



# “A.B.C.” of Immunotherapy in Hematological Malignancies...Promise and Perils

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## Abstract

The treatment landscape of hematological malignancies has been evolving at an extremely fast pace. Hematological malignancies are diverse and distinct from solid tumors. These constitute challenges, which are also unique opportunities for immunotherapy. The five categories of immunotherapies that have found success in the management of hematological malignancies are allogeneic hematopoietic stem cell transplant, monoclonal antibodies and innovative designs, immune checkpoint inhibitors, chimeric antigen receptor (CAR) T cells, and B cell targeting small immunomodulatory molecules. Allogeneic stem cell transplant rightly called our bluntest weapon is the oldest form of successful immunotherapy. Alternate donor transplants and improvement in supportive care have improved the scope of this immunotherapy option. Among monoclonal antibodies, rituximab forms the prototype on which over a dozen other antibodies have been developed. The bispecific T-cell engager (BiTE) blinatumomab engages cytotoxic CD3 T cells with CD19 acute lymphoblastic leukemia (ALL) cells, which is an effective treatment method for relapsed refractory ALL. Immune checkpoint inhibitors have established their role in hematological malignancies with high PD-L1 expression, including relapsed refractory Hodgkin's lymphoma and primary mediastinal B cell lymphoma (BCL). Small immunomodulatory drugs targeting the B cell receptor downstream signaling through BTK inhibitors, SYK inhibitors, PI3K inhibitors (idelalisib), and BCL-2 inhibitors (venetoclax), and immunomodulatory imide drugs (lenalidomide) have also emerged as exciting therapeutic avenues in immunotherapy. CAR T cells are one of the most exciting and promising forms of adoptive immunotherapy. CAR T cells are rightly called living drugs or serial killers to keep patients alive. CAR T cells are genetically engineered, autologous T cells that combine the cytotoxicity of T cells with the antigen-binding specificity of CARs. CARs are antigen-specific but major histocompatibility complex/human leukocyte antigen-independent. There are five approved CAR T cell products for the management of relapsed refractory leukemias, lymphoma, and multiple myeloma. The past and present of immunotherapy have been really exciting and the future looks incredibly promising. The challenges include widening the availability and affordability beyond specialized centers, identification of potentially predictive biomarkers of response, and

## Keywords

- ▶ allogeneic stem cell transplant
- ▶ CAR T cells
- ▶ hematological malignancies
- ▶ immune checkpoint inhibitors
- ▶ immunotherapy
- ▶ monoclonal antibodies

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experience in the management of complications of these novel agents. The combinational approach of multiple immunotherapies might be the way forward to complement the treatment strategies to harness the immune system and to improve survival with good quality of life.

## Introduction

The treatment landscape of hematological malignancies has been evolving at an extremely fast pace. Immunotherapy, the fifth pillar of oncology, is carving a niche for itself in the crowded therapeutic landscape. Harnessing the power of the immune system to fight malignancy has been a dream in oncology. In the recent years, a better understanding of the interaction between the immune system and cancer cells has created novel and powerful forms of immunotherapy. Hematological malignancies are diverse and distinct from solid tumors in many aspects. These constitute challenges that are also unique opportunities for immunotherapy.

In this review, we discuss the past, present, and future of immunotherapy in hematological malignancies and its promise and perils.

### Why do Hematological Malignancies Pose Challenges which are also Unique Opportunities for Immunotherapy?

1. All hematological malignancies originate from corrupt immune cells, which are in constant contact with healthy immune cells in the same microenvironment. This makes it conducive to constant immune surveillance.
2. All hematological malignancies are diseases of primary and secondary lymphoid organs. Normal immune cell development and differentiation also happens in the same sites. Hence, malignant cells can hijack the niche that belongs to normal immune cells.
3. Acute leukemia arises from hematopoietic stem cells, leading to deficient hematopoiesis, cytopenia, and immunosuppression.

4. Many hematological malignancies have a low tumor mutational burden.
5. Blood is easily accessible to sample immune cells for modification, cell engineering, and reinfusion.
6. Many hematological malignancies have precursor states which can help in studying the role of immune surveillance.

### What are the Immunotherapy Options that have Found Success in Hematological Malignancies?

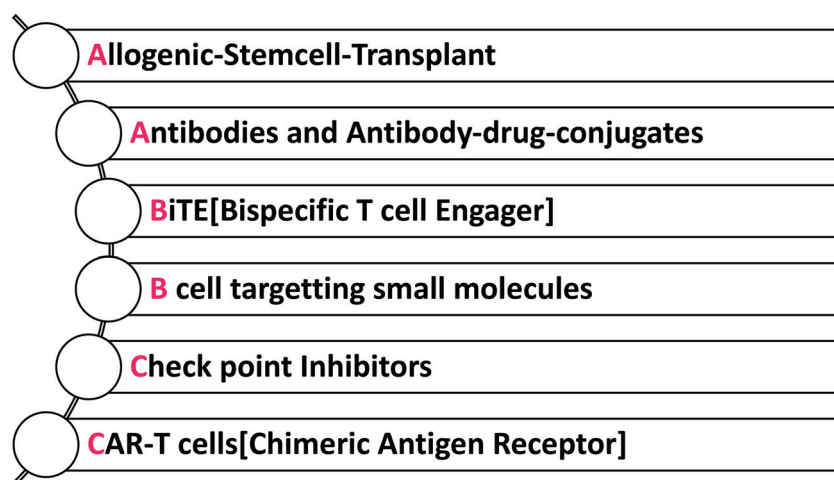
There are five categories of immunotherapies (A.A.B.B.C.C.) that have found success in the management of hematological malignancies, which will be discussed in this review.

*[Acronym of A.A.B.B.C.C.]*

1. **A**llogeneic hematopoietic stem cell transplant.
2. **A**ntibodies and innovative designs of ADC and **B**iTES (bispecific T-cell engager).
3. **B** cells as ripe targets: small immunomodulatory molecules.
4. Immune **C**heckpoint inhibitors.
5. **C**AR T cells (► **Fig. 1**).

#### 1. Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic hematopoietic stem cell transplantation (AlloHSCT) is the earliest form of successful cancer immunotherapy in hematological malignancies. The first AlloHSCT was performed by Dr. Donnall Thomas in 1968. This still holds today as one of the most curative treatment modalities in hematological malignancies. It is often called the chemotherapist’s bluntest weapon, as it does carpet bombing eradicating both the hematopoietic and immune systems



**Fig. 1** The “A.B.C.” of immunotherapies in hematological malignancies.

of the patient. This forms an ideal model to take our knowledge forward on immunotherapy.

The proof of principle of sensitivity of graft-versus-leukemia (tumor) effect<sup>1,2</sup> comes from the efficacy of AlloHSCT in refractory disease settings,<sup>3,4</sup> the success of donor lymphocyte infusion/withdrawal of immunosuppression in relapsed setting,<sup>5</sup> and the use of conditioning regimens (reduced intensity/non-myeloablative) that depend<sup>6</sup> more on the immunological rationale and less on chemotherapy dose for disease eradication.

The increasing use of alternate donor transplants and improvements in nonrelapse mortality with advanced supportive care is improving the outcomes. Haploidentical donor transplant with posttransplant cyclophosphamide has outcomes comparable to matched unrelated donor transplants.<sup>7,8</sup> These novel strategies have revolutionized the field of allogeneic stem cell transplant.

## 2. Monoclonal Antibodies and Innovative Designs

Passive immunotherapy with monoclonal antibodies is one of the most commonly used forms of immunotherapies in hematological malignancies. Rituximab, the first Food and Drug Administration (FDA)-approved monoclonal antibody in oncology, is a type 1 anti-CD20 antibody used to treat B cell malignancies. Since then, it has become the prototype for the development of other monoclonal antibodies.

Monoclonal antibodies<sup>9</sup> are developed based on either lineage-specific antigens (LSAs) or non-LSAs (NLSAs).

- LSAs are antigens specific to different stages of the same lineage of hematopoietic differentiation like CD20 for B cells and CD3 for T cells.
- NLSAs are antigens that play important roles in the malignant transformation of cells and are not restricted to a specific hematopoietic lineage of cells. These can be oncogenic receptors or glycoproteins like CD52 for chronic lymphocytic leukemia and SLAMF7 for multiple myeloma.

Mechanisms of action:

- Antibody-dependent cellular cytotoxicity.
- Antibody-dependent phagocytosis.
- Complement-dependent cytotoxicity.
- Direct cytotoxicity and apoptosis.

## 3. Bispecific T Cell Engagers and Bispecific Killer Cell Engagers

Bispecific antibodies are an innovative design in which single-chain variable fragments of two antibodies are fused to give specificity for two different antigens.

- BiTE is a type of bispecific antibody, in which one target is T cell engaging domain with anti-CD3 antibody and the other target is tumor-associated antigen such as anti-CD19 antibody in acute lymphoblastic leukemia (ALL). The binding of BiTE to two targets mediates a cytolytic synapse resembling a natural immunological synapse. Blinatumomab, a CD3 × CD19 BiTE, is the only FDA-approved BiTE for the treatment of R/R B cell precursor ALL (pre-B-ALL).<sup>10-12</sup> Blinatumomab in relapsed refractory B-ALL with active disease yielded a

complete response (CR) rate of 43%, while patients with minimal residual disease had a CR rate of 80%. Blinatumomab-based combination immunotherapy is being tested.

- **Bispecific killer cell engagers** are bispecific antibodies targeting natural killer cell receptor CD16. They are in the process of development with the hope of utilizing the power of the innate immune system.

► **Table 1** gives a comprehensive list of approved monoclonal antibodies used in the treatment of hematological malignancies.

## 4. Immune Checkpoint Inhibitors: Checkmate with Checkpoint Inhibitors

The introduction of immune checkpoint inhibitors (ICIs) as immunomodulatory antibodies, has gained spotlight in the management of several solid malignancies like melanoma, non-small cell lung cancer, renal cell carcinoma, and urothelial bladder cancers. The primary targets for checkpoint inhibition have been programmed cell death receptor-1 (PD-1) or programmed cell death ligand-1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). They are negative regulators or brakes of the immune system that help the cancer cells evade immune surveillance. Their established role in hematological malignancies is currently limited to tumors with high PD-L1 expression, including Hodgkin's lymphoma (HL) and primary mediastinal B cell lymphoma (PMBCL).

### 4.1 Why the Success of ICI in Hodgkin's Lymphoma?

The therapeutic benefit of PD-1 blockade is best demonstrated in patients with HL.

The unique immunological milieu of HL that could critically contribute to the success of ICI therapy include:

1. The immunologically hot (or inflamed) tumor microenvironment (TME) of classical HL (cHL) consists of malignant Hodgkin Reed-Sternberg cells (less than 1%) and an abundant inflammatory immune cell infiltrate which is different from the TME observed in non-HL (NHL).<sup>13,14</sup>
2. Amplification of 9p24.1 (locus-containing JAK2/PDL1/PDL2), induces aberrant overexpression of PD-L1 on malignant cells.<sup>15</sup>
3. Epstein-Barr virus (EBV) infection contributes to PD-L1 upregulation.<sup>16</sup> EBV-positive Hodgkin cases have been shown to have higher PD-L1 expression levels.<sup>17</sup>

### 4.2 Evidence for ICI in Hodgkin's Lymphoma and PMBCL

The early studies in heavily pretreated Hodgkin's patients, receiving either nivolumab<sup>18</sup> or pembrolizumab<sup>19</sup> were very encouraging. This led to larger phase 2 trials (CHECKMATE 205<sup>20-22</sup> and KEYNOTE-087,<sup>23</sup> respectively). These two studies had several similarities, with some significant differences resulting in variance in approved indications during licensing. Both studies included three cohorts of patients defined according to prior autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) exposure (► **Table 2**), but only KEYNOTE-087<sup>23</sup> included patients who were transplant-naïve (a cohort of patients deemed transplant-ineligible, mainly because of chemo-refractoriness). The overall response rates were similar

**Table 1** The monoclonal antibodies approved for the treatment of hematological malignancies

Name	Target	Indications	Approval year	MOA	Reference
Rituximab	CD20	B-NHL, DLBCL, CLL, FL	1997, 2006, 2010, 2011	CDC, ADCC, PCD	25-28
Ofatumumab	CD20	CLL	2009	CDC, ADCC, PCD	29
Obinutuzumab	CD20	CLL, FL	2013, 2016	CDC, ADCC, PCD	30,31
Tafasitamab	CD19	DLBCL	2020	ADCC/ADCP	32
Alemtuzumab	CD52	CLL	2001	ADCC/CDC/ADCP	33,34
Mogamulizumab	CCR4	MF, SS	2018	ADCC	35
Daratumumab	CD38	MM	2016	ADCC/CDC/ADCP	36
Isatuximab	CD38	MM	2020	ADCC/CDC/ADCP	37
Elotuzumab	SLAMF7	MM	2015	ADCC	38
Brentuximab	CD30	HL, ALCL	2011, 2018	ADC	39,40
Moxetumomab	CD22	HCL	2018	ADC	41
Gemtuzumab	CD33	AML	2017, 2020	ADC	42,43
Polatuzumab	CD79b	DLBCL	2019	ADC	44

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; ALCL, anaplastic large cell lymphoma; AML, acute myeloid leukemia; B-NHL, B non-Hodgkin’s lymphoma; CDC, complement-dependent cytotoxicity; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; HCL, hairy cell leukemia; HL, Hodgkin’s lymphoma; MF, mycosis fungoides; MM, multiple myeloma; MOA, monoclonal antibody; PCD, programmed cell death; SS, Sézary syndrome.

in both studies at approximately 70%, with most being partial. CRs were documented in 14 to 32%, depending on the study cohort. The median duration of response ranged from 11 to 25 months. The overall survival rate at 2 years exceeded 85% in all cohorts. These impressive results led to regulatory approvals for patients who had failed ASCT and brentuximab (BV) for both drugs, with additional approval for pembrolizumab in the setting of ASCT ineligibility and failure of BV.

PMBCL shares many histologic and genetic features with HL, including aberrations at 9p24 and overexpression of PD-L1. Objective response rates of approximately 46% were reported in the phase IB KEYNOTE-013 (n = 21) and phase II KEYNOTE-170 (n = 53) pembrolizumab studies, with a CR rate of 13% in the larger phase II study. Progression-free survival was significantly associated with PD-L1 expression, which in turn was associated with the magnitude of the 9p24 abnormality. As with HL, combination strategies with anti-PD-1 antibodies are also being evaluated.

Unlike cHL and PMBCL, PD-L1 overexpression is not commonly seen on B NHL cells. There is some evidence of 9p24 mutations in primary testicular lymphoma and primary central nervous system diffuse large B cell lymphoma, with selected use in these specific subgroups.

**4.3 Approved Indications for Immune Checkpoint Inhibitors in Hematological Malignancies**

*Nivolumab*

1. Relapsed and refractory HL post-autologous HSCT (auto-HSCT) and brentuximab.
2. Relapsed HL after three or more lines of therapy including auto-HSCT.

*Pembrolizumab*

1. Relapsed and refractory HL in adults post-auto-HSCT and brentuximab.
2. Pediatric relapsed/refractory HL.
3. Relapsed HL post two or more lines of therapy.
4. PMBCL: adult and pediatric patients with refractory PMBCL, or who have relapsed after two or more prior lines of therapy. (Limitations of Use: it is not recommended for the treatment of PMBCL patients who require urgent cytoreductive therapy.)

**4.4 The Challenges in Immune Checkpoint Inhibitors Therapy and Potential Solutions to Overcome Them**

1. Antigen presentation: The use of major histocompatibility complex (MHC)-independent treatment options like chimeric antigen receptor T cell therapy (CAR T cell therapy) or BiTE.
2. Tumor-associated macrophages resistance: Anti-cerebrospinal fluid antibodies or phosphatidyl 3-kinase-γ (PI3K) inhibitors.
3. TME: Novel checkpoint inhibitors like LAG-3 (lymphocyte activation gene-3) and TIM-3 (T cell immunoglobulin and mucin-domain containing-3) inhibitors.
4. Genetic and epigenetic factors: Epigenetic therapies like deoxyribonucleic acid methyltransferase inhibitors (DNMTi) and histone deacetylase inhibitors (HDACi).
5. Immunosuppressive metabolites: Indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor like epacadostat.
6. Biomarker response: Identify biomarkers beyond PD-1/PDL-1/TMB like serum interferon-γ levels and CD8-positive tumor-infiltrating lymphocytes.

**Table 2** Landmark trials of immune checkpoint inhibitors in Hodgkin's lymphoma

	CHECKMATE-205 (nivolumab)				KEYNOTE-087 (pembrolizumab)		
	Arm A	Arm B	Arm C	Arm C	Cohort 1	Cohort 2	Cohort 3
Patient features	Failed ASCT, brentuximab-naive	Failed ASCT and brentuximab	Failed ASCT, brentuximab exposed before/after ASCT	Failed ASCT, brentuximab	Failed ASCT and brentuximab	ASCT ineligible, failed chemo and brentuximab	Failed ASCT, no subsequent brentuximab
Number of patients	63	80	100	100	69	81	60
Median age (y)	33	37	32	32	34	40	32
Prior lines of treatment	2	4	4	4	4	4	3
ORR (%)	65	71	75	75	77	67	73
CR rate (%)	32	14	20	20	26	26	32
PFS (mo)	17	12	15	15	16	11	19
OS at 2 y (%)	90	86	86	86	93	91	89

Abbreviations: ASCT, autologous stem cell transplant; CR, complete response; ORR, objective response rate; PFS, progression-free survival.

► **Table 2** shows the results of landmark immunotherapy trials that led to the approval of ICI in HL.

**5. B Cells Ripe Target Small Molecules**

Small immunomodulatory drugs targeting the B cell receptor downstream signaling through BTK inhibitors, SYK inhibitors, PI3K inhibitors, and BCL-2 inhibitors, and immunomodulatory imide drugs (thalidomide, lenalidomide, pomalidomide) have also emerged as exciting therapeutic avenues in immunotherapy.

**6. CART Cells AS “Living Drugs” OR “Serial Killers” to Keep Patients Alive**

CAR T cells are one of the most exciting and promising forms of adoptive immunotherapy. CAR T cells are rightly called living drugs or serial killers to keep patients alive. CAR T cells are genetically engineered, autologous T cells that combine the cytotoxicity of T cells with the antigen-binding specificity of CARs. CARs are antigen-specific but MHC/human leukocyte antigen-independent.

**6.1 CAR Design and Generations: CARs in Nut and Bolt Phase...**

CARs are artificial transmembrane proteins. They have three domains<sup>24</sup>:

- (a) *Extracellular ectodomain* with two parts:
  1. *Antigen-binding domain*: confers specificity to the product. It is usually a single-chain variable fragment of an antibody that recognizes and binds to specific tumor-associated antigens on cell surfaces like CD19 on the surface of B cells.
  2. *Spacer*: is a flexible hinge that decides the orientation of the ectodomain and keeps it away from the cell surface to bind effectively with the antigens.
- (b) *Transmembrane domain*: is to effectively anchor the CAR on the T cell membrane.
- (c) *Intracellular endodomain*:

This is the signaling domain which consists of the CD3ζ chain and costimulatory signaling domains (CD28/41BB) and cytokines. This decides the construct of successive generations of CARs with improved cytotoxicity, proliferation, engraftment, and persistence.

- Generation 1 CAR: Signaling domain with only CD3 chain.
- Generation 2 CAR: Signaling domain with CD3 and one other costimulatory domain like CD28.
- Generation 3 CAR: Signaling domain with CD3 and two other costimulatory domains.

Generation 4 CAR or TRUCK (“T cells redirected for antigen-unrestricted cytokine-initiated killing”): Combines the direct cytotoxicity of CAR T cell with immune modulation of cytokines.

**6.2 CAR T Cells on a Test Drive to the Clinic: Cell-Processing Procedure and Steps**

- 1. Harvesting of autologous T cells by leukapheresis.

2. Stimulation with T cell mitogen (magnetic microbeads coated with mitogenic antibody).
3. Transduction of CARs into T cells with a viral vector.
4. Expansion and culture of T cells.
5. Cryopreservation of CAR T cell product.
6. Lymphodepleting conditioning to patient.
7. Thawing and reinfusion of CAR T cell product to the patient.
8. Monitoring and follow-up.

### 6.3 Causes of Chimeric Antigen Receptor T Cell Treatment Failure

#### *Failure to Receive the CAR T Cell Product on Time*

A significant proportion of patients might fail to receive the CAR T cell product on time due to rapidly progressive disease in the relapsed refractory state, long manufacturing times, and failed manufacture. Possible solutions include shifting CAR T cells earlier in the treatment landscape, improvement in the manufacturing process with shorter times of release of the product, and finally off the shelf allogeneic CAR T cells.

#### *Antigen-Negative Escape*

Relapse with antigen-negative disease is the most important reason for treatment failure. This can be targeted with bispecific or trispecific CAR T cells.

#### *Failure of Chimeric Antigen Receptor T Cell Engraftment or Expansion*

CD19+ relapse of B-ALL after initial remission occurs due to loss of T cell persistence/engraftment. It is usually due to patient-related factors like age, disease burden, and comorbidities, CAR-related factors like CAR construct with costimulatory molecules, murine ectodomain, and viral vector used for transduction, and fitness of T cell. This could be improved by modified CAR constructs like humanized proteins.

### 6.4 Toxicity Caused by Chimeric Antigen Receptor T Cells

- Cytokine release syndrome.
- Neurotoxicity or “immune cell-associated neurotoxicity syndrome” (ICANS).
- Off-tumor, on-target toxicity: B cell aplasia and hypogammaglobulinemia.
- Post-CAR cytopenia.

### 6.5 Future Directions for Chimeric Antigen Receptor T Cell Therapy

- Strategies to improve efficacy: Dual antigen targeting with dual signaling/bispecific tandem CAR.
- Strategies to improve specificity: Switchable suicide gene switch CAR and synthetic splitting receptor CAR.
- Strategies to reduce immunotoxicity: Detuning and tuning of CAR T cells.
- Dasatinib to induce reversible inactivation.

- Addressing antigenicity with humanized CARs.
- Universal CARs.
- “Off-The-Shelf” allogeneic CAR T cells.
- TRUCKS.
- Combinational strategies with immune checkpoint inhibitors/AlloHSCT/BitES.

*A summary of the approved CAR T cell products and their landmark trials is given in ►Table 3.*

The summary of immunotherapy options in hematological malignancies is depicted in ►Fig. 2.

### Limitations of this Review

- There is no detailed probing of clinical trials or weighing of evidence that led to the approval of various immunotherapy options.
- There is no elaboration on the side effect profile and management strategies of immunotherapy complications.

### Questions and Future Directions in Immunotherapy

- How to widen the availability of immunotherapy options?
- How to screen for potential prognostic and predictive biomarkers of response?
- What is the best combination treatment strategy and rational sequence?
- How to effectively reduce the off-target and on-target toxicities?
- What is the role of gut-microbiome in immune responses?
- What would be the best surrogate endpoints in clinical trials of immunotherapy?
- How is the quality of life of patients affected by immunotherapy?
- How can we make these magic bullets more affordable to our patients?

### Conclusion

The past and present of immunotherapy have been really exciting and the future looks incredibly promising. The challenges include widening the availability and affordability beyond specialized centers, experience in the management of complications of these novel agents, and defining appropriate endpoints for response assessment of these agents. The combinational approach of multiple immunotherapies might be the way forward, to complement the treatment strategies, harness the immune system, and improve quantity and quality of life. Hopefully, in the future, we can dream of a synergism of the vision of Dr. Donnal Thomas and Paul Ehrlich, where “the bluntest weapon” may be combined with novel immunotherapies as “true magic bullets.”

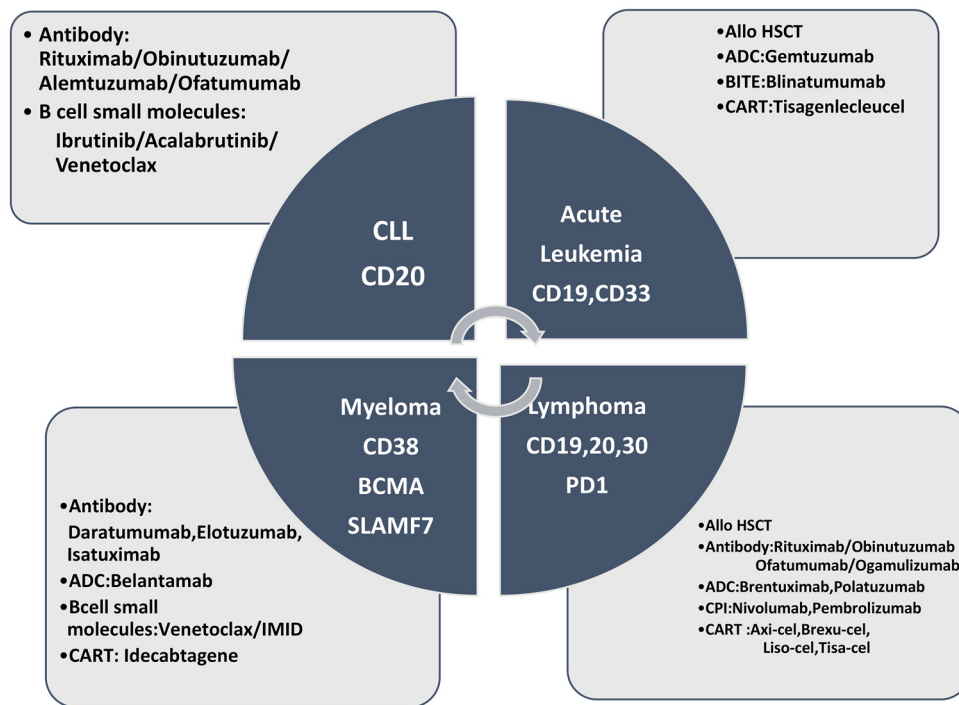
#### Conflict of Interest

None declared.

**Table 3** Approved CAR T cell products and landmark trials

CAR T cell product name	Indication	Year of approval	Trial name	Results	Ref:-
Tisagenlecleucel	Relapsed refractory ALL	2017	ELIANA	CR: 81%, EFS: 50%, OS: 76%	45
Axicabtagene	Relapsed refractory DLBCL, PMBCL	2017	ZUMA-1	ORR: 82%, CR: 58%, PFS: 44%	46
Tisagenlecleucel	Adult R/R DLBCL	2018	JULIET	ORR: 52%, CR: 40%, OS: 49%	47
Brexucabtagene	Mantle cell lymphoma	2020	ZUMA-2	ORR: 93%, CR: 67%, PFS: 61%, OS: 83%	48
Lisocabtagene	R/R large B cell lymphoma	2021	TRANSCEND	ORR: 75%, CR: 53%, PFS: 44%, OS: 58%	49
Axicabtagene	R/R follicular lymphoma	2021	ZUMA-5	ORR: 94%, CR: 80%, PFS: 74%, OS: 93%	50
Idecabtagene	Multiple myeloma	2021	KarMma	ORR: 73%, CR: 33%, PFS: 8.8 months, OS: 78%	

Abbreviations: ALL, acute lymphoblastic leukemia; CAR T cell, chimeric antigen receptor T cell; CR, complete response; DLBCL, diffuse large B cell lymphoma; EFS, event-free survival; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal B cell lymphoma.



**Fig. 2** Summary of immunotherapy in hematological malignancies.

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