Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Research

AGIHO guideline on evidence-based management of COVID-19 in cancer patients: 2022 update on vaccination, pharmacological prophylaxis and therapy in light of the omicron variants

Nicola Giesen [a,*,1], Elena Busch [b,1], Enrico Schalk [c], Gernot Beutel [d,e], Maria M. Rüthrich [f], Marcus Hentrich [g], Bernd Hertenstein [h], Hans H. Hirsch [i,j,k], Meinolf Karthaus [l], Yascha Khodamoradi [m], Philipp Koehler [n,o], William Krüger [p], Michael Koldehoff [q,r], Robert Krause [s], Sibylle C. Mellinghoff [n,o,t], Olaf Penack [u], Michael Sandherr [v], Ruth Seggewiss-Bernhardt [w,x], Karsten Spiekermann [y], Rosanne Sprute [n,o,t], Jannik Stemler [n,o,t], Florian Weissinger [z], Bernhard Wörmann [aa], Hans-Heinrich Wolf [ab], Oliver A. Cornely [n,o,t,ac], Christina T. Rieger [ad], Marie von Lilienfeld-Toal [ae,af]

[a] *Department of Hematology, Oncology and Palliative Care, Robert Bosch Hospital, Stuttgart, Germany*
[b] *Department of Medical Oncology, National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg, Germany*
[c] *Department of Hematology and Oncology, Medical Centre, Otto-von-Guericke University Magdeburg, Magdeburg, Germany*
[d] *Department for Haematology, Haemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany*
[e] *Working Party Intensive Care in Haematologic and Oncologic Patients (iCHOP) of the German Society of Haematology and Medical Oncology (DGHO), Germany*
[f] *Department of Interdisciplinary Intensive Care Medicine, Vivantes Humboldt-Klinikum, Berlin, Germany*
[g] *Department of Hematology and Oncology, Red Cross Hospital Munich, Munich, Germany*
[h] *Klinikum Bremen-Mitte, Bremen, Germany*
[i] *Transplantation & Clinical Virology, Department Biomedicine (Haus Petersplatz), University of Basel, Basel, Switzerland*
[j] *Clinical Virology, Laboratory Medicine, University Hospital Basel, Basel, Switzerland*
[k] *Infectious Diseases & Hospital Epidemiology, University Hospital Basel, Basel, Switzerland*
[l] *Department of Hematology, Oncology and Palliative Care, Klinikum Neuperlach/Klinikum Harlaching, Munich, Germany*
[m] *Department of Internal Medicine, Infectious Diseases, Goethe University Frankfurt, Frankfurt Am Main, Germany*

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* *Corresponding author*: Department of Hematology, Oncology and Palliative Care, Robert Bosch Hospital, Auerbachstr. 110, 70376 Stuttgart, Germany. Tel.: +49-711-8101-5506.
E-mail address: nicola.giesen@rbk.de (N. Giesen).
[1] equal contribution.

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[n] University of Cologne, Faculty of Medicine and University Hospital Cologne, Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany
[o] University of Cologne, Faculty of Medicine and University Hospital Cologne, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD) and Excellence Center for Medical Mycology (ECMM), Cologne, Germany
[p] Department of Hematology and Oncology, Stem Cell Transplantation, Palliative Care, University Hospital Greifswald, Greifswald, Germany
[q] Department of Bone Marrow Transplantation, West German Cancer Center, University Hospital Essen, University Duisburg-Essen, Essen, Germany
[r] Department of Hygiene and Environmental Medicine, University Hospital Essen, University Duisburg-Essen, Essen, Germany
[s] Division of Infectious Diseases, Department of Internal Medicine, Medical University of Graz, Graz, Austria
[t] German Center for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, Germany
[u] Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Hematology, Oncology and Tumorimmunology, Berlin, Germany
[v] MVZ Penzberg, Department of Hematology and Oncology, Weilheim, Germany
[w] Medizinische Klinik V, Sozialstiftung Bamberg, Bamberg, Germany
[x] Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany
[y] Department of Medicine III, University Hospital, LMU Munich, Munich, Germany
[z] Department of Internal Medicine, Hematology, Oncology, Stem Cell Transplantation and Palliative Care, Evangelisches Klinikum Bethel, Bielefeld, Germany
[aa] Division of Haematology, Oncology and Tumor Immunology, Department of Medicine, Charité-Universitätsmedizin Berlin, Berlin, Germany
[ab] Department of Hematology, Oncology and Hemostaseology, Südharzklinikum Nordhausen, Nordhausen, Germany
[ac] University of Cologne, Faculty of Medicine and University Hospital Cologne, Clinical Trials Centre Cologne (ZKS Köln), Cologne, Germany
[ad] Hemato-Oncology Germering & Interdisciplinary Tumorcenter, Ludwig-Maximilians-University Munich, Munich, Germany
[ae] Department of Haematology and Medical Oncology, Clinic for Internal Medicine II, University Hospital Jena, Jena, Germany
[af] Leibniz Institute for Natural Product Research and Infection Biology, Hans Knöll Institute, Jena, Germany

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Abstract The novel coronavirus SARS-CoV-2 and the associated infectious disease COVID-19 pose a significant challenge to healthcare systems worldwide. Patients with cancer have been identified as a high-risk population for severe infections, rendering prophylaxis and treatment strategies for these patients particularly important. Rapidly evolving clinical research, resulting in the recent advent of various vaccines and therapeutic agents against COVID-19, offers new options to improve care and protection of cancer patients. However, ongoing epidemiological changes and rise of new virus variants require repeated revisions and adaptations of prophylaxis and treatment strategies to meet these new challenges. Therefore, this guideline provides an update on evidence-based recommendations with regard to vaccination, pharmacological prophylaxis and treatment of COVID-19 in cancer patients in light of the currently dominant omicron variants. It was developed by an expert panel of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO) based on a critical review of the most recent available data.

1. Introduction

Since their first description in late 2019, the novel severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) and the associated infectious coronavirus disease (COVID-19) have swept throughout the world, posing a serious strain on health care systems but also triggering an unprecedented scientific outreach to meet the challenge [1,2]. Patients with cancer were early on identified as a particular at-risk population, and mortality rates of cancer patients with COVID-19 of around 30% have been reported [3–5]. With a better understanding of the disease and the advent of vaccines and novel therapeutic options,

the outcome of COVID-19 has also improved in cancer patients [6,7].

Since the beginning of 2022, the SARS-CoV-2 variant of concern (VOC) omicron is dominant in many regions, including Europe and Northern America [8]. While transmissibility seems to be increased, it has been associated with a lower hospitalisation and mortality rate, in particular, compared with the preceding delta variant [9–11]. COVID-19, however, still remains a potentially fatal disease, in particular, in immunocompromised cancer patients [12]. Furthermore, protracted courses of COVID-19 are often observed in these patients, leading to treatment interruptions and thus potentially endangering the success of oncologic therapies [13]. Adequate prophylaxis and treatment strategies of COVID-19 are therefore of the utmost importance in this patient population.

Major advances in the development of COVID-19 vaccines [14–18], anti-SARS-CoV-2 monoclonal antibodies [19–23] and specific antiviral agents [24–26] have shifted the focus towards prevention of severe COVID-19 both by active or passive immunisation and by early treatment of non-hospitalised patients. As immunocompromised cancer patients are at particular risk for severe COVID-19 and often do not mount an adequate immune response to SARS-CoV-2 infection or COVID-19 vaccine [27–31], specific strategies with regard to vaccination and treatment have to be applied to protect this high-risk patient population.

Given the rapid advancements of new prophylactic and therapeutic options in the field of SARS-CoV-2/COVID-19 and the continuous change in dominant variants of concern, we feel that a new update of our previously published guidelines [32,33] is warranted. This guideline update focuses in particular on vaccination and treatment strategies of COVID-19 in adult patients with solid tumours or haematologic malignancies in light of the new omicron variant and its dominant sublineages. It offers evidence-based recommendations to help treating physicians make informed decisions on their patients' care.

2. Methods

This guideline was developed in a formalised process by an expert panel from the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). This panel consisted of 28 specialists certified in medical oncology, haematology, infectious diseases, critical care, emergency medicine and virology.

First, a systematic search of relevant literature on pre-defined topics was performed on MEDLINE for publications using one of the following search terms: 'SARS-CoV-2', 'COVID-19', 'vaccine/vaccination', 'prophylaxis/prevention', or 'therapy/treatment'. Due to the fast developments in COVID-19 research, publications available only on the preprint server www.medRxiv.org were also included; however, the lack of formal peer review was considered with regard to the grading of the quality of evidence. Publications were evaluated that appeared online until 15 October 2022.

After the collection of relevant literature, a thorough review was performed, and the data were extracted and rated. Based on the results of the data analysis, preliminary recommendations were discussed and revised in a formalised step-by-step process by the expert panel. The strength of recommendation and quality of evidence were graded according to the scale proposed by the European Society of Clinical Microbiology and Infectious Diseases (Table 1) [34]. The final recommendations as presented in this guideline were discussed and agreed upon by the AGIHO general assembly.

3. Vaccination

Although patients with cancer have not been part of initial clinical trials, the clinical efficacy of vaccination against COVID-19 has now been proven for this population as well [35]. Although the rate of seroconversion as well as absolute antibody levels seem to be lower in cancer patients compared with the healthy individuals [36,37], overall, a clinical efficacy with an 80–90% prevention rate of symptomatic COVID-19 can be expected in patients with cancer [38]. However, cancer patients remain at an increased risk of severe disease despite vaccination compared with the general population [39,40] and thus, several aspects need to be taken into account:

Table 1
Grading system for strength of recommendation (SoR) and quality of evidence (QoE) as proposed by European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [34]].

Strength of recommendation	
A	AGIHO strongly supports a recommendation for use
B	AGIHO moderately supports a recommendation for use
C	AGIHO marginally support a recommendation for use
D	AGIHO supports a recommendation against use
Quality of evidence	
I	Evidence from at least one properly designed randomised controlled trial
II*	Evidence from at least one well-designed clinical trial, without randomisation; from cohort–control or case–control analytic studies (preferably from more than one centre); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinion of respected authorities, based on clinical experience, descriptive case studies or report of expert committees
*Added index for level II	
r	Meta-analysis or systematic review of randomised controlled trials
t	Transferred evidence, that is, results from different patients' cohorts or similar immune status situation
h	Comparator group is a historical control
u	Uncontrolled trial
a	Abstract published at an international meeting or manuscript available on preprint server only

1) Patients with cancer are often of advanced age and harbour comorbidities, which may lead to reduced vaccine efficacy [38].
2) Patients with cancer in general seem to exhibit a more rapidly waning immunity than the general population, which requires more frequent and earlier booster doses than the general population [35,41,42].
3) Patients with cancer are often undergoing therapy with immunosuppressive drugs, which reduce the immune response to vaccines [43]. Amongst these, therapy with B-cell depleting agents, such as CD20-antibodies, Bruton's tyrosine kinase (BTK) inhibitors or B-cell maturation antigen (BCMA)-directed therapy, is associated with the lowest rate of seroconversion: 0% in some studies, around 30% in most studies [38,43].

We therefore recommend vaccines effective against COVID-19 unrestrictedly for patients with cancer as per recommendation by the respective local authorities and subject to availability (**AIIt**; see Table 2). This also applies to bivalent vaccines if available, as they may provide increased protection against current VOC [44]. Of note, in clinical studies, the messenger RNA (mRNA) vaccines and particularly the mRNA-1273 vaccine appears to result in the best clinical protection. As a guidance, we recommend that if given the choice, mRNA vaccines with the highest possible dose should be chosen (**BII**). We recommend prioritisation of patients with cancer for booster vaccination (**AIIt**). This is especially important, given the rapid decline of humoral vaccine response observed in cancer patients compared with healthy individuals [42]. Booster vaccination has been shown to be effective in increasing antibody levels and lowering the risk of severe disease in cancer patients and may even lead to seroconversion in initial non-responders [39,45]. A significant increase in antibody levels after booster vaccination was observed in cancer patients undergoing a variety of antineoplastic treatments, including chemotherapy, targeted therapy, immunotherapy or prior stem cell transplantation (SCT) [41]. With regard to the management of cancer therapy during vaccination, we do not recommend pausing ongoing cancer therapy (**DIII**), but if it is possible to apply the vaccine before the beginning of the cancer therapy, this should be attempted (**AIIt**). Also, we recommend simultaneous vaccination against influenza if the vaccination against COVID-19 coincides with the scheduled seasonal influenza vaccination in autumn (**AIIt**).

Regarding toxicity, there is no evidence that patients with cancer have a higher rate of adverse reactions than the general population [37,38]. This is also true for patients undergoing immune checkpoint inhibition [46]. Also, there is no evidence whatsoever that vaccination against COVID-19 increases the risk of de novo or relapsed cancer. However, there are specific clinical situations, which may be associated with symptoms, that may appear worrisome. One situation may be diagnostic confusion in the event of enlarged reactive lymph nodes after vaccination, which may be confused with progressive malignant disease [47]. Another situation that should be kept in mind concern patients after radiation since a radiation recall phenomenon has been described after COVID-19 vaccination [48–50]. The third situation has been observed in patients after allogeneic SCT, which have been described to exhibit a 10% rate of flare of graft-versus-host disease as well as temporary cytopenias [51–53]. However, none of the abovementioned situations justifies refraining from vaccination.

The level of protection in this extremely vulnerable patient group is of high interest for treating physicians as for the patients [54]. It is tempting to measure a serological response with the expectation of a clinically meaningful result. In the general population, there is good evidence that the level of (neutralising) antibody response correlates with clinical efficacy [55] although a

Table 2
Recommendations on vaccination against COVID-19 in patients with cancer.

Population	Intention	Intervention	SoR	QoE	Reference
Cancer patients	Reduce rate of symptomatic COVID	Full vaccination against COVID	A	IIt	[139,140]
Cancer patients	Reduce rate of hospitalisation	Full vaccination against COVID	A	IIt	[139]
Cancer patients	Reduce mortality	Full vaccination against COVID	A	IIt	[139,140]
Cancer patients	Increase immunogenicity	Booster as recommended by national authorities	A	IIt	[39,41,45,141–143]
Cancer patients before start of therapy	Increase immunogenicity	Vaccinate before start of chemotherapy*	A	IIt	
Cancer patients due to receive other vaccination		Co-administration of needed vaccinations such as influenza	A	III	
Cancer patients	Maintain immunogenicity	Pause cancer therapy	D	IIu	[144,145]
Cancer patients	Induce best possible vaccination response	Choose mRNA vaccines over all other vaccines	B	IIu	[145,146]
Cancer patients	Induce best possible vaccination response	Choose highest approved vaccine dose (no increased toxicity in patients with cancer)	B	IIu	[139,145,147]

COVID, coronavirus; mRNA, messenger RNA; QoE, quality of evidence; SoR, strength of recommendation.

clear cut-off value for protection has not been set. However, in patients with cancer, there are a number of pitfalls with routine testing of the serological response: first, in patients with cancer, the humoral and cellular response may be discordant – most prominently with a higher rate of cellular response despite lack of antibody response in patients undergoing B-cell depletion and a lack of cellular response despite the presence of antibodies after allogeneic SCT [43,56]. Measuring antibody levels therefore does not capture the full immune response, and in those without antibodies, there may still be relevant protection by specific T cells. This is still the case after booster vaccinations [56]. Second, even if neutralising antibodies are found, a breakthrough infection may yet occur with a novel VOC, which is not recognised by the antibodies present [57]. Third, the significance of B-cell and T-cell response with regard to protection from infection and from severe course of disease is yet to be determined [58] and last but not least, the presence of monoclonal antibodies after passive immunisation may be confused with a vaccine response. Therefore, the result of routine testing of antibodies may not be helpful in the clinical context, as it is difficult to draw conclusions from it [58].

4. Pharmacological prophylaxis

While vaccination is most effective in the prevention of severe COVID-19 in the general population, in some cancer patients with severe immunosuppression, vaccination is either not expected to result in adequate seroprotection, for example, in those undergoing haematopoietic SCT, or they fail to mount an adequate immune response despite repeated boostering [43]. For these patient populations, passive immunisation strategies via pre- or post-exposure prophylaxis with monoclonal antibodies are valuable options (see Table 3).

The long-acting anti-S monoclonal antibody combination tixagevimab/cilgavimab has been evaluated as pre-exposure prophylaxis in patients with high risk of poor vaccine response or high risk of exposure in a large placebo-controlled randomised controlled trial (RCT) [19]. Although the overall number of symptomatic COVID-19 cases was low during the observation period, the primary efficacy end-point, a significant reduction in symptomatic COVID-19, was met (0.2% versus 1.0%) [19]. Given the trial design, it is important to note that these results are mainly transferable to cancer patients in whom active vaccination is unlikely to result in sufficient vaccine response or those with proven inadequate vaccine response despite full vaccination. This also includes patients undergoing SCT who are expected to lose any prior vaccine-induced seroprotection. For these patient populations, we moderately recommend monoclonal anti-S antibodies with efficacy against the locally predominant SARS-CoV-2 variants, in particular long-acting antibodies, as pre-exposure prophylaxis (**BIIt**). The complexity of assessing vaccine response, given the diverse impacts of anti-cancer treatments on B-cell and T-cell responses as delineated previously, has to be kept in mind. Furthermore, it has to be stated clearly that pre-exposure prophylaxis should not be used as an alternative strategy to vaccination in patients in whom successful vaccination is possible (**AIII**).

Monoclonal antibodies as post-exposure prophylaxis have been successfully evaluated in a large RCT in unvaccinated household contacts of a person with SARS-CoV-2 infection [20]. Casirivimab/imdevimab administered within 96 h after diagnosis were associated with a lower risk of symptomatic COVID-19 compared with placebo (1.5% versus 7.8%) [20]. In vitro studies suggest that neutralising activity of casirivimab/imdevimab is severely reduced against the currently predominant omicron BA.4/5 variants compared with the ancestral strain [59,60]. Therefore, this particular antibody combination might currently not be a suitable option. However, the strategy of applying monoclonal anti-S antibodies as post-exposure prophylaxis has been shown to be safe and efficacious, and we therefore strongly recommend post-exposure prophylaxis in unvaccinated cancer patients or those with poor vaccine response with monoclonal anti-S antibodies as early as possible if antibody preparations active against the

Table 3
Recommendations on prophylaxis against COVID-19 in cancer patients.

Population	Intention	Intervention	SoR	QoE	Reference
Cancer patients without adequate vaccine protection[a], pre-exposure prophylaxis	To prevent infection	Anti-S monoclonal antibodies[b]	B	IIt	[19]
Cancer patients without adequate vaccine protection[a], post-exposure prophylaxis	To prevent infection	Anti-S monoclonal antibodies[b]	A	IIt	[20]
Cancer patients, pre- or post-exposure prophylaxis	To prevent infection	High-titer convalescent plasma	D	IIt	[62]
Cancer patients, pre- or post-exposure prophylaxis	To prevent infection	Any antiviral (nirmatrelvir/ritonavir, remdesivir, molnupiravir)	D	III	

COVID-19, coronavirus 2019; QoE, quality of evidence; SoR, strength of recommendation.

[a] That is, cancer patients in whom vaccination is not feasible, at high risk of poor vaccine response or with proven inadequate vaccine response despite full vaccination.

[b] If available against the locally predominant SARS-CoV-2 variant.

currently predominant SARS-CoV-2 variants are available (**AIIt**).

It is important to note that published data on RCTs evaluating monoclonal anti-S antibodies as prophylaxis or treatment strategies have all been conducted before the predominance of the omicron variant, in particular, the currently predominant BA.4/5 subvariants. So far, data on the efficacy of the various monoclonal antibodies against BA.4/5 are based almost exclusively on in vitro neutralisation assays making predictions on clinical efficacy inherently fraught [59,60]. Summing up the currently available in vitro evidence, it seems that neutralising efficacy against omicron BA.4/5 of casirivimab/imdevimab, bamlanivimab/etesevimab and sotrovimab is too strongly reduced to retain clinical efficacy, and of tixagevimab/cilgavimab is moderately reduced [59,60]. Some preliminary data suggest doubling the dosage of tixagevimab/cilgavimab in the setting of less susceptible omicron subvariants may increase efficacy [61]. Neutralising activity of bebtelovimab seems to be retained against BA.4/5,[60] although this monoclonal antibody is so far only approved by the Food and Drug Administration (FDA) and not by European Medicines Agency (EMA).

High-titer convalescent plasma (CP) as post-exposure prophylaxis was evaluated in a smaller RCT and failed to show prevention of SARS-CoV-2 infection [62]. CP is therefore not recommended as a prophylaxis strategy (**DIIt**).

There is currently no data on the antiviral agents remdesivir, nirmatrelvir/ritonavir or molnupiravir as pre- or post-exposure prophylaxis in cancer patients, which can therefore not be recommended (**DIII**).

5. Treatment

Treatment options in COVID-19 are a rapidly evolving field. To best devise treatment strategies in cancer patients with COVID-19, several important aspects have to be considered: the patient's immune status, in particular, with regard to prior COVID vaccinations and COVID vaccine response; the severity of COVID-19 and time lapse since the onset of symptoms; the local epidemiology and presence of variants of concern; the national approval and local availability of anti-COVID-19 drugs. In the following, evidence-based recommendations on treatment of COVID-19 in cancer patients are given with differentiation of patients' clinical status according to the World Health Organization (WHO) clinical progression scale, that is, outpatient mild disease (score 1–3), hospitalised moderate disease (score 4–5) and hospitalised severe disease (score 6–9) [63].

Especially in the early months of the COVID-19 pandemic, a plethora of potential medications to treat COVID-19 were evaluated that had to be discarded later on. Based on current data, the following drugs are not indicated for COVID-19 in cancer patients of any severity due to lack of proven efficacy: hydroxychloroquine ± azithromycin (**DIIt**) [64–66], lopinavir/ritonavir (**DIIt**) [67], umifenovir (**DIItr**) [68], favipiravir (**DIItr**) [69] and ivermectin (**DIItr**) [70].

5.1. Out-patient mild disease (WHO score 1–3)

For immunocompromised cancer patients with COVID-19 and outpatient mild disease, both monoclonal antibodies and antiviral agents offer effective options of early therapy. Evidence-based recommendations in this setting are summarised in Table 4. Initiation of therapy should be initiated as early after symptom onset and/or positive test for SARS-CoV-2 as possible, ideally within 3–7 days (**AIII**). However, a later time point should not be considered a contraindication to therapy initiation, especially in high-risk patients with uncontrolled infection. Confirmation of a positive rapid antigen test via nucleic acid amplification technique should be attempted. However, given the advantage of early treatment initiation, therapy should not be delayed awaiting nucleic acid amplification technique test results in such cases.

Various monoclonal antibodies against the SARS-CoV-2 spike have been evaluated in placebo-controlled

Table 4
Recommendations on treatment of cancer outpatients with mild COVID-19 (WHO score 1–3).

Population	Intention	Intervention	SoR	QoE	Reference
Cancer patients with COVID-19 – outpatient, mild [1–3]	To prevent hospitalisation and/or death	Anti-S monoclonal antibodies[a]	A	IIt	[21–23,72]
Cancer patients with COVID-19 – outpatient, mild [1–3]	To prevent hospitalisation and/or death	High-titer convalescent plasma	C	IIt	[73–75]
Cancer patients with COVID-19 – outpatient, mild [1–3]	To prevent hospitalisation and/or death	Nirmatrelvir/ritonavir	A	IIt	[25]
Cancer patients with COVID-19 – outpatient, mild [1–3]	To prevent hospitalisation and/or death	Remdesivir	B	IIt	[26]
Cancer patients with COVID-19 – outpatient, mild [1–3]	To prevent hospitalisation and/or death	Molnupiravir	C	IIt	[24]

COVID-19, coronavirus 2019; QoE, quality of evidence; SoR, strength of recommendation; WHO, World Health Organisation.
[a] If available against the locally predominant SARS-CoV-2 variant, particularly indicated in unvaccinated patients or those at risk of poor vaccine response.

RCTs in ambulatory patients with COVID-19 early after symptom onset, defined as within 3–7 days after symptom onset or diagnosis of COVID-19 across the respective trials [21–23,71,72]. Although these trials addressed particularly patients at high risk for severe COVID-19, including cancer patients, cancer patients constituted only a small minority of trial participants. Furthermore, as vaccinated patients were excluded from trial participation, the evidence is best transferable to cancer patients without vaccination or with presumed or proven inadequate vaccine response. The primary end-point of a significant reduction in the rate of hospitalisation or death compared with placebo was met for the following monoclonal antibodies or antibody combinations: casirivimab/imdevimab [21], bamlanivimab/etesevimab [23], regdanvimab [71], sotrovimab [22] and tixagevimab/cilgavimab [72]. A relative risk reduction of 50.5%–85% was observed [21–23,71,72]. It is important to acknowledge that these clinical trials were all conducted before the dominance of the omicron variants. With regard to the efficacy of currently available monoclonal antibodies against the omicron variants, in particular, the newer BA.4/BA.5 subvariants, mainly data from in vitro neutralisation assays as well as from small observational studies are available. For a summary of these data, please refer to the previous paragraph.

Taking into account the caveats mentioned previously, monoclonal antibodies seem to be a drug class particularly suitable for immunocompromised cancer patients, as these patients are prone to mount only an inadequate vaccine response and often take multiple medications making potential drug–drug interactions (DDIs), such as with some of the antiviral agents, a concern. We therefore strongly recommend the drug class of monoclonal anti-S antibodies for early treatment of outpatient cancer patients (**AIIt**), if preparations effective against the locally dominant SARS-CoV-2 variant are available. Given their mechanism of action and the available trial data, monoclonal anti-S antibodies are particularly recommended for either unvaccinated patients or patients with inadequate vaccine response (**AIII**). Laboratory assessment of vaccine response is not necessary before therapy initiation; rather, known risk factors of inadequate vaccine response in cancer patients should be taken into consideration to guide treatment decisions [38].

High-titer CP has been evaluated in several RCTs in high-risk outpatients with COVID-19 with overall mixed results [73–75]. We marginally recommend CP early after symptom onset in cancer outpatients with COVID-19 (**CIIt**). Given the superior efficacy data of some monoclonal antibodies in this setting, CP should only be administered if monoclonal antibody preparations efficacious against the locally predominant variants or antivirals are not available.

As of today, three different antiviral agents have been approved by both FDA and EMA for early treatment of COVID-19 in high-risk patients: nirmatrelvir/ritonavir, remdesivir and molnupiravir. While the major clinical trials on these agents have all been conducted before the rise of the omicron variant, recent in vitro as well as retrospective clinical studies suggest that activity of all three agents against the currently predominant BA.4/5 omicron subvariants is preserved [59,76,77]. Nirmatrelvir is an oral inhibitor of the viral 3CL-protease and is used in fixed combination with ritonavir as an inhibitor of CYP3A4 to increase bioavailability. In the placebo-controlled EPIC-HR RCT, nirmatrelvir/ritonavir met its primary end-point of a significant reduction compared with placebo in COVID-19–related hospitalisation or death in unvaccinated, high-risk patients treated no later than 5 days after the onset of symptoms (0.8% versus 6.3%, relative risk reduction 88%) [25]. Again, despite the fact that active cancer was featured among the prespecified risk factors, only a minority of trial participants were cancer patients. While data in the setting of dominance of the omicron VOC is still limited, a recently published large real-world data analysis reported a relative risk reduction with regard to hospitalisation due to COVID-19 of 73% and with regard to the death of 79% in older adults who received nirmatrelvir/ritonavir compared with those who did not [77]. We strongly recommend nirmatrelvir/ritonavir as early therapy in outpatient cancer patients with COVID-19 (**AIIt**). As ritonavir is a potent CYP3A4 inhibitor, possible DDI have to be considered, which can be a particular issue in cancer patients who often take multiple medications. A comprehensive and regularly updated list of potential DDI between nirmatrelvir/ritonavir and concomitant medications is readily accessible, for example, via the National Institutes of Health Web page and many others [78].

Remdesivir applied intravenously for 3 days was assessed as early therapy against placebo in the similarly designed PINETREE RCT, resulting in an 87% relative risk reduction of COVID-related hospitalisation or death in unvaccinated high-risk outpatients with COVID-19 within 7 days of symptom onset [26]. While the intravenous mode of application has logistic challenges in the outpatient setting, the lesser potential of DDI compared with nirmatrelvir/ritonavir may make this an attractive treatment option for certain patients. We therefore moderately recommend remdesivir as early therapy in ambulatory cancer patients with COVID-19 (**BIIt**).

Molnupiravir, an oral prodrug of a nucleoside analogue interfering with the viral RNA polymerase, has been evaluated in the similarly designed phase III MOVe-OUT trial in unvaccinated high-risk outpatients with COVID-19. In contrast to favourable reports from the interim analysis, final trial results showed only a relative risk reduction of 30%. Up to now, molnupiravir has not been approved by EMA but can be administered within a compassionate use programme. We marginally

recommend molnupiravir as early therapy in ambulatory cancer patients with COVID-19 (**CIIt**), in particular, if more potent therapeutic options are contraindicated or not available. Due to its mutations, inducing mechanism of action, molnupiravir is absolutely contraindicated in pregnant or breast-feeding women.

As antibody-based therapies and antiviral agents possess different mechanisms of action, it is conceivable that combination therapies of these two drug classes might be beneficial, in particular, in severely immunocompromised cancer patients. However, no published trial data are available so far; therefore, no definite recommendations can be made on such a strategy. Similarly, it remains currently unclear whether prolonged treatment or repeated dosing might be an advisable strategy in immunocompromised cancer patients with prolonged viral shedding of SARS-CoV-2.

Inhaled corticosteroids such as budesonide or ciclesonide were assessed in several smaller studies in non-high-risk adults and in a large open-label RCT in high-risk adult outpatients with COVID-19. Although associated with improved patient-reported outcomes, there was no impact on hospitalisation rates or mortality [79–81]. We therefore do not see sufficient evidence of benefit and recommend against the administration of inhaled corticosteroids in cancer outpatients with COVID-19 who are not already on these medications as part of their standard of care (**DIIt**).

The serotonin re-uptake inhibitor fluvoxamine showed a lower likelihood of clinical deterioration compared with placebo in a small placebo-controlled RCT in non-high-risk adult outpatients with COVID-19. However, the study was underpowered to evaluate a potential impact on stronger end-points [82]. While fluvoxamine might be considered as an off-label treatment option, if antibody-based therapies or antivirals are unavailable, there is currently not enough evidence to make any definite recommendations in this regard. Similarly, data on the anti-inflammatory drug colchicine is inconclusive and as of yet lacking in high-risk patients, thus precluding any definite recommendations [83].

Immunosuppressant drugs, in particular dexamethasone, anti-interleukin (IL)-6 or anti-IL-1 monoclonal antibodies, or Janus kinase (JAK) inhibitors, are not recommended as treatment options in outpatient cancer patients with COVID-19 (**DIII**).

5.2. Hospitalized moderate disease (WHO score 4–5) and severe disease (WHO score 6–9)

For the management of hospitalised cancer patients with COVID-19, it is helpful to differentiate between moderate disease, that is, no or low-flow oxygen only (WHO score 4–5), and severe disease, that is, high-flow oxygen, non-invasive ventilation (NIV) or mechanical ventilation (MV; WHO score 6–9). While in earlier phases of disease, active viral replication seems to be a major pathogenetic factor, and in later, more severe disease, hyperinflammation predominates resulting in different treatment strategies at different time points (see Table 5) [84].

In hospitalised patients with moderate COVID-19 and hypoxic pneumonia and/or low-flow oxygen support, administration of remdesivir early after symptom onset was significantly associated with a shortened time to recovery in the ACTT-1 double-blind placebo-controlled RCT, with a trend towards reduced mortality in the low-flow oxygen group [85]. The open-label DisCoVeRy trial and the interim analysis of the large, equally open-label WHO Solidarity trial failed to detect any clinical benefit of remdesivir treatment in hospitalised patients [86,87]. The final analysis of the WHO Solidarity trial, however, showed a small but significant reduction in mortality in hospitalised patients with oxygen support but without MV (14.6% versus 16.3%) [88]. No benefit was seen in patients already on MV [88]. In a large observational multicentre study, remdesivir-treated patients had a lower 14-day mortality compared with patients without, regardless of the mode of oxygen support [89]. In cancer patients who might be particularly prone to impaired viral clearance, a large retrospective study also reported a potential benefit of remdesivir on mortality [90]. In summary, we moderately recommend remdesivir for up to a maximum of 10 days in hospitalised cancer patients with moderate COVID-19 and with severe COVID-19 not yet on MV (WHO scale 4–6, **BIIt**), whereas the current evidence does not support the use of remdesivir in patients with MV or on Extracorporeal membrane oxygenation (ECMO) (WHO scale 7–9, **DIIt**).

However, it is important to note that COVID-19 patients, and cancer patients in particular, often experience rapid clinical deterioration with escalation from low-flow oxygen to MV within 24 h in some cases. We therefore recommend to account for the patient's course of disease and consider remdesivir or other adjuncts, such as IL-6 or JAK inhibitors (see below), within the first 24 h after intensive care unit admission, even if MV was already initiated.

With regard to the oral antivirals nirmatrelvir/ritonavir and molnupiravir, no published trial data are available in patients hospitalised because of COVID-19 with need for supplemental oxygen, so currently, no recommendation can be made in this indication. One retrospective trial in hospitalised patients with mild COVID-19 without supplemental oxygen showed a reduced disease progression (including death) in nirmatrelvir/ritonavir- or molnupiravir-treated patients aged >65 years [91]. Obviously, to patients who are hospitalised for other reasons without specific symptoms suggesting COVID-19 pneumonia, all considerations for the outpatient setting as described above apply.

Table 5
Recommendations on treatment of hospitalized cancer patients with moderate to severe COVID-19 (WHO score 4–9).

Population	Intention	Intervention	SoR	QoE	Reference
Cancer patients with COVID-19 – hospitalized, moderate to severe [4–6]	To shorten time to recovery	Remdesivir	B	IIt	[64,85,87,88,90]
Cancer patients with COVID-19 – hospitalized, severe [7–9]	To reduce mortality	Remdesivir	D	IIt	[64,85,87,88,90]
Cancer patients with COVID-19 – hospitalized, moderate to severe [4–6], seronegative	To reduce mortality	Anti-S monoclonal antibodies[a]	B	IIt	[92,148]
Cancer patients with COVID-19 – hospitalized, moderate to severe [4–6], seropositive	To reduce mortality	Anti-S monoclonal antibodies[a]	D	IIt	[92,148]
Cancer patients with COVID-19 – hospitalized, moderate [4–5], seronegative	To reduce mortality	High-titer convalescent plasma	C	III	[93–95]
Cancer patients with COVID-19 – hospitalized, moderate [4–5], seropositive	To reduce mortality	High-titer convalescent plasma	D	IIt	[93–95]
Cancer patients with COVID-19 – hospitalized, severe [6–9]	To reduce mortality	High-titer convalescent plasma	D	IIt	[94,96]
Cancer patients with COVID-19 – hospitalized, moderate [4]	To reduce mortality	Dexamethasone, anti-IL-6 or anti-IL-1 monoclonal antibodies, JAK inhibitors	D	IIt	[97–99]
Cancer patients with COVID-19 – hospitalized, moderate to severe [5–9]	To reduce mortality	Dexamethasone	A	IIt	[97]
Cancer patients with COVID-19 – hospitalized, moderate to severe [5–6] and systemic inflammation	To reduce mortality	Anti-IL6 monoclonal antibodies	B	IIt	[100,101]
Cancer patients with COVID-19 – hospitalized, severe [7–9] and systemic inflammation	To reduce mortality	Anti-IL-6 monoclonal antibodies	C	IIt	[100–102]
Cancer patients with COVID-19 – hospitalized, moderate to severe [5–6] and systemic inflammation	To reduce mortality	Anti-IL-1 monoclonal antibodies	C	IIt	[103,104]
Cancer patients with COVID-19 – hospitalized, severe [7–9] and systemic inflammation	To reduce mortality	Anti-IL-1 monoclonal antibodies	D	IIta	[102]
Cancer patients with COVID-19 – hospitalized, moderate to severe [5–6] and systemic inflammation	To reduce mortality	JAK inhibitors	C	IIt	[98,99,106]

COVID-19, coronavirus 2019; JAK, Janus kinase; IL, interleukin; QoE, quality of evidence; SoR, strength of recommendation; WHO, World Health Organisation.
[a] If available against the locally predominant SARS-CoV-2 variant.

In hospitalized patients with moderate to severe disease, the randomised, open-label RECOVERY trial evaluated the impact of the monoclonal antibody combination casirivimab/imdevimab on mortality [92]. Although no effect was seen in seropositive patients, mortality at day 28 in seronegative patients was significantly reduced by monoclonal anti-S antibody therapy (24% versus 30%) [92]. Although casirivimab/imdevimab are no longer considered sufficiently active against the currently predominant omicron BA.4/5 variants [59], the strategy of administering monoclonal anti-S antibodies to hospitalised seronegative cancer patients seems sensible, if preparations with activity against the locally predominant variants are available, especially taking into account the often impaired humoral immune response in cancer patients. We therefore moderately recommend monoclonal anti-S antibodies to hospitalised seronegative cancer patients with WHO scale 4–6 disease (**BIIt**). As only 2% of patients in the RECOVERY trial were on MV, no recommendation can be made with regard to a potential benefit of monoclonal antibodies in patients with WHO scale 7–9 disease. In seropositive hospitalised patients, monoclonal anti-S antibodies are not recommended (**DIIt**).

Clinical data on high-titer CP in hospitalised patients with moderate disease are so far inconclusive. Some retrospective analyses have noted a benefit, especially in immunocompromised patients and patients with haematological malignancies [93–95]. Hence, high-titer CP administration can be discussed in selected seronegative cancer patients with moderate disease if monoclonal antibodies against the locally predominant variants are not accessible (**CIII**). In seropositive patients as well as in those with severe disease, the current evidence does not support the use of CP (**DIIt**) [93,94,96].

Immunosuppressive agents, in particular, dexamethasone, are an important part of therapy in severely ill COVID-19 patients. In hospitalised patients without oxygen support (WHO scale 4), however, dexamethasone was associated with a trend towards increased mortality in the large RECOVERY RCT and is therefore contraindicated in these patients (**DIIt**) [97]. The

same holds true for other immunosuppressive agents, such as anti-IL-6 monoclonal antibodies or JAK inhibitors in this patient population (**DIIt**) [98,99].

In patients requiring oxygen support, the addition of dexamethasone at 6 mg/day for a 10-day course significantly improved clinical outcomes and reduced mortality in the RECOVERY RCT by about a fifth in patients with low- or high-flow oxygen (WHO scale 5–6) and by about a third in mechanically ventilated patients (WHO scale 7–9) and is therefore strongly recommended in these patient population (**AIIt**) [97].

If systemic inflammation is present, for example, highly elevated C-reactive protein (CRP) levels in the absence of bacterial infection, the addition of anti-IL-6 monoclonal antibodies, such as tocilizumab or sarilumab, to dexamethasone treatment can be considered in patients with oxygen support but without mechanical (WHO scale 5–6) and is recommended here with moderate strength (**BIIt**) [100,101]. Ideally, anti-IL-6 antibodies are initiated early after symptom onset and before MV (**BIIt**). As discussed above, exceptions can be made in rapidly progressing patients, but anti-IL-6 monoclonal antibodies are only marginally recommended in patients with recently initiated mechanical (WHO scale 7–9, **CIIt**) [100–102] and are not indicated in patients with already prolonged mechanical.

As an alternative to anti-IL-6 antibodies, anti-IL-1 monoclonal antibodies, such as anakinra, can be considered in hospitalised patients with systemic inflammation and low- or high-flow oxygen support (WHO scale 5–6); however, the available data are less conclusive (**CIIt**) [103,104]. In patients on NIV or MV, anti-IL-1 monoclonal antibodies failed to demonstrate a survival benefit and are not indicated (**DIIta**) [102].

JAK inhibitors, such as baricitinib and tofacitinib, demonstrated a survival benefit in addition to dexamethasone in hospitalised patients, especially in patients on high-flow oxygen or NIV (WHO scale 5–6), and represent another alternative in patients with systemic inflammation (**CIIt**) [99,105,106]. Patients on MV or ECMO were not included in these trials; hence, no recommendations can be made in this regard.

Monoclonal anti-IL-6 and anti-IL-1 antibodies and JAK inhibitors must not be given concomitantly (**DIII**), and the second immunomodulator of choice should always be given in addition to standard dexamethasone treatment (**AIIt**).

5.3. Supportive therapy

Correction of vitamin D deficiency in cancer patients may positively influence the clinical outcome in the case of COVID-19, although the evidence is based on mainly indirect observational data because patients with vitamin D deficiency experience inferior COVID-19 outcomes (**BIIt**; see Table 6) [107]. However, vitamin D supplementation is not recommended as a prophylactic measure in cancer patients without vitamin D deficiency (**DIIt**) [108,109].

Cancer patients are per se considered to be at increased risk of thromboembolic complications. Prevention of these complications in the setting of COVID-19 therefore deserves particular attention. In cancer patients with mild COVID-19 who are still in outpatient management, thromboembolic prophylaxis with low-dose low-molecular-weight heparin (LMWH) can be considered especially in patients with additional risk factors, for example, immobilisation (**CIII**) [110]. This

Table 6
Recommendations on supportive care in cancer patients with COVID-19.

Population	Intention	Intervention	SoR	QoE	Reference
Cancer patients, uninfected [0] or with COVID-19 [1–9], with vitamin D deficiency	To improve clinical outcome in case of COVID-19	Vitamin D supplementation	B	IIt	[107]
Cancer patients, uninfected [0] or with COVID-19 [1–9], without vitamin D deficiency	To improve clinical outcome in case of COVID-19	Vitamin D supplementation	D	IItr	[108,109]
Cancer patients with COVID-19 – ambulatory, mild [1–3]	To prevent thromboembolic complications	Low-dose LMWH	C	III	[110]
Cancer patients with COVID-19 – hospitalized, moderate to severe [4–9]	To prevent thromboembolic complications	Low-dose LMWH	A	IIt	[111,112]
Cancer patients with COVID-19 – hospitalized, moderate [4–5] plus additional risk factors	To prevent thromboembolic complications and reduce mortality	Therapeutic anticoagulation	B	IIt	[112–115]
Cancer patients with COVID-19 – hospitalized, severe [6–9]	To prevent thromboembolic complications and reduce mortality	Routine intermediate-dose LMWH	D	IIt	[113,116]
Cancer patients with COVID-19 – hospitalized, severe [6–9]	To prevent thromboembolic complications and reduce mortality	Routine therapeutic anticoagulation	D	IIt	[112,117,149]

COVID-19, coronavirus 2019; LMWH, low-molecular-weight heparin.

rationale builds on the observation that COVID-19 patients have been reported to often present with thromboembolic complications already within the first 24 h after hospital admission [110]. Contraindications must be considered. In hospitalised cancer patients with moderate to severe COVID-19, thromboembolic prophylaxis with low-dose LMWH is strongly recommended (**AIIt**) [111,112]. In patients with moderate COVID-19 plus additional risk factors, for example, significantly elevated D-dimer levels or prior thromboembolic complications, therapeutic anticoagulation can be considered to prevent further thromboembolic complications and to reduce mortality in patients with a low risk of bleeding (**BIIt**) [112–115]. In severely ill patients on high-flow oxygen, MV or ECMO, routine application of intermediate-dose LMWH is discouraged (**DIIt**) [113,116]. Likewise, routine therapeutic anticoagulation is not recommended in this patient cohort (**DIIt**) [112,116,117] outside of specific indications. In cancer patients at high risk for thromboembolic complications and low bleeding risk, prophylactic anticoagulation may be continued after discharge from hospitalisation for COVID-19 (**CIIt**) [118]. Aspirin should not be initiated as treatment of COVID-19 in hospitalised cancer patients not already on chronic aspirin therapy due to other indications (**DIIt**) [119].

Concerning neutropenic cancer patients with COVID-19, granulocyte colony-stimulating factor should not be routinely administered outside of current guidelines (**DIII**), as granulocyte colony-stimulating factor application in neutropenic cancer patients was reported to be associated with a risk of worsening respiratory situation [120].

Generally, current guidelines for intensive care unit management in COVID-19 patients should also be applied to cancer patients with COVID-19, including the time point of intubation (which should not be delayed to prolong NIV respiratory support) and the definition of therapy goals (**AIII**).

5.4. Long COVID

A subset of patients suffers from a variety of symptoms after a SARS-CoV-2 infection [121]. A clinical case definition of a post-COVID-19 condition was provided by the WHO: Long COVID occurs in patients with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from onset, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis [121]. Common symptoms include, but are not limited to, fatigue, shortness of breath and cognitive dysfunction and generally have an impact on everyday functioning [121].

In cancer patients, long COVID is common, with a prevalence of up to 15%, and in particular, older cancer patients with more comorbidities seem to be at increased risk of developing COVID-19 sequelae [122]. Cancer patients with COVID-19 have a higher 1-year all-cause mortality than non-cancer COVID-19 patients, yet cancer patients have no more symptoms after 1 year post-COVID-19 than other patients [123]. While the currently available data is insufficient to make specific evidence-based recommendations for the prevention and treatment of long COVID other than those presented above for the prevention and treatment of (severe) COVID-19, we think it useful to briefly summarise possible strategies.

Patients with haematological malignancies experience prolonged viral shedding and have a higher maximal viral load than patients without malignancies [124]. Anti-CD20 treatment <1 year (odds ratio [OR] 3.04), SCT/cellular therapy <1 year (OR 3.64) and chronic lymphopenia (<500/μL; OR 3.78) are predictors for SARS-CoV-2 persistence [125]. It remains, however, unclear whether viral clearance contributes to preventing long COVID [126].

In a prospective non-interventional study, treatment with remdesivir was independently associated with a 35% risk reduction of long COVID [127]. Impaired pulmonary function or dyspnoea is a frequent symptom in cancer patients with long COVID [122]. In a small RCT in patients with clinical-radiological suspicion of COVID-19 and requirement of oxygen support, a short course of methylprednisolone was shown to improve pulmonary function at day 120 [128]. Furthermore, in COVID-19 patients with interstitial lung disease, the application of prednisolone was reported to be beneficial with regard to the prevention of pulmonary fibrosis with permanent functional deficit [129]. In a small observational study, systemic corticosteroids administered during the acute phase of COVID-19 were associated with reduced symptoms and better quality of life 1 year after initial admission for COVID-19 [130]. Of note, in an observational study in health care workers, vaccination against COVID-19 was associated with an 84% relative risk reduction of long COVID after three doses of vaccine, again highlighting the importance of vaccination [131].

To improve a variety of long COVID symptoms, for example, fatigue or olfactory impairment, brain function, functional capacity or emotional well-being, a plethora of alimentary supplementation of vitamins, minerals, amino acids and plant extracts have been suggested, as well as systemic prednisone, nasal irrigation or hyperbaric oxygen therapy, so far with little to no conclusive evidence of clinical benefit [132–136]. Furthermore, multidisciplinary outpatient neuropsychological rehabilitation measures have been reported as helpful [137,138].

6. Conclusion and outlook

Cancer patients still constitute a population at high risk of severe and prolonged COVID-19. Major advances with regard to the development of vaccines and therapeutic agents against COVID-19 have significantly

broadened the options for the prevention and treatment of this infectious disease. Improving response to vaccination in immunocompromised cancer patients, devising optimal treatment strategies for these patients and addressing the symptoms of long COVID still remain significant challenges.

Author contributions

All authors actively participated in the guideline panel. N.G. coordinated the guideline panel. N.G., E.B., E.S. and M.v.L.T. wrote the final version of the article. All authors agreed on guideline topics, performed a systematic literature search, extracted and rated the data, discussed and agreed on the final recommendations, helped in writing and critically revised the first draft of the article and approved the final version of the article.

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