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Mavrilimumab
COVID-19 Pneumonia and Hyperinflammation

May 2020

Forward Looking Statements

This presentation (together with any other statements or information that we may make in connection herewith) contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 with respect to Kiniksa Pharmaceuticals, Ltd. (and its consolidated subsidiaries, collectively, unless context otherwise requires, "Kiniksa," "we," "us" or "our"). In some cases, you can identify forward looking statements by terms such as "may," "will," "should," "expect," "plan," "anticipate," "could," "intend," "goal," "design," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions, although not all forward-looking statements contain these identifying words. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation, statements regarding our strategy for mavrilimumab and diseases with cytokine storm and hyperinflammation; collaborations; potential additional indications to explore; potential market opportunities, differentiation and competitive position; on going, planned and potential clinical trials and other studies; timing and potential impact of clinical data; and regulatory and other communications, submissions, applications and approvals.

These statements involve known and unknown risks, uncertainties, and other important factors that may cause our actual results, performance or achievements to be materially different from those expressed or implied by the forward-looking statements, including without limitation potential delays or difficulties with our current and planned clinical trials with mavrilimumab; potential inability to demonstrate safety or efficacy or otherwise producing negative, inconclusive or uncompetitive results; potential for changes in final data from preliminary or interim data; potential inability to replicate in later clinical trials positive results from earlier trials and studies; impact of additional data from us or other companies; our reliance on third parties for manufacturing and conducting clinical trials, research and other studies; potential changes in our strategy, operating plan and funding requirements; drug substance and/or drug product shortages; substantial new or existing competition; potential impact of the COVID-19 pandemic, and measures taken in response to the pandemic, on our business and operations as well as the business and operations of our manufacturers, contract research organizations, and other third parties with whom we conduct business or otherwise engage; and our ability to attract and retain qualified personnel. These and the important factors discussed under the caption "Risk Factors" in our Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (the "SEC") on May 4, 2020 and other filings subsequently filed with the SEC. These forward-looking statements reflect various assumptions of Kiniksa's management that may or may not prove to be correct. No forward-looking statement is a guarantee of future results, performance, or achievements, and one should avoid placing undue reliance on such statements. Except as otherwise indicated, this presentation speaks as of the date of this presentation. We undertake no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.

This presentation also contains estimates, projections, and/or other information regarding our industry, our business and the markets for certain of our product candidates, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, clinical trials, studies and similar data prepared by market research firms and other third parties, from industry, medical and general publications, and from government data and similar sources. Information that is based on estimates, forecasts, projections, market research, or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information.

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Mavrilimumab: Potential Treatment of COVID-19 Pneumonia and Hyperinflammation

Mechanism	• GM-CSF is a key growth factor and cytokine in autoinflammation and autoimmunity.[1] • Mavrilimumab is a monoclonal antibody inhibitor targeting GM-CSFRα.
Rationale	• GM-CSF is implicated in the mechanism of excessive and aberrant immune cell infiltration and activation in the lungs thought to contribute significantly to mortality in COVID-19.[2] • Robust literature evidence showing a consistent immunophenotype and pathology of ARDS across inflammatory/infectious etiologies (influx of neutrophils and upregulation of immature, pro-inflammatory macrophages).[3]
Clinical Data	• Evidence of treatment response with mavrilimumab observed in an open-label treatment protocol in Italy in 13 non-mechanically ventilated patients with severe COVID-19 pneumonia and hyperinflammation.[4]
Differentiation	• Mavrilimumab is believed to be the only GM-CSF receptor blocker; other anti-GM-CSF therapeutic approaches inhibit the ligand. • GM-CSFRα blockade potentially prevents pathogenic cells from infiltrating into the target tissue, and suppresses multiple markers of inflammation (e.g., IL-2Rα, IL-6, CRP)[5,6,7] • Once hyperinflammation and CRS have begun, anti-virals may be less effective[8] • Vaccines likely to provide incomplete population immunity + limited supply/access; vaccine does not help once virus occurs[9]
Development Status	• The safety of mavrilimumab has been evaluated in a Phase 2 trial: Mavrilimumab was dosed in over 550 patients with rheumatoid arthritis through Phase 2b by MedImmune in Europe and achieved prospectively-defined primary safety and efficacy endpoints. • Kiniksa has engaged with the U.S. Food and Drug Administration (FDA) and is preparing for a potential registrational development program for mavrilimumab in COVID-19 pneumonia and hyperinflammation. In parallel, academic investigators in the U.S. and Italy are planning investigator-initiated placebo-controlled-studies.

1) Wicks, Roberts, Nature Review Immunology, 2015; Hamilton, Expert Review of Clinical Immunology, 11:4, 457-465; 2) Zhou et al. bioRxiv. 2020; 3) Huang et al. 2018; Huang et al 2005; Rosseau et al 2000; Thompson et al., NEJM 2017; 4) Data as of 4/28/2020; 5) De Alessandris et al., J Leukoc Biol. 2019; 6) Sterner et al., Blood 2019; 7) Guo et al., Rheumatology 2017; 8) Darwish, Muvareka, Liles. Expert Rev. Anti Infect: Ther. 9(7), 2011; 9) Osterholm et al., The Lancet Infectious Diseases, 2012; ARDS = Acute Respiratory Distress Syndrome; CRS = Cytokine Release Syndrome

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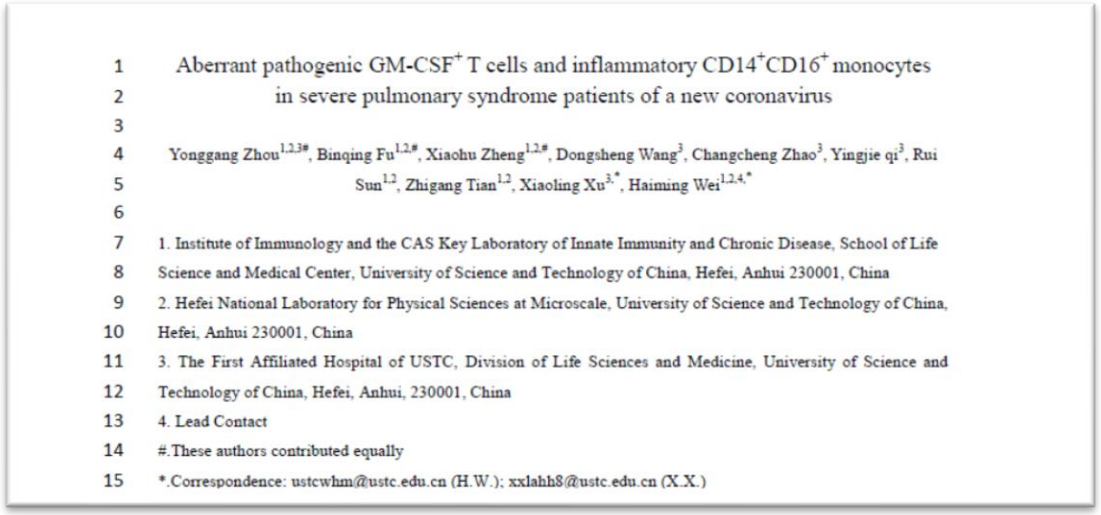
Emerging Literature Support Rationale for Mavrilimumab in COVID-19



Aberrant pathogenic GM-CSF$^+$ T cells and inflammatory CD14$^+$CD16$^+$ monocytes in severe pulmonary syndrome patients of a new coronavirus

Yonggang Zhou[1,2,3#], Binqing Fu[1,2,#], Xiaohu Zheng[1,2,#], Dongsheng Wang[3], Changcheng Zhao[3], Yingjie qi[3], Rui Sun[1,2], Zhigang Tian[1,2], Xiaoling Xu[3,*], Haiming Wei[1,2,4,*]

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- Recent data provide scientific rationale implicating GM-CSF in the mechanism of excessive and aberrant immune cell infiltration and activation in the lungs thought to contribute significantly to mortality in the disease.
- The emerging data indicate that patients with COVID-19 have elevated serum levels of pro-inflammatory cytokines, including GM-CSF, and interferon-gamma, which are thought to be drivers of a cytokine storm that plays a significant role in clinical complications and acute lung injury.
- Infiltration of immune cells in the lungs of COVID-19 patients, as part of an exaggerated immune response despite falling viral loads, results in severe lung complications.
- These data suggest that it may be the excessive, non-effective host immune response by pathogenic T cells and inflammatory monocytes that causes the severe lung pathology most often associated with mortality.

Zhou et al. bioRxiv. 2020

Mavrilimumab Treatment Protocol in COVID-19 Pneumonia and Hyperinflammation

Improved clinical outcomes compared to matched contemporaneous controls, including earlier weaning from supplemental oxygen, shorter hospitalizations, and no deaths

The mavrilimumab open-label treatment protocol was a prospective, interventional, single-active-arm, single-center pilot experience in Italy.

- Thirteen non-mechanically ventilated patients with severe COVID-19 pneumonia and hyperinflammation were treated with a single intravenous dose of mavrilimumab upon admission to the hospital.
- Twenty-six contemporaneous non-mechanically ventilated patients with severe COVID-19 pneumonia and hyperinflammation and with similar characteristics upon admission to the hospital, including comorbidities, baseline inflammatory markers and respiratory dysfunction, were evaluated as a control group.
- All patients in the treatment protocol received optimum local standard of care, including protease inhibitors and antiviral therapies.

Main outcome: Time to clinical improvement (defined as improvement ≥ 2 categories on a 7-point scale for assessment of clinical status)

Clinical Outcomes:

- Over the course of the 14-day follow-up period, mavrilimumab-treated patients experienced greater and earlier clinical improvements than control-group patients, including earlier weaning from supplemental oxygen, shorter hospitalizations, and no deaths.
  - At day 14 of the follow-up period, 85% (n=11/13) of mavrilimumab-treated patients and 42% (n=11/26) of control-group patients had attained the clinical improvement endpoint (defined as improvement of ≥ 2 categories on a 7-point scale for assessment of clinical status) (p=0.017).
  - Mavrilimumab-treated patients reached the clinical improvement endpoint earlier compared to control-group patients (median [95% CI]: 8.0 [5.0–11.0] days vs. NE (not estimable) [11.0–NE], p=0.001).
  - During the 14-day follow-up period, there was a 0% (n=0) incidence of death in mavrilimumab-treated patients compared to 27% (n=7) in control-group patients (p=0.046 for time to death).
  - Eight percent (n=1) of mavrilimumab-treated patients received mechanical ventilation, compared to 35% (n=9) of control-group patients (p=0.077 for time to mechanical ventilation or death).
  - Mavrilimumab-treated patients were discharged from the hospital earlier than control-group patients (median [95% CI]: 10.0 [9.0–12.0] days vs. NE [12.0–NE], p=0.013).
- Mavrilimumab was well-tolerated in all patients, without infusion reactions. P-values above are unadjusted for multiplicity.

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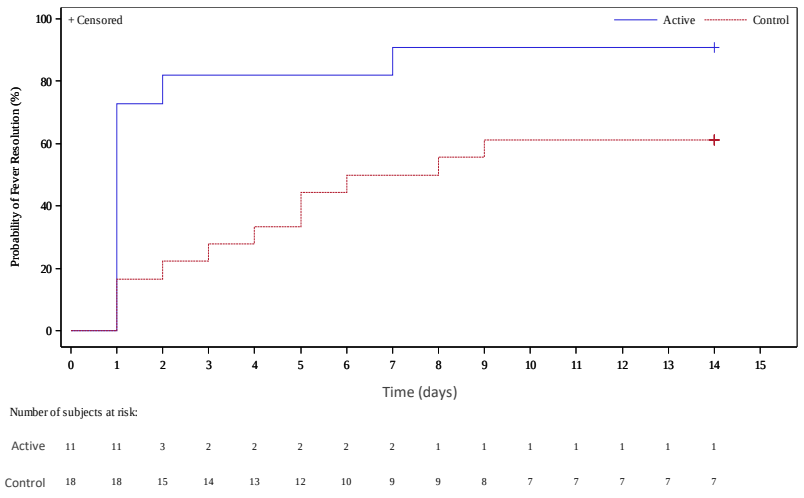
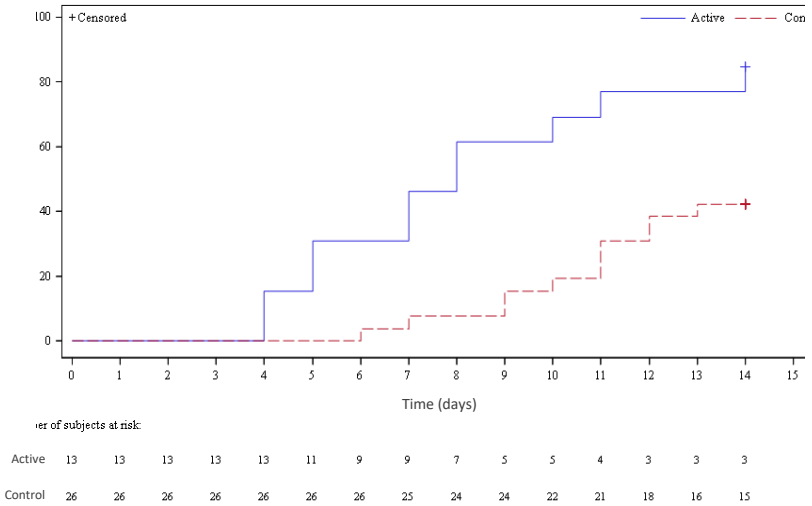
Mavrilimumab Treatment Protocol in Patients with COVID-19 Pneumonia & Hyperinflammation Showed Improved Clinical Outcomes Compared to Matched Contemporaneous Controls[1]

Time to Fever Resolution



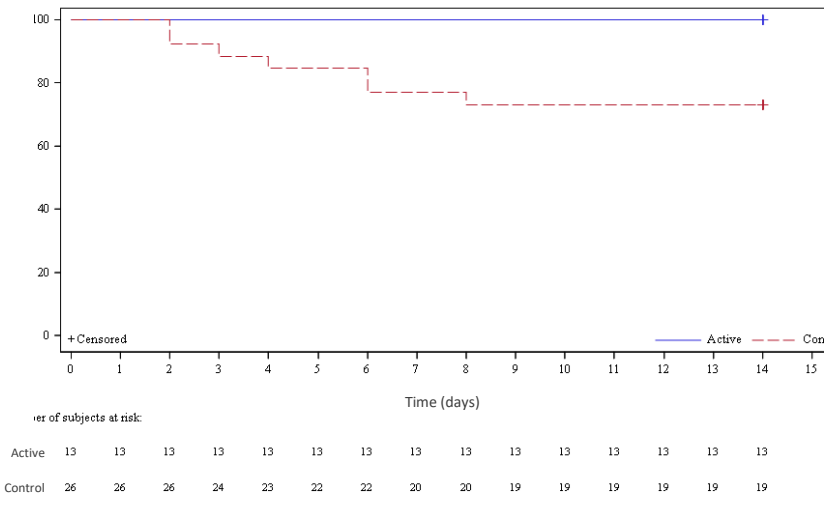
Time to resolution of fever was significantly shorter in mavrilimumab-treated patients than control-group patients (median [95% CI] = 1.0 [1.0–2.0] days vs 7.0 [3.0 - NE] days, respectively, log-rank χ2=6.75, p=0.009)

Time to Clinical Improvement



Mavrilimumab-treated patients reached the clinical improvement endpoint earlier compared to control-group patients (median [95% CI]: 8.0 [5.0–11.0] days vs. NE (not estimable) [11.0–NE], p=0.001)

Cumulative Survival



During the 14-day follow-up period, there was a 0% (n=0) incidence of death in mavrilimumab-treated patients compared to 27% (n=7) in control-group patients (p=0.046 for time to death)

---- Control-group

---- Mavrilimumab

1) The treatment protocol with the investigational drug mavrilimumab was conducted by Professor Lorenzo Dagna, MD, FACP, Head, Unit of Immunology, Rheumatology, Allergy and Rare Diseases IRCCS San Raffaele Scientific Institute and Vita-Salute San Raffaele University in Milan, Italy within a COVID-19 Program directed by Professor Alberto Zangrillo, Head of Department of Anesthesia and Intensive Care of the Scientific Institute San Raffaele Hospital and Professor in Anesthesiology and Intensive Care, Università Vita-Salute San Raffaele; p-values above are unadjusted for multiplicity.

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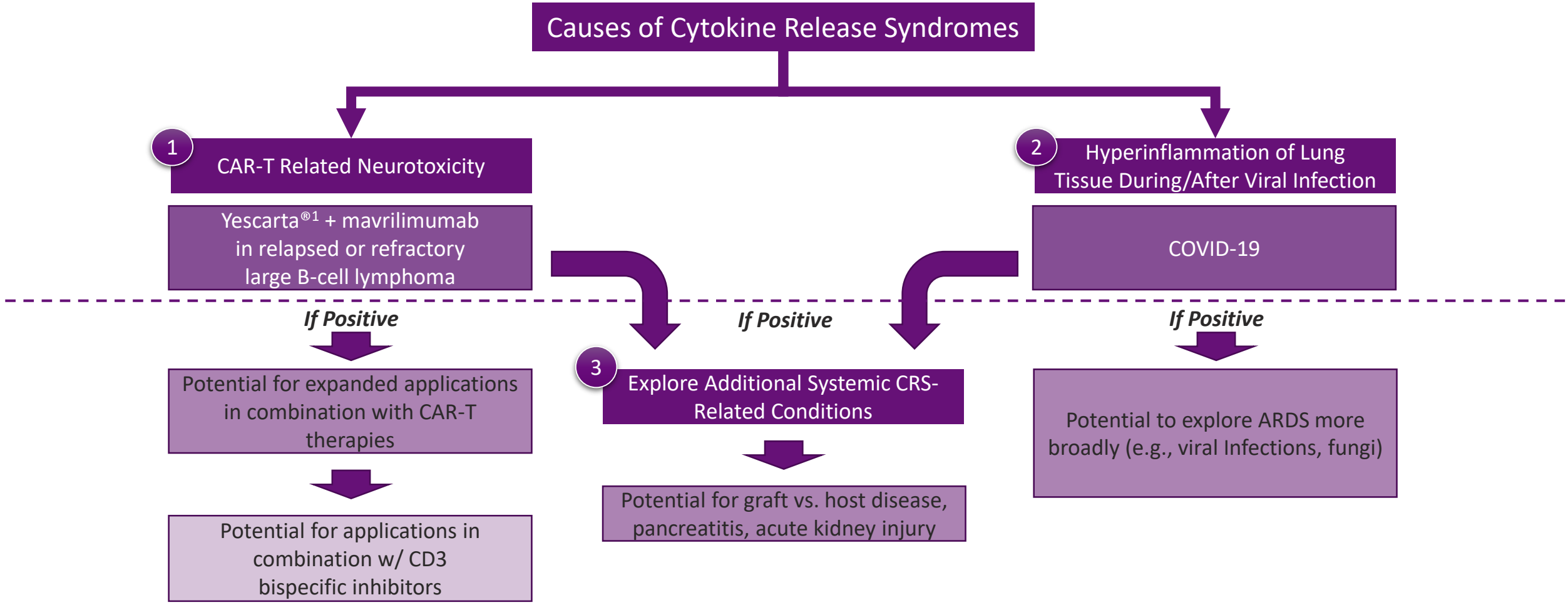
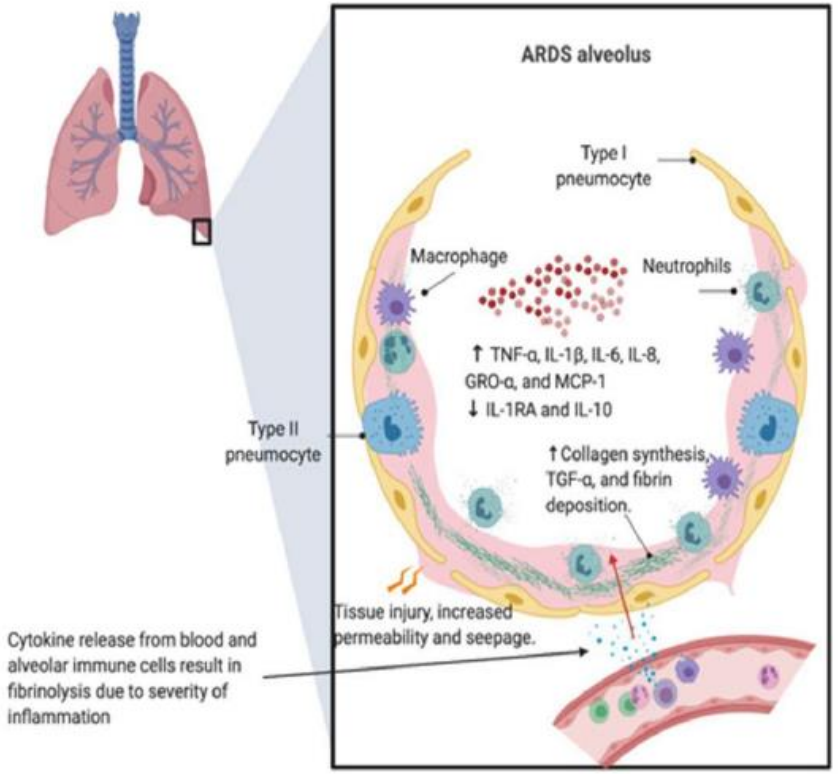
Kiniksa's Development Strategy for Diseases with Cytokine Storm and Hyperinflammation



1) Yescarta® is a registered trademark of Gilead Sciences, Inc., or its related companies; CRS = Cytokine Release Syndrome; Sterner et al., Blood 2019; Mehta et al., The Lancet 2020:https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)30628-0.pdf

Viral Infections Causing ARDS (i.e., influenza, H1N1, RSV, COVID-19, etc.) Have an *Inflammatory* Pathophysiology, Primarily Precipitated by Cytokine Storm

- Uncontrolled pro-inflammatory response, originating from the focal infected area, spreading through circulation and manifests as a **multiorgan failure** and **ARDS**
- Inflammation of the alveolar epithelial cells drives development of severe disease, destroying gas exchange and allowing **further viral exposure**
- Approach to treatment is **addressing host response** directly by targeting innate immune pathways that amplify inflammatory signals and contribute to epithelial damage



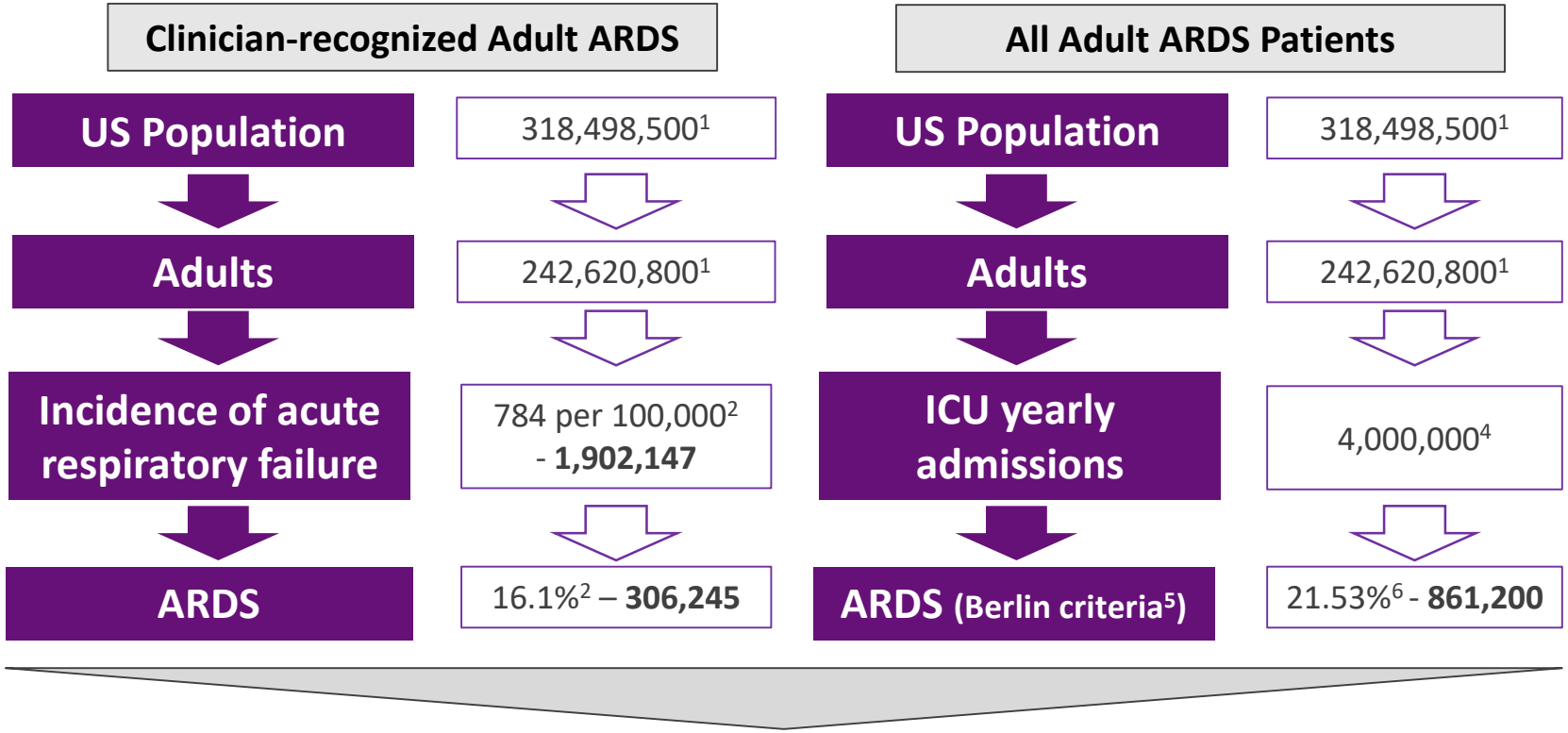
McGonagle, et al., Autoimmunity Reviews (2020), https://doi.org/10.1016/j.autrev.2020.102537

Under-diagnosis of viral infections causing ARDS

- Viral infection is sufficient to cause severe pneumonia and ARDS, but it can also act in conjunction with or be followed by bacterial agents, (most commonly by S. aureus and S. pneumoniae)
- Clinicians fail to clinically diagnose influenza in **up to two-thirds** of patients with confirmed influenza

1) Kalil A.C and Thomas P.G. Critical Care (2019) 23:258
2) Guo XZ, Thomas PG,. Semin Immunopathol. 2017 July ; 39(5): 541–550. doi:10.1007/s00281-017-0636-y.
3) Zhang, et al. Clinical Immunology 214 (2020) 108393

There are between 300k and 860k Cases of Adult ARDS in the U.S. Every Year; Significant Unmet Need Remains in These Populations



- Excludes ARDS associated with COVID-19
- Pediatric ARDS occurs less often
- Most common causes of ARDS are pneumonia (59%) and sepsis (16%)[3]
- 84.5% of ARDS cases require mechanical ventilation[7]
- Considerable mortality (~40%[8]) with no effective treatments outside mechanical ventilation

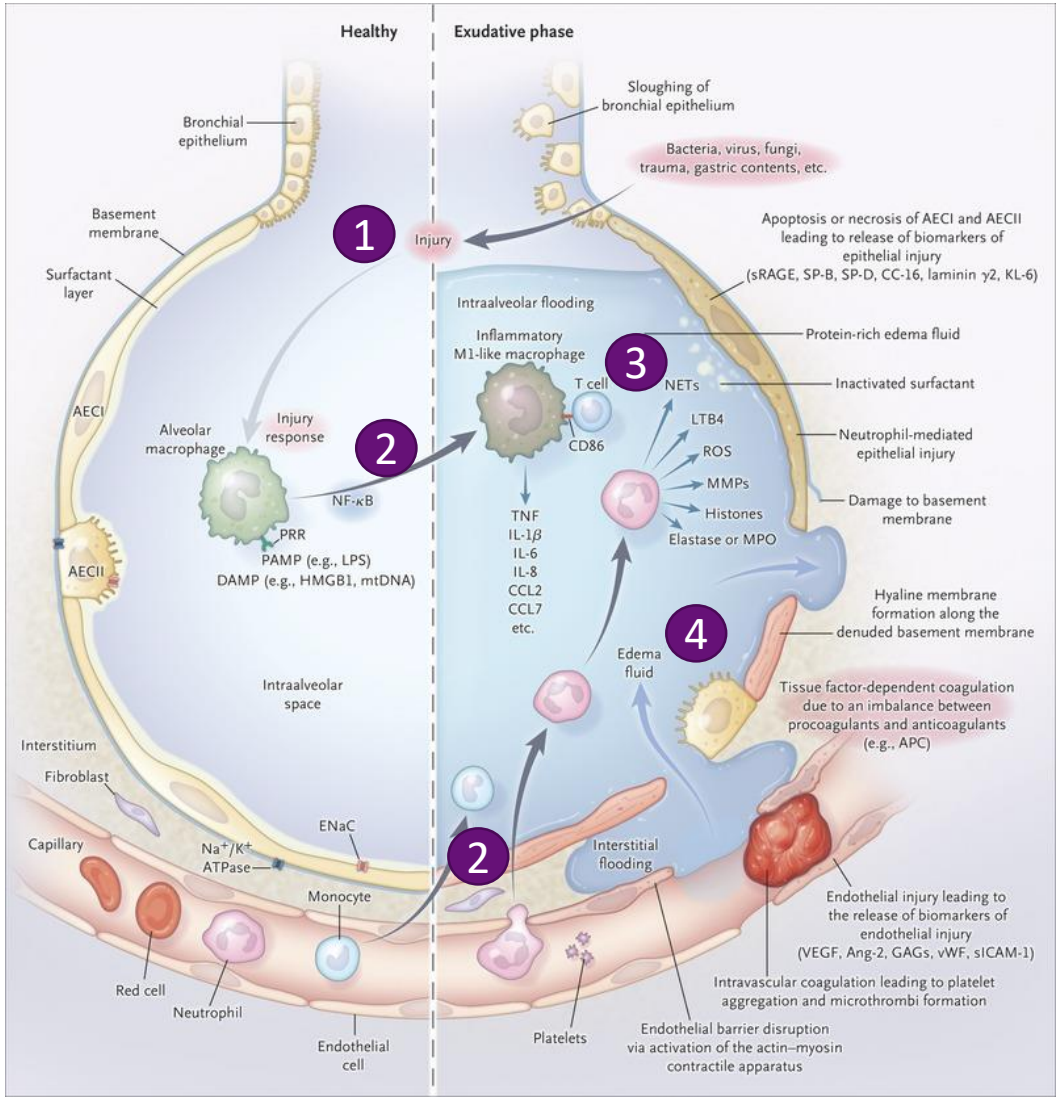
~300,000 – 860,000 ARDS Cases Annually in US*

1) KFF's State Health Facts. Population Distribution by Age [Kaiser Family Foundation estimates based on the Census Bureau's American Community Survey, 2008-2018].
2) Stefan MS, Shieh MS, Pekow PS, et al. J Hosp Med. 2013;8(2):76–82. doi:10.1002/jhm.2004
3) Bellani G, Laffey JG, Pham T, et al JAMA. 2016;315(8):788–800. doi:10.1001/jama.2016.0291
4) Mullins PM, Goyal M, Pines JM. Acad Emerg Med. 2013;20(5):479–486. doi:10.1111/acem.12134
5) ARDS Definition Task Force. JAMA 20112;307(23):2526-2533.
6) Laffey JG, Madotto F, Bellani G, et al. Lancet Resp Med. 2017;5(8):627-638
7) Bellani G, Laffey JG, Pham T, et al Am J Respir Crit Care Med 2017:195(1):67–77
8) Calfee CS, Delucchi KL, Sinha P, et al. Lancet Respir Med. 2018;6(9):691–698. doi:10.1016/S2213-2600(18)30177-2

*There may be different ARDS phenotypes – some of which may not be ideal for GM-CSF inhibition. Further research is needed to understand which patient sub-types would best benefit from treatment with mavrilimumab

Cytokine Cascade Amplification System in the Pathophysiology of ARDS

Pathophysiology of ARDS (Exudative Phase)



1
- Inflammatory insults, either locally from the lungs or systemically from extra-pulmonary sites, affect bronchial epithelium, alveolar macrophages, and vascular endothelium

2
- **Resident alveolar macrophages** secrete proinflammatory cytokines, leading to **neutrophil** and **monocyte** or **macrophage** recruitment, as well as activation of **alveolar epithelial cells** and **effector T cells**, to promote and sustain inflammation and tissue injury.

3
- Hyperactivation of myeloid cells and T-cells produce large amounts of inflammatory cytokines, which in turn lead to **endothelial activation** and microvascular injury ultimately leading to barrier disruption in ARDS which can worsened by mechanical stretch.

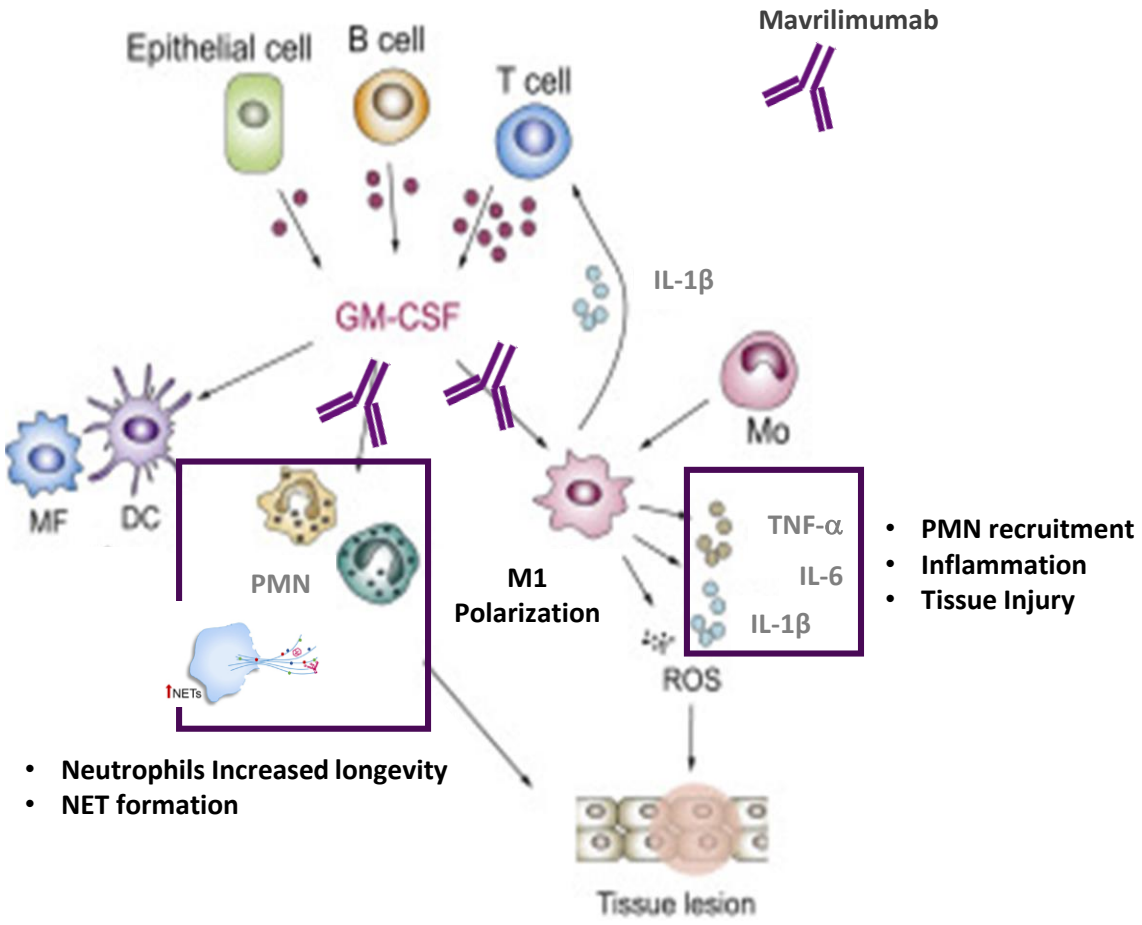
4
- Extensive damage to lung epithelia and endothelia results in an impaired alveolar-capillary barrier.
- Disruption of this barrier allows protein-rich fluid to enter the alveoli causing fluid accumulation in alveolar spaces (pulmonary edema) interfering with gas exchange

ARDS = Acute Respiratory Distress Syndrome

The New England Journal of Medicine. 2017

The Role of Mavrilimumab Throughout the Immune System and its Potential to Treat COVID-19 Pneumonia and ARDS More Broadly

Mechanisms driving ARDS pathophysiology	Targetable by Mavrilimumab[4-14]	Targetable by anti-IL-6[15-20]	Targetable by anti-IL-1β[21-26]
Recruitment of neutrophils	√	√	√
Neutrophil longevity	√	Conflicting evidence	
Formation of neutrophil extra cellular traps (NET)	√		
Activation of AM & polarization to M1-like phenotype	√		
Th1 inflammation[1-3]	√		
Th17 inflammation[1-3]	√	√	√



Evidence of targetable pathways by anti-IL-6

[1]Wu J Microbiol, Immunol and Infection (2020), [2] Xu Lancet Respir Med (2020), [3] Huang Lancet (2020).

Evidence of targetable pathways by anti-IL-6

[4] De Alessandris JLB (2019), [5] Matute-Bello Am J Resp Crit Care Med (1997), [6] Juss Am J Resp Crit Care Med 1997 (2016), [7] Yousefi Cell Death and Differentiation (2009), [8] Gray Thorax (2018), [9] Fleetwood JI (2007), [10] Dalrymple BMC Immunol. (2013), [11] Benmerzoug Sci Rep (2018), [12] Krausgruber Nat Imm (2011), [13] Shiomi JI (2014), [14] Shiomi Med Inflamm (2015).

Evidence of targetable pathways by anti-IL-6

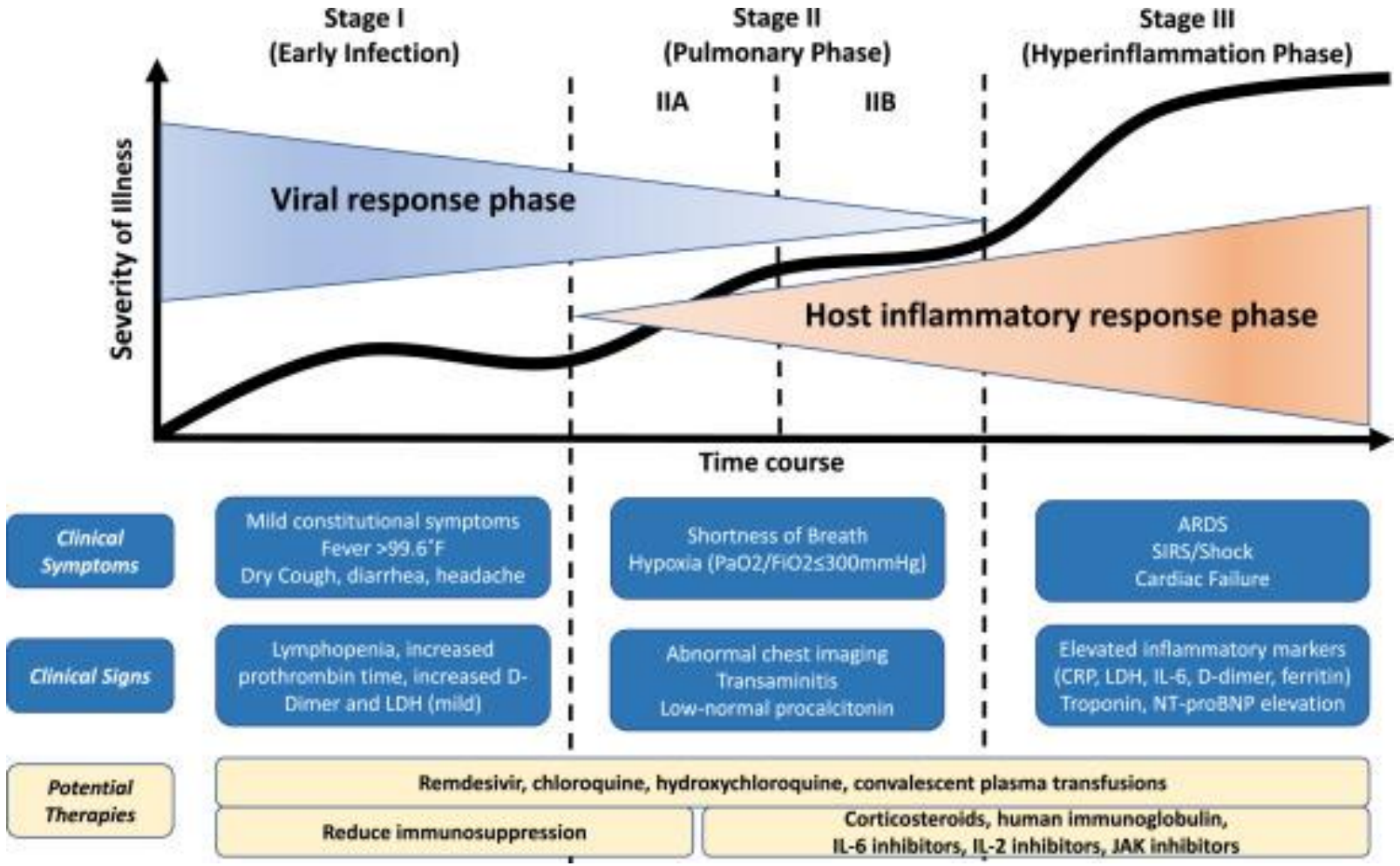
[15] Jones J Infect Dis (2006), [16] Wright Rheumatology (2014), [17] Afford JBC (1992), [18] Biffl JLB (1995), [19] Oh J Exp Med (2011), [20] Yan Sci Rep (2016).

Evidence of targetable pathways by anti-IL-1β

[21] Sichelstiel PLOS One (2014), [22] Jones AJRCB (2014), [23] Ganter Circ Res (2008), [24] Frank Thorax (2008), [25] Wu JI (2013), [26] Gasse PLOS One (2011).

ARDS = Acute Respiratory Distress Syndrome
Becher B. et al., Immunity 45, (2016)

Escalating Phases of Disease Progression with COVID-19



Source:
Hasan K. Siddiqi MD, MSCR , Mandeep R. Mehra MD, MSc , COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal, Journal of Heart and Lung Transplantation (2020), doi: https://doi.org/10.1016/j.healun.2020.03.012

ARDS = Acute respiratory distress syndrome; CRP = C-reactive protein; IL = Interleukin; JAK = Janus Kinase; LDH=Lactate DeHydrogenase; SIRS = Systemic inflammatory response syndrome

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