SARS-COV-2: LA TERAPIA ANTIVIRALE

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Disclosures

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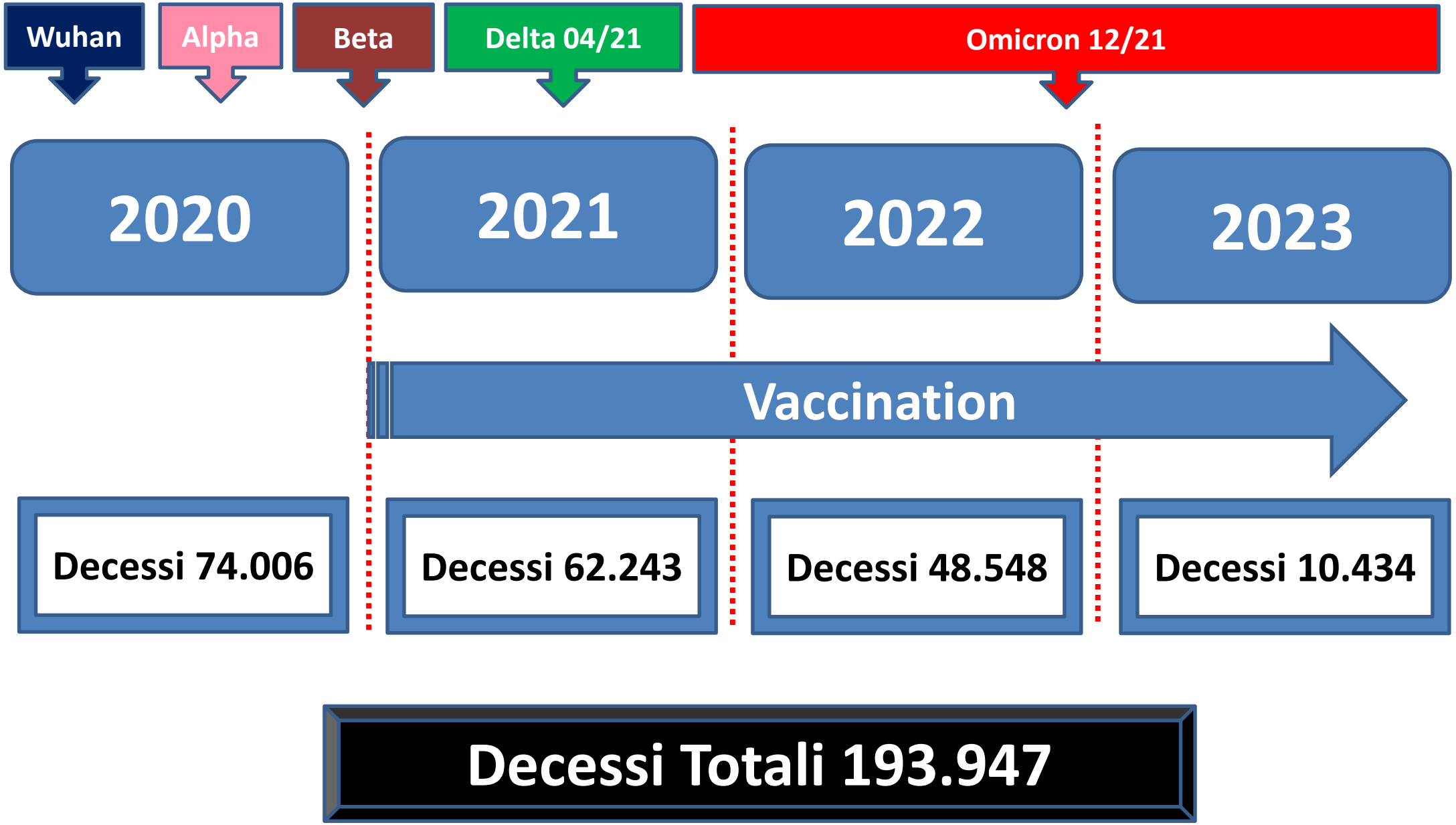
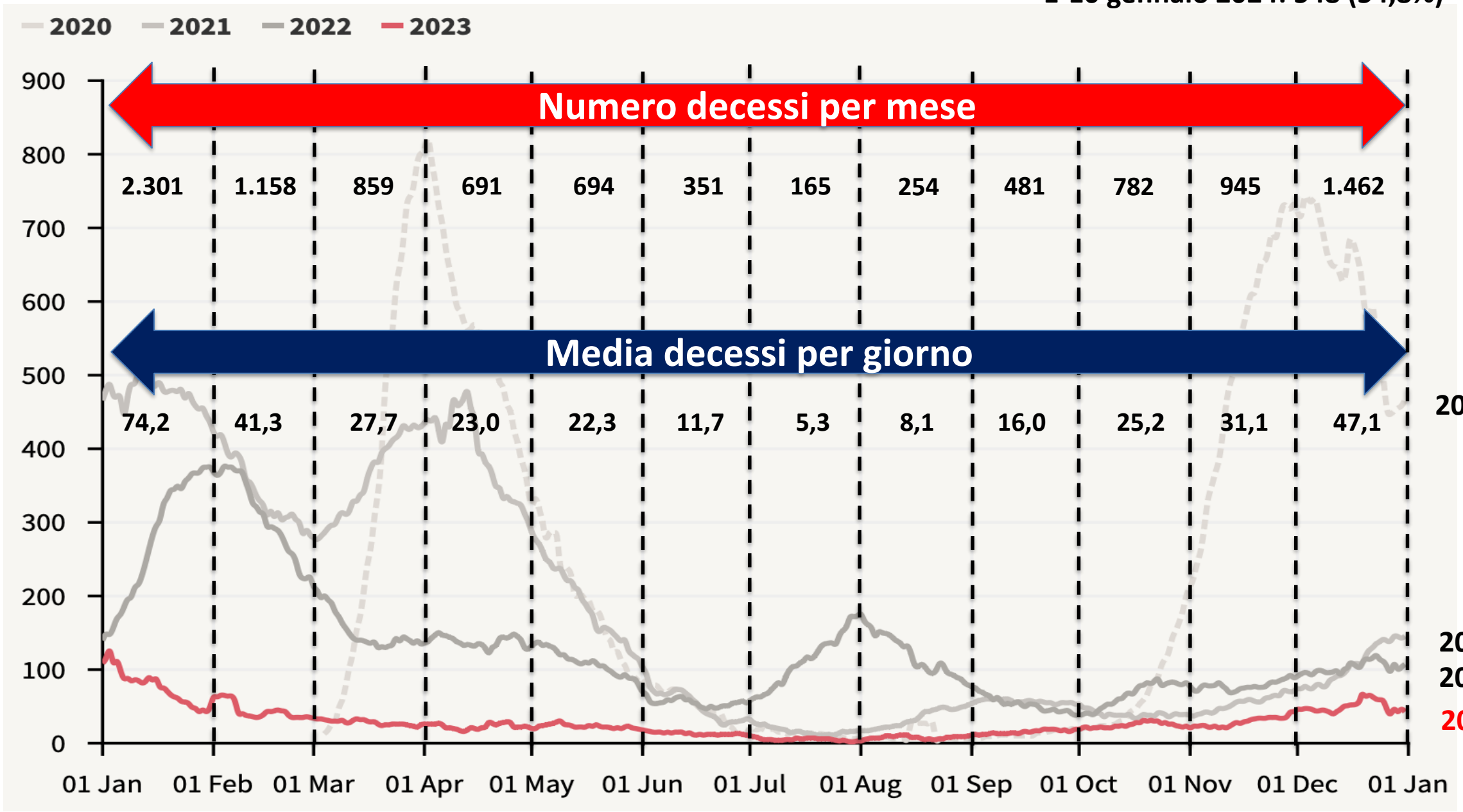
- Merck Sharp and Dohme
- Abbvie
- Angelini
- Pfizer
- GSK
- Menarini
- Astra-Zeneca

Decessi per COVID-19 in Italia

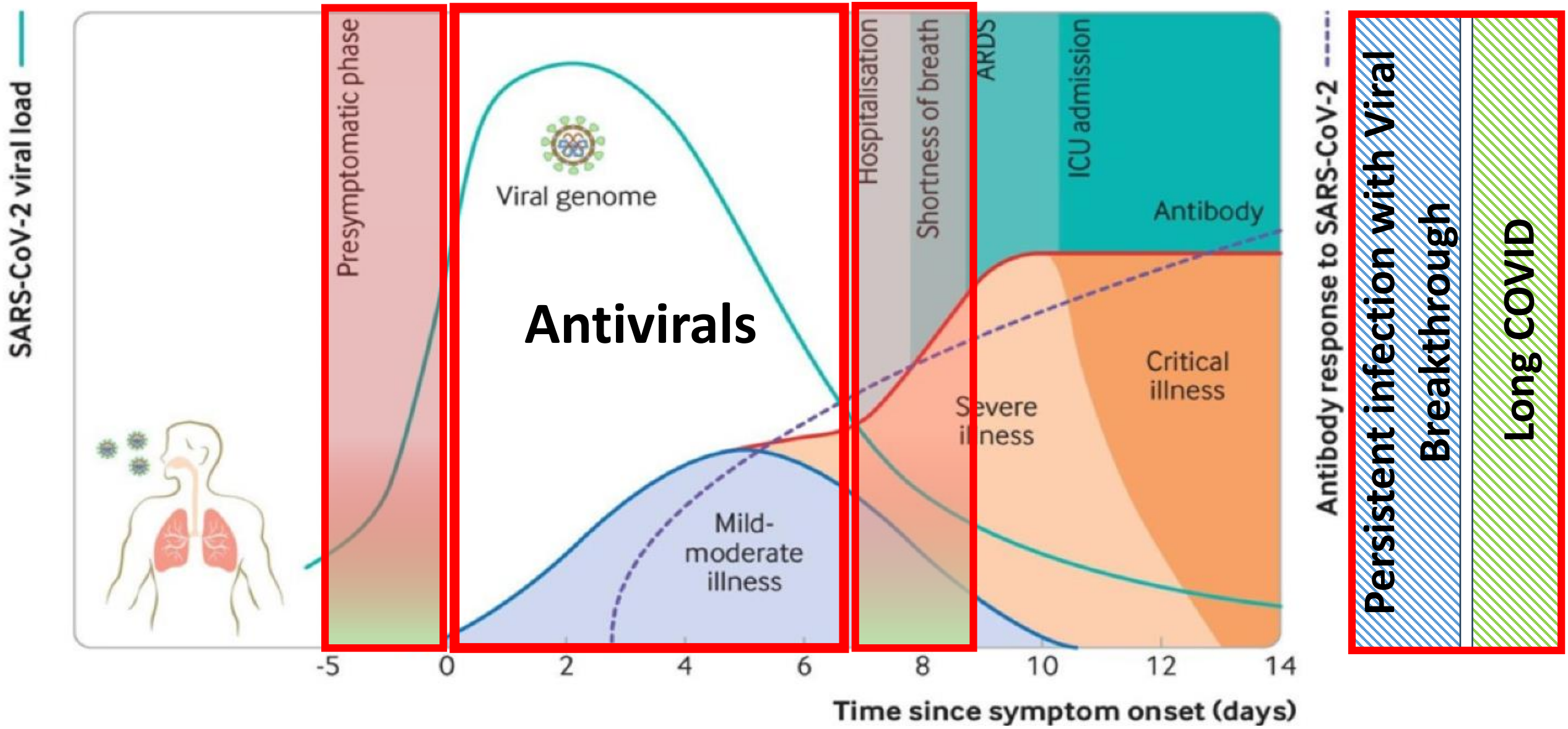


Confronto numero di decessi per COVID-19 nei mesi del 2023

1-10 gennaio 2024: 548 (54,8%)

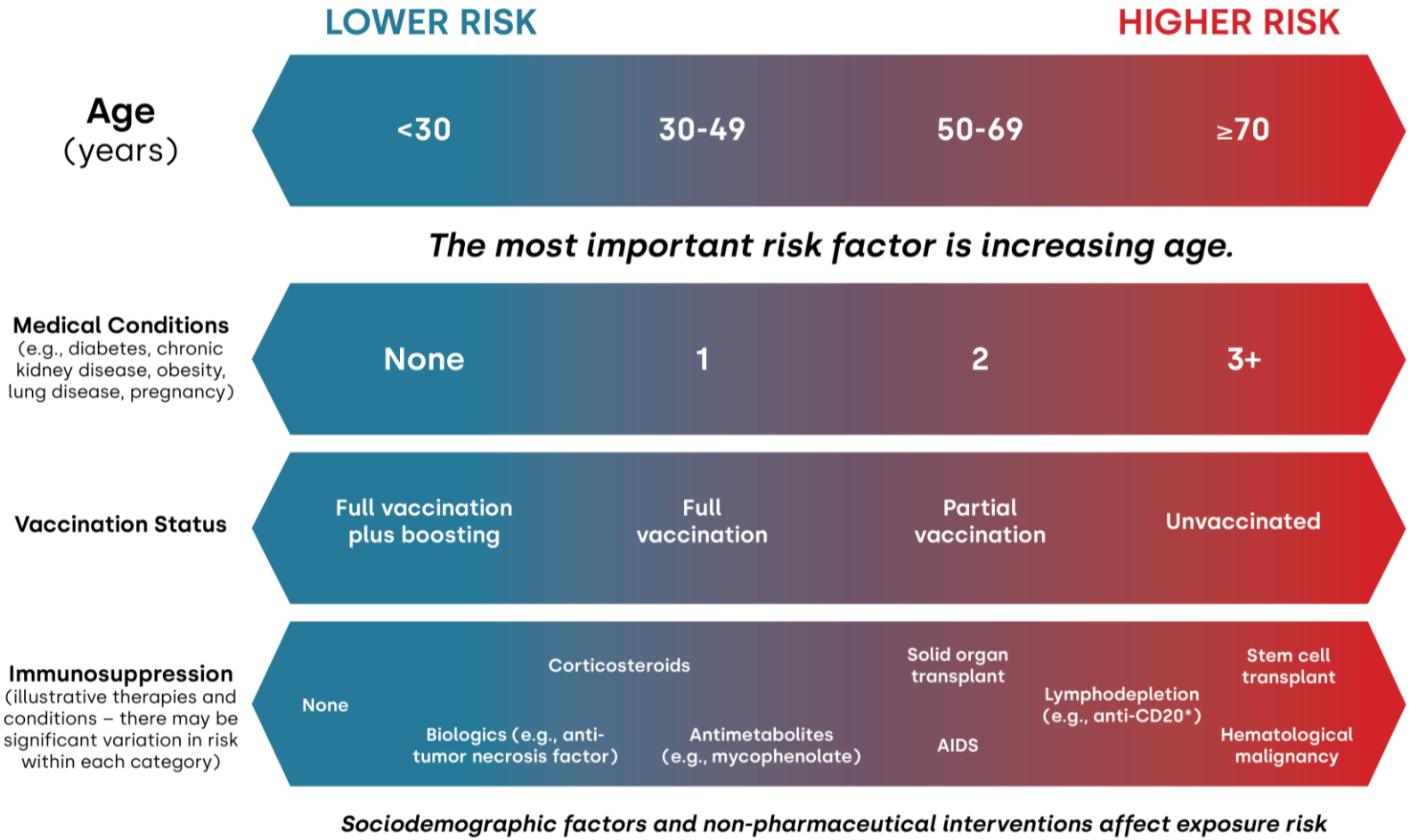


Clinical Manifestations of COVID-19 and Antiviral Therapy



Modifierd Cevik M BMJ 2020; 371:m3862

COVID-19 Risk Continuum



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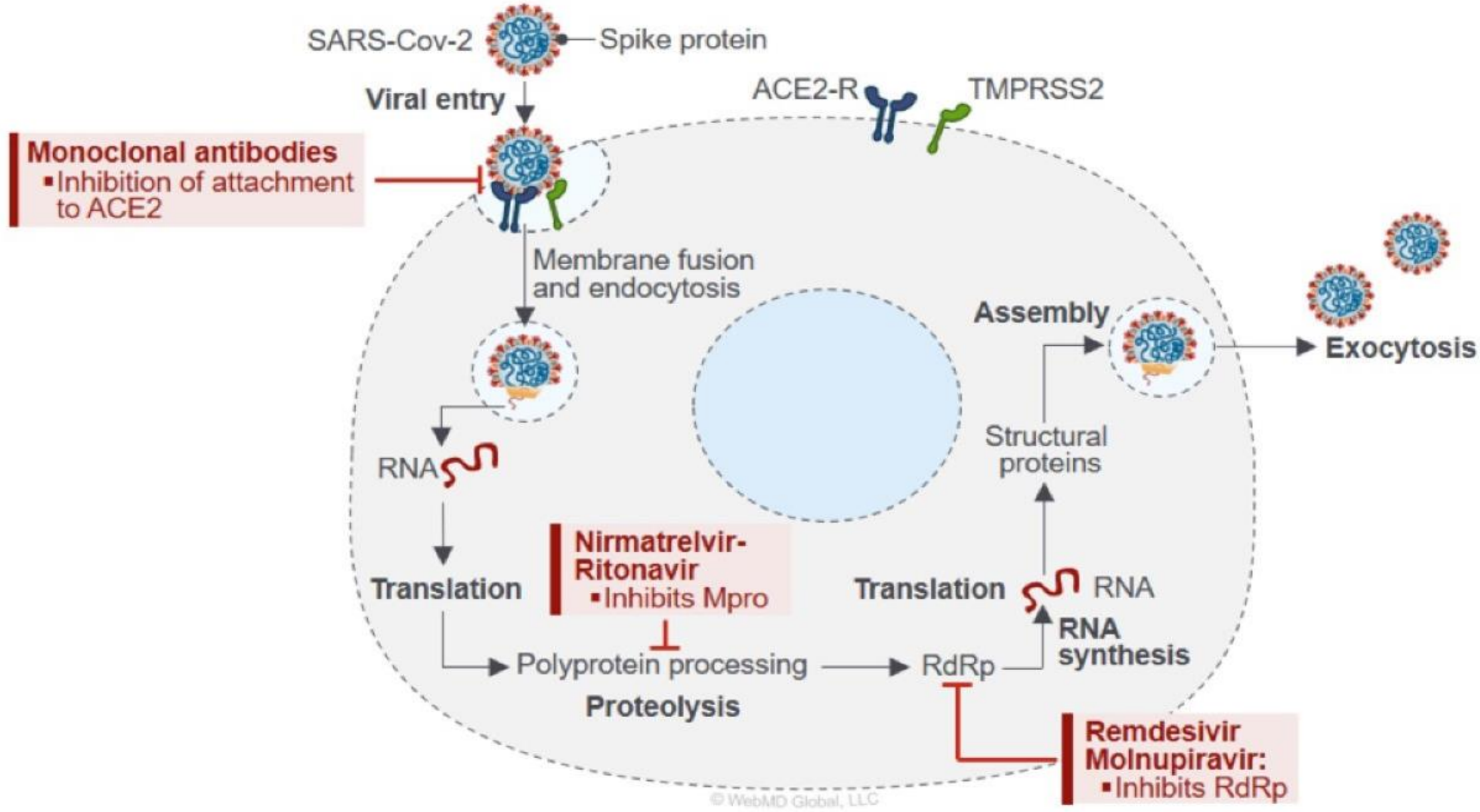
Original illustration by Dr. William Werbel. Adapted for the COVID-19 Real-Time Learning Network. Brought to you by CDC and IDSA

https://www.idsociety.org/covid-19-real-time-learning-network/disease-manifestations--complications/understanding-risk-for-severe-covid-19/

COVID-19 Antiviral Mechaninsm of Action



Rahmah L, et al. Pharmacol Rep. 2022;74:1255–1278.

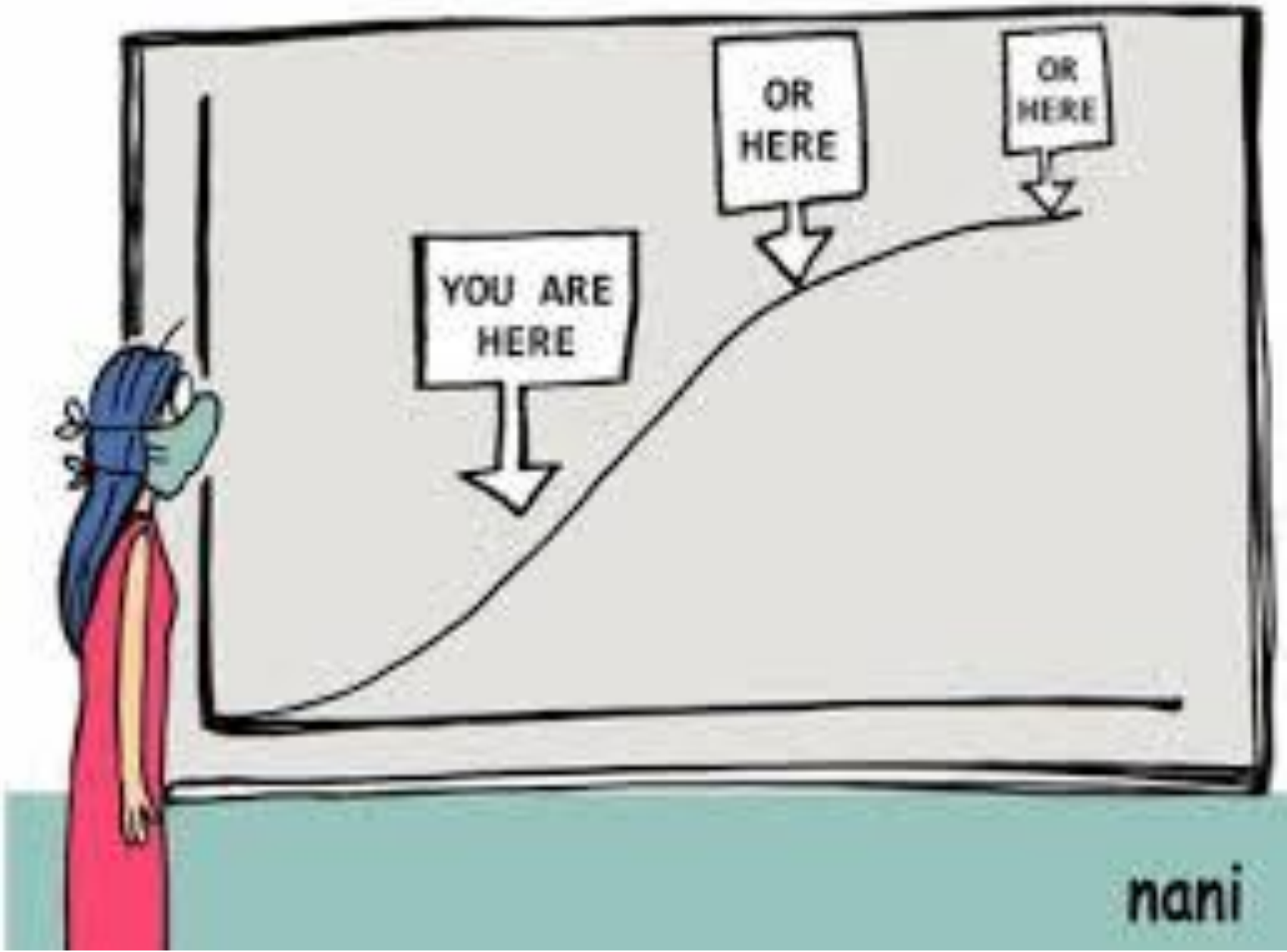
Antiviral treatment of SARS-Cov-2 infection

- **Antivirali diretti**

✓Nirmatrelvir/ritonavir
✓Remdesivir
✓Molnupiravir
✓Ensitrelvir

- **MoAbs**

✓Sotrovimab



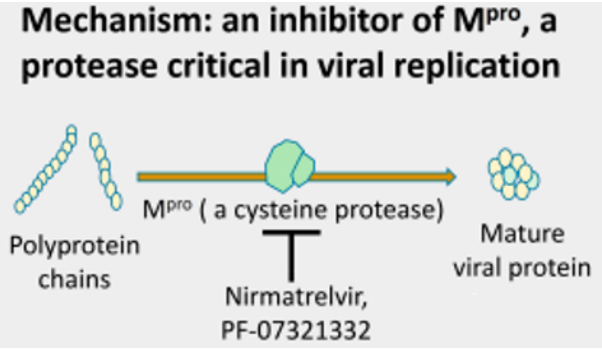
La terapia antivirale per la malattia COVID-19 rappresenta oggi uno dei principali successi per il contenimento della pandemia

Remdesivir, (molnupiravir) e nirmatrelvir/ritonavir mantengono l'efficacia nei confronti di tutte le diverse varianti e sottovarianti virali

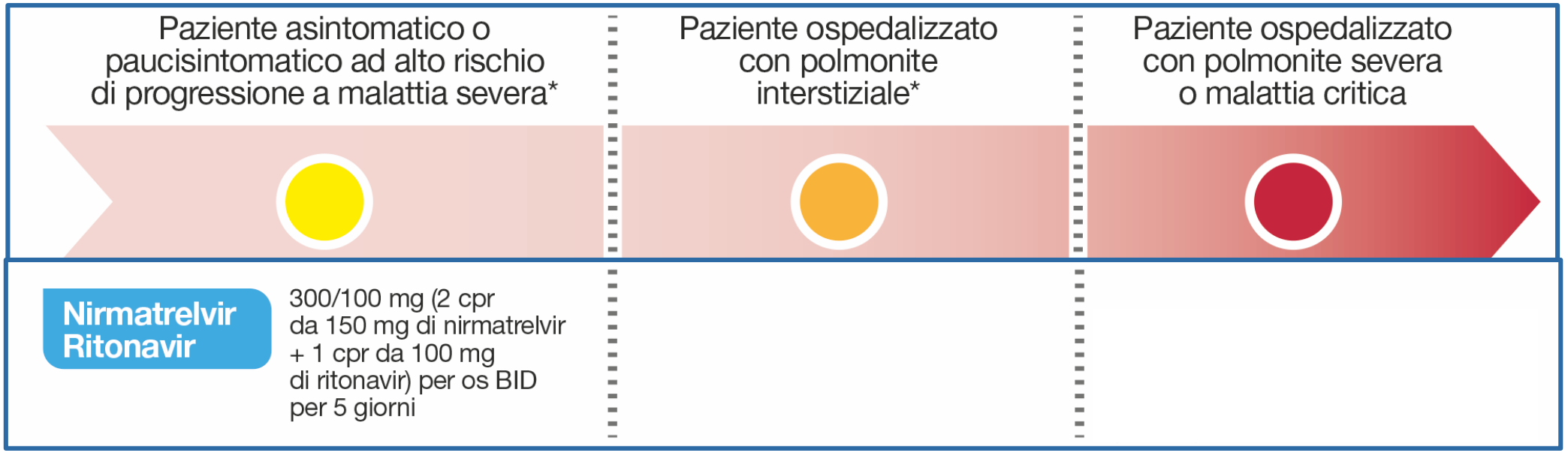
Questioni aperte

- Impatto dell'abbattimento rapido della carica virale con farmaci antivirali sul rischio della comparsa di sintomatologia riconducente a *Long-Covid*
- Prolungamento del tempo di somministrazione dei farmaci e/o della necessità di eseguire più cicli terapeutici soprattutto in soggetti immunocompromessi per contenere casi di *breakthrough* virale
- Combinazioni di farmaci antivirali, anche in relazione alla dimostrazione di una attività sinergica *in vitro* nei confronti del virus

Nirmatrelvir/ritonavir

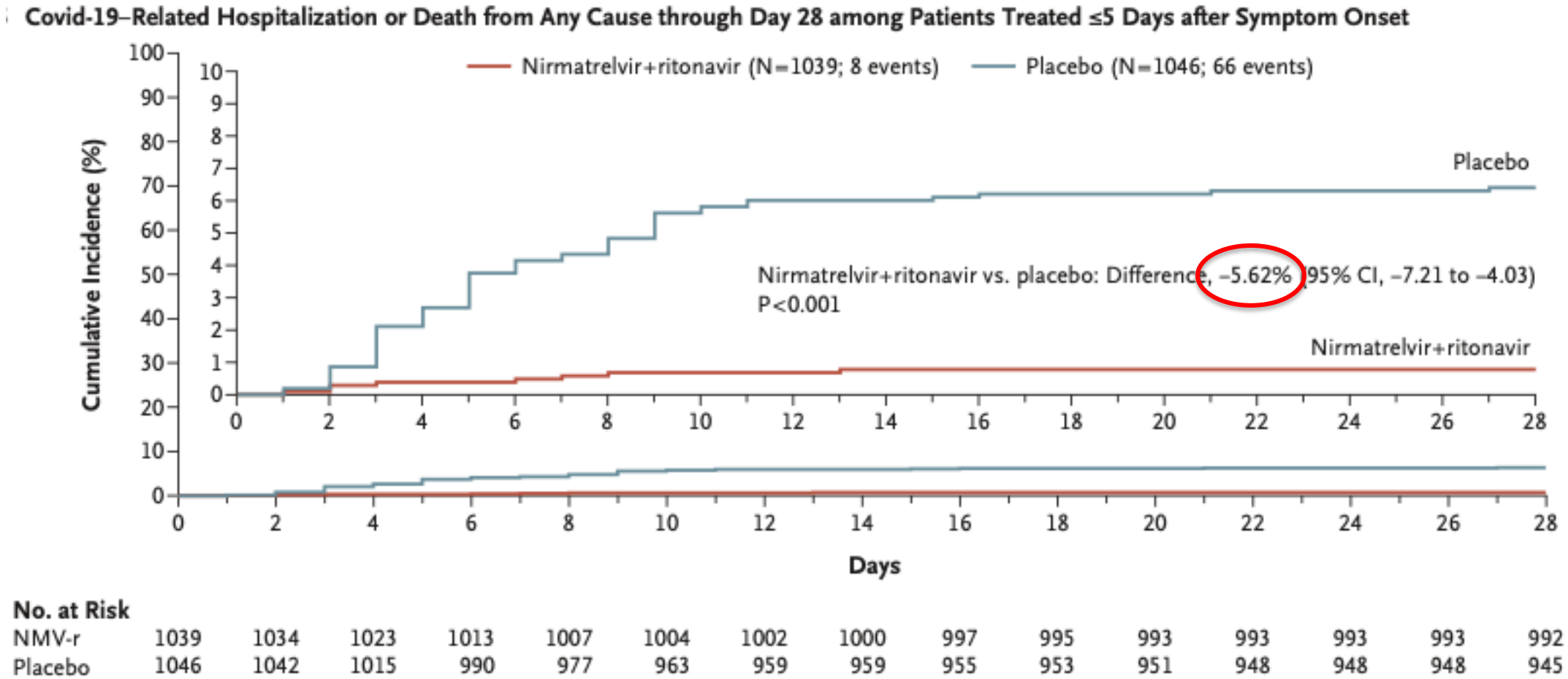


- **Inibitore della proteasi con booster**
- adulti **che non necessitano di ossigenoterapia** supplementare e che sono **ad elevato rischio di progressione*** a COVID-19 severa
- somministrato 300/100 mg/BID per 5 giorni ed **entro 5 giorni** dall'insorgenza dei sintomi
- eGFR <30 mL/minuto: controindicato; eGFR 30-60 mL/minuto: metà dose nirmatrelvir
- Non usare se Child-Pugh C



The NEW ENGLAND JOURNAL of MEDICINE

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19



L'efficacia è stata mantenuta nell'analisi finale su 1.379 pazienti (mITT) con una differenza di -5,62 punti percentuali (IC95%: -7,78 - -3,84; p<0.001) con riduzione del rischio relativo: 88,9%.

Tutti i 13 decessi si sono verificati nel gruppo placebo

Hammond J NEJ April 14, 2022 vol. 386 no.

Anti-SARS-CoV-2 Antiviral Drugs: Nirmatrelvir/ritonavir

Drug name	Dosing regimen	Adverse events	Drug-drug interaction potential	Comment
RTV-boosted nirmatrelvir FDA approved in adults and authorized under an FDA EUA in children for high-risk mild-to-moderate COVID-19	*eGFR ≥ 60 mL/min* ▪ Nirmatrelvir 300 mg (two 150-mg tablets) with RTV 100 mg (one 100-mg tablet) twice daily for 5 days *eGFR ≥ 30 to 60 mL/min* ▪ Nirmatrelvir 150 mg (one 150-mg tablet) with RTV 100 mg (one 100-mg tablet) twice daily for 5 days *eGFR < 30 mL/min* ▪ Not recommended *Severe hepatic impairment* ▪ Not recommended	▪ Dysgeusia ▪ Diarrhea ▪ Anaphylaxis, serious skin reactions, and other HSRs	▪ RTV-boosted nirmatrelvir has significant drug-drug interactions ▪ Before prescribing RTV-boosted nirmatrelvir, carefully review concomitant medications, including OTC medicines, herbal supplements, and recreational drugs	▪ Both nirmatrelvir and RTV tablets can be taken with or without food ▪ The FDA prescribing information/EUA advises against crushing nirmatrelvir and RTV tablets

eGFR, estimated glomerular filtration rate; EUA, emergency use authorization; FDA, Food and Drug Administration; HSR, hypersensitivity reaction; OTC, over-the-counter; RTV, ritonavir.

NIH COVID Treatment Guidelines. Table 4e. Characteristics of Antiviral Agents, Including Antibody Products. Accessed August 3, 2023. https://www.covid19treatmentguidelines.nih.gov/tables/antiviral-antibody-characteristics/

Nirmatrelvir + Ritonavir: CYP3A Metabolism

Select Recommendations	
Contraindicated	**Use With Caution**
↑ alfuzosin ↑ piroxicam ↑ ranolazine ↑ amiodarone ↑ anticancer drugs (eg, apalutamide) ↑ rivaroxaban ↑ colchicine ↑ glecaprevir/pibrentasvir ↑ salmeterol ↑ sildenafil ↑ midazolam ↓ voriconazole	↑↓ warfarin (monitor INR) ↑ apixaban ↑ dabigatran ↓ bupropion ↑ trazadone ↑ anti-HIV protease inhibitor (eg, darunavir) ↓ raltegravir ↑ clarithromycin/erythromycin ↑ rifabutin ↑ quetiapine ↑ digoxin ↓ ethinyl estradiol (use add'l contraception) ↑ immunosuppressants (eg, tacrolimus) ↑ corticosteroid (eg, prednisone) ↑ fentanyl ↓ methadone
Phenytoin, carbamazepine, rifampin, St John's wort all ↓ nirmatrelvir + ritonavir	*Hold if giving to avoid increase: lovastatin, simvastatin, atorvastatin, rosuvastatin, bosentan*

- Review patient's medications and supplements
- Nirmatrelvir + ritonavir = **CYP3A inhibitor**, so may increase levels of other drugs
- When used with CYP3A inducers, may not achieve adequate levels of nirmatrelvir

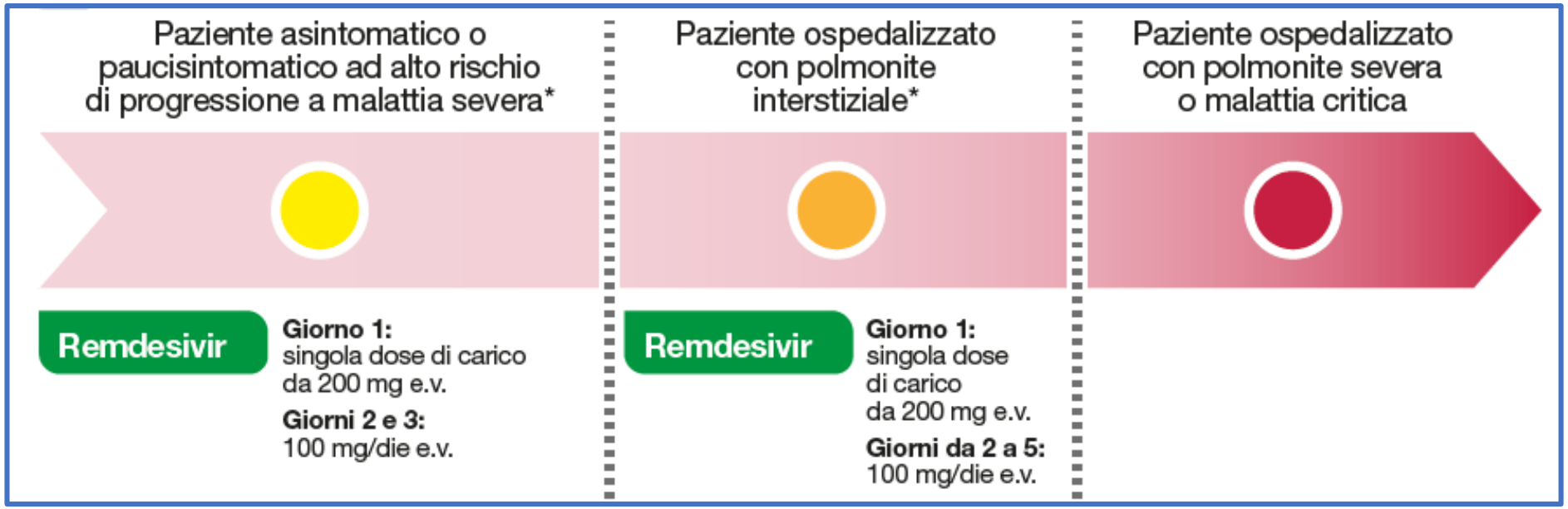
fda.gov/media/155050/download

Slide credit: clinicaleducationalliance.com: cea clinical education alliance

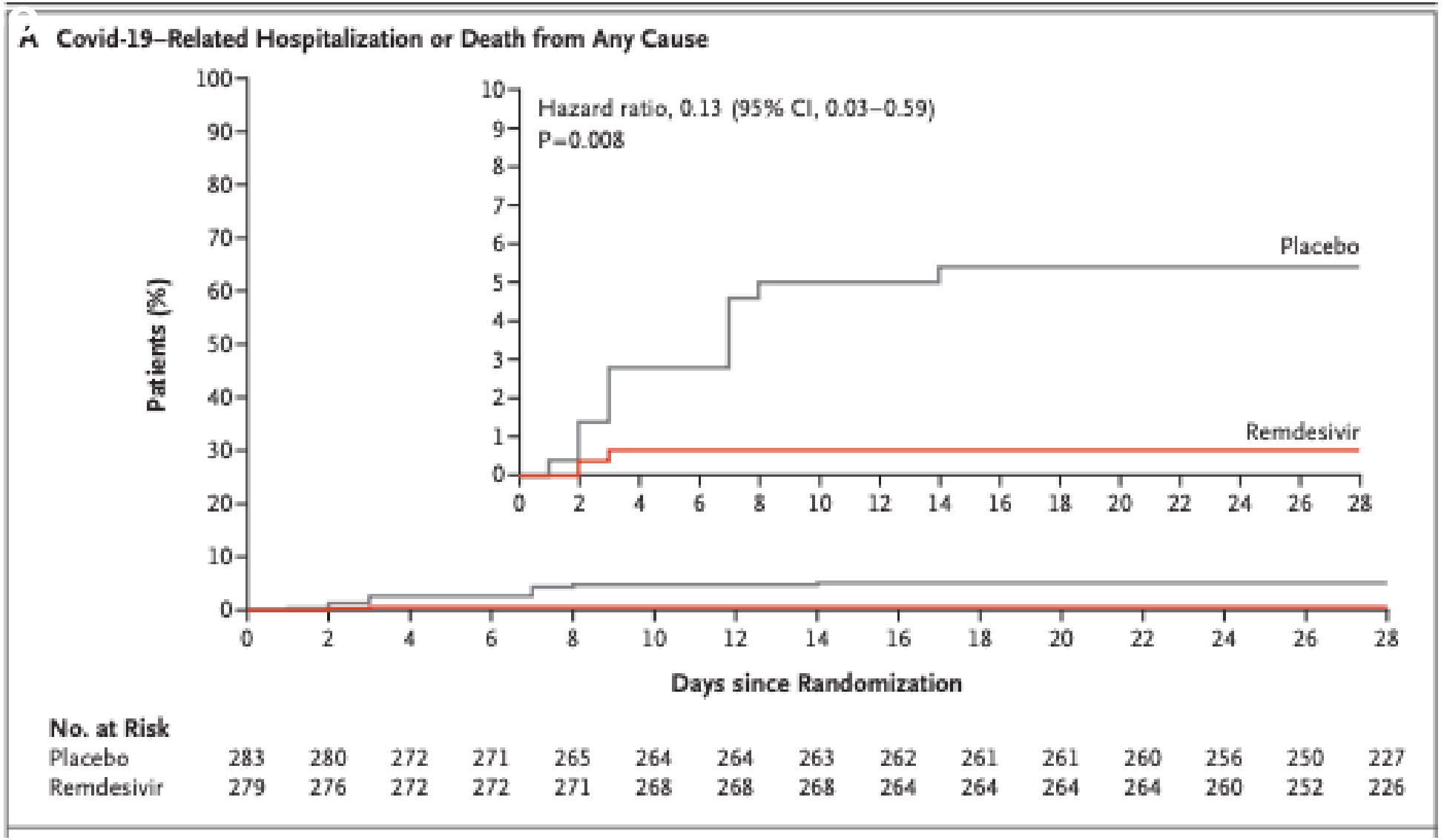
Remdesivir

- **Inibitore della polimerasi virale**
- eGFR >30 mL/minuto e ALT <5 volte il limite superiore dell'intervallo di riferimento
- **Soggetti non ospedalizzati**: somministrato per 3 giorni **entro 7 giorni** dalla comparsa dei sintomi
- funzionalità epato-renale conservata che non richiedono ossigenoterapia supplementare
- **Soggetti ospedalizzati**: somministrato per 5 giorni e non più di 10 giorni
- richiedono ossigenoterapia supplementare (bassi o alti flussi o altro tipo di ventilazione non invasiva)

- **Attività antivirale *in-vitro:*** filoviruses (Ebola) e coronaviruses (SARS-CoV e MERS-CoV)



A 3-day course of remdesivir had an acceptable safety profile and resulted in an 87% lower risk of hospitalization or death than



Anti-SARS-CoV-2 Antiviral Drugs: Remdesivir

Drug name	Dosing regimen	Adverse events	Drug-drug interaction potential	Comment
Remdesivir Approved by the FDA for the treatment of COVID-19 in individuals aged ≥ 28 days and weighing ≥ 3 kg	**Dose for Adults and Children Weighing ≥ 40 kg** ▪ RDV 200 mg IV on day 1, then RDV 100 mg IV once daily from day 2 **Dose for Children Aged ≥ 28 Days and Weighing 3 kg to < 40 kg** ▪ RDV 5 mg/kg IV on day 1, then RDV 2.5 mg/kg IV once daily from day 2 **Total Treatment Duration** *Non-hospitalized patients* ▪ 3 days *Hospitalized patients* ▪ 5 days or until hospital discharge ▪ If a patient does not clinically improve, clinicians may extend the treatment course for ≤ 5 days (total duration of 10 days)	▪ Nausea ▪ ALT and AST elevations ▪ HSRs ▪ Increases in prothrombin time	Clinical drug-drug interaction studies of RDV have not been conducted	RDV may be used without dose adjustment in patients with renal impairment, including those receiving dialysis

ALT, alanine transaminase; AST, aspartate aminotransferase; RDV, remdesivir.

NIH COVID Treatment Guidelines. Table 4e. Characteristics of Antiviral Agents, Including Antibody Products. Accessed August 3, 2023. https://www.covid19treatmentguidelines.nih.gov/tables/antiviral-antibody-characteristics/

IV Remdesivir in Patients With Severe Kidney Dysfunction
Secondary Analysis of the CATCO Randomized Trial

Study design

- Patients with impaired kidney function (eGFR < 30 mL/min/1.73 m^2 at randomization) received open-label remdesivir or best-quality supportive care
- Lyophilized remdesivir was diluted and administered intravenously with a loading dose of 200 mg on day 1, followed by daily 100-mg doses for 9 days or until discharge
- There was no dose adjustment for baseline kidney dysfunction or dialysis

Clinical Outcomes of Patients With eGFR < 30 mL/min/1.73 m^2 at Time of Randomization

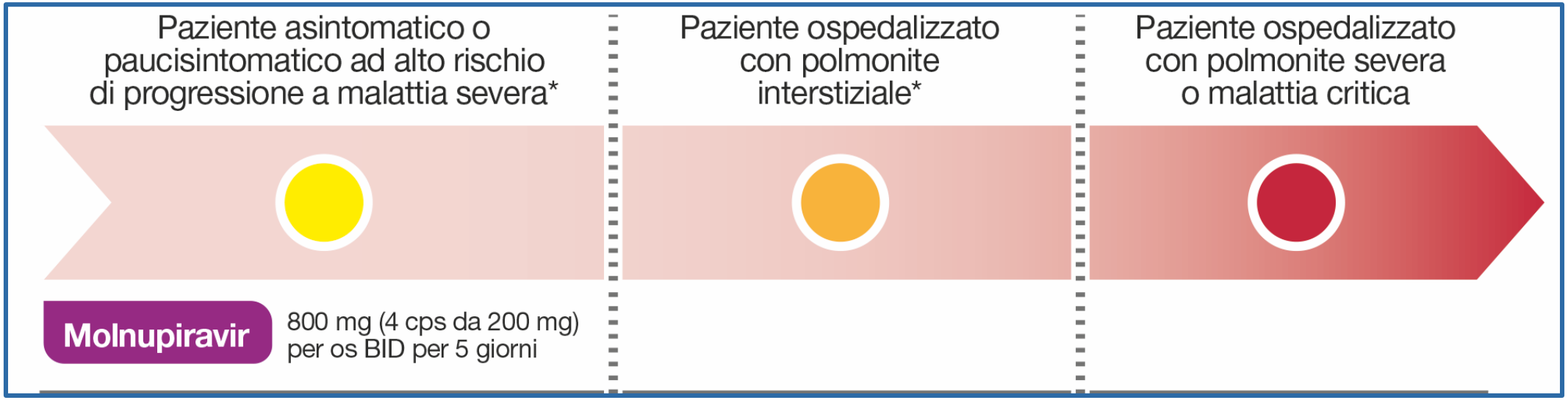
Variable	Remdesivir (n = 34)	Standard care (n = 25)	Difference in means (95% CI)
Hospital death, No. (%), unadjusted	13 (40.6)	13 (52.0)	RR, 0.78 (0.41 to 1.49)
New mechanical ventilation in those not ventilated at baseline, No. (%)	4 (14.8)	6 (26.1)	RR, 0.57 (0.15 to 1.80)
Total length of stay, d			
Mean (SD)	23.1 (20.5)	21.6 (28.8)	1.5 (-11.5 to 14.6)
Median (IQR)	16.5 (10-29.5)	11 (6-25)	NA
Day 5 creatinine, mg/dL[b]			
Mean (SD)	2.83 (2.15)	4.12 (2.41)	-1.29 (-2.66 to 0.09)
Median (IQR)	1.80 (1.32-3.40)	3.47 (2.02-5.99)	NA
Day 5 eGFR, mL/min/1.73 m^2[b]			
Mean (SD)	31.2 (19.2)	20.5 (13.9)	10.7 (0.20 to 21.2)
Median (IQR)	29.2 (14.2-45)	16.5 (8.5-30.9)	NA
ANCOVA for change in eGFR			-0.26 (-7.95 to 7.42)
Day 5 ALT[c]			
Mean (SD)	40.8 (36.4)	91.9 (187)	-51.1 (-177.2 to 75.0)
Median (IQR)	32.5 (15-47)	31 (22-52)	NA
New dialysis in those not receiving dialysis at baseline, No. (%)	5 (20.0)	4 (21.1)	RR, 0.95 (0.25 to 3.56)
Any adverse event, No. (%)	3 (8.8)	6 (24.0)	RR, 0.37 (0.05 to 1.33)

Cheng M, et al. JAMA Netw Open. 2022;5:e2229236.

Molnupiravir

- **Inibitore della polimerasi virale** (lethal mutagenesis)
- autorizzato per gli adulti **che non necessitano di ossigenoterapia** supplementare e che sono **ad elevato rischio di progressione*** a COVID-19 severa
- somministrato 800 mg/BID (4cps da 200 mg X 2) per 5 giorni ed **entro 5 giorni** dall'insorgenza dei sintomi

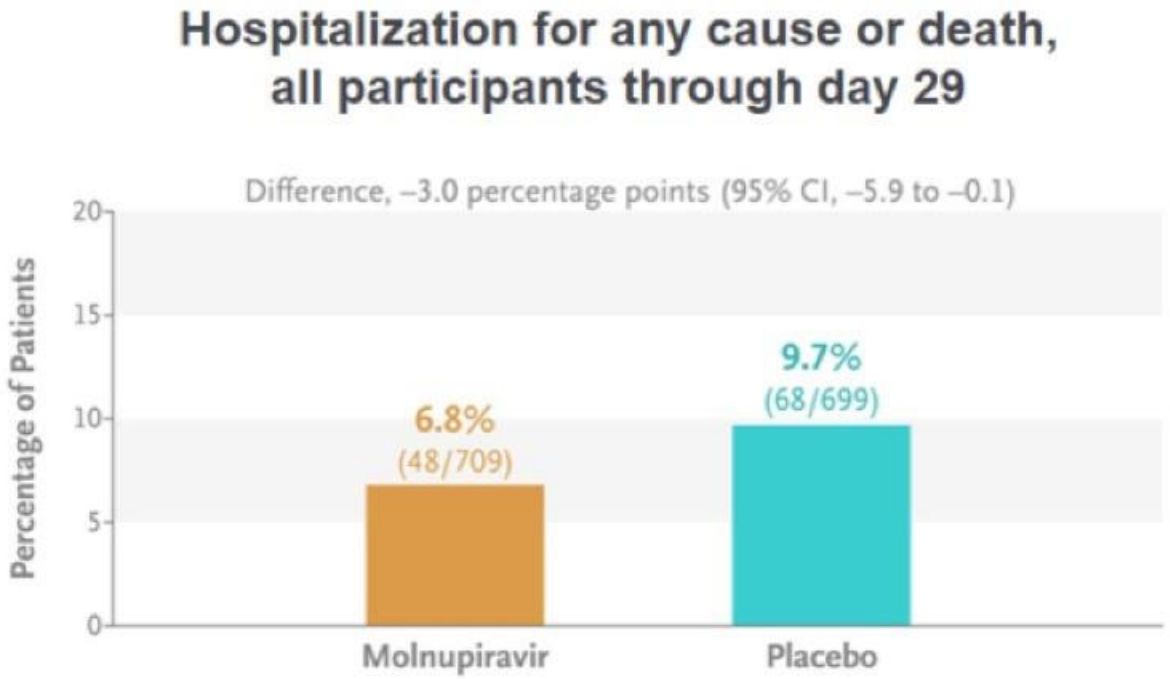
- **Attività antivirale *in-vitro*:** SARS-1, MERS, SARS-CoV-2, influenza, RSV, filoviruses (Ebola), Flaviviruses (Zika, Dengue), chikungunya, e alphaviruses (e.g., Venezuelan Equine encephalitis Virus [VEEV])

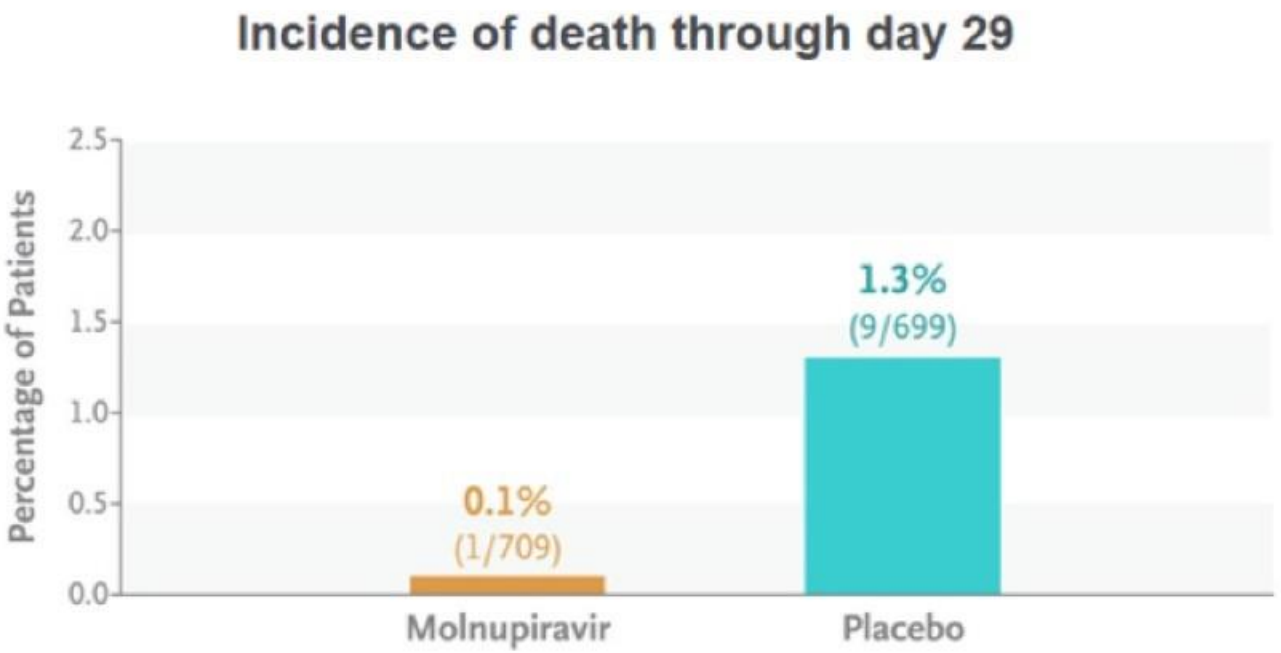


**fattori di rischio: età ≥ 60 anni, BMI >25, fumo, cancro in fase attiva, malattia renale cronica, malattia polmonare cronica, malattia/terapia immunosoppressiva, malattie cardiovascolari, diabete, ipertensione, anemia falciforme*

Molnupiravir in Non-Hospitalized, Unvaccinated Adults With Mild-to-Moderate COVID-19: MOVe-OUT Randomized Trial

30% reducrion of hospitalization or death





Bernal J, et al. N Engl J Med. 2022;386:509-520.

Anti-SARS-CoV-2 Antiviral Drugs: Molnupiravir

Drug name	Dosing regimen	Adverse events	Drug-drug interaction potential	Comment
Molnupiravir Authorized under an FDA EUA for the treatment of mild-to-moderate COVID-19 in high-risk individuals aged ≥ 18 years	▪ MOV 800 mg (four 200-mg capsules) orally every 12 hours for 5 days	▪ Diarrhea ▪ Nausea ▪ Dizziness ▪ Per the EUA, the 5-day course of MOV has a low risk for genotoxicity	▪ Clinical drug-drug interaction studies of MOV have not been conducted ▪ Drug-drug interactions related to hepatic metabolism are not expected	▪ People of reproductive potential who are sexually active should use effective contraception during and after treatment ▪ Pregnant patients should also be offered the opportunity to participate in the MOV pregnancy surveillance program ▪ Lactating people should not breastfeed their infants during treatment with MOV and for 4 days after treatment ▪ MOV can be taken with or without food

MOV, molnupiravir.

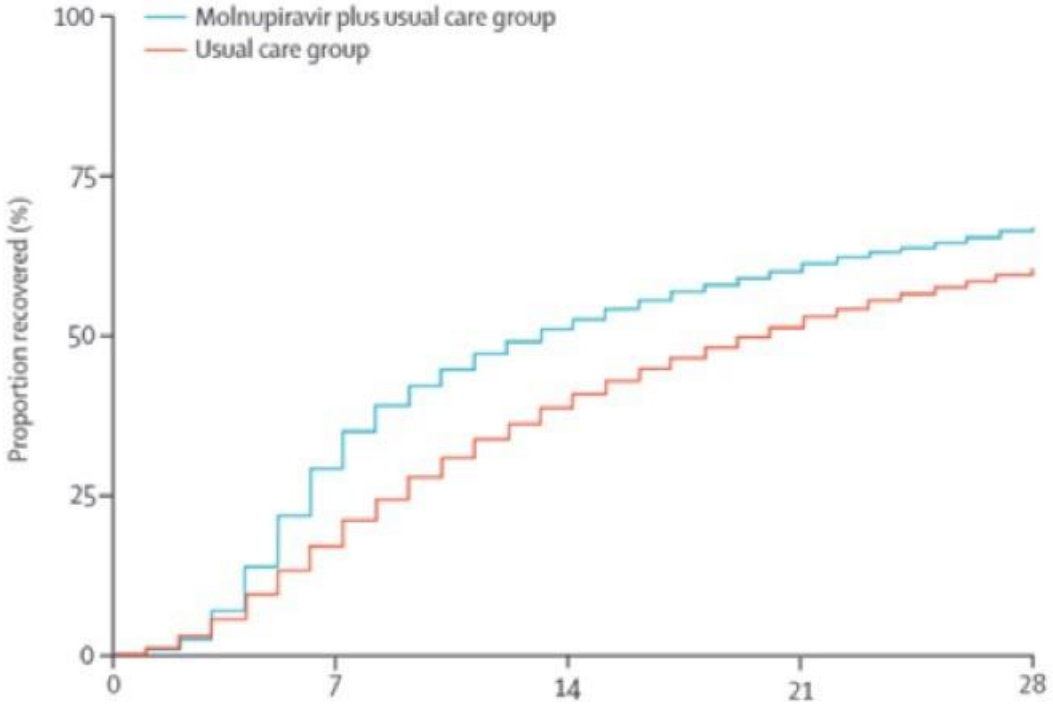
NIH COVID Treatment Guidelines. Table 4e. Characteristics of Antiviral Agents, Including Antibody Products. Accessed August 3, 2023. https://www.covid19treatmentguidelines.nih.gov/tables/antiviral-antibody-characteristics/

Molpupiravir Plus Usual Care for Increased-Risk COVID-19
PANORAMIC Randomized Trial

Key findings

- Hospitalization or death were recorded in 105 (1%) of 12,529 participants in the molnupiravir plus usual care group vs 98 (1%) of 12,525 in the usual care group (adjusted odds ratio, 1.06; probability of superiority, 0.33)
- However, molnupiravir was associated with reduced time to recovery overall and for key individual symptoms, reduced healthcare seeking for some primary care services, and reduced viral load

Time from randomization to first reported recovery from COVID-19



Molnupiravir plus usual care group					
Not yet recovered	12403	7934	4661	3221	2168
Censored	0	141	260	387	594
Recovered	0	4328	7482	8795	9641
Usual care group					
Not yet recovered	12140	9411	6121	4175	2774
Censored	0	271	542	781	1113
Recovered	0	2458	5477	7184	8253

Butler C, et al. Lancet. 2023. doi:10.1016/S0140-6736(22)02597-1

Select Patient Characteristics

Select Patient Characteristics Before Propensity-Score Matching

Characteristic	NMT/RIT (N = 11,270)	MOV (N = 2,374)
Age in years (mean, SD)	56 (16.4)	62 (15.6)
Ethnicity (%)		
Hispanic/Latinx	22.0	2.8
Not Hispanic/Latinx	61.5	86.8
Unknown	16.6	10.4
Race (%)		
Asian	2.5	0.9
Black	8.2	5.3
White	82.2	89.3
Unknown	6.8	4.5
Adverse socioeconomic determinants of health (%)[a]	9.0	23.0
Pre-existing medical conditions and treatments (%)		
Heart diseases	13.0	28.3
Cancer	43.6	58.6
Hypertension	46.4	67.1
Cerebrovascular diseases	8.8	19.6
Chronic lower respiratory diseases	30.2	41.4

Characteristic	NMT/RIT (N = 11,270)	MOV (N = 2,374)
Pre-existing medical conditions and treatments (%) *[continued]*		
Chronic kidney diseases	9.0	32.7
Chronic liver diseases	12.6	19.9
Overweight and obesity	30.4	37.7
Type 2 diabetes	19.1	36.2
Disorders involving the immune mechanisms	4.4	7.2
Congenital disorders	13.6	22.6
Mood disorders including depression	28.4	42.7
Psychotic disorders	1.9	4.7
Substance use disorders	15.4	24.3
HIV	2.4	5.6
Organ transplant	0.8	3.6
Tobacco smoker	8.1	13.8
Immunosuppressants	6.5	9.5
COVID-19 vaccine documented in EHR (%)	19.9	12.7

Before propensity score matching adjustment, relative to the NMT/RIT cohort, the MOV cohort was:

- Older
- More socioeconomically disadvantaged
- More likely to have comorbidities

Propensity score matching was utilized to increase comparability between the NMT/RIT and MOV cohorts. The two cohorts were matched 1:1 on demographics, adverse socioeconomic determinants of health, comorbidities, immunosuppressant usage, history of organ transplantation, and COVID-19 vaccination status as documented in the EHR.

[a]a composite variable comprising education, employment, occupational exposure, housing, and physical, social, and psychosocial environment.
EHR, electronic health record; HIV, human immunodeficiency virus; MOV, molnupiravir; NMT/RIT, nirmatrelvir/ritonavir; SD, standard deviation.
Wang et al. 2022. *medRxiv (PREPRINT). 2022.* https://www.medrxiv.org/content/10.1101/2022.06.21.22276724v1.full.pdf (Accessed July 29th, 2022)

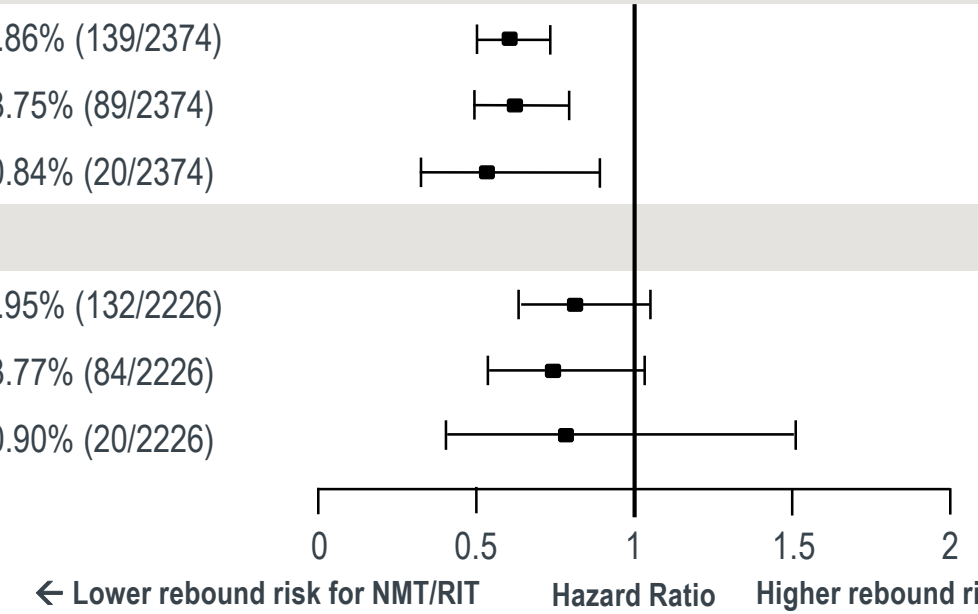
Back to Previous Section

MSD

Study Results: Rates and Relative Risks for COVID-19 Rebound After NMT/RIT vs MOV

7-Day Risk for COVID-19 Rebounds in Patients Who Take NMT/RIT vs MOV (Before and After Propensity-Score Matching)

Rebound Outcome	NMT/RIT	MOV	HR (95% CI)
Before Matching			
COVID infections	3.53% (398/11270)	5.86% (139/2374)	0.60 (0.50–0.73)
COVID symptoms	2.31% (260/11270)	3.75% (89/2374)	0.62 (0.49–0.79)
Hospitalizations	0.44% (50/11270)	0.84% (20/2374)	0.53 (0.32–0.89)
After Matching			
COVID infections	4.54% (101/2226)	5.95% (132/2226)	0.81 (0.63–1.05)
COVID symptoms	2.61% (58/2226)	3.77% (84/2226)	0.74 (0.53–1.03)
Hospitalizations	0.67% (15/2226)	0.90% (20/2226)	0.78 (0.40–1.51)



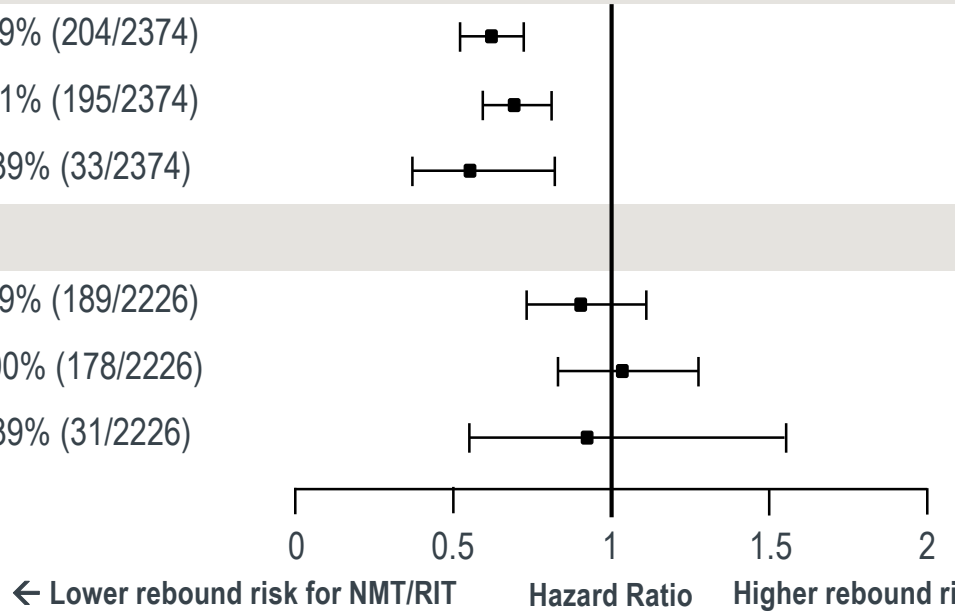
HR, hazard ratio; MOV, molnupiravir; NMT/RIT, nirmatrelvir/ritonavir.

Wang et al. 2022. *medRxiv (PREPRINT). 2022.* https://www.medrxiv.org/content/10.1101/2022.06.21.22276724v1.full.pdf (Accessed July 29th, 2022)

Study Results: Rates and Relative Risks for COVID-19 Rebound After NMT/RIT vs MOV (*continued*)

30-Day Risk for COVID-19 Rebounds in Patients Who Take NMT/RIT vs MOV (Before and After Propensity-Score Matching)

Rebound Outcome	NMT/RIT	MOV	HR (95% CI)
Before Matching			
COVID infections	5.40% (609/11270)	8.59% (204/2374)	0.62 (0.52–0.72)
COVID symptoms	5.87% (662/11270)	8.21% (195/2374)	0.69 (0.59–0.81)
Hospitalizations	0.77% (87/11270)	1.39% (33/2374)	0.55 (0.37–0.82)
After Matching			
COVID infections	7.14% (159/2226)	8.49% (189/2226)	0.90 (0.73–1.11)
COVID symptoms	7.55% (168/2226)	8.00% (178/2226)	1.03 (0.83–1.27)
Hospitalizations	1.21% (27/2226)	1.39% (31/2226)	0.92 (0.55–1.55)



HR, hazard ratio; MOV, molnupiravir; NMT/RIT, nirmatrelvir/ritonavir.

Wang et al. 2022. *medRxiv (PREPRINT). 2022.* https://www.medrxiv.org/content/10.1101/2022.06.21.22276724v1.full.pdf (Accessed July 29th, 2022)

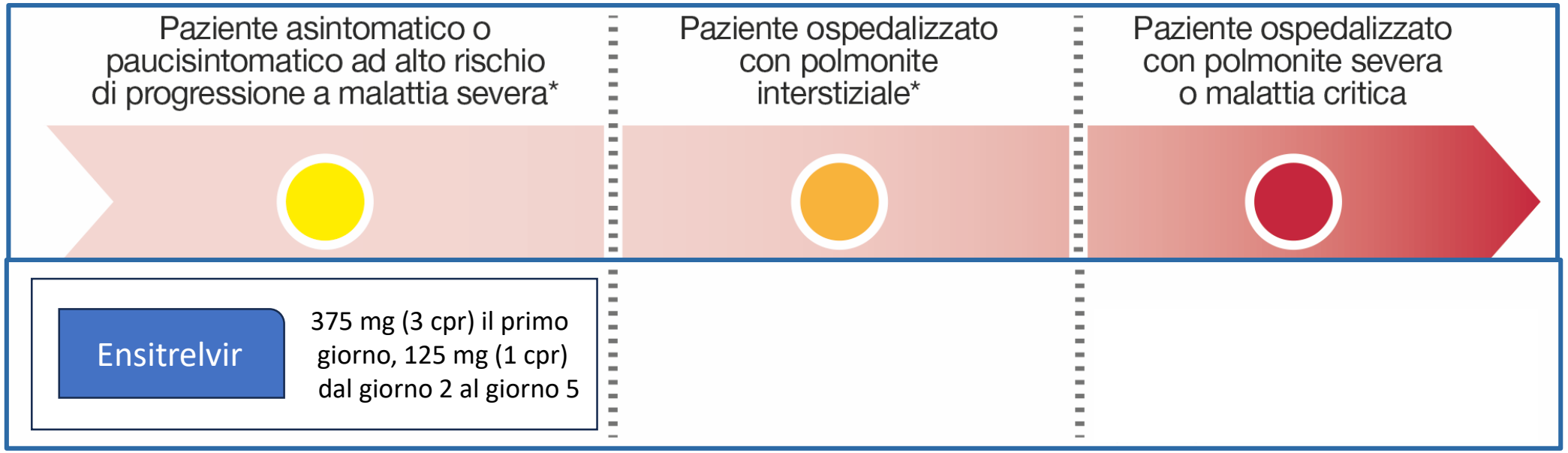
Molnupiravir Real World Evidence

Preprint Data	Published Data	Congress Poster Data
• Severe COVID-19 Prevention (UK) Zheng et al. • Outpatient Effectiveness (Hong Yip et al. • Outpatient Effectiveness (Hor Wong et al. • Kidney Transplant Recipients Gleeson et al. • COVID-19 Rebound (US) Wang et al. • Hospitalized Elderly Patients Gonda et al. • Kidney Transplant Recipients Villamarin et al. • Mid and Moderate COVID (Ita Gentile et al. • Early MOV + Usual Care vs Us Adults at Increased Risk (Unit Butler et al. • MOV Use and Severe COVID-19 Surge (Israel) Arbel et al.	• Solid Organ Transplant Recipients (US) Radcliffe et al.	• Immunocompromised Outpatients (Spain) Alvarez Marin et al. h-Risk Patients (Italy) OVID-19 (Italy) Between Molnupiravir and D-19 (Italy) g Risk of Hospitalization clonal Antibodies and Italy) ntiviral Agents (Italy) MOV in patients with MM e)

In a population of vaccinated participants with COVID-19 at increased risk for severe COVID-19 outcomes, **MOV did not reduce the already low hospital admission but resulted in shorter time to recovery, sustained recovery, reduced contact with GP services, and reduced viral detection and viral load.**

Ensitrelvir

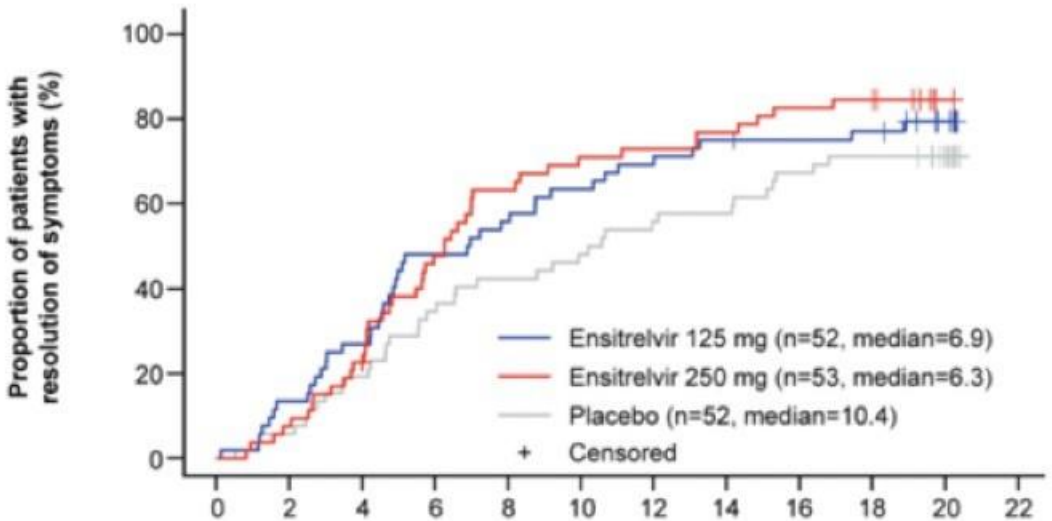
- **Inibitore della proteasi**
- adulti **che non necessitano di ossigenoterapia** supplementare e che sono **ad elevato rischio di progressione*** a COVID-19 severa
- somministrato 375 mg giorno 1 e 125 mg dal giorno 2 al giorno 5.
- **entro 5 giorni** dall'insorgenza dei sintomi



Ensitrelvir in Mild-to-Moderate COVID-19 in the Community

Time to resolution of COVID-19 symptoms in the patient group with < 72 h from onset to randomization[a]

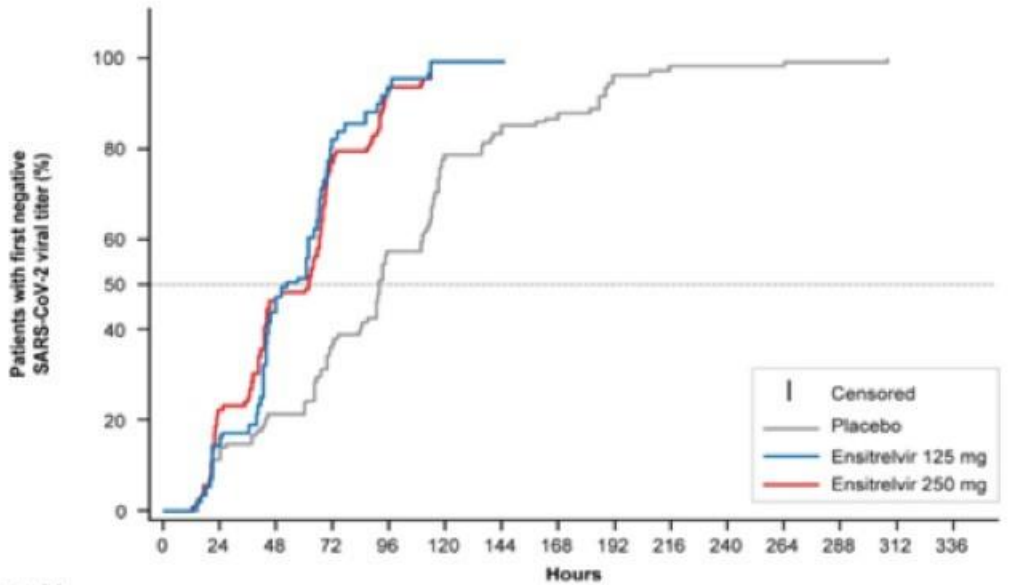
Phase 2b study: treatment in patients with mild-to-moderate COVID-19 within 120 hours from onset; study interventions administered orally, once daily, for 5 days



No. at risk																					
Ensitrelvir 125 mg	52	51	45	41	38	29	27	25	23	20	19	17	16	15	13	12	12	12	11	8	5
Ensitrelvir 250 mg	53	51	49	45	41	32	27	21	19	17	15	15	14	14	12	10	9	8	8	6	1
Placebo	52	51	49	44	42	37	34	31	30	29	27	24	23	22	22	20	17	15	15	15	9

Time to first negative SARS-CoV-2 viral titer[b]

Phase 2/3 study: randomization of patients with mild-to-moderate COVID-19 within 120 hours from onset; study interventions administered orally, once daily, for 5 days



Number at risk															
Placebo	108	95	85	69	46	23	17	14	4	3	2	2	1	0	0
Ensitrelvir 125 mg	111	93	58	20	7	1	1	0	0	0	0	0	0	0	0
Ensitrelvir 250 mg	113	87	59	26	8	1	0	0	0	0	0	0	0	0	0

	Ensitrelvir 125 mg n = 111	Ensitrelvir 250 mg n = 113	Placebo n = 108
Median (hours) [95% CI]	51.3 [44.1, 61.8]	62.1 [43.7, 66.5]	91.9 [84.0, 109.9]
Difference from placebo (hours) [95% CI]	−40.6 [−58.5, −26.5]	−29.8 [−52.0, −23.6]	–
P Value	<.0001	<.0001	–

a. Yotsuyanagi H, et al. Medicine (Baltimore). 2023;102:e33024; b. Mukae H, et al. CID. 2023;76:1403-1411.

ENS Metabolism and Effect on Drug-Metabolizing Enzymes

Dosage	375 mg on day 1 and 125 mg from days 2 to 5
Metabolism	Metabolized by multiple CYPs, with the major contribution being from CYP3A4/5 ▪ **Not recommended with strong CYP3A4 inducers** ▪ Moderate CYP3A4 inducers estimated to reduce ENS AUC by 24% (not considered clinically relevant) ▪ Strong CYP3A4 inhibitors unlikely to significantly increase ENS exposure
Effect on drug-metabolizing enzymes	▪ No significant induction on CYPs and UGTs ▪ No significant inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 ▪ ENS is a **strong CYP3A4 inhibitor** (midazolam AUC increased by 6.77-fold) and has a long elimination half-life (42-48 h) ⇒ **inhibition will last upon discontinuation of ENS**

University of Liverpool. Accessed September 13, 2023. https://www.covid19-druginteractions.org; Shimizu R, et al. Clin Drug Investig. 2023;43:335-346.

Ensitrelvir SCORPIO Trial
Long COVID Symptoms

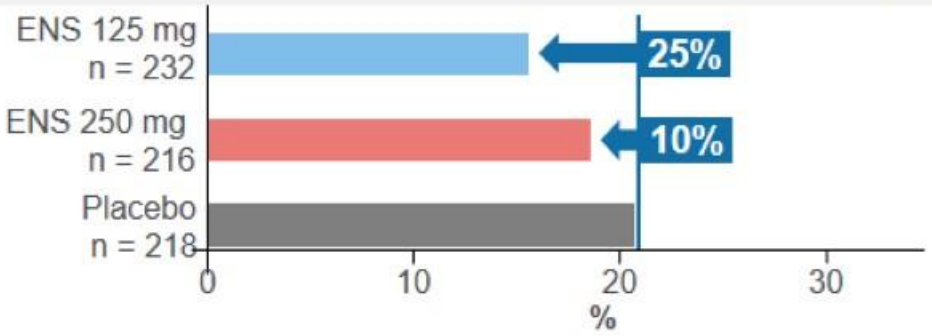
Definition for presence of long COVID symptoms in post hoc analysis:

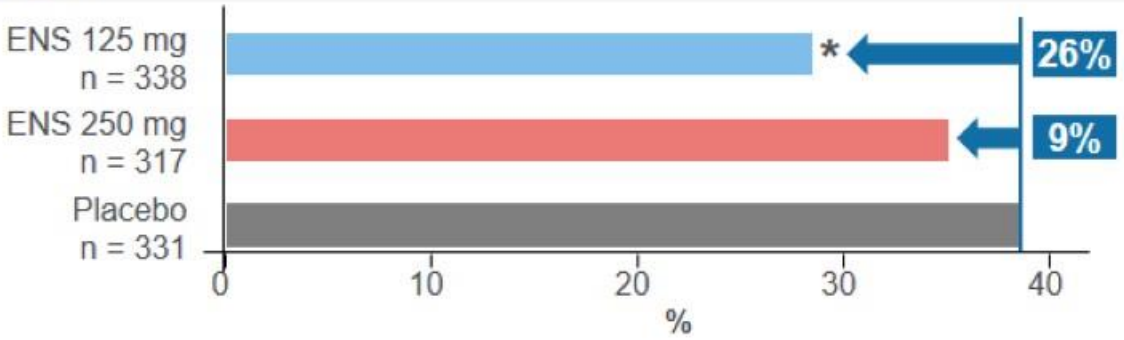
- Symptoms listed in 14 COVID-19 symptom questionnaire: at least 2 consecutive time points with a mild or more severe symptom continuing from the last observation in the follow-up (eg, day 21) to day 169
- Symptoms listed only in PASC questionnaire: 1 mild or more severe symptom at day 85 OR day 169
- Relationship with COVID-19: Yes (related) or unknown symptoms (exclude No [not related])

Proportion With Ongoing Symptoms (14 COVID-19 Symptoms)

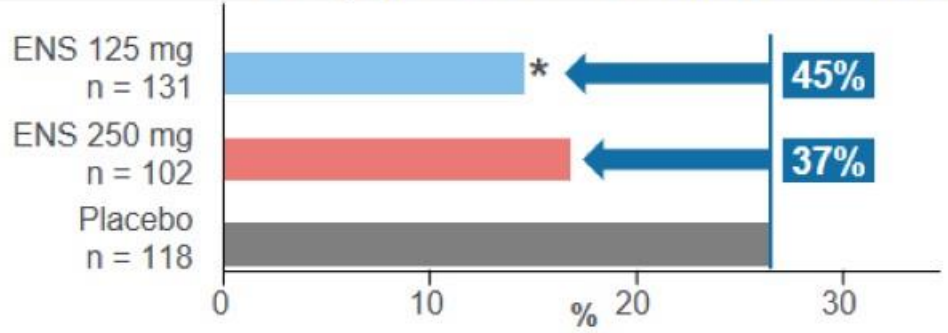
Proportion of 4 Neurological Symptoms in PASC Questionnaire

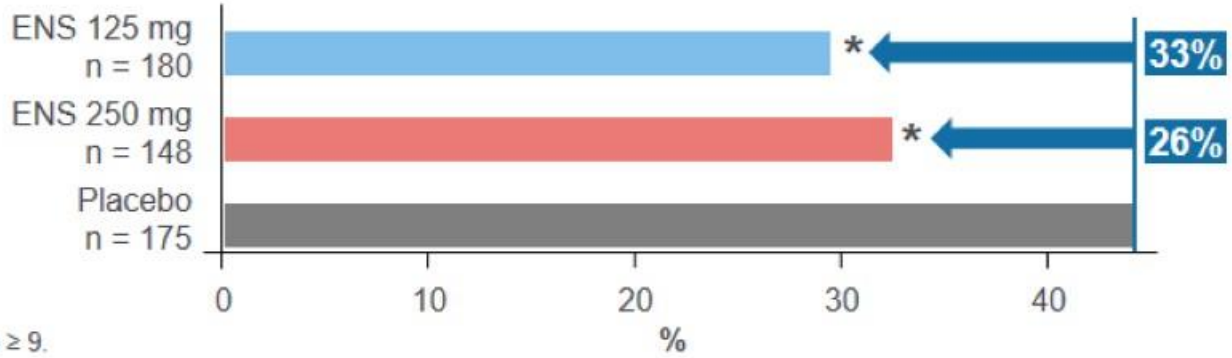
Overall Population





Subpopulation of Patients Who Have High Symptom Score for 14 Symptoms at Baseline[a]





*P value by Fisher exact test < .05; [a]High symptom score is defined as the total score of 14 symptoms at baseline ≥ 9.
PASC, postacute sequelae of SARS-CoV-2.

Uehara T, et al. Presented at: CROI 2023; February 19-22, 2023; Seattle, WA. Abstract 166.

NEWS | 17 October 2023 | Clarification 17 October 2023

New pill helps COVID smell and taste loss fade quickly

The antiviral drug ensitrelvir, which shortens sensory problems, is one of the few COVID-19 drugs available to people not at high risk of grave illness.

New clinical-trial data suggest that an antiviral pill called ensitrelvir shortens the duration of two unpleasant symptoms of COVID-19: loss of smell and taste. The medication is among the first to alleviate these effects and, unlike other COVID-19 treatments, is not reserved only for people at high risk of severe illness.
At the start of the study, 20% of participants reported some level of smell or taste loss. After the third day of treatment, the proportion of participants reporting such symptoms in the ensitrelvir groups started dropping more sharply than did the proportion in the placebo group. At day seven, the percentage of participants with smell or taste loss was 39% lower in the group taking 250-milligram pills than in the placebo group. Three weeks after treatment began, all groups reported similar symptom scores.

In Japan the drug is available to individuals with mild to moderate symptoms, regardless of their risk factors.

12 October 2023. IDWeek, Boston, Massachusetts.

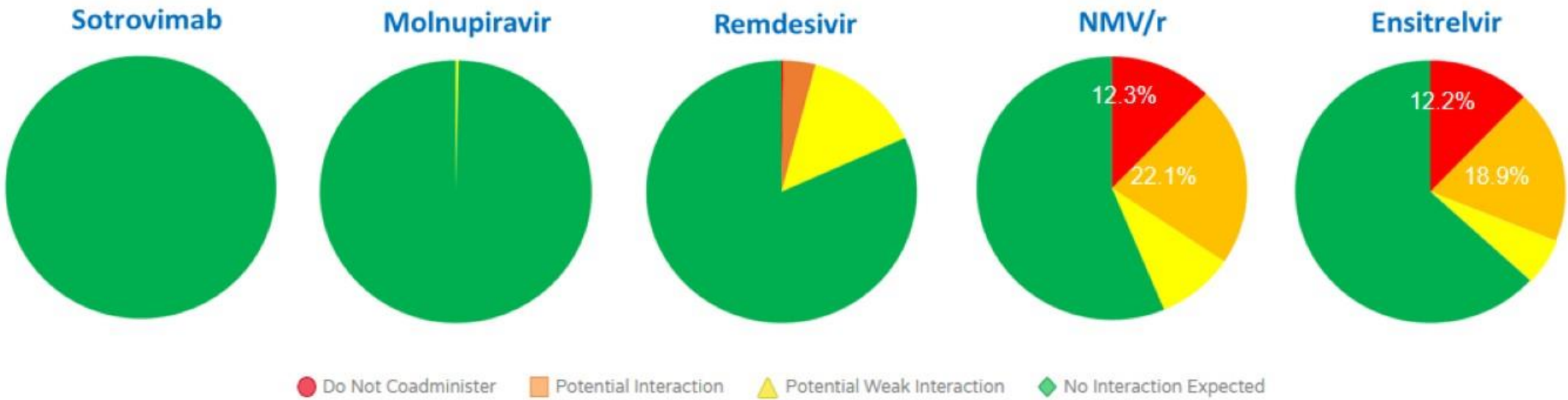
Drug-Drug Interactions

	RDV[1]	MOL[2]	NMVr[3,4]	ENS[5]
DDIs	**Low** (inhibits 3A4, OATP1B1/1B3) (infusion-related bradycardia)	**Low**	**High** Strong CYP3A4 inhibitor Strong inducers – avoid	**High** Strong inhibitor of CYP3A4; inhibits OATP1B1/1B3, BCRP, and P-gp
Kidney impairment	No dose adjustment (US label July 2023)	No dose adjustment	eGFR 30-60 mL/min: ↓ 150/100 mg twice daily eGFR < 30 mL/min: dialysis - avoid (label), or dose modify	No data
Liver impairment	No data	Mild-moderate: no adjustment Severe: expected ↑↑	CPT-A or -B: no adjustment CPT-C: avoid	No data, expected ↑↑
Swallowing difficulties[6]	IV administration	Capsules can be opened and mixed with water for NG tube feeding (FDA EUA)	Can be crushed or split and mixed with food/water	No data
Pregnancy	No data Active metabolite GS-441524 penetrates breastmilk in animals	**Contraindicated** Reproductive toxicity in animals; stop breastfeeding until 4 d after completion	(Possible animal toxicity) Stop breastfeeding until 7 d after completion	**Contraindicated** Reproductive toxicity in rabbits at ↑ exposures

BRCP, breast cancer resistance protein; DDI, drug-drug interaction; ENS, ensitrelvir; EUA, emergency use authorization; FDA, Food and Drug Administration; IV, intravenous; NG, nasogastric; NMVr, nirmatrelvir-ritonavir; OATP1B1/1B3, organic anion transporter family member 1B1/1B3; P-gp, P-glycoprotein.

1. Remdesivir. EMC SmPC. Accessed September 21, 2023. https://www.medicines.org.uk/emc/product/11597; 2. Molnupiravir. EMC SmPC. Accessed September 21, 2023. https://www.medicines.org.uk/emc/product/13044; 3. Nirmatrelvir, ritonavir. EMC SmPC. Accessed September 21, 2023. https://www.medicines.org.uk/emc/product/13145; 4. Chan GCK, et al. Clin Infect Dis. 2023. doi:10.1093/cid/ciad371 [Epub ahead of print]; 5. Shimizu R, et al. Clin Drug Investig. 2023;43:335-346; 6. Liverpool Drug Interactions Group. Updated April 5, 2022. Accessed September 21, 2023. www.covid19-druginteractions.org/prescribing_resources/guidance-swallowing

Prevalence of DDIs With COVID-19 Antivirals



- Prevalence of clinically significant DDIs among 913 co-meds
- Co-meds initially selected as high frequency or high consequence
- Around 300 co-meds added in 2022
- Existing evidence base is continually updated
- QA processes

QA, quality assurance.
University of Liverpool. Accessed April 25, 2023. https://www.covid19-druginteractions.org

COVID-19 Guidelines
Use of Directly Acting Antivirals in Adults

	WHO January 13, 2023	NIH August 8, 2022	NICE March 29, 2023	AWMF September 12, 2022	NCET March 27, 2023
Community					
Standard risk	NMVr				
High risk	NMVr RDV Mol[a]	NMVr RDV Mol[a]	NMVr RDV Mol[a] Sotrovimab	NMVr RDV Mol[a] Sotrovimab	NMVr RDV Mol[a]
Hospitalized					
Hypoxia	RDV	RDV		RDV	RDV
Critical, ventilated	RDV			RDV	RDV

SARS-CoV-2 test positive within specified window.
Symptomatic disease in adult patients.

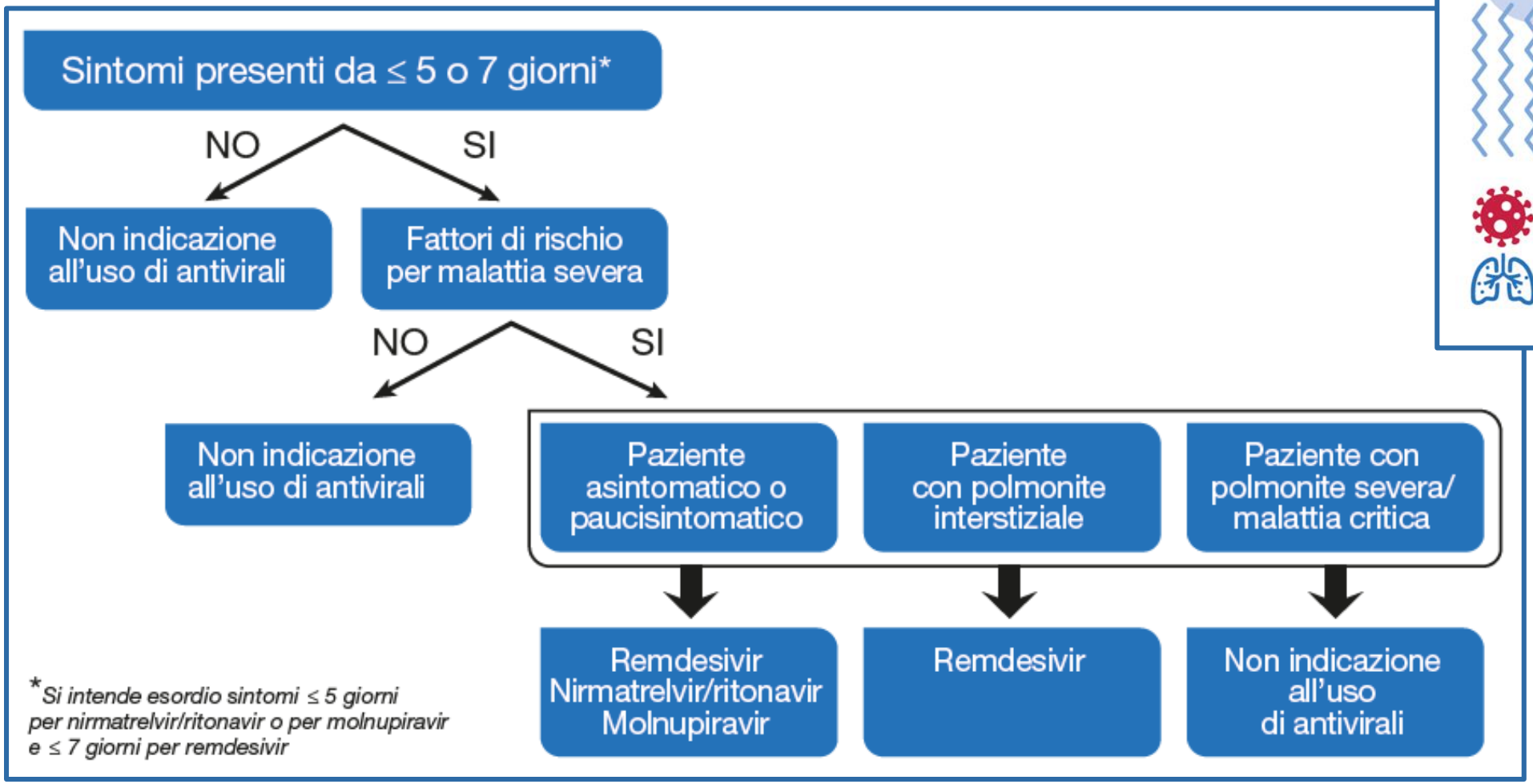
Strong for / A / recommended	Conditional or weak for / B or C / alternative	Conditional against / weak against	Strong against / not recommended

*Avoid in children and pregnancy.

AWMF, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften; Mol, molnupiravir; NCET, National Clinical Evidence Taskforce; NICE, National Institute for Health and Care Excellence; NIH, National Institutes of Health; Pax, Paxlovid; RDV, remdesivir; WHO, World Health Organization.

NIH. Accessed September 21, 2023. https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults

Uso degli antivirali nel paziente adulto



Persistent COVID-19 high tract respiratory infection

- **COVID19 patients with clinical and virological evidence of persistent respiratory tract infection** could define a new target of COVID patients
- All items should be present:
  1. COVID patients with **prolonged persistent respiratory symptoms or compartmentalized low respiratory infection** well after acute respiratory syndrome
  2. Usually patients with previous **hematological/oncological/neurological disorders**, few of them previously treated with **anti CD20 monoclonal agents**
  3. **Microbiological evidence** of persistent positive NPS or biological samples representative of low respiratory tract (spontaneous or induced sputum/BAL/BAL)
  4. **Negative or low-titer serological** evidence against **SARS-CoV-2 at day 20 since infection**

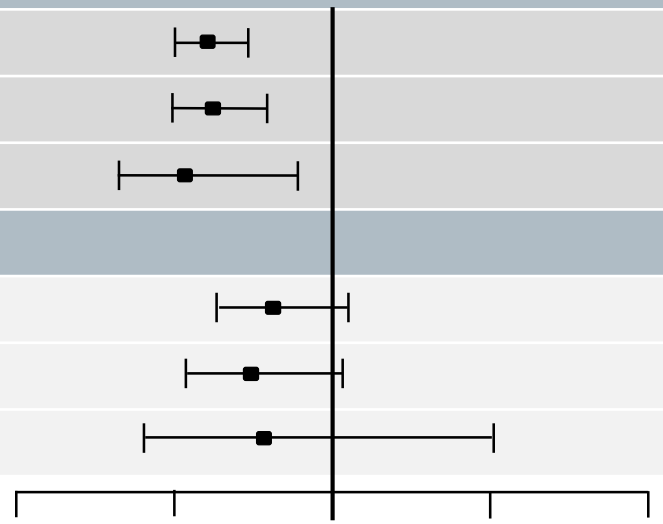
- In these COVID patients a **combined treatment using Sars-CoV-2 monoclonal antibodies against S protein and antivirals** can be used under off-label and/or compassionate use program

Study Results: Rates and Relative Risks for COVID-19 Rebound After NMT/RIT vs MOV

7-Day Risk for COVID-19 Rebounds

(Before and After Propensity-Score Matching)

Rebound Outcome	NMT/RIT	MOV	HR (95% CI)
Before Matching			
COVID infections	3.53% (398/11270)	5.86% (139/2374)	0.60 (0.50−0.73)
COVID symptoms	2.31% (260/11270)	3.75% (89/2374)	0.62 (0.49−0.79)
Hospitalizations	0.44% (50/11270)	0.84% (20/2374)	0.53 (0.32−0.89)
After Matching			
COVID infections	4.54% (101/2226)	5.95% (132/2226)	0.81 (0.63−1.05)
COVID symptoms	2.61% (58/2226)	3.77% (84/2226)	0.74 (0.53−1.03)
Hospitalizations	0.67% (15/2226)	0.90% (20/2226)	0.78 (0.40−1.51)



HR, hazard ratio; MOV, molnupiravir; NMT/RIT, nirmatrelvir/ritonavir.

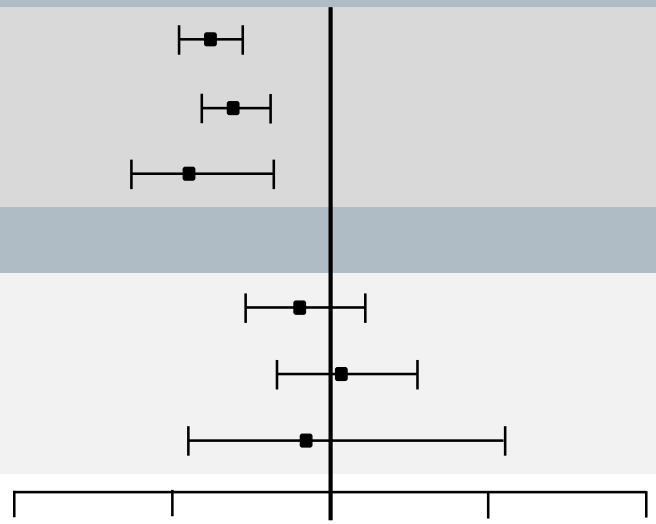
Wang et al. 2022. *medRxiv 2022.*

Study Results: Rates and Relative Risks for COVID-19 Rebound After NMT/RIT vs MOV (*continued*)

30-Day Risk for COVID-19 Rebounds

(Before and After Propensity-Score Matching)

Rebound Outcome	NMT/RIT	MOV	HR (95% CI)
Before Matching			
COVID infections	5.40% (609/11270)	8.59% (204/2374)	0.62 (0.52−0.72)
COVID symptoms	5.87% (662/11270)	8.21% (195/2374)	0.69 (0.59−0.81)
Hospitalizations	0.77% (87/11270)	1.39% (33/2374)	0.55 (0.37−0.82)
After Matching			
COVID infections	7.14% (159/2226)	8.49% (189/2226)	0.90 (0.73−1.11)
COVID symptoms	7.55% (168/2226)	8.00% (178/2226)	1.03 (0.83−1.27)
Hospitalizations	1.21% (27/2226)	1.39% (31/2226)	0.92 (0.55−1.55)



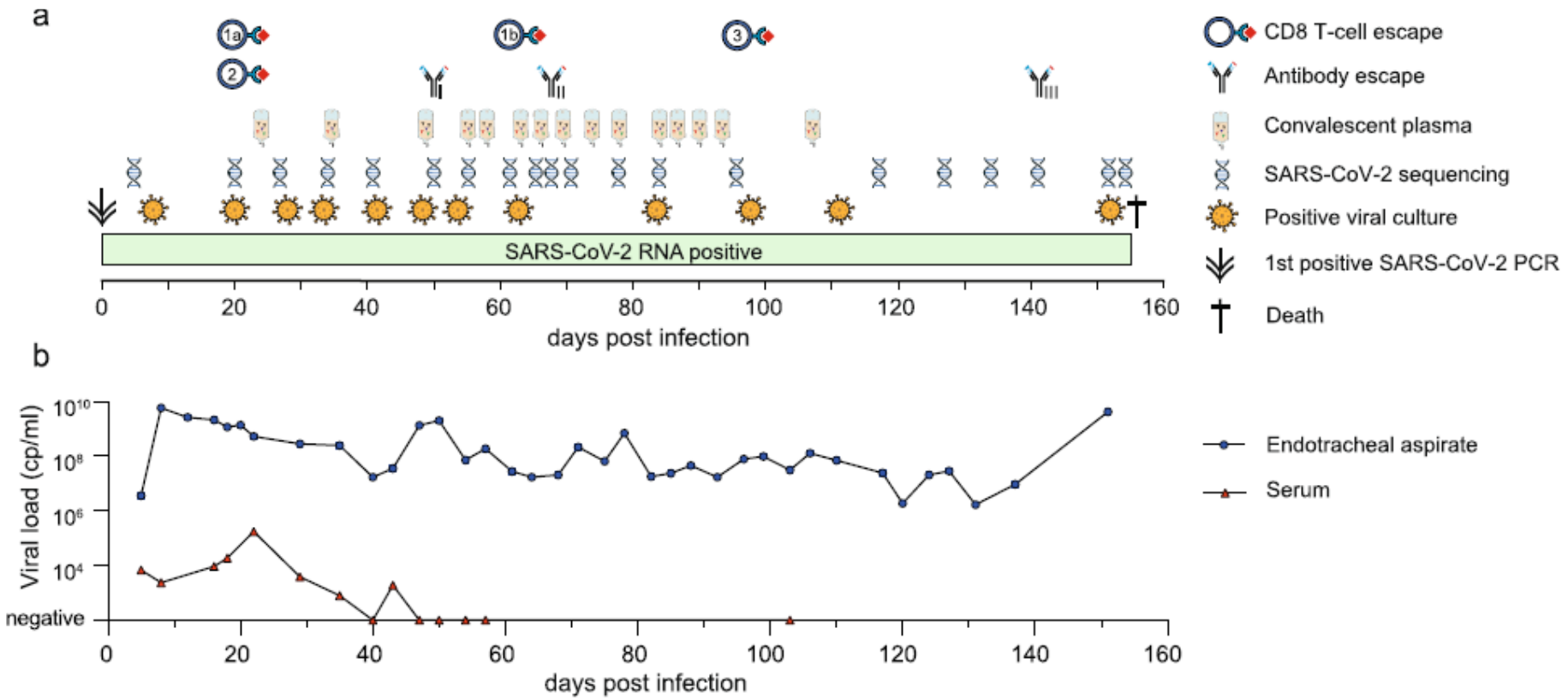
HR, hazard ratio; MOV, molnupiravir; NMT/RIT, nirmatrelvir/ritonavir.

Wang et al. 2022. *medRxiv 2022.*

nature communications

Accumulation of mutations in antibody and CD8 T cell epitopes in a B cell depleted lymphoma patient with chronic SARS-CoV-2 infection

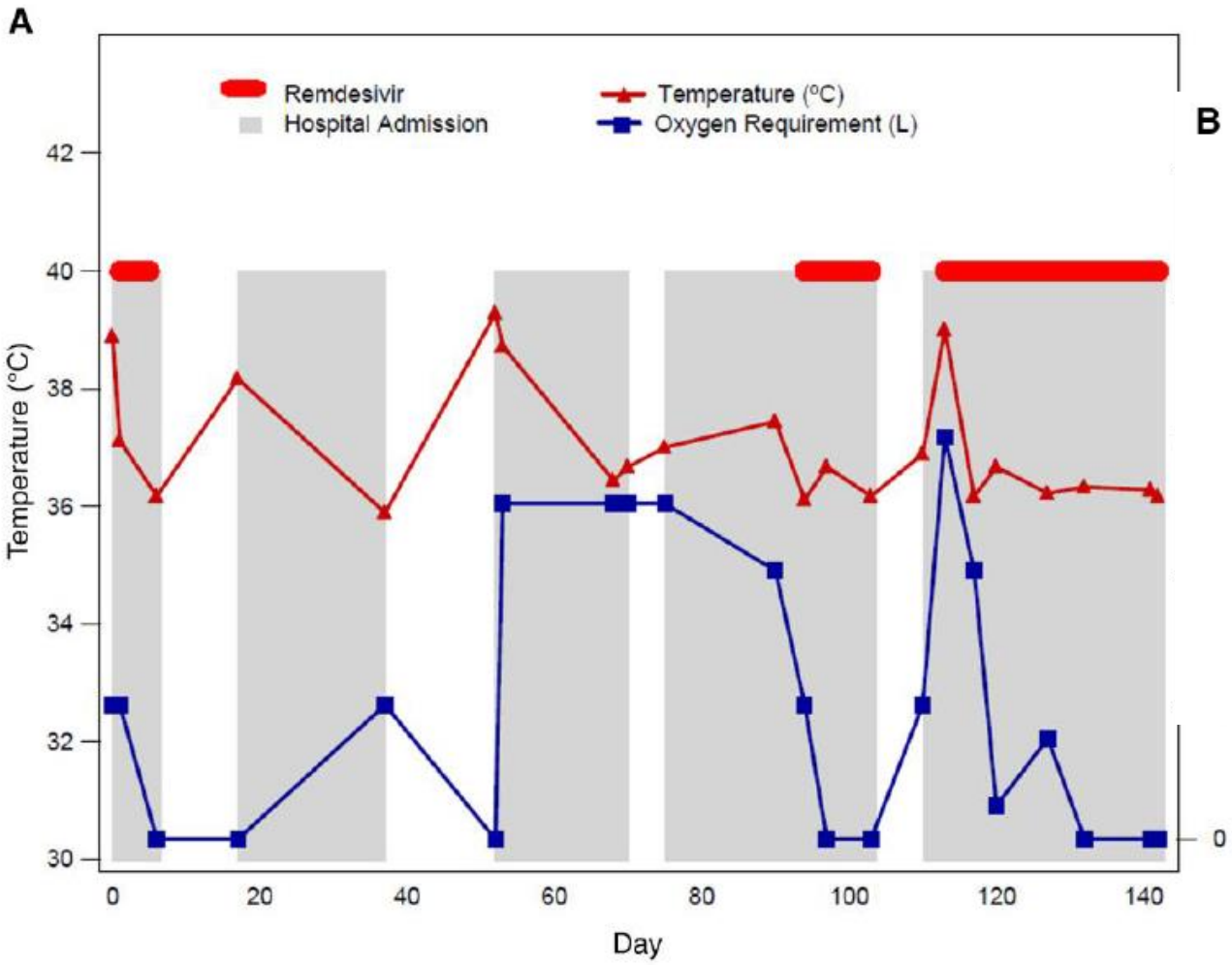
SARS- CoV-2 sequences in a B cell-depleted lymphoma patient: three mutations in the spike protein that dampen convalescent plasma-mediated neutralization of SARS-CoV-2. Additionally, four mutations emerge in non-spike regions encoding three CD8 T cell epitopes, including one nucleoprotein epitope affected by two mutations.

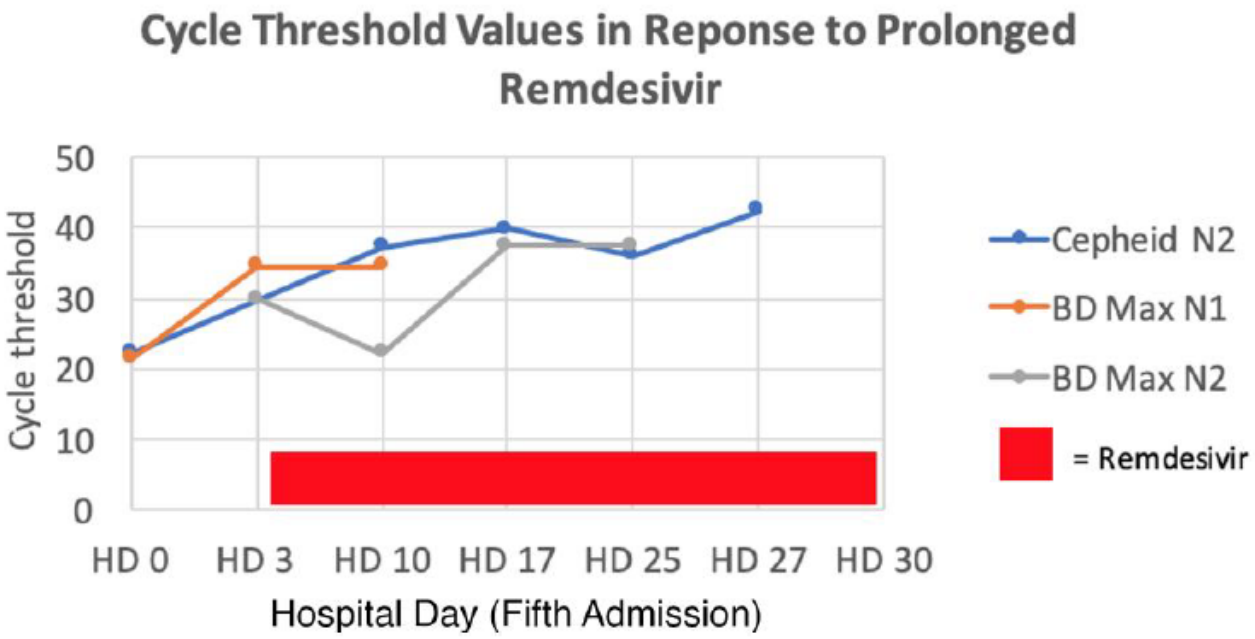


Khatamzas et al, Nat Commun 09.22

Extended Remdesivir Infusion for Persistent Coronavirus Disease 2019 Infection

Open Forum Infectious Diseases





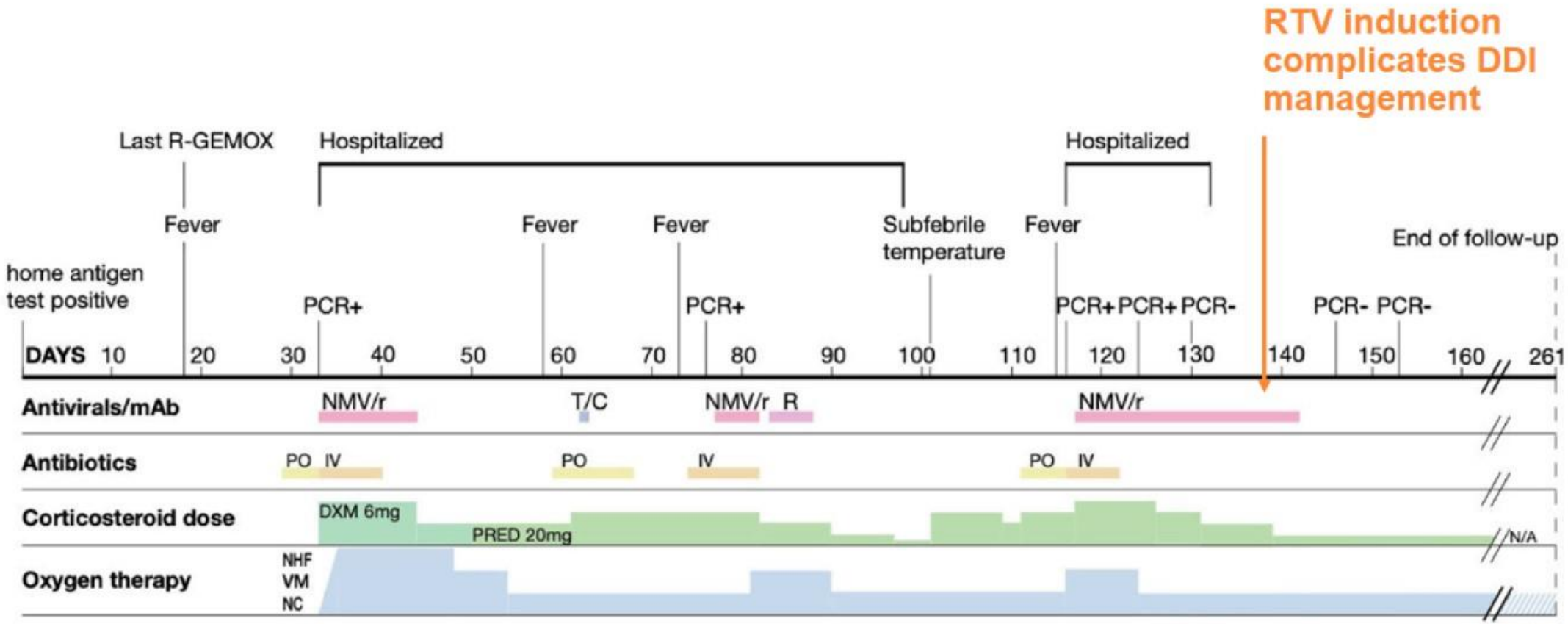
5-month persistent COVID19 in a **44 male granulomatosis with polyangiitis and secondary hypogamma** successfully treated **with 30 days of remdesivir**, desametasone e IVG. Ab Mono not available in August 2020

Martinez OFID 07.22

Prolonged and Repeated Courses of NMVr

SARS-CoV-2 now causes severe illness in immunosuppressed patients

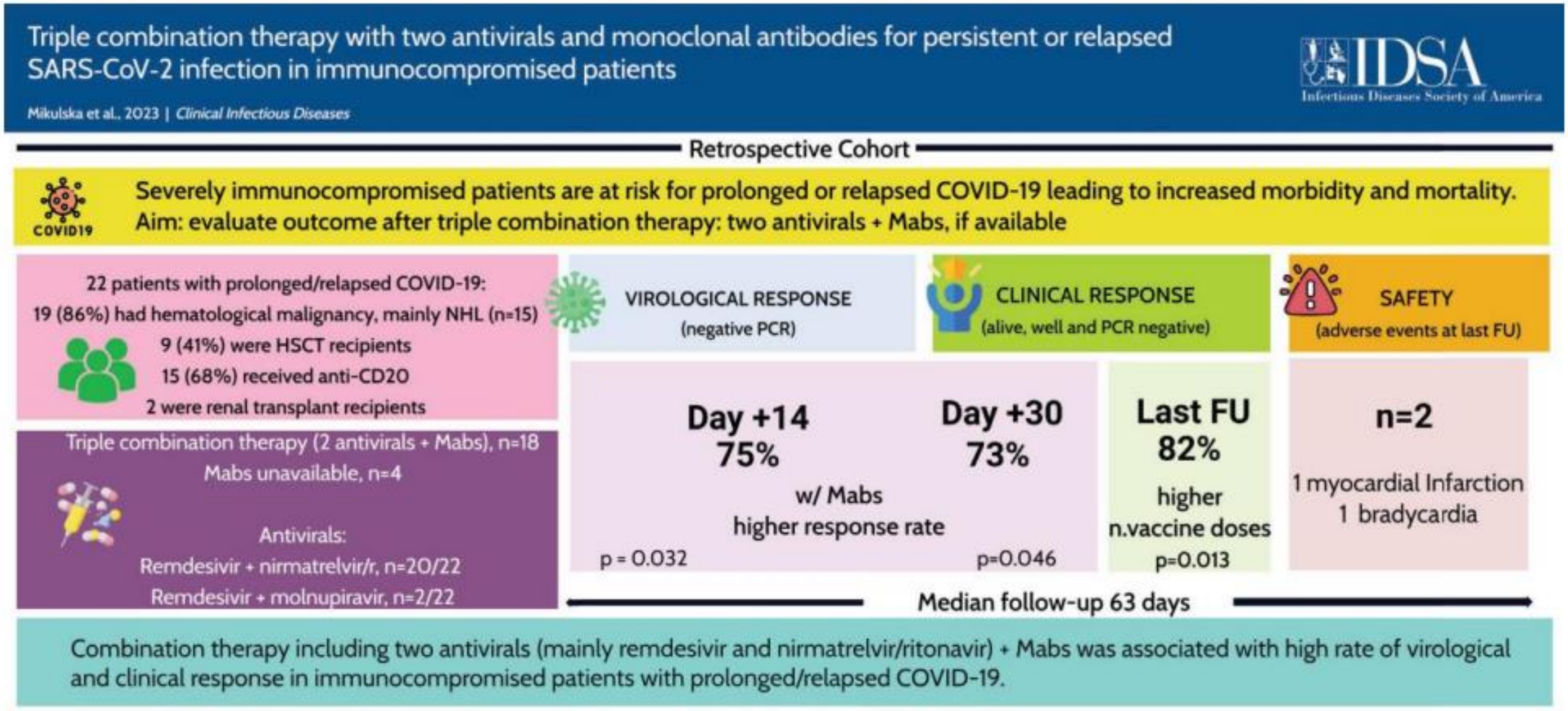
May develop persistent or relapsing infection



DXM, dexamethasone; N/A, not applicable; NC, nasal cannula; NHF, nasal high-flow cannula; PCR, polymerase chain reaction; PO, by mouth; PRED, prednisolone; R, remdesivir; R-GEMOX, rituximab-gemcitabine-oxaliplatin combination; T/C, tixagevimab/cilgavimab: VM, venturi mask.

Lindahl AL, et al. Infect Dis (Lond). 2023;55:585-589.

Triple combination therapy with two antivirals and monoclonal antibodies for persistent or relapsed SARS-cov-2 infection in immunocompromised patients



Mikulska M et al CID 03.23

Infection
https://doi.org/10.1007/s15010-023-02125-5

RESEARCH

Early combination therapy of COVID-19 in high-risk patients

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Abstract

Purpose Prolonged shedding of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been observed in immunocompromised hosts. Early monotherapy with direct-acting antivirals or monoclonal antibodies, as recommended by the international guidelines, does not prevent this with certainty. Dual therapies may therefore have a synergistic effect.

Methods This retrospective, multicentre study compared treatment strategies for corona virus disease-19 (COVID-19) with combinations of nirmatrelvir/ritonavir, remdesivir, molnupiravir, and/ or mABs during the Omicron surge. Co-primary endpoints were prolonged viral shedding ($\geq 10^6$ copies/ml at day 21 after treatment initiation) and days with SARS-CoV-2 viral load $\geq 10^6$ copies/ml. Therapeutic strategies and risk groups were compared using odds ratios and Fisher's tests or Kaplan–Meier analysis and long-rank tests. Multivariable regression analysis was performed.

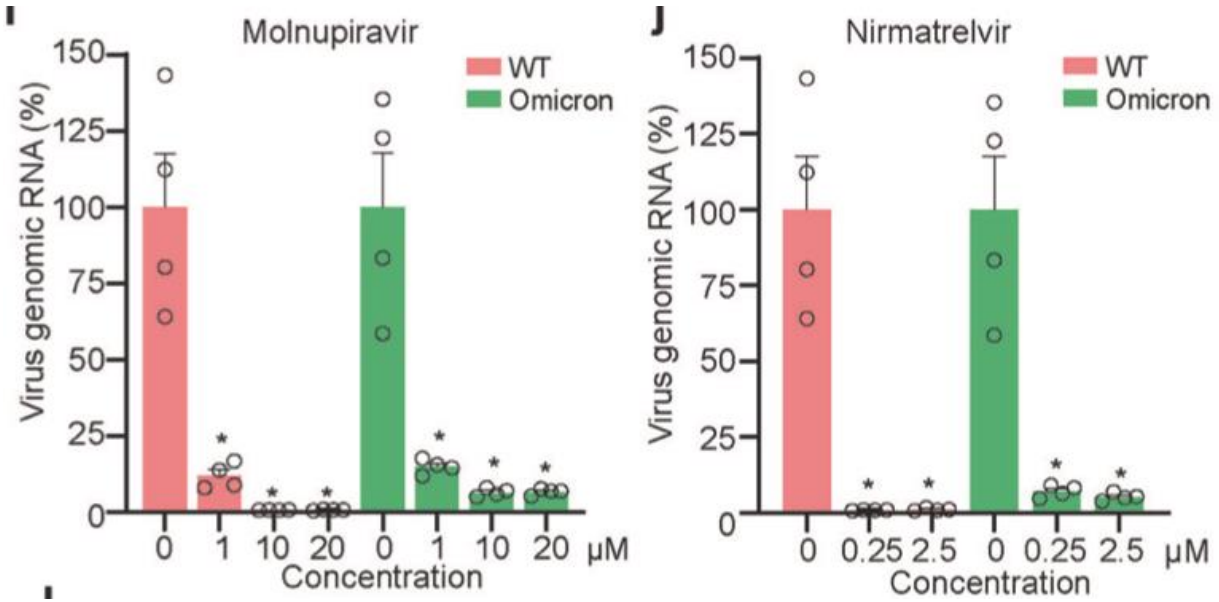
Results 144 patients were included with a median duration of SARS-CoV-2 viral load $\geq 10^6$ copies/ml of 8.0 days (IQR 6.0–15.3). Underlying haematological malignancies (HM) ($p=0.03$) and treatment initiation later than five days after diagnosis ($p<0.01$) were significantly associated with longer viral shedding. Prolonged viral shedding was observed in 14.6% ($n=21/144$), particularly in patients with underlying HM (OR 3.5; 95% CI 1.2–9.9; $p=0.02$). Clinical courses of COVID-19 were mild to moderate with only few adverse effects potentially related to combination treatment.

Conclusion Early combination treatment of COVID-19 effectively prevented prolonged viral shedding in 85.6% of cases. Considering the rapid viral clearance rates and low toxicity, individualized dual therapy approaches may be beneficial in high-risk patients.

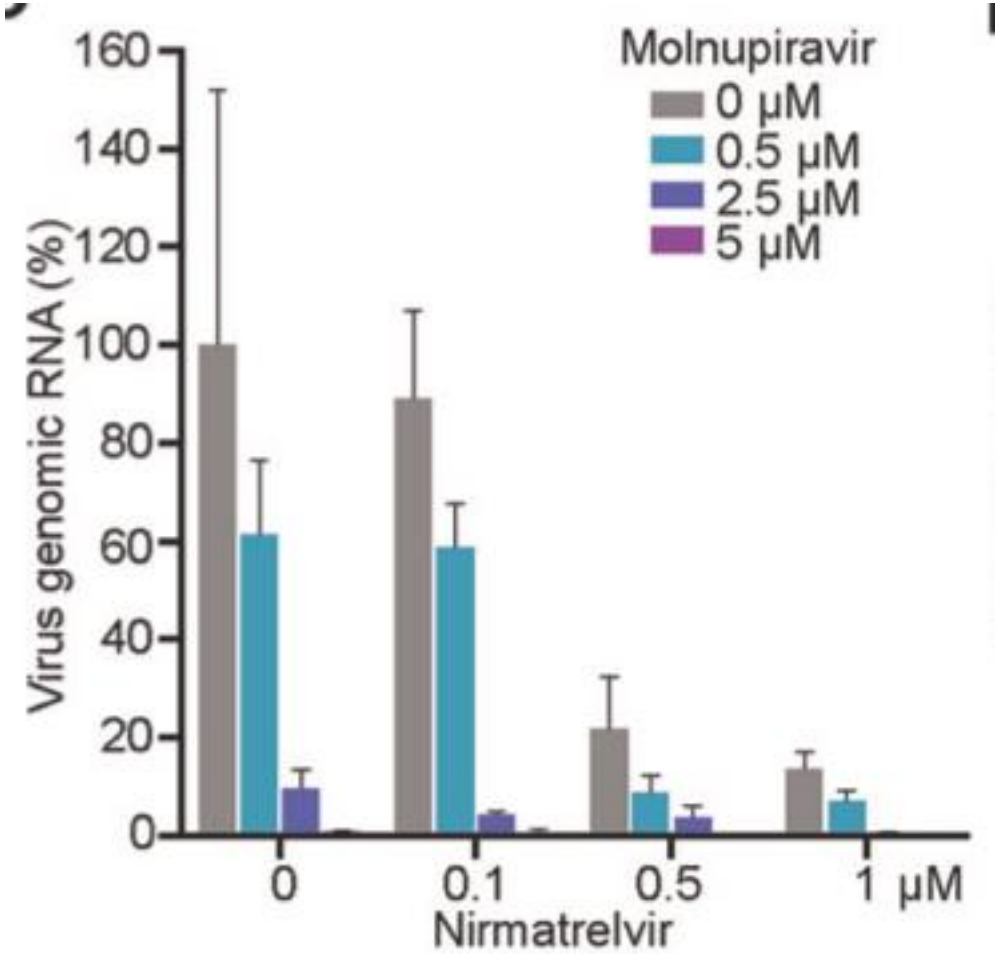
LETTER TO THE EDITOR OPEN

SARS-CoV-2 Omicron variant is highly sensitive to molnupiravir, nirmatrelvir, and the combination

The effects of molnupiravir (n = 4) and nirmatrelvir (n = 4) on intracellular viral RNA levels of WT and Omicron SARS-CoV-2 in hAOs.



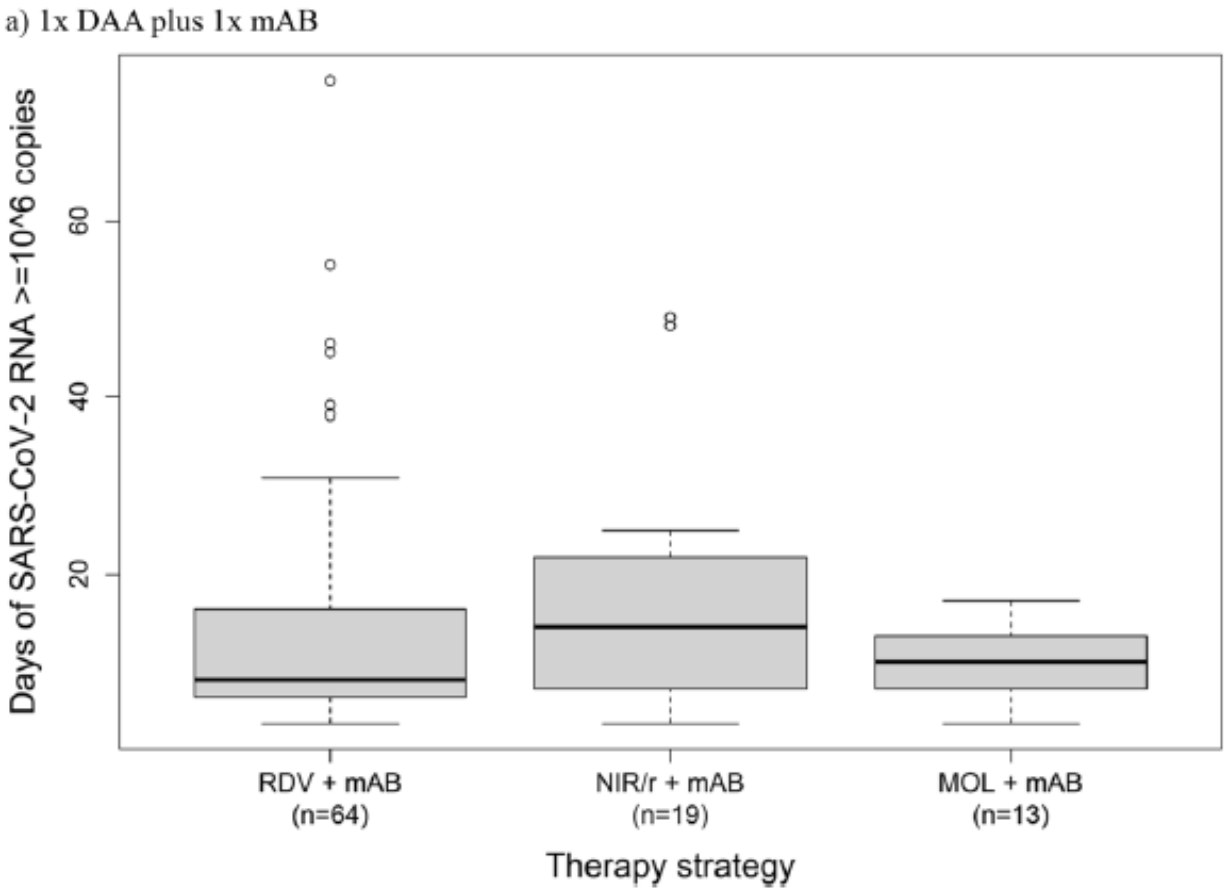
The antiviral effects of **combining molnupiravir and nirmatrelvir in Omicron** SARS-CoV-2 infected cells

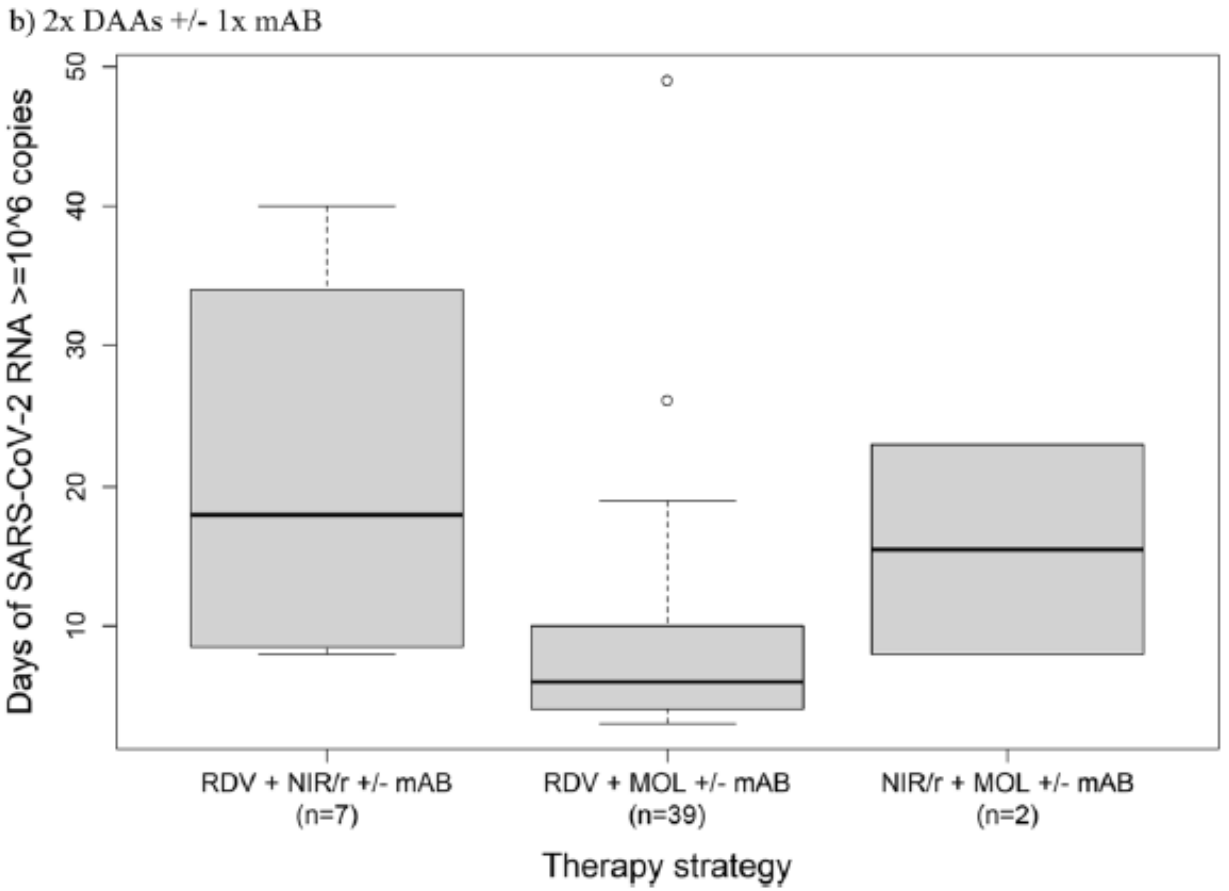


Time with SARS-CoV-2 virasl load >10^6 RNA copies/ml

No difference using an effective mAB combined with RDV (14.1 days), MOL 9.9 days) or NIR/r 16.7 days)

Combination of RDV with MOL appeared to be beneficial compared to combination RDV with NIR/r 8.9 vs 21.8 days, p<0.01)





RDV: Remdesivir; NIR/r: Nirmatrelvir/Ritonavir; MOL: Molnupiravir;

HM Horth, Infection, 2023 Nov 29.doi: 10.1007/s15010-023-02125-5.

Cohort study (databases of the US Department of Veterans Affairs) to identify patients who had at least 1 risk factor for progression to severe COVID-19 illness and who had survived the first 30 days after SARS-CoV-2 diagnosis. Those who were treated with oral nirmatrelvir within 5 days after the positive test (n = 35 717) and those who received no COVID-19 antiviral or antibody treatment during the acute phase of SARS-CoV-2 infection (control group, n =

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Characteristic	No. (%)		
	Overall cohort (n = 281 793)	Control group (n = 246 076)	Nirmatrelvir group (n = 35 717)
Age, mean (SD), y	65.70 (13.39)	65.76 (13.39)	65.64 (13.38)
Vaccination			
Without prior vaccination	47 144 (16.73)	41 129 (16.71)	5982 (16.75)
With 1 shot of vaccination	10 173 (3.61)	8861 (3.60)	1296 (3.63)
With 2 shots of vaccination	60 191 (21.36)	52 372 (21.28)	7655 (21.43)
With booster	164 285 (58.30)	143 711 (58.40)	20 784 (58.19)
Cancer	50 864 (18.05)	44 569 (18.11)	6425 (17.99)
Chronic lung disease	63 403 (22.50)	55 468 (22.54)	8019 (22.45)
Dementia	20 120 (7.14)	17 358 (7.05)	2582 (7.23)
Diabetes type 2	100 318 (35.60)	87 820 (35.69)	12 684 (35.51)
Cardiovascular disease	83 157 (29.51)	734,09 (29.83)	10 426 (29.19)
Hyperlipidemia	111 889 (39.66)	97 741 (39.72)	14 148 (39.61)
Immune dysfunction	15 978 (5.67)	14036 (5.70)	2010 (5.63)
Medications that would have drug-drug interaction with nirmatrelvir-ritonavir			
On concomitant medication that requires temporary hold	146 138 (51.86)	128 353 (52.16)	18 411 (51.55)
On concomitant medication that requires dosing adjustment	109 617 (38.90)	96 523 (39.23)	13 780 (38.58)
On concomitant medication that requires monitoring for adverse events	107 307 (38.08)	946,38 (38.46)	13 467 (37.71)

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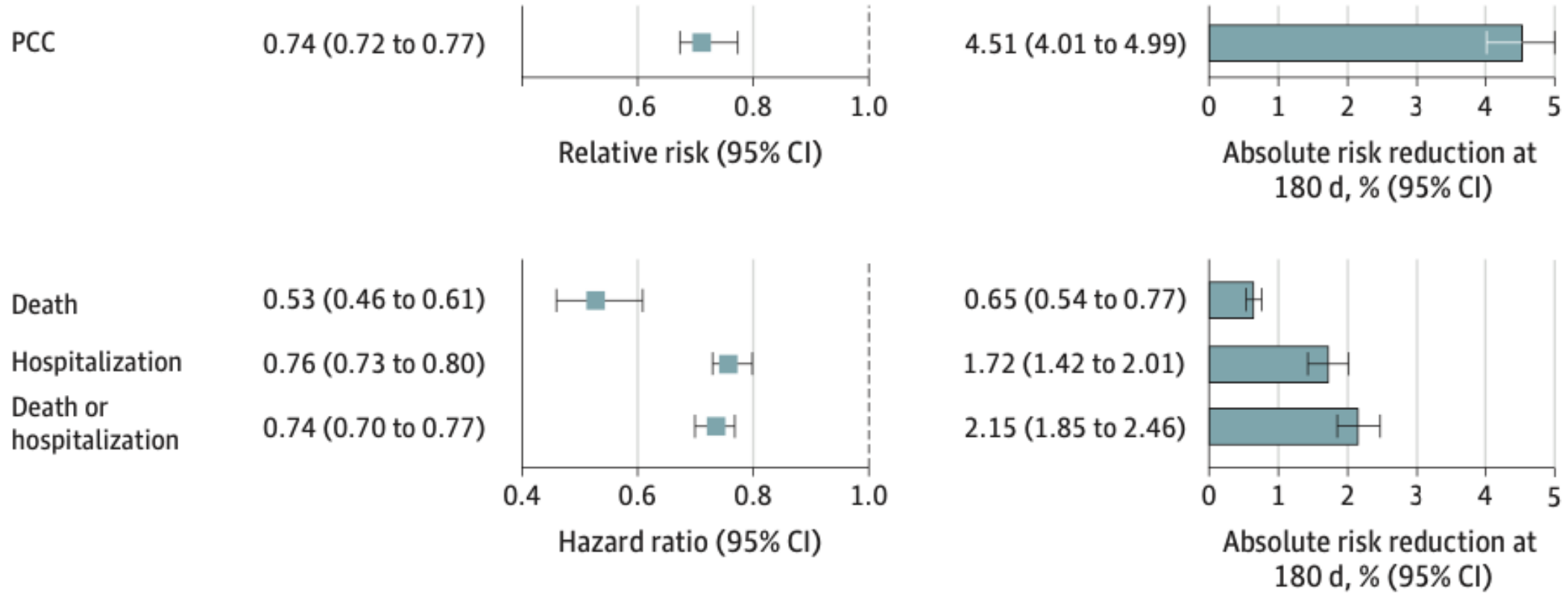
Relative and Absolute Risk Reduction of Nirmatrelvir Compared With the No-Treatment Control Group



Post–COVID-19 condition (PCC),
The association of nirmatrelvir with PCC was tested at 180 days after infection

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