

Acute Myeloid and Lymphoid Leukemias

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Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Speakers Bureau: Sanofi, Pfizer

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Objectives

- Present molecular and genetic prognostic markers
- Review current chemotherapy
- Discuss progress in targeted/immunotherapy

AML 2018 Prognostic Factors*

- Cytogenetics and Molecular Studies
 - Favorable
 - CBF inv(16); t(16;16), t(8,21)
 - *NPM1* in absence of *FLT3-ITD* or *FLT3-ITD^{low}* or *biallelic CEBPA*
 - Intermediate
 - CN, +8 alone, t(9;11)
 - CBF with *c-KIT*, *NPM1* and *FLT3-ITD^{high}*
 - Unfavorable
 - Complex, MK, -5 (q), -7(q), 11q23, inv(3), t(3;3), t(6;9), t(9,22)
 - CN with *FLT3-ITD*, *TP53* mutation, *RUNX1*, *ASXL1*

*NCCN Guidelines 1.2018

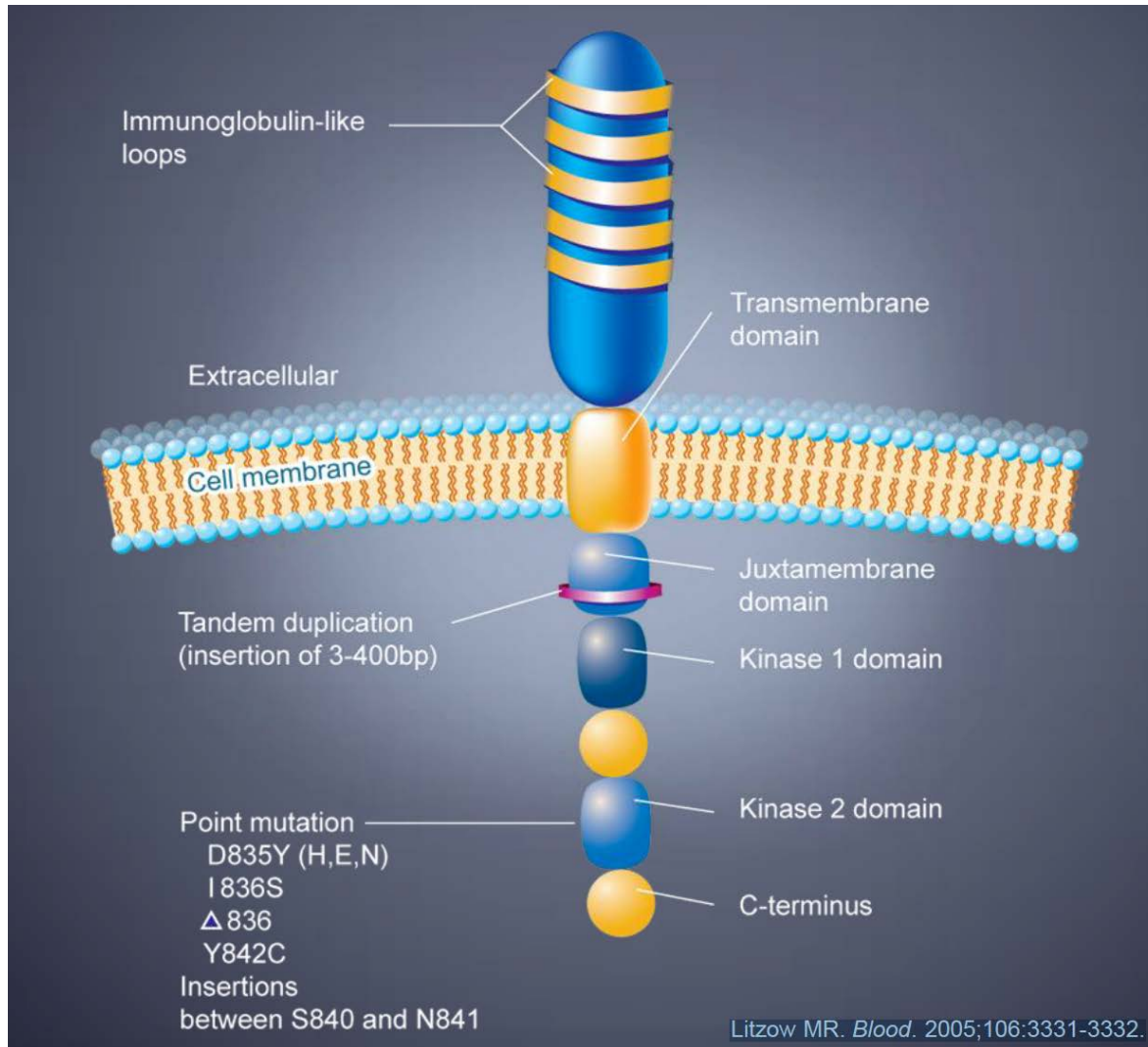
Points in Changes in NCCN Guidelines

- *FLT3* high and low allelic burdens
- Midostaurin added for *FLT3-mutated* AML based on RATIFY trial
- First assessment of MR should not be made until count recovery
- MRD is under investigation and may have prognostic significance

Induction Approach

- High-dose anthracyclines are safe
 - Multiple regimens
 - Most 7+3 based
 - Consider clinical trial always
- Idarubicin and daunorubicin are equivalent at higher doses
- Add targeted therapy when possible
- Rec: BM at day 14-21 from SOT

Activating *FLT3* Mutations in AML



Prevalence:
ITD: 25-30%
High relapse, poor prognosis
TKD: 5-10%

Effect:
Constitutive tyrosine phosphorylation

Midostaurin + chemotherapy

- Phase 3 trial
- 3277 screened, 18-59 years
- 717 FLT3-mutated randomized
 - 360 midostaurin, 357 standard
 - 7+3 +/- midostaurin induction
 - HiDAC +/- midostaurin consolidation
- CR rates equivalent 59% v 54%

Stone RM et al.

N Engl J Med 2017. DOI: 10.1056/NEJMoa1614359

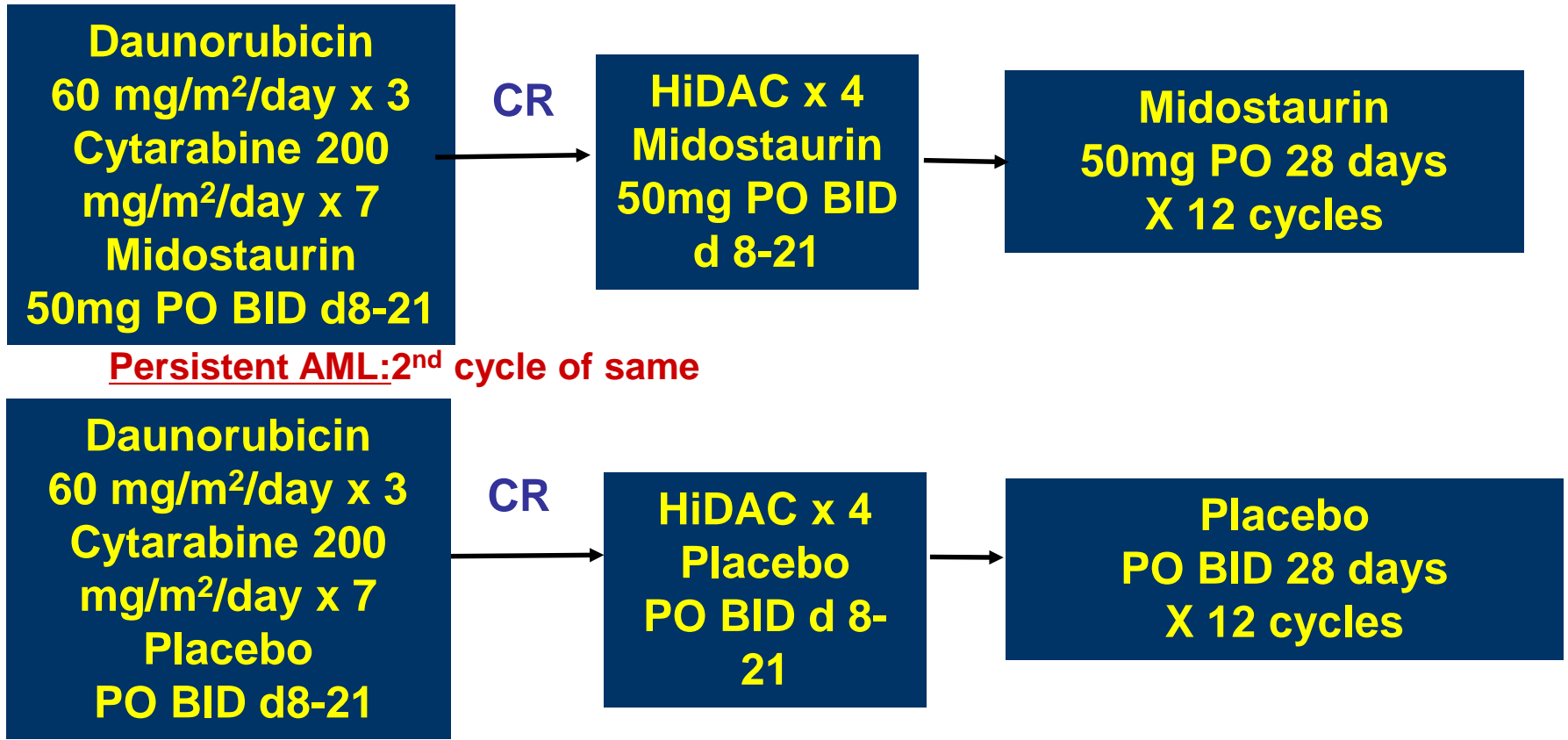
CALGB 10603 Schema

RATIFY Trial

Induction

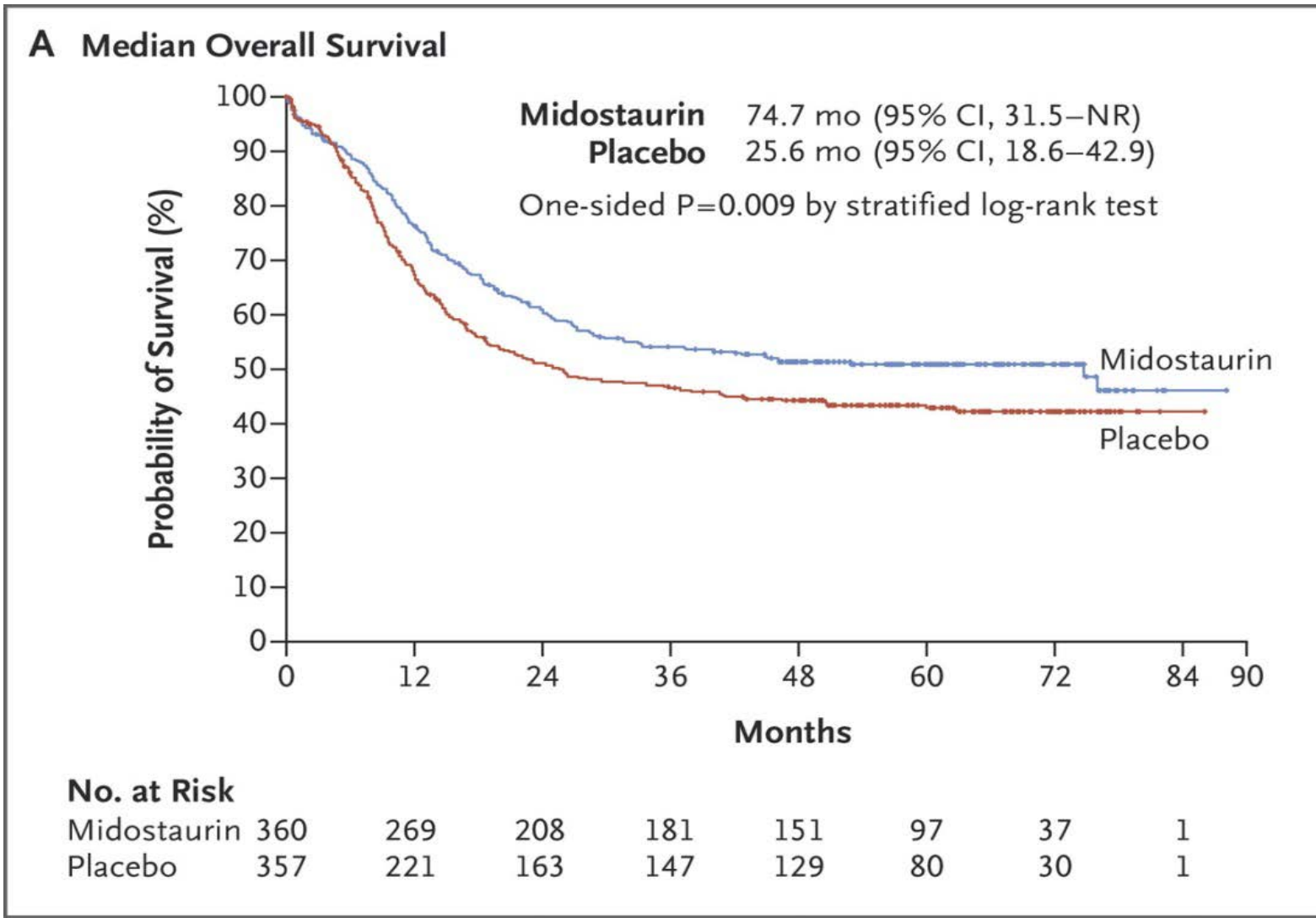
Consolidation

Maintenance



Stone RM et al.
N Engl J Med 2017. DOI: 10.1056/NEJMoa1614359

Overall Survival



Stone RM et al.
 N Engl J Med 2017. DOI: 10.1056/NEJMoa1614359

FT3-ITD Today: What we know

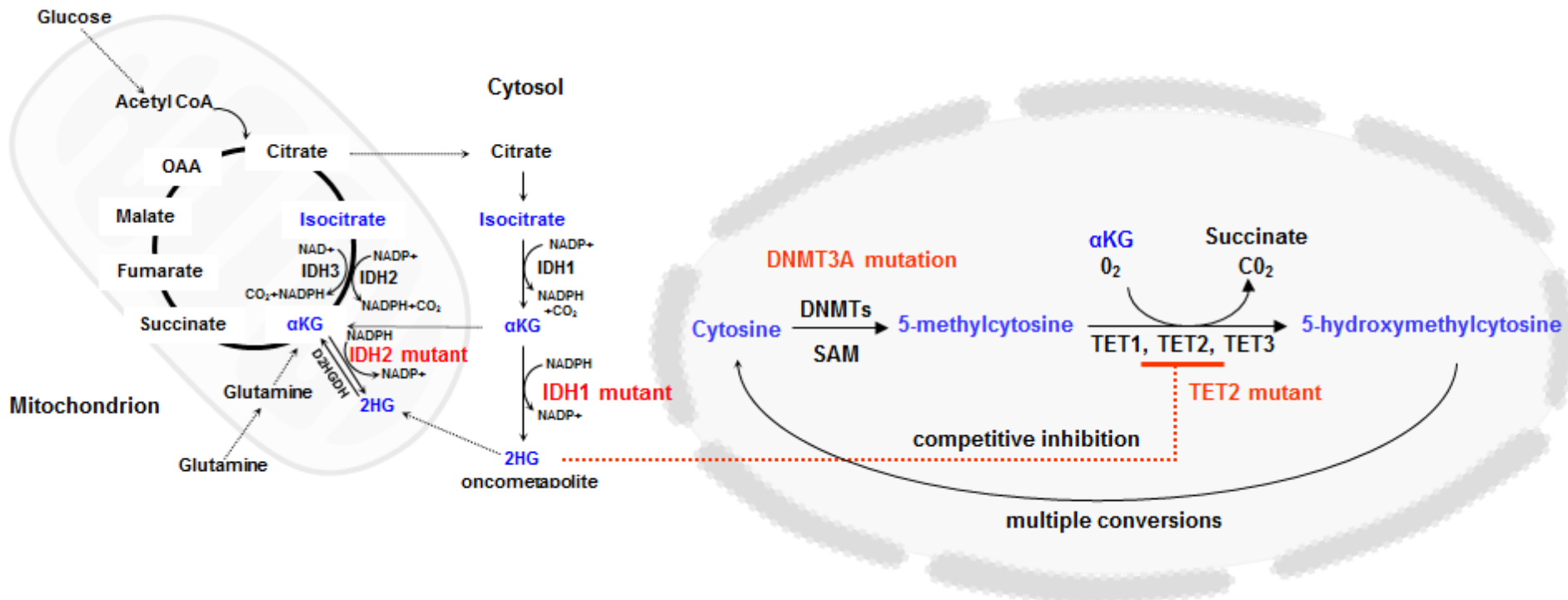
- PCR to diagnose- quick TAT
 - Midostaurin ASAP in induction
- Use in consolidation, maintenance¹
- HCT still important in consolidation
 - Midostaurin is safe post HCT (RADIUS trial results (ASH 2016)²
- Other *FLT-3* inhibitors under study

1. Stone RM, NEJM 2017, 2. Mazirz R, ASH 2016

IDH 1 and IDH2 in AML

- Identified in 2009
- Recurrent somatic mutations
- ~20% of AML patients
- Produces altered pathway of D-2-hydroxyglutarate (D-2HG)
- Leads to hypermethylation → impaired hematopoietic differentiation
- Older, CN, higher platelets
- Associated with NPM1, FLT3-ITD
- IDH2-R172- responds well to HiDAC

IDH, TET2 interaction



IDH differentiation syndrome

- Clinical Picture: culture-negative fever, edema, hypotension, and pleural and/or pericardial effusions
- Neutrophil-predominant leukocytosis
- Described in ~5% to 10% of patients across IDH inhibitor clinical trials
- **Can happen at any time**
- Treatment
 - Dexamethasone 10 mg Q12 hours
 - Stop drug until symptoms improve

Enasidenib (AG-221)

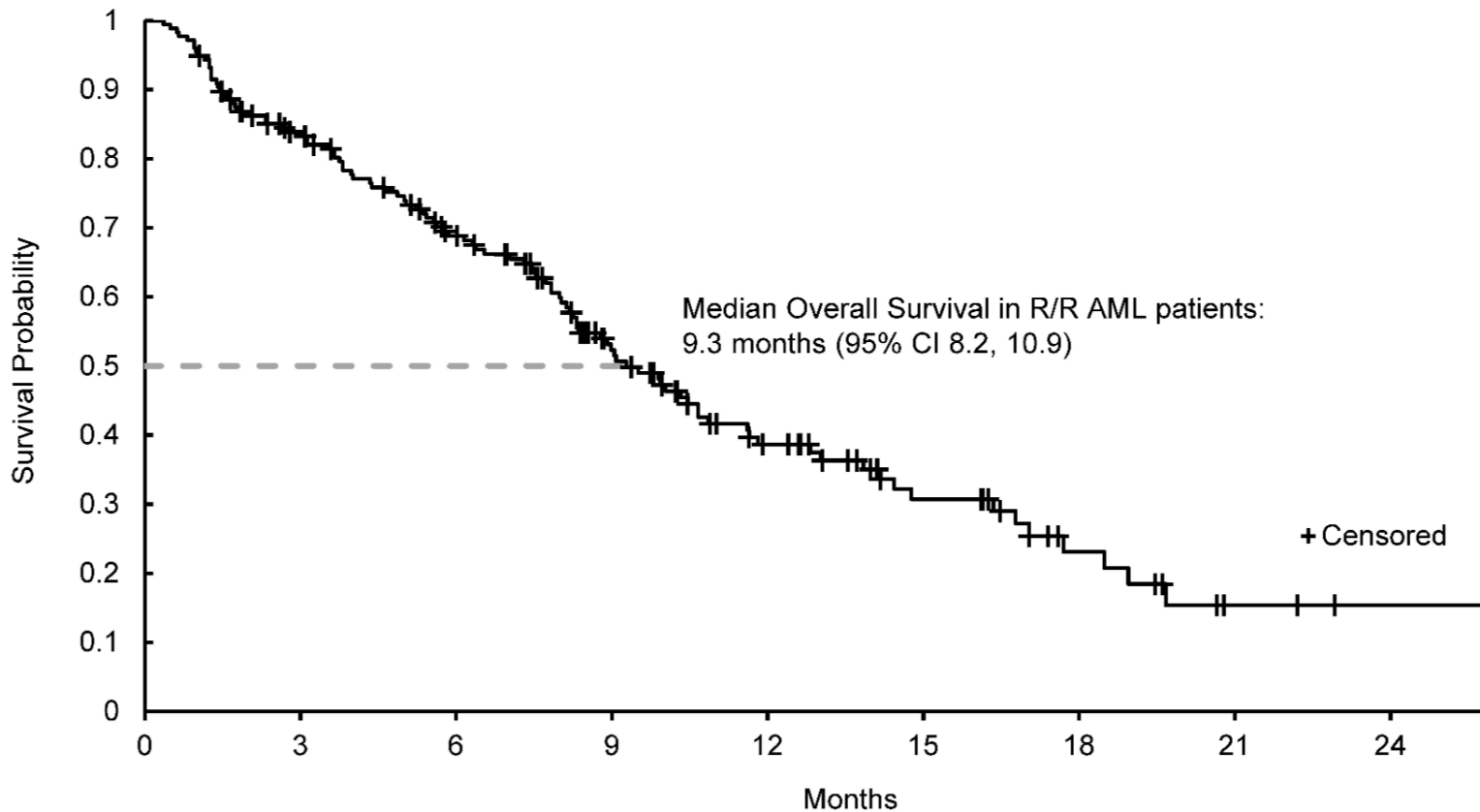
- Oral IHD2-R140 and R-172 inhibitor
- MTD 650mg/day from phase I
- Safety on 239 patients
- Phase I- 41% RR, CR of 18%
- Grade 3/4 Side effects
 - Hyperbilirubinemia (UGT1A1) 12%
 - Differentiation syndrome 7%

IDH inhibitor (NCT01915498)

- phase I/II study of enasidenib
- Patients with AML age ≥ 60 with *IDH2* mutation and relapsed or refractory AML therapy
 - 100mg/day effective dose based on PK and IDH blockade efficacy
- 176 patients
- RR= 40.3% duration 5.8 months

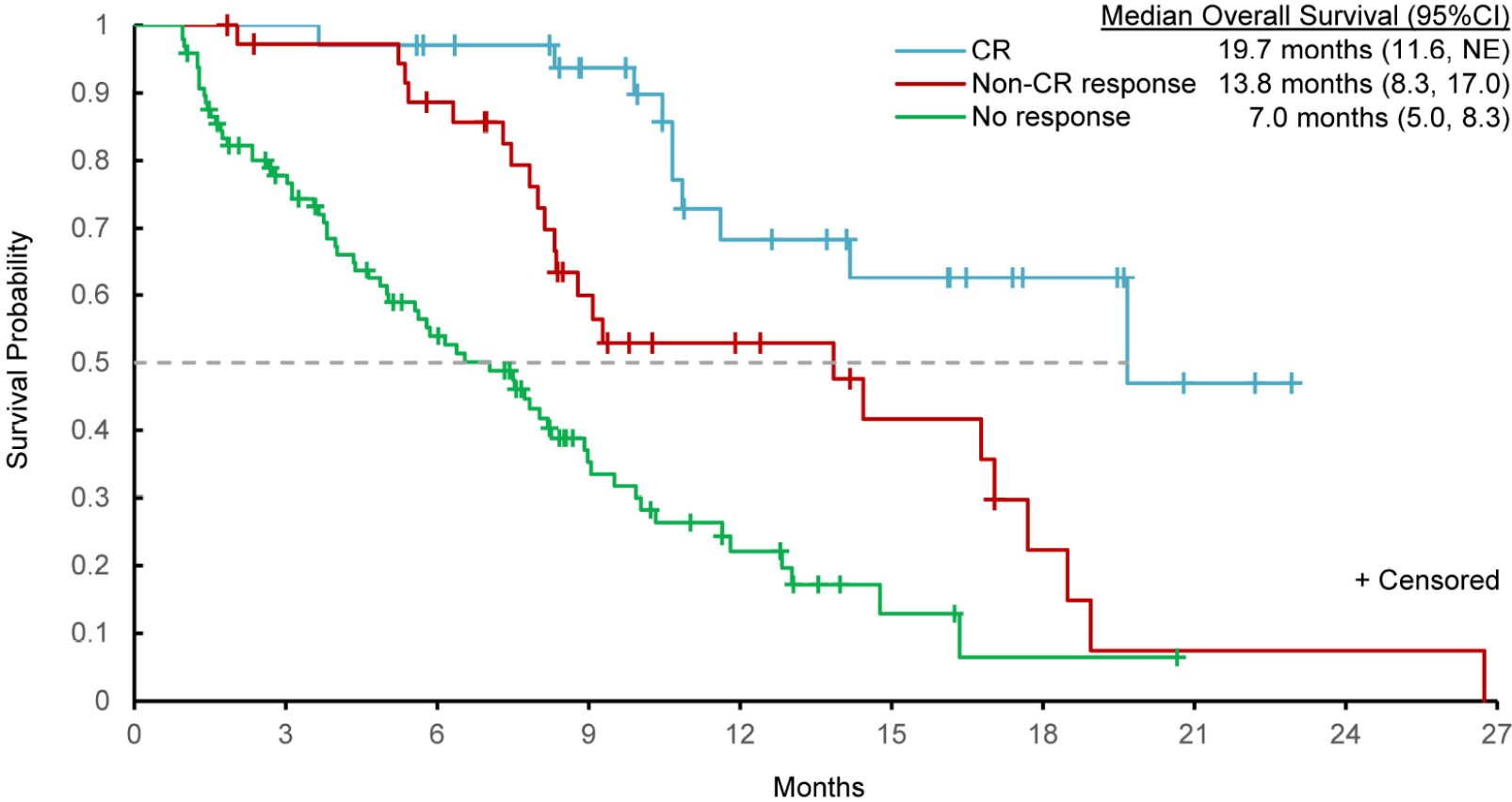
Stein & DiNardo et al, Blood 2017

Enasidenib (AG-221) OS



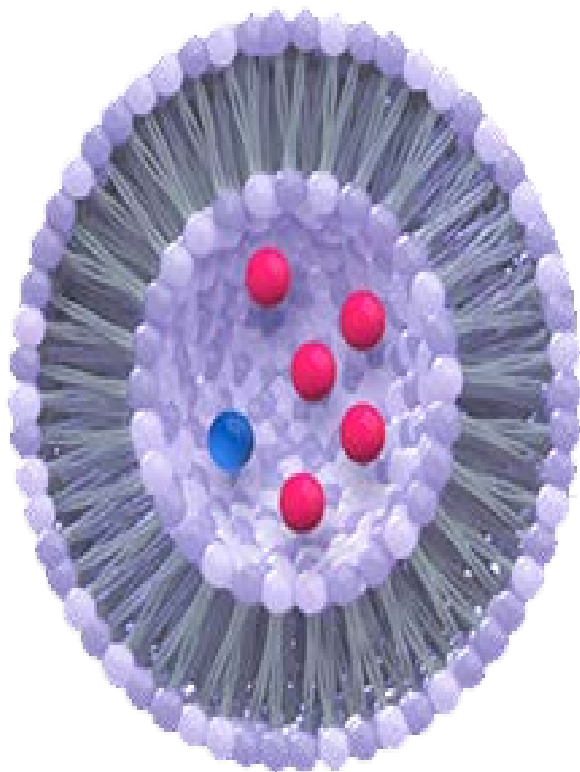
Enasidenib AG-221 OS on Response

B



Stein & Dinardo et al., Blood 2017

CPX-351 Uses a Nano-Scale Delivery

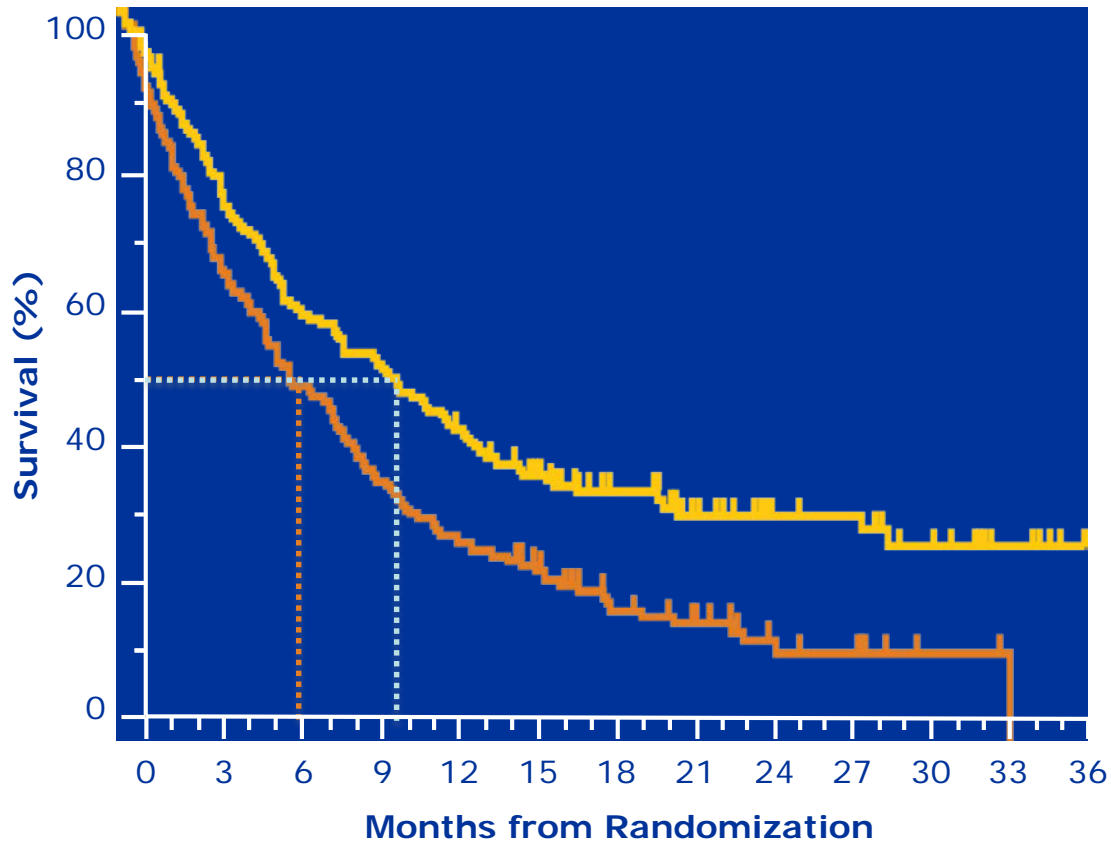


- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin
- Better BM penetration
- Phase 2 Study
 - Well tolerated
 - Improved CR, OS for s-AML

Overall Survival Was Greater in the CPX-351 Arm

**Kaplan-Meier Curve for Overall Survival
ITT Analysis Population**

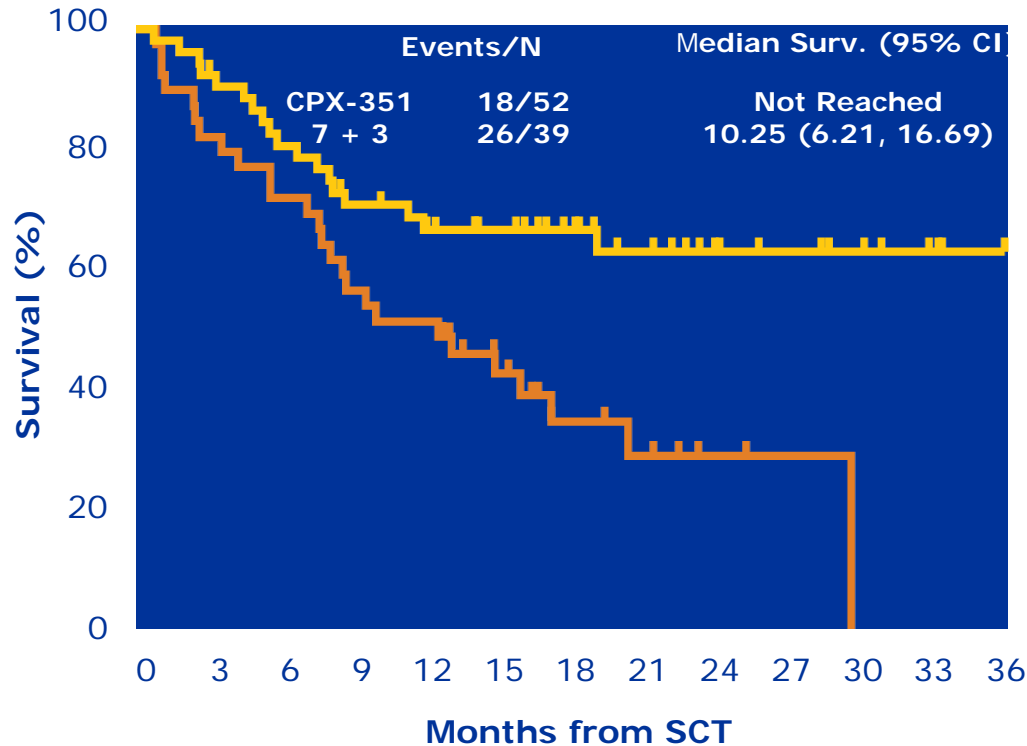
	Events/N	Median Surv. (95% CI)
CPX-351	104/153	9.56 (6.60, 11.86)
7+3	132/156	5.95 (4.99, 7.75)



CPX-351	153	122	92	79	62	46	34	21	16	11	5	1
7+3	156	110	77	56	43	31	20	12	7	3	2	0

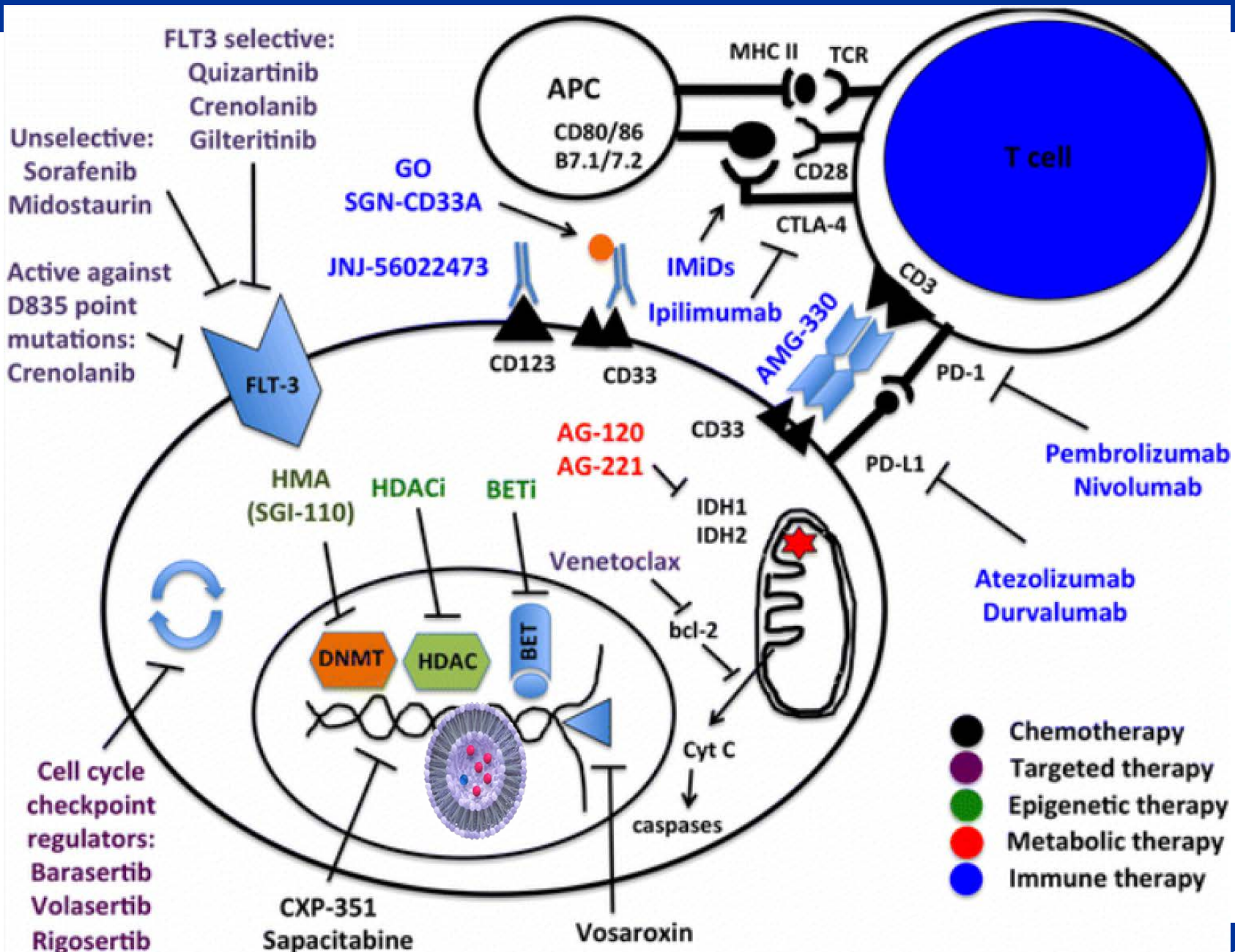
Lancet J et al , JCO 2018

Kaplan-Meier Curve for Overall Survival Landmarked at Stem Cell Transplant - ITT Analysis Population



CPX-351	52	46	40	34	27	20	15	9	6	3	0	0
7 + 3	39	31	27	20	15	7	4	1	1	0	0	0

Lancet J et al , JCO 2018



HCT in AML

- 74% eligible for HCT
 - Intermediate risk 35%
 - Unfavorable risk 39%
- Fitness of patient
- Age is not an issue
- Early HLA typing on all patients
 - Siblings too
- Referral to HCT center ASAP

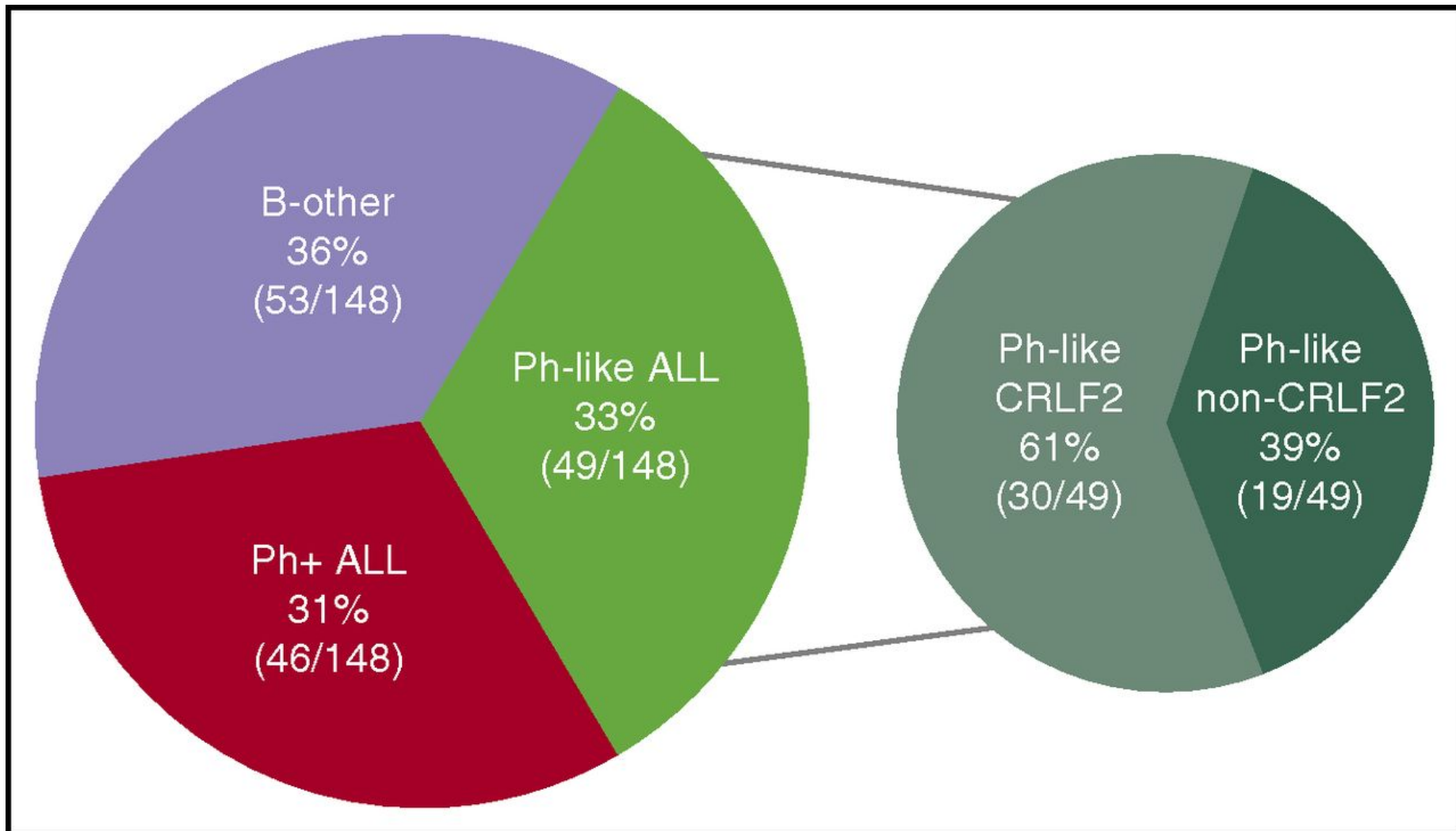
ALL Prognostic Features

- Age
 - Children
 - Adolescents and Young Adults (15-39)
 - Older (≥ 40)
- WBC (B-30K; T- 100K)
- Cytogenetics
- Minimal residual disease

ALL Cytogenetics in Adults

- Good Risk
 - Hyperdiploidy (51-65, +4,+10,+17) 7
 - t(12;21)(p13;q22): ETV6-RUNX 2
- Poor risk
 - Ph-like ALL 30
 - t (9;22) *BCR/ABL* 25
 - t (4;11) and t(____;11q23) *KMT2A rearranged* 10
 - Hypodiploidy (<44) 2
 - Complex (>5 chromosomal abnormalities)
 - (iAMP21)

Frequency of B-ALL subtypes in adults (N = 148)



Nitin Jain et al.

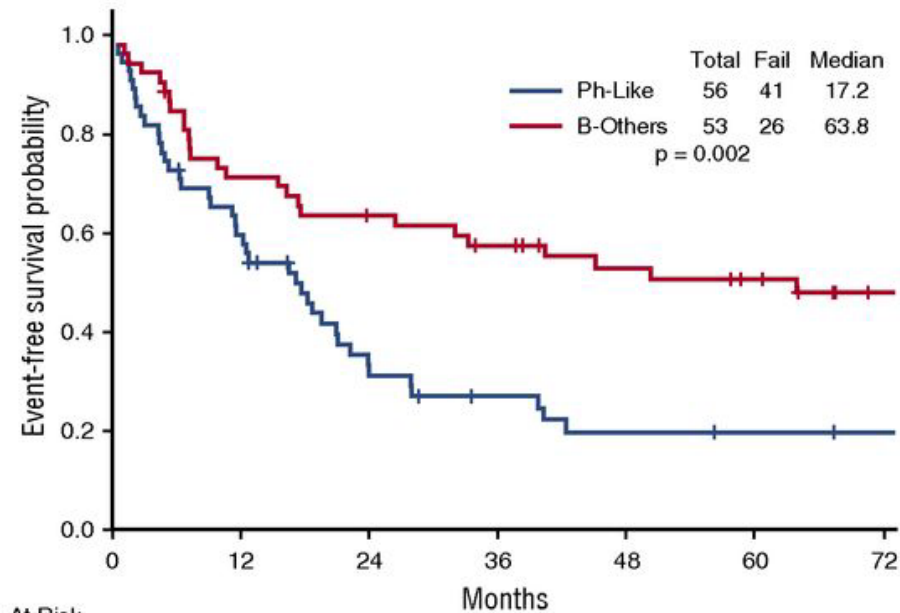
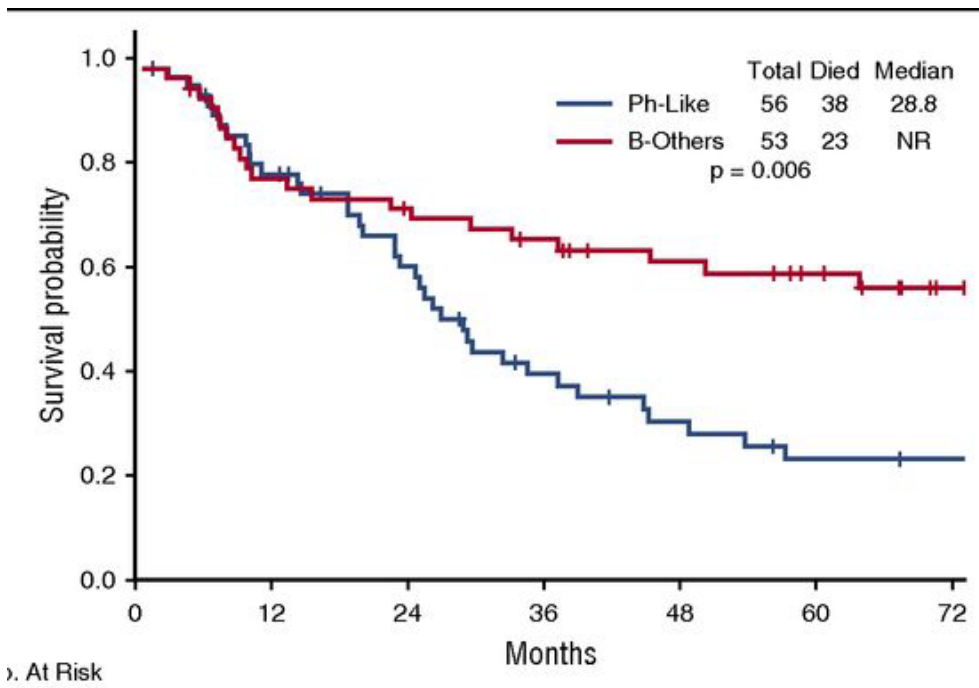
Blood 2017;129:572-581

Ph-like ALL

- Distinct clinical entity
 - Associated with CRLF2 (51%), JAK2/EPOR(12.4%), ABL (9.8%),JAK/STAT (7.2%)
- High WBC at diagnosis ~50K
- Hispanic propensity (68%), male predominance (64%)
- Have a poor prognosis
 - OS 23% vs 59%
- HCT recommended

Roberts, et al, JCO 2017, Jain et al , Blood 2017

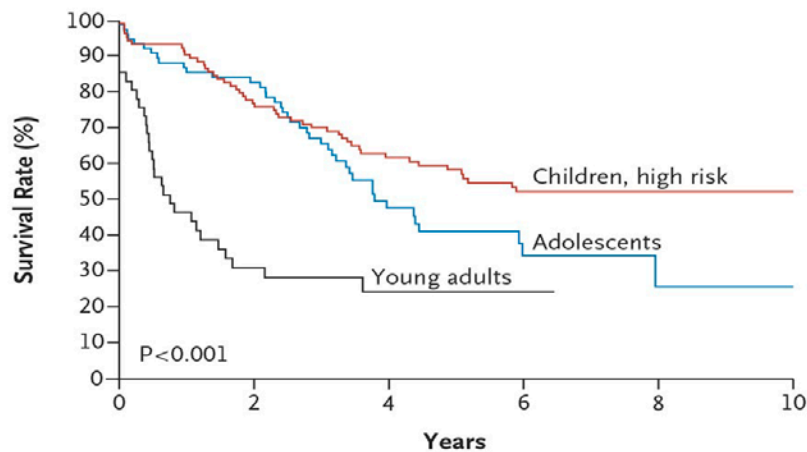
Ph-like ALL and B-other ALL: OS and EFS



Nitin Jain et al. Blood 2017;129:572-581

Kaplan–Meier Estimates of EFS and OS among Patients with Ph-like ALL

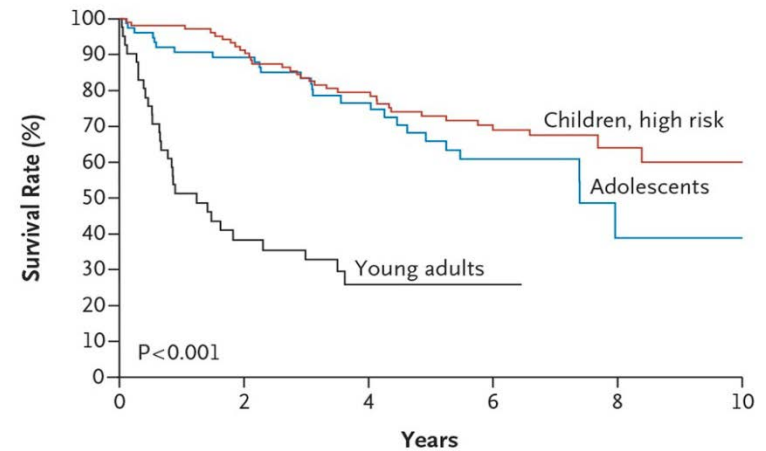
A Event-free Survival



No. at Risk

	0	2	4	6	8	10
Children, high risk	105	93	71	49	27	9
Adolescents	76	63	42	17	6	3
Young adults	41	18	10	3		

B Overall Survival



No. at Risk

	0	2	4	6	8	10
Children, high risk	105	101	85	61	37	13
Adolescents	76	63	53	28	11	4
Young adults	41	20	12	4		

Roberts KG et al.
N Engl J Med 2014;371:1005-1015

Kinase Fusions Identified in Ph-like ALL

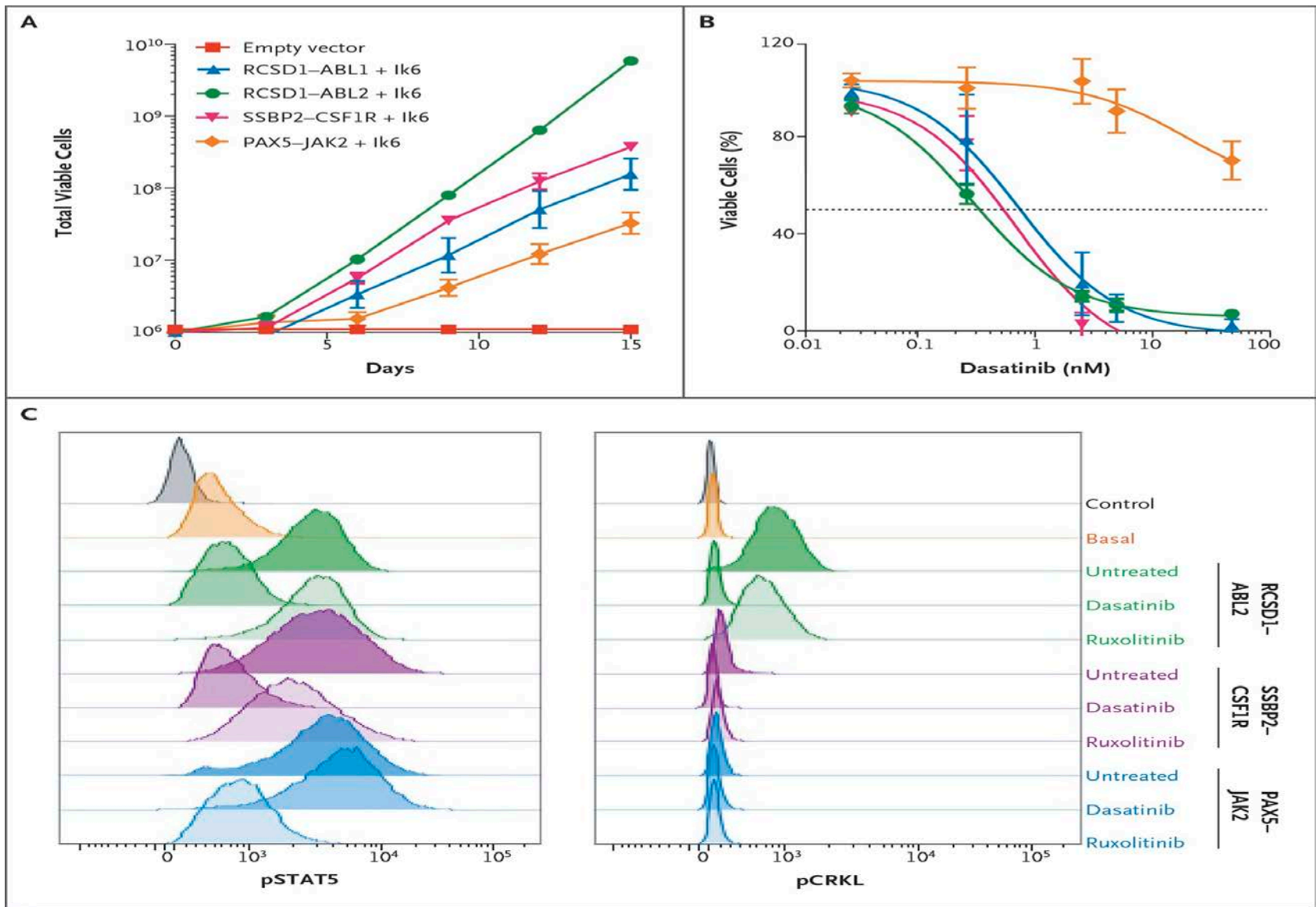
Table 1. Kinase Fusions Identified in Ph-like Acute Lymphoblastic Leukemia.

Kinase Gene	Tyrosine Kinase Inhibitor	Fusion Partners	Patients	5' Genes
		<i>number</i>		
<i>ABL1</i>	Dasatinib	6	14	<i>ETV6</i> , ¹¹ <i>NUP214</i> , ¹¹ <i>RCSD1</i> , ¹¹ <i>RANBP2</i> , ¹¹ <i>SNX2</i> , ¹⁹ <i>ZMIZ1</i> ²⁰
<i>ABL2</i>	Dasatinib	3	7	<i>PAG1</i> ,* <i>RCSD1</i> ,* <i>ZC3HAV1</i> *
<i>CSF1R</i>	Dasatinib	1	4	<i>SSBP2</i> *
<i>PDGFRB</i>	Dasatinib	4	11	<i>EBF1</i> , ¹¹⁻¹³ <i>SSBP2</i> ,* <i>TNIP1</i> ,* <i>ZEB2</i> *
<i>CRLF2</i>	JAK2 inhibitor	2	30	<i>IGH</i> , ²¹ <i>P2RY8</i> ²²
<i>JAK2</i>	JAK2 inhibitor	10	19	<i>ATF7IP</i> ,* <i>BCR</i> , ¹¹ <i>EBF1</i> ,* <i>ETV6</i> , ²³ <i>PAX5</i> , ¹¹ <i>PPFIBP1</i> ,* <i>SSBP2</i> , ²⁴ <i>STRN3</i> , ¹¹ <i>TERF2</i> ,* <i>TPR</i> *
<i>EPOR</i>	JAK2 inhibitor	2	9	<i>IGH</i> , ¹¹ <i>IGK</i> *
<i>DGKH</i>	Unknown	1	1	<i>ZFAND3</i> *
<i>IL2RB</i>	JAK1 inhibitor, JAK3 inhibitor, or both	1	1	<i>MYH9</i> *
<i>NTRK3</i>	Crizotinib	1	1	<i>ETV6</i> ²⁵⁻²⁷ †
<i>PTK2B</i>	FAK inhibitor	2	1	<i>KDM6A</i> ,* <i>STAG2</i> *
<i>TSLP</i>	JAK2 inhibitor	1	1	<i>IQGAP2</i> *
<i>TYK2</i>	TYK2 inhibitor	1	1	<i>MYB</i> *

* The gene is a previously unreported fusion partner.

† *ETV6-NTRK3* has been reported in multiple cancers, including congenital fibrosarcoma^{25,26} and secretory breast carcinoma,²⁷ but it has not previously been described in acute lymphoblastic leukemia.^{28,29}

Response to Tyrosine Kinase Inhibitors



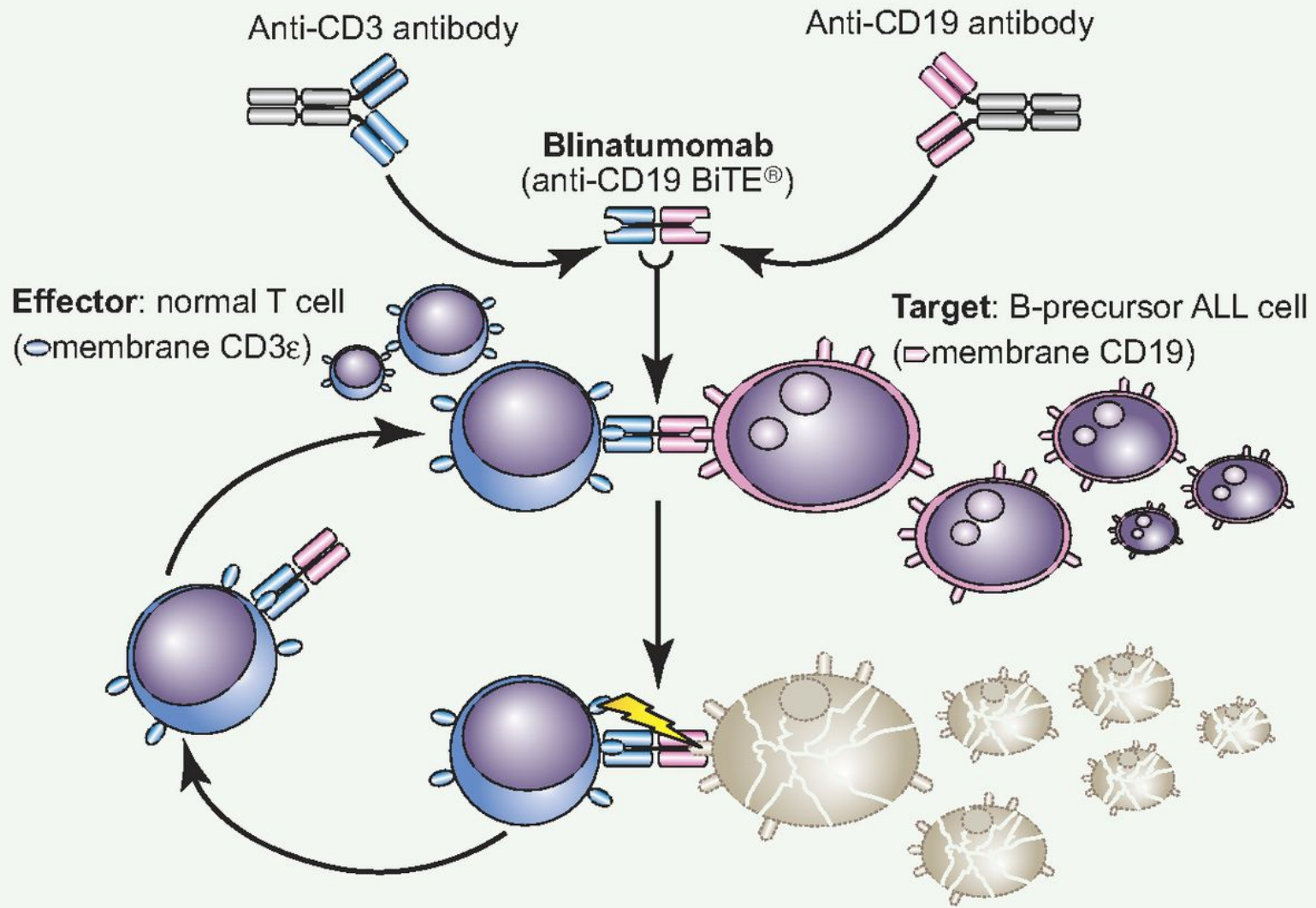
Roberts KG et al.
N Engl J Med 2014;371:1005-1015

TKI in Ph⁺ ALL-Need to know

- Increased CR rates and duration
 - ~90%
- Lower Pre-HCT tumor burden
- Allows for donor search
 - Sib, MUD, Haplo
 - MAC younger, RIC older
- Does not affect HCT toxicities
- Usually stopped 1 week prior to HCT

Ph Positive ALL

- Induction with chemotherapy + TKI
 - BFM+ Imatinib (EsPhALL)
 - HyperC-VAD + dasatinib- MDACC
 - Continuous dosing recommended
- HCT is still mainstay of therapy
- No standard for post HCT maintenance
- MRD post HCT requires indeterminate length of therapy



Blinatumomab V Chemotherapy

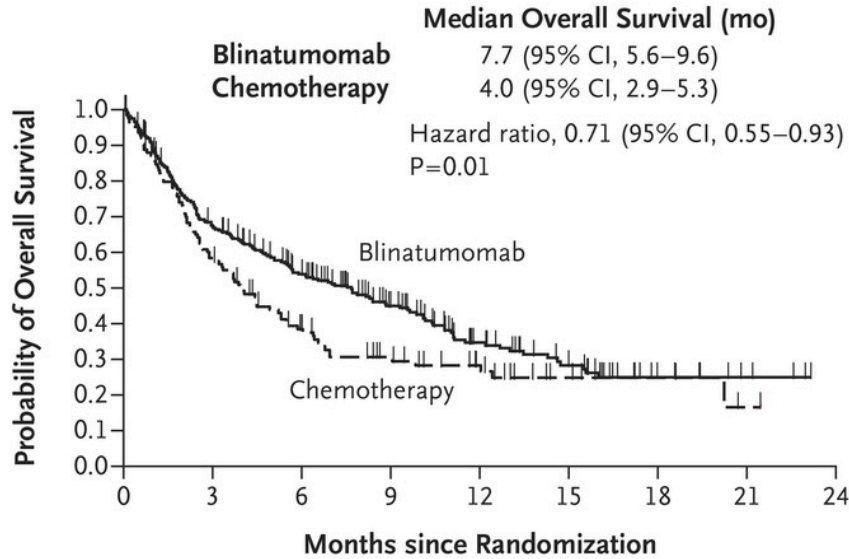
- Phase 3, multi-institution
- 405 patients- Blin-271, Chemo-134

<u>Responses</u>	<u>Blin</u>	<u>Chemo</u>
– CR	34%	16%
– OR	44%	25%
– EFS 6 month	31%	12%
– OS	7.7m	4.0m
– 24% proceeded to allo HCT		

Kantarjian H et al. *N Engl J Med*
2017;376:836-847

Blinatumomab: Efficacy End Points.

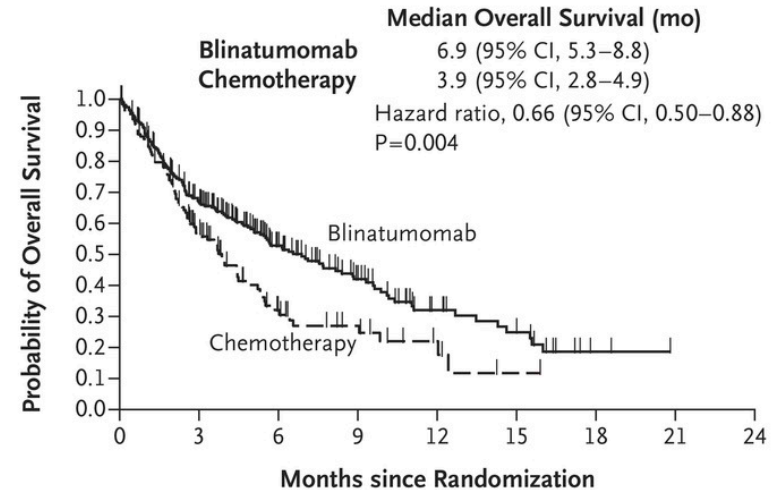
A Overall Survival



No. at Risk

	0	3	6	9	12	15	18	21	24
Blinatumomab	271	176	124	79	45	27	9	4	0
Chemotherapy	134	71	41	27	17	7	4	1	0

Overall Survival Censored at Time of Stem-Cell Transplantation



No. at Risk

	0	3	6	9	12	15	18	21	24
Blinatumomab	271	163	80	44	21	13	2	0	0
Chemotherapy	134	56	21	12	5	1	0	0	0

Kantarjian H et al. *N Engl J Med* 2017;376:836-847

Inotuzumab vs Chemo

- Anti-CD22 moAb + calicheamicin
- Ino v chemo for RR ALL
- 326 patients (218 ITT)

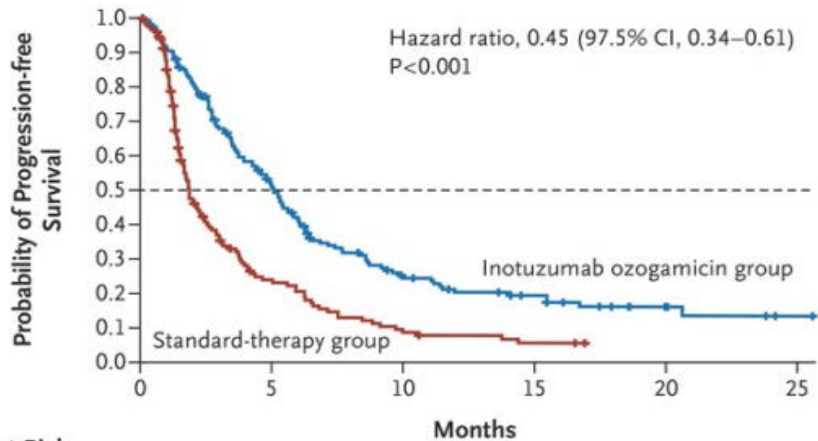
<u>Responses</u>	<u>Ino</u>	<u>Chemo</u>
– CR/CRi	80.7%	29.4%
– MRD	78.4%	28.1%
– PFS	5.8m	1.8m
– OS	7.7m	6.7m

- VOD occurred in 11% of Ino patients

Kantarjian H et al. N Engl J Med
2017;376:836-847

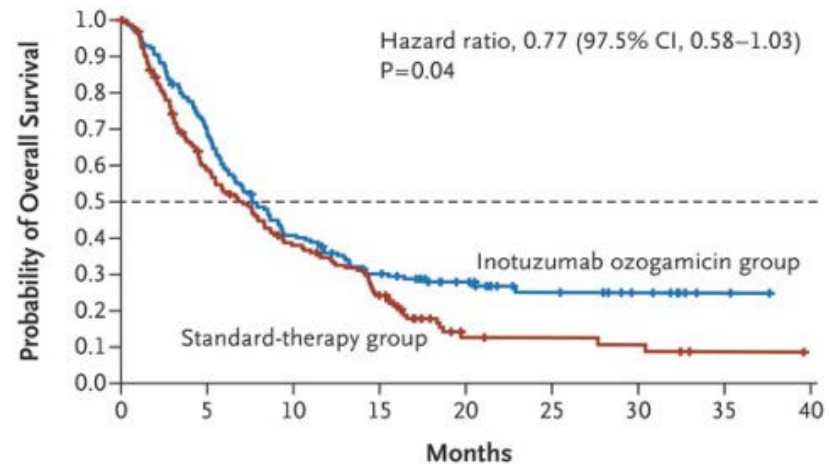
Inotuzumab: PFS, and OS

B Progression-free Survival



No. at Risk		Months					
		0	5	10	15	20	25
Inotuzumab ozogamicin group	164	72	28	16	6	1	
Standard-therapy group	162	24	6	2	0	0	

C Overall Survival



No. at Risk		Months									
		0	5	10	15	20	25	30	35	40	
Inotuzumab ozogamicin group	164	112	62	41	24	13	8	2	0		
Standard-therapy group	162	85	51	30	6	5	4	1	0		

Targeting ALL with CAR-Ts

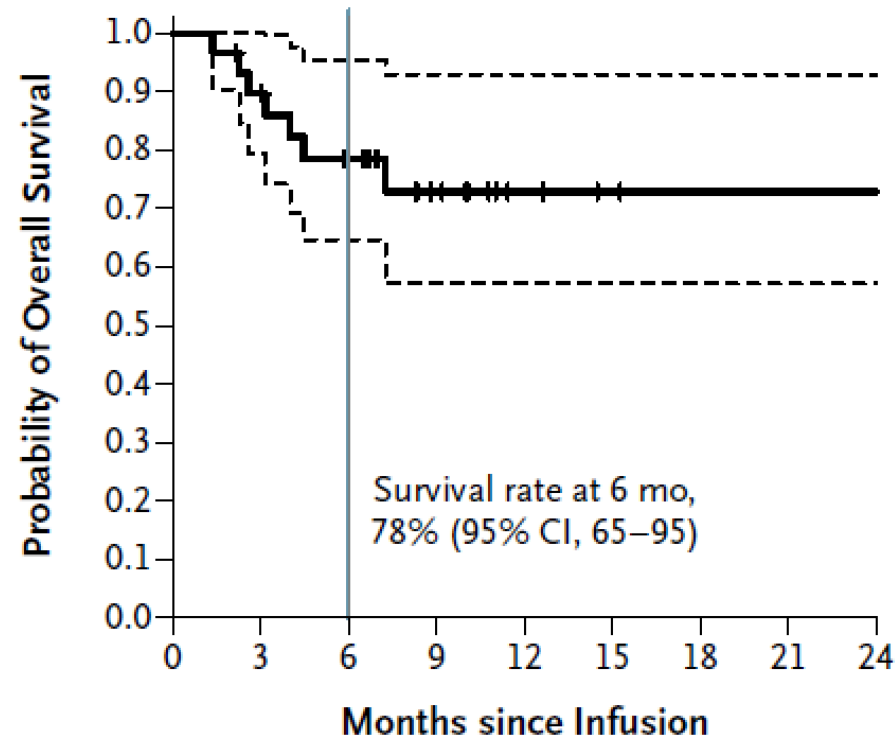
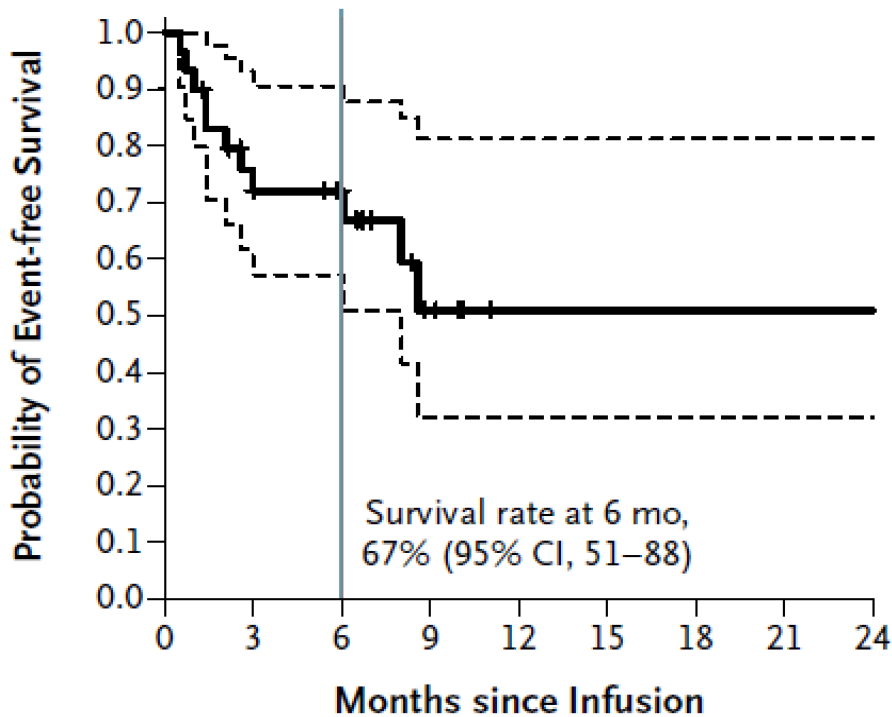
- Re-induction in R/R disease
- Multiple companies with different constructs
 - Novartis with first FDA filing for Peds, AYA
- Requires specialty center
 - Apheresis
 - Cell processing/GMP (Company driven)
 - Clinical team
 - Heme/Onc
 - Neurology
 - ICU care
 - Guidelines for Cytokine Release Syndrome

CAR-T

- CD19 directed CAR-T (tisagenleucel)
- Dose escalation 0.76 -20.6 x 10⁶ CTL019 cells/kg
- 30 children and adults (15 prior HCT)
- CR- 90%, 6 mo EFS- 67%
- OS- 78%
- CRS was seen in all
 - Treated with anti-IL6-tocilizumab

Maude S et al., NEJM 2014

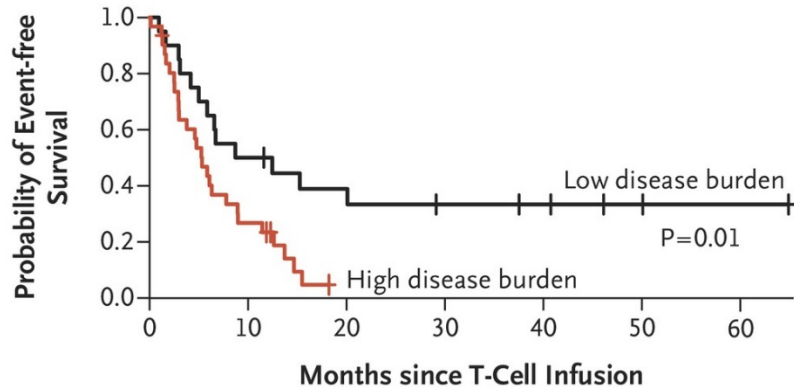
CTL019 EFS and OS



Maude S et al., NEJM 2014

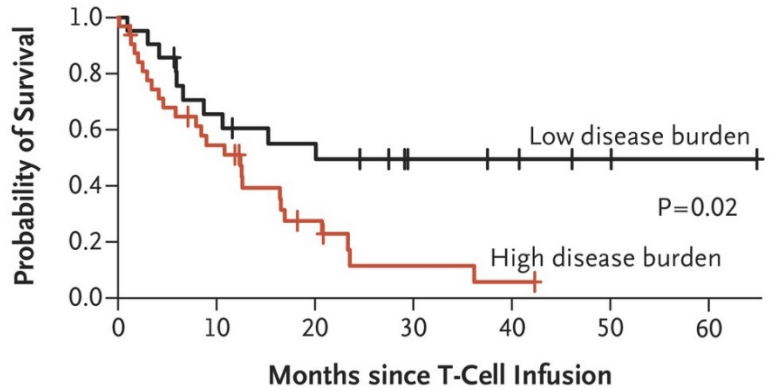
Event-free Survival and Overall Survival According to Pre-treatment Disease Burden

A Event-free Survival, According to Disease Burden



No. at Risk	0	10	20	30	40	50	60
Low burden	20	10	7	5	4	2	1
High burden	31	8	0	0	0	0	0

B Overall Survival, According to Disease Burden



No. at Risk	0	10	20	30	40	50	60
Low burden	21	13	10	5	4	2	1
High burden	32	16	6	2	1	0	0

Park JH et al.
N Engl J Med 2018;378:449-459

HCT in ALL

- In adults
 - AYA with high risk features
 - Ph+ and Ph-like
 - Older all patients
- Adjust regiment to suit patient
 - RIC appropriate for over 55
- Care with inotuzumab –VOD
- TKI do not affect Ph⁺

Conclusions

- Unique disorders
 - Aggressive therapy
 - Best chance to do it right is upfront
- Risk stratification requires complete evaluation
 - Cytogenetic and molecular
- Mutations are targetable in both diseases