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Targeting TIM-3 for hematological malignancy: latest updates from the 2022 ASH annual meeting

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Abstract

T cell immunoglobulin domain and mucin domain-3 (TIM-3) is an important immune checkpoint (IC) protein in cancer immunosuppression that is considered a novel target for immunotherapy. Moreover, TIM-3, an immuno-myeloid regulator, is highly expressed on the cells of several solid tumors and myeloid leukemia stem cells (LSCs). TIM-3 blockade was shown to have dual effects for directly inhibiting leukemia cells and restoring T cell activation. We summarize several of the latest reports on the role of TIM-3 in immunotherapy for hematological malignancies from the 2022 ASH Annual Meeting (ASH2022).

Keywords TIM-3, Gal-9, Immunotherapy, Hematological malignancies

To the editor,

T cell immunoglobulin domain and mucin domain-3 (TIM-3), is significantly expressed on the T cells of cancer and leukemia patients and has been discovered to be associated with tumor progression [1]. Moreover, malignant cells can also express TIM-3, and it is preferentially expressed on myeloid leukemia stem cells (LSCs) [2]. Thus, TIM-3 is not only considered a T cell exhaustion molecule but also a potential target for myeloid cells as an immuno-myeloid regulator. Anti-TIM-3 antibodies have been shown to have efficacy and be safe for the treatment of advanced solid tumors. Recently, TIM-3 inhibitors have been used to treat acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) in clinical trials. Here, we summarize several of the latest reports on the role of TIM-3 in immunotherapy for HMs from the 2022 ASH Annual Meeting (*A*SH2022).

Influence of CAR-T cell activation and BiTE function

Chimeric antigen receptor (CAR) –T cell exhaustion or senescence in vivo remains a major issue. Increased expression of immune checkpoint proteins, such as that of TIM-3 during CART19-28ζ cell exhaustion, results in a decrease in cytotoxicity [3]. Moreover, CART19-BBζ cells are more prone to developing a senescent phenotype compared to CART19-28ζ cells [4].

Bispecific antibodies, such as CD19-CD3 T cell engagers (BiTE), have been used for B cell malignancy immunotherapy [5]. In ASH2022, the multicohort, open-label, phase 1/2 MajesTEC-1 study, which investigated the safety/efficacy of teclistamab (B-cell maturation antigen (BCMA)-CD3 bispecific IgG4 antibody) in patients with relapsed/refractory multiple myeloma (RRMM), demonstrated encouraging efficacy. Lower T cell numbers and a higher frequency of T cells expressing IC

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markers, including TIM-3, are underlying reasons for non-responders with unfavorable immune characteristics at baseline [6]. Overall, the above studies are consistent with the finding of terminally exhausted PD-1 + Tim-3 + T cells in a mouse model of B-cell tumors [7].

TIM-3 blockade for AML and MDS immunotherapy

The first anti-TIM-3 antibody, sabatolimab (MBG453), demonstrated safety and efficacy in a phase I/Ib clinical trial (NCT02608268) in advanced solid tumors. In the STIMULUS clinical trial (NCT03066648), 53 patients with very high risk/high risk (vHR/HR)-MDS and 48 patients with newly diagnosed (ND) AML were treated with sabatolimab plus hypomethylating agent (HMA). A higher overall response rate (ORR) and 1-year progression-free survival (PFS) were shown for 51 vHR/HR-MDS and 40 ND-AML patients (Table 1). At present, 3 of 11 clinical studies involving TIM-3 inhibitors in AML/MDS have completed recruitment (NCT03066648, NCT03946670, and NCT04266301). In ASH2022, primary results from the ongoing STIMULUS-MDS1 (NCT03946670) were reported [8]. This trial is a randomized, double-blind, placebo-controlled, Ph II study of sabatolimab + HMA in patients with intermediate risk (IR), HR, or vHR-MDS who were ineligible for intensive chemotherapy or hematopoietic stem cell transplantation at screening. A total of 127 patients were randomized to either sabatolimab + HMA or placebo + HMA (Table 1). The primary complete remission (CR) rate was 21.5% vs. 17.7%, respectively, for these two groups. The CR + partial remission (PR) + hematologic improvement (HI) was 49.2% (sabatolimab + HMA) vs. 37.1% (placebo + HMA), respectively. In addition, the ongoing Ph III STIMULUS-MDS2 trial, which has a primary endpoint of overall survival (OS) (NCT04266301), has completed accrual. Another clinical trial of sabatolimab combined with an oral HMA drug (NCT04878432) is underway. Overall, sabatolimab + HMA was associated with a favorable safety profile in patients with HR-MDS [9].

In contrast, TIM-3-CD28 fusion proteins that turn inhibitory signals derived from TIM-3 engagement into activation by CD28 have been designed. These fusion proteins alone demonstrate the strongest response upon stimulation with anti-CD3 antibodies. Importantly, these proteins can increase the proliferation, activation, and cytotoxic capacity of conventional anti-CD19 CAR T cells [10]. Thus, combining IC fusion proteins with anti-CD19 CARs has the potential to increase the T cell proliferation capacity. In 2021, Lee et al. designed second-generation anti-TIM-3 CAR-T cells that exhibit potent anti-AML activity, including primary LSCs. Thus, anti-TIM-3 CAR-T cell therapy might be considered following first-line therapy to eradicate the LSCs present in minimal residual disease.

Targeting the TIM-3 ligand Gal-9 for HM immunotherapy

Targeting the TIM-3 ligand galectin-9 (Gal-9) was recently considered as a novel immunotherapy for HMs. LYT-200, a fully humanized IgG4 αGAL-9 antibody, has been well tolerated in a phase I clinical trial for solid tumors. In ASH2022, a study reported the efficacy of LYT-200 in vitro and in vivo in multiple HMs. Further study demonstrated that LYT-200 also has in vivo protection and survival benefit in murine models of T cell acute lymphoblastic leukemia (T-ALL) and AML [11].

Table 1 The efficacy of sabatolimab in the treatment of AML and MDS

Clinical trial identifier	NCT03066648				NCT03946670			
Phase	Ib				IIb			
Interventions	MBG453 + HMA				MBG453 + HMA		Placebo + HMA	
Cancer type (population, N)	vHR/HR-MDS(N = 51)	MDS with TP53	ND-AML(N = 40)	AML with TP53/RUNX1/ASXL1	IR/HR/vHR-MDS (N = 65)	MDS (BM blasts < 10%,N = 32)	IR/HR/vHR-MDS (N = 62)	MDS (BM blasts < 10%, N = 29)
mDOR of CR (month)	21.5		23		18.0		9.2	
ORR rate (%)	56.9	71.4	40	53.8	/			
mDOR (month)	16.1	21.5	12.6	12.6	/			
1 year PFS (%)	51.9		27.9		/			
mPFS (month)	/				11.1	11.3	8.5	8.3
CR rate (%)	/				23.1	28.1	21.0	17.2
CR + PR + HI rate (%)	/				49.2	53.1	37.1	34.5
M (CR + PR + HI) (month)	/				13.4		9.2	
OS (month)	/				19.0		18.0	

Notes: AML, acute myeloid leukemia; BM, bone marrow; CR, complete remission; HMA, hypomethylating agent; IR, intermediate risk; MDS, myelodysplastic syndromes; mDOR, median duration of response; ND, new diagnosis; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial remission; vHR/HR, very high risk/high risk

Table 2 Targeted agents against TIM-3

type	products	mechanism	phase	disease or cell line	reference
Anti-TIM-3 antibody	sabatolimab (MBG453)	reverse T-cell exhaustion and anti-myeloid leukemia cell proliferation	Clinical Ib	vHR/HR-MDS, ND-AML	Brunner AM, et al. Blood. 2021
			Clinical II	IR/HR/vHR-MDS	Zeidan AM, et al. Blood. 2022
			Clinical III	IR/vHR/HR-MDS, CMML	Santini V, et al. Blood. 2022
TIM-3-CD28 fusion proteins	TIM-3/CD28-5 and TIM-3/CD28-6	increase proliferation of CAR-T cells, enhance cytokine secretion, proliferation of T cell	preclinical	K562 cell line	Blaeschke F, et al. Front Immunol. 2022
TIM-3-CAR-T cells	T3/28-CD19-CAR-T cells	enhance CAR-T cytotoxicity, cytokine secretion and persistence	preclinical	B-cell lymphoma	Zhao S, et al. J Immunother Cancer. 2021
	Anti-TIM-3 CAR-T cells	eradicate primary TIM-3 + CD34 + LSCs and sparing the TIM-3-CD34 + cells	preclinical	AML	Lee WS, et al. Mol Cancer Ther. 2021
Anti-GAL-9 antibody	aGal-9 antibody	reverse T-cell exhaustion	preclinical	CLL	Llaó Cid L, et al. Blood. 2022
	LYT-200	increase the ability to kill leukemia cells	preclinical	B/T-ALL, AML and DLBCL	Henry CJ, et al. Blood. 2022

Notes: AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CAR, Chimeric antigen receptor; DLBCL, diffuse large B cell lymphoma; GAL-9, galectin-9; IR, intermediate risk; LSCs, leukemia stem cells; MDS, myelodysplastic syndromes; ND, newly diagnosed; B/T-ALL, B/T cell-acute lymphoblastic leukemia; TIM-3, T cell immunoglobulin domain and mucin domain-3; vHR/HR, very high risk/high risk

In ASH2022, another investigation with single-cell omics analyses demonstrated that Gal-9 expressed on chronic lymphocytic leukemia (CLL) cells led to T cell exhaustion, and Gal-9 antibody treatment of the CLL mouse model reduced disease development. These findings further supported that Gal-9 can be a novel immunotherapy target for CLL [12].

In summary, targeting TIM-3 has dual effects for directly inhibiting leukemia cells and restoring T cell activation. In addition, Gal-9 may serve as a novel immunotherapeutic target. Several targeted agents against TIM-3 are at different stages of development (Table 2).

Abbreviations

AML	acute myeloid leukemia
AEs	adverse events
BiTE	Bispecific T-cell engagers
BCMA	B-cell maturation antigen
CLL	chronic lymphocytic leukemia
CAR	Chimeric antigen receptor
GAL-9	galectin-9
HMs	hematological malignancies
HI	hematologic improvement
IC	Immune checkpoint
IR	intermediate risk
LSCs	leukemia stem cells
MDS	myelodysplastic syndromes
ND	newly diagnosed
ORR	overall response rate
PFS	progression-free survival
PR	partial remission
RRMM	relapsed/refractory multiple myeloma
T-ALL	T cell-acute lymphoblastic leukemia
TIM-3	T cell immunoglobulin domain and mucin domain-3
vHR/HR	very high risk/high risk

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Authors' contributions
YQL and HT designed the study. YQL and JXT drafted the manuscript. JXT prepared the tables. HT helped to revise the manuscript. All authors participated in the process of drafting and revising the manuscript. All authors read and approved the final manuscript

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Data Availability
The material supporting the conclusion of this study has been included within the article.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
This is not applicable for this summary.

Consent for publication
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