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Review

T-cell-based Immunotherapies for Haematological Cancers, Part A: A SWOT Analysis of Immune Checkpoint Inhibitors (ICIs) and Bispecific T-Cell Engagers (BiTEs)

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Abstract. *Haematology has been at the vanguard of cancer immunotherapy. Immune checkpoint inhibitors (ICIs), bispecific T-cell engagers (BiTEs), allogeneic haematopoietic stem cell transplantation (allo-HSCT) and donor lymphocyte infusion (DLI), as well as adoptive T-cell therapies outside the setting of allo-HSCT, have been approved for distinct haematologic malignancies producing durable responses in otherwise untreatable patients. Despite recent advances, immunotherapies do not benefit most patients, due to resistance or lack of response, and are only approved in specific settings. Moreover, immunotherapies are expensive and may produce severe immune related adverse reactions. Combination therapy complicates the picture and requires further evaluation. This review considers the current status and future perspectives of ICIs and BiTEs approved for haematological malignancies by analysing their strengths, weaknesses, opportunities and threats (SWOT). The biological rationale for anti-cancer mechanisms, clinical data for specific haematological cancers, efficacy, toxicity, response and resistance profiles, novel strategies to improve these characteristics as well as the potential targets to enhance or expand the application of ICIs and BiTEs are also discussed.*

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Cancer immunotherapy has revolutionised oncology care, prolonging survival in rapidly fatal diseases. The number of patients eligible for immune-based cancer treatments is increasing, with immunotherapies being adopted in first line setting (1). Novel targets and combination therapies are set to expand cancer immunotherapy applications. Haematology has been central to these advances.

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) was the first clinical application of cancer immunotherapy (1957), while monoclonal antibodies (mAb) were the next success story with the approval of rituximab (anti-CD20 mAb) for B-cell malignancies (1997). These breakthroughs contributed valuable advances to the evolution of cancer immunotherapies. Immune checkpoint inhibitors, developed through mAbs, target T-cells and upregulate anticancer immunity, producing remarkable success in solid and haematologic malignancies. Bispecific T-cell engager (BiTE) antibodies, which redirect T-cells to tumour cells to perform target cell killing, were originally approved for B-cell precursor acute lymphoblastic leukaemia (BCP-ALL), with blinatumomab gaining approval in 2014. Development of novel adoptive T-cell (ATC) therapies in haematology, such as chimeric antigen receptor (CAR)-T-cells, has generated great interest with potential for disease cure.

Yet, despite these advances, several challenges remain. Limited breadth of application, unpredictable efficacy, and limiting toxicity profiles attest the need to drive forward change. This review discusses the strengths, weaknesses, opportunities and threats (SWOT) associated with immune checkpoint inhibitors (ICIs) and BiTEs, providing an up-to-date review of licensed agents for haematological malignancies. The biological rationale for anti-cancer mechanism; clinical data in specific haematological cancers; efficacy, toxicity, response and resistance profiles; novel strategies to improve these

characteristics; and potential targets to enhance or expand the application of these agents are discussed.

Immune Checkpoint Inhibitors

Biological rationale for anti-cancer mechanism. Immune checkpoints, compromising co-inhibitory and co-stimulatory co-signalling T-cell-receptor systems regulate T-cell activation (2) and ensure self-tolerance as per the two-signal hypothesis of T-cell activation (3-6) (Figure 1). Cancers upregulate inhibitory immune checkpoints within the tumour microenvironment (TME), supressing $CD4^+$ T-cell response to tumour associated antigens (TAA) and evading immune destruction (7). Targeting inhibitory immune checkpoints restores anti-tumour immunity. Programmed cell death 1 (PD-1) and cytotoxic T lymphocyte antigen 4 (CTLA-4, CD152), two functionally dominant T-cell immune checkpoint molecules, have demonstrated remarkable therapeutic potential (8). CTLA-4 and PD-1 co-inhibitory receptor systems belong to the B7-CD28 superfamily, the most potent T-cell co-signalling receptor immunoglobulin (Ig) family (1, 9).

Physiological role of CTLA-4 signalling and therapeutic targeting in cancer. CTLA-4 (CD152) is rapidly expressed following T-cell activation (10), countering the co-stimulation *via* CD28 which is constitutively expressed (11-13). Two B7 ligand family members, B7-1/BB1 (CD80) (14-17) and B7-2/B70 (CD86) (18-20), bind CD28 and CTLA-4. CTLA-4 binds with 10-100 times higher affinity and avidity as it homodimerizes, binding B7 bivalently (21-24). Reduced T-cell proliferation and cytokine secretion results.

Other than competitive antagonism against CD28 (25), CTLA-4 exerts inhibitory effects through phosphatase activity at its cytoplasmic tail (Figure 2). CTLA-4 induces T-cell tolerance (26, 27) by inhibiting nuclear accumulation of activator protein 1 (AP-1), NF-κB, and nuclear factor of activated T-cells (NFAT) (28, 29); thus halting cell cycle progression of T-cells by directly inhibiting cyclin-dependent kinase 4 (CDK4), CDK6, and cyclin D3 (30), and selectively inactivating microtubule-associated protein kinase (MAPK), extracellular signal-regulated kinase-1 (ERK), and c-Jun NH_2-terminal kinase (JNK), which stimulate IL-2 production (31, 32).

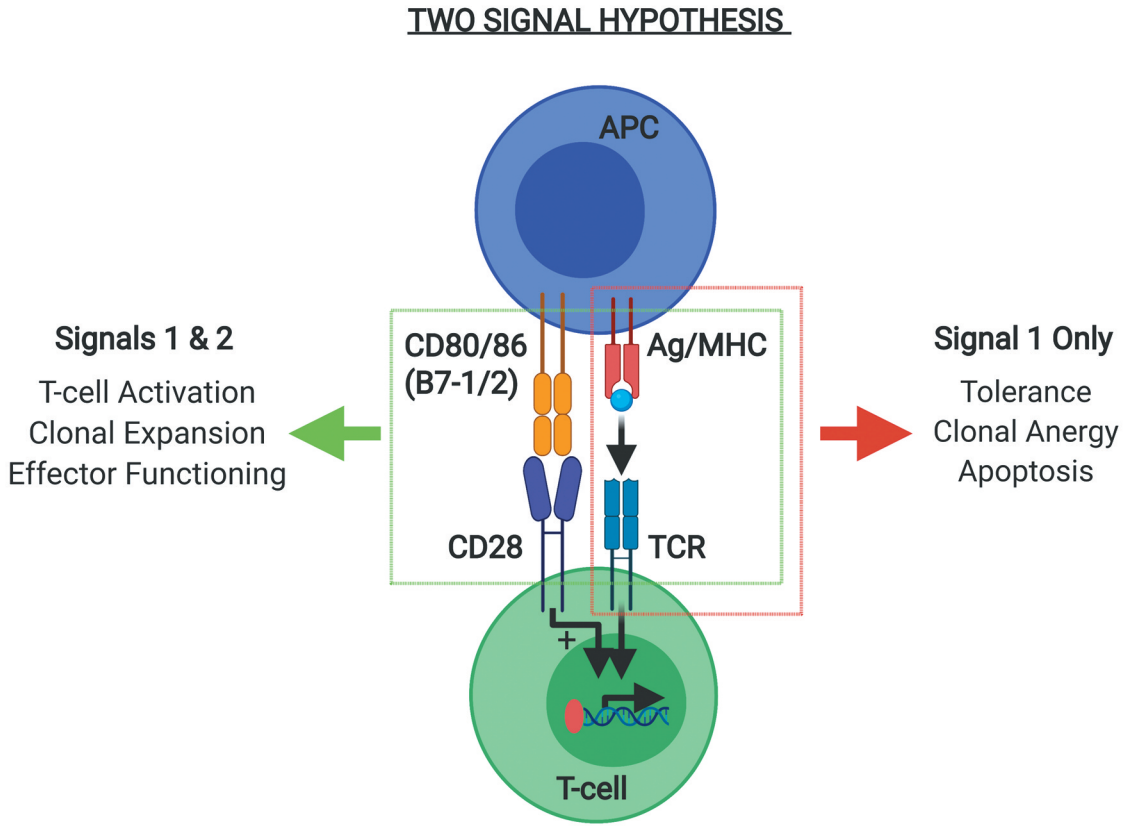

Figure 1. *Two signal hypothesis for T-cell activation. Signal 1 is generated from the interaction of the T-cell receptor (TCR) with its antigen-major histocompatibility complex (ag/MHC) ligand on the antigen presenting cell (APC). Signal 2 is generated from an interaction between costimulatory molecules on the APC such as CD80 and CD86 with T-cell counter-receptors such as CD28. In the presence of only signal 1, T-cells undergo tolerance, anergy or apoptosis, whereas in the presence of both signals, T-cells undergo activation, clonal expansion and effector function.*

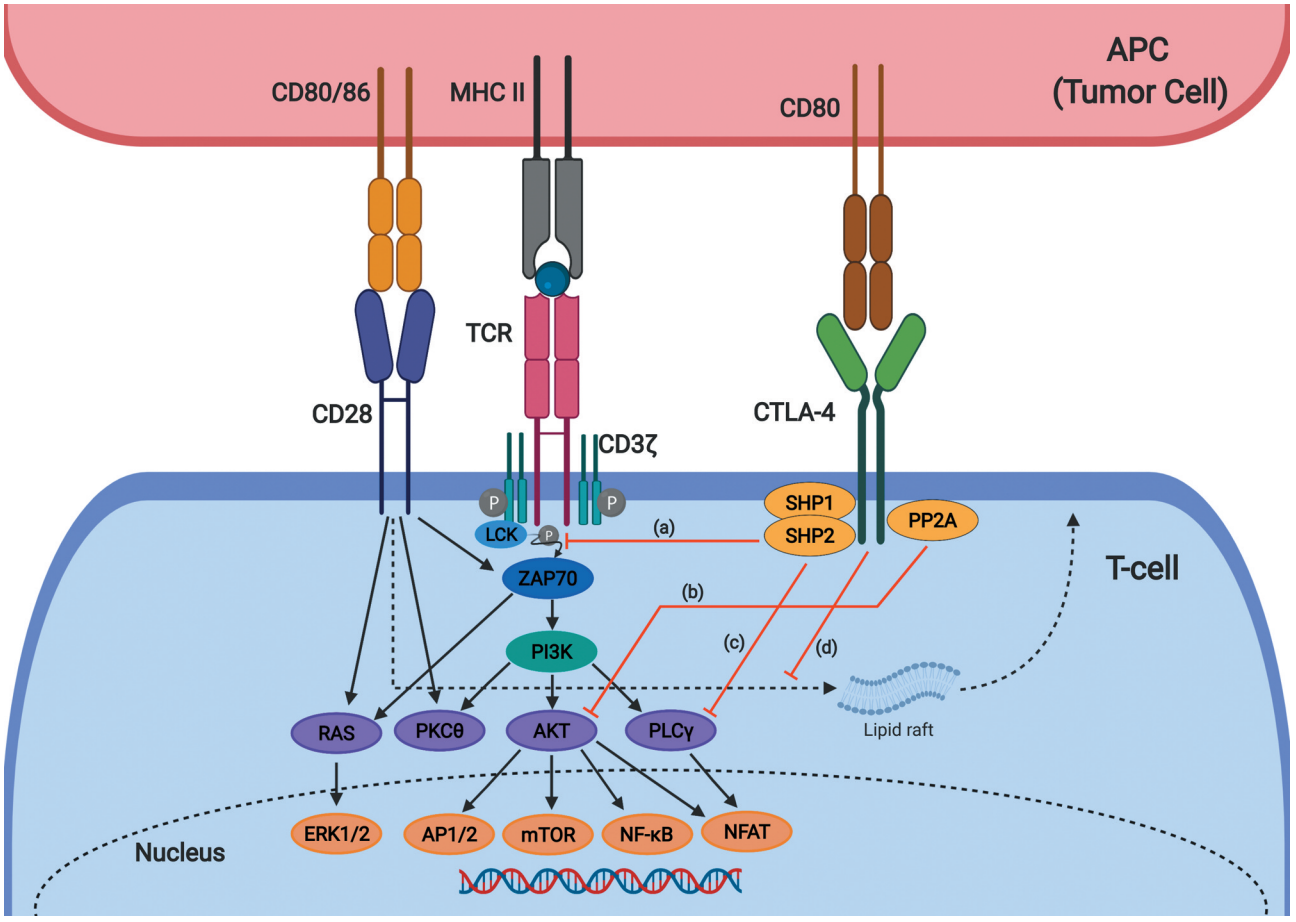

Figure 2. *CTLA-4 signalling cascade. In resting T-cells, CTLA-4 is retained within secretory granules, however, upon T-cell-receptor (TCR) activation, CTLA-4 expression is upregulated on the T-cell plasma membrane and CTLA-4 binds to B7 ligands (CD80 and CD86) on antigen presenting cells (APCs) with 10- to 100-fold higher avidity and affinity than CD28. Ligation reduces T-cell proliferation and decreasing cytokine secretion through distinct mechanisms: a) direct antagonism of TCR signalling by recruitment of Src-homology 2 domain-containing phosphatase (SHP)-1 and SHP-2; b) PP2A-mediated inhibition of AKT and its downstream signalling cascade; c) SHP-2-mediated inhibition of PLCγ and its downstream effector NFAT; and d) inhibition of CD28-mediated lipid raft formation.*

Anti-CTLA-4 antibodies bind CTLA-4 inhibiting B7 ligation. Prolonged T-cell activation, restored T-cell proliferation, and amplified T-cell-mediated anti-tumour immunity result. High TAA burden predicts favourable response. In addition to boosting effector T cells, anti-CTLA-4 therapy depletes local intra-tumoral regulatory T-cells (Tregs) through antibody-dependent T-cell-mediated cytotoxicity, thus shifting the TME from immunosuppression. The ratio of effector T-cells to tumour infiltrating Tregs predicts treatment outcome (33, 34).

Physiological role of PD-1 signalling and therapeutic targeting in cancer. PD-1 is another co-inhibitory receptor B7-CD28 superfamily member (35) that interacts with PD-L1 (36) (B7-H1) (37) or PD-L2 (38) (B7-DC) (39), maintaining an exhausted T-cell phenotype (38). PD-1 ligands are constitutively expressed on antigen presenting cells (APCs). PD-1 expression is induced after T-cell receptor (TCR) stimulation, similarly to CTLA-4, and declines following inflammatory resolution (32). PD-1 acts locally within peripheral tissues whereas CTLA-4 acts within lymphoid organs (40). PD-1 acts later in T-cell activation than CTLA-4.

PD-1 regulates immune responses through inhibitory intracellular signalling in effector T-cells and Treg cells (41). Ligation induces phosphorylation of PD-1 cytoplasmic tails causing recruitment of phosphatase SHP1 and SHP2, which inactivate downstream effectors *via* dephosphorylation. These effectors are essential for T-cell activation (36) and CD28 signalling (42) (Figure 3) (43). PI3K–Akt–mTOR and Ras–MEK–ERK pathway activation is also inhibited *via* SHP2 independent mechanisms (44, 45); T-cell exhaustion or apoptosis results.

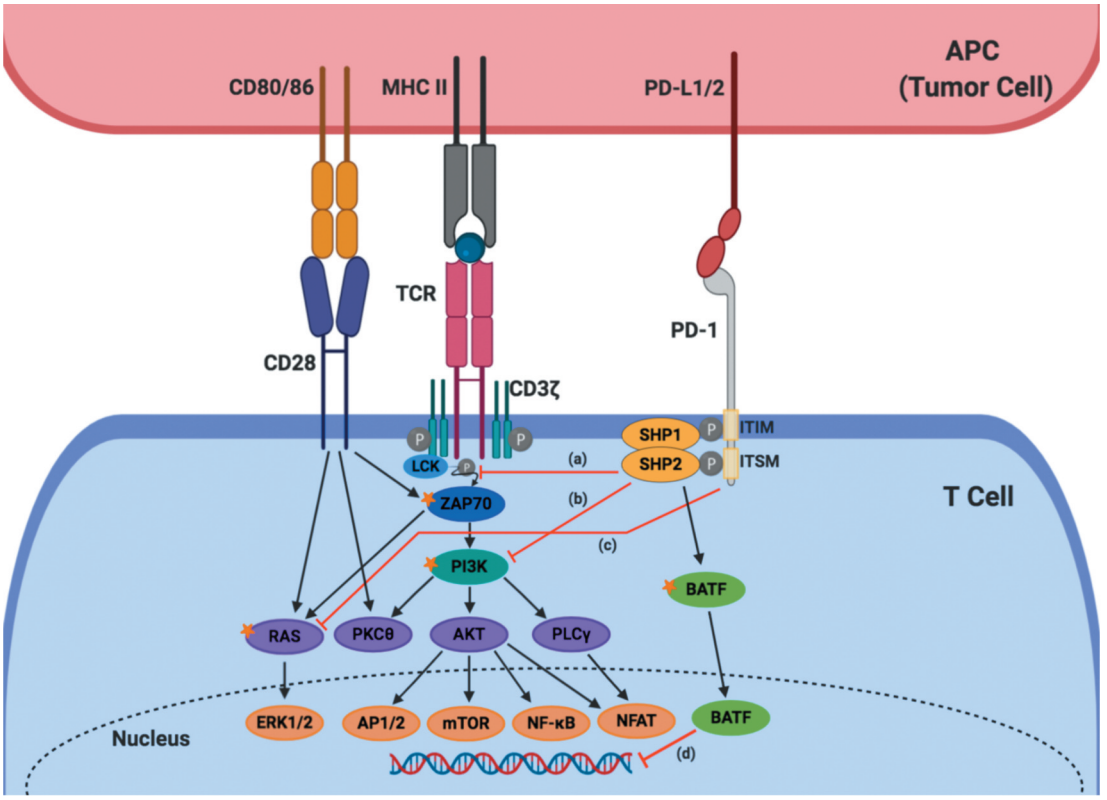

Figure 3. *PD-1 signalling cascade. PD-1 expression on T-cells is upregulated following T-cell-receptor (TCR) engagement and activation similar to CTLA-4. The ligands, PD-L1 and PD-L2, are constitutively expressed on antigen presenting cells (APC). Ligation inhibits lymphocyte activation signals and inhibits T-cell function through distinct mechanisms: a) direct antagonism of TCR signalling occurs by recruitment of Src-homology 2 domain-containing phosphatase (SHP)-1 and SHP-2 to tyrosine-based inhibitory motifs (ITM; immunoreceptor tyrosine-based motifs) in the PD-1 tail; b) inhibition of metabolism, survival, nutrient sensing, cell growth and cell cycle progression occur via targeting of rapamycin (mTOR) pathway through PI3K/AKT inhibition; c) cell cycle arrest and reduced T-cell proliferation occur by Ras pathway inhibition; d) repressed expression of effector gene transcription occurs through increased expression of basic leucin zipper transcription factor and activating transcription factor (ATF)-like transcription factor (BATF). PD-1 signalling events also impair T-cell stability and motility, hindering the formation of immune synapses with APCs.*

Anti-PD1 antibodies prevent PD-1 ligation and demonstrate broader utility than CTLA-4. PD-1 inhibition augments anti-tumour immunity and limits haematogenous seeding and metastasis (46). Increased PD-1 receptor and ligand expression in human cancers is a negative prognostic biomarker (47, 48), while PD-L1 expression in >50% of tumour cells correlates to improved efficacy with PD-1 inhibitor pembrolizumab in non-small-cell lung cancer (NSCLC) (49). Anti-PD-L1 targets ligands instead of receptors.

Clinical translation.

The CTLA-4 inhibitor ipilimumab was the first ICI to be approved in 2011 for metastatic melanoma. Six ICIs have been approved since: PD-1 inhibitors nivolumab, pembrolizumab, cemiplimab and PD-L1 inhibitors atezolizumab, avelumab, and durvalumab (50). Nivolumab and pembrolizumab are licensed for specific Hodgkin's and non-Hodgkin lymphomas.

Nivolumab. In May 2016, nivolumab received accelerated FDA and European Medicines Agency (EMA) approval for relapsed or progressive classical Hodgkin's lymphoma (cHL) post-autologous stem cell transplantation and post-transplantation brentuximab vedotin (BV) therapy, an anti-CD30 antibody-drug conjugate (ADC), or in pre-treated cHL after three therapies including autologous HSCT (51). Approval was based on pooled phase I and II (CheckMate-039 and -205), single-arm, multicentre trial results (52, 53). A 65% overall response rate (ORR) with 8.7-month median duration was observed and 2.1-month median time to respond. Rare (1-5%) immune-related adverse reactions (irARs) included rash, hyperthyroidism, pneumonitis, hepatitis, and colitis. Complications of allogeneic HSCT after nivolumab, including severe or hyperacute graft-versus-

Table I. *Active clinical trials investigating nivolumab as treatment for lymphoid, plasma cell, myeloid, and mixed haematological malignancies.*

Malignancies	Clinical trial #	Phase	Study description	Study name
Lymphoid neoplasm	NCT02181738	2	Study of Nivolumab in Patients With Classical Hodgkin's Lymphoma (Registrational) (CheckMate 205)	CheckMate 205
	NCT02857426	2	A Study of Nivolumab in Relapsed/Refractory Primary Central Nervous System Lymphoma (PCNSL) and Relapsed/Refractory Primary Testicular Lymphoma (PTL)	-
	NCT03337919	2	ANIMATE: Phase II Study of Nivolumab Monotherapy for Relapsed/ Refractory Hodgkin Lymphoma	ANIMATE
	NCT03016871	2	Nivolumab, Ifosfamide, Carboplatin, and Etoposide as Second-Line Therapy in Treating Patients With Refractory or Relapsed HL	-
	NCT03620578	2	DA-EPOCH-R Induction Followed by Nivolumab Consolidation in Newly Diagnosed MYC, BCL2 and/or BCL6 Rearranged HGBL	HO152
	NCT03436862	2	Nivolumab Maintenance Therapy After Autologous Stem Cell Transplant in Hodgkin Lymphoma Patients at Relapse/Progression Risk	-
	NCT04091490	2	Combination of Nivolumab and DHAP in Patients With Relapsed or Refractory Classical Hodgkin Lymphoma (Nivo-DHAP)	-
	NCT03258567	2	Nivolumab in Epstein-Barr Virus (EBV)-Positive Lymphoproliferative Disorders and EBV-Positive Non-HodgkinLymphomas	-
	NCT04401774	2	Nivolumab Maintenance in Newly Diagnosed PCNSL With Persistent CSF Circulating Tumor DNA After Completion of First-Line Chemotherapy	-
	NCT03586999	1-2	Nivolumab With Standard of Care Chemotherapy for Peripheral T Cell Lymphomas	-
	NCT03311958	1	Molecular Monitoring With Circulating Tumor DNA and Nivolumab Maintenance	-
	NCT02973113	1	Nivolumab With Epstein Barr Virus Specific T Cells (EBVSTS), Relapsed/Refractory EBV Positive Lymphoma (PREVALE)	PREVALE
	NCT03927105	2	Nivolumab and the Antagonistic CSF-1R Monoclonal Antibody Cabiralizumab (BMS-986227) in Patients With Relapsed/Refractory Peripheral T Cell Lymphoma	-
	NCT03884998	1	Copanlisib and Nivolumab in Treating Participants With Richter's Transformation or Transformed Indolent Non-Hodgkin's Lymphoma	-
	NCT04431635	1	Dose De-escalation Study of the PI3k Alpha/Delta Inhibitor, Copanlisib Given in Combination With the Immunotherapeutic Agents, Nivolumab and Rituximab in Patients With Relapsed/Refractory Indolent Lymphoma	-
	NCT03569696	2	Improving the Outcome of High-risk Aggressive B-cell Lymphoma Patients With Nivolumab Maintenance Therapy	NivoM
	NCT03480334	2	Abscopal Effect of Radiotherapy and Nivolumab in Relapsed Hodgkin Lymphoma After Anti-PD1 Therapy	AERN
	NCT03305445	1-2	Nivolumab/Ipilimumab-Primed Immunotransplant for DLBCL	-
	NCT03892044	1	Duvelisib and Nivolumab in Treating Patients With Richter Syndrome or Transformed Follicular Lymphoma	-
	NCT03502733	1	Testing the Combination of Copanlisib, Nivolumab and Ipilimumab in Patients With Advanced Cancer and Lymphoma	-
	NCT02572167	1-2	A Study of Brentuximab Vedotin Combined With Nivolumab for Relapsed or Refractory Hodgkin Lymphoma	-
	NCT03138499	3	A Study of Nivolumab Plus Brentuximab Vedotin Versus Brentuximab Vedotin Alone in Patients With Advanced Stage Classical Hodgkin Lymphoma, Who Are Relapsed/Refractory or Who Are Not Eligible for Autologous Stem Cell Transplant	CheckMate 812
	NCT03245021	1	Nivolumab Plus Rituximab in First-line Follicular Lymphoma gr 1-3A	1stFLOR
	NCT02857426	2	A Study of Nivolumab in Relapsed/Refractory Primary Central Nervous System Lymphoma (PCNSL) and Relapsed/Refractory Primary Testicular Lymphoma (PTL)	CheckMate 647
	NCT02581631	1-2	An Investigational Immuno-therapy Safety and Effectiveness Study of Nivolumab in Combination With Brentuximab Vedotin to Treat Non-Hodgkin Lymphomas	CheckMate 436
	NCT03061188	1	Nivolumab and Veliparib in Treating Patients With Recurrent or Refractory Stage IV Solid Tumors That Cannot Be Removed by Surgery or Lymphoma With or Without Alterations in DNA Repair Genes	-
	NCT03484819	2	Copanlisib Hydrochloride and Nivolumab in Treating Patients With Recurrent or Refractory Diffuse Large B-cell Lymphoma or Primary Mediastinal Large B-cell Lymphoma	-

Table I. *Continued*

Table I. *Continued*

Malignancies	Clinical trial #	Phase	Study description	Study name
	NCT03704714	1-2	Nivolumab and Combination Chemotherapy in Treating Participants With Diffuse Large B-Cell Lymphoma	
	NCT02038946	2	Study of Nivolumab in Subjects With Relapsed or Refractory Follicular Lymphoma (FL) (CheckMate 140)	CheckMate 140
	NCT03580408	2	Study Of Nivolumab Alone, Or In Combination With Vinblastin In Patients With Classical Hodgkin Lymphoma	-
	NCT02940301	2	Ibrutinib and Nivolumab in Treating Patients With Relapsed or Refractory Classical Hodgkin Lymphoma	-
	NCT03703050	2	Nivolumab for Pediatric and Adult Relapsing/Refractory ALK+ Anaplastic Large Cell Lymphoma, for Evaluation of Response in Patients With Progressive Disease (Cohort 1) or as Consolidative Immunotherapy in Patients in Complete Remission After Relapse (Cohort 2)	NIVO-ALCL
	NCT03920631	1	Microtransplantation and Checkpoint Blockade Immunotherapy for Relapsed or Refractory B Cell Lymphomas	MicroBLITZ
	NCT03770416	2	Nivolumab and Ibrutinib in Treating Patients With Relapsed or Refractory Central Nervous System Lymphoma	-
	NCT03843294	1	Tumor Associated Antigen Specific T Cells (TAA-T) With PD1 Inhibitor for Lymphoma	-
	NCT02927769	2	A Study of Nivolumab Plus Brentuximab Vedotin in Patients Between 5 and 30 Years Old, With Hodgkin's Lymphoma (cHL), Relapsed or Refractory From First Line Treatment	CheckMate 744
	NCT02397720	1	Nivolumab and Azacitidine With or Without Ipilimumab in Treating Patients With Refractory/Relapsed or Newly Diagnosed Acute Myeloid Leukemia	-
	NCT02181738	2	Study of Nivolumab in Patients With Classical Hodgkin's Lymphoma (Registrational)	CheckMate 205
	NCT03121677	1	Personalized Tumor Vaccine Strategy and PD-1 Blockade in Patients With Follicular Lymphoma	-
	NCT04134325	1	Study of PD-1 Inhibitors After CD30.CAR T Cell Therapy in Relapsed/Refractory Hodgkin Lymphoma	-
	NCT01716806	2	A Study of Brentuximab Vedotin With Hodgkin Lymphoma (HL) and CD30-expressing Peripheral T-cell Lymphoma (PTCL)	-
	NCT03057795	2	After Stem Cell Transplant in Treating Patients With Relapsed or Refractory High-Risk Classical Hodgkin Lymphoma	-
	NCT03749018	2	Nivolumab With DA-REPOCH Chemotherapy Regimen in Treating Patients With Aggressive B-Cell Non-Hodgkin's Lymphoma Vedotin,	-
	NCT03233347	2	Doxorubicin Hydrochloride, Vinblastine, Dacarbazine, Brentuximab and Nivolumab in Treating Patients With Stage I-II Hodgkin Lymphoma	-
	NCT03004833	2	Nivolumab and AVD in Early-stage Unfavorable Classical Hodgkin Lymphoma	-
	NCT03585465	1-2	Nivolumab in Combination With Metronomic Chemotherapy in Paediatrics Refractory/Relapsing Solid Tumors or Lymphoma	-
	NCT01896999	1-2	Brentuximab Vedotin and Nivolumab With or Without Ipilimumab in Treating Patients With Relapsed or Refractory Hodgkin Lymphoma	-
	NCT03033914	1-2	A(B)VD Followed by Nivolumab as Frontline Therapy for Higher Risk Patients With Classical Hodgkin Lymphoma (HL)	-
	NCT03907488	3	Immunotherapy (Nivolumab or Brentuximab Vedotin) Plus Combination Chemotherapy in Treating Patients With Newly Diagnosed Stage III-IV Classic Hodgkin Lymphoma	-
	NCT03004833	2	Nivolumab and AVD in Early-stage Unfavorable Classical Hodgkin Lymphoma	-
Plasma cell neoplasm	NCT01592370	1	An Investigational Immuno-Therapy Study to Determine the Safety and Effectiveness of Nivolumab and Daratumumab in Patients With Multiple Myeloma	-
	NCT02726581	3	An Investigational Immuno-therapy Study of Nivolumab, Pomalidomide and Dexamethasone Combinations in Patients With Multiple Myeloma	CheckMate 602
	NCT03782064	2	Dendritic Cell (DC)/Myeloma Fusions in Combination With Nivolumab in Patients With Relapsed Multiple Myeloma	-
	NCT01592370	1-2	An Investigational Immuno-Therapy Study to Determine the Safety and Effectiveness of Nivolumab and Daratumumab in Patients With Multiple Myeloma	-

Table I. *Continued*

Table I. *Continued*

Malignancies	Clinical trial #	Phase	Study description	Study name
	NCT02726581	3	An Investigational Immuno-therapy Study of Nivolumab, Pomalidomide and Dexamethasone Combinations in Patients With Multiple Myeloma	CheckMate 602
	NCT03634800	2	Radiotherapy With Immunotherapy for Systemic Effect in Myeloma (RISE-M)	RISE-M
	NCT02719613	2	Continuing Treatment for Participants Who Have Participated in a Prior Protocol Investigating Elotuzumab	-
Myeloid neoplasms	NCT02530463	2	Nivolumab and/or Ipilimumab With or Without Azacitidine in Treating Patients With Myelodysplastic Syndrome	-
	NCT02275533	2	Nivolumab in Eliminating Minimal Residual Disease and Preventing Relapse in Patients With Acute Myeloid Leukemia in Remission After Chemotherapy	-
	NCT03184194	2	Nivolumab Combined With Daratumumab With or Without Low-dose Cyclophosphamide	-
	NCT03600155	1	Nivolumab and Ipilimumab After Donor Stem Cell Transplant in Treating Patients With High Risk Refractory or Relapsed Acute Myeloid Leukemia or Myelodysplastic Syndrome	-
	NCT03681561	1-2	Nivolumab With Ruxolitinib in Relapsed or Refractory Classical Hodgkin Lymphoma	-
	NCT02275533	2	Nivolumab in Eliminating Minimal Residual Disease and Preventing Relapse in Patients With Acute Myeloid Leukemia in Remission After Chemotherapy	-
	NCT02397720	2	Nivolumab and Azacitidine With or Without Ipilimumab in Treating Patients With Refractory/Relapsed or Newly Diagnosed Acute Myeloid Leukemia	-
	NCT03358719	1	DEC-205/NY-ESO-1 Fusion Protein CDX-1401, Poly ICLC, Decitabine, and Nivolumab in Treating Patients With Myelodysplastic Syndrome or Acute Myeloid Leukemia	-
	NCT03092674	2-3	Azacitidine With or Without Nivolumab or Midostaurin, or Decitabine and Cytarabine Alone in Treating Older Patients With Newly Diagnosed Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome	-
	NCT02530463	2	Nivolumab and/or Ipilimumab With or Without Azacitidine in Treating Patients With Myelodysplastic Syndrome	-
	NCT03292263	1-2	ASCT With Nivolumab in Patients With Multiple Myeloma	-
	NCT03825367	1-2	Nivolumab in Combination With 5-azacytidine in Childhood Relapsed/Refractory AML	-
	NCT04361058	1	Nivolumab for High-Risk MDS/AML Patients After Allogeneic Stem Cell Transplant With Post-Transplant Cyclophosphamide	-
	NCT02846376	1	Single Agent and Combined Inhibition After Allogeneic Stem Cell Transplant	-
Mixed haematological malignancies	NCT03146468	2	Nivolumab for Relapsed or Residual Haematological Malignancies After Allogeneic Stem Cell Transplantation	-
	NCT02681302	1-2	Check Point Inhibition After Autologous Stem Cell Transplantation in Patients at High Risk of Post Transplant Recurrence	-
	NCT02663518	1	A Trial of TTI-621 for Patients With Hematologic Malignancies and Selected Solid Tumors	-
	NCT02693535	2	TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer	TAPUR
	NCT02978625	2	Talimogene Laherparepvec and Nivolumab in Treating Patients With Refractory Lymphomas or Advanced or Refractory Non-melanoma Skin Cancers	-
	NCT02304458	1-2	Nivolumab With or Without Ipilimumab in Treating Younger Patients With Recurrent or Refractory Solid Tumors or Sarcomas	-
	NCT02758717	2	Nivolumab and Brentuximab Vedotin in Treating Older Patients With Untreated Hodgkin Lymphoma	-
	NCT03739619	1-2	Gemcitabine, Bendamustine, and Nivolumab in Patients With Relapsed or Refractory Classical Hodgkin Lymphoma	-
	NCT01822509	1	Ipilimumab or Nivolumab in Treating Patients With Relapsed Hematologic Malignancies After Donor Stem Cell Transplant	-
	NCT02420912	2	Nivolumab and Ibrutinib in Treating Patients With Relapsed, Refractory, or High-Risk Untreated Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma, or Richter Transformation	-
	NCT02329847	1-2	A Study to Evaluate Safety, Pharmacokinetics, Pharmacodynamics and Preliminary Efficacy of the Combination of Ibrutinib With Nivolumab in Participants With Hematologic Malignancies	-

Table I. *Continued*

Table I. *Continued*

Malignancies	Clinical trial #	Phase	Study description	Study name
	NCT03712202	2	Brentuximab Vedotin and Nivolumab in Treating Patients With Early Stage Classic Hodgkin Lymphoma	-
	NCT03038672	2	Nivolumab With or Without Varlilumab in Treating Patients With Relapsed or Refractory Aggressive B-cell Lymphomas	-
	NCT03015896	1-2	Nivolumab and Lenalidomide in Treating Patients With Relapsed or Refractory Non-Hodgkin or Hodgkin Lymphoma	-
	NCT04439214	2	Testing Nivolumab as a Potential Targeted Treatment in Cancers With Mismatch Repair Deficiency (MATCH-Subprotocol Z1D)	MATCH-Subprotocol Z1D
	NCT04205409	2	Nivolumab for Relapsed, Refractory, or Detectable Disease Post Chimeric Antigen Receptor T-cell Treatment in Patients With Hematologic Malignancies	-

HGBL, High grade B-cell lymphoma; EBV, Epstein-Bar virus; EBVSTS, Epstein-Bar virus specific T cells; DLBCL, diffuse large B-cell lymphoma; PTL, primary testicular lymphoma; FL, follicular lymphoma; TAA-T, tumour associated antigen-specific T-cells; HL, Hodgkin lymphoma; cHL, classical Hodgkin lymphoma; PTCL, peripheral T-cell lymphoma; DC, dendritic cell; FDA, Food and Drug Administration.

host disease (GVHD) and transplant-related mortality, caused a Warning and Precaution to be issued (51). Phase I-III trials investigating nivolumab for treatment of lymphoid, plasma cell, myeloid, and mixed haematological malignancies are shown in Table I.

Pembrolizumab. In 2017, pembrolizumab was granted accelerated approval for adults and children with relapsed or refractory (R/R) cHL after three prior therapies (54). The nonrandomized, single-arm, phase II, open-label trial (KEYNOTE-087) demonstrated 22% complete response (CR) and 47% partial response (PR) rate of 11.1 months median duration (55). Few patients (5%) discontinued treatment due to ARs, and others (26%) stopped treatment temporarily.

In 2018, approval was expanded to non-Hodgkin lymphoma (NHL), specifically primary mediastinal large B-cell lymphoma (PMBCL), a subtype of diffuse large B-cell lymphoma (DLBCL) following the phase IB and phase II, KEYNOTE-013 and -170 studies (56). ORRs of 48% and 45% were observed, with duration of response (DOR) not reached at 29.1 months and 12.5 months median follow-up duration in KEYNOTE-013 and -170, respectively. No CR patients in KEYNOTE-170 had relapsed at data cut-off; median PFS 5.5 months. Grade 3-4 ARs (23%) included neutropenia; 11% experienced irARs including grade 4 pneumonitis (2%). Active clinical trials investigating PD-1 inhibitors are ongoing (57).

Strengths of ICIs.

Responses in heavily pre-treated/resistant disease. As with other immunotherapies, a major advantage of ICIs is their ability to achieve a response in heavily pre-treated relapsed or refractory patients which is a testament to their therapeutic potency. Indeed, Marjanska et al. demonstrate the efficacy of nivolumab in heavily pre-treated paediatric patients including one patient with stage IV cHL who achieved CR with no significant ARs (58). Among patients with platinum-refractory, recurrent squamous-cell carcinoma of the head and neck, nivolumab produced longer OS and resulted in longer overall survival than treatment with standard, single-agent therapy (methotrexate, docetaxel, or cetuximab) (59).

Durable response. A hallmark of cancer immunotherapy is the durability of response that translates into clinical benefit (60). ICIs can potentially sustain the anti-tumour immune response indefinitely (61) due to T-cell immunologic memory (62-64).

Relatively well-tolerated. ICIs are tolerated better than chemotherapeutics and do not induce severe myelosuppression or sepsis, thus improving quality-of-life.

Weaknesses of ICIs.

Rare but severe toxicities. Autoimmune neurotoxicity, cardiotoxicity, pneumotoxicity, hepatoxicity, colitis, and endocrine toxicity may warrant ICI treatment discontinuation. Rarely, irARs can cause prolonged disability, be life-threatening, or fatal. Examples include progressive neuropathies, such as Guillain Barre syndrome, aseptic meningitis/encephalitis, and neuromuscular conditions, such as myasthenia gravis (1-2%) (65).

Slow response, pseudoprogression, and hyperprogression. ICIs demonstrate different patterns of kinetics and disease progression to chemotherapeutics, producing an initial "tumour flare" termed pseudoprogression. Pseudoprogression (~10%) is a radiologically observed increase in tumour size due to T-cell infiltration, mimicking progressive disease (PD), though remission follows.

Pseudoprogression challenges clinical decision making. Immune-specific related response criteria have been developed (66). These define PD differently, allowing for treatment

beyond initial progression, thus avoiding inappropriate early treatment discontinuation indicated by conventional Response Evaluation Criteria in Solid Tumours (RECIST).

Hyperprogression describes rapid PD after immunotherapy, corresponding to tumour growth and reduced survival. Hyperprogression is observed in 4-29% of ICI-treated solid tumours (67). Predictive markers for progression, hyperprogression and pseudoprogression are needed.

Limited response and associated resistance: Most ICI-treated patients fail to respond (60). Even patients with similar tumour biomarkers respond differently. Single-agent PD-1 blockade response in unselected patients is ~40-70% in some diseases and 10-25% in others (61). cHL demonstrates high ICI response rates, with 65-87% ORR (68).

Aside from primary resistance, adaptive and acquired resistance may emerge. Acquired resistance rates vary between tumours. In cHL acquired resistance rates range between 19-57% in studies [reviewed in (61)]. An inverse relationship between PD-1 therapy ORR and acquired resistance indicates disease-specific acquired resistance mechanisms, through this association is absent in cHL (61).

Opportunities for ICIs.

New targets. Aside from B7-CD28, other potent immune receptor co-signalling superfamilies include tumour necrosis factor receptor (TNFR), T-cell immunoglobulin domain and mucin domain (TIM), poliovirus receptor (PVR)-like proteins, semaphorins, and butyrophilin (BTN)-like molecules (69). Within these, noteworthy targets include lymphocyte activation gene-3 (LAG-3, CD223), T-cell immunoglobulin and mucin domain-containing protein-3 (TIM-3), T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT), or B- and T-lymphocyte attenuator (BTLA) (57).

Resistance mechanisms and response prediction. In HL, primary ICI resistance mechanisms include: $CD8^+$ T-cell exclusion and increased Tregs within the TME; insufficient T-cell activation by lack of antigen presentation; upregulated indoleamine 2,3-dioxygenase (IDO) metabolism; and augmented immunosuppression *via* tumour-associated macrophages (TAMs) or natural killer (NK) cells. Acquired resistance occurs *via* PD-1, LAG-3 and TIM upregulation following anti-PD-1 therapy and increased adenosine levels, though this may present in primary resistance (68, 70). IDO, LAG-3 and TIM inhibitors are being investigated in solid tumours as a means to overcome resistance (71-73). Potential ICI response prediction biomarkers correlating to resistance mechanisms have been identified in solid tumours (74, 75). High tumour mutation burden and PD-L1 expression have been shown to be independent predictors of ICI efficacy in various solid cancers according to one meta-analysis (76). Another meta-analysis showed that EGFR mutations are a negative predictor of ICI efficacy in NSCLC (77), while a single-centre study showed that KRAS mutations predict superior response to immunotherapy in NSCLC (78). Differential tumour infiltrating lymphocyte density in metastatic and primary tumour sites could also contribute to ICI response prediction according to one case report (79). PD-L1/2 expression is potentially a novel prognostic predictor according to a recent study (80).

ICI combination therapy with other immunotherapies. Combination therapy decreases resistance rates and improves efficacy. In HL, ipilimumab plus nivolumab demonstrated 74% ORR (81) while this concurrent combination has also demonstrated rapid and deep tumour regression in advanced melanoma with manageable safety profile (82). Combination therapy may enhance the efficacy of developing agents. PD-L1/PD-1 blockade with CD33/CD3 BiTE enhanced T-cell proliferation and IFN-γ production (83). Benefits are also demonstrated with CAR-T cells.

ICI combination therapy with chemotherapy. Chemotherapies alter the TME, which is important when considering adjunct ICIs, along with timings, dose, and administration sequence. Preclinically, chemotherapies are immunostimulatory, by immunosuppressive cell inhibition, effector cell activation, or increased immunogenicity by enhanced T-cell infiltration (84). Clinical results of anti-PD-1/PD-L1 antibodies plus chemotherapy in advanced or metastatic non-squamous NSCLC support this combination as first-line therapy (85-87). In HL, nivolumab followed by adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) is being investigated (88). Pembrolizumab plus cytarabine in AML demonstrated 35% CR and 56% minimal residual disease (MRD)-negative remission (89).

ICI combination therapy with targeted therapies. In HL, nivolumab plus BV produced 82% ORR and 61% CR as first-line salvage therapy (90) while nivolumab, ipilimumab, and BV yielded 82% ORR and 68% CR (91). Hypomethylating agents (HMAs), increased PD-L1, PD-L2, PD-1, and CTLA-4 expression in haematologic cancer patients, indicating that immune checkpoint pathways may mediate HMA resistance (92). HMAs induced PD-1 promoter demethylation, upregulating PD-1 expression on T-cells which promoted tumour-specific T-cell exhaustion and cancer immune escape (93). HMA and ICI combination is being investigated in trials.

ICI combination therapy with radiotherapy. Radiotherapy promotes tumour-specific antigen presentation. The abscopal effect is a systemic immune mediated regression of non-irradiated lesions distant from the primary irradiation site (94). Preclinical evidence supports combination of stereotactic body radiation therapy (SBRT) with ICIs (95). Radiotherapy sequencing and fractionation alters responses. Radiotherapy combination with anti-CTLA-4 only produced an abscopal effect with fractionation (96). Abscopal response is facilitated *via* altered antibody response to TAA, modified peripheral blood immune cells, and increased antigen responsiveness

(97). Increased tumour-infiltrating lymphocytes were observed in non-irradiated lymph nodes of patients treated with ICI plus radiation (98).

Threats to ICIs.
Despite their clinical efficacy, ICIs' spectrum of use is narrow in haematological malignancies, whereas their role is more prominent in solid tumours. Even though ICIs are a cost-effective, off-the-shelf immunotherapy with universal utility across patients, their use in haematological malignancies will likely be overshadowed by the advent of more novel immunotherapeutic approaches, for example, T-cell-redirecting immunotherapies and adoptive cell therapies.

Bispecific T-cell Engagers (BiTEs)

Biological rationale for anti-cancer mechanism and development.
The concept of selectively targeting tumours *via* antibodies was proposed over a century ago by Paul Ehrlich (99). Monoclonal antibodies (mAbs) have constituted a weapon in the oncologists' anti-cancer armamentarium since 1997, commencing with the approval of rituximab, a chimeric anti-CD20 agent for low-grade B-cell lymphoma (100). Improvements in antibody engineering technology (101) have enabled scientists to develop bispecific T-cell-redirecting antibodies which bind TAAs, redirecting cytotoxic T-cells to tumours. Bispecific T-cell engagers (BiTEs), consisting of two different single-chain variable fragments (scFvs) derived from the antigen-binding domains of anti-CD3 and anti-TAA antibodies covalently bound *via* small linker peptides (102).

BiTEs are producible in large quantities through mammalian cell line culture and recombinant single-chain polypeptide secretion (103). Upon simultaneous binding of BiTEs to TAAs and CD3 TCR, a lytic immune synapse forms between T-cells and cancer cells (Figure 4) (104). Simultaneous high affinity binding is facilitated by small size (~55 kDa) and high flexibility of BiTEs due to lack of antibody constant (Fc) regions, which also contributes to reduced half-life and decreased toxicity due to lack of Fc-receptor (FcR) recycling and FcR-mediated effector functions, respectively (105). These characteristics are crucial for *in vitro* and *in vivo* efficacy. T-cell-mediated tumour cell killing was observed at very low concentrations (10-100 pg/ml) and low effector-cell to T-cell

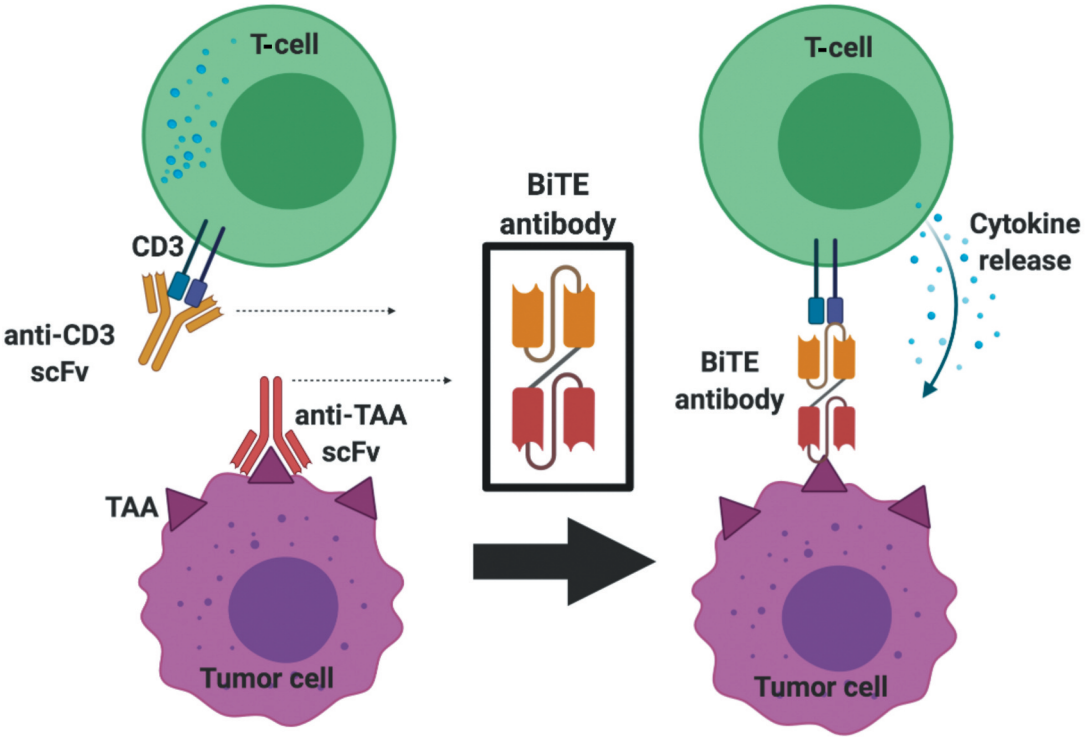

Figure 4. *Schematic illustration of Bispecific T-cell Engager (BiTE) structure and mechanism of action. An anti-tumour-associated antigen (TAA) single-chain variable fragment (scFv) (shown in green) is linked via a small linker molecule to an anti-CD3 scFv (shown in pink). Binding of anti-TAA to tumour cell surface antigens redirects T-cells to target the tumour cell via anti-CD3 binding causing the formation of a lytic immune synapse with cytokine release. Adapted with permission from Marayati et al. (104).*

ratios (<1:90), without immune co-stimulation (106-108). Hence, blinatumomab ultimately became the first approved BiTE and is still used in ALL subtypes. Several trials are investigating BiTEs in haematological and solid malignancies (109). Mosunetuzumab was recently pre-approved for R/R follicular lymphoma (FL).

Clinical translation.

Blinatumomab (Blincyto®). In 2014 blinatumomab, an anti-CD19 and anti-CD3 agent, was approved for Ph chromosome (Ph)-negative (110), and subsequently Ph-positive (111), B-cell precursor acute lymphoblastic leukaemia (BCP-ALL); nearly 60 years after the first report of human-synthesised bispecific antibodies (112, 113). Blinatumomab approval has been expanded to adults and children with R/R BCP-ALL, and adults and children with MRD-positive BCP-ALL in remission.

FDA approval was based on a phase II, open-label, single-arm, multicentre trial of R/R Ph^- BCP-ALL patients in which 33% CR and 10% CRh (complete remission with partial haematological recovery) was achieved, with 6.9-month median OS (114). A phase III randomised trial reported similar results with 44% CR/CRh rate and 7.7-month median OS. Blinatumomab was superior to chemotherapy (115). The open-label, multicentre, single-arm study granting blinatumomab approval for MRD^+ BCP-ALL evaluated patients experiencing first- or second-time CR with detectable MRD in a >1 in 1,000 bone marrow cells (116). MRD conversion to <0.01% after one blinatumomab cycle was achieved in 85.2% and 72.0% of first- and second-CR patients, respectively, with 35.2-month and 12.3-months median haematologic relapse-free survival, respectively, indicating durable response. At 5 years, 50% remained in remission (117). A phase I/II trial was the first to demonstrate the safety and efficacy of single-agent blinatumomab in paediatric patients with R/R BCP-ALL achieving complete minimal residual disease response (118).

Blinatumomab is generally well-tolerated. Toxicities reflect CD3-activation (109). Cytokine release syndrome (CRS) and neurotoxicity were rare but severe dose-limiting ARs issued Boxed Warnings in addition to pancreatitis, serious infection and sepsis (114, 115).

Mosunetuzumab (BTCT4465A). In July 2020, mosunetuzumab, an anti-CD20 and anti-CD3 agent, received pre-approval by the FDA, through breakthrough therapy designation, for the treatment of adults with R/R follicular lymphoma (FL) after at least two prior systemic therapies. The phase I/Ib, multicentre, open-label, dose-escalation study evaluated the safety and pharmacokinetics of mosunetuzumab in 270 heavily pre-treated R/R NHL (119). ORR and CR was observed in indolent (63% and 43%) and aggressive lymphomas (37% and 19%) across doses. CRS and neurological ARs occurred in 29% and 44%, respectively, but only three were grade 3 cases in each. Notably, patients previously receiving CAR-T-cell therapy (n=18) achieved 39% ORR (n=7) and 22% CR (n=4) (120). Investigators observed a lymphocyte expansion, including residual CAR-T-cells, and CRs with and without CAR-T-cell expansions offering potential for mosunetuzumab salvage therapy after CAR-T-cells, though it could potentially be a bridging approach as well by stimulating T-cells.

Strengths of BiTEs.

Superior anti-tumour efficacy. Preclinically, BiTE efficacy is superior to mAbs and other bispecific antibodies (106, 121). Higher binding specificity due to two antigens and effector immune cell mediated redirection to tumour cells enhance cytotoxicity. Targeting two pathways improves efficacy and resistance (122). Indeed, in a phase I/Ib study mosunetuzumab demonstrated clinical activity and durable response in R/R B-cell NHL patients who were considered refractory to anti-CD20 therapy and in patients who had relapsed following CD19-directed CAR-T therapy, while the safety profile also appeared favourable compared to standard anti-lymphoma therapies including T-cell directed agents (123).

Lack of MHC and HLA restriction. Lack of major histocompatibility complex (MHC)- and human leukocyte antigen (HLA)-restriction in BiTEs allows for universal off-the-shelf use unlike CAR-T-cells. MHC-independent cancer elimination prevents resistance *via* MHC-molecule downregulation, loss of MHC-I associated β2-microglobulin or intracellular peptide transporters (124).

Weaknesses of BiTEs.

Rare but severe toxicities. CRS, observed in mAb, bispecific antibody, and CAR-T-cell treatments, is a direct result of lymphoid- and/or myeloid-cell activation which stimulates cytokine production, including interleukin IL-6 and interferon-γ (IFN-γ) (125). While mild CRS produces fever, severe cases can mimic macrophage activation syndrome or hemophagocytic lymphohistiocytosis (126). CRS has been observed with blinatumomab (127) and occurs within days from the first cycle but not subsequent infusions (128). CRS incidence is positively correlated with dose and disease burden (114, 128-130). CRS also correlates with better response, though severity is not response-associated (131). Prophylactic dexamethasone and stepwise dosing decreased CRS incidence (114, 132). Tocilizumab, an anti-IL-6 receptor mAb for CD19-CAR-T-cell CRS (125, 133), can treat blinatumomab-associated CRS (134).

Blinatumomab-treatment neurotoxicity (52%) encompasses a spectrum of presentations (109). Most are mild such as grade 2 tremor (17%), while seizures (2%) or encephalopathy (5%) are rare. BiTE neurotoxicity has been attributed to extravasation of adhesive T-cells to the perivascular space in the central nervous system, stimulating endothelial activation which attracts leukocytes, including monocytes, inducing

neuroinflammation and neurotoxicity (135). Neurological ARs are reversible on treatment discontinuation and dexamethasone therapy. Similar to CRS, prophylactic dexamethasone and stepwise dosing regimens are advised.

Relapse and resistance. Increased tumour mutational burden negatively correlates to blinatumomab response due to mutation-associated primary resistance (136). Lineage switch to acute myeloid leukaemia (AML) by rearrangement of the myeloid/lymphoid or mixed lineage leukaemia (MLL) lysine (K)-specific methyltransferase 2A (KMT2A) gene expressed on B-cell ALL can cause relapse or resistance (137). TAA target downregulation is a significant cause of blinatumomab resistance (138). Decreased CD19 expression on leukemic blasts prior to, and after blinatumomab therapy confers primary and secondary resistance, respectively (139). CD19 gene mutations and alternate splicing of CD19 mRNA produce truncated receptor variants conferring resistance (140).

Opportunities for BiTEs.
New antigen targets. Over 100 bispecific antibody formats are known (101, 141, 142), a quarter of which are being commercialised by pharmaceutical companies for therapeutic development (143). CD20, BCMA, CD138, CD33, CD123, CLL1, WT1, CD13 TAA-directed domains are being investigated in haematological cancers (109).

New antibody formats. Dual-affinity re-targeting (DART) offers competing diabody format with additional stability through a C-terminal disulphide bridge (144). *In vitro* CD19xCD3 DARTs outperform BiTEs in cytotoxicity assays (145). DARTs demonstrate higher CD3-association, lower CD19 dissociation, and more efficient T- and B-cell cross-linking. CD19xCD3 DART, duvortuxizumab, demonstrated response in phase I dose escalation. However, high neurotoxicity rates terminated licensing due to high competition against B-cell malignancy therapies. CD32BxCD16 and CD32BxCD79B DARTs provide an alternative T-cell activation mechanism, highlighting bispecific antibody adaptability.

Threats to BiTEs.
Interest in BiTEs has decreased given unsuccessful attempts to translate agents despite numerous trials. Other designs, such as DARTs, have gained interest. Adoptive cell therapies threaten the sustainability of BiTEs. CD19-CAR-T-cell therapy approval for ALL is altering blinatumomab prescribing. Novel adoptive cell therapies are superior and offer durable remission (109).

Discussion

ICIs and BiTEs are exceptional treatments for haematological malignancies. Yet, biotechnological advancements underlying immunotherapeutic development are costly. Thus, close consideration of the strengths, weaknesses, opportunities and threats of each immunotherapeutic modality is essential to direct future research (Table II). Both ICIs and BiTEs are cost-effective "off-the-shelf" drugs. ICIs generate durable response in heavily pre-treated and disease refractory patients. However, limited response across patients and diseases, primary and acquired resistance, and rare but severe toxicities, have set ICIs behind novel ATC therapies such as CARs. Nevertheless, lower costs and longer history of approval compared to BiTEs and novel ATC therapies lends to their continued interest. BiTEs represent powerful immunotherapies with superior anti-tumour efficacy to other antibody contracts. However, costly initial synthesis and competitive licensing have restricted their use, though newer constructs may change this.

Table II. *Summary of strengths, weaknesses, opportunities and threats associated with immune checkpoint inhibitors and bispecific T-cell engagers.*

	Immune checkpoint inhibitors	Bispecific T-cell engagers
Strengths	Responses in heavily pre-treated/resistant disease Durable response Relatively well-tolerated Lack of MHC and HLA restriction	Superior anti-tumour efficacy Lack of MHC and HLA restriction
Weaknesses	Rare but severe toxicities Slow response, pseudoprogression, and hyperprogression Limited response and associated resistance	Rare but severe toxicities Relapse and resistance
Opportunities	New targets Resistance mechanisms and response prediction Combination therapy	New antibody formats New antigen targets
Threats	Novel T-cell-redirecting immunotherapies (*e.g.*, BiTEs) Novel adoptive cell therapies (*e.g.*, CAR-T-cells)	Novel adoptive cell therapy agents (*e.g.*, CAR-T-cells)

Conclusion

With new molecular targets being discovered, more progress is to be expected in T-cell-based cancer immunotherapy. The diverse repertoire of molecular targets offers exceptional potential for combination treatments. Clinically, combination immunotherapy is still at its relative infancy with further research necessary to determine how to optimise and translate treatment regimens into routine clinical practice. The potential to combine immunotherapies with chemotherapy, radiotherapy, and targeted molecular therapies is significant and requires systematic investigation.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

K.S.R. has contributed to reviewing the literature, drafting and revising the article, figure illustrations, and final approval of the version to be published. C.R.T.H. has contributed to revising the article and final approval of the version to be published. M.S. has contributed to revising the article and final approval of the version to be published. J.K.F. has contributed to the conceptualization of the work, revising the article, supervising the work, and final approval of the version to be published.

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