Review Article

Report from the Lymphoma Research Foundation Adolescent and Young Adult (AYA) Lymphoma Scientific Workshop, May 2019

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Abstract: Adolescent and young adult (AYA) lymphoma is defined as lymphoma diagnosed in patients between 15 and 39 years of age. When compared to children and adults, AYAs have not seen the same improvement in survival over recent years, even with the introduction of novel agents and interventions. This survival gap is driven by multiple compounding factors, including unique disease biology, challenges with survivorship care, socioeconomic factors, and cancer care treatment setting, among others. There is no established standard of care for AYA lymphomas, and many clinical trials do not evaluate AYAs as a separate subgroup or include measures that are of particular importance to AYAs. The Lymphoma Research Foundation (LRF), the nation's largest non-profit organization dedicated exclusively to lymphoma research and patient advocacy, hosted its inaugural AYA Consortium Meeting to discuss research findings that support the recognition of AYAs as a distinct group of lymphoma patients. Attendees, comprised of expert lymphoma researchers and clinicians, discussed unmet needs, gaps in data, and strategies for improving AYA care clinical and psychosocial outcomes. This report, which includes a summary of each presentation, aims to review recent findings in AYA lymphoma research and highlight potential areas for future study.

Keywords: Lymphoma biology; lymphoma treatment; adolescent and young adult cancers; survivorship; epidemiology

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Introduction

Lymphoma in adolescent and young adult (AYA) patients is associated with worse outcomes than lymphoma in children and older adults. The contributing factors appear to be complex in nature and range from differences in basic disease biology all the way to gaps in survivorship care. To better understand the nature of this disparity and to develop strategies that may be employed to improve outcomes in the AYA population, cross-disciplinary collaboration is required. Recognizing this unmet need, LRF began an initiative to engage and support the AYA research community, as well as patients and their families. In 2015, LRF convened an AYA Symposium with clinicians and basic scientists from pediatric and adult disciplines to examine the state of the science for AYA lymphoma, precisely review

the gaps in research for this population, and discuss the unique challenges and burden for the AYA lymphoma population. Prior to this event, no other formal cross-disciplinary collaborations had occurred. A summary of the symposium proceedings was published in *Blood Advances* in October 2017. Importantly, this publication compared pediatric and adult approaches to lymphoma management including Hodgkin lymphoma, mature B-cell lymphomas, and anaplastic large cell lymphoma. As a result of low rates of clinical trial enrollment in this age group, systematically generated evidence is lacking. Thus, lymphoma treatment for AYA is not necessarily dictated by empiric evidence specific to age group, but rather by community referral patterns, individual physician preference, and treatment location. In addition, the publication highlighted knowledge gaps surrounding AYA cancer biology, care delivery, and therapeutic efficacy.

The current proceedings represent discussions that took place at the Inaugural AYA Lymphoma Consortium Meeting. This consortium brought together physicians and researchers from more than 40 academic and medical institutions, federal agencies, and companies. It is the first collaboration of its kind aimed at advancing the study of AYA lymphomas and improving treatments and care for this patient population, from the point of diagnosis through long-term survival. In addition to exploring the current evidence and gaps in research, the workshop focused on clinical trial planning and enrollment, care delivery, survivorship, and long-term effects and impacts of AYA lymphoma.

Following multiple panel discussions aimed at thorough review of these topics, participants developed a blueprint for subsequent AYA lymphoma research and an action plan for the formulation and work of the Consortium (*Table 1*). Attendees created blueprints for understanding biology, immunobiology and epidemiology; guiding clinical trials and drug development; characterizing ideal care delivery and patient outcomes; and better understanding survivorship and late effects. The blueprints generated for each topic were presented to the audience for discussion and refinement.

Proceedings

Epidemiology—Lindsay Morton, PhD, National Cancer Institute (Moderator)

To open the session, Lindsay Morton, PhD, (National Cancer Institute) discussed epidemiologic perspectives on AYA. Overall, lymphomas represent about one-third of malignancy diagnoses in AYA populations. Data on the heterogeneity of lymphoid malignancies in the AYA population were presented, revealing that Hodgkin lymphoma and precursor lymphoma/leukemia represent the highest proportion of lymphoma diagnoses, which represents roughly between 35% and 70%, followed by diffuse large B-cell lymphoma (DLBCL), which represents between 10% and 20% (1). Both the proportion of malignancy accounted for by lymphoma as a whole and the relative proportions of disease type shift over time. In addition, incidence patterns that are influenced by sex and race/ethnicity vary over time and are different in the AYA population than in adults or pediatrics. For example, in follicular lymphoma (FL), disease is more common in males in the pediatric setting, becomes less so throughout the AYA population, and then is equally represented in males and females in the adult population (1). These findings highlight the question of whether lymphomas in the AYA population are biologically distinct from those present in the pediatric and adult populations and suggest that in terms of biology, susceptibility, and exposure, they may be. There is a need for specific studies to understand whether AYA lymphomas are different from those in other populations because this dictates whether clinical findings in other populations may be applied to AYAs and used to guide treatment. Factors that may contribute to the observed age-based variation in disease include evolution of the immune system, changing impact of genetic susceptibility, and viral and/or occupational exposure. Each of these contributing factors is well supported by evidence and may impact both the etiology of the disease as well as prognosis and the nature of the ideal treatment approach. Future studies could identify risk factors unique to the AYA population and could be used to develop a risk score to guide treatment selection.

Dr. Wendy Cozen, DO, MPH (Keck School of Medicine of the University of Southern California) continued the discussion of the importance of epidemiology in cancer by presenting her research on genetic risk factors and etiological models of AYA Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Because the peak HL incidence occurs in AYA, there is substantial information on risk factors. AYA HL varies geographically and is highest in economically developed countries and among the highest socioeconomic status, which is different than HL that occurs in older adults. There is evidence for strong genetic risk, with a very high risk to identical twins of HL patients

and genetic variants in immune response genes *IL13*, *GATA3*, *TCF3*, *REL* and others, in addition to multiple HLA types (2). Some of these varied by histology subtype and Epstein-Barr tumor status. Genome-wide association studies (GWAS) revealed that HL shares more markers with immune-related diseases than solid tumors. Additional variants were identified at 6p21.31, 6q23.3, 11q23.1, 16p11.2, and 20q13.12 that influence risk for HL (3). There are now 23 reported risk variants, all of which are associated with genetic predisposition implicating germinal center dysfunction, disrupted T-cell function, and NF-κB activation in the pathogenesis of HL. This raises the question of how immune function and HL disease etiology are associated. Dr. Cozen presented both the polio model and the hygiene hypothesis as potential models to explain epidemiological observations supporting a lack of exposure to microbes as a young child as a risk factor. There is much less information on AYA NHL, but there is a suggestion that there are some differences in genetic risk. A few cohort studies have shown that infants hospitalized for an infection in the first year of life had a higher risk of NHL up to age 40, suggesting that a subclinical immunodeficiency is a risk factor (4,5). It is important to study the role of these risk factors in the AYA population, and Dr. Cozen noted that the identified risk factors may have utility to generate polygenic risk scores for screening and identifying siblings at risk for AYA HL and NHL. Future research should focus on early life factors and immunological changes at puberty to elucidate risk pathways and interventions.

In the next talk, Thomas M. Habermann, MD (Mayo Clinic College of Medicine and Science) described findings from the Lymphoma Epidemiology of Outcomes (LEO) Consortium (6). The aims of the LEO Consortium (U01 CA195568) include a better understanding of different lymphoma populations with regard to genomics, serum biomarkers, tissue studies, clinical studies, and lifestyle environment analyses, including the AYA population. Most studies of NHL outcomes are based on small institutional databases that contain highly selected participants, which limits the number of AYA patients. On the other hand, larger cohorts and national databases often lack meaningful data on progression, relapse, and patient-reported outcomes and are not accompanied by tumor tissue. In the LEO U01 protocol, the initial diagnosis data including clinical data (physician- and patient-reported) tumor tissue studies, lifestyle and environmental factors, was expanded to include an extensive tumor bank, a bank of serum and germline DNA, and well-annotated clinical, treatment, and epidemiological data. The cohort will be prospectively followed, and the findings, along with supporting tissue samples and clinical documentation will facilitate research projects and promote interaction with established trial networks. Dr. Habermann reviewed the epidemiology questionnaire, procedure for baseline blood and DNA samples and baseline pathology, and the informatics infrastructure. Participants enrolled in the study will be contacted every 6 months for 3 years and then annually thereafter. Follow up will include disease status, retreatment, and survivorship issues and will validate all disease progressions, retreatments, and second cancers. There is also a protocol in place for reviewing deaths. By the spring of 2019, accrual was 5442 patients, 597 (10.9%) of whom are in the AYA age group (18 to 40 years). Dr. Habermann presented the LEO histology subtypes by age, noting that DLBCL is highest among AYA in the LEO cohort (3.8% of all patients, 36.5% of AYA patients) followed by FL (1.7% of all patients, 16.4% of AYA).

In a separate age 18–39 cohort from the Lymphoma Specialized Program of Research Excellence (SPORE) Molecular and Epidemiology Research (MER), HL accounts for 52.4%, T-cell lymphoma for 15.7%, and DLBCL for 11.4%. Importantly, in the MER cohort, higher physical activity after diagnosis and at 3 years was significantly associated with better overall survival (OS), event-free survival (EFS) and lymphoma-specific survival (LSS) (7). Highlighting another important factor in survival, Dr. Haberman noted that in a study of 236 patients (8), attendance in survivorship clinic has a strong effect on overall health perception in younger patients.

Building on Dr. Haberman's introduction of functional outcomes, Susan K. Parsons, MD, MRP (Tufts University School of Medicine and Medical Center) presented her work on the functional impact of HL on AYAs during treatment. Though 40% of all HL cases are diagnosed in patients between the ages of 15 and 34 years and HL is the most common cancer in patients in this age group, the disease burden of HL in AYAs is not well characterized. In this age group, a unique set of developmental tasks include attainment of educational and vocational goals, healthy social and intimate relationships, establishment of independent living, and financial stability. Dr. Parsons described that in the AYA Health Outcomes and Patient Experience (HOPE) study, 524 patients between the ages of 15 and 39 years were surveyed at study entry and 12 months later. Two-thirds of patients reported a negative impact on finances, and 11% lost insurance coverage in the prior year.

Patients also reported negative impacts on employment and education as well as a disruption in social roles. These findings are recapitulated in the Medical Expenditure Panel Survey (MEPS) and St. Jude cohorts (9,10).

To further characterize the AYA experience, a systematic review of health-related quality of life (HRQL) after diagnosis with HL was carried out (11). A total of 65 studies between 1980 and 2015 were identified. Of these, only 5 evaluated patients on and off treatment, and 3 followed patients from diagnosis to 10 years following treatment. HRQL measures varied widely across studies. This analysis revealed a profound knowledge gap surrounding functional outcomes in pediatric and AYA HL. Dr. Parsons cited the Children's Oncology Group (COG) AHOD1331 study as an example of how longitudinal assessment of HRQL can be embedded within trial design. Approaches for future studies of functional impact in the AYA population should include standardized measurements to allow comparison across studies. Global HQRL assessment, multi-item fatigue scale, chemotherapy-induced peripheral neuropathy (CIPN), and financial toxicity measures are central. Further, the connection between patient-reported outcomes and biology may be explored. Examples include the connection between fatigue and cytokine levels or genetic polymorphisms with CIPN.

Panel discussion

Following the presentation, the floor was opened for comments. The following points were raised by audience members for consideration.

- Continuous data collection in the AYA population represents an opportunity to incorporate personal technology.
- One audience member emphasized the importance of financial toxicity. This can be made worse when patients are unaware of how to navigate the transition from their parents' insurance. A financial ambassador or treatment navigator may be able to help.
  - Financial toxicity in the 20s is different from in the 30s. Should these patients be analyzed separately?
  - There are other maturity factors at play (e.g., a 21-year-old with a house and 2 kids *vs.* a 30-year-old who is barely financially independent).
  - Longer-term measures could include job loss and bankruptcy filings.
- Microbiome diversity and composition is of particular interest in the context of twin studies, as it may help to shed light on how the microbiome affects the development of lymphoma in the general population.
- There is a need for crosspollination between LEO and existing data sets (e.g., Kaiser, Veteran's Affairs, or other state insurers).
  - Integration of data from multiple sources will be critical for answering these questions.
- The transition in disease subtype frequency in the AYA population that can be observed with epidemiological data may reflect a transition in underlying disease biology.

Disease biology—Christian Steidl, MD, British Columbia Cancer (Moderator)

Christian Steidl, MD (British Columbia Cancer) presented recent progress in HL and primary mediastinal large B-cell lymphoma (PMBCL). Overall, standard treatment for pediatric HL is more intense than for adults, and long-term toxicities are viewed in the context of long-term therapeutic success. In pediatrics, there are no molecular biomarkers to guide treatment. Together, these factors raise the question of whether EFS can be predicted so that long-term toxicity can be reduced while maintaining a high cure rate. Using the nanoString gene expression profiling system, 23 genes of interest were evaluated in HL cohorts at the BC Cancer, and in the Southwest Oncology Group (SWOG) and Response Adapted Treatment for HL (RATHL) cohorts. Three cellular components were found to be associated with positive outcomes, while six components were significantly associated with inferior outcomes in pediatric patients, whereas the opposite prognostic significance was observed in adults. Following further analysis, Thymus and activation-regulated chemokine (TARC) and interferon (IFN)-γ were shown to be negatively and positively correlated with EFS, respectively (Mottok A, 2019 unpublished data). Together, these data are evidence of biological differences between AYA and adult disease.

For PMBCL, clinical, morphological, biological, and immunological overlaps with childhood HL (cHL) complicate diagnosis (12). Similarly, the biological overlap between PMBCL and DLBCL can also cause confusion in initial diagnostics. A recent analysis using the nanoString platform (13) identified 6 genes with higher expression in DLBCL and 24 genes with higher expression in PMBCL (14). These genes are of particular interest because in most previously published datasets, gene values could overlap between disease states. To

validate these markers, a cohort with 88 PMBCL and 72 DLBCL patients was evaluated using these markers; 83% of DLBCL cases were predicted correctly and 85% of PMBCL were predicted correctly (14). Thus, gene-expression profiling provides more accurate subtyping of aggressive lymphomas (PMBCL *vs.* DLCBL) using routinely available formalin-fixed, paraffin-embedded tissues. In addition, the mutational landscape study of PMBCL confirms a close relationship to cHL and a contrasting relationship with DLBCL.

Next, Lisa Roth, MD (Weill Cornell Medicine) presented findings on the genomics of Hodgkin Reed Sternberg (HRS) cells. In HL biopsies, the majority of cells are infiltrated cells, making the study of HRS genetic alterations difficult. In order to study these cells, they must be isolated to increase DNA yield and purity. In addition, library preparation must be customized for ultra-low input. Dr. Roth presented her work on whole exome sequencing of HRS cells using flow sorting to generate pure HRS populations. Within HRS cells, there is a high number of gene gains and losses, mostly due to large-segment alterations. In Dr. Roth's research, there were recurrent gains in chromosome 2 (containing *REL*, *BCL11A*, *XPO1*, and *MYCN*) and common losses in areas containing *TNFAIP3*, *MLL*, *PRDM1*, and *MLL4*. Gains in the region of chromosome 9 that includes *PDL1* and *JAK2* were also observed. In addition, beta-2 microglobulin (B2M) biallelic inactivating mutations were associated with loss of MHC class 1 in HRS cells (15). To answer the question of whether there are molecular differences in HL across the age spectrum, Dr. Roth is conducting a multicenter study to determine the feasibility of sorting AYA HRS cells from centers across the US. Across five centers, there was a 71% success rate for obtaining samples with evaluable DNA for sequencing, indicating that the research could be scaled up. Future research will focus on understanding alterations across the age spectrum, using technology to identify and evaluate novel drug targets, and integrating the evaluation of HRS cells into clinical trials.

Kieron Dunleavy, MD (GW Cancer Center, George Washington University) then presented findings on DLBCL and PMBCL in AYA. As age increases, the complexity of DLBCL increases. Younger patients have fewer genetic aberrations (16), and the relative percentages of subtypes are skewed towards more aggressive forms as patients age (the ABC subtype is more common with increasing age) (17). EFS in DLBCL is improved with rituximab, but standard therapy is ineffective for a significant percentage of patients, especially those with intermediate- and high-risk disease (18). Interestingly, in younger adults (≤60 years), there is a survival advantage for R-ACVBP over R-CHOP (19). Importantly there are no AYA-specific studies on DLBCL, and thus many questions remain regarding the underlying disease biology and optimal treatment for this demographic are unanswered (20). It is unclear if DLBCL is clinicopathologically distinct in AYAs, and the rarity of these tumors makes it difficult to thoroughly study. In AYAs, it is also unclear if more dose-intensive approaches are needed (as suggested by the superiority of R-ACVBP versus R-CHOP) and if there are distinct pharmacokinetics in the AYA population.

For PMBCL, EFS and OS lags behind that for DLBCL in pediatric patients (21), and it remains unclear if disease biology and the optimal approach are different for AYAs. Studies using interim measurements of circulating tumor DNA (ctDNA) in DLBCL (including PMBCL) importantly demonstrate that interim ctDNA positivity is associated with inferior outcomes (22). This finding has thus far only been shown retrospectively and needs to be studied prospectively and in the future, may be helpful towards better understanding the reasons for treatment failure in AYA and pediatric PMBCL. This may be an important step towards identifying subsets of AYA and other patients who may require novel treatment approaches in the upfront setting.

Next, Eric Lowe, MD (Children's Hospital of the King's Daughters) presented data on anaplastic large cell lymphoma (ALCL). ALCL is a distinct form of NHL that accounts for ~15% of all childhood NHL and ~2% to 3% of adult NHL. ALCL is characterized by malignant cell expression of CD30 and can further be divided into subtypes based on ALK positivity. ALK+ is most common in the first 3 decades of life and represents 95% of childhood ALCL and 40% to 50% of adult ALCL, while ALK- is more common in patients ages 50 to 70 years. Within the pediatric setting, multiple treatment strategies have been tested, including B-cell and T-cell strategies, but EFS remains low at 59% to 76%. Based on the results of previous trials, it is clear that ALK translocation drives tumor biology (23). This raises the question of whether it is possible to specifically target ALK. Crizotinib, a therapy that was originally approved in lung cancer, was tested in relapsed adult ALCL (24) and pediatric ALCL. In pediatric patients with relapsed ALCL, treatment resulted in an 83% complete remission (CR) rate (25). With these results in

Table 1 Goals of the scientific workshop on adolescent and young adult lymphoma

Session	Concerns	Immediate Actions and solutions (1–5 years)	Long-term solutions (more than 5 years)
Epidemiology	Epidemiology and genomic risk data on the AYA population are not well characterized in all lymphoma subtypes and there is an age-adjusted increase in the incidence rates of NHL with age. There is a male preponderance for any histology, particularly black males older than the age of 20	Further identify genetic risk factors in each lymphoma subtype. Further identify epidemiology risk factors for each lymphoma subtype in the AYA population. Prioritize prognostic factor data	Identify key genetic and epidemiologic risk factors and modify outcomes
Disease biology	Distinct different AYA biology versus adult biology in AYA subtypes are not well uniformly described	Prioritize disease biology studies in all AYA subtypes. Characterize differences in AYA population versus adult population	Develop molecular targets in each subtype. Further understand the microenvironment
Clinical trials	There is limited data on AYA outcomes in the different AYA histologic subtypes	Prioritize studies focused on improving outcomes in relapsed/ refractory lymphoblastic lymphoma, Burkitt lymphoma and post stem cell transplantation relapsed DLBCL where current therapies are associated with dismal results	Prioritize enrollment on clinical trials for young adults as less than 2% of patients aged 20–30 years of age are enrolled on clinical trials in contrast to 10–15% of patients are aged 15–19. Prioritize development of clinical trials aimed at improving outcomes for patients with relapsed HL following stem cell transplantation, relapsed refractory Burkitt lymphoma, and relapsed refractory lymphoblastic lymphoma
AYA oncology drug development	Drug development in AYA lymphoma appears to be a secondary priority	Prioritize and increase awareness of AYA outcomes, especially in the relapsed setting. Develop public-informatics	Advocate and produce tangible results in AYA lymphomas
Pediatric and adult clinical care, service delivery, and disparities	Racial disparities, resource allocation, and the impact of treatment are not optimally defined in the AYA population	Define resource utilization of the AYA population in the community and academic health centers	Impact the service deliveries and disparities in the AYA population. lack of insurance or Medicaid insured status in the USA and lower income has been associated with increased mortality and must be addressed
Uncommon pediatric and AYA histologies	Pediatric and AYA follicular lymphoma, extranodal marginal zone lymphoma, primary CNS lymphoma, T-lymphoblastic lymphoma, (NK)/T-cell lymphoma and grey zone lymphoma are poorly understood	Further define treatment and natural history of these entities	Improve understanding of the natural history of these entities. Improve outcomes of these entities
Patient outcomes, late effects and survivorship	The description and management of cumulative and late toxicities in survivors of hematologic malignancy is inconsistent, inadequate, not histology dependent, not treatment related, or missing. Non-cancer-related mortality is the leading cause of death by approximately 30 years from cancer diagnosis. The numbers are increasing, and it is currently estimated that there will be 35,000 AYA survivors of NHL by 2020. More than two-thirds of survivors self-report one or more chronic health conditions, and greater than one-third, a severe or life-threatening conditions	Standardize use and content of survivorship care plans. Develop and support infrastructure. Further understand the 3–9 folds increased risk of developing a second neoplasm with a more significant risk in females and those with primary mediastinal neoplasms. Further define the role of exercise in long-term survival. Define all endocrine late effects in each of the lymphoma histologies	Increase funding for survivorship research. Link patient reported outcomes, delayed, or long-term complications of hematologic malignancies, and their baseline treatment in electronic medical records. Increase survivorship clinics. Further understand chronic health conditions (pulmonary and cardiac) and cumulative risk of chronic health conditions including neurocognitive, health QOL, lower social attainment, memory, executive function, and body image. Further understanding of hypertension, hyperlipidemia, overweight, infertility, secondary malignancies, personal care needs, and other health conditions in the AYA population long-term

hand, there are other remaining questions, such as whether prolonged use will give rise to resistance and how to best use crizotinib in combination with other therapies, among others. Because higher ALK antibody titers are associated with better survival, targeting the immune system is a viable approach for these patients. Other elements of the immune system represent an avenue for complementary drug development.

When considering future trials for ALCL, it is important to recognize that ALCL is a rare disease. Thus, cooperation between physicians, academia, pharmaceutical companies, and regulatory agencies will be central to the success of new clinical trials or therapies. Like in many rare diseases, the challenges of trial design are shaped by the extremely small number of patients. Dr. Lowe noted that in a recent ALCL trial, 75 sites were required to enroll 136 patients. Nevertheless, ALCL represents a rare opportunity in rare disease and in oncology, as ALK is an identified and known driver of disease that is present in most patients.

Panel discussion

Following the presentation, the floor was opened for comments. The following points were raised by audience members for consideration.

- HRS cells may be used as a predictor and surrogate for the microenvironment in HL.
- The primary challenge of assessing HRS cells is the scarcity of the cells themselves. More research is needed to better understand the relative contributions of the malignant cells and microenvironment.
- One audience member suggested using the nanoString platform to assess signatures in multiethnic populations.
- Epstein-Barr virus status should be included in protocols.
- Pediatric cancers are associated with fewer mutations that are more closely linked to the cancer, while adult cancers more often have an increased number of mutations that are not necessarily cancer driving mutations.
    - Because of small numbers, it is difficult to assess the relative prevalence of double-hit and triple-hit lymphomas and how they relate to outcomes.
- Underlying immunodeficiency may be a contributing factor to risk.
- Cells in the microenvironment are normal immune cells, as measured by single-cell transcriptome analysis.
- One audience member reiterated the need to study NHL in older patients and AYAs separately. Because excisional biopsies are becoming less frequent and incisional core needle biopsies are less invasive, perhaps more people will be willing to participate. In addition, biopsy may become less important as technologies that allow noninvasive sampling improve.
- When considering the use of crizotinib in the AYA population, it will be critical to have as much data as possible on long-term use and long-term effects.
    - Currently, it is unclear when crizotinib therapy can be stopped.
- Most often, families with younger AYA patients will prefer oral therapies; in contrast, AYAs participate in the decision-making process tend to prefer the "best shot at survival, regardless of effects."

AYA lymphoma clinical trials—Sonali Smith, MD, The University of Chicago (Moderator)

To open the session on AYA lymphoma clinical trials, the panelists provided an overview of trials that had been developed collaboratively between adult and pediatric research groups. Catherine Diefenbach, MD (New York University Langone Medical Center) presented the protocol and preliminary results for the ECOG-ACRIN Cancer Research Group study ECOG E4412. The study is a phase I/II study of the combination of ipilimumab, nivolumab, and brentuximab vedotin in patients with relapsed/refractory HL. This combination is hypothesized to both attack the tumor cells and prime the microenvironment for attack of the tumor cells. The study schema and eligibility criteria were presented. To date, the most common grade 2 toxicities associated with triplet therapy include nausea, peripheral sensory issues, fatigue, and diarrhea. The most common grade 3 toxicities include fatigue, vomiting, decreased white blood count, maculopapular rash and colitis. So far, there are 19 evaluable patients who have received triplet therapy. The overall response for evaluable patients is 95%, and CR is 84 (26). Data for the other arms of the study were also presented, but overall, the triplet therapy appears to be most effective in terms of OS and PFS (27,28). Of note, the protocol is being amended to include a wider range of AYA by expanding eligibility to patients between the ages of 12 and 18 years. In interpreting the results, age will be used as a stratification factor. Remaining questions include optimal dosing for different therapies, in particular among different age groups, additional details of

how triplet therapy will impact outcomes before and after transplant, the impact of low-grade chronic side effects, and different efficacy and toxicity in the AYA population, among others.

Next, Jonathan W. Friedberg, MD, MMSc (James P. Wilmot Cancer Institute, University of Rochester) discussed the process for planning the S1826 study: a phase III randomized trial of nivolumab or brentuximab vedotin plus AVD in patients (age ≥12 years) with newly diagnosed advanced stage classical HL. Importantly, the planning process for this study included particular consideration of the AYA population and utilizes measures that may capture issues specific to this population. In AYAs in particular, there is still room for improvement in outcomes for advanced-stage HL. Cure rate can be improved in high-risk patients, and toxicity can be improved for low-risk patients, particularly in light of the long-term follow-up of the previous NCTN trial S0816, demonstrating late relapses and limitations of a response-adapted treatment approach (29). In North American clinical practice, there is a marked difference between the pediatric and adult approaches. The pediatric backbone chemotherapy regimen has been ABVE-PC, and the adult regimen has been ABVD (30,31). Because disease biology does not conform to an 18-year-old cut off, which of these approaches is most appropriate for AYAs is unclear. Treatment approach is not standard and is often driven by the experience of the physician. Dr. Friedberg noted that because the cure rate in these patients is so high, community physicians may be reluctant to refer them to a center for clinical trials. When assessing outcomes in AYAs with HL in the US cooperative group protocols (E2496 and COG AHOD0031), the failure-free survival probability is lower for AYAs than adults or pediatrics (32). Thus, when planning for the S1826 study, an inclusive intergroup process was used. Participants from COG, SWOG, ECOG-ACRIN, ALLIANCE, and CCTG are included, and over 900 patients will be enrolled. This number provides sufficient power to detect an improvement in 2-year PFS from 82% to 88% comparing nivolumab-AVD (33) to brentuximab-AVD (34). In addition to PFS, EFS, OS, and CR, planned analyses include PD-1 expression, correlative imaging studies, quality of life (QoL), and patient-reported outcomes, as well as economic analyses. In addition to including AYAs in the studies, many of these planned analyses are of particular importance in this group.

Kara Kelly, MD (Roswell Park Comprehensive Cancer Center) continued the discussion of AYAs and clinical trial design by presenting the COG/ALLIANCE AHOD 1931: early-stage AYA HL study that is currently in development. Currently, there is a lack of consensus surrounding the best treatment for early-stage HL (35). The most efficacious and least toxic chemotherapy backbone, the optimal augmented treatment, and the best approach for reducing RT exposure in patients with bulky disease remain unclear. The incorporation of targeted agents represents an opportunity for toxicity reduction and treatment augmentation. The primary aim of the 1931 study is to maintain the 3-year EFS in AYAs with newly diagnosed early-stage cHL with adverse features who achieve a rapid early response (RER) after 2 cycles of brentuximab vedotin with and without doxorubicin, vinblastine, and dacarbazine (Bv-AVD) and to determine if this rate is non-inferior to the historical rate of 91% (36). Key secondary endpoints include safety and tolerability of adding nivolumab to augment therapy in slow early responders (SERs), estimation of the extent of financial hardship of treatment and its association with HRQL, and measurement of involved-site radiation use. Though the opportunities to better define the process of optimal treatment in AYAs and the nature of the secondary outcomes are present, the path for AYA clinical study development is undefined. The lack of standard of care in this population complicates the control arm. Further, collaboration for study development and review processes requires alignment of strategy between different investigators, which is challenging. In addition, the study population represents a rare subset of HL patients, which is challenging for recruitment. Currently, the protocol has been approved with stipulations by the COG steering committee.

Ann LaCasce, MD (Harvard Medical School, Dana-Farber Cancer Institute) presented the development pathway for a randomized phase III trial protocol of a PD-1 inhibitor in combination with chemoimmunotherapy for the treatment of newly diagnosed PMBCL. PMBCL is a high-priority disease for AYA lymphoma research because while overall PFS is 85%, real-world outcomes in patients under 21 may be inferior (37,38). In addition, there is a need to limit late toxicity of chest radiotherapy (RT), particularly in young women. Finally, PMBCL is a rare disease with no existing randomized studies. Together, these features make PMBCL an optimal disease for a pediatric and adult cooperative trial. Patients are treated with one of three rituxan + chemotherapy regimens (Rchemo):

RCHOP + planned RT; RCHOP; or DA-REPOCH. These patients are then randomized into PD-1 inibitor + Rchemo or Rchemo. In order to enhance accrual, investigators are allowed to pick the chemotherapy backbone. Challenges include PET scan interpretation (volumetric, metabolic volume, and glycolysis as measures of response) which can be difficult to standardize and placing the use of RT within the study design. Importantly, included within the study is an exploration of correlatives for biomarker development. These include 9p24.1 alterations, ctDNA, T-cell subsets, and imaging. Discussions are currently underway with potential pharmaceutical sponsors.

Panel discussion

Following the presentation, the floor was opened for comments. The following points were raised by audience members for consideration.

- One challenge in designing a trial with AYA-specific aims is that the limits of AYA classification are unclear. If the underlying biology in a proportion of patients is driving poorer outcomes, it is important to understand those factors.
  - It is unclear if it is ever appropriate to study patients in their late 30s in a unique way unless there is an underlying difference in tumor biology.
- The broader we can be, the better. In the advanced stage, patients 12 years and up should be studied, and response-adapted approaches may be incorporated into protocols.
  - AYA-specific measures, rather than specific endpoints, should be part of analysis.
  - Within trials, enhancing QoL measures and designing specific AYA measures for quantitating response to treatment and adaptive dosing require different levels of organization.
- One audience member was hopeful that these trials will be able to provide samples for the creation of a central tissue bank soon. Some of the biomarkers may eventually be validated for treatment selection.
- One audience member noted that the National Cancer Institute (NCI) wants correlative studies, but the application for funding is separate, which is a barrier. It is hard to explore when there is no funding for the analysis.
- In rare disease, the number of centers with varied experience that must be involved can make sampling difficult.
- It is exciting to have pediatricians and adult physicians executing trials together. As more studies are approved, is there a way to standardize how the studies are carried out so that in the future it does not take as long to initiate the trials?
- There is a prostate cancer trial in the United Kingdom that is adaptive and never closes (STAMPEDE). In the adaptive trial design, a new experimental arm can be adopted as an amendment. This stops the trial from closing completely and reopening repeatedly. In the case of lymphoma, we do not learn anything in 3-year chunks. Can we use STAMPEDE as a model?
  - It is important that in planning these trials, we do not fragment the population further. Different groups, even within the same institutions, and treating patients differently can result in lost cohesiveness.
- When considering AEs, it is important to note that deeper toxicities occur in patients with more robust immune systems.
- Drop-out rates in the 18- to 20-year-old subset suggest that biology and treatment aside, support services really matter.
  - A 19-year-old treated at a pediatric center vs an adult center will have different experiences.
  - In pediatrics, we just say what MUST happen. In adult centers, we are less paternalistic and allow patients to participate in decision making, which for good or bad, leads to variability.
- With triplet therapy in particular, cost is an issue. When dealing with a curative disease, cost is less of an issue. Though some treatments may be less expensive at face value, hospitalizations and long-term effects must be considered.
  - In the United States, it is an approved regimen, so it should be paid for. Higher-risk patients had more benefit.
  - What if patients are randomized to an arm where there is an imbalance of AYAs between 2 arms?

The future of AYA oncology drug development—Nita Seibel, MD, National Cancer Institute/CTEP (Moderator)

Dr. Seibel opened the session by introducing each speaker and then asking them to speak about their research and areas of interest in AYA populations and to share what they feel the greatest challenges and opportunities are in the area of AYA oncology drug development. Following introductions, several questions were posed to the panel,

and members shared their perspectives. In this section, audience comments are integrated with the discussion topics.

Panel members:

- Ken Carson, MD, PhD (Flatiron Health);
- Andy Evens, DO, MSc (Robert Wood Johnson Medical School, Rutgers Cancer Institute of New Jersey);
- John P. Perentesis, MD, FAAP (Cincinnati Children's);
- Nicholas Richardson, DO, MPH (Food and Drug Administration);
- Nita L. Seibel, MD (National Cancer Institute/CTEP, Moderator);
- Nancy Whiting, PharmD, BCOP (Seattle Genetics).

Panelists noted several obstacles in drug development in AYA oncology. From the perspective of the pharmaceutical companies, there is a fear associated with running phase I studies. Development of AYA-specific therapies will require a shift in mindset. One requirement for building understanding of disease in AYAs is strong preclinical models, including cell-line and animal model development. Preclinical models will be central to better understanding AYA subtypes. Development is also complicated by the rarity and heterogeneity of disease, which makes it difficult to capture samples and understand the biological underpinnings of differential response. In order to understand the impact of therapies, there must be harmonization and collaboration between study organizers so that outcomes may be assessed in aggregate. This is an opportunity for the use of large datasets to better understand outcomes. Often, AYAs who see oncologists outside of major adult and pediatric centers do not receive the latest standard-of-care therapies, making it difficult to improve outcomes in those patients. Overall, there is a need for a unified, 4-part approach to AYA drug development: clinical research infrastructure (e.g., NCI and pharmaceutical companies), regulatory bodies (e.g., Food and Drug Administration [FDA]), academic and community practitioners, and patient engagement.

Though data that is currently being collected could be evaluated to identify age-related differences, data exist across multiple trials and in different formats and are not being analyzed in a systematic fashion. More rational clinical trial designs based on AYA characteristics are needed. One panelist noted that flagging electronic health records or identifying a central institutional review board to expedite enrollment in trials may help to improve enrollment. In addition, efforts are needed to engage community physicians. In contrast to pediatrics, young adults are often cared for in the community. A public outreach initiative highlighting that AYAs are an important population could educate communities about clinical trials and create a relationship.

Panelists discussed whether comparative analysis or historical controls can be used in AYA studies. Is it possible to move away from randomization, knowing that there is a large dataset of patients previously exposed to R-CHOP? Panelists also advocated for adolescent patients younger than 18 to be considered in the trial development phase.

In order to enroll and follow AYAs, it is critical that sponsors identify activities that require a visit and those that can be done online. Millennials and Generation Zs who comprise the AYA population have different expectations of how to interact with the healthcare system. It is critical that the clinical trial enterprise meet AYAs in the middle when it comes to efficiently utilizing technology. It is important to invest in direct patient-reported outcomes and to do it digitally. It is faster, better, less expensive, and can be done reliably. Clinical testing, including patient recruitment and monitoring and data collection, must be modernized. This is an opportunity for technology and connectedness with patients, as well as with smaller centers that do not typically participate in AYA trials. Beyond participation in trials themselves, utilization of technology to communicate what clinical trials are and how they work to AYAs may help to improve the public's perception of clinical studies.

Though the current research supports the idea that AYA toxicities are different from adult or pediatric toxicities, there is no way to predict the nature or severity of toxicities. A primary challenge is that more patients are needed in clinical trials to build a digital dataset of symptoms and toxicities. Even as our understanding of AYA toxicities is emerging, oncology in general is beginning to regard toxicities in a more personalized way. Some toxicities may be increased for AYAs, but not in all cases. With better data, risk factors for specific side effects may be identified and the risks mitigated. One example is an analysis of ~1,000 patients, mostly AYA, on the last large COG HL study. In that study, patients consented to DNA analysis aimed at understanding how they metabolized drugs. The study revealed variant slow drug metabolism genes that potentially predicted for severe lung damage from the drug bleomycin. While these variant slow metabolism genes do not result in phenotypes normally, in the context of HL therapy, they were associated with pulmonary complications. Because there are viable treatment pathways in HL that do not use

bleomycin, these types of data may be used to personalize treatment. Toxicity data from big data on existing trials may help to obtain a clearer picture of AYA risk, but cooperative efforts and diligent harmonized planning ahead of trials will likely allow for big-data analysis that will be most fruitful. Finally, ASCO's guidelines as coordinated with the FDA have advocated for patients with HIV be included in studies. When FDA sees exclusion of HIV in lymphoma studies, they encourage the sponsor to include HIV patients on HART therapy and stable viral load to ensure that risks are also captured for these patients, especially those with HIV-associated malignancies (39). HIV physicians are careful with drug-drug interactions, and these specialists should be included in studies.

Long-term toxicity is especially important for AYAs, but it becomes more challenging as regimens become more complex. One element that is important for community oncologists is guidance on fertility preservation. Beyond guidance for long-term care, telemedicine can be used as a more formalized approach for community oncologists to have contact with expert knowledge at AYA centers of excellence. The initiative could be particularly beneficial in rural health clinics where outcomes are not as good. AYA centers of excellence could be a central part of disseminating knowledge to the broader community where so many AYAs are treated, and LRF could help in identifying these centers and facilitating communication with community physicians. Big data may also facilitate the development of models for projecting late effects that could eventually be used to guide decision making. In addition, survivorship studies should be carefully designed. Particularly for survivors, the long-term effects of commonly and uncommonly used agents are unclear.

While the separate pursuit of therapies for adult and pediatric treatments may once have been a hindrance to improvements for AYA a few years ago, there have been major initiatives at the FDA and NCI to change the landscape of access to new drugs for AYAs, at least through clinical trials. The NCI has refined and broadened its national clinical trial efforts through its National Clinical Trials Network (NCTN). With the formation of the NCTN an AYA working group across the adult and pediatric cooperative groups has been initiated to target and coordinate development of AYA-focused clinical trials in a "best of both worlds" approach. To help facilitate awareness of the AYA trials within the NCTN, study champions from each of the groups are identified to help publicize the trial to their individual group. NCI Is working to increase visibility of AYA oncology trials by creating an NCTN AYA portfolio of trials with the same attention paid to cancers like lung, breast, brain, and gastrointestinal malignancies. In addition, NCTN has been championing tissue agnostic trials like MATCH. NCI central IRBs also enable NCTN sites to provide approval for AYA trials regardless of whether the institution primarily treats adults or children/adolescents.

Importantly, the FDA has 3 large, novel approaches that advance AYA oncology. Beyond the 2017 FDA reauthorization act that mandates pediatric studies in novel targeted agents relevant to a pediatric cancer, they have issued an important draft guidance that recommends to pharmaceutical companies to lower the age of eligibility to 12 years in clinical trials for new anticancer drugs. They also provided strong guidance by including considerations for dosing and pharmacokinetic evaluations, safety monitoring, and ethical considerations. Second, the FDA is now approving, and licensing, drugs based on strong signals in small groups as well as approving treatments in a histology-blind fashion and across diseases, a significant advantage in AYA cancers in which molecular targets are rare and often would not be sufficient for a clinical trial. Third, the FDA is approving drugs based on strong efficacy signals even in small studies (40). The end result of these efforts is that new drugs are being prescribed much faster to the right patients, both in clinical trials and ultimately with approval.

Pediatric and adult clinical care, service delivery, disparities—Julie Wolfson, MD, MSHS, University of Alabama at Birmingham School of Medicine (Moderator)

To open the discussion, Julie Wolfson, MD, MSHS (University of Alabama at Birmingham School of Medicine) presented data on the impact of treatment site in AYA cancer patients. The NCI definition of an AYA cancer patient is a patient diagnosed with cancer between 15 and 39 years of age. When compared to children and adults, AYAs have not seen the same improvement in survival. This survival gap prompted the NCI to deem AYAs a vulnerable population. There are multiple compounding factors that contribute to the gap, including survivorship care, access to health care, socioeconomic factors, and care setting, among others. Due to the lack of widespread quality care measures for AYAs, it has been difficult to identify the most impactful factors. However, treatment site and access to care encompass many of these issues. Indeed, for lymphoma, survival probability is affected by treatment setting nearly as much as age (15 to

39 years) (P<0.0001; P=0.004, respectively) (41). This pattern is repeated in other cancers, including central nervous system cancers and acute leukemias (41,42). With increasing age, AYAs are less likely to receive care at a cancer center (43), and insurance status as well as race/ethnicity are also drivers of care setting. These disparities are critically important, as care at a cancer center for AYAs results in elimination of the significant gap in survival between HL patients ages 1–29 *vs.* 30–39 years (P<0.001) observed at non Comprehensive Cancer Center (CCC)/COG patients (43). In addition, access to clinical trials is a central tenet of improving survival. There is a strong correlation between annual percentage change in survival and enrollment in trials (correlation: r=0.93, P=0.006) (44) and only a small minority of AYAs are enrolled in clinical trials (<5% of AYA *vs.* >60% of children) (45).

Helen Parsons, PhD, MPH (University of Minnesota) presented research on resource utilization for AYAs treated in pediatric vs adult cancer institutions. Referral of AYAs to pediatric facilities decreases greatly with age, in particular for patients with less traditionally "pediatric" cancers and increasing distance to pediatric oncology centers. Across all ages, the percentage of patients who are treated at NCI or other designated cancer centers do not change (between 63% and 69%). However, older AYAs are less likely to be treated in a hospital with a residency program (46). Patients with HL and NHL are less likely than patients with acute lymphocytic leukemia (ALL) to be treated in the pediatric care setting. While differences in treatment regimens have been shown to improve survival, little is known about resource utilization in each treatment setting. In the presented study, intensity and duration of care, as well as costs and type of care, were analyzed for AYAs diagnosed between ages 15 and 17 years in Ontario, Canada between 1995 and 2010. Overall, 60.5% of patients were treated in a pediatric institution and 39.5% were treated in an adult institution. Hospitalizations were evaluated in the pretreatment, initial, continuing, and terminal care stages. In the initial stages of care, the median number of hospitalizations was significantly different between the pediatric setting (n=4), and in the adult setting (n=0) (47). The average number of emergency room visits was higher for pediatric center patients in the initial phase, but higher for adult center patients in the continuing care phase. These differences are, in part, responsible for the higher cost of care for younger AYAs treated in pediatric vs adult institutions. Additional population-level data representative of international health systems are needed for multivariate analysis to better understand the nature of resource utilization by AYAs in these settings. The outcomes of this work will be important for developing evidence-based interventions to improve outcomes.

Theresa Keegan, PhD, MS (UC Davis Comprehensive Cancer Center) then presented work aimed at better understanding barriers to clinical trial participation among AYAs with lymphoma. Poorer outcomes in AYA lymphoma patient are thought to be related to low participation in clinical trials, poorer access to care, receipt of treatment in facilities without AYA experience, and patient tumor biology. In AYAs diagnosed in 2006, population-based data from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) program show a low overall clinical trial enrollment (14%), with lower enrollment among the uninsured and those treated by non-pediatric oncologists (48). Reasons for low enrollment are not well understood, but include system level factors, provider factors (e.g., knowledge of trials), and patient factors (49). Data from the SEER program revealed several patterns. First, AYA enrollment in studies is highest in leukemia and sarcoma (as high as ~35%) and lower in lymphomas (~10%) (49,50). Even in specialty children's hospitals, enrollment decreases with age. Importantly, most studies have not found increases in clinical trial enrollment over time. With the exception of acute lymphoblastic leukemia, steady declines in treatment trial accruals for AYAs have been reported (44). Proportional enrollment of AYAs on COG trials decreased from 34% (2004 to 2008) to 31% (2009 to 2013) (P<0.001) (38). Clinical trial enrollment is higher in the pediatric setting, with one study showing that 42% of AYAs in the pediatric hospital setting are enrolled in clinical trials vs 11% of AYAs in the adult NCI-designated cancer setting (51). Further, 15% of AYAs on clinical trials are in a pediatric hospital setting compared with lower enrollments of 3% in the affiliated adult NCI-designated cancer centers and 5% in the affiliated adult public hospitals (52). Together, these patterns indicate that there are barriers to enrollment, particularly in the adult setting. In addition, health insurance status and race/ethnicity impact the likelihood of enrollment in a clinical trial (48,50,53). Given that many AYAs receive care in the adult setting, provider awareness of trials and the burden of referral and enrollment in studies becomes a factor. A systematic review of AYA patients identified barriers that may be somewhat unique to the AYA population (54). The most frequently cited barriers included prolonged hospitalizations required by the clinical trial and being

uncomfortable with experimentation. In addition, the time commitment and lack of peer support were cited. Finally, feeling coerced by physicians was cited as a deterrent in 50% of studies (54). Together, these findings can guide the creation of communication tools to raise awareness among both physicians and patients. With limited data available on the perceptions that influence accrual among AYA cancer patients, especially in those treated at adult centers, future studies in larger adult cohorts should be carried out to identify the factors that influence participation, assess the impact of AYA-specific care, and identify solutions for overcoming identified barriers.

Justine Kahn, MD, MS (Herbert Irving Comprehensive Cancer Center) presented ongoing work examining the impact of age on survival in patients <1–21 years (median age: 14 years), treated for Hodgkin lymphoma (HL) on contemporary phase III Children's Oncology Group (COG) trials between 2002 and 2012 (55). Recent guidelines from the American Society of Clinical Oncology call for including children ≥12 years on late phase trials spanning children and adults, thus the study examined whether age 12 years, and/or age 15 years [the lower limit of "AYA" as defined by the National Cancer Institute (NCI)] would be associated with outcomes.

Across the full cohort of 1,733 patients pooled EFS at five years was 82%. When examining EFS between older and younger age groups, it was observed that older patients (i.e. teenagers and adolescents) had significantly higher rates of relapse and worse EFS. Five-year cumulative incidence of relapse in patients ≥12 years was 18% *vs.* 11% in patients <12 years (P=0.008). Similarly, relapse incidence was significantly higher when using an age cutoff of 15 years. Patients aged ≥15 years had a 19% cumulative incidence of relapse *vs.* 13% in the younger patients. EFS differed using both age cutoffs as well. The 5-year EFS for patients ≥12 years was 80% *vs.* 88% in younger patients (P=0.015) and was 80% *vs.* 85% using an age threshold of 15 years (P=0.02). Cox regression models examined the influence of age on EFS and OS, adjusting for race/ethnicity, sex, insurance, histology, Ann Arbor stage, B symptoms, bulk disease, study, and receipt of RT. Multivariable modeling demonstrated that adolescent age remained an independent risk factor for EFS using a threshold of both 12 and 15 years, and that age ≥15 years remained an independent risk factor for OS.

Dr. Kahn suggests that while it is well-established that AYAs have worse outcomes compared to younger aged patients with HL, a clear age threshold that predicts inferior survival has not yet been defined (56). Specifically, although the NCI defines the lower limit of "AYA" as 15 years of age, perhaps the lower threshold that defines an at-risk HL age group is even younger. Next steps for Dr. Kahn and her colleagues are to determine the optimal age thresholds that define "AYA" for patients with HL in order to inform biology studies and identify a clearly defined group in need of novel treatment approaches.

Thomas Gross, MD, PhD (Center for Global Health, National Cancer Institute) presented treatment strategies for AYA patients with aggressive NHL. Because of the rarity of the patient population, international collaborations are particularly important. Further, to conduct successful research, it is critical to consider the differences in pediatric and adult cancer care "cultures." These differences primarily lie in the approach that serves as default when patients have aggressive disease. Importantly, the treatment goals in the AYA population are somewhat different, and the values are distinct from pediatric and adult values. Patients most often opt for outpatient treatment, and there are concerns about preserving fertility.

In an international trial for pediatric mature B-NHL (Burkitt and DLBCL; INT-BNHL-2010/ANHL1131), investigators sought to determine the 3-year EFS of chemotherapy vs chemotherapy plus rituximab. This study required an international collaboration of 9 pediatric cooperative groups from 12 countries and 350 sites. The first interim analysis of 350 patients with a median follow-up of 11.5 months showed a treatment benefit. Randomization was halted, and patients who were randomized not to receive rituximab and were still on treatment were crossed over. After a median follow-up of 39.9 months, EFS with rituximab was 93.9% [95% confidence interval (CI), 89.1 to 96.7] and without rituximab was 82.3% (95% CI, 75.7 to 87.5). The hazard ratio for EFS was 0.32 and for OS was 0.36, favoring the addition of rituximab. For patients that received rituximab, failures due to toxicity match the toxicities due to failure of disease control (57). While this study represents a significant level of collaboration, Dr. Gross noted several recent challenges that have emerged for the planning and execution of international trials, mainly challenges in meeting new regulations in timely data sharing and patient privacy protection associated with substantial penalties for noncompliance.

Panel discussion

Following the presentation, the floor was opened for comments. The following points were raised by audience

members for consideration.

- LRF does well with communication and outreach. One challenge is that physicians who are taking care of AYAs do not know that they are a special group.
  - It is important to reach out to providers.
  - The best advocates are in attendance at the meeting. We all know that outcomes are "good," but how do we spread the news that it is not "good enough?"
- Partnering with community physicians can be a powerful way to ensure AYAs are getting the care they need. As more programs and centers arise across the county, physicians with AYA lymphoma patients need to have at least a one-time consult.
  - The process of consultation could evolve from "I call someone" to a more automatic and formal process.
- The concerns surrounding coercion were somewhat surprising. Do shared decision-making tools exist for the AYA patient population?
  - A representative from LRF commented that materials are in the process of being created and that they will eventually be disseminated.
  - Materials about the importance of clinical trials, even if they just address what clinical trials are and how they work, would be helpful.
  - As we think about resources, we should think about where patients are in terms of their diagnosis and care when they are provided with information.
- Differences in care models are important, but especially in aggressive lymphomas, there is the important question of biology. We have to integrate biology when we think about resources and care settings. B-cell lymphoma is not the same disease in a 20-year-old as it is in a 50-year-old. If we are going to move the goal post, we have to understand the biology.
  - We will never get there unless we enroll AYAs in studies.
  - There is an extraordinary knowledge gap. If we want to move things, we need to find some way to guide clinical decisions in the community.
- Physicians use the National Comprehensive Cancer Network (NCCN) guidelines. The current guidelines do not emphasize the unique position of AYA therapies. Physicians and scientists who have a specific interest and knowledge are underrepresented on guideline committees.
- One audience member pointed out that they do not want someone to start treating AYA lymphoma like adult FL. There are real issues, and there are cases where the risk of doing the wrong thing is high, especially if the disease is something that you have never seen before.
- It is important to remember that as patients are "graduating" from pediatric care, they are also moving into adult life. We need to have a document for survivorship care plans that patients can have with them so they know what to do. LRF could help generate the materials.
  - Patient "hand-off" between pediatric and adult care is a big issue and is a question of care across the cancer continuum.
- 90% of survivors are cared for in the community by primary care providers with poor understanding of follow-up care for those patients.
  - Switches in insurance are another challenge for AYAs. Providing resources about how to shop for insurance plans and the implications of what is covered and knowing what they are willing to spend could be helpful.
- In some datasets, it is difficult to interpret enrollment. There is no way to know how many trials were available and open at sites. With NCTN, we have an opportunity to better understand patterns of accrual. If centers could track the patients, the trials available, and if enrollment was offered, we could learn more. Some trials are available at adult centers but not activated at the site. There is a knowledge gap surrounding physician and patient barriers.
  - Looking at the COG pooled analysis, when we ask if it is biology or access, the answer is "yes, both," because we see that PFS changes at one age cut-off and EFS at another, though both then go on to have a poorer OS.
  - When thinking about biomarkers, it is important to remember that for age, we have a far lower standard than for gene expression profiling. If we treat age the same way as a biomarker, it would be good for the field.
- Not only do we have changing and variable disease biology in AYAs, the way in which AYAs utilize resources and participate in trials varies over time and between individuals. A 16-year-old and a 25-year-old can have the same biological disease. A 23-year-old can have 2 kids and a job, while a 30-year-old is still

struggling with keeping insurance straight. Age is not the same for every individual; it is more about what is going on in their life. We have to think about how much life changes, even between 15 and 25 years.

- One audience member brought up the parallels with geriatric oncology. There are many instruments to use in geriatrics, and in practice, these may not be used, and the centers do things differently. An AYA assessment tool that can be used in any care setting could be helpful for physicians who are not going to take the time to implement every tool.

Patient outcomes, late effects, and survivorship—Melissa Hudson, MD, St. Jude Children's Research Hospital (Moderator)

Melissa Hudson, MD (St. Jude Children's Research Hospital) opened the session by presenting on the evolving spectrum of late effects in HL and NHL. In both HL and NHL, cumulative mortality has decreased with evolving treatments (58). In addition, these same changes in treatment are thought to have precipitated a decrease in the cumulative incidence of neoplasms, though the numbers reported in the literature are likely underestimates, and it should be noted that some patients will have multiple neoplasms (59). There is a strong relationship between chest radiation and development of breast cancer; 15% of HL patients who receive chest radiation will develop breast cancer by age 40 years compared to 8% of patients with other childhood cancers. The rate of breast cancer in HL by age 50 years (35%) is comparable to the rates of cancer in *BRCA1* carriers (31%) (60). Risk categories for cardiotoxic treatments (e.g., anthracycline) have been defined, and heart failure is the primary driver of cumulative cardiac incidence (61). In addition, risk categories for gonadotoxic treatments have been defined for women treated with alkylators and radiation, and risk categories have also been defined for men (62,63). Finally, financial toxicity and adverse effects on emotional health, including somatization, anxiety, depression, and suicidal ideation, have been shown to further affect survivors (64). Together, these data highlight a need for effective interventions that aim to prevent adverse effects and preserve health across survivors as well as for additional research aimed at understanding risk factors and the most effective way to deliver optimal survivor care.

David Hodgson, MD, MPH [Cancer Clinical Research Unit (CCRU), Princess Margaret Cancer Centre] presented AYA survivorship research informed by outcomes of survivors diagnosed with cancer at >21 years old. Most AYA survivors are young adults who are seen in adult facilities. The relative risks of second malignancies, such as breast and thyroid cancer, can translate into high absolute risk over time. There is evidence that patient host-factors can substantially modify the risk of developing late effects. For example, the duration of intact ovarian function after lymphoma treatment influences breast cancer risk among lymphoma survivors (65) and in breast cancer survivors hypertension can have an impact on cytotoxicity of certain agents over time (66). Fertility management for patients also becomes more complex. For example, in breast cancer patients treated with alkylating agents, AMH levels indicate an ovarian reserve similar to controls who are 20 years older (67), and normal menstrual cycles are not a reliable indicator of preserved fertility. Data showing that the doses of alkylators considered "safe" in pediatric oncology can be seriously gonadotoxic, with older age highlighting the differences between pediatric and AYA populations. In addition to fertility issues, fatigue in the young adult population is well characterized as a substantial issue. Many young adult patients start treatment with fatigue, which increases on treatment and never returns to normal (68). Overall, late effects specific to young adult survivors are understudied. Further compounding the issue are the variations in the definition of AYA in terms of age and disease biology. This variability will affect the biology of late effects, the appropriate interventions, and the appropriate clinical models of care to ameliorate those effects.

Continuing the discussion of late effects, Gita Thanarajasingam, MD (Mayo Clinic Rochester) discussed how to best improve toxicity assessment in lymphoma survivors using patient-reported outcomes and cohort studies. Current reporting and analysis of adverse events (AEs) in clinical trials are inadequate for understanding late effects in the AYA population. In particular, current methods fail to capture adequate information on tolerability and chronic low grade effects (69). Though improvements in AE analysis, such as longitudinal analysis of toxicity over time (ToxT) (70), have been developed and implemented in clinical trials, there is a need for a framework to improve the capture of AEs in a way that can benefit real world patients. An international commission on improving AE assessment in hematology produced a call to action paper that included multiple recommendations, two of which,

Dr. Thanarajasingam noted, are of particular interest for AYA patients (70). First, the recommendations cited a need for better assessment of patient-reported outcomes and called for electronic real-time capture of events though the development of programs for wearables, smartphones, or other technology (71). Second, recommendations called for improved infrastructure for collecting long-term data on adult survivors, such as the efforts of the Lymphoma Epidemiology and Outcomes (LEO) cohort (6). These initiatives will harness patient-reported outcomes data to allow for better identification of toxicity and late effects. The data can then be used to provide better education for AYA survivors and guidance for the management of late effects.

Tara Henderson, MD, MPH (Childhood and AYA Cancer Survivor Center, The University of Chicago) presented on risk-based healthcare and interventions for AYA cancer survivors. Recently updated guidelines from the Children's Oncology Group (COG) recommended an annual mammogram and breast MRI starting at the age of 25 or 8 years after exposure to any chest RT (previous guidelines specified >20 Gy) (72). Beyond screening, one study of 274 childhood cancer survivors with breast cancer compared to 1,095 women with *de novo* breast cancer revealed that childhood cancer survivors were 5 times more likely to die of other health-related causes, including pulmonary and cardiovascular disease (73). Of note, 85.4% of AYA survivors received healthcare in the community with primary care. Only 46% of high-risk survivors were compliant with mammography guidelines, 27% were compliant with skin exam guidelines, and 12% were compliant with colonoscopy screening guidelines (74). These patterns highlight the need to make sure that primary care physicians are aware of the long-term follow-up guidelines that are available for AYA cancer survivors. Indeed, a case vignette presented to community physicians revealed that 5% of general internists, 2% of family physicians, and 33% of pediatric oncologists would appropriately screen the presented case-study of a female Hodgkin lymphoma patient for breast cancer, left ventricular dysfunction and thyroid disease in a manner concordant with COG guidelines (75). In order to improve adherence to guidelines, improvements are required in three domains. Survivor-related factors (e.g., core health beliefs such as health motivation), health system-related effects, and provider-related factors must each be addressed in order to successfully implement risk-based healthcare in AYA survivors. For providers, treatment summary/care plans, ongoing contact with cancer centers, and educational initiatives are valuable modes of improving awareness of and adherence to guidelines. For AYA patients, eHealth tools, online support, and AYA centers of excellence will be central to improving survivor-related factors. In addition, identification of stakeholders and advocacy within healthcare systems will be critical for widespread adherence to guidelines (75).

Panel discussion

Following the presentation, the floor was opened for comments. The following points were raised by audience members for consideration.

- The lack of guideline uptake is certainly not based in lack of evidence. It is important that we identify the true barriers for physicians.
- While improving reach and engagement, it will be important to collect data so that patient-reported outcomes can also be assessed.
- When thinking about collecting ongoing data, it is important to consider the impact on the patient of having constant reminders of illness.
    - There is cost and worry associated with ongoing imaging and monitoring. One audience member indicated that they were not sure that it was a good thing to remind the patient every year that they had cancer.
- Physicians know that they are overscreening, and they should discuss key risks with patients. In the end, it may be most important to focus on a healthy lifestyle.
- When refining guidelines, it is important to do so in the context of research.
- Breast cancer data are strong, and an audience member indicated that it would be malpractice not to do it.
- Screening for cardiac disease is important. You do ultimately need to look at the heart.
- Modifying blood pressure may be better than monitoring with echocardiographs. What are the influences of modifying blood pressure and how does that change risk?
- Because of the efficacy of treatments, we now have a chronic disease paradigm. It is important that patients understand this and know the therapy they received and to alert their doctor.
- The data presented show that one-third of survivors who received RT will get breast cancer. We need more absolute numbers to stratify risk based on area of treatment, dosing, and age of treatment.

- We could inform individual risk and understand if the absolute risk is 2% *vs.* 30%.

- Fatigue in HL is interesting, because even 3 to 4 years after treatment, markers of fatigue persist. Do we think it is treatment or is it etiological and it was always there?
  - One audience member indicated that they think biology, and possibly interleukin effects, affect long-term fatigue.
- When thinking about communication between patients and physicians for ongoing monitoring, liability will emerge as a concern. For example, when a physician takes a phone call in the middle of the night and talks to a patient, that physician is as liable for their outcomes as the treating physician.
  - Weekly reports of patient fatigue, among other measures, may quickly overwhelm an office. We have to set thresholds that determine when we are alerted, otherwise it will be too resource intensive.
  - So far, we have been able to provide a disclaimer that data will only be evaluated at the monthly visit.
  - For many of the younger fellows, *everything* is in real time. The pace and mode of communication for them is different.
- One audience member indicated that they keep thinking about measures such as being able to go back to work. Is there a way that industry can describe outcomes in a way that will be more useful to AYAs?
  - Low-grade diarrhea is intolerable.
  - Late-grade toxicity is also very important and is not usually captured.
- Regulators may respond better to stronger plans for long-term AE monitoring ahead of protocol submission, especially in AYAs.
- In partnering with the FDA, we want to see if we can use tools to build a platform that is useable across settings (between pediatric and adult oncology and across international sites).
  - Industry and stakeholders must collaborate to get some consensus around which measures are most important.
  - Neuroblastoma patients can serve as an example for effective engagement and programs that build understanding long-term effects of therapy. It would be helpful if the lymphoma community can engage and understand the late effects of immune checkpoint inhibitor in the same way.
- Regardless of the agent used, the issue is that when the study ends, there must be something in place to follow the patients in a less expensive way. Currently, re-recruitment is the only way to follow patients. With collaboration, the process can be more streamlined.

Creating a national AYA lymphoma research blueprint

Following presentations and panel discussion, attendees were invited to participate in one of four working groups in which participants discussed lymphoma research priorities. Each working group then presented their outcomes. The top priorities identified by each group are summarized below, and a table with the suggested blueprint concludes the section.

Lymphoma, biology, immunobiology, and epidemiology

Moderators: *Catherine Bollard*, *MD*, *MBCHB (George Washington University*, *Children's National Health Center)*; *Lindsay Morton*, *PhD (National Cancer Institute)*; *Christian Steidl*, *MD (British Columbia Cancer)*.

The Lymphoma, Biology, Immunobiology, and Epidemiology working group identified several key gaps and research priorities. The lack of integrative datasets, including clinical data, biospecimens, epidemiology, and pathology, is an obstacle for understanding differences in etiology and biology between AYA vs pediatric and adult disease. In addition, study designs and data collection are most often informed by general lymphoma variables, and AYA considerations are secondary at best. The above diligence in terms of data collection will help identify optimal therapeutic approaches, and in particular, the effects of novel agents (e.g., immune and cell therapies), dosing, and predictors of response (including pharmacogenomics), and relationship of age to long-term toxicities. One clinical obstacle is that biomarkers are not always transferable to the AYA population. Further, there are no known AYA-specific biomarkers. Thus, prognostic and predictive systems in AYA are lacking. In addition, the importance of the tumor microenvironment in AYA pathogenesis (i.e., in HL, PMBCL, ALCL) needs to be reflected in biology and immunology studies. Compounding the impact of gaps in survival and clinical outcomes faced by AYA patients is the profound knowledge deficit with respect to functional outcomes for pediatric and AYA patients with lymphomas, particularly the long-term consequences of treatment.

Importantly, in order to build better understanding of AYA lymphomas, it is critical that the impact of selection bias and treatment heterogeneity is recognized and that the real-world population is markedly different from clinical trial populations.

Clinical trials and drug development

Moderators: *Kieron Dunleavy*, *MD (George Washington University)*; *Kara Kelly*, *MD*, *(Roswell Park Comprehensive Cancer Center*, *University at Buffalo Jacobs School of Medicine)*; *Ann LaCasce*, *MD (Harvard Medical School*, *Dana-Farber Cancer Institute)*.

The Clinical Trials and Drug Development working group identified several key gaps and research priorities. First, data on both AYA-specific biomarkers and the degree to which adult biomarkers may be applied to AYAs are lacking. When tailoring treatment for AYAs, physicians are faced with a lack of toxicity/response data on novel agents in younger adolescents due to the exclusion of patients <18 years in most phase 1 trials. Further, the relatively small number of AYA patients precludes the ability to perform randomized phase 3 trials. Thus, long-term toxicity data are limited. One challenge in AYA clinical trials is that separate trials initiated for adult and pediatric populations stalls early clinical development. Once treatments are available, pediatric and adult cooperative groups have little experience working together, causing delays in the development of trials. Finally, the limited use of big data prevents acquisition of insights from pooled clinical trial and registry data or combined electronic medical record systems.

Care delivery and patient outcomes

Moderators: *Tom Gross*, *MD*, *PhD (Center for Global Health*, *National Cancer Institute)*; *Thomas M. Habermann*, *MD (Mayo Clinic*, *Rochester)*.

The Care Delivery and Patient Outcomes working group identified several key gaps and research priorities. First, there is a need to create uniform treatment strategies for AYA patients that can be adopted by designated or accredited AYA centers. In order to do this, it is important to identify optimal information dissemination solutions (e.g., NCCN AYA guidelines). In addition to harmonizing care, it is a priority to better understand the AYA patient experience and identify barriers to care and enrollment in clinical trials. It is critical that data generated from AYA participation is fully leveraged and enhanced, and/or novel data collection mechanisms should be implemented. Finally, in order to optimize care, new resources and partnership opportunities to study disparities in care and outcomes survival must be identified.

Survivorship and late effects

Moderator: *Tara Henderson*, *MD*, *MPHD (Childhood and AYA Cancer Survivor Center*, *The University of Chicago)*.

The Survivorship and Late Effects working group identified several unmet needs in the arena of long-term survivorship data. Long-term data are needed on psychosocial outcomes, fertility, comorbidities, and long-term effects of newer therapies. In order to meet this need, a lymphoma research infrastructure to centralize data across institutions is needed. Of particular interest is optimizing transitions in care and generating models for transitions in order to optimize outcomes and minimize risk. The models may include care plans as well as strategies for bridging the gap between specialists and primary care physicians. Resources needed include plans for screening for and treating late effects and subsequent cancers. Finally, there is a need to address socioeconomic and cultural disparities that may underpin higher risk and/or poor management of late effects.

Summary

The inaugural 2019 Adolescent and Young Adult Lymphoma Scientific Workshop covered recent research in multiple areas that have been identified as contributors to the survival gap in AYA lymphoma. Identifying and exploring these contributors allows for advocacy of AYAs as a distinct group of patients and thus paves the way for the development of collaborative efforts that will be required to learn more about AYA lymphoma biology and treatment outcomes. In addition, deliberate inclusion of AYA measures in future clinical trials and sharing of trial data will allow for a clearer picture of disease biology and risk, as well as risks associated with specific treatments and late effects. Continuing efforts are needed to best understand how to capture AYA-specific outcomes and how to leverage technology to learn more about toxicities and impacts of treatment over time. In the future, outcomes of current and new studies may inform treatment selection, drug development, and initiation of programming that serves the specific risks faced by AYA survivors.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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