OPEN ACCESS Freely available online

Advances in Medical Research

Commentary Article

Liquid Tumors at a Glance: Innovations, Challenges and Future Directions in Hematologic Oncology

Ashraf Abdullah Saad*

Department of Pediatric Hematologic Oncology and BMT, Sultan Qaboos University Hospital, Muscat, Oman

ABSTRACT

Hematologic malignancies, commonly referred to as liquid tumors, encompass a diverse group of cancers such as leukemias, lymphomas, and myelomas. Defined by unique genetic, molecular, and clinical characteristics, these diseases present significant challenges in diagnosis, treatment, and prognosis. Despite advances in therapeutic strategies —including immunotherapy, targeted therapies, and Hematopoietic Stem Cell Transplantation (HSCT)— patients with high-risk or relapsed disease often face poor outcomes. Notably, multiple myeloma (MM) remains an incurable plasma cell malignancy despite recent innovations, underscoring the need for more effective and durable treatment strategies. This article offers a comprehensive review of the classification, pathophysiology, and molecular features of liquid tumors, with a particular focus on emerging therapeutic approaches and unmet clinical needs. By addressing current challenges and future opportunities, this work seeks to contribute to the advancement of care for patients with these complex malignancies.

Keywords: leukemia, lymphoma, multiple myeloma, myeloproliferative neoplasms, fenretinide.

INTRODUCTION

The first hematologic malignancy was described by Thomas Hodgkin in 1832. The disease was called "Hodgkin's disease" until it was officially renamed "*Hodgkin lymphoma*" in the late 20th century. The published descriptions of other hematologic malignancies, such as leukemia and MM, soon followed. Hematologic malignancies have distinct genetic and epigenetic signatures and are traditionally categorised by site according to whether cancer is first detected in the blood (leukemias), lymph nodes (lymphomas - Hodgkin and non-Hodgkin) or bone marrow (myelomas) [1]. Despite its relatively lower frequency, tumor protein 53 (*TP53*) alterations (including *TP53* mutations or 17p deletions] are closely linked with complex karyotype, poor prognosis, and chemotherapeutic response in hematologic malignancies [2]. Somatic *TP53* alterations have been reported in acute lymphoblastic leukemia (ALL) (16%) [3], acute myeloid leukemia (AML) (12%) [4,5], chronic lymphocytic leukemia (CLL) (7%) [6,7,8], and myelodysplastic syndromes (MDS) (6%) [9,10,11]. As a matter of fact, the tumor suppressor gene *TP53* is the most frequently mutated gene in human cancers, with mutations occurring in more than 50% of human primary tumors [12,13]. Interestingly, the frequency of *TP53* mutations is even higher in tumors that relapse after therapy. Notably, the p53 protein (commonly referred to as the "guardian of the genome"), made by the *TP53* gene, normally prevents the propagation of genetically defective cells by supervising the repair of damaged DNA. Consequently, defective p53 renders cells relatively resistant to chemo- and radiotherapies and promotes a "mutator phenotype" prone to rapid accumulation of additional mutations [14]. Moreover, patients with germline *TP53* mutations [the underlying cause of Li-Fraumeni and Li-Fraumeni-like syndromes] have a twenty-five-fold greater risk of early-onset cancers (e.g., leukemia, sarcomas, breast cancer, and brain tumors) [15]. The mainstay treatment for high-risk or relapsed/refractory (R/R) hematologic malignancies (including leukemias) has historically revolved around allogeneic-HSCT (allo-HSCT). Despite increasing survival rates, allo-HSCT is associated with long-term morbidity and mortality, mainly due to chronic graft-versus-host disease (cGvHD) which remains a very challenging and serious complication of allo-HSCT. In this context, cGvHD is stigmatised by futile treatment options lying between the harmful corticosteroids as the standard first-line treatment and elusive second-line therapies [16]. In addition,

Correspondence to: Ashraf Abdullah Saad, Department of Pediatric Hematologic Oncology and BMT, Sultan Qaboos University Hospital, Muscat, Oman, E-mail: dr.ashraf123321@gmail.com

Received: 26-Sep-2024, Manuscript No. LDAMR-24-34316; **Editor assigned:** 01-Oct-2024, PreQC No. LDAMR-24-34316 (PQ); **Reviewed:** 18-Oct-2024, QCNo. LDAMR-24-34316; **Revised:** 25-Oct-2024, Manuscript No. LDAMR-24-34316 (R); **Published:** 05-Nov-2024, DOI: 10.12715/2564-8942.24.7.042

Citation: Saad AA (2024). Liquid Tumors at a Glance: Innovations, Challenges and Future Directions in Hematologic Oncology. J Adv Med Res. 7:042

given the poor prognosis of patients who relapse after allo-HSCT, targeted immunotherapies have emerged as a promising therapeutic option in hematologic oncology [17].

Leukemias

Leukemia is a blood cancer caused by the rapid production of abnormal white blood cells and is the most common cancer in children and adolescents. Despite advances made in therapeutic strategies, allo-HSCT remains a standard-of-care across various leukemia subtypes for curative intent [18]. Leukemia classification is based on the type of blood cell affected (includes both lymphoblastic and myeloid leukemias) and the rate of leukemia progression [includes an acute or chronic forms]. Acute leukemias represent a clonal expansion and arrest at a specific stage of myeloid or lymphoid hematopoiesis [19]. Acute leukemias are characterized by greater than 20% blast cells in the bone marrow (BM) or peripheral blood (PB) leading to a more rapid onset of symptoms. Nevertheless, the 20% blast cutoffs were eliminated for most AML types with 'defining genetic abnormalities' (DGAs) (see below) [20,21,22]. Although allo-HSCT is an important therapeutic modality for acute leukemia, its outcomes remain unsatisfactory [23]. In contrast, chronic leukemia has less than 20% blasts with a relatively chronic onset of symptoms [24]. Unlike acute leukemias, blast cells in chronic leukemias are more mature and can carry out some of their normal functions [25]. Principally, leukemia is subdivided into four major subtypes: ALL, CLL, AML, and chronic myeloid leukemia (CML) [26]. However, this classification is an over-simplification. In the WHO classification, precursor B- and T-lymphoblastic neoplasms overlap with their corresponding lymphoma i.e., B-cell lymphoblastic leukemia/lymphoma (B-ALL/B-LBL) and T-lymphoblastic leukemia/lymphoma (T-ALL/T-LBL) respectively [27]. It is important to note that mature B-ALL has been eliminated from the 2008 WHO classification of B-ALL as it is inseparable from *Burkitt lymphoma* (mature B-ALL is treated as stage IV *Burkitt lymphoma*) [28]. In addition, CML is classified as a myeloproliferative neoplasm (MPN). Importantly, CML is not to be confused with chronic myelomonocytic leukemia (CMML). CMML is a hybrid or mixed myelodysplastic/myeloproliferative neoplasm characterized by a large heterogeneity of clinical features but allo-HSCT remains the only potentially curative option. However, the inherent toxicity of this procedure makes the decision to proceed to allo-HSCT challenging, particularly because patients with CMML are mostly older and comorbid [29].

Acute lymphoblastic leukemia (ALL)

ALL is still an important cause of morbidity and mortality in children and adults [30]. Accounting for 25% of all childhood cancers, ALL is the most common malignant neoplastic disease in children. Eighty–five percent of the cases of childhood ALL are of the B–lineage (B–ALL) [31]. Despite cure rates exceeding 90% in children with B-ALL, outcomes of older adolescents and young adults with ALL still lag behind those of their younger counterparts despite pediatric-inspired chemotherapy regimens [32]; and yet, childhood R/R ALL is associated with poor outcomes. Altogether, ALL still represents the leading causes of cancer-related death, underscoring a critical unmet need for effective new therapies [33]. Rearrangements of the human Histone-lysine N-methyltransferase 2A (*KMT2A*) or myeloid/lymphoid/mixed lineage leukemia genes (*MLL*), detected in approximately 5% of childhood ALL, are most frequent in infants (<12 months of age) and are associated with poor outcome [34,35]. Approximately 70% of infants with B-ALL have a *KMT2A* rearrangement (*KMT2A*-R), and their outcome is particularly unfavorable compared to infant ALL without *KMT2A* rearrangements (often referred to as *KMT2A* germline/*KMT2A*-G) [36]. In this context, infant ALL constitutes another rare ALL subtype for which innovative therapies are urgently needed, since their unfavorable outcome remains essentially unchanged over the past several decades [37]. Strikingly, even though noninfants with *KMT2A*-R ALL have a superior outcome to infants, their outcomes remain clearly inferior to those of childhood ALL and even allo-HSCT has failed to improve their outcome [38]. Moreover, there is an unmet need for developing immunotherapies for the large cohort of patients who are deemed unfit for post-remission intensive chemotherapy or HSCT in first remission because of toxicity to previous chemotherapy or significant co-morbidities [39]. In a similar vein, the poor outcome associated with philadelphia chromosome (Ph)-like ALL (characterized by a gene expression profile similar to that of Ph^+ ALL, but lacks the canonical *BCR-ABL1* fusion) which has been improved significantly by the early addition of imatinib or related tyrosine kinase inhibitors (TKIs) to intensive chemotherapy regimens with or without HSCT in first complete remission (CR1) provided a compelling rationale to harness targeted therapies or precision medicine approaches for ALL [40]. Nevertheless, most molecularly targeted approaches have thus far failed to improve long-term outcomes in relapsed ALL [41]. Remarkably, the emergence of immunotherapies has transformed therapy for relapsed ALL. As CD19 is expressed by essentially all B-cell malignancies at clinical presentation, the prototype Bi-specific T-cell engager (BiTE) therapy (Blinatumomab) and chimeric antigen receptor (CAR)-T cell therapy (Tisagenlecleucel) respectively, were granted approval by the United States Food and Drug Administration (FDA or US FDA) as CD19-targeting B-cell malignancies. Nevertheless, relapses with loss or reduction in CD19 surface expression were increasingly recognized as a cause of treatment failure [42,43,44]. In the case with blinatumomab, the high initial overall response rate is frequently accompanied by subsequent relapse or refractoriness to treatment [45]. Relapses with loss or reduction in CD19 surface expression are being increasingly recognized as a cause of treatment failure of blinatumomab. Mechanistically, reduction in response may be due to low CD19 antigen expression or antigen loss from alternative splicing, non-functional membrane chaperone proteins, transformation to myeloid lineages, or CD19 mutations. It is the author's experience that a 21-months old child had developed blinatumomab-induced lineage switch of B-ALL with t (4:11) (q21; q23) KMT2A/AFF1 into an aggressive AML. Intriguingly, similar mechanisms of resistance also develop in response to CD19-targeted CAR T-cell therapies. In addition, the increased expression level of PD-L1 in blinatumomab-resistant patients is another explanation for tumor escape [46]. Remarkably, blinatumomab does not obviate the need for intrathecal therapy due to the lack of sufficient evidence to suggest that it crosses the blood-brain barrier (BBB) [47]. In this vein, despite that cranial irradiation was omitted from treatment protocols for children with newly diagnosed ALL, intrathecal therapy alone was strongly associated with cognitive impairment [48]. Despite that T-LBL represents the second most frequent subtype of *Non-Hodgkin lymphoma* (NHL) in children and adolescents [49], T-LBL and T-ALL have historically been considered a spectrum of the same disease. Owing to the

great overlap in their morphological, clinical, and immune-phenotypic features [50,51], it is often debated whether T-LBL and T-ALL are different entities or represent manifestations of the same disease [52]. It is worth noting that T-ALL/T-LBL accounts for approximately 15% of pediatric and 25% of adult ALL [53]. While risk stratification is well-developed for patients with B-ALL, it remains challenging for those with T-ALL [54]. In addition, immunotherapeutic approaches for T-ALL has lagged significantly behind B-ALL [55]. Indeed, the search and identification of selective targets for T-ALL blasts not expressed by normal T-cells remains the main challenge [56]. Not surprisingly, outcomes for T-ALL are still lagging behind those for B-ALL by 5–10% in most studies [57]. In particular, relapsed T-ALL and T-LBL portend a poor prognosis [58]. Given the poor salvage rates of <25% and <15%, respectively, early intensification of therapy to improve outcomes is essential [59,60,61]. Intriguingly, recent evidence demonstrating differential responses to chemotherapy raise the possibility that T-LBL and T-ALL are distinct clinical and biologic entities [62].

Acute myeloid leukemia (AML)

AML is the most common acute leukemia in adults. AML is not just one disease, but rather a heterogeneous group of disorders caused by chromosomal translocations and rearrangements resulting in the uncontrolled proliferation of myeloid blast cells (myeloblasts) in the BM and impaired production of normal thrombocytes, erythrocytes, and leukocytes [63,64]. Strikingly, AML is an aggressive hematologic malignancy that has been suffering from stagnant survival curves for decades. More than 90% of patients with newly diagnosed AML fall into an intermediate or poor risk category per the European Leukemia Network (ELN) criteria, and in this patient population, allo-HSCT in CR1 serve as the only chance for cure [65,66]. According to 5th edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours (WHO-HEM5, also called WHO 2022), AML entities are now grouped into AML defined by differentiation [previously known as as AML-NOS] and AML with DGAs including *PML::RARA, RUNX1::RUNX1T1, CBFB::MYH11, RBM15::MRTFA* and *DEK::NUP214*; rearrangements involving *KMT2A, MECOM (EVI1)* and *NUP98*; and *NPM1* mutation. However, the biggest difference is the removal of the blast cutoff for all genetically defined AML cases except AML with *BCR*::ABL1 fusion, AML with CEBPA mutation and myelodysplasia-related AML (AML-MR). Notably, the presence of AML-DGA excludes a diagnosis of MDS, particularly in cases having >2% and >5% blasts in PB and BM respectively [67]. In addition, the remaining AML categories retain the 20% blast cutoff, discriminating it from MDS [68]. However, in parallel to the WHO-HEM5, an alternative International Consensus Classification (ICC) has been proposed. In contrast to the WHO-HEM5, ICC sets the blast cutoff for AML-DGA to 10%, assigning cases with 10–19% blasts without DGA to a new category MDS/AML (several key differences between WHO-HEM5 and ICC were highlighted by S. Huber et a.) [69]. In contrast to the WHO system (established in 2008), the French–American–British (FAB) classification (established in 1976) does not take into account chromosomal and molecular features but assigns AML into eight subtypes [M0-M7] based on the type of cells from which the leukemia developed and the maturity of cells [Table-1]. Basically, subtypes M0 through M5 all start in immature forms of white blood cells called myeloblasts. M6 AML starts in very immature forms of red blood cells, while M7 AML starts in immature forms of cells that make platelets [megakaryocytes] [70]. Despite that acute promyelocytic leukemia (APL or APML; AML-M3) is the most curable subtype of AML [71], it is considered a medical emergency with a very high pre-treatment mortality [72]. Approximately 10% of patients with AML-M3 still experience disease relapse following front-line therapy [73]. The poor prognosis of AML is usually secondary to high-risk genetic features or due to antecedent hematologic disorders e.g., myelodysplastic syndrome (MDS). More than one-third of newly diagnosed children and adolescents with AML continue to relapse and experience suboptimal long-term outcomes [74]. On the other hand, AML is the most common acute leukemia affecting the elderly, with the average age of diagnosis being 70 years old [75], where it poses a great therapeutic challenge to the clinical hematologist [76]. The 5-year survival rate for adult patients with AML is at approximately 40% according to the WHO [77]. The nucleoside analogue cytarabine (Ara-C) combined with an anthracycline such as daunorubicin continues to be the backbone of therapy for AML. However, chemoresistance remains the main cause of poor long-term survival associated with high relapse rate in AML [78]. The occurrence of AML relapse is attributed to the persistence and clonal evolution of leukemic stem cells (LSCs) that hijack stem cell programs (such as self-renewal capacity) to fuel leukemogenesis and progression [79,80]. Further, LSCs show different degrees of inherent treatment resistance and may acquire secondary resistance during treatment through genetic and non-genetic mechanisms [81]. On the other hand, despite that HSCT is an established curative treatment option for patients with AML, transplant recipients were at substantially higher risk of developing severe/life-threatening conditions and premature death [82]. The most frequent genetic alteration in AML is mutation of the FMS-like tyrosine kinase 3 [*FLT3*] gene wich encodes the *FLT3* receptor [CD135], emerging as a prognostic factor, a new marker for measurable residual disease [MRD], and a potential novel therapeutic target in AML [83,84]. By the way, *FLT3* is a type III receptor tyrosine kinase that contributes to normal HSC survival. There are two major types of *FLT3* mutations: internal tandem duplication mutations in the juxtamembrane domain (*FLT3*-ITD) and point mutations or deletion in the tyrosine kinase domain (*FLT3*-TKD). *FLT3*-ITD is an independent poor prognostic factor that is strongly associated with high WBC and an increased blast percentage at diagnosis and frequently found in cytogenetically normal AML [85]. *FLT3*-ITD in the juxtamembrane region is thought to destroy the self-suppressing conformation of *FLT3* receptor, thereby activating downstream pathways continuously, including MAPK/ERK, STAT5 and PI3K [86]. *FLT3*-ITD is found in approximately 25% of adult patients but in more than 30% of patients over 55 years of age [87,88]. In contrast, *FLT3*-ITD occur in 10%-15% of pediatric de novo AML patients [89,90], and those with high *FLT3*-ITD AR [> 0.4] have inferior outcomes with survival of approximately 50%-65% with HSCT [91]. The ELN introduced the allelic ratio [AR] of *FLT3*-ITD for risk stratification. Several groups demonstrated that high *FLT3*-ITD AR (≥0.5) (*FLT3*-ITD^{high}) is associated with a poor prognosis but not the low *FLT3*-ITD AR [<0.5] (*FLT3*-ITD^{low}) [92]. Remarkably, the natural history of *FLT3*-mutated AML changed after the approval of the *FLT3* inhibitors midostaurin for frontline therapy and gilteritinib for R/R patients [93]. Because *FLT3* inhibitor-based therapy has improved survival [94], the new ELN classification (2022)

categorized AMLs with *FLT3*-ITD in the intermediate-risk group, irrespective of the allelic ratio or concurrent presence of *NPM1* mutation [95]. The reclassification of *FLT3*-ITD mutational status into the intermediate- risk group was one of most important changes provided by the ELN 2022 risk classification [96]. On the other hand, the clinical impact of *FLT3*-TKD, found in about 7% of patients at diagnosis, on the long-term outcome is controversial but in general is not considered a poor prognostic factor. Consequently, neither do the National Comprehensive Cancer Network (NCCN) or ELN consider the presence of *FLT3*-TKD mutations as a recommendation for allo-HSCT [97,98]. Nonetheless, the treatment of patients with *FLT3*-mutated AML remains challenging despite the approval of several *FLT3* inhibitors over the last few years [99]. In this vein, Tarlock et al., recently demonstrated that *FLT3* inhibition is not an effective target for therapeutic intervention in ITD^{pos}/*NUP98::NSD1* AML in a large cohort of patients with *FLT3*-ITD (included 3033 pediatric and young adult patients, aged 1 month-29 years); highlighting that further efforts to study the early intervention of novel and targeted therapies are urgently needed for those patients [100]. This supports recent studies indicating that *FLT3*-ITD cooccurring with *WT1*, *UBTF*, or *NUP98-NSD1* is associated with significantly inferior prognosis [101,102,103,104,105].

Table 1: The French–American–British (FAB) AML classification system[1]

FAB subtype	Name
M0	Undifferentiated acute myeloblastic leukemia
M1	Acute myeloblastic leukemia with minimal maturation
M2	Acute myeloblastic leukemia with maturation
M3	Acute promyelocytic leukemia (APL)
M4	Acute myelomonocytic leukemia
M4 eos	Acute myelomonocytic leukemia with eosinophilia
M5	Acute monocytic leukemia
M6	Acute erythroid leukemia
M7	Acute megakaryoblastic leukemia

Note: [1]Society AC. Acute Myeloid Leukemia (AML) Subtypes and Prognostic Factors 2018 [Available from: https://www.cancer.org/cancer/acute-myeloid-leukemia/detection-diagnosis-staging/howclassified.html.

Myelodysplastic syndromes (MDS)

Myelodysplastic syndromes (MDS) are a heterogeneous clonal disease of myeloid neoplasms characterized by inefective hematopoiesis, variable degree of cytopenias, and an increased risk of progression to AML. The threshold for defining dysplasia is recommended as 10% for all lineages; for megakaryocytes, micromegakaryocytes are the most specific indicator of MDS, and a higher threshold of dysplasia may be warranted when other types of dysmegakaryopoiesis are included [106,107]. MDS entities are separated into two major groups: MDS with defining genetic abnormalities and MDS defined morphologically. MDS with defining genetic abnormalities includes the following entities: MDS with biallelic *TP53* inactivation, MDS with low blasts and SF3B1 mutation (MDS-SF3B1) and MDS with low blasts and del(5q). MDS defined morphologically includes MDS with low blasts, hypoplastic MDS, MDS with increased blasts-1, MDS with increased blasts-2 and MDS with fibrosis. Although the 20% blast cutoffs were eliminated for most AML types with DGAs, this 20% blast cutoff was retained to delineate MDS from AML in order to avoid overtreatment of patients. In this context, the family of MDS with increased blasts (IBs) includes disease with <20% blasts [108]. Despite the approval of five MDS-specific therapies in the USA since 2004 and the increasing use of allo-HSCT, the prognosis remains dismal for most patients with higher-risk MDS (HR-MDS) [109]. Mutations in *TP53*, *RUNX1*, *ASXL1*, Janus kinase 2 [*JAK2*], and RAS pathway genes are associated with significantly shorter overall survival (OS) or relapse-free survival (RFS) after allo-HSCT, with *TP53* mutations being particularly adverse [110,111,112]. One potential mechanism underlying the poor prognosis associated with *TP53* mutations is the induction of an immunosuppressive microenvironment that permits immune evasion of tumor cells [113,114,115]. Supporting this hypothesis, AM Zeidan, JP Bewersdorf et al., recently found both a higher T-cell population and upregulation of inhibitory immune checkpoint proteins such as PD-L1 compared to *TP53* wild-type in BM from *TP53*-mutated AML/HR-MDS. Moreover, RNA sequencing analyses revealed higher expression of the myeloid immune checkpoint gene *LILRB3* in *TP53*-mutant samples suggesting a novel therapeutic target [116]. The DNA methyltransferase inhibitors azacitidine and decitabine, also known as hypomethylating agents (HMAs), have become standard-of-care for patients with HR-MDS [117]. Both HMAs are administered parenterally (requiring daily visits to a treatment centre for 5 consecutive days or 7 consecutive days of every 28-day treatment cycle) which represent a substantial burden for the older adult population with this disease (median age of 73 years at diagnosis) as well as is associated with so-called time toxicity [118]. Nonetheless, only half of the HR-MDS patients treated with HMAs achieves objective responses, and most responders (only 10–20% of patients) eventually lose response within 1-2 years [119,120,121,122,123]. Unfortunately, there are no standard-of-care therapeutic options for patients after HMA failure [124]. Up to the present, the prognosis of patients with HMA failure remains bleak [125]. Moreover, outcomes with allo-HSCT in the context of *TP53*-mutated MDS/AML are quite poor [126]. Consequently, the most appropriate treatment recommendation for *TP53*-mutated MDS/AML is enrollment in a clinical trial [127].

Pediatric MDS

Childhood MDS (cMDS, defined as <18 years of age) is biologically distinct from adult MDS [128]; for example, MDS with del(5q) and MDS with mutated SF3B1 virtually never occur in children. Therefore, 'pediatric-type' MDS classification criteria often do not fit into 'adult-type' MDS classification criteria [129]. cMDS can either be primary ("de novo") or secondary, with secondary MDS being associated with antecedent or predisposing conditions such as certain genetic mutations, inherited bone marrow failure syndromes (IBMFSs), prior chemotherapy/radiation therapy [therapy-related MDS], or acquired severe aplastic anemia (SAA). Notably, MDS in children often occur in the context of IBMFs and germ line syndromes [e,g., mutations in *GATA2, ETV6, SRP72,* and *SAMD9/SAMD9-L]* [130,131,132]. Notably, germline

mutations in certain genes may confer substantially increased risk of MDS with an onset after age 18, such as *ATG2B/GSKIP, TET2* [133,134,135], and *DDX41*. Importantly, cMDS is divided into two main categories: (1) refractory cytopenia of childhood (RCC)/MDS with low blasts for cases with <2% PB and <5% BM blasts and (2) MDS-excess blasts/MDS-increased blasts for cases with 2% PB or 5% BM blasts. While the 5th edition of the WHO replaces RCC with "childhood MDS with low blasts" (cMDS-LB), the ICC retained the terminology of RCC for cases meeting defined morphologic criteria including <2% blasts in the PB and <5% blasts in the BM. WHO classifies pediatric MDS with 5% blasts in the BM and/or 2% blasts in the PB as "childhood MDS with increased blasts (cMDS-IB)", while the ICC classifies pediatric MDS with PB blasts between 2% and 19% and/or BM blasts between 5% and 19% as MDS with excess blasts (MDS-EB) [136]. Strikingly, RCC is the most common subtype of MDS in children [137]. In this context, RCC must be distinguished from SAA and IBMFs as clinical and histopathologic distinction between them is of crucial therapeutic value [138,139]. Notably, cMDS has a different biological signature. Monosomy 7 and del[7q] are the most common cytogenetic abnormalities in pediatric MDS. In contrast to adult MDS cases, the mutational landscape of cMDS often contains somatic RAS pathway or *SETBP1*, *ASXL1*, and/or *RUNX1* mutations (the frequently mutated genes in adult MDSs including TET2, *DNMT3A*, and *TP53* and the spliceosome complex are not involved in disease pathogenesis in cMDS) [140,141,142]. The treatment strategies for cMDS are context-dependent i.e., depends on the diagnosis (with or without excess blasts), clinical scenario, and cytogenetics. There are three main treatment strategies for cMDS: watch-and-wait, immunosuppressive therapy (IST), and HSCT [143]. Generally speaking, patients with lower-risk disease may be managed conservatively while patients with higher-risk disease (particularly with excess blasts, therapy-related MDS, or complex karyotype) are optimally managed by allo-HSCT [144].

Myeloid leukemia associated with Down syndrome

Constitutional trisomy 21 (T21), which results in the development of Down syndrome (DS), is a state of aneuploidy associated with high incidence of childhood AML. Myeloid leukemia associated with DS (ML-DS) phenotypically reflects acute megakaryoblastic leukemia (M7 AML) observed in patients without DS. However, ML–DS has distinct clinical and biological features reflecting a model of step-wise leukemogenesis with perturbed hematopoiesis already presenting in utero [145]. ML-DS is preceded by a a pre-leukemic state called transient abnormal myelopoiesis (TAM). While TAM is triggered by truncating mutations in GATA1 generating a short GATA1 isoform (GATA1s), ML-DS emerges due to secondary mutations in hematopoietic clones bearing GATA1s [146]. Notably, MDS almost always precedes AML in patients with DS [147,148]. It is well recognized that many children with ML-DS present with a low blast count and a more myelodysplastic picture. While in many cases progression from MDS to AML is slow, all cases with MDS will eventually progress to full-blown AML. Therefore, it is recommended to commence treatment of MDS even with low blast counts. Unsurprisingly, ML-DS encompasses both MDS and AML occurring in DS under the WHO classification [149,150] Despite the highly favorable prognosis in children with primary ML-DS, outcomes for patients with R/R ML-DS remain dismal, with no standardized treatment recommendation available [151]. Intriguingly, recent evidence highlights fenretinide as a novel *GATA1*-targeting agent in M6 and M7 AML cells, capable of overcoming chemoresistance, synergizing with current standard-of-care therapies, and outperforming them as a single agent [152]. Building on this, I believe fenretinide could be employed in the context of ML-DS in a twofold manner: first, as a prophylactic treatment for TL-DS by inducing *GATA1* loss, thereby eliminating the future risk of progression to ML-DS; and second, as a therapeutic agent for established ML-DS, either alone or in combination with less toxic chemotherapy regimens.

Chronic Myeloid Leukemia (CML)

CML is one of myeloproliferative neoplasms (MPN). CML is defined by the *BCR::ABL1* fusion resulting from t(9;22)(q34;q11). The natural history of untreated CML before the introduction of targeted TKIs was biphasic or triphasic: an initial indolent chronic phase (CML-CP) followed by a blast crisis (CML-BC), with or without an intervening accelerated phase (CML-AP). CML treatment improved significantly following development of ABL TKIs, such as imatinib, dasatinib, nilotinib, bosutinib, and ponatinib. The incidence of progression to advanced phase disease has decreased, and the 10-year OS rate for CML is 80–90% [153]. However, development of drug resistance to TKIs due to BCR-ABL point mutations, such as the E255K, Y253F/H [P-loop], H396R (activation loop) or the T315I (gatekeeper), poses a major challenge in the clinical treatment of CML [154]. In particular, the "gatekeeper" mutation T315I confers resistance against all approved TKIs, with the only exception of ponatinib, a third-generation multi-target kinase inhibitor [155]. Despite that ponatinib exhibits good therapeutic activity against the T315I mutation, its clinical utility is somewhat limited due to its cardiovascular toxicity [156]. Consequently, it is vital to develop new therapeutic strategies that are effective against TKI-resistant CML cells.

Adult T-cell leukemia/lymphoma (ATLL)

ATLL is a mature T-cell neoplasm most often composed of highly pleomorphic lymphoid cells. The disease is caused by the human lymphotropic virus type 1 (HTLV-1) [157,158]. In 2018 alone, HTLV-1 caused about 3600 cases of ATLL [157]. Most ATLL patients present with widespread lymph node involvement as well as involvement of PB. ATLL is endemic in several regions of the World, in particular south-western Japan, the Caribbean basin, and parts of central Africa. ATLL is an aggressive malignancy associated with poor prognosis because of intrinsic chemoresistance and severe immunosuppression [160]. The treatment of ATLL is usually dependent on the ATLL subtype. Patients with aggressive forms [acute and lymphoma] have a very poor prognosis [161,162,163,164]. Patients with indolent ATLL [chronic or smoldering subtypes] have a better prognosis, but long-term survival is poor when these patients are managed with a watchful-waiting policy or with chemotherapy [165].

Multiple myeloma (MM)

Plasma cell neoplasms including multiple myeloma (MM) and lymphoid leukemias are considered B-cell lymphoid malignancies in the WHO classification system [166]. MM is an incurable B-cell malignancy characterized by monoclonal proliferation of plasma cells within the BM. These malignant plasma cells produce and secrete a characteristic monoclonal immunoglobulin [M-protein]

[167]. This M-protein is crucial for diagnosis and monitoring the disease status [168]. MM accounts for 1.8% of new cancer cases annually and about 10% of hematological malignancies [169]. Patients with MM usually suffer from hypercalcemia, renal damage, anemia, bone lesions and immunodeficiency [170]. In particular, bone disease is the main cause of MM morbidity. Intriguingly, MM exists on a continuous disease spectrum [171,172]. Almost all patients with MM begin with an asymptomatic pre-malignant stage termed monoclonal gammopathy of undetermined significance (MGUS) [173], progressing to an intermediate asymptomatic but more advanced pre-malignant stage referred to as smoldering multiple myeloma [SMM] which can be recognized clinically [174], and lastly to MM. Strikingly, genetic abnormalities, epigenetic alterations, and microenvironmental factors co-operate in the development of symptomatic MM [175]. Although MM is still considered a single disease, it is increasingly recognized as a collection of several different plasma cell malignancies [176,177], characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness [178,179]. In this vein, the presence of del(17p), t(4;14), t(14;16), t(14;20), gain 1q, del 1p, or p53 mutation is considered high-risk MM. Presence of any two high risk factors is considered double-hit myeloma; three or more high risk factors is triple-hit myeloma [180].

Despite advances in treatment strategies, ranging from conventional chemotherapy with alkylating agents and HSCT, to the use of antiangiogenetic or proteasome inhibiting drugs, MM is still an incurable disease [181], where almost all patients with MM eventually relapse or become refractory to treatment at some point in their lives [182,183]. As resistance to chemotherapy is one of the main challenges in MM management [184], targeting tumor antigens with immunotherapy is rapidly emerging as a promising avenue for treatment of MM [185]. Nevertheless, around 40% of newly diagnosed MM patients treated with immunotherapy regimens containing daratumumab, a CD38-targeted monoclonal antibody (mAb), progress prematurely [186]. In this line, the majority of patients treated with either daratumumab or isatuximab (both are mAbs that target CD38) will ultimately progress while on treatment or relapse after therapy. Strikingly, patients progressing after CD38 mAb-based therapies are also frequently resistant to other commonly used anti-myeloma agents such as lenalidomide and bortezomib [187]. In a similar vein, despite that the B-cell maturation antigen (BCMA) is preferentially expressed on mature B-cells [188], while >70% of patients with R/R MM initially responded to anti-BCMA CAR T-cell therapy, clinical relapse and disease progression occur in most cases [189]. Intriguingly, Ledergor et al., introduced the importance of cell states in vivo as possible predictors of outcome after CAR T-cell therapy. By using single-cell transcriptomics to study changes in immune cells in patients with MM receiving anti-BCMA CAR T-cells, they found that patients with short-lived responses had increased frequencies of exhausted cytotoxic $CD4^+$ CAR T-cells, whereas those with durable responses possessed a significantly higher proportion of $CD8^+$ T-effector memory cells. In addition, the relevant exhaustion coexpressed markers are TIM-3 and TIGIT, rather than other canonical markers of exhaustion such as PD-1 or CTLA-4, which might inform future combination therapeutic approaches [190,191]. Furthermore, severe (grade ≥ 3) and persistent (40% at day +90) cytopenia (particularly thrombocytopenia)- leading to severe (50%) bacterial (68%) infections occurring within 30 days (moderate viral infections were more prevalent later)- remains a challenge after anti-BCMA CAR T-cell therapy [192]. Not surprisingly, most physicians believed that post CAR T-cell prolonged cytopenia could be a potential barrier to the next-line relapse therapy, especially that nearly half of patients were offered a stem cell boost [191]. Strikingly, MM with extramedullary disease (EMD), defined as paraskeletal or organ involvement with high mortality and an average OS time of 36 months [194,195,196], is a well-established marker of inferior prognosis in MM, even in the era of novel therapies [197,198]. Based on current knowledge, extramedullary spread of MM may occur either at diagnosis (7%-18%), during the course of the disease (6%), or at relapse (up to 20%) [199,200]. Recently, Gagelmann et al., showed that patients with organ involvement have significantly worse progression-free survival [PFS] despite posttransplant maintenance, while patients with paraskeletal involvement appeared to be associated with similar outcomes in comparison with patients without EMD [201]. In a similar vein, the presence of EMD is an independent risk factor for inferior PFS despite CAR T-cell therapy. Among 351 patients with R/R MM from 11 US academic centers, who had EMD prior to Idecabtagene vicleucel (Ide-cel) infusion, have demonstrated significantly inferior Day 90 objective response rates (ORR) [202,203].

HODGKIN LYMPHOMA AND *NON-HODGKIN LYMPHOMA*

Hodgkin lymphoma (HL)

HL accounts for approximately 10% of lymphoma cases. It is developed in the lymphatic system and occurs mostly sporadically. It can also be associated with the Epstein-Barr virus (EBV) or HIV/AIDS and originates from the lymph node [204]. Hodgkin/Reed-Sternberg (HRS) cells are the hallmark cells of HL [205]. HL is divided into two distinct categories that demonstrate different pathologic and clinical features: classical *Hodgkin lymphoma* (cHL) and nodular lymphocyte-predominant *Hodgkin lymphoma* (NLP-HL). cHL accounts for approximately 95 percent of HL and is further subdivided into four subgroups: nodular sclerosis (NSHL), lymphocyte-rich (LRHL), mixed cellularity (MCHL), and lymphocyte-depleted (LDHL) [206]. cHL is characterized by the recurrent genetic rearrangement 9p24.1 that shares the locus of PD-L1, PD-L2, and *JAK2*, leading to enhanced PD-L1/PD-L2 upregulation of HRS cells, which constitutes a mechanism to escape the immune-mediated anti-tumor response. Although PD-1/PD-L1 axis blockade has demonstrated efficacy in the treatment of R/R HL, many patients develop primary or secondary resistance to these agents, attributed, at least in part, to the expression of other immune checkpoints on HRS cells or in the tumor microenvironment (TME) such as LAG-3/CD223 and TIM-3. NSHL is the most frequently diagnosed subtype of HL and tends to occur in young adults, usually under age 50 years. Anterior mediastinal involvement is extremely common (90% of the cases) in NSHL, with subsequent involvement of cervical and supraclavicular lymph nodes, upper abdominal lymph nodes, and spleen [207]. Histologically, NSCHL is characterized by collagen bands that surround at least one nodule, and by HRS cells with lacunar-type morphology.

Non-Hodgkin lymphoma (NHL)

NHL includes all lymphomas except for *Hodgkin lymphomas*, which comprises more than 50 different neoplasms that arise from immature or mature B-cells, T-cells, or natural killer (NK) cells [effector lymphocytes of the innate immune system] [208]. The relative frequencies of various subtypes of NHL vary significantly in different geographic regions of the World, and environmental and lifestyle factors, as well as host genetic makeup, appear to contribute to the development of NHL [209]. NHL is generally divided into 2 main types, based on whether it starts in B lymphocytes (B-NHL) or T lymphocytes (T-NHL). NHLs are also classified by whether it is aggressive (fast-growing) or indolent (slow-growing). There are huge differences between the fast-growing aggressive lymphomas (aNHLs; about 60% of all NHL cases) and the slow-growing indolent lymphomas. While DLBCL is the most common aggressive form of B-NHL, FL, and CLL are slow-growing lymphomas [210]. Notably, apart from cHL and primary mediastinal B-cell lymphoma (PMBL) [211], combination therapies with PD-1/PD-L1 blockade have not resulted in obvious clinical responses in patients with other lymphomas [212]. Strikingly, PD-L1 has been reported expressed by tumor cells and PD-1 by tumor-associated T cells in DLBCL [213,214]. A multicenter cohort study of 288 DLBCL patients shows that high level of soluble PD-L1 (sPD-L1) in peripheral blood at the time of diagnosis is significantly associated with poorer OS for patients diagnosed with aggressive DLBCL, particularly for those treated with standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) [215].

Burkitt lymphoma (BL)

BL is an aggressive mature B-cell lymphoma derived from germinal center (GC) or post GC B-cells. BL is characterized by a very high proliferation rate and believed to be the fastest growing human tumor [216]. With a Ki67 (a cellular marker for proliferation) expression of nearly 100%, the clinical course of BL usually is highly aggressive requiring prompt institution of therapy [217]. In contrast to B-lymphomas with predominant lymph node involvement, BL most commonly involves extranodal sites such as the jaw, bones, gastrointestinal tract, gonads, or breasts. There are three clinical variants of BL: endemic [African-derived], sporadic [nonendemic], and human immunodeficiency virus (HIV-associated BL. BLs occurring in each of these settings are histologically identical but differ in some clinical, genotypic, and virologic characteristics. Endemic BL is a pediatric cancer accounting for 30–50% of all childhood cancers in regions where malarial transmission is year-round [218,219,220,221]. Essentially all endemic BLs are latently infected with EBV, which is also present in about 25% of HIV-associated tumors and 15% to 20% of sporadic cases. However, how EBV contributes to the BL lymphomagenesis is still to be defined [222]. All forms of BL are highly associated with translocations of the MYC gene (a potent oncogene located at chromosome locus 8q24.21) that lead to increased MYC protein levels. The translocation partner for MYC is usually the IgH locus (t (8;14)) but may also be the Ig κ (t(2;8)) or λ (t(8;22)) light chain loci. Rearrangement of MYC with immunoglobulin genes is a hallmark of *Burkitt lymphoma* [223]. In addition to BL, dysregulation of MYC has been shown to be an independent negative prognostic factor in other aNHLs [224,225,226].

Diffuse large B cell lymphoma (DLBCL)

DLBCL is the most common hematologic malignancy as well as the most common form of B-NHLs comprising 30–40% of cases, with slight over-representation of the male gender [227,228,229]. DLBCL belongs to the family of large B-cell lymphomas (LBCL), a heterogeneous class of tumors characterized by large lymphoid cells of the B-cell lineage that by definition form sheets or clusters. "Large cell" cytology is usually defined as a lymphoid cell with a nucleus that is larger than that of a macrophage or twice the size of a normal lymphocyte [230]. Notwithstanding the significantly improved outcomes of R/R LBCL induced by the autologous CD19-directed CAR T-cell therapy compared to standard-of-care salvage chemoimmunotherapy [231], most patients do not have durable benefit and post-CAR T-cell relapses are difficult to salvage [232].

DLBCL is characterized by a striking degree of genetic and clinical heterogeneity [233,234,235,236,237]. Based on gene expression profiling, three major molecular subtypes have been identified: GC B-cell-like [GCB-DLBCL], Activated-B-cell-like (ABC-DLBCL) and PMBL [238]. However, around 10%-15% of cases are categorized as unclassifiable. The ABC-DLBCL and GCB-DLBCL subtypes show differences in chromosomal alterations, signaling pathway activation, and clinical outcome. The ABC-DLBCL has demonstrated inferior clinical outcome compared with the GCB-DLBCL. Although R-CHOP therapy remains the mainstay of treatment for DLBCL, this fails to achieve remission in about 40% of patients. In addition, despite the recent advances in management of DLBCL, outcomes for high-risk patients continue to remain suboptimal [239]. Hence, research is needed to discover novel therapeutic strategies [240]. Mechanistically, B-cell antigen receptor (BCR) signaling that activates downstream oncogenic pathways such as the nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) or phosphatidylinositol 3-kinase (PI3K) plays a critical role in pathogenesis of B cell malignancies, including DLBCL and CLL [241,242,243,244,245].

There are two fundamentally distinct mechanisms of BCR pathway activation in B cell lymphomas: antigen-dependent and antigen-independent BCR signaling [246,247]. The hallmark of ABC-DLBCLs is chronic active antigen-dependent BCR signaling resulting in constitutive NF-κB activity which blocks apoptosis [248]. In fact, ABC-DLBCL cells are highly dependent on NF-κB for their viability [249,250]. Although chronic active BCR signaling in ABC DLBCL shares characteristics with antigen-dependent BCR signaling in normal B cells, intact BCR signal transduction pathway is tightly regulated and self-limited by the availability of antigen and other negative controls [251].

On the other hand, genomic data have shown that GCB-DLBCL lines exclusively use an antigen-independent signal, termed 'tonic BCR signaling' [252]. Unlike chronic active BCR signaling, tonic BCR signaling is mediated by PI3Kα and PI3Kδ/AKT/mTOR (but not the NF-κB pathway) to promote the proliferation and survival of malignant B cells [253]. In contrast to BL where MYC rearrangements are present in almost all of the cases, alterations in MYC have been detected in approximately 5% to 15% of DLBCL cases. However, MYC overexpression is one of the key prognostic and predictive biomarkers for survival in DLBCL, and some authors even showed that MYC overexpression is associated with the worst survival rates [254,255,256,257,258].

Follicular lymphoma (FL)

FL is a $CD5^-$ and $CD10^+$ indolent lymphoma representing approximately 40% of all NHLs. The genetic hallmark of FL is the t(14;18) translocation resulting in B cell lymphoma-2 (Bcl-2) oncoprotein overexpression [found in up to ~85% of patients] [259]. Bcl-2 is a prototypic anti-apoptotic protein (promotes tumor cell survival) and its overexpression in FL is the classic example of its anti-apopototic mechanism (prevents programmed cell death by limiting the exit of cytochrome c from mitochondria). The pathobiology of FL is complex and involves alterations within the FL microenvironment in addition to the cell-intrinsic genetic changes, frequently including (in addition to the hallmark t(14;18) translocation) mutations in histone-encoding genes (in ~40% of cases), the SWI/SNF complex or the interconnected BCR and CXCR4 chemokine receptor signaling pathways [260].

Chronic lymphocytic leukemia (CLL)

CLL is a disease of the elderly population. Although it is the most common adult leukemia in western countries, it is less common in Asia and relatively rare in Japan and Korea, even among Japanese people who immigrate to western counties [261]. CLL is a malignancy of mature, antigen-experienced B lymphocytes that is characterized by the accumulation of mature circulating IgM^{low} $CD5^+$ B cells [262]. In simple words, CLL is a cancer of $CD19^+$ B cells that co-express the T cell marker CD5. CLL cells proliferate in distinct microanatomical tissue sites called "proliferation centers" or "pseudofollicles", a hallmark finding in CLL histopathology [263]. Despite a common $CD5^+CD19^+$ phenotype, CLL is marked by a heterogeneous clinical course ranging from a benign disease to one that can be fatal within a few years of diagnosis [264]. As a disorder of B-lymphocytes, CLL is intrinsically characterized by adaptive immune response dysfunction, but alterations of multiple elements and effectors of the innate immune response are also found in CLL patients [265]. Interestingly, CLL and small lymphocytic lymphoma (SLL) are morphologically, phenotypically, and genotypically indistinguishable, differing only in the degree of peripheral lymphocytosis [266]. Despite being a slow-proliferating disease and the great progress recently achieved in the management of CLL, the disease remains potentially incurable [267]. Prognostic biomarkers and risk scoring systems play important roles in guiding CLL treatment decisions [268]. In this context, several genetic aberrations with prognostic value and impact on treatment decisions in CLL have been described. These include deletions of the chromosomal regions 17p13 (containing the *TP53* tumor suppressor gene), 11q23 (containing DNA damage checkpoint protein ATM), or 13q14 (miR-15a, miR-16-1), and trisomy of chromosome 12 [269,270]. Patients with *TP53* alterations including *TP53* mutations or 17p deletions are classified as 'high-risk' and usually associated with an unfavorable prognosis and poor response to chemotherapy and immunotherapy [271,272]. On the basis of somatic hypermutation status of the immunoglobulin heavy-chain variable region gene (*IGHV*), CLL can be grouped into mutated CLL (M-CLL) and unmutated CLL (UM-CLL). M-CLL (derived from post-GC B cells) has a more favourable prognosis than those with UM-CLL [derived from $CD5^+$ mature B cells] [273]. Numerous genes like ZAP-70 (zeta-associated protein 70), CD38 and LPL (lipoprotein 73 lipase), whose expression was associated with an unmutated status of *IGHV* genes and poor outcome, were proposed as surrogate markers [274,275,276,277,278]. Although the expression of these markers was found to correlate with the expression of unmutated *IGHV* genes, this correlation is not absolute [279].

Strikingly, novel immunotherapies showed disappointing results in CLL, in contrast to several B-cell lymphomas where responses were impressive. Mechanistically, the strong immunomodulatory effect of CLL causes low response rates to immunotherapy strategies [280]. For instance, CLL cells have the ability to transform the effector functions of the bystander T cells in the TME, thus rendering them a source of trophic signals for the survival and proliferation of the malignant clone. Indeed, substantial evidence implicates T cells present in the TME in the natural history of the CLL as well as in the establishment of certain CLL hallmarks such as tumor evasion and immune suppression. Although CLL cells are able to manipulate T-cell functionality, T cell abnormalities in CLL appear to be reversible, which is why therapies targeting the T cell compartment, including CAR-T cells, immune checkpoint blockade and immunomodulation, represent a reasonable therapeutic option in CLL [281]. Nevertheless, novel targeted therapies demonstrated improved PFS and OS that were superior to chemoimmunotherapy. Nowadays, Bruton's tyrosine kinase [BTK] inhibitors, Bcl-2 inhibitors, and CD20 mAbs are established treatments for CLL, both in frontline and R/R settings [282]. In this context, substantial evidence has established the central role of chronic BCR-mediated signaling in CLL pathogenesis [283]. It is worth noting that BTK, a signal transduction pathway located downstream to the BCR, is essential for constitutively active pathways implicated in CLL cell survival [284,285,286,287]. On the other hand, metabolic reprogramming is a hallmark of CLL and underlies disease progression and relapse but the exploitation of metabolic dependencies in clinical settings is still minimal [288]. Notably, Richter transformation (RT, also known as Richter's syndrome), the progression of CLL into an aggressive lymphoproliferative disorder, primarily DLBCL-although HL, plasmablastic lymphoma, or other rare lymphomas have been also reported [289]- occurs in approximately 2-10% of patients with CLL [290]. Intriguingly, RT is associated with poor response to chemotherapy and short survival [291], e.g., the overall response rates for patients treated with chemoimmunotherapy such as R-CHOP are <40% with a median OS of 6–8 months [292]. Since RT remains a therapeutic challenge, innovative management of this grave complication is warranted [293]. Interestingly, MYC aberrations were found in most RT cases [294]. The association of MYC translocation with an unfavorable prognosis of CLL/ RT patients was confirmed in several studies [295,296,297].

Mantle cell lymphoma (MCL)

MCL results from malignant transformation of B lymphocytes in the mantle zones surrounding GCs [298]. MCL is a very rare form of aggressive B-NHL with a dismal prognosis. Similar to CLL and ABC-DLBCL, MCL also show activation of the BCR pathway and constitutive NF-κB signaling [299,300]. On the other hand, primary resistance curbed the initial effectiveness of several inhibitors targeting BCR-associated kinases (BTK, spleen tyrosine kinase (SYK), or PI3K, in DLBCL and MCL, especially in the case of first generation BTK inhibitors (e.g, ibrutinib) [301]. The pathognomic feature of MCL is the chromosomal translocation t (11;14) (q13; q32 (IGH/CCND1), which is observed in >95% of cases, resulting in the constitutive overexpression of G1-phase cell cycle protein cyclin D1 (CCND1) [302,303]. MCL usually overexpress IgM as compared to normal B cells, which likely

contribute to the pathogenesis of this lymphoma type [304]. *TP53* mutations have been associated with an inferior prognosis in MCL and patients usually have a poor response to standard chemotherapy [305]. Therefore, patients with *TP53* mutations should be considered for alternative frontline treatment [306].

Myeloproliferative Neoplasms (MPNs)

MPNs are clonal hematopoietic stem cell disorders with overproduction of mature myeloid blood cells. MPNs include CML, polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia (CEL), juvenile myelomonocytic leukemia (JMML) and MPN, not otherwise specified (MPN-NOS). The WHO classifies CML, PV, ET, and PMF as classical MPNs. The classical MPNs represent clonal myeloid disorders whose pathogenesis is driven by well-defined molecular abnormalities [307]. In this context, CML is the only MPN driven by a reciprocal translocation between chromosomes 9 and 22 creating the Philadelphia chromosome (Ph) and specifically the fusion gene *BCR-ABL1*. Consequently, classical MPNs are further classified as Ph-positive CML and Ph-negative MPNs including PV, ET, and PMF [308]. Whereas ET and PV are characterized by platelet and erythrocyte overproduction, respectively, PMF is marked by aberrant proliferation of cells of the megakaryocytic lineage and progressive BM fibrosis [309]. However, PMF, ET and PV share common MPN-initiating somatic mutations in the genes that encode for *JAK2*, thrombopoietin receptor [TPO-R, also known as myeloproliferative leukemia protein or MPL], and calreticulin (*CALR*) leading to the activation of the MPL and downstream signaling pathways (MPL-JAK-STAT signalling) in MPN stem cells [310]. Of these, the *JAK2* V617F mutation was the first identified, and, is present in 95% of PV, and about 55% and 60% of ET and PMF patients, respectively. *CALR* and MPL mutations are almost always associated with an ET or MF phenotype, but not a PV phenotype. MPL mutations are present in about 3% ET patients and about 7% of PMF patients [311]. *CALR* is mutated in the majority of *JAK2*/MPL mutation-negative patients, which corresponds to about a quarter of all ET and PMF patients [312,313,314]. ET has the most favorable prognosis among MPNs but a minority of patients who develop progression to MF or AML, referred to as blast-phase (BP) MPN, have a much poorer outcome [315]. In a large cohort of patients with ET (1000 patients), major thromboses at the time of diagnosis were documented in 19%, with a predominance of arterial (13%) versus venous (6%) events [316]. On the other hand, PMF is the most aggressive subtype among classical *BCR-ABL1* negative MPNs. Approximately 1 of 3 responds to currently approved JAK inhibitor treatment; however, hematotoxicity (especially in patients with cytopenic MF) results in treatment discontinuation for many patients. PMF results when cytokines produced by the MPN clone stimulate bone marrow stromal cells (BMSCs) to deposit an excess of collagens and other extracellular matrix (ECM) proteins, consequently destroying the hematopoietic microenvironment [317,318,319]. PMF is morphologically characterized by abnormal megakaryocyte proliferation that is often accompanied by reticulin fibrosis [320]. The fibrotic BM remodeling and pronounced systemic inflammation cause BM failure, extramedullary hematopoiesis, splenomegaly, profound constitutional symptoms and a median survival of around 5 years [321]. However, the mechanisms by which the hematopoietic tissue in the BM is replaced by a fibrotic scar tissue are not yet fully understood [322]. Common fatal complications of PMF include transformation to acute leukemia, thrombohemorrhagic events, organ failure, and infections [323]. Patients who develop acute leukemia (typically involves the myeloid lineages (secondary AML (sAML)) but, rarely, lymphoid transformation (secondary ALL) may also occur) have a median survival time of less than 3 months [324]. Approximately 90% of patients harbor a mutation affecting *JAK2*, *MPL*, or *CALR*. As mutations in these genes all converge on JAK/STAT signaling, the JAK1/2 inhibitor ruxolitinib is currently front-line therapy for MF [325]. In contrast, PMF that lacks these canonical alterations, termed triple-negative PMF (TN-PMF), is associated with poor prognosis [326,327]. In addition to PMF, PV and ET can also progress to post-PV (PPV) MF and post-ET (PET) MF, also known as secondary myelofibrosis (SMF) [328]. Despite approval of JAK inhibitors and novel agents, allo-HSCT remains the only potentially curative treatment for for both PMF and SMF [329]. Nonetheless, HSCT is limited by its highly concerning risks of TRM and therapy-related complications [330]. Increased risk of post-transplantation relapse was observed for accelerated phase MF (compared with chronic phase MF) and patients with splenomegaly prior to transplantation [331]. Recently, Gagelmann et al., identified a novel very high-risk group in patients with MF undergoing HSCT [332]. Compared to patients with monoallelic *TP53* mutated (*TP53*mut) MF, patients with *TP53* multi-hit (*TP53*^{MH}) MF following HSCT had an increased relapse risk. In a similar vein, this study has also shown that AML transformation was a more frequent relapse presentation in patients with *TP53*^{MH}, compared with patients with monoallelic *TP53*mut/*TP53*WT which highlights a need for an alternative approach to allo-HSCT in this subgroup [333]. In this regard, clonal evolution to secondary (sAML) is one of the most feared complications of MPN. A significant proportion of patients with MPN (10%–20%) transform to devastating and rapidly fatal sAML, characterized by cytopenias, increased myeloid blasts, acquisition of aberrant LSC properties by hematopoietic stem/progenitor cells (HSPCs) and median survival of less than one year [334,335]. Notably, the risk of AML transformation was highest for patients with MF (occurring in up to 20% of patients) [336]. Collectively, *TP53* mutations are detected in approximately 20–35% of post-MPN sAML (known as *TP53*-sAML) [337,338,339]. Recently, Rodriguez-Meira et al., has disentangled the mechanistic basis for this phenomenon by implicating inflammation in *TP53*-driven clonal evolution [340].

CONCLUSION

Hematologic malignancies, encompassing leukemias, lymphomas, and myelomas, represent a diverse and complex group of cancers that continue to challenge modern oncology. Since the first documented case of *Hodgkin lymphoma* in 1832, advances in understanding their genetic and molecular underpinnings have paved the way for targeted therapies and innovative treatment strategies. However, high rates of relapse, resistance to therapy, and significant treatment-related complications underscore the need for further advancements. This article delves into the classification, pathophysiology, and clinical features of liquid tumors, highlighting current therapeutic approaches and emerging frontiers in treatment. By addressing these challenges, it aims to equip researchers and clinicians with the knowledge needed to improve outcomes for patients with these devastating diseases.

REFERENCES

1. Roman E, Kane E, Howell D, Lamb M, Bagguley T, Crouch S, et al. Cohort profile update: The Haematological Malignancy Research Network (HMRN) UK population-based cohorts. Int J Epidemiol.2022;51(3):e87-94.
2. Alkhatabi H, Yasin EB, Mirza Z, Alserihi R, Felimban R, Elaimi A, et al. *TP53* Expression and Mutational Analysis in Hematological Malignancy in Jeddah, Saudi Arabia. Diagnostics (Basel). 2022;12(3):724.
3. Stengel A, Schnittger S, Weissmann S, Kuznia S, Kern W, Kohlmann A, et al. *TP53* mutations occur in 15.7% of all and are associated with *MYC*-rearrangement, low hypodiploidy, and a poor prognosis. Blood J Am Soc Hematol. 2014;124:251-258.
4. Grossmann V, Schnittger S, Kohlmann A, Eder C, Roller A, Dicker F, et al. A novel hierarchical prognostic model of AML solely based on molecular mutations. Blood J Am Soc Hematol. 2012;120:2963-2972.
5. Rücker FG, Schlenk RF, Bullinger L, Kayser S, Teleanu V, Kett H, et al. *TP53* alterations in acute myeloid leukemia with complex karyotype correlate with specific copy number alterations, monosomal karyotype, and dismal outcome. Blood J Am Soc Hematol. 2012;119:2114-2121.
6. Döhner H, Stilgenbauer S, Benner A, Leupolt E, Kröber A, Bullinger L, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343:1910-1916.
7. Rossi D, Cerri M, Deambrogi C, Sozzi E, Cresta S, Rasi S, et al. The prognostic value of *TP53* mutations in chronic lymphocytic leukemia is independent of Del17p13: Implications for overall survival and chemorefractoriness. Clin Cancer Res. 2009;15:995-1004.
8. Jeromin S, Weissmann S, Haferlach C, Dicker F, Bayer K, Grossmann V, et al. *SF3B1* mutations correlated to cytogenetics and mutations in *NOTCH1, FBXW7, MYD88, XPO1* and *TP53* in 1160 untreated CLL patients. Leukemia. 2014;28:108-117.
9. Cazzola M, Della-Porta MG, Malcovati L. The genetic basis of myelodysplasia and its clinical relevance. Blood J Am Soc Hematol. 2013;122:4021-4034.
10. Papaemmanuil E, Gerstung M, Malcovati L, Tauro S, Gundem G, Van-Loo P, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood J Am Soc Hematol. 2013;122:3616-3627.
11. Haferlach T, Nagata Y, Grossmann V, Okuno Y, Bacher U, Nagae G, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia. 2014;28:241-247.
12. Vaddavalli PL, Schumacher B. The *p53* network: Cellular and systemic DNA damage responses in cancer and aging. Trends Genet. 2022;38:598-612.
13. Chen X, Zhang T, Su W, Dou Z, Zhao D, Jin X, et al. Mutant *p53* in cancer: From molecular mechanism to therapeutic modulation. Cell Death Dis. 2022;13(11):974.
14. Kumar V, Abbas AK, Aster JC. Robbins and Kumar Basic Pathology: First South Asia Edition-E-Book. Elsevier Health Sciences; 2017
15. Olivier M, Hollstein M, Hainaut P. *TP53* mutations in human cancers: Origins, consequences, and clinical use. Cold Spring Harb Perspect Biol. 2010;2(1):a001008.
16. Malard F, Mohty M. Updates in chronic graft-versus-host disease management. Am J Hematol. 2023;98(10):16370-1644.
17. Scherer LD, Rouce RH. Targeted cellular therapy for treatment of relapsed or refractory leukemia. Best Pract Res Clin Haematol. 2023;36(3):101481.
18. Chiad Z, Chojecki A. Graft *versus* Leukemia in 2023. Best Pract Res Clin Haematol. 2023;36(3):101476.
19. Pillai PM, Carroll WL, Yırtımcı TA. Retrospective evaluation of pediatric cases diagnosed with acute leukemia, including admission complaints, physical examination findings and laboratory results at the time of diagnosis. Fish. 413-438: (2022).
20. Siddiqui M, Konoplev S, Issa G, Kantarjian H, Daver N, Ravandi F, et al. Biologic features and clinical outcomes in newly diagnosed myelodysplastic syndrome with *KMT2A* rearrangements. Am J Hematol. 2023;98(4):E91-4.
21. Cui W, Sun J, Cotta CV, Medeiros LJ, Lin P. Myelodysplastic syndrome with inv(3)(q21q26.2) or t(3;3)(q21;q26.2) has a high risk for progression to acute myeloid leukemia. Am J Clin Pathol. 2011;136(2):282-288.
22. Gough SM, Slape CI, Aplan PD. *NUP98* gene fusions and hematopoietic malignancies: Common themes and new biologic insights. Blood. 2011;118(24):6247-6257.
23. Nannya Y, Viswabandya A, Lu P. Advances in Allogeneic Hematopoietic stem cell transplantation for acute Leukemia. Blood Cell Ther. 2022;5:S25-S33.
24. Chennamadhavuni A, Lyengar V, Mukkamalla SKR, et al. Leukemia. StatPearls Publishing 2023.
25. Types of Leukemia. 2024.
26. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: Rationale and important changes. Blood J Am Soc Hematol. 2009;114(5):937-951.
27. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IB, Berti E, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: Lymphoid neoplasms. Leukemia. 2022;36(7):1720-1748.
28. Terwilliger T, Abdul HM. Acute lymphoblastic leukemia: A comprehensive review and 2017 update. Blood Cancer J. 2017;7(6):e577.
29. Onida F, Gagelmann N, Chalandon Y, Kobbe G, Robin M, Symeonidis A, et al. Management of adult patients with CMML undergoing allo-HCT: Recommendations from the EBMT PH&G Committee. Blood. 2024;143(22):2227-2244.

30. Iacobucci I, Mullighan CG. Genetic basis of acute lymphoblastic leukemia. J Clin Oncol. 2017;35(9):975-983.

31. Bhojwani D, Yang JJ, Pui CH. Biology of childhood acute lymphoblastic leukemia. Pediatr Clin North Am. 2015;62(1):47-60.

32. Stock W, Luger SM, Advani AS, Yin J, Harvey RC, Mullighan CG, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: Results of CALGB 10403 Blood. 2019;133(14):1548-1559.

33. Smith MA, Seibel NL, Altekruse SF, Ries LA, Melbert DL, O'Leary M, et al. Outcomes for children and adolescents with cancer: Challenges for the twenty-first century. J Clin Oncol. 2010;28(15):2625-2634.

34. Meyer C, Hofmann J, Burmeister T, Gröger D, Park TS, Emerenciano M, et al. The *MLL* recombinome of acute leukemias in 2013. Leukemia. 2013;27(11):2165-2176.

35. Andersson AK, Ma J, Wang J, Chen X, Gedman AL, Dang J, et al. The landscape of somatic mutations in infant MLL-rearranged acute lymphoblastic leukemias. Nat Genet. 2015;47(4):330-337.

36. Antić Ž, Lentes J, Bergmann AK. Cytogenetics and genomics in pediatric acute lymphoblastic leukaemia. Best Pract Res Clin Haematol. 2023;36(4):101511.

37. Rheingold SR, Ji L, Xu X, Devidas M, Brown PA, Gore L, et al., Prognostic factors for survival after relapsed acute lymphoblastic leukemia (ALL): A children's oncology group (COG) study. JCO 37, 10008-10008(2019).

38. Attarbaschi A, Möricke A, Harrison CJ, Mann G, Baruchel A, De Moerloose B, et al. Outcomes of childhood noninfant acute Lymphoblastic Leukemia With 11q23/*KMT2A* rearrangements in a modern therapy era: A retrospective International study. J Clin Oncol. 2023;41(7):1404-1422.

39. Hodder A, Mishra AK, Baird S, Bisho I, Bonney D, Clesham K, et al. Blinatumomab as toxicity sparing first line treatment of children and young persons with B-Precursor acute lymphoblastic leukaemia (B-ALL). Blood.2022;140 (Supplement 1): 8987–8988.

40. Tasian SK, Loh ML, Hunger SP. Philadelphia chromosome-like acute lymphoblastic leukemia. Blood. 2017;130(19):2064-2072.

41. Tran TH, Hunger SP. The genomic landscape of pediatric acute lymphoblastic leukemia and precision medicine opportunities. Semin Cancer Biol. 2022;84:144-152.

42. Myers RM, Taraseviciute A, Steinberg SM, Lamble AJ, Sheppard J, Yates B, et al. Blinatumomab nonresponse and high-disease burden are associated with Inferior outcomes after CD19-CAR for B-ALL. J Clin Oncol. 2022;40(9):932-944.

43. Braig F, Brandt A, Goebeler M, Tony HP, Kurze AK, Nollau P, et al. Resistance to anti-CD19/CD3 BiTE in acute lymphoblastic leukemia may be mediated by disrupted CD19 membrane trafficking. Blood. 2017;129(1):100-104.

44. Sotillo E, Barrett DM, Black KL, Bagashev A, Oldridge D, Wu G, et al. Convergence of acquired mutations and alternative splicing of cd19 enables resistance to cart-19 immunotherapy. Cancer Discov. 2015;5(12):1282-1295.

45. Jacoby E. Relapse and resistance to CAR-T cells and blinatumomab in hematologic malignancies. Clin Hematol Int. 2019;1(2):79-84.

46. Köhnke T, Krupka C, Tischer J, Knösel T, Subklewe M. Increase of PD-L1 expressing B-precursor ALL cells in a patient resistant to the CD19/CD3-bispecific T cell engager antibody blinatumomab. J Hematol Oncol. 2015;8:1-5.

47. Kopmar NE, Cassaday RD. How I prevent and treat central nervous system disease in adults with acute lymphoblastic leukemia. Blood. 2023;141(12):1379-1388.

48. Jacola LM, Conklin HM, Krull KR, Pei D, Cheng C, Reddick WE, et al. The impact of intensified CNS-directed therapy on neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia treated without cranial irradiation. J Clin Oncol. 2022;40(36):4218-4227.

49. Peterson JF, Baughn LB, Pearce KE, Williamson CM, Benevides Demasi JC, Olson RM, et al. *KMT2A* (*MLL*) rearrangements observed in pediatric/young adult T-lymphoblastic leukemia/lymphoma: A 10-year review from a single cytogenetic laboratory. Genes Chromosomes and Cancer. 2018;57(11):541-6.

50. Burkhardt B. Paediatric lymphoblastic T-cell leukaemia and lymphoma: One or two diseases? Br J Haematol. 2010;149(5):653-668.

51. Basso K, Mussolin L, Lettieri A, Brahmachary M, Lim WK, Califano A, et al. T-cell lymphoblastic lymphoma shows differences and similarities with T-cell acute lymphoblastic leukemia by genomic and gene expression analyses. Genes Chromosomes Cancer. 2011; 50(12):1063-1075.

52. Raetz EA, Perkins SL, Bhojwani D, Smock K, Philip M, Carroll WL, et al. Gene expression profiling reveals intrinsic differences between T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma. Pediatr Blood Cancer. 2006;47(2):130-140.

53. Khanam T, Sandmann S, Seggewiss J, Ruether C, Zimmermann M, Norvil AB, et al. Integrative genomic analysis of pediatric T-cell lymphoblastic lymphoma reveals candidates of clinical significance. Blood. 2021;137(17):2347-2359.

54. Pölönen P, Mullighan CG, Teachey DT. Classification and risk stratification in T-lineage acute lymphoblastic leukemia. Blood.2024.

55. Chergui A, Reagan JL. Immunotherapy in Acute Leukemias: Past Success Paves the Way for Future Progress. Cancers [Basel]. 2023;15[16]:4137. Published 2023 Aug 17. doi:10.3390/cancers15164137

56. Caracciolo D, Mancuso A, Polerà N, et al. The emerging scenario of immunotherapy for T-cell Acute Lymphoblastic Leukemia: advances, challenges and future perspectives. Exp Hematol Oncol. 2023;12[1]:5. Published 2023 Jan 9. doi:10.1186/s40164-022-00368-w

57. Teachey DT, Pui CH. Comparative features and outcomes

between paediatric T-cell and B-cell acute lymphoblastic leukaemia. Lancet Oncol. 2019;20(3):e142-e154.

58. Teachey DT, Devidas M, Wood BL, Chen Z, Hayashi RJ, Hermiston ML, et al. Children's Oncology Group Trial AALL1231: a phase III clinical trial testing bortezomib in newly diagnosed T-cell acute lymphoblastic leukemia and lymphoma. J Clin Oncol. 2022;40(19):2106-2108.

59. Burkhardt B, Hermiston ML. Lymphoblastic lymphoma in children and adolescents: review of current challenges and future opportunities. Br J Haematol. 2019;185(6):1158-1170.

60. Schmidt E, Burkhardt B. Lymphoblastic lymphoma in childhood and adolescence. Pediatr Hematol Oncol. 2013;30(6):484-508.

61. Mitsui T, Mori T, Fujita N, Inada H, Horibe K, Tsurusawa M, et al. Retrospective analysis of relapsed or primary refractory childhood lymphoblastic lymphoma in Japan. Pediatr Blood Cancer. 2009;52(5):591-595.

62. Si Lim SJ, Ford JB, Hermiston ML. How I treat newly diagnosed and refractory T-cell acute lymphoblastic lymphoma in children and young adults. Blood. 2023;141(25):3019-3030.

63. Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. N Engl J Med. 2015;373(12):1136-1152.

64. Beaton M, Peterson GJ, O'Brien K. Acute myeloid leukemia: Advanced practice management from presentation to cure. J Adv Pract Oncol. 2020;11(8):836-844.

65. Magee G, Ragon BK. Allogeneic hematopoietic cell transplantation in acute myeloid leukemia. Best Pract Res Clin Haematol. 2023;36(2):101466.

66. Shah NA. Donor lymphocyte infusion in acute Myeloid Leukemia. Best Pract Res Clin Haematol. 2023;36(3):101484.

67. Loghavi S, Kanagal SR, Khoury JD, Medeiros LJ, Naresh KN, Nejati R, et al. 5th edition of the world health classification of tumors of the hematopoietic and lymphoid tissues. Mod Pathol. 2023;100397

68. Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, Kvasnicka HM, et al. International consensus classification of myeloid neoplasms and acute Leukemias: Integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228.

69. Huber S, Baer C, Hutter S, Dicker F, Meggendorfer M, Pohlkamp C, et al. AML classification in the year 2023: How to avoid a babylonian confusion of languages. Leukemia. 2023;37(7):1413-1420.

70. Skopek R, Palusińska M, Kaczor-Keller K, Pingwara R, Papierniak-Wyglądała A, Schenk T, et al. Choosing the right cell line for acute Myeloid Leukemia (aml) research. Int J Mol Sci. 2023;24(6):5377.

71. Löwenberg B, Griffin JD, Tallman MS. Acute myeloid leukemia and acute promyelocytic leukemia. Hematol Am Soc Hematol Educ Program. 2003;82-101.

72. Cingam SR, Koshy NV. Acute promyelocytic leukemia. 2024

73. Mohty R, Reljic T, Yassine F, Kettaneh C, Al-Husni D, Keller K, et al. Efficacy of autologous and allogeneic hematopoietic cell transplantation in adults with acute promyelocytic leukemia: Results of a systematic review and meta-analysis. Transplant Cell Ther. 2024.

74. Egan G, Tasian SK. Relapsed pediatric acute myeloid leukaemia: State-of-the-art in 2023. Haematologica. 2023;108(9):2275.

75. uliusson G, Lazarevic V, Hörstedt AS, Hagberg O, Höglund M. Swedish Acute Leukemia Registry GroupAcute myeloid leukemia in the real world: Why population-based registries are needed. Blood. 2012;119(17): 3890-3899

76. Ossenkoppele G, Löwenberg B. How I treat the older patient with acute myeloid leukemia. Blood. 2015;125(5):767-774.

77. World Health Organization. AML classification biology and prognosis. Geneva: World Health Organization; 2017.

78. Murphy T, Yee KW. Cytarabine and daunorubicin for the treatment of acute myeloid leukemia. Expert Opin Pharmacother. 2017;18(16):1765-1780

79. Fleischmann M, Schnetzke U, Hochhaus A, Scholl S. Management of acute myeloid leukemia: Current treatment options and future perspectives. Cancers (Basel). 2021;13(22):5722.

80. Abdellateif MS, Kassem AB, El-Meligui YM. Combined expression of CD34 and *FLT3*-internal tandem duplication mutation predicts poor response to treatment in acute myeloid leukemia. Int J Gen Med. 2020;16:867-879.

81. Waclawiczek A, Leppä AM, Renders S, Trumpp A. An arms-race against resistance: Leukemic stem cells and lineage plasticity. Mol Oncol. 2024;18(3):475-478.

82. Armenian SH, Chen Y, Hageman L, Wu J, Landier W, Bosworth A, et al. Burden of long-term morbidity borne by survivors of acute myeloid leukemia treated with blood or marrow transplantation: The results of the BMT survivor study. J Clin Oncol. 2022;40(28):3278-3288.

83. Kandeel EZ, El Sayed G, Elsharkawy N, Eldin DN, Nassar HR, Ibrahiem D, et al. Impact of *FLT3* receptor (CD135) detection by flow cytometry on clinical outcome of adult acute myeloid leukemia patients. Clin Lymphoma Myeloma Leuk. 2018;18(8):541-547.

84. Grafone T, Palmisano M, Nicci C, Storti S. An overview on the role of *FLT3*-tyrosine kinase receptor in acute myeloid leukemia: Biology and treatment. Oncol Rev. 2012;17;6(1):e8.

85. Kiyoi H, Kawashima N, Ishikawa Y. *FLT3* mutations in acute myeloid leukemia: Therapeutic paradigm beyond inhibitor development. Cancer Sci. 2020;111(2):312-322.

86. Radomska HS, Alberich-Jordà M, Will B, Gonzalez D, Delwel R, Tenen DG, et al. Targeting CDK1 promotes *FLT3*-activated acute myeloid leukemia differentiation through C/EBPalpha. J Clin Invest. 2012;122(8):2955-2966.

87. Kiyoi H, Naoe T. FLT3 in human hematologic malignancies. Leuk Lymphoma. 2002;43:1541-1547.

88. Stirewalt DL, Kopecky KJ, Meshinchi S, Appelbaum FR, Slovak ML, Willman CL, et al. *FLT3*, *RAS*, and *TP53*

mutations in elderly patients with acute myeloid leukemia. Blood. 2001;97(11):3589-3595.

89. Meshinchi S, Alonzo TA, Stirewalt DL, Zwaan M, Zimmerman M, Reinhardt D, et al. Clinical implications of *FLT3* mutations in pediatric AML. Blood. 2006;108(12):3654-3661

90. Bolouri H, Farrar JE, Triche T Jr, Ries RE, Lim EL, Alonzo TA, et al. The molecular landscape of pediatric acute myeloid leukemia reveals recurrent structural alterations and age-specific mutational interactions. Nat Med. 2018;2491):103-112.

91. Pollard JA, Alonzo TA, Gerbing R, Brown P, Fox E, Choi J, et al. Sorafenib in combination with standard chemotherapy for children with high allelic ratio FLT3/ITD$^+$ acute myeloid leukemia: A report from the children's oncology group protocol AAML1031. J Clin Oncol. 2022;40(18):2023-2035.

92. Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447.

93. Perl A.E. Availability of FLT3 inhibitors: How do we use them? Blood. 2019;134(9):741-745.

94. Song GY, Kim HJ, Kim T, Ahn SY, Jung SH, Kim M, et al. Validation of the 2022 European LeukemiaNet risk stratification for acute myeloid leukemia. Sci Rep. 2024;14(1):8517.

95. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140:1345-1377.

96. Jiménez-Vicente C, Charry P, Castaño-Diez S, Guijarro F, López-Guerra M, Pérez-Valencia AI, et al. Evaluation of European LeukemiaNet 2022 risk classification in patients undergoing allogeneic haematopoietic stem cell transplantation for acute myeloid leukaemia: Identification of a very poor prognosis genetic group. Br J Haematol. 2024;205(1):256-267

97. Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Buchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424–447.

98. O'Donnell MR, Tallman MS, Abboud CN, Altman JK, Appelbaum FR, Arber DA, et al. Acute myeloid leukemia, version 3.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2017;15(7):926-957.

99. Lap CJ, Abrahim MS, Nassereddine S. Perspectives and challenges of small molecule inhibitor therapy for FLT3-mutated acute myeloid leukemia. Ann Hematol. 2023;103(7):2215-2229.

100. Tarlock K, Gerbing RB, Ries RE, Smith JL, Leonti A, Huang BJ, et al. Prognostic impact of cooccurring mutations in FLT3-ITD pediatric acute myeloid leukemia. Blood Adv. 2024;8(9):2094-2103.

101. Ostronoff F, Othus M, Gerbing RB Loken MR, Raimondi SC, Hirsch BA, et al. NUP98/NSD1 and FLT3/ITD co-expression is more prevalent in younger AML patients and leads to induction failure: A COG and SWOG report. Blood. 2014;124(15):2400-2407.

102. Niktoreh N, Walter C, Zimmermann M, von Neuhoff C, von Neuhoff N, Rasche M, et al. Mutated *WT1*, *FLT3-ITD*, and *NUP98-NSD1* fusion in various combinations define a poor prognostic group in pediatric acute myeloid leukemia. J Oncol. 2019:1609128.

103. Umeda M, Ma J, Huang BJ, Hagiwara K, Westover T, Abdelhamed S, et al. Integrated genomic analysis identifies *ubtf* tandem duplications as a recurrent lesion in pediatric acute myeloid leukemia. Blood Cancer Discov. 2022;3(3):194-207.

104. Kaburagi T, Shiba N, Yamato G, Yoshida K, Tabuchi K, Ohki K, et al. *UBTF*-internal tandem duplication as a novel poor prognostic factor in pediatric acute myeloid leukemia. Genes Chromosomes Cancer. 2023;62(4):202-209.

105. Shiba N, Ichikawa H, Taki T, Park MJ, Jo A, Mitani S, et al. *NUP98-NSD1* gene fusion and its related gene expression signature are strongly associated with a poor prognosis in pediatric acute myeloid leukemia. Genes Chromosomes Cancer. 2013;52(7):683-693.

106. Matsuda A, Germing U, Jinnai I, Iwanaga M, Misumi M, Kuendgen A, et al. Improvement of criteria for refractory cytopenia with multilineage dysplasia according to the WHO classification based on prognostic significance of morphological features in patients with refractory anemia according to the FAB classification. Leukemia. 2007;21(4):678-686.

107. Della Porta MG, Travaglino E, Boveri E, Ponzoni M, Malcovati L, Papaemmanuil E, et al. Minimal morphological criteria for defining bone marrow dysplasia: A basis for clinical implementation of WHO classification of myelodysplastic syndromes. Leukemia. 2015;29(1):66-75.

108. Zavras PD, Sinanidis I, Tsakiroglou P, Karantanos T. Understanding the continuum between high-risk myelodysplastic syndrome and acute myeloid leukemia. Int J Mol Sci. 2023;24(5):5018

109. Mohty R, Al Hamed R, Bazarbachi A, Brissot E, Nagler A, Zeidan A, et al. Treatment of myelodysplastic syndromes in the era of precision medicine and immunomodulatory drugs: A focus on higher-risk disease. J Hematol Oncol. 2022;15(1):124.

110. Lindsley RC, Saber W, Mar BG, Redd R, Wang T, Haagenson MD, et al. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. N Engl J Med. 2017;376(6):536-547.

111. Della Porta MG, Galli A, Bacigalupo A, Zibellini S, Bernardi M, Rizzo E, et al. Clinical effects of driver somatic mutations on the outcomes of patients with myelodysplastic syndromes treated with allogeneic hematopoietic stem-cell transplantation. Clin Oncol. 2016;34(30):3627-3637.

112. Bejar R, Stevenson KE, Caughey B, et al. Somatic mutations

predict poor outcome in patients with myelodysplastic syndrome after hematopoietic stem-cell transplantation. J Clin Oncol. 2014;32(25):2691-2698.

113. Sallman DA, McLemore AF, Aldrich AL, Lindsley RC, Mar BG, Stojanov P, et al. *TP53* mutations in myelodysplastic syndromes and secondary AML confer an immunosuppressive phenotype. Blood. 2020;136(24):2812-2823.

114. Vadakekolathu J, Lai C, Reeder S, Church SE, Hood T, Lourdusamy A, et al. *TP53* abnormalities correlate with immune infiltration and associate with response to flotetuzumab immunotherapy in AML. Blood Adv. 2020;4(20):5011-5024. [PubMed]

115. Williams P, Basu S, Garcia-Manero G, Hourigan CS, Oetjen KA, Cortes JE, et al. The distribution of T-cell subsets and the expression of immune checkpoint receptors and ligands in patients with newly diagnosed and relapsed acute myeloid leukemia. Cancer. 2019;125(9):1470-1481.

116. Zeidan AM, Bewersdorf JP, Hasle V, Shallis RM, Thompson E, de Menezes DL, et al. Integrated genetic, epigenetic, and immune landscape of *TP53* mutant AML and higher risk MDS treated with azacitidine. Ther Adv Hematol. 2024;15:20406207241257904.

117. Gil-Perez A, Montalban-Bravo G. Management of myelodysplastic syndromes after failure of response to hypomethylating agents. Ther Adv Hematol. 2019;10:2040620719847059.

118. Garcia-Manero G, McCloskey J, Griffiths EA, Yee KW, Zeidan AM, Al-Kali A, et al. Oral decitabine-cedazuridine *versus* intravenous decitabine for myelodysplastic syndromes and chronic myelomonocytic leukaemia (ASCERTAIN): A registrational, randomised, crossover, pharmacokinetics, phase 3 study. Lancet Haematol. 2024;11(1):e15-e26.

119. Zeidan AM, Kharfan-Dabaja MA, Komrokji RS. Beyond hypomethylating agents failure in patients with myelodysplastic syndromes. Curr Opin Hematol. 2014;21(2):123-130.

120. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: A randomised, open-label, phase III study. Lancet Oncol. 2009;1093):223-232.

121. Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Odchimar-Reissig R, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: A study of the cancer and leukemia group B. J Clin Oncol. 2002;20(10):2429–2440.

122. Kantarjian H, Issa JP, Rosenfeld CS, Bennett JM, Albitar M, DiPersio J, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: Results of a phase III randomized study. Cancer. 2006;106(8):1794-1803.

123. Lubbert M, Suciu S, Baila L, Rüter BH, Platzbecker U, Giagounidis A, et al. Low-dose decitabine *versus* best supportive care in elderly patients with intermediate-or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: Final results of the randomized phase III study of the European organisation for research and treatment of cancer leukemia group and the German MDS study group. J Clin Oncol. 2011;29(15):1987-1996.

124. Santini V. How I treat MDS after hypomethylating agent failure. Blood. 2019;133(6):521-529.

125. Garcia-Manero G. Myelodysplastic syndromes: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023;98(8):1307-1325.

126. Nawas MT, Kosuri S. utility or futility? a contemporary approach to allogeneic hematopoietic cell transplant In *Tp53*-mutated MDS And AML. Blood Adv. 2024;8(3):553-561

127. El Chaer F, Hourigan CS, Zeidan AM. How I treat AML incorporating the updated classifications and guidelines. Blood. 2023;141(23):2813-2823.

128. Schwartz JR, Ma J, Lamprecht T, Walsh M, Wang S, Bryant V, et al. The genomic landscape of pediatric myelodysplastic syndromes. Nat Commun. 2017;8(1):1557.

129. Babcock S, Calvo KR, Hasserjian RP. Pediatric myelodysplastic syndrome. Semin Diagn Pathol. 2023;40(3):152-171.

130. Furutani E, Shimamura A. Germline genetic predisposition to hematologic malignancy. J Clin Oncol. 2017;35(9):1018-1028.

131. Godley LA, Shimamura A. Genetic predisposition to hematologic malignancies: Management and surveillance. Blood. 2017;130(4):424-432.

132. Hasle H. Myelodysplastic and myeloproliferative disorders of childhood. Hematology Am Soc Hematol Educ Program. 2016;2016(1):598-604.

133. Pegliasco J, Hirsch P, Marzac C, Isnard F, Meniane JC, Deswarte C, et al. Germline ATG2B/GSKIP-containing 14q32 duplication predisposes to early clonal hematopoiesis leading to myeloid neoplasms. Leukemia. 2022;36(1):126-137.

134. Wu X, Deng J, Zhang N, Liu X, Zheng X, Yan T, et al. Pedigree investigation, clinical characteristics, and prognosis analysis of haematological disease patients with germline *TET2* mutation. BMC Cancer. 2022;22(1):262.

135. Avagyan S, Shimamura A. Lessons from pediatric MDS: Approaches to germline predisposition to hematologic malignancies. Front Oncol. 2022;12:813149.

136. Rudelius M, Weinberg OK, Niemeyer CM, Shimamura A, Calvo KR. The international consensus Classification (ICC) of hematologic neoplasms with germline predisposition, pediatric myelodysplastic syndrome, and juvenile myelomonocytic leukemia. Virchows Arch. 2023;482(1):113-130.

137. Passmore SJ, Chessells JM, Kempski H, Hann IM, Brownbill PA, Stiller CA, et al. Paediatric myelodysplastic syndromes and juvenile myelomonocytic leukaemia in the UK: A population-based study of incidence and survival. Br J Haematol. 2003;121(5):758-767.

138. Niemeyer CM, BaumannI. Classification of childhood

aplastic anemia and myelodysplastic syndrome. Hematology Am Soc Hematol Educ Program. 2011;2011:84-89.

139. Baumann I, Fuhrer M, Behrendt S, Campr V, Csomor J, Furlan I, et al. Morphological differentiation of severe aplastic anaemia from hypocellular refractory cytopenia of childhood: Reproducibility of histopathological diagnostic criteria. Histopathology. 2012;61(1):10-17.

140. Hirabayashi S, Flotho C, Moetter J, Heuser M, Hasle H, Gruhn B, et al. Spliceosomal gene aberrations are rare, coexist with oncogenic mutations, and are unlikely to exert a driver effect in childhood MDS and JMML. Blood. 2012;119(11):e96-e99.

141. Malcovati L, Papaemmanuil E, Ambaglio I, Elena C, Gallì A, Della Porta MG, et al. Driver somatic mutations identify distinct disease entities within myeloid neoplasms with myelodysplasia. Blood. 2014;124(9):1513-1521.

142. Pastor V, Hirabayashi S, Karow A, Wehrle J, Kozyra EJ, Nienhold R, et al. Mutational landscape in children with myelodysplastic syndromes is distinct from adults: Specific somatic drivers and novel germline variants. Leukemia. 2017;31(3):759-762.

143. Chisholm KM, Bohling SD. Childhood myelodysplastic syndrome. Clin Lab Med. 2023;43(4):639-655.

144. Locatelli F, Strahm B. How I treat myelodysplastic syndromes of childhood. Blood. 2018;131(13):1406-1414.

145. Grimm J, Heckl D, Klusmann JH. Molecular mechanisms of the genetic predisposition to acute megakaryoblastic leukemia in infants with down syndrome. Front Oncol. 2021;11:636633.

146. Chen CC, Silberman RE, Ma D, Perry JA, Khalid D, Pikman Y, et al. Inherent genome instability underlies trisomy 21-associated myeloid malignancies. Leukemia. 2024;38(3):521-529.

147. Lange BJ, Kobrinsky N, Barnard DR, Perry JA, Khalid D, Pikman Y, et al. Distinctive demography, biology, and outcome of acute myeloid leukemia and myelodysplastic syndrome in children with down syndrome: Children's cancer group studies 2861 and 2891. Blood. 1998;91(2):608-615

148. Xavier AC, Ge Y, Taub JW. Down syndrome and malignancies: A unique clinical relationship: A paper from the 2008 William Beaumont hospital symposium on molecular pathology. J Mol Diagn. 2009;11(5):371-380.

149. Hasle H, Niemeyer CM, Chessells JM, Baumann I, Bennett JM, Kerndrup G, et al. A pediatric approach to the WHO classification of myelodysplastic and myeloproliferative diseases. Leukemia. 2003;17(2):277-282.

150. Zipursky A, Thorner P, De Harven E, Christensen H, Doyle J. Myelodysplasia and acute megakaryoblastic leukemia in Down's syndrome. Leuk Res.1994;18(3):163-171.

151. Miladinovic M, Reinhardt D, Hasle H, Goemans BF, Tomizawa D, Hitzler J, et al. Guideline for treating relapsed or refractory myeloid leukemia in children with Down syndrome. Pediatr Blood Cancer. 2024;71(9):e31141.

152. Raza Y, Elmasry M, Yu G, Chiappone SB, Liu S, Luberto C, et al. Fenretinide targets GATA1 to induce cytotoxicity in GATA1 positive Acute Erythroid and Acute Megakaryoblastic Leukemic cells. bioRxiv. 2025:2025-01

153. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the world health organization classification of haematolymphoid tumours: Myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703-1719.

154. Hochhaus A, Larson RA, Guilhot F, Radich JP, Branford S, Hughes TP, et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. N Engl J Med. 2017;376:917–27. [PubMed

155. Zafar U, Yusuf M, Chakraborty R, Lalani EN, Mian AA. The ''gatekeeper'' mutation T315i In Bcr/Abl confers additional oncogenic activities to philadelphia chromosome positive leukemia. Blood. 2019;134:5196.

156. Chan O, Talati C, Isenalumhe L, Shams S, Nodzon L, Fradley M, et al. Side-effects profile and outcomes of ponatinib in the treatment of chronic myeloid leukemia. Blood Adv. 2020;4:530-538.

157. Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H. Adult T-cell leukemia: Clinical and hematologic features of 16 cases. Blood. 1977;50(3):481-492.

158. Bazarbachi A, Ghez D, Lepelletier Y, Nasr R, El-Sabban ME, Hermine O, et al. New therapeutic approaches for adult T-cell leukaemia. Lancet Onco. 2004;5(11):664-672.

159. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancers attributable to infections in 2018: A worldwide incidence analysis. Lancet Glob Health. 2020;8(2):e180-190.

160. Bazarbachi A, Suarez F, Fields P, Hermine O. How I treat adult T-cell leukemia/lymphoma. Blood. 2011;118(7):1736-1745.

161. Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the lymphoma Study Group (1984-87). Br J Haematol.1991;79(3):428-437.

162. Hermine O, Wattel E, Gessain A, Bazarbachi A. Adult T cell leukaemia: A review of established and new treatments. BioDrugs. 1998;10(6):447-462.

163. Bazarbachi A, Hermine O. Treatment of adult T-cell leukaemia/lymphoma: Current strategy and future perspectives. Virus Res. 2001;78(1-2):79-92

164. Tobinai K. Current management of adult T-cell leukemia/lymphoma. Oncology. 2009;23(14):1250-1256.

165. Takasaki Y, Iwanaga M, Imaizumi Y, Tawara M, Joh T, Kohno T, et al. Long-term study of indolent adult T-cell leukemia-lymphoma. Blood. 2010;115(22):4337-4343

166. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES, et al. The 2008 WHO classification of lymphoid neoplasms and beyond: Evolving concepts and practical applications. Blood. 2011;117(19):5019-5032.

167. Röllig C, Knop S, Bornhäuser M. Multiple myeloma. Lancet.2015;385: 2197-2208.

168. Willrich MAV, Murray DL, Kyle RA. Laboratory testing for monoclonal gammopathies: Focus on monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. Clin Biochem.2018;51:38-47.

169. Kumar SK, Rajkumar V, Kyle RA. Multiple myeloma. Nat Rev Dis Primers. 2017;3:17046.

170. Röllig C, Knop S, Bornhäuser M. Multiple myeloma. Lancet. 2014. 2197-2208.

171. Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med. 2002;346(8):564-569.

172. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al. Monoclonal Gammopathy of Undetermined Significance (MGUS) consistently precedes multiple myeloma: A prospective study. Blood. 2009:113(22):5412-5417.

173. Weiss BM, Abadie J, Verma P, Howard RS, Kuehl WM. A monoclonal gammopathy precedes multiple myeloma in most patients. Blood. 2009;113(22):5418-5422.

174. Kyle RA, Remstein ED, Therneau TM, Dispenzieri A, Kurtin PJ, Hodnefield JM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. N Engl J Med. 2007;356(25):2582-2590.

175. Bianchi G, Munshi NC. Pathogenesis beyond the cancer clone(s) in multiple myeloma. Blood. 2015;125(20):3049-3058.

176. Kumar SK, Rajkumar SV. The multiple myelomas-current concepts in cytogenetic classification and therapy. Nat Rev Clin Oncol. 2018;15(7):409-421.

177. Moreau P, Rajkumar SV. Multiple myeloma--translation of trial results into reality. Lancet. 2016;388(10040):111-113.

178. Mayo stratification for myeloma and risk-adapted therapy. 2023.

179. Myeloma stratification and risk-adapted therapy with reflex to minimal residual disease, bone marrow. 2024.

180. Rajkumar SV. Multiple myeloma: 2024 update on diagnosis, risk-stratification, and management. Am J Hematol. 2024;99(9):1802-1824.

181. Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, et al. Continued improvement in survival in multiple myeloma: Changes in early mortality and outcomes in older patients. Leukemia. 2014;28(5):1122-1128.

182. Ahmed A, Killeen RB. Relapsed and refractory multiple myeloma. 2023.

183. Raje N, Mateos MV, Iida S, Reece D. Clinical evidence for immune-based strategies in early-line multiple myeloma: Current challenges in decision-making for subsequent therapy. Blood Cancer J. 2023;13(1):104.

184. Solimando AG, Vacca A, Ribatti D. A comprehensive biological and clinical perspective can drive a patient-tailored approach to multiple myeloma: Bridging the gaps between the plasma cell and the neoplastic niche. J Oncol. 2020:6820241.

185. Di Meo F, Iyer A, Akama K, et al. A target discovery pipeline identified ILT3 as a target for immunotherapy of multiple myeloma. Cell Rep Med. 2023;4(7):101110.

186. Maura F, Boyle EM, Coffey D, Cheng R, Yu C, Cesarano A, et al. Genomic and immune signatures predict clinical outcome in newly diagnosed multiple myeloma treated with immunotherapy regimens. Nat Cancer.2023;4(7):101110

187. Zamanillo I, Medina de Alba L, Gil R, de la Puerta R, Alonso R, Jimenez-Ubieto A, et al. Clinical outcomes of patients with multiple myeloma after daratumumab failure. Life (Basel). 2023;13(9):1841.

188. Shah N, Chari A, Scott E, Mezzi K, Usmani SZ. B-Cell Maturation Antigen (BCMA) in multiple myeloma: Rationale for targeting and current therapeutic approaches. Leukemia. 2020;34(4):985-1005.

189. Dhakal B, Hari PN, Usmani SZ, Hamadani M. Chimeric antigen receptor T cell therapy in multiple myeloma: promise and challenges. Bone Marrow Transplant. 2021;56(1):9-19.

190. Ledergor G, Fan Z, Wu K, McCarthy E, Hyrenius-Wittsten A, Starzinski A, et al. CD4$^+$ CAR-T cell exhaustion associated with early relapse of multiple myeloma after BCMA CAR-T cell therapy. Blood Adv. 2024;8(13):3562-3575.

191. Dhodapkar MV. Understanding CAR-T therapy in myeloma: 1 cell at a time. Blood Adv. 2024;8(13):3560-3561.

192. Logue JM, Peres LC, Hashmi H, Colin-Leitzinger CM, Shrewsbury AM, Hosoya H, et al. Early cytopenias and infections after standard-of-care idecabtagene vicleucel in relapsed or refractory multiple myeloma. Blood Adv. 2022;6(24):6109-6119.

193. Hashmi H, Kumar A, Kharfan-Dabaja MA, Munshi PN, Inamoto Y, DeFilipp Z, et al. ASTC committee on practice guidelines survey on evaluation and management of relapsed refractory multiple myeloma after failure of chimeric antigen receptor t-cell therapy. Transplant Cell. 2024;30(8):750-759

194. Usmani SZ, Heuck C, Mitchell A, Szymonifka J, Nair B, Hoering A, et al. Extramedullary disease portends poor prognosis in multiple myeloma and is over-represented in high-risk disease even in the era of novel agents. Haematologica. 2012;97:1761-1767..

195. Gozzetti A, Cerase A, Lotti F, Rossi D, Palumbo A, Petrucci MT, et al. Extramedullary intracranial localization of multiple myeloma and treatment with novel agents: A retrospective survey of 50 patients. Cancer. 2012;118:1574-84.

196. Bansal R, Rakshit S, Kumar S. Extramedullary disease in multiple myeloma. Blood Cancer J. 2021;11(9):161.

197. Bladé J, de Larrea CF, Rosiñol L. Extramedullary involvement in multiple myeloma. Haematologica. 2012;97(11):1618-1619.

198. Jelinek T, Sevcikova T, Zihala D, Popkova T, Kapustova V, Broskevicova L, et al. Limited efficacy of daratumumab in multiple myeloma with extramedullary disease. Leukemia. 2022;36(1):288-291.

199. Bladé J, Fernández de Larrea C, Rosiñol L, Cibeira MT, Jiménez R, Powles R, et al. Soft-tissue plasmacytomas in multiple myeloma: Incidence, mechanisms of extramedullary spread, and treatment approach. J Clin Oncol. 2011;29(28):3805-3812.

200. Varettoni M, Corso A, Pica G, Mangiacavalli S, Pascutto C, Lazzarino M, et al. Incidence, presenting features and outcome of extramedullary disease in multiple myeloma: A longitudinal study on 1003 consecutive patients. Ann Oncol. 2009;21:325-330.

201. Gagelmann N, Eikema DJ, Koster L, Netelenbos T, McDonald A, Stoppa AM, et al. Impact of newly diagnosed extramedullary myeloma on outcome after first autograft followed by maintenance: A CMWP-EBMT study. Eur J Haematol. 2023;111(2):181-190.

202. O'Donnell PH, Milowsky MI, Petrylak DP, Hoimes CJ, Flaig TW, Mar N, et al. Enfortumab vedotin with or without pembrolizumab in cisplatin-ineligible patients with previously untreated locally advanced or metastatic urothelial cancer. J Clin Oncol. 2023;41(25):4107-4117.

203. Zanwar S, Sidana S, Shune L, Puglianini OC, Pasvolsky O, Gonzalez R, et al. Impact of extramedullary multiple myeloma on outcomes with idecabtagene vicleucel. J Hematol Oncol. 2024;17(1):42.

204. Grewal R, Irimie A, Naidoo N, Mohamed N, Petrushev B, Chetty M, et al. Hodgkin's lymphoma and its association with EBV and HIV infection. Crit Rev Clin Lab Sci. 2018;55(2):102-114.

205. Küppers R, Hansmann ML. The Hodgkin and Reed/Sternberg cell. Int J Biochem Cell Biol. 2005;37(3):511-517.

206. Kaseb H, Babiker HM. *Hodgkin Lymphoma*. 2022

207. Feldman AL, Pittaluga S, Jaffe ES. Classification and histopathology of the lymphomas. Lymphomas. 2006;2-38.

208. Sonja I. Berndt, Non-Hodgkin lymphoma Complex etiology, including the role of immune function. Chapter 5.19. In: Wild CP, Weiderpass E, Stewart BW, editors (2020). World Cancer Report: Cancer Research for Cancer Prevention. Lyon, France: International Agency for Research on Cancer.

209. Perry AM, Diebold J, Nathwani BN, MacLennan KA, Müller-Hermelink HK, Bast M, et al. *Non-Hodgkin lymphoma* in the developing world: Review of 4539 cases from the International *non-Hodgkin lymphoma* classification project. Haematologica. 2016;101:1244-1250.

210. Karabon L, Partyka A, Ciszak L, Pawlak-Adamska E, Tomkiewicz A, Bojarska-Junak A, et al. Abnormal expression of BTLA and CTLA-4 Immune checkpoint molecules in chronic lymphocytic leukemia patients. J Immunol. Res. 2020:6545921.

211. Katsuya H, Suzumiya J, Kimura S. Clinical PD-1/PD-L1 blockades in combination therapies for lymphomas. Cancers (Basel). 2023;15(22):5399.

212. Younes A, Brody J, Carpio C, Lopez-Guillermo A, Ben-Yehuda D, Ferhanoglu B, et al. Safety and activity of ibrutinib in combination with nivolumab in patients with relapsed *non-Hodgkin lymphoma* or chronic lymphocytic leukaemia: A phase 1/2a study. Lancet Haematol. 2019;6:67-78.

213. Rosenwald A, Wright G, Leroy K, Yu X, Gaulard P, Gascoyne RD, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to *hodgkin lymphoma*. J Exp Med. 2003;198(6):851-862.

214. Xerri L, Chetaille B, Serriari N, Attias C, Guillaume Y, Arnoulet C, et al. Programmed death 1 is a marker of angioimmunoblastic T-cell lymphoma and B-cell small lymphocytic lymphoma/chronic lymphocytic leukemia. Hum Pathol. 2008;39(7):1050-1058.

215. Rossille D, Gressier M, Damotte D, Maucort-Boulch D, Pangault C, Semana G, et al. High level of soluble programmed cell death ligand 1 in blood impacts overall survival in aggressive *diffuse large B-Cell lymphoma*: Results from a French multicenter clinical trial. Leukemia. 2014;28(12):2367-2375.

216. Tepper JE, Niederhuber JO, Armitage JH, Doroshow MB, Kastan JE. Childhood lymphoma. In: Abeloff's clinical oncology. 5th ed. Philadelphia: WB Saunders; 2014. Chapter 97.

217. Hübel K, Montoto S, Güven M, Duarte RF. Other B- and T-Aggressive lymphomas and lymphomas associated with HIV. EBMT Handbooks. 2024;11:791-797

218. Hämmerl L, Colombet M, Rochford R, Ogwang DM, Parkin DM. The burden of *burkitt lymphoma* in africa. Infect Agent Cancer. 2019;14:17.

219. Molyneux EM, Rochford R, Griffin B, Newton R, Jackson G, Menon, et al. Burkitt's lymphoma. Lancet 2012;379(9822):1234-1244.

220. Bornkamm GW. Epstein-Barr virus and the pathogenesis of Burkitt's lymphoma: More questions than answers. Int J Cancer. 2009;124(8):1745-1755.

221. Lenze D, Leoncini L, Hummel M, Volinia S, Liu CG, Amato T, et al. The different epidemiologic subtypes of *burkitt lymphoma* share a homogenous micro RNA profile distinct from *diffuse large B-cell lymphoma*. Leukemia. 2011;25(12):1869-1876.

222. Ward BJH, Schaal DL, Nkadi EH, Scott RS. EBV association with lymphomas and carcinomas in the oral compartment. Viruses. 2022;14(12):2700.

223. Seegmiller AC, Garcia R, Huang R, Maleki A, Karandikar NJ, Chen W, et al. Simple karyotype and bcl-6 expression predict a diagnosis of *burkitt lymphoma* and better survival in IG-MYC rearranged high-grade B-cell lymphomas. Mod Pathol. 2010;23(7):909-920.

224. Schrader A, Bentink S, Spang R, Lenze D, Hummel M, Kuo M, et al. High *Myc* activity is an independent negative prognostic factor for diffuse large B cell lymphomas. Int J Cancer. 2012;131(4):348-361.

225. Ott G, Rosenwald A, Campo E. Understanding MYC-driven aggressive B-cell lymphomas: Pathogenesis and classification.

Blood. 2013;122(24):3884-3891.

226. Meyer N, Penn LZ. Reflecting on 25 years MYC. Nat Rev Cancer. 2008;8(12):976-990.

227. A clinical evaluation of the International lymphoma study group classification of non-Hodgkin's lymphoma. Blood. 1997;89:3909-3918.

228. Sehn LH, Salles G. *Diffuse large B-cell lymphoma*. N Engl J Med. 2021;384:842-885.

229. Yoo KH, Lee H, Suh C. Lymphoma epidemiology in Korea and the real clinical field including the Consortium for Improving Survival of Lymphoma (CISL) trial. Int J Hematol. 2018;107:395-404.

230. Kurz KS, Ott M, Kalmbach S, Steinlein S, Kalla C, Horn H, et al. Large B-Cell lymphomas in the 5th edition of the WHO-classification of haematolymphoid neoplasms-updated classification and new concepts. Cancers (Basel). 2023;15(8):2285.

231. Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med. 2022;386(7):640-654.

232. Spiegel JY, Dahiya S, Jain MD, Tamaresis J, Nastoupil LJ, Jacobs MT, et al. Outcomes of patients with large B-cell lymphoma progressing after axicabtagene ciloleucel therapy. Blood. 2021;137(13):1832-1835.

233. Zhang J, Grubor V, Love CL, Banerjee A, Richards KL, Mieczkowski PA, et al. Genetic heterogeneity of *diffuse large B-cell lymphoma*. Proc Natl Acad Sci U S A. 2013;110:1398-1403.

234. Lohr JG, Stojanov P, Lawrence MS, Auclair D, Chapuy B, Sougnez C, et al. Discovery and prioritization of somatic mutations in *diffuse large B-cell lymphoma* (DLBCL) by whole-exome sequencing. Proc Natl Acad Sci U S A. 2012;109:3879–3884.

235. Morin RD, Mendez-Lago M, Mungall AJ, Goya R, Mungall KL, Corbett RD, et al. Frequent mutation of histone-modifying genes in *non-hodgkin lymphoma*. Nature. 2011;476:298-303.

236. Pasqualucci L, Trifonov V, Fabbri G, Ma J, Rossi D, Chiarenza A, et al. Analysis of the coding genome of *diffuse large B-cell lymphoma*. Nat Genet. 2011;43:830-837.

237. Zhang J, Grubor V, Love CL, Banerjee A, Richards KL, Mieczkowski PA, et al. Genetic heterogeneity of *diffuse large B-cell lymphoma*. Proc Natl Acad Sci U S A. 2013;110:1398-1403.

238. Iqbal J, Shen Y, Huang X, Liu Y, Wake L, Liu C, et al. Global microRNA expression profiling uncovers molecular markers for classification and prognosis in aggressive B-cell lymphoma. Blood. 2015;125(7):1137-1145.

239. Tavakkoli M, Barta SK. 2024 Update: Advances in the risk stratification and management of large B-cell lymphoma. Am J Hematol. 2023;98(11):1791-1805.

240. Whitehair R, Rosti R, Obiorah I. Molecular classification of diffuse large B cell lymphoma. Adv Mol Pathol. 2023;6(1):25-37.

241. Xu W, Berning P, Lenz G. Targeting B-cell receptor and PI3K signalling in *diffuse large B-cell lymphoma*. Blood. 2021;138(13):1110-1119.

242. Burger JA. Nurture *versus* nature: The microenvironment in chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program. 2011;2011:96-103.

243. Stevenson FK, Krysov S, Davies AJ, Steele AJ, Packham G. B-cell receptor signalling in chronic lymphocytic leukemia. Blood. 2011;118(16):4313-4320.

244. Woyach JA, Johnson AJ, Byrd JC. The B-cell receptor signalling pathway as a therapeutic target in CLL. Blood. 2012;120(6):1175-1184.

245. Efremov DG, Wiestner A, Laurenti L. Novel agents and emerging strategies for targeting the b-cell receptor pathway in CLL. Mediterr J Hematol Infect Dis. 2012;4(1):e2012067.

246. Haselager MV, Kater AP, Eldering E. Proliferative signals in chronic lymphocytic leukemia; What are we missing? Front Oncol. 2020;10:592205.

247. Kraus M, Alimzhanov MB, Rajewsky N, Rajewsky K. Survival of resting mature B lymphocytes depends on BCR signaling *via* the Igalpha/beta heterodimer. Cell. 2004;117(6):787-800.

248. Davis RE, Ngo VN, Lenz G, Tolar P, Young RM, Romesser PB, et al. Chronic active B-cell-receptor signalling in *diffuse large B-cell lymphoma*. Nature. 2010;463(7277):88-92.

249. Davis RE, Brown KD, Siebenlist U, Staudt LM. Constitutive nuclear factor kappa B activity is required for survival of activated B cell-like diffuse large B cell lymphoma cells. J Exp Med. 2001;194(12):1861-1874.

250. Ngo VN, Davis RE, Lamy L, Yu X, Zhao H, Lenz G, et al. A loss-of-function RNA interference screen for molecular targets in cancer. Nature. 2006;441(7089):106-110.

251. Young RM, Phelan JD, Wilson WH, Staudt LM. Pathogenic B-cell receptor signalling in lymphoid malignancies: New insights to improve treatment. Immunol Rev. 2019;291(1):190-213.

252. Havranek O, Xu J, Köhrer S, Wang Z, Becker L, Comer, et al. Tonic B-cell receptor signaling in *diffuse large B-cell lymphoma*. Blood. 2017;130:995-1006.

253. Burger JA, Wiestner A. Targeting B cell receptor signalling in cancer: Preclinical and clinical advances. Nat Rev Cancer. 2018;18(3):148-167.

254. Johnson NA, Slack GW, Savage KJ, Connors JM, Ben-Neriah S, Rogic S, et al. Concurrent expression of MYC and BCL2 in *diffuse large B-cell lymphoma* treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2012;30(28):3452-3459.

255. Valera A, López-Guillermo A, Cardesa-Salzmann T, Climent F, González-Barca E, Mercadal S, et al. MYC protein expression and genetic alterations have prognostic impact in patients with *diffuse large B-cell lymphoma* treated with immunochemotherapy. Haematologica. 2013;98910):1554-

1562.

256. Perry AM, Alvarado-Bernal Y, Laurini JA, Smith LM, Slack GW, Tan KL, et al. MYC and BCL2 protein expression predicts survival in patients with *diffuse large B-cell lymphoma* treated with rituximab. Br J Haematol. 2014;165(3):382–391.

257. Zhou K, Xu D, Cao Y, Wang J, Yang Y, Huang M. C-MYC aberrations as prognostic factors in *diffuse large B-cell lymphoma*: A meta-analysis of epidemiological studies. PLoS ONE. 2014;9(4):e95020.

258. Kluk MJ, Chapuy B, Sinha P, Roy A, Dal CP, Neuberg DS, et al. Immunohistochemical detection of MYC-driven *diffuse large B-cell lymphomas*. PLoS ONE. 2012;7(4):e33813.

259. Kridel R, Sehn LH, Gascoyne RD. Pathogenesis of follicular lymphoma. J Clin Invest. 2012;122(10):3424-3431.

260. Krysiak K, Gomez F, White BS, Matlock M, Miller CA, Trani L, et al. Recurrent somatic mutations affecting B-cell receptor signaling pathway genes in follicular lymphoma. Blood. 2017;129(4):473-483.

261. Kipps TJ, Stevenson FK, Wu CJ, Croce CM, Packham G, Wierda WG, et al. Chronic lymphocytic leukaemia. Nat Rev Dis Prim 2017;3:16096.

262. Ammann EM, Shanafelt TD, Wright KB, McDowell BD, Link BK, Chrischilles EA, et al. Updating survival estimates in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) based on treatment-free interval length. Leuk Lymphoma. 2018;59(3):643-649.

263. Stein H, Bonk A, Tolksdorf G, Lennert K, Rodt H, Gerdes J, et al. Immunohistologic analysis of the organization of normal lymphoid tissue and non-Hodgkin's lymphomas. J Histochem Cytochem. 1980;28(8):746-760.

264. Fabbri G, Dalla-Favera R. The molecular pathogenesis of chronic lymphocytic leukaemia. Nat Rev Cancer. 2016;16(3):145-162.

265. Arruga F, Gyau BB, Iannello A, Vitale N, Vaisitti T, Deaglio S, et al. Immune response dysfunction in chronic lymphocytic leukemia: Dissecting molecular mechanisms and microenvironmental conditions. Int J Mol Sci. 2020;21(5):1825.

266. Kumar V, Abbas AK, Aster JC. Hematopoietic and Lymphoid Systems. In: Kumar V, Abbas AK, Aster JC, eds. Robbins Basic Pathology. 10th ed. Philadelphia, PA: Elsevier; 2018:441-494.

267. Sharma S, Rai KR. Chronic Lymphocytic Leukemia (CLL) treatment: So many choices, such great options. Cancer. 2019;125(9):1432-1440.

268. Yun X, Zhang Y, Wang X. Recent progress of prognostic biomarkers and risk scoring systems in chronic lymphocytic leukemia. Biomark Res. 2020;8:40.

269. Kil LP, Yuvaraj S, Langerak AW, Hendriks RW. The role of B cell receptor stimulation in CLL pathogenesis. Curr Pharm Des. 2012;18:3335-3355.

270. Zenz T, Eichhorst B, Busch R, Denzel T, Habe S, Winkler D, et al. *TP53* mutation and survival in chronic lymphocytic leukemia. J Clin Oncol. 2010;28(29):4473-4479.

271. Robak P, Robak T. Novel synthetic drugs currently in clinical development for chronic lymphocytic leukemia. Expert Opin Investig Drugs. 2017;26(11):1249-1265.

272. Perri F, Pisconti S, Della Vittoria Scarpati G. *P53* mutations and cancer: A tight linkage. Ann Transl Med. 2016;4(24):522.

273. Pal Singh S, Dammeijer F, Hendriks RW. Role of bruton's tyrosine kinase in B cells and malignancies Mol Cancer. 2018;17(1):57.

274. Moreno C, Montserrat E. New prognostic markers in chronic lymphocytic leukemia. Blood Rev. 2008;22(4):211-219.

275. Rassenti LZ, Jain S, Keating MJ, Wierda WG, Grever MR, Byrd JC, et al. Relative value of ZAP-70, CD38, and immunoglobulin mutation status in predicting aggressive disease in chronic lymphocytic leukemia. Blood. 2008;112(5):1923-1930.

276. Montillo M, Hamblin T, Hallek M, Montserrat E, Morra E. Chronic lymphocytic leukemia: Novel prognostic factors and their relevance for risk-adapted therapeutic strategies. Haematologica. 2005;90(3):391-399.

277. Oppezzo P, Vasconcelos Y, Settegrana C, Jeannel D, Vuillier F, Legarff-Tavernier M, et al. The *LPL/ADAM29* expression ratio is a novel prognosis indicator in chronic lymphocytic leukemia. Blood. 2005;106(2):650-657.

278. van't Veer MB, Brooijmans AM, Langerak AW, Verhaaf B, Goudswaard CS, Graveland WJ, et al. The predictive value of lipoprotein lipase for survival in chronic lymphocytic leukemia. Haematologica. 2006;91(1):56-63.

279. Hallek, M; German CLL Study Group. Prognostic factors in chronic lymphocytic leukemia. Ann Oncol. 2008:19:51-3.

280. Hofland T, Eldering E, Kater AP, Tonino SH. Engaging cytotoxic t and nk cells for immunotherapy in chronic lymphocytic leukemia. Int J Mol Sci. 2019;20(17):4315.

281. Vlachonikola E, Stamatopoulos K, Chatzidimitriou A. T cells in chronic lymphocytic leukemia: A two-edged sword. Front Immunol. 2021;11:612244.

282. Jain N, Wierda WG, O'Brien S. Chronic lymphocytic leukaemia. Lancet. 2024;404(10453):694-706.

283. Muggen AF, Singh SP, Hendriks RW, Langerak AW. Targeting signaling pathways in chronic lymphocytic leukemia. Curr Cancer Drug Targets. 2016;16(8):669-688.

284. Singh SP, Pillai SY, de Bruijn MJW, Stadhouders R, Corneth OBJ, van den Ham HJ, et al. Cell lines generated from a chronic lymphocytic leukemia mouse model exhibit constitutive Btk and Akt signaling. Oncotarget. 2017;8(42):71981-71995.

285. Herman SE, Gordon AL, Hertlein E, Ramanunni A, Zhang X, Jaglowski S, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. Blood. 2011;117(23):6287-6296.

286. Ponader S, Chen SS, Buggy JJ, Balakrishnan K, Gandhi V, Wierda WG, et al. The bruton tyrosine kinase inhibitor PCI-

32765 thwarts chronic lymphocytic leukemia cell survival and tissue homing *in vitro* and *in vivo*. Blood. 2012;119(5):1182-1189.

287. Kil LP, de Bruijn MJ, van Hulst JA, Langerak AW, Yuvaraj S, Hendriks RW, et al. Bruton's tyrosine kinase mediated signaling enhances leukemogenesis in a mouse model for chronic lymphocytic leukemia. Am J Blood Res. 2013;3(1):71-83.

288. Iyer P, Wang L. Emerging Therapies in CLL in the era of precision medicine. Cancers (Basel). 2023;15(5):1583.

289. Ding W. Richter transformation in the era of novel agents. Hematol Am Soc Hematol Educ Program. 2018;2018(1):256-263.

290. Al-Sawaf O, Robrecht S, Bahlo J, Fink AM, Cramer P, v Tresckow J, et al. Richter transformation in chronic lymphocytic leukemia (CLL)-a pooled analysis of German CLL Study Group (GCLLSG) front line treatment trials. Leukemia. 2021;35(1):169-176.

291. Al-Sawaf O, Ligtvoet R, Robrecht S, Stumpf J, Fink AM, Tausch E et al. Tislelizumab plus zanubrutinib for richter transformation: The phase 2 RT1 trial. Nat Med. 2024;30(1):240-248

292. Condoluci A, Rossi D. Biology and treatment of richter transformation. Front Oncol. 2022;12:829983.

293. Abrisqueta P, Nadeu F, Bosch-Schips J, Iacoboni G, Serna A, Cabirta A, et al. From genetics to therapy: Unraveling the complexities of richter transformation in chronic lymphocytic leukemia. Cancer Treat Rev (2023) 120:102619.

294. Korać P, Dotlić S, Matulić M, Zajc Petranović M, Dominis M. Role of MYC in B Cell lymphomagenesis. Genes (Basel). 2017;8(4):115.

295. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press. 2008.

296. Woroniecka R, Rymkiewicz G, Grygalewicz B, Błachnio K, Rygier J, Jarmuż-Szymczak M, et al. Cytogenetic and flow cytometry evaluation of richter syndrome reveals MYC, CDKN2A, IGH alterations with loss of CD52, CD62L and increase of CD71 antigen expression as the most frequent recurrent abnormalities. Am J Clin Pathol. 2015;143(1):25-35.

297. Fonseka LN, Tirado CA. C-MYC Involvement in Chronic Lymphocytic Leukemia (CLL): A molecular and cytogenetic update. J Assoc Genet Technol. 2015;41(4):176-183.

298. Cheah CY, Seymour JF, Wang ML. Mantle cell lymphoma. J Clin Oncol. 2016;34(11):1256-1269.

299. Saba NS, Liu D, Herman SE, Underbayev C, Tian X, Behrend D, et al. 2016. Pathogenic role of B-cell receptor signaling and canonical NF-κB activation in mantle cell lymphoma. Blood. 2016;128(1): 82-92.

300. Rahal R, Frick M, Romero R, Korn JM, Kridel R, Chun Chan F, et al. Pharmacological and genomic profiling identifies NF-κB-targeted treatment strategies for mantle cell lymphoma. Nat Med. 2014;20(1):87-92.

301. Profitós-Pelejà N, Santos JC, Marín-Niebla A, Roué G, Ribeiro ML. Regulation of b-cell receptor signaling and its therapeutic relevance in aggressive b-cell lymphomas. Cancers (Basel). 2022;14(4):860.

302. Inamdar AA, Loo A, Mikhail N, Lee P. An aggressive presentation of mantle cell lymphoma with unique molecular features. Cureus. 2021;13(8):e17598.

303. Bertoni F, Rinaldi A, Zucca E, Cavalli F. Update on the molecular biology of mantle cell lymphoma. Hematol Oncol. 2006;24(1):22-27.

304. Myklebust JH, Brody J, Kohrt HE, Kolstad A, Czerwinski DK, Wälchli S, et al. Distinct patterns of B-cell receptor signaling in *non-Hodgkin lymphomas* identified by single-cell profiling. Blood.2017;129(6):759-770.

305. Hammons L, Fenske TS. Treatment of mantle cell lymphoma in the frontline setting: Are we ready for a risk-adapted approach? J Pers Med. 2022;12(7):1134.

306. Eskelund CW, Dahl C, Hansen JW, Westman M, Kolstad A, Pedersen LB, et al. *TP53* mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy. Blood. 2017;130(17):1903-1910.

307. Shallis RM, Wang R, Davidoff A, Ma X, Podoltsev NA, Zeidan AM, et al. Epidemiology of the classical myeloproliferative neoplasms: The four corners of an expansive and complex map. Blood Rev. 2020 ;42:100706.

308. Reuther GW. Myeloproliferative neoplasms: Molecular drivers and therapeutics. Prog Mol Biol Transl Sci. 2016;144:437-484.

309. Campbell PJ, Green AR. The myeloproliferative disorders. N Engl J Med. 2006;355(23): 2452-2466.

310. Mead AJ, Mullally A. Myeloproliferative neoplasm stem cells. Blood. 2017;129(12):1607-1616.

311. Tefferi A, Pardanani A. Myeloproliferative neoplasms: A contemporary review. JAMA Oncol. 2015;1(1):97-105.

312. Tefferi A, Guglielmelli P, Larson DR, Finke C, Wassie EA, Pieri L, et al. Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis. Blood. 2014;124(16):2507-2513.

313. Klampfl T, Gisslinger H, Harutyunyan AS, Nivarthi H, Rumi E, Milosevic JD, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013;369(25):2379-2390.

314. Nangalia J, Massie CE, Baxter EJ, Nice FL, Gundem G, Wedge DC, et al. Somatic *CALR* mutations in myeloproliferative neoplasms with nonmutated *JAK2*. N Engl J Med. 2013;369(25):2391-2405.

315. Godfrey AL, Green AC, Harrison CN. Essential thrombocythemia: Challenges in clinical practice and future prospects. Blood. 2023;141(16):1943-1953.

316. Loscocco GG, Gesullo F, Capecchi G, Atanasio A, Maccari C, Mannelli F, et al. One thousand patients with essential thrombocythemia: The florence-CRIMM experience. Blood

Cancer J. 2024;14(1):10.

317. Wen QJ, Yang Q, Goldenson B, Malinge S, Lasho T, Schneider RK, et al. Targeting megakaryocytic-induced fibrosis in myeloproliferative neoplasms by AURKA inhibition. Nat Med. 2015;21(12):1473-1480.

318. Malara A, Gruppi C, Abbonante V, Cattaneo D, De Marco L, Massa M, et al. EDA fibronectin-TLR4 axis sustains megakaryocyte expansion and inflammation in bone marrow fibrosis. J Exp Med. 2019;216(3):587-604

319. Psaila B, Wang G, Rodriguez-Meira A, Li R, Heuston EF, Murphy L, et al. Single-cell analyses reveal megakaryocyte-biased hematopoiesis in myelofibrosis and identify mutant clone-specific targets. Mol Cell. 2020;78(3):477-492

320. Vallapureddy RR, Mudireddy M, Penna D, Lasho TL, Finke CM, Hanson CA, et al. Leukemic transformation among 1306 patients with primary myelofibrosis: Risk factors and development of a predictive model. Blood Cancer J. 2019;9(2):12.

321. Masarova L, Bose P, Pemmaraju N, Daver NG, Sasaki K, Chifotides HT, Z, et al. Improved survival of patients with myelofibrosis in the last decade: Single-center experience. Cancer. 2022;128(8):1658-1665.

322. Pritchard JE, Pearce JE, Snoeren IAM, Fuchs SN, Götz K, Peisker F, et al. Non-canonical hedgehog signaling mediates profibrotic hematopoiesis-stroma crosstalk in myeloproliferative neoplasms. Cell Rep. 2024;43(1):113608.

323. Mughal TI, Vaddi K, Sarlis NJ, Verstovsek S. Myelofibrosis-associated complications: Pathogenesis, clinical manifestations, and effects on outcomes. Int J Gen Med. 2014;29(7):89-101.

324. Mesa RA, Li CY, Ketterling RP, Schroeder GS, Knudson RA, Tefferi A, et al. Leukemic transformation in myelofibrosis with myeloid metaplasia: A single-institution experience with 91 cases. Blood. 2005;105(3):973-977

325. Pardanani A, Tefferi A. How I treat myelofibrosis after failure of JAK inhibitors. Blood. 2018;132(5):492-500.

326. Al-Ghamdi YA, Lake J, Bagg A, Thakral B, Wang SA, Bueso-Ramos C, et al. Triple-negative primary myelofibrosis: A bone marrow pathology group study. Mod Pathol. 2023;36(3):100016.

327. Aguirre LEE, Jain AG, Ball S, Al Ali N, Tinsley-Vance SM, Sallman DA, et al. Triple-negative myelofibrosis: Disease features, response to treatment and outcomes. Blood. 2021;138:1494.

328. Mora B, Guglielmelli P, Rumi E, Maffioli M, Barraco D, Rambaldi A, et al. Impact of bone marrow fibrosis grade in post-polycythemia vera and post-essential thrombocythemia myelofibrosis: A study of the MYSEC group. Am J Hematol. 2020;95(1):1-3.

329. Kröger N, Wolschke C, Gagelmann N. How I treat transplant-eligible patients with myelofibrosis. Blood. 2023;142(20):1683-1696.

330. Kröger N, Giorgino T, Scott BL, Ditschkowski M, Alchalby H, Cervantes F, et al. Impact of allogeneic stem cell transplantation on survival of patients less than 65 years of age with primary myelofibrosis. Blood. 2015;125(21):3347-3350.

331. Kröger N, Bacigalupo A, Barbui T, Ditschkowski M, Gagelmann N, Griesshammer M,et al. Indication and management of allogeneic haematopoietic stem-cell transplantation in myelofibrosis: updated recommendations by the EBMT/ELN International working Group. Lancet Haematol. 2024;11(1):62-74.

332. Gagelmann N, Badbaran A, Salit RB, Schroeder T, Gurnari C, Pagliuca S, et al. Impact of *TP53* on outcome of patients with myelofibrosis undergoing hematopoietic stem cell transplantation. Blood. 2023;141(23):2901-2911.

333. Krishnamurthy P. Double, double, *TP53*, and trouble in myelofibrosis. Blood. 2023;141(23):2793-2795.

334. Celik H, Krug E, Zhang CR, Han W, Issa N, Koh WK, et al. A humanized animal model predicts clonal evolution and therapeutic vulnerabilities in myeloproliferative neoplasms. Cancer Discov. 2021;11(12):3126-3141.

335. Dunbar AJ, Rampal RK, Levine R. Leukemia secondary to myeloproliferative neoplasms. Blood. 2020;136(1):61-70.

336. Grinfeld J, Nangalia J, Baxter EJ, Wedge DC, Angelopoulos N, Cantrill R, et al. Classification and personalized prognosis in myeloproliferative neoplasms. N Engl J Med. 2018;379(15):1416-1430.

337. Lasho TL, Mudireddy M, Finke CM, Hanson CA, Ketterling RP, Szuber N, et al. Targeted next-generation sequencing in blast phase myeloproliferative neoplasms. Blood Adv. 2018;2(4):370-380.

338. Luque Paz D, Jouanneau-Courville R, Riou J, Ianotto JC, Boyer F, Chauveau A, et al. Leukemic evolution of polycythemia vera and essential thrombocythemia: Genomic profiles predict time to transformation Blood Adv. 2020;4(19):4887-4897.

339. Rampal, R, Ahn J, Abdel-Wahab O, Nahas M, Wang K, Lipson D, et al. Genomic and functional analysis of leukemic transformation of myeloproliferative neoplasms. Proc Natl Acad Sci USA. 2014;111(50):5401-5410.

340. Rodriguez-Meira A, Norfo R, Wen S, Chédeville AL, Rahman H, O'sullivan J, et al. Single-cell multi-omics identifies chronic inflammation as a driver of *TP53*-mutant leukemic evolution. Nat Genet. 2023;55(9):1531-1541.