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SIOG COVID-19 working group recommendations on COVID-19 therapeutic approaches in older adults with cancer

Chiara Russo, Anna Rachele Mislant, Domenico Ferraioli, Enrique Soto-Perez-de-Celis, Giuseppe Colloca, Grant R. Williams, Shane O'Hanlon, Lisa Cooper, Anita O'Donovan, Riccardo A. Audisio, Kwok-Leung Cheung, Regina Gironés Sarrió, Reinhard Stauder, Michael Jaklitsch, Clarito Cairo, Luiz Antonio Gil, Schroder Sattar, Kumud Kantilal, Kah Poh Loh, Stuart M. Lichtman, Etienne Brain, Ravindran Kanesvaran, Nicolò Matteo Luca Battisti



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SIOG COVID-19 Working Group recommendations on COVID-19 therapeutic approaches in older adults with cancer

Chiara Russo

Department of Medical Oncology

Léon Bérard, Comprehensive Cancer Centre

Lyon, France

Chiara.RUSSO@lyon.unicancer.fr

Anna Rachelle Mislant

Department of Medical Oncology

Flinders Centre for Innovation in Cancer

College of Medicine and Public Health, Flinders University

Bedford Park, SA, 5042, Australia

anna.mislant@sa.gov.au

Domenico Ferraioli

Department of Gynaecology

Léon Bérard, Comprehensive Cancer Centre

Lyon, France

ferraioli.domenico@gmail.com

Enrique Soto-Perez-de-Celis

Department of Geriatrics

Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán

Mexico City, Mexico

enrique.sotop@incmnsz.mx

Giuseppe Colloca

Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia,

Fondazione Policlinico Universitario A. Gemelli IRCCS

Rome, Italy

giuseppeferdinando.colloca@policlinicogemelli.it

Grant R. Williams

Institute for Cancer Outcomes and Survivorship

University of Alabama at Birmingham School of Medicine

Birmingham, AL, USA

grwilliams@uabmc.edu

Shane O'Hanlon

University College Dublin

St Vincent's University Hospital

Dublin, Ireland

shaneohanlon@svhg.ie

Lisa Cooper

Department of Geriatric Medicine

Rabin Medical Center

Sackler Faculty of Medicine, Division of Aging, Department of Medicine

Tel Aviv University,

Israel

lisacooper113@gmail.com

Anita O'Donovan

Applied Radiation Therapy Trinity (ARTT), Trinity St James's Cancer Institute,

Trinity College, Dublin, Ireland

Anita.ODonovan@tcd.ie

Riccardo A. Audisio

Department of surgery

Sahlgrenska Academy - University of Gothenburg

Gothenburg, Sweden

raudisio@doctors.org.uk

Kwok-Leung Cheung

School of Medicine

University of Nottingham, Royal Derby Hospital Centre

Derby, UK

Kwok_Leung.Cheung@nottingham.ac.uk

Regina Gironés Sarrió

Department of Medical Oncology

Hospital Universitari i Politècnic La FE

Valencia, Spain

reginagiro@hotmail.com

Reinhard Stauder

Department of Internal Medicine V (Haematology and Oncology)

Innsbruck Medical University

Innsbruck, Austria

reinhard.stauder@i-med.ac.at

Michael Jaklitsch

Brigham and Women's Hospital – Dana-Farber Cancer Institute

Harvard Medical School

Boston, MA, USA

mjaklitsch@bwh.harvard.edu

Clarito Cairo Jr

National Integrated Cancer Control Program

Department of Health

Manila, Philippines

dokclar@gmail.com

Luiz Antonio Gil Jr

Geriatric Center for Advanced Medicine - Hospital Sirio-Libanês,

São Paulo, SP, Brazil

gil.luizantonio@gmail.com

Schroder Sattar

College of Nursing – University of Saskatchewan

Saskatoon, Canada

schroder.sattar@usask.ca

Kumud Kantilal

School of Pharmacy

University of East Anglia

Norwich, UK

k.kantilal@uea.ac.uk

Kah Poh Loh

University of Rochester Medical Center

Division of Hematology/Oncology, Department of Medicine

James P. Wilmot Cancer Institute

Rochester, NY, USA

kahpoh_loh@urmc.rochester.edu

Stuart M. Lichtman

Department of Medicine

Memorial Sloan Kettering Cancer Center

New York, NY, USA

_lichtmas@mskcc.org

Etienne Brain

Department of Medical Oncology

Institut Curie

Saint-Cloud & Paris, France

Etienne.brain@curie.fr

Hans Wildiers

Department of General Medical Oncology

University Hospitals Leuven

Leuven, Belgium

hans.wildiers@uzleuven.be

Ravindran Kanesvaran

Division of Medical Oncology

National Cancer Centre Singapore

ravindran.kanesvaran@singhealth.com.sg

Nicolò Matteo Luca Battisti

Breast Unit – Department of Medicine Department

The Royal Marsden NHS Foundation Trust

Breast Cancer Research Division

The Institute of Cancer Research, London, UK

nicolo.battisti@rmh.nhs.uk

Corresponding author:

Chiara Russo

Department of Medical Oncology

Léon Bérard, Comprehensive Cancer Centre

Lyon, France

Chiara.RUSSO@lyon.unicancer.fr

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Older adults remain at higher risk for severe COVID-19 infection outcomes and, although the development of vaccines has changed the course of the disease, immunosenescence can result in lower vaccine immunogenicity¹. Older patients with solid tumours or haematologic malignancies receiving anti-cancer treatment are often immunocompromised and unable to provide an adequate immune response to COVID-19 vaccination²⁻⁵, which may lead to worse COVID-19 clinical outcomes⁶⁻¹⁰. Today, several drugs are available for the treatment of COVID-19 infection, with the best treatment option for each individual patient determined by their therapeutic indication, efficacy, availability, feasibility of administration, safety, and prevalence of infection variants.

Older adults with cancer represent a vulnerable population. The impact of geriatric syndromes, comorbidities, immunosuppression, increased risk of side effects, and drug-drug interactions due to polypharmacy and/or oncological treatment, must be considered in the risk-benefit balance influencing the choice of COVID-19 treatments¹¹. The SIOG COVID-19 Working Group continues to advocate for the optimal management of older adults with cancer during the pandemic era. Therefore, we reviewed the data on currently available COVID-19 treatments mainly in outpatients setting and their potential use among older adults with cancer.

Available Data on COVID-19 Pharmacologic Treatments in Older Patients with Cancer

The COVID-19 pandemic has triggered an unprecedented acceleration in drug development. Patients with mild to moderate COVID-19 infection, considered to be at higher risk for COVID-19 adverse outcomes, may benefit from different therapies. High-risk groups for SARS-CoV-2 complications and death are defined according to age, vaccination status, immune status, and the presence of risk factors for clinical progression¹². Age alone is a key

risk factor, but comorbidities, often prevalent among older adults, may further increase the risk of COVID-19 disease progression and poor outcomes¹³. Although older individuals may derive significant benefits from novel COVID-19 treatments, studies published to date mostly included very selected populations.

Currently, therapeutic strategies for COVID-19 involve antiviral agents (often administered at early stages of the disease), steroids, and immunotherapeutic agents.

Ritonavir-Boosted Nirmatrelvir

For non-hospitalised adults affected by mild or moderate COVID-19 at high risk of disease progression, ritonavir-boosted nirmatrelvir or remdesivir are considered first-line treatment options¹². The protease inhibitor nirmatrelvir is combined with the strong cytochrome P450 (CYP) 3A4 inhibitor and pharmacokinetic boosting agent ritonavir. Coadministration of ritonavir is required to increase nirmatrelvir concentrations to the target therapeutic range¹⁴. The Evaluation of Protease Inhibition for COVID-19 in High-Risk patients (EPIC-HR) phase 2–3 trial¹⁵ demonstrated the efficacy of oral nirmatrelvir associated to ritonavir within three days after the onset of symptoms. Authors reported an 89.1% relative risk reduction in COVID-19–related hospitalizations or deaths from any cause by day 28 compared to placebo among unvaccinated, non-hospitalised adults at high risk for progression to severe disease. In this study, 1.9% of the patients were aged ≥ 65 years and efficacy was supported by subgroup analyses (age, coexisting health conditions, etc). Fewer serious adverse events occurred in the population treated with nirmatrelvir plus ritonavir. Dysgeusia and diarrhoea are potentially dangerous events in older adults and occurred more frequently in ritonavir-boosted nirmatrelvir patients compared with placebo (6% *versus* 0.3% and 3% *versus* 2%, respectively). Ritonavir-boosted nirmatrelvir use involves a high risk of drug-drug interactions with concomitant medications that may increase the risk of toxicities. CYP3A4 inhibition occurs rapidly after initiating ritonavir, with maximum inhibition occurring within 48 hours. After ritonavir is discontinued, 70% to 90% of CYP3A4 inhibition resolves within two to three

days. The time to resolution of inhibition varies based on the patient's age and resolution may take longer in older adults^{12,16}.

Ritonavir is also a well-known strong combined inhibitor of p-glycoprotein, therefore it can interact with oral anticoagulants and drug-drug interaction management is required. In this real-world series of 72 patients co-prescribed nirmatrelvir-ritonavir and an oral anticoagulant, recommended drug-drug interaction management strategies for apixaban, rivaroxaban, and warfarin seemed effective at minimizing adverse events¹⁷.

Also, a careful evaluation is required in older patients with cancer because of the risk of potential interactions with myelosuppressive agents and the risk of increasing concentrations of concomitant medications, including certain chemotherapeutic agents¹². Ritonavir-boosted nirmatrelvir should be used with caution in patients with pre-existing liver disease and is not recommended in the context of severe hepatic impairment. Dose reductions are also required in patients with moderate renal impairment. However, limited data are available for patients with advanced kidney disease. Regardless, older patients with cancer and renal failure are at high risk for COVID-19 morbidity and mortality and should not be excluded from treatment. Alternative antiviral options may be considered and a discussion between the physician and the patient about the potential risks and benefits of this drug is necessary prior to administering an adapted dose of nirmatrelvir/ritonavir¹⁸.

Remdesivir

Intravenous remdesivir is approved for mild to moderate COVID-19 in patients at high risk of disease progression^{12,19}. Benefits of combining dexamethasone and remdesivir have been reported in different studies, although data in older individuals are limited^{20,21}. The double blind, randomized, placebo-controlled, Adaptive COVID-19 Treatment Trial (ACTT) trial²² evaluated remdesivir in unvaccinated, hospitalised adults with COVID-19. The study demonstrated a benefit on clinical recovery (7 versus 9; recovery rate ratio 1.45, 95% confidence interval [CI] 1.18–1.79) and mortality (hazard ratio [HR] for death 0.30, 95%CI 0.14–0.64) in patients requiring low-flow oxygen therapy. No significant benefit was shown in

patients requiring high-flow oxygen (HFO) or non-invasive ventilation (NIV) (recovery rate ratio 1.09, 95%CI 0.76–1.57). Mean age was 58.9 years and 35% of patients were aged ≥ 65 years old. Half of the patients had more than two coexisting conditions, most commonly hypertension (50.2%), obesity (44.8%), and type 2 diabetes (30.3%). Only 8% (N = 80) had malignant neoplasms. The efficacy of remdesivir in hastening recovery did not vary according to prespecified age categories. Serious adverse events were similar between arms (25% versus 32%)²². A subsequent retrospective study compared survival outcomes in 34,230 patients treated with remdesivir within two days of hospitalization versus patients who were not. In the remdesivir group, 8% of the patients were aged ≥ 85 , 19% were 75-84, and 25% were 65-74 years old. About 8% had cancer and were immunosuppressed, 78% cardiovascular disease, 40% obesity, and 42% diabetes. Remdesivir initiation upon hospital admission was associated with improved survival²³. Another prospective, observational study (median age 69 years) showed that among hospitalized patients affected by COVID-19 pneumonia who required oxygen supplementation, early (<5 days from symptom onset) remdesivir might reduce progression. Patients admitted within the first five days of symptom onset were older and had a higher prevalence of comorbidities and frailty²⁴. The phase 3, randomised, controlled, open-label DisCoVeRy trial²⁵, included unvaccinated, hospitalised patients with moderate or severe COVID-19. Although remdesivir delayed worsening of respiratory symptoms, the study showed no clinical and mortality benefit for treated patients. Median age was 64 years, 74% had one or more coexisting conditions and 8% had cancer. Remdesivir has also been tested in the ambulatory setting. The double-blind, placebo-controlled PINETREE study included non-hospitalised patients with COVID-19 at high risk for disease progression and demonstrated that three consecutive days of remdesivir resulted in a 87% relative reduction in the risk of hospitalisation or death (0.7% versus 5.3%; HR 0.13, 95%CI 0.03–0.59; $p = 0.008$). The study population of 562 patients included 30% aged ≥ 60 years, among whom 60% were affected by diabetes, 55% by obesity, and 45% by hypertension, with only 5.3% (N = 30) having a diagnosis of cancer²⁶. Remdesivir may be

associated with gastrointestinal toxicity, elevated transaminase levels, prolonged prothrombin time without change in the international normalized ratio, and hypersensitivity reactions¹⁹. Remdesivir is available in two formulations (concentrated solution and lyophilized powder) containing sulfobutylether beta-cyclodextrin sodium (SBECD), which is eliminated by the kidneys and may result in toxicity in patients with renal impairment. Importantly, while some clinical trials excluded patients with an estimated glomerular filtration rate (eGFR) <50 mL/min, other studies involved an eGFR cutoff of <30 mL/min^{27,28}. Nonetheless, remdesivir may be considered also for patients with an eGFR of <30 mL/min if the potential benefits outweigh the risks²⁹. A study by Kai ai et al.³⁰ suggested that remdesivir's safety profile was comparable in hospitalized patients older or younger than 80 years, with no significant differences in the incidence of liver dysfunction, renal dysfunction, and asthenia between both groups.

Dexamethasone

Systemic glucocorticoids are recommended for the treatment of patients with COVID-19 requiring supplemental oxygen¹². The multicentre, open-label, Randomized Evaluation of COVID-19 Therapy (RECOVERY) study³¹, showed that dexamethasone may reduce mortality in hospitalised patients with COVID-19 requiring supplemental oxygen, without significant survival differences between younger and older adults. Participants' mean age was 66 years and 56% of study population had one or more comorbidities (diabetes in 24%), without a report regarding the number of patients with cancer included. Gallay et al.³² supported the use of corticosteroids in patients aged ≥ 80 years with severe COVID-19, with improved overall survival at day 14. In this study, corticosteroids were prescribed less often in patients with lower level of independence at baseline, as measured by the Group Iso Ressource score. Low autonomy was reported in 14% of the patients in the treatment group and 21% in the control group (Groupe Iso Ressource score 1/2). Among 131 patients receiving corticosteroids, 17% developed adverse events, including hyperglycaemia, heart failure, confusion, and infection. The COronavirus disease in Very elderly Intensive care

Patients (COVIP) study³³ included 3,082 critically ill patients with COVID-19 aged ≥ 70 years. Univariate rates of 30-day mortality were higher in patients receiving corticosteroids (53% *versus* 42%; adjusted odds ratio [aOR] 1.16, 95%CI 1.28-2.02; $p < 0.001$) and this treatment remained associated with increased 30-day mortality after multivariable adjustment (aOR 1.60, 95%CI 1.26-2.04; $p < 0.001$). The benefit/risk ratio of systemic corticosteroid use in older adults remains unclear in the context of potential adverse events, such as delirium, hyperglycaemia, falls, immunosuppression, secondary infections, opportunistic fungal infections, reactivation of latent infections, gastrointestinal bleeding, and/or neuromuscular weakness. In addition, dexamethasone may reduce the efficacy of concomitant CYP3A4 substrates. These drug-related adverse effects may be more severe in older patients, especially in those with a cancer diagnosis who are also immunocompromised.

Monoclonal Antibodies

Monoclonal Antibodies (mAbs) may reduce the risk of COVID-19 progression and death, particularly if ritonavir-boosted nirmatrelvir and remdesivir are not available or clinically appropriate, but few data are available in older adults¹². Bebtelovimab or tixagevimab plus cilgavimab are authorised for SARS-CoV-2 pre-exposure prophylaxis in individuals who may have an inadequate immune response to COVID-19 vaccination or are ineligible for vaccination and who have not been exposed to the infection. These could include older patients with cancer and/or haematological malignancies undergoing anticancer treatment. While the TACKLE study³⁴ showed a statistically and clinically significant protection against progression to severe COVID-19 or death in unvaccinated individuals, only 13% (N = 116) were aged ≥ 65 years, limiting generalizability to older adults. Some mAbs are not effective against COVID-19 variants, so the prevalence of resistant variants should be considered in decision-making³⁵. The Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) phase 3 trial³⁶ showed that among high-risk outpatients, bamlanivimab plus etesevimab was associated with a lower incidence of hospitalisation and

death compared with placebo. The trial included 1,035 patients with one or more risk factors for severe COVID-19 (age ≥ 65 years; body-mass index ≥ 35 ; and coexisting conditions), with 31% aged ≥ 65 years. Adverse events were similar between groups, and no patients discontinued treatment due to toxicity. In a retrospective study including 429 patients aged ≥ 65 years with mild to moderate SARS-CoV-2, treatment with bamlanivimab or casirivimab/imdevimab was associated with a lower risk of hospitalisation³⁷. Sotrovimab also reduced the incidence of all-cause hospitalisation and death among patients with mild to moderate COVID-19. In this series of 520 patients, 20% were aged ≥ 65 years³⁸. Potential side effects include hypersensitivity, nausea, rash, dizziness, diarrhoea, and hypertension. As the Omicron variant has become dominant, the COVID-19 Treatment Guidelines Panel recommends against the use of bamlanivimab plus etesevimab, casirivimab plus imdevimab or sotrovimab for the treatment of COVID-19 disease¹².

Molnupiravir

In December 2021, molnupiravir was authorized for the treatment of adults with mild to moderate COVID-19 infection at high risk of progression to severe disease, within five days of symptom onset and for whom alternative antiviral therapies are unaffordable or clinically inappropriate³⁹. Data from the phase 3 MOVE-OUT trial⁴⁰ showed that molnupiravir reduced the risk of hospitalisation or death in at-risk, unvaccinated adults with COVID-19. The analysis included 1,433 participants, of whom 17% were aged ≥ 60 years. Among the participants, 74% had a body mass index ≥ 30 and 16% were affected by diabetes. Only 29 patients, representing 2% of the entire sample, had any active cancer. Serious adverse events (diarrhoea, nausea, and dizziness) were less frequent in the molnupiravir group. No drug-drug interactions were observed. Severely immunocompromised adults, such as patients affected by haematological malignancies receiving anticancer treatment, may have prolonged SARS-CoV-2 replication potentially leading to rapid viral evolution. In this setting,

a single antiviral agent may be associated with the development of variants resistant to antivirals¹². However, the role of combined antiviral therapy in severely immunocompromised patients is still unclear and more research is warranted.

Tocilizumab

The anti-interleukin (IL)-6 monoclonal antibody tocilizumab has been utilised for hospitalised patients with COVID-19 infection requiring supplemental oxygen or ventilatory support. The RECOVERY study⁴¹ randomised 4,116 patients with progressive COVID-19 to tocilizumab versus standard care. Tocilizumab was associated with a lower 28-day mortality compared to standard care alone (Tocilizumab: 31%; standard care: 35%; rate ratio 0.85; 95%CI 0.76-0.94; $p=0.0028$). The mean age was 64 years, including 11% of patients aged >80 years in the tocilizumab group and 12% in standard care. No differences in comorbidities were found between both groups. A Spanish single centre retrospective observational study⁴², documented a survival benefit in hospitalised patients aged >80 years with tocilizumab plus corticosteroids (HR 0.09, 95%CI: 0.01–0.74), with no benefits seen in patients receiving corticosteroids alone (HR 0.95, 95%CI: 0.53–1.71).

Convalescent Plasma

COVID-19 convalescent plasma (CCP) is authorised for use in immunocompromised patients. A randomised, double-blind, placebo-controlled trial of 160 non-hospitalised older patients showed that early administration of CCP to mildly ill older patients reduced disease progression. The study was conducted in 160 immunocompetent older adults affected by one or more comorbidities. Participants' mean age was 77 years, 45% were aged 65-74 years, and 55% were ≥ 75 years. No imbalances in baseline characteristics were found between CCP and placebo groups⁴³. Serious adverse reactions were infrequent and consistent with those of plasma infusions for other indications. Most clinical trials were completed before the appearance of circulating SARS-CoV-2 variants, so data regarding the use of CCP against variants are not available¹².

Miscellaneous Drugs

Trials that evaluated colchicine in outpatients with COVID-19 failed to reach the efficacy endpoint of reducing hospitalizations and death⁴⁴, or the time of recovery from COVID-19⁴⁵. In addition, more gastrointestinal adverse events were reported in patients receiving colchicine. Due to the lack of specific data, fluvoxamine should not be used as a preferred option for older adults with cancer. Regarding ivermectin, more data are needed to evaluate the use of this drug in the treatment of COVID-19¹².

Recommendations and Conclusions

Relative to the disease burden of COVID-19 among older adults, especially those with cancer, this population is underrepresented in most clinical trials of COVID-19 therapeutics, and evidence for making strong recommendations is lacking. In light of this limited evidence, the SIOG COVID-19 Working Group recommends following existing guidelines for other populations of older adults, and prioritizing treatments based on their availability, efficacy, and safety profile (Table 1). The following recommendations mainly concern outpatients.

Table 1 Recommendations of the SIOG COVID-19 working group on the use of COVID-19 drugs in older adults and in older patients with cancer

COVID-19 THERAPEUTICS AND RECOMMENDATIONS	SPECIFIC CONSIDERATIONS IN OLDER ADULTS WITH CANCER
Ritonavir-boosted nirmatrelvir is recommended for the early treatment of non-hospitalised older adults with cancer affected by mild or moderate COVID-19 at high risk of disease progression who do	<ul style="list-style-type: none"> • Monitoring of gastrointestinal side effects is required. • Pharmaceutical analysis of patient concomitant medications and potential drug-drug interactions, especially in polypharmacy, is requested before prescribing treatment. (https://www.covid19druginteractions.org/checker)

<p>not require supplemental oxygen, particularly those who have not completed an approved vaccination schedule.</p>	<ul style="list-style-type: none"> • Particular attention is required in older adults with cancer because of the risk of interactions with immunosuppressants and of increasing concentrations of concomitant chemotherapeutic agents. • Adapted dosing is required in patients affected by moderate kidney disease. In severe disease category, evaluation of treatment risk/benefit is requested. • Particular attention is required in patients affected by liver diseases. Treatment is not recommended in severe hepatic impairment. • Treatment is available in oral form. An evaluation of cognitive function, social support, and ability to adhere to treatment is recommended before starting therapy in older adults with cancer.
<p>Remdesivir is recommended for the early treatment of non-hospitalised older adults with cancer with mild or moderate COVID-19 at high risk of disease progression who do not require supplemental oxygen or for whom minimal supplemental oxygen is required, particularly those who have not completed an approved vaccination schedule.</p> <p>Remdesivir might be co-prescribed with systemic corticosteroids for the treatment of hospitalised older adults with cancer and COVID-19 who require high-</p>	<ul style="list-style-type: none"> • Monitoring of gastrointestinal side effects is required. • Evaluation of liver function and prothrombin time tests is required before starting and during treatment. • Adapted dose is required in patients affected by moderate kidney disease. In severe disease category, evaluation of treatment risk/benefit is required. • The feasibility of administering parenteral medications in the outpatient setting must be considered. An evaluation of the patient's ability to obtain transportation and of social support is recommended.

<p>flow device supplemental oxygen or non-invasive ventilation.</p>	
<p>Treatment with corticosteroids is recommended for hospitalised older adults with cancer and COVID-19 who require supplemental oxygen, high-flow oxygen, non-invasive ventilation, or mechanical ventilation.</p>	<ul style="list-style-type: none"> • The use of corticosteroids in the older adults and in older patients with cancer may be associated with side effects such as delirium and falls. The risk/benefit decision must be evaluated for each individual patient, and evidence-based geriatric interventions should be implemented early. • Pharmaceutical analysis of patient's concomitant medications and potential drug-drug interactions, especially in polypharmacy, is required before prescribing treatment • Close inpatient monitoring of potential side effects, especially in patients affected by geriatric syndromes, coexisting conditions, solid tumour and/or haematological malignancies, and polypharmacy. • Careful monitoring of secondary infections, opportunistic fungal infections, reactivation of latent infections, is necessary in older patients with cancer, particularly those who are receiving immunosuppressants.
<p>Monoclonal antibodies should not be the first option for the treatment of older adults with cancer and COVID-19, due to the lack of older-adult specific data and the low effectiveness against newer COVID-19 strains. Monoclonal antibodies could be utilized in cases where other more effective therapies are not available, particularly in those who have</p>	<p>Due to the lack of older adult specific data and the availability of other antiviral agents with improved results, monoclonal antibodies should not be a preferred option for older adults with cancer.</p>

not completed an authorized vaccination schedule or who may not have an appropriate antibody response.	
Molnupiravir should not be the first option for the treatment of non-hospitalised older adults with cancer affected by mild or moderate COVID-19. This treatment could be considered in cases where alternative antiviral therapies are not accessible or clinically appropriate.	Due to the lack of older adult specific data, the under-representation of patients with cancer in clinical trials, and the availability of other antiviral agents demonstrating better outcomes, molnupiravir should not be used as a preferred option for older adults with cancer.
Tocilizumab should be considered in hospitalised older adults with cancer and COVID-19 who require supplemental oxygen, high-flow oxygen, non-invasive ventilation, or mechanical ventilation.	Due to the lack of older adult specific data and the under-representation of patients with cancer in clinical trials, tocilizumab should not be the preferred treatment in older adults with cancer and should only be utilized in conjunction with other treatments.
Although COVID-19 convalescent plasma is authorized for patients with COVID-19 affected by immunocompromising conditions or receiving immunosuppressive treatment, data regarding its effectiveness is scarce.	Available data on effectiveness do not allow to make a recommendation regarding the use of convalescent plasma in older adults with cancer.

SARS-CoV-2: severe acute respiratory syndrome coronavirus-2

Despite the development and use of new therapies against COVID-19, the key intervention to protect older adults with cancer worldwide is increasing the availability of vaccines and

implementing evidence-based public health measures. Since older adults are at high risk for severe complications of COVID-19, vaccination programmes are critical and should also include caregivers.

Most of the reviewed studies included very selected patient populations, few older adults, and a minimal number of patients with active cancer. Although some observational studies also support the efficacy, safety, and efficiency of COVID-19 therapies in populations seen routinely in clinical practice, such as older adults with cancer, more research is needed to explore the efficacy of novel therapeutics against COVID-19 variants in the context of the emerging new variants with enhanced transmissibility or virulence, and in vaccinated populations. Early diagnosis of COVID-19 is also required to expedite the use of appropriate treatment.

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Author Contributions

Study Concepts and design: CR, AM, DF, ES, GC, GW, S OH, LC, A OD, RA, KL C, R GS, RS, MJ, CC, LA G, SS, KK, KL, SL, EB, HW, RK, NB

Collection and assembly of data: CR, DF

Data analysis and interpretation: CR, DF

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