Accepted Manuscript

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Agents targeting lymphoid or myeloid cells surface antigens [II]: CD22, CD30, CD33, CD38, CD40, SLAMF-7 and CCR4)

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PII: S1198-743X(18)30232-5

DOI: 10.1016/j.cmi.2018.03.022

Reference: CMI 1253

To appear in: *Clinical Microbiology and Infection*

Please cite this article as: Drgona L, Gudiol C, Lanini S, Salzberger B, Ippolito G, Mikulska M, ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Agents targeting lymphoid or myeloid cells surface antigens [II]: CD22, CD30, CD33, CD38, CD40, SLAMF-7 and CCR4), *Clinical Microbiology and Infection* (2018), doi: 10.1016/j.cmi.2018.03.022.

Revised manuscript (CLM-17-12788.R1) [for AA publication]

Review paper

Title page

Complete title: ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Agents targeting lymphoid or myeloid cells surface antigens [II]: CD22, CD30, CD33, CD38, CD40, SLAMF-7 and CCR4)

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- ***Word length*** (excluding title page, figure legends and references): 5,373
- ***Number of figures:*** 1
- ***Number of tables:*** 3
- ***Number of references:*** 76
- ***Funding sources*****:** This research was partially supported by Plan Nacional de I+D+I 2013-2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Spanish Ministry of Economy and Competitiveness, Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/0002) - co-financed by the

European Development Regional Fund (EDRF) *"A way to achieve Europe"*. M.F.R. holds a clinical research contract "Juan Rodés" (JR14/00036) from the Instituto de Salud Carlos III, Spanish Ministry of Economy and Competitiveness.

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Abstract (250 words)

Background: The present review is part of the ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies.

Aims: To review, from an Infectious Diseases perspective, the safety profile of agents targeting CD22, CD30, CD33, CD38, CD40, SLAMF-7 and CCR4 and to suggest preventive recommendations.

Sources: Computer-based MEDLINE searches with MeSH terms pertaining to each agent or therapeutic family.

Content: The risk and spectrum of infections in patients receiving CD22-targeted agents (i.e., inotuzumab ozogamicin) are similar to those observed with anti-CD20 antibodies. Anti-*Pneumocystis* prophylaxis and monitoring for cytomegalovirus (CMV) infection is recommended for patients receiving CD30-targeted agents (brentuximab vedotin). Due to the scarcity of data, the risk posed by CD33-targeted agents (gemtuzumab ozogamicin) cannot be assessed. Patients receiving CD38-targeted agents (i.e., daratumumab) face an increased risk of varicella-zoster virus (VZV) infection. Therapy with CD40-targeted agents (lucatumumab or dacetuzumab) is associated with opportunistic infections similar to those observed in hyper-IgM syndrome, and prevention strategies (including anti-*Pneumocystis* prophylaxis and pre-emptive therapy for CMV infection) are warranted. CD319-targeted agents (elotuzumab) induce lymphopenia and increase the risk of infection (particularly due to VZV). The impact of CCR4-targeted agents (mogamulizumab) on infection susceptibility is difficult to distinguish from the effect of underlying diseases and concomitant therapies. However, anti-*Pneumocystis* and anti-herpesvirus prophylaxis and screening for chronic hepatitis B virus (HBV) infection are recommended.

Implications: Specific management strategies should be put in place to reduce the risk and/or the severity of infectious complications associated to the reviewed agents.

Keywords: inotuzumab ozogamicin; moxetumomab pasedotox; brentuximab vedotin; gemtuzumab ozogamicin; daratumumab; lucatumumab; mogamulizumab; infection

Introduction

The present review paper is part of a larger effort launched by the ESCMID (European Society of Clinical Microbiology and Infectious Diseases) Study Group for Infections in Compromised Hosts (ESGICH) and aimed at analyzing, from an Infectious Diseases perspective, the safety profile of biological and targeted therapies. By means of a set of unrestricted computer-based MEDLINE (National Library of Medicine, Bethesda, MD) searches based on the MeSH terms appropriate for each agent or therapeutic family, we identified literature pertaining to the subject. In addition, package information and boxed warning alerts from regulatory agencies (European Medicines Agency [EMA] and US Food and Drug Administration [FDA]) were reviewed. Methodological details are provided in the Introduction section of the present Supplement issue [1]. For each agent (or class of agents), a common outline is offered: (a) summary of mechanism of action, approved indications and most common off-label uses; (b) theoretically expected impact on the host's susceptibility to infection; (c) available evidence emerging from the clinical use of that agent (i.e., randomized clinical trials [RCTs], post-marketing studies, case series and single case reports); and (d) suggested preventive and risk minimization strategies. The present section is the second one analyzing therapeutic families targeted at surface antigens on lymphoid or myeloid cells, and mostly used in patients with hematological malignancies. In detail, the infection risk entailed by the use of monoclonal antibodies and antibody constructs targeting CD22, CD30, CD33, CD38, CD40, signalling lymphocytic activation molecule F7 (SLAMF-7, also known as CD319) and CCR4 will be reviewed.

Over the last two decades there has been an increasing interest in developing monoclonal antibodies targeting different surface proteins on cells of lymphoid and myeloid lineages for the treatment of leukaemia, lymphoma and, more recently, multiple myeloma. Initial studies are usually performed in patients with a relapsed or refractory disease, thus making it difficult to establish the additional risk of infections conferred by novel agents and the effect of previous or concomitant cytotoxic chemotherapies, concurrent neutropenia, and the role of the underlying disease. In fact, only RCTs allow to definitively establish the specific risk of a given agent. However, caution must be exerted even if pivotal studies do not report an increased infectious risk. Indeed, in the past, most of the data on particular, and usually quite rare, infectious complications occurring during treatment with novel agents have been discovered only after

extensive post-marketing use, and reported either as case series or data from large observational studies.

The development status, therapeutic indications and the potential impact on the infectious risk of the reviewed agents are summarized in **Table 1**. The available data on infectious complications extracted from studies that included a control group are outlined in **Table 2**. Finally, the suggested strategies for the prevention of infection in patients treated with these agents are depicted in **Table 3**. It should be emphasized, however, that in view of the limited data available so far for many of these agents, the suggestions provided in this paper are open for constant modifications based on new results and clinical observations. Clinicians should pay particular attention to infectious complications associated with novel agents, report them promptly and collect information systematically within collaborative groups in order not to miss rare but particular infections [2-4].

CD22-targeted agents: epratuzumab, inotuzumab ozogamicin, moxetumomab pasedotox and combotox

Mechanism of action, approved indications and off-label uses

The antigen CD22 is a transmembrane glycoprotein expressed on mature B-cells and on up to 90% of B-blasts, but not on other non-B lineages including haematopoietic stem cells. Therefore, CD22-targeted treatment is not expected to affect other tissues. Its function is unclear; however, recent studies suggest that it regulates B-cell functions via B-cell receptor (BCR) activation, has an impact on their survival, and serves as an adhesion molecule [5]. *In vivo* animal studies demonstrated that combined therapy with epratuzumab and rituximab was more effective in controlling lymphoma growth and prolonging survival than either the agent alone [5]. The effect in systemic lupus erythematosus (SLE) is exerted via CD22 binding, resulting in modulation and inhibition of B-cell proliferation, thus diminishing SLE-related hyperactivity of B-cells without depleting them. Of note, the phase 3 trials in SLE failed to show the superiority of epratuzumab compared to placebo [6].

In August 2017 the FDA granted approval for inotuzumab ozogamicin (Besponsa®, Wyeth Pharmaceuticals) for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL), currently being the only anti-CD22 agent approved for clinical use.

Epratuzumab is a humanized IgG1 kappa monoclonal antibody targeting CD22 receptor on B-cells. It is being evaluated for the treatment of non-Hodgkin lymphoma (NHL) and ALL, and for autoimmune diseases such as SLE or Sjögren syndrome. Additionally, it has been also studied as a conjugate with SN-38, a topoisomerase I inhibitor with low nanomolar potency derived from the prodrug irinotecan [7].

Inotuzumab ozogamicin is a humanized anti-CD22 IgG4 monoclonal antibody covalently linked via an acid-labile linker with the antitumor antibiotic calicheamicin (a toxic natural product of *Micromonospora echinospora*) [8]. Upon binding of this compound to CD22 on the B-cell surface, the cytotoxic agent is released intracellularly and induces DNA strand cleavage, with the subsequent cell death mediated through calicheamicin-induced apoptosis and not by CD22 signalling [9].

Moxetumomab pasudotox (HA22, CAT-8015) is a second-generation recombinant immunotoxin containing the variable fragment of monoclonal antibody targeting CD22 fused to a 38-kDa fragment of *Pseudomonas* exotoxin A, called PE38. After binding, the immunotoxin-CD22 complex is internalized through clathrin-coated pits into the endocytic compartment. Following cleavage, the ADP-ribosylating domain of PE38 is transported to the endoplasmic reticulum and the cytosol, where the toxin induces a rapid drop in the levels of the anti-apoptotic protein Mcl-1, thus initiating the apoptotic cascade [10].

Combotox is a mixture (in 1:1 proportion) of the anti-CD19 (HD37-dgRTA) and anti-CD22 (RFB4-dgRTA) immunotoxins. This compound is reviewed with the other CD19-targeted agents. The clinical status of epratuzumab, inotuzumab ozogamicin and moxetumomab pasudotox is detailed in **Table 1**.

Expected impact on the susceptibility to infection

According to the mechanisms of action displayed and the targeted antigen on the surface of B-cells, it may be assumed that the risk and spectrum of infection for patients treated with anti-CD22 agents would be similar to those observed with anti-CD20 monoclonal antibodies such as rituximab. Peripheral blood kinetics of CD19+ B-cells were determined in clinical studies with epratuzumab. Approximately 90% of patients suffered from a reduction in B-cell levels of 75% or higher within 4 weeks from the initiation of therapy, with B-cell recovery occurring at 9 to 12 months after the last infusion. Serum immunoglobulin levels were measured before, during and

after drug exposure, and no significant decrease was documented [11,12]. In SLE patients a median reduction of 30-40% in peripheral blood B-cell levels was observed, although T-cell and serum IgA and IgG levels remained stable throughout therapy, whereas IgM levels decreased by 20% from baseline among epratuzumab-treated patients [6].

The number of circulating CD22+ B-cells rapidly declined following the administration of inotuzumab ozogamicin [13-15]. On the other hand, preliminary data on the safety profile of moxetumomab pasudotox did not suggest any mechanism potentially contributing to increase the susceptibility to infection, and long-term B-cells depletion was not observed [10].

Available clinical data

Previous RCTs of epratuzumab versus placebo (plus standard therapy in both cases) for SLE showed no differences in the overall rates of infection in 1,664 patients included [6,16]. Several phase 2 studies in patients with relapsed or refractory lymphoid malignancies did not observe an excess in the expected incidence of infectious complications typical for this patient population (upper respiratory tract infection, herpes zoster, febrile neutropenia or sepsis) [11,17-19]. Inotuzumab ozogamicin was compared with standard intensive chemotherapy in a large (218 patients) open-label phase 3 RCT in patients with relapsed or refractory B-cell precursor ALL. Hematologic cytopenias were the most common adverse events associated with this CD22-targeted agent, although the occurrence of grade 3-4 febrile neutropenia was lower than with standard therapy (24% versus 49%). In addition, the incidence of infection (sepsis or pneumonia) was similar between both study arms or slightly lower with inotuzumab ozogamicin. Liver toxicity (including veno-occlusive disease) was more commonly observed in the inotuzumab ozogamicin arm [15]. There are no available data to assess the infection risk associated to the use of moxetumomab pasudotox.

Suggested prevention strategies

- In view of mechanism of action (similar to other B-cell-targeted drugs such as anti-CD20 monoclonal antibodies) and available data (mainly restricted to epratuzumab and inotuzumab ozogamicin), therapy with CD22-targeted agents does not meaningfully increase the risk of infection.
- No benefit is expected from the universal use of antibacterial, antiviral or anti-*Pneumocystis* prophylaxis for patients receiving CD22-targeted therapy. However, infection

risk should be individually evaluated at the light of patient's co-morbidities and the concomitant administration of other immunosuppressive agents.

- Screening for chronic and resolved hepatitis B virus (HBV) infection should be performed before starting treatment with CD22-targeted agents. Antiviral prophylaxis while on therapy may be considered for hepatitis B surface antigen (HBsAg)-positive patients for preventing HBV reactivation, while HBV-DNA monitoring and pre-emptive antiviral treatment may be appropriate for HBsAg negative but anti-HBc positive patients.

CD30-targeted agents: brentuximab vedotin

Mechanism of action, approved indications and off-label uses

Brentuximab vedotin (Adcetris®, Takeda) is an antibody-drug conjugate composed of a human/murine chimeric anti-CD30 IgG1 monoclonal antibody conjugated via a protease-cleavable linker with the microtubule disrupting agent monomethyl auristatin E (MMAE), a synthetic derivative of a natural cytostatic pseudopeptide originally isolated from the marine mollusc *Dorabella auricularia* (**Figure 1**) [20]. Brentuximab vedotin was the first antibody-drug conjugate approved in 2011 by the FDA and in 2012 by the EMA for the treatment of relapsed/refractory Hodgkin lymphoma (HL) and anaplastic large T-cell lymphoma.

Expected impact on the infection risk

A member of the tumor necrosis factor (TNF)/nerve growth factor receptor superfamily, CD30 is a 120-kDa transmembrane glycoprotein that has been long used as a marker for the Reed-Sternberg cells in HL [21]. In addition, CD30 is also expressed in various cellular types, including T-cells, B-cells, monocytes, and activated natural killer cells. The precise biological functions of this molecule remain to be fully elucidated, although it has been implied in the regulation of the balance between Th1 and Th2 responses and in the generation of memory and effector T-cells [22,23]. Therefore, CD30-targeted agents may affect antibody-dependent cell-mediated cytotoxicity (ADCC) and exert a deleterious impact on humoral immunity.

Available clinical data

In two pivotal phase 2 studies including 102 patients with in relapsed/refractory HL [24] and 58 with anaplastic large T-cell lymphoma [25], no specific infectious complications were observed, although approximately 20% of participants developed neutropenia. Likewise, in a RCT

evaluating brentuximab vedotin as a consolidation therapy for autologous hematopoietic stem cell transplant (HSCT) recipients with HL at high risk of relapse or progression, no increase in the rates of upper respiratory tract infection and severe infection was reported for 167 patients receiving brentuximab compared to 160 receiving placebo [26]. Neutropenia, peripheral sensory neuropathy, thrombocytopenia, pulmonary toxicity (when given in association with bleomycin) and anemia were the most common adverse events in pivotal RCTs with brentuximab vedotin. Of note, the use of prophylaxis for herpesviruses and *Pneumocystis jirovecii* pneumonia (PCP) was mandatory in these studies.

Progressive multifocal leukoencephalopathy (PML) is a life-threatening complication described in patients receiving brentuximab vedotin, although the direct impact of CD30 blockade is difficult to delineate since all of them had previously received other cytostatic and immunosuppressive agents. It should be noted that the time to symptom onset and the prior duration of therapy were much shorter (with cases occurring after only 2 or 3 doses of brentuximab vedotin administered every 3 weeks) compared to patients developing PML after exposure to anti-CD20 monoclonal antibodies (median of 63 weeks from initial exposure) or natalizumab (median of 26 months). The case fatality rate among reported cases was 80% [2,27-29]. These clinical observations prompted the FDA to launch a Risk Evaluation and Mitigation Strategy (REMS) program modelled after that established for natalizumab, including appropriate label warning [2,3].

The occurrence of severe cytomegalovirus (CMV) disease with retinal involvement has been also recently reported. Of note, evolution was favourable in all cases upon initiation of antiviral therapy, although infection relapsed after rechallenge with brentuximab vedotin, emphasizing the need of secondary prophylaxis if additional cycles of therapy are to expected [30].

Conclusions and suggested prevention strategies

- In view of mechanism of available data, therapy with CD30-targeted agents does not meaningfully increase the risk of overall infection, with observed rates comparable to those expected for patients with relapsed or refractory lymphoma. However, the use of brentuximab vedotin carries an additional risk of neutropenia, which might be associated with typical pattern of infections.
- Anti-herpesvirus and anti-*Pneumocystis* prophylaxis should be administered to autologous

HSCT recipients treated with brentuximab vedotin as consolidation therapy.

- PML is a life-threatening complication occasionally associated with the use of brentuximab vedotin. The new onset of neurological symptoms among patients treated with brentuximab should prompt suspicion of PML, early drug discontinuation and appropriate diagnostic work-up.
- Regular monitoring for CMV infection during the course of brentuximab vedotin therapy is advisable in CMV-seropositive patients or in presence of clinically suspected CMV disease (especially with retinal involvement). Secondary anti-CMV prophylaxis should be considered for patients scheduled to receive additional cycles of brentuximab vedotin.

CD33-targeted agents: gemtuzumab ozogamicin

Mechanism of action, approved indications and off-label uses

Gemtuzumab ozogamicin (Mylotarg®, Pfizer) is an immunoconjugate composed of a humanized IgG4 kappa monoclonal antibody targeting CD33 covalently attached to the potent antitumor antibiotic calicheamicin (N-acetyl-γ-calicheamicin) via the bifunctional AcBut linker. The anti-CD33 antibody, lacking cytotoxic activity by itself, binds to the CD33 antigen, which is expressed on the surface of normal and leukaemic myeloid cells, as well as leukaemic blasts in more than 80% of cases of acute myeloid leukaemia (AML), but not on normal precursor haematopoietic cells. The conjugate is then internalised and delivers the calicheamicin derivative to the inside of the leukaemic cell [31,32]. It was approved by the FDA in 2000 for the treatment of AML, whereas the EMA issued a negative opinion for granting a Marketing Authorisation in 2008. In view of data coming from a large follow-up extension study showing no survival improvement and increased early deaths, the drug manufacturer voluntarily withdrew the US New Drug Application in 2010. However, it has been reapproved by the FDA in 2017 on the basis of a meta-analysis [33] that reported better survival in adults AML patients with favorable- and intermediate-risk cytogenetics [34]. Gemtuzumab ozogamicin is currently used in some countries (e.g., Japan) for relapsed AML.

Expected impact on the infection risk

CD33 is expressed on monocytes, granulocytes, mast cells and myeloid progenitors. Due to the cytotoxic effect exerted on immature myeloid cells, CD33-targeted therapy leads to profound

neutropenia and thrombocytopenia. The expected impact of gemtuzumab ozogamicin on the incidence of infection would be thus similar to that observed with other therapies inducing severe and long-lasting neutropenia (e.g., induction to remission cytotoxic therapies for AML).

Available clinical data

Results from phase 2 and phase 3 trials (overall including 1105 patients) in which gemtuzumab ozogamicin was administered within cytotoxic combination therapies demonstrated rates of infection similar to comparator groups (based on other cytotoxic regimens) (**Table 2**) [35-37]. No specific additional infections have been reported in pivotal or phase 2 trials or in case series. An anecdotal case of PML was reported in an allogenic HSCT recipient previously treated with gemtuzumab ozogamicin [38].

Conclusions and suggested prevention strategies

- In view of available data, the impact of therapy with gemtuzumab ozogamicin on risk of infection cannot be appropriately established.
- Standard prophylactic strategies should be administered to AML patients experiencing drug-induced neutropenia in the course of treatment with gemtuzumab ozogamicin.

CD38-targeted agents: daratumumab and isatuximab

Mechanism of action, approved indications and off-label uses

The human CD38 antigen is a 46-kDa type II transmembrane glycoprotein that was initially recognized as a lymphocyte differentiation and activation antigen. It was later found that CD38 has multiple receptor and enzymatic functions. Through binding to CD31, CD38 is involved in leukocyte adhesion, activation and proliferation. In addition to this receptor function, CD38 has bifunctional ectoenzymatic activity. It acts as a cyclic ADP ribose hydrolase that regulates intracellular Ca^{2+} flux and leads to the activation of signalling pathways. It is expressed on lymphoid and myeloid cells as well as on several non-haematopoietic tissues. Virtually, all myeloma cells express high levels of CD38 on their surface, similar to normal plasma cells [39]. Therefore, CD38 serves as an attractive therapeutic target, in particular for multiple myeloma and potentially for other CD38-positive disorders (i.e., NHL). The expression of CD38 on normal lymphoid and myeloid cells is low.

Daratumumab (Darzalex®, Janssen) is a fully human IgG1 kappa monoclonal antibody targeting

CD38 that has been approved by the FDA and EMA for the treatment of relapsed and refractory multiple myeloma in adult patients, either in monotherapy (approval in 2015-2016) or in combination with bortezomib and dexamethasone or lenalidomide and dexamethasone (approval in 2017) [40]. Isatuximab (SAR650984, Sanofi Genzyme) is a chimeric anti-CD38 IgG1 monoclonal antibody not yet approved, although clinical studies are ongoing for relapsed and/or refractory multiple myeloma as a sole agent or in combination.

Expected impact on the infection risk

CD38 is highly and ubiquitously expressed on multiple myeloma cells and, at low levels, on normal lymphoid and myeloid cells [40]. Daratumumab induces myeloma cell death by means of complement-dependent cytotoxicity (CDC), ADCC and antibody-dependent cellular phagocytosis (ADCP). In addition, it has been suggested that this agent (and it is likely that also isatuximab) is able to induce myeloma cell apoptosis by modulating CD38 enzymatic functions and, indirectly, by enhancing antitumor activity through the blockade of CD38-positive immunosuppressive cells (i.e., regulatory T- [Tregs] and B-cells [Bregs] and myeloid-derived suppressor cells). The latter mechanism would lead to increase CD8+ T-cells effector functions. In view of these mechanisms of action, there is a low theoretical probability of an additive effect on the baseline risk of infection associated with the use of anti-CD38 agents.

Available clinical data

Pooled analysis of two phase 2 studies with daratumumab monotherapy reported a rate of grade 3-4 neutropenia of 10.1% and a rate of severe upper respiratory tract infection as low as 0.7% among 148 included patients [41]. Pivotal RCTs documented an incidence of grade 3-4 infection of 21.4% and 28.3% for the daratumumab arms (537 patients) compared to 19% and 22.8% for the comparator arms (530 patients). Grade 3-4 neutropenia was found in 13 to 52% of patients treated with daratumumab combinations and in 4 to 37% of those in the comparator arms. The rate of serious (grade 3-4) pneumonia was similar in each arm (approximately 9%). Combination therapy with daratumumab resulted in a slightly increased rate of grade 3-4 febrile neutropenia (5.7% versus 2.5% in the control group) [42,43].

The rate of varicella zoster virus (VZV) infection in the daratumumab arms of the pivotal studies for relapsed/refractory myeloma ranged from 2% to 5% [42,43]. This finding is likely explained by the inclusion of immunomodulatory agents, proteasome inhibitors and corticosteroids within

the combination regimens evaluated in these trials. In addition, it should be noted that the rate of infection among myeloma patients is higher for relapsed/refractory cases and those with progressive disease [44].

Isatuximab is another potent anti-CD38 monoclonal antibody, and several phase 2 studies are ongoing to evaluate its role in heavily pre-treated myeloma patients. Pneumonia and sepsis were documented in 6.3% and 5.2% of patients on monotherapy, respectively [45], while pneumonia occurred in 9% of 57 patients receiving isatuximab in combination with lenalidomide and dexamethasone [46].

Conclusions and suggested prevention strategies

- In view of available data (mainly restricted to daratumumab), therapy with CD38-targeted agents does not meaningfully increase the risk of infection. Despite its slightly different mode of action, a similar profile of infection is expected for isatuximab, although no firm conclusions can be made yet in view of the scarcity of data [47].
- Clinicians caring for patients receiving CD38-targeted agents should be aware of the increased risk of VZV infection, especially in the presence of combination therapy with protease inhibitors and/or corticosteroids. Anti-herpesvirus prophylaxis with (val)acyclovir should be administered to VZV-seropositive patients at least 1 week before starting daratumumab therapy and for at least 12 weeks after its discontinuation.
- Seasonal influenza vaccination should be encouraged, when feasible, in patients treated with daratumumab [48].

CD40-targeted agents: dacetuzumab and lucatumumab

Mechanism of action, approved indications and off-label uses

CD40 is a member of the TNF receptor superfamily that functions as a co-stimulatory molecule upon interaction with its ligand CD40L (also known as CD154) on the surface of T-cell. CD40 acts as a receptor on antigen-presenting cells that plays an essential role in mediating a wide array of immune responses, including T cell-dependent immunoglobulin class switching, memory B-cell development, and germinal centre formation in spleen and lymph nodes. Mutations affecting the gene encoding for CD40 are associated with autosomal recessive hyper-IgM immunodeficiency type 3 [49].

Currently there are no approved CD40-targeted agents. Dacetuzumab is a humanized monoclonal antibody studied in phase 2 trials for relapsed diffuse large B-cell lymphoma, and in phase 1 trials for CLL and multiple myeloma. Lucatumumab is a fully human monoclonal antibody that has been evaluated in phase 2 trials for patients with refractory lymphomas and in phase 1 studies for CLL and multiple myeloma. Its clinical development was discontinued by Novartis in 2013, whereas there are no registered ongoing trials with lucatumumab.

Expected impact on the infection risk

As CD40 is expressed on different lymphoid and non-lymphoid cells, including conjunctival tissue, CD40-targeted therapy is generally associated with a wide array of toxicity including cytopenias, B-cell depletion, ocular toxicities and, potentially, impaired T-function. Patients with hyper-IgM syndrome type 3 or 1, that harbour mutations in CD40 or its ligand CD40L, are prone to severe opportunistic infections such as PCP, CMV infection, cryptococcosis or severe protozoan infections (such as diarrhoea or cholangitis due to *Cystoisospora belli* or *Cryptosporidium* spp). They have also an increased risk of neutropenia, low levels of IgG, and frequent upper and lower respiratory tract infections [50-53].

Available clinical data

A phase 2 RCT performed in 40 patients with relapsed NHL showed higher rate of infectious complications in the dacetuzumab group, as detailed in **Table 2** [54].

Conclusions and suggested prevention strategies

- In view of scarce available data (mainly restricted to dacetuzumab), therapy with CD40-targeted agents is associated with an increase in the risk of infection and, likely, neutropenia.
- Clinicians caring for patients receiving CD40-targeted agents might theoretically expect a spectrum of opportunistic infections (including PCP, CMV infection, invasive fungal infection or protozoan infections) mirroring that reported in hyper IgM syndrome.
- Appropriate prevention strategies (including anti-*Pneumocystis* prophylaxis, regular monitoring for CMV infection among CMV-seropositive patients or in presence of clinically suspected CMV disease, and early diagnosis of opportunistic infections) might be needed for patients receiving such therapy.

CD319-targeted agents: elotuzumab

Mechanism of action, approved indications and off-label uses

Elotuzumab (Empliciti®, Bristol-Myers Squibb) is an immunostimulatory, humanized IgG1 monoclonal antibody targeted at the SLAMF7, previously known as cell-surface glycoprotein CD2 subset 1 (CS1) or CD319. SLAMF7 is a glycoprotein almost universally (>95%) and highly expressed on malignant plasma cells, although not in most normal tissues. The precise function of SLAMF7 in the setting of multiple myeloma is still unclear, although it may play an important role in the interaction between myeloma cells, in their adhesion to bone marrow stromal cells (which contributes in turn to their survival and growth), and in NK cell activation [55]. The antitumor activity displayed by elotuzumab include the disruption of the adhesion between myeloma cells and bone marrow stromal cells, the enhancement of NK cell cytotoxicity, and the killing of malignant cells by ADCC (but not CDC).

The activity, efficacy and safety of elotuzumab (either alone or in combination with other agents) have been assessed in several phase 1-3 RCTs, mainly in the setting of relapsed or refractory multiple myeloma, and are currently being further explored. Elotuzumab in monotherapy has been shown to exert anti-tumour activity in patients with multiple myeloma [56]. However, its efficacy significantly increases when used in combination with established therapies for multiple myeloma, such as bortezomib [57,58], lenalidomide and dexamethasone [59-61], and thalidomide [62]. Moreover, elotuzumab appears to be effective also in elderly patients and in those who have received several prior lines of therapy. Ongoing clinical studies are investigating the application of elotuzumab in other populations (including earlier stages and high-risk smouldering myeloma) or in combination with other newer therapies (such as nivolumab and pomalidomide [ClinicalTrials.gov identifier: NCT02726581]).

Expected impact on the infection risk

In addition to plasma cells, SLAMF7 (CD319) is expressed in some leukocyte subsets, in particular NK cells, NK-like T-cells, CD8+ T-cells, activated monocytes, and dendritic cells [63]. The most frequent adverse event reported in patients treated with elotuzumab is lymphopenia. Since elotuzumab is mainly used in combination with other anti-myeloma drugs, it is difficult to discern if the observed infections may be directly attributable to the effect of elotuzumab. The

expected impact would be similar to that associated to usual anti-myeloma drugs, such as protease inhibitors, lenalidomide or dexamethasone.

Available clinical data

Grade 3-4 lymphopenia and neutropenia have been reported in 142 patients included in small, non-comparative, phase 1 and 2 dose-escalation trials of elotuzumab combined with lenalidomide and dexamethasone [60,61] and with thalidomide [62]. The infectious complications observed in these studies were upper respiratory tract infections (incidence rate of 47%), episodes of fatal sepsis (although none of them were deemed to be related to elotuzumab) [61], pneumonia (incidence rate of 14%) and febrile neutropenia (7%) [62].

A moderately increased risk of infection was observed in 389 patients recruited within the elotuzumab arms across larger RCTs (**Table 2**) [57,59]. However, in a pivotal phase 3 trial with over than 300 patients allocated to each group, the rates of overall infection after adjustment for drug exposure were similar (197 events per 100 patient-years) for elotuzumab plus lenalidomide and dexamethasone or for lenalidomide and dexamethasone alone [59]. Of note, there was an almost two-fold increase in the risk of VZV infection with elotuzumab (4.1 versus 2.2 episodes per 100 patient-years) and, additionally, the rates of opportunistic infections and lymphopenia (but not neutropenia) were also higher than in the control group. Death was attributed to infection in 2 patients in the elotuzumab group and in 5 patients in the control group [59].

Conclusions and suggested prevention strategies

- In view of available data, therapy with elotuzumab seems to be associated with an increase in the risk of infection (in particular due to VZV).
- Anti-herpesvirus prophylaxis with (val)acyclovir should be considered for VZV-seropositive patients, especially in case of repeated episodes of VZV reactivation (herpes zoster).
- In addition, clinicians caring for patients receiving elotuzumab should be aware of the increased risk of lymphopenia. Therefore, close monitoring of total lymphocyte and peripheral blood lymphocyte subpopulation counts should be performed.

CCR4-targeted agents*:* mogamulizumab

Mechanism of action, approved indications and off-label uses

Mogamulizumab (Poteligeo®, Kyowa Hakko Kirin) is a recombinant humanized IgG1 monoclonal antibody that targets CC chemokine receptor 4 (CCR4) and depletes CCR4-expressing cells by ADCC. Mogamulizumab was developed for the treatment of adult T-cell leukaemia/lymphoma (ATLL), which is an aggressive peripheral T-cell neoplasm characterized by the clonal proliferation of human T-cell lymphotropic virus type 1 (HTLV-1)-infected T-cells, since most ATLL cells were found to express CCR4 [64]. It was later proved effective also in cutaneous T-cell lymphomas (CTCLs), which are a heterogeneous group of lymphomas caused by mature skin-invasive T-cells, such as mycosis fungoides, Sézary syndrome, and anaplastic large cell lymphoma [65].

Additionally, mogamulizumab has been shown to deplete a subset of terminally differentiated, highly immunosuppressive CCR4-positive Tregs (CD45RA- FoxP3^{hi} CD4+ Tregs). These Treg cells are involved in the tumour escape from host immunity in the tumour microenvironment, making it an attractive target in the treatment of many solid tumours. The blockade of this Treg subset seems responsible for the high rate of graft versus host disease observed among allogeneic HSCT recipients previously treated with mogamulizumab [66].

Mogamulizumab was approved in 2012 by the Japanese Ministry of Health, Labour and Welfare for the treatment of relapsed or refractory CCR4+ ATLL and, subsequently, in 2014 for the treatment of primary ATLL, relapsed or refractory CCR4+ peripheral T-cell lymphoma (PTCL), and CTCL. In addition to studies in T-cell malignancies, trials in subjects with solid tumours (either has sole agent or associated with immune checkpoint inhibitors [ClinicalTrials.gov identifiers: NCT02705105, NCT02867007, NCT02301130]) and HTLV-1-associated myelopathy/tropical spastic paraparesis (ClinicalTrials.gov identifier: NCT03191526) are currently ongoing.

Expected impact on the infection risk

CCR4 is the dominant chemokine receptor of Th2 lymphocytes, some Treg cells, and cutaneous lymphocyte antigen (CLA)-positive skin-homing T-cells [67]. Infectious complications typical for patients with T-cell malignancies are to be expected with the use of mogamulizumab, and immunological exacerbation of response to infectious stimuli (mirroring the immune reconstitution inflammatory syndrome observed in HIV patients) might be hypothesised on the basis of the eventual impairment of Treg function.

Available clinical data

Four phase 2 trials found no significant differences in the incidence of infections between study groups. In the first single-arm trial in 27 patients with relapsed ATLL, no data on infections were provided, although per protocol all the participants received prophylaxis with trimethoprim/sulfamethoxazole, fluconazole and acyclovir [68]. In the second single arm trial in 37 patients with relapsed peripheral or cutaneous T- cell lymphoma, 30% of participant developed fever, and single cases of oral candidiasis, pneumonia, herpes esophagitis and CMV retinitis were diagnosed [69]. In the third phase 2 trial performed in 53 patients newly diagnosed with aggressive ATLL, infectious complications were present in 66% (19/29) and 67% (16/24) of patients in the mogamulizumab and control group, respectively. A slightly higher rates of CMV infection (4 episodes [14%]) and CMV pneumonia (2 episodes [7%]) were observed among 29 patients treated with mogamulizumab, compared to no cases of such infections in the control group [70]. Of note, almost all the patients developed neutropenia and lymphopenia, and 90% had at least one episode of febrile neutropenia [70]. Finally, in the fourth single-arm phase 2 trial in 38 patients with relapsed or refractory peripheral T-cell lymphoma receiving mogamulizumab monotherapy, fever and neutropenia occurred in 23% and 10% of participants, respectively, and 2 patients (5%) died due to serious infections (septic shock and pneumonia) [71].

Post-marketing anecdotal reports of infectious complications include cases of reactivation of resolved (i.e., occult) HBV infection, fatal parainfluenza pneumonia and disseminated *Mycobacterium chelonae* infection [72-76].

In a retrospective study of 24 ATLL patients with apparently resolved HBV infection (i.e., hepatitis B core antibody [anti-HBc]-positive, HBsAg-negative), 2 of 11 patients who received mogamulizumab developed HBV reactivation (defined as the detection of HBV-DNA), although none of these cases resulted in hepatitis due to the rapid initiation of treatment with entecavir. In comparison, HBV reactivation occurred in only 1 of 13 patients receiving chemotherapy without mogamulizumab [72]. Two additional cases of reactivation of apparently resolved, occult HBV infection have been reported [73,74]. One was successfully treated with entecavir [73]. In the other case, the progression to fatal fulminant hepatitis occurred despite entecavir treatment once mogamulizumab was started in a patient already diagnosed with high-HBV-DNA-level

(>9.1 log copies/mL) reactivation after previous chemotherapy [74]. Finally, conventional anti-*Pneumocystis* prophylaxis has been shown to be effective.

Conclusions and suggested prevention strategies

- In view of available data, therapy with mogamulizumab (which induces drug-related lymphopenia) may be associated with an increase in the risk of infection, although the precise contribution of CCR4 blockade to such susceptibility is difficult to distinguish from the intrinsic impact of ATLL and other concomitant lymphotoxic therapies.
- Based on experience from pivotal trials and general recommendations for patients with T-cell lymphomas, anti-*Pneumocystis* and anti-herpesvirus prophylaxis is recommended for patients receiving mogamulizumab.
- Prevention strategies for CMV infection (antiviral prophylaxis or preemptive therapy guided by CMV-DNA detection or symptom-based approach) should be applied to CMV-seropositive patients receiving mogamulizumab.
- Screening for chronic or resolved HBV infection should be performed before starting treatment with mogamulizumab. Antiviral prophylaxis (i.e., entecavir) while on therapy should be offered to HBsAg-positive patients for preventing HBV reactivation. Particular caution must be exerted in patients with high-level HBV-DNA since Treg downregulation might result in severe hepatitis. In addition, regular (usually monthly) monitoring for HBV viral load or, alternatively, antiviral prophylaxis (i.e., lamivudine) should be offered to HBsAg-negative/anti-HBc-positive patients to detect or prevent the eventual reactivation of an apparently resolved (occult) HBV infection. Hepatitis specialist referral could be considered.

Figure legends

Figure 1. Mode of action of brentuximab vedotin, an antibody-drug conjugate targeting CD30. Upon binding to CD30 on the surface of T-cell malignant cell, brentuximab vedotin is internalized via endocytosis. The exposure of protease-sensitive dipeptide linker to proteolytic lysosomal enzymes results in the release of monomethyl auristatin A (MMAE) molecules in the intracellular space. Binding of MMAE to tubulin disrupts the microtubule network, leading to induction of G2/M-phase cell cycle arrest and subsequent apoptosis.

Table 1. Description of the main agents targeting lymphoid and myeloid cell surface antigens.

Agent	Mechanism of action	Status of development (year of approval)	Approved indications	Off-label or experimental uses	Use as single agent / combination	Use as first-line treatment	Cellular expression
Epratuzumab	Anti-CD22 monoclonal antibody (also conjugated with the topoisomerase I inhibitor SN-38)	Phase 1 and 2 trials in follicular lymphoma, NHL, ALL; phase 3 RCT in SLE	NA	Refractory or relapsed DLBCL, previously untreated DLBCL, refractory or relapsed follicular lymphoma, ALL	Yes / yes	Yes	B-cells (mature and malignant)
Inotuzumab ozogamicin	Anti-CD22 monoclonal antibody conjugated with a calicheamicin agent	Approved, FDA (2017) Studies as single agent or combined with rituximab in refractory or relapsed NHL	Relapsed or refractory B-cell ALL	Follicular lymphoma, aggressive NHL (DLBCL)	Yes / yes	No	
Moxetumomab pasudotox	Variable fragment of anti-CD22 monoclonal antibody conjugated with *Pseudomonas* exotoxin A	Phase 3 trial in hairy cell leukemia; phase 1 studies in NHL and CLL; phase 2 trial in ALL	FDA ODD (2016) for hairy cell leukemia	ALL, NHL, CLL	Yes / no	No	
Brentuximab vedotin	Anti-CD30 monoclonal antibody conjugated to anti-tubulin agent MMAE	Approved, EMA (2012), FDA (2011)	Relapsed or refractory HL and anaplastic large T-cell lymphoma	CD30-positive haematological malignancies	Yes / yes (ongoing trials with ibrutinib)	Yes	Activated T- and B-cells, monocytes, activated NK and Reed-Sternberg cells
Gemtuzymab ozogamicin	Anti-CD33 monoclonal antibody conjugated with a calicheamicin agent	Approved, FDA (2000 and later reapproved in 2017), EMA refused (2008)	AML, in 2017 CD33-positive AML	Acute promyelocytic leukaemia	Yes / yes	No	Monocytes, granulocytes, mast cells and myeloid progenitors
Daratumumab	Anti-CD38 monoclonal antibodies, enhancing	Approved, EMA (2016), FDA (2015)	Relapsed or refractory MM	Potentially lymphomas, amyloidosis, MDS	Yes / yes	No	Plasma cells, early T- and B-cells,

Isatuximab	antitumor activity, modulation of CD38 ectoenzyme function (immunomodulation)	Phase 2 study in MM	NA	ALL, CD38-positive haematological malignancies	Yes / yes	No	activated T-cells and germinal centre B-cells
Dacetuzumab	Anti-CD40 monoclonal antibody	Phase 2 in DLBCL; phase 1 in MM and CLL	NA	MM, CLL	Yes / Yes	No	B-cells, monocytes, macrophages, follicular DCs, fibroblasts and keratinocytes
Elotuzumab	Anti-CD319 (SLAMF7) monoclonal antibody	Approved, EMA (2016), FDA (2015)	Previously treated MM	NA	No / yes	No	Germinal centre B-cells, follicular DCs
Mogamulizumab	Anti-CCR4 monoclonal antibody	Approved, Japanese Ministry of Health, Labour and Welfare (2012)	Relapsed or refractory ATLL, peripheral and cutaneous T-cell lymphoma	Solid tumors and HTLV-1-associated myelopathy / tropical spastic paraparesis	Yes / no (only in ongoing studies)	Yes	ATLL cells, highly immunosuppressive Treg subset

ALL: acute lymphoblastic leukaemia; ATLL: adult T-cell leukaemia/lymphoma; CLL: chronic lymphocytic leukaemia; DCs: dendritic cells; DLBCL: diffuse large B-cell lymphoma; EMA: European Medicines Agency; FDA: Food and Drug Administration; HTLV-1: human T-cell lymphotropic virus type 1; MDS: myelodysplastic syndrome; MM: multiple myeloma; NA: not available; NHL: non-Hodgkin's lymphoma; ODD: orphan drug designation; SLE: systemic lupus erythematosus.

Table 2. Summary of infectious events in patients treated with agents targeted different lymphoma and leukemia cells surface antigens across RCTs and observational studies that included a control group.

Agent	Type of study	Treatment arms	No. of subjects	Rate of infection (novel agent vs. comparator)
Epratuzumab	Phase 2 RCT for SLE [76]	Epratuzumab (200-3,600 mg) vs. placebo	189 vs. 38	Overall infection: 24-51% vs. 40%; URTI: 0-15% vs. 5%; UTI: 3-5% vs. 5%; viral infection: 0-3% vs. 5%; pneumonia: 0% vs. 5%
	Phase 3 RCT for SLE [16]	Epratuzumab (360-720 mg/m^2) vs. placebo	53 vs. 37	Overall infection: 64-70% vs. 70%; serious infection: 12-36% vs. 12%
	Two phase 3 RCTs for SLE [6]	Epratuzumab (600 mg/m^2 weekly or 1,200 mg/m^2 every 2 weeks) plus standard therapy vs. placebo plus standard therapy	1,048 vs. 526	Overall infection: 52-61% vs. 60%; URTI: 12-15% vs. 11-14%; UTI: 10-14% vs. 11-18%; VZV: 1-4% vs. 2-3%
Inotuzumab ozogamicin	Phase 3 RCT for relapsed or refractory ALL [15]	Inotuzumab-ozogamicin vs. standard therapy	109 vs.109	Febrile neutropenia (grade 3-4): 11% vs. 18%; pneumonia: 4% vs. 1%; sepsis: 2% vs. 5%; septic shock: 1% vs. 1%
Brentuximab vedotin	Phase 3 RCT for consolidation therapy after allogenic HSCT in HL [26]	Brentuximab vs. placebo	167 vs. 160	Neutropenia: 35% vs. 12%; URTI: 26% vs. 23%; severe infection: 7% vs. 6%
Gemtuzumab ozogamicin	RCTs for AML [35-37]	Gemtuzumab plus chemotherapy vs. chemotherapy	622 vs. 483	Serious infection (grade 3-4) in induction phase: 44% vs 47%; febrile neutropenia in induction phase: 24% vs. 26%
Daratumumab	Phase 3 RCT for relapsed or refractory MM [43]	Daratumumab plus bortezomib plus dexamethasone vs. bortezomib plus dexamethasone	251 vs. 247	Serious infection (grade 3-4): 21.4% vs. 19%; pneumonia (grade 3-4): 8.2% vs. 9.7%; neutropenia (grade 3-4): 12.8% vs. 4.2%; VZV: 5% vs. 3%
	Phase 3 RCT for relapsed or refractory MM [42]	Daratumumab plus lenalidomide plus dexamethasone vs lenalidomide plus dexamethasone	286 vs. 283	Serious infection (grade 3-4): 28.3% vs. 22.8%; pneumonia (grade 3-4): 7.8% vs. 8.2%; neutropenia (grade 3-4): 51.9% vs.

				37%; febrile neutropenia (grade 3-4): 5.7% vs. 2.5%;VZV: 2% vs. 2%
Dacetuzumab	Phase 2 RCT for relapsed NHL after R-CHOP [54]	Dacetuzumab plus rituximab, ifosfamide, carboplatin and etoposide (R-ICE) vs. placebo plus R-ICE	75 vs. 76	Neutropenia (grade 3-4): 33% vs. 24%; febrile neutropenia (grade 3-4): 16% vs. 9%; leukopenia (grade 3-4): 19% vs. 16%
Elotuzumab	Open-label phase 2 randomised trial for relapsed or refractory MM [57]	Elotuzumab plus bortezomib plus dexamethasone vs. bortezomib plus dexamethasone	77 vs. 75	Overall infection: 67% vs. 53%; serious infection (grade 3-4): 21% vs. 13%
	Phase 3 RCT for relapsed or refractory MM [59]	Elotuzumab plus lenalidomide and dexamethasone vs. lenalidomide and dexamethasone	321 vs. 325	Overall infection: 81% vs. 74%; lymphopenia (grade 3-4): 77% vs. 49%; neutropenia (grade 3-4): 34% vs. 44%; rate of VZV: 4.1 vs. 2.2 per 100 pts-years
Mogamulizumab	Phase 2 RCT for aggressive adult T-cell leukaemia-lymphoma [70]	Mogamulizumab plus mLSG15 multidrug regimen (vincristine, cyclophosphamide, doxorubicin and prednisolone; doxorubicin, ranimustine and prednisolone; vindesine, etoposide, carboplatin and prednisolone) vs. mLSG15	29 vs. 24	Overall infection: 66% vs. 67%; CMV infection: 14% vs. 0%; bacteremia: 14% vs. 13%; febrile neutropenia: 90% vs. 88%; neutropenia (grade 3-4): 100% vs. 92%; lymphopenia (grade 3-4): 97% vs 75%

AML: acute myeloid leukaemia; CMV: cytomegalovirus; HL: Hodgkin lymphoma; HSCT: hematopoietic stem cell transplant; LRTI: lower respiratory tract infection; MM: multiple myeloma; NHL: non-Hodgkin lymphoma; RCT: randomized control trial; RR, relative risk; SLE: systemic lupus erythematosus; URTI: upper respiratory tract infection; UTI: urinary tract infection; VZV: varicella zoster virus.

Table 3. Summary of risk of infectious complications and possible management strategies for the reviewed targeted agents.

Group	Agent	Risk of neutropenia	Risk of HSV and VZV (anti-herpesvirus prophylaxis warranted)	Risk of PCP (anti-*Pneumocystis* prophylaxis warranted)	Risk of HBV reactivation (prophylaxis warranted for HBsAg+ / HBsAg-antiHBc+)	Risk of CMV infection (monitoring warranted)	Other infections to be considered
CD22-targeted agents	Epratuzumab	No	No	Possible (consider if concomitant corticosteroid therapy)	ND (theoretically possible)	No	ND
	Inotuzumab ozogamicin	No	No	Possible	ND (theoretically possible)	No	ND
CD30-targeted agents	Brentuximab vedotin	Yes	ND (most HSCT recipients received prophylaxis)	ND (most HSCT recipients received prophylaxis)	Yes / yes	Yes	PML
CD33-targeted agents	Gemtuzumab ozogamicin	No	ND (patients received standard prophylaxis for AML)	ND (patients received standard prophylaxis for AML)	ND (patients received standard prophylaxis for AML)	ND (patients received standard prophylaxis for AML)	ND
CD38-targeted agents	Daratumumab (no data yet available for isatuximab)	Yes	Yes (VZV)	Possible (consider if concomitant corticosteroid therapy)	Possible (consider if concomitant corticosteroid therapy)	No	ND
CD40-targeted agents	Dacetuzumab (scarce data available for lucatumumab)	Yes	Possible	Possible	ND (patients received standard prophylaxis for lymphoma)	Possible	Anticipated occurrence of OIs similar to hyper IgM syndrome (PCP, CMV infection, IFI, protozoa)

CD319-targeted agents	Elotuzumab	No	Yes (especially VZV)	Possible (consider if concomitant corticosteroid therapy)	ND (patients received standard prophylaxis for multiple myeloma)	No	ND
CCR4-targeted agents	Mogamulizumab	Possible	ND (prophylaxis may be warranted according to underlying condition)	ND (prophylaxis may be warranted according to underlying condition)	Yes	Yes	ND

AML: acute myeloid leukaemia; CMV: cytomegalovirus; HBc: hepatitis B core; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HSCT: hematopoietic stem cell transplant; HSV: herpes simplex virus; IFI: invasive fungal infection; ND: data not available; OI: opportunistic infection; PCP: *Pneumocystis jirovecii* pneumonia; PML: progressive multifocal encephalopathy; VZV: varicella-zoster virus.

Transparency declaration

- ***Conflict of interest disclosure:*** B.S. received personal fees from GSK, Sanofi-Aventis, AbbVie and Chiesi. M.M. received an investigational grant and non-financial support from Gilead, as well as personal fees from Gilead, MSD, Jansen, Pfizer and Astellas. The remining authors declare no conflicts of interest (i.e., payment or services from a third party; relevant financial activities outside the submitted work; or patents planned, pending or issued broadly relevant to the sumitted work).
- ***Funding sources:*** This research was partially supported by Plan Nacional de I+D+I 2013-2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Spanish Ministry of Economy and Competitiveness, Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/0002 and 0008) - co-financed by the European Development Regional Fund (EDRF) *"A way to achieve Europe"*. M.F.R. holds a clinical research contract "Juan Rodés" (JR14/00036) from the Instituto de Salud Carlos III, Spanish Ministry of Economy and Competitiveness.

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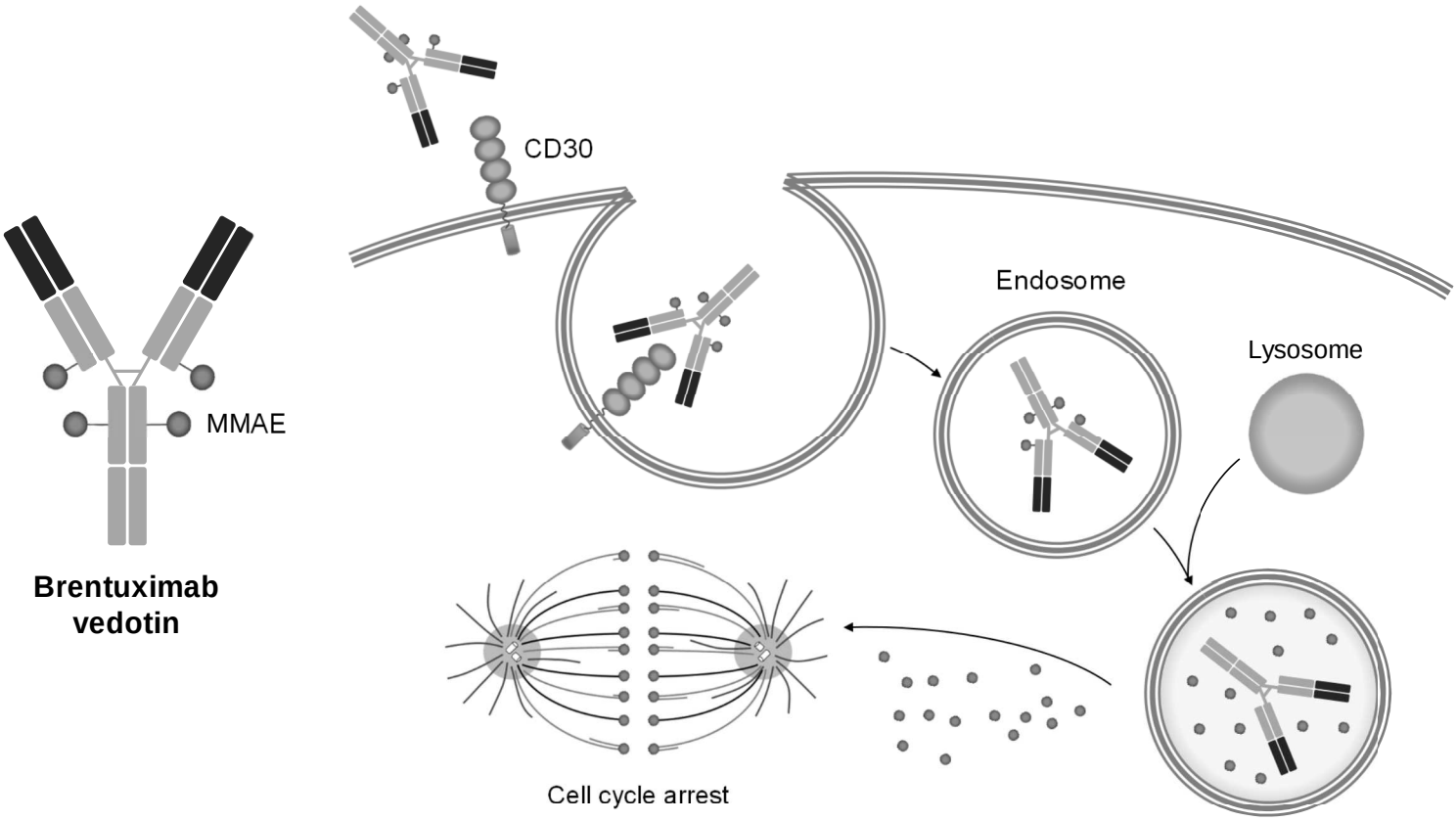
MMAE
Brentuximab vedotin
CD30
Endosome
Lysosome
Cell cycle arrest