Antibodies to Watch in a Pandemic

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August 27, 2020 (updated slides)

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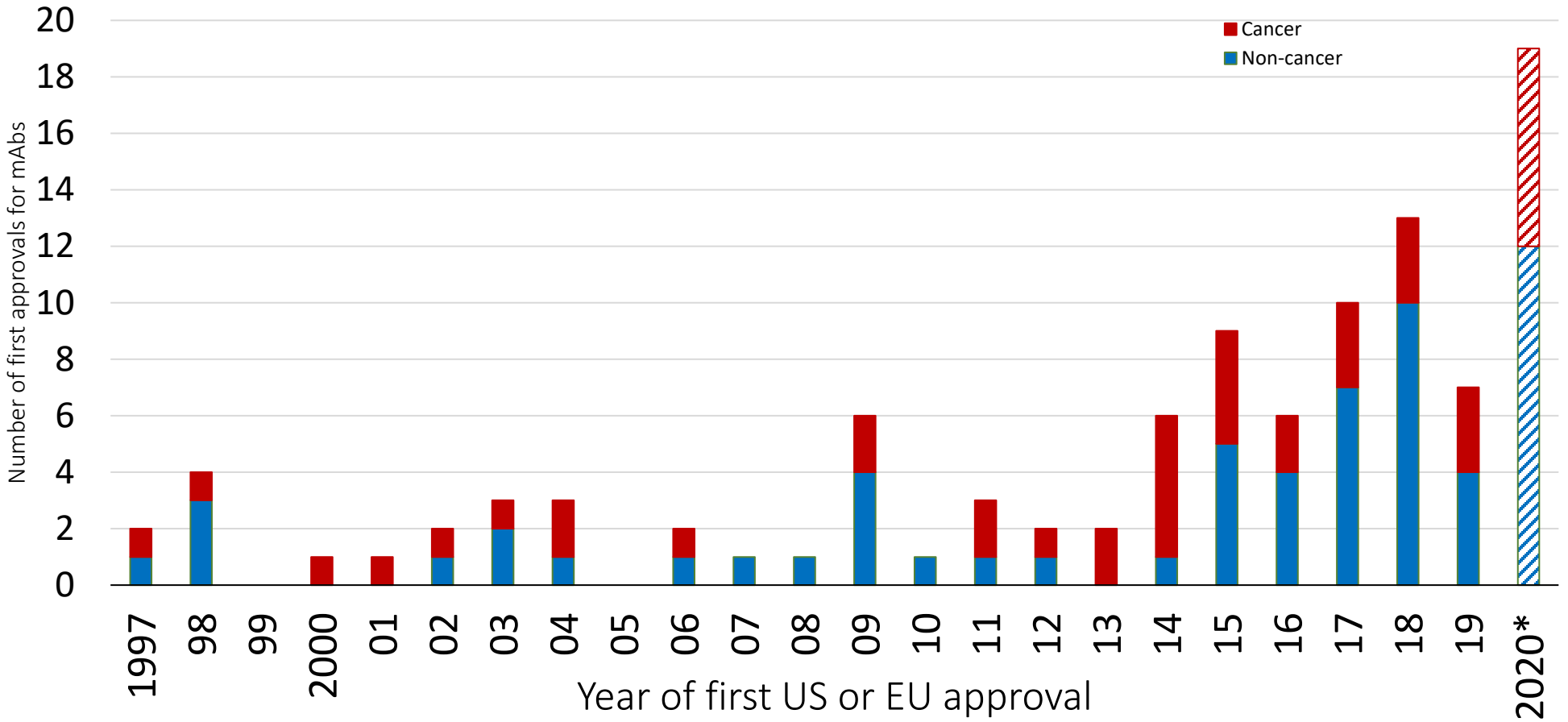
Agenda

- US or EU approvals in 2020
  - Granted as of late July 2020
  - Anticipated by the end of 2020
- Overview of antibody-based COVID-19 interventions in development
  - Repurposed antibody-based therapeutics that treat symptoms
  - Newly developed anti-SARS-CoV-2 antibodies
- Q&A

Annual first approvals in either the US or EU



*Estimate based on the number actually approved and those in review as of July 15, with assumption of approval on the first cycle.
Tables of approved mAbs and antibodies in review available at https://www.antibodysociety.org/resources/approved-antibodies/

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First approvals US or EU in 2020

- Teprotumumab (Tepezza): anti-IGF-1R mAb for thyroid eye disease
  - FDA approved on January 21
- Eptinezumab (Vyepti): anti-CGRP IgG1 for migraine prevention
  - FDA approved on February 21
- Isatuximab (Sarclisa): anti-CD38 IgG1 for multiple myeloma
  - FDA approved on March 2, also approved in the EU on June 2
- Sacituzumab govitecan (Trodelvy): anti-TROP-2 ADC for triple-neg. breast cancer
  - FDA approved on April 22
- Inebilizumab-cdon (Uplizna): anti-CD19 IgG1 for the treatment of neuromyelitis optica spectrum disorder
  - FDA approved on June 11

- See *Antibodies to watch in 2020* for more information: https://www.tandfonline.com/doi/full/10.1080/19420862.2019.1703531
- Complete list of US- and EU-approved mAbs (1986 to present) and antibodies in review available at: https://www.antibodysociety.org/resources/approved-antibodies/

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First approvals US or EU in 2020

- Tafasitamab (MOR208): anti-CD19 IgG1 for diffuse large BCL
  - FDA approved on July 31, 2020; EU review
  - Breakthrough Therapy, Fast Track, Orphan Drug designations in US
- Belantamab mafodotin: anti-BCMA IgG1 ADC for multiple myeloma
  - FDA approved on August 5, 2020; EC decision expected by the end of Sep
  - Breakthrough Therapy (US) and PRIME (EU) designations
- Satralizumab: anti-IL-6R for NMOSD
  - FDA approved on August 14, 2020
  - EU review; accelerated assessment in EU

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Potential approvals in 2020/21: 16 in US or EU regulatory review

US or EU review: PDUFA dates Sep-Dec

- REGN-EB3: mixture of 3 IgG1 mAbs for Ebola virus infection
  - US review, Breakthrough Therapy designation; October 25 PDUFA date
- Sutimlimab: anti-C1s IgG4 for cold agglutinin disease
  - US review, Breakthrough Therapy designation; November 13 PDUFA date
- Naxitamab: anti-GD2 IgG1 for neuroblastoma
  - US review; Rare Pediatric Disease, Breakthrough Therapy, Orphan designations; November 30 PDUFA date
- Margetuximab: anti-HER2 IgG1 mAb for breast cancer
  - US review, Fast Track designation; December PDUFA date
- Tanezumab: anti-NGF IgG2 for osteoarthritis pain
  - US and EU review, Fast Track designation; December PDUFA date

US review: PDUFA date unknown

- Narsoplimab: anti-mannan-binding lectin-associated serine protease-2 (MASP-2) IgG4 for hematopoietic stem cell transplant-associated thrombotic microangiopathy
  - US review; Breakthrough Therapy designation, rolling BLA
- Oportuzumab monatox (Vicineum®): anti-EpCAM scFv immunotoxin for bladder cancer
  - US review; Fast Track designation; FDA aligned with use of Accelerated Approval pathway with rolling review
- Dostarlimab (TSR-042): anti-PD-1 IgG4 for recurrent MSI-H tumors
  - US and EU review

Likely 2021 approvals

- Evinacumab: anti-angiopoietin-like protein 3 IgG4 for hypercholesterolemia
  - US review; Breakthrough Therapy designation
  - Feb 11, 2021 PDUFA date
- Aducanumab: anti-amyloid β IgG1 for early Alzheimer's disease
  - US review; Fast Track designation, rolling BLA; PRIME designation
  - March 7, 2021 PDUFA date
- Tralokinumab: anti-IL-13 IgG4 for atopic dermatitis
  - US and EU review
  - PDUFA date in Q2 2021

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More possible 2021 approvals

- Teplizumab (PRV-031): anti-CD3 IgG1 for type 1 diabetes
  - US review; Breakthrough Therapy designation, PRIME designation
- Omburtamab: anti-B7-H3 mAb for CNS/leptomeningeal metastases from neuroblastoma
  - US review
- Inolimomab: anti-CD25 murine mAb for acute graft-vs-host disease
  - US review
- Ansuvimab: anti-Ebola virus human IgG1
  - US review
- Bimekizumab: anti-IL-17A humanized IgG1 for psoriasis
  - US and EU review

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Overview of antibody-based COVID-19 interventions

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Medical conditions associated with COVID-19

- Coronavirus SARS-CoV-2 targets angiotensin-converting enzyme 2 (ACE2) via its spike protein
- Disease resulting from infection leads to:
  - Cytokine storm-induced acute respiratory distress syndrome
  - Moderate to severe COVID-19 pneumonia
  - Tissue damage resulting from hyper-inflammation, e.g., multisystem inflammatory syndrome in children
  - Abnormal clotting
- Possible biologics drug interventions
  - Existing drugs already in development or marketed for other purposes
    - Relevant targets include: IL-1, IL-6, IL-8, GM-CSF
    - Potential to treat symptoms
  - Novel anti-SARS-CoV-2 targeting molecules
    - Antibodies
    - Other proteins that can bind to the virus (e.g., DARPin)

Repurposed antibody-based therapies as possible treatments for symptoms

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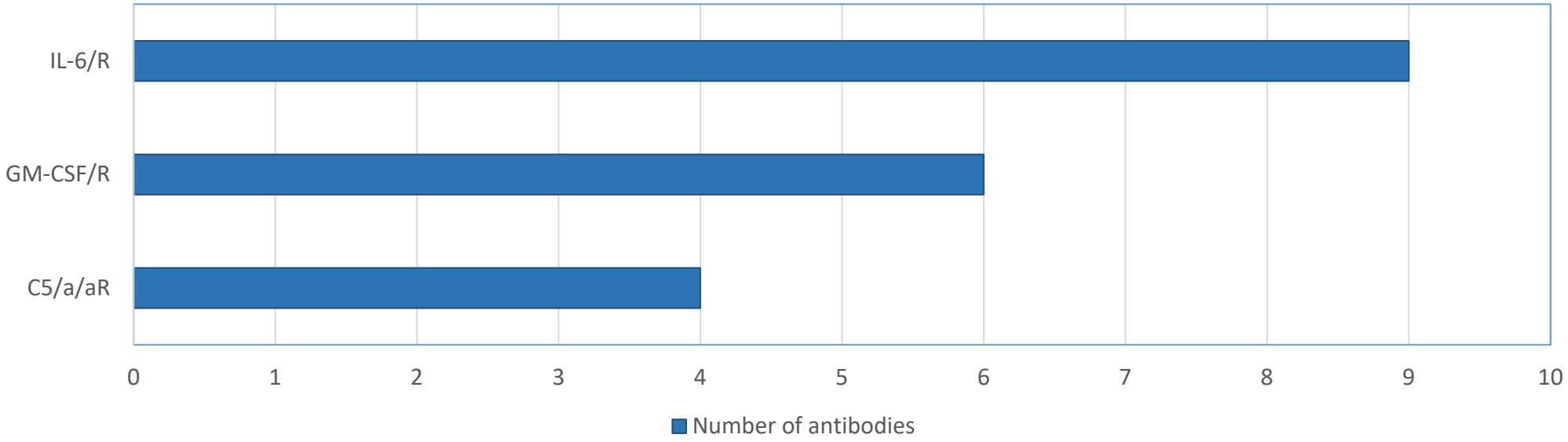
~50 Abs* for symptoms: Frequent targets



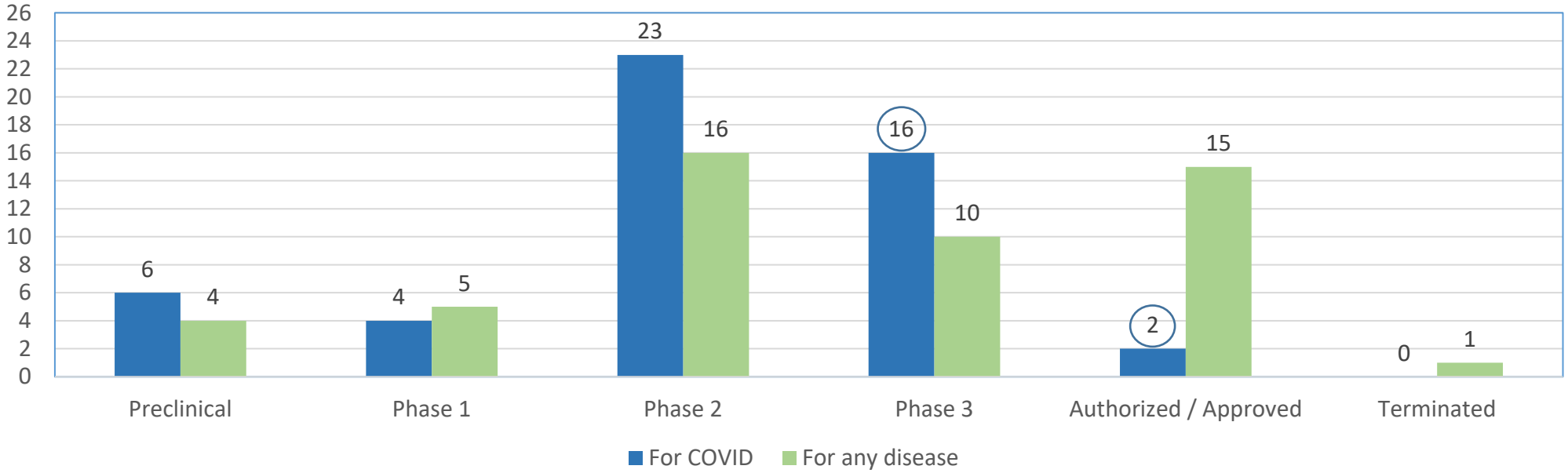
* As of mid-July 2020

Less frequent targets (1-2 molecules*)

- ✓Ang-2, C2, CCR5, CD14, CD6, CD73, CD80/86, connective tissue growth factor, CSF1R/CD115, CXCL10;
- ✓Danger-associated molecular patterns (DAMPS), Factor XIIa;
- ✓IFNγ, IL-1, IL-17A, IL-22R, IL-33R, IL-8;
- ✓LIGHT, Neutropilin 2, Nicotinamide phosphoribosyltransferase NKG2A, Plasma kallikrein, P-selectin;
- ✓*Staph. aureus* α toxin, TLR4, TNF, urokinase plasminogen activator receptor, VEGF, Vimentin

*For details about the antibodies, see chineseantibody.org/covid-19-track/

Most advanced phase of development*



*Includes pending clinical studies listed on clinicaltrials.gov.
Phase 2 = Phase 1/2 + Phase 2; Phase 3 = Phase 2/3 + Phase 3

Authorized as therapy for COVID-19: Levilimab

- Levilimab (trade name Ilsira) registered in Russia for treatment of patients with severe COVID-19.
  - Human mAb targeting membrane-bound and soluble forms of IL-6R
  - Developed by Biocad, levilimab was originally developed for treatment of rheumatoid arthritis.
  - Phase 3 study was initiated on April 24, 2020, and includes 204 participants who received a single subcutaneous administration of levilimab at a dose of 324 mg in combination with standard therapy.
  - According to Biocad, the results of a clinical trial of the drug demonstrate that levilimab therapy can significantly reduce mortality among patients with COVID-19.
  - Registered on June 5, 2020 through a fast-track mechanism according to Decree No. 441 of the Government of the Russian Federation, effective as of April 4, 2020.

Authorized as therapy for COVID-19: Itolizumab

- Itolizumab (trade name Alzumab) was granted restricted emergency use in India for the treatment of cytokine release syndrome in COVID-19 patients with moderate to severe acute respiratory distress syndrome (ARDS)
  - Humanized IgG1 targeting CD6
  - Developed by Biocon, itolizumab was previously approved in India for plaque psoriasis
  - Emergency use was granted based on a randomized, controlled, open-label study at four hospitals in India, enrolling a total of 30 hospitalized COVID-19 patients with moderate to severe ARDS. Twenty patients were randomized to receive itolizumab plus best supportive care, while 10 patients received best supportive care alone. The primary endpoint was mortality at one month. (July 11, 2020 press release)

Most advanced in clinical studies for COVID-19

- Products already approved for another indication
  - Anti-IL-6R Tocilizumab
    - First approved in Japan in 2005. Currently marketed for rheumatoid arthritis in adults, juvenile rheumatoid arthritis, treatment of chimeric antigen receptor T cell-induced *severe or life-threatening cytokine release syndrome* (CRS) in patients two years of age and older. Tocilizumab is included in over 55 clinical studies of COVID-19 patients
    - Phase 3 studies of patients with COVID-19 pneumonia sponsored by Genentech/Roche have primary completion dates of:
      - July 31, tocilizumab +remdesivir vs remdesiver only; recruiting 450 patients at 32 study sites
      - Aug 5, recruiting 379 patients at 32 study sites
    - Phase 3 COVACTA study of tocilizumab vs placebo did not meet its primary endpoint of improved clinical status in hospitalized adult patients with severe COVID-19 associated pneumonia or key secondary endpoints, which included the difference in patient mortality at week four.

More in late-stage clinical studies for COVID-19

- Marketed mAbs
  - Anti-IFNγ Emapalumab
    - Approved for primary hemophagocytic lymphohistiocytosis
    - Phase 2/3 study of emapalumab and Anakinra (Interleukin-1(IL-1) Receptor Antagonist) vs standard of care, in reducing hyper-inflammation and respiratory distress in patients with SARS-CoV-2 infection has a primary completion date in July 2020.
  - Anti-IL-1β Canakinumab
    - Approved for adult-onset Still's disease, juvenile rheumatoid arthritis, cryopyrin (CIAS1)-associated periodic syndromes, tumor necrosis factor receptor-associated periodic syndrome, hyperimmunoglobulin D syndrome / mevalonate kinase deficiency, familial Mediterranean fever in combination with colchicine
    - Phase 3 study of canakinumab on Cytokine Release Syndrome in Patients With COVID-19-induced Pneumonia has a primary completion date of July 31, 2020
  - Anti-C5 Ravulizumab
    - Approved for paroxysmal nocturnal hemoglobinuria
    - Phase 3 study in patients with COVID-19 severe pneumonia, acute lung injury, or acute respiratory distress syndrome has a primary completion date in November 2020.

Next steps for repurposed biologics

- Possible Emergency Use Authorization (EUAs)
  - FDA can allow use of unapproved medical products or unapproved uses of approved medical products to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents, such as SARS-CoV-2, when there are no adequate, approved, and available alternatives.
- Limitations to the scope and duration of the authorizations, as well as specific conditions, apply to EUAs. An EUA is not an approval.
- Sponsoring organizations may also pursue authorizations outside the US

EUA request submitted for leronlimab

- Leronlimab is a humanized IgG4 antibody targeting C-C chemokine receptor type 5.
- On August 12, 2020, Cytodyn requested that the Food and Drug Administration grant an EUA for leronlimab for mild to moderate COVID-19 based on data from the Phase 2 CD10 study (NCT04343651).
- In this study, patients were randomized to receive weekly doses of 700 mg leronlimab or placebo, both of which were administered via subcutaneous injection.
- Top-level results of the study showed that, in patients with Total Clinical Symptom Scores of ≥ 4 at baseline (higher scores equate to poorer health state), at Day 3, more subjects treated with leronlimab reported improvement in total clinical symptom score compared to the placebo group (90% on leronlimab arm vs. 71% on placebo).

Anti-SARS-CoV-2 antibodies

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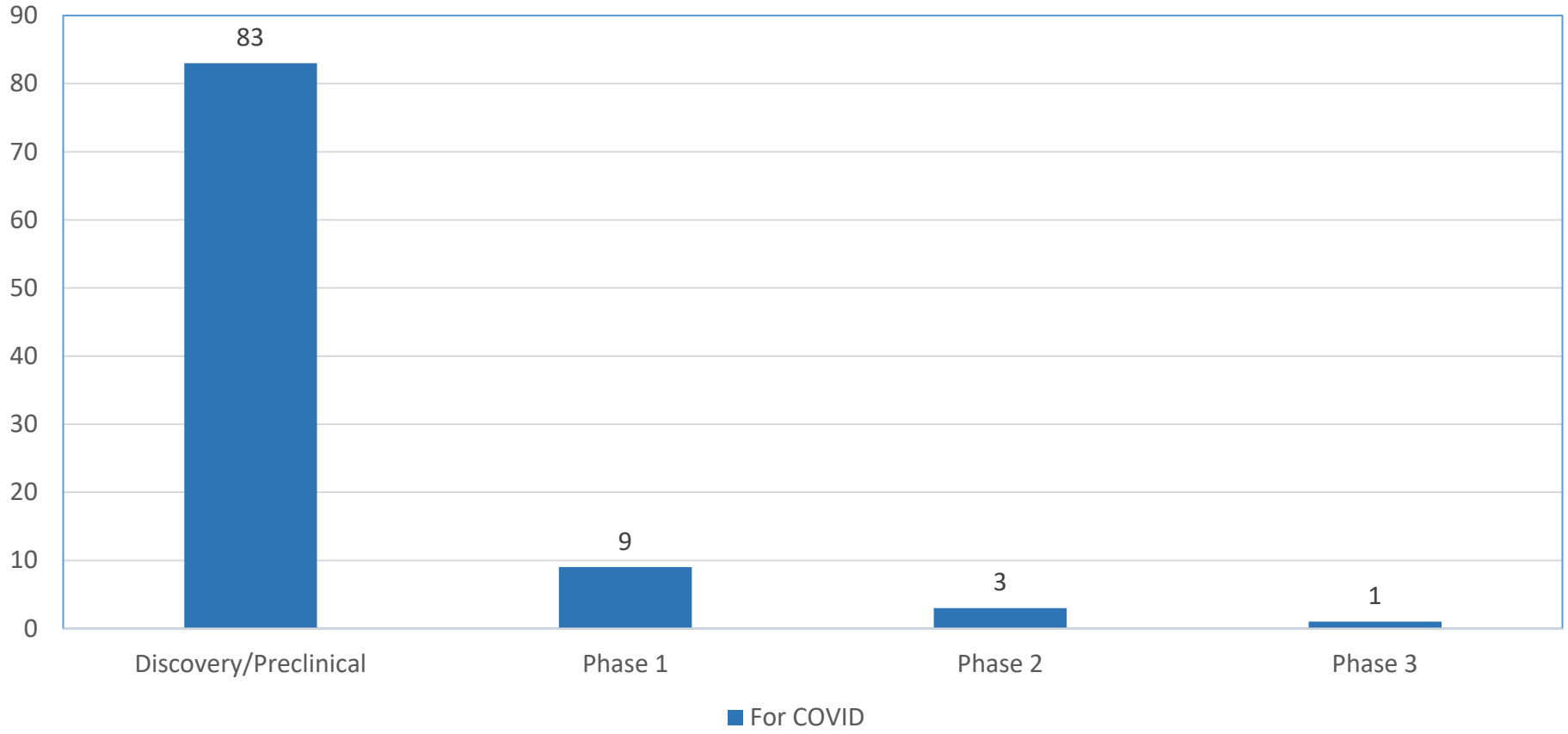
Characteristics of anti-SARS-CoV-2 biologics

- Of ~95 commercially sponsored molecules/programs we are currently tracking:
  - ~88% are mAb-based therapeutics, incl. nanobodies
    - Several in preclinical development are bispecific
  - ~12% are other composition of matter (e.g., DARPin, Fc fusion protein, nucleic acid) or recombinant or transgenic animal-derived polyclonals)
- SARS-CoV-2 target is the Spike protein, according to the available information

Most advanced phase of development*



*Based on public disclosures as of July 23, 2020.
Phase 1 total includes pending studies.

Anti-SARS-CoV-2 mAbs in Phase 1*

Sponsors	Drug code	Status	Trial ID	Est. start	Est. primary completion
Junshi Biosciences / Eli Lilly and Company	JS016	Phase 1	NCT04441918	6/5/2020	Dec 2020
Tychan Pte. Ltd.	TY027	Phase 1	NCT04429529	6/9/2020	Oct 2020
Brii Biosciences	BRII-196	Phase 1	NCT04479631	7/12/2020	Mar 2021
Brii Biosciences	BRII-198	Phase 1	NCT04479644	7/13/2020	Mar 2021
Celltrion	CT-P59	Phase 1	NCT04525079	7/18/2020	Nov 2020
Sinocelltech Ltd.	SCTA01	Phase 1	NCT04483375	7/25/2020	Nov 2020
Sorrento Therapeutics	COVI-GUARD (STI-1499)	Phase 1	NCT04454398 (pending)	Aug 2020	Jan 2021
AstraZeneca	AZD7442 (AZD8895 + AZD1061)	Phase 1	NCT04507256	8/17/2020	Sep 2021

*As of Aug 25, 2020

Anti-SARS-CoV-2 mAbs in Phase 3*

Sponsors	Drug codes	Most advanced study	Trial ID	Est. start	Est. primary completion
AbCellera / Eli Lilly and Company	LY-CoV555, aka LY3819253	Phase 3	NCT04411628 (Phase 1); NCT04427501 (Phase 2) NCT04497987 (Phase 3) NCT04501978 (Phase 3)	5/28/2020; 6/13/2020; 8/3/2020; 8/4/2020	8/23/2020; 9/15/2020; 3/8/2021; July 2021
Regeneron	REGN-COV2 (REGN10933 + REGN10987)	Phase 3	NCT04425629 (Phase1/2); NCT04426695 (Phase 1/2); NCT04452318 (Phase 3)	6/9/2020; 6/12/2020; 6/30/2020	11/21/2020; 3/13/2021; 4/11/2021

*As of Aug 6, 2020

Clinical study details: REGN10933 + REGN10987

- Phase 1/2 studies are master protocols assessing the safety, tolerability, and efficacy of anti-spike (S) SARS-CoV-2 monoclonal antibodies for the Treatment of Hospitalized or Ambulatory Patients With COVID-19
  - Estimated enrollment = 1806 and 1054, respectively
  - IV administration
- Phase 3, randomized, double-blind, placebo-controlled study assessing the efficacy and safety of anti-spike SARS-CoV-2 monoclonal antibodies in Preventing SARS-CoV-2 Infection in Household Contacts of Individuals Infected With SARS-CoV-2
  - Estimated enrollment = 2000 participants
  - SC administration

Clinical study details: LY-CoV555/LY3819253

- Phase 1 study
  - Subjects are hospitalized patients with COVID-19; long-term follow-up is ongoing
- Phase 2 BLAZE-1 study
  - Subjects are people recently diagnosed with COVID-19 in the ambulatory setting
  - Enrollment is estimated to be completed in Sep; initial data readout soon thereafter
- Phase 3 BLAZE-2 study
  - Subjects are residents and staff who live or work at facilities that have had a recently diagnosed case of COVID-19 and who are now at a high risk of exposure.
  - Study will evaluate the efficacy and safety of LY-CoV555 for the prevention of SARS-CoV-2 infection and COVID-19, testing whether a single dose of LY-CoV555 reduces the rate of SARS-CoV-2 infection through 4 weeks, as well as complications of COVID-19 through 8 weeks.
  - Estimated enrollment = 2400 participants
- Phase 3 NIAID-sponsored Activ-3 / TICO study
  - Comparison of mAb vs. remdesivir vs placebo in 10,000 hospitalized patients

Other anti-SARS-CoV-2 proteins in clinical study*

Sponsors	Drug code	Status	Trial ID	Est. start	Est. primary completion
SAB Biotherapeutics	SAB-185 (Human IgG from immunized transgenic cows)	Phase 1	NCT04468958; NCT04469179 (pending)	July 2020	Sep 2020
Ostrich Pharma USA	Ostrich-derived SARS-CoV-2 antibodies	Phase 1	NA; 1 site in Japan	NA	NA
Xenothera, LFB	XAV-19 (Heterologous swine glyco-humanized polyclonal antibody)	Phase 2	NCT04453384 (pending)	7/6/2020	Sep 2020
APEIRON Biologics	APN01 (Recombinant human angiotensin-converting enzyme 2)	Phase 2	NCT04335136	4/30/2020	Sep 2020

*As of Aug 5, 2020

Clinical entry proposed for July– Dec 2020*

- Over 20 companies plan to progress anti-SARS-CoV-2 molecules into the clinic by the end of 2020, including:
  - CORAT Therapeutics (Yumab spinout)
  - Vir Biotechnology, Inc. / Humabs Biomed SA, with partners
  - AstraZeneca, with partners, e.g., Vanderbilt University Medical Center
  - IDBiologics
  - Centivax/ Distributed Bio / SwiftScale Biologic
  - Virna Therapeutics / University of Toronto
  - Boehringer Ingelheim
  - Adagio Therapeutics (Adimab spinout)
  - Memo Therapeutics AG
  - Molecular Partners (DARPin molecule)

*For details about these antibodies, see chineseantibody.org/covid-19-track/

Non-canonical approaches in early development

- Cytovia Therapeutics, Inc.
  - Bispecific mAb targeting SARS-CoV-2 and NKp46
- Neurimmune AG and Ethris GmbH
  - mRNA-encoded anti-SARS-CoV-2 antibodies administered by inhalation
- Molecular Partners
  - Anti-SARS-CoV-2 DARPin® candidates are half-life-extended and contain three distinct monomer DARPin® proteins that can simultaneously target the virus in different key areas
- Sorrento Therapeutics
  - STI-4398 is a proprietary ACE2-Fc fusion protein (COVIDTRAP)

Learnings from EUA of convalescent plasma

- On August 23, FDA announced that they had issued an EUA for convalescent plasma as a treatment of COVID-19 in hospitalized patients
- Relevant data from National Convalescent Plasma Expanded Access Protocol (EAP) sponsored by the Mayo Clinic.
  - As of August 13, 2020, over 90,000 patients have been enrolled
- Trends toward reduced mortality when patients receive CCP with higher antibody levels and at earlier time points.
  - In the subgroup of patients less than 80 years of age who were not intubated and who were within 72 hours of diagnosis, a significant reduction in 7-day mortality from 11.3 to 6.3% ($p = 0.0008$) was observed when titers are binned to low versus high.
- However, there was no difference in 7-day survival in the overall population between subjects transfused with high versus low titer CCP, and there was no apparent association between neutralizing antibody titers and 7-day mortality in intubated subjects.

COVID-19 resources at antibodysociety.org

- "Coronavirus in the Crosshairs"
  - 9-part (so far) series examining the ongoing discovery and development of COVID-19 interventions for broad use, including small molecule and biologic drugs, and vaccines. Diagnostics are also discussed.
  - www.antibodysociety.org/guide-to-coronavirus-in-the-crosshairs/
- COVID-19 Biologics Tracker
  - Information for clinical studies of anti-SARS-CoV-2 antibodies
    - www.antibodysociety.org/covid-19-biologics-tracker/
  - Link to COVID-19 Antibody Therapeutics Tracker, a collaborative project of The Antibody Society and the Chinese Antibody Society
    - chineseantibody.org/covid-19-track/

Key messages

- Projections indicate that 2020 may be a record year for approvals of antibody therapeutics *if the regulatory agencies resources are not diverted to COVID-19-related work*
- Pandemic is likely to continue into 2021, thus the global need for effective therapeutics and vaccines will not abate
- Emergency Use Authorizations are likely for at least some of the repurposed mAbs
- The extraordinary response by numerous organizations developing anti-SARS-CoV-2 antibodies may lead to EUAs for 15-20 antibodies or other targeted proteins

Thank you to CAS colleagues!

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- Mitchell Ho

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Thank you!

Questions?
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