TREATING ADOLESCENTS AND YOUNG ADULTS (AYA) WITH BLOOD CANCER

October 11, 2023

LEUKEMIA & LYMPHOMA SOCIETY®

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WELCOME AND INTRODUCTIONS

Lesley Hoerst, BSN, RN
Senior Manager, Professional Education Programs
The Leukemia & Lymphoma Society
Rye Brook, NY

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SPEAKERS

Sharon M. Castellino MD, MSc
Professor, Department of Pediatrics
Emory University School of Medicine
Director, Leukemia and Lymphoma Program
Aflac Cancer and Blood Disorders Center
Children's Healthcare of Atlanta
Atlanta, GA

Julie Anna Wolfson, MD, MSHS
Associate Professor, Pediatric Hematology-Oncology
Institute for Cancer Outcomes and Survivorship
Director, AYA Oncology and Oncofertility Program
University of Alabama at Birmingham
Birmingham, AL

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DISCLOSURES

Sharon M. Castellino, MD, MSc, has a financial interest/relationship or affiliation in the form of:
Advisory Board/Consultant: Bristol Myers Squibb

The following relationships have ended within the last 24 months:
Advisory Board/Consultant: Seagen Inc.

Unlabeled Uses in Pediatrics
- Nivolumab
- Brentuximab vedotin (BV) (approved in high-risk; front line)
- Pembrolizumab (approved in rr/HL)

Julie Anna Wolfson, MD, MSHS, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

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DISCLOSURE

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Planner
Lauren Berger, MPH
The Leukemia & Lymphoma Society

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All of the relevant financial relationships of individuals for this activity have been mitigated.

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TARGET AUDIENCE

This activity is intended for hematologist/oncologists, nurses, social workers, and other healthcare professionals involved in the care of patients with blood cancer.

EDUCATIONAL OBJECTIVES

After completing this activity, the participant should be better able to:

- Describe blood cancers common in adolescent and young adults (AYAs)
- Identify signs and symptoms of common blood cancers in AYAs and diagnostic tests used
- Explain treatment options, including new and emerging data and the role of clinical trials
- Discuss the management of short and long-term effects, as well as unique considerations for AYAs
- List resources to support patients and their caregivers

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CE DESIGNATION

Accreditation, Credit and Support

In support of improving patient care, this activity has been planned and implemented by Medical Learning Institute, Inc., and The Leukemia & Lymphoma Society. Medical Learning Institute, Inc. is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physician Continuing Medical Education

Medical Learning Institute, Inc. (MLI) designates this live activity for a maximum of 1.0 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nursing Continuing Professional Development

Approval for nurses has been obtained by the National Office of The Leukemia & Lymphoma Society under Provider Number CEP 5832 to award 1.0 continuing education contact hour through the California Board of Registered Nursing.

Social Worker Continuing Education

The Leukemia & Lymphoma Society (LLS) Provider Number 1105, is approved as an ACE provider to offer social work continuing education by the Association of Social Work Boards (ASWB) Approved Continuing Education (ACE) program. Regulatory boards are the final authority on courses accepted for continuing education credit. ACE provider approval period: 12/10/2020-12/10/2023. Social workers completing this course receive 1.0 clinical continuing education credit.

The Leukemia & Lymphoma Society (LLS) is recognized by the New York State Education Departments State Board for Social Work as an approved provider of continuing education for licensed social workers #0117. LLS maintains responsibility for the program. Social workers will receive 1.0 clinical CE contact hour for this activity.

Interprofessional Continuing Education Credit

IPCE CREDIT™

This activity was planned by and for the healthcare team, and learners will receive 1.0 Interprofessional Continuing Education (IPCE) credit for learning and change.

Support Statement

There is no commercial support associated with this CE activity.

Providers

This activity is provided by The Leukemia & Lymphoma Society and Medical Learning Institute, Inc.

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METHOD OF PARTICIPATION

There are no fees for participating in or receiving credits for this accredited activity. For information on applicability and acceptance of continuing education credit for this activity, please consult your professional licensing board.

Learners must participate in the entire CE activity and submit the online evaluation form to earn credit, by clicking the link at the end of the presentation. Once submitted, the certificate will be generated. If you have questions regarding your certificate, please contact via email at ndane@mlieducation.org.

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UAB SCHOOL OF MEDICINE
Institute for Cancer Outcomes and Survivorship

UAB HEERSINK SCHOOL OF MEDICINE
The University of Alabama at Birmingham

O'NEAL COMPREHENSIVE CANCER CENTER
UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Children's of Alabama

Adolescents and Young Adults (AYA) with Blood Cancer

The Leukemia & Lymphoma Society

Julie Anna Wolfson, MD, MSHS
Associate Professor, Pediatric Hematology-Oncology
Member, Institute for Cancer Outcomes and Survivorship
Director, AYA Oncology & Oncofertility Program
October 11, 2023

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Polling Question #1

What is the NCI definition of an adolescent or young adult (AYA)?

a) **15 years – 39 years**
b) **15 years – 24 years**
c) **12 years – 21 years**
d) **12 years – 24 years**
e) **They act like a teenager**

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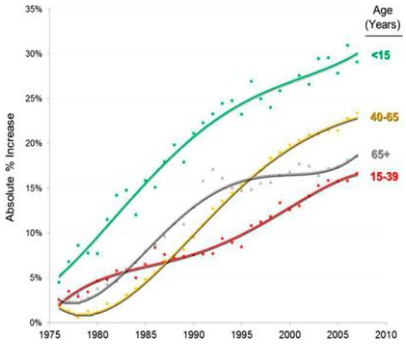
Adolescents and Young Adults (AYA) with Cancer

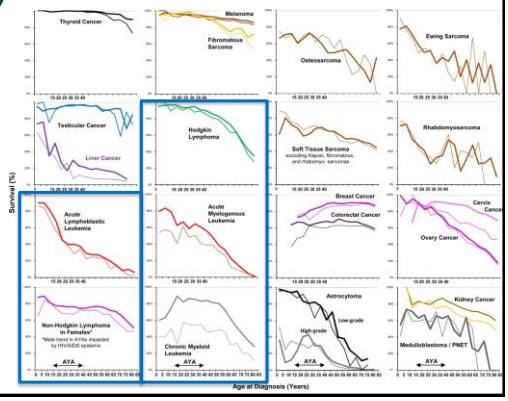
- Share diagnoses with older and/or younger patients



Bleyer, Cancer 2006

Have **not** seen same improvement in survival over time

AYA GAP



Keegan, Cancer 2016.

UAB SCHOOL OF MEDICINE
Institute for Cancer Outcomes and Survivorship

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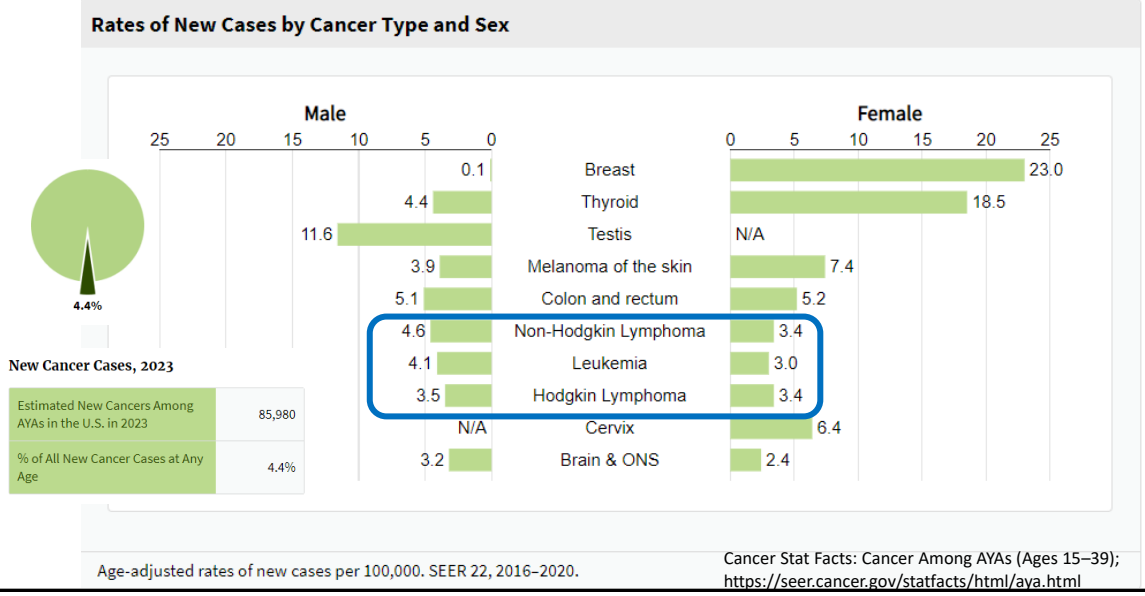
What Blood Cancers are AYAs Diagnosed with?



Cancer Stat Facts: Cancer Among AYAs (Ages 15–39); https://seer.cancer.gov/statfacts/html/aya.html

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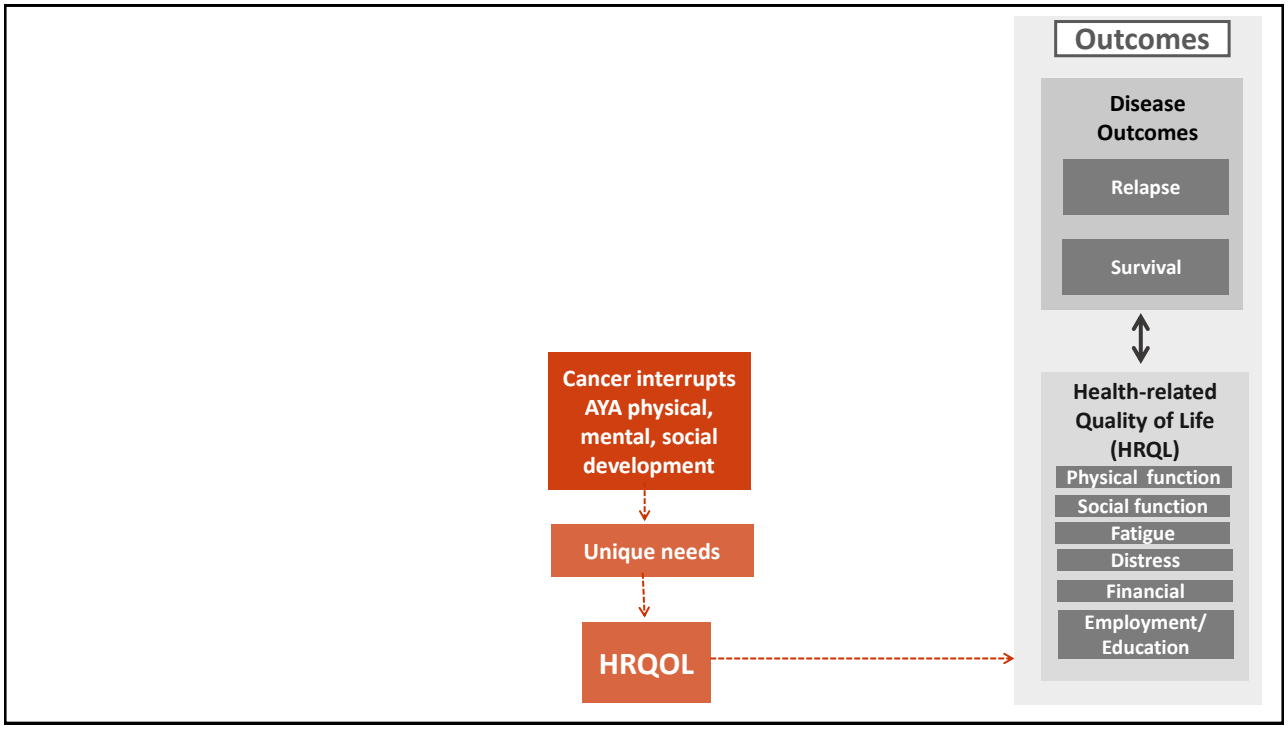
Outcomes
Disease Outcomes
Relapse
Survival
Health-related Quality of Life (HRQL)
Physical function
Social function
Fatigue
Distress
Financial
Employment/ Education
Cancer interrupts AYA physical, mental, social development
Unique needs
HRQOL

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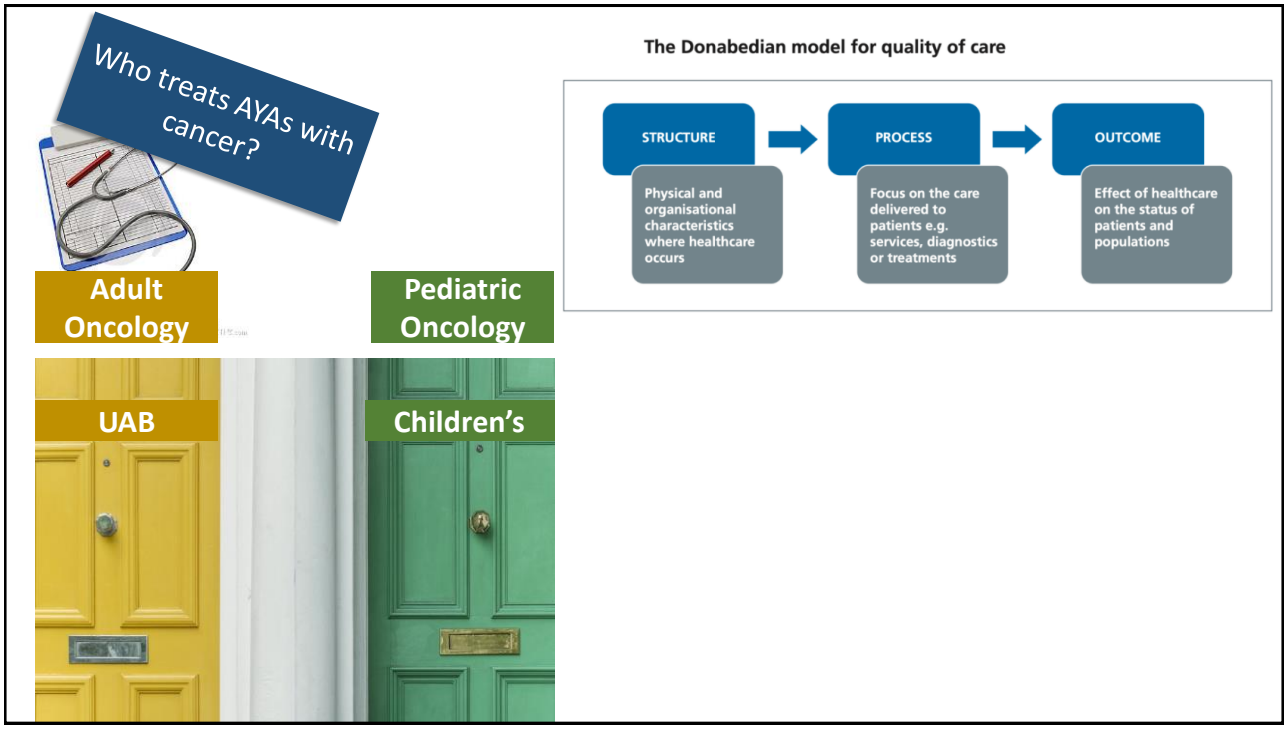
Who treats AYAs with cancer?
Adult Oncology
Pediatric Oncology
UAB
Children's
The Donabedian model for quality of care
STRUCTURE
Physical and organisational characteristics where healthcare occurs
PROCESS
Focus on the care delivered to patients e.g. services, diagnostics or treatments
OUTCOME
Effect of healthcare on the status of patients and populations

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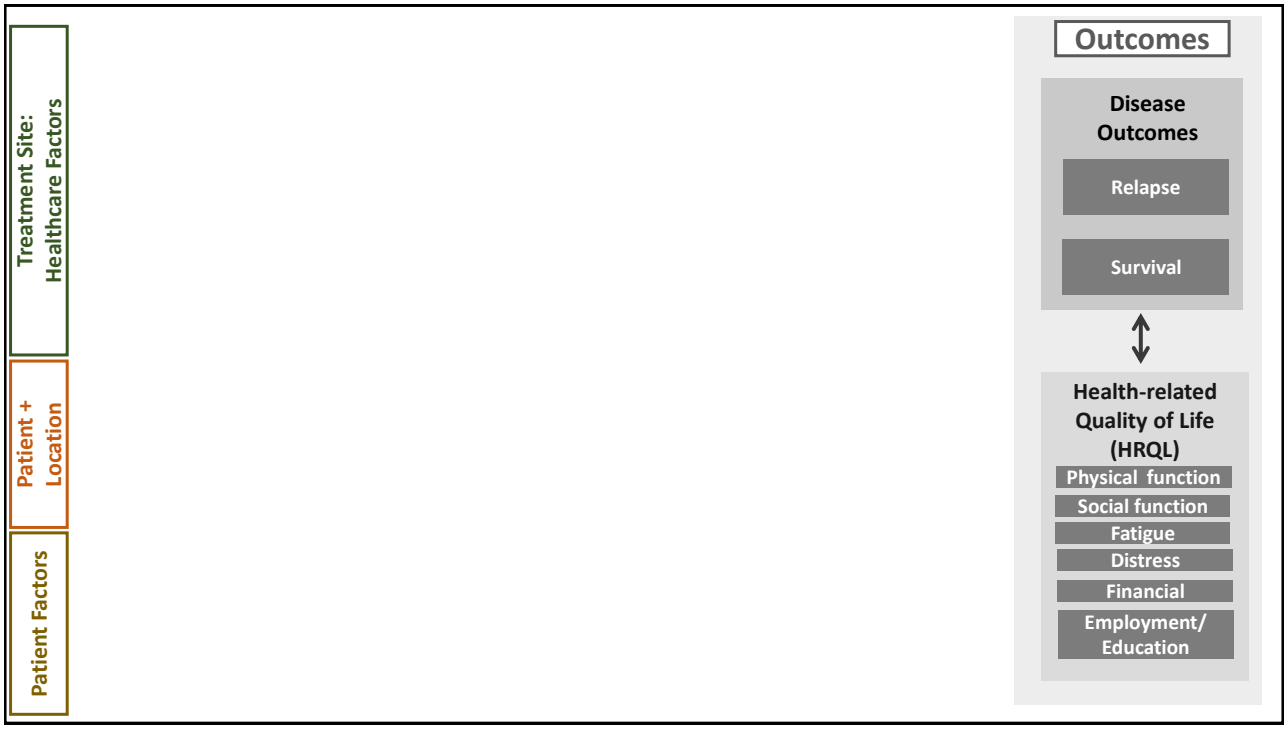
Treatment Site: Healthcare Factors
Patient + Location
Patient Factors
Outcomes
Disease Outcomes
Relapse
Survival
Health-related Quality of Life (HRQL)
Physical function
Social function
Fatigue
Distress
Financial
Employment/ Education

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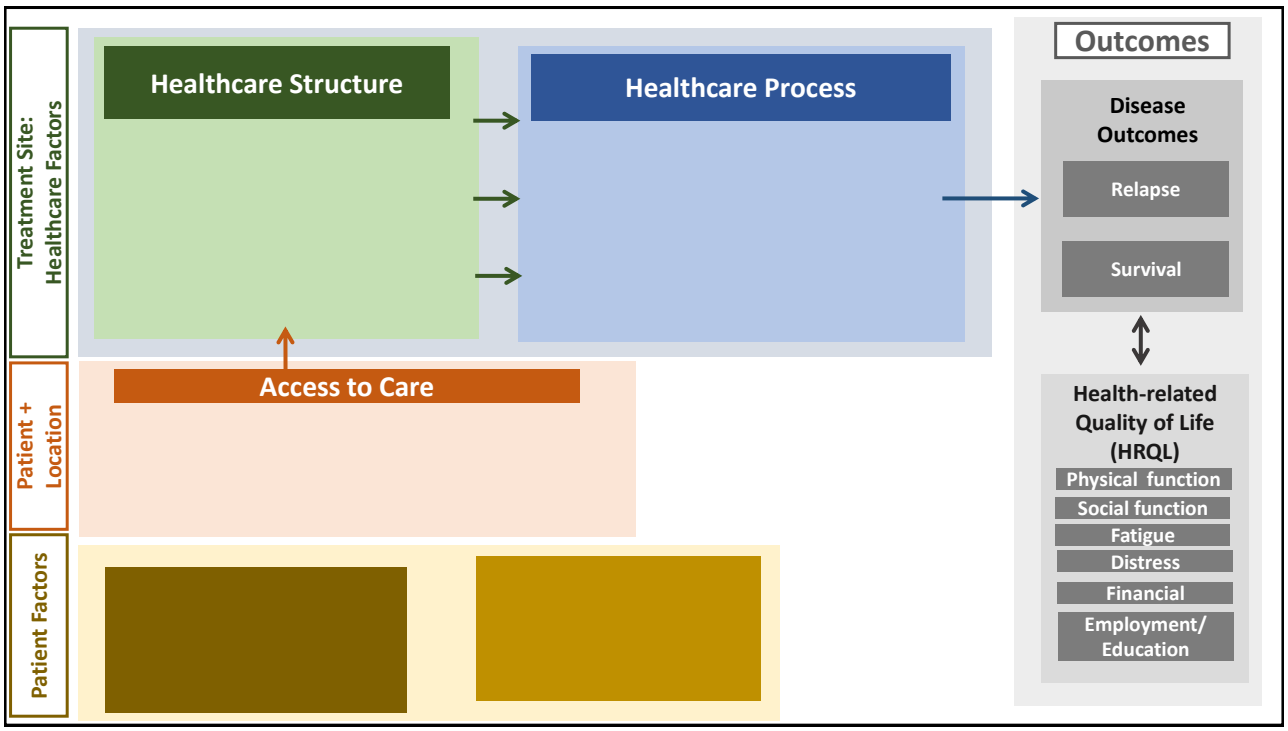
Treatment Site: Healthcare Factors
Patient + Location
Patient Factors
Healthcare Structure
Healthcare Process
Access to Care
Outcomes
Disease Outcomes
Relapse
Survival
Health-related Quality of Life (HRQL)
Physical function
Social function
Fatigue
Distress
Financial
Employment/ Education

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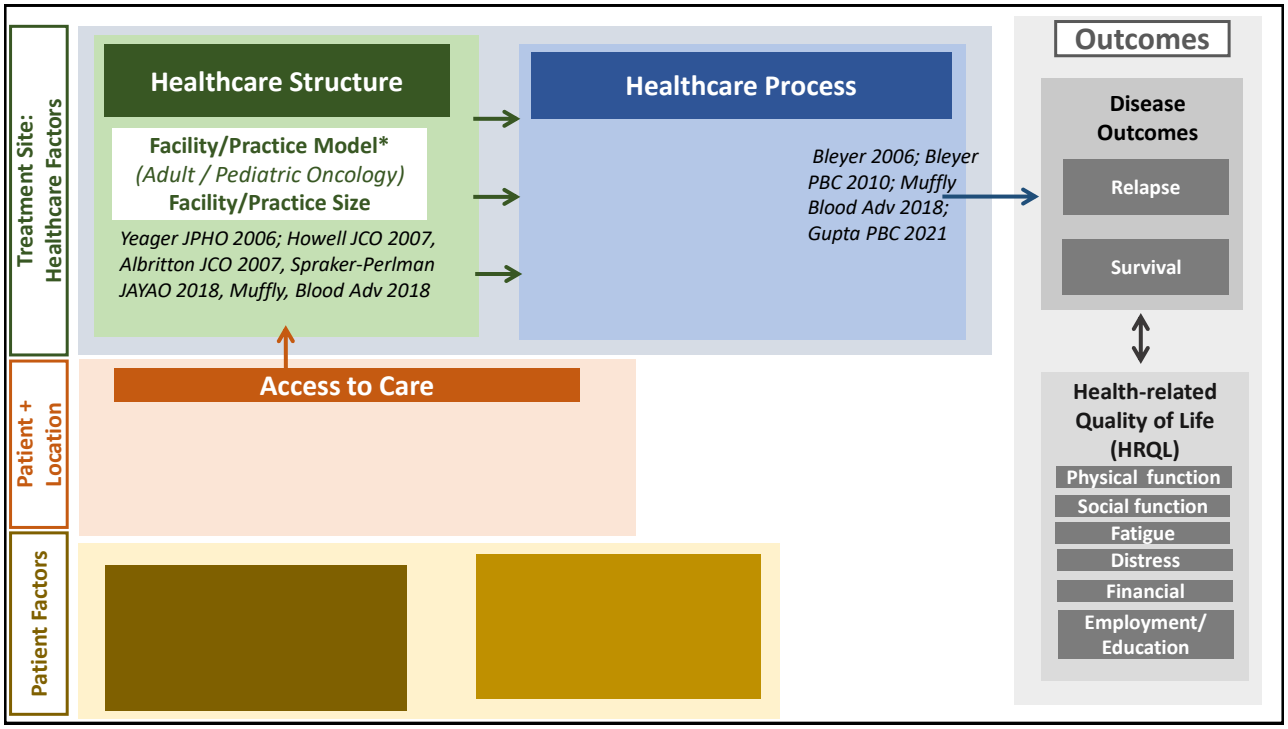
Treatment Site: Healthcare Factors
Patient + Location
Patient Factors
Healthcare Structure
Facility/Practice Model*
(Adult / Pediatric Oncology)
Facility/Practice Size
Yeager JPHO 2006; Howell JCO 2007, Albritton JCO 2007, Spraker-Perlman JAYAO 2018, Muffly, Blood Adv 2018
Healthcare Process
Bleyer 2006; Bleyer PBC 2010; Muffly Blood Adv 2018; Gupta PBC 2021
Access to Care
Outcomes
Disease Outcomes
Relapse
Survival
Health-related Quality of Life (HRQL)
Physical function
Social function
Fatigue
Distress
Financial
Employment/ Education

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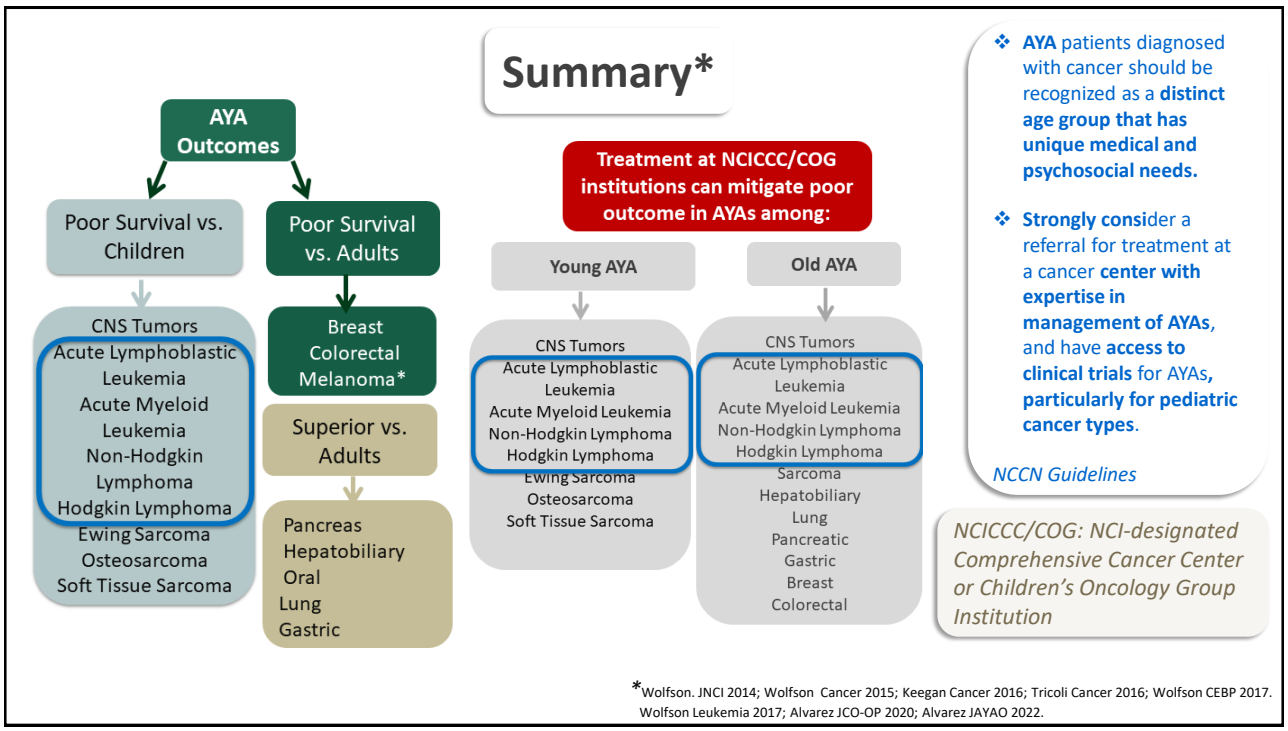
Summary*
AYA Outcomes
Poor Survival vs. Children
Poor Survival vs. Adults
CNS Tumors
Acute Lymphoblastic Leukemia
Acute Myeloid Leukemia
Non-Hodgkin Lymphoma
Hodgkin Lymphoma
Ewing Sarcoma
Osteosarcoma
Soft Tissue Sarcoma
Breast
Colorectal
Melanoma*
Superior vs. Adults
Pancreas
Hepatobiliary
Oral
Lung
Gastric
Treatment at NCICCC/COG institutions can mitigate poor outcome in AYAs among:
Young AYA
CNS Tumors
Acute Lymphoblastic Leukemia
Acute Myeloid Leukemia
Non-Hodgkin Lymphoma
Hodgkin Lymphoma
Ewing Sarcoma
Osteosarcoma
Soft Tissue Sarcoma
Old AYA
CNS Tumors
Acute Lymphoblastic Leukemia
Acute Myeloid Leukemia
Non-Hodgkin Lymphoma
Hodgkin Lymphoma
Sarcoma
Hepatobiliary
Lung
Pancreatic
Gastric
Breast
Colorectal
AYA patients diagnosed with cancer should be recognized as a distinct age group that has unique medical and psychosocial needs.
Strongly consider a referral for treatment at a cancer center with expertise in management of AYAs, and have access to clinical trials for AYAs, particularly for pediatric cancer types.
NCCN Guidelines
NCICCC/COG: NCI-designated Comprehensive Cancer Center or Children's Oncology Group Institution
*Wolfson. JNCI 2014; Wolfson Cancer 2015; Keegan Cancer 2016; Tricoli Cancer 2016; Wolfson CEBP 2017. Wolfson Leukemia 2017; Alvarez JCO-OP 2020; Alvarez JAYAO 2022.

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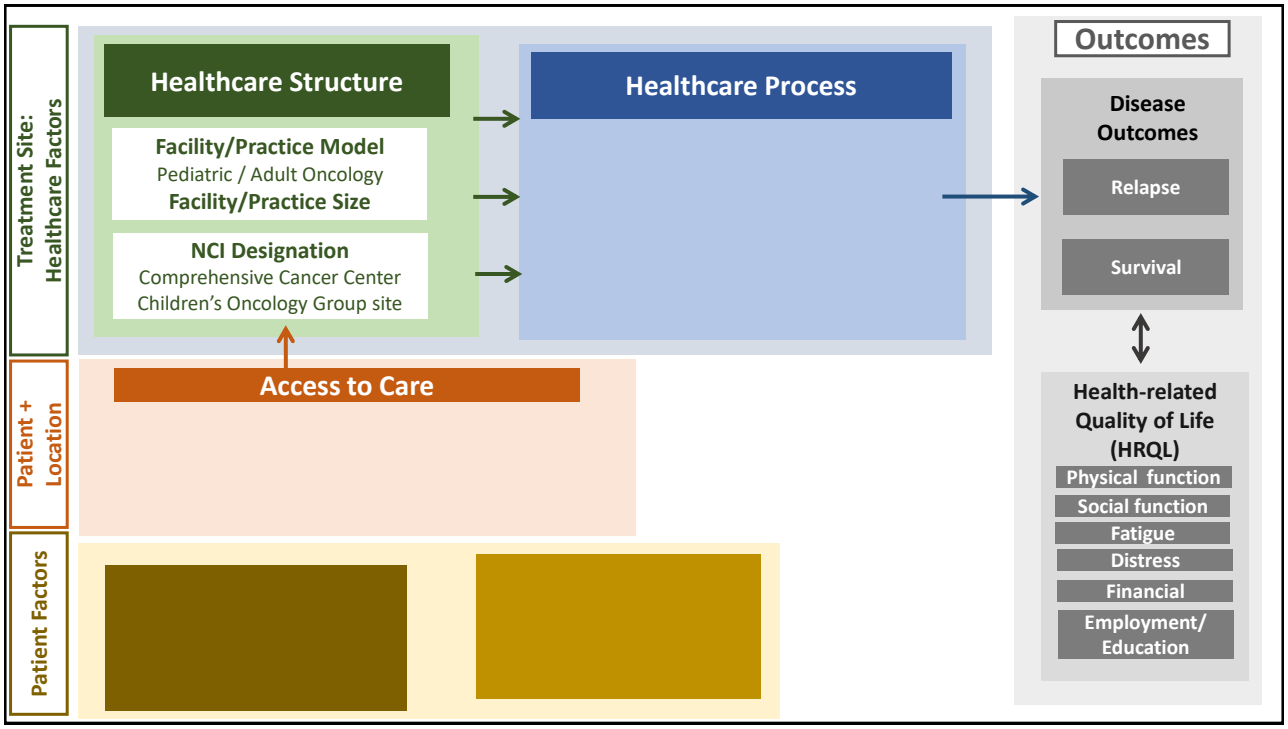

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Lower Odds of Care at NCICCC/COG

Patients ≤21yo

Age alone

22-39y: malignancies common to children/ AYAs

- Public / No Insurance
- Low SES
- Distance from the nearest age-appropriate NCICCC/COG

22-39y: adult-onset malignancies (AYAs/

- African-American/Black
- Hispanic/Latino
- Public Insurance
- No Insurance
- Low SES
- Distance from the nearest age-appropriate NCICCC/COG

NCICCC/COG: NCI-designated Comprehensive Cancer Center or Children's Oncology Group Institution

*Wolfson. JNCI 2014; Wolfson Cancer 2015; Keegan Cancer 2016; Tricoli Cancer 2016; Wolfson CEBP 2017; Wolfson Leukemia 2017. Alvarez Cancer 2017; Rao JAYAO 2021; Alvarez JAYAO 2022.

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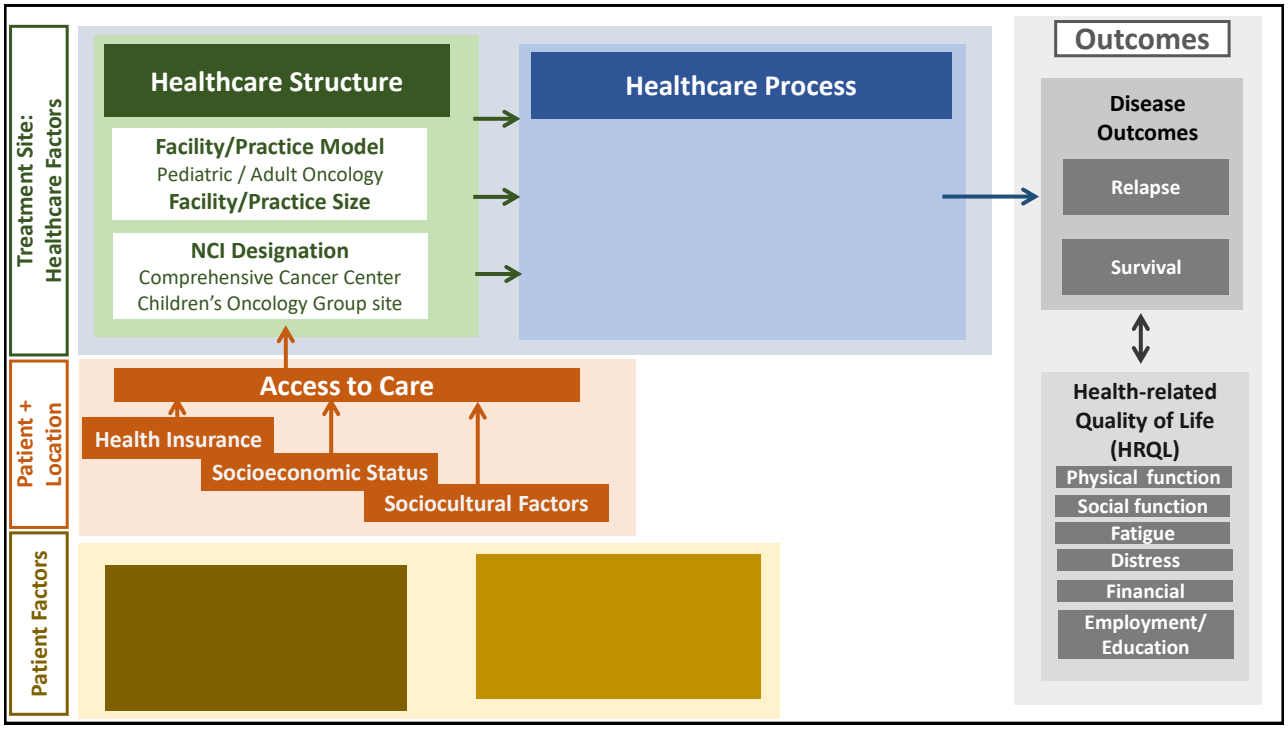
Treatment Site: Healthcare Factors
Healthcare Structure
Facility/Practice Model
Pediatric / Adult Oncology
Facility/Practice Size
NCI Designation
Comprehensive Cancer Center
Children's Oncology Group site
Healthcare Process
Patient + Location
Access to Care
Health Insurance
Socioeconomic Status
Sociocultural Factors
Patient Factors
Outcomes
Disease Outcomes
Relapse
Survival
Health-related Quality of Life (HRQL)
Physical function
Social function
Fatigue
Distress
Financial
Employment/ Education

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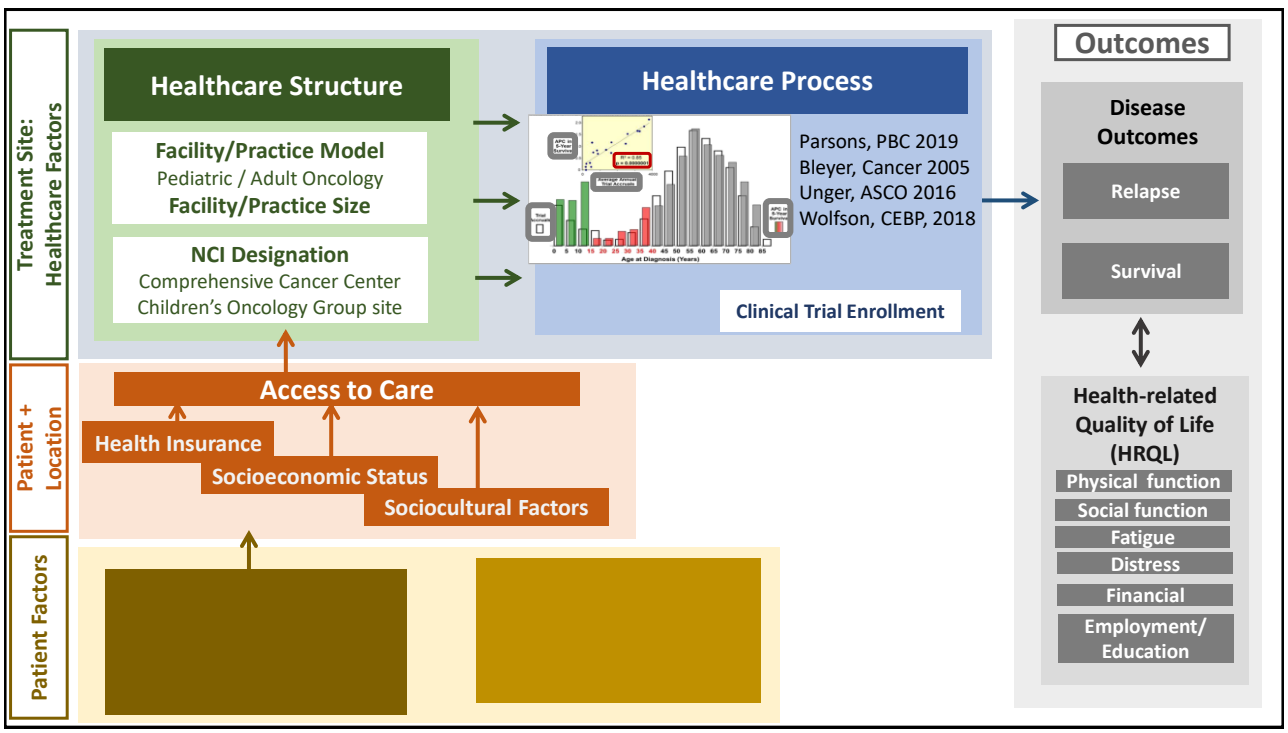
Treatment Site: Healthcare Factors
Healthcare Structure
Facility/Practice Model
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Facility/Practice Size
NCI Designation
Comprehensive Cancer Center
Children's Oncology Group site
Healthcare Process
Parsons, PBC 2019
Bleyer, Cancer 2005
Unger, ASCO 2016
Wolfson, CEBP, 2018
Clinical Trial Enrollment
Patient + Location
Access to Care
Health Insurance
Socioeconomic Status
Sociocultural Factors
Patient Factors
Outcomes
Disease Outcomes
Relapse
Survival
Health-related Quality of Life (HRQL)
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Financial
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2005-2006
AYA Progress Review Group
NCI + Lance Armstrong Foundation
Closing the Gap: Research & Care Imperatives for AYAs with Cancer

Launched 2014 (est. 2010)
NCI National Clinical Trials Network

- *Focus on increasing awareness of trials for AYAs*
- *4 medical oncology, 1 pediatric oncology, 1 international group*

- Proportion of CTEP treatment trials represented by AYAs pre-/post-creation of NCTN: 9.5% (95% CI, 7.6-11.8) vs, 14.0% (95% CI, 9.9-18.3). Mean difference in proportions: 4.4% (0.7%-8.3%).

Sankaran…Seibel (Cancer, 2022)
Cancer.gov

AYA Discipline Committees

CHILDREN'S ONCOLOGY GROUP
Southwest Oncology Group
A National Clinical Research Group
Alliance for Clinical Trials in Oncology
ECOG-ACRIN cancer research group
Reshaping the future of patient care

2022
Joint Adult + Pediatric NCTN/SARC AYA Clinical Trials Sarcoma Working Group
Whiteway et al, JAYAO 2023

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CTEP Cancer Therapy Evaluation Program

Home | Investigator Resources | Protocol Development | Industry Collaborations | Initiatives / Programs | More Links | About CTEP

Initiatives/Programs

NCTN Trial Portfolios by Disease

NCI's National Clinical Trials Network (NCTN) is conducting trials of cancer treatment therapies in the areas listed below. To see trials that are active for a specific disease area, please click that disease area from the following list.

Note: For full functionality, it is recommended that users download the PDF file, and open with a PDF reader.

NCTN Trial Portfolio (including all disease areas) (pdf)

Cancer trials by disease area:

- Brain (pdf)
- Breast (pdf)
- Gastrointestinal (pdf)
- Genitourinary (pdf)
- Gynecological (pdf)
- Head and Neck (pdf)
- Leukemia (pdf)
- Lymphoma (pdf)
- Myeloma (pdf)
- Sarcoma (pdf)
- Skin (Mainly Melanoma) (pdf)
- Thoracic (pdf)
- Adolescent and Young Adult (AYA) (pdf)

CTEP Branches and Offices

NCTN Adolescent to Young Adult (AYA) Cancer Trials Portfolio (Open as of 9/15/2023)

Click on trial number to go to the associated ClinicalTrials.gov webpage, to view the protocol title and the study information.

Newly Diagnosed Disease		Recurrent Disease
Rhabdomyosarcoma (RMS): ARST2031 (High risk)	Germ Cell Tumors: AGCT1531, AGCT1532	Acute Lymphoblastic Leukemia (ALL): AALL1821
Osteosarcoma (Pulmonary Mets): AOST2031	Acute Lymphoblastic Leukemia (ALL): A041501	Classical Hodgkin Lymphoma: E4412
Osteosarcoma (Metastatic): AOST2032	Nongerminomatous germ cell tumor of the CNS: ACNS2021	Osteosarcoma (Pulmonary Mets): AOST2031
Classical Hodgkin Lymphoma: AHOD2131	Mediastinal (thymic) large B-cell lymphoma: ANHL1931	

Legend by Disease Types: Blue = ALL; Lime Green = Osteosarcoma; Light Purple = CNS NGGCT; Gray = PMBCL

NCTN Adolescent to Young Adult (AYA) Cancer Trials (Open as of 9/15/2023)

Protocol Number	Phase	Protocol Title
A041501	III	A Phase III Trial to Evaluate the Efficacy of the Addition of Inotuzumab Ozogamicin (a Conjugated Anti-CD22 Monoclonal Antibody) to Frontline Therapy in Young Adults (Ages 18-39 Years) with Newly Diagnosed Precursor B-Cell ALL
AALL1821	II	A Phase 2 Study of Blinatumomab (NSC# 765986) in Combination with Nivolumab (NSC # 748726), a Checkpoint Inhibitor of PD-1, in B-ALL Patients Aged >/= 1 to < 31 Years Old with First Relapse
ACNS2021	II	A Phase 2 Trial of Chemotherapy Followed by Response-Based Whole Ventricular & Spinal Canal Irradiation (WVSCI) for Patients with Localized Non-Germinomatous Central Nervous System Germ Cell Tumor
AGCT1531	III	A Phase 3 Study of Active Surveillance for Low Risk and a Randomized Trial of Carboplatin vs. Cisplatin for Standard Risk Pediatric and Adult Patients with Germ Cell Tumors
AGCT1532	III	A Randomized Phase 3 Trial of Accelerated Versus Standard BEP Chemotherapy for Patients with Intermediate and Poor-Risk Germ Cell Tumors
ANHL1931	III	A Randomized Phase 3 Trial of Nivolumab (NSC# 748726) in Combination with Chemo-Immunotherapy for the Treatment of Newly Diagnosed Primary Mediastinal B-Cell Lymphoma
AHOD2131	III	A Randomized Phase 3 Interim Response Adapted Trial Comparing Standard Therapy with Immuno-oncology Therapy for Children and Adults with Newly Diagnosed Stage I and II Classic Hodgkin Lymphoma
AOST2031	III	A Phase 3 Randomized Controlled Trial Comparing Open vs Thoracoscopic Management of Pulmonary Metastases in Patients with Osteosarcoma
AOST2032	II/III	A Feasibility and Randomized Phase 2/3 Study of the VEFGR2/MET Inhibitor Cabozantinib in Combination with Cytotoxic Chemotherapy for Newly Diagnosed Osteosarcoma
ARST2031	III	A Randomized Phase 3 Trial of Vincristine, Dactinomycin, and Cyclophosphamide (VINO-AC) Plus Maintenance Chemotherapy with Vincristine and Oral Cyclophosphamide (VINO-CPO) vs Vincristine, Dactinomycin and Cyclophosphamide (VAC) Plus VINO-CPO Maintenance in Patients with High Risk Rhabdomyosarcoma (HR-RMS)
E4412	I/II	A Phase I Study with an Expansion Cohort/Randomized Phase II Study of the Combinations of Ipilimumab, Nivolumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma

This portfolio shows NCTN trials. For information about NCORP trials, please see: https://ncorp.cancer.gov/find-a-study/

CTSU
(NCI Clinical Trials Support Unit)

- AYA (NCTN)
  - ALLIANCE
    - A151804
  - COG
    - ACNS2021
    - AGCT1531
    - AGCT1532
    - AHOD2131
    - ANHL1931
    - AOST2031
    - ARST2031
  - ECOG-ACRIN
    - EAY191
  - SWOG
    - S1823

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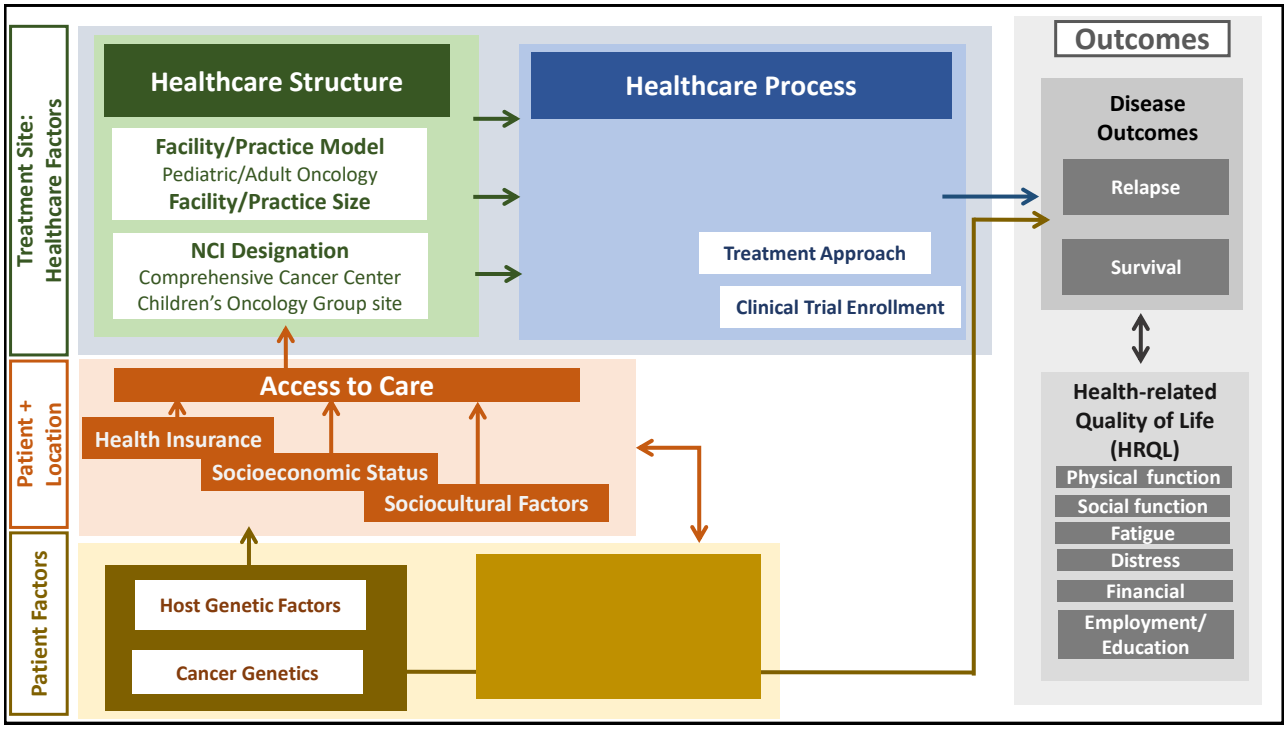

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Retrospective review of clinical trial data among AYAs (of the same age) with ALL treated on pediatric and adult trials

Superior survival on pediatric trials

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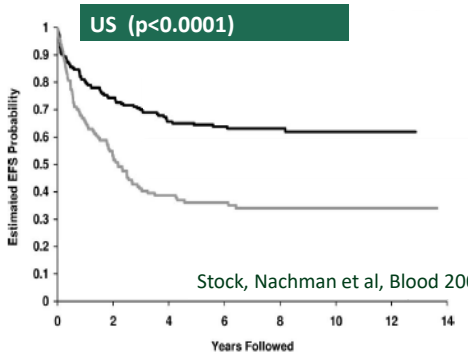
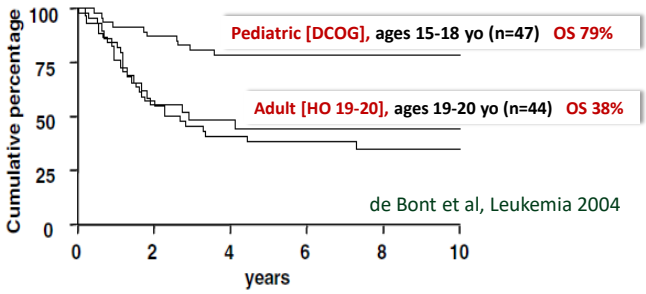
US (p<0.0001)



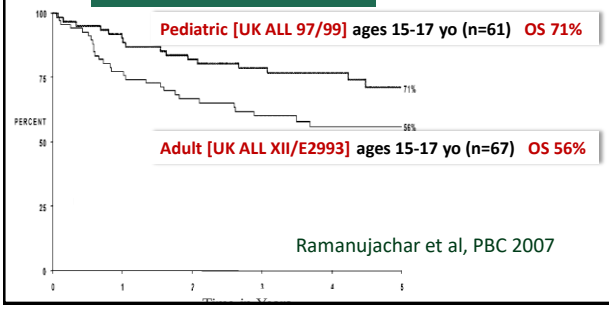
Stock, Nachman et al, Blood 2008

NETHERLANDS (p<0.0001)



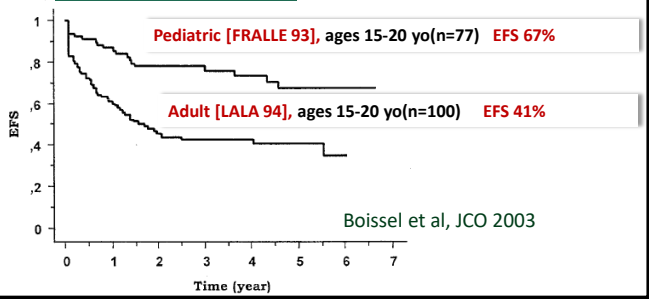
de Bont et al, Leukemia 2004

UK (p<0.0001)



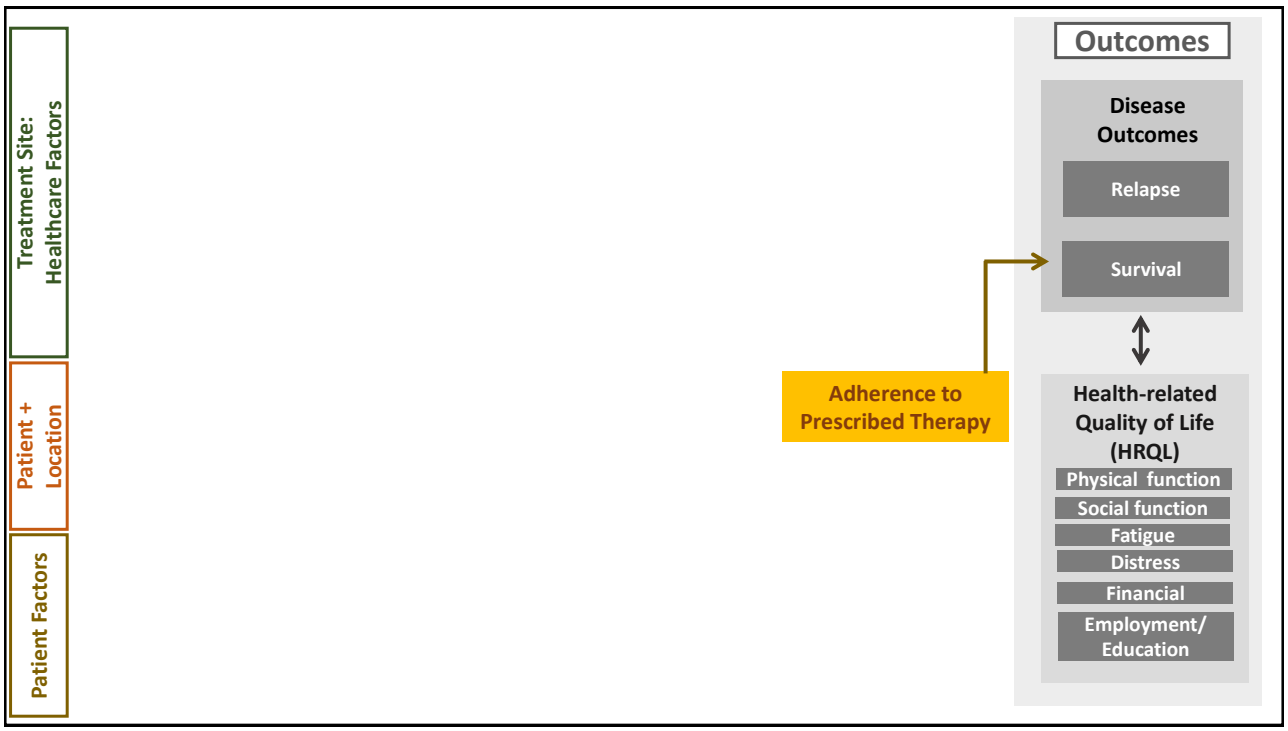
Ramanujachar et al, PBC 2007

FRANCE (p<0.0001)



Boissel et al, JCO 2003

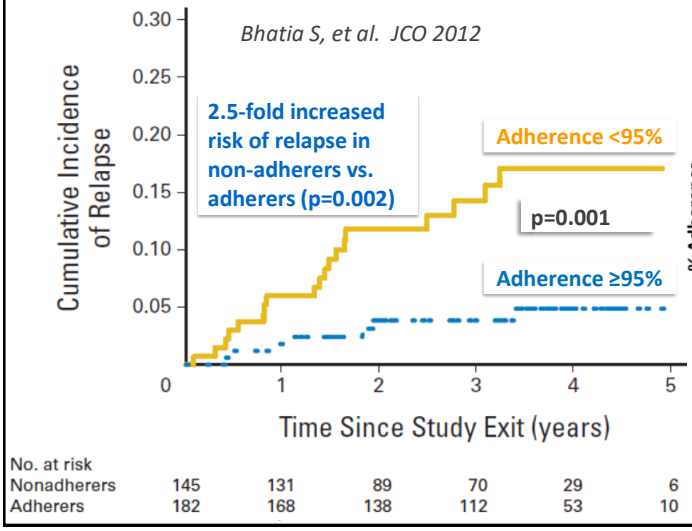
27

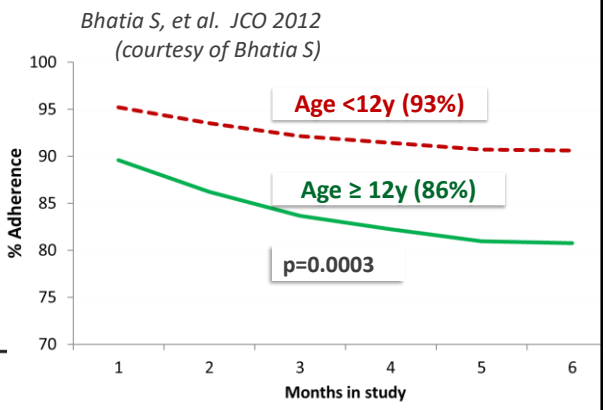


28

Childhood, Adolescent and Young Adult ALL: Relapse and Adherence

- Multisite Children's Oncology Group study (>94 sites) [Bhatia, Landier et al]
- Electronic monitoring of medication adherence (MEMS)
- Median age 6y, range 1-21y





Slide courtesy of Smita Bhatia, MD, MPH.

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Adherence is the critical factor for achieving **molecular responses** in patients with **chronic myeloid leukemia** who achieve complete **cytogenetic responses** on imatinib

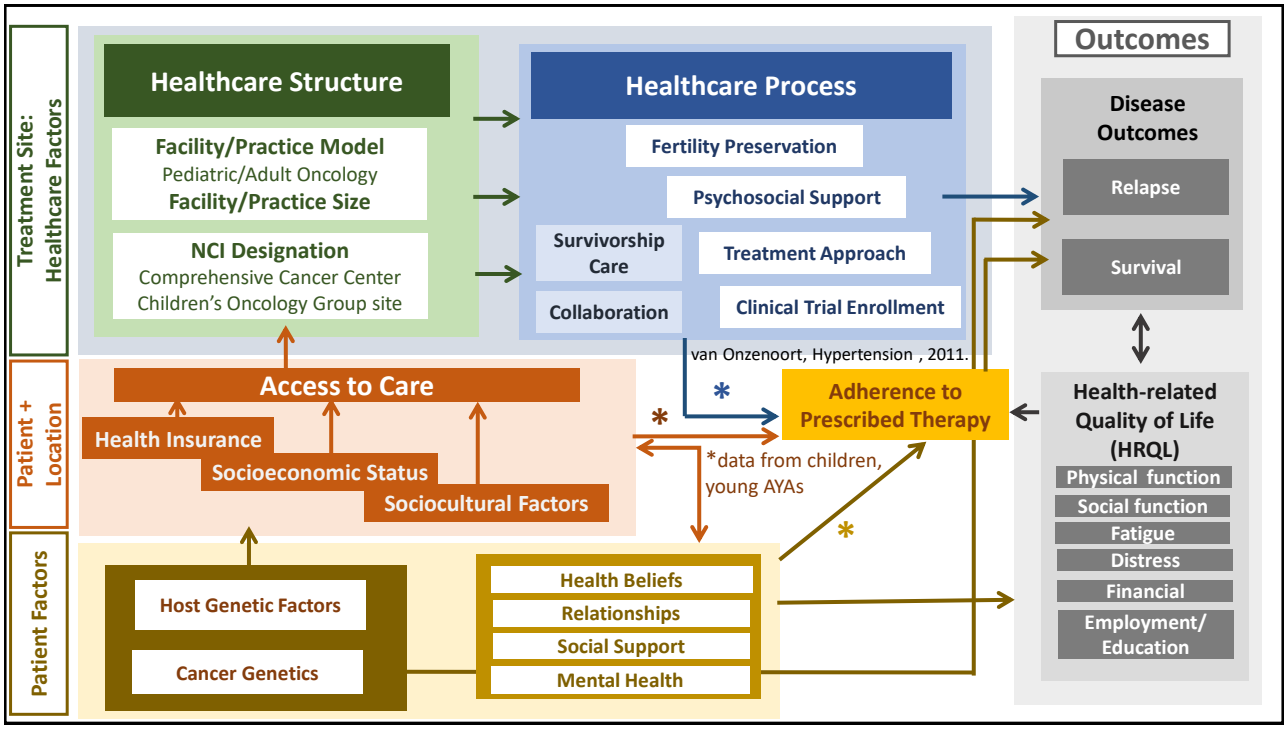
Marin D et al. J Clin Oncol. 2010;28:2381-8

- Median adherence rate 98% (24% to 104%).
- 26.4% had adherence ≤ 90%; 14% had adherence ≤ 80%
- Strong correlation between adherence (≤ 90% or > 90%) and 6-year probability of MMR (28.4% v 94.5%; P < .001)
- Multivariate analysis: adherence was independent predictor for response
- No molecular responses observed when adherence was ≤80% (P < .001)

"Imatinib works better if you take it!"

Slide courtesy of Ravi Bhatia, MD.

30

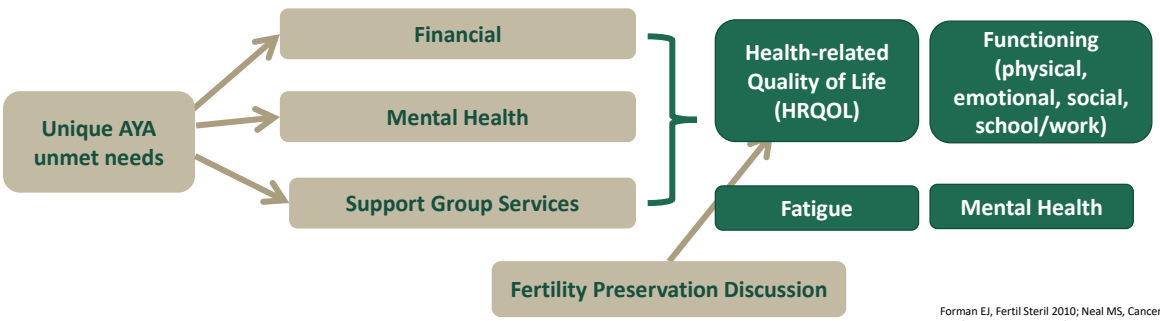


31

Cancer Therapy Confers a Risk for Infertility for AYAs

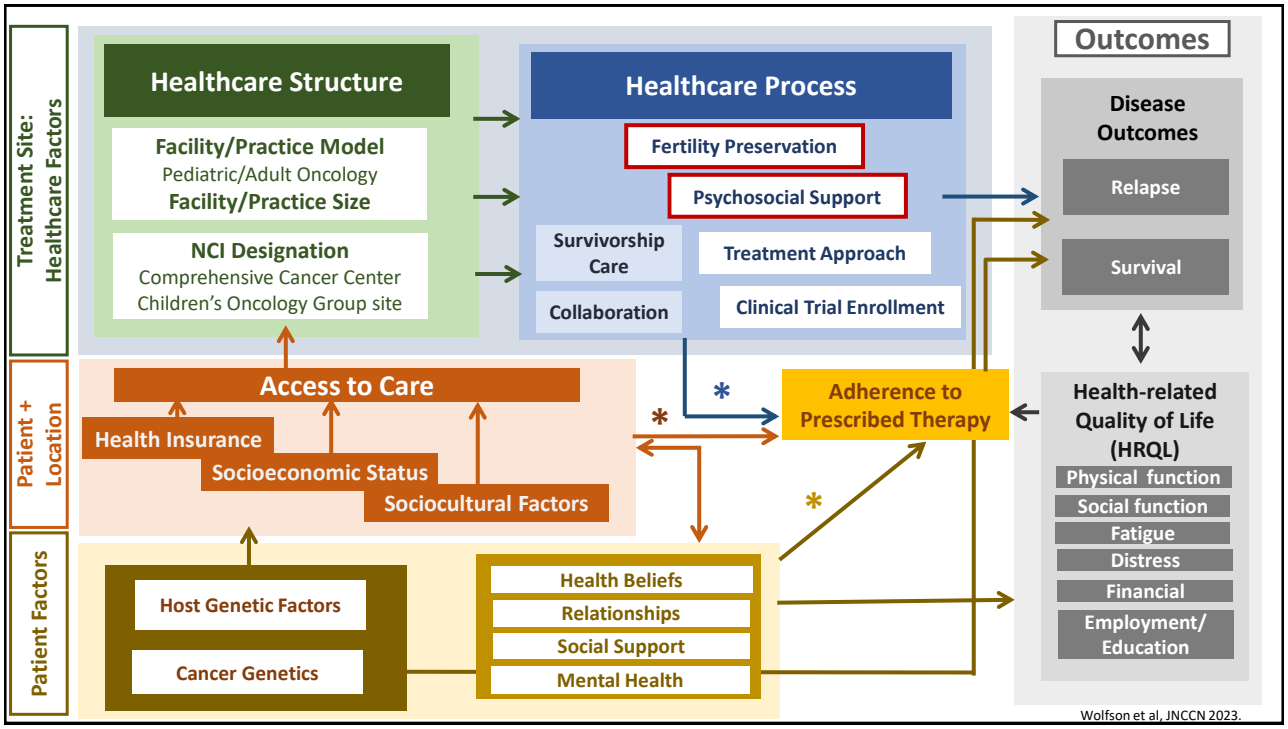
- National guidelines recommend discussing fertility risks and offering referral for preservation *before* starting *gonadotoxic* therapy
- However, fertility preservation referrals are very inconsistent

Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update



Forman EJ, Fertil Steril 2010; Neal MS, Cancer 2007
Ginsberg JP, PBC 2008; Schover LR, JCO 2002
Partridge AH, JCO 2004; Schover LR, Med Ped Onc 1999
Schover LR, JCO 2002; Schover LR, PBC 2009
Zebrack BJ, Psychooncology 2004; Smith AW, PBC 2019
Burns KC, J Ped Hem Onc 2006; Keegan T, JCS 2012
Smith AW, Frontiers Onc 2013;
Wettergren L, Psychooncology 2017

32



33

Polling Question #2

When you refer an AYA for a fertility preservation consultation before they start chemotherapy, how much is able to be done at your institution vs. outside your institution?

a) In-house: Oocyte cryopreservation, embryo cryopreservation, ovarian tissue cryopreservation, sperm banking; Outside referrals: none

b) In-house: Oocyte cryopreservation, embryo cryopreservation; Outside referrals: ovarian tissue cryopreservation, sperm banking

c) In-house: sperm banking; Outside referrals: Oocyte cryopreservation, embryo cryopreservation, ovarian tissue cryopreservation,

d) In-house: none; Outside referrals: Oocyte cryopreservation, embryo cryopreservation, ovarian tissue cryopreservation, sperm banking

e) Other

34

Treatment Options and New Emerging Data: Leukemias

Chronic Myeloid Leukemia: CML

Acute Lymphoblastic Leukemia: ALL

Acute Myeloid Leukemia: AML

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CML: Staging and Disease Response

Staging of CML (MD Anderson criteria)

Chronic phase
None of the criteria for accelerated or blastic phase
Accelerated phase
Blasts ≥ 15% in blood or BM
Blasts plus progranulocytes ≥ 30% in blood or BM
Basophilia ≥ 20% in blood or BM
Platelets < 100 × 10^9/L unrelated to therapy
Cytogenetic clonal evolution
Blast phase
≥ 30% blasts in blood or BM
Extramedullary disease with localized immature blasts

Response to TKI is the most important prognostic factor

- Initial response to therapy provides a sensitive measure of future clinical outcome
- Measurement of BCR-ABL1 transcript levels using RT-Q-PCR standardized to the international reporting scale (IS)
- Based on achievement of CCyR or MMR at key time points
- Treatment failure defined as *BCR-ABL1* >10% at 6 months and >1% at 12 months

	BCR-ABL1 (IS)	3 months	6 months	12 months[l]
	>10%[m]	YELLOW	RED	
(CCyR)	>1%–10%	GREEN		YELLOW
(MMR)	>0.1%–1%	GREEN		LIGHT GREEN
	≤0.1%	GREEN		

NCCN Guidelines Version 1.2022: Chronic Myeloid Leukemia

Slide courtesy of Ravi Bhatia, MD

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Choice of TKIs

First Line

*Most patients receive imatinib as first-line treatment with good long-term disease control

Second line

Improved outcomes with second generation TKI after imatinib failure

Third line

Standard of care beyond second line therapy is not well defined

Many patients receive a second-generation TKI as frontline treatment
- higher risk category
- more rapid and deeper molecular response; allows more rapid attempt at TFR
- no overall survival benefit
- cost, toxicity

*Improved PFS but not OS with second generation TKIs

Slide courtesy of Ravi Bhatia, MD.

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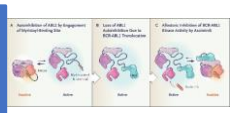
Failure of 2nd generation TKIs

Treatment decisions based on reason for failure, mutation profile, comorbidities and AE risk profile

- Transplant
- Alternative 2nd-generation TKI
- Ponatinib-3rd-generation TKI — T315I mutations and resistance or intolerance to ≥2 prior TKIs
- Asciminib (ABL Myristoyl Pocket inhibitor) — Binds to the myristoyl pocket of BCR-ABL1 and stabilizes the inactive state of the kinase (mimics autoinhibitory mechanism in ABL1 lost in BCR-ABL1)



N Engl. J Med 381;24, 2019

- Clinical trials- Investigational agents

Slide courtesy of Ravi Bhatia, MD.

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Clinical Trials

- **HQP1351 (Olverembatinib):** a **3G TKI** with in vitro activity against **T315I and other mutants**
- **PF-114:** **3G TKI** with efficacy at nanomolar concentrations against **mutated BCR-ABL1, including the T315I mutation**; similar to Ponatinib but designed to **minimize interaction with VEGFR**
- **K0706 (Vodobatinib):** a **2G TKI** effective against **wild-type and mutated BCR-ABL1** isoforms with **reduced off-target activity** compared to existing TKIs
- **Non BCR-ABL targets**

Slide courtesy of Ravi Bhatia, MD.

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Important Considerations for AYAs

- **Women** who take **TKIs** are at **risk of miscarriage and birth defects**, and are strongly advised to use birth control
- Women on TKI who **become pregnant** must **choose between ending the pregnancy or stopping the TKI temporarily**
- For women who choose to stop TKI treatment and continue with the pregnancy, and require **treatment, options include apheresis, and treatment with interferon alfa**
- **Breastfeeding** women are **advised to avoid TKIs** because these **medications are passed into breast milk**

Slide courtesy of Ravi Bhatia, MD.

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Treatment Options and New Emerging Data: Leukemias

Chronic Myeloid Leukemia: CML

Acute Lymphoblastic Leukemia: ALL

Acute Myeloid Leukemia: AML

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Polling Question #3

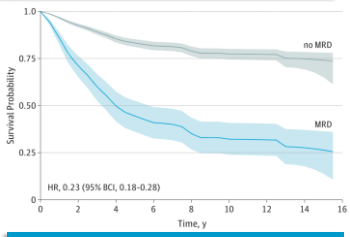
What therapy is the best practice based on guidelines to treat AYAs with Ph-negative Acute Lymphoblastic Leukemia (ALL)?

a) CALGB 10403 or AALL1732
b) DFCI ALL (001, etc)
c) GRALLE-2005
d) PETHEMA ALL-96
e) Hyper-CVAD (without addition of other agents)
f) Hyper-CVAD + Rituximab
g) Hyper-CVAD + other targeted agent(s)
h) Linker 4-drug regimen
i) USC-MSKCC regimen (based on CCG1882)

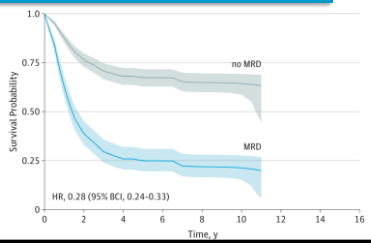
42

Presence of MRD is BAD in Adult and Pediatric ALL…

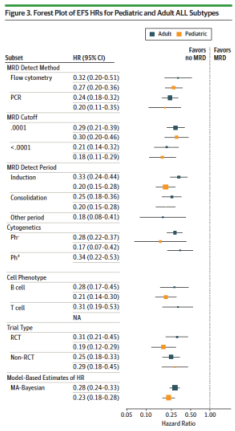
EFS for Pediatric ALL
20 studies with 11,249 patients

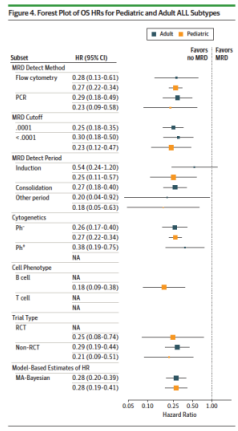


EFS for Adult ALL
16 studies with 2,065 patients



… Regardless of MRD Method, Detection Period, or ALL Subgroup



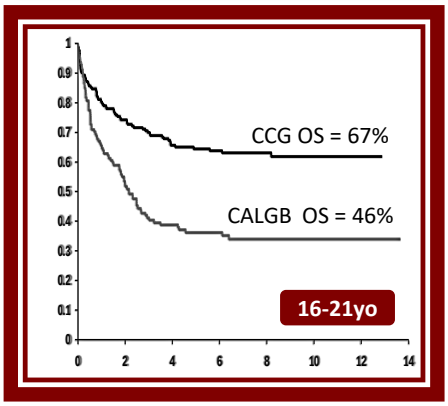


Berry et al, JAMA Onc, 2017
Slide courtesy of Wendy Stock, MD.

43

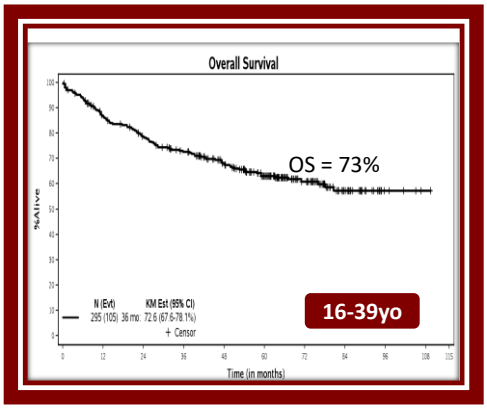
Young Adults: Treatment Standard has Changed

2000: Historical CALGB vs. CCG



Stock et al, Blood, 2008

2019: CALGB 10403

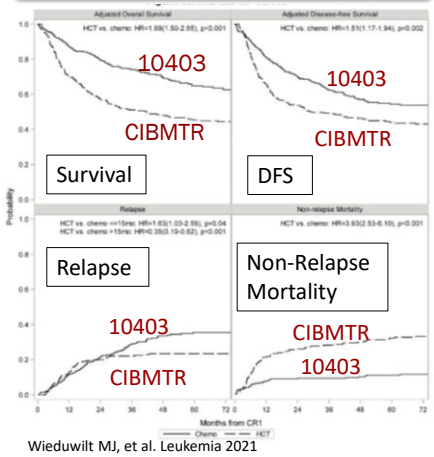


Stock et al, Blood, 2019

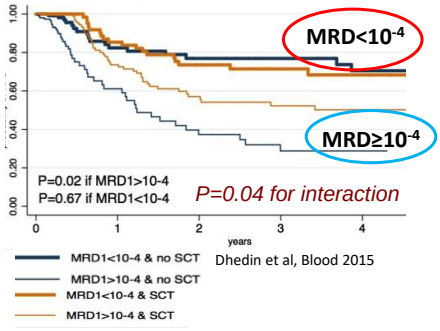
Slide courtesy of Wendy Stock, MD.

44

Transplant in CR1 for AYAs? No survival benefit → **SCT in CR1 Beneficial for Poor MRD Response** → **Early MRD eradication should be our goal**

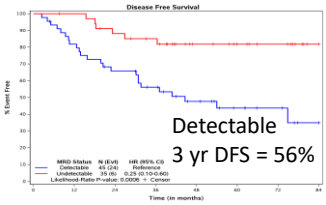


Wieduwilt MJ, et al. Leukemia 2021



Dhedin et al, Blood 2015

Benefit of SCT
- ❑ **Whole high-risk population**
- ❑ **Patients with MRD1 ≥10^{-4}**



HR = 0.25, p = 0.0006

Only 40% of patients are MRD negative early in treatment

Q-PCR following Induction

Stock et al, Blood, 2019

Slide courtesy of Wendy Stock, MD.

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Blinatumomab
Inotuzumab

↓

Incorporate for B-cell ALL

? CD38 targeting

↓

Incorporate for T-cell ALL

Moving Immune Targeting into Frontline Therapy for B-ALL

Slide courtesy of Wendy Stock, MD.

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Blina in Frontline Phase III: E1910 for untreated B-ALL 30-60 years old

- Phase III randomized trial adding blina treatment modules at several treatment timepoints in a modified BFM backbone
  - 4 cycles of Blina are given; 2 cycles after intensification; 2 during late consolidation
- Initial goal was to evaluate efficacy of blinatumomab in frontline as treatment for both MRD- and MRD+ disease
- With approval of blinatumomab for MRD+ in 2018, only MRD- were subsequently randomized
- Completed enrollment fall 2019
- ASH 2022: Median follow-up 43 months, survival advantage of Blina (manuscript pending)

Slide courtesy of Wendy Stock, MD.

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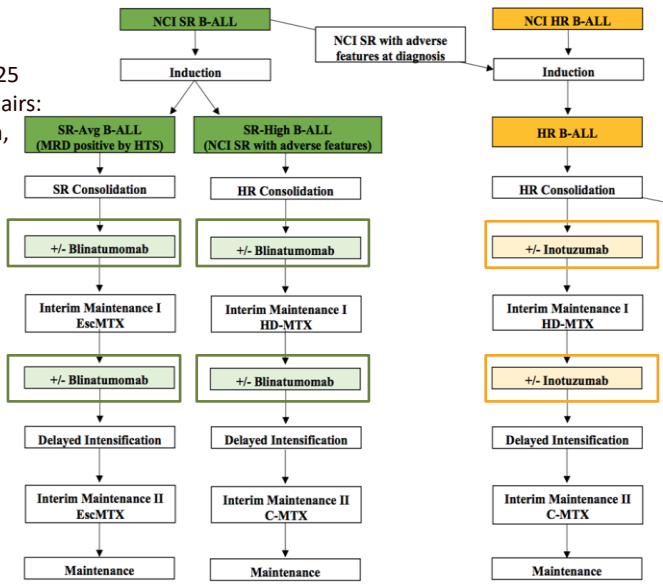
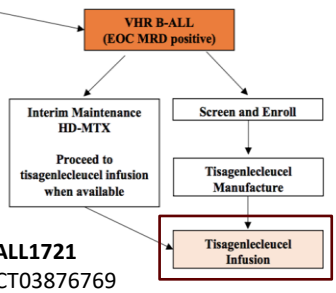
B-ALL: The Future - Incorporation of Immunotherapy into Frontline Therapy

Pediatric (AYA) Trials

AALL1731
NCT03914625
Study Co-Chairs:
Sumit Gupta,
Rachel Rau



AALL1732
NCT03959085
Study Co-Chairs:
Jennifer McNeer,
Maureen O'Brien



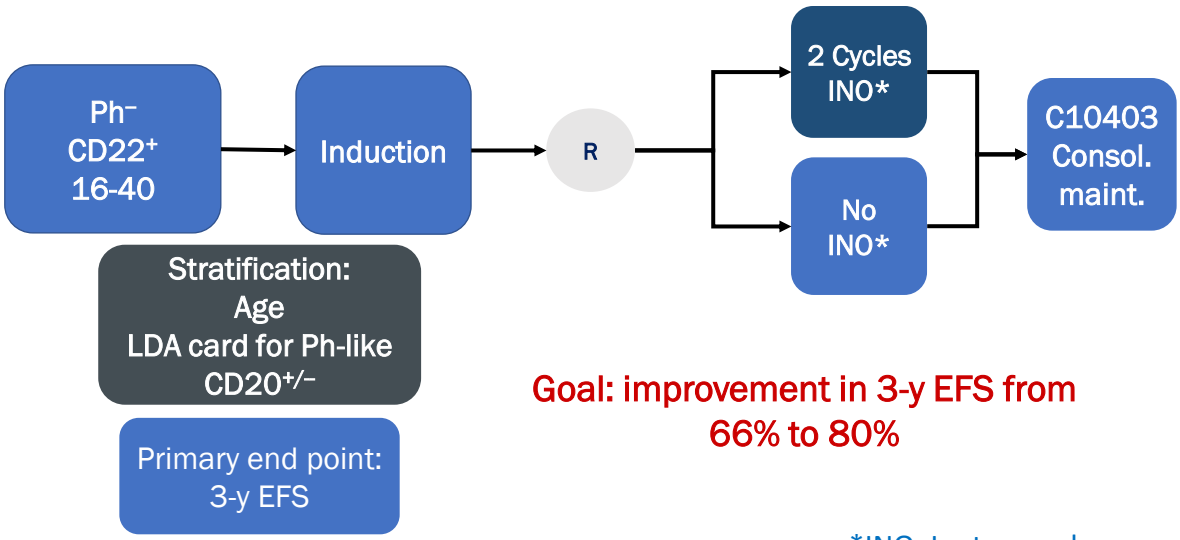
AALL1721
NCT03876769
Study Chair:
Shannon Maude

Slide courtesy of Jennifer McNeer, MD.

48

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

Adult AYA Trial

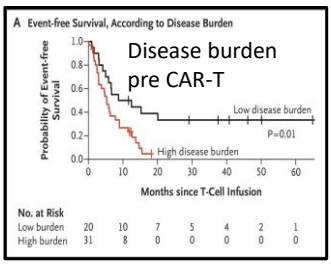


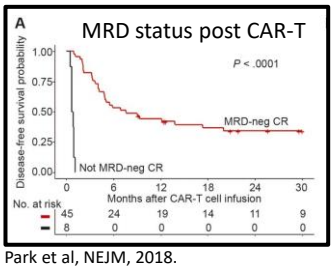
Goal: improvement in 3-y EFS from 66% to 80%

*INO: Inotuzumab

49

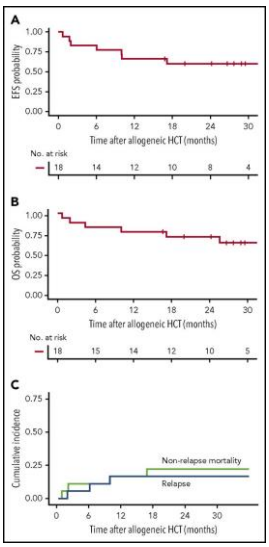
Disease status predicts survival after CAR-T





Park et al, NEJM, 2018.
Hay et al, Blood, 2019.

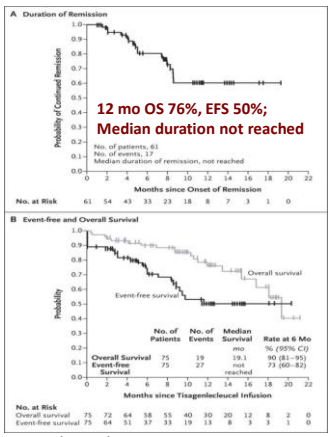
Allogeneic Transplant post CAR-T therapy improves EFS



Hay et al, Blood, 2019.

Association with EFS: HR 0.39, p=.088

Pediatric ELIANA trial: HCT necessary?



Maude et al, NEJM, 2018.

Overall response rate

- Within 3 mos (all MRD neg): 81%
- Intent to treat: 66%
- SCT rate: 13% (all alive)

Slide courtesy of Wendy Stock, MD.

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Cellular Therapy: New Directions

- **"Off the shelf" CART**
  - Faster, doesn't require patient's cells to manufacture
  - Efficacy proven in early trials
- **Dual Targeted CART**
  - CD19, CD22 targeted CART cells have high response rates
  - May minimize emergence of resistant CD19 negative clones
- **Early phase CD5 targeted CAR-T**
  - Ongoing work;
  - Being viewed as bridge to transplant
- **Natural Killer (NK)-CAR**
  - No need for HLA full matching; NK cells may be derived from cord blood
  - Activity has been demonstrated using CAR-NK cells in CD19+ Lymphoma, CLL,

Lu et al, Abstract 284, ASH 2019; Huang et al, Cells 2022.
Schultz et al, Abstract 744, ASH 2019; Spiegel et al, Nat Med. 2021.
Liu et al, NEJM, 2020.
Slide courtesy of Wendy Stock, MD

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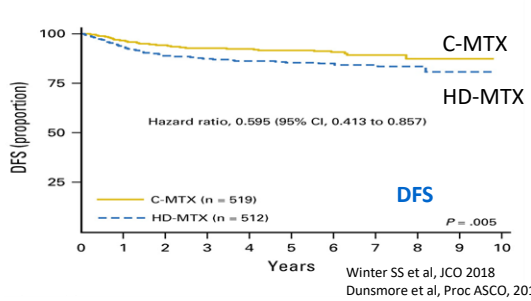
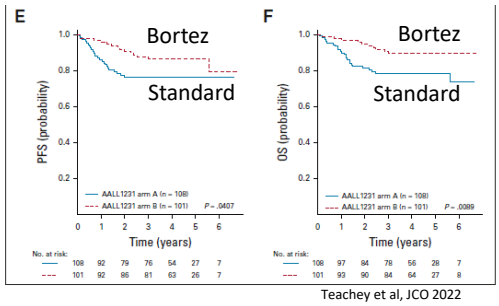
T-ALL: Nelarabine Improves Survival in COG AALL0434



Winter SS et al, JCO 2018
Dunsmore et al, Proc ASCO, 2018.

- **Nelarabine incorporated into ABFM; six 5-day courses**
- **AYAs 20-30yo: 3% of the 1895 patients**
- **4yr DFS was 88.9% with nelarabine vs. 83% DFS without**

TLLy: Improved EFS and OS with Bortezomib (AALL1231)



Teachey et al, JCO 2022

- **Bortezomib incorporated into frontline therapy**
- **4-year EFS**
  - **76.5% ± 5.1% vs. 86.4% ± 4.0%(p =0.041)**
- **4-year OS**
  - **78.3% ± 4.9% vs. 89.5% ± 3.6% (p= 0.009)**

Slide courtesy of Wendy Stock, MD.

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T-ALL: Immunotherapy

Target

- **CD38**
  - Daratumumab

- **Phase 2 DELPHINUS study**
  - Daratumumab + chemo
  - 24 pediatric, 5 young adult pts
  - ORR
    - Pediatric ALL: 83.3%
    - Young Adult ALL: 60%
    - LLy: 40%

Move to frontline therapy?

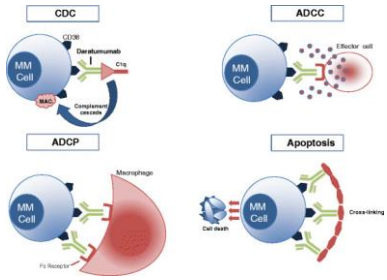

Figure from: Sanchez, et al. J Hematol Oncol. 2016
Hogan, et al. JCO 2022, ASCO Annual Meeting.

Slide courtesy of Jennifer McNeer, MD.

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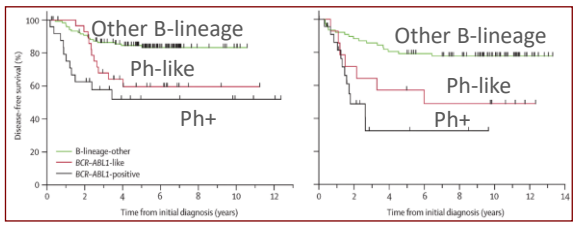
B-ALL: Molecular Diagnostics - Ph-like B-ALL



5y DFS (+ validation cohort)

- Ph-Like: 59.5%
- Ph+: 51.9%
- Other B-lineage: 84%

Current Trials for Philadelphia chromosome-like ALL

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*,[11] *ZMIZ1*[11]
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*,[11] *P2RY8*[11]
JAK2	JAK2 inhibitor	10	19	*ATF7IP*,* *BCR*,[11] *EBF1*,* *ETV6*,[11] *PAX5*,[11] *PPFIBP1*,* *SSBP2*,[11] *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*[17-17]†
PTK2B	FAK inhibitor	2	1	*KDM6A*,* *STAG2**
TSLP	JAK2 inhibitor	1	1	*IQGAP2**
TYK2	TYK2 inhibitor	1	1	*MYB**

- **Driven by a variety of signaling pathways**
- **Potential for targeted therapy in Ph-like ALL**
  - **JAK/STAT pathway**
    - **Ruxolitinib** (**AALL1521,** recently closed to accrual)
  - **ABL-class fusions**
    - **Dasatinib, Imatinib** (**AALL1631**)

Den Boer, et al. Lancet Oncol 2009
Roberts et al, NEJM, 2014
Slide courtesy of Jennifer McNeer, MD.

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Treatment Options and New Emerging Data: Leukemias

Chronic Myeloid Leukemia: CML

Acute Lymphoblastic Leukemia: ALL

Acute Myeloid Leukemia: AML

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2022 ELN AML Risk-Stratification (Adult)

Risk Category	Cytogenetic and Molecular Classification	Transplant Recommendation
Favorable	• t(15;17) • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11* • t(8;21)(q22;q22.1)/*RUNX1*::*RNX1T1* • Mutated *NPM1* without *FLT3-ITD* • bZIP in-frame mutated *CEPBA*	CR2
Intermediate	• Mutated NPM1 with FLT3-ITD mutation • Wild-type NPM1 with FLT3-ITD (w/o adverse genetic lesions) • t(9;11)(p21.3;q23.3)/MLLT3::KMT2A • Cytogenetic and/or abnormalities not classified as favorable or adverse	CR1 for the majority of patients
Adverse	• t(6;9)(p23.3;q34.1)/DEK::NUP214 • t(v;11q23.3)/KMT2A-rearranged • t(9;22)(q34.1;q11.2)/BCR::ABL1 • t(8;16)(p11.2;p13.3)/KAT6A::CREBBP • Inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2, MECOM(EV11) • T(3q26.2;v)/MECOM(EV11) –rearranged • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype, monosomal karyotype • Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2 • t(9;11)(p21.3;q23.3)/MLLT3::KMT2A • Mutated TP53	CR1

Slide courtesy of Kristen O'Dwyer, MD.
Dohner H et al. Blood 2022; 140(12):1345-1377.

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Risk Stratification – Pediatrics
(AAML1831)

Table 3.1 Risk Stratification

	Low Risk								High Risk					
	LR1 4 chemo courses		LR2 5 chemo courses						HR 3 chemo courses and HSCT					
FLT3 ITD allelic ratio > 0.1	-	-	-	-	-	-	+	-	-	-	-	+	+/-	+
FLT3 activating mutations (not ITD)	-	-	-	+	-	-	+/-	+/-	+/-	+	+	+/-	+/-	+/-
t(8;21) or inv(16)/t(16;16)	+[1]	-	-	+/-	+	-	-	+[2]	-	+	-	+/-	+/-	-
NPM1 or CEBPA	-	+	-	+/-	-	+	+	-	-	-	+	-	+/-	+
RAM phenotype or any unfavorable cytogenetic and/or NGS marker EXCEPT FLT3/ITD allelic ratio > 0.1*	-	-	-	-	-	-	-	-	-	-	-	+/-	+	-
Measurable residual disease after Induction 1	-	-	-	-	+	+	-	-	+	+	+	+/-	+/-	+

FAVORABLE PROGNOSTIC MARKERS	
Cytogenetics	**Genes**
t(8;21)(q21.3;q22)	*RUNX1-RUNX1T1*
inv(16)/ t(16;16)(p13.1q22.1)	*CBFB-MYH11*
No associated cytogenetic abnormality	*NPM1* mutation positive
No associated cytogenetic abnormality	*CEBPA* bZIP mutation positive

UNFAVORABLE PROGNOSTIC MARKERS	
Cytogenetics	**Genes**
inv(3)(q21.3q26.2) / t(3;3)(q21.3q26.2)	*RPN1-MECOM*
t(3;21)(26.2;q22)	*RUNX1-MECOM*
t(3;5)(q25;q34)	*NPM1-MLF1*
t(6;9)(p22.3;q34.1)	*DEK-NUP214*
t(8;16)(p11.2;p13.3) (if 90 days or older at diagnosis)	*KAT6A-CREBBP* (if 90 days or older at diagnosis)
t(16;21)(p11.2;q22.2)	*FUS-ERG*
inv(16)(p13.3q24.3)	*CBFA2T3-GLIS2*
t(4;11)(q21;q23.3)	*KMT2A-AFF1 (MLL-MLLT2)*
t(6;11)(q27;q23.3)	*KMT2A-AFDN (MLL-MLLT4)*
t(10;11)(p12.3;q23.3)	*KMT2A-MLLT10*
t(10;11)(p12.1;q23.3)	*KMT2A-ABI1*
t(11;19)(q23.3;p13.3)	*KMT2A-MLLT1(MLL-ENL)*
11p15 rearrangement	*NUP98-any partner gene*
12p13.2 rearrangement	*ETV6- any partner gene*
Deletion 12p to include 12p13.2	Loss of *ETV6*

UNFAVORABLE PROGNOSTIC MARKERS	
Cytogenetics	**Genes**
Monosomy5/Del(5q) to include 5q31	Loss of *EGR1*
Monosomy 7	No associated gene
10p12.3 rearrangement	*MLLT10- any partner gene*
No associated cytogenetic abnormality	*FLT3/ITD* + with allelic ratio > 0.1%
RAM phenotype as evidenced by flow cytometry	

Slide courtesy of Jennifer McNeer, MD.

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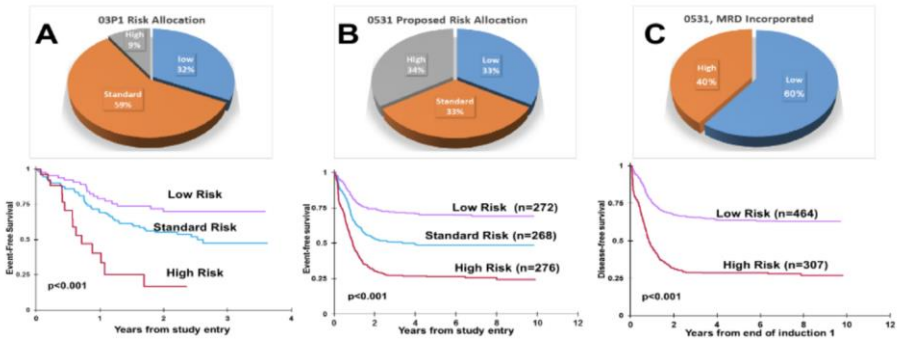
Updated karyotype/FISH, new immunophenotypic, and NGS data applied retrospectively to prior COG AML patients

Figure 2.1 Risk Allocation



Thus, AAML1831 risk stratification more nuanced than prior studies.

Risk groups from AAML03P1
SR 60%
LR 30%
HR 10%

Initially proposed risk groups applied to AAML0531 data (~30% in each group)

Applying EOI MRD 0.1% to SR group then further stratifies them into HR vs LR groups

Slide courtesy of Jennifer McNeer, MD.

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New/Targeted Therapies in AML

- **Gemtuzumab**
  - Anti-CD33 conjugated to calicheamicin
  - AAML0531: outcome benefit (Gamis, JCO 2014)
    - CD33 expression (Pollard, JCO 2016)
    - FLT3/ITD (Tarlock, Clin Cancer Res 2016)
    - KMT2A (Pollard, JCO 2021)
    - Thus – added for all patients (**AAML1831**)
  - May increase risk of SOS with HSCT
  - FDA-approved 2017: adult CD-33+ AML, and peds ≥ 2 yrs with R/R CD33+ AML
- **Sorafenib, Gilteritinib**
  - Sorafenib: Multi-target TKI that targets *FLT3*, *c-KIT, PDGF, VEGF, RAF/MED/ERK (AAML0531)*
  - Gilteritinib: Multi-target TKI that targets FLT3 (ITD and TKD), with weak activity against c-Kit, and inhibits AXL (implicated in FLT3 inhibitor resistance) – **AAML1831**
- **CPX-351**
  - Liposomal 5:1 preparation of cytarabine:daunorubicin
  - Less cardiotoxicity
  - FDA-approved 2017 for adults with t-AML, or AML with MDS-related changes
    - COG AAML1421 (r/r), **COG AAML1831** (de novo)
- **Venetoclax**
  - BCL2 inhibitor (BCL2 is anti-apoptotic)
  - 2016/2017 – Breakthrough designation for AML
- **Azacitidine, Decitabine**
  - Epigenetic Modifiers
  - AML16 (St. Jude trial)

Slide courtesy of Jennifer McNeer, MD.

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Recent AML Updates

- **AAML1031: Up front study**
  - Randomization ± Bortezomib
    - No benefit with bortezomib
  - 4 cycles of chemo
    - 4 cycles inferior to 5 when compared to historical data
- **AAML1331 (recently closed)**
  - Phase 3 study of arsenic and ATRA for APML
  - Omit anthracycline for standard-risk patients
  - Minimize anthracycline for high-risk patients
- **AAML1531**
  - Disease-response based treatment for DS-AML
    - >90 days and <4 years
  - Original study – omit HD-AraC for standard-risk patients.
    - Worse outcomes than historical control
      - 2-year EFS 85.6% vs 93.5%, p=0.0002
      - HD-AraC re-introduced

Slide courtesy of Jennifer McNeer, MD.

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THANK YOU

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Children's Healthcare of Atlanta | Aflac Cancer & Blood Disorders Center

EMORY UNIVERSITY

Diagnostic and Management Considerations for AYA with Lymphoma

LLS Webinar
Sharon M Castellino, MD, MSc
Professor of Pediatrics, Emory School of Medicine
Program Leader: Pediatric Leukemia and Lymphoma
October 11, 2023

-

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Poll Question #4

- What is the most common lymphoma in patients age 15-39 in the U.S.

a) A. Nodular Sclerosing Hodgkin Lymphoma (HL)
b) B. DLBCL
c) C. Primary CNS lymphoma
d) D. Nodular lymphocyte predominant HL

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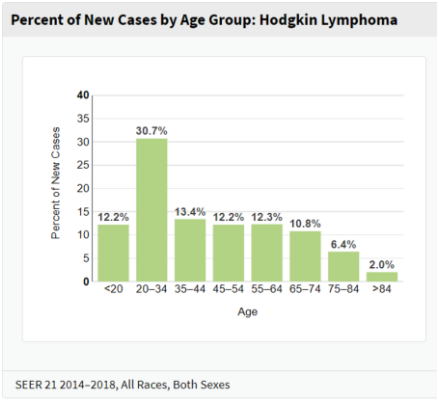
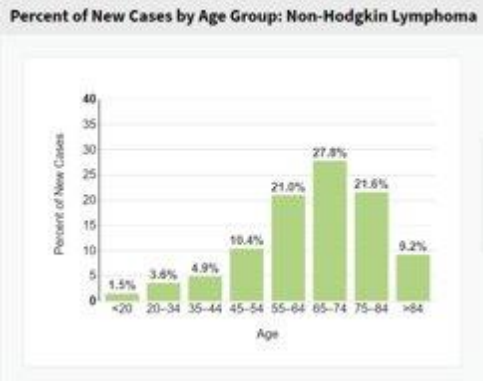
Epidemiology

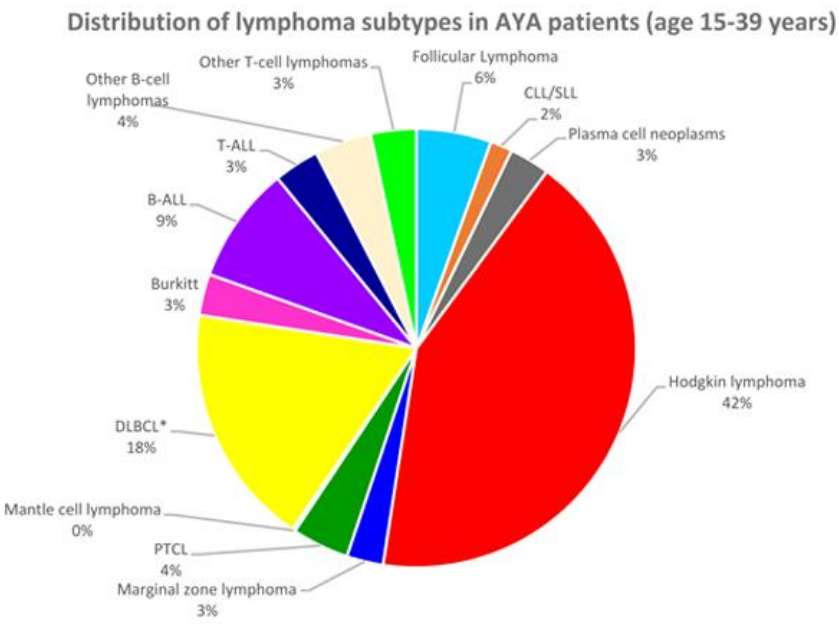
Lymphoma accounts for 20% of cancers in AYA





https://www.researchgate.net/figure/Age-specific-rates-of-incidence-based-on-data-from-SEER-Cancer-Statistics-Review-16_fig1_49833144

64



Blum, K et al. Br J Haem 2018.

65

Disparities in Outcomes for AYA with Lymphoma

- Compared to pediatric patients:
  - AYA patients more likely to present with:
    - Advanced stage disease
    - B symptoms
- Clinical presentation:
  - Indolent: HL
  - Acutely ill with rapid progression in many NHL
- Diagnosis
  - Challenges associated with evolving molecular features in NHL subtypes

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Drivers of Disparities in AYA Lymphoma

- Timely Access to care
  - Lack of insurance; underinsurance; non-continuous coverage
  - Distance to care
  - Delays in diagnosis
  - Lack of access to AYA resourced care (i.e. cancer centers)
  - Lack of enrollment to clinical trials
- Non-White Race
- Social determinants of health
- Lack of guideline concordant care through the continuum of post treatment/survivorship
- Unmet psychosocial needs → impact adherence to therapy

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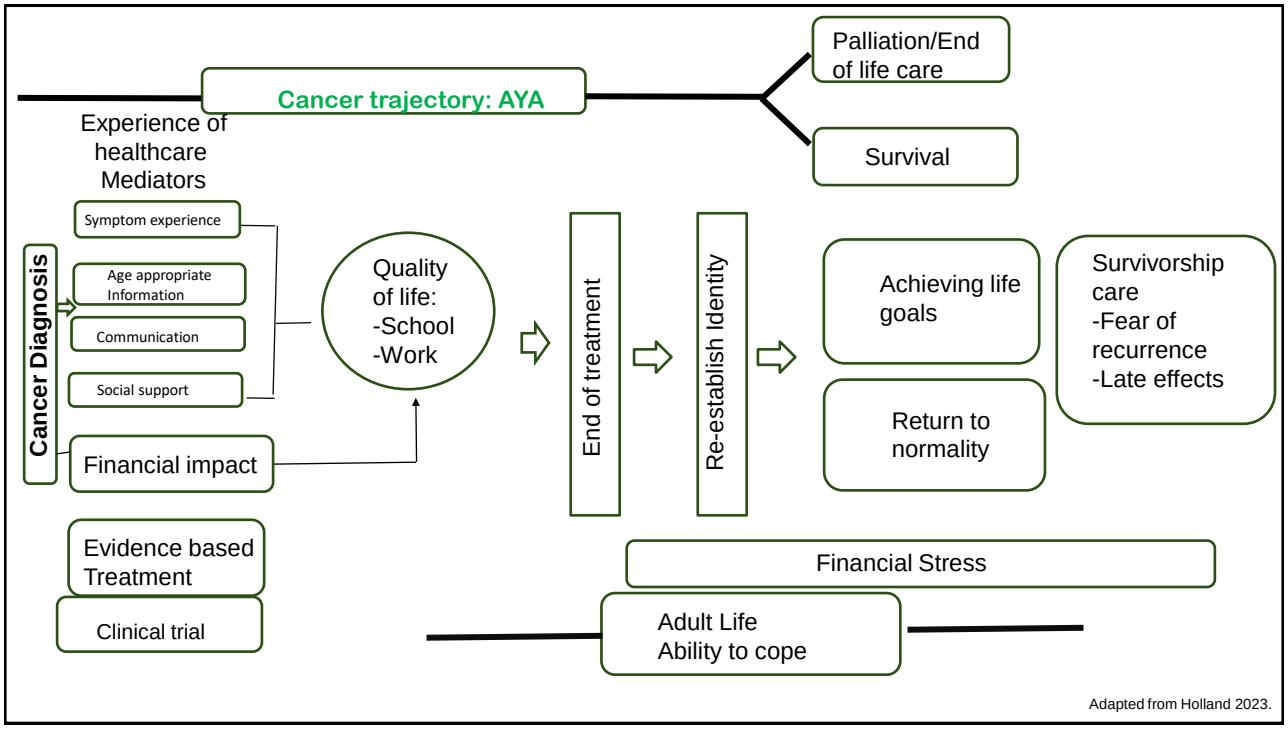

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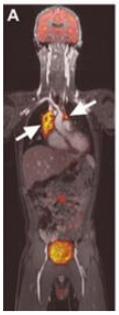
Diagnostic Workup: Lymphoma in AYA

- **Essential for Lymphoma**:
  - History and physical
    - B symptoms, lymph node, splenomegaly
  - Excisional Node Biopsy
  - CBC with differential
  - ESR and/or CRP
  - Complete metabolic panel
  - Echocardiogram
  - Chest X-ray: PA and lateral views
  - FDG-PET/CT or FDG-PET/MRI

- **Additional for NHL**:
  - LDH; uric acid
  - Hepatitis B/C testing
- Bilateral bone marrow
- Lumbar puncture
- Immunodeficiency
- Tissue Diagnostics (not comprehensive)
  - IHC
    - CD20, CD30 , Ki-67, Tdt
    - ALK
  - Flow cytometry: surface kappa/lambda
  - FISH
    - MYC, BCL2, BCL6; t(8;14)
  - Microarray: 11 q aberrations



https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf

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AYA Specific Considerations at Diagnosis of Lymphoma

- Pulmonary function test
- HIV
- Health Insurance

- Sexual health assessment
- Pregnancy test
- Fertility preservation-discussion and services
- Psychosocial assessment
- Counseling on substance use and smoking cessation
- Work/school issues
- Social support/network
- Financial toxicity

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AYA Lymphoma: Goals

- Balancing risk of relapse against:
  - Acute toxicity
  - Late toxicity
  - Quality of life
- During Therapy:
  - Understand tolerability through Patient Reported Outcomes (PRO)
  - Understand how symptomatic and non symptomatic AEs contribute to adherence to dose intensity of therapy

Popali et al. sJHaem 2023.

71

Hodgkin Lymphoma: Peds vs. Adult Oncology Approaches

- Histology distribution varies: younger patients; race/ethnicity
- Risk classification
  - Bulk – definitions differ between adults and peds
  - Prognostic scores- created in older adult cohorts treated with conventional therapy
- Treatment approaches: Risk based, response adapted
  - Chemotherapy back-bone (ABVE-PC vs. ABVD/BEACOPP)
  - Combined modality
    - Tailored radiation use and dose in older adolescents and YAs
- Trial Endpoints (EFS) – events include subsequent malignant neoplasms (SMN)
  - Goals of care: Person-years of life considered, HRQL
  - Late effects: Cardiac; fertility

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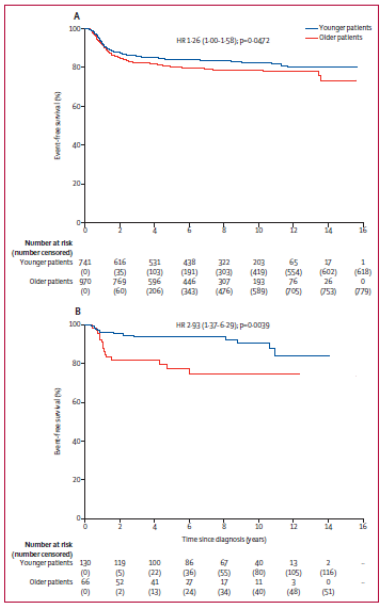

Survival by age in paediatric and adolescent patients with Hodgkin lymphoma: a retrospective pooled analysis of children's oncology group trials

Justine M Kahn, Qinglin Pei, Debra L Friedman, Joel Kaplan, Frank G Keller, David Hodgson, Yue Wu, Burton E Appel, Smita Bhatia, Tara O Henderson, Cindy L Schwartz, Kara M Kelly, Sharon M Castellino

Supplementary Table 3: Age ≥12 years. Multivariable model of event-free survival (EFS) and overall survival (OS) in N=1,711 patients with non-MC histology treated for HL on Children's Oncology Group (COG) trials (2002 – 2012).

Variables	EFS			OS		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (R: <12 years)						
≥12	1·48	1·03, 2·13	0·03	1·99	0·69, 5·70	0·20
Sex (R: Female)						
Male	1·14	0·90, 1·44	0·28	1·37	0·73, 2·59	0·33
Race (R: Non-Hispanic White)						
Non-Hispanic Black	0·88	0·58, 1·33	0·65	2·19	0·93, 5·17	0·25
Hispanic	1·20	0·86, 1·68		2·08	0·93, 4·67	
Asian/Pacific Island	1·31	0·69, 2·48		0·98	0·13, 7·35	
Other	0·98	0·56, 1·75		0·76	0·10, 5·74	
Study (R: AHOD0031)						
AHOD0431	3·47	2·10, 5·75	<0·0001	*		0·94
AHOD0831	0·48	0·27, 0·85		0·78	0·19, 3·22	
Stage (R: I and II)						
III	1·39	0·93, 2·08	0·0001	0·89	0·32, 2·43	0·94
IV	2·30	1·56, 3·40		1·07	0·37, 3·12	
B symptoms (R: No)						
Yes	2·04	1·44, 2·90	<0·0001	1·93	0·86, 4·33	0·11
Bulky Disease (R: No)						
Yes	2·06	1·44, 2·95	<0·0001	1·59	0·66, 3·85	0·30
Radiation (R: Yes)						
No	1·53	1·18, 1·98	0·001	1·10	0·53, 2·28	0·79
Payment (R: Private)						
Government	0·85	0·65, 1·11	0·22	0·84	0·42, 1·70	0·94
Other + Unknown	1·17	0·71, 1·93		0·80	0·18, 3·48	
Self-Pay or None	0·49	0·20, 1·22		0·67	0·09, 5·03	

Abbreviations: MC: Mixed cellularity; HL: Hodgkin lymphoma; HR: Hazard ratio; CI: confidence interval; cHL, NOS: Classical Hodgkin lymphoma, not-otherwise-specified

Kahn et al. Lancet Haematol 2022.

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Collaboration→ Accelerate Novel Approaches … and AYA enrollment

- NCTN (National Clinical Trials Network) - launched 2014
  - Goal: Increase trial participation in rare cancers and in AYA
    - Central support: CTSU; NCI CIRB
  - Increase in phase 3 trials
  - Increase in AYA enrollment ; 9.5% →14.0%
- Pharma
  - > 10 years (avg.) between regulatory approval and labeling of innovative therapy for adults and children
  - Prolonged off label use in pediatric patients
- International and other consortium partnerships

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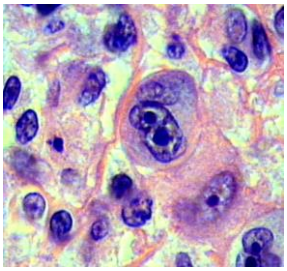
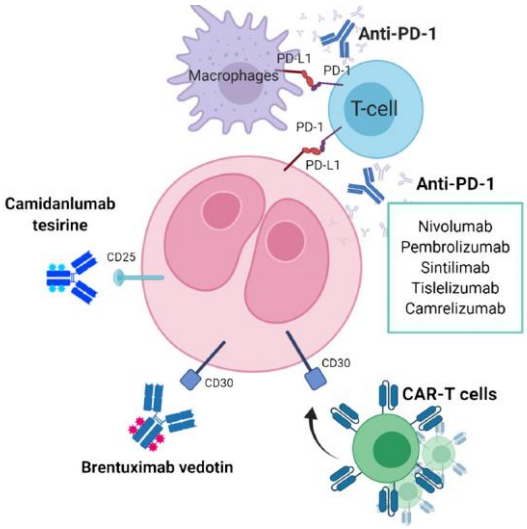
HL: Exploiting biology of HRS cell and the Tumor Microenvironment



HRS = Reed-Sternberg cell



Andrade-Gonzalez, Ansell. Curr Treat Options Oncol. 2021.

75

"A Phase III, Randomized Study of Nivolumab (Opdivo) Plus AVD or Brentuximab Vedotin (Adcetris) Plus AVD in Patients **(Age ≥ 12 years)** with Newly Diagnosed Advanced Stage Classical Hodgkin Lymphoma."

S1826 – Activated 7/19/2019

SWOG Chairs: Alex Herrera, MD; Jonathan Friedberg MD, MMSc
Pediatrics/COG Chair: Sharon Castellino, MD, MSc COG Champion: Angela Punnett MD
QOL Chair: Susan Parsons, MD, MRP

SWOG CANCER RESEARCH NETWORK

NCI National Clinical Trials Network a National Cancer Institute program NCI Community Oncology Research Program

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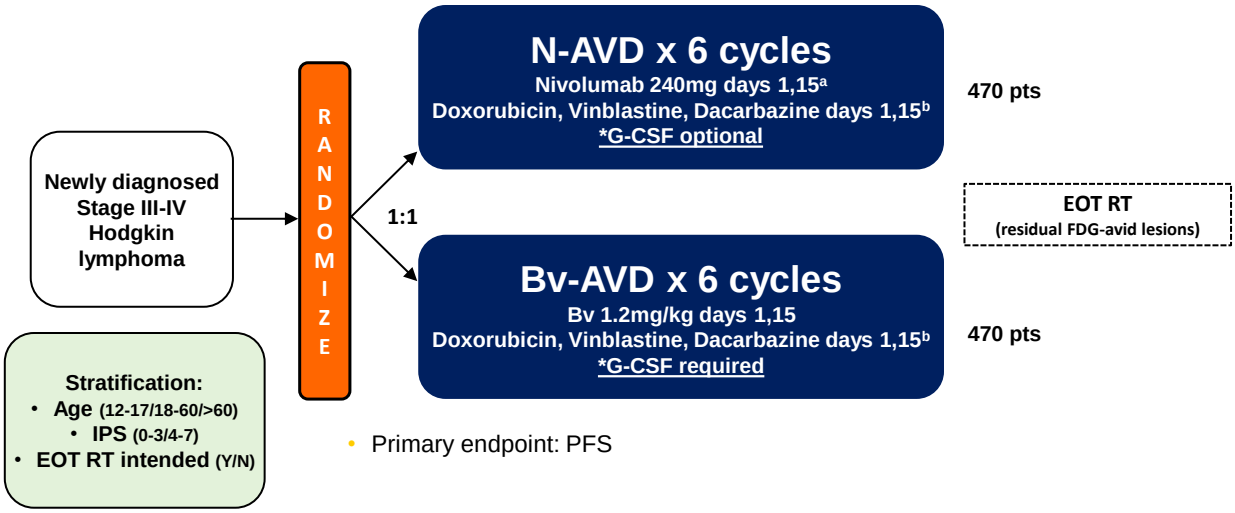
S1826 Study Design



[a] Nivolumab 3mg/kg for ages ≤ 17, max 240mg
[b] Conventional doses of AVD: Stephens DM et al Blood 2019, Ansell SM et al NEJM 2022

Alex F. Herrera, MD ASCO 2023.

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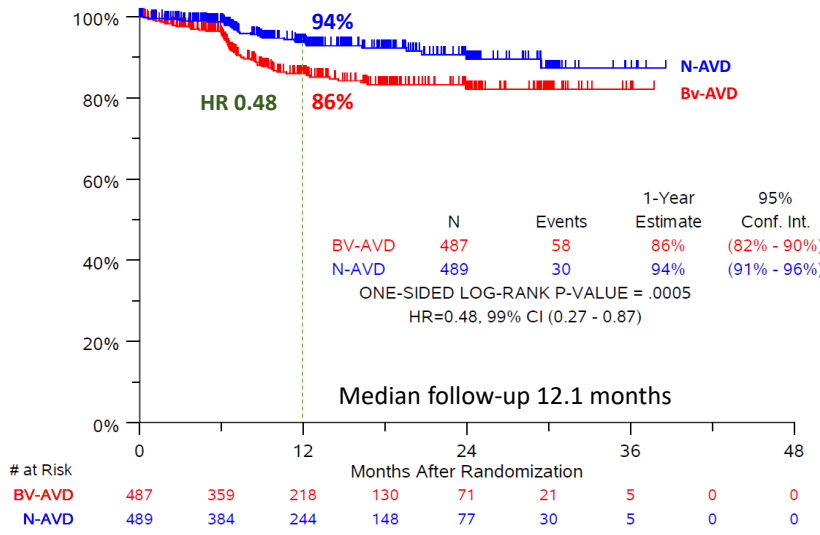
N-AVD improves PFS compared to Bv-AVD



1-year PFS
N-AVD 94%
Bv-AVD 86%

Alex F. Herrera, ASCO 2023.

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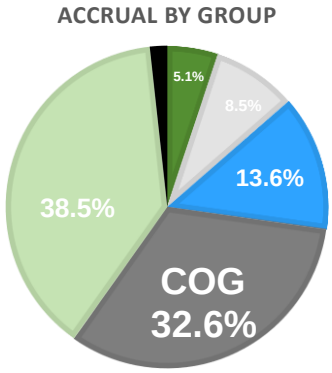
Successful Collaboration with the Adult NCTN

- Earlier access to novel agents for adolescents
- Harmonize approaches across pediatric and adult providers for AYAs with advanced stage HL
- Parallel design: Compare Bv-AVD against Bv-AVEPC (AHOD1331)
- Evaluation of the role of RT in the setting of new agents
- PROs will facilitate measurement of tolerability of new agents across the age spectrum

S1826 Accrual (n=994) (enrollment closed Oct 5, 2022)



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Cumulative Chemotherapy Dosing

	AHOD1331 (BV-AVE-PC x 5)	S1826 (N-AVD x 6)
Brentuximab Vedotin	9 mg/kg	
Nivolumab		36 mg/m2
Adriamycin	250 mg/m2	300 mg/kg
Vincristine	7 mg/m2	
Vinblastine		72 mg/m2
Etoposide	1875 mg/m2	
Prednisone	1400 mg/m2	
Cyclophosphamide	6000 mg/m2	
Dacarbazine		4500 mg/m2
Radiation dose	21 Gy 9 Gy boost to sites of residual avidity on EOT PET	30-36 Gy

CHILDREN'S ONCOLOGY GROUP

Courtesy: M. Heneghan

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Chemotherapy Administration

	AHOD1331 (BV-AVE-PC x 5)	S1826 (N-AVD x 6)
Cycle Length	21 days	28 days
Total Duration	105 days	168 days
Days of IV chemo	Day 1, 2, 3, and 8	Day 1 and 15
Total days of IV chemo	20 days	12 days
Growth Factor	Required	Optional
Dexrazoxane	Permitted not required	Permitted not required

CHILDREN'S ONCOLOGY GROUP

Courtesy: M. Heneghan

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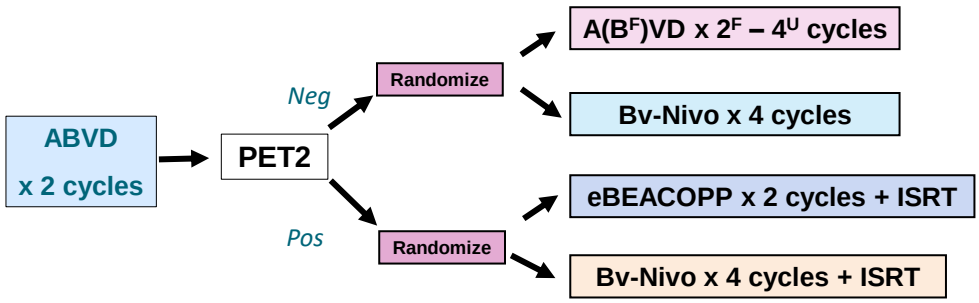
AHOD2131: Stage I/II – Activated April 2023



[a] 1 cycle = 28 days
[b] PET2 positive defined as Deauville 4 or 5
F favorable; U unfavorable

CHILDREN'S ONCOLOGY GROUP

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Non-Hodgkin Lymphoma in AYA

- More Common Pediatric/Adolescent NHL
  - Mature B-cell lymphomas
    - Diffuse Large B-cell Lymphoma
    - Burkitt Lymphoma
    - Primary Mediastinal B-cell Lymphoma
  - Anaplastic Large Cell Lymphoma
  - Lymphoblastic Lymphoma/Leukemia
    - T differentiation
    - B differentiation
  - Post-transplant lymphoproliferative disease (PTLD)
- Less Common Pediatric/Adolescent NHL
  - Pediatric follicular lymphoma
  - Marginal zone & MALT lymphoma
  - Primary CNS lymphoma
  - Peripheral T-cell lymphoma NOS
- Lack of harmonization in staging systems in NHL
  - Ann Arbor Staging (adults)
  - International Pediatric NHL Staging System
  - Lack of Prognostic scores relevant to younger patients

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Novel Agents in NHL

- CD 30: Brentuximab vedotin
- CD20: Rituximab
- ALK: crizotinib
- Amplified PD1: Checkpoint inhibitors
- Small molecule inhibitors: Ibrutinib; ventoclax

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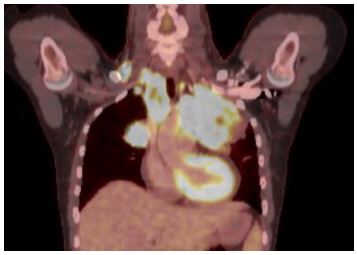
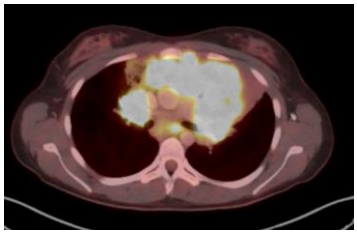
Primary Mediastinal B-cell Lymphoma

- Rare subtype of NHL
- Peak incidence in AYA, F>M
- Presents as large mediastinal mass
  - Pleural, pericardial effusions common
- Biology overlaps with classic HL
  - CD30+
  - Overexpression PD-1
  - Sensitive to immune checkpoint blockade





CHILDREN'S ONCOLOGY GROUP

Courtesy : L Giulino-Roth

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ANHL1931: Randomized phase III trial of nivolumab in PMBCL

Physician declares chemotherapy backbone: R-CHOP or DA-EPOCH-R

R-CHOP or DA-EPOCH-R x 6 cycles

Nivo + R-CHOP or Nivo + DA-EPOCH-R x 6 cycles

Primary Endpoint: PFS as determined by independent review committee

Consolidative RT permitted only in the following circumstances:
1) Physician declares R-CHOP + RT regardless of EOT imaging
2) + biopsy at EOT

Open NCTN wide across all age groups

Opened to accrual June 2021
Anticipated to enroll 186 patients over 3.8 years

Courtesy: : L Giulino-Roth.

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POLLING QUESTION #5

- What percent of AYA patients with a blood cancer should receive a survivorship care plan?
  - A) 11-25%
  - B) 26-50%
  - C) 50%
  - D) 100%

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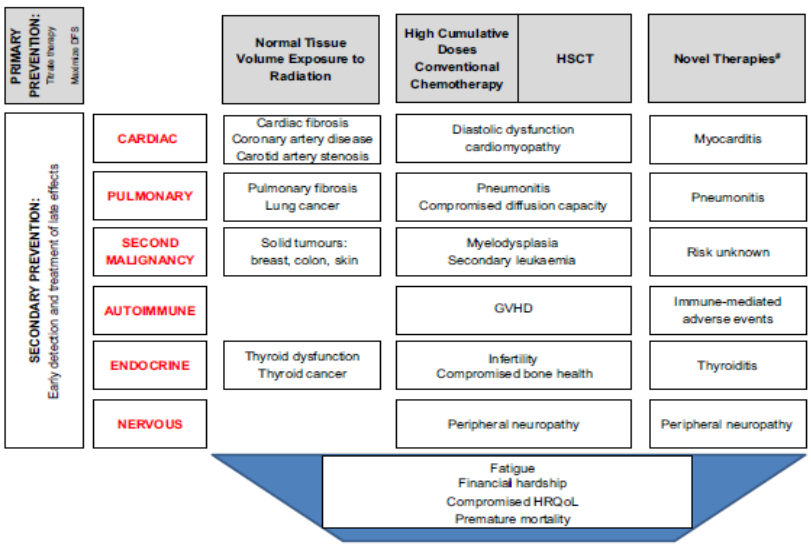
Addressing the Survivorship Gap… Begin With the End in Mind



Castellino SM, et al. *Br J Haematol.* 2019;187:573.

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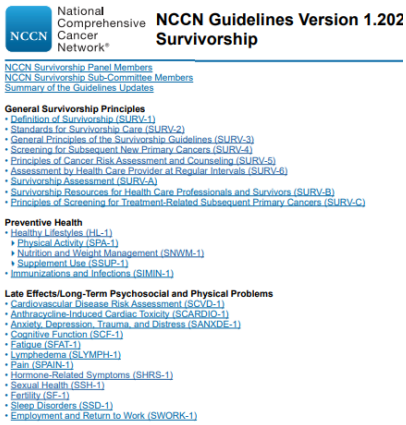
Secondary Prevention

Children's Oncology Group Guidelines: Exposure based



- ❑ Need for new models for AYAs who often do not return to treating institution
- ❑ Opportunities for mHealth
- ❑ Evidence will be a long time in coming for novel agents
- ❑ Need biomarkers for late toxicity

http://www.survivorshipguidelines.org/

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Survivorship Care Plans

- Document that summarizes an individual patient's treatment-cumulative doses and modalities of therapy received
- Summary of :
  - Therapy associated late effects
  - Recommendations for follow-up care
  - Health promotion for screening and health behaviors

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Thank You

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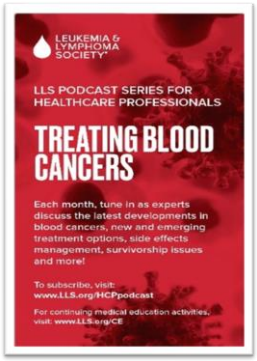
FREE LLS RESOURCES FOR HEALTHCARE PROVIDERS

- CME and CE courses: www.LLS.org/CE
- Fact Sheets for HCPs: www.LLS.org/HCPbooklets
- Videos for HCPs: www.LLS.org/HCPvideos
- Podcast series for HCPs: www.LLS.org/HCPpodcast



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FREE LLS RESOURCES FOR PATIENTS

- **Information Specialists** – Personalized assistance for managing treatment decisions, side effects, and dealing with financial and psychosocial challenges (IRC).

- **Clinical Trial Nurse Navigators** – RNs and NPs provide a personalized service for patients seeking treatment in a clinical trial, sift through the information and provide information to bring back to their HC team (CTSC).
  - www.LLS.org/CTSC

- **Nutrition Education Services Center (NESC)** – LLS provides **Nutrition Education Services** to patients and caregivers of all cancer types. *Our **registered dietitians** have expertise in oncology nutrition.* To schedule a free consultation:
  - visit www.LLSnutrition.org
  - call 800-955-4572

- **Reach out Monday–Friday, 9 am to 9 pm ET**
  - Phone: (800) 955-4572
  - Live chat: www.LLS.org/IRC
  - Email: infocenter@LLS.org
  - HCP Patient Referral Form: www.LLS.org/HCPreferral

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FREE LLS RESOURCES FOR PATIENTS AND CAREGIVERS

- **Webcasts, Videos, Podcasts**:
  - www.LLS.org/Webcasts
  - www.LLS.org/EducationVideos
  - www.LLS.org/Podcast

- **www.LLS.org/youngadults**

- **Support Resources**
  - Financial Assistance: www.LLS.org/Finances
  - Other Support: www.LLS.org/Support
    - LLS Regions
    - Live Online Weekly Chats: “Living with NHL”
      - Facilitated by Oncology SW
    - LLS Community Social Media Platform
    - First Connection Peer to Peer Program

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FREE LLS RESOURCES FOR YOUR PATIENTS

BOOKLETS AND FACT SHEETS

English – www.LLS.org/Booklets
Spanish – www.LLS.org/Materiales

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Questions?

Ask a question by web:
-Click “Ask a question”
-Type your question
-Click “Submit”

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INSTRUCTIONS FOR CREDIT

Participants must complete the evaluation to receive credit.
After completing this process, your certificate will automatically generate.

Link to complete evaluation: https://mli.link/llsaya

For questions or concerns, please contact Profeducation@lls.org

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