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The immunotherapy landscape in AML: Defining knowledge gaps toward rational combinatorial strategies

Marion Subklewe[a,b,c,*], Sergio Rutella[d], Antonio Curti[e]

[a] Department of Medicine III, University Hospital LMU Munich, Munich, Germany
[b] Laboratory for Translational Cancer Immunology, Gene Center LMU, Munich, Germany
[c] German Cancer Consortium (DKTK), Partner Site Munich, a partnership between the DKFZ Heidelberg and LMU University Hospital, Munich, Germany
[d] Sergio Rutella, John van Geest Cancer Research Centre, Nottingham Trent University, Nottingham, UK
[e] Antonio Curti, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Institute of Hematology "Seràgnoli", Bologna, Italy

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ABSTRACT

Immunotherapy has dramatically improved outcomes in lymphoid malignancies. In B cell cancers, CD19-directed CAR T cells and T-cell engagers have produced high remission rates and durable responses, now forming the cornerstone of treatment in many relapsed or refractory settings. In contrast, acute myeloid leukemia (AML) has not experienced a comparable breakthrough. To date, only antibody-drug conjugates have reached regulatory approval, with gemtuzumab ozogamicin approved in combination with intensive induction and consolidation therapy for newly diagnosed CD33-positive AML. This divergence is rooted in the biological and immunologic complexity of AML. Unlike B-cell malignancies with lineage-restricted surface markers such as CD19, AML lacks leukemia-specific antigens. Most targets are shared with normal hematopoietic progenitors, leading to on-target/off-leukemia toxicity. Moreover, AML exerts local and systemic immunosuppression through both tumor-intrinsic and microenvironmental mechanisms, limiting T-cell persistence and function. This review will introduce the current immunotherapy platforms under investigation in AML, starting with antibody-based approaches, followed by T-cell redirecting therapies, and culminating in an overview of immune resistance, the bone marrow microenvironment, and strategies toward personalized combinatorial immunotherapy. By synthesizing recent clinical data and mechanistic insights, including those from early CAR and T-cell engager trials, we aim to provide a translational framework for how immunotherapy might still reshape AML care—through integration of immune contexture of the bone marrow environment aiming for rational combinatorial approaches.

Introduction—The missed revolution in AML

Immunotherapy has dramatically improved outcomes in lymphoid malignancies. In B-cell cancers, CD19-directed CAR T cells and T-cell engagers have produced high remission rates and durable responses, now forming the cornerstone of treatment in many relapsed or refractory settings [1–4]. In contrast, acute myeloid leukemia (AML) has not experienced a comparable breakthrough. To date, only antibody-drug conjugates (ADCs) have reached regulatory approval, with gemtuzumab ozogamicin approved in combination with intensive induction and consolidation therapy for newly diagnosed CD33-positive AML [5] (Fig. 1).

This divergence is rooted in the biological and immunologic complexity of AML. Unlike B-cell malignancies with lineage-restricted surface markers such as CD19, AML lacks leukemia-specific antigens. Most targets are shared with normal hematopoietic progenitors, leading to on-target/off-leukemia toxicity [6,7]. Moreover, AML exerts local and systemic immunosuppression through both tumor-intrinsic and microenvironmental mechanisms, limiting T-cell persistence and function [8] as well as T-cell cytotoxicity via SOCS1 over-expression [9].

This review will introduce the current immunotherapy platforms under investigation in AML, starting with antibody-based approaches, followed by T-cell redirecting therapies (Fig. 2), and culminating in an overview of immune resistance, the bone marrow microenvironment, and strategies toward personalized combinatorial immunotherapy.

By synthesizing recent clinical data and mechanistic insights, including those from early CAR and T-cell engager trials [10–12], we aim to provide a translational framework for how immunother-

* Corresponding author. Marion Subklewe, MD, Department of Medicine III, University Hospital LMU Munich, Marchioninistraße 15, 81377 Munich, Germany.
E-mail address: Marion.Subklewe@med.uni-muenchen.de (M. Subklewe).

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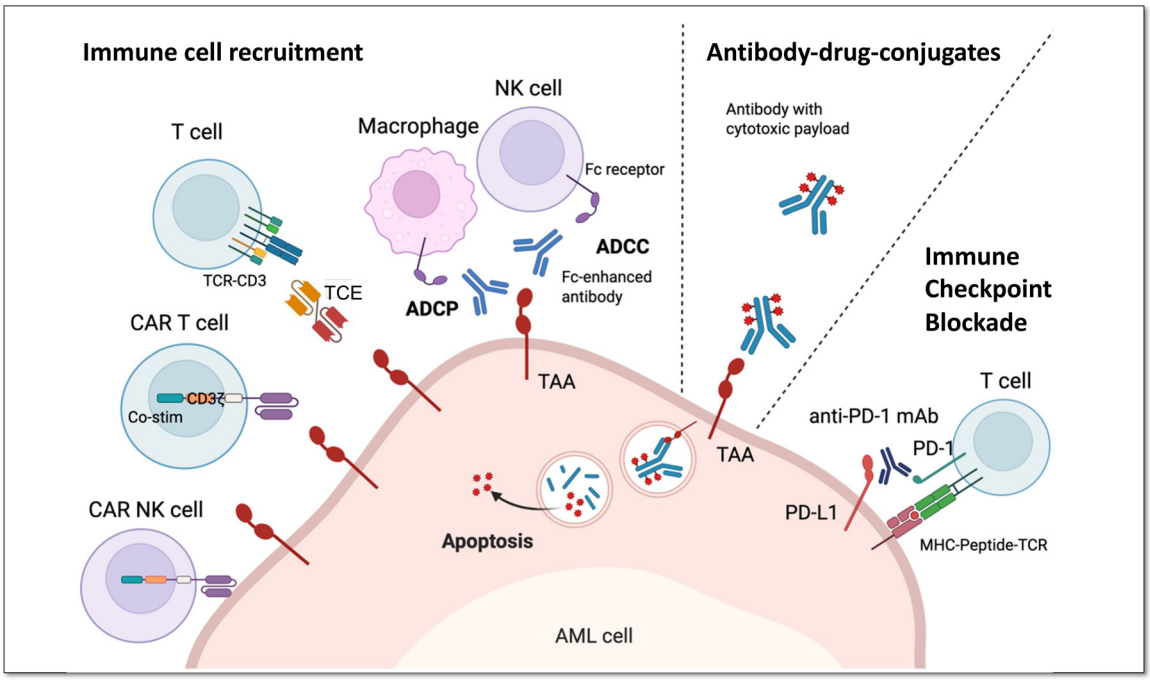

Fig. 1. Immunotherapy platforms in AML.

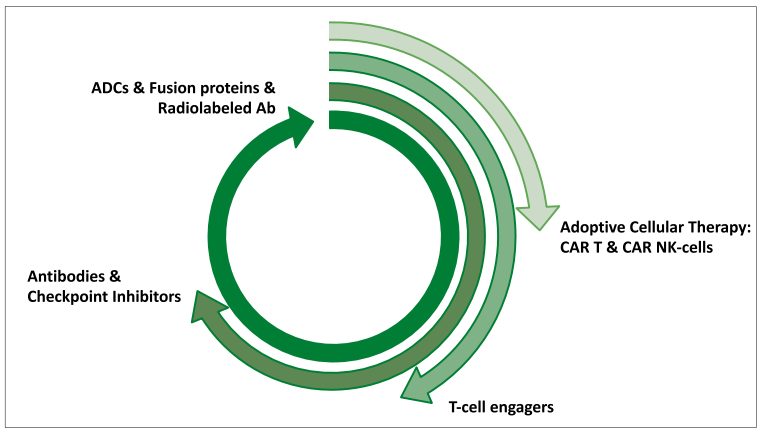

Fig. 2. Immunotherapy platforms are at different stages of clinical development.

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Target antigens for immunotherapy in AML

The identification of suitable immunotherapeutic targets remains one of the most formidable challenges in the treatment of AML (Fig. 3). Similar to B-cell malignancies—where antigens such as CD19, CD20, and CD22 are largely lineage-restricted—most AML-associated antigens that are currently being targeted are of myeloid lineage and hence, are also expressed on normal hematopoietic progenitor cells. This raises the risk of profound and prolonged bone marrow aplasia, a toxicity that, unlike B-cell aplasia, cannot be mitigated by immunoglobulin replacement therapy and is incompatible with long-term survival [13,14].

Leukemia-associated and lineage-restricted antigens

Lineage antigens such as CD33 and CD123 are widely expressed on leukemic blasts and leukemic stem cells (LSCs), and remain the most clinically advanced targets to date. Gemtuzumab ozogamicin, a CD33-directed ADC, remains the only approved immunotherapy in AML, approved in combination with induction and consolidation chemotherapy for newly diagnosed patients [15]. CD123 has been explored in various formats including monoclonal antibodies, bispecific T-cell engagers (e.g., flotetuzumab), and CAR T cells, but without definitive clinical benefit [16–18].

Newer targets such as CD70 and ILT3 exhibit more restricted expression on AML cells and LSCs while being largely absent on normal hematopoietic stem cells. These antigens are also functionally involved in immune regulation, and their targeting may offer dual benefits—direct leukemic cytotoxicity and modulation of the immunosuppressive microenvironment [19,20].

Leukemia-specific and intracellular antigens

Intracellular target antigens have the benefit of a more restricted target antigen expression profile, albeit expression levels tend to be lower compared to surface antigen. In particular, neoantigens derived from recurrent mutations such as NPM1, FLT3-ITD, and TP53 represent highly specific targets for immunotherapy.

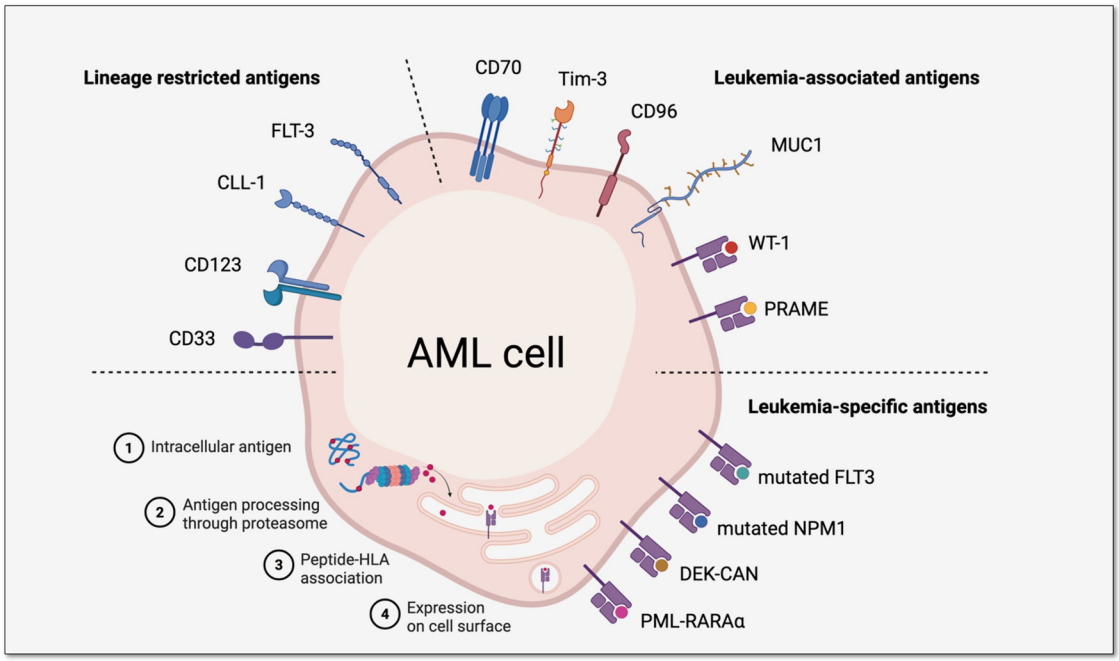

Fig. 3. Target antigens in AML.

These intracellular proteins are processed and presented by HLA molecules to be recognized by engineered TCRs or TCR-mimetic antibodies. While technically complex, this approach allows targeting of AML cells with minimal expression overlap with healthy tissue. A prominent clinical example is the bispecific T-cell engager RO7283420, targeting an HLA-A2–restricted WT1 peptide RMFPNAPYL, which demonstrated immune activation but limited clinical efficacy before program termination [21].

Dual targeting to enhance specificity and prevent immune escape

Several groups are exploring combinatorial targeting strategies to overcome immune escape and increase AML specificity. AND-gate approaches require the co-expression of 2 antigens, while NOT-gate logic excludes cells expressing a predefined safety antigen. Tandem CARs or bispecific T-cell engagers with dual-target logic are currently in early-phase testing and may mitigate the risks of antigen heterogeneity and loss [22–24].

Novel technologies for antigen discovery

To overcome the limitations of current targets, novel technologies are being employed to systematically identify antigens with restricted expression profiles. Mass spectrometry-based surfaceome mapping, including glycoprotein elution methods, has uncovered previously unrecognized AML targets such as CD148, ITGA4 and Integrin beta-7 [25]. Parallel single-cell RNA sequencing (scRNA-seq) efforts are characterizing transcriptional heterogeneity in AML subclones and their immunophenotypes, but also enabling novel antigen discovery [26]. Combining these RNA- and protein-based approaches may lead to identification of more leukemia-restricted targets. This might also be beneficial to reduce T-cell exhaustion through chronic antigen exposure [27] and reduce issues in pharmakokinetics by reducing “antigen sink” phenomena linked to widespread target expression of commonly internalizing antigens.

Antibody-based immunotherapies

Antibody drug conjugates

ADCs link monoclonal antibodies to cytotoxic payloads via cleavable linkers, aiming to enhance tumor specificity while minimizing systemic toxicity. Gemtuzumab ozogamicin (GO), targeting CD33, was the first ADC approved for AML and remains the only one with clinical routine use, primarily in patients with favorable or intermediate-risk disease undergoing intensive chemotherapy.

Efforts to expand ADCs in AML have been hampered by a narrow therapeutic window, due to heterogeneous antigen expression and on-target/off-tumor toxicity, particularly in the myeloid lineage. Most investigational ADCs utilize pyrrolobenzodiazepine (PBD) dimers or auristatins as payloads, targeting CD33 or CD123.

CD33-directed approaches beyond GO also include lintuzumab-based constructs. Lintuzumab-Ac225, a radioimmunoconjugate, showed marrow blast clearance in early trials and promising remission rates in combination with CLAG-M salvage therapy, even in TP53-mutated AML [28]. A next-generation conjugate, GLK-33, couples lintuzumab to MMAU and demonstrated improved tolerability, broad activity, and efficacy against multidrug-resistant AML cells [29].

CD123-targeting ADCs such as tagraxofusp have been approved in BPDCN and tested in AML with modest single-agent efficacy. However, combinations with azacitidine and venetoclax are under active investigation, showing encouraging responses even in high-risk and TP53-mutant subsets [30]. Novel CD123-targeting ADCs like pivekimab sunirine (IMGN632) show single-agent activity and are being explored in triplet regimens [31].

Novel antigen targets for antibody-based approaches

To overcome lineage promiscuity and toxicity of existing ADC targets, newer antigens with restricted hematopoietic expression are under preclinical and clinical investigation.

CLL-1 (CLEC12A): Expressed on AML blasts and leukemic stem cells (LSCs) but not on normal HSCs. ADCs targeting CLL-1, including DCLL9718S and CLT030, have shown reduced myelotoxicity in preclinical models, though early trials faced hepatic toxicity and limited efficacy [32].

CD37: A tetraspanin also found on AML blasts. CD37-targeted ADCs like Debio 1562 demonstrated selectivity for AML cells and limited HSC toxicity, showing robust preclinical activity and therapeutic potential in xenografts [33].

LILRB4 (ILT3): Overexpressed in monocytic AML (M4/M5). LILRB4-ADCs exert potent in vitro/in vivo effects with minimal off-target effects. Clinical trials of IO-202, a monoclonal antibody, demonstrated responses in LILRB4-high AML, particularly in combination with azacitidine [34].

LAIR1: A collagen-binding inhibitory receptor essential for AML development. Preclinical data support LAIR1-ADC use to selectively target LSCs while sparing HSCs [35].

FLT3: Highly expressed in FLT3-ITD AML. Novel ADCs (e.g., 20D9-ADC, 20D9h3-DUBA) eliminate AML blasts and LSCs in PDX models and exhibit synergy with FLT3 inhibitors like midostaurin [36,37].

Monoclonal antibodies and checkpoint inhibition

The clinical success of immune checkpoint blockade in solid tumors has not been recapitulated in AML. PD-1 and PD-L1 inhibitors, such as nivolumab, atezolizumab and pembrolizumab [38], were explored predominantly in combination with hypomethylating agents (HMAs) to increase neoantigen expression on leukemic cells. However, phase II trials in relapsed/refractory or newly diagnosed elderly AML patients failed to demonstrate significant clinical benefit, with no consistent improvement in response rates or overall survival [39,40], and inability to overcome AML-induced T-cell dysfunctional states. Addition of venetoclax also did not rescue efficacy. Consequently, enthusiasm for PD-1/PD-L1-based strategies in AML has markedly declined.

Alternative checkpoints such as TIM-3 and LAG-3, expressed on leukemic stem cells and immunoregulatory subsets (Tregs, MDSCs), have garnered interest. Sabatolimab, a TIM-3–directed antibody, was evaluated in early-phase studies in high-risk MDS and AML. However, in a randomized phase II trial enrolling 127 MDS patients, no superiority over HMA monotherapy was observed, leading to discontinuation of the development program [41]. Clinical activity in AML was similarly limited.

Newer strategies involve combinatorial checkpoint blockade. Dual PD-1/LAG-3 inhibition, effective in melanoma and solid tumors, is under early investigation in AML (e.g., AARON trial with relatlimab + nivolumab + azacitidine ± venetoclax), but data are still pending [42].

Targeting macrophage-mediated immune evasion has emerged as an alternative. The CD47–SIRPα axis delivers a potent "don't eat me" signal to myeloid phagocytes. Blockade of CD47 sensitizes AML blasts to macrophage-mediated phagocytosis. Magrolimab, a first-in-class CD47 antibody, showed encouraging responses in early-phase trials in TP53-mutated AML (CR/CRi > 40% in combination with azacitidine) [43]. However, the ENHANCE-2 and ENHANCE-3 phase III trials failed to replicate these outcomes, leading to termination of the program [44,45]. Next-generation CD47-targeting agents with improved selectivity and reduced red blood cell binding are under evaluation.

Overall, while checkpoint inhibitors and macrophage modulators remain mechanistically attractive, none have yet advanced into routine clinical use in AML. Rational combinations, biomarker-driven selection, and optimized timing may be key to unlocking their therapeutic potential.

T cell–redirecting therapies

T cell engagers

Bispecific T-cell engagers (TCEs) are antibody-based constructs that link CD3 on T cells to tumor-associated antigens (TAAs) on leukemia cells, initiating cytotoxicity independent of TCR specificity or MHC restriction. This modality has transformed the treatment landscape in B-cell malignancies, but translation to AML has been more challenging due to lineage promiscuity of target antigens, immune evasion, and on-target myelotoxicity.

Clinical experience with CD33- and CD123-directed TCEs

The most advanced constructs in AML target CD33 or CD123—lineage antigens broadly expressed on leukemic blasts and normal progenitors (Fig. 4). AMG 330, a CD3xCD33 BiTE® molecule, was the first TCE evaluated in relapsed/refractory AML. In a phase I trial ($n = 55$), step-up dosing was essential to mitigate cytokine release syndrome (CRS), which occurred in >70% of patients but was reversible with supportive care [46]. Although the overall response rate was 19%, responses were restricted to patients with lower disease burden. The antigen sink from normal myeloid cells and high antigen turnover likely limited efficacy, necessitating high doses and prolonged exposure.

Similar observations were made for other CD33-directed TCEs such as JNJ-67571244 and AMV564, which demonstrated acceptable safety but modest activity in heavily pretreated patients (Fig. 5).

CD123-targeting TCEs include flotetuzumab and vibecotamab. Flotetuzumab (CD123xCD3 DART®) showed preliminary efficacy in patients with primary induction failure or early relapse, particularly in immune-infiltrated and interferon-γ-dominant AML subtypes [47]. Vibecotamab (XmAb14045), a half-life extended BiTE, was evaluated in a phase I trial ($n = 51$) in relapsed/refractory AML. Responses (CR/CRi ~30%) were again enriched in patients with low blast counts, and CRS was manageable with premedication and step-up dosing [48].

Novel formats: Trispecifics and dual-antigen targeting

To improve therapeutic index, multispecific constructs are in development. MP0533, a trispecific antibody targeting CD33, CD123, CD70, and CD3, aims to restrict activity to cells co-expressing myeloid antigens. In a first-in-human study, early CRs were observed even at low doses in patients with relapsed/refractory AML, particularly among those with lower leukemic burden [49].

Dual-antigen logic gates (e.g., AND gating) are also being implemented to enhance selectivity and prevent myelotoxicity. CD33xCLL-1xCD3 constructs or CD123xCD33xCD3 combinations are in preclinical and early clinical stages.

TCR-mimic engagers: WT1-TCB as a blueprint

A novel approach uses T-cell engagers directed against intracellular neoantigens presented in the context of HLA. WT1-TCB, a bispecific antibody targeting the WT1_126–134 peptide/HLA-A*02:01 complex and CD3, demonstrated potent activity in vitro and in vivo against AML cells [50]. A step-up dosing regimen effectively mitigated CRS in preclinical primate models, and no toxicity was observed against normal tissues. WT1-TCB represents a first-in-class TCR-mimic TCE and opens the field for further exploration of MHC-restricted targets. Unfortunately, a phase I trial utilizing the WT1-TCB construct was terminated early due to limited efficacy, albeit

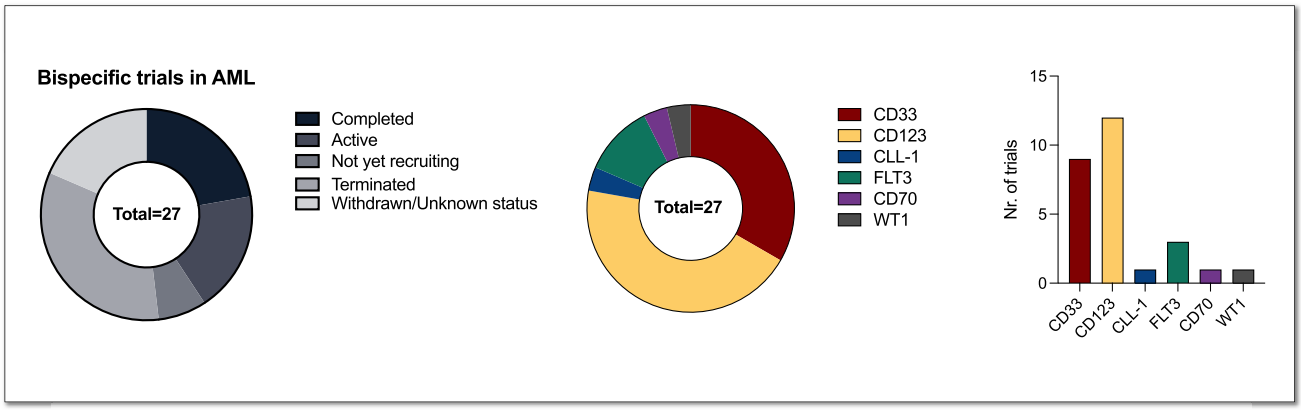

Fig. 4. Clinical trials in AML using TCEs.

Ab type	CD33			CD123			CD123	CLL-1
	AMG330[1]	AMG 673[2]	AMV-564[3]	Flotetuzumab[4]	JNJ-63709178[5]	Vibecotamab[6]	SAR443579[7-9]	MCLA-117[10]
Structure								
Manufacturer	Amgen	Amgen	Amphivena	Macrogenics	Janssen	Xencor	Innate/Sanofi	Merus
Phase	1	1	1	1, RP2D	1	1/2	I/II	1
N	96	46	53	246	62	106	23	62
Histology	r/r AML, MRD⁺ AML	r/r AML	r/r AML	r/r AML	r/r AML	r/r AML, B-ALL, CML	r/rAML, B-ALL and MDS	r/r AML, ND elderly
Prior Therapies	≥1	≥4	≥1	≥2	1-10	1-8	1-10	0-≥4
CRS (grade ≥3)	67% (13%)	50% (13%)	n.a. (0%)	50% (7%)	44% (15%)	58% (15%)	9% (n.r.), IRR 43%	36% (9%)
ORR	**19%**	**44% (12/27)**	**49%**	**30%**	**n.a.**	**>0.75 µg/kg 14% (7/51)**	5% (0 %)	**n.a.**
CR/CR$_i$	**17% (7/42)**	**4% (1/27)**	**6% (2/35)**	**27% (8/30)**	**0% (0/62)**	**10% (5/51)**	**12 % (3/23)**	**0% (0/58)**

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Fig. 5. Selection of clinical trials utilizing T-cell engaging bispecific antibodies.

blast clearance was observed at higher dose, in particular in patients with low Treg numbers and an increased number of naive T cells [21].

Challenges and outlook

The clinical development of TCEs in AML faces unique barriers:

- **High leukemia burden** is associated with severe CRS and limited efficacy.
- **Antigen sink** from non-leukemic myeloid cells necessitates higher dosing and increases toxicity risk.
- **Step-up dosing** has emerged as essential to reduce CRS risk while preserving efficacy.
- **Target antigen promiscuity** remains a major limitation, necessitating dual or tri-antigen targeting and refined patient selection.

Biomarker-guided trials, rational combinations (e.g., with venetoclax or hypomethylating agents), and next-generation constructs with tailored CD3 affinity may help unlock the full potential of TCEs in AML.

CAR-T cells in AML—What have we learned?

CAR-T cell therapy

The remarkable clinical success of CD19-directed CAR-T cells in B-cell malignancies has spurred intensive efforts to translate this strategy to myeloid malignancies. However, CAR-T development in AML remains constrained by 3 major challenges: the lack of leukemia-specific antigens, frequent high tumor burden, and a profoundly immunosuppressive bone marrow microenvironment. Consequently, most responses observed in early trials have been transient, and long-term remissions remain rare. Nonetheless, several strategies are being pursued to overcome these limitations and position CAR-T therapy within the broader AML treatment landscape.

Strategic approaches for CAR-T integration

Bridge to allogeneic stem cell transplantation (allo-HCT)

In the absence of curative efficacy from current CAR constructs, the most pragmatic use remains in the integration of the cytoreduction prior to allo-HCT. This approach has shown encouraging

Concept	Bridge to Transplant	Engineered SCT + CAR T*	Possibly „Stand alone“
Sequence	CAR T/NK => allo SCT (alternatively TCE, moAb)	Target-KO or Epitope edited SCT => CAR T (TCE, moAb)	CAR T/NK
Target Antigen	Myeloid antigens, e.g. CD33, CD123, CLL1, CD117	Engineered stem cell graft, e.g. CD45, CD123, FLT-3, KIT	Restricted expression, e.g. ADGRE2, TCR based, e.g. FLT3-TKD^{mut}, NPM1^{mut}
Hemato-poeitic Toxicity	Yes CART depletion, Stem Cell Salvage	No normal hematopoiesis invisible	Yes / No, depends
CAR	2nd/3rd generation CART, Compound CART	2nd/3rd generation CART, Dual CART	2nd CART, Split CART, „if better“, adapter CART, TCR transgenic T cells
Cell Source	auto or allo T & NK cells, no persistence	donor derived, possibly autologous	patient derived, allo CAR T/NK donor derived post allo SCT
Potential	Improve outcome post SCT; decrease conditioning and thereby increase number of pts eligible for allo SCT	Increase safety by decreasing on-target-off-leukemia toxicity; multiple-targeting possible to overcome antigen escape	Replace allo SCT, applicable to the majority of AML pts
References	Driouk et al, Front Immunol 2020; Zhang et al, Leukemia 2022, Budde et al, Blood 2017; 130, Tambaro et al, Leukemia 2021; Zhang et al, Clin Cancer Res 2021; Liu et al, Blood 2018; 132. Sallman et al, ASH 2022, ASGCT 2023; ASH 2023: Shah et al, #771, Zhang et al, #2106	Kim et al, Cell 2018; Borot F. et al, PNAS 2019; Wellhausen et al, STM 2023; Humbert et al, Leukemia 2019, Chiesa et al, NEJM 2023; Casirati et al, Nature 2023; Marone et al, J Exp Med 2023; Reviews: Kim. Trends in Cancer 2023; Saniei et al, Cell Stem Cell 2023, Volta et al, J Exp Med 2023	Haubner et al, Cancer Cell 2023; Sallman et al, Blood 2019; 134:3826 and Blood 2020;136:(Suppl1); Biernracki etal, JCI 2020, Giannakopoulou et al, Nature Cancer2023 Wermke et al, Blood 2021; Nixdorf et al, Leukemia 2023; Wermke et al, ASH 2023 #3465

* or other immunotherapy tools, e.g. ADCs, TCE

Fig. 6. CAR-T & NK cells in AML.

early-phase activity. Several trials targeting CD33, CD123, or CLL-1 have demonstrated complete remission (CR/CRi) rates of 30% to 70%, often in patients with lower leukemia burden. However, these remissions are frequently short-lived unless consolidated by transplant. For example, CD33-directed CAR-T cells (NCT03927261) yielded 3 CRs among 11 patients, enabling bridging in a subset (Fig. 6).

Gene-edited stem cell grafts with antigen-matched CAR-T cells

To circumvent the problem of on-target toxicity to normal hematopoietic stem cells (HSCs), a novel strategy involves engineering HSC grafts lacking the CAR-targeted antigen. This allows subsequent administration of CAR-T cells directed against the same antigen. Preclinical work with CD33-knockout HSCs has shown functional multilineage engraftment. A phase I trial of CD33-directed CAR-T cells in this setting is ongoing (NCT04849910). This model could serve as a template for other antigen-engineered graft-CAR pairings, enabling durable remissions without ablation of healthy hematopoiesis. Proof-of-concept has been demonstrated by allogeneic HSC grafts deleted of CD33 (Trem-Cel), followed by the application of Gemtuzumab-Ozogamamicin, without drop of counts or signs of hematotoxicity [51].

Stand-alone curative CAR-T therapy

Adapter CAR-T cell platforms are being evaluated as a way to dynamically switch generic CAR-T cells on/off, and thereby control toxicity [52]. The Avencell platform targeting CD123 is currently under clinical investigation utilizing autologous CAR-T, but in a follow up trial also allogeneic CAR-T. At least increase of safety could be demonstrated by reversing immune related adverse events through interruption of adapter infusion. Furthermore, novel smart gating strategies are being developed to enhance selectivity and reduce off-tumor toxicity. ADREG2, an AND-gate design combining recognition of CLL-1 (“if-better”) demonstrated enhanced AML specificity in preclinical models [22] and has advanced to an early clinical trial.

Advances in CAR-T design

CAR-T constructs are evolving to address antigen specificity, tumor heterogeneity, and immune escape:

- **Dual-targeting CARs** using OR-gate logic can improve cytoreduction but may lack selectivity.
- **AND-gate or NOT-gate constructs** can enhance specificity by requiring or excluding antigen co-expression.
- **Adapter CARs**, which use a universal CAR backbone with tumor-targeting adaptors (e.g., tagged antibodies), offer flexibility, controllability, and the potential for multiplexed targeting. Adapter CAR-T platforms are entering early-phase trials in AML.
- **CAR-NK cells** and armored CAR-Ts with cytokine payloads or checkpoint blockade are being explored to improve fitness in the immunosuppressive AML microenvironment.

Despite these innovations, longer-term follow-up across all platforms remains limited. The role of CAR-T therapy as a *standalone curative strategy* will likely depend on further advances in antigen targeting, T-cell fitness, and patient selection. Importantly, consensus guidelines by the IMPACT AML consortium are in preparation to harmonize reporting of CAR-T trials to allow cross-trial comparison and increase the learning curve.

The bone marrow microenvironment: Friend or foe?

The bone marrow microenvironment (BMME) plays a central role in modulating immune responses in AML. Beyond supporting hematopoiesis, it provides sanctuary to leukemic stem and progenitor cells, shielding them from immune surveillance and therapeutic elimination. The BMME is composed of a complex cellular network, including mesenchymal stromal cells (MSCs), osteoblasts, endothelial cells, and diverse immune subsets. In AML, this environment becomes hijacked by malignant cells to create an immunosuppressive niche.

Immune suppression within the BMME is orchestrated by elevated levels of regulatory T cells (Tregs), myeloid-derived

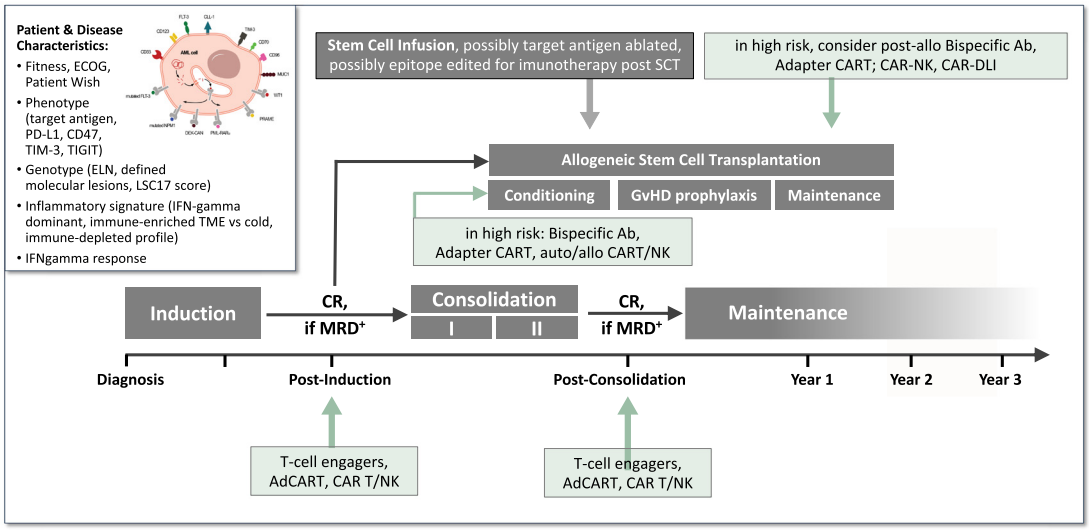

Fig. 7. TCE & CAR-T placement in AML: early (CR1) & in low disease burden (MRD$^+$/MRD$^-$).

suppressor cells (MDSCs), and alternatively activated (M2-like) macrophages. These cell types secrete inhibitory cytokines (e.g., IL-10, TGF-β), express immune checkpoint ligands, and interfere with dendritic cell function, collectively dampening anti-leukemic T cell responses [53]. Moreover, leukemia cells actively remodel the BMME by upregulating checkpoint molecules and secreting immunomodulatory exosomes and metabolites, creating a milieu conducive to immune escape, as extensively reviewed elsewhere [54].

MSCs—key architects of the BMME—contribute to leukemic progression by promoting AML cell survival, immune evasion, and therapy resistance through direct cell-cell contact, cytokine secretion, and metabolic support. In AML, MSCs adopt a reprogrammed phenotype characterized by reduced immunostimulatory capacity and increased production of immunosuppressive factors (e.g., IDO1, NO), fostering a leukemia-protective niche [7].

Spatial heterogeneity further complicates the immune landscape. AML-induced changes in vascular permeability, nitric oxide production, and regional hypoxia differentially affect immune cell infiltration and function in central vs. endosteal marrow zones. These spatial cues, together with altered stromal interactions, limit T cell trafficking, persistence, and synapse formation—critical elements for effective immunotherapies.

The macroenvironment: Systemic immune dysfunction in AML

Beyond the bone marrow, AML patients frequently exhibit systemic immune dysregulation. Chronic inflammation, recurrent infections, cytopenias, and treatment-related toxicity converge to blunt immune competence. Circulating T cells display features of exhaustion and senescence, characterized by upregulation of inhibitory receptors (e.g., PD-1, LAG-3) and reduced cytokine production. Moreover, prior cytotoxic therapies may deplete naïve T cell pools, narrowing the immune repertoire and impairing responses to T cell-based therapies [55,56].

Host factors, including immune aging (immunosenescence), comorbidities, and microbiome alterations, further modulate systemic immunity and may affect responsiveness to immunotherapeutic interventions. Importantly, AML-derived cytokines and soluble factors can perturb the systemic cytokine balance, sustaining a state of chronic immune activation that paradoxically promotes tolerance and immune exhaustion.

Altogether, the interplay between the local and systemic environments imposes profound constraints on immunotherapy efficacy in AML. Strategies to reprogram the microenvironment, enhance T cell trafficking and survival, and modulate systemic inflammation are essential components of next-generation immune-based therapies.

Future perspectives

Combination therapies and MRD-guided approaches in AML

The development of combination strategies for AML immunotherapy is gaining momentum, as monotherapies have shown limited durability and antigen escape remains a significant hurdle. One emerging paradigm is the rational integration of T cell engagers (TCEs) with backbone therapies such as hypomethylating agents (HMAs) and BCL-2 inhibitors (see Fig. 7).

Recent data by Gerulf Hänel and colleagues support this approach: azacitidine and venetoclax, the current standard for unfit AML patients, do not impair T cell function in vitro. In fact, the combination with a WT1-targeted TCE enhanced AML cell killing, a finding further validated in xenograft models, where dual therapy significantly improved survival and reduced leukemic burden compared to monotherapy arms [57].

This concept is further supported by mechanistic insights from Saar Gill's group [8], who demonstrated that T cell-derived cytokines, particularly GM-CSF, can induce a resistant phenotype in AML blasts via upregulation of anti-apoptotic BCL-2. This acquired resistance was reversed by co-treatment with venetoclax, providing a compelling biological rationale for combining TCEs with BCL-2 blockade.

Beyond pharmacologic synergy, MRD is emerging as a biomarker to guide the timing and intensity of immunotherapy. T cell–redirecting approaches may be most effective in the context of low disease burden, where antigen availability is sufficient but T cell exhaustion and tumor-induced immunosuppression are less pronounced. Ongoing clinical trials are exploring this hypothesis by deploying bispecific antibodies or CAR-T cells in the MRD$^+$ post-remission setting, aiming to prevent overt relapse.

Overall, the integration of immunotherapy with existing AML backbones, and its strategic deployment in MRD-defined windows of vulnerability, may substantially enhance therapeutic efficacy and improve long-term outcomes.

Conclusion and outlook: Toward personalized immunotherapy in AML

Despite extraordinary progress in the treatment of lymphoid malignancies through immunotherapy, AML has proven far more resistant to this revolution. The reasons are multifactorial: a lack of leukemia-specific surface targets, the immunosuppressive nature of the bone marrow microenvironment, and the immune evasiveness of leukemic stem cells.

Nevertheless, allogeneic HSC transplantation has proven and preclinical and early-phase clinical data suggest that immunotherapy can work in AML—particularly when it is precisely timed, intelligently combined, and biologically informed. The future of AML immunotherapy will depend not only on better target antigen selection and engineering of more potent effector platforms, but also on integrating immune-based treatments with established backbones such as azacitidine/venetoclax and hematopoietic stem cell transplantation.

Novel approaches, including MRD-guided therapy, combinatorial regimens, and immune-modulating interventions targeting both the micro- and macroenvironment, are already being explored. The development of multi-targeted, switchable, or conditionally activated T cell–redirecting agents, alongside advances in spatial biology, single-cell profiling, and proteogenomics, will help refine patient selection and treatment sequencing.

Ultimately, the way forward is not a one-size-fits-all solution but a personalized immunotherapeutic strategy that adapts to each patient's leukemic and immunological landscape—dynamic and context-sensitive. While AML may not yet have had its immunotherapy revolution, the knowledge how to improve safety and efficacy is growing.

Declaration of competing interest

None.

CRediT authorship contribution statement

Marion Subklewe: Writing – original draft. **Sergio Rutella:** Writing – review & editing, Conceptualization. **Antonio Curti:** Writing – review & editing, Conceptualization.

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