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Review

Vaccinations in hematological patients in the era of target therapies: Lesson learnt from SARS-CoV-2

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ABSTRACT

Novel targeting agents for hematologic diseases often exert on- or off-target immunomodulatory effects, possibly impacting on response to anti-SARS-CoV-2 vaccinations and other vaccines. Agents that primarily affect B cells, particularly anti-CD20 monoclonal antibodies (MoAbs), Bruton tyrosine kinase inhibitors, and anti-CD19 chimeric antigen T-cells, have the strongest impact on seroconversion. JAK2, BCL-2 inhibitors and hypomethylating agents may hamper immunity but show a less prominent effect on humoral response to vaccines. Conversely, vaccine efficacy seems not impaired by anti-myeloma agents such as proteasome inhibitors and immunomodulatory agents, although lower seroconversion rates are observed with anti-CD38 and anti-BCMA MoAbs. Complement inhibitors for complement-mediated hematologic diseases and immunosuppressants used in aplastic anemia do not generally affect seroconversion rate, but the extent of the immune response is reduced under steroids or anti-thymocyte globulin. Vaccination is recommended prior to treatment or as far as possible from anti-CD20 MoAb (at least 6 months). No clearcut indications for interrupting continuous treatment emerged, and booster doses significantly improved seroconversion. Cellular immune response appeared preserved in several settings.

1. Introduction

Hematological patients had an estimated COVID-19 related mortality of up to 35% during the initial pandemic waves [1,2], with different risk depending on disease status (2 fold risk in those with progressive disease), patients' characteristics (nearly 2 fold risk in those aged >60 years) and ongoing therapies (mortality rate ranging from 12% to 56% with different chemotherapy, targeted agents, or combination) [2]. In this setting, prioritized massive SARS-CoV2 vaccination contributed to decrease COVID-related morbidity and mortality to around 10-15% in more recent international reports [3–7], also varying with SARS-CoV-2 variants [7] and number of vaccine doses [6]. However, the efficacy and safety of SARS-CoV-2 vaccines in hematological patients might be different as compared to the general population, and little information was available about other vaccines such as those against capsulated bacteria, *Influenza* and hepatitis viruses, etc. [8]. In fact, the immune system of many hematological patients is impaired due to the disease itself and the several therapies used [8,9]. The latter include traditional chemotherapy and cytotoxic immunosuppressants as well as novel drugs that enrich the therapeutical landscape of hematologic diseases. For instance, monoclonal antibodies (MoAbs) targeting B-cells may deplete adaptive immunity and cause long-term hypogammaglobulinemia in lymphoma and myeloma patients [10]). Tyrosine kinase inhibitors may impair B- and T-cell functioning, as well as innate immunity, increasing infectious risk [11,12]. Novel agents with cytotoxic effect, such as hypomethylating agents and BCL-2 inhibitor venetoclax, may also cause severe neutropenia [13]. Finally, complement inhibitors used in complement-mediated hematologic diseases (i.e. paroxysmal nocturnal hemoglobinuria and cold agglutinin disease) may hamper the function of this homeostatic system [14]. In this review we discuss available literature regarding vaccines efficacy and safety in the setting of biologic drugs used in hematological conditions with special regard to SARS-CoV2 vaccination. Data on vaccines against other infectious agents are not directly comparable with anti-SARS-CoV-2 ones, particularly regarding the broader immunologic activity of the latter. Still, they represent a new frontier for optimized management of hematologic patients and have been therefore included.

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2. Anti-CD20 monoclonal antibodies

MoAbs targeting B-cell CD20, particularly rituximab, in combination with chemotherapy have become the standard of care of many non-hodgkin lymphomas (NHL) [15,16]. Treatment with rituximab may induce B-cell depletion, with clinical evidence of hypogammaglobulinemia. This may persist over 6 to 9 months from the last infusion exposing patients to increased risk of infections. Furthermore, rituximab may interfere with non-specific immunity with some patients experiencing late-onset neutropenia [17].

Regarding SARS-CoV-2 vaccination, it clearly emerged that seroconversion was lower in patients with lymphoproliferative disorders treated with rituximab (Table 1)[18]. Responses ranged from 0% in subjects on maintenance treatment to 66% in those vaccinated at least 6 months after rituximab [19–22]. Seroconversion rates further improve in patients vaccinated after 12 months from the last dose of anti-CD20 moAb. Notably, non-responders to the first two doses may still experience seroconversion to a further booster dose [23]. Timing also impacts on booster doses efficacy: if performed during active anti-CD20 treatment did not significantly change the rate of seroconversion (i.e. from 15 to 22% in a large study), whilst after treatment completion and within 12 months an improvement from 40 to 70% was observed [24], Cellular immunity was documented in nearly 50-60% of patients vaccinated after a median of 16 months from the last dose of anti-CD20 Ab. Cellular response appears less associated with time from last treatment and is also independent from humoral response [25–30]. Obinutuzumab was shown to be even more immunosuppressive, with no patients experiencing seroconversion in one experience [31]. Backbone chemotherapy may also hamper immunity, and lower seroconversion rates were registered after bendamustine. Furthermore, lower absolute lymphocyte count and pre-vaccine hypogammaglobulinemia were associated with reduced humoral response [9,31–35] along with vaccination during active disease phase [31] and the diagnosis of aggressive lymphoma [23,25].

Likewise, a detrimental effect of rituximab on seroconversion was described in autoimmune cytopenias. A large Italian study reported

Table 1
Vaccine response in patients treated with anti-CD20 monoclonal antibodies-based therapy *

Reference	Malignancy type	Vaccine type	Number of patients	Seroconversion rate	Negative prognostic factors for seroconversion
Van der Kolk L, Blood 2002 [18]	B-NHL	HAV vaccine	11	0%	
Horwitz SM, Blood 2004[46]	B-NHL	*H. influenzae* vaccine	22	77%	
Horwitz SM, Blood 2004[46]	B-NHL	*Tetanus* toxoid	22	68%	
Horwitz SM, Blood 2004[46]	B-NHL	*Pneumococcus* vaccine	22	41%	
Takata T, J Clin Exp Hematop. 2009 [42]	B-NHL	*Influenza* vaccine	7	0-29%	
Yri E, Blood 2011 [37]	B-NHL	*Influenza* vaccine	67	7%	
Bedognetti D, J Immunol 2011[38]	B-NHL	*Influenza* vaccine	31	3-29%	1) Previous fludarabine-based chemotherapy 2) low IgA or IgM serum levels
De Lavallade H, Hematologica 2011 [43]	B-NHL + CLL	*Influenza* vaccine	12	42%:	1) Distance from last anti-CD20 moAbs dose
Bedognetti D, Blood 2012 [39]	B-NHL	*Influenza* vaccine	14	29-64%	
Hottinger A, Oncologist 2012 [40]	B-NHL	*Influenza* vaccine	11	18%	
Villa D, Leuk Lymphoma 2013 [41]	B-NHL	*Influenza* vaccine	14	14%	
Berglund A, Acta Oncol 2014 [44]	B-NHL	*Influenza* vaccine	12	0%	
Berglund A, Acta Oncol 2014 [44]	B-NHL	*Pneumococcus* vaccine	8	0%	
Mustafa SS, Clin Lymphoma Myeloma Leuk. 2020 [45]	B-NHL	*Tetanus* toxoid	15	7%	
Mustafa SS, Clin Lymphoma Myeloma Leuk. 2020 [45]	B-NHL	*Diphteria* toxoid	15	20%	
Mustafa SS, Clin Lymphoma Myeloma Leuk. 2020 [45]	B-NHL	*Pneumococcus* vaccine	15	20%	
Jurgens EM, AJH 2021 [22]	B-NHL+ CLL	SARS-CoV2 vaccine	34	47%	1) Time period <24 months from the last anti-CD20 treatment 2) Active treatment
Gavriatopoulou M, Blood advances 2021 [20]	WM	SARS-CoV2 vaccine	17	34%	1) Active treatment
Roeker L, Leukemia. 2021 [26]	CLL	SARS-CoV2 vaccine	21	0-14%	1) Association with venetoclax
Perry C, Blood 2021 [19]	B-NHL	SARS-CoV2 vaccine	121	0%-66%	1) Shorter time since exposure to anti-CD20 Abs 2) Lower lymphocytic count
Shen Y, Br J Haematol 2022 [35]	CLL	SARS-CoV2 vaccine	9	22%	1) Lower baseline IgM serum levels 2) Active therapy
Avivi I, BJH 2022 [23]	B-NHL	SARS-CoV2 vaccine booster	44	29.54%	1) Aggressive lymphoma 2) Time from last exposure to anti-CD20 moAb
Gurion R, Haematologica 2022 [31]	B-NHL	SARS-CoV2 vaccine	98	3-80%	1) Time period <12 months from the last anti-CD20 treatment 2) Presence of active lymphoma
Liebers N, Blood 2022 [30]	B-NHL+ CLL	SARS-CoV2 vaccine	80	41%	1) Time period <12 months from the last anti-CD20 treatment 2) Low CD4 cell count
Marasco V, BJH 2021 [25]	B-NHL+ CLL	SARS-CoV2 vaccine	58	17.6-40%	
Benjamini O, Haematologica 2022 [21]	CLL	SARS-CoV2 vaccine	143	27%	1) Time period <12 months from the last anti-CD20 treatment
Bacova B, Clin Exp Med. 2022 [28]	B-NHL	SARS-CoV2 vaccine	16	0%	
Haggenburg S, Blood Adv 2022 [27]	B-NHL	SARS-CoV2 vaccine	46	0-26%	1) Older age 2) Low baseline IgG4 serum levels 3) Low baseline NK and B-cells counts 4) Use of rituximab, venetoclax and CD-19 directed CAR-T cells

B-NHL: B-non Hodgkin lymphoma; CLL: Chronic lymphocytic leukemia; WM: Waldenstrom Macroglobulinemia; HAV: Hepatitis A virus.
* Associated chemotherapy was administered in most cases, but pooled seroconversion is provided.

lower antibody titers even in patients vaccinated after years from last rituximab infusion [36]. This may be tentatively explained by pre-existing underdiagnosed immunodeficiencies or lymphoproliferative disorders that may be associated with secondary autoimmune cytopenias.

Discouraging results also emerged for other vaccines administered during anti-CD20 therapy. Concerning influenza vaccine, seroconversion rate ranged from 0% up to 64% [37–42], independently of vaccine dosing and type. Again, humoral responses improved along with time from the last anti-CD20 infusion, and with boosters [43]. Similar results were reported for anti-*Pneumococcus* [44] and anti-Diphtheria vaccinations [45], with seroconversion rates of 20-40%. Contrarily, seroconversion of up to 70% were documented for anti-*Tetanus* and anti-Haemophilus in a single experience [46].

Taken together, seroconversion to vaccinations in patients treated with anti-CD20 MoAbs is reduced but tends to improve after 12 months from last infusion and with booster doses. Patients vaccinated during treatment may be revaccinated after immune reconstitution to achieve protective titers. Cellular immunity appears preserved in a time-independent manner. Therefore, administration of vaccines as far as possible from last anti-CD20 infusion or prior to therapy appears advisable.

3. Ibrutinib and other BTK inhibitors

Ibrutinib is a first-generation downstream Bruton Tyrosin-kinase inhibitor used for the treatment of chronic lymphocytic leukemia (CLL) [47] and several lymphoid neoplasms such as mantle cell lymphoma [48], marginal zone lymphoma [49] and Waldenstrom macroglobulinemia (WM) [50]. Ibrutinib and other BTK-inhibitors (BTKi) impair B-cell functions inducing both humoral and cellular imbalance [51]. Accordingly, SARS-CoV-2 vaccines induced seroconversion in only 20-30% (maximum 60% in a report [22]) of patients actively treated with BTKi (Table 2) [20,27]. Factors such as younger age, higher baseline IgG4 levels and NK-cell counts were associated to higher responses and were tentatively included in predictive scores [21], whilst timing of administration, differently from anti-CD20 MoAbs, has no impact since treatment with BTKi is continuous. Notably, booster doses may improve seroconversion [52], and cellular immunity seems less influenced with responses in up to 80% of patients [26–28,35,53–55].

Similar data were reported for *Influenza* vaccines, where two trials in ibrutinib-treated CLL patients showed a seroconversion of 7% and 26%, respectively [56,57]. Impaired seroconversion was also reported after 13 and 23 valent *Pneumococcus* vaccine (PCV13 and PPV23) [58–60]. On the contrary, recombinant *Varicella Zoster* vaccine (rVZV) was associated with higher seroconversion rates (41 to 75%), although with lower responses in those receiving BTKi for longer period [61–64].

Table 2
Vaccine response in BTK-inhibitors treated patients.

Reference	Malignancy type	Vaccine type	Number of patients	Seroconversion rate	Negative prognostic factors for seroconversion
Sun C, JAMA Oncol. 2016 [56]	CLL	*Influenza* vaccine	19	11-26%	
Douglas A, Haematologica. 2017 [57]	B-NHL+ CLL	*Influenza* vaccine	14	7%	1) Prior treatment 2) Shorter time since last chemotherapy
Andrick B, Br J Haematol. 2018 [58]	CLL	*Pneumococcus* vaccine	4	0%	
Mauro F, Leukemia 2021 [59]	CLL	*Pneumococcus* vaccine	35	9%	1) Age $\geq$ 60 years 2) IgG levels <400 mg/dL 3) Prior treatment 4) Uncontrolled disease
Hassan H, Hematol Oncol Stem Cell Ther. 2022 [60]	CLL	*Tetanus* toxoid	10	30%	
Hassan H, Hematol Oncol Stem Cell Ther. 2022 [60]	CLL	*Diphteria* toxoid	10	40%	
Hassan H, Hematol Oncol Stem Cell Ther. 2022 [60]	CLL	*Pneumococcus* vaccine	10	0%	
Jurgens EM, AJH 2021 [22]	WM + CLL	SARS-CoV2 vaccine	10	60%	1) Time period <24 months from the last anti-CD20 treatment 2) Active treatment
Roeker L, Leukemia. 2021 [26]	CLL	SARS-CoV2 vaccine	14	21%	
Herishanu Y, Blood 2021 [33]	CLL	SARS-CoV2 vaccine	50	16%	1) Age $\geq$ 65 years 2) Active treatment 3) Baselinge IgG levels <550 mg/dL 4) Baseline IgM levels <40 mg/dL 5) Male sex
Zent C, Leukemia 2021 [61]	WM + CLL	rVZV vaccine	32	75%	1) Longer duration of pre-vaccination BTKi treatment
Pleyer C, Blood 2021 [62]	CLL	HBV vaccine	26	4%	
Pleyer C, Blood 2021 [62]	CLL	rVZV revaccine	41	41%	
Benjamini O, Haematologica 2022 [21]	CLL	SARS-CoV2 vaccina	106	23%	1) Active treatment
Shen Y, Br J Haematol 2022 [35]	CLL	SARS-CoV2 vaccine	21	15%	1) Lower baseline IgM serum levels 2) Active therapy
Bacova B, Clin Exp Med. 2022 [28]	B-NHL+ CLL	SARS-CoV2 vaccine	16	19%	
Haggenburg S, Blood Adv 2022 [27]	CLL	SARS-CoV2 vaccine	38	27%	1) Older age 2) Low baseline IgG4 serum levels 3) Low baseline NK and B-cells counts 4) Use of rituximab, venetoclax and CD-19 directed CAR-T cells
Diamantopoulos P, Ther Adv Hematol 2022[54]	CLL	SARS-CoV2 vaccine	7	14%	
Pleyer C, Blood Adv 2022 [63]	CLL	rVZV vaccine	50	40%	
Muchtar E, Am J Hematol 2022 [64]	CLL	rVZV vaccine	25	36%	

B-NHL: B-non Hodgkin lymphoma; CLL: Chronic lymphocytic leukemia; WM: Waldenstrom Macroglobulinemia; BTKi: Bruton-tyrosine kinase inhibitor; HBV: Hepatitis B virus; rVZV: Recombinant varicella zoster virus

Overall, BTKi seem to significantly impair seroconversion to several viral and bacterial agents; the detrimental effect is magnified by previous B-cell depleting MoAbs and may be efficiently predicted by baseline IgG levels. Cellular immune response seems less affected, although BTKi also show some T-cell directed effect. According to available literature, BTKi do not need to be interrupted in case of vaccination and booster doses ameliorate immunological response.

4. Tyrosine-kinase inhibitors (TKI) for myeloproliferative syndromes (MPN)

BCR-ABL tyrosine-kinase inhibitors (TKI) represent the mainstay of care for chronic myeloid leukemia (CML) and may induce off-target B-cell impairment [65]. However, almost all subjects on treatment with TKI obtained seroconversion to SARS-CoV-2 vaccination in clinical experiences (Table 3) [9,27,66,67]. Similarly, vaccination against *Influenza* induced seroconversion in all CML patients investigated, particularly after the second dose. However, cellular response appeared reduced (29%) highlighting the potential immune effect of these drugs [43]. Regarding *Pneumococcus* vaccine, humoral response was documented in 40% patients only, with a cellular immune response comparable to healthy controls [65]. Finally, a limited experience in the pediatric setting showed long-term seroconversion after Measles-Mumps-Rosolia (MMR) and *Varicella* vaccines in only 25-50% of patients [68].

Regarding the JAK1/2 inhibitor ruxolitinib, used in myelofibrosis, polycythemia vera (PV) and steroid-refractory graft-versus-host disease, it has been reported to suppress NK and T-cell functions, and to reduce the release of proinflammatory cytokines [69]. The reported seroconversion rate to SARS-CoV-2 ranged from 16 to 80% after 2 doses of mRNA-vaccine (Table 4). Antibody titers were significantly lower than in non-ruxolitinib treated subjects, although improving with booster doses [70–74]. Consistently, a reduced production of IL2 and IFN cytokines after SARS-CoV-2 vaccine in ruxolitinib treated subjects was reported [75].

Overall, seroconversion in TKI-treated CML patients appears heterogeneous, ranging from 40% after Pneumococcal to about 90- 100% after *Influenza* and SARS-CoV-2 vaccines. With ruxolitinib, the rate of seroconversion to SARS-CoV2-vaccines seems preserved, although with a reduced quality. TKI discontinuation during vaccination seems not necessary, and booster doses improve seroconversion.

5. Venetoclax and hypometilating agents (HMA)

Hypomethylating agents and the anti-BCL2 inhibitor venetoclax are increasingly used for acute myeloid leukemias and myelodysplastic syndromes [76,77]. Similarly to BTKi, TKI and ruxolitinib, these agents are administered continuously, and may induce immune disruption with increased incidence of invasive fungal and bacterial infections [78]. Recently a seroconversion rate of about 90% was reported in AML/MDS patients vaccinated for SARS-CoV2 and treated with HMA alone or in combination with venetoclax (Table 5) [79,80]. Different results were reported by our group [9] and in another experience [27], where venetoclax plus HMA was accompanied by a seroconversion rate of only 33% versus 88% with HMA alone.

Venetoclax impaired response to vaccine even in chronic lymphocytic leukemia and mantle cell leukemia, with a pooled response to SARS-CoV-2 vaccination of 26% in a recent meta-analysis [21,26,33,35,54,81].

Altogether, HMA treated patients generally respond well to vaccines but venetoclax association may dampen seroconversion. This favors the administration of booster doses in these patients and may suggest the use of additional prophylaxis strategies (i.e. anti-viral pre-emptive therapies).

6. Anti-myeloma agents

Plasma cell dyscrasias are characterized by intrinsic immunosuppression, even in pre-malignant stage as monoclonal gammopathy of unknow significance (MGUS) [82], and up to 10-fold and 7-fold increased risk of viral and bacterial infectious has been estimated in myeloma patients [83]. Regarding SARS-CoV-2 vaccines, multiple myeloma (MM) patients displayed a reduced immune response compared to the general population [84] (Table 6). One of the major predictors of seroconversion was disease control (partial or complete remission) at the time of vaccination [85–87]. Nevertheless, anti-CD38 moAbs were associated with lower seroconversion rate in comparison to other anti-myeloma treatments (50% versus 92.9% respectively) in several reports [74,87]. Similarly, treatment with the anti-BCMA belantamab mafodotin was negatively associated with seroconversion, despite the small number of patients [88]. Lower baseline immunoglobulins, lymphocyte count, and treatment with steroids were identified as additional negative factors [27,84], as well as the number of previous line therapies [9,87,89,90]. Booster doses were associated with improving responses (Table 6) [91,92].

Heterogeneous responses were also observed with *Influenza* vaccination, with seroconversion ranging from 31% to 65% [93,94], the lowers observed during treatment with anti-CD38 MoAb (20%) [95,96].

Maintenance with lenalidomide after autologous transplant hampered seroconversion after Poliovirus vaccine (26%), but not after

Table 3
Seroconversion in patients treated with TKI for CML.

Reference	Malignancy type	Vaccine type	Number of patients	Seroconversion rate	Negative prognostic factors for seroconversion
De Lavallade H, Hematologica 2011 [43]	CML	*Influenza* vaccine	32	90%	
De Lavallade H, Blood 2013 [65]	CML	Pneumococcal vaccine	45	40%	
Bettoni C, Front Immun 2020 [68]	CML	MMR vaccine	4	50%	
Bettoni C, Front Immun 2020 [68]	CML	VZV vaccine	2	50%	
Pimpinelli F, J Hematol Oncol 2021 [74]	CML	SARS-CoV2 vaccine	20	100%	
Hanngington P, BJH 2021 [66]	CML	SARS-CoV2 vaccine	16	87.5%	
Haggenburg S, Blood Adv 2022 [27]	CML	SARS-CoV2 vaccine	52	100%	1) Older age 2) Low baseline IgG4 serum levels 3) Low baseline NK and B-cells counts 4) Use of rituximab, venetoclax and CD-19 directed CAR-T cells
Rotterdam J, Ann Hematol 2022 [67]	CML	SARS-CoV2 vaccine	66	98%	
Fattizzo B, Front Imm, 2022 [9]	CML	SARS-CoV2 vaccine	48	99%	

CML: Chronic myeloid leukemia; TKI: Tyrosine-kinase inhibitors; MMR: Mumps-measles-rosolia; VZV: Varicella zoster vaccine

Table 4
Vaccine in MPN patients treated with Ruxolitinib.

Reference	Agent	Malignancy type	Vaccine type	Number of patients	Seroconversion rate	Negative prognostic factors for seroconversion
Fiorino F, Biomedicines 2021 [71]	Ruxolitinib	MF	SARS-CoV2 vaccine	16	68%	
Guglielmelli P, Am J Hematol 2021 [70]	Ruxolitinib	MPN	SARS-CoV2 vaccine	18	33%	
Pimpinelli F, J Hematol Oncol 2021 [74]	Ruxolitinib	MPN	SARS-CoV2 vaccine	8	62.5%	
Caocci G, Ann Hematol 2022 [73]	Ruxolitinib	MF	SARS-CoV2 vaccine	10	60%	
Ikeda D, Front Med (Lausanne). 2022 [72]	Ruxolitinib	MPN	SARS-CoV2 vaccine	20	80%	
Fattizzo B, Front Imm, 2022 [9]	Ruxolitinib	MPN	SARS-CoV2 vaccine	36	75%	
Harrington P, Blood Cancer Journal 2022 [75]	Ruxolitinib	MPN	SARS-CoV2 vaccine	12	50%	
Haggenburg S, Blood Adv 2022 [27]	Ruxolitinib	MPN	SARS-CoV2 vaccine	38	49%	1) Older age 2) Low baseline IgG4 serum levels 3) Low baseline NK and B-cells counts
Rotterdam J, Ann Hematol 2022 [67]	Ruxolitinib+Fedratinib	MPN	SARS-CoV2 vaccine	24	16%	

MPN: Myeloproliferative neoplasms; MF: Myelofibrosis.

Table 5
Treatment for MDS and AML patients and vaccine response.

Reference	Agent	Malignancy type	Vaccine type	Number of patients	Seroconversion rate	Negative prognostic factors for seroconversion
Roeker L, Leukemia. 2021 [26]	Venetoclax	CLL	SARS-CoV2 vaccine	7	0%	
Herishanu Y, Blood 2021 [33]	Venetoclax	CLL	SARS-CoV2 vaccine	22	13.6%	1) Age $\geq$ 65 years 2) Active treatment 3) Baseline IgG levels <550 mg/dL 4) Baseline IgM levels <40 mg/dL 5) Male sex
Benjamini O, Haematologica 2022 [21]	Venetoclax	CLL	SARS-CoV2 vaccine	62	24%	1) Association with anti-CD20 moAbs
Diamantopoulos P, Ther Adv Hematol 2022 [54]	Venetoclax	CLL	SARS-CoV2 vaccine	11	36%	
Shen Y, Br J Haematol 2022 [35]	Venetoclax	CLL	SARS-CoV2 vaccine	4	25%	1) Lower baseline IgM serum levels 2) Active therapy
Gagelmann, Haematologica 2022 [81]	Venetoclax	B-NHL + CLL	SARS-CoV2 vaccine	155	26%	
Haggenburg S, Blood Adv 2022 [27]	HMA	MDS + AML	SARS-CoV2 vaccine	19	41%	1) Older age 2) Low baseline IgG4 serum levels 3) Low baseline NK and B-cells counts 4) Use of rituximab, venetoclax and CD-19 directed CAR-T cells
Candoni A, Blood Adv 2022 [79]	HMA	MDS + AML	SARS-CoV2 vaccine	24	94%	
Candoni A, Blood Adv 2022 [79]	HMA + Venetoclax	MDS + AML	SARS-CoV2 vaccine	22	88%	
Chan W, BJH 2022 [80]	HMA	MDS + AML	SARS-CoV2 vaccine	8	96%	
Chan W, BJH 2022 [80]	HMA + Venetoclax	MDS + AML	SARS-CoV2 vaccine	20	96%	
Fattizzo B, Front Imm 2022 [9]	HMA	MDS + AML	SARS-CoV2 vaccine	16	88%	
Fattizzo B, Front Imm 2022 [9]	HMA + Venetoclax	MDS + AML	SARS-CoV2 vaccine	12	33%	

MDS: Myelodysplastic syndrome; AML: Acute myeloid leukemia; HMA: Hypomethylating agents.

Pneumococcus, MMR or VZV vaccines [97]. Given the evidence of the immunogenicity and safety of adjuvanted recombinant VZV vaccine [98], the European Myeloma Network recommends recombinant VZV vaccination over attenuated one [99].

Overall, MoAbs anti-CD38 and anti-BCMA seem to hamper seroconversion to vaccines in MM patients; booster doses and optimization of timing and schedules should be further investigated in this setting. Contrarily, good immune responses are obtained in those treated with proteasome inhibitors or immunomodulatory drugs.

7. Complement inhibitors

Over the last decade complement inhibitors have become the standard of care in several complement-mediated hematological diseases, including PNH, atypical hemolytic uremic syndrome (aHUS) and, more recently, cold agglutinin disease (CAD). These drugs dampen the

Table 6
Vaccine response in anti-myeloma agents.

Reference	Agent	Malignancy type	Vaccine type	Number of patients	Seroconversion rate	Negative prognostic factors for seroconversion
Noonan K, Clin Cancer Rev. 2012 [92]	IMiDs	Multiple myeloma	*Pneumococcus* vaccine	17	NA	1) Active disease
Branagan AR, Clin Lymphoma Myeloma Leuk. 2017 [94]	IMiDs	Multiple myeloma	*Influenza* vaccine	22	39-55%	1) Active disease 2) Suppression of uninvolved Ig classes 3) Active treatment except for IMiD
Palazzo M, Biol Blood Marrow Transplant. 2018 [97]	Lenalidomide after ASCT	Multiple myeloma	H. *Influenza* vaccine	91	95%	
Palazzo M, Biol Blood Marrow Transplant. 2018 [97]	Lenalidomide after ASCT	Multiple myeloma	*Pneumococcus* vaccine	91	52%	
Palazzo M, Biol Blood Marrow Transplant. 2018 [97]	Lenalidomide after ASCT	Multiple myeloma	Poliovirus vaccine	91	26%	
Palazzo M, Biol Blood Marrow Transplant. 2018 [97]	Lenalidomide after ASCT	Multiple myeloma	*Tetanus* toxoid	91	93%	
Palazzo M, Biol Blood Marrow Transplant. 2018 [97]	Lenalidomide after ASCT	Multiple myeloma	*Diphteria* toxoid	91	70%	
Palazzo M, Biol Blood Marrow Transplant. 2018 [97]	Lenalidomide after ASCT	Multiple myeloma	Pertussis vaccine	91	91%	
Palazzo M, Biol Blood Marrow Transplant. 2018 [97]	Lenalidomide after ASCT	Multiple myeloma	HAV vaccine	91	55%	
Palazzo M, Biol Blood Marrow Transplant. 2018 [97]	Lenalidomide after ASCT	Multiple myeloma	HBV vaccine	91	48%	
Greenberg RS, BMC Cancer 2021 [91]	IMiDs	Multiple myeloma	SARS-CoV2 vaccine	21	95%	
Terpos E, Blood Cancer J 2021 [88]	IMiDs-based regimens	Multiple myeloma	SARS-CoV2 vaccine	125	74%	1) Treatment with Belantamab mafodotin or anti-CD38 moAbs 2) Lymphopenia
Terpos E, Blood 2021 [86]	IMiD-based regimens	Multiple myeloma	SARS-CoV2 vaccine	23	25%	
Bird S, Lancet Haematol 2021 [90]	IMiD-based regimens	Multiple myeloma	SARS-CoV2 vaccine	44	45%	1) Active disease 2) Immunoparesis 3) More previous lines of therapy
Bird S, Lancet Haematol 2021 [90]	IMiD-based regimens	Multiple myeloma	SARS-CoV2 vaccine	44	45%	1) Active disease 2) Immunoparesis 3) More previous lines of therapy
Pimpinelli F, J Hematol Oncol 2021 [74]	IMiDs-based regimen	Multiple myeloma	SARS-CoV2 vaccine	19	92.9%	
Pettine L, Hematol Oncol 2022 [87]	IMiDs-based regimens	Multiple myeloma	SARS-CoV2 vaccine	88	85%	1) Active disease 2) Older age 3) >2 prior therapy lines
Marasco V, BJH 2022 [25]	IMiDs	Multiple myeloma	SARS-CoV2 vaccine	26	84.6%	
Haggenburg S, Blood Adv 2022 [27]	IMiDs	Multiple myeloma	SARS-CoV2 vaccine	55	77%	1) Older age 2) Low baseline IgG4 serum levels 3) Low baseline NK and B-cells counts 4) Use of rituximab, venetoclax and CD-19 directed CAR-T cells
Rosati M, Cancers 2022 [96]	IMiD+PI	Multiple myeloma	SARS-CoV2 vaccine booster	20	95%	
Branagan AR, Clin Lymphoma Myeloma Leuk. 2017 [94]	Proteasome inhibitor	Multiple myeloma	*Influenza* vaccine	16	39-55%	1) Active disease 2) Suppression of uninvolved Ig classes 3) Active treatment except fot IMiD
Terpos E, Blood Cancer J 2021 [88]	PI-based regimens	Multiple myeloma	SARS-CoV2 vaccine	67	62%	1) Treatment with Belantamab mafodotin or anti-CD38 moAbs 2) Lymphopenia
Pimpinelli F, J Hematol Oncol 2021 [74]	PI-based regimens	Multiple myeloma	SARS-CoV2 vaccine	9	92.9%	
Greenberg RS, BMC Cancer 2021 [91]	Proteasome inhibitors	Multiple myeloma	SARS-CoV2 vaccine	4	75%	
Terpos E, Blood 2021 [86]	PI-based regimens	Multiple myeloma	SARS-CoV2 vaccine	11	25%	
Bird S, Lancet Haematol 2021 [90]	PI-based regimens	Multiple myeloma	SARS-CoV2 vaccine	18	56%	1) Active disease 2) Immunoparesis 3) More previous lines of therapy
Pettine L, Hematol Oncol 2022 [87]	PI-based regimens	Multiple myeloma	SARS-CoV2 vaccine	22	95%	1) Active disease 2) Older age 3) >2 prior therapy lines
Frerichs KA, Haematologica 2020 [95]	Daratumumab	Multiple myeloma	*Pneumococcus* vaccine	17	68.8%	

(*continued on next page*)

Table 6 (*continued*)

Reference	Agent	Malignancy type	Vaccine type	Number of patients	Seroconversion rate	Negative prognostic factors for seroconversion
Frerichs KA, Haematologica 2020 [95]	Daratumumab	Multiple myeloma	*H. influenzae* vaccine	17	66.7%	
Frerichs KA, Haematologica 2020 [95]	Daratumumab	Multiple myeloma	*Influenza* vaccine	13	17-25%	
Greenberg RS, BMC Cancer 2021 [91]	Daratumumab	Multiple myeloma	SARS-CoV2 vaccine	7	100%	
Terpos E, Blood Cancer J 2021 [88]	Anti-CD38 moAbs-based regimens	Multiple myeloma	SARS-CoV2 vaccine	55	55%	1) Treatment with Belantamab mafodotin or anti-CD38 moAbs 2) Lymphopenia
Pimpinelli F, J Hematol Oncol 2021 [74]	Anti-CD38 moAbs-based regimens	Multiple myeloma	SARS-CoV2 vaccine	14	50%	
Terpos E, Blood 2021 [86]	Anti-CD38 moAbs-based regimens	Multiple myeloma	SARS-CoV2 vaccine	8	25%	
Bird S, Lancet Haematol 2021 [90]	Anti-CD38 moAbs-based regimens	Multiple myeloma	SARS-CoV2 vaccine	12	52%	1) Active disease 2) Immunoparesis 3) More previous lines of therapy
Rosati M, Cancers 2022 [96]	Anti-CD38 moAbs-based regimens	Multiple myeloma	SARS-CoV2 vaccine booster	17	50%	
Pettine L, Hematol Oncol 2022 [87]	Anti-CD38 moAbs-based regimens	Multiple myeloma	SARS-CoV2 vaccine	26	80%	1) Active disease 2) Older age 3) >2 prior therapy lines
Marasco V, BJH 2022 [25]	Anti-CD38 moAbs	Multiple myeloma	SARS-CoV2 vaccine	10	100%	
Haggenburg S, Blood Adv 2022 [27]	Daratumumab	Multiple myeloma	SARS-CoV2 vaccine	52	69%	1) Older age 2) Low baseline IgG4 serum levels 3) Low baseline NK and B-cells counts 4) Use of rituximab, venetoclax and CD-19 directed CAR-T cells
Greenberg RS, BMC Cancer 2021 [91]	Teclistamab	Multiple myeloma	SARS-CoV2 vaccine	1	0%	
Terpos E, Blood Cancer J 2021 [88]	Belantamab mafodotin-based regimens	Multiple myeloma	SARS-CoV2 vaccine	11	36%	1) Treatment with Belantamab mafodotin or anti-CD38 moAbs 2) Lymphopenia
Terpos E, Blood 2021 [86]	Belantamab mafodotin	Multiple myeloma	SARS-CoV2 vaccine	2	25%	
Rosati M, Cancers 2022 [96]	Anti-BCMA therapy	Multiple myeloma	SARS-CoV2 vaccine booster	3	10-30%	
Pettine L, Hematol Oncol 2022 [87]	Belantamab mafodotin	Multiple myeloma	SARS-CoV2 vaccine	1	0%	1) Active disease 2) Older age 3) >2 prior therapy lines

PI: Proteasome inhibitor; IMiDs: Immunomodulatory drugs; ASCT: Autologous stem cells transplantation; HAV: Hepatitis A virus; HBV: Hepatitis B virus.

protection against capsulated bacteria such *Neisseria meningitidis*, *Haemophilus influenzae* and *Pneumococcus* (Table 7). An overall rate of 0,25 meningococcal infections per 100 patients per years was reported with the anti-C5 eculizumab, with a total of 8 fatal cases [100]. Therefore, all patients should receive quadrivalent meningococcal serogroup A, C, W, Y conjugate vaccine and serogroup B vaccine before anti-C5 therapy, extended to anti-Haemophilus and *Pneumococcus* in case of proximal inhibitors use [101]. Regarding the efficacy of SARS-CoV2 vaccination,

Table 7
Vaccine response with anti-complement inhibitors.

Reference	Agent	Malignancy type	Vaccine type	Number of patients	Seroconversion rate	Negative prognostic factors for seroconversion
Struijk GH, Am J Transplant 2013 [109]	Eculizumab	PNH	MenACWY vaccine	1	0%	
Cullinan N, Pediatrics 2015 [111]	Eculizumab	PNH	MenACWY vaccine	1	0%	
McNamara LA, MMWR Morb Mortal Wkly Rep. 2017 [108]	Eculizumab	PNH	MenACWY vaccine	14	0%	
Parikh SR, Pediatrics 2017 [110]	Eculizumab	PNH	MenACWY and 4CMenB vaccine	1	0%	
Alashkar F, Ann Hematol 2017 [107]	Eculizumab	PNH	MenACWY vaccine	23	48-87%	
Yu ZY, J Microbiol Immunol Infect. 2020[112]	Ravulizumab	PNH	MenACWY vaccine	1	0%	
Gäckler A, Nephrol Dial Transplant. 2020 [115]	Eculizumab	PNH	Meningococcal conjugate vaccine	25	20%	
Pike A, Lancet Haemat 2022 [102]	Complement inhibitor therapy	PNH	SARS-CoV2 vaccine	74	63%	
Pike A, Lancet Haemat 2022 [102]	Complement inhibitor therapy	PNH + SAA	SARS-CoV2 vaccine	47	68%	

PNH: Paroxysmal nocturnal hemoglobinuria; SAA: Severe aplastic anemia; MenACWY vaccine: Vaccine against *meningococcus* strain A, C,W,Y; 4CMenB: Multicomponent meningococcal serogroup B vaccine.

seroconversion rate was 60% after the first dose, and nearly 100% after a second dose [102] in a large experience (Table 8). Even in the experience of an Italian reference center, PNH and CAD patients under complement inhibitors showed excellent rates of seroconversion [36]. The major warning in this setting is that of boosting complement activity thus inducing breakthrough hemolytic flares (BTH). BTH was reported in about 3% of PNH patients after SARS-CoV-2 vaccines [103–105] and in about 10% of CAD [106], managed conservatively in most cases.

Concerning other vaccines, Meningococcal vaccinations induced up to 87% seroconversion rate in patients on eculizumab [107]. Importantly, meningococcal infections may occur despite vaccination [108–112]; accordingly decreased meningococci killing was documented in blood samples of healthy individuals exposed to eculizumab or complement factor D inhibitor [113,114].

To further complicate the picture, aHUS and CAD also receive other immunosuppressive treatments that may hamper seroconversion after *Meningococcus* vaccination. In aHUS, a full immune response was obtained in 20% of cases only, and 52% developed protective antibody titers against at least one of the three serogroups [115].

Overall, SARS-CoV-2 vaccines appear protective in patients treated with complement inhibitors. Monitoring of blood counts and hemolytic markers in the first days after vaccines is recommended, since the activation of the classical complement pathway may lead to BTH. Administration of vaccines in the days immediately following the administration of complement inhibitors may reduce the phenomenon.

8. Cyclosporine, anti-thymocyte globulin, and eltrombopag (Table 8)

Among autoimmune cytopenias, aplastic anemia is affected by high frequency of infections (due to disease itself and immunosuppressive treatment (IST). Data on safety and immunogenicity of vaccination during IST mainly regard SARS-CoV-2 vaccines. In a recent report, IST with cyclosporine (CsA) or tacrolimus did not impact on seroconversion after SARS-CoV-2 vaccination, and all the patients developed protective titers (Table 8) [102]. The exposure to ATG was not associated with a reduced humoral response, although median time to ATG administration was >12 months [102,116]. Similarly, in an Italian experience [36] all CsA treated patients seroconverted, despite showing lower anti-Spike IgG titers, further reduced in case of steroids association.

It should be mentioned that some cases of aplastic anemia occurring after SARS-CoV2 vaccination have been described [117–119]. Finally, the thrombopoietin receptor agonist eltrombopag used in patients with aplastic anemia and immune thrombocytopenia had no impact on seroconversion [9,36]. Similarly, in myelodysplastic syndromes, the activin inhibitor luspatercept did not hamper seroconversion in the Italian experience [36,120].

Overall, CsA and ATG seem to allow safe and effective vaccinations, although T-cell response has not been extensively studies and may be likely hampered. Reducing and, if possible, eliminating steroids, and allowing the longest interval from ATG infusion to vaccination might be beneficial.

9. Chimeric antigen T-cells (CAR-T)

Chimeric antigen T-cells (CAR-T) represent a new frontier for the treatment of lymphoid neoplasms and multiple myeloma. This treatment strategy induces prolonged B-cell lymphopenia that may account for lower seroconversion to vaccines. Table 9 recapitulates available data on seroconversion to vaccines in CAR-T cells recipients: most data regard SARS-CoV-2 and show a reduced pooled humoral response rate of about 30% that did not significantly improve after booster doses. Whilst after autologous and allogenic stem cell transplants booster doses and allowing time from transplant did improve seroconversion, this was not the case of CAR-T [27]. A small prospective study demonstrated that 3/5 (60%) patients vaccinated pre-CAR-T maintained anti-spike antibodies at day 30 post-CAR T-cell therapy, suggesting a potential role for vaccination prior to CAR T-cell therapy [121]. A significant lower humoral response occurred in recipients of CD19-directed CAR-T versus BCMA- or CD138-directed CAR-T therapy recipients that reached about 70% in multiple myeloma patients. This may be related to the different lymphodepleting potential as well as to a deeper immune derangement in B-cell lymphomas versus multiple myeloma patients [122]. This was also highlighted by the longest minimal interval after autologous hematopoietic cell transplantation to reach adequate seroconversion in lymphomas versus myeloma patients (8 versus <2 months). Importantly, various groups demonstrated that CAR-T recipients demonstrate normal or heightened functional T-cell responses (>80% across all studies), including antiviral T-cell activity against SARS-CoV-2 variants including Omicron [123]. Finally, low rates of seroconversion were reported for Pneumococcus and Influenza vaccines in CAR-T-cell recipients. However, some responses were observed even in case of lymphopenia or hypogammaglobulinemia, supporting the consideration for vaccination before and after CAR-T-cell therapy for influenza and other relevant pathogens such as SARS-CoV-2, irrespective of hypogammaglobulinemia or B cell aplasia [124,125].

Very limited data were found regarding bispecific T-cell engaging (BiTE) monoclonal antibodies and response to SARS-CoV-2: Abid et al. reported an encouraging seroconversion rate of 67% among 9 BiTE recipients, with a detrimental effect of concomitant corticosteroid usage and no differences regarding vaccine type [126].

Collectively, these data reinforce the importance of COVID-19 vaccination following CD19 CAR T-cell therapy, despite long-term B-cell aplasia.

10. Conclusions

Novel agents significantly improved outcomes of hematological diseases but may impair immune response to pathogens as well as to several vaccinations including anti-SARS-CoV-2, *Influenza*, Measles-Mumps-Rosolia, *Varicella*, *Pneumococcus*, and *Meningococcus*. If possible, vaccinations should be administered prior to therapy since B-cell memory appears to persist beyond treatment. However, the need of urgent treatment or ongoing continuous therapies (anti-CD38 and anti-BCMA MoAbs, BTKi, TKI, HMA, venetoclax, etc.) may prevent this strategy. In lymphomas and autoimmune cytopenias, the time from the

Table 8
Vaccine response with anti-thymocyte globulin (ATG) and ciclosporine (CsA).

Reference	Agent	Malignancy type	Vaccine type	Number of patients	Seroconversion rate	Negative prognostic factors for seroconversion
Pike A, Lancet Haemat 2022 [102]	ATG	Aplastic Anemia	SARS-CoV2 vaccine	60	100%	
Pike A, Lancet Haemat 2022 [102]	CsA/ Tacrolimus	Aplastic Anemia	SARS-CoV2 vaccine	39	100%	
Fattizzo B, Sci Rep 2022 [36]	CsA	Aplastic Anemia	SARS-CoV2 vaccine	19	100%	1) Association with steroids
Walter J, Eur J Haemat 2022 [116]	CsA + ATG	Aplastic Anemia	SARS-CoV2 vaccine	16	100%	

Table 9
Vaccine response with chimeric antigen receptor T cells (CAR-T).

Reference	Malignancy type	Vaccine type	Number of patients	Seroconversion rate
Ram R, Transplant Cell Ther 2021 [127]	Lymphoma	SARS-CoV-2 vaccine	14	36%
Bergman P, BioMedicine 2021 [128]	Lymphoma	SARS-CoV-2 vaccine	3	0%
Fox TA, Br J Haematol 2021 [129]	Lymphoma	SARS-CoV-2 vaccine	9	22%
Tamari R, Blood Cancer Discov 2021 [130]	Not reported	SARS-CoV-2 vaccine	7	29%
Van Oekelen O, Cancer Cell 2021 [131]	Myeloma	SARS-CoV-2 vaccine	19	79%
Reimann H, Blood Adv 2022 [132]	Lymphoma	SARS-CoV2 vaccine	15	13%
Gossi S, Cancers 2022 [133]	Lymphoma/ acute leukemia	SARS-CoV2 vaccine	46	39-43%
Wu X, J Hematol Oncol 2022 [134]	Lymphoma/ Leukemia	SARS-CoV2 vaccine	174 (pooled analysis)	36%
Jarisch A, Transplant Cell Ther 2022 [135]	Leukemia	SARS-CoV-2 vaccine	8	12.5%
Abid MB, Cancer Cell 2022 [126]	Myeloma/ Lymphoma	SARS-CoV-2 vaccine	10	40%
Ram R, Transplant Cell Ther 2022 [136]	Lymphoma	SARS-CoV-2 vaccine	6	17%
Dahiya S, Blood Adv 2022 [137]	Lymphoma	SARS-CoV-2 vaccine	14	7%
Greenberger LM, Blood Cancer Discov 2022 [138]	Lymphoma/ Myeloma	SARS-CoV-2 vaccine	12	14-80%
Gastinne T, Br J Haematol 2022 [139]	Lymphoma/ Leukemia	SARS-CoV-2 vaccine	23	30%
Haggenburg S, Blood Adv 2022 [27]	Lymphoma/ Leukemia	SARS-CoV-2 vaccine	44	11%
Parvathaneni K, Jama Oncol 2022 [140]	Lymphoma/ Leukemia	SARS-CoV-2 vaccine	12	42%
Aleissa MM, Transplant Cell Ther 2023 [141]	Lymphoma/ Myeloma	SARS-CoV-2 vaccine	50	64%
Pinana JL, BMT 2023[142]	Lymphoma/ leukemia	SARS-CoV2 vaccine	22	59-62%
Wirth SRM, Cancers 2023 [143]	Lymphoma	SARS-CoV2 vaccine	12	33-66%
Walti CS, J Immunother Cancer 2021 [124]	Lymphoma/ Myeloma	*Influenza* vaccine	18	31-40%
Lee D, Transplant Cell Ther 2022 [125]	Lymphoma	*Pneumococcus* vaccine	76	25%

last anti-CD20 MoAb to vaccine administration significantly impacts vaccine responses, suggesting allowing at least 6 months from the last MoAb dose. Other predictors include hypogammaglobulinemia and lymphopenia as possible consequence of disease itself or previous treatments, and active disease in MM patients. Small molecules such as BTKi, ruxolitinib, and venetoclax, may impact negatively on seroconversion, unlike TKI and hypomethylating agents, but discontinuation during vaccination is not advised. In fact, booster doses may improve seroconversion, and additional preventive measures such as anti-Spike protein MoAbs may be considered. Complement inhibitors and aplastic anemia treatments do not hamper immune responses. However, in the setting of complement mediated disorders, hemolytic reactivations after vaccines should be taken into account (as reported for SARS-CoV-2 vaccines and anti-*Meningococcus* B in PNH and CAD) and properly monitored. Finally, anti-CD19 CAR-T cells recipients also showed very limited seroconversion after SARS-CoV-2, *Pneumococcus*, and *Influenza* vaccines, but high cellular responses irrespective of lymphopenia or hypogammaglobulinemia, suggesting to pursue vaccination even in this setting.

As illustrated in Fig. 1, different rates of immune response were documented depending on the different drugs and disease-related features. Nevertheless, vaccinations remain the mainstay of primary prophylaxis against SARS-CoV-2 and other agents in hematologic patients. No significant differences regarding SARS-CoV-2 vaccine types (mainly including mRNA-based ones) emerged from available literature. The proper timing of administration and booster doses may aid to optimize the rate of seroconversion. The evolving epidemiology with high heterogeneity in SARS-CoV-2 variants, regional contagions and vaccination campaigns preclude definite conclusions regarding vaccine efficacy in reducing contagions in specific therapeutic settings. However, overall data indicate a reduction in morbidity and mortality after SARS-CoV-2 vaccination, with breakthrough infections being generally less severe.

11. Future considerations

The next step would be to personalize vaccination campaigns on patient' disease, comorbidities, and therapies. This has been only partly done during anti-SARS-CoV-2 vaccination venture, where "frail" patients included heterogenous subject groups, with different ages, diseases, and treatments. The difference in vaccines type and immunogenicity further complicates the picture.

A further open issue is how to evaluate vaccine response (i.e., humoral versus cellular and with what cut-offs?). The standardization of the binding antibody units (BAU) levels indicative of effective neutralizing antibodies is an example of international effort but should be pursued with well-designed prospective studies even for other commonly administered vaccines (i.e. *Influenza*, Hepatitis, capsulated bacteria, etc.). This is also true for cellular response, that might be systematically studied and generated through simplified and wide available techniques as for interferon release tests, similarly to what has been done for quantiferon in tubercolosis. Finally, an effort should be done to include clinical endpoints, such as the number and severity of breakthrough infections after vaccination in this patient population.

Given the high heterogeneity emerged and the deepening knowledge built on anti-SARS-CoV-2 vaccines, the decision on *"who and when"* to vaccinate against a certain agent will be likely addressed in a precision medicine fashion. Moreover, the timing of assessment, the type of response (humoral versus cellular) and the method used need harmonization among different countries and clinical settings. This will require prospective and systematic studies, accounting for patients and diseases subgroups, with a global effort from the scientific/clinical community, the companies, and the regulatory agencies. Indeed, the unprecedent number of clinical trials of drugs and vaccines run in a short period of time represents the answer to the enormous lives loss of SARS-CoV-2 pandemics and will likely boost the rate of discoveries in the field of vaccinations and infectious protection.

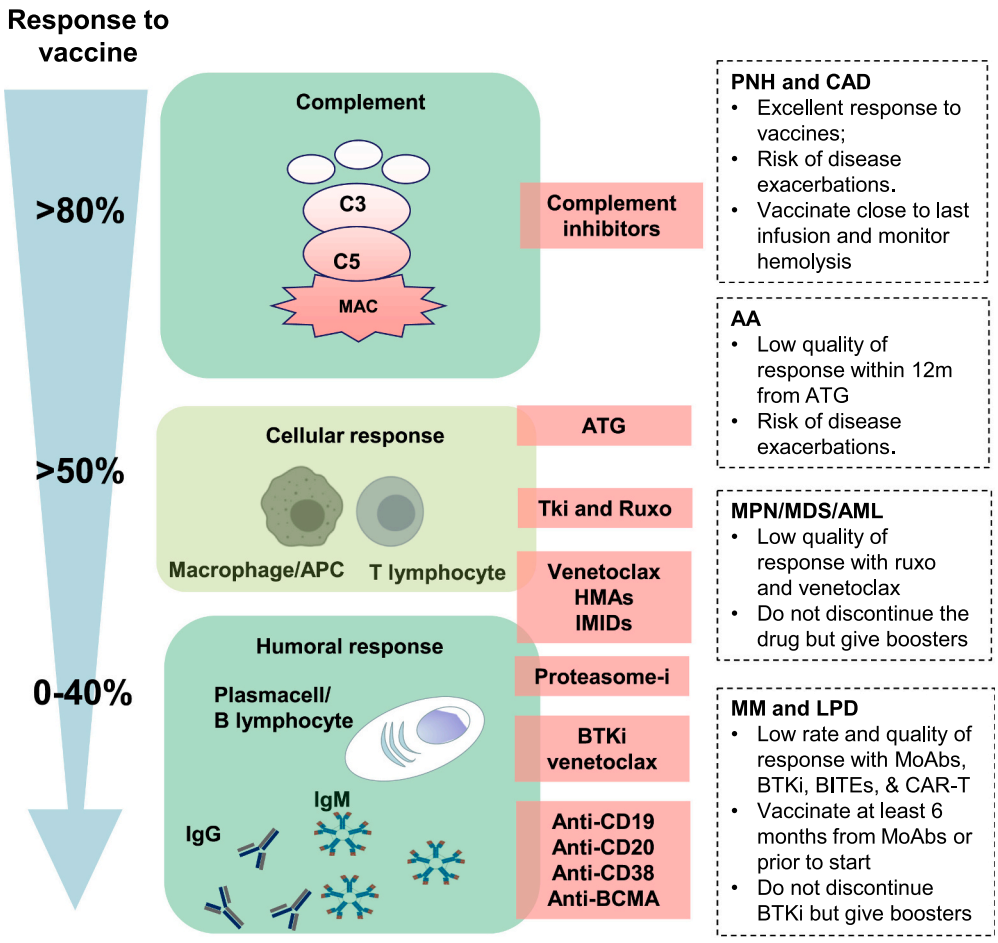

Fig. 1. Response to vaccines with different targeting hematologic drugs.
Targeting hematologic drugs may hamper the different subsets (complement, cellular, and humoral) of the immune system. Response rates are maximal in patients treated with complement inhibitors (i.e. those with paroxysmal nocturnal hemoglobinuria, PNH, and cold agglutinin disease, CAD). Responses to vaccines may be reduced in patients with aplastic anemia (AA) treated with anti-thymocyte globulin (ATG) within the last 12 months. For PNH, CAD and AA, disease flare after vaccinations should be monitored. Vaccine efficacy is mildly reduced in patients treated with tyrosine kinase inhibitors (TKI), including ruxolitinib (ruxo) for myeloproliferative neoplasms (MPN), or with hypomethylating agents (HMA), particularly in association with venetoclax for myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). Response to vaccines is severely impaired in patients receiving anti-B-cell therapies including Bruton TKi (BTKi) and monoclonal antibodies (MoABs) anti-CD20 for lymphoproliferative disorders (LPD), MoAbs anti-CD38 and anti B-cell maturation antigen (BCMA) for multiple myeloma (MM), bi-specific T-cell engaging MoAbs (BITEs), and chimeric antigen T-cells (CAR-T) in LPD and MM. Immunomodulating agents (IMIDs) and proteasome inhibitors (Proseasome-i) for MM do not seem to hamper response to vaccines. MAC membrane attack complex; APC antigen presenting cell.

12. Practice points

- The rate of seroconversion after vaccines in hematologic patients on treatment with biologic drugs is lower than the general population.
- Worse humoral responses are observed in patients with lymphoproliferative diseases, in those treated with anti-B-cell MoAbs, and in those with hypogammaglobulinemia and lymphopenia.
- To improve the rate of seroconversion, allowing at least 6 months from anti-B-cell MoAbs or vaccination before treatment are advised.
- Small molecules including BTKi, ruxolitinib, and venetoclax, as well as HMAs reduce the rate of seroconversion but treatment should not be stopped before vaccination.
- In complement mediated conditions vaccinations may trigger disease reactivation, suggesting monitoring of disease activity in the following days and/or vaccinating just after treatment.
- Vaccinations remain a pivotal prevention strategy in hematologic patients, and booster doses generally improve efficacy and are advised.

13. Research agenda

- Prediction of seroconversion rate by clinical/laboratory scores.
- Clinical value of prospective-systematic studies of vaccination in disease/treatment subgroups.
- Relationship between modifiable risk factors (timing of therapy, Ig levels, blood counts, etc.) and the rate of seroconversion.
- Harmonization of method of assessment and timing among different countries and clinical settings.
- Understanding of the clinical significance of cellular response to vaccines.
- Pharmacological research to further improve vaccination strategies and for infectious protection in poor responders.

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References

[1] Passamonti F, Cattaneo C, Arcaini L, Bruna R, Cavo M, Merli F, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. Lancet Haematol 2020;7:e737–45. https://doi.org/10.1016/S2352-3026(20)30251-9.

[2] Vijenthira A, Gong IY, Fox TA, Booth S, Cook G, Fattizzo B, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. Blood. 2020;136:2881–92. https://doi.org/10.1182/blood.2020008824.

[3] Oliva A, Cogliati Dezza F, Petrucci F, Romani FE, Morviducci M, Mirabelli FM, et al. Outcome of COVID-19 patients with haematological malignancies after the introduction of vaccination and monoclonal antibodies: results from the HM-COV

2.0 study. Clin Exp Med 2023:1–11. https://doi.org/10.1007/s10238-023-01027-y.
[4] Gobbato M, Clagnan E, Toffolutti F, Del Zotto S, Burba I, Tosolini F, et al. Vaccination against SARS-CoV-2 and risk of hospital admission and death among infected cancer patients: a population-based study in northern Italy. Cancer Epidemiol 2023;82:102318. https://doi.org/10.1016/j.canep.2022.102318.
[5] Pagano L, Salmanton-García J, Marchesi F, López-García A, Lamure S, Itri F, et al. COVID-19 in vaccinated adult patients with hematological malignancies: preliminary results from EPICOVIDEHA. Blood 2022;139:1588–92. https://doi.org/10.1182/blood.2021014124.
[6] Salmanton-García J, Marchesi F, Glenthøj A, Bilgin YM, van Praet J, Dávila-Valls J, et al. Improved clinical outcome of COVID-19 in hematologic malignancy patients receiving a fourth dose of anti-SARS-CoV-2 vaccine: an EPICOVIDEHA report. Hemasphere 2022;6:e789. https://doi.org/10.1097/HS9.0000000000000789.
[7] Blennow O, Salmanton-García J, Nowak P, Itri F, Van Doesum J, López-García A, et al. Outcome of infection with omicron SARS-CoV-2 variant in patients with hematological malignancies: an EPICOVIDEHA survey report. Am J Hematol 2022;97:E312–7. https://doi.org/10.1002/ajh.26626.
[8] Ehmsen S, Asmussen A, Jeppesen SS, Nilsson AC, Østerlev S, Vestergaard H, et al. Antibody and T cell immune responses following mRNA COVID-19 vaccination in patients with cancer. Cancer Cell 2021;39:1034–6. https://doi.org/10.1016/j.ccell.2021.07.016.
[9] Fattizzo B, Bortolotti M, Rampi N, Cavallaro F, Giannotta JA, Bucelli C, et al. Seroconversion to mRNA SARS-CoV-2 vaccines in hematologic patients. Front Immunol 2022;13:852158. https://doi.org/10.3389/fimmu.2022.852158.
[10] Kridin K, Ahmed AR. Post-rituximab immunoglobulin M (IgM) hypogammaglobulinemia. Autoimmun Rev 2020;19:102466. https://doi.org/10.1016/j.autrev.2020.102466.
[11] Lussana F, Cattaneo M, Rambaldi A, Squizzato A. Ruxolitinib-associated infections: a systematic review and meta-analysis. Am J Hematol 2018;93:339–47. https://doi.org/10.1002/ajh.24976.
[12] Ball S, Das A, Vutthikraivit W, Edwards PJ, Hardwicke F, Short NJ, et al. Risk of infection associated with Ibrutinib in patients with B-cell malignancies: a systematic review and Meta-analysis of randomized controlled trials. Clin Lymphoma Myeloma Leuk 2020;20:87–97.e5. https://doi.org/10.1016/j.clml.2019.10.004.
[13] Liu B, Guo Y, Deng L, Qiao Y, Jian J. The efficacy and adverse events of venetoclax in combination with hypomethylating agents treatment for patients with acute myeloid leukemia and myelodysplastic syndrome: a systematic review and meta-analysis. Hematol (United Kingdom) 2020;25:414–23. https://doi.org/10.1080/16078454.2020.1843752.
[14] Girmenia C, Barcellini W, Bianchi P, Di Bona E, Iori AP, Notaro R, et al. Management of infection in PNH patients treated with eculizumab or other complement inhibitors: unmet clinical needs. Blood Rev 2022;58:101013. https://doi.org/10.1016/j.blre.2022.101013.
[15] Vose JM, Link BK, Grossbard ML, Czuczman M, Grillo-Lopez A, Gilman P, et al. Phase II study of rituximab in combination with CHOP chemotherapy in patients with previously untreated, Aggressive Non-Hodgkin's Lymphoma. J Clin Oncol 2001;19:389–97.
[16] Ertrand Oiffier BC, Ric Epage EL, Osette Rière JB, Aoul Erbrecht RH, Ervé Illy HT, Eda Ouabdallah RB, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. N Engl J Med 2002;346:235–42. https://doi.org/10.1056/NEJMoa011795.
[17] Dunleavy K, Hakim F, Kim HK, Janik JE, Grant N, Nakayama T, et al. B-cell recovery following rituximab-based therapy is associated with perturbations in stromal derived factor-1 and granulocyte homeostasis. Blood 2005;106:795–802. https://doi.org/10.1182/blood-2004-08-3198.
[18] Van Der Kolk LE, Baars JW, Prins MH, Van Oers MHJ. Rituximab treatment results in impaired secondary humoral immune responsiveness. Blood 2002;100:2257–9 [PMID: 12200395].
[19] Perry C, Luttwak E, Balaban R, Shefer G, Morales MM, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with B-cell non-Hodgkin lymphoma. Blood Adv 2021;5:3053–61. https://doi.org/10.1182/bloodadvances.2021005094.
[20] Gavriatopoulou M, Terpos E, Ntanasis-Stathopoulos I, Briasoulis A, Gumeni S, Malandrakis P, et al. Poor neutralizing antibody responses in 106 patients with WM after vaccination against SARS-CoV-2: a prospective study. Blood Adv 2021;5:4398–405. https://doi.org/10.1182/bloodadvances.2021005444.
[21] Benjamini O, Rokach L, Itchaki G, Braester A, Shvidel L, Goldschmidt N, et al. Safety and efficacy of the BNT162b mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Haematologica 2022;107:625–34. https://doi.org/10.3324/haematol.2021.279196.
[22] Jurgens EM, Ketas TJ, Zhao Z, Satlin MJ, Small CB, Sukhu A, et al. Serologic response to mRNACOVID-19 vaccination inlymphoma patients. Am J Hematol 2021:E410–3. https://doi.org/10.1172/JCI138554.
[23] Avivi I, Luttwak E, Saiag E, Halperin T, Haberman S, Sarig A, et al. BNT162b2 mRNA COVID-19 vaccine booster induces seroconversion in patients with B-cell non-Hodgkin lymphoma who failed to respond to two prior vaccine doses. Br J Haematol 2022;196:1329–33. https://doi.org/10.1111/bjh.18029.
[24] Haggenburg S, Hofsink Q, Lissenberg-Witte BI, Broers AEC, Van Doesum JA, Van Binnendijk RS, et al. Antibody response in immunocompromised patients with hematologic cancers who received a 3-dose mRNA-1273 vaccination schedule for COVID-19. JAMA Oncol 2022;8:1477–83. https://doi.org/10.1001/jamaoncol.2022.3227.
[25] Marasco V, Carniti C, Guidetti A, Farina L, Magni M, Miceli R, et al. T-cell immune response after mRNA SARS-CoV-2 vaccines is frequently detected also in the absence of seroconversion in patients with lymphoid malignancies. Br J Haematol 2022;196:548–58. https://doi.org/10.1111/bjh.17877.
[26] Roeker LE, Knorr DA, Thompson MC, Nivar M, Lebowitz S, Peters N, et al. COVID-19 vaccine efficacy in patients with chronic lymphocytic leukemia. Leukemia 2021;35:2703–5. https://doi.org/10.1038/s41375-021-01270-w.
[27] Haggenburg S, Lissenberg-Witte BI, van Binnendijk RS, den Hartog G, Bhoekhan MS, Haverkate NJE, et al. Quantitative analysis of mRNA-1273 COVID-19 vaccination response in immunocompromised adult hematology patients. Blood Adv 2022;6:1537–46. https://doi.org/10.1182/bloodadvances.2021006917.
[28] Bacova B, Kohutova Z, Zubata I, Gaherova L, Kucera P, Heizer T, et al. Cellular and humoral immune response to SARS-CoV-2 mRNA vaccines in patients treated with either Ibrutinib or rituximab. Clin Exp Med 2022:1–9. https://doi.org/10.1007/s10238-022-00809-0.
[29] Tvito A, Ronson A, Ghosheh R, Kharit M, Ashkenazi J, Magen S, et al. Anti-CD20 monoclonal antibodies inhibit seropositive response to Covid-19 vaccination in non-Hodgkin lymphoma patients within 6 months after treatment. Exp Hematol 2022;107:20–3. https://doi.org/10.1016/j.exphem.2021.12.396.
[30] Liebers N, Speer C, Benning L, Bruch P-M, Kraemer I, Meissner J, et al. Humoral and cellular responses after COVID-19 vaccination in anti-CD20-treated lymphoma patients. Blood 2022;139:142–7. https://doi.org/10.1182/blood.2021013429.
[31] Gurion R, Rozovski U, Itchaki G, Gafter-Gvili A, Leibovitch C, Raanani P, et al. Humoral serological response to the BNT162b2 vaccine is abrogated in lymphoma patients within the first 12 months following treatment with anti-CD2O antibodies. Haematologica 2022;107:715–4720. https://doi.org/10.3324/haematol.2021.279216.
[32] Perry C, Luttwak E, Balaban R, Shefer G, Morales MM, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with B-cell non-Hodgkin lymphoma. Blood Adv 2021;5:3053–61. https://doi.org/10.1182/bloodadvances.2021005094.
[33] Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine inpatients with chronic lymphocytic leukemia. Blood 2021;137:3165–73. https://doi.org/10.1182/BLOOD.2019000962.
[34] Chang A, Akhtar A, Linderman SL, Lai L, Orellana-Noia VM, Valanparambil R, et al. Humoral responses against SARS-CoV-2 and variants of concern after mRNA vaccines in patients with non-Hodgkin lymphoma and chronic lymphocytic leukemia. J Clin Oncol 2022;40:3020–31. https://doi.org/10.1200/JCO.22.00088.
[35] Shen Y, Freeman JA, Holland J, Solterbeck A, Naidu K, Soosapilla A, et al. COVID-19 vaccine failure in chronic lymphocytic leukaemia and monoclonal B-lymphocytosis; humoural and cellular immunity. Br J Haematol 2022;197:41–51. https://doi.org/10.1111/bjh.18014.
[36] Fattizzo B, Bortolotti M, Giannotta JA, Consonni D, Cantoni S, Barcellini W. Seroconversion to mRNA SARS-CoV-2 vaccines in patients with autoimmune cytopenias and bone marrow failures. Sci Rep 2022;12:7743. https://doi.org/10.1038/s41598-022-11857-7.
[37] Yri OE, Torfoss D, Hungnes O, Tierens A, Waalen K, Nordøy T, et al. Rituximab blocks protective serologic response to influenza a (H1N1) 2009 vaccination in lymphoma patients during or within 6 months after treatment. Blood 2011;118:6769–71. https://doi.org/10.1182/blood-2011-08-372649.
[38] Bedognetti D, Zoppoli G, Massucco C, Zanardi E, Zupo S, Bruzzone A, et al. Impaired response to influenza vaccine associated with persistent memory B cell depletion in non-Hodgkin's lymphoma patients treated with rituximab-containing regimens. J Immunol 2011;186:6044–55. https://doi.org/10.4049/jimmunol.1004095.
[39] Bedognetti D, Ansaldi F, Zanardi E, Durando P, Roberto Sertoli M, Massucco C, et al. Seasonal and pandemic (A/H1N1 2009) MF-59–adjuvanted influenza vaccines in complete remissionnon-Hodgkin lymphoma patients previously treated with rituximab containing regimens. Blood 2012;120:1954–7. https://doi.org/10.1182/blood-2012-06-438689.
[40] Hottinger AF, George A-CC, Bel M, Favet L, Combescure C, Meier S, et al. A prospective study of the factors shaping antibody responses to the AS03-Adjuvanted influenza a/H1N1 vaccine in cancer outpatients. Oncologist 2012;17:436–45. https://doi.org/10.1634/theoncologist.2011-0342.
[41] Villa D, Gubbay J, Robert Sutherland D, Laister R, McGeer A, Cooper C, et al. Evaluation of 2009 pandemic H1N1 influenza vaccination in adults with lymphoid malignancies receiving chemotherapy or following autologous stem cell transplant. Leuk Lymphoma 2013;54:1387–95. https://doi.org/10.3109/10428194.2012.742524.
[42] Takata T, Suzumiya J, Ishikawa T, Takamatsu Y, Ikematsu H, Tamura K. Attenuated antibody reaction for the primary antigen but not for the recall antigen of influenza vaccination in patients with non-Hodgkin B-cell lymphoma after the Administration of Rituximab-CHOP. J Clin Exp Hematop 2009;49:9–13. https://doi.org/10.3960/jslrt.49.9.
[43] de Lavallade H, Garland P, Sekine T, Hoschler K, Marin D, Stringaris K, et al. Repeated vaccination is required to optimize seroprotection against H1N1 in the immunocompromised host. Haematologica 2011;96:307–14. https://doi.org/10.3324/haematol.2010.032664.
[44] Berglund Å, Willén L, Grödeberg L, Skattum L, Hagberg H, Pauksens K. The response to vaccination against influenza A(H1N1) 2009, seasonal influenza and Streptococcus pneumoniae in adult outpatients with ongoing treatment for cancer

with and without rituximab. Acta Oncol (Madr) 2014;53:1212–20. https://doi.org/10.3109/0284186X.2014.914243.
[45] Mustafa SS, Jamshed S, Vadamalai K, Ramsey A. The use of 20% subcutaneous immunoglobulin replacement therapy in patients with B cell non-Hodgkin lymphoma with humoral immune dysfunction after treatment with rituximab. Clin Lymphoma Myeloma Leuk 2020;20:e590–6. https://doi.org/10.1016/j.clml.2020.04.006.
[46] Horwitz SM, Negrin RS, Blume KG, Breslin S, Stuart MJ, Stockerl-Goldstein KE, et al. Rituximab as adjuvant to high-dose therapy and autologous hematopoietic cell transplantation for aggressive non-Hodgkin lymphoma. Blood 2004;103:777–83. https://doi.org/10.1182/blood-2003-04-1257.
[47] Burger JA, Tedeschi A, Barr PM, Robak T, Owen C, Ghia P, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med 2015;373:2425–37. https://doi.org/10.1056/nejmoa1509388.
[48] Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS, et al. Targeting BTK with Ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med 2013;369:507–16. https://doi.org/10.1056/nejmoa1306220.
[49] Noy A, de Vos S, Thieblemont C, Martin P, Flowers CR, Morschhauser F, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. Blood 2017;129:2224–32. https://doi.org/10.1182/blood-2016-10.
[50] Treon SP, Tripsas CK, Meid K, Warren D, Varma G, Green R, et al. Ibrutinib in previously treated Waldenström's Macroglobulinemia. N Engl J Med 2015;372:1430–40. https://doi.org/10.1056/nejmoa1501548.
[51] Williams ALM, Baran AM, Meacham PJ, Feldman MM, Valencia HE, Newsom-Stewart C, et al. Analysis of the risk of infection in patients with chronic lymphocytic leukemia in the era of novel therapies. Leuk Lymphoma 2018;59:625–32. https://doi.org/10.1080/10428194.2017.1347931.
[52] Diamantopoulos PT, Kontandreopoulou CN, Stafylidis C, Vlachopoulou D, Giannakopoulou N, Vardaka M, et al. Immunogenicity of a third dose of the BNT162b2 COVID-19 vaccine in patients with CLL: effects on treatment selection. Ann Hematol 2022;101:2711–7. https://doi.org/10.1007/s00277-022-05003-6.
[53] Molica S, Giannarelli D, Lentini M, Zappala D, Mannella A, Loiacono D, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia: a serologic and cellular study. Chemotherapy 2022;67:91–5. https://doi.org/10.1159/000521229.
[54] Diamantopoulos PT, Stafylidis C, Vlachopoulou D, Kontandreopoulou CN, Giannakopoulou N, Vardaka M, et al. Safety and immunogenicity of the BNT162b2 mRNA Covid-19 vaccine in patients with chronic lymphocytic leukemia: a prospective study. Ther Adv Hematol 2022;13. https://doi.org/10.1177/20406207221090150. 20406207221090150.
[55] Terpos E, Gavriatopoulou M, Fotiou D, Giatra C, Asimakopoulos I, Dimou M, et al. Poor neutralizing antibody responses in 132 patients with cll, nhl and hl after vaccination against sars-cov-2: a prospective study. Cancers (Basel) 2021;13:4480. https://doi.org/10.3390/cancers13174480.
[56] Sun C, Gao J, Couzens L, Tian X, Farooqui MZ, Eicheberger MC, et al. Seasonal influenza vaccination in patients with chronic lymphocytic leukemiatreated with Ibrutinib. JAMA Oncol 2016;2:1656–7. https://doi.org/10.1001/jamaoncol.2016.2070.
[57] Douglas AP, Trubiano JA, Barr I, Leung V, Slavin MA, Tam CS. Ibrutinib may impair serological responses to influenza vaccination. Haematologica 2017;102:e397–9. https://doi.org/10.3324/haematol.2017.164285.
[58] Andrick B, Alwhaibi A, DeRemer DL, Quershi S, Khan R, Bryan LJ, et al. Lack of adequate pneumococcal vaccination response in chronic lymphocytic leukaemia patients receiving ibrutinib. Br J Haematol 2018;182:712–4. https://doi.org/10.1111/bjh.14855.
[59] Mauro FR, Giannarelli D, Galluzzo CM, Vitale C, Visentin A, Riemma C, et al. Response to the conjugate pneumococcal vaccine (PCV13) in patients with chronic lymphocytic leukemia (CLL). Leukemia 2021;35:737–46. https://doi.org/10.1038/s41375-020-0884-z.
[60] Hassan H, Ammad Ud Din M, Jamshed S, Bress J, Mustafa SS. Effect of ibrutinib on humoral dysfunction in patients with chronic lymphocytic leukemia: a single-center experience. Hematol/Oncol Stem Cell Ther 2022;15:208–12. https://doi.org/10.1016/j.hemonc.2021.07.004.
[61] Zent CS, Brady MT, Delage C, Strawderman M, Laniewski N, Contant PN, et al. Short term results of vaccination with adjuvanted recombinant varicella zoster glycoprotein E during initial BTK inhibitor therapy for CLL or lymphoplasmacytic lymphoma. Leukemia 2021;35:1788–91. https://doi.org/10.1038/s41375-020-01074-4.
[62] Pleyer C, Ali MA, Cohen JI, Tian X, Soto S, Ahn IE, et al. Effect of Bruton tyrosine kinase inhibitor on efficacy ofadjuvanted recombinant hepatitis B and zoster vaccines. Blood 2021;137:185–9. https://doi.org/10.1182/blood.2020008758.
[63] Pleyer C, Laing KJ, Ali MA, McClurkan CL, Soto S, Ahn IE, et al. BTK inhibitors impair humoral and cellular responses to recombinant zoster vaccine in CLL. Blood Adv 2022;6:1732–40. https://doi.org/10.1182/BLOODADVANCES.2021006574.
[64] Muchtar E, Koehler AB, Johnson MJ, Rabe KG, Ding W, Call TG, et al. Humoral and cellular immune responses to recombinant herpes zoster vaccine in patients with chronic lymphocytic leukemia and monoclonal B cell lymphocytosis. Am J Hematol 2022;97:90–8. https://doi.org/10.1002/ajh.26388.
[65] de Lavallade H, Khoder A, Hart M, Sarvaria A, Sekine T, Alsuliman A, et al. Tyrosinekinase inhibitors impair B-cell immune responses in CML through off-target inhibition of kinases important for cell signaling. Blood 2013;122:227–38. https://doi.org/10.1182/blood-2012-11-465039.
[66] Harrington P, Doores KJ, Radia D, O'Reilly A, Lam HPJ, Seow J, et al. Single dose of BNT162b2 mRNA vaccine against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) induces neutralising antibody and polyfunctional T-cell responses in patients with chronic myeloid leukaemia. Br J Haematol 2021;194:999–1006. https://doi.org/10.1111/bjh.17568.
[67] Rotterdam J, Thiaucourt M, Weiss C, Schwaab J, Reiter A, Kreil S, et al. Definition of factors associated with negative antibody response after COVID-19 vaccination in patients with hematological diseases. Ann Hematol 2022;101:1825–34. https://doi.org/10.1007/s00277-022-04866-z.
[68] Bettoni da Cunha-Riehm C, Hildebrand V, Nathrath M, Metzler M, Suttorp M. Vaccination with live attenuated vaccines in four children with chronic myeloid leukemia while on Imatinib treatment. Front Immunol 2020;11:628. https://doi.org/10.3389/fimmu.2020.00628.
[69] Schönberg K, Rudolph J, Vonnahme M, Yajnanarayana SP, Cornez I, Hejazi M, et al. JAK inhibition impairs NK cell function in myeloproliferative neoplasms. Cancer Res 2015;75:2187–99. https://doi.org/10.1158/0008-5472.CAN-14-3198.
[70] Guglielmelli P, Mazzoni A, Maggi L, Kiros ST, Zammarchi L, Pilerci S, et al. Impaired response to first SARS-CoV-2 dose vaccination in myeloproliferative neoplasm patients receiving ruxolitinib. Am J Hematol 2021;96:E408–10. https://doi.org/10.1002/ajh.26305.
[71] Fiorino F, Sicuranza A, Ciabattini A, Santoni A, Pastore G, Simoncelli M, et al. The slower antibody response in myelofibrosis patients after two doses of MRNA sars-COV-2 vaccine calls for a third dose. Biomedicines 2021;9:1480. https://doi.org/10.3390/biomedicines9101480.
[72] Ikeda D, Terao T, Miura D, Narita K, Fukumoto A, Kuzume A, et al. Impaired antibody response following the second dose of the BNT162b2 vaccine in patients with myeloproliferative neoplasms receiving Ruxolitinib. Front Med (Lausanne) 2022;9:826537. https://doi.org/10.3389/fmed.2022.826537.
[73] Caocci G, Mulas O, Mantovani D, Costa A, Galizia A, Barabino L, et al. Ruxolitinib does not impair humoral immune response to COVID-19 vaccination with BNT162b2 mRNA COVID-19 vaccine in patients with myelofibrosis. Ann Hematol 2022;101:929–31. https://doi.org/10.1007/s00277-021-04613-w.
[74] Pimpinelli F, Marchesi F, Piaggio G, Giannarelli D, Papa E, Falcucci P, et al. Fifth-week immunogenicity and safety of anti-SARS-CoV-2 BNT162b2 vaccine in patients with multiple myeloma and myeloproliferative malignancies on active treatment: preliminary data from a single institution. J Hematol Oncol 2021;14:81. https://doi.org/10.1186/s13045-021-01090-6.
[75] Harrington P, Doores KJ, Saunders J, de Lord M, Saha C, Lechmere T, et al. Impaired humoral and T cell response to vaccination against SARS-CoV-2 in chronic myeloproliferative neoplasm patients treated with ruxolitinib. Blood Cancer J 2022;12:73. https://doi.org/10.1038/s41408-022-00651-3.
[76] DiNardo KW, LeBlanc TW, Chen H. Novel agents and regimens in acute myeloid leukemia: latest updates from 2022 ASH annual meeting. J Hematol Oncol 2023;16:17. https://doi.org/10.1186/s13045-023-01411-x.
[77] Cassanello G, Pasquale R, Barcellini W, Fattizzo B. Novel therapies for unmet clinical needs in myelodysplastic syndromes. Cancers (Basel) 2022;14:4941. https://doi.org/10.3390/cancers14194941.
[78] On S, Rath CG, Lan M, Wu B, Lau KM, Cheung E, et al. Characterisation of infections in patients with acute myeloid leukaemia receiving venetoclax and a hypomethylating agent. Br J Haematol 2022;197:63–70. https://doi.org/10.1111/bjh.18051.
[79] Candoni A, Callegari C, Zannier ME, Fanin R. Antibody response to mRNA vaccination for COVID-19 in patients with AML receiving hypomethylating agents alone or with venetoclax. Blood Adv 2022;6:3068–71. https://doi.org/10.1182/bloodadvances.2021006949.
[80] Chan WY, Zhu C, Sanchez E, Gupta R, Fielding AK, Khwaja A, et al. Antibody responses to SARS-CoV-2 vaccination in patients with acute myeloid leukaemia and high risk MDS on active anti-cancer therapies. Br J Haematol 2022;198:478–81. https://doi.org/10.1111/bjh.18248.
[81] Gagelmann N, Passamonti F, Wolschke C, Massoud R, Niederwieser C, Adjalle R, et al. Antibody response after vaccination against SARS-CoV-2 in adults with hematological malignancies: a systematic review and meta-analysis. Haematologica 2022;107:1840–9. https://doi.org/10.3324/haematol.2021.280163.
[82] Karlsson J, Andréasson B, Kondori N, Erman E, Riesbeck K, Hogevik H, et al. Comparative study of immune status to infectious agents in elderly patients with multiple myeloma, Waldenstrom's macroglobulinemia, and monoclonal gammopathy of undetermined significance. Clin Vaccine Immunol 2011;18:969–77. https://doi.org/10.1128/CVI.00021-11.
[83] Blimark C, Holmberg E, Mellqvist UH, Landgren O, Bjorkholm M, Hultcrantz M, et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. Haematologica 2015;100:107–13. https://doi.org/10.3324/haematol.2014.107714.
[84] Stampfer SD, Goldwater MS, Jew S, Bujarski S, Regidor B, Daniely D, et al. Response to mRNA vaccination for COVID-19 among patients with multiple myeloma. Leukemia 2021;35:3534–41. https://doi.org/10.1038/s41375-021-01354-7.
[85] Bitoun S, Henry J, Vauloup-Fellous C, Dib N, Belkhir R, Mouna L, et al. Response to COVID-19 mRNA vaccination in multiple myeloma is conserved but impaired compared to controls. J Hematol Oncol 2021;14:166. https://doi.org/10.1186/s13045-021-01183-2.
[86] Terpos E, Trougakos IP, Gavriatopoulou M, Papassotiriou I, Sklirou AD, Ntanasis-Stathopoulos I, et al. Low neutralizing antibody responses against SARS-CoV-2 in older patients with myeloma after the first BNT162b2 vaccine dose. Blood 2021;137:3674–6. https://doi.org/10.1001/jama.
[87] Pettine L, Bortolotti M, Fattizzo B, da Vià MC, Consonni D, Pompa A, et al. Response to SARS-CoV-2 vaccination and antibodies persistence in multiple

myeloma patients. Hematol Oncol 2023;41:210–2. https://doi.org/10.1002/hon.3051.
[88] Terpos E, Gavriatopoulou M, Ntanasis-Stathopoulos I, Briasoulis A, Gumeni S, Malandrakis P, et al. The neutralizing antibody response post COVID-19 vaccination in patients with myeloma is highly dependent on the type of anti-myeloma treatment. Blood Cancer J 2021;11:138. https://doi.org/10.1038/s41408-021-00530-3.
[89] Ghandili S, Schönlein M, Lütgehetmann M, Schulze Zur Wiesch J, Becher H, Bokemeyer C, et al. Post-vaccination anti-sars-cov-2-antibody response in patients with multiple myeloma correlates with low cd19+ b-lymphocyte count and anti-cd38 treatment. Cancers (Basel) 2021;13:3800. https://doi.org/10.3390/cancers13153800.
[90] Bird S, Ponpoulou A, Shea RL, Tsui M, Caso R, Sud A, et al. Response to first vaccination against SARS-CoV-2 in patients with multiple myeloma. Lancet Haematol 2021;8:e389–92. https://doi.org/10.1182/blood.2020007512.
[91] Greenberg RS, Ruddy JA, Boyarsky BJ, Werbel WA, Garonzik-Wang JM, Segev DL, et al. Safety and antibody response to two-dose SARS-CoV-2 messenger RNA vaccination in patients with multiple myeloma. BMC Cancer 2021;21:1354. https://doi.org/10.1186/s12885-021-09097-5.
[92] Noonan K, Rudraraju L, Ferguson A, Emerling A, Pasetti MF, Huff CA, et al. Lenalidomide-induced immunomodulation in multiple myeloma: impact on vaccines and antitumor responses. Clin Cancer Res 2012;18:1426–34. https://doi.org/10.1158/1078-0432.CCR-11-1221.
[93] Hahn M, Schnitzler P, Schweiger B, Kunz C, Ho AD, Goldschmidt H, et al. Efficacy of single versus boost vaccination against influenza virus in patients with multiple myeloma. Haematologica 2015;100:e285–8. https://doi.org/10.3324/haematol.2014.116772.
[94] Branagan AR, Duffy E, Albrecht RA, Cooper DL, Seropian S, Parker TL, et al. Clinical and serologic responses after a two-dose series of high-dose influenza vaccine in plasma cell disorders: a prospective, single-arm trial. Clin Lymphoma Myeloma Leuk 2017;17:296–304.e2. https://doi.org/10.1016/j.clml.2017.02.025.
[95] Frerichs KA, Bosman PWC, van Velzen JF, Fraaji PLA, Koopmans MPG, Rimmelzwaan GF, et al. Effect of daratumumab on normal plasma cells, polyclonal immunoglobulin levels, and vaccination responses in extensively pre-treated multiple myeloma patients. Haematologica 2020;105:e304–6. https://doi.org/10.3324/haematol.2019.231860.
[96] Rosati M, Terpos E, Bear J, Burns R, Devasundaram S, Ntanasis-Stathopoulos I, et al. Low spike antibody levels and impaired BA.4/5 neutralization in patients with multiple myeloma or Waldenstrom's Macroglobulinemia after BNT162b2 booster vaccination. Cancers (Basel) 2022;14:5816. https://doi.org/10.3390/cancers14235816.
[97] Palazzo M, Shah GL, Copelan O, Seier K, Devlin SM, Maloy M, et al. Revaccination after autologous hematopoietic stem cell transplantation is safe and effective in patients with multiple myeloma receiving Lenalidomide maintenance. Biol Blood Marrow Transpl 2018;24:871–6. https://doi.org/10.1016/j.bbmt.2017.12.795.
[98] Dagnew AF, Ilhan O, Lee WS, Woszczyk D, Kwak JY, Bowcock S, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis. Lancet Infect Dis 2019;19:988–1000. https://doi.org/10.1016/S1473-3099(19)30163-X.
[99] Ludwig H, Boccadoro M, Moreau P, San-Miguel J, Cavo M, Pawlyn C, et al. Recommendations for vaccination in multiple myeloma: a consensus of the European myeloma network. Leukemia 2021;35:31–44. https://doi.org/10.1038/s41375-020-01016-0.
[100] Socié G, Caby-Tosi MP, Marantz JL, Cole A, Bedrosian CL, Gasteyger C, et al. Eculizumab in paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome: 10-year pharmacovigilance analysis. Br J Haematol 2019;185:297–310. https://doi.org/10.1111/bjh.15790.
[101] MacNeil JR, Rubin LG, Patton M, Ortega-Sanchez IR, Martin SW. Recommendations for use of meningococcal conjugate vaccines in HIV-infected persons - advisory committee on immunization practices, 2016. MMWR Morb Mortal Wkly Rep 2016;65:1189–94. https://doi.org/10.15585/mmwr.mm6543a3.
[102] Pike A, McKinley C, Forrest B, Zhakata T, Harland M, Clarke D, et al. COVID-19 vaccination antibody responses in patients with aplastic anaemia and paroxysmal nocturnal haemoglobinuria. Lancet Haematol 2022;9:e553–6. https://doi.org/10.1016/S2352-3026(22)00175-2.
[103] Gerber GF, Yuan X, Yu J, Cher BAY, Braunstain EM, Chaturvedi S, et al. COVID-19 vaccines induce severe hemolysis in paroxysmal nocturnal hemoglobinuria. Blood 2021;137:3670–3. https://doi.org/10.1182/BLOOD.2019000962.
[104] Giannotta JA, Fattizzo B, Bortolotti M, Girmenia C, Ielo C, Metafuni E, et al. SARS-CoV-2 vaccination in patients with paroxysmal nocturnal hemoglobinuria: an Italian multicenter survey. Am J Hematol 2022;97:E229–32. https://doi.org/10.1002/ajh.26545.
[105] Cavallaro F, Pasquini MC, Giannotta JA, Cattina F, Barcellini W, Fattizzo B. Breakthrough haemolysis in paroxysmal nocturnal haemoglobinuria after COVID-19 infection and COVID vaccination: what is worse? Blood Transfus 2022;20:437–40. https://doi.org/10.2450/2022.0039-22.
[106] Fattizzo B, Pasquale R, Bellani V, Barcellini W, Kulasekararaj AG. Complement mediated hemolytic anemias in the COVID-19 era: case series and review of the literature. Front Immunol 2021;12:791429. https://doi.org/10.3389/fimmu.2021.791429.
[107] Alashkar F, Vance C, Herich-Terhürne D, Preising N, Dührsen U, Röth A. Serologic response to meningococcal vaccination in patients with paroxysmal nocturnal hemoglobinuria (PNH) chronically treated with the terminal complement inhibitor eculizumab. Ann Hematol 2017;96:589–96. https://doi.org/10.1007/s00277-017-2924-y.
[108] Mcnamara LA, Topaz N, Wang X, Hariri S, Fox L, Macneil JR. High risk for invasive meningococcal disease among patients receiving Eculizumab (Soliris) despite receipt of meningococcal vaccine. MMWR Morb Mortal Wkly Rep 2017;66:734–7. https://doi.org/10.15585/mmwr.mm6627e1.
[109] Struijk GH, Bouts AHM, Rijkers GT, Kuin EAC, ten Berge IJM, Bemelman FJ. Meningococcal sepsis complicating eculizumab treatment despite prior vaccination. Am J Transplant 2013;13:819–20. https://doi.org/10.1111/ajt.12032.
[110] Parikh SR, Lucidarme J, Bingham C, Warwicker P, Goodship T, Borrow R, et al. Meningococcal B vaccine failure with a penicillin-resistant strain in a young adult on long-term Eculizumab. Pediatrics 2017;140:e20162452. https://doi.org/10.1542/peds.2016-2452.
[111] Cullinan N, Gorman KM, Riordan M, Waldron M, Goodship THJ, Awan A. Case report: benefits and challenges of long-term eculizumab in atypical hemolytic uremic syndrome. Pediatrics 2015;135:e1506–9. https://doi.org/10.1542/peds.2014-3503.
[112] Yu ZY, Tsai MJ, Lin YJ, da Liu W, Chou SC, Hung CC. Disseminated gonococcal infection in a patient with paroxysmal nocturnal hemoglobinuria having received ravulizumab and meningococcal vaccine. J Microbiol Immunol Infect 2020;53:660–2. https://doi.org/10.1016/j.jmii.2020.06.013.
[113] Konar M, Granoff DM. Eculizumab treatment and impaired opsonophagocytic killing of meningococci by whole blood from immunized adults. Blood 2017;130:891–9. https://doi.org/10.1182/blood-2017-05-781450.
[114] Langereis JD, van den Broek B, Franssen S, Joosten I, Blijlevens NMA, de Jonge MI, et al. Eculizumab impairs Neisseria meningitidis serogroup B killing in whole blood despite 4CMenB vaccination of PNH patients. Blood Adv 2020;4:3615–20. https://doi.org/10.1182/bloodadvances.2020002497.
[115] Gäckler A, Kaulfuß M, Rohn H, Vogel U, Claus H, Feldkamp T, et al. Failure of first meningococcal vaccination in patients with atypical haemolytic uraemic syndrome treated with eculizumab. Nephrol Dial Transplant 2020;35:298–303. https://doi.org/10.1093/ndt/gfy225.
[116] Walter J, Kricheldorf K, Isfort S, Brümmendorf TH, Panse J, Beier F. Antibody titers after SARS-CoV-2 mRNA vaccination in patients with aplastic anemia—A single-center study. Eur J Haematol 2022;108:528–31. https://doi.org/10.1111/ejh.13756.
[117] Cecchi N, Giannotta JA, Barcellini W, Fattizzo B. A case of severe aplastic anaemia after SARS-CoV-2 vaccination. Br J Haematol 2022;196:1334–6. https://doi.org/10.1111/bjh.17947.
[118] Röth A, Bertram S, Schroeder T, Haverkamp T, Voigt S, Holtkamp C, et al. Acquired aplastic anemia following SARS-CoV-2 vaccination. Eur J Haematol 2022;109:186–94. https://doi.org/10.1111/ejh.13788.
[119] Woo S, Kim B, Lee SC, Kim MS, Yoon YA, Choi YJ. Very severe immune aplastic anemia after mRNA vaccination against COVID-19 responds well to immunosuppressive therapy: clinical characteristics and comparison to previous reports. Hematology 2022;27:1191–5. https://doi.org/10.1080/16078454.2022.2140986.
[120] Anastasi E, Marziali M, Preziosi A, Berardelli E, Losardo AA, Ribersani M, et al. Humoral immune response to Comirnaty (BNT162b2) SARS-Cov2 mRNA vaccine in thalassemia major patients. Microbes Infect 2022;24:104976. https://doi.org/10.1016/j.micinf.2022.104976.
[121] Gonzalez MA, Bhatti AM, Fitzpatrick K, Boonyaratanakornkit J, Huang M-L, Campbell VL, et al. Humoral and cellular responses to SARS-CoV-2 vaccines before and after chimeric antigen receptor-modified T cell therapy. Blood Adv 2022. https://doi.org/10.1182/bloodadvances.2022008338.
[122] Uyemura BS, Abid MA, Suelzer E, Abid MB. Efficacy of SARS-CoV-2 primary and booster vaccine doses in CAR-T recipients – targeting the target antigen. Bone Marrow Transplant 2022;57:1727–31. https://doi.org/10.1038/s41409-022-01795-3.
[123] Atanackovic D, Luetkens T, Omili D, Iraguha T, Lutfi F, Hardy NM, et al. Vaccine-induced T-cell responses against SARS-CoV-2 and its omicron variant in patients with B cell–depleted lymphoma after CART therapy. Blood 2022;140:152–6. https://doi.org/10.1182/blood.2022016175.
[124] Walti CS, Loes AN, Shuey K, Krantz EM, Boonyaratanakornkit J, Keane-Candib J, et al. Humoral immunogenicity of the seasonal influenza vaccine before and after CAR-T-cell therapy: a prospective observational study. J Immunother Cancer 2021;9:e003428. https://doi.org/10.1136/jitc-2021-003428.
[125] Lee D, Jordan AI, Menges MA, Lazaryan A, Nishihori T, Gaballa SR, et al. Pneumococcal conjugate vaccine does not induce humoral response when administrated within the six months after CD19 CAR T-cell therapy. Transplant Cell Ther 2022;S2666-6367(22). https://doi.org/10.1016/j.jtct.2022.08.011.01549-4.
[126] Abid MB, Rubin M, Ledeboer N, Szabo A, Longo W, Mohan M, et al. Efficacy of a third SARS-CoV-2 mRNA vaccine dose among hematopoietic cell transplantation, CAR T cell, and BiTE recipients. Cancer Cell 2022;40:340–2. https://doi.org/10.1016/j.ccell.2022.02.010.
[127] Ram R, Hagin D, Kikozashvilli N, Freund T, Amit O, Bar-On Y, et al. Safety and immunogenicity of the BNT162b2 mRNA COVID-19 vaccine in patients after allogeneic HCT or CD19-based CART therapy—A single-center prospective cohort study. Transplant Cell Ther 2021;27:788–94. https://doi.org/10.1016/j.jtct.2021.06.024.
[128] Bergman P, Blennow O, Hansson L, Mielke S, Nowak P, Chen P, et al. Safety and efficacy of the mRNA BNT162b2 vaccine against SARS-CoV-2 in five groups of immunocompromised patients and healthy controls in a prospective open-label

clinical trial. EBioMedicine 2021;74:103705. https://doi.org/10.1016/j.ebiom.2021.103705.
[129] Fox TA, Kirkwood AA, Enfield L, O'Reilly M, Arulogun S, D'Sa S, et al. Low seropositivity and suboptimal neutralisation rates in patients fully vaccinated against COVID-19 with B-cell malignancies. Br J Haematol 2021;195:706–9. https://doi.org/10.1111/bjh.17836.
[130] Tamari R, Politikos I, Knorr DA, Vardhana SA, Young JC, Marcello LT, et al. Predictors of humoral response to SARS-CoV-2 vaccination after hematopoietic cell transplantation and CAR T-cell therapy. Blood Cancer Discov 2021;2:577–85. https://doi.org/10.1158/2643-3230.bcd-21-0142.
[131] Van Oekelen O, Gleason CR, Agte S, Srivastava K, Beach KF, Aleman A, et al. Highly variable SARS-CoV-2 spike antibody responses to two doses of COVID-19 RNA vaccination in patients with multiple myeloma. Cancer Cell 2021;39:1028–30. https://doi.org/10.1016/j.ccell.2021.06.014.
[132] Reimann H, Kremer AN, Blumenberg V, Schmidt KG, Aigner M, Jacobs B, et al. Cellular and humoral immune responses to SARS-CoV-2 vaccination in patients after CD19.CAR-T cell therapy. Blood Adv 2022. https://doi.org/10.1182/bloodadvances.2022007806.
[133] Gössi S, Bacher U, Haslebacher C, Nagler M, Suter F, Staehelin C, et al. Humoral responses to repetitive doses of COVID-19 mRNA vaccines in patients with CAR-T-cell therapy. Cancers (Basel) 2022;14:3527. https://doi.org/10.3390/cancers14143527.
[134] Wu X, Wang L, Shen L, He L, Tang K. Immune response to vaccination against SARS-CoV-2 in hematopoietic stem cell transplantation and CAR T-cell therapy recipients. J Hematol Oncol 2022;15:81. https://doi.org/10.1186/s13045-022-01300-9.
[135] Jarisch A, Wiercinska E, Huenecke S, Bremm M, Cappel C, Hauler J, et al. Immune responses to SARS-CoV-2 vaccination in Young patients with anti-CD19 chimeric antigen receptor T cell-induced B cell aplasia. Transplant Cell Ther 2022;28. https://doi.org/10.1016/j.jtct.2022.04.017. 366.e1-366.e7.
[136] Ram R, Freund T, Halperin T, Ben-Ami R, Amit O, Bar-On Y, et al. Immunogenicity of a third dose of the BNT162b2 mRNA Covid-19 vaccine in patients with impaired B cell reconstitution after cellular therapy—A single center prospective cohort study. Transplant Cell Ther 2022;28:278.e1–4. https://doi.org/10.1016/j.jtct.2022.02.012.
[137] Dahiya S, Luetkens T, Lutfi F, Avila S, Iraguha T, Margiotta P, et al. Impaired immune response to COVID-19 vaccination in patients with B-cell malignancies after CD19 CAR T-cell therapy. Blood Adv 2022;6:686–9. https://doi.org/10.1182/bloodadvances.2021006112.
[138] Greenberger LM, Saltzman LA, Gruenbaum LM, Xu J, Reddy ST, Senefeld JW, et al. Anti-spike T-cell and antibody responses to SARS-CoV-2 mRNA vaccines in patients with hematologic malignancies. Blood Cancer Discov 2022;3:481–9. https://doi.org/10.1158/2643-3230.bcd-22-0077.
[139] Gastinne T, Le Bourgeois A, Coste-Burel M, Guillaume T, Peterlin P, Garnier A, et al. Safety and antibody response after one and/or two doses of BNT162b2 anti-SARS-CoV-2 mRNA vaccine in patients treated by CAR T cells therapy. Br J Haematol 2022;196:360–2. https://doi.org/10.1111/bjh.17818.
[140] Parvathaneni K, Torres-Rodriguez K, Meng W, Hwang W-T, Frey N, Naji A, et al. SARS-CoV-2 spike-specific T-cell responses in patients with B-cell depletion who received chimeric antigen receptor T-cell treatments. JAMA Oncol 2022;8:164. https://doi.org/10.1001/jamaoncol.2021.6030.
[141] Aleissa MM, Little JS, Davey S, Saucier A, Zhou G, Gonzalez-Bocco IH, et al. SARS-CoV-2 vaccine immunogenicity among chimeric antigen receptor T-cell therapy recipients. Transplant Cell Ther 2023;S2666-6367(23):01163–6. https://doi.org/10.1016/j.jtct.2023.03.005.
[142] Piñana JL, Martino R, Vazquez L, López-Corral L, Pérez A, Chorão P, et al. SARS-CoV-2-reactive antibody waning, booster effect and breakthrough SARS-CoV-2 infection in hematopoietic stem cell transplant and cell therapy recipients at one year after vaccination. Bone Marrow Transplant 2023. https://doi.org/10.1038/s41409-023-01946-0.
[143] Wirth SRM, Podar K, Pecherstorfer M, Wohlfarth P, Jaeger U, Singer J. Evaluation of antibody responses in patients with B-cell malignancies after two and three doses of anti-SARS-CoV-2 S vaccination—A retrospective cohort study. Cancers (Basel) 2023;15:524. https://doi.org/10.3390/cancers15020524.