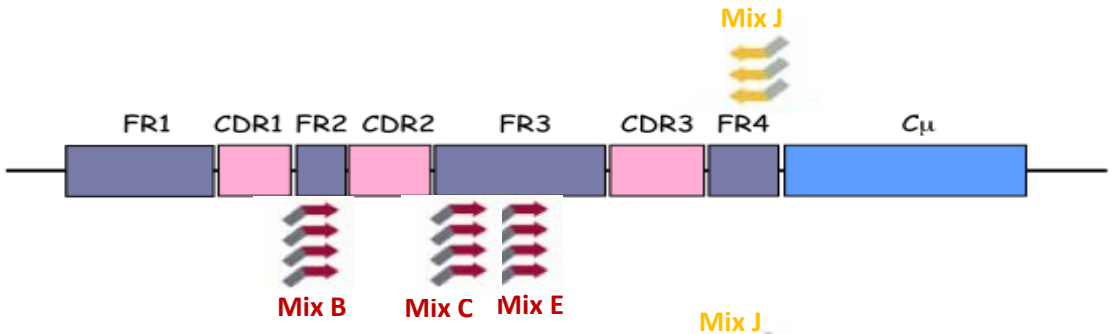
Next Generation Sequencing (NGS): Technical principles

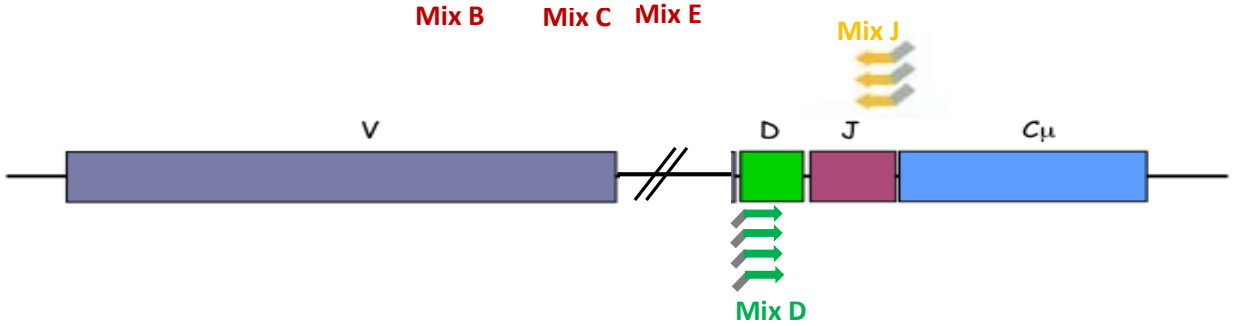
Sequenta Lymphosight, now Adaptive Biotechnologies

Functional Allele

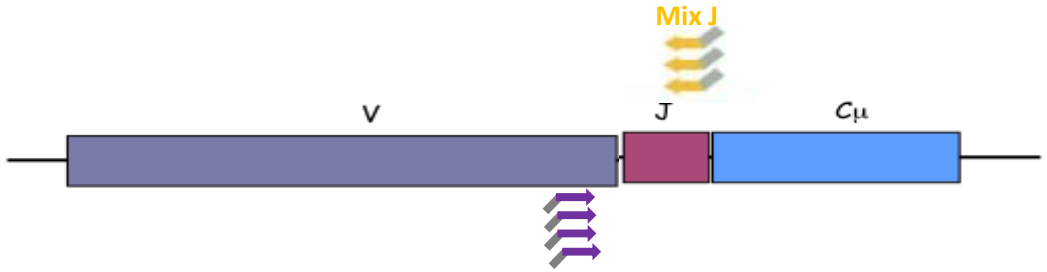
Locus IGH 14q32



Non Functional Allele

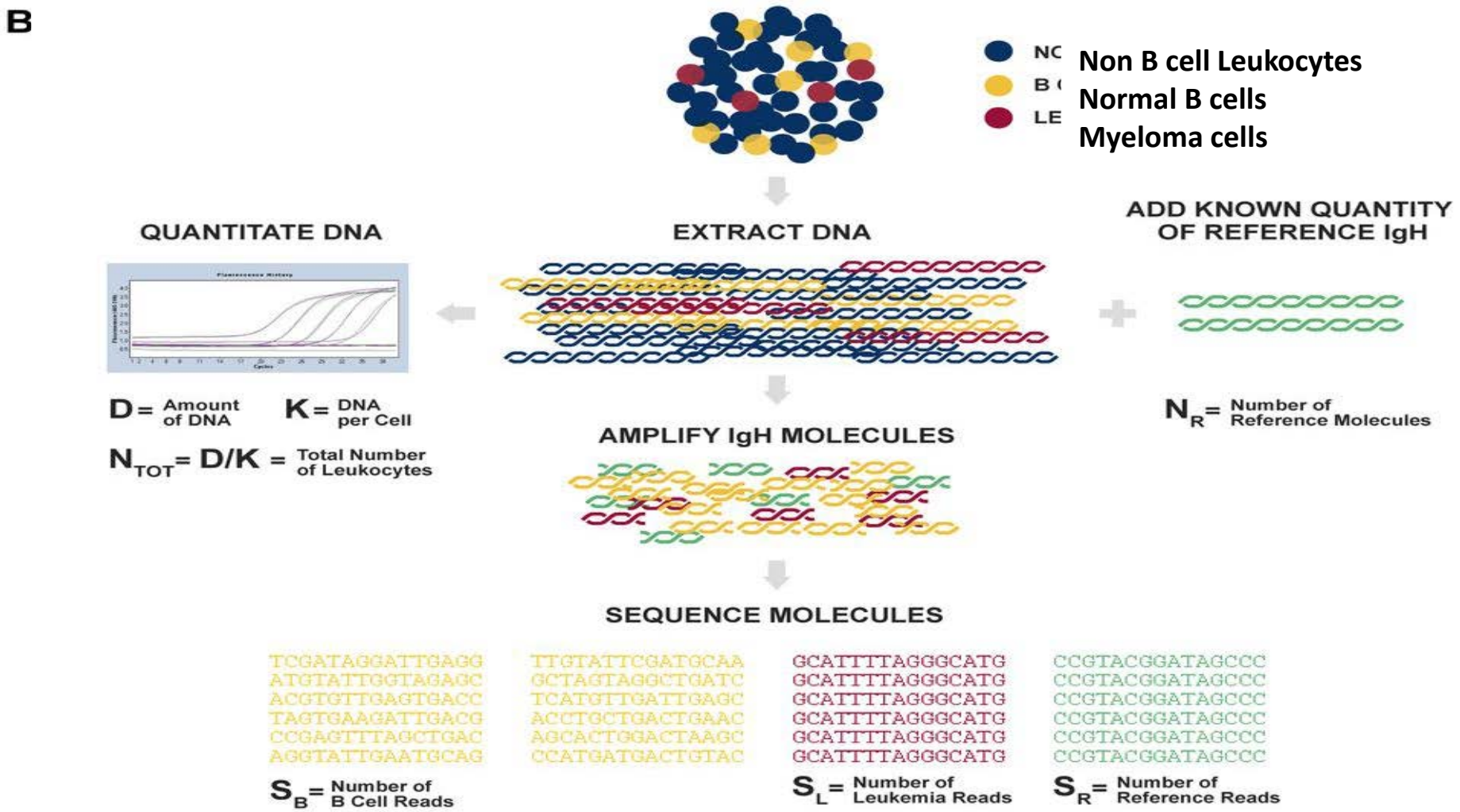


Locus IGK 2p11



Courtesy H Avet-Loiseau
Blood 2017 130:435

NGS: Technical principles



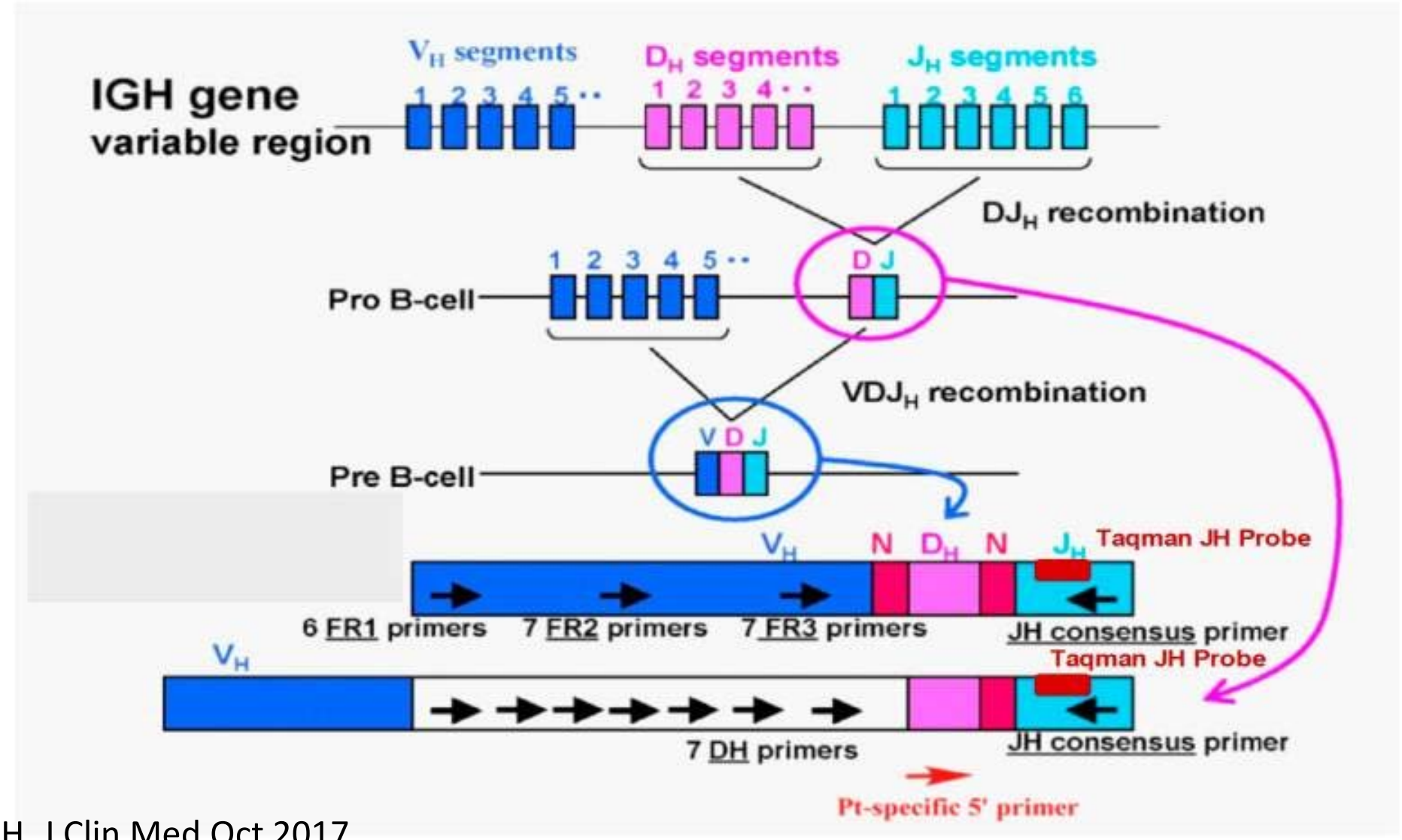
Courtesy H Avet-Loiseau
Blood 2017 130:435

FREQUENCY OF MYELOMA CLONE AMONG B CELLS = $S_L / (S_L + S_B)$

NUMBER OF MYELOMA MOLECULES PER LEUKOCYTE = $S_L \times (N_R/S_R) / N_{TOT}$

- FDA News Release September 28, 2018
- FDA authorizes first next generation sequencing-based test to detect very low levels of remaining cancer cells in patients with acute lymphoblastic leukemia or multiple myeloma
- The FDA granted marketing authorization of ClonoSEQ assay to Adaptive Biotechnologies
  - Retrospective analysis of 3 previously conducted clinical studies
  - ALL: 273 patients
  - MM: 323 patients in an ongoing study and a study of 706 patients (IFM)
  - ALL
    - ClonoSEQ assay assessed MRD at various disease burden thresholds
    - MRD level correlated with EFS
    - MRD negative, longer EFS and MRD positive, lower EFS
  - MM
    - ClonoSEQ assay demonstrated similar associations with PFS and DFS
  - https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm622004.htm

Allele-specific oligonucleotide-quantitative PCR (ASO-qPCR) method to detect minimal residual disease (MRD), and design of ASO-qPCR primers and probes.



Takamatsu H, J Clin Med Oct 2017

RPCC Comparison of MFC panels used for MRD testing over time

		Monoclonal Antibody per Fluorochrome								
Panel Years	**Tube #**	**FITC**	**PE**	**PerCPy5.5**	**PECy7**	**APC**	**APCC750**	**BV421**	**BV510**	**# events / sensitivity**
A 2007- 2010	**4 color, 6 mAB**									A <250,000 /10^{-4}
	1	CD38	CD138	CD45		CD56				
	2	CD38	cLambda	CD138		cKappa				
B 2010- 2014	**4 color, 11 mAB**									B 250,000-1,000,000 /10^{-4} - 10^{-5}
	1	CD38	CD10	CD19		CD34				
	2	CD38	CD138	CD45		CD56				
C 2014- 2016	3	CD38	CD117	CD45		CD28				C 1-2,000,000 /10^{-5}
	4	CD38	cLambda	CD138		cKappa				
D 2014- 2016	**8 color, 10 mAb**									D 1-6,000,000 /10^{-5} - 10^{-6}
	1	CD38	CD56	CD45	CD19	CD117	CD81	CD138	CD27	
	2	CD38	CD56	CD45	CD19	cKappa	cLambda	CD138	CD27	

[1] PerCP; [2] Horizon V450, [3] LDAqua: Fixable Live Dead Aqua (viability)

Ammannagari et al ASH 2016, Abstract 2274; Manuscript in Preparation

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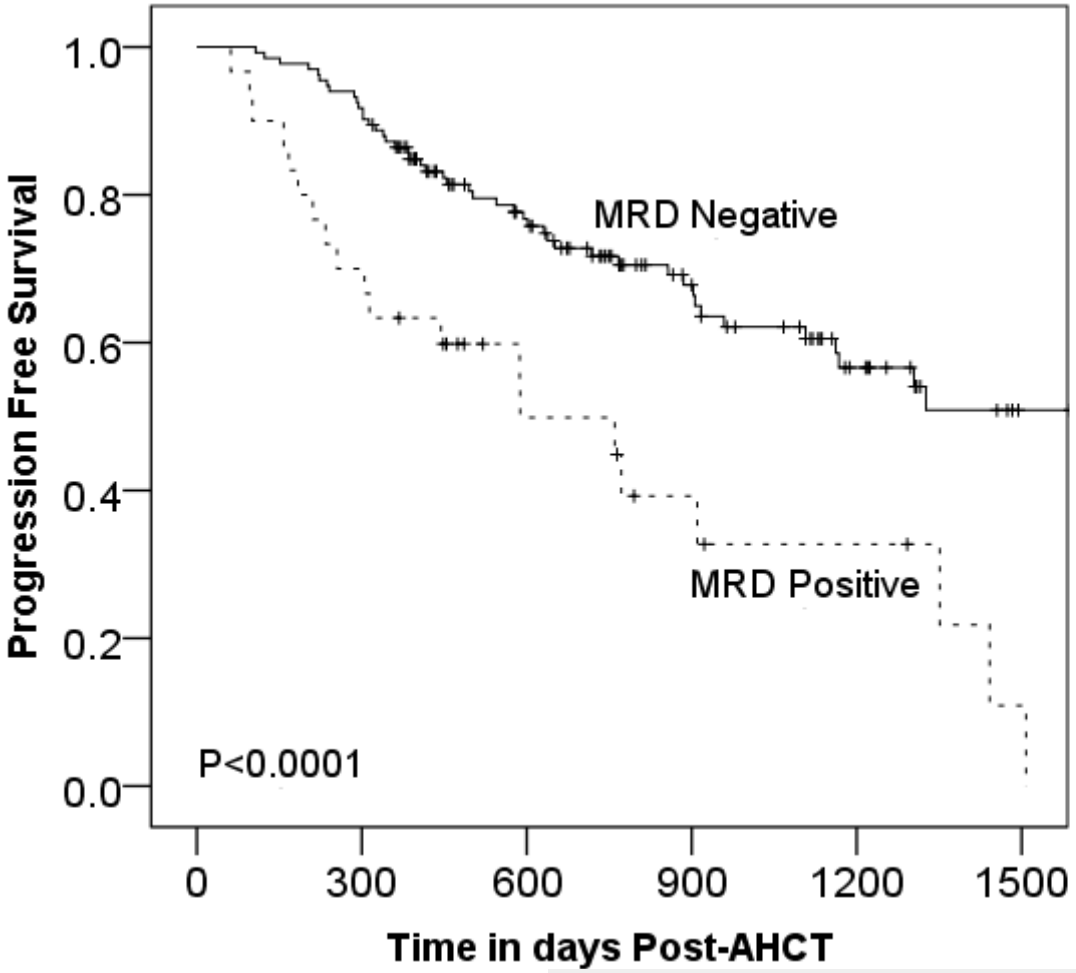
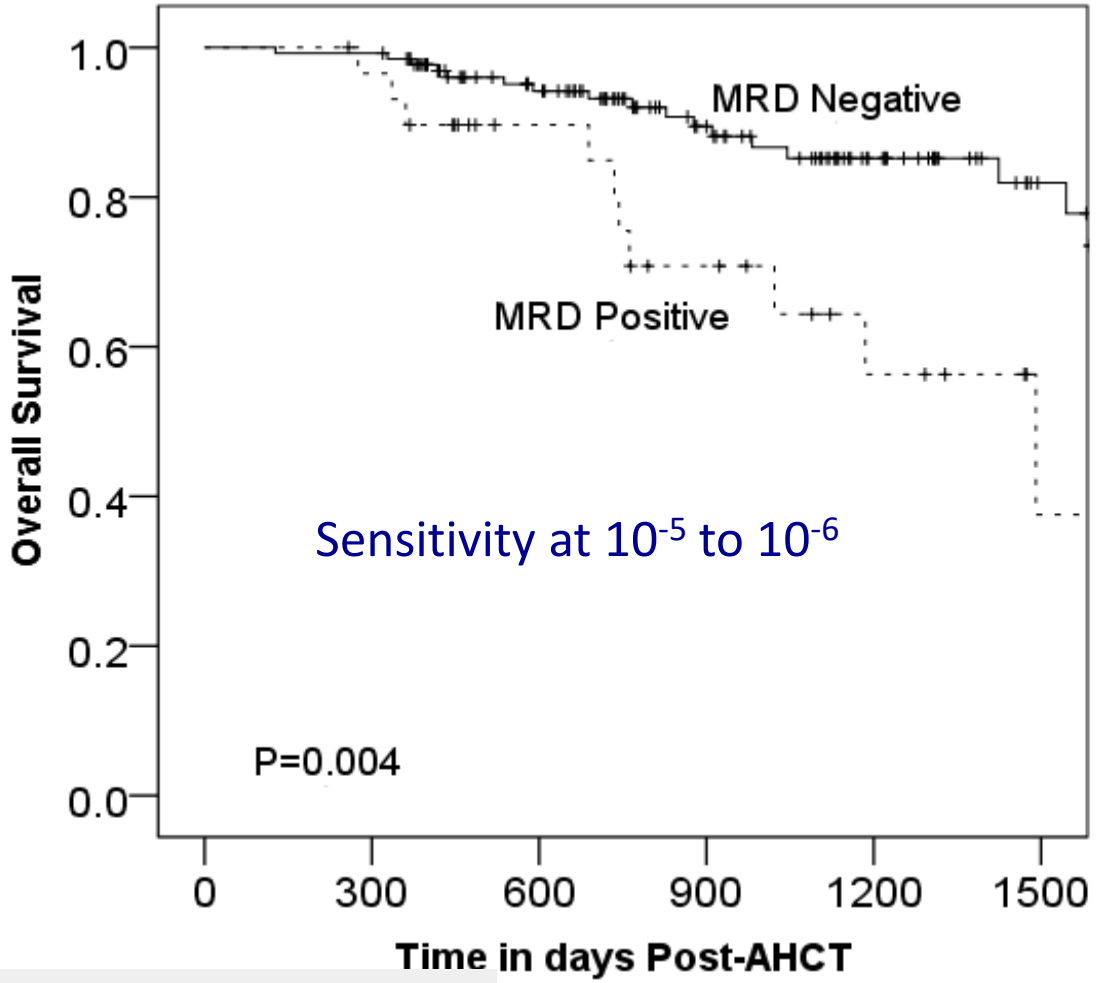
Progression free survival (PFS) and overall survival (OS) according to MRD status by multiparameter flow cytometry at day +100 post-AHCT





N=172:

3-yr PFS 62% (95% CI: 52-72%) vs 33% (95% CI: 12-53%), P <0.0001)
3-year OS 85% (95% CI: 78-93%) vs 64% (95% CI: 44-85%), P=0.004).

Ammannagari et al ASH 2016, Abstract 2274; Manuscript in Preparation

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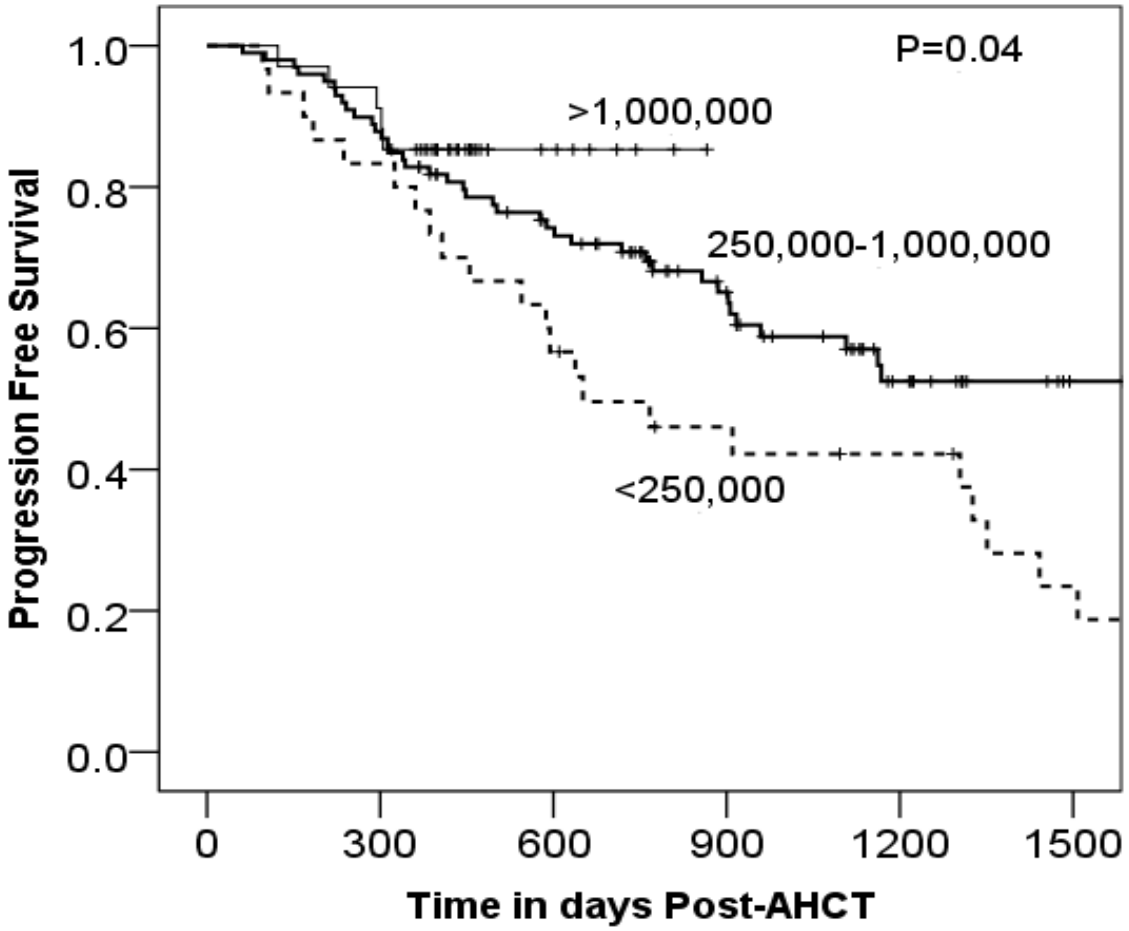
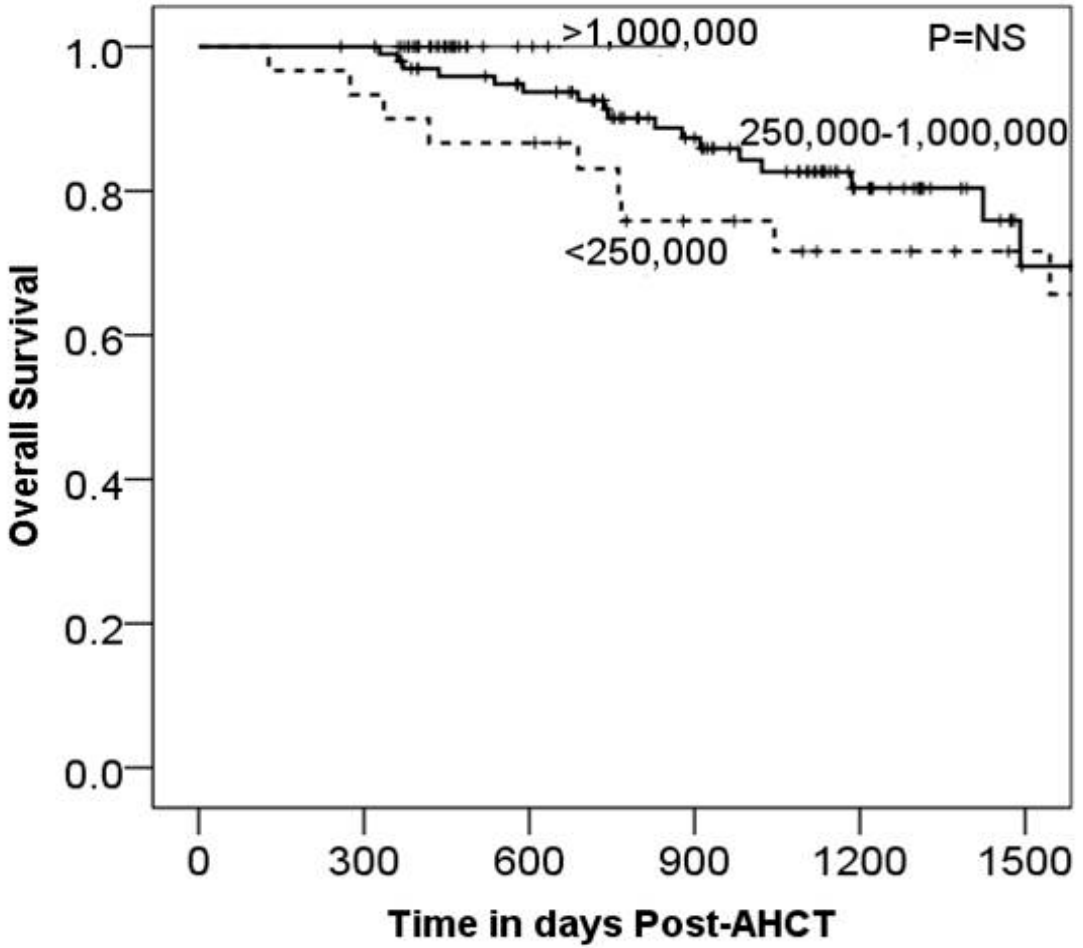
Progression free survival (PFS) and overall survival (OS) in patients who are MRD negative at day +100 post AHCT, stratified by numbers of analyzed plasma cells (PCN)





N=172: **3-yr PFS at Day 100:**
PCN<250,000: 42% (95% CI: 20- 63%);
PCN=250,000-1,000,000: 65% (95% CI 54-76%)
PCN>1,000,000: 89% (CI 78-101%) (P=0.03).

Ammannagari et al ASH 2016, Abstract 2274; Manuscript in Preparation

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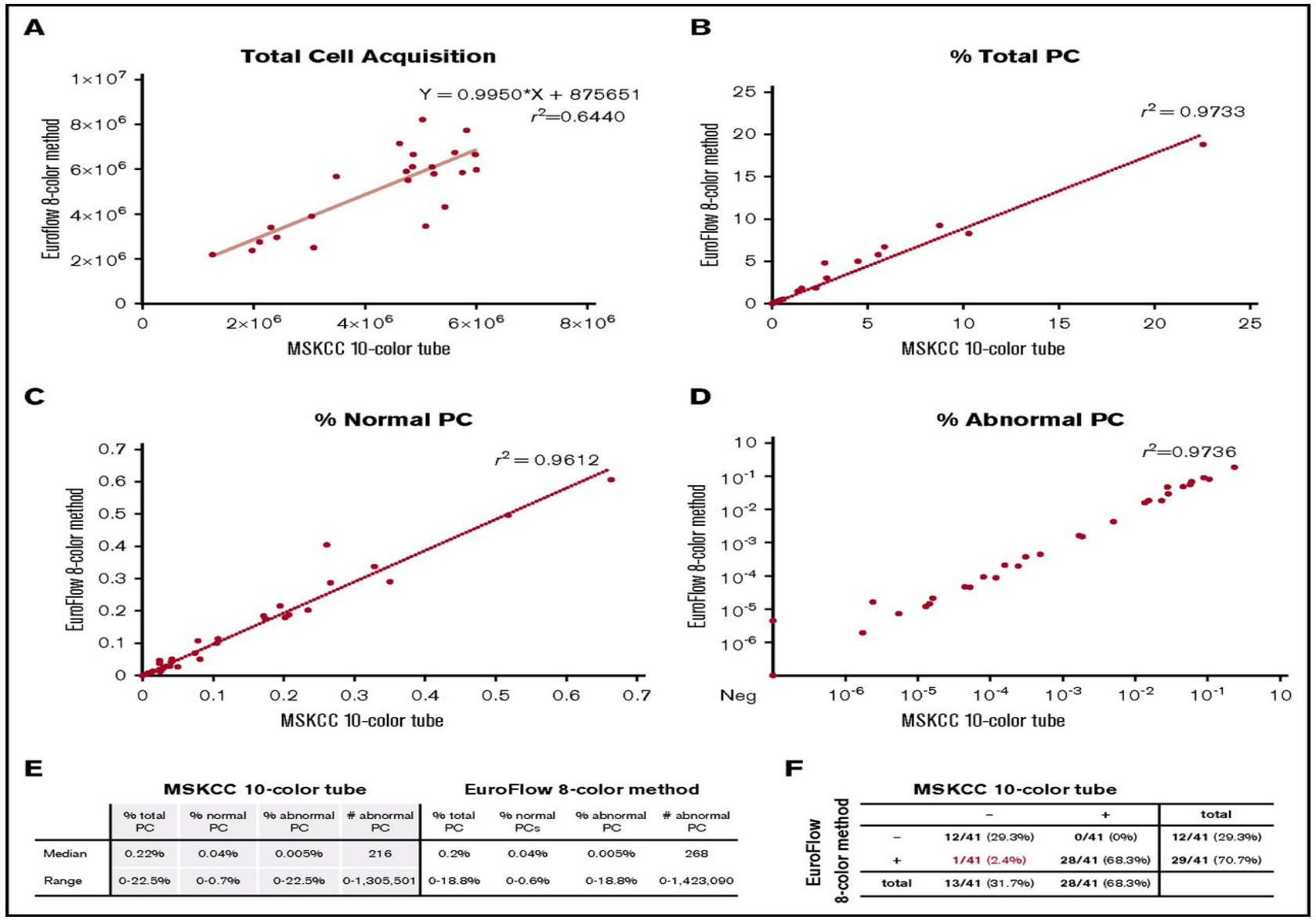
Comparison of MSKCC single 10-color tube and EuroFlow two 8-color tubes.



E

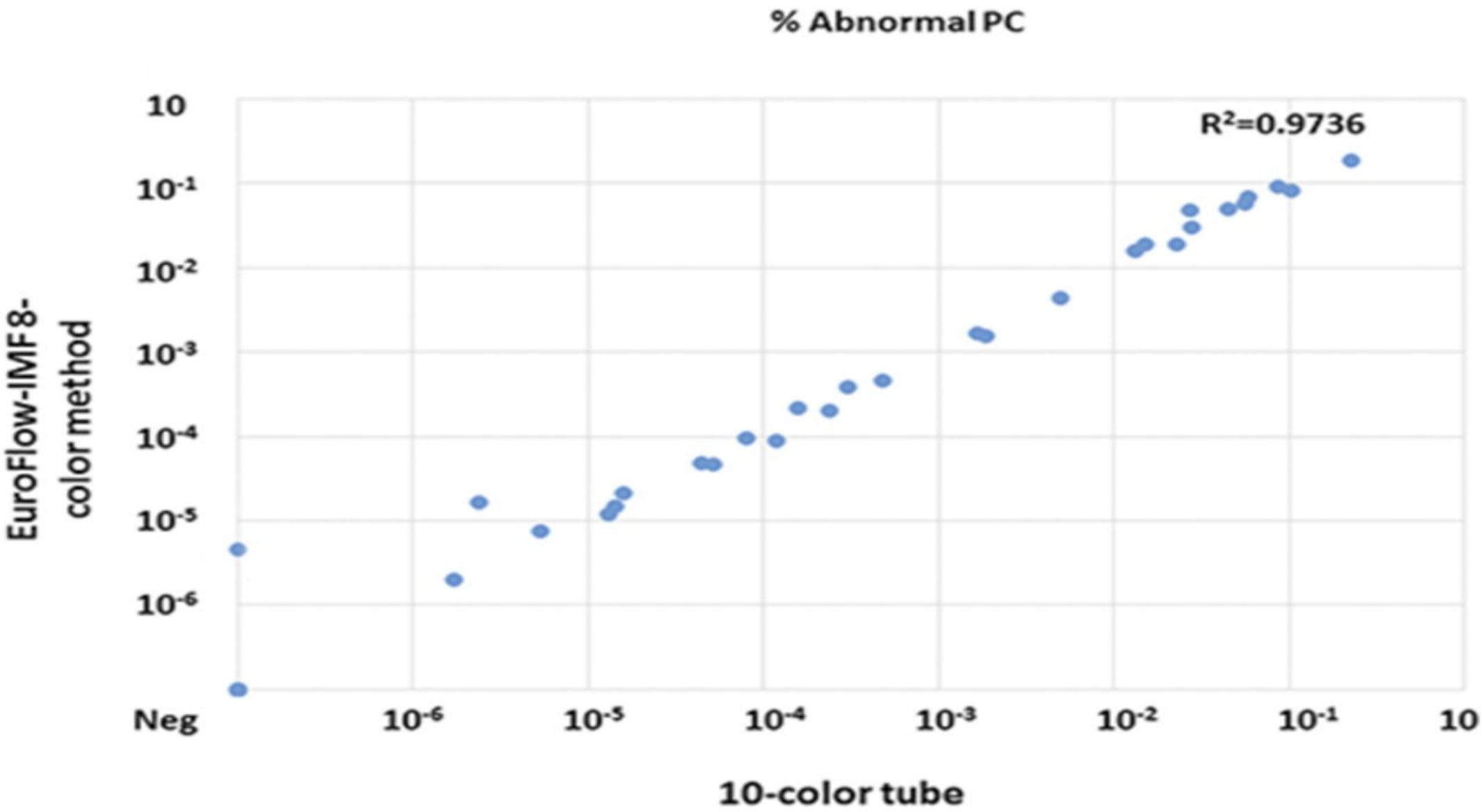
	MSKCC 10-color tube				EuroFlow 8-color method			
	% total PC	% normal PC	% abnormal PC	# abnormal PC	% total PC	% normal PCs	% abnormal PC	# abnormal PC
Median	0.22%	0.04%	0.005%	216	0.2%	0.04%	0.005%	268
Range	0-22.5%	0-0.7%	0-22.5%	0-1,305,501	0-18.8%	0-0.6%	0-18.8%	0-1,423,090

F

EuroFlow 8-color method	MSKCC 10-color tube –	MSKCC 10-color tube +	total
–	**12/41** (29.3%)	**0/41** (0%)	**12/41** (29.3%)
+	**1/41** (2.4%)	**28/41** (68.3%)	**29/41** (70.7%)
total	**13/41** (31.7%)	**28/41** (68.3%)	

Mikhail Roshal et al. Blood Adv 2017;1:728-732

blood advances



Mikhail Roshal et al. Blood Adv 2017;1:728-732

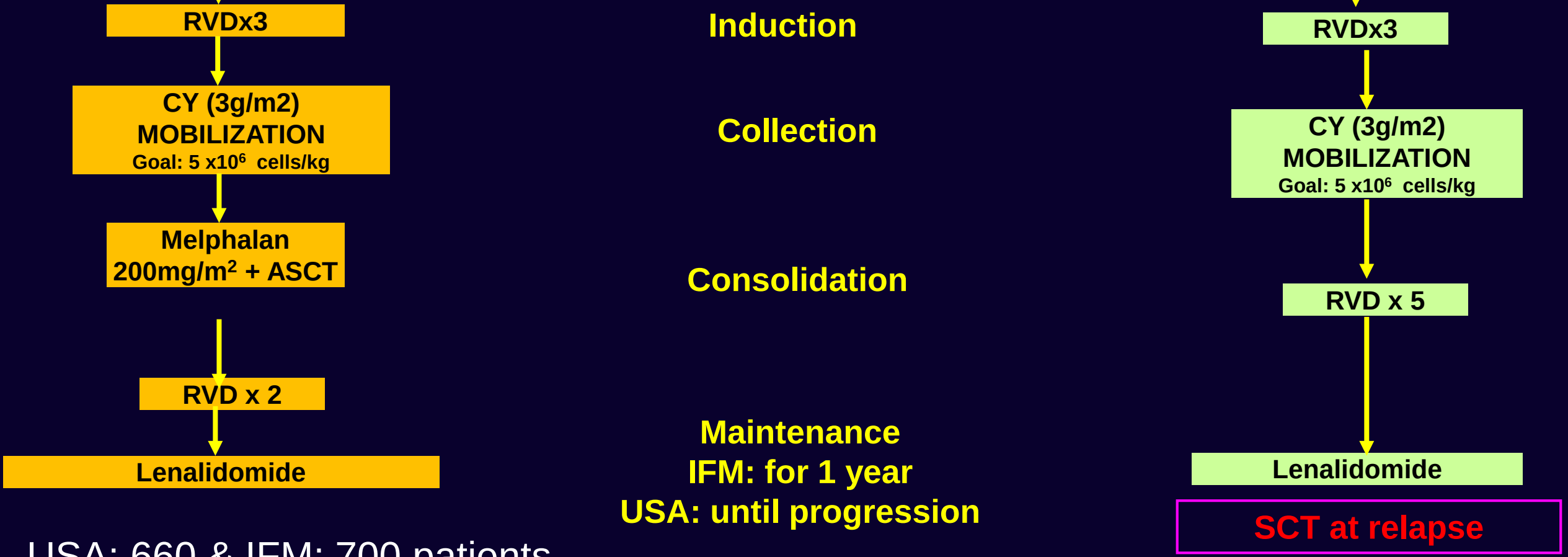
blood advances

The DETERMINATION Trial

IFM/DFCI 2009 Phase 3 Study

Newly Diagnosed MM (SCT candidates; n= originally 1000, now 1360)

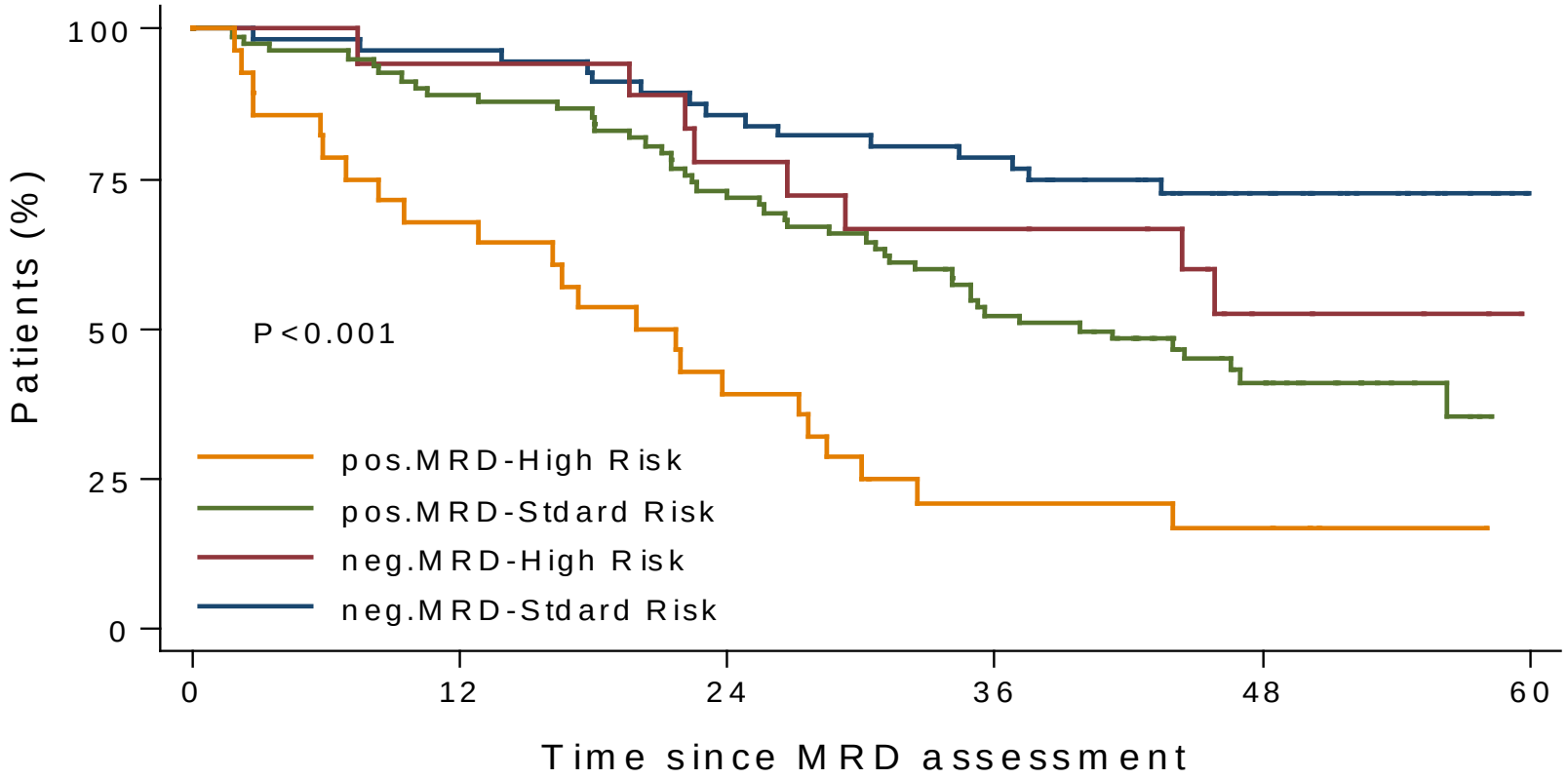
Randomize



USA: 660 & IFM: 700 patients

RVD=Revlimid®,Velcade®, dexamethasone. Cy=Cyclophosphamide, **Courtesy P Richardson**

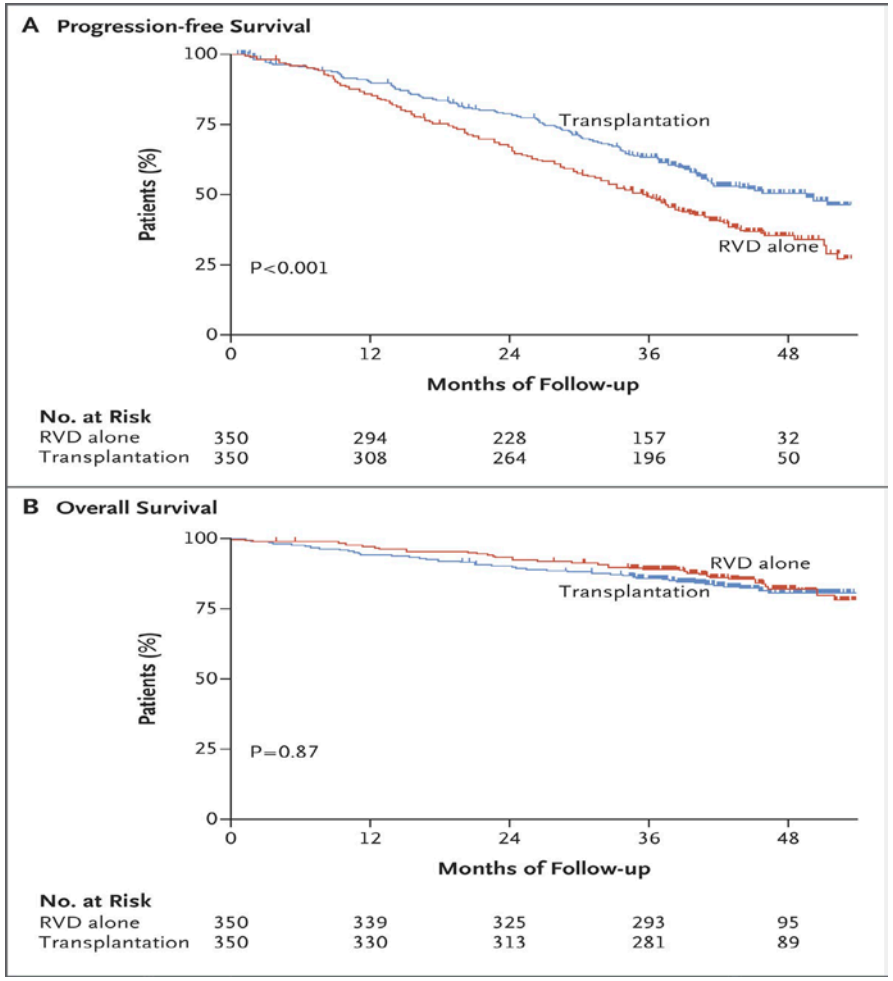
Impact of cytogenetic risk?

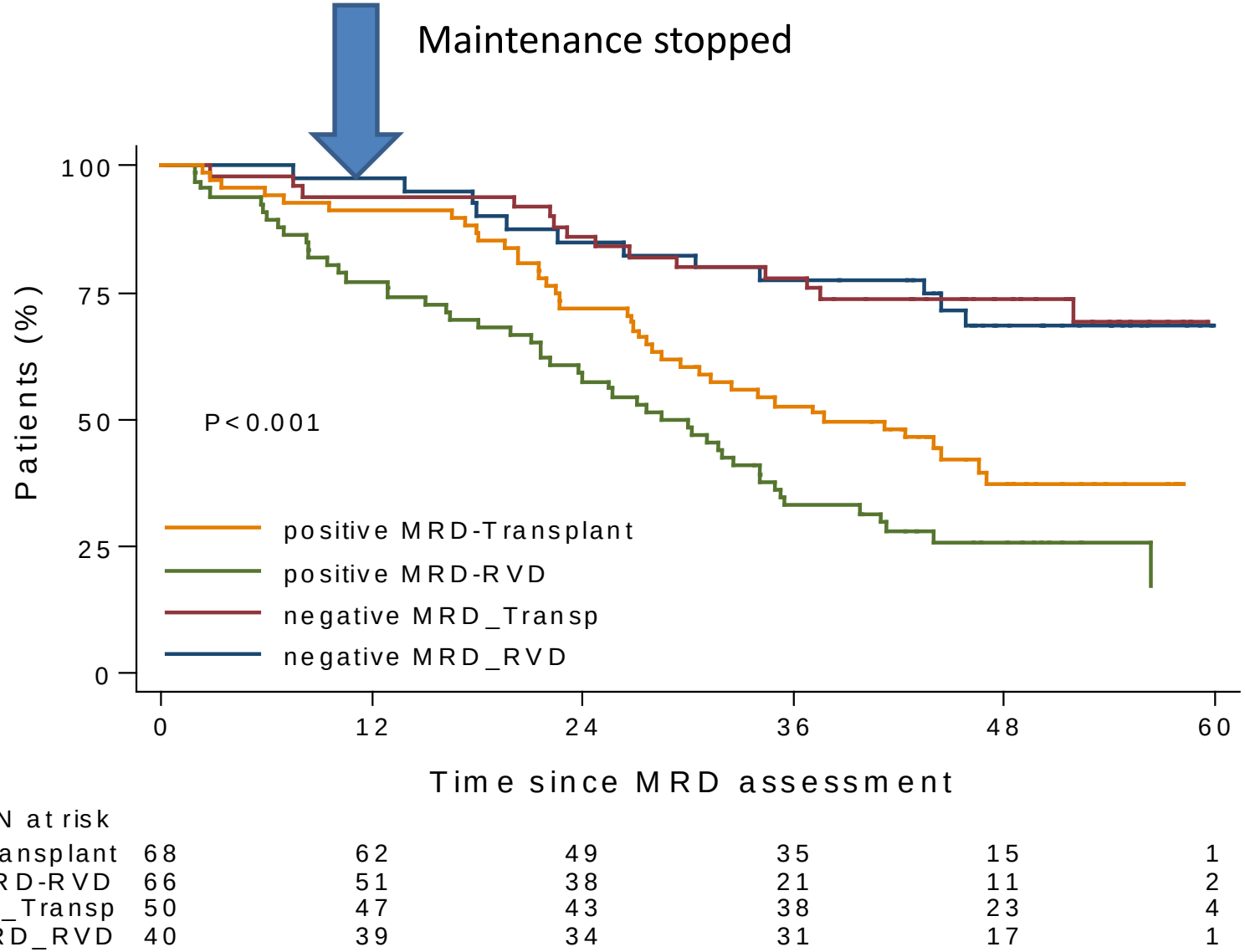


N at risk						
pos.MRD-High Risk	28	19	11	5	4	0
pos.MRD-Stdard Risk	82	73	59	42	21	3
neg.MRD-High Risk	18	17	14	12	5	1
neg.MRD-Stdard Risk	56	54	48	43	25	4

Courtesy H Avet-Loiseau
Blood 2017 130:435

Impact of treatment arm?



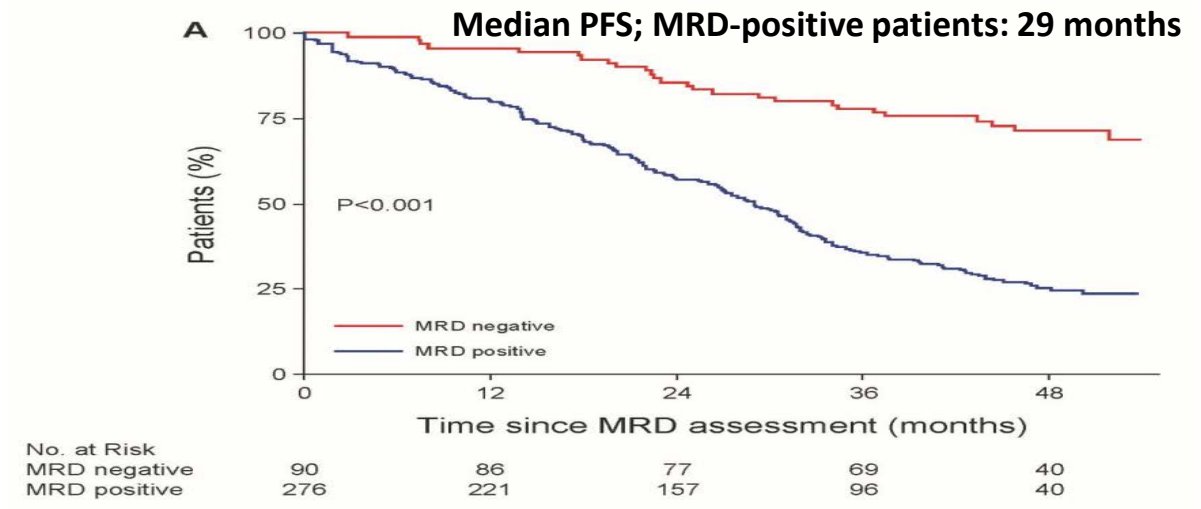


N at risk						
positive MRD-Transplant	68	62	49	35	15	1
positive MRD-RVD	66	51	38	21	11	2
negative MRD_Transp	50	47	43	38	23	4
negative MRD_RVD	40	39	34	31	17	1

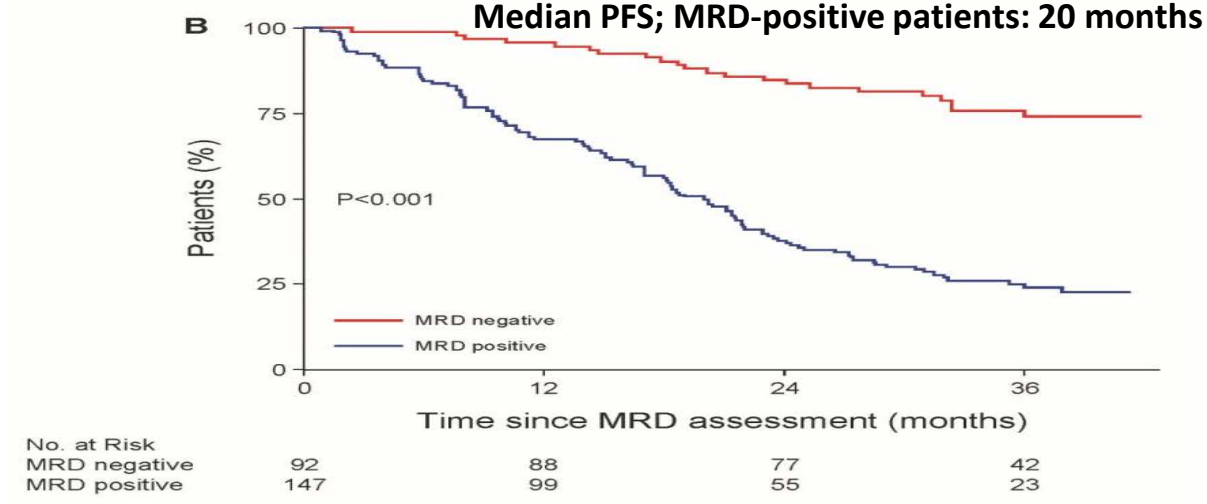
Courtesy H Avet-Loiseau
Blood 2017 130:435

A: K-M Curves for PFS by MRD Status at the Start of Maintenance Therapy.
B: K-M Curves for PFS by MRD Status after 12 months of maintenance therapy.

Median PFS; MRD-negative patients: NR
Median PFS; MRD-positive patients: 29 months



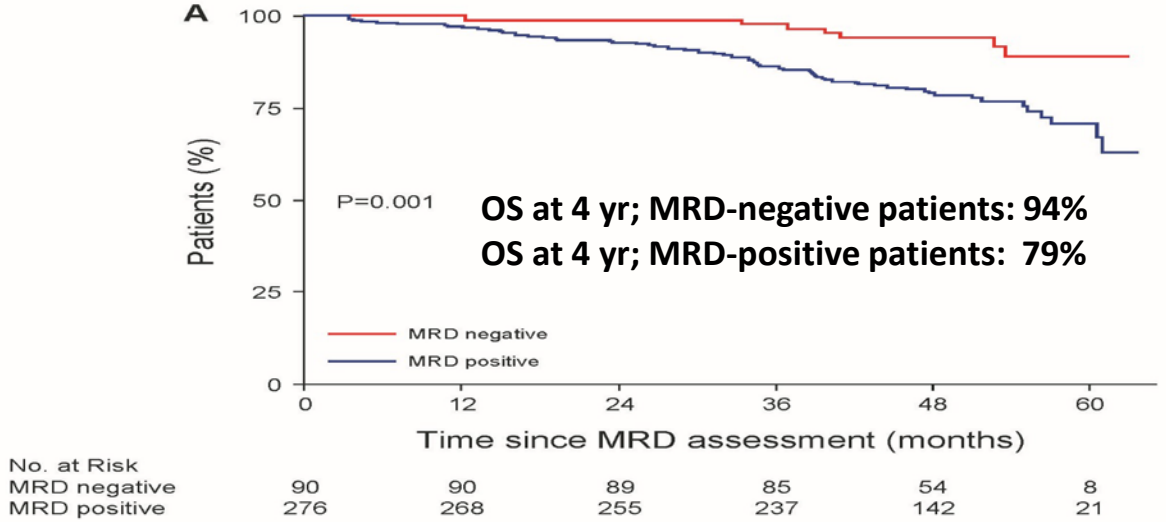
Median PFS; MRD-negative patients: NR
Median PFS; MRD-positive patients: 20 months



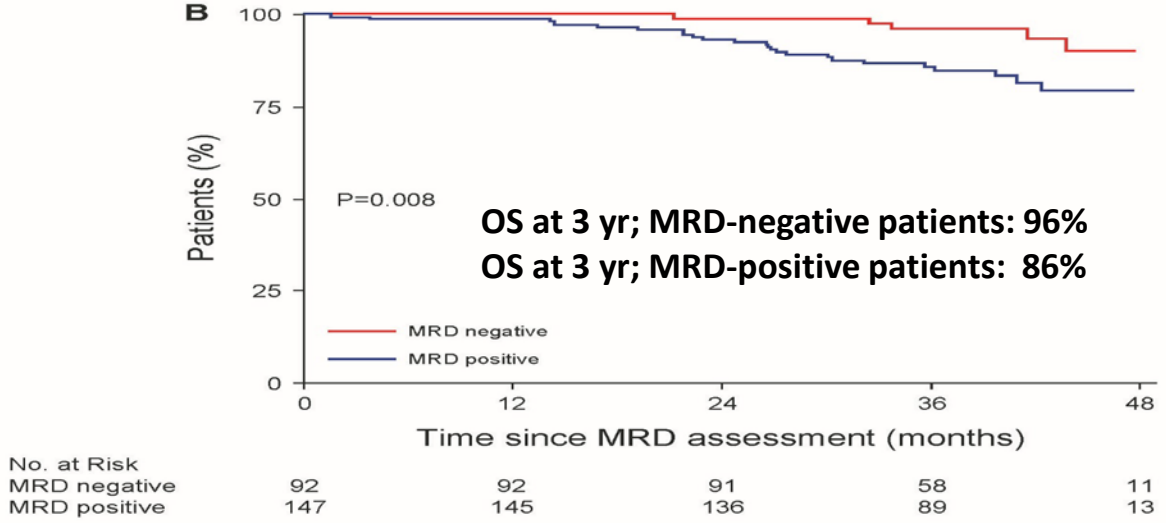
Perrot A et al Blood 2018, courtesy H Avet Loiseau

A: K-M Curves for OS by MRD Status at the Start of Maintenance Therapy.
B: K-M Curves for OS by MRD Status after 12 months of maintenance therapy.

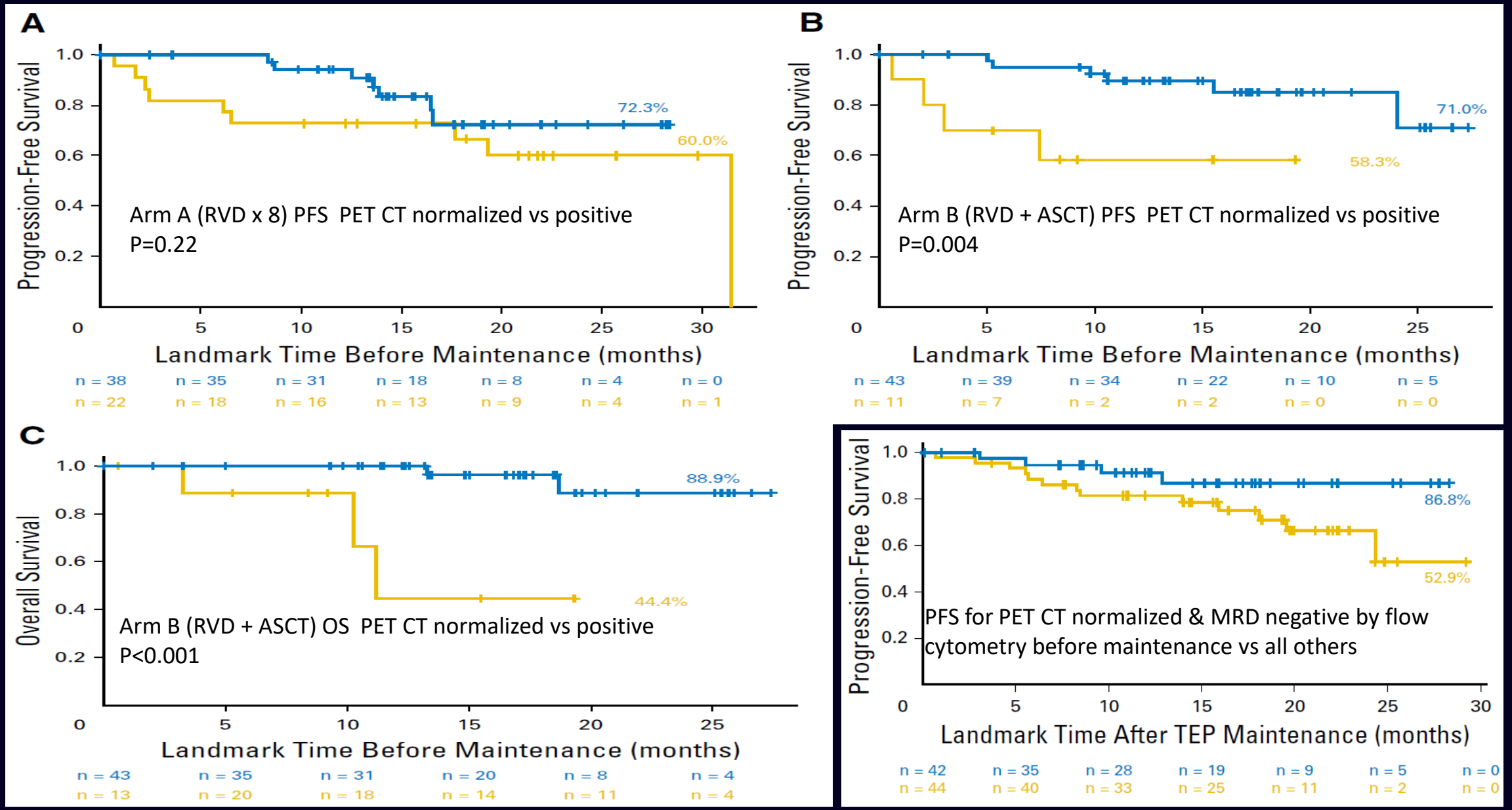
OS at 4 yr; MRD-negative patients: 94%
OS at 4 yr; MRD-positive patients: 79%



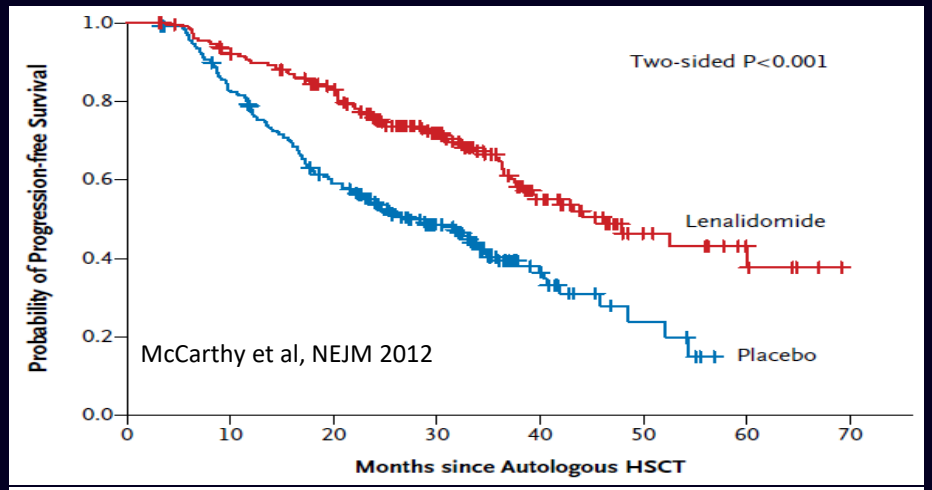
OS at 3 yr; MRD-negative patients: 96%
OS at 3 yr; MRD-positive patients: 86%

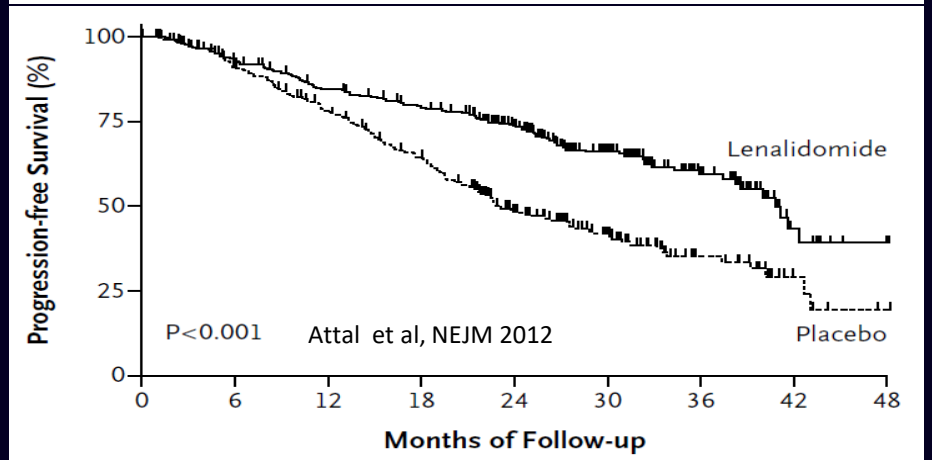


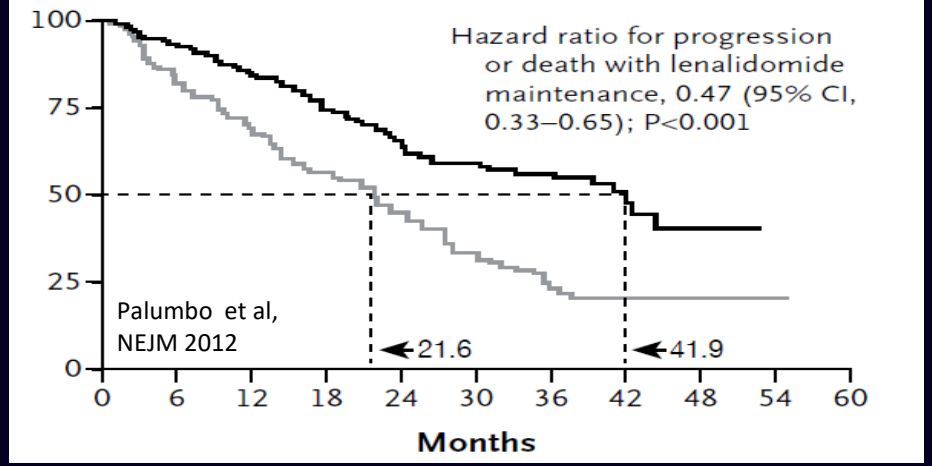
PFS/OS after PET CT normalization before Maintenance



Moreau et al JCO 35:2911, 2017

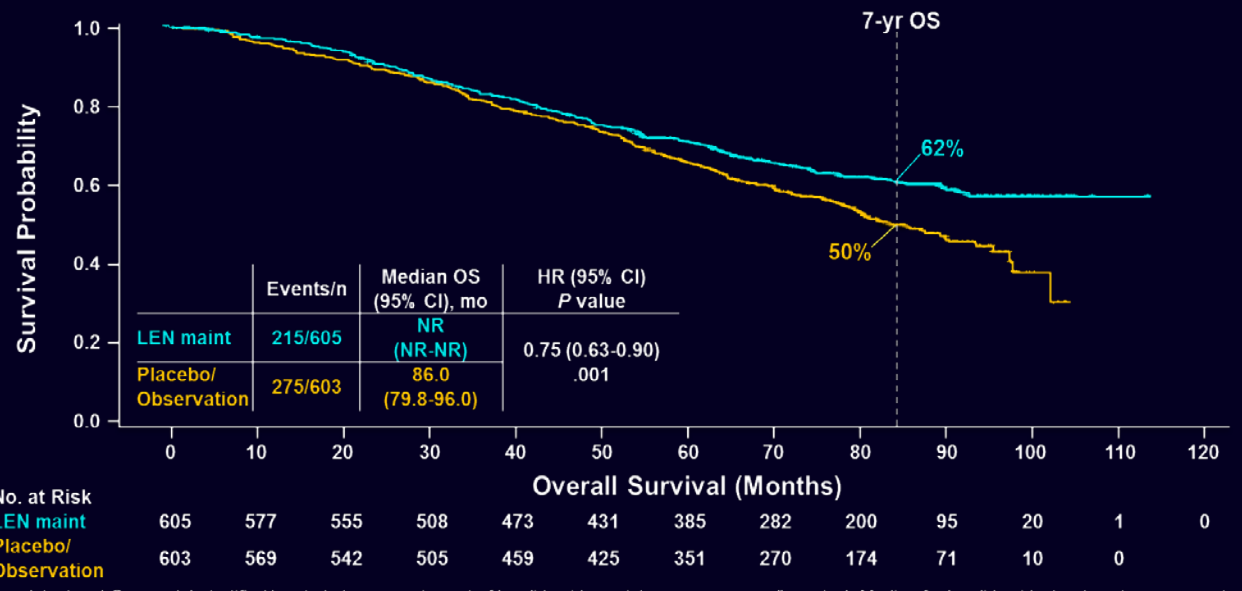






Overall Survival: Median Follow-Up of 80 Months

There is a 25% reduction in risk of death, representing an estimated 2.4-year increase in median survival (March 2015 data cutoff)[a]



	Events/n	Median OS (95% CI), mo	HR (95% CI) *P* value
LEN maint	215/605	NR (NR-NR)	0.75 (0.63-0.90) .001
Placebo/ Observation	275/603	86.0 (79.8-96.0)	

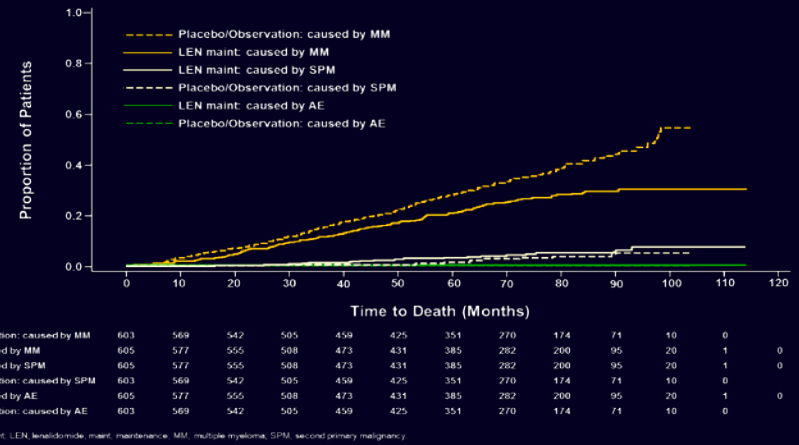
No. at Risk													
LEN maint	605	577	555	508	473	431	385	282	200	95	20	1	0
Placebo/ Observation	603	569	542	505	459	425	351	270	174	71	10	0	

[a] Log-rank test and Cox model stratified by study to assess impact of lenalidomide maintenance on overall survival. Median for lenalidomide treatment arm was extrapolated to be 115 months based on median of the control arm and HR (median, 86 months; HR = 0.75).

HR, hazard ratio; maint, maintenance; NR, not reached; OS, overall survival.

McCarthy et al, JCO, 2017; 35:3279-3289

Time to Death by Cause of Death



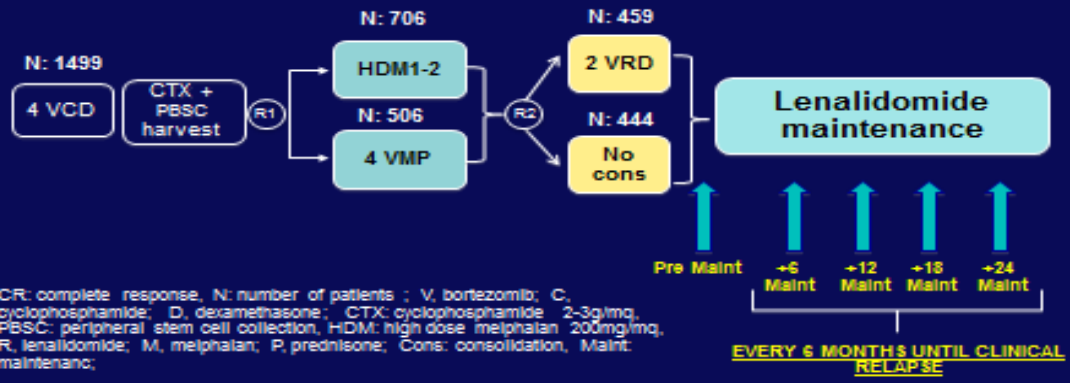
No. at Risk													
Placebo/Observation: caused by MM	603	569	542	505	459	425	351	270	174	71	10	0	
LEN maint: caused by MM	605	577	555	508	473	431	385	282	200	95	20	1	0
LEN maint: caused by SPM	605	577	555	508	473	431	385	282	200	95	20	1	0
Placebo/Observation: caused by SPM	603	569	542	505	459	425	351	270	174	71	10	0	
LEN maint: caused by AE	605	577	555	508	473	431	385	282	200	95	20	1	0
Placebo/Observation: caused by AE	603	569	542	505	459	425	351	270	174	71	10	0	

AE, adverse event; LEN, lenalidomide; maint, maintenance; MM, multiple myeloma; SPM, second primary malignancy.

Methods

MM patients enrolled in the RV-MM-COOP-0556 (EMN02/HO95 MM; NCT01208766)

- Newly diagnosed ≤ 65 years
- MRD assessement in patients achieving suspected CR before lenalidomide maintenance



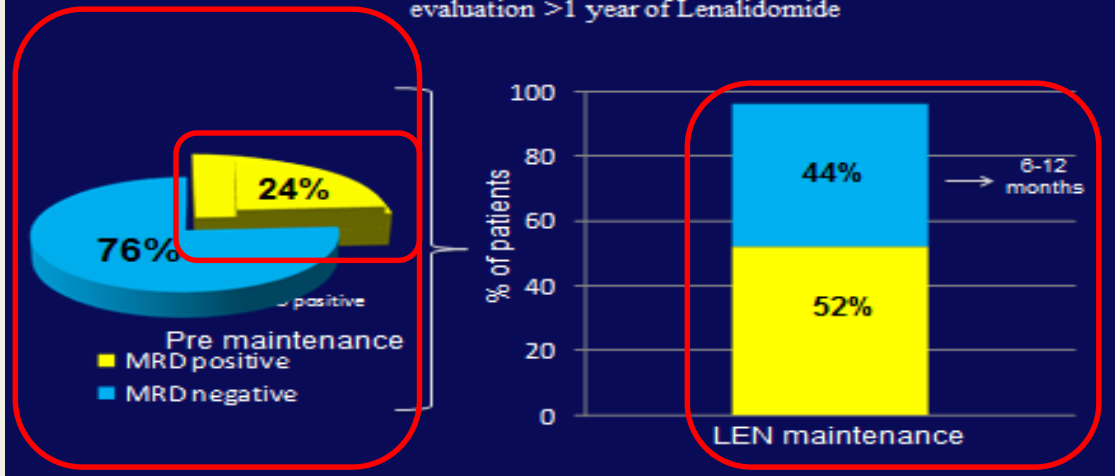
CR: complete response, N: number of patients ; V, bortezomib; C, cyclophosphamide; D, dexamethasone; CTX: cyclophosphamide 2-3g/mq, PBSC: peripheral stem cell collection, HDM: high dose melphalan 200mg/mq, R, lenalidomide; M, melphalan; P, prednisone; Cons: consolidation, Maint: maintenanc;

Cavo M et al. ASH 2016; Abstract 673. Sonneveld P. et al. ASH 2016; Abstract 292

Results

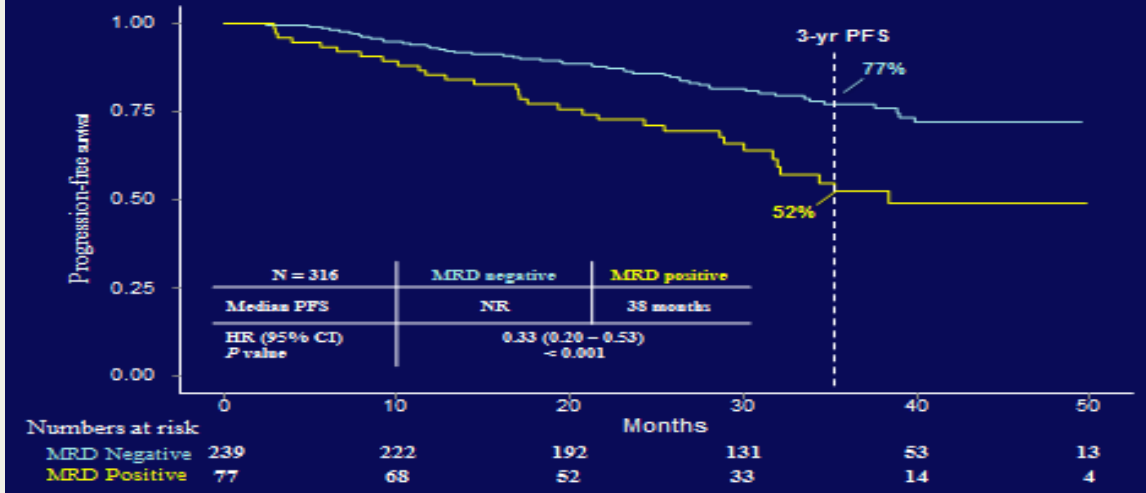
MRD status at pre-maintenance

Sub-analysis on MRD positive patients at pre-maintenance who had a second MRD evaluation >1 year of Lenalidomide



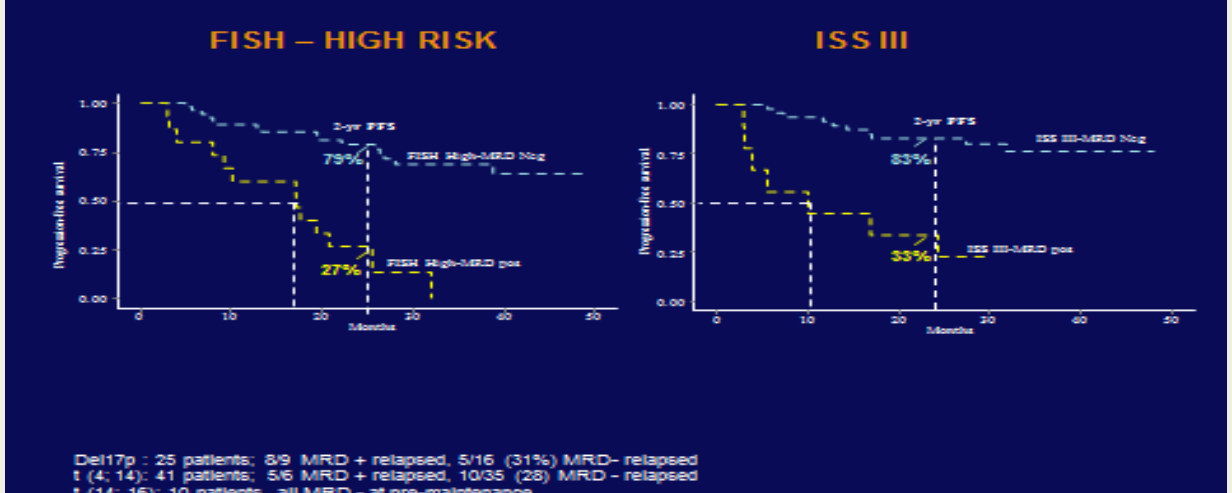
Results

Progression free Survival: Median Follow-Up from MRD enrollement of 33 Months



Results

Subgroup analyses for PFS: High Risk patients and MRD



Del17p : 25 patients; 8/9 MRD + relapsed, 5/16 (31%) MRD- relapsed
t (4; 14): 41 patients; 5/6 MRD + relapsed, 10/35 (28) MRD - relapsed
t (14; 16): 10 patients, all MRD - at pre-maintenance

Oliva et al J Clin Oncol 35, 2017 (suppl; abstr 8011); Oliva et al EHA 2017, S102

Minimal Residual Disease by Flow Cytometry and ASO-RQ-PCR in Myeloma Patients Receiving Lenalidomide Maintenance: A Pooled Analysis

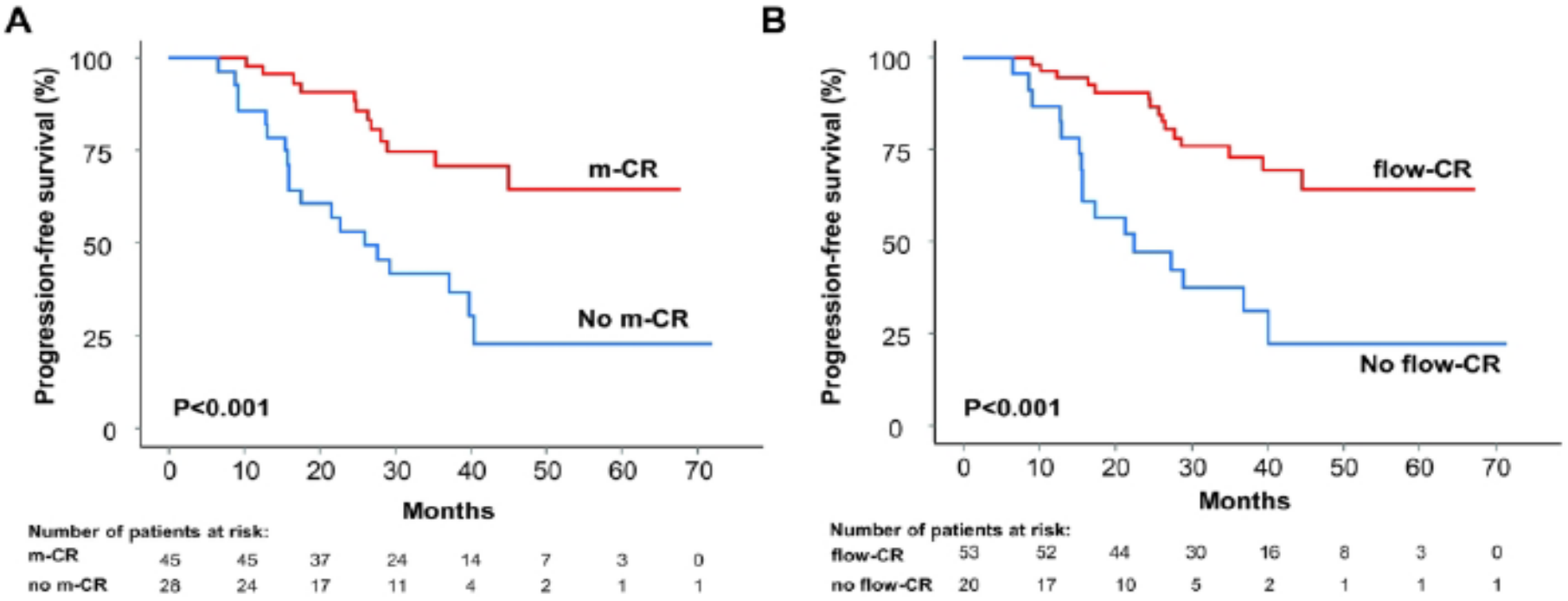
MRD and ASO-RQ-PCR in MM patients

Manuela Gambella[1], Paola Omedé[1], Stefano Spada[1], Vittorio Emanuele Muccio[1], Milena Gilestro[1], Elona Saraci[1], Sara Grammatico[2], Alessandra Larocca[1], Concetta Conticello[3], Annalisa Bernardini[1], Barbara Gamberi[4], Rossella Troia[1], Anna Marina Liberati[5], Massimo Offidani[6], Alberto Rocci[7,8], Antonio Palumbo[1*], Michele Cavo[9], Pieter Sonneveld[10], Mario Boccadoro[1], and Stefania Oliva[1]

73 NDMM patients on RV-MM-EMN-441, NCT01091831 (CRD vs Mel 200) and RV-MM-COOP-0556 NCT01208766 (VCD followed by VMP vs Mel 200) Both studies: len maintenance
ASCT and no ASCT patients

Cancer 2018 in press

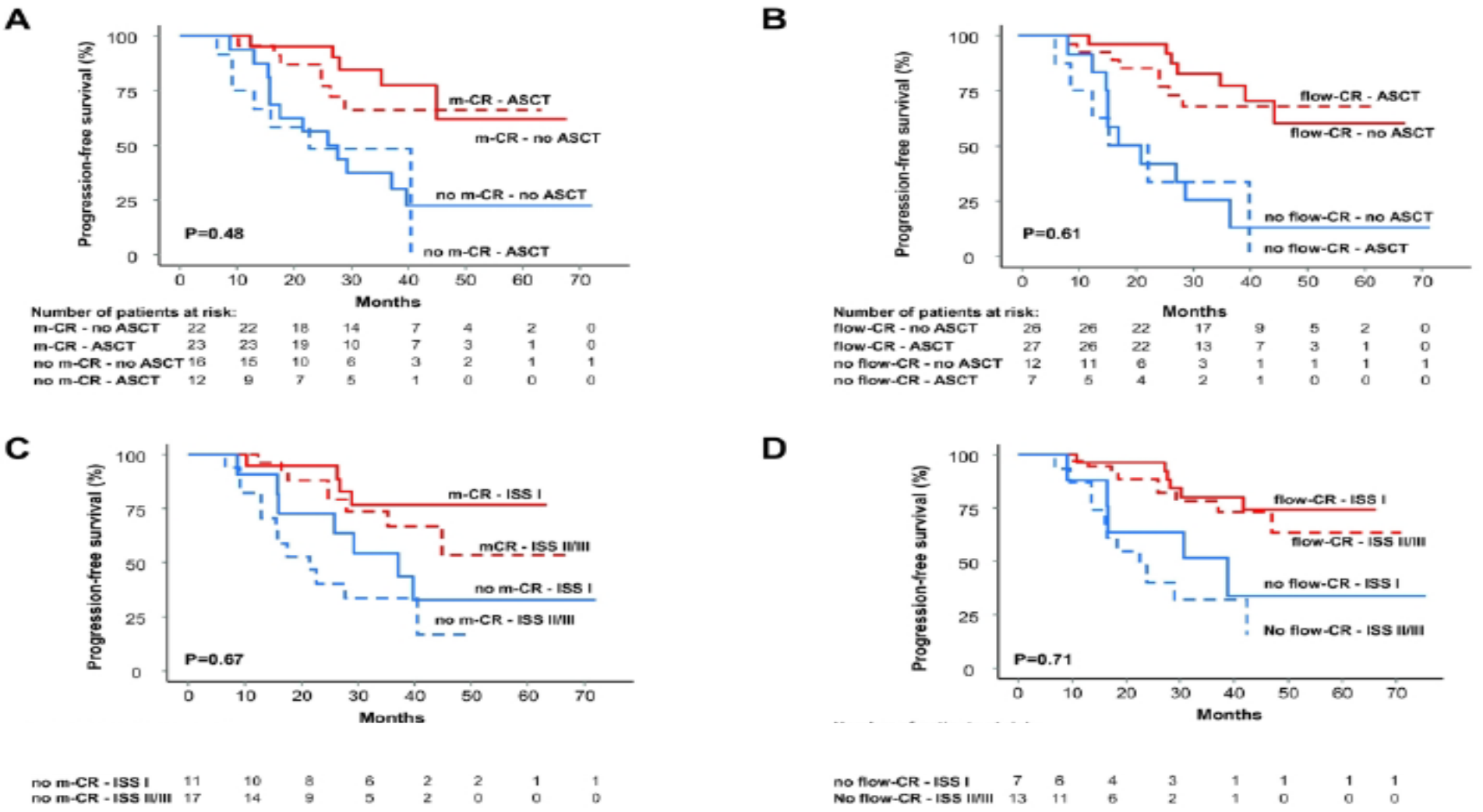
K-M estimates of PFS during Maintenance, PFS by Allelic-specific oligonucleotide real-time quantitative polymerase chain reaction (ASO-RQ-PCR) and Multiparameter flow cytometry (MFC)



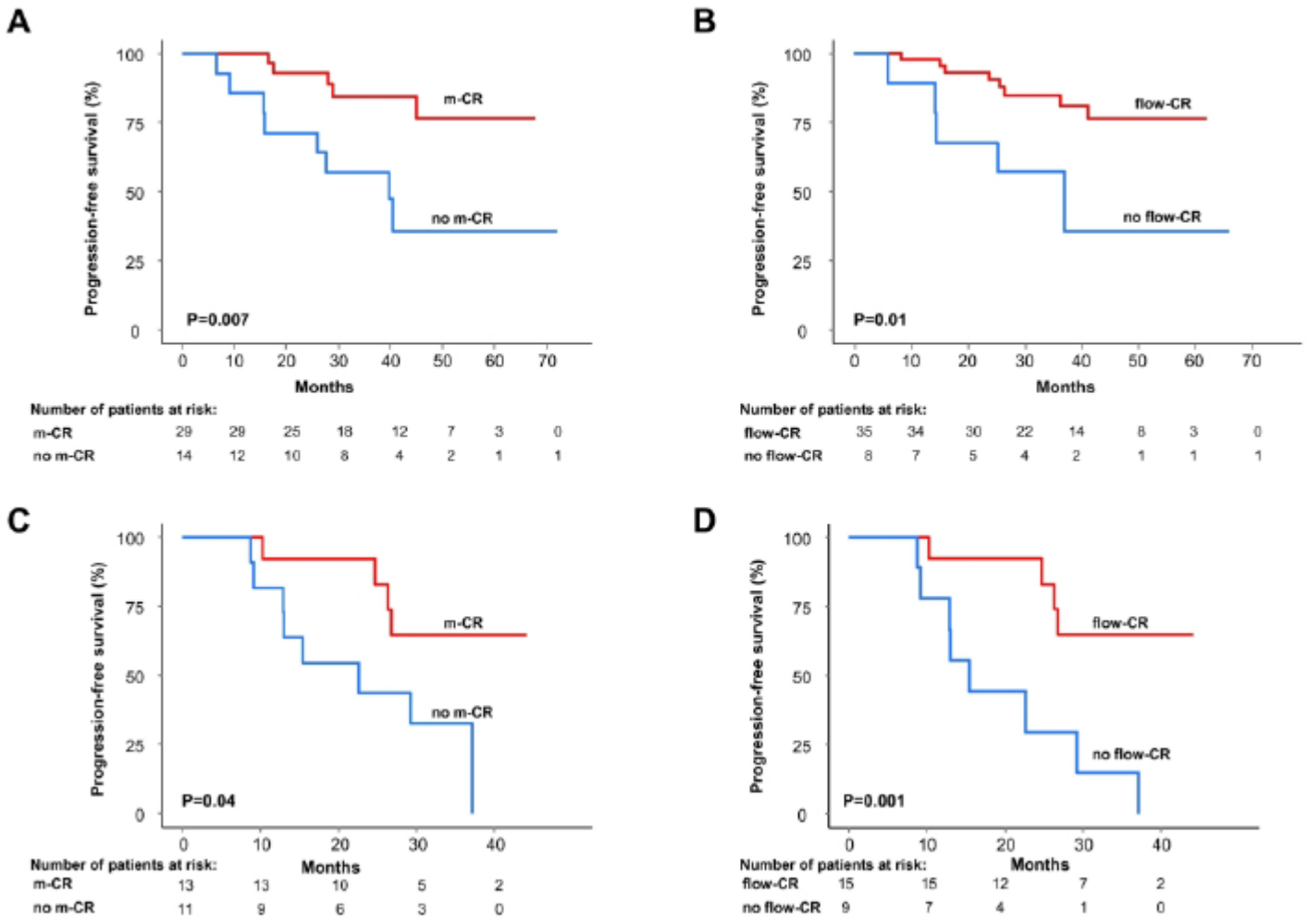
m-CR, molecular complete response; flow-CR, flow-complete response; 73 patients started len maintenance.
ASO-RQ-PCR, median PFS for m-CR not reached vs 26 months for no-m-CR respectively p<0.001
MFC median PFS for MRD-negative not reached vs 19.5 months for MRD-positive respectively p<0.001

Gambella M et al Cancer 2018 in press

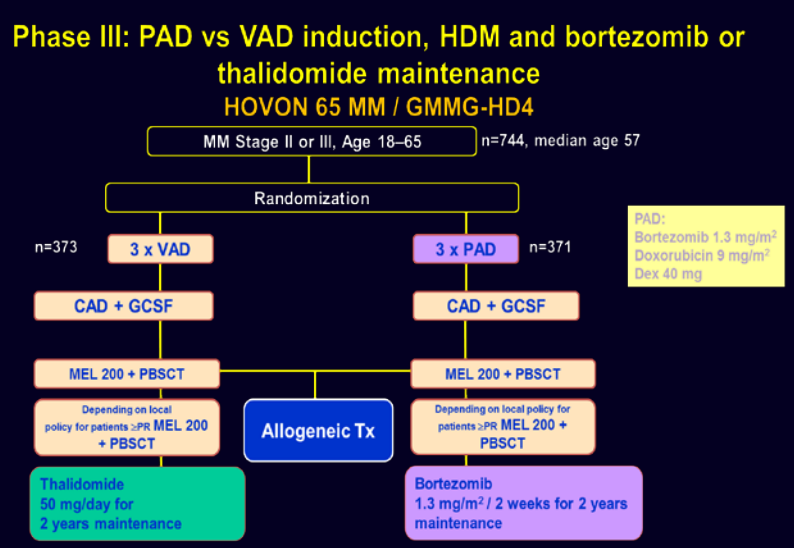
PFS during maintenance according to therapy (ASCT vs no ASCT) by ASO-RQ-PCR and MFC and ISS I vs ISS II/III

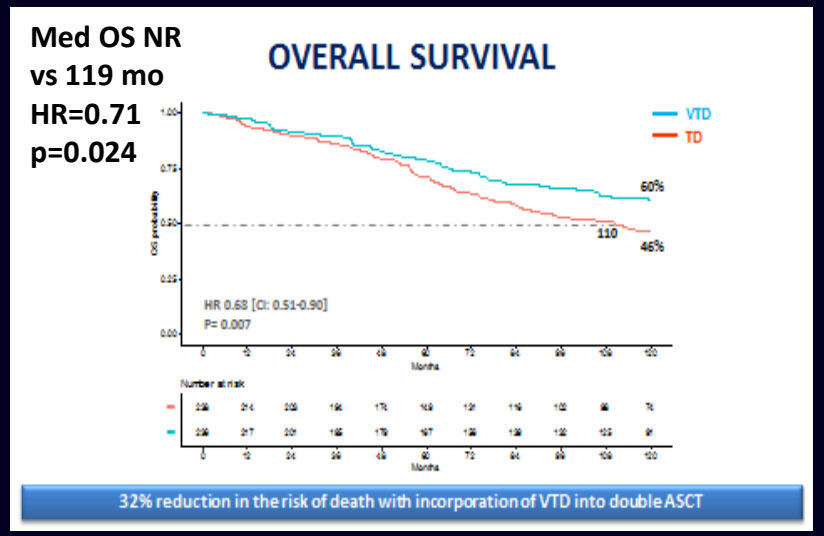


PFS during Maintenance according to Cytogenetic Risk

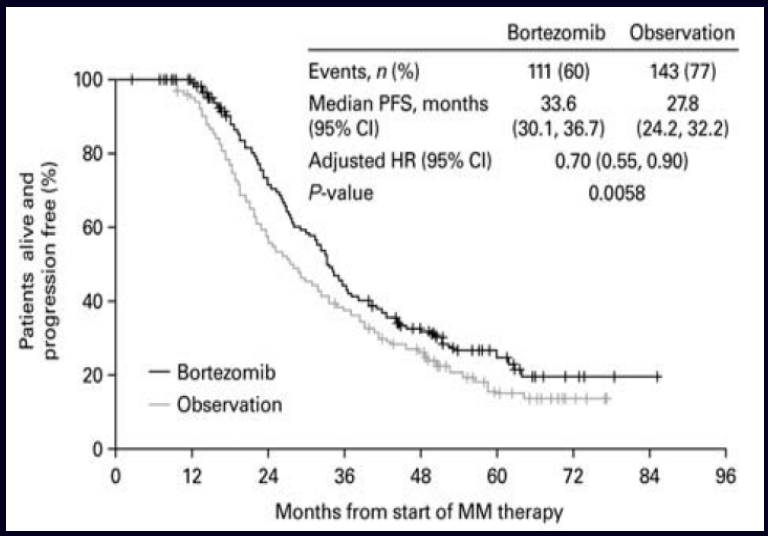


A/B: PFS Standard Risk Cytogenetics by ASO-RQ-PCR and MFC
C/D: PFS, High Risk Cytogenetics by ASO-RQ-PCR and MFC

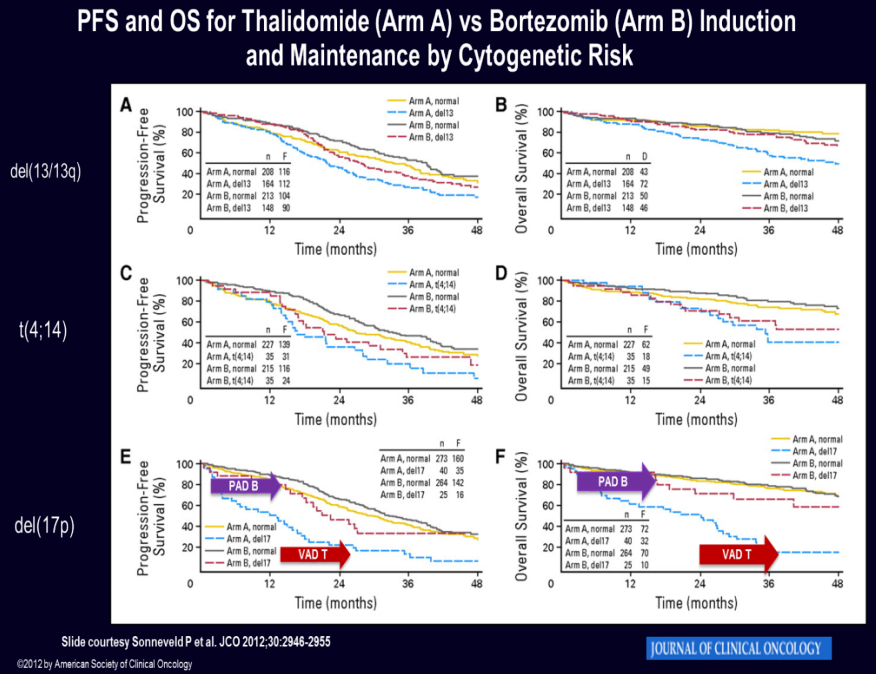




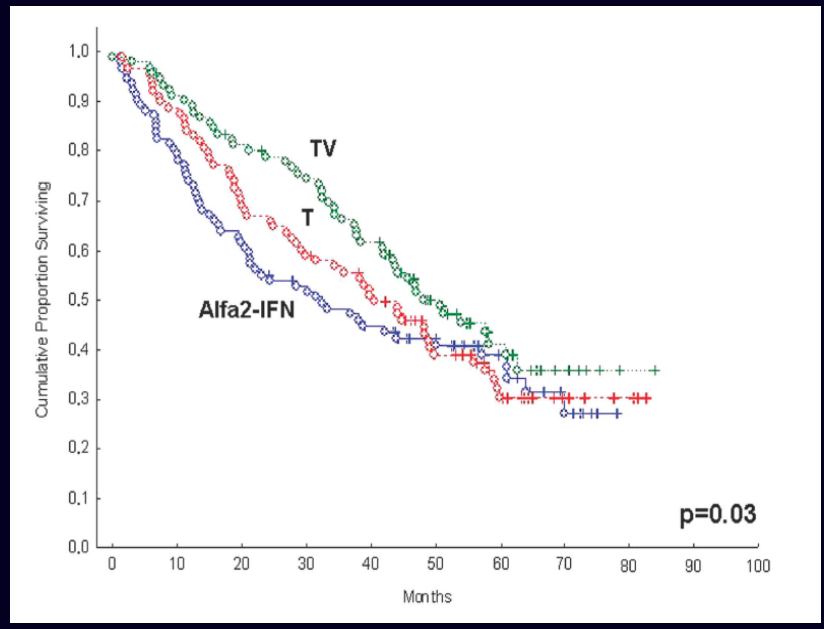
Cavo M et al Blood 2012; Tacchetti et al EHA 2018



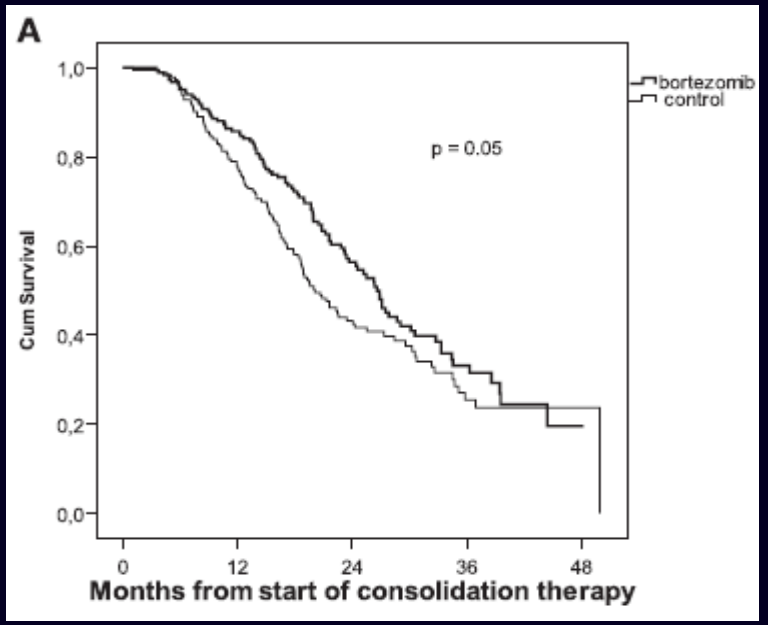
Einsele H et al Leukemia 2017



Sonneveld et al JCO 2012



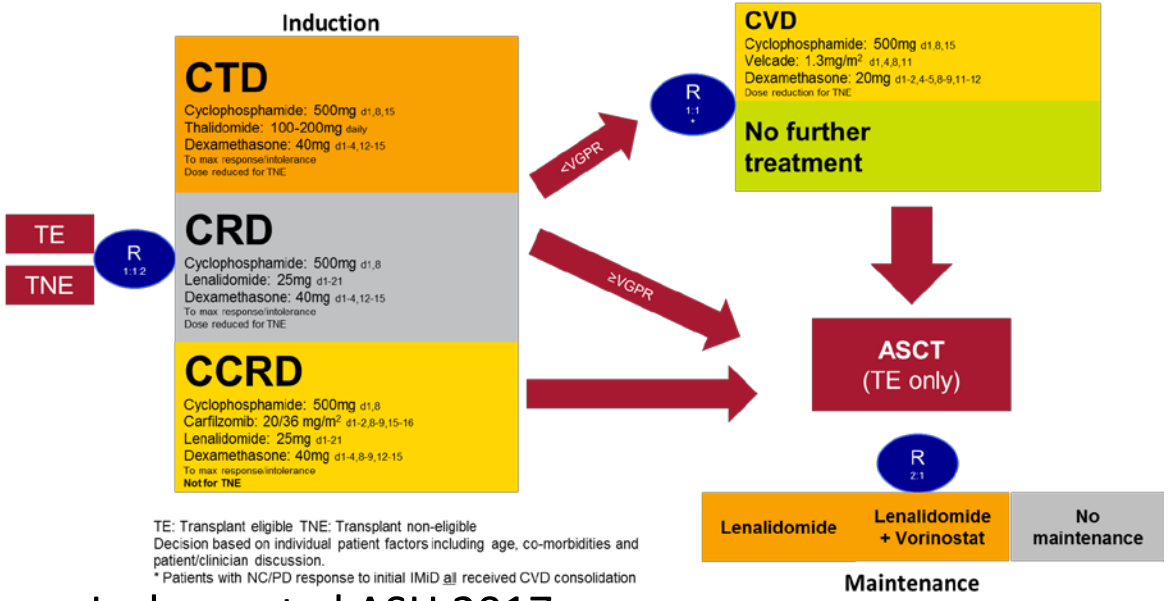
Rosinol L et al Leukemia 2017



Mellqvist et al Blood 2013

(Chief Investigator – Prof Graham Jackson)

Myeloma XI+



TE: Transplant eligible TNE: Transplant non-eligible
Decision based on individual patient factors including age, co-morbidities and patient/clinician discussion.
* Patients with NC/PD response to initial IMiD all received CVD consolidation

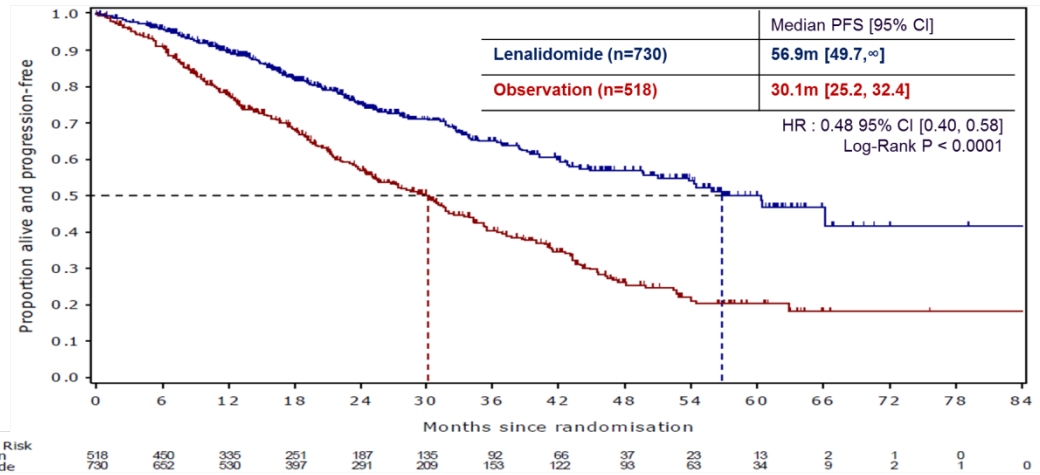
Jackson et al ASH 2017

Myeloma XI

Transplant eligible pathway

Lenalidomide improved PFS from 30 to 57 months, hazard ratio of 0.47

71



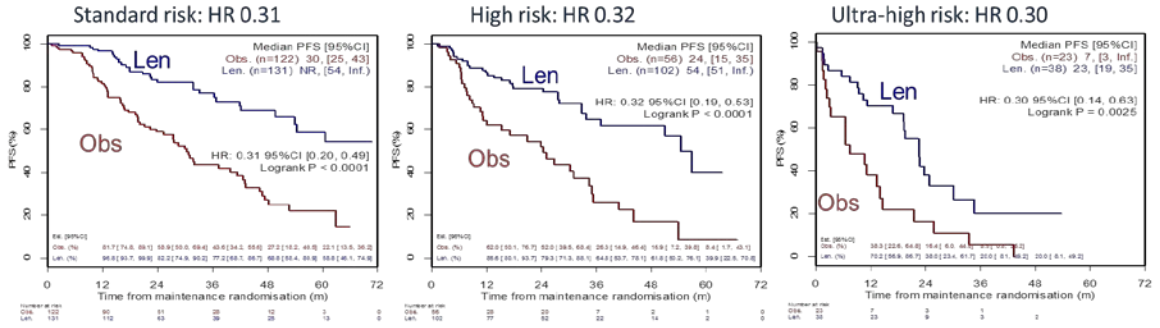
PFS: progression-free survival

Myeloma XI

Cytogenetic risk groups

Lenalidomide improved PFS irrespective of cytogenetic risk

74



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

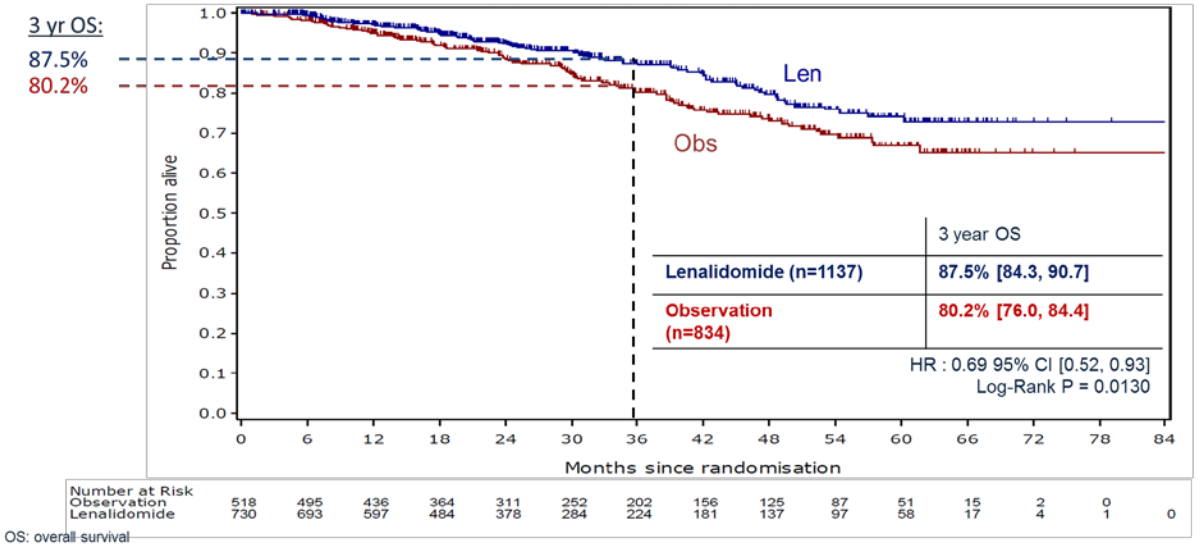
PFS: progression-free survival

Myeloma XI

Transplant eligible pathway

Lenalidomide improved 3 yr OS from 80.2% to 87.5%, hazard ratio of 0.69

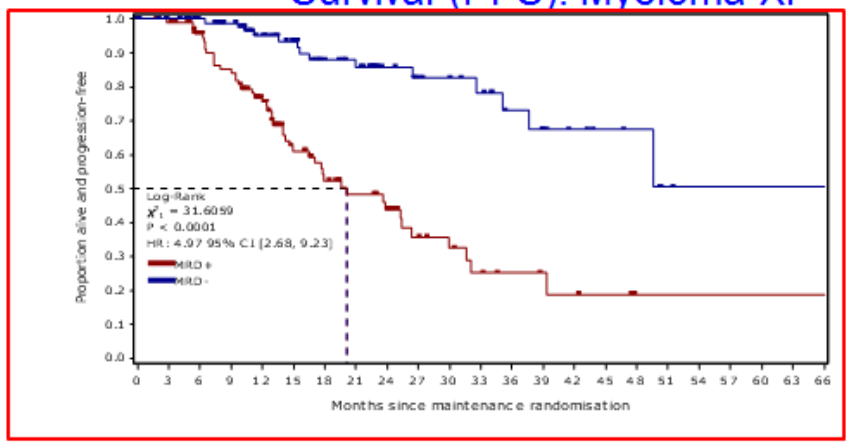
75



OS: overall survival

Myeloma XI: MRD Testing by Flow Cytometry

Impact of MRD post maintenance on Progression Free Survival (PFS): Myeloma XI



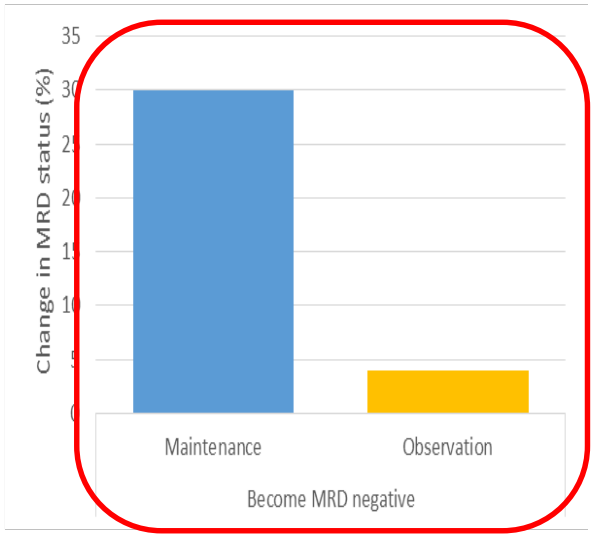
Impact of MRD results for patients with an informative sample at 6 months post maintenance randomization

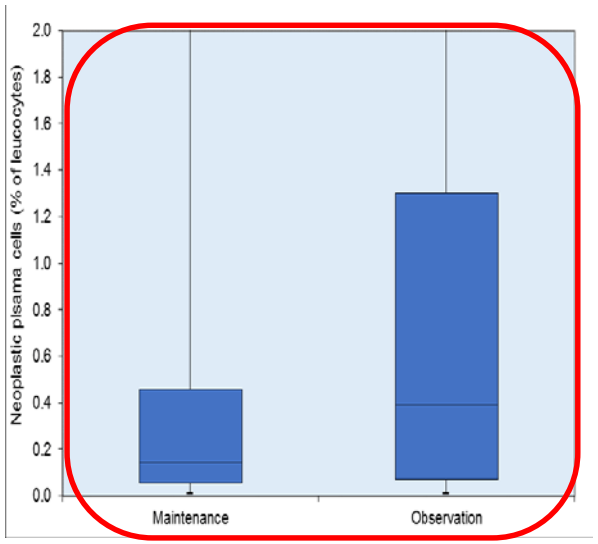
PFS is superior in the MRD- patients (>50 months vs 20 months, *P*<0.0001, HR 0.2, 95% CI 0.11-0.37)

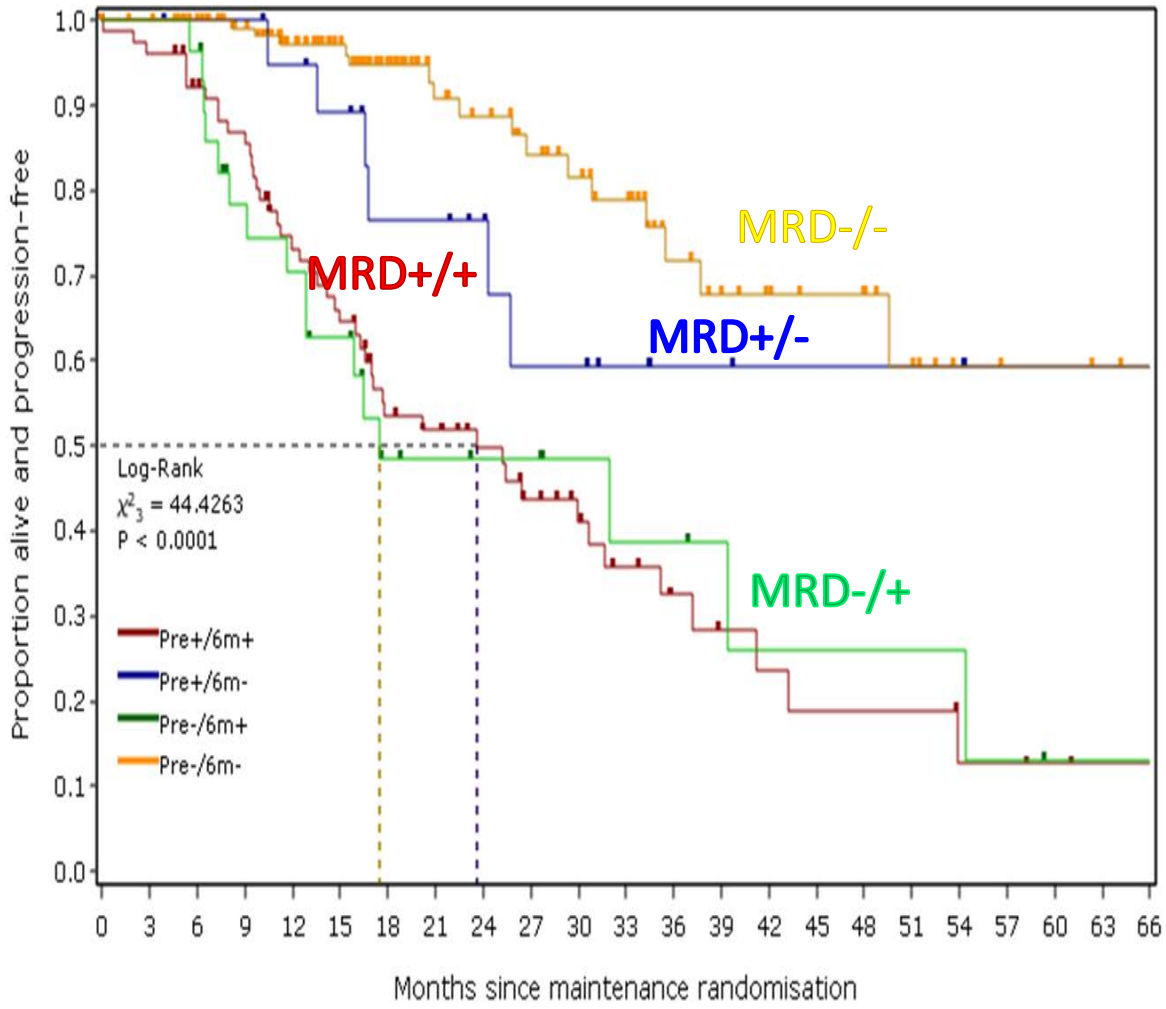
N=409

30% of MRD + converted to MRD – with len compared to 4% on no maintenance(p=0.0045).

For MRD +: median plasma cells 0.13% on maintenance vs 0.39% p=0.04



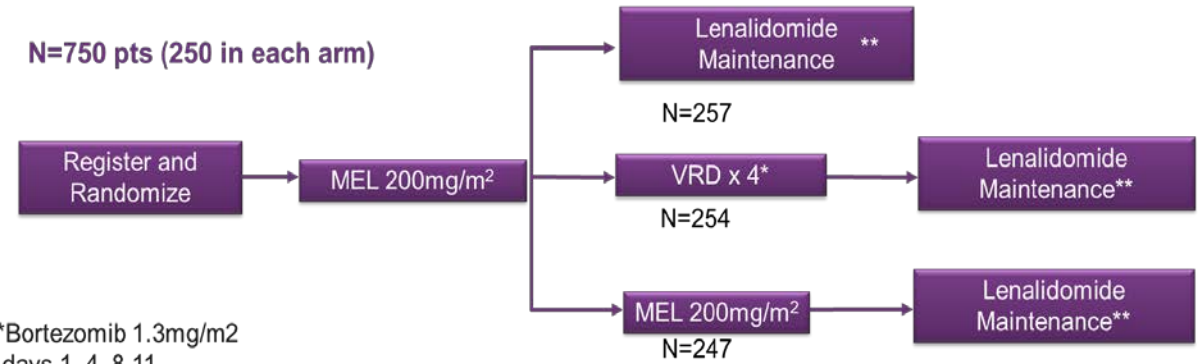




MRD testing at start of and 6 months after maintenance

de Tute et al, ASH 2017; Blood 2017 130:90

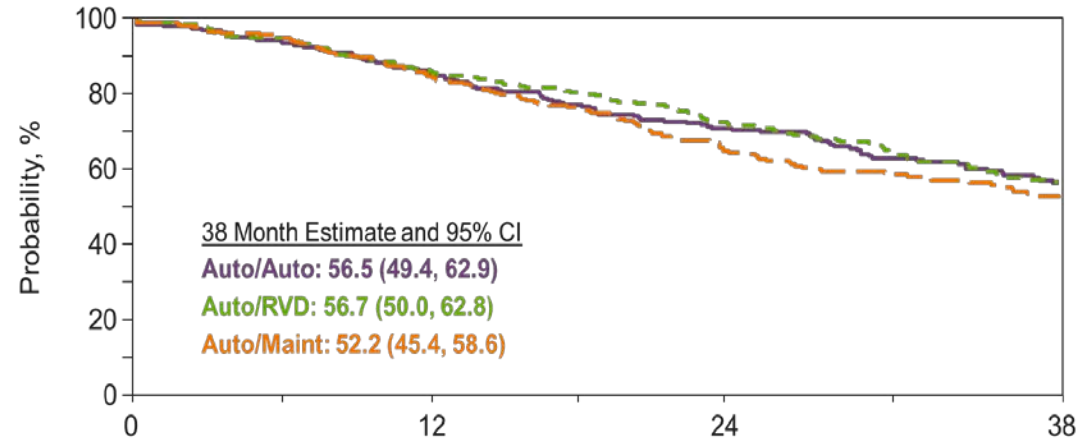
BMT CTN 0702 Stem Cell Transplantation for Multiple Myeloma Incorporating Novel Agents: SCHEMA



*Bortezomib 1.3mg/m2
days 1, 4, 8,11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg
days 1, 8, 15
Every 21 days

**Lenalidomide x 3years :
10mg/d for 3 cycles , then 15 mg/d
Amendment in 2014 changed Lenalidomide maintenance until disease progression after report of CALGB 100104.

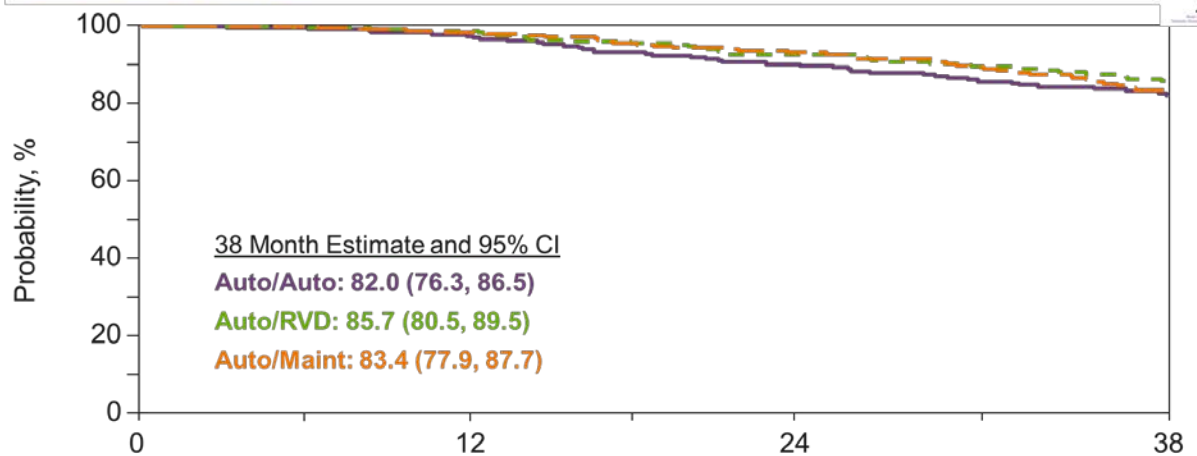
Primary Endpoint: Progression-free Survival



N at risk				
Auto/Auto	247	200	153	87
Auto/RVD	254	215	172	99
Auto/Maint	257	213	158	80

Stadtmauer E et al ASH 2016, Courtesy M Pasquini

Overall Survival



N at risk				
Auto/Auto	247	231	204	147
Auto/RVD	254	246	229	166
Auto/Maint	257	247	227	148

Stadtmauer et al ASH 2016, Courtesy M Pasquini

BMT CTN 0702: Regimens prior to Transplant

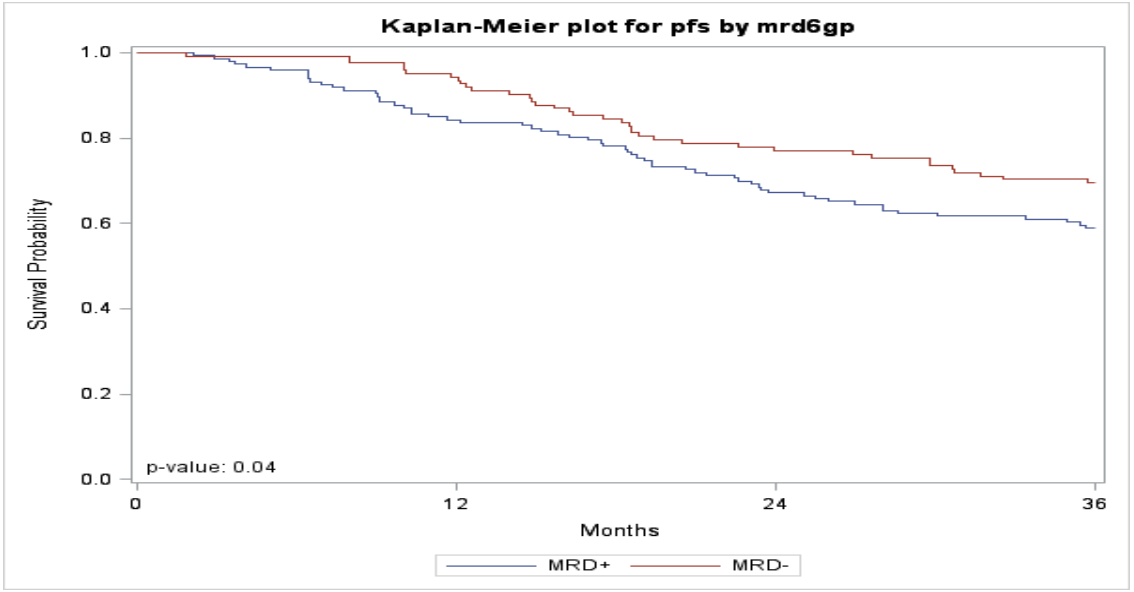
	Auto/Auto (N=247)		Auto/RVD (N=254)		Auto/Maint (N=257)	
	N	%	N	%	N	%
Initial Therapy						
Bort/Len/Dex	141	57.1	134	52.8	143	55.6
Cy/Bort/Dex	33	13.4	35	13.8	40	15.6
Len/Dex	24	9.7	28	11.0	22	8.6
Bort/Dex	28	11.3	32	12.6	32	12.5
Other	21	8.5	25	9.8	20	7.8

Bort, bortezomib; Cy, cyclophosphamide; Dex, dexamethasone; Len, lenalidomide

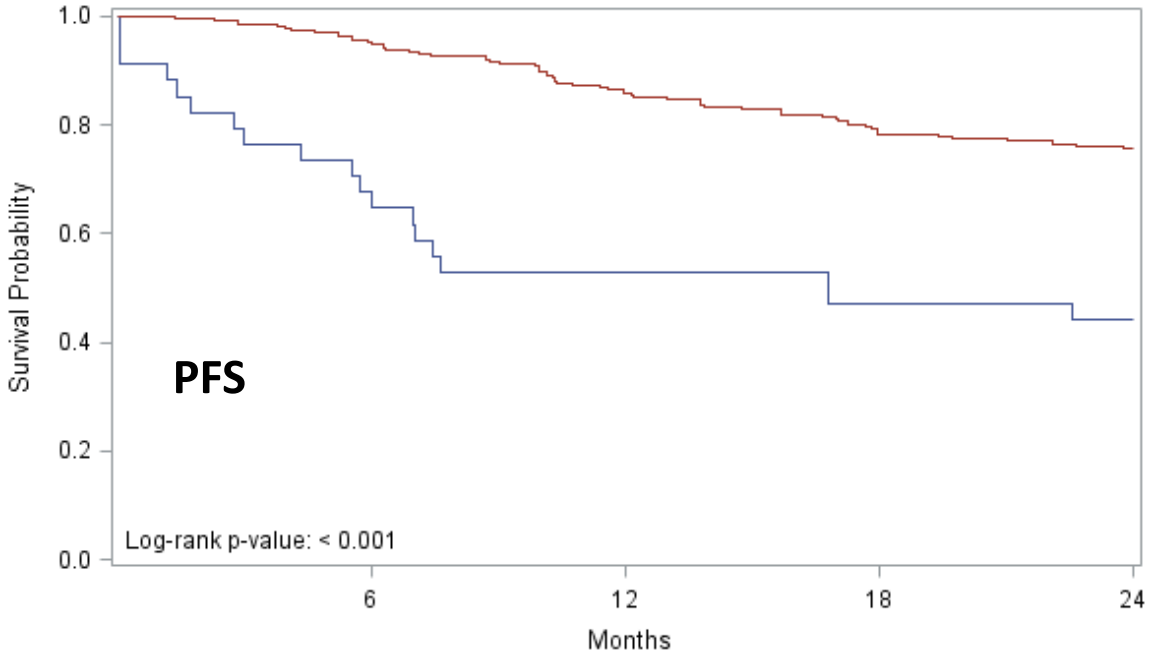
Stadtmauer et al ASH 2016, Courtesy M Pasquini

BMT CTN 0702

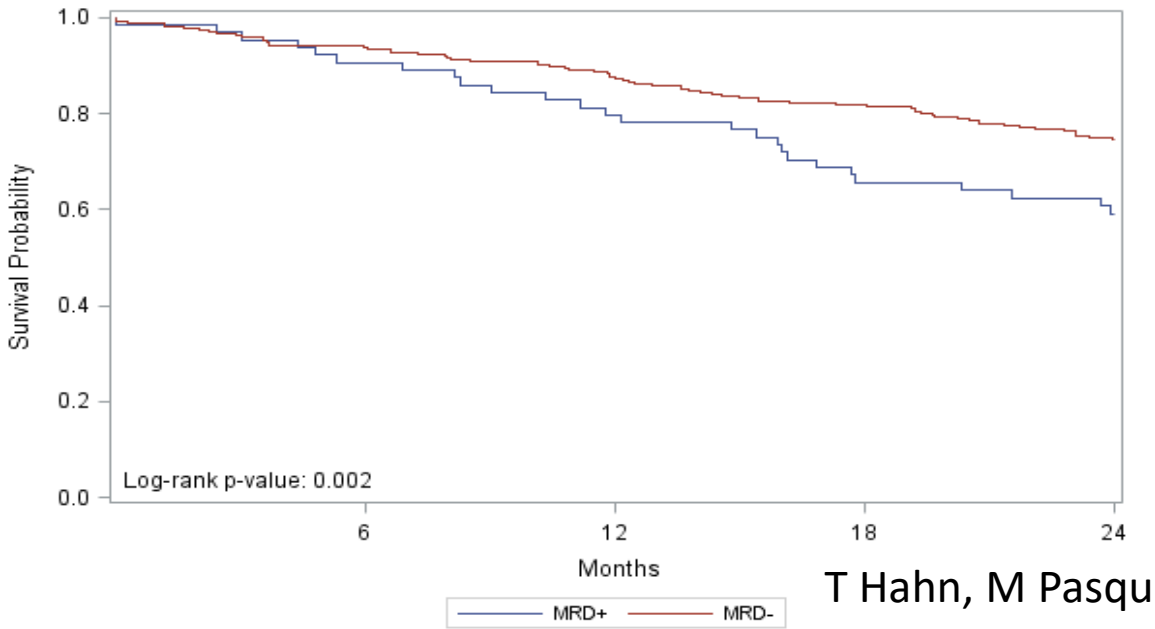
PFS by MRD status post induction

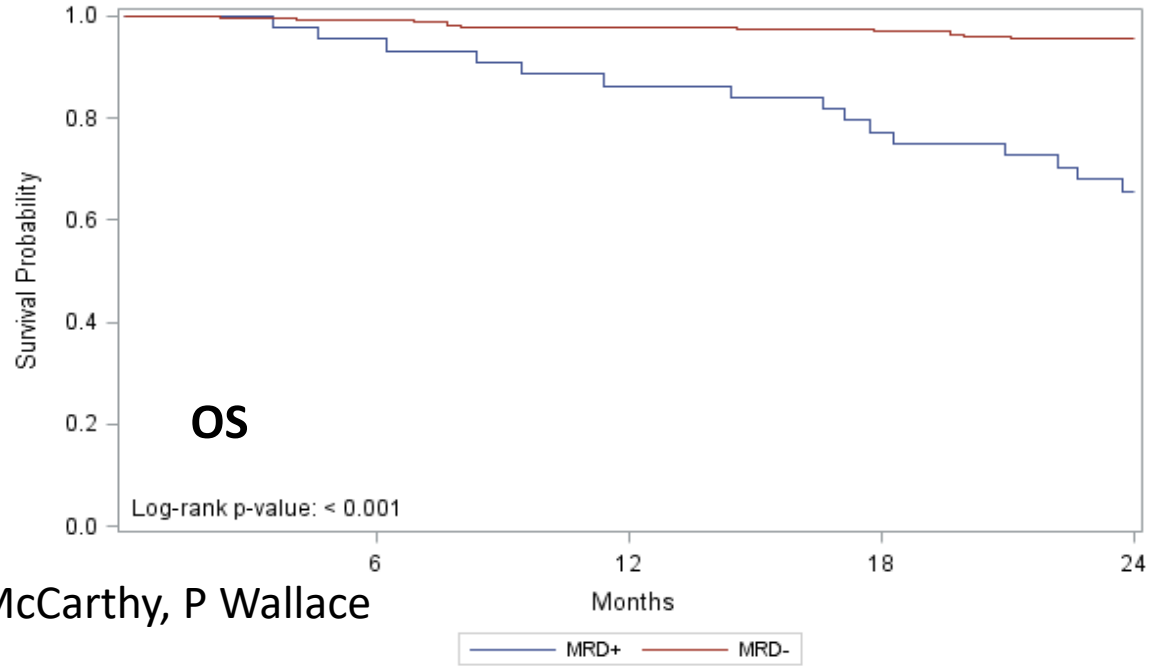


PFS/OS by MRD status at one year on maintenance therapy



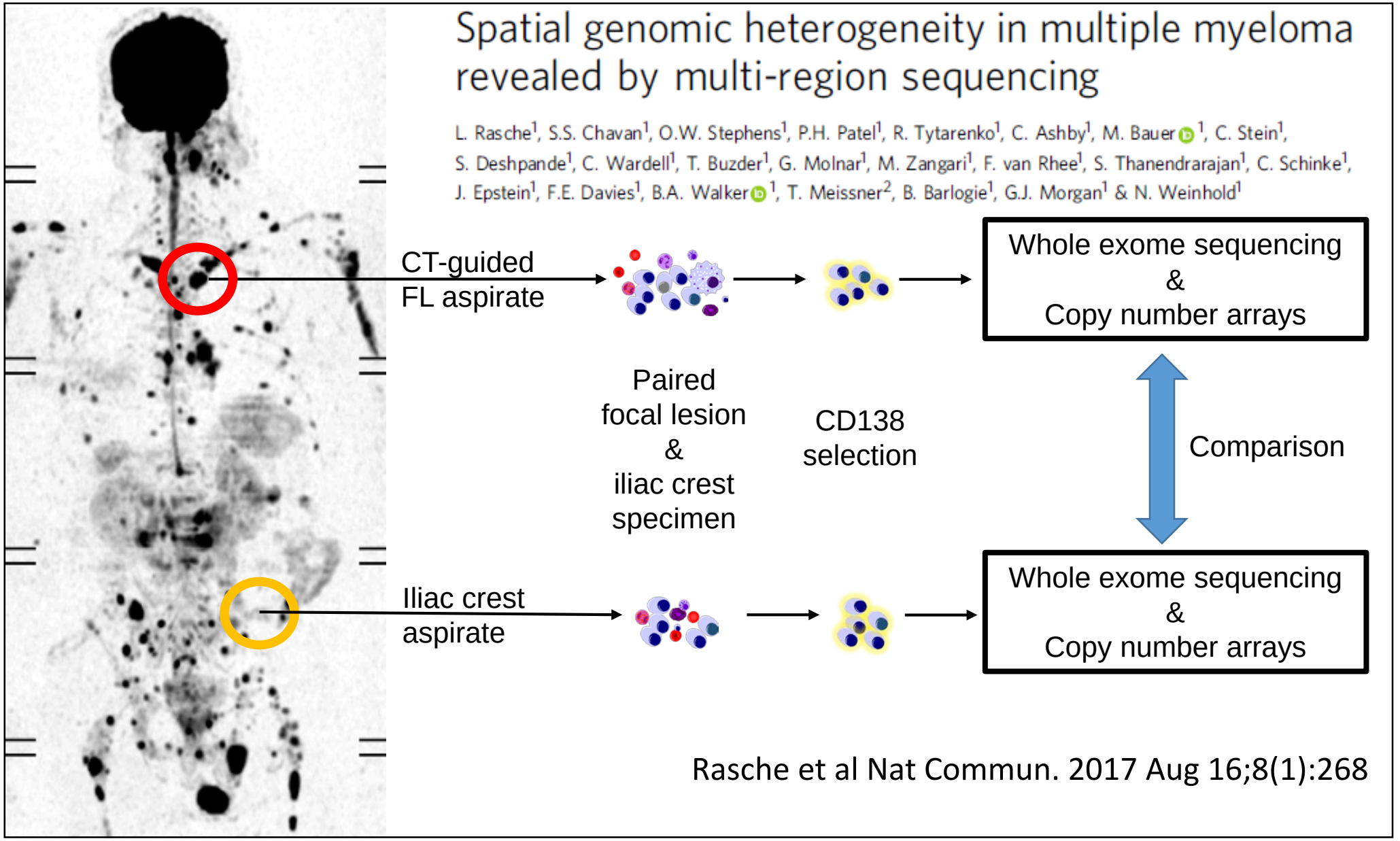
PFS by MRD status pre-maintenance



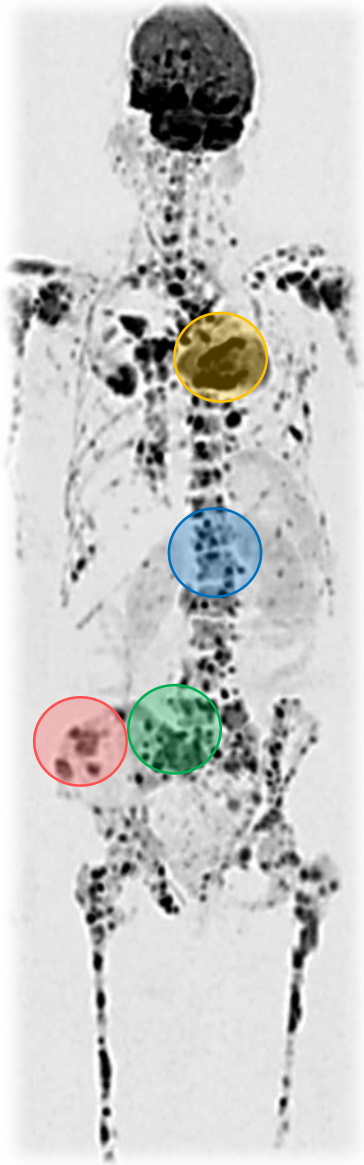


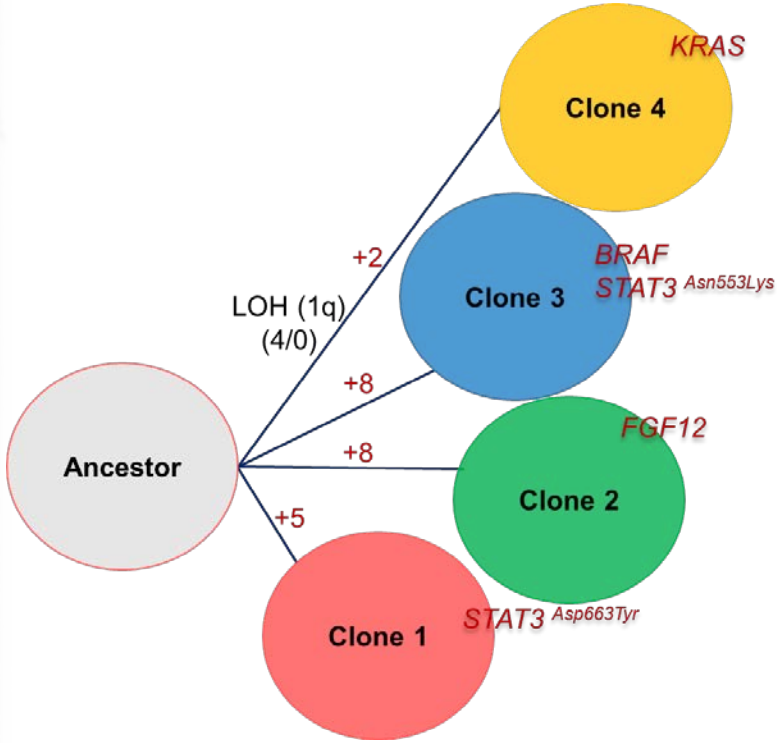
T Hahn, M Pasquini, P McCarthy, P Wallace

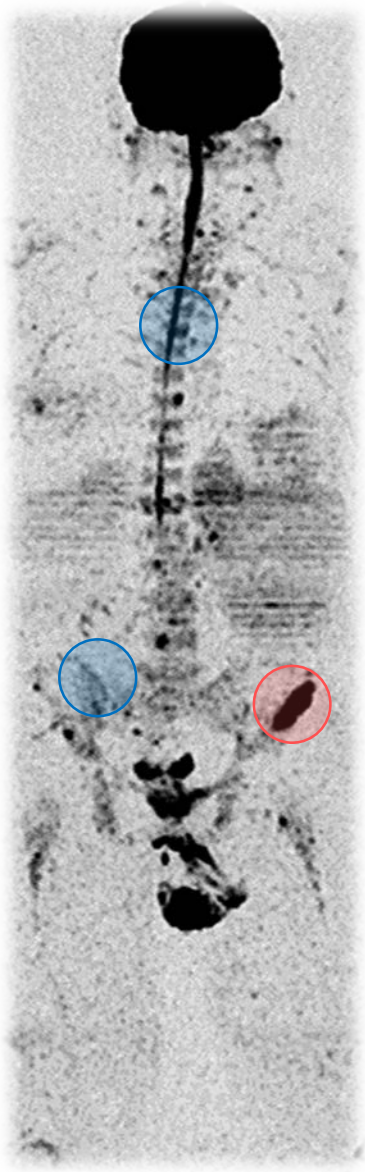
Analysis of focal lesions by multi-region sequencing

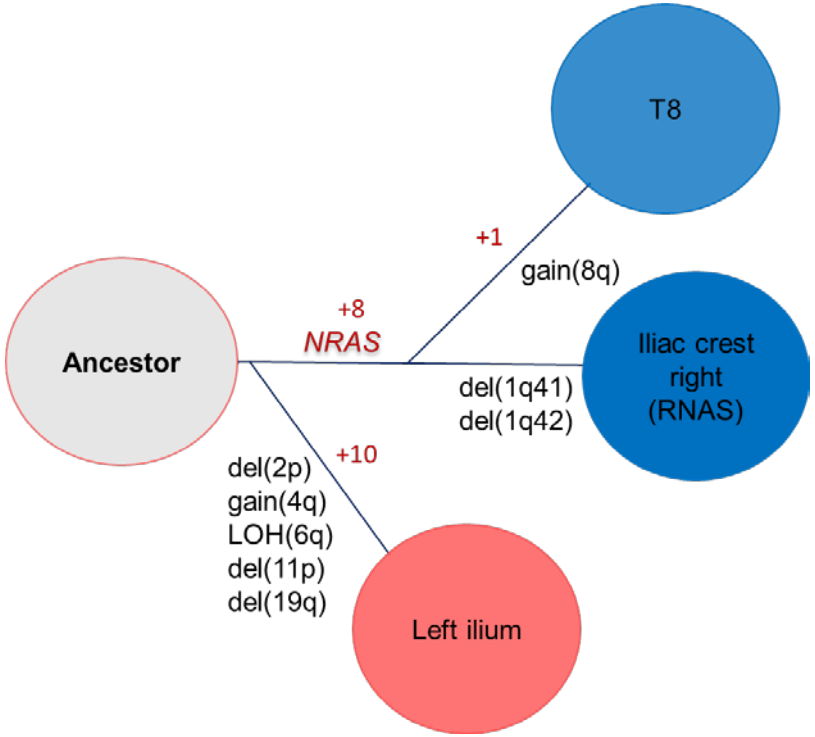


Spatial heterogeneity in myeloma



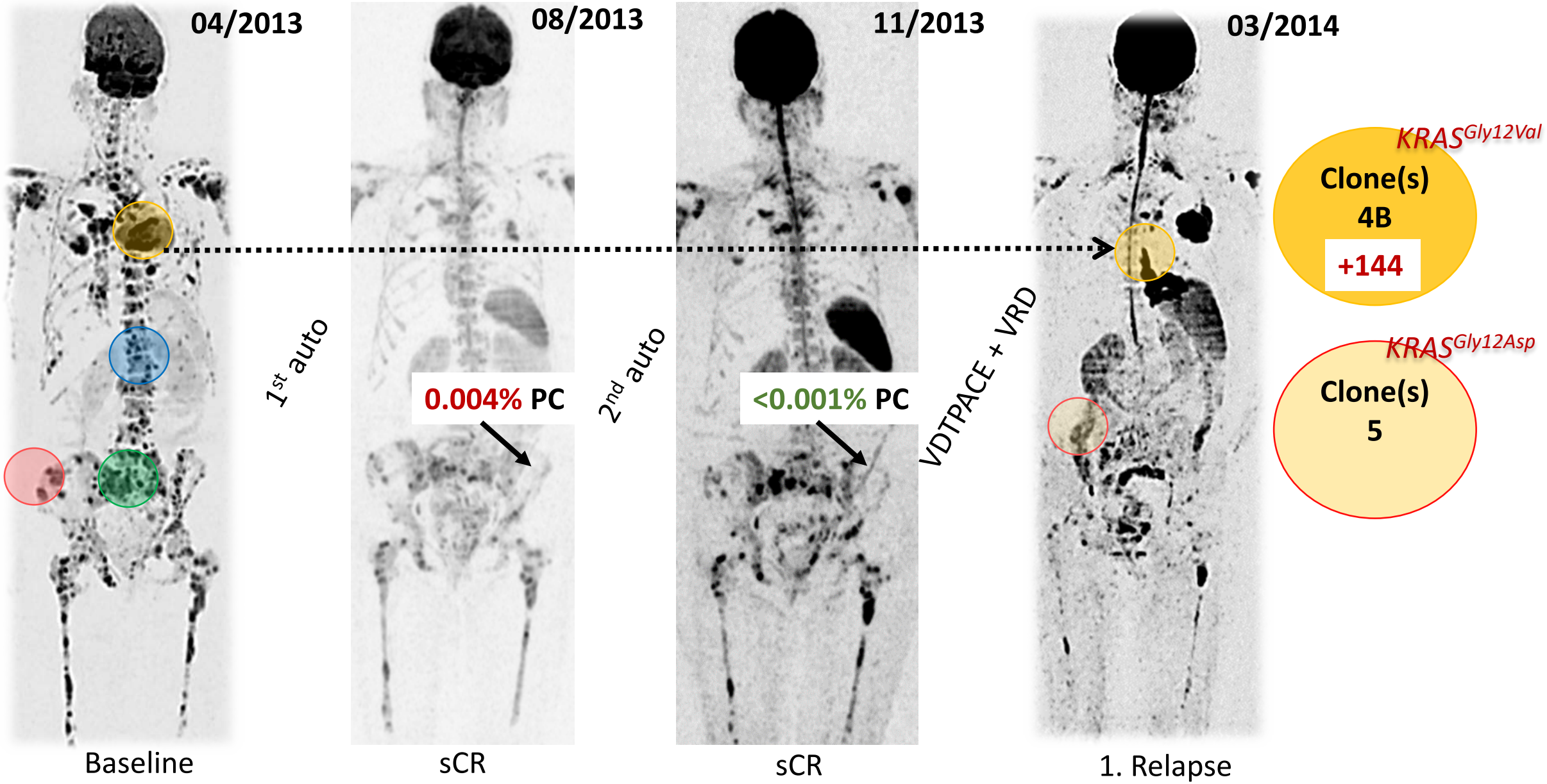






Rasche *et al. Nature Commun.* 2017 Aug 16;8(1):268

Multiple resistant sub-clones but MRD negativity…



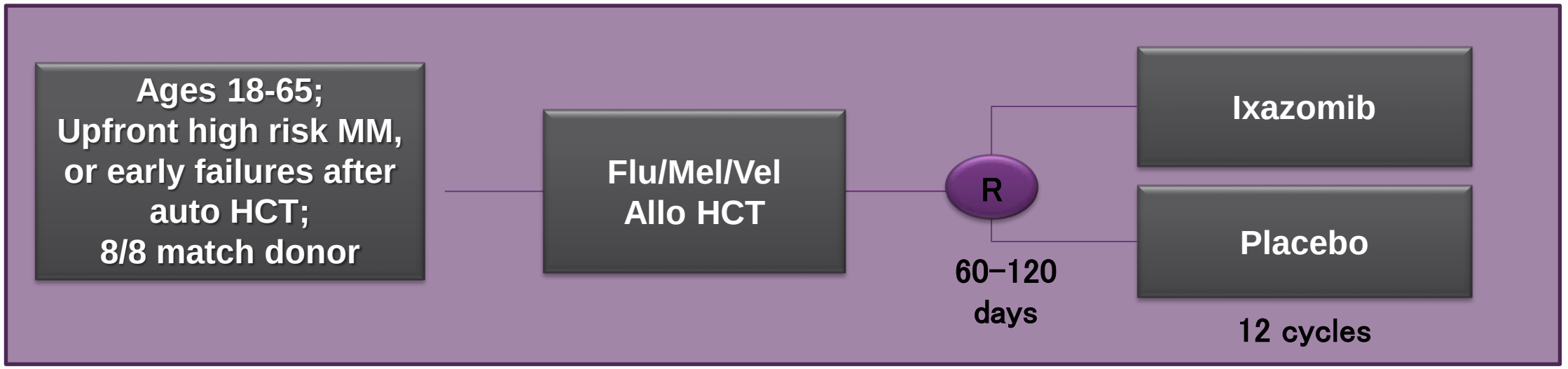
Rasche *et al. Nature Commun.* 2017 Aug 16;8(1):268

Comparison of the Three Techniques

Test Details	ASO PCR	NGF	NGS
% Informative Samples	Up to 70%	~100%	85-90%
Diagnostic Bone Marrow (BM) Sample	Needed for patient specific probes	Not needed	Needed or sample with enough myeloma cells
Plasma cells needed	Up to 10^6	5 x 10^6 or more	Up to 10^6 (more if possible)
Fresh or processed sample	Either	Fresh	Either
Sample quality control	Cannot evaluate BM	Yes, analyze BM	Cannot evaluate BM
Standardization	Yes	Yes	Early
Availability	Yes in certified lab	Yes in certified lab	Two companies but not certified for clinical use
Sensitivity	10^{-4} to 10^{-6} 0.0001% to 0.000001%	10^{-5} to 10^{-6} 0.00001% to 0.000001%	10^{-6} 0.000001%

ROSWELL PARK COMPREHENSIVE CANCER CENTER

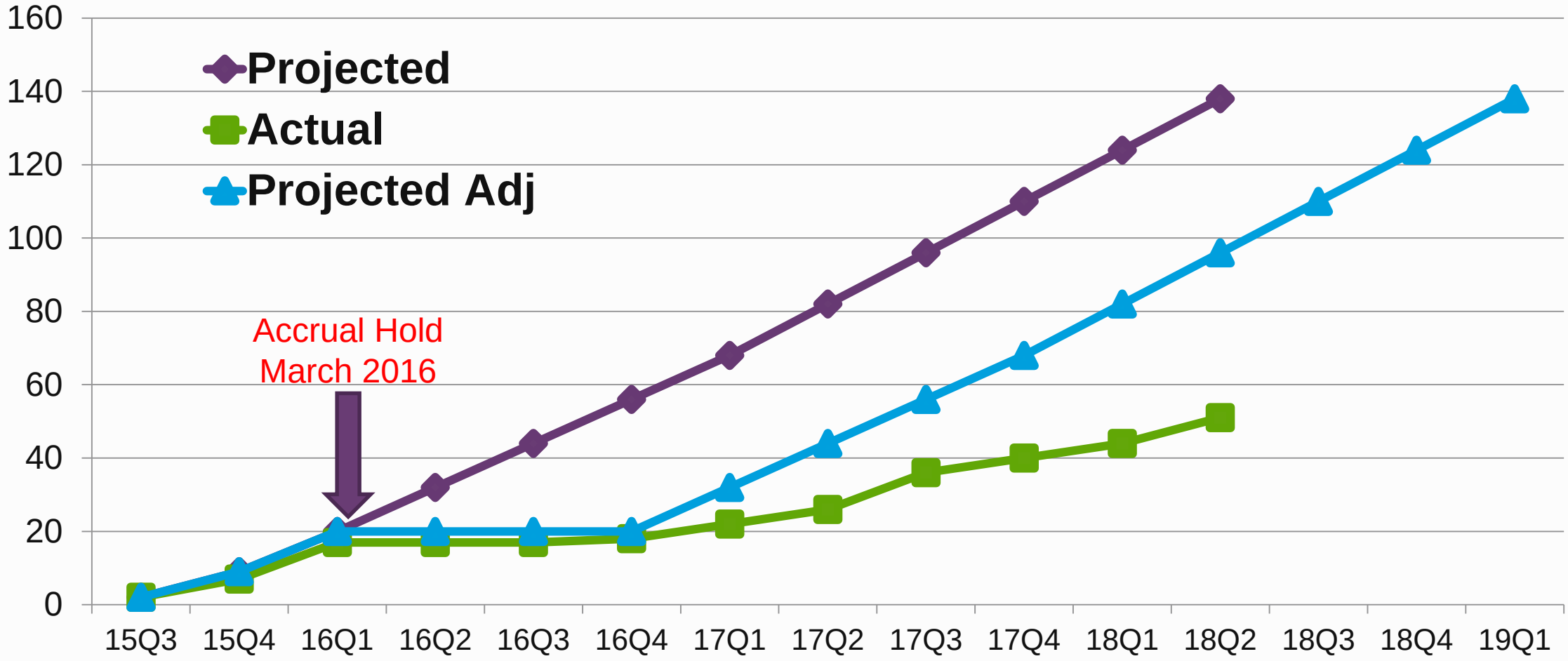
BMT CTN 1302: Study Outline



- Primary end point: PFS as a time to event from randomization
- Sample size: 138 patients (110 randomized patients)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 1302: Accrual to date (n=51, Rand, N=38) – 63% predicted



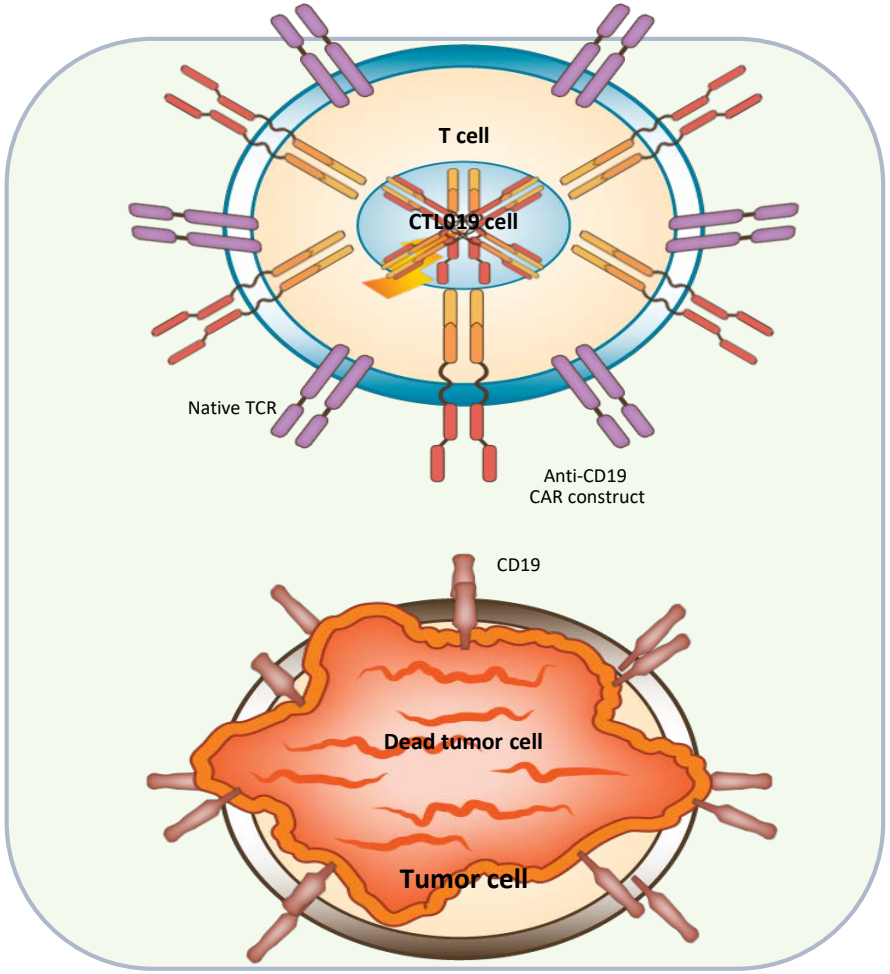
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Chimeric Antigen Receptor (CAR) T cell therapy

- Gene transfer technology stably expresses CARs on T cells[1,2]
- CAR T cell therapy takes advantage of the cytotoxic potential of T cells, killing tumor cells in an *antigen-dependent* manner[1,3,4]
- Persistent CAR T cells consist of both effector (cytotoxic) and central memory T cells[3,4]
- First human trial in resistant CLL patients[4]
- **T cells are *non-cross resistant* to chemotherapy**

1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464.
2. Hollyman D, et al. *J Immunother.* 2009;32:169-180.
3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.
4. Porter DL et al. *NEJM* 2011. 365:725-33

Original Slide Courtesy of D Porter



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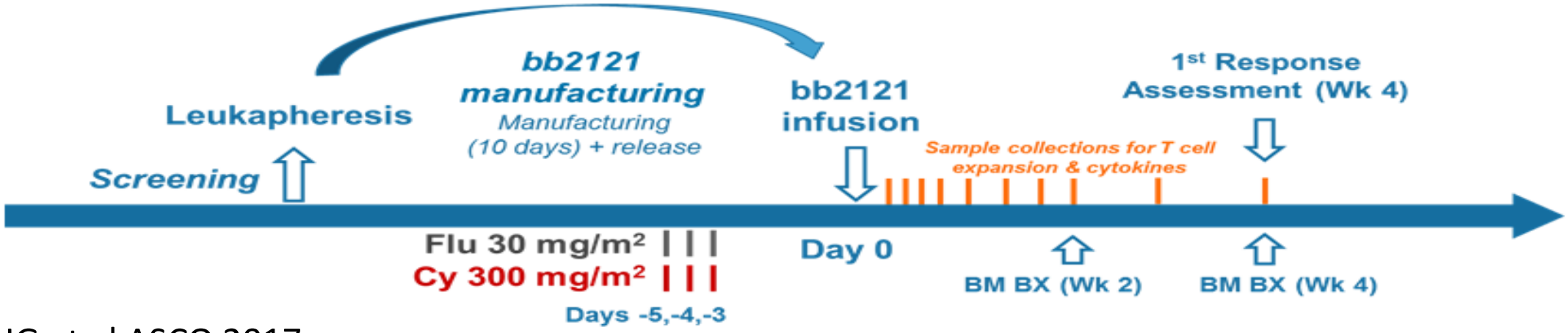
Bluebird BCMA CAR T Cells

- bb2121 is a second-generation CAR construct targeting BCMA, consisting of autologous T cells transduced with a lentiviral vector encoding a novel CAR incorporating an anti-BCMA scFv, a 4-1BB costimulatory motif to promote proliferation and persistence, and a CD3-zeta T cell activation domain
- Construct demonstrated potent preclinical *in vivo* activity with low tonic signaling and showed BCMA-specific cell killing

3 + 3 Dose Escalation of CAR + T Cells

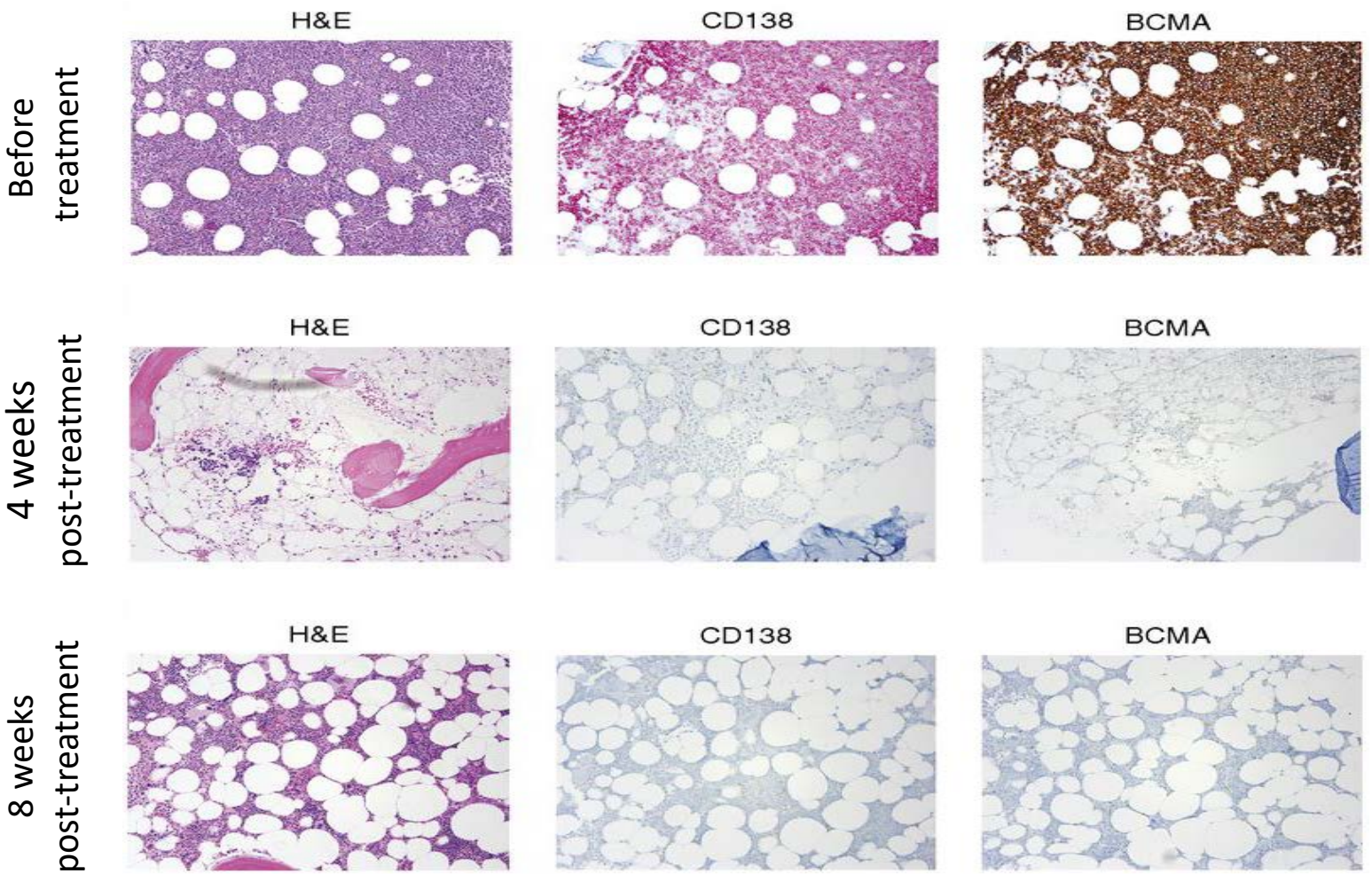
50×10^6 ▶ 150×10^6 ▶ 450×10^6 ▶ 800×10^6 ▶ $1200 \times 10^{6*}$

1200×10^6 dose cohort no longer planned



Berdeja JG et al ASCO 2017

BCMA+ CAR T therapy For Multiple Myeloma



Syed Abbas Ali et al. Blood 2016;128:1688-1700

Fan et al. LBA3001 ASCO 2017

- 100% ORR
- 33/35 patients in remission within 2 months after BCMA CAR T therapy

Berdeja et al ASH 2017 Abs 740

- 85% ORR

November 17th, 2017
FDA Breakthrough Designation

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Conclusions

- **MRD Testing in MM patients after primary therapy**
  - **MRD can be tested by ASO PCR, NGF (MFC) and NGS**
    - **When to test?**
      - **After induction, before maintenance, at fixed time point after maintenance?**
  - **The level of sensitivity is important**
    - **Dependent on technique, quality of sample, % of malignant plasma cells and non malignant cells and total number of cells analyzed**
  - **MRD negativity after primary therapy appears to predict for outcome**
  - **Not all MRD negative patients remain in remission**
  - **Some MRD positive patients do not have disease progression**
  - **As therapies improve, early endpoints are critical for predicting long term outcome**
  - **There is a need to incorporate other factors such as immune profiling, cytogenetic stratification, PET-CT and Whole Body MRI to determine long term prognosis**
  - Reference:
    - Takamatsu H, J Clin Med Oct 2017. Comparison of Minimal Residual Disease Detection by Multiparameter Flow Cytometry, ASO-qPCR, Droplet Digital PCR, and Deep Sequencing in Patients with Multiple Myeloma Who Underwent Autologous Stem Cell Transplantation

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5664006/?report=classic

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Carthage was the sworn enemy of Rome.

Cato the Elder ended all his speeches regardless of topic to the Roman Senate by saying, *Carthago delenda est, Carthage must be destroyed,* emphasizing the point of defeating Carthage

In an era when median PFS are approaching >5 years and OS approaching 10 years, "*Early surrogate endpoints for long term outcome (PFS/OS) must be tested in clinical trials so as to prevent studies that must remain open for 10 years or longer especially for an OS endpoint*"

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People and Services who make the BMT program possible

- S Balderman
- G Chen
- C Ho
- M Ross
- M Aungst
- M Burgess
- M Everett
- S Griebner
- A Koeppel
- J Lex-Sikinoff
- A Nemmer
- S Myszka
- A Phillips-Hall
- P Paplham
- R Russell
- A Beck
- S Flavin
- D Oliansky
- F Zhang
- A Kariapper
- H Jacobson
- R McKenzie
- S Oakley
- D Manfredi
- L Martin
- T Hahn
- M Herr
- S Schinnagel
- L Privitere
- K West
- J Pleskow
- M Cimino
- M Steward
- D Swinnich
- K Stawicki
- D Cipolla
- K Dubel
- P Lipka
- S Siconolfi
- C Warren
- L Yoerg
- S Pry
- R De Wald
- L Markel
- R Kumpf
- K Dunn
- A Kader
- J Nichols
- H Bashaw
- S Clarke
- K Odunsi
- M Oprychal
- T Chodon
- R Koya
- C Choi
- A Hutson
- J Becker
- E Duman
- L Vesneske
- Rad Onc Service
- Radiology Svc
- Surgery Svc
- Pathology Svc
- Lab Medicine
- Stem Cell Lab
- Apheresis Unit
- S Szeglowski
- L Regan
- S Segal
- J Kapinos
- A Singh
- ID service
- B Segal
- N Almyroudis
- D DePaolo
- Managed Care and Finance Svc
- S Randolph
- M Budd
- Medical Oncology Fellows
- Leukemia, Lymphoma and Myeloma Services
- 5 East, 5 North and 6 North Nursing and Secretarial Staff
- Hospitalist Staff
- J Hillengass
- F Hernandez
- E Wang
- M Ernstoff
- J Lau
- E Repasky and Lab
- H Mohammadpour
- J Sarow
- P Wallace
- J Tario
- Y Zhang
- S Johnson
- C Johnson
- V Filadora
- T Schwaab
- B Kuvshinoff
- Support by RPCI Alliance, RPCI Core Grant,
- NCI, NHLBI and B and E McCarthy

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Acknowledgements

- The patients and caregivers who participated in these studies
- The clinicians who provided care for these patients
- The site research staff for protocol monitoring
- The Alliance, ECOG, SWOG, BMT-CTN, IFM, and GIMEMA colleagues participating in the lenalidomide meta-analysis
  - P Richardson, K Anderson, S Holstein, C Linker, K Owzar, C Hofmeister, D Hurd, R Vij, J Moreb, NS Callander, K van Besien, T Gentile, L Isola, R Maziarz, D Gabriel, A Bashey, T Shea, S Devine, H Hassoun, D Weisdorf, T Martin, E Stadtmauer, S Giralt, M Pasquini, A Krishnan, M Horowitz, Jim Omel, D Sargent, and Duke and Mayo Alliance Statistical Centers
  - M Attal, P Moreau, V Lauwers-Cances, C Hulin, D Caillot, G Marit, T Facon, AM Stoppa, L Benboubker, L Garderet, O Decaux, S Leyvraz, M-C Vekemans, L Voillat, M Michallet, B Pegourie, C Dumontet, M Roussel, Z Leleu, C Mathiot, C Payen, H Avet-Loiseau, J-L Harousseau
  - A Palumbo, F Cavallo, P Tosi, V Magarotto, F Gay, M Petrucci, F Di Raimondo, DB Yehuda, S Pezzatti, T Caravita, C Cerrato, E Ribakovsky, M Genuardi, A Cafro, M Marcatti, L Catalano, M Offidani, AM Carella, E Zamagni, F Patriarca, P Musto, A Evangelista, G Ciccone, P Omedé, C Crippa, P Corradini, A Nagler, M Boccadoro, and M Cavo
- The NCI: R Little, H Streicher
- RPCI: T Hahn, P Wallace, S Balderman, G Chen, F Hernandez, C Ho, K Lee, M Ross, P Torka, J Hillengass, P Wallace, J Tario
- Jane and our family who support my work schedule

Excitement on the horizon!

Lenticular Cloud over Chile which is reminiscent of a Red Blood Cell

Thank you very much!

Courtesy of Rosie McCarthy who found this on:
http://www.flickr.com/photos/dcml/217552761/

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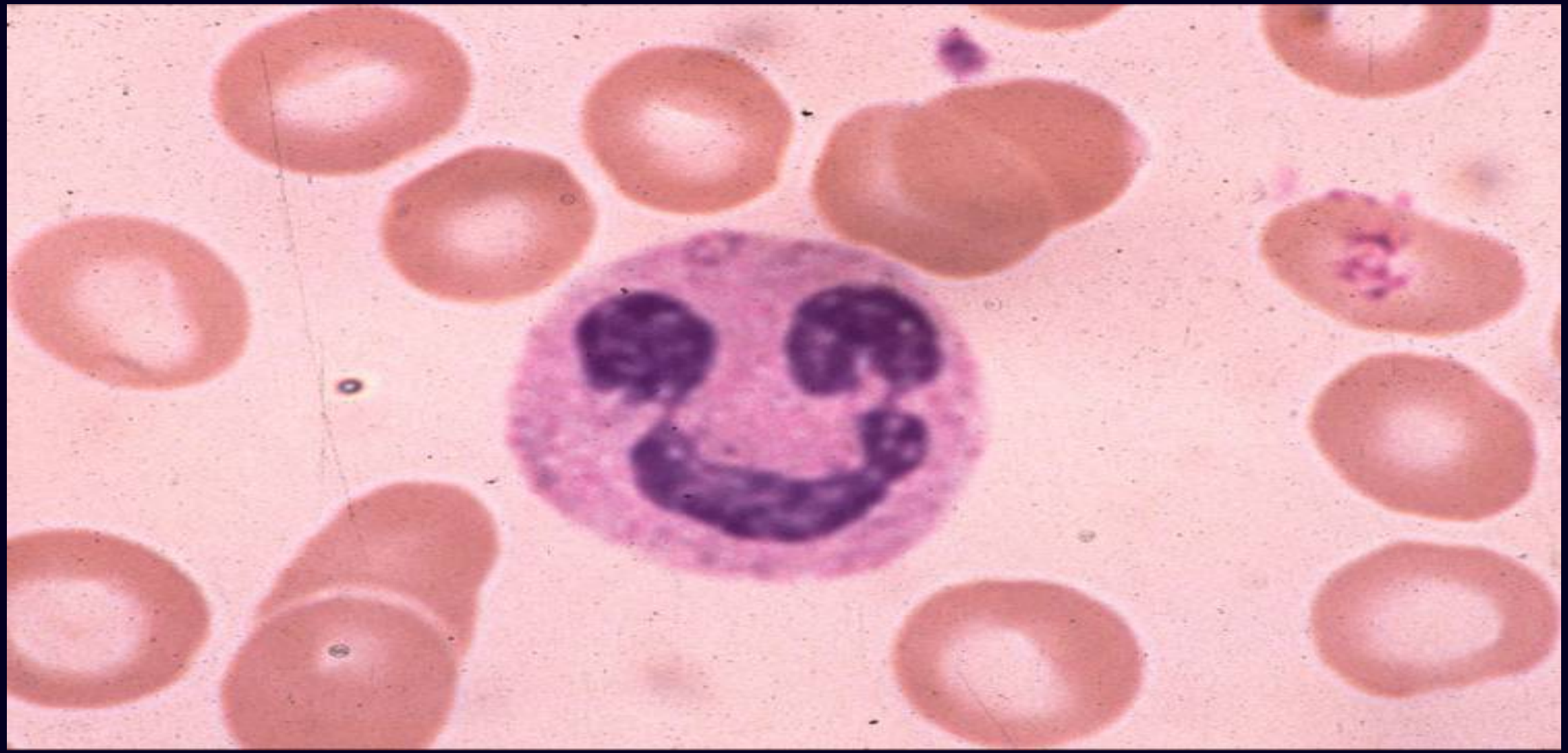
Thank you very much



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The Villain Returns: AML and ALL Relapse Following HCT and Treatment Strategies

Veronika Bachanova, MD, PhD
University of Minnesota

November 9, 2018

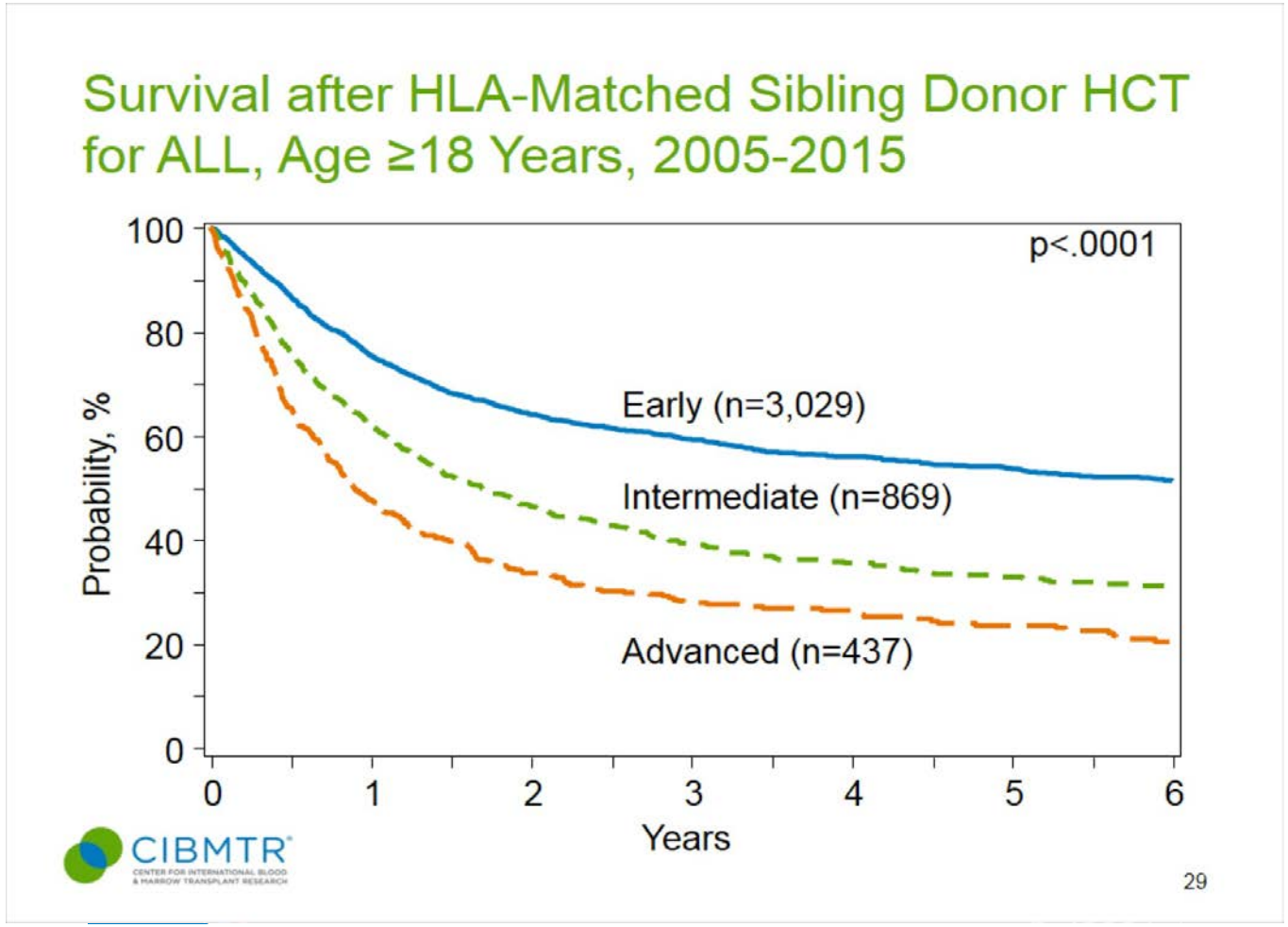
NATIONAL MARROW DONOR PROGRAM®

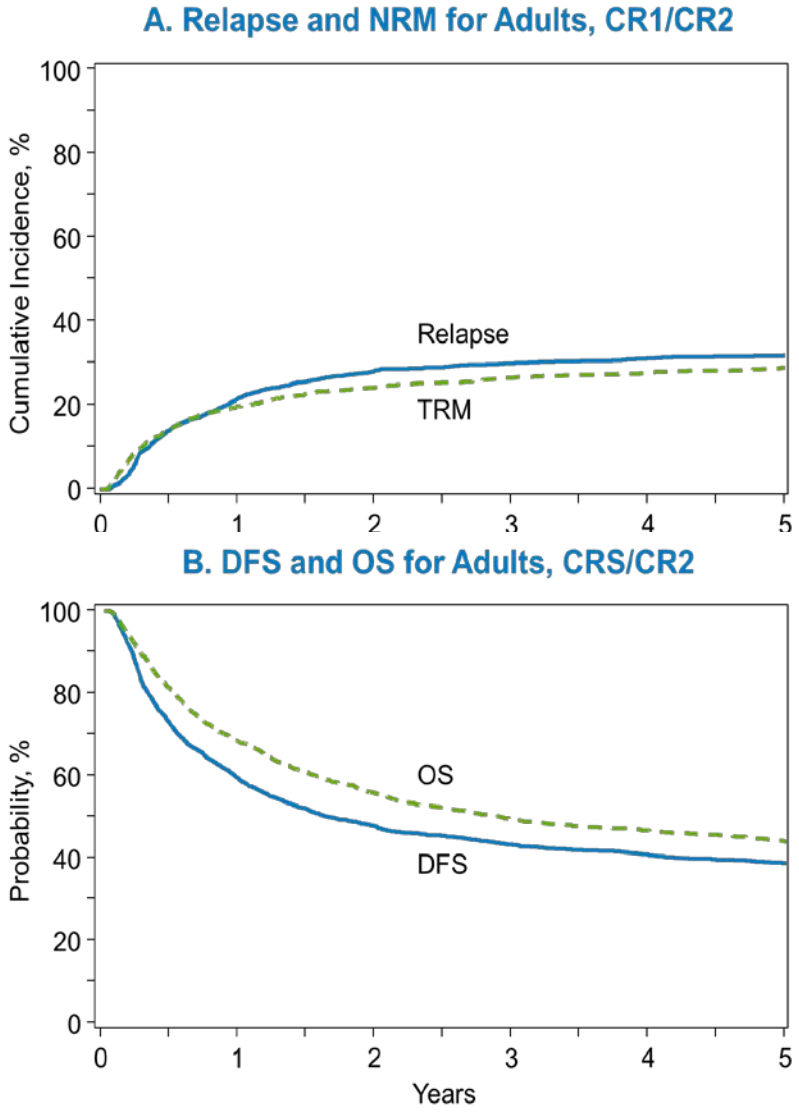
BE THE MATCH®

Outline

- ✓ Discover the incidence and continuing challenges of ALL and AML relapse following HCT
- ✓ Compare factors influencing detection of MRD in ALL and AML
- ✓ Describe the examples of novel therapeutic strategies to treat and prevent relapse in HCT patients

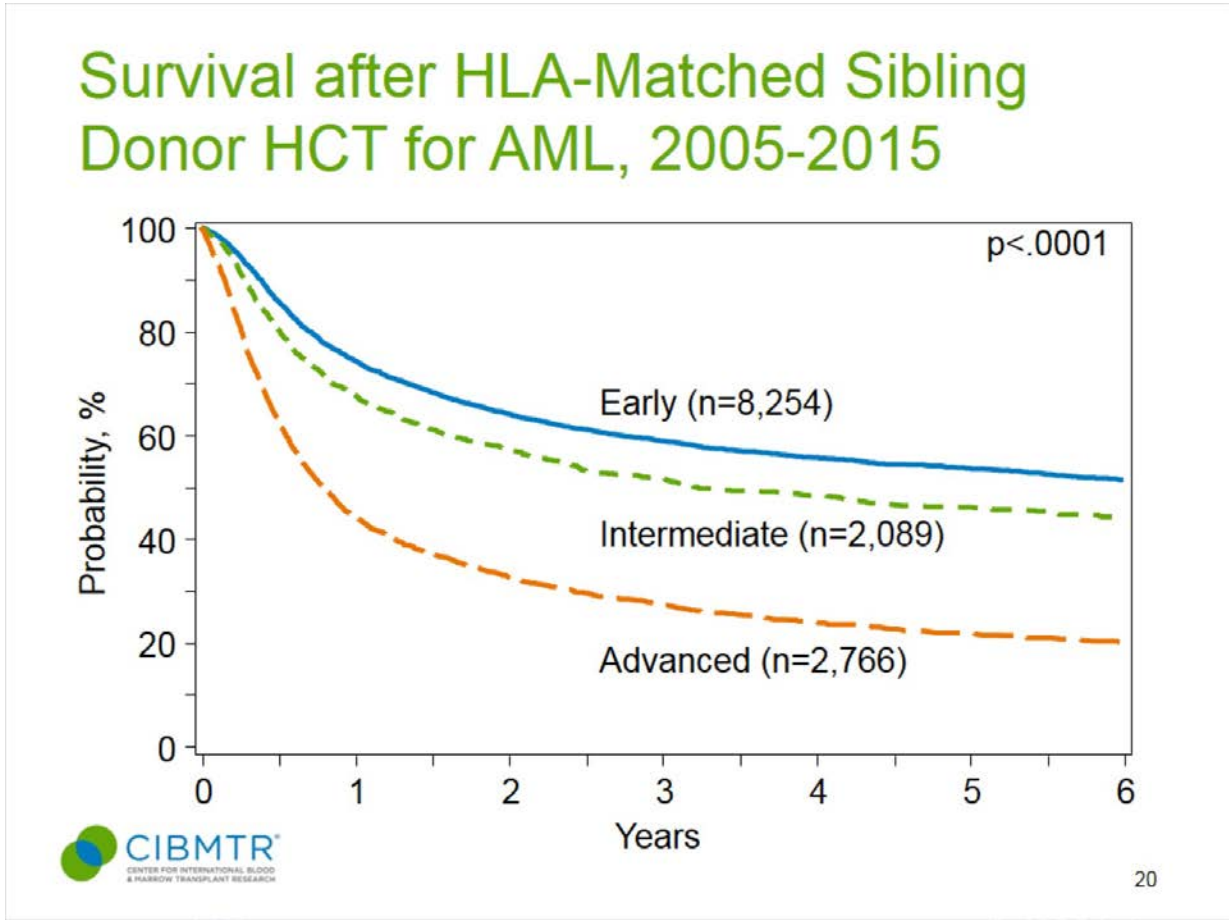
Relapse after HCT is the most common reason for transplant failure

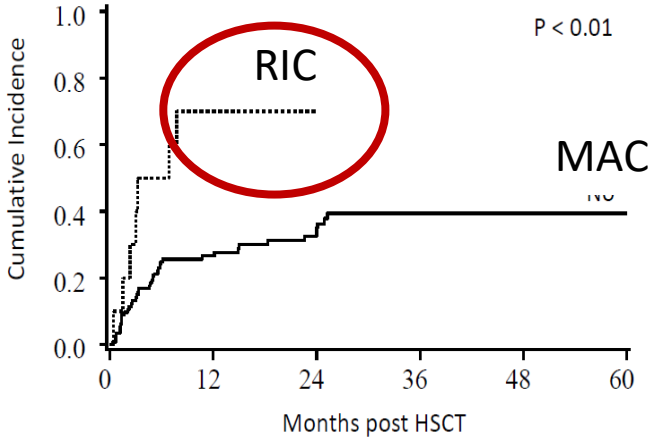


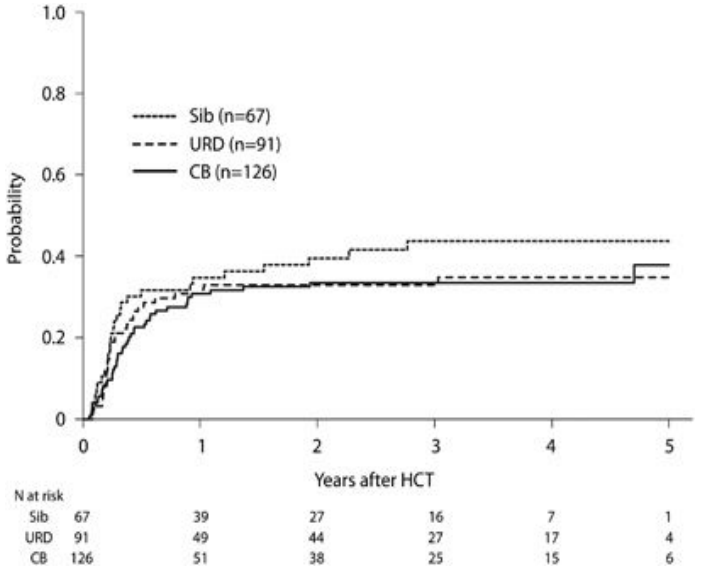


Yessurun, Bachanova, Blood Advances 2018

Acute Myeloid Leukemia Overall Survival and Relapse







SOURCE: CIBMTR®, the research program of NMDP/Be The Match

Ustun C et al Leukemia 2017

Measurable Residual Disease is the Major Predictor for Relapse in Acute Leukemia

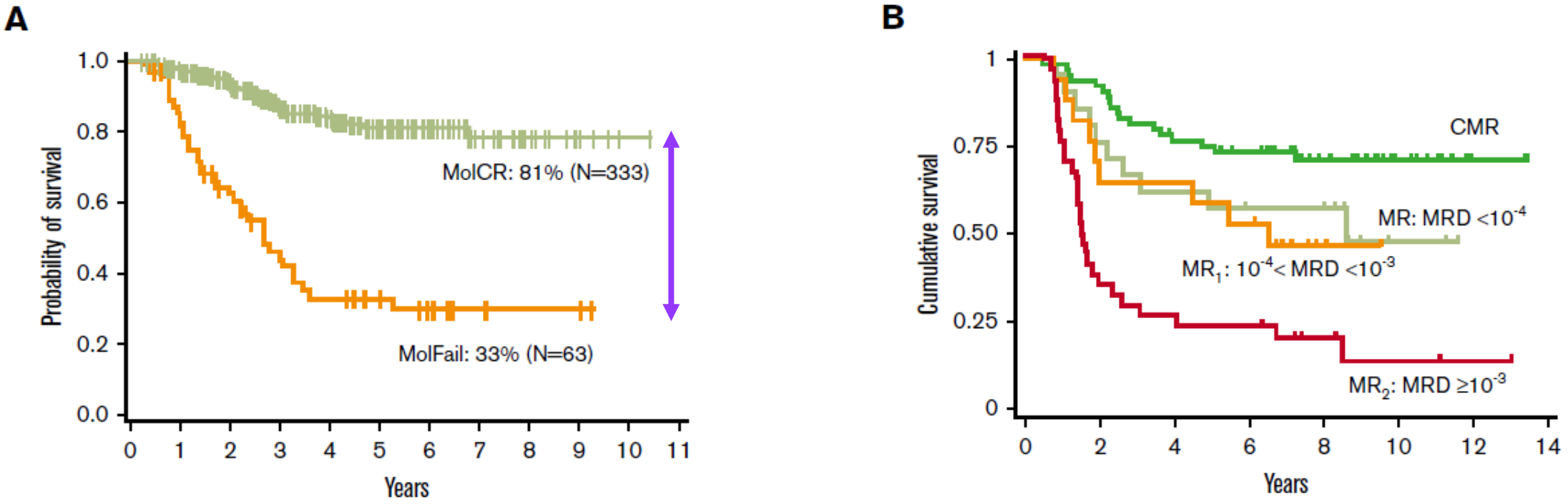
Methods of MRD monitoring in ALL

- **Multiparameter Flow Cytometry: 6-8 color** immunophenotype has sensitivity to 0.01% (1 out of 10 000 cells)
- PCR for IgH re-arrangement
- detection of BCR-ABL transcript by PCR with a sensitivity of 1/10,000
- FISH or cytogenetics (MLL gene re-arrangement, other)
- Bone Marrow (Standard) vs Peripheral Blood (not standard)

MRD after induction is the most critical high risk prognostic factor

Overall Survival of GMAAL Ph- patients, stratified by MRD after induction/early consolidation.

- B Overall Survival according to post-induction MRD.

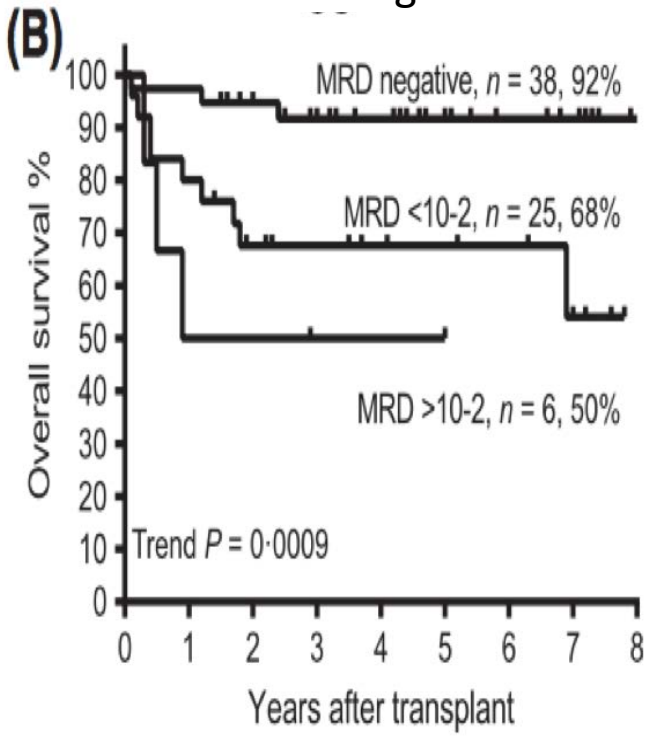


1: Hematology 2017: 13-21

Impact of MRD Pre-HCT on Survival

- n=81
- Pediatric
- All Cell Type
- CR1-3
- IgH PCR

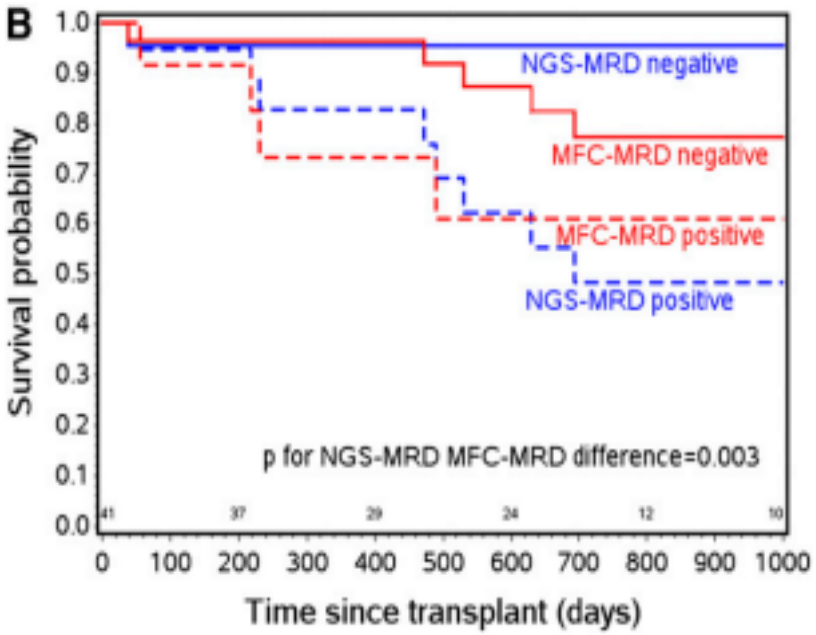
OS



Sutton et al Bri J Haem 2014, the ANZCHOG ALL8 trial

- n=56
- Pediatric
- B Cell
- CR1 and 2
- NSG IgVH vs. FC

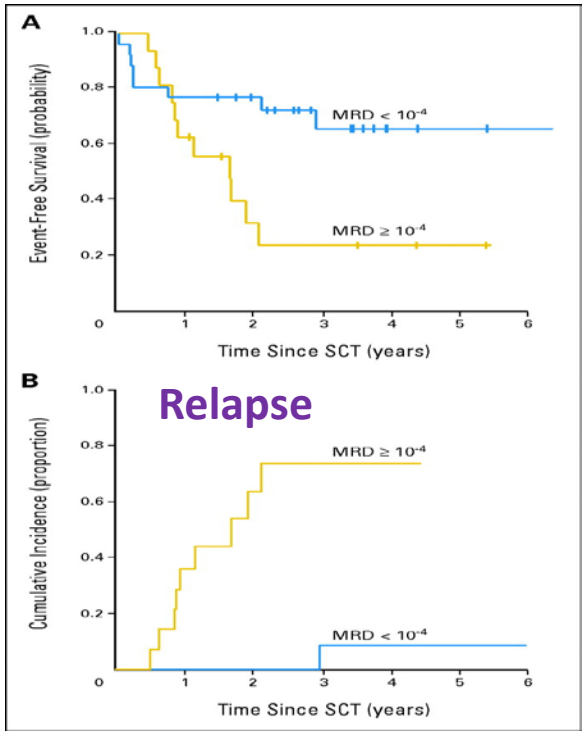
OS



Pulsipher et al. Blood 2015

- n=91
- Pediatric
- B Cell
- CR2
- IgVH PCR

EFS

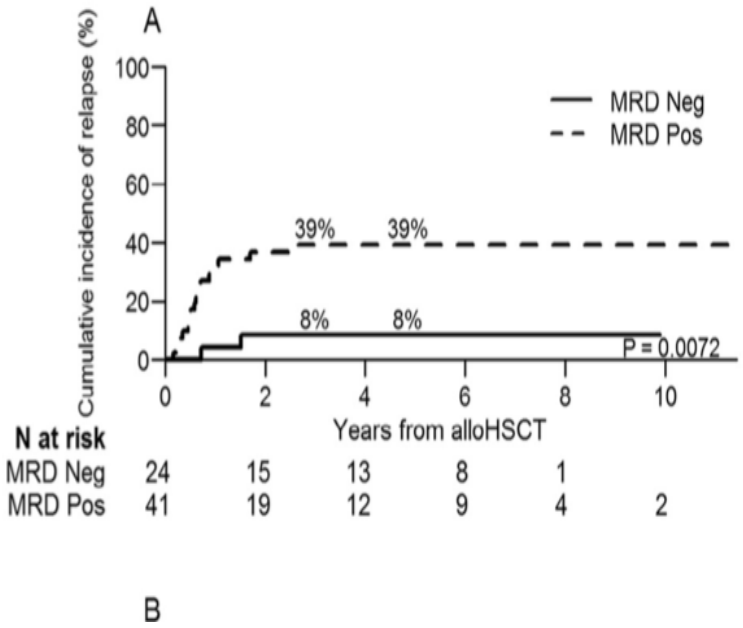


Bader et al JCO 2009 ALL Relapse Berlin-Frankfurt-Munster (ALL-REZ BFM) Study Group

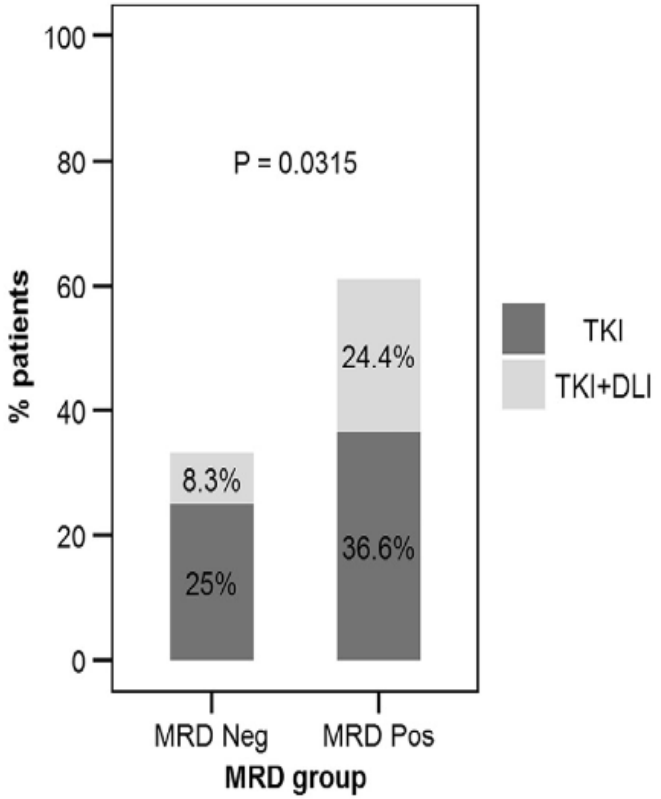
MRD Impact Pre-HCT In CR1 Ph+ ALL in TKI era

- n=65
- Adult
- BCR/ABL1

Relapse



Post-HCT Preventive Measures



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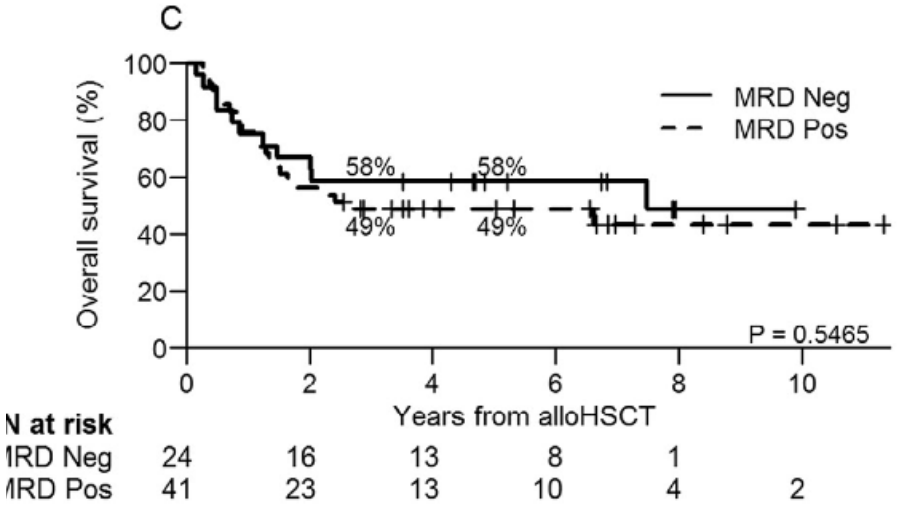


Lussana et al BBMT 2016

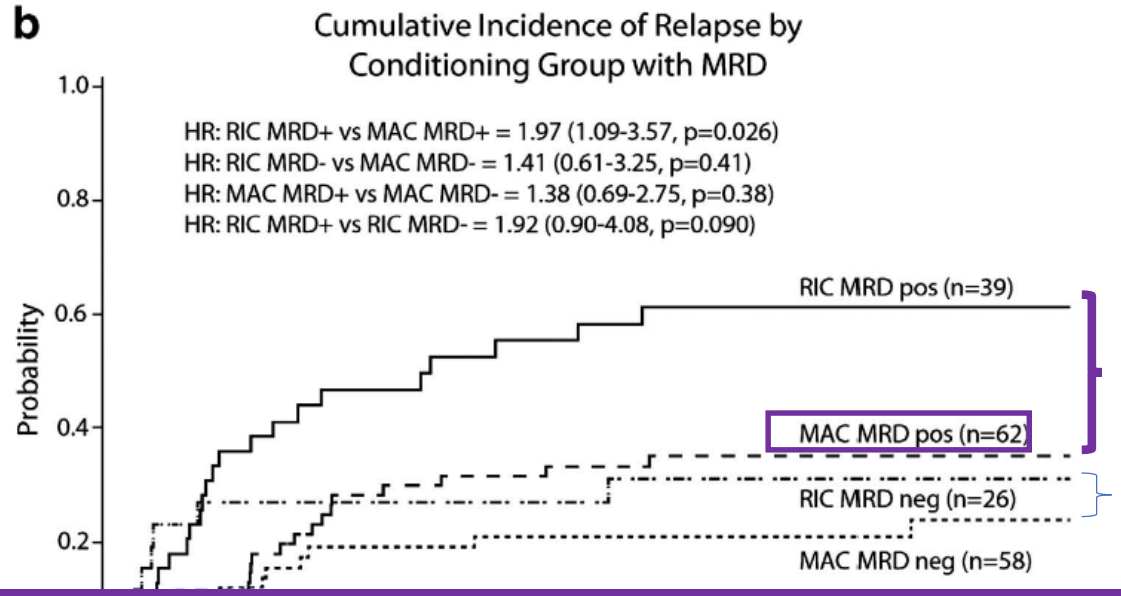
Impact of Conditioning (RIC vs MA) on Outcomes in Ph+ ALL with and without MRD

- **Registry (CIBMTR) analysis** of alloHCT for Ph+ ALL in CR1 using myeloablative and reduced intensity conditioning
- 197 patients with Ph+ in CR1 (MAC 130 patients; RIC 67)

  Matched pair (2:1) analysis
- 70% received TKI pre-transplant
- Depth of remission was analyzed pre-HCT by FISH and/or RT-PCR
- MRD negative 49% (MAC) and 39% (RIC)

Bachanova V, Leukemia, 2014 Mar;28(3):658-65

Depth of remission (MRD) pre-HCT has significant impact on relapse



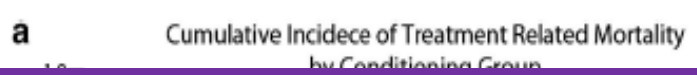
Lowest relapse occurred in patients treated with TKI and MRD neg prior to HCT: 17% (MAC) and 20% (RIC).

Myeloablative alloHCT may overcome persistent minimal residual disease

Bachanova V. et.al; Leukemia, 2014 Mar;28(3):658-65

Myeloablative and RIC yield similar survival for Ph+ ALL. A CIBMTR study

	RIC (n=67)	MAC (130)	P-value
DFS @3y	26%	28%	0.75
OS @3y	39%	35%	0.62



RIC is a valid alternative strategy for Ph+ ALL patients ineligible for MAC and MRDneg status is preferred pre-HCT

Overall Survival ~ 55% (TKI and MRDneg)

Bachanova V et al., Leukemia, 2014 Mar;28(3):658-65

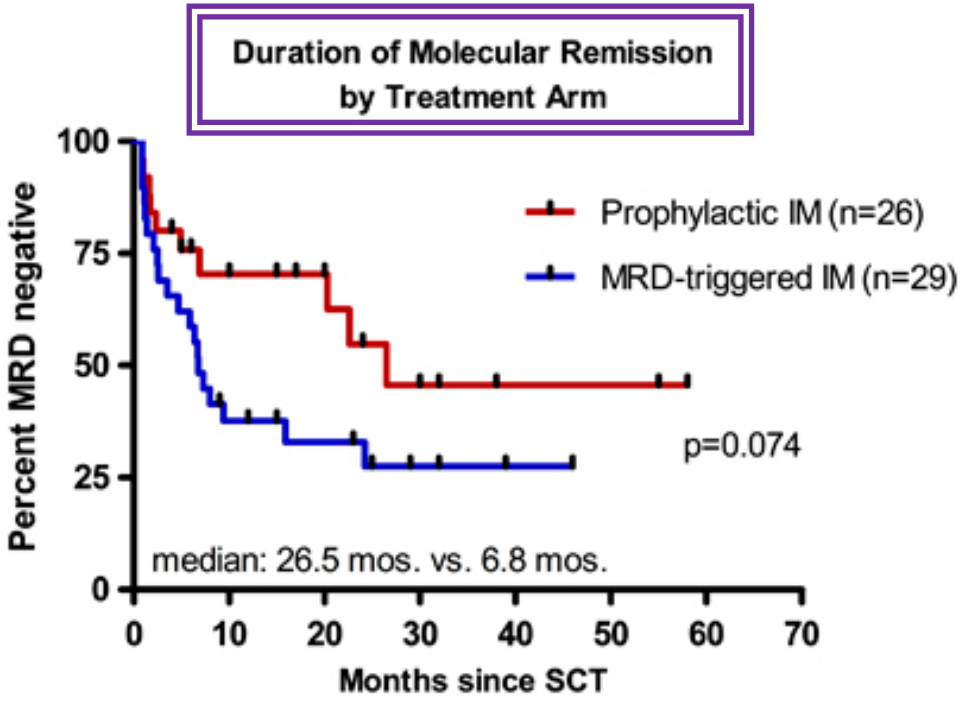
Use of TKI post-allo HCT.
Can we prevent the relapse of Ph+ALL?

- Randomized comparison of prophylactic and MRD-triggered imatinib after alloHCT for Ph+ ALL

  Imatinib 400-600mg/d

  n=54 patients in CR1/CR2

  Duration of administration **207 vs 121 days**
  2/3rds stopped imatinib prematurely



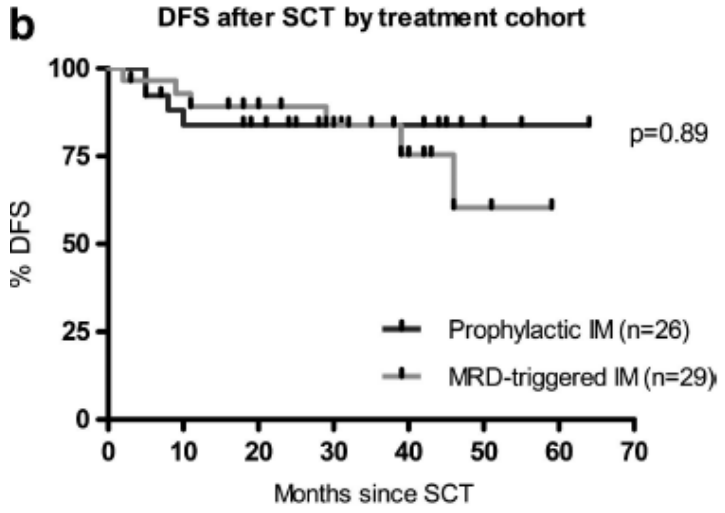
Pfeifer H etl al., Leukemia 2013Leukemia. 2013 Jun;27(6):1254-62

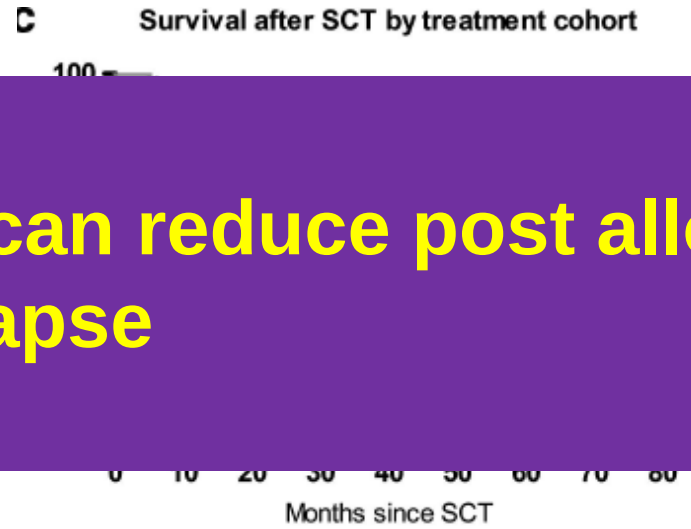
Randomized comparison of prophylactic and MRD-triggered imatinib after alloHCT for Ph+ ALL

DFS (5y) 83 vs 77%
OS (5y) 69 vs 62%

2 caveats:

Early molecular recurrence and/or transcripts >10*4 derived limited benefit from imatinib

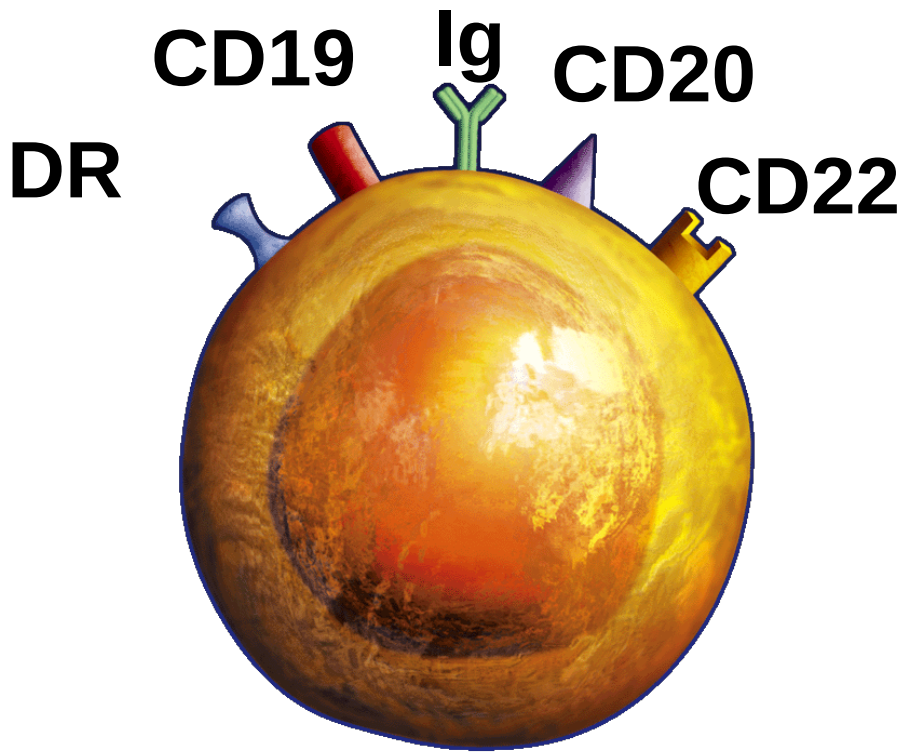




Imatinib maintenance can reduce post alloHCT relapse

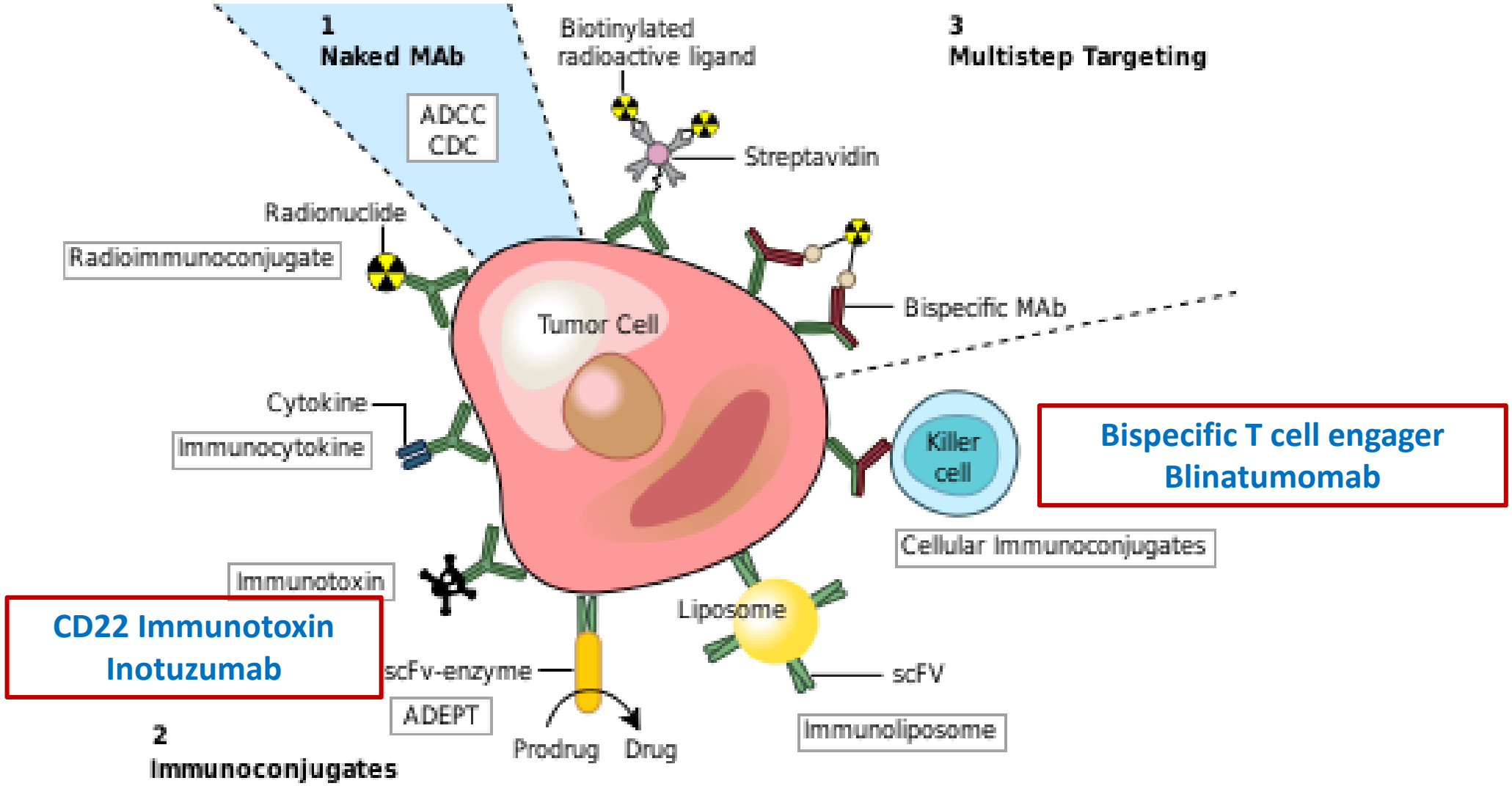
Pfeifer, H; Leukemia. 2013 Jun;27(6):1254-62

Immunotherapy Targets on B-cells



- Surface proteins targeted by immunotherapy
  - Rituximab
  - Ofatumumab
  - Obinotuzumab

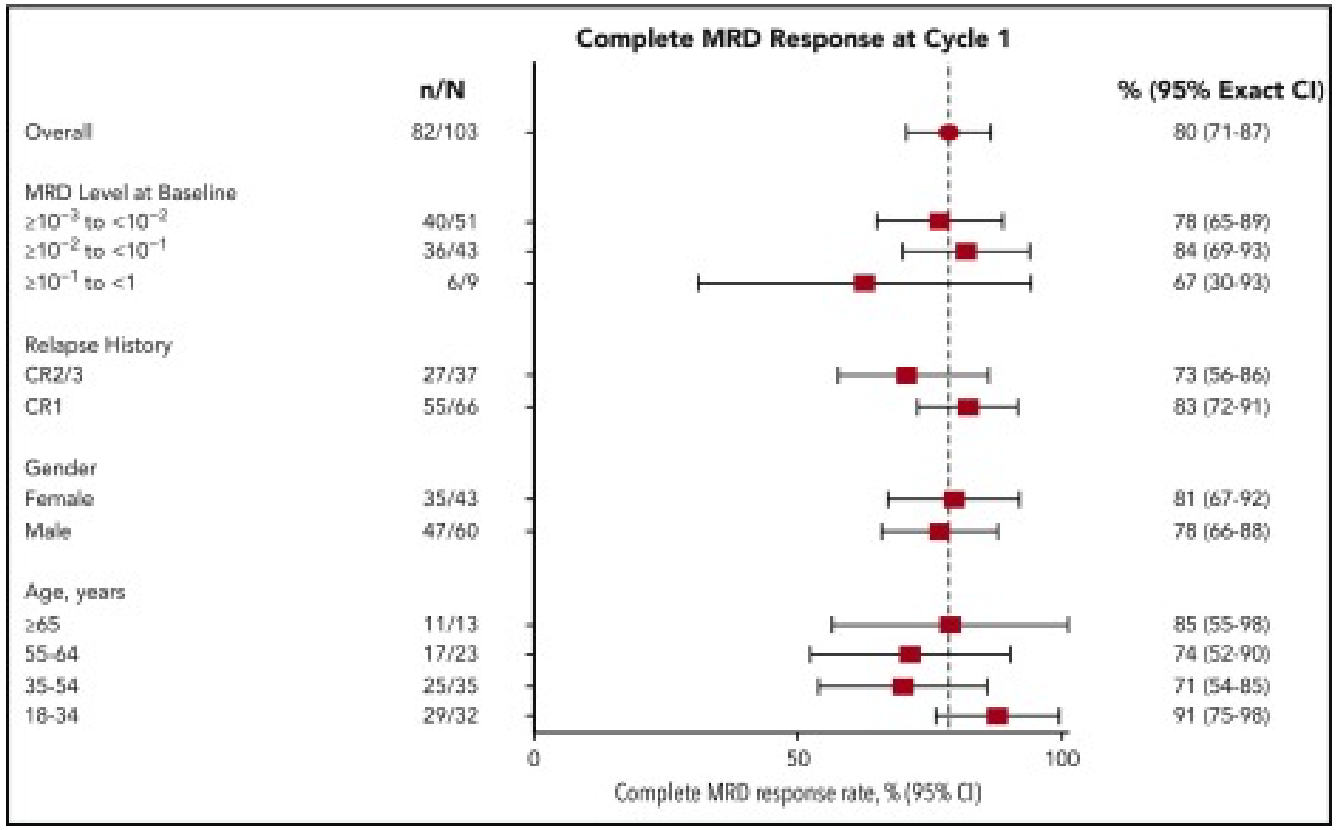
Novel Immune based approach for cancer cell killing



Bispecific T cell engager
Blinatumomab

CD22 Immunotoxin
Inotuzumab

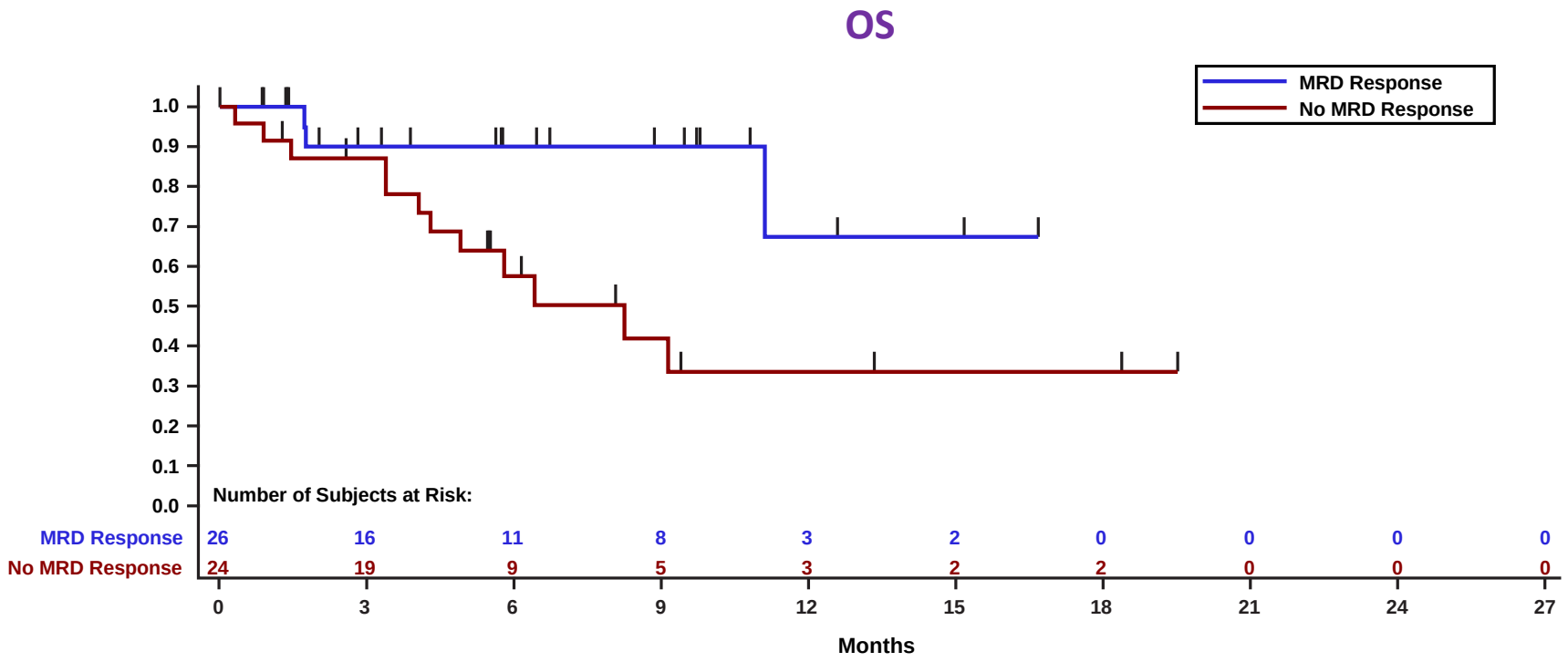
Blinatumomab is effective in ALL with MRD



Gökbuget N, Blood, 2018 Apr 5;131(14)

Blinatumomab induced MRD- State Pre-HCT is Beneficial

CR/CRi	
MRD (n = 26) vs no MRD (n = 24)	
Cox HR (95% CI)	0.23 (0.07, 0.83)
Log-rank p:	0.014
MRD Response	**No MRD Response**
Median time from HSCT to OS (95% CI), Months	
NE (11.1, NE)	8.3 (4.3, NE)



Courtesy of Dr. Jabbour, Tandem Meeting 2018

Active post-HCT Relapse Prevention Clinical Trials

- Blinatumumab post –HCT
- Inotuzumab post-HCT
- Infusion of g/d T cell post HCT
- CAR-T19 for post HCT relapse ?

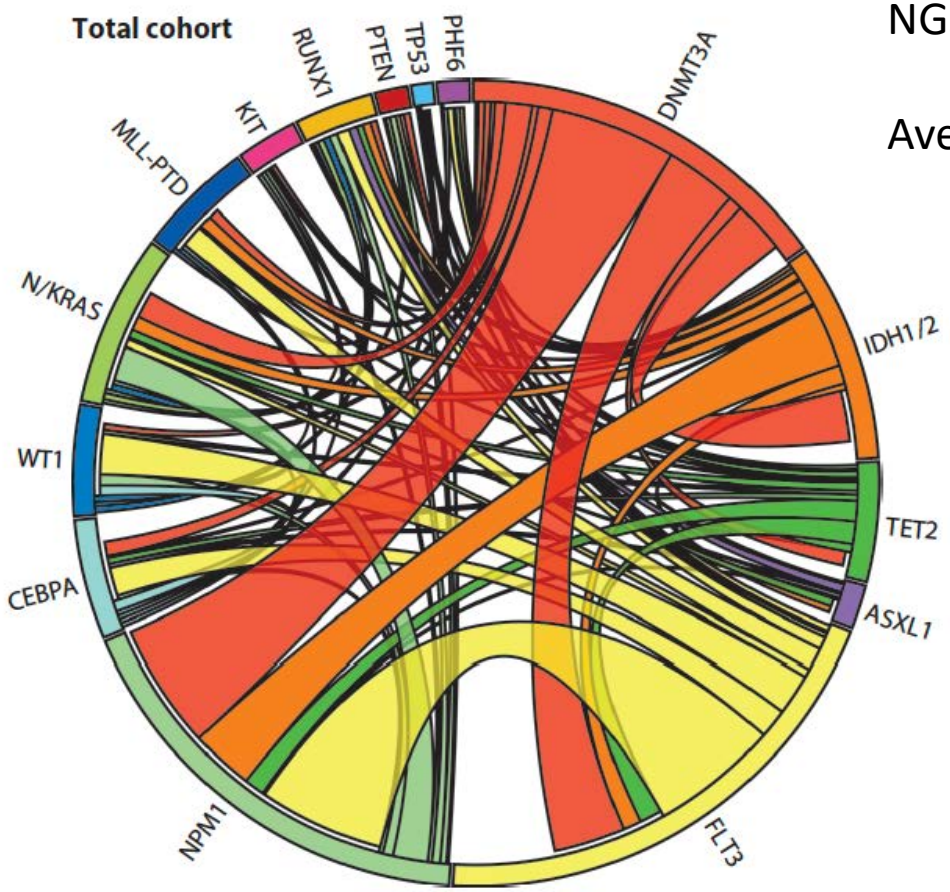
Measurable Residual Disease in AML

- Multiparameter Flow Cytometry
- Multigene Next Generation Sequencing (targeted gene panels)

Somatic mutations associated with acute myeloid leukemia.

Gene	Overall frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2

482 patients with AML



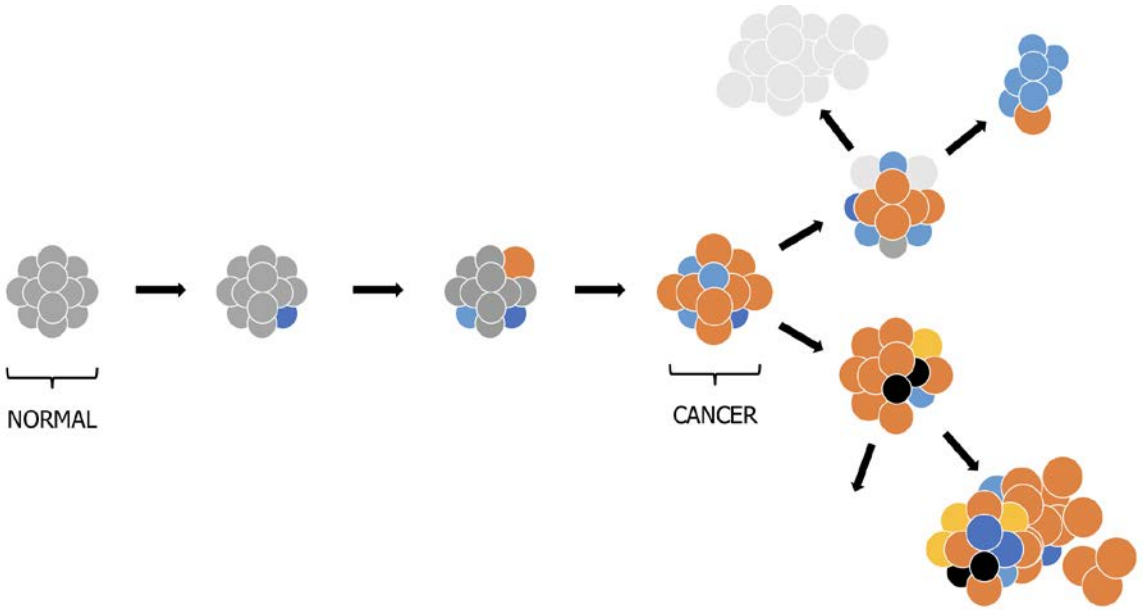
NGS

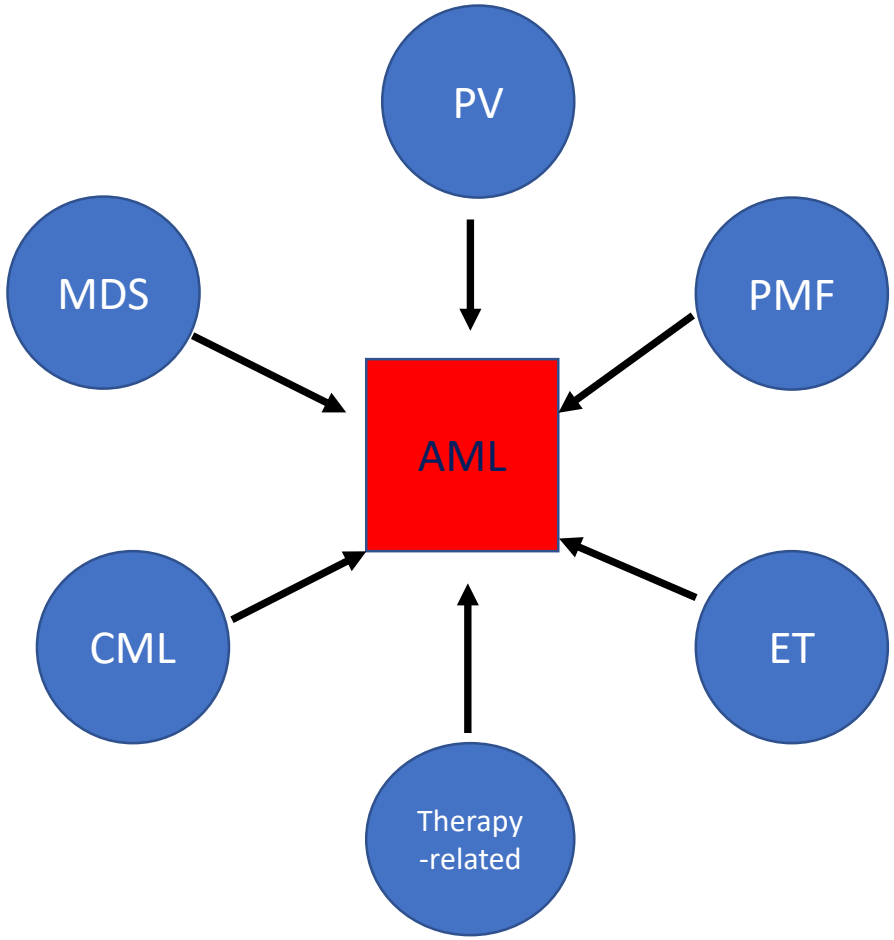
Average 13 mutations in each cell:

- **DNA signaling genes (59%)**
- **Methylation-related genes (44%)**
- **Chromatin-modifying genes (30%)**
- **Myeloid transcription-factor genes (22%)**
- **Transcription-factor fusions (18%)**
- **Tumor suppressors (16%),**
- **Spliceosome-complex genes (14%)**
- **Cohesin-complex genes (13%).**

AML….Complicated

- MANY RELATED CLONES
- DIFFERENT SIZES
- DIFFERENT GROWTH RATES

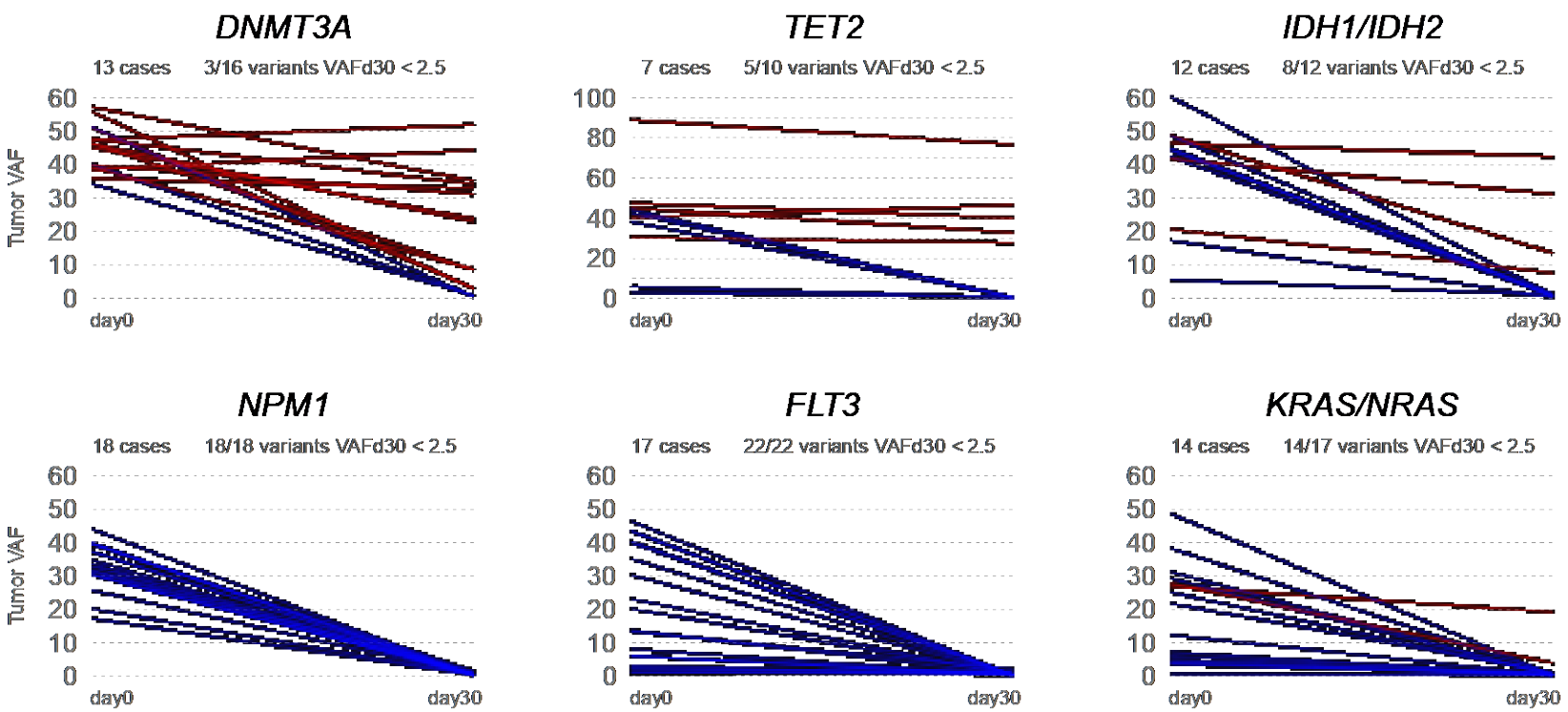




Courtesy of Dr.Radich

Initiating Mutations (*DNMT3A, TET2, IDH1/2* are Less Likely to be Cleared than Cooperating Mutations (*FLT3, NPM1, KRAS/NRAS)*

B

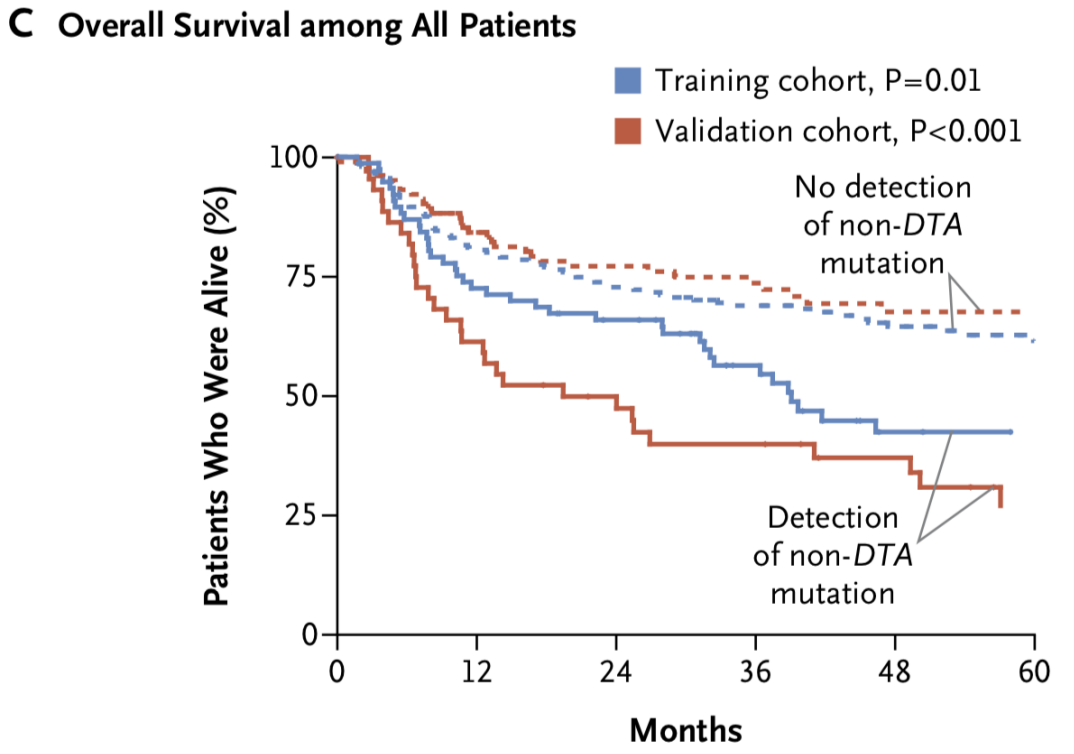


Red=mutations that are not cleared on day 30

Klco et al, JAMA, 2015

…but clinical implications of persistent mutations are very different

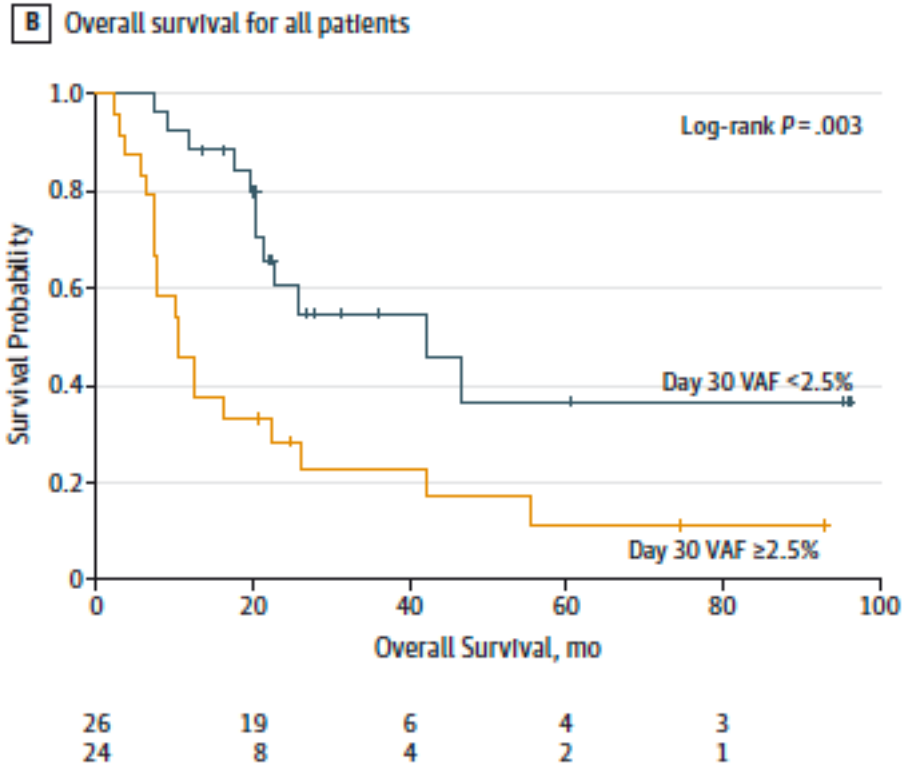
DNMT3A, *TET2*, and *ASXL1 had no effect*



No. at Risk						
Training cohort						
Detection	78	57	49	30	18	16
No detection	205	164	141	118	83	53
Validation cohort						
Detection	44	27	19	16	12	7
No detection	103	84	73	55	39	29

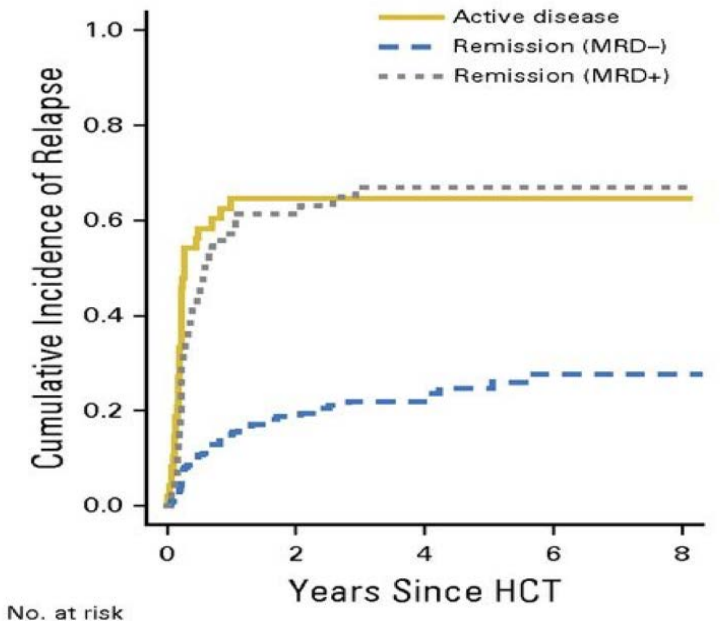
Jongen-Lavrencic NEJM 2018

DNMT3A, *TET2*, and *ASXL1 had effect*

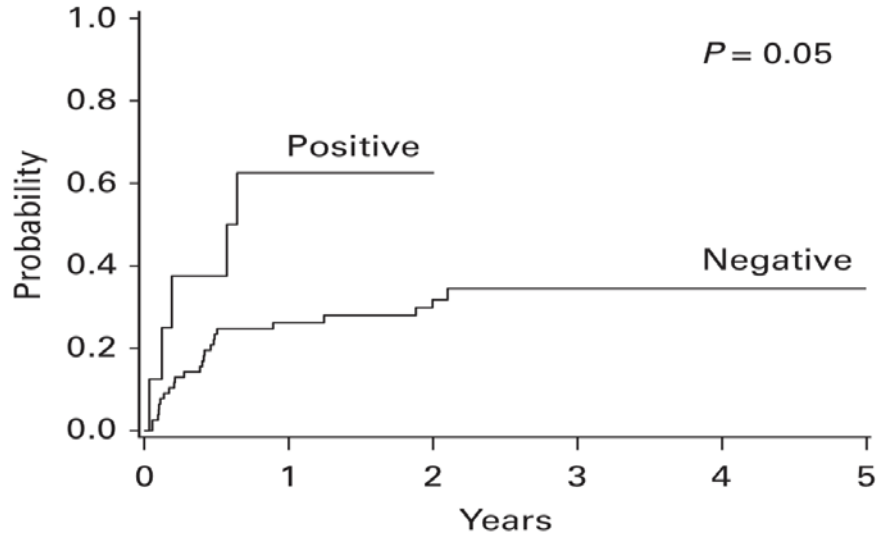


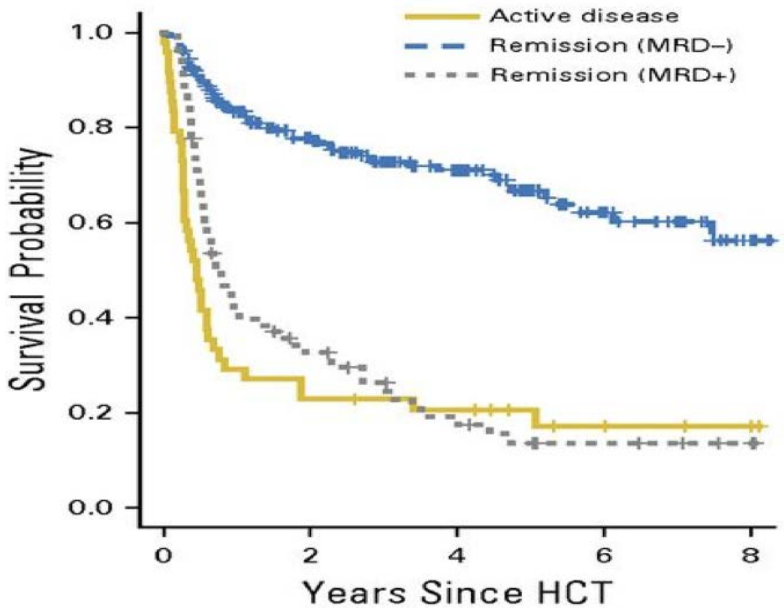
Klco et al, JAMA, 2015

Negative Impact of MRD (FC) Pre-HCT

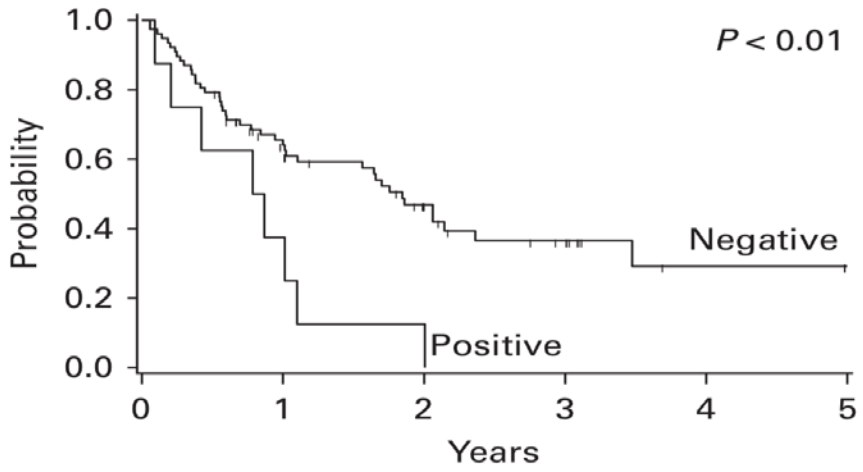


Relapse





OS

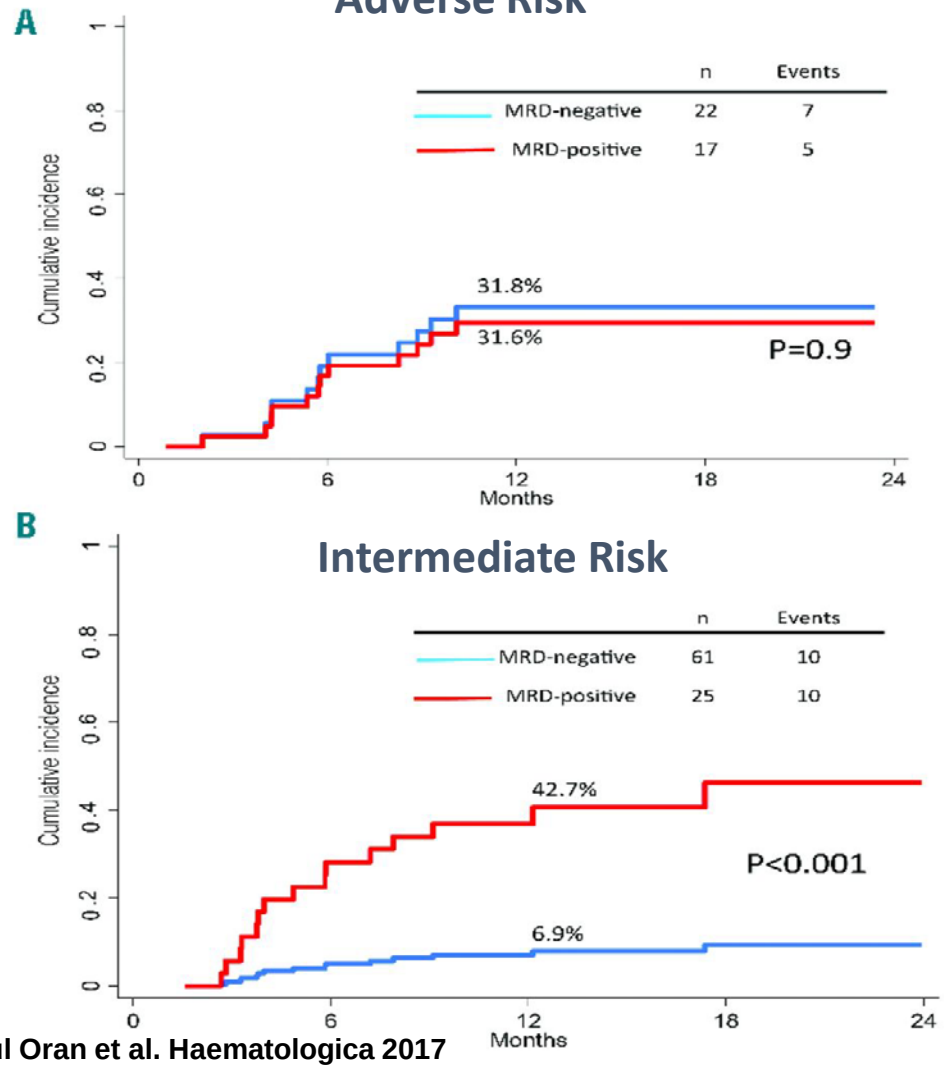


Daisuke Araki et al. JCO 2016

Ustun C et al. BMT 2013

FC MRD ⟷ CYTOGENETIC RISK GROUP

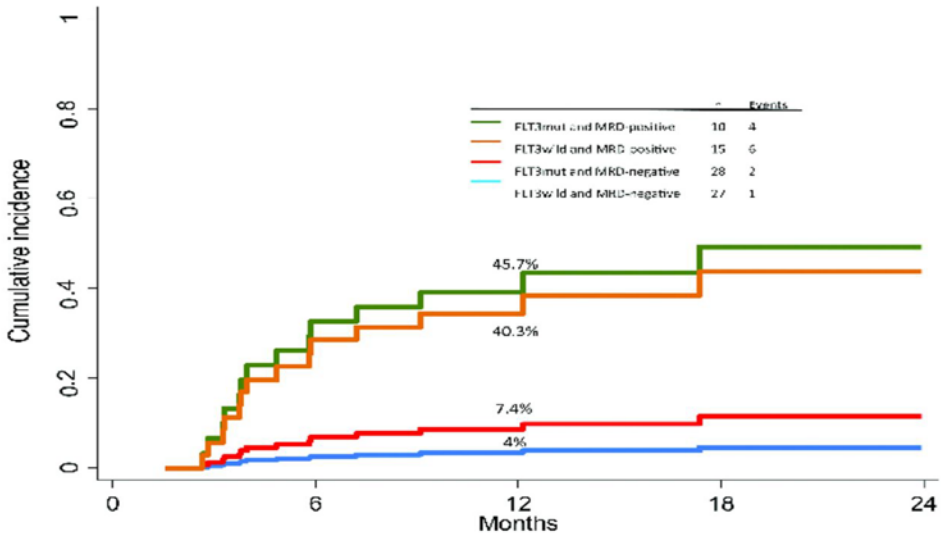
Relapse



Betül Oran et al. Haematologica 2017

FC MRD ⟷ FLT3

Relapse



FLT3+ MRD+
FLT3- MRD+

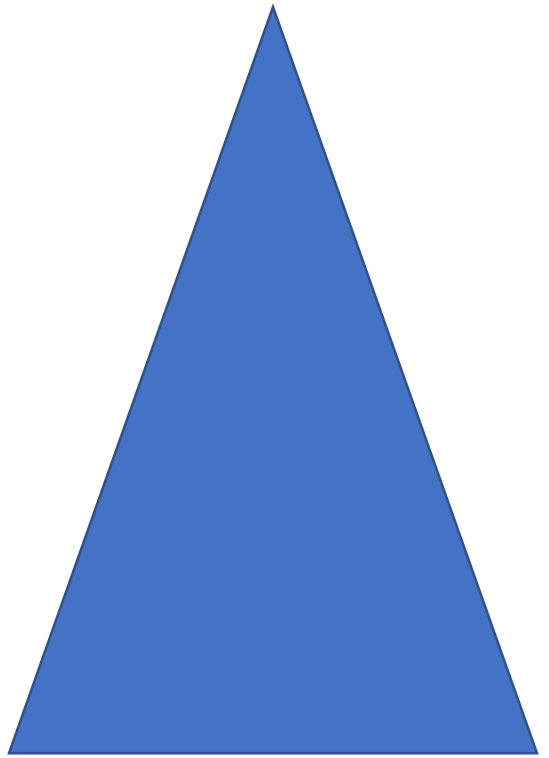
FLT3+ MRD-
FLT3- MRD-

T H M

- The effect of MRD is important in patients with intermediate cytogenetic risk patients
- Alters the prognosis of patients with FLT3+ patients
- But no effect in adverse risk patients

Effect of MRD is important, but not constant in all AML Spectrum

- Complex Cytogenetics
- >CR2
- FLT3/Intermediate Risk
- Favorable Group



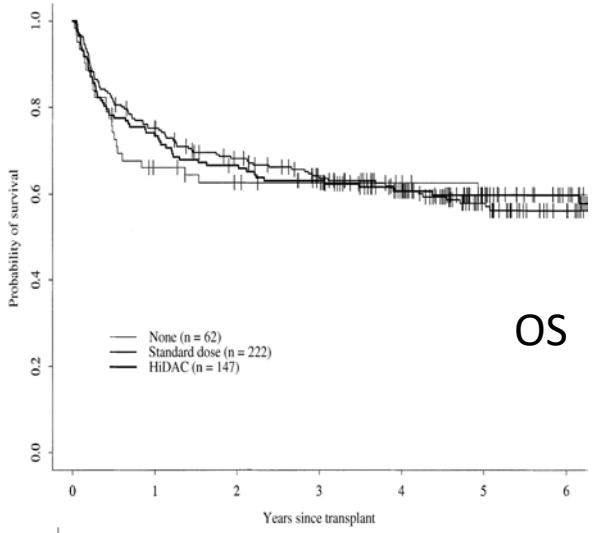
If MRD+ before HCT in AML, what can we do about it ?

- Administer more chemotherapy (consolidations)

- Prevention of relapse after HCT

No Impact of Additional Postremission therapy on Sibling alloHCT for AML in CR1

Myeloablative Conditioning



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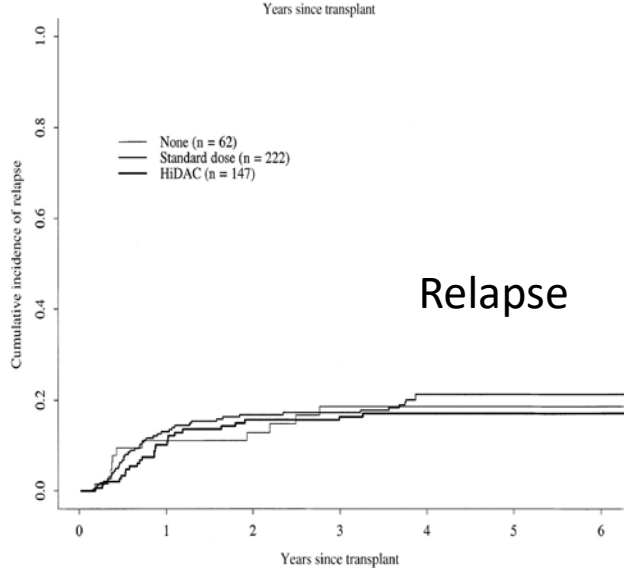
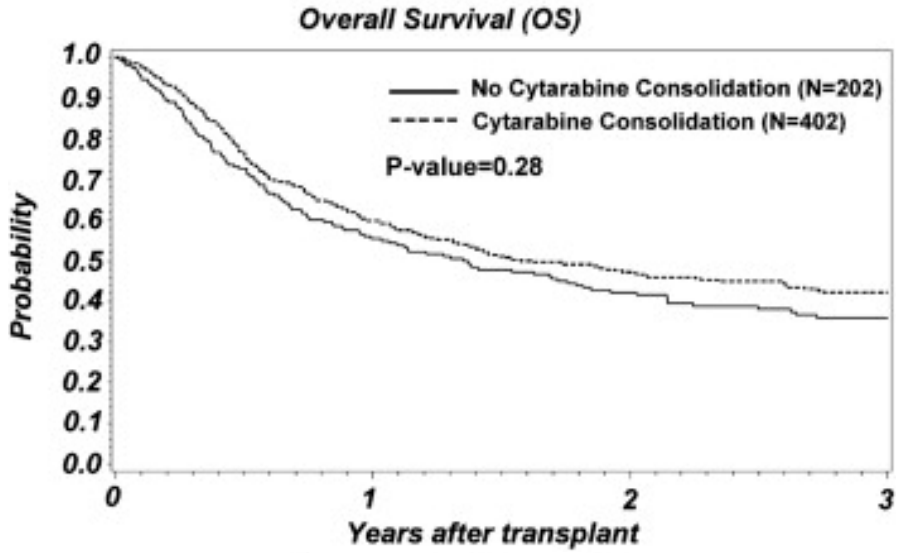


Relapse

RIC



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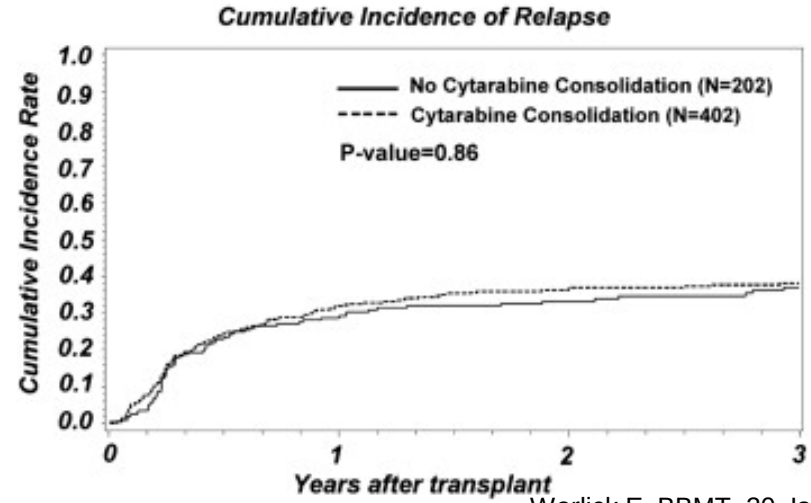


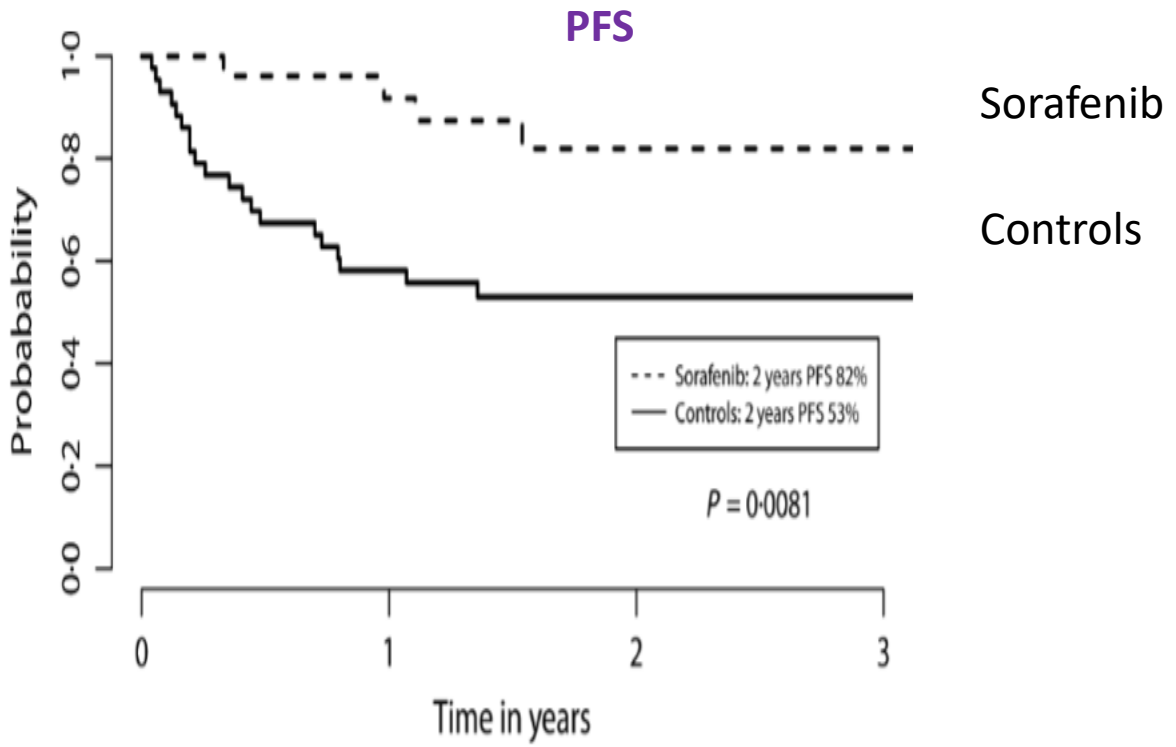
Relapse

Tallman M S et al. Blood 2000;96:1254-1258

Warlick E, BBMT 20, Issue 2, 2014, 202 - 208

Posttransplant Sorafenib to prevent relapse in high risk patients

Sorafenib maintenance in FLT3 + AML Patients

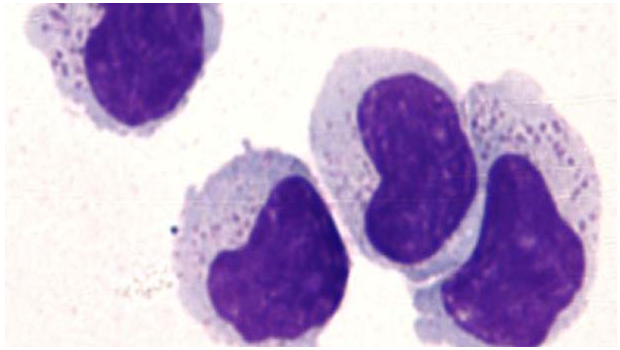


Brunner et al Haematologica 2016

Other post HCT relapse prevention strategies in AML

- FLt3 Inhibitors
- Demethylating agents Azacytidine and Decitabine
- Tyrosine kinase Inhibitors (IDH2 etc)
- Immune-based approaches

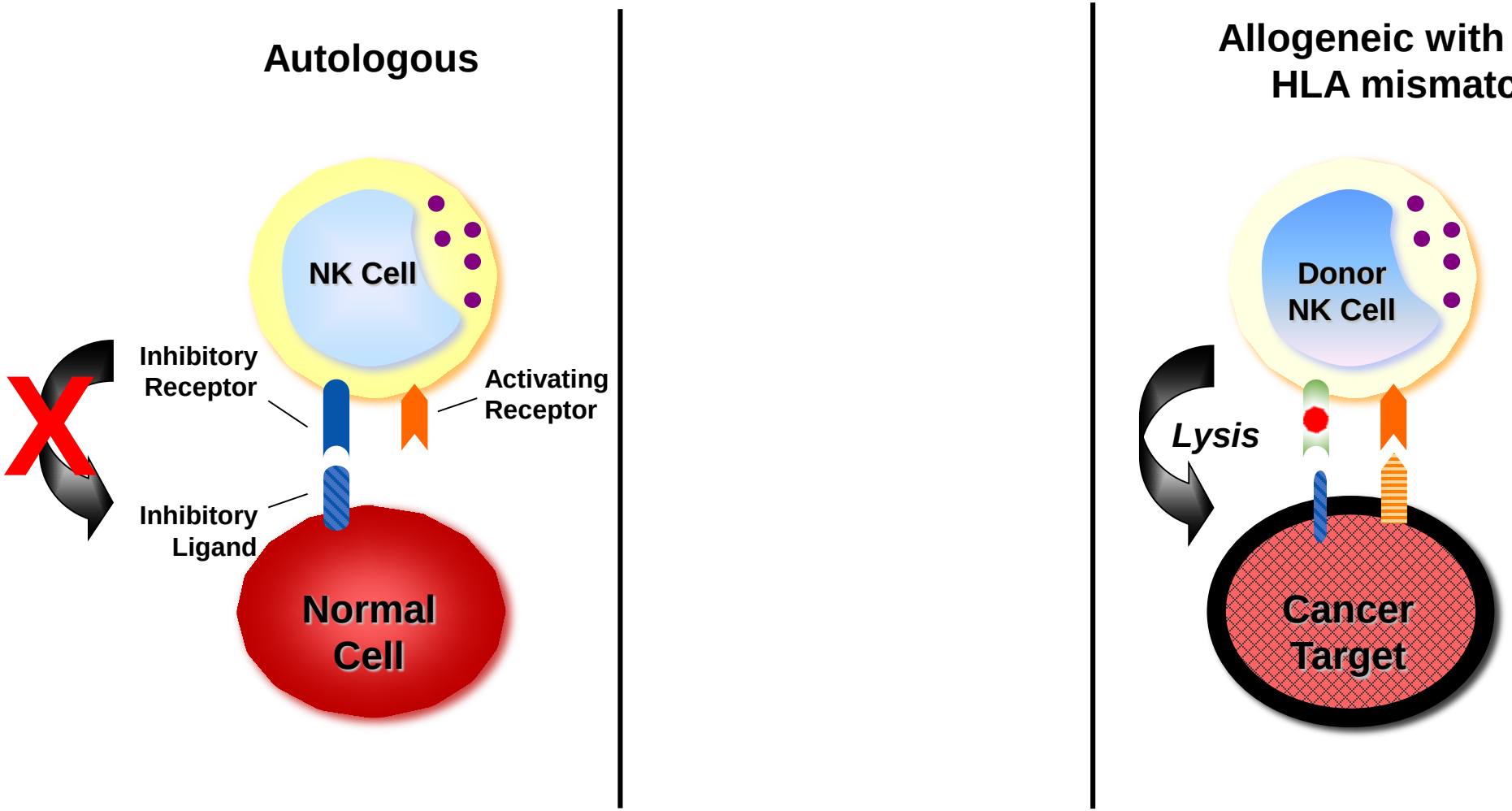
Harnessing Natural Killer Cells for Cancer Therapy in AML



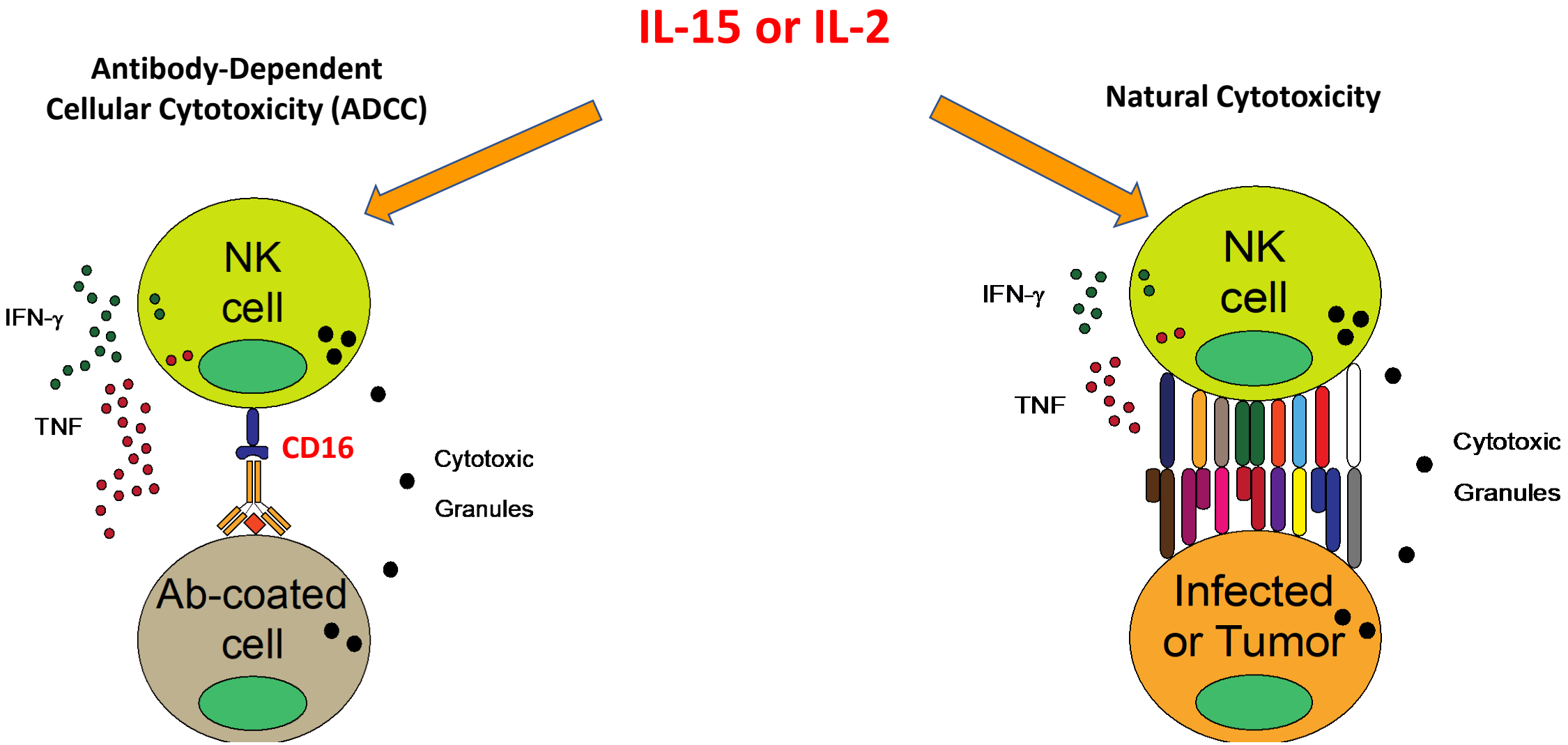
Natural killer (NK) cells play a critical role in infection control, tumor surveillance and cancer cell killing

- Strategies to enhance donor NK cell function
- Bi and Tri-specific AML targeting NK cell engagers (BiKE, TriKE)

Donor derived NK Cells Are Alloreactive



What Turns NK Cells On ?



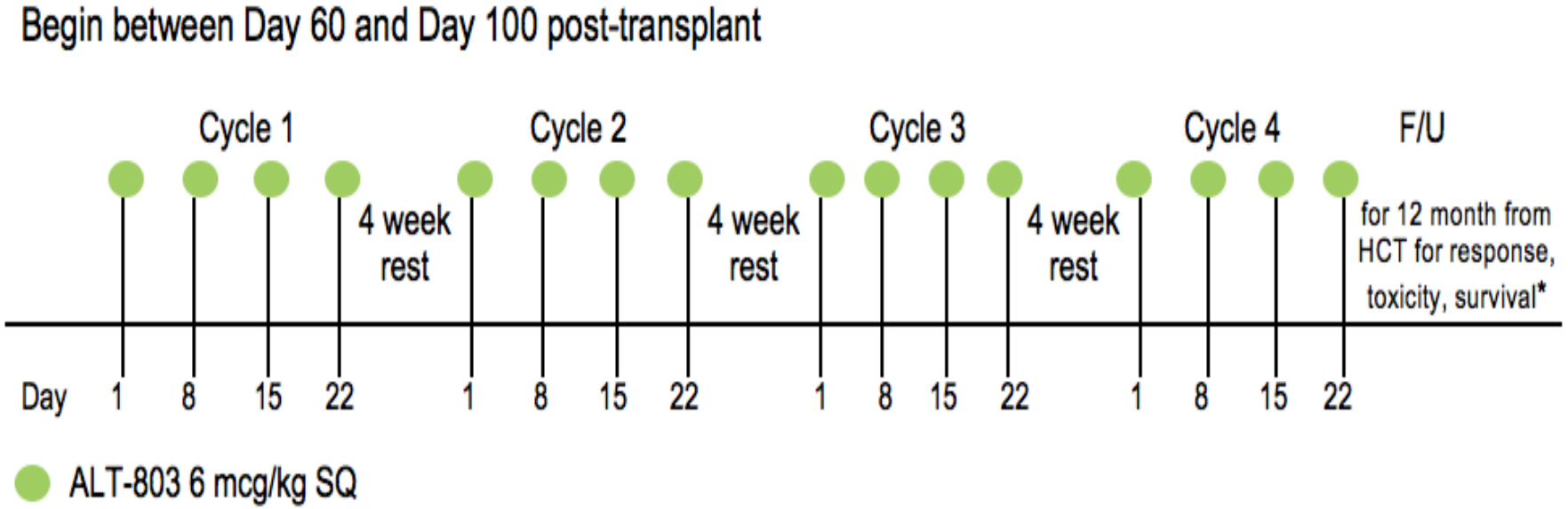
IL-15 Super Agonist ALT-803 to Prevent Relapse Of High Risk Acute Myelogenous Leukemia and Myelodysplastic syndrome Following Allogeneic Stem Cell Transplantation

University of Minnesota

Participating Affiliate Institutions :

- **Emory University**
- **Ohio State University**
- **University of Washington, Seattle**
- **Washington University at St Louis**

Study Schema



A multicenter, open label Phase II Study of 6 mcg/kg sq once a week begin ALT-803 between **Day 60 and Day 100** post-transplant

Primary Objective:

- CI of Relapse rate at 1 year after alloHCT

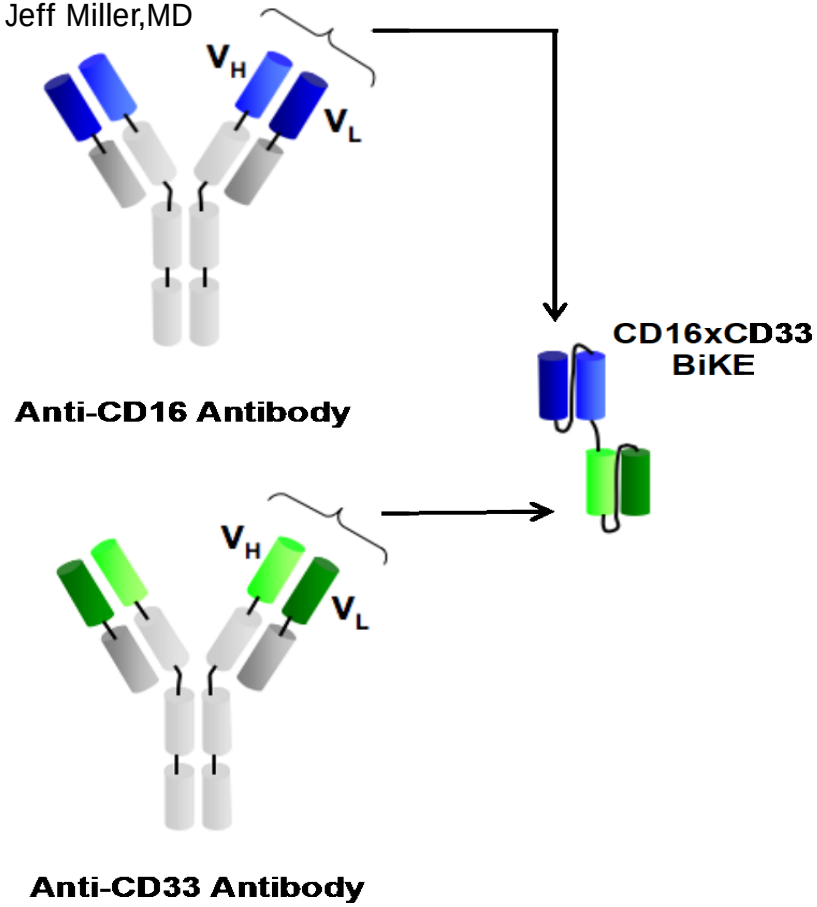
Eligibility:

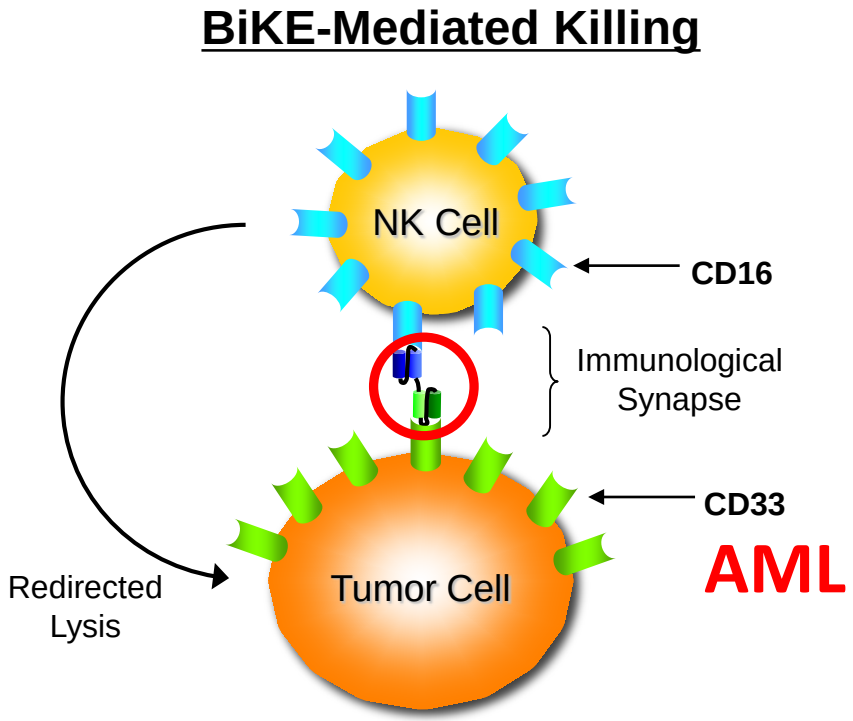
Patients with high risk AML or with high risk MDS

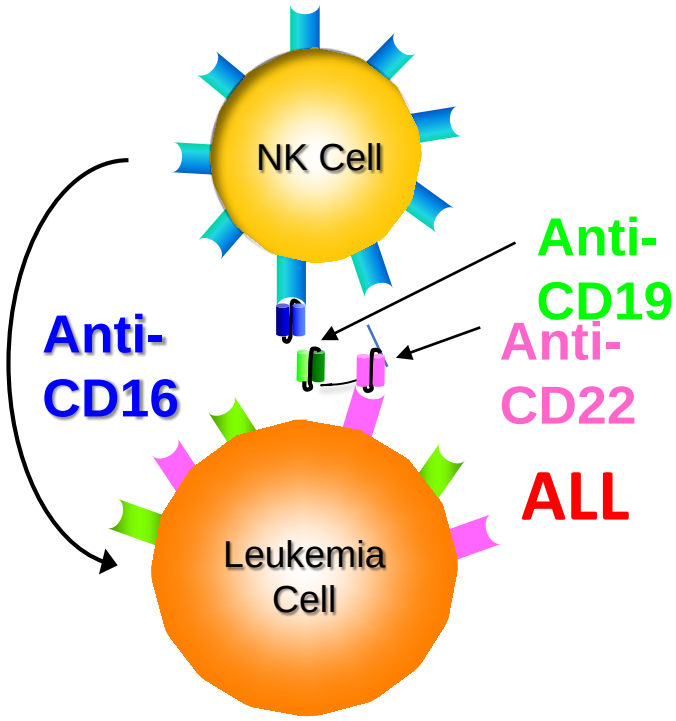
FUTURE CLASS OF IMMUNOTHERAPY:
Bi- Tri-specific NK Cell Engagers

Prof. Jeff Miller,MD

Prof. Dan Vallera, PhD





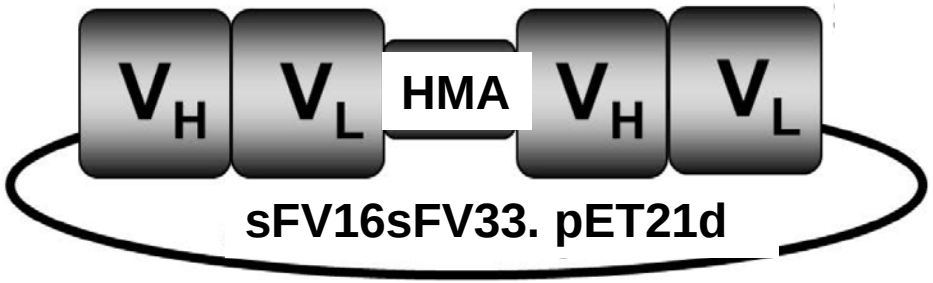


BiKEs

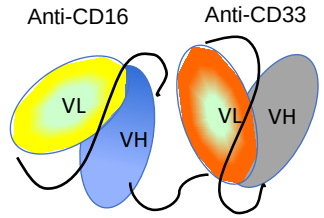
TriKEs

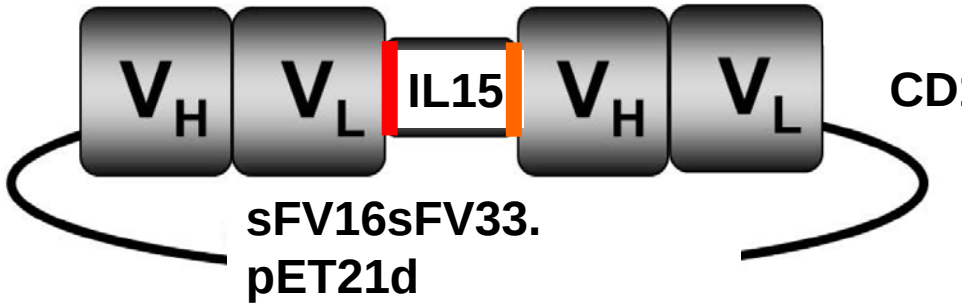
Rationale For Trike

- T-CAR are successful because they are antigen specific and have a 41BB-L or CD28 intracellular domain to induce proliferation

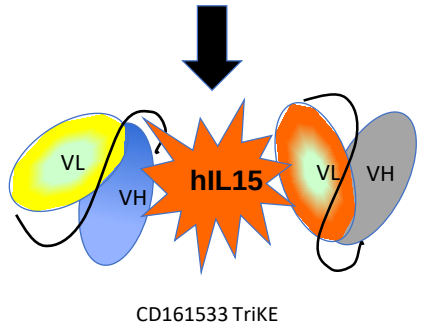


CD1633 BiKE

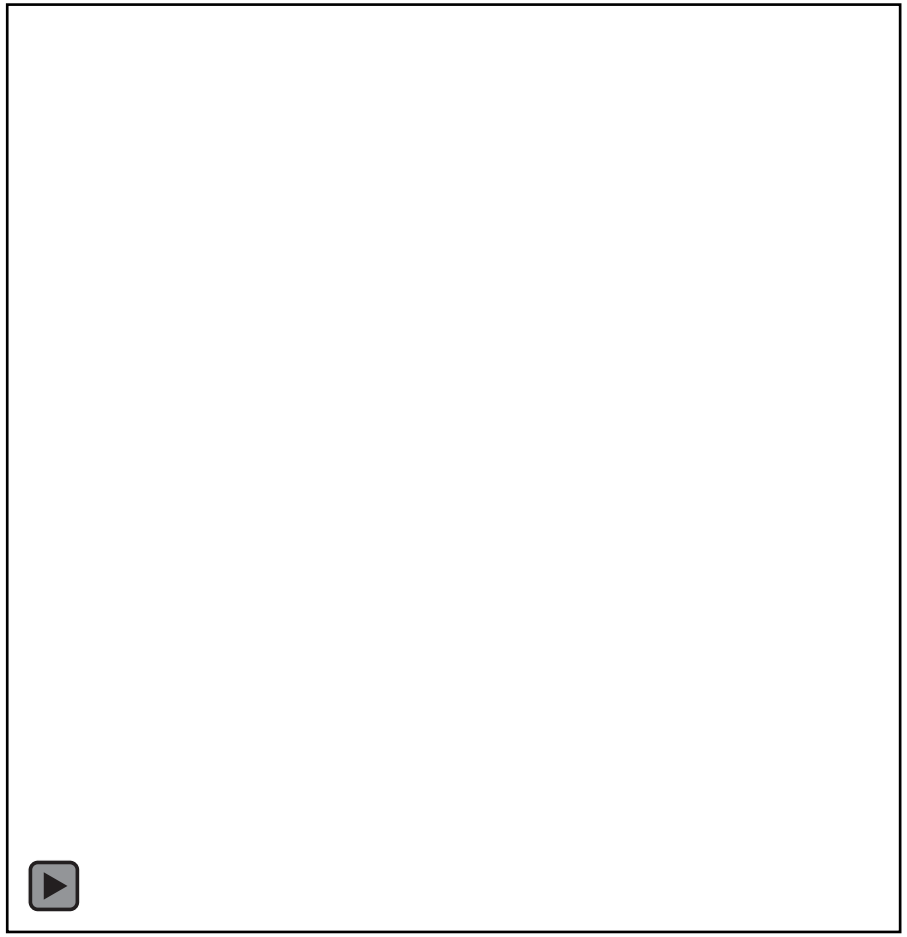




CD161533 TriKE



161533 TriKE enhance serial killing of AML Blasts



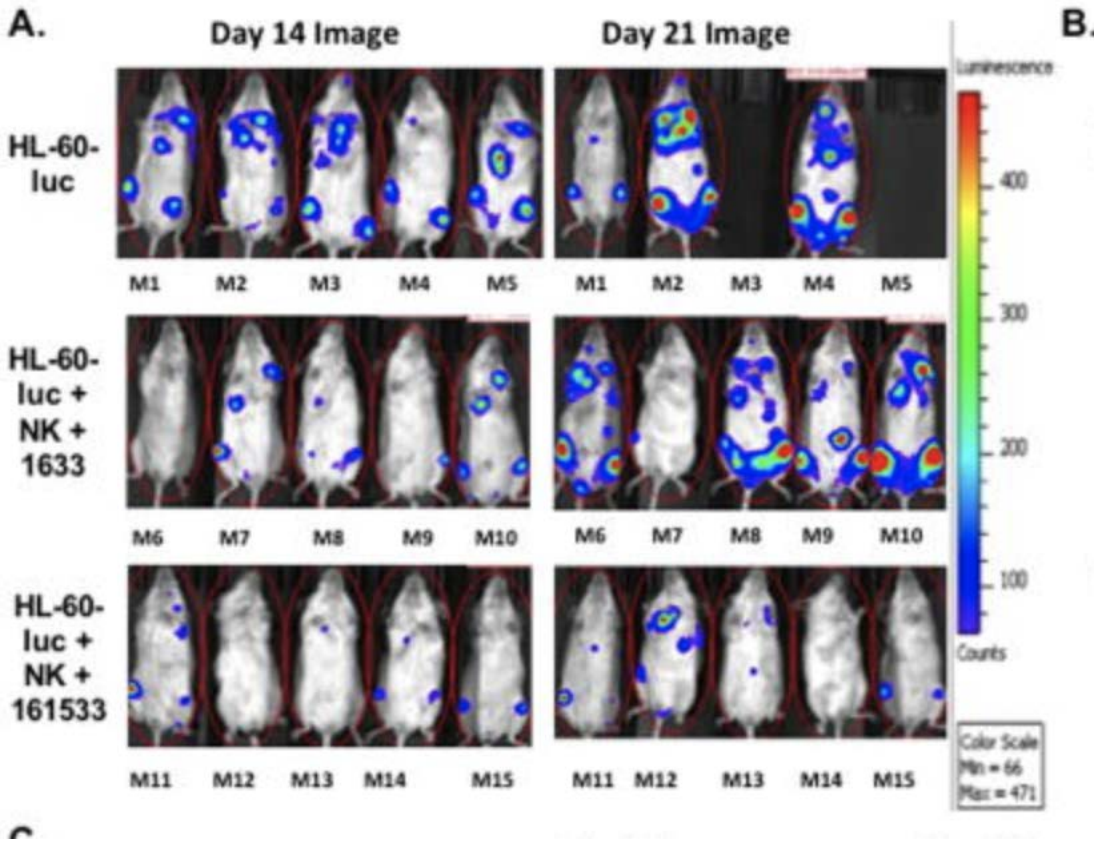
Legend:

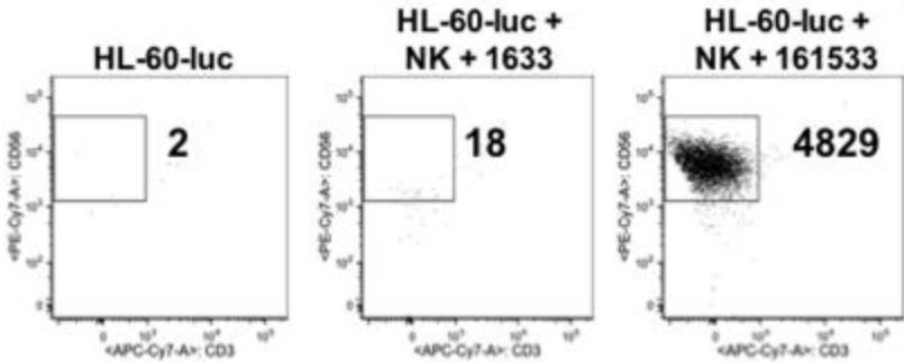
Blue =NK cell
Green =Live AML
Red =Dead AML

AML is the HL60 Target

Bjorn Onfelt
Microbiology, Tumor and Cell Biology, Karolinska Institutet

IL15-CD33 Targeting TriKE: Preclinical Data and Phase 1 Trial





Phase 1 Study of CD16/IL-15/CD33 Tri-Specific Killer Engagers (TriKEs) for High Risk Heme Malignancies is enrolling patients

Questions?

Thank you!

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