

Perspective Article

HOW I TREAT NEWLY DIAGNOSED ACUTE LYMPHOBLASTIC LEUKEMIA

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Treatment algorithms differ for adult patients with Philadelphia-negative (Ph-) and Philadelphia-positive (Ph+) acute lymphoblastic leukemia (ALL). For Ph- ALL intensive induction-consolidation chemotherapy using “pediatric-inspired” protocols is a standard of care. Allogeneic hematopoietic cell transplantation (allo-HCT) from either an HLA-matched sibling, unrelated or haploidentical donor should be considered for patients with high estimated risk of relapse. Inadequate response at the level of measurable residual disease (MRD) is the strongest adverse prognostic factor. Patients with B-ALL and detectable MRD should be treated with blinatumomab. In the future, the use of blinatumomab and/or inotuzumab ozogamycin in addition to first-line chemotherapy may become a new standard of care reducing the role of allo-HCT. For patients with Ph+ ALL, tyrosine kinase inhibitors (TKI) are the most important components of treatment protocols, while the intensity of chemotherapy may be reduced. Allo-HCT is recommended for all patients treated with imatinib along with low-intensity chemotherapy. Results of phase-II studies using front-line dasatinib or ponatinib in sequence or in combination with blinatumomab are very promising. Such a strategy may allow the avoidance of systemic chemotherapy. The future role of allo-HCT in this context appears uncertain.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease. According to the International Consensus Classification, more than 30 genetically defined subtypes of precursor lymphoid neoplasms may be distinguished and split into precursor B-cell neoplasms (B-cell acute lymphoblastic leukemia/lymphoma, B-ALL/LBL) and precursor T-cell neoplasms (T-cell acute lymphoblastic leukemia/lymphoma, T-ALL/LBL).¹ At present, however, from the clinical point of view, only one subtype, i.e., Philadelphia chromosome-positive (Ph+) ALL, characterized by the presence of a t(9;22)(q34.1;q11.2) and corresponding *BCR-ABL1* gene rearrangement requires particular treatment, while for the remaining ones (Philadelphia-negative, Ph- ALL) the first-line therapy is relatively consistent.

The treatment of adults with ALL traditionally consists of polychemotherapy. It includes several phases: a pre-treatment phase, mainly using glucocorticoids, followed by an induction phase, aimed at achieving complete remission (CR), and a consolidation phase to perpetuate the state

of CR. Follow-up is either maintenance therapy or an allogeneic hematopoietic cell transplantation (allo-HCT), which is recommended for patients with a high estimated risk of disease recurrence.

In the 21st century, Ph+ and Ph- ALL treatment algorithms evolved differently. With the introduction of tyrosine kinase inhibitors (TKI), the treatment results for Ph+ ALL markedly improved. TKI became a backbone, while the intensity of chemotherapy tended to decrease. In contrast, for Ph-, there was a trend to escalate the intensity of chemotherapy following the pediatric experience. The use of so-called pediatric-inspired regimens (PIR) became a common practice, especially among adolescents and young adults (AYA). However, the definition of PIR and the upper age limit for AYA have not been well defined.

FIRST-LINE TREATMENT OF PH- ALL: CURRENT STATUS

For patients with Ph- ALL, PIR is a standard of care. A meta-analysis of 25 studies comparing the results of pe-

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diatric protocols with those originally designed for adults showed an approximately 20% overall survival advantage at 5 years in favor of the pediatric ones in AYA.² Direct implementation of pediatric protocols may be considered for patients up to 40 years old. The treatment intensity should be tapered for individuals between 40 and 55 years old. For those aged 55 years or more, the therapy should be personalized and adjusted to the performance status and comorbidities.

Details of the first-line treatment protocols differ among countries and study groups. The pre-treatment phase is usually based on glucocorticosteroids, mainly dexamethasone +/- cyclophosphamide (CP), administered for 5-7 days. After the initial reduction of the tumor burden, induction therapy is initiated, usually consisting of anthracyclines, vincristine (VCR), dexamethasone, and asparaginase. It may be followed by a second course, including CP, cytosine arabinoside (AraC), mercaptopurine, and methotrexate (MTX). CR is achieved in approximately 90% of patients.³ It is defined as bone marrow blasts < 5%, absence of blasts in the peripheral blood, absence of extramedullary disease, absolute neutrophil count > $1 \times 10^9/L$, platelet count > $100 \times 10^9/L$, and independence of red blood cell transfusions.⁴ The reasons for treatment failure include primary resistance or early death due to treatment complications, both affecting approximately 5% of patients.³ The consolidation phase includes alternating courses of chemotherapy, consisting of high doses (HD) of MTX, HD-AraC, CP, etoposide, asparaginase, and dexamethasone. The treatment algorithm may include a re-induction phase, i.e., a repeated course of the drugs used during initial induction. Repeated administration of high doses of polyethylene glycol (PEG)-asparaginase ($2000 \text{ IU}/\text{m}^2$) is a feature of PIR.⁵ Although the drug appears critical to increasing the overall treatment efficacy, it is associated with a substantial risk of severe complications, including thrombotic events, hepatotoxicity, and pancreatitis.⁶ The incidence of liver toxicity is higher in adults than in children.⁷ While the induction phase usually lasts 4-8 weeks, the consolidation phase takes approximately 6 months. Either maintenance or allo-HCT follows the consolidation phase. Maintenance lasts up to 2 years and includes mercaptopurine, MTX, vincristine, and glucocorticosteroids.

In parallel to systemic chemotherapy, intrathecal use of cytostatics, usually MTX, AraC, and dexamethasone, is obligatory to prevent relapse in the central nervous system (CNS). The same drugs are used to treat initial CNS involvement, if present. In addition, HD-MTX (usually $3 \text{ g}/\text{m}^2$) administered during consolidation penetrates the blood-brain barrier and contributes to protection from CNS recurrence.⁸

Allo-HCT effectively prevents relapse in ALL adults, combining the conditioning regimen's anti-leukemic activity and beneficial graft-versus-leukemia reaction mediated by donor-derived immune cells. Unfortunately, it is associated with a significant risk of non-relapse mortality (NRM) affecting 15-22% of patients, depending on the donor type.⁹ Therefore, Ph-ALL allo-HCT in the first CR is considered only for patients with a high estimated risk of relapse. Precise indications vary among study groups.¹⁰ The

most commonly accepted high-risk feature is an inadequate response to induction, detected as measurable residual disease (MRD) or MRD persistence/recurrence after consolidation. MRD can be evaluated by real-time quantitative polymerase chain reaction (RQ-PCR) to detect specific Ig/TCR gene rearrangements, or by multiparametric flow cytometry to detect leukemia-specific phenotypes.¹¹ RQ-PCR is more expensive and time-consuming but associated with higher sensitivity (10^{-5}), while flow cytometry is fast but less sensitive (10^{-4}).^{12,13} The negative prognostic value of detectable MRD has been well-documented using both methods.¹⁴⁻¹⁸ The sensitivity level may further be increased by using digital droplet PCR or next-generation sequencing.¹⁹ The latter allows for the detection of ALL subclones. However, these methods have not been sufficiently standardized in ALL and, therefore, cannot be recommended for routine evaluation of MRD. Among other high-risk factors, most study groups consider high initial leukocyte count and adverse genetic subtypes, particularly KMT2A rearranged ALL.¹⁰

In recent years, immunotherapy appears increasingly important in addition to chemotherapy for adults with Ph-ALL. As demonstrated by the French study group, introducing an anti-CD20 antibody, rituximab, to all treatment phases for patients with CD20-positive ALL contributes to improved event-free survival (EFS) and reduced incidence of relapse.²⁰ Such an effect could not be demonstrated by the UK study group that included all patients regardless of CD20 expression.²¹ In the latter study, rituximab was restricted to the induction phase. Although rituximab is not approved for treating ALL, several study groups included it in their treatment protocols.

Data from a retrospective propensity-score analysis by the MD Anderson Cancer Center (MDACC, Houston, USA) suggest improved results with ofatumumab, a fully human anti-CD20 monoclonal antibody, in combination with a hyper-CVAD (CP, VCR, doxorubicin, dexamethasone) protocol when compared to rituximab + hyper-CVAD. However, the differences in EFS and overall survival (OS) did not reach statistical significance.²²

Blinatumomab, a bispecific anti-CD19/anti-CD3 T-cell enhancer, has been approved for treating patients in CR with MRD levels $>10^{-3}$ in the bone marrow. As shown by the results of the phase II study, it may allow for the eradication of MRD in 78% of patients in the first or subsequent CR.²³ It may be considered a bridge to allow HCT. However, the need for transplantation after blinatumomab remains controversial.

The use of modern PIR, incorporating all approved and available drugs, offers a chance of long-term survival to 50-70% of adults with Ph-ALL.²⁴⁻³⁴ Relapse and transplant-related mortality are the most frequent causes of treatment failure. The outcomes are inferior in older patients due to higher frequency of adverse molecular subtypes, poor tolerance of intensive chemotherapy and ineligibility for myeloablative allo-HCT.³⁵ The current treatment algorithm for adults with Ph-ALL is shown in [Fig. 1](#).

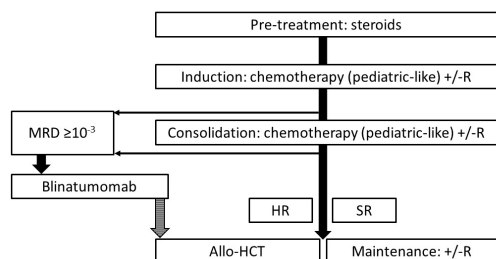


Fig. 1. How do I treat newly diagnosed Ph-negative ALL in 2023?

R, rituximab; MRD, measurable residual disease; SR, standard risk; HR, high risk; allo-HCT, allogeneic hematopoietic cell transplantation

FIRST-LINE TREATMENT OF PH- ALL: PERSPECTIVES

While in the first 2 decades of the 21st century the intensity of chemotherapy for patients with Ph- ALL tended to increase, this trend may reverse in view of results of modern studies incorporating immunotherapy to the first-line treatment. A series of phase-2 studies demonstrated feasibility of administration of either blinatumomab, inotuzumab ozogamicin (InO, immunoconjugate of anti-CD22 monoclonal antibody and calicheamicin) or both, in combination or in sequence, with standard chemotherapy.³⁶⁻³⁹

In the GIMEMA LAL2317 trial, 2 courses of blinatumomab were administered, in addition to the standard induction-consolidation.³⁶ Among 146 patients aged 18-65 years, the probabilities of OS and disease-free survival (DFS) at 12 months were 84% and 72%, respectively. In the French QUEST study, high risk patients, i.e. those presenting *KMT2A*-rearrangement, *IKZF1* intragenic deletion, and/or MRD post-induction $\geq 10^{-4}$, received up to 5 cycles of blinatumomab during consolidation and maintenance phases, or as a bridge to allo-HCT.³⁷ Among 94 evaluable individuals, the OS rate at 2.5 years was 79%, while the probability of DFS was 72%. In a study by Short et al., 45 patients aged 14-59 years were administered 4-7 cycles of blinatumomab +/- InO in addition to hyper-CVAD regimen.³⁸ Three-year continuous remission and OS rates were 84% and 85%, respectively. Among those receiving InO, no relapses or NRM were observed at one year follow-up. Finally, in the ECOG-ACRIN E1910 phase-III trial, patients aged 30-70 years old who achieved CR with MRD $< 10^{-4}$ after induction and early intensification were randomly assigned to receive either standard chemotherapy or chemotherapy in sequence with 4 blocks of blinatumomab.³⁹ The risk of mortality was significantly reduced in the blinatumomab arm (median OS: not reached versus 71.4 months; hazard ratio = 0.42, 95% CI: 0.24 - 0.75; $p=0.003$). These data strongly indicate that blinatumomab should be considered a standard of care in both MRD-positive and -negative disease status.

The use of immunotherapy in front-line treatment appears particularly attractive for older patients with Ph- B-

ALL. Stelljes et al. reported results of the German phase-II trial where 45 patients with a median age of 64 years (range, 56-80 years) received induction based on InO combined with dexamethasone, followed by 2 courses of InO monotherapy, consolidation, reinduction and maintenance.⁴⁰ The CR rate was 100%, while the probabilities of OS and EFS at 2 years were 81% and 73%, respectively. In the EWALL-INO study, 131 patients with a median age of 68 years (55-84) were induced with low doses of chemotherapy (VCR, CP, dexamethasone) including InO, followed by chemotherapy-based consolidation and maintenance.⁴¹ The OS and DFS rates at 2 years were 54% and 50%, respectively. In another prospective German study, 34 patients aged 65 (56-76) years were treated with induction, including idarubicin, VCR, and dexamethasone, followed by a single course of blinatumomab in sequence with chemotherapy.⁴² OS and DFS rates at 1 year were 84% and 89%, respectively. Overall, the results of the above-cited trials are much better than historical data with chemotherapy only, giving hope for a cure in older patients with Ph- B-ALL.⁴³

T-ALL accounts for 20-25% of adult ALL. So far, humoral immunotherapy forms are unavailable for this disease subtype. Conventional chemotherapy remains a backbone, with attempts to personalize treatment by incorporating nelarabine in first-line protocols. In the UKALL14 trial, three doses of nelarabine were administered following the second phase of induction.⁴⁴ This addition had no impact on any of the study outcomes. On the other hand, according to a retrospective analysis by MDACC, the use of nelarabine may contribute to improved outcomes in T-ALL subtypes other than early T-cell precursor ALL.⁴⁵ Further prospective studies are needed to verify this finding.

Ph-like ALL is a disease subtype characterized by a gene expression profile similar to Ph+ ALL in the absence of *BCR-ABL1* fusion gene.⁴⁶ This subtype may be further subclassified according to the type of molecular alterations and affected pathways, and is associated with poor outcomes.⁴⁷ *ABL1* class mutations may be targeted by TKIs, like imatinib or dasatinib. JAK2 fusions, EPOR rearrangements, and activating JAK-STAT mutations are potentially sensitive to the JAK2 inhibitor ruxolitinib.⁴⁸ The use of these agents in first-line treatment is under clinical investigation. So far, however, data on adults are scarce. Furthermore, the identification of Ph-like ALL is not routine clinical practice.

Perspectives for treating adults with Ph- ALL are presented in [Fig. 2](#).

FIRST-LINE TREATMENT OF PH+ ALL: CURRENT STATUS

Ph+ ALL is the most common molecular subtype. Its frequency increases with age, being 5-15% in adolescents, 25-30% in patients aged 25-35 years and more than 35-40% in patients older than 35 years.^{49,50} Historically, Ph+ ALL was associated with a dismal prognosis, and considered a very high-risk subtype. Results improved dramatically with the introduction of TKIs.^{51,52} So far, imatinib is the only TKI approved for use in first-line treatment. The combina-

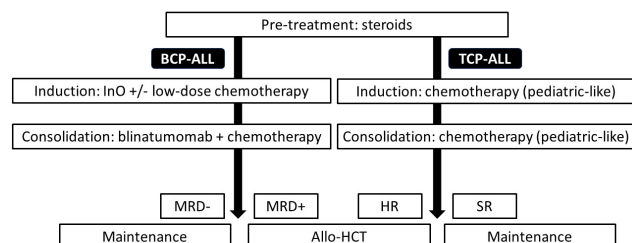


Fig. 2. How would I like to treat newly diagnosed Ph-negative ALL?

BCP-ALL, B-cell precursor acute lymphoblastic leukemia; TCP-ALL, T-cell precursor acute lymphoblastic leukemia; InO, inotuzumab ozogamycin; MRD, measurable residual disease; SR, standard risk; HR, high risk; allo-HCT, allogeneic hematopoietic cell transplantation

tion of imatinib with either corticosteroids or multi-agent chemotherapy results in 90-100% CR rate.⁵³⁻⁵⁶ Unfortunately, without subsequent allo-HCT most patients experience relapse. The role of intensity of concomitant chemotherapy was addressed in the GRAAPH-2005 study.⁵⁷ Patients were randomly assigned to receive induction consisting of either imatinib in combination with vincristine and dexamethasone or imatinib + hyper-CVAD. CR rates were 98.5% and 91% ($p=0.006$), respectively, with increased early mortality observed in the hyper-CVAD arm. The 5-year EFS and OS rates were higher for the “low-intensity” arm, although the differences were not significant. Allo-HCT was intended for all patients. A post-hoc analysis revealed improved outcomes for those having an HLA-matched sibling donor (MSD) or matched unrelated donor (MUD) and actually treated with allo-HCT compared to the remaining individuals. Based on results of that study the use of imatinib in combination with low intensity chemotherapy became a standard of care. It should be accompanied by intrathecal prophylaxis of CNS relapse, as well as high doses of methotrexate in consolidation. Allo-HCT is recommended for all eligible patients. Strict MRD monitoring, based on BCR-ABL1 transcript detection, is obligatory. Persistence or recurrence of MRD may implicate the introduction of a second (dasatinib) or third (ponatinib) generation TKI, optimally after verification of the presence of point mutations within the ABL1 kinase domain. The use of TKI is also recommended as a maintenance after allo-HCT. It may be introduced either prophylactically, regardless of MRD status, or as a pre-emptive approach, in case of MRD-positivity.⁵⁸ Detailed guidelines have been elaborated by the European Society for Blood and Marrow Transplantation (EBMT).⁵⁹

The current treatment standard for adults with Ph+ ALL is presented in [Fig. 3](#).

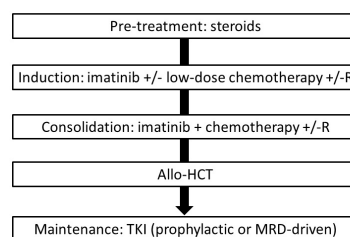


Fig. 3. How do I treat newly diagnosed Ph-positive ALL in 2023?

R, rituximab; allo-HCT, allogeneic hematopoietic cell transplantation; TKI, tyrosine kinase inhibitor; MRD, measurable residual disease

FIRST-LINE TREATMENT OF PH+ ALL: PERSPECTIVES

The upfront use of second or third generation TKI may contribute to an increased rate of molecular responses. When combined with intensive chemotherapy and/or modern immunotherapy, there is a potential for cure without allo-HCT. The only prospective, randomized trial comparing imatinib and dasatinib administered in parallel to intensive chemotherapy was performed in the pediatric population.⁶⁰ The use of dasatinib was associated with improved EFS (71% versus 49% at 4 years) and OS (88% versus 69% at 4 years), with reduced incidence of relapse, including CNS relapse. Dasatinib is the only TKI that crosses the blood-brain barrier.

In the adult population, only results of phase-II studies are available. The combination of dasatinib with hyper-CVAD led to 96% CR rate and 46% probability of the OS at 5 years, with only 17% of patients treated with allo-HCT.⁶¹ The outcomes appear even better for ponatinib used in parallel to hyper-CVAD: 98% CR, 67% EFS and 71% OS rates at 5 years, with 30% of patients treated with allo-HCT.⁶² In the older population (>55 years old) dasatinib combined with intermediate dose chemotherapy allowed for a 36% 5-year OS rate, while allo-HCT was applied to 10% of patients.⁶³

An Italian group performed a study using dasatinib + dexamethasone in induction, followed by 2-5 cycles of blinatumomab and dasatinib maintenance.⁶⁴ The CR rate was 98%, including 60% molecular responses. EFS and OS rates at 18 months were 88% and 95%, respectively. The treatment was free from systemic chemotherapy except for 38% of patients referred for allo-HCT. Jabbour et al. performed a study combining ponatinib and blinatumomab for up to 5 cycles with subsequent ponatinib maintenance.⁶⁵ Among 40 patients with median age of 57 (20-83) years, 96% achieved CR, while the probability of OS at 2 years was 95%. Only one patient received allo-HCT in CR1.

Taken together, it seems that the use of second or third generation TKI in combination or in sequence with blinatumomab may markedly improve the prognosis of patients

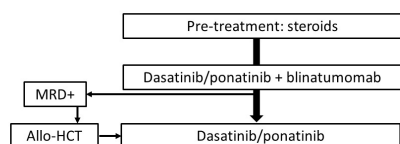


Fig. 4. How would I like to treat newly diagnosed Ph-positive ALL?

MRD, measurable residual disease; allo-HCT, allogeneic hematopoietic cell transplantation

with Ph+ ALL, reducing the role of allo-HCT as part of the first-line treatment. However, longer follow-up is needed to draw final conclusions. The perspectives of the treatment of adults with Ph+ ALL are summarized in [Fig. 4](#).

ALLO-HCT IN FIRST-LINE TREATMENT

Allo-HCT is currently recommended for high-risk patients with Ph- ALL and all patients with Ph+ ALL treated with up-front imatinib. The choice of potential donors is wide, including MSD, MUD, mismatched unrelated donors (MMUD) and haploidentical relatives. The intensity of conditioning may be adjusted to the recipient's biological status, which means that almost all patients with indications for allo-HCT may be offered this procedure.

The impact of donor type on the results of allo-HCT in ALL was a subject of several retrospective analyses. In a study by the EBMT Acute Leukemia Working Party, no significant difference could be detected between transplantations from MUD, MMUD and haploidentical donors.⁶⁶ In another study, allo-HCT from haploidentical donors was associated with increased non-relapse-mortality compared to MSD transplants which, however, was counterbalanced by a reduced risk of relapse.⁶⁷ Hence, it seems that in terms of survival, all donor types may be considered equally valuable.

Studies focused on haploidentical transplantations showed better results for unmanipulated grafts with the use of post-transplant cyclophosphamide as a backbone of immunosuppression, compared to regimens based on anti-thymocyte globulin.⁶⁸ Bone marrow, as compared to peripheral blood as a source of stem cells, was associated with improved OS and leukemia-free survival, mainly as a consequence of reduced risk of GVHD and non-relapse mortality.⁶⁹ Finally, as shown by the EBMT, results of haploidentical transplantations for patients with ALL tend to improve over time.⁷⁰

The outcome of allo-HCT may be affected by the type of conditioning regimen. Results from retrospective analyses indicated that the use of myeloablative total body irradiation (TBI) was associated with a reduced risk of relapse

and improved survival, compared to chemotherapy-based regimens.^{9,71,72} These findings were confirmed by a global study on a pediatric population. The outcomes were significantly better for patients treated with TBI at a dose of 12 Gy combined with etoposide, than for those treated with thiotepea and fludarabine combined with either busulfan or treosulfan.⁷³ On the other hand, a prospective study in adults indicated non-inferiority of busulfan + cyclophosphamide compared to TBI at a total dose of 9 Gy + cyclophosphamide.⁷⁴ That study, however, was restricted to B-ALL with standard-risk cytogenetics. Therefore, the choice of TBI dose as well as chemotherapy counterpart may play a role. The use of anti-thymocyte globulin for patients with ALL is a matter of controversy, as results from large scale registry-based studies indicate reduced incidence of chronic GVHD but increased risk of relapse in both Ph- and Ph+ ALL.^{75,76}

CAR T-CELLS NOW AND IN FUTURE

Chimeric antigen receptor (CAR) T-cells are genetically engineered T lymphocytes able to recognize and destroy cancer cells. Two products representing autologous CAR T-cells, tisagenlecleucel and brexucaptogene autoleucel have been approved for the treatment of relapsed/refractory B-ALL.^{77,78} Such therapy could potentially be offered to patients in CR1 with detectable MRD. In this clinical situation, CAR T-cells would be a final treatment, allowing to avoid allo-HCT. Clinical studies exploring this concept are ongoing.

Multiple preclinical and clinical studies are being conducted with the aim to optimize CAR T-cell products in terms of both their efficacy and safety. Among others, this includes simultaneous or sequential targeting of two antigens, as well as the ability to switch-off and switch-on the expression of the CAR.⁷⁹ Similarly, allogeneic CAR T-cells are being engineered, with the objective to simplify the logistics of the procedure.⁸⁰ Taking into account its very high research and development potential, it can be hypothesized that, in the future, CAR T-cells will become a predominant treatment tool, and may substitute all other forms of systemic therapy.

SUMMARY

For adults with Ph- ALL, conventional chemotherapy using PIR remains a standard of care. Allo-HCT from either MSD, MUD, MMUD or haploidentical donors should be considered for patients with high risk of relapse. Patients with B-ALL and detectable MRD should be treated with blinatumomab ([Fig. 1](#)). In the future, the use of blinatumomab and/or InO in addition to first-line chemotherapy may become a new standard of care reducing the role of allo-HCT ([Fig. 2](#)).

For patients with Ph+ ALL the use of TKI is a priority. Imatinib in combination with reduced-intensity chemotherapy, followed by allo-HCT is currently recommended ([Fig. 3](#)). Front-line dasatinib or ponatinib, in sequence or in combination with blinatumomab, is a promis-

ing strategy, which may allow to avoid systemic chemotherapy. The future role of allo-HCT in this context appears uncertain (**[Fig. 4](#).

(advisory boards, speakers bureau, honoraria), Roche (advisory boards, speakers bureau, honoraria), Angelini (advisory boards, speakers bureau, honoraria), Servier (speakers bureau, honoraria).

COMPETING INTERESTS

Novartis (advisory boards, speakers bureau, honoraria), Gilead (advisory boards, speakers bureau, honoraria), Amgen (advisory boards, speakers bureau, honoraria), Pfizer

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