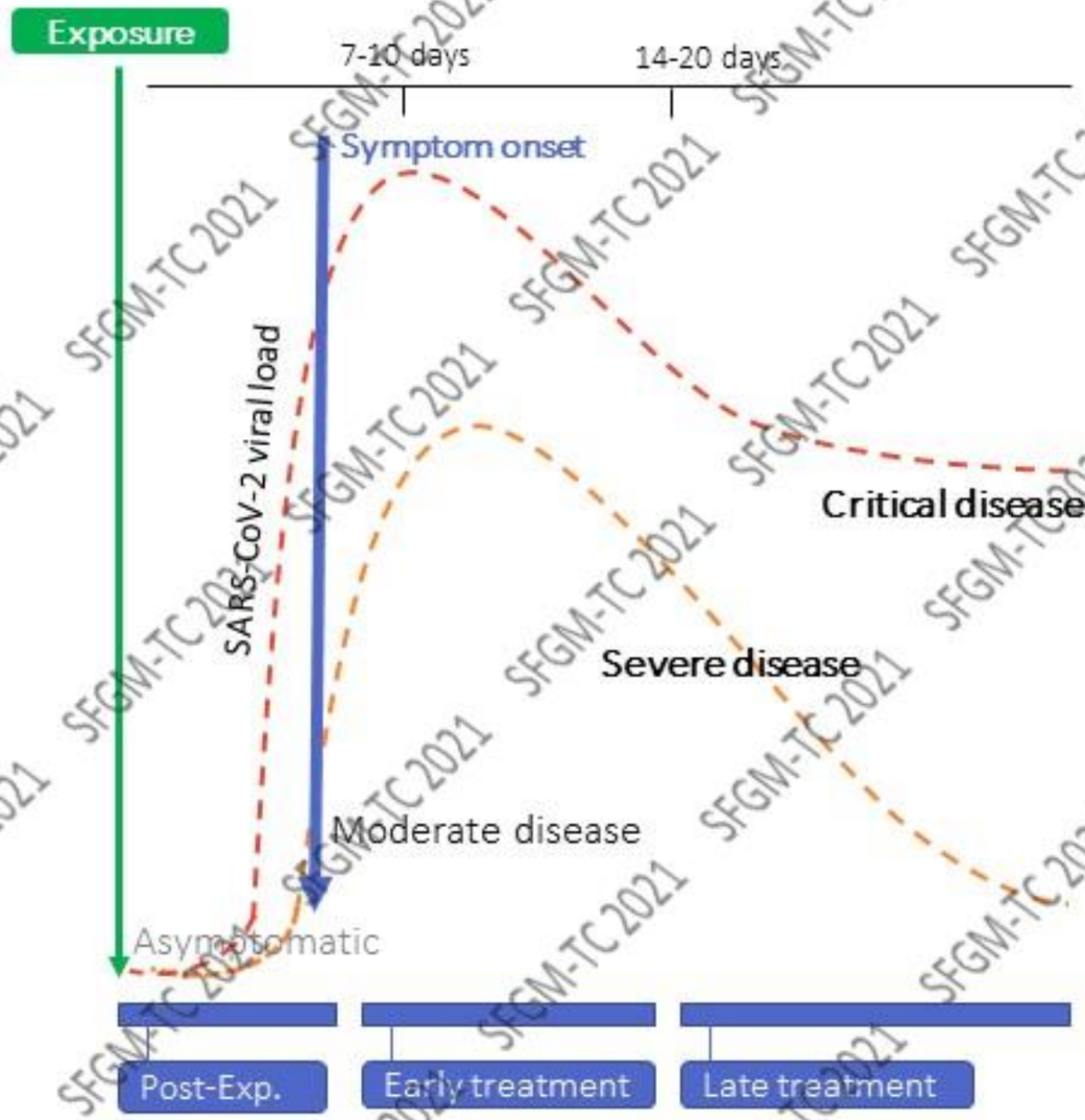
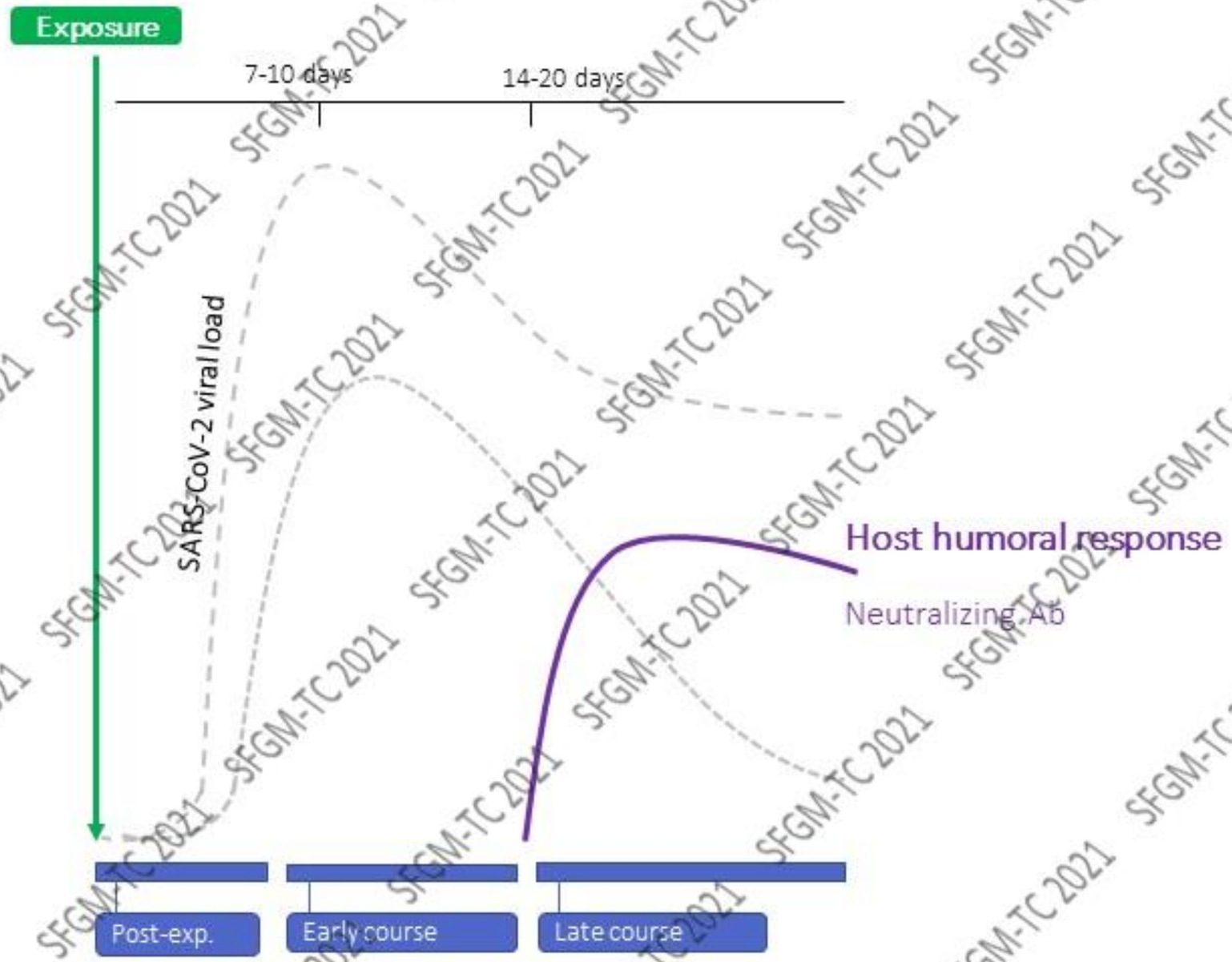
COVID-19: d'où vient-on et où va-t-on ? – point de vue de l'infectiologue

Florence ADER, M.D, Ph.D
Département des Maladies infectieuses et tropicales, CHU de Lyon, France
Inserm 1111 CIRI, Université Claude Bernard Lyon 1 University, Lyon, France

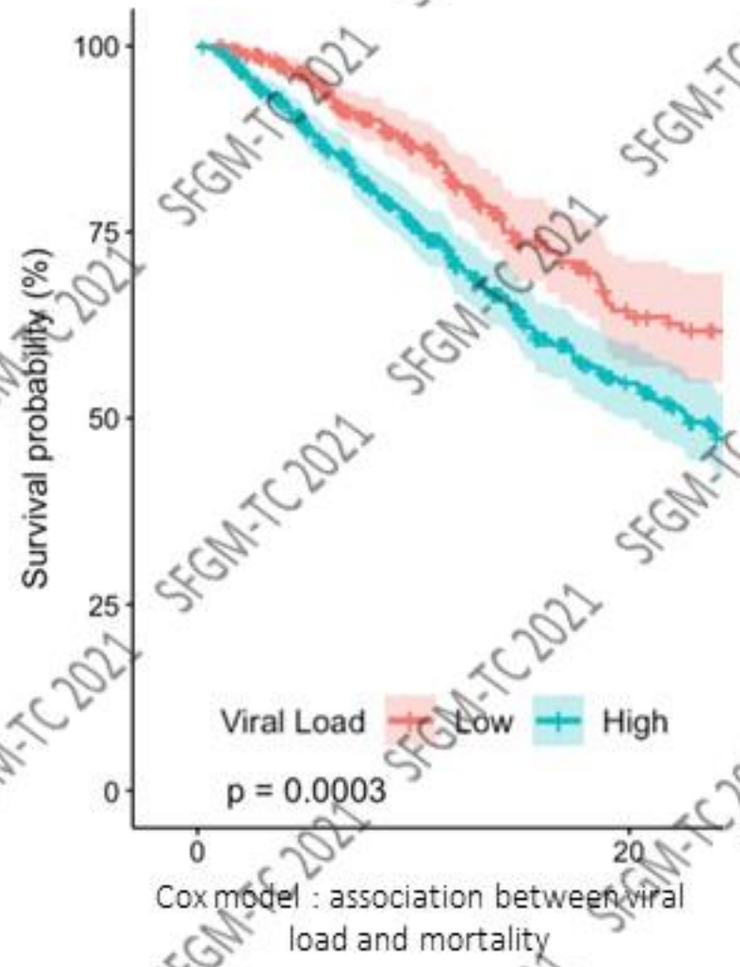


Adapted from Corti D et al. Cell 184, June 10, 2021 and Muge Cevik et al. BMJ 2020;371:bmj.m3862



Adapted from Corti D et al. Cell 184, June 10, 2021 and Muge Cevik et al. BMJ 2020;371:bmj.m3862

SARS-CoV-2 dynamics is associated with mortality in hospitalized patients



Cox model : association between viral load and mortality

n=1145 hospitalized COVID-19 patients

Independent association between SARS-CoV-2 viral load and mortality : HR 1.07 [95% CI 1·03–1·11], p=0.0014

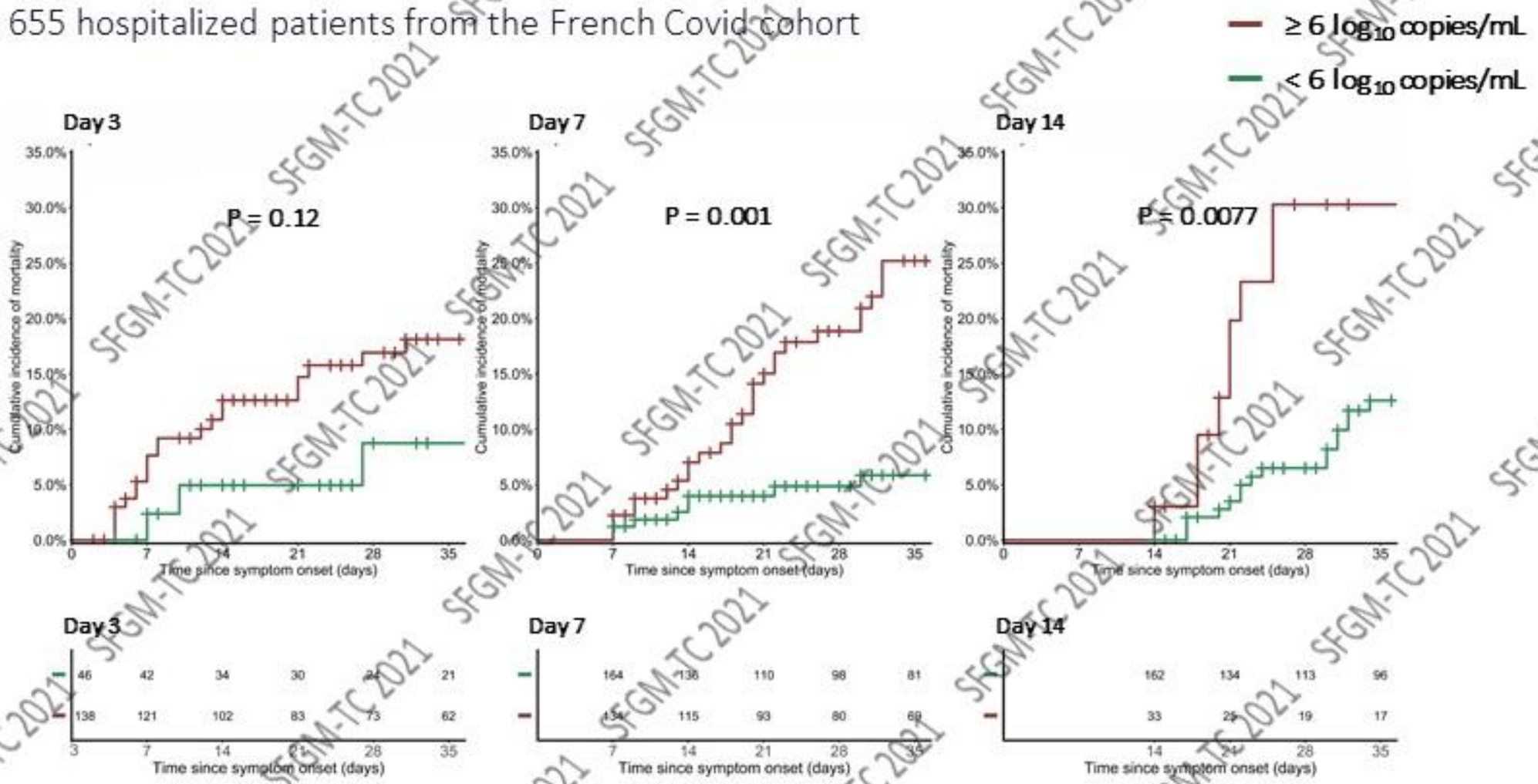
7% increase in hazard for each log transformed copy per mL

High viral load > overall mean log10 viral load of 5.6 copies/mL

Pujadas E et al. SARS-CoV-2 viral load predicts COVID-19 mortality. Lancet Respir Med 2020

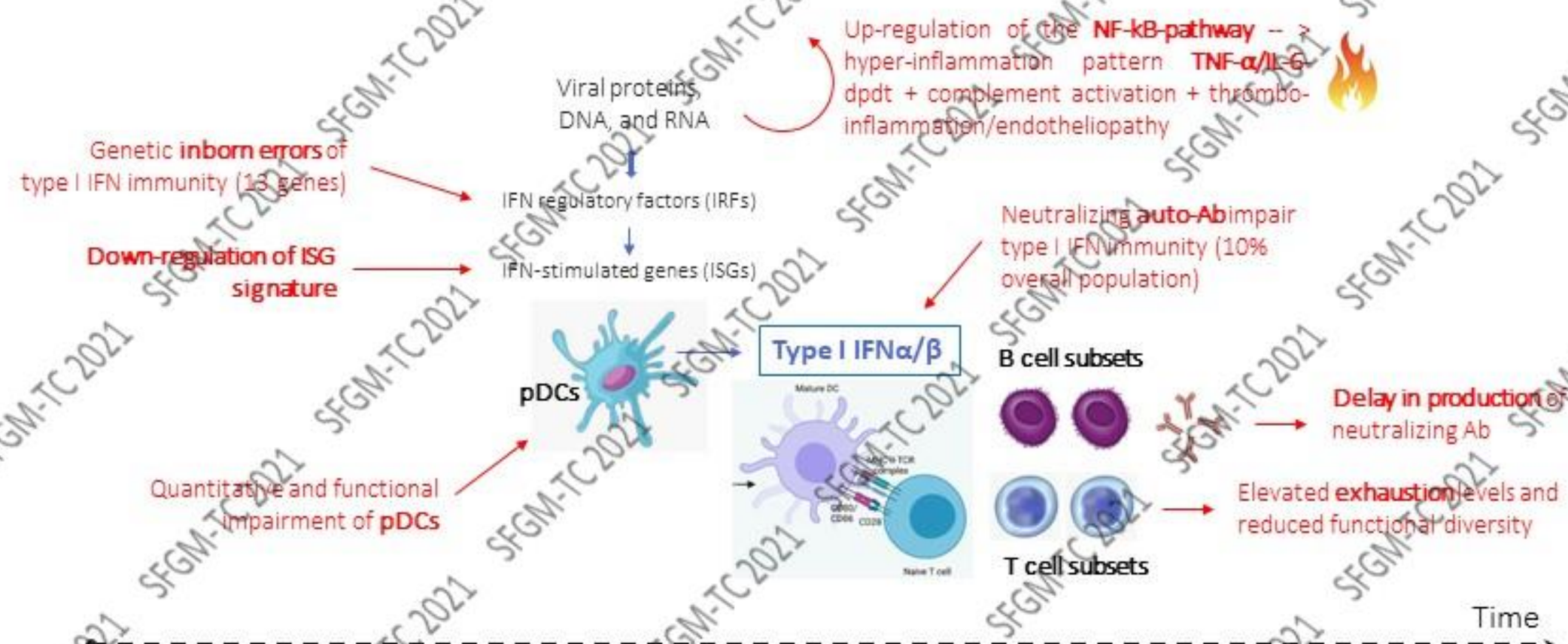
Mortality according to viral load at different landmark times since symptom onset

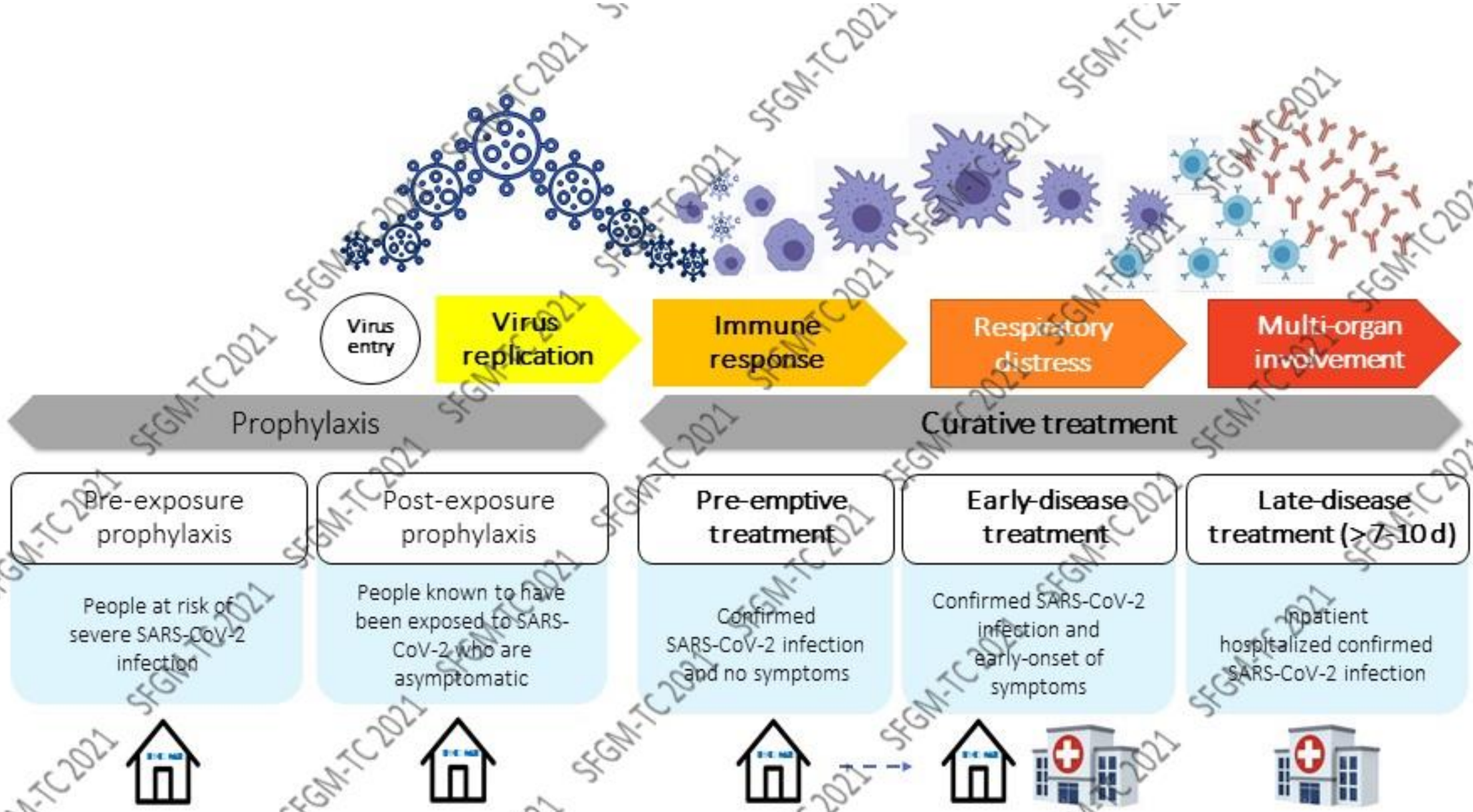
655 hospitalized patients from the French Covid cohort



FRENCHCOVID Néant N et al. PNAS 2021

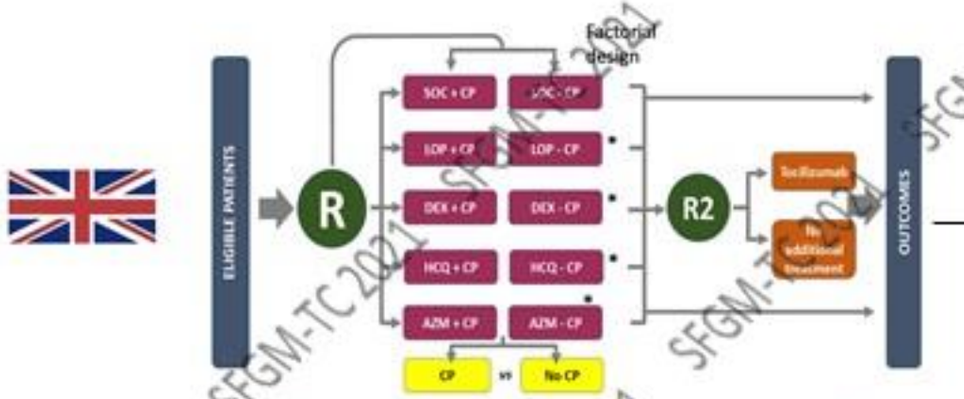
Biphasic disease --> “viral sepsis”




Virus entry
Virus replication
Immune response
Respiratory distress
Multi-organ involvement
Prophylaxis
Curative treatment
Pre-exposure prophylaxis
Post-exposure prophylaxis
Pre-emptive treatment
Early-disease treatment
Late-disease treatment (>7-10 d)
People at risk of severe SARS-CoV-2 infection
People known to have been exposed to SARS-CoV-2 who are asymptomatic
Confirmed SARS-CoV-2 infection and no symptoms
Confirmed SARS-CoV-2 infection and early-onset of symptoms
Inpatient hospitalized confirmed SARS-CoV-2 infection

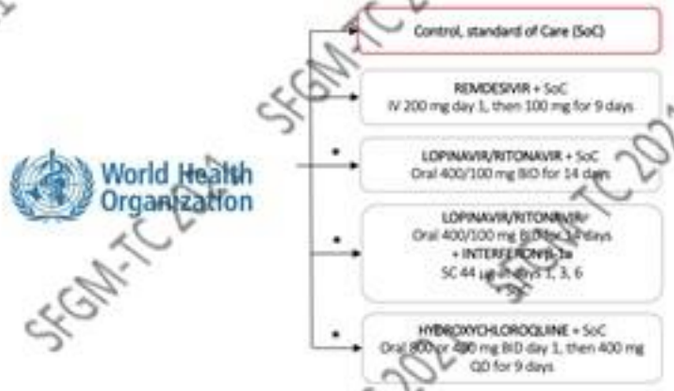
VIEWPOINT

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments



Evolving design

ACTIV-1 to 6



World Health Organization

Pro

⇢ sufficiently powered data to conclude to futility on raw/critical efficacy endpoints

⇢ open adaptive platform = flexibility to stop or start arms

⇢ gaining insights through key secondary endpoints : safety PK, pathogen kinetics, imagery, biocollections for ancillary studies

Cons

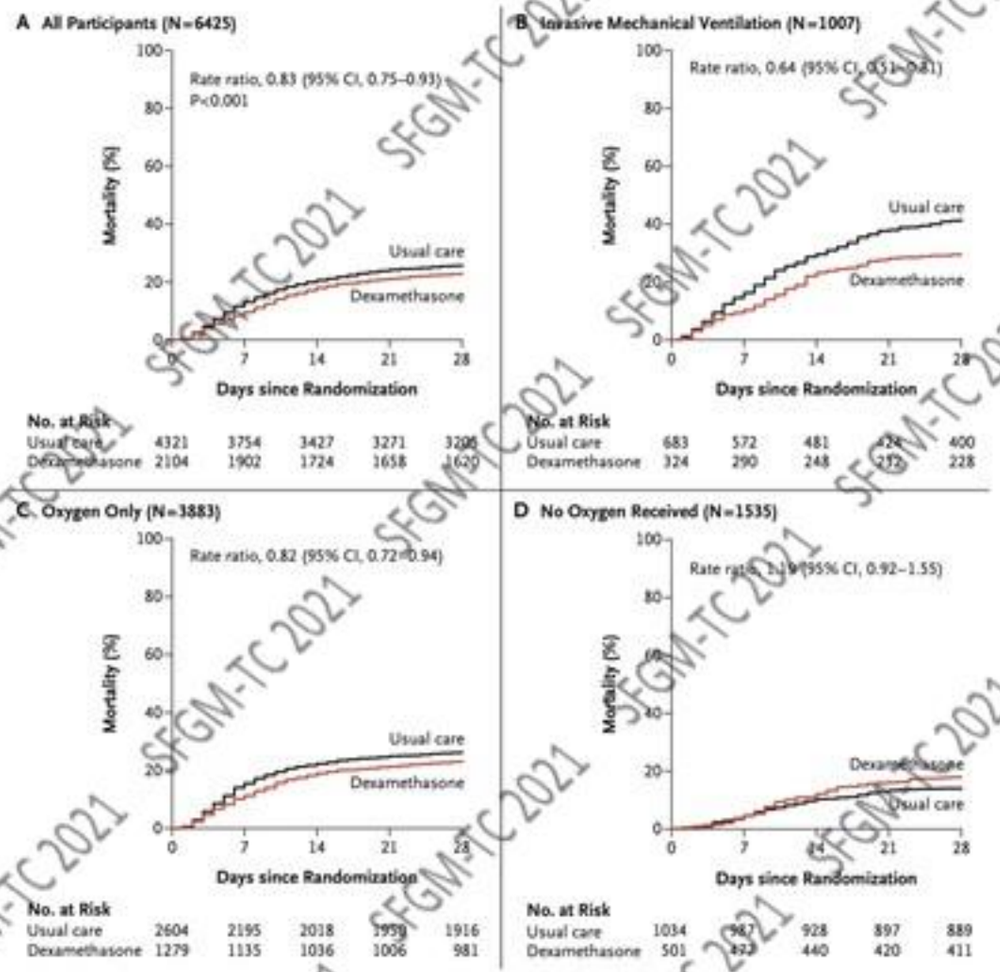
⇢ Heterogeneity of recruitment

→ **difficulty for properly stratifying**

⇢ **Evolving SoC comparator** and progression in medical management

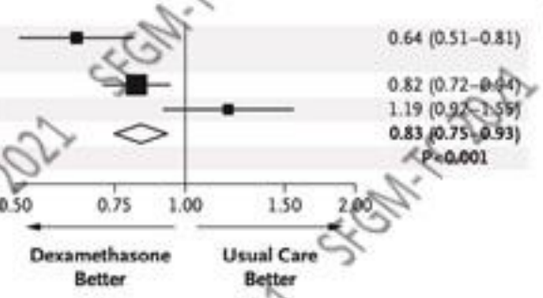
⇢ double-blinding/placebo design not always possible

June 16, 2020 – Effect of dexamethasone on 28-Day mortality, according to respiratory support at randomization



Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	98/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.92–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P=0.001

Chi-square trend across three categories: 11.6



RECOVERY collaborative group – Horby et al. N Engl J Med July 2020

From the physician's perspective : basis for treatment decision

Risk factors/comorbidities/particular subgroup ?

History of anti-SARS-CoV-2 vaccination ?

Onset of symptoms ?

Current clinical presentation/stage of the disease ?

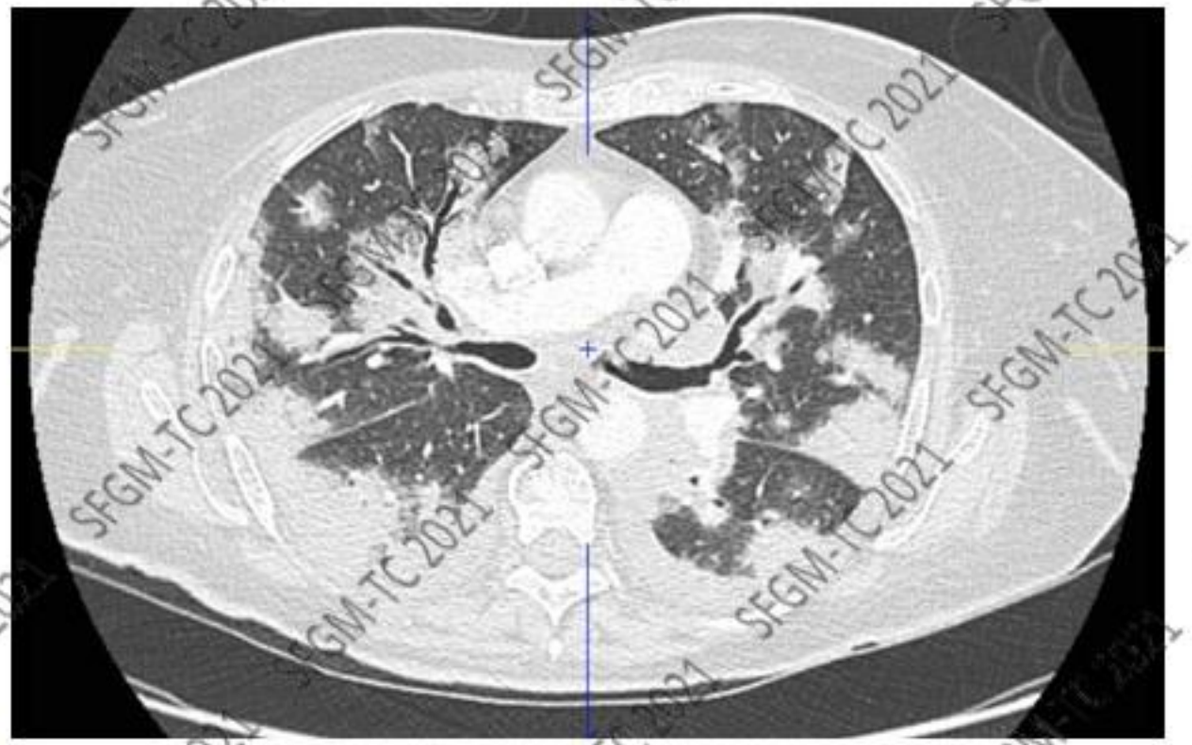
Wild type virus or variant ? Viral load (Ct) ?

Serology result : neutralizing Ab ?

One fits all ???? Challenging the "anti-inflammatory package" in the hematological setting

Agressive B-cell malignancy (R-CHOP)
D+9 after onset of symptoms
ICU-High flow oxygen
SARS-CoV-2 PCR in NP swab: pos. Ct 20
SARS-CoV-2 viremia: pos. Ct 28
SARS-CoV-2 serology: neg.
Ferritinémia: 2583 μg/L (N < 388)
D-Dimer: 2137 μg/L (N < 500)
Fibrinogen: 7.8 g/L (N < 3.5)
C-RP: 425 mg/L (N < 10)
Total Lc count: 0.1 G/L
IgG: 2.3 g/L (N > 7 g/L)
CT-scan: 25-50%

DXM + TCZmAb ????



???
-- > Sd myélodysplasiques
-- > LAM
-- > Allo/auto-HSCT < 12 mois

As vaccine-mediated immunization is rarely achieved in the hematological setting…let's focus on treatment

Passive immunotherapy

Polyclonal convalescent plasma

Neutralizing monoclonal antibodies

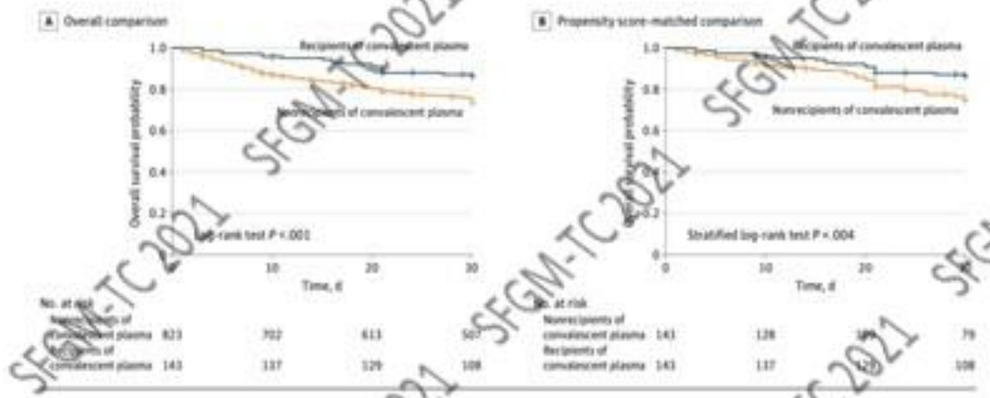
Antiviral drugs

Molnupinavir

Protease inhibitor PF-07321332

JAMA Oncology | Original Investigation

Association of Convalescent Plasma Therapy With Survival in Patients With Hematologic Cancers and COVID-19



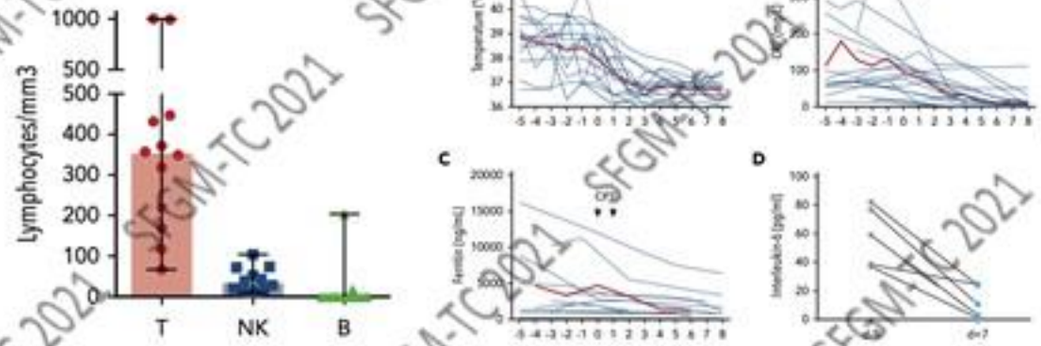
The crude mortality rate 13.3% CPT *vs.* 24.8% non CPT (HR, 0.60; 95% CI, 0.37-0.97; *P* = .03)

Thompson MA et al JAMA Oncol. 2021;7(8):1167-1175

blood
Brief Report

CLINICAL TRIALS AND OBSERVATIONS

Convalescent plasma therapy for B-cell–depleted patients with protracted COVID-19



Hueso T, et al. Blood 2020

→ cas/témoin hémopathies malignes
Nichée 89 hémopathies lymphoïdes B
Diminution mortalité 63% (95%CI=31%-80%)
Meilleur pronostic sous-gp ayant reçu RTXM

- mAbs currently approved or under conditional/provisional authorization or "accessible" through emergency use authorization (EUA) in various countries (as of November 18, 2021)

  Bamlanivimab [LY-CoV555] + Etesevimab [LY-CoV16] – IV

  Casirivimab [REGN10933] + Indevimab [REGN10987] (REGN-CoV-2) – IV, SC

  Sotrovimab [VIR-7831] – IV

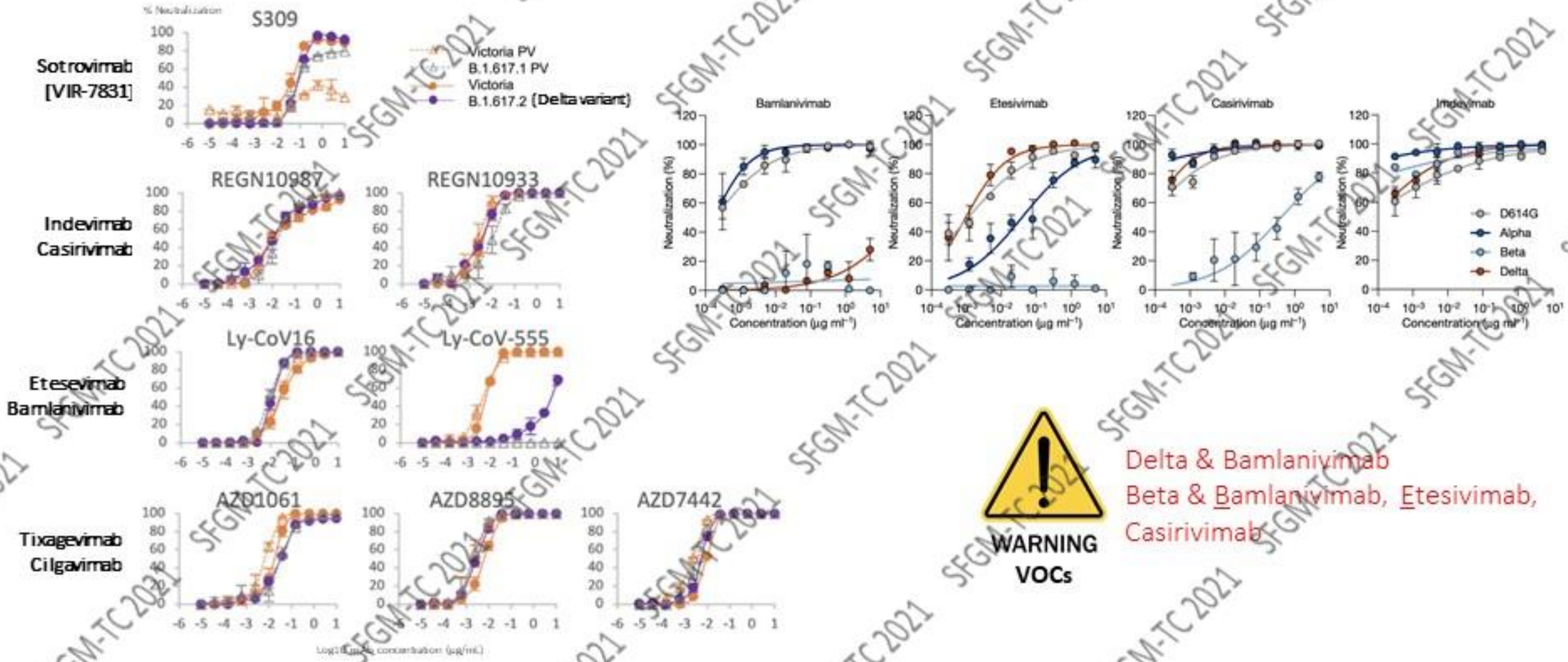
  Regdanvimab [CT-P59] – IV

- mAbs in the process of getting EUA (as of November 18, 2021)

  #Tixagevimab + Cilgavimab [AZD7442 (AZD8895+AZD1061)] – IV, IM

  #Long-acting Ab (Ab recycling mechanism) extending half-life of 90 days on average. Phase I study: estimated residual protection of 83% at 6 months

% of neutralization of the SARS-CoV-2 variants D614G, Alpha, Beta and Delta achieved by therapeutic mAbs (dose-response assays)

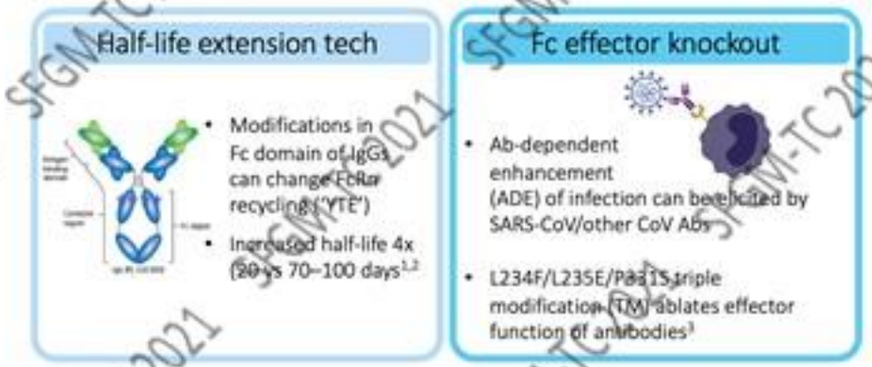


WARNING
VOCs

Delta & Bamlanivimab
Beta & Bamlanivimab, Etesivimab, Casirivimab

Liu C, Ginn HM, Dejnirattisai W, et a. Cell. 2021 Aug 5;184(16):4220-4236.e13. doi: 10.1016/j.cell.2021.06.020. Epub 2021 Jun 17. PMID: 34242578; PMCID: PMC8218332.
Planas D, Veyer D, Baidaliuk A et al. Nature. 2021 Aug;596(7871):276-280. doi: 10.1038/s41586-021-03777-9. Epub 2021 Jul 8. PMID: 34237773.
Starr, T. N., Greaney, A. J., Dingens, A. S. & Bloom, J. D.. Cell Rep. Med. 2, 100255 (2021).

Pre-exposure prophylaxis



Pivotal RCTs	Patients	Design, n	Primary endpoint	Main results
Tixagevimab + Cilgavimab **AZD7442** **PROVENT** NCT04625725	Outpatients 600mg (2xIM of 300mg) --- > Planned for a 15-months follow-up	86 sites 2:1 75% with comorbidities 5197	PCR+ symptomatic illness (-> day 90) (-> day 180)	**Primary endpoint met** **77% and 83% reduction of the risk of developing symptomatic COVID-19 at 90 and 180 days.** No cases of severe COVID-19 or COVID-19-related deaths in those treated with AZD7442 *vs.* 3 and 2 in the placebo arm at 90 days.

- - > AstraZeneca has sought EUA from US/EU regulators and other countries for AZD7442

Press release 20/08/2021; https://www.astrazeneca.com/media-centre/press-releases/2021/azd7442-prophylaxis-trial-met-primary-endpoint.html

Pre-emptive and symptomatic early-disease treatement (< 5-7 d) in outpatients

Pivotal RCTs	Patients	Design, n	Phase III	Primary endpoint	Main results
Bamlanivimab + Etesevimab BLAZE-1 NCT04427501	**COVID-19 outpatients** Mild-to-moderate	x2-blinded *vs.* placebo 1035	1:1 < 3 days	COVID-19-related hospitalization or death from any cause by day 29	**Primary endpoint met** Absolute risk difference, −4.8%; 95% CI, -7.4 to -2.3; RR difference, 70%; P<0.001
Casirivimab + Indevimab REGEN-COV2 NCT04425629	**COVID-19 outpatients** ≥ 1 risk factor(s) for severe COVID-19 Two IV doses: - 2400 (1200 each) - 1200 (600 each)	115 sites x2-blinded *vs.* placebo 2519	1:1:1	COVID-19-related hospitalization or all-cause death through day 29	**Primary endpoint met** 2400 or 1200mg similarly reduced COVID-19-related hospitalization or all-cause death by 71.3%; 95% CI: 51.7%; 82.9%; P<0.0001) and 70.4%; 95% CI: 31.6%; 87.1%; P<0.0024), respectively

WARNING
Delta variant

Dougan M, et al. Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. N Engl J Med. 2021 Jul 14:NEJMoa2102685
Weinreich DM, Sivapalasingam S, Norton T, e tal. REGEN-COV antibody cocktail clinical outcomes study in covid-19 outpatients. [Preprint.] medRxiv 2021:2021.05.19.21257469. doi: 10.1101/2021.05.19.21257469

Late-disease treatement (> 7-10 d) in hospitalized COVID-19 patients

ACTIV-3/TICO sub-studies :

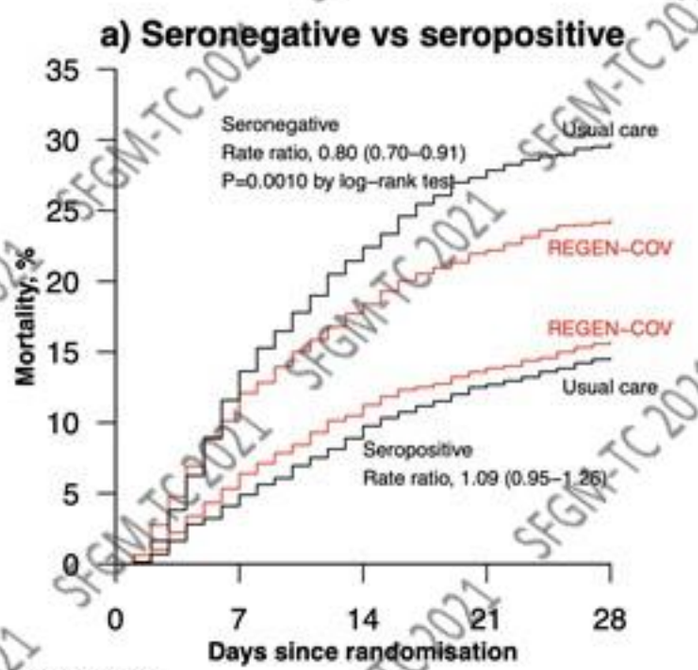
- Bamlanivimab [LY-CoV555] + Remdesivir (95%) = futility (halted on October 26, 2020)
- Sotrovimab [VIR-7831] = futility (halted on March 1, 2021)

Pivotal RCT	Design, n	Primary efficacy endpoint	Major outcomes
Casirivimab 4g + Indevimad 4g **RECOVERY** NCT04381936	Open-label *vs.* SoC 1:1 9785 3153 (32%) seronegative 5272 (54%) seropositive 1360 (14%) unknown	28-day mortality assessed among : - seronegative patients at randomisation - overall population	Seronegative patients : reduction of 28-day mortality (rate ratio 0·80; 95% CI 0·70-0·91; P=0·0010) Overall: no reduction (rate ratio 0·94; 95% CI 0·86-1.03; P=0,17)

[1] *ACTIV-3/TICO LY-CoV555 Study Group. N Engl J Med 2021; 384:905-914*

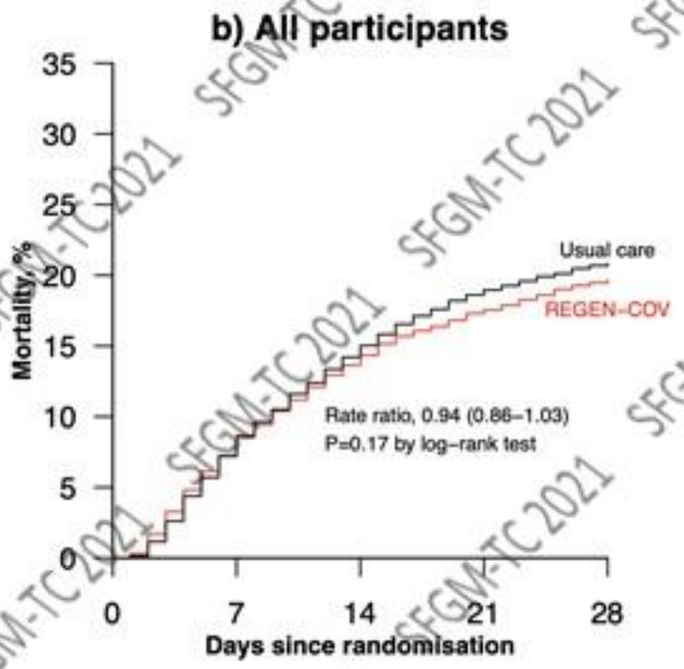
[2] *RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. [Preprint.] medRxiv 2021:2021.06.15.21258542*

Effect of allocation to casirivimab 4g + indevimab 4g on 28-day mortality



No. at risk, Seronegative					
REGEN–COV	1633	1429	1325	1260	1224
Usual Care	1520	1308	1173	1088	1059

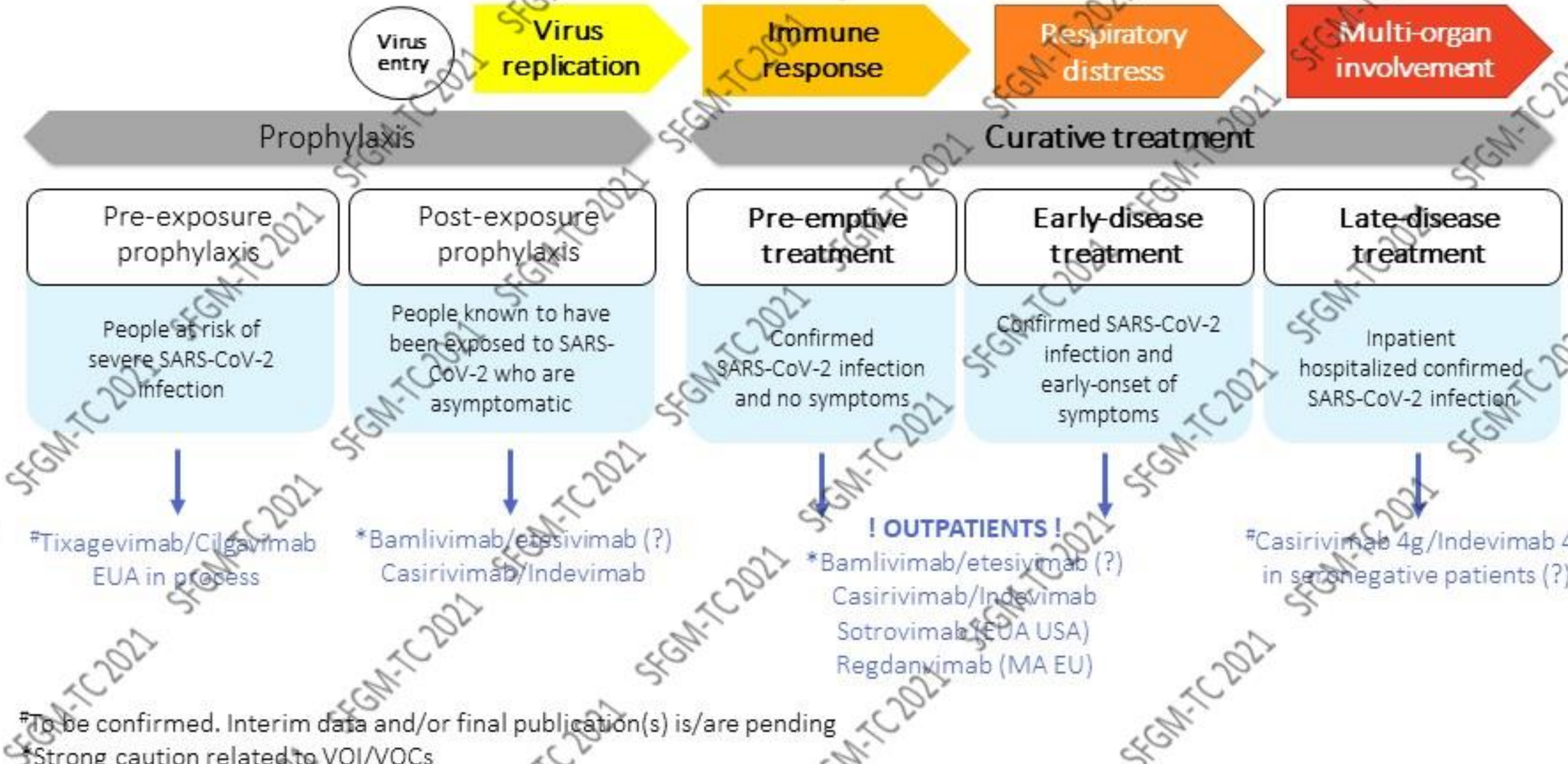
No. at risk, Seropositive					
REGEN–COV	2636	2452	2322	2252	2201
Usual Care	2636	2503	2375	2292	2243



No. at risk					
REGEN–COV	4839	4388	4112	3952	3848
Usual Care	4946	4504	4182	3980	3886

RECOVERY Collaborative Group. Casirivimab and Imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. [Preprint.] medRxiv 2021:2021.06.15.21258542

Summary (as of November 18, 2021)



#To be confirmed. Interim data and/or final publication(s) is/are pending

*Strong caution related to VOI/VOCs

Abbreviations: EUA, emergency use authorization; EU: European union; MA: marketing authorization; USA: United States of America

PrEP
Séronégatifs à 3 doses
(< Ac anti-S <30 BAU/mL)

Ultra-prioritaires

Allogreffe de CSH: 1er J T post-transplant, séronégatifs à 3 doses
Si faiblement répondeur à 3 doses -- > 4 doses, dès feu vert

Anti-CD20 (RTXM, GA101 Obinutuzumab) séronégatifs à 3 doses
Rem: Incitation à vacciner 3 doses les lymphodéplétés B quel que soit le délai (sauf si chth lymphodépletive T associée)

Receveurs de **CAR T-cells** séronégatifs à 3 doses

DIP = **DICV** > 12 ans, séronégatifs à 3 doses, agammaglobulinémie, atteinte pulmonaire sévère

Molnupiravir [MK-4482]

Efficacy and safety of Molnupiravir (MK-4482) in non-hospitalized adult participants with COVID-19
NCT04575597

Mechanism of action : **RNA mutation promoter** = impairment of SARS-CoV-2 replication through molnupiravir-induced RNA mutagenesis resulting in a higher frequency of RNA mutations (increase G to A and C to U transition mutations in replicating coronaviruses)

Phase III interim analysis 01/10/2021
Dose/response 200mg-400mg-800mg/12h – 5 days (10 doses)
x2-blinded *vs.* placebo 1:1:1:1
170 sites
n=775

Primary efficacy outcome : % of participants who are hospitalized and/or die up to 29 days

Results: molnupiravir reduced the risk of hospitalization or death by approximately **50%**;
- Hospitalization -> day 29 : molnupiravir **7.3%** (28/385) of patients *vs.* **14.1%** (53/377) placebo; p=0.0012.
- Deaths -> day 29 : molnupiravir n=0 *vs.* placebo n=8

Selective pressure induction ? Mutagenic RNA interaction --> teratogenic ?

PAXLOVID™ (PF-07321332; ritonavir)

EPIC trial Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients **NCT**

Mechanism of action : **protease inhibitor** -- > blockade of SARS-CoV-2-3CL protease + low dose ritonavir (slow and breakdown of metabolism)

Phase III interim analysis 05/11/2021
Dose : 1 tablet/12h – 5 days (10 doses) within 3 days of symptom onset
x2-blinded *vs.* placebo 1:1
> 50 sites, 45% in the US
n=1219 -- > planned 3000 -- > interrupted by DSMB for efficacy

Primary efficacy outcome : % of participants who are hospitalized and/or die up to 28 days

Results: PAXLOVID™ reduced the risk of hospitalization or death by approximately **83%**;
- Hospitalization - > day 28 : PAXLOVID™ 0.8% (3/389) of patients *vs.* 7% (27/385) placebo; p<0.0001.
- Deaths - > day 28 : PAXLOVID™ n=0 *vs.* placebo n=7
- Neutral safety profile

Selective pressure induction ?

Key messages

Acknowledging the limitations of platform trials in the setting of compromised hosts = challenging the universal standard of care approach (DXM, TCZmAb)

Major issue of current vaccination strategies : decreased immunogenicity and effectiveness in compromised hosts :

⇢ maintaining at all cost protection measures and cocooning strategy

⇢ antivirals

mAbs = the first game changer in the antiviral approach against SARS-CoV-2

. pre-exposure
preemptively in high-risk patients recently exposed to SARS-CoV-2

. in adults and adolescents with COVID-19 who do not require supplemental oxygen and who are at increased ris
of their disease becoming severe.

. "off-label" to be considered in seronegative hospitalized COVID-19 patients (?) -> further validation is required i
specific subsets of patients and necessity to assess the non-inferiority of a lower dose (4g/4g --> 1.2g/1.2g)

WARNING
VOIs
VOCs

What is next ?

⇢ Pre-exposure prophylaxis in high-risk patients and/or vaccine-resistant using **long-acting mAbs**

⇢ Early-phase **combination**: mAbs + any other new antiviral drug(s)

⇢ **Sub-group** approaches: pregnancy, immunocompromised, elderly, etc...

Acknowledgements

Inserm
La science pour la santé
From science to health

ciri

anrs
MALADIES INFECTIEUSES EMERGENTES

DISCOVERY
Study group

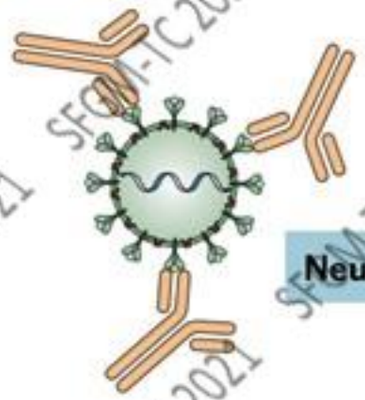
EU
RESPONSE

Fab : epitope-binding site

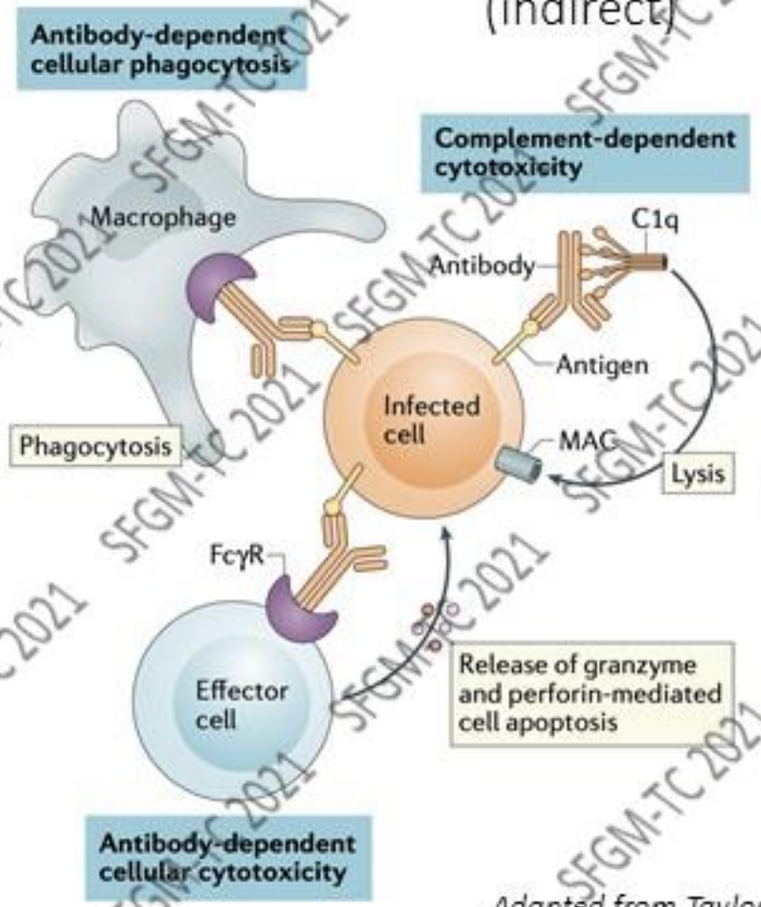
Fc : executive segment

Neutralizing activity/capacity (direct)

Effector functions (indirect)



Neutralization



Opsonization

Adapted from Taylor PC et al. Nature Rev Immunol 2021