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Management of ALL in Adults: 2023 ELN Recommendations from a European Expert Panel

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Abstract:
Experts from the European Leukemia Net (ELN) working group for adult acute lymphoblastic leukemia have identified an unmet need for guidance regarding management of adult ALL from diagnosis to aftercare. The group has previously summarized their recommendations regarding diagnostic approaches, prognostic factors and assessment of ALL (cross-reference). The current recommendation summarizes clinical management. It covers treatment approaches including the use of new immunotherapies, application of MRD for treatment decisions, management of specific subgroups and challenging treatment situations as well as late effects and supportive care. The recommendation provides guidance for physicians caring for adult ALL patients which has to be complemented by regional expertise preferably provided by national academic study groups. -

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Management of Adult Acute Lymphoblastic Leukemia. 2024 ELN Recommendations from a European Expert Panel

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Abstract

Experts from the European Leukemia Net (ELN) working group for adult acute lymphoblastic leukemia have identified an unmet need for guidance regarding management of adult ALL from diagnosis to aftercare. The group has previously summarized their recommendations regarding diagnostic approaches, prognostic factors and assessment of ALL (cross-reference). The current recommendation summarizes clinical management. It covers treatment approaches including the use of new immunotherapies, application of MRD for treatment decisions, management of specific subgroups and challenging treatment situations as well as late effects and supportive care. The recommendation provides guidance for physicians caring for adult ALL patients which has to be complemented by regional expertise preferably provided by national academic study groups.

Introduction

The European Working Group for Adult is part of the European Leukemia Net (ELN) and was founded by representatives of national national academic multicenter study groups for adult acute lymphoblastic leukemia (ALL) in Europe. The group has identified an unmet need for guidance regarding management of adult ALL from diagnosis to aftercare. A previous publication covered diagnostic approaches, prognostic factors and assessment of adult ALL (cross-reference). With increasing complexity of therapeutic options there is also a need for guidance regarding clinical management. Standard therapy with pediatric-based (p-b) regimens is successful but still requires optimization. THus, treatment decisions based on minimal residual disease (MRD) require standards. Immunotherapy is integrated to an increasing extent into first line therapies whereas management of relapse is still a considerable challenge. Treatment approaches must be adapted to specific subgroups such as older patients or Ph/BCR::ABL1-positive ALL and practical management is challenging in specific situations such as secondary leukemia. Finally, the increasing number of long-term survivors highlights the need for optimized aftercare and surveillance for late-effects. Therefore, the group decided to develop an ELN Recommendation for management of ALL as published for other entities[1,2].

Methods

The panel includes 17 members representing national study groups. Members met in person and defined topics, tables, and responsibilities of co-authors (Table S1). Coauthors performed literature searches of PubMed database and considered relevant abstracts. The manuscript was reviewed by all co-authors. Formal corrections were performed by the corresponding author. Disagreements were summarized and discussed in the whole group. The whole group agreed on the final version of the manuscript. Due to rapid innovation and availability of new data together with a lack of randomized trials for many essential questions, most of the statements have an evidence level of 'expert recommendation' for clinical practice.

Induction and Consolidation Therapy in Ph- ALL

General Principles

The aim of intensive induction and consolidation therapy is to obtain a complete remission (CR) in as many patients and as early, safely, and deep as possible. CR rate in adults aged 15-18 to 55-65 years with Ph/BCR::ABL1-negative (Ph-) ALL is about 90%[3]. Roughly 5% display primary resistance after two cycles, and around 5% die early of disease- or therapy-related complications. Treatment is usually risk-adapted utilizing prognostic-factors (PF) and course of MRD for treatment decisions regarding intensity of chemotherapy, use of immunotherapies or indication for stem cell transplantation (SCT). A comprehensive diagnostic characterization is the basis for optimal management as described previously (cross-reference).

Pediatric-based Chemotherapy (p-b) in Adult ALL

In a meta-analysis 25 out of 27 reports clearly favored the p-b approach as standard of care (SoC)[4]. In patients up to 45-55 years overall survival (OS) improved to an average of 60% (Table S2). Comparison of p-b regimens versus standard Hyper-CVAD led to similar conclusions in a monocentric trial[4]. P-b therapy was particularly effective in standard risk ALL[5-8] and MRD-negative patients[5,9-11] ensuring OS around 70%[12-15]. The typical compounds are corticosteroids (especially dexamethasone), vincristine, antimetabolites (6-thiopurines, cytarabine, methotrexate) and asparaginase (ASP; pegylated or not) plus intensive supportive care, avoidance of inappropriate dose reductions/delays and a risk-adapted SCT.

Induction

For pre-phase corticosteroids are usually administered for 5-7 days; other drugs are occasionally added e.g. cyclophosphamide (CP) and intrathecal (IT) prophylaxis after

sampling of cerebrospinal fluid (CSF). First induction lasts about 4 weeks and carries the highest risk of complications, mandating for intensive support including Granulocyte-colony-stimulating factor (G-CSF), transfusions and optimal prophylaxis and management of infections. The induction backbone consists of vincristine, steroids, an anthracycline, and ASP. Dexamethasone (Dexa) is highly active, including activity in the central nervous system (CNS), but requires careful adaption of dose and schedule. If Dexamethasone is administed over a prolonged period, an increasd risk of severe infections has been observed. Therefore, shorter term application with interruptions has been implemented by several groups during induction therapy. Early high dose (HD) anthracyclines worsen myelotoxicity and mucositis[16]. A randomized trial failed to demonstrate an advantage from increasing the CP dose upfront, however fractionated doses were of benefit to patients >55 years receiving less intensive consolidation[12]. Pegylated asparaginase (PEG-ASP) provides a longer asparagine depletion (serum enzymatic activity ≥ 0,1 IU/mL detectable for 14-30 days depending on dose) compared to the native compound[4,13,14,17,18]. Compared to native ASP, the drug causes rarely severe allergic reactions. ASP in general can cause coagulopathy, thrombosis, hyperglycemia, pancreatitis and liver toxicity, this latter more frequent and of greater concern in adults than children[19,20]. It is crucial to establish a specific schedule for toxicity monitoring and management[19,20]; PEG-ASP schedule and dosing should be adapted to age, body mass index (higher toxicity if >30 kg/m^2) and hepatosteatosis (higher toxicity if positive ultrasound scan)[13,14] and to the intended duration of activity. Any other potentially hepatotoxic drugs should not be given during expected ASP activity duration, with the exception of strict clinical indication[17,21]. More recently pre-medication before use of PEG-ASP has been discussed to reduce the risk of infusion reactions which are sometimes difficult to differentiate from real allergic reactions. Any pre-medication should only be administered if drug monitoring can be offered. Otherwise, there is the risk to overlook inactivation of ASP.

The second induction/first consolidation consists usually of CP, cytarabine (AC) and mercaptopurine (MP) or HD-methotrexate (MTX) / HD-AC[22] or HD-AC/idarubicin[12]. The few patients failing to enter CR after two induction courses have highly resistant ALL and are candidates to alternative immunotherapies depending on the protocol.

Consolidation

Consolidation is administered to patients in CR. Outcome is best with rotational multidrug cycles consisting of HD-MTX and HD-AC (also useful as CNS-penetrating agent), PEG-ASP and other drugs (**Table S2**). BFM (Berlin-Frankfurt-Munster group)-based regimens include a delayed reinduction phase. The average duration of consolidation is 6 or more months, for 6-8 total courses. HD-AC, HD-MTX, etoposide and CP were essential to improve outcome of high-risk subsets and T-ALL. HD-AC (4-8 doses at 1-3 g/m^2), PEG-ASP and HD-MTX (1-1.5 g/m^2, followed by folinic acid rescue) are administered in blocks. Higher MTX dosages of 3-5 g/m^2 are used especially for high-risk patients and T-ALL. A randomized trial demonstrated an improved outcome for patients receiving consolidation MTX at 3 versus 0.5 g/m^2, however the lower dose is unusual[11]. A phase II trial in adolescents and young adults (AYA) used a lower MTX dose with weekly dose adaptions (Capizzi style)[5]. Capizzi MTX showed in pediatric trials (up to age 30) superior outcome compared to MTX 5 g/m^2 in T- but not B-ALL[23,24].

Given the heterogeneous consolidation protocols, the comparable results after adjustment for patient age and risk class, and the lack of randomized comparisons, at present no single regimen can be recommended as SoC for Ph- ALL. P-b regimens are favored. It is strongly recommended to participate in (or adopt) prospective clinical trials. Experience and established guidelines at the sites are important for adoption of distinct protocols.

Frontline Targeted Therapy of Ph- B-lineage (B-LIN) ALL

Because of the many opportunities offered by immunotherapies[25], modified regimens with targeting agents are tested to increase response, OS, and if possible, to reduce the high toxicity burden due to intensive chemotherapy and SCT. The identification of surface

markers as target for immunotherapies is therefore essential part of initial diagnosis (cross-reference). The compounds and mechanisms of action are discussed in the following.
Evidence is accumulating rapidly that immunotherapy can improve antileukemic efficacy (**Table 1)**. Anti-CD20 antibodies, the bispecific CD19/CD3-antibody Blinatumomab (Blina) and the CD22-antibody-drug conjugate Inotuzumab Ozogamicin (InO) have been integrated into frontline and salvage regimens in clinical trials.
Approximately 40% of adult B-LIN ALL express the CD20 antigen in >10-20% ALL blasts. Anti-CD20 antibodies were succesfully tested in *de novo* ALL[26,27]. In a randomized study, Rituximab (Ritux) decreased significantly the relapse risk (RR), contributing to increase the rate of SCT realization and improved OS[27]. Interestingly, Ritux treated patients developed fewer allergic reactions to ASP; yet early MRD response was not improved. A randomized trial administering Ritux irrespective of CD20 expression failed to demonstrate a benefit [28]; however, in this study only 4 doses were prescribed (vs. at least 8 doses in other trials).
Preliminary data with Blina, partly in association with InO are encouraging and confirm high rates of conversion to MRD negativity, with low RR and an improved OS at limited follow-up between 1-4 years[29-32]. A randomized trial with Blina consolidation added to a standard backbone for MRD negative ALL aged between 30-70 years indicates an advantage for Blina treated patients in terms of OS according to a preliminary analysis[33]. Thus, there is increasing evidence, that Blina likely benefits in consolidation of MRD negative and positive patients.
Overall, the use of Ritux is recommended for the management of CD20+ ALL, for at least 8 doses. Similarly, because of the favorable early results and high expectations with upfront InO and Blina in CD22+ and CD19+ B-ALL, participation into InO and Blina trials for untreated patients is recommended until results from ongoing studies are available. The concurrent use of an anti-CD20 antibody in CD20+ ALL represents SoC as well as the use of Blina in case of molecular failure.

Maintenance Therapy
Maintenance therapy is strongly recommended in all patients. Maintenance therapy was not tested in randomized trials but any attempts to omit maintenance have resulted in inferior outcomes[34,35]. Insufficient maintenance therapy significantly worsens OS[6,34]. Long-term drug exposure is probably needed to eradicate MRD[35].
MP and MTX are the main drugs in maintenance. Continued IT prophylaxis is part of most regimens. Some groups include other compounds such as the POMP regimen (MP, MTX, prednisone, vincristine)[6,12,34], while the benefit is debated. Also, data on a potential benefit of vincristine/steroid pulses in pediatric patients with Δ*IKZF1* are controversial[36,37]. The use of Dexa instead of prednisone in maintenance may lead to an increased incidence of infectious deaths[38]. Therefore, maintenance without vincristine/steroid pulses is preferred by most groups. A total treatment duration of 2-2.5 years including maintenance is recommended. Intervals of approximately 3 months are suggested for MRD testing during maintenance.

CNS-directed Prophylaxis
CNS infiltration occurs in 5-10% of adults at diagnosis. It can be classified as none (CNS-1), fewer than 5 white cells/ul (CNS-2), more than 5 white cells/ul or a cranial nerve palsy (CNS-3) but pragmatically, one should be suspicious if any blast cells are seen in the CSF[39]. It must be routinely ruled out and subsequently monitored by analysis of cytospin preparations and/or multicolor flow-cytometry (MFC) analysis of CSF obtained at or soon after the time of diagnosis. Some protocols recommend waiting until peripheral blood (PB) blasts have been cleared or are reduced below a certain cut-off to prevent the risk of ‘seeding’ the CNS from a traumatic procedure. Postponing of lumbar puncture bears on the other hand the risk to not detect initial CNS involvement which may be even more frequent in patients with high white blood cell count (WBC). Factors predicting a higher risk of initial CNS disease are T-ALL, high presenting WBC, high-risk cytogenetics such as Ph+ ALL and t(4;11)(cross-reference) [40]. MRD detection in CSF has been attempted but is not part of standard management.

All patients require CNS-prophylaxis. Cranial irradiation, IT chemotherapy and components of systemic therapy which cross the blood-brain barrier have all been used. Cranial irradiation is nowadays rarely given as prophylaxis. There are insufficient data to clearly dissect the relative values of CNS penetrating systemic therapy versus IT prophylaxis; therefore, both are recommended although the critical component is most likely the latter.

IT chemotherapy.

MTX, ARAC and steroids can all be safely given IT, and all have been used, either singly or in combination with no clear benefits to any specific IT regimen. IT medications should be given in sufficient volume to distribute well throughout the CSF. An equivalent volume of CSF to the volume of drug is usually removed prior to administration and the CSF should always be sent for analysis. The patient should remain recumbent for at least one hour[41]. It is a critical that conventional "cutting" needles carry a high risk of hygroma[42] and subdural haemorrhage; therefore atraumatic needles are recommended[43]. The ideal number of IT injections is undetermined, but most protocols recommend 8-15 total doses. Close attention must be given to the supportive care such as blood product support. In rare instances when lumbar punctures are difficult to perform an Ommaya reservoir can be considered as an individual alternative taking procedure related risks and uncertainties regarding adequate dosing into account. Practical aspects of IT treatment are reviewed in[44].

Systemic Chemotherapy

Systemic chemotherapy may also help prevent CNS relapse. A meta-analysis of 43 trials showed a benefit to adding HD-MTX in terms of reduction in RR and improved EFS, although only a small effect on CNS disease[45]. A recent randomised trial showed a benefit in terms of disease-free survival (DFS) (but no impact on CNS relapse) for 3g/m^2 over 0.5g/m^2 with no excess toxicity for the higher dose[46]. Dexa may be superior to prednisolone in reducing CNS RR[47].

MRD-Based Treatment Modification

Given the paramount prognostic impact of MRD response, most groups recommend therapy changes based on MRD. As described previously MRD based treatment decisions require adequate and standardized methodology for MRD detection (cross-reference). Important decision factors are time-point and level of MRD, method, presence of other PFs and suggested treatment modifications[32]. Early good MRD response is associated with favorable outcome. In one series 12% of standard-risk patients showed no detectable MRD at day 11 of induction and had an excellent prognosis[48]. A later time-point after first consolidation was identified as most prognostically relevant for RR[49]. Thus, earlier time-points could be suitable to identify patients for potential de-escalation of therapy in clinical trials, whereas later time-points are helpful to recognize candidates for treatment escalation. The most relevant time-point depends on protocol. If it is the primary goal to identify patients with chemotherapy resistance, all relevant chemotherapy compounds should have been administered before changes are made keeping in mind that MRD testing does not represent the extramedullary compartment. In most protocols, the relevant time-point will be around 2-3 months from diagnosis.

It is also important to identify the most predictive level of MRD. A threshold of 0.01% (i.e. 10^{-4}) is often considered since this is in line with the sensitivity of MRD assays. Each log-level increase of MRD is associated with shorter time to subsequent hematologic relapse[50]. The median time to hematologic relapse was 7.6 months versus 4.9 months for patients with MRD above 0.01% versus 0.1% respectively[49]. Patients with low level MRD i.e. below 0.01% may have an intermediate prognosis[51,52] and should be considered for MRD-based treatment interventions in the future.

Also, the method of MRD detection influences treatment decisions. Thus, quantitative polymerase chain reaction (PCR) measurement of clonal immunoglobulin/T-cell receptor rearrangements (IG/TR) requires 4-6 weeks to set-up the appropriate assay. MFC may deliver results more quickly but may yield uncertain results particularly in regenerating bone

marrow (BM). Decisions based on the safe confirmation of negative MRD status require strict adherence to methodological pre-requisites (cross-reference). This requires MRD assessement in an experienced reference laboratory and a sensitivity of at least 0.01% for the time-point which is considered for the treatment decision.

Most trials on the prognostic impact of MRD were conducted in newly diagnosed patients. In adult ALL limited data demonstrate a correlation between persistent MRD after therapy with new targeted compounds in the relapsed/refractory (R/R) setting[53] but correlation is less stringent than in first-line therapy. Neverthess, MRD response to salvage therapy indicates the antileukemic efficacy of a defined approach and is relevant for patients.

Very few attempts for reduction of standard therapy have been made so far. One randomized trial in standard risk pediatric patients with good MRD response evaluated the outcome with a reduced reinduction regimen. This modification was associated with an inferior DFS, particularly in children older than 10 years[54]. Further clinical trials are warranted to evaluate treatment reduction particulary in the era of immunotherapies.

Most groups build their indication for SCT on MRD. SCT provides a survival advantage for patients with poor MRD response[49,55]. However, the realization of SCT requires time and many patients relapse during this period despite continued chemotherapy[49]. In addition, a high MRD level before SCT is associated with a higher RR after SCT[56-59]. The prognostic impact of MRD before SCT is correlated to the time-interval between MRD detection and transplant, the potential interim therapies, the conditioning regimens, and other transplant related factors.

It is recommended to change therapy in patients with persistent or recurrent MRD. Compounds with different mechanisms of action compared to chemotherapy are potentially most promising. Up to now, Blina is the only compound tested in a pivotal trial for MRD positive B-LIN ALL. Patients with an MRD above 0.1% were included either in first or later remission. The primary endpoint, achievement of a complete molecular remission (CMR) after one cycle, was achieved in 78%. Furthermore, a favorable median survival of 36.5 months was obtained and patients achieving a CMR had a significant benefit. This treatment was a bridge to SCT in 67% of the patients. The RR after SCT was low. However, OS was impaired by a treatment-related mortality (TRM) above 30% which is explained by the higher median age (42 years), the high rate of full-conditioning and mismatch donors [60,61]. On the other hand, most patients without subsequent SCT relapsed and beyond complete molecular remission no factors predicting RR in patients without SCT were identified. In the future immunotherapies or other targeted drugs should be evaluated in the setting of MRD persistence.

Overall, patients with MRD above 0.01% after 3 blocks of standard therapy have an indication for SCT and for targeted therapies. Up to now there is no evidence that treatment reduction, except for abundance of SCT, can be recommended outside of clinical trials in patients with favorable course of MRD. Whether SCT can be omitted in all patients with molecular CR, including those in specifically unfavourable subgroups should be investigated[62]. After conversion from MRD positive to MRD negative status using new compounds such as Blina, subsequent SCT remains the standard in younger patients with matched donor. In older patients with high risk of TRM either dose-reduced conditioning regimens or a consolidation/maintenance strategy should be followed.

Stem Cell Transplantation

SCT is a complex multistep, multifactorial, and highly individualized treatment concept. A such, it is considered an effective treatment for preventing relapse, combining myeloablative doses of chemotherapy and/or radiotherapy with potential beneficial graft-versus-leukemia reaction. Unfortunately, it is also associated with significant incidence of TRM, reaching 13% after SCT from Human-Leukocyte-Antigen (HLA)-matched sibling donors (MSD) and 21% for SCT from unrelated donors (URD)[63]. Haploidentical SCT with post-transplant CP is increasingly implemented in many countries. Overall, indication for SCT is weighed against the reduction of the RR and the risk of TRM. Despite attempts to elaborate prognostic scores, the potential benefit in many individual cases is uncertain[64]. The role of autologous

(auto) SCT appears questionable and mainly affected by the MRD status[65]. Results of recent SCT trials are summarized in Table 2.

Ph-negative ALL

Most prospective studies evaluating the role of SCT have been conducted considering the availability of MSD. Patients in CR1 with MSD were offered SCT, while those lacking MSD were treated either with auto SCT or chemotherapy. Most of the trials demonstrated a beneficial effect of MSD-SCT (reviewed in [3,66]). However, these studies were performed before the era of routine assessment of MRD and with non-p-b comparator arms. Currently, MRD status is considered the most important PF, driving SCT indication. In two subsequent trials 522 Ph- high-risk patients up to the age of 55 years were intended for SCT[55]. Among these, 54% received a transplant in CR1 (MSD or URD). SCT was associated with longer LFS in patients with post-induction MRD $\geq 10^{-3}$ but not in good MRD responders. This observation, however, may not necessarily apply to less intensive chemotherapy protocols and a randomized trial assessing SCT indication in MRD-negative high-risk patients is ongoing[32].

Indications for SCT refer mainly to younger adults up to 55-60 years and vary among study groups[67] (cross-reference). There is no consensus regarding older patients. High variability in clinical practice between study groups and individual centers has been reported[67]. In MRD-negative older patients SCT should not be used outside prospective clinical trials. It is crucial to continue MRD monitoring after SCT to identify upcoming relapses.

Ph+ ALL

SCT was associated with significant OS benefit in patients treated with imatinib and chemotherapy[68] and therefore remains SoC. Indications may be restricted with the introduction of third generation tyrosine-kinase inhibitors (TKI) or with consideration of specific PFs. This, however, requires verification in prospective trials with sufficiently long follow-up. Clinical trials with 3rd generation TKI and immunotherapy in older patients may provide relevant data on long-term survival without SCT.

Strict MRD monitoring should be performed after SCT[69]. MRD positive patients should be treated with TKIs according to the ABL-kinase domain (KD) mutation status, level, and time of MRD reoccurrence. Patients with early MRD-negative status may either be treated prophylactically or pre-emptively for at least one year of continuous molecular CR. Both strategies have been documented feasible in a prospective randomized trial[70].

SCT Procedure Aspects

Donor type choice does not differ from other leukemias. All, MSD, URD or haploidentical donors may be considered. However, the choice of conditioning regimen may influence outcome. A randomized trial in pediatric ALL showed a clear benefit of myeloablative total body irradiation (TBI) (12 Gray)-based conditioning over chemotherapy-based regimens mainly due to reduced RR[71]. In case of limited access to TBI or for patients who cannot tolerate this procedure, conditioning based on intravenous busulfan or HD thiotepa may be an alternative[72,73]. Resuts of prospective study in adults indicate non-inferiority of busulfa/ CP compared to TBI at a total dose of 9 Gray + CP[74]. For older patients reduced-intensity conditioning (RIC) should be considered preferably within clinical trials. The broadest experience comes from a trial which offered conditioning with Fludarabine, Melphalan and Alemtuzumab[75]. Nevertheless, the role of RIC SCT in older patients remains uncertain, particularly with the availability of immunotherapies and 3rd generation TKI.

Anti-thymocyte globulin (ATG) as part of conditioning prevents chronic graft-versus host disease as confirmed by two recent retrospective studies by the EBMT but was associated with increased RR without significant impact on OS[76,77]. G-CSF mobilized PB stem cells is the most frequently source of stem cells[78].

Treatment of Specific Subgroups

Adolescents and Young Adults

AYA with cancer have been recognized as a vulnerable population in transition between childhood and adulthood aged 15-20 years. A definition of 15-39 years old was used defining therapeutic strategies based on unmodified pediatric protocols, whereas it is also recognized that patients aged 15-25 years old are more exposed to psychosocial issues[79]. Nowadays intensive p-b protocols are used up to the age of 55-65 years. The outcome of AYA is lower than in children even within pediatric trials. Contributing factors include differences in disease biology, historically different therapeutic approaches, and lack of inclusion in clinical trials. Psychosocial issues may decrease adherence[80] to long-lasting and complex protocols. Multidisciplinary teams aware of these complex situations should be involved in treating AYA with ALL.

Biology in AYA: The incidence of ALL is lower in AYA than in children or older adults. T-ALL and LBL are more frequent. Some molecular entities are identified more frequently in AYAs such as iAMP21, *IGH@* rearrangements, *MEF2D* rearrangements, or Ph-like ALL.

Ph- ALL: Many historical comparisons addressed the outcome of AYA concomitantly treated in pediatric studies or historic trials designed for adult ALL (reviewed in[81]) and confirmed the advantage of pediatric strategies. These observations have led to different strategies in variable age groups including i) the expansion of p-b protocols in adult patients[13,32,82-85], ii) the setting of specific AYA trials[86], or iii) the extension of upper age limit in pediatric trials[9]. Thereby outcome of AYA has improved significantly (Table S2). Currently, there is no evidence that AYA have poorer results with modern p-b regimens compared to unmodified pediatric protocols. Any age cut-offs for defined protocols should be based on a clear rationale.

Ph+ ALL: Whereas most adult groups use dose-reduced chemotherapy plus TKI but recommend SCT, pediatricians have maintained intensive chemotherapy and reduced SCT indications mostly based on early response including MRD[87]. Due to the rarity of the disease in AYA, patients should be included in prospective trials.

Older patients (>55-65 years)

Many groups set an upper age limit for unmodified p-b protocols at the age of 55 years. This is supported by a recent publication indicating a mortality in CR of around 35% in patients aged between 55-59 years and treated according to an intensive p-b protocol[12].

Biologic and clinical features: Older patients usually suffer from B-LIN ALL[88,89]. The incidence of poor PFs such as pro-B-ALL, including *KMT2A*-rearranged ALL, and early T-ALL increases with age[89,90]. There is a high incidence of Ph+ALL (24-51%) or complex aberrations[88,91]. Older patients' performance status frequently deteriorates quickly with the onset of disease and comorbidities are frequent. In one study the incidence of any comorbidity assessed by the HCT-CI (Hematopoietic Cell Transplantation Comorbidity Score) was 76%. Early death (ED) was significantly associated with comorbidity[92]. Furthermore, secondary ALL is more frequent in the older population[93].

Prognostic factors: Potential PFs for ED risk included comorbidity, age, and performance status before onset of leukemia[88,89]. PFs for RR are like those in younger patients. In older patients with less intensive therapy, a higher rate of MRD persistence can be expected[89]. Therefore, prospective evaluation of MRD is essential to identify those who could benefit from alternative, experimental treatments.

Management: A prephase therapy can be essential particularly for stabilisation of the general condition. Induction therapy is the most critical phase for management. ED has a wide range (0-42%) (Table 3). The most frequent cause is infection (reviewed in [88]). Even with an age adjusted chemotherapy more than 95% of the patients experience grade III-IV hematologic toxicity during induction. The Swedish registry reported Intensive Care Unit admission in 17% of the patients older than 55 years[94] and ED was similar with intensive or so called palliative approaches[95].

Outcome: Population based studies reported CR rates of 40-70% and OS of 6-30% [91,94-96]. With protocols specifically designed for older ALL patients CR rates of 43-90% and OS rates below 30-40% after 5 years can be achieved (Table 3). As in protocols for younger patients,

steroids and vincristine are the most important drugs in induction therapy. One central question is whether anthracyclines must be included, which type of anthracycline and which dose-intensity. Anthracyclines contribute considerably to BM toxicity. One approach is the use of idarubicin in induction based on a potentially lower cardiac and hepatic toxicity. The results of liposomal anthracyclines in elderly ALL are not convincing. Tolerability of ASP is reduced in induction in older patients (reviewed in[88]). One group reported an induction mortality of 34% in patients aged 60-65 years treated with an intensive induction including Dexa, high doses of daunorubicin and two doses of PEG-ASP[21]. Overall, it is advisable to start ASP in older patients later during consolidation.

Whereas options for intensification of induction therapy are limited, there is still space for intensification of consolidation therapy. To date the largest prospective trial was conducted by the GMALL used a p-b 2-phase induction followed by alternating consolidation cycles and maintenance up to 2.5 years. In CD20 positive ALL 8 doses of Ritux were added. The median age was 67 (55–85) years. The CR rate was 76% in 268 patients; ED rate was 14% and mortality in CR 6%. OS at 5 years was 23%[97]. Based on this protocol a consensus treatment approach for older patients with ALL was defined by the EWALL. The Hyper-CVAD protocol was associated with a CR rate of 88%, death in CR of 31% and OS at 5 years of 21%[26]. With the most recent version of the GMALL protocol including MRD-based immunotherapy a CR rate of 75%, ED of 9% and OS or 50% at 3 yrs was reported[89] (Table 3).

Overall, these standard regimens are the basis for further improvement by moderate time- and dose intensification in consolidation, consideration of SCT with RIC and decision on targeted therapies based on MRD. Immunotherapies such as Blina should be considered in older patients with _B-LIN ALL showing persistent MRD[60]; also patients with PR or failure after induction can benefit from treatement with InO or Blina. Older patients may also benefit from the addition of Ritux to the chemotherapy backbone.

Further improvement can be expected from complementing or replacing chemotherapy with immunotherapy independent of MRD. Older patients show a similar tolerability of Blina and InO as younger patients[98,99]. In the first experience with a combination of InO with dose reduced chemotherapy and Ritux in patients older than 63 years a CR rate of 98% was reported in 48 evaluable patients. 78% of the patients achieved negative MRD status. However, despite the use of dose-reduced chemotherapy, 93% of the patients developed grade III-V infections, 17% increases of Bilirubine or transaminases and 81% had prolonged thrombocytopenias of more than 6 weeks with Grade III-IV haemorrhage in 15%. VOD was observed in 8% of the cases. The mortality in CR was however 22-25% and the 3-year OS was 56%[100]. Importantly, the dose of InO was adapted during the trial in a total of 5 steps and in a further modification Blina was added in the latest cohort after 4 cycles of InO-based chemotherapy.

In older patients trials with different combinations of chemotherapy and sequential trials with Blina and chemotherapy are ongoing and yielded promising interim results[101-105]. Longer follow-up will be essential, but it is of interest that despite reduced chemotherapy, the risk of TRM was quite high in some trials[101,105]. Particularly in patients older than 70 years with poor risk cytogenetics outcome was very poor[105].

Whereas these combined approaches are of great interest and bear promise for older patients, it will be a challenge to define new standard regimens and demonstrate their benefit compared to historical data which would be necessary to obtain not only marketing authorisation of immunotherapies for first line but also reimbursement in different health-care systems.

Ph/BCR::ABL1 positive (Ph+) ALL

Diagnosis and Molecular Features: Clinical presentation and diagnosis are comparable to Ph- ALL. Cardiovascular assessment is particularly important due to the safety profile of TKIs and attention to the echocardiography is relevant as some TKI may cause QT prolongation.

Confirmation of Ph+ ALL relies on karyotyping and/or molecular genetics (cross reference). Additional chromosomal aberrations have been linked to inferior outcome[106-108]. PCR analysis of BCR::ABL1 should not be the sole diagnostic test as atypical BCR::ABL1 transcripts may be missed but determining the BCR::ABL1 isoform is important for subsequent MRD analysis. There is no unequivocal data on the prognostic relevance of the more frequent p190 isoform versus the p210 breakpoint present in one third of patients.

Principles of treatment: TKIs induce CR in 90-95% of patients, display low toxicity and enable a greater proportion of patients to undergo SCT. TKI should be initiated as early as possible, as delays during induction reduce their efficacy. During induction it is possible to rely on a TKI only to achieve CR, but in practice TKI are usually combined with steroids and often vincristine. Simultaneous administration with most chemotherapeutic agents is feasible. CNS-prophylaxis is mandatory.

Induction and Post-Remission Chemotherapy: The combination of imatinib with non-intensive induction was prospectively studied, demonstrating a higher CR rate and lower induction mortality without compromising OS[68]. Chemotherapy de-escalation during induction is applicable to all age groups but has not been universally adopted[109-111]. As a minority of patients achieve a deep molecular response after TKI-only induction, additional anti-leukemic modalities are required as post-remission therapy[112] (reviewed in [113])(Table 3).

Post-remission therapy is commonly initiated with one or two consolidation cycles combining a TKI with more intensive chemotherapy, analogous to treatment of Ph- patients; use of ASP is discouraged by some groups[114]. Depending on comorbidities, transplant risk, age, patient preference and MRD level, further post-remission therapy will then consist either of SCT, continued consolidation and maintenance therapy or switching to an alternative treatment if response is deemed unsatisfactory. Consolidation is followed by maintenance with the initial or an alternative TKI, depending on tolerability and efficacy[115-117]. Stopping the TKI in non-transplanted patients is discouraged, even in patients with prolonged MRD-negativity.

MRD: MRD monitoring for Ph+ ALL should rely on BCR-ABL1 measurement but complemented by one additional method (cross-reference).

Kinase domain (KD) mutations: Point mutations in the KD of BCR::ABL1 contribute to most relapses on TKI. Increasing BCR::ABL1 transcripts should prompt mutational analysis[118] as the type of mutation may inform which TKI to switch to. In most cases ponatinib will be the TKI of choice. Switching even to the most appropriate TKI will rarely induce a prolonged response in case of overt hematologic relapse. NGS with a sensitivity of 1-5% is the method of choice to detect evolving mutated clones in the MRD setting[118]. The clinical relevance of low-level mutations at diagnosis remains unclear[117,119].

Selecting TKI: Published studies with long-term data indicate that RD and OS with regimens combining chemotherapy and either imatinib or 2nd generation TKI is comparable[120] which may in part be attributable to SCT as a confounding factor. In contrast, a randomized study in pediatric patients showed superiority of dasatinib over imatinib when combined with intensive chemotherapy[121]. One caveat of this trial is however the imatinib dosing, which was lower than typically prescribed for pediatric ALL. Treatment strategies that do not rely on SCT or combination with intensive chemotherapy may benefit from 2nd and 3rd generation TKI. Thus, 1st-line ponatinib combined with hyperCVAD resulted in high CR and molecular CR rates and the 5-year OS (71%) was superior to historical controls[122]. In a Phase 2 trial of ponatinib plus standard induction and consolidation chemotherapy in patients with newly diagnosed Ph+ ALL, the 3-year EFS and OS rates were 70% and 96% respectively[123](Table 4). Pre-liminary data of a randomized trial with Ponatinib versus Imatinib in combination with dose-reduced chemotherapy in 245 patients Ponatinib yielded a significantly higher MRD response rate (34% versus 17%) whereas OS data were not different[124].

Dosing considerations apply to all TKI; for imatinib maintaining a high initial dose (800 mg/day for 6-8 weeks) has been associated with better outcome[110]. Ponatinib (45 mg/day) and nilotinib have been linked to cardiovascular adverse events, lowering the ponatinib dose when CR is reached to 30mg/day reduces the risk of arterial occlusive events without compromising efficacy[109]. Doses lower than 15 mg/day (QD) ponatinib are discouraged by pharmacokinetic data[109,125]. Rigorous attention to normalization of blood pressure, blood

glucose and lipids is essential. Other comorbidities to be considered include pulmonary disease (dasatinib) and diabetes (nilotinib). Nilotinib and ponatinib may cause clinically symptomatic pancreatitis, particularly in patients with a history of pancreatitis. Selecting TKI for first-line therapy depends on treatment regimen, comorbidities, and drug approval in different health care systems.

Immunotherapy: Combining TKI with immunotherapy may enhance anti-leukemic activity. Whether addition of Ritux enhances efficacy as in Ph- ALL has not been established. Blina was shown to be highly effective in postremission therapy combined with dasatinib[126]. In this trial, all but one patient (98%) achieved a CR after dasatinib, and up to 60% obtained molecular response measured by BCR::ABL1 MRD after two cycles of Blina. At 18 months median follow-up, DFS was 88%. Observation of several CNS relapses emphasizes the need for intensive CNS-directed prophylaxis. The role of SCT in this setting remains to be established, since approximately 50% of the patients received SCT based on investigators' choice. Several ongoing trials are evaluating the combination of TKI with Blina as 1st-line therapy for older patients with Ph+ ALL. Also, the role of SCT may be defined in the context of ongoing randomized trials (NCT06061094).

CNS prophylaxis: Dasatinib crosses the blood brain barrier[127] but the clinical relevance of CSF penetration of TKI is not well described. Therefore, prophylaxis of CNS relapses is an essential part of all TKI based regimens and usually relies on intensive and prolonged application of IT prophylaxis.

Salvage therapy: Other than TKI, the modalities are the same as for other B-LIN ALL; most patients will have developed KD mutations. Second and 3rd generation TKI have response rates of 16-46%[128,129] with OS of 6-9 months[125]. OS is poor even in patients referred for SCT[130]. With InO in R/R Ph+ ALL higher response rates, longer PFS and a higher rate of SCT compared with SoC were observed, but no benefit in OS[99,131]. Single agent Blina induced CR/CRh in 36% of R/R Ph+ ALL, including patients with the T315I mutation[132]. Median RFS and OS were 6.7 months and 7.1 months, respectively. Concurrent use of Blina and ponatinib in R/R Ph+ ALL resulted in a remarkably high CR rate (96%) and encouraging OS (median 20 months), with acceptable tolerability[133]. Optimal positioning of CAR T-cell therapy in the treatment of Ph+ ALL remains to be determined. Avoiding relapse is paramount as salvage therapies remain unsatisfactory. In addition to immunotherapies, BH3-inhibitors, and the novel allosteric kinase inhibitor ABL001 (asciminib) are of interest; both have a favorable toxicity profile and act synergistically with available therapeutic modalities used in Ph+ ALL.

Ph-like ALL

Approximately 10-30% of cases with B-LIN ALL are characterized by a gene expression profile like that of Ph+ ALL and they were therefore named BCR::ABL1-like or Ph-like ALL.

Diagnosis: Ph-like ALL was first described in adult ALL[134,135]. One signature in pediatric ALL, named BCR::ABL1-like, was based on hierarchical clustering of 110 gene probe sets[136]. Another signature with of 257 gene probe sets, named Ph-like, was based on the prediction analysis of microarrays (PAM) classifier[137]. A comparison of both classifiers found a relatively small degree of overlapping, with only 18% of patients consistently classified. However, both classifiers identified patients with a poor outcome and tyrosine kinase fusion genes[138]. Only 9 probe sets overlapped between the two lists, most likely due to different approaches, algorithms, and patient demographics.

The identification of Ph-like ALL remains challenging and is not SoC. A 15-gene LFS(LDA) gene expression card can be used in clinical diagnostics using quantitative RT-PCR coupled with a mathematical algorithm. The LDA card includes gene probes for the most frequent tyrosine kinase genomic lesions in Ph-like ALL. The concordance rate between the LDA card and the PAM method is 87%[139]. Another approach is the “BCR::ABL1-like predictor”, based on the RQ-PCR quantification of 9 specifically overexpressed genes[140]. For comparability of clinical trials the method for identification of Ph-like ALL should be clearly described. There is however no sufficient evidence for the need to identify Ph-like ALL as a whole subgroup upfront in all patients outside of clinical trials.

Molecular Characterization: Genomic screens and NGS have revealed a highly diverse range of aberrations; these include many new fusion genes, including ABL1-class and JAK-class fusion genes[141]. Ph-like ALL aberrations can be grouped in five major subclasses (Table S3). Since most studies were carried out in children and young adults, the type of genomic lesions in older adults are less well understood and might differ.

Incidence: The incidence of Ph-like ALL differs by geographic region, age, reference group and the methods used for identification. With the PAM-classifier the incidence of Ph-like cases in US cohorts was 20-24% in adolescents and older adults (>39 years old), with a higher incidence of 28% in younger adults (aged 21-39 years)[140] (Table 5). It is essential to note whether incidences refer to B-LIN as a whole or to a group named B-other i.e. those without distinct cyctogenetic/molecular aberrations.

MRD response and prognostic significance: Adults with Ph-like ALL had higher rates of MRD positivity after induction. This was associated with an inferior event-free survival (EFS) and OS. 70% of patients with Ph-like ALL remained MRD positive[142]. This was confirmed in other adult populations[143,144]. Data on the impact of MRD response in Ph-like ALL are conflicting. The high RR does not always correlate with MRD response[29]. On the other hand, pediatric patients with Ph-like ALL and negative MRD status after standard treatment had no inferior outcome[145]. Therefore, aiming at MRD negativity retains prognostic importance also in this subgroup.

Treatment: Novel immunotherapies such as Blina and InO are investigated[29,122,146] and appear to be effective according to anectodal reports of successful treatment. Most groups rely on an MRD-based approach and would offer SCT and/or targeted therapy due to poor MRD response. There are no studies confirming that SCT overcomes the higher RR in this subgroup.

Given the genetic heterogeneity in Ph-like ALL, translation of this subtype to a useful treatment algorithm is a challenge. The ABL class fusions, usually identified by fluorescence-in-situ hybridisation were sensitive to SRC/ABL TKIs, such as imatinib and dasatinib and there are several anecdotal clinical reports[147]. JAK2 fusions, EPOR rearrangements and activating JAK-STAT mutations were highly sensitive to the JAK2 inhibitor, ruxolitinib in preclinical studies. Another approach could be the use of ponatinib [140,147]. For clinical practice identification of ABL-fusions and MRD-based treatment modifications are essential.

T-ALL

T-ALL comprises 25% of adult ALL[148] and treatment is similar to B-LIN ALL. After standard induction an intensification phase containing CP and AC is usual. Intensive use of ASP was highly effective in pediatric T-ALL[149]. It is not clear whether nelarabine as consolidation

improves outcome in adults. When combined with the hyper-CVAD protocol in newly diagnosed adults with T-ALL/LBL, there was no OS benefit with the addition of nelarabine compared with the historical data[150]. A randomized pediatric trial has evaluated nelarabine in newly diagnosed T-ALL/LBL[151]. In this study, the 5-year DFS was 88% in the nelarabine group *versus* 82% in the no-nelarabine group, with an acceptable toxicity. The benefit of nelarabine was not observed in OS. Of note, the rate of isolated and combined CNS relapses was reduced in nelarabine treated patients. In adult ALL a recent trial did not show a benefit of one course of nelarabine instead of induction phase II[152]. The GMALL 08/2013 trial added 2 cycles of nelarabine in standard-risk ALL and reported excellent outcome; the exact role of nelarabine in this intensive p-b regimen remains to be defined. On the other hand nelarabine had limited efficacy in MRD positive immature T-ALL[153] (Table 1). The MDACC reported improved OS for nelarabine-treated patients compared to retrospective controls, with the notable exception of ETP ALL which did poorly[154]. All trials in adults did not reveal specific safety concerns. It is recommended to participate in nelarabine-based trials whenever possible and until more robust data will be available.
As for B-LIN ALL MRD testing is of utmost importance and provides guidance for SCT indication. ETP ALL appears to have a poor prognosis with chemotherapy and unfavourable oncogenetics should also lead to consideration of SCT indication. Older patients with high-risk T-ALL may benefit from a RIC if they have a well-matched donor[75].

Lymphoblastic Lymphoma (LBL)

LBL is a rare entity of 1-3% NHL. 80-90% are T-cell (T-LBL). LBL and ALL are separated by an arbitrary cut-point of 25% BM infiltration. GEP and SNP profiling revealed differences between T-ALL and T-LBL[155]. T-LBL shows a prevalence 70% of thymic subtype with a favourable outcome compared to 18% early T and 9% mature T-type.
Patient characteristics and PF: T-LBL has a male predominance, presents most often with advanced stage III-IV, and 90% of T-LBL patients have a mediastinal bulky mass, sometimes with concomitant pleural and pericardial effusions. CNS involvement is seen in 5-10%, lymph node or other organ involvement in 70% and mostly LDH values are increased. In contrast to T-ALL PB values are most often normal. There are no accepted adverse PFs. They differ in various trials, such as increased LDH, CNS involvement and in one study a gene-classifier was prognostic[156].
Therapy: Rarely tumor lysis syndrome and in some cases thoracic compression require immediate therapeutic intervention by corticosteroids. Treatment should be based on ALL regimens[156,157]. The CR rate in most studies is 70-90%, the EFS is 60-70% at 5 years and the OS range is also between 60-70%. CNS prophylaxis is administered as in ALL.
In earlier studies despite mediastinal irradiation of 24-36Gy for residual tumors, the mediastinal relapse rate was high[157]. This is now compensated by more intensive systemic chemotherapy. PET may theoretically guide therapy of residual disease[158]; however the exact timing, the predictive role and treatment consequences after positive PET are not established. MRD in the BM or PB may help to evaluate the response. SCT has obtained equal results of an OS of 70% compared to chemotherapy alone; the known selection bias for SCT must be considered, however. SCT is therefore reserved for T-LBL patients in second CR, or refractory cases[153,156].

Relapsed/Refractory (R/R) ALL

Conventional Chemotherapy Salvage

Depending on protocol and subtype 5-10% of patients will be primary refractory, and an additional 30-60% of patients will relapse. Although BM is the most frequent site of relapse, extramedullary relapses can occur, and incidence may even increase with more widespread use of immunotherapies. Adult patients with R/R ALL have a poor prognosis with salvage chemotherapies. A new CR is attained in 20-40% of patients depending on treatment line, but these remissions are in general not durable despite subsequent SCT. Prolonged disease-free survival (DFS) and cure are observed in around 10-15%[94,159-164] (Table S4). An international study of 1706 patients with R/R Ph- B-LIN ALL reported 3-year OS of only 10%[164]. Predictors for outcomes include age, duration of first remission, response to initial salvage therapy and ability

to undergo SCT. For patients who are candidates for salvage therapy, the choice of regimens will be based on the patient age and comorbidities, disease characteristics (eg, immunophenotype, genetic characteristics, extramedullary involvement, among others), type of prior therapy (including SCT), and duration of prior remission. R/R ALL is an emergency and patients should be referred to experienced centers to establish a comprehensive management plan since sequencing and timing of salvage therapies are essential for outcome. SCT indication should be considered in all patients with R/R ALL.

Treatment of Extramedullary Relapses

CNS is the most frequent site of extramedullary relapse. CNS-directed treatment followed by combined systemic therapy is warranted[165]. Recurrences within the CNS usually coincide with or predict systemic relapse; immediate MRD testing is therefore recommended. Although rapid improvement in neurological symptoms and signs can often be achieved with intravenous or oral Dexa, IT therapy should be started promptly twice per week until the CSF is negative. Systemic re-induction therapy should include drugs able to cross the blood-brain barrier such as HD-MTX or -AC. Patients with isolated or combined CNS relapse are candidates for SCT. Although there are no data to support any conditioning regimen in these circumstances, TBI regimens are preferred. A cranial boost of 6 Gy has been shown to be tolerable in adults receiving TBI-based conditioning[166]. There are no randomized data on the potential benefit or harms of giving additional IT therapy posttransplant, and the practice varies by institution. MRD testing in the CSF may help to guide management. Regarding immunotherapies, elimination of CNS leukemia has been observed in patients treated with CD19 CAR T cells. Treatment of other extramedullary relapses is rather individualised, depending on location. Usually, chemotherapy or local therapies e.g. irradiation are attempted since the efficacy of immunotherapies is not clear in this stetting.

New chemotherapeutic and targeted drugs

Liposomal vincristine was developed with the goal of increasing drug exposure of vincristine to leukemic cells while minimizing dose-limiting neurotoxicity. The overall response rate was (CR,CRi,PR) was 32% with a median RD of 23 weeks and median OS of 4.6 months[167]. Grades 3-4 neuropathy occurred in 25% of patients.

Clofarabine, a nucleoside analogue approved for use in children with R/R ALL, has as single agent a response rate of only 12% in adults. Response to combination regimens (etoposide/mitoxantrone, cyclophosphamide or cytarabine) have ranged from 17%-36%[168] but the toxicity of these regimens is high, precluding the use of subsequent SCT in most patients.

Nelarabine was approved for R/R T-ALL/LBL. The first study showed a CR rate of 23% in 26 adult patients with R/R disease. A larger Phase II study including 126 heavily pretreated R/R adult patients (ages 18-81) showed a CR rate of 36% and a PR rate of 10%, with 80% of CR patients bridged to SCT[169]. Significant neurologic toxicities are observed in around 10%. It is not clear whether combination therapies yield higher responses and with the increasing use of Nelarabin in first-line therapy (see above) the options in R/R ALL are more limited.

Immunotherapies

Antigens expressed on the surface of ALL cells (CD19, CD20, CD22, CD52) have proven to be appropriate targets for monoclonal antibodies (MoAb), used either alone or in combination with chemotherapy. MoAb and CAR T-cells have thus been developed, demonstrating high anti-leukemic activity essentially when targeting the B-lineage CD19 and CD22 surface antigens (Table 6). Data for first-line have been already discussed. Antigen targeting is more difficult to develop in T-ALL patients, even if the potential of targeting CD38, CD3, CD5, CD7, CD1a and CCR9 is currently investigated.

Inotuzumab: *InO* is an anti-CD22 antibody conjugated to calicheamicin, a cytotoxic antibiotic agent. InO has been approved for R/R CD22-positive ALL based on a randomized study, the rate of CR/CRi was 81% after InO *versus* 33% after standard salvage chemotherapy[99] Among responders, the rate of MRD negativity was 78% in the InO group *versus* 28% in the control group. Median OS was 7.7 *versus* 6.7 months, respectively. Liver-related adverse events (AE) were more common in the InO group, with an 11% incidence of veno-occlusive disease (VOD)

versus 1%, respectively. Results were confirmed in long-term follow-up[170]. It is open whether combination of InO and chemotherapy can further improve outcome of R/R ALL. To reduce the VOD risk, it is recommended to administer only up to 2 cycles InO before SCT, to avoid double alkylators in conditioning and to strinctly monitor patients for VOD signs after SCT. InO retains effectiveness also in patient with high proliferative relapse[171] and shows some efficacy in extramedullary relapse[172]. An close surveillance of liver function tests is advised.

Blinatumomab (Blina): Blina is a bispecific T-cell engager antibody construct that enables autologous CD3-positive T-cells to target and eliminate CD19-positive B-cells including B-LIN blasts. Blina has been approved for R/R ALL based on a randomized study. The CR/CRi rate was 44% after Blina *versus* 25% after standard salvage chemotherapy[173]. MRD negativity was 76% in the Blina group *versus* 48% in the control group and median OS was 7.7 *versus* 4.4 months, respectively. The gain was more marked in patients receiving Blina as first salvage therapy and in patients with BM infiltration below 50%[174]. AE of interest were manageable cytokine release syndrome (CRS) and transient neurologic events. More favorable results with Blina were observed in MRD-positive ALL as discussed above. Two recent pediatric randomized studies have also investigated the use of Blina as post-reinduction therapy in first relapse in an MRD setting and as bridge to transplant[175,176]. These studies demonstrated fewer and less severe toxicities, higher rates of MRD response, greater likelihood of proceeding SCT and improved DFS and OS in the Blina arm.

Genetically engineered T-cells (CAR-T)*:* CAR-T targeting the CD19 antigen have generated promising results in children and adults with R/R ALL. Characteristics and results of largest non-comparative CAR-T studies published to date are detailed in Table 6[177-185]. Median ages were relatively low. Overall response rates ranged from 67-97% in patients who were infused, and complete MRD response by MFC was achieved in most responders. Most patients had very advanced disease with a substantial proportion of patients relapsing after prior SCT. In order to make results comparable to other approaches in R/R ALL the evaluation of intent-to-treat populations is essential, since not all patients receive an intended CAR-T-cell therapy due to relapse or death during bridging or toxicities. Overall applicability of the procedure has been evaluated in the mainly pediatric ELIANA trial, in which 75 of the 92 patients (81%) screened were infused[181]. The rationale for an upper age-limit of 25 years in this trial is unclear. It led to the approval of tisagenlecleucel for patients aged 1-25 years old with R/R ALL.

Data in adult ALL are still limited and data from clinical trials and real-world indicate that the treatment principle is less effective in full cytologic relapse. The Zuma-3 trial yielded promising results in 55 patients with heavily pretreated adult R/R ALL and a median age of 40 (28–52) years. Overall, 71 patients were enrolled. 62% of the treated patients had BM infiltration above 25% at time of infusion. The CR/CRi rate was 71% in the infused patients and 54% of all patients. The median OS of treated patients was 18 months and the median RFS 11.6 months. This trial led to marketing authorization of Brexucaptagene Autoleucel[185].

CRS and neurotoxicity are more common and more severe with CAR-T as compared to Blina, likely because of massive, induced CAR-T expansion/activation and endothelial activation[186]. This makes CAR-T a therapy that should be administered in specialized centers with a trained intensive care unit. Many issues still need to be elucidated, including the impact of CAR-T subsets and persistence and the role of prior alloSCT and disease burden at infusion time on CAR-T efficacy and the need for subsequent SCT. Genetically engineered "off-the-shelf" allogeneic CAR-T, aiming to increase the applicability and rapidity of the procedure, are under clinical development. Due to a relatively high incidence of CD19-negative ALL recurrence, strategies combining CD19 and CD22 targeting, using dual or bispecific CAR-T, are also investigated.

In countries with all options available, the selection and sequencing of Blina, InO and CAR-T in R/R BLIN ALL is debated. There is no clear recommendation, as no comparative studies have been conducted to date; furthermore, the availability of CAR-T-cells is limited. One might propose favoring Blina in patients with relatively low disease burden and preserved T-cell functions, while InO might be used to reduce high disease burden though trials were limited to patients with peripheral blasts below 10000/ul. A sequence of both compounds – InO followed by Blina is also of interest. CAR-T might be indicated to treat more advanced disease,

particularly recurrence after SCT. Even if CAR-T have been used as a bridge-to-transplant in most patients treated to date, the question of whether CAR-T could replace SCT in the next future is of great clinical interest. The potential negative impact of Blina[187] or InO failure prior to CAR-T infusion requires larger evaluation. It remains unclear whether prior failure is a selection of unfavorable disease biology or whether there is a specific underlying mechanism.

Other investigational drugs

The most promising targeted agents are those targeting major molecular pathways controlling cell proliferation and apoptotic response (eg, multiple kinases and members of BCL-2, TP53, RAS, mTOR/PI3K, pre-B/B-cell receptor, and NOTCH networks)[25]. A variety of precision medicine approaches are under investigation though often based on considerations of disease biology and anecdotal cases only[188]. Further investigation in prospective clinical trials remains a challenge. Some anecdotal remissions have been reported using FLT3 inhibitors, JAK inhibitors in activated *IL7R* pathway cases, imatinib or dasatinib in *NUP214-ABL1* mutated cases. Targeted therapy is less developed in T-ALL[189]. The CD38 antigen has been considered as a potential target in T-ALL. Combining targeting of CD38 with conventional relapse therapy has been explored[190,191]. Targeting apoptotic pathways with BCL-2 inhibitors are currently tested in clinical trials. Thus a selective BCL-2 inhibitor, with low-dose navitoclax, a BCL-X_L/BCL-2 inhibitor was evaluated in 47 patients with relapsed T- and B-cell disease and achieved a remarkable 60% CR rate with 28% proceeding to potentially curative therapy[192]. Frequent activation of the NOTCH pathway in T-ALL/LBL, through *NOTCH1* or *FBXW7* gene mutations, led to developing NOTCH targeting approaches such as gamma-secretase inhibitors (GSIs) or NOTCH inhibiting antibodies[193]. Several groups are attempting to develop CAR-T cells for relapsed T cell disease that avoid the problem of fratricide and prolonged T-cell aplasia[194]. A first-in-man trial of donor-derived CAR T cells from China in 20 patients has made major progress with high efficacy and acceptable toxicity[195].

Late Effects

With improving cure rates in adult ALL, research in late effects, quality of life and prognostic factors for late AE becomes increasingly important. Survivors of childhood cancer have a higher mortality, more chronic medical conditions, impaired general and mental health, functional impairment, and poorer social parameters compared to healthy relatives and the general population[196,197]. The GMALL group has recently summarized medical conditions in 538 long-term survivors of ALL therapy. 66% of the patients had no comorbidity. The most frequent diagnoses were infections (12%), fatigue (13%) and GvHD (15%) whereas the most frequently affected organs classes were endocrine (17% men 24% women), neurologic (27%) and skin (18%)[198]. Late effects can include general sexual hormone deficiency, thyroid disorders, premature menopause, infertility, osteonecrosis and osteoporosis, cardiotoxicities, neuropsychological disorders, fatigue and second malignancies. The incidence of late effects is higher in patients with SCT compared to those without and additional late effects such as skin disorders in the context of chronic GvHD, sicca syndrome, restrictive and obstructive pulmonary disorders and cataract may occur[198,199]. Whereas patients can maintain their fertility after chemotherapy[200], infertility is observed in almost all transplanted patients[201,202].

Avascular osteonecrosis is a clinically relevant problem which is particularly observed in AYA. Intensified treatment with steroids is a risk factor. Effects may be enhanced by asparaginase or HD-MTX. In one pediatric study with postinduction Dexa or prednisone pulses the incidence of skeletal toxicity was overall 13% (11% fractures, 4% osteonecrosis). It was higher (25% vs 11%) in older children (> 10 years versus < 10 years) treated with Dexa pulses[203,204]. In contrast the UKALL/ECOG2993 study for adult ALL found an overall incidence of 4% osteonecrosis. The incidence was higher in younger (<20 years) versus older patients[205]. Nearly half of pediatric patients with osteonecrosis underwent surgical procedures[206]. There might be a correlation between coagulation disturbances and osteonecrosis. A PAI-1 gene polymorphism, which has been previously associated with risk of thrombosis was also associated with osteonecrosis in childhood ALL[207]. Recently a potential correlation between hypertriglyceridemia – a side effect of ASP – and osteonecrosis has been reported[208]. Most cases of osteonecrosis in ALL patients

occur within the first 3 years of treatment and hip and knees are the most frequent locations. The most sensitive diagnostic method is magnetic resonance imaging (MRI). Some authors suggest performing at least in high-risk populations one regular MRI of hip and knees at the end of therapy. Early detection, prevention and management of osteonecrosis is a major joint challenge for pediatric and adult hematologists[209].

Cardiotoxicity, particularly cardiomyopathy, pericarditis, or congestive heart failure, is often attributed to anthracyclines[210]. The risk seems to be correlated with the overall drug dose, although it may also be idiosyncratic and occur after few applications. Factors like mediastinal irradiation, infections, or combination of different cardiotoxic drugs may enhance the risk[210]. Cardioprotection with dexroxazone may be an option e.g in patients with higher cumulative doses of anthracyclines[211]. Cardiotoxicity e.g. manifested as a reduced ejection fraction may become manifest years after treatment. Cardiovascular check-up should therefore be part of aftercare.

Unspecific neuropsychological disorders are often described in adult ALL patients[198]. This includes complaints about cognitive disturbances. For this phenomenon, known as “chemo-brain”, a physiological correlate is unknown[212]. A relevant number of cured ALL patients suffer from fatigue[198,213]. Fatigue is probably underdiagnosed in aftercare[214]; its detection e.g. by specific questionnaires should be attempted.

Survivors of ALL have an additional risk to develop cancer. PFs for secondary malignancies may be alkylating agents, epipodophyllotoxins, CNS irradiation, TBI conditioning before SCT and moreover different gene aberrations[215]. In adult ALL survivors the most frequent second malignancies are hematopoietic neoplasias which mostly occur within the first 5-10 years after end of chemotherapy[216]. Also, a variety of solid tumors is observed such as breast, thyroid, gastrointestinal, lung, skin, urogenital, brain or sarcoma[161].

It is very important to provide all physicians involved in aftercare with sufficient information about treatment and the relevant aspects of after-care. Long-term observation of cured ALL patients is an essential part of ongoing and future clinical trials and a major challenge in an environment of limited financial ressources for academic groups. Depending on the different health care systems joint forces in dedicated late effect clinics can combine pediatric and adult hematology teams.

Management of Specific Situations

ALL in Pregnancy

Acute leukemia is estimated to affect two in 100,000 pregnancies. Current treatments are typically chosen based on case reports and retrospective analyses and depend heavily on personal and societal considerations as well as the medical considerations of gestational age, disease biology and the patient’s clinical status. A comparison of 15 women treated during pregnancy to 330 non-pregnant controls provided evidence, that pregnancy does not necessarily affect the overall outcome of ALL[217]. Pregnant women with ALL should always be managed in experienced centers with close cooperation with the obstetric and foetal medicine teams. The management depends on the trimester of pregnancy. During the first trimester, termination of pregnancy is a strong consideration since foetal safety precludes delivering of standard ALL therapy. Subsequently, many chemotherapy agents can be safely administered to achieve maternal CR although systemic antifolates should be avoided at any time during pregnancy. The potential use of ASP later during pregnancy is debated, particularly due to its effects on coagulation and depending on risk-benefit ratio it should rather be postponed to treatment cycles after delivery. The use of specific steroids for fetal lung maturation should be considered. Delivery should be timed for the date consistent with foetal survival and be performed in the setting of adequate maternal haematopoiesis.

Mixed phenotype acute leukaemias (MPAL)

Leukaemias of ambiguous lineage origin present a problem for both diagnosis and management (reviewed in[218,219]cross-reference). In pediatric MPAL initial treatment with ALL-oriented regimens is recommended[220]. Lack of response should prompt a switch to AML-orientated

regimens. A similar strategy for adults is reasonable. It is debated whether the diagnosis of MPAL represents an indication for SCT in CR1 in general or only in cases of persistent MRD.

Secondary ALL

ALL arising as a second malignancy (with or without cytotoxic therapy for a prior malignancy) is increasingly recognized (reviewed in[221]). Secondary ALL occurs after a variety of antecedent diagnosis including breast cancer, lymphomas, myeloma, sarcomas, and neuroblastoma. Where there has been no prior cytotoxic therapy, inherited germline mutations in tumor suppressor genes or oncogenes such as *TP53* (Li-Fraumeni syndrome) or mismatched repair genes (*MSH2*, *MLH1*, *MSH6* and *PMS2*) should be suspected[222]. For ALL after prior cytotoxic therapy, US SEER registry data showed a median latency of 60 months and a significantly inferior median 5-year survival compared to *de novo* ALL[223]. Development of ALL after therapy with lenalidomide may represent a specific biologic correlation[224]. Generally, treatment strategy is like newly diagnosed ALL although a higer risk of toxicity might be expected.

ALL and Down Syndrome

Individuals with Down Syndrome (DS) have a 10-20-fold increased risk of ALL, which usually occurs during childhood and is associated with a genetic susceptibility. ALL correlated to DS is well described for pediatric patients. Recently three distinct molecular subtypes with higher incidence in DS-ALL have been described (CRLF2 rearranged, C/EBP alteration and IGH::IGF2BP1 rearrangement)[225]. Pediatric patients with DS-ALL have an increased RR and TRM, mainly due to infections. Although standard therapies are usually offered to DS-ALL patients, some modifications are recommended such as reduction of anthracyclines and high-dose methotrexate. Intensive prophylaxis and monitoring for infections is essential. Replacement of toxic chemotherapies by immumotherapies is tested in clinical trials. DS-ALL in adults should be managed accordingly [226].

Supportive Care

Supportive care recommendations of the EWALL have been published[227]. In the following, only selected specific aspects for management of ALL will be reviewed.

High WBC

When patients present with very high WBC, leukostasis with resultant tissue damage can occur in vulnerable capillary regions, causing organ compromise. Leukostasis is diagnosed on the presence of unexplained hypoxia, neurological symptoms, renal failure, cardiac ischaemia, priapism or severe retinopathy. Management of *symptomatic* leukostasis is a medical emergency. It may be treated with leukapheresis, but this should not be seen as a substitute for prompt initiation of ALL therapy such as steroid pre-phase.

Tumor Lysis Syndrome (TLS)

Patients with high risk of developing TLS (WBC > 100 x 10^9/L, high tumor burden)[228] should receive increased hydration (3l/m²/d), unless evidence of renal insufficiency and oliguria, and rasburicase prophylaxis. Urinary alkalinization is no longer recommended[228]. Intractable fluid overload, hyperkalemia, hyperuricemia, hyperphosphatemia or hypocalcaemia are indications for renal dialysis.

Anti-infection prophylaxis

Antibacterial, antifungal and antiviral prophylaxis and active management of infections is of utmost importance, given the fact that infections are still the major cause of death in CR. Management should be performed according to respective guidelines.

Growth Factors

The prophylactic administration of G-CSF in ALL shortened neutropenia duration [229-232], improved adherence to chemotherapy schedule and in one study reduced the incidence of infections [230]. Based on these data the majority of European study groups have implemented prophylactic use of G-CSF in their pediatric-based protocols since decades. A joint analysis of long-term follow-up data from 5 European clinical trials revealed survival advantages in the G-CSF group, particularly in DFS (5y DFS 38% vs 24%) and OS in T-ALL (5y 51% vs 29%),

probably as the result of improved dose-dense administration of chemotherapy courses without significant decrease of the 8 weeks mortality rate[233].

Menstruation prophylaxis

To suppress menorrhagia during thrombocytopenic periods and avoid undesired pregnancy during chemotherapy, continuous administration of progestational agents is preferred over combined oral contraception, especially during ASP treatment period and its prothrombotic state. For norethisterone a non-significant association between exposure to higher doses and risk of thromboembolism has been described; medroxyprogesterone acetate was discussed as preferable option in patients with high risk of venous embolism [234] Progestational agents should not be used longer than 6 months to prevent meningioma occurrence that has been reported lately.

Preservation of fertility

As part of informed consent before ALL therapy, hematologists should address the possibility of infertility with patients treated during their reproductive years, discuss fertility preservation options, and refer all patients to appropriate reproductive specialists. Sperm cryopreservation should be proposed in all men before start of chemotherapy. In women, ovarian tissue cryopreservation is an option to be considered before SCT. To limit the risk for disease reintroduction after ovarian tissue transplantation, quantification of ovarian MRD is being explored to decide for ovarian re-implantation[235]. So far there is no clear recommendation for the use of GnRH agonists (GnRHa) for fertility preservation, particularly due to conflicting data on their effect on the risk of ovarial insufficiency and likelihood of later pregnancy. Patients should have the opportunity for counseling on the different available options and GnRHa may be used based on individual considerations[236]. It is recommended to reevaluate ovarian function after completion of chemotherapy (AMH, antral follicular count).

Summary and Outlook

The basis for adequate management of ALL is the application of comprehensive diagnostic tools, the identification of prognostic factors including the continous monitoring of MRD (cross-reference). The standard treatment of ALL is often defined by national study groups and international consortia[237] as part of prospective treatment optimization trial. Furthermore, the clinical data bases of study groups often include comprehensive data on biologic markers and are sources of reliable real-world data.

Nowadays excellent results are achieved with current standard p-b chemotherapy particularly in younger patients. To reduce the burden of morbidity and mortality, less toxic regiments are an important goal. The gap between healthcare systems is increasing. Whereas many new compounds can be used in first-line based on integration into NCCN guidelines in the US[238], specific marketing authorization and reimbursement decisions are required in most European countries.

Immunotherapy with antibodies is standard for R/R ALL. Availability of CAR-T as well as data in adult ALL are still limited and the sequencing of these therapies will be a challenge. The indication for CAR-T in relapse after SCT is generally accepted, if possible, already in the setting of MRD relapse. In R/R ALL the definition of adequate bridging therapies and the criteria to decide on the need of subsequent (second) SCT are essential.

For Ph+ ALL the selection of TKIs, the efficacy of chemotherapy-free regimens, indications for change of TKI, the impact of MRD measured with different methods, the role of immunotherapies and HSCT will be important research questions.

Less progress has been made regarding prognostic classification of T-ALL and there are few promising new compounds[239]. Whereas overall prognosis of T-ALL is quite favorable, new approaches are urgently required for poor prognostic subgroups since survival after relapse is rare.

Late effects of treatment, such as osteonecrosis are increasingly relevant with improved ALL survival, requiring joint efforts of pediatric and adult study groups to better understand biology, improve surveillance and define potential treatment modifications.

Many new treatment approaches are applicable only in small subcohorts of ALL and represent a challenge for successful clinical trials. This applies also for the need of more individualized relapse therapies integrating molecular and immune targets as well as in-vitro response data. These strategies require international collaboration including joint forces of pediatric and adult study groups.

Regulatory pre-requisites are expanding regarding marketing authorization and reimbursement for new drugs in ALL, which is treated with complex combination therapies. The evaluation of new compounds in rare molecular subgroups of ALL will require European-level collaboration with the European Medical Agency and intergroup data-sharing, as in the Harmony IMI initiative (https://www.harmony-alliance.eu). New strategies for clinical trial design must be developed in concertation with patient representatives and there is an urgent need to support and maintain the successful infrastructure of independent academic study groups through funding programs[237].

In the next years these challenges will become evident for the integration of new monoclonal antibodies and cell therapies into first line. Several clinical trials are ongoing in Europe and worldwide requiring harmonization to enable future meta-analyses[50,164,240]. First-line therapies will not address the impact of a single compound but on new combination strategies, risk stratifications and approaches like SCT. One major research question will certainly focus on the future role of SCT in adult and pediatric ALL.

Future ALL treatment will be based on very successful standards with increasing implementation of immunotherapies. The goal is to improve the prognosis of high-risk patients but also significantly reduce treatment-related morbidity and mortality for patients of all ages.

Author Contribution statement

All coauthors reviewed literature, wrote parts of the manuscript, reviewed the manuscript and approved the final manuscript.

Conflict of Interest Statement

NG has received institutional research funding from Amgen, Clinigen, Incyte, Jazz, Novartis, Pfizer and Servier, received speaker honoraria or fees for advisory board participation from Amgen, Astra Zeneca, Autolus, Celgene, Clinigen, Gilead, Incyte Jazz, Novartis, Pfizer and Servier. NB received honoraria from Amgen, Incyte, Jazz Pharma, Novartis, Pfizer, Servier and research grants from Amgen, Novartis, Incyte, Jazz Pharma and Sanofi. SC served in advisory boards of Incyte, Pfizer and Abbie and as consultant for Gilead and Amgen. HD received research funding from Amgen, Astellas, Celgene, Incyte, Jazz, Pfizer and Servier and honoraria from Daiichy Sankyo, Incyte, Jazz and Servier. MD received research support from AstraZeneca. Robin Foa received speaker honoraria from Amgen, Novartis and Astra Zeneca and served in advisory boardsfrom MSD. SG received speaker honoraria or joint advisory boards of Amgen, Novartis, Pfizer, Gilead received speaker honorariy from Angelini, travel grants from Gilead and served in advisory boards of Zentiva. MH received research support from Novartis, travel support from Abbvie and Beigene, speaker honoraria and joined advisory boards from Servier, and was part of advisory boards from Amgen and Clinigen. DM provided consulting for Pfizer, Novartis and Kite. OO received speaker honoraria, joined advisory boards and received research grants from Incyte, research support from Amgen and Celgene and received honoraria for advisory boards from Autolus. AR received research support from Servier. PR received research grants from Pfizer and Incyte. JR received speaker honoraria and joined advisory board from Amgen, Pfiizer, Shire, Ariad, Incyte, jointed advisory Boards

from Takeda and received research support from Amgen. RB joined advisory boards from Novartis, Kite/Gilead, received honoraria or travel support from Amgen, Incyte, Servier, Jazz and Pfizer.

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Table 1. Trials with Upfront Targeted or Subset-Specific Therapy in Adult Ph- ALL

Study (Ref.)	ALL subset	Combination treatment	Age (y)	No.	CR (%)	CRD/ RFS (%)	OS (%)	EFS (%)	FUP	Annotations
Rituximab/Ofatumumab (anti-CD20 antibody)										
MDACC[26]	CD20+ B-ALL	Hyper-CVAD + R x 8 in cycles 1-4, x4 in maintenance cycles 6, 18	≤ 60	68	100	70	75	-	3-y	Better outcome vs. no R patients (P<0.001 for CRD, P=0.003 for OS); outcome not improved by R in patients aged 60+
GMALL[241]	CD20+ B-ALL	GMALL 07/2003 + R x8 (SR), x3 (HR) in induction/consolidation	15-55	117	94	64	75	-	3-y	Better outcome vs. no R patients (P<0.009 for CRD), with better/faster MRD clearing (MRD < 0.01% 60% at day 21)
GRAALL-2003[27]	CD20+ B-ALL	A: SOC B: SOC + R x16-18 during induction/consolidation	40 (24-53)	105 104	94 92	-	50 61	43 55	4-y	Better outcome vs. no R patients (P<0.04 for EFS, P=0.02 for relapse incidence)
UKALL 14[28]	CD20+/- B-ALL (29% Ph+)	A: SOC B: SOC + R x4 in induction	25-65	288 289	92 94	-	-	42 48	3-y	No overall benefit from R (P=0.28), better outcome with R after MAC SCT (EFS 72% vs. 50%, P=0.03)
MDACC[242]	CD20+/- B-ALL	Hyper-CVAD + Ofatumumab x8 in induction/consolidation	41 (18-71)	46 CD20+ 23 CD20-	93	-	66 70	61 65	4-y	CD20+: EFS and OS with R 43% (P=0.119) and 48% (P=0.123); CD20-: EFS and OS with R 50% (P=0.89) and 62% (P=0.61)
Blinatumomab										
GIMEMA LAL 2317[29]	CD19+ B-ALL	SOC + Blinatumomab x2 in consolidation	18-65	146	90	56-87	65-91	48-85	1.5-y	95% MRD negative after blinatumomab I (P=0.001); OS by age (P=0.0009) and DFS/EFS by Ph-like (P=0.006) and MRD (P=0.0002)
GRAALL-2014-QUEST[30]	CD19+ B-ALL (high risk)	SOC + blinatumomab x5 in consolidation/ maintenance	35 (18-60)	95	NR	69-90	92	-	1.5-y	74% MRD negative after blinatumomab; DFS by high or very high risk class (P=0.018)
MDACC[243]	B-ALL	Hyper-CVAD + Blinatumomomab x2 after induction and/or x2-4 after	34 (17-59)	58 (20 with InO)	100	84	85	-	3-y	76% and 95% MRD negative after cycle 1 and overall, respectively; no relapse/death in

		consolidation +/- R/Ofatumumab (CD20+) +/- InO x4 after consolidation								InO-treated group (OS 100%)
MDACC[31]	B-ALL	Hyper-CVAD 4 cycles (50% dose reduction) + Blinatumomab x4 after induction and x3 after consolidation + R/Ofatumumab (CD20+) in induction/consolidation	37 (29-45)	38	100	73	81	-	3-y	Amended to HyperCVAD 2 cycles (75% dose reduction) in HR patients; overall MRD negativity 97%; OS 88% no HR feature vs. 76% any HR feature
HOVON [244]	CD19+ B-ALL (37% Ph+)	SOC + Blinatumomab x2 (prephase and after consolidation I)	53 (18-70)	71	77	-	53 (Ph-)	68 (Ph-)	2-y	53% and 91% MRD negative after Blinatumomab I and II, respectively; EFS and OS 71% and 73% in patients ≤ 60 years
GMALL08 [32]	CD19+ B-ALL (MRD positive)	Blinatumomab 1 cycle in MRD positive patients after consolidation I	18-35	63	all CR/ MRD +	-	-	71%	3y	55% molecular CR after Blinatumomab I; subsequent SCT indicated in all patients
ECOG-ACRIN (Phase 3)[33]	CD19+ B-ALL (MRD negative)	A: SOC consolidation B: SOC consolidation + Blinatumomab x4	51 (30-70)	112 112	81	-	NR 71.4	-	5y	CR rate on all study patients (n=488); median OS arm B not reached (NR, >70% at 5 years) vs. 71.4 months (P=0.003)
Nelarabine (T-specific nucleoside analog)										
MDACC[154]	T-ALL/LBL	Hyper-CVAD + Nelarabine after course 8 (x2) or 5 and 7 (x1 each)	30 (13-78)	81	NR	-	57	52	5-y	OS non-ETP 63% vs. ETP 32% (P<0.001); non-ETP: OS nelarabine 83% vs. no nelarabine 38% (P=0.003)
UKALL 14 (Phase 3)[152]	T-ALL	A: SOC B: SOC + Nelarabine x1 after Induction II	25-65	75 69	90 87	-	61 65	57 61	3-y	No benefit from single Nelarabine course (3 doses), all P values not significant

Abbreviations: GMALL, German Multicenter Group for Adult ALL; MDACC, M.D. Anderson Cancer Center; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; GRAALL, Group for Research on Adult ALL; HOVON, Hemato-Oncology Foundation for Adults in the Netherlands; CR, complere remission; CRD/RFS, CR duration/relapse-free survival; OS, overall survival; EFS, event-free survival; FUP, follow-up R, Rituximab; InO, Inotuzumab Ozogamicin; A, B: study arms in randomized trials; SoC, standard of care (chemotherapy); MAC SCT, myeloablative conditioned SCT; NR, not reported; LBL, lymphoblastic lymphoma

Table 2. Results of HSCT for Adults with ALL (Selected Studies)

Study	Population	Donor	N	OS (%)	LFS (%)	RI (%)	TRM (%)
Nishiwaki et al, 2013[245]	Ph- in CR1	MSD	388	65 (4y)	62 (3y)	25 (3y)	13 (3y)
		URD	434	64 (4y)	61 (3y)	17 (3y)	22 (3y)
		Cord blood	95	57 (4y)	51 (3y)	22 (3y)	27 (3y)
	Ph- in CR>1	MSD	89	47 (4y)	48 (3y)	31 (3y)	21 (3y)
		URD	158	39 (4y)	38 (3y)	26 (3y)	36 (3y)
		Cord blood	53	48 (4y)	44 (3y)	29 (3y)	27 (3y)
Giebel et al, 2016 [63]	Ph+ and Ph-, CR1	MSD	252	71 (2y)	61 (2y)	26 (2y)	13 (2y)
		URD	310	67 (2y)	60 (2y)	19 (2y)	21 (2y)
Cahu X, et al., 2016 [246]	T-ALL in CR1	MSD+URD	414	54 (5y)	51 (5y)	-	-
	T-ALL in CR2		93	37 (5y)	33 (5y)	-	-
	T-ALL in CR>2 or active disease		94	12 (5y)	9 (5y)	-	-
Brissot et al, 2015 [247]	Ph+ in CR1	MSD	234	45 (5y)	36 (5y)	43 (5y)	20 (5y)
		URD	249	47 (5y)	40 (5y)	30 (5y)	30 (5y)
Giebel et al, 2018[248]	Ph+ in molecular CR1	MSD	255	70 (2y)	55 (2y)	28 (2y)	18 (2y)
		URD	247	69 (2y)	60 (2y)	19 (2y)	22 (2y)
		Autologous	67	70 (2y)	52 (2y)	47 (2y)	2 (2y)
Pavlu et al, 2017[249]	Ph+ and Ph-, primary induction failure*	Various	86	23 (5y)	17 (5y)	54 (5y)	29 (5y)
Shem-Tov et al, 2020 [250]	Ph+ and Ph- in CR1	Matched URD	809	62 (3y)	53 (3y)	28 (3y)	19 (3y)
		Mismatched URD	289	62 (3y)	55 (3y)	25 (3y)	20 (3y)
		Haploidentical**	136	54 (3y)	49 (3y)	28 (3y)	23 (3y)
Nagler et al 2021 [251]	Ph+ and Ph- in CR1 or CR2	MSD	1891	67 (2y)	55 (2y)	32 (2y)	13 (2y)
		Haploidentical**	413	59 (2y)	51 (2y)	26 (2y)	23 (2y)
Beelen et al, 2022[252]	Ph-, HR, CR1, prospective trial	MSD	176	59%(5y)	56%(5y)	23%(5y)	21%(5y)
		URD	366	58%(5y)	55%(5y)	25%(5y)	20%(5y)
Marks et al, 2022[75]	Unfit for myeloablative conditioning, CR1	MSD/URD	249	55 (4y)	47 (4y)	34 (4y)	20 (4y)

Abbreviations: MSD, matched sibling donor; URD, unrelated donor; MUD, matched unrelated donor (10/10); MMUD, mismatched unrelated donor (9/10); *no CR after at least 2 cycles of induction; **unmanipulated graft

Table 3: Results of Chemotherapy and Antibody Therapy in Older Patients

Author	Year	Age	Ph+	Patients (N)	CR/CRi rate	Early death	Failure	CCR*	DFS/EFS*	OS**
Chemotherapy										
Hunault-Berger et al[253]	2010 Arm 1 Arm 2	 68 (55-77) 66 (60-80)	 no	 31 29	 90% 72%	 7% 10%	 3% 17%	 32% (2 y) 52% (2 y)	 n.r.	 35% (2 y) 24% (2 y)
Gökbuget et al[97]	2012	57 (55-85)	no	268	76%	14%	10%	32% (5 y)	n.r.	23% (5 y)
Fathi et al[254]	2016	58 (51-72)	yes	30	67%	3%	30%	n.r.	52% (2 y)	52% (2 y)
Ribera et al[255]	2016	66 (56-79)	no	54	74%	14%	14%	n.r.	8;24% (2y)***	12; 30% (2y)***
Kozlowski et al [94]****	2017	69 (62-82)	yes	35	71%	20%	9%	n.r.	n.r.	20% (3 y)
Kozlowski et al [94]*****	2017	63 (55-79)	yes	79	89%	13%	n.r.	n.r.	n.r.	39% (3 y)
Gökbuget et al[89]	2022 Cohort1 Cohort2	68 (56-86)	No	841 593 248	73% 72% 75%	14% 15% 9%	13% 13% 16%	37% (3 y)	n.r.	28% (5 y) 32% 50%
Chemo-Immunotherapy										
Stelljes et al[103] InO Chemo	2022	64 (56-80)	no	43	100%	0%	0%	n.r.	73% (2y)	81% (2y)
Chevallier et al[101] InO Chemo	2022	68 (55-84)	No	131	90%	n.r.	n.r.	n.r.	50% (2y)	54% (2y)
Gökbuget et al[104] Chemo Blina	2021	65 (56-76)	No	34	83%	7%	10%	n.r.	89% (1y)	84% (1y)
Advani et al[102] Blina Mono	2022	75 (66-84)	No	29	66%	n.r.	n.r.	n.r.	37% (3y)	37% (3y)
Nasnas et al[105] InO Blina Chemo	2022	68 (60-87)	No	80	99%	0%	0%	n.r.	n.r.	46% (5y)

Abbreviations: Ph+, Ph/BCR::ABL1 positive ALL included yes or no; Arm 1 continuous infusion Doxorubicin; Arm 2 pegylated Doxorubicin; Cohort1: Original version of protocol; Cohort 2: more dose density, PEG-Asp consolidation, MRD-based Blina; Blina, Blinatumomab; InO, Inotuzumab Ozogamicin; CCR continuous complete remission; DFS disease free survival; EFS event free survival; OS overall survival; * median months or probability; ** probability; *** estimated from Kaplan Meier Curve; ****EWALL protocol; ***** ABCVD protocol

Table 4: Prospective trials of 2nd and 3rd generation TKI as front-line therapy for Ph+ ALL

TKI	Reference	N	Age	Treatment	CR rate	Molecular response	Allogeneic SCT rate	RFS/EFS	Survival
Dasatinib									
70 mg BID	Foa et al, 2011[112]	53	54 (24-77)	Prednisone		15% (d 85)	42%	22% (20 mos.)	31% (20 mos.)
50mg BID/100mg QD 100mg QD-70 mg QD	Ravandi et al, 2015[116]	72	55 [21-80]	HyperCVAD	96%	65%	17%	44% (5y)	46%(5y)
50mg BID/100mg QD 70 mg QD	Ravandi et al, 2016[111]	97	44 [20-60]	HyperCVAD	88%	—	42%	62% (3y)	69% (3y)
140 mg QD; >70y: 100 mg QD	Rousselot et al, 2016[117]	71	69 [55-83]	EWALL backbone		24%	10%	28% (5y)	36% (5y)
140 mg QD	Foa et al, 2020[126]	63	54 [24-82]	Cortico-steroids	98%	60% (2 cycles blinatumomab	38%	88% (18 mo. med. FU)	95% (18 mos. med. FU)
Nilotinib									
400 mg BID	Kim et al, 2015[256]	90	47 [17-71]	Intensive chemotherapy	91%	77% (3 mo)	63%	72% (2y)	72% (2y)
400 mg BID	Ottmann et al, 2018[257]	72	66 [55-85]	EWALL backbone	94%	58% <0.01%	33%	42% (4y)	47% (4y)
Ponatinib									
45-30-15 mg QD	Jabbour et al, 2018[109]	76	47 [IQR 39-61]	HyperCVAD	98%	83%	20%	67% (5y)	71 (5y)
30-15 mgQD	Ribera et al 2022[123]	30	49 (19-59)	Intensive Chemotherapy	100%	71%(wk 16)	87%	70 (3y)	96 (3y)
45-30-15 QD	Martinelli et al, 2022 [258]	44	66.5	Alone	90.9 at week 6, 86.4 at month 6	47.7% t week 6 40.9 at month 6	11% (transplant unplanned)	48% at 3y	58% at 3y

Table 5: Results in Adult Ph-like ALL

Author, year	Age group (yrs)	Total patients and frequency of Ph-like ALL in B-other	5 year survival (EFS or OS)
Roberts et al, 2014[141]	16-20 21-39	77 (21%) 46 (27%)	EFS 41%, OS 66% EFS 24%, OS 26%
Herold et al, 2014[259]	16-20 21-39 40-55 55-84	5 (19%) 12 (18%) 4 (9%) 5 (7%)	DFS (all ages) 19% OS (all ages) 22%
Boer et al, 2015[138]	16-20 21-39 40-71	6 (25%) 9 (19%) 6 (11%)	EFS (all ages) 24% OS (all ages) 30%
Jain et al, 2017[260]	15-39 40-84	33 (42%) 16 (24%)	OS (all ages) 23%
Roberts et al, 2017[142]	21-39 40-59 60-86	96 (28%) 62 (20%) 36 (24%)	EFS 24% EFS 21% EFS 8%
Chiaretti et al, 2018[140]	0-15 15-35 35	2 (9%) 29 (29%) 23 (31)%	EFS (excl. children) 22% OS (excl. children) 37%
Stock et al, 2019[5]	17-39	41 (31%)	OS (3y): 63%
Chiaretti et al, 2021 [144]	18-65	28 (32%)	EFS (2y), 34% OS (2y), 40%

Table 6: Immunotherapy Studies in R/R BCP-ALL

Multicentre Antibody-Based Studies

Reference	Study	Eligibility	Patients, N	Median age (range)	Prior alloHSCT	ORR	Molecular response	Bridge to alloHSCT	OS estimate or median
Kantarjian et al, 2016[99]	INO Phase 3 (INO-VATE)	≥18 years R/R CD22+ ALL	109 (67% salvage 1)	47 years	16%	81%	63%	40%	7.7 months
Topp et al, 2015[261]	Blinatumomab Phase 2	≥18 years Ph-neg R/R ALL CR1 <12 months	189 (61% salvage 1)	36 years	34%	43%	35%	40%	6.1 months
Kantarjian et al, 2017[173]	Blinatomomab Phase 3 (TOWER)	≥18 years Ph-neg R/R ALL CR1 <12 months	271 (42% salvage 1)	37 years	35%	44%	36%	14%	7.7 months
Gökbuget et al,2018[60]	Blinatumomab Phase 2 (BLAST)	≥18 years ALL in HCR MRD≥0.1%	116 (65% CR1)	45 years	NA	NA	80% complete MRD response	67%	36.5 months
Brown et al,2021[175]	Blinatumomab COG AALL1331	1-30 years HR/IR ALL in first relapse	105 (all salvage 1)	9 years	NA	NA	79%	73%	79% at 24 months
Locatelli et al, 2021[176]	Blinatunomab Phase III International	1-18 years HR, in firstrelapse	108 (all salvage 1)	5 years	NA	NA	90%	89%	80% at 24 months

CART19 studies

Reference	Institution	Co-activation domain	Patients			ORR %	CRS incidence, %	Neurotoxicity incidence, %	OS estimate or median
			Screened, N	Median age (range)	Infused, N				
Maude et al,2014[177]	Penn	4-1BB	NR	14 years (5-60)	30	90%	100% (severe, 27%)	43%	78% at 6 months
Davila et al, 2014[178]	MSKCC	CD28	NR	50 years (NA)	16	88%	44% (severe)	25% (Gr 3/4)	NR
Lee et al, 2015[179]	NCI	CD28	NR	15 years (5-27)	21	67%	76% (Gr 3/4, 29%)	19% (Gr 3/4, 5%)	52% at 12 months
Turtle et al,2016[180]	FHCRC	4-1BB	32	40 years (20-73)	30	97%	83%	50% (Gr 3/4, 50%)	NA
Gardner et al, 2017[181]	SCRI	4-1BB	45	12 years (1-25)	43	93%	93% (severe, 23%)	44% (severe, 21%)	69.5% at 12 months
Maude et al, 2018[182]	Multicentre	4-1BB	92	11 years (3-23)	75	81%	77%	40% (Gr 3/4, 13%)	76% at 12 months
Park et al, 2018[183]	MSKCC	CD28	83	44 years (23-74)	53	83%	85% (Gr 3/4, 26%)	48% (Gr 3/4, 42%)	median, 12.5 months
Hay et al, 2019[184]	FHCRC	4-1BB	59	39 years (20-76)	53	85%	NR	NR	median, 20 months in MRD-neg pts
Shah et al, 2021[185]	Multicentre	CD28	71	44 years (30–59)	55	71%	89% (Gr3/4 24%)	60% (Gr3/4/5 26%)	Median 18.2 months

NCI: National Cancer Institute; FHCRC: Fred Hutchinson Cancer Research Center; SCRI: Seattle Children's Research Institute; MSKCC: Memorial Sloan Kettering Cancer Center; HR: high risk; IR: intermediate risk; HCR: hematologic CR; ORR: overall response rate; CRS: cytokine release syndrome; OS: overall survival; NR: not recorded; NA: