Letter to the editor

Title:

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

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

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 immunogenicity[1]. 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 vaccination[2-5], which may lead to worse COVID-19 clinical outcomes[6-10]. 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 treatments[11]. 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 progression[12]. 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 outcomes[13]. 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 options[12]. 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 range[14]. The Evaluation of Protease Inhibition for COVID-19 in High-Risk patients (EPIC-HR) phase 2–3 trial[15] 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, 12% 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 events[17].

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 agents[12]. 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/ritonavir[18].

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) trial[22] 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 survival[23]. 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 frailty[24]. The phase 3, randomised, controlled, open-label DisCoVeRy trial[25], 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 cancer [26]. Remdesivir may be associated with gastrointestinal toxicity, elevated transaminase levels, prolonged prothrombin time without change in the international normalized ratio, and hypersensitivity reactions[19]. 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 risks[29]. A study by Kanai 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 oxygen[12]. The multicentre, open-label, Randomized Evaluation of COVID-19 Therapy (RECOVERY) study[31], 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) study[33] 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 adults[12]. 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 study[34] 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-making[35]. The Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) phase 3 trial[36] 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 hospitalisation[37]. 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 years[38]. 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 disease[12].

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 inappropriate[39]. Data from the phase 3 MOVe-OUT trial[40] 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 antivirals[12]. 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 study[41] 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 study[42], 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 groups[43]. 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 available[12].

Miscellaneous Drugs

Trials that evaluated colchicine in outpatients with COVID-19 failed to reach the efficacy endpoint of reducing hospitalizations and death[44], or the time of recovery from COVID-19[45]. 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-19[12].

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	• Monitoring of gastrointestinal side effects is required.

of non-hospitalised older adults with cancer affected by mild or moderate COVID-19 at high risk of disease progression who do not require supplemental oxygen, particularly dose who have not completed an approved vaccination schedule.	• Pharmaceutical analysis of patient concomitant medications and potential drug-drug interactions, especially in polypharmacy, is requested before prescribing treatment. (https://www.covid19druginteractions.org/checker) • Particular attention is required in older adults with cancer because of the risk of interactions with **i**mmunosuppressants 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.
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.	• 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

Remdesivir might be co-prescribed with systemic corticosteroids for the treatment of hospitalised older adults with cancer and COVID-19 who require high-flow device supplemental oxygen or non-invasive ventilation.	considered. An evaluation of the patient's ability to obtain transportation and of social support is recommended.
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.	• 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.
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-	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.

19 strains. Monoclonal antibodies could be utilized in cases where other more effective therapies are not available, particularly in those who have 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 were 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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References

1. Collier DA, Ferreira IATM, Kotagiri P et al. Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. Nature 2021 596; 417-422

2. Barriere J, Chamorey E, Adjtoutah Z, et al. Impaired immunogenicity of BNT162b2 anti-SARS-CoV-2 vaccine in patients treated for solid tumors. Ann Oncol. 2021; 32(8):1053-1055

3. Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood. 2021;137(23):3165-3173

4. Kuderer NM, Choueiri TK, Shah DP, et al. COVID-19 and Cancer ConsortiumClinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet 2020; 395(10241):1907-1918

5. Grivas P, Khaki A R, Wise-Draper T M, et al. Association of clinical factors and recent anticancer therapy with COVID-19 severity among patients with cancer: a report from the COVID-19 and Cancer Consortium. Ann Oncol 2021; 32(6):787-800

6. Dai M, Liu D, Liu M, et al. Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. Cancer Discov. 2020; 10(6):783-791

7. Shah V, Ko Ko T, Zuckerman M, et al. Poor outcome and prolonged persistence of SARS-CoV-2 RNA in COVID-19 patients with haematological malignancies; King's College Hospital experience. Br J Haematol. 2020; 190(5):e279-e282

8. Yang K, Sheng Y, Huang C, et al. Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study. Lancet Oncol. 2020; 21(7):904-913

9. Robilotti EV, Babady NE, Mead PA, et al. Determinants of COVID-19 disease severity in patients with cancer. Nat Med. 2020; 26(8):1218-1223

10. Giannakoulis VG, Papoutsi E, Siempos, II. Effect of cancer on clinical outcomes of patients with COVID-19: a meta-analysis of patient data. JCO Glob Oncol. 2020; 6:799-808

11. Elkrief A, Hennessy C, Kuderer NM, et al. Geriatric risk factors for serious COVID-19 outcomes among older adults with cancer: a cohort study from the COVID-19 and cancer consortium. Lancet Healthy Longev 2022; 3:e143–52

12. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/

13. Battisti NML, Mislang AR, Cooper L, et al. Adapting care for older cancer patients during the COVID-19 pandemic: Recommendations from the International Society of Geriatric Oncology (SIOG) COVID-19 Working Group. J Geriatric Oncol 2020; 11:1190–8

14. Owen DR, Allerton CMN, Anderson AS, et al. An oral SARS-CoV-2 M(pro) inhibitor clinical candidate for the treatment of COVID-19. Science 2021; 374:1586-1593

15. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. N Engl J Med 2022; 386:1397-1408

16. Katzenmaier S, Markert C, Riedel KD, et al. Determining the time course of CYP3A inhibition by potent reversible and irreversible CYP3A inhibitors using a limited sampling strategy. Clin Pharmacol Ther. 2011; 90:666-73

17. Vazquez SR, Wilson AS, Witt DM. Management of potential drug-drug interactions with nirmatrelvir-ritonavir and oral anticoagulants: a case series. J Thromb Thrombolysis. 2022; 54(4): 583–586

18. Hiremath S, McGuinty M, Argyropoulos C, et al. Prescribing Nirmatrelvir/Ritonavir for COVID-19 in Advanced CKD. Clin J Am Soc Nephrol. 2022; CJN.05270522

19. Remdesivir. Food and Drug Administration. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf

20. Benfield T, Bodilsen J, Brieghel C, et al. Improved Survival Among Hospitalized Patients With Coronavirus Disease 2019 (COVID-19) Treated With Remdesivir and Dexamethasone. A Nationwide Population-Based Cohort Study. Clin Infect Dis. 2021; 73:2031-2036

21. Wong CKH, Lau KTK, Au ICH, et al. Optimal timing of remdesivir initiation in hospitalized COVID-19 patients administered with dexamethasone. Clin Infect Dis. 2021; ciab728

22. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19—final report. N Engl J Med. 2020; 383:1813-1826

23. Mozaffari E, Chandak A, Zhang Z, et al. Remdesivir Treatment in Hospitalized Patients With COVID-19: A Comparative Analysis of In-hospital All-cause Mortality in a Large Multicenter Observational Cohort. Clinical Infectious Diseases 2021; ciab875

24. Falcone M, Suardi LR, Tiseo G, et al. Early use of remdesivir and risk of disease progression in hospitalized patients with mild to moderate COVID-19. Clin Ther 2022; 44(3):364-373.

25. Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a Phase 3, randomised, controlled, open-label trial. Lancet Infect Dis. 2022; 22(2): 209–221

26. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. N Engl J Med. 2022; 386:305-315

27. Pettit NN, Pisano J, Nguyen CT, et al. Remdesivir use in the setting of severe renal impairment: a theoretical concern or real risk? Clin Infect Dis. 2021; 73:e3990-e3995

28. Ackley TW, McManus D, Topal JE, et al. A valid warning or clinical lore: an evaluation of safety outcomes of remdesivir in patients with impaired renal function from a multicenter matched cohort. Antimicrob Agents Chemother. 2021; 65(2): e02290-20

29. Adamsick ML, Gandhi RG, Bidell MR, et al. Remdesivir in patients with acute or chronic kidney disease and COVID-19. J Am Soc Nephrol. 2020; 31 (7) 1384-1386

30. Kanai O, Fujita K, Nanba K et al. Safety of remdesivir for patients 80 years of age or older with Coronavirus Disease 2019 (COVID-19). Drugs Aging 2021; 38(12):1067-1074

31. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021; 384:693-704

32. Gallay L, Tran VT, Perrodeau E, et al. Fourteen day survival among older adults with severe infection with severe acute respiratory syndrome Coronavirus 2 treated with corticosteroid: a cohort study. Clin Microbiol Infect 2021; 27(8):1145-1150

33. Jung C, Wernly B, Fjølner J, et al. Steroid use in elderly critically ill COVID-19 patients. Eur Respir J 2021; 58:2100979

34. Montgomery H, Richard Hobbs F D, Padilla F, et al. Efficacy and safety of intramuscular administration of tixagevimab-cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2022; S2213-2600(22)00180-1

35. Hoffmann M, Krüger N, Schulz S, et al. The Omicron variant is highly resistant against antibody-mediated neutralization: implications for control of the COVID-19 pandemic. Cell 2022; 185:447-456.e11

36. Dougan M, Nirula A, Azizad M, et al, the BLAZE-1 Investigators. Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. N Engl J Med. 2021; 385:1382-1392

37. Sobolewski KA, Smoke S, Brophy A, et al. Real-world evaluation of the impact of two anti-SARS-CoV-2 monoclonal antibody regimens on COVID-19 hospitalizations in older adults. Medical virology 2022; 94:2493-2499.

38. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Effect of sotrovimab on hospitalization or death among high-risk patients with mild to moderate COVID-19: a randomized clinical trial. JAMA. 2022; 327:1236-1246

39. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for molnupiravir. 2021.

40. Bernal A, Gomes da Silva M, Musungaie D, el al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med 2022; 386(6):509-520

41. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021; 397:1637-1645

42. Duarte-Millan MA, Mesa-Plaza N, Guerrero-Santillan M et al. Prognostic factors and combined use of tocilizumab and corticosteroids in a Spanish cohort of elderly COVID-19 patients. J Med Virol 2022; 94:1540-1549

43. Libster R, Perez Marc G, Wappner D, et al. Early high-titer plasma therapy to prevent severe COVID-19 in older adults. N Engl J Med. 2021; 384:610-618

44. Tardif JC, Bouabdallaoui N, L'Allier PL, et al. Colchicine for community-treated patients with COVID-19 (COLCORONA): a Phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. Lancet Respir Med. 2021;9(8):924-932

45. Dorward J, Yu L, Hayward G, et al. Colchicine for COVID-19 in the community (PRINCIPLE): a randomised, controlled, adaptive platform trial. Br J Gen Pract. 2022