# Prognostic Factors in AML

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## 7.1 Introduction

Prognostication in acute myeloid leukemia (AML) is the result of a multilayer, comprehensive assessment, comprising a wide diversity of variables, including patient-related features, disease manifestations at the time of presentation, and intrinsic disease-related genetic features, such as cytogenetic abnormalities and driver mutations (Table 7.1). Moreover, prognostic allocation of AML patients will depend not only on baseline variables, identifiable at diagnosis, but also on evolutive markers, such as measurable residual disease at different critical time points during treatment.

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Disease outcome is a multistage function, including early death rate, treatment refractoriness, disease recurrence, outcome after salvage therapy, and mortality due to treatment-related complications. The impact of prognostic variables varies during disease and treatment phase. Thus, disease features at presentation and patient-related factors have a strong impact on the risk of early death, usually quantified as mortality rate at 30 days after diagnosis. On the other hand, AML genetic background is highly predictive of response to chemotherapy as well as relapse risk. Patient-related variables such as comorbidity or Eastern Cooperative Oncology Group (ECOG) have a high impact on treatment-related death, especially in the setting of hematopoietic cell transplantation (HCT). Outcome measures reported in AML studies can broadly be divided into short-term versus long-term and disease-specific versus global assessments. These metrics are now standardized for clinical trials (Table 7.2).

Importantly, the relative contribution of each prognostic factor is influenced by treatment, and many inconsistencies in the literature have been attributed to differences in treatment intensity or modalities, notably regarding post-remission therapy (e.g., autologous versus allogeneic transplant). Though intensive chemotherapy remains the mainstay of AML therapy, the addition of novel agents, or the development of novel therapy backbones in unfit patients, may impact the prognostic value of different patient- or disease-related factors. Accurate



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**Table 7.1** Prognostic factors in AML

| Prognostic factors | Evaluation measures & scales | References |
|---|---|---|
| ***Patient-related*** | | |
| Age | >75 years, or <75 years with significant comorbidity is a usual definition to define patients not candidate for intensive chemotherapy | Juliusson et al. (2009), Pulte et al. (2016), Bower et al. (2016), Appelbaum et al. (2006a) |
| Performance status | ECOG | Appelbaum et al. (2006a) |
| Comorbidity index | Hematopoietic cell transplantation-comorbidity index (HCT-CI score) | Sorror et al. (2007a, b, 2014) |
| Individual organ severe dysfunction (e.g., renal, cardiac, hepatic, pulmonary) | Renal insufficiency<br>LVEF<45% | Hupfer et al. (2018), Bhatt (2019), Klepin et al. (2013), Hshieh et al. (2018) |
| Geriatric assessment | Cumulative illness rating scale geriatrics (CIRS-G) | Kirkhus et al. (2016) |
| | Geriatric assessment for Hematology (GAH) | Bonanad et al. (2015) |
| ***Disease presentation*** | | |
| Severe infection | | Cannas et al. (2012) |
| AML-related coagulopathy | | Slichter (2004), Lad et al. (2017), De Stefano et al. (2005) |
| Leukostasis | | Giammarco et al. (2017) |
| Tumor lysis syndrome | | Cairo and Bishop (2004) |
| Hyperleukocytosis | | Canaani et al. (2017), Tien et al. (2018a) |
| Extramedullary disease | | Chang et al. (2004), Tallman et al. (2004), Tallman et al. (1993), Byrd et al. (1997), Kobayashi et al. (2007), Tsimberidou et al. (2008), Ganzel et al. (2016), Cheng et al. (2015), Del Principe et al. (2018), Rozovski et al. (2015) |
| ***Disease biology*** | | |
| AML ontogeny | De novo/primary vs Secondary AML arising from antecedent hematological disorders (MDS, MPN, MDS/MPN, BMF)<br>Therapy-related AML | Hulegårdh et al. (2015), Granfeldt Østgård et al. (2015), Lindsley et al. (2015), Kayser et al. (2011), Schmaelter et al. (2020) |
| Dysplastic features | | Devillier et al. (2015b), Armand et al. (2007), Ossenkoppele and Montesinos (2019) |
| Immunophenotypic markers | Leukemia-stem cell phenotype | Nakase et al. (1997), Fujiwara et al. (2017), Kauer et al. (2019), Märklin et al. (2020), Chisini et al. (2017), Costa et al. (2017), Repp et al. (2003), Mason et al. (2006), Minetto et al. (2018), van Solinge et al. (2018) |
| Cytogenetics (see Table 7.2) | | |
| Recurrent genetic mutations (see Table 7.3) | Individual gene mutation | Grimwade and Mrózek (2011), Döhner et al. (2017), Arber et al. (2016) |
| | Gene-gene interactions (e.g., *NPM1-FLT3-DNMT3A*) | Papaemmanuil et al. (2016), Loghavi et al. (2014), Wang et al. (2016), Bezerra et al. (2020) |
| | European LeukemiaNet classification | (Döhner et al. 2017) |

**Table 7.1** (continued)

| Prognostic factors | Evaluation measures & scales | References |
|---|---|---|
| Gene-expression profile | Leukemia stem-cell-like signature | Gentles et al. (2010), Jung et al. (2015), Levine et al. (2015), Metzeler et al. (2008), Eppert et al. (2011), Marcucci et al. (2014), Bullinger et al. (2004), Li et al. (2013), Ng et al. (2016), Duployez et al. (2019), Bill et al. (2020) |
| Non-coding RNA expression pattern & signature | | Schwind et al. (2010b), Marcucci et al. (2013), Díaz-Beyá et al. (2014), Beck et al. (2018) |
| DNA methylation status | | Bullinger et al. (2010), Figueroa et al. (2010), Deneberg et al. (2010), Li et al. (2016), Lin et al. (2011), Yang et al. (2019), Deneberg et al. (2011), Jost et al. (2014), Kroeze et al. (2014), Luskin et al. (2016), DiNardo et al. (2017) |
| ***Treatment administered*** | | See Chaps. 8–10 |
| Treatment intensity | Intensive chemotherapy vs. low intensity | |
| Post-remission therapy | AlloHCT (CR1) | |
| | Maintenance therapy | |
| ***Response to therapy*** | | See Chap. 18 |
| No. of cycles to achieve complete remission | >1 course | |
| Measurable residual disease | Early evaluation (after induction/ two courses) | |
| | Pre-allogeneic stem cell transplantation | |
| | Follow-up measurement | |
| ***Appropriate management and access to health resources*** | | See Chaps. 8–10 |
| Adequate supportive treatment | Transfusional support | |
| | Prophylactic & treatment of infections | |
| Access to allogeneic HCT | | |
| ***Integrative multilayer scores*** | | |
| Risk classification integrations clinical, genetic and treatment data | https://cancer.sanger.ac.uk/aml-multistage | Gerstung et al. (2017), Huet et al. (2018), Fenwarth et al. (2019) |

prognostic evaluation plays a key role in treatment choice. Specifically, the benefit of allogeneic hematopoietic cell transplantation (HCT) is mostly restricted to patients predicted to have the highest risk of relapse without HCT. However, it must be emphasized that prognostic assessment in a given therapeutic context is methodologically distinct from the study of interactions between a "theranostic" factor and different treatment options. The present chapter thus focuses on prognosis, and how prognostic factors influence treatment choice in newly diagnosed AML is presented in Chaps. 8–10.

Biology-driven prognostication of AML has long relied on cytogenetics. A limited number of gene mutations were then included, initially to refine the prognosis of patients with normal karyotype. They are now used in all patients regardless of cytogenetics. The broader panel of recurrent gene mutations uncovered in the genomics era occurring, along with cytogenetic alterations, in a myriad of combinations, challenges conventional risk stratification approaches. Baseline gene expression data have also been proposed to refine prognosis in

**Table 7.2** Outcome metrics

| Outcome | Definition | Comments |
|---|---|---|
| **Response to treatment** | | |
| Complete remission (CR) | BM blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0*10^9/L; PLT ≥1.0*10^9/L | According to NCCN, patients should be independent of transfusions |
| CR with incomplete hematologic recovery (CRi) | All CR criteria except for residual neutropenia (ANC < 1.0*10^9/L) or thrombocytopenia (PLT <1.0*10^9/L) | According to NCCN, patients should be independent of transfusions |
| Morphologic leukemia-freestate (MLFS) | BM blasts <5%; absence of blasts with Auer rods;absence of extramedullary disease; no hematologic recovery required | BM not merely "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10% |
| Partial remission (PR) | All hematologic criteria of CR; decrease of BM blast percentage to 5–25% and decrease of pretreatment BM blast percentage by at least 50% | Especially important in the context of phase 1–2 clinical trials |
| Primary refractory disease | No CR or CRi after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause | 1. primary refractory disease is also called primary induction failure<br>2. death in aplasia is used for deaths occurring >7 days following completion of initial treatment while cytopenic without evidence of persistent leukemia; death due to indeterminate cause refers to cases occurring before 7 days after the end of treatment or in cases without BM examination |
| CR without minimal residualdisease (CRmrd-) | If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC | 1. test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories<br>2. according to NCCN, cytogenetic CR can also be defined (in patients with a previous abnormality) and molecular CR is firmly established for clinical use only in for APL and Ph positive leukemias |
| Hematologic relapse | BM blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease | After CRmrd-, CR, CRi |
| Molecular relapse | Reoccurrence of MRD as assessed by RT-qPCR or by MFC | After CRmrd-; test applied, sensitivity of the assay, and cutoff values used must be reported; analyses should be done in experienced laboratories |
| **Survival measures** | | |
| Overall survival (OS) | Measured from the date of entry into a clinical trial or from the date of diagnosis to the date of death from any cause | Defined for all patients of a trial; patients not known to have died at last follow-up are censored on the date they were last known to be alive |
| Event-free survival (EFS) | Measured from the date of entry into a clinical trial or from the date of diagnosis to the date of primary refractory disease, or relapse from CR (or CRi), or death from any cause | Defined for all patients of a trial; patients not known to have died at last follow-up are censored on the date they were last known to be alive |

**Table 7.2** (continued)

| Outcome | Definition | Comments |
|---|---|---|
| Relapse-free survival (RFS) | Measured from the date of achievement of a remission until the date of relapse or death from any cause | Defined only for patients achieving CR, or CRi; patients not known to have relapsed or died at last follow-up are censored on the date they were last examined; clinical trials in which the response criterion CRmrd-, should include molecular relapse as a criterion for relapse |
| Cumulative incidence of relapse (CIR) | Measured from the date of achievement of a remission until the date of relapse; patients who died without relapse are counted as a competing cause of failure | Defined for all patients achieving CR, CRi; patients not known to have relapsed are censored on the date they were last examined; clinical trials in which the response criterion CRmrd-, should include molecular relapse as a criterion for relapse; it is important to provide estimates of cumulative incidence o f death as well |
| Time to neutrophil recovery | No. of days from day 1 of commencing induction therapy to first day ANC 0.5 ≥ 1.0*10^9/L | And to first day ANC ≥1.0*10^9/L |
| Time to platelet recovery | No. of days from day 1 of commencing inductiontherapy to first day PLTS ≥50*10^9/L | And to first day PLTS ≥100*10^9/L |

*APL* acute promyelocytic leukemia, *ANC* absolute neutrophil count, *BM* Bone marrow, *MFC* multiparameter flow cytometry, *NCCN* national comprehensive cancer network, *PLTS* platelets, *PH* Philadelphia, *RT-qPCR* real-time polymerase chain reaction
Adapted from Dohner, Blood 2017 and NCCN V3 2020, AML

AML. Initially focused on a limited set of genes, they are now expanding to gene expression signatures, leading to further issues related to standardization. Unbiased, systematic integration of these different prognostic factors into personalized predictions is only beginning. Finally, the relative contribution of baseline prognostic factors, compared to dynamic assessment of Measurable Residual Disease (Chap. 18), is another area of future investigation in AML. Here we review the prognostic contribution of recurrent molecular lesions. For further insight into the pathophysiologic role of these lesions or to their diagnostic tools, we refer the reader to Chaps. 2 and 5, respectively.

## 7.2 Host-Related Factors

### 7.2.1 Age

Age is a major determinant of patient outcome in AML, for different reasons. First, the distribution of AML genetic characteristics differs markedly with age, with an increasing incidence of high-risk cytogenetics subtypes and genetic features in older patients accounting for treatment resistance. Specifically, the incidence of MDS-related cytogenetics such as chromosomal aneuploidies with loss of 5q, 7q, and 17p regions surpasses 30 (×100.000 inhabitants/years), an almost ten-fold increase compared to individuals younger than 60 years of age (Lazarevic et al. 2014). Moreover, incidence of many high-risk mutations such as those in *RUNX1*, *ASXL1*, *TP53*, or spliceosome genes (e.g., *SRSF2*, *U2AF1*) is markedly age-dependent (The Cancer Genome Atlas Research Network 2013). Overall, virtually half of elderly patients are diagnosed with an unfavorable subtype of AML according to European LeukemiaNet (ELN) classification (Nagel et al. 2017). Second, older age is associated with poorer performance status (PS), and higher incidence of frailty and comorbidity. Thus, the proportion of PS ≥ 2 according to the ECOG scale is ≥50% over 70 years (Juliusson et al. 2009). The prognostic relevance of age is reflected on the modest improvement on patient outcome observed in elderly patients in recent years, compared to a higher improvement in younger individuals.

Thus, median survival and 5-year survival remain inferior to 1 year and 20% in individuals over 70, with limited improvement in recent years (Pulte et al. 2016; Bower et al. 2016).

### 7.2.2 Performance Status, Comorbidity, and Frailty

Performance status (PS), as an instantaneous picture of general condition, and comorbidity are two important prognostic factors, with a clear impact on early death rate, chance to achieve complete response, and long-term outcome (Appelbaum et al. 2006a). Although PS is clearly related to age and coexistent chronic diseases, PS might be largely determined by disease presentation, and improve with disease treatment. Comorbidity assessment is evaluated using different scales aimed to identify relevant acute and chronic illnesses that impact patient outcome. The Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI score), initially designed for predicting risk of non-relapse mortality in patients undergoing allogeneic HCT, evaluates 17 different items, including pre-existing renal, liver, pulmonary, cardiac, endocrine, and digestive diseases (Sorror et al. 2005). This score has also demonstrated predictive value among patients receiving intensive induction chemotherapy (Sorror et al. 2007a, b, 2014). Individual organ dysfunction might constitute a limitation for specific antileukemic agents, such as use of anthracyclines in patients with depressed cardiac contractility or standard chemotherapy in patients with impaired renal function.

The choice of an adequate therapy in elderly patients is a difficult exercise, which may require the use of integrative geriatric scales, aimed to assess frailty and autonomy of these patients (Hupfer et al. 2018; Bhatt 2019). These scales analyze different functional spheres, including comorbidity, cognitive function, mobility capability, autonomy, emotional status, nutritional status, or concomitant medication, which can interact with antileukemic agents (Klepin et al. 2013; Hshieh et al. 2018). Some of the most used geriatric scales are CIRS-G (Cumulative Illness Rating Scale Geriatrics) and GAH Geriatric Assessment for Hematology (GAH) (Bonanad et al. 2015; Kirkhus et al. 2016).

### 7.2.3 Disease Presentation

Hyperleukocytosis, defined by a WBC count >50–100 * $10^9$/L in different studies, is present in 5–13% of AML. Risk factors for hyperleukocytosis include younger age, myelomonocytic/monoblastic morphology, microgranular APL variant, 11q23 rearrangements, inv(16), and *FLT3*-ITD mutations (Ganzel et al. 2012).

Hyperleukocytosis is associated with a high risk of early mortality due to associated complications (see *infra*). However, higher WBC remains associated with higher risk of relapse and inferior overall survival beyond remission, even when adjusting for confounding oncogenetic factors, such as *FLT3*-ITD mutations (Canaani et al. 2017; Tien et al. 2018a).

Extramedullary disease (EMD) is present at diagnosis in 2–30% of AML patients, notably those with high WBC count. This wide distribution is explained by the lack of standardized evaluation, for example, with $^{18}$Fluorodesoxy-glucose positron emission tomography/computed tomography ($^{18}$FDG-PET/CT) imaging, which reveals EMD in ~20% of unselected AML patients (Stölzel et al. 2014). EMD frequently involves the gingiva, liver, spleen, skin, and lymph nodes but can affect any organ, manifesting as a mass ("chloroma," or myeloid sarcoma) or diffuse organ infiltration. EMD is more frequent in AML with t(8;21) and in patients with high WBC count. The prognostic value of EMD is debated (Chang et al. 2004; Tallman et al. 2004; Tallman et al. 1993; Byrd et al. 1997; Kobayashi et al. 2007; Tsimberidou et al. 2008), but in the largest study published so far, lacked independent prognostic value when accounting for the poor prognostic value of higher WBC count (Ganzel et al. 2016).

Central nervous system (CNS) involvement as a specific form of EMD is reported in 5–30% of AML patients, based on the presence of blasts in the Cerebrospinal fluid (CSF) detected by cytomorphology and/or multiparameter flow cytom-

etry, the presence of neurological symptoms, or both. Some studies indicate an adverse prognostic value of CNS involvement, mostly in pediatric cohorts where diagnostic lumbar puncture remains standard of care (Chang et al. 2004; Kobayashi et al. 2007; Cheng et al. 2015; Del Principe et al. 2018; Rozovski et al. 2015). Lack of systematic CSF evaluation in adults with AML in the era of high-dose cytarabine makes it difficult to ascertain this prognostic value independent of other clinical and oncogenetic features.

### 7.2.4 Initial Complications

Determined complications at presentation constitute a real threat for a fatal outcome. Among these, severe infection, coagulation disorders including disseminated intravascular coagulation (DIC), leukostasis, or tumor lysis syndrome (TLS) should be evaluated and rapidly reverted.

First, due to the hematopoietic impairment caused by AML, patients can present with a concomitant severe infection that needs to be properly and quickly assessed. However, infectious complications normally appear during the treatment course due to the usage of cytotoxic agents. Cannas et al. analyzed the frequency of infectious complications in AML patients included in the multicenter Acute Leukemia French Association (ALFA)-9802 trial and found that 18% of patients presented with fever of unknown origin and 16% with a documented infection at the time of diagnosis, most often involving the ear-nose-throat area (Cannas et al. 2012).

Second, coagulation disorders at presentation are common in AML, clinically evident in 40–70% of patients at diagnosis. Underlying mechanisms can be multiple, highlighting platelet abnormalities and coagulopathic situations (DIC, excessive fibrinolysis, liver dysfunction). Thrombocytopenia at presentation is common, although it is unlikely to present spontaneous bleeding with a platelet count >20 * $10^9$/L. (Slichter 2004) DIC is biologically present in all APL patients, being the most common cause of death of these patients due to intracranial hemorrhage. In non-APL AML, DIC can be also present (10–50%), depending upon the subtype of leukemia (Lad et al. 2017). Thrombotic events, most often deep vein thrombosis, can also be present at the time of presentation (3.9%) (De Stefano et al. 2005).

Hyperleukocytosis is the most important risk factor for leukostasis, which is the mechanical obstruction of the microcirculation due to blast accumulation, affecting pronominally brain, lungs, and kidney vessels (Giammarco et al. 2017). Finally, TLS occurs at disease presentation or in the early therapeutic phase, caused by the massive death of malignant cells. Currently, the Cairo–Bishop definition and grading criteria are widely used for TLS diagnosis, taking into account analytic and clinical variables (Cairo and Bishop 2004). In a study conducted by Montesinos et al., the incidence of TLS and clinical TLS in AML patients was 17% and 5%, respectively (Montesinos et al. 2008). In a single-center study, patients having required intense care during the induction phase had comparable disease-free survival (Schellongowski et al. 2011). Further studies are required to determine the long-term impact of such early complications on relapse incidence.

## 7.3 AML Ontogeny

Secondary AML (sAML), as opposed to de novo or primary AML presentation, is a well-recognized unfavorable prognostic factor in multiple studies. The concept of secondary AML is often vague and has received multiple definitions, referring to patients with an antecedent hematological disorder (AHD) on complete blood counts available before AML diagnosis, patients with a bona fide antecedent myeloid neoplasm before transformation such as MDS, MPN, or MDS/MPN (including CMML), patients with an antecedent congenital bone marrow failure syndrome, and therapy-related AML (tAML), that is, AML arising in a patient with a previous exposure to genotoxic agents (mainly chemo-radiotherapy for lymphoma and solid tumors) or immunosuppressants. Regardless of the precise definition, the inferior outcome of sAML has been confirmed in population-based studies, with a lower

response rate after intensive treatment and inferior overall survival compare to de novo AML, especially among younger patients (Hulegårdh et al. 2015; Granfeldt Østgård et al. 2015). The proportion of AHD-AML and tAML in both studies was similar, comprising approximately 20% and 7%, respectively, of all AML registered cases. Since patients with AHD-AML are older and harbor a higher proportion of adverse cytogenetics and worse mutational profile, the independent value of AML ontogeny per se has been debated. Patients with sAML more often present with complex karyotype, mutations of genes involved in RNA splicing (e.g., *SF3B1*, *SRSF2*, *U2AF1*, and *ZRSR2*), epigenetic regulation, chromatin modification (e.g., *ASXL1*, *EZH2*, *BCOR*), RAS signaling, myeloid transcription, and cohesion complex such as *STAG2*, typically found in MDS, and often lack oncogenetic events characteristic of de novo AML such as *NPM1*, *KMT2A*, or core-binding factor rearrangements (Lindsley et al. 2015). Moreover, patients with tAML, who have received chemotherapy or radiation therapy for a preceding cancer, can present with a poorer PS and higher comorbidity and eventual immune impairment as a consequence of cumulated toxicity derived from treatment received. Consequently, higher non-relapse mortality has been reported in tAML patients treated intensively, especially among those undergoing allogeneic HCT (Kayser et al. 2011). Indeed, sAML remains an adverse prognostic factor beyond CR in patients receiving an allogeneic transplant, independent of cytogenetic risk (Schmaelter et al. 2020). Novel therapeutic options in these patients, including the liposomal chemotherapeutic formulation CPX-351 in fit patients, or the combination of azacitidine and venetoclax in unfit patients, may challenge the prognostic value of AML ontogeny in these populations (Lancet et al. 2016; DiNardo et al. 2019).

## 7.4 Cytogenetic Abnormalities

Cytogenetic abnormalities are present in 55–60% of AML patients and are essential elements both for the classification and the prognostic stratification of AML (Grimwade and Mrózek 2011; Döhner et al. 2017; Arber et al. 2016). Indeed, recurrent cytogenetic abnormalities have been the cornerstone of biology-driven prognostic classifications in AML (Byrd et al. 2002; Grimwade et al. 1998; Slovak et al. 2000; Grimwade et al. 2001) and their prognostic stratification has now been consolidated by European (ELN 2017) (Döhner et al. 2017) and US (NCCN 2020) (Tallman et al. 2019) guidelines thanks to large-scale cohorts. Cytogenetic alterations contribute both to the risk of induction failure and to post-remission outcome (Slovak et al. 2000). The recurrence of cytogenetic alterations is crucial to robustly capture their prognostic role, explaining the "intermediate" risk value attributed to most rare lesions. Below we summarize the prognostic role of the most frequent translocations and copy number of alterations. For their role in the pathophysiology of AML, we refer the reader to Chap. 5. The interactions between specific factors and treatment modalities, hence their contribution to the choice of upfront (e.g., intensive chemotherapy versus non-intensive approaches) or post-remission therapy, are discussed in Chaps. 11–13.

### 7.4.1 Favorable-Risk Translocations

The best example of cytogenetic-defined AML entity is represented by acute promyelocytic leukemia (APL), which is almost exclusively characterized by the t(15;17)(q22;q21) leading to the *PML-RARA* fusion gene and which can be cured in the vast majority of the cases with specific arsenic trioxide-ATRA-based treatment protocols (Sanz et al. 2019). Given its unique nature, APL is now considered as a separate entity and is discussed elsewhere (Chap. 8).

Approximately 10–15% of AMLs belong to the group of core-binding factor (CBF) leukemias, which include AML with t(8;21)(q22;q22), and inv(16)(p13.1q22), or t(16;16)(p13.1;q22), leading to the *RUNX1-RUNX1T1* and *CBFB-MYH11* fusion genes, respectively (Grimwade and Mrózek 2011; Kuykendall et al. 2018). Those entities, which are more common in children and younger adults (Creutzig et al. 2016), respond

well to intensive chemotherapy, with complete remission (CR) rate usually above 85–90%, and are associated with generally favorable long-term overall survival (OS), exceeding 60% in recent reports (Jourdan et al. 2013; Schlenk et al. 2004; Marcucci et al. 2005a; Burnett et al. 2013; Boddu et al. 2018). Even though often grouped together, these two entities are biologically distinct (Faber et al. 2016). Some reports have shown superior results for *CBFB-MYH11* compared to *RUNX1-RUNX1T1* leukemias (Schlenk et al. 2004; Papaemmanuil et al. 2016; Mosna et al. 2015; Appelbaum et al. 2006b; Vasu et al. 2018; Fröhling et al. 2006; Herold et al. 2020). Other studies did not find differences in outcomes between these two entities (Jourdan et al. 2013; Boddu et al. 2018; Ishikawa et al. 2020; Opatz et al. 2020; Cher et al. 2016). Additional chromosomal abnormalities are frequently seen in CBF leukemias (Faber et al. 2016; Duployez et al. 2018), but their prognostic impact, with the possible exception of trisomy 22 in *CBFB-MYH11* patients as a favorable prognostic factor, has been inconsistent among different reports (Byrd et al. 2002; Schlenk et al. 2004; Marcucci et al. 2005a; Papaemmanuil et al. 2016; Appelbaum et al. 2006b; Ishikawa et al. 2020; Opatz et al. 2020; Duployez et al. 2018; Paschka et al. 2013; Shin et al. 2019; Zhou et al. 2020; Grimwade et al. 2010; Krauth et al. 2014; Christen et al. 2019). Thus, the impact of these aberrations is not taken into account by current guidelines (Döhner et al. 2017; Tallman et al. 2019). Elderly (i.e., >60 years old) patients with CBF leukemias can achieve CR in the vast majority of cases as well, but their long-term outcomes have been historically poorer, at least in part because intensive consolidation could be administered to only a fraction of the cases (Appelbaum et al. 2006b; Fröhling et al. 2006; Prébet et al. 2009; Farag et al. 2006).

### 7.4.2 Intermediate and Adverse-Risk Translocations

Balanced translocations involving the *KMT2A* gene (formerly *MLL*) at 11q23 are found in up to 5% of AML cases (Grimwade et al. 2010, 2016). *KMT2A* gene fusions involve multiple partners (Meyer et al. 2018), are frequently found in therapy-related AML (Bloomfield et al. 2002), most commonly after topoisomerase II inhibitors exposure, and are generally associated with unfavorable outcomes (Papaemmanuil et al. 2016; Schoch et al. 2003). Some subgroups, however, seem to achieve slightly better outcomes. Patients with t(9;11)(p22;q23), the most frequent translocation which leads to the *KMT2A-MLLT3* fusion gene, show relatively acceptable results with intensive chemotherapy (Grimwade et al. 2010; Mrózek et al. 1997; Stölzel et al. 2016; Chen et al. 2013; Pigneux et al. 2015), placing them in the intermediate risk group according to ELN 2017 classification (Döhner et al. 2017), while patients with t(11;19)(q23;p13) were considered at intermediate risk by some (Grimwade et al. 2010; Pigneux et al. 2015), but not all (Döhner et al. 2017; Chen et al. 2013; Bhatnagar et al. 2016), studies. Of note, associated (cyto)genetic lesions should not be accounted for in the context of *KMT2A* gene fusions. For instance, t(9;11)(p22;q23) can be found along with additional cytogenetic alterations in a "complex" karyotype, but should still be considered of intermediate prognostic value in this case (Grimwade et al. 2010).

Among recurrent translocations associated with unfavorable outcomes, t(6;9)(p23;q34.1) leading to the *DEK-NUP214* fusion gene occurs roughly in 1% of AML patients. This entity has been associated with relatively younger age, bone marrow dysplasia, high incidence of *FLT3*-ITD, and high relapse risk (Papaemmanuil et al. 2016; Grimwade et al. 2010; Slovak et al. 2006). It is thus regarded as an adverse risk entity (Döhner et al. 2017). Additional cytogenetic aberrations occur in 10–20% of the cases, without a clear prognostic impact.

Inv(3;3)(q21.3q26.2) or t(3;3)(q21.3;q26.2) is a rare entity representing 1–2% of AMLs, driven by the repositioning of the *GATA2* enhancer (located at 3q21), which leads to the overexpression of *MECOM* (*EVI1*) (located at 3q26) and to the haploinsufficiency of *GATA2*. Consequently,

*EVI1* overexpression can be found in virtually all these patients, but also in the majority of cases with other 3q abnormalities and in up to 10% cases without any 3q aberrations, with significant prognostic implications (see *below*) (Hinai and Valk 2016).

Inv(3;3)/t(3;3) AML has been uniformly associated with very low CR rate after intensive chemotherapy (usually <30–40%) and dismal prognosis (Papaemmanuil et al. 2016; Grimwade et al. 2010; Lugthart et al. 2010; Sitges et al. 2020). Conversely, although often associated with poor outcomes, the impact of other 3q aberrations has been less firmly established, possibly due to their heterogeneity (Lugthart et al. 2010). Thus, 3q aberrations other than inv(3;3)/t(3;3) are not incorporated in the ELN 2017 classification (Döhner et al. 2017), but are considered high-risk alterations according to the Medical Research Council (MRC) classification (Table 7.3) (Grimwade et al. 2010). Recently, atypical 3q26 rearrangements have been shown to be biologically very similar to inv(3)/t(3;3) AML, suggesting that these cases could be incorporated with inv(3;3)/t(3;3) AML in the broader 3q26-rearranged AML group, and treated consequently (Ottema et al. 2020). The most frequent additional chromosomal aberration in inv(3;3)/t(3;3) patients is monosomy 7, which does not seem to independently worsen prognosis (Grimwade et al. 2010), unless in the context of a monosomal karyotype (Lugthart et al. 2010; Sitges et al. 2020).

*BCR-ABL1*-positive AML was recently introduced as a provisional entity in the 2016 WHO classification (Arber et al. 2016), distinguishing it from myeloid blast crisis of chronic myeloid leukemia (Neuendorff et al. 2016). Although ELN guidelines place this entity in the adverse risk category (Döhner et al. 2017), it has been suggested that its prognosis largely depends on co-occurring genetic abnormalities. Besides, the incorporation of TKIs in the treatment strategy is likely to change its natural history and alloHCT was associated with favorable long-term survival in some reports (Lazarevic et al. 2018; Neuendorff et al. 2018). Further effort is required to define more accurately this entity.

### 7.4.3 Adverse-Risk Aneuploidies

Among patients with an abnormal karyotype lacking recurrent translocations, the adverse prognostic role of deletion 5q/−5, deletion 7q/−7, and deletion 17p/−17 is well established (Byrd et al. 2002; Slovak et al. 2000; Seifert et al. 2009; Nahi et al. 2008). Of note, despite being grouped together in some reports (Slovak et al. 2000; Grimwade et al. 2010), the majority of studies have shown that patients harboring monosomy 7 have a worse outcome compared to those with del(7q) (Byrd et al. 2002; Grimwade et al. 1998, 2010), which is consistent with data in MDS (Greenberg et al. 2012; Schanz et al. 2012). These results were also confirmed for patients undergoing alloHCT (Poiré et al. 2020; Canaani et al. 2019). Thus, only monosomy 7 is regarded as an adverse risk abnormality according to ELN 2017 classification (Döhner et al. 2017) (Table 7.3).

The role of other aneuploidies or rare translocations has been more controversial. The MRC group performed a detailed analysis including 5876 intensively treated younger AML patients, in order to clarify their impact. The authors derived a revised cytogenetic classification (Grimwade et al. 2010) that has largely, but not entirely, been incorporated into the current ELN risk stratification (Döhner et al. 2017). As a matter of fact, del(7q) and the abnormalities of 3(q) are defined as high risk by the MRC classification only, which conversely excludes from this category patients with t(11;19) and those with three unrelated abnormalities (see *below* and Table 7.3).

The presence of a complex karyotype (CK), currently defined by the 2017 ELN guidelines as the presence of at least 3 unrelated chromosome abnormalities—whether or not in the same clone—in the absence of one of the WHO-designated recurrent translocations or inversions (Döhner et al. 2017; Byrd et al. 2002; Slovak et al. 2000; Schoch et al. 2001), occurs in 10–15% of AML patients. Its incidence increases with age. CK has invariably been associated with unfavorable outcomes in AML (Byrd et al. 2002; Grimwade et al. 2001; Creutzig et al. 2016;

**Table 7.3** Current prognostic classifications

| Risk category | Genetic abnormality | Comments |
|---|---|---|
| **Favorable** | t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* | According to NCCN only, alloHCT should be considered for t(8;21) in case of *KIT* mutations. Favorable risk irrespective of additional cytogenetic abnormalities |
| | Inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* | Favorable risk irrespective of additional cytogenetic abnormalities |
| | Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITDlow* | If allelic ratio is not available, *FLT3*-ITD pos patients are high risk, or intermediate if also *NPM1* positive (NCCN)<br>ELN states that *NPM1* positive cases (without *FLT3*-ITD or with *FLT3*-ITDlow) are considered favorable risk regardless of cytogenetics. However, a recent large multinational report suggests this might not be true if an adverse risk cytogenetic aberration is present.§ |
| | Biallelic mutated *CEBPA* | ELN states that biallelic mutated *CEBPA* positive cases are considered favorable risk regardless of cytogenetics |
| **Intermediate** | Mutated *NPM1* and *FLT3*-ITDhigh* | |
| | Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITDlow* | In the absence of adverse-risk genetic lesions |
| | t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* | The presence of t(9;11)) takes precedence over rare, concurrent adverse-risk gene mutations. According to the MRC cytogenetic classification, t(11;19)(q23;p13) is also an intermediate risk abnormality |
| | Cytogenetic abnormalities not favorable or adverse | Very large consortium data may be necessary to assign prognostic value to rare entities |
| **Adverse** | t(6;9)(p23;q34.1); *DEK-NUP214* | |
| | t(v;11q23.3); *KMT2A*-rearranged | According to the MRC cytogenetic classification, t(11;19)(q23;p13) is an intermediate risk abnormality |
| | t(9;22)(q34.1;q11.2); *BCR-ABL1* | |
| | Inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* | According to the MRC cytogenetic classification, all abn(3q), excluding t(3;5)(q21 25;q31 35), are adverse risk |
| | Monosomy 5 or del(5q) | |
| | Monosmy 7 | According to the MRC cytogenetic classification, del(7p) is also a high risk abnormality |
| | Monosmy 17/abn(17p) | |
| | Complex karyotype | Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions. According to the MRC cytogenetic classification, at least 4 abnormalities are required |
| | Monosomal karyotype | One single monosomy (excluding loss of X or Y) with at least 1 additional monosomy or structural chromosome abnormality |
| | Wild-type *NPM1* and *FLT3*-ITDhigh* | |
| | Mutated *RUNX1* | Not an adverse prognostic marker if co-occurring with favorable-risk AML subtypes |
| | Mutated *ASXL1* | Not an adverse prognostic marker if co-occurring with favorable-risk AML subtypes |
| | Mutated *TP53* | |

* Low (<0.5) or high (≥0.5) allelic ratio is derived by semi-quantitative assessment using DNA fragment analysis and is determined as ratio of the area under the curve "*FLT3*-ITD" divided by area under the curve "FLT3-wild type".
§ Angenendt et al. (2019).
Adapted from Dohner, Blood 2017, NCCN V3 2020 AML and Grimwade Blood 2010 NCCN national comprehensive cancer network; MRC Medical Research Council

Stölzel et al. 2016). It is important to stress that CK should not be considered as an unfavorable feature in patients with favorable or intermediate risk translocations, including t(8;21), inv(16), or t(9;11) (Grimwade et al. 2010). This suggests that, in the absence of these recurrent founder lesions, CK is only an indirect surrogate of an unfavorable disease subtype. Several attempts have thus been made to define more accurately this subgroup.

Authors initially stressed the importance of the number of cytogenetic alterations. According to the MRC classification, 4 abnormalities (Grimwade et al. 2010) (or, formerly, 5) (Grimwade et al. 2001) were necessary to define CK. Stölzel and colleagues analyzed the outcome of 3526 AML patients included in three prospective trials of the Study Alliance Leukemia. They found that patients with ≥4 abnormalities have an adverse risk per se, while patients with 3 abnormalities have a borderline intermediate-adverse outcome, in the absence of individual abnormalities of strong influence (Stölzel et al. 2016). However, irrespectively of the cutoff chosen, each additional aberration worsens prognosis (Papaemmanuil et al. 2016; Grimwade et al. 2010).

Others studied the respective contribution of complexity and aneuploidy, given the strong correlation between CK and chromosome 5, 7, and 17 complete or partial monosomy. Indeed, patients with monosomies had unfavorable outcomes, with long-term survival not exceeding 15% (Breems et al. 2008). Among those cases, Breems and colleagues identified a group with extremely poor outcomes, with 4-year OS of less than 5%, characterized by a monosomal karyotype (MK). They defined MK as the presence of two or more distinct autosomal chromosome monosomies or one single autosomal monosomy in the presence of at least one structural abnormality. Thus defined, MK showed a greater prognostic impact than CK, as patients with CK but lacking MK had relatively better outcomes. The negative prognostic value of MK was confirmed in the following reports analyzing independent patient cohorts (Grimwade et al. 2010; Kayser et al. 2012; Medeiros et al. 2010; Weinberg et al. 2014; Wierzbowska et al. 2017). Further studies indicated that CK defined by exactly 3 alterations, in the absence of MK, was associated with a better outcome than MK and/or CK with 4 or more abnormalities (Haferlach et al. 2012). Consistently (Slovak et al. 2000; Breems et al. 2008; Chilton et al. 2014), Mrózek and colleagues recently reported that atypical CK, that is, lacking 5q, 7q, and/or 17p loss, represents a biologically distinct entity and it is associated with a relatively superior prognosis compared to typical CK (Mrózek et al. 2019).

Hyperdiploidy (i.e., ≥49 chromosomes) is infrequent in AML (less than 2% of AML). Its prognosis appears heterogeneous, with a poor prognosis restricted in most (Chilton et al. 2014; Lazarevic et al. 2015; Abaza et al. 2018), but not all (Stölzel et al. 2016), reports to patients also harboring adverse risk abnormalities (i.e., chromosome 5, 7, or 17 abnormalities), while those with pure hyperdiploid karyotype showed an intermediate risk.

In an attempt to define the biological process underlying the poor prognosis of MK and CK, authors have turned to indirect markers of chromothripsis, a term coined to describe a phenomenon of multiple chromosome fragmentation in a single catastrophic event, and initially identified in cancers through whole genome sequencing rather than karyotyping (Stephens et al. 2011). These authors could show that presence of marker chromosomes, which reflects gross structural chromosomal damage and is sometimes seen in patients with CK, was associated with chromothripsis, defined by array of comparative genomic hybridization, and with poor outcomes independently of adverse-risk karyotype according to MRC or ELN. A strong association of chromothripsis with *TP53* mutations was found, but whether both exert an independent prognostic impact remains to be established (Bochtler et al. 2017; Fontana et al. 2018).

## 7.5 Gene Mutations

Knowledge on the biological implications, prognostic relevance, and clinical impact of recurrent gene mutations has greatly expanded in recent years. Extensive molecular characterization at

diagnosis has become standard practice in AML (The Cancer Genome Atlas Research Network 2013; Papaemmanuil et al. 2016; Grimwade et al. 2016; Metzeler et al. 2016; Bullinger et al. 2017; Patel et al. 2012). Below we describe the prognostic relevance of the most frequent gene mutations (Table 7.4). Importantly, only a few (*NPM1*, *CEBPA*) can be considered as "founder," class-defining lesions in AML on the basis of their near complete exclusivity one from another and from the recurrent translocations listed above (Papaemmanuil et al. 2016).

### 7.5.1 FLT3

*FLT3* is the most commonly mutated gene in younger AML patients (Papaemmanuil et al. 2016; Nakao et al. 1996). It is associated with cytogenetically normal AML (CN-AML), APL, and t(6;9)(p23;q34.1) (Thiede et al. 2002), and the prognostic relevance of its aberrations has been extensively explored. Point mutations in the Tyrosine Kinases Domain (TKD), more frequently in the D835 residue, occur in 7–10% of the patients and do not exert a significant independent prognostic role (Döhner et al. 2017; Tallman et al. 2019; Grimwade et al. 2016), with some conflicting results (Bacher et al. 2008; Mead et al. 2007; Fröhling et al. 2002). *FLT3-TKD* mutations could exert distinct prognostic impact depending on the context (i.e., CBF, *NPM1* vs. *KMT2A*-PTD-positive AML, see also *below*) (Papaemmanuil et al. 2016; Eisfeld et al. 2018; Boddu et al. 2017; Perry et al. 2018). Conversely, Internal Tandem Duplications (ITDs), which occur in the juxtamembrane (JM) domain and/or first tyrosine kinase domain (TKD1) of the FLT3 receptor, have been consistently associated with unfavorable outcomes (Kiyoi et al. 1999; Kottaridis et al. 2001; Port et al. 2014; Whitman et al. 2010). *FLT3*-ITD can be categorized based on allelic ratio, size of the insertion, and location of the insertion. In several reports, the adverse prognostic value of *FLT3*-ITD seemed mostly restricted to patients with high ITD/wild-type allelic ratios (Thiede et al. 2002; Blau et al. 2013; Gale et al. 2008; Chen et al. 2019; Schnittger et al. 2011a; Schlenk et al. 2014; Whitman et al. 2001). *FLT3*-ITD allelic ratio is defined as the ratio of the area under the curve of the *FLT3*-ITD signal divided by the area under the curve of the wild-type signal in conventional DNA fragment analysis. Thus defined, allelic ratio differs from Variant Allele Frequencies (VAF) for other genetic lesions, which report the relative abundance of the mutated allele over the total (mutant + wild type) allele burden. Among the different cutoffs reported in the literature (Thiede et al. 2002; Cornelissen and Blaise 2016; Ho et al. 2016; de Jonge et al. 2011), the current version of the ELN guidelines adopted the value of 0.5 to define low (<0.5) and high (≥0.5) *FLT3*-ITD allelic ratios (Döhner et al. 2017). Of note, in some patients, multiple ITDs may coexist, presumably in independent clones. In those cases, the sum of allelic ratios should be compared to the 0.5 threshold. An important effort has yet to be done to guarantee the inter-laboratory reproducibility of such allelic ratio results, which currently rely on partly standardized PCR assays (Daver et al. 2019). Finally, though the length and site of the insertion may also play a prognostic role, with longer ITDs being associated with the insertion in the TKD1 domain, and potentially with a more unfavorable outcome in several reports (Chen et al. 2019; Schlenk et al. 2014; Kayser et al. 2009; Stirewalt et al. 2006; Kim et al. 2015; Arreba-Tutusaus et al. 2016; Liu et al. 2019; Fischer et al. 2017), these parameters are currently not used to stratify patients according to current guidelines (Döhner et al. 2017; Tallman et al. 2019), because of conflicting results (Blau et al. 2013; Gale et al. 2008; Ponziani et al. 2006; Kusec et al. 2006), and of ongoing efforts to standardize the detailed molecular assessment of *FLT3*-ITDs (Schwartz et al. 2019).

### 7.5.2 NPM1

*NPM1* mutations are also common in AML, with an overall incidence around 30%. They are mostly detected in patients with normal karyotype. *NPM1* mutations have overall been associated with favorable outcomes and good response to intensive chemotherapy in most, but

**Table 7.4** Prognostic role of recurrent gene mutations

| Gene | Mutation | Prognostic significance | Subset and interactions | References |
|---|---|---|---|---|
| ***FLT3*** | **ITD** | Unfavorable | Independently worse OS | Kiyoi et al. (1999) |
| | | | Independently worse EFS, RFS, OS | Kottaridis et al. (2001) |
| | | | Independently worse RFS and OS only if high mutant level | Thiede et al. (2002) |
| | | | Independently worsen OS | Fröhling et al. (2002) |
| | | | Independently worse RFS and OS, worsening with increasing mutant level | Gale et al. (2008) |
| | | | Independently worse RFS and OS in AML > 60 years | Whitman et al. (2010) |
| | | | Only high AR adverse prognostic impact in *NPM1*-mutated AML | Schnittger et al. (2011a, b) |
| | | | *FLT3*-ITD worsen prognosis in *NPM1* mutated AML, especially if high AR | Schneider et al. (2012) |
| | | | Independently worsen OS | How et al. (2012) |
| | | | *FLT3*-ITD worsen OS, EFS, RFS but only if high AR in *NPM1*-mutated AML | Pratcorona et al. (2013) |
| | | | Independently worsen RFS | Metzeler et al. (2016) |
| | | | Independently worsen OS | Papaemmanuil et al. (2016) |
| | **TKD** | Controversial | Improved EFS in AML with *NPM1*- or *CEBPA* mutations | Bacher et al. (2008) |
| | | | Improved OS (only if mutant level >25%) | Mead et al. (2007) |
| | | | Improved RFS and a trend for OS in *NPM1*-mutated AML | Boddu (2017) |
| | | | Independently improved CR rate, no impact on OS and RFS | Metzeler et al. (2016) |
| | | | Impact strongly dependent on the presence of *KMT2A*-PTD | Papaemmanuil et al. (2016) |
| | | | Improved OS in *NPM1*-mutated AML > 60 years | Eisfeld et al. (2018) |
| | | | Improved OS in *NPM1*-mutated AML | Perry et al. (2018) |
| ***NPM1*** | | Favorable | Improve CR rate | Falini et al. (2005) |
| | | | No impact on CR and OS in IR-AML | Boissel et al. (2005) |
| | | | Improved CR rate and RFS | Suzuki et al. (2005) |
| | | | Improved CR rate, OS, RFS in absence *FLT3*-ITD | Thiede et al. (2006) |
| | | | Improved CR rate and OS in absence *FLT3*-ITD | Döhner et al. (2005) |
| | | | Improved CR rate, EFS, OS in the absence of *FLT3*-ITD | Schnittger et al. (2005) |
| | | | Improved EFS, OS, RFS in the absence of *FLT3*-ITD | Verhaak et al. (2005) |
| | | | Improved OS and RFS | Gale et al. (2008) |

**Table 7.4** (continued)

| Gene | Mutation | Prognostic significance | Subset and interactions | References |
|---|---|---|---|---|
| | | | Improved CR rate, OS, RFS in absence *FLT3*-ITD | Schlenk et al. (2008) |
| | | | Improved CR rate, OS, RFS in absence *FLT3*-ITD | Büchner et al. (2009) |
| | | | Improved CR rate, OS, RFS in>60 years CN AML | Becker et al. (2010) |
| | | | Favorable OS in absence FLT3 ITD | How et al. (2012) |
| | | | Favorable OS and EFS in absence FLT3 ITD | Grossmann et al. (2012) |
| | | | Favorable OS and EFS in absence FLT3 ITD, intermediate if FLT3 low AR | Schneider et al. (2012) |
| | | | Favorable OS and EFS in absence FLT3 ITD or if *FLT3*-ITD with low AR | Pratcorona et al. (2013) |
| | | | Improved CR rate and, in de absence of *FLT3*-ITD, improved OS | Kihara et al. (2014) |
| | | | Improved OS for in absence of *FLT3*-ITD only 55-65y, not >65 years | Ostronoff et al. (2015) |
| | | | Improved CR rate and favorable OS (in the absence of *FLT3*-ITD) | Metzeler et al. (2016) |
| | | | Favorable impact on OS | Papaemmanuil et al. (2016) |
| ***DNMT3A*** | **Globally** | Controversial, mostly unfavorable | Independently reduce OS, irrespectively of age an type of mutations | Ley et al. (2010) |
| | | | Independently reduce OS but not CR or RFS globally, lower OS and CR in CN-AML | Thol et al. (2011) |
| | | | Independently reduced OS and RFS | Hou et al. (2012) |
| | | | Independently reduced OS and EFS in CN AML | Shen et al. (2011) |
| | | | Independently reduced OS and RFS < 60 years | Ribeiro et al. (2012) |
| | | | Independently reduced for EFS and OS in CN AML <60 years | Renneville et al. (2012) |
| | | | Independently worse RFS and, only in AML <60 years, OS and CR rate | Metzeler et al. (2016) |
| | | | No clear independent prognostic value (only with some co-mutational patterns) | Papaemmanuil et al. (2016) |
| | | | Worse OS in each ELN2017 defined subgroup | Herold et al. (2020) |
| | **R882** | | Shorted DFS, not independently worse OS. Different impact R882 vs others according to age | Marcucci et al. (2012) |
| | | | No effect on OS and EFS globally; negative only in unfavorable ELN risk and for R882 mutation | Gaidzik et al. (2013) |
| | | | R822 mutations worsen OS, DFS and increase CIR; particularly bad with *FLT3*-ITD and *NPM1* | Bezerra et al. (2020) |
| | | | Non-R882 mutations worsen CIR and RFS in *NPM1*-mutated AML | Peterlin et al. (2015) |
| ***CEBPA*** | **Globally** | Favorable (restricted to bi-allelic) | First study reporting the favorable clinical impact of *CEBPA* mutations on OS | Preudhomme et al. (2002) |

(continued)

**Table 7.4** (continued)

| Gene | Mutation | Prognostic significance | Subset and interactions | References |
|---|---|---|---|---|
| | | | *CEBPA* independently improve OS | Schlenk et al. (2008) |
| | **Biallelic** | | Only bi*CEBPA* independent favorable effect on OS and EFS | Wouters et al. (2009) |
| | | | Only bi*CEBPA* independent favorable effect on OS and EFS | Shen et al. (2011) |
| | | | Only bi*CEBPA* independent favorable effect on OS and EFS | Rockova et al. (2011) |
| | | | Only bi*CEBPA* independent favorable effect on OS and RFS | Pabst et al. (2009) |
| | | | Only bi*CEBPA* independent favorable effect on OS; *FLT3*-ITD abolish this favorable effect | Green et al. (2010) |
| | | | Only bi*CEBPA* independent favorable effect on OS and EFS | Dufour et al. (2010) |
| | | | Only bi*CEBPA* independent favorable effect on OS and EFS | Taskesen et al. (2011) |
| | | | bi*CEBPA* favorable impact on OS | Grossmann et al. (2012) |
| | | | Only bi*CEBPA* independent favorable effect on OS, *TET2* worsen outcomes while *GATA2* has positive effect | Fasan et al. (2014) |
| | | | bi*CEBPA* better OS compared to monoallelic mutation only at univariate analysis | Marceau-Renaut et al. (2015) |
| | | | bi*CEBPA* favorable long-term OS compared to monoallelic mutation | Pastore et al. (2014a, b) |
| | | | bi*CEBPA* favorable long-term OS | Papaemmanuil et al. (2016) |
| | | | bi*CEBPA* favorable long-term OS (borderline significance) | Metzeler et al. (2016) |
| | | | bi*CEBPA* increased CR, OS, RFS; concomitant *WT1* mutations worsen OS and RSF | Tien et al. (2018a, b) |
| ***KMT2A*** | **PTD** | Controversial, mostly unfavorable | OS and RFS significantly worse in CN-AML | Schnittger et al. (2000) |
| | | | Independently worsen RFS | Döhner et al. (2002) |
| | | | Worsen OS | Shiah et al. (2002) |
| | | | Independently worse RFS | Schlenk et al. (2008) |
| | | | Only worsen RFS in <60 years, not OS | Steudel et al. (2003) |
| | | | Independently worse EFS | Grossmann et al. (2012) |
| | | | Independently worsen OS | Kihara et al. (2014) |
| | | | Worsen EFS and OS only at univariate analysis | Fasan et al. (2014) |
| | | | No clear impact on any survival outcomes | Metzeler et al. (2016) |

**Table 7.4** (continued)

| Gene | Mutation | Prognostic significance | Subset and interactions | References |
|---|---|---|---|---|
| | | | Impact on OS mainly if *FLT3*-TKD co-occurs | Papaemmanuil et al. (2016) |
| | | | No impact on OS and EFS. Unfavorable outcome restricted to *DNMT3A* and *NRAS* comutated | Hinai et al. (2019) |
| ***RUNX1*** | | Unfavorable (mostly) | Independently worsen OS | Tang et al. (2009) |
| | | | Independently worsen EFS | Gaidzik et al. (2011) |
| | | | Independently worsen OS | Schnittger et al. (2011a, b) |
| | | | Independently worsen OS in CN-AML | Greif et al. (2012) |
| | | | Independently worsen CR rate, EFS, OS RFS | Mendler et al. (2012) |
| | | | Independently worsen OS | Kihara et al. (2014) |
| | | | Worsen EFS and OS only at univariate analysis | Fasan et al. (2014) |
| | | | Independently worsen EFS | Gaidzik et al. (2016) |
| | | | No independent prognostic impact in AML-NOS | Weinberg et al. (2017) |
| | | | Independently worse RFS and, only in AML <60 years, OS and CR rate | Metzeler et al. (2016) |
| | | | No independent prognostic value | Papaemmanuil et al. (2016) |
| | | | Worse prognosis of multiple versus single *RUNX1* mutation (loss of wt allele) | Stengel et al. (2018) |
| | | | No independent prognostic impact in de novo AML | Quesada et al. (2020) |
| | | | Impact on OS more pronounced in AML with MDS-related changes | Nguyen et al. (2020) |
| ***ASXL1*** | | Unfavorable (mostly) | Detrimental effect on OS lost at multivariate analysis | Chou et al. (2010) |
| | | | Independent effect on OS in CN-AML only | Patel et al. (2012) |
| | | | Worse CR rate, RFS, OS and EFS among ELN2010 favorable patients | Metzeler et al. (2011a, b) |
| | | | Independently worse OS | Grossmann et al. (2012) |
| | | | Independently worse OS | Pratcorona et al. (2012) |
| | | | Independently worse OS in intermediate-risk AML | Schnittger et al. (2013) |
| | | | Worsen EFS and OS only at univariate analysis | Fasan et al. (2014) |
| | | | Independently worsen OS only when co-occur with *RUNX1* | Paschka et al. (2015) |
| | | | Independently worsen OS in AML-MRC | Devillier et al. (2015) |
| | | | No independent prognostic value | Metzeler et al. (2016) |

(continued)

**Table 7.4** (continued)

| Gene | Mutation | Prognostic significance | Subset and interactions | References |
|---|---|---|---|---|
| | | | Independently worse OS | Papaemmanuil et al. (2016) |
| ***TET2*** | | Controversial | No prognostic impact | Nibourel et al. (2010) |
| | | | Impact on OS lost at multivariable analysis | Chou et al. (2011a, b) |
| | | | Shorter EFS, lower CR rate, and shorter RFS only among favorable-risk CN-AML | Metzeler et al. (2011a, b) |
| | | | Shorter EFS in favorable-risk de novo CN-AML | Weissmann et al. (2012) |
| | | | Impact on OS lost at multivariable analysis | Gaidzik et al. (2012) |
| | | | Worse OS in CN-AML | Patel et al. (2012) |
| | | | No significant prognostic impact | Metzeler et al. (2016) |
| ***IDH*** | **Grouped *IDH1/2*** | Controversial | Impact on OS lost at multivariable analysis | Gaidzik et al. (2012) |
| | | | Worse OS and RFS only in *NPM1*-mutated *FLT3*-ITD negative AML | Paschka et al. (2010) |
| | ***IDH1*** | | Favorable OS in *NPM1*-mutated AML | Patel et al. (2012) |
| | | | No prognostic impact | Metzeler et al. (2016) |
| | | | Inferior CR rate and OS in intensively treated AML over 75 years | Prassek et al. (2018) |
| | | | Worse OS and RFS only in *NPM1*-mutated *FLT3*-ITD negative AML | Marcucci et al. (2010) |
| | | | Worse OS and RFS only in *NPM1*-mutated *FLT3*-ITD negative AML | Boissel et al. (2010) |
| | | | No prognostic impact in CN AML | Wagner et al. (2010) |
| | | | Worse OS and EFS only in NPM1wt FLT3wt AML | Abbas et al. (2010) |
| | | | Independently worse EFS | Schnittger et al. (2010) |
| | | | No prognostic impact | Green et al. (2011) |
| | | | No prognostic impact | Shenet et al. (2011) |
| | | | Worse RFS and higher CIR in *NPM1*-mutated AML | Peterlin et al. (2015) |
| | ***IDH2* (all)** | | No prognostic impact | Metzeler et al. (2016) |
| | | | No prognostic impact | Thol et al. (2010) |
| | | | No prognostic impact | Shen et al. (2011) |
| | | | No prognostic impact | Abbas et al. (2010) |
| | **R140** | | Favorable OS, especially in *NPM1*-mutated CN AML | Patel et al. (2012) |
| | | | No independent impact, strongly dependent on co-mutations | Papaemmanuil et al. (2016) |
| | | | Worse OS and RFS only in *NPM1*-mutated *FLT3*-ITD negative AML | Marcucci et al. (2010) |

**Table 7.4** (continued)

| Gene | Mutation | Prognostic significance | Subset and interactions | References |
|---|---|---|---|---|
| | | | Favorable OS and reduced CIR | Green et al. (2011) |
| | | | Favorable OS | Chou et al. (2011a, b) |
| | | | No prognostic impact | Boissel et al. (2011) |
| | **R172** | | Trend for better outcomes | Papaemmanuil et al. (2016) |
| | | | Lower CR rate and trend for lower OS in older AML | Marcucci et al. (2010) |
| | | | Worse OS and higher CIR | Green et al. (2011) |
| | | | Independently worse OS and RFS | Boissel et al. (2010) |
| | | | Favorable OS | Chou et al. (2011a, b) |
| ***WT1*** | | Controversial | Independently worse CR rate, CIR, RFS and OS | Virappane et al. (2008) |
| | | | Independently worse OS and RFS | Paschka et al. (2008) |
| | | | No independent prognostic impact in CN-AML | Gaidzik et al. (2009) |
| | | | Independently worse RFS in CN-AML | Renneville et al. (2009a, b) |
| | | | Independently worse OS in CN-AML | Patel et al. (2012) |
| | | | No significant prognostic impact.. | Metzeler et al. (2016) |
| ***TP53*** | | Unfavorable | Independently worse OS in AML > 55 years | Stirewalt et al. (2001) |
| | | | Independently worse OS and EFS | Grossmann et al. (2012) |
| | | | Independently worse OS, RFS and CR rate AML with adverse risk cytogenetics | Bowen et al. (2009) |
| | | | Independently worse EFS, RFS, OS in AML with CK | Rücker et al. (2012) |
| | | | Independently worse OS | Kihara et al. (2014) |
| | | | Independently worse OS in therapy-related AML | Ok et al. (2015) |
| | | | Worse OS irrespective of age and treatment intensity (only univariate data) | Kadia et al. (2016) |
| | | | Independently worse OS and RFS | Metzeler et al. (2016) |
| | | | Independently worse OS | Papaemmanuil et al. (2016) |
| | | | Independently worse OS in AML > 60 years | Yanada et al. (2016) |
| | | | Independently worse OS | Stengel et al. (2017) |
| | | | Significantly shorter RSF in AML > 75 treated intensively | Prassek et al. (2018) |

(continued)

**Table 7.4** (continued)

| Gene | Mutation | Prognostic significance | Subset and interactions | References |
|---|---|---|---|---|
| ***KIT*** | | Controversial, mostly unfavorable in t(8;21) | Exon 8 mutations increased CIR in inv(16) | Care et al. (2003) |
| | | | Shorter EFS and RFS in t(8;21) but not inv(16) | Boissel et al. (2006) |
| | | | Worse OS and higher CIR in inv(16); Higher CIR similar OS in t(8;21) | Paschka et al. (2006) |
| | | | Worse OS and higher CIR in t(8;21); no impact in inv(16) | Cairoli et al. (2006) |
| | | | Lower OS and EFS in patients with t(8;21) (D816 Mut at exon 17) | Schnittger et al. (2006) |
| | | | Worse OS and EFS in adult t(8;21) for exon 17 Mut; no impact in inv(16) and pediatric | Park et al. (2011) |
| | | | Worse OS and EFS t(8;21) for mutations D816 at exon 17 | Kim et al. (2013) |
| | | | Worse RFS in inv(16), mainly if exon 8 mutations | Paschka et al. (2013) |
| | | | No significant prognostic impact | Riera et al. (2013) |
| | | | Higher CIR (if mutant level > 25%) in t(8;21) | Allen et al. (2013) |
| | | | Higher CIR, worse DFS and OS in adult t(8;21) AML; no impact inv(16) and pediatric AML | Qin et al. (2014) |
| | | | D816 mutations negatively impacted on OS in t(8;21) | Krauth et al. (2014) |
| | | | No impact in pediatric t(8;21) | Klein et al. (2015) |
| | | | Exon 17 mutations worsen RFS and OS | Cher et al. (2016) |
| | | | Exon 17 mutations worsen OS and EFS | Faber et al. (2016) |
| | | | Higher CIR (if mutant level > 35%) in t(8;21) | Duployez et al. (2016) |
| | | | No independent prognostic impact in any subgroup | Itzykson et al. (2018a, b) |
| | | | Lower CR,EFS,OS, RFS in t(8;21), but outperformed by MRD | Rücker et al. (2019) |
| | | | Inferior RFS and OS (if mutant level > 25%) in t(8;21) | Christen et al. (2019) |
| | | | D816 mutation negatively impacted on RFS in t(8;21) | Opatz et al. (2020) |
| | | | Exon 17 mutations worsen RFS in t(8;21) but not inv(16) | Ishikawa et al. (2020) |

not all, studies (Falini et al. 2005; Boissel et al. 2005; Suzuki et al. 2005). These discrepancies were soon found to reflect the strong interaction between *NPM1* and *FLT3*-ITD statuses to determine outcome. *NPM1* mutations and *FLT3*-ITD co-occur in 40–45% of the cases. The favorable outcome of *NPM1*-mutated patients is mostly restricted to those not harboring *FLT3*-ITD (Thiede et al. 2006; Döhner et al. 2005; Schlenk et al. 2008; Schnittger et al. 2005; Verhaak et al. 2005), as initially outlined by the ELN 2010 classification (Döhner et al. 2010; Mrózek et al. 2012; Röllig et al. 2011), or to those with low allelic ratios *FLT3*-ITDs as defined above (Döhner et al. 2017), while *NPM1*-mutated patients with *FLT3*-ITD with high allelic ratio (*FLT3*-ITD$^{high}$) have an outcome comparable to *NPM1*wt patients with intermediate risk disease

(Table 7.2) (Schnittger et al. 2011a; Schneider et al. 2012; Pratcorona et al. 2013).

The role of *FLT3*-ITD allelic ratio and its interaction with *NPM1* status remain an area of controversy (Daver et al. 2019; Pratz and Levis 2017; Straube et al. 2018; Boddu et al. 2019; Versluis and Hout 2017; Harada et al. 2018; How et al. 2012). The MRC group reported that *NPM1*-mutated patients with *FLT3*-ITD have an increased relapse risk and decreased survival, irrespective of the allelic ratio (Linch et al. 2014), and a recent Japanese study showed that patients with *NPM1*-mutated AML with *FLT3*-ITD$^{low}$ experienced unfavorable long-term outcomes when alloHCT was not performed in CR1 (Sakaguchi et al. 2018). Conversely, a recent analysis on the RATIFY trial, which demonstrated the beneficial effect of midostaurin added to chemotherapy for *FLT3*-mutated patients, confirmed the ELN 2017 approach on *FLT3*-ITD allelic ratio and its interaction with *NPM1* mutations. As a matter of fact, patients belonging to the three prognostic subgroups showed markedly different OS, EFS, and CIR, both in the midostaurin and in the placebo arm (Döhner et al. 2020).

Another controversial topic is the prognostic relevance of cytogenetic lesions in *NPM1*-mutated patients. These cytogenetic lesions can be found in 15–20% of patients and are typically nonrecurrent, except for trisomy 8 (Thiede et al. 2006; Verhaak et al. 2005; Haferlach et al. 2009). Most (Thiede et al. 2006; Haferlach et al. 2009) but not all (Harada et al. 2018; Micol et al. 2009; Balsat et al. 2017) studies initially suggested that these infrequent cases with abnormal karyotype behaved similarly to *NPM1*-mutated CN-AML. This led to discard normal cytogenetics as a prerequisite to class *NPM1*-mutated patients in the 2017 ELN classification (Döhner et al. 2017). However, a recent meta-analysis of 2426 *NPM1*-mutated *FLT3*-ITD$^{neg/low}$ patients showed that those with adverse-risk chromosomal abnormalities (3.4%) had significantly worse CR rate, OS, and increased relapse incidence, independently of other risk factors, thus challenging this modification (Angenendt et al. 2019).

Finally, additional co-mutation such as *IDH1/2* and *DNMT3A* plays a major role, which has yet to be fully explored (Papaemmanuil et al. 2016; Eisfeld et al. 2018) (*see below*).

### 7.5.3 CEBPA

CCAAT/enhancer binding protein α (*CEBPA*) gene mutations occur in around 10% AML of patients and have been initially associated with a favorable prognostic value (Schlenk et al. 2008; Fröhling et al. 2004; Pabst et al. 2001; Preudhomme et al. 2002; Renneville et al. 2009a). However, several reports have subsequently clarified that only patients harboring biallelic *CEBPA* (bi*CEBPA*) mutations, generally involving an N-terminal frameshift on one allele and an in-frame C-terminal mutation in the C-terminal bZIP domains, showed favorable outcomes (i.e., classical bi*CEBPA*), with 5-year OS often reaching 60–70% after intensive treatments. Conversely, single allele mutations had no prognostic impact (Metzeler et al. 2016; Wouters et al. 2009; Green et al. 2010; Fasan et al. 2014; Pastore et al. 2014a; Marceau-Renaut et al. 2015; Pabst et al. 2009; Tien et al. 2018b; Li et al. 2015; Rockova et al. 2011). Besides, single *CEBPA* mutations frequently co-occur in other well-defined AML entities, while biallelic ones define a specific AML genetic subgroup (Papaemmanuil et al. 2016; Fasan et al. 2014; Dufour et al. 2010; Konstandin et al. 2018; Taskesen et al. 2011; Grossmann et al. 2012). It should be considered that patients with atypical bi*CEBPA* mutations might not achieve results as favorable as classical cases (El-Sharkawi et al. 2018), although further validation of these findings is required. So far, no significant impact of karyotype abnormalities has emerged in this context (Fasan et al. 2014; Schlenk et al. 2013).

### 7.5.4 TP53

*TP53* mutations occur in 10–15% of AML patients. Their incidence increases with age and they are strongly associated with previous

chemo-radiotherapy exposure, CK/MK, poor response to intensive chemotherapy, and dismal prognosis (Papaemmanuil et al. 2016; Herold et al. 2020; Metzeler et al. 2016; Grossmann et al. 2012; Prassek et al. 2018; Rücker et al. 2012; Bowen et al. 2009; Haferlach et al. 2008; Kadia et al. 2016; Christiansen et al. 2016; Kihara et al. 2014; Yanada et al. 2016; Stengel et al. 2017; Ok et al. 2015; Stirewalt et al. 2001). Among patients with CK, *TP53* aberrations occur in up to 70% of the cases and worsen survival, even outweighing the role of MK (Rücker et al. 2012). This observation was recently confirmed in a large cohort of patients with myelodysplastic syndromes, including a few low blast count AMLs (International Working Group for MDS Molecular Prognostic Committee et al. 2019). As previously discussed, del(17p), leading to *TP53* inactivation, is associated with poor outcomes in AML and often co-occurs with a *TP53* mutations (Seifert et al. 2009; Rücker et al. 2012). Several studies are focusing on the impact of mono vs. biallelic *TP53* alterations, but, unlike in MDS, data available so far do not clearly demonstrate a worse outcome of patients with *TP53* biallelic involvement (Rücker et al. 2012; Stengel et al. 2017), possibly due to epigenetic mechanisms for bi-allelic TP53 silencing in patients with mono-allelic genetic inactivation (Moison et al. 2019).

Survival of *TP53*-mutated AML remains poor after alloHCT, not exceeding 10–20% at 3–5 years (Qin et al. 2017; Middeke et al. 2016; Della Porta et al. 2016). Interestingly, a recent Japanese study on a vast cohort of MDS and secondary AML patients who underwent alloHCT suggested that patients with *TP53* mutations without CK can experience fairly good long-term outcomes, while those with both aberrations have dismal results (Yoshizato et al. 2017), as already seen in the general intensively treated AML population (Papaemmanuil et al. 2016). Additional observations suggest that highly select subgroups of patients (i.e., very fit and in CR before alloHCT) can achieve long-term survival (Ciurea et al. 2018). It should be noted, however, that the majority of data come from patients with MDS and secondary AML, and it remains to be fully proven that these observations hold true in de novo AML.

### 7.5.5 *RUNX1* and *ASXL1*

*RUNX1* mutations are found in roughly 10% of AML patients—more frequently in the elderly—and have been associated with male gender, secondary AML, and intermediate-risk cytogenetics. Several studies have assessed their prognostic implications, consistently showing reduced CR rate, EFS, and OS (Kihara et al. 2014; Mendler et al. 2012; Tang et al. 2009; Gaidzik et al. 2011, 2016; Schnittger et al. 2011b; Greif et al. 2012). However, recent data suggest that the negative impact of *RUNX1* mutations might be more pronounced in secondary AML and AML with myelodysplasia-related changes, while truly de novo cases could achieve better results despite harboring this abnormality (Quesada et al. 2020; Nguyen et al. 2020; Weinberg et al. 2017). Interestingly, in the two largest studies which explored the impact of an extensive panel of somatic mutations in AML, Papaemmanuil et al. did not find an independent detrimental effect of *RUNX1* mutations on OS (Papaemmanuil et al. 2016), which conversely was significant—but only in patients <60 years—in the report by Metzeler et al. (2016) Of note, a recent study showed that multiple *RUNX1* mutations and loss of wild-type *RUNX1* are associated with a worse prognosis compared to a single mutation (Stengel et al. 2018).

*ASXL1* mutations are also more common in older age, male sex, and secondary AML and have been associated with the presence of trisomy 8. Several studies have linked this aberration with poor otcomes (Papaemmanuil et al. 2016; Grossmann et al. 2012; Devillier et al. 2015a; Pratcorona et al. 2012; Schnittger et al. 2013), although in some cases its impact was not confirmed in multivariate analyses (Metzeler et al. 2016; Fasan et al. 2014; Chou et al. 2010) or was limited to selected subgroups (Patel et al. 2012; Metzeler et al. 2011a).

Given the vast majority of studies showed an independent unfavorable prognostic impact of *RUNX1* and *ASXL1* mutations, particularly when they co-occur (Papaemmanuil et al. 2016; Stengel et al. 2018; Paschka et al. 2015), they were both incorporated in the 2017 ELN classification as

adverse risk mutations, except in cases with favorable risk abnormalities (Table 7.2) (Döhner et al. 2017).

### 7.5.6 Other Genes

A partial tandem duplication (PTD) in *KMT2A* is detected in roughly 5% of AML patients. *KMT2A*-PTDs are associated with older age and several reports have shown that this lesion is associated with unfavorable outcome (Schlenk et al. 2008; Kihara et al. 2014; Vetro et al. 2020; Schnittger et al. 2000; Döhner et al. 2002; Shiah et al. 2002; Dicker et al. 2010). However, it has not been uniformly accepted as an independent prognostic marker (Döhner et al. 2017; Grimwade et al. 2016; Bullinger et al. 2017), possibly because of the discordant result of some studies (Metzeler et al. 2016; Fasan et al. 2014; Steudel et al. 2003; Hinai et al. 2019) and the importance of the co-mutation patterns (Papaemmanuil et al. 2016; Hinai et al. 2019).

*DNMT3A* mutations, which are strongly associated with age and clonal hematopoiesis, were shown to be independently associated with unfavorable outcomes (Herold et al. 2020; Grimwade et al. 2016; Ley et al. 2010; Hou et al. 2012; Renneville et al. 2012; Thol et al. 2011; Shen et al. 2011; Ribeiro et al. 2012), but their role was not consistent among all studies as their prognostic role could be influenced by age, co-occurring molecular alterations, and possibly the type of mutations (i.e., R882 versus others) (Papaemmanuil et al. 2016; Metzeler et al. 2016; Bullinger et al. 2017; Gaidzik et al. 2013; Ahn et al. 2016; Marcucci et al. 2012). Likewise, the prognostic role of *TET2 (*Metzeler et al. 2016*;* Patel et al. 2012*;* Chou et al. 2011a*;* Gaidzik et al. 2012*;* Metzeler et al. 2011b*;* Weissmann et al. 2012*;* Nibourel et al. 2010*)* or *WT1 (*Metzeler et al. 2016*;* Patel et al. 2012*;* Virappane et al. 2008*;* Paschka et al. 2008*;* Gaidzik et al. 2009*;* Renneville et al. 2009b*)* mutations has been controversial (Döhner et al. 2017).

The clinical implications of *IDH1* and *IDH2* mutations have been debated as well (Papaemmanuil et al. 2016; Metzeler et al. 2016; Patel et al. 2012; Prassek et al. 2018; Paschka et al. 2010; Marcucci et al. 2010; Peterlin et al. 2015; Boissel et al. 2010, 2011; Chou et al. 2011b; Thol et al. 2010; Abbas et al. 2010), with a recent meta-analysis suggesting a detrimental effect of *IDH1* R132 mutations and a positive impact of *IDH2* aberrations (Xu et al. 2017). However, *IDH2* R140 and R172 mutations should not be grouped together, because they are associated with different co-mutations and clinical outcomes (Papaemmanuil et al. 2016; Boissel et al. 2011; Green et al. 2011). Of note, the role of *IDH1* single nucleotide polymorphism rs11554137 has not been consistent among different reports (Wagner et al. 2010; Ho et al. 2011). The impact of many more recurrently mutated genes in AML has been explored, but results among studies have been globally inconsistent and they do not presently have a recognized prognostic relevance (Bullinger et al. 2017). However, it should be noted that patients belonging to the genetic chromatin-spliceosome group, that is, harboring at least one mutations in splicing (*SRSF2, SF3B1,U2AF1*, and *ZRSR2*), chromatin (*STAG2, BCOR, EZH2*, *PHF6* in addition to *ASXL1*, and *KMT2A-PTD*), or in *RUNX1* in the absence of other class defining lesions, showed very unfavorable outcomes in large patient cohorts (Papaemmanuil et al. 2016; Ahn et al. 2018). Besides, several of these mutations (namely, *SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR,* and *STAG2*) were shown to be highly specific for secondary AML and define an entity with poor clinical results (Lindsley et al. 2015; Gardin et al. 2020). Nonetheless, more data are required before firm recommendations can be made for these patients.

## 7.6 Integration of Prognostic Factors

Historically, the integration of the prognostic value of cytogenetic and genetic lesions in AML has been done in a hierarchical manner. For instance, gene mutations were initially considered only in patients with normal cytogenetics. Currently, used prognostic classifications rely on a limited number of well-identified, empirically determined pairwise interactions between (cyto)

genetic lesions, as exemplified by *NPM1* and *FLT3*-ITD. The identification of mutually exclusive, class-defining "founder" cytogenetic, or molecular lesions, such as CBF translocations, or *NPM1* mutations, has set the ground for the proposal of many class-specific prognostic systems. Indeed, the pattern of co-mutations in AML is particularly complex to decipher and the prognostic impact of different genetic driver combinations is only partially known so far. Thus, with the exception of the NCCN (but not ELN) proposal to account for *KIT* status in CBF leukemias (Döhner et al. 2017; Tallman et al. 2019), none has been sufficiently validated to be implemented in routine practice (Table 7.2).

## 7.6.1 In Specific Molecular Groups

### 7.6.1.1 CBF-AML

In the cytogenetic subgroup of CBF leukemias, the role of signaling genes has been explored in several studies, most of which have focused on the prognostic influence of *KIT* aberrations, which occur in up to 20–35% of the cases (Faber et al. 2016; Ishikawa et al. 2020; Opatz et al. 2020; Duployez et al. 2016; Itzykson et al. 2018a; Eisfeld et al. 2017). The impact of *KIT* mutations has been globally inconsistent in *CBFB-MYH11* AML (Paschka et al. 2013; Care et al. 2003; Boissel et al. 2006; Riera et al. 2013; Qin et al. 2014; Paschka et al. 2006; Park et al. 2011), while they have been associated with increased relapse risk and worse OS in *RUNX1-RUNX1T1* patients in several (Boissel et al. 2006; Paschka et al. 2006; Park et al. 2011; Cairoli et al. 2006; Schnittger et al. 2006; Rücker et al. 2019; Chen et al. 2016; Kim et al. 2013), but not all (Itzykson et al. 2018a; Klein et al. 2015), reports, including some in which their impact was restricted to a subgroup of *KIT* mutations (e.g., above a certain VAF cutoff or only when present in a specific exon of the gene (Faber et al. 2016; Ishikawa et al. 2020; Opatz et al. 2020; Krauth et al. 2014; Christen et al. 2019; Duployez et al. 2016; Kim et al. 2013; Allen et al. 2013)). While NCCN recommendations take *KIT* mutations into account for *RUNX1-RUNX1T1* patients, suggesting that those cases should be entered in clinical trials and considered for alloHCT in CR1 (Tallman et al. 2019), ELN 2017 guidelines do not account for *KIT* mutations in CBF patients, since their impact is outperformed by measurable residual disease (MRD) (Döhner et al. 2017), as detailed in Chap. 18. *FLT3* aberrations are present in 10–20% of CBF leukemias (Paschka et al. 2013; Christen et al. 2019; Duployez et al. 2016) and there is some evidence (Paschka et al. 2013; Boissel et al. 2006), possibly restricted to *FLT3*-ITD$^{high}$ (Christen et al. 2019), of a negative prognostic role of these alterations. Indeed, a recent international survey on 65 AML patients with CBF-AML and *FLT3*-ITD showed inferior results compared to the general CBF population, with 4-year OS around 50% (Kayser et al. 2019). Nonetheless, this has not been consistently seen (Itzykson et al. 2018a; Santos et al. 2011). Further studies are needed to better understand the impact of *FLT3* aberrations in CBF leukemias, which could be influenced by treatments such as FLT3 inhibitors or gemtuzumab ozogamicin (Cerrano and Itzykson 2019). A few reports also suggested that *JAK2* V617F mutations might be detrimental (Christen et al. 2019; Illmer et al. 2007).

Recently, researchers have focused on the impact of additional genetic lesions belonging to chromatin modifiers/cohesin pathway, which are more prevalent in *RUNX1-RUNX1T1* compared to *CBFB-MYH11* patients (Faber et al. 2016; Duployez et al. 2016) Although these aberrations did not show an independent prognostic impact per se, (Faber et al. 2016; Duployez et al. 2016) they were associated with a poor prognosis in patients with concurrent signaling mutations, hinting at synergic cooperation between these events (Duployez et al. 2016).

### 7.6.1.2 *NPM1*-Mutated AML

The impact of the co-mutation pattern in the large group of *NPM1*-mutated AML has been extensively studied, and is emerging as one of the most important factors to define the outcome of these patients. As already discussed (see *above*), *FLT3*-ITD plays a major role, while the role of *FLT3*-TKD is debated.

The implications of the presence of *DNMT3A* mutations have been thoroughly studied by Papaemmanuil and colleagues, who found that the adverse prognostic impact of *FLT3*-ITD in *NPM1*-mutated patients was restricted to those with concurrent *DNMT3A* mutations (Papaemmanuil et al. 2016), as suggested in other reports (Patel et al. 2018; Loghavi et al. 2014; Wang et al. 2016; Bezerra et al. 2020). *DNMT3A* was able to influence the prognostic impact of other genetic profiles as well, including *NPM1:NRAS*$^{G12/13}$. Besides, Dunlap and colleagues showed that a reduced OS was associated with the combination *NPM1:DNMT3A:IDH1–2* (Dunlap et al. 2019) and Papaemmanuil et al. found that *NPM1:IDH2* patients had reduced CR and increased relapse rates (Papaemmanuil et al. 2016), consistent with some (Paschka et al. 2010), but not all (Patel et al. 2012), previous observations.

#### 7.6.1.3 bi*CEBPA* AML

Frequent co-mutations in bi*CEBPA*-mutated patients affect the *GATA2* (Greif et al. 2012) and *CSF3R* (Lavallée et al. 2016) genes, while mutations in chromatin, cohesin, and splicing genes are less frequent (Wilhelmson and Porse 2020). Mutations of the latter groups, in particular of *WT1* (Tien et al. 2018b) *or TET2* (Fasan et al. 2014; Grossmann et al. 2013a), have been associated with lower response and survival rates (Konstandin et al. 2018). Besides, some evidence suggests that the presence of *FLT3*-ITD, which is rarely found in bi*CEBPA* AML, could impact on the favorable outcomes of this entity (Green et al. 2010; Zhang et al. 2019), but this finding was not consistent in all reports (Tien et al. 2018b; Grossmann et al. 2013a). The unfavorable impact of other signaling mutations, including *CSF3R*, is even more controversial (Konstandin et al. 2018; Zhang et al. 2019; Su et al. 2018, 2019). Conversely, *GATA2* mutations were shown to exert a favorable impact in earlier reports (Grossmann et al. 2013a; Fasan et al. 2013, 2014), but this finding was not confirmed in recent studies (Su et al. 2018; Theis et al. 2016).

#### 7.6.1.4 *KMT2A*-Rearranged AML

The signaling/RAS pathway is the most frequently mutated in *KMT2A*-rearranged AML and its alterations have been shown to be associated with chemotherapy residence in experimental models (Esposito 2019). However, unlike in *KMT2A*-rearranged infant ALL (Driessen et al. 2013), no clear prognostic impact has been observed in AML (Vetro et al. 2020; Grossmann et al. 2013b). Conversely, concurrent *TP53* mutations might be associated with reduced OS (Grossmann et al. 2013b).

#### 7.6.1.5 *DEK-NUP214* AML

*FLT3*-ITD is present in roughly 70% of patients harboring *DEK-NUP214*, but its prognostic impact has been controversial in this context. While earlier data suggested a detrimental effect (Thiede et al. 2007), additional studies could not confirm this finding (Díaz-Beyá et al. 2020; Sandahl et al. 2014; Tarlock et al. 2014).

### 7.6.2 In Specific Clinical Groups

Most of our knowledge on the prognostic impact of genetic aberrations come from cohorts of younger AML patients enrolled in clinical trials. However, things might be different in biologically distinct subgroups, which are underrepresented in most studies.

#### 7.6.2.1 Older Patients

Median age of AML diagnosis isabove 65 years, but data on the prognostic impact of genetic aberrations are less abundant in older patients.The favorable prognostic role of *NPM1* mutations has been challenged in this context (Straube et al. 2018; Prassek et al. 2018; Becker et al. 2010; Lazenby et al. 2014; Juliusson et al. 2020). Some reports confirmed the relatively favorable outcome of these patients, although they rarely reached a long-term survival plateau indicative of cure (Hefazi et al. 2015; Daver et al. 2013; Büchner et al. 2009; Scholl et al. 2008). Data from the Southwest Oncology Group (SWOG) showed that isolated *NPM1*-mutated patients >65 years had unfavorable results even early after diagnosis (2 year-OS around 30%) (Ostronoff et al. 2015).The relatively favorable outcome of *NPM1*-mutated AML thus results fromtheir

chemosensitivity, andis thus dependent on treatment intensity. This illustrates the need to interpret prognosis in a given therapeutic context. This becomes challenging in a dynamic therapeutic landscape (see Chap 12).

In addition, the impact of other mutations has been controversial, including *FLT3-ITD* (Straube et al. 2018; Prassek et al. 2018; Juliusson et al. 2020; Heiblig et al. 2019). Differences in the patterns of co-mutations between older and younger patients could contribute to these differences (Prassek et al. 2018; Silva et al. 2017).

Globally, the applicability of current prognostic stratifications has been weaker in patients above 60 years (Mrózek et al. 2012; Röllig et al. 2011). Thus, specific prognostic classification systems have been developed in this population (Eisfeld et al. 2018; Itzykson et al. 2018b; Tsai et al. 2016). Recently, in a large cohort of intensively treated patients above 60 years, the ALFA group showed that the presence of secondary AML-type mutations (as defined by Lindsley et al. (2015), excluding *ASXL1*) could refine the 2017 ELN classification, identifying among intermediate-risk patients those with worse outcome whocould possibly benefit from alloHCT (Gardin et al. 2020). These new classification systems have yet to be validated in independent cohorts.

#### 7.6.2.2 Childhood AML

AML is a rare disease in children, with significant biological and clinical differences compared to adult disease. The molecular landscape of pediatric AML is different, lacking almost entirely certain aberrations relevant for adults (e.g., *DNMT3A* mutations (Bolouri et al. 2018)), but being enriched for other entities virtually absent in adults.

Acute megakaryoblast leukemia (AMKL) is not uncommon in infants and young children. While in patients with Down Syndrome (DS)—generally experiencing positive results—this entity has been associated with *GATA1* mutations and excellent long-term OS (around 90%) in recent studies (Taub et al. 2017), clinical results in non-DS patients is more heterogeneous. AMKL patients with t(1;22)(p13;q13) leading to the *RBM15-MKL1* translocation (Ma et al. 2001) generally show intermediate-to-favorable outcomes. Those harboring the *CBFA2T3-GLIS2* fusion gene, which characterizes an extremely aggressive subtype—frequent in non-DS AMKL leukemia but not limited to this entity—experience dismal outcomes (de Rooij et al. 2017; Masetti et al. 2019; Inaba et al. 2015).

CBF leukemias, which are more common among older children and adolescents, are associated with favorable prognosis, like in the adult population (Harrison et al. 2010; von Neuhoff et al. 2010). Recently, a rare entity characterized by the t(16;21)(q24;q22), resulting in the *RUNX1-CBFA2T3* fusion and whose gene expression profile resembles that of *RUNX1-RUNX1T1* AML, was shown to be associated with favorable outcomes. Conversely, a completely different entity characterized by the t(16;21)(p11;q22) translocation resulting in the fusion *FUS-ERG* has been associated with very poor survival (Noort et al. 2018).

*KMT2A* rearrangements are significantly more common in children than adults, being observed in roughly 20% of AML cases, especially in infants and young children. Globally, the outcome of *KMT2A*-rearranged AML is considered similar to that of patients not harboring this abnormality, thus intermediate (Harrison et al. 2010; von Neuhoff et al. 2010; Marceau-Renaut et al. 2018). However, this subgroup is quite heterogeneous, with some entities such as t(10;11)(p12;q23) and t(6;11) (q27;q23) being associated with poor prognosis, while others, such as t(1;11)(q21;q23), showing favorable outcomes. Of note, the positive results reported in some studies for t(9;11)(p22;q23), the most common *KMT2A* translocation, were not confirmed in a large retrospective international report (Balgobind et al. 2009, 2011).

*NPM1* mutations, which are less frequent in children compared to adults, are also relatively favorable in this context (Bolouri et al. 2018; Hollink et al. 2009). Conversely, the prognostic role of *FLT3*-ITD has been more controversial, although a detrimental effect was demonstrated in the majority of reports, especially in cases with *FLT3*-ITD$^{high}$ (Marceau-Renaut et al. 2018; Meshinchi et al. 2006; Manara et al. 2017; Shimada et al. 2018; Wu et al. 2016). The *NUP98-*

*NSD1* fusion gene, which is cryptic at conventional karyotype analysis and more frequent in children and young adults (Hollink et al. 2011; Thol et al. 2013), exerts a negative prognostic role which is significantly increased by the presence of *FLT3*-ITD, leading to CR rates below 30% and dismal long-term OS (Ostronoff et al. 2014). Indeed, this was recently confirmed by Bolouri and colleagues, who demonstrated that *FLT3*-ITD positive patients' prognosis could be stratified according to co-occurring aberrations: while those with concomitant *NPM1* mutations were confirmed to experience rather favorable outcomes, *FLT3*-ITD in association with *NUP98-NSD1* (or *WT1* mutations) was associated with reduced CR rate and dismal EFS (Bolouri et al. 2018). The role of another *NUP98* rearrangement, *NUP98-KDM5A*, which demonstrated a trend toward poor outcomes in non-DS AMKL (de Rooij et al. 2017), was explored in a recent large multinational pediatric study outside AMKL. *NUP98-KDM5A* was associated with different clinical features compared to *NUP98-NSD1,* but retained an adverse prognosis (Noort et al. 2021).

Although the impact of several—but not all—adult AML prognostic factors was often confirmed in children, including recent data on *RUNX1* mutations (Yamato et al. 2018), the performance of stratification systems developed in the adult population is less robust in pediatric patients. Recently, the French group showed that ELN 2017 classification was able to identify good risk patients but failed to separate intermediate from adverse risk ones. Conversely, the presence of *NUP98* fusions, *WT1*, *RUNX1*, and *PHF6* mutations were able to identify a poor molecular subgroup with 3-year OS below 50%, underling the need of larger studies to better clarify the impact of gene mutations in pediatric AML and to improve patients' stratification (Marceau-Renaut et al. 2018).

#### 7.6.2.3 Secondary AML

Secondary AML (sAML) occurring after an antecedent MDS (or more rarely MPN or MDS/MPN) is an entity distinct from WHO-defined therapy-related myeloid neoplasms (t-MN, when blasts are ≥20%). The WHO classification proposed to group sAML along with de novo AML presenting with myelodysplasia-related cytogenetic or morphologic changes (Arber et al. 2016), while others have attempted to identify a molecular portrait of sAML (notably mutations in *SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR,* and *STAG2*) that could then be applied to de novo AML to define "secondary-type" AML (Lindsley et al. 2015).

Secondary AML has historically been associated with unfavorable outcome (Arber et al. 2016; Kuykendall et al. 2018), but this category is heterogeneous. Response to treatment and prognosis can vary considerably among patients. Along with clinical differences (e.g., s-AML arising from myeloproliferative neoplasms is associated with worse outcome compared to AML secondary to MDS (Granfeldt Østgård et al. 2015)), the genetic profile plays a major role. Cytogenetic risk stratification remains a major determinant of outcome in sAML, although unfavorable subtypes are overrepresented compared to de novo cases. Most, but not all (Schoch et al. 2004), studies suggested that the clinical prognostic factors of AML with myelodysplasia-related changes or t-MN could lose their significance when cytogenetic risk is taken into account, outlining the importance of this parameter in this context (Devillier et al. 2015b; Armand et al. 2007; Ossenkoppele and Montesinos 2019). Specifically, favorable translocations such as t(15;17) or CBF translocations induced by anthracyclines/epipodophyllotoxins exposures retain their favorable prognosis in t-MNs (Braun et al. 2015; Heuser 2016). Other therapy-related AML, notably those induced by alkylating agents, are characterized by a high frequency of *TP53* mutations (Ok et al. 2015; Christiansen et al. 2001). Globally, adverse risk mutations have been shown to maintain their adverse impact in sAML and t-AML (Rücker et al. 2012; Devillier et al. 2015a).

#### 7.6.2.4 Relapsed AML

Even though the impact of genetic aberrations at AML relapse has not been completely explored so far, it is emerging as one of the most important predictors of response to treatment and patients' long-term outcomes (Montesinos et al. 2019). In

intensively treated patients, the role of cytogenetics has been confirmed, with patients with CBF leukemias, especially those with *CBFB-MYH11,* showing relatively high salvage rates, adverse cytogenetic abnormalities being associated with poor prognosis (Breems et al. 2005; Chevallier et al. 2011). Among gene mutations, bi*CEBPA* have been associated with relatively good salvage rates while *NPM1* mutations do not seem to exert a positive impact in this context (Schlenk et al. 2017; Bergua et al. 2016). Relapsed patients with *FLT3*-ITD have been consistently shown to obtain dismal results with conventional treatments and *IDH1* mutations have emerged as a negative prognostic factor in a recent report as well (Wattad et al. 2017). This picture will probably change with the advent of novel targeted therapies (Cerrano and Itzykson 2019). Indeed, considering the frequent changes in the molecular landscape compared to diagnosis (Greif et al. 2018), obtaining a detailed genetic reassessment at relapse before choosing the therapeutic approach is now mandatory (detailed in Chaps. 11–12).

## 7.7 Clonal Architecture

Despite significant progresses, the extensive cytogenetic and mutational characterization routinely obtained at AML diagnosis cannot comprehensively depict its biological basis, and it is not always able to accurately estimate disease behavior and response to treatments in individual patients. Thus, other aspects of AML are being explored to improve patients' stratification.

As discussed *supra, FLT3*-ITD impact strongly depends on its mutated/wild-type ratio, prompting its integration in current guidelines (Döhner et al. 2017). Besides, the clinical implications of mutational burden are emerging for several candidate genes in specific contexts. Several studies found that *KIT* and *FLT3*-ITD prognostic impact in CBF leukemias was restricted to those above a certain burden threshold (Christen et al. 2019; Duployez et al. 2016; Allen et al. 2013), likewise *FLT3*-TKD or *NRAS/KRAS* mutations in other reports (Mead et al. 2007; Duployez et al. 2016). A recent study by Patel and colleagues suggested that *NPM1* mutational burden could also be important. The authors showed that patients with *NPM1* mutations having a variant allele frequency (VAF) above the upper quartile had a significantly reduced OS, independently of other baseline known prognostic variables (Patel et al. 2018). However, this finding has been mitigated (Linch et al. 2020), or infirmed (Abbas et al. 2019), in the following reports, suggesting that *NPM1* VAF impact might be mostly due to co-mutations and/or a reflection of higher leukemia burden. Several reports explored the impact of the allele burden of other mutations, including *DNMT3A (*Yuan et al. 2019*)*, *TP53 (*Prochazka et al. 2019*)*, and *ASXL1 (*Sasaki et al. 2020*)*, without being validated so far. With the possible exception of *FLT3*-ITD, further validation and better standardization methods (Touw and Sanders 2020) are thus necessary to account for mutational burden for daily prognostic purposes.

Mounting evidence suggests that a better understanding of clonal architecture may refine risk stratification. Intra-tumor heterogeneity is associated with unfavorable outcomes in many cancers (Andor et al. 2016), but its precise role remains to be defined in AML. Indeed, a higher number of driver lesions has been proven to be a marker of poor prognosis (Papaemmanuil et al. 2016; Wakita et al. 2016). However, whether this unfavorable outcome has to be attributed to the additive fitness of driver lesions accumulated in a single clone or to the presence of clonal heterogeneity is not clear. In CBF leukemias, the presence of clonal interference, that is, the co-existence of clones sharing a common ancestor and harboring independent lesions targeting the same pathway—signaling in this case—was associated with reduced event-free survival, independent of other baseline clinical variables and MRD (Itzykson et al. 2018a). Besides, a higher number of clones, as assessed by conventional cytogenetic, was shown to worsen prognosis in AML, but mainly in the context of complex karyotype (Bochtler et al. 2013; Medeiros et al. 2015), while clonal dominance, as assessed by the Shannon diversity Index (Maley et al. 2017), may

worsen prognosis (Cerrano et al. 2021). Further efforts are needed to fully understand the impact of clonal architecture and dynamics on AML behavior.

## 7.8 Other Biological Risk Factors

Additional biological factors have been explored in AML, with a vast number of studies outlying their prognostic implications. Although the majority of the data we present below do not affect the clinical management of AML patients in current practice, with the implementation of more comprehensive diagnostic platforms some of the risk factors described below might soon be integrated in prognostic stratification algorithms.

### 7.8.1 Gene Expression

Several studies have focused on the impact of the over-expression of certain genes. One of the most extensively studied is *MECOM* (or *EVI1*), the hallmark of inv(3)/t(3;3), which is overexpressed also in up to 10% of AML cases that do not carry any 3q aberrations, most commonly in those harboring monosomy 7 and 11q23 abnormalitis (Hinai and Valk 2016). High *MECOM* expression was associated with unfavorable outcomes in several studies, especially in CN (Barjesteh van Waalwijk van Doorn-Khosrovani et al. 2003; Gröschel et al. 2010; Lugthart et al. 2008; Valk et al. 2004) and *KMT2A*-rearranged AML (Gröschel et al. 2013), thus assigning patients to the adverse risk group according to some authors (Cornelissen and Blaise 2016). The overexpression of other genes (Damm et al. 2011), including *BAALC (*Weber et al. 2014*;* Torrebadell et al. 2018*;* Schwind et al. 2010a*;* Baldus et al. 2006*;* Langer et al. 2008*)*, *ERG (*Schwind et al. 2010a*;* Metzeler et al. 2009*;* Marcucci et al. 2005b, 2007*)*, and *MN1* (Langer et al. 2009), has been linked to adverse outcome as well, but their independent prognostic value has been questioned due to the correlations with relevant genetic alterations (Weber et al. 2016). They are not employed to stratify patients' risk by current guidelines (Döhner et al. 2017; Tallman et al. 2019).

Additional efforts have been made to derive gene expression profiles (GEP) to stratify AML patients. Among many signatures and scores proposed (Gentles et al. 2010; Jung et al. 2015; Levine et al. 2015; Metzeler et al. 2008; Eppert et al. 2011; Marcucci et al. 2014; Bullinger et al. 2004; Li et al. 2013), Ng and colleagues established a panel of 17 genes defining a "stemness" signature called LSC17 (i.e., indicating overrepresented gene sets with stem cell-like properties), the expression of which was highly indicative of poor clinical outcomes in multiple AML cohorts (Ng et al. 2016; Duployez et al. 2019), even in the context of ELN 2017 classification (Bill et al. 2020). In this regard, it has been suggested the applicability and performance of genetic signatures might be improved if restricted to defined patient subgroups (Wiggers et al. 2019). Interestingly, Herold and colleagues recently validated a score integrating 29 gene expression markers and the MRC cytogenetic risk groups. This score which was able to accurately predict resistance to induction chemotherapy, outperforming currently available models (Herold et al. 2018).

In addition, also microRNA expression might play a role in CN-AML stratification (Marcucci et al. 2008). The up-regulation of miR-181a was shown to be associated with favorable prognosis, whereas higher expression of miR-155, miR-196b, and miR-644 was independently associated with shorter overall survival (Schwind et al. 2010b; Marcucci et al. 2013; Díaz-Beyá et al. 2014). Expression signatures of large non-coding RNAs, such as long intergenic non-coding RNAs (lincRNA) involved in gene expression regulation and cell lineage and differentiation, have demonstrated added prognostic value to standard cytogenetic and genetic molecular stratification (Beck et al. 2018).

### 7.8.2 Flow Cytometry

Flow cytometry has entered routine clinical practice in AML diagnosis, almost completely replacing cytochemical stains. Besides, the prognostic implications of the immunophenotypic charac-

terization of AML blasts have been extensively explored.

For instance, the expression of CD25 (IL-2 receptor alpha) has been associated with reduced response to chemotherapy and inferior survival (Nakase et al. 1997; Fujiwara et al. 2017) and CD105 was shown to be associated with unfavorable outcomes in AML (Kauer et al. 2019), including in the HCT setting (Märklin et al. 2020). Many additional immunophenotypic markers have been shown to exert a meaningful prognostic impact, including but not limited to CD7, CD56, CD82, CD93, CXCR4, CD262, CD120a, hMICL, CD96,CD11b, CD117, CD34, CD13, CD14, CD15 (Chisini et al. 2017), some of these recently reviewed by Costa et al. (2017), but these and the aforementioned findings have neither been consistent nor been robustly validated in adequately sized independent cohorts.

The combination of multiple immunophenotypic markers could also be prognostically informative. Initial studies suggested that patterns of myeloid lineage differentiation could impact on outcomes (Repp et al. 2003); however, results have been inconsistent (Mason et al. 2006). Recently, the co-expression of CD56, CD123, CD4 was shown to identify a subgroup of *NPM1*-mutated patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN)-like AML with poor prognosis, an intriguing finding which needs to be validated (Minetto et al. 2018).

Globally, the prognostic value of immunophenotype has been difficult to reproduce, probably because of the size and heterogeneity of patient cohorts, and difficulties to standardize MFC in a multicentric way. Besides, the association of immunophenotypic markers with relevant genetic alterations interferes with their prognostic impact (van Solinge et al. 2018), which has not been firmly proven to add independent information so far.

### 7.8.3 Proteomic

The impact of protein expression in AML has been studied for more the 20 years, with earlier reports focusing mostly on the impact of proteins involved in chemotherapy resistance, such as P-glycoprotein (the *MDR1* gene product), MRP1 (multidrug resistance-associated protein 1), and LRP (lung resistance protein). The majority of these reports associated the hyperexpression of these proteins with worse prognosis, especially for P-glycoprotein, albeit with some inconsistencies (Pirker et al. 1991; Leith et al. 1997, 1999; Tsuji et al. 2000; Legrand et al. 1998; Laupeze et al. 2002).

In addition, several studies assessed the impact of the hyperexpression of anti-apoptotic proteins (e.g., BCL-2 and survivin) or pro-apoptotic ones (e.g., measuring BAX levels or BAX/BCL2 ratio) suggesting they can affect outcomes in opposite ways, although with some contrasting results (Ong et al. 2000; Lauria et al. 1997; Del Poeta et al. 2003; Karakas et al. 2002; Carter et al. 2012; Venditti et al. 2004; Zhou et al. 2019a).

Subsequent functional protein studies showed that signal transduction pathways activation had an adverse effect on prognosis (Kornblau et al. 2006), and that specific functional proteomic profiles correlated with known morphologic features, cytogenetics, and outcome (Kornblau et al. 2009, 2010a, 2011).

Investigators also explored the role of circulating cytokines and chemokines, which were shown to be differently expressed in AML compared to healthy controls and whose patterns of expression might have prognostic relevance (Kornblau et al. 2010b). Many of these studies were performed before the genomics era. Thus, the independence prognostic value of protein expression in AML remains to be determined.

### 7.8.4 DNA Methylation

Deregulation of DNA methylation plays a key role in AML pathogenesis, and genes involved in its regulations (i.e., *DNMT3A, TET2, IDH1/2*) are among the most frequently mutated in AML. Along with these gene mutations (discussed *supra*), several studies have explored the clinical and prognostic implications of DNA methylation patterns. Unsupervised clustering analysis demonstrated that some cytogenetic sub-

groups (e.g., CBF leukemias) are associated with distinct epigenetic modifications. Besides, DNA methylation signatures could also sub-stratify large genetic groups, such as *NPM1*-mutated AML, possibly identifying new clinically relevant disease entities (The Cancer Genome Atlas Research Network 2013; Bullinger et al. 2010; Figueroa et al. 2010).

Aberrant DNA methylation was shown to be independently associated with outcomes (Deneberg et al. 2010; Li et al. 2016), and specific quantitative methylation patterns could give significant prognostic information. Further studies suggested that aberrant methylation of individual (Deneberg et al. 2010; Lin et al. 2011; Yang et al. 2019) or multiple genes (Marcucci et al. 2014; Figueroa et al. 2010; Deneberg et al. 2011; Jost et al. 2014) was associated with clinical outcomes.

In addition, the level of hydroxy-methylation, measured by 5-hydroxymethylcytosine levels, was shown to offer meaningful prognostic information (Kroeze et al. 2014), although these findings need validation.

Beyond clinical validation, simple and reliable methylation assays are warranted before these potential biomarkers enter yet clinical practice. Recently, Luskin and colleagues developed a microsphere-based assay for simultaneous assessment of DNA methylation status at multiple loci and generated, in relatively large AML cohort, a methylation-based risk score (M-score), which was independently associated with CR and OS probability, and validated in independent cohorts (Luskin et al. 2016; DiNardo et al. 2017). This approach, if confirmed robust in additional studies, might be implemented in routine AML diagnostic panels.

## 7.9 Global Risk Assessment Strategies

Currently available (cyto)genetic prognostic stratification models are simple and provide reliable prognostic stratification (Table 7.2). Their performance has improved over time. Indeed, ELN 2017 classification has been validated, and was shown to be globally superior to previous stratification models (Döhner et al. 2017; Boddu et al. 2019; Harada et al. 2018). Further improvements to ELN 2017 could be brought by the inclusion of additional genes on its backbone (Herold et al. 2020; Gardin et al. 2020).

However, clinical parameters, such as age, WBC count, performance status, or previous hematologic malignancies, exert a meaningful prognostic impact and interact with genetic parameters to influence patients' outcome (Papaemmanuil et al. 2016). Recommendations for alloHCT in CR1 are starting to incorporate most of these factors and weighting them against the risk of non-relapse mortality in an integrated system aiming to develop a tailored approach to the individual patient (Cornelissen and Blaise 2016; Cornelissen et al. 2012).

To integrate cytogenetic, molecular, and clinical factors in a more objective way, different scoring systems have been proposed (Pastore et al. 2014b; Stölzel et al. 2011; Zhou et al. 2019b; Malagola et al. 2011), but they are not able to keep up with complex and frequently changing molecular data and their use is not widespread. Indeed, the comparison of various risk stratification tools based on genetics and/or gene expression profiling revealed that several of them can add significantly to the current prognostic models (Wang et al. 2017), but it has been difficult to incorporate them in clinical practice.

It is now clear that approaches based on a hierarchical, step-by-step integration of (cyto)genetic lesions are currently reaching their limit. First, not all gene lesions may have the same impact. This is well known for *FLT3* (ITD vs TKD) or *KMT2A* (fusions vs PTD, fusion depending on partner). Other examples may include *DNMT3A* (R882 vs others) (Peterlin et al. 2015) or *KIT* (exon 8 vs 17) (Paschka et al. 2013). Second, three-gene interactions have recently been reported to be of major importance in patients stratification (Papaemmanuil et al. 2016; Bezerra et al. 2020).

To overcome these limitations, two approaches have been undertaken, the first relying on the integration of (cyto)genetic lesions into a global "clonal architecture" of each AML to derive prog-

nosis (see *supra*). The second relies on machine learning approaches to integrate all available prognostic information layers, agnostic to biological studies on specific genetic interactions. Gerstung and colleagues recently reported on a "knowledge bank approach" (Gerstung et al. 2017) able to improve OS prediction compared to current risk classifications, thanks to the use of matched genomic–clinical data derived from over 1500 AML patients (Papaemmanuil et al. 2016). Importantly, this multistage model was able to predict the probability of different causes of mortality in each patient (i.e., death without remission, death after relapse, death without relapse), and to weight the impact of alloHCT on these probabilities. The use of this system might significantly impact on patients' care, and the authors estimated that this tailored approach could reduce the number of alloHCT by 20–25%, while maintaining OS rates. An online tool, which allows an accurate prediction even if some of the data originally used for the development of the model are missing, was also developed (https://cancer.sanger.ac.uk/aml-multistage). The performance of this "knowledge bank" approach was recently validated in the real life setting (Huet et al. 2018) and could possibly be combined with ELN2017 risk stratification to optimize indications of alloHCT in CR1 (Fenwarth et al. 2019). Knowledge banks could optimize personally tailored therapeutic decisions; however, they require frequent updating. As new effective drugs are becoming available (Cerrano and Itzykson 2019), the survival estimation of a given patient might become inaccurate if the knowledge bank relies only on data of patients treated with "3 + 7" like traditional chemotherapy program. Besides, inclusive cohorts are necessary, not to underrepresent certain subgroups (e.g., elderly patients less often enrolled in clinical trials) and all the important prognostic factors identified should ideally be considered, including recently discovered ones (Walker et al. 2019; Nibourel et al. 2017), stressing the need for constant update. Finally, such global risk assessment strategies will increasingly rely on MRD (see Chap. 18), which have yet to be implemented in these models (Schuurhuis et al. 2018; Estey and Gale 2017; Patkar et al. 2019). Large cohorts are required to accurately estimate the impact of rare co-mutational patterns, as discussed *supra.* International consortia, such as the European Union funded HARMONY project, will likely be instrumental to that prospect (Bullinger et al. 2019). Such "big data" analyses including many layers of information are hoped to be a turning point on the road toward precision medicine in AML.

## References


Abaza Y, Cortes J, Ravandi F et al (2018) Prognostic significance of hyperdiploidy in adult acute myeloid leukemia. Am J Hematol 93(11):E357–E360

Abbas S, Lugthart S, Kavelaars FG et al (2010) Acquired mutations in the genes encoding IDH1 and IDH2 both are recurrent aberrations in acute myeloid leukemia: prevalence and prognostic value. Blood 116(12):2122–2126

Abbas HA, Ravandi F, Loghavi S et al (2019) NPM1 mutant variant allele frequency correlates with leukemia burden but does not provide prognostic information in NPM1-mutated acute myeloid leukemia. Am J Hematol 94(6):E158–E160

Ahn J-S, Kim H-J, Kim Y-K et al (2016) DNMT3A R882 mutation with FLT3-ITD positivity is an extremely poor prognostic factor in patients with normal-karyotype acute myeloid leukemia after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 22(1):61–70

Ahn J-S, Kim H-J, Kim Y-K et al (2018) Assessment of a new genomic classification system in acute myeloid leukemia with a normal karyotype. Oncotarget 9(4):4961–4968

Allen C, Hills RK, Lamb K et al (2013) The importance of relative mutant level for evaluating impact on outcome of KIT, FLT3 and CBL mutations in core-binding factor acute myeloid leukemia. Leukemia 27(9):1891–1901

Andor N, Graham TA, Jansen M et al (2016) Pan-cancer analysis of the extent and consequences of intratumor heterogeneity. Nat Med 22(1):105–113

Angenendt L, Röllig C, Montesinos P et al (2019) Chromosomal abnormalities and prognosis in NPM1-mutated acute myeloid Leukemia: a pooled analysis of individual patient data from nine international cohorts. JCO. 37(29):2632–2642

Appelbaum FR, Gundacker H, Head DR et al (2006a) Age and acute myeloid leukemia. Blood 107(9):3481–3485

Appelbaum FR, Kopecky KJ, Tallman MS et al (2006b) The clinical spectrum of adult acute myeloid leukaemia associated with core binding factor translocations. Br J Haematol 135(2):165–173

Arber DA, Orazi A, Hasserjian R et al (2016) The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 127(20):2391–2405

Armand P, Kim HT, DeAngelo DJ et al (2007) Impact of cytogenetics on outcome of de novo and therapy-related AML and MDS after allogeneic transplantation. Biol Blood Marrow Transplant 13(6):655–664

Arreba-Tutusaus P, Mack T, Bullinger L et al (2016) Impact of FLT3-ITD location on sensitivity to TKI-therapy in vitro and in vivo. Leukemia 30(5):1220–1225

Bacher U, Haferlach C, Kern W, Haferlach T, Schnittger S (2008) Prognostic relevance of FLT3-TKD mutations in AML: the combination matters—an analysis of 3082 patients. Blood 111(5):2527–2537

Baldus CD, Thiede C, Soucek S et al (2006) BAALC expression and FLT3 internal tandem duplication mutations in acute myeloid leukemia patients with normal cytogenetics: prognostic implications. J Clin Oncol 24(5):790–797

Balgobind BV, Raimondi SC, Harbott J et al (2009) Novel prognostic subgroups in childhood 11q23/MLL-rearranged acute myeloid leukemia: results of an international retrospective study. Blood 114(12):2489–2496

Balgobind BV, Zwaan CM, Pieters R, Van den Heuvel-Eibrink MM (2011) The heterogeneity of pediatric MLL-rearranged acute myeloid leukemia. Leukemia 25(8):1239–1248

Balsat M, Renneville A, Thomas X et al (2017) Postinduction minimal residual disease predicts outcome and benefit from allogeneic stem cell transplantation in acute myeloid leukemia with *NPM1* mutation: a study by the Acute Leukemia French Association Group. J Clin Oncol 35(2):185–193

Barjesteh van Waalwijk van Doorn-Khosrovani S, Erpelinck C, van Putten WLJ et al (2003) High EVI1 expression predicts poor survival in acute myeloid leukemia: a study of 319 de novo AML patients. Blood 101(3):837–845

Beck D, Thoms JAI, Palu C et al (2018) A four-gene LincRNA expression signature predicts risk in multiple cohorts of acute myeloid leukemia patients. Leukemia 32(2):263–272

Becker H, Marcucci G, Maharry K et al (2010) Favorable prognostic impact of NPM1 mutations in older patients with cytogenetically normal de novo acute myeloid leukemia and associated gene- and microRNA-expression signatures: a Cancer and Leukemia Group B study. J Clin Oncol 28(4):596–604

Bergua JM, Montesinos P, Martinez-Cuadrón D et al (2016) A prognostic model for survival after salvage treatment with FLAG-Ida +/− gemtuzumab-ozogamicine in adult patients with refractory/relapsed acute myeloid leukaemia. Br J Haematol 174(5):700–710

Bezerra MF, Lima AS, Piqué-Borràs M-R et al (2020) Co-occurrence of DNMT3A, NPM1, FLT3 mutations identifies a subset of acute myeloid leukemia with adverse prognosis. Blood 135(11):870–875

Bhatnagar B, Blachly JS, Kohlschmidt J et al (2016) Clinical features and gene- and microRNA-expression patterns in adult acute leukemia patients with t(11;19)(q23;p13.1) and t(11;19)(q23;p13.3). Leukemia 30(7):1586–1589

Bhatt VR (2019) Personalizing therapy for older adults with acute myeloid leukemia: role of geriatric assessment and genetic profiling. Cancer Treat Rev 75:52–61

Bill M, Nicolet D, Kohlschmidt J et al (2020) Mutations associated with a 17-gene leukemia stem cell score and the score's prognostic relevance in the context of the European LeukemiaNet classification of acute myeloid leukemia. Haematologica 105(3):721–729

Blau O, Berenstein R, Sindram A, Blau IW (2013) Molecular analysis of different FLT3-ITD mutations in acute myeloid leukemia. Leuk Lymphoma 54(1):145–152

Bloomfield CD, Archer KJ, Mrózek K et al (2002) 11q23 balanced chromosome aberrations in treatment-related myelodysplastic syndromes and acute leukemia: report from an international workshop. Genes Chromosomes Cancer 33(4):362–378

Bochtler T, Stölzel F, Heilig CE et al (2013) Clonal heterogeneity as detected by metaphase karyotyping is an indicator of poor prognosis in acute myeloid leukemia. J Clin Oncol 31(31):3898–3905

Bochtler T, Granzow M, Stölzel F et al (2017) Marker chromosomes can arise from chromothripsis and predict adverse prognosis in acute myeloid leukemia. Blood 129(10):1333–1342

Boddu P, Kantarjian H, Borthakur G et al (2017) Co-occurrence of FLT3-TKD and NPM1 mutations defines a highly favorable prognostic AML group. Blood Adv 1(19):1546–1550

Boddu P, Gurguis C, Sanford D et al (2018) Response kinetics and factors predicting survival in core-binding factor leukemia. Leukemia 32(12):2698–2701

Boddu PC, Kadia TM, Garcia-Manero G et al (2019) Validation of the 2017 European LeukemiaNet classification for acute myeloid leukemia with NPM1 and FLT3-internal tandem duplication genotypes. Cancer 125(7):1091–1100

Boissel N, Renneville A, Biggio V et al (2005) Prevalence, clinical profile, and prognosis of NPM mutations in AML with normal karyotype. Blood 106(10):3618–3620

Boissel N, Leroy H, Brethon B et al (2006) Incidence and prognostic impact of c-kit, FLT3, and Ras gene mutations in core binding factor acute myeloid leukemia (CBF-AML). Leukemia 20(6):965–970

Boissel N, Nibourel O, Renneville A et al (2010) Prognostic impact of isocitrate dehydrogenase enzyme isoforms 1 and 2 mutations in acute myeloid leukemia: a study by the Acute Leukemia French Association Group. J Clin Oncol 28(23):3717–3723

Boissel N, Nibourel O, Renneville A et al (2011) Differential prognosis impact of IDH2 mutations in cytogenetically normal acute myeloid leukemia. Blood 117(13):3696–3697

Bolouri H, Farrar JE, Triche T et al (2018) The molecular landscape of pediatric acute myeloid leukemia reveals

recurrent structural alterations and age-specific mutational interactions. Nat Med 24(1):103–112
Bonanad S, De la Rubia J, Gironella M et al (2015) Development and psychometric validation of a brief comprehensive health status assessment scale in older patients with hematological malignancies: the GAH scale. J Geriatr Oncol 6(5):353–361
Bowen D, Groves MJ, Burnett AK et al (2009) TP53 gene mutation is frequent in patients with acute myeloid leukemia and complex karyotype, and is associated with very poor prognosis. Leukemia 23(1):203–206
Bower H, Andersson TM-L, Björkholm M et al (2016) Continued improvement in survival of acute myeloid leukemia patients: an application of the loss in expectation of life. Blood Cancer J 6(2):e390
Braun T, Cereja S, Chevret S et al (2015) Evolving characteristics and outcome of secondary acute promyelocytic leukemia (APL): a prospective analysis by the French-Belgian-Swiss APL Group. Cancer 121(14):2393–2399
Breems DA, Van Putten WLJ, Huijgens PC et al (2005) Prognostic index for adult patients with acute myeloid leukemia in first relapse. J Clin Oncol 23(9):1969–1978
Breems DA, Van Putten WLJ, De Greef GE et al (2008) Monosomal karyotype in acute myeloid leukemia: a better indicator of poor prognosis than a complex karyotype. J Clin Oncol 26(29):4791–4797
Büchner T, Berdel WE, Haferlach C et al (2009) Age-related risk profile and chemotherapy dose response in acute myeloid leukemia: a study by the German Acute Myeloid Leukemia Cooperative Group. J Clin Oncol 27(1):61–69
Bullinger L, Döhner K, Bair E et al (2004) Use of gene-expression profiling to identify prognostic subclasses in adult acute myeloid leukemia. N Engl J Med 350(16):1605–1616
Bullinger L, Ehrich M, Döhner K et al (2010) Quantitative DNA methylation predicts survival in adult acute myeloid leukemia. Blood 115(3):636–642
Bullinger L, Döhner K, Döhner H (2017) Genomics of acute myeloid leukemia diagnosis and pathways. J Clin Oncol 35(9):934–946
Bullinger L, Valk P, Versluis J et al (2019) Harmony alliance: European public-private data collection leads the way—first results of the "proof-of-principle" study in acute myeloid leukemia: PS1003. HemaSphere 3:451
Burnett AK, Russell NH, Hills RK et al (2013) Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the Medical Research Council AML15 trial. J Clin Oncol 31(27):3360–3368
Byrd JC, Weiss RB, Arthur DC et al (1997) Extramedullary leukemia adversely affects hematologic complete remission rate and overall survival in patients with t(8;21)(q22;q22): results from Cancer and Leukemia Group B 8461. J Clin Oncol 15(2):466–475
Byrd JC, Mrózek K, Dodge RK et al (2002) Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461) presented in part at the 43rd annual meeting of the American Society of Hematology, Orlando, FL, December 10, 2001, and published in abstract form.59. Blood 100(13):4325–4336
Cairo MS, Bishop M (2004) Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 127(1):3–11
Cairoli R, Beghini A, Grillo G et al (2006) Prognostic impact of c-KIT mutations in core binding factor leukemias: an Italian retrospective study. Blood 107(9):3463–3468
Canaani J, Labopin M, Socié G et al (2017) Long term impact of hyperleukocytosis in newly diagnosed acute myeloid leukemia patients undergoing allogeneic stem cell transplantation: an analysis from the acute leukemia working party of the EBMT: Canaani et al. Am J Hematol 92(7):653–659
Canaani J, Labopin M, Itälä-Remes M et al (2019) Prognostic significance of recurring chromosomal abnormalities in transplanted patients with acute myeloid leukemia. Leukemia 33(8):1944–1952
Cannas G, Pautas C, Raffoux E et al (2012) Infectious complications in adult acute myeloid leukemia: analysis of the Acute Leukemia French Association-9802 prospective multicenter clinical trial. Leuk Lymphoma 53(6):1068–1076
Care RS, Valk PJM, Goodeve AC et al (2003) Incidence and prognosis of c-KIT and FLT3 mutations in core binding factor (CBF) acute myeloid leukaemias. Br J Haematol 121(5):775–777
Carter BZ, Qiu Y, Huang X et al (2012) Survivin is highly expressed in CD34+38− leukemic stem/progenitor cells and predicts poor clinical outcomes in AML. Blood 120(1):173–180
Cerrano M, Itzykson R (2019) New treatment options for acute myeloid leukemia in 2019. Curr Oncol Rep 21(2):16
Cerrano M, Duchmann M, Kim R et al (2021) Clonal dominance is an adverse prognostic factor in acute myeloid leukemia treated with intensive chemotherapy. Leukemia 35(3):712–723
Chang H, Brandwein J, Yi Q-L et al (2004) Extramedullary infiltrates of AML are associated with CD56 expression, 11q23 abnormalities and inferior clinical outcome. Leuk Res 28(10):1007–1011
Chen Y, Kantarjian H, Pierce S et al (2013) Prognostic significance of 11q23 aberrations in adult acute myeloid leukemia and the role of allogeneic stem cell transplantation. Leukemia 27(4):836–842
Chen W, Xie H, Wang H et al (2016) Prognostic significance of KIT mutations in core-binding factor acute myeloid leukemia: a systematic review and meta-analysis. PLoS One 11(1):e0146614
Chen F, Sun J, Yin C et al (2019) Impact of FLT3-ITD allele ratio and ITD length on therapeutic outcome in cytogenetically normal AML patients without NPM1 mutation. Bone Marrow Transplant 55(4):740–748
Cheng C-L, Li C-C, Hou H-A et al (2015) Risk factors and clinical outcomes of acute myeloid leukaemia

with central nervous system involvement in adults. BMC Cancer 15(1):344
Cher CY, Leung GMK, Au CH et al (2016) Next-generation sequencing with a myeloid gene panel in core-binding factor AML showed KIT activation loop and TET2 mutations predictive of outcome. Blood Cancer J 6(7):e442
Chevallier P, Labopin M, Turlure P et al (2011) A new leukemia prognostic scoring system for refractory/relapsed adult acute myelogeneous leukaemia patients: a GOELAMS study. Leukemia 25(6):939–944
Chilton L, Hills RK, Harrison CJ et al (2014) Hyperdiploidy with 49-65 chromosomes represents a heterogeneous cytogenetic subgroup of acute myeloid leukemia with differential outcome. Leukemia 28(2):321–328
Chisini M, Stefanizzi C, Ceglie T et al (2017) Independent prognostic impact of CD15 on complete remission achievement in patients with acute myeloid leukemia. Hematol Oncol 35(4):804–809
Chou W-C, Huang H-H, Hou H-A et al (2010) Distinct clinical and biological features of de novo acute myeloid leukemia with additional sex comb-like 1 (ASXL1) mutations. Blood 116(20):4086–4094
Chou W-C, Chou S-C, Liu C-Y et al (2011a) TET2 mutation is an unfavorable prognostic factor in acute myeloid leukemia patients with intermediate-risk cytogenetics. Blood 118(14):3803–3810
Chou W-C, Lei W-C, Ko B-S et al (2011b) The prognostic impact and stability of isocitrate dehydrogenase 2 mutation in adult patients with acute myeloid leukemia. Leukemia 25(2):246–253
Christen F, Hoyer K, Yoshida K et al (2019) Genomic landscape and clonal evolution of acute myeloid leukemia with t(8;21): an international study on 331 patients. Blood 133(10):1140–1151
Christiansen DH, Andersen MK, Pedersen-Bjergaard J (2001) Mutations with loss of heterozygosity of p53 are common in therapy-related myelodysplasia and acute myeloid leukemia after exposure to alkylating agents and significantly associated with deletion or loss of 5q, a complex karyotype, and a poor prognosis. J Clin Oncol 19(5):1405–1413
Christiansen DH, Andersen MK, Pedersen-Bjergaard J (2016) Mutations with loss of heterozygosity of p53 are common in therapy-related myelodysplasia and acute myeloid leukemia after exposure to alkylating agents and significantly associated with deletion or loss of 5q, a complex karyotype, and a poor prognosis. J Clin Oncol 19(5):1405–1413
Ciurea SO, Chilkulwar A, Saliba RM et al (2018) Prognostic factors influencing survival after allogeneic transplantation for AML/MDS patients with TP53 mutations. Blood 131(26):2989–2992
Cornelissen JJ, Blaise D (2016) Hematopoietic stem cell transplantation for patients with AML in first complete remission. Blood 127(1):62–70
Cornelissen JJ, Gratwohl A, Schlenk RF et al (2012) The European LeukemiaNet AML working party consensus statement on allogeneic HCT for patients with AML in remission: an integrated-risk adapted approach. Nat Rev Clin Oncol 9(10):579–590
Costa AFO, Menezes DL, Pinheiro LHS et al (2017) Role of new Immunophenotypic markers on prognostic and overall survival of acute myeloid leukemia: a systematic review and meta-analysis. Sci Rep 7(1):4138
Creutzig U, Zimmermann M, Reinhardt D et al (2016) Changes in cytogenetics and molecular genetics in acute myeloid leukemia from childhood to adult age groups. Cancer 122(24):3821–3830
Damm F, Heuser M, Morgan M et al (2011) Integrative prognostic risk score in acute myeloid leukemia with normal karyotype. Blood 117(17):4561–4568
Daver N, Liu Dumlao T, Ravandi F et al (2013) Effect of NPM1 and FLT3 mutations on the outcomes of elderly patients with acute myeloid leukemia receiving standard chemotherapy. Clin Lymphoma Myeloma Leuk 13(4):435–440
Daver N, Schlenk RF, Russell NH, Levis MJ (2019) Targeting FLT3 mutations in AML: review of current knowledge and evidence. Leukemia 33(2):299–312
de Jonge HJM, Valk PJM, de Bont ESJM et al (2011) Prognostic impact of white blood cell count in intermediate risk acute myeloid leukemia: relevance of mutated NPM1 and FLT3-ITD. Haematologica 96(9):1310–1317
de Rooij JDE, Branstetter C, Ma J et al (2017) Pediatric non–Down syndrome acute megakaryoblastic leukemia is characterized by distinct genomic subsets with varying outcomes. Nat Genet 49(3):451–456
De Stefano V, Sorà F, Rossi E et al (2005) The risk of thrombosis in patients with acute leukemia: occurrence of thrombosis at diagnosis and during treatment. J Thromb Haemost 3(9):1985–1992
Del Poeta G, Venditti A, Del Principe MI et al (2003) Amount of spontaneous apoptosis detected by Bax/Bcl-2 ratio predicts outcome in acute myeloid leukemia (AML). Blood 101(6):2125–2131
Del Principe MI, Buccisano F, Soddu S et al (2018) Involvement of central nervous system in adult patients with acute myeloid leukemia: incidence and impact on outcome. Semin Hematol 55(4):209–214
Della Porta MG, Gallì A, Bacigalupo A et al (2016) Clinical effects of driver somatic mutations on the outcomes of patients with myelodysplastic syndromes treated with allogeneic hematopoietic stem-cell transplantation. J Clin Oncol 34(30):3627–3637
Deneberg S, Grövdal M, Karimi M et al (2010) Gene-specific and global methylation patterns predict outcome in patients with acute myeloid leukemia. Leukemia 24(5):932–941
Deneberg S, Guardiola P, Lennartsson A et al (2011) Prognostic DNA methylation patterns in cytogenetically normal acute myeloid leukemia are predefined by stem cell chromatin marks. Blood 118(20):5573–5582
Devillier R, Mansat-De Mas V, Gelsi-Boyer V et al (2015a) Role of ASXL1 and TP53 mutations in the molecular classification and prognosis of acute myeloid leuke-

mias with myelodysplasia-related changes. Oncotarget 6(10):8388–8396
Devillier R, Gelsi-Boyer V, Murati A et al (2015b) Prognostic significance of myelodysplasia-related changes according to the WHO classification among ELN-intermediate-risk AML patients. Am J Hematol 90(1):E22–E24
Díaz-Beyá M, Brunet S, Nomdedéu J et al (2014) MicroRNA expression at diagnosis adds relevant prognostic information to molecular categorization in patients with intermediate-risk cytogenetic acute myeloid leukemia. Leukemia 28(4):804–812
Díaz-Beyá M, Labopin M, Maertens J et al (2020) Allogeneic stem cell transplantation in AML with t(6;9)(p23;q34);DEK-NUP214 shows a favourable outcome when performed in first complete remission. Br J Haematol 189(5):920–925
Dicker F, Haferlach C, Sundermann J et al (2010) Mutation analysis for RUNX1, MLL-PTD, FLT3-ITD, NPM1 and NRAS in 269 patients with MDS or secondary AML. Leukemia 24(8):1528–1532
DiNardo CD, Luskin MR, Carroll M et al (2017) Validation of a clinical assay of multi-locus DNA methylation for prognosis of newly diagnosed AML. Am J Hematol 92(2):E14–E15
DiNardo CD, Pratz K, Pullarkat V et al (2019) Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood 133(1):7–17
Döhner K, Tobis K, Ulrich R et al (2002) Prognostic significance of partial tandem duplications of the MLL gene in adult patients 16 to 60 years old with acute myeloid leukemia and normal cytogenetics: a study of the Acute Myeloid Leukemia Study Group Ulm. J Clin Oncol 20(15):3254–3261
Döhner K, Schlenk RF, Habdank M et al (2005) Mutant nucleophosmin (NPM1) predicts favorable prognosis in younger adults with acute myeloid leukemia and normal cytogenetics: interaction with other gene mutations. Blood 106(12):3740–3746
Döhner H, Estey EH, Amadori S et al (2010) Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood 115(3):453–474
Döhner H, Estey E, Grimwade D et al (2017) Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 129(4):424–447
Döhner K, Thiede C, Jahn N et al (2020) Impact of NPM1/FLT3-ITD genotypes defined by the 2017 European LeukemiaNet in patients with acute myeloid leukemia. Blood 135(5):371–380
Driessen EMC, van Roon EHJ, Spijkers-Hagelstein JAP et al (2013) Frequencies and prognostic impact of RAS mutations in MLL-rearranged acute lymphoblastic leukemia in infants. Haematologica 98(6):937–944
Dufour A, Schneider F, Metzeler KH et al (2010) Acute myeloid leukemia with biallelic CEBPA gene mutations and normal karyotype represents a distinct genetic entity associated with a favorable clinical outcome. J Clin Oncol 28(4):570–577
Dunlap JB, Leonard J, Rosenberg M et al (2019) The combination of NPM1, DNMT3A, and IDH1/2 mutations leads to inferior overall survival in AML. Am J Hematol 94(8):913–920
Duployez N, Marceau-Renaut A, Boissel N et al (2016) Comprehensive mutational profiling of core binding factor acute myeloid leukemia. Blood 127(20):2451–2459
Duployez N, Boudry-Labis E, Roumier C et al (2018) SNP-array lesions in core binding factor acute myeloid leukemia. Oncotarget 9(5):6478–6489
Duployez N, Marceau-Renaut A, Villenet C et al (2019) The stem cell-associated gene expression signature allows risk stratification in pediatric acute myeloid leukemia. Leukemia 33(2):348–357
Eisfeld A-K, Mrózek K, Kohlschmidt J et al (2017) The mutational oncoprint of recurrent cytogenetic abnormalities in adult patients with de novo acute myeloid leukemia. Leukemia 31(10):2211–2218
Eisfeld A-K, Kohlschmidt J, Mrózek K et al (2018) Mutation patterns identify adult patients with de novo acute myeloid leukemia aged 60 years or older who respond favorably to standard chemotherapy: an analysis of alliance studies. Leukemia 32(6):1338–1348
El-Sharkawi D, Sproul D, Allen CG et al (2018) Variable outcome and methylation status according to CEBPA mutant type in double-mutated acute myeloid leukemia patients and the possible implications for treatment. Haematologica 103(1):91–100
Eppert K, Takenaka K, Lechman ER et al (2011) Stem cell gene expression programs influence clinical outcome in human leukemia. Nat Med 17(9):1086–1093
Esposito MT (2019) The impact of PI3-kinase/RAS pathway cooperating mutations in the evolution of KMT2A-rearranged leukemia. Hemasphere 3(3):e195
Estey E, Gale RP (2017) How good are we at predicting the fate of someone with acute myeloid leukaemia? Leukemia 31(6):1255–1258
Faber ZJ, Chen X, Gedman AL et al (2016) The genomic landscape of core-binding factor acute myeloid leukemias. Nat Genet 48(12):1551–1556
Falini B, Mecucci C, Tiacci E et al (2005) Cytoplasmic nucleophosmin in acute myelogenous leukemia with a normal karyotype. N Engl J Med 352(3):254–266
Farag SS, Archer KJ, Mrózek K et al (2006) Pretreatment cytogenetics add to other prognostic factors predicting complete remission and long-term outcome in patients 60 years of age or older with acute myeloid leukemia: results from Cancer and Leukemia Group B 8461. Blood 108(1):63–73
Fasan A, Eder C, Haferlach C et al (2013) GATA2 mutations are frequent in intermediate-risk karyotype AML with biallelic CEBPA mutations and are associated with favorable prognosis. Leukemia 27(2):482–485
Fasan A, Haferlach C, Alpermann T et al (2014) The role of different genetic subtypes of CEBPA mutated AML. Leukemia 28(4):794–803

Fenwarth L, Itzykson R, De Botton S et al (2019) Integrating ELN criteria and a "knowledge bank" approach to guide allogeneic stem cell transplantation (SCT) indication in younger adults with acute myeloid leukemia (AML): an Acute Leukemia French Association Study. Blood 134(Suppl_1):1423

Figueroa ME, Lugthart S, Li Y et al (2010) DNA methylation signatures identify biologically distinct subtypes in acute myeloid leukemia. Cancer Cell 17(1):13–27

Fischer M, Schnetzke U, Spies-Weisshart B et al (2017) Impact of FLT3-ITD diversity on response to induction chemotherapy in patients with acute myeloid leukemia. Haematologica 102(4):e129–e131

Fontana MC, Marconi G, Feenstra JDM et al (2018) Chromothripsis in acute myeloid leukemia: biological features and impact on survival. Leukemia 32(7):1609–1620

Fröhling S, Schlenk RF, Breitruck J et al (2002) Prognostic significance of activating FLT3 mutations in younger adults (16 to 60 years) with acute myeloid leukemia and normal cytogenetics: a study of the AML Study Group Ulm. Blood 100(13):4372–4380

Fröhling S, Schlenk RF, Stolze I et al (2004) CEBPA mutations in younger adults with acute myeloid leukemia and normal cytogenetics: prognostic relevance and analysis of cooperating mutations. J Clin Oncol 22(4):624–633

Fröhling S, Schlenk RF, Kayser S et al (2006) Cytogenetics and age are major determinants of outcome in intensively treated acute myeloid leukemia patients older than 60 years: results from AMLSG trial AML HD98-B. Blood 108(10):3280–3288

Fujiwara S, Muroi K, Yamamoto C et al (2017) CD25 as an adverse prognostic factor in elderly patients with acute myeloid leukemia. Hematology 22(6):347–353

Gaidzik VI, Schlenk RF, Moschny S et al (2009) Prognostic impact of WT1 mutations in cytogenetically normal acute myeloid leukemia: a study of the German-Austrian AML Study Group. Blood 113(19):4505–4511

Gaidzik VI, Bullinger L, Schlenk RF et al (2011) RUNX1 mutations in acute myeloid leukemia: results from a comprehensive genetic and clinical analysis from the AML Study Group. J Clin Oncol 29(10):1364–1372

Gaidzik VI, Paschka P, Späth D et al (2012) TET2 mutations in acute myeloid leukemia (AML): results from a comprehensive genetic and clinical analysis of the AML Study Group. J Clin Oncol 30(12):1350–1357

Gaidzik VI, Schlenk RF, Paschka P et al (2013) Clinical impact of DNMT3A mutations in younger adult patients with acute myeloid leukemia: results of the AML Study Group (AMLSG). Blood 121(23):4769–4777

Gaidzik VI, Teleanu V, Papaemmanuil E et al (2016) RUNX1 mutations in acute myeloid leukemia are associated with distinct clinico-pathologic and genetic features. Leukemia 30(11):2160–2168

Gale RE, Green C, Allen C et al (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(5):2776–2784

Ganzel C, Becker J, Mintz PD, Lazarus HM, Rowe JM (2012) Hyperleukocytosis, leukostasis and leukapheresis: practice management. Blood Rev 26(3):117–122

Ganzel C, Manola J, Douer D et al (2016) Extramedullary disease in adult acute myeloid leukemia is common but lacks independent significance: analysis of patients in ECOG-ACRIN Cancer research group trials, 1980-2008. J Clin Oncol 34(29):3544–3553

Gardin C, Pautas C, Fournier E et al (2020) Added prognostic value of secondary AML-like gene mutations in ELN intermediate-risk older AML: ALFA-1200 study results. Blood Adv 4(9):1942–1949

Gentles AJ, Plevritis SK, Majeti R, Alizadeh AA (2010) Association of a leukemic stem cell gene expression signature with clinical outcomes in acute myeloid leukemia. JAMA 304(24):2706–2715

Gerstung M, Papaemmanuil E, Martincorena I et al (2017) Precision oncology for acute myeloid leukemia using a knowledge bank approach. Nat Genet 49(3):332–340

Giammarco S, Chiusolo P, Piccirillo N et al (2017) Hyperleukocytosis and leukostasis: management of a medical emergency. Expert Rev Hematol 10(2):147–154

Granfeldt Østgård LS, Medeiros BC, Sengeløv H et al (2015) Epidemiology and clinical significance of secondary and therapy-related acute myeloid Leukemia: a National Population-Based Cohort Study. JCO 33(31):3641–3649

Green CL, Koo KK, Hills RK et al (2010) Prognostic significance of CEBPA mutations in a large cohort of younger adult patients with acute myeloid leukemia: impact of double CEBPA mutations and the interaction with FLT3 and NPM1 mutations. J Clin Oncol 28(16):2739–2747

Green CL, Evans CM, Zhao L et al (2011) The prognostic significance of IDH2 mutations in AML depends on the location of the mutation. Blood 118(2):409–412

Greenberg PL, Tuechler H, Schanz J et al (2012) Revised international prognostic scoring system for myelodysplastic syndromes. Blood 120(12):2454–2465

Greif PA, Konstandin NP, Metzeler KH et al (2012) RUNX1 mutations in cytogenetically normal acute myeloid leukemia are associated with a poor prognosis and up-regulation of lymphoid genes. Haematologica 97(12):1909–1915

Greif PA, Hartmann L, Vosberg S et al (2018) Evolution of cytogenetically normal acute myeloid Leukemia during therapy and relapse: an exome sequencing study of 50 patients. Clin Cancer Res 24(7):1716–1726

Grimwade D, Mrózek K (2011) Diagnostic and prognostic value of cytogenetics in acute myeloid Leukemia. Hematol Oncol Clin North Am 25(6):1135–1161

Grimwade D, Walker H, Oliver F et al (1998) The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties. Blood 92(7):2322–2333

Grimwade D, Walker H, Harrison G et al (2001) The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. Blood 98(5):1312–1320

Grimwade D, Hills RK, Moorman AV et al (2010) Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood 116(3):354–365

Grimwade D, Ivey A, Huntly BJP (2016) Molecular landscape of acute myeloid leukemia in younger adults and its clinical relevance. Blood 127(1):29–41

Gröschel S, Lugthart S, Schlenk RF et al (2010) High EVI1 expression predicts outcome in younger adult patients with acute myeloid leukemia and is associated with distinct cytogenetic abnormalities. J Clin Oncol 28(12):2101–2107

Gröschel S, Schlenk RF, Engelmann J et al (2013) Deregulated expression of EVI1 defines a poor prognostic subset of MLL-rearranged acute myeloid leukemias: a study of the German-Austrian Acute Myeloid Leukemia Study Group and the Dutch-Belgian-Swiss HOVON/SAKK Cooperative Group. J Clin Oncol 31(1):95–103

Grossmann V, Schnittger S, Kohlmann A et al (2012) A novel hierarchical prognostic model of AML solely based on molecular mutations. Blood 120(15):2963–2972

Grossmann V, Haferlach C, Nadarajah N et al (2013a) CEBPA double-mutated acute myeloid leukaemia harbours concomitant molecular mutations in 76·8% of cases with TET2 and GATA2 alterations impacting prognosis. Br J Haematol 161(5):649–658

Grossmann V, Schnittger S, Poetzinger F et al (2013b) High incidence of RAS signalling pathway mutations in MLL-rearranged acute myeloid leukemia. Leukemia 27(9):1933–1936

Haferlach C, Dicker F, Herholz H et al (2008) Mutations of the TP53 gene in acute myeloid leukemia are strongly associated with a complex aberrant karyotype. Leukemia 22(8):1539–1541

Haferlach C, Mecucci C, Schnittger S et al (2009) AML with mutated NPM1 carrying a normal or aberrant karyotype show overlapping biologic, pathologic, immunophenotypic, and prognostic features. Blood 114(14):3024–3032

Haferlach C, Alpermann T, Schnittger S et al (2012) Prognostic value of monosomal karyotype in comparison to complex aberrant karyotype in acute myeloid leukemia: a study on 824 cases with aberrant karyotype. Blood 119(9):2122–2125

Harada Y, Nagata Y, Kihara R et al (2018) Prognostic analysis according to the 2017 ELN risk stratification by genetics in adult acute myeloid leukemia patients treated in the Japan Adult Leukemia Study Group (JALSG) AML201 study. Leuk Res 66:20–27

Harrison CJ, Hills RK, Moorman AV et al (2010) Cytogenetics of childhood acute myeloid leukemia: United Kingdom Medical Research Council treatment trials AML 10 and 12. J Clin Oncol 28(16):2674–2681

Hefazi M, Siddiqui M, Patnaik M et al (2015) Prognostic impact of combined NPM1+/FLT3− genotype in patients with acute myeloid leukemia with intermediate risk cytogenetics stratified by age and treatment modalities. Leuk Res 39(11):1207–1213

Heiblig M, Labussière-Wallet H, Nicolini FE et al (2019) Prognostic value of genetic alterations in elderly patients with acute myeloid leukemia: a single institution experience. Cancers (Basel) 11(4):570

Herold T, Jurinovic V, Batcha AMN et al (2018) A 29-gene and cytogenetic score for the prediction of resistance to induction treatment in acute myeloid leukemia. Haematologica 103(3):456–465

Herold T, Rothenberg-Thurley M, Grunwald VV et al (2020) Validation and refinement of the revised 2017 European LeukemiaNet genetic risk stratification of acute myeloid leukemia. Leukemia 34:3161–3172

Heuser M (2016) Therapy-related myeloid neoplasms: does knowing the origin help to guide treatment? Hematology Am Soc Hematol Educ Program 2016(1):24–32

Hinai AA, Valk PJM (2016) Review: aberrant EVI1 expression in acute myeloid leukaemia. Br J Haematol 172(6):870–878

Hinai ASAA, Pratcorona M, Grob T et al (2019) The landscape of KMT2A-PTD AML: concurrent mutations, gene expression signatures, and clinical outcome. Hemasphere 3(2):e181

Ho PA, Kopecky KJ, Alonzo TA et al (2011) Prognostic implications of the IDH1 synonymous SNP rs11554137 in pediatric and adult AML: a report from the Children's Oncology Group and SWOG. Blood 118(17):4561–4566

Ho AD, Schetelig J, Bochtler T et al (2016) Allogeneic stem cell transplantation improves survival in patients with acute myeloid Leukemia characterized by a high allelic ratio of mutant FLT3-ITD. Biol Blood Marrow Transplant 22(3):462–469

Hollink IHIM, Zwaan CM, Zimmermann M et al (2009) Favorable prognostic impact of NPM1 gene mutations in childhood acute myeloid leukemia, with emphasis on cytogenetically normal AML. Leukemia 23(2):262–270

Hollink IHIM, van den Heuvel-Eibrink MM, Arentsen-Peters STCJM et al (2011) NUP98/NSD1 characterizes a novel poor prognostic group in acute myeloid leukemia with a distinct HOX gene expression pattern. Blood 118(13):3645–3656

Hou H-A, Kuo Y-Y, Liu C-Y et al (2012) DNMT3A mutations in acute myeloid leukemia: stability during disease evolution and clinical implications. Blood 119(2):559–568

How J, Sykes J, Gupta V et al (2012) Influence of FLT3-internal tandem duplication allele burden and white blood cell count on the outcome in patients with

intermediate-risk karyotype acute myeloid leukemia. Cancer 118(24):6110–6117
Hshieh TT, Jung WF, Grande LJ et al (2018) Prevalence of cognitive impairment and association with survival among older patients with hematologic cancers. JAMA Oncol 4(5):686–693
Huet S, Paubelle E, Lours C et al (2018) Validation of the prognostic value of the knowledge bank approach to determine AML prognosis in real life. Blood 132(8):865–867
Hulegårdh E, Nilsson C, Lazarevic V et al (2015) Characterization and prognostic features of secondary acute myeloid leukemia in a population-based setting: a report from the Swedish acute Leukemia registry. Am J Hematol 90(3):208–214
Hupfer V, Grishina O, Schmoor C et al (2018) Validation of a frailty score predicting survival of elderly, non-fit aml patients receiving hypomethylating therapy: results of the decider trial. Blood 132(Suppl 1):720
Illmer T, Schaich M, Ehninger G, Thiede C (2007) Tyrosine kinase mutations of JAK2 are rare events in AML but influence prognosis of patients with CBF-leukemias. Haematologica 92(1):137–138
Inaba H, Zhou Y, Abla O et al (2015) Heterogeneous cytogenetic subgroups and outcomes in childhood acute megakaryoblastic leukemia: a retrospective international study. Blood 126(13):1575–1584
International Working Group for MDS Molecular Prognostic Committee, Haase D, Stevenson KE et al (2019) TP53 mutation status divides myelodysplastic syndromes with complex karyotypes into distinct prognostic subgroups. Leukemia 33(7):1747–1758
Ishikawa Y, Kawashima N, Atsuta Y et al (2020) Prospective evaluation of prognostic impact of KIT mutations on acute myeloid leukemia with RUNX1-RUNX1T1 and CBFB-MYH11. Blood Adv 4(1):66–75
Itzykson R, Duployez N, Fasan A et al (2018a) Clonal interference of signaling mutations worsens prognosis in core-binding factor acute myeloid leukemia. Blood 132(2):187–196
Itzykson R, Fournier E, Braun T et al (2018b) Oncogenic predictors of outcome in older AML patients treated intensively. Analysis of the ALFA-1200 trial. Blood 132(Suppl 1):993
Jost E, Lin Q, Weidner CI et al (2014) Epimutations mimic genomic mutations of DNMT3A in acute myeloid leukemia. Leukemia 28(6):1227–1234
Jourdan E, Boissel N, Chevret S et al (2013) Prospective evaluation of gene mutations and minimal residual disease in patients with core binding factor acute myeloid leukemia. Blood 121(12):2213–2223
Juliusson G, Antunovic P, Derolf Å et al (2009) Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. Blood 113(18):4179–4187
Juliusson G, Jädersten M, Deneberg S et al (2020) The prognostic impact of FLT3-ITD and NPM1 mutation in adult AML is age-dependent in the population-based setting. Blood Adv 4(6):1094–1101
Jung N, Dai B, Gentles AJ, Majeti R, Feinberg AP (2015) An LSC epigenetic signature is largely mutation independent and implicates the HOXA cluster in AML pathogenesis. Nat Commun 6(1):1–12
Kadia TM, Jain P, Ravandi F et al (2016) TP53 mutations in newly diagnosed acute myeloid leukemia: clinicomolecular characteristics, response to therapy, and outcomes. Cancer 122(22):3484–3491
Karakas T, Miething CC, Maurer U et al (2002) The coexpression of the apoptosis-related genes bcl-2 and wt1 in predicting survival in adult acute myeloid leukemia. Leukemia 16(5):846–854
Kauer J, Schwartz K, Tandler C et al (2019) CD105 (Endoglin) as negative prognostic factor in AML. Sci Rep 9(1):1–11
Kayser S, Schlenk RF, Londono MC et al (2009) Insertion of FLT3 internal tandem duplication in the tyrosine kinase domain-1 is associated with resistance to chemotherapy and inferior outcome. Blood 114(12):2386–2392
Kayser S, Döhner K, Krauter J et al (2011) The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood 117(7):2137–2145
Kayser S, Zucknick M, Döhner K et al (2012) Monosomal karyotype in adult acute myeloid leukemia: prognostic impact and outcome after different treatment strategies. Blood 119(2):551–558
Kayser S, Elliott MA, Luskin M et al (2019) Characteristics and outcome of patients with core binding factor acute myeloid leukemia and FLT3-ITD: results from an international collaboration. Blood 134(Suppl_1):2693
Kihara R, Nagata Y, Kiyoi H et al (2014) Comprehensive analysis of genetic alterations and their prognostic impacts in adult acute myeloid leukemia patients. Leukemia 28(8):1586–1595
Kim H-J, Ahn HK, Jung CW et al (2013) KIT D816 mutation associates with adverse outcomes in core binding factor acute myeloid leukemia, especially in the subgroup with RUNX1/RUNX1T1 rearrangement. Ann Hematol 92(2):163–171
Kim Y, Lee GD, Park J et al (2015) Quantitative fragment analysis of FLT3-ITD efficiently identifying poor prognostic group with high mutant allele burden or long ITD length. Blood Cancer J 5(8):e336
Kirkhus L, Jordhøy M, Šaltytė Benth J et al (2016) Comparing comorbidity scales: attending physician score versus the cumulative illness rating scale for geriatrics. J Geriatr Oncol 7(2):90–98
Kiyoi H, Naoe T, Nakano Y et al (1999) Prognostic implication of FLT3 and N-RAS gene mutations in acute myeloid leukemia. Blood 93(9):3074–3080
Klein K, Kaspers G, Harrison CJ et al (2015) Clinical impact of additional cytogenetic aberrations, cKIT and RAS mutations, and treatment elements in Pediatric t(8;21)-AML: results from an international retrospective study by the International Berlin-Frankfurt-Münster Study group. J Clin Oncol 33(36):4247–4258

Klepin HD, Geiger AM, Tooze JA et al (2013) Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. Blood 121(21):4287–4294

Kobayashi R, Tawa A, Hanada R et al (2007) Extramedullary infiltration at diagnosis and prognosis in children with acute myelogenous leukemia. Pediatr Blood Cancer 48(4):393–398

Konstandin NP, Pastore F, Herold T et al (2018) Genetic heterogeneity of cytogenetically normal AML with mutations of CEBPA. Blood Adv 2(20):2724–2731

Kornblau SM, Womble M, Qiu YH et al (2006) Simultaneous activation of multiple signal transduction pathways confers poor prognosis in acute myelogenous leukemia. Blood 108(7):2358–2365

Kornblau SM, Tibes R, Qiu YH et al (2009) Functional proteomic profiling of AML predicts response and survival. Blood 113(1):154–164

Kornblau SM, Singh N, Qiu Y et al (2010a) Highly phosphorylated FOXO3A is an adverse prognostic factor in acute myeloid leukemia. Clin Cancer Res 16(6):1865–1874

Kornblau SM, McCue D, Singh N et al (2010b) Recurrent expression signatures of cytokines and chemokines are present and are independently prognostic in acute myelogenous leukemia and myelodysplasia. Blood 116(20):4251–4261

Kornblau SM, Qiu YH, Zhang N et al (2011) Abnormal expression of FLI1 protein is an adverse prognostic factor in acute myeloid leukemia. Blood 118(20):5604–5612

Kottaridis PD, Gale RE, Frew ME et al (2001) The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. Blood 98(6):1752–1759

Krauth M-T, Eder C, Alpermann T et al (2014) High number of additional genetic lesions in acute myeloid leukemia with t(8;21)/RUNX1-RUNX1T1: frequency and impact on clinical outcome. Leukemia 28(7):1449–1458

Kroeze LI, Aslanyan MG, van Rooij A et al (2014) Characterization of acute myeloid leukemia based on levels of global hydroxymethylation. Blood 124(7):1110–1118

Kusec R, Jaksic O, Ostojic S et al (2006) More on prognostic significance of FLT3/ITD size in acute myeloid leukemia (AML). Blood 108(1):405–406

Kuykendall A, Duployez N, Boissel N, Lancet JE, Welch JS (2018) Acute myeloid Leukemia: the good, the bad, and the ugly. Am Soc Clin Oncol Educ Book 38:555–573

Lad D, Jain A, Varma S (2017) Complications and management of coagulation disorders in leukemia patients. Blood Lymphat Cancer 7:61–72

Lancet JE, Uy GL, Cortes JE et al (2016) Final results of a phase III randomized trial of CPX-351 versus 7+3 in older patients with newly diagnosed high risk (secondary) AML. JCO 34(15_suppl):7000

Langer C, Radmacher MD, Ruppert AS et al (2008) High BAALC expression associates with other molecular prognostic markers, poor outcome, and a distinct gene-expression signature in cytogenetically normal patients younger than 60 years with acute myeloid leukemia: a Cancer and Leukemia Group B (CALGB) study. Blood 111(11):5371–5379

Langer C, Marcucci G, Holland KB et al (2009) Prognostic importance of MN1 transcript levels, and biologic insights from MN1-associated gene and microRNA expression signatures in cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. J Clin Oncol 27(19):3198–3204

Laupeze B, Amiot L, Drenou B et al (2002) High multidrug resistance protein activity in acute myeloid leukaemias is associated with poor response to chemotherapy and reduced patient survival. Br J Haematol 116(4):834–838

Lauria F, Raspadori D, Rondelli D et al (1997) High bcl-2 expression in acute myeloid leukemia cells correlates with CD34 positivity and complete remission rate. Leukemia 11(12):2075–2078

Lavallée V-P, Krosl J, Lemieux S et al (2016) Chemo-genomic interrogation of CEBPA mutated AML reveals recurrent CSF3R mutations and subgroup sensitivity to JAK inhibitors. Blood 127(24):3054–3061

Lazarevic V, Hörstedt A-S, Johansson B et al (2014) Incidence and prognostic significance of karyotypic subgroups in older patients with acute myeloid leukemia: the Swedish population-based experience. Blood Cancer J 4(2):e188–e188

Lazarevic V, Rosso A, Juliusson G et al (2015) Prognostic significance of high hyperdiploid and triploid/tetraploid adult acute myeloid leukemia. Am J Hematol 90(9):800–805

Lazarevic VL, Labopin M, Depei W et al (2018) Relatively favorable outcome after allogeneic stem cell transplantation for BCR-ABL1-positive AML: a survey from the acute leukemia working party of the European Society for Blood and Marrow Transplantation (EBMT). Am J Hematol 93(1):31–39

Lazenby M, Gilkes AF, Marrin C et al (2014) The prognostic relevance of flt3 and npm1 mutations on older patients treated intensively or non-intensively: a study of 1312 patients in the UK NCRI AML16 trial. Leukemia 28(10):1953–1959

Legrand O, Simonin G, Perrot JY, Zittoun R, Marie JP (1998) Pgp and MRP activities using calcein-AM are prognostic factors in adult acute myeloid leukemia patients. Blood 91(12):4480–4488

Leith CP, Kopecky KJ, Godwin J et al (1997) Acute myeloid leukemia in the elderly: assessment of multidrug resistance (MDR1) and cytogenetics distinguishes biologic subgroups with remarkably distinct responses to standard chemotherapy. A Southwest Oncology Group study. Blood 89(9):3323–3329

Leith CP, Kopecky KJ, Chen IM et al (1999) Frequency and clinical significance of the expression of the multidrug resistance proteins MDR1/P-glycoprotein, MRP1, and LRP in acute myeloid leukemia: a Southwest Oncology Group study. Blood 94(3):1086–1099

Levine JH, Simonds EF, Bendall SC et al (2015) Data-driven phenotypic dissection of AML reveals progenitor-like cells that correlate with prognosis. Cell 162(1):184–197

Ley TJ, Ding L, Walter MJ et al (2010) DNMT3A mutations in acute myeloid leukemia. N Engl J Med 363(25):2424–2433

Li Z, Herold T, He C et al (2013) Identification of a 24-gene prognostic signature that improves the European LeukemiaNet risk classification of acute myeloid leukemia: an international collaborative study. J Clin Oncol 31(9):1172–1181

Li H-Y, Deng D-H, Huang Y et al (2015) Favorable prognosis of biallelic CEBPA gene mutations in acute myeloid leukemia patients: a meta-analysis. Eur J Haematol 94(5):439–448

Li S, Garrett-Bakelman FE, Chung SS et al (2016) Distinct evolution and dynamics of epigenetic and genetic heterogeneity in acute myeloid leukemia. Nat Med 22(7):792–799

Lin T-C, Hou H-A, Chou W-C et al (2011) CEBPA methylation as a prognostic biomarker in patients with de novo acute myeloid leukemia. Leukemia 25(1):32–40

Linch DC, Hills RK, Burnett AK, Khwaja A, Gale RE (2014) Impact of FLT3(ITD) mutant allele level on relapse risk in intermediate-risk acute myeloid leukemia. Blood 124(2):273–276

Linch DC, Hills RK, Burnett AK, Russell N, Gale RE (2020) Analysis of the clinical impact of NPM1 mutant allele burden in a large cohort of younger adult patients with acute myeloid leukaemia. Br J Haematol 188(6):852–859

Lindsley RC, Mar BG, Mazzola E et al (2015) Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. Blood 125(9):1367–1376

Liu S-B, Dong H-J, Bao X-B et al (2019) Impact of FLT3-ITD length on prognosis of acute myeloid leukemia. Haematologica 104(1):e9–e12

Loghavi S, Zuo Z, Ravandi F et al (2014) Clinical features of de novo acute myeloid leukemia with concurrent DNMT3A, FLT3 and NPM1 mutations. J Hematol Oncol 7(1):74

Lugthart S, van Drunen E, van Norden Y et al (2008) High EVI1 levels predict adverse outcome in acute myeloid leukemia: prevalence of EVI1 overexpression and chromosome 3q26 abnormalities underestimated. Blood 111(8):4329–4337

Lugthart S, Gröschel S, Beverloo HB et al (2010) Clinical, molecular, and prognostic significance of WHO type inv(3)(q21q26.2)/t(3;3)(q21;q26.2) and various other 3q abnormalities in acute myeloid leukemia. J Clin Oncol 28(24):3890–3898

Luskin MR, Gimotty PA, Smith C et al (2016) A clinical measure of DNA methylation predicts outcome in de novo acute myeloid leukemia. JCI Insight 1(9):e87323

Ma Z, Morris SW, Valentine V et al (2001) Fusion of two novel genes, RBM15 and MKL1, in the t(1;22)(p13;q13) of acute megakaryoblastic leukemia. Nat Genet 28(3):220–221

Malagola M, Skert C, Vignetti M et al (2011) A simple prognostic scoring system for newly diagnosed cytogenetically normal acute myeloid leukemia: retrospective analysis of 530 patients. Leuk Lymphoma 52(12):2329–2335

Maley CC, Aktipis A, Graham TA et al (2017) Classifying the evolutionary and ecological features of neoplasms. Nat Rev Cancer 17(10):605–619

Manara E, Basso G, Zampini M et al (2017) Characterization of children with FLT3-ITD acute myeloid leukemia: a report from the AIEOP AML-2002 Study Group. Leukemia 31(1):18–25

Marceau-Renaut A, Guihard S, Castaigne S et al (2015) Classification of CEBPA mutated acute myeloid leukemia by GATA2 mutations. Am J Hematol 90(5):E93–E94

Marceau-Renaut A, Duployez N, Ducourneau B et al (2018) Molecular profiling defines distinct prognostic subgroups in childhood AML: a report from the French ELAM02 study group. HemaSphere 2(1):e31

Marcucci G, Mrózek K, Ruppert AS et al (2005a) Prognostic factors and outcome of core binding factor acute myeloid leukemia patients with t(8;21) differ from those of patients with inv(16): a Cancer and Leukemia Group B study. J Clin Oncol 23(24):5705–5717

Marcucci G, Baldus CD, Ruppert AS et al (2005b) Overexpression of the ETS-related gene, ERG, predicts a worse outcome in acute myeloid leukemia with normal karyotype: a Cancer and Leukemia Group B study. J Clin Oncol 23(36):9234–9242

Marcucci G, Maharry K, Whitman SP et al (2007) High expression levels of the ETS-related gene, ERG, predict adverse outcome and improve molecular risk-based classification of cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. J Clin Oncol 25(22):3337–3343

Marcucci G, Radmacher MD, Maharry K et al (2008) MicroRNA expression in cytogenetically normal acute myeloid leukemia. N Engl J Med 358(18):1919–1928

Marcucci G, Maharry K, Wu Y-Z et al (2010) IDH1 and IDH2 gene mutations identify novel molecular subsets within de novo cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. J Clin Oncol 28(14):2348–2355

Marcucci G, Metzeler KH, Schwind S et al (2012) Age-related prognostic impact of different types of DNMT3A mutations in adults with primary cytogenetically normal acute myeloid leukemia. J Clin Oncol 30(7):742–750

Marcucci G, Maharry KS, Metzeler KH et al (2013) Clinical role of microRNAs in cytogenetically normal acute myeloid leukemia: miR-155 upregulation independently identifies high-risk patients. J Clin Oncol 31(17):2086–2093

Marcucci G, Yan P, Maharry K et al (2014) Epigenetics meets genetics in acute myeloid leukemia: clinical impact of a novel seven-gene score. J Clin Oncol 32(6):548–556

Märklin M, Hagelstein I, Hinterleitner C et al (2020) CD105 (Endoglin) as risk marker in AML patients undergoing stem cell transplantation. Int J Hematol 112(1):57–64

Masetti R, Bertuccio SN, Pession A, Locatelli F (2019) CBFA2T3-GLIS2-positive acute myeloid leukaemia. A peculiar paediatric entity. Br J Haematol 184(3):337–347

Mason KD, Juneja SK, Szer J (2006) The immunophenotype of acute myeloid leukemia: is there a relationship with prognosis? Blood Rev 20(2):71–82

Mead AJ, Linch DC, Hills RK et al (2007) FLT3 tyrosine kinase domain mutations are biologically distinct from and have a significantly more favorable prognosis than FLT3 internal tandem duplications in patients with acute myeloid leukemia. Blood 110(4):1262–1270

Medeiros BC, Othus M, Fang M, Roulston D, Appelbaum FR (2010) Prognostic impact of monosomal karyotype in young adult and elderly acute myeloid leukemia: the southwest oncology group (SWOG) experience. Blood 116(13):2224–2228

Medeiros BC, Othus M, Fang M, Appelbaum FR, Erba HP (2015) Cytogenetic heterogeneity negatively impacts outcomes in patients with acute myeloid leukemia. Haematologica 100(3):331–335

Mendler JH, Maharry K, Radmacher MD et al (2012) RUNX1 mutations are associated with poor outcome in younger and older patients with cytogenetically normal acute myeloid leukemia and with distinct gene and MicroRNA expression signatures. J Clin Oncol 30(25):3109–3118

Meshinchi S, Alonzo TA, Stirewalt DL et al (2006) Clinical implications of FLT3 mutations in pediatric AML. Blood 108(12):3654–3661

Metzeler KH, Hummel M, Bloomfield CD et al (2008) An 86-probe-set gene-expression signature predicts survival in cytogenetically normal acute myeloid leukemia. Blood 112(10):4193–4201

Metzeler KH, Dufour A, Benthaus T et al (2009) ERG expression is an independent prognostic factor and allows refined risk stratification in cytogenetically normal acute myeloid leukemia: a comprehensive analysis of ERG, MN1, and BAALC transcript levels using oligonucleotide microarrays. J Clin Oncol 27(30):5031–5038

Metzeler KH, Becker H, Maharry K et al (2011a) ASXL1 mutations identify a high-risk subgroup of older patients with primary cytogenetically normal AML within the ELN favorable genetic category. Blood 118(26):6920–6929

Metzeler KH, Maharry K, Radmacher MD et al (2011b) TET2 mutations improve the new European LeukemiaNet risk classification of acute myeloid leukemia: a Cancer and Leukemia Group B study. J Clin Oncol 29(10):1373–1381

Metzeler KH, Herold T, Rothenberg-Thurley M et al (2016) Spectrum and prognostic relevance of driver gene mutations in acute myeloid leukemia. Blood 128(5):686–698

Meyer C, Burmeister T, Gröger D et al (2018) The MLL recombinome of acute leukemias in 2017. Leukemia 32(2):273–284

Micol JB, Boissel N, Renneville A et al (2009) The role of cytogenetic abnormalities in acute myeloid leukemia with NPM1 mutations and no FLT3 internal tandem duplication. Blood 114(20):4601–4602

Middeke JM, Herold S, Rücker-Braun E et al (2016) TP53 mutation in patients with high-risk acute myeloid leukaemia treated with allogeneic haematopoietic stem cell transplantation. Br J Haematol 172(6):914–922

Minetto P, Guolo F, Clavio M et al (2018) A blastic plasmacytoid dendritic cell neoplasm-like phenotype identifies a subgroup of npm1-mutated acute myeloid leukemia patients with worse prognosis. Am J Hematol 93(2):E33–E35

Moison C, Lavallée V-P, Thiollier C et al (2019) Complex karyotype AML displays G2/M signature and hypersensitivity to PLK1 inhibition. Blood Adv 3(4):552–563

Montesinos P, Lorenzo I, Martín G et al (2008) Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model. Haematologica 93(1):67 LP–74 LP

Montesinos P, Bergua J, Infante J et al (2019) Update on management and progress of novel therapeutics for R/R AML: an Iberian expert panel consensus. Ann Hematol 98(11):2467–2483

Mosna F, Papayannidis C, Martinelli G et al (2015) Complex karyotype, older age, and reduced first-line dose intensity determine poor survival in core binding factor acute myeloid leukemia patients with long-term follow-up. Am J Hematol 90(6):515–523

Mrózek K, Heinonen K, Lawrence D et al (1997) Adult patients with de novo acute myeloid leukemia and t(9; 11)(p22; q23) have a superior outcome to patients with other translocations involving band 11q23: a Cancer and Leukemia Group B study. Blood 90(11):4532–4538

Mrózek K, Marcucci G, Nicolet D et al (2012) Prognostic significance of the European LeukemiaNet standardized system for reporting cytogenetic and molecular alterations in adults with acute myeloid leukemia. J Clin Oncol 30(36):4515–4523

Mrózek K, Eisfeld A-K, Kohlschmidt J et al (2019) Complex karyotype in de novo acute myeloid leukemia: typical and atypical subtypes differ molecularly and clinically. Leukemia 33(7):1620–1634

Nagel G, Weber D, Fromm E et al (2017) Epidemiological, genetic, and clinical characterization by age of newly diagnosed acute myeloid leukemia based on an academic population-based registry study (AMLSG BiO). Ann Hematol 96(12):1993–2003

Nahi H, Lehmann S, Bengtzen S et al (2008) Chromosomal aberrations in 17p predict in vitro drug resistance and short overall survival in acute myeloid leukemia. Leuk Lymphoma 49(3):508–516

Nakao M, Yokota S, Iwai T et al (1996) Internal tandem duplication of the flt3 gene found in acute myeloid leukemia. Leukemia 10(12):1911–1918

Nakase K, Kita K, Kageyama S et al (1997) Clinical importance of interleukin-2 receptor alpha-chain expression in acute leukemia. The Japan Cooperative Group of Leukemia/Lymphoma. Cancer Detect Prev 21(3):273–279

Neuendorff NR, Burmeister T, Dörken B, Westermann J (2016) BCR-ABL-positive acute myeloid leukemia: a new entity? Analysis of clinical and molecular features. Ann Hematol 95(8):1211–1221

Neuendorff NR, Hemmati P, Arnold R et al (2018) BCR-ABL+ acute myeloid leukemia: are we always dealing with a high-risk disease? Blood Adv 2(12):1409–1411

Ng SWK, Mitchell A, Kennedy JA et al (2016) A 17-gene stemness score for rapid determination of risk in acute leukaemia. Nature 540(7633):433–437

Nguyen L, Zhang X, Roberts E et al (2020) Comparison of mutational profiles and clinical outcomes in patients with acute myeloid leukemia with mutated RUNX1 versus acute myeloid leukemia with myelodysplasia-related changes with mutated RUNX1. Leuk Lymphoma 61(6):1395–1405

Nibourel O, Kosmider O, Cheok M et al (2010) Incidence and prognostic value of TET2 alterations in de novo acute myeloid leukemia achieving complete remission. Blood 116(7):1132–1135

Nibourel O, Guihard S, Roumier C et al (2017) Copy-number analysis identified new prognostic marker in acute myeloid leukemia. Leukemia 31(3):555–564

Noort S, Zimmermann M, Reinhardt D et al (2018) Prognostic impact of t(16;21)(p11;q22) and t(16;21)(q24;q22) in pediatric AML: a retrospective study by the I-BFM study group. Blood 132(15):1584–1592

Noort S, Wander P, Alonzo TA et al (2021) The clinical and biological characteristics of NUP98-KDM5A in pediatric acute myeloid leukemia. Haematologica 106(2):630–634

Ok CY, Patel KP, Garcia-Manero G et al (2015) TP53 mutation characteristics in therapy-related myelodysplastic syndromes and acute myeloid leukemia is similar to de novo diseases. J Hematol Oncol 8:45

Ong YL, McMullin MF, Bailie KE et al (2000) High bax expression is a good prognostic indicator in acute myeloid leukaemia. Br J Haematol 111(1):182–189

Opatz S, Bamopoulos SA, Metzeler KH et al (2020) The clinical mutatome of core binding factor leukemia. Leukemia:1–10

Ossenkoppele G, Montesinos P (2019) Challenges in the diagnosis and treatment of secondary acute myeloid leukemia. Crit Rev Oncol Hematol 138:6–13

Ostronoff F, Othus M, Gerbing RB et al (2014) NUP98/NSD1 and FLT3/ITD coexpression is more prevalent in younger AML patients and leads to induction failure: a COG and SWOG report. Blood 124(15):2400–2407

Ostronoff F, Othus M, Lazenby M et al (2015) Prognostic significance of NPM1 mutations in the absence of FLT3-internal tandem duplication in older patients with acute myeloid leukemia: a SWOG and UK National Cancer Research Institute/Medical Research Council report. J Clin Oncol 33(10):1157–1164

Ottema S, Mulet-Lazaro R, Beverloo HB et al (2020) Atypical 3q26/MECOM rearrangements genocopy inv(3)/t(3;3) in acute myeloid leukemia. Blood 136(2):224–234

Pabst T, Mueller BU, Zhang P et al (2001) Dominant-negative mutations of CEBPA, encoding CCAAT/enhancer binding protein-alpha (C/EBPalpha), in acute myeloid leukemia. Nat Genet 27(3):263–270

Pabst T, Eyholzer M, Fos J, Mueller BU (2009) Heterogeneity within AML with CEBPA mutations; only CEBPA double mutations, but not single CEBPA mutations are associated with favourable prognosis. Br J Cancer 100(8):1343–1346

Papaemmanuil E, Gerstung M, Bullinger L et al (2016) Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med 374(23):2209–2221

Park SH, Chi H-S, Min S-K et al (2011) Prognostic impact of c-KIT mutations in core binding factor acute myeloid leukemia. Leuk Res 35(10):1376–1383

Paschka P, Marcucci G, Ruppert AS et al (2006) Adverse prognostic significance of KIT mutations in adult acute myeloid leukemia with inv(16) and t(8;21): a Cancer and Leukemia Group B study. J Clin Oncol 24(24):3904–3911

Paschka P, Marcucci G, Ruppert AS et al (2008) Wilms' tumor 1 gene mutations independently predict poor outcome in adults with cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. J Clin Oncol 26(28):4595–4602

Paschka P, Schlenk RF, Gaidzik VI et al (2010) IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. J Clin Oncol 28(22):3636–3643

Paschka P, Du J, Schlenk RF et al (2013) Secondary genetic lesions in acute myeloid leukemia with inv(16) or t(16;16): a study of the German-Austrian AML study group (AMLSG). Blood 121(1):170–177

Paschka P, Schlenk RF, Gaidzik VI et al (2015) ASXL1 mutations in younger adult patients with acute myeloid leukemia: a study by the German-Austrian Acute Myeloid Leukemia Study Group. Haematologica 100(3):324–330

Pastore F, Kling D, Hoster E et al (2014a) Long-term follow-up of cytogenetically normal CEBPA-mutated AML. J Hematol Oncol 7(1):55

Pastore F, Dufour A, Benthaus T et al (2014b) Combined molecular and clinical prognostic index for relapse and survival in cytogenetically normal acute myeloid leukemia. J Clin Oncol 32(15):1586–1594

Patel JP, Gönen M, Figueroa ME et al (2012) Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med 366(12):1079–1089

Patel SS, Kuo FC, Gibson CJ et al (2018) High NPM1-mutant allele burden at diagnosis predicts unfavorable outcomes in de novo AML. Blood 131(25):2816–2825

Patkar N, Shaikh AF, Kakirde C et al (2019) A novel machine-learning-derived genetic score correlates with measurable residual disease and is highly predictive of outcome in acute myeloid leukemia with mutated NPM1. Blood Cancer J 9(10):1–4

Perry M, Bertoli S, Rocher C et al (2018) FLT3-TKD mutations associated with NPM1 mutations define a favorable-risk group in patients with acute myeloid Leukemia. Clin Lymph Myeloma Leukemia 18(12):e545–e550

Peterlin P, Renneville A, Abdelali RB et al (2015) Impact of additional genetic alterations on the outcome of patients with NPM1-mutated cytogenetically normal acute myeloid leukemia. Haematologica 100(5):e196–e199

Pigneux A, Labopin M, Maertens J et al (2015) Outcome of allogeneic hematopoietic stem-cell transplantation for adult patients with AML and 11q23/MLL rearrangement (MLL-r AML). Leukemia 29(12):2375–2381

Pirker R, Wallner J, Geissler K et al (1991) MDR1 gene expression and treatment outcome in acute myeloid leukemia. J Natl Cancer Inst 83(10):708–712

Poiré X, Labopin M, Polge E et al (2020) The impact of concomitant cytogenetic abnormalities on acute myeloid leukemia with monosomy 7 or deletion 7q after HLA-matched allogeneic stem cell transplantation. Am J Hematol 95(3):282–294

Ponziani V, Gianfaldoni G, Mannelli F et al (2006) The size of duplication does not add to the prognostic significance of FLT3 internal tandem duplication in acute myeloid leukemia patients. Leukemia 20(11):2074–2076

Port M, Böttcher M, Thol F et al (2014) Prognostic significance of FLT3 internal tandem duplication, nucleophosmin 1, and CEBPA gene mutations for acute myeloid leukemia patients with normal karyotype and younger than 60 years: a systematic review and meta-analysis. Ann Hematol 93(8):1279–1286

Prassek VV, Rothenberg-Thurley M, Sauerland MC et al (2018) Genetics of acute myeloid leukemia in the elderly: mutation spectrum and clinical impact in intensively treated patients aged 75 years or older. Haematologica 103(11):1853–1861

Pratcorona M, Abbas S, Sanders MA et al (2012) Acquired mutations in ASXL1 in acute myeloid leukemia: prevalence and prognostic value. Haematologica 97(3):388–392

Pratcorona M, Brunet S, Nomdedéu J et al (2013) Favorable outcome of patients with acute myeloid leukemia harboring a low-allelic burden FLT3-ITD mutation and concomitant NPM1 mutation: relevance to post-remission therapy. Blood 121(14):2734–2738

Pratz KW, Levis M (2017) How I treat FLT3-mutated AML. Blood 129(5):565–571

Prébet T, Boissel N, Reutenauer S et al (2009) Acute myeloid leukemia with translocation (8;21) or inversion (16) in elderly patients treated with conventional chemotherapy: a collaborative study of the French CBF-AML Intergroup. J Clin Oncol 27(28):4747–4753

Preudhomme C, Sagot C, Boissel N et al (2002) Favorable prognostic significance of CEBPA mutations in patients with de novo acute myeloid leukemia: a study from the Acute Leukemia French Association (ALFA). Blood 100(8):2717–2723

Prochazka KT, Pregartner G, Rücker FG et al (2019) Clinical implications of subclonal TP53 mutations in acute myeloid leukemia. Haematologica 104(3):516–523

Pulte D, Jansen L, Castro FA et al (2016) Survival in patients with acute myeloblastic leukemia in Germany and the United States: major differences in survival in young adults. Int J Cancer 139(6):1289–1296

Qin Y-Z, Zhu H-H, Jiang Q et al (2014) Prevalence and prognostic significance of c-KIT mutations in core binding factor acute myeloid leukemia: a comprehensive large-scale study from a single Chinese center. Leuk Res 38(12):1435–1440

Qin T, Wu S, Zhao H et al (2017) Molecular predictors of post-transplant survival in acute myeloid leukemia. Blood Cancer J 7(12):1–5

Quesada AE, Montalban-Bravo G, Luthra R et al (2020) Clinico-pathologic characteristics and outcomes of the World Health Organization (WHO) provisional entity de novo acute myeloid leukemia with mutated RUNX1. Mod Pathol 33(9):1678–1689

Renneville A, Boissel N, Gachard N et al (2009a) The favorable impact of CEBPA mutations in patients with acute myeloid leukemia is only observed in the absence of associated cytogenetic abnormalities and FLT3 internal duplication. Blood 113(21):5090–5093

Renneville A, Boissel N, Zurawski V et al (2009b) Wilms tumor 1 gene mutations are associated with a higher risk of recurrence in young adults with acute myeloid leukemia: a study from the Acute Leukemia French Association. Cancer 115(16):3719–3727

Renneville A, Boissel N, Nibourel O et al (2012) Prognostic significance of DNA methyltransferase 3A mutations in cytogenetically normal acute myeloid leukemia: a study by the Acute Leukemia French Association. Leukemia 26(6):1247–1254

Repp R, Schaekel U, Helm G et al (2003) Immunophenotyping is an independent factor for risk stratification in AML. Cytometry B Clin Cytom 53(1):11–19

Ribeiro AFT, Pratcorona M, Erpelinck-Verschueren C et al (2012) Mutant DNMT3A: a marker of poor prognosis in acute myeloid leukemia. Blood 119(24):5824–5831

Riera L, Marmont F, Toppino D et al (2013) Core binding factor acute myeloid leukaemia and c-KIT mutations. Oncol Rep 29(5):1867–1872

Rockova V, Abbas S, Wouters BJ et al (2011) Risk stratification of intermediate-risk acute myeloid leukemia: integrative analysis of a multitude of gene mutation

and gene expression markers. Blood 118(4):1069–1076

Röllig C, Bornhäuser M, Thiede C et al (2011) Long-term prognosis of acute myeloid Leukemia according to the new genetic risk classification of the European LeukemiaNet recommendations: evaluation of the proposed reporting system. JCO 29(20):2758–2765

Rozovski U, Ohanian M, Ravandi F et al (2015) Incidence of and risk factors for involvement of the central nervous system in acute myeloid leukemia. Leuk Lymphoma 56(5):1392–1397

Rücker FG, Schlenk RF, Bullinger L et al (2012) TP53 alterations in acute myeloid leukemia with complex karyotype correlate with specific copy number alterations, monosomal karyotype, and dismal outcome. Blood 119(9):2114–2121

Rücker FG, Agrawal M, Corbacioglu A et al (2019) Measurable residual disease monitoring in acute myeloid leukemia with t(8;21)(q22;q22.1): results from the AML Study Group. Blood 134(19):1608–1618

Sakaguchi M, Yamaguchi H, Najima Y et al (2018) Prognostic impact of low allelic ratio FLT3-ITD and NPM1 mutation in acute myeloid leukemia. Blood Adv 2(20):2744–2754

Sandahl JD, Coenen EA, Forestier E et al (2014) t(6;9)(p22;q34)/DEK-NUP214-rearranged pediatric myeloid leukemia: an international study of 62 patients. Haematologica 99(5):865–872

Santos FPS, Jones D, Qiao W et al (2011) Prognostic value of FLT3 mutations among different cytogenetic subgroups in acute myeloid leukemia. Cancer 117(10):2145–2155

Sanz MA, Fenaux P, Tallman MS et al (2019) Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. Blood 133(15):1630–1643

Sasaki K, Kanagal-Shamanna R, Montalban-Bravo G et al (2020) Impact of the variant allele frequency of ASXL1, DNMT3A, JAK2, TET2, TP53, and NPM1 on the outcomes of patients with newly diagnosed acute myeloid leukemia. Cancer 126(4):765–774

Schanz J, Tüchler H, Solé F et al (2012) New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. J Clin Oncol 30(8):820–829

Schellongowski P, Staudinger T, Kundi M et al (2011) Prognostic factors for intensive care unit admission, intensive care outcome, and post-intensive care survival in patients with de novo acute myeloid leukemia: a single center experience. Haematologica 96(2):231–237

Schlenk RF, Benner A, Krauter J et al (2004) Individual patient data-based meta-analysis of patients aged 16 to 60 years with core binding factor acute myeloid leukemia: a survey of the German Acute Myeloid Leukemia Intergroup. J Clin Oncol 22(18):3741–3750

Schlenk RF, Döhner K, Krauter J et al (2008) Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. N Engl J Med 358(18):1909–1918

Schlenk RF, Taskesen E, van Norden Y et al (2013) The value of allogeneic and autologous hematopoietic stem cell transplantation in prognostically favorable acute myeloid leukemia with double mutant CEBPA. Blood 122(9):1576–1582

Schlenk RF, Kayser S, Bullinger L et al (2014) Differential impact of allelic ratio and insertion site in FLT3-ITD-positive AML with respect to allogeneic transplantation. Blood 124(23):3441–3449

Schlenk RF, Frech P, Weber D et al (2017) Impact of pretreatment characteristics and salvage strategy on outcome in patients with relapsed acute myeloid leukemia. Leukemia 31(5):1217–1220

Schmaelter A-K, Labopin M, Socié G et al (2020) Inferior outcome of allogeneic stem cell transplantation for secondary acute myeloid leukemia in first complete remission as compared to de novo acute myeloid leukemia. Blood Cancer J 10(3):26–26

Schneider F, Hoster E, Unterhalt M et al (2012) The FLT3ITD mRNA level has a high prognostic impact in NPM1 mutated, but not in NPM1 unmutated, AML with a normal karyotype. Blood 119(19):4383–4386

Schnittger S, Kinkelin U, Schoch C et al (2000) Screening for MLL tandem duplication in 387 unselected patients with AML identify a prognostically unfavorable subset of AML. Leukemia 14(5):796–804

Schnittger S, Schoch C, Kern W et al (2005) Nucleophosmin gene mutations are predictors of favorable prognosis in acute myelogenous leukemia with a normal karyotype. Blood 106(12):3733–3739

Schnittger S, Kohl TM, Haferlach T et al (2006) KIT-D816 mutations in AML1-ETO-positive AML are associated with impaired event-free and overall survival. Blood 107(5):1791–1799

Schnittger S, Haferlach C, Ulke M, Alpermann T, Kern W, Haferlach T. IDH1 mutations are detected in 6.6% of 1414 AML patients and are associated with intermediate risk karyotype and unfavorable prognosis in adults younger than 60 years and unmutated NPM1 status. Blood. 2010;116(25):5486–96.

Schnittger S, Bacher U, Kern W et al (2011a) Prognostic impact of FLT3-ITD load in NPM1 mutated acute myeloid leukemia. Leukemia 25(8):1297–1304

Schnittger S, Dicker F, Kern W et al (2011b) RUNX1 mutations are frequent in de novo AML with noncomplex karyotype and confer an unfavorable prognosis. Blood 117(8):2348–2357

Schnittger S, Eder C, Jeromin S et al (2013) ASXL1 exon 12 mutations are frequent in AML with intermediate risk karyotype and are independently associated with an adverse outcome. Leukemia 27(1):82–91

Schoch C, Haferlach T, Haase D et al (2001) Patients with de novo acute myeloid leukaemia and complex karyotype aberrations show a poor prognosis despite intensive treatment: a study of 90 patients. Br J Haematol 112(1):118–126

Schoch C, Schnittger S, Klaus M et al (2003) AML with 11q23/MLL abnormalities as defined by the WHO classification: incidence, partner chromosomes, FAB

subtype, age distribution, and prognostic impact in an unselected series of 1897 cytogenetically analyzed AML cases. Blood 102(7):2395–2402

Schoch C, Kern W, Schnittger S, Hiddemann W, Haferlach T (2004) Karyotype is an independent prognostic parameter in therapy-related acute myeloid leukemia (t-AML): an analysis of 93 patients with t-AML in comparison to 1091 patients with de novo AML. Leukemia 18(1):120–125

Scholl S, Theuer C, Scheble V et al (2008) Clinical impact of nucleophosmin mutations and Flt3 internal tandem duplications in patients older than 60 yr with acute myeloid leukaemia. Eur J Haematol 80(3):208–215

Schuurhuis GJ, Heuser M, Freeman S et al (2018) Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD working party. Blood 131(12):1275–1291

Schwartz GW, Manning B, Zhou Y et al (2019) Classes of ITD predict outcomes in AML patients treated with FLT3 inhibitors. Clin Cancer Res 25(2):573–583

Schwind S, Marcucci G, Maharry K et al (2010a) BAALC and ERG expression levels are associated with outcome and distinct gene and microRNA expression profiles in older patients with de novo cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. Blood 116(25):5660–5669

Schwind S, Maharry K, Radmacher MD et al (2010b) Prognostic significance of expression of a single microRNA, miR-181a, in cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. J Clin Oncol 28(36):5257–5264

Seifert H, Mohr B, Thiede C et al (2009) The prognostic impact of 17p (p53) deletion in 2272 adults with acute myeloid leukemia. Leukemia 23(4):656–663

Shen Y, Zhu Y-M, Fan X et al (2011) Gene mutation patterns and their prognostic impact in a cohort of 1185 patients with acute myeloid leukemia. Blood 118(20):5593–5603

Shiah H-S, Kuo Y-Y, Tang J-L et al (2002) Clinical and biological implications of partial tandem duplication of the MLL gene in acute myeloid leukemia without chromosomal abnormalities at 11q23. Leukemia 16(2):196–202

Shimada A, Iijima-Yamashita Y, Tawa A et al (2018) Risk-stratified therapy for children with FLT3-ITD-positive acute myeloid leukemia: results from the JPLSG AML-05 study. Int J Hematol 107(5):586–595

Shin H-J, Min W-S, Min YH et al (2019) Different prognostic effects of core-binding factor positive AML with Korean AML registry data. Ann Hematol 98(5):1135–1147

Silva P, Neumann M, Schroeder MP et al (2017) Acute myeloid leukemia in the elderly is characterized by a distinct genetic and epigenetic landscape. Leukemia 31(7):1640–1644

Sitges M, Boluda B, Garrido A et al (2020) Scute myeloid leukemia with inv(3)(q21q26.2)/t(3;3)(q21;q26.2): study of 61 patients treated with intensive protocols. Eur J Haematol 105(2):138–147

Slichter SJ (2004) Relationship between platelet count and bleeding risk in thrombocytopenic patients. Transfus Med Rev 18(3):153–167

Slovak ML, Kopecky KJ, Cassileth PA et al (2000) Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. Blood 96(13):4075–4083

Slovak ML, Gundacker H, Bloomfield CD et al (2006) A retrospective study of 69 patients with t(6;9)(p23;q34) AML emphasizes the need for a prospective, multicenter initiative for rare 'poor prognosis' myeloid malignancies. Leukemia 20(7):1295–1297

Sorror ML, Maris MB, Storb R et al (2005) Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 106(8):2912–2919

Sorror ML, Giralt S, Sandmaier BM et al (2007a) Hematopoietic cell transplantation–specific comorbidity index as an outcome predictor for patients with acute myeloid leukemia in first remission: combined FHCRC and MDACC experiences. Blood 110(13):4606–4613

Sorror ML, Sandmaier BM, Storer BE et al (2007b) Comorbidity and disease status–based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. J Clin Oncol 25(27):4246–4254

Sorror ML, Storb RF, Sandmaier BM et al (2014) Comorbidity-age index: a clinical measure of biologic age before allogeneic hematopoietic cell transplantation. J Clin Oncol 32(29):3249–3256

Stengel A, Kern W, Haferlach T et al (2017) The impact of TP53 mutations and TP53 deletions on survival varies between AML, ALL, MDS and CLL: an analysis of 3307 cases. Leukemia 31(3):705–711

Stengel A, Kern W, Meggendorfer M et al (2018) Number of RUNX1 mutations, wild-type allele loss and additional mutations impact on prognosis in adult RUNX1-mutated AML. Leukemia 32(2):295–302

Stephens PJ, Greenman CD, Fu B et al (2011) Massive genomic rearrangement acquired in a single catastrophic event during cancer development. Cell 144(1):27–40

Steudel C, Wermke M, Schaich M et al (2003) Comparative analysis of MLL partial tandem duplication and FLT3 internal tandem duplication mutations in 956 adult patients with acute myeloid leukemia. Genes Chromosomes Cancer 37(3):237–251

Stirewalt DL, Kopecky KJ, Meshinchi S et al (2001) FLT3, RAS, and TP53 mutations in elderly patients with acute myeloid leukemia. Blood 97(11):3589–3595

Stirewalt DL, Kopecky KJ, Meshinchi S et al (2006) Size of FLT3 internal tandem duplication has prognostic significance in patients with acute myeloid leukemia. Blood 107(9):3724–3726

Stölzel F, Pfirrmann M, Aulitzky WE et al (2011) Risk stratification using a new prognostic score for patients

with secondary acute myeloid leukemia: results of the prospective AML96 trial. Leukemia 25(3):420–428
Stölzel F, Lüer T, Parmentier SB et al (2014) The prevalence of extramedullary AML detected by 18-FDG/PET-CT: results from the prospective PET-AML trial. Blood 124(21):2270–2270
Stölzel F, Mohr B, Kramer M et al (2016) Karyotype complexity and prognosis in acute myeloid leukemia. Blood Cancer J 6(1):e386
Straube J, Ling VY, Hill GR, Lane SW (2018) The impact of age, NPM1mut, and FLT3ITD allelic ratio in patients with acute myeloid leukemia. Blood 131(10):1148–1153
Su L, Tan Y, Lin H et al (2018) Mutational spectrum of acute myeloid leukemia patients with double CEBPA mutations based on next-generation sequencing and its prognostic significance. Oncotarget 9(38):24970–24979
Su L, Gao S, Tan Y et al (2019) CSF3R mutations were associated with an unfavorable prognosis in patients with acute myeloid leukemia with CEBPA double mutations. Ann Hematol 98(7):1641–1646
Suzuki T, Kiyoi H, Ozeki K et al (2005) Clinical characteristics and prognostic implications of NPM1 mutations in acute myeloid leukemia. Blood 106(8):2854–2861
Tallman MS, Hakimian D, Shaw JM et al (1993) Granulocytic sarcoma is associated with the 8;21 translocation in acute myeloid leukemia. J Clin Oncol 11(4):690–697
Tallman MS, Kim HT, Paietta E et al (2004) Acute monocytic leukemia (French-American-British classification M5) does not have a worse prognosis than other subtypes of acute myeloid leukemia: a report from the Eastern Cooperative Oncology Group. J Clin Oncol 22(7):1276–1286
Tallman MS, Wang ES, Altman JK et al (2019) Acute myeloid Leukemia, version 3.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw 17(6):721–749
Tang J-L, Hou H-A, Chen C-Y et al (2009) AML1/RUNX1 mutations in 470 adult patients with de novo acute myeloid leukemia: prognostic implication and interaction with other gene alterations. Blood 114(26):5352–5361
Tarlock K, Alonzo TA, Moraleda PP et al (2014) Acute myeloid leukaemia (AML) with t(6;9)(p23;q34) is associated with poor outcome in childhood AML regardless of FLT3-ITD status: a report from the Children's Oncology Group. Br J Haematol 166(2):254–259
Taskesen E, Bullinger L, Corbacioglu A et al (2011) Prognostic impact, concurrent genetic mutations, and gene expression features of AML with CEBPA mutations in a cohort of 1182 cytogenetically normal AML patients: further evidence for CEBPA double mutant AML as a distinctive disease entity. Blood 117(8):2469–2475
Taub JW, Berman JN, Hitzler JK et al (2017) Improved outcomes for myeloid leukemia of Down syndrome: a report from the Children's Oncology Group AAML0431 trial. Blood 129(25):3304–3313
The Cancer Genome Atlas Research Network (2013) Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med 368(22):2059–2074
Theis F, Corbacioglu A, Gaidzik VI et al (2016) Clinical impact of GATA2 mutations in acute myeloid leukemia patients harboring CEBPA mutations: a study of the AML study group. Leukemia 30(11):2248–2250
Thiede C, Steudel C, Mohr B et al (2002) Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. Blood 99(12):4326–4335
Thiede C, Koch S, Creutzig E et al (2006) Prevalence and prognostic impact of NPM1 mutations in 1485 adult patients with acute myeloid leukemia (AML). Blood 107(10):4011–4020
Thiede C, Bloomfield CD, Coco FL et al (2007) The high prevalence of FLT3-ITD mutations is associated with the poor outcome in adult patients with t(6;9)(p23;q34) positive AML—results of an international metaanalysis. Blood 110(11):761–761
Thol F, Damm F, Wagner K et al (2010) Prognostic impact of IDH2 mutations in cytogenetically normal acute myeloid leukemia. Blood 116(4):614–616
Thol F, Damm F, Lüdeking A et al (2011) Incidence and prognostic influence of DNMT3A mutations in acute myeloid leukemia. J Clin Oncol 29(21):2889–2896
Thol F, Kölking B, Hollink IHI et al (2013) Analysis of NUP98/NSD1 translocations in adult AML and MDS patients. Leukemia 27(3):750–754
Tien F-M, Hou H-A, Tsai C-H et al (2018a) Hyperleukocytosis is associated with distinct genetic alterations and is an independent poor-risk factor in de novo acute myeloid leukemia patients. Eur J Haematol 101(1):86–94
Tien F-M, Hou H-A, Tang J-L et al (2018b) Concomitant WT1 mutations predict poor prognosis in acute myeloid leukemia patients with double mutant CEBPA. Haematologica 103(11):e510–e513
Torrebadell M, Díaz-Beyá M, Kalko SG et al (2018) A 4-gene expression prognostic signature might guide post-remission therapy in patients with intermediate-risk cytogenetic acute myeloid leukemia. Leuk Lymphoma 59(10):2394–2404
Touw IP, Sanders MA (2020) Mutant allelic burden in acute myeloid leukaemia: why bother? Br J Haematol 188(6):817–818
Tsai C-H, Hou H-A, Tang J-L et al (2016) Genetic alterations and their clinical implications in older patients with acute myeloid leukemia. Leukemia 30(7):1485–1492
Tsimberidou A-M, Kantarjian HM, Wen S et al (2008) Myeloid sarcoma is associated with superior event-free survival and overall survival compared with acute myeloid leukemia. Cancer 113(6):1370–1378
Tsuji K, Motoji T, Sugawara I et al (2000) Significance of lung resistance-related protein in the clinical outcome of acute leukaemic patients with reference to P-glycoprotein. Br J Haematol 110(2):370–378

Valk PJM, Verhaak RGW, Beijen MA et al (2004) Prognostically useful gene-expression profiles in acute myeloid leukemia. N Engl J Med 350:1617–1628. https://doi.org/10.1056/NEJMoa040465

van Solinge TS, Zeijlemaker W, Ossenkoppele GJ, Cloos J, Schuurhuis GJ (2018) The interference of genetic associations in establishing the prognostic value of the immunophenotype in acute myeloid leukemia. Cytometry B Clin Cytom 94(1):151–158

Vasu S, Kohlschmidt J, Mrózek K et al (2018) Ten-year outcome of patients with acute myeloid leukemia not treated with allogeneic transplantation in first complete remission. Blood Adv 2(13):1645–1650

Venditti A, Poeta GD, Maurillo L et al (2004) Combined analysis of bcl-2 and MDR1 proteins in 256 cases of acute myeloid leukemia. Haematologica 89(8):934–939

Verhaak RGW, Goudswaard CS, van Putten W et al (2005) Mutations in nucleophosmin (NPM1) in acute myeloid leukemia (AML): association with other gene abnormalities and previously established gene expression signatures and their favorable prognostic significance. Blood 106(12):3747–3754

Versluis J, Hout FEM (2017) In 't, Devillier R, et al. Comparative value of post-remission treatment in cytogenetically normal AML subclassified by NPM1 and FLT3 -ITD allelic ratio. Leukemia 31(1):26–33

Vetro C, Haferlach T, Meggendorfer M et al (2020) Cytogenetic and molecular genetic characterization of KMT2A-PTD positive acute myeloid leukemia in comparison to KMT2A-rearranged acute myeloid leukemia. Cancer Genet 240:15–22

Virappane P, Gale R, Hills R et al (2008) Mutation of the Wilms' tumor 1 gene is a poor prognostic factor associated with chemotherapy resistance in normal karyotype acute myeloid leukemia: the United Kingdom Medical Research Council Adult Leukaemia Working Party. J Clin Oncol 26(33):5429–5435

von Neuhoff C, Reinhardt D, Sander A et al (2010) Prognostic impact of specific chromosomal aberrations in a large group of pediatric patients with acute myeloid leukemia treated uniformly according to trial AML-BFM 98. J Clin Oncol 28(16):2682–2689

Wagner K, Damm F, Göhring G et al (2010) Impact of IDH1 R132 mutations and an IDH1 single nucleotide polymorphism in cytogenetically normal acute myeloid leukemia: SNP rs11554137 is an adverse prognostic factor. J Clin Oncol 28(14):2356–2364

Wakita S, Yamaguchi H, Ueki T et al (2016) Complex molecular genetic abnormalities involving three or more genetic mutations are important prognostic factors for acute myeloid leukemia. Leukemia 30(3):545–554

Walker CJ, Kohlschmidt J, Eisfeld A-K et al (2019) Genetic characterization and prognostic relevance of acquired uniparental disomies in cytogenetically normal acute myeloid leukemia. Clin Cancer Res 25(21):6524–6531

Wang B, Liu Y, Hou G et al (2016) Mutational spectrum and risk stratification of intermediate-risk acute myeloid leukemia patients based on next-generation sequencing. Oncotarget 7(22):32065–32078

Wang M, Lindberg J, Klevebring D et al (2017) Validation of risk stratification models in acute myeloid leukemia using sequencing-based molecular profiling. Leukemia 31(10):2029–2036

Wattad M, Weber D, Döhner K et al (2017) Impact of salvage regimens on response and overall survival in acute myeloid leukemia with induction failure. Leukemia 31(6):1306–1313

Weber S, Alpermann T, Dicker F et al (2014) BAALC expression: a suitable marker for prognostic risk stratification and detection of residual disease in cytogenetically normal acute myeloid leukemia. Blood Cancer J 4(1):e173

Weber S, Haferlach T, Haferlach C, Kern W (2016) Comprehensive study on ERG gene expression in normal karyotype acute myeloid leukemia: ERG expression is of limited prognostic value, whereas the accumulation of adverse prognostic markers stepwise worsens the prognosis. Blood Cancer J 6(12):e507

Weinberg OK, Ohgami RS, Ma L et al (2014) Acute myeloid leukemia with monosomal karyotype: morphologic, immunophenotypic, and molecular findings. Am J Clin Pathol 142(2):190–195

Weinberg OK, Gibson CJ, Blonquist TM et al (2017) NPM1 mutation but not RUNX1 mutation or multilineage dysplasia defines a prognostic subgroup within de novo acute myeloid leukemia lacking recurrent cytogenetic abnormalities in the revised 2016 WHO classification. Am J Hematol 92(7):E123–E124

Weissmann S, Alpermann T, Grossmann V et al (2012) Landscape of TET2 mutations in acute myeloid leukemia. Leukemia 26(5):934–942

Whitman SP, Archer KJ, Feng L et al (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(19):7233–7239

Whitman SP, Maharry K, Radmacher MD et al (2010) FLT3 internal tandem duplication associates with adverse outcome and gene- and microRNA-expression signatures in patients 60 years of age or older with primary cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. Blood 116(18):3622–3626

Wierzbowska A, Wawrzyniak E, Siemieniuk-Rys M et al (2017) Concomitance of monosomal karyotype with at least 5 chromosomal abnormalities is associated with dismal treatment outcome of AML patients with complex karyotype—retrospective analysis of Polish Adult Leukemia Group (PALG). Leuk Lymphoma 58(4):889–897

Wiggers CRM, Baak ML, Sonneveld E et al (2019) AML subtype is a major determinant of the association between prognostic gene expression signatures and

their clinical significance. Cell Rep 28(11):2866–2877.e5

Wilhelmson AS, Porse BT (2020) CCAAT enhancer binding protein alpha (CEBPA) biallelic acute myeloid leukaemia: cooperating lesions, molecular mechanisms and clinical relevance. Br J Haematol 190(4):495–507

Wouters BJ, Löwenberg B, Erpelinck-Verschueren CAJ et al (2009) Double CEBPA mutations, but not single CEBPA mutations, define a subgroup of acute myeloid leukemia with a distinctive gene expression profile that is uniquely associated with a favorable outcome. Blood 113(13):3088–3091

Wu X, Feng X, Zhao X et al (2016) Prognostic significance of FLT3-ITD in pediatric acute myeloid leukemia: a meta-analysis of cohort studies. Mol Cell Biochem 420(1–2):121–128

Xu Q, Li Y, Lv N et al (2017) Correlation between isocitrate dehydrogenase gene aberrations and prognosis of patients with acute myeloid leukemia: a systematic review and meta-analysis. Clin Cancer Res 23(15):4511–4522

Yamato G, Shiba N, Yoshida K et al (2018) RUNX1 mutations in pediatric acute myeloid leukemia are associated with distinct genetic features and an inferior prognosis. Blood 131(20):2266–2270

Yanada M, Yamamoto Y, Iba S et al (2016) TP53 mutations in older adults with acute myeloid leukemia. Int J Hematol 103(4):429–435

Yang X, Wong MPM, Ng RK (2019) Aberrant DNA methylation in acute myeloid leukemia and its clinical implications. Int J Mol Sci 20(18):4576

Yoshizato T, Nannya Y, Atsuta Y et al (2017) Genetic abnormalities in myelodysplasia and secondary acute myeloid leukemia: impact on outcome of stem cell transplantation. Blood 129(17):2347–2358

Yuan X-Q, Chen P, Du Y-X et al (2019) Influence of DNMT3A R882 mutations on AML prognosis determined by the allele ratio in Chinese patients. J Transl Med 17(1):220

Zhang Y, Wang F, Chen X et al (2019) Companion gene mutations and their clinical significance in AML with double mutant CEBPA. Cancer Gene Ther 27(7-8):599–606

Zhou J, Zhang T, Xu Z et al (2019a) BCL2 overexpression: clinical implication and biological insights in acute myeloid leukemia. Diagn Pathol 14:68

Zhou F, Zhou F, Du M et al (2019b) Comprehensive prognostic scoring systems could improve the prognosis of adult acute myeloid leukemia patients. Int J Hematol 110(5):575–583

Zhou W, Chen G, Gong D et al (2020) Loss of the Y chromosome predicts a high relapse risk in younger adult male patients with t(8;21) acute myeloid leukemia on high-dose cytarabine consolidation therapy: a retrospective multicenter study. Leuk Lymphoma 61(4):820–830