
58th ASH 2016
SAN DIEGO CA

The best of ASH

Immunotherapy

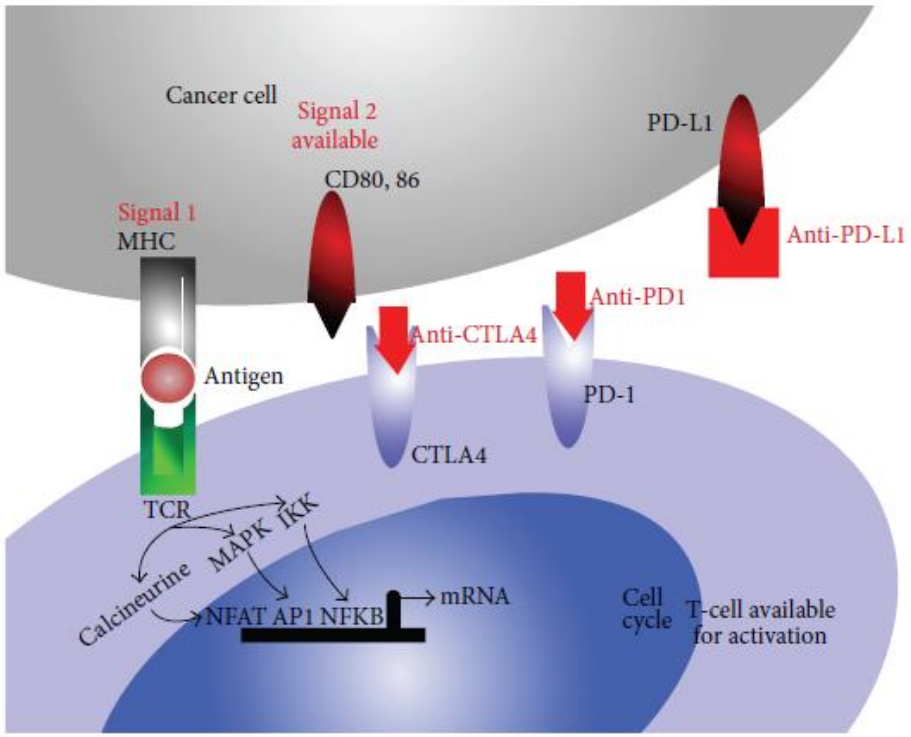
- PD-1/PD-L1 inhibition
- CART cells

CRISPR Cas technology

Selected oral abstracts

- Presidential session
- Late breaking abstracts
- "Best of" session

Checkpoint inhibition

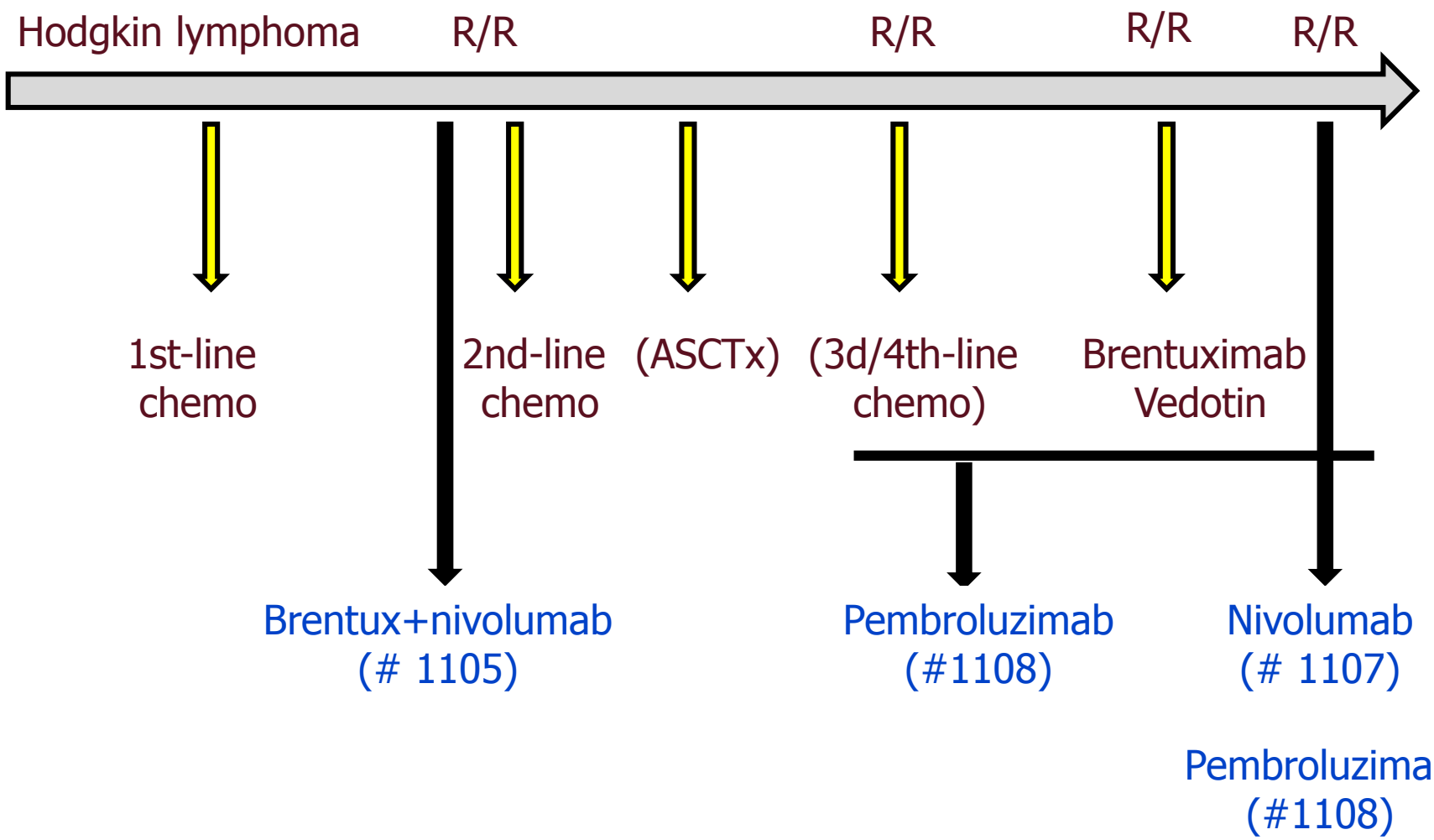


Ipilimumab (anti-CTLA4)
Tremelimomab (anti-CTLA4)
Pidilizumab (anti-PD1)
Nivolumab (anti-PD1)
Pembroluzimab (anti-PD1)
Atezolimumab (anti-PD-L1)
Durvalumab (anti-PD-L1)
Avelumab (anti-PD-L1)

Combinations with other monoclonal antibodies under investigation

- UTOMILUMAB, URELUMAB: anti-CD137 → stimulation of T cell cytotoxicity, ADCC
- Cp870-893, DACETUZUMAB, LUCATUMUMAB: anti-CD40 → T cell activation
- MOGAMULIZUMAB: anti-CCR4 (developed for ATL) → Treg depletion

Checkpoint inhibition in Hodgkin lymphoma

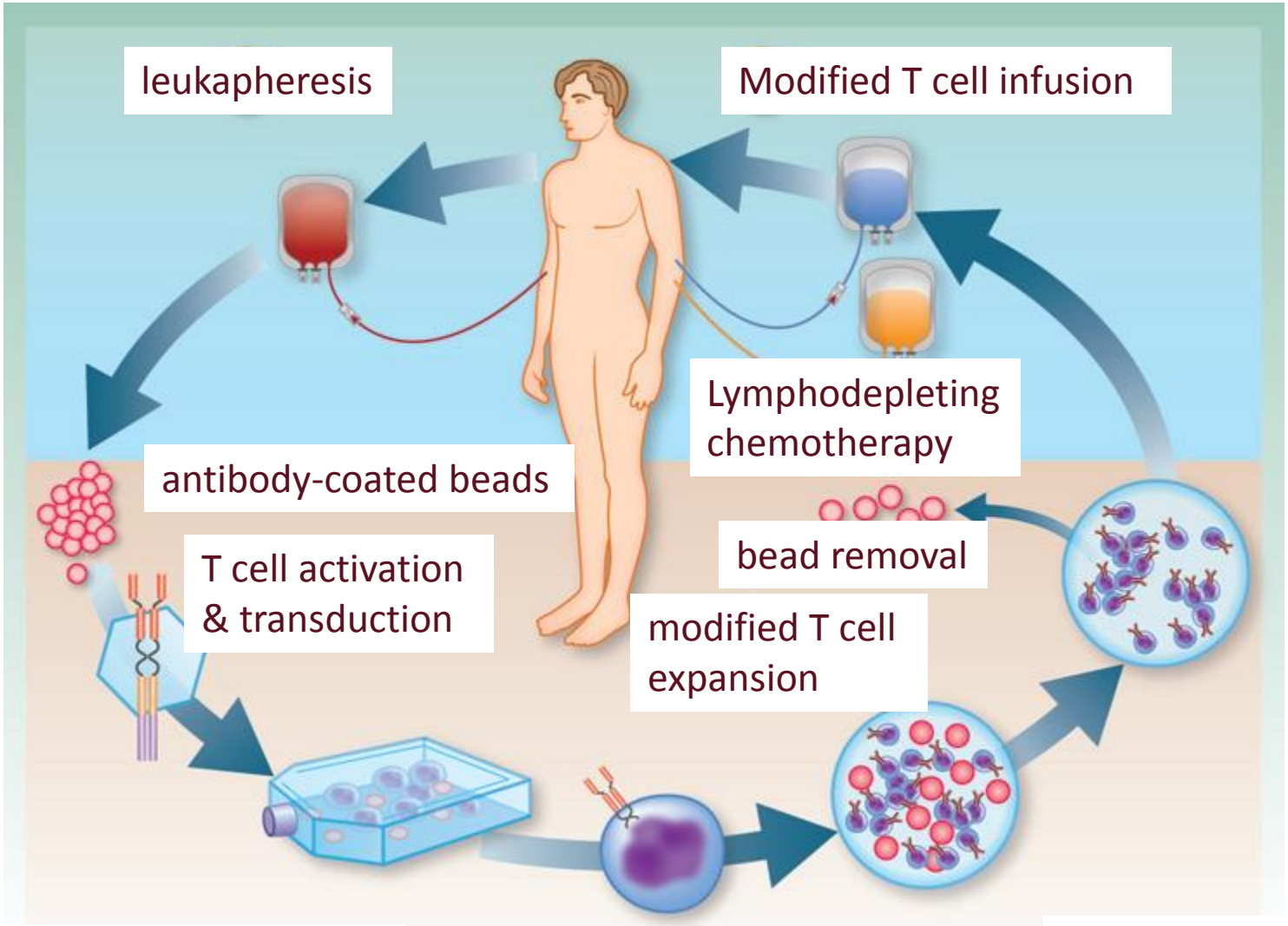


Checkpoint inhibitors in Hodgkin lymphoma

Patients	Regimen	Efficacy	Toxicity	Abstr
N=80 PD after Brentux after failed autoTx	NIVO (3 mg/kg) q2wks (Checkmate 205B)	**CR 8% PR 60%** Median duration = 13 mths	Fatigue (28%), infusion reaction (20%), arthralgia (15%) rash (15%); few SAE.	#1110
N=31 PD after Brentux after failed autoTx	PEMBRO (10mg/kg/2wks)	**CR 16% PR 49%** 70% of responses ctd > 6 mths	Hypothyroidism/ thyroiditis (20%) GIT (15%) Pneumonitis (10%)	#1108
N=210 R/R 71% prior Brentux	PEMBRO fixed dose 200 mg/2wks (Keynote-087)	**ORR 60%-70%** 80% of responses durable	Pyrexia (11%), hypothyroidism (10.5%), diarrhea (7%), fatigue (7%), headache (6%), rash (6%), nausea (6%)	#1107
N=25 R/R after standard first line	Brentux (1.8 mg/kg) + NIVO (3 mg/kg) q3wks (fase 1/2)	6/6 ORR	13% grade 3 AE, 1 pt SAE (fatigue, nausea, rash, dyspnea, myalgia, pruritus)	#1105

CART cell therapy

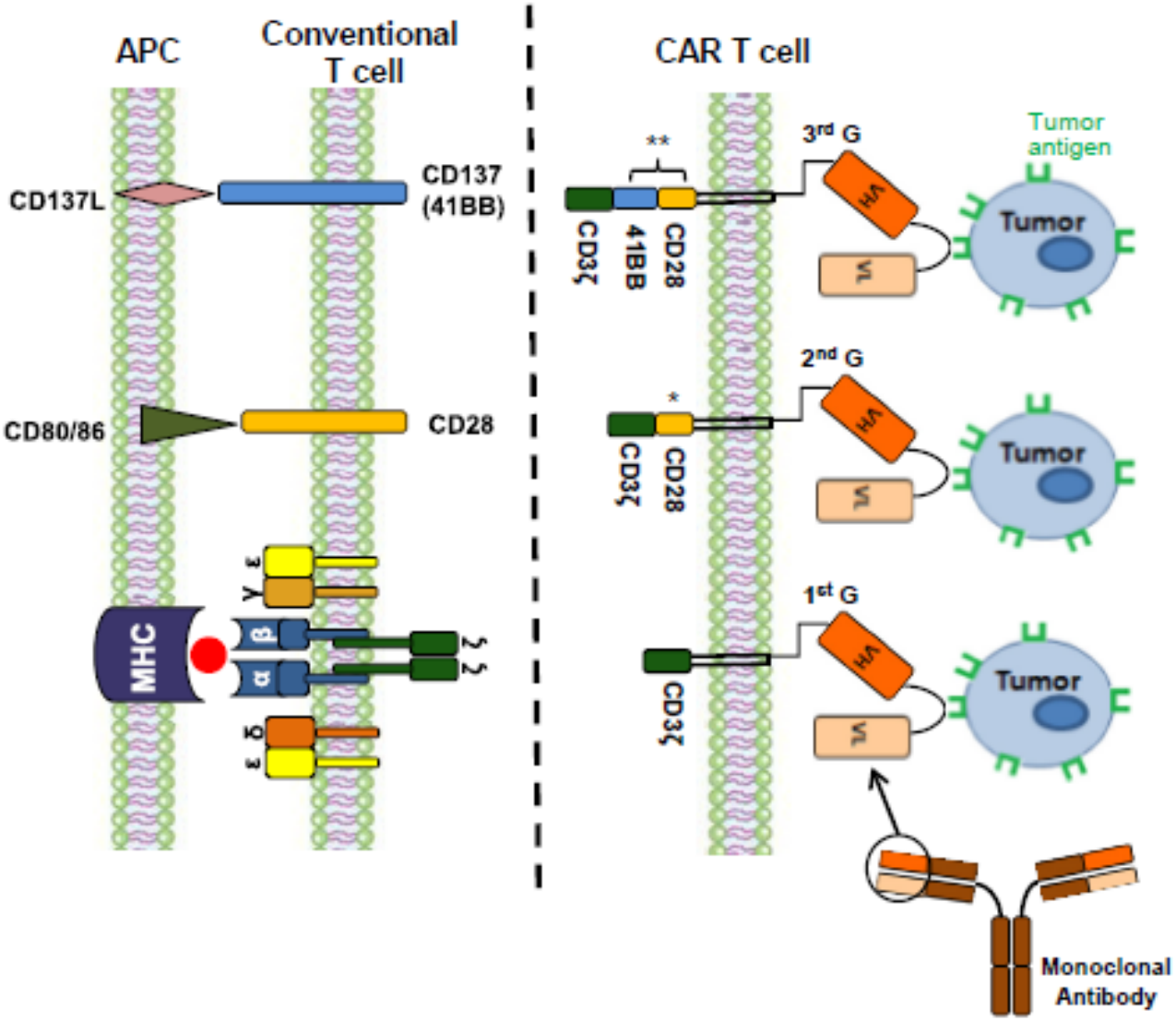
Lymphodepletion: e.g. fludarabine+cyclophosphamide



Beads: e.g. anti-CD3/CD28
Transduction: lentiviral vector

Preparation: 6-20 days

CART cells



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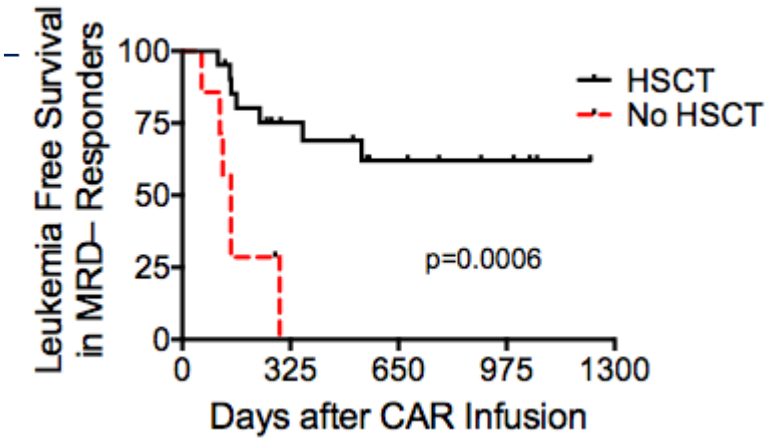
CART cells in R/R ALL

Patients	Regimen	Efficacy	Toxicity	Abstract
N=30 Prior alloSCT (18) or CART (11); CNS (6)	Humanized anti-CD19 (CTL119)	**87% CR; 100% CR** if no prior CART	Severe CRS 4; encephalopathy 5; seizures 4	#217
N=53	Lymphodepletion Disease-burden adapted	**61% CR** (90% MRD-); Median LFS responders= 18 mths Most had alloSCTafter CART	Severe CRS 13.5%; 10% severe neurotoxicity	#218



CART cells in R/R ALL

Patients	Regimen	Efficacy	Toxicity	Abstract
N=43	CD4/CD8 selected CART	**93% CR** (MRDneg) 51% LFS at 12 mths	Severe CRS 23%; Severe CNS 21%	#219
N=34 **Multicenter** registration trial CTL019*	Lymphodepletion disease-burden adapted	**83% CR** (MRD-);	Severe CRS 44%; 21% severe neurotoxicity	#221
N=125 **Multicenter** China	4th generation: CD19/CD28/ CD137/CD27/ CD3zeta-iCasp9 (=4SCAR19)	**CR91%** (<50%BMBL) **CR76%** (>50%BMBL)	20% severe CRS in high tumor burden pts	#587

*Novartis

CART cells in R/R ALL: summary

- Very high response rates + high quality reponses in advanced ALL (# 217, #218, #219, #221, #587)
- Most patients relapse due to
  - Emergence of CD19 neg ALL
  - Exhaustion of CART
    - Anti-mouse reactivity
    - Related to CD19 antigen burden in BM at time of lymphodepletion
- Kinetics of CART after infusion important for efficacy
  - Rapid initial expansion and slower decay (#220)
- Best results if used as bridge to alloTx (#219)
- Severe CRS and CNS toxicities are observed 20-40%
- Technical advances
  - CD4/CD8 selected CART
  - Fully humanized CART
  - Anti-CD22 (# 650)
  - IL-18 secreting CART (#816)

CART cells in ibrutinib refractory CLL

- Anti-CD19 CART cells from CD4+ and CB8+ T cell subsets
  - N = 18 pts very advanced B-CLL (3-9 lines, 3 alloTx)
  - 11 were ibrutinib refractory, 3 inbrutinib intolerant, 4 venetoclax intolerant
  - 12 complex karyotype, 2 CNS disease
- Lymphodepletion with cyclophosphamide + fludarabine
- Most received 2x 10 exp6 CART cells
  - 4 received second cycle at higher cell doses
- ORR = 76% (8 PR and 5 CR)
  - Higher peak percentages of CD8+ CART cells observed in CR pts
  - Less response in nodal sites
  - CRs were stable at 8+ mths
- 4 grade 3/4 CRS and 4 grade 3 neurotoxicity

ZUMA-1 trial: CART cells in refractory DLBCL

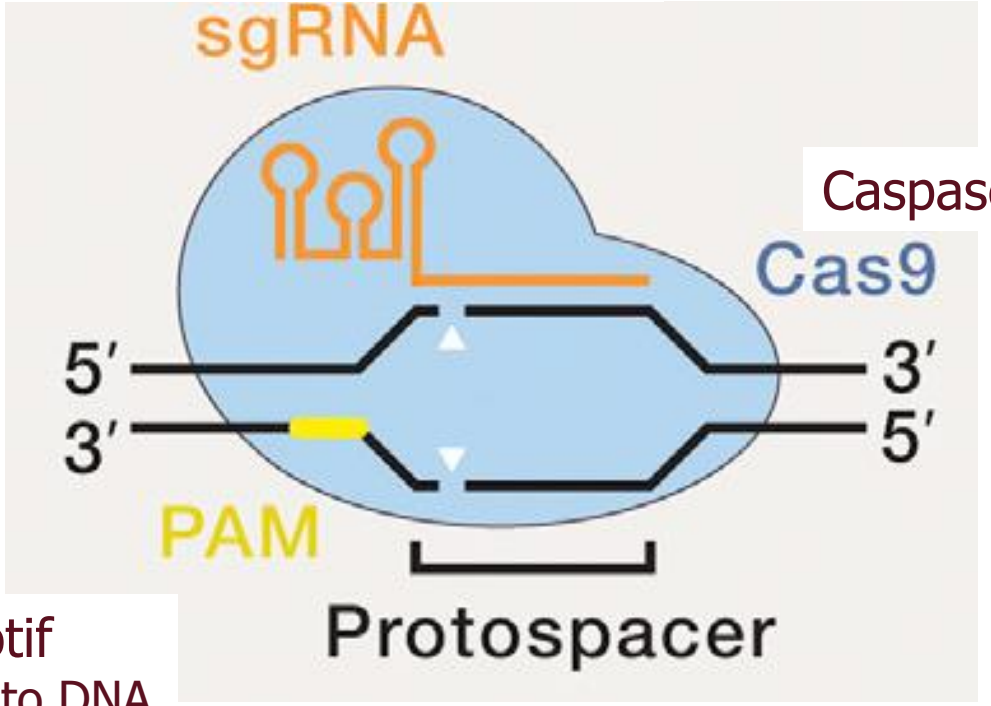
- Multicenter (n = 22) trial
- 2x 10exp6 anti-CD19 CART (KTE-C19)
- Prior cyclophosphamide 500 mg/m² + fludarabine 30 mg/m² x 3 days
- 51 patients eligible for analysis: 78% refractory, 20% relapse < 12 mths after ASCTx, 61% ≥ 3 lines prior therapy
- Average turn around time = 17.4 days
- ORR = 76% (47% CR and 29% PR), 92% during first month
- 39% had ongoing results at 3 mths
- ≥ 3 AEs were cytopenias, encephalopathy 24%, CRS 20%
- Peak expansion after infusion associated with ongoing response

#LBA-6

CRISPR Cas

Clustered Regularly Interspaced Short Palendromic Repeat

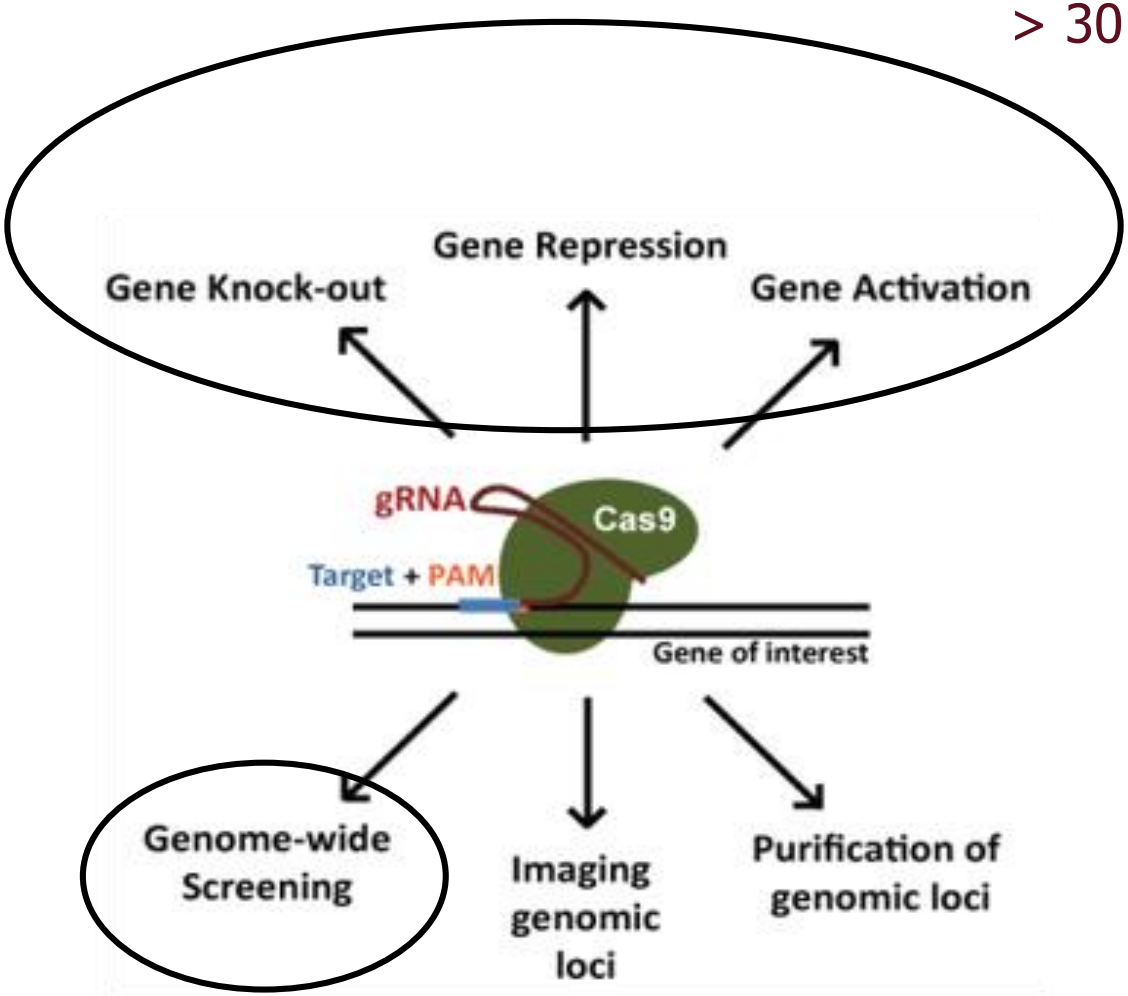
Single guide RNA
Targets CAS9 to specific genome locus (protospacer)



Protospacer Adjacent Motif
Necessary for Cas9 to bind to DNA

CRISPR for "genome editing"

> 30 oral abstracts



CRISPR oral abstracts

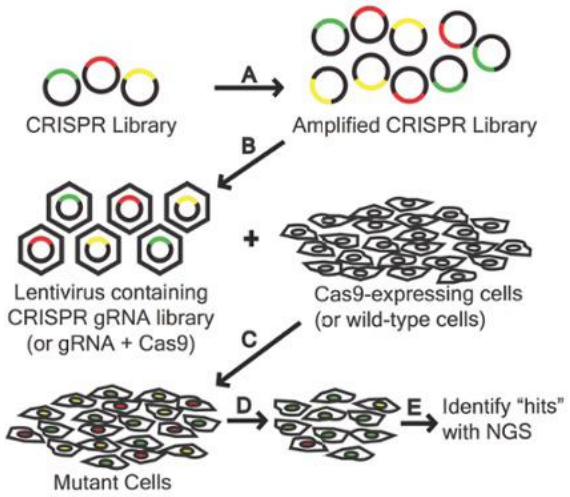
- Study function of genes (by KO or KI) or DNA regions in cell lines +/- mouse models (e.g. xenograft) or iPS
  - **PAX5** function in transformed **B cells** (#437)
  - Create **models of malignant hematopoiesis** by multiplex gene (DNMT3, TET2, FLT3, ..) editing (#741)
  - Create **CD33 knock outs** before CART (anti-CD33) treatment of **AML** (#1000)
  - Examine properties of **mutated SRSF2** in **MDS** (#962)
  - Study function of **SETD2** in normal and **leukemic hematopoiesis** (#1055)
  - Study function **of mutant CALR** (#954)
  - Investigating BCR downstream pathways (e.g. AKT) to develop biomarker-guided **therapeutic strategies B cell neoplasms** (#779)
  - Identify mutated **PPM1D** as key driver for therapy-related **MDS and AML** and assessing "**drugability"** (#740)
  - Study role of mutated **MEF2C** in **AML chemoresistance** (#436)
  - Study role of **MCL-1** in **ABT-199 (BCL-2 inhibitor) resistance**, also biomarker (#1081)
  - Disrupt protein expression important for **ROR-1/Wint** interactions in **B-CLL**, possible target for monoclonal antibodies (#349)
  - Identify mutated genes to be involved in **AML chemoresistance** (#600)

CRISPR Cas and physiopathology of MPN

- JAK2V617F frequently found in MPN
- DNMT3 methylates DNA residues leading to transcriptional repression and is mutated in 15% of MPN type MF
- Mouse HSPC → use CRISP-CAS9 to
  - Disrupt DNMT function and
  - Knock in JAK2V617F allele
- DNMT3dysf in JAK2V617F HSPC
  - Increases more immature stem cell features (self-renewal capacity)
  - Upregulation pathways controlling cell cycle progression, oncogenesis, DNA damage
- DNMT3dysf in JAK2V617F HSPC → irradiated mice
  - Panmyelosis + thrombocytosis → myelofibrosis
- → better understanding of mechanisms promoting advanced disease in MPN

CRISPR oral abstracts

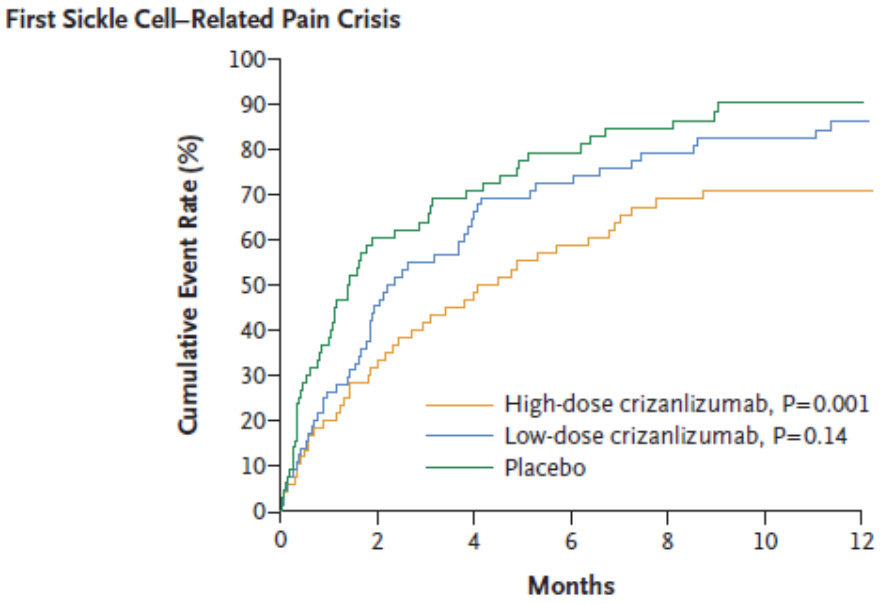
- Perform genome-wide CRISPR library screens ("functional genomics") to compare cell populations (e.g. malignant vs non-malignant, primary versus metastatic, ..)

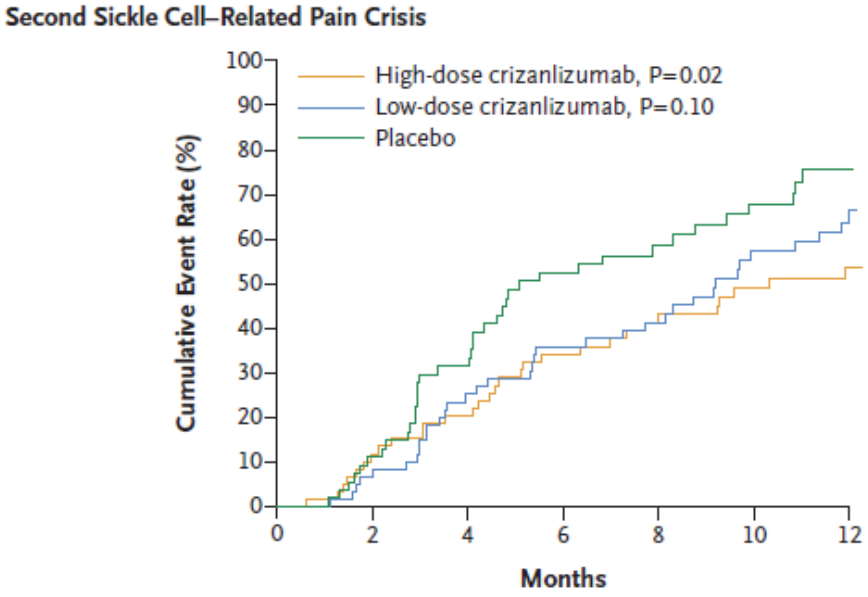


- Explore **potential new targets** in regulating tumor dissemination and metastasis in **myeloma** (#1137)
- **Compare primary and metastatic clones** to identify key regulators (EGR3 and ATF3) of dissemination in **myeloma** (#799)


TECNOFARMA
SELECTION OF BEST ASH ABSTRACTS

SUSTAIN trial: anti-selectin in sickle cell disease





- P-selectin = adhesion molecule on activated endothelial cells and plts involved in leucocyte rolling on vessel wall
- **Crizanlizumab** = anti-P-selectin
- Multicenter phase II trial, monthly IV, n= 198 pts
- Overall 1 vs 3 crises per year in treated patients

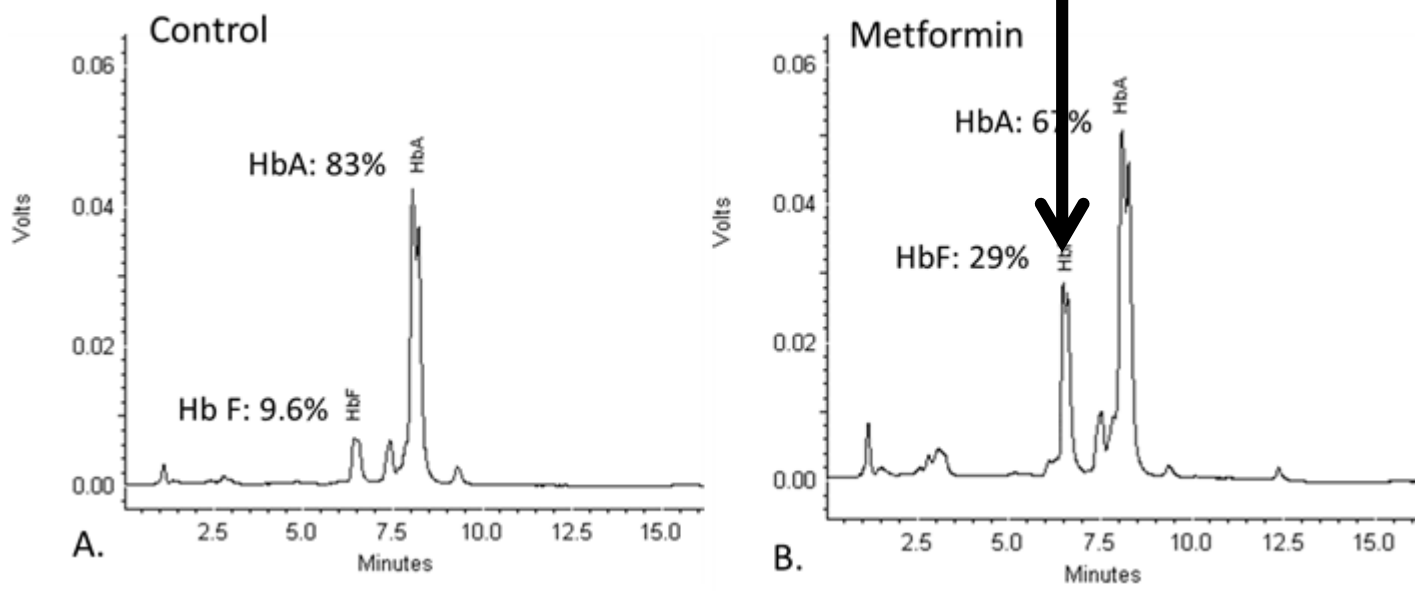
Ataga et al. NEJM dec 2016

#001

Metformin in sickle cell disease

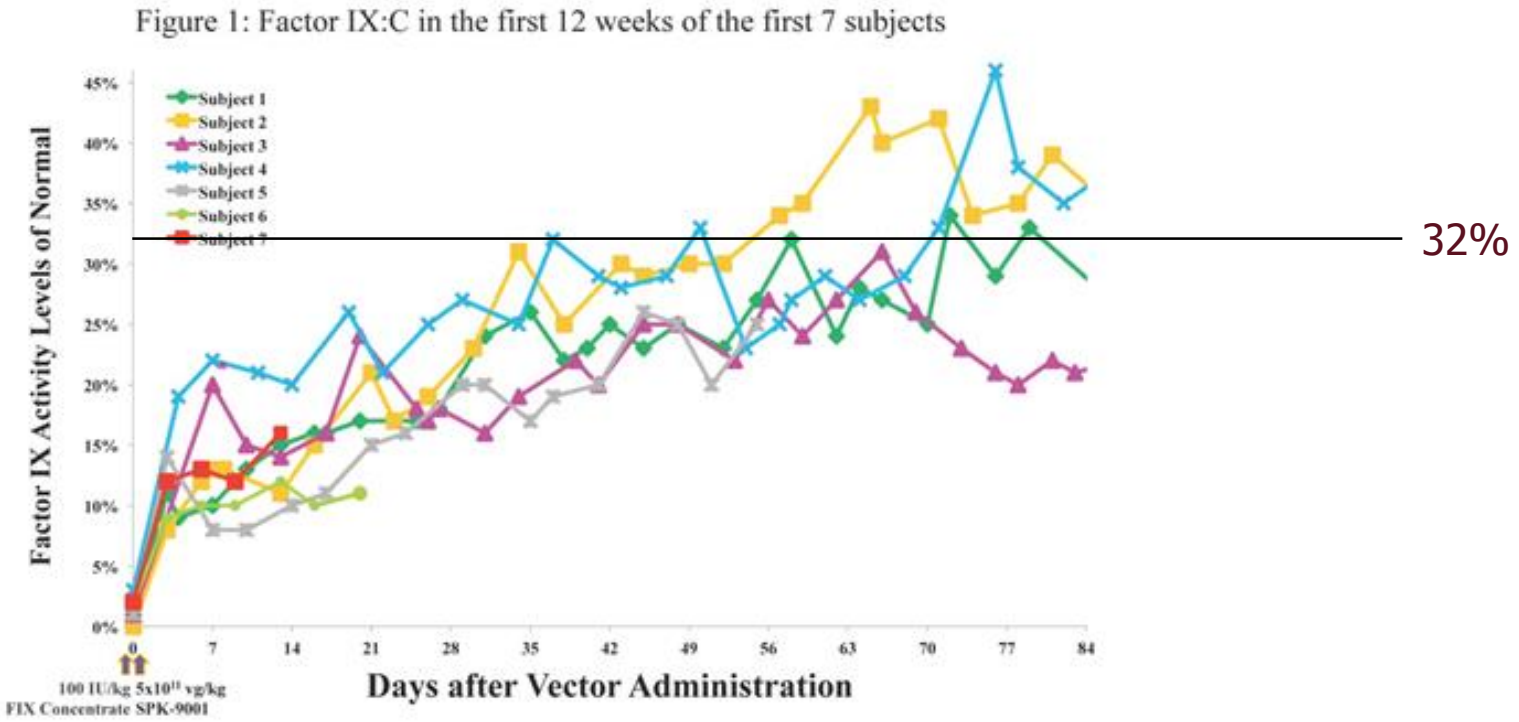
Use of CD34+ HPSC

Metformin → Activation of transcription factor FOXO3



#322

Gene therapy for hemophilia B

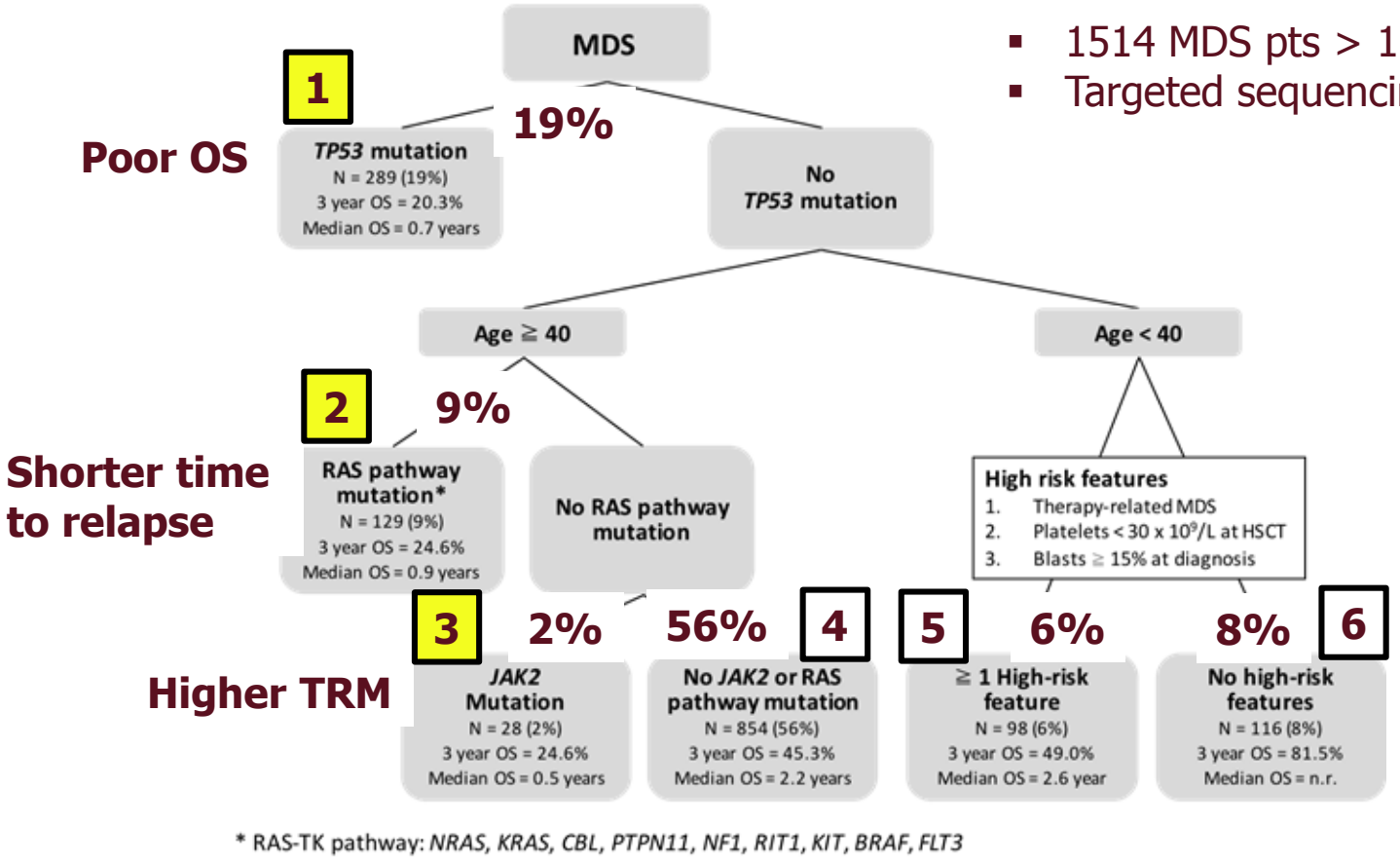


- Adeno-associated virus mediated gene transfer
- 12% FIX levels required (cfr previous gene therapy levels: 5%)
- SPK-9001 = bioengineered AAV capsid with liver specific tropism
- FIX Padua = X 8 activity
- Stable **+/- 32%** FIX concentrations
- 2/9 had cytotoxic anti-capsid immune responses, no inhibitor
- FIX pophylactic infusions stopped in 4 patients, 1.200.000 USD savings

#003

Precision medicine in MDS

Multivariable prognostic model for MDS alloSCT



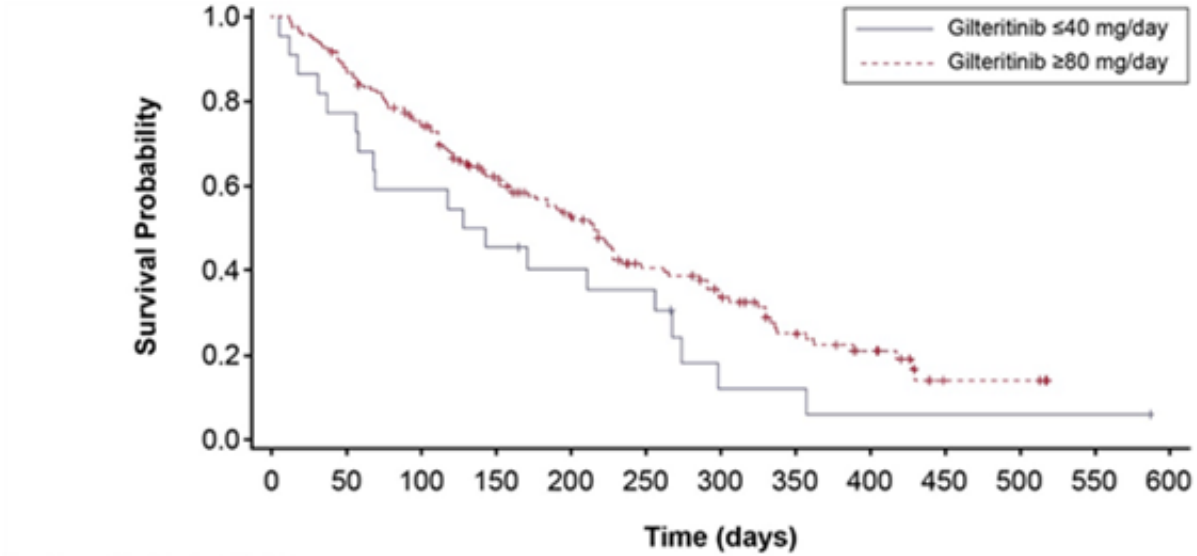
- 1514 MDS pts > 130 Tx centers
- Targeted sequencing of 127 genes

* RAS-TK pathway: *NRAS, KRAS, CBL, PTPN11, NF1, RIT1, KIT, BRAF, FLT3*

Chrysalis trial: FLT3 inhibition in R/R AML

- Gilteritinib = novel highly selective FLT3/AXL inhibitor
- Phase 1/2 clinical trial "first in human"
- N= 252 advanced AML (194 confirmed FLT3 mutations)
- Diarrhea and/or fatigue in 15%
- **ORR = 49% in FLT3 mutated pts,** median duration = 5 mths

Figure: Overall Survival in FLT3^{mut+} Patients Treated with <80 mg or ≥80 mg Gilteritinib



Number of Subjects At Risk

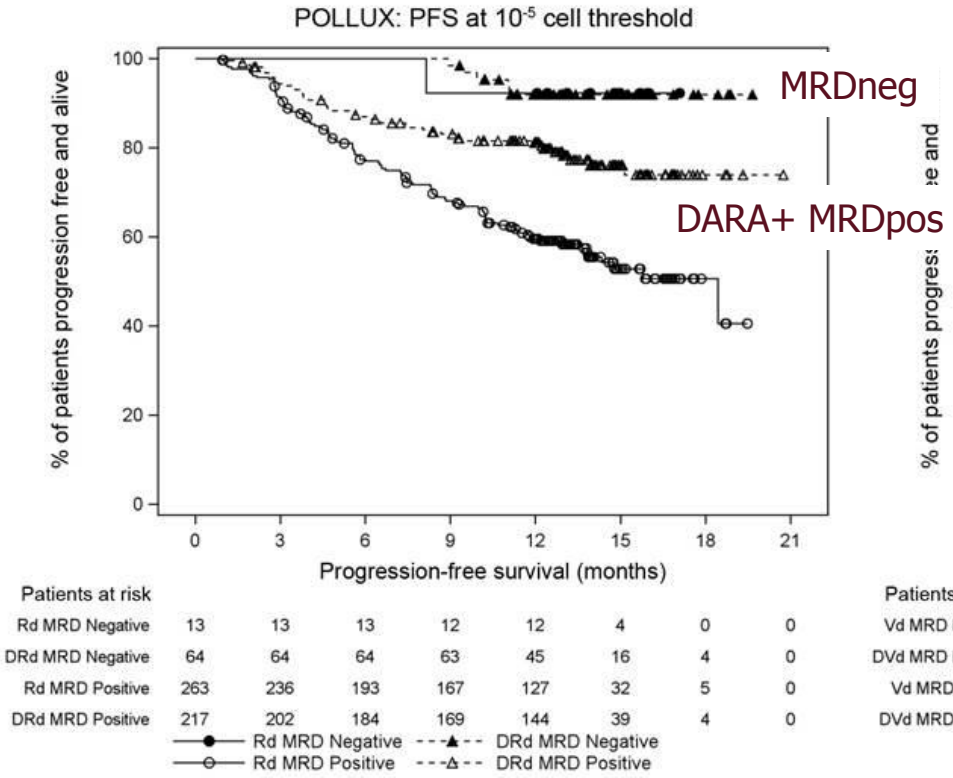
Gilteritinib ≤40 mg/day	22	17	13	10	8	7	2	2	1	1	1	1
Gilteritinib ≥80 mg/day	169	147	120	83	64	42	32	20	13	3	3	

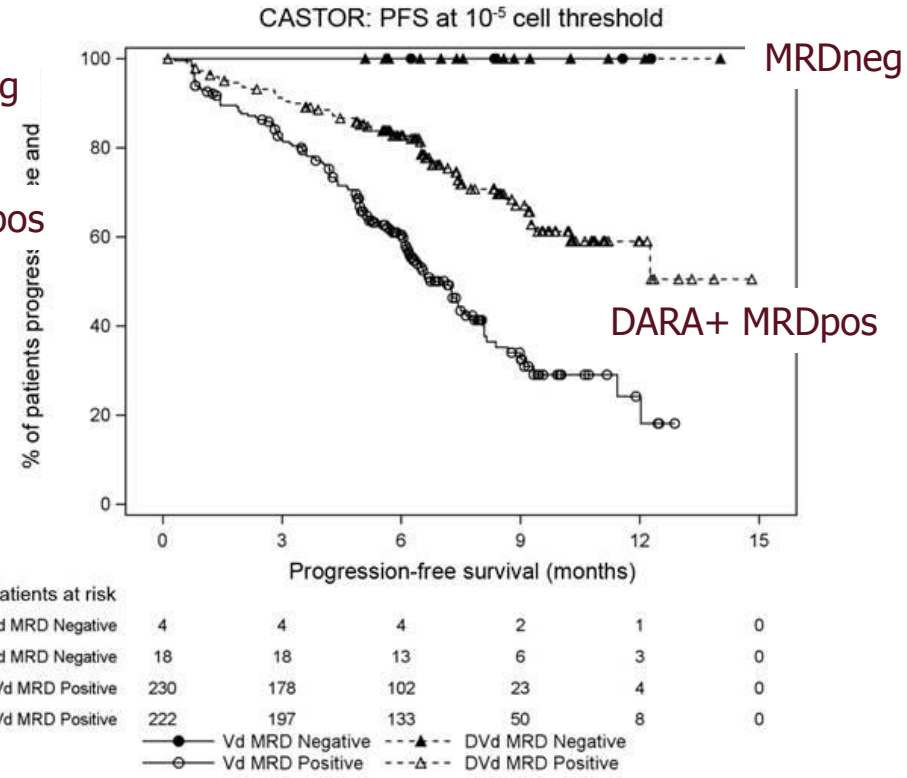
#1069

Daratumumab and MRD in relapsed MM

Sensitivity Threshold	POLLUX DRd vs Rd	CASTOR DVd vs Vd
10^{-4}	29.0% vs 7.8% OR (95% CI): 4.85 (2.93-8.03) *P*<0.000001	13.5% vs 2.8% OR (95% CI): 5.37 (2.33-12.37) *P*=0.000006
10^{-5}	22.4% vs 4.6% OR (95% CI): 5.99 (3.21-11.15) *P*<0.000001	7.2% vs 1.6% OR (95% CI): 4.69 (1.57-14.07) *P*=0.0017
10^{-6}	9.8% vs 2.1% OR (95% CI): 5.01 (2.04-12.30) *P*=0.000060	3.6% vs 0.8% OR (95% CI): 4.56 (0.97-21.30) *P*=0.028
OR, odds ratio.		

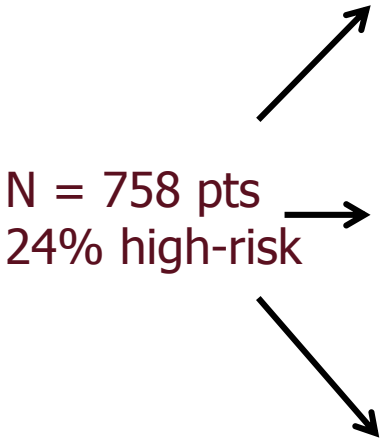
Method = ClonoSEQ (DNA) assay





#246

Autotransplantation in MM



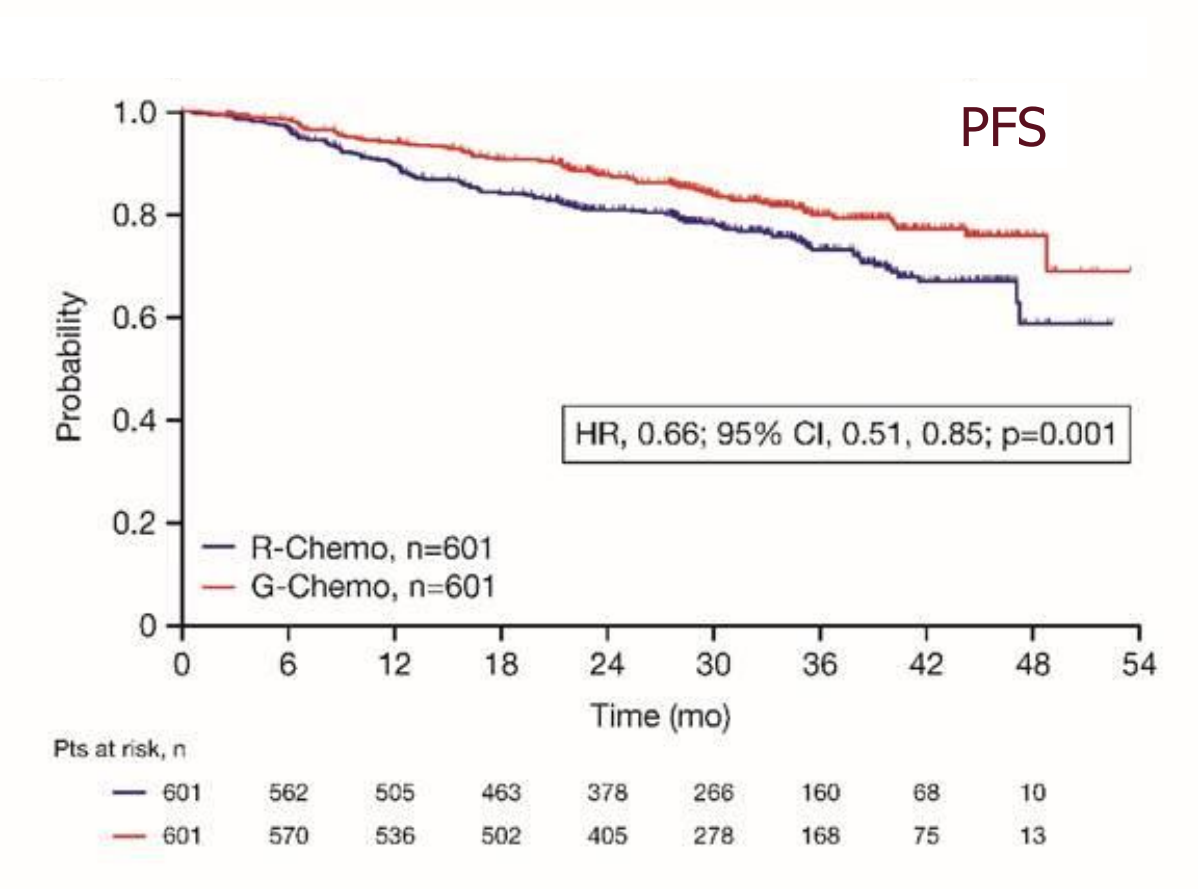
	at 38 mths		
	PFS	OS	PD
ASCTx + len maintenance	**52%**	**83%**	**47%**
ASCTx + RVD consolidation + len maintenance	**57%**	**86%**	**42%**
2x ASCTx + len maintenance	**56%**	**82%**	**42%**

CCL = NO DIFFERENCE

#LBA-1

GALLIUM study: obinotuzumab vs rituximab

- Follicular NHL stage III/IV or stage II bulky
- N= 1202
- Benda 57%, CHOP 33%, CVP 10%
- More AEs but similar SAE



→ Estimated **+ 3 years in PFS**

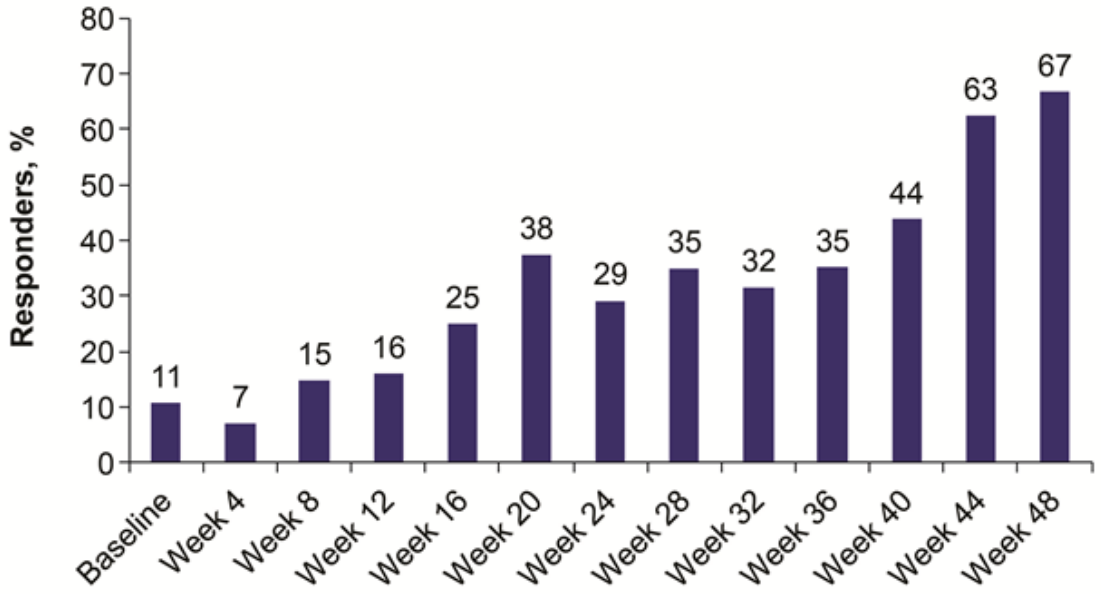
#006

Schots - Best of ASH 2016

Ibrutinib in steroid refractory CGVHD

- N =42 pts
- Median duration of CGVHD prior to therapy = 13.7 mths
- 1-3 prior regimens
- **ORR = 67% (21% CR, 45% PR)**
- **48% had sustained responses > 32 weeks**
- Fatigue 57%, diarrhea 36%, muscle spasms 29%, nausea 26%, bruising 24%
- Grade 3/4 AE > 3pts: pneumonia, fatigue, diarrhea
- SAE 52% (infections)
- 5 discontinuations for progressive CGVHD

Figure 2. Proportion of Responders Requiring Corticosteroid Doses <0.15 mg/kg/d Over Time



#LBA-3

Schots - Best of ASH 2016


Mission Beach San Diego