

# Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up<sup>†</sup>

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## incidence and epidemiology

The estimated overall incidence of acute lymphoblastic leukaemia (ALL) and lymphoblastic lymphoma in Europe is 1.28 per 100 000 individuals annually, with significant age-related variations (0.53 at 45–54 years, ~1.0 at 55–74 years and 1.45 at 75–99 years) and that of Burkitt leukaemia/lymphoma is between 0.17 and 0.33 in the same age groups [1]. These figures qualify ALL as a rare disease in adults, making assessment and care at qualified centres highly desirable. Predisposing risk factors for adult ALL are not known, contrary to childhood ALL [2]. Therapeutic progress is undeniable as shown by large registry data. In Europe, 5-year overall survival (OS) improved from 29.8% in the years 1997–1999 to 41.1% in 2006–2008 ( $P < 0.0001$ ), still as a function of age. Compared with the reference group (age 15–54 years: OS >50%), OS was <30% in the 55–64 years age group (hazard ratio 2.05) and <20% in the ≥65 years age group (hazard ratios 2.71 and 3.75) [3].

## diagnosis and pathology/molecular biology

A comprehensive diagnostic approach requires the study of cell morphology, immunophenotype, genetics/cytogenetics and genomics, as detailed in the 2008 World Health Organization (WHO) classification [4] and recently reviewed [I, A] [5, 6].

## morphology/immunophenotype/molecular screening

The initial diagnostic work-up (Table 1) must be carried out expeditiously and before any chemotherapy (within 1–2 working days) to:

- confirm ALL diagnosis,

- distinguish B-cell precursor (BCP) ALL from T-cell ALL (T-ALL),
- distinguish Burkitt leukaemia (B-ALL) from BCP-ALL (different treatment required),
- distinguish Philadelphia (Ph) chromosome-positive (Ph+) ALL from Ph-negative (Ph-) ALL (different treatment required), and
- shorten time to treatment start.

Aspiration of bone marrow is a standard procedure, with a core marrow biopsy being necessary only in case of insufficient cell yield. The bone marrow must contain at least 20% blast cells, as a criterion to differentiate ALL from lymphoblastic lymphoma with/without marrow involvement, even if therapeutic consequences are very limited. The proportion of circulating blasts is highly variable. ALL blasts are atypical lymphoid or undifferentiated cells. Once minimally differentiated acute myelogenous leukaemia (AML) has been ruled out, the morphological analysis is uninformative in ALL, if not for the common association between FAB L3 morphology and B-ALL [7]. The immunophenotype study plays the key diagnostic role, demonstrating commitment of the blast cell population to the B- or T-cell lineage. The European Group for the Immunological Characterization of Leukemias (EGIL) recognised distinct BCP/T-ALL subsets, providing a rational immunological classification along with criteria for differential diagnosis [8]. Original EGIL standards and definitions of mixed-lineage leukaemias (MLLs) variously expressing B-, T- and myeloid-associated antigens were updated and improved [9, 10]. Further indications on how to best perform diagnostic flow cytometry were presented by a panel of experts [11]. The early diagnostic step is completed by a rapid molecular screening by means of reverse transcriptase polymerase chain reaction (RT-PCR) or fluorescence *in situ* hybridisation (FISH) assays primarily for the detection of *BCR-ABL1* gene rearrangements, denoting an underlying t(9;22)(q34;q11)/*BCR-ABL1* chromosomal translocation typical of Ph+ ALL and sensitive to targeted therapy with tyrosine kinase inhibitors (TKIs) [I, A] [12].

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**Table 1.** Diagnostic work-up in adult ALL

Diagnostic step	Results/ALL subsets	Recommendations
<b>Morphology</b>		
- Bone marrow and peripheral blood	- Lymphoid/undifferentiated blasts (≥20% bone marrow involvement)	Mandatory
- Cerebro-spinal fluid	- FAB L3 morphology in Burkitt leukaemia	Recommended
	- CNS involvement	Mandatory
<b>Immunophenotype</b>		
- MPO (differential diagnosis versus AML)	- MPO negative; B/T markers >20% (CD3, CD79a >10%)	Mandatory
- B-lineage markers: CD19, CD79a, cCD22 (at least 2); others: TdT, CD10, CD20, CD24, cIgM, sIg (kappa or lambda)	- B-lineage ALL: Pro-B/B-I (CD19/CD79a/cCD22+) Common/B-II (CD10+/cIgM-) Pre-B/B-III (cIgM+/sIg-) Mature-B/B-IV (sIg+)	Mandatory
- T-lineage markers: cCD3; others: TdT, CD1a, CD2, CD5, CD7 CD4, CD8, TCR α/β or γ/δ	- T-lineage ALL: Pro-T/T-I (cCD3/CD7+) Pre-T/T-II (CD2/CD5) Cortical-T/T-III (CD1a+) Mature-T/T-IV (CD3+/CD1a-)	Mandatory
- Stem/myeloid cell markers (variable): CD34, CD13, CD33, CD117		
<b>Cytogenetics/genetics</b>		
- Cytogenetics/FISH/RT-PCR	- ALL with adverse clinico-biological features: Ph+ ALL (rapid detection, to TKI therapy) t(4;11)+ ALL t(1;19)+ ALL other high-risk cytogenetics	Mandatory
- CGH/SNP/GEP/NGS	- ALL with adverse clinico-biological features: Ph-like ALL ETP ALL NOTCH1/FBW7-unmutated/RAS/ PTEN-altered T-ALL IKZF1, CLRF2, MLL, TP53, CREBBP, RAS alterations	Recommended for new clinical trials
<b>MRD study</b>		
- MRD marker(s): LAIP (immunophenotype)/molecular probe (PCR)	- MRD-based risk classification	Mandatory
<b>Storage of diagnostic material</b>		
- Cell banking/storage of DNA/RNA/protein lysates	- Additional/future studies	Highly recommended
<b>HLA typing</b>		
- Patient/siblings	- Early application of SCT if required	Recommended

ALL, acute lymphoblastic leukaemia; CNS, central nervous system; MPO, myeloperoxidase; AML, acute myelogenous leukaemia; c, cytoplasmic; IgM, immunoglobulin M; s, surface; Ig, immunoglobulin; FISH, fluorescence *in situ* hybridisation; RT-PCR, reverse transcriptase polymerase chain reaction; Ph+, Philadelphia-positive; TKI, tyrosine kinase inhibitor; CGH, comparative genomic hybridisation; SNP, single nucleotide polymorphism; GEP, gene expression profiling; NGS, next-generation sequencing; Ph, Philadelphia; ETP, early T-cell precursor; T-ALL, T-cell ALL; MRD, minimal residual disease; LAIP, leukaemia-associated immunophenotype; PCR, polymerase chain reaction; HLA, human leucocyte antigen; SCT, stem-cell transplantation.

**cytogenetics/genetics**

Results from cytogenetics, genetics and genomics are available at a later stage, allowing the recognition of several ALL syndromes with prognostic and/or therapeutic implications (reviewed in references [2] and [6]). Standard cytogenetics/FISH and especially RT-PCR are routinely performed to obtain a rapid diagnosis of Ph+ ALL and identify other intermediate/high- and high-risk karyotypes/gene rearrangements, mainly:

- t(4;11)(q21;q23)/*MLL-AFA4*, abn11q23/*MLL*, t(1;19)(q23;p13)/*PBX-E2A*, t(8;14) or other abn14q32 in non-Burkitt ALL,
- del(6q), del(7p), del(17p), -7, +8, low hypodiploidy, i.e. with 30–39 chromosomes/near triploidy with 60–78 chromosomes,
- complex (≥5 unrelated clonal abnormalities), and
- T-ALL lacking *NOTCH1/FBXW7* mutations and/or with *RAS/PTEN* abnormalities [I, A] [13–17].

The more prognostically favourable cytogenetic/genetic subsets are t(12;21)(p13;q22)/*TEL-AML1* + ALL (rare in adults) and hyperdiploid ALL, and *NOTCH-1/FBXW7*-mutated T-ALL.

### new genetics/genomics

The integration of above studies with new genetics/genomics, i.e. array-comparative genomic hybridisation, gene expression profiling, single-nucleotide polymorphism array analysis and next-generation sequencing, led to the recognition of highly specific poor-risk conditions, whose global incidence is ~30%. These are: Ph-like ALL, characterised by a gene expression profile similar to Ph+ ALL and associated with *IKZF1* deletion, *CLRF2* overexpression and tyrosine kinase-activating rearrangements involving *ABL1*, *JAK2*, *PDGFRB* and several other genes [16]; and early T-cell precursor (ETP) ALL, characterised by lack of CD1a and CD8, weak CD5 expression, at least one myeloid/stem cell marker, a specific transcriptional profile and the possible involvement of several critical genes [18]. Other genetic aberrations that impart an inferior outlook are other *MLL* gene rearrangements, *TP53* and *CREBBP* mutations, and deregulation of *RAS* signalling components (*NRAS*, *KRAS*, *FLT3*, *NF1*). Although these assays are still investigational and not regularly carried out in the clinical practice, they are recommended for new clinical trials to improve the risk classification and support targeted therapies [III, B].

*other.* The diagnostic phase is completed by the search for a sensitive molecular marker or an aberrant leukaemia-associated immunophenotype (LAIP) for the detection and monitoring of minimal residual disease (MRD) [III, B] [19]. Human leucocyte antigen (HLA) typing of patients and relatives is recommended at this stage, to facilitate subsequent application of an early stem-cell transplantation (SCT), according to study/treatment indications [V, B].

### risk assessment and prognostic factors

While the suggested diagnostic work-up permits the identification of some high-risk (HR) subsets, clinical risk groups are further defined by several disease-related factors and some host-related factors [20, 21], and the individual prognosis is highly refined by ALL response dynamics (Table 2). Patients presenting with no risk factors are defined as standard risk (SR). Older age, reduced tolerability to treatments and higher white blood cell (WBC) count on presentation (reflecting higher tumoural burden) are universally recognised as independent risk variables predicting for lower complete remission (CR) rate and shorter CR duration. The kinetics of response to early treatment steps is also well recognised and increasingly sought-for prognostic information. This can be obtained through different methodologies and at different treatment times, ranging from pre-phase therapy (prednisone response) to induction day 8–15 (marrow blast cell clearance), end of induction (time to CR, MRD) and post-induction phase (MRD) [III, A].

### minimal residual disease

Quantification of MRD is a major and well-established risk factor and should be obtained whenever possible for all patients also outside of clinical trials. Methods for MRD evaluation and standardisation of MRD quantification have been intensively described [22–24]. Molecular response can be evaluated only for patients in complete cytologic remission (Table 3), with one marker or more for MRD analysis and samples available at the respective time points. Definition of responses are summarised in Table 3. If MRD is measured by flow cytometry, a good MRD response is often defined as less than  $10^{-3}$ , although MRD levels less than  $10^{-4}$  can be achieved with the 8–12 colour flow cytometers.

Achievement of complete molecular remission (molCR)/molecular remission is the most relevant independent prognostic factor for disease-free survival (DFS) and OS. Patients with

**Table 2.** High-risk factors in adult ALL

Risk factors	Risk subsets (notes)	Recommendations
<b>Patient-related</b>		
– Age (years)	– >40/55/65	Mandatory
– Performance status (ECOG score)	– >1	Highly recommended
<b>Disease-related</b>		
– WBC ( $\times 10^9/l$ )	– >30 (B-lineage)/>100 (T-lineage)	Mandatory
– Immunophenotype (B-T-subsets)	– Pro-B/early and mature-T	Mandatory
– Cytogenetics (karyotype)	– Ph+/t(4;11)+/other adverse	Mandatory
– Genetics	– BCR-ABL1+/MLL+/PBX-E2A/ Ph-like/IKZF1 del/ETP/unmutated NOTCH1	Mandatory Recommended for new clinical trials
– Miscellaneous	– Central nervous system involvement	Mandatory
<b>Response dynamics</b>		
– corticosteroid sensitivity (blast count after pre-phase)	– Poor prednisone response ( $\geq 1 \times 10^9/l$ )	Recommended
– early blast cell response (BM morphology)	– Day 8–15 blasts $\geq 5\%$	Recommended
– time to CR (no. of courses)	– >1 cycle (late CR)	Mandatory
– MRD (molecular/LAIP)	– MRD+ (post-induction)	Mandatory

ALL, acute lymphoblastic leukaemia; ECOG, Eastern Cooperative Oncology Group; WBC, white blood cells; Ph+, Philadelphia-positive; Ph, Philadelphia; ETP, early T-cell precursor; BM, bone marrow; CR, complete remission; MRD, minimal residual disease; LAIP, leukaemia-associated immunophenotype.

**Table 3.** Response parameters according to MRD

Terminology	Definitions
CR (complete haematological remission)	- Leukaemic cells not detectable by light microscopy in BM/PB/CSF (BM < 5% blasts)
MolCR (complete molecular remission/MRD negativity)	- Patient in CR - MRD not detectable by sensitive molecular probe(s) (sensitivity $\geq 10^{-4}$ )
MolR (molecular/MRD response, less than molCR)	- Patient in CR, not in molCR - Low-level non-quantifiable MRD ( $< 10^{-4}/0.01\%$ , i.e. <1 leukaemic cell in 10 000) - Assessable by MFC (lower detection limit, between $10^{-3}$ and $10^{-4}$ , higher sensitivity with 8–12 colour techniques)
MolFail (molecular failure/MRD positivity)	- Patient in CR, not in molCR/molR - Quantifiable MRD ( $\geq 10^{-4}/0.01\%$ , i.e. $\geq 1$ leukaemic cell in 10 000) - Assessable by MFC (lower detection limit, between $10^{-3}$ and $10^{-4}$ )
MolRel (molecular/MRD relapse)	- Patient still in CR, prior molCR/molR - Loss of molCR/molR status ( $\geq 10^{-4}/0.01\%$ , i.e. >1 leukaemic cell in 10 000) - Assessable by MFC (lower detection limit, between $10^{-3}$ and $10^{-4}$ )
Relapse	- Loss of CR status - Haematological relapse (BM ALL blasts >5%) - Extramedullary relapse (CNS, other site)

MRD, minimal residual disease; BM/PB/CSF, bone marrow/peripheral blood/cerebro-spinal fluid; MFC, multiparameter flow cytometry; ALL, acute lymphoblastic leukaemia; CNS, central nervous system.

molCR after induction therapy in several studies had significantly superior outcomes, with a DFS of 54%–74%, compared with 17%–40% for MRD-positive patients [25–31]. Patients with molecular failure (molFail) after induction proceeded to allogeneic haematopoietic SCT, and their outcome was thereby substantially improved, compared with the chemotherapy-only arm [29, 32, 33].

The question arises as to whether the evaluation of MRD overcomes all of the pre-therapeutic risk factors, or whether MRD should be combined with the pre-therapeutic factors [27, 34, 35]. A practical approach is to bring the conventional prognostic factors and MRD into a decision algorithm. At diagnosis, patients are stratified into SR and HR groups, since HR patients are potential candidates for SCT in first complete remission (CR1), and an early donor search is warranted. However, it is not clear how to proceed with HR patients in molCR/molecular remission, although some studies suggest a lack of benefit from SCT in these patients. Also, MRD is not available for all patients, and the risk stratification in those patients should rely on conventional risk factors. Overall, a rapid yet comprehensive diagnostic approach is essential for accurate risk definitions and appropriate risk-related treatment choices (Figure 1).

## treatment of newly diagnosed ALL

### pre-phase therapy and supportive measures

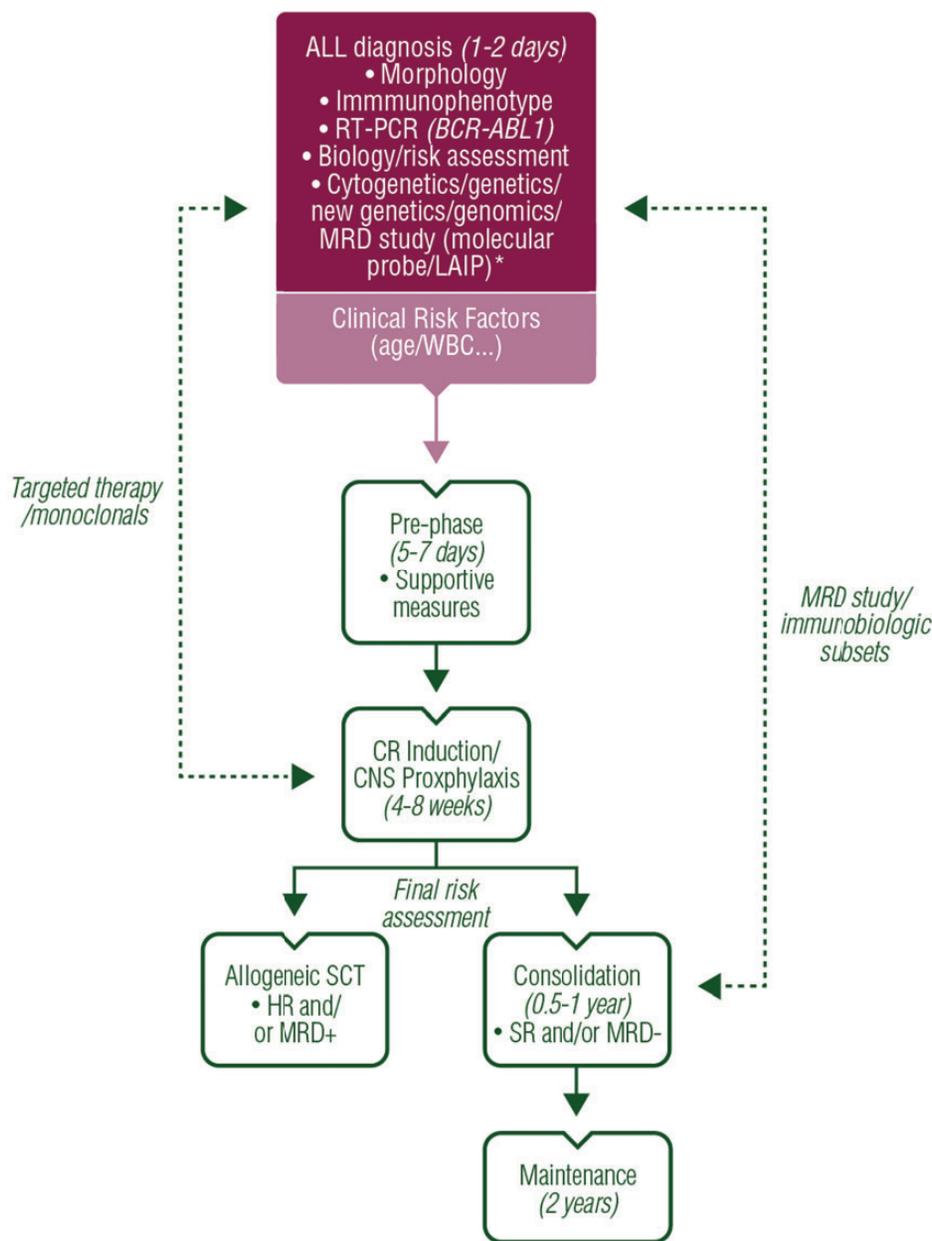
When the diagnosis is established, treatment should start immediately, preferably in a specialised hospital; that is, physicians with experience in the treatment of acute leukaemia, a well-trained nursing staff, sufficient supportive care (e.g. platelet substitution) and access to an intensive care unit. A pre-phase therapy with corticosteroids (usually prednisone 20–60 mg/day

or dexamethasone 6–16 mg/day, both i.v. or p.o.) alone, or in combination with another drug (e.g. vincristine, cyclophosphamide), is often given together with allopurinol and hydration for ~5–7 days. The first intra-thecal therapy for central nervous system (CNS) prophylaxis is administered in this period in some studies. The pre-phase therapy allows a safe tumour reduction, avoiding in most cases a tumour lysis syndrome (TLS) [35]. In some cases, rasburicase may be given to prevent TLS. In cases with a very high WBC count (e.g. >100 000/ $\mu$ l), either measure is sufficient, and a leukapheresis is needed only in very rare cases. The time needed for pre-phase therapy will also allow to obtain the results of the diagnostic work-up, e.g. cytogenetics, molecular genetics. The response to pre-phase therapy defines the chemosensitivity of the disease, and is included in some studies for risk assessment, since good responders to prednisone may have a better outcome [36].

Supportive therapy should be initiated whenever necessary early on, e.g. to treat infections or to substitute platelets/erythrocytes. Severe neutropaenia (<500/ $\mu$ l) is often seen at diagnosis and is most frequent (>80%) during induction therapy, causing infections and infection-related death. A joint analysis of five randomised trials revealed a shorter duration of neutropaenia, and reduction in the rate of febrile neutropaenia in some but not all cases [37], and based on that, prophylactic granulocyte colony-stimulating factor should be considered during induction therapy [II, B].

### treatment: remission induction therapy and consolidation

*induction of complete remission.* The goal of induction therapy is the achievement of a CR, or even better, a molCR/good molecular response, usually evaluated within 6–16 weeks from



\* available at a later stage

**Figure 1.** Diagnosis and risk assessment in adult ALL for achievement of CR and risk-oriented post-remission therapy. Major diagnostic subsets are identified within 1–2 days to allow start of pre-phase therapy, identify cases eligible to targeted therapy (TKI in Ph+ ALL), and set up the MRD study. Pre-phase therapy allows for management/prevention of metabolic/infectious/haemorrhagic complications before start of induction therapy, and checks HLA identity between patient and siblings. Induction/early consolidation therapy (incorporating CNS prophylaxis) aims to induce CR with a deep MRD response, to support subsequent risk- and MRD-oriented therapy with/without allogeneic SCT. ALL, acute lymphoblastic leukaemia; RT-PCR, reverse transcriptase polymerase chain reaction; MRD, minimal residual disease; LAIP, leukaemia-associated immunophenotype; WBC, white blood cells; CR, complete remission; CNS, central nervous system; SR, standard risk; HR, high risk; SCT, stem-cell transplantation; TKI, tyrosine kinase inhibitor; Ph+, Philadelphia-positive; HLA, human leucocyte antigen.

start of chemotherapy, after which time the achievement of molCR is rather uncommon. Most regimens are centred on vincristine, corticosteroids, and anthracycline (daunorubicin, doxorubicin, rubidazole, idarubicin), with or without cyclophosphamide or cytarabine. L-Asparaginase is the only ALL-specific drug that depletes the asparagine levels and has been particularly explored in paediatric trials. It is now more intensively used in adults. Pegylated

asparaginase (PEG-Asp) has the advantage of a significantly longer period of asparagine depletion. Dexamethasone is often preferred to prednisone, since it penetrates the blood–brain barrier and also acts on resting leukaemic blast cells (LBCs).

*results of induction therapy.* There are no randomised trials comparing different induction regimens; however, there is a

substantial number of large (>100 patients) prospective non-randomised trials. In 6617 patients from 14 studies, the weighted mean for the CR rate was 83% (62%–92%) [35]. Using current approaches, the CR rate had increased to 80%–90%, higher for SR patients at  $\geq 90\%$ , and less in HR patients at  $\sim 75\%$ . There is only one randomised study for induction therapy; this compares prednisone to dexamethasone [38], demonstrating equal outcome [I, C].

**treatment principles.** There are two chemotherapy regimens; one is a widespread schema patterned after the paediatric BFM (Berlin–Frankfurt–Münster) protocols with Induction I, Induction II, Consolidation cycles, sometimes an intermittent re-induction cycle, and is mostly used in European adult ALL trials. A schematic treatment algorithm in adult ALL, including diagnosis and risk assessment for achievement of CR and risk-oriented post-remission therapy, is given in Figure 1.

Another approach is to repeat two different alternating intensive chemotherapy cycles, identical for Induction and Consolidation, accounting for a total of eight cycles, such as the hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) protocol, preferentially used in the United States, but also in other parts of the world.

**post-remission consolidation.** The rationale to use systemic high-dose (HD) therapy is particularly to reach sufficient drug levels in sanctuary sites, such as the CNS. Most protocols employ 6–8 courses which contain either HD methotrexate or HD cytarabine  $\pm$  asparaginase. HD cytarabine is usually administered for 4–12 doses at 1–3 g/m<sup>2</sup> and methotrexate at 1–1.5 g/m<sup>2</sup> and up to 3 g/m<sup>2</sup>.

### maintenance therapy

Maintenance therapy usually consists of daily 6-mercaptopurine and weekly methotrexate. In some treatment regimens, repeated cycles of vincristine, dexamethasone or other drugs in monthly or longer intervals are given. In one randomised study, the maintenance arm with reinforcement cycles was not superior to conventional maintenance therapy (37% versus 38% at 8 years) [36]. A treatment duration of 2.5–3 years is optimal and is usually recommended.

Omission of maintenance worsens outcome significantly in BCP-ALL, but less so in T-ALL [39], and not in B-ALL [40].

### CNS prophylaxis

Effective prophylaxis to prevent CNS relapse is an essential part of ALL therapy. Treatment modalities of CNS prophylaxis are CNS irradiation, intra-thecal (i.th.) methotrexate, mono- or i.th. triple (usually methotrexate, steroids, cytarabine) and systemic HD therapy with either methotrexate and/or cytarabine. With a combination of these CNS prophylactic measures, the CNS relapse rate in recent adult ALL trials could be reduced from 10% to <5%. CNS irradiation is also effective to eradicate residual LBCs in the CNS; however, in most studies, it is either omitted or restricted to HR patients. Furthermore, it is given only as an irradiation of the skull (mostly 24 Gy), and no longer of the whole neuroaxis, since this aggravates cytopenias. Patients with CNS involvement (mostly of the leptomeninges) at diagnosis are treated with the standard chemotherapy regimen, and additional i.th. applications

until blast clearance in the spinal fluid. Their OS is identical to the CNS-negative cohort of patients, or slightly inferior [41].

### age-adapted protocols

The outcome of ALL is strictly related to the age of a patient, with cure rates from 80% to 90% in childhood ALL, decreasing to <10% in elderly/frail ALL patients. Therefore, age-adapted protocols have emerged, where the age limits are mainly directed by the haematological and non-haematological toxicities. Although there is no uniform consensus, the following age groups are separated:

- **Adolescents and young adults (AYA)**, differently defined from 15/18 to 35/40 years,
- **Adult ALL**, age range 35/40 up to  $\leq 55/60$  years,
- **Elderly ALL** protocols for patients above the age of >55/60 years, and
- **Frail patients** not suitable for any intensive therapy, usually considered above the age of 70/75 years.

**adolescents and young adults.** Paediatric-inspired therapy provides an increased drug intensity at several treatment steps, including larger cumulative doses of drugs such as corticosteroids, vincristine, L-asparaginase and consequent CNS-directed therapy, which should be strictly adhered to, with a reduced role of SCT. In a systemic review and meta-analysis in 2012, in 11 trials including 2489 AYA patients, paediatric-inspired regimens were superior to conventional adult chemotherapy [42]. None of the trials were a randomised comparison. In recent studies for AYAs [43–45], survival rates at 5 years were 67%–78%, compared with 34%–41% with the former protocols.

**adult ALL.** The treatment results for adult ALL patients have also improved. In the above-mentioned 14 studies, the weighted mean for DFS was 34% (25% at 5 years, 48% at 3 years) and the OS 38% (27% at 9 years, 54% at 5 years). Currently, the OS rates for SR adult ALL patients is 50%–70% with chemotherapy alone. The outcome for HR patients has also improved, from 20%–30% to  $\sim 50\%$  when they receive an allogeneic SCT in CR1. Prospective adult studies applying the same drugs and time-dose intensity, using or not using the term ‘paediatric-inspired’, or some using the term ‘paediatric-derived’, achieved identical results compared with AYAs, with survival rates of 60%–70% or more [46–49].

**elderly ALL.** The incidence of ALL is increasing after the age of 50 years [50]. Different approaches have been applied in this patient cohort [51]. Older patients (55–91 years) with a palliative treatment had a CR rate of 43% (34%–53%), an early death rate of 24% (18%–42%) and an OS of only 7 months (3–10 months). In contrast, those with an intensive chemotherapy designed for adult ALL had a CR rate of 56% (40%–81%), but still an early death rate of 23% (6%–42%), and an OS of 14 months (3–29 months). In recent decades, several elderly specific ALL protocols have been initiated. Their principle is a less intensive therapy, based on corticosteroids, vincristine and asparaginase, and largely avoiding anthracyclines and alkylating agents, to reduce early treatment-related death. In nine prospective studies for older ALL patients (55–81 years), with this less intensive protocol, the CR rate was 71% (43%–90%), early death decreased to 15% (0%–36%)

and OS was significant at 33 months (16–71 months). Thus, all patients, irrespective of age, should be offered a treatment.

### targeted therapies

There is still a need to improve the outcome in adult and elderly ALL that is achieved with chemotherapy/SCT alone. Currently, there are two major new approaches, particularly for B-lineage ALL patients; either therapies with antibodies, or, for Ph+ ALL, targeted therapies with TKIs.

**antibodies.** The anti-CD20 MoAb rituximab has substantially improved the outcome in Burkitt leukaemia/lymphoma, as demonstrated by a single randomised trial [52]. Repeated short cycles of intensive chemotherapy, combined with rituximab increased OS from 62% to 83% (reviewed in [40]). The anti-CD20 antibody is also being applied in CD20-positive *de novo* B-lineage ALL, with encouraging results [53], and randomised trials are ongoing. The monoclonal antibodies directed against CD22, linked to cytotoxic agents, either to calicheamicin (inotuzumab ozogamicin) or to plant or bacterial toxins (epratuzumab), are explored in refractory/relapsed childhood and adult ALL [54]. Targeting CD19 is of great interest, as it is expressed in all B-lineage cells, most likely including early lymphoid precursor cells. The bispecific antibody blinatumomab combines single chain antibodies to CD19 and CD3, and thereby T cells lyse the CD19-bearing B cells. It is effective in patients with positive MRD [55] or refractory/relapsed ALL [56]. The CD19 antigen is also the target for a promising new approach, the use of chimaeric antigen receptor-modified T cells (CAR T cells) [57, 58].

In T-ALL, specific antibodies as in B-lineage ALL are not available. The few new drugs under investigation are nelarabine, which is active in advanced disease [59, 60] (currently evaluated in first-line therapy), and  $\gamma$ -secretase inhibitors blocking Notch1 signalling.

**tyrosine kinase inhibitors in Ph+ ALL.** When compared with the pre-imatinib era [61, 62], CR rates improved from 60%–70% to 80%–90% or even higher and short-term outcome was much better in relatively small non-randomised studies, which mostly simply added imatinib to their previous standard chemotherapy regimens in Ph+ ALL patients [63, 64]. These marked improvements were then confirmed in the long term [65–68], with survival reaching ~50%, compared with  $\leq$ 20% in the pre-imatinib era, making combined imatinib/chemotherapy the standard treatment of Ph+ ALL. Early enthusiasm was such that even the place of allogeneic SCT in first CR (which was considered as the only curative option for Ph+ ALL patients) was challenged. Nevertheless, a recent prospective trial from the GRAALL (Group for Research on Adult Acute Lymphoblastic Leukemia) suggests that allogeneic SCT is still associated with a better relapse-free survival in younger Ph+ ALL patients [69]. These younger patients may receive standard myeloablative conditioning (MAC), but the role of reduced-intensity conditioning (RIC)-SCT in older patients remains to be prospectively evaluated. After SCT, a recent randomised study from the GMALL (German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia) suggests that prophylactic imatinib maintenance is probably the best option to prevent post-

SCT relapse after MAC-SCT [70]. This remains to be studied after RIC-SCT.

Whether a subset of good-risk patients may be treated with continuous TKI/chemotherapy and be proposed allogeneic SCT in first CR is still under evaluation, as is the optimal TKI/chemotherapy combination that could be offered to such patients. Achievement of a good early MRD response (here evaluated on *BCR-ABL1* transcript levels) might be of great help in defining these good-risk patients [71]. In older Ph+ ALL patients, usually not candidates for allogeneic SCT, a poor MRD response but also the presence of additional chromosomal abnormalities at diagnosis were both associated with a worse outcome [72]. It has also been shown that the presence of *IKZF1* gene deletion, a frequent event in Ph+ ALL, may be of poor prognostic value, as also observed in Ph– ALL patients [73, 74].

The last issue relies on which is the best TKI/chemotherapy front-line combination. Usually, TKI therapy is initiated in front-line therapy together with the first chemotherapy cycle. A continuous TKI exposure should be favoured, even if a few weeks off may be needed to limit myelosuppression [75]. To date, there is no comparative study evaluating second-generation TKIs (nilotinib, dasatinib) versus imatinib as first-line treatment. The use of nilotinib and dasatinib may result in achieving a good MRD response more quickly, which could be of interest before SCT. On the other hand, more potent TKIs could induce a higher incidence of rate of resistance mutation, as was observed with T315I mutations at relapse in older patients receiving front-line dasatinib [72]. Combination of TKIs with dose-reduced chemotherapy should probably be preferred, compared with standard intensive chemotherapy/TKI combinations [76]. This has been randomly demonstrated in the GRAAPH-2005 trial, with lower early mortality and higher CR rate in patients receiving imatinib, combined with less intensive chemotherapy compared with those receiving Hyper-CVAD/imatinib [69]. GIMEMA (the Italian Group for Haematological Diseases in Adults) has also reported very good response rates and short-term outcomes in older patients treated almost exclusively with front-line dasatinib [77]. Once CR has been reached, autologous SCT might also be a good option, at least in patients who have reached a good MRD response, or in those who cannot tolerate allogeneic SCT [69, 78, 79].

In patients with persistent MRD or progressive disease, the recommendation is to switch to another TKI while screening for TKI resistance mutations and then to adapt TKI choice according to the resistance profile. The third-generation TKI ponatinib is currently the only option in patients progressing with the T315I mutation.

**tyrosine kinase inhibitors in Ph-like ALL.** TKIs might be also used as targeted treatment in some patients with Ph– ALL. The Ph-like entity has recently been described as associated with a gene expression signature similar to Ph+ ALL, but with no Ph chromosome or *BCR-ABL1* rearrangement. Kinase-activating events, including *ABL1* itself, *PDGFR-beta*, *JAK2* or other kinases are frequently found in this poor-prognosis ALL subset [16], and some remarkable cases of TKI treatment success have been reported in these patients [80, 81]. Imatinib, dasatinib or even ruxolitinib could thus be evaluated in these patients, who frequently have primary refractory ALL or very early relapse. See Table 4.

**Table 4.** Recommendations for TKI/chemotherapy combinations in adults with Ph+ ALL

	Recommendation
Adults with Ph+ ALL should be treated front line with a combination of imatinib or second-generation TKI and chemotherapy.	Mandatory
Reduced-intensity chemotherapy may be used in combination with TKI during the first treatment cycles, to minimise early toxicity and mortality.	Recommended
TKI should be administered as continuously as possible, with respect to haematological tolerance.	Recommended
There is no standard post-remission treatment in patients not receiving allogeneic SCT because of no donor or advanced age. Prolonged administration of imatinib/consolidation chemotherapy followed by imatinib maintenance should be applied.	Recommended
Allogeneic SCT in first CR with a standard myeloablative conditioning probably remains the best post-remission option in younger patients with a donor. The role of reduced-intensity conditioning allogeneic SCT remains to be evaluated in this ALL subset.	Recommended
Post-SCT imatinib maintenance is recommended for 1–2 years of duration.	Recommended
Prolonged monitoring of <i>BCR-ABL1</i> MRD levels is recommended, associated with resistance mutation screening in patients with persistent MRD detection or re-increasing MRD levels. Results should be used to guide the switch towards a second- or third-generation TKI in these higher risk patients.	Recommended

TKI, tyrosine kinase inhibitor; Ph+, Philadelphia-positive; ALL, acute lymphoblastic leukaemia; SCT, stem-cell transplantation; CR, complete remission; MRD, minimal residual disease.

### stem-cell transplantation

Despite the existence of studies and meta-analyses comparing chemotherapy and SCT [82], the issue of the indications of SCT in adult ALL patients in first CR is not defined in a satisfactory way and requires continuous update. This is due to the improving results with conventional and targeted chemotherapy regimens on one hand and to the decreasing mortality and broader availability of SCT on the other. Several attempts have been made to provide evidence-based guidelines for indication of SCT (Table 5, ref. [83]) [84–86] [V, A]. From these guidelines, the OS for SCT was superior to chemotherapy in HR patients [I, A], but left the role of SCT in SR open [I, C]. On the other hand, there is a general agreement that SCT is clearly the best therapeutic option for patients in second or later CR [III, A].

Some important issues emerged from the results of recent studies:

- 1) *Whether or not SCT should be offered to AYA with SR factors treated with paediatric-based or -inspired protocols that provide long-term OS rates ~70% [87].* In view of these results, most groups skip SCT in these patients to avoid acute mortality and long-term effects [III, B].
- 2) *The use of MRD (the most important prognostic factor in ALL) to guide the decision of chemotherapy or SCT after consolidation.* Data from recent studies have shown that SCT offers better results than chemotherapy in patients with high MRD levels after consolidation, regardless of the conventional risk factors at baseline [29] [III, A]. The question remains whether SCT is justified in patients with conventional HR features but low or negative MRD after consolidation, for whom OS rates >50% are expected with chemotherapy [29, 31–33]. Phase III studies addressing this point are desirable, because the trials included in the most recent meta-analysis [82] did not incorporate the MRD analysis as a decision tool.
- 3) *The indication for the different types of SCT.* Regarding allogeneic SCT, there is increasing evidence that sibling and very well-matched, unrelated donors (MUD) SCT can be considered equivalent options in terms of results and, therefore, MUD

SCT can be offered to patients lacking a sibling donor [IV, A]. Umbilical cord blood can be an alternative source when an HSCT is needed urgently or when the search for a very well-matched, unrelated donor is unsuccessful [88–90]. Haploidentical SCT could be an option in patients without a matched sibling or MUD, but prospective comparative studies are lacking. In turn, autologous SCT is considered inferior to chemotherapy and to allogeneic SCT [91] [I, A], but could be reconsidered in MRD-negative patients [92] unfit for allogeneic SCT [IV, D], as has been shown in patients with Ph+ ALL [71].

- 4) *The intensity of the conditioning.* There is no standard MAC regimen, but total body irradiation-based regimens seem to have better anti-leukaemic activity than busulfan-based preparative regimens [93] [IV, B]. RIC regimens are increasingly considered as an option for elderly HR patients or patients with contraindications for MAC-SCT [84, 94] [IV, B], but no prospective comparative studies between these two types of preparative regimens have been conducted in young, fit patients.
- 5) *The need for SCT in specific genetically defined groups of ALL, such as *BCR-ABL1*-positive (as previously reviewed) or *MLL*-positive cases.* Allogeneic SCT is currently carried out for *MLL*-rearranged ALL in most trials and, in the largest study conducted to date, better results have been observed compared with chemotherapy [95] [IV, A].

### treatment of relapsed or refractory ALL

Relapsed ALL in adults is still a major clinical challenge. There is no universally accepted treatment protocol and a lack of evidence based on randomised, controlled trials. However, there is consensus on the general approach to managing these patients.

#### diagnostic work-up

Therapy-related AML should be excluded. Enumeration of CD19, CD20 and CD22 expression on blast cells is important as it may have therapeutic relevance. Cytogenetic evaluation should take into account fusion proteins that may indicate a *BCR-ABL*-like phenotype [16, 81]. If allogeneic SCT is a possible therapeutic option, and if this was not done at diagnosis, the HLA profiling of the patient and siblings should be carried out urgently, and an

**Table 5.** Recommendations for SCT in adult ALL (data from [83])

Question	Recommendations
CR1. AutoSCT versus non-transplantation	<ul style="list-style-type: none"> <li>– Not recommended outside a clinical trial</li> <li>– Maintenance therapy, biological therapy, or TKIs may improve outcomes in selected patients</li> </ul>
CR1. AlloSCT versus non-transplantation	<ul style="list-style-type: none"> <li>– AlloSCT recommended in all patients with poor early MRD response</li> <li>– AlloSCT not recommended in SR patients with sustained molecular response</li> <li>– Indication unclear in HR patients with sustained molecular response</li> </ul>
CR $\geq$ 2. AlloSCT versus non-transplantation	<ul style="list-style-type: none"> <li>– AlloSCT superior</li> </ul>
AlloSCT versus autoSCT	<ul style="list-style-type: none"> <li>– Advantage for alloSCT</li> <li>– Insufficient data in patients with negative MRD levels, including Ph+ ALL</li> </ul>
Sibling donor versus MUD	<ul style="list-style-type: none"> <li>– Similar, and possibly equivalent survival outcomes</li> </ul>
UD CBT versus UD BMT	<ul style="list-style-type: none"> <li>– Consider CBT if no HLA-well-matched donor or need for urgent SCT</li> <li>– Haploidentical SCT should also be considered in this setting</li> </ul>
Conditioning regimens	<ul style="list-style-type: none"> <li>– Benefit of TBI regimens for myeloablative SCT</li> <li>– RIC regimens appropriate only for adults in remission unfit for myeloablative conditioning and elderly fit patients</li> </ul>
Areas of research needed	Comments
AlloSCT versus more intensive/specific CHT regimens	<ul style="list-style-type: none"> <li>– Re-evaluate, especially in the context of biological therapies and TKIs</li> </ul>
MRD to guide therapy in ALL	<ul style="list-style-type: none"> <li>– Increasing importance of the monitoring of MRD during initial treatment to guide individual patient eligibility and timing of allogeneic SCT</li> </ul>
MRD monitoring after SCT	<ul style="list-style-type: none"> <li>– To detect early post-SCT relapse for pre-emptive therapy</li> <li>– Effective therapies are under development</li> </ul>
RIC versus MAC regimens	<ul style="list-style-type: none"> <li>– Further studies needed, adjusted for a patient's tolerance of conditioning toxicity balanced against the risk of relapse</li> </ul>
CBT techniques	<ul style="list-style-type: none"> <li>– Single unit, double unit, <i>ex vivo</i> expansion, third-party donor. Larger multicentre experience needed to evaluate the broader applicability of CB grafting for adults with ALL</li> </ul>
Haploidentical SCT	<ul style="list-style-type: none"> <li>– Comparative studies with SCT from other sources needed (non-randomised comparisons show similar results)</li> </ul>
QoL and functional status after successful SCT	<ul style="list-style-type: none"> <li>– Evaluation and measures for improvement needed</li> </ul>

SCT, stem-cell transplantation; ALL, acute lymphoblastic leukaemia; CR1, first complete remission; autoSCT, autologous stem-cell transplantation; TKIs, tyrosine kinase inhibitors; alloSCT, allogeneic stem-cell transplantation; MRD, minimal residual disease; SR, standard risk; HR, high risk; CR  $\geq$ 2, second or later complete remission; Ph+, Philadelphia-positive; MUD, matched unrelated donor; UD, unrelated donor; CBT, cord blood transplantation; BMT, bone marrow transplantation; HLA, human leucocyte antigen; TBI, total body irradiation; RIC, reduced-intensity conditioning; CHT, chemotherapy; MAC, myeloablative conditioning; CB, cord blood; QoL, quality of life.

unrelated donor search should be initiated if a sibling match is not available. In the case of Ph+ ALL, *BCR-ABL1* tyrosine kinase domain mutations should be evaluated [96].

Overall evaluation of the clinical situation should take into account the disease-specific factors (BCP-ALL or T-ALL, *BCR-ABL1* status), patient factors (age, performance status, organ function and presence of extramedullary disease, in particular CNS), previous therapy (with particular reference to prior allograft, anthracycline dose) and specific toxicities of prior treatment which might guide therapeutic selection (e.g. osteonecrosis, vinca alkaloid neuropathy and specific infectious complications such as fungal infections).

### treatment principles

Treatment with a curative aim involves achievement of CR followed by allogeneic SCT. In four large trials, the outcome was very similar [59, 97–99]. The rate of second CR achieved was 44%–45%, the median OS 4.5–8.4 months (24% at 3 years in one study). Long duration of first CR (>2 years), then re-induction with a standard induction regimen—such as that used for original treatment—may be used [59, 97–99]. Short first CR or primary refractory disease is a very high-risk situation, and consideration should immediately be given to the availability of trials of novel agents that may be non-cross-resistant with chemotherapy. For BCP-ALL, such agents are now more widely available. Both

blinatumomab [56] and inotuzumab [96] have shown promising results in phase II studies and are being evaluated in randomised, controlled trials where the comparator arm is 'standard of care' chemotherapy. A clinical trial involving immunotherapy with CD19 CAR T-cell therapy [58] is also a possibility.

*chemotherapy for relapsed ALL.* The most commonly used regimens in Europe are fludarabine- and anthracycline-containing regimens, for example, FLAG-Ida (fludarabine, high-dose ara-C,

granulocyte colony-stimulating factor and idarubicin). Despite its common use and inclusion as 'standard of care' arm in current randomised, controlled trials of relapsed ALL, there is remarkably little published on FLAG-Ida in relapsed ALL [97]. Clofarabine-based regimens including cytarabine, cyclophosphamide or etoposide are also commonly used based mostly on data in childhood ALL [98]. Liposomal vincristine [99] is licensed for the treatment of relapsed ALL. These standard chemotherapy approaches are applicable in BCP-ALL as well as in T-ALL.

**Table 6.** Summary of recommendations for adult ALL

Diagnostic work-up of ALL

- Morphology, immunophenotype and cytogenetics to confirm the diagnosis and ALL subsets are mandatory
- New genetics and molecular genetics are recommended to detect rare subtypes, such as Ph-like ALL, ETP ALL
- Targets for therapy with TKIs or antibodies have to be identified
- Minimal residual disease by immunophenotype or molecular probe at diagnosis, for MRD-based risk classification and treatment algorithm, mandatory

Risk assessment and prognostic factors

- It is essential to stratify patients as standard-risk or high-risk patients
- Risk stratification is currently determined by a combination of prognostic factors at diagnosis and treatment-related parameters, preferentially MRD
- MRD during therapy is now the most relevant prognostic parameter for treatment decisions

Treatment

Treatment algorithm

- Chemotherapy includes induction therapy 1–2 months, consolidation cycles (alternating) 6–8 months and maintenance therapy 2–2.5 years
- Ongoing chemotherapy protocols for AYAs use paediatric-type regimens
- Prophylactic treatment to prevent CNS relapse is mandatory

Antibody therapy

- Anti-CD20 rituximab in combination with a chemotherapy is strongly recommended for Burkitt leukaemia/lymphoma
- Anti-CD22 immunoconjugates directed against CD22 currently under investigation
- Anti-CD19; activation of patients' own T cells directed against CD19
- Bispecific (CD3/CD19) blinatumomab under investigation
- Chimeric antigen receptor-modified T cells directed against CD19 in early phase

Targeted therapy with TKIs in Ph+ ALL

- A TKI should be combined with chemotherapy in front-line therapy
- The TKI imatinib (400–800 mg/day) should be administered continuously, also post-SCT
- Prolonged monitoring of *BCR-ABL-1* MRD is recommended, as well as resistance mutation screening. In case of persisting MRD, increasing MRD level, or resistance mutation, switch to a second- or third-generation TKI

SCT

- AlloSCT in CR1 significantly improves OS and EFS in high-risk patients/MRD+ patients and is the best post-remission option for Ph+ ALL and *MLL*-rearranged ALL
- Conditioning regimens are age-adapted with full allo versus RIC for elderly patients or patients unfit for full conditioning
- The role of autoSCT should be investigated for MRD-negative patients, in the setting of clinical trials
- All patients in CR  $\geq 2$  are candidates for alloSCT

Approach for relapsed/ refractory ALL

- Full diagnostic work-up necessary to exclude/reveal clonal aberrations, and to provide bases for targeted therapies
- Different treatment for patients with short versus long first remission duration (>18/24 months) where re-induction is considered
- Treatment; there is no standard re-induction therapy established, most often used new drugs

ALL, acute lymphoblastic leukaemia; Ph, Philadelphia; ETP, early T-cell precursor; MRD, minimal residual disease; AYAs, adolescents and young adults; CNS, central nervous system; TKI, tyrosine kinase inhibitor; Ph+, Philadelphia-positive; SCT, stem-cell transplantation; alloSCT, allogeneic SCT; CR1, first complete remission; OS, overall survival; EFS, event-free survival; RIC, reduced-intensity conditioning; autoSCT, autologous SCT; CR  $\geq 2$ , second or later complete remission.

**Table 7.** Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America–United States Public Health Service Grading System<sup>a</sup>)

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

<sup>a</sup>By permission of the Infectious Diseases Society of America [100].

Additionally, nelarabine is licensed for this indication, and a response rate of about 50% is noted [59]. Myelotoxicity is mild to moderate, but the neurotoxicity can be severe and irreversible. Co-administration with agents used to treat CNS disease can increase the risk.

*Ph+ ALL.* Patients with relapsed *Ph+ ALL* should be offered the new generations of TKIs, according to the results of mutational analysis of their *BCR-ABL1* transcripts. Patients who have lost response to imatinib may respond to nilotinib or dasatinib and there is even an option, ponatinib, for patients with the T3151 mutation. Although TKIs are not without adverse events (ponatinib, in particular, carries a risk of cardiovascular events), they are nonetheless a vastly superior option compared with repetitive treatment with myelosuppressive chemotherapy, as they preserve performance status and are better tolerated by elderly patients. There is no evidence of long-term survival induced by TKIs post-relapse and the majority of patients will have to receive allogeneic SCT. Second allografts are being reported, and there are case reports of good outcomes, although of uncertain long-term benefit.

Even in a palliative setting *BCR-ABL1*, kinase domain mutational analysis should be carried out and used to guide therapy with TKIs and to monitor treatment response and impending relapse.

## personalised medicine

Progress in the diagnosis of ALL with identification of genomic-defined sub-entities, the evaluation of MRD, and new targeted therapies have led to a substantial realisation of personalised medicine in adult ALL. Current options such as less intensive chemotherapy, new modalities of SCT, incorporation of targeted therapies and optimal combinations of treatments require prospective, cooperative research, hereby further refining the individualised approach to each patient.

## follow-up and long-term implications

The follow-up of asymptomatic patients should include blood cell counts and routine chemistry during maintenance therapy; usually every 2 weeks during the first 2 years to adjust treatment accordingly. Thereafter, follow-up should be 3-monthly in years 1, 2 and 3, since the majority of relapses occur within the first 2.5 years after initiation of treatment; then half-yearly in the 4th and 5th year. For evaluation of MRD, which is now the most important prognostic parameter, bone marrow aspiration is required 3-monthly. It is also desirable in *Ph+ MRD* to search for MRD (*BCR-ABL*) and, if possible, for mutations to switch to another TKI inhibitor.

In adults, adverse long-term effects are fewer compared with children with ALL, and most adult ALL patients are in good clinical conditions. Relevant late toxicities are: endocrinological disorders (thyroid, gonadal), osteonecrosis/osteoporosis, skin and mucosal disorders, cataract, cardiovascular disorders, infection, graft versus host disease/sicca syndrome, fatigue and cognitive disorders. Second malignancies can also occur but with a low frequency (<3%) after chemotherapy as well as SCT. Long-term observation including quality-of-life assessment of cured ALL patients is an essential part of treatment optimisation studies.

## methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development, <http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology>. The relevant literature has been selected by the expert authors. A summary of recommendations is presented in Table 6. Levels of evidence and grades of recommendation have been applied using the system is provided in Table 7. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer review process.

## conflict of interest

DH has reported advisory boards for Amgen, Pfizer, Erytech and Bristol-Myers Squibb. AF has reported advisory boards for Amgen and Pfizer. CB has reported honoraria from Roche, Pfizer, Celgene, Pharmacyclics and Janssen and research grants from Roche and Janssen. RB, JR and HD have reported no potential conflicts of interest.

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