

REVIEW

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New antibody approaches to lymphoma therapy

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Abstract

The CD20-directed monoclonal antibody rituximab established a new era in lymphoma therapy. Since then other epitopes on the lymphoma surface have been identified as potential targets for monoclonal antibodies (mAb). While most mAbs eliminate lymphoma cells mainly by antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity or direct cell death, others counter mechanisms utilized by malignant cells to evade immune surveillance. Expression of PD-L1 on malignant or stromal cells in the tumor environment for example leads to T-cell anergy. Targeting either PD-1 or PD-L1 via mAbs can indirectly eliminate cancer cells by unblocking the host intrinsic immune response. Yet another mechanism of targeted therapy with mAbs are bi-specific T-cell engagers (BiTE) such as blinatumomab, which directly engages the host immune cells. These examples highlight the broad spectrum of available therapies targeting the lymphoma surface with mAbs utilizing both passive and active immune pathways. Many of these agents have already demonstrated significant activity in clinical trials. In this review we will focus on novel CD20-directed antibodies as well as mAbs directed against newer targets like CD19, CD22, CD40, CD52 and CCR4. In addition we will review mAbs unblocking immune checkpoints and the BiTE blinatumomab. Given the success of mAbs and the expansion in active and passive immunotherapies, these agents will play an increasing role in the treatment of lymphomas.

Keywords: Bispecific T-cell engager, Cd-20, Pd-1, Cd-22, Monoclonal, Lymphoma, Antibodies

Introduction

In 1997 the CD20-directed monoclonal antibody (mAb) rituximab became the first mAb approved for the treatment of lymphoma after it demonstrated significant single agent activity in indolent B-cell lymphomas [1]. Since then rituximab has become an indispensable component in the treatment of all types of B-cell Non-Hodgkin lymphomas (NHL), both alone and in combination with chemotherapeutic agents [2].

While rituximab can lead to direct cytotoxicity by induction of apoptosis, it also eliminates lymphoma cells by antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity [3]. Its success has spawned an immense interest in using the hosts' immune system in selectively targeting tumor cells by attacking tumor-specific surface antigens. These surface epitopes represent ideal targets as they allow effective anticancer therapy while relatively sparing normal tissues.

mAbs represent the cornerstone of passive immunotherapy, which involves engineering of B or T cell receptors

targeting a desired antigen and infusion into patients with disease. Methods to potentially increase their efficacy include conjugation of mAbs with potent cell toxin or radioisotopes, exemplified by antibody-drug conjugates (ADC) and radioimmunotherapy (RIT) respectively. Another more recent mode of passive immunotherapy is termed adoptive T-cell transfer: autologous T-cells with genetically modified T-cell receptors (chimeric antigen receptors; CARs) that specifically recognize a tumor epitope are reinfused and exert their newly acquired antilymphoma potency in the host [4]. BiTEs or bispecific T cell engagers are also examples for newer passive therapy that activates T cell destruction of lymphoma cells.

Active immunotherapy on the other hand enables the patient's own immune system to re-engage into recognizing malignant cells which originally escaped immune surveillance. The classical example for active immunotherapy is tumor vaccines. More recently antibodies directed against CTLA4 or the PD-1/PD-L1 pathway, which unblock immune checkpoints, have demonstrated significant antitumor activity [3].

This review focuses on recent advances in targeting the lymphoma surface directly or indirectly with mAbs

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representative of active and passive immunotherapies (Figure 1), and agents that have either just reached the clinical practice or hold promise to change standard of care. Lymphoma therapy with ADCs, RIT, vaccines or adoptive T-cell transfer is reviewed elsewhere [3,5-7].

Monoclonal antibodies against B-cell antigens

Targeting CD20

CD20 is a surface antigen found on all mature B-cells. Its main function is to activate B-cells, allowing proliferation and differentiation. As it is also present on most mature B-cell NHL cells, it represents an ideal therapeutic target. While mAbs against CD20 target mature B-cells, they spare B cell progenitors, allowing normal B-cell regeneration [2].

Rituximab was the first mAb to target CD20 and represents a type I mAbs that cause cell death through: [8] a direct apoptotic effect; complement-dependent cytotoxicity (CDC), in which binding of the mAb activates the complement cascade; and ADCC, in which immune cells expressing Fcγ receptors attack antibody-coated cells. Certain polymorphisms in the FcγRIIIa protein alter activation of effector cells causing less ADCC and result in significantly lower response rates (RR) following rituximab monotherapy [9-11]. Newer mAbs are being designed to better target carriers of these polymorphisms (Table 1).

Obinutuzumab (GA101; Gazyva™) represents a type II mAb; while type I mAbs work primarily through CDC by stabilizing CD20 on lipid rafts, type II mAbs work mainly by direct cell death and ADCC [12-15]. Obinutuzumab is a glycoengineered CD20 mAb derived from the murine Bly-1 antibody [16]. Afucosylation (which increases affinity to Fc gamma receptor IIIa) of the Fc

region leads to improved activation of effector cells [17], leading to BCL-2 and caspase independent apoptosis, and hypothetically circumvents resistance [12]. As compared to rituximab, it results in increased ADCC and direct apoptosis both in vitro and in vivo [9,17]. Type II mAbs are thought to have an advantage because type I mAbs are faced with complement-resistance factors, depletion of complement proteins [18], and bind C1q, which interferes with FcγR binding and decreases ADCC [19]. Furthermore, type II mAbs result in longer persisting anti-CD20 mAb complexes [20] and higher binding affinity thereby increasing ADCC.

In November 2013, obinutuzumab was FDA approved for the treatment of previously untreated CLL in combination with chlorambucil (Cb). In a phase 3 study in treatment naïve elderly patients, Cb with obinutuzumab showed superior RR and progression free survival [PFS] compared to Cb alone and Cb with rituximab (complete response [CR] rate 21%; overall response rate [ORR] 78%) [21]. In addition, obinutuzumab has been tested in combination with other chemotherapeutic agents in CLL [22] and more aggressive B-cell NHL, such as diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) [23], demonstrating promising results. The main non-hematologic side effects (SE) were grade 1 or 2 infusion-related reactions (IRRs) and the most common hematologic SE was neutropenia.

Ofatumumab

Ofatumumab (HuMax-CD20; Arzerra®) is another humanized CD20-directed mAb. It binds to both loop domains of CD20 at a different epitope than rituximab and induces CDC [24]. As compared with rituximab and obinutuzumab, ofatumumab results in the greatest complement activation and antibody-dependent phagocytosis (ADP) [25].

Ofatumumab is FDA-approved in combination with chlorambucil for the treatment of CLL patients for whom fludarabine-based therapy is considered inappropriate [26] and those who are refractory to fludarabine and alemtuzumab [27]. The most common SE were IRRs and infections that were grade I/II events. Additionally, in combination with pentostatin and cyclophosphamide it compared favorably to historical controls treated with fludarabine, cyclophosphamide and rituximab (FCR) [28-30]. When combined with fludarabine and cyclophosphamide (O-FC) the results were comparable to what has been reported with other similar chemoimmunotherapy (CIT) regimens [31]. Trials directly comparing rituximab-based CIT to ofatumumab-based CIT in CLL are currently ongoing.

Ofatumumab has also been tested in indolent and aggressive NHL either as single agent or in combination with chemotherapy [32-35]. It appears that while the

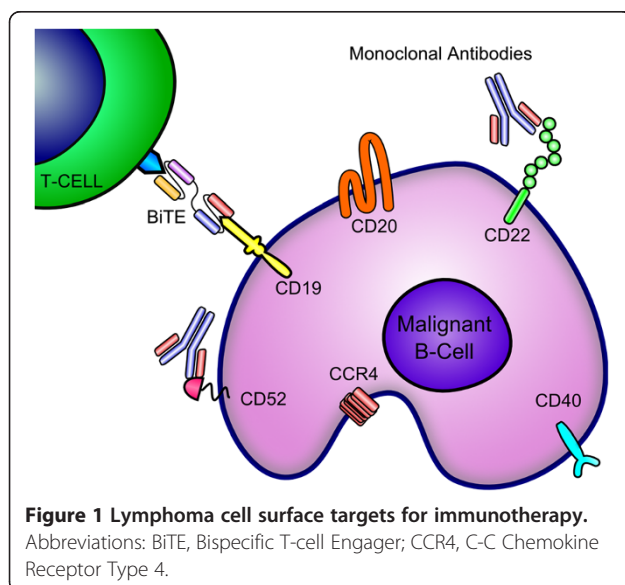


Table 1 Anti-CD20 monoclonal antibodies currently approved or being investigated in clinical trials for B-cell lymphomas

mAb	Type of CD20 antibody*	Generation**	Structure	Mechanism of action (ADCC/CDC/PCD)	Comparison to rituximab	Indications tested	Phase of development	References
Rituximab	I	1	IgG1 Human Mouse chimeric	++/++/+	-	NHL/CL/DLBCL	FDA approved for NHL, CLL, DLBCL	[8-11]
Obinutuzumab (GA101; Gazyva™)	II	3	Murine bly-I derived humanized IgG1	++++/-/++++	Superior PCD/ADCC; no CDC	CLL/NHL	Phase 2/3 Approved in 2013 for untreated CLL in combination with Clb	[12-20]
Ofatumumab (HuMax-CD20; Arzerra®)	I	1	Fully human IgG1	+++/++++/++	Superior CDC, decreased PCD	CLL/NHL	Phase 2/3 Approved for untreated CLL in combination with Clb & refractory CLL	[21-35]
Veltuzumab	I	2	Humanized IgG1	++/++/+	Longer "off-rate", more avid CD20 binding. can be given subcutaneously	R/R NHL/CLL	Phase 1/2	[36-38]
Ocrelizumab	I	2	Humanized fusion IgG1	+++/+/+	Enhanced binding to FCγRIIa	NHL	Phase 3	[39]
LY2469298	I	3	Modified Fc region human IgG1	+++/++/++	Enhanced Fc binding; superior ADCC	NHL	Phase 1/2	[40]
BM-ca	I/II***	3	Humanized IgG	++++/+++/++++	Different epitope, superior ACDD, CDC and PCD	NHL	Phase 1	[42-44]

ADCC: Antibody dependent cellular cytotoxicity; CDC: Complement dependent cytotoxicity; Clb: chlorambucil; CLL: Chronic lymphocytic leukemia; DLBCL: Diffuse large B cell lymphoma; PCD: programmed cell death; mAb: Monoclonal antibody; Moa: Mechanism of action; NHL: Non-Hodgkin lymphoma.

*Type of mAb: compared to a type I mAb, a type 2 mAb does not evoke a complement response, however, may have increased PCD/ADCC.

**Generations of mAb.

1st generation: originally approved mAb against a clinically validated target 2nd generation: follow-up antibodies with improved variable domains that target the same epitopes with higher or lower affinity, or have different antibody formats, e.g. Pegylation and Fc-fusion proteins. 3rd generation: target different epitopes or trigger other mechanisms of action; often engineered for improved Fc-associated immune functions or half-life.

***BM-ca demonstrates properties of both Types I and II mAbs.

toxicities are similar to rituximab-based therapy the efficacy compares favorably.

Veltuzumab

Veltuzumab is a humanized anti-CD20 mAb that was constructed on the framework regions of the anti-CD22 mAb epratuzumab (see below). Structurally it differs from rituximab by only one amino acid. It has a significantly higher potency than rituximab in preclinical models, exhibiting a greater CDC and possessing a slower off-rate resulting in longer cell surface retention [36].

In a phase 1/2 study of 82 patients with refractory NHL, the drug was well tolerated, with no serious side effects. In patients with follicular lymphoma (FL) who had prior exposure to rituximab, veltuzumab was associated with an ORR of 44% and a CR rate of 27% [37]. RR were higher in rituximab-naïve patients (ORR 57%; CR/CRu (unconfirmed CR) rate 43%). Among non-follicular histologies, the ORR was 35%, with 27% achieving a CR. Although developed for IV use, veltuzumab has been shown to have similar efficacy as a SQ injection [38].

Ocrelizumab

Ocrelizumab is another humanized IgG1 anti-CD20 mAb. It differs from rituximab at the complementarity-determining regions, and is derived from a different allotype of human Fc. Like rituximab, ocrelizumab works through ADCC, CDC and apoptosis, although it has been shown to have better ADCC and lower CDC. Importantly, ocrelizumab has better binding to the low-affinity variants of the Fcγ receptor IIIa. Patients with the high affinity variant of FcγRIIIa have shown superior outcomes following rituximab compared with patients with the low affinity variant; thus it is hypothesized that ocrelizumab may have better clinical efficacy [9,11]. In a phase 1/2 trial, ocrelizumab was tested as single agent in patients with relapsed/refractory (R/R) FL [39]. Overall, the drug was well tolerated, (a similar safety profile as rituximab monotherapy) with an ORR of 38%, which is comparable to rituximab re-treatment.

LY2469298

LY2469298 (AME-133v) is a humanized IgG1 anti-CD20 mAb with a 13–20 fold higher affinity to CD20 than rituximab. A limited number of amino acid substitutions in the Fc region of the mAb result in enhanced ADCC (6-fold more potent *in vitro*) but with 50% less CDC compared with rituximab [40]. and potentially more efficacy than rituximab in those patients who were carriers of the low affinity FcγRIIIa allele. In a phase 1 trial of patients with previously treated FL who were FcγRIIIa carriers, the drug was well tolerated; responses (PR or CR) were observed in 22% of patients [41]. In a Japanese phase 1 study the ORR was 50% in

previously rituximab-treated FL patients carrying the FcγRIIIa variant [40].

BM-ca

BM-ca is a novel mAb targeting CD20 that recognizes a unique epitope as compared to rituximab, and was stronger than rituximab in ADCC and direct anti-cell proliferation assays [42,43]. In phase I studies, it was shown to be well tolerated with promising preliminary anti-lymphoma activity in B cell NHL (2 CR and 2 PR out of 12 patients) [44].

Targeting CD22

CD22 is a sialic acid-binding immunoglobulin (Ig)-like lectin involved in cellular adhesion, regulation of B-cell homing and modulation of B-cell activation [45]. It is expressed by pre-B, mature, and normal B-cells as well as in many malignant B-lymphocytes [46]. During early B-cell development it is found in the cytoplasm, then on the cell surface of mature B-cells [47]. Quickly internalized when bound by mAbs, it is then re-expressed on the cell membrane after modulation, a property not found in CD20 [48,49]. This, and the role CD22 plays in B-cell signaling, makes it an ideal target in lymphoid B-cell malignancies (Table 2).

Epratuzumab

The mAb targeting CD22 furthest along in development is the IgG1 humanized mAb, epratuzumab. The actual mechanism of epratuzumab has not been formally explored, but it is reasonable to assume that it includes ADCC, CDC and direct cytotoxicity [50]. Single agent epratuzumab has been studied in indolent as well as aggressive NHL. In an early phase 1/2 trial, epratuzumab was well tolerated and showed the best response in FL (ORR 24%) [51], while 15% of patients with DLBCL showed a response [52]. The drug was very well tolerated, with no dose-limiting toxicity.

Epratuzumab plus rituximab has been tested in R/R NHL and compared to single agent use, resulted in a higher ORR of 47% with the highest RR again in FL (64%) [53]. Another multicenter trial showed an ORR of 54% for patients with FL and 57% for small lymphocytic lymphoma (SLL) [54]. The combination of epratuzumab with rituximab was also studied in patients with newly diagnosed FL, and the RR of was 88.2% [55].

In aggressive lymphomas, when combined with R-CHOP for patients with DLBCL, the ORR was 96% [50], which compares favorably with studies using R-CHOP for upfront treatment. Of note, approximately 15% of patients with DLBCL do not express CD22; in this trial CD22-negative patients were ineligible [56].

Targeting CD19

CD 19 is a transmembrane glycoprotein that is expressed by normal and malignant B-cells from early

Table 2 Monoclonal antibodies directed against non-CD20 surface epitopes

mAB	Target	Structure	Unique properties	Indication tested	Phase of development	References
Epratuzumab	CD22	Humanized IgG1	Enhanced ADCC, no PCD	NHL/DLBCL	Phase 1/2	[50-56]
Medi 551	CD19	Afucosylated humanized IgG1	Enhanced ADCC, no CDC	NHL/DLBCL/ALL	Phase 1/2	[60,61]
Lucatumumab	CD40	Humanized IgG1	Also being tested in myeloma. ADCC	NHL/CLL/HL/MZL/MALT	Phase 1/2	[64,69,70]
Dacetuzumab	CD40	Humanized IgG1	Partial agonist. Enhanced ADCC/CDC/PCD	DLBCL	Phase 1	[71-76]
Alemtuzumab (Campath®)	CD 52	Humanized IgG1	Enhanced ADCC/CDC/PCD	CLL/T-Cell NHL Approved for del17p CLL	Phase 2/3	[81-89]
Mogalizumab	CCR4	Afucosylated humanized IgG1	Enhanced ADCC	PTCL/CTCL	Phase 1/2	[91-98]
Pidilizumab (CT-011)	PD-1*	Humanized IgG1 Kappa recombinant	Reverses T-cell anergy	NHL/DLBCL	Phase 1/2	[101-113]
Blinatumomab	BiTE (CD3/CD19)	Single-chain bispecific antibody construct with variable regions of two antibodies.	Bispecific T-cell Engager	DLBCL/ALL	Phase 2/3	[118-120]

ADCC: Antibody dependent cellular cytotoxicity; ALL: Acute lymphoblastic leukemia; BiTE: Bispecific T-cell Engager; CDC: Complement dependent cytotoxicity; CLL: Chronic lymphocytic leukemia; CTCL: Cutaneous T Cell Lymphoma; DLBCL: Diffuse large B cell lymphoma; HL: Hodgkin lymphoma; mAB: Monoclonal antibody; MALT: Mucosa associated Lymphoid tissue lymphoma; MoA: Mechanism of action; MZL: Marginal zone lymphoma; NHL: Non Hodgkin lymphoma; PCD: programmed cell death; PTCL: Peripheral T Cell Lymphoma.

*PD1 is mainly expressed on regulatory T cell surface, while its ligand PDL-1 is often expressed on malignant cells. Stimulation of this pathway results in immune energy towards malignant cells.

pre-B maturation to terminal plasma cell differentiation [57,58]. It is found on a wide range of B-cell malignancies, including those arising from early B-cell precursors, which cannot be effectively targeted with CD20 Abs [57]. Like CD22, but unlike CD20, it is also efficiently internalized. Its function encompasses regulating cell signaling thresholds and serving as a co-stimulatory molecule for B-cell receptor (BCR) signaling [59].

MEDI-551

MEDI-551 is an afucosylated anti-human CD19 mAb with in vitro and in vivo activity against lymphoma [60]. Results from a phase 1 trial of single agent MEDI-551 in R/R B-cell malignancies show an acceptable safety profile and ORR of 24%, 24%, and 31% in heavily pre-treated CLL, DLBCL and FL patients respectively [61]. Phase 2 trials in DLBCL patients are currently recruiting.

Targeting CD40

CD40 is a type-1 transmembrane protein and expressed in more than 90% of B-cell malignancies [62-65]. It is thought to have a greater range of expression than CD20 and is present in the pro-B to the plasma cell phase of B-cell development. Studies have showed that activation of CD40 results in enhanced survival of neoplastic B-cells, thus targeting CD40 with mAbs could help block this [64]. Additionally, CD40 signaling impacts resistance mechanisms to chemotherapy. In CLL, CD40 activation triggers

phosphorylation of ERK1/2 and IKK, and up-regulates Mcl-1 and Bcl-xl, which creates a malignant phenotype [64]. Similar mechanisms have been shown in Hodgkin lymphoma (HL) [66]. The prognostic significance of CD40 expression on lymphoma cells [67] and/or the bone marrow stromal cells [68] as well as the impact of CD40-related BCR signaling are areas of ongoing investigation.

Lucatumumab

Lucatumumab, a human anti-CD40 mAb, was shown to cause more B-cell lysis than rituximab in preclinical models [64]. In a phase 1 trial in CLL, stable disease (SD) was observed in 17 of 26 patients [69]. In another phase 1/2 trial of 111 patients with R/R NHL or HL, the drug was well tolerated with ORR of 33% in FL patients and 11% in those with DLBCL and marginal zone lymphoma (MZ) [70].

Dacetuzumab

Dacetuzumab is another CD40 mAb that acts as a partial agonist at the CD40 receptor [71]. It works through direct signal transduction, ADCC and ADP [71]. In lymphoma xenograft models it demonstrates synergy with rituximab and gemcitabine [72]. Dacetuzumab monotherapy appears to be well tolerated and without major adverse events (AEs) [73,74]. When combined with rituximab and gemcitabine for elderly patients with R/R DLBCL (n = 33) 47% achieved a response (20% CR) [75]. These results are

comparable to the efficacy of R-GemOx in the 2nd-line setting for DLBCL [76].

Targeting CD 52

The CD52 antigen is a cell surface glycoprotein of unknown function that is expressed on both B- and T-lymphocytes [77]. It is recognized by a humanized mAb named alemtuzumab, which works by complement-induced cell lysis, direct cell-mediated cytotoxicity and induction of apoptosis [78-80].

Alemtuzumab

Alemtuzumab (Campath®) first received accelerated approval in the U.S. in 2001 for CLL patients who had failed fludarabine. Then, based on the results of a trial comparing alemtuzumab to chlorambucil as 1st-line treatment, it received full approval in 2007 in the U.S. and 2008 in Europe [81,82]. The subgroups that appeared to benefit the most included patients with 17p deletion, bone marrow infiltration and refractory autoimmune cytopenia [83]. In T-cell lymphomas (TCL), alemtuzumab has shown efficacy as a single agent and in combination with conventional chemotherapy in R/R or untreated peripheral TCL (PTCL) as well as in advanced cutaneous TCL (CTCL) [84-86].

More recent trials looked at improving the safety profile of alemtuzumab, and its effectiveness in combination with other regimens. Previous trials with alemtuzumab had been associated with significant toxicity, stemming mainly from profound immunosuppression. Lower doses of alemtuzumab showed similar effectiveness with a better safety profile [87]. Subcutaneous alemtuzumab in combination with rituximab in fludarabine-refractory CLL patients was also well-tolerated and allowed patients to achieve adequate cytoreduction prior to stem cell transplantation [88]. A recent phase 2 trial tested alemtuzumab consolidation after CHO(E) P-14 in 41 patients with untreated PTCL [89]. While the combination was quite effective (59% of patients achieved a CR), it was associated with significant treatment-related adverse events (the main grade 3/4 toxicities were infections and neutropenia, including one potentially treatment-related death). Therefore, although alemtuzumab is an active drug in lymphomas, its use has been limited by its toxicities.

Targeting CCR4

The chemokine receptor CCR4 is expressed on a subset of Type 2 helper (T_H) and regulatory T-cells (Treg) and is involved in lymphocyte trafficking. Many adult PTCL express both CCR4 and its ligands. CCR4 (+) T-cell lymphomas are associated with a poorer prognosis, possibly because of downregulation of T-cell mediated antitumor host response [90]. Mogamulizumab

(KW-0761) is a mAb that targets CCR4(+) tumor cells by ADCC and downregulates Treg trafficking to the tumor microenvironment.

Mogamulizumab

Preliminary data shows responses in a subset of T-cell lymphomas with traditionally poor prognosis. In a phase 1 trial of 16 patients with R/R CCR4(+) mature T-cell lymphomas, 31% (n = 5) achieved a response (CR: 13%; n = 2) [91]. Results of a phase 2 trial in 28 patients with R/R CCR4(+) adult T-cell leukemia/lymphoma (ATLL) showed an ORR of 50%, a median PFS of 5.2 months and OS of 13.7 months, which lead to its approval in Japan for this indication [92]. A US trial of single agent mogamulizumab in patients with both CCR4(+) and CCR4(-) R/R CTCL (n = 38) demonstrated an ORR of 35% [93]. In a consecutive study in patients with CCR4(+) PTCL or CTCL (n = 38), the ORR was 35% (n = 13) and 14% (n = 5) showed a CR with a median PFS of 3 months [94]. Infusion reactions were common (59%), but only 2% were grade III or higher. Skin and subcutaneous tissue disorders occurred in 50% of patients with 12% being grade III or higher. Viral reactivation, lymphopenia, and neutropenia were other notable AEs.

While CCR4 mAbs have primarily been studied in T-cell NHL, it has been hypothesized that influencing the tumor microenvironment by halting Treg trafficking through CCR4 blockade may be broadly beneficial in many cancers [95-98].

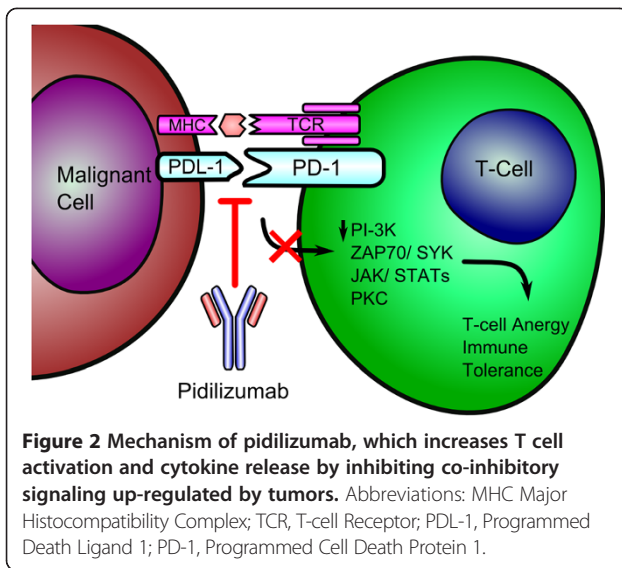
mAbs unblocking immune checkpoints

While most mAbs in this category only indirectly target the lymphoma surface, they are included in this review as they exemplify the concept of active immunotherapy.

PD-1/PD-L1 pathway

Programmed cell death 1 (PD-1) is a negative costimulatory receptor critical for the suppression of T-cell activation. It is part of an immunoglobulin superfamily (B7) and expressed on T- and B-lymphocytes, natural killer (NK) cells, monocytes, and dendritic cells [99]. There are two PD-1 ligands: PD-1 ligand 1 (PD-L1/B7-H1) and PD-L2/B7-DC. The expression of PD-1 is significantly increased on CD4+ and CD8+ T cells following chronic exposure and stimulation with antigens related to infection or tumors [100].

On binding to its ligand, PD-1 generates a TCR-PD-1 microcluster [101], decreasing the phosphorylation of the multiple downstream signaling molecules (including Zap70, PI3K, and PKC-θ [102]) by recruiting SHP2, which in turn results in the attenuation of T-cell activation and so called "T-cell exhaustion". Blockade of the PDL-1/PD-L2 and PD-1 interaction was shown to render previously anergic T-cells responsive to antigen [103] (Figure 2).



Infiltration of anergic PD-1 positive T-cells has been demonstrated in lymphomas [104]. PD-L1 expression can be shown in a variety of B- and T-cell lymphomas [105-108]. Additionally, expression of PD-1 peripheral blood CD4+ and CD8+ lymphocytes has been described as markedly elevated in patients with lymphomas, including T-cell NHL, especially at the time of relapse [109].

Pidilizumab

Pidilizumab (formerly CT-011) is a humanized IgG-1κ recombinant mAb that targets PD1. A phase 1 trial conducted by Berger et al. [110] enrolled 17 patients with advanced hematological malignancies including acute myeloid leukemia (AML), CLL, NHL, HL and multiple myeloma (MM). It concluded that CT-011 was safe and well tolerated, with clinical benefit observed in 33%.

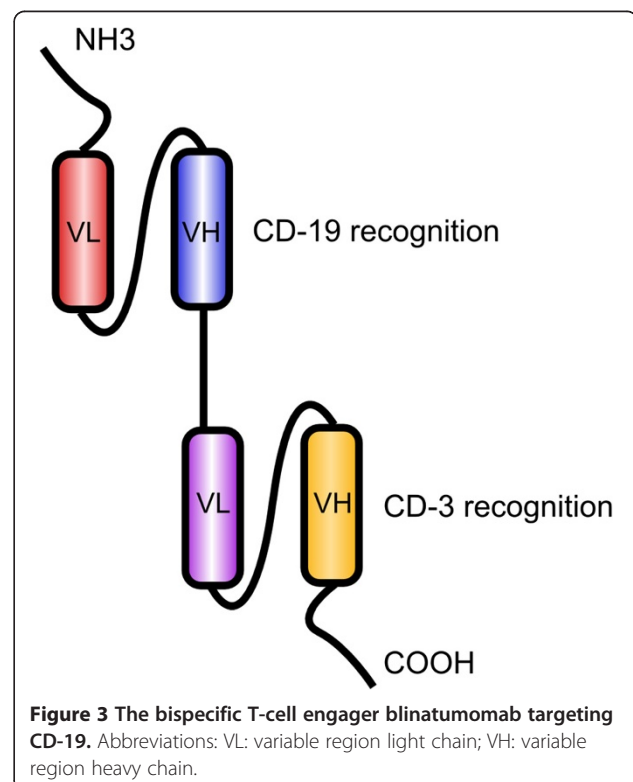
This was followed by a phase 2 international trial studying patients with DLBCL, primary mediastinal B-cell NHL or transformed indolent NHL, undergoing autologous stem cell transplant (ASCT) [111]. Patients received pidilizumab for three cycles, beginning 30 to 90 days after their ASCT. Among the 66 eligible patients, 16-month PFS was 72% while 16-month OS was 85%. No severe unexpected toxicities, significant autoimmune toxicities or treatment-related mortality was observed.

Another phase 2 study explored the efficacy of PD-1 blockade in combination with rituximab in relapsed rituximab-sensitive FL (n = 30) [112]. Pidilizumab was dosed every 4 weeks times four (additional doses for patients with SD or better) with weekly rituximab infusions times 4. Of 29 patients evaluable for activity, 19 (66%) achieved an objective response. CR was identified in 15 (52%) and PR in 4 (14%) patients; median PFS was 18.8 months. The combination was well tolerated, with no severe autoimmune or treatment-related AEs.

Other mAbs targeting PD-1 or PD-L1 directly are under investigation. While it appears that PD-L1 expression on tumor cells is a necessary prerequisite [113], further research is needed to identify subsets of patients who most likely benefit from blockade of this axis. Potential biomarkers of response are tumor infiltrating lymphocytes, certain T-effector cell gene signatures or increased expression of PDL-1 in circulatory leucocytes [112].

Like PD-1, CTLA-4 is a negative regulator of T-cell activation that serves to dampen antitumor immune responses. Its ligand, B7-1, is found on APCs, B-cells and certain tumor cells. Blockade of CTLA-4 has yielded increased T-cell mediated anti-tumor responses, most notably in metastatic melanoma [114]. Ipilimumab (Yervoy®), a CTLA-4 mAb, has been approved for treatment of metastatic melanoma. In a phase 1 trial ipilimumab was used to treat 18 patients with R/R DLBCL [115]. Responses were seen in 2 patients (1 with a CR lasting >31 months) and the drug was generally well tolerated, with diarrhea and fatigue as the only severe AE. Larger studies are ongoing to further explore the use of CTLA-4 blockade in hematological malignancies.

Unusual toxicities are a concern when unblocking immune checkpoints. Even though preliminary studies indicate that pidilizumab is well tolerated, studies involving other PD-1 inhibitors (e.g. nivolumab) and CTLA-4 mAbs have reported a myriad of AEs, including 3 treatment-related deaths reported with the use of nivolumab due



to pneumonitis. Common AEs include autoimmune disorders such as endocrinopathies (e.g. hypophysitis, hypothyroidism), skin disorders (e.g. rash, vitiligo), pneumonitis and colitis [116].

Bispecific T-cell engagers (BiTE)

BiTE molecules are engineered to contain the variable domains of two antibodies joined together: one antibody binds CD19 and one binds the CD3 antigen of T-cells. When bound to a CD3/CD19 complex, a BiTE brings the two cells in close proximity and thus activates T-cells to destroy the tumor cell via perforin-mediated apoptosis (Figure 3) [117].

Blinatumomab

Blinatumomab is a BiTE molecule that has been the forerunner of BiTE molecule testing and stands for B-lineage anti-tumoral mAb. Promising activity has been demonstrated in patients with B-lineage ALL, specifically in MRD eradication [118-120].

The first phase 1 trial of blinatumomab as single agent given as continuous intravenous infusion in NHL began in 2004. The initial cohort of 38 patients had R/R B-cell NHL and received a continuous infusion at different doses for 4–8 weeks. Eleven patients (28.9%) had measurable response after treatment; 4 (11%) achieved a CR and 7 (18%) a PR [121]. The trial established the maximum tolerated dose (MTD) of 60 $\mu\text{g}/\text{m}^2/\text{d}$. By 2011, the study had enrolled 62 patients. Of the 22 patients who received the MTD, 18 (82%) showed an objective response and duration of response lasted up to 32 months.

Because of its clinical benefits and tolerability in indolent lymphomas, the study was expanded to include patients with DLBCL [122]. Twelve patients were enrolled with 9 patients evaluable for response. Five out of 9 patients (56%) showed responses, the longest lasting 428 days. This set the stage for a phase 2 trial of blinatumomab in R/R DLBCL. Of the 11 patients recruited so far, 7 were evaluable for response: 3 patients experienced progression of disease, while 4 responded resulting in an ORR of 57% [120].

The most common clinical AEs regardless of grade included pyrexia, fatigue, headache, diarrhea, and weight increase. The dose-limiting factor was CNS related toxicity ranging from tremor, disorientation, speech disorder, cerebellar symptoms, to seizures.

While the results are intriguing, the optimal setting for blinatumomab in lymphomas remains to be defined. Multiple trials studying blinatumomab in B-cell malignancies are ongoing, the focus being B-lineage ALL.

Conclusion

Tremendous advances have been made in targeting the lymphoma surface. Initially only seen as a way to more

precisely target tumors, actively harnessing the ability of the patients' own immune system in the fight against cancer is revolutionizing therapy. This involves rethinking current treatment paradigms in terms of response assessment [123] and side effect management. Unleashing the immune system can result in never-before encountered side effects. While results are promising, one remaining challenge is to identify which patient will respond to immunotherapy. Nevertheless, next to the classical modalities surgery, radiation, chemotherapy, and more recently molecularly targeted therapies, many regard immunotherapy now as the fifth pillar of oncology [124].

Abbreviations

mAB: Monoclonal antibodies; NHL: Non Hodgkin's lymphoma; ADCC: Antibody dependent cellular cytotoxicity; ADC: Antibody drug conjugates; RIT: Radioimmunotherapy; CaRs: Chimeric antigen receptors; BiTEs: Bispecific t-cell engagers; CDC: Complement dependent cytotoxicity; RR: Response rates; PFS: Progression free survival; CR: Complete response; ORR: Overall response rate; DLBCL: Diffuse large b-cell lymphoma; MCL: Mantle cell lymphoma; ADP: Antibody dependent phagocytosis; FCR: Fludarabine + cyclophosphamide + rituximab; O-FC: Fludarabine + cyclophosphamide; CIT: Chemoimmunotherapy; FL: Follicular lymphoma; R/R: Relapsed/refractory; Ig: Immunoglobulin; SLL: Small lymphocytic lymphoma; BCR: B-cell receptor; HL: Hodgkin's lymphoma; SD: Stable disease; MZ: Marginal zone lymphoma; TCL: T cell lymphomas; PTCL: Peripheral t cell lymphoma; TCL (CTCL): Advanced cutaneous; Treg: Regulatory t cells; ATLL: Adult T cell leukemia/lymphoma; PD-1: Programmed cell death 1; NK: Natural killer; AML: Acute myeloid leukemia; MM: Multiple myeloma; ASCT: Autologous stem cell transplant.

Competing interests

Dr. Stefan Barta is part of the speakers bureau of Onyx, Celgene, and Janssen/Pharmacylics. He is on the advisory board of Seattle genetics and gets research funding from Otsuka.

Authors' contributions

All authors helped to draft and approved the manuscript.

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Received: 4 June 2014 Accepted: 29 July 2014

Published online: 09 September 2014

References

- McLaughlin P, Grillo-Lopez AJ, Link BK, Levy R, Czuczman MS, Williams ME, Heyman MR, Bence-Bruckler I, White CA, Cabanillas F, Jain V, Ho AD, Lister J, Wey K, Shen D, Dallaire BK: **Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program.** *J Clin Oncol* 1998, **16**:2825–2833.
- Cheson BD, Leonard JP: **Monoclonal antibody therapy for B-cell non-Hodgkin's lymphoma.** *N Engl J Med* 2008, **359**:613–626.
- Brody J, Kohrt H, Marabelle A, Levy R: **Active and Passive Immunotherapy for Lymphoma: Proving Principles and Improving Results.** *J Clin Oncol* 2011, **29**:1864–1875.
- Brentjens RJ, Curran KJ: **Novel cellular therapies for leukemia: CAR-modified T cells targeted to the CD19 antigen.** *Hematology Am Soc Hematol Educ Program* 2012, **2012**:143–151.
- Feld J, Barta SK, Schinke C, Braunschweig I, Zhou Y, Verma AK: **Linked-In: Design and Efficacy of Antibody Drug Conjugates in Oncology.** *Oncotarget* 2013, **4**(3):397–412.

6. Tomblyn M: Radioimmunotherapy for B-cell non-hodgkin lymphomas. *Cancer Control* 2012, **19**:196–203.
7. Kochenderfer JN, Rosenberg SA: Treating B-cell cancer with T cells expressing anti-CD19 chimeric antigen receptors. *Nat Rev Clin Oncol* 2013, **10**:267–276.
8. Beers SA, Chan CH, French RR, Cragg MS, Glennie MJ: CD20 as a target for therapeutic type I and II monoclonal antibodies. *Semin Hematol* 2010, **47**:107–114.
9. Cartron G, Dacheux L, Salles G, Solal-Celigny P, Bardos P, Colombat P, Watier H: Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcγRIIIa gene. *Blood* 2002, **99**:754–758.
10. Ghielmini M, Rufibach K, Salles G, Leoncini-Frascini L, Leger-Falandry C, Cogliatti S, Fey M, Martinelli G, Stahel R, Lohri A, Ketterer N, Wernli M, Cerny T, Schmitz SF: Single agent rituximab in patients with follicular or mantle cell lymphoma: clinical and biological factors that are predictive of response and event-free survival as well as the effect of rituximab on the immune system: a study of the Swiss Group for Clinical Cancer Research (SAKK). *Ann Oncol* 2005, **16**:1675–1682.
11. Weng WK, Levy R: Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. *J Clin Oncol* 2003, **21**:3940–3947.
12. Alduaij W, Ivanov A, Honeychurch J, Cheadle EJ, Potluri S, Lim SH, Shimada K, Chan CH, Tutt A, Beers SA, Glennie MJ, Cragg MS, Illidge TM: Novel type II anti-CD20 monoclonal antibody (GA101) evokes homotypic adhesion and actin-dependent, lysosome-mediated cell death in B-cell malignancies. *Blood* 2011, **117**:4519–4529.
13. Chan HT, Hughes D, French RR, Tutt AL, Walshe CA, Teeling JL, Glennie MJ, Cragg MS: CD20-induced lymphoma cell death is independent of both caspases and its redistribution into triton X-100 insoluble membrane rafts. *Cancer Res* 2003, **63**:5480–5489.
14. Cragg MS, Glennie MJ: Antibody specificity controls in vivo effector mechanisms of anti-CD20 reagents. *Blood* 2004, **103**:2738–2743.
15. Glennie MJ, French RR, Cragg MS, Taylor RP: Mechanisms of killing by anti-CD20 monoclonal antibodies. *Mol Immunol* 2007, **44**:3823–3837.
16. Golay J, Da Roit F, Bologna L, Ferrara C, Leusen JH, Rambaldi A, Klein C, Introna M: Glycoengineered CD20 antibody obinutuzumab activates neutrophils and mediates phagocytosis through CD16B more efficiently than rituximab. *Blood* 2013, **122**:3482–3491.
17. Mossner E, Brunker P, Moser S, Mossner E, Brunker P, Moser S, Puntener U, Schmidt C, Herter S, Grau R, Gerdes C, Nopora A, van Puijenbroek E, Ferrara C, Sondermann P, Jager C, Strein P, Fertig G, Friess T, Schull C, Bauer S, Dal Porto J, Del Nagro C, Dabbagh K, Dyer MJ, Poppema S, Klein C, Umana P: Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. *Blood* 2010, **115**:4393–4402.
18. Cartron G, Watier H, Golay J, Solal-Celigny P: From the bench to the bedside: ways to improve rituximab efficacy. *Blood* 2004, **104**:2635–2642.
19. Wang SY, Racila E, Taylor RP, Weiner GJ: NK-cell activation and antibody-dependent cellular cytotoxicity induced by rituximab-coated target cells is inhibited by the C3b component of complement. *Blood* 2008, **111**:1456–1463.
20. Beers SA, French RR, Chan HT, Lim SH, Jarrett TC, Vidal RM, Wijayaweera SS, Dixon SV, Kim H, Cox KL, Kerr JP, Johnston DA, Johnson PW, Verbeeck JS, Glennie MJ, Cragg MS: Antigenic modulation limits the efficacy of anti-CD20 antibodies: implications for antibody selection. *Blood* 2010, **115**:5191–5201.
21. Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner CM, Chagorova T, de la Serna J, Dilhuydy MS, Illmer T, Opat S, Owen CJ, Samoylova O, Kreuzer KA, Stilgenbauer S, Dohner H, Langerak AW, Ritgen M, Kneba M, Asikhanu E, Humphrey K, Wenger M, Hallek M: Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med* 2014, **370**:1101–1110.
22. Radford J, Davies A, Cartron G, Morschhauser F, Salles G, Marcus R, Wenger M, Lei G, Wassner-Fritsch E, Vitolo U: Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: results of the GAUDI study (BO21000). *Blood* 2013, **122**:1137–1143.
23. Morschhauser FA, Cartron G, Thieblemont C, Solal-Celigny P, Haioun C, Bouabdallah R, Feugier P, Bouabdallah K, Asikhanu E, Lei G, Wenger M, Wassner-Fritsch E, Salles GA: Obinutuzumab (GA101) monotherapy in relapsed/refractory diffuse large b-cell lymphoma or mantle-cell lymphoma: results from the phase II GAUGUIN study. *J Clin Oncol* 2013, **31**:2912–2919.
24. Teeling JL, Mackus WJ, Wiegman LJ, van den Brakel JH, Beers SA, French RR, van Meerten T, Ebeling S, Vink T, Slootstra JW, Parren PW, Glennie MJ, van de Winkel JG: The biological activity of human CD20 monoclonal antibodies is linked to unique epitopes on CD20. *J Immunol* 2006, **177**:362–371.
25. Rafiq S, Butchar JP, Cheney C, Mo X, Trotta R, Caligiuri M, Jarjoura D, Tridandapani S, Muthusamy N, Byrd JC: Comparative assessment of clinically utilized CD20-directed antibodies in chronic lymphocytic leukemia cells reveals divergent NK cell, monocyte, and macrophage properties. *J Immunol* 2013, **190**:2702–2711.
26. Wierda WG, Kipps TJ, Mayer J, Padmanabhan S, Chan GW, Gupta IV, Lisby S, Osterborg A: Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. *J Clin Oncol* 2010, **28**:1749–1755.
27. Wierda WG, Padmanabhan S, Chan GW, Gupta IV, Lisby S, Osterborg A: Ofatumumab is active in patients with fludarabine-refractory CLL irrespective of prior rituximab: results from the phase 2 international study. *Blood* 2011, **118**:5126–5129.
28. Shanafelt T, Lanasa MC, Call TG, Beaven AW, Leis JF, Laplant B, Bowen D, Conte M, Jelinek DF, Hanson CA, Kay NE, Zent CS: Ofatumumab-based chemoimmunotherapy is effective and well tolerated in patients with previously untreated chronic lymphocytic leukemia (CLL). *Cancer* 2013, **119**:3788–3796.
29. Kay NE, Geyer SM, Call TG, Shanafelt TD, Zent CS, Jelinek DF, Tschumper R, Bone ND, Dewald GW, Lin TS, Heerema NA, Smith L, Grever MR, Byrd JC: Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. *Blood* 2007, **109**:405–411.
30. Hallek M, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, Hensel M, Hopfinger G, Hess G, von Grunhagen U, Bergmann M, Catalano J, Zinzani PL, Caligaris-Cappio F, Seymour JF, Berrebi A, Jager U, Cazin B, Trnely M, Westermann A, Wendtner CM, Eichhorst BF, Staib P, Buhler A, Winkler D, Zenz T, Botzcher S, Ritgen M, Mendila M, Kneba M, Dohner H, et al: Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet* 2010, **376**:1164–1174.
31. Wierda WG, Kipps TJ, Durig J, Griskevicius L, Stilgenbauer S, Mayer J, Smolej L, Hess G, Griniute R, Hernandez-Ilizaliturri FJ, Padmanabhan S, Gorczyca M, Chang CN, Chan G, Gupta I, Nielsen TG, Russell CA: Chemoimmunotherapy with O-FC in previously untreated patients with chronic lymphocytic leukemia. *Blood* 2011, **117**:6450–6458.
32. Czuczman MS, Fayad L, Delwail V, Cartron G, Jacobsen E, Kuliczowski K, Link BK, Pinter-Brown L, Radford J, Hellmann A, Gallop-Evans E, DiRienzo CG, Goldstein N, Gupta I, Jewell RC, Lin TS, Lisby S, Schultz M, Russell CA, Hagenbeek A: Chemoimmunotherapy with ofatumumab in combination with CHOP in previously untreated follicular lymphoma. *Br J Haematol* 2012, **157**:438–445.
33. Czuczman MS, Fayad L, Delwail V, Cartron G, Jacobsen E, Kuliczowski K, Link BK, Pinter-Brown L, Radford J, Hellmann A, Gallop-Evans E, DiRienzo CG, Goldstein N, Gupta I, Jewell RC, Lin TS, Lisby S, Schultz M, Russell CA, Hagenbeek A: Ofatumumab monotherapy in rituximab-refractory follicular lymphoma: results from a multicenter study. *Blood* 2012, **119**:3698–3704.
34. Coiffier B, Radford J, Bosly A, Martinelli G, Barca G, Davies A, Decaudin D, Gallop-Evans E, Padmanabhan-Iyer S, Van Eygen K, Wu KL, Gupta IV, Lin TS, Goldstein N, Jewell RC, Winter P, Lisby S: A multicentre, phase II trial of ofatumumab monotherapy in relapsed/progressive diffuse large B-cell lymphoma. *Br J Haematol* 2013, **163**:334–342.
35. Matasar MJ, Czuczman MS, Rodriguez MA, Fennessy M, Shea TC, Spitzer G, Lossos IS, Khafan-Dabaja MA, Joyce R, Fayad L, Henkel K, Liao Q, Edvardsen K, Jewell RC, Fecteau D, Singh RP, Lisby S, Moskowitz CH: Ofatumumab in combination with ICE or DHAP chemotherapy in relapsed or refractory intermediate grade B-cell lymphoma. *Blood* 2013, **122**:499–506.
36. Goldenberg DM, Rossi EA, Stein R, Goldenberg DM, Rossi EA, Stein R, Cardillo TM, Czuczman MS, Hernandez-Ilizaliturri FJ, Hansen HJ, Chang CH: Properties and structure-function relationships of veltuzumab (hA20), a humanized anti-CD20 monoclonal antibody. *Blood* 2009, **113**:1062–1070.

37. Morschhauser F, Leonard JP, Fayad L, Coiffier B, Petillon MO, Coleman M, Schuster SJ, Dyer MJ, Horne H, Teoh N, Wegener WA, Goldenberg DM: **Humanized anti-CD20 antibody, veltuzumab, in refractory/recurrent non-Hodgkin's lymphoma: phase I/II results.** *J Clin Oncol* 2009, **27**:3346–3353.
38. Negrea GO, Elstrom R, Allen SL, Rai KR, Abbasi RM, Farber CM, Teoh N, Horne H, Wegener WA, Goldenberg DM: **Subcutaneous injections of low-dose veltuzumab (humanized anti-CD20 antibody) are safe and active in patients with indolent non-Hodgkin's lymphoma.** *Haematologica* 2011, **96**:567–573.
39. Morschhauser F, Marlton P, Vitolo U, Linden O, Seymour JF, Crump M, Coiffier B, Foa R, Wassner E, Burger HU, Brennan B, Mendila M: **Results of a phase I/II study of ocrelizumab, a fully humanized anti-CD20 mAb, in patients with relapsed/refractory follicular lymphoma.** *Ann Oncol* 2010, **21**:1870–1876.
40. Tobinai K, Ogura M, Kobayashi Y, Uchida T, Watanabe T, Oyama T, Maruyama D, Suzuki T, Mori M, Kasai M, Cronier D, Wooldridge JE, Koshiji M: **Phase I study of LY2469298, an Fc-engineered humanized anti-CD20 antibody, in patients with relapsed or refractory follicular lymphoma.** *Cancer Sci* 2011, **102**:432–438.
41. Forero-Torres A, de Vos S, Pohlman BL, Pashkevich M, Cronier DM, Dang NH, Carpenter SP, Allan BW, Nelson JG, Slapak CA, Smith MR, Link BK, Wooldridge JE, Ganjoo KN: **Results of a phase 1 study of AME-133v (LY2469298), an Fc-engineered humanized monoclonal anti-CD20 antibody, in FcgammaRIIIa-genotyped patients with previously treated follicular lymphoma.** *Clin Cancer Res* 2012, **18**:1395–1403.
42. Kobayashi H, Matsunaga Y, Uchiyama Y, Nagura K, Komatsu Y: **Novel humanized anti-CD20 antibody BM-ca binds to a unique epitope and exerts stronger cellular activity than others.** *Cancer Med* 2013, **2**:130–143.
43. Uchiyama S, Suzuki Y, Otake K, Yokoyama M, Ohta M, Aikawa S, Komatsu M, Sawada T, Kagami Y, Morishima Y, Fukui K: **Development of novel humanized anti-CD20 antibodies based on affinity constant and epitope.** *Cancer Sci* 2010, **101**:201–209.
44. Kensei Tobinai MO, Dai M, Tatsuya S, Yukio K, Toshiaki U, Suguru F, Takashi O, Tomoharu F, Yasuhiko K, National Cancer Center Hospital, Tokyo, Japan; Nagoya Daini Red Cross Hospital, Nagoya, Japan; BioMedics Japan Inc., Tokyo, Japan: **Phase I study of a novel humanized anti-CD20 antibody, BM-ca, in patients (pts) with relapsed or refractory indolent B cell non-Hodgkin lymphoma (B-NHL) pretreated with rituximab.** 2013 ASCO Annual Meeting; 2013. *J Clin Oncol* 2013, **31**(suppl; abstr 8551).
45. Daridon C, Blassfeld D, Reiter K, Mei HE, Giesecke C, Goldenberg DM, Hansen A, Hostmann A, Frolich D, Dorner T: **Epratuzumab targeting of CD22 affects adhesion molecule expression and migration of B-cells in systemic lupus erythematosus.** *Arthritis Res Ther* 2010, **12**:R204.
46. Kreitman RJ, Pastan I: **Antibody fusion proteins: anti-CD22 recombinant immunotoxin moxetumomab pasudotox.** *Clin Cancer Res* 2011, **17**:6398–6405.
47. Tedder TF, Tuscano J, Sato S, Kehrl JH: **CD22, a B lymphocyte-specific adhesion molecule that regulates antigen receptor signaling.** *Annu Rev Immunol* 1997, **15**:481–504.
48. Shan D, Press OW: **Constitutive endocytosis and degradation of CD22 by human B cells.** *J Immunol* 1995, **154**:4466–4475.
49. Shih LB, Lu HH, Xuan H, Goldenberg DM: **Internalization and intracellular processing of an anti-B-cell lymphoma monoclonal antibody, LL2.** *Int J Cancer* 1994, **56**:538–545.
50. Micallef IN, Maurer MJ, Wiseman GA, Nikcevich DA, Kurtin PJ, Cannon MW, Perez DG, Soori GS, Link BK, Habermann TM, Witzig TE: **Epratuzumab with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy in patients with previously untreated diffuse large B-cell lymphoma.** *Blood* 2011, **118**:4053–4061.
51. Leonard JP, Coleman M, Ketas JC, Chadburn A, Ely S, Furman RR, Wegener WA, Hansen HJ, Ziccardi H, Eschenberg M, Gayko U, Cesano A, Goldenberg DM: **Phase I/II trial of epratuzumab (humanized anti-CD22 antibody) in indolent non-Hodgkin's lymphoma.** *J Clin Oncol* 2003, **21**:3051–3059.
52. Leonard JP, Coleman M, Ketas JC, Chadburn A, Furman R, Schuster MW, Feldman EJ, Ashe M, Schuster SJ, Wegener WA, Hansen HJ, Ziccardi H, Eschenberg M, Gayko U, Fields SZ, Cesano A, Goldenberg DM: **Epratuzumab, a humanized anti-CD22 antibody, in aggressive non-Hodgkin's lymphoma: phase I/II clinical trial results.** *Clin Cancer Res* 2004, **10**:5327–5334.
53. Strauss SJ, Morschhauser F, Rech J, Repp R, Solal-Celigny P, Zinzani PL, Engert A, Coiffier B, Hoelzer DF, Wegener WA, Teoh NK, Goldenberg DM, Lister TA: **Multicenter phase II trial of immunotherapy with the humanized anti-CD22 antibody, epratuzumab, in combination with rituximab, in refractory or recurrent non-Hodgkin's lymphoma.** *J Clin Oncol* 2006, **24**:3880–3886.
54. Leonard JP, Schuster SJ, Emmanouilides C, Couture F, Teoh N, Wegener WA, Coleman M, Goldenberg DM: **Durable complete responses from therapy with combined epratuzumab and rituximab: final results from an international multicenter, phase 2 study in recurrent, indolent, non-Hodgkin lymphoma.** *Cancer* 2008, **113**:2714–2723.
55. Grant BW, Jung SH, Johnson JL, Kostakoglu L, Hsi E, Byrd JC, Jones J, Leonard JP, Martin SE, Cheson BD: **A phase 2 trial of extended induction epratuzumab and rituximab for previously untreated follicular lymphoma: CALGB 50701.** *Cancer* 2013, **119**:3797–3804.
56. Cesano A, Gayko U: **CD22 as a target of passive immunotherapy.** *Semin Oncol* 2003, **30**:253–257.
57. Carter RH, Myers R: **Germinal center structure and function: lessons from CD19.** *Semin Immunol* 2008, **20**:43–48.
58. Tedder TF: **CD19: a promising B cell target for rheumatoid arthritis.** *Nat Rev Rheumatol* 2009, **5**:572–577.
59. Tedder TF, Inaoki M, Sato S: **The CD19-CD21 complex regulates signal transduction thresholds governing humoral immunity and autoimmunity.** *Immunity* 1997, **6**:107–118.
60. Herbst R, Wang Y, Gallagher S, Mittereder N, Kuta E, Damschroder M, Woods R, Rowe DC, Cheng L, Cook K, Evans K, Sims GP, Pfarr DS, Bowen MA, Dall'Acqua W, Shlomchik M, Tedder TF, Kiener P, Jallal B, Wu H, Coyle AJ: **B-cell depletion in vitro and in vivo with an afucosylated anti-CD19 antibody.** *J Pharmacol Exp Ther* 2010, **335**:213–222.
61. Hamadani M, Fanale MA, Bello CM, Kipps TJ, Offner F, Verhoef G, Federico M, Gregory SA, Sonet A, Assouline S, Pérez De Oteyza J, Tomas JF, Cuneo A, Elgeiوشي N, Goswami T, Ibrahim R, Herbst R, Cheson BD: **Safety Profile and Clinical Response To MEDI-551, a Humanized Monoclonal Anti-CD19, In a Phase 1/2 Study In Adults With Relapsed Or Refractory Advanced B-Cell Malignancies.** *Blood* 2013, **122**:1810.
62. Carbone A, Ghoghini A, Zagonel V, Aldinucci D, Gattei V, Degani M, Improta S, Sorio R, Monfardini S, Pinto A: **The expression of CD26 and CD40 ligand is mutually exclusive in human T-cell non-Hodgkin's lymphomas/leukemias.** *Blood* 1995, **86**:4617–4626.
63. Gruss HJ, Dower SK: **Tumor necrosis factor ligand superfamily: involvement in the pathology of malignant lymphomas.** *Blood* 1995, **85**:3378–3404.
64. Luqman M, Klabunde S, Lin K, Georgakis GV, Cherukuri A, Holash J, Goldbeck C, Xu X, Kadel EE 3rd, Lee SH, Aukerman SL, Jallal B, Aziz N, Weng WK, Wierda W, O'Brien S, Younes A: **The antileukemia activity of a human anti-CD40 antagonist antibody, HCD122, on human chronic lymphocytic leukemia cells.** *Blood* 2008, **112**:711–720.
65. Uckun FM, Gajl-Peczalska K, Myers DE, Jaszcz W, Haissig S, Ledbetter JA: **Temporal association of CD40 antigen expression with discrete stages of human B-cell ontogeny and the efficacy of anti-CD40 immunotoxins against clonogenic B-lineage acute lymphoblastic leukemia as well as B-lineage non-Hodgkin's lymphoma cells.** *Blood* 1990, **76**:2449–2456.
66. Aldinucci D, Ghoghini A, Pinto A, Colombatti A, Carbone A: **The role of CD40/CD40L and interferon regulatory factor 4 in Hodgkin lymphoma microenvironment.** *Leuk Lymphoma* 2012, **53**:195–201.
67. Rydstrom K, Linderth J, Nyman H, Ehinger M, Joost P, Bendahl PO, Leppa S, Jerkeman M: **CD40 is a potential marker of favorable prognosis in patients with diffuse large B-cell lymphoma treated with immunochemotherapy.** *Leuk Lymphoma* 2010, **51**:1643–1648.
68. Franco G, Guarnotta C, Frossi B, Piccaluga PP, Boveri E, Gulino A, Fuligni F, Rigoni A, Porcasi R, Buffa S, Betto E, Florena AM, Franco V, Iannitto E, Arcaini L, Pileri SA, Pucillo C, Colombo MP, Sangaletti S, Tripodo C: **Bone marrow stroma CD40 expression correlates with inflammatory mast cell infiltration and disease progression in splenic marginal zone lymphoma.** *Blood* 2014, **123**:1836–1849.
69. Byrd JC, Kipps TJ, Flinn IW, Cooper M, Odenike O, Bendiske J, Rediske J, Bilic S, Dey J, Baeck J, O'Brien S: **Phase I study of the anti-CD40 humanized monoclonal antibody luatumumab (HCD122) in relapsed chronic lymphocytic leukemia.** *Leuk Lymphoma* 2012, **53**:2136–2142.
70. Fanale M, Assouline S, Kuruvilla J, Solal-Celigny P, Heo DS, Verhoef G, Corradini P, Abramson JS, Offner F, Engert A, Dyer MJ, Carreon D, Ewald B, Baeck J, Younes A, Freedman AS: **Phase IA/II, multicentre,**

- open-label study of the CD40 antagonistic monoclonal antibody lucatumumab in adult patients with advanced non-Hodgkin or Hodgkin lymphoma. *Br J Haematol* 2014, **164**:258–265.
71. Law CL, Gordon KA, Collier J, Klussman K, McEarchern JA, Cerveny CG, Mixan BJ, Lee WP, Lin Z, Valdez P, Wahl AF, Grewal IS: **Preclinical antilymphoma activity of a humanized anti-CD40 monoclonal antibody, SGN-40.** *Cancer Res* 2005, **65**:8331–8338.
72. Lewis TS, McCormick RS, Emmerton K, Lau JT, Yu SF, McEarchern JA, Grewal IS, Law CL: **Distinct apoptotic signaling characteristics of the anti-CD40 monoclonal antibody dacetuzumab and rituximab produce enhanced antitumor activity in non-Hodgkin lymphoma.** *Clin Cancer Res* 2011, **17**:4672–4681.
73. Advani R, Forero-Torres A, Furman RR, Rosenblatt JD, Younes A, Ren H, Harrop K, Whiting N, Drachman JG: **Phase I study of the humanized anti-CD40 monoclonal antibody dacetuzumab in refractory or recurrent non-Hodgkin's lymphoma.** *J Clin Oncol* 2009, **27**:4371–4377.
74. Furman RR, Forero-Torres A, Shustov A, Drachman JG: **A phase I study of dacetuzumab (SGN-40, a humanized anti-CD40 monoclonal antibody) in patients with chronic lymphocytic leukemia.** *Leuk Lymphoma* 2010, **51**:228–235.
75. Forero-Torres A, Bartlett N, Beaven A, Myint H, Nasta S, Northfelt DW, Whiting NC, Drachman JG, Lobuglio AF, Moskowicz CH: **Pilot study of dacetuzumab in combination with rituximab and gemcitabine for relapsed or refractory diffuse large B-cell lymphoma.** *Leuk Lymphoma* 2013, **54**:277–283.
76. Lopez A, Gutierrez A, Palacios A, Blancas I, Navarrete M, Morey M, Perello A, Alarcon J, Martinez J, Rodriguez J: **GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: a phase II study.** *Eur J Haematol* 2008, **80**:127–132.
77. Rossmann ED, Lundin J, Lenkei R, Mellstedt H, Osterborg A: **Variability in B-cell antigen expression: implications for the treatment of B-cell lymphomas and leukemias with monoclonal antibodies.** *Hematol J* 2001, **2**:300–306.
78. Mone AP, Cheney C, Banks AL, Tridandapani S, Mehter N, Guster S, Lin T, Eisenbeis CF, Young DC, Byrd JC: **Alemtuzumab induces caspase-independent cell death in human chronic lymphocytic leukemia cells through a lipid raft-dependent mechanism.** *Leukemia* 2006, **20**:272–279.
79. Riechmann L, Clark M, Waldmann H, Winter G: **Reshaping human antibodies for therapy.** *Nature* 1988, **332**:323–327.
80. Xia MQ, Hale G, Waldmann H: **Efficient complement-mediated lysis of cells containing the CAMPATH-1 (CDw52) antigen.** *Mol Immunol* 1993, **30**:1089–1096.
81. Demko S, Summers J, Keegan P, Pazdur R: **FDA drug approval summary: alemtuzumab as single-agent treatment for B-cell chronic lymphocytic leukemia.** *Oncologist* 2008, **13**:167–174.
82. Hillmen P, Skotnicki AB, Robak T, Jaksic B, Dmoszynska A, Wu J, Sirard C, Mayer J: **Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia.** *J Clin Oncol* 2007, **25**:5616–5623.
83. Osterborg A, Foa R, Bezars RF, Dearden C, Dyer MJ, Geisler C, Lin TS, Montillo M, van Oers MH, Wendtner CM, Rai KR: **Management guidelines for the use of alemtuzumab in chronic lymphocytic leukemia.** *Leukemia* 2009, **23**:1980–1988.
84. Enblad G, Hagberg H, Erlanson M, Lundin J, MacDonald AP, Repp R, Schetelig J, Seipelt G, Osterborg A: **A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas.** *Blood* 2004, **103**:2920–2924.
85. Gallamini A, Zaja F, Patti C, Billio A, Specchia MR, Tucci A, Levis A, Manna A, Secondo V, Rigacci L, Pinto A, Iannitto E, Zoli V, Torchio P, Pileri S, Tarella C: **Alemtuzumab (Campath-1H) and CHOP chemotherapy as first-line treatment of peripheral T-cell lymphoma: results of a GITIL (Gruppo Italiano Terapie Innovative nei Linfomi) prospective multicenter trial.** *Blood* 2007, **110**:2316–2323.
86. Lundin J, Hagberg H, Repp R, Cavallin-Stahl E, Freden S, Juliusson G, Rosenblad E, Tjonnfjord G, Wiklund T, Osterborg A: **Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome.** *Blood* 2003, **101**:4267–4272.
87. Gritti G, Reda G, Maura F, Picocchi A, Baldini L, Molica S, Neri A, Cortelezzi A: **Low dose alemtuzumab in patients with fludarabine-refractory chronic lymphocytic leukemia.** *Leuk Lymphoma* 2012, **53**:424–429.
88. Brown JR, Messmer B, Werner L, Davids MS, Mikler E, Supko JG, Fisher DC, LaCasce AS, Armand P, Jacobsen E, Dalton V, Tesar B, Fernandes SM, McDonough S, Ritz J, Rassenti L, Kipps TJ, Neuberg D, Freedman AS: **A phase I study of escalated dose subcutaneous alemtuzumab given weekly with rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma.** *Haematologica* 2013, **98**:964–970.
89. Binder C, Ziepert M, Pfreundschuh M, Dührsen U, Eimermacher H, Aldaoud A, Rosenwald A, Loeffler M, Schmitz N, Truemper L: **CHO(E)P-14 followed by alemtuzumab consolidation in untreated peripheral T cell lymphomas: final analysis of a prospective phase II trial.** *Ann Hematol* 2013, **92**:1521–1528.
90. Ishida T, Ueda R: **CCR4 as a novel molecular target for immunotherapy of cancer.** *Cancer Sci* 2006, **97**:1139–1146.
91. Yamamoto K, Utsunomiya A, Tobinai K, Tsukasaki K, Uike N, Uozumi K, Yamaguchi K, Yamada Y, Hanada S, Tamura K, Nakamura S, Inagaki H, Ohshima K, Kiyoi H, Ishida T, Matsushima K, Akinaga S, Ogura M, Tomonaga M, Ueda R: **Phase I study of KW-0761, a defucosylated humanized anti-CCR4 antibody, in relapsed patients with adult T-cell leukemia-lymphoma and peripheral T-cell lymphoma.** *J Clin Oncol* 2010, **28**:1591–1598.
92. Ishida T, Joh T, Uike N, Yamamoto K, Utsunomiya A, Yoshida S, Saburi Y, Miyamoto T, Takemoto S, Suzushima H, Tsukasaki K, Nosaka K, Fujiwara H, Ishitsuka K, Inagaki H, Ogura M, Akinaga S, Tomonaga M, Tobinai K, Ueda R: **Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study.** *J Clin Oncol* 2012, **30**:837–842.
93. Kim Y, Pinter-Brown L, Foss F, Sokol L, Jorgensen J, Spitalny G, Duvic M: **CO26. Results of a phase 1/2 study for KW-0761, a monoclonal antibody directed against CC chemokine receptor type 4 (CCR4), in CTCL patients.** *Melanoma Res* 2011, **21**:e15–e16.
94. Ogura M, Ishida T, Hatake K, Taniwaki M, Ando K, Tobinai K, Fujimoto K, Yamamoto K, Miyamoto T, Uike N, Tanimoto M, Tsukasaki K, Ishizawa K, Suzumiya J, Inagaki H, Tamura K, Akinaga S, Tomonaga M, Ueda R: **Multicenter phase II study of mogamulizumab (KW-0761), a defucosylated anti-cc chemokine receptor 4 antibody, in patients with relapsed peripheral T-cell lymphoma and cutaneous T-cell lymphoma.** *J Clin Oncol* 2014, **32**:1157–1163.
95. Curiel TJ, Coukos G, Zou L, Alvarez X, Cheng P, Mottram P, Evdemon-Hogan M, Conejo-Garcia JR, Zhang L, Burow M: **Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival.** *Nat Med* 2004, **10**:942–949.
96. Strauss L, Bergmann C, Szczepanski M, Gooding W, Johnson JT, Whiteside TL: **A unique subset of CD4+ CD25highFoxp3+ T cells secreting interleukin-10 and transforming growth factor-β1 mediates suppression in the tumor microenvironment.** *Clin Cancer Res* 2007, **13**:4345–4354.
97. Mizukami Y, Kono K, Kawaguchi Y, Akaike H, Kamimura K, Sugai H, Fujii H: **CCL17 and CCL22 chemokines within tumor microenvironment are related to accumulation of Foxp3+ regulatory T cells in gastric cancer.** *Int J Cancer* 2008, **122**:2286–2293.
98. Gobert M, Treilleux I, Bendriss-Vermare N, Bachelot T, Goddard-Leon S, Arfi V, Biota C, Doffin AC, Durand I, Olive D: **Regulatory T cells recruited through CCL22/CCR4 are selectively activated in lymphoid infiltrates surrounding primary breast tumors and lead to an adverse clinical outcome.** *Cancer Res* 2009, **69**:2000–2009.
99. Keir ME, Butte MJ, Freeman GJ, Sharpe AH: **PD-1 and its ligands in tolerance and immunity.** *Annu Rev Immunol* 2008, **26**:677–704.
100. Agata Y, Kawasaki A, Nishimura H, Ishida Y, Tsubata T, Yagita H, Honjo T: **Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes.** *Int Immunol* 1996, **8**:765–772.
101. Yokosuka T, Takamatsu M, Kobayashi-Imanishi W, Hashimoto-Tane A, Azuma M, Saito T: **Programmed cell death 1 forms negative costimulatory microclusters that directly inhibit T cell receptor signaling by recruiting phosphatase SHP2.** *J Exp Med* 2012, **209**:1201–1217.
102. Sheppard KA, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, Qiu Y, Jussif JM, Carter LL, Wood CR, Chaudhary D: **PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCθ.** *FEBS Lett* 2004, **574**:37–41.
103. Tsushima F, Yao S, Shin T, Flies A, Flies S, Xu H, Tamada K, Pardoll DM, Chen L: **Interaction between B7-H1 and PD-1 determines initiation and reversal of T-cell anergy.** *Blood* 2007, **110**:180–185.

104. Myklebust JH, Irish JM, Brody J, Czerwinski DK, Houot R, Kohrt HE, Timmerman J, Said J, Green MR, Delabie J, Kolstad A, Alizadeh AA, Levy R: **High PD-1 expression and suppressed cytokine signaling distinguish T cells infiltrating follicular lymphoma tumors from peripheral T cells.** *Blood* 2013, **121**:1367–1376.
105. Chen BJ, Chapuy B, Ouyang J, Sun HH, Roemer MG, Xu ML, Yu H, Fletcher CD, Freeman GJ, Shipp MA, Rodig SJ: **PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies.** *Clin Cancer Res* 2013, **19**:3462–3473.
106. Kozako T, Yoshimitsu M, Fujiwara H, Masamoto I, Horai S, White Y, Akimoto M, Suzuki S, Matsushita K, Uozumi K, Tei C, Arima N: **PD-1/PD-L1 expression in human T-cell leukemia virus type 1 carriers and adult T-cell leukemia/lymphoma patients.** *Leukemia* 2009, **23**:375–382.
107. Andorsky DJ, Yamada RE, Said J, Pinkus GS, Betting DJ, Timmerman JM: **Programmed death ligand 1 is expressed by non-hodgkin lymphomas and inhibits the activity of tumor-associated T cells.** *Clin Cancer Res* 2011, **17**:4232–4244.
108. Munir S, Andersen GH, Woetmann A, Odum N, Becker JC, Andersen MH: **Cutaneous T cell lymphoma cells are targets for immune checkpoint ligand PD-L1-specific, cytotoxic T cells.** *Leukemia* 2013, **27**:2251–2253.
109. Prochazka V, Novak M, Pikalova Z, Papajik T, Indrak K, Divoky V: **Number of PD-1+/CD8+ Cells in Peripheral Blood of Patients with Lymphoma Reflects Tumor Burden, Lymphoma Subtype, Disease Phase and Is Significantly Higher Compared to Healthy Volunteers.** *ASH Annu Meet Abstr* 2012, **120**:2670.
110. Berger R, Rotem-Yehudar R, Slama G: **Phase I safety and pharmacokinetic study of CT-011, a humanized antibody interacting with PD-1, in patients with advanced hematologic malignancies.** *Clin Cancer Res* 2008, **14**:3044–3051.
111. Armand P, Nagler A, Weller EA, Devine SM, Avigan DE, Chen YB, Kaminski MS, Holland HK, Winter JN, Mason JR, Fay JW, Rizzieri DA, Hosing CM, Ball ED, Uberti JP, Lazarus HM, Mapara MY, Gregory SA, Timmerman JM, Andorsky D, Or R, Waller EK, Rotem-Yehudar R, Gordon LI: **Disabling immune tolerance by programmed death-1 blockade with pidilizumab after autologous hematopoietic stem-cell transplantation for diffuse large B-cell lymphoma: results of an international phase II trial.** *J Clin Oncol* 2013, **31**:4199–4206.
112. Westin JR, Chu F, Zhang M, Fayad LE, Kwak LW, Fowler N, Romaguera J, Hagemester F, Fanale M, Samaniego F, Feng L, Baladandayuthapani V, Wang Z, Ma W, Gao Y, Wallace M, Vence LM, Radvanyi L, Muzzafar T, Rotem-Yehudar R, Davis RE, Neelapu SS: **Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial.** *Lancet Oncol* 2014, **15**:69–77.
113. Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, Brahmer JR, Lawrence DP, Atkins MB, Powderly JD, Leming PD, Lipson EJ, Puzanov I, Smith DC, Taube JM, Wigginton JM, Kollia GD, Gupta A, Pardoll DM, Sosman JA, Hodi FS: **Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer.** *N Engl J Med* 2012, **366**:2443–2454.
114. Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, Brahmer JR, Lawrence DP, Atkins MB, Powderly JD, Leming PD, Lipson EJ, Puzanov I, Smith DC, Taube JM, Wigginton JM, Kollia GD, Gupta A, Pardoll DM, Sosman JA, Hodi FS: **Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab.** *J Clin Oncol* 2014, **32**:1020–1030.
115. Ansell SM, Hurvitz SA, Koenig PA, LaPlant BR, Kabat BF, Fernando D, Habermann TM, Inwards DJ, Verma M, Yamada R, Erlichman C, Lowy I, Timmerman JM: **Phase I study of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with relapsed and refractory B-cell non-Hodgkin lymphoma.** *Clin Cancer Res* 2009, **15**:6446–6453.
116. O'Sullivan Coyne G, Madan RA, Gullely JL: **Nivolumab: promising survival signal coupled with limited toxicity raises expectations.** *J Clin Oncol* 2014, **32**:986–988.
117. Baeuerle PA, Reinhardt C: **Bispecific T-cell engaging antibodies for cancer therapy.** *Cancer Res* 2009, **69**:4941–4944.
118. Topp MS, Zugmaier G, Goebuegt N, Kufer P, Goebeler M, Klinger M, Degenhard E, Baeuerle PA, Schmidt M, Nagorsen D, Neumann S, Horst HA, Raff T, Viardot A, Stelljes M, Schmid M, Ottmann OG, Burmeister T, Einsele H, Riethmueller G, Hoelzer D, Bargou RC: **Report of a Phase II Trial of Single-Agent BiTE(R) Antibody Blinatumomab in Patients with Minimal Residual Disease (MRD) Positive B-Precursor Acute Lymphoblastic Leukemia (ALL).** *ASH Annu Meet Abstr* 2009, **114**:840.
119. Topp MS, Kufer P, Gökbuget N, Goebeler M, Klinger M, Neumann S, Horst HA, Raff T, Viardot A, Schmid M, Stelljes M, Schaich M, Degenhard E, Köhne-Volland R, Brüggemann M, Ottmann O, Pfeifer H, Burmeister T, Nagorsen D, Schmidt M, Lutterbueser R, Reinhardt C, Baeuerle PA, Kneba M, Einsele H, Riethmüller G, Hoelzer D, Zugmaier G, Bargou RC: **Targeted Therapy With the T-Cell-Engaging Antibody Blinatumomab of Chemotherapy-Refractory Minimal Residual Disease in B-Lineage Acute Lymphoblastic Leukemia Patients Results in High Response Rate and Prolonged Leukemia-Free Survival.** *J Clin Oncol* 2011, **29**:2493–2498.
120. Goebeler M, Pfreundschuh M, Adrian N, Libicher M, Degenhard E, Stieglmaier J, Zhang A, Nagorsen D, Bargou RC: **Open-Label Phase 2 Study Of The Bispecific T-Cell Engager (BiTE®) Blinatumomab In Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma.** *Blood* 2013, **122**:1811.
121. Bargou R, Leo E, Zugmaier G, Klinger M, Goebeler M, Knop S, Noppeney R, Viardot A, Hess G, Schuler M, Einsele H, Brandl C, Wolf A, Kirchinger P, Klappers P, Schmidt M, Riethmüller G, Reinhardt C, Baeuerle PA, Kufer P: **Tumor regression in cancer patients by very low doses of a T cell-engaging antibody.** *Science* 2008, **321**:974–977.
122. Viardot A, Goebeler M, Noppeney R, Krause SW, Kallert S, Ferstl B, Mackensen A, Rupertus K, Soekler M, Kanz L, Knop S, Topp MS, Scheele J, Nagorsen D, Zugmaier G, Degenhard E, Schmidt M, Kufer P, Libicher M, Einsele H, Bargou R: **Blinatumomab Monotherapy Shows Efficacy in Patients with Relapsed Diffuse Large B Cell Lymphoma.** *ASH Annu Meet Abstr* 2011, **118**:1637.
123. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, Maio M, Binder M, Bohnsack O, Nichol G, Humphrey R, Hodi FS: **Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria.** *Clin Cancer Res* 2009, **15**:7412–7420.
124. Pardoll D: **AACR Cancer Report 2013 - Special Feature on Immunotherapy.** *Clin Cancer Res* 2013, **19**(Supplement 1):S1–S88.

doi:10.1186/s13045-014-0058-4

Cite this article as: Suresh et al.: New antibody approaches to lymphoma therapy. *Journal of Hematology & Oncology* 2014 **7**:58.

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