19 Future Developments: Immunotherapy in AML

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Abbreviations

alloSCT	Allogeneic stem cell transplantation
AML	Acute myeloid leukemia
BCP-ALL	B-cell precursor acute lymphoblastic leukemia
BissCAR	Bispecific and split chimeric antigen receptor
BiTE	Bispecific T-cell engager
CAR	Chimeric antigen receptor
cCAR	Compound chimeric antigen receptor
CR	Complete remission
CRS	Cytokine release syndrome
DART	Dual affinity retargeting
DLBCL	Diffuse large B-cell lymphoma
FC	Crystallizable fragments
GvHD	Graft-versus-host disease
GvL	Graft-versus-leukemia
HLA	Human leukocyte antigen
HMA	Hypomethylating agent
HSC	Hematopoietic stem cell
HSPC	Hematopoietic stem and progenitor cells
ICPIs	Immune checkpoint inhibitor
LSC	Leukemic stem cell
MDS	Myelodysplastic syndrome
MHC	Major histocompatibility complex
MRD	Measurable (minimal) residual disease
Nb	Nanobody
ORR	Objective response rate
STAR	Sequentially tumor-selected antibody and antigen retrieval
TCR	T-cell receptor

19.1 Challenges of Immunotherapy in AML

The five-year survival rate in acute myeloid leukemia (AML) remains low due to a high incidence of relapse caused by chemo-refractory residual leukemic cells. These relapse-initiating cells are the target of novel immunotherapeutic strategies (Yang et al. 2017; DiNardo and Cortes 2016). Consolidation therapy with allogeneic stem cell transplantation (alloSCT) has been shown to be the most successful anti-leukemic treatment strategy in AML (Koreth et al. 2009). Donor T-cells represent the key contributors to the success of this therapy facilitating the desired graft-versus-leukemia (GvL) effect and reactivating the power of the immune system to fight against AML blasts and precursor cells. Nevertheless, alloSCT is limited to a small subset

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of patients and is associated with severe complications including graft-versus-host disease (GvHD). The success of alloSCT is further compromised by a significant relapse rate attributed to several AML-associated immune escape mechanisms. These include reduced expression of major histocompatibility complex (MHC) molecules, enhanced expression of inhibitory ligands, reduced expression of activating ligands and receptors, and manipulation of soluble factors within the microenvironment (Khaldoyanidi et al. 2021).

Several immunomodulatory platforms were developed against hematologic malignancies to enable T-cell-based therapy outside the alloSCT setting and thereby have the potential to (1) increase therapeutical efficacy and (2) reduce T-cell cytotoxicity against healthy tissues. Immune checkpoint inhibitors (ICPIs) have evolved within the last decade as valuable tools in cancer immunotherapy by blocking inhibitory checkpoints and reactivating the immune system's abbilities to fight cancer cells. Checkpoint inhibitors rely on the reactivation of endogenous T-cell responses whereas other immunotherapy platforms rely on the recognition of AML-associated surface antigens. Bispecific T-cell engagers (BiTEs) and other T-cell recruiting antibody constructs represent a novel class of antibody constructs that bind to T-cells and cancer cells simultaneously enhancing the T-cell-mediated cytotoxic activity against the tumor cell. Chimeric antigen receptor (CAR) T-cells are genetically modified T-cells featuring an extracellular single-chain variable fragment targeting a specific tumor-associated antigen together with at least one intracellular costimulatory signaling domain. The mentioned techniques will be described and discussed in more detail in the following sections of this chapter. The chapter will not cover vaccine-based approaches that aim to induce and possibly reactivate endogenous T-cell responses against AML-associated target antigens. Albeit dendritic cell-based vaccines have shown promising data, the number of patients treated in early clinical trials is still rather small. Also omitted in this chapter are antibody–drug conjugates as this topic is integrated into other chapters addressing intense induction chemotherapy combinations.

In hematology, ICPIs have only been approved for the treatment of Hodgkin's lymphoma and primary mediastinal B-cell lymphoma. To date, bispecific antibody constructs and CAR T-cells are restricted for the treatment of B-cell neoplasia. The BiTE blinatumomab is used in B-cell precursor acute lymphoblastic leukemia (BCP-ALL) and CAR T-cells were successfully applied in heavily pretreated BCP-ALL (until the age of 26) and diffuse large B-cell lymphoma (DLBCL) patients (Kantarjian et al. 2017; Burt et al. 2019).

Although these promising results were achieved for B-cell neoplasia, the strategies cannot be easily translated to AML due to the lack of suitable target antigens.

19.2 Target Antigens in T-Cell-Based Immunotherapy in AML

In cancer immunotherapy, T-cells are valuable tools as they secrete cytokines and generate cytotoxic reactions against other cells that feature cancerous alterations. The efficacy and safety of such T-cell-based therapies depend on the choice of the right target antigens. Based on the current knowledge, three different groups of target antigens in AML can be classified.

19.2.1 Leukemia-Specific Antigens

Tumor-specific antigens, or tumor neoantigens, play a crucial role in tumor-specific T-cell-mediated anti-tumor immunity. In the case of leukemia, specific neoantigens ideally originate from leukemogenic mutations and are therefore exclusively expressed in malignant clones that make them suitable AML-specific target anti-

gens. However, most of the leukemia-specific neoantigens are intracellularly expressed human leukocyte antigen (HLA)-restricted antigens that can only be recognized by T-cell receptors (TCRs). The benefit of leukemia-specific neoantigens is their high specificity to tumor cells and their absence in normal cells, but some limitations including the low number of protein-coding mutations in hematologic malignancies and the potential of the malignant cell to reduce HLA expression as an escape mechanism make this approach highly challenging (Biernacki and Bleakley 2020). In clinical trials, leukemia-specific neoantigen-based therapy concepts have not been introduced so far.

19.2.2 Lineage-Restricted Antigens

For the therapy of AML, another concept is to use lineage-restricted antigens of the myeloid lineage. Myeloid progenitor antigens like CD33 and CD123 are expressed on both AML and hematopoietic stem cells (HSCs; Fig. 19.1). Clinical trials utilizing antibody constructs or CAR T-cells in AML patients commonly target lineage-restricted antigens like CD33 and CD123. Different modifications are under evaluation to shorten observed HSC ablation and resulting myelosuppression (Lulla et al. 2019).

19.2.3 Leukemia-Associated Antigens

The selection of leukemia-associated antigens is based on their overexpression in AML cells compared to healthy tissue. Leukemia-associated antigens are usually not lineage-specific, which reduces undesired HSC ablation, but these antigens are also expressed in non-hematopoietic tissues, leading to on-target, off-tumor toxicities. A considerable number of AML-related antigens have been characterized within the last decades, but only a small number of leukemia-associated antigens, like WT1 and PRAME, were selected for investigation in early phase clinical trials on patients with AML so far (Tawara et al. 2017; Anguille et al. 2017; Lichtenegger et al. 2020). In current studies, alternative leukemia-associated target antigens like CD44v6 or TIM3, which are not expressed on HSCs, are also tested for their applicability in AML treatment. In one study, the expression of CD44v6 in keratinocytes did not promote CAR T-cell-induced lysis of this physiological cell type. This phenomenon might be explained by the significant co-expression of PD-L1 together with CD44v6 on the keratinocytes and demonstrated that not all target antigen-expressing tissues and cell types are comparably prone to

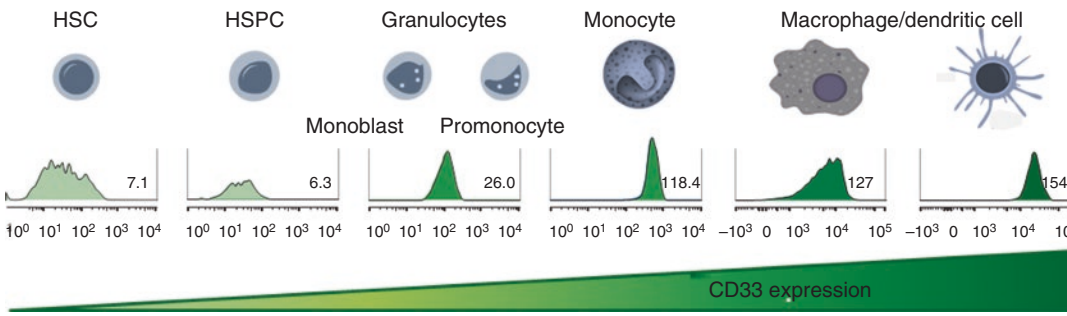

Fig. 19.1 CD33 expression during the healthy myeloid hematopoiesis. CD33, a member of the sialic-acid-binding immunoglobulin-like lectin family, is used as both a diagnostic marker and a therapeutic target for AML. Despite its expression in AML cell populations, CD33 is also present on the surface of normal myeloid cells with increasing expression intensity during maturation. Although hematopoietic stem cells (HSC) and progenitor cells (HSPCs) feature low levels of this antigen, anti-CD33 antibodies might also target these healthy cell populations and induce fatal HSC ablation

T-cell-induced cytotoxicity (Casucci et al. 2013). Whether comparable resistance mechanisms can be adopted by AML bulk cells and leukemic stem cells (LSCs) remains unclear.

19.2.3.1 Exploring New Target Antigen Candidates in AML

Several characteristics must be considered when the applicability of a target antigen in cancer immunotherapy is evaluated. The first important aspect is the cellular localization of the antigen. Intracellular antigens can only be targeted via the specific T-cell receptor while antigens expressed on the cellular surface can be directly targeted by Fab domains of bispecific antibody constructs or CAR T-cells. Secondly, the intensity of antigen expression represents a potential limiting factor as some antigens can be expressed at very low levels, which cannot be detected even by highly sensitive techniques like flow cytometry in the clinical approach. In addition to the intensity of expression, the distribution of an antigen affects its applicability as a target antigen. The expression pattern of the target antigen might influence the pharmacokinetics, efficacy, and toxicity of the targeted molecule.

19.3 Immune Checkpoint Inhibitors in AML

The characterization and functional utilization of blocking the immune checkpoints CTLA-4 and PD-1/PD-L1 was a hallmark of the last decade infighting cancer. More recently, checkpoint inhibitors have also received approval for treatment of relapsed/refractory Hodgkin's lymphoma. Preclinical studies and preliminary data from early clinical trials suggest their utilization in hematological malignancies including AML and myelodysplastic syndrome (MDS) (Boddu et al. 2018; Robert 2020).

An important factor related to the efficacy and safety of ICPIs as a single-agent strategy in AML is prior or subsequent alloSCT. The incidence of alloSCT-related GvHD is known to be a multivariable event, including the allograft donor source, the type of post-alloSCT GvHD prophylaxis, the history of individual GvHD, and the dosing and duration of the applied ICPI (Oran and Daver 2019).

Combinatorial therapies significantly improved response and long-term survival rates. The diversity of successful combinational therapies mirrors the complexity of both, the immunosuppressive biology of the tumor microenvironment and the heterogeneity of antitumor immunity (Teague and Kline 2013). Especially in AML, different ICPI monotherapies were identified to be less effective compared to the same strategies applied to solid tumors. This divergence is mainly related to the pronounced heterogeneity of AML and the relatively lower number of mutational alterations in AML bulk cells compared to solid tumor cell populations. Furthermore, the protective bone marrow microenvironment is also assumed to exert an immunosuppressive role either by preventing access of T-cells to AML blasts or potentially by secretion of immune-dampening metabolites (Teague and Kline 2013). Many targeted and non-targeted therapies have recently been approved for AML, and strategies combining ICPIs with different regimens are presented below.

19.4 Combinatorial Therapy of ICPIs and Chemotherapy in AML

The combination of chemotherapy with other therapeutic interventions is currently being investigated in clinical trials. The cytotoxic effects of chemotherapy vice versa might also activate the immune response against cancer cells and their specific microenvironment and make them more vulnerable to subsequent therapeutic strategies like ICIPs. In mouse models, injection of cytosine arabinoside (cytarabine) induced the expression of the costimulatory molecules CD80/CD86 and reduced the expression of PD-1 on leukemic cells, making them more susceptible to cytotoxic T-cell-mediated killing (Vereecque et al. 2004). Exposure of calreticulin on the surface of dying leukemic cells after exposure to chemotherapy has been shown to enhance cellular anti-tumor

immune responses in AML patients (Wemeau et al. 2010). In a phase II clinical trial, high-dose cytarabine was followed by the anti-PD-1 ICPI pembrolizumab (Zeidner et al. 2019). The overall response rate was 46% and the complete response/complete response with incomplete blood recovery rate was 38%. This study is still ongoing and the relevance of the combination of checkpoint inhibition and chemotherapy remains unclear.

19.5 Combinatorial Therapy of ICPIs and Hypomethylating Agents in AML

Hypomethylating agents (HMAs) feature two different mechanisms important for AML treatment. On the one hand, HMAs promote anti-tumor immune response, and on the other hand, HMAs reduce the immune response by increased immune checkpoint molecule expression. The enhanced expression of immune checkpoint molecules is assumed to be responsible for the commonly observed resistance of AML cell populations against HMAs like azacytidine. Therefore, the combination of HMAs and ICPIs is supposed as a valuable tool in AML therapy and several combinations are currently under investigation in early clinical trials (Stahl and Goldberg 2019).

The combination of azacytidine with different ICPIs is based on the fact that demethylation of genomic regions called CpG islands affects gene expression of PD-1 and CTLA-4 in T-cells, and PD-L1 expression in tumor cells, resulting in an azacytidine-induced reduction of the T-cell-based anti-tumorigenic immune response. Therefore, the combination of azacytidine with ICPIs targeting these antigens features promising synergies. Nivolumab and pembrolizumab (anti-PD1 ICPIs), ipilimumab and tremelimumab (targeting CTLA-4 receptors on T-cells), and durvalumab and atezolizumab (anti-PD-L1 ICPIs) are currently under investigation for combinational therapy with azacytidine in AML patients (Daver et al. 2018).

19.6 CD47: A Macrophage Immune Checkpoint in AML

All previously mentioned strategies utilizing immunotherapeutic approaches to fight AML are based on stimulation of the adaptive immune system via T-cell recruitment. A different strategy is targeting the innate immune system. As macrophages are the key mediators of the innate immune response, a macrophage checkpoint protein, namely CD47, became of interest in current preclinical and early clinical studies. Activation of the CD47-SIRPα pathway induces the "do not eat me" signal of a cell, which allows tumor cells to evade phagocytosis by macrophages. CD47 expression was observed to be highly upregulated in myeloid malignancies, but blocking of CD47 resulted in engulfment of the leukemic cells by macrophages. This anti-cancer activity was tested in multiple AML and MDS clinical studies using the first-in-class anti-CD47 antibody magrolimab (Hu5F9-G4) (Chao et al. 2020). At the 2020 American Society of Hematology Meeting, an update of the phase 1b trial was given reporting on 52 AML patients that were treated with magrolimab plus azacytidine. Noteworthy, the majority of patients were of poor-risk cytogenetics including 65% of patients carrying a p53 mutation. Overall, 22 or 34 evaluable patients achieved an objective response (44% of the patients achieving a complete remission [CR]). Treatment-related adverse events were generally transient and reversible. Further data of the expansion cohort with longer follow-up are expected in 2021.

19.6.1 Bispecific Antibodies in AML

In the 1980s, the combination of antigen recognition sites of two or more antibodies in one bispecific antibody enabled the simultaneous binding to multiple targets and introduced this technique to redirect the immune system against tumor cells (Guy and Uy 2018). Bispecific T-cell engagers (BiTEs) and other bispecific antibody constructs (e.g., dual affinity retargeting [DART]) represent a specific class of bispecific antibodies

designed to harness the immune system. These recombinant proteins recruit T-cells through CD3 engagement and target tumor cells through binding to a tumor-associated antigen. Up to date, only one bispecific candidate, namely blinatumomab, was approved in the United States and Europe. This BiTE was designed to bind to CD19 on B-cells and CD3 on T-cells and was successfully applied in patients with refractory BCP-ALL and adult patients with measurable residual disease (MRD; previously termed minimal residual disease (Schuurhuis et al. 2018)). The success of this BiTE is based on the specificity of CD19 for B-cell malignancies. In AML the lineage-restricted antigens like CD33, CD123, CLL-1 (CLEC12A), and FLT3 are currently under evaluation in early clinical trials. Additionally, combination strategies of BiTEs with anti-PD-1 and anti-PD-L1 antibodies are assumed to improve the efficacy of this treatment strategy. Therefore, the combination of an anti-CD33 BiTE antibody construct with the PD-1 inhibitor pembrolizumab is currently under investigation in an early clinical trial (NCT04478695).

The toxicity profile of bispecific antibodies is dominated by cytokine release syndrome (CRS), and anti-inflammatory prophylaxis and individual dose adjustments are utilized to allow high doses of bispecific antibodies being administered to patients. Different formats of bispecific antibodies are currently evaluated in ongoing trials. Smaller-sized constructs feature shorter in vivo half-lives, which allow interrupting or adjusting doses faster, but require continuous infusion. Larger-sized constructs enable slower clearance increasing their in vivo half-lives and do not require continuous infusion. Furthermore, the implementation of crystallizable fragments (FC) in larger constructs can increase their efficacy by promoting FC-mediated cell killing (Brinkmann and Kontermann 2017; Labrijn et al. 2019).

The ubiquitous expression of a target antigen, like CD33, might also interfere with the efficacy of a BiTE construct raised against this protein. The widespread expression of CD33 on different cell types (monocytes, immature granulocytes, HSCs, and Kupffer cells) induces an increased number of BiTE molecules to bind to off-tumor targets. This failure increases the risk for on-target, off-tumor toxicity, but also reduces the presumed anti-tumorigenic effect. The reduction of efficacy by nonlinear pharmacokinetics was also observed for patients receiving the anti-CD47 antibody magrolimab. The expression of CD47 is not restricted to AML cells, and therefore the CD47 antibody was bound to several different cell types in addition to the tumor cells, which made it less effective than a highly specific antibody detecting a tumor-specific antigen. Despite this on-target, off-leukemia effect, a high objective response rate (ORR) even in p53 mutated AML was observed. Clearly, the specificity of the target antigen represents a key component for a successful introduction of antibody constructs in AML therapy.

19.6.2 Chimeric Antigen Receptor T-Cell Therapy in AML

In B-lineage malignancies, anti-CD19 CAR T-cell therapies were successfully introduced in clinical practice and approved in the United States and Europe (Schuster et al. 2019). In contrast to B-lineage malignancies, most of the potential AML target antigens are not restricted to the tumor cells and are additionally expressed in HSCs and different cell populations of healthy organs as mentioned before. This circumstance increases the risk of on-target, off-tumor toxicity of CAR T-cell therapies in AML and has to be strongly considered in the process of target antigen evaluation.

In 2013, the first reported clinical trial utilizing a second-generation CD28-ζ CAR directed against the Lewis Y antigen was published (Ritchie et al. 2013). Although limited efficacy was reported, that study demonstrated first-time biological activity of CAR T-cells in AML in the absence of overt hematopoietic toxicity. Current early phase clinical trials (NCT03018405, NCT02159495) applying CAR T-cells in AML are mostly targeting CLL-1, CD33, or CD123. More than 60% of AML blasts are positive for both CLL-1 and CD33, indicating that this might be a suitable target antigen combination (Ma

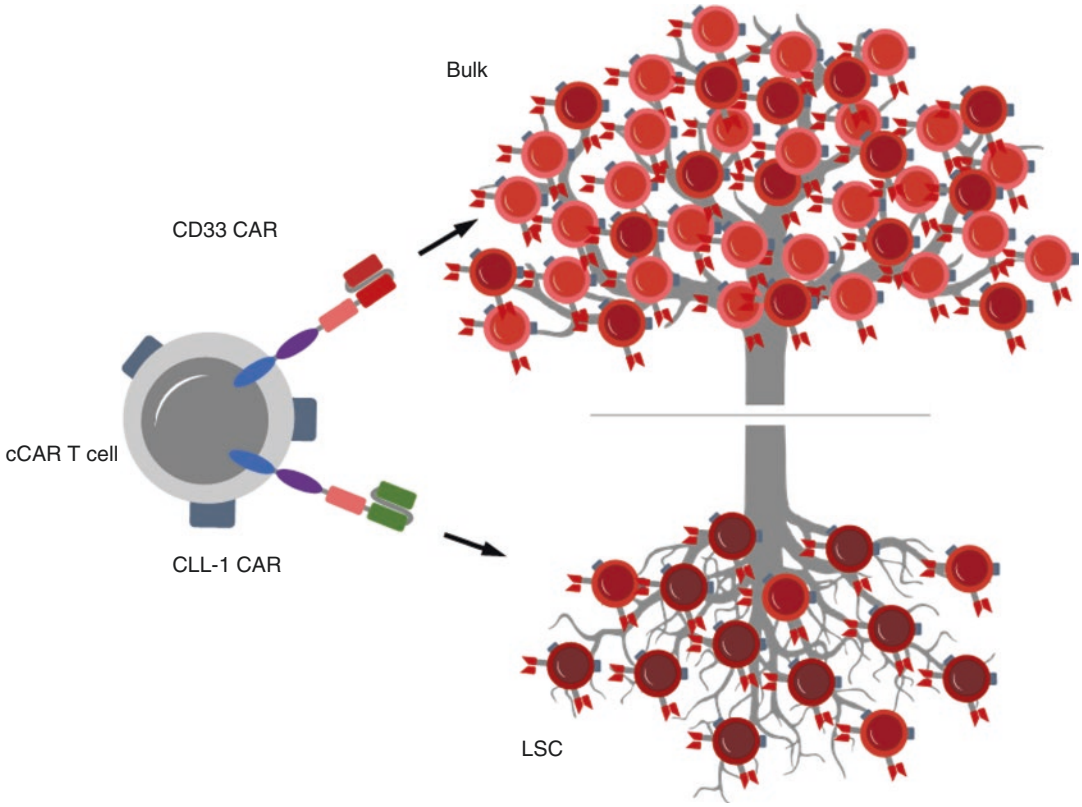

Fig. 19.2 Advanced chimeric antigen receptor (CAR) T-cell immune therapy in AML. The development of compound CAR (cCAR) T-cells allows the combination of two different CARs expressed on one CAR T-cell. This new technology enables the targeting of leukemic stem cells (LSCs) via, e.g., CLL-1 antigen expression and CD33 positive AML cell populations. The combination of these two antigen recognition sites increases the efficacy of the CLL1-CD33 cCAR T-cells to target AML cells. Alternative CAR T-designs based on conditional recognition of two antigens might increase specificity and thereby reduce the risk of on-target, off-tumor toxicity

et al. 2019). Compound CAR (cCAR) targeting two AML-associated antigens is currently evaluated in a phase I clinical study (Fig. 19.2) (Liu et al. 2018; Sallman et al. 2018). The increase in the specificity of a CAR T-cell system will enhance the efficacy and safety of this therapeutic approach.

Another new strategy to combine different recognizing elements in one CAR T-cell in AML is based on the recent discovery of nanobodies, which represent the "third-generation" of potential therapeutic antibodies. Nanobodies are the smallest, functional monoclonal antibody fragments featuring only two heavy chains with a single variable domain of about 15 kDa as the antigen-binding element. This domain features high affinity and specificity for the respective target antigen, with low off-target accumulation reducing potential toxicity. Furthermore, their small size allows nanobodies to penetrate tumors deeply, additionally increasing their efficacy (Yang and Shah 2020). Such nanobodies were recently isolated via a sequentially tumor-selected antibody and antigen retrieval (STAR) system in AML and nanobody (Nb) 157 was identified with a high affinity for CD13 (He et al. 2020). Based on this observation, a bispecific and split CAR (BissCAR) T-cell was designed targeting CD13 via Nb 157 together with TIM3, an antigen highly expressed in LSCs. The combination of these two recognition elements redirected the BissCAR T-cells effectively against AML cells in murine models and patient-derived xenografts. Due to its increased specificity, BissCAR

T-cell-therapy induced reduced toxicity to normal HSCs, progenitors, and other organ systems in these preclinical settings (He et al. 2020). The STAR system represents a valuable tool to isolate AML-specific and CAR-compatible nanobodies that can redirect BissCAR T-cells specifically to eradicate human AML. Nanobodies feature increased affinity to bind target antigens and their structure allows binding to traditionally inaccessible cavity-like epitopes. These characteristics introduce a broader spectrum of potential AML target antigens and specific epitopes and thus make nanobodies a promising new approach for developing an effective CAR T-cell therapy for AML.

19.7 Conclusions and Outlook

The introduction of new technologies and the steadily increasing understanding of the immune biology of AML promote the development of novel T-cell-based and macrophage-based strategies to fight AML. The notable heterogeneity of this disease makes it difficult to find a consistent therapeutic strategy. Searching for valid biomarkers will help to identify patients most likely to respond to specific therapeutic approaches and to foster personalized therapeutic strategies. The identification and optimization of novel checkpoint proteins and AML-specific target genes, as well as the increasing awareness and improved management of therapy-induced immune toxicities and prolonged myelosuppression, will enable the evolvement of new immunotherapeutic strategies in AML in the upcoming years.

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