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 mavrilimumab in COVID-19 pneumonia and hyperinflammation; 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; our interactions with the FDA and other governmental agencies; and our ability to attract and retain qualified personnel. These and the important factors discussed under the caption "Risk Factors" in our Annual Report on Form 10-K filed with the Securities and Exchange Commission (the "SEC") on February 25, 2021 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.

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]
- In U.S. IIS data showed an early signal of efficacy, with trends toward clinical improvement as well as lower mortality and shorter duration of mechanical ventilation in patients treated with mavrilimumab on top of corticosteroids.

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
- Enrollment in the Phase 3 Portion of an adaptive design Phase 2/3 clinical trial of mavrilimumab in severe COVID-19 pneumonia and hyperinflammation is ongoing

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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Phase 2/3 Clinical Trial of Mavrilimumab in Severe COVID-19 Pneumonia and Hyperinflammation

Key Inclusion Criteria:
- Positive COVID-19 test within 14 days prior to randomization
- Hospitalized for COVID-19
- Bilateral pneumonia on chest x-ray or computed tomography
- Active fever or recently documented fever within 72 hours prior to randomization
- Clinical laboratory results indicative of hyper-inflammation
- Cohort 1: Non-ventilated; requiring supplemental oxygen to maintain oxygen saturation (SpO2) ≥ 92% and not-intubated
- Cohort 2: Recently ventilated with mechanical ventilation prior to randomization
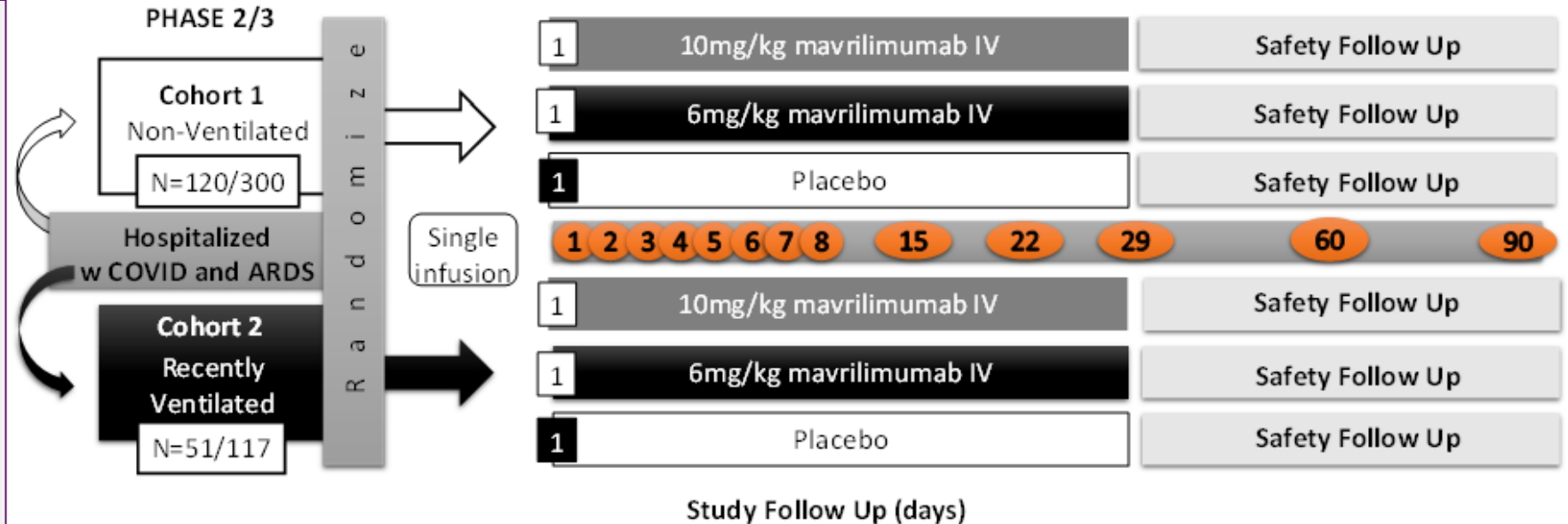
Cohort 1:

Primary Efficacy Endpoint:
- Proportion of patients alive and without mechanical ventilation at Day 29.

Secondary Efficacy Endpoints:
- Time to 2-point improvement by Day 29
- Time to return to Room Air or Discharge by Day 29
- Mortality rate at Day 29

Prespecified evidentiary standard for Phase 2 endpoints was a 2-sided p value of 0.2, without adjustment for multiplicity

Data from Phase 2 Portion of the Phase 2/3 trial of Mavrilimumab in Severe COVID-19 Pneumonia and Hyperinflammation

The Phase 2/3 trial is a global, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of mavrilimumab treatment in adults hospitalized with severe COVID-19 pneumonia and hyperinflammation.

- In the non-mechanically ventilated cohort (Cohort 1), 116 patients with hypoxia and severe COVID-19 pneumonia/hyperinflammation were enrolled across sites in the United States, Brazil, Chile, Peru, and South Africa. Patients were randomized in a 1:1:1 ratio to receive a single intravenous (IV) dose of mavrilimumab 10 mg/kg, 6 mg/kg, or placebo.
- Baseline demographics were balanced across treatment arms: the population was ethnically/racially diverse (43% non-white), 49% were obese (body mass index ≥ 30), and 29% were older than 65 years.
- Local standard of care therapy: 96% received corticosteroids/dexamethasone and 29% received antivirals/remdesivir.

Primary Efficacy Endpoint: The proportion of patients alive and free of mechanical ventilation at Day 29.

Key Secondary Efficacy Endpoints: Time to two-point clinical improvement on the NIAID[1] scale, time to return to room air, and mortality at Day 29.

The prespecified evidentiary standard for Phase 2 endpoints was a 2-sided alpha value of 0.2, without adjustment for multiplicity.

Non-mechanically ventilated patients (Cohort 1) treated with mavrilimumab demonstrated a reduction in mechanical ventilation and death at Day 29 pooled across dose levels:

- The proportion of patients alive and free of mechanical ventilation at Day 29 was 12.3 percentage points higher in mavrilimumab recipients (86.7%) compared to placebo recipients (74.4%) (Primary efficacy endpoint; p=0.1224).
   - Mavrilimumab recipients experienced a 65% reduction in the risk of mechanical ventilation or death (Hazard Ratio (HR) = 0.35; p=0.0175).
- Day 29 mortality was 12.5 percentage points lower in mavrilimumab recipients (8%) compared to placebo recipients (20.5%) (p=0.0718).
   - Mavrilimumab recipients experienced a 61% reduction in the risk of death (HR= 0.39; p=0.0726).
- No apparent differences were observed between the 10 mg/kg and 6mg/kg IV treatment arms.

Mavrilimumab was well-tolerated and exhibited a favorable safety profile:

- One treatment-emergent serious adverse event related to study drug was reported on placebo, and there were no notable dose-related adverse events.
- Infections were noted in all groups including placebo recipients. All thrombotic events occurred in placebo recipients.

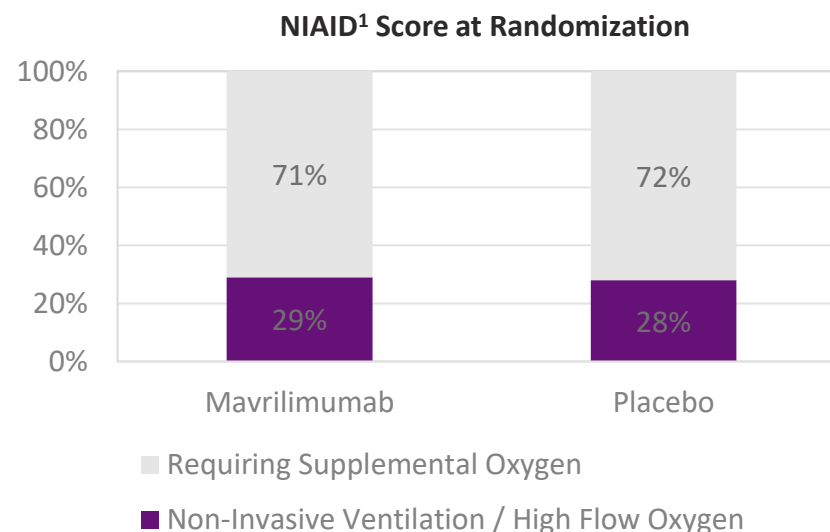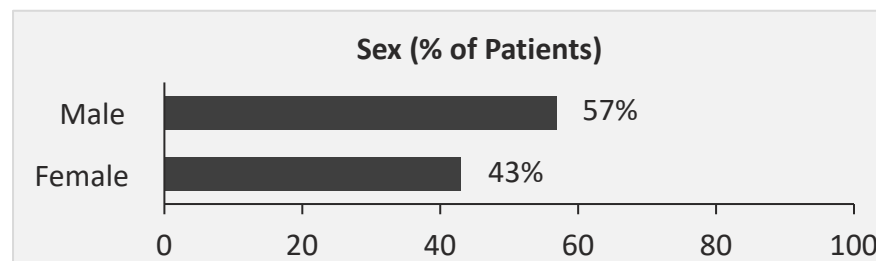1) National Institute of Allergy and Infectious Diseases

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Median time to randomization from diagnosis was 7 days

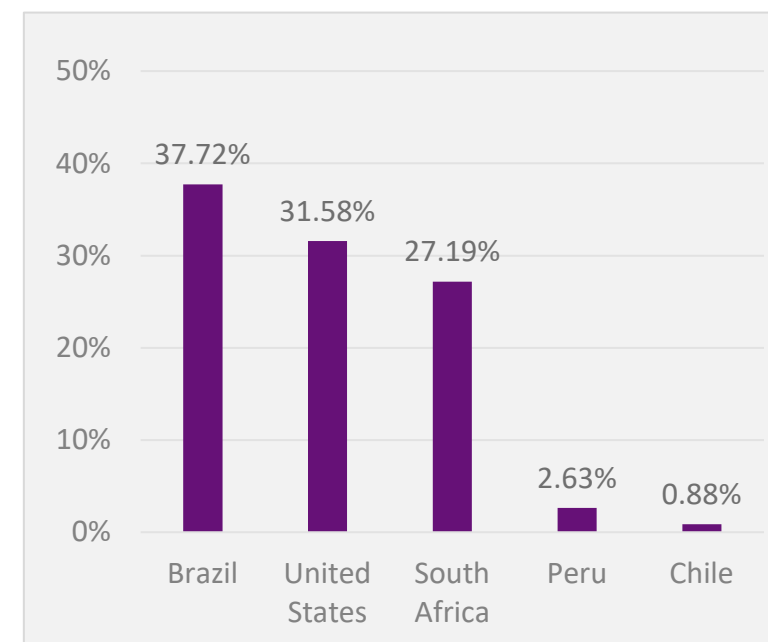| Baseline Demographics were Balanced Across Treatment Arms	
Mean Age (years)	57.1
Age Range (years)	29-86
> 65 years old	29%
Non-white	43%
Body mass index ≥ 30	49%

Local Standard of Care During 29-Day Treatment Period	
Received Corticosteroids/Dexamethasone	96%
Received Antivirals/Remdesivir	29%

Sex (% of Patients)

Male 57%
Female 43%

NIAID[1] Score at Randomization

Mavrilimumab: Requiring Supplemental Oxygen 71%, Non-Invasive Ventilation / High Flow Oxygen 29%
Placebo: Requiring Supplemental Oxygen 72%, Non-Invasive Ventilation / High Flow Oxygen 28%

■ Requiring Supplemental Oxygen
■ Non-Invasive Ventilation / High Flow Oxygen

Randomized Number of Patients by Country[2]

Brazil 37.72%
United States 31.58%
South Africa 27.19%
Peru 2.63%
Chile 0.88%

1) National Institute of Allergy and Infectious Diseases; 2) One patient randomized to Cohort 2 but analyzed as part of Cohort 1

Non-Mechanically Ventilated Patients Treated with Mavrilimumab Demonstrated a Reduction in Mechanical Ventilation and Death at Day 29 Pooled Across Dose Levels
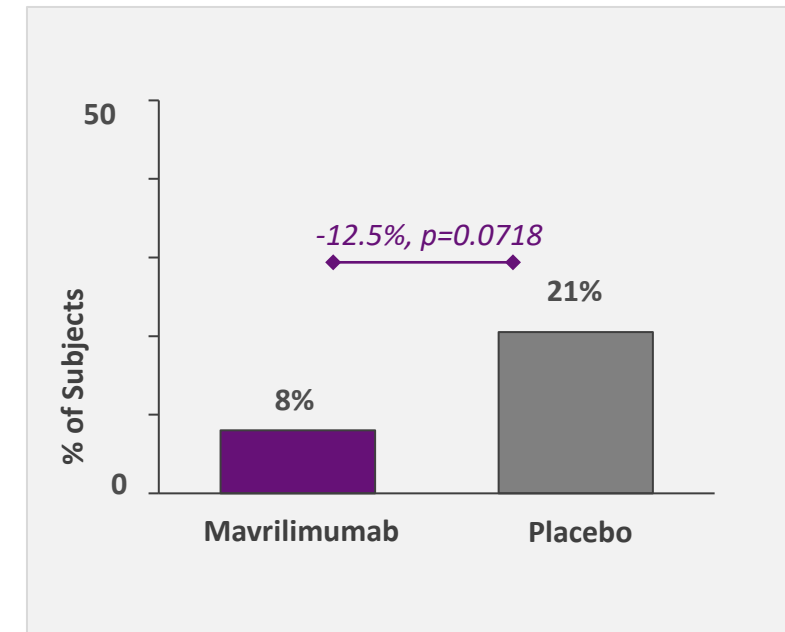
Phase 2 Portion of Phase 2/3 trial of Mavrilimumab in Severe COVID-19 Pneumonia and Hyperinflammation

Primary Endpoint: Proportion of Patients Alive and Free of Mechanical Ventilation at Day 29

+12.3%, p=0.1224

100 — 87% (Mavrilimumab) — 74% (Placebo) — 0

% of Subjects

Mavrilimumab   Placebo
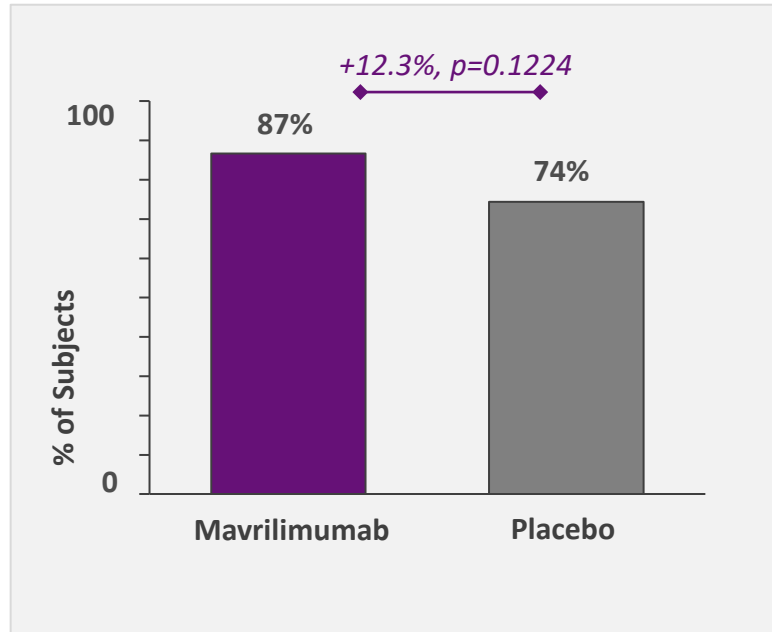
Mavrilimumab recipients experienced a 65% reduction in the risk of mechanical ventilation or death (Hazard Ratio (HR) = 0.35; p=0.0175).

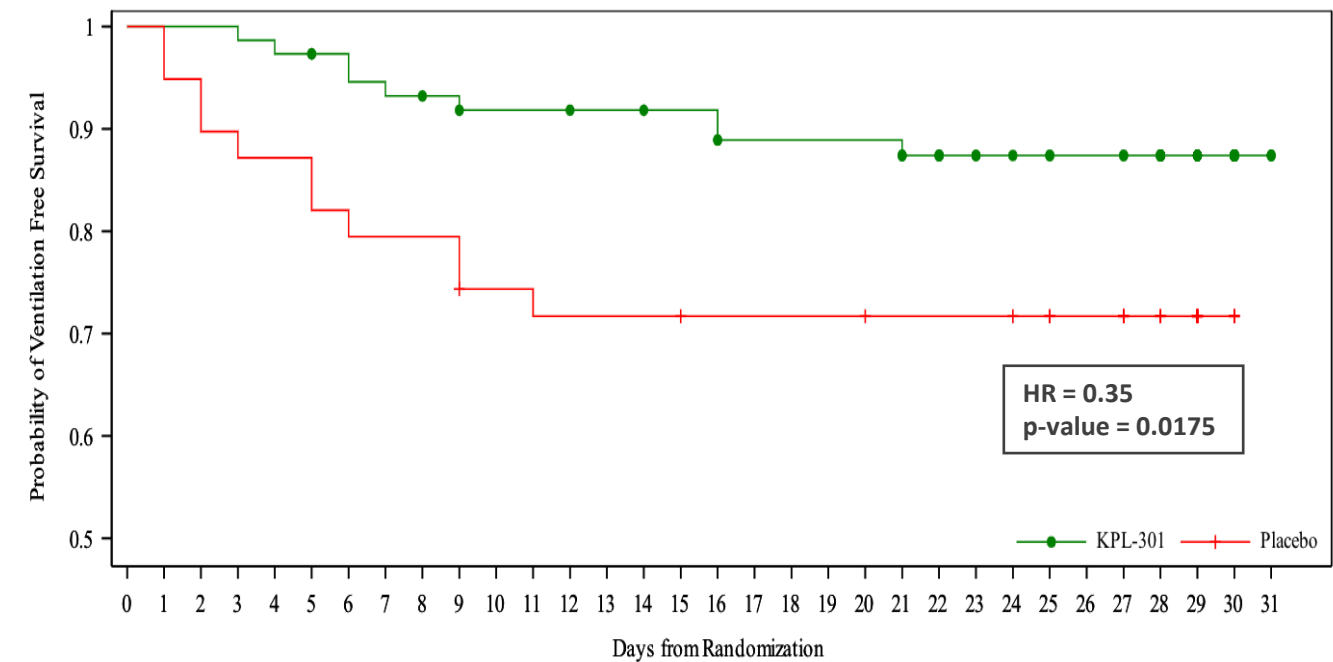**Key Secondary Endpoint: Mortality at Day 29**

-12.5%, p=0.0718

50 — 8% (Mavrilimumab) — 21% (Placebo) — 0

% of Subjects

Mavrilimumab   Placebo

Mavrilimumab recipients experienced a 61% reduction in the risk of death (HR= 0.39; p=0.0726).

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The prespecified evidentiary standard for Phase 2 endpoints was a 2-sided alpha value of 0.2, without adjustment for multiplicity.

Note: Time to ventilation or death by Day 29 is defined as time (in days) from randomization to the date of death or start date of using mechanical ventilation (NIAID <= 2) by Day 29. All subjects who never had NIAID <= 2 by Day 29 will be censored at last assessment date of NIAID 8-point ordinal scale.

Category	KPL-301 10mg/kg (N=35) n (%)	KPL-301 6mg/kg (N=41) n (%)	Placebo (N=40) n (%)
Treatment Emergent Adverse Events (TEAEs)	19 (54.3)	19 (46.3)	26 (65.0)
TEAEs by Maximum Severity [1]			
Mild	10 (28.6)	8 (19.5)	6 (15.0)
Moderate	5 (14.3)	5 (12.2)	6 (15.0)
Severe	4 (11.4)	6 (14.6)	14 (35.0)
TEAEs related to KPL-301 or Placebo [2]	2 (5.7)	3 (7.3)	4 (10.0)
Serious TEAEs (SAE)	4 (11.4)	5 (12.2)	13 (32.5)
SAEs related to KPL-301 or Placebo [2]	0	0	1 (2.5)
TEAEs Leading to Death	3 (8.6)	4 (9.8)	9 (22.5)
TEAEs Leading to Dose Interruption	0	0	1 (2.5)
TEAEs of Special Interest [1]	3 (8.6)	2 (4.9)	6 (15.0)

1) AESIs include: Hepatic Function Abnormality / induced Liver Injury, Acute and Delayed, Hypersensitivity Reactions, Neutropenia, Serious Infection, Worsening of Cytokine Release Syndrome

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.
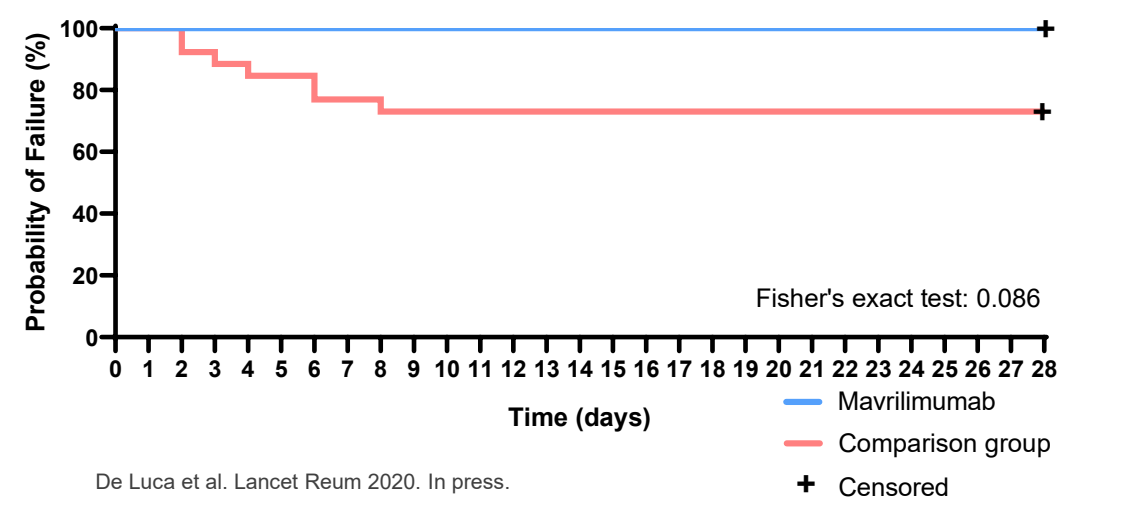
– Thirteen non-mechanically ventilated patients with severe COVID-19 pneumonia and hyperinflammation were treated with a single intravenous dose of mavrilimumab upon admission to the hospital.

– 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 28-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.

– Death occurred in 0% (n=0/13) of mavrilimumab-treated patients by Day 28, compared to 27% (n=7/26) of control-group patients (p=0.086).

– 8% (n=1/13) of mavrilimumab-treated patients progressed to mechanical ventilation by Day 28, compared to 35% (n=9/26) of control-group patients who progressed to mechanical ventilation or died (p=0.077).

– 100% (n=13/13) of mavrilimumab-treated patients and 65% (n=17/26) of control-group patients attained the clinical improvement endpoint (defined as improvement of ≥ 2 categories on a 7-point scale for assessment of clinical status) by Day 28 (p=0.0001).

– Fever resolved in 91% (n=10/11 febrile patients) of mavrilimumab-treated patients by Day 14, compared to 61% (n=11/18 febrile patients) of control-group patients (p=0.0093).

– Representative mavrilimumab-treated patients showed significant improvement in lung opacification on computerized tomography (CT) scans, consistent with the overall improvement in their clinical status.

• Mavrilimumab was well-tolerated in all patients, without infusion reactions. P-values above are unadjusted for multiplicity.

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Probability of Failure (%) — Time (days)

Fisher's exact test: 0.086

— Mavrilimumab
— Comparison group
+ Censored

De Luca et al. Lancet Reum 2020. In press.

Probability of Failure (%) — Time (days)

$\chi2=3.12$, p=0.077

— Mavrilimumab
— Non-Treated
+ Censored

De Luca et al. Lancet Reum 2020. In press.

Patients at Risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Mavrilimumab	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
Comparison group	26	26	26	24	23	22	22	20	20	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19
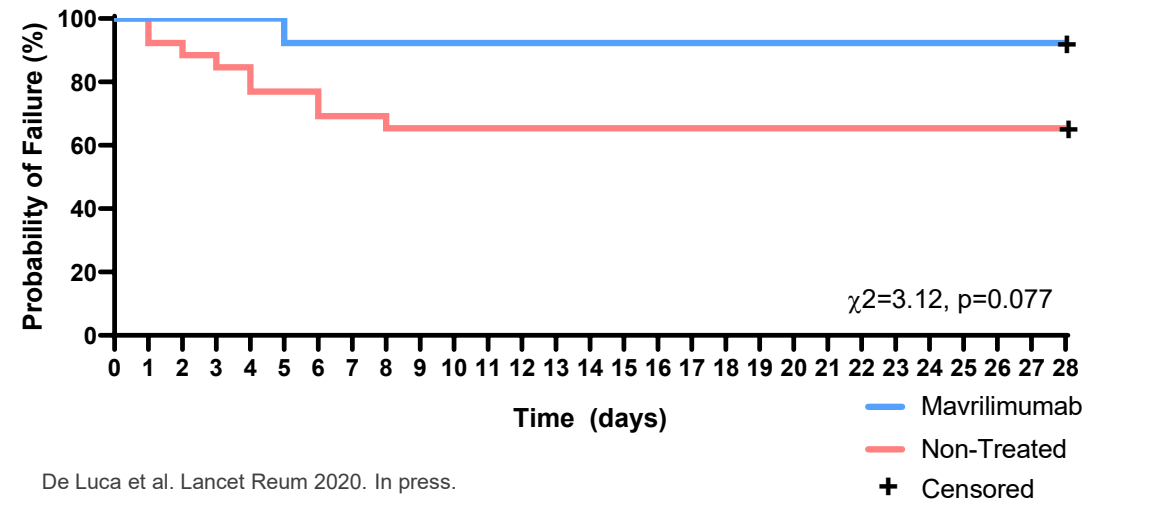
Patients at Risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Mavrilimumab	13	13	13	13	13	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Comparison group	26	26	24	23	22	20	20	18	18	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17

Death occurred in 0% (n=0/13) of mavrilimumab-treated patients by Day 28, compared to 27% (n=7/26) of control-group patients (p=0.086)

8% (n=1/13) of mavrilimumab-treated patients progressed to mechanical ventilation by Day 28, compared to 35% (n=9/26) of control-group patients who progressed to mechanical ventilation or died (p=0.077)

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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Mavrilimumab Treatment Protocol in Patients with COVID-19 Pneumonia & Hyperinflammation Showed Improved Clinical Outcomes Compared to Matched Contemporaneous Controls[1]
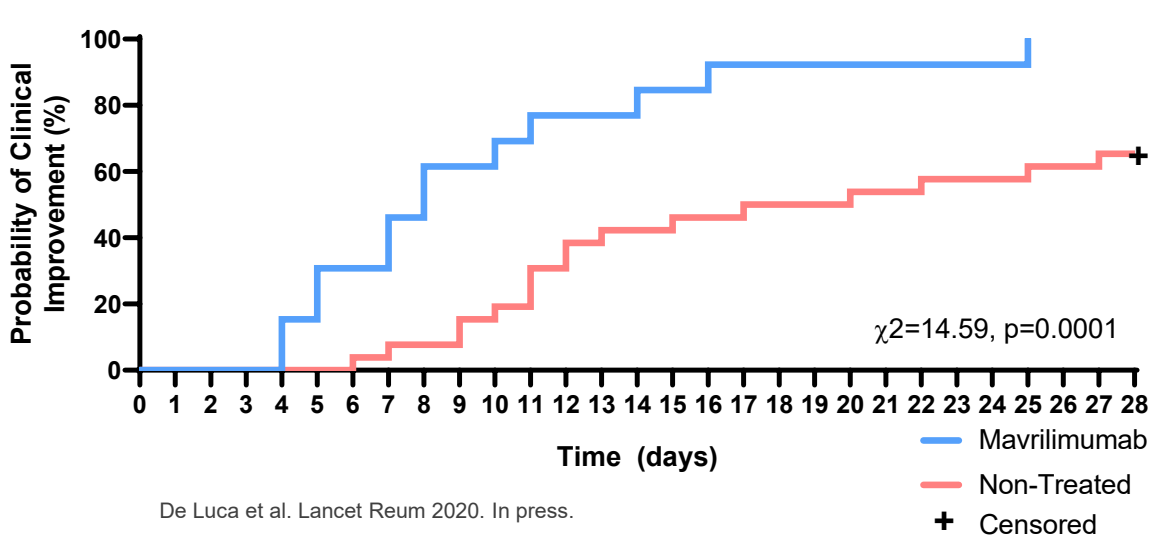
$\chi2=14.59$, p=0.0001

De Luca et al. Lancet Reum 2020. In press.

Patients at Risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Mavrilimumab	13	13	13	13	13	11	9	9	7	5	5	4	3	3	3	2	2	1	1	1	1	1	1	1	1	1			
Comparison group	26	26	26	26	26	26	26	25	24	24	22	21	18	16	15	15	14	14	13	13	13	12	12	11	11	11	10	10	9

100% (n=13/13) of mavrilimumab-treated patients and 65% (n=17/26) of control-group patients attained the clinical improvement endpoint (defined as improvement of ≥ 2 categories on a 7-point scale for assessment of clinical status) by Day 28 (p=0.0001)
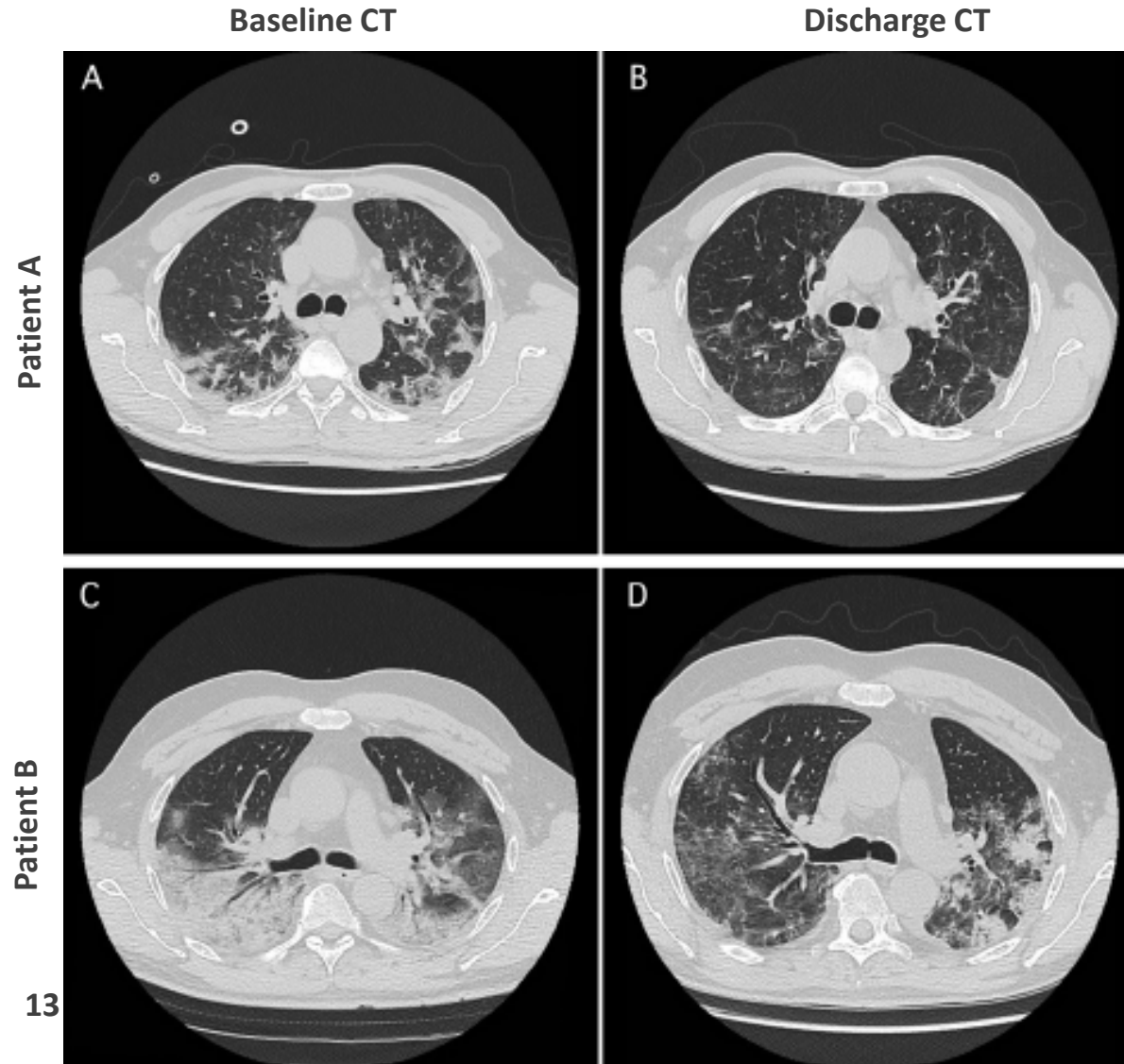

$\chi2=6.76$, p=0.0093

De Luca et al. Lancet Reum 2020. In press.
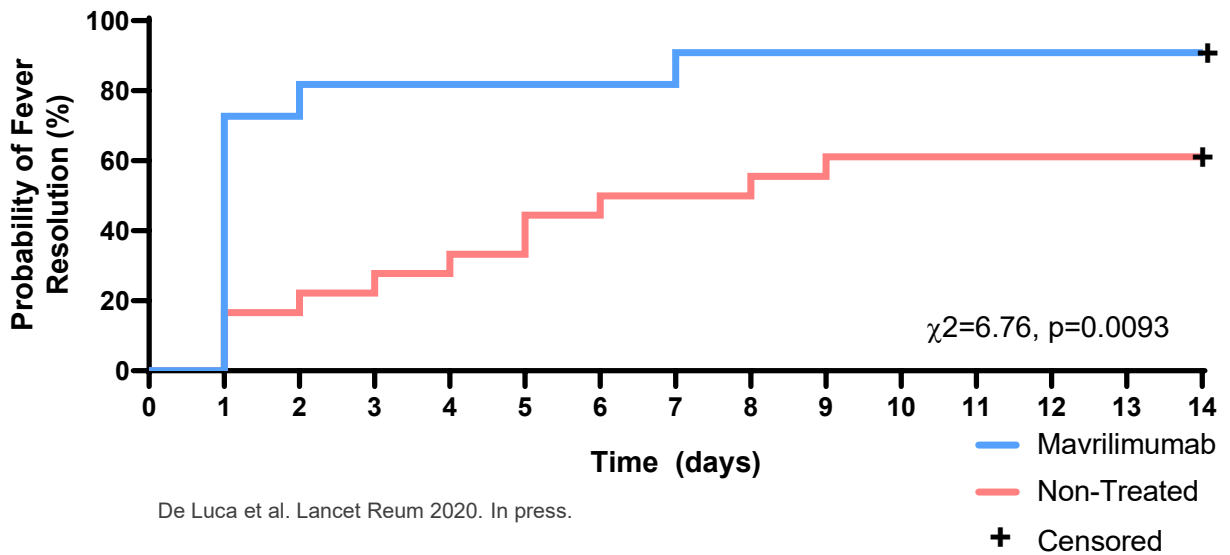
Patients at Risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Mavrilimumab	11	11	3	2	2	2	2	2	1	1	1	1	1	1	1
Comparison group	18	18	15	14	13	12	10	9	9	8	7	7	7	7	7

Fever resolved in 91% (n=10/11 febrile patients) of mavrilimumab-treated patients by Day 14, compared to 61% (n=11/18 febrile patients) of control-group patients (p=0.0093)

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Representative mavrilimumab-treated patients showed significant improvement in lung opacification on computerized tomography (CT) scans, consistent with the overall improvement in their clinical status

Baseline CT

Discharge CT

Patient A

Patient B

Patient A: 58 year old male.
- At day 0: febrile, receiving O2 through a facemask; FiO2 0.4, PaO2 86 mmHg, lactic acid dehydrogenase (LDH) 374 U/L, C-reactive protein (CRP) 100 mg/L.

- At day 7: afebrile, on room air, SpO2 98%, LDH normalized, CRP 12.5 mg/L.

Patient B: 56 year old male
- At day 0: febrile, receiving high-low O2 through a facemask with reservoir bag + 12 hours/day of CPAP, PaO2 176 mmHg, LDH 944 U/L, CRP 177 mg/L.

- At day 14: afebrile, on room air, SpO2 98%, LDH normalized, CRP 28.2 µg/mL (28.2 mg/L).

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Data from U.S. Investigator-Initiated Study of Mavrilimumab in Severe COVID-19 Pneumonia and Hyperinflammation

The investigator-initiated study was a randomized, double-blind, placebo-controlled study across a consortium of U.S. academic sites designed to evaluate the efficacy and safety of mavrilimumab versus placebo on top of standard of care therapy in patients with severe COVID-19 pneumonia and hyperinflammation.

– Enrolled 40 patients with severe COVID-19 pneumonia (all patients presented with pneumonia and hypoxia: all patients required supplemental oxygen, 50% of patients required non-invasive ventilation, none required mechanical ventilation at baseline; median PaO2/FiO2 ratio 137) and hyperinflammation (median C-reactive protein 13.1 mg/dL).

– Concomitant medications at baseline included corticosteroids (65% of patients) and remdesivir (75% of patients). Patients were randomized 1:1 to a single intravenous (IV) infusion of mavrilimumab 6mg/kg (n=21) or placebo (n=19) and were followed for at least 60 days.
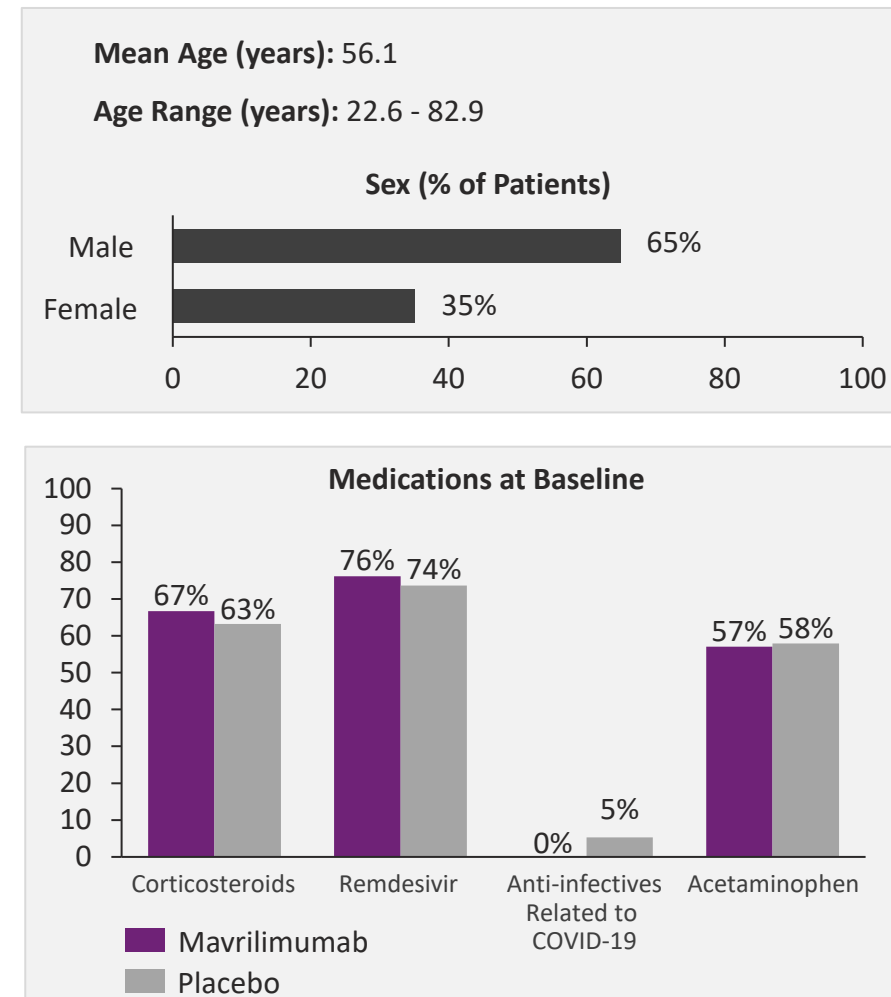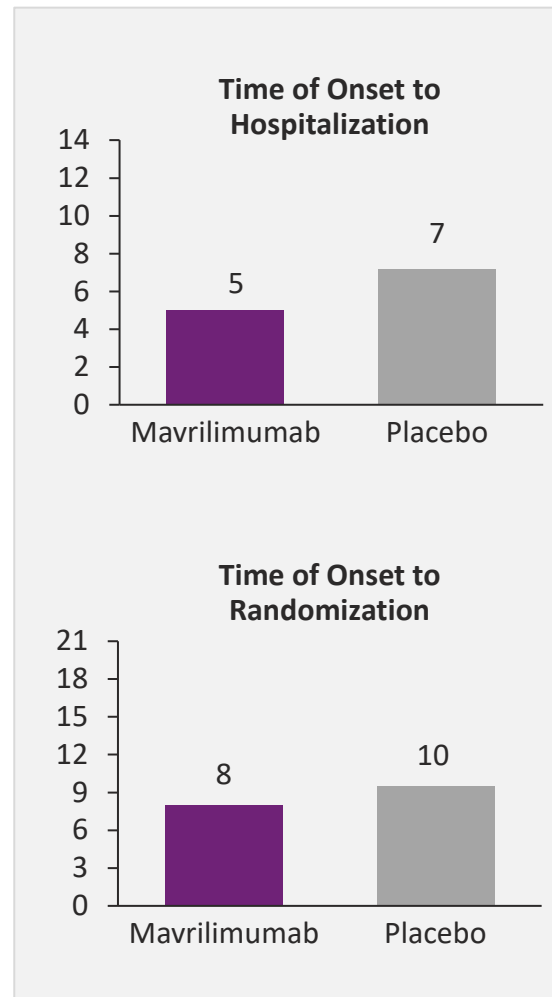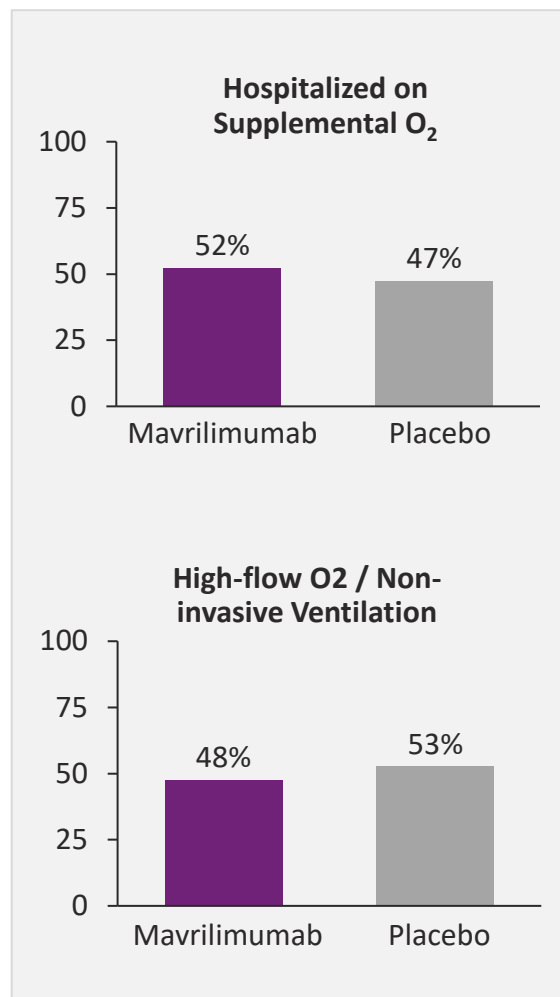
Data showed an early signal of efficacy, with trends toward clinical improvement as well as lower mortality and shorter duration of mechanical ventilation in patients treated with mavrilimumab on top of corticosteroids, including dexamethasone, and/or remdesivir.

Clinical Outcomes:

– There was a 20.5% relative increase in the primary efficacy endpoint, the proportion of patients alive and off supplemental oxygen at Day 14 (mavrilimumab: 57.1% [n=21]; placebo: 47.4% [n=19]; nominal p=0.536).

– There was a 20.7% relative increase in the secondary efficacy endpoint, the proportion of patients alive and without respiratory failure[1] at Day 28 (mavrilimumab: 95.2%; placebo: 78.9%; nominal p=0.172).

– There was 1 death (4.8%) in the mavrilimumab arm by Day 28, compared to 3 deaths (15.8%) in the placebo arm (nominal p=0.222). By Day 60 there was 1 death (4.8%) in the mavrilimumab arm, compared to 4 deaths (21.1%) in the placebo arm (nominal p=0.108).

– While the percentage of patients who progressed to mechanical ventilation was similar between treatment arms (mavrilimumab: 23.8% [n=5]; placebo: 21.1% [n=4]), the median (interquartile) duration of mechanical ventilation was shorter in the mavrilimumab arm (12 [9.0, 18.0] days) compared to the placebo arm (17 [11.0, 24.5] days). Additionally, 4 of the 5 patients who progressed to mechanical ventilation in the mavrilimumab arm had recovered by Day 28, whereas all patients in the placebo arm who progressed to mechanical ventilation had died by Day 28.

– There was no difference in serious adverse events between the mavrilimumab arm and the placebo arm.

[1] Need for mechanical ventilation, Non-Invasive Ventilation, Hi Flow Oxygen

Encouraging Trends toward Reduced Mortality and Duration of Mechanical Ventilation
U.S. investigator-initiated study in patients with severe COVID-19 pneumonia and hyperinflammation
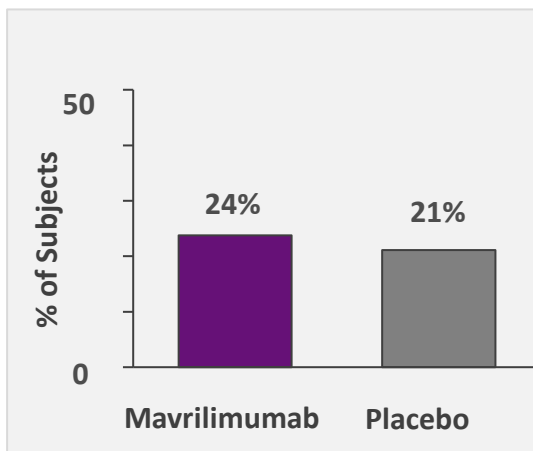

Primary Endpoint: Proportion of Patients Alive and off Supplemental Oxygen at Day 14

+20.5%, nominal p=0.536

Mavrilimumab: 57% | Placebo: 47%
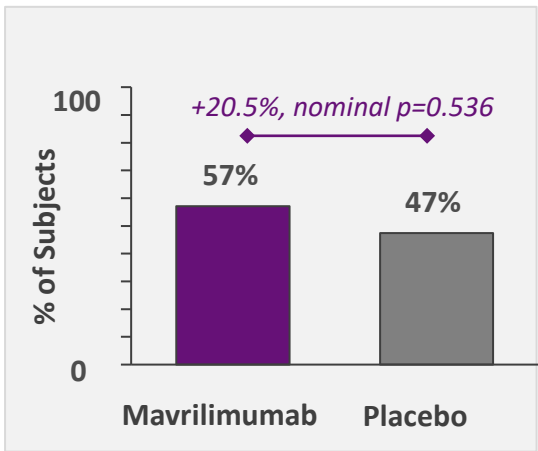
Secondary Endpoint: Proportion of Patients Alive and Without Respiratory Failure at Day 28
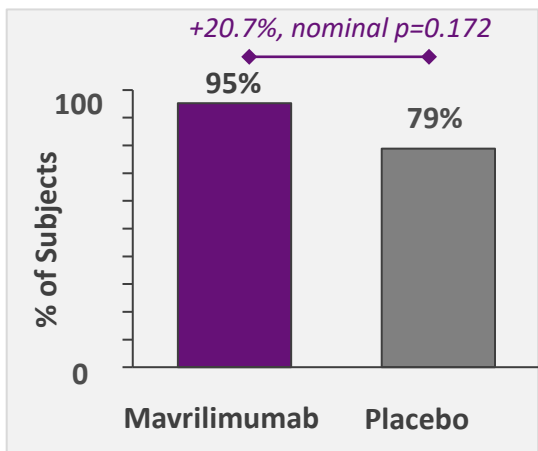
+20.7%, nominal p=0.172

Mavrilimumab: 95% | Placebo: 79%

Percentage of Patients who Progressed to Mechanical Ventilation
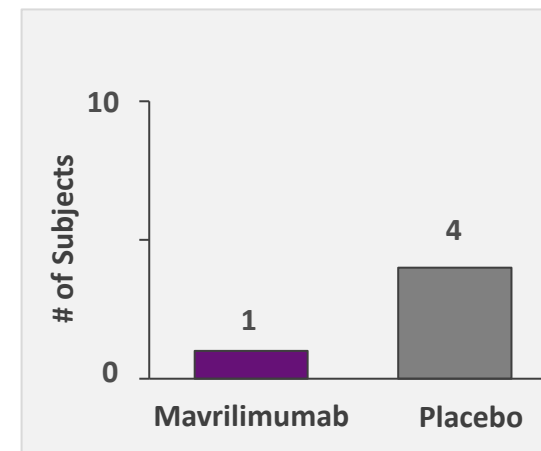
Mavrilimumab: 24% | Placebo: 21%

The percentage of patients who progressed to mechanical ventilation was similar between treatment arms (mavrilimumab: 23.8% [n=5]; placebo: 21.1% [n=4]).

Duration of Mechanical Ventilation
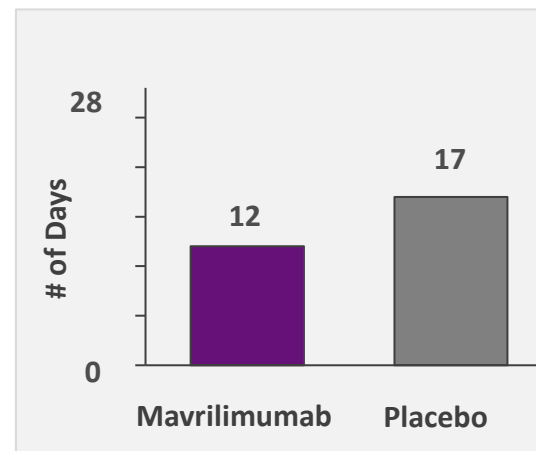
Mavrilimumab: 12 | Placebo: 17

The median (interquartile) duration of mechanical ventilation was shorter in the mavrilimumab arm (12 [9.0, 18.0] days) compared to the placebo arm (17 [11.0, 24.5] days). 4 of the 5 patients who progressed to mechanical ventilation in the mavrilimumab arm had recovered by Day 28, whereas all patients in the placebo arm who progressed to mechanical ventilation had died by Day 28.

Death by Day 60

Mavrilimumab: 1 | Placebo: 4

There was 1 death (4.8%) in the mavrilimumab arm by Day 28, compared to 3 deaths (15.8%) in the placebo arm (nominal p=0.222). By Day 60 there was 1 death (4.8%) in the mavrilimumab arm, compared to 4 deaths (21.1%) in the placebo arm (nominal p=0.108).

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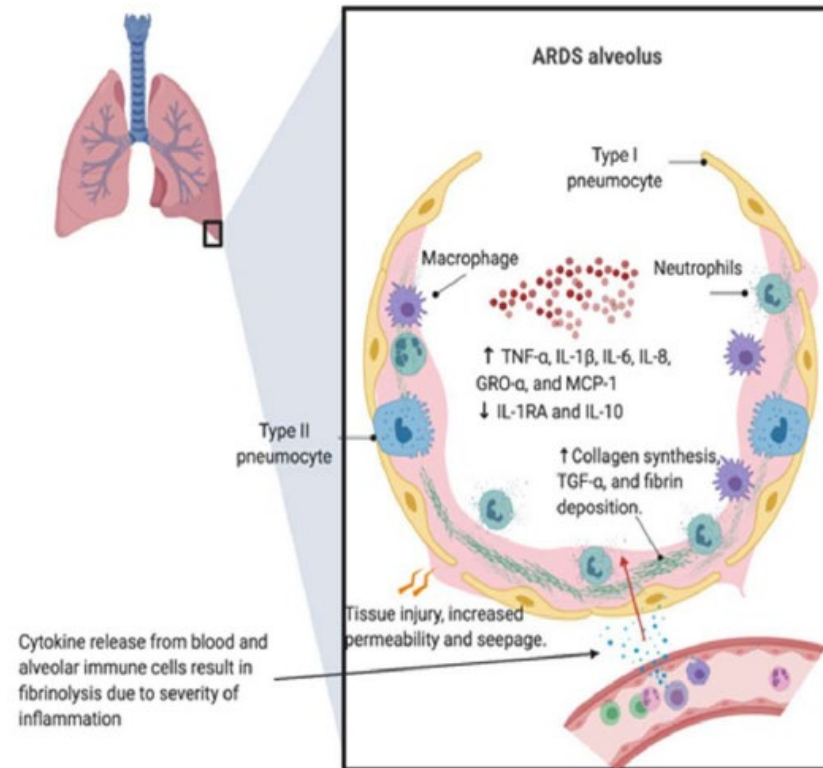
McGonale, et al., Autoimmunity Reviews (2020), https://doi.org/10.1016/j.autrev.2020.102537

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

Clinician-recognized Adult ARDS

US Population	318,498,500[1]
Adults	242,620,800[1]
Incidence of acute respiratory failure	784 per 100,000[2] - **1,902,147**
ARDS	16.1%[2] – **306,245**

All Adult ARDS Patients

US Population	318,498,500[1]
Adults	242,620,800[1]
ICU yearly admissions	4,000,000[4]
ARDS (Berlin criteria[5])	21.53%[6] - **861,200**
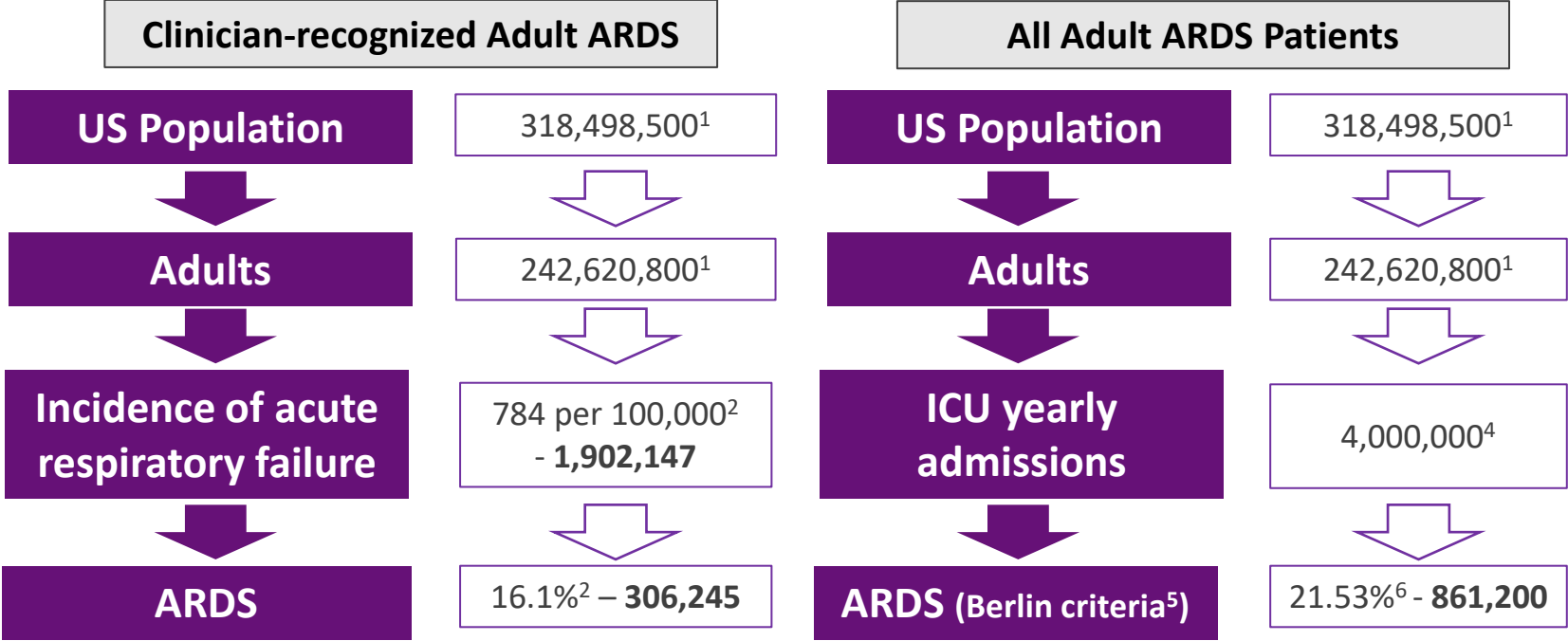
- Excludes ARDS associated with COVID-19
- Pediatric ARDS occurs less often
- Most common causes of ARDS are pneumonia (59%) and sepsis (16%)[3]
- 84.5% of ARDS cases require mechanical ventilation[7]
- Considerable mortality (~40%[8]) with no effective treatments outside mechanical ventilation

~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

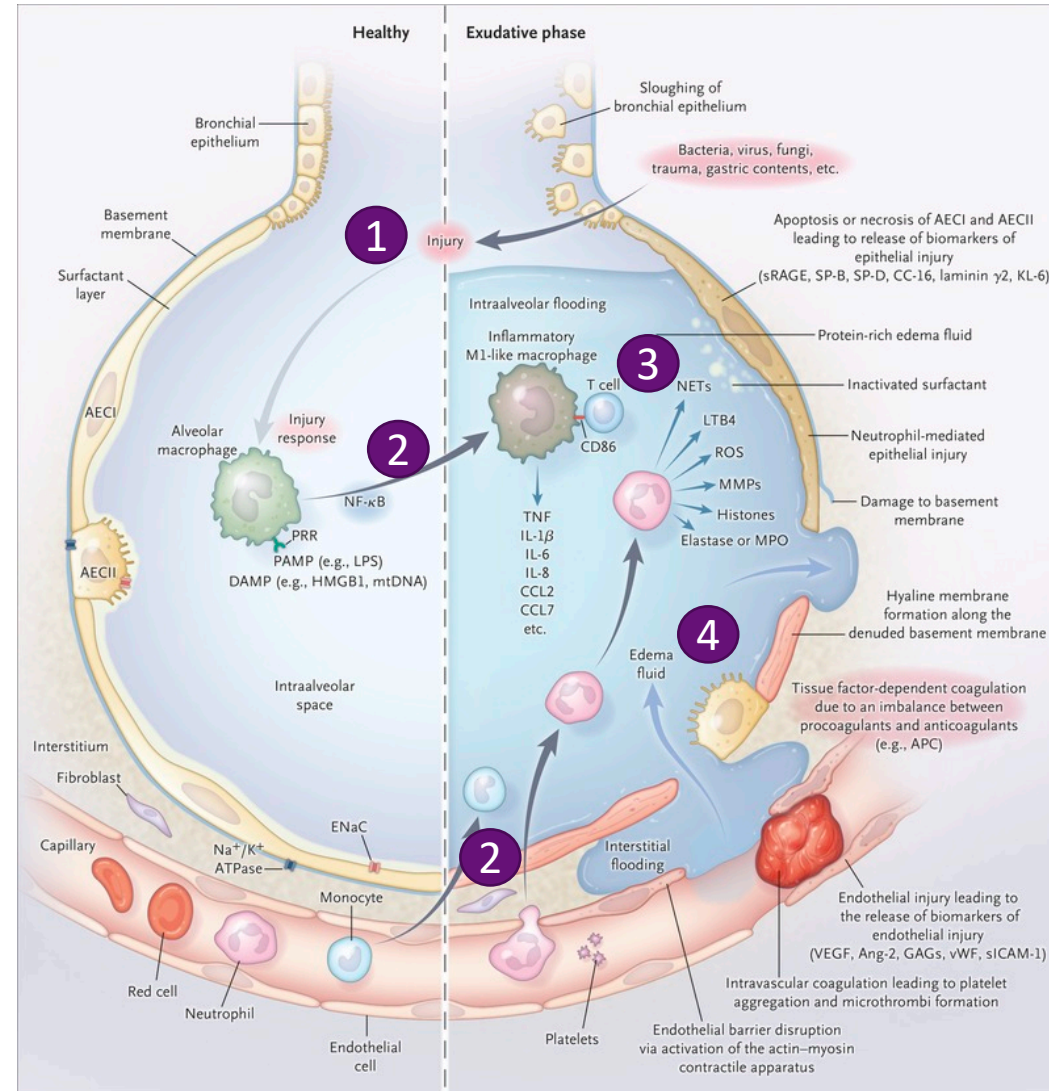# Cytokine Cascade Amplification System in the Pathophysiology of ARDS

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

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

Pathophysiology of ARDS (Exudative Phase)

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.

19

ARDS = Acute Respiratory Distress Syndrome
The New England Journal of Medicine. 2017

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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]	√	√	√

- Neutrophils Increased longevity
- NET formation

- PMN recruitment
- Inflammation
- Tissue Injury

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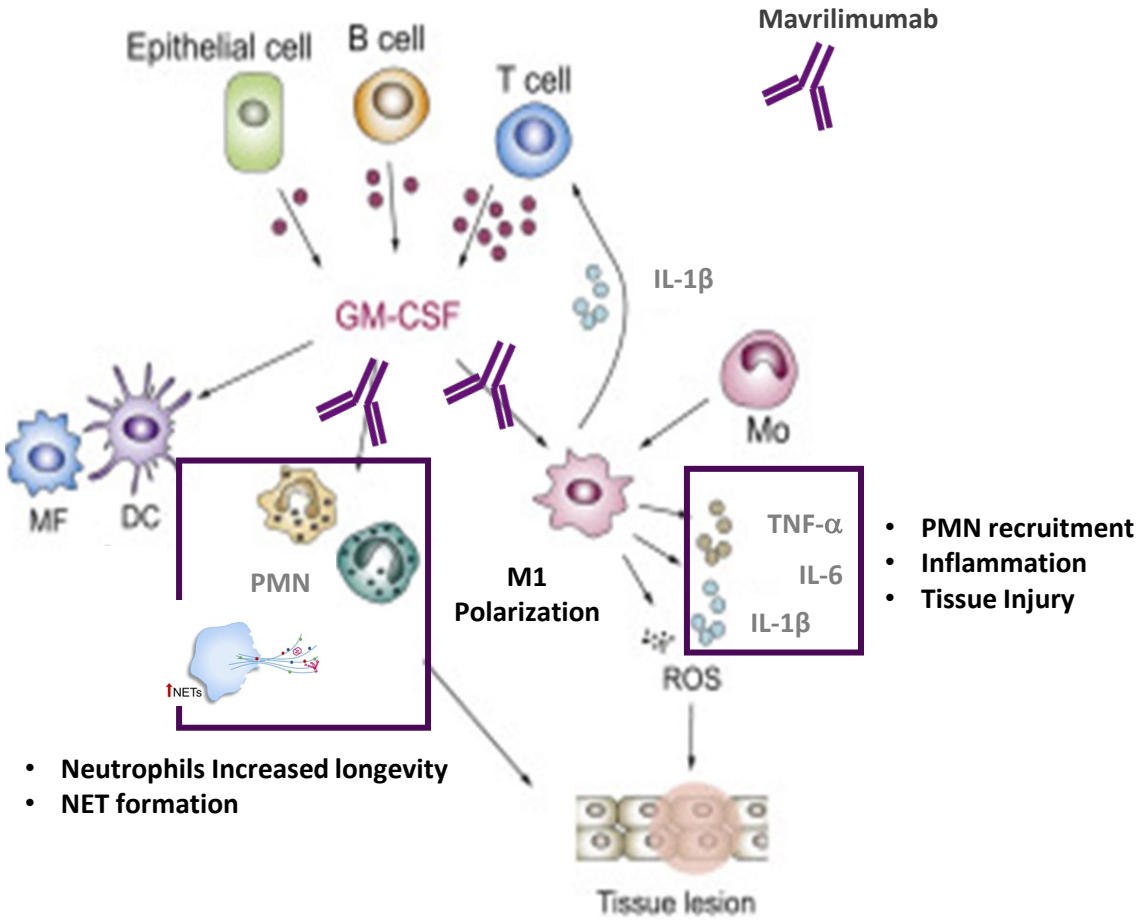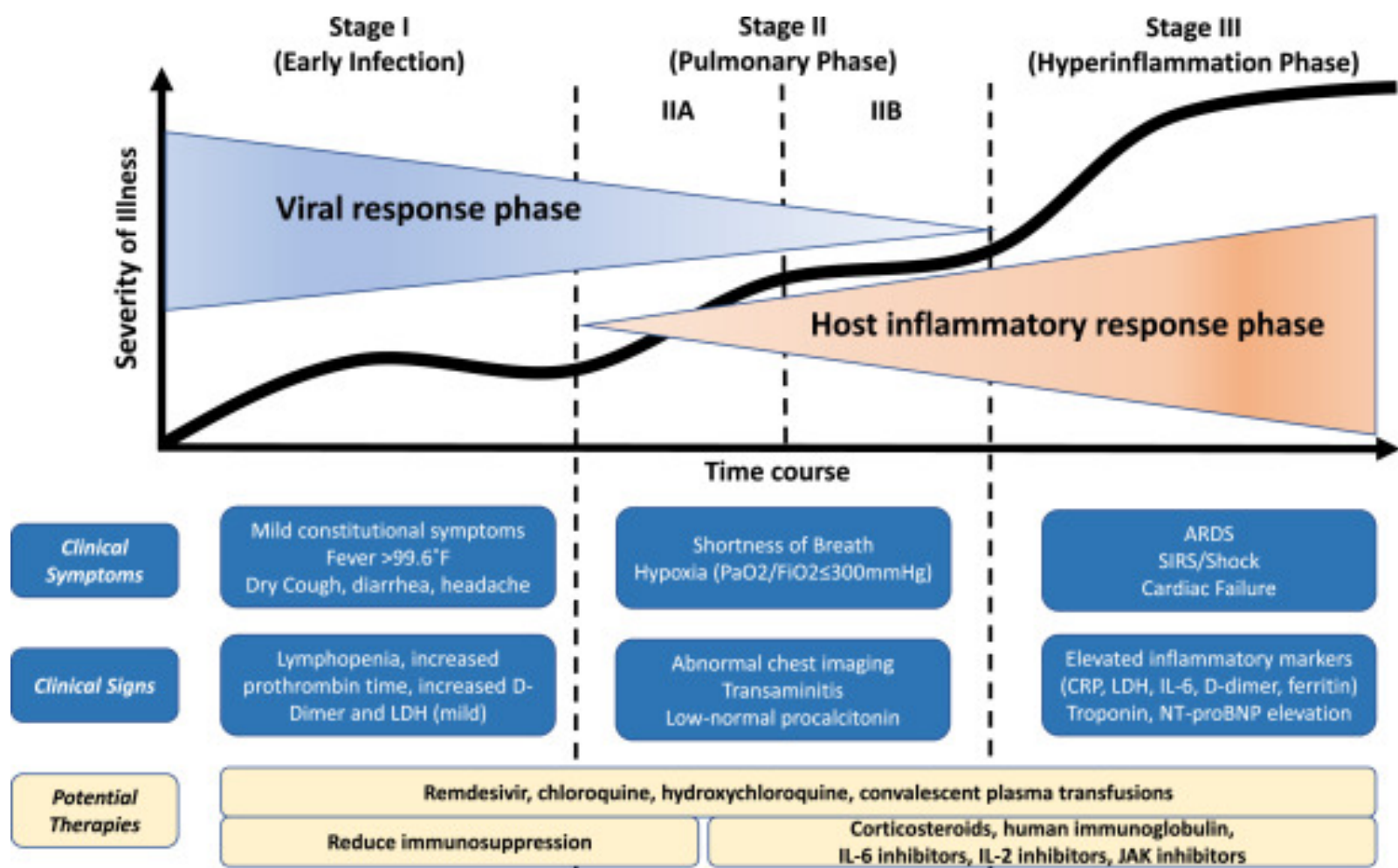
Source:
Hasan K. Siddiqi MD, MSCR , Mandeep R. Mehra MD, MSc , COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal, Journal of Heart and Lung Transplantation (2020), doi: https://doi.org/10.1016/j.healun.2020.03.012

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