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Commentary

What Is Next in Pediatric B-Cell Precursor Acute Lymphoblastic Leukemia

Aimee C. Talleur [1,*], Ching-Hon Pui [2] and Seth E. Karol [2,*]

[1] Department of Bone Marrow Transplantation and Cellular Therapy, St. Jude Children's Research Hospital, Memphis, TN 38105, USA
[2] Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA
* Correspondence: aimee.talleur@stjude.org (A.C.T.); seth.karol@stjude.org (S.E.K.)

Abstract: Cure rates now exceed 90% in many contemporary trials for children with B-cell acute lymphoblastic leukemia (B-ALL). However, treatment remains suboptimal, and therapy is toxic for all patients. New treatment options potentially offer the chance to reduce both treatment resistance and toxicity. Here, we review recent advances in ALL diagnostics, chemotherapy, and immunotherapy. In addition to describing recently published results, we also attempt to project the impact of these new developments into the future to imagine what B-ALL therapy may look like in the next few years.

Keywords: acute lymphoblastic leukemia; childhood; treatment

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1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer in children, with more than 50,000 children newly diagnosed each year globally [1]. In children with ALL, approximately 75% to 88% present with B-cell precursor immunophenotype disease, depending on their ancestry [2]. Serial clinical trials have improved overall survival (OS) in high resource settings to more than 85%, and many trial groups are now reporting OS rates over 90% at 5 years [3–7]. However, survival in resource-limited settings remains below 70%, and, due to a lack of disease detection and documentation in such areas, survival is likely much lower than these data suggest [1,5]. Moreover, specific molecular subtypes with prognostic significance are associated with genetic ancestry, accounting for some of the racial and ethnic disparities in outcomes [2]. Furthermore, for those patients with relapsed disease, outcomes are much poorer across treatment settings [8–10].

As we consider the future of therapy for B-ALL, we recognize that such a future will proceed along multiple paths simultaneously, including: (i) the use of novel agents to improve survival and reduce toxicity in patients treated in high-resource settings, (ii) the application of molecular subtype-driven treatment individualization to improve efficacy and to eliminate racial and ethnic gaps in outcomes, and (iii) the expansion of access to additional effective therapies in middle- and low-resource settings. Additional considerations will include the timing of novel therapies in the disease course, in both the up-front and relapsed patient populations; replacement of or reduction in traditional chemotherapy agents; advancements in the availability and quality of diagnostic modalities; and further development of targeted therapies for specific disease subtypes.

This review will focus on emerging classifications and treatment strategies that may play a larger role in the treatment of children with B-ALL in high-resource settings in the coming years. We will divide the discussion of therapeutic strategies into two categories, reflecting the intertwining modalities driving modern therapy for ALL: chemotherapy, including both conventional agents and new antigen-directed chemo-immunotherapy drugs; and cellular therapy, including allogeneic hematopoietic cell transplantation (HCT) and chimeric antigen receptor (CAR) T-cell therapy.

2. Improvements to Risk Stratification and Biological Classification

Despite differences in several important components of therapy, most trial groups are now reporting event-free survival (EFS) of over 80% [5]. Recent up-front treatment studies in pediatric B-ALL trials have evaluated the optimal steroid selection and schedule during induction [6,11,12], the role of high-dose methotrexate across different disease subsets [6,13,14], and modifications to risk stratification based on either minimal residual disease (MRD) or genomics [15]. Several additional studies have evaluated modifications in asparaginase formulation or its schedule [13,16–22]. While interactions between treatment backbone, risk stratification, and study intervention preclude the identification of a single optimal regimen for all patients, recent data have continued to refine the patient populations which are appropriate for therapy intensification or deintensification.

Looking forward, we anticipate that ongoing improvements in risk stratification will provide opportunities for further treatment modulation of initial therapy to reduce both acute and long-term toxicity for lower-risk patient subsets. Although it provides valuable prognostic information, the National Cancer Institute (NCI) risk stratification [23] for B-ALL alone is insufficient for optimal treatment intensification/deintensification [24,25]. The identification of low-level persistent disease following morphologic remission has historically utilized either flow cytometry (FC) or patient-specific T-cell receptor (TCR) or immunoglobulin heavy chain (IgH) polymerase chain reaction (PCR) testing as MRD methods. On the other hand, it has also relied on the persistence of molecular aberrancy in chromosomal analysis, florescence in situ hybridization, or detection of persistent gene fusions through PCR. These modalities dramatically improve risk stratification compared to morphology alone [16,26–29]. High-throughput sequencing (HTS, sometimes called next-generation sequencing)-based MRD testing provides the ability to detect residual leukemic clones at 10- to 100-fold lower levels than PCR or FC [30,31]. Importantly, HTS also appears to identify patients who appear to be MRD negative by conventional FC or PCR assays, but who have residual leukemia [32,33]. The HTS-based MRD test is helpful in identifying low-risk patients who have exceptionally favorable outcomes and those who are likely to relapse after allogeneic transplantation or CAR T-cell therapy [29–34]. Moreover, HTS-based MRD can also identify subgroups of patients who lack immunoglobulin gene rearrangements at diagnosis and have poor outcomes [30].

Ongoing efforts to integrate our evolving understanding of B-ALL genomics will further change the way we think about risk and treatment. Prior work has demonstrated that the prognostic impact of low-level MRD in patients with hyperdiploid ALL is lower than similarly low levels of MRD in either patients with *ETV6::RUNX1* ALL or other patients with B-ALL. This is likely related to the sensitivity of hyperdiploid ALL to antimetabolite therapies, which are not included in induction [35]. Indeed, patients with hyperdiploid ALL who fail to achieve complete remission after conventional induction therapy have a high salvage rate without the need of allogeneic transplantation, presumably because many of them are highly sensitive to the high-dose methotrexate and mercaptopurine that were used for post-remission therapy [36]. Additional work has integrated newly identified genomic subsets of ALL to further identify patients who perform poorly despite their apparent rapid responses to chemotherapy [37,38]. As comprehensive genomic analyses become more common, our understanding of the interactions between genomic lesions will expand, identifying combinations of lesions with prognostic and therapeutic significance. Such work has already begun, and we believe that progress in this area will continue to accelerate [39]. We anticipate that future treatments will intensify therapy for these patients despite the MRD response, mirroring strategies which are already being employed for patients with *KMT2A*-rearranged and hypodiploid ALL in many groups. Finally, we expect that newly identified ALL subsets will further offer opportunities for targeted additions or subtractions of therapy for these patients. In vitro drug sensitivity testing, integrated with genomic information, will provide opportunities to identify subtype-specific vulnerabilities or resistance patterns in order to enable such therapeutic modifications [40–42].

3. Incorporation of Novel Agents

It is impossible to consider the future of B-ALL therapy without considering how new agents may be integrated. Recent attempts to intensify therapy with either higher doses of conventional chemotherapy [3,7] or the addition of cytotoxic agents, such as etoposide or clofarabine, have been unsuccessful [43,44]. This suggests that further improvements to therapy for patients with high-risk disease will require novel strategies. Current trials for patients with B-ALL are exploring integration of the CD22-targeted antibody–drug conjugate inotuzumab as part of backbone therapy for higher-risk patients (NCT04307576 and NCT03959085). Other studies are evaluating the CD3-CD19 bispecific antibody construct blinatumomab to attempt to improve therapeutic outcomes for both NCI standard-risk (NCT03914625) and high-risk populations (NCT03117751 and NCT03643276). While current studies are using these agents to either supplement existing therapy or replace weeks of low-intensity maintenance therapy with blocks of these novel agents, future studies are likely to replace intensive blocks of conventional therapy with these agents in an attempt to reduce the long-term toxicities observed in survivors. Further experience with newly approved formulations of asparaginase, including Calaspargase pegol and asparaginase erwinia chrysanthemi (recombinant), will also reveal whether toxicity profiles with these agents differ from historical formulations of this pediatric backbone agent.

For patients with relapsed B-ALL, in recent years, the activity of the novel agents described above has been demonstrated. These agents have shown high response rates even in children with refractory disease after relapse. Data from both clinical trials and compassionate access use of inotuzumab have consistently demonstrated its activity as a single agent in both high-bulk and lower disease burden states [45–47]. Blinatumomab has also been incorporated into multiple treatment backbones, with moderate efficacy in bulk disease and excellent activity in patients in morphologic remission with low disease burden [9,48–50]. Recent studies on BCL-2 homology domain 3 (BH3) inhibitors have provided hope for this patient population. Data obtained from adults and children have suggested that the BCL-2 inhibitor venetoclax [51] and the BCL2-2, BCL-xL, and BCL-w inhibitor navitoclax [52] are active both preclinically and in patients with relapsed ALL. For patients with *KMT2A*-rearranged ALL, there is hope that menin inhibitors may improve outcomes for this high-risk population [53,54]. Given the high failure rates of conventional reinduction strategies such as the UKALL R3 regimen, [8,55] we anticipate that current and future studies will evaluate optimal ways to integrate novel agents in both the reinduction and consolidation of children with relapsed B-ALL. New strategies will also be needed for patients with extramedullary relapse, as they appear not to respond well to either blinatumomab or inotuzumab.

4. Cellular Therapies

Cellular therapy is often used to treat pediatric patients with high-risk B-ALL who have either failed traditional chemotherapy regimens or who are deemed to be at a high risk of subsequent disease relapse despite an initial response to therapy [56–58]. Given the presumed chemo-resistance of these patient subsets, allogeneic HCT offers an alternative treatment approach by which the use of donor cells provides an immunotherapeutic graft-versus-leukemia (GVL) effect. Outcomes after allogeneic HCT have improved over time, owing to advances in both transplantation and supportive care approaches, which, in turn, contribute to improved leukemia-free survival (LFS) as well as a reduction in transplant-related mortality (TRM) [59–62]. This includes progress related to conditioning regimens, donor typing, graft manipulation, expansion of access to alternative donors, graft-versus-host disease (GVHD) prophylaxis and treatment, and infection prevention and control [62–78]. Furthermore, advances in leukemic diagnostics, genetic subtyping, and leukemia-directed therapies have decreased the number of patients proceeding to HCT and, for those who are deemed candidates, have enhanced the depth of remission which patients achieve prior to HCT [9,48,49]. Recent findings that HTS-detectable MRD is associated with inferior outcomes in patients who are FC MRD-negative after tisagenlecleucel highlights the

impacts of these changes and the role of transplant in these settings [32]. Importantly, with the continued advent of new treatment strategies in both the up-front and relapse settings, there are likely patients that can achieve long-term remission without the use of HCT. Given the risk of morbidity and mortality with current HCT approaches, it will be particularly prudent to continue to re-evaluate indications for transplant in this patient population.

Despite these advances in HCT, there is much work ahead to improve LFS for patients with refractory B-ALL pre-HCT, as outcomes remain dismal in this cohort, primarily due to high rates of disease relapse after HCT [79,80]. In addition to efforts to reduce the disease burden pre-HCT through further discovery and incorporation of novel agents in relapse therapy regimens, it is imperative that research continues to focus on immunotherapeutic strategies to promote GVL while not increasing the risk of GVHD. This includes exploration into graft manipulation and donor sources, the use of selective cell add-back (e.g., NK cells, Tregs), post-HCT pre-emptive therapies (e.g., blinatumomab, ABL tyrosine kinase inhibitors, and/or cytokine support), and GVHD prophylaxis approaches. For this high-risk patient population, combinatorial therapies will likely be needed to overcome leukemia resistance mechanisms while minimizing overlapping toxicity profiles.

Beyond HCT, CD19-redirected CAR T-cell therapy has transformed treatment options for pediatric patients with historically incurable relapsed/refractory B-ALL, inducing remission in the majority of patients treated. These outcomes have been consistent across numerous trials despite differences in CAR construct, clinical trial design, patient inclusion/exclusion criteria, lymphodepleting regimens, and decisions about post-CAR T-cell therapy, such as consolidative allogeneic HCT [81–86]. Importantly, real-world outcomes using the FDA-approved product tisagenlecleucel have continued to mirror those seen in the initial clinical trials [83,87–90].

Despite these successes, relapse after treatment with CD19-CAR T-cell therapy continues to be a significant clinical challenge, with approximately 50% of treated patients experiencing subsequent disease relapse across different products. This includes a subset of patients with antigen escape, during which the CD19 target is lost [83,91,92]. Importantly, outcomes for those patients with initial non-response or subsequent relapse are quite poor [93]. While close monitoring for the loss of B-cell aplasia and improvements in post-CAR disease monitoring, such as next-generating sequencing MRD measurement, provides some further information to guide treatment decisions after CD19-CAR T-cell therapy, relapse still occurs [83,88–90]. For some patients, CAR T-cell therapy is, therefore, used as a bridge to a planned consolidative allogeneic HCT [89,94,95]. However, given the morbidity and mortality risk of HCT, there is a critical need to continue to improve CAR T-cell approaches to promote sustained remission, as well as efforts to better define high-risk patients prior to CD19-CAR T-cell treatment. We anticipate that such work will accelerate, as recent work has already begun to identify patients with lower response rates to existing CAR T-cell therapies [96].

A primary area of investigation to improve outcomes after CAR T-cell therapy for pediatric patients with B-ALL includes the evaluation of alternative antigens, primarily CD22 alone or in combination with CD19 [85,89]. Several trials are currently underway in the pediatric space, with promising interim results. Additionally, efforts to promote persistence and limit immune rejection of infused autologous CAR T-cell products include reinfusion [85,89,97–100], humanized CAR T cell products [101], the addition of PD-1 inhibitors [102], gene editing of autologous T cells, and allogeneic approaches [103–105]. Data from prior trials also adds evidence which can be used to explore T-cell biology further for potential modifiable factors that may augment treatment responses, such as reducing DNMT3A-driven methylation resulting in T-cell exhaustion [106] or new CAR constructs which utilize priming antigens to control CAR expression [107]. An ongoing commitment from laboratory scientists to identify strategies to improve CAR T-cell therapy, from clinician scientists to evaluate these approaches in early phase trials, and from industry and regulatory partners to allow broad access to such new treatments will be needed.

Furthermore, traditional risk factors for treatment failure, both in newly diagnosed and relapsed pediatric patients, are not consistently replicated after treatment with CD19-CAR T-cell therapy, suggesting that this treatment may overcome the excess risk observed in some populations. This includes subgroups with high-risk cytogenetics [108], Down syndrome [109], infants [110,111], and extramedullary disease [112]. Encouraged by the ability of CD19-CAR T cells to eradicate leukemic cells in the cerebrospinal fluid of patients with relapsed B-ALL, several studies tested this approach in the treatment of isolated extramedullary relapse [112–115]. The preliminary results are encouraging, especially for patients with testicular relapse. CAR T-cell therapy could become a therapeutic option for patients with extramedullary relapse, sparing them from receiving local irradiation. This highlights the potential of CAR T-cell therapies to expand treatment options and circumvent previously defined high-risk characteristics, thereby re-defining our approaches for these patients. Crucially, while there is a growing body of literature reporting on such potential factors, continued evaluation of such therapies across larger patient cohorts is necessary to further elucidate the associations, including those patient groups treated with commercially available and novel experimental products. This will allow for more prudent risk stratification of pediatric patients with relapsed/refractory B-ALL, informing choices of CAR T-cell therapy, post-infusion monitoring, and/or treatment strategies.

5. Conclusions

While serial clinical trials over the last 60 years have transformed B-ALL from an almost universally fatal disease to one in which more than 9/10 children can expect to be long-term survivors, much effort is still needed to improve treatment for this common pediatric cancer. Recent progress in more sensitive disease detection methods and the availability of novel cellular and chemotherapy options provides hope that further improvements to the cure can be achieved, while simultaneously decreasing the short- and long-term therapy toxicity levels. We anticipate that trials over the next decade will continue to transform the care in this field, with benefits to thousands of children and their families annually.

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References

1. Rodriguez-Galindo, C.; Friedrich, P.; Alcasabas, P.; Antillon, F.; Banavali, S.; Israels, L.C.T.; Jeha, S.; Harif, M.; Sullivan, M.J.; Quah, T.C.; et al. Toward the Cure of All Children with Cancer through Collaborative Efforts: Pediatric Oncology as a Global Challenge. *J. Clin. Oncol.* **2015**, *33*, 3065–3073. [CrossRef]
2. Lee, S.H.R.; Antillon-Klussmann, F.; Pei, D.; Yang, W.; Roberts, K.G.; Li, Z.; Devidas, M.; Yang, W.; Najera, C.; Lin, H.P.; et al. Association of Genetic Ancestry with the Molecular Subtypes and Prognosis of Childhood Acute Lymphoblastic Leukemia. *JAMA Oncol.* **2022**, *8*, 354. [CrossRef] [PubMed]
3. Jeha, S.; Pei, D.; Choi, J.; Cheng, C.; Sandlund, J.T.; Coustan-Smith, E.; Campana, D.; Inaba, H.; Rubnitz, J.E.; Ribeiro, R.C.; et al. Improved CNS Control of Childhood Acute Lymphoblastic Leukemia without Cranial Irradiation: St Jude Total Therapy Study 16. *J. Clin. Oncol.* **2019**, *37*, 3377–3391. [CrossRef] [PubMed]
4. Pui, C.-H.; Yang, J.J.; Hunger, S.P.; Pieters, R.; Schrappe, M.; Biondi, A.; Vora, A.; Baruchel, A.; Silverman, L.B.; Schmiegelow, K.; et al. Childhood Acute Lymphoblastic Leukemia: Progress through Collaboration. *J. Clin. Oncol.* **2015**, *33*, 2938–2948. [CrossRef]
5. Pui, C.-H.; Yang, J.J.; Bhakta, N.; Rodriguez-Galindo, C. Global efforts toward the cure of childhood acute lymphoblastic leukaemia. *Lancet Child Adolesc. Health* **2018**, *2*, 440–454. [CrossRef] [PubMed]
6. Larsen, E.C.; Devidas, M.; Chen, S.; Salzer, W.L.; Raetz, E.A.; Loh, M.L.; Mattano, L.A., Jr.; Cole, C.; Eicher, A.; Haugan, M.; et al. Dexamethasone and High-Dose Methotrexate Improve Outcome for Children and Young Adults with High-Risk B-Acute Lymphoblastic Leukemia: A Report From Children's Oncology Group Study AALL0232. *J. Clin. Oncol.* **2016**, *34*, 2380–2388. [CrossRef]
7. Maloney, K.W.; Devidas, M.; Wang, C.; Mattano, L.A.; Friedmann, A.M.; Buckley, P.; Borowitz, M.J.; Carroll, A.J.; Gastier-Foster, J.M.; Heerema, N.A.; et al. Outcome in Children with Standard-Risk B-Cell Acute Lymphoblastic Leukemia: Results of Children's Oncology Group Trial AALL0331. *J. Clin. Oncol.* **2020**, *38*, 602–612. [CrossRef]

8. Brown, P.A.; Ji, L.; Xu, X.; Devidas, M.; Hogan, L.; Borowitz, M.J.; Raetz, E.A.; Zugmaier, G.; Sharon, E.; Gore, L.; et al. A Randomized Phase 3 Trial of Blinatumomab Vs. Chemotherapy as Post-Reinduction Therapy in High and Intermediate Risk (HR/IR) First Relapse of B-Acute Lymphoblastic Leukemia (B-ALL) in Children and Adolescents/Young Adults (AYAs) Demonstrates Superior Efficacy and Tolerability of Blinatumomab: A Report from Children's Oncology Group Study AALL1331. *Blood* **2019**, *134*, LBA-1. [CrossRef]
9. Locatelli, F.; Zugmaier, G.; Rizzari, C.; Morris, J.D.; Gruhn, B.; Klingebiel, T.; Parasole, R.; Linderkamp, C.; Flotho, C.; Petit, A.; et al. Effect of Blinatumomab vs Chemotherapy on Event-Free Survival Among Children with High-risk First-Relapse B-Cell Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. *JAMA* **2021**, *325*, 843–854. [CrossRef]
10. Sun, W.; Malvar, J.; Sposto, R.; Verma, A.; Wilkes, J.J.; Dennis, R.; Heym, K.; Laetsch, T.W.; Widener, M.; Rheingold, S.R.; et al. Outcome of children with multiply relapsed B-cell acute lymphoblastic leukemia: A therapeutic advances in childhood leukemia & lymphoma study. *Leukemia* **2018**, *32*, 2316–2325. [CrossRef]
11. Jackson, R.K.; Liebich, M.; Berry, P.; Errington, J.; Liu, J.; Parker, C.; Moppett, J.; Samarasinghe, S.; Hough, R.; Rowntree, C.; et al. Impact of dose and duration of therapy on dexamethasone pharmacokinetics in childhood acute lymphoblastic leukaemia—A report from the UKALL 2011 trial. *Eur. J. Cancer* **2019**, *120*, 75–85. [CrossRef]
12. Teachey, D.T.; Devidas, M.; Wood, B.L.; Chen, Z.; Hayashi, R.J.; Hermiston, M.L.; Annett, R.D.; Archer, J.H.; Asselin, B.L.; August, K.J.; et al. Children's Oncology Group Trial AALL1231: A Phase III Clinical Trial Testing Bortezomib in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia and Lymphoma. *J. Clin. Oncol.* **2022**, *40*, 2106–2118. [CrossRef]
13. Winter, S.S.; Dunsmore, K.P.; Devidas, M.; Wood, B.L.; Esiashvili, N.; Chen, Z.; Eisenberg, N.; Briegel, N.; Hayashi, R.J.; Gastier-Foster, J.M.; et al. Improved Survival for Children and Young Adults with T-Lineage Acute Lymphoblastic Leukemia: Results From the Children's Oncology Group AALL0434 Methotrexate Randomization. *J. Clin. Oncol.* **2018**, *36*, 2926–2934. [CrossRef] [PubMed]
14. Kirkwood, A.A.; Goulden, N.; Moppett, J.; Samarasinghe, S.; Mee, J.; Hough, R.; Kearns, P.R.; Lawson, S.; Rowntree, C.J.; Vora, A. High Dose Methotrexate Does Not Reduce the Risk of CNS Relapse in Children and Young Adults with Acute Lymphoblastic Leukaemia and Lymphoblastic Lymphoma. Results of the Randomised Phase III Study UKALL 2011. *Blood* **2022**, *140* (Suppl. 1), 516–518. [CrossRef]
15. Vrooman, L.M.; Blonquist, T.M.; Harris, M.H.; Stevenson, K.E.; Place, A.E.; Hunt, S.K.; O'brien, J.E.; Asselin, B.L.; Athale, U.H.; Clavell, L.A.; et al. Refining risk classification in childhood B acute lymphoblastic leukemia: Results of DFCI ALL Consortium Protocol 05-001. *Blood Adv.* **2018**, *2*, 1449–1458. [CrossRef] [PubMed]
16. Borowitz, M.J.; Wood, B.L.; Devidas, M.; Loh, M.L.; Raetz, E.A.; Salzer, W.L.; Nachman, J.B.; Carroll, A.J.; Heerema, N.A.; Gastier-Foster, J.M.; et al. Prognostic significance of minimal residual disease in high risk B-ALL: A report from Children's Oncology Group study AALL0232. *Blood* **2015**, *126*, 964–971. [CrossRef] [PubMed]
17. Kloos, R.Q.; Pieters, R.; Jumelet, F.M.; De Groot-Kruseman, H.A.; Bos, C.V.D.; Van Der Sluis, I.M. Individualized Asparaginase Dosing in Childhood Acute Lymphoblastic Leukemia. *J. Clin. Oncol.* **2020**, *38*, 715–724. [CrossRef]
18. Mondelaers, V.; Suciu, S.; De Moerloose, B.; Ferster, A.; Mazingue, F.; Plat, G.; Yakouben, K.; Uyttebroeck, A.; Lutz, P.; Costa, V.; et al. Prolonged versus standard native E. coli asparaginase therapy in childhood acute lymphoblastic leukemia and non-Hodgkin lymphoma: Final results of the EORTC-CLG randomized phase III trial 58951. *Haematologica* **2017**, *102*, 1727–1738. [CrossRef]
19. Pieters, R.; de Groot-Kruseman, H.; Van der Velden, V.; Fiocco, M.; van den Berg, H.; de Bont, E.; Egeler, R.M.; Hoogerbrugge, P.; Kaspers, G.; Van der Schoot, E.; et al. Successful Therapy Reduction and Intensification for Childhood Acute Lymphoblastic Leukemia Based on Minimal Residual Disease Monitoring: Study ALL10 From the Dutch Childhood Oncology Group. *J. Clin. Oncol.* **2016**, *34*, 2591–2601. [CrossRef] [PubMed]
20. Tram Henriksen, L.; Gottschalk Hojfeldt, S.; Schmiegelow, K.; Frandsen, T.L.; Skov Wehner, P.; Schrøder, H.; Klug Albertsen, B.; Nordic Society of Pediatric Hematology and Oncology, NOPHO Group. Prolonged first-line PEG-asparaginase treatment in pediatric acute lymphoblastic leukemia in the NOPHO ALL2008 protocol-Pharmacokinetics and antibody formation. *Pediatr. Blood Cancer* **2017**, *64*, e26686. [CrossRef]
21. Vora, A.; Goulden, N.; Mitchell, C.; Hancock, J.; Hough, R.; Rowntree, C.; Moorman, A.V.; Wade, R. Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): A randomised controlled trial. *Lancet Oncol.* **2014**, *15*, 809–818. [CrossRef]
22. Vrooman, L.M.; Blonquist, T.M.; Stevenson, K.E.; Supko, J.G.; Hunt, S.K.; Cronholm, S.M.; Koch, V.; Kay-Green, S.; Athale, U.H.; Clavell, L.A.; et al. Efficacy and Toxicity of Pegaspargase and Calaspargase Pegol in Childhood Acute Lymphoblastic Leukemia: Results of DFCI 11-001. *J. Clin. Oncol.* **2021**, *39*, 3496–3505. [CrossRef] [PubMed]
23. Smith, M.; Arthur, D.; Camitta, B.; Carroll, A.J.; Crist, W.; Gaynon, P.; Gelber, R.; Heerema, N.; Korn, E.L.; Link, M.; et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. *J. Clin. Oncol.* **1996**, *14*, 18–24. [CrossRef] [PubMed]
24. Campana, D. Minimal residual disease in acute lymphoblastic leukemia. *Hematol. Am. Soc. Hematol. Educ. Program* **2010**, *2010*, 7–12. [CrossRef] [PubMed]

25. Schultz, K.R.; Pullen, D.J.; Sather, H.N.; Shuster, J.J.; Devidas, M.; Borowitz, M.J.; Carroll, A.J.; Heerema, N.A.; Rubnitz, J.E.; Loh, M.L.; et al. Risk- and response-based classification of childhood B-precursor acute lymphoblastic leukemia: A combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG). *Blood* **2007**, *109*, 926–935. [CrossRef]
26. Gupta, S.; Devidas, M.; Loh, M.L.; Raetz, E.A.; Chen, S.; Wang, C.; Brown, P.; Carroll, A.J.; Heerema, N.A.; Gastier-Foster, J.M. Flow-cytometric vs. -morphologic assessment of remission in childhood acute lymphoblastic leukemia: A report from the Children's Oncology Group (COG). *Leukemia* **2018**, *32*, 1370–1379. [CrossRef]
27. Pui, C.-H.; Pei, D.; Raimondi, S.C.; Coustan-Smith, E.; Jeha, S.; Cheng, C.; Bowman, W.P.; Sandlund, J.T.; Ribeiro, R.C.; Rubnitz, J.E.; et al. Clinical impact of minimal residual disease in children with different subtypes of acute lymphoblastic leukemia treated with Response-Adapted therapy. *Leukemia* **2017**, *31*, 333–339. [CrossRef]
28. Pui, C.-H.; Pei, D.; Coustan-Smith, E.; Jeha, S.; Cheng, C.; Bowman, W.P.; Sandlund, J.T.; Ribeiro, R.C.; Rubnitz, J.E.; Inaba, H.; et al. Clinical utility of sequential minimal residual disease measurements in the context of risk-based therapy in childhood acute lymphoblastic leukaemia: A prospective study. *Lancet Oncol.* **2015**, *16*, 465–474. [CrossRef]
29. O'Connor, D.; Moorman, A.V.; Wade, R.; Hancock, J.; Tan, R.M.; Bartram, J.; Moppett, J.; Schwab, C.; Patrick, K.; Harrison, C.J.; et al. Use of Minimal Residual Disease Assessment to Redefine Induction Failure in Pediatric Acute Lymphoblastic Leukemia. *J. Clin. Oncol.* **2017**, *35*, 660–667. [CrossRef]
30. Sekiya, Y.; Xu, Y.; Muramatsu, H.; Okuno, Y.; Narita, A.; Suzuki, K.; Wang, X.; Kawashima, N.; Sakaguchi, H.; Yoshida, N.; et al. Clinical utility of next-generation sequencing-based minimal residual disease in paediatric B-cell acute lymphoblastic leukaemia. *Br. J. Haematol.* **2017**, *176*, 248–257. [CrossRef]
31. Faham, M.; Zheng, J.; Moorhead, M.; Carlton, V.E.H.; Stow, P.; Coustan-Smith, E.; Pui, C.-H.; Campana, D. Deep-sequencing approach for minimal residual disease detection in acute lymphoblastic leukemia. *Blood* **2012**, *120*, 5173–5180. [CrossRef] [PubMed]
32. Pulsipher, M.A.; Han, X.; Maude, S.L.; Laetsch, T.W.; Qayed, M.; Rives, S.; Boyer, M.W.; Hiramatsu, H.; Yanik, G.A.; Driscoll, T.; et al. Next-Generation Sequencing of Minimal Residual Disease for Predicting Relapse after Tisagenlecleucel in Children and Young Adults with Acute Lymphoblastic Leukemia. *Blood Cancer Discov.* **2022**, *3*, 66–81. [CrossRef] [PubMed]
33. Wood, B.; Wu, D.; Crossley, B.; Dai, Y.; Williamson, D.; Gawad, C.; Borowitz, M.J.; Devidas, M.; Maloney, K.W.; Larsen, E.; et al. Measurable residual disease detection by high-throughput sequencing improves risk stratification for pediatric B-ALL. *Blood* **2018**, *131*, 1350–1359. [CrossRef] [PubMed]
34. Pulsipher, M.A.; Carlson, C.; Langholz, B.; Wall, D.A.; Schultz, K.R.; Bunin, N.; Kirsch, I.; Gastier-Foster, J.M.; Borowitz, M.; Desmarais, C.; et al. IgH-V(D)J NGS-MRD measurement pre- and early post-allotransplant defines very low- and very high-risk ALL patients. *Blood* **2015**, *125*, 3501–3508. [CrossRef] [PubMed]
35. Borowitz, M.J.; Pullen, D.J.; Shuster, J.J.; Viswanatha, D.; Montgomery, K.; Willman, C.L.; Camitta, B. Minimal residual disease detection in childhood precursor-B-cell acute lymphoblastic leukemia: Relation to other risk factors. A Children's Oncology Group study. *Leukemia* **2003**, *17*, 1566–1572. [CrossRef]
36. Schrappe, M.; Hunger, S.P.; Pui, C.-H.; Saha, V.; Gaynon, P.S.; Baruchel, A.; Conter, V.; Otten, J.; Ohara, A.; Versluys, A.B.; et al. Outcomes after Induction Failure in Childhood Acute Lymphoblastic Leukemia. *N. Engl. J. Med.* **2012**, *366*, 1371–1381. [CrossRef]
37. Jeha, S.; Choi, J.; Roberts, K.G.; Pei, D.; Coustan-Smith, E.; Inaba, H.; Rubnitz, J.E.; Ribeiro, R.C.; Gruber, T.A.; Raimondi, S.C.; et al. Clinical Significance of Novel Subtypes of Acute Lymphoblastic Leukemia in the Context of Minimal Residual Disease–Directed Therapy. *Blood Cancer Discov.* **2021**, *2*, 326–337. [CrossRef]
38. O'Connor, D.; Enshaei, A.; Bartram, J.; Hancock, J.; Harrison, C.J.; Hough, R.; Samarasinghe, S.; Schwab, C.; Vora, A.; Wade, R.; et al. Genotype-Specific Minimal Residual Disease Interpretation Improves Stratification in Pediatric Acute Lymphoblastic Leukemia. *J. Clin. Oncol.* **2018**, *36*, 34–43. [CrossRef]
39. Brady, S.W.; Roberts, K.G.; Gu, Z.; Shi, L.; Pounds, S.; Pei, D.; Cheng, C.; Dai, Y.; Devidas, M.; Qu, C.; et al. The genomic landscape of pediatric acute lymphoblastic leukemia. *Nat. Genet.* **2022**, *54*, 1376–1389. [CrossRef]
40. Lee, S.H.R.; Yang, W.; Gocho, Y.; John, A.; Rowland, L.; Smart, B.; Williams, H.; Maxwell, D.; Hunt, J.; Yang, W.; et al. Pharmacotypes across the genomic landscape of pediatric acute lymphoblastic leukemia and impact on treatment response. *Nat. Med.* **2023**, *29*, 170–179. [CrossRef]
41. Letai, A. Functional Precision Medicine: Putting Drugs on Patient Cancer Cells and Seeing What Happens. *Cancer Discov.* **2022**, *12*, 290–292. [CrossRef] [PubMed]
42. Frismantas, V.; Dobay, M.P.; Rinaldi, A.; Tchinda, J.; Dunn, S.H.; Kunz, J.; Richter-Pechanska, P.; Marovca, B.; Pail, O.; Jenni, S.; et al. Ex vivo drug response profiling detects recurrent sensitivity patterns in drug-resistant acute lymphoblastic leukemia. *Blood* **2017**, *129*, e26–e37. [CrossRef] [PubMed]
43. Salzer, W.L.; Burke, M.J.; Devidas, M.; Chen, S.; Gore, L.; Larsen, E.C.; Borowitz, M.; Wood, B.; Heerema, N.A.; Carroll, A.J.; et al. Toxicity associated with intensive postinduction therapy incorporating clofarabine in the very high-risk stratum of patients with newly diagnosed high-risk B-lymphoblastic leukemia: A report from the Children's Oncology Group study AALL1131. *Cancer* **2018**, *124*, 1150–1159. [CrossRef]

44. Burke, M.J.; Salzer, W.L.; Devidas, M.; Dai, Y.; Gore, L.; Hilden, J.M.; Larsen, E.; Rabin, K.R.; Zweidler-McKay, P.A.; Borowitz, M.J.; et al. Replacing cyclophosphamide/cytarabine/mercaptopurine with cyclophosphamide/etoposide during consolidation/delayed intensification does not improve outcome for pediatric B-cell acute lymphoblastic leukemia: A report from the COG. *Haematologica* **2019**, *104*, 986–992. [CrossRef] [PubMed]
45. O'Brien, M.M.; Ji, L.; Shah, N.N.; Rheingold, S.R.; Bhojwani, D.; Yuan, C.M.; Xu, X.; Yi, J.S.; Joanna, S.; Harris, A.C.; et al. Phase II Trial of Inotuzumab Ozogamicin in Children and Adolescents with Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia: Children's Oncology Group Protocol AALL1621. *J. Clin. Oncol.* **2022**, *40*, 956–967. [CrossRef] [PubMed]
46. Brivio, E.; Locatelli, F.; Lopez-Yurda, M.; Malone, A.; Díaz-De-Heredia, C.; Bielorai, B.; Rossig, C.; van der Velden, V.H.J.; Ammerlaan, A.C.J.; Thano, A.; et al. A phase 1 study of inotuzumab ozogamicin in pediatric relapsed/refractory acute lymphoblastic leukemia (ITCC-059 study). *Blood* **2021**, *137*, 1582–1590. [CrossRef]
47. Bhojwani, D.; Sposto, R.; Shah, N.N.; Rodriguez, V.; Yuan, C.; Stetler-Stevenson, M.; O'brien, M.M.; McNeer, J.L.; Quereshi, A.; Cabannes, A.; et al. Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *Leukemia* **2019**, *33*, 884–892. [CrossRef]
48. Brown, P.A.; Ji, L.; Xu, X.; Devidas, M.; Hogan, L.E.; Borowitz, M.J.; Raetz, E.A.; Zugmaier, G.; Sharon, E.; Bernhardt, M.B.; et al. Effect of postreinduction therapy consolidation with blinatumomab vs chemotherapy on disease-free survival in children, adolescents, and young adults with first relapse of B-cell acute lymphoblastic leukemia: A randomized clinical trial. *JAMA* **2021**, *325*, 833–842. [CrossRef]
49. Keating, A.K.; Gossai, N.; Phillips, C.L.; Maloney, K.; Campbell, K.; Doan, A.; Bhojwani, D.; Burke, M.J.; Verneris, M.R. Reducing minimal residual disease with blinatumomab prior to HCT for pediatric patients with acute lymphoblastic leukemia. *Blood Adv.* **2019**, *3*, 1926–1929. [CrossRef]
50. Von Stackelberg, A.; Locatelli, F.; Zugmaier, G.; Handgretinger, R.; Trippett, T.M.; Rizzari, C.; Bader, P.; O'brien, M.M.; Brethon, B.; Bhojwani, D.; et al. Phase I/Phase II Study of Blinatumomab in Pediatric Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia. *J. Clin. Oncol.* **2016**, *34*, 4381–4389. [CrossRef]
51. Place, M.A.E.; Karol, S.E.; Forlenza, C.J.; Gambart, M.; Cooper, D.T.M.; Fraser, M.C.; Cario, G.; O'Brien, M.M.; Gerber, N.U.; Barnette, P.; et al. Pediatric Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia Harboring Heterogeneous Genomic Profiles Respond to Venetoclax in Combination with Chemotherapy. *Blood* **2020**, *136* (Suppl. 1), 37–38. [CrossRef]
52. Pullarkat, V.A.; Lacayo, N.J.; Jabbour, E.; Rubnitz, J.E.; Bajel, A.; Laetsch, T.W.; Leonard, J.; Colace, S.I.; Khaw, S.L.; Fleming, S.A.; et al. Venetoclax and Navitoclax in Combination with Chemotherapy in Patients with Relapsed or Refractory Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma. *Cancer Discov.* **2021**, *11*, 1440–1453. [CrossRef]
53. Krivtsov, A.V.; Evans, K.; Gadrey, J.Y.; Eschle, B.K.; Hatton, C.; Uckelmann, H.J.; Ross, K.N.; Perner, F.; Olsen, S.N.; Pritchard, T.; et al. A Menin-MLL Inhibitor Induces Specific Chromatin Changes and Eradicates Disease in Models of MLL-Rearranged Leukemia. *Cancer Cell* **2021**, *36*, 660–673.e11. [CrossRef] [PubMed]
54. Grembecka, J.; He, S.; Shi, A.; Purohit, T.; Muntean, A.G.; Sorenson, R.J.; Showalter, H.D.; Murai, M.J.; Belcher, A.M.; Hartley, T.; et al. Menin-MLL inhibitors reverse oncogenic activity of MLL fusion proteins in leukemia. *Nat. Chem. Biol.* **2012**, *8*, 277–284. [CrossRef] [PubMed]
55. Raetz, E.A.; Borowitz, M.J.; Devidas, M.; Linda, S.B.; Hunger, S.P.; Winick, N.J.; Camitta, B.C.; Gaynon, P.S.; Carroll, W.L. Reinduction platform for children with first marrow relapse of acute lymphoblastic Leukemia: A Children's Oncology Group Study. *J. Clin. Oncol.* **2008**, *26*, 3971–3978. [CrossRef] [PubMed]
56. Snowden, J.A.; Sánchez-Ortega, I.; Corbacioglu, S.; Basak, G.W.; Chabannon, C.; de la Camara, R.; Dolstra, H.; Duarte, R.F.; Glass, B.; Greco, R.; et al. Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: Current practice in Europe, 2022. *Bone Marrow Transplant.* **2022**, *57*, 1217–1239. [CrossRef]
57. Kanate, A.S.; Majhail, N.S.; Savani, B.N.; Bredeson, C.; Champlin, R.E.; Crawford, S.; Giralt, S.A.; LeMaistre, C.F.; Marks, D.I.; Omel, J.L.; et al. Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy. *Biol. Blood Marrow Transplant.* **2020**, *26*, 1247–1256. [CrossRef]
58. Kansagra, A.J.; Frey, N.V.; Bar, M.; Laetsch, T.W.; Carpenter, P.A.; Savani, B.N.; Heslop, H.E.; Bollard, C.M.; Komanduri, K.V.; Gastineau, D.A.; et al. Clinical utilization of Chimeric Antigen Receptor T-cells (CAR-T) in B-cell acute lymphoblastic leukemia (ALL)–an expert opinion from the European Society for Blood and Marrow Transplantation (EBMT) and the American Society for Blood and Marrow Transplantation (ASBMT). *Bone Marrow Transplant.* **2019**, *54*, 1868–1880. [CrossRef]
59. Ifversen, M.; Meisel, R.; Sedlacek, P.; Kalwak, K.; Sisinni, L.; Hutt, D.; Lehrnbecher, T.; Balduzzi, A.; Diesch, T.; Jarisch, A.; et al. Supportive Care During Pediatric Hematopoietic Stem Cell Transplantation: Prevention of Infections. A Report From Workshops on Supportive Care of the Paediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT). *Front. Pediatr.* **2021**, *9*, 705179. [CrossRef]
60. Wood, W.A.; Lee, S.J.; Brazauskas, R.; Wang, Z.; Aljurf, M.D.; Ballen, K.K.; Buchbinder, D.K.; Dehn, J.; Freytes, C.O.; Lazarus, H.M.; et al. Survival Improvements Following Myeloablative Allogeneic Hematopoietic Cell Transplantation For Acute Lymphoblastic Leukemia In Adolescents and Young Adults Have Been Comparable To Younger Children: A Study From The Cibmtr. *Blood* **2013**, *122*, 554. [CrossRef]
61. Passweg, J.R.; Baldomero, H.; Chabannon, C.; Basak, G.W.; de La Cámara, R.; Corbacioglu, S.; Dolstra, H.; Duarte, R.; Glass, B.; Greco, R.; et al. Hematopoietic cell transplantation and cellular therapy survey of the EBMT: Monitoring of activities and trends over 30 years. *Bone Marrow Transplant.* **2021**, *56*, 1651–1664. [CrossRef] [PubMed]

62. Phelan, R.; Chen, M.; Bupp, C.; Bolon, Y.-T.; Broglie, L.; Brunner-Grady, J.; Burns, L.J.; Chhabra, S.; Christianson, D.; Cusatis, R.; et al. Updated Trends in Hematopoietic Cell Transplantation in the United States with an Additional Focus on Adolescent and Young Adult Transplantation Activity and Outcomes. *Transplant. Cell. Ther.* **2022**, *28*, 409.e1–409.e10. [CrossRef] [PubMed]
63. Mamcarz, E.; Madden, R.; Qudeimat, A.; Srinivasan, A.; Talleur, A.; Sharma, A.; Suliman, A.; Maron, G.; Sunkara, A.; Kang, G.; et al. Improved survival rate in T-cell depleted haploidentical hematopoietic cell transplantation over the last 15 years at a single institution. *Bone Marrow Transplant.* **2019**, *55*, 929–938. [CrossRef] [PubMed]
64. Nava, T.; Ansari, M.; Dalle, J.-H.; De Heredia, C.D.; Güngör, T.; Trigoso, E.; Falkenberg, U.; Bertaina, A.; Gibson, B.; Jarisch, A.; et al. Supportive care during pediatric hematopoietic stem cell transplantation: Beyond infectious diseases. A report from workshops on supportive care of the Pediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant.* **2020**, *55*, 1126–1136. [CrossRef] [PubMed]
65. Naik, S.; Triplett, B.M. Selective depletion of naïve T cells by targeting CD45RA. *Front. Oncol.* **2023**, *12*, 1009143. [CrossRef]
66. Raghunandan, S.; Gorfinkel, L.; Graiser, M.; Bratrude, B.; Betz, K.; Suessmuth, Y.; Gillespie, S.; Westbrook, A.L.; Williams, K.M.; Schoettler, M.; et al. Abatacept for the Prevention of Gvhd in Pediatric and Adult Patients Receiving 7/8 HLA-Mismatched Unrelated Transplant for Hematologic Malignancies: A Real-World Analysis. *Blood* **2022**, *140* (Suppl. 1), 7653–7655. [CrossRef]
67. Przepiorka, D.; Le, R.Q.; Ionan, A.; Li, R.-J.; Wang, Y.-H.; Gudi, R.; Mitra, S.; Vallejo, J.; Okusanya, O.O.; Ma, L.; et al. FDA Approval Summary: Belumosudil for Adult and Pediatric Patients 12 Years and Older with Chronic GvHD after Two or More Prior Lines of Systemic Therapy. *Clin. Cancer Res.* **2022**, *28*, 2488–2492. [CrossRef]
68. Locatelli, F.; Kang, H.J.; Bruno, B.; Gandemer, V.; Rialland, F.; Faraci, M.; Takahashi, Y.; Koh, K.; Bittencourt, H.; Cleary, G.; et al. Ruxolitinib in Pediatric Patients with Treatment-*Naïve* or Steroid-Refractory Acute Graft-Versus-Host Disease: Primary Findings from the Phase I/II REACH4 Study. *Blood* **2022**, *140* (Suppl. 1), 1376–1378. [CrossRef]
69. Klingebiel, T.; Cornish, J.; Labopin, M.; Locatelli, F.; Darbyshire, P.; Handgretinger, R.; Balduzzi, A.; Owoc-Lempach, J.; Fagioli, F.; Or, R.; et al. Results and factors influencing outcome after fully haploidentical hematopoietic stem cell transplantation in children with very high-risk acute lymphoblastic leukemia: Impact of center size: An analysis on behalf of the Acute Leukemia and Pediatric Disease Working Parties of the European Blood and Marrow Transplant group. *Blood* **2010**, *115*, 3437–3446. [CrossRef]
70. Pérez-Martínez, A.; Ferreras, C.; Pascual, A.; Vicent, M.G.; Alonso, L.; Badell, I.; Navarro, J.M.F.; Regueiro, A.; Plaza, M.; Hurtado, J.M.P.; et al. Haploidentical transplantation in high-risk pediatric leukemia: A retrospective comparative analysis on behalf of the Spanish working Group for bone marrow transplantation in children (GETMON) and the Spanish Grupo for hematopoietic transplantation (GETH). *Am. J. Hematol.* **2020**, *95*, 28–37. [CrossRef]
71. Haroun, E.; Agrawal, K.; Leibovitch, J.; Kassab, J.; Zoghbi, M.; Dutta, D.; Lim, S.H. Chronic graft-versus-host disease in pediatric patients: Differences and challenges. *Blood Rev.* 2023; 101054, *in press*. [CrossRef] [PubMed]
72. Handgretinger, R. New Approaches to Graft Engineering for Haploidentical Bone Marrow Transplantation. *Semin. Oncol.* **2012**, *39*, 664–673. [CrossRef]
73. Auletta, J.J.; Kou, J.; Chen, M.; Bolon, Y.-T.; Broglie, L.; Bupp, C.; Christianson, D.; Cusatis, R.N.; Devine, S.M.; Eapen, M.; et al. Real-World Data Showing Trends and Outcomes by Race and Ethnicity in Allogeneic Hematopoietic Cell Transplantation: A Report from the Center for International Blood and Marrow Transplant Research. *Transplant. Cell. Ther.* 2023; *in press*. [CrossRef] [PubMed]
74. Verneris, M.; Burke, M.; He, W.; Davies, S.; Eapen, M.; Wagner, J. Impact Of Reduced Intensity Conditioning (RIC) in Pediatric Acute Lymphoblastic Leukemia (ALL): A Report From the CIBMTR. *Biol. Blood Marrow Transplant.* **2009**, *15* (Suppl. 2), 28. [CrossRef]
75. Gatza, E.; Reddy, P.; Choi, S.W. Prevention and Treatment of Acute Graft-versus-Host Disease in Children, Adolescents, and Young Adults. *Biol. Blood Marrow Transplant.* **2020**, *26*, e101–e112. [CrossRef] [PubMed]
76. Groll, A.H.; Pana, D.; Lanternier, F.; Mesini, A.; Ammann, R.A.; Averbuch, D.; Castagnola, E.; Cesaro, S.; Engelhard, D.; Garcia-Vidal, C.; et al. 8th European Conference on Infections in Leukaemia: 2020 guidelines for the diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or post-haematopoietic cell transplantation. *Lancet Oncol.* **2021**, *22*, e254–e269. [CrossRef]
77. Lehrnbecher, T.; Averbuch, D.; Castagnola, E.; Cesaro, S.; Ammann, R.A.; Garcia-Vidal, C.; Kanerva, J.; Lanternier, F.; Mesini, A.; Mikulska, M.; et al. 8th European Conference on Infections in Leukaemia: 2020 guidelines for the use of antibiotics in paediatric patients with cancer or post-haematopoietic cell transplantation. *Lancet Oncol.* **2021**, *22*, e270–e280. [CrossRef]
78. Carpenter, P.A.; Kang, H.J.; Yoo, K.H.; Zecca, M.; Cho, B.; Lucchini, G.; Nemecek, E.R.; Schultz, K.R.; Stepensky, P.; Chaudhury, S.; et al. Ibrutinib Treatment of Pediatric Chronic Graft-versus-Host Disease: Primary Results from the Phase 1/2 iMAGINE Study. *Transplant. Cell. Ther.* **2022**, *28*, 771.e1–771.e10. [CrossRef]
79. Bader, P.; Kreyenberg, H.; Henze, G.H.; Eckert, C.; Reising, M.; Willasch, A.; Barth, A.; Borkhardt, A.; Peters, C.; Handgretinger, R.; et al. Prognostic Value of Minimal Residual Disease Quantification Before Allogeneic Stem-Cell Transplantation in Relapsed Childhood Acute Lymphoblastic Leukemia: The ALL-REZ BFM Study Group. *J. Clin. Oncol.* **2009**, *27*, 377–384. [CrossRef]
80. Pulsipher, M.A.; Langholz, B.; Wall, D.A.; Schultz, K.R.; Bunin, N.; Carroll, W.; Raetz, E.; Gardner, S.; Goyal, R.K.; Gastier-Foster, J.; et al. Risk factors and timing of relapse after allogeneic transplantation in pediatric ALL: For whom and when should interventions be tested? *Bone Marrow Transplant.* **2015**, *50*, 1173–1179. [CrossRef]

81. Curran, K.J.; Margossian, S.P.; Kernan, N.A.; Silverman, L.B.; Williams, D.A.; Shukla, N.; Kobos, R.; Forlenza, C.J.; Steinherz, P.; Prockop, S.; et al. Toxicity and response after CD19-specific CAR T-cell therapy in pediatric/young adult relapsed/refractory B-ALL. *Blood* **2019**, *134*, 2361–2368. [CrossRef]
82. Gardner, R.A.; Finney, O.; Annesley, C.; Brakke, H.; Summers, C.; Leger, K.; Bleakley, M.; Brown, C.; Mgebroff, S.; Kelly-Spratt, K.S.; et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. *Blood* **2017**, *129*, 3322–3331. [CrossRef]
83. Laetsch, T.W.; Maude, S.L.; Rives, S.; Hiramatsu, H.; Bittencourt, H.; Bader, P.; Baruchel, A.; Boyer, M.; De Moerloose, B.; Qayed, M.; et al. Three-Year Update of Tisagenlecleucel in Pediatric and Young Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia in the ELIANA Trial. *J. Clin. Oncol.* **2023**, *41*, 1664–1669. [CrossRef] [PubMed]
84. Shah, N.N.; Lee, D.W.; Yates, B.; Yuan, C.M.; Shalabi, H.; Martin, S.; Wolters, P.L.; Steinberg, S.M.; Baker, E.H.; Delbrook, C.P.; et al. Long-Term Follow-Up of CD19-CAR T-Cell Therapy in Children and Young Adults with B-ALL. *J. Clin. Oncol.* **2021**, *39*, 1650–1659. [CrossRef]
85. Talleur, A.C.; Qudeimat, A.; Métais, J.-Y.; Langfitt, D.; Mamcarz, E.; Crawford, J.C.; Huang, S.; Cheng, C.; Hurley, C.; Madden, R.; et al. Preferential expansion of CD8+ CD19-CAR T cells postinfusion and the role of disease burden on outcome in pediatric B-ALL. *Blood Adv.* **2022**, *6*, 5737–5749. [CrossRef] [PubMed]
86. Maude, S.L.; Frey, N.; Shaw, P.A.; Aplenc, R.; Barrett, D.M.; Bunin, N.J.; Chew, A.; Gonzalez, V.E.; Zheng, Z.; Lacey, S.F.; et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N. Engl. J. Med.* **2014**, *371*, 1507–1517. [CrossRef]
87. Bader, P.; Rossig, C.; Hutter, M.; Ayuk, F.A.; Baldus, C.D.; Buecklein, V.L.; Bonig, H.; Cario, G.; Einsele, H.; Holtick, U.; et al. CD19-CAR-T Cells Are Effective and Safe Treatment of Post-Transplant Relapse in Pediatric and Young Adult Patients with B-Lineage ALL: Real-World Data from Germany. *Blood* **2022**, *140* (Suppl. 1), 10407–10409. [CrossRef]
88. Pasquini, M.C.; Hu, Z.-H.; Curran, K.; Laetsch, T.; Locke, F.; Rouce, R.; Pulsipher, M.A.; Phillips, C.L.; Keating, A.; Frigault, M.J.; et al. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. *Blood Adv.* **2020**, *4*, 5414–5424. [CrossRef] [PubMed]
89. Ravich, J.W.; Huang, S.; Zhou, Y.; Brown, P.; Pui, C.-H.; Inaba, H.; Cheng, C.; Gottschalk, S.; Triplett, B.M.; Bonifant, C.L.; et al. Impact of High Disease Burden on Survival in Pediatric Patients with B-ALL Treated with Tisagenlecleucel. *Transplant. Cell. Ther.* **2022**, *28*, 73.e1–73.e9. [CrossRef] [PubMed]
90. Schultz, L.M.; Baggott, C.; Prabhu, S.; Pacenta, H.L.; Phillips, C.L.; Rossoff, J.; Stefanski, H.E.; Talano, J.-A.; Moskop, A.; Margossian, S.P.; et al. Disease Burden Affects Outcomes in Pediatric and Young Adult B-Cell Lymphoblastic Leukemia After Commercial Tisagenlecleucel: A Pediatric Real-World Chimeric Antigen Receptor Consortium Report. *J. Clin. Oncol.* **2022**, *40*, 945–955. [CrossRef]
91. Gardner, R.; Wu, D.; Cherian, S.; Fang, M.; Hanafi, L.-A.; Finney, O.; Smithers, H.; Jensen, M.C.; Riddell, S.R.; Maloney, D.G.; et al. Acquisition of a CD19-negative myeloid phenotype allows immune escape of MLL-rearranged B-ALL from CD19 CAR-T-cell therapy. *Blood* **2016**, *127*, 2406–2410. [CrossRef]
92. Mo, G.; Wang, H.-W.; Talleur, A.C.; Shahani, S.A.; Yates, B.; Shalabi, H.; Douvas, M.G.; Calvo, K.R.; Shern, J.F.; Chaganti, S.; et al. Diagnostic approach to the evaluation of myeloid malignancies following CAR T-cell therapy in B-cell acute lymphoblastic leukemia. *J. Immunother. Cancer* **2020**, *8*, e001563. [CrossRef]
93. Schultz, L.M.; Eaton, A.; Baggott, C.; Rossoff, J.; Prabhu, S.; Keating, A.K.; Krupski, C.; Pacenta, H.; Philips, C.L.; Talano, J.-A.; et al. Outcomes After Nonresponse and Relapse Post-Tisagenlecleucel in Children, Adolescents, and Young Adults with B-Cell Acute Lymphoblastic Leukemia. *J. Clin. Oncol.* **2023**, *41*, 354–363. [CrossRef] [PubMed]
94. Molina, J.C.; Steinberg, S.M.; Yates, B.; Lee, D.W.; Little, L.; Mackall, C.L.; Shalabi, H.; Shah, N.N. Factors Impacting Overall and Event-Free Survival following Post-Chimeric Antigen Receptor T Cell Consolidative Hematopoietic Stem Cell Transplantation. *Transplant. Cell. Ther.* **2022**, *28*, 31.e1–31.e9. [CrossRef] [PubMed]
95. Summers, C.; Wu, Q.V.; Annesley, C.; Bleakley, M.; Dahlberg, A.; Narayanaswamy, P.; Huang, W.; Voutsinas, J.; Brand, A.; Leisenring, W.; et al. Hematopoietic Cell Transplantation after CD19 Chimeric Antigen Receptor T Cell-Induced Acute Lymphoblastic Leukemia Remission Confers a Leukemia-Free Survival Advantage. *Transplant. Cell. Ther.* **2022**, *28*, 21–29. [CrossRef] [PubMed]
96. Myers, R.M.; Taraseviciute, A.; Steinberg, S.M.; Lamble, A.J.; Sheppard, J.; Yates, B.; Kovach, A.E.; Wood, B.; Borowitz, M.J.; Stetler-Stevenson, M.; et al. Blinatumomab Nonresponse and High-Disease Burden Are Associated with Inferior Outcomes After CD19-CAR for B-ALL. *J. Clin. Oncol.* **2022**, *40*, 932–944. [CrossRef] [PubMed]
97. Elizabeth, M.H.; John, C.M.; Kniya, D.; Moyer, D.; Zhou, T.; Yuan, C.M.; Wang, H.-W.; Stetler-Stevenson, M.; Mackall, C.; Fry, T.J.; et al. Efficacy of second CAR-T (CART2) infusion limited by poor CART expansion and antigen modulation. *J. Immunother. Cancer* **2022**, *10*, e004483.
98. Myers, R.M.; Devine, K.; Li, Y.; Lawrence, S.; Leahy, A.B.; Liu, H.; Vernau, L.; Callahan, C.; Baniewicz, D.; Kadauke, S.; et al. Outcomes after Reinfusion of CD19-Specific Chimeric Antigen Receptor (CAR)-Modified T Cells in Children and Young Adults with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia. *Blood* **2021**, *138* (Suppl. 1), 474. [CrossRef]
99. Galletta, T.J.; Rubinstein, J.D.; Krupski, C.; Nelson, A.S.; Khoury, R.; Dandoy, C.E.; Davies, S.M.; Phillips, C.L. Durable remissions achieved with reinfusion of CD19-directed CAR-T despite failure to induce or maintain B-cell aplasia and single-center experience with reinfusion of tisagenlecleucel. *Pediatr. Blood Cancer* **2023**, *70*, e30271. [CrossRef]

100. Boyer, M.W.; Chaudhury, S.; Davis, K.L.; Driscoll, T.A.; Grupp, S.A.; Hermiston, M.; John, S.; Keating, A.K.; Kovacs, C.; Magley, A.; et al. HESTER: A Phase II Study Evaluating Efficacy and Safety of Tisagenlecleucel Reinfusion in Pediatric and Young Adult Patients with Acute Lymphoblastic Leukemia Experiencing Loss of B-Cell Aplasia. *Blood* **2020**, *136* (Suppl. 1), 23–24. [CrossRef]
101. Myers, R.M.; DiNofia, A.M.; Li, Y.; Diorio, C.; Aplenc, R.; Baniewicz, D.; Brogdon, J.L.; Callahan, C.; Engels, B.; Fraietta, J.A.; et al. CD22-Targeted CAR-Modified T-Cells Safely Induce Remissions in Children and Young Adults with Relapsed, CD19-Negative B-ALL after Treatment with CD19-Targeted CAR T-Cells. *Blood* **2022**, *140* (Suppl. 1), 2376–2377. [CrossRef]
102. Li, A.M.; Hucks, G.E.; Dinofia, A.M.; Seif, A.E.; Teachey, D.T.; Baniewicz, D.; Callahan, C.; Fasano, C.; McBride, B.; Gonzalez, V.; et al. Checkpoint Inhibitors Augment CD19-Directed Chimeric Antigen Receptor (CAR) T Cell Therapy in Relapsed B-Cell Acute Lymphoblastic Leukemia. *Blood* **2018**, *132* (Suppl. 1), 556. [CrossRef]
103. Benjamin, R.; Graham, C.; Yallop, D.; Jozwik, A.; Mirci-Danicar, O.C.; Lucchini, G.; Pinner, D.; Jain, N.; Kantarjian, H.; Boissel, N.; et al. Genome-edited, donor-derived allogeneic anti-CD19 chimeric antigen receptor T cells in paediatric and adult B-cell acute lymphoblastic leukaemia: Results of two phase 1 studies. *Lancet* **2020**, *396*, 1885–1894. [CrossRef] [PubMed]
104. Ottaviano, G.; Georgiadis, C.; Gkazi, S.A.; Syed, F.; Zhan, H.; Etuk, A.; Preece, R.; Chu, J.; Kubat, A.; Adams, S.; et al. Phase 1 clinical trial of CRISPR-engineered CAR19 universal T cells for treatment of children with refractory B cell leukemia. *Sci. Transl. Med.* **2022**, *14*, eabq3010. [CrossRef]
105. Benjamin, R.; Jain, N.; Maus, M.V.; Boissel, N.; Graham, C.; Jozwik, A.; Yallop, D.; Konopleva, M.; Frigault, M.J.; Teshima, T.; et al. UCART19, a first-in-class allogeneic anti-CD19 chimeric antigen receptor T-cell therapy for adults with relapsed or refractory B-cell acute lymphoblastic leukaemia (CALM): A phase 1, dose-escalation trial. *Lancet Haematol.* **2022**, *9*, e833–e843. [CrossRef]
106. Prinzing, B.; Zebley, C.C.; Petersen, C.T.; Fan, Y.; Anido, A.A.; Yi, Z.; Nguyen, P.; Houke, H.; Bell, M.; Haydar, D.; et al. Deleting DNMT3A in CAR T cells prevents exhaustion and enhances antitumor activity. *Sci. Transl. Med.* **2021**, *13*, eabh0272. [CrossRef] [PubMed]
107. Choe, J.H.; Watchmaker, P.B.; Simic, M.S.; Gilbert, R.D.; Li, A.W.; Krasnow, N.A.; Downey, K.M.; Yu, W.; Carrera, D.A.; Celli, A.; et al. SynNotch-CAR T cells overcome challenges of specificity, heterogeneity, and persistence in treating glioblastoma. *Sci. Transl. Med.* **2021**, *13*, eabe7378. [CrossRef]
108. Leahy, A.B.; Devine, K.J.; Li, Y.; Liu, H.; Myers, R.M.; DiNofia, A.; Wray, L.; Rheingold, S.R.; Callahan, C.; Baniewicz, D.; et al. Impact of high-risk cytogenetics on outcomes for children and young adults receiving CD19-directed CAR T-cell therapy. *Blood* **2022**, *139*, 2173–2185. [CrossRef]
109. Laetsch, T.W.; Maude, S.L.; Balduzzi, A.; Rives, S.; Bittencourt, H.; Boyer, M.W.; Buechner, J.; De Moerloose, B.; Qayed, M.; Phillips, C.L.; et al. Tisagenlecleucel in pediatric and young adult patients with Down syndrome-associated relapsed/refractory acute lymphoblastic leukemia. *Leukemia* **2022**, *36*, 1508–1515. [CrossRef]
110. Moskop, A.; Pommert, L.; Baggott, C.; Prabhu, S.; Pacenta, H.L.; Phillips, C.L.; Rossoff, J.; Stefanski, H.E.; Talano, J.-A.; Margossian, S.P.; et al. Real-world use of tisagenlecleucel in infant acute lymphoblastic leukemia. *Blood Adv.* **2022**, *6*, 4251–4255. [CrossRef]
111. Ghorashian, S.; Jacoby, E.; De Moerloose, B.; Rives, S.; Bonney, D.; Shenton, G.; Bader, P.; Bodmer, N.; Quintana, A.M.; Herrero, B.; et al. Tisagenlecleucel therapy for relapsed or refractory B-cell acute lymphoblastic leukaemia in infants and children younger than 3 years of age at screening: An international, multicentre, retrospective cohort study. *Lancet Haematol.* **2022**, *9*, e766–e775. [CrossRef]
112. Fabrizio, V.A.; Phillips, C.L.; Lane, A.; Baggott, C.; Prabhu, S.; Egeler, E.; Mavroukakis, S.; Pacenta, H.L.; Rossoff, J.; Stefanski, H.E.; et al. Tisagenlecleucel outcomes in relapsed/refractory extramedullary ALL: A Pediatric Real World CAR Consortium Report. *Blood Adv.* **2022**, *6*, 600–610. [CrossRef] [PubMed]
113. Leahy, A.B.; Newman, H.; Li, Y.; Liu, H.; Myers, R.; DiNofia, A.; Dolan, J.G.; Callahan, C.; Baniewicz, D.; Devine, K.; et al. CD19-targeted chimeric antigen receptor T-cell therapy for CNS relapsed or refractory acute lymphocytic leukaemia: A post-hoc analysis of pooled data from five clinical trials. *Lancet Haematol.* **2021**, *8*, e711–e722. [CrossRef] [PubMed]
114. Chen, X.; Wang, Y.; Ruan, M.; Li, J.; Zhong, M.; Li, Z.; Liu, F.; Wang, S.; Chen, Y.; Liu, L.; et al. Treatment of Testicular Relapse of B-cell Acute Lymphoblastic Leukemia with CD19-specific Chimeric Antigen Receptor T Cells. *Clin. Lymphoma Myeloma Leuk.* **2020**, *20*, 366–370. [CrossRef] [PubMed]
115. Wang, T.; Tang, Y.; Cai, J.; Wan, X.; Hu, S.; Lu, X.; Xie, Z.; Qiao, X.; Jiang, H.; Shao, J.; et al. Coadministration of CD19- and CD22-Directed Chimeric Antigen Receptor T-Cell Therapy in Childhood B-Cell Acute Lymphoblastic Leukemia: A Single-Arm, Multicenter, Phase II Trial. *J. Clin. Oncol.* **2023**, *41*, 1670–1683. [CrossRef] [PubMed]