Growing UP: Progress in Treatment of Young Adults with ALL

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Lois O'Grady

June 9, 1936 – December 23, 2007

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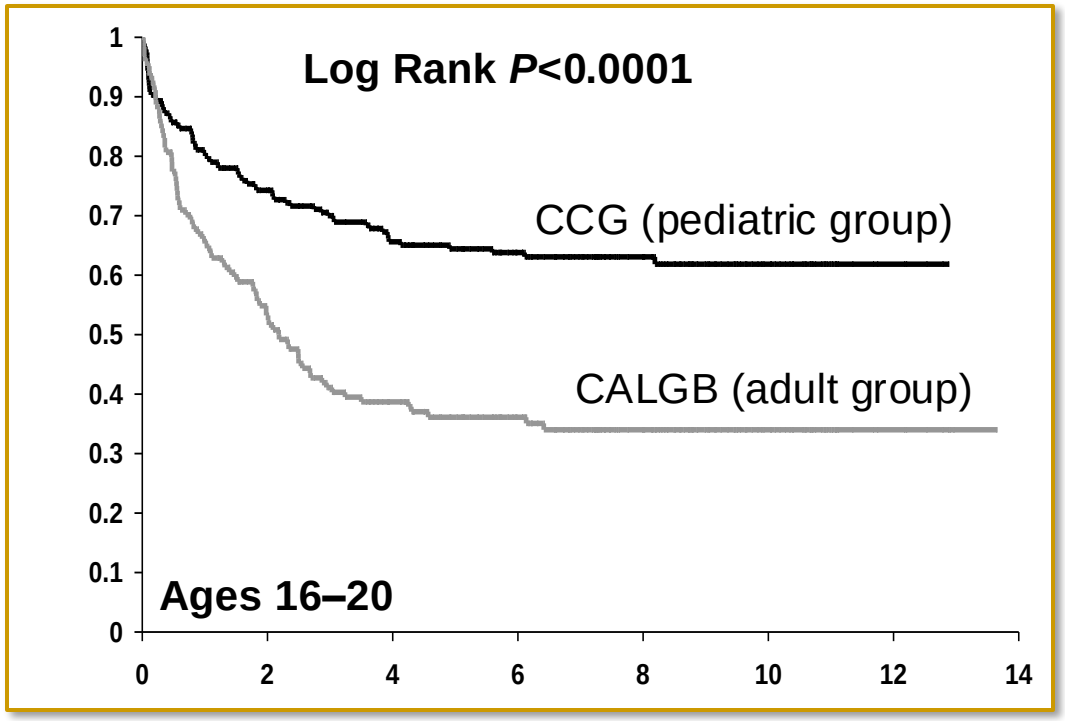
A bad bet pays off!

"Pediatricians know best!"
……how to treat ALL!"

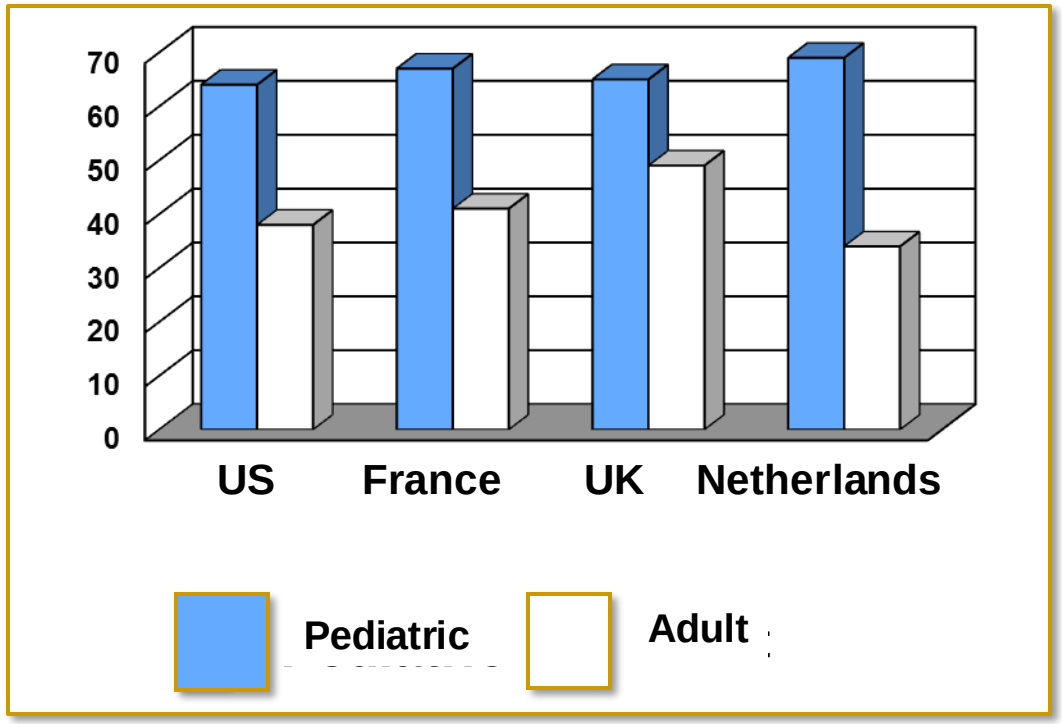
Jim Nachman MD, 1949-2011

Survival Differences in ALL Are Dramatic *Depends on Which "Door" You Enter*

Event-free Survival of Adolescents/Young Adults (AYA), Ages 16–20 years



Similar results World-wide



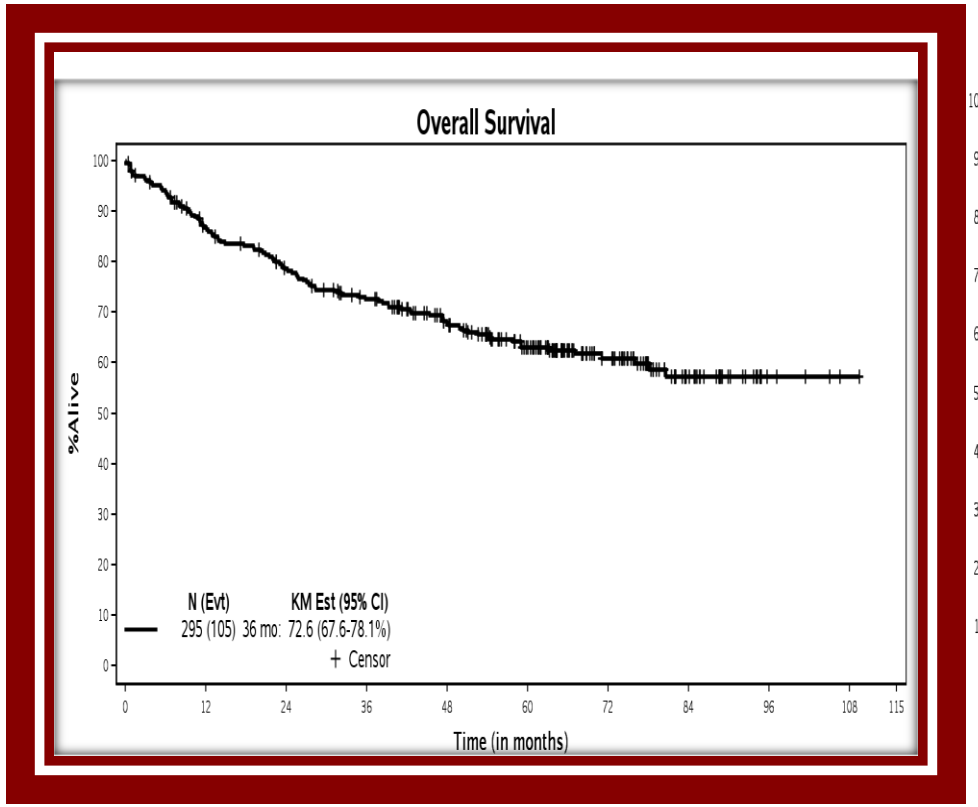
AT THE FOREFRONT
UChicagoMedicine

CALGB, Cancer and Leukemia Group B; CCG, Children's Cancer Group.

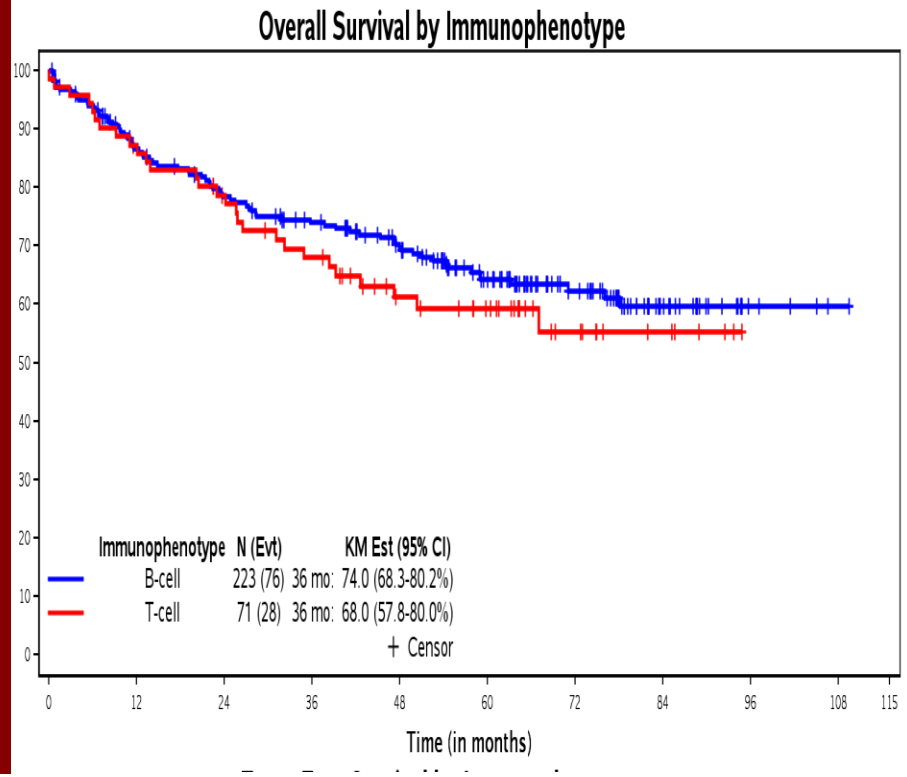
Stock W, et al. *Blood.* 2008.;

Improved Survival for AYAs: CALGB 10403

- 73% Survival at 3 years



- Immunophenotype: B vs T



Stock et al, Blood 2019

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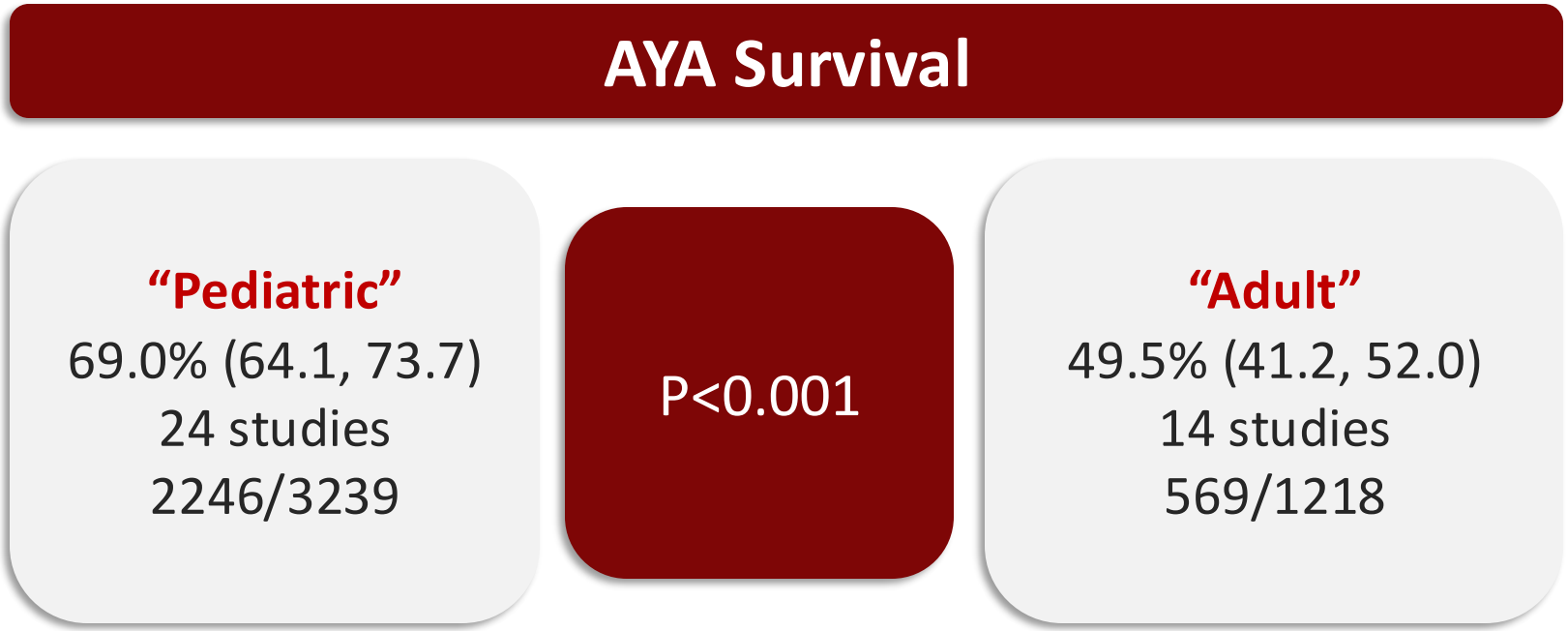
Typical “Pediatric” Regimen: Dose Dense Asparaginase

I	C	IM	DI	M
DNR	Cyclo	MTX	DOX	DEX
VCR	VCR	VCR	Cyclo	VCR
Pred	Dex	Peg-ASP	Dex	6MP
Peg-Asp	Peg-Asp	IT-MTX	Peg-Asp	MTX
IT-MTX	Ara-C		Ara-C	IT-MTX
IT-AraC	6MP		6-TG	
	IT-MTX		IT-MTX	

Maintenance therapy continues for 2 (F) – 3 (M) years

ASH Guideline: Favors “Pediatric” over “Adult”



ASH 2023: Issued by AYA Guideline Committee

Systematic Review Favors Pediatric Regimens

Event-Free Survival

8 Comparative Studies
Effect Size = 1.66 (1.24, 2.23)
23 Single Groups
64.6% vs. 41.2%P<0.001

Disease-Free Survival

4 Comparative Studies
Effect Size = 1.56 (1.30, 1.86)
12 Single Groups
65.0% vs. 38.4% P=0.001

Relapse-Free Survival

3 Comparative Studies
Effect Size = 1.36 (1.01, 1.82)
8 Single Groups
72.6% vs. 61.0% P=0.055

Complete Remission

10 Comparative Studies
Effect Size = 1.04 (0.99, 1.10)
27 Single Groups
93.5% vs. 87.8% P=0.035

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ASH AYA Guideline: Panel Recommendation

The panel drafted a strong recommendation:

- In favor of **pediatric- (asparaginase-containing)** over adult-inspired regimens
- **Moderate certainty** of evidence
  - **Observational** studies
- **Large mortality reductions**
- Accompanied by **remarks** about **implementation challenges in community settings** and **generalizability to immunotherapy-containing** regimens

ASH 2023: Issued by AYA Guideline Committee

AYA ALL : Totally Solved?

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Areas to ATTACK!

- Access / Disparities
- Toxicity – Tweaking the Pediatric Approach
- Disease Biology – Overcoming Resistance
- Holistic Care - Survivorship

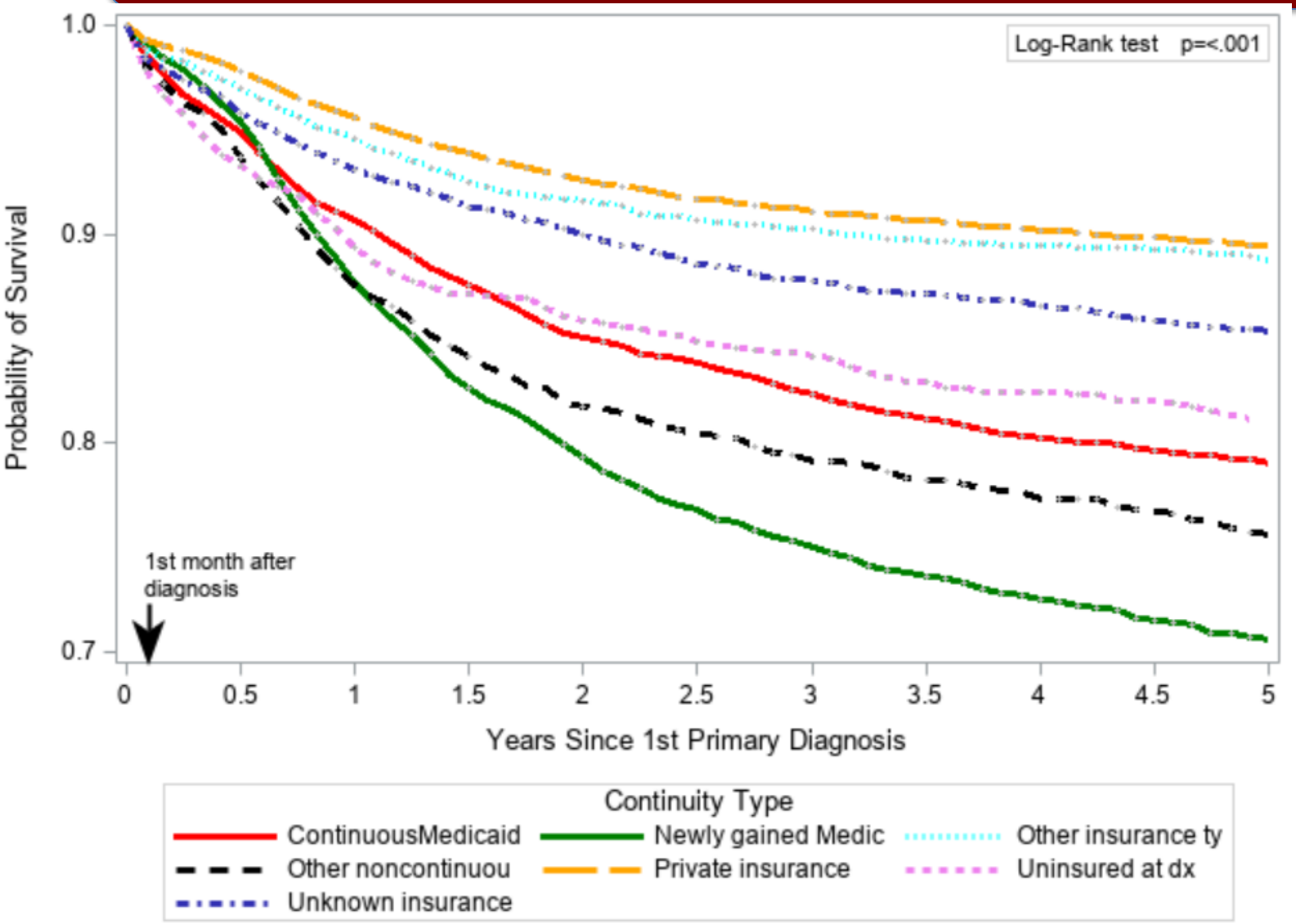
Access: Health Insurance Continuity Critical

- Assess the association between health insurance continuity and survival in children and AYAs newly diagnosed with blood cancer

  - Hypothesis: Compared to children and AYAs with continuous Medicaid coverage, those with newly gained Medicaid coverage at the point of or after diagnosis will experience worse survival

Ji et al, ASCO 2023 ; Manuscript under review

Overall Survival by Insurance Continuity: Age 0-39 years



5-year overall survival rate:

Private insurance at diagnosis: **89.4%**
Other insurance at diagnosis: **88.8%**

Unknown insurance: **85.3%**

Uninsured at diagnosis: **81.1%**

Continuous Medicaid: **79.1%**

Other noncontinuous Medicaid: **75.6%**

Newly gained Medicaid: **70.6%**

Proportion of AYAs with newly obtained MEDICAID was significantly higher than in Children

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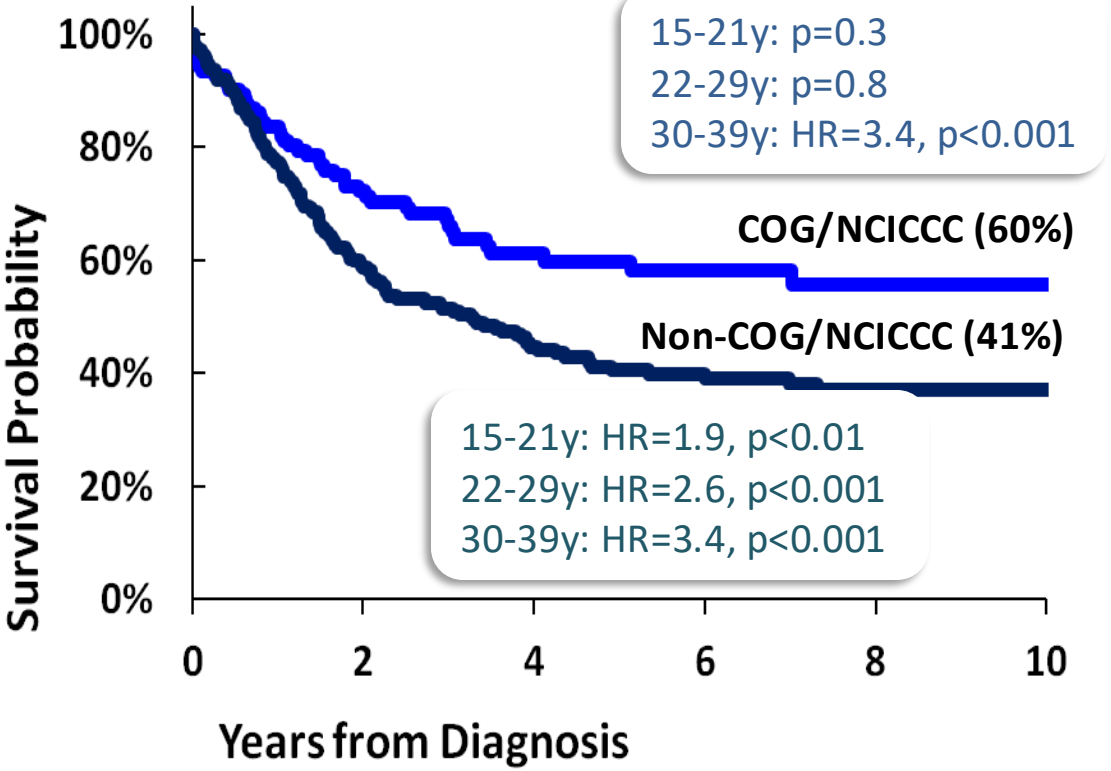
Access to Trials: Experienced CARE Matters

15-39y with ALL: Superior Overall Survival at COG/NCICCC *(p=0.004) Los Angeles County, 1998-2008*

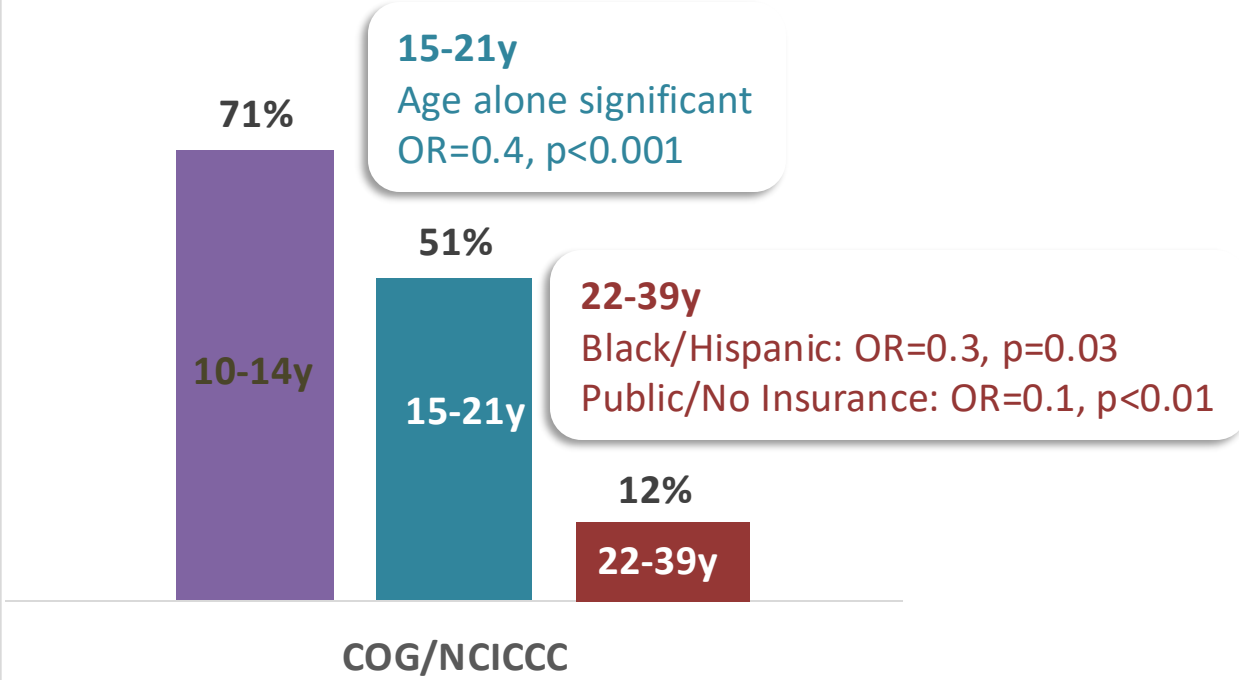
**multivariable analysis – risk of mortality vs. child, adjusting for sex, race/ethnicity, payor, SES*



Wolfson, CEPB 2017

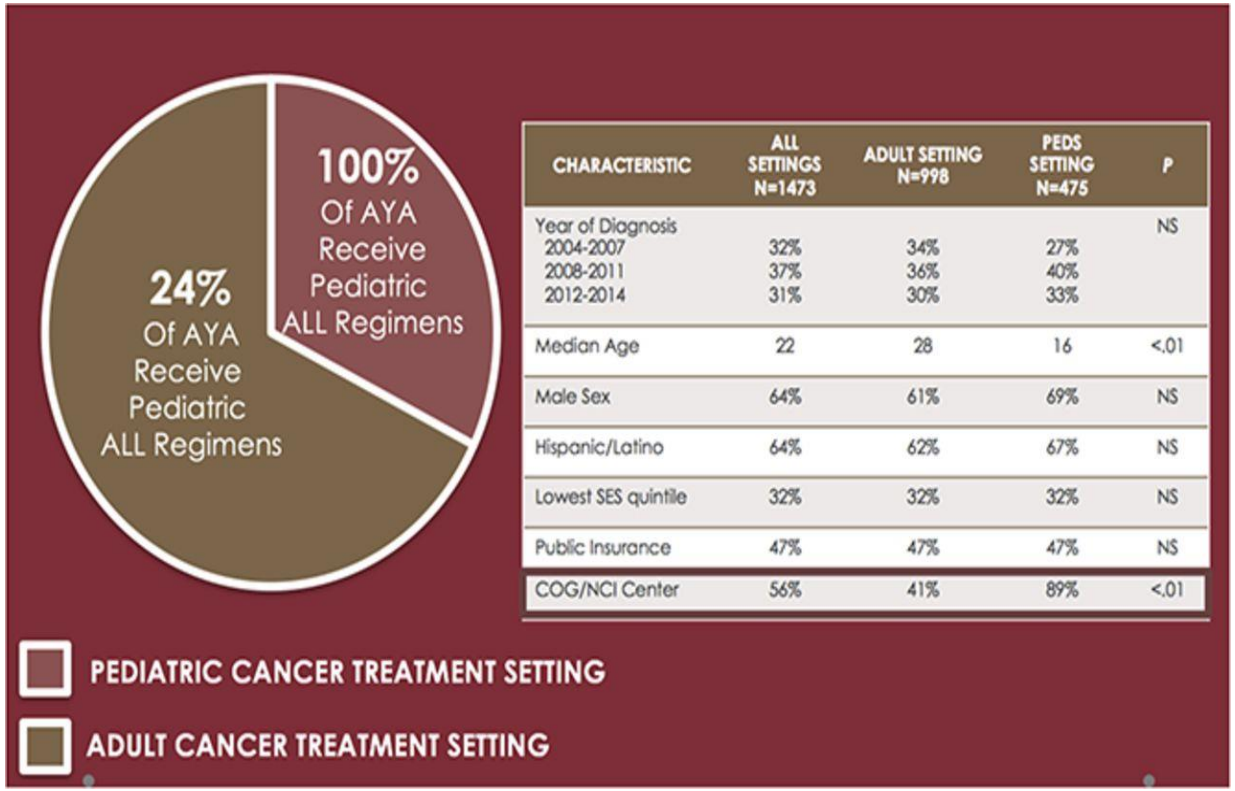
Many AYAs with ALL are Not Treated at COG/NCICCCs

**multivariable analysis – odds of treatment at COG/NCICCC, adjusting for sex, race/ethnicity, payor, SES, distsance*

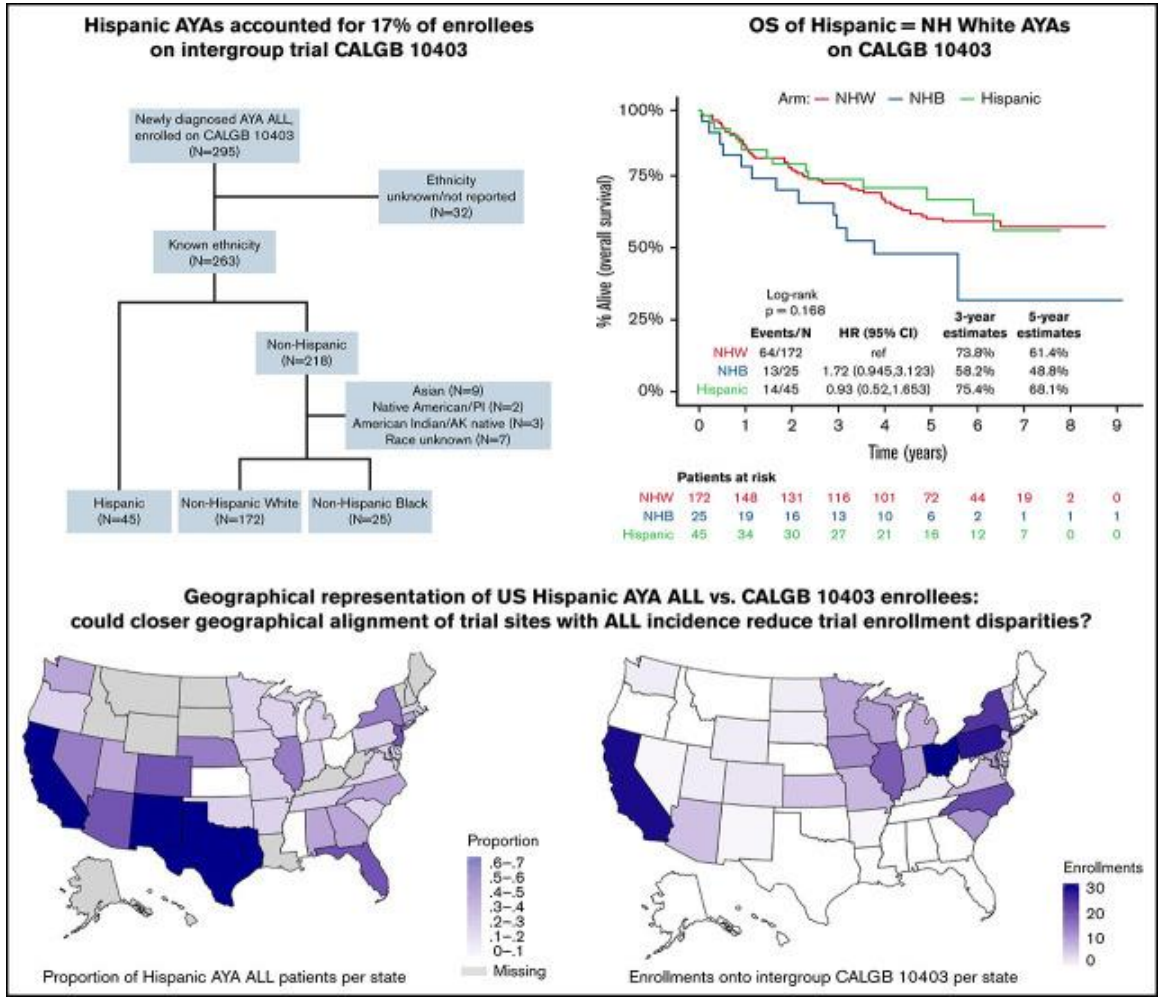


Wolfson, CEPB 2017

Access to Care: Location, Location, Location!



CHARACTERISTIC	ALL SETTINGS N=1473	ADULT SETTING N=998	PEDS SETTING N=475	P
Year of Diagnosis				NS
2004-2007	32%	34%	27%	
2008-2011	37%	36%	40%	
2012-2014	31%	30%	33%	
Median Age	22	28	16	<.01
Male Sex	64%	61%	69%	NS
Hispanic/Latino	64%	62%	67%	NS
Lowest SES quintile	32%	32%	32%	NS
Public Insurance	47%	47%	47%	NS
COG/NCI Center	56%	41%	89%	<.01



Muffly et al, Blood Advances, 2018; Muffly et al, Blood Advances 2022

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"CALGB 10403" in Low/Middle Income Countries

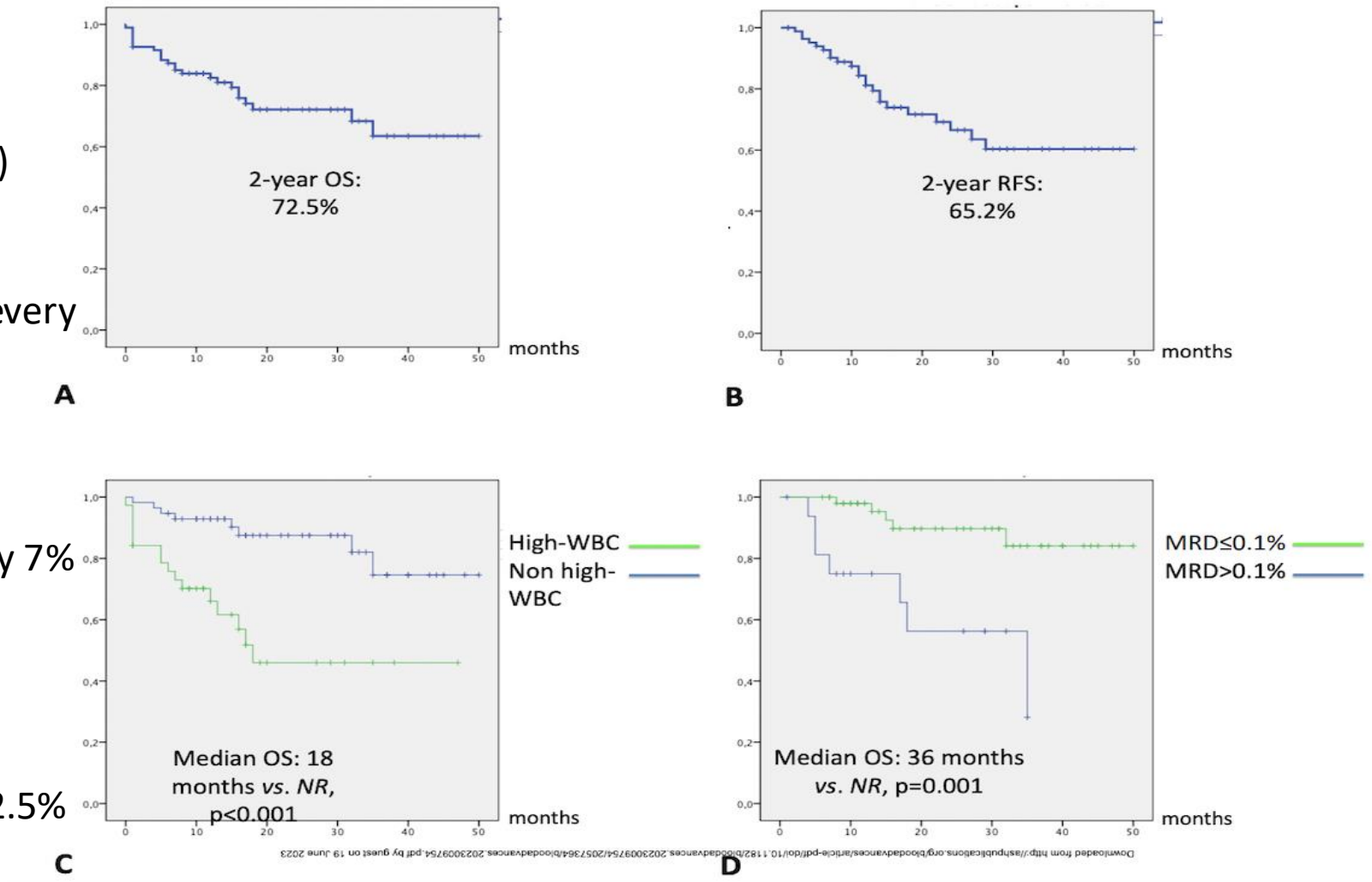
95 patients, Mexico
Age 14-49 years (median 23 yrs)

Substituted 6 doses of e coli asparaginase at 6000u/m2 for every dose of PEG-ASP;
6MP instead of 6TG
Rituximab for all CD20+

89% CR rate, induction mortality 7%

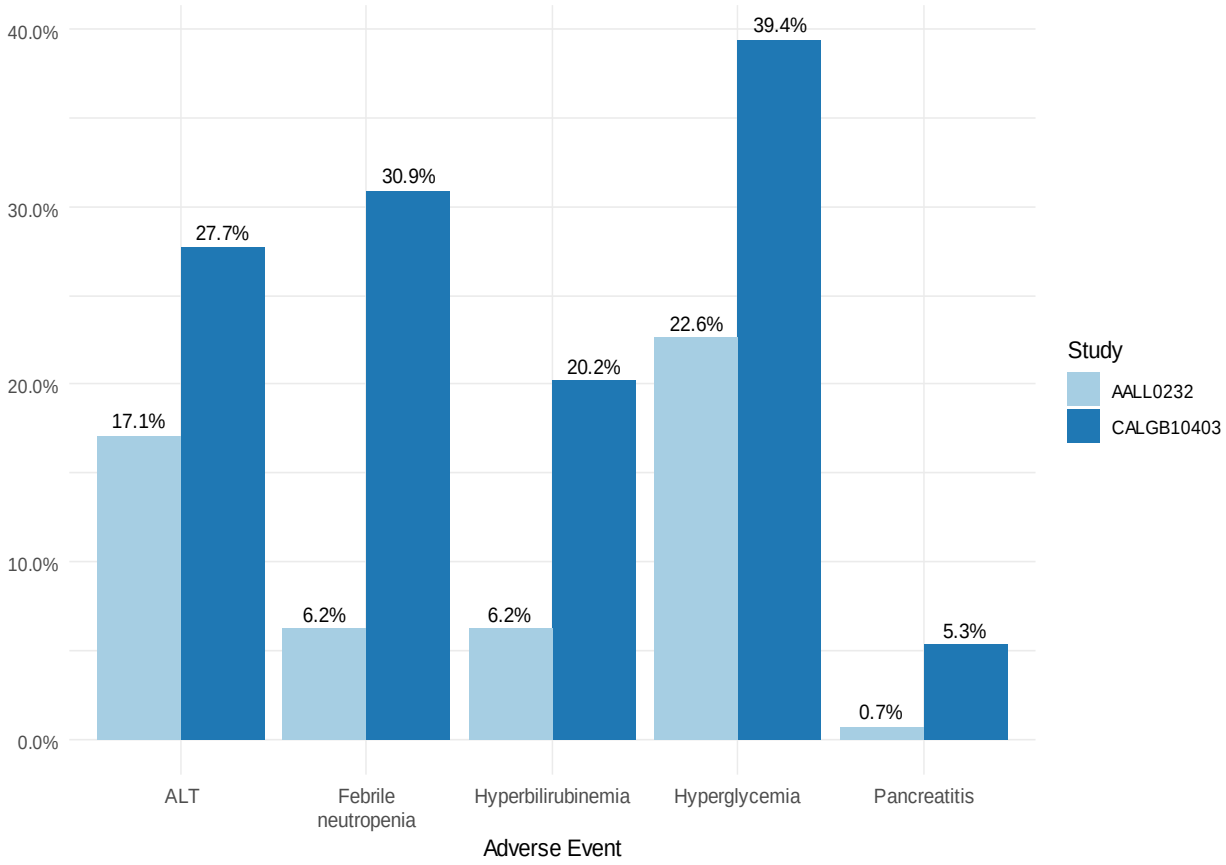
Median follow-up 26.5 months;
23 % relapsed; TRM 9%

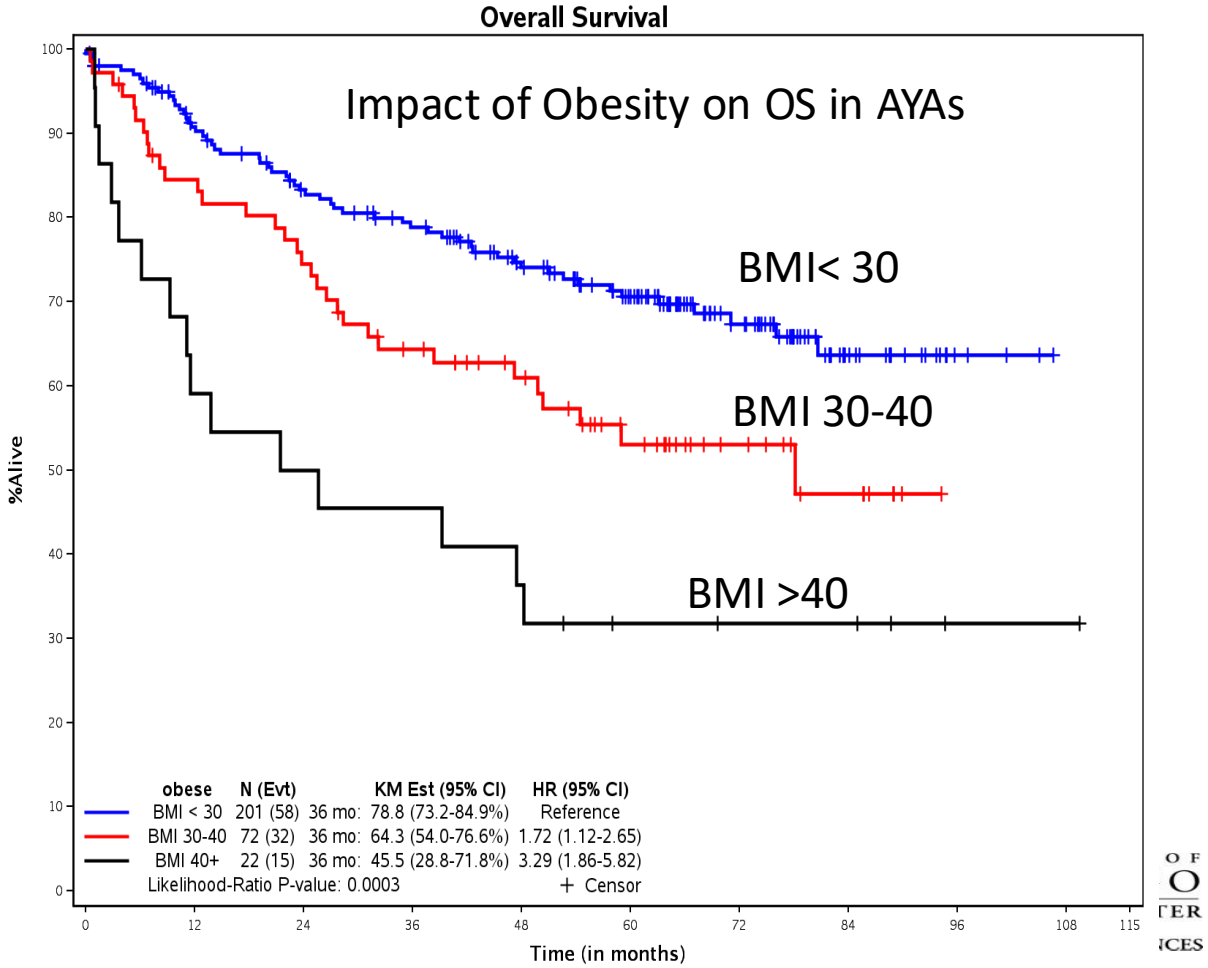
2 year RFS= 65%; 2 year OS = 72.5%



Rangel-Patino et al, Blood Advances 2023

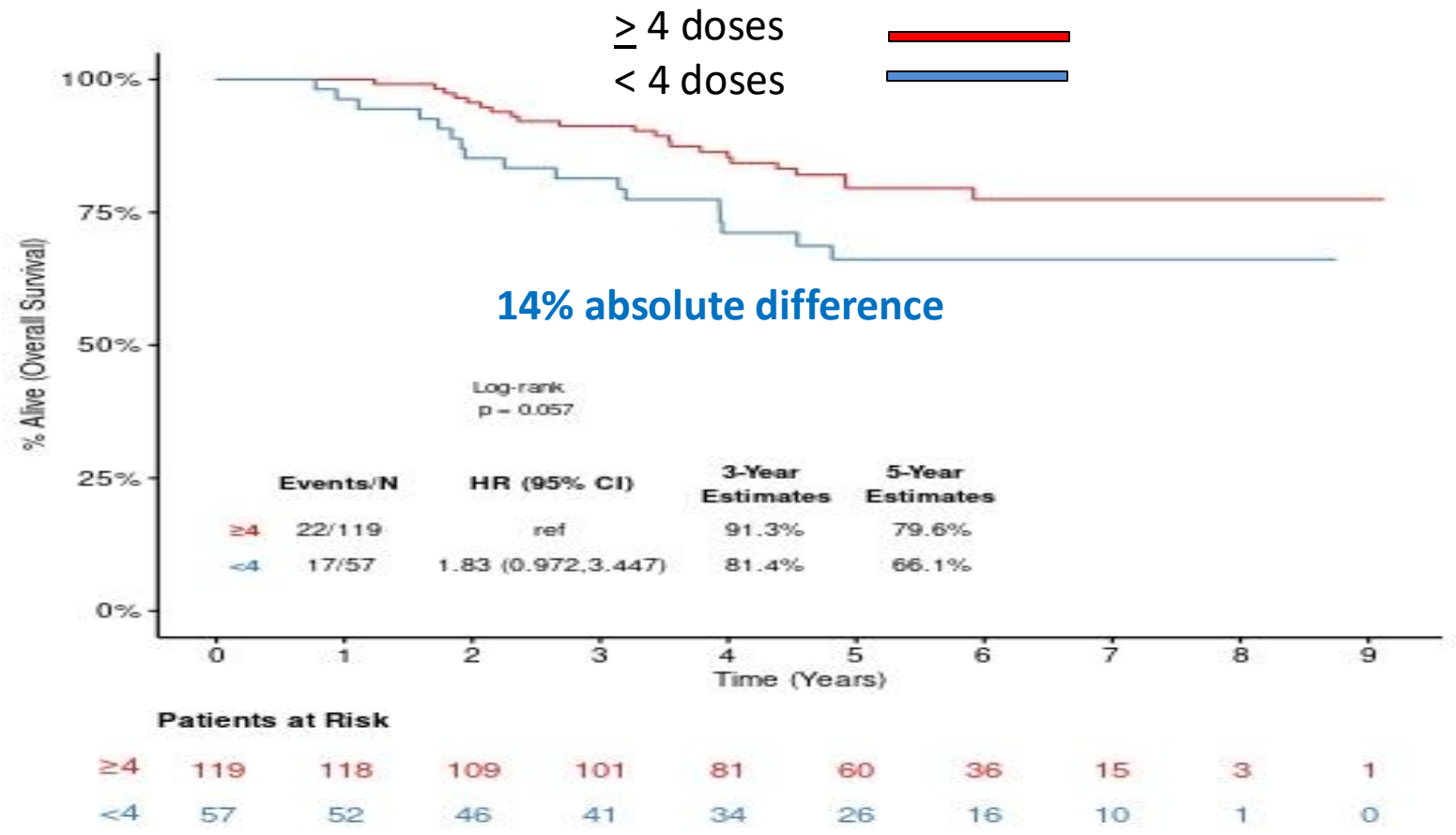
Treatment Toxicities, Obesity: Serious Challenges in AYAs





Advani et al, *Blood Advances*, 2021; Stock et al, Blood 2019

CALGB 10403: Peg-ASP matters!



Evaluated Peg-Asp doses delivered prior to DI

- Median # of PEG-asp doses= 5 (1-5)
- # of pts who discontinued PEG-asp after
  - 1 dose= 13 (7%)
  - 2 doses = 23 (13%)
  - 3 doses = 21 (12%)
  - 4 doses = 17 (10%)

- *<4 doses=* **57 (32%),** a median of 2 (1-3) doses

- *≥ 4 doses=* **119 (68%)**, a median of 5 (4-6) doses

- Older AYAs received fewer doses; surprisingly, not dependent on BMI

Aldoss et al, Blood Advances 2022

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Are we “overdosing” Peg-Asp in AYAs?

- Pilot study of 51 pts using modified CALGB 10403
- Median age = 46 years (25%–75% interquartile range (33–60)
- Peg-Asp dose reduced to 1000U/m^2 IV vs standard dose of 2750U/m^2
  - Further dose reduction to 500 U/m^2 if BMI>30, Age> 50, Baseline LFT abnormalities, Diabetes
- Goal was ≥ 0.1 IU/mL, measured weekly after dose

- 81% achieved therapeutic levels with lower dosing
  - Majority with adequate levels for at least 2 weeks

- **Overall, decreased grade 3-4 liver/thrombotic toxicities; p = 0.04**

Derman et al, 2019 Leuk Lymphoma; Patel et al, 2021; EJ Haem; Goldberg et al; ASCO 2024

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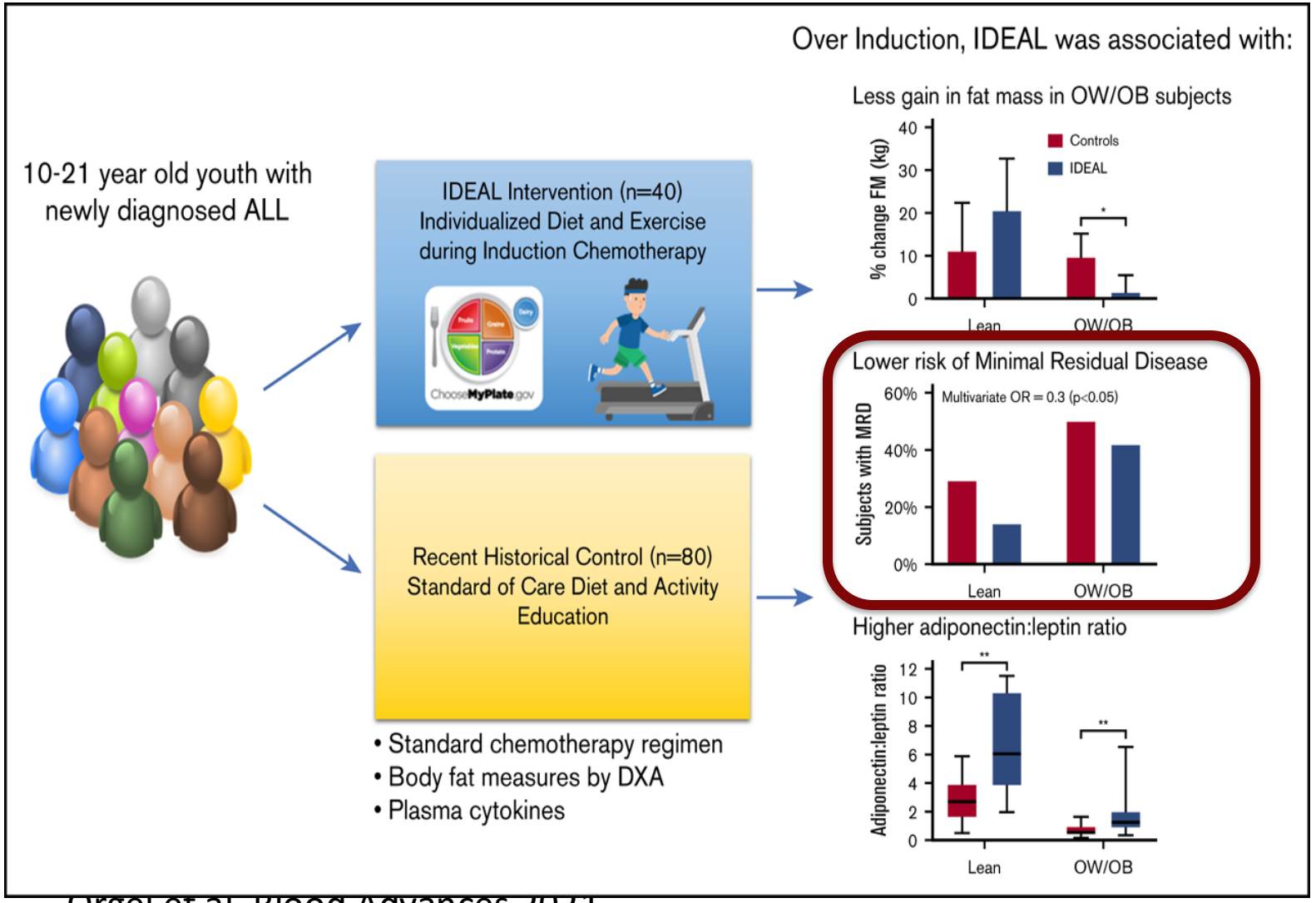
Exercise/Dietary Control: Higher rates of MRD-



Orgel et al, Blood Advances 2021

FINDINGS of IDEAL

- Integrating caloric restriction into B-ALL induction is feasible, reduces fat gain in the overweight, and improves disease response.
- Insulin and adiponectin are identified as potential biomarkers of B-ALL chemosensitivity.
- First study in any hematologic malignancy to demonstrate potential benefit from caloric restriction via diet/exercise to augment chemotherapy efficacy and improve disease response

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NEOMA Trial: Feasibility Study
Nutrition and Exercise to Optimize Muscle and Adiposity

INTERVENTIONS

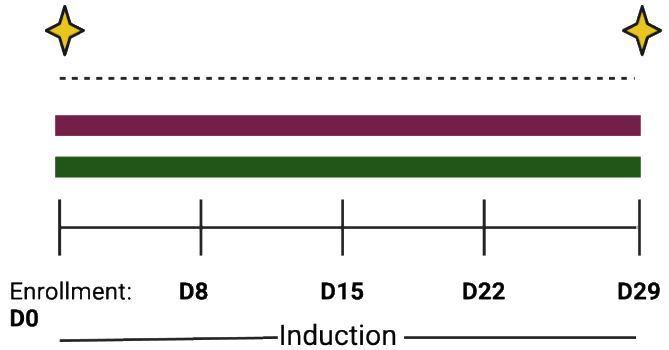
1) **Target a 10% calorie deficit** calculated from the patients Basal Metabolic Rate (WHO/Schofield) utilizing a high protein (>25%), low fat (<25%), low glycemic index/high fiber (45-55%) diet
2) **Target 200 minutes of moderate physical activity,** as defined by Metabolic Equivalents (METs), made up of aerobic and resistance training activities
3) **Assess body composition and metabolomic changes** during induction therapy using a modified folch extraction to measure both lipids and polar metabolites on a dedicated LC-MS system (Thermo IQ-X)
4) **Assess end induction MRD, and ≥ gr 3 toxicities** including hyperglycemia, hepatotoxicity compared to historical controls

Inclusion criteria:

1. Newly diagnosed B-ALL
2. Age≥18 years
3. Receiving intensive induction chemotherapy regimen

Exclusion criteria:

1. BMI≤18.5 kg/m^2 at diagnosis
2. Be unable to comply with both the recommended diet and exercise regimen as deemed by the research or treatment team.
3. Pregnant



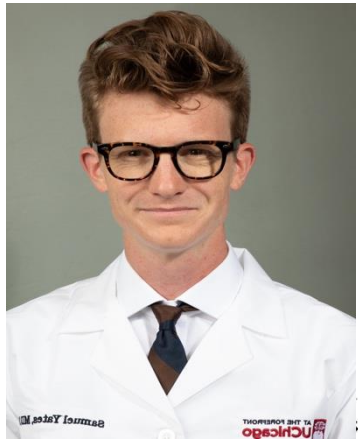
Exercise intervention. Physical therapist to evaluate patient's at a minimum every 2 days

Nutrition intervention. Dietician to evaluate patients at a minimum every 2 days.

Measures:

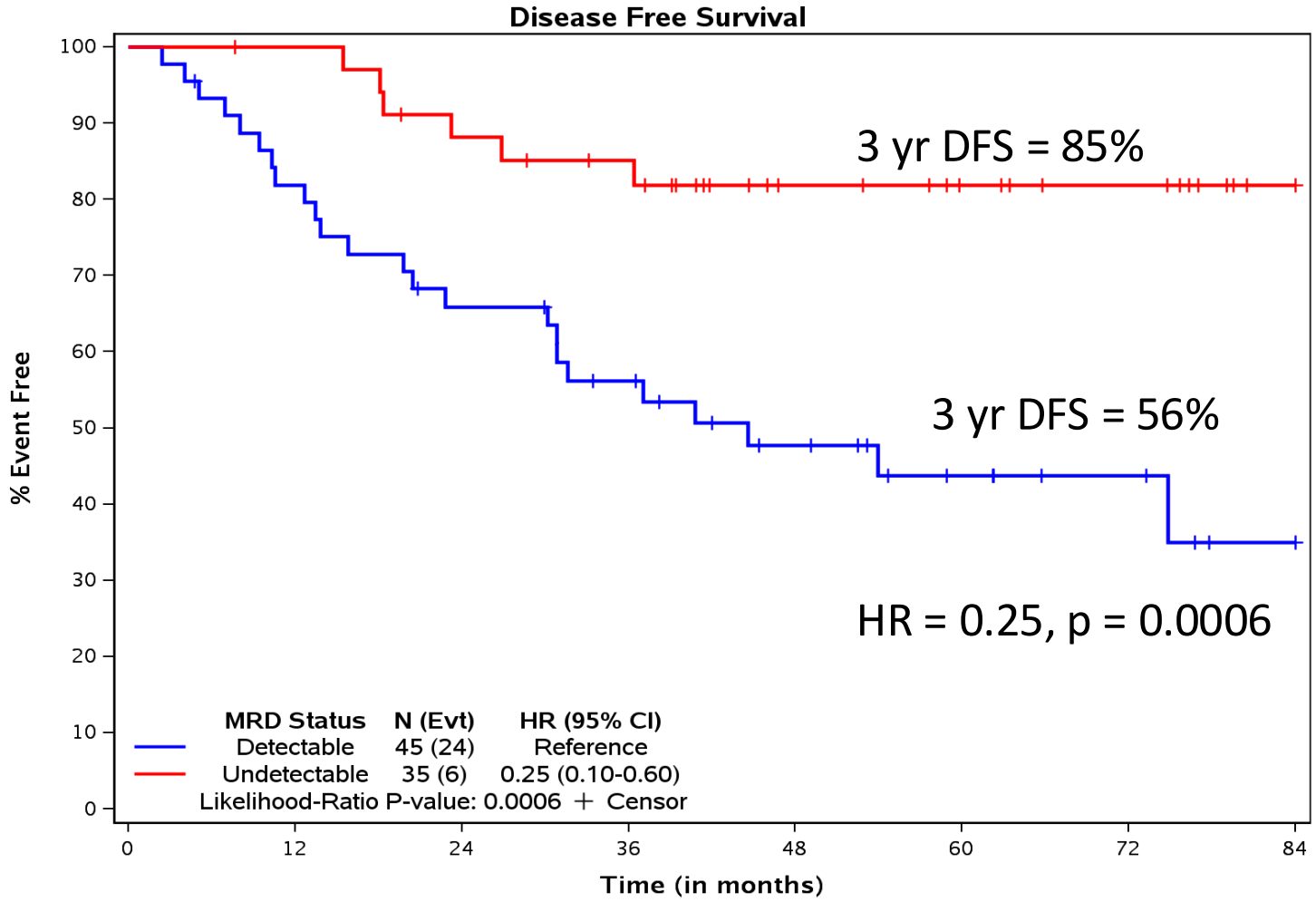
- Nutrition and body composition: Visceral Adiposity and sarcopenia assessment by CT chest, BMI, weight.
- Health-related Quality of Life
- Bone Marrow Aspirate and Biopsy
- System Usability Scale Questionaire (D29 only)

Daily serum metabolomics profile.



Sam Yates, UC Fellow, ASH RTAF Award 2024

More Chemo-resistance in AYAs: ”tougher nuts to crack”



Q-PCR following Induction

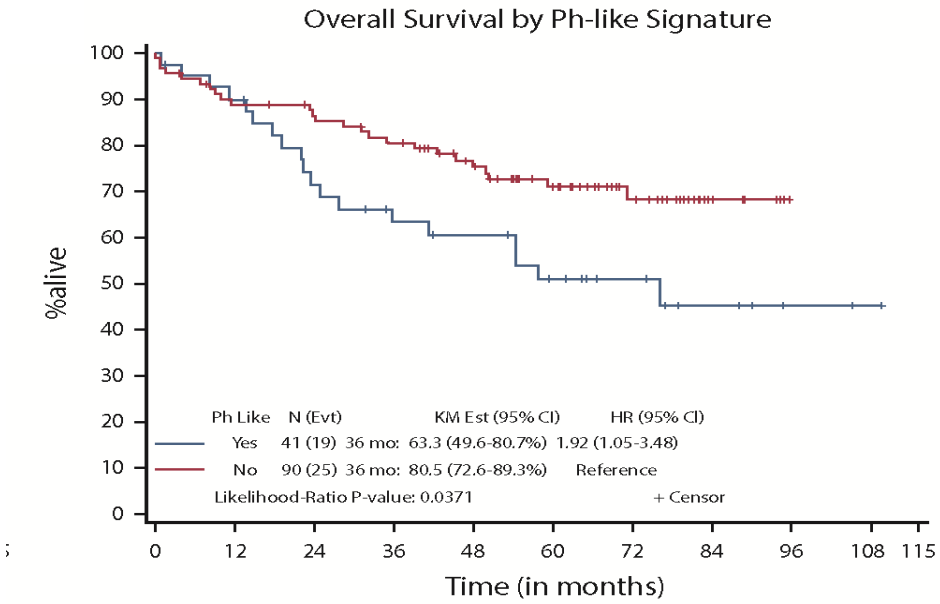
Stock et al Blood, 2019; 133, 1548-1559

Only 40% of patients are MRD negative early in treatment

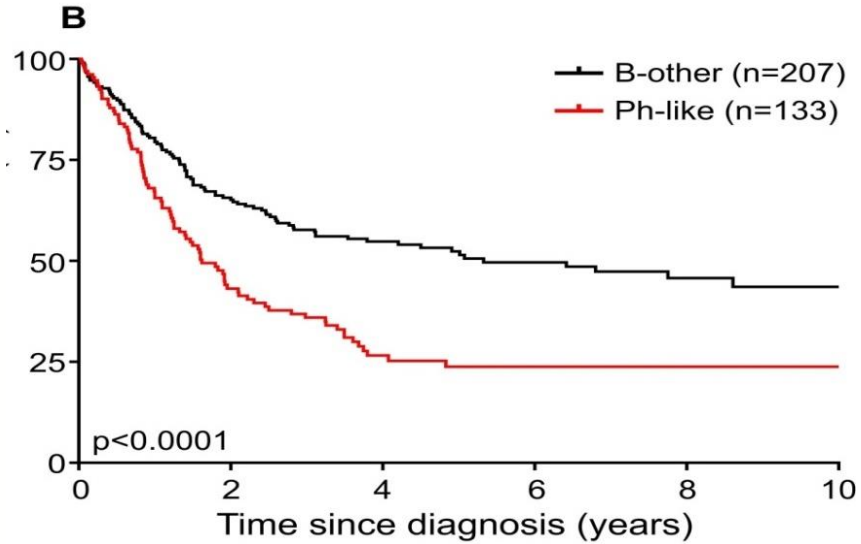
Ph-like ALL : Common and Outcomes Poor

>0.01% MRD at end of induction	
BCR-ABL1-like	40% (16/40)
Not BCR-ABL1-like	15% (46/301)

Age 18-40



Age 21-86



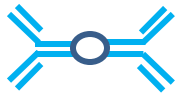
Up to 30% of AYAs with B-ALL have Ph-like ALL

Roberts, et al. JCO 2014
Stock, et al, Blood 2019
Roberts, JCO 2017

NEXT STEPS: INCORPORATING ANTIBODIES INTO FRONTLINE THERAPY, BH3 MIMETICS

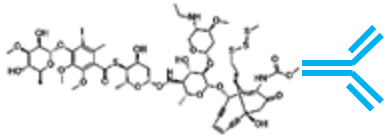
Relapsed B-ALL in Adults: Great Options!

Blinatumomab



- **CD19 - CD3 BiTE[1]**
- **CR:** 34%
- **ORR:** 44%
- **MRD-neg:** 76% of ORR
- **SCT:** 24%
- **Median OS:** 7.7 mos

Inotuzumab ozogamicin



- **CD22 Ab drug conjugate[2]**
- **CR:** 36%
- **ORR:** 81%
- **MRD-neg:** 78% of ORR
- **SCT:** 41%
- **Median OS:** 7.7 mos

CAR T-cell Therapy

- **Anti-CD19 Zuma-3[3]**
- **CR:** 56%
- **MRD-neg:** 97% of CR
- **SCT:** 18%
- **Median PFS:** 12.8 months (95% CI 8·7-not estimable
- **Median OS:** 18.2 months (15·9-not estimable)

1: Kantarjian et al, N Engl J Med 2017; 376:836-847
2: Kantarjian et al, N Engl J Med 2016; 375:740-53
3: Shah et al, Lancet. 2021 Jun 3:S0140-6736

Targeted antibodies for Ph-like ALL: Inotuzumab Ozogamycin (InO) and Blinatumomab (Blina)

- Ph-like cases are usually strongly CD19 and CD22 positive

  Relapsed/ Refractory Ph-like ALL (post-hoc analysis)

CVP/ Ino	5 Ph-like pts:	60% CR/ CRi[1]
InO Single agent:	12 Ph-like pts:	58% CR/ CRh[2]
Blina single agent:	16 CRLF2 pts:	75% CR[3]

[1]Advani et al. Blood 2019; 134 (Suppl 1): 227; [2]Jabbour et al. Blood 2019; 134 (Suppl 1): 1641; [3]Zhao et al, Blood 2021 137: 471-484

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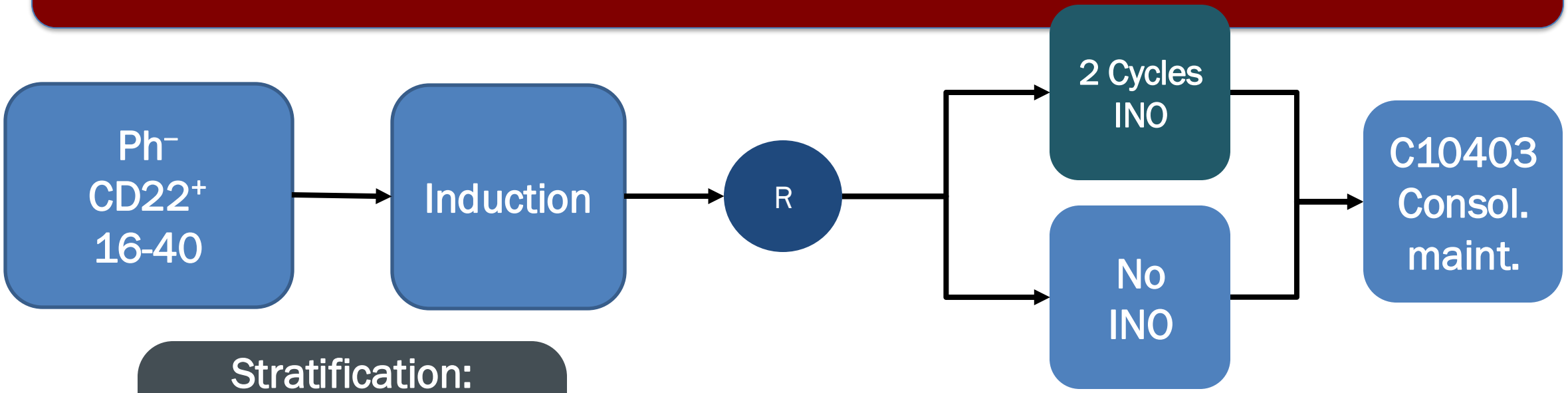
A041501 for AYAs 18-39 years: Can We Improve EFS to 80%?



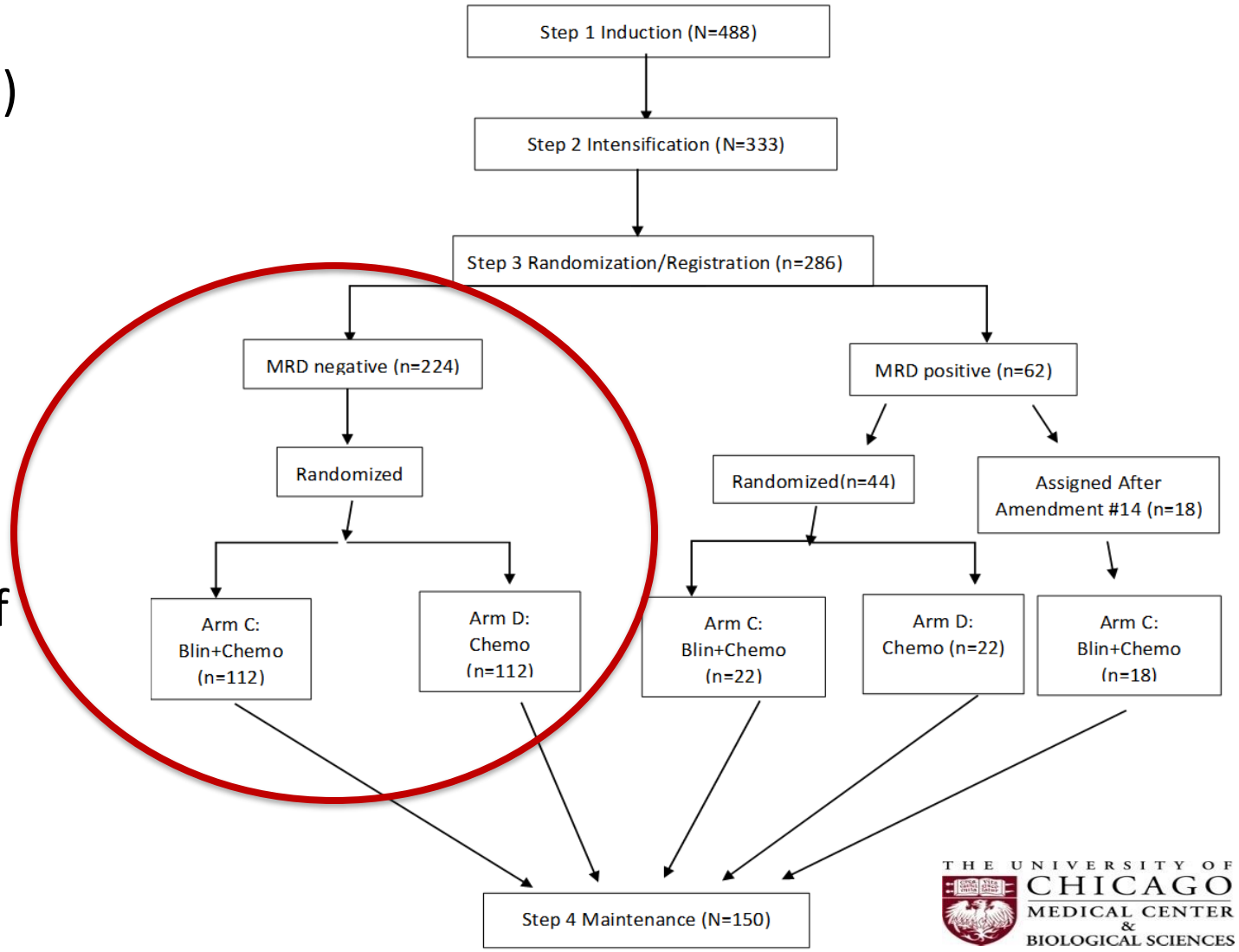
Stratification:
Age
LDA card for Ph-like
CD20$^{+/-}$

Primary end point:
3-y EFS

Goal: improvement in 3-y EFS from 66% to 80%

E1910 Results: MRD Negative Cohort Benefits from Blina

- 488 pts enrolled
- Median age: 51yrs (range 30-70yrs)
- Median follow-up 3.6 yrs
- CR/CRi rate 81% (395/488 pts)
  - CR 75% (364 pts)
  - CRi 6% (31 pts)
- 224 MRD-neg patients
  - Among MRD-neg, 22 patients in each arm underwent alloHSCT
  - 80% of pts received ≥2 cycles of blinatumomab



Litzow et al, NEJM, July 2024

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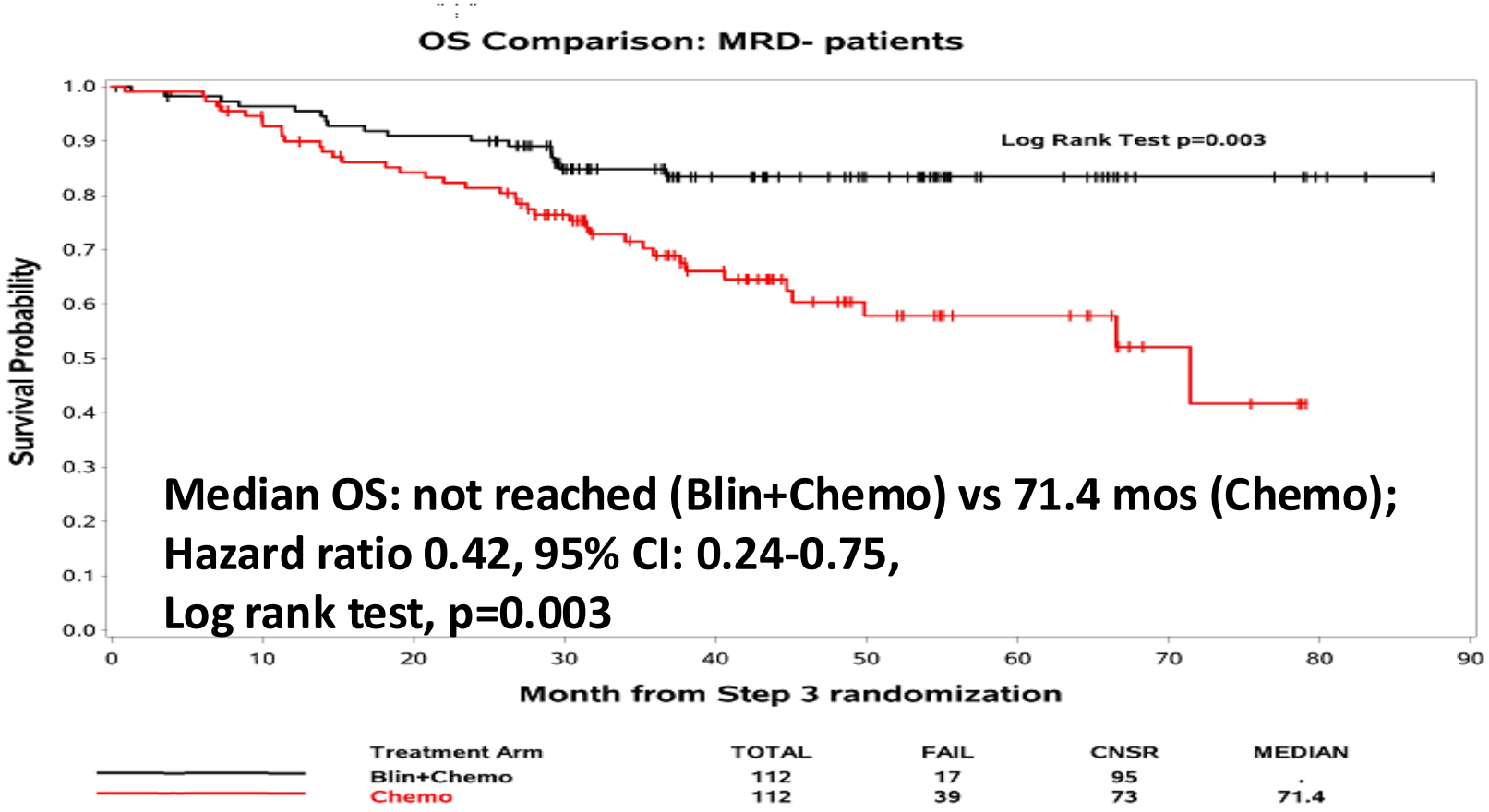
E1910 Overall Survival : MRD negative patients

Come see updated results today at EHA ALL session: Mattison et al



Deaths on Blin+Chemo Arm=17 (2° to ALL=8, NRM=9), Chemo Arm=39 (2° to ALL=20, NRM=17, Unknown=2)

Litzow et al, ASH 2022

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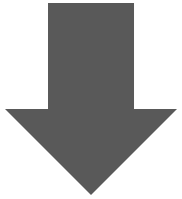
Proposed modification of A041501: Amendment to CTEP

Inotuzumab (D1 and 15)
cycles 1 and 2*



I	C	IM	Blina	DI	M
DNR VCR Dex Peg-Asp or CAL-ASP IT-MTX IT-AraC	Cyclo VCR Dex Peg-Asp or CAL-ASP Ara-C 6MP IT-MTX (R-CD20+)	MTX VCR Peg-ASP or CAL-ASP IT-MTX (R-CD20+)	Blinatumomab 2 cycles IT MTX	DOX Cyclo Dex Peg-Asp Ara-C 6-TG IT-MTX (R-CD20+)	DEX VCR 6MP MTX IT-MTX

Maintenance therapy continues for 2 (F) to 3 (M) years CD22 positive B-cell ALL[2]

*Blinatumomab allowed for MRD positive following INO.

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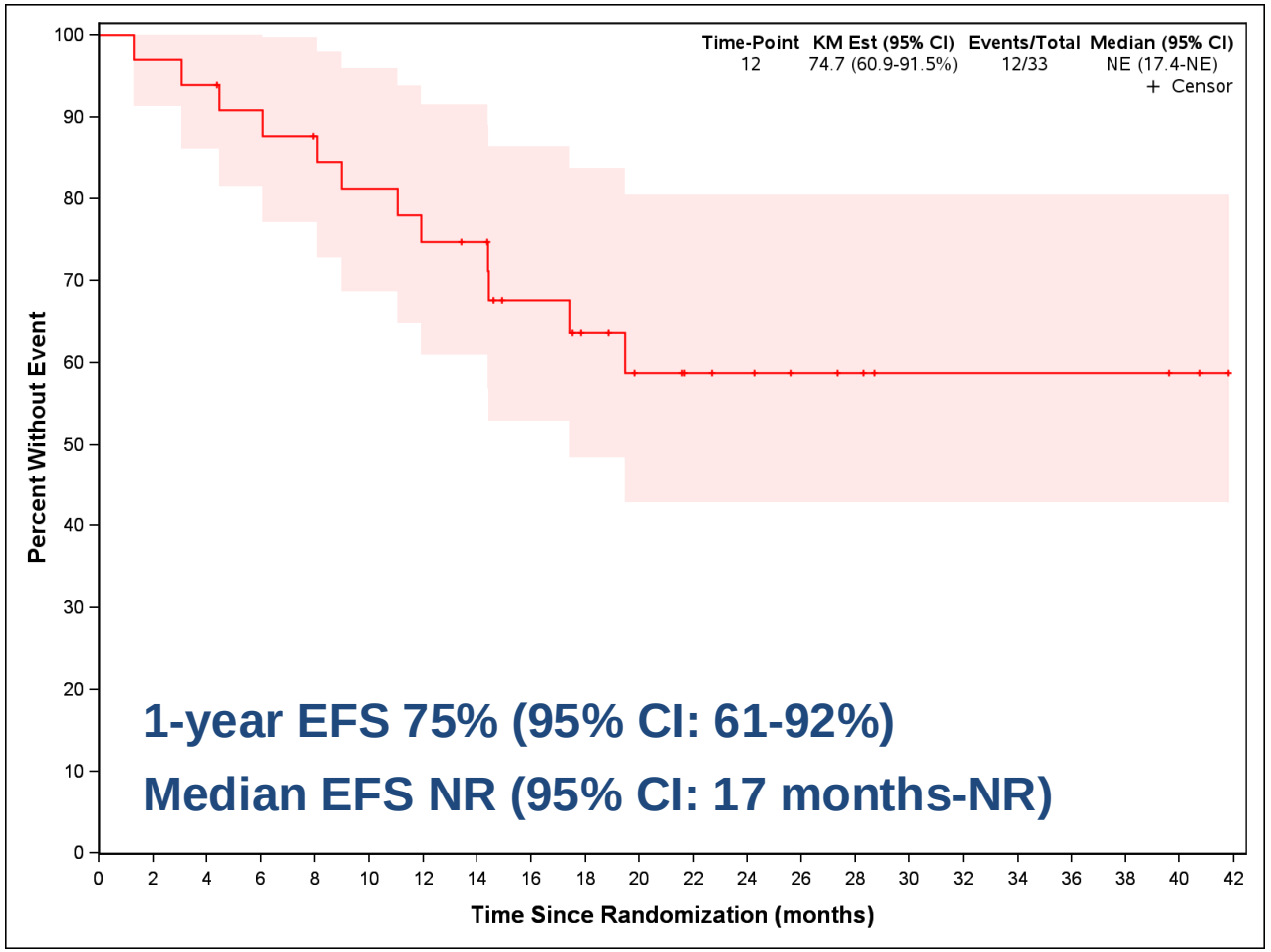
Alliance A041703: Chemo-Free!! InO ➡ Blina



EFS (%)

Months

Wieduwilt et al, EHA 2023

Adults ≥ 60 years old with CD22+ B-ALL; includes t-ALL

Median age = 71 yrs

2 cycles INO ➡ 4 cycles Blina

CNS prophylaxis: IT chemo

No maintenance therapy

Composite CR = 96%

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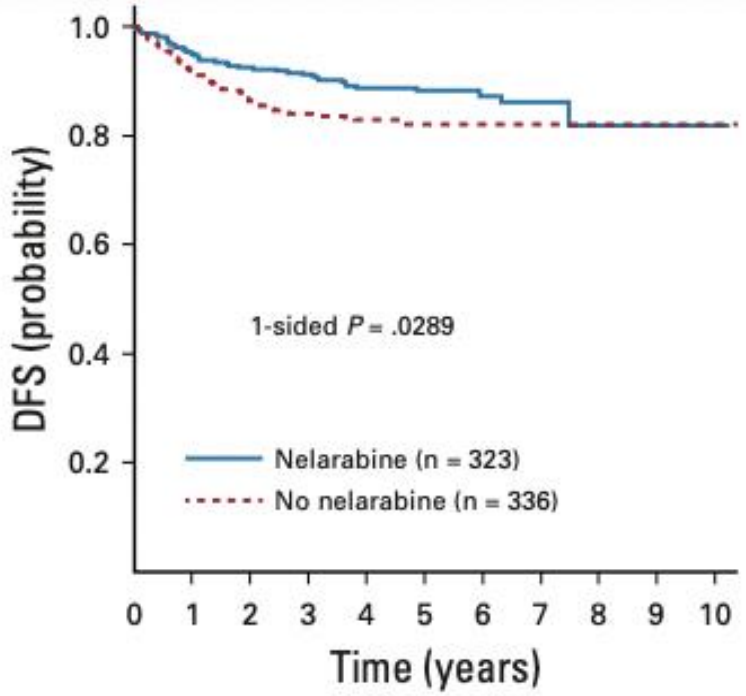
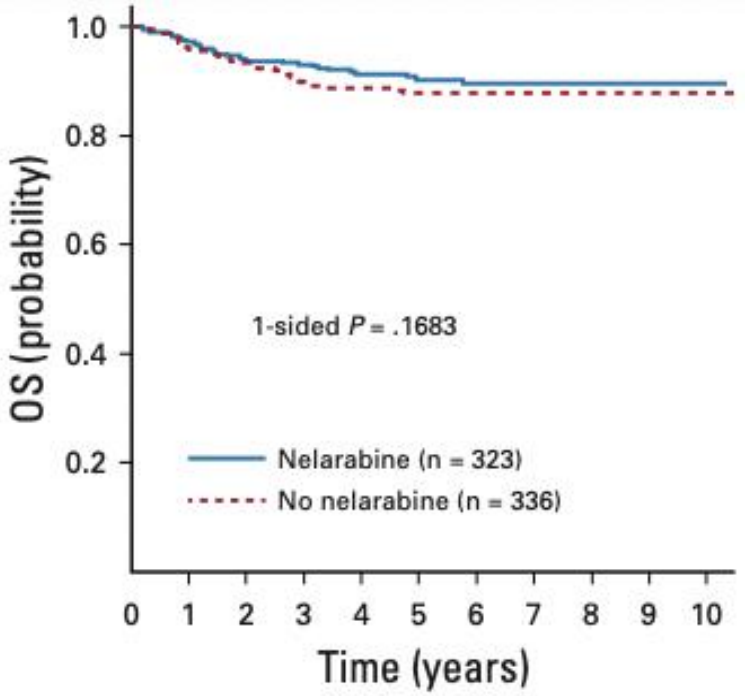
Nelarabine improves DFS





No. at risk:											
Nelarabine	323	303	293	285	222	156	91	32	15	6	1
No nelarabine	336	304	284	273	224	167	97	43	17	8	2

No. at risk:											
Nelarabine	323	310	296	291	234	164	100	37	15	6	2
No nelarabine	336	319	306	290	240	177	108	45	20	9	2

- **Nelarabine incorporated into ABFM; six 5-day courses**
- **3% of the 1895 patients were AYAs between 20-30 years old**
- **5 yr DFS was 88.2% with nelarabine vs 82% DFS without (p=.02)**

Dunsmore et al, J Clin Oncol 2020:28, 3282-3293

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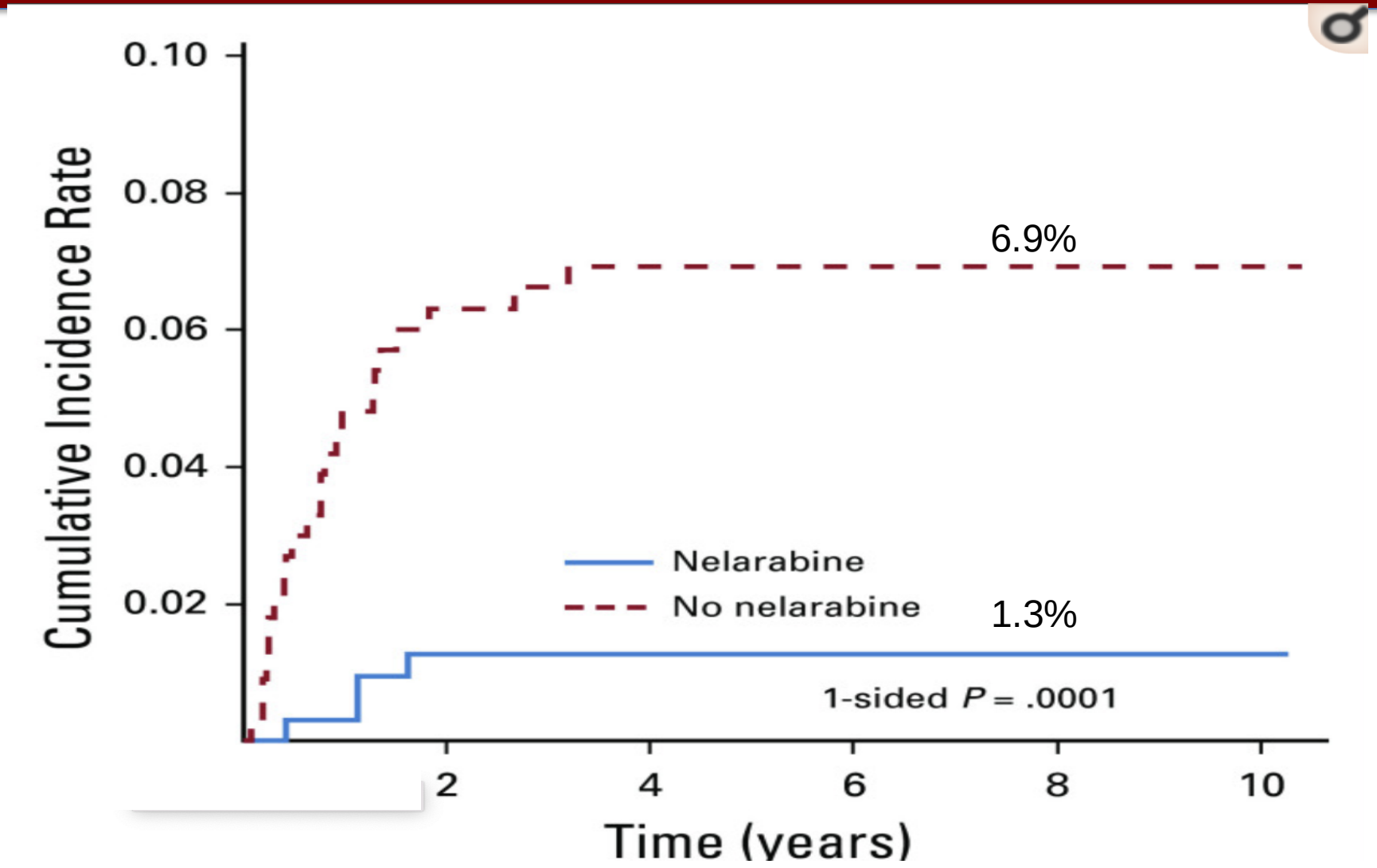
Nelarabine reduces CNS relapse



Dunsmore et al, J Clin Oncol 2020:28, 3282-3293

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Venetoclax/Navitoclax in combination with chemotherapy has activity in relapsed/refractory T-ALL

Response	B-ALL (n=25)	T-ALL (n=19)	LL (n=3)	All Patients (N=47)
CR/CRi/CRp, n (%)	**16 (64)**	**10 (53)**	**2 (67)**	**28 (60)**
ALL patients with ≥5% BM blasts at baseline, n/N	15/23 (65)	7/14 (50)	NA	22/37 (59)
ALL patients with morphologic CR at baseline, n/N	0/1 (NE)	3/4 (75)	NA	3/4 (75)
PR, n (%)	3 (12)	0 (0)	0 (0)	3 (6)
MRD-negative CR/CRi/CRp in ALL, n/N (%)	9/16 (56)	6/10 (60)	NA	15/26 (58)
Median DOR (95% CI), mo	9.1 (1.4–14.6)	4.2 (0.8–12.3)	NE (NE–NE)	4.2 (2.3–11.5)
Median OS (95% CI), mo	9.7 (4.0–15.7)	6.6 (3.2–12.5)	NR (2.0–NE)	7.8 (4.0–12.5)
Proceeded to SCT or CAR-T, n (%)	8 (32)	3 (16)	2 (67)	13 (28)

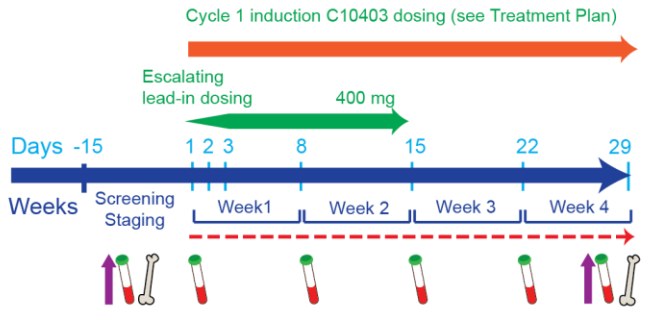
- Of 12 pediatric patients, 9 (75%) achieved CR/CRi/CRp, and of those, 6 achieved MRD-negative CR/CRi/CRp
- 4/32 (13%) patients achieved CR/CRi/CRp on Day 8 with Ven + Nav prior to starting chemotherapy on Day 9
- **CR rates were ≥50% across patient subgroups, including in those who had relapsed or were refractory to:**
  - **Blinatumomab: 8/13 (62%)**
  - **Inotuzumab ozogamicin: 8/14 (57%)**
  - **SCT: 5/8 (63%)**
  - **CAR T-cell therapy: 3/6 (50%)**

Pullarkat et al, Cancer Discovery 2021

Venetoclax + 10403 for AYA ALL:

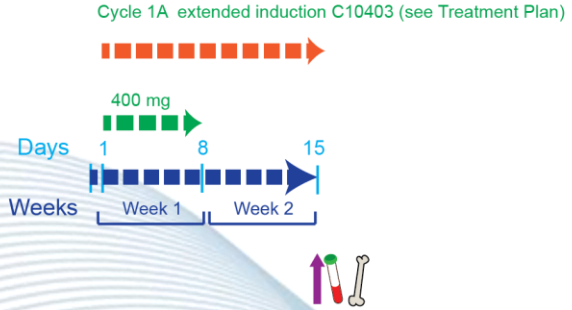
EUROPEAN HEMATOLOGY ASSOCIATION

Cycle 1: Induction



Dose Level	Venetoclax dose
DL 1	400 mg/day on days 1-14 during IND + CON
DL -1	200 mg/day on days 1-14 during IND + CONS

Cycle 1A: Extended Induction for patients in PR or SD at week 4



Cycle 2: Consolidation for patients with CR, CRi or CRh after Cycle 1 or 1A

Eligibility

- ND B-cell ALL
- 18-54 yrs
- Adequate organs function

Exclusion

- *BCR::ABL1*
- *KMT2A-r*
- *ETV6::RUNX1*
- *TCF3::PBX1*

Primary objectives

- Safety
- RP2D

Secondary objectives:

- CR/CRi rate
- MRD- rate post CONS in all pts, and in Ph-like ALL pts
- OS, LFS

MRD- was defined as <0.01%

Aldoss et al, EHA 2024

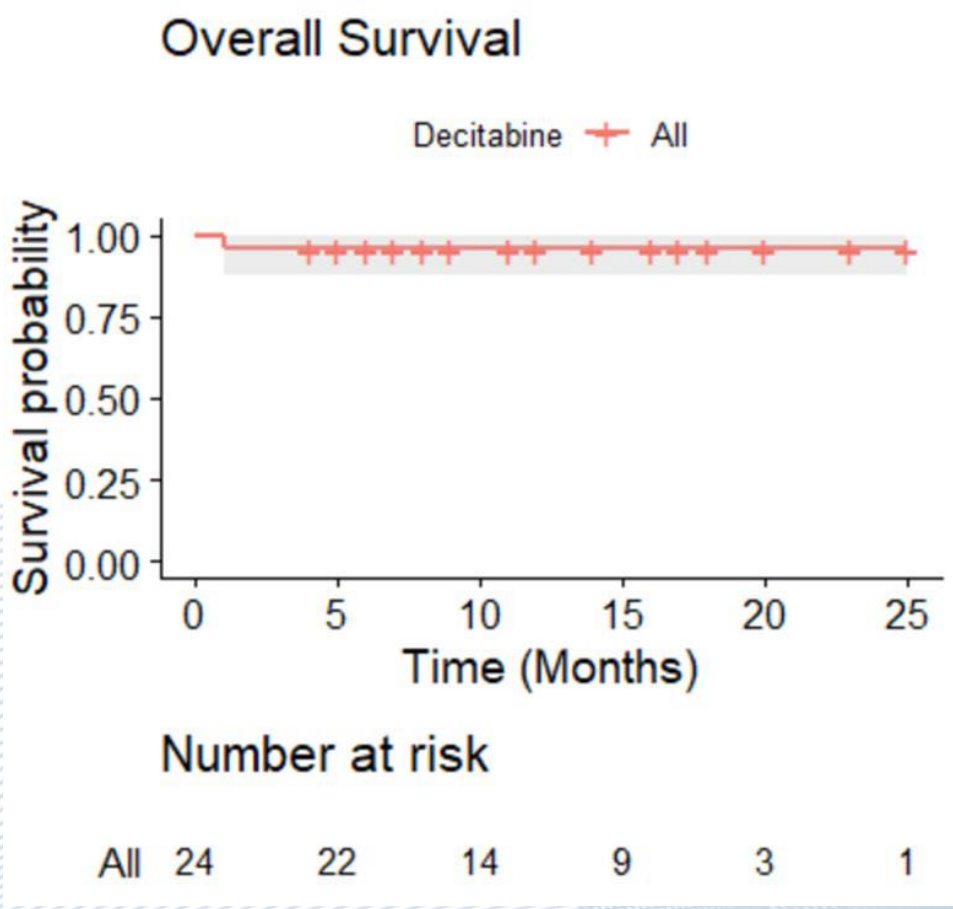
Efficacy outcomes and disposition

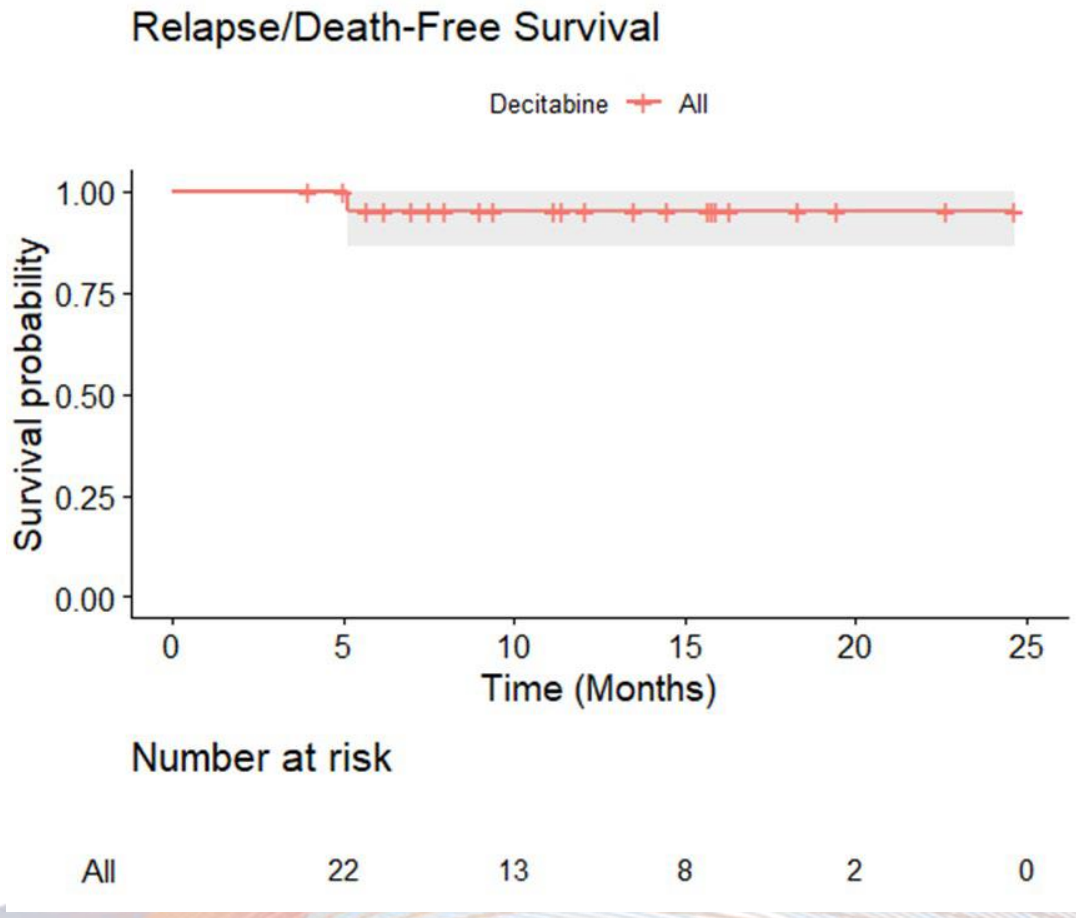
	All patients (%)	Ph-like (%)	Non-Ph-like (%)
Number	24	**12**	12
CR/CRi after induction/extended induction	23/23 (100)	**12/12 (100)**	11/11 (100)
Patients required extended induction	2/23 (9)	**2/12 (17)**	0/11 (0)
CR/CRi after consolidation	22/22 (100)	**12/12 (100)**	10/10 (100)
MRD- (<0.01%) rate post induction	11/23 (48)	**2/12 (17)**	9/11 (82)
MRD- (<0.01%) rate post consolidation	20/22 (91)	**11/12 (92)#**	9/10 (90)
MRD- by NGS (<0.0001%) post consolidation	13/21 (62)	**5/11 (45)**	8/10 (80)
HSCT in CR1	7/23 (30)	**6/12 (50)**	1/11 (9)
Immediate post study treatment			
Blinatumomab +/- chemo	17 (74)	**10 (83)**	7 (64)
Chemotherapy	4 (17)	**1 (8)**	3 (27)
HSCT	1 (4)	**1 (8)**	0
Lost of follow up	1 (4)	**0**	1 (9)
Early death (within 60 days)	1 (4)	**0**	1 (8)
Relapse	1 (4)	**1 (8)**	0

 # the only Ph-like patient with MRD+ post CONS had a MRD of 0.01% by flow and was negative by clonoSEQ

Aldoss et al, EHA 2024

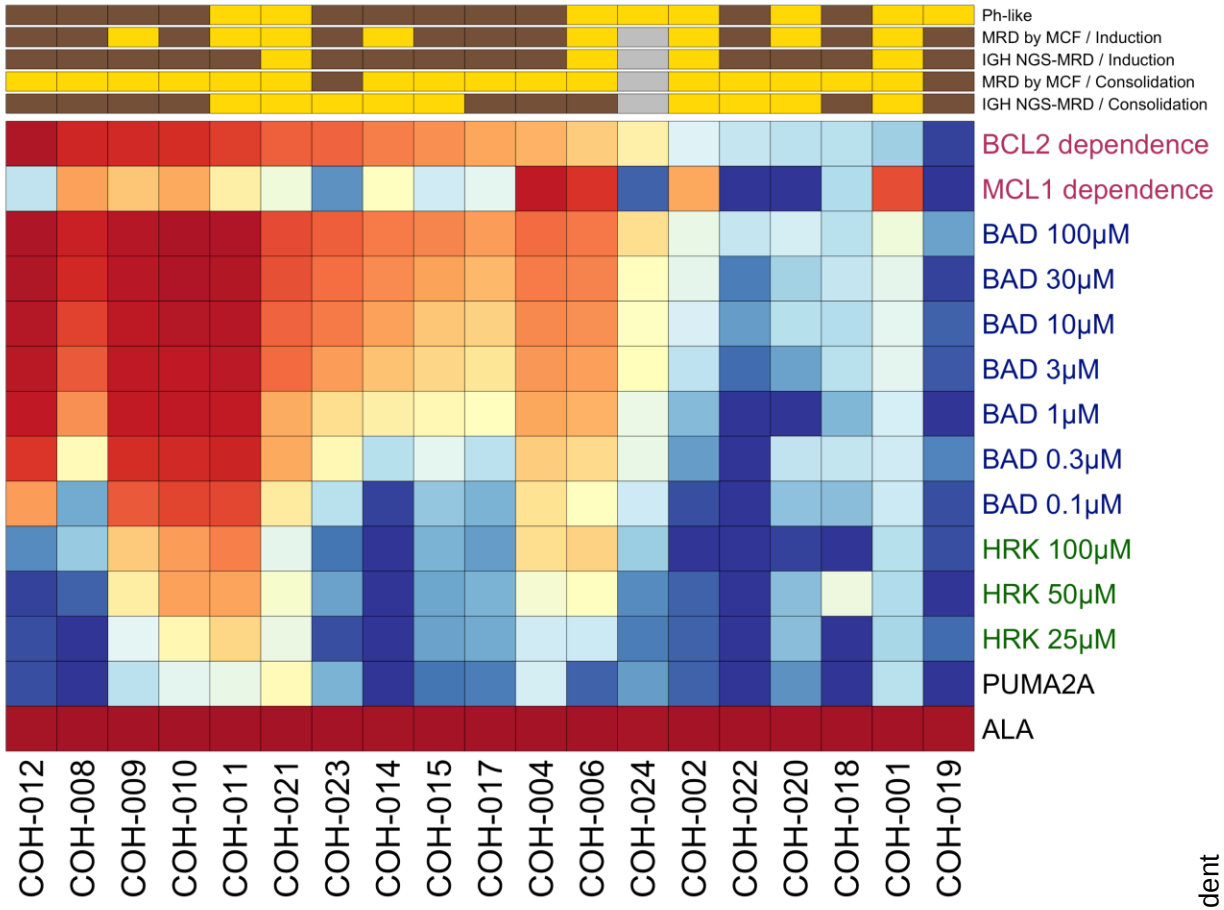
- Median follow up was 11.8 (range:1.1-24.7) months

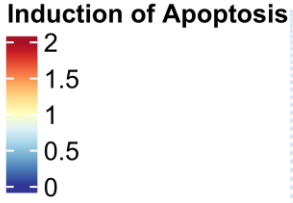


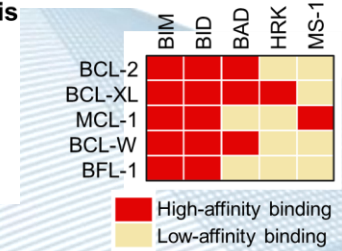


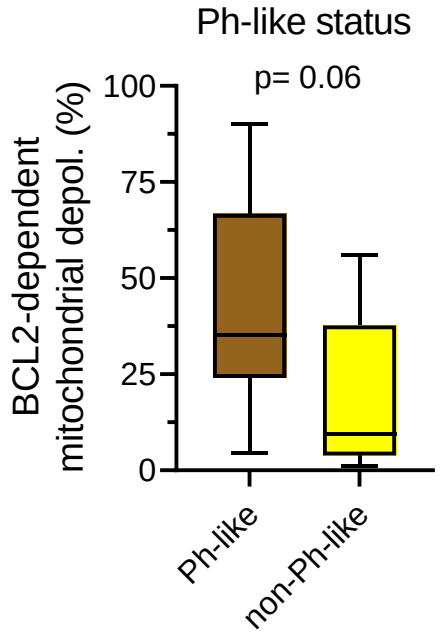
Aldoss et al, EHA 2024

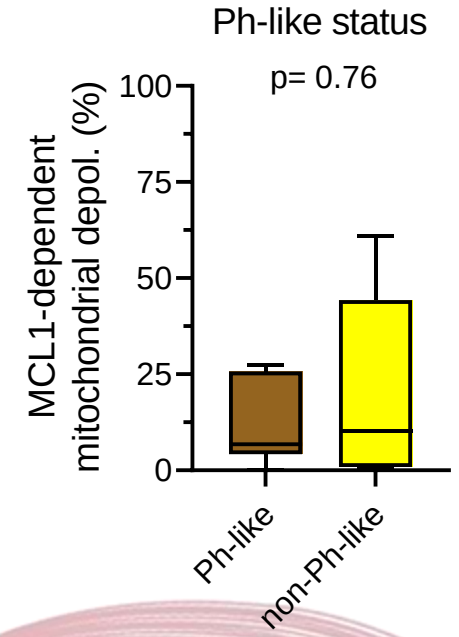
Ph-like B-ALL cases had a greater BCL-2-dependency compared to non-Ph-like, but no correlation between MRD response and BCL2 dependency

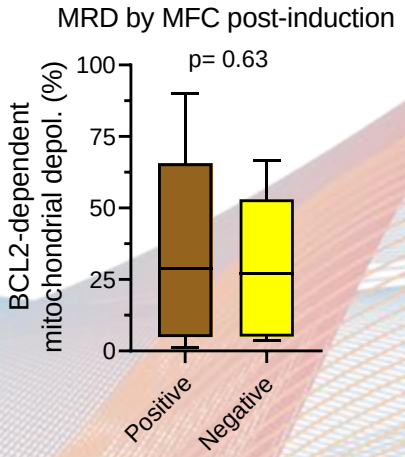


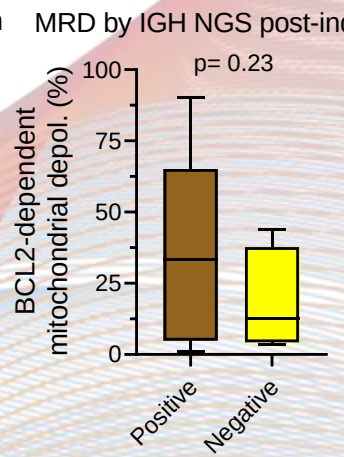


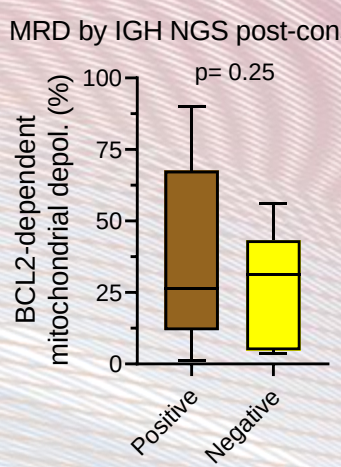








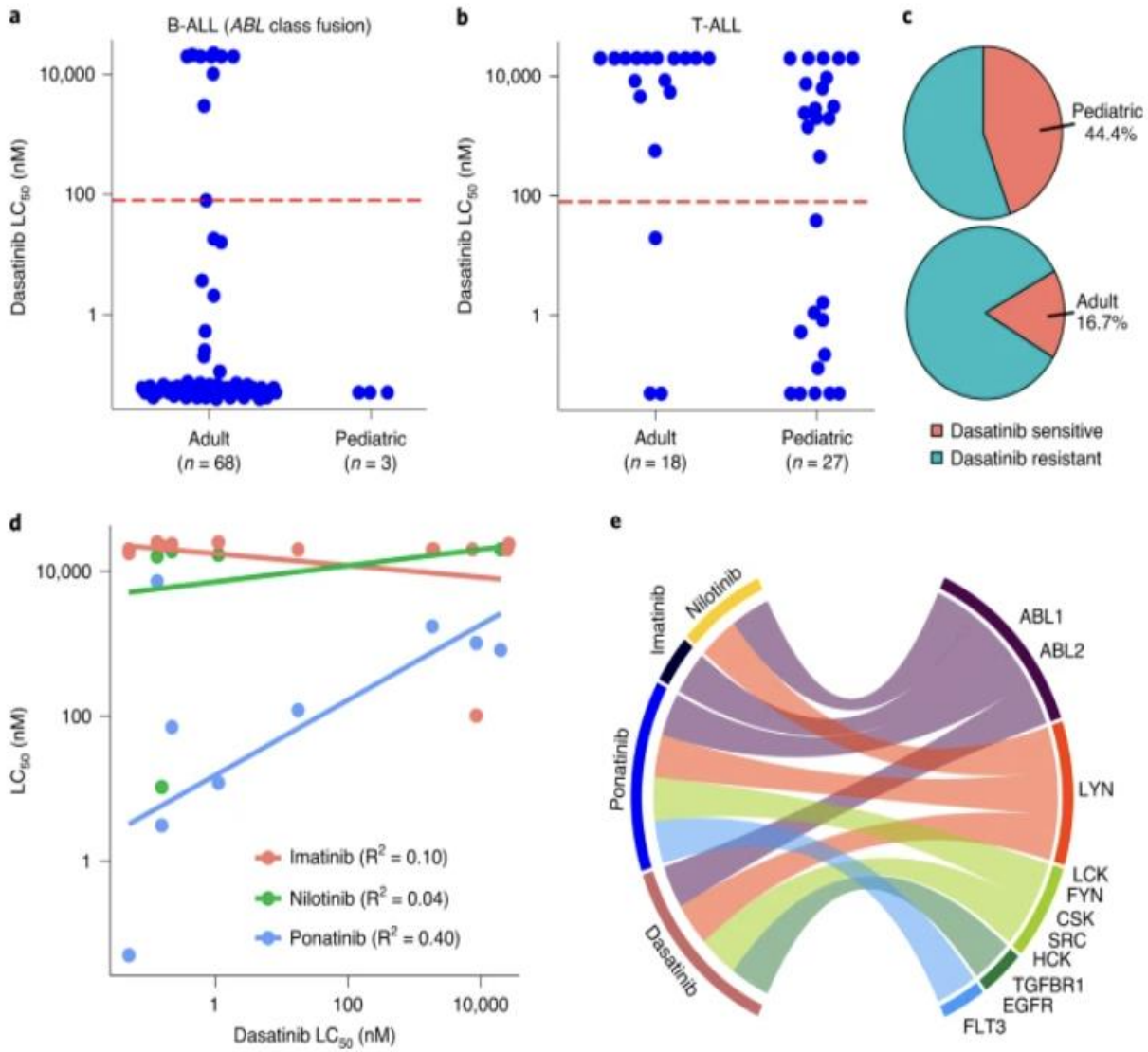




Other Potential Targets: Looking Forward

- Dual BH3 mimetic therapy with LP-118 (Newave)
  - Targets BCL2 and BCLXL
- Repurposing TKIs that block LCK (dasatinib, ponatinib)
  - Interferes with T-cell signaling to maintain leukemogenic state
  - May overcome venetoclax resistance
- Menin Inhibitors in T-ALL with H*OXA/MEIS1* deregulation
  - Preclinical data supportive
    - Shimamoto et al, ASH 2024

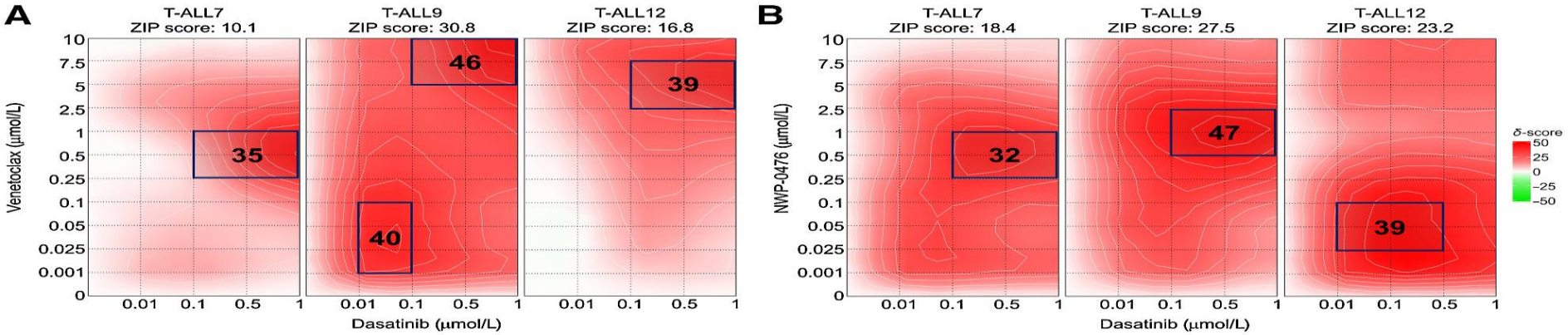
Pharmacotyping Reveals Dasatinib Sensitivity in T-ALL



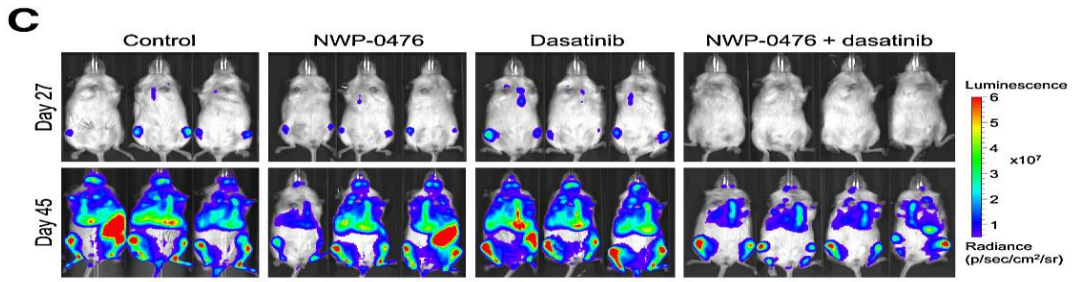
- Aberrant Pre-TCR signaling through LCK maintain leukemogenic state
- Dasatinib, Ponatinib inhibits LCK signaling; induces differentiation

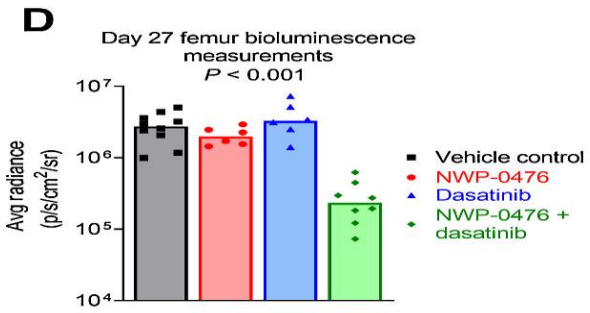
Gocho et al, Nature Cancer 2021

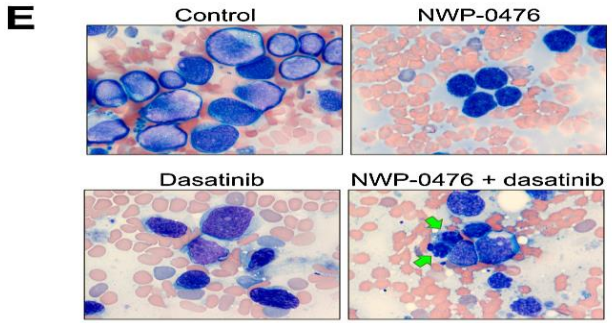
Overcoming Resistance : BH3 mimetics + TKI

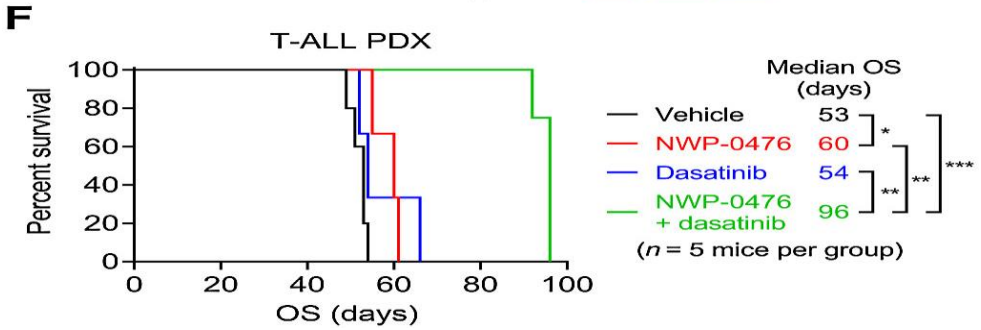


Caner Saygin, MD









Clin Cancer Resesarch 2023

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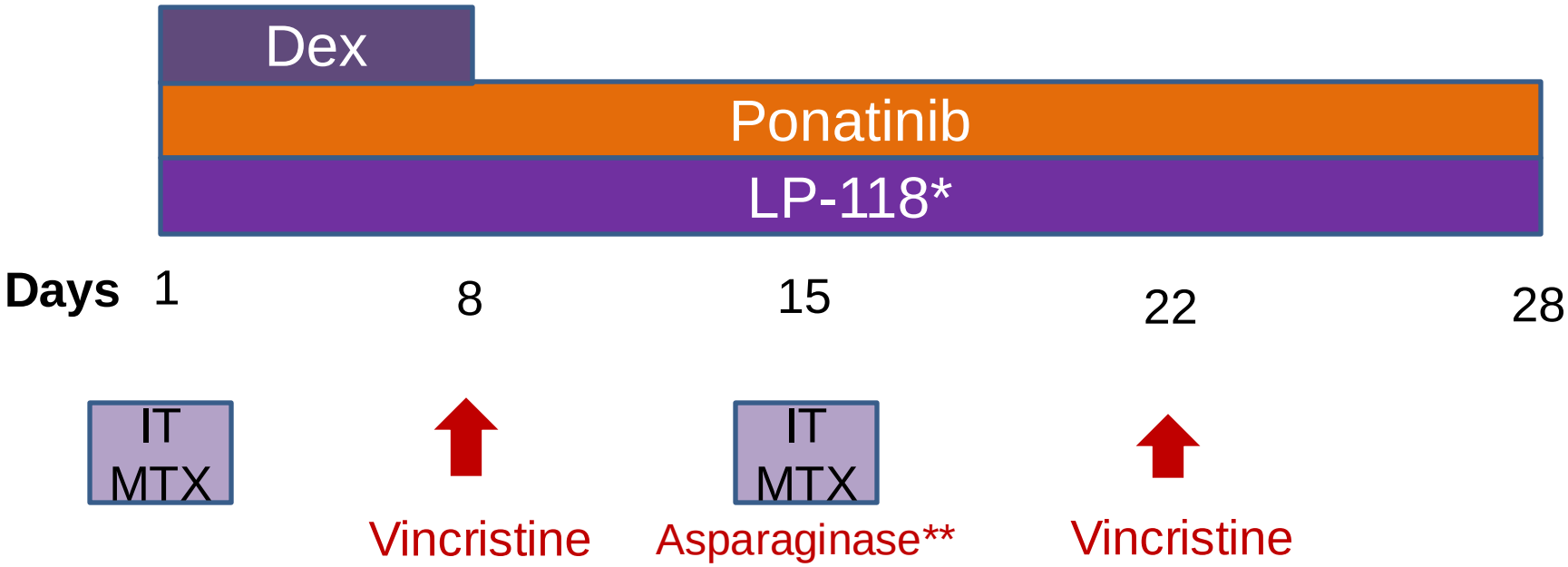
Phase I Study of LP-118 + Ponatinib



* LP-118 will be given for 28 days on cycle 1. The duration will be shortened to 14-21 days in subsequent cycles based on cytopenias.
** Asparaginase dose: 500 U/m^2 for >40 yrs, 1000 U/m^2 for <40 years.

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HOLISTIC CARE: U CHICAGO AYA CLINIC

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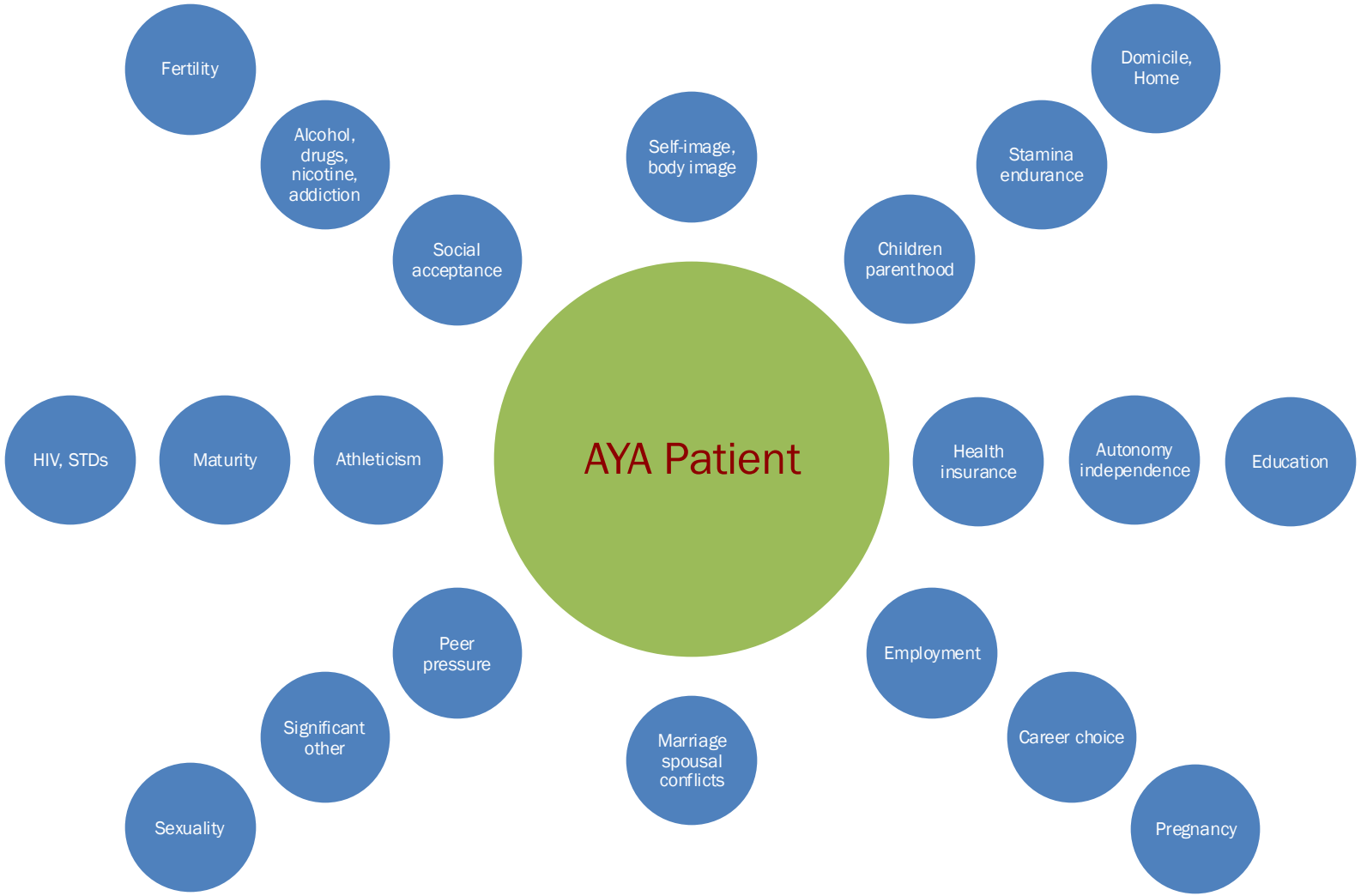
AYA with Cancer: Bombardment from all sides



- Husson O, et al. *Blood.* 2018:132:385-392.

The AYA Psyche and Treatment Adherence

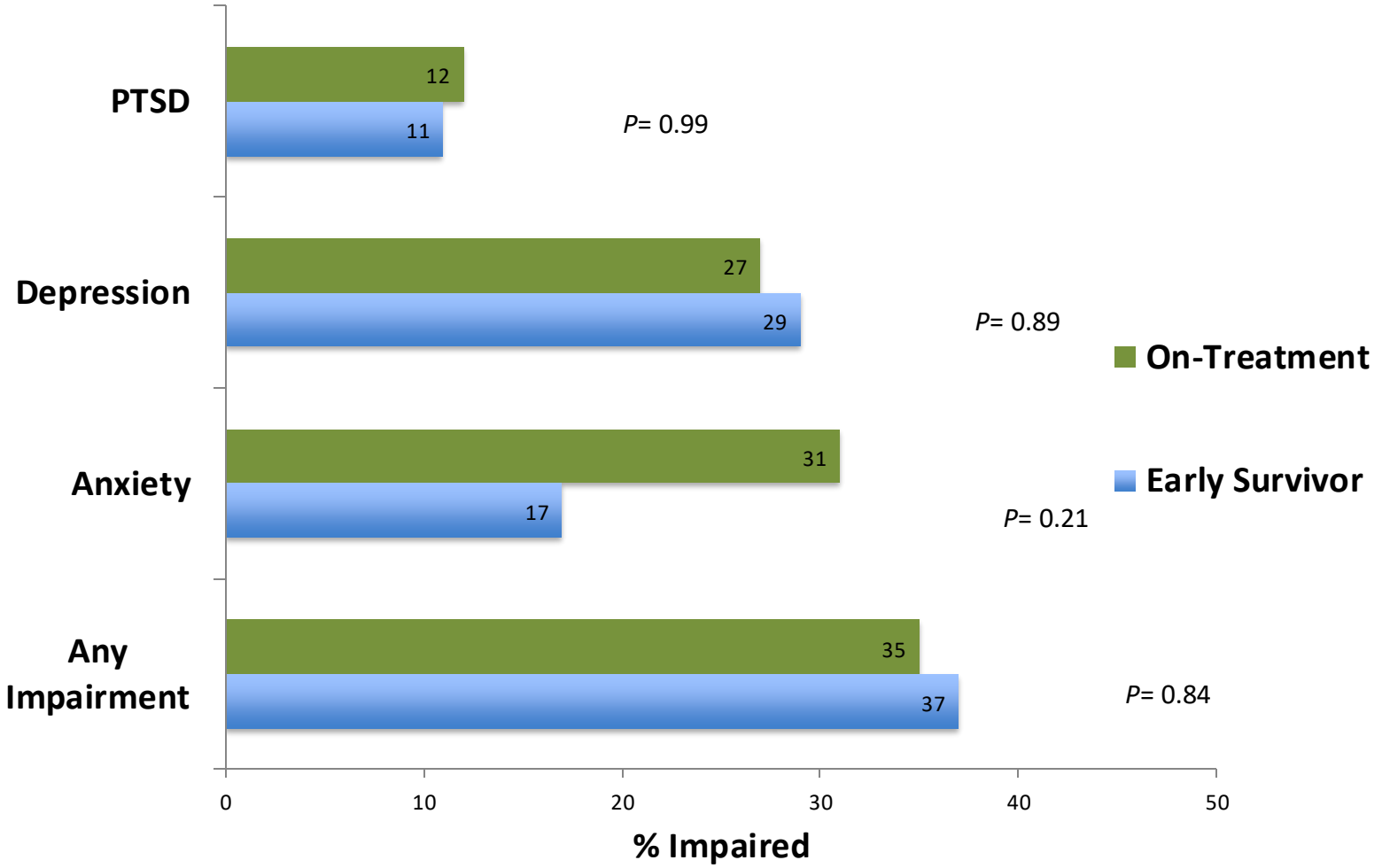
- Lower levels of well-being than patients with cancer in other age groups
  - Higher levels of isolation, depression

- Non-adherence in adolescents and young adults with cancer are high, ranging from 27-60%
  - Associated with higher rates of morbidity and lower survival rates

- On C10403, only 40% of all patients completed all therapy (multifactorial)
  - Must do better!

Kroenke et al, JCO 22:1849, 2004; Kondryn et al; Lancet Oncology 12:100, 2011; Bleyer et al, CA Cancer J Clin 57;242, 2007; Kondryn et al Psychooncology 18; 1327, 2009

Survivorship Support Crucial: Psychological Impairments Common]Amongst AYAs with Hematologic Malignancies



Muffly et al, Cancer 2016

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Late effects: Similar to Childhood Survivors?

Data lacking in young adult survivors of ALL…….

- Cardiovascular
- Neurocognitive
- Obesity
- Musculoskeletal – AVN
- Fertility
- Second Cancers

It takes a Village: AYA Clinic at UChicago

AYA Clinic Goals:

- Provide comprehensive therapeutic, fertility preservation guidance and psychosocial support:
  PharmD, Psychologist, AYA programming, Nursing continuity, Supportive/Palliative Care
- Improved patient well-being and alliance with medical team
- Improved treatment adherence leading to better outcomes
- Survivorship care

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Summary

- Pediatric regimens have become the standard of care for young adults with ALL with > 70% survival
- Still opportunities to optimize AYA ALL therapy
  - Decrease toxicity
  - Increase survival: Blina/Ino, Nelarabine
    - BH3 mimetics, Menin inhibitors for B and T-ALL
    - T-ALL innovation: Nelarabine in frontline, BH3 mimetics, CD38 targeting
- Specialized AYA care makes a difference! Care Access is Crucial
- For relapsed T-ALL: early CAR-T trials,
  - Preclinical insights: Repurposing TKIs, Menin inhibition

Summary: AYA ALL "Keys" to Further Improvements

- **Pediatric inspired approach affords improved survival for AYAs**
  - Systematic review demonstrates superiority, **but we can do better….**
- Addressing essential components of care:
  - **Access, equity, expertise**
  - **Toxicity reduction, obesity control**
- Addressing disease biology to **eradicate MRD**
  - **Targeted antibodies**, BH3 mimetics for T-ALL
- **Holistic approach** to care – enhancing treatment and survivorship

Gratitude

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