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La terapia con anticorpi monoclonali: ruolo attuale e prospettive future

SCHOOL OF MEDICINE AND SURGERY

Disclosure of conflicts of interest

- I herewith declare the following paid or unpaid consultancies, business interests, grants and research support or sources of honoraria payments for the past three years, and anything else which could potentially be viewed as a conflict of interest:

- Travel Grants &/or Congress Registration : Abbvie, Gilead Sciences, Pfizer

- Research grants: Abbvie, Gilead Sciences

- Honoraria: Abbvie, Gilead Sciences, Merck, GSK, Astra Zeneca, Takeda, Novartis

La terapia con anticorpi monoclonali: ruolo attuale e prospettive future
- Outline

- Anticorpi monoclonali in infettivologia e nel trattamento e prevenzione COVID-19
- Impiego degli anticorpi monoclonali in Italia
- Resistenza ed inefficacia in era Omicron
- Dati nel paziente immunocompromesso ed ematologico
- Raccomandazioni delle linee guida
- Prospettive future
- Conclusioni

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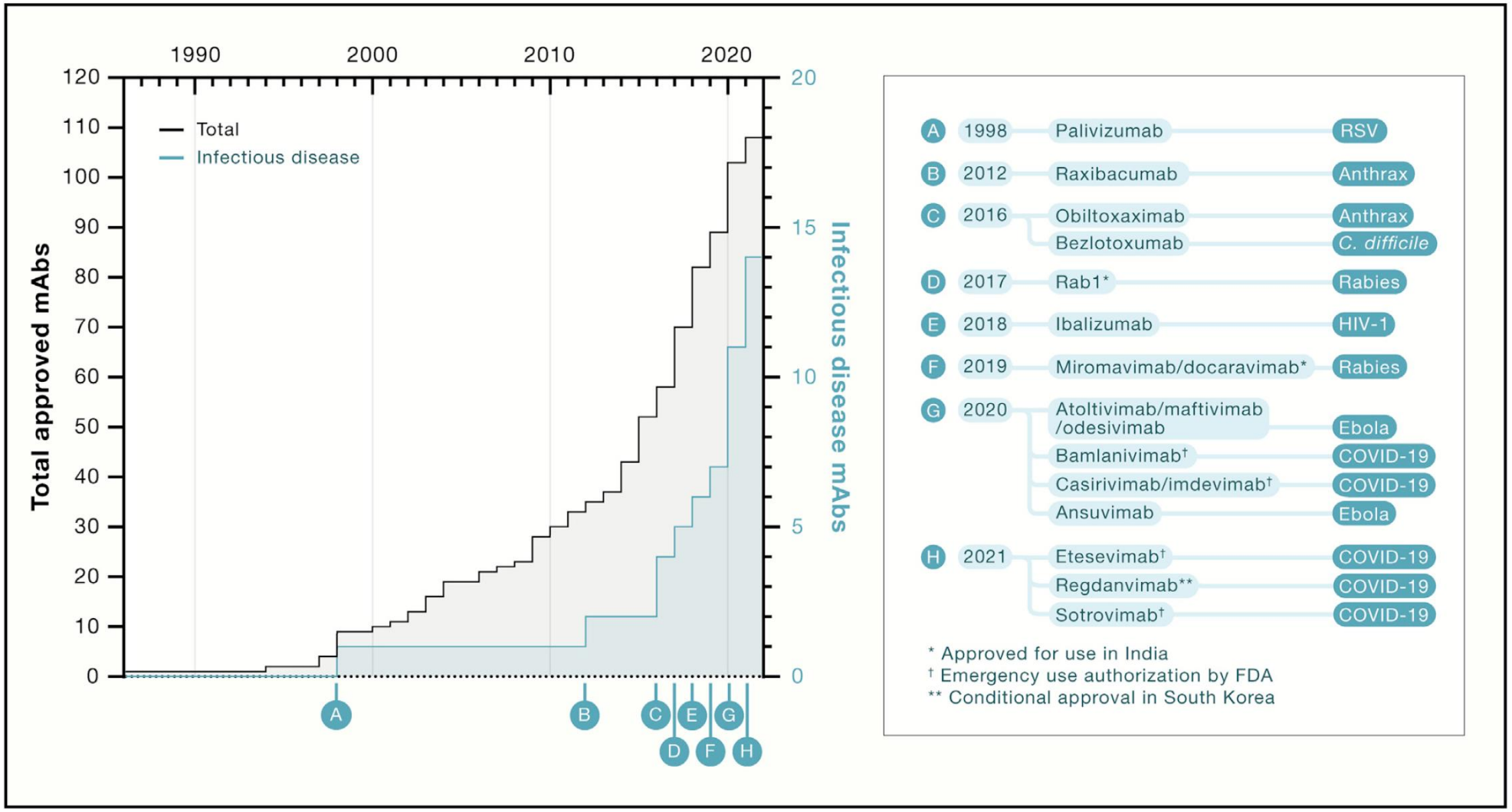
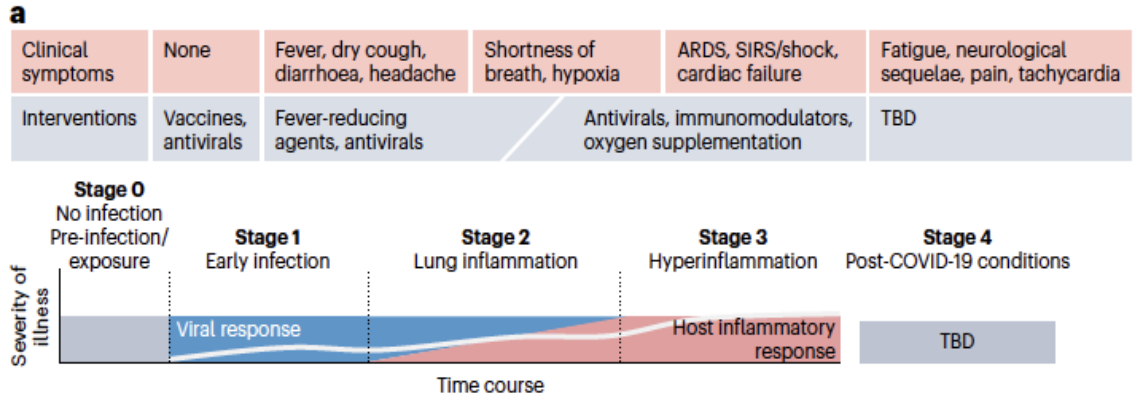
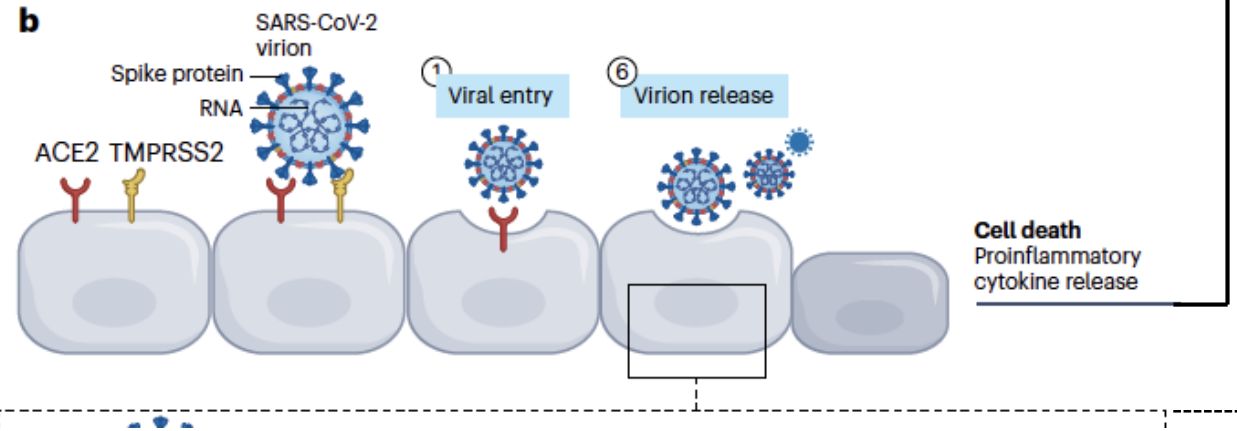
Timeline of approval of mAbs for all indications and for infectious disease (2021)

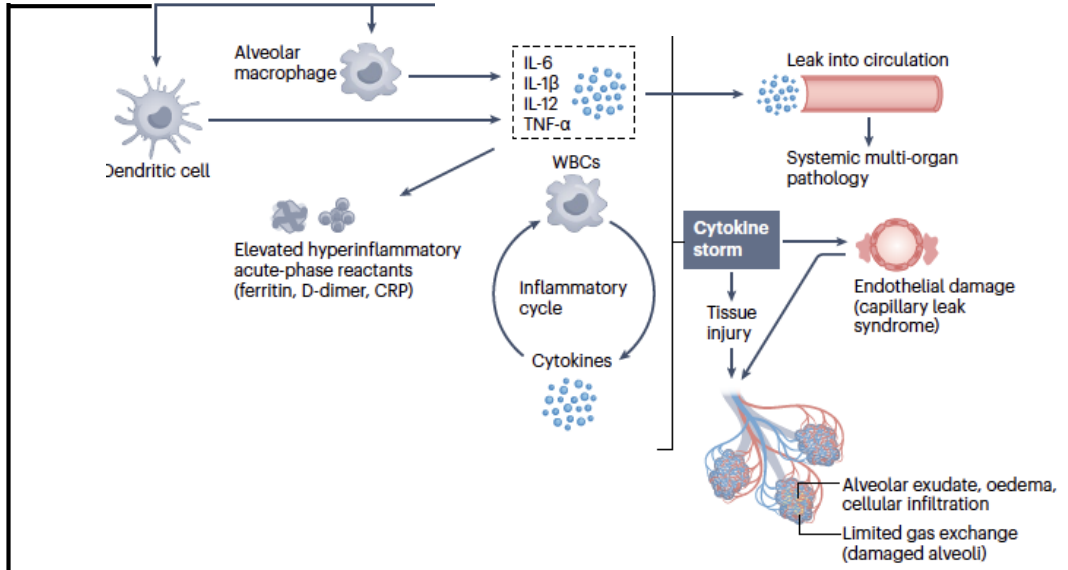


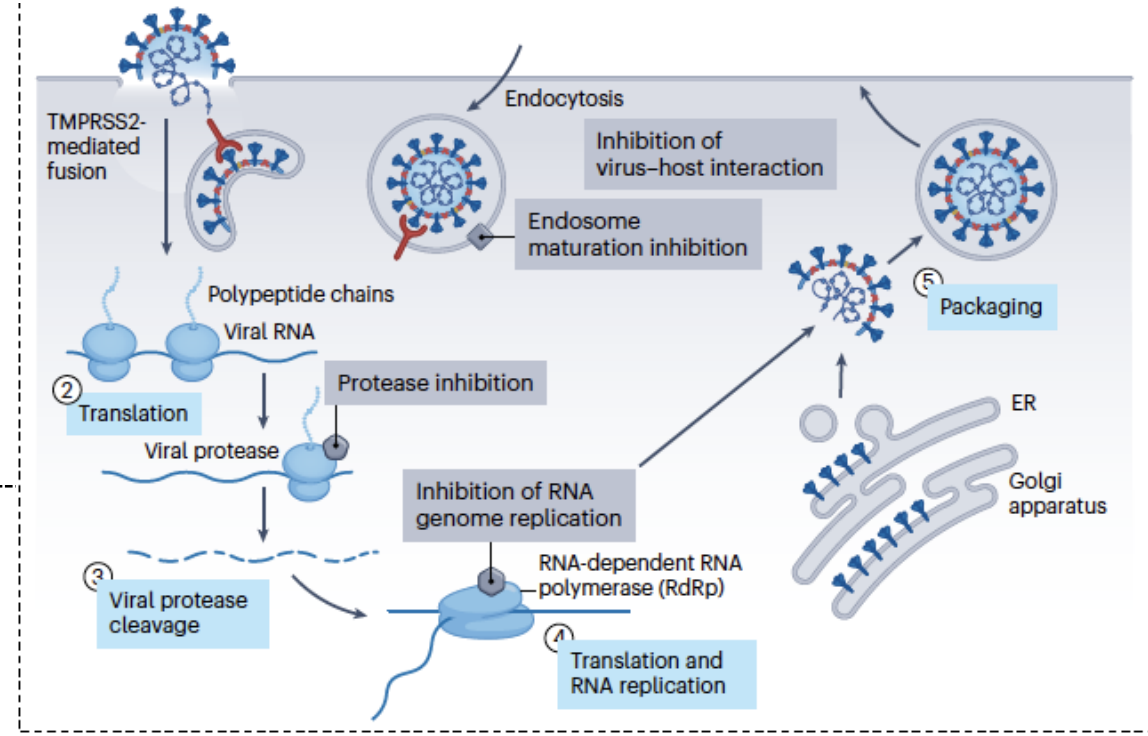
Approved mAbs= 108
Approved for ID = 14
Approved for COVID-19 =5

Therapeutics for COVID-19



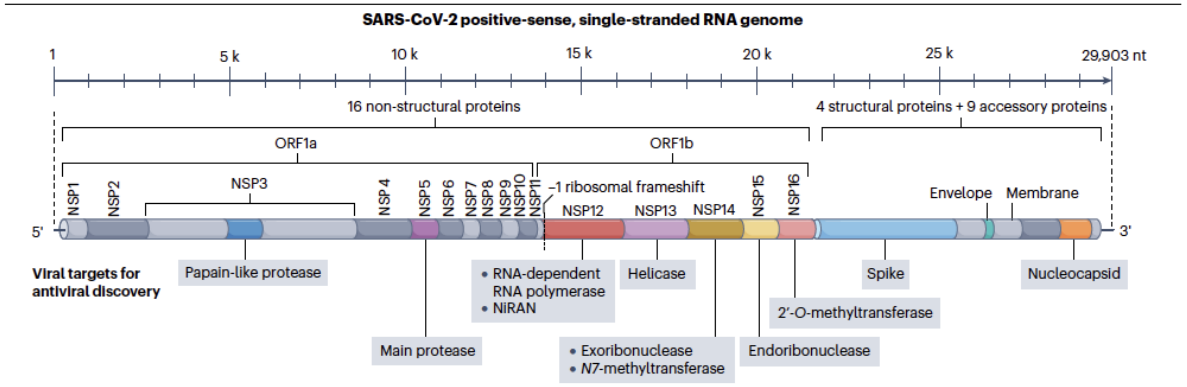






Toussi S et al Nature Microbiology 2023; 8: 771–786

Treatment for SARS-CoV-2 infection

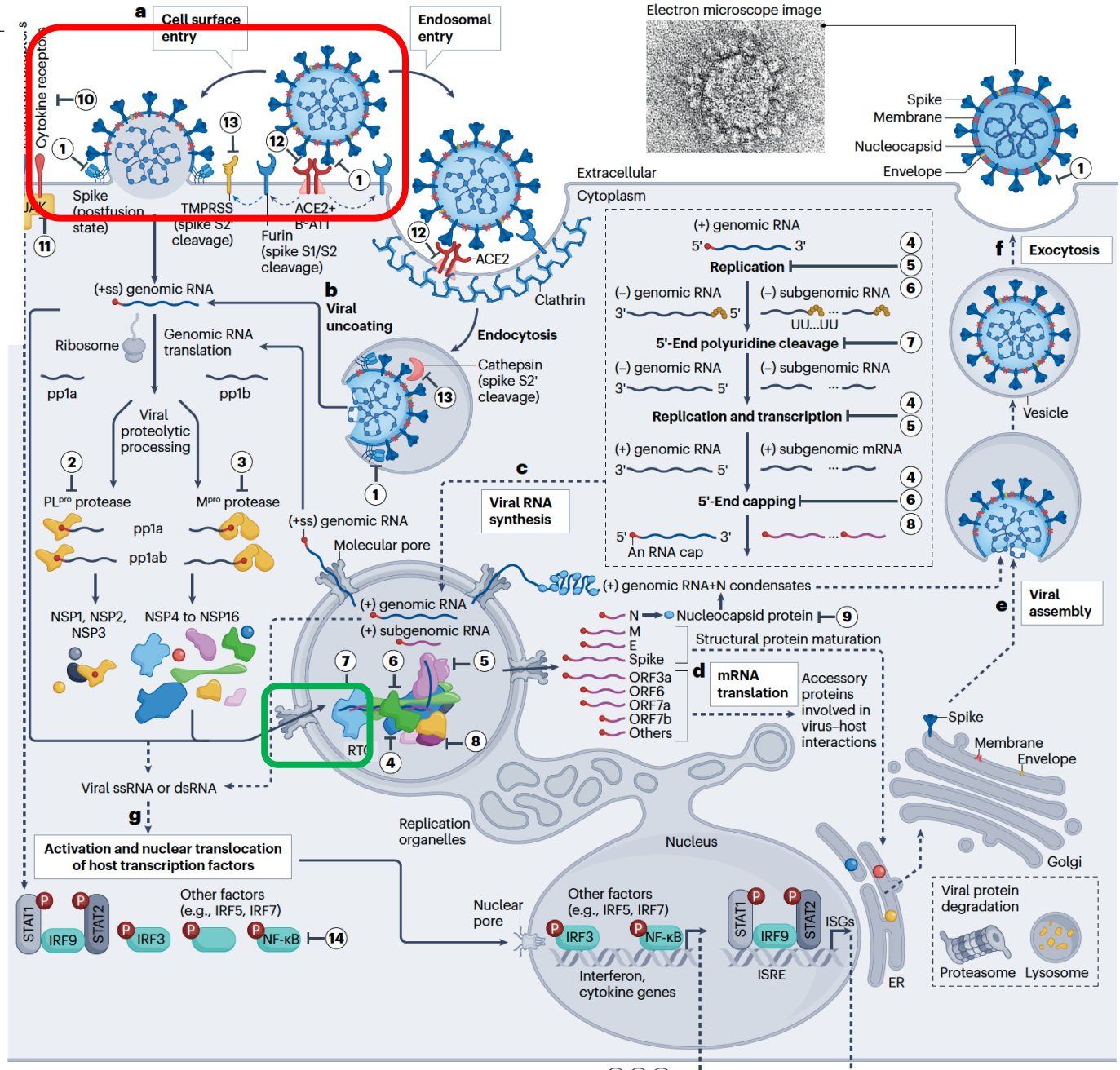


Virus-targeted agents

1. Spike inhibitors
2. PL^{pro} inhibitors
3. M^{pro} inhibitors
4. NSP12 inhibitors
5. NSP13 inhibitors
6. NSP14 inhibitors
7. NSP15 inhibitors
8. NSP16 inhibitors
9. Nucleocapsid inhibitors

Host-targeted agents

10. Cytokine inhibitors
11. JAK inhibitors
12. ACE2 inhibitors
13. Host protease inhibitors
14. Glucocorticoids
15. Anticoagulants



Li G aet al Nat Rev Drug Disc https://doi.org/10.1038/s41573-023-00672-y

Dual action of antiviral Mabs : Neutralization and effector functions

Neutralization activity against viruses in vitro and in vivo, which protects uninfected cells from becoming infected[1]

Effector functions in vitro that may

- activate complement and complement related virolysis
- recruit the host immune system to kill already infected cells[1]

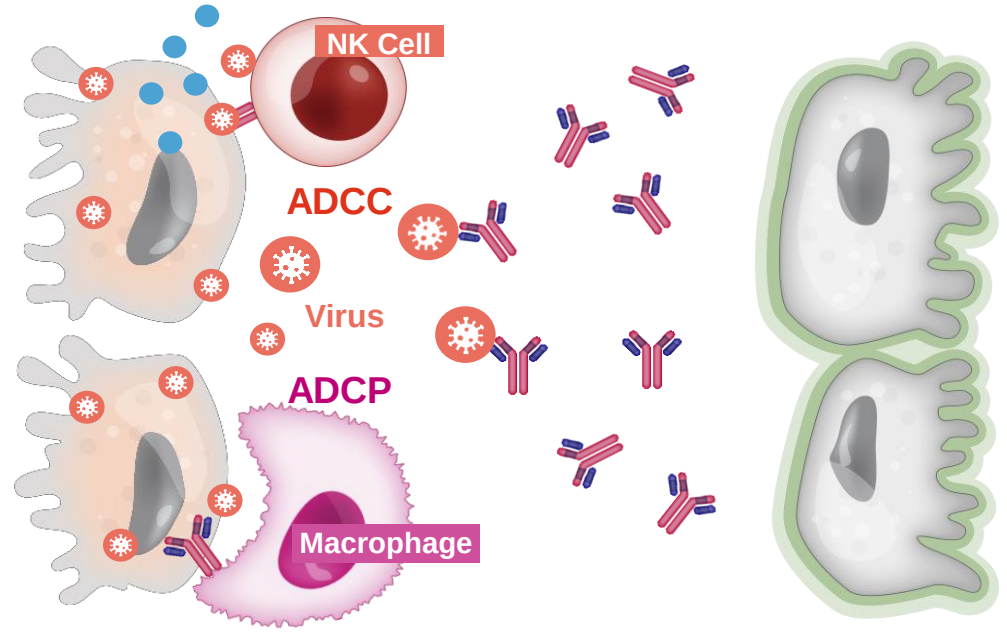
Antibody-dependent cell cytotoxicity (ADCC)[1–3]:

- mediated by natural killer cells
- triggers apoptosis of virus-infected target cells

Antibody-dependent cellular phagocytosis (ADCP)[1,2,4]:

- mediated by macrophages or dendritic cells
- helps clear virus and infected cells by engulfing/ destroying viral particles and stimulating a T-cell response

Neutralizing Activity and Antibody Effector Mechanisms

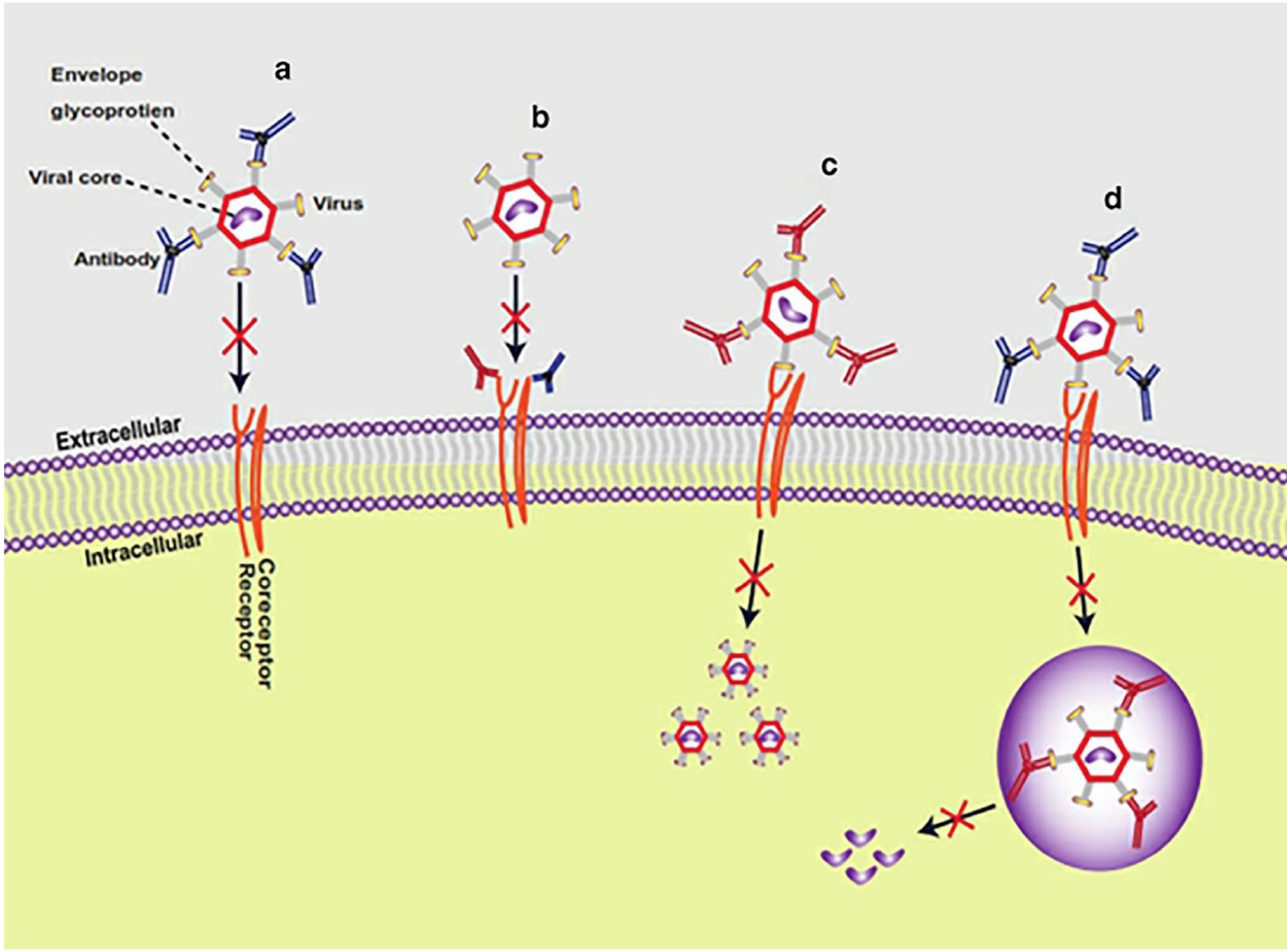


NK, natural killer; SARS-CoV, severe acute respiratory syndrome coronavirus.

1. Cathcart AL, et al. *bioRxiv* (preprint). doi: 10.1101/2021.03.09.434607; 2. Pinto D, et al. *Nature*. 2020;583:290–5; 3. Jegaskanda S, et al. *J Immunol*. 2014;193(2):469-475; 4. Sicca F, et al. *Expert Rev Vaccines*. 2018;17:785–95.

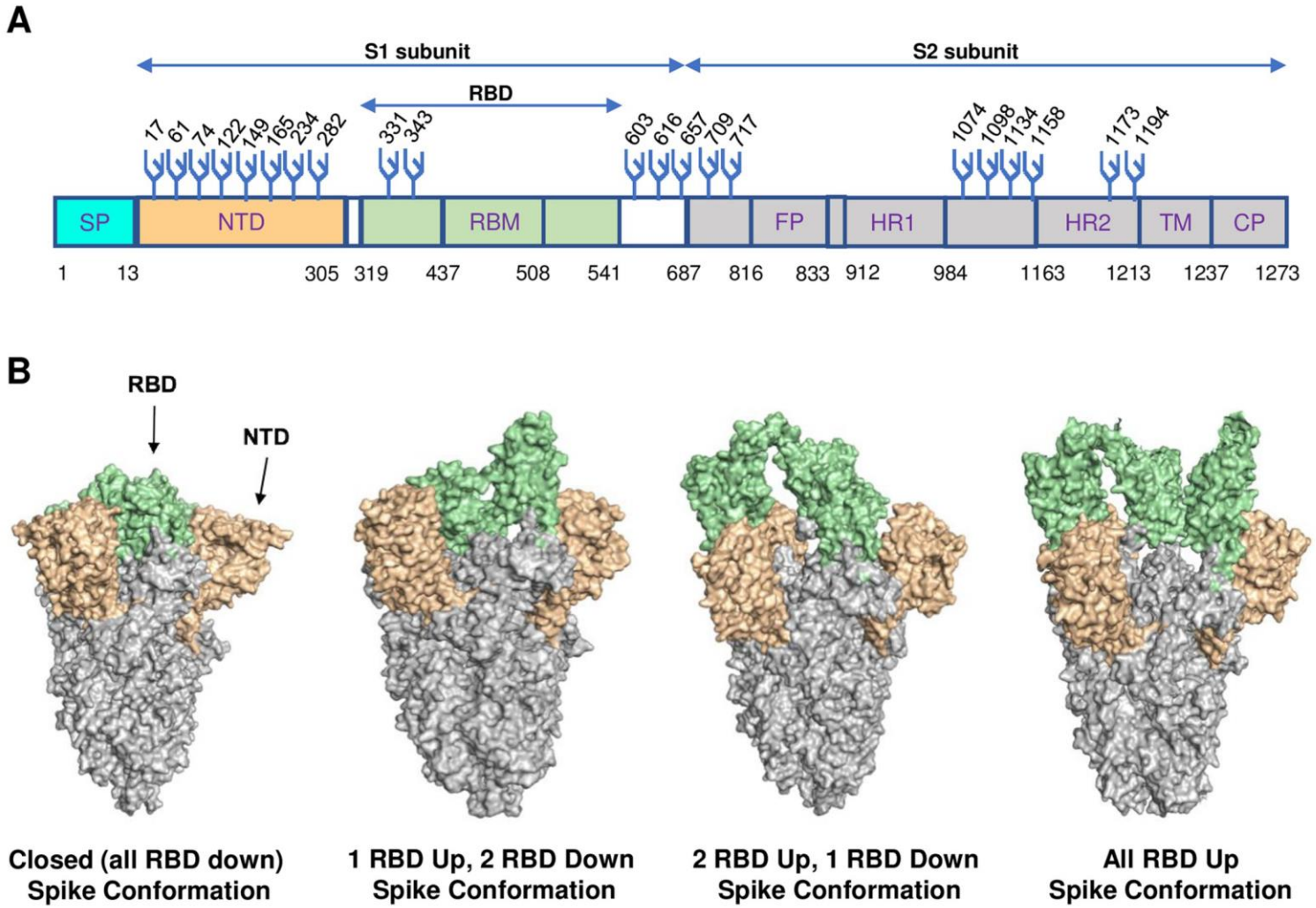
Modes of activity of antiviral antibodies: Neutralization

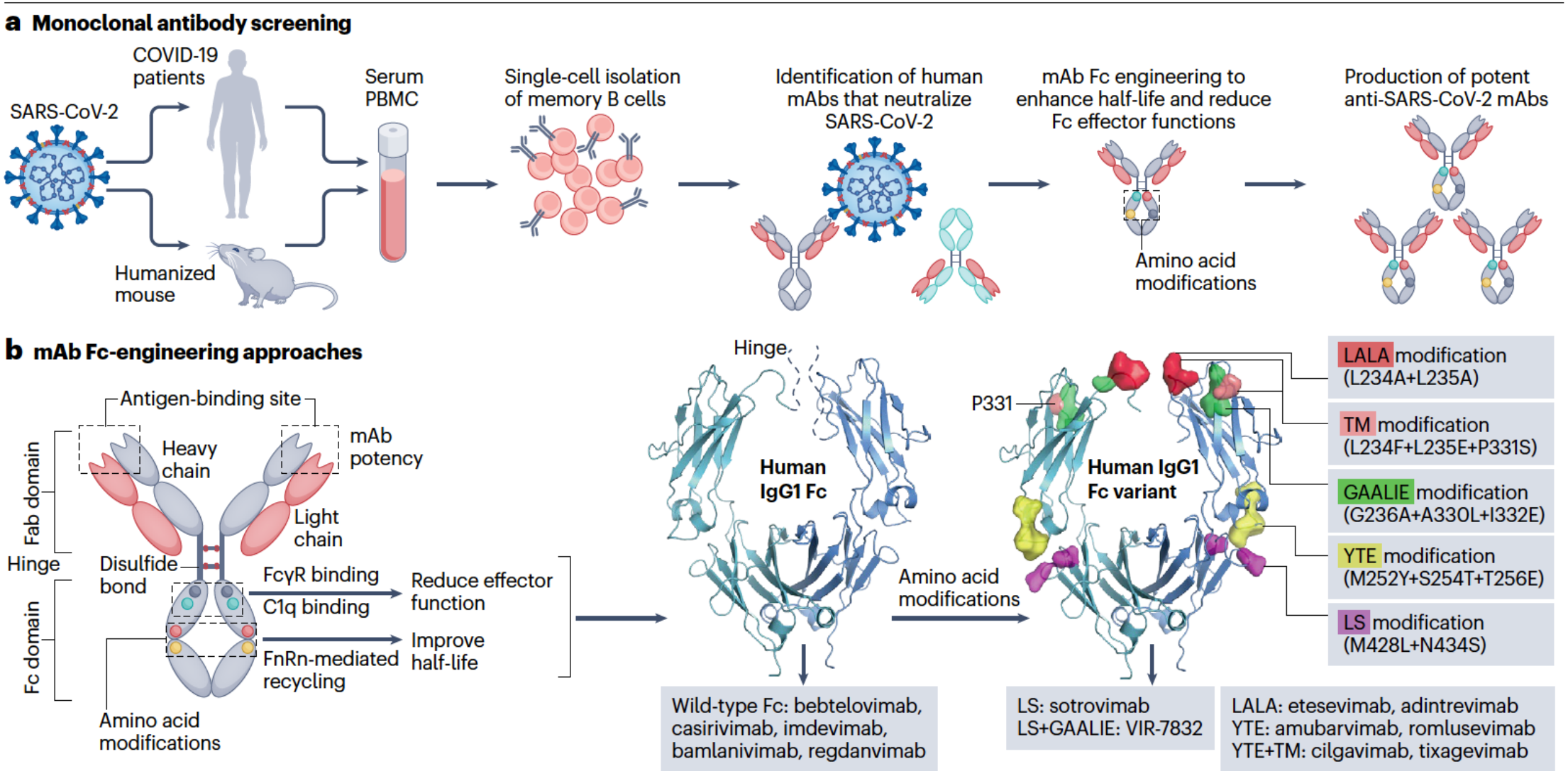
- Antibodies neutralize viruses by
- Inhibition of virus entry
  - Binding to an epitope in the viral glycoprotein envelope, lead to inhibit attachment to host cells.
  - (Antibodies through the fab region can bind to host cell receptors or coreceptors (have Fcγr)) lead to inhibit viral entry.
- Post binding inhibition of antibody-virus complex as
  - antibodies can bind to a non-binding region in the virus envelope lead to inhibit the conformational change to allow membrane fusion.
  - for certain viruses that need low endosomal PH for conformational change, antibodies bind to viral inside the endosome lead to inhibit the change in PH to achieve the membrane fusion, and antibodies can inhibit the release of the viral virio



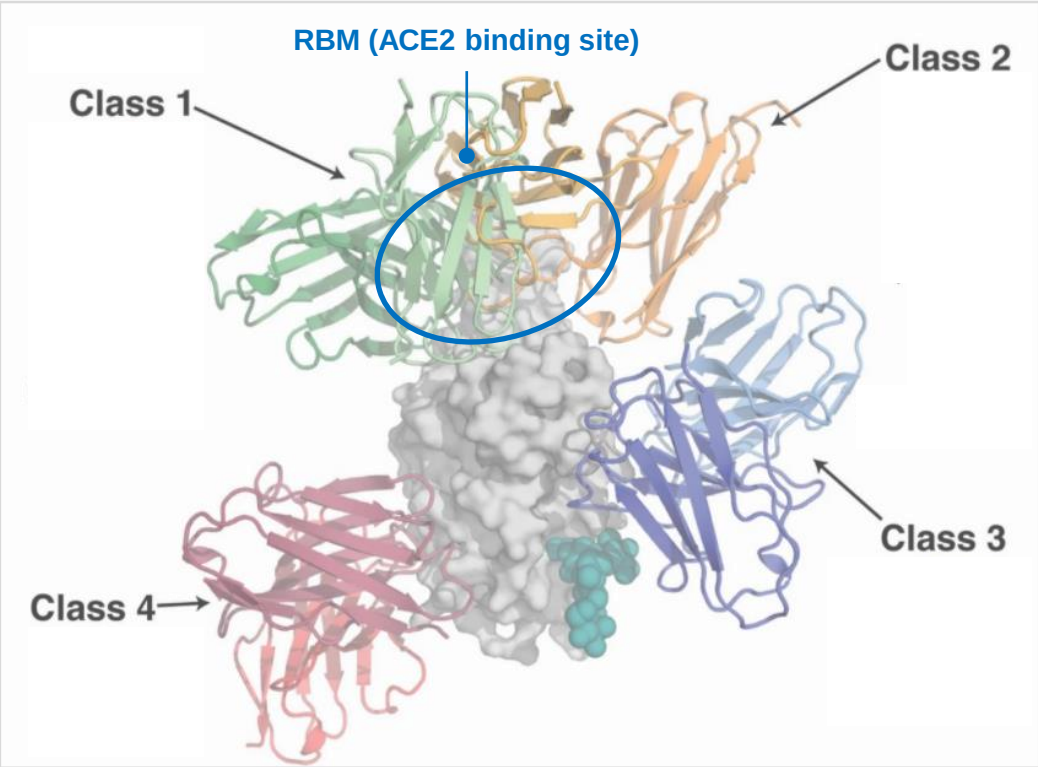
Ali GM et al Immunologic Research (2020) 68:325–339

SARS-CoV-2 spike protein structure and conformation




a Monoclonal antibody screening
COVID-19 patients
SARS-CoV-2
Humanized mouse
Serum PBMC
Single-cell isolation of memory B cells
Identification of human mAbs that neutralize SARS-CoV-2
mAb Fc engineering to enhance half-life and reduce Fc effector functions
Amino acid modifications
Production of potent anti-SARS-CoV-2 mAbs
b mAb Fc-engineering approaches
Antigen-binding site
Heavy chain
mAb potency
Light chain
Fab domain
Hinge
Disulfide bond
Fc domain
Amino acid modifications
FcγR binding
C1q binding
Reduce effector function
FnRn-mediated recycling
Improve half-life
Hinge
Human IgG1 Fc
Wild-type Fc: bebtelovimab, casirivimab, imdevimab, bamlanivimab, regdanvimab
Amino acid modifications
P331
Human IgG1 Fc variant
LS: sotrovimab
LS+GAALIE: VIR-7832
LALA modification (L234A+L235A)
TM modification (L234F+L235E+P331S)
GAALIE modification (G236A+A330L+I332E)
YTE modification (M252Y+S254T+T256E)
LS modification (M428L+N434S)
LALA: etesevimab, adintrevimab
YTE: amubarvimab, romlusevimab
YTE+TM: cilgavimab, tixagevimab

Antibodies against the SARS-CoV-2 spike protein are classified according to their binding site



The illustration has been reproduced with permission from Barnes CO, et al. *Nature* 2020;588:682–7

Classification	Structural characteristics
Class 1/Site Ia	• Blocks ACE2 • Binds only to 'up' RBDs
Class 2/Site Ib	• Blocks ACE2 • Binds both 'up' and 'down' RBDs • Can contact adjacent RBDs
Class 3/Site IV	• Binds outside the RBM (ACE2 binding site) • Recognizes both 'up' and 'down' RBDs
Class 4/Site IIa IIc	• Does not block ACE2 • Binds only to 'up' RBDs

ACE2, angiotensin-converting enzyme 2; RBD, receptor binding domain; RBM, receptor binding motif

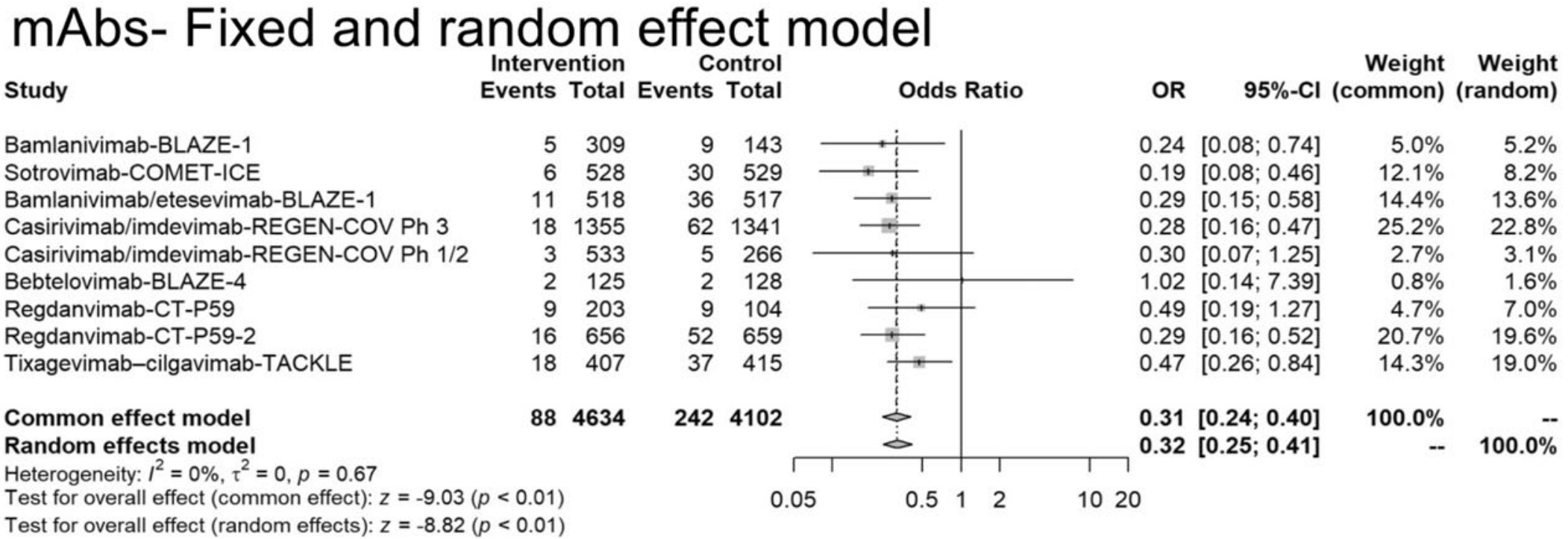
1. Barnes CO, et al. *Nature* 2020;588:682–7

mAb	Company	Stage	PDB	Target
STI-2020	Sorrento Therapeutics	Phase 2		
Adintrevimab	Adagio Therapeutics	Phase 3	7U2D	RBD Core Cluster I
C135	Rockefeller University	Phase 2/3	7K8Z	RBD Core Cluster I
ABBV-47D11	Utrecht University & AbbVie	Phase 1	7AKD	RBD Core Cluster I
Sotrovimab	Vir Biotechnol	EUA	6WPS	RBD Core Cluster I
Imdevimab	Regeneron	EUA	6XDG	RBD Core Cluster I
Romlusevimab	Brii Biosciences	CN-Approved		RBD Core Cluster II
Regdanvimab	Celltrion	KR-Approved	7CM4	RBM Class I
Casirivimab	Regeneron	EUA	6XDG	RBM Class I
Etesevimab	Eli Lilly	EUA	7C01	RBM Class I
Tixagevimab	AstraZeneca	EUA	7L7E	RBM Class I
Amubarvimab	Brii Biosciences	CN-Approved	7CDI	RBM Class I
DXP-604	Singlomics Biopharmaceuticals	CN-Approved	7CH4	RBM Class I
Cilgavimab	AstraZeneca	EUA	7L7E	RBM Class II
Bebtelovimab	Eli Lilly	EUA	7MMO	RBM Class II
Bamlanivimab	Eli Lilly	EUA	7KMG	RBM Class II
C144	Rockefeller University	Phase 2/3	7K90	RBM Class III

- RBD core mAbs target a surface accessible part of the RBD that is separate from the RBM. 2

- RBM (receptor binding motif) is the part of the receptor binding domain (RBD) that contains the spike ACE2 binding residues.
  - RBM class I mAbs bind epitopes dominated by ACE2-binding residues and as a result bind solely when the RBD is in the up/open position.
  - RBM class II mAbs have a smaller ACE2-binding footprint and can often bind the RBD in down/closed position.

Metanalysis Odds ratio for Hospitalization in trials with mAbs



Sullivan D et al J Med Virol. 2023;95:e29310. https://doi.org/10.1002/jmv.29310

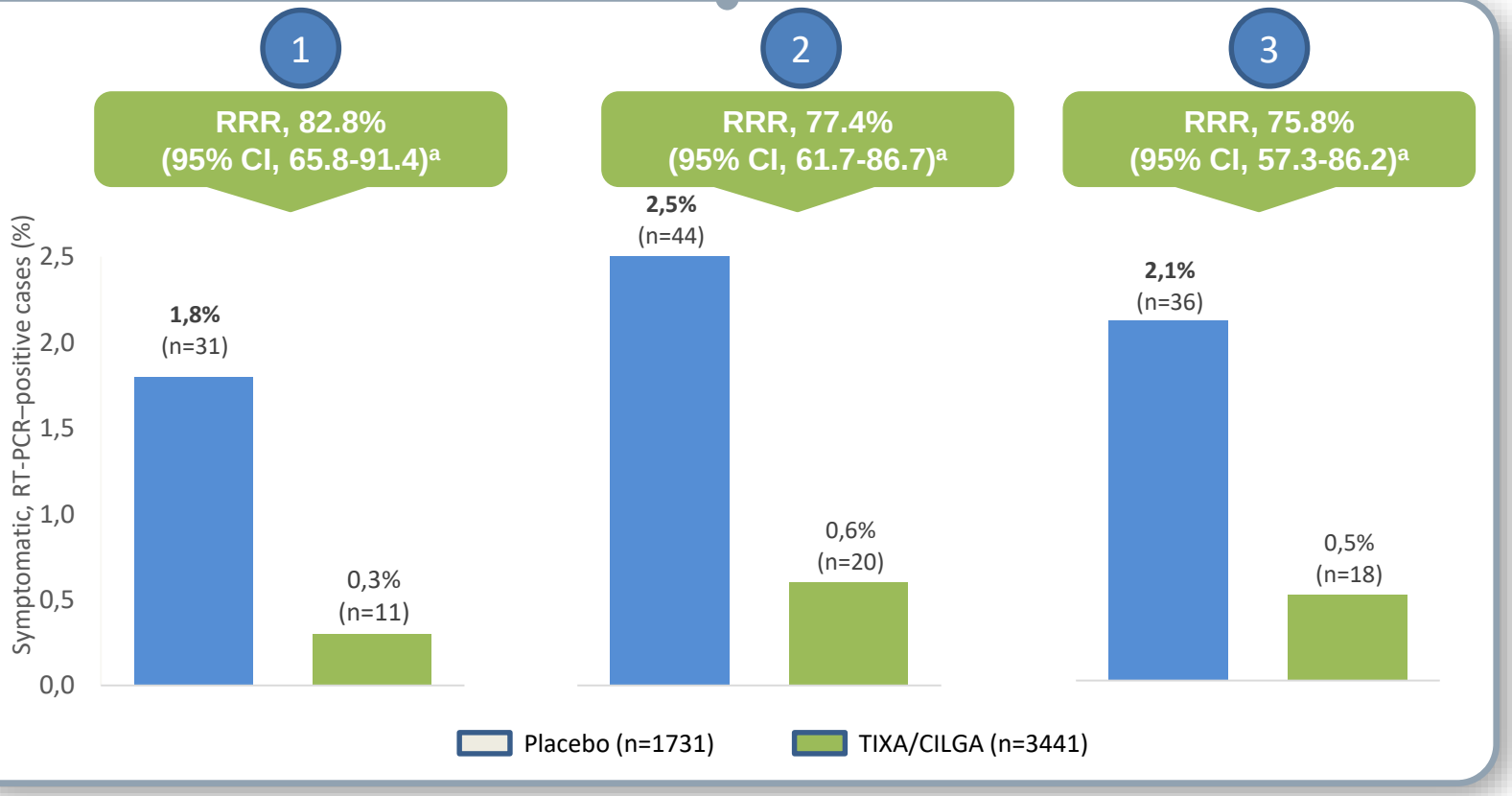
PROVENT: Phase III Randomized, Double-blind, Parallel-Group, Placebo-Controlled, Multicenter Study of Tixagevimab/Cilgavimab for Pre-exposure Prophylaxis in 5197 Participants[1,2]

ClinicalTrials.gov identifier: NCT04625725
Status: active, not recruiting
Completion date: June 2022

Primary and key supportive efficacy endpoints

1. **Primary:** First SARS-CoV-2 RT-PCR–positive symptomatic illness (censored at unblinding or receipt of COVID-19 vaccine)
2. **Key supportive:** First case of SARS-CoV-2 RT-PCR–positive symptomatic illness (regardless of unblinding or receipt of COVID-19 vaccine)
3. **Key supportive:** First case of SARS-CoV-2 RT-PCR–positive symptomatic illness including all deaths (censored at unblinding or receipt of COVID-19 vaccine)

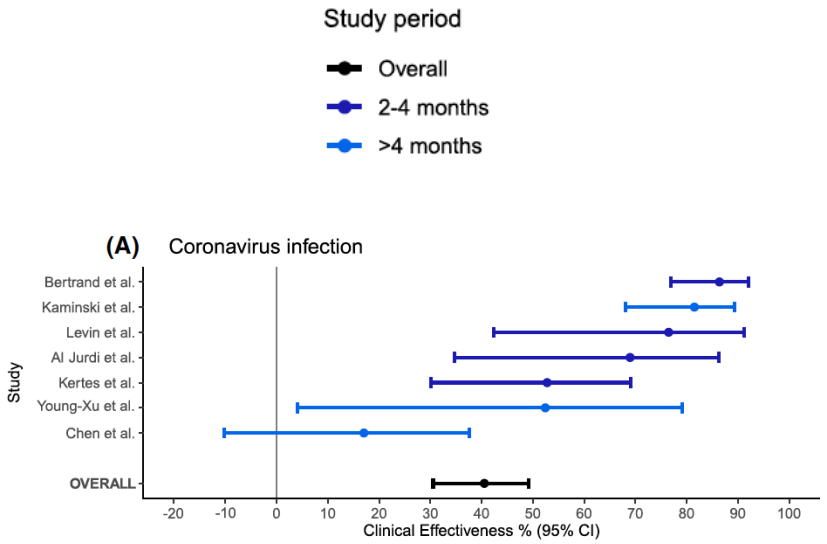
The median 6-month follow-up data analyses demonstrated greater reductions in COVID-19 incidence



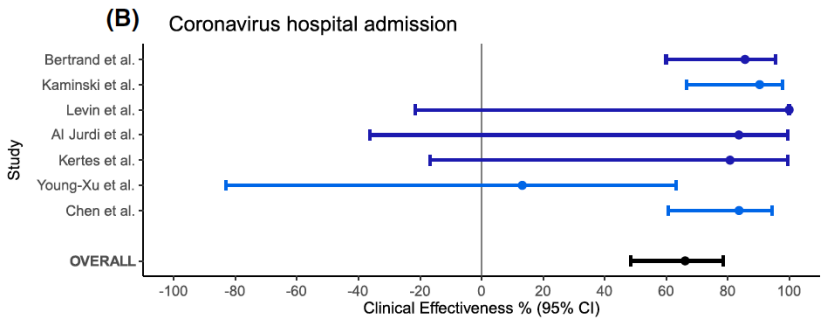
[a]The analysis was not prespecified in the study protocol, so p-values were not calculated.[2]
CI = confidence interval; COVID-19 = coronavirus disease 2019; RRR = relative risk reduction; RT-PCR = reverse transcriptase–polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TIXA/CILGA = tixagevimab/cilgavimab.

1. Study NCT04625725. ClinicalTrials.gov website; 2. Levin MJ et al. Online ahead of print. *N Engl J Med*. 2022.

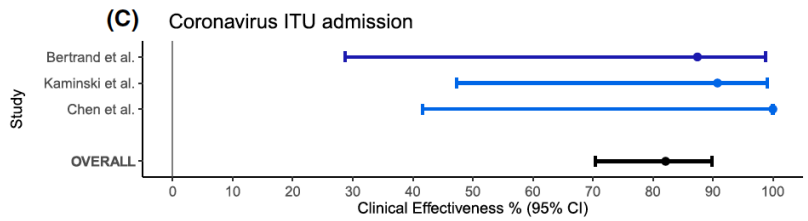
Systematic review and meta-analysis of the clinical effectiveness of tixagevimab/cilgavimab for prophylaxis of COVID-19 in immunocompromised patients



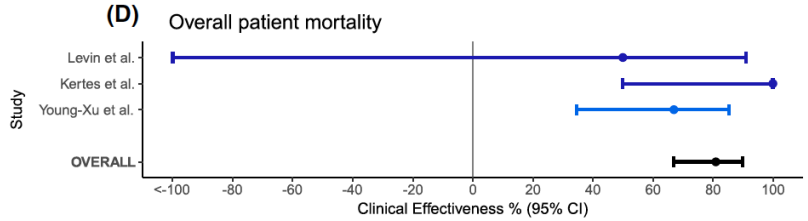
Study	Intervention (n/N)	Control (n/N)
Bertrand et al.	28/412	56/160
Kaminski et al.	41/333	42/97
Levin et al.	8/3441	17/1731
Al Jurdi et al.	11/222	32/222
Kertes et al.	29/825	308/4299
Young-Xu et al.	9/1733	69/6354
Chen et al.	102/1295	121/1295
OVERALL	228/8261	645/14158



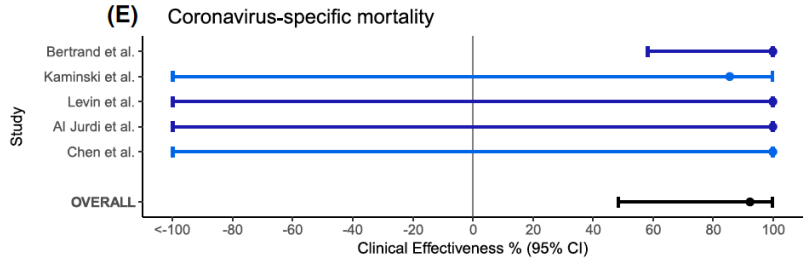
Study	Intervention (n/N)	Control (n/N)
Bertrand et al.	6/412	15/160
Kaminski et al.	4/333	11/97
Levin et al.	0/3441	3/1731
Al Jurdi et al.	1/222	6/222
Kertes et al.	1/825	27/4299
Young-Xu et al.	9/1733	38/6354
Chen et al.	6/1295	36/1295
OVERALL	27/8261	136/14158



Study	Intervention (n/N)	Control (n/N)
Bertrand et al.	2/412	6/160
Kaminski et al.	2/333	6/97
Chen et al.	0/1295	8/1295
OVERALL	17/8059	163/13941



Study	Intervention (n/N)	Control (n/N)
Levin et al.	4/3461	4/1736
Kertes et al.	0/825	40/4299
Young-Xu et al.	9/1733	99/6354
OVERALL	13/6019	143/12389



Study	Intervention (n/N)	Control (n/N)
Bertrand et al.	0/412	5/160
Kaminski et al.	1/333	2/97
Levin et al.	0/3461	2/3461
Al Jurdi et al.	0/222	3/222
Chen et al.	0/1295	0/1295
OVERALL	1/5723	12/5235

Suribathla R et al *Br J Haematol. 2023;201:813–823.*

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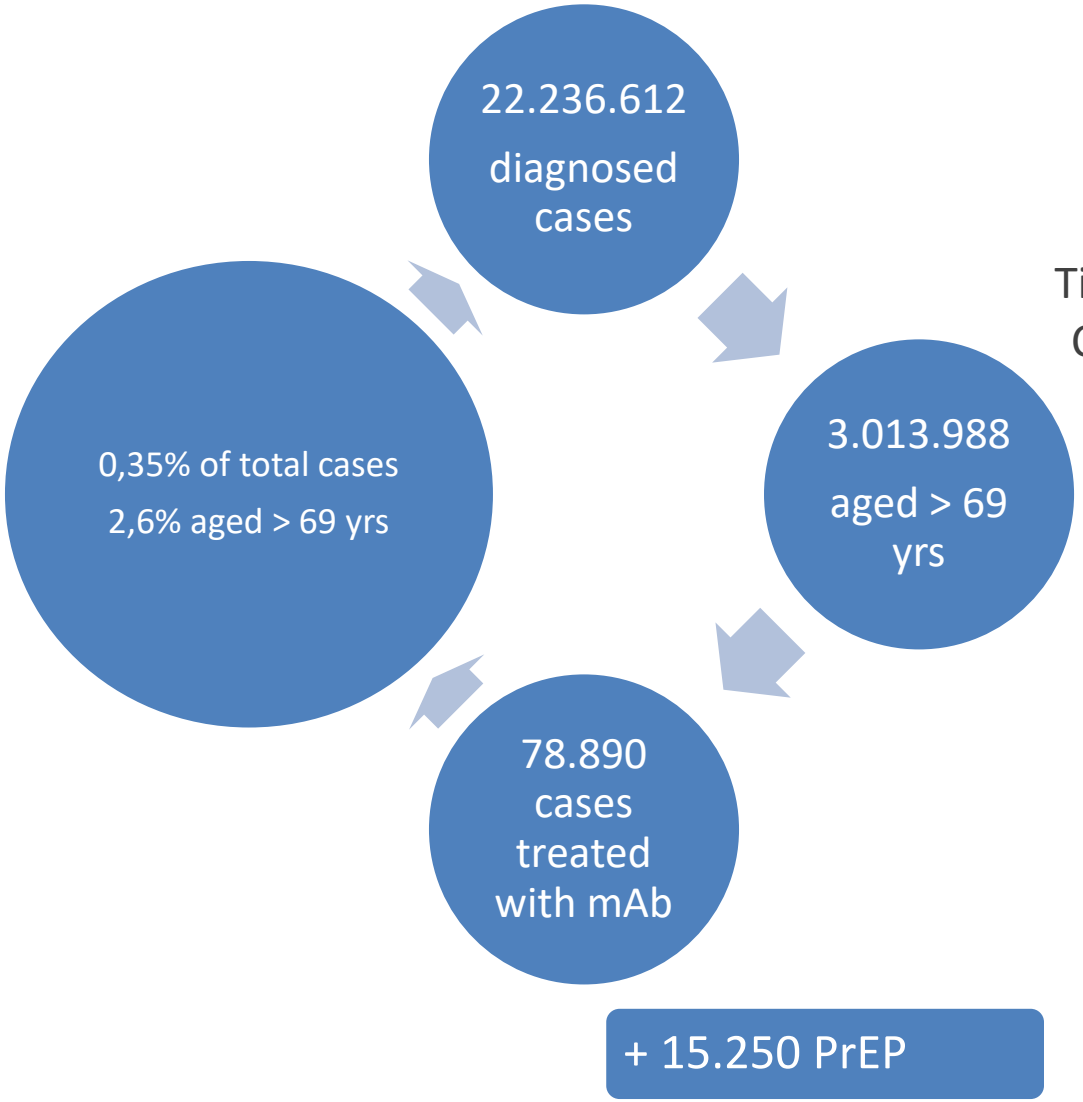
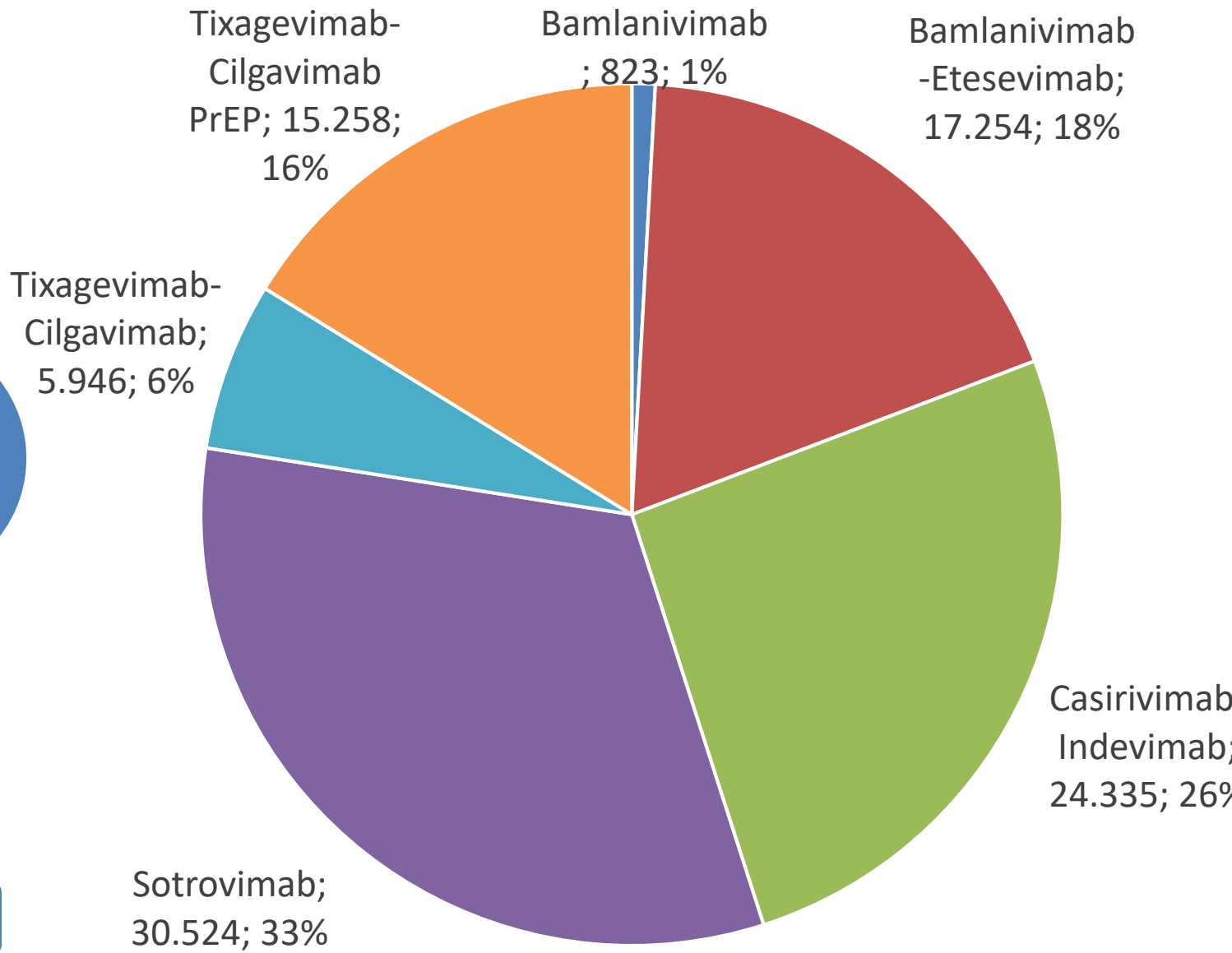
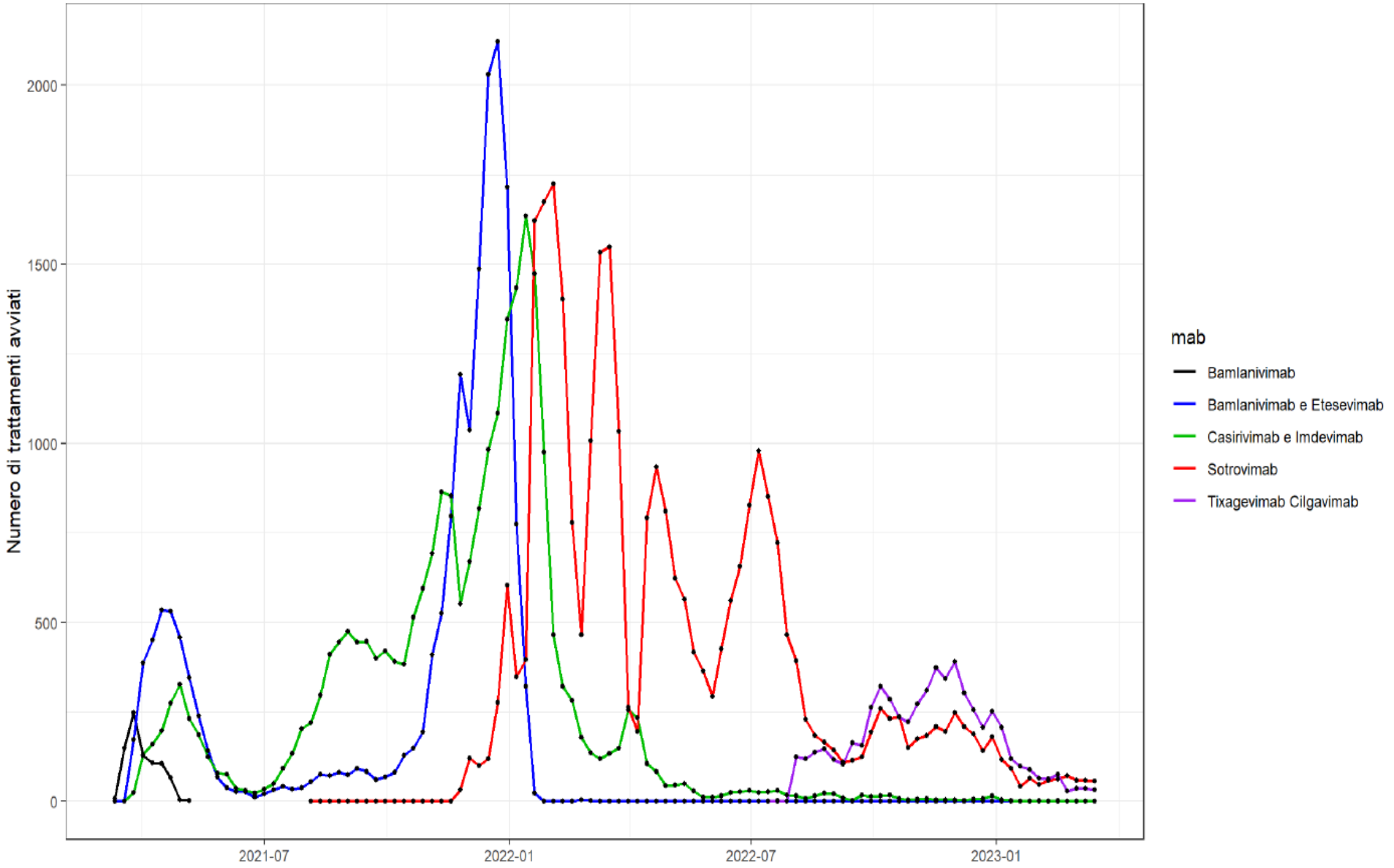
Treatments with mab in Italy from Apr 2021 to March 2023





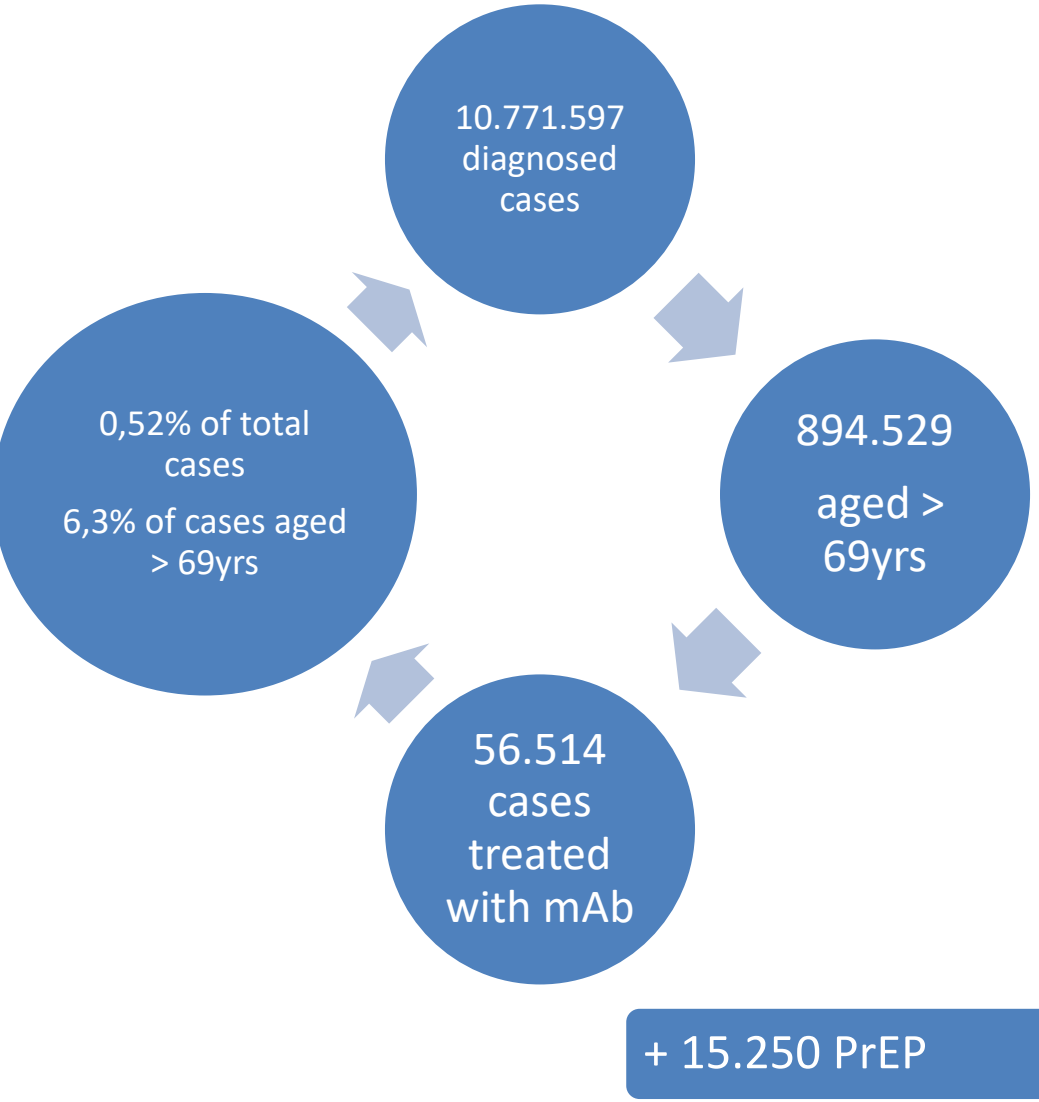
https://www.aifa.gov.it/emergenza-covid-19
https://www.epicentro.iss.it/coronavirus/sars-cov-2-sorveglianza-dati-archivio

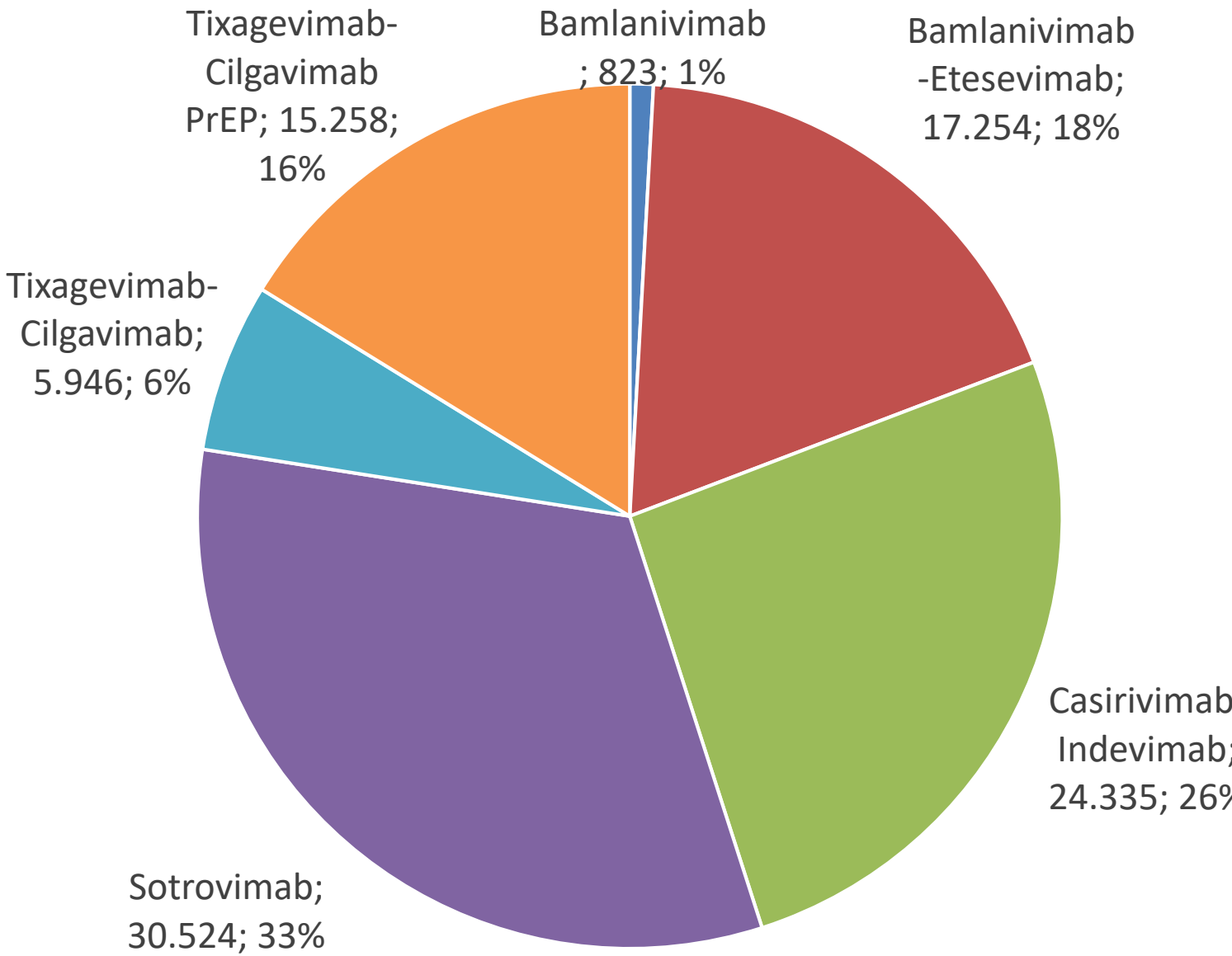
Treatments with mab for COVID-.19 in Italy: trends over time



https://www.aifa.gov.it/emergenza-covid-19

Treatments with mab in Italy from Apr 2021 to March 2022 (pre-Omicron era)





https://www.aifa.gov.it/emergenza-covid-19
https://www.epicentro.iss.it/coronavirus/sars-cov-2-sorveglianza-dati-archivio

Exploring the Use of Monoclonal Antibodies and Antiviral Therapies for Early Treatment of COVID-19 Outpatients in a Real-World Setting: A Nationwide Study from England and Italy

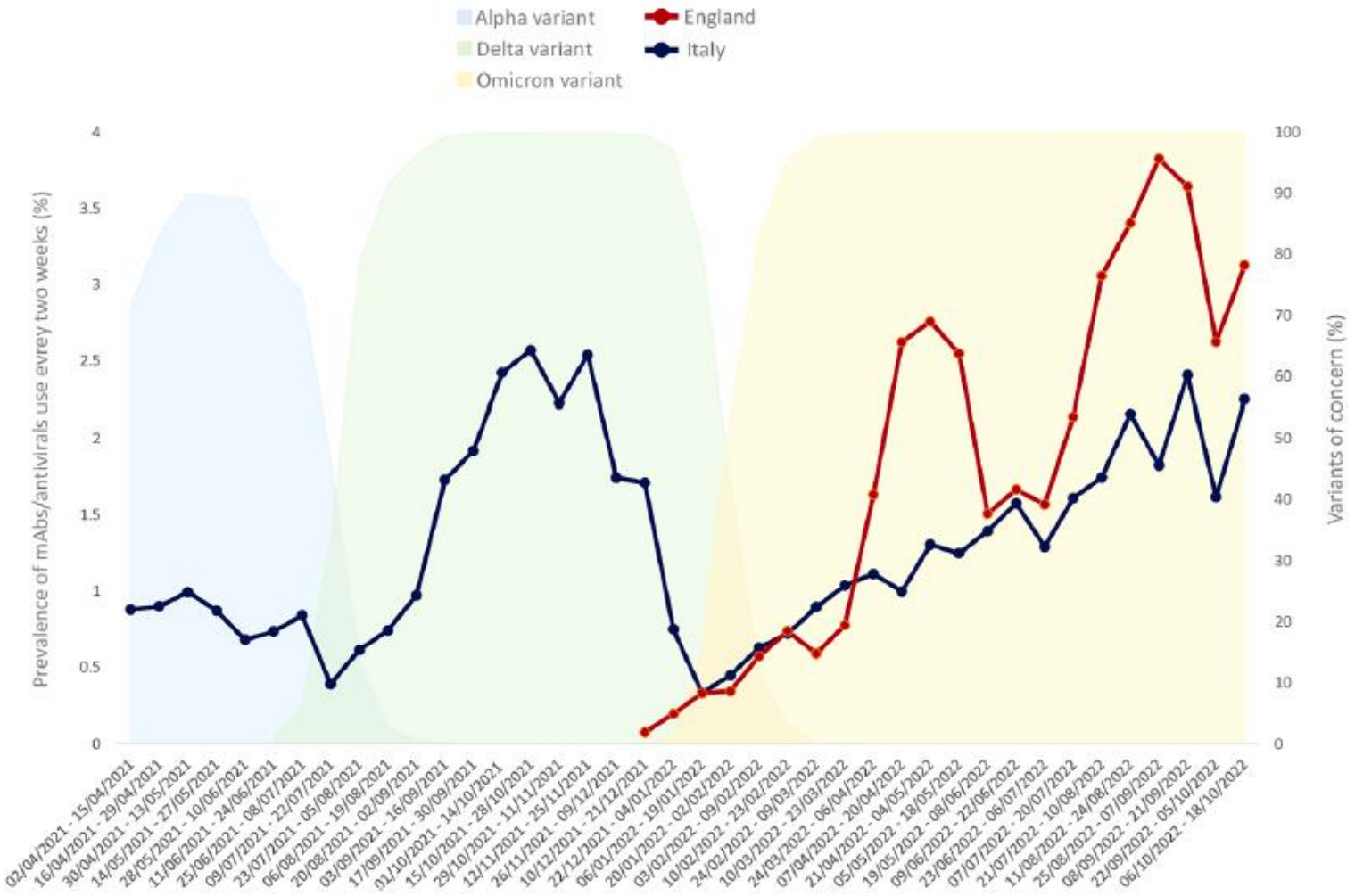


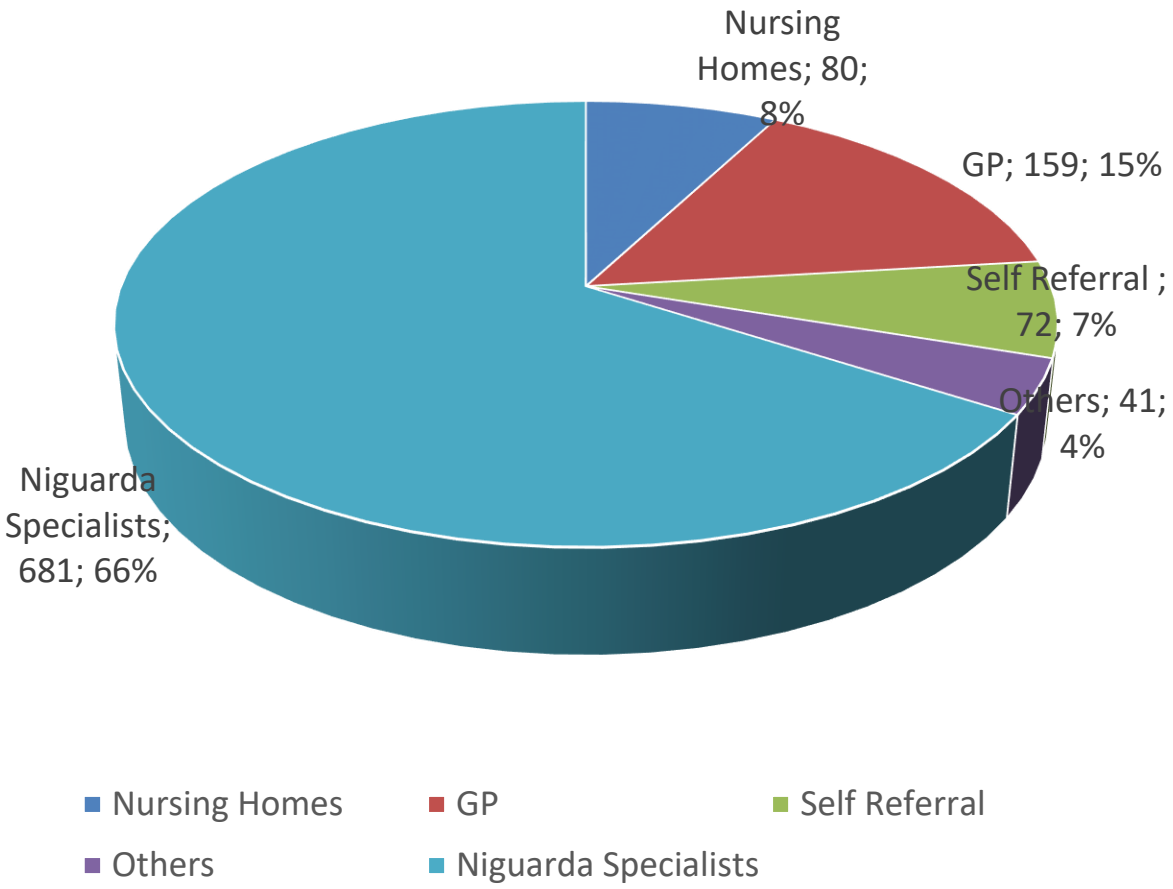
Fig. 2 Prevalence of use every 2 weeks of mAbs/antivirals as a whole for early treatment of COVID-19 outpatients based on the distribution of specific SARS-CoV-2 variants in England and Italy from December 2021 to October 2022. *mAbs* monoclonal antibodies

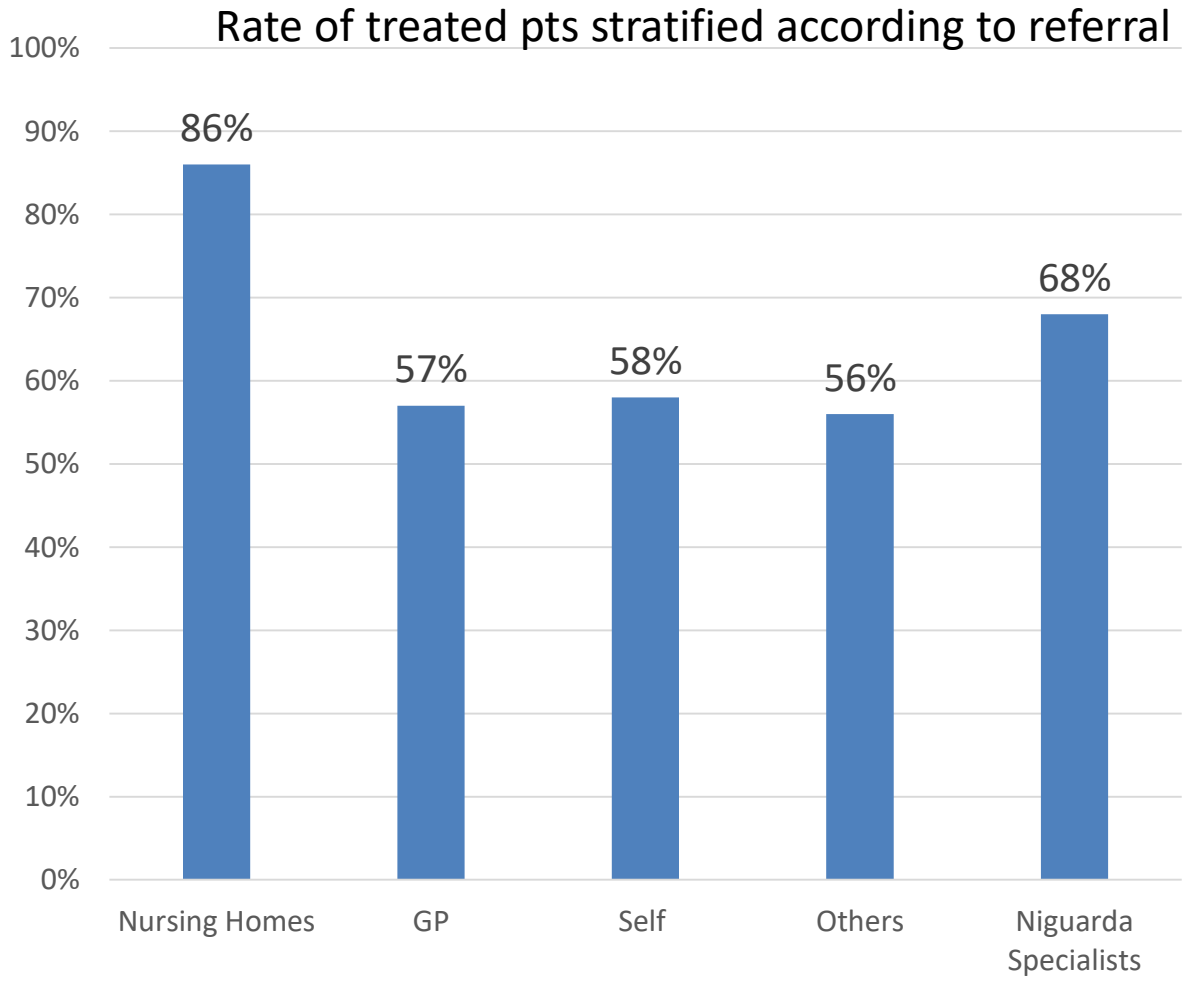
Ciccimarra F et al BioDrugshttps://doi.org/10.1007/s40259-023-00601-w

Ospedale Niguarda | Sistema Socio Sanitario Regione Lombardia

ASST GOM Niguarda COVID outpatient clinic: referral from February 1° 2022 to February 28° 2023

1033 referred pts with mild COVID-19
687 treated with antivirals and/or mab





Sistema Socio Sanitario
Ospedale Niguarda
Regione Lombardia

DIREZIONE SANITARIA

PROFILASSI PRE ESPOSIZIONE A SARS-CoV-2 con Tixagevimab + Cilgavimab (EVUSHELD ®)

1. Oggetto e scopo

Oggetto della procedura è la profilassi pre-esposizione a SARS-CoV-2 con Tixagevimab + Cilgavimab (EVUSHELD ®).
Scopo del documento è definire i criteri di eleggibilità e le modalità prescrittive del trattamento.

2. Campo di applicazione

La procedura si applica alle Strutture sanitarie coinvolte nell'attività.

Sistema Socio Sanitario
Ospedale Niguarda
Regione Lombardia

PROFILASSI PRE ESPOSIZIONE A SARS-CoV-2 con EVUSHELD ®

tixagevimab 150 mg in 1,5 mL (100 mg/mL)

cilgavimab 150 mg in 1,5 mL (100 mg/mL)

INFORMAZIONI PER IL PAZIENTE

Sistema Socio Sanitario
Ospedale Niguarda
Regione Lombardia

GENERALITÀ DEL PAZIENTE CANDIDATO A EVUSHELD

COGNOME e NOME _____
CODICE FISCALE _____
LUOGO e DATA DI NASCITA _____
RESIDENZA _____
TELEFONO _____

INFORMAZIONI SULLO STATO VACCINALE (RACCOMANDATO)

Numero dosi ☐ 1 ☐ 2 ☐ 3 ☐ 4
Data ultima dose __/__/____
Tipo vaccino somministrato _____

CRITERIO DI ELEGGIBILITÀ (OBBLIGATORIO annerire una casella; in assenza di un criterio il paziente non è candidabile)

- ☐ Assunzione nell'ultimo anno terapie che comportano depleziione dei linfociti B (ad es. rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- ☐ Trapianto di polmone (Data trapianto __/__/____)
- ☐ Trapianto di cellule ematopoietiche con malattia da rigetto o con assunzione di farmaci immunosoppressori in corso (Data trapianto __/__/____)
- ☐ Trapianto di organo solido (diverso dal trapianto di polmone) entro 1 anno dal trapianto
- ☐ Trapianto di organo solido con recente trattamento per rigetto acuto con agenti che riducono le cellule T o B
- ☐ Trattamento con inibitori della tirosin-chinasi Bruton
- ☐ Trattamento con CarT
- ☐ Malattia onco-ematologica in fase attiva
- ☐ Immunodeficienze combinate gravi
- ☐ Infezione da HIV non in trattamento e una conta dei linfociti T CD4 <50 cellule/mm3
- ☐ Altra compromissione del sistema immunitario che ha determinato mancata sieroconversione (esplicitare)
  - ☐ *Terapia attiva cronica con dosi elevate di cortisone: ≥20 mg prednisone o equivalente al giorno per ≥2 settimane*
  - ☐ *Terapia cronica con agenti alchilanti*
  - ☐ *Terapia cronica con antimetaboliti*
  - ☐ *In terapia cronica immunosoppressiva dopo trapianto di organo solido*
  - ☐ *In chemioterapia anti tumorale con effetto immunosoppressivo*
  - ☐ *In terapia con farmaci biologici ad attività immunosoppressiva od immunomodulatrice*
  - ☐ *In terapia immunosoppressiva per Sclerosi Multipla od altre neuropatie infiammatorie*
  - ☐ *Infezione da HIV*
  - ☐ *Paziente in lista attiva per trapianto di organo solido e trapianto di cellule ematopoietiche*

Se presenti indicare altre patologie/condizioni tra quelli in elenco che potrebbero aggravare prognosi

☐ ADHD	☐ HIV	☐ Tubercolosi attiva	☐ Cardiopatie gravi	☐ Gravidanza
☐ Fibrosi cistica	☐ Paralisi cerebrale	☐ Lesioni spinali	☐ Schizofrenia	☐ Obesità (BMI ≥30)
☐ Tumori non in terapia immunosoppressiva	☐ Deficit dell'apprendimento	☐ Malformazioni congenite	☐ Malattie cerebro-vascolare grave	☐ Malattie croniche polmonari interstiziali; embolia polmonare; bronchiectasie; COPD; ipertensione polmonare
☐ Malattia renale con insufficienza ≥ III e dializzati	☐ Disabilità fisiche, intellettuali o dello sviluppo	☐ Limitazioni nella cura di sé o nelle attività quotidiane	☐ Diabete mellito non controllato o con complicanze d'organo	
☐ Malattie croniche di fegato: cirrosi; steatoepatite non alcolica; epatopatia alcolica; epatite autoimmune				

ASST presso cui è seguito per il criterio di eleggibilità _____
Preso in carico dal centro di riferimento ☐ SI ☐ NO ☐ NON NOTO
TNF pre invio paziente __/__/____
Infezione covid pregressa (se si data) __/__/____

DATA __/__/____ TIMBRO E FIRMA

Inviare a MalattieInfettiveBG@OspedaleNiguarda.it
Preferibilmente con allegato protetto da password, comunicata separatamente

Tixagevimab/Cilgavimab: Attività Prescrittiva 2022

Centro di Costo	SC	DO/Esterni (DH, MAC, Ambulatorio)	N fiale somministrate	Semestre
R00006360 + R00006340	Ematologia	DH/MAC	136	Primo
R00001811	Ematologia	DO	4	Primo
R00002130	Malattie Infettive	DO	2	Primo
R00001371	Epatologia	DO	1	Primo
R00006360	Ematologia	DH/MAC	70	Secondo
R00002130	Malattie Infettive	DO	37	Secondo
R00003792	Neurologia	DH/MAC	26	Secondo
R0000216D	Malattie Infettive	DH COVID/AMB	25	Secondo
R00002370	Reumatologia	Amb/MAC	18	Secondo
R00006530 + R00001811+ R00001821	Ematologia	DO	9	Secondo
R00003760	Neurologia	DO	4	Secondo
R00002211	Dialisi	AMB	4	Secondo
R00002250 + R00002251	Nefrologia	AMB/MAC	4	Secondo
R00001361 + R00001390 + R00001350 + R00001351	Epatologia	AMB/MAC	5	Secondo
	Altre degenze	DO	3	Secondo

Primo semestre: 140
Ematologia 97%

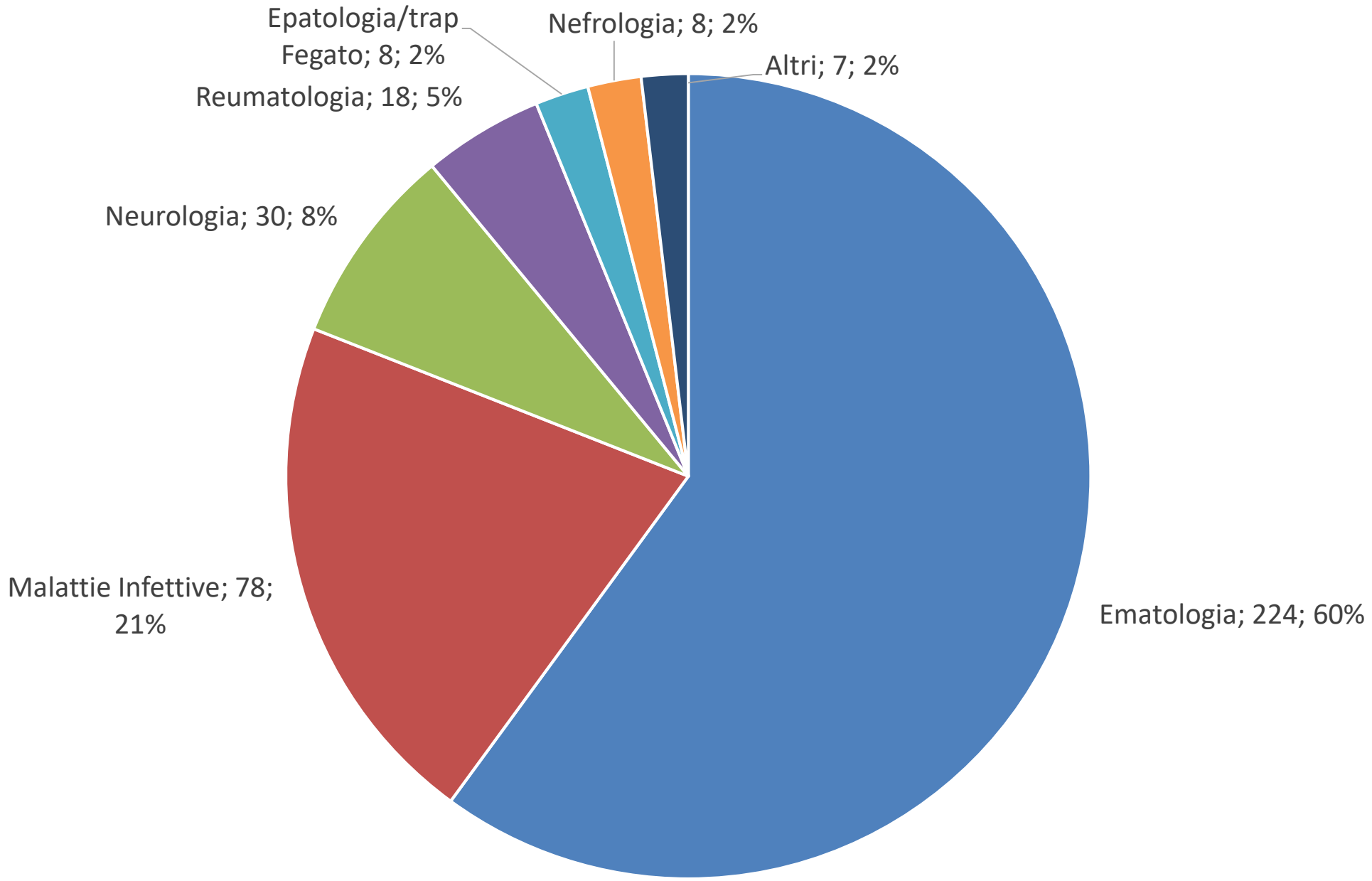
Secondo semestre
205
Ematologia 38%
Malattie Infettive 30%
Neurologia 15%
Reumatologia 9%
Nefrologia 4%
Epatologia 2,4%

Tixagevimab/Cilgavimab: Attività Prescrittiva 2023

Centro di Costo	SC	DO/Esterni (DH, MAC, Ambulatorio)	N fiale somministrate
R00002130	Malatie Infettive	DO	14
R00006360 + R00006360	Ematologia	DH/MAC/AMB	9
R00003671	Chir Trapianti	DO	2
R00001811	Ematologia	DO	1
R00002150	Malattie Infettive	AMB	1
R00001390	Epatologia	AMB	1

Totale 28
Malattie Infettive 50%
Ematologia 32%

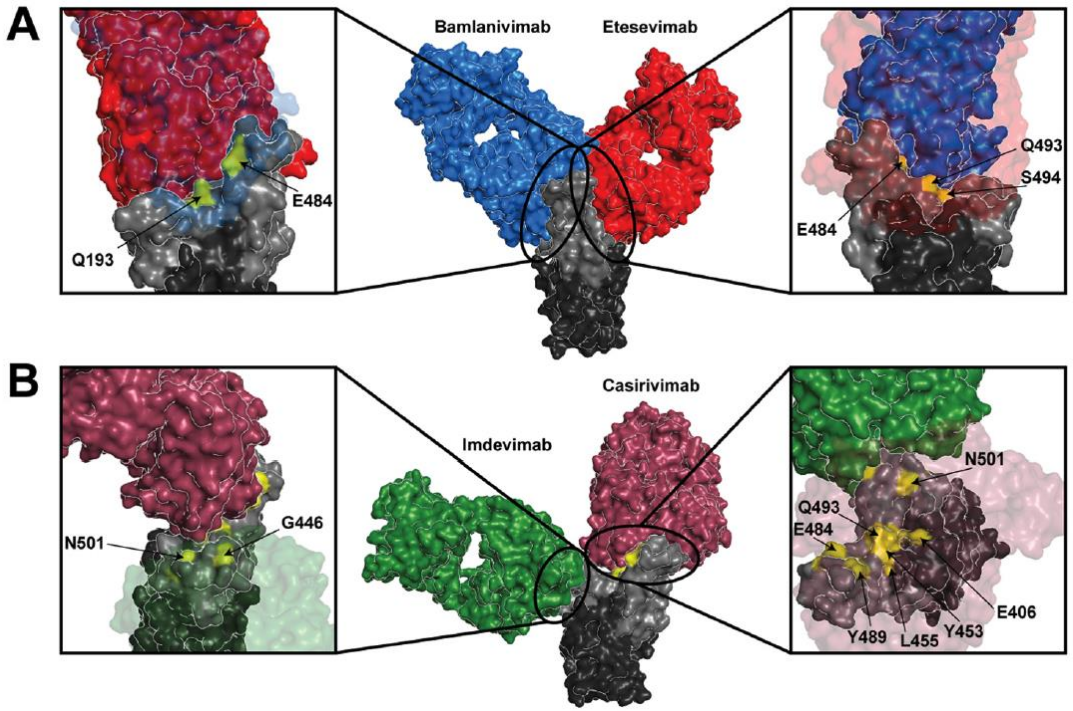
ASST Niguarda Distribuzione prescrizione 373 fiale Tigaxevimab-Cilgavimab anni 2022-23 per specialità

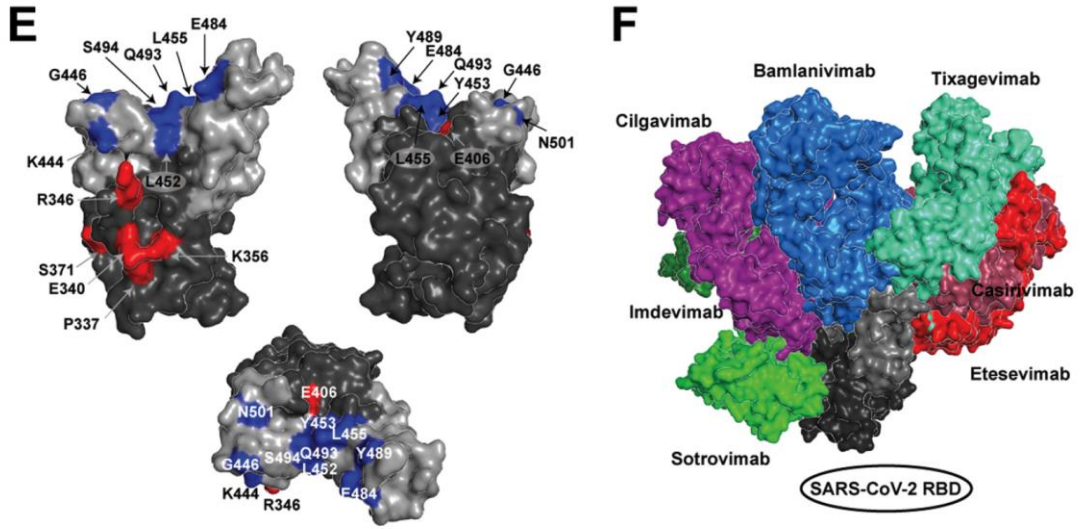


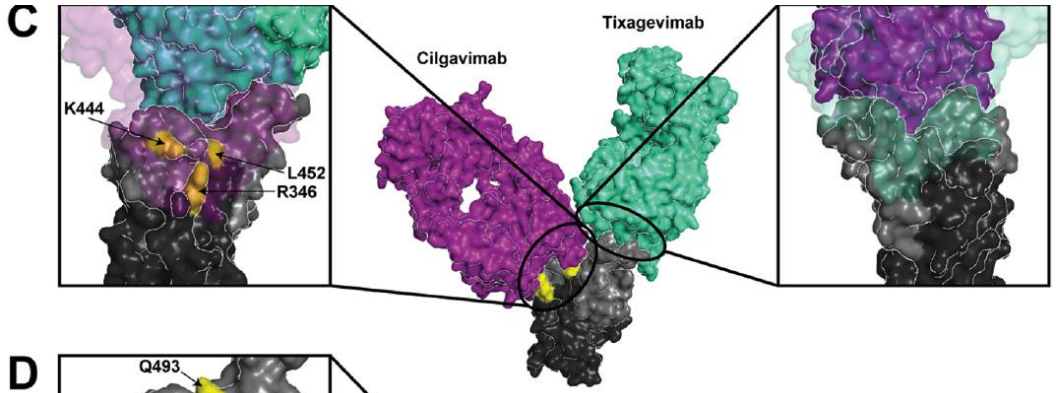
La terapia con anticorpi monoclonali: ruolo attuale e prospettive future - Outline

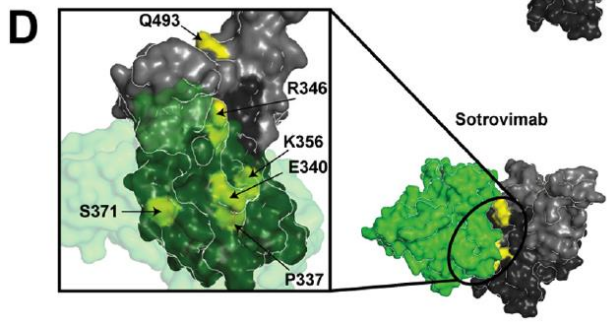
- Anticorpi monoclonali in infettivologia e nel trattamento e prevenzione COVID-19
- Impiego degli anticorpi monoclonali in Italia
- Resistenza ed inefficacia in era Omicron
- Dati nel paziente immunocompromesso ed ematologico
- Raccomandazioni delle linee guida
- Prospettive future
- Conclusioni

Resistance mutations on the Spike receptor binding domain (RBD) reported after treatment with authorized anti-Spike mAbs



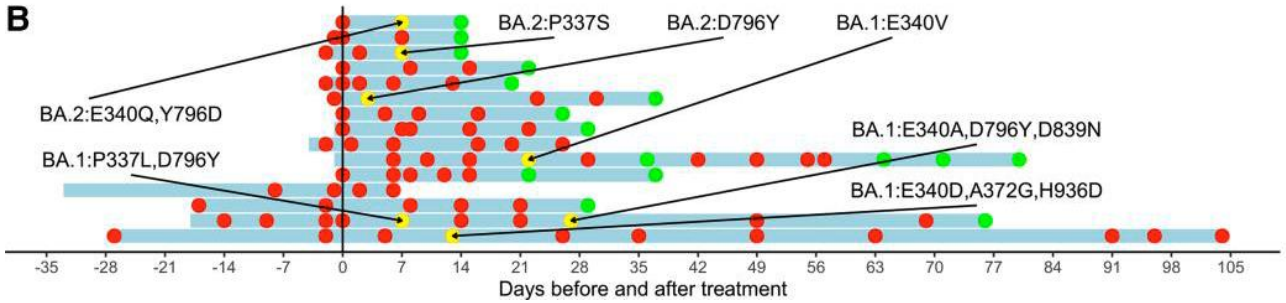




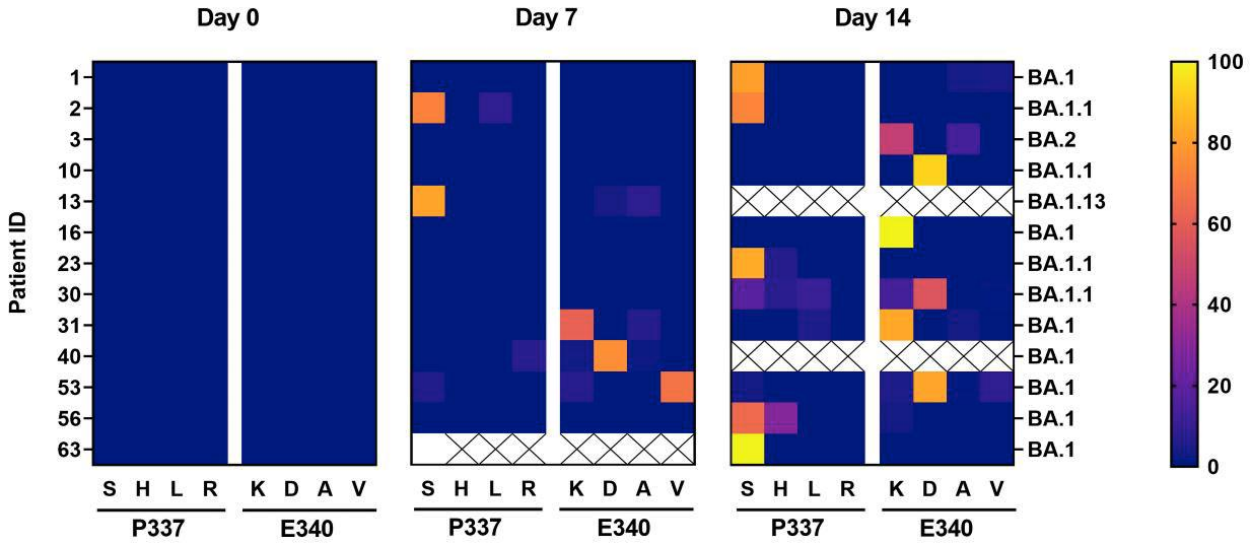


Focosi D et al Drug Res Updates 2023 71 100991

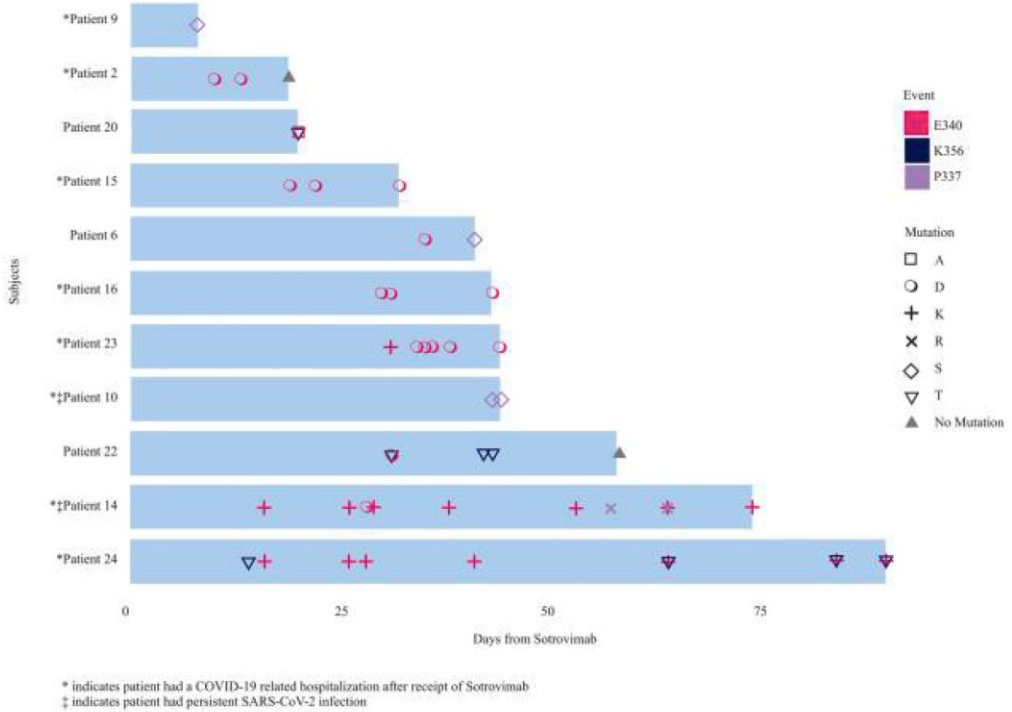
Persistence After Treatment of Immunocompromised Patients Infected With the Severe Acute Respiratory Syndrome Coronavirus 2 Omicron Variant



Huygens S et al CID 2023:76



Gliga S et al CID 2023:76: 408- 415



Yan J et al CID 2023;76(8):1476–82

Anti SARS-CoV-2 monoclonal antibodies: treatment emergent resistance

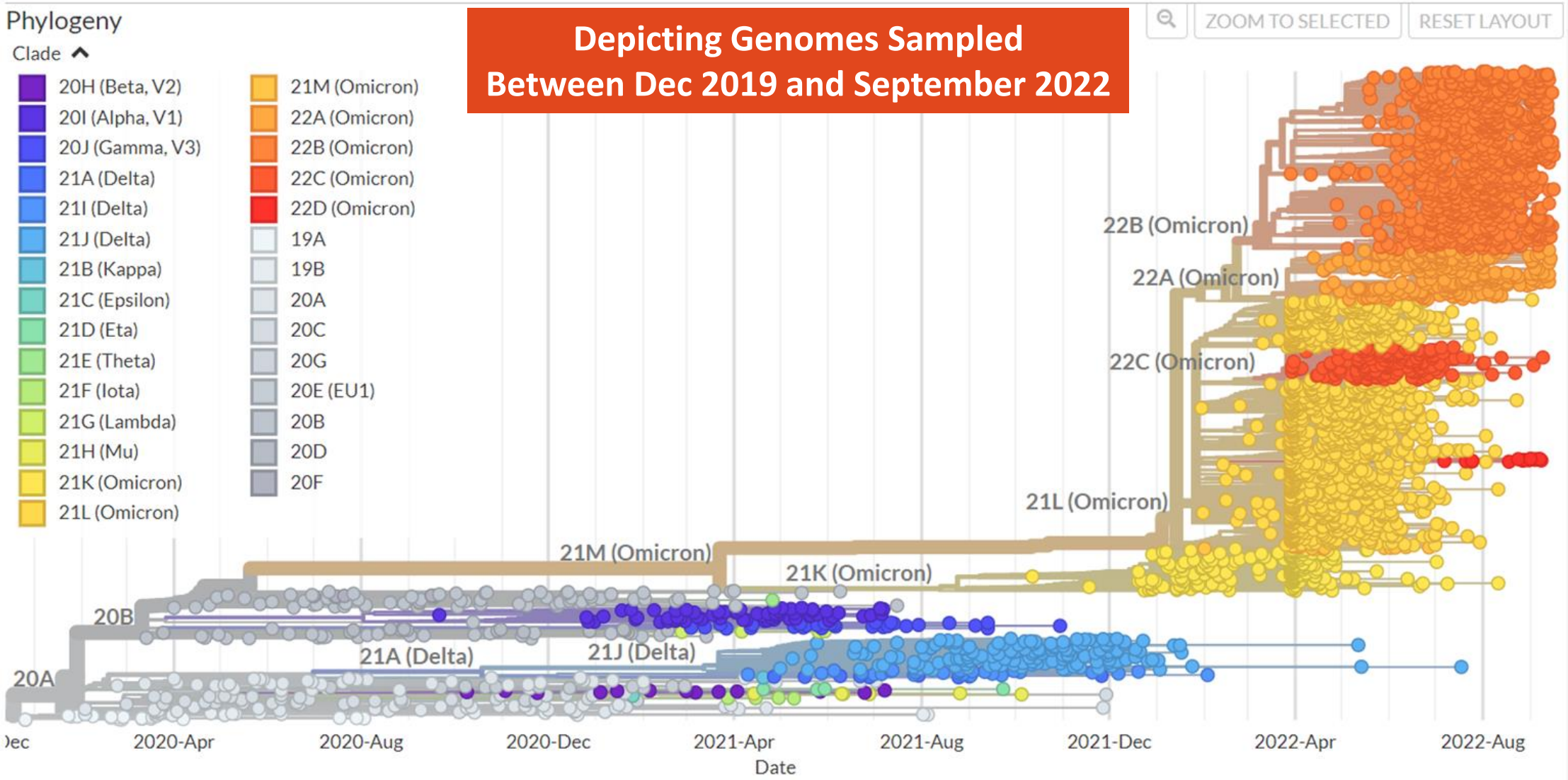
Frequencies of treatment-emergent resistance.

mAb (n = number of cohort series)	# of patients developing treatment-emergent resistance mutations across all case series	total # of patients across all case series	percent of patients developing treatment-emergent resistance across all case series	number of additional single case reports
bamlanivimab (n = 5)	23	160	14.4%	11
bamlanivimab+ etesevimab (n = 5)	15	270	5.6%	2
casirivimab+ imdevimab (n = 3)	16	185	8.6%	1
sotrovimab (n = 11)	146	449	33.2%	8
cilgavimab-tixagevimab (n = 2)	10	37	27.0%	0
bebtelovimab (n = 0)	n.a.	n.a.	n.a.	1
Total	210	1101	19.1	15

Focosi D et al Drug Res Updates 2023 71 100991

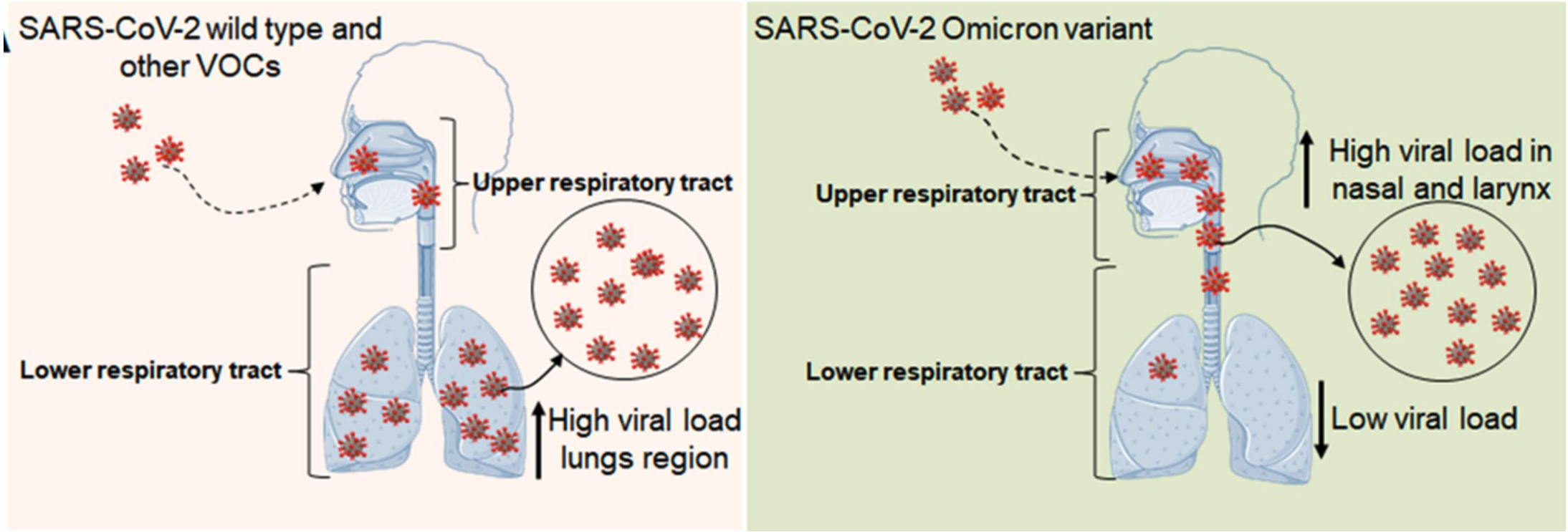
Genomic Epidemiology of SARS-CoV-2:

A rapid replacement of SARS-CoV-2 over time by variants



GISAID. Updated September, 2022. gisaid.org/phylodynamics/global/nextstrain/.

Viral load in the respiratory tract and the lungs during an infection with the wild strain of SARS-CoV-2 and Omicron.



Chatterjee S et al. Viruses 2023, 15, 167.

What do Variants mean by a clinical point of view?

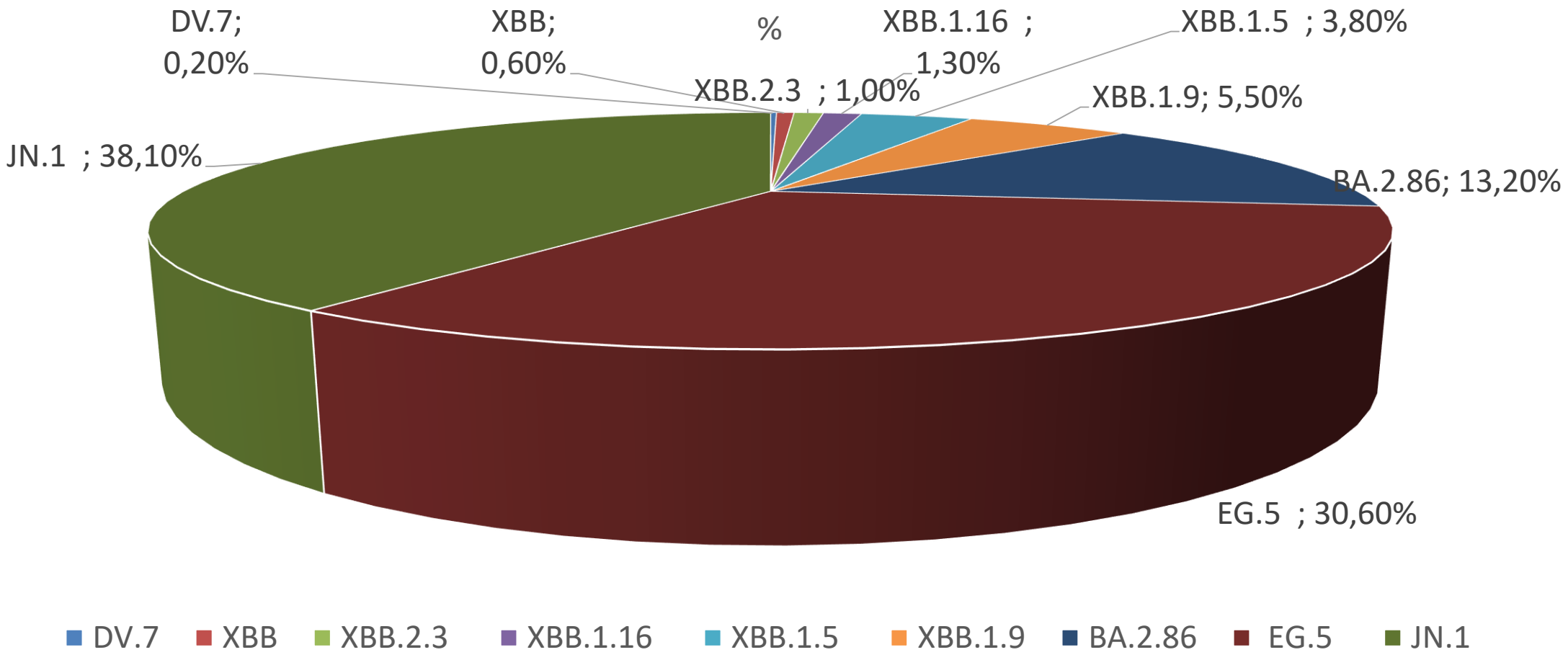
- ***Transmissibility***
- ***Disease Severity***
- ***Immunity***
- ***Diagnostics***
- ***Drug Efficacy***

Variants of Interest (VOI)

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Transmission in EU/EEA
Omicron	BA.2.75 (x)	India	(y)	May 2022	Unclear (1)	Similar to Baseline (2-4)	No evidence	Community
Omicron	XBB.1.5-like (a)	United States	N460K, S486P, F490S	n/a	Similar to Baseline (5, 6)	Reduced (v) (5, 7)	Similar to Baseline (8)	Community
Omicron	XBB.1.5-like + F456L (b) (e.g. EG.5, FL.1.5.1, XBB.1.16.6, and FE.1)	n/a	F456L, N460K, S486P, F490S	n/a	Baseline	Baseline (9)	Baseline	Dominant
Omicron	BA.2.86	n/a	I332V, D339H, R403K, V445H, G446S, N450D, L452W, N481K, 483del, E484K, F486P	n/a	Unclear (10)	Unclear (10-12)	No evidence	Community

https://www.ecdc.europa.eu/en/covid-19/variants-concern

Stima della prevalenza delle principali varianti del virus SARS-CoV-2 circolanti in Italia (Dicembre 2023)



JN.1 (discendente di BA.2.86 JN.1 mostra rispetto al lignaggio parentale BA.2.86.1, una mutazione addizionale in una regione chiave per il riconoscimento anticorpale (S:L455S)), E.G 5 riconducibile ad XBB

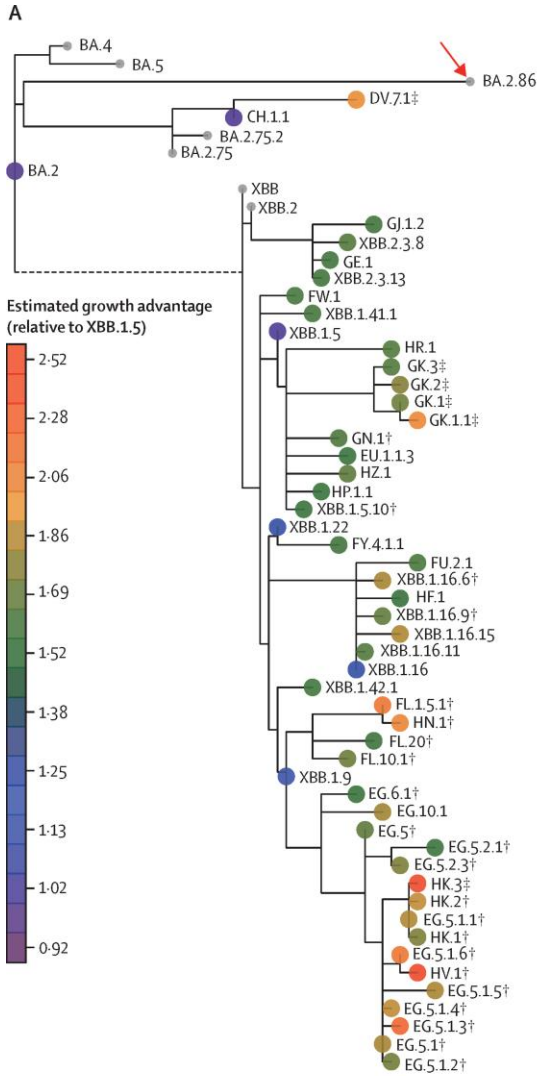
Stanford University
CORONAVIRUS ANTIVIRAL & RESISTANCE DATABASE
A Stanford HIVDB team website. Last updated on 12/19/2023, 10:12:16 PM.

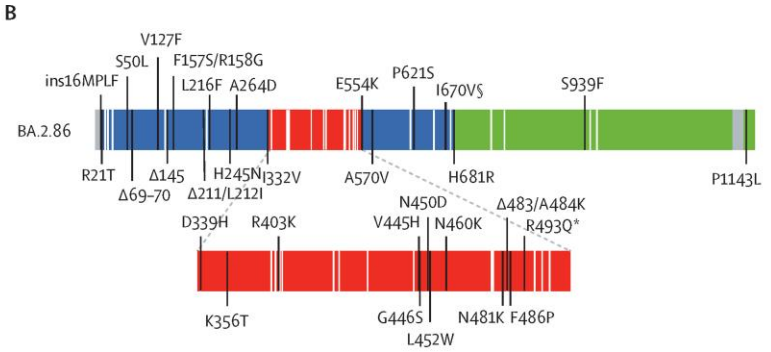
VIRUS VARIANTS VS MONOCLONAL ANTIBODIES

Fold reduced neutralizing susceptibility to monoclonal antibodies under Emergency Use Authorization (EUA)

Test\mAb	BAM	ETE	BAM/ETE	CAS	IMD	CAS/IMD	CIL	TIX	CIL/TIX	SOT	BEB	ADI
Alpha	1_{23}	13_{20}	1.3_{9}	1_{32}	0.6_{33}	0.9_{14}	0.6_{15}	1.5_{14}	0.8_{14}	1.8_{30}	0.9_{6}	1.3_{6}
Beta	$>1000_{29}$	516_{25}	990_{12}	91_{38}	0.6_{38}	1.6_{19}	1.1_{16}	5.8_{17}	1.7_{16}	1_{31}	1_{8}	2.8_{6}
Gamma	$>1000_{16}$	348_{16}	404_{4}	124_{24}	0.4_{24}	1_{9}	0.5_{12}	3.7_{11}	0.9_{10}	1_{23}	1_{5}	2.2_{6}
Delta	$>1000_{25}$	0.4_{25}	1_{9}	0.7_{33}	1.5_{34}	1.3_{14}	2.4_{15}	1.0_{16}	1_{17}	1.1_{31}	1_{12}	1.5_{8}
Omicron/BA.1	$>1000_{42}$	459_{42}	980_{17}	$>1000_{50}$	$>1000_{51}$	$>1000_{23}$	263_{48}	264_{50}	63_{35}	3.8_{64}	1_{28}	108_{20}
Omicron/BA.2	$>1000_{24}$	515_{24}	744_{15}	$>1000_{34}$	219_{33}	387_{23}	1.8_{41}	894_{39}	8_{36}	20_{54}	1_{36}	$>1000_{15}$
Omicron/BA.2.12.1	$>1000_{12}$	515_{12}	794_{8}	$>1000_{13}$	125_{13}	250_{9}	2.8_{15}	410_{15}	9.1_{10}	20_{18}	1_{13}	968_{6}
Omicron/BA.2.75	$>1000_{9}$	383_{9}	554_{5}	477_{11}	$>1000_{11}$	$>1000_{7}$	13_{16}	29_{15}	24_{11}	12_{15}	3.1_{16}	437_{7}
Omicron/BA.2.75.2	556_{2}	489_{2}	$>1000_{1}$	589_{4}	588_{4}	$>1000_{3}$	$>1000_{7}$	$>1000_{7}$	$>1000_{7}$	8_{9}	2.8_{7}	509_{2}
Omicron/XBB	$>1000_{1}$	$>1000_{1}$	-	589_{2}	588_{2}	200_{1}	$>1000_{3}$	$>1000_{3}$	738_{2}	14_{4}	$>1000_{5}$	$>1000_{1}$
Omicron/XBB.1	$>1000_{1}$	$>1000_{1}$	$>1000_{1}$	880_{3}	$>1000_{3}$	887_{3}	$>1000_{7}$	$>1000_{6}$	$>1000_{6}$	15_{8}	$>1000_{7}$	-
Omicron/XBB.1.5	-	-	-	650_{2}	572_{2}	751_{2}	433_{3}	$>1000_{3}$	867_{3}	15_{6}	800_{5}	-
Omicron/XBB.1.16	-	-	-	420_{1}	143_{1}	615_{1}	127_{1}	448_{1}	488_{1}	9.7_{2}	149_{1}	-
Omicron/BA.4/5	$>1000_{19}$	504_{19}	588_{11}	$>1000_{26}$	143_{26}	387_{17}	8.1_{34}	$>1000_{33}$	25_{27}	22_{40}	0.9_{31}	$>1000_{13}$
Omicron/BA.4.6	556_{2}	489_{2}	$>1000_{1}$	589_{4}	173_{4}	738_{3}	527_{6}	819_{6}	738_{6}	44_{5}	1_{7}	509_{2}
Omicron/BQ.1	-	-	-	177_{1}	175_{1}	200_{1}	$>1000_{3}$	$>1000_{3}$	$>1000_{3}$	26_{5}	900_{4}	-
Omicron/BQ.1.1	$>1000_{2}$	972_{2}	$>1000_{1}$	$>1000_{4}$	$>1000_{4}$	$>1000_{3}$	$>1000_{8}$	$>1000_{7}$	$>1000_{6}$	118_{9}	$>1000_{9}$	$>1000_{2}$
Omicron/BF.7	-	-	-	$>1000_{1}$	383_{1}	878_{1}	$>1000_{3}$	$>1000_{3}$	$>1000_{3}$	48_{5}	1.3_{4}	-
Omicron/CH.1.1	-	-	-	$>1000_{1}$	$>1000_{1}$	$>1000_{1}$	$>1000_{3}$	$>1000_{2}$	$>1000_{2}$	16_{3}	$>1000_{3}$	-

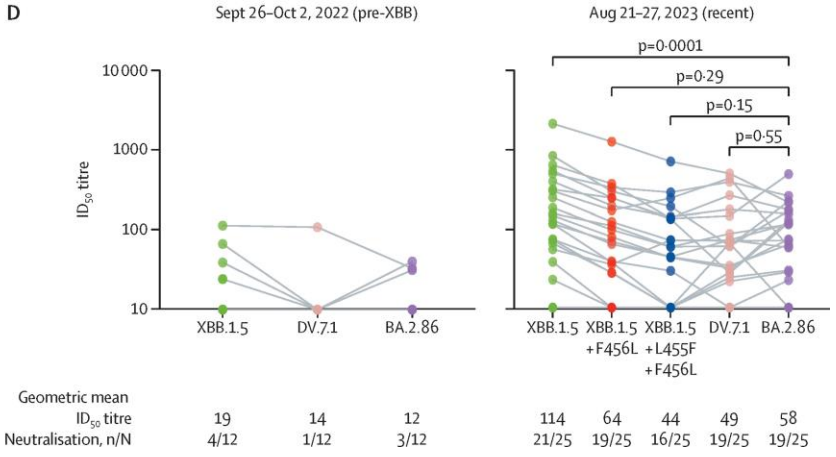
Sensitivity of the SARS-CoV-2 BA.2.86 variant to prevailing neutralising antibody responses





C

	IC_{50} (ng/ml)		
	BA.2	XBB.1.5	BA.2.86
Cilgavimab	26	>1000	>1000
Tixagevimab	>1000	>1000	>1000
LY-CoV1404 (bebtelovimab)	1	>1000	>1000
S309 (sotrovimab)	559	416	>10000



Se-eward DE et al Lancet Inf Dis 2023 Nov VOLUME 23, ISSUE 11, E462-E463,

Sotrovimab as early Tx for mild COVID-19 – Real life data in Omicron era

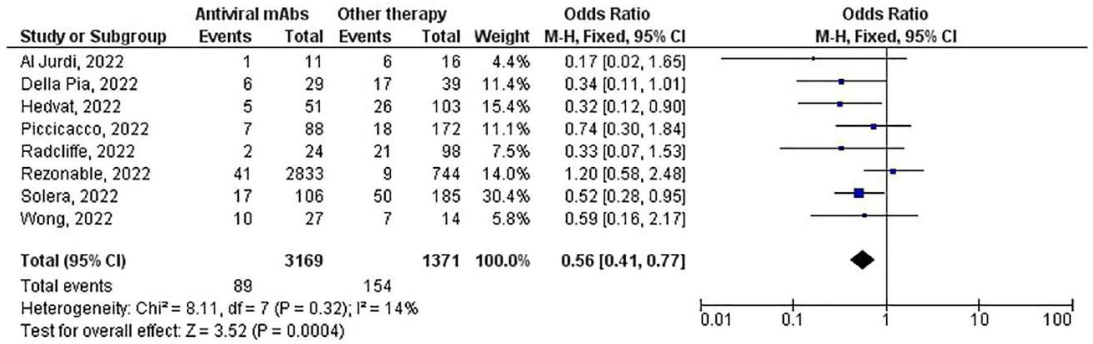
Author (country, Region)	Study period	Design of the study	Cases	Controls	Endpoint	Results
Manciulli (Italy, Tuscany)	1→ 3/22	Retrosp. Case control	314 at risk of progression	205 MOL 142 RMD 120 NRM/r	Death (0,3%)or hospital. at 28 d (2,3%)	HR 0.14, 95%CI 0.03–0.56, p = 0.005) vs RMD no vs MOL or NRM/r
Casutt (CH)	10/21→ 7/22	Retrospe ctive	36 Lung Tx Mab according to circulating variants	24 Lung Tx	Hospitalization within 28 d	HR 0.23 (0.06–0.87) vs no Mab
Agarwal (USA)	26/12/21 → 10/3/22	Observat ional cohort study	1542 at risk of progression	3664	Hospitalization at 28 days Mortality	OR 0.82, (95% CI 0.55, 1.19) omicron vs delta OR 0.85 (OR 0.62, 95% CI 0.07, 2.78).omicron vs delta OR 0.39
Blondel GM (France)	24/1/22-> 10/5/22	Cohort Study	195 at risk of progression	66 treated with NRM/r	Faster conversion to negative PCR	HR 2.35;(95%CI,1.56-3.56)
Cheng MM (USA)	4/21 → 5/22	Adm. DB	15.633 at risk of progression	1.514.868	Hospitalization or mortality at 30 days	PS RR 0.39 (0.35, 0.43) no significant change over time
Evans A (UK, Wales)	2/22 → April 22	Admin DB	618 at risk of progression	2516	Hospitalization or death at 28 d	HR 0.70 (0.48–1.03)
Woo MS (Germany)	12/21 → 6/22	Retrospe ctive cohort	185	1069	Hospitalization or death at 30 days	No difference

Tixagevimab/Cilgavimab as a PREP in the omicron era

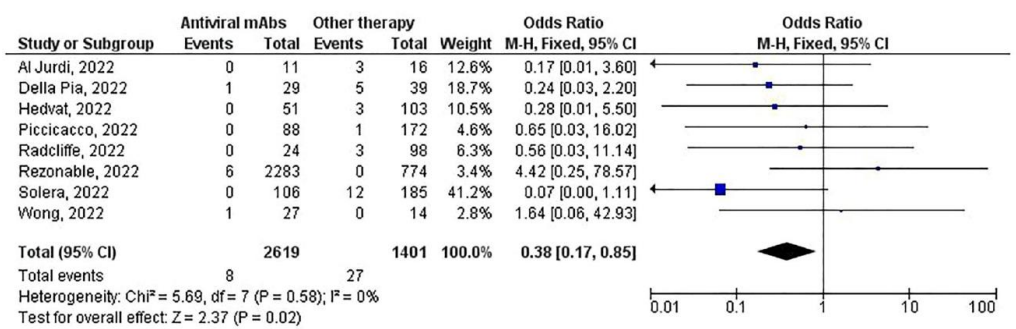
Author (country, Region)	Study period	Design of the study	Cases	Controls	Endpoint	Results
Al Yurdi A (USA)	December 28, 2021 and April 13, 2022	Retrospective cohort study	222 SOT recipients	222	Breakthrough infection	5 vs 14% Log Rank p<0.001
Kertes J (Israel)	23/2/22 → 2/5/22	Administrative database	825 Immunocompromised	4299	Breakthrough infection	3,5 vs 7,2% OR 0.51 (0.30 – 0.84)
Jakimowsky J (USA)	1/22->7/22	Single center retrospective study	31 neuroinflammatory diseases treated with anti-CD20	126	Breakthrough infection	6.5 vs 34% p<0.001
Chen B (USA)	1/22→ 7/22	Admin database	1295 post T/C	1295 pre T/c	Hospitalization	7,1% vs 8% 0 ICU vs 6,7%
Gottlieb (USA)	2/22→10/22	Retrospective cohort study	438 Lung Tx R	1019	Breakthrough infections	19 vs 40% p<0.01 No difference in severity
Sindu D (USA)	122/21→ 8/22	Retrospective cohort study	203 Lung Tx R	343	Breakthrough infections	HR, 0.430; 95% CI, 0.165-1.118; P = 0.083 No difference in severity

Clinical efficacy of anti-SARS-CoV-2 monoclonal antibodies in preventing hospitalisation and mortality among patients infected with Omicron variants: A systematic review and meta-analysis

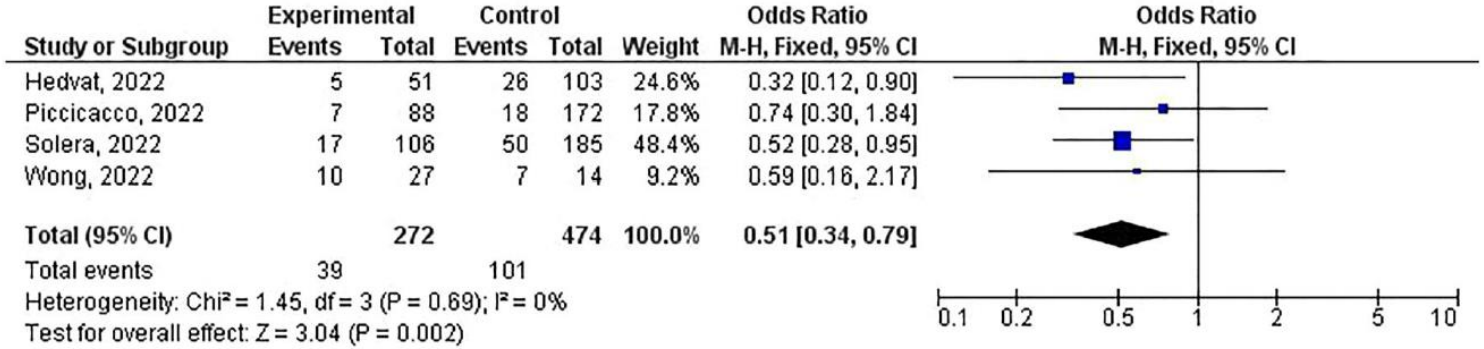
Hospitalisation



Mortality



Hospitalisation SOT only



Miljianovic M et al Rev Med Virol. 2023;33:e2439.

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- Prospettive future
- Conclusioni

Studies on monotherapy in non Haematological immune compromised patients

Author year	Study design	Findings
Pulvirenti F 2022	Mab treatment in **8 pts with primary antibody defect** vs 10 controls	**Shorter median time to PCR negativization** in 8 patients treated with mAbs (22 days vs 37 days, P = .026).
Garzi G 2022	**192 pts** with inborn error of immunity treated with mabs or antivirals	efficacy of antivirals on the risk of hospitalization, while mabs offered a positive effect on hospitalization, and COVID-19 severity. This **protection was consistent across the alpha, delta and early omicron waves**, although the emergence of BA.2 reduced the effect of available mabs. Hospitalized patients treated with mabs and antivirals had a lower risk of ICU admission.
Pinchera B 2022	Sotrovimab in 15 SOT recipients	87% clinical recovery at 1 week 66,7% negative NFS at 28 days

Antivirals and mab are protective in persons with inborn immune defects and SOT recipients

Breakthrough COVID-19 in vaccinated patients with hematologic malignancies:results from the EPICOVIDEHA survey

1548 cases
Omicron 33%
Lymphoid malignancies 76%

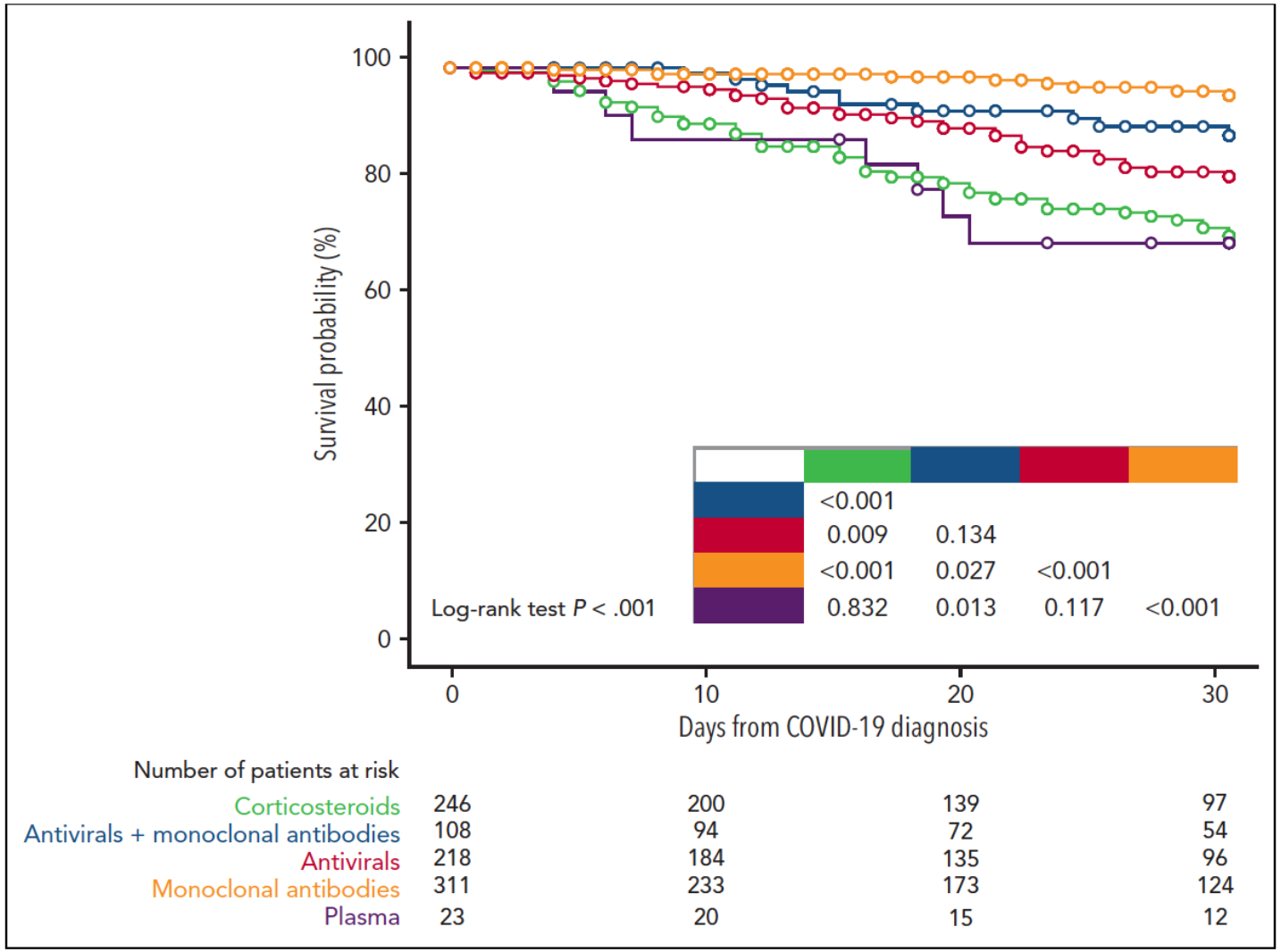
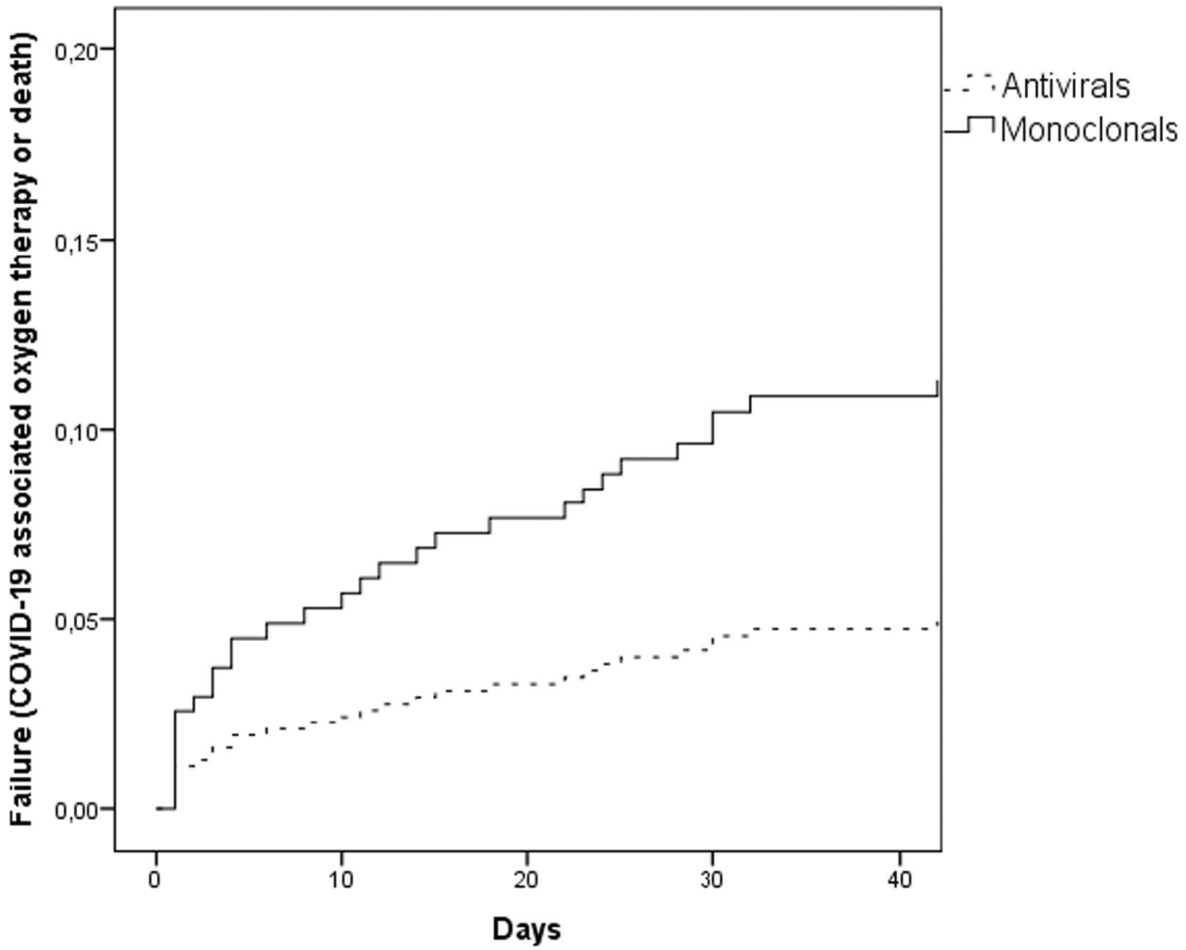


Figure 3. Survival probability of patients by COVID-19 treatment.

Pagano L et al Blood 2022; 140: 2773-2787

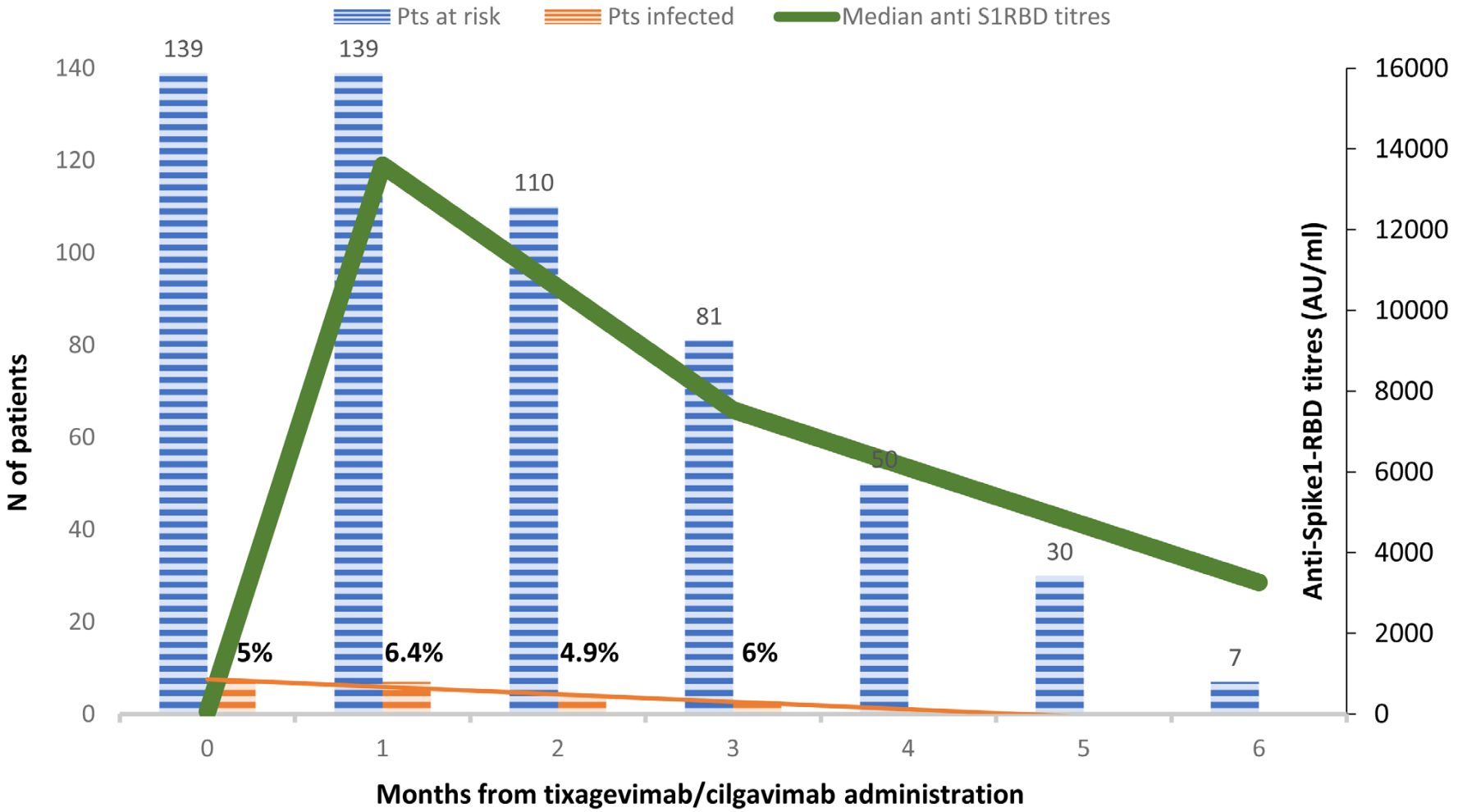
Outcome of early treatment of SARS-CoV-2 infection in patients with haematological disorders

- Retrospective study 328 HM patients treated for mild/moderate COVID-19 between March 2021 and July 2022. (n = 309, 94%) during the Omicron period
- End-point= treatment failure (severe COVID-19 or COVID-19- related death).
- 328 : MABs (n = 120, 37%; sotrovimab, n = 73) or antivirals (n = 208, 63%; nirmatrelvir/ritonavir, n = 116) over a median of two days after symptoms started;
  - 111 (33.8%) NHL;
  - 89 (27%) were transplant/ CAR-T



Mikulska M et al Br J Haematol. 2023;201:628–639.

Tixagevimab/Cilgavimab Pre-exposure Prophylaxis in Patients With Lymphoproliferative Disorders on BTKi



- 139 pts from March to September 2022
- rate of breakthrough and severe infections was higher than in literature (breakthrough infections, 1.6%–4.4%; severe infections, 0%–0.5%; and mortality, 0%–0.2%)
- Previous COVID-19 only protective factor

Zamprogna G et al HemaSphere (2023) 7:5(e880).

Nirmatrelvir /r + Remdesivir treatment for persistent COVID-19 in Haematological pts

	Case 1	Case 2	Case 3	Case 4	Caso 5	Caso 6
Age and sex	78, M	72, M	76, M	67, F	73, F	80. F
Hematological disease diagnosis	DLBCL NHL	CLL+ Richter syndrome	CLL	Follicular NHL	Follicular NHL	Follicular NHL
Date of diagnosis	09.2019	2017 + Richter syndrome in 2022	2019	2022	2004	2022
Type of immuno-chemotherapy (cycle numbers)	- Rituximab+ bendamustin (6) - R-COMP (6) - Obinutuzumab+ Glofitamab (1)	- FCR (6) - Ibrutinib (3) - Venetoclax	- Ibrutinib	- Rituximab+ bendamustin (2)	- CHOP (6) - Rituximab+ cyclophosphamide (4) - Rituximab+ Ara C - R-CVP (4) - Obinutuzumab+ bendamustin	- Ruxolitinib
Positivity duration	215 days	270 days	30 days	25 days	60 days	24 days
Previous antiviral treatments at symptoms onset	Remdesivir PREP with tixagevimab/ cilgavimab	PREP Tixagevimab/cilgavimab+ IVIG	None	Nirmatrelvir/ritonavir	None	PREP tixagevimab/cilgavimab
Symptoms	Pneumonia	Asymptomatic, pneumonia at the debut	Pneumonia	Fever	Pneumonia	Pneumonia
PCR-rt nasal swab at admission	Positive at 13 TC	NA	Positive at 22 TC	Positive at 30 TC	Positive	Positive
5th day test (antigen nasal swab)	Negative	Negative	Negative	Negative	Negative	Positive
10th day nasal swab test						
PCR-rt test	Positive at 32 TC	Negative	Positive at > 35 TC	NA	NA	Negative
Antigen test	Negative	Negative	Negative	Negative	Negative	Negative
Coviferon ®	Negative	Negative	Negative	Positive	NA	Anergic
Follow up	Died	60 days	30 days	30 days	45 days	30 days

Peracchi F Br J Haematol in press

Studies on combo antiviral treatment of immunocompromised patients

Author year	Study design	Findings
Palomba E 2021	Case report Combo RDV + mab for Relapse of COVID-19 in a patient with X-linked agammaglobulinemia	No Adverse events
Dell'Isola GB 2021	Acute BLL with COVID-18ì9 treated with CP + RDV	No adverse events
Baldi F 2022	NRM/RTV + RDV + Sotrovimab in 2 cases 1 NHLB and 1 granulomatous poliangyitis	Favourable outcome
D'Abramo A 20222	21 B-cell depleted consecutive hospitalized patients with COVID-19 all treated with RDV+steroids 16 mab; 2 CP; 3 CP + mab,	All treated pts recovered No adverse events
Mikulska M 2023	22 immunocompromised patients with prolonged/relapse COVID-19 treated with NRM/RTV + RDV or MNP + Sotrovimab in 18; 4 with 2 courses	Clinical + virological response 75% (15/20 evaluable), 73% (16/22) and 82% (18/22). **Day 14 and 30 response rates were significantly higher when combination therapy included Mabs**. One bradycardia 1 myocardial infarction

Efficacy of Combo treatment in Haematological patients with persistent COVID-19: could it be the first line ?

Early combination with remdesivir, nirmatrelvir/ritonavir and sotrovimab for the treatment of COVID-19 in immunocompromised hosts

	Overall N=11	Early combination treatment N=7	Late combination treatment N=4	p-value
Age, years, median (IQR)	51 (36-57)	52 (35-56)	63 (42-77)	0.667
Females, n (%)	5 (45.5)	3 (43)	2 (50)	0.652
Charlson Comorbidity Index, median (IQR)	0.5 (0-1.25)	0 (0-1)	2 (0.25-3)	0.517
Vaccinated, n (%)	8 (72)	5 (71)	3 (75)	0.721
SARS-CoV-2 vaccine doses, median (IQR)	3 (3)	3 (3)	3 (3)	1
Hematologic malignancy				
Acute myeloid leukemia	3 (27)	3 (42)	0 (0)	0.3
Non-Hodgkin lymphoma	4 (36)	2 (28)	2 (50)	0.646
Chronic lymphatic leukemia	1 (9)	1 (14)	0 (0)	0.308
Multiple myeloma	1 (9)	0 (0)	1 (25)	0.462
Other immunodeficiencies, n (%)	2 (18)	1 (14)	1 (25)	0.538
Use of anti-CD20, n (%)	2 (18)	0 (0)	2 (50)	0.109
Deaths, n (%)	0 (0)	0 (0)	0 (0)	
Length of stay, days, median (IQR)	14 (12.5-23)	13 (11.5-16.5)	21 (12.5-38)	0.2
Early COVID-19 therapy, n (%)	1 (9)	0 (0)	1 (25)	0.364
Preventive TIX-CIL, n (%)	1 (9)	1 (14)	0 (0)	0.325
Previous therapy for COVID-19, n (%)	3 (27)	0 (0)	3 (75)	0.8
Days from COVID-19 symptoms to combination therapy, median (IQR)	9 (3.75-48)	5 (3-9)	79 (48-112)	0.017
Remdesivir 10 d + N/r, n (%)	11	7	4	
Remdesivir 10 d + N/r + Sotrovimab, n (%)	10	6	4	
SARS-CoV-2 infection duration from the end of therapy, days, median (IQR)	10 (7-22.5)	11 (8-28)	8 (3.75-16)	0.183
Negative NFS at 14d, n (%)	4 (36.4)	4 (57)	0 (0)	0.106
Negative NFS at 30d, n (%)	9 (81)	7 (100)	2 (50)	0.109
alive and well at FU, n (%)	10 (90)	7 (100)	3 (75)	0.364
Days of follow up, median (IQR)	44 (10-92)	40 (1-81)	65 (11-108)	0.183
Use of immunomodulatory drug for COVID-19, n (%)	2 (18)	0 (0)	2 (50)	0.109
COVID-19 steroid treatment, n (%)	6 (54)	2 (29)	4 (100)	0.045
Worst WHO severity grade, median (IQR)	3 (3-4.2)	3 (3)	4.5 (4-5)	0.017
Need for O2, n (%)	5 (45.5)	1 (14)	4 (100)	0.015
ADR, n (%)	1 (9)	1 (14)	0	0.636
Lowest lymphocyte value, cells/mm^3, median (IQR)	0.39 (0.15-0.9)	0.68 (0.2-1.2)	0.16 (0.07-0.32)	0.067
Highest CRP value, mg/dL, median (IQR)	3.8 (0.3-15)	2.3 (0.3-5)	17 (8-23.4)	0.117
Highest LDH value, IU/mL, median (IQR)	287 (231-446)	251 (225-436)	488 (297-708)	0.267
Highest ferritin value, median (IQR)	495 (302-1635)	424 (253-907)	2000 (542-2000)	0.286
Highest D-dimer, median (IQR)	863 (571-1580)	620 (571-1658)	1422 (1084-1931)	0.383

Table 1 – Demographic and clinical characteristics. *TIX-CIL: tixagevimab-cilgavimab; N/r: nirmatrelvir/ritonavir; NFS: nasopharyngeal swab; FU: follow-up; WHO: World Health Organization; ADR: adverse drug reaction; CRP: C-reactive protein.*

"The combination of antiviral and sotrovimab in early phase of COVID-19 in immunocompromised patients is well tolerated and associated with 100% of virological clearance. Patients treated later have lower response rate and higher disease severity, but a causative role of the therapy in such finding is yet to be demonstrated"

Gentile I. Et al. medRxiv preprint doi: https://doi.org/10.1101/2023.09.07.23295202

La terapia con anticorpi monoclonali: ruolo attuale e prospettive future
- Outline

- Anticorpi monoclonali in infettivologia e nel trattamento e prevenzione COVID-19
- Impiego degli anticorpi monoclonali in Italia
- Resistenza ed inefficacia in era Omicron
- Dati nel paziente immunocompromesso ed ematologico
- Raccomandazioni delle linee guida
- Prospettive future
- Conclusioni

Guidelines for Mab treatment in pts with mild-moderate COVID-19

Guidelines	MAb	Selection criteria	Recommendation
ESCMID	Any	Symptom onset < 8 days Risk factor for progression Mab potentially effective (sequencing or epidemiological monitoring for variant and subvariants)	Recommended
European Myeloma Network	TGX/CIL	Myeloma patients in pts with BA.2.12.1, BA.4, BA.5, BQ.1.1, XBB and XBB.1.5.	Prophylaxis no longer recommended
NIH	All Mab	All pts	Not recommended
IDSA	All Mab	All pts	Not recommended
NICE	SOT	Mild COVID at risk of progression < 8 days	Recommended in pts not eligible for NRM/r
	All other Mab		Not Recommended
German Guidelines	SOT	Pts with mild COVID & risk for progression Symptoms < 8 d	Recommended in pts not eligible for NRM/r or RMD
	All other Mab		Not Recommended

Trattamento precoce con anticorpi monoclonali nel paziente fragile o ad alto rischio con infezione da SARS-CoV-2: quali evidenze e indicazioni pratiche

Pazienti fragili:

- soggetti immunocompromessi
- pazienti affetti da neoplasie
- pazienti affetti da insufficienza renale cronica

- Cosa Fare
  - Profilassi vaccinale mediante ciclo primario e successive dosi booster;
  - profilassi pre-esposizione mediante anticorpi monoclonali in soggetti immunodepressi (con scarsa o assente risposta anticorpale alla vaccinazione) e in soggetti in cui la vaccinazione è controindicata (tixagevimab-cilgavimab)
  - Terapia precoce dell'infezione mediante anticorpi monoclonali (Tixagevima/Cilgavimab o Sotrovimab) o farmaci antivirali.
- Sotrovimab: mantiene un'effectiveness nei confronti delle varianti circolanti al momento di diversi studi real life (Delta, Omicron BA.1, BA.2 e BA.5) sia nei confronti del rischio di ospedalizzazione che di morte.
- Tixagevimab-cilgavimab: diversi studi osservazionali ne suggeriscono il mantenimento dell'effectiveness in presenza di varianti Omicron BA.1 e BA.2.
- Necessità di ulteriori studi, ma anticorpi monoclonali rimangono quindi una valida opzione in quei soggetti fragili in cui gli antivirali risultino controindicati.

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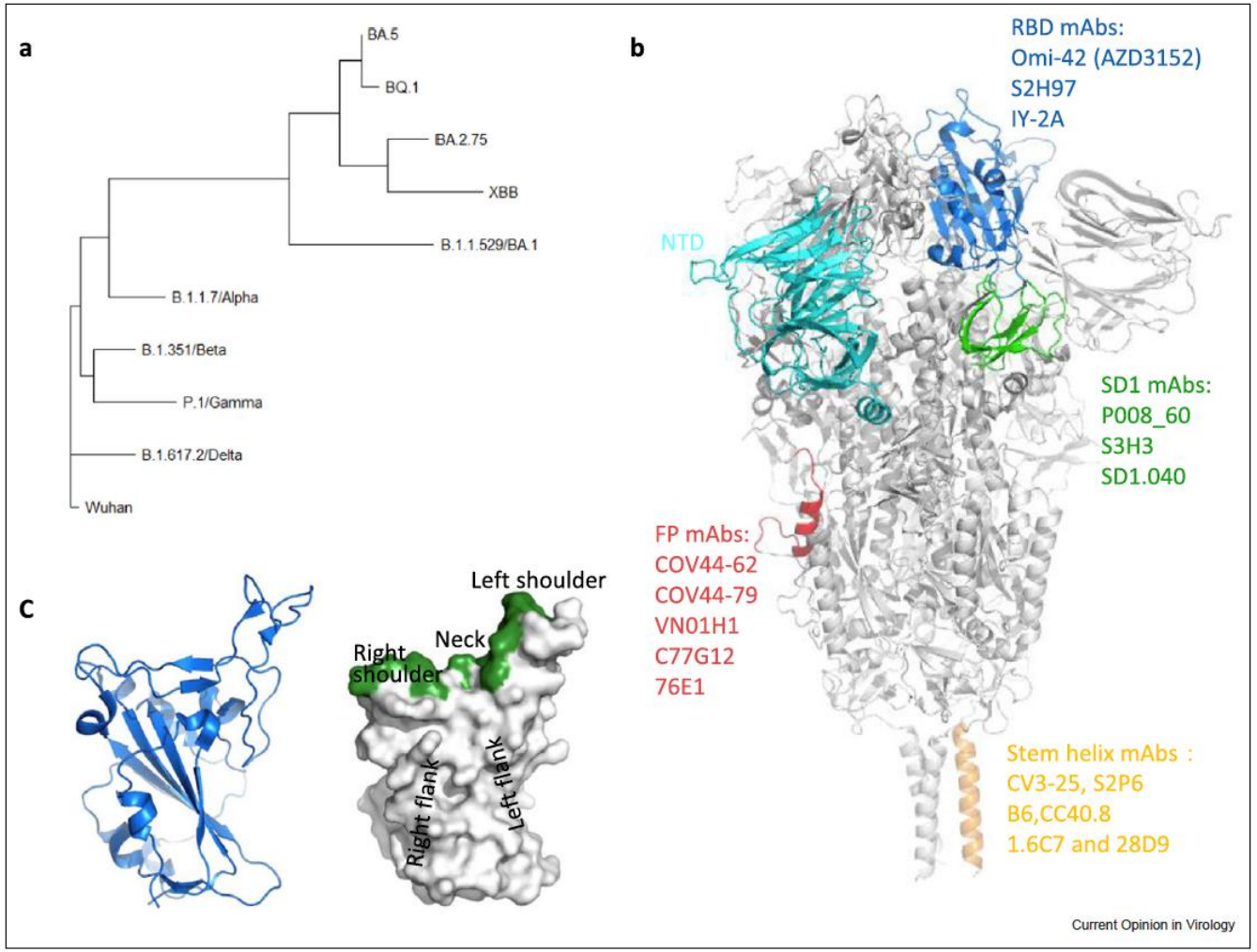
Broadly neutralizing antibodies against SARS-CoV-2



(a) Phylogenetic tree of SARS-CoV-2 previous VoCs (Wuhan, Alpha, Beta, Gamma, Delta, and Omicron BA.1) and currently dominant strains (BA.5, BQ.1, BA.2.75, and XBB). The tree is based on the amino acid sequences of the spike protein. **(b)** Regions of SARS-CoV-2 spike protein (in gray, PDB: 6XR8) targeted by 4 types of broadly neutralizing mAbs. The RBD, NTD, SD1, fusion peptide, and stem helix are colored in blue, cyan, green, red, and orange, respectively. **(c)** Cartoon representation of the RBD (left) and the surface representation of the RBD showing the locations of the left shoulder, neck, right shoulder, left flank, and right flank (right), PDB: 7BEI. The binding site of ACE2 on the RBD is colored in green.

Zhou D et al Current Opinion in Virology 2023, 61:101332

Broadly Neutralizing antibodies

- Neutralizing antibodies have been identified that bind at either the left flank or back of the RBD, two large areas that are highly conserved across all SARS-CoV-2 variants.
- In addition, antibodies have been found against the SD1 domain in S1 and the stem helix and the fusion peptide in S2, all of which are functionally essential and highly conserved.
- MAbs targeting these regions are potentially very broadly neutralizing, although they are usually not very potent, and so may not be very effective when used alone.
- To reduce the likelihood of antibody escape of SARS-CoV-2, in principle, broadly neutralizing mAbs targeting different epitopes can be used as cocktails and these weak mAbs can be combined with potent anti- RBD mAbs.
- Bispecific antibodies can also be developed, with two different broadly neutralizing Fabs in the two arms of one IgG molecule. Some well-designed bispecific antibodies showed higher binding and neutralization activities against SARS-CoV-2, with their two arms interacting simultaneously with a single-spike protein

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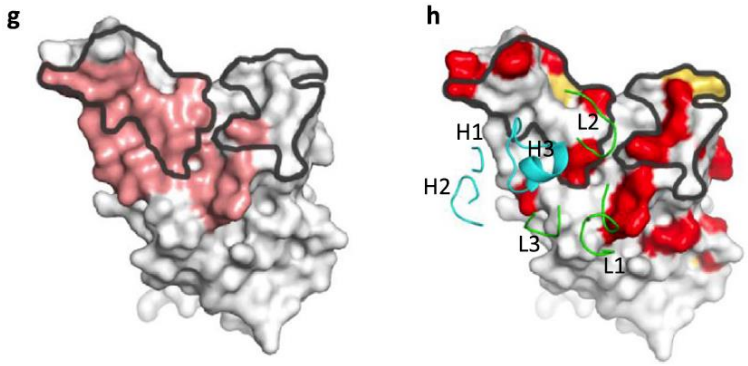
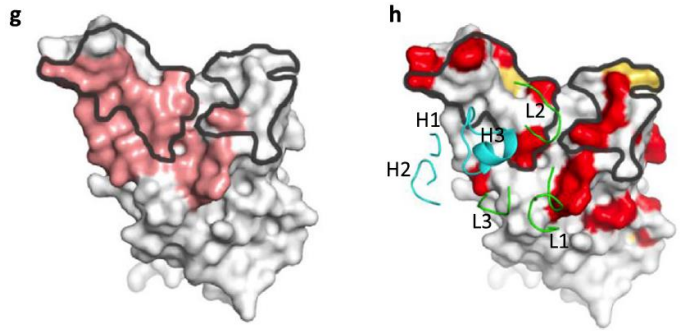
AZD 3152/AZD5156



- Omi-42 to bind at the back of the left shoulder
- Omi-42 and ACE2 have substantially overlapping binding footprints on the RBD , so mutations in the overlap region that compromise ACE2 binding would not be allowed.
- The mutations that are on the edge of the ACE-binding site and may affect binding of Omi-42 are K417N, S477N, Q493R, and Y505H. Structural analysis proves that these four amino acid residues all interact with Omi-42 but Omi-42 retains its potency both in a live-virus neutralization assay in vitro and a hamster challenge study, despite the mutations at these sites.
- A slightly modified version of Omi-42, AZD3152, has been combined with cilgavimab as AZD5156 that is in Phase- I/-III clinical trial (https://clinicaltrials.gov/ct2/show/ NCT05648110) for pre-exposure prophylaxis of immunocompromised patients.

Zhou D et al Current Opinion in Virology 2023, 61:101332

AZD 3152/AZD 5156



- AZD3152 potently neutralizes:
  - authentic viral variants (EC50 range, 8.3 to 110.9 ng/mL) and
  - SARS-CoV-2 pseudoviruses (EC50 range of 3.2 to 25.0 ng/mL), including XBB.1.5.
- Prophylactic administration of AZD3152 conferred dose-dependent protection to hamsters following challenge.
- Even at a suboptimal dose of 6.7 mg/kg, < 5% weight loss and 2 logs reduction in lung viral subgenomic RNA were observed.
- AZD3152 was not associated with any adverse findings in NHP and the no observed-adverse-effect-level was the highest dose tested (150 mg/kg).
- Toxicokinetics demonstrated similar systemic exposure following IM and IV dosing with bioavailability of 94.9% and half-life range of 15.2-26.5 days by IM
- Ongoing clinical studies
  - Safety, Neutralizing Activity and Efficacy of AZD3152 in Adults With Conditions Increasing Risk of Inadequate Protective Immune Response After Vaccination and Thus Are at High Risk of Developing Severe COVID-19 (**NOVELLA**) Estimated Study Completion Date : May 27, 2024
  - Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies (**SUPERNOVA**) Sub-study: Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies (SUPERNOVA) Sub-study (SUPERNOVA) Estimated Study Completion Date : January 31, 2025

Francica D et al ID: ofad500.1192

Nanobodies

- Nanobodies, produced primarily from the Camelidae family, offer an alternative to traditional monoclonal antibodies.
- Due to their extraordinary refolding ability, small (15KDa) size, and recombinant nature, nanobodies undergo limitless number of potential changes

Nanobodies for viral diseases

Sl. no.	Name of the virus	Nanobodies neutralize the infection	Source
1.	Influenza virus (Type A)	R1a-B6 M2–7A	Alpaca –
2.	HIV-1 virus	m36 JM4 J3	Llama Llama Llama
3.	Enteric virus	ARP1 3B2 Nano-85, Nano-25	Llama – Alpaca
4.	Herpes simplex virus 2 (HSV-2)	R33	Llama
5.	Respiratory syncytial virus (RSV)	Nb017 ALX-0171	Llama –
6.	Ebola virus	M24	–
7.	Hepatitis C virus	D03 Anti-NS3, anti-NS5B and antiprotease nanobodies	Alpaca Humanized-camel phage library

Sl. No.	Nanobodies	Virus name	Status
1	Palivizumab	Respiratory syncytial virus	FDA approved
2	V_{HH} nanobody	Dengue virus	Pre-clinical
3	Multiple V_{HH} monovalent	Polio virus	Pre-clinical
4	V_{HH} bivalent/albumin-linked	Rabies virus	Pre-clinical
5	MD3606-human Fc trivalent nanobody	Influenza virus	Pre-clinical
6	V_{HH} nanobody	Hepatitis C virus	Pre-clinical
7	Anti-CXCR4 monovalent and bivalent	HIV	Pre-clinical
8	Multiple V_{HH} monovalent	Norovirus	Pre-clinical
9	V_{HH} /human Fc hybrid	MERS-CoV	Pre-clinical
10	H5N1-HA bivalent nanobody	Influenza virus	Pre-clinical

Anti SARS-CoV2 Nanobodies

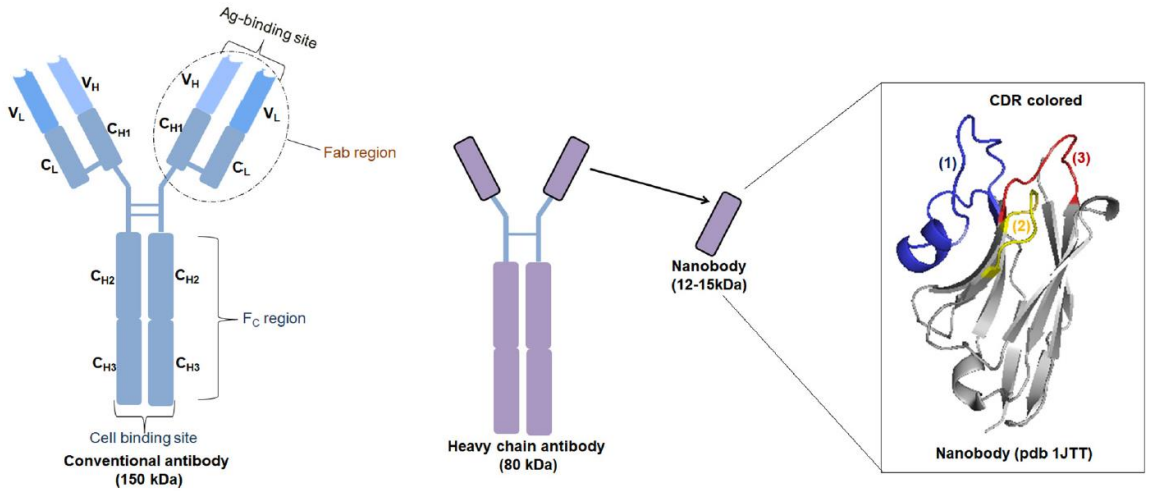
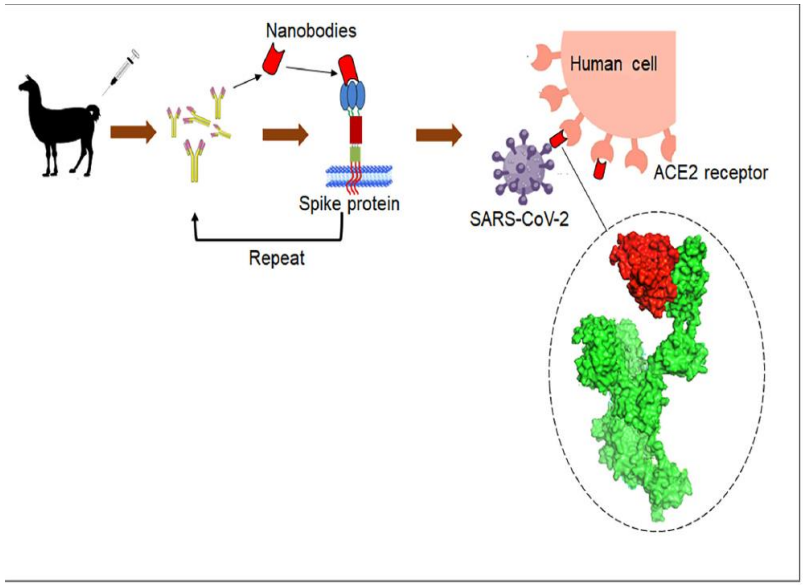


Fig. 2. Fine structure of conventional, Heavy-Chain antibody (HCAb), and single-domain antibodies (nanobodies). The ribbon representation of a nanobody (PDB ID: 1JTT). The framework regions are in grey, the hypervariable H1, H2 and H3 antigen binding loops are in [1] blue [2] yellow, and [3] red, respectively.

Features of nanobodies compare to conventional antibodies.

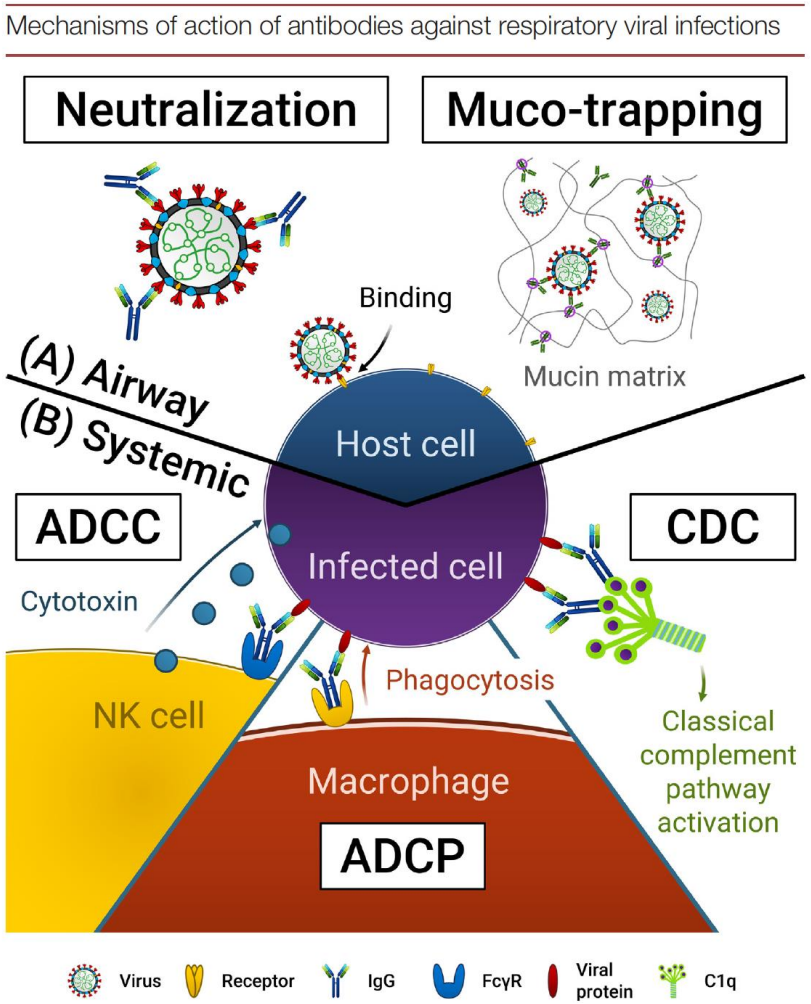
a	Nanobodies are able to recognize native epitopes, which are unusual for the classical antibodies.
b	Lesser amount of immunogenicity.
c	High stability and solubility in the harsh environments (denaturing conditions or high temperatures).
d	Small size facilitated to higher tissue penetration.
e	Nanobodies can be produced easily in yeast and bacteria. Its lack the Fc domain (glycan-harboring), and are easy to make than the standard mAbs.
f	Due to the absence of Fc regions, nanobodies have low risk of antibody-dependent enhancement of infection.
g	Life span of nanobodies can be enhanced by adding human albumin or polyethylene glycol.
h	Nanobodies can be used for new immunobiotechnological purposes and are very easy to manipulate.
i	Effortless for the selection by phage display.



Various nanobodies, their sources, and mechanism of action against SARS-CoV-2.

Sl. No.	Nanobodies	Source	Dissociation constant (K_D) value (nM) against protein of SARS-CoV-2	Mechanism of action
1.	Ty1	Alpaca		Targets the RBD of the Spike protein with a greater affinity.
2.	H-11 D4	Ilama	39 (±2)	Blocks the attachment of the ACE2 receptor with the Spike protein
3.	H-11 H4	Ilama	12 (±1.5)	Blocks the attachment of the ACE2 receptor with the Spike protein.
4.	Sb23	Library of synbodies	10.6 (± 2)	Blocks the interaction of the ACE2 receptor and the RBD
5.	K-874A	Camels (no modifications are included)	1.4	Inhibits the fusion of the viral membrane and prevents viral replication
6.	Nb11–59	*Pichia pastoris*	21.6	Blocks the interaction of the ACE2 receptor and the RBD
7.	Nb16–68		36	
8.	VNAR	Sharks	38.5–60.3	Targets the S1-RBD and breaks the salt bridge between ACE2 and RBD
9.	n3113.1-Fc	–	5.3	Binds to the RBD of the Spike protein without involving ACE2 receptor

Inhalable neutralizing antibodies



Types of antibodies	Structure and MW	Characteristics and Mechanisms of action	Current stage of development
Monoclonal antibody (IgG)	 ~150 kDa	• Full-length antibody contains both Fc and Fab domains for immune response and viral neutralization activity, respectively • The Fc domain of muco-trapping antibody can crosslink with mucin and contributes to immobilization of viruses	• Approval for use in COVID-19 but limited parenteral administration • Inhaled monoclonal antibodies against influenza virus and SARS-CoV-2 were evaluated in animal models • Inhaled muco-trapping antibody (IN-006) against SARS-CoV-2 was studied in clinic trial (Phase 1)
Nanobody	 ~15 kDa	• Single-domain antibody that contains heavy-chain only antigen binding fragment for viral neutralization activity • Typically derived from camelid species • May require humanization to avoid undesirable immunological responses	• Inhaled trimeric nanobody (ALX-0171) against RSV was studied in clinical trial (stopped after Phase 2 was completed) • Several inhaled nanobodies against SARS-CoV-2 are currently investigated in animal models
Single-chain variable fragment (scFv)	 ~27 kDa	• Contains variable regions of the light-chain and heavy-chain, joined with a peptide linker to allow antigen binding function for viral neutralization activity	• Inhaled scFv against SARS-CoV-2 are currently investigated in animal studies
Bispecific single-domain antibody	 ~27 kDa	• Contains two single-domain antibodies, each directs against different epitope for viral neutralization activity	• Inhaled bispecific single-domain antibody against SARS-CoV-2 are currently investigated in animal studies

La terapia con anticorpi monoclonali: ruolo attuale e prospettive future
- Conclusioni

- L’impiego in terapia di anticorpi monoclonali ha rappresentato una delle più grandi rivoluzioni della medicina
- L’impiego di anticorpi monoclonali in infettivologia molto limitato fino al 2019 ha avuto un incremento rilevante in occasione della pandemia da COVID-19
- Diversi anticorpi monoclonali sono stati immessi sul mercato preceduti da trials che ne dimostravano l’efficacia
- L’impiego in Italia di questa risorsa trerapeutica è risultato limitato per lo scarso coinvolgimento delle cure primarie e di specialisti non infettivologi
- La comparsa di mutazioni della proteina spike associate ad inefficacia in individui trattati con replicazione virale persistente e della «zuppa» di varianti dell’era omicron ha limitato l’efficacia di questi farmaci negli ultimi 2 anni
- La maggior parte delle linee guida non raccomanda o raccomanda solo in seconda linea l’impiego di anticorpi monoclonali nella profilassi pre-esposizione e nel trattamento del COVID-19
- Un possibile impiego di Sotrovimab sostenuto da alcuni dati confortanti può ancora essere valutato in soggetti immunodepressi in combinazione con trattamenti antivirali
- Anticorpi neutralizzanti ad ampio spettro, nanobodies e anticorpi inalabili possono rappresentare prospettive future d’impiego degli anticorpi neutralizzanti nel trattamento del COVID-19 e di altre patologie infettive

Acknowledgments

- Doctors, Nurse, Data Manager and all the persons working in the Infectious Diseases Unit of Niguarda Hospital