19th International Ultmann Chicago Lymphoma Symposium

LIVE Symposium

APRIL 29-30
2022

19TH ULTMANN

THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES

COVID-19 in Patients with Lymphoma

Treatment Approaches, Vaccination, and Prophylactic Strategies

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Information in presentation is current as of 4/24/2022

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Disclosures

- Speaker has received consultant/advisor honorarium from Eli Lilly (baricitinib) and will be discussing off-label and investigative use of drugs

Objectives

- Review the epidemiology of the COVID-19 pandemic and its impact on patients with lymphoma
- Discuss available COVID-19 vaccines and prophylactic monoclonal antibody options and their effectiveness
- Assess how changing variants can affect the choice of preferred monoclonal antibody therapy
- Outline available therapeutic options for the treatment of COVID-19

COVID-19 Cases and Deaths

Worldwide
>130 million cases / >3.5 million deaths
Mortality rate: 0.1-19%*

United States
>80 million cases / >950,000 deaths
Mortality rate: 1.2%

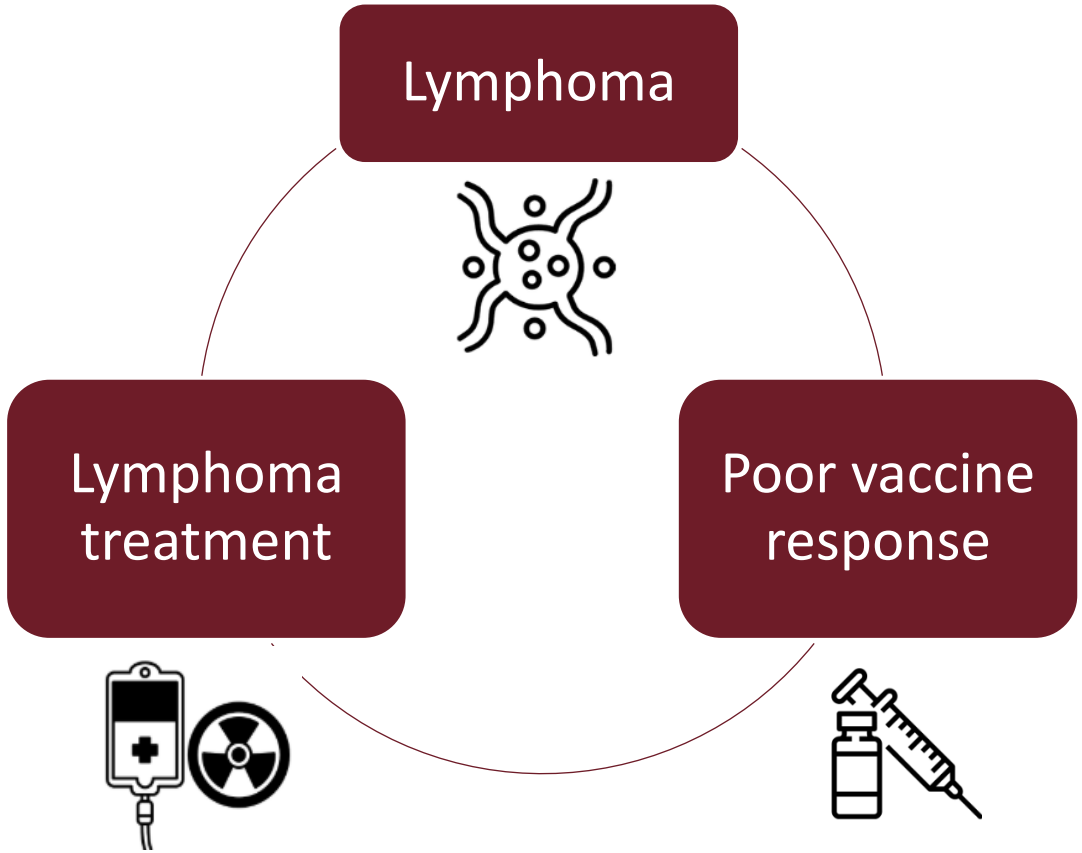
Patients with Cancer (*any type*)
Reported range 1%-8% of all COVID-19 cases occur in patients with cancer
Mortality rate: ~30-60%

Patients with Lymphoma
Among cancer patients with COVID-19, lymphoma accounts for 5% of cases
Mortality rate: 13-55%

Bonuomo V, et al. World J Virol 2021;10:312-325
New York Times and Our World data
Visco C, et al. Blood Adv 2022;6:327338
Fillmore NR, et al. JNCI J Natl Cancer Inst 2021;113:691-698

* Varies according to country, 1.2% overall mortality rate

Lymphoma and COVID-19 Risk



- Lymphoma
  - More comorbidities, underlying immunosuppressive conditions
  - More frequent contact with medical care
  - Crippled cellular and humoral immunity
- Lymphoma treatment
  - B-cell depleting therapy with anti-CD20 monoclonal antibodies (e.g. rituximab) part of standard treatment
  - Bendamustine also used in some cases, potent inducer of T-cell immune deficiency
- Poor vaccine response
  - Many patients with lymphoma do not mount an adequate response to vaccines
  - Especially among those that have received Anti-CD20 therapies within past 6 mos

Vijenthira A, et al. Blood Adv (2021) 5 (12): 2624–2643
Bonuomo V, et al. World J Virol 2021;10:312-325

Predictors of survival among lymphoma patients with COVID-19

- Multi-center cohort study (Italian Hematology Alliance on COVID-19) with the aim of developing a prognostic model for patients with lymphoma (N=856)
  - On multivariate analysis, ***strongest predictors of mortality:***

Age >65	Absolute lymphocyte count <650 x 10-9/L
Male Gender	Platelet count <100 x 10-9/L

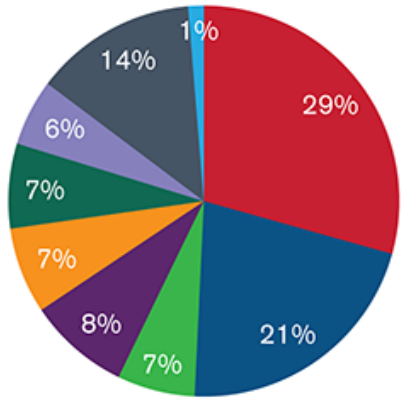
  - No difference in mortality observed among those that received anti-CD20 immunotherapy or those actively receiving anti-lymphoma therapy
  - Patients with Hodgkin's lymphoma had better survival
  - Time interval between lymphoma diagnosis and COVID-19 infection inversely related to mortality

Visco C, et al. Blood Adv 2022;6:327338

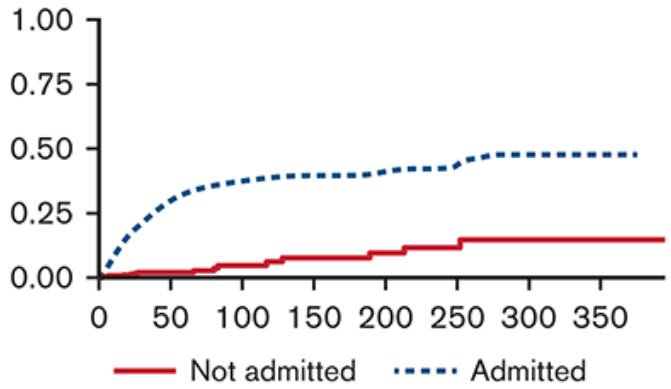
A prognostic model for predicting outcome in lymphoma patients and COVID-19 infection: an Italian multicentre study

1. Large study cohort

856 lymphoma patients

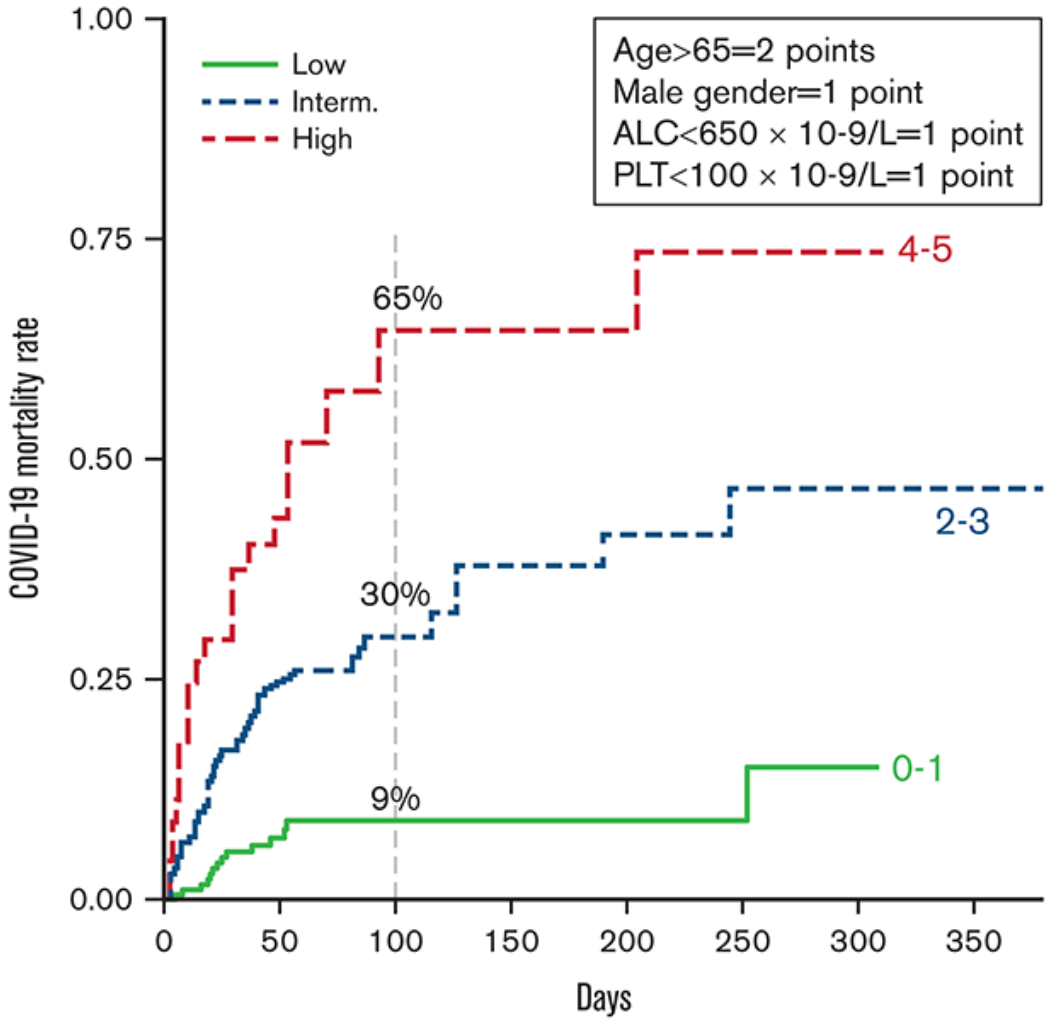


DLBCL FL HG-NOS, DHL MZL
LPL MCL T-cell cHL LP-HL



2. High rate of COVID-related death in hospitalized patients

3. A prognostic easy-to-use model for outcome prediction



Visco C, et al. Blood Adv 2022;6:327338

Additional Factors Associated with Poor Outcomes Among Lymphoma Patients with COVID-19

- Relapsed/refractory lymphoma
- Lymphomas stratified with a high-risk score at diagnosis
- Active disease (DLBCL)
- Active treatment (FL)*
- Hypogammaglobulinemia
- Persistently positive (>6 weeks) SARS-CoV-2 PCR
- Hypertension
- Diabetes
- Heart disease
- Chronic kidney disease
- Other cancer
- CURB-65 score $\geq$3
- Elevated inflammatory markers (CRP, d-dimer, LDH)

Lamure S, et al. E Clin Med 2020;27:1—549
Garcia-Sancho AM, et al. Hematol Oncol. 2021 Jun; 39(Suppl 2):10.1002/hon.200_2880
Regalado-Artamendi I, et al. HemaSphere 2021;5:e5339

* Available data is variable on whether this is a risk factor for mortality, 1 retrospective study found higher mortality among those with FL on active therapy

COVID-19 Vaccine Recommendations for Immunocompromised Patients

Based on CDC recommendations as of 4/24/2022

Pfizer-BioNTech (mRNA)

Ages 5+

- Dose 1
- 21 days
- Dose 2
- 28 days
- Dose 3
- 3 months
- Dose 4
  Ages 12+
- 4 months
- Dose 5
  Ages 12+
  (optional)

Moderna (mRNA)

Ages 18+

- Dose 1
- 28 days
- Dose 2
- 28 days
- Dose 3
- 3 months
- Dose 4
  Ages 12+
- 4 months
- Dose 5
  Ages 12+*
  (optional)

J&J (viral vector)

Ages 18+

- Dose 1
- 28 days
- Dose 2
  mRNA vaccine
- 2 months
- Dose 3
  mRNA vaccine
- 4 months
- Dose 4
  mRNA vaccine
  Ages 12+*
  (optional)

* For patients 12-17 yo, only Pfizer vaccine recommended, 18+ can be Pfizer or Moderna, boosters not recommended for ages 5-11, mRNA vaccines preferred for boosters

NCCN Guidance on COVID-19 Vaccination in Cancer Patients

- All patients with hematologic malignancies (HM) should receive a 3-dose primary vaccine series, followed by recommended booster doses
- mRNA vaccines preferred (Pfizer BioNTech or Moderna)
- Vaccination timing for patients with HM:
  - Receiving intensive cytotoxic chemotherapy: Delay until ANC recovery, but if not expected to recover, give ASAP
  - If marrow failure from disease and/or therapy expected to have limited or no recovery: give ASAP
  - Long-term maintenance therapy (e.g. targeted agents for CLL, myeloproliferative neoplasms): give ASAP
  - HSCT or CAR-T: wait *at least* 3 months
- Do NOT recommend use of antibody titers to determine if a patient should receive additional doses
- Following vaccination, given known reduced efficacy in patients with cancer, patients should still follow current prevention guidance

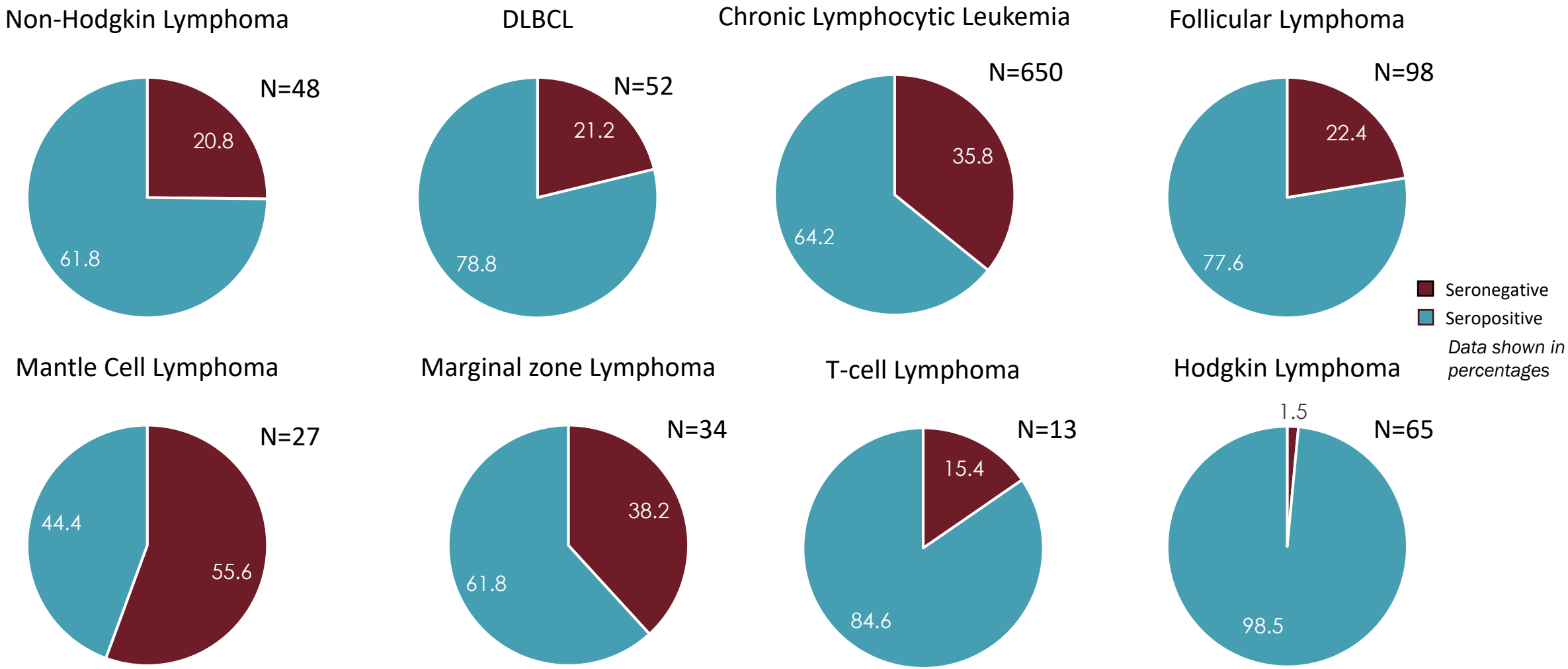
NCCN: Cancer and COVID-19 Vaccination. Version 5.0 01/04/2022. Available at: https://www.nccn.org/docs/default-source/covid-19/2021_covid-19_vaccination_guidance_v5-0.pdf?sfvrsn=b483da2b_110

COVID-19 Vaccine Response in Lymphoma Patients

- Rate of vaccine response
  - Range: **44-79%** *(following 2-doses)*
    - Following a 3rd-dose an additional 23-55% seroconvert
  - Rates of response variable according to:
    - Type of lymphoma
    - Receipt of anti-CD20 monoclonal antibodies or BTK inhibitors
      - Active or therapy w/in prior 6 months, response rate: ~40%
    - Type of mRNA vaccine?
      - Pre-omicron studies have shown higher response rates (seroconversion) with Moderna vs. Pfizer BioNTech among patients with lymphoma/other HMs
      - But will this remain true with omicron and subsequent variants?

Greenberger LM, et al. Cancer Cell 2021;39(8):1031-1033
Greenberger LM, et al. Cancer Cell 2021;39(10):1297-1299
Bagacean C, et al. Blood Adv 2022;6:207-211
Perry C, et al. Blood Adv 2021;5:3053-3061
Lim SH, et al. Nat Cancer 2022;Mar 24;10.1038/s43018-022-00364-3(Epub ahead of print)

COVID-19 Vaccine Primary Series Effectiveness Among Lymphoma Patients



Greenberger LM, et al. Cancer Cell 2021;39:1031-1033

Data from Leukemia & Lymphoma Society National Registry, includes antibody response rate following 2 mRNA vaccine doses

COVID-19 Vaccination – Clinical Considerations

- *Is one mRNA vaccine preferred to the other?*
  - CDC recommends either mRNA vaccine as preferred
  - Higher seropositive rates with Moderna versus Pfizer BioNTech vaccine observed in solid-organ transplant and leukemia/lymphoma patient populations
    - Possibly due to higher amount of spike mRNA (100mcg vs. 30mcg), different dosing schedules, and differences in the coding sequence of the mRNA or lipid composition of the vaccines which may alter penetration of the mRNA into host cells
- *Is it better to mix and match vaccines?*
  - Improved vaccine response mixing J&J with an mRNA vaccine and with mRNA vaccines (using a different mRNA booster than primary mRNA series)
  - CDC and NCCN advise mixing/matching J&J with mRNA but to generally stick with same mRNA vaccine

CDC. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#immunocompromised

Audience Response Question

- When providing COVID-19 mRNA booster doses to patients, do you mix and match between the two vaccines? *(e.g. if gave the Pfizer vaccine as the primary series, recommending the Moderna vaccine for booster doses)*
  - A) Yes
  - B) No

COVID-19 Vaccines – Clinical Considerations

- *Timing of vaccine relative to receipt of lymphocyte depleting therapy?*
  - Consider deferring vaccination until 6 months after completion of therapy or until evidence of recovery of lymphocyte numbers (Memorial Sloan Kettering guidance*)
  - Vaccinate BEFORE starting therapy if possible (series completion ≥14 days prior)
- *Timing relative to monoclonal antibodies?*
  - Bebtelovimab: no separation is recommended
    - Usually just have them come for their vaccine once meeting criteria for being off quarantine
  - Tixagevimab/cilgavimab: must wait two weeks after vaccine to receive this monoclonal antibody
- *What antibody level correlates with vaccine effectiveness?*
  - Experts are still working on identifying this value
  - Available data suggests a level of >1000 U/mL (fewer patients with breakthrough infection)
  - Some experts recommend >2500 U/mL (upper level of detection)
  - T-cell response is also important to consider, studies evaluating T-cell response to COVID-19 vaccination are underway

*Guideline available at: https://www.asco.org/sites/new-www.asco.org/files/content-files/covid-19/2021-MSK-COVID19-VACCINE-GUIDELINES.pdf

Bergwerk M, et al. N Engl J Med 2021;385:1474-1484
CDC. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#immunocompromised

Pre-exposure Prophylaxis with SARS-CoV-2 Monoclonal Antibody Therapy

- **Tixagevimab/cilgavimab** - SARS-CoV-2 spike protein attachment inhibitor
  - Emergency use authorization (EUA) indication for use:

Pre-exposure Prophylaxis (Adult, Pediatrics 12+)
NOT currently infected AND have moderate-to-severe immune-compromise* AND who may not mount an adequate immune response to COVID-19 vaccination

NOT recommended for treatment of COVID-19, or for post-exposure prophylaxis if exposed to someone with COVID-19. It is NOT a substitute for vaccination (unless patient has preclusion to receipt of the vaccine (e.g. severe allergy to COVID-19 vaccine)

Dose/Administration
300mg T + 300mg C / IM Injection

1x dose, no current recommendations for re-dosing

Monitoring:
Clinically monitor patient 60 min

Fact Sheet for Healthcare Providers: EUA for Evusheld, available at: https://www.fda.gov/media/154701/download

* Includes active treatment for hematologic malignancies

Tixagevimab/cilgavimab – Clinical Data

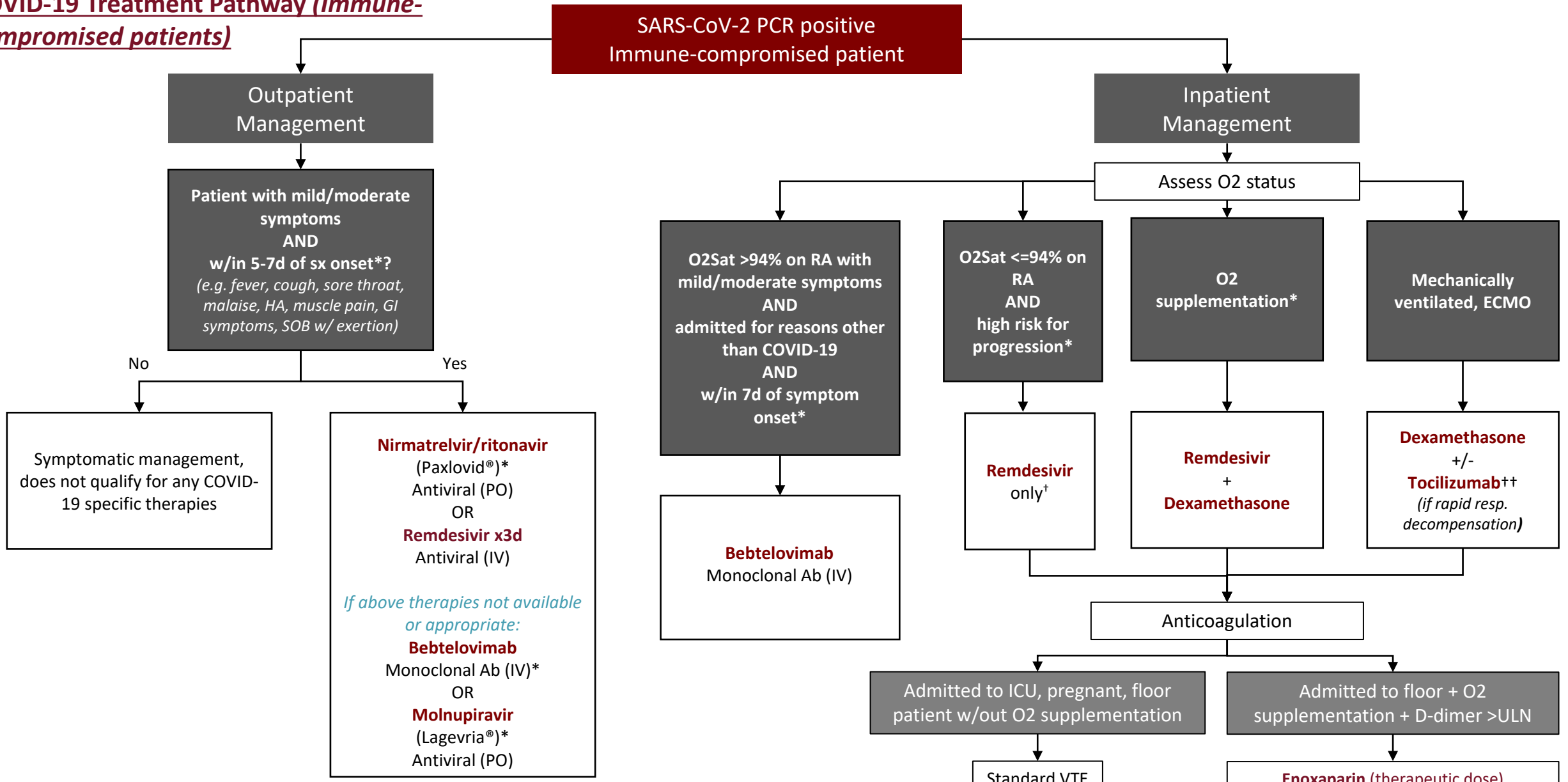
- PROVENT Trial
  - Phase III RCT evaluating use as **pre-exposure prophylaxis**
  - Adult patients either ≥ 60 yo, had a pre-specified comorbidity, or at increased risk 2/2 living situation; all patients unvaccinated
  - N=3441 T/C vs. 1731 placebo
  - **Primary endpoint (incidence of COVID-19): 77% reduction**
    - 0.2% T/C vs. 1% placebo
  - Adverse events:
    - Most common: headache, nausea, fatigue
    - Slightly higher rates of CV events
- STORM CHASER Trial
  - Phase III RCT evaluating use as **post-exposure prophylaxis**
  - Adult patients, not vaccinated, within 8 days of exposure
  - N=749 T/C vs. 372 placebo
  - Primary endpoint (incidence of COVID-19): 33% reduction *(non-significant)*
    - 3.1% T/C vs. 4.6% placebo
  - **Study did NOT show a benefit for T/C in preventing COVID-19 following exposure**

Fact Sheet for Healthcare Providers: EUA for Evusheld, available at: https://www.fda.gov/media/154701/download

Tixagevimab/cilgavimab - Clinical Considerations

- *Do we need to be concerned about the increased rate of CV events?*
  - A higher proportion of patients in the PROVENT trial that received T/C reported MI and cardiac failure (0.6% vs. 0.2%)
    - Most events occurred in patients with cardiac risk factors and/or prior history of CVD
    - No clear temporal pattern
  - Not observed in the STORM CHASER trial, included younger patients and those with fewer risk factors
- *When can I give T/C after active infection or after exposure?*
  - Wait until the patient meets criteria for being off quarantine
  - Refer to CDC guidance on definition of exposure and current recommended quarantine period
    - https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/determine-close-contacts.html
- *Can I give T/C immediately prior to or on the same day of chemotherapy?*
  - There is no contraindication to giving T/C around/at the same time as chemotherapy

COVID-19 Treatment Pathway *(Immune-compromised patients)*



*Symptom onset must be w/in 5d to for PO antivirals, w/in 7d for bebtelovimab; *ideally* w/in 7d for remdesivir

†If symptoms progress while on remdesivir and a patient now requires O2 support, add dexamethasone

††If tocilizumab not available sarilumab may be used, or alternatively consider JAK inhibitors (baricitinib or tofacitinib); may consider these therapies in patients requiring O2 supplementation with rapid respiratory decompensation

Monoclonal Antibody (mAb) Therapy for Treatment of Active Infection

- **Bebtelovimab** is the current SARS-CoV-2 mAb du jour
  - Most effective mAb for the Omicron BA.2 sublineage
- EUA indication:

Treatment of mild-moderate COVID-19 (Adults, Pediatrics 12+)
COVID-19 positive AND at high risk for clinical progression AND other treatment options are not accessible or appropriate

Give WITHIN 7 DAYS of symptom onset

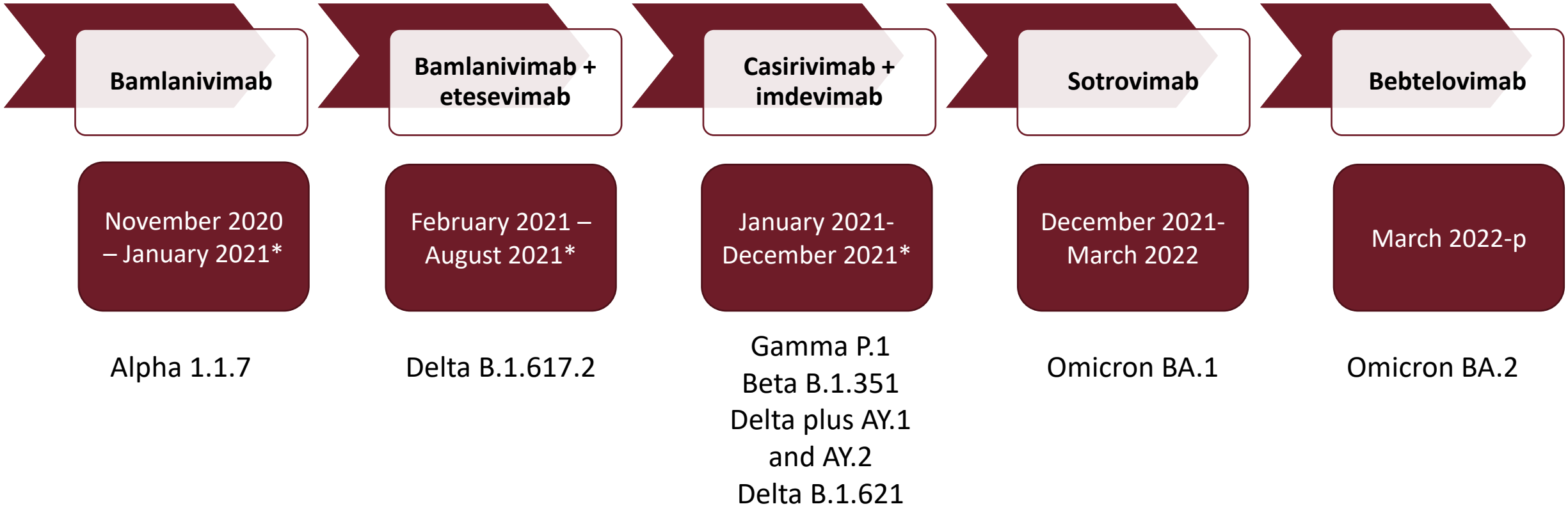
NOT recommended in geographic regions where infection is likely caused by a non-susceptible variant, NOT for patients hospitalized due to COVID-19 OR that require O2 support OR that require an increase in baseline O2 support due to COVID-19 if on O2 support at baseline

Dose/Administration
175mg / IV push over ≥ 30 sec

Monitoring:
Clinically monitor patient 60 min

Fact Sheet for Healthcare Providers: EUA for bebtelovimab, available at: https://www.fda.gov/media/156152/download

COVID-19 Monoclonal Antibody Therapy – Timeline*



*FDA began recommending against certain mAb's based on distribution of circulating variants that were known to have reduced neutralizing activity for; noted are the variants each mAb was active against that became the predominant variant during the dates shown

Monoclonal Antibodies vs. COVID-19 Variants/Sublineages

- Monoclonal Ab's have varying neutralizing activity depending on the SARS-CoV-2 variant
- For the most recent, predominant variant (Omicron BA.2) – bebtelovimab has the most reliable activity

Etesevimab
Casirivimab
Bamlanivimab
Imdevimab
Sotrovimab
Bebtelovimab

Fold change in IC_{50} relative to D614G	RBD mAbs													NTD mAbs					
	Class 1			Class 2				Class 3						Class 4					
	CB6	Brii-196	1-20	REGN 10933	COV2-2196	LY-CoV 555	2-15	REGN 10987	COV2-2130	S309	2-7	Brii-198	LY-CoV 1404	ADG-2	DH1047	10-40	S2X259	4-18	5-7
BA.1	<–428	–298	<–429	<–2,201	–306	<–1,496	<–2,716	<–1,716	–83.5	–6.9	–195	2.3	1.4	–11.0	–14.2	–21.1	–13.7	<–26.7	–4.1
BA.1+R346K	<–428	–135	<–429	–415	–187	<–1,496	<–2,716	<–1,716	<–687	–4.5	–82.1	<–22	1.5	–15.7	–7.9	–20.5	–7.5	<–26.7	–5.5
BA.2	<–428	–322	<–429	<–2,201	–680	<–1,496	<–2,716	–253	–1.9	–27.0	–7.3	–10.5	1.1	<–555	<–58.0	<–114	<–96	<–26.7	<–171
T19I	–3.1	–4.9	–5.3	–3.7	–1.9	–2.2	–2.0	–2.1	–1.5	–1.8	–5.1	–1.6	–1.7	–1.7	–1.5	–2.7	–2.9	–6.1	–3.3
L24S	–2.9	–4.0	–4.6	–3.2	–2.4	–2.4	–2.8	–4.2	–2.1	–1.5	–2.6	–2.2	–1.6	–1.3	–1.1	–2.4	–2.0	–3.1	–1.1
Del25–27	–1.2	–2.6	–2.0	–1.3	–1.0	–1.4	–1.2	–1.3	1.0	–1.3	–2.8	2.0	–1.2	1.1	1.6	–1.8	1.1	–23.1	–16.8
V213G	–2.5	–3.1	–3.0	–3.1	–1.5	–1.1	–1.6	–2.2	–2.0	–1.2	–3.2	–1.1	–1.5	1.1	1.0	–2.0	–1.7	1.9	–2.8
S371F	–143	–126	–95.1	–27.9	–26.1	–5.1	–6.3	–86.6	–1.3	–20.5	–30.6	<–22	–2.4	–43.0	–60.9	<–114	–77.5	7.8	2.3
T376A	–1.9	–3.1	–2.5	–2.1	–1.3	–1.7	–1.3	–1.9	–1.8	1.0	–2.7	2.0	–1.7	1.1	1.1	–1.5	–2.3	1.3	–1.3
D405N	–25.6	–2.3	–2.9	–2.8	–2.1	–1.9	–1.7	–1.6	1.0	1.5	–3.1	–1.6	1.3	3.3	–1.2	–3.9	–2.2	5.6	1.5
R408S	1.4	–1.1	–1.3	–1.1	1.5	–1.6	–1.3	1.2	1.0	1.0	1.2	1.4	–1.4	–1.6	–2.1	–1.2	–3.6	1.1	–1.3

Iketani S, et al. Nature. 2022 Mar 3. doi: 10.1038/s41586-022-04594-4. Epub ahead of print.

>3	<–3	<–10	<–100

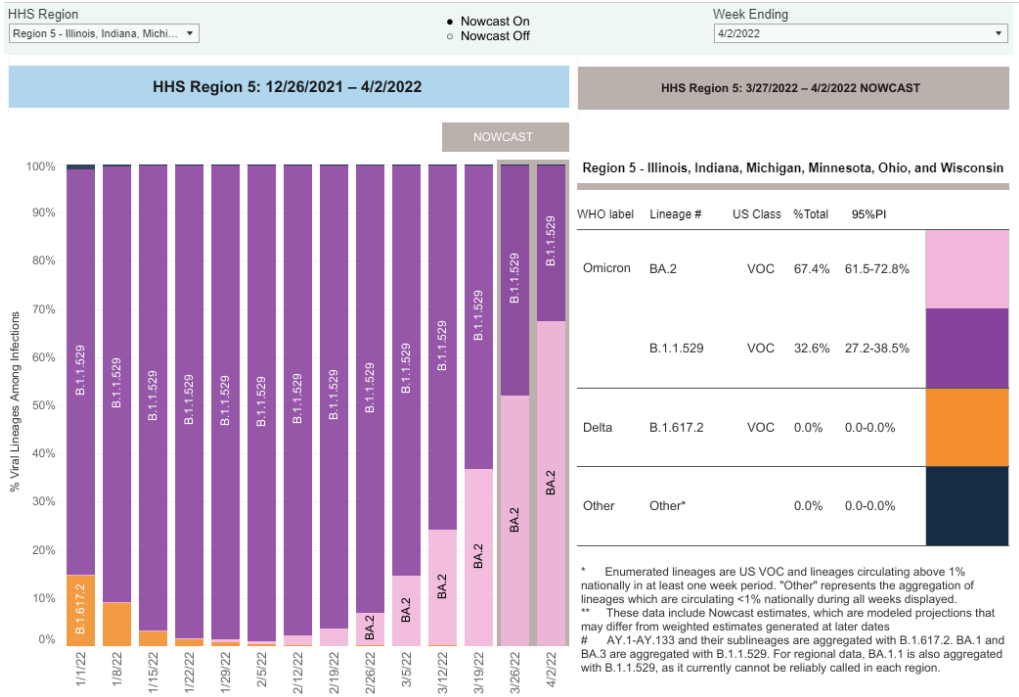
Monoclonal Antibody Therapy for COVID-19 Clinical Data

- Bebtelovimab
  - Phase II RCT evaluating clinical efficacy of mono- and combination mAb therapy in low-risk and high-risk non-hospitalized patients with mild-moderate COVID-19 (BLAZE-4 Trial)
  - Patients in high risk group received either bebtelovimab + bamlanivimab/etesevimab vs. bebtelovimab alone (within 3d of testing positive)
  - Primary efficacy endpoint (COVID-19 related hospitalization or death): 2% combination mAb, 3% bebtelovimab alone (placebo groups in other trials: 3.2-6%)
- Previous mAbs
  - Reduction in risk for COVID-19 related hospitalization or death in *high-risk patients* from Phase III Trials
    - Sotrovimab: 85% (COMET-ICE)
    - Casirivimab/imdevimab: 70.4% (COV-2067)
    - Bamlanivimab/etesevimab: 87% (BLAZE-1)

Dougan M, et al. N Engl J Med 2021;385:1382-1392
Gupta A, et al. N Engl J Med 2021;385:1941-1950
Weinreich DM, et al. N Engl J Med 2021;384:238-251
Fact Sheet for Healthcare Providers. EUA for bebtelovimab, available at: https://www.fda.gov/media/156152/download

Monoclonal Antibody Therapy for COVID-19 - Clinical Considerations

- *How long after receiving bebtelovimab can someone receive the COVID-19 vaccine?*
  - CDC no longer recommends waiting 90 days, consider waiting until meets criteria for being off quarantine
- *How do I know what variants are circulating in my region/city and if I will need to change the mAb we use?*
  - FDA, state and city departments of health notify providers
  - CDC data tracker available that reports distribution of circulating variants by region



CDC COVID Data Tracker: Variant Proportions

CDC. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#immunocompromised

Oral Antivirals: Nirmatrelvir/ritonavir and Molnupiravir

	Nirmatrelvir/ritonavir	Molnupiravir
Mechanism of Action	Protease inhibitor	Nucleoside analogue (mutagenesis)
EUA Indication††	Adult and pediatric 12+, mild to moderate COVID-19, at high risk for progression to severe disease	Adults 18+, mild to moderate COVID-19, at high risk for progression to severe disease, *ONLY when other therapies not available*
Efficacy data*	RRR: 88%	RRR: 30%
Dosing	300/100 mg q12h x5 days	800 mg q12h x5 days
Timing of administration†	5 days	5 days
Pertinent clinical considerations	• Significant DDI potential • Renal dose adjustment *(CrCl <60ml/min)* • Not recommended if severe renal *(CrCl <30ml/min)* or hepatic dysfunction	• Embryo-fetal toxicity (avoid use if pregnant or if childbearing potential) • Bone cartilage toxicity (avoid if < 18 yo)

RRR: Relative Risk Reduction; DDI: drug-drug-interaction; *RRR hospitalization or death, †Timing relative to symptom onset (days), †† Both agents are NOT indicated for patients hospitalized for COVID-19 or for the prevention of COVID-19 and should not be used for >5 days

Fact Sheet for Healthcare Providers. EUA for Paxlovid, available at: https://www.fda.gov/media/155050/download
Fact Sheet for Healthcare Providers. EUA for Lagevrio, available at: https://www.fda.gov/media/155054/download

Nirmatrelvir/ritonavir – Drug Interactions!

- Co-administration with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions is CONTRAINDICATED
  - Potent inhibition of CYP3A4 and P-glycoprotein/ABCB1
  - Weak inhibition of 2D6
  - Moderate induction of 2B6
  - Extensive list of medications to avoid or that may need dosage adjustment available in EUA document
  - Providers should also refer to Liverpool COVID-19 Drug Interaction Checker
    - Liverpool COVID-19 Interactions (covid19-druginteractions.org)

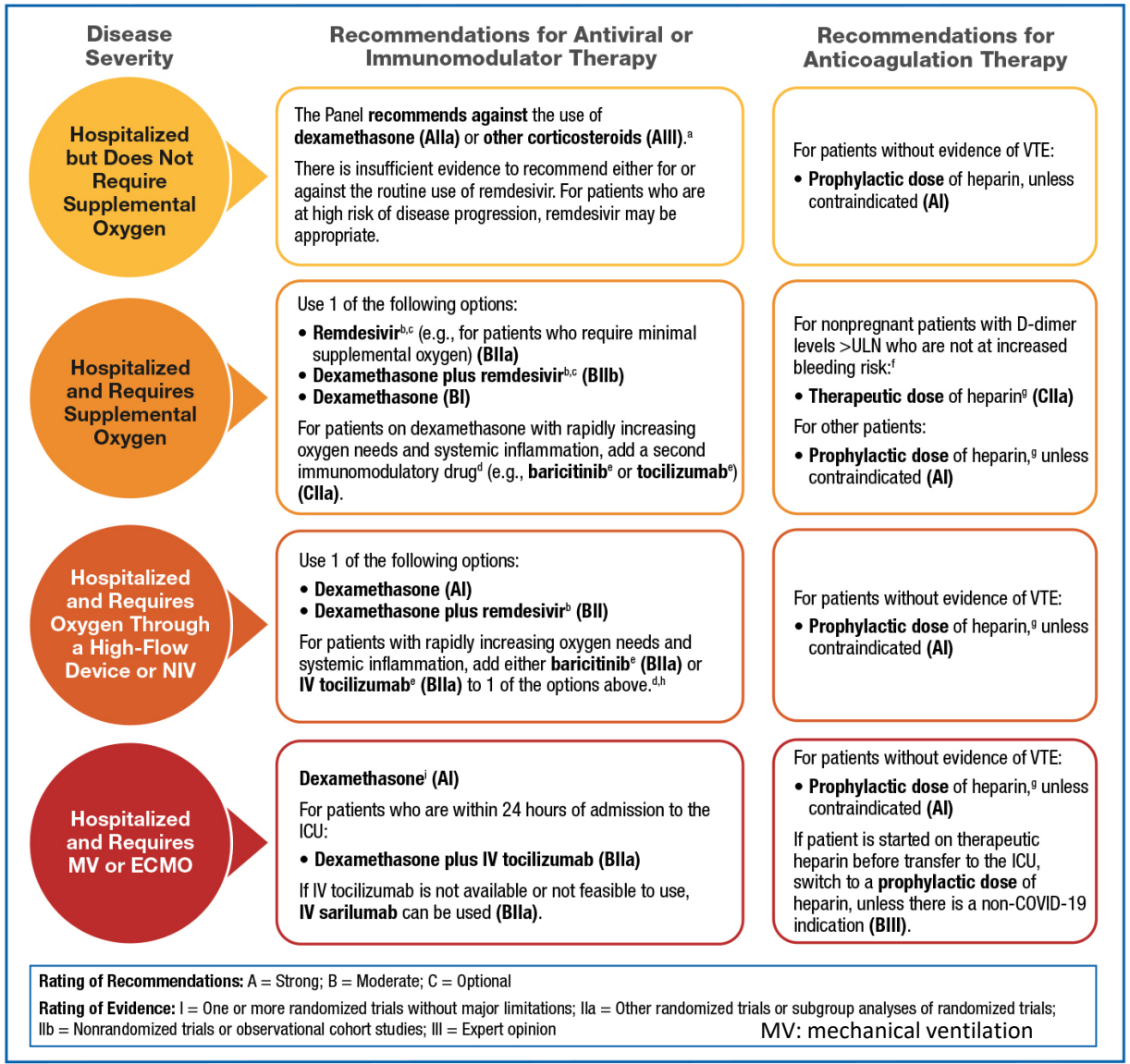
Drugs to Avoid *(not a complete list)*	
Venetoclax	Voriconazole
Ibrutinib	Rifampin
Ivosidenib	Lovastatin
Amiodarone	Simvastatin
Flecainide	Atorvastatin (consider)
Propafenone	Rosuvastatin (consider)
Carbamazepine	Sirolimus
Phenytoin	Tacrolimus (if cannot monitor)
Phenobarbital	Cyclosporine (if cannot monitor)

Fact Sheet for Healthcare Providers. EUA for Paxlovid, available at: https://www.fda.gov/media/155050/download

Common Front-Line Lymphoma Therapy, Interactions with Nirmatrelvir/ritonavir

	Effect on Concentration	Clinical Comments
Rituximab	--	
Cyclophosphamide	↑Cyclophosphamide and its active metabolite	Monitor for increased cyclophosphamide toxicities (e.g. mucositis, neutropenia)
Doxorubicin	--	
Vincristine	↑Vincristine	Avoid. Risk of peripheral neuropathies and other toxicities
Vinblastine	↑Vinblastine	Avoid. Severe neutropenia when combined with ritonavir
Bendamustine	--	
Bleomycin	--	
Dacarbazine	--	
Methotrexate	--	
Cytarabine	--	
Brentuximab	↑Brentuximab active metabolite	Monitor for increased brentuximab toxicities (e.g. peripheral neuropathy, GI side effects, neutropenia)
Lenalidomide	--	

Inpatient COVID-19 Management: Remdesivir, Dexamethasone, Anticoagulation



Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy	Recommendations for Anticoagulation Therapy
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, remdesivir may be appropriate.	For patients without evidence of VTE: • **Prophylactic dose** of heparin, unless contraindicated **(AI)**
Hospitalized and Requires Supplemental Oxygen	Use 1 of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b,c] **(BIIb)** • **Dexamethasone (BI)** For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug[d] (e.g., **baricitinib**[e] or **tocilizumab**[e]) **(CIIa)**.	For nonpregnant patients with D-dimer levels >ULN who are not at increased bleeding risk:[f] • **Therapeutic dose** of heparin[g] **(CIIa)** For other patients: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	Use 1 of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BII)** For patients with rapidly increasing oxygen needs and systemic inflammation, add either **baricitinib**[e] **(BIIa)** or **IV tocilizumab**[e] **(BIIa)** to 1 of the options above.[d,h]	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires MV or ECMO	**Dexamethasone**[i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** If IV tocilizumab is not available or not feasible to use, **IV sarilumab** can be used **(BIIa)**.	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)** If patient is started on therapeutic heparin before transfer to the ICU, switch to a **prophylactic dose** of heparin, unless there is a non-COVID-19 indication **(BIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

MV: mechanical ventilation

- **Remdesivir** — 200mg x1, 100mg IV q12 x5 d
  - Recommended for hospitalized patients requiring supplemental O2 or O2 through high flow device
  - May be considered in those with no O2 requirement if high risk
  - NOT recommended for patients requiring MV or on ECMO
- **Dexamethasone** — 6mg PO q24 x10d
  - Recommended for patients requiring supplemental O2, O2 therapy through high flow device, or if MV or on ECMO
- **Anticoagulation** — LMWH or IV UFH x14d
  - Therapeutic anticoagulation recommended in floor patients requiring O2 supplementation with a D-dimer > ULN

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 4/6/2022.

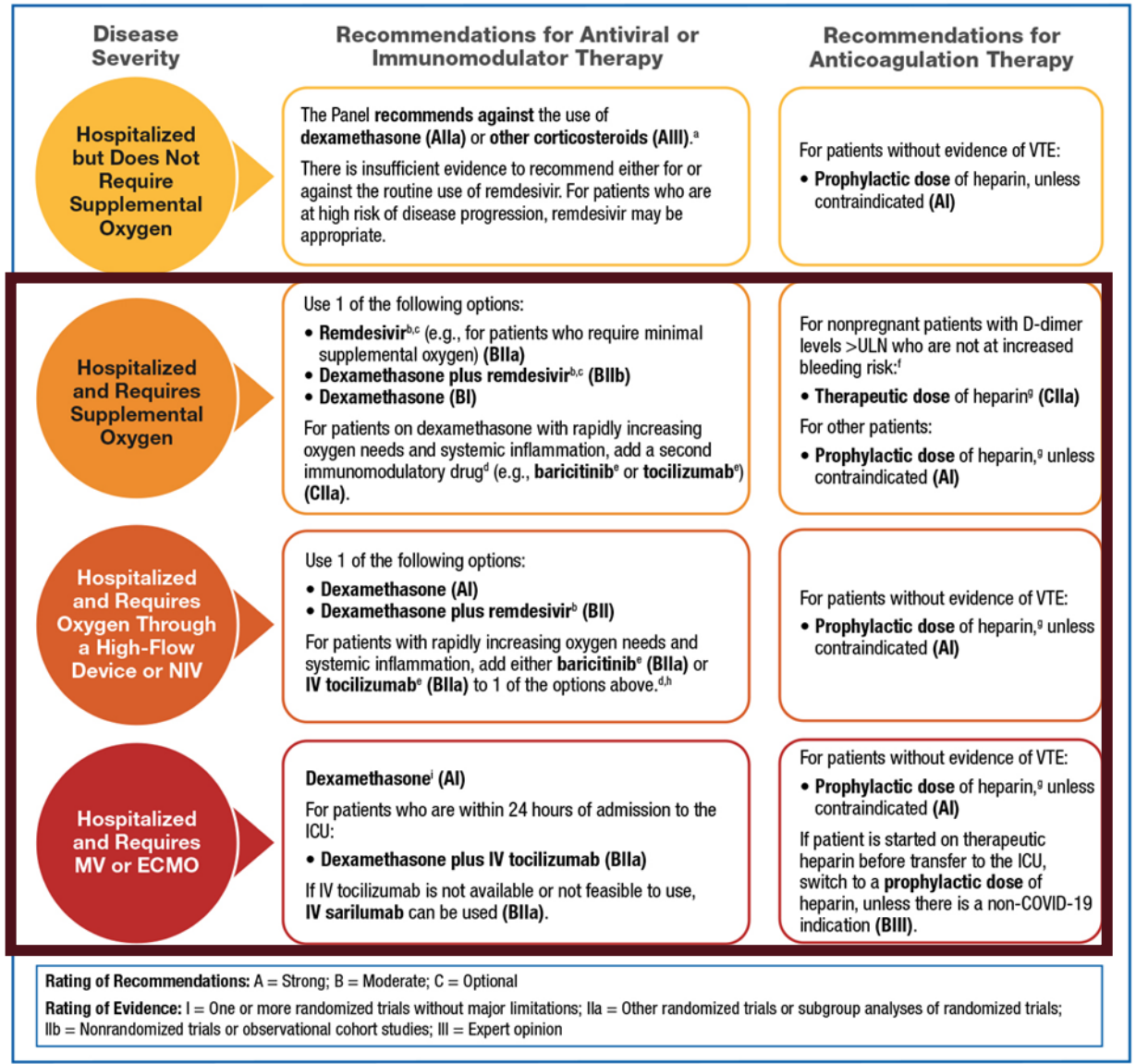
Clinical Data Overview: Remdesivir, Dexamethasone, Anticoagulation

	Remdesivir	Dexamethasone†	Anticoagulation
Key Clinical data	• SOLIDARITY Trial • DisCoveRy Trial • SIMPLE-severe Trial • ACTT-1 Trial • Moderate disease, 5d vs 10d	• RECOVERY Trial • WHO meta-analysis	• ATTACC Trial • ACTIV-4a Trial • REMAP-CAP Trial • RAPID Trial • HEP-COVID Trial • INSPIRATION Trial
Patient population with benefit	Patients with mild hypoxia or less severe disease, early in course of illness (w/in 7 days)	Hospitalized patients requiring O2 supplementation	Non-critically ill patients, with elevated D-dimer
Mortality benefit (RCT)	No*	**Yes**	No
Other outcomes	Reduced time to clinical improvement	Better clinical improvement at d5 and d10, lower ventilator requirements, shorter LOS	Increased organ support free days

*Some observational studies have found mortality benefit

† Studies have also evaluated the use of hydrocortisone as well, same benefit

The Role of IL-6 and Janus-Kinase (JAK) Inhibitors



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- **Tocilizumab*** — **8mg/kg IV x1 dose**
  - Recommended in combination with dexamethasone, for patients exhibiting rapid respiratory decompensation
  - AVOID use in patients that are significantly immunosuppressed (e.g. recent use of other biologic immunomodulating drugs) or if uncontrolled bacterial, fungal other-viral infection
- **Barcitinib†** — **4mg q24h PO x14d††**
  - Alternative to tocilizumab for patients with rapidly progressing disease in combination with dexamethasone
  - Alternative to dexamethasone if patient cannot receive corticosteroids
  - Infection risk higher when used with corticosteroids

*If tocilizumab not available substitute with sarilumab

†If baricitinib not available substitute with tofacitinib

†† Reduced dose for patients 2 to <9 yo (2mg q24h)

Clinical Data Overview: Tocilizumab and Baricitinib

	Tocilizumab	Baricitinib
Key Clinical data	COVACTA Trial EMPACTA Trial REMAP CAP Trial RECOVERY Trial	COV-BARRIER Trial ACTT-2 Trial
Patient population with benefit	Patients with rapidly progressing severe disease with elevated CRP, also on corticosteroids	Patients requiring supplemental O2 or non-invasive ventilation at baseline with rapidly progressing disease, also on corticosteroids
Mortality benefit (RCT)	**Yes**	**Yes** *Secondary endpoint in COV-BARRIER Trial, most patients were on corticosteroids, but few patients were on remdesivir*
Other outcomes	Lower likelihood to progress to mechanical ventilation or death, shortened time to hospital discharge	Shorter time to recovery, better odds of improved clinical status by d15

Inpatient COVID-19 Management – Clinical Considerations

- ***Should remdesivir be given over a longer duration (10 days) in severely immunocompromised patients?***
  - NCCN guidance suggests the consideration of a 10 day course based on clinical status and comorbid conditions
  - Data regarding whether a 10 day course is more efficacious than 5 days for immunocompromised patients is lacking
- ***Is it safe to use tocilizumab for COVID-19 in severely immunocompromised patients?***
  - It is suggested to avoid use in severely immunocompromised patients
  - Some data suggests increased risk of secondary infections (bacterial, fungal)

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 4/6/2022.
NCCN Best Practices Guidance: Management of COVID-19 Infection in Patients with Cancer. March 2021. Available at: https://www.nccn.org/docs/default-source/covid-19/2021-covid-infectious-disease-management.pdf?sfvrsn=63f70c30_7

What Happened to Hydroxychloroquine and Ivermectin?

Hydroxychloroquine	Ivermectin
• EUA granted March 2020 and revoked June 2020 • RCTs did not show clinical benefit • Use associated with significant cardiac adverse events • **Use is no longer recommended for patients with COVID-19 (treatment or prophylaxis)**	• Never endorsed by FDA to use for COVID-19 • FDA warning issued April 2020 to avoid unauthorized use • ***Doses 50-100x higher than maximum approved dose would be required to inhibit SARS-CoV-2 replication*** • Meta-analyses of available trial data shows no benefit • TOGETHER trial terminated early for futility (no difference in need for hospitalization or mortality) • **NIH guidance: insufficient evidence, not recommended outside of a clinical trial**

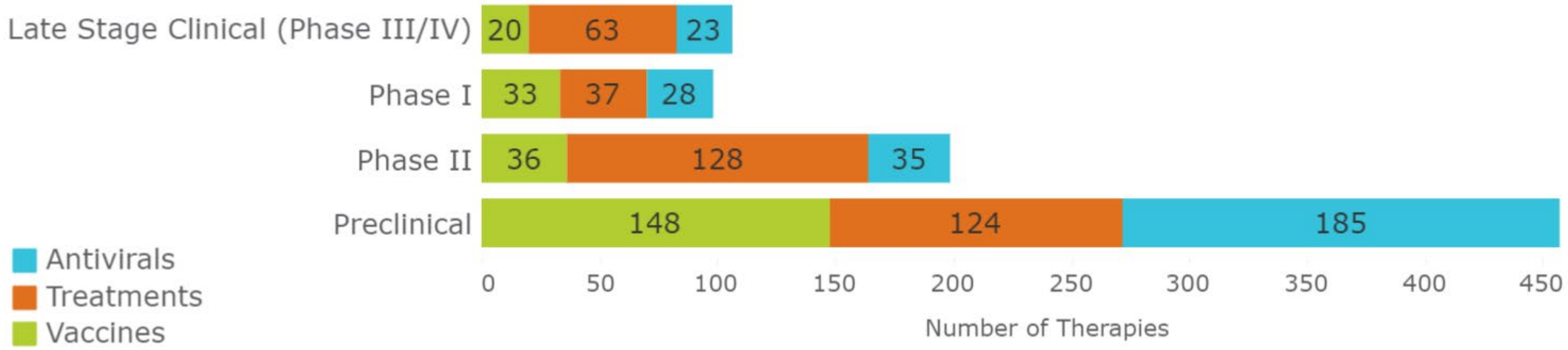
Roman YM, et al. Clin Infect Dis 2022;74:1022-1029
RECOVERY Collaborative Group. N Engl J Med 2020;383:2030-2040

What About Convalescent Plasma (CP)?

- EUA granted August 2020, updated February 2021 limiting use to 'high titer' plasma in patients with impaired humoral immunity
  - Case series data suggests some benefit in patients with severely impaired humoral immunity
- Several RCTs terminated early given lack of benefit, low enrollment, most recipients having baseline neutralizing Ab's
- Meta-analysis found that CP was NOT associated with decreased mortality, decreased LOS or need for MV
- NIH guidance:
  - Insufficient evidence to support use of CP in hospitalized patients with impaired humoral immunity
  - Insufficient evidence to support use in non-hospitalized patients

Perrine J, et al. JAMA 2021;325:1185-1195
Delgado-Fernández M, et al. 2021; Feb 11:S0213-005X(21)00035-5(Epub ahead of print)

COVID-19 Vaccine and Treatment Pipeline



- Vaccine candidates in late phase trials include primarily non-mRNA vaccine technology (e.g. cell-based, viral-based, and protein-based)
- Antivirals and other treatments (e.g. anti-inflammatory agents, anticoagulation) in late phase trials include some repurposed drugs and vary widely in mechanism and viral target
  - Sabizabulin: 55% reduction in deaths in patients hospitalized at high risk for ARDS, seeking EUA

Source: Biotechnology Innovation Organization. BIO COVID-19 Therapeutic Development Tracker. Available at: https://www.bio.org/policy/human-health/vaccines-biodefense/coronavirus/pipeline-tracker

Veru News Release. Sabizabulin. Available at: https://verupharma.com/news/verus-novel-covid-19-drug-candidate-reduces-deaths-by-55-in-hospitalized-patients-in-interim-analysis-of-phase-3-study-independent-data-monitoring-committee-halts-study-early-for-overwhelmin/

COVID-19 Vaccination, Prevention, and Treatment in Lymphoma Overview

All patients should receive a COVID-19 vaccine
- mRNA vaccines preferred
- 3-dose series + 2-booster doses *(as of 4/24/2022)*

All patients should receive tixagevimab/cilgavimab
- Not a replacement for the vaccine but an adjunctive measure

Prompt initiation of treatment is critical for primary therapies
- Monoclonal antibodies, oral antivirals, remdesivir, dexamethasone

Therapies to modulate severe inflammatory response can be considered in severe disease
- Tocilizumab, baricitinib *(warning: risk of secondary infection)*

Do NOT recommend the use of hydroxychloroquine or ivermectin.
Convalescent plasma may be a consideration if no other options.

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MEDICINE & BIOLOGICAL SCIENCES