Acute Myeloid and Lymphoid Leukemias

Hugo F. Fernandez, MD

Department of Malignant Hematology & Cellular Therapy
Moffitt at Memorial Healthcare System

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Hugo Fernandez, MD

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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, NPM1and 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

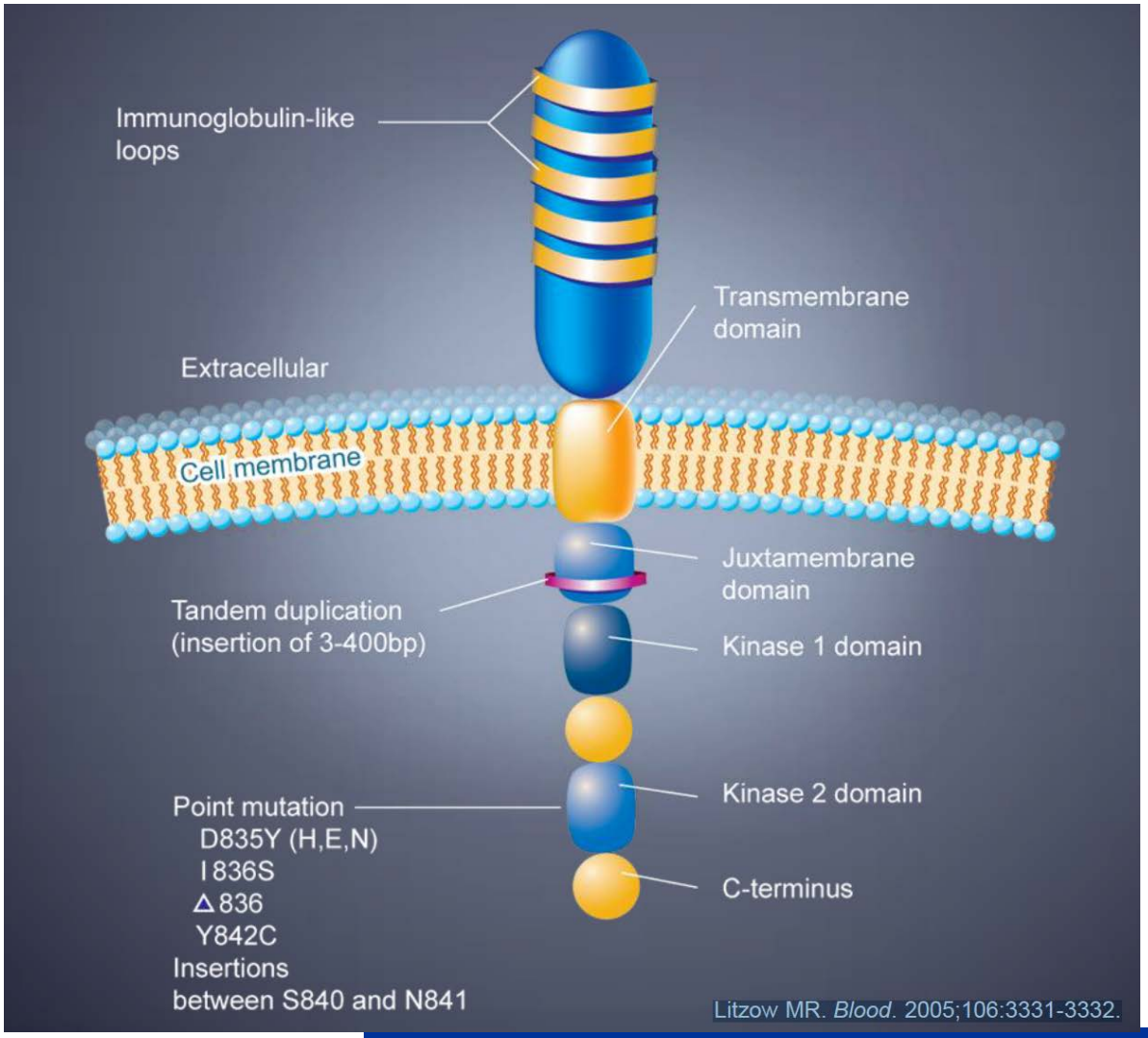
Points in Changes in NCCN Guidelines

- *FLT3* high and low alleic 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%

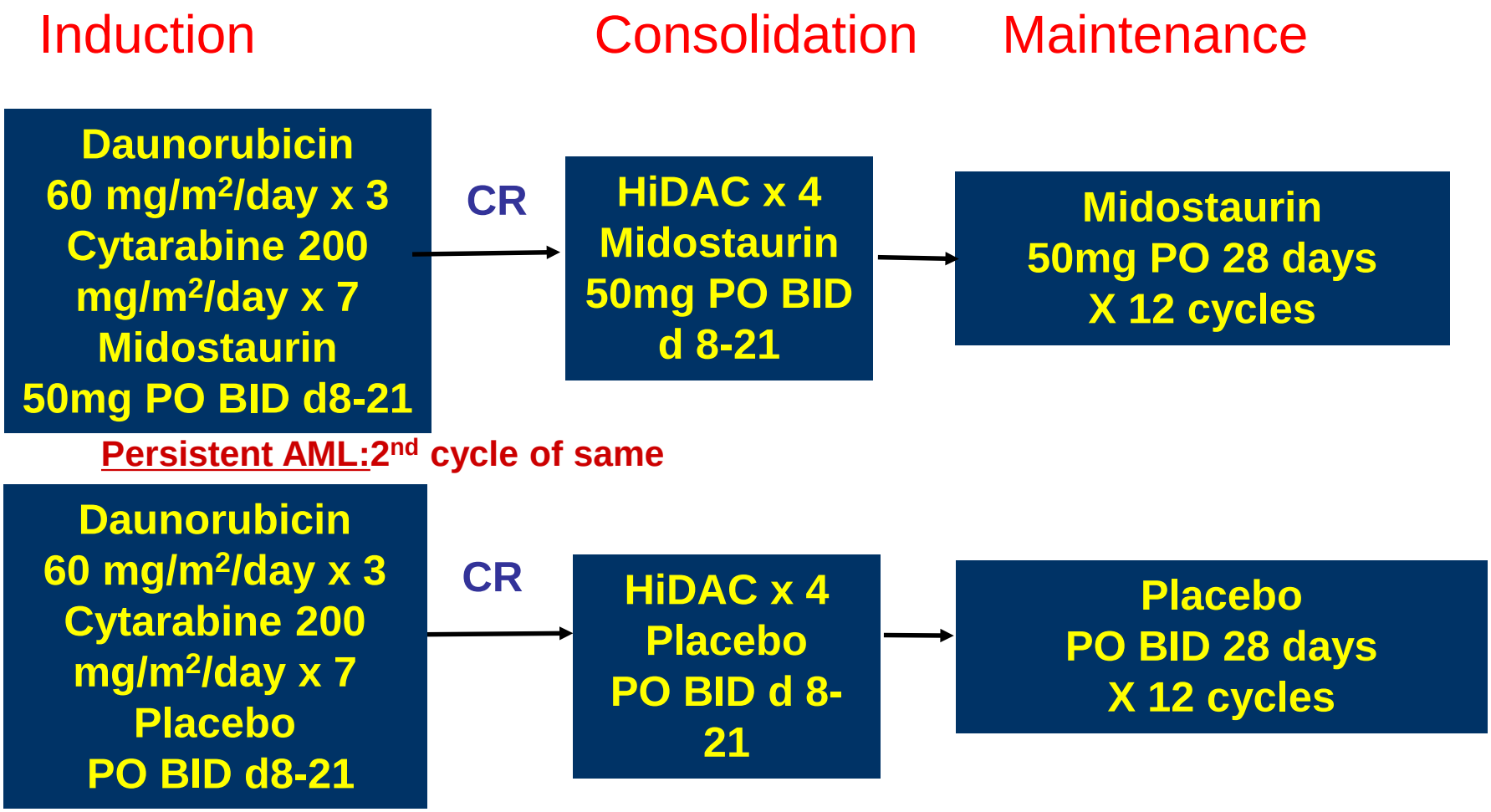
Effect:
Constitutive tyrosine phosphorylation

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



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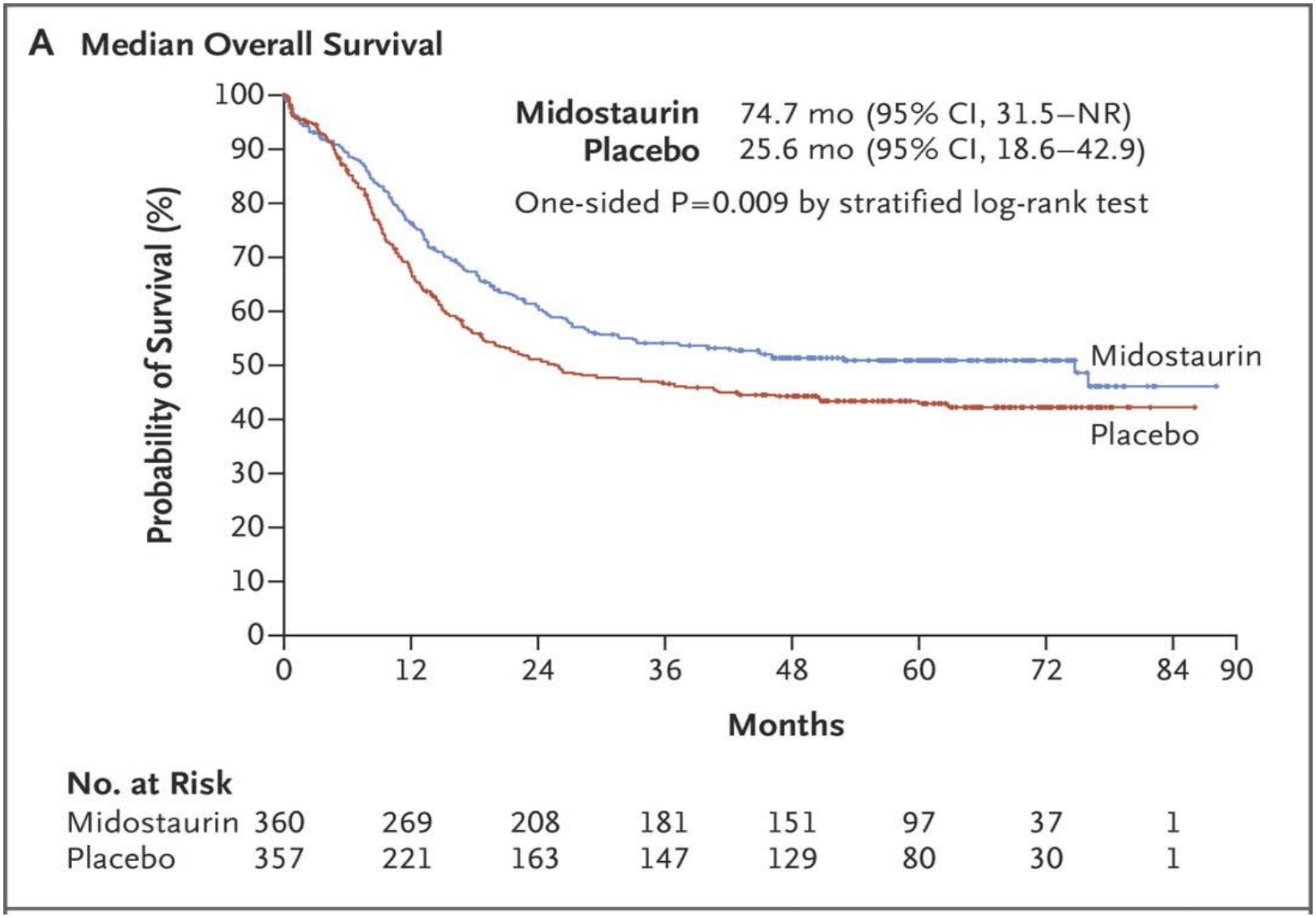
Overall Survival



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, maintenance[1]

- 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

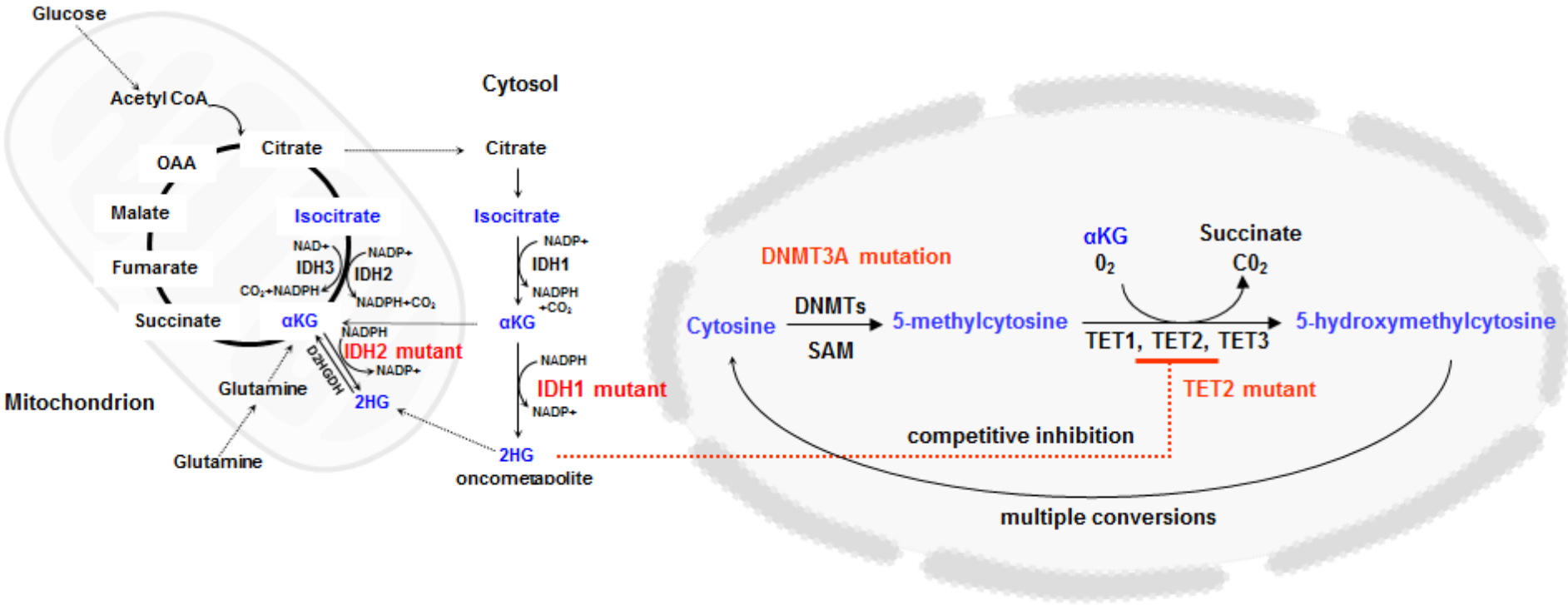
IDH 1 and IDH2 in AML

- 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 inhibitors

- Block αKG conversion to the oncometabolite D-2HG
- Reduces histone and DNA methylation
- Returns normal differentiation over weeks

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
- Treatment
    - Decadron 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)

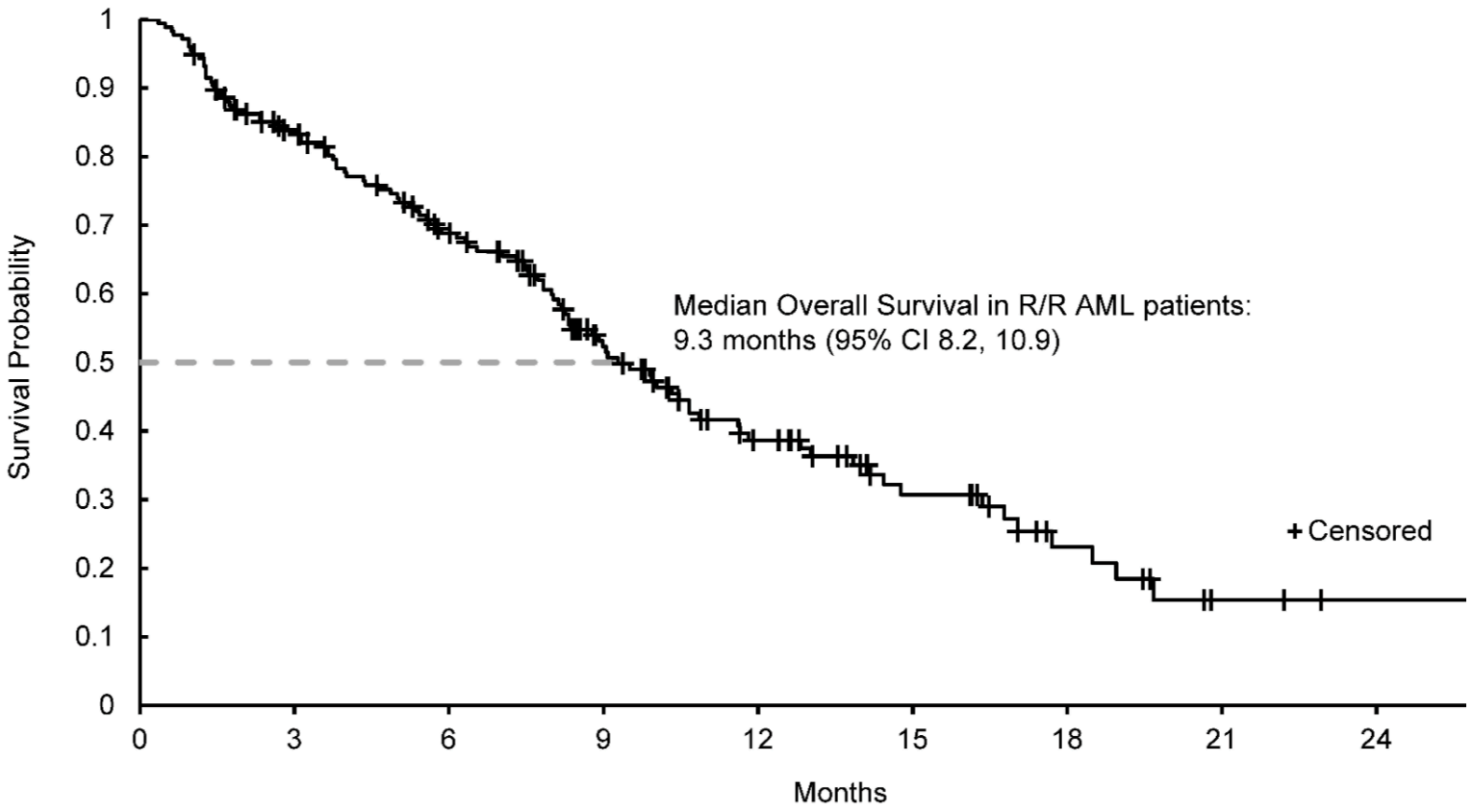
- phase I/II study of enasidenib
- Patients with AML age ≥60 with *IDH2* mutation and relapsed or refectory AML therapy

– 100mg/day effective dose based on PK and IDH blockade efficacy

- 176 patients
- RR= 40.3% duration 5.8 months

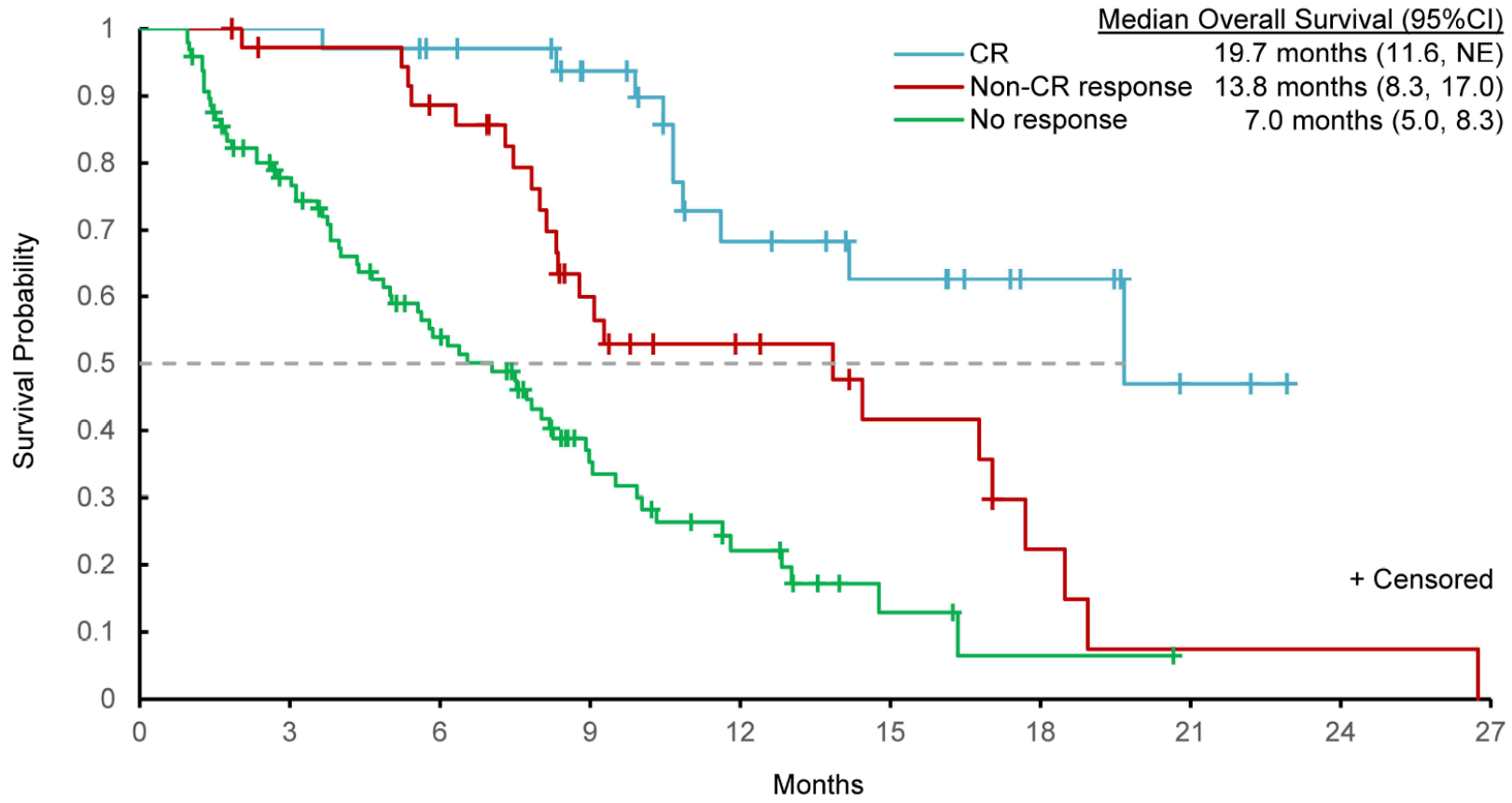
Stein & DiNardo et al, Blood 2017

Enasidenib (AG-221) OS



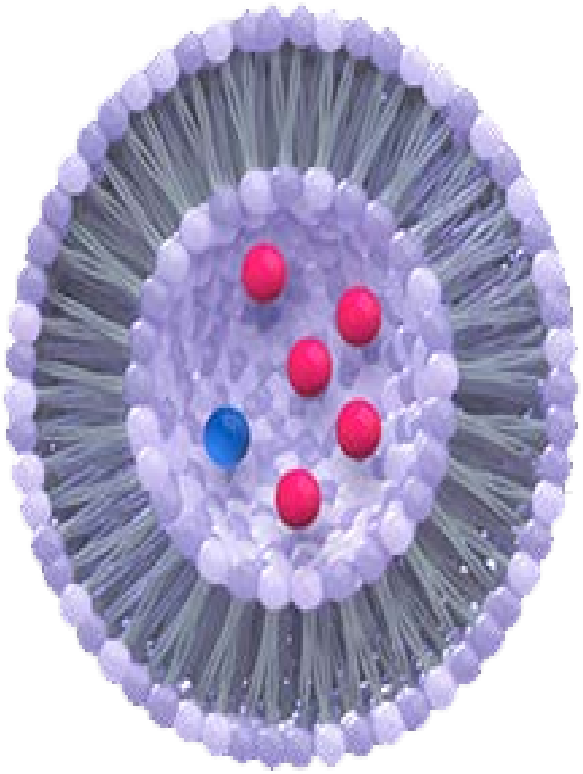
Enasidenib AG-221 OS on Response

B



Stein & Dinardo et al., Blood 2017

CPX-351 Uses a Nano-Scale Delivery

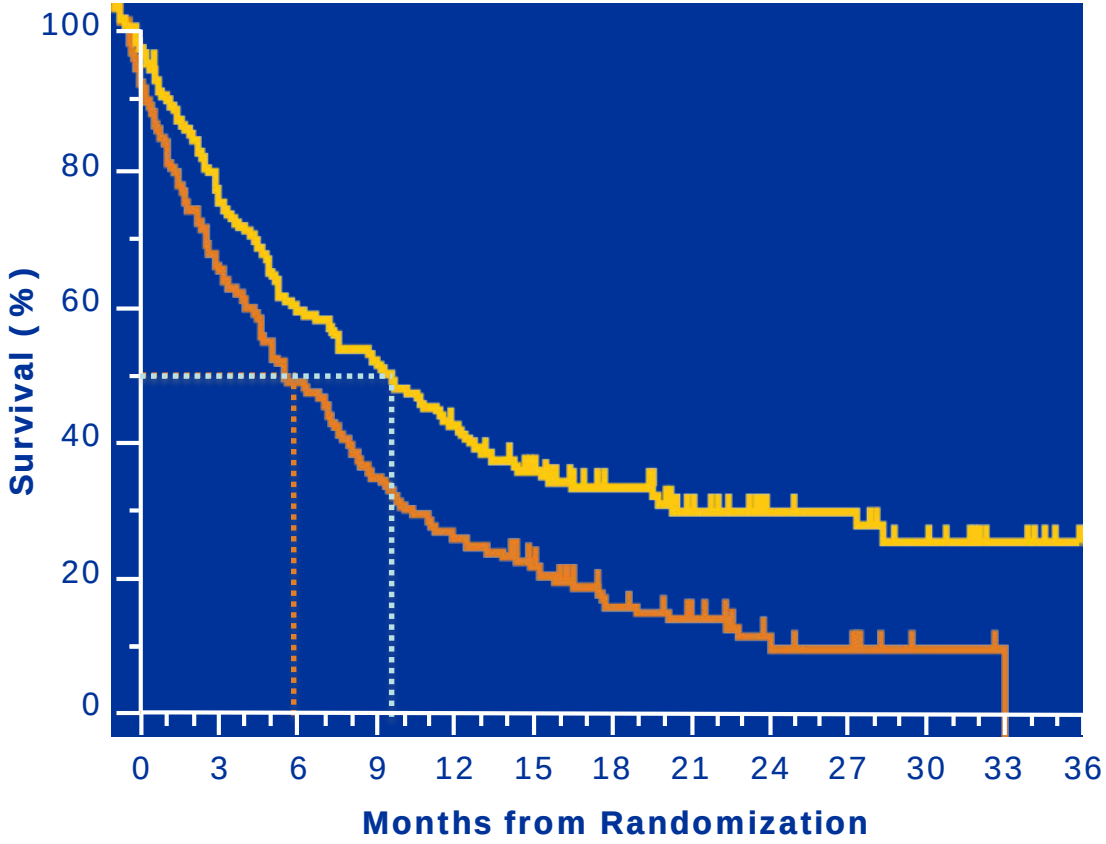


- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin
- Better BM penetration
- Phase 2 Study
  - Well tolerated
  - Improved CR, OS for s-AML

Overall Survival Was Greater in the CPX-351 Arm

Kaplan-Meier Curve for Overall Survival
ITT Analysis Population

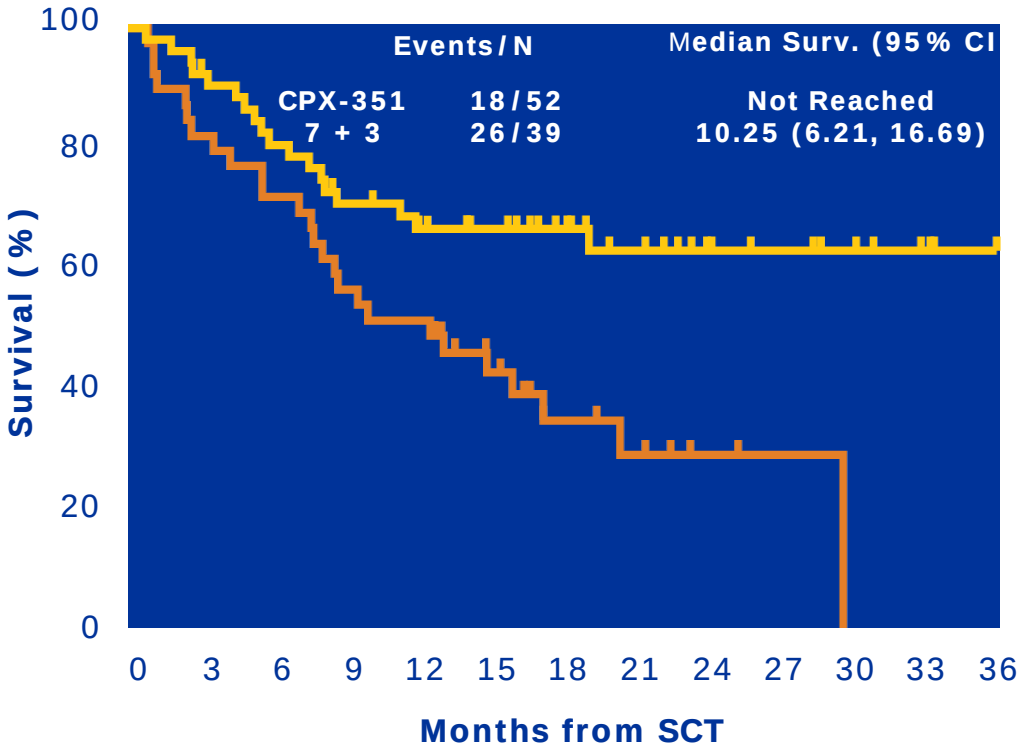
	Events/N	Median Surv. (95% CI
CPX-351	104/153	9.56 (6.60, 11.86)
7+3	132/156	5.95 (4.99, 7.75)



Hazard Ratio = 0.69
p-value = 0.005

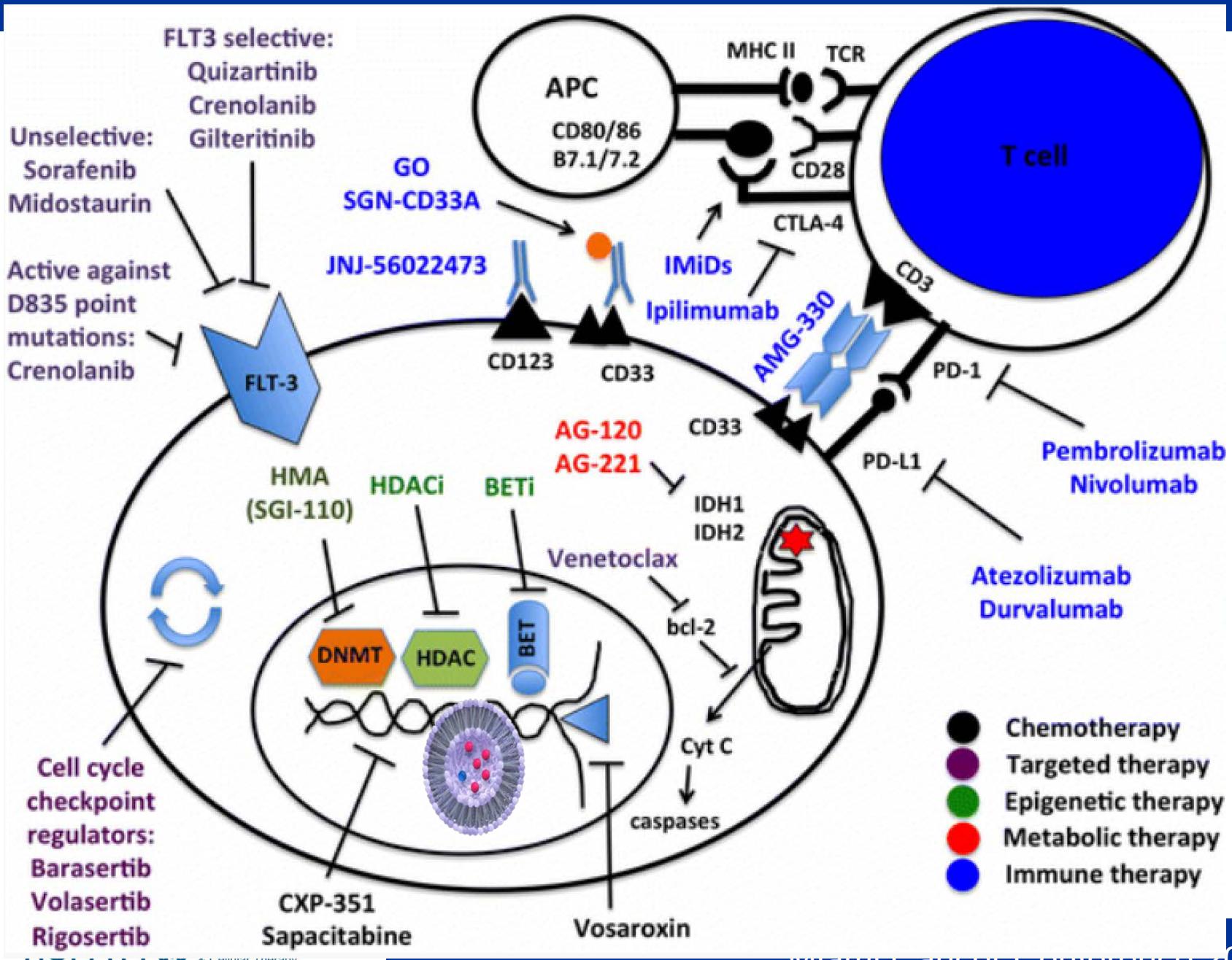
CPX-351	153	122	92	79	62	46	34	21	16	11	5	1
7+3	156	110	77	56	43	31	20	12	7	3	2	0

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



Hazard Ratio = 0.46
p-value = 0.0046

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


FLT3 selective:
Quizartinib
Crenolanib
Gilteritinib
Unselective:
Sorafenib
Midostaurin
Active against
D835 point
mutations:
Crenolanib
FLT-3
APC
CD80/86
B7.1/7.2
MHC II
TCR
CD28
T cell
CTLA-4
CD3
GO
SGN-CD33A
JNJ-56022473
IMiDs
Ipilimumab
AMG-330
CD123
CD33
PD-1
PD-L1
Pembrolizumab
Nivolumab
Atezolizumab
Durvalumab
AG-120
AG-221
IDH1
IDH2
HMA
(SGI-110)
HDACi
BETi
Venetoclax
bcl-2
DNMT
HDAC
BET
Cyt C
caspases
Cell cycle
checkpoint
regulators:
Barasertib
Volasertib
Rigosertib
CXP-351
Sapacitabine
Vosaroxin
Chemotherapy
Targeted therapy
Epigenetic therapy
Metabolic therapy
Immune therapy

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

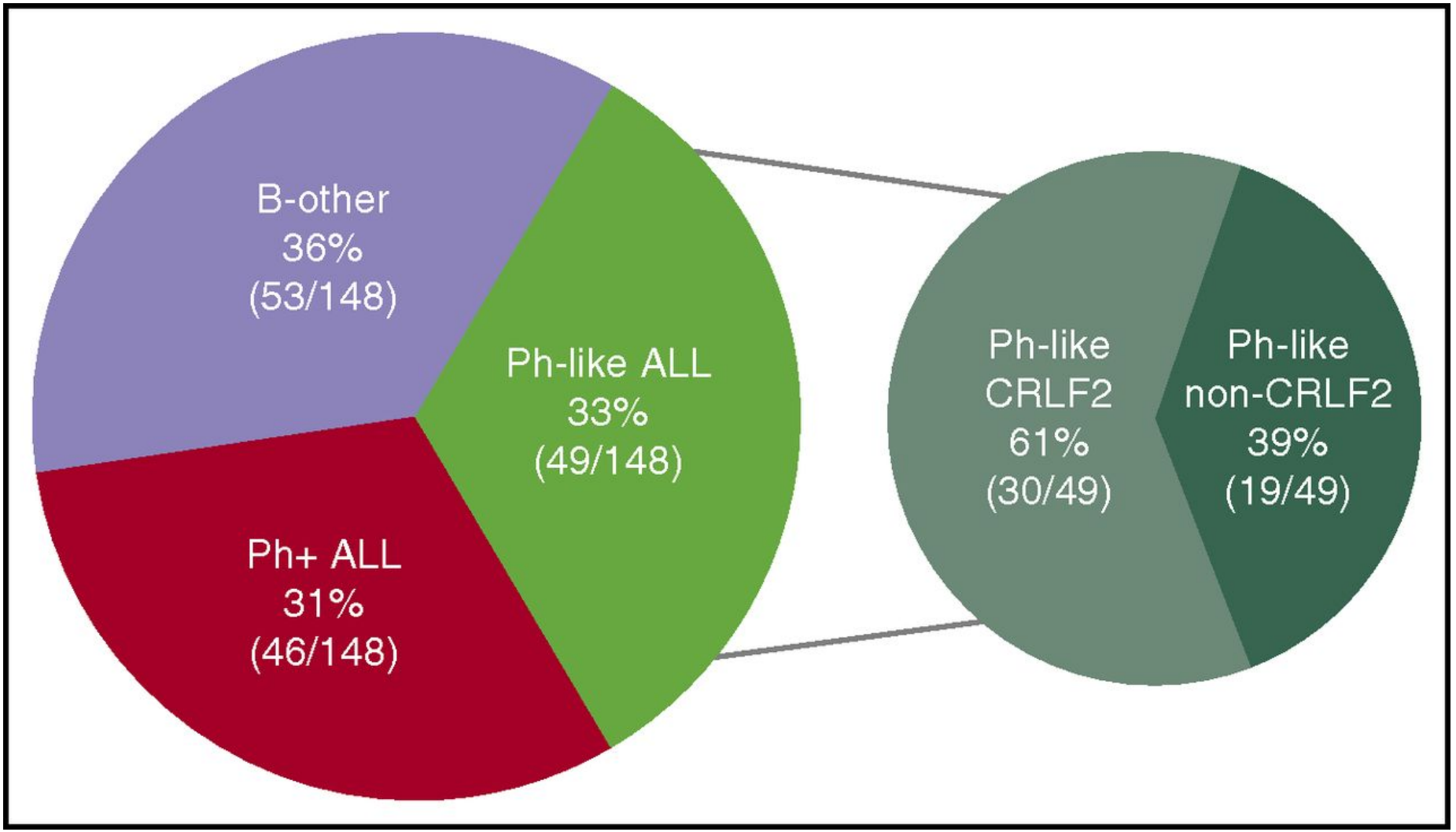
- Age
  - Children
  - Adolescents and Young Adults (15-39)
  - Older (≥40)

- 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)



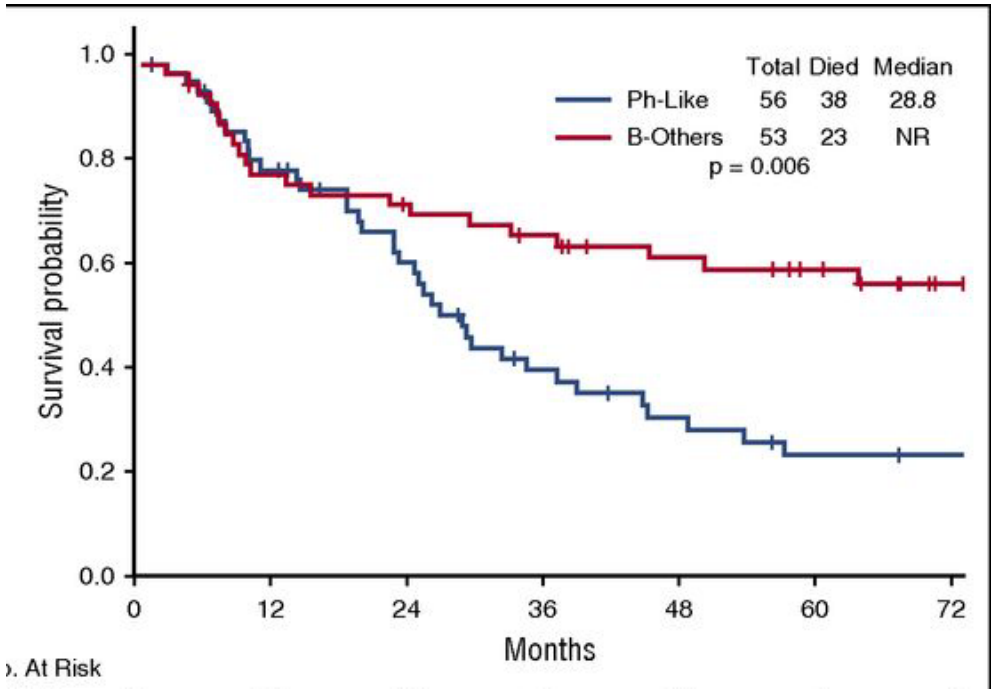
Nitin Jain et al.
Blood 2017;129:572-581

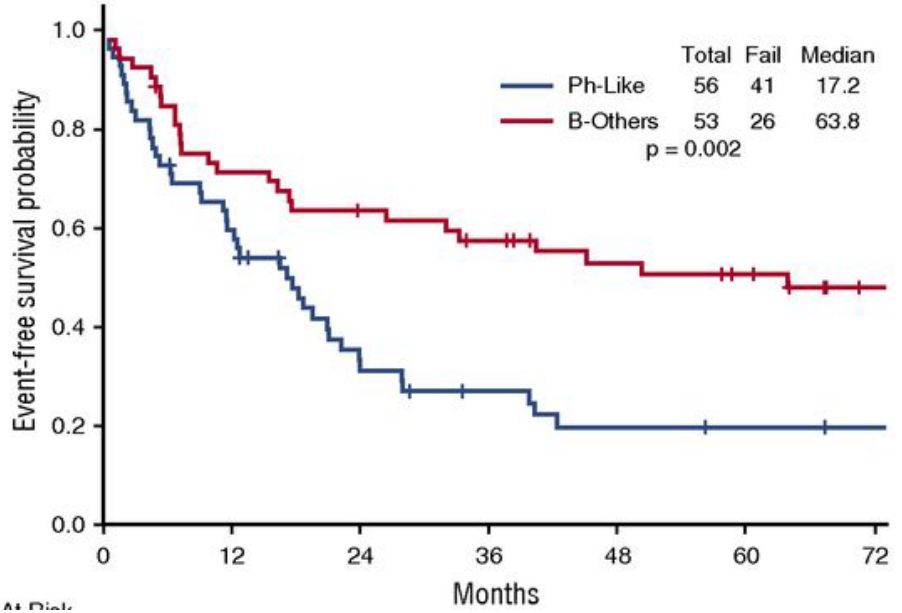
Ph-like ALL

- 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

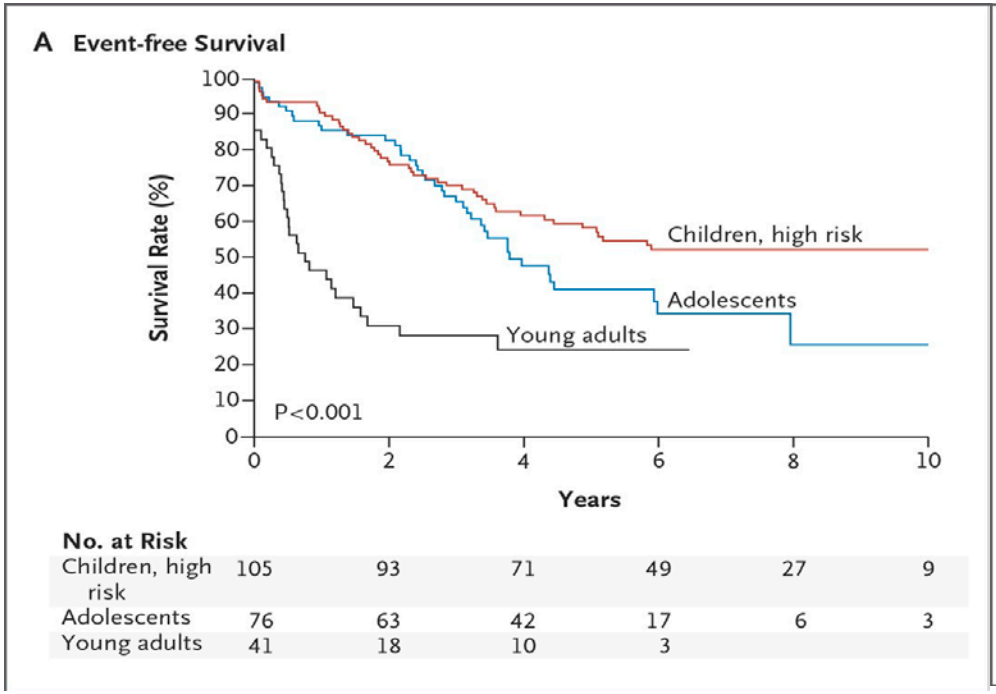
Ph-like ALL and B-other ALL: OS and EFS



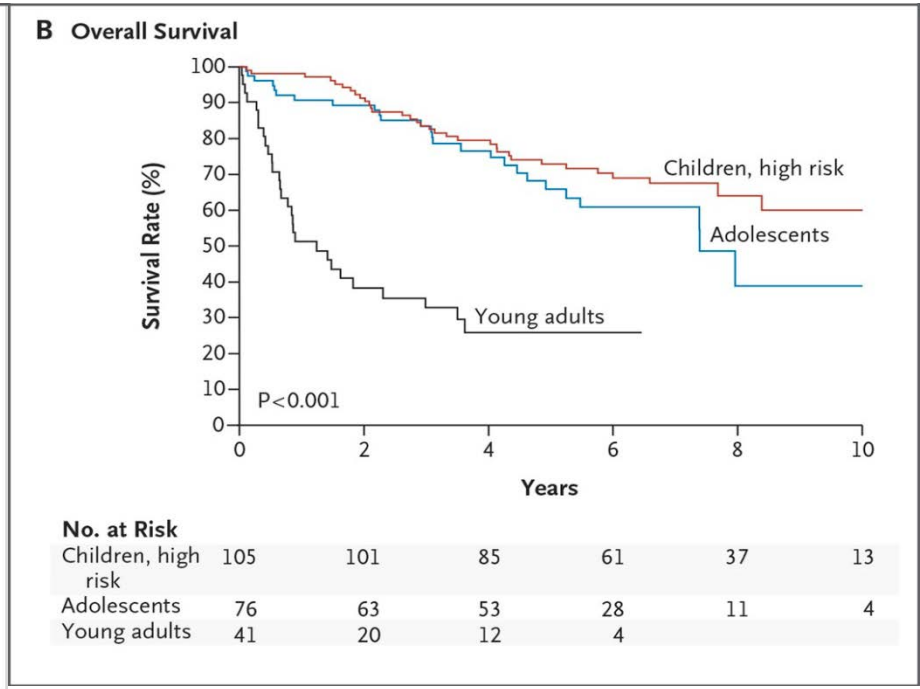


Nitin Jain et al. Blood 2017;129:572-581

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



No. at Risk						
Children, high risk	105	93	71	49	27	9
Adolescents	76	63	42	17	6	3
Young adults	41	18	10	3		



No. at Risk						
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

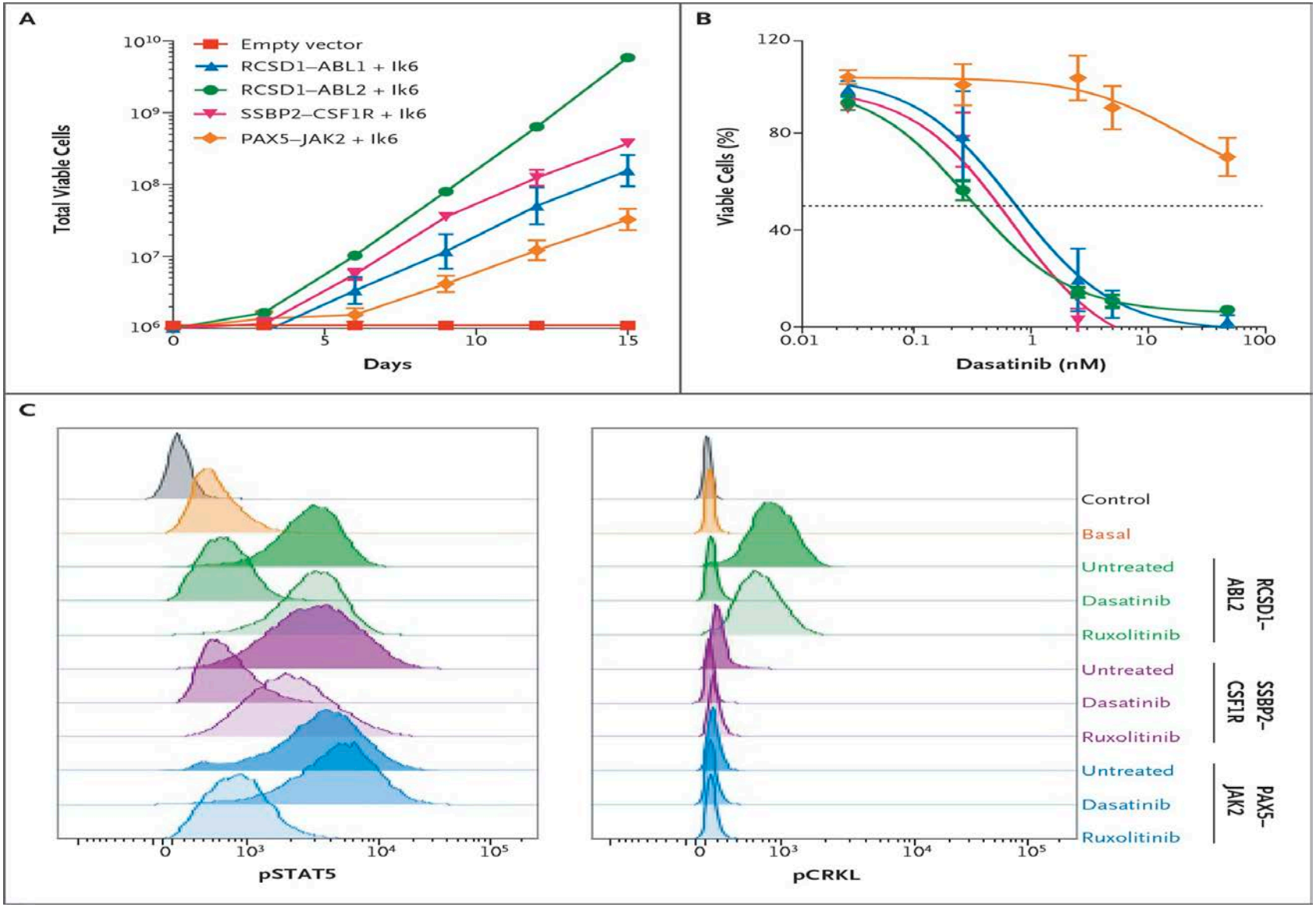
Kinase Fusions Identified in Ph-like Acute Lymphoblastic Leukemia

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

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

* 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



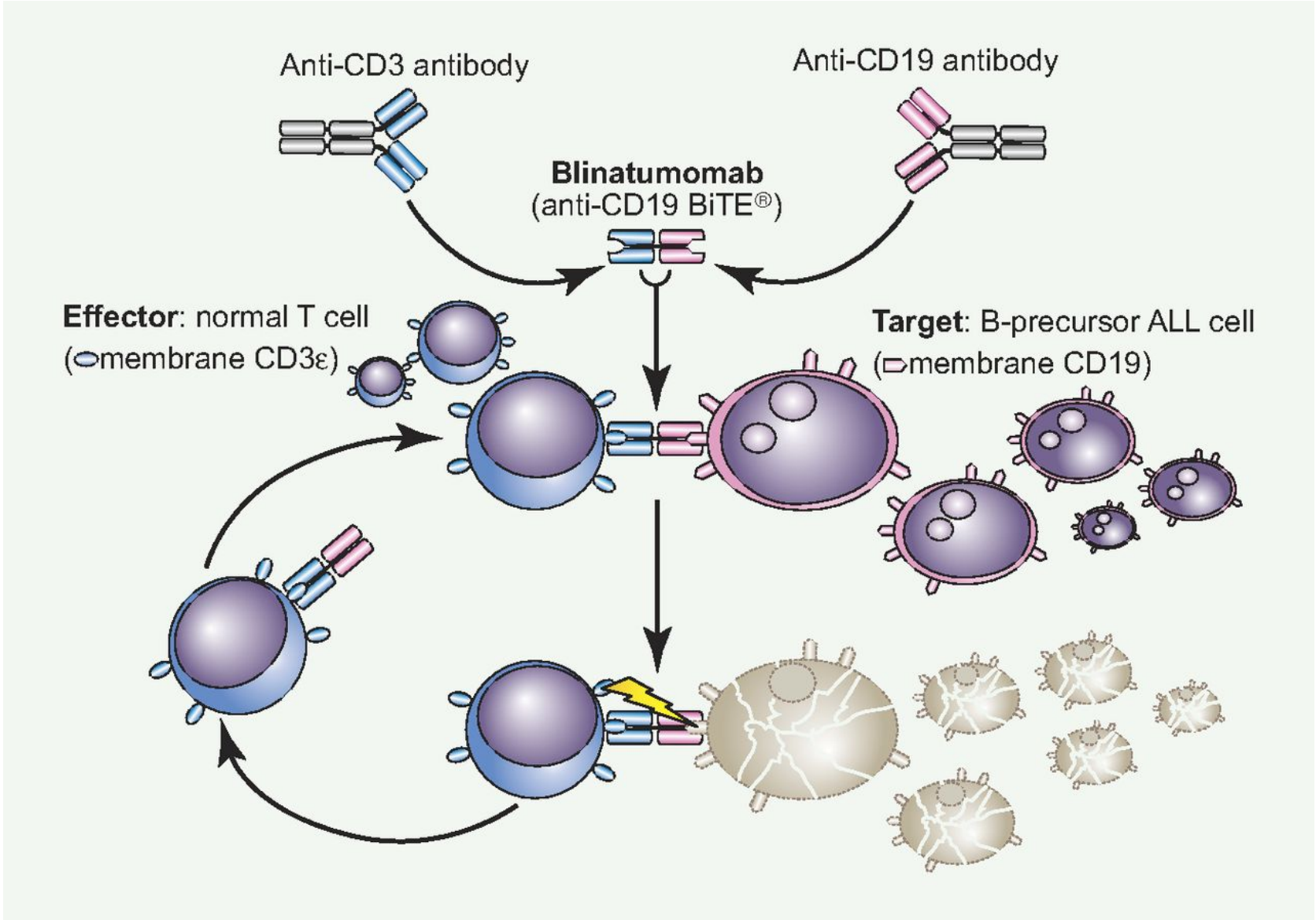
Roberts KG et al.
N Engl J Med 2014;371:1005-1015

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



Bassan R Blood 2012;120:5094-5095

Blinatumomab V Chemotherapy

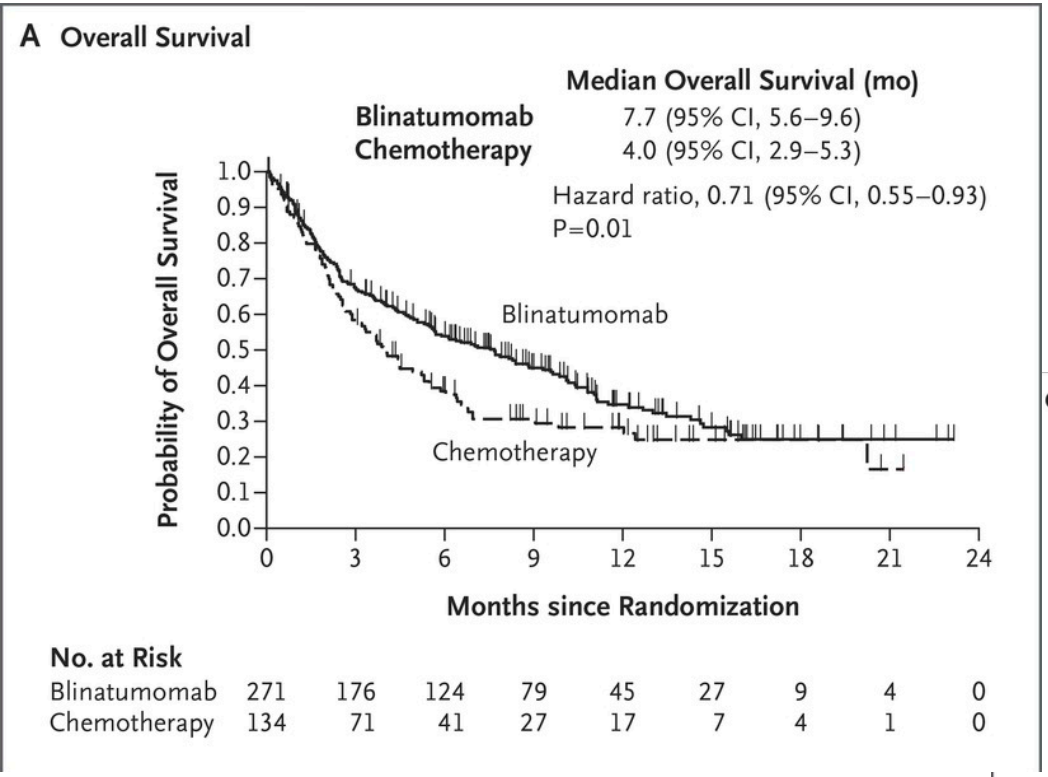
- Phase 3, multi-institution
- 405 patients- Blin-271, Chemo-134
- Responses

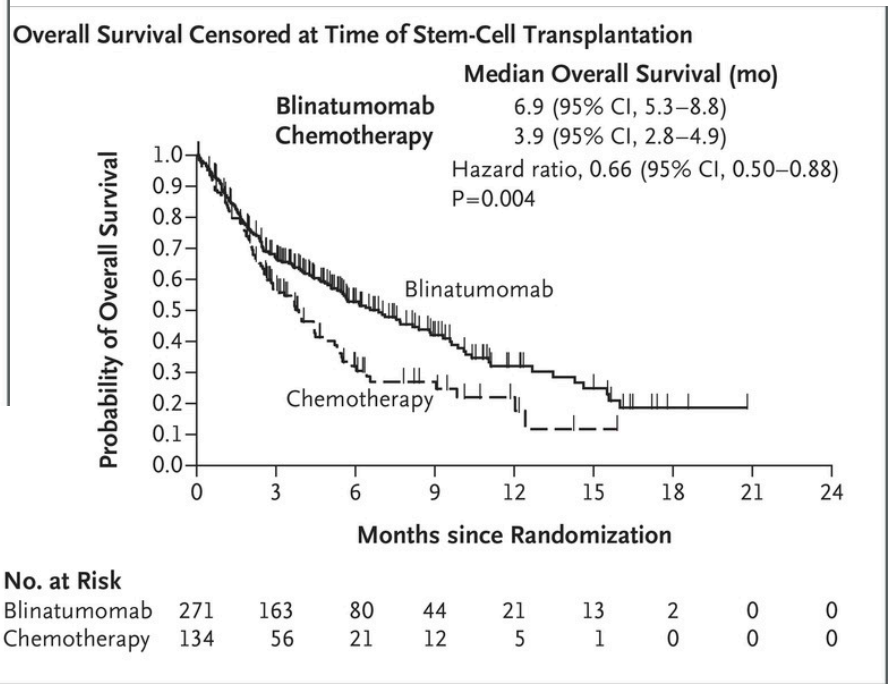
Responses	Blin	Chemo
– CR	34%	16%
– OR	44%	25%
– EFS 6 month	31%	12%
– OS	7.7m	4.0m

  – 24% proceeded to allo HCT

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

Blinatumomab: Efficacy End Points.





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

Inotuzumab vs Chemo

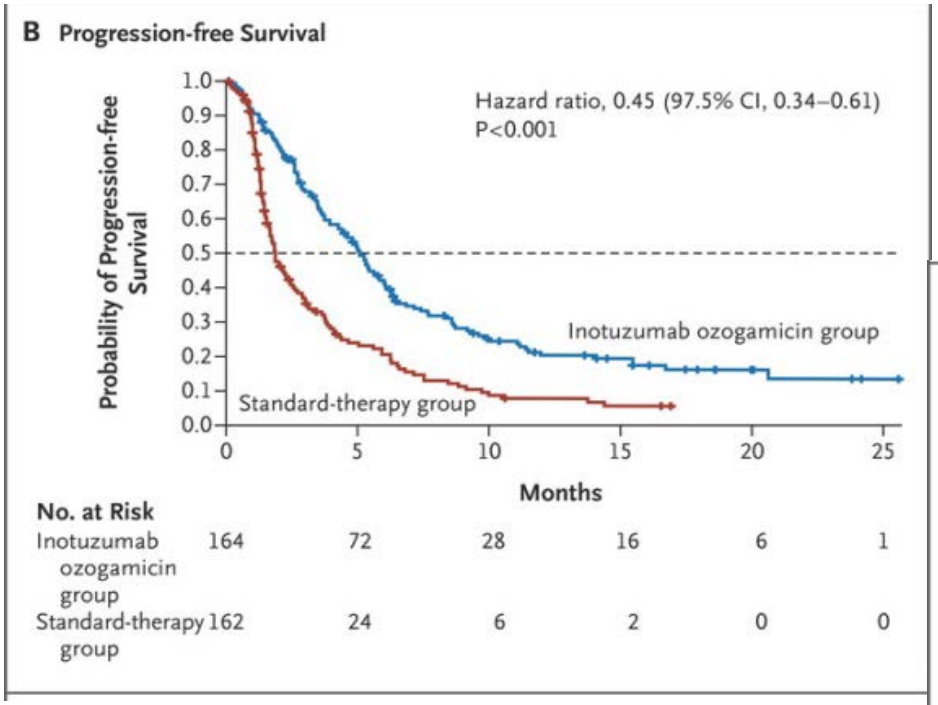
- Anti-CD22 moAb + calicheamicin
- Ino v chemo for RR ALL
- 326 patients (218 ITT)

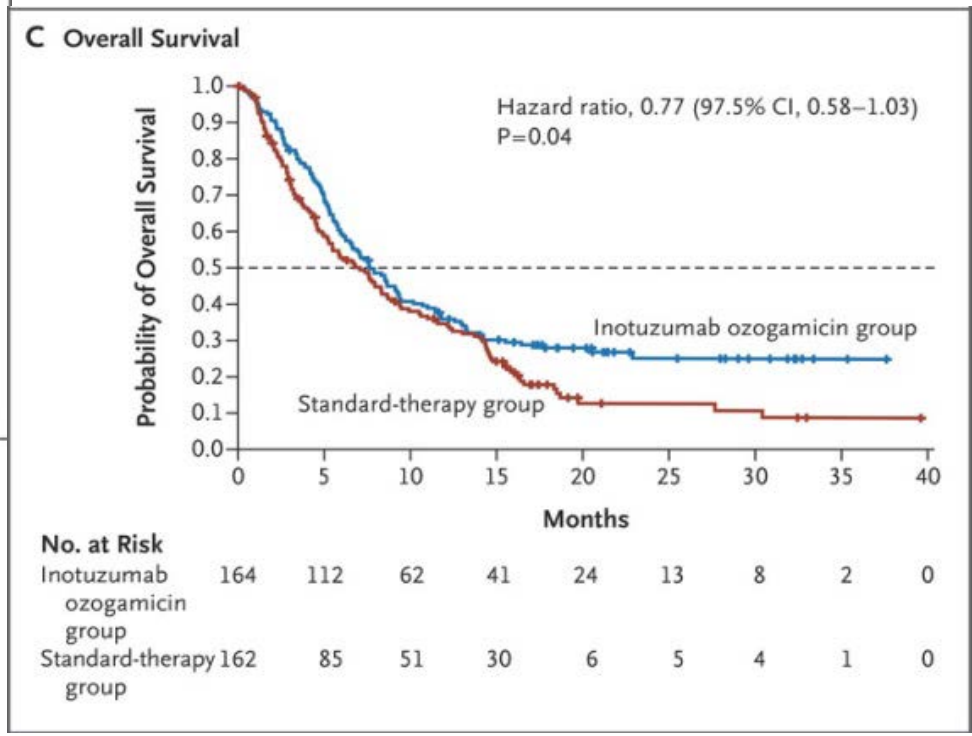
Responses	Ino	Chemo
CR/CRi	80.7%	29.4%
MRD	78.4%	28.1%
PFS	5.8m	1.8m
OS	7.7m	6.7m

- VOD occurred in 11% of Ino patatients

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

Inotuzumab: PFS, and OS





Kantarjian HM et al.
N Engl J Med 2016. DOI: 10.1056/NEJMoa1509277

Targeting ALL with CAR-Ts

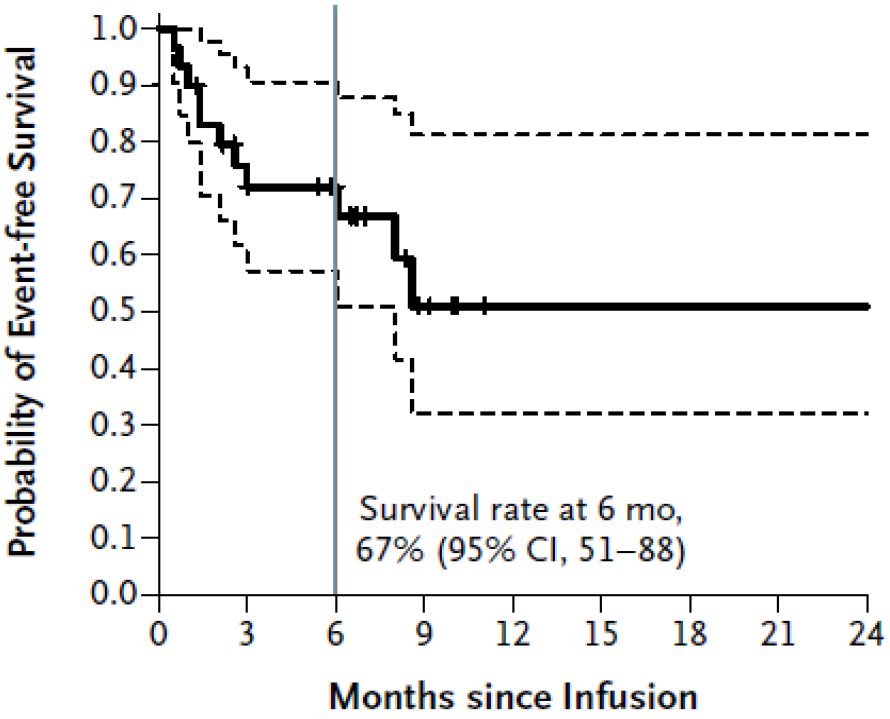
- Re-induction in R/R disease
- Multiple companies with different constructs
  - Novartis with first FDA filing for Peds, AYA
- Requires specialty center
  - Apheresis
  - Cell processing/GMP (Company driven)
  - Clinical team
    - Heme/Onc
    - Neurology
  - ICU care
  - Guidelines for Cytokine Release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

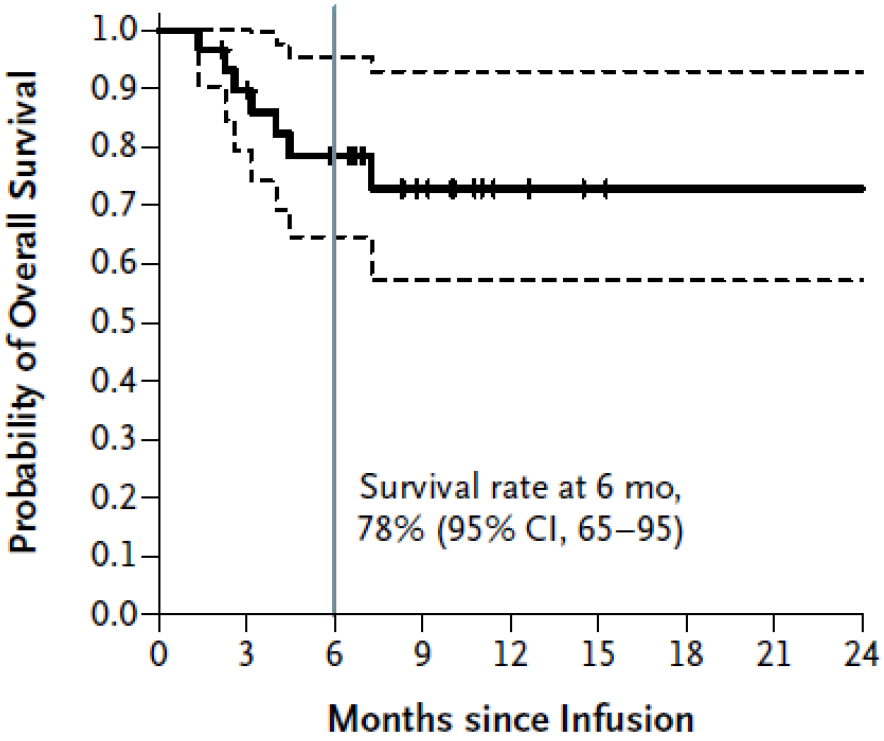
CAR-T

- CD19 directed CAR-T (tisagenleucel)
- Dose escalation 0.76 -20.6 x 10^6 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

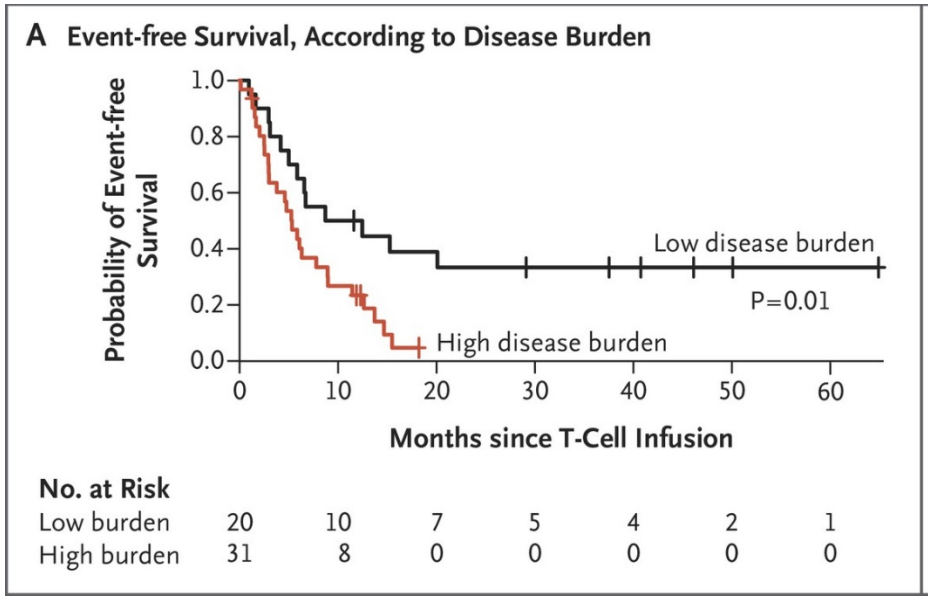
CTL019 EFS and OS

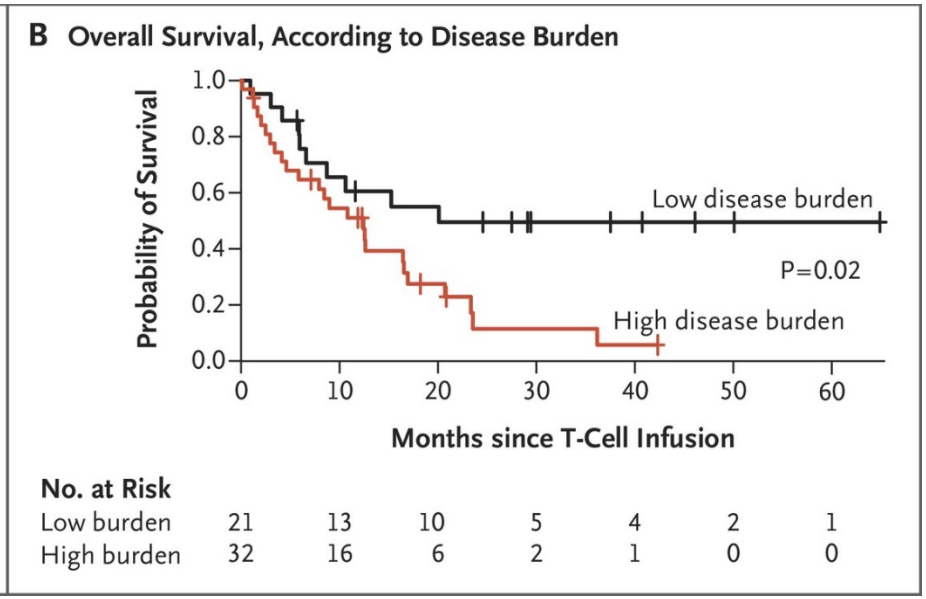




Maude S et al., NEJM 2014

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





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

HCT in ALL

- In adults
  - AYA with high risk features
  - 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
- Mutations are targetable in both diseases