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Molnupiravir compared to nirmatrelvir/ritonavir for COVID-19 in high-risk patients with haematological malignancy in Europe. A matched-paired analysis from the EPICOVIDEHA registry

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ABSTRACT

Introduction: Molnupiravir and nirmatrelvir/ritonavir are antivirals used to prevent progression to severe SARS-CoV-2 infections and decrease hospitalisation and mortality rates. Nirmatrelvir/ritonavir was authorised in Europe in December 2021, whereas molnupiravir is not yet licensed in Europe as of February 2022. Molnupiravir may be an alternative to nirmatrelvir/ritonavir because it is associated with fewer drug-drug interactions and contraindications. A caveat for molnupiravir is the mode of action induces viral mutations. Mortality rate reduction with molnupiravir was less pronounced than that with nirmatrelvir/ritonavir in patients without haematological malignancy. Little is known about the comparative efficacy of the two drugs in patients with haematological malignancy at high-risk of severe COVID-19. Thus, molnupiravir and nirmatrelvir/ritonavir were compared in a cohort of patients with haematological malignancies.

Methods: Clinical data from patients treated with molnupiravir or nirmatrelvir/ritonavir monotherapy for COVID-19 were retrieved from the EPICOVIDEHA registry. Patients treated with molnupiravir were matched by sex, age (±10 years), and severity of baseline haematological malignancy to controls treated with nirmatrelvir/ritonavir.

Results: A total of 116 patients receiving molnupiravir for the clinical management of COVID-19 were matched to an equal number of controls receiving nirmatrelvir/ritonavir. In each of the groups, 68 (59%) patients were male; with a median age of 64 years (interquartile range [IQR] 53-74) for molnupiravir recipients and 64 years (IQR 54-73) for nirmatrelvir/ritonavir recipients; 56.9% (n=66) of the patients had controlled baseline haematological malignancy, 12.9% (n=15) had stable disease, and 30.2% (n=35) had active disease at COVID-19 onset in each group. During COVID-19 infection, one third of patients from each group were admitted to hospital. Although a similar proportion of patients in the two groups were vaccinated (molnupiravir n=77, 66% vs. nirmatrelvir/ritonavir n=87, 75%), more of those treated with nirmatrelvir/ritonavir had received four vaccine doses (n=27, 23%) compared with those treated with molnupiravir (n=5, 4%) ($P<0.001$). No differences were detected in COVID-19 severity ($P=0.39$) or hospitalisation ($P=1.0$). No statistically significant differences were identified in overall mortality rate ($P=0.78$) or survival probability (d30 $P=0.19$, d60 $P=0.67$, d90 $P=0.68$, last day of follow up $P=0.68$). Deaths were either attributed to COVID-19, or the infection was judged by the treating physician to have contributed to death.

Conclusions: Hospitalisation and mortality rates with molnupiravir were comparable to those with nirmatrelvir/ritonavir in high-risk patients with haematological malignancies and COVID-19. Molnupiravir is a plausible alternative to nirmatrelvir/ritonavir for COVID-19 treatment in patients with haematological malignancy.

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Introduction

Immediately after the coronavirus disease 2019 (COVID-19) pandemic was declared [1], an unprecedented effort was undertaken to overcome the severity and mortality of this disease. First, with specific vaccines [2,3] and, later, with monoclonal antibodies [4–6] and antivirals [7–9] targeting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Even though these strategies reduce hospital admission and mortality, some patient populations remain at high risk for severe forms of COVID-19. For example, patients with haematological malignancies have impaired immune systems and anti-SARS-CoV-2 vaccines may not trigger an adequate immune response in such patients [10–12]. Up to January 2023, three antivirals had been developed: molnupiravir [7], nirmatrelvir/ritonavir [8], and remdesivir [9]. The first two are for oral administration, and the latter is for intravenous injection, with the associated limitations for ambulatory use. However, molnupiravir is not currently authorised for regular administration.

Molnupiravir is an oral nucleoside analogue that inhibits SARS-CoV-2 viral replication by promoting mutations during the replication process. This mode of action has been viewed critically, as it may promote the evolution of new virus variants [7,13,14]. The target patients for this drug are adults aged over 18 years, of any weight, who are at high risk of developing severe COVID-19 [15]. No contraindications or drug-drug interactions have yet been described. A 30% reduction in mortality was observed in clinical trials with volunteers without haematological malignancies [7].

Nirmatrelvir/ritonavir interacts with the SARS-CoV-2 protease, inhibiting viral replication [8]. Comparable with molnupiravir, nirmatrelvir/ritonavir is an oral medicine for adult patients that is administered to reduce progression from mild to severe COVID-19 [7,8]. However, contraindications and drug-drug interactions have been described for nirmatrelvir/ritonavir. Clinical trials in patients without haematological malignancy showed a 90% reduction in mortality rates with nirmatrelvir/ritonavir vs. placebo [8].

Both molnupiravir and nirmatrelvir/ritonavir are authorised for administration in Israel [16,17], the United Kingdom [18,19] and the United States [20,21]. and are recommended by experts for patients with haematological malignancy [22]. Yet, unlike nirmatrelvir/ritonavir [23], molnupiravir is not authorised in Europe [24].

The current study was conducted to compare the effectiveness of molnupiravir and nirmatrelvir/ritonavir in terms of hospitalisation rates and survival rates on days 30, 60, and 90 after COVID-19 diagnosis in patients with haematological malignancy, and to determine whether molnupiravir may be an alternative to nirmatrelvir/ritonavir in European patients.

Methods

This non-randomised, observational analysis was performed as a routine effort using data extracted from the online EPICOVIDEHA registry (NCT04733729), which comprises worldwide clinical data from patients with baseline haematological malignancies who developed SARS-CoV-2 infection. Survey details, accessible via www.clinicalsurveys.net (EFS Summer 2021, TIVIAN, Cologne, Germany), are described elsewhere [25]. EPICOVIDEHA has its central Ethics Committee at the Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Università Cattolica del Sacro Cuore of Rome, Italy (Study ID: 3226). According to specific local regulation, each of the participating institutions might have their own ethical approval as appropriate.

Patients included in the analysis had to fulfil the basic inclusion criteria of the EPICOVIDEHA registry: adults aged ≥18 years, and baseline active haematological malignancy at any point within the last five years prior to laboratory-confirmed COVID-19 diagnosis. Additionally, for this specific analysis, patients had to be treated for their COVID-19 exclusively with either molnupiravir or nirmatrelvir/ritonavir monotherapy. The use of corticosteroids and/or convalescent plasma was not considered as exclusionary. There were no pre-set geographical or diagnosis date exclusion parameters. However, the obtainability of each oral antiviral in the respective participating institution limited the patient recruitment to Europe, specifically from October 2021 to January 2023.

Patients who received molnupiravir monotherapy were matched 1:1 to controls who received nirmatrelvir/ritonavir. Fifty of these controls were described previously [26]. Variables for matching patients to controls were age, sex, and malignancy status at COVID-19 diagnosis. These variables were chosen based on previous use of the EPICOVIDEHA registry for mortality-associated variables in vaccinated and unvaccinated patients with baseline haematological malignancies [27–30].

Categorical variables are presented with frequencies and percentages, using X^2 test or Fisher's exact test for proportion comparison, as appropriate. Continuous variables are summarised using median, interquartile range (IQR) and range. Mann-Whitney U test was used to compare continuous variables. Patients receiving any of the oral antivirals (either molnupiravir or nirmatrelvir/ritonavir) were matched as described above, reducing any potential selection bias. Antiviral effectiveness was calculated by comparing hospitalisation and mortality rates on days 30, 60 and 90 after SARS-CoV-2 infection diagnosis and on last day of follow-up. Additionally, Kaplan-Meier survival plots were created to compare antivirals based on the log-rank test. $P \leq 0.05$ was considered significant.

Results

As of January 2023, 338 patients documented in the EPICOVIDEHA registry were receiving either molnupiravir (n=124, 36.7%) or nirmatrelvir/ritonavir (n=214, 63.3%) as monotherapy for the treatment of COVID-19. From those, 116 patients receiving molnupiravir as first-line treatment (cases) were matched to an equal number of patients receiving nirmatrelvir/ritonavir (controls). Patients were from all over Europe, including Italy (n=92, 39.7%), the Czech Republic (n=35, 15.1%) and Spain (n=33, 14.2%; Table 1, Figure 1).

In both groups, 68 (58.6%) patients were male. The median age was 64 years (IQR 53-74, range 21-86) for the cases and 64 years (IQR 54-73, range 18-91) for the controls. In both treatment groups, almost half the patients did not have any underlying comorbidity at onset of SARS-CoV-2 infection beyond the haematological malignancy (molnupiravir cases: n=55, 47.4%; nirmatrelvir/ritonavir controls: n=56, 48.3%). The most prevalent comorbidity was chronic cardiopathy, in around one-third of patients in each group (molnupiravir cases: n=40, 34.5%; nirmatrelvir/ritonavir controls: n=43, 37.1%), with no significant difference (P=0.784). Statistically significant differences were observed in the number of patients with baseline renal dysfunction: 11 (9.5%) cases receiving molnupiravir vs. 2 (1.7%) controls receiving nirmatrelvir/ritonavir (P=0.019). Leukaemia (n=49, 42.2%) was more common in patients treated with molnupiravir than in those treated with nirmatrelvir/ritonavir (n=42, 36.2%). On the contrary, plasma cell disorders were statistically significantly more prevalent in the nirmatrelvir/ritonavir controls (n=33, 30.2%) than in molnupiravir cases (n=27, 23.3%) (P=0.005). Malignancy status at onset was a matching criterion and was evenly distributed in the two groups: 66 (56.9%) patients had controlled baseline haematological malignancy, 15 (12.9%) had stable disease, and 35 (30.2%) had active disease at onset of SARS-CoV-2 infection. Seven (6.0%) cases and six (5.2%) controls had not received any malignancy treatment by the time of COVID-19 diagnosis. Neutropenia (molnupiravir cases: n=8, 6.9%; nirmatrelvir/ritonavir controls: n=5, 4.3%) and lymphopenia (molnupiravir cases: n=18, 15.5%; nirma-

Table 1
Patient characteristics.

	Molnupiravir		Nirmatrelvir/ritonavir		*P* value
	n	%	*n*	%	
Sex					1.000
Female	48	41.4	48	41.4	
Male	68	58.6	68	58.6	
Age, *in years*	64 (53-74) [21-86]		64 (54-73) [18-91]		0.704
Comorbidities at onset					
No comorbidities	55	47.4	56	48.3	0.795
1 comorbidity	32	27.6	37	31.9	
2 comorbidities	21	18.1	17	14.7	
3 or more comorbidities	8	6.9	6	5.2	
Chronic cardiopathy	40	34.5	43	37.1	0.784
Chronic pulmonary disease	13	11.2	9	7.8	0.502
Diabetes mellitus	13	11.2	14	12.1	1.000
Liver disease	3	2.6	4	3.4	1.000
Obesity	2	1.7	5	4.3	0.446
Renal impairment	11	9.5	2	1.7	0.019
Smoking history	6	5.2	8	6.9	0.784
Baseline malignancy					0.005
Leukaemia	49	42.2	42	36.2	
Acute lymphoid leukaemia	9	7.8	6	5.2	
Chronic lymphoid leukaemia	17	14.7	8	6.9	
Acute myeloid leukaemia	15	12.9	11	9.5	
Chronic myeloid leukaemia	7	6.0	2	1.7	
Myelodisplastic syndrome	1	0.9	15	12.9	
Lymphoma	38	32.8	37	31.9	
Hodgkin lymphoma	4	3.4	2	1.7	
Non-Hodgkin lymphoma	34	29.3	35	30.2	
PH negative myeloproliferative diseases	3	2.6	2	1.7	
Myelofibrosis	2	1.7	1	0.9	
Polycythemia vera	1	0.9	1	0.9	
Plasma cell disorders	27	23.3	33	28.4	
Multiple myeloma	26	22.4	32	27.6	
Amyloid light-chain amyloidosis	1	0.9	1	0.9	
Other haematological malignancies	0	0.0	1	0.9	
Aplastic anaemia	0	0.0	1	0.9	
Malignancy status at onset					1.000
Controlled disease	66	56.9	66	56.9	
Stable disease	15	12.9	15	12.9	
Active disease	35	30.2	35	30.2	
Last malignancy treatment at onset					0.172
No treatment	7	6.0	6	5.2	
alloHSCT	4	3.4	11	9.5	
In the last 6 months	3	2.6	2	1.7	
>6 months	1	0.9	9	7.8	
autoHSCT	7	6.0	4	3.4	
In the last 6 months	6	5.2	4	3.4	
>6 months	1	0.9	0	0.0	
CAR-T	0	0.0	2	1.7	
In the last 6 months	0	0.0	2	1.7	
>6 months	0	0.0	0	0.0	
Conventional chemotherapy	22	19.0	12	10.3	
In the last 3 months	21	18.1	9	7.8	
>3 months	1	0.9	2	1.7	
Unknown	0	0.0	1	0.9	
Demethylating agents	4	3.4	8	6.9	
In the last 3 months	4	3.4	7	6.0	
Unknown	0	0.0	1	0.9	
Immuno-chemotherapy	39	33.6	55	47.4	
In the last 3 months	30	25.9	51	44.0	
>3 months	9	7.8	4	3.4	
Immunotherapy	6	5.2	4	3.4	
In the last 3 months	6	5.2	1	0.9	
Unknown	0	0.0	3	2.6	
Targeted therapy	26	22.4	11	9.5	
In the last 3 months	25	21.6	11	9.5	
>3 months	1	0.9	0	0.0	
Supportive measures	1	0.9	3	2.6	
Neutrophils					0.442
<501	8	6.9	5	4.3	
501 - 999	4	3.4	2	1.7	
>999	83	71.6	92	79.3	

(*continued on next page*)

Table 1 (*continued*)

	Molnupiravir		Nirmatrelvir/ritonavir		*P* value
	n	%	*n*	%	
Lymphocytes					0.039
<201	18	15.5	7	6.0	
201 - 499	7	6.0	9	7.8	
>499	66	56.9	82	70.7	
Anti-SARS-CoV-2 vaccination at onset					<0.001
Days from last administration to onset	155 (91-272) [14-641]		247 (175-318) [39-588]		
Not vaccinated	39	33.6	29	25.0	
One dose	3	2.6	1	0.9	
Days from last administration to onset	229 (21-488) [21-488]		229 (229-229) [229-229]		
Two doses	27	23.3	12	10.3	
Days from last administration to onset	256 (160-288) [21-641]		300 (191-377) [39-588]		
Three doses	42	36.2	47	40.5	
Days from last administration to onset	113 (80-158) [14-319]		197 (134-287) [42-394]		
Four doses	5	4.3	27	23.3	
Days from last administration to onset	273 (230-407) [230-407]		928 (235-385) [69-439]		
Type of last anti-SARS-CoV-2 vaccine at onset					<0.001
mRNA	60	51.7	84	72.4	
BioNTech/Pfizer	60	51.7	63	54.3	
Moderna	0	0.0	21	18.1	
Vector-based	3	2.6	1	0.9	
AstraZeneca Oxford	2	1.7	1	0.9	
Janssen	1	0.9	0	0.0	
Inactivated	11	9.5	1	0.9	
CoronaVac	2	1.7	0	0.0	
Sinopharm	9	7.8	1	0.9	
Unknown	3	2.6	2	1.7	
SARS-CoV-2 variant					1.000
Delta	1	0.9	1	0.9	
Omicron	29	25.0	29	25.0	
Not tested	86	74.1	86	74.1	
Time of SARS-CoV-2 infection diagnosis					<0.001
October-December 2021	9	7.8	1	0.9	
January-March 2022	63	54.3	12	10.3	
April-June 2022	12	10.3	35	30.2	
July-September 2022	18	15.5	39	33.6	
October-December 2022	14	12.1	28	24.1	
January-March 2023	0	0.0	1	0.9	
SARS-CoV-2 infection severity					0.392
Asymptomatic	19	16.4	19	16.4	
Mild infection	34	29.3	29	25.0	
Severe infection	57	49.1	66	56.9	
Critical infection	6	5.2	2	1.7	
Stay during SARS-CoV-2 infection					1.000
Home	77	66.4	76	65.5	
Hospital	39	33.6	40	34.5	
Length of stay	15 (8-19) [2-29]		7 (2-10) [1-37]		
ICU	6	5.2	2	1.7	
Length of stay	15 (13-18) [2-26]		5 (5-5) [5-5]		
SARS-CoV-2 infection treatment					
Day of start since infection diagnosis	1 (0-2) [0-34]		1 (0-2) [0-47]		0.368
Antiviral treatment days	4 (4-4) [2-26]		4 (4-5) [1-10]		0.559
Outcome					1.000
Observation time	53 (23-81) [0-310]		43 (17-93) [0-327]		
Mortality, day 30	6	5.2	2	1.7	0.280
Mortality, day 60	7	6.0	5	4.3	0.768
Mortality, day 90	8	6.9	6	5.2	0.784
Alive, *last day of follow-up*	108	93.1	110	94.8	0.784
Observation time	55 (26-84) [0-310]		43 (17-94) [0-327]		
Dead, *last day of follow-up*	8	6.9	6	5.2	
Observation time	23 (13-34) [12-85]		38 (22-59) [14-67]		
Reason for death					0.592
COVID-19	5	4.3	2	1.7	
COVID-19 + haematological malignancy	3	2.6	4	3.4	

Continuous variables are summarised using median, interquartile range (IQR) and range

alloHSCT, allogeneic haematopoietic stem-cell transplantation; autoHSCT, autologous haematopoietic stem-cell transplantation; CAR-T, chimeric antigen receptors T cell receptors; COVID-19, coronavirus disease 2019; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome causing coronavirus type 2

*Molnupiravir: 23 (19.8%) patients received molnupiravir + corticosteroids, 3 (2.6%) patients molnupiravir + plasma, and 1 (0.9%) patient molnupiravir + corticosteroids + plasma. Nirmatrelvir/ritonavir: 12 (10.3%) patients received nirmatrelvir/ritonavir + corticosteroids.

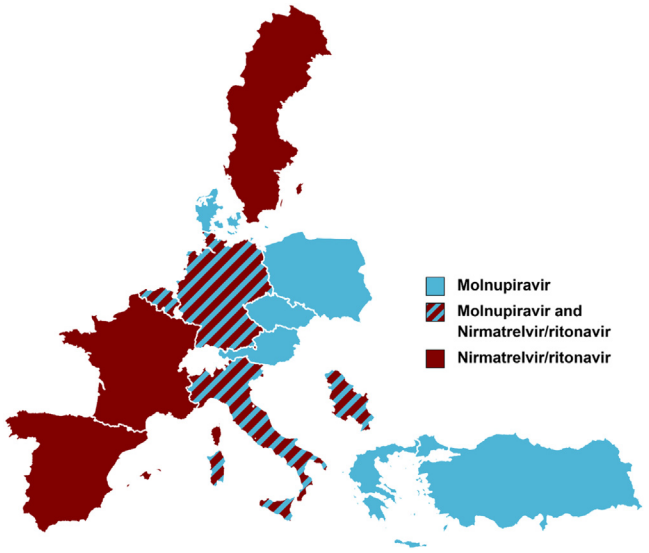

Figure 1. Geographical distribution of patients included in the matched-paired analysis. Red colour indicates patients with nirmatrelvir/ritonavir: Italy (n=38), Czech Republic (n=35), Serbia (n=19), Poland (n=11), Turkey (n=6), Austria (n=3), and Belgium, Denmark, Germany, Greece, and Sweden (n=1, each). Blue colour indicates patients with molnupiravir: Italy (n=54), Spain (n=33), Belgium (n=18), Serbia (n=4), and Germany and France (n=3, each). The pattern indicates that both treatments have been administered to patients as monotherapy.

trelvir/ritonavir controls: n=7, 6.0%) were more common in cases than in controls, with a significant difference for lymphopenia (P=0.039) but not for neutropenia (P=0.453). The percentage of unvaccinated patients was similar in the two groups (molnupiravir cases: n=39, 33.6%; nirmatrelvir/ritonavir controls: n=29, 25.0%). Over half the patients treated with molnupiravir had received two or three vaccine doses (cases: n=69, 59.5%), whereas over half the patients treated with nirmatrelvir/ritonavir had received three or four vaccine doses (controls: n=74, 63.8%; P<0.001). Inactivated vaccines were used as the last type of SARS-CoV-2 vaccine in 11 (9.5%) patients receiving molnupiravir and in one (0.9%) patient receiving nirmatrelvir/ritonavir ($P\leq$0.001, Table 1).

Over half the patients treated with molnupiravir (n=72, 62.1%) developed SARS-CoV-2 infection before April 2022, whereas 103 (88.8%) control patients treated with nirmatrelvir/ritonavir were infected after April 2022 (P<0.001). Although not a matching criterion, asymptomatic/mild COVID-19 was observed in a similar proportion of patients in the two treatment groups (molnupiravir cases: n=53, 45.7%; nirmatrelvir/ritonavir controls: n=48, 41.4%). Six (5.2%) cases and two (1.7%) controls had critical COVID-19 (P=0.280). One-third of patients in each group (molnupiravir cases: n=39, 33.6%; nirmatrelvir/ritonavir controls: n=40, 34.5%) were admitted to hospital during their COVID-19 episodes (P=1.000). Antiviral treatment was started a median of one day after SARS-CoV-2 infection diagnosis (P=0.368) and median duration of treatment was four days (P=0.559, Table 1).

Similar mortality rates were reported for the two groups at 30 days (molnupiravir cases: n=6, 5.2%; nirmatrelvir/ritonavir controls: n=2, 1.76%) (P=0.280), 60 days (molnupiravir cases: n=7, 6.0%; nirmatrelvir/ritonavir controls: n=5, 4.3%) (P=0.768), and 90 days (molnupiravir cases: n=8, 6.9%; nirmatrelvir/ritonavir controls: n=6, 5.2%) (P=0.784) after COVID-19 diagnosis. In the Kaplan-Meier plots for survival probability, no differences between drugs were observed at days 30 (P=0.190), 60 (P=0.671), and 90 (P=0.684) after diagnosis of SARS-CoV-2 infection (Table 1, Figure 2).

Discussion

Treating COVID-19 in patients at increased risk of progression to severe and critical disease has become standard clinical practice [22,31]. For logistical reasons, oral treatments are preferred over intravenous treatments for outpatients, and the current oral options are molnupiravir and nirmatrelvir/ritonavir [24]. Comparative studies are scarce [32,33]. The current study in patients with haematological malignancy matched cases and controls using well-established prognostic factors, and showed similar rates of clinical progression with these antiviral treatments. Hospitalisation and mortality rates at days 30, 60, and 90 did not differ significantly between patients receiving first-line treatment with either molnupiravir or nirmatrelvir/ritonavir.

For this analysis, cases treated with molnupiravir were matched 1:1 to controls receiving nirmatrelvir/ritonavir, based on variables of major relevance for mortality in vaccinated and unvaccinated patients with baseline haematological malignancies - age, sex, and status of malignancy at COVID-19 diagnosis [27–30] - thereby reducing potential bias. Such reduction in bias is noted through the lack of statistically significant differences in almost every comparison, with certain exceptions.

One of these exceptions was the prevalence of renal dysfunction. A significantly higher proportion of patients treated with molnupiravir had baseline kidney failure compared with controls. This may be explained by one of the caveats for the use of nirmatrelvir/ritonavir: glomerular filtration rate [8]. Medical teams must scrutinise glomerular filtration rates in their patients and adjust the nirmatrelvir/ritonavir dose, when needed, to minimise any potential adverse effect. Molnupiravir may be a safer option [7,24].

Other observed differences between the patients receiving molnupiravir and those receiving nirmatrelvir/ritonavir were in the vaccination schemes used before SARS-CoV-2 infection. Patients on molnupiravir received fewer vaccine doses, mainly two or three doses, than patients on nirmatrelvir/ritonavir, who mostly received three or four doses. Additionally, most of the patients who had received inactivated vaccines prior to SARS-CoV-2 infection diagnosis were receiving molnupiravir. Patients diagnosed with COVID-19 earlier in the course of the pandemic more often received molnupiravir. This may be explained by the fact that molnupiravir was made available earlier in Europe (November 2021) [24] than nirmatrelvir/ritonavir (December 2021) [34] for patients at high risk. Additionally, the sooner the diagnosis was made, the lower the chances were to have received further doses of anti-SARS-CoV-2 vaccine, in line with evolving vaccination campaigns [35]. The difference in the type of the last vaccine received before diagnosis (i.e., mRNA-based, vector-based, or inactivated) was associated with the geographical setting of molnupiravir patients. The 11 patients receiving inactivated vaccines were from institutions in Serbia and Turkey. Of those 11 patients, 10 were treated with molnupiravir. In both countries there was a wider variety of vaccines available than in other European countries [36–38].

Patients receiving molnupiravir had a higher prevalence of lymphopenia at onset of SARS-CoV-2 infection. A larger number of patients with baseline leukaemia, together with the reported drug-drug interactions and associated contraindications to nirmatrelvir/ritonavir administration, may explain physician preference for molnupiravir over nirmatrelvir/ritonavir in these patients.

Cases and controls were hospitalised at similar rates during the COVID-19 episode. Twice as many patients receiving molnupiravir compared with those receiving nirmatrelvir/ritonavir were admitted to an ICU but there was no evidence of a possible correlation with the outcome. Of note, only three of the seven patients admitted to the ICU had lymphocyte levels below 500 cells/μL at COVID-19 onset.

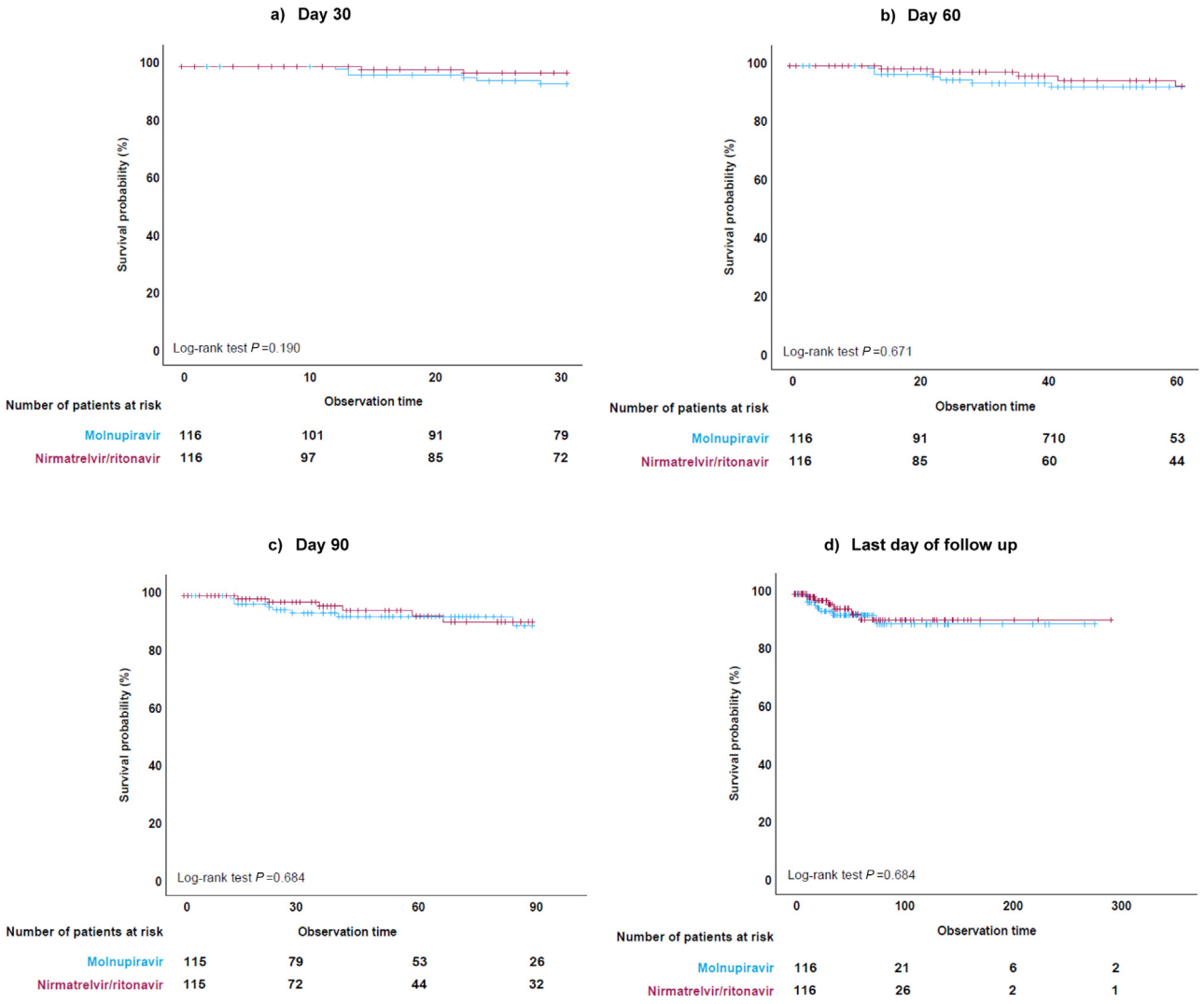

Figure 2. Survival probability of patients at days 30, 60 and 90 since SARS-CoV-2 infection and at last day of follow-up.

Indications for antiviral use are similar for molnupiravir and nirmatrelvir/ritonavir: treatment is to start within the first five days of SARS-CoV-2 infection and for a five-day duration [21,39]. In both groups (cases and controls), the data showed that the median treatment initiation was immediately after confirmation of diagnosis, in line with current recommendations. Interestingly, for both drugs the median administration time was only four days instead of the recommended five days. As described in a previous analysis of nirmatrelvir/ritonavir use in the EPICOVIDEHA registry [26], 50 patients of which have been included in the current comparative analysis, access to oral antivirals during the COVID-19 pandemic was not always stable. Thus, antiviral administration according to manufacturers' information, although important, may be hampered during a pandemic.

The main goal of the current work was to analyse whether there were significant differences in survival rates between patients treated with molnupiravir and those treated with nirmatrelvir/ritonavir. There were no statistically significant differences between treatments in mortality rates and survival probabilities at 30, 60 and 90 days after SARS-CoV-2 infection diagnosis and at last day of follow up. Considering the matched-paired nature of this analysis, and the lack of significant differences between cases and controls in factors potentially associated with mortality, the results support molnupiravir as an effective treatment preventing COVID-19 progression to severe forms in haematological patients. Although concerns have been raised about the mutagenicity of molnupiravir, these have not yet been confirmed [13,40].

Limitations of the current analysis include the retrospective nature of the EPICOVIDEHA registry and the predefined set of variables collected not being directed to drug safety information. The current administration practices for antivirals in Europe may be influenced by drug accessibility. Many participating hospitals could not access molnupiravir tablets as their use was not authorised in these institutions. In many cases, as described by patient contributors, the only alternative for nirmatrelvir/ritonavir was intravenous remdesivir. The reason for preference for one drug over the other could not be established; this would be an interesting study in settings where both oral antivirals are available. Finally, the number of patients analysed is only 338. EPICOVIDEHA was initiated in April 2020 and comprises more than 9000 patients with haematological malignancy and COVID-19. As oral antivirals became available only recently, the number of patients treated with these drugs is low. However, the authors acknowledge the medical need to share data as early as they evolve. Further analyses may also consider viral mutations, long-term complications of COVID-19, or post-acute sequelae of COVID-19.

In conclusion, patients with baseline haematological malignancies at high-risk for severe COVID-19 benefit from the administra-

tion of molnupiravir. Moreover, molnupiravir is an alternative to nirmatrelvir/ritonavir in patients with limited treatment options, for example, because of baseline renal compromise or concomitant drugs with relevant drug-drug interactions.

Declarations

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Competing Interests: JSG reports speaker honoraria from Gilead and Pfizer, outside of the submitted work.

PK reports grants or contracts from German Federal Ministry of Research and Education (BMBF) B-FAST (Bundesweites Forschungsnetz Angewandte Surveillance und Testung) and NAPKON (Nationales Pandemie Kohorten Netz, German National Pandemic Cohort Network) of the Network University Medicine (NUM) and the State of North Rhine-Westphalia; Consulting fees Ambu GmbH, Gilead Sciences, Mundipharma Resarch Limited, Noxxon N.V. and Pfizer Pharma; Honoraria for lectures from Akademie für Infektionsmedizin e.V., Ambu GmbH, Astellas Pharma, BioRad Laboratories Inc., Datamed GmbH, European Confederation of Medical Mycology, Gilead Sciences, GPR Academy Ruesselsheim, HELIOS Kliniken GmbH, Lahn-Dill-Kliniken GmbH, medupdate GmbH, MedMedia GmbH, MSD Sharp & Dohme GmbH, Pfizer Pharma GmbH, Scilink Comunicación Científica SC and University Hospital and LMU Munich; Participation on an Advisory Board from Ambu GmbH, Gilead Sciences, Mundipharma Resarch Limited and Pfizer Pharma; A pending patent currently reviewed at the German Patent and Trade Mark Office (DE 10 2021 113 007.7); Other nonfinancial interests from Elsevier, Wiley and Taylor & Francis online outside the submitted work.

AT reports conflicts of interest from Pfizer, Sanofi, GSK, and MSD, outside of the submitted work.

AG reports consultancy and/or advisory board from Agios, bluebird bio, Bristol Myers Squibb, Novartis, Novo Nordisk, and Pharmacosmos and research support from Agois, Bristol Myers Squibb, Saniona, and Sanofi.

LP reports conflict of interest from PFIZER, GILEAD, JAZZ, JANNSEN, CIDARA, MENARINI, and STEMLINE, outside of the submitted work.

OAC reports grants or contracts from Amplyx, Basilea, BMBF, Cidara, DZIF, EU-DG RTD (101037867), F2G, Gilead, Matinas, MedPace, MSD, Mundipharma, Octapharma, Pfizer, Scynexis; Consulting fees from Abbvie, Amplyx, Biocon, Biosys, Cidara, Da Volterra, Gilead, IQVIA, Janssen, Matinas, MedPace, Menarini, Molecular Partners, MSG-ERC, Noxxon, Octapharma, Pardes, Pfizer, PSI, Scynexis, Seres; Honoraria for lectures from Abbott, Abbvie, Al-Jazeera Pharmaceuticals, Astellas, Gilead, Grupo Biotoscana/United Medical/Knight, Hikma, MedScape, MedUpdate, Merck/MSD, Mylan, Noscendo, Pfizer, Shionogi; Payment for expert testimony from Cidara; Participation on a Data Safety Monitoring Board or Advisory Board from Actelion, Allecra, Cidara, Entasis, IQVIA, Janssen, MedPace, Paratek, PSI, Pulmocide, Shionogi, The Prime Meridian Group; A patent at the German Patent and Trade Mark Office (DE 10 2021 113 007.7); Stocks from CoRe Consulting, EasyRadiology, outside of the submitted work.

Ethical Approval: EPICOVIDEHA has its central Ethics Committee at the Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Università Cattolica del Sacro Cuore of Rome, Italy (Study ID: 3226). According to specific local regulation, each of the participating institutions might have their own ethical approval as appropriate.

Sequence Information: Not applicable

Author contributions

JSG, FM, LP and OAC contributed to study design and study supervision. JSG did the statistical plan and analysis. JSG, PK and OAC interpreted the data and wrote the initial draft of the manuscript. All the authors recruited, and documented participants, critically read and reviewed, and agreed to publish the manuscript.

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