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Immune checkpoint therapy in pediatric and adolescent lymphomas

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Immune checkpoint therapy in pediatric lymphoma

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Authors contributions

MSC conceptualized the study and supervised the review. *DJH* conceptualized the study, wrote the first version of the manuscript. All authors wrote the manuscript.

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Abstract

Immune checkpoint therapy (ICT) is designed to unleash the anti-tumor activity of T-lymphocytes. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibition and programmed death 1 (PD-1) inhibition are the most commonly utilized ICTs in clinical cancer therapy, and they enhance anti-tumor immunity by interrupting the inhibitory signals CTLA-4 and programmed death ligand 1 (PD-L1) respectively. In pediatric Hodgkin lymphoma, ICT has demonstrated remarkable efficacy in both high-risk and relapsed disease, with investigation into the efficacy in low-risk disease ongoing. Pediatric mature B-cell lymphomas have variable expression of PD-L1 with very limited experience incorporating ICT. Primary mediastinal B-cell lymphoma (PMBCL), anaplastic large cell lymphoma (ALCL), aggressive natural killer-cell lymphoma (ANKL), and peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) all consistently express PD-L1, providing strong biologic rationale for the use of ICT in these diseases. In PMBCL, the Children's Oncology Group (COG) and the National Cancer Institute (NCI) National Clinical Trials Network (NCTN) recently completed a randomized phase III trial of nivolumab in combination with chemo-immunotherapy in children and adults with newly diagnosed PMBCL. Results of this trial are expected in 2027. In ALCL and ANKL, ongoing clinical trials are evaluating the efficacy of ICT. Given the transformational role of ICT for pediatric Hodgkin lymphoma, there is significant promise for the use of ICT in multiple subtypes of pediatric non-Hodgkin lymphoma with increased expression of PD-L1.

Keywords (MeSH):

Lymphoma, non-Hodgkin; lymphoma, Hodgkin; Pediatrics; Immunotherapy; Programmed death 1; Programmed death ligand 1

Introduction

Immune checkpoint therapy (ICT) is designed to unleash the anti-tumor activity of T-lymphocytes which are "the established lynchpins of anti-tumor immunity"[1]. The United States Food and Drug Administration's (FDA) approval of the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor ipilimumab in 2011 and the programmed death 1 (PD-1) inhibitors nivolumab and pembrolizumab in 2014 have ushered in a new era of cancer immunotherapy for numerous different forms of cancer[2]. Mechanistically, CTLA-4 inhibitors increase T-cell expansion by interrupting the inhibitory interaction of CTLA-4 on T-cells with B7 on antigen presenting cells[3]. Alternatively, PD-1 inhibitors prevent T-cell exhaustion by interrupting the inhibitory interaction of programmed death ligands 1 and 2 (PD-L1 and PD-L2) on tumor cells with PD-1 receptors on T-cells[3]. Through both mechanisms, anti-tumor immunity is enhanced (Figure 1). More recently, modulation of additional immune regulatory pathways including those mediated by lymphocyte activation gene-3 (LAG-3), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), and T-cell immunoglobulin and immunoreceptor-tyrosine-based-inhibitory-motif domain (TIGIT) are being explored in order to build on the success of CTLA-4 and PD-1 inhibitors[1]. Additionally, combination therapy with ICT and various other forms of anti-cancer therapy (cytotoxic chemotherapy, small molecule inhibitors, ionizing radiation, antibody-drug conjugates, cancer vaccines, etc) are either already approved by the FDA or are being actively interrogated (Table 1)[4]. Collectively, these agents represent an established and expanding cancer immunotherapy treatment arsenal with significant therapeutic potential. Unique to the ICT agents is the tumor agnostic FDA approval for use when various biomarkers of ICT response are present. PD-L1 tumor positivity by immunohistochemistry (IHC) (for e.g. 22C3 PD-L1 antibody clone for pembrolizumab, 28-8 PD-L1 antibody clone for nivolumab, and

SP142 PD-L1 antibody clone for atezolizumab) with either the established tumor proportion score (percentage of tumor cells that are PD-L1 positive) or combined positive score (percentage of tumor and immune cells that are PD-L1 positive) are FDA approved companion diagnostic assays for PD-1/PD-L1 inhibitors[5]. Additionally, as an increased quantity of tumor neoantigens has been recognized as a positive predictor of response to ICT, high tumor mutation burden (>10 mutations per Mbp) and high microsatellite instability (often defined as instability of >2 of 5 microsatellite repeats determined by polymerase chain reaction [PCR]) are two additional tumor agnostic companion biomarkers that support the use of ICT[5]. This ability to begin to predict which patients will benefit from ICT has led to broad ranging applications of ICT therapy across a multitude of cancer types.

Importantly, ICT is but one form of a burgeoning arsenal of anti-lymphoma immunotherapies. While chimeric antigen receptor T-cell (CAR-T) therapy has demonstrated remarkable efficacy in the treatment of pediatric B-cell acute lymphoblastic leukemia, the use of CAR-T for pediatric lymphoma is still under active investigation with early reports of efficacy demonstrated in both mature B-cell lymphomas [6, 7] and CD30 positive Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) [8]. Compared to CAR-T therapy, ICT does not require extensive cellular processing which is advantageous for aggressive lymphomas that require timely therapy, and promotes anti-tumor effects through a variety of neoantigens instead of the 1 or 2 tumor targets incorporated in the current iterations of CAR-T therapy. Bi-specific T-cell engagers (BiTEs) like the CD20 x CD3 BiTE glofitimab have also demonstrated early efficacy in pediatric mature B-cell lymphoma [9]. Finally, antibody drug conjugates, for example brentuximab vedotin for anaplastic large cell lymphoma [10] have also demonstrated efficacy in pediatric lymphoma when a

suitable drug-target pair is present. Thus, ICT can be viewed as the "tip of the spear" of emerging immunotherapies for pediatric lymphoma.

Given the extensive immune infiltrates in selected lymphomas, the use of ICT for NHL is a rational extrapolation and extension of the early successes of ICT in melanoma and HL[11]. There is differential expression of PD-L1 within the pediatric lymphoma tumor microenvironment (TME) (Figure 2). Interestingly, in adult patients with lymphoma, dramatically different response rates to ICT have been observed based on the histologic subtype[12]. Kline et al have suggested that tumoral expression of PD-L1 combined with the extent of "tumor inflammation," characterized by immune cell infiltration and activated T-cell phenotypes, are the best predictors of response to ICT in lymphoma[13]. While much is known about the benefit of ICT in various forms of adult lymphomas, less is known about the benefit of ICT in pediatric lymphomas and the distribution of histologic subtypes of NHL and HL is significantly different in pediatric and adult populations . Here, we provide a comprehensive review of the current clinical use of ICT in selected pediatric and adolescent HL and NHL.

Hodgkin lymphoma

As a group, lymphomas are the third most frequent category of malignancy in children aged 0-14 and the most common in patients aged 15-19 years, with HL being the single most common cancer in this age range[14]. The incidence of HL is bimodal with peaks occurring in the 20s and 50s in industrialized countries, with younger peak incidence in lower income countries[15]. Classic HL (cHL) consists of multiple histologic subtypes determined by the presence or absence of fibrosis, the number of Hodgkin Reed-Sternberg (HRS) cells, and the characteristics of the inflammatory cellular infiltrate. The malignant cells of cHL are the HRS cells, a clonal

population usually derived from germinal center B-cells[16-18]. Although the HRS cells comprise <1% of the reactive inflammatory infiltrate[19], secretion of pro-inflammatory cytokines, chemokines, and tumor necrosis factor receptor (TNF-R) family products determines the histologic subtype[20-22]. In cHL the HRS cell immunophenotype is nearly always positive for CD30, and the majority also express CD15 (~70%), with only 6-10% expressing CD20[19, 22, 23]. HRS cells do not express CD45, CD19, or CD79A, hematologic markers usually expressed in B-cell NHL[19, 22, 23].

Recurrent genomic alterations drive proliferation in cHL by upregulating the Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) pathway. These alterations include activating variants in *STAT6* [24, 25], chromosome 9p gains and amplifications[24-26], and inactivating variants in JAK-STAT negative regulators and inhibitors including SOCS1[25, 27] and PTPN1[24, 28]. Additional mutations that augment the NF-kappaB (NF-*k*B) pathway include inactivating variants of NF-*k*B inhibitors such as *TNFAIP3*[24, 29, 30]. In Epstein-Barr virus (EBV) positive cases, EBV latent membrane protein (LMP1) functions like a constitutively active TNF-R family member and signals through NF-*k*B[31]. Also seen in HL are mutations that contribute to immune evasion in HL. These include inactivating variants in the *B2M* and gene fusions in *CIITA* resulting in reduced or absent expression of major histocompatibility complex (MHC) class I[24, 32, 33] and MHC class II expression[34, 35] respectively. Most cases of HL also include chromosome 9p24 amplification or copy number gains[36, 37] which result in increased expression of immune checkpoint genes *CD274* and *PDC1LG2* which encode PD-L1 and PD-L2, respectively[36, 37]. These immunoregulatory checkpoint proteins aid in immune evasion by reducing T-cell proliferation, decreasing cytokine production, impairing T-cell effector function, and inducing T-cell exhaustion and anergy.

Historically, treatment for pediatric HL has been multimodal and consisted of multiagent non-cross-resistant chemotherapy and radiation therapy (RT). This multimodal approach has been associated with late effects including secondary malignancies, cardiovascular disease, pulmonary dysfunction, endocrinopathies (thyroid dysfunction, infertility) and persistent fatigue[38]. Contemporary trials for HL are risk-stratified and response-adapted[39-42]. Cure rates for even high-risk HL exceed 90%, and therefore contemporary clinical trials must balance maintaining high cure rates with limiting acute toxicities and late effects of treatment. Strategies include use of less toxic agents, lower cumulative doses of cytotoxic chemotherapy, eliminating or reducing toxic treatment modalities (such as radiation), and the addition of targeted chemoimmunotherapy and immunotherapy[43]. Although there are age-related differences in the frequency of histologic subtypes, the majority of pediatric and adult HL share overlapping morphology, immunophenotype and genetic alterations, and recent clinical trials have expanded eligibility to include children, adolescents and young adults (CAYA).

In the HL TME, PD-L1 is expressed both on HRS cells and on tissue associated macrophages. Nivolumab and pembrolizumab are anti-PD-1 monoclonal antibodies that interrupt the interaction of PD-L1 and PD-L2 with PD-1 on cytotoxic T-cells in the HL TME. These ICTs restore T-cell effector function and permit immune-mediated elimination of HRS cells[36, 44, 45]. Among lymphomas in children, ICTs have been best studied and most established in HL. Early phase I/II trials with nivolumab and pembrolizumab generated pediatric pharmacokinetic and safety data and demonstrated activity in pediatric patients with relapsed or refractory (R/R) solid tumors and HL (Table 2)[46, 47]. Subsequently, The Children's Oncology Group (COG) and EuroNet collaborative trial AHOD1721 (CheckMate 744) was the first risk-stratified, response-adapted phase II trial using ICT in CAYA patients aged 5-30 years with R/R HL[40, 41]. In this

trial, in patients with a low-risk relapse (R1 cohort), treatment with 4 cycles of brentuximab vedotin (Bv) combined with nivolumab (BvN) resulted in complete metabolic remission (CMR) in 23 of 28 patients (82%)[40]. Intensification with Bv and bendamustine (BvB) was reserved only for patients with incomplete response to BvN. In the total R1 cohort 93% achieved a CMR prior to consolidation with RT and without autologous hematopoietic stem cell transplantation (AHSCT). With a 3-year event-free survival (EFS) of 87% and 3-year progression-free survival (PFS) of 95%, this trial reduced the use of conventional chemotherapy and demonstrated that a subset of patients with low-risk relapse can be cured without AHSCT. Future randomized trials comparing AHSCT with a transplant-free approach are needed. In the second cohort (R2) of this study, patients with standard risk R/R cHL had a 59% CMR rate (23 of 43 patients) after four induction cycles of BvN[37]. Similar to the R1 cohort, intensification therapy with BvB was reserved for patients without CMR and resulted in 94% of all R2 patients achieving a CMR prior to consolidation with AHSCT. The 1-year PFS was 91% for this cohort.

The safety and efficacy of ICT in R/R HL have resulted in their incorporation into clinical trials for front-line therapy for patients with high-risk HL. Most notable is the S1826 phase III clinical trial which included adolescents and adults with pediatric patients (12 to 17 years) comprising ~24% of the study population[40]. Patients with newly diagnosed advanced stage (stage III and IV) cHL were randomized to receive six cycles of doxorubicin, vinblastine, and dacarbazine (AVD) with either nivolumab or brentuximab vedotin (N-AVD, Bv-AVD). The N-AVD arm was better tolerated than the Bv-AVD arm with discontinuation in 9.4% and 22.2% of patients, respectively and also demonstrated superior outcomes with 2-year PFS of 92% vs. 83%. 3-year PFS and OS of 93% and 100% were recently reported for adolescent patients treated on this study[48]. These excellent outcomes combined with <1% of patients in either arm receiving consolidative RT has

established the N-AVD arm as the current standard of care for advanced-stage HL in both the adolescent and adult populations.

An additional ongoing study in patients with high-risk HL is the KEYNOTE-667 trial (NCT03407144) which is a phase 2 trial enrolling patients aged 3-25 years of age with newly diagnosed high-risk cHL. In this trial, patients receive 2 cycles of standard induction with vincristine, etoposide, prednisone, and doxorubicin (OEPA), and those with a slow early response (SER) defined as Deauville score 4-5 by positron emission tomography (PET) are treated with pembrolizumab in addition to standard cyclophosphamide, vincristine, prednisone, and dacarbazine (COPDAC-28) consolidation. In the interim analysis, PET-negative responses at the end of therapy were observed in 27 of 42 patients (64%) suggesting that the addition of pembrolizumab to consolidation may augment responses in this high-risk population[49]. Given the dramatic success of ICT in high-risk HL, ICT has been incorporated into additional clinical trials for patients with low-risk and intermediate-risk HL.

First, a North American Hodgkin Consortium phase II trial compared standard doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) therapy with chemoimmunotherapy (BvN). This trial included adolescents and adults (>16 years) with newly diagnosed cHL[50]. Patients with non-bulky stage I & II cHL with CMR after 2 cycles of standard ABVD were randomized to 2 additional ABVD cycles followed by consolidation with 6 doses of nivolumab over 3 months (n=36) vs. 3 cycles of BvN (n=45). PFS at 24 months was 100% in both groups. Patients with bulky disease and CMR after 2 cycles (n=35) were non-randomly assigned 2 additional cycles of standard ABVD therapy followed by 3 months of nivolumab consolidation and had 2-year PFS of 86% (95% CI: 67-95%). All patients without CMR after 2 cycles (n=37) were non-randomly assigned to receive intensified therapy with 4 cycles of Bv-ABVD followed by consolidation

nivolumab therapy and had a 2-year PFS of 77% (95% CI: 57-89%). The second notable trial in the low stage HL population is the ongoing PET-adapted COG led Intergroup study AHOD2131 (NCT05675410). This is a phase III trial in children and adults (age 5-60) with newly diagnosed stage I and II cHL, and compares standard therapy to the incorporation of BvN in early stage cHL[49]. This trial stratifies patients based on favorable or unfavorable features (large mediastinal mass, >3 nodal sites, B symptoms with erythrocyte sedimentation rate (ESR) >30, ESR > 50 without B symptoms, and age >50 years) and metabolic response after 2 cycles of standard ABVD therapy. Rapid early responders are randomized to receive BvN x 4 cycles vs. ABVD x 2 (favorable risk) or AVD x 4 (unfavorable risk). All SER were randomized to receive BvN x 4 vs. eBEACOPP (escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) or eBPDac (escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, dacarbazine) x 2 cycles. All SER receive involved site RT. The trial aim is to use immunotherapy to improve PFS, maintain overall survival (OS), and minimize long-term morbidity and treatment-related mortality by reducing exposure to RT and cumulative doses of cytotoxic chemotherapy.

In the ongoing investigator-initiated study (RADICAL, NCT05253495), nivolumab replaces doxorubicin after induction therapy in de novo intermediate and high-risk cHL in CAYA. The chemoimmunotherapy approach includes the use of Bv to target HRS cells along with the anti-CD20 antibody rituximab, nivolumab, doxorubicin, dacarbazine, and vinblastine (Figure 3A and 3B). Furthermore, 50 have completed therapy (n=20 as part of the RADICAL study). All patients have achieved complete remission (CR) and there was no evidence of nivolumab toxicity. Only 4 patients have required RT, with an EFS and OS of 100% (median follow-up >90 months, range 2-159 months)[51].

The last 20 years has witnessed a dramatic shift in the treatment of HL from multimodal chemotherapy with RT to chemoimmunotherapy with ICT and minimal (or involved field) RT as the standard of care in the treatment of HL (Figure 4). Future trials involving CAYA will undoubtably continue to incorporate ICT for newly diagnosed patients with the goals of improving or maintaining outcomes and reducing long-term toxicities for increasing numbers of patients. In addition, in CAYA patients with relapsed cHL, trials using ICT will seek to increase remission rates, better define patients who do not require consolidative AHSCT for cure, and improve outcomes for patients who proceed with AHSCT without a CMR. In addition, ICT may be explored as consolidation for newly diagnosed patients or combined with Bv as maintenance following AHSCT[52]. As ICT becomes the standard of care in front-line therapy, new clinical trials will be needed to determine optimal retrieval approaches in R/R patients with prior exposure to ICT.

Mature B-cell lymphoma

Mature B cell lymphoma, including Burkitt lymphoma (BL) and diffuse large B cell lymphoma (DLBCL), is the most common NHL in children and adolescents. OS in pediatric patients treated with intensive multiagent chemotherapy, and for those with high risk disease, intensive chemotherapy with the addition of rituximab is excellent [53]. However, current therapy is associated with substantive acute or long-term toxicities and for the small percentage of patients with R/R disease, chance of cure remains limited [54-56].

In pediatric and adult BL, including post-transplant lymphoproliferative disease with Burkitt morphology, PD-L1 expression is generally low or absent (Figure 2)[57-59]. Conversely, PD-L1 expression in DLBCL is variable and in adult patients is enriched in specific disease subtypes,

including primary mediastinal B-cell lymphoma (PMBCL, see below), T-cell/histiocyte-rich large-B-cell lymphoma, and tumors that are EBV positive[60]. In a pediatric retrospective case series, 19/33 (57%) of patients with DLBCL had PD-L1 positive disease, with a higher proportion in those whose pathology demonstrated EBV positivity and 9p24.1 copy gains[57]. Immunotherapy as a strategy for improvement of outcomes in children with R/R mature B-cell lymphoma is an active area of investigation, currently primarily focused on bispecific T-cell engager therapy, antibody drug conjugates, and chimeric antigen receptor therapy[61]. Experience with ICT in pediatric mature B cell lymphoma is extremely limited. A study of nivolumab in pediatric patients with R/R solid tumors had 3 patients with BL and 3 with DLBCL, none of whom had a complete response[62]. Ongoing studies in children with DLBCL include studies investigating combination therapies including PD-1 agents with tumor-associated antigen-specific T cells (NCT03843294), the LAG-3 inhibitor relatlimab (NCT05255601) and decitabine (NCT05816746).

Primary mediastinal B-cell lymphoma

PMBCL is a rare and aggressive subtype of NHL which originates from thymic B-cells. Patients typically present with a large mediastinal mass that can involve the chest wall or lung. Pleural or pericardial effusions are also common. PMBCL accounts for 2-4% of NHL, is more common in females, and affects predominantly adolescents and young adults[63]. Previously, PMBCL was classified as a subtype of DLBCL, however recent molecular characterization has demonstrated similarities to HL including dysregulation of JAK-STAT and NF-κB signaling, and amplification of 9p24 which leads to overexpression of PD-L1[64].

Currently, there is no single standard of care for the treatment of PMBCL in pediatric or adult patients. In pediatrics, patients with PMBCL have historically been included on prospective trials for mature B-NHL, which were designed to treat BL, the most common subtype of B-NHL in pediatrics[63, 65]. In contrast, PMBCL in adults is typically managed similar to DLBCL, the most common B-NHL in adults. The most common chemotherapy regimens used to treat adults with PMBCL in North America are rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with or without RT and dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH-R)[66]. Recently, DA-EPOCH-R was also studied in pediatric patients with PMBCL. In a prospective international study, among 46 pediatric patients treated with DA-EPOCH-R, EFS was 69.6% (95% CI 55.2%-80.9%), similar to that observed in prior trials with LMB-based pediatric regimens[67]. Retrospective series have also reported outcomes for children treated with DA-EPOCH-R with EFS ranging from 81% to 84%[68, 69]. Among the 15-30% of patients who experience relapse or primary refractory disease, outcomes are poor and novel therapies are needed[70].

Given overexpression of PD-L1/PD-L2 in PMBCL, ICT represents a promising therapeutic approach. Anti-PD-1 agents have been studied in adults with R/R PMBCL with promising results. KEYNOTE-013 (NCT01953692) and KEYNOTE-170 (NCT02576990) were international, open-label, phase Ib and II trials respectively in which patients ≥18 years with R/R PMBCL received pembrolizumab for up to 2 years. The objective response rate (ORR) was 48% (33% CR) in the phase Ib trial and 45% (13% CR) in the phase II trial, both in heavily pre-treated populations[71]. Long-term follow-up (median 48.7 months) of the phase II trial KEYNOTE-170 demonstrated that pembrolizumab monotherapy had 4-year durable responses. Among the 11 patients with a CR, all remained in CR at this late follow-up without additional

therapy[72]. Results from these trials, as well as safety data for pembrolizumab in children [47], supported FDA approval for pembrolizumab in adult and pediatric patients with refractory PMBCL or who have relapsed after 2 or more prior lines of therapy. Combination strategies with anti-PD-1 therapy have also been explored. Nivolumab in combination with the anti-CD30 antibody-drug conjugate Bv was studied in a phase II trial that included 29 adults with R/R PMBCL. With a median follow-up of 39.6 months, the ORR was 73.3% and CR was 37%. PFS and OS at 24 months were 55.5% and 75.5%, respectively[73].

With evidence for the safety and efficacy for anti-PD-1 in the relapsed setting, the next advance in PMBCL will be to understand the role for anti-PD-1 in the upfront management. The COG, in collaboration with the NCI NCTN, completed a randomized phase III trial of nivolumab in combination with chemo-immunotherapy in children and adults age ≥2 years with newly diagnosed PMBCL (NCT04759586). Patients on this trial received treatment using a chemo-immunotherapy backbone of either DA-EPOCH-R or R-CHOP based on physician preference. Patients were randomized 1:1 to receive chemo-immunotherapy alone or chemo-immunotherapy + nivolumab (Figure 5A). This trial completed accrual in May 2025 and is expected to read out in early 2027. Results from this study are expected to provide critical insight into the integration of immune checkpoint inhibitors to the upfront management of PMBCL and may ultimately allow future trials to reduce the use of standard chemotherapy.

Anaplastic large cell lymphoma

Anaplastic large cell lymphoma (ALCL) is a T-cell NHL that accounts for 10-15% of de novo pediatric NHL[74]. ALCL is subdivided based on the expression of the anaplastic lymphoma kinase (ALK) with over 95% of pediatric ALCL cases expressing ALK[75]. ALK expression is a

result of a fusion oncoprotein, with NPM-ALK t(2;5)(p23;q35) being the most common fusion, present in approximately 75% of ALK+ ALCL cases [76]. ALK is a known oncogenic driver leading to cell proliferation and survival through RAS/RAF/MEK/ERK, PI3K/AKT, and JAK/STAT signaling pathways[77]. The presence of the NPM-ALK fusion oncoprotein stimulates an anti-ALK autoantibody in patients with ALK+ ALCL and the presence of high-titer (often defined as >1:750) anti-ALK autoantibodies at the time of ALK+ ALCL diagnosis is associated with a decreased risk of relapse in patients treated with traditional chemotherapeutic regimens (ALCL99, NHL-BFM95, AIEOP-LNH97)[78-81]. Additionally, PD-L1 expression assessed by IHC is seen in 76%-100% of ALK+ ALCL specimens and Iwafuchi et al. demonstrated that elevated PD-L1 expression is associated with a poor prognosis in pediatric ALK+ ALCL[57, 82, 83]. These observations highlight the potential of ICT to augment anti-tumor immunity and mitigate the immunosuppressive TME in pediatric ALK+ ALCL.

Although there is a strong biologic rationale for the use of ICT in ALK+ ALCL, a robust evaluation of the clinical utility of ICT in children with ALK+ ALCL has not been reported. However, three different case reports have described dramatic responses (CR, CR, CR) to PD-1 inhibitors in heavily pre-treated patients with R/R ALK+ ALCL[84-86]. This promising early clinical experience led to the development of the European NIVO-ALCL trial (NCT03703050) in which nivolumab monotherapy is given to patients with active R/R ALK+ ALCL (Cohort 1) and given to patients in a second or greater remission after treatment with Bv or an ALK inhibitor. Early results of that trial indicate that for patients in Cohort 1, single agent nivolumab led to an overall response rate of 50% and a 2 year progression free survival of only 17%[87]. Encouragingly, no severe or unexpected side effects were reported. Interestingly, Cohort 2 was closed early due to patient relapses triggering stopping rules. These results demonstrate that

nivolumab is an active agent in ALK+ ALCL but is not curative monotherapy suggesting that it cannot replace allogeneic stem cell transplantation (allo-SCT) for definitive curative consolidative therapy. One additional trial, RELATIVITY-069 (NCT05255601), recently evaluated the efficacy of nivolumab in combination with the LAG-3 inhibitor relatlimab in children and young adults with R/R lymphoma. This trial included patients with ALCL but was closed due to slow accrual. The ACCELERATE ALCL trial (NCT07013562) began in 2025 and is evaluating the use of nivolumab in a combinatorial, risk adapted, re-induction therapy followed by reduced toxicity conditioning and allo-SCT in CAYA with R/R high-risk ALK+ ALCL (Figure 5B). To the authors' knowledge, there are no additional active trials evaluating ICT in pediatric ALCL. Thus, there remains a strong biologic rationale for further clinical evaluation of the benefit of ICT in pediatric ALCL.

Rare mature lymphomas of T/NK-cell origin

Excluding ALK+ ALCL, mature lymphomas of T/natural killer (NK)-cell origin correspond to less than 10% of all lymphomas occurring in children. Given their rarity and diversity of subtypes, pediatric treatment standards have not been established yet, and most of the available information regarding their pathophysiology and treatment is derived from adult literature. In this review, we will comment on two of those entities, aggressive NK-cell leukemia/lymphoma (ANKL) and peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) highlighting the known aspects of the TME relationship and the potential for ICT use. Both ANKL and PTCL, NOS are the mature T/NK-cell neoplasms currently recognized by the World Health Organization Classification of Paediatric Tumors[88].

ANKL is an EBV-driven malignancy that is exceedingly rare in Western countries. The adult counterpart of ANKL is the extranodal NK-cell lymphoma (ENKL). In children, ANKL can arise from chronic active EBV infection[88]. EBV latency genes II (*LMP1/2A/2B*, *EBNA1*, *EBER1/2*) pattern is found in a clonal episomal form, and EBV-encoded small RNA *in situ* hybridization (EBER) is almost universally detected in lymphoma cells. The importance of EBV in this cancer goes beyond lymphomagenesis. Its relationship with the host is represented by the correlation between detectable plasma EBV viremia (by PCR) and disease activity, dissemination, response to therapy and outcomes (Figure 6)[89, 90]. The EBV integration leads to cell division, migration, apoptosis, and activation of multiple diverse signaling pathways[91]. In fact, three ANKL molecular subtypes have been described in association with specific genomic alterations: TSIM (mutations in JAK/STAT pathway, *TP53*, and amp9p24.1/*JAK2* locus, amp17q21.2/*STAT3/5B/5A* locus, amp9p24.1/*PD-L1*/2 locus, and del6q21), MB (*MGA* mutation and 1p22.1/*BRDT* LOH) and HEA (*HDAC9*, *EP300*, and *ARID1A* mutations)[92]. These molecular subtypes are not only associated with cell-of-origin NK- (TSIM, MB) or T-cell (HEA, MB), but also with survival. Adult patients with ANKL MB subtype bear a poor outcome in comparison to TSIM or HAE subtypes independent of stage or performance status at presentation[92]. To date, molecular ANKL subtypes in pediatric cases have not yet been described.

Upregulation of *PD-L1/2* is observed in the most common subtype TSIM, resulting in potential sensitivity to ICTs. In fact, PD-L1 expression is often found in R/R ANKL samples, also suggesting a potential mechanism of tumor evasion. The use of ICT has been tested in patients with refractory ENKL, including post use of L-asparaginase-containing regimens[93-95]. A systematic review of 14 articles on pembrolizumab use in adult NK/T-cell lymphoma found an ORR of 84.5% with CR in 61% and disease-free survival ranging from 2 to 48 months[96]. For

CAYA with ANKL, the NCT03719105 study is using pembrolizumab to rescue patients not in CR after induction with daratumumab + modified SMILE chemotherapy prior to consolidation with an allo-SCT (NCT03719105)[97].

In PTCL, NOS the expression of PD-1/PD-L1 is variable, and dependent on the IHC cutoff of detection, with reported ranges from 40% to near 100% [98-100]. PD-L1 expression seems to correlate with outcomes, with highly PD-L1 positive tumor expressors resulting in better response to ICTs [100] and affecting staging and outcomes as well[101, 102]. Interestingly, gene-expression signatures linked to tumor-infiltrating immune cells, but not to the cancerous T-cell correlate with outcome[103]. Favorable outcomes are associated with both B- and dendritic cell signatures, with a macrophage signature portending a worse prognosis. Interestingly, PTCL,NOS cases with a macrophage infiltration had elevated expression of PD-L1/2, suggesting that ICTs could potentially result in therapeutic responses in this patient subset[103]. In children, there is lack of information regarding the genomic profile, TME, treatment approaches, and outcomes in PTCL, NOS[104]. In the NCT03719105 study, CAYA patients with PTCL, NOS are also eligible for enrollment testing Bv (anti-CD30ADC) and pralatrexate as novel therapeutic agents[97]. Of note, 2 pediatric patients with refractory PTCL, NOS were treated with nivolumab leading to CR (patient 1, off therapy: IHC PD-L1 tumor expression 5%) and very good partial response (patient 2, therapy ongoing: IHC PD-L1 tumor expression 80%) (ACX, personal communication).

Conclusion and summary

We are at the "end of the beginning" of the investigations of ICT therapy in pediatric and adolescent lymphoma. Based on PD-L1 and PD-L2 expression and Phase I/II safety and efficacy data, the histological lymphoma subtypes most likely to respond positively to ICT (PD-L1/L2

inhibitors) include cHL PMBCL, ALCL and mature EBV-associated NK/T subtypes in pediatric and adolescent patients. Conversely, BL, germinal center B-cell-like DLBCL, and B- and T-lymphoblastic lymphomas are unlikely to respond to ICT in pediatric and adolescent patients. ICT investigations in cHL, PMBCL, ALCL and mature EBV-associated T/NK-cell lymphomas should be initially focused both in the R/R setting but also subsequently in the upfront setting to reduce the burden of chemoradiotherapy acute and long-term effects, while maintaining $\geq$90% EFS and OS. Finally, the role of CTLA-4 inhibitors is relatively unknown in pediatric and adult lymphoma. However, based on the lymphoma TME in cHL, PMBCL and ALCL and the presence of APCs in the TME, future investigations may be warranted to determine the safety and efficacy of CTLA-4 inhibitors in the different pediatric and adolescent lymphoma histological subtypes.

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Tables

Table 1. List of immune checkpoint therapies that have received US Food and Drug administration approval.

Immune Checkpoint Therapy	Generic Name
PD-1 inhibitors	Pembrolizumab Nivolumab Cemiplimab Dostarlimab Retifanlimab Tislelizumab Toripalumab
PD-L1 inhibitors	Atezolizumab Avelumab Durvalumab Cosibelimab
CTLA-4 inhibitors	Ipilimumab Tremelimumab
LAG-3 inhibitor	Relatlimab

PD-1: programmed death-1; PD-L1: programmed death-ligand 1; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; LAG-3: lymphocyte-activation gene 3

Table 2. Comparative Analysis of ICT in Pediatric Lymphoma.

Lymohoma Histology	Trial	Patient Population	Treatment Regimen	Efficacy	Key Safety Findings	Reference
Hodgkin Lymphoma	CheckMate 744 NCT02927769	Low-risk Relapse 5-30 years of age n=28	Nivolumab + BV ± ISRT	3-year EFS/PFS 87%/95%	Treatment-related immune-mediated adverse event 21%	40
	CheckMate 744 NCT02927769	Standard-risk Relapse 5-30 years of age n=44	Nivolumab + BV ± BV + Bendamustine	1-year PFS 91%	Treatment-related grade 3-4 events 18%	41
	COG ADVL1412 NCT02304458	Relapsed or refractory solid tumors 1-18 years of age n=10	Nivolumab	ORR 30% in R/R Hodgkin lymphoma	Treatment-related grade 3-4 events 36%	62
	KEYNOTE-051 NCT02332668	Relapsed or refractory solid tumors 6 months-17 years of age n=155	Pembrolizumab	ORR 60% in R/R Hodgkin lymphoma	Treatment-related grade 3-5 events 8%	47
	COG/SWOG S1826 NCT3907488	De Novo Stage III or IV 12-17 years of age n=240	Nivolumab-AVD	3-year PFS/OS 93%/100%	Grade ≥3 neutropenia 45% Grade ≥ peripheral sensory neuropathy 7% Thyroid dysfuction 7%	48
	KEYNOTE-667 NCT03407144	De Novo High Risk Disease with slow early response to chemotherapy n=84	Pembrolizumab + COPDAC-28 ± RT	ORR 99% CR 26%	Treatment-related grade 3-4 events 19%	49
Mature B-cell Lymphoma	COG ADVL1412 NCT02304458	Relapsed or refractory solid tumors 1-18 years of age n=6	Nivolumab	ORR 0% in mature B-cell lymphoma	Treatment-related grade 3-4 events 36%	62
Primary Mediastinal B-cell Lymphoma	COG ADVL1412 NCT02304458	Relapsed or refractory solid tumors 1-18 years of age n=3	Nivolumab	ORR 33% in PMBCL	Treatment-related grade 3-4 events 36%	62
Anaplastic Large Cell Lymphoma	NIVO-ALCL NCT03703050	Relapsed or refractory ALCL >6 months of age	Nivolumab	ORR 50% 2-year PFS 17% 2-year OS 83%	None reported	87

		n=12				

N: number of participants; BV: brentuximab vedotin; ISRT: involved site radiation therapy; EFS: event free survival; PFS: progression free survival; COG: Children's Oncology Group; ORR: overall response rate; R/R: relapse/refractory; SWOG: Southwest Oncology Group; CR: complete response.

Figure Legends

Figure 1. Mechanisms of T-cell activation via CTLA-4 and PD-1. CTLA-4 is an immune checkpoint receptor expressed on T-cells that competes with CD28 to bind B7 which then leads to cell cycle arrest and decreased T-cell proliferation. PD-1 is a negative regulator of T-cell activity that, when bound to its ligands PD-L1 and PD-L2 leads to inhibition of T-cell function. CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; MHC: major histocompatibility complex; PD-1: programmed death 1; PD-L1: programmed death ligand 1; PD-L2: programmed death ligand 2; TCR: T-cell receptor.

Figure 2. Differential PD-L1 expression in the tumor microenvironment of different pediatric non-Hodgkin and Hodgkin lymphomas.

Figure 3. Study Schema for (A) RADICAL Intermediate-Risk Group, (B) RADICAL High-Risk Group. (A) Intermediate-Risk HL participants will receive 2 cycles of Bv-AVD-R 1 and 2. Response assessment will be performed with FDG-PET scan after 2 cycles of Bv-AVD-R. RER will continue therapy with 2 cycles of Bv-NVD-R. Patients deemed to be SER after 2 cycles of Bv-AVD-R will continue therapy with 4 cycles of Bv-NVD-R. RT will be given at completion of therapy only for SER patients not achieving CR at the end of chemoimmunotherapy. **(B)** High-Risk HL participants will receive 2 cycles of Bv-AVD-R. Response assessment will be performed with FDG-PET scan after 2 cycles of Bv-AVD-R. RER will continue therapy with 4 cycles of Bv-NVD-R. Patients deemed to be SER after 2 cycles of Bv-AVD-R will receive 2 cycles of Bv-NAVD-R, followed by 4 cycles of Bv-NVD-R. RT will be given at completion of therapy only for SER patients not achieving CR at the end of chemoimmunotherapy.

HL: Hodgkin lymphoma; Bv-AVD-R: Brentuximab vedotin (Bv), doxorubicin, vinblastine, dactinomycin, and rituximab; FDG (fluorodeoxyglucose)-PET (positron emission tomography); RER: rapid early responder; Bv-NVD-R, Bv: vinblastine, dactinomycin, nivolumab, and rituximab; (SER): slow early responders; RT: radiation therapy; CR: complete remission.

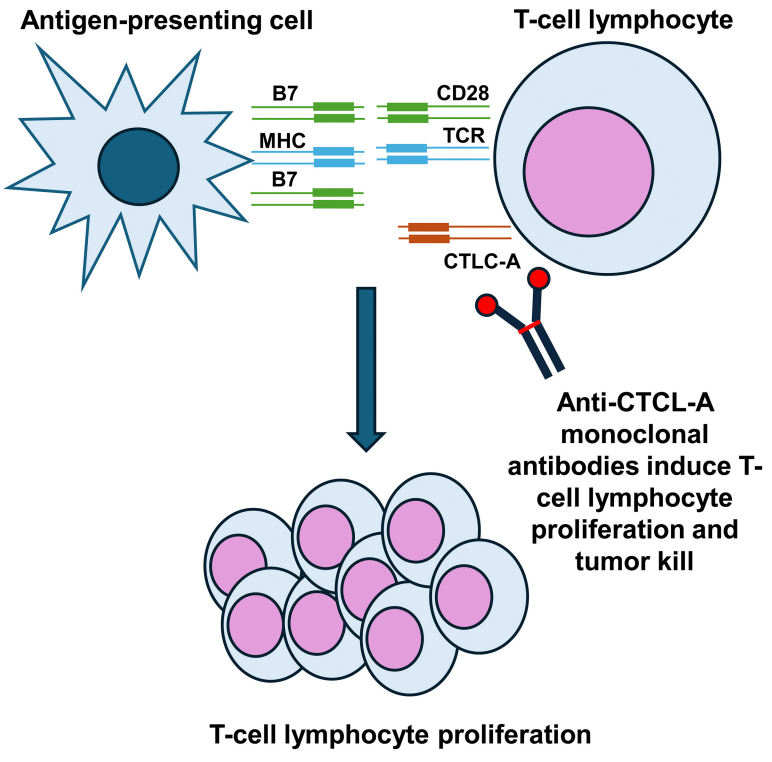
Figure 4. The evolution of Hodgkin lymphoma clinical trials. From chemo-radiotherapy to chemo-immunotherapy. Artificial intelligence was used to create this figure.

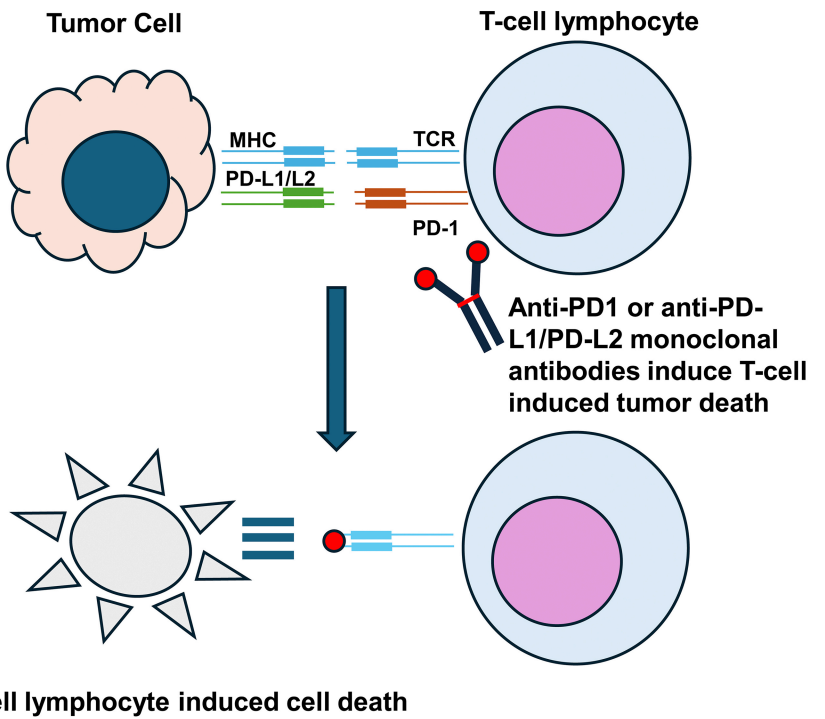
Figure 5. Study Schema for (A) ANHL1931, and (B) ACCELERATE ALCL (A) Participants (n=244) were randomized 1:1 to receive chemoimmunotherapy alone or chemoimmunotherapy with nivolumab for a total of 6 cycles. Disease evaluation was conducted at baseline, after cycle 2 and after cycle 6. Radiation therapy at the completion of chemotherapy was restricted to patients who chose R-CHOP+RT upfront or those with biopsy proven disease at the end of therapy. **(B)** High-risk ALK+ ALCL participants with no previous exposure to Brentuximab vedotin (BV naïve cohort) will receive 2 cycles of Induction therapy with BV and Nivolumab (NIVO) [BV + NIVO], then undergo disease assessment. Patients in CR will proceed with consolidation with RTC allogeneic SCT (HSCT). If patient has PR/SD, they will receive 2 cycles of BV, VBL, and NIVO [BV + VBL + NIVO], then undergo disease evaluation. Patients in CR will proceed with consolidation with RTC HSCT. If response is PR/SD, they will be eligible to receive salvage chemotherapy with ifosfamide, carboplatin and etoposide (ICE) followed by disease evaluation and consolidation with RTC HSCT if in CR/PR. Patients after ICE with SD/PD will be off study. High-risk ALK+ ALCL participants with previous exposure to Bv (Bv prior) will receive 2 cycles of Induction therapy with VBL and NIVO [VBL + NIVO], then

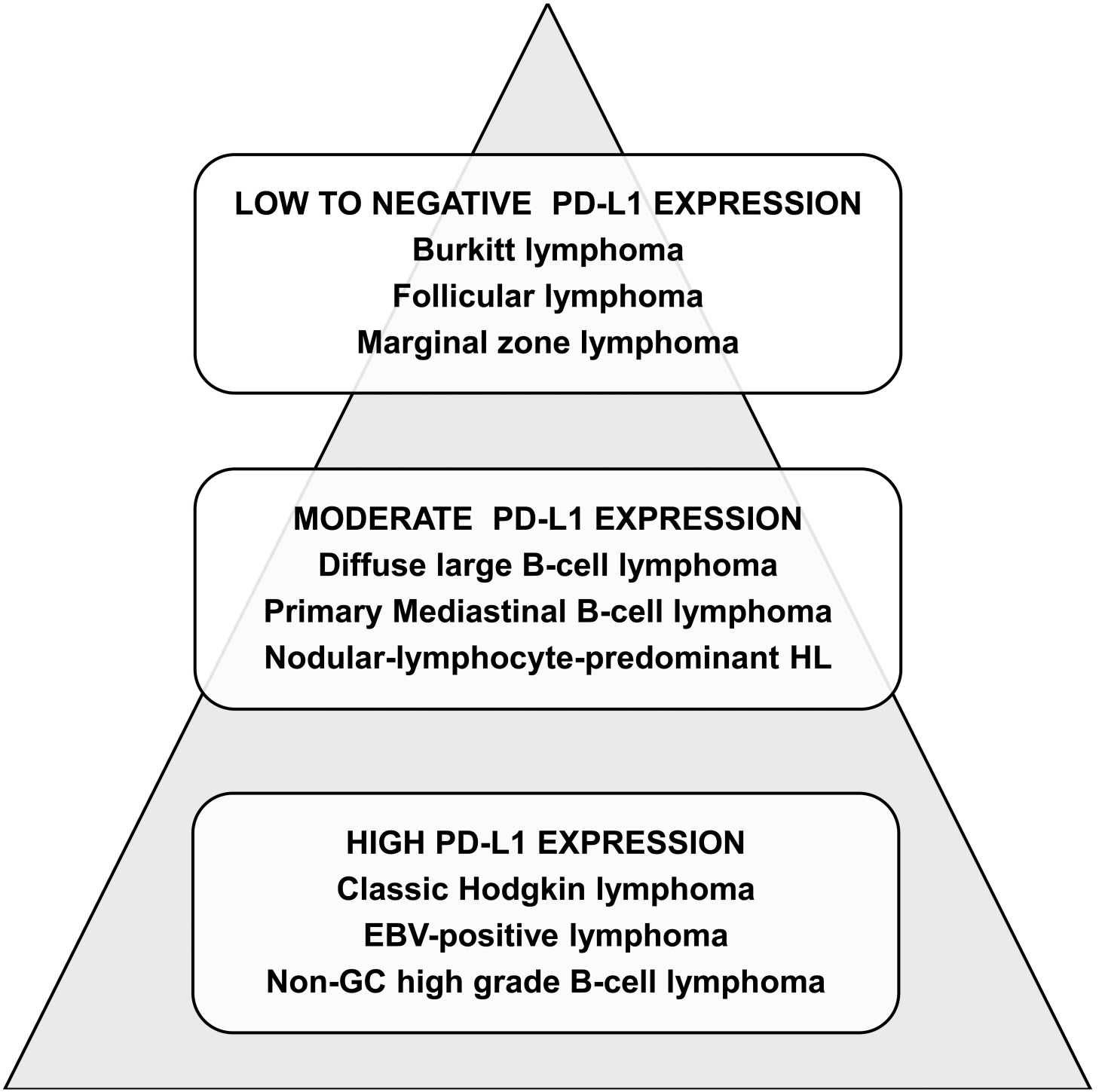
undergo disease assessment. Patients in CR will proceed with consolidation with RTC HSCT. If patient has PR/SD, they will receive 2 cycles of BV, VBL, and NIVO [BV + VBL + NIVO], then undergo disease evaluation. Patients in CR will proceed with consolidation with RTC HSCT. If response is PR/SD, they will be eligible to receive salvage with ICE followed by disease evaluation and consolidation with RTC HSCT if in CR/PR. Patients after ICE with SD/PD will be off study. Bv-NAVD-R): Bv, nivolumab, doxorubicin, vinblastine, dactinomycin, and rituximab; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; PMBCL: primary mediastinal B cell lymphoma; DA-EPOCH-R: dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; PFS: progression-free survival; OS, overall survival; EFS: event-free survival; ALCL: anaplastic large T-cell lymphoma; VBL: vinblastine; NIVO: nivolumab RTC: reduced toxicity conditioning; HSCT: hematopoietic stem cell transplant; PR: partial response; SD: stable disease; ICE: ifosfamide, carboplatin and etoposide.

Figure 6. EBV viremia is associated with NK/T lymphoma malignant transformation and EBV viremia persistence following therapy is significantly associated with inferior ORR, PFS, and OS. EBV: Epstein-Barr virus; NK: natural killer; ESA: etoposide, dexamethasone, pegaspargase; MESA: methotrexate, etoposide, dexamethasone, pegaspargase; RNAseq: RNA sequencing; TME: tumor microenvironment; ORR: overall response rate; PFS: progress-free survival; OS: overall survival. Reprinted from Xavier/Liao/Cairo[89]

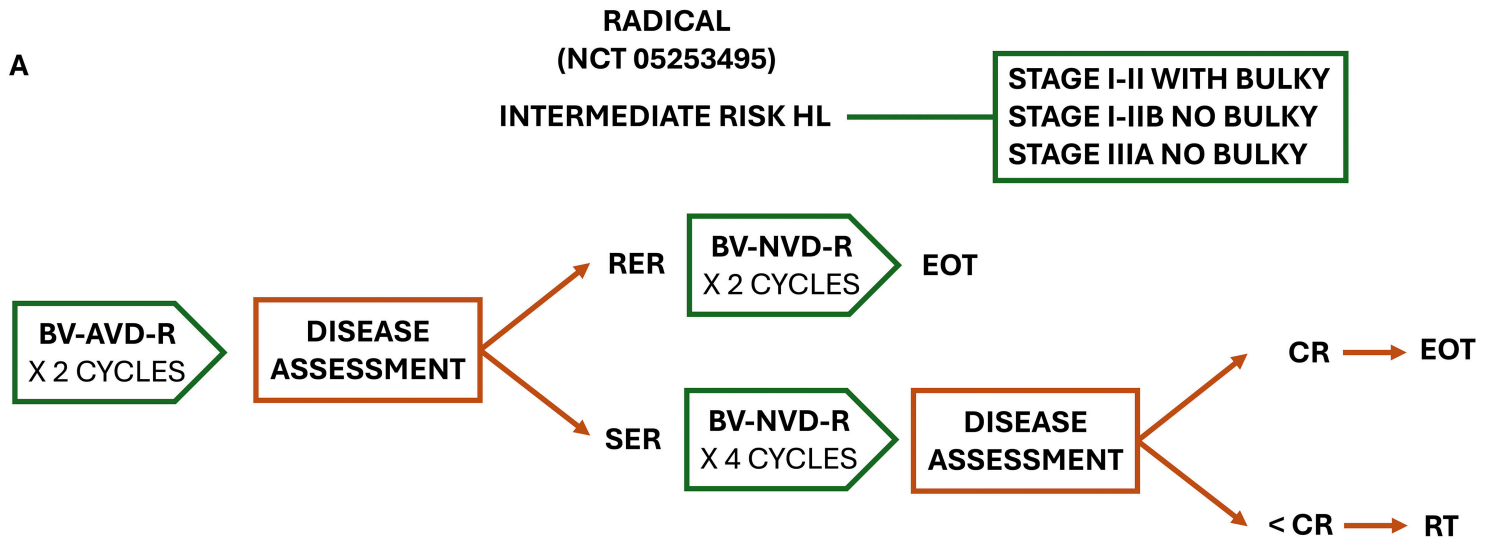
T-CELL ACTIVATION and TUMOR CELL DEATH






LOW TO NEGATIVE PD-L1 EXPRESSION
Burkitt lymphoma
Follicular lymphoma
Marginal zone lymphoma
MODERATE PD-L1 EXPRESSION
Diffuse large B-cell lymphoma
Primary Mediastinal B-cell lymphoma
Nodular-lymphocyte-predominant HL
HIGH PD-L1 EXPRESSION
Classic Hodgkin lymphoma
EBV-positive lymphoma
Non-GC high grade B-cell lymphoma

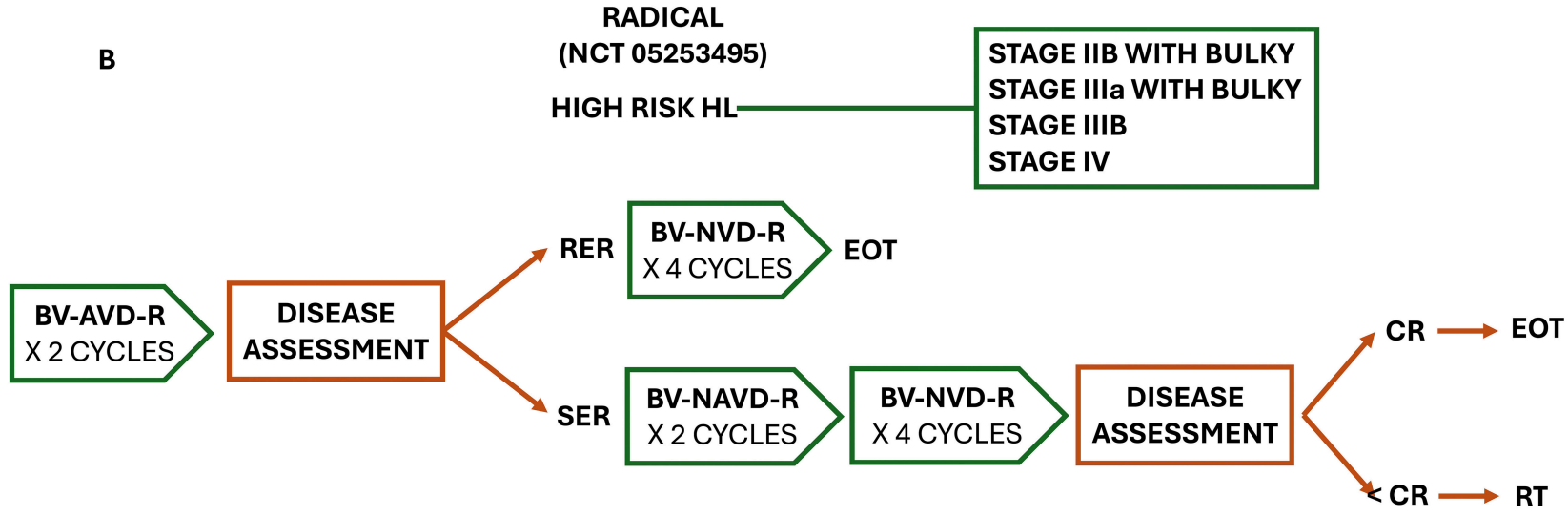
A



BV-AVD-R: BRENTUXIMAB VEDOTIN, DOXORUBICIN, VINBLASTINE, DACARBAZINE, RITUXIMAB
BV-NVD-R: BRENTUXIMAB VEDOTIN, NIVOLUMAB, VINBLASTINE, DACARBAZINE, RITUXIMAB

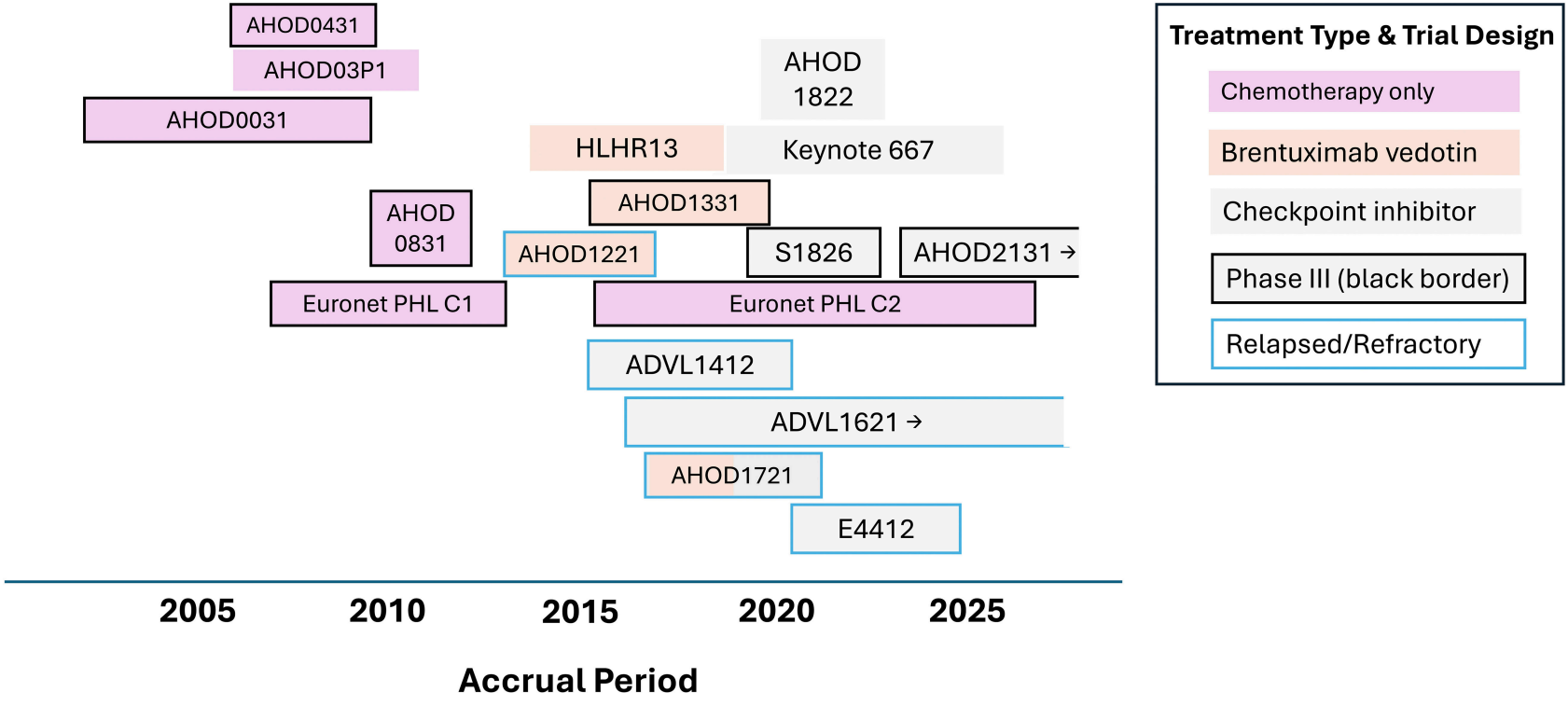
ANTHRACYCLINE CUMULATIVE DOSE = 100 MG/M2

B



BV-AVD-R: BRENTUXIMAB VEDOTIN, DOXORUBICIN, VINBLASTINE, DACARBAZINE, RITUXIMAB
BV-NVD-R: BRENTUXIMAB VEDOTIN, NIVOLUMAB, VINBLASTINE, DACARBAZINE, RITUXIMAB
BV-NAVD-R: BRENTUXIMAB VEDOTIN, NIVOLUMAB, DOXORUBICIN, VINBLASTINE, DACARBAZINE, RITUXIMAB

ANTHRACYCLINE CUMULATIVE DOSE = 100 – 200 MG/M2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HLHR13
Keynote 667
AHOD1331
AHOD 0831
AHOD1221
S1826
AHOD2131 →
Euronet PHL C1
Euronet PHL C2
ADVL1412
ADVL1621 →
AHOD1721
E4412
2005
2010
2015
2020
2025
Accrual Period
Treatment Type & Trial Design
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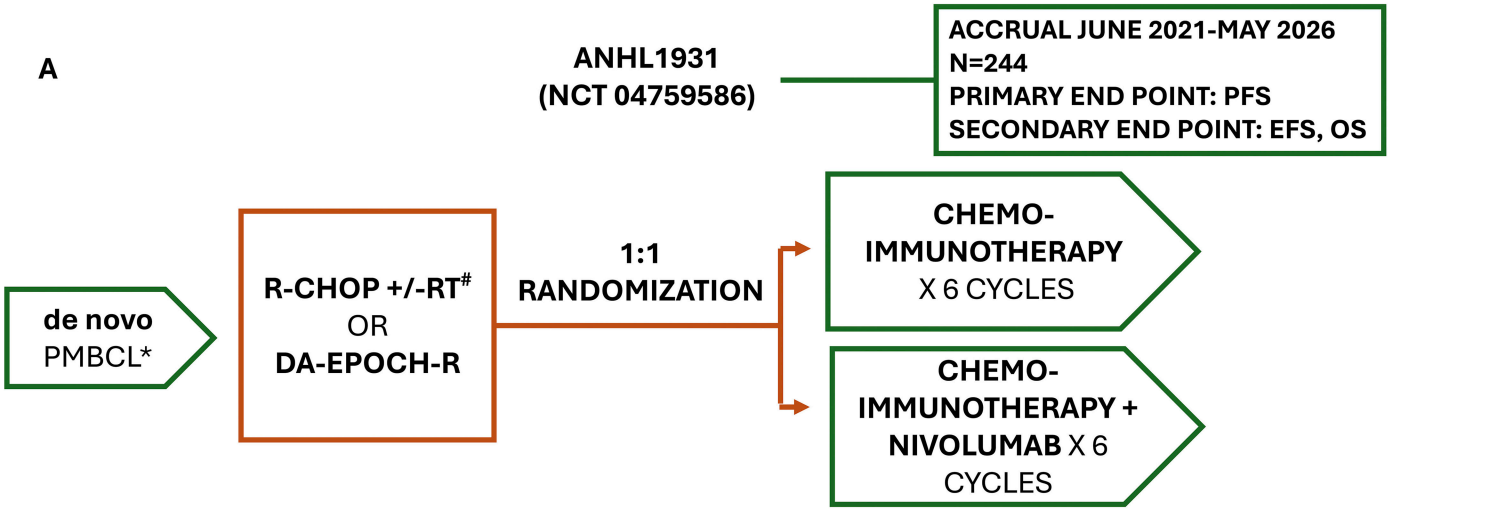
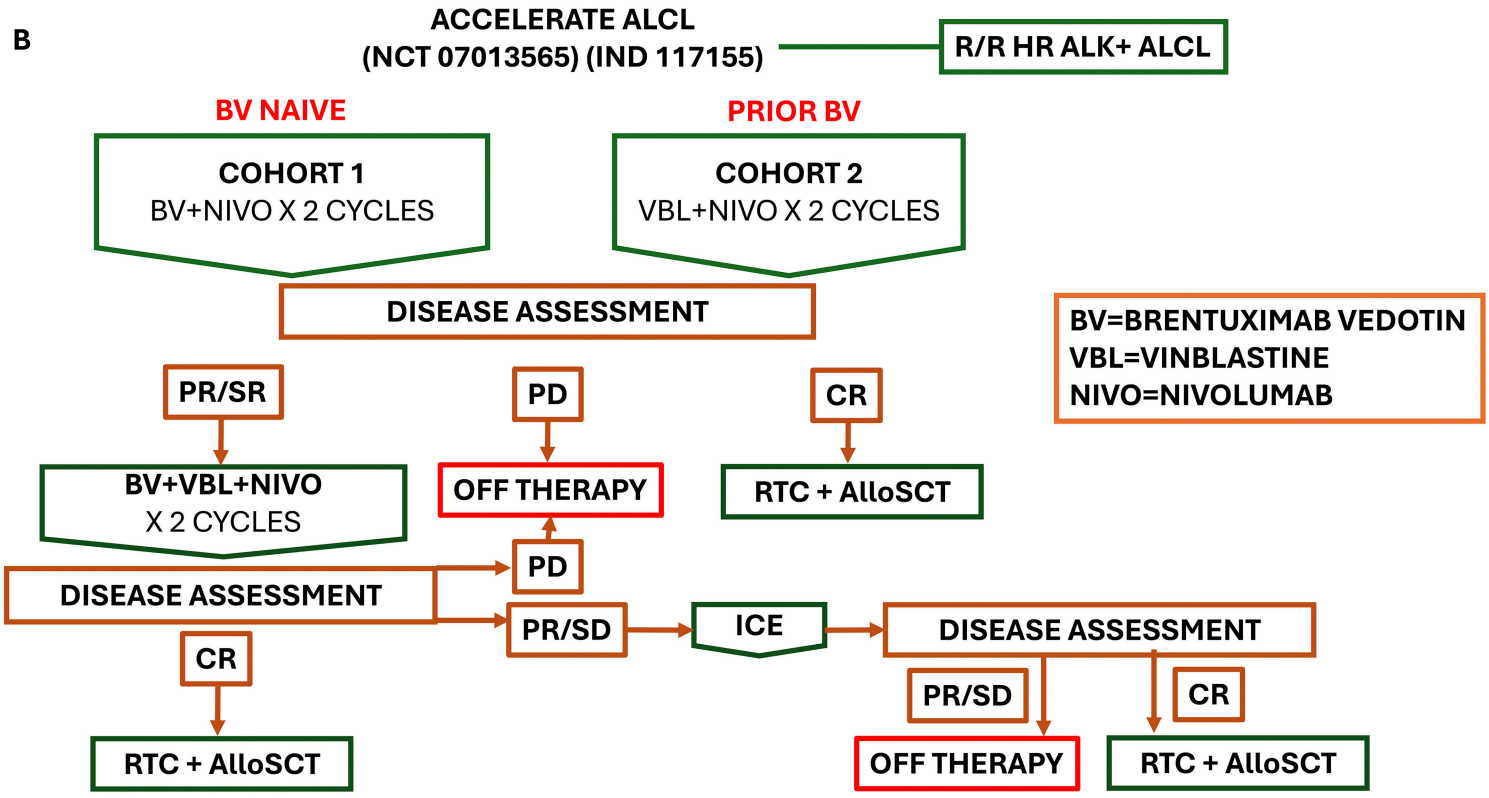
Brentuximab vedotin
Checkpoint inhibitor
Phase III (black border)
Relapsed/Refractory

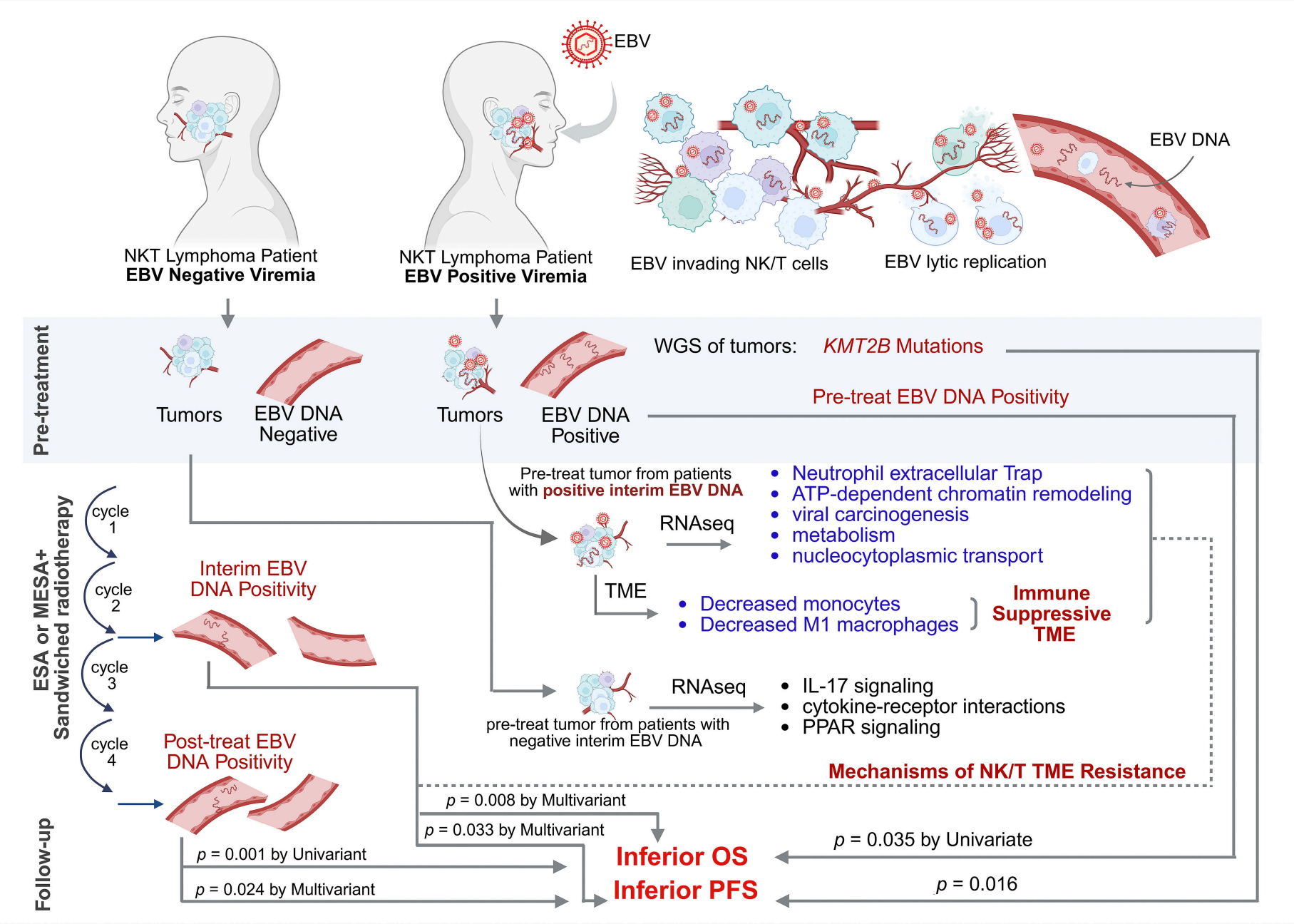


R-CHOP +/- RT: CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, PREDNISONE, RITUXIMAB +/- RADITION THERAPY
DA-EPOCH-R: DOSE-ADJUSTED ETOPOSIDE, PREDNISONE, VINCRISTINE, CYCLOPHOSPHAMIDE, DOXORUBICIN,RITUXIMAB

PHYSICIAN'S CHOICE TO TREAT PATIENT WITH EITHER R-CHOP-R, R-CHOP, OR DA-EPOCH-R

*age at diagnosis ≥ 2 years; #RT only for R-CHOP + RT backbone OR biopsy-proven disease at the end-of-therapy




EBV
NKT Lymphoma Patient
EBV Negative Viremia
NKT Lymphoma Patient
EBV Positive Viremia
EBV invading NK/T cells
EBV lytic replication
EBV DNA
Pre-treatment
Tumors
EBV DNA Negative
Tumors
EBV DNA Positive
WGS of tumors:
KMT2B Mutations
Pre-treat EBV DNA Positivity
Pre-treat tumor from patients with positive interim EBV DNA
RNAseq
Neutrophil extracellular Trap
ATP-dependent chromatin remodeling
viral carcinogenesis
metabolism
nucleocytoplasmic transport
TME
Decreased monocytes
Decreased M1 macrophages
Immune Suppressive TME
ESA or MESA+ Sandwiched radiotherapy
cycle 1
cycle 2
cycle 3
cycle 4
Interim EBV DNA Positivity
RNAseq
IL-17 signaling
cytokine-receptor interactions
PPAR signaling
pre-treat tumor from patients with negative interim EBV DNA
Mechanisms of NK/T TME Resistance
Post-treat EBV DNA Positivity
p = 0.008 by Multivariant
p = 0.033 by Multivariant
p = 0.035 by Univariate
p = 0.001 by Univariant
p = 0.024 by Multivariant
Inferior OS
Inferior PFS
p = 0.016
Follow-up