UC San Diego Health

How I Treat Acute Lymphoblastic Leukemia in the Era of BiTEs, CARs, and MRD

Oncology Updates: Current Best Practices and Future Directions Webinar Series

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Disclosures:

Advisory Boards: Astellas Bio, Pfizer, Gilead, Rigel Pharma, CITI Biopharma, Autolus, Jazz, Daiichi-Sankyo

Safety and Monitoring Committee: Kura Oncology

Demographics of San Diego County, California

- In San Diego County, California, population is 42% non-Hispanic White and 35% Hispanic.
  - 26.6 cases ALL/million for Latinos
  - 16 cases ALL/million for Non-Hispanic Whites
- 66% higher incidence in Latinos in USA, enriched in Ph like B-ALL.
- In children, 57 cases ALL/million in Mexico City, highest incidence in the world.

AYA WITH PHILADELPHIA NEGATIVE B-ALL

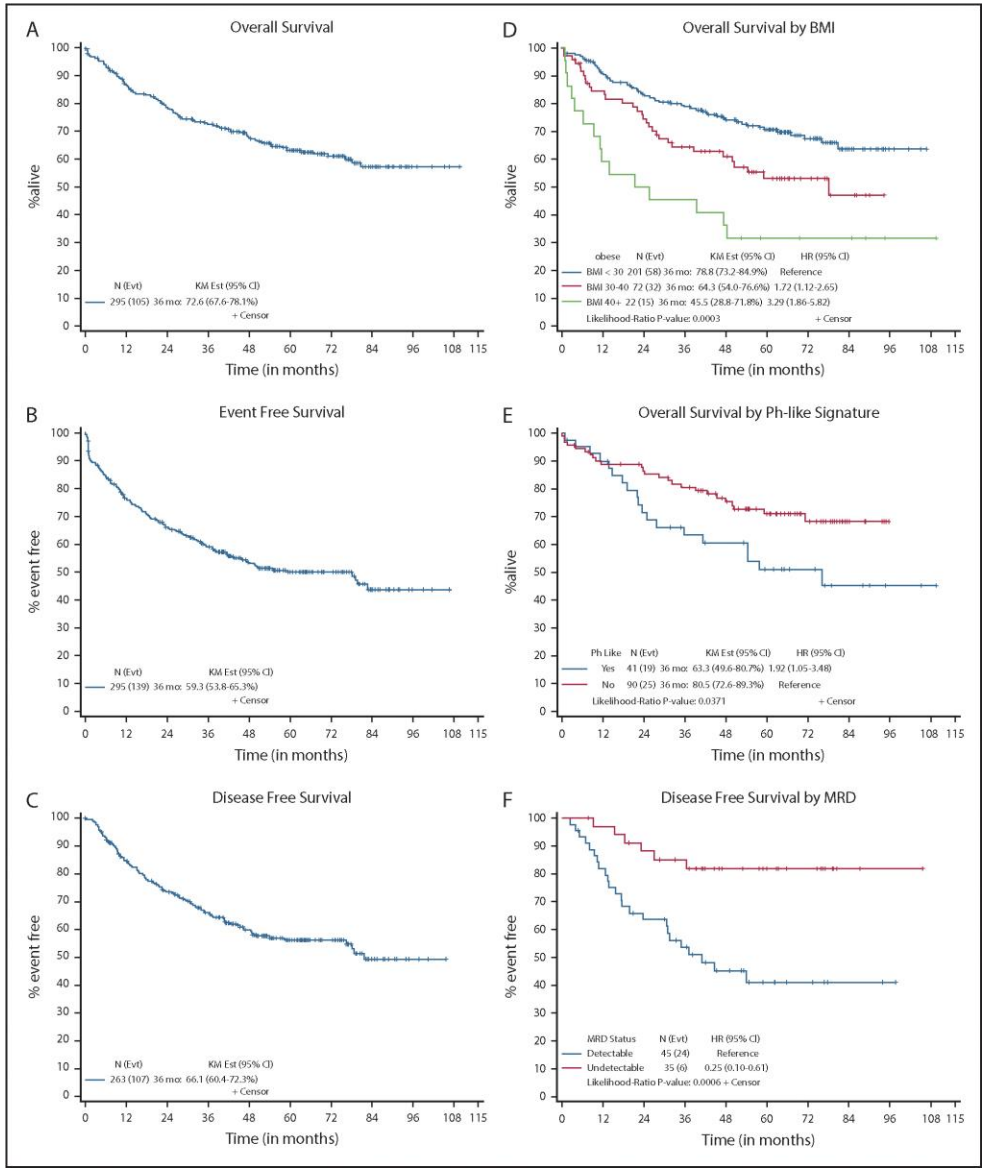
- Pediatric and AYA protocols, Rationale:

- SEER database survival of ALL based on age at dx:
  - 17: 75% survival
  - 20: 48% survival
  - 70: 15% survival

- US CALGB 10403 study:
  - EFS in the 296 patients treated at median follow-up of 28 months was double that of patients not treated on pediatric/AYA
  - Protocols. About 2/3 long term cures, and they are finding that many of the failures have the high risk Ph like genetic profile.
  - About 2-3% treatment related mortality.
  - Heavy on PEG-asparaginase, intrathecal chemotherapy.

- Ph like ALL: particularly poor prognosis. About 25% of patients between 20-40 have this profile, less common in patients >40. About 60% have mutations in CRLF2, 40% have other mutations including Jak2 mutations. Striking incidence amongst Latinos.

A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403



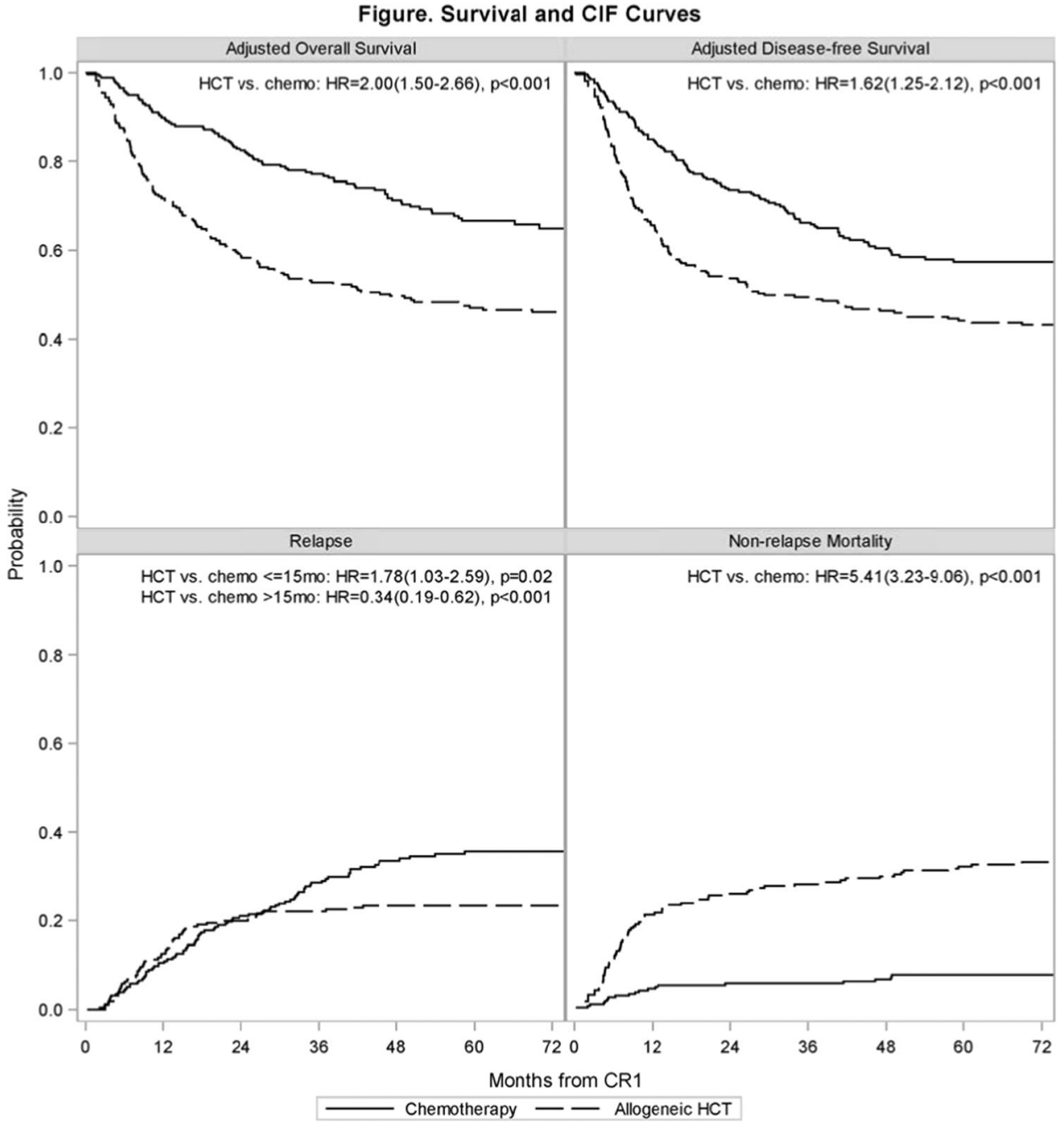
Ph like: 41/131 = 31% of pts with data

----> 11% Ph like

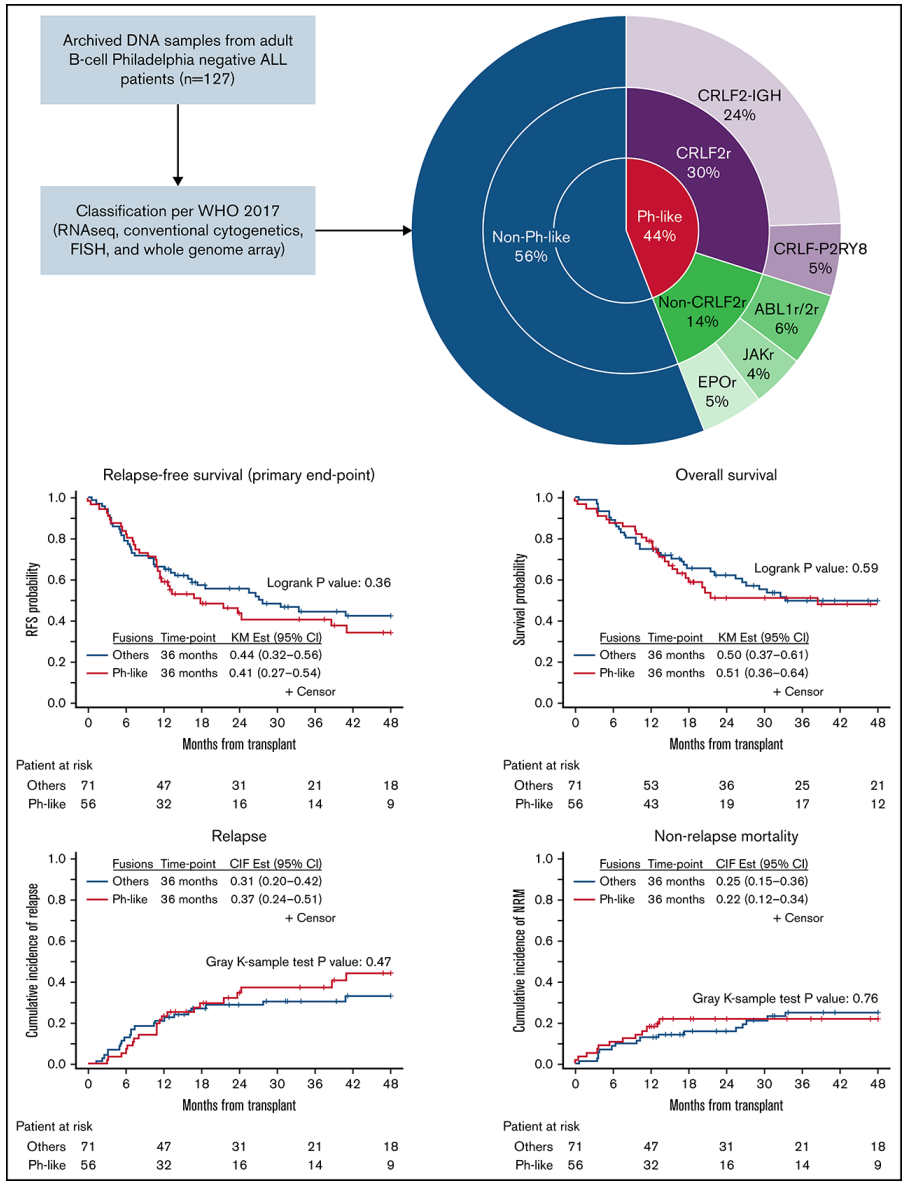
----> 46% Ph like

MRD at end of induction
Detectable means >10^-4

Superior survival with pediatric-style chemotherapy compared to myeloablative allogeneic hematopoietic cell transplantation in older adolescents and young adults with Ph-negative acute lymphoblastic leukemia in first complete remission: analysis from CALGB 10403 and the CIBMTR



Outcomes of allogeneic hematopoietic cell transplantation in adults with fusions associated with Ph-like ALL



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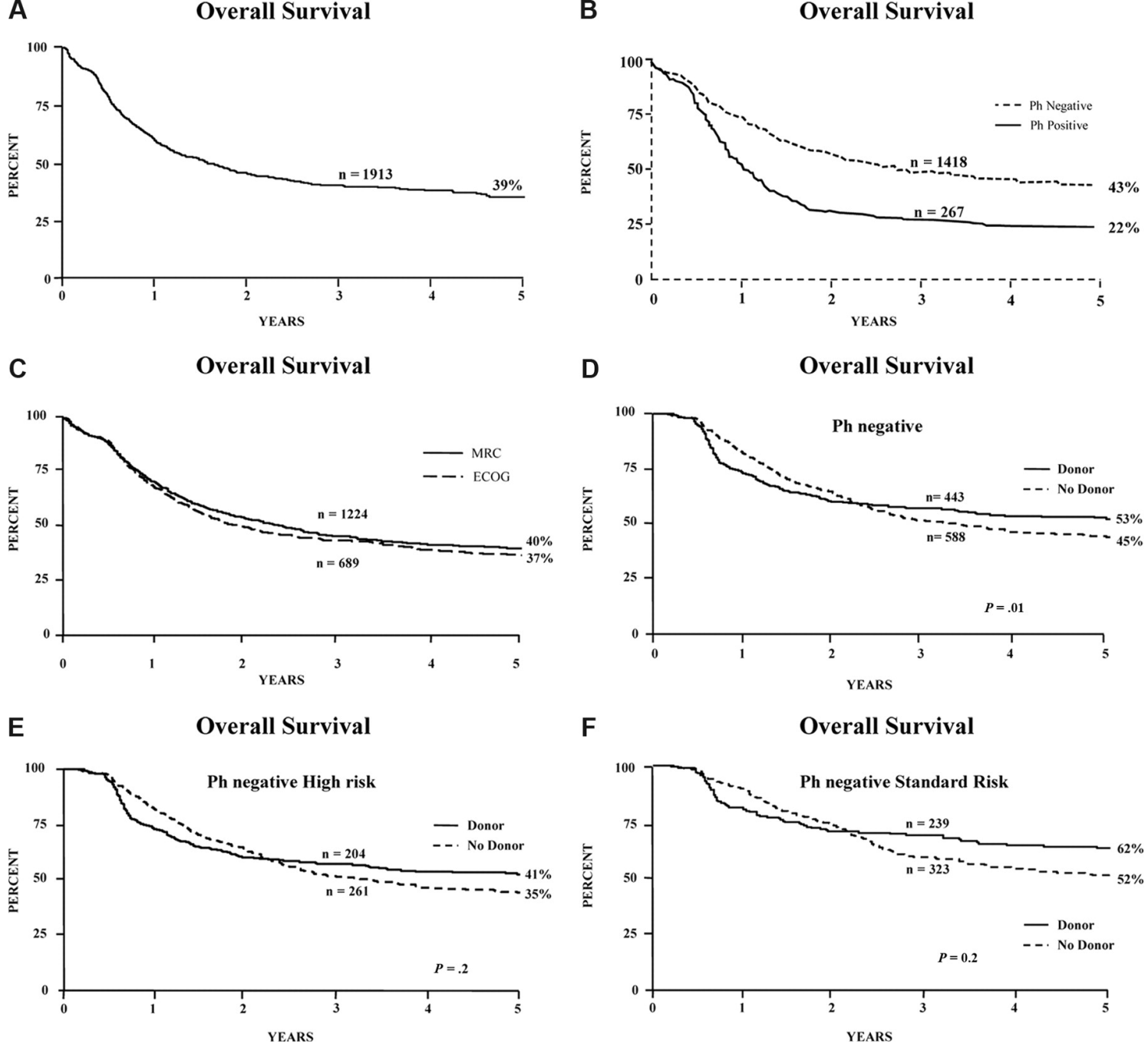
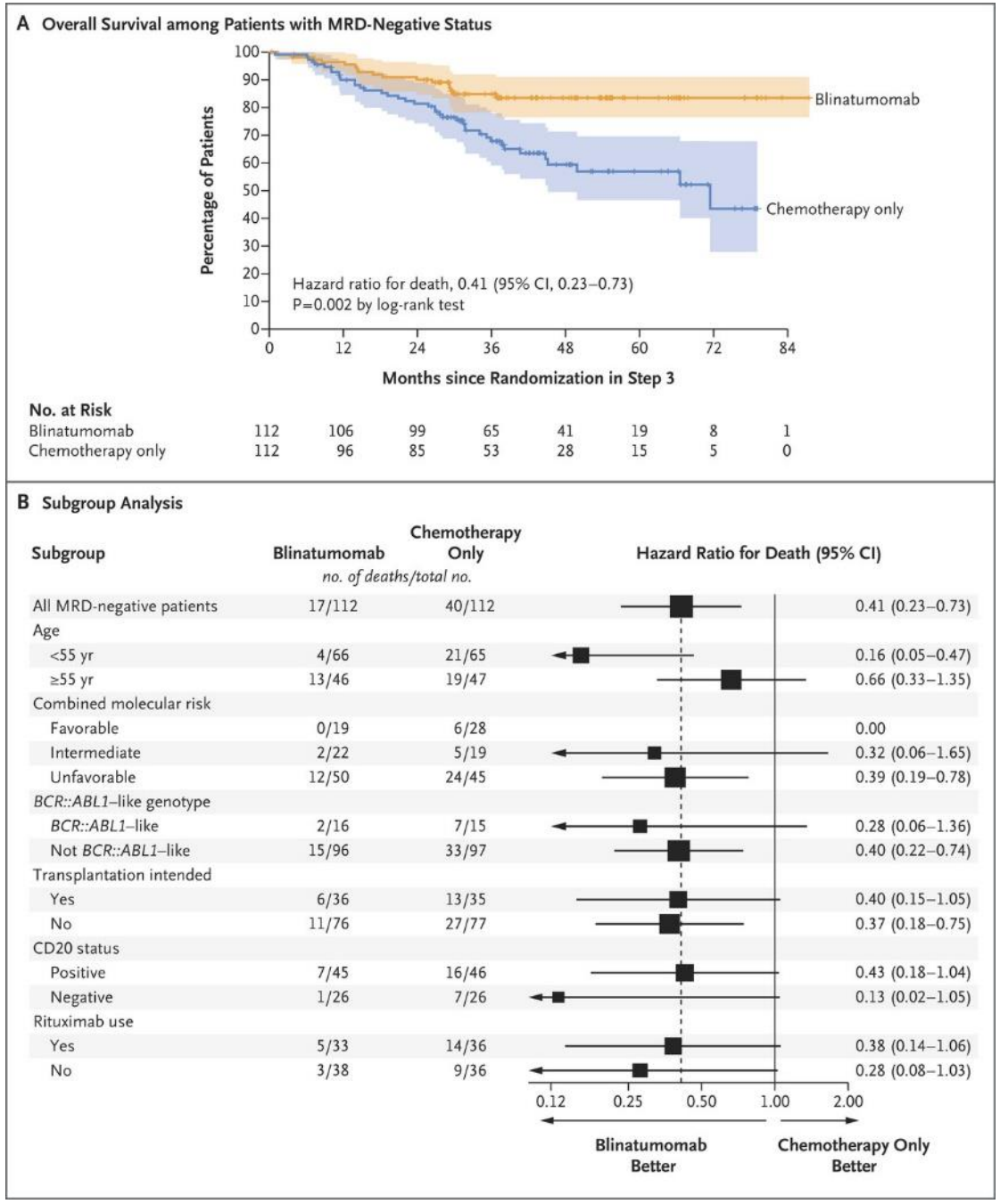
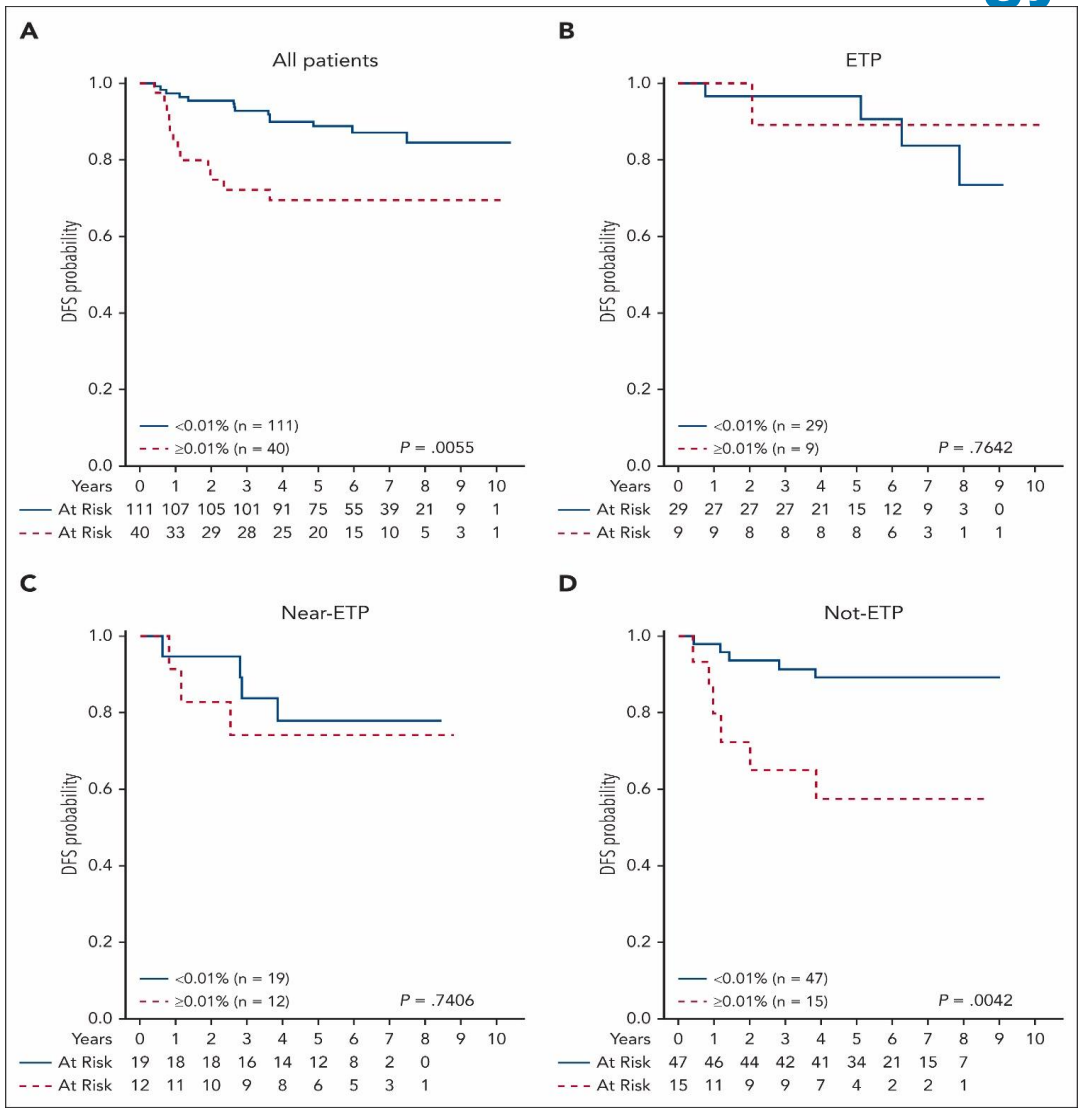
ECOG 2993:


A
Overall Survival
PERCENT
YEARS
n = 1913
39%
B
Overall Survival
Ph Negative
Ph Positive
n = 1418
43%
n = 267
22%
C
Overall Survival
MRC
ECOG
n = 1224
40%
n = 689
37%
D
Overall Survival
Ph negative
Donor
No Donor
n= 443
53%
n= 588
45%
P = .01
E
Overall Survival
Ph negative High risk
Donor
No Donor
n = 204
41%
n = 261
35%
P = .2
F
Overall Survival
Ph negative Standard Risk
n = 239
62%
n = 323
52%
Donor
No Donor
P = 0.2



- Blinatumomab for MRD-Negative Acute Lymphoblastic Leukemia in Adults
- 14% Ph-like in this MRD Neg cohort
- MRD measured at end of course II, intensification

Prognostic significance of ETP phenotype and minimal residual disease in ALL: A Children's Oncology Group study



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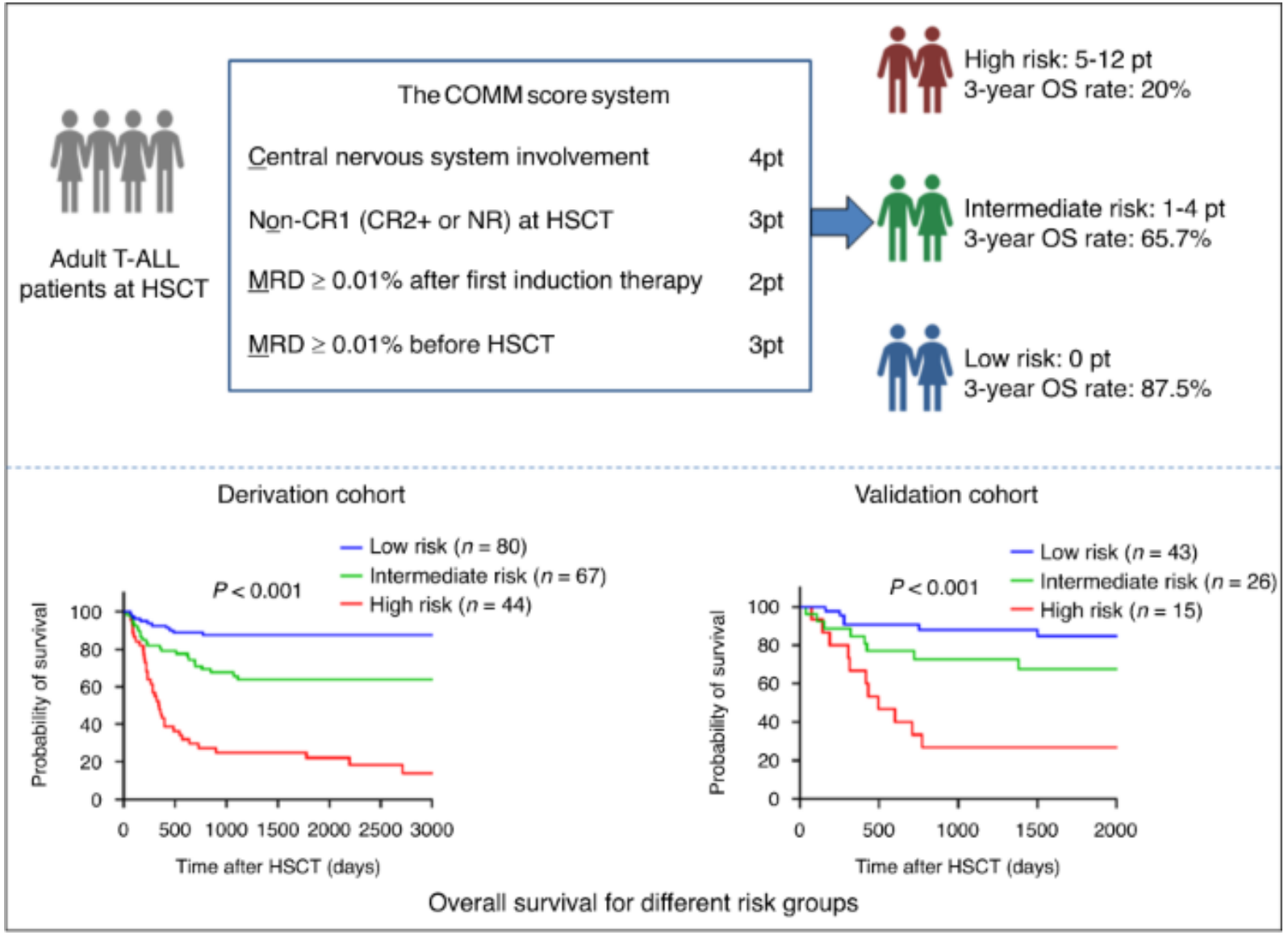
Prognostic Score for Allo SCT for Adult T-ALL



- In pediatric protocols, EOI MRD is not used for risk stratification in ETP-ALL.

Adults with Ph positive B-cell ALL

- Formerly dismal prognosis. Of note, incidence of Ph chromosome in adults dramatically increases with age and is present in 50% of patients >60 with B-cell ALL.

- ECOG 2993: DVP chemotherapy, multicourse, followed by allo SCT or not

- 22% long term survival in all adults with Ph positive B-ALL treated in pre-imatinib era. Virtually no long term survivors over age 50.

- 38% long term survival in all adults with Ph positive B-ALL treated in the imatinib era, and more patients went to allo transplant on the imatinib arm.

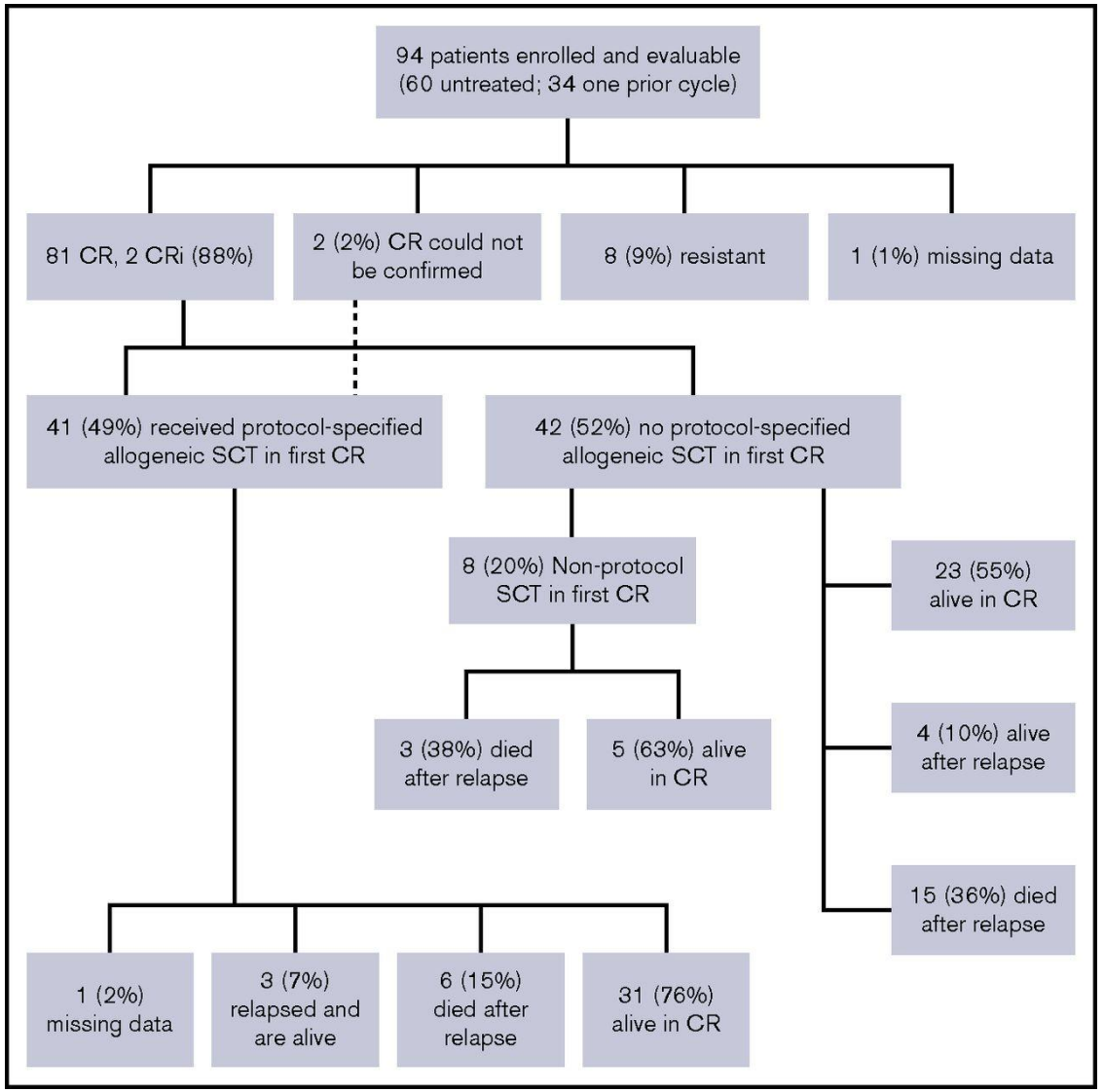
SWOG 0805

- Hyper CVAD plus dasatinib followed by allo SCT if 10/10 donor or maintenance chemotherapy if no 10/10 donor.

- 94 patients, 41 went on to transplant.

- OS at 3 years: 69%
  Advantage to transplant arm by about 20%, excellent outcomes overall.

US intergroup study of chemotherapy plus dasatinib and allogeneic stem cell transplant in Philadelphia chromosome positive ALL



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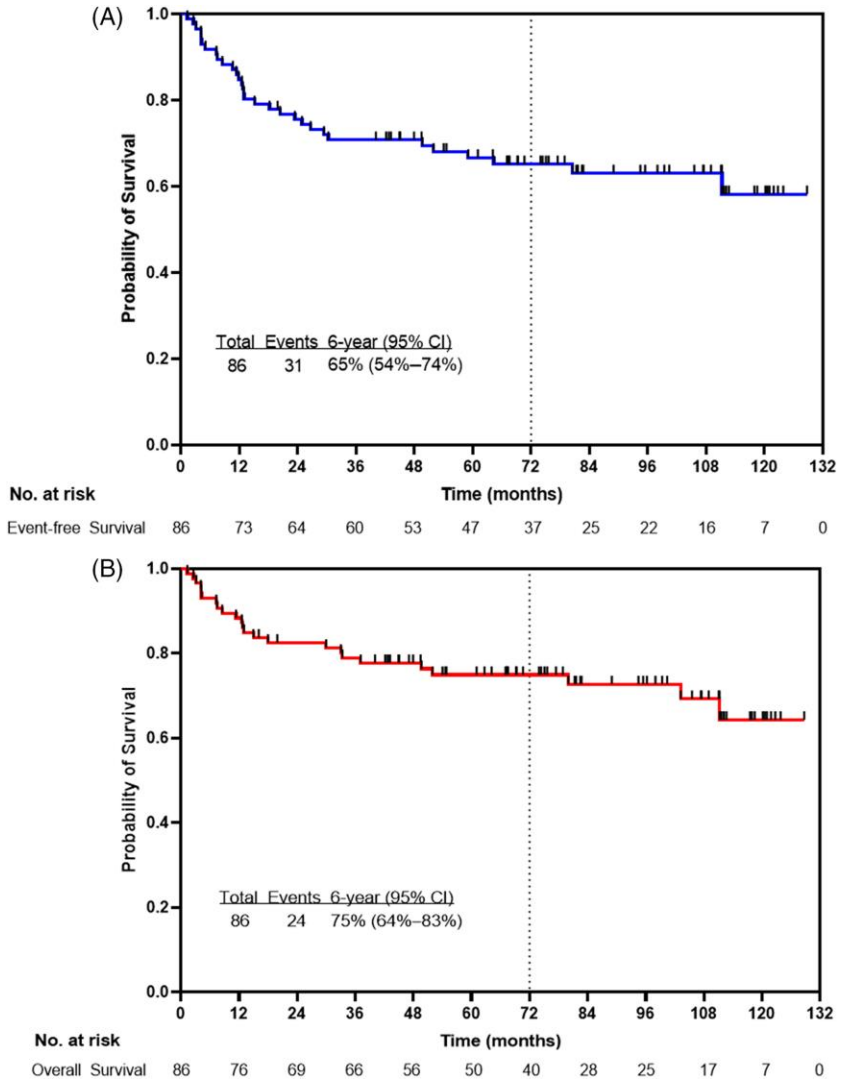
Frontline combination of ponatinib and hyper-CVAD in Philadelphia chromosome-positive acute lymphoblastic leukemia: 80-months follow-up results



- Landmark analysis showed no difference in OS based on transplant (23%) versus no transplant (77%).
- 6 year OS 79% for those who achieved CMR at 3 months and 68% for those who did not.

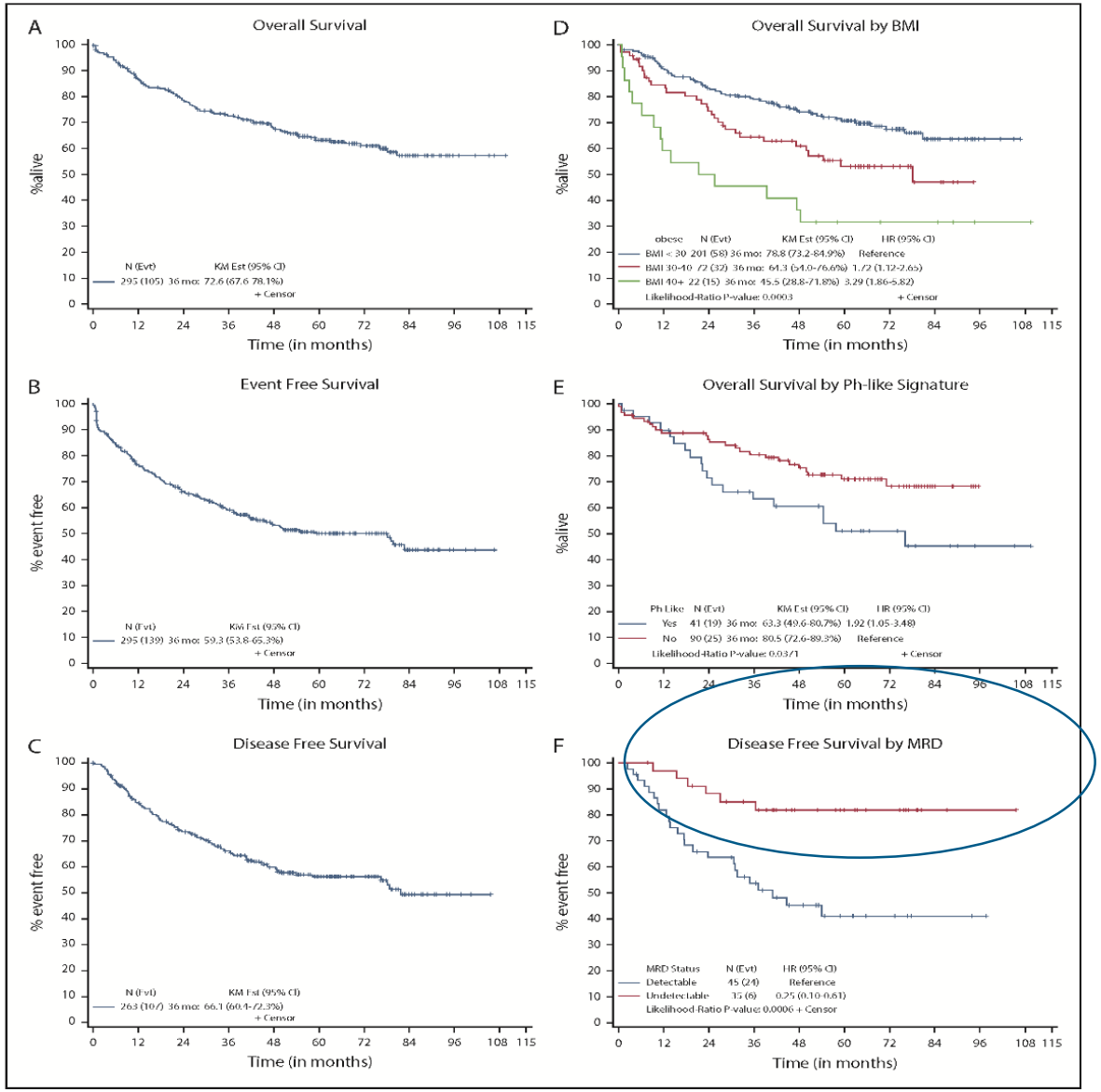
**EA9181: Phase III Randomized Trial of Steroids + Tyrosine Kinase Inhibitor (TKI) Induction with Chemotherapy or Blinatumomab for Newly Diagnosed BCR-ABL-positive Acute Lymphoblastic Leukemia (ALL) in Adults

- Patients are randomized to blinatumomab plus TKI versus chemotherapy plus TKI. If MRD negative at all timepoints, can complete a nearly chemotherapy free regimen. If MRD positive after blina, then get chemo and vice versa. Transplant is at investigator's discretion.

- MRD negative patients on hyper CVAD arm do not get blina.
- "Historical data show that for patients with Ph positive B-ALL who are MRD negative and on continuous TKI the relapse rate is expected to be very low."

A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403

- Can we improve on outcomes in MRD – arms of CALGB10403 with blina?
- Interim analysis of AALL1731 suggests answer is yes….no longer randomizing to no blina... …closed AALL1732 which was going to randomize blina vs no blina in high risk pediatric ALL



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The Evolving Role of Allogeneic SCT in ALL

2005	2025
• All Ph negative B-ALL with sibling donor	• Ph negative B-ALL who are MRD+ at EOI or intensification (includes t(4;11), and many Ph-likes
• All Ph positive B-ALL with sib or MUD donor	• Ph positive B-ALL with failure to achieve CMR at 3 months, or persistent or rising MRD
• All T-cell ALL with sibling donor	• All T-ALL ages 40-70 Non-ETP AYA T-all with EOI MRD+ near-ETP and ETP AYA T-ALL with >10% blasts at EOI

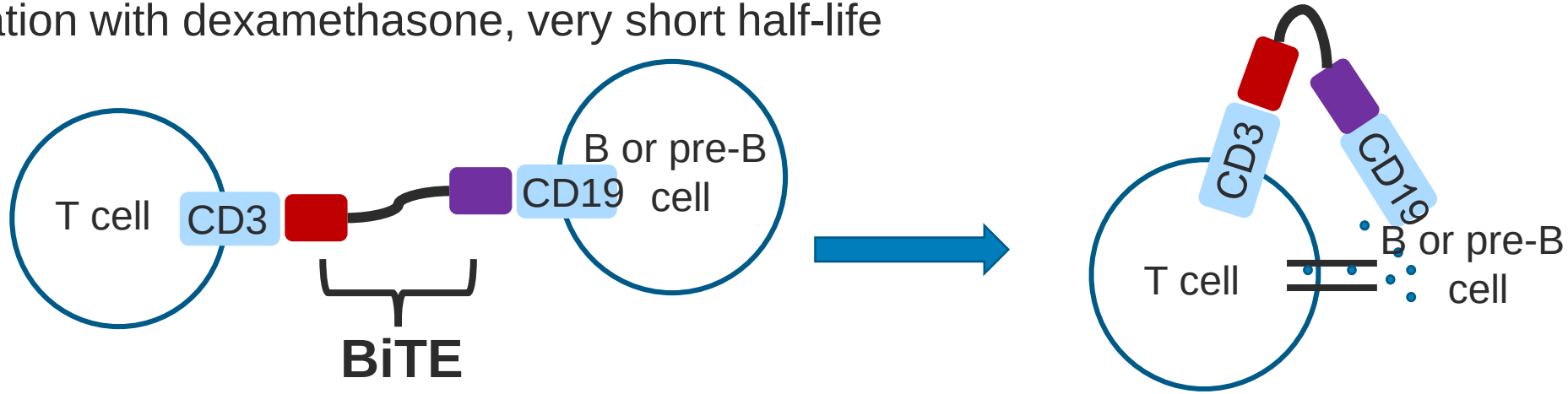
Long-Term Results of Allogeneic Stem Cell Transplantation in Adult Ph- Negative High-Risk Acute Lymphoblastic Leukemia

- 542 allos in Germany analyzed, ages 15-55
- MA conditioning
- MRD status was the most powerful predictor of relapse:
  - 45% CIR for Molecular Failure (MRD positive) versus 6% CIR for Molecular CR p <0.00001
  - (consolidation MRD, week 16, this was the “pre-transplant” timepoint)
- The MRD analysis was NGS based
- TRM doubled from 15% to 30% from ages 15-25 to ages 45-55.
- 5 year survival was 58%
- Relapse risk was 23%

- Blinatumomab: 7/11/17 FDA approved for relapsed or refractory pre-B ALL in adults and children, confirmed clinical benefit after accelerated approval and expanded indication to Ph+ relapse or refractory pre-B ALL

- TOWER (NCT02013167)
  - Blinatumomab at 9 mcg/day on days 1-7 and 28mcg/day on days 8-28 and for subsequent cycles
  - Improved OS with median 7.7 months vs. 4.0 months in the SOC arm
- ALCANTARA (NCT02000427)
  - Expanded indication to Ph+ with 45 patients with disease resistance or intolerance to second generation TKI and imatinib
  - 36% complete remission rate, duration median 6.7 months

- Premedication with dexamethasone, very short half-life



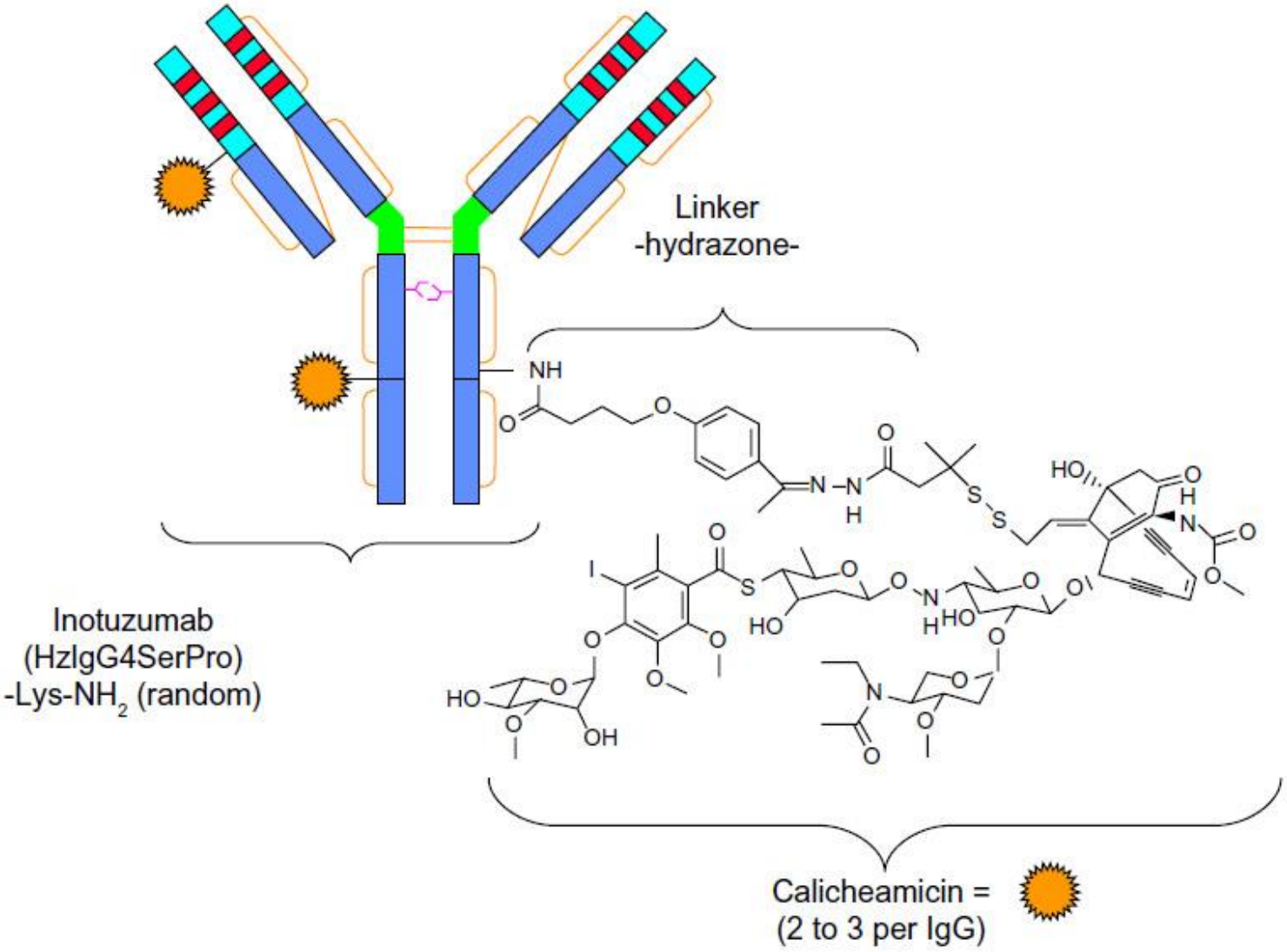
Blinatumomab TOWER STUDY For Relapsed/REFRACTORY ALL N=189

- Response Rate:
  - CR and CRh: 43% of patients within the first 2 cycles
    - 82% of whom were MRD negative
    - 40% bridged to allo SCT, which led to durable remissions

- Toxicities
  - **Neurologic** (delirium, seizure, other)
    - 58% any grade; 13% Grade 3 or 4
    - Mostly in Cycle 1
  - **Cytokine Release Syndrome**
    - 2% Grade 3
    - >50% blasts; pre-phase treatment with high dose dexamethasone
    - Stepwise dosing for cycle 1 (9µg/d x 7 days then 28µg/d x 21 days)
    - Pre-treatment 20mg Dexamethasone before D1 and Dose Escalations
  - **Fever** occurs in 60%
  - **Mortality**
    - 23 (12%) fatal adverse events (mostly sepsis)
    - No patient in remission died during therapy

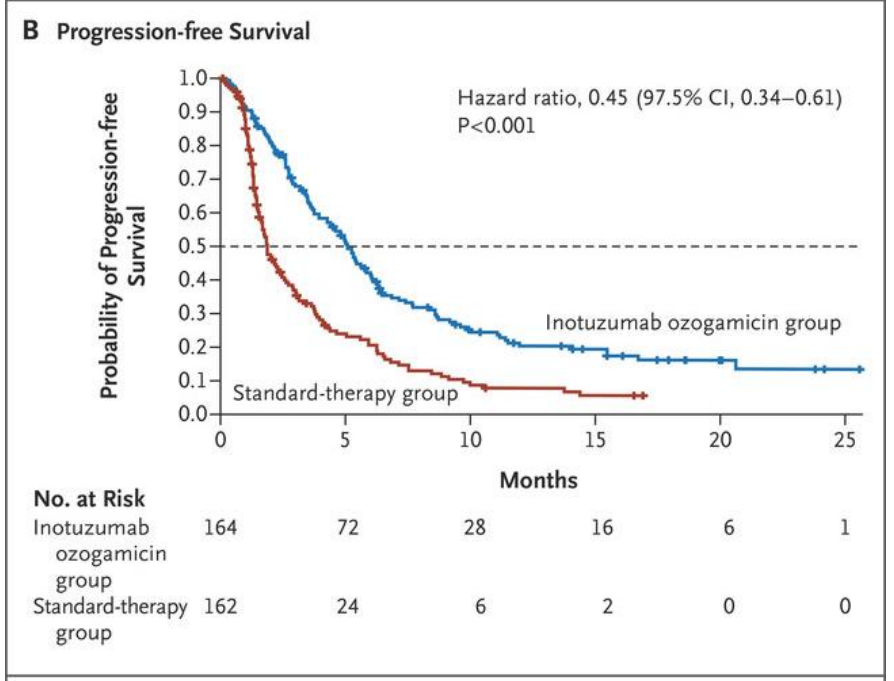
Inotuzumab Ozogamicin 8-17-17

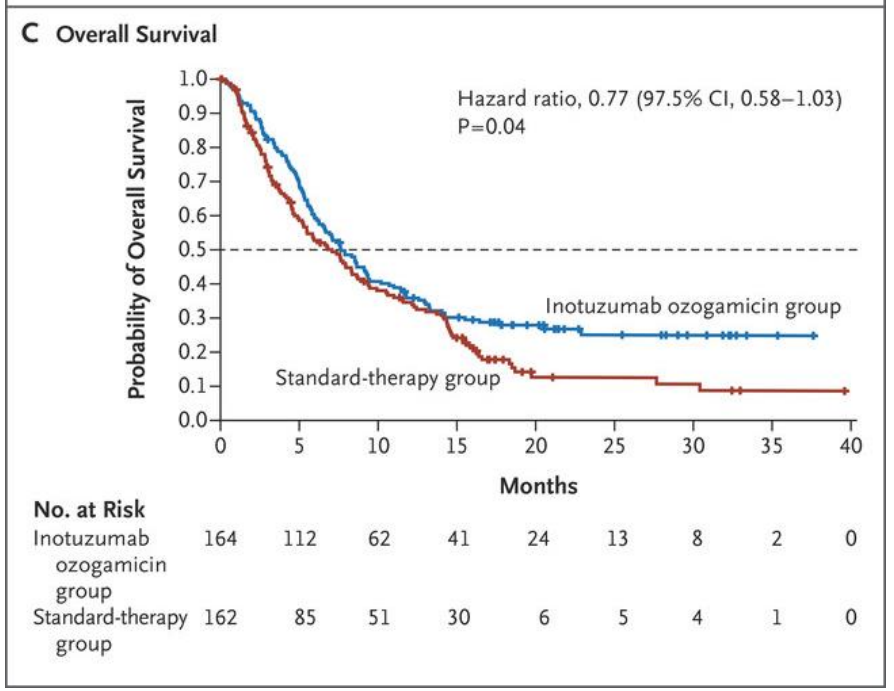
- CD22 MoAb bound to calicheamicir
- Adverse Reactions:
  - Cytopenias
  - Infection
  - Hemorrhage
  - Neutropenic fever/fever
  - Nausea
  - Headache
  - Transaminitis, hyperbilirubinemia
  - Abdominal pain
  - VOD/SOS in 11%
  - May prolong the QT when combined with other QT prolonging agents



Inotuzumab Ozogamicin 8-17-17

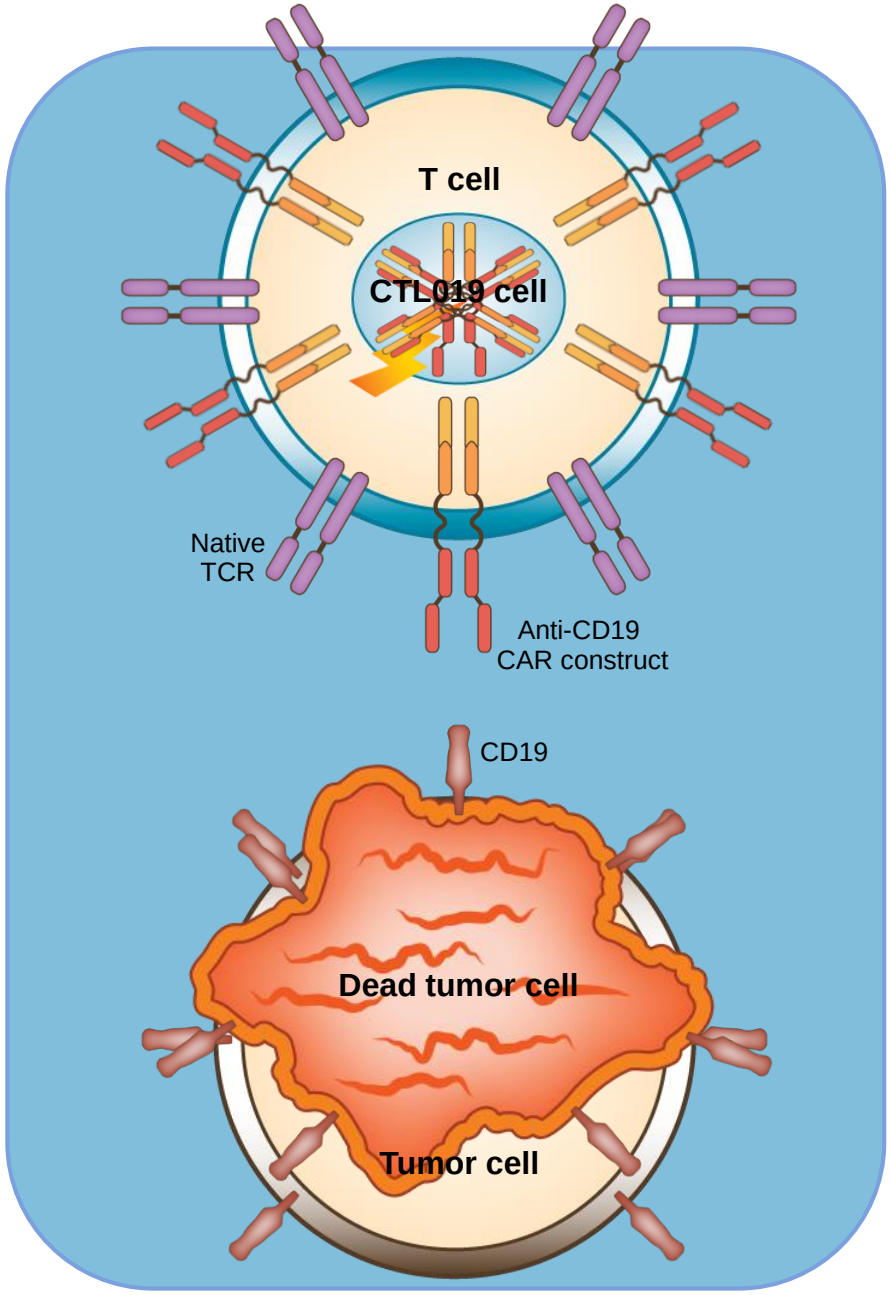
- FDA approved for relapsed/refractory pre-B ALL
  - Dosing 0.8 mg/m2 on Day 1, then 0.5mg/m2 on Days 8 and 15
  - First cycle 21-28 days, subsequent cycles 28 days with full dosing if CR not achieved
- Phase 3 INO-VATE ALL (NCT01564784) n= 326
  - Inotuzumab ozogamicin (n=164) vs. investigator's choice chemo (n=162)
  - ITT analysis CR/CRi rate was 80.7% (78.4% MRD negative) vs. 29.4% (28.1% MRD negativity)
  - PFS was 5 vs. 1.8 months; OS was 7.7 vs. 6.7 months





Tisagenlecleucel (KYMRIAH) 8-30-2017

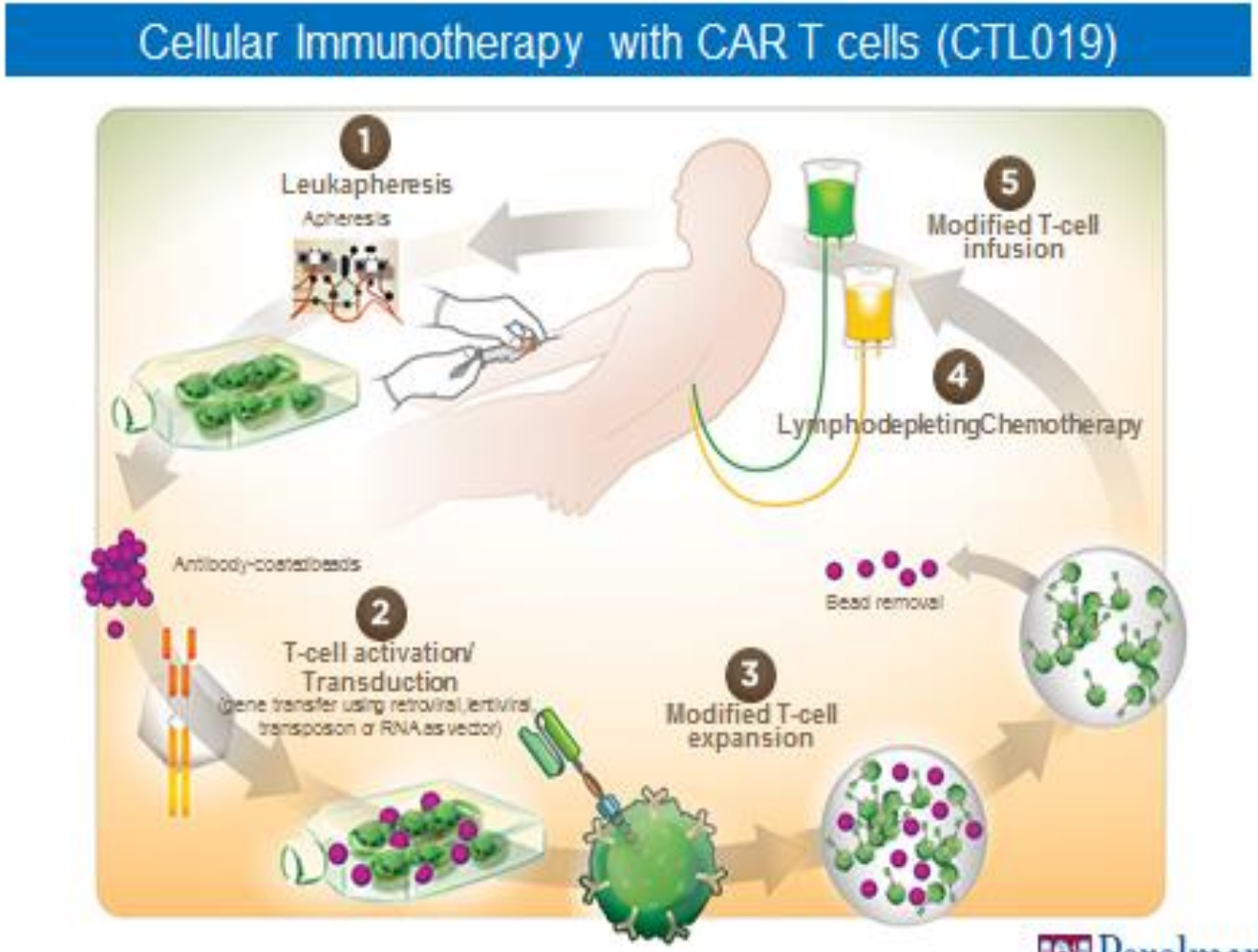
- 2nd or later relapse for ALL age ≤25 years
- Approval based on trial of 63 pediatric and young adult patients with an 83% remission rate at 3 months
- Black box warning for cytokine release syndrome (CRS), which can be treated with Tocilizumab, REMS program required
- Black box warning for neurologic symptoms



Milone, et al. *Mol Ther* 2009
Carpenito, et al. *PNAS* 2009

ELIANA: first global multi-center CAR T cell trial in Pediatric ALL

- 94% of pts received CTL019
  - 25 centers across 11 countries (US, EU, Canada, Australia, Japan)
- CRS manageable with no deaths due to CRS
- CR/CRi 83%



Tecartus 10-1-2021

- FDA approved for adults with relapsed or refractory B-cell ALL. Kymriah only approved for R/R B-ALL ages 25 and under.
- ZUMA-3 trial Shah BD et al, The Lancet, 398 (102), 2021, 71% CR or CR (i), 56% CR rate in adults with B-ALL, median 40 years old. Median OS not reached amongst responders.
- Open question what % of adults can we cure with Tecartus.

Aucatzyl 11-8-2024

FDA approved for adults with R/R B-cell ALL, no age restriction

FELIX Trial: Roddie et al, NEJM, **N Engl J Med 2024;391:2219-2230**

BLINA, INO and CAR-T--IN WHAT ORDER?

- 20 yo woman dxed with Ph like B-ALL, Jak2 mutated, neg for CRLF rearrangements, normal karyotype in August 2023, during 3rd trimester of pregnancy
- Refractory to attenuated induction per CALGB 10403 with PEG omitted
- Delivered healthy baby boy at 34 weeks
- Completed course II per CALGB 10403 with day 36-39 cytarabine and day 43 PEG held due to severe transaminitis
- BMBx 1/25/2024 showed 5-10% blasts
- Collected for Tecartus on 2/14/24
- BMBx 2/28/24 packed with B-ALL, pt admitted with bacteremia, transaminitis
- Decision to use INOTUZUMAB as bridge to CAR-T, first dose 3/6/24
- BMBx after 1 cycle of INO on 4/4/24 showed MRD negative CR
- Plan for allo SCT, but decided to consolidate MRD negative CR with blinatumomab on 4/27/24
- 6/2024: rapidly enlarging b/l breast masses, biopsy shows B-ALL
- Peripheral blood with rapidly rising blasts
- Received hyper CVAD B cycle given very large burden of extramedullary disease
- After hyper CVAD B, excellent response in breast disease, BMBx showed morphologic CR but MRD + with 0.6% lymphoblasts
- CSF with B-lymphoblasts, received 2 IT chemotherapy treatments, then Tecartus on 7/3/24
- Now in MRD negative CR by BMBx 8/8/24 with CSF clear after Tecartus
- Plan for Cy/TBI allo from 10/10 MUD

BLINA, INO and CAR-T--IN WHAT ORDER?

- CAR-T is the most definitive therapy and associated with potential of cure in some patients, so try to get patients with active disease to CAR-T. Collect everyone who is a candidate at time of relapse.
- In this case, patient was bacteremic and had severe transaminitis with rapidly growing B-ALL at time of planned start of lymphodepletion for CAR-T—needed a salvage option
- Transplant is fraught with logistics: have more breathing room to set it up for pt in CR after CAR-T then for patient getting salvage blina or INO with chance of progression—median OS after blina and INO is still on the order of 7-8 months so it's easy to run into trouble after or during either of them.
- If CAR-T is goal, I tend not to bridge to CAR-T with another CD19 directed therapy
- I also tend to not use blina or CAR-T with high burden of disease if it can be avoided due to concerns about CRS/neurotoxicity
- Improved transaminitis with DEX and used INO as bridge to CAR-T in this case. Now INO will be months away from allo SCT, reducing VOD risk.
- Now patient in MRD negative CR—can she be cured with Tecartus alone??
- In the three year update of ELIANA, median EFS for responding patients had not been reached.
- Oluwole O, et al, ASCO Abstract 6531, 2024: 4 year survival outcomes for ZUMA-3. Median OS was 47 months for patients who achieved a CR/Cri. But median OS was 60 months in 15 pts with 1 prior therapy and 25 months in 63 pts with 2 or more prior therapies.