



Complement System: a Neglected Pathway in Immunotherapy

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Abstract

Approved for the treatment of autoimmune diseases, hematological malignancies, and solid cancers, several monoclonal antibodies (mAb) make use of complement in their mechanism of action. Such an assessment is based on comprehensive investigations that used mouse models, in vitro studies, and analyses from patients at initiation (basal level to highlight deficiencies) and after treatment initiation (mAb impact on complement), which have further provided key insights into the importance of the complement activation and/or complement deficiencies in mAb activity. Accordingly, new approaches can now be developed with the final objective of increasing the clinical efficacy of mAb. These improvements include (i) the concurrent administration of fresh frozen plasma during mAb therapy; (ii) mAb modifications such as immunoglobulin G subclass switching, Fc mutation, or IgG hexamerization to improve the fixation and activation of C1q; (iii) optimization of the target recognition to induce a higher complement-dependent cytotoxicity (CDC) and/or complement-dependant cellular cytotoxicity (CDCC); and (iv) the control of soluble and cellular complement inhibitors.

Keywords Monoclonal antibody · Complement · Autoimmunity cancer

Introduction

Within therapeutic innovations from the last two decades, immunotherapeutic drugs have gained worldwide acceptance as they are able to selectively target cells. In addition, lessons from the utilization of blockbusters and first-line immunotherapy treatment in cancer and autoimmunity have revealed an impressive efficacy when drugs are initiated [1–3]. However, these strategies have also demonstrated some limitations with

an overall non-response/relapse of the patients, while some patients respond very well. As a consequence and as the immunotherapeutic options are growing, there is a necessity to start with the most appropriate immunotherapy and, in those with non-response/relapse, to better understand the mechanisms and to propose new drugs and/or associations [4–7]. Among the different mechanisms, complement activation could be the predominant mechanism in vivo and this notion is supported by recent considerations.

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The complement system is part of the innate immune system and represents an evolutionarily well-conserved system implicated in the destruction of damaged and/or non-self material such as aberrant endogenous proteins or bacteria [8, 9]. This system involves approximately 50 proteins and protein fragments including circulating proteins and cell membrane receptors [10]. As the main source of complement proteins, the liver produces inactive circulating precursors and, to be activated, specific proteases are required during complement activation leading to the release of opsonins, anaphylatoxins, chemoattractants, and activation of the cell-killing membrane attack complex (MAC). Three biochemical pathways referred to as the alternative complement pathway, the lectin pathway, and the classical pathway converge at a common amplification stage characterized by the formation of C3 convertase followed by C5 convertase, which initiates the terminal pathway of complement activation to form the MAC. The alternative complement pathway is continuously activated in the plasma by hydrolysis of C3b and such a process is increased when C3b can bind to either host cells or pathogen surfaces. Next, C3b binds factor B to form the C3 convertase (C3bBb) and binding with properdin stabilizes this enzyme (Fig. 1). The lectin pathway involves the mannan-binding lectin (MBL) or the ficolin that binds mannose residues present on the pathogen surface activating in turn the MBL-associated serine proteases, MASP-1, and MASP-2 [11]. MASPs are C1r and C1s homologues (MASP-1 and MASP-2 with C1r and C1s, respectively), MASP-2 cleaving C4 and C2 to form C3 convertase, while MASP-1 may cleave C3 directly. When produced, the C2a and C4b fragments can attach to the cell surface to become the catalytic component of

the C3 convertase (C4b2a). Last but not least, C1q can be recruited by antibodies (Ab) generated either by the adaptive immune system or by monoclonal antibodies (mAb), which constitute the classical complement pathway as described in the following paragraph.

This review underlines the link between mAb used in immunotherapy, complement activation, and their implications in autoimmune diseases and cancer therapies. Limits of this strategy as well as the areas for improvement are also developed.

The Classical Complement Pathway

Antibody-Mediated C1q Recruitment and C3 Convertase Activation

When an immunoglobulin recognizes antigens notably present on cell surface membranes, binding is associated with important changes in its crystallizable region fragment (Fc). As a consequence, the C1q molecule is able to fix the constant heavy (CH)4 domain of IgM or the CH2 domain of IgG3, IgG1, and to a lesser extent IgG2 [12, 13]. In addition, to fix the Fc part of the IgG, C1q binding requires hexamerization of IgG to be activated [12, 14, 15]. C1q is a protein consisting of six collagen-like arms, each containing an N-terminal triple helix and a C-terminal immunoglobulin-binding globular head domain [16] with an overall shape like a bunch of tulips and their changed form induces recruitment of two proteases, C1r and C1s [14, 17, 18]. The C1 complex (C1q-C1r-C1s) cleaves in a cascade the C2 followed by the C4 proteins to generate the C3 convertase (C4b2a) such as described in the alternative and lectin complement pathways.

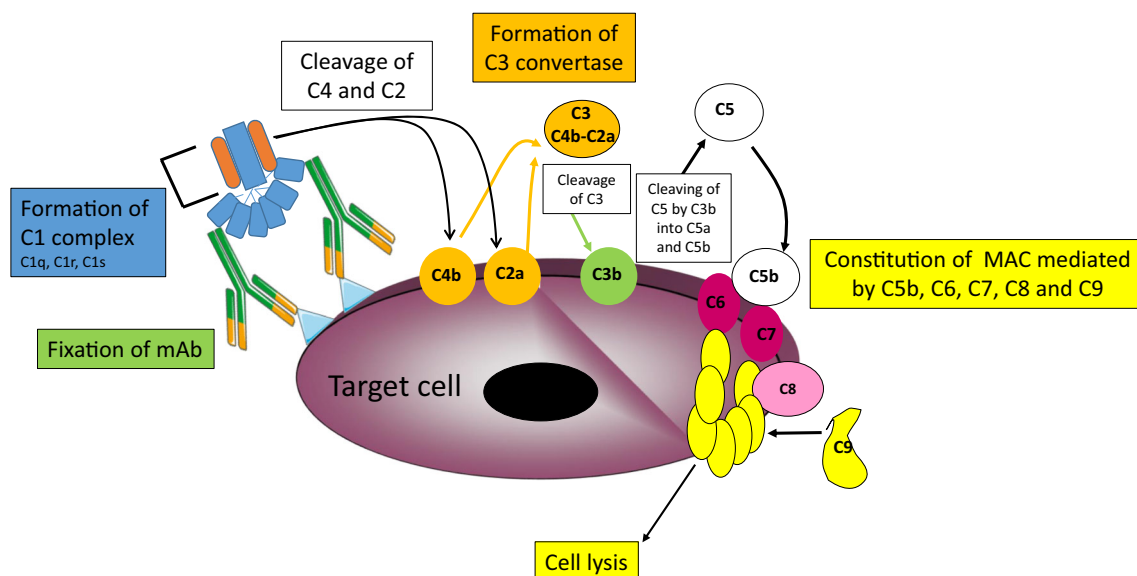


Fig. 1 Classical complement activation pathways. MAC membrane attack complex

Anaphylatoxins

Complement activation leads likewise to the production of anaphylatoxins (C3a, C4a, and C5a), molecules implicated in vascular permeability, smooth muscle contraction, histamine release from mast cells, and elaboration of reactive oxygen species [19]. Moreover, anaphylatoxins are chemoattractants and participate in the recruitment of the cellular immune system through specific receptors [20–22]. Notably, this has been reported for C5a which acts as a chemoattractant for the recruitment of macrophages and participates in the up-regulation of the activating Fc receptors while down-regulating the inhibitory receptor FcRIIb [23–26]. The increase of Fc receptors allows ADCC (antibody-dependent cellular cytotoxicity) mediated predominantly by NK (natural killers) cells and to a lesser extent by macrophages and granulocytes. Less effective than C5a, C3a can also recruit immune effector cells via the C3a receptor [27–30].

Opsonins

Opsonins (C3b, iC3b, and C4b) are also produced during complement activation and their deposition on target cells promotes CDCC (complement-dependent cellular cytotoxicity) through binding to specific complement receptors present on monocytes/macrophages, granulocytes, and NK cells (Fig. 2) [27–29, 31–33]. Combining opsonization

of target cells via the complement receptors (CR) and the fixation of antibody via Fc receptors induces phagocytosis of these cells by macrophages in a phenomenon referred to as ADCP (antibody-dependent cellular phagocytosis).

Soluble Inhibitors

Soluble regulators of the classical complement pathway include, but are not limited to, C1 inhibitor, C4-binding protein (C4BP), factor I, factor H, and complement factor H-related (CFHR) proteins (Table 1). C1 inhibitor is a protease inhibitor that controls the activity of the C1 complex, thereby preventing the first step in complement activation by antibodies [37]. By competitively binding the C4 component, C4BP is effective in inhibiting the C3 convertase formation. Factor I regulation occurs downstream of C3 convertase by degrading the active C3b product into inactive breakdown products. C3b degradation often involves the help of factor H or of the complement factor H-related (CFHR)3, both of which exhibit cofactor activity for factor I [39, 42]. In addition to cofactor activity on C3b, factor H promotes dissociation of the alternative pathway C3 convertase by displacing factor B from C3b. The functions of CFHR proteins are less known, but it has been demonstrated that CFHR1 can inhibit C5 convertase and reduce C5b deposition on target cell surfaces [41]. Due to high sequence homology, it is proposed that the other CFHR proteins share similar complement regulatory functions.

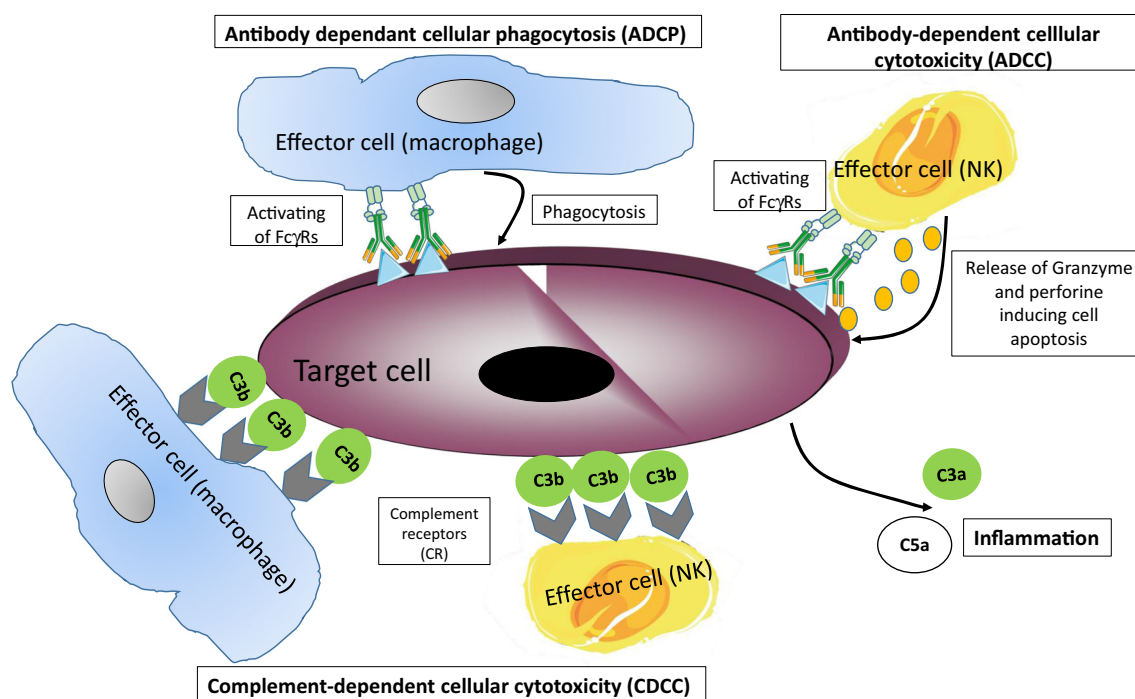


Fig. 2 Complement lysis activation pathways. ADCC antibody-dependent cellular cytotoxicity, ADCP antibody-dependent cellular phagocytosis, CDCC complement-dependent cellular cytotoxicity, CR complement receptor, FcγR fragment crystallizable gamma receptor

Table 1 Main inhibition functions of complement regulatory molecules

Number	Role	References
Membrane molecules		
CD46	Inactivates, through cleavage, complement components C3b and C4b by serum factor I	[34]
CD55	Prevents formation of new enzymes C3- and C5-convertases, and also accelerates decay of these preformed enzymes	[35]
CD59	Interferes with MAC formation through its physical incorporation to the forming complex, avoiding the binding of C9	[35]
Sialic acids	Favors adhesion of factor H on the cell membrane and has an inhibitory effect on C3	[36]
Soluble molecules		
C1 inhibitor	Irreversibly binds to and inactivates C1r and C1s proteases in the C1 complex.	[37]
C4BP	Inactivates MASP-1 and MASP-2 proteases in MBL complexes Inhibits the classical C3 convertase by competitively binding the C4 component Accelerates decay of C3-convertase	[38]
Factor I	Is a cofactor for serine protease factor I which cleaves C4b and C3b. Is responsible for specific cleavage of C3b and C4b	[39]
Factor H	Displays decay acceleration activity that promotes dissociation of the alternative pathway C3 convertase and acts as a cofactor for the factor I-mediated proteolytic inactivation of C3b	[40]
CFHR	Inhibits the C5 convertase and reduces C5b deposition on target cell surfaces	[41]

Cellular Membrane Regulators

Membrane-bound regulators of complement activation (mRCA) include CD46 (membrane cofactor protein), CD55 (decay accelerating factor, DAF), and CD59 (protectin) (Table 1). CD46 serves as a cofactor for factor I and promotes C3b degradation to its inactive form, iC3b. CD55 prevents CDC by inhibiting the C3 convertase and thus C3b generation. There is also evidence that CD55 can negatively regulate T cell-mediated immunity [43, 44]. CD59 prevents MAC formation downstream of C5b deposition. In addition to the membrane-bound complement regulators, expression of sialic acids on the cell surface was found to be important (Table 1). Sialic acids act frequently via a α 2–3 or α 2–6 glycosidic linkage to galactose and N-acetylgalactosamine. Enzymes that support these sialylation reactions belong to the sialyltransferase (ST) family, and they are unlikely to be expressed in normal B cells [45]. The presence of sialic acids is implicated in the recruitment of soluble complement inhibitors such as factors H and I [36], that, in turn, control the mAb-capacity to induce complement activation [46, 47].

Therapeutic Monoclonal Antibodies and Complement Activity

Animal Models

Several animal models support a critical role for complement in mAb activity. As an example, the C1q-deficient mice

exhibit a defective response to rituximab (RTX), an anti-CD20 mAb, in a lymphoma tumor mouse model, delineating the importance of CDC and/or CDCC as important effector mechanisms in immunotherapy instead of ADCC as such an effect was not reported after depletion of either NK cells or granulocyte cells [48]. On the other hand, mAb efficiency in mouse models can be improved by enhancing complement activation and this was demonstrated by changing the IgG1 heavy chain of the anti-CD20 RTX to IgG3 which is more efficient in binding C1q [49].

Lessons from Anti-CD20 mAbs

The implication of a role for complement in mAb-mediated immunotherapy was demonstrated first in patients treated with RTX since this mAb was one of the first therapeutic mAbs approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to be used in non-Hodgkin's lymphomas (NHL), in chronic lymphocytic leukemia (CLL) [50], and later in autoimmune diseases such as rheumatoid arthritis [51] and autoimmune hemolytic anemia [52]. In patients with systemic lupus erythematosus (SLE), RTX is not recommended as a first line of treatment although some case reports have confirmed a long-term beneficial effect [2].

Efficacy of RTX varies from patient to patient and a higher rate of relapse has been observed in CLL patients compared with NHL [53]. RTX mediates its efficacy by different mechanisms of B cell death mediated by complement-dependent pathways through MAC formation (CDC) and the clearance of C3b(i) opsonized cells by macrophages (ADCP); or by

non-complement-dependent mechanisms (ADCC and direct apoptosis) [48, 54–59]. Following treatment with RTX, the CD20 molecules are clustered in lipid rafts (LRs) allowing RTX hexamer formation that is necessary for the fixation of C1q [60].

In order to induce a higher CDC, the fully humanized anti-CD20 mAb ofatumumab (2F2, HuMax-CD20, Genmab/GSK) was developed. Ofatumumab binds to a portion of CD20 closer to the B cell membrane, and located in the CD20 small extracellular loop. Preclinical studies have thus far established that ofatumumab has a slower rate of dissociation from CD20 than RTX and greater CDC power [61] with sustained success [62]. However, such an effect may be deleterious on mAb activity since ofatumumab administration leads to a rapid and significant depletion of circulating C4 levels in CLL patients with initial lymphocytosis. Indeed, C4 depletion is suspected of having a therapeutic impact based on a report of non-response in a patient with an accelerated depletion, while a partial depletion of circulating CLL was observed in those patients with a partial response [63]. Moreover, additional mAbs targeting different CD20 epitopes and displaying complement activation have been approved by the FDA and are summarized in Table 2 [70–75, 77–79].

Other mAbs

The success of anti-CD20 mAbs has encouraged drug developers to propose novel mAbs of specific B cell lineage such as CD19 or CD22 (Table 2). All these mAbs are IgG1 in order to mediate complement activation [81–86].

Furthermore, in hematological malignancies, targeting non-specific B cell lineage tumor-related antigens such as oncogenic receptors, chemokine receptors, and molecules involved in the formation and preservation of the tumor micro-environment represents another way of research. To this end, different mAbs have been developed and some of them (typically IgG1 mAbs) allow activation of complement and are identified in Table 3. Succinctly, alemtuzumab, an anti-CD52, was created and demonstrated an activation of complement and efficiency in CLL [87]. An anti-DKK1 (BHQ880) was generated for the treatment of osteolytic lesions in multiple myeloma and its action is mediated both by ADCC and CDC, although well tolerated the clinical benefits of this mAb are limited. [88]. Other mAbs use not only ADCC but also activation of complement through CDC and/or ADCP to induce their efficiencies (Table 3). These other mAbs include mAbs targeting immune checkpoints (CD80, CD40, and CD70), receptors of cytokines (BAFF-R, IL-3R α (CD123)), chemokine and its receptor (CCR4, CXCR4), signaling pathways (GRP78, CD98 (4F2, FRP-1), CD38, CD157 (BST-1), SLAMF7 (signaling lymphocytic activation molecule family

member F7) (CD319, CS1), EPHA3 (ephrin type-A receptor 3)), ganglioside (M2 (GM2)), and CD37 (but its exact biological function has not yet been elucidated).

In addition, mAbs with complement activity are not limited to hematological malignancies and autoimmune diseases since other mAbs directed against solid tumors are effective through the activation of complement (Table 4). We can note as targets: epithelial cell adhesion molecule (EpCAM), a cell surface glycoprotein implicated in cell adhesion, present in epithelial tissues and highly expressed on carcinomas [134]; HER2 (human epidermal growth factor receptor 2), a glycoprotein of the tyrosine kinase family enhancing cell proliferation and favoring survival with expression cell location similar to EpCAM [135]; EGFR (epidermal growth factor receptor) a glycoprotein of the tyrosine kinase family inducing cell proliferation and differentiation with an expression of epithelial cells [136]; and GD2 (glycolipid disialoganglioside 2), a cell surface glycolipid receptor implicated in the attachment of tumor cells to extracellular matrix, present on nervous system cells and melanocytes, highly expressed on neuroblastomas and melanomas [137].

A Specific Case: Eculizumab

The atypical hemolytic uremic syndrome (aHUS) is caused by C3 mutations with a gain of function or caused by a deficiency of the complement inhibitor CD46 [138, 139]. Against this phenomenon, a therapeutic anti-C5 antibody, eculizumab, which inhibits the complement terminal pathway initiation, was developed and approved for aHUS therapy [140–142].

Eculizumab is also recommended in paroxysmal nocturnal hemoglobinuria (PNH) as this disease is characterized by defective control of the complement pathway at the membrane level of red blood cells and platelets [143]. Indeed, somatic mutations in the X-linked *PIG-A* (phosphatidylinositol glycan anchor biosynthesis class A) gene which is involved in glycosylphosphatidylinositol (GPI) anchor biosynthesis underlie a group of congenital syndromes characterized by severe neurodevelopment defects. Among the 30 enzymes that require GPI biosynthesis, the two regulatory complement proteins CD55 and CD59 are important to prevent hemolytic anemia [144].

Eculizumab is used, furthermore, to control complement activation during (i) myasthenia gravis [145], (ii) thrombotic microangiopathy complications associated with SLE, and (iii) thrombotic events related to the anti-phospholipid syndrome (APS) [146]. Because of the suppression of the complement activation pathway, great care must be taken in patients treated with eculizumab to prevent the development of infections [147].

Table 2 In chronological order of medical therapeutic use, characteristics of monoclonal antibodies directed to B cell-specific antigens, for which activation of complement was observed

Target	mAb (<i>brand name</i> /pharmaceutical society)	IgG class-format	Complement-mediated anti-tumor activities of mAbs	Hematologic malignancy(ies)	References
CD20	Rituximab (<i>Rituxan</i> /Roche Biogen/Genentech)	IgG1 chimeric	CDC ADCC	B-NHL, CLL	[64] [65]
	Ofatumumab (<i>Arzerra</i> /Novartis)	Fully humanized IgG1 kappa	CDC ADCC	CLL HL B-NHL FL	[66] [67] [68] [69]
	Veltuzumab, IMMU-106, h20 (Immunomedics)	Humanized IgG1	CDC ADCC	B-NHL CLL ITP FL	[70] [71] [72]
	Ocrelizumab, PRO70769 (<i>Ocrevus</i> /Biogen Idec; Genentech)	Humanized IgG1	CDC ADCC	CLL	[73]
	Obinutuzumab, GA101, (<i>Gazyva</i> /Roche Glycart Biotech)	Humanized IgG1 glycoengineered Fc fragment	CDC ADCC	B-NHL	[74] [75]
	Ocaratuzumab, AME-133v, LY2469298 (Applied Molecular Evolution)	Humanized IgG1 glycoengineered Fc fragment	CDC ADCC	FL	[76] [77]
	Ublituximab, TG-1101, LFB-R603 (LFB Biotech.; rEVO Biologies)	Chimeric IgG1 glycoengineered Fc fragment	CDC ADCC	CLL	[78]
	Inebilizumab, MEDI 551 (Collective Therapeutics)	Humanized IgG1 glycoengineered Fc fragment	ADCC CDC	B-NHL CLL DLBCL B-NHL	[79] [80] [81] [82]
	MOR00208, XmAb5574 (Xencor)	Humanized IgG1 glycoengineered Fc fragment	ADCC ADCP	CLL B-NHL	[83]
	MDX-1342 (Medarex)	Fully human IgG1 glycoengineered Fc fragment	ADCC	CLL	[84]
CD22	Epratuzumab, AMG-412, IMMU-103 (Immunomedics)	Humanized IgG1	ADCC	B-ALL B-NHL FL	[85] [86]

mAb, monoclonal antibody; *CDC*, complement-dependent cytotoxicity; *ADCC*, antibody-dependent cell-mediated cytotoxicity; *ADCP*, antibody-dependent cell-mediated phagocytosis; *B-NHL*, B cell non-Hodgkin's lymphoma; *HL*, Hodgkin's lymphoma; *CLL*, chronic lymphocytic leukemia; *DLBCL*, diffuse large B cell lymphoma; *MM*, multiple myeloma; *FL*, follicular lymphoma; *B-ALL*, B cell acute lymphoblastic leukemia

Table 3 In chronological order of medical therapeutic uses, characteristics of monoclonal antibodies directed to non B cell-specific antigens, for which activation of complement was observed

Target	mAb (<i>brand name</i> /pharmaceutical society)	Ig class-format	Complement-mediated anti-tumor activities of mAbs	Hematologic malignancy(ies)	References
CD52	Alentuzumab (<i>Campath</i> /Genzyme)	Humanized IgG1	ADCC CDC	CLL	[87]
DKK-1	BHQ880 (MorphoSys; Nartis)	Fully human IgG1 glycoengineered Fc fragment	ADCC?	MM	[88]
CD80	Galiximab (Biogen Idec)	Human-primate chimeric IgG1	ADCC	FL B-NL	[89, 90]
CD40	Lucatumumab, CHIR-12, 12, HCD-122 (Novartis; Xoma)	Fully human IgG1	ADCC	MM CLL	[91–93]
	Dacetuzumab, SGN-40 (Seattle Genetics)	Humanized IgG1	ADCC ADCP	FL DLBCL CLL	[94–96]
BAFF-R	VAY736, ianalumab, NOV-5 (MorphoSys; Novartis)	Fully human IgG1 glycoengineered Fc fragment	ADCC	MM CLL	[97]
CD70	ARGX-110 (arGEN-X)	Humanized IgG1 glycoengineered Fc fragment	ADCC ADCP CDC	AML MDS	[98]
CD37	BI836826 (Boehringer Ingelheim)	Chimeric IgG1 glycoengineered Fc fragment	ADCC	DLBCL CLL	[99]
	Otlertuzumab, TRU-016 (Tribion Pharmaceuticals)	Fv-Fc	ADCC	CLL B-NHL	[100, 101]
GRP78 (BiP)	PAT-SM6 (OncoMab GmbH)	Fully human IgM	CDC	MM	[102]
CD98 (4F2, FRP-1)	IGN523 (Igenica)	Humanized IgG1	ADCC CDC	AML	[103]
Ganglioside M2 (GM2)	BIW-8962 (Kyowa Hakko Kirin Co.)	Humanized IgG1	ADCC	MM	[104]
ICAM-1 (CD54)	BI-505 (BioInvent International)	Fully human IgG1	ADCC ADCP	MM	[105, 106]
EPHA3	Ifabotuzumab, KB004 (Humanigen)	Humanized IgG1 kappa	ADCC	AML	[107]
CD157 (BST-1)	OBT357, MEN1112 (Menarini; Oxford BioTherapeutics)	Humanized IgG1 glycoengineered Fc fragment	ADCC	AML	[107]
CD38	Daratumumab, JNJ-54767414 (<i>Darzalex</i> /Janssen Biotech)	Humanized IgG1	ADCC CDC ADCP	MM MCL DLBCL FL ALL	[108] [109–112]
	Isatuximab, SAR650984 (ImmunoGen)	Humanized IgG1	ADCC CDC	AML MM T-ALL	[113, 114]
	MOR202, MOR03087 (MorphoSys)	Humanized IgG1	ADCP ADCC	T-NHL MM	[115]

Table 3 (continued)

Target	mAb (<i>brand name</i> /pharmaceutical society)	Ig class-format	Complement-mediated anti-tumor activities of mAbs	Hematologic malignancy(ies)	References
SLAMF7 (CD319, CS1)	Elotuzumab, HuiLuc63, BMS-901608 (<i>Empliciti</i>)/Bristol-Myers Squibb)	Humanized IgG1	ADCP ADCC	MM	[116]
CCR4	Mogamulizumab, KW-0761 (<i>Poteligeo</i> /Kyowa Hakko Kirin Co.)	Humanized IgG1	ADCC	ATL CTCL PTCL NK lymphoma	[117–120]
CXCR4	PF-06747143 (Pfizer)	Humanized IgG1	ADCC	AML	[121, 122]
IL-3R α (CD123)	CSL360 (CSL)	Chimeric IgG1	CDC ADCC	CLL AML	[123]
	Talacotuzumab, JNJ-56022473, CSL362 (CSL)	Humanized IgG1 glycoengineered Fc fragment	ADCC	AML MDS	[124]
	XmAb14045 (Xencor)	Fully human IgG1	ADCC	AML B-ALL DC Neoplasm	[125]
	KHK2823 (Kyowa Hakko Kirin Co.)	Fully human IgG1	ADCC	CML AML MDS	

mAb, monoclonal antibody; *CDC*, complement-dependent cytotoxicity; *ADCC*, antibody-dependent cell-mediated cytotoxicity; *ADCP*, antibody-dependent cell-mediated phagocytosis; *B-NHL*, B cell non-Hodgkin's lymphoma; *T-NHL*, T cell non-Hodgkin's lymphoma; *CLL*, chronic lymphocytic leukemia; *CML*, chronic myeloid leukemia; *DLBCL*, diffuse large B cell lymphoma; *MM*, multiple myeloma; *FL*, follicular lymphoma; *ALL*, acute lymphoblastic leukemia; *T-ALL*, T cell acute lymphoblastic leukemia; *B-ALL*, B cell acute lymphoblastic leukemia; *AML*, acute myeloid leukemia; *ATL*, adult T cell leukemia/lymphoma; *CTCL*, cutaneous T cell lymphoma; *PTCL*, peripheral T cell lymphoma; *NK lymphoma*, natural killer lymphoma; *MDS*, myelodysplastic syndrome; *DC neoplasm*, dendritic cell neoplasm

Table 4 In chronological order of medical therapeutic uses, characteristics of monoclonal antibodies directed to solid tumor antigens, for which activation of complement was observed

Target	mAb (brand name/pharmaceutical society)	Ig class-format	Complement-mediated anti-tumor activities of mAbs	Solid tumors	References
EpCAM	Edrecolomab (<i>Panorex</i> /GlaxoSmith Kline)	Murine IgG2a	ADCC CDC ADCP ADCC	EpCAM $\pm$ colon cancer	[126]
HER2	Pertuzumab (<i>Perjeta</i> /Genentech)	Humanized IgG1		Breast cancer Metastatic gastric or gastro-esophageal junction cancer	[127, 128]
Epidermal growth factor receptor (EGFR)	Trastuzumab (<i>Herceptin</i> /Genentech)	Humanized IgG1		Breast cancer	[129, 130]
	Necitumumab (<i>Portrazza</i> /Eli Lilly and Co.)	Human IgG1	ADCC ADCP ADCC	Gastric cancer HNSCC	[131]
	Cetuximab (<i>Erbix</i> /ImClone LLC)	Chimeric IgG1	ADCC	HNSCC	[132]
EpCAM/CD3	Catumaxomab (<i>Removab</i> /Trion Pharma/Biotech)	Rat/mouse bispecific monoclonal antibody	ADCC CDC ADCP	EpCAM $\pm$ carcinoma-related ascites	[133]

mAb, monoclonal antibody; ADC, antibody–drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer

Complement Altered Pathways and Immunotherapy

For effective efficacy of the mAb, the complement pathway needs to be effective since innate or acquired complement deficiencies can be observed in those patients treated with mAb and this is particularly true for patients with autoimmune diseases, hematological malignancies, or tumoral aggressiveness [148, 149]. To illustrate this purpose, some patients with Sjögren's syndrome present an innate homozygous deficiency of complement C4A or C4B, which promotes the autoimmune disease and among these patients the acquisition of a severe deficit in C4 is associated with the apparition of a mucosa-associated lymphoid tissue lymphoma (MALT) [150, 151].

On the other hand, enhancing the complement pathway could be favorable for tumor establishment and progression due to the pathway's involvement in many diverse functions including angiogenesis, trophoblast invasion, and tissue remodeling [152]. As a consequence, an uncontrolled increase activity of the complement pathway when using mAb may be beneficial for the tumor and can lead moreover to chronic inflammation and tissue damage notably because of the lack of effective complement inhibitors or of the increase of complement proteins [153–155].

Autoimmune Diseases

During autoimmune diseases, complement activation and inflammation could be detrimental for patients. To prevent these phenomena, eculizumab was tested for the treatment of SLE and RA but had limited results compared with other treatments [156]. In order to improve its efficacy in RA, Durigutto et al. have proposed fusing eculizumab with a synovial homing peptide in order to better inhibit the classical complement pathway activation by immune complexes in joints [157, 158]. In the APS, eculizumab was used in association with RTX and demonstrated some beneficial results [159]. As indicated before, eculizumab may be at increased risk for developing serious infections, especially with encapsulated bacteria, by preventing the formation of MAC. Then, development of new mAbs was lead as reported for the anti-C5a mAb IFX-1, which does not interfere with the constitution of MAC [160]. Alternatively, the effects of C5a could be neutralized by blocking its receptor C5aR. Antibodies targeting C5aR or another C5a receptor, C5L2, have demonstrated their utility in experimental models and they have been tested in human clinical trials [161–164]. C5 is also a target in other diseases such as age-related macular degeneration (AMD) for which chronic low-grade complement activation together with inflammation was reported but the efficacy of eculizumab in this indication has not been demonstrated [165].

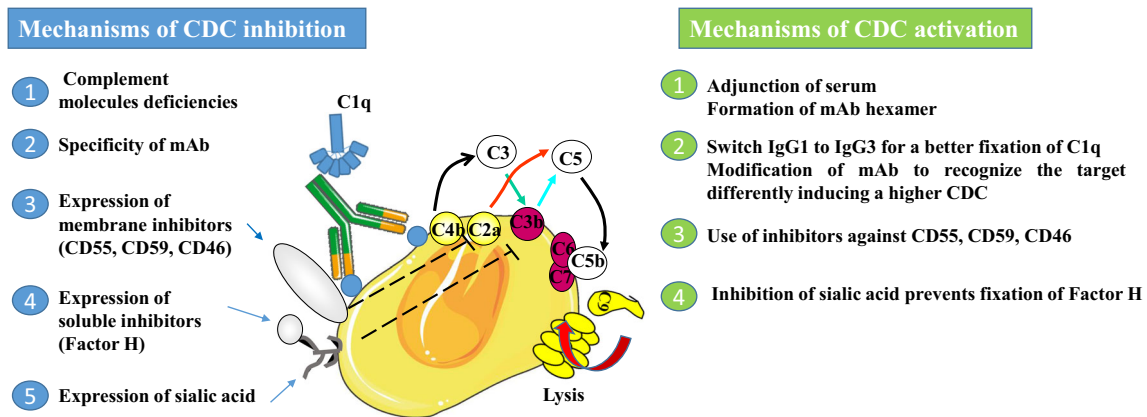


Fig. 3 Mechanisms for inhibiting complement-dependent cytotoxicity and strategies for correcting this inhibition. CDC complement-dependent cytotoxicity, mAb monoclonal antibody

On the contrary, there are also early protein deficiencies of the classical complement pathway, either innate or acquired that could impact mAb therapy. Complete deficiencies (homozygotes or composite heterozygotes) in proteins of the early phase of the classical pathway (C1q, C1r, C1s, C1s, C4, C2) are associated with a predisposition to SLE and related diseases including Sjögren's syndrome. Ninety percent of patients diagnosed with complete C1q deficiency have SLE, making it the highest susceptibility factor for SLE disease [166]. The link between complement and SLE is ambiguous [149, 167]. The fact that hereditary or early protein deficiencies of the classical pathway are associated with SLE suggests that complement plays a beneficial role in SLE pathophysiology, probably because of its role in the clearance of immune complexes and apoptotic cells. On the other hand, this activation of the complement contributes to tissue damage and inflammation. Treatment with fresh frozen plasma has been proposed in SLE to restore complement activity in those patients with deficiency [168] and improvement was reported in a clinical trial [169]. Combination of plasma exchange and RTX has been proposed in APS [170] even if the clinical benefit has not been confirmed by Abisror et al. [171].

Hematological Diseases

Complement deficiencies are reported in CLL patients and suspected of limiting anti-CD20 mAb efficacy *in vivo* [172]. In this disease, serum complement is quickly consumed upon administration of RTX or with ofatumumab [32, 63]. The serum complement levels declined quickly *in vitro* as assessed by complement hemolytic activity on sheep erythrocytes [32]. Additionally, C1 and C4 levels were below normal in more than 50% of the sera tested [173]. To further support the importance of the complement pathway, it was established that RTX therapeutic activity was strongly enhanced in CLL patients resistant to RTX after concurrent administration of fresh frozen plasma [174].

Moreover, in follicular (FL) and diffuse large B cell lymphoma (DLBCL), C1QA polymorphisms and complement regulatory CFH and CFHR5 gene expression may affect the clinical response and duration of response to RTX therapy, suggesting functional complement is important for anti-tumor effects by immunotherapies [175, 176]. Some authors (including ourselves) have not confirmed such results [177].

Solid Tumors and Complement Activation

In solid tumors, alternative complement pathway activation is often observed. For example, in colorectal tumors, a positive correlation was found with the serum level of MASP-2 and the aggressiveness of the disease [178]. In glioblastoma multiform (GBM), MBL deficiency is significantly more frequent in healthy controls than in GBM patients, pointing to a pro-tumor role for increased alternative complement pathway activation [179]. Some tumor cells can induce intracellular activation of C3 promoting the accumulation and immune-suppressive activity of tumor-associated macrophages (TAMs) in a C3aR-dependent mechanism. Blocking C3 and immunosuppressive TAM enhances the anti-tumor activity of anti-PDL1 mAb [180]. Conversely, activation of complement could be benefit for immune response as demonstrated in mice with intra-tumoral delivery of antigen with complement C3-bound liposomes [181]. Then, the challenge is to be able to amplify the activity of antibodies by activating the complement while ensuring that this activation does not benefit the tumor.

Perspectives

As described, an effective complement pathway is necessary for efficient immunotherapy in many cases and this can be compromised particularly in those patients with autoimmune

diseases and cancers (Fig. 3). New strategies are currently in development to improve complement activation by mAb:

-The addition of serum to restore innate and/or acquired complement deficiencies in order to enhance the action of the mAb as reported with rituximab [182].

-Promoting mAb hexamerization on opsonized cells is another option to improve C1q recruitment as demonstrated with a Fc mutated IgG1 anti-epidermal growth factor receptor (EGFR) mAb [183]. Other alternatives are to perform single-point mutations in the Fc domain of the IgG (e.g., E345K or E430G) to enhance Fc:Fc interaction or to perform IgG subclass switch to IgG3 for better fixation of C1q [49].

-The use of bispecific antibodies targeting tumor antigens and neutralizing complement regulators overexpressed on cancer cells has been developed [184].

-Development of strategies to neutralize soluble and cellular complement regulators represent two other strategies to increase the efficacy of immunotherapy [185].

Conclusion

Complement is implicated positively in innate and specific immunity against tumors but also negatively in these same diseases and in autoimmune disorders. Understanding the innate mechanisms as reviewed in this special issue [186–194] and controlling complement in these pathologies represents an important challenge not only to have a better view of the pathophysiology of the disease but also to develop and improve the efficacy of the immunotherapy. Due to the importance of the complement pathway on mAb activity, such aspects need to be taken into consideration from the beginning of an immunotherapy development effort [182].

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Bagacean C, Zdrenghea M, Tempescul A, Cristea V, Renaudineau Y (2016) Anti-CD20 monoclonal antibodies in chronic lymphocytic leukemia: from uncertainties to promises. *Immunotherapy* 8:569–581
2. Seret G, Hanrotel C, Bendaoud B, Le Meur Y, Renaudineau Y (2013) Homozygous FCGR3A-158F mutation is associated with delayed B-cell depletion following rituximab but with preserved efficacy in a patient with refractory lupus nephritis. *Clin Kidney J* 6:74–76
3. Devauchelle-Pensec V, Pennec Y, Morvan J, Pers JO, Daridon C, Jousse-Joulin S, Roudaut A, Jamin C, Renaudineau Y, Roué IQ, Cochenier B, Youinou P, Saraux A (2007) Improvement of Sjogren's syndrome after two infusions of rituximab (anti-CD20). *Arthritis Rheum* 57:310–317
4. Gazeau P, Alegria GC, Devauchelle-Pensec V, Jamin C, Lemerle J, Bendaoud B, Brooks WH, Saraux A, Cornec D, Renaudineau Y (2017) Memory B cells and response to abatacept in rheumatoid arthritis. *Clin Rev Allergy Immunol* 53:166–176
5. Gazeau P, Devauchelle-Pensec V, Pochard P, Pers JO, Saraux A, Renaudineau Y, Cornec D (2016) Abatacept efficacy in rheumatoid arthritis is dependent upon baseline blood B-cell levels. *Rheumatology (Oxford)* 55:1138–1140
6. Bagacean C, Tempescul A, Ternant D, Banet A, Douet-Guilbert N, Bordron A, Bendaoud B, Saad H, Zdrenghea M, Berthou C, Paintaud G, Renaudineau Y (2019) 17p deletion strongly influences rituximab elimination in chronic lymphocytic leukemia. *J Immunother Cancer* 7:22
7. Bagacean C, Tomuleasa C, Tempescul A et al (2019) Apoptotic resistance in chronic lymphocytic leukemia and therapeutic perspectives. Critical reviews in clinical laboratory sciences. In Press, pp 1–32
8. Nonaka M, Kimura A (2006) Genomic view of the evolution of the complement system. *Immunogenetics* 58:701–713
9. Bordet J (1895) Les leucocytes et les propriétés actives du sérum chez les vaccins. *Annales de l'Institut Pasteur* 9:462–506
10. Kemper C, Pangburn MK, Fishelson Z (2014) Complement nomenclature 2014. *Mol Immunol* 61:56–58
11. Ali YM, Lynch NJ, Haleem KS, Fujita T, Endo Y, Hansen S, Holmskov U, Takahashi K, Stahl GL, Dudler T, Girija UV, Wallis R, Kadioglu A, Stover CM, Andrew PW, Schwaible WJ (2012) The lectin pathway of complement activation is a critical component of the innate immune response to pneumococcal infection. *PLoS Pathog* 8:e1002793
12. Diebolder CA, Beurskens FJ, de Jong RN, Koning RI, Strumane K, Lindorfer MA, Voorhorst M, Ugurlar D, Rosati S, Heck AJR, van de Winkel JGJ, Wilson IA, Koster AJ, Taylor RP, Ollmann Saphire E, Burton DR, Schuurman J, Gros P, Parren PWHI (2014) Complement is activated by IgG hexamers assembled at the cell surface. *Science* 343:1260–1263
13. Raju TS (2008) Terminal sugars of Fc glycans influence antibody effector functions of IgGs. *Curr Opin Immunol* 20:471–478
14. Burton DR, Gregory L, Jefferis R (1986) Aspects of the molecular structure of IgG subclasses. *Monogr Allergy* 19:7–35
15. Cattaneo A, Neuberger MS (1987) Polymeric immunoglobulin M is secreted by transfectants of non-lymphoid cells in the absence of immunoglobulin J chain. *EMBO J* 6:2753–2758
16. Reid KB, Porter RR (1976) Subunit composition and structure of subcomponent C1q of the first component of human complement. *The Biochemical journal* 155:19–23
17. Czajkowsky DM, Shao Z (2009) The human IgM pentamer is a mushroom-shaped molecule with a flexural bias. *Proc Natl Acad Sci U S A* 106:14960–14965
18. Feinstein A, Richardson N, Taussig MI (1986) Immunoglobulin flexibility in complement activation. *Immunol Today* 7:169–174
19. Zhou W (2012) The new face of anaphylatoxins in immune regulation. *Immunobiology* 217:225–234

20. Derer S, Beurskens FJ, Rosner T, Peipp M, Valerius T (2014) Complement in antibody-based tumor therapy. *Crit Rev Immunol* 34:199–214
21. Chen NJ, Mirtsos C, Suh D, Lu YC, Lin WJ, McKerlie C, Lee T, Baribault H, Tian H, Yeh WC (2007) C5L2 is critical for the biological activities of the anaphylatoxins C5a and C3a. *Nature* 446:203–207
22. Walport MJ (2001) Complement. First of two parts. *N Engl J Med* 344:1058–1066
23. Shushakova N, Skokowa J, Schulman J, Baumann U, Zwirner J, Schmidt RE, Gessner JE (2002) C5a anaphylatoxin is a major regulator of activating versus inhibitory FcγR in immune complex-induced lung disease. *J Clin Invest* 110:1823–1830
24. Schmidt RE, Gessner JE (2005) Fc receptors and their interaction with complement in autoimmunity. *Immunol Lett* 100:56–67
25. Huber-Lang M, Sarma JV, Zetoune FS, Rittirsch D, Neff TA, McGuire SR, Lambris JD, Warner RL, Flierl MA, Hoesel LM, Gebhard F, Younger JG, Drouin SM, Wetzel RA, Ward PA (2006) Generation of C5a in the absence of C3: a new complement activation pathway. *Nat Med* 12:682–687
26. Kumar V, Ali SR, Konrad S, Zwirner J, Verbeek JS, Schmidt RE, Gessner JE (2006) Cell-derived anaphylatoxins as key mediators of antibody-dependent type II autoimmunity in mice. *J Clin Invest* 116:512–520
27. Vetvicka V, Thornton BP, Wieman TJ, Ross GD (1997) Targeting of natural killer cells to mammary carcinoma via naturally occurring tumor cell-bound iC3b and beta-glucan-primed CR3 (CD11b/CD18). *J Immunol* 159:599–605
28. Klein E, Di Renzo L, Yefenof E (1990) Contribution of CR3, CD11b/CD18 to cytotoxicity by human NK cells. *Mol Immunol* 27:1343–1347
29. Li B, Allendorf DJ, Hansen R, Marroquin J, Ding C, Cramer DE, Yan J (2006) Yeast beta-glucan amplifies phagocyte killing of iC3b-opsonized tumor cells via complement receptor 3-Syk-phosphatidylinositol 3-kinase pathway. *J Immunol* 177:1661–1669
30. Brekke OL, Christiansen D, Fure H, Fung M, Mollnes TE (2007) The role of complement C3 opsonization, C5a receptor, and CD14 in *E. coli*-induced up-regulation of granulocyte and monocyte CD11b/CD18 (CR3), phagocytosis, and oxidative burst in human whole blood. *J Leukoc Biol* 81:1404–1413
31. Kennedy AD, Solga MD, Schuman TA, Chi AW, Lindorfer MA, Sutherland WM, Foley PL, Taylor RP (2003) An anti-C3b(i) mAb enhances complement activation, C3b(i) deposition, and killing of CD20+ cells by rituximab. *Blood* 101:1071–1079
32. Kennedy AD, Beum PV, Solga MD, DiLillo DJ, Lindorfer MA, Hess CE, Densmore JJ, Williams ME, Taylor RP (2004) Rituximab infusion promotes rapid complement depletion and acute CD20 loss in chronic lymphocytic leukemia. *J Immunol* 172:3280–3288
33. Gorter A, Meri S (1999) Immune evasion of tumor cells using membrane-bound complement regulatory proteins. *Immunol Today* 20:576–582
34. Weng WK, Levy R (2001) Expression of complement inhibitors CD46, CD55, and CD59 on tumor cells does not predict clinical outcome after rituximab treatment in follicular non-Hodgkin lymphoma. *Blood* 98:1352–1357
35. Golay J, Lazzari M, Facchinetti V, Bernasconi S, Borleri G, Barbui T, Rambaldi A, Introna M (2001) CD20 levels determine the in vitro susceptibility to rituximab and complement of B-cell chronic lymphocytic leukemia: further regulation by CD55 and CD59. *Blood* 98:3383–3389
36. Meri S, Pangburn MK (1990) Discrimination between activators and nonactivators of the alternative pathway of complement: regulation via a sialic acid/polyanion binding site on factor H. *Proc Natl Acad Sci U S A* 87:3982–3986
37. Davis AE 3rd (2004) Biological effects of C1 inhibitor. *Drug News Perspect* 17:439–446
38. Rawal N, Pangburn MK (2007) Role of the C3b-binding site on C4b-binding protein in regulating classical pathway C5 convertase. *Mol Immunol* 44:1105–1114
39. Sanchez-Gallego JI, Groeneveld TW, Krentz S et al (2012) Analysis of binding sites on complement factor I using artificial N-linked glycosylation. *J Biol Chem* 287:13572–13583
40. Weiler JM, Daha MR, Austen KF, Fearon DT (1976) Control of the amplification convertase of complement by the plasma protein beta1H. *Proc Natl Acad Sci U S A* 73:3268–3272
41. Heinen S, Hartmann A, Lauer N, Wiehl U, Dahse HM, Schirmer S, Gropp K, Enghardt T, Wallich R, Halbach S, Mihlan M, Schlotzer-Schrehardt U, Zipfel PF, Skerka C (2009) Factor H-related protein 1 (CFHR-1) inhibits complement C5 convertase activity and terminal complex formation. *Blood* 114:2439–2447
42. Skerka C, Chen Q, Fremeaux-Bacchi V, Roumenina LT (2013) Complement factor H related proteins (CFHRs). *Mol Immunol* 56:170–180
43. Liu J, Miwa T, Hilliard B, Chen Y, Lambris JD, Wells AD, Song WC (2005) The complement inhibitory protein DAF (CD55) suppresses T cell immunity in vivo. *J Exp Med* 201:567–577
44. Varela JC, Imai M, Atkinson C, Ohta R, Rapisardo M, Tomlinson S (2008) Modulation of protective T cell immunity by complement inhibitor expression on tumor cells. *Cancer Res* 68:6734–6742
45. Keppler OT, Moldenhauer G, Oppenlander M et al (1992) Human Golgi beta-galactoside alpha-2,6-sialyltransferase generates a group of sialylated B lymphocyte differentiation antigens. *Eur J Immunol* 22:2777–2781
46. Bordron A, Bagacean C, Mohr A, Tempescul A, Bendaoud B, Deshayes S, Dalbès F, Buors C, Saad H, Berthou C, Pers JO, Renaudineau Y (2018) Resistance to complement activation, cell membrane hypersialylation and relapses in chronic lymphocytic leukemia patients treated with rituximab and chemotherapy. *Oncotarget* 9:31590–31605
47. Donin N, Jurianz K, Ziporen L et al (2003) Complement resistance of human carcinoma cells depends on membrane regulatory proteins, protein kinases and sialic acid. *Clin Exp Immunol* 131:254–263
48. Di Gaetano N, Cittera E, Nota R et al (2003) Complement activation determines the therapeutic activity of rituximab in vivo. *J Immunol* 171:1581–1587
49. Sato F, Ito A, Ishida T, Mori F, Takino H, Inagaki A, Ri M, Kusumoto S, Komatsu H, Iida S, Okada N, Inagaki H, Ueda R (2010) A complement-dependent cytotoxicity-enhancing anti-CD20 antibody mediating potent antitumor activity in the humanized NOD/Shi-scid, IL-2Rγnull mouse lymphoma model. *Cancer Immunol Immunother* 59:1791–1800
50. Robak T, Lech-Maranda E, Robak P (2010) Rituximab plus fludarabine and cyclophosphamide or other agents in chronic lymphocytic leukemia. *Expert Rev Anticancer Ther* 10:1529–1543
51. Henry J, Gottenberg JE, Rouanet S, Pavy S, Sellam J, Tubach F, Belkhir R, Mariette X, Seror R, for the Auto-Immunity and Rituximab investigators (2018) Doses of rituximab for retreatment in rheumatoid arthritis: influence on maintenance and risk of serious infection. *Rheumatology (Oxford)* 57:538–547
52. Iskandar A, Hwang A, Dasanu CA (2018) Severe warm-antibody autoimmune hemolytic anemia due to multicentric Castleman disease: responding to rituximab. *J Oncol Pharm Pract*. In Press: 1078155218816775
53. Huhn D, von Schilling C, Wilhelm M, Ho AD, Hallek M, Kuse R, Knauf W, Riedel U, Hinke A, Srock S, Serke S, Peschel C, Emmerich B, German Chronic Lymphocytic Leukemia Study Group (2001) Rituximab therapy of patients with B-cell chronic lymphocytic leukemia. *Blood* 98:1326–1331

54. Clynes RA, Towers TL, Presta LG, Ravetch JV (2000) Inhibitory Fc receptors modulate in vivo cytotoxicity against tumor targets. *Nat Med* 6:443–446
55. Veeramani S, Wang SY, Dahle C, Blackwell S, Jacobus L, Knutson T, Button A, Link BK, Weiner GJ (2011) Rituximab infusion induces NK activation in lymphoma patients with the high-affinity CD16 polymorphism. *Blood* 118:3347–3349
56. Zent CS, Elliott MR (2017) Maxed out macs: physiologic cell clearance as a function of macrophage phagocytic capacity. *FEBS J* 284:1021–1039
57. Grandjean CL, Montalvao F, Celli S, Michonneau D, Breart B, Garcia Z, Perro M, Freytag O, Gerdes CA, Bousso P (2016) Intravital imaging reveals improved Kupffer cell-mediated phagocytosis as a mode of action of glycoengineered anti-CD20 antibodies. *Sci Rep* 6:34382
58. Gul N, Babes L, Siegmund K et al (2014) Macrophages eliminate circulating tumor cells after monoclonal antibody therapy. *J Clin Invest* 124:812–823
59. Montalvao F, Garcia Z, Celli S, Breart B, Deguine J, van Rooijen N, Bousso P (2013) The mechanism of anti-CD20-mediated B cell depletion revealed by intravital imaging. *J Clin Invest* 123:5098–5103
60. Semac I, Palomba C, Kulangara K, Klages N, van Echten-Deckert G, Borisch B, Hoessli DC (2003) Anti-CD20 therapeutic antibody rituximab modifies the functional organization of rafts/microdomains of B lymphoma cells. *Cancer Res* 63:534–540
61. Beum PV, Lindorfer MA, Beurskens F, Stukenberg PT, Lokhorst HM, Pawluczukowicz AW, Parren PWI, van de Winkel GJJ, Taylor RP (2008) Complement activation on B lymphocytes opsonized with rituximab or ofatumumab produces substantial changes in membrane structure preceding cell lysis. *J Immunol* 181:822–832
62. Hagenbeek A, Gadeberg O, Johnson P, Moller Pedersen L, Walewski J, Hellmann A, Link BK, Robak T, Wojtukiewicz M, Pfreundschuh M, Kneba M, Engert A, Sonneveld P, Flensburg M, Petersen J, Losic N, Radford J (2008) First clinical use of ofatumumab, a novel fully human anti-CD20 monoclonal antibody in relapsed or refractory follicular lymphoma: results of a phase 1/2 trial. *Blood* 111:5486–5495
63. Tempescul A, Bagacean C, Riou C, Bendaoud B, Hillion S, Debant M, Buors C, Berthou C, Renaudineau Y (2016) Ofatumumab capacity to deplete B cells from chronic lymphocytic leukaemia is affected by C4 complement exhaustion. *Eur J Haematol* 96:229–235
64. Nguyen DT, Amess JA, Doughty H, Hendry L, Diamond LW (1999) IDEC-C2B8 anti-CD20 (rituximab) immunotherapy in patients with low-grade non-Hodgkin's lymphoma and lymphoproliferative disorders: evaluation of response on 48 patients. *Eur J Haematol* 62:76–82
65. Winkler U, Jensen M, Manzke O et al (1999) Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood* 94:2217–2224
66. Wierda WG, Kipps TJ, Mayer J, Stilgenbauer S, Williams CD, Hellmann A, Robak T, Furman RR, Hillmen P, Trneny M, Dyer MJ, Padmanabhan S, Piotrowska M, Kozak T, Chan G, Davis R, Losic N, Wilms J, Russell CA, Osterborg A, Hx-CD20-406 Study Investigators (2010) Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. *J Clin Oncol* 28:1749–1755
67. Martinez C, Diaz-Lopez A, Rodriguez-Calvillo M et al (2016) Phase II trial of ofatumumab plus ESHAP (O-ESHAP) as salvage treatment for patients with relapsed or refractory classical Hodgkin lymphoma after first-line chemotherapy. *Br J Haematol* 174:859–867
68. Bello C, Veliz M, Pinilla-Ibarz J (2011) Ofatumumab in the treatment of low-grade non-Hodgkin's lymphomas and chronic lymphocytic leukemia. *Expert Rev Clin Immunol* 7:295–300
69. 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, on behalf of the 405 Study Investigators (2012) Ofatumumab monotherapy in rituximab-refractory follicular lymphoma: results from a multicenter study. *Blood* 119:3698–3704
70. Milani C, Castillo J (2009) Veltuzumab, an anti-CD20 mAb for the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia and immune thrombocytopenic purpura. *Curr Opin Mol Ther* 11:200–207
71. Morschhauser F, Leonard JP, Fayad L, Coiffier B, Petillon MO, Coleman M, Schuster SJ, Dyer MJS, Home H, Teoh N, Wegener WA, Goldenberg DM (2009) Humanized anti-CD20 antibody, veltuzumab, in refractory/recurrent non-Hodgkin's lymphoma: phase I/II results. *J Clin Oncol* 27:3346–3353
72. Morschhauser F, Marlton P, Vitolo U, Linden O, Seymour JF, Crump M, Coiffier B, Foa R, Wassner E, Burger HU, Brennan B, Mendila M (2010) Results of a phase I/II study of ocrelizumab, a fully humanized anti-CD20 mAb, in patients with relapsed/refractory follicular lymphoma. *Ann Oncol* 21:1870–1876
73. Salles G, Morschhauser F, Lamy T, Milpied N, Thieblemont C, Tilly H, Bieska G, Asikanus E, Carlile D, Birkett J, Pisa P, Cartron G (2012) Phase 1 study results of the type II glycoengineered humanized anti-CD20 monoclonal antibody obinutuzumab (GA101) in B-cell lymphoma patients. *Blood* 119:5126–5132
74. 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 MJS, Poppema S, Klein C, Umana P (2010) 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* 115:4393–4402
75. 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, Döhner H, Langerak AW, Ritgen M, Kneba M, Asikanus E, Humphrey K, Wenger M, Hallek M (2014) Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med* 370:1101–1110
76. Wayne JL, Ganjoo KN, Pohlman BL et al, editors. Efficacy of ocaratuzumab (AME-133v) in relapsed follicular lymphoma patients refractory to prior rituximab. ASCO Meeting; 2012
77. 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 (2011) Phase I study of LY2469298, an Fc-engineered humanized anti-CD20 antibody, in patients with relapsed or refractory follicular lymphoma. *Cancer Sci* 102:432–438
78. Church AK, VanDerMeid KR, Baig NA et al (2016) Anti-CD20 monoclonal antibody-dependent phagocytosis of chronic lymphocytic leukaemia cells by autologous macrophages. *Clin Exp Immunol* 183:90–101
79. Sawas A, Farber CM, Schreeder MT, Khalil MY, Mahadevan D, Deng C, Amengual JE, Nikolinakos PG, Kolesar JM, Kuhn JG, Sportelli P, Miskin HP, O'Connor OA (2017) A phase 1/2 trial of ublituximab, a novel anti-CD20 monoclonal antibody, in patients with B-cell non-Hodgkin lymphoma or chronic lymphocytic leukaemia previously exposed to rituximab. *Br J Haematol* 177:243–253
80. Ward E, Mittereder N, Kuta E, Sims GP, Bowen MA, Dall'Acqua W, Tedder T, Kiener P, Coyle AJ, Wu H, Jallal B, Herbst R (2011)

- A glycoengineered anti-CD19 antibody with potent antibody-dependent cellular cytotoxicity activity in vitro and lymphoma growth inhibition in vivo. *Br J Haematol* 155:426–437
81. Jurczak W, Bryk AH, Mensah P, Gałazka K, Trofimiuk–Möldner M, Wyrobek Ł, Sawiec A, Skotnicki AB (2016) Single-agent MOR208 salvage and maintenance therapy in a patient with refractory/relapsing diffuse large B-cell lymphoma: a case report. *J Med Case Rep* 10:123
 82. Horton HM, Bernett MJ, Pong E, Peipp M, Karki S, Chu SY, Richards JO, Vostiar I, Joyce PF, Repp R, Desjarlais JR, Zhukovsky EA (2008) Potent in vitro and in vivo activity of an Fc-engineered anti-CD19 monoclonal antibody against lymphoma and leukemia. *Cancer Res* 68:8049–8057
 83. Woyach JA, Awan F, Flinn IW, Berdeja JG, Wiley E, Mansoor S, Huang Y, Lozanski G, Foster PA, Byrd JC (2014) A phase 1 trial of the Fc-engineered CD19 antibody XmAb5574 (MOR00208) demonstrates safety and preliminary efficacy in relapsed CLL. *Blood* 124:3553–3560
 84. Cardarelli PM, Rao-Naik C, Chen S, Huang H, Pham A, Moldovan-Loomis MC, Pan C, Preston B, Passmore D, Liu J, Kuhne MR, Witte A, Blanset D, King DJ (2010) A nonfucosylated human antibody to CD19 with potent B-cell depletive activity for therapy of B-cell malignancies. *Cancer Immunol Immunother* 59:257–265
 85. Wei G, Wang J, Huang H, Zhao Y (2017) Novel immunotherapies for adult patients with B-lineage acute lymphoblastic leukemia. *J Hematol Oncol* 10:150
 86. 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 (2003) Phase I/II trial of epratuzumab (humanized anti-CD22 antibody) in indolent non-Hodgkin's lymphoma. *J Clin Oncol* 21:3051–3059
 87. Thieblemont C, Bouafia F, Hornez E et al (2004) Maintenance therapy with a monthly injection of alemtuzumab prolongs response duration in patients with refractory B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (B-CLL/SLL). *Leuk Lymphoma* 45:711–714
 88. Fulciniti M, Tassone P, Hideshima T, Vallet S, Nanjappa P, Ettenberg SA, Shen Z, Patel N, Tai YT, Chauhan D, Mitsiades C, Prabhala R, Raje N, Anderson KC, Stover DR, Munshi NC (2009) Anti-DKK1 mAb (BHQ880) as a potential therapeutic agent for multiple myeloma. *Blood* 114:371–379
 89. Czuczman MS, Leonard JP, Jung S, Johnson JL, Hsi ED, Byrd JC, Cheson BD (2012) Phase II trial of galiximab (anti-CD80 monoclonal antibody) plus rituximab (CALGB 50402): Follicular Lymphoma International Prognostic Index (FLIPI) score is predictive of upfront immunotherapy responsiveness. *Ann Oncol* 23:2356–2362
 90. Czuczman MS, Leonard JP, Jung S, Johnson JL, Hsi ED, Byrd JC, Cheson BD (2018) Phase II trial of galiximab (anti-CD80 monoclonal antibody) plus rituximab (CALGB 50402): Follicular Lymphoma International Prognostic Index (FLIPI) score is predictive of upfront immunotherapy responsiveness. *Ann Oncol* 29:2271
 91. Bensinger W, Maziarz RT, Jagannath S, Spencer A, Durrant S, Becker PS, Ewald B, Bilic S, Rediske J, Baeck J, Stadtmayer EA (2012) A phase 1 study of lucatumumab, a fully human anti-CD40 antagonist monoclonal antibody administered intravenously to patients with relapsed or refractory multiple myeloma. *Br J Haematol* 159:58–66
 92. Byrd JC, Kipps TJ, Flinn IW, Cooper M, Odenike O, Bendiske J, Rediske J, Bilic S, Dey J, Baeck J, O'Brien S (2012) Phase I study of the anti-CD40 humanized monoclonal antibody lucatumumab (HCD122) in relapsed chronic lymphocytic leukemia. *Leuk Lymphoma* 53:2136–2142
 93. Fanale M, Assouline S, Kuruvilla J, Solal-Céligny P, Heo DS, Verhoef G, Corradini P, Abramson JS, Offner F, Engert A, Dyer MJS, Carreon D, Ewald B, Baeck J, Younes A, Freedman AS (2014) 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* 164:258–265
 94. de Vos S, Forero-Torres A, Ansell SM, Kahl B, Cheson BD, Bartlett NL, Furman RR, Winter JN, Kaplan H, Timmerman J, Whiting NC, Drachman JG, Advani R (2014) A phase II study of dacetuzumab (SGN-40) in patients with relapsed diffuse large B-cell lymphoma (DLBCL) and correlative analyses of patient-specific factors. *J Hematol Oncol* 7:44
 95. Furman RR, Forero-Torres A, Shustov A, Drachman JG (2010) A phase I study of dacetuzumab (SGN-40, a humanized anti-CD40 monoclonal antibody) in patients with chronic lymphocytic leukemia. *Leuk Lymphoma* 51:228–235
 96. Hussein M, Berenson JR, Niesvizky R, Munshi N, Matous J, Sobecks R, Harrop K, Drachman JG, Whiting N (2010) A phase I multidose study of dacetuzumab (SGN-40; humanized anti-CD40 monoclonal antibody) in patients with multiple myeloma. *Haematologica* 95:845–848
 97. Dorner T, Posch MG, Li Y et al (2019) Treatment of primary Sjogren's syndrome with inalumab (VAY736) targeting B cells by BAFF receptor blockade coupled with enhanced, antibody-dependent cellular cytotoxicity. *Ann Rheum Dis In Press* 78: 641–647
 98. Silence K, Dreier T, Moshir M, Ulrichs P, Gabriels SME, Saunders M, Wajant H, Brouckaert P, Huyghe L, van Hauwermeiren T, Thibault A, de Haard HJ (2014) ARGX-110, a highly potent antibody targeting CD70, eliminates tumors via both enhanced ADCC and immune checkpoint blockade. *mAbs* 6:523–532
 99. Krause G, Baki I, Kerwien S, Knöden E, Neumann L, Göckeritz E, Landwehr T, Heider KH, Hallek M (2016) Cytotoxicity of the CD37 antibody BI 836826 against chronic lymphocytic leukaemia cells in combination with chemotherapeutic agents or PI3K inhibitors. *Br J Haematol* 173:791–794
 100. Robak T, Hellmann A, Kloczko J, Loscertales J, Lech-Maranda E, Pagel JM, Mato A, Byrd JC, Awan FT, Hebart H, Garcia-Marco JA, Hill BT, Hallek M, Eisenfeld AJ, Stromatt SC, Jaeger U (2017) Randomized phase 2 study of otlertuzumab and bendamustine versus bendamustine in patients with relapsed chronic lymphocytic leukaemia. *Br J Haematol* 176:618–628
 101. Pagel JM, Spurgeon SE, Byrd JC, Awan FT, Flinn IW, Lanasa MC, Eisenfeld AJ, Stromatt SC, Gopal AK (2015) Otlertuzumab (TRU-016), an anti-CD37 monospecific ADAPTIR() therapeutic protein, for relapsed or refractory NHL patients. *Br J Haematol* 168:38–45
 102. Rasche L, Duell J, Castro IC, Dubljevic V, Chatterjee M, Knop S, Hensel F, Rosenwald A, Einsele H, Topp MS, Brandlein S (2015) GRP78-directed immunotherapy in relapsed or refractory multiple myeloma - results from a phase 1 trial with the monoclonal immunoglobulin M antibody PAT-SM6. *Haematologica* 100:377–384
 103. Bajaj J, Konuma T, Lytle NK, Kwon HY, Ablack JN, Cantor JM, Rizzieri D, Chuah C, Oehler VG, Broome EH, Ball ED, van der Horst EH, Ginsberg MH, Reya T (2016) CD98-mediated adhesive signaling enables the establishment and propagation of acute myelogenous leukemia. *Cancer Cell* 30:792–805
 104. Baz RC, Zonder JA, Gasparetto C, Reu FJ, Strout V (2016) Phase I study of anti-GM2 ganglioside monoclonal antibody BIW-8962 as monotherapy in patients with previously treated multiple myeloma. *Oncol Ther* 4:287–301
 105. Hansson M, Gimsing P, Badros A, Niskanen TM, Nahi H, Offner F, Salomo M, Sonesson E, Mau-Sorensen M, Stenberg Y,

- Sundberg A, Teige I, van Droogenbroeck J, Wichert S, Zangari M, Frendeus B, Korsgren M, Poelman M, Tricot G (2015) A phase I dose-escalation study of antibody BI-505 in relapsed/refractory multiple myeloma. *Clin Cancer Res* 21:2730–2736
106. Wichert S, Juliusson G, Johansson A, Sonesson E, Teige I, Wickenberg AT, Frendeus B, Korsgren M, Hansson M (2017) A single-arm, open-label, phase 2 clinical trial evaluating disease response following treatment with BI-505, a human anti-intercellular adhesion molecule-1 monoclonal antibody, in patients with smoldering multiple myeloma. *PLoS One* 12: e0171205
 107. Cuesta-Mateos C, Alcaraz-Serna A, Somovilla-Crespo B, Munoz-Calleja C (2017) Monoclonal antibody therapies for hematological malignancies: not just lineage-specific targets. *Front Immunol* 8: 1936
 108. Krupka C, Lichtenegger FS, Kohnke T et al (2017) Targeting CD157 in AML using a novel, Fc-engineered antibody construct. *Oncotarget* 8:35707–35717
 109. Chehab S, Panjic EH, Gleason C, Lonial S, Nooka AK (2018) Daratumumab and its use in the treatment of relapsed and/or refractory multiple myeloma. *Future Oncol* 14:3111–3121
 110. Shah NN, Singavi AK, Harrington A (2018) Daratumumab in primary effusion lymphoma. *N Engl J Med* 379:689–690
 111. Ganzel C, Kharit M, Duksin C, Rowe JM (2018) Daratumumab for relapsed/refractory Philadelphia-positive acute lymphoblastic leukemia. *Haematologica* 103:e489–e490
 112. Buteyn NJ, Fatehchand K, Santhanam R, Fang H, Dettorre GM, Gautam S, Harrington BK, Henderson SE, Merchand-Reyes G, Mo X, Benson DM, Carson WE III, Vasu S, Byrd JC, Butchar JP, Tridandapani S (2018) Anti-leukemic effects of all-trans retinoic acid in combination with daratumumab in acute myeloid leukemia. *Int Immunol* 30:375–383
 113. Richardson PG, Attal M, Campana F, le-Guenec S, Hui AM, Risse ML, Corzo K, Anderson KC (2018) Isatuximab plus pomalidomide/dexamethasone versus pomalidomide/dexamethasone in relapsed/refractory multiple myeloma: ICARIA phase III study design. *Future Oncol* 14:1035–1047
 114. van de Donk NW, Janmaat ML, Mutis T et al (2016) Monoclonal antibodies targeting CD38 in hematological malignancies and beyond. *Immunol Rev* 270:95–112
 115. Busch L, Mougiakakos D, Buttner-Herold M et al (2018) Lenalidomide enhances MOR202-dependent macrophage-mediated effector functions via the vitamin D pathway. *Leukemia* 32: 2445–2458
 116. Dimopoulos MA, Lonial S, Betts KA, Chen C, Zichlin ML, Brun A, Signorovitch JE, Makenbaeva D, Mekan S, Sy O, Weisel K, Richardson PG (2018) Elotuzumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended 4-year follow-up and analysis of relative progression-free survival from the randomized ELOQUENT-2 trial. *Cancer* 124:4032–4043
 117. Inoue Y, Endo S, Matsuno N, Kikukawa Y, Shichijo T, Koga K, Takaki A, Iwanaga K, Nishimura N, Fuji S, Fukuda T, Nosaka K, Matsuoka M (2019) Safety of mogamulizumab for relapsed ATL after allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant* 54:338–342
 118. (2018) Mogamulizumab tops standard of care for CTCL. *Cancer Discov* 8:OF1
 119. Fujita Y, Nakaya A, Fujita S et al (2016) Mogamulizumab treatment of refractory peripheral T-cell lymphoma following autologous stem cell transplantation: a case report. *Mol Clin Oncol* 4: 151–153
 120. Tobinai K (2016) Disease-oriented treatment of T/NK-cell lymphomas. [Rinsho ketsueki. *Jpn J Clin Hematol* 57:1044–1051
 121. Kashyap MK, Amaya-Chanaga CI, Kumar D, Simmons B, Huser N, Gu Y, Hallin M, Lindquist K, Yafawi R, Choi MY, Amine AA, Rassenti LZ, Zhang C, Liu SH, Smeal T, Fantin VR, Kipps TJ, Parnasetti F, Castro JE (2017) Targeting the CXCR4 pathway using a novel anti-CXCR4 IgG1 antibody (PF-06747143) in chronic lymphocytic leukemia. *J Hematol Oncol* 10:112
 122. Zhang Y, Saavedra E, Tang R, Gu Y, Lappin P, Trajkovic D, Liu SH, Smeal T, Fantin V, de Botton S, Legrand O, Delhommeau F, Parnasetti F, Louache F (2017) Targeting primary acute myeloid leukemia with a new CXCR4 antagonist IgG1 antibody (PF-06747143). *Sci Rep* 7:7305
 123. He SZ, Busfield S, Ritchie DS, Hertzberg MS, Durrant S, Lewis ID, Marlton P, McLachlan AJ, Kerridge I, Bradstock KF, Kennedy G, Boyd AW, Yeadon TM, Lopez AF, Ramshaw HS, Iland H, Bamford S, Barnden M, DeWitte M, Bassar R, Roberts AW (2015) A phase 1 study of the safety, pharmacokinetics and anti-leukemic activity of the anti-CD123 monoclonal antibody CSL360 in relapsed, refractory or high-risk acute myeloid leukemia. *Leuk Lymphoma* 56:1406–1415
 124. Reichert JM (2017) Antibodies to watch in 2017. *mAbs* 9:167–181
 125. Assi R, Kantarjian H, Ravandi F, Daver N (2018) Immune therapies in acute myeloid leukemia: a focus on monoclonal antibodies and immune checkpoint inhibitors. *Curr Opin Hematol* 25:136–145
 126. Punt CJ, Nagy A, Douillard JY et al (2002) Edrecolomab alone or in combination with fluorouracil and folinic acid in the adjuvant treatment of stage III colon cancer: a randomised study. *Lancet* 360:671–677
 127. Murthy RK, Raghavendra AS, Hess KR, Fujii T, Lim B, Barcenas CH, Zhang H, Chavez-MacGregor M, Mittendorf EA, Litton JK, Giordano SH, Thompson AM, Valero V, Moulder SL, Tripathy D, Ueno NT (2018) Neoadjuvant pertuzumab-containing regimens improve pathologic complete response rates in stage II to III HER-2/neu-positive breast cancer: a retrospective, single institution experience. *Clin Breast Cancer* 18:e1283–e1288
 128. Roviello G, Generali D (2018) Pertuzumab therapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer. *Lancet Oncol* 19:1270–1272
 129. Martin AP, Downing J, Cochrane M, Collins B, Francis B, Haycox A, Alfirevic A, Pirmohamed M (2018) Trastuzumab uptake in HER2-positive breast cancer patients: a systematic review and meta-analysis of observational studies. *Crit Rev Oncol Hematol* 130:92–107
 130. Chen ZL, Zhao A, Li P et al (2018) Clinical use of trastuzumab combined with different chemotherapy regimens in multi-line treatment of advanced human epidermal growth factor receptor 2-positive gastric cancer: a case report. *Oncol Lett* 16:4614–4620
 131. Fala L (2016) Portrazza (necitumumab), an IgG1 monoclonal antibody, FDA approved for advanced squamous non-small-cell lung cancer. *Am Health Drug Benefits* 9:119–122
 132. Addeo R, Montella L, Mastella A, Vincenzi B, Mazzone S, Ricciardiello F, del Prete S (2018) Maintenance therapy with bi-weekly cetuximab: optimizing schedule can preserve activity and improves compliance in advanced head and neck cancer. *Oncology* 95:353–359
 133. Knodler M, Korfer J, Kunzmann V et al (2018) Randomised phase II trial to investigate catumaxomab (anti-EpCAM x anti-CD3) for treatment of peritoneal carcinomatosis in patients with gastric cancer. *Br J Cancer* 119:296–302
 134. Trzpis M, McLaughlin PM, de Leij LM, Harmsen MC (2007) Epithelial cell adhesion molecule: more than a carcinoma marker and adhesion molecule. *Am J Pathol* 171:386–395
 135. Iqbal N, Iqbal N (2014) Human epidermal growth factor receptor 2 (HER2) in cancers: overexpression and therapeutic implications. *Mol Biol Int* 2014:852748
 136. Normanno N, De Luca A, Bianco C et al (2006) Epidermal growth factor receptor (EGFR) signaling in cancer. *Gene* 366:2–16

137. Navid F, Santana VM, Barfield RC (2010) Anti-GD2 antibody therapy for GD2-expressing tumors. *Curr Cancer Drug Targets* 10:200–209
138. Richards A, Kathryn Liszewski M, Kavanagh D, Fang CJ, Moulton E, Fremeaux-Bacchi V, Remuzzi G, Noris M, Goodship THJ, Atkinson JP (2007) Implications of the initial mutations in membrane cofactor protein (MCP; CD46) leading to atypical hemolytic uremic syndrome. *Mol Immunol* 44:111–122
139. Stuhlinger W, Kourilsky O, Kanfer A, Sraer JD (1974) Letter: Haemolytic-uraemic syndrome: evidence for intravascular C3 activation. *Lancet* 2:788–789
140. Hillmen P, Muus P, Roth A et al (2013) Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol* 162:62–73
141. Keating GM (2013) Eculizumab: a review of its use in atypical haemolytic uraemic syndrome. *Drugs* 73:2053–2066
142. Wong EK, Goodship TH, Kavanagh D (2013) Complement therapy in atypical haemolytic uraemic syndrome (aHUS). *Mol Immunol* 56:199–212
143. Lee JW, Peffault de Latour R, Brodsky RA, Jang JH, Hill A, Röth A, Schrezenmeier H, Wilson A, Marantz JL, Maciejewski JP (2019) Effectiveness of eculizumab in patients with paroxysmal nocturnal hemoglobinuria (PNH) with or without aplastic anemia in the International PNH Registry. *Am J Hematol* 94:E37–E41
144. Kinoshita T (2018) Congenital defects in the expression of the glycosylphosphatidylinositol-anchored complement regulatory proteins CD59 and decay-accelerating factor. *Semin Hematol* 55:136–140
145. Dalakas MC (2019) Immunotherapy in myasthenia gravis in the era of biologics. *Nat Rev Neurol* 15:113–124
146. Kello N, Khoury LE, Marder G et al (2018) Secondary thrombotic microangiopathy in systemic lupus erythematosus and antiphospholipid syndrome, the role of complement and use of eculizumab: case series and review of literature. *Seminars in arthritis and rheumatism*. In Press
147. McNamara LA, Topaz N, Wang X et al (2017) High risk for invasive meningococcal disease among patients receiving eculizumab (Soliris) despite receipt of meningococcal vaccine. *MMWR Morb Mortal Wkly Rep* 66:734–737
148. Ross SC, Densen P (1984) Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. *Medicine* 63:243–273
149. Truedsson L, Bengtsson AA, Sturfelt G (2007) Complement deficiencies and systemic lupus erythematosus. *Autoimmunity* 40:560–566
150. Herreman G, Ferme I, Diebold J, Baviera E, Audouin J, Bazin C, Godeau P (1983) Gougerot-Sjogren syndrome, periarteritis nodosa, non-Hodgkin's lymphoplasmocytic lymphoma and acquired C4 deficiency. *Ann Med Interne* 134:19–25
151. Liesmaa I, Paakkanen R, Jarvinen A, Valtonen V, Lokki ML (2018) Clinical features of patients with homozygous complement C4A or C4B deficiency. *PLoS One* 13:e0199305
152. Bossi F, Tripodo C, Rizzi L, Bulla R, Agostinis C, Guarnotta C, Munaut C, Baldassarre G, Papa G, Zorzet S, Ghebrehiwet B, Ling GS, Botto M, Tedesco F (2014) C1q as a unique player in angiogenesis with therapeutic implication in wound healing. *Proc Natl Acad Sci U S A* 111:4209–4214
153. Ballanti E, Perricone C, Greco E, Ballanti M, di Muzio G, Chimenti MS, Perricone R (2013) Complement and autoimmunity. *Immunol Res* 56:477–491
154. Chen M, Daha MR, Kallenberg CG (2010) The complement system in systemic autoimmune disease. *J Autoimmun* 34:J276–J286
155. Wagner E, Frank MM (2010) Therapeutic potential of complement modulation. *Nat Rev Drug Discov* 9:43–56
156. Barilla-Labarca ML, Toder K, Furie R (2013) Targeting the complement system in systemic lupus erythematosus and other diseases. *Clin Immunol* 148:313–321
157. Durigutto P, Macor P, Ziller F, de Maso L, Fischetti F, Marzari R, Sblattero D, Tedesco F (2013) Prevention of arthritis by locally synthesized recombinant antibody neutralizing complement component C5. *PLoS One* 8:e58696
158. Macor P, Durigutto P, De Maso L et al (2012) Treatment of experimental arthritis by targeting synovial endothelium with a neutralizing recombinant antibody to C5. *Arthritis Rheum* 64:2559–2567
159. Rodriguez-Pinto I, Espinosa G, Cervera R (2016) Catastrophic antiphospholipid syndrome: the current management approach. *Best Pract Res Clin Rheumatol* 30:239–249
160. Ward PA, Guo RF, Riedemann NC (2012) Manipulation of the complement system for benefit in sepsis. *Crit Care Res Pract* 2012:427607
161. Bekker P, Dairaghi D, Seitz L, Leleti M, Wang Y, Ertl L, Baumgart T, Shugarts S, Lohr L, Dang T, Miao S, Zeng Y, Fan P, Zhang P, Johnson D, Powers J, Jaen J, Charo I, Schall TJ (2016) Characterization of pharmacologic and pharmacokinetic properties of CCX168, a potent and selective orally administered complement 5a receptor inhibitor, based on preclinical evaluation and randomized phase 1 clinical study. *PLoS One* 11:e0164646
162. Jayne DRW, Bruchfeld AN, Harper L, Schaier M, Venning MC, Hamilton P, Burst V, Grundmann F, Jadoul M, Szombati I, Tesar V, Segelmark M, Potarca A, Schall TJ, Bekker P, CLEAR Study Group (2017) Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. *J Am Soc Nephrol* 28:2756–2767
163. Xiao H, Dairaghi DJ, Powers JP, Ertl LS, Baumgart T, Wang Y, Seitz LC, Penfold MET, Gan L, Hu P, Lu B, Gerard NP, Gerard C, Schall TJ, Jaen JC, Falk RJ, Jennette JC (2014) C5a receptor (CD88) blockade protects against MPO-ANCA GN. *J Am Soc Nephrol* 25:225–231
164. Rittirsch D, Flierl MA, Nadeau BA, Day DE, Huber-Lang M, Mackay CR, Zetoune FS, Gerard NP, Cianflone K, Köhl J, Gerard C, Sarma JV, Ward PA (2008) Functional roles for C5a receptors in sepsis. *Nat Med* 14:551–557
165. Weber BH, Charbel Issa P, Pauly D, Herrmann P, Grassmann F, Holz FG (2014) The role of the complement system in age-related macular degeneration. *Dtsch Arztebl Int* 111:133–138
166. Schejbel L, Skattum L, Hagelberg S, Åhlin A, Schiller B, Berg S, Genel F, Truedsson L, Garred P (2011) Molecular basis of hereditary C1q deficiency—revisited: identification of several novel disease-causing mutations. *Genes Immun* 12:626–634
167. Pickering MC, Botto M, Taylor PR, Lachmann PJ, Walport MJ (2000) Systemic lupus erythematosus, complement deficiency, and apoptosis. *Adv Immunol* 76:227–324
168. Ekinci Z, Ozturk K (2018) Systemic lupus erythematosus with C1q deficiency: treatment with fresh frozen plasma. *Lupus* 27:134–138
169. Damato E, Chilov M, Lee R, Singh A, Harper S, Dick A (2011) Plasma exchange and rituximab in the management of acute occlusive retinal vasculopathy secondary to systemic lupus erythematosus. *Ocul Immunol Inflamm* 19:379–381
170. Costa R, Fazal S, Kaplan RB, Spero J, Costa R (2013) Successful plasma exchange combined with rituximab therapy in aggressive APS-related cutaneous necrosis. *Clin Rheumatol* 32(Suppl 1):S79–S82
171. Abisror N, Mekinian A, Brechignac S, Ruffatti A, Carbillon L, Fain O (2015) Inefficacy of plasma exchanges associated to rituximab in refractory obstetrical antiphospholipid syndrome. *Presse Med* 44:100–102
172. Middleton O, Cosimo E, Dobbin E, McCaig AM, Clarke C, Brant AM, Leach MT, Michie AM, Wheadon H (2015) Complement

- deficiencies limit CD20 monoclonal antibody treatment efficacy in CLL. *Leukemia* 29:107–114
173. Fust G, Czink E, Minh D et al (1985) Depressed classical complement pathway activities in chronic lymphocytic leukaemia. *Clin Exp Immunol* 60:489–495
 174. Klepfish A, Gilles L, Ioannis K, Rachmilewitz EA, Schattner A (2009) Enhancing the action of rituximab in chronic lymphocytic leukemia by adding fresh frozen plasma: complement/rituximab interactions & clinical results in refractory CLL. *Annals of the New York Academy of Sciences* 1173:865–873
 175. Charbonneau B, Maurer MJ, Fredericksen ZS, Zent CS, Link BK, Novak AJ, Ansell SM, Weiner GJ, Wang AH, Witzig TE, Dogan A, Slager SL, Habermann TM, Cerhan JR (2012) Germline variation in complement genes and event-free survival in follicular and diffuse large B-cell lymphoma. *Am J Hematol* 87:880–885
 176. Racila E, Link BK, Weng WK, Witzig TE, Ansell S, Maurer MJ, Huang J, Dahle C, Halwani A, Levy R, Weiner GJ (2008) A polymorphism in the complement component C1qA correlates with prolonged response following rituximab therapy of follicular lymphoma. *Clin Cancer Res* 14:6697–6703
 177. Cornec D, Tempescul A, Querellou S, Hutin P, Pers JO, Jamin C, Bendaoud B, Berthou C, Renaudineau Y, Youinou P (2012) Identification of patients with indolent B cell lymphoma sensitive to rituximab monotherapy. *Ann Hematol* 91:715–721
 178. Ytting H, Christensen IJ, Thiel S, Jensenius JC, Nielsen HJ (2005) Serum mannan-binding lectin-associated serine protease 2 levels in colorectal cancer: relation to recurrence and mortality. *Clin Cancer Res* 11:1441–1446
 179. Bouwens TA, Trouw LA, Veerhuis R et al (2015) Complement activation in glioblastoma multiforme pathophysiology: evidence from serum levels and presence of complement activation products in tumor tissue. *J Neuroimmunol* 278:271–276
 180. Zha H, Wang X, Zhu Y, Chen D, Han X, Yang F, Gao J, Hu C, Shu C, Feng Y, Tan Y, Zhang J, Li Y, Wan YY, Guo B, Zhu B (2019) Intracellular activation of complement C3 leads to PD-L1 antibody treatment resistance by modulating tumor-associated macrophages. *Cancer Immunol Res* 7:193–207
 181. Francian A, Namen S, Stanley M et al (2018) Intratumoral delivery of antigen with complement C3-bound liposomes reduces tumor growth in mice. *Nanomedicine*. In Press
 182. Xu W, Miao KR, Zhu DX, Fang C, Zhu HY, Dong HJ, Wang DM, Wu YJ, Qiao C, Li JY (2011) Enhancing the action of rituximab by adding fresh frozen plasma for the treatment of fludarabine refractory chronic lymphocytic leukemia. *International journal of cancer Journal international du cancer* 128:2192–2201
 183. Tammen A, Derer S, Schwanbeck R, Rösner T, Kretschmer A, Beurskens FJ, Schuurman J, Parren PWHI, Valerius T (2017) Monoclonal antibodies against epidermal growth factor receptor acquire an ability to kill tumor cells through complement activation by mutations that selectively facilitate the hexamerization of IgG on opsonized cells. *J Immunol* 198:1585–1594
 184. Yu J, Wang W, Huang H (2019) Efficacy and safety of bispecific T-cell engager (BiTE) antibody blinatumomab for the treatment of relapsed/refractory acute lymphoblastic leukemia and non-Hodgkin's lymphoma: a systemic review and meta-analysis. *Hematology* 24:199–207
 185. Macor P, Secco E, Mezzaroba N, Zorzet S, Durigutto P, Gaiotto T, de Maso L, Biffi S, Garrovo C, Capolla S, Tripodo C, Gattei V, Marzari R, Tedesco F, Sblattero D (2015) Bispecific antibodies targeting tumor-associated antigens and neutralizing complement regulators increase the efficacy of antibody-based immunotherapy in mice. *Leukemia* 29:406–414
 186. Hillion S, Arleevskaya MI, Brooks WH et al (2019) The innate part of the adaptive immune system. *Clin Rev Allerg Immunol*. In Press
 187. Guia S, Vivier E, Narni-Mancinelli E (2019) Helper-like innate lymphoid cells: definition, functions and clinical implications in inflammatory diseases and cancer. *Clin Rev Allerg Immunol*. In Press
 188. Grasseau A, Boudigou M, Le Pottier L et al (2019) Innate B-cells: the archetype of protective immune cells. *Clin Rev Allerg Immunol*. In Press
 189. Brilland B, Scherlinger M, Khoryati L et al (2019) Platelets and IgE: shaping the innate immune response in systemic lupus erythematosus. *Clin Rev Allerg Immunol*. In Press
 190. Maddur MS, Lacroix-Desmazes S, Dimitrov JD et al (2019) Natural antibodies: from first line defense against pathogens to perpetual immune homeostasis. *Clin Rev Allerg Immunol*. In Press
 191. Defendia F, Thielensb NM, Clavarinao G, Cesbron JY, Dumestre-Pérard C (2019) Autoantibodies targeting complement components and associated diseases. *Clin Rev Allerg Immunol*. In Press
 192. Arleevskaya MI, Larionova RV, Brooks WH, Bettacchioli E, Renaudineau Y (2019) TLR, infections and rheumatoid arthritis. *Clin Rev Allerg Immunol*. In Press
 193. Arleevskaya MI, Aminov R, Brooks WH, Manukyan G, Renaudineau Y (2019) Editorial: shaping oh human immune system and metabolic processes by viruses and microorganisms. *Front Microbiol* 10:816
 194. Charras A, Arvaniti P, Le Dantec C et al (2019) JAK1/2 inhibitors suppress epigenetic reprogramming of two innate immune cytokines (IFN α , IFN γ) and reactive oxygen species: a promise for patients with Sjögren's syndrome. *Clin Rev Allerg Immunol*. In Press

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