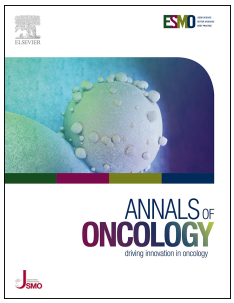

ESMO Clinical Practice Guideline interim update on the use of targeted therapy in acute lymphoblastic leukaemia

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ESMO Clinical Practice Guideline interim update on the use of targeted therapy in acute lymphoblastic leukaemia

D. Hoelzer[1], R. Bassan[2], N. Boissel[3], C. Roddie[4], J. M. Ribera[5] & M. Jerkeman[6], on behalf of the ESMO Guidelines Committee*

[1]ONKOLOGIKUM Frankfurt am Museumsufer, Frankfurt, Germany; [2]Hematology Unit, Ospedale dell'Angelo e Ospedale SS, Giovanni e Paolo, Mestre-Venezia, Italy; [3]Hematology Department, Saint-Louis Hospital, APHP, Institut de Recherche Saint-Louis, Université de Paris Cité, Paris, France; [4]Research Department of Haematology, UCL Cancer Institute, London, UK; [5]Clinical Hematology Department, ICO-Hospital Germans Trias i Pujol, Jose Carreras Research Institute, Universitat Autonoma de Barcelona, Barcelona, Spain; [6]Department of Oncology, Skåne University Hospital and Lund University, Lund, Sweden.

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, CH-6900 Lugano, Switzerland.

E-mail: clinicalguidelines@esmo.org (ESMO Guidelines Committee)

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Highlights (online only):

- This ESMO Clinical Practice Guideline update provides key recommendations for managing acute lymphoblastic leukaemia.

- The update covers recent developments in the use of targeted therapies.
- Algorithms for the management of newly diagnosed and relapsed or refractory disease are provided.
- The author group encompasses a multidisciplinary group of experts from different institutions in Europe.
- Recommendations are based on available scientific data and the authors' collective expert opinion.

The following ESMO Clinical Practice Guideline (CPG) has been recently updated with new treatment recommendations:

Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[1]

EUPDATE

View the original CPG here: https://www.esmo.org/guidelines/guidelines-by-topic/haematological-malignancies/acute-lymphoblastic-leukaemia

INTRODUCTION

The introduction of immunotherapy with monoclonal antibodies (mAbs) is a major step forward for adults and children with B-lineage acute lymphoblastic leukaemia (ALL) and will change the treatment paradigm substantially.

With intensive multi-agent chemotherapy (ChT) in children with ALL, long-term cure has been achieved in ≥90% of patients; however, this approach is often associated with long-term sequelae. Until recently, aggressive ChT has also been used in adult patients, with an overall cure rate of 50%. Survival rates are higher (~70%) in adolescents and young adults (AYAs) but lower (<20%) in elderly patients. The major hazard of treatment is myelotoxicity leading to infection, which causes death in the induction and consolidation phases in 1%-3% of children and ≤10% of adults, increasing to ≤20% of elderly patients aged >70 years. With haematopoietic stem cell transplantation (HSCT), cure can be achieved in approximately half of adults; however, this approach is also associated with substantial toxicity and treatment-related mortality (TRM) rates of 10%-20%.

Immunotherapy may provide new possibilities for B-lineage ALL, with very promising response and cure rates. Immunotherapy is associated with toxicities, but these are manageable and the TRM rate is low (~1%). Immunotherapeutic approaches have been explored in different disease settings, initially in relapsed or refractory (r/r) ALL and in patients with minimal residual disease (MRD), and more recently as first-line therapy, either as monotherapy or in combination with ChT. **Table 1** provides an overview of currently available targeted therapies.

MRD can be evaluated in >95% of patients with B-lineage ALL and is measured by flow cytometry or quantitative PCR of immunoglobulin (Ig) and T-cell receptor (Ig/TR) rearrangements, and specific gene rearrangements (e.g. *BCR::ABL1*). It requires diagnostic material and can be followed in each patient individually. MRD negativity is commonly defined as <0.01% of blast cells in the sample.[1] MRD negativity after induction or consolidation therapy is achieved in ~70% of standard-risk patients. These patients have a good prognosis, with a 5-year overall survival (OS) rate of ≥70%.[2] In high-risk patients defined by conventional prognostic criteria [e.g. white

blood cell count ≥30 000 μL at diagnosis, immunological adverse subtypes, late complete remission (CR) achieved after course 2], the rate of MRD negativity after induction or consolidation is ~50%. Patients remaining MRD positive have a poor prognosis, since nearly all adults relapse and are difficult to rescue.[3]

mAbs target B-cell antigens corresponding to the different stages of B-cell differentiation. **Table 2** provides an overview of mAbs that have been explored in prospective clinical trials. Most mAbs for the treatment of ALL target cluster of differentiation (CD)20, CD22 or CD19, since these cell surface markers are highly expressed in ALL blasts. The CD20 antigen is present in 86%-100% of Burkitt lymphoma/leukaemia cases and 30%-50% of B-cell precursor ALL (BCP-ALL) cases. CD22 is expressed in >90% of BCP-ALL cases and CD19 expression ranges from 95% to 100% in BCP-ALL (see **Table 2**).[4-6]

TREATMENT OF NEWLY DIAGNOSED ALL

A proposed algorithm for the treatment of newly diagnosed ALL is shown in **Figure 1**.

Targeted therapies

Rituximab in Burkitt lymphoma/leukaemia. Rituximab is a chimeric antibody against the surface CD20 antigen with a murine variable region and a human fragment crystallisable region. Rituximab was first explored in non-Hodgkin lymphoma (NHL) and Burkitt lymphoma/leukaemia, and later in CD20 B-lineage ALL. In most studies, a CD20 expression of ≥20% was required for inclusion.

In 14 studies of 739 patients with Burkitt lymphoma/leukaemia receiving several ChT regimens, CR was achieved in 83% (range 63%-95%) of patients and the 3-year OS rate was 62% (see **Supplementary Table S1**, available at *Annals of Oncology* online).[7] Patients aged ≤79 years were included, with reduced regimens permitted for patients aged >55/60 years. These successful ChT regimens were then combined with rituximab (see **Supplementary Table S1**, available at *Annals of Oncology* online). Most of the studies were large, national multicentre trials. An M. D. Anderson Cancer Center (MDACC) study[8] concluded that the addition of rituximab to

hyperfractionated cyclophosphamide–vincristine–doxorubicin–dexamethasone (hyper-CVAD) may improve outcomes in adult Burkitt-type lymphoma or B-cell ALL (B-ALL), particularly in elderly patients. Younger age and the addition of rituximab were identified as favourable prognostic factors. In the largest Burkitt trial of the German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia (GMALL),[7] which included 363 patients across 99 centres, a high CR rate of 86% was achieved with rituximab–ChT. The full treatment could be applied in 86% of patients. The most important prognostic factors were International Prognostic Index (IPI)[9,10] score (0-2 versus 3-5, *P* = 0.0005), age-adjusted IPI score (0-1 versus 2-3, *P* = 0.0001) and gender (male versus female, *P* = 0.004).

The Group for Research on Adult ALL (GRAALL) and the Lymphoma Study Association (LYSA) study group[11] evaluated rituximab–ChT in a randomised trial in Burkitt leukaemia/lymphoma. Patients were stratified into two groups based on disease extension: either absence or presence of bone marrow or central nervous system (CNS) involvement, both non-adverse factors. They were further stratified according to age (<40 years, 40-60 years and >60 years). Rituximab was associated with significant improvements in 3-year event-free survival (EFS) rate (75% versus 62% in the rituximab and non-rituximab arms, respectively, *P* = 0.025) and 3-year OS rate (83% versus 70%, *P* = 0.012). In the Alliance Cancer and Leukemia Group B (CALGB) 10002 study,[12] high remission rates and durable remissions were achieved with rituximab–ChT; however, the regimen was associated with substantial toxicity. Seven patients died from treatment-related causes, including five patients aged >60 years. Thus, high-risk patients still had worse outcomes in terms of CR rate, EFS and OS. The United States-National Cancer Institute (US-NCI) multicentre trial[13] included patients aged ≤86 years. The study investigators concluded that rituximab–ChT was effective in adult Burkitt lymphoma regardless of age or human immunodeficiency virus status but noted that improved strategies for adults with cerebrospinal fluid involvement are needed.

In the above studies, response rates were only marginally improved by the addition of rituximab, with CR rates of 83%-88%. Long-term EFS, however, improved substantially to 80%-89% in all studies, which is an improvement of ~20%. Based on

these results, the addition of rituximab to intensive ChT in adult Burkitt lymphoma/leukaemia is now considered standard of care (SoC).

Treatment schedule. Rituximab was administered at the standard dose of 375 mg/m^2 intravenously 1 day before ChT, as in NHL trials. In most studies, eight infusions of rituximab were applied and this is the recommended standard.

Rituximab in adult CD20-positive BCP-ALL. Rituximab was evaluated in adult CD20-positive (CD20+) BCP-ALL in combination with ChT in the first-line setting (see **Supplementary Table S2**, available at *Annals of Oncology* online). In the MDACC study,[14] the hyper-CVAD protocol was combined with eight doses of rituximab over the course of four cycles. This led to an increase in 3-year CR duration rate from 40% with SoC to 67% with added rituximab. A benefit in 3-year OS rate was observed in patients aged <60 years (47% with SoC versus 75% with added rituximab), but there was no advantage for patients aged ≥60 years (34% versus 28%, respectively), most likely due to a high rate of death in CR in this age group.

In a GMALL group study,[15] standard-risk patients received eight doses of rituximab in induction and consolidation cycles. In patients receiving rituximab, the CR rate was 94% and the rate of MRD negativity was higher than in the non-rituximab group, achieving a molecular remission rate of 90% by week 16 compared with 59% in patients receiving ChT alone. This translated into a 5-year OS rate of 71%. High-risk patients received only four rituximab doses since they underwent HSCT and, therefore, the effect of rituximab cannot be evaluated. Nevertheless, an HSCT rate of 69% was achieved in high-risk patients due to a high MRD negativity rate. In a randomised study of the GRAALL group,[16] the addition of 16-18 rituximab infusions had no significant effect on CR or MRD negativity rates. There was, however, a significant improvement in EFS, with reduced incidence of relapse. More patients underwent allogeneic HSCT (allo-HSCT) in the rituximab arm compared with the SoC arm. In the randomised United Kingdom Acute Lymphoblastic Leukaemia (UKALL-14) study,[17] patients received only four doses of rituximab. There was no statistically significant difference in CR or MRD negativity rates. A statistically

significant benefit was observed, however, with rituximab–SoC in patients who received myeloablative allo-HSCT, with a 3-year EFS rate of 72.2% (*n* = 40) versus 50.7% with SoC (*n* = 53, *P* = 0.03), although it seems unlikely this effect is solely attributable to the four doses of rituximab.

CD20 expression. In the studies described above, with the exception of the UKALL-14 study, only patients with CD20 expression in ≥20% of leukaemic blast cells were included in the analyses of rituximab–ChT efficacy.[18] After the demonstration that corticosteroids can increase CD20 expression in ALL, and taking into account that corticosteroids are included in induction therapy in children and adults, it was considered that all patients with BCP-ALL should receive rituximab, irrespective of CD20 expression levels. A recent study[17] reported that the best cut-off for expression of CD20 in blast cells was 11.7%, but this has not been further confirmed. Thus, rituximab is still the SoC if CD20 expression is ≥20%.

Ofatumumab. In an MDACC study,[19] ofatumumab, a second-generation anti-CD20 antibody with higher complement-dependent cytotoxicity and a slower dissociation rate compared with rituximab, was combined with hyper-CVAD in CD20+ BCP-ALL in a first-line setting. Ninety eight percent of the patients (aged 18-71 years) achieved CR, with an MRD negativity rate of 93% and an estimated 4-year OS rate of 68%. The regimen was not superior to hyper-CVAD–rituximab in patients with CD20 expression in ≥20% of blast cells, but there was evidence of improved OS with ofatumumab compared with rituximab in patients with low CD20 expression (≥1%).

Blinatumomab. Blinatumomab is a CD3/CD19 bispecific T-cell-engager (BiTE) antibody that consists of a small single-chain peptide connecting two single-chain variable fragments, which simultaneously binds both CD19 on lymphoblasts and CD3 on T cells (BiTE mechanism). After binding to its CD19 target, blinatumomab activates T cells and leads to polyclonal expansion of cytotoxic CD8+ T cells, T-cell activation and cell lysis of CD19+ lymphoblasts via release of cytokines and cytotoxic granules.[20]

Treatment schedule. Blinatumomab is usually given as a 28-day continuous infusion at a dose of 9 µg/day for the first week of induction, followed by 28 µg/day

thereafter. Blinatumomab has a short half-life and therefore requires continuous infusion (subcutaneous administration is in development). Dexamethasone prophylaxis is often given for patients with a high disease burden.

Toxicity. The major toxicities of blinatumomab are cytokine release syndrome (CRS) and neurotoxicity. Any-grade CRS has been reported in 3%-14% of patients and grade ≥3 CRS in 2%-6%.[21] Any-grade neurotoxicity occurred in 20%-53% of patients and grade ≥3 in 7%-14%.[21] Both toxicities can be severe but are manageable, and there is a reduction in adverse events (AEs) after subsequent cycles of blinatumomab.

Blinatumomab in first-line therapy. Blinatumomab as first-line therapy in adult ALL has been explored in phase II and III studies, as summarised below, and in another ongoing phase III [GOLDEN GATE (NCT04994717)]. These studies have combined blinatumomab with ChT in Philadelphia chromosome-negative ALL (Ph– ALL) and with tyrosine kinase inhibitors (TKIs) in Philadelphia chromosome-positive ALL (Ph+ ALL), with highly promising early results in both conditions (see **Supplementary Table S3**, available at *Annals of Oncology* online).

In an MDACC group study of patients aged 64-72 years with Ph– ALL,[22] inotuzumab ozogamicin (INO) was combined with low intensity hyperfractionated cyclophosphamide–vincristine–dexamethasone (mini-hyper-CVD) with or without blinatumomab. In 64 evaluable patients, a very high CR rate of 98% was achieved, with a corresponding MRD negativity rate of 97%. The MDACC group also applied hyper-CVAD–blinatumomab in younger patients with Ph– ALL.[23] All patients achieved CR and 96% achieved MRD negativity, with a 1-year OS rate of 89%. Overall, both studies support the notion that the combination of blinatumomab with intensive hyper-CVAD or hyper-CVD is feasible and that encouraging results can be achieved.

The Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) group[24] applied intensive ChT plus two blinatumomab cycles in 146 adults (aged 18-65 years) with Ph– ALL. The CR rate was 90%, and 95% of patients with CR were MRD negative following the first course of blinatumomab. The 1-year OS rate was 84%, with a very

low relapse rate (3.2%) in patients who did not express a Philadelphia chromosome-like (Ph-like) gene signature. The GRAALL group[25] treated 95 adult patients with Ph– ALL and high-risk characteristics defined by genetics and/or MRD with a consolidation programme alternating intensive ChT with blinatumomab (five cycles). The MRD conversion rate was 74% in evaluable patients and 42% of patients underwent HSCT. The 1.5-year OS rate was 92%, with low pre-blinatumomab MRD and post-blinatumomab MRD negativity acting as favourable prognostic factors for disease-free survival (DFS).

The Australasian Leukemia and Lymphoma Group (ALLG)[26] treated 30 older adults (median age 52 years) with Ph– ALL with sequential reduced intensity induction ChT followed by hyper-CVAD consolidation alternating with blinatumomab (three cycles). All patients achieved CR and 83% became MRD negative. The predicted 2-year OS rate was 69%, with a low transplantation rate. The GMALL group[27] treated 34 older patients (median age 65 years) with Ph– ALL with de-intensified ChT and blinatumomab as consolidation. CR and MRD negativity rates were in the 70% range, with 84% survival at 1 year. The Southwest Oncology Group (SWOG) 1318 study[28] treated 29 patients with Ph– ALL (median age 75 years, range 66-84) with blinatumomab as induction and consolidation therapy followed by maintenance ChT with prednisone–vincristine–6-mercaptopurine–methotrexate. The CR rate was 66% and the 3-year DFS and OS rates were both 37%.

The phase III ECOG-ACRIN Consortium E1910 study treated 488 adult patients with Ph– ALL (aged 30-70 years) using a Berlin-Frankfurt-Münster (BFM)-like ChT schedule adapted from the ECOG2993/UKALLXII protocol, randomising patients with CR who had achieved MRD negativity (<0.01% by flow cytometry) to zero (control arm) or four additional blinatumomab courses during consolidation therapy.[29] In total, 224 MRD-negative patients were randomised (112 in each arm). Median OS was not reached in blinatumomab arm versus 71.4 months in the control arm (P = 0.003). The study established the superiority of blinatumomab-containing consolidation therapy in older adults with MRD-negative Ph– ALL.

Blinatumomab in MRD-positive ALL. A first pilot study of the GMALL group[30] evaluated whether blinatumomab monotherapy could benefit patients remaining MRD positive after induction or consolidation therapy. Of the 20 enrolled patients (aged 20-77 years), 80% had a conversion from MRD positivity to negativity, including patients with Ph+ ALL and t(4;11) translocation. In most patients, the MRD conversion was achieved with one cycle of blinatumomab. Median OS was equal for patients with or without subsequent HSCT. Following these encouraging findings, a large international confirmatory study (BLAST)[31] was initiated across 46 centres. Of 116 patients (aged 18-76 years), 78% achieved MRD negativity with blinatumomab, as well as a median OS of 36.5 months at 5 years and an HSCT rate of 82%. Blinatumomab was tolerable, with grade 3 and grade 4 neurological AEs reported in 10% and 3% of patients, respectively, and CRS reported in 3%. Based on these results, the Food and Drug Administration (FDA) approved blinatumomab for patients with BCP-ALL in morphological remission with MRD. Whether patients achieving MRD negativity after blinatumomab are candidates for HSCT is unknown and currently under prospective evaluation.

INO. INO is an antibody–drug conjugate, which consists of calicheamicin, a DNA-binding cytotoxic antibiotic, covalently linked to an anti-CD22 IgG4 mAb.[32] Recently, first-line studies have suggested that INO may be combined with ChT for the treatment of elderly patients with CD22+ ALL (see **Supplementary Table S4**, available at *Annals of Oncology* online). In a phase II study by the MDACC group,[33] 52 patients aged >60 years with Ph– ALL received a combination of six cycles of low-intensity ChT (mini-hyper-CVD) with INO given as a single dose on day 3 of the first four cycles (1.3-1.8 mg/m^2 at cycle 1, 1.0-1.3 mg/m^2 in subsequent cycles). The overall response rate (ORR) was 98% [95% confidence interval (CI) 94% to 100%]. The 2-year progression-free survival (PFS) and OS rates were 59% (95% CI 43% to 72%) and 66% (95% CI 50% to 78%), respectively. Four patients (8%) developed veno-occlusive disease (VOD); one of these occurred after allo-HSCT and had a fatal outcome. These encouraging results in the elderly population were recently confirmed by the phase II EWALL-INO study[34] that evaluated the combination of ChT with sequential INO in 90 patients aged ≥55 years with newly diagnosed CD22+ Ph– ALL. The ORR was 86% and 1-year relapse-free survival (RFS) and OS rates were

75% (95% CI 64% to 83%) and 78.5% (95% CI 68% to 86%), respectively. Three patients developed VOD (3.3%); one of these occurred after allo-HSCT. Phase III studies are ongoing predominantly in children and AYAs with Ph– ALL, with a specific focus on improving the outcome of patients who are not eligible for allo-HSCT [e.g. ALLTogether (NCT04307576), ALLIANCE A041501 (NCT03150693), COG ALL1732 (NCT03959085)].

Ph+ ALL. Recently, important advances have been made in the treatment of Ph+ ALL (see **Supplementary Tables S5** and **S6**, available at *Annals of Oncology* online):

- Attenuation of induction ChT;
- Administration of TKIs as maintenance therapy after allo-HSCT;
- Use of third-generation TKIs upfront in the setting of clinical trials;
- Incorporation of immunotherapy to first-line therapy;
- ChT-free regimens for induction and consolidation.

Third-generation TKIs as first-line therapy in adults with Ph+ ALL. A phase II trial combined hyper-CVAD with ponatinib, initially at a dose of 45 mg/day.[35] The protocol was amended to reduce the dose of ponatinib to 30 mg/day at cycle 2, with further reduction to 15 mg/day once a complete molecular response (CMR) was achieved. The most recent results from the study reported a complete haematological response (CHR) rate of 100% for the 65 patients with active disease at enrolment, with CMR achieved in 63 of 76 patients (83%) included in the trial.[35] The 3-year EFS and OS rates were 70% and 76%, respectively, remaining unmodified with prolonged follow-up. Only 20% of patients underwent allo-HSCT. The phase II PONALFIL trial combined ponatinib (30 mg/day) with standard induction and consolidation ChT followed by allo-HSCT in 30 patients aged 18-60 years.[36] Ponatinib was only given after allo-HSCT if MRD positivity persisted or reappeared. CHR was achieved in all patients and allo-HSCT was carried out in 26

patients (20 in CMR and 6 in major molecular response). The 3-year EFS and OS rates were 70% and 97%, respectively.

Imatinib and dasatinib were compared in an open-label, phase III randomised clinical trial in children with newly diagnosed Ph+ ALL in China.[37] The 4-year EFS (primary outcome) and OS rates were 71.0% and 88.4%, respectively, in the dasatinib group versus 48.9% and 69.2%, respectively, in the imatinib group. PhALLCON is a global open-label phase III registration study, which randomises newly diagnosed adult patients with Ph+ ALL 2:1 to receive ponatinib (30 mg/day) or imatinib (600 mg/day) plus reduced-intensity ChT.[38] PhALLCON is the first randomised study to compare the efficacy and safety of first-line ponatinib versus imatinib with reduced-intensity ChT. The composite primary endpoint is MRD-negative (*BCR::ABL1* ≤0.01%) CR for 4 weeks at end of induction (EOI). EFS is a key secondary endpoint. Among the 245 patients randomised, a significantly higher MRD-negative CR rate at EOI was observed with ponatinib versus imatinib (34.4% versus 16.7%, *P* =0.0021). At data cut-off, median EFS was reached with imatinib but not with ponatinib [hazard ratio (HR) 0.65, 95% CI 0.39-1.10].

To date, dasatinib and ponatinib have not been compared in a head-to-head trial. Outcomes of the hyper-CVAD–ponatinib trial were compared with that of hyper-CVAD–dasatinib with 1:1 matching propensity score.[39] The 3-year EFS rates for hyper-CVAD–ponatinib and hyper-CVAD–dasatinib were 69% and 46%, respectively (*P* = 0.04), and the 3-year OS rates were 83% and 56%, respectively (*P* = 0.03). A propensity score analysis comparing the PONALFIL and ALLPh08 trials (using the same schedule with imatinib instead of ponatinib) demonstrated a significant improvement in OS for patients treated with ponatinib (3-year OS rate of 97% versus 53%, *P* = 0.001).[36]

Immunotherapy in adults with newly diagnosed Ph+ ALL. In recent years, immunotherapy with blinatumomab has been incorporated in first-line therapy for adults with Ph+ ALL, with the aim of reducing or eliminating induction ChT and achieving a deeper molecular remission status (the ‘chemo-free approach’). **Section**

1 of the **Supplementary Material** and **Supplementary Table S7**, available at *Annals of Oncology* online, summarise the most important studies.

It is notable that most of these advances have resulted from phase II clinical trials. In the phase II D-ALBA trial, dasatinib was administered alongside glucocorticoids, followed by up to 5 cycles of blinatumomab as first-line therapy in adults with newly diagnosed Ph+ ALL.[40] The primary endpoint was sustained molecular response in the bone marrow after the first two cycles of blinatumomab. CHR was achieved in 98% of the 63 patients included, and 29% had a molecular response at the end of dasatinib induction. This increased to 60% after two cycles of blinatumomab. Transplantation was carried out in 29 of 58 patients (50%) who started blinatumomab. At a median follow-up of 40 months, the estimated 4-year OS and DFS rates were 78% and 75%, respectively.[41] An ongoing phase II study from the SWOG is evaluating the feasibility of combining dasatinib, prednisone and blinatumomab for older patients with *de novo* Ph+ ALL.[42] The CHR rate in the first 25 patients was 92%, with MRD-negative status at day 28 in 38% of patients. With a median follow-up of 1.7 years, the 3-year DFS and OS rates were 85% and 80%, respectively. An ongoing phase II, ChT-free trial combines ponatinib and blinatumomab during the induction and consolidation phases in patients with newly diagnosed Ph+ ALL.[43] The most recent results showed that CMR was achieved in 33 of 38 patients (87%), with a 2-year EFS and OS rate of 93%.Only one patient received allo-HSCT in this trial.

Several ongoing phase III trials are comparing ponatinib–blinatumomab versus TKI–ChT schedules. In the GIMEMA ALL2820 study (NCT04722848), ponatinib is being evaluated in induction, followed by consolidation with blinatumomab versus standard or attenuated ChT–imatinib. Another phase III study is comparing blinatumomab–TKI with hyper-CVAD–TKI in newly diagnosed Ph+ ALL (NCT04530565). These trials may lead to a change in the first-line SoC for these patients.

Apart from the evaluation of the role of immunotherapies (mAbs and cellular therapies) in the early phases of treatment, several unresolved issues remain regarding the management of Ph+ ALL:

- Identification of patients who can be cured without allo-HSCT;
- Duration of maintenance therapy with TKIs;
- Management of patients with a poor genetic background [e.g. deletion of *IKZF1* co-occurring with one or more deletions in *CDKN2A*, *CDKN2B*, *PAX5* or *PAR1* and in the absence of *ERG* deletion (*IKZF1*^{plus}) and monosomy of chromosome 7, among others];
- Definition of the best method for MRD assessment [e.g. real time quantitative PCR for *BCR::ABL*, PCR for Ig/TR rearrangements, next-generation sequencing (NGS)];
- Role of TKIs not directed to the *ABL* pocket (e.g. asciminib);
- Role of targeted therapies other than TKIs [e.g. B-cell lymphoma 2 (Bcl-2) or Bcl-xL inhibitors];

Ph-like ALL. Ph-like ALL is a high-risk subgroup of BCP-ALL. Patients with Ph-like ALL have a gene expression profile similar to those with Ph+ ALL but lack the characteristic *BCR::ABL1* fusion. This ALL subtype occurs more commonly in AYAs, accounts for 20% of ALL cases and is especially frequent in Hispanic and Latino patients.[44,45] Inferior outcomes are observed in Ph-like ALL compared with patients without Ph-like ALL.[46]

A specific approach does not yet exist for the treatment of patients with Ph-like ALL; these patients are treated with intensive ChT followed by allo-HSCT. The majority of Ph-like ALL cases carry fusion genes involving tyrosine kinases (i.e. *ABL*-class and *JAK2* and *CRLF2* rearrangements). Among other cooperating events, a relevant role is played by *IKZF1* deletions, which are present in ~70% of cases. Clinical trials aimed at testing the efficacy of dasatinib, ruxolitinib, the histone deacetylase inhibitor chidamide and blinatumomab are ongoing. Information on outcomes of patients receiving such targeted therapies is scarce at present. A retrospective study by Tanasi et al.[47] evaluated early use of a combination of ChT and TKI (imatinib or dasatinib, given at a median of 49 days from diagnosis) during first-line treatment of

19 patients with Ph-like ALL with *ABL*-class fusions. The introduction of TKIs increased the MRD negativity rate and was associated with a 3-year OS rate of 77% (96% CI 50% to 91%). A similar study in children and adolescents showed that patients with *ABL*-class fusions who received a TKI in first remission had a reduced risk of r/r disease (0% versus 63% at four years).[48]

The published experience with immunotherapy [blinatumomab, INO and CD19 chimeric antigen receptor T-cell (CAR-T) therapy] in Ph-like ALL is scarce and mainly limited to retrospective studies in patients with r/r disease (see **Section 2** of the **Supplementary Material** and **Supplementary Table S8**, available at *Annals of Oncology* online). Studies have shown higher CR, CR with incomplete count recovery and allo-HSCT rates in patients treated with immunotherapy compared with those who receive rescue ChT. Data from the aforementioned GIMEMA study of blinatumomab in newly diagnosed adult patients demonstrated a significantly higher cumulative incidence of relapse in patients with Ph-like ALL (40.1% versus 3.2%).[24]

Immune checkpoint inhibitors and other novel agents. The clinical use of immune checkpoint inhibitors (ICIs) is the third and most recent advance in targeted therapies. These molecules inhibit immune checkpoints, which malignant cells can use to avoid recognition by the immune system (immune evasion). ICIs are antibodies directed against, for example, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1) and programmed death-ligand 1. Selected clinical studies of ICIs in ALL are listed in **Supplementary Table S9**, available at *Annals of Oncology* online. Ixazomib is the first orally-available proteasome inhibitor, which works by inhibiting the cellular complexes that break down proteins. When added to first-line ChT in elderly patients with B-lineage ALL, the maximum tolerated dose of 2.3 mg was well tolerated and associated with a promising CR rate of 79%. Five patients proceeded to HSCT.[49]

T-lineage ALL. T-lineage ALL accounts for ~10%-15% of childhood ALL cases and up to 25% of adult cases.[50] According to the 2016 revision of the World Health Organization classification of acute leukaemia, T-lineage ALL is subdivided into early T-precursor, mature and cortical (thymic) T-cell ALL (T-ALL).[51] The treatment

strategy is identical to that of B-lineage ALL, but the purine analogue nelarabine is often added for consolidation therapy. Outcomes are favourable, with a haematological CR rate of ~90% and a molecular CR rate of 60%-70%. Overall outcomes differ by subtype, with 5-year OS rates of >80% for thymic T-ALL and ~60% for early T-precursor and mature T-ALL. In first-line treatment, the addition of nelarabine to ChT resulted in no demonstrable EFS benefit (5-year EFS rate 55.5% with nelarabine versus 54.1% with SoC).[52]

Recommendations

- The addition of rituximab to intensive ChT in adult Burkitt lymphoma/leukaemia and CD20+ BCP-ALL is strongly recommended [I, A; not European Medicines Agency (EMA) approved, not FDA approved].
- It is considered SoC to add rituximab to first-line ChT in adults with CD20+ BCP-ALL with CD20 expression ≥20% [I, A; not EMA approved, not FDA approved].
- Ofatumumab in addition to hyper-CVAD is a safe and highly effective regimen in patients with CD20+ Ph– ALL, particularly those with low (≥1%) CD20 expression in blast cells [III, C; not EMA approved, not FDA approved]. Further studies with ofatumumab are needed to give a final recommendation.
- Consolidation with blinatumomab improves the MRD response and outcome of patients with Ph– ALL and MRD persistence after induction and consolidation [I, A].
- Consolidation with blinatumomab improves the outcome of patients with Ph– ALL with complete MRD response after induction [II, A; not EMA approved, not FDA approved].
- INO combined with low intensity ChT in first-line treatment of elderly patients has obtained high CR and MRD negativity rates and encouraging short-term OS [III, A; not EMA approved, not FDA approved].

- For Ph+ ALL, low intensity ChT and a first- or second-generation TKI followed by allo-HSCT is considered the standard therapy for newly diagnosed patients [I, A].
- For Ph+ ALL, ponatinib–ChT may improve patient outcomes when compared with first- or second-generation TKIs [III, A; not EMA approved, not FDA approved].
- In Ph+ ALL, dasatinib or ponatinib combined with blinatumomab provide high rates of molecular response and promising OS and EFS [III, A; not EMA approved, not FDA approved]
- ChT followed by allo-HSCT is considered as standard therapy for patients with Ph-like ALL who have a poor MRD response outside of clinical trials [III, B]. There is insufficient evidence to provide a recommendation for patients with adequate MRD clearance.
- TKIs are recommended in patients with Ph-like ALL with *ABL*-class fusion [IV, B].
- The use of JAK inhibitors for Ph-like ALL is not recommended outside of clinical trials [IV, D].
- ICIs are not yet recommended for first-line therapy in ALL [IV, D].

TREATMENT OF R/R ALL

A proposed algorithm for the treatment of r/r ALL is shown in **Figure 2**.

Targeted therapies

Blinatumomab in r/r ALL. Blinatumomab has been evaluated in several prospective multicentre trials in r/r ALL (see **Supplementary Table S3**, available at *Annals of Oncology* online). In a prospective multicentre trial in Germany,[53,54] CR rate was only moderately improved after two cycles of blinatumomab monotherapy compared with ChT, but the rate of MRD negativity was high (>80%), leading to an improved median OS. In addition, the HSCT rate was 40% due to the high rate of MRD negativity. In an international multicentre trial,[55] adult patients with Ph+ ALL who

were intolerant or refractory to the TKI imatinib received two cycles of blinatumomab. Thirty-six percent of patients achieved a CR and 88% of those achieved MRD negativity. Remarkably, patients with resistant *T315I* mutations also achieved CR. The international randomised TOWER study[56] compared blinatumomab with SoC ChT. The CR rate (44% versus 25%, $P < 0.001$) and MRD negativity rate (76% versus 48%) were significantly higher with blinatumomab versus ChT. Median OS was significantly longer in the blinatumomab arm (7.7 months versus 4.0 months with ChT at 2 years). The HSCT rate was identical in both arms during the observation period (24%) but increased to 42% in blinatumomab-treated patients in a follow-up analysis.[57] Interestingly, toxicity did not differ between the two treatment groups, with grade ≥3 AEs reported in 87% of patients receiving blinatumomab and 92% of patients receiving ChT.

Blinatumomab in relapsed ALL in children and AYAs. Two large prospective randomised studies have evaluated blinatumomab in children with relapsed ALL (see **Supplementary Table S3**, available at *Annals of Oncology* online). In the Children's Oncology Group (COG) AALL1331 study,[2] high- and intermediate-risk children and AYAs in first relapse received two blinatumomab consolidation cycles or two ChT consolidations. Blinatumomab was associated with significantly improved MRD negativity, OS and HSCT rates compared with ChT. In addition, the toxicity rate was lower in the blinatumomab arm. The randomisation was, therefore, terminated early by the Data and Safety Monitoring Board. In the phase III Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) and BFM group study,[58] high-risk patients (aged ≤18 years) in first relapse were randomised to receive one blinatumomab consolidation cycle or one ChT consolidation. Blinatumomab monotherapy led to significantly better EFS and HSCT rates, a lower risk of relapse and fewer grade ≥3 AEs. Based on these encouraging results, blinatumomab was approved by the FDA for high-risk patients in first relapse and is now moving to consolidation for first-line therapy of high-risk children and AYAs in ongoing studies.

INO. Based on the results of the phase III INO-VATE study,[59] INO was approved by the FDA in 2017 for the treatment of adults with r/r CD22+ BCP-ALL. In this international, open-label trial, 326 adult patients with r/r Ph+ and Ph– CD22+ BCP-

ALL were randomised to receive either INO or SoC ChT (see **Supplementary Table S4**, available at *Annals of Oncology* online). INO was administered weekly at a dose of 0.8 mg/m^2 on day 1 and 0.5 mg/m^2 on days 8 and 15 for the first cycle, with the first dose reduced to 0.5 mg/m^2 for subsequent cycles. Cycles could be repeated every 3-4 weeks and patients could undergo allo-HSCT. The CR rate was significantly higher in the INO arm (80.7% versus 29.4% in the SoC arm, $P < 0.001$), with significantly more patients achieving a complete MRD response (78.4% with INO versus 28.1% with SoC, $P < 0.001$). PFS was significantly longer with INO (HR 0.45, 97.5% CI 0.34-0.60, $P < 0.0001$), as was OS (HR 0.75, 97.5% CI 0.57-0.99, $P = 0.0105$). The most frequent grade ≥3 AEs observed after INO were haematological and liver-related, including VOD in 11% of patients, mostly observed after subsequent allo-HSCT. In patients who received allo-HSCT, conditioning regimens containing two alkylating agents or busulfan, pretransplant elevated bilirubin concentration and age ≥55 years were associated with an increased risk of VOD.

Treatment with INO should therefore be preferentially considered in patients with r/r B-ALL and no prior liver disease (e.g. history of portal hypertension, cirrhosis or other chronic liver diseases). To decrease the risk of liver toxicity in patients who undergo transplant after INO, the following are recommended: (i) limit INO treatment to two cycles, (ii) carefully monitor liver tests including bilirubin before commencing transplant conditioning, (iii) avoid conditioning regimens with two alkylating agents, (iv) use VOD prophylaxis with ursodeoxycholic acid or defibrotide, if available. VOD prophylaxis with defibrotide is still under investigation in adult patients.

CAR-T therapy. CAR-T therapy targeting CD19 has shown remarkable efficacy in r/r B-ALL, leading to FDA and EMA approval of tisagenlecleucel (tisa-cel) for patients aged ≤25 years[60,61] and brexucabtagene autoleucel for adults.[62] Consistently high response rates of ~80%, the majority of which are MRD negative by flow cytometry, are achieved in patients with B-ALL within 1 month of CAR-T infusion, irrespective of product, manufacture platform or patient age.[60-67] Complications of CAR-T therapy for B-ALL include significant (and sometimes life-threatening) immunotoxicity, namely CRS and immune effector cell-associated neurotoxicity syndrome, the severity of which varies according to the CAR-T trial and product (**Table 3**), as well

as pretreatment disease burden.[62,64] Strategies to prevent immunotoxicity include early or pre-emptive use of immune modulators such as tocilizumab and corticosteroids,[68-70] fractionated CAR-T dosing,[64,65,71] and a modified CAR-T design, such as fast off-rate CD19-binding elements.[65,72]

Longer-term follow-up data suggest that ~40%-60% of patients will relapse within the first year after CAR-T therapy.[73] Consolidative allo-HSCT can be used to try to prevent relapse, but problems with the universal application of this approach include high TRM rates and the inevitable ablation of CD19-directed immunosurveillance. To date, no clinical trials of allo-HSCT versus 'watch and wait' have been carried out to demonstrate superiority of one approach over the other, with most data on post-CAR-T allo-HSCT outcomes emerging from phase I/II single-arm CAR-T clinical trials.[67,73-76] Park et al. and Shah et al. reported no EFS difference in adults undergoing allo-HSCT consolidation after CD28 CAR-T therapy.[62,74] In contrast, a study of 19 adults with B-ALL who underwent allo-HSCT after CAR-T reported superior RFS with allo-HSCT (61% at 24 months).[66] In terms of toxicity, the 1-year non-relapse mortality rate was 21%, with factors predictive of higher mortality including delayed allo-HSCT (>80 days after CAR-T therapy) and a high HSCT comorbidity index score.[76]

Research to define pretreatment factors, disease and patient factors, and product factors predisposing to CAR-T failure is key to help inform discussions on the role of allo-HSCT after CAR-T therapy, so that it can be targeted specifically to patients at high risk of relapse.[77] The insights into factors associated with CAR-T failure discussed here derive from both adult and paediatric or AYA patient datasets.

In r/r T-ALL, there are several ongoing trials evaluating CAR-T therapy, including CD5 CAR-T (Phase I, NCT03081910), CD7 CAR-T (Phase I, NCT03690011) and NS7CAR (Phase I, NCT04572308). In a 2-year follow-up analysis of a donor-derived CD7 CAR-T therapy, durable efficacy was demonstrated in a subset of patients with r/r T-ALL, with a 2-year OS rate of 42.3%.[78] The main cause of treatment failure was disease relapse.

Pretreatment factors. Prior antileukaemia treatments, particularly B-cell targeting immunotherapies, may negatively impact CAR-T efficacy. Dourthe et al. reported shorter EFS and OS from CD19-negative (CD19–) relapse in blinatumomab-exposed paediatric or AYA patients treated with commercial tisa-cel,[79] suggesting a blinatumomab-induced selection pressure precipitating antigen escape. Building on this, Myers et al. recently published an assessment of 6-month EFS in 420 paediatric or AYA patients, stratified by prior blinatumomab use.[80] Blinatumomab-exposed patients were more likely to have *KMT2A* rearrangement and to have undergone prior allo-HSCT, possibly denoting a higher-risk patient population. Blinatumomab-nonresponder patients had a lower CR rate (64.5%) compared with blinatumomab-responders (92.9%) or blinatumomab-naïve patients (93.5%) and a lower 6-month EFS rate (27.3% compared with 66.9% and 72.6%, respectively). Blinatumomab-exposed patients were more likely to have CD19-dim or -partial expression before CAR-T infusion (13.3% versus 6.5% in blinatumomab-naïve patients), which was associated with shorter EFS and RFS. Clearly, sequencing of immune therapies in r/r B-ALL is an increasingly important consideration.

Emerging data suggest that prior INO therapy may confer inferior CAR-T outcomes. Dourthe et al. reported death from progressive B-ALL after CAR-T therapy in 7 of 11 INO-exposed paediatric patients, and the authors suggest that profound INO-induced B-cell depletion can potentially compromise CAR-T expansion and persistence.[79] This is the subject of ongoing evaluation in clinical studies.

Disease and patient factors. Emerging data suggest that high disease burden before CAR-T therapy, but not high-risk cytogenetics,[81] is associated with inferior EFS. Hay et al. reported significantly worse EFS with surrogates for high B-ALL disease burden, namely elevated lactate dehydrogenase and low platelet count (<100 000/μL).[66] Recent reports show that ≥5% blasts in the bone marrow at baseline confers significantly worse PFS, and that CD19-modulated or -negative relapse is more common in those with high disease burden.[80,82] Park et al. note that the best outcomes using their CD28z CAR were observed in patients with MRD prior to CAR-T therapy.[74] Other B-ALL correlates for worse EFS include non-CNS

extramedullary disease, relapsed (but not primary refractory) disease and the presence of circulating blasts.[80]

CAR-T treatment and product factors. CAR-T treatment is conventionally delivered with fludarabine and cyclophosphamide lymphodepletion to ablate cytokine sinks before CAR-T infusion to improve engraftment. Turtle et al. showed that omission of fludarabine is associated with inferior outcomes in B-ALL and a higher risk of cell-mediated CAR-T cell rejection.[83] The cytokine flux that follows fludarabine administration is thought to play a vital role in early CAR-T expansion,[84] and expansion has been shown to correlate with likelihood of achieving CR.[62,66] For B-ALL in particular, CAR-T persistence, evidenced by ongoing CAR-T engraftment and B-cell aplasia, appears to be important for prolonged EFS.[60,77,82] CAR-T design features that may potentiate long-term persistence include the use of 41BBz (rather than CD28z) co-stimulatory endodomains,[60,62,67,85] infusion of CAR-T products enriched for central memory and stem cell memory T-cell populations,[86,87] shorter duration *ex vivo* CAR-T manufacture methods[88-90] and the use of low-affinity CD19 binders.[72] Nevertheless, ongoing CAR-T-mediated immune surveillance does not protect against CD19– relapse. Data suggest that CD19– escape is associated with high, early CAR-T expansion,[66] is likely to occur within the first six months after infusion[66,80] and is more common in patients with high disease burden.[80] Standardised, validated laboratory methods to quantify CD19 expression density and antigen loss by flow cytometry for all patients is a requirement for the field, and together with NGS approaches to delineate CD19– clones before CAR-T therapy, may help to guide patient selection for CAR-T in the future.[88,91] Strategies to prevent CD19– escape include the use of dual-targeting (CD19 and CD22) CAR-T products, but to date this has not definitively shown superiority over single antigen-targeted approaches.[88,92,93]

ICIs and other novel agents. Selected clinical studies of ICIs in ALL are listed in **Supplementary Table S9**, available at *Annals of Oncology* online. Ipilimumab is an mAb that activates the immune system by targeting CTLA-4. When applied in relapsed haematological malignancies after allo-HSCT in adults, ipilimumab was associated with a CR rate of 23%.[94] The authors suggested that the antibody dose

may be important after transplantation and that CTLA-4 blockade may be effective after allo-HSCT by inducing a dormant graft-versus-tumour response.[94]

Pembrolizumab targets the PD-1 receptor on lymphocytes. A phase II study of pembrolizumab monotherapy was terminated due to lack of efficacy.[95] It was therefore combined with other drugs and the combination of blinatumomab–pembrolizumab led to a promising CR rate of 50% in patients with r/r ALL, albeit in small studies.[96,97] Nivolumab is a human IgG4 monoclonal antibody that blocks PD-1. Combination of nivolumab with induction therapy or blinatumomab–ipilimumab has been associated with promising CR rates.[98,99]

In large paediatric COG trials for T-ALL,[100,101] the proteasome inhibitor bortezomib in combination with the BFM protocol ChT backbone resulted in 3-year OS rates of >80%. In adult patients with r/r ALL, the CR rate with bortezomib–ChT was high (61%) and the 2-year OS rate was 28%.[102]

Bcl-2 protein overexpression in many cancers increases drug resistance and tumour cell survival. Venetoclax is a Bcl-2 inhibitor and navitoclax is an orally-active anticancer drug that inhibits not only Bcl-2, but also Bcl-xL and Bcl-w proteins. The inhibition of Bcl-xL by navitoclax, however, can reduce platelet lifespan, causing dose-limiting thrombocytopenia. In a multicentre phase I study[103] of 47 patients with r/r ALL or lymphoblastic lymphoma, venetoclax–navitoclax–ChT was associated with a CR rate of 60% and a 1-year OS rate of 36%. Thirteen patients (28%) proceeded to HSCT or CAR-T therapy. In patients with T-ALL, the CR rate was 52%. When combined with liposomal vincristine as the only ChT drug, venetoclax was associated with a CR rate of only 22%.[104] Several ongoing studies are combining venetoclax with immunotherapies or the third-generation TKI ponatinib.

HSCT

Allo-HSCT is still a curative option in adult ALL. It is indicated for (i) r/r disease, (ii) first-line therapy for certain high-risk groups, (iii) MRD-positive disease. In all of these groups, an immunotherapy agent should be applied to achieve a lower MRD load (or MRD negativity) before the transplant. Recent studies that evaluated a

combination of immunotherapy (blinatumomab) and TKI (dasatinib) in Ph+ ALL indicated that the combination of two biological principles with low intensity ChT may lead to a reduction in the frequency of allo-HSCT. It should be noted, however, that in a study proposing ChT-free treatment, the rate of allo-HSCT was 46% at any stage of disease.[41] In contrast, in a US study of elderly patients with Ph+ ALL which had a good overall outcome, nearly no HSCT was carried out.[42] Thus, a combination of two biological principles—immunotherapy and a potent TKI (particularly ponatinib)—may substantially reduce the need for allo-HSCT.[105]

Recommendations

- Blinatumomab monotherapy is superior to standard ChT [I, A], although tumour burden reduction should be considered before initiating blinatumomab [IV, B].
- INO monotherapy is superior to standard ChT [I, A] and should be preferentially considered in patients with no prior liver disease [V, B].
- Sequencing of CD19-targeted immune therapies in r/r B-ALL is important for CAR-T outcomes [IV, B].
- Bridging to CAR-T with blinatumomab is not recommended [V, D]
- Validated antigen assessment tools are required to define the risk of antigen negative relapse [V, C].
- Patients with r/r ALL are candidates for allo-HSCT, but MRD should be substantially reduced with bridge therapy [IV, B].
- ICIs are a new area of targeted therapy and may be particularly promising when combined with other immunotherapies, e.g. blinatumomab in B-lineage ALL [III, B].
- Bcl-2 or Bcl-xL inhibitors combined with ChT may be of high relevance in T-ALL, for which no antibody therapy is currently available [III, B].

CONCLUSIONS

Targeted therapy is the great challenge in the treatment of B-lineage ALL. Fortunately, for the major antigens expressed, such as CD19, CD20 and CD22, antibody therapies are available and very successful.

TKIs have changed outcomes for patients with Ph+ ALL, particularly elderly patients. The additional benefit of ICIs is currently being explored. There are, however, subtypes of ALL, such as early T-cell precursor ALL and Ph-like ALL, where improvement is still required. The challenge is currently to explore the optimal combination and sequencing of the available targeted therapies.

METHODOLOGY

This eUpdate was developed in accordance with the ESMO standard operating procedures for CPG development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. The FDA/EMA or other regulatory body approval status of new therapies/indications are reported at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in **Supplementary Table S10**, available at *ESMO Open* online.[106] Statements without grading were considered justified standard clinical practice by the authors. Future updates to the ALL CPG will be published on esmo.org as a Living Guideline version or an eUpdate, to be made available at: https://www.esmo.org/guidelines/guidelines-by-topic/haematological-malignancies/acute-lymphoblastic-leukaemia.

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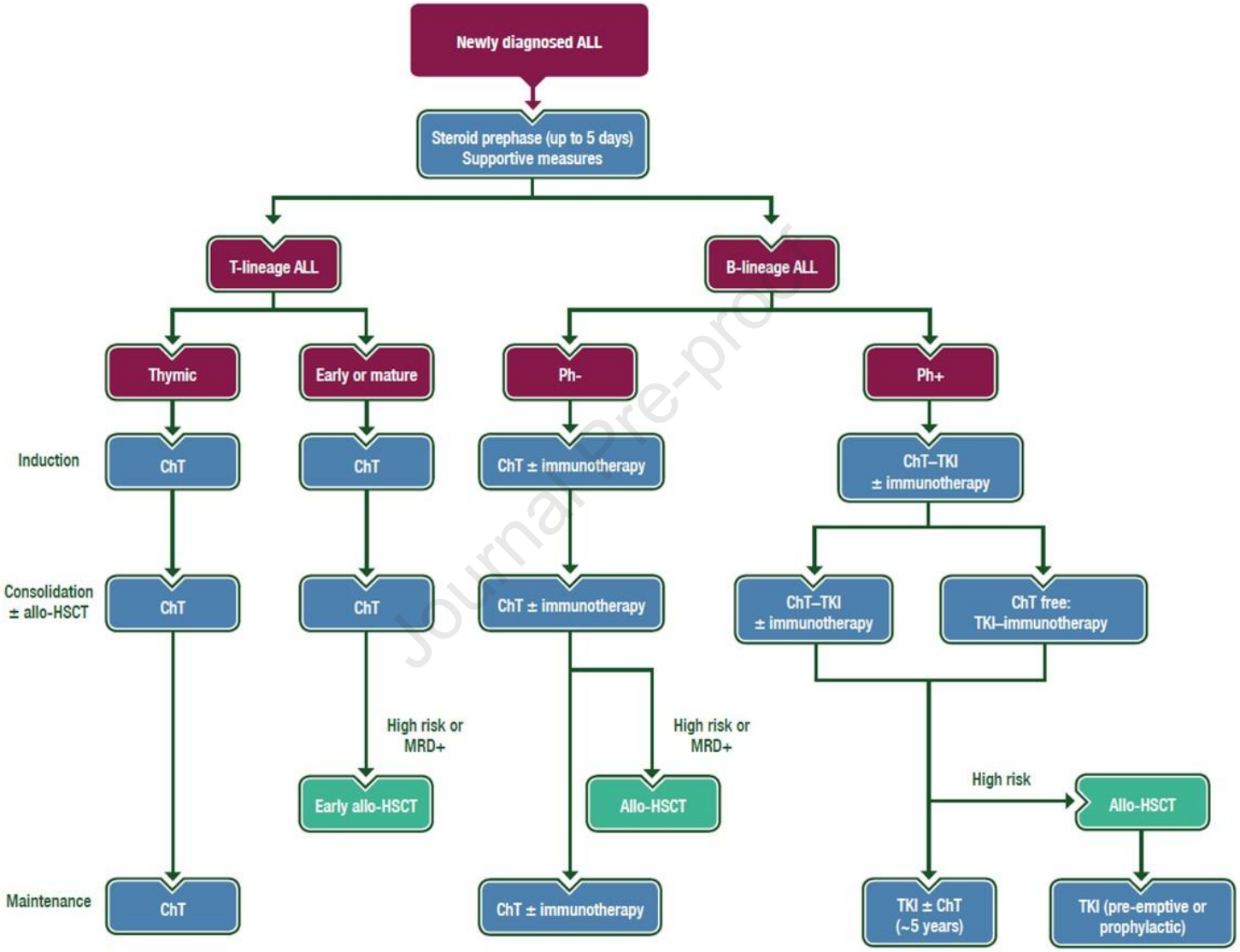
FIGURES

Figure 1. Treatment algorithm for newly diagnosed ALL.

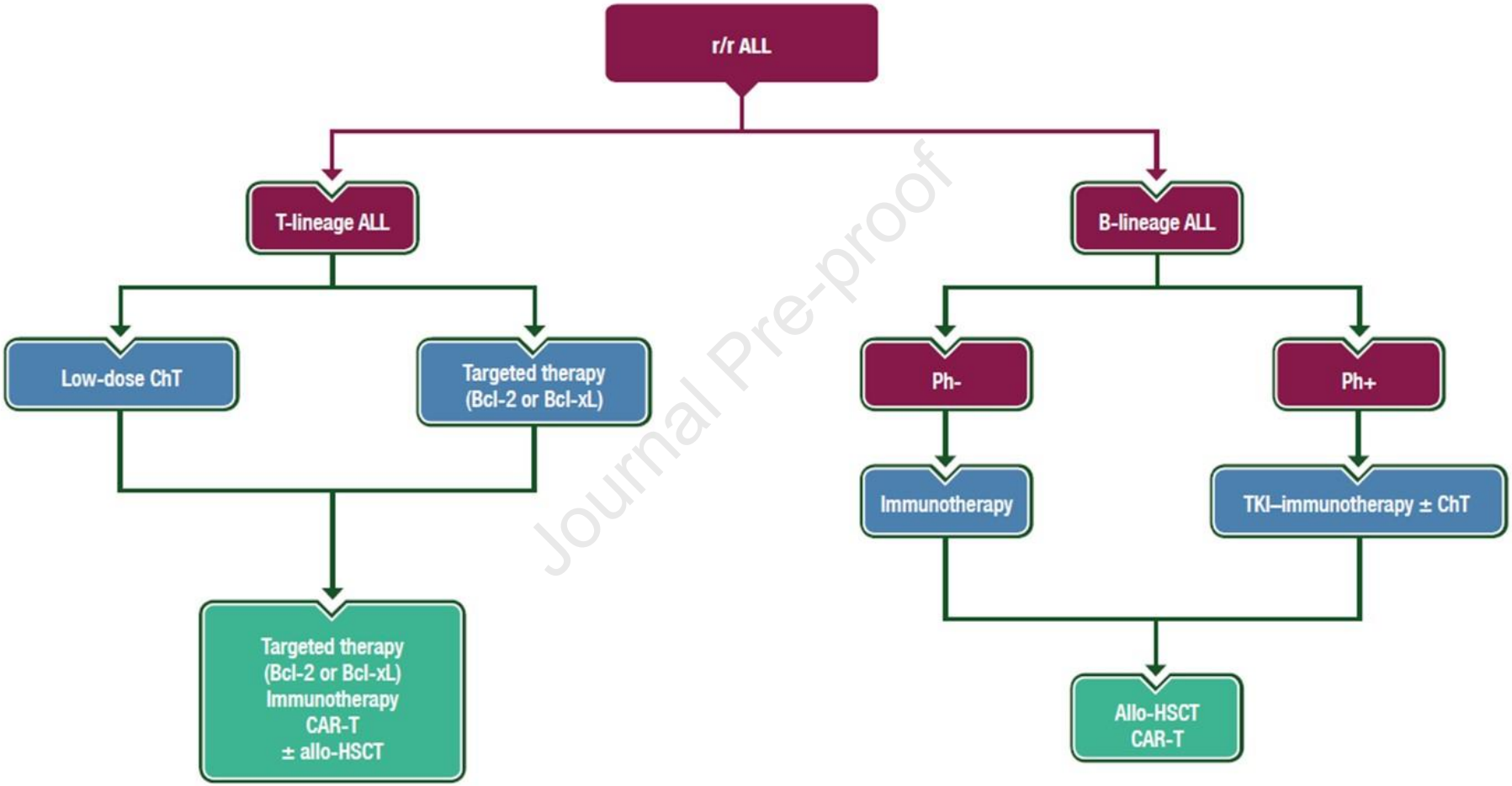

Newly diagnosed ALL
Steroid prephase (up to 5 days)
Supportive measures
T-lineage ALL
B-lineage ALL
Thymic
Early or mature
Ph-
Ph+
Induction
ChT
ChT
ChT ± immunotherapy
ChT–TKI
± immunotherapy
Consolidation
± allo-HSCT
ChT
ChT
ChT ± immunotherapy
ChT–TKI
± immunotherapy
ChT free:
TKI–immunotherapy
High risk or
MRD+
High risk or
MRD+
High risk
Early allo-HSCT
Allo-HSCT
Allo-HSCT
Maintenance
ChT
ChT ± immunotherapy
TKI ± ChT
(~5 years)
TKI (pre-emptive or
prophylactic)

Purple: general categories or stratification; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.

Systemic ChT should be accompanied by intrathecal ChT for prevention of CNS relapse in all patient categories.

ALL, acute lymphoblastic leukaemia; allo-HSCT, allogeneic haematopoietic stem cell transplantation; ChT, chemotherapy; CNS, central nervous system; MRD+, minimal residual disease positive; Ph+, Philadelphia chromosome positive; Ph–, Philadelphia chromosome negative; TKI, tyrosine kinase inhibitor.

Figure 2. Treatment algorithm for r/r ALL.



Purple: general categories or stratification; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments.

ALL, acute lymphoblastic leukaemia; allo-HSCT, allogeneic haematopoietic stem cell transplantation; Bcl, B-cell lymphoma; CAR-T; chimeric antigen receptor T-cell; ChT, chemotherapy; Ph+, Philadelphia chromosome positive; Ph–, Philadelphia chromosome negative; r/r, relapsed or refractory; TKI, tyrosine kinase inhibitor.

.

Table 1. Progress in adult ALL with targeted therapies

Antibody therapy	
Anti-CD20	Rituximab, ofatumumab
Anti-CD22	Inotuzumab ozogamicin
Anti-CD19	T-cell activating therapies: blinatumomab, CAR-T
TKIs	
Ph+ or *BCR::ABL* ALL	Imatinib, dasatinib, nilotinib, bosutinib, ponatinib, asciminib
Ph– or *BCR::ABL*-like ALL	
ABL1, ABL2	Dasatinib
JAK2	Ruxolitinib
ICIs	
Proteasome inhibitors	Bortezomib, ixazomib
Bcl-2 inhibitors	Venetoclax, navitoclax
PD-1 inhibitors	Pembrolizumab, nivolumab
CTLA-4 inhibitors	Ipilimumab

ALL, acute lymphoblastic leukaemia; Bcl-2, B-cell lymphoma 2; CAR-T, chimeric antigen receptor T-cell; CD, cluster of differentiation; CTLA-4; cytotoxic T lymphocyte-associated antigen 4; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1; Ph+, Philadelphia chromosome positive; Ph–, Philadelphia chromosome negative; TKI, tyrosine kinase inhibitor.

Table 2. Expression of antigens in B-cell lineage ALL and available antibody therapies

Surface antigen	ALL subtype	Expression on LBCs	Monoclonal antibody
CD20	Burkitt lymphoma/leukaemia B-precursor	86%-100% 30%-50%	Rituximab Ofatumumab
CD22	B-precursor Mature B-ALL	>90%	Inotuzumab ozogamicin Epratuzumab Moxetumomab pasudotox
CD19	B-precursor Mature B-ALL	≤100%	T-cell activating therapies: Blinatumomab (bispecific CD3/CD19) CAR-T

ALL, acute lymphoblastic leukaemia; B-ALL, B-cell acute lymphoblastic leukaemia; CAR-T, chimeric antigen receptor T-cell; CD, cluster of differentiation; LBC, leukaemic blast cell.

Table 3. Main studies of CD19 CAR-T therapy for adult patients with B-ALL

Reference	CAR endodomain	Patients treated, n	Median age, years (range)	Prior allo-HSCT, %	Prior B, %	CR, %	CRS, %	ICANS, %
Shah et al. 2021[62]	CD28	55	40 (28-52)	42	45	71	89% 25% ≥G3	60% 23% G3/4 1 G5
Roddie et al. 2021[65]	41BB	20	42 (18-62)	65	25	85	55% None ≥G3	20% 15% G3
Ortiz-Maldonado et al. 2021[63]	41BB	38	24 (3-67)	87	26	85	13% ≥G3	2.6% ≥G3
Wang et al. 2020[107]	41BB	23	42 (10-67)	0	NR	83	100% 27% ≥G3	43%
Frey et al. 2020[64]	41BB	35	34 (20-76)	37	31	69	94% 9% G4/5	40% 6% G3

Reference	CAR endodomain	Patients treated, n	Median age, years (range)	Prior allo-HSCT, %	Prior B, %	CR, %	CRS, %	ICANS, %
Hay et al. 2019[66]	41BB	53	39 (20-76)	43	20	85	75% 19% G3/4	23%
Park et al. 2018[74]	CD28	53	44 (23-64)	36	25	83	85% 26% ≥G3	42% G3/4
Aldoss et al. 2023[108]	CD28	46	38 (22-72)	63	63	87	7% ≥G3	17% ≥G3
Roddie et al. 2023[109]	41BB	94	50 (20-81)	38	35	76	3% ≥G3	7% ≥G3

Allo-HSCT, allogeneic haematopoietic stem cell transplantation; B, blinatumomab; B-ALL, B-cell acute lymphoblastic leukaemia; CAR, chimeric antigen receptor; CAR-T, chimeric antigen receptor T-cell; CD, cluster of differentiation; CR, complete remission; CRS, cytokine release syndrome; G, grade; ICANS, immune effector cell-associated neurotoxicity syndrome; NR, not recorded.