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Hematological malignancies and molecular targeting therapy

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ABSTRACT

Recent genetic analysis using next-generation sequencing (NGS) vastly improved the understanding of molecular mechanism of hematological malignancies. Many molecular targeting drugs have since been used in the clinic, which is timely as clinical outcomes using conventional chemotherapy and hematopoietic stem cell transplantation (HSCT) reached a plateau. The first memorable success in this field was imatinib, a first-generation tyrosine kinase inhibitor (TKI), which has been applied in chronic myeloid leukemia (CML) since 2001. Imatinib drastically changed CML treatment and many CML patients no longer require HSCT. Recently, the second generation TKIs, dasatinib, nilotinib, and ponatinib, have also been available for CML patients. Acute lymphoblastic leukemia (ALL) is sub-categorized based on cytogenetic or molecular genetic abnormalities. Chemotherapy and HSCT combined with TKI improved the event-free survival rate from 20% to 80% in Philadelphia (Ph) chromosome-positive ALL. Reportedly, another Ph-like ALL subgroup with poor prognosis can also be treated by TKIs; additionally, cell therapies that include bispecific T-cell engagers or chimeric antigen receptor (CAR)-T therapy are emerging. Acute myeloid leukemia (AML) is a heterogenous disease and FMS-like related tyrosine kinase-3 (*FLT3*)-internal tandem duplication, is the most robust marker for poor prognosis. Several first-generation TKIs have been studied for clinical use. Notably, chemotherapy plus midostaurin improved survival compared with chemotherapy alone. Therefore, midostaurin was approved to treat adult AML patients with *FLT3*-ITD in 2017. Gemtuzumab ozogamicin, a selective anti-CD33 antibody–calicheamicin conjugate, is approved for clinical practice. Many molecular targeting agents are now being used for hematological malignancies.

1. Introduction

Recently, great advances have been observed in molecular targeting therapy for almost all hematological malignancies, including chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), myeloproliferative neoplasm (MPN), chronic lymphoblastic leukemia (CLL), malignant lymphoma, and multiple myeloma. These successful advances were obtained based on the investigation of genetic/epigenetic alterations in hematological malignancies over several decades using high through-put genetic/epigenetic analysis technologies including next-generation sequence (NGS). Importantly, neoplasms and cancers, including hematological malignancies, have been shown to develop and grow through the accumulation of many genetic/epigenetic events, in what has come to be called “multistep tumorigenesis” (Chaffer and Weinberg, 2015). If we find the “driver mutations” rather than “accompanying mutations” in each disease, we will have good targets for innovative molecular targeting therapy. For example, a recent study of lung cancer revealed that more than 60% of non-small cell lung carcinomas express the epidermal growth factor receptor (EGFR), a transmembrane protein with cytoplasmic kinase activity that transduces important growth factor signaling from the extracellular milieu to the cell (Chapman et al., 2016). Notably, tyrosine kinase inhibitors (TKIs) are especially effective in patients whose tumors harbor activating mutations in the tyrosine kinase domain of the *EGFR* gene (Zhang et al., 2016). Therefore, if we are going to use an EGFR inhibitor, analysis of *EGFR* gene mutations is recommended. This is called “companion diagnostics” (Jørgensen and Hersom, 2016). Subsequently, in an initial “umbrella trial,” several subgroups of the disease were divided according to biomarkers such as prognostic and genetic information and treated differently to conventional therapy (Simon, 2017).

TKIs, such as imatinib or dasatinib, drastically improved outcomes of CML, which had previously been treated with hydroxylurea, interferon and hematopoietic stem cell transplantation (HSCT). However, treatments for ALL and AML are still based on older chemotherapeutic drugs, and have not greatly changed for a few decades. For example, steroids (predonisolone or dexamethasone), vincristine, L-asparagninase and anthracycline are used in induction therapy, and 6-mercaptopurine and methotorexate were crucial maintenance therapies for ALL; and antracycleine (idarubicine or daunorubicine), cytarabine, and

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etoposide were basic therapies for AML. Combining these drugs with HSCT boosted patients' outcomes for a few decades but improvements plateaued. Therefore, new drugs, especially molecular targeting agents—including TKIs, bispecific antibodies (blinatumomab, etc.), antibody–drug conjugates (ADC; inotuzumab ozogamicine, gemtuzumab ozogamicine, etc.) and bromodomain and extra-terminal protein (BET) inhibitor—are expected to improve clinical outcomes.

To use molecular targeting agents including TKIs, there are two major methods; TKIs alone or in combination with conventional chemotherapeutic drugs. Notably, severe myelosuppression is found when using a combination of TKIs with chemotherapies. Furthermore, combinations with TKIs, inotuzumab ozogamicine, blinatumomab and chemotherapy have been proposed for relapsed/refractory adult ALL. In this review article, we will discuss the recent advances and future directions in molecular targeting therapy for hematological malignancies, especially in CML, ALL, AML, and MPN.

2. Chronic myeloid leukemia and tyrosine kinase inhibitors

Chronic myeloid leukemia (CML) is a representative myeloproliferative neoplasm (MPN) caused by a translocation between chromosomes 9 and 22, t(9; 22)(q34; q11.2), involving a fusion of the Abelson oncogene (*ABL*) from chromosome 9q34 with the breakpoint cluster region (*BCR*) gene on chromosome 22q11.2 leading to a chimeric gene product known as *BCR-ABL* (Bhatia, 2017). The BCR-ABL fusion protein has constitutively activated Abl tyrosine kinase activity which is responsible for the uncontrolled proliferation in CML (Fig. 1). The existence of leukemic stem cells (LSCs) in CML is suspected and their persistent existence explains disease relapse (Holyoake and Vetrie, 2017). The natural history of CML has three clinical phases, a chronic phase (CP, elevated WBC and platelet counts without subjective symptoms after 3–5 years from diagnosis), an accelerated phase (AP, accelerated differentiation abnormalities in granulocytes) and blast crisis (BC, increased undifferentiated blasts, similar to acute leukemia) (Hehlmann, 2012). Patients frequently have leukocytosis or splenomegaly. The TKIs, imatinib, dasatinib, and nilotinib, are the current first-line TKIs approved by the United States Food and Drug Administration (US FDA) for CML treatment. Treatment outcome is defined in terms of hematological response, cytogenetic response (CyR), and molecular response (MR) (Baccarani et al., 2013). European Leukemia Net recommended that the response is assessed with standardized real-time quantitative polymerase chain reaction (qPCR) and/or cytogenetics at 3, 6, and 12 months. *BCR-ABL* transcript levels ≤10% at 3 months, < 1% at 6 months, and ≤0.1% from 12 months onward define an optimal response, whereas > 10% at 6 months and > 1% from 12 months onward define treatment failure, mandating a change in therapy (Baccarani et al., 2013, 2015). Similarly, partial cytogenetic response (PCyR) at 3 months and complete cytogenetic response (CCyR) from 6 months onward define an optimal response, whereas no CyR (Philadelphia chromosome-positive [Ph+] > 95%) at 3 months, less than PCyR at 6 months, and less than CCyR from 12 months onward define failure. Recently, MR was defined to measure the ratio of *BCR-ABL1* transcript/*ABL1* transcript by qPCR, which will be adjusted by an International Scale and reported as *BCR-ABL1*^{IS} (Table 1).

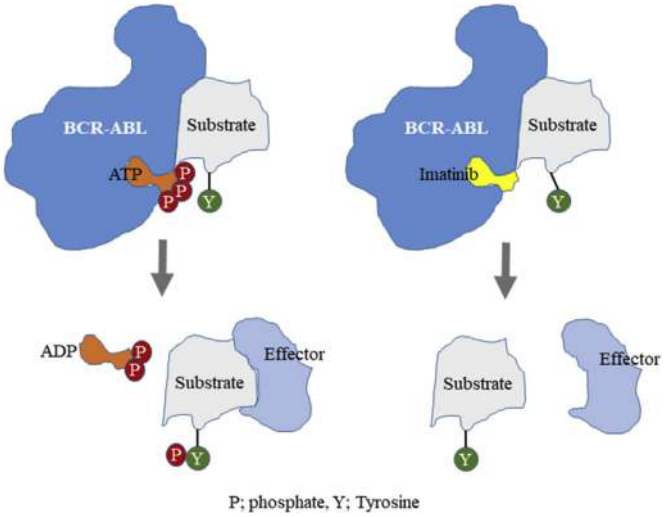

Fig. 1. BCR-ABL fusion gene product detected in CML patients, which results in uncontrolled cell proliferation in CML. BCR-ABL fusion product constitutively activates ABL kinase, which sticks to ATP in the kinase pocket and phosphorylates the substrate, then interacts with other downstream effector molecules. Small molecule tyrosine kinase inhibitors, such as imatinib, competitively stick to the ATP pocket and stop the proliferative signaling. (P: phosphate, Y: Tyrosine).

Before the imatinib era, CML was a MPN, therefore CML patients were treated with hydroxyuria, interferon-α, or hematopoietic stem cell transplantation (HSCT). Imatinib became the first choice of therapy for CML-CP because the treatment outcome of imatinib was superior to that of interferon-α with low dose cytarabine (Druker et al., 2006). However, the inhibition of ABL1 kinase by imatinib is less effective than that of the 2nd generation TKIs dasatinib or nilotinib. Therefore, newer TKIs were brought into use for imatinib-refractory CML patients. A comparative study of each TKI with imatinib confirmed their efficacy as 1st line therapy for CML-CP (Saglio et al., 2010; Kantarjian et al., 2010). If resistance or intolerance to a 1st line TKI was observed, the TKI should be changed in accordance with genetic information on the *ABL1* kinase mutation. The 2nd generation TKI bosutinib or the 3rd generation TKI ponatinib are recommended for patients with TKI resistant CML. Bosutinib is effective for several kinase domain mutations in the *ABL1* gene, except for T315I (Cortes et al., 2018a). In contrast, ponatinib is effective even in CML patients with T315I (Cortes et al., 2018b).

The clinical outcome of CML patients has been dramatically improved due to the introduction of TKI therapy. Therefore, allogeneic HSCT (allo-HSCT) is not recommended for CML-CP patients, because of the possibility of early death due to therapy-related toxicities of allo-HSCT. However, CML-BC or AP patients who demonstrate TKI resistance are still recommended to receive allo-HSCT.

Recently the goal of CML treatment changed. Interestingly, in CML-CP patients who stopped imatinib therapy after they achieved complete MR (CMR) there was no relapse. Discontinuation of imatinib in patients with CML who have maintained CMR for at least 2 years was investigated in the prospective, multicenter Stop Imatinib (STIM) trial performed in France (Etienne et al., 2017). 100 patients were enrolled between July 9, 2007, and December 17, 2009. Median follow-up was 17 months (range 1–30), and 69 patients had at least 12 months follow-up (median 24 months, range 13–30). At 12 months, the rate of persistent CMR was 41% (95% CI 29–52). Surprisingly, all patients who relapsed responded to reintroduction of imatinib. Sixteen of the 42 patients who relapsed showed a decrease in their *BCR-ABL* levels, and 26 achieved CMR that was sustained after imatinib rechallenge. With a long-term follow-up with a median of more than 6 years after treatment discontinuation, the STIM1 study demonstrates that imatinib can be safely discontinued in patients with a sustained deep molecular response with no late MR (Etienne et al., 2017). This concept was supported by another study. In contrast, several CML patients relapsed after discontinuation of imatinib, this suggests the persistence of LSCs with *BCR-ABL1*. CML-CP LSCs are believed to be quiescent and refractory to apoptosis, because several activated signals, including the Janus kinase (JAK) signal transducer and the activator of transcription (STAT) pathway protect CML LSCs (Holyoake and Vetrie, 2017). Furthermore, several cytokines in the bone marrow microenvironment, and direct interaction with this niche, protect the CML LSCs. Therefore, novel combinations of drugs to kill these LSCs, such as TKI plus JAK inhibitors, may be needed in the future (Gleixner et al., 2017; Yagi et al., 2018). The eradication of LSCs is challenging in most CML

Table 1
European Leukemia Net definition of the response to TKIs, first-line.

Time	Optimal	Warning	Failure
Baseline	NA	High risk or CCA/Ph+, major route	NA
3 months	BCR/ABL1 ≤ 10% or Ph + ≤35%	BCR-ABL1 > 10% or Ph + 36–95%	Non CHR or Ph+ > 95%
6 months	BCR-ABL1 ≤ 1% or Ph + 0 (CCyR)	BCR-ABL1 1–10% or Ph + 1–35% (PCyR)	BCR-ABL1 > 10% or Ph+ > 35%
12 months	BCR-ABL 1 ≤ 0.1% (MMR)	BCR-ABL1 0.1–1%	BCR-ABL1 > 1% or Ph + ≥1%

NA: not applicable, Reference; Baccarani, M. et al. (2013, 2015).

patients, even with few *BCR–ABL* copy numbers.

However, the long-term efficacy and well-established safety profile of dasatinib in imatinib-resistant or -intolerant CML-CP patients has already been reported (Shah et al., 2016). The DASISION trial further demonstrated that dasatinib 100 mg once daily was a safe and effective first-line for CML-CP (Cortes et al., 2016).

3. Acute lymphoblastic leukemia and molecular targeting therapy

Acute lymphoblastic leukemia (ALL) is a frequent hematological malignancy in the pediatric population compared with adults. Since the 1960s, overall survival (OS) rates for children with ALL have risen from 10% to nearly 90% (Margolin, 2011; Pui et al., 2015). This marked improvement in clinical outcome was due to the combination of multi-agent chemotherapeutic drugs as induction chemotherapy, which included steroid (prednisolone or dexamethasone), vincristine, L-asparagine and anthracycline, followed by risk stratified consolidation chemotherapy (Pui and Evans, 2006). Although relapse still occurs in 15%–20% of patients, if patients relapse, allo-HSCT is needed and recommended. However, all patients are not rescued by allo-HSCT. For example, ALL patients who were hypodiploid by karyotype analysis, especially with a chromosome number less than 43, have a poor prognosis. Therefore, allo-HSCT at the 1st CR is recommended for these patients (Nachman et al., 2007). Recently, allo-HSCT was also recommended according to the presence of minimal residual disease (MRD) after induction chemotherapy (Inbar et al., 2017). It is true that clinical outcome such as good prognosis or bad prognosis would be changed according to the treatment protocol, however, MRD is the strongest independent prognostic factor in both children and adults with ALL (Béné and Eveillard, 2018; Brüggemann and Kotrova, 2017). A recent advance in targeted therapy in ALL was in Philadelphia chromosome-positive ALL (Ph-ALL), in which the *BCR-ABL1* chimera was found in 20%–30% of adults ALL and 3%–4% of children with ALL. The OS using only conventional chemotherapeutic drugs with allo-HSCT was 30%, however, the Children's Oncology Group (COG) AALL0031 study revealed that imatinib add-on chemotherapy with allo-HSCT reached an OS of 80% (Schultz et al., 2009). The long-term outcome of chemotherapy with TKI was similar to the result of related or unrelated HSCT (Schultz et al., 2014). Furthermore, the COG AALL0622 study demonstrated that the clinical outcome of chemotherapy combined with dasatinib was similar to that of chemotherapy combined with imatinib, even in adolescents and young adults (Slayton et al., 2018). In contrast, chemotherapy combined with imatinib showed a high complete remission (CR) rate and improvement of OS in the Japan Adult Leukemia Study Group (JALSG) 208 study and another adult leukemia study (Fujisawa et al., 2017; Fielding et al., 2014).

However, some Ph-ALL patients are resistant or refractory to imatinib, in such cases, dasatinib or nilotinib is recommended. A recent COG study revealed that dasatinib used in pediatric Ph-ALL showed better outcomes (Hunger, 2011). Our previous study revealed that *ABL* kinase mutation in diagnostic samples is rarely detected, although a *ABL* kinase mutated clone was found in a relapsed sample after TKI treatment (Aoe et al., 2018). However, the NGS-analysis revealed that *IKZF1* deletions were simultaneously found in the majority of first diagnostic samples with other coding mutations, indel, and copy number variations. Ph-ALL patients can be divided into subgroups according to their risk classification, such as *IKZF1* deletion and whether allo-HSCT is evadable or not, which is a matter of concern for many pediatric study groups. Furthermore, it should be noted that the combination of conventional chemotherapeutic drugs with TKI results in deep bone marrow repression, therefore the recovery of hematopoiesis is delayed. Thus, these patients require intensive supportive care (Fujisawa et al., 2017).

Similarly, Ph-like ALL, also referred to as *BCR-ABL1*-like ALL, is a high-risk subset with a gene expression profile that shares significant overlap with that of Ph-ALL, which is suggestive of activated kinase signaling (Roberts et al., 2014; Tasian et al., 2017; Reshmi et al., 2017). These alterations can be grouped into major subclasses that include *ABL*-class fusions involving *ABL1*, *CSF1R*, and *PDGFRβ* with alterations of *CRLF2*, *JAK2*, and *EPOR* that finally activate JAK/STAT signaling. Therefore, a current COG study separates these patients and treats each with a specific kinase inhibitor add-on chemotherapy (Fig. 2) (Tasian et al., 2017). Diagnostic leukemia cells from children with high risk B-ALL are first screened for the Ph-like ALL gene expression signature using an 8-gene low density microarray that includes *CRLF2* as one of the 8 assessed genes. Specimens with the Ph-like ALL signature that lack *BCR-ABL1* fusion undergo additional genetic testing. Those with high *CRLF2* expression are assessed for *P2RY8-CRLF2* and *IGH-CRLF2* rearrangements by RT-PCR and FISH, respectively, and for *JAK1*, *JAK2* and *IL7R* mutations by PCR. If these mutations are found, patients are treated with ruxoltinib combined with chemotherapy (A). Ph-like ALL specimens without *CRLF2* overexpression undergo multiplex RT-PCR

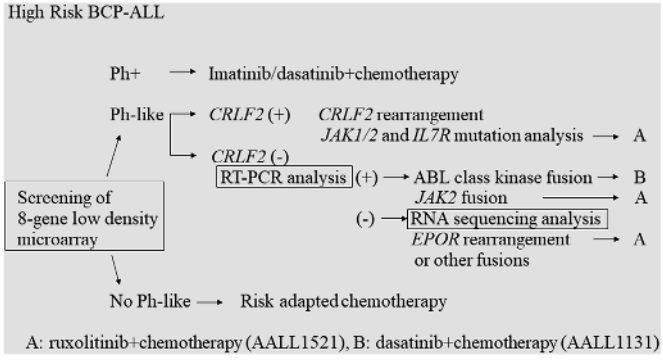

Fig. 2. Current Ph-like ALL genetic testing algorithm used by the Children's Oncology Group. Diagnostic leukemia cells from children with high risk BCP-ALL are first screened for the Ph-like ALL gene expression signature using an 8-gene low density microarray that includes CRLF2 as one of the 8 assessed genes. Specimens with the Ph-like ALL signature that lack BCR-ABL1 fusion (Ph + ALL) undergo additional genetic testing. Those with high CRLF2 expression are assessed for *P2RY8–CRLF2* and *IGH–CRLF2* rearrangements using RT-PCR and FISH, respectively; and for *JAK1*, *JAK2* and *IL7R* mutations using PCR. Ph-like ALL specimens without CRLF2 overexpression undergo multiplex RT-PCR fusion testing to detect *ABL*-class, *JAK2*, and *EPOR* rearrangements. Not all Ph-like fusions will be detected by this algorithm. Complete assessment may require alternative assays for identification, such as RNA-sequencing or unbiased fusion testing capable of identifying new 5′ partners (modified Figure in Tasian, SK., et al. Blood, 2017, 130, 2064–2072).

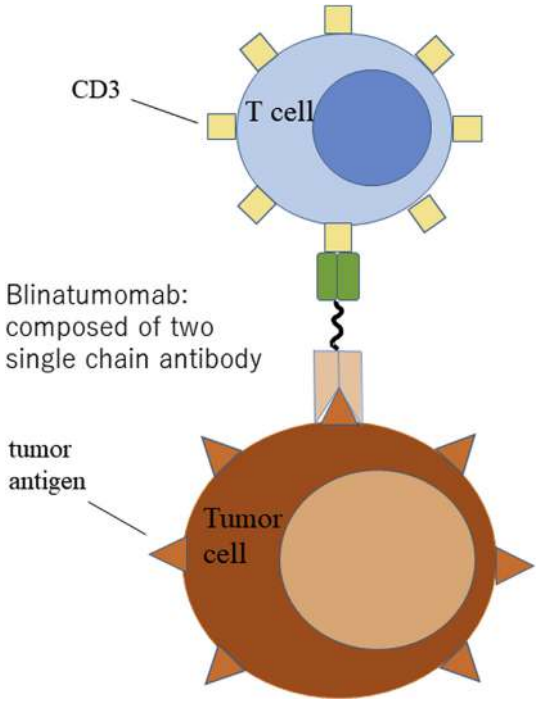

Fig. 3. Construction of a bispecific T-cell engagers (BiTE) is shown. The single chain fragment variables (Fab-binding domains) of the two desired antibodies are joined via amino acid linkage. The BiTE binds CD3, a T-cell coreceptor, and the tumor-associated antigen, CD19. The linkage forces the formation of an immunological synapse by drawing the two together, causing recognition of the TAA and activation of the T-cell, which trigger cytotoxic granules and cytokines, and T cell proliferation. (Modified Figure in Baeuerle, P. A., and Reinhardt, C. (2009) Cancer Res. 69, 4941-4.).

fusion testing to detect *ABL*-class, *JAK2*, and *EPOR* rearrangements. If *ABL*-class kinase fusion genes are found, patients are treated with dasatinib combined with chemotherapy (B).

Another type of molecular targeting agent is blinatumomab, the first FDA-approved bi-specific antibody used in targeted immunotherapy for the treatment of B-cell malignancies. Its novel mechanism of action involves *in vivo* engagement of the patient's CD3-expressing T cells and CD19-expressing tumor cells in BCP-ALL (Fig. 3) (Topp et al., 2011, Kantarjian et al., 2017). Treatment with blinatumomab results in significantly longer OS than chemotherapy among adult patients with relapsed or refractory BCP ALL. Furthermore, in not relapsed/refractory BCP-ALL, on March 29, 2018 the US FDA granted accelerated approval for blinatumomab for the treatment of adults and children with BCP-ALL in first or second CR with MRD greater than or equal to 0.1% (Jen et al., 2019; Gökbuget et al., 2018). Despite intensive induction/consolidation chemotherapy with CR rates of 80%–90%, approximately 30%–50% of adult ALL and 10%–20% of pediatric ALL patients with CR exhibit MRD (Bassan et al., 2009; van Dongen et al., 1998). MRD persistence or recurrence indicates resistance to standard chemotherapy and is the strongest risk factor for hematological relapse in BCP-ALL (Borowitz et al., 2008; Berry et al., 2017). However, cytokine release syndrome and neurotoxicity remain significant risks to the use blinatumomab. Therefore, the US FDA requires confirmation of clinical benefit in a randomized trial. Among adults with MRD-positive ALL in hematological remission after chemotherapy, 78% achieved a complete MRD response with blinatumomab which was associated with significantly improved OS.

Another promising target in B-ALL is CD22. Inotuzumab ozogamicin (INO) is an ADC that consists of a humanized anti-CD22 monoclonal antibody linked to a cytotoxic agent, calicheamicin, which can cause double-strand DNA breaks and lead to apoptosis (Kantarjian et al., 2012). A phase-3 trial randomly assigned adults with relapsed or refractory ALL to receive either INO or standard therapy. The rate of complete remission was higher in the INO group than in the standard-therapy group, and a higher percentage of patients in the INO group had results below the threshold for MRD. Both progression-free and overall survival were longer with INO group. However, veno-occlusive liver disease occurred more commonly in the INO group than in the standard-therapy group (Kantarjian et al., 2016). Another rising cell therapy is CAR-T, chimeric antigen receptor (CAR) modified T cells targeting CD19 (Maude et al., 2014; Lee et al., 2015; Frey and Porter, 2016). It has shown effectiveness in a case series of patients with BCP-ALL and B-cell lymphomas (Schuster et al., 2017). Unexpectedly, remission rates of 67%–90% were observed in adult and pediatric patients with relapsed and refractory BCP-ALL. Remissions have been sustained in many patients without further treatment, a phenomenon that often correlates with CAR T-cell persistence (Maude et al., 2014; Lee et al., 2015). Specifically, remission was sustained from 2 to > 24 months in 19 patients from the initial cohort, including 15 patients who received no further treatment. The durable remissions observed in patients not bridged to allo-SCT correlated with CAR T-cell persistence and the biological correlates of ongoing CAR T-cell activity and consequent B-cell aplasia. Major treatment-related toxicities include B-cell aplasia, neurologic toxicities, and potentially severe cytokine release syndrome (Maude et al., 2014; Frey and Porter, 2016). Cytokine release syndrome is a systemic inflammatory response which correlates with *in vivo* activation and proliferation of CAR T-cells. Its clinical features are associated with high levels of inflammatory markers and cytokines, including C-reactive protein, ferritin, interferon-ϒ, and interleukin-6. Many patients show high fever and require intensive care (Lee et al., 2015).

Apart from BCP-ALL, remarkable progress has been made in elucidating the genomic landscape of T-ALL over the past few years, including the discovery of activating mutations in *NOTCH1* and *FBXW7* in the majority of T-ALL patients (Litzow and Ferrando, 2015). The use of pediatric intensive combination chemotherapy regimens in adolescents and young adults has significantly improved the outcome of patients with T-ALL (Marks and Rowntree, 2017). For relapsed and refractory T-ALL, based on observations in patients with purine nucleoside phosphorylase deficiency, a guanosine nucleoside analogue, arabinosylguanine (ara-G) was developed that provided T-cell specificity. Nelarabine was developed as the water-soluble, clinically useful-prodrug of ara-G and based on its activity was approved for the treatment of relapsed or refractory T-ALL. The use of nelarabine for relapsed and refractory T-ALL results in partial effectiveness, with neurotoxicity responses in a minority of patients (Kadia and Gandhi, 2017).

4. Acute myeloid leukemia and molecular targeting therapy

AML is dominant in adults and the frontline therapeutic strategy for AML has not substantially changed in 40 years. An initial intensive induction with 7-days of cytarabine plus 3 days of an anthracycline treatment (7 + 3 regimen) is commonly used to produce CR and represents the backbone of AML treatment (Döhner et al., 2017; De Kouchkovsky and Abdul-Hay, 2016). The CR rate is 60%–80% in younger adults and 40%–60% in AML patients older than 65 years. A 5-year relapse free survival (RFS) of approximately 40% was obtained using the following consolidation chemotherapy of anthracycline (idarubicin or daunorubicin), and cytarabine with or without allo-HSCT according to the risk classification. AML prognosis is clearly different in each subgroup of age, performance status, chromosomal abnormalities, and genetic abnormalities. Recent advances in the understanding of genetic abnormalities in AML were significant and correlated well with the cytogenetic abnormalities and prognosis (Table 2). The representative genetic abnormalities are in fms-related tyrosine 3 kinase (*FLT3*), nucleophosmin 1 (*NPM1*), CCAAT/enhancer-binding protein alpha (*CEBPA*), runt-related transcription factor 1 (*RUNX1*), and *TP53*

Table 2
Prognostic-risk group according to the cytogenetic profile and molecular abnormalities.

Prognostic-risk group	Cytogenetic profile alone	Cytogenetic profile and molecular abnormalities
Favorable	t(8:21)(q22; q22) inv(16)(p13; 1q22) t(15; 17)(q22; q12)	t(8:21)(q22; q22) with no c-KIT mutation inv(16)(p13; 1q22) t(15; 17)(q22; q12) Mutated NPM1 without FLT3-ITD (CN-AML) Mutated biallelic CEBPA (CN-AML)
Intermediate	CN-AML t(9; 11)(p22; q23) Cytogenetic abnormalities not included in the favorable or adverse prognostic risk groups	t(8:21)(q22; q22) with mutated c-KIT CN-AML other than those included in the favorable or adverse prognostic group t(9; 11)(p22; q23) Cytogenetic abnormalities not included in the favorable or adverse prognostic risk groups
Adverse	inv(3)(q21q26.2) t(6; 9)(p23; q34) 11q abnormalities other than t(9; 11) −5 or del(5q) −7 Complex karyotype	TP53 mutation, regardless of cytogenetic profile CN with FLT3-ITD CN with DNMT3A CN with KMT2A-PTD inv(3)(q21q26.2) t(6; 9)(p23; q34) 11q abnormalities other than t(9; 11) −5 or del(5q) −7 Complex karyotype

Abbreviations: AML, acute myeloid leukemia; ITD, internal tandem duplications. CN, cytogenetically normal, Reference; De Kouchkovsky, I. et al. (2016).

(Moarii and Papaemmanuil, 2017). In pediatric AML, the treatment is similar to than in adults, however, it has an 80%–90% induction rate and 60%–70% RFS (Tsukimoto et al., 2009; Creutzig et al., 2012). AML is believed to be a relatively difficult disease to treat because of its high level of heterogeneity and the presence of LSCs. Improved genetic analyses found several subclones in the first diagnostic samples from individual AML patients. After relapse, a few subclones expanded under therapy pressure, which is called “clonal evolution” or “clonal selection.” Bachas C. et al. showed that immunophenotypically defined cell subpopulations that were prominent at relapse could be traced back as very minor immature (CD34 + /CD38 − /dim) subpopulations of cells at diagnosis, which indicates LSCs (Bachas et al., 2012). Therefore, intratumor heterogeneity caused by clonal evolution is a major problem in cancer treatment; and the most effective LSCs-directed therapy will probably differ between individual patients.

Although, standard chemotherapy with allo-HSCT is performed, high relapse rates are still observed in both adult and pediatric studies (Tsirigotis et al., 2016). Thus, the final clinical outcome in AML has not vastly improved for over a decade. Notably, *FLT3* and v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (*KIT*) are the major membrane tyrosine kinases which affect hematopoietic cell proliferation due to stimulation by FLT3 ligand or stem cell factor. Internal tandem duplication (ITD) of *FLT3* is found in approximately 30% of adults and 15% of children with AML. The intracellular FLT3 signal transduction pathways including the Phosphoinositide 3-kinase (PI3K)-AKT, mitogen-activated protein kinase kinase (MEK)-mitogen-activated protein kinase (MAPK), JAK-STAT pathways are autonomously activated, and AML blasts having *FLT3*-ITD can proliferate without stimulation by FLT3 ligand (Fig. 4) (Small, 2006). Clinically, AML patients with *FLT3*-ITD demonstrate marked leukocytosis and a higher blast percentage, therefore, *FLT3*-ITD is a strong poor prognostic factor in AML. Furthermore, although OS is 20%–30% in adults and 40% in children, recent findings revealed that the prognosis is changed according to accompanying mutations, such as those in the *NPM1* gene (Gale et al., 2008; Döhner et al., 2017; Shimada et al., 2018). High allelic ratio of *FLT3*-ITD vs *FLT3*-wild type display a poor prognosis (Whitman et al., 2001). First-generation FLT3 inhibitors are relatively nonspecific for FLT3 and usually inhibit other receptor tyrosine kinase such as KIT and platelet derived growth factor receptor (PDGFR)

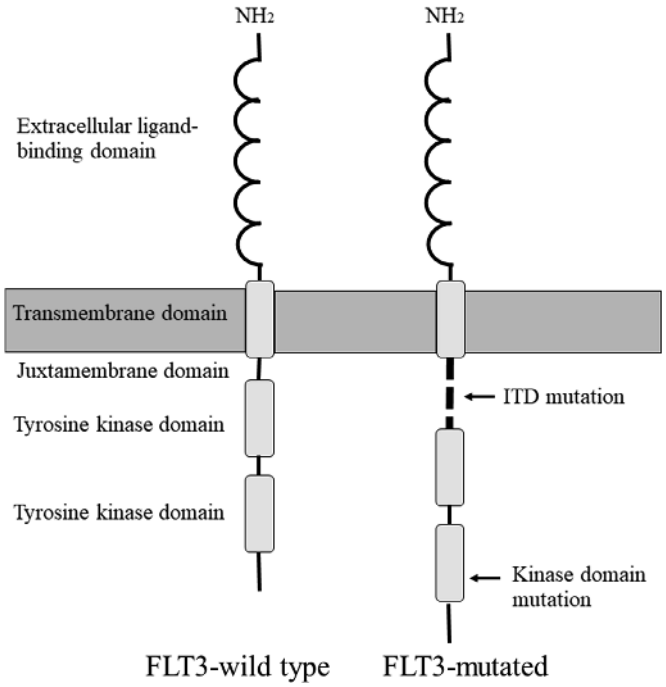

Fig. 4. Cartoon of FMS-related tyrosine kinase (FLT3)—wild type and mutated structures. Shown in schematic fashion are the 5 immunoglobulin-like folds that make up the ligand-binding extracellular domain, single transmembrane domain, and cytoplasmic domain made up of a kinase domain interrupted by a kinase insert. Internal tandem duplication (ITD) (3-400bps) is found mainly in the juxtamembrane domain. FLT3-ITD is constitutively activated without the stimuli of FLT3 ligand. It causes the uncontrolled proliferation of AML blasts. Kinase domain mutation is also found.

(Lancet, 2015). Off-target inhibition may therefore be associated with increased toxicity and only modest clinical benefit. First-generation FLT3 inhibitors include tandutinib, sunitinib, sorafenib, midostaurin, and lestaurtinib. Several first-generation FLT3-inhibitors have been investigated in clinical trials in AML. For example, sorafenib is a Raf kinase inhibitor which also inhibits several cell surface membrane

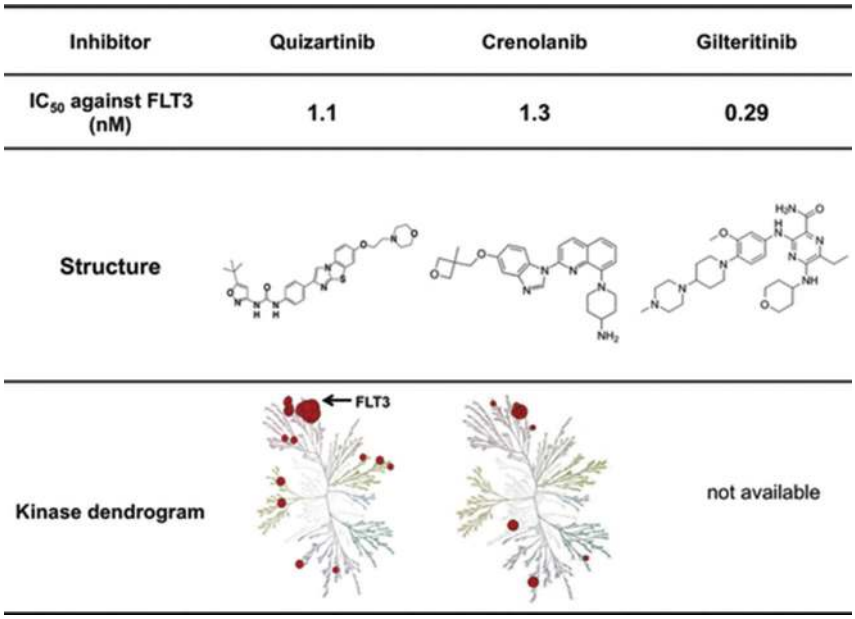

Fig. 5. Second-generation FLT3 inhibitors: quizartinib, crenolanib, and gilteritinib. IC_{50}, structures, and kinase dendrograms (Figs in https://oncohemakey.com/flt3-inhibitors/).

kinases, including vascular endothelial growth factor receptor (VEGFR)-1/2/3, KIT, PDGFR-β, and FLT3. The addition of sorafenib versus placebo to standard therapy in patients aged 60 years or younger with newly diagnosed AML (SORAML study) revealed improved 3-year EFS in the sorafenib group vs placebo (40% and 22%, respectively; $P = 0.013$); however, there was no difference in OS (Röllig et al., 2015). However, sorafenib add-on treatment also demonstrated an increase in toxicity, especially diarrhea and skin rash.

In contrast, midostaurin add-on chemotherapy showed an improvement in clinical outcome. The RATIFY study (CALGB 10603), a Phase III, randomized, controlled trial, has shown that midostaurin, added to intensive induction and consolidation therapy followed by 1-year maintenance, leads to a significant improvement in OS (median OS 74.7 vs 25.6 months, $P = 0.009$) and EFS, although CR rates were not different between the midostaurin and placebo arms. The US FDA approved this drug for use in AML in 2017 (Stone et al., 2017).

Another recent advance was the development of second generation TKIs, such as quizartinib, crenolanib, and gilteritinib, which have high selectivity for FLT3 and are now in clinical trials (Fig. 5). Specifically, quizartinib is a selective inhibitor of *FLT3*-ITD but is not active against the kinase domain mutation variants such as D835. Several patients who showed relapse after CR from quizartinib acquired kinase domain mutations, which could be heterogenous even within a single patient (Smith et al., 2017).

Midostaurin has been studied for a different use, for combination with hypomethylating agents such as azacitidine and decitabine, and as a single-agent maintenance therapy. MRD of *FLT3*-ITD-positive AML before or after HSCT will be an indicator of relapse, therefore, FLT3-inhibitors will be recommended for use in AML patients with *FLT3*-ITD after allo-HSCT (Stone et al., 2017; Stansfield and Pollyea, 2017).

Similar to *FLT3*-ITD, AML patients with *c-KIT* mutations show poor prognosis, especially those with core binding factor-leukemia including t(8; 21) or inv(16) (Shimada et al., 2006). Therefore, it is also recommended to develop KIT-specific inhibitors, although dasatinib is currently under investigation (Kampa-Schittenhelm et al., 2018).

Another molecular targeting agent for AML is gemtuzumab ozogamicin (GO), which is a recombinant, humanized anti-CD33 monoclonal antibody covalently attached to the cytotoxic antitumor antibiotic calicheamicin via a bifunctional linker (Godwin et al., 2017). Past studies showed a high frequency of deep myelosuppression and sinusoidal obstruction syndrome (SOS), formerly known as hepatic VOD, which is a serious and life-threatening complication of HSCT. A new clinical trial with a reduced dose of GO has been started and showed both a clinical response and the reduction of SOS/VOD (Appelbaum and Bernstein, 2017).

Other new candidate agents for AML include CPX-351, IDH1/2 inhibitors, and a BCL-2 antagonist. CPX-351 is a new liposomal formulation that encapsulates cytarabine and daunorubicin in a fixed 5:1 M ratio, and showed superior antileukemic activity compared to free-drug cocktails *in vivo* (Tardi et al., 2009). Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) are metabolic enzymes located in the cytoplasm, peroxysomes, and mitochondria, respectively, and they catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate. *IDH1* and *IDH2* mutations were found in approximately 20% of all adult AML cases, affecting 7%–14% and 8%–19% of patients, respectively, but are rarely reported in children (Montalban-Bravo and DiNardo, 2018). The specific inhibitor of IDH1 ivosidenib (AG-120) and the selective inhibitor of IDH2 enasidenib (AG-221) have presented an acceptable tolerability profile and are now under investigation.

Venetoclax (ABT-199) is a mimetic of the B-cell lymphoma-2 (BCL-2) homology 3 domain-only proteins that specifically antagonizes BCL-2 activity; therefore it blocks the anti-apoptotic Bcl-2 protein, leading to programmed cell death. In 2016, the US FDA approved venetoclax for use in patients with CLL who have the 17p deletion. *In vitro* and *ex vivo* preclinical studies demonstrated that AML cells are very sensitive to treatment with this agent (Pan et al., 2014).

Apart from the genetic alterations, epigenetic modification such as DNA methylation and histone modification, alters DNA accessibility and chromatin structure, thereby regulating gene expression patterns. Therefore, it will be an interesting and important target for AML treatment, as secondary AML develops from myelodysplastic syndrome (MDS). High risk groups of patients with MDS who are not applicable for allo-HSCT are recommended azacitidine, a hypomethylating agent, as a first line therapy (Fenaux et al., 2010; Odenike, 2017). Furthermore, azacitidine is used for bridge therapy for HSCT (Voso et al., 2017). Recently, azacitidine was used for advanced MDS in children or before allo-HSCT (Cseh et al., 2016; Waespe et al., 2016). Especially, in older patients (> 65 years old) who were not applicable for induction chemotherapy, azacitidine increased median OS by 3.8 months vs current commonly used AML treatments, and its safety profile was

consistent with those of other trials (Fenaux et al., 2010).

BET protein also seems to be a candidate for a novel epigenetic approach (Fu et al., 2015). BET proteins have multiple functions, including the initiation and elongation of transcription, and cell-cycle regulation. Recently, BET protein inhibitors have been developed as anticancer agents, but they appear to have limited efficacy as single agents. Pericole et al. reported that BRD4 inhibition enhances azacitidine efficacy in AML and MDS (Pericole et al., 2019).

5. Myeloproliferative neoplasm and molecular targeting therapy

Myeloproliferative neoplasms (MPNs) are hematopoietic stem cell diseases, the classical *BCR-ABL1*-negative MPNs include essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF), which are all characterized by expansion of one or more myeloid lineages with cellular differentiation (Patel et al., 2016). MPN patients are at 5- to 7-fold higher risk for thrombosis compared with the general population. These clonal disorders share certain clinical and genetic features, and sometimes evolve into acute leukemia. Somatic mutation of *JAK2* V617F was first found in these diseases in 2005, which revolutionized MPN diagnosis. The *JAK2* V617F mutation is found in 95% of PV, 55% of ET, and 65% of MF (Geyer and Mesa, 2014). Other mutations were also found in the *CALR* and *MPL* genes in the adult population (Jeromin et al., 2016). However, the number of pediatric MPN patients is very limited, and the *JAK2* V617F was only found in 30% of ET patients and no other gene mutations were found in our previous study (Sekiya et al., 2016). MPN patients were treated with low-dose aspirin, phlebotomy, and cytoreductive medicines such as hydroxyuria, and the only curative treatment is allo-HSCT. If MPN patients have *JAK2* mutations, they can be treated with JAK inhibitors. Several reports suggest that the JAK1/2 inhibitor ruxolitinib prolongs the OS of adult PV, ET, and MF patients (Geyer and Mesa, 2014; Griesshammer and Sadjadian, 2017). Ruxolitinib is approved for MF based on the two COMFORT studies, which successfully demonstrated its effects on splenomegaly, symptom improvement, and survival (Harrison et al., 2012). In a 3.5-year follow-up analysis of the COMFORT-II data, ruxolitinib was associated with a 42% reduction in risk of death compared with best-available therapy (BAT). At 3.5 years, the probability of survival was 54% and 71% in the BAT and ruxolitinib arms, respectively (Harrison et al., 2016). Unfortunately, the information in pediatric MPN remains very limited.

Other types of MDS/MPN included chronic myelomonocytic leukemia (CMML) in adults and juvenile myelomonocytic leukemia (JMML) in children. Many molecular findings have been observed in CMML, but there remains a lack of molecular targeting agents (Solary and Itzykson, 2017). In contrast, JMML is a difficult disease to treat, being mainly diagnosed under 5 years old (mainly infant), and having leukocytosis and hepatosplenomegaly (Hasle, 2016; Locatelli and Niemeyer, 2015). Notably, a high relapse rate is observed even after allo-HSCT. The molecular mechanism in this disease is mutation of the RAS pathway including *N-/K-RAS*, *PTPN11*, and *CBL*. Some mutations are somatic but some are germline. MEK inhibitors were hypothesized to be candidates to repress the proliferation of JMML cells, which will hopefully be evident in current clinical trials (Tasian et al., 2019).

6. Conclusion

Several molecular targeting therapies have been developed and achieved great success in hematological malignancies. Their improvement is ongoing as knowledge of dysregulation of signal transduction in tumor cells by NGS technology accumulates. However, whether molecular targeting therapy alone could cure hematological diseases is unclear. Therefore, precise use of these agents combined with conventional chemotherapy or HSCT should be analyzed in future studies.

Conflicts of interest

The author declares no conflict of interest.

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References

Aoe, M., Ishida, H., Matsubara, T., Karakawa, S., Kawaguchi, H., Fujiwara, K., Kanamitsu, K., Washio, K., Okada, K., Shibakura, M., Shimada, A., 2018. Simultaneous detection of ABL1 mutation and IKZF1 deletion in Philadelphia chromosome-positive acute lymphoblastic leukemia using a customized target enrichment system panel. Int J Lab Hematol 40, 427–436. https://doi.org/10.1111/ijlh.12805.

Appelbaum, F.R., Bernstein, I.D., 2017. Gemtuzumab ozogamicin for acute myeloid leukemia. Blood 130, 2373–2376. https://doi.org/10.1182/blood-2017-09-797712.

Baccarani, M., Castagnetti, F., Gugliotta, G., Rosti, G., 2015. A review of the European LeukemiaNet recommendations for the management of CML. Ann. Hematol. 94 (Suppl. 2), S141–S147. https://doi.org/10.1007/s00277-015-2322-2.

Baccarani, M., Deininger, M.W., Rosti, G., Hochhaus, A., Soverini, S., Apperley, J.F., Cervantes, F., Clark, R.E., Cortes, J.E., Guilhot, F., Hjorth-Hansen, H., Hughes, T.P., Kantarjian, H.M., Kim, D.W., Larson, R.A., Lipton, J.H., Mahon, F.X., Martinelli, G., Mayer, J., Müller, M.C., Niederwieser, D., Pane, F., Radich, J.P., Rousselot, P., Saglio, G., Saußele, S., Schiffer, C., Silver, R., Simonsson, B., Steegmann, J.L., Goldman, J.M., Hehlmann, R., 2013. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood 122, 872–884. https://doi.org/10.1182/blood-2013-05-501569.

Bachas, C., Schuurhuis, G.J., Assaraf, Y.G., Kwidama, Z.J., Kelder, A., Wouters, F., et al., 2012. The role of minor subpopulations within the leukemic blast compartment of AML patients at initial diagnosis in the development of relapse. Leukemia 26, 1313–1320. https://doi.org/10.1038/leu.2011.383.

Bassan, R., Spinelli, O., Oldani, E., Intermesoli, T., Tosi, M., Peruta, B., et al., 2009. Improved risk classification for risk-specific therapy based on the molecular study of minimal residual disease (MRD) in adult acute lymphoblastic leukemia (ALL). Blood 113, 4153–4162. https://doi.org/10.1182/blood-2008-11-185132.

Béné, M.C., Eveillard, M., 2018. Evaluation of minimal residual disease in childhood ALL. Int J Lab Hematol 40 (Suppl. 1), 104–108. https://doi.org/10.1111/ijlh.12835.

Berry, D.A., Zhou, S., Higley, H., Mukundan, L., Fu, S., Reaman, G.H., Wood, B.L., Kelloff, G.J., Jessup, J.M., Radich, J.P., 2017. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: a meta-analysis. JAMA Oncol 3, e170580. https://doi.org/10.1001/jamaoncol.2017.0580.

Bhatia, R., 2017. Novel approaches to therapy in CML. Hematology Am Soc Hematol Educ Program 1, 115–120. https://doi.org/10.1182/asheducation-2017.1.115.

Borowitz, M.J., Devidas, M., Hunger, S.P., Bowman, W.P., Carroll, A.J., Carroll, W.L., Linda, S., Martin, P.L., Pullen, D.J., Viswanatha, D., Willman, C.L., Winick, N., Camitta, B.M., Children's Oncology Group, 2008. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. Blood 111, 5477–5485. https://doi.org/10.1182/blood-2008-01-132837.

Brüggemann, M., Kotrova, M., 2017. Minimal residual disease in adult ALL: technical aspects and implications for correct clinical interpretation. Blood Adv 1, 2456–2466. https://doi.org/10.1182/bloodadvances.2017009845.

Chaffer, C.L., Weinberg, R.A., 2015. How does multistep tumorigenesis really proceed? Cancer Discov. 5, 22–24. https://doi.org/10.1158/2159-8290.CD-14-0788.

Chapman, A.M., Sun, K.Y., Ruestow, P., Cowan, D.M., Madl, A.K., 2016. Lung cancer mutation profile of EGFR, ALK, and KRAS: meta-analysis and comparison of never and ever smokers. Lung Cancer 102, 122–134. https://doi.org/10.1016/j.lungcan.2016.10.010.

Cortes, J.E., Kim, D.W., Pinilla-Ibarz, J., le Coutre, P.D., Paquette, R., Chuah, C., Nicolini, F.E., Apperley, J.F., Khoury, H.J., Talpaz, M., DeAngelo, D.J., Abruzzese, E., Rea, D., Baccarani, M., Müller, M.C., Gambacorti-Passerini, C., Lustgarten, S., Rivera, V.M., Haluska, F.G., Guilhot, F., Deininger, M.W., Hochhaus, A., Hughes, T.P., Shah, N.P., Kantarjian, H.M., 2018a. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. Blood 132, 393–404. https://doi.org/10.1182/blood-2016-09-739086.

Cortes, J.E., Gambacorti-Passerini, C., Deininger, M.W., Mauro, M.J., Chuah, C., Kim, D.W., Dyagil, I., Glushko, N., Milojkovic, D., le Coutre, P., Garcia-Gutierrez, V., Reilly, L., Jeynes-Ellis, A., Leip, E., Bardy-Bouxin, N., Hochhaus, A., Brümmendorf, T.H., 2018b. Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: results from the randomized BFORE trial. J. Clin. Oncol. 36, 231–237. https://doi.org/10.1200/JCO.2017.74.7162.

Cortes, J.E., Saglio, G., Kantarjian, H.M., Baccarani, M., Mayer, J., Boqué, C., Shah, N.P., Chuah, C., Casanova, L., Bradley-Garelik, B., Manos, G., Hochhaus, A., 2016. Final 5-year study results of DASISION: the dasatinib versus imatinib study in treatment-naïve chronic myeloid leukemia patients trial. J. Clin. Oncol. 34https://doi.org/10.1200/JCO.2015.64.8899. 2333-2240.

Creutzig, U., van den Heuvel-Eibrink, M.M., Gibson, B., Dworzak, M.N., Adachi, S., de Bont, E., Harbott, J., Hasle, H., Johnston, D., Kinoshita, A., Lehrnbecher, T., Leverger,

G., Mejstrikova, E., Meshinchi, S., Pession, A., Raimondi, S.C., Sung, L., Stary, J., Zwaan, C.M., Kaspers, G.J., Reinhardt, D., AML Committee of the International BFM Study Group, 2012. Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendations from an international expert panel. Blood 120, 3187–3205. https://doi.org/10.1182/blood-2012-03-362608. 2012.

Cseh, A.M., Niemeyer, C.M., Yoshimi, A., Catala, A., Frühwald, M.C., Hasle, H., van den Heuvel-Eibrink, M.M., Lauten, M., De Moerloose, B., Smith, O.P., Bernig, T., Gruhn, B., Kulozik, A.E., Metzler, M., Olcay, L., Suttorp, M., Furlan, I., Strahm, B., Flotho, C., 2016. Therapy with low-dose azacitidine for MDS in children and young adults: a retrospective analysis of the EWOG-MDS study group. Br. J. Haematol. 172, 930–936. https://doi.org/10.1111/bjh.13915.

De Kouchkovsky, I., Abdul-Hay, M., 2016. 'Acute myeloid leukemia: a comprehensive review and 2016 update. Blood Canc. J. 6, e441. https://doi.org/10.1038/bcj.2016.50.

Döhner, H., Estey, E., Grimwade, D., Amadori, S., Appelbaum, F.R., Büchner, T., Dombret, H., Ebert, B.L., Fenaux, P., Larson, R.A., Levine, R.L., Lo-Coco, F., Naoe, T., Niederwieser, D., Ossenkoppele, G.J., Sanz, M., Sierra, J., Tallman, M.S., Tien, H.F., Wei, A.H., Löwenberg, B., Bloomfield, C.D., 2017. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 129, 424–447. https://doi.org/10.1182/blood-2016-08-733196.

Druker, B.J., Guilhot, F., O'Brien, S.G., Gathmann, I., Kantarjian, H., Gattermann, N., Deininger, M.W., Silver, R.T., Goldman, J.M., Stone, R.M., Cervantes, F., Hochhaus, A., Powell, B.L., Gabrilove, J.L., Rousselot, P., Reiffers, J., Cornelissen, J.J., Hughes, T., Agis, H., Fischer, T., Verhoef, G., Shepherd, J., Saglio, G., Gratwohl, A., Nielsen, J.L., Radich, J.P., Simonsson, B., Taylor, K., Baccarani, M., So, C., Letvak, L., Larson, R.A., IRIS Investigators, 2006. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N. Engl. J. Med. 355, 2408–2417.

Etienne, G., Guilhot, J., Rea, D., Rigal-Huguet, F., Nicolini, F., Charbonnier, A., Guerci-Bresler, A., Legros, L., Varet, B., Gardembas, M., Dubruille, V., Tulliez, M., Noel, M.P., Ianotto, J.C., Villemagne, B., Carré, M., Guilhot, F., Rousselot, P., Mahon, F.X., 2017. Long-term follow-up of the French stop imatinib (STIM1) study in patients with chronic myeloid leukemia. J. Clin. Oncol. 35, 298–305.

Fenaux, P., Mufti, G.J., Hellström-Lindberg, E., Santini, V., Gattermann, N., Germing, U., Sanz, G., List, A.F., Gore, S., Seymour, J.F., Dombret, H., Backstrom, J., Zimmerman, L., McKenzie, D., Beach, C.L., Silverman, L.R., 2010. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J. Clin. Oncol. 28, 562–569. https://doi.org/10.1200/JCO.2009.23.8329.

Fielding, A.K., Rowe, J.M., Buck, G., Foroni, L., Gerrard, G., Litzow, M.R., Lazarus, H., Luger, S.M., Marks, D.I., McMillan, A.K., Moorman, A.V., Patel, B., Paietta, E., Tallman, M.S., Goldstone, A.H., 2014. UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. Blood 123, 843–850. https://doi.org/10.1182/blood-2013-09-529008.

Frey, N.V., Porter, D.L., 2016. CAR T-cells merge into the fast lane of cancer care. Am. J. Hematol. 91, 146–150. https://doi.org/10.1002/ajh.24238.

Fu, L.L., Tian, M., Li, X., Li, J.J., Huang, J., Ouyang, L., Zhang, Y., Liu, B., 2015. Inhibition of BET bromodomains as a therapeutic strategy for cancer drug discovery. Oncotarget 6, 5501–5516.

Fujisawa, S., Mizuta, S., Akiyama, H., Ueda, Y., Aoyama, Y., Hatta, Y., Kakihana, K., Dobashi, N., Sugiura, I., Onishi, Y., Maeda, T., Imai, K., Ohtake, S., Miyazaki, Y., Ohnishi, K., Matsuo, K., Naoe, T., 2017. Phase II study of imatinib-based chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia. Am. J. Hematol. 92, 367–374. https://doi.org/10.1002/ajh.24653.

Gale, R.E., Green, C., Allen, C., Mead, A.J., Burnett, A.K., Hills, R.K., Linch, D.C., Medical Research Council Adult Leukaemia Working Party, 2008. The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. Blood 111, 2776–2784.

Geyer, H.L., Mesa, R.A., 2014. Therapy for myeloproliferative neoplasms: when, which agent, and how? Hematology Am Soc Hematol Educ Program 2014, 277–286. https://doi.org/10.1182/asheducation-2014.1.277.

Gleixner, K.V., Schneeweiss, M., Eisenwort, G., Berger, D., Herrmann, H., Blatt, K., Greiner, G., Byrgazov, K., Hoermann, G., Konopleva, M., Waliul, I., Cumaraswamy, A.A., Gunning, P.T., Maeda, H., Moriggl, R., Deininger, M., Lion, T., Andreeff, M., Valent, P., 2017. Combined targeting of STAT3 and STAT5: a novel approach to overcome drug resistance in chronic myeloid leukemia. Haematologica 102, 1519–1529. https://doi.org/10.3324/haematol.2016.163436.

Godwin, C.D., Gale, R.P., Walter, R.B., 2017. Gemtuzumab ozogamicin in acute myeloid leukemia. Leukemia 31, 1855–1868. https://doi.org/10.1038/leu.2017.187.

Gökbuget, N., Dombret, H., Bonifacio, M., Reichle, A., Graux, C., Faul, C., Diedrich, H., Topp, M.S., Brüggemann, M., Horst, H.A., Havelange, V., Stieglmaier, J., Wessels, H., Haddad, V., Benjamin, J.E., Zugmaier, G., Nagorsen, D., Bargou, R.C., 2018. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood 131, 1522–1531. https://doi.org/10.1182/blood-2017-08-798322.

Griesshammer, M., Sadjadian, P., 2017. The BCR-ABL1-negative myeloproliferative neoplasms: a review of JAK inhibitors in the therapeutic armamentarium. Expert Opin. Pharmacother. 18, 1929–1938. https://doi.org/10.1080/14656566.2017.1404574.

Harrison, C.N., Vannucchi, A.M., Kiladjian, J.J., Al-Ali, H.K., Gisslinger, H., Knoops, L., Cervantes, F., Jones, M.M., Sun, K., McQuitty, M., Stalbovskaya, V., Gopalakrishna, P., Barbui, T., 2016. Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis. Leukemia 30, 1701–1707. https://doi.org/10.1038/leu.2016.148.

Harrison, C., Kiladjian, J.J., Al-Ali, H.K., Gisslinger, H., Waltzman, R., Stalbovskaya, V., McQuitty, M., Hunter, D.S., Levy, R., Knoops, L., Cervantes, F., Vannucchi, A.M., Barbui, T., Barosi, G., et al., 2012. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N. Engl. J. Med. 366, 787–798. https://doi.org/10.1056/NEJMoa1110556.

Hasle, H., 2016. Myelodysplastic and myeloproliferative disorders of childhood. Hematology Am Soc Hematol Educ Program 2016, 598–604.

Hehlmann, R., 2012. How I treat CML blast crisis. Blood 120, 737–747. https://doi.org/10.1182/blood-2012-03-380147.

Holyoake, T.L., Vetrie, D., 2017. The chronic myeloid leukemia stem cell: stemming the tide of persistence. Blood 129, 1595–1606. https://doi.org/10.1182/blood-2016-09-696013.

Hunger, S.P., 2011. Tyrosine kinase inhibitor use in pediatric Philadelphia chromosome-positive acute lymphoblastic anemia. Hematology Am Soc Hematol Educ Program 2011, 361–365. https://doi.org/10.1182/asheducation-2011.1.361.

Inbar, T., Rowe, J.M., Horowitz, N.A., 2017. Which patients should I transplant with acute lymphoblastic leukemia? Best Pract. Res. Clin. Haematol. 30, 249–260. https://doi.org/10.1016/j.beha.2017.07.005.

Jen, E.Y., Xu, Q., Schetter, A., Przepiorka, D., Shen, Y.L., Roscoe, D., Sridhara, R., Deisseroth, A., Philip, R., Farrell, A.T., Pazdur, R., 2019. FDA approval: blinatumomab for patients with B-cell precursor acute lymphoblastic leukemia in morphologic remission with minimal residual disease. Clin. Cancer Res. 25, 473–477. https://doi.org/10.1158/1078-0432.CCR-18-2337.

Jeromin, S., Kohlmann, A., Meggendorfer, M., Schindela, S., Perglerová, K., Nadarajah, N., Kern, W., Haferlach, C., Haferlach, T., Schnittger, S., 2016. Next-generation deep-sequencing detects multiple clones of CALR mutations in patients with BCR-ABL1 negative MPN. Leukemia 30, 973–976. https://doi.org/10.1038/leu.2015.207.

Jørgensen, J.T., Hersom, M., 2016. Companion diagnostics-a tool to improve pharmacotherapy. Ann. Transl. Med. 4, 482. https://doi.org/10.21037/atm.2016.12.26.

Kadia, T.M., Gandhi, V., 2017. Nelarabine in the treatment of pediatric and adult patients with T-cell acute lymphoblastic leukemia and lymphoma. Expert Rev. Hematol. 10, 1–8. https://doi.org/10.1080/17474086.2017.1262757.

Kampa-Schittenhelm, K.M., Vogel, W., Bonzheim, I., Fend, F., Horger, M., Kanz, L., et al., 2018. Dasatinib overrides the differentiation blockage in a patient with mutant-KIT D816V positive CBFβ-MYH11 leukemia. Oncotarget 9, 11876–11882. https://doi.org/10.18632/oncotarget.24376.

Kantarjian, H., Shah, N.P., Hochhaus, A., Cortes, J., Shah, S., Ayala, M., Soekler, M., Schittenhelm, M.M., 2010. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N. Engl. J. Med. 362, 2260–2270. https://doi.org/10.1056/NEJMoa1002315. 2010.

Kantarjian, H., Thomas, D., Jorgensen, J., Jabbour, E., Kebriaei, P., Rytting, M., York, S., Ravandi, F., Kwari, M., Faderl, S., Rios, M.B., Cortes, J., Fayad, L., Tarnai, R., Wang, S.A., Champlin, R., Advani, A., O'Brien, S., 2012. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. Lancet Oncol. 13, 403–411. https://doi.org/10.1016/S1470-2045(11)70386-2.

Kantarjian, H.M., DeAngelo, D.J., Stelljes, M., Martinelli, G., Liedtke, M., Stock, W., Gökbuget, N., O'Brien, S., Wang, K., Wang, T., Paccagnella, M.L., Sleight, B., Vandendries, E., Advani, A.S., 2016. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N. Engl. J. Med. 375, 740–753. https://doi.org/10.1056/NEJMoa1509277.

Kantarjian, H., Stein, A., Gökbuget, N., Fielding, A.K., Schuh, A.C., Ribera, J.M., Wei, A., Dombret, H., Foà, R., Bassan, R., Arslan, Ö., Sanz, M.A., Bergeron, J., Demirkan, F., Lech-Maranda, E., Rambaldi, A., Thomas, X., Horst, H.A., Brüggemann, M., Klapper, W., Wood, B.L., Fleishman, A., Nagorsen, D., Holland, C., Zimmerman, Z., Topp, M.S., 2017. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N. Engl. J. Med. 376, 836–847. https://doi.org/10.1056/NEJMoa1609783.

Lancet, J.E., 2015. FLT3 inhibitors for acute myeloid leukemia. Clin. Adv. Hematol. Oncol. 13, 573–575.

Lee, D.W., Kochenderfer, J.N., Stetler-Stevenson, M., Cui, Y.K., Delbrook, C., Feldman, S.A., Fry, T.J., Orentas, R., Sabatino, M., Shah, N.N., Steinberg, S.M., Stroncek, D., Tschernia, N., Yuan, C., Zhang, H., Zhang, L., Rosenberg, S.A., Wayne, A.S., Mackall, C.L., 2015. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet 385, 517–528. https://doi.org/10.1016/S0140-6736(14)61403-3.

Litzow, M.R., Ferrando, A.A., 2015. How I treat T-cell acute lymphoblastic leukemia in adults. Blood 126, 833–841. https://doi.org/10.1182/blood-2014-10-551895.

Locatelli, F., Niemeyer, C.M., 2015. How I treat juvenile myelomonocytic leukemia. Blood 125, 1083–1090. https://doi.org/10.1182/blood-2014-08-550483.

Margolin, J.F., 2011. Molecular diagnosis and risk-adjusted therapy in pediatric hematologic malignancies: a primer for pediatricians. Eur. J. Pediatr. 170, 419–425. https://doi.org/10.1007/s00431-011-1424-7.

Marks, D.I., Rowntree, C., 2017. Management of adults with T-cell lymphoblastic leukemia. Blood 129, 1134–1142. https://doi.org/10.1182/blood-2016-07-692608.

Maude, S.L., Frey, N., Shaw, P.A., Aplenc, R., Barrett, D.M., Bunin, N.J., Chew, A., Gonzalez, V.E., Zheng, Z., Lacey, S.F., Mahnke, Y.D., Melenhorst, J.J., Rheingold, S.R., Shen, A., Teachey, D.T., Levine, B.L., June, C.H., Porter, D.L., Grupp, S.A., 2014. Chimeric antigen receptor T cells for sustained remissions in leukemia. N. Engl. J. Med. 371, 1507–1517. https://doi.org/10.1056/NEJMoa1407222.

Moarii, M., Papaemmanuil, E., 2017. Classification and risk assessment in AML: integrating cytogenetics and molecular profiling. Hematology Am Soc Hematol Educ Program 37–44. https://doi.org/10.1182/asheducation-2017.1.37. 2017.

Montalban-Bravo, G., DiNardo, C.D., 2018. The role of IDH mutations in acute myeloid leukemia. Future Oncol. 14, 979–993. https://doi.org/10.2217/fon-2017-0523.

Nachman, J.B., Heerema, N.A., Sather, H., Camitta, B., Forestier, E., Harrison, C.J., Dastugue, N., Schrappe, M., Pui, C.H., Basso, G., Silverman, L.B., Janka-Schaub, G.E., 2007. Outcome of treatment in children with hypodiploid acute lymphoblastic

leukemia. Blood 110, 1112–1115 2007.
Odenike, O., 2017. Incorporating novel approaches in the management of MDS beyond conventional hypomethylating agents. Hematology Am Soc Hematol Educ Program 460–469. https://doi.org/10.1182/asheducation-2017.1.460. 2017.
Pan, R., Hogdal, L.J., Benito, J.M., Bucci, D., Han, L., Borthakur, G., Cortes, J., DeAngelo, D.J., Debose, L., Mu, H., Döhner, H., Gaidzik, V.I., Galinsky, I., Golfman, L.S., Haferlach, T., Harutyunyan, K.G., Hu, J., Leverson, J.D., Marcucci, G., Müschen, M., Newman, R., Park, E., Ruvolo, P.P., Ruvolo, V., Ryan, J., Schindela, S., Zweidler-McKay, P., Stone, R.M., Kantarjian, H., Andreeff, M., Konopleva, M., Letai, A.G., 2014. Selective BCL-2 inhibition by ABT-199 causes on-target cell death in acute myeloid leukemia. Cancer Discov. 4, 362–375. https://doi.org/10.1158/2159-8290.CD-13-0609.
Patel, A.B., Vellore, N.A., Deininger, M.W., 2016. New strategies in myeloproliferative neoplasms: the evolving genetic and therapeutic landscape. Clin. Cancer Res. 22, 1037–1047. https://doi.org/10.1158/1078-0432.CCR-15-0905.
Pericole, F.V., Lazarini, M., de Paiva, L.B., Duarte, A.D.S.S., Vieira Ferro, K.P., Niemann, F.S., Roversi, F.M., Olalla Saad, S.T., 2019. BRD4 inhibition enhances azacitidine efficacy in acute myeloid leukemia and myelodysplastic syndromes. Front Oncol 9, 16. https://doi.org/10.3389/fonc.2019.00016. eCollection 2019.
Pui, C.H., Evans, W.E., 2006. Treatment of acute lymphoblastic leukemia. N. Engl. J. Med. 354, 166–178.
Pui, C.H., Yang, J.J., Hunger, S.P., Pieters, R., Schrappe, M., Biondi, A., Vora, A., Baruchel, A., Silverman, L.B., Schmiegelow, K., Escherich, G., Horibe, K., Benoit, Y.C., Izraeli, S., Yeoh, A.E., Liang, D.C., Downing, J.R., Evans, W.E., Relling, M.V., Mullighan, C.G., 2015. Childhood acute lymphoblastic leukemia: progress through collaboration. J. Clin. Oncol. 33, 2938–2948. https://doi.org/10.1200/JCO.2014.59.1636.
Reshmi, S.C., Harvey, R.C., Roberts, K.G., Stonerock, E., Smith, A., Jenkins, H., Chen, I.M., Valentine, M., Liu, Y., Li, Y., Shao, Y., Easton, J., Payne-Turner, D., Gu, Z., Tran, T.H., Nguyen, J.V., Devidas, M., Dai, Y., Heerema, N.A., Carroll 3rd, A.J., Raetz, E.A., Borowitz, M.J., Wood, B.L., Angiolillo, A.L., Burke, M.J., Salzer, W.L., Zweidler-McKay, P.A., Rabin, K.R., Carroll, W.L., Zhang, J., Loh, M.L., Mullighan, C.G., Willman, C.L., Gastier-Foster, J.M., Hunger, S.P., 2017. Targetable kinase gene fusions in high-risk B-ALL: a study from the Children's Oncology Group. Blood 129, 3352–3361. https://doi.org/10.1182/blood-2016-12-758979.
Roberts, K.G., Li, Y., Payne-Turner, D., Harvey, R.C., Yang, Y.L., Pei, D., McCastlain, K., Ding, L., Lu, C., Song, G., Ma, J., Becksfort, J., Rusch, M., Chen, S.C., Easton, J., Cheng, J., Boggs, K., Santiago-Morales, N., Iacobucci, I., Fulton, R.S., Wen, J., Valentine, M., Cheng, C., Paugh, S.W., Devidas, M., Chen, I.M., Reshmi, S., Smith, A., Hedlund, E., Gupta, P., Nagahawatte, P., Wu, G., Chen, X., Yergeau, D., Vadodaria, B., Mulder, H., Winick, N.J., Larsen, E.C., Carroll, W.L., Heerema, N.A., Carroll, A.J., Grayson, G., Tasian, S.K., Moore, A.S., Keller, F., Frei-Jones, M., Whitlock, J.A., Raetz, E.A., White, D.L., Hughes, T.P., Guidry Auvil, J.M., Smith, M.A., Marcucci, G., Bloomfield, C.D., Mrózek, K., Kohlschmidt, J., Stock, W., Kornblau, S.M., Konopleva, M., Paietta, E., Pui, C.H., Jeha, S., Relling, M.V., Evans, W.E., Gerhard, D.S., Gastier-Foster, J.M., Mardis, E., Wilson, R.K., Loh, M.L., Downing, J.R., Hunger, S.P., Willman, C.L., Zhang, J., Mullighan, C.G., 2014. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N. Engl. J. Med. 371, 1005–1015. https://doi.org/10.1056/NEJMoa1403088.
Röllig, C., Serve, H., Hüttmann, A., Noppeney, R., Müller-Tidow, C., Krug, U., Baldus, C.D., Brandts, C.H., Kunzmann, V., Einsele, H., Krämer, A., Schäfer-Eckart, K., Neubauer, A., Burchert, A., Giagounidis, A., Krause, S.W., Mackensen, A., Aulitzky, W., Herbst, R., Hänel, M., Kiani, A., Frickhofen, N., Kullmer, J., Kaiser, U., Link, H., Geer, T., Reichle, A., Junghanß, C., Repp, R., Heits, F., Dürk, H., Hase, J., Klut, I.M., Illmer, T., Bornhäuser, M., Schaich, M., Parmentier, S., Görner, M., Thiede, C., von Bonin, M., Schetelig, J., Kramer, M., Berdel, W.E., Ehninger, G., Leukaemia, Study Alliance, 2015. Addition of sorafenib versus placebo to standard therapy in patients aged 60 years or younger with newly diagnosed acute myeloid leukaemia (SORAML): a multicentre, phase 2, randomised controlled trial. Lancet Oncol. 16, 1691–1699. https://doi.org/10.1016/S1470-2045(15)00362-9.
Saglio, G., Kim, D.W., Issaragrisil, S., le Coutre, P., Etienne, G., Lobo, C., Pasquini, R., Clark, R.E., Hochhaus, A., Hughes, T.P., Gallagher, N., Hoenekopp, A., Dong, M., Haque, A., Larson, R.A., Kantarjian, H.M., Investigators ENESTnd, 2010. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N. Engl. J. Med. 362, 2251–2259. https://doi.org/10.1056/NEJMoa0912614.
Schultz, K.R., Bowman, W.P., Aledo, A., Slayton, W.B., Sather, H., Devidas, M., Wang, C., Davies, S.M., Gaynon, P.S., Trigg, M., Rutledge, R., Burden, L., Jorstad, D., Carroll, A., Heerema, N.A., Winick, N., Borowitz, M.J., Hunger, S.P., Carroll, W.L., Camitta, B., 2009. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. J. Clin. Oncol. 27, 5175–5181. https://doi.org/10.1200/JCO.2008.21.2514.
Schultz, K.R., Carroll, A., Heerema, N.A., Bowman, W.P., Aledo, A., Slayton, W.B., Sather, H., Devidas, M., Zheng, H.W., Davies, S.M., Gaynon, P.S., Trigg, M., Rutledge, R., Jorstad, D., Winick, N., Borowitz, M.J., Hunger, S.P., Carroll, W.L., Camitta, B., Children's Oncology Group, 2014. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: children's Oncology Group study AALL0031. Leukemia 28, 1467–1471. https://doi.org/10.1038/leu.2014.30.
Schuster, S.J., Svoboda, J., Chong, E.A., Nasta, S.D., Mato, A.R., Anak, Ö., Brogdon, J.L., Pruteanu-Malinici, I., Bhoj, V., Landsburg, D., Wasik, M., Levine, B.L., Lacey, S.F., Melenhorst, J.J., Porter, D.L., June, C.H., 2017. Chimeric antigen receptor T cells in refractory B-cell lymphomas. N. Engl. J. Med. 377, 2545–2554. https://doi.org/10.1056/NEJMoa1708566.
Sekiya, Y., Okuno, Y., Muramatsu, H., Ismael, O., Kawashima, N., Narita, A., Wang, X., Xu, Y., Hama, A., Fujisaki, H., Imamura, T., Hasegawa, D., Kosaka, Y., Sunami, S., Ohtsuka, Y., Ohga, S., Takahashi, Y., Kojima, S., Shimada, A., 2016. JAK2, MPL, and CALR mutations in children with essential thrombocythemia. Int. J. Hematol. 104, 266–267. https://doi.org/10.1007/s12185-016-2022-.
Shah, N.P., Rousselot, P., Schiffer, C., Rea, D., Cortes, J.E., Milone, J., Mohamed, H., Healey, D., Kantarjian, H., Hochhaus, A., Saglio, G., 2016. Dasatinib in imatinib-resistant or -intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180-034. Am. J. Hematol. 91, 869–874. https://doi.org/10.1002/ajh.24423.
Shimada, A., Iijima-Yamashita, Y., Tawa, A., Tomizawa, D., Yamada, M., Norio, S., Watanabe, T., Taga, T., Iwamoto, S., Terui, K., Moritake, H., Kinoshita, A., Takahashi, H., Nakayama, H., Koh, K., Goto, H., Kosaka, Y., Saito, A.M., Kiyokawa, N., Horibe, K., Hara, Y., Oki, K., Hayashi, Y., Tanaka, S., Adachi, S., 2018. Risk-stratified therapy for children withFLT3-ITD-positive acute myeloid leukemia: results from the JPLSG AML-05 study.Int. J. Hematol. 107, 586–595. https://doi.org/10.1007/s12185-017-2395-x.
Shimada, A., Taki, T., Tabuchi, K., Tawa, A., Horibe, K., Tsuchida, M., Hanada, R., Tsukimoto, I., Hayashi, Y., 2006. KIT mutations, and not FLT3 internal tandem duplication, are strongly associated with a poor prognosis in pediatric acute myeloid leukemia with t(8;21): a study of the Japanese Childhood AML Cooperative Study Group. Blood 107, 1806–1809.
Simon, R., 2017. Critical review of umbrella, basket, and platform designs for oncology clinical trials. Clin. Pharmacol. Ther. 102, 934–941. https://doi.org/10.1002/cpt.814.
Slayton, W.B., Schultz, K.R., Kairalla, J.A., Devidas, M., Mi, X., Pulsipher, M.A., Chang, B.H., Mullighan, C., Iacobucci, I., Silverman, L.B., Borowitz, M.J., Carroll, A.J., Heerema, N.A., Gastier-Foster, J.M., Wood, B.L., Mizrahy, S.L., Merchant, T., Brown, V.I., Sieger, L., Siegel, M.J., Raetz, E.A., Winick, N.J., Loh, M.L., Carroll, W.L., Hunger, S.P., 2018. Dasatinib plus intensive chemotherapy in children, adolescents, and young adults with Philadelphia chromosome-positive acute lymphoblastic leukemia: results of children's oncology group trial AALL0622. J. Clin. Oncol. 36, 2306–2314. https://doi.org/10.1200/JCO.2017.76.7228.
Small, D., 2006. FLT3 mutations: biology and treatment. Hematology Am Soc Hematol Educ Program 178–184 2006.
Smith, C.C., Paguirigan, A., Jeschke, G.R., Lin, K.C., Massi, E., Tarver, T., Chin, C.S., Asthana, S., Olshen, A., Travers, K.J., Wang, S., Levis, M.J., Perl, A.E., Radich, J.P., Shah, N.P., 2017. Heterogeneous resistance to quizartinib in acute myeloid leukemia revealed by single-cell analysis. Blood 130, 48–58. https://doi.org/10.1182/blood-2016-04-711820.
Solary, E., Itzykson, R., 2017. How I treat chronic myelomonocytic leukemia. Blood 130, 126–136. https://doi.org/10.1182/blood-2017-04-736421.
Stansfield, L.C., Pollyea, D.A., 2017. Midostaurin: a new oral agent targeting FMS-like tyrosine kinase 3-mutant acute myeloid leukemia. Pharmacotherapy 37, 1586–1599. https://doi.org/10.1002/phar.2039.
Stone, R.M., Mandrekar, S.J., Sanford, B.L., Laumann, K., Geyer, S., Bloomfield, C.D., Thiede, C., Prior, T.W., Döhner, K., Marcucci, G., Lo-Coco, F., Klisovic, R.B., Wei, A., Sierra, J., Sanz, M.A., Brandwein, J.M., de Witte, T., Niederwieser, D., Appelbaum, F.R., Medeiros, B.C., Tallman, M.S., Krauter, J., Schlenk, R.F., Ganser, A., Serve, H., Ehninger, G., Amadori, S., Larson, R.A., Döhner, H., 2017. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N. Engl. J. Med. 377, 454–464. https://doi.org/10.1056/NEJMoa1614359.
Tardi, P., Johnstone, S., Harasym, N., Xie, S., Harasym, T., Zisman, N., Harvie, P., Bermudes, D., Mayer, L., 2009. In vivo maintenance of synergistic cytarabine:daunorubicin ratios greatly enhances therapeutic efficacy. Leuk. Res. 33, 129–139. https://doi.org/10.1016/j.leukres.2008.06.028.
Tasian, S.K., Loh, M.L., Hunger, S.P., 2017. Philadelphia chromosome-like acute lymphoblastic leukemia. Blood 130, 2064–2072. https://doi.org/10.1182/blood-2017-06-743252.
Tasian, S.K., Casas, J.A., Posocco, D., Gandre-Babbe, S., Gagne, A.L., Liang, G., Loh, M.L., Weiss, M.J., French, D.L., Chou, S.T., 2019. Mutation-specific signaling profiles and kinase inhibitor sensitivities of juvenile myelomonocytic leukemia revealed by inducedpluripotent stem cells. Leukemia 33, 181–190. https://doi.org/10.1038/s41375-018-0169-y.
Topp, M.S., Kufer, P., Gökbuget, N., Goebeler, M., Klinger, M., Neumann, S., Horst, H.A., Raff, T., Viardot, A., Schmid, M., Stelljes, M., Schaich, M., Degenhard, E., Köhne-Volland, R., Brüggemann, M., Ottmann, O., Pfeifer, H., Burmeister, T., Nagorsen, D., Schmidt, M., Lutterbuese, R., Reinhardt, C., Baeuerle, P.A., Kneba, M., Einsele, H., Riethmüller, G., Hoelzer, D., Zugmaier, G., Bargou, R.C., 2011. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J. Clin. Oncol. 29, 2493–2498. https://doi.org/10.1200/JCO.2010.32.7270.
Tsirigotis, P., Byrne, M., Schmid, C., Baron, F., Ciceri, F., Esteve, J., Gorin, N.C., Giebel, S., Mohty, M., Savani, B.N., Nagler, A., 2016. Relapse of AML after hematopoietic stem cell transplantation: methods of monitoring and preventive strategies. A review from the ALWP of the EBMT. Bone Marrow Transplant. 51, 1431–1438. https://doi.org/10.1038/bmt.2016.167.
Tsukimoto, I., Tawa, A., Horibe, K., Tabuchi, K., Kigasawa, H., Tsuchida, M., Yabe, H., Nakayama, H., Kudo, K., Kobayashi, R., Hamamoto, K., Imaizumi, M., Morimoto, A., Tsuchiya, S., Hanada, R., 2009. Risk-stratified therapy and the intensive use of cytarabine improves the outcome in childhood acute myeloid leukemia: the AML99 trial from the Japanese Childhood AML Cooperative Study Group. J. Clin. Oncol. 27, 4007–4013. https://doi.org/10.1200/JCO.2008.18.7948.
van Dongen, J.J., Seriu, T., Panzer-Grumayer, E.R., Biondi, A., Pongers-Willemse, M.J., Corral, L., Stolz, F., Schrappe, M., Masera, G., Kamps, W.A., Gadner, H., van Wering, E.R., Ludwig, W.D., Basso, G., de Bruijn, M.A., Cazzaniga, G., Hettinger, K., van der Does-van den Berg, A., Hop, W.C., Riehm, H., Bartram, C.R., 1998. Prognostic value of minimal residual disease in acute lymphoblastic leukaemia in childhood. Lancet

352, 1731–1738.
Voso, M.T., Leone, G., Piciocchi, A., Fianchi, L., Santarone, S., Candoni, A., Criscuolo, M., Masciulli, A., Cerqui, E., Molteni, A., Finelli, C., Parma, M., Poloni, A., Carella, A.M., Spina, F., Cortelezzi, A., Salvi, F., Alessandrino, E.P., Rambaldi, A., Sica, S., 2017. Feasibility of allogeneic stem-cell transplantation after azacitidine bridge in higher-risk myelodysplastic syndromes and low blast count acute myeloid leukemia: results of the BMT-AZA prospective study. Ann. Oncol. 28 (7), 1547–1553 2017 Jul 1.
Waespe, N., Van Den Akker, M., Klaassen, R.J., Lieberman, L., Irwin, M.S., Ali, S.S., Abdelhaleem, M., Zlateska, B., Liebman, M., Cada, M., Schechter, T., Dror, Y., 2016. Response to treatment with azacitidine in children with advanced myelodysplastic syndrome prior to hematopoietic stem cell transplantation. Haematologica 101, 1508–1515.
Whitman, S.P., Archer, K.J., Feng, L., Baldus, C., Becknell, B., Carlson, B.D., Carroll, A.J., Mrózek, K., Vardiman, J.W., George, S.L., Kolitz, J.E., Larson, R.A., Bloomfield, C.D., Caligiuri, M.A., 2001. Absence of the wild-type allele predicts poor prognosis in adult de novo acute myeloid leukemia with normal cytogenetics and the internal tandem duplication of FLT3: a cancer and leukemia group B study. Cancer Res. 61, 7233–7239.
Yagi, K., Shimada, A., Sendo, T., 2018. Pharmacological inhibition of JAK3 enhances the antitumor activity of imatinib in human chronic myeloid leukemia. Eur. J. Pharmacol. 825, 28–33. https://doi.org/10.1016/j.ejphar.2018.02.022.
Zhang, Y.L., Yuan, J.Q., Wang, K.F., Fu, X.H., Han, X.R., Threapleton, D., Yang, Z.Y., Mao, C., Tang, J.L., 2016. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget 7, 78985–78993. https://doi.org/10.18632/oncotarget.12587.