mesoblast

the regenerative medicine company

# Top-line Results for Remestemcel-L in COVID-19 ARDS

## 2021 Stem Cells, Cell Therapies, and Bioengineering in Lung Biology and Diseases

JULY 2021

ASX: MSB; Nasdaq: MESO

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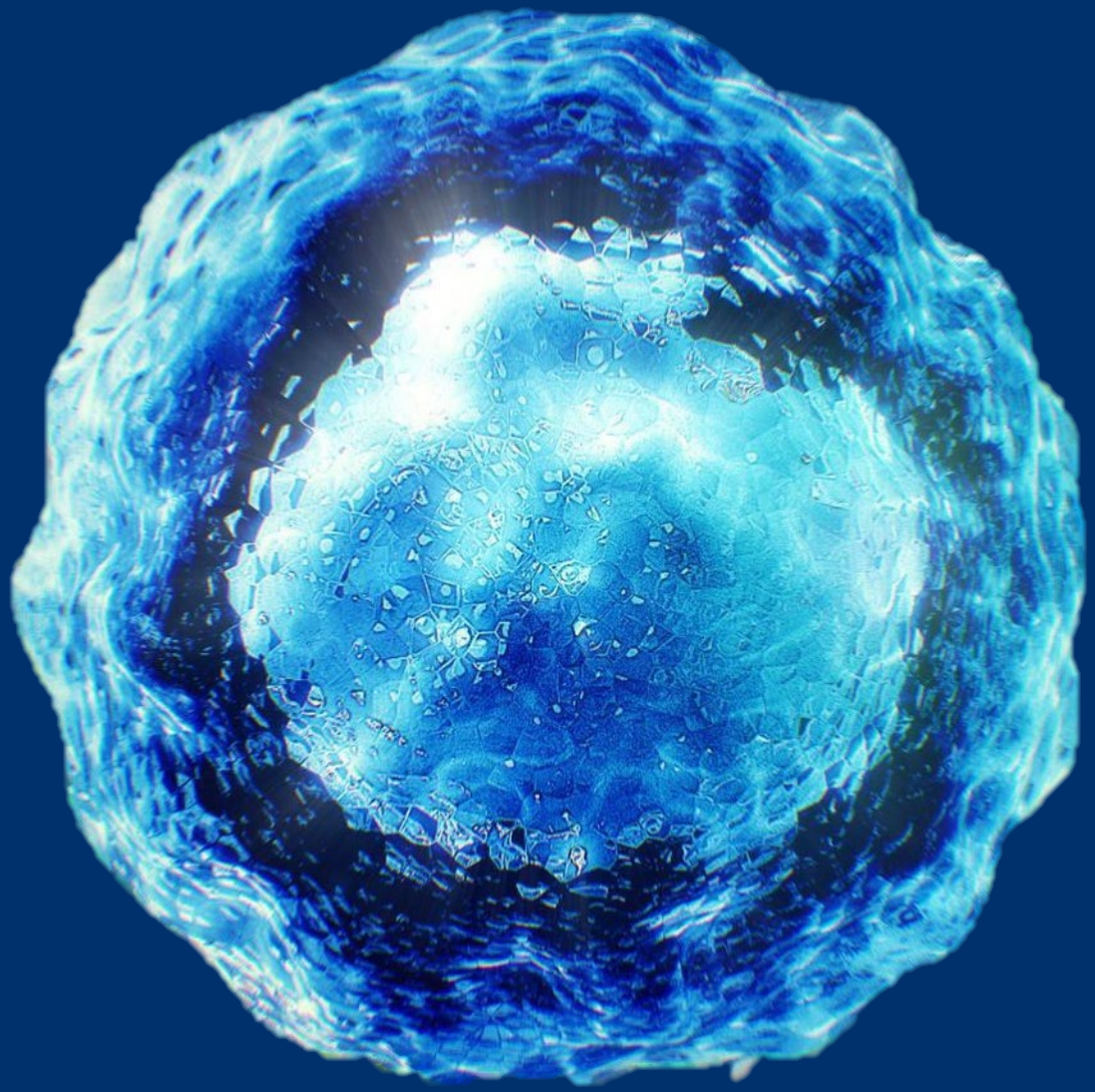
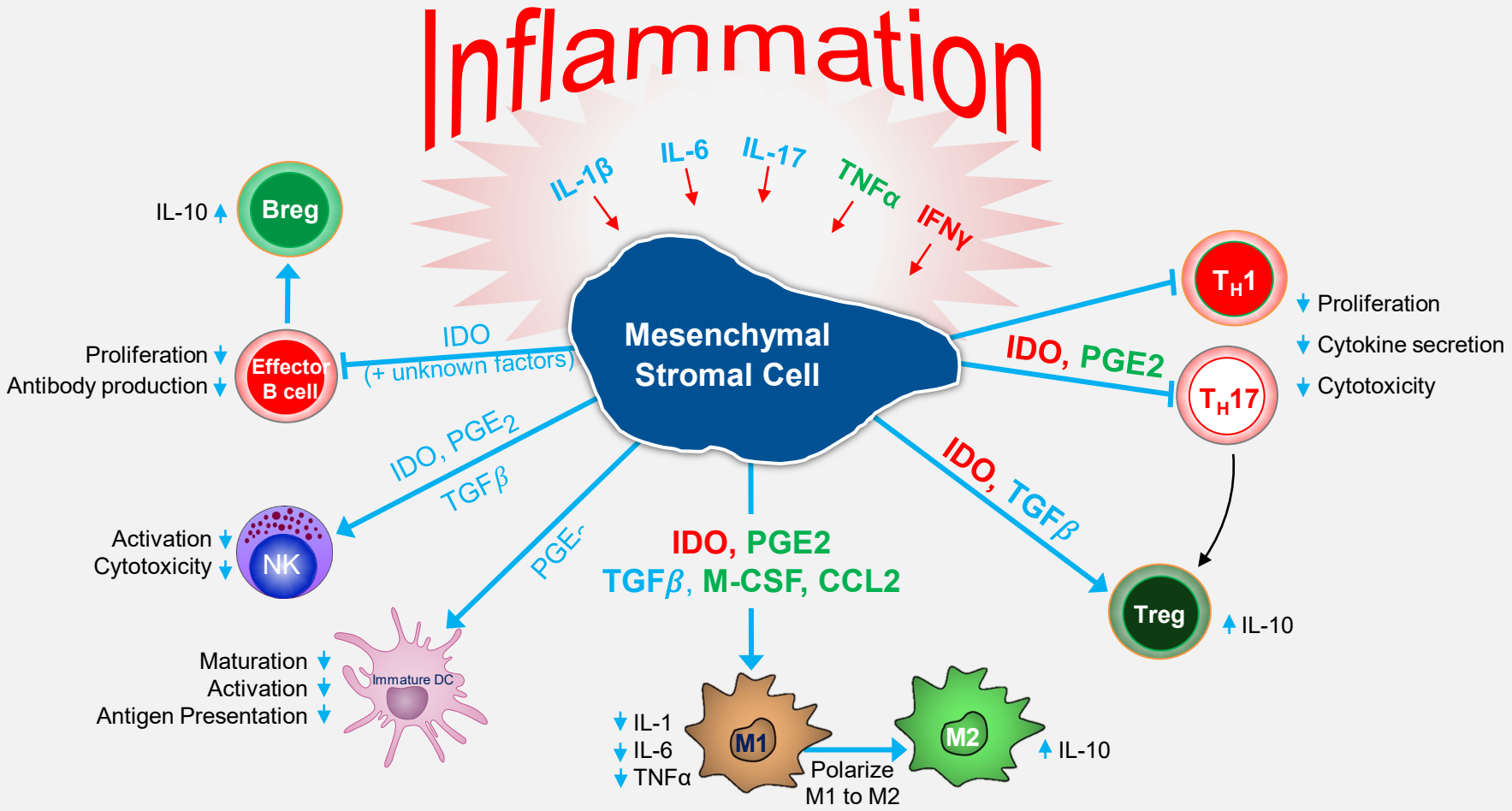
# Our Mission

Mesoblast is committed to bringing to market innovative cellular medicines to treat serious and life-threatening illnesses



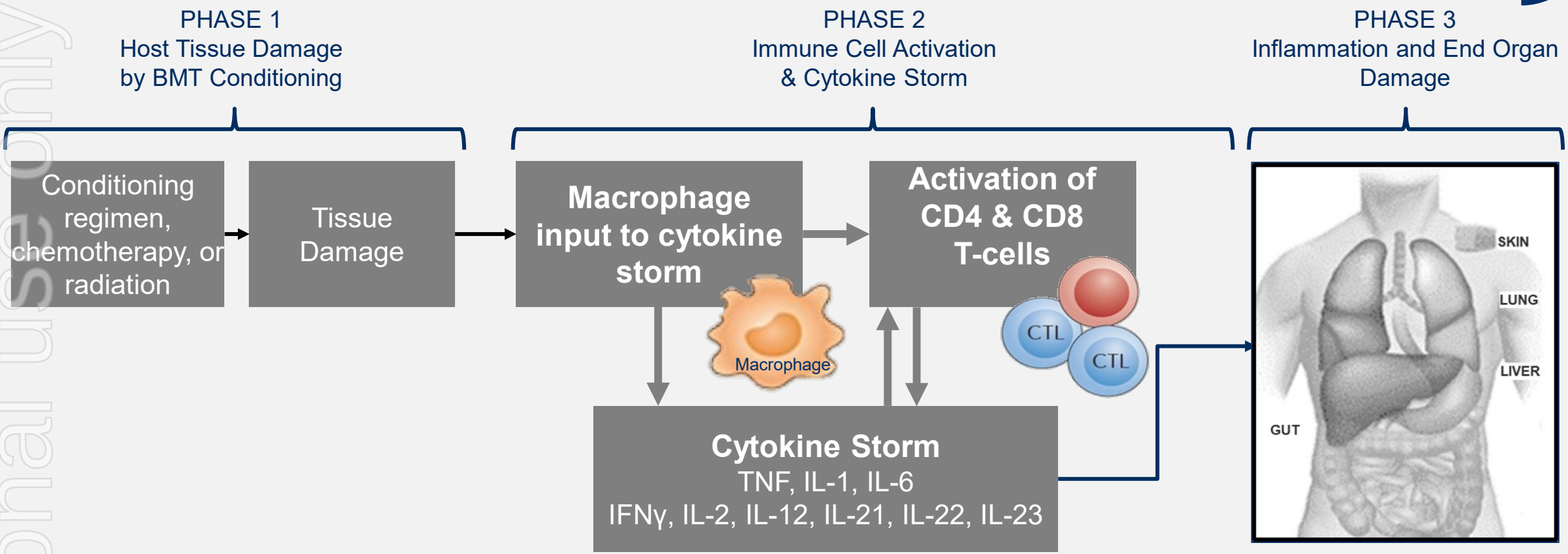
# Platform Technology – Mechanism of Action (MOA)

Our mesenchymal stromal cells respond to and are activated by multiple inflammatory cytokines through surface receptors, resulting in orchestration of an anti-inflammatory cascade




Source: Data on file

# Acute Graft versus Host Disease (GVHD): A Prototypic Disease Driven by Cytokine Storm




Modified from Blazar et al., Nature Reviews Immunology 12: 443 – 458

# Remestemcel-L in Steroid Refractory Acute GVHD: Clinical Evidence for a MOA Applicable to Various Inflammatory Conditions

## Consistent efficacy and safety outcomes in a total of 309 children from three studies:

- Remestemcel-L was used as first-line therapy in a randomized controlled Phase 3 trial of 260 patients, with SR-aGVHD, including 27 children
- Remestemcel-L was used as salvage therapy in an expanded access program in 241 children with SR-aGVHD, 80% of whom had Grade C/D disease, and failed institutional standard of care
- Remestemcel-L was used as first-line therapy in Mesoblast's open-label Phase 3 trial in 54 children with SR-aGVHD, 89% of whom had Grade C/D disease

| | | Protocol 280 (pediatric) | | EAP 275 | Study 001 |
|---|---|---|---|---|---|
| | MAGIC[1] N=30[2] | Placebo N=13 | Remestemcel-L N=14 | Remestemcel-L N=241 | Remestemcel-L N=54[3] |
| **Day 28 Overall Response** | **43%** | **38%** | **64%** | **65%** | **69%** |
| **Day 100 Survival** | **57%** | **54%** | **79%** | **66%** | **74%** |

Source: ODAC Advisory Committee Briefing Document and Presentation August 2020.

1. Mount Sinai Acute GVHD International Consortium (MAGIC) - a group of ten BMT centers throughout the US and Europe whose purpose is to conduct ground-breaking clinical trials in GVHD, including developing informative biorepositories that assist in developing treatments that can guide GVHD therapy.
2. Two subjects in the MAGIC cohort had follow-up <100 days; these subjects are excluded from the respective survival analyses.
3. GVHD001 had 55 randomized patients, however one patient dropped out before receiving any dose of remestemcel-L

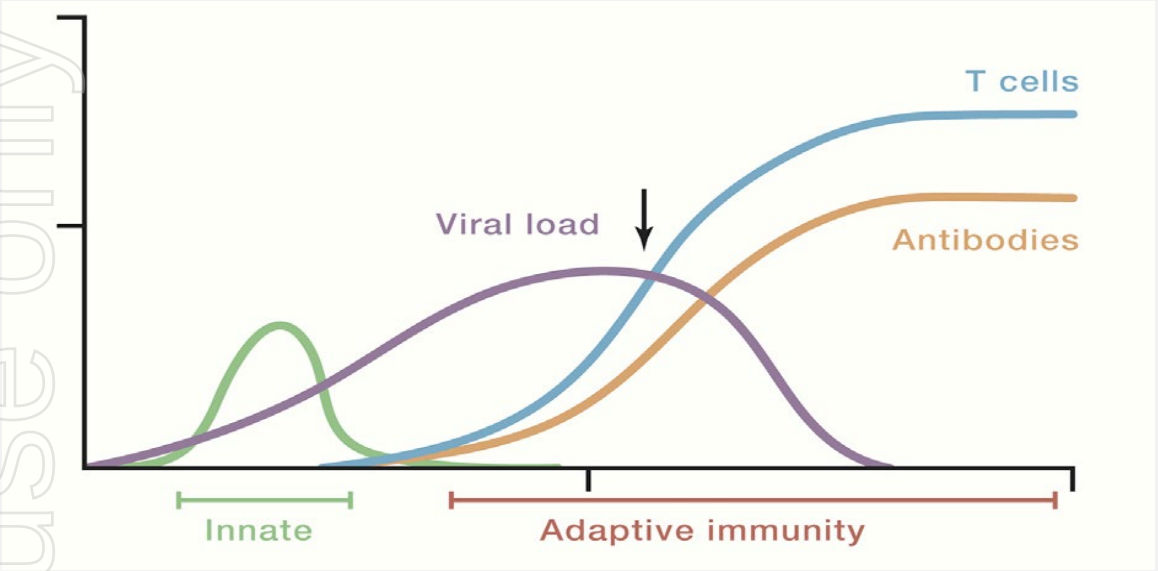
# Cytokine Storm in COVID-19 ARDS Closely Resembles Secondary Hemophagocytic Lymphohistiocytosis (sHLH): A T Cell Driven Disease

- Secondary (or acquired) hemophagocytic lymphohistiocytosis (sHLH) is a life-threatening disease characterized by lymphocyte and macrophage hyperinflammation triggered by viral infections such as EBV, CMV, HHV)[1]
- Lung involvement including ARDS is common and of poor prognosis (>50% mortality)[2]
- Hematological manifestations involve severe anemia due to activated macrophages engulfing red blood cells.
- Excessive immune activation driven by cytotoxic T cells and macrophages resulting in cytokine storm and release of IFN-$\gamma$, IL-6 and TNF-$\alpha$, and reduction in regulatory T cells[3]
- Activated CD8 T cells producing IFN-$\gamma$ appear to be central to disease pathogenesis

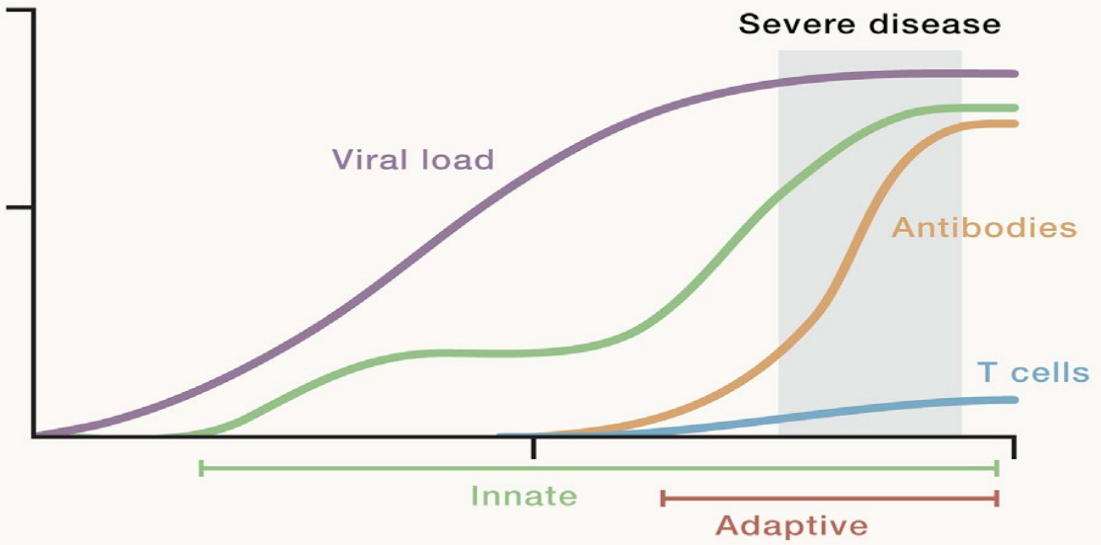

1. Bode et al. Recent advances in the diagnosis and treatment of hemophagocytic lymphohistiocytosis. *Arthritis Res Ther*. 2012 Jun 8;14(3):213
2. Seguin et al. Pulmonary Involvement in Patients With Hemophagocytic Lymphohistiocytosis. *Chest*. 2016 May;149(5):1294-301
3. Humblet-Baron et at. IFN-γ and CD25 drive distinct pathological features during hemophagocytic lymphohistiocytosis. *J Allergy Clin Immunol*. 2019 Jun; 143(6): 2215–2226.e7

# Robust Adaptive *Naïve* T Cell Response in COVID-19 is Critical for Viral Clearance
# Lack of Adequate T Cell Response Results in Increased Viral Load and Severe Disease

**Average SARS2 infection**




**Severe SARS2 infection**




- Analysis of SARS-CoV-2-specific adaptive immune responses during acute COVID-19 identifies coordination between SARS-CoV-2-specific CD4 T cells and CD8 T cells to limit disease severity
- Aged individuals often exhibit uncoordinated adaptive responses, potentially tied to scarcity of naive T cells highlighting immunologic risk factors linked to disease severity



Rydyznski Moderbacher et al., Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity. 2020, Cell 183, 996–1012; doi.org/10.1016/j.cell.2020.09.038
Sette A and Crotty S. Adaptive immunity to SARS-CoV-2 and COVID19.https://doi.org/10.1016/j.cell.2021.01.007

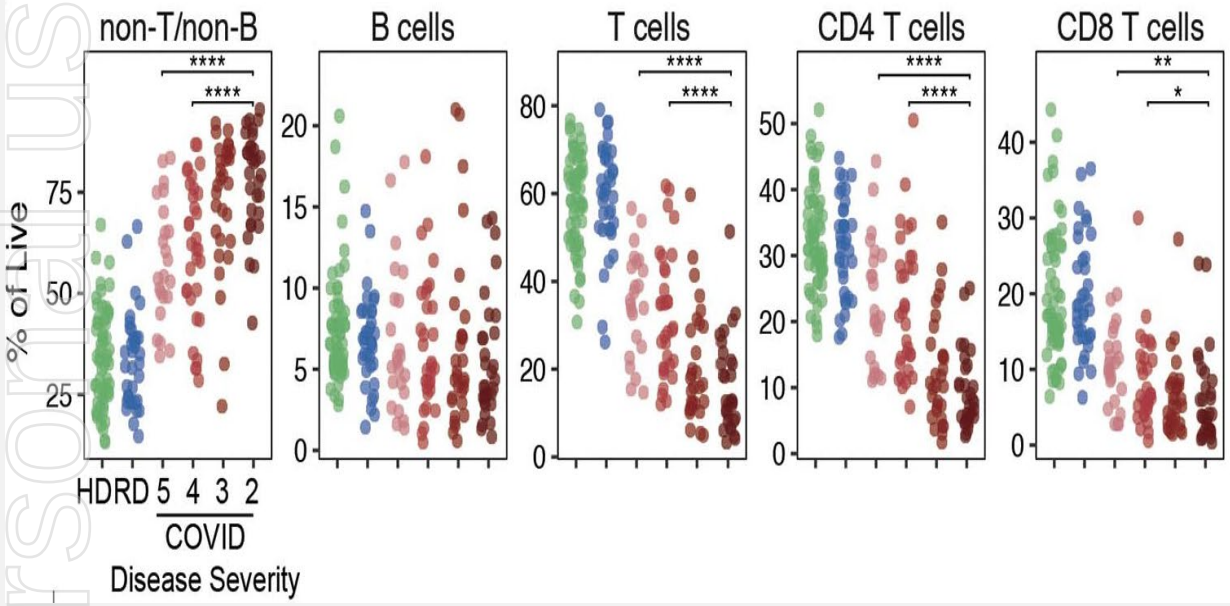
# Severe COVID-19 Disease is Associated with Progressive **Depletion** of *Naïve* T Cells, and Aberrant **Activation** of *Non-Naïve* CD4 and CD8 T Cells

| | | |
|---|---|---|
| Death | COVID 1 | Death |
| | COVID 2 | Invasive mechanical ventilation |
| | COVID 3 | Non-invasive ventilation |
| | COVID 4 | Supplemental Oxygen |
| | COVID 5 | No supplemental Oxygen; Requires medical care |
| | COVID 6 | No supplemental Oxygen; No medical care |
| | COVID 7 | Limitation in activities and/or requiring Oxygen |
| Mild | COVID 8 | No limitation in activities |

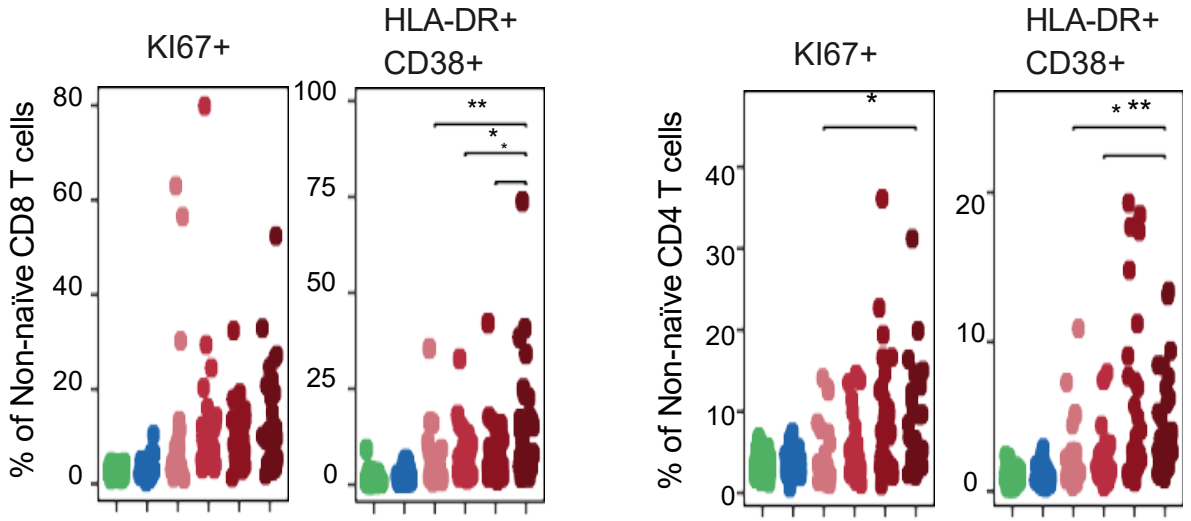
Hospitalization

Based off NIH Ordinal Scale

## *Naïve T Cells*




## *Non-Naïve Activated T Cells*




Frequencies of activated CD8 or CD4 T cells, shown as percent of non-naïve CD8 and CD4 T cells expressing KI67⁺ and HLA-DR⁺CD38⁺



D. Mathew et al., Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications Science 369, eabc8511 (2020). DOI:10.1126/science.abc8511

# Severity of COVID-19 Infection is Associated with Increased Activated T Cells Producing IFN-γ and GM-CSF

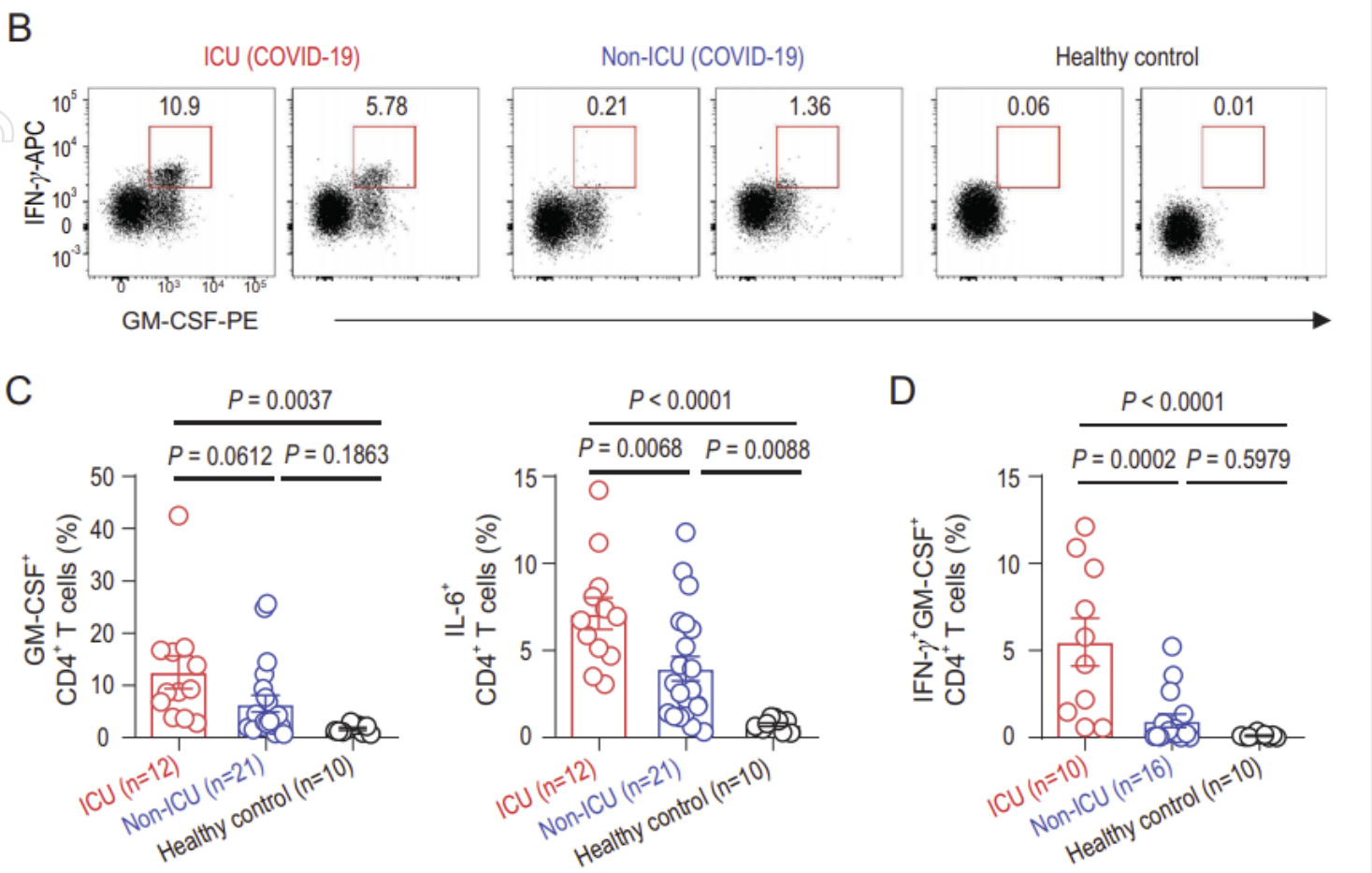



Figure: Pathogenic Th1 cells with high expression of GM-CSF in COVID-19 patients.

(B) Representative density plots showing an analysis of co-expression of GM-CSF and IFN-γ in gated CD45+CD3+CD4+ T-cells isolated from peripheral blood in healthy controls, ICU and non-ICU patients of COVID-19.

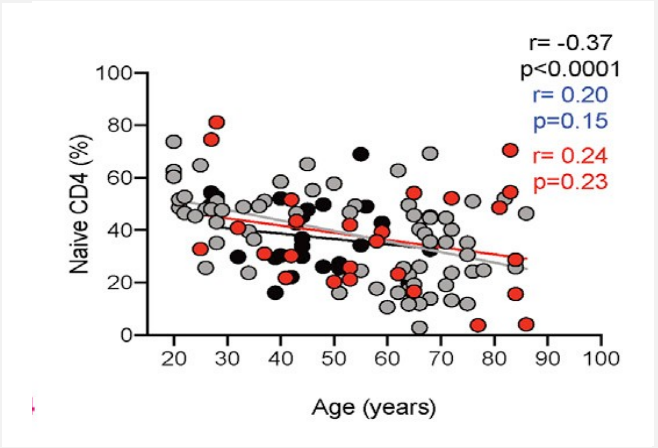
(C) Statistics calculated by the percentage of GM-CSF+ or IL-6+ cells from CD4+ T-cells.

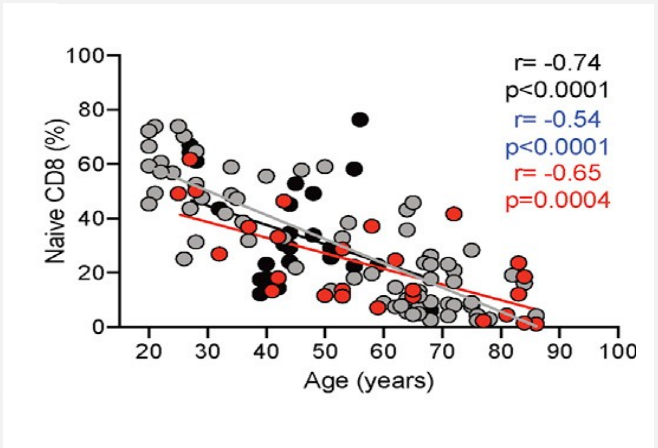
(D) Statistics calculated by the percentage of GM-CSF+ and IFN-γ + co-expressing CD4+ T-cells. Data represent the mean ± SEM. One-way ANOVA. P < 0.05 was considered statistically significant.

Zhou Y, et al. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. Natl Sci Rev. 2020;nwaa041

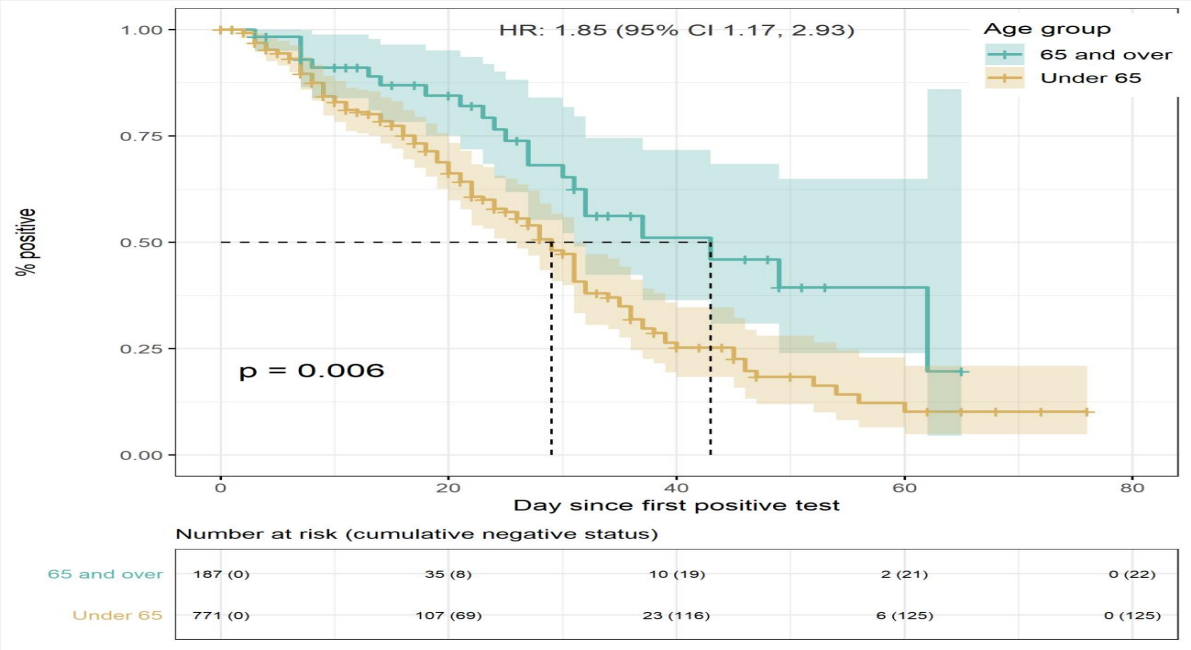
# Age > 65 years is Associated with Reduced Naïve T Cell Response to SARS-CoV-2, Delayed Viral Clearance and Greater Disease Severity

Naïve CD4 and CD8 T Cells reduced in age > 65

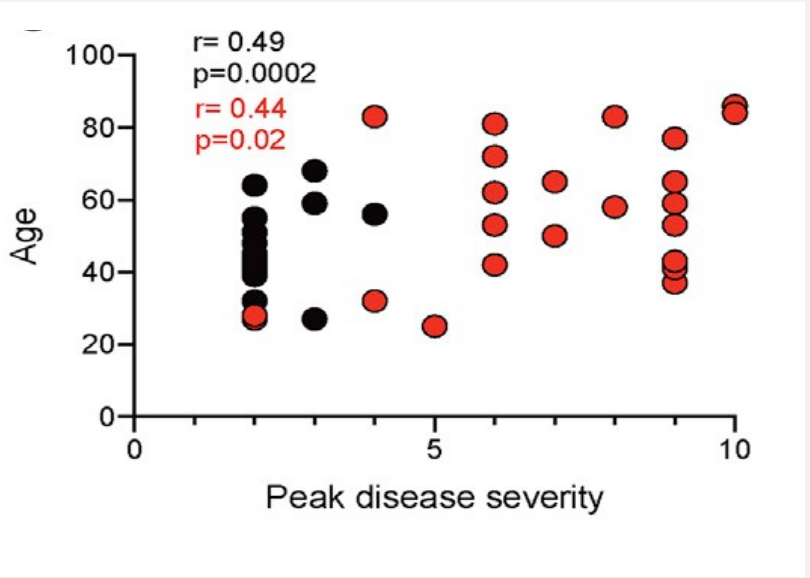



Median duration to negative status longer in subjects over 65 years (43 days) compared with under 65 years (29 days)




Age > 65 associated with greater COVID-19 peak disease severity



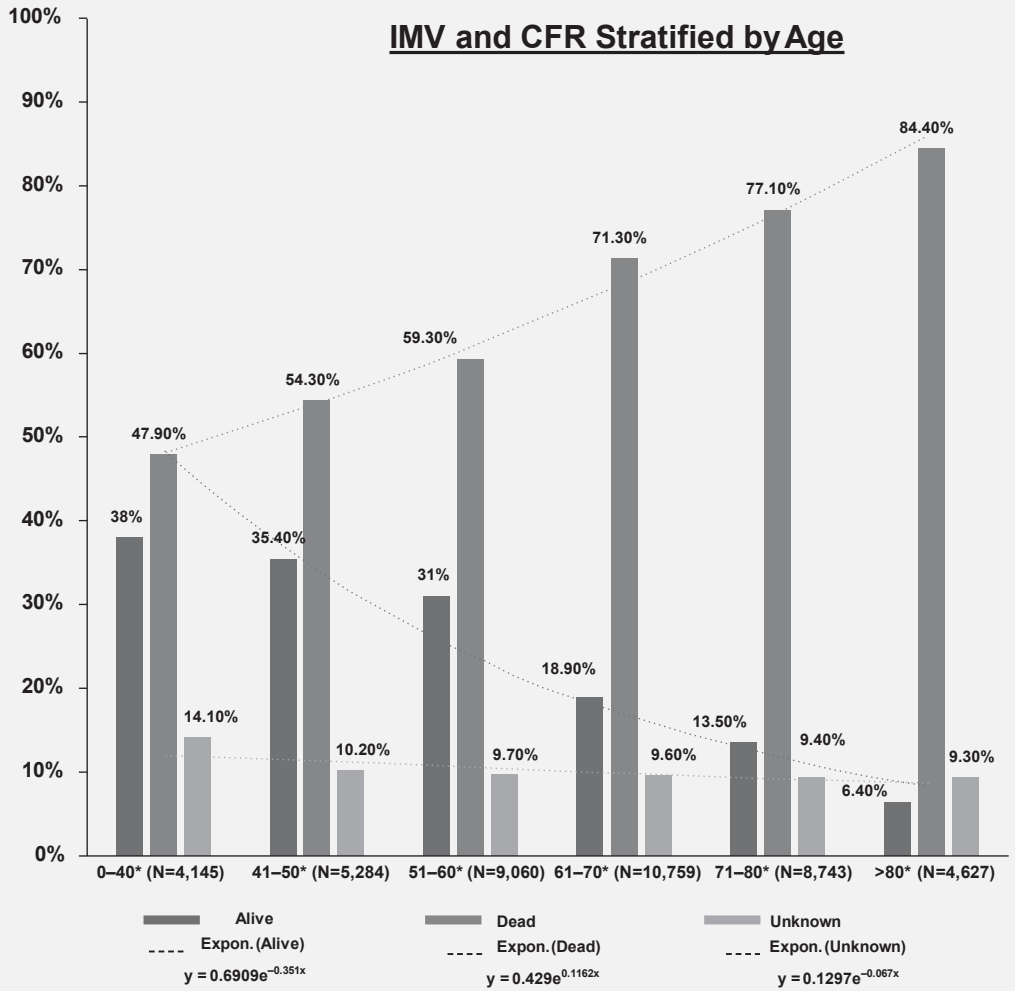



Rydyznski Moderbacher et al., Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity. 2020, Cell 183, 996–1012; doi.org/10.1016/j.cell.2020.09.038
Stehlik P et al. Repeat testing for SARS-CoV-2: persistence of viral RNA is common, and clearance is slower in older people. Medical Journal of Australia 2021; doi:10.5694/mja2.51036

# Meta-Analysis of Case Fatality Rates (CFR) for COVID-19 Patients on Invasive Mechanical Ventilation (IMV): Mortality Significantly Increases with Age

| Age | Alive n (%, 95% CI) | Dead n (%, 95% CI) | Unknown n (%, 95% CI) |
|---|---|---|---|
| ≤40* (N=4,145) | 1,575 (38.0, 36.5–39.5) | 1,985 (47.9, 46.4–49.4) | 585 (14.1, 13.1–15.2) |
| 41–50* (N=5,284) | 1,872 (35.4, 34.1–36.7) | 2,870 (54.3, 53.0–55.7) | 542 (10.2, 9.5–11.1) |
| 51–60* (N=9,060) | 2,809 (31.0, 30.1–32.0) | 5,373 (59.3, 58.3–60.3) | 878 (9.7, 9.1–10.3) |
| 61–70* (N=10,759) | 2,033 (18.9, 18.2–19.6) | 7,676 (71.3, 70.5–72.2) | 1,050 (9.6, 9.2–10.3) |
| 71–80* (N=8,743) | 1,180 (13.5, 12.8–14.2) | 6,740 (77.1, 76.2–78.0) | 823 (9.4, 8.8–10.0) |
| >80* (N=4,627) | 295 (6.4, 5.7–7.1) | 3,903 (84.4, 83.3–85.4) | 429 (9.3, 8.5–10.1) |

Reported case fatality rates for patients receiving invasive mechanical ventilation stratified by age, reported in six studies. *Age stratification for ICNARC was 16–39, 40–49, 50–59, 60–69, 70–79, and >80. CFR = case fatality rate; CI = confidence interval; Expon. = exponential; ICNARC = Intensive Care National Audit and Research Centre; IMV = invasive mechanical ventilation.




Source: Am J Respir Crit Care Med Vol 203, Issue 1, pp 54–66, Jan 1, 2021. Sixty-nine studies were included, describing 57,420 adult patients with COVID-19 who received IMV. Fifty-four of 69 studies stated whether hospital outcomes were available but provided a definitive hospital outcome on only 13,120 (22.8%) of the total IMV patient population.

# Objectives of Immunomodulation with Remestemcel-L in COVID ARDS

MSCs have the potential to:

- Reduce activated *non-naïve* CD4 and CD8 T cells
- Reduce inflammatory cytokines produced by *non-naive* T cells to reduce macrophage and neutrophil influx, activation and cytokine storm
- Expand and enhance survival of *naïve* CD4 and CD8 T cells to accelerate viral clearance
- Improve pulmonary epithelial integrity

# Clinical Experience with Remestemcel-L in COVID-19 ARDS

## Emergency IND in Ventilator-Dependent COVID-19 ARDS

- 11 patients (10/11 were < 65 years) with moderate or severe ARDS on ventilators, received two infusions of remestemcel-L 2 million cells/kg within five days at Mt. Sinai Hospital in New York City
- Nine patients (82%) successfully came off ventilator and were discharged from the ICU
- Experience under the emergency IND informed the dosing regimen for the randomized controlled Phase 2b/3 trial, however no data on this dosing regimen in patients ≥ 65 years

## Phase 3 Randomized Controlled Trial in COVID-19 ARDS

- Multi-center, randomized, controlled, blinded study to assess safety and efficacy of remestemcel-L versus placebo in ventilator-dependent patients with moderate/severe ARDS due to COVID-19
- Up to 300 patients randomized 1:1 to receive placebo or two infusions of remestemcel-L within 3-5 days
- 222 patients enrolled before the study was stopped by DSMB as unlikely to meet primary endpoint of 43% overall mortality reduction
- The median age increased from 59 in the first half of the trial to 67 in the second half ($p<0.0001$)
- Preliminary results based on 60-day patient follow-up post randomization
- Pre-specified analysis of results stratified by age < or ≥ 65: 125 patients < 65 years, 97 patients ≥ 65 years

# Baseline Summary Data: Intent to Treat Patients Pre-Specified Age < 65 & ≥ 65

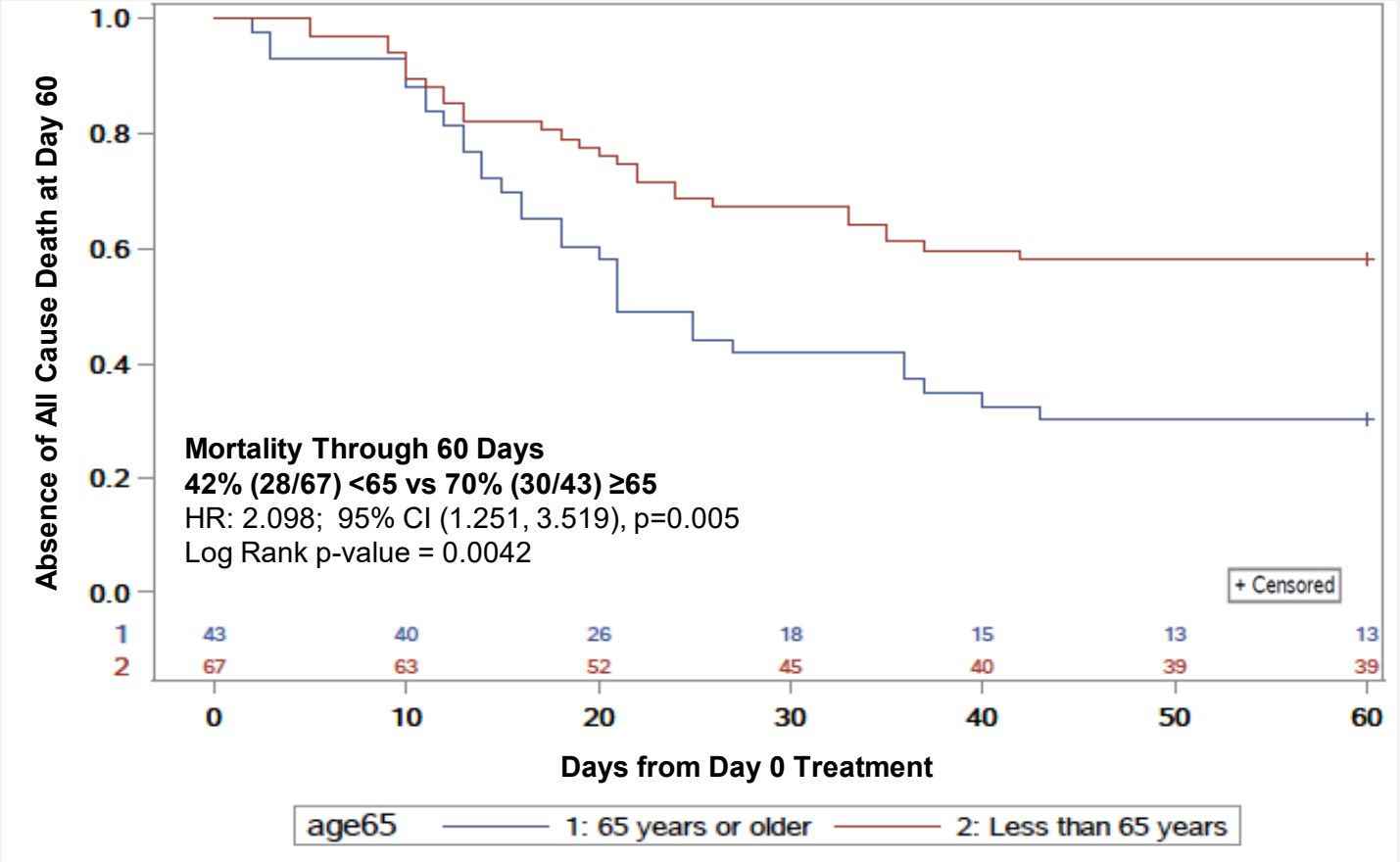
| Category | ITT Patients < 65 years | | ITT Patients ≥ 65 years | |
|---|---|---|---|---|
| | REM Mean n=58 | Control Mean n=67 | REM Mean n=54 | Control Mean n=43 |
| Sex (%)<br>Male<br>Female | <br>76%<br>24% | <br>70%<br>30% | <br>65%<br>35% | <br>65%<br>35% |
| **Age (Yrs)** | **52 (9.9)** | **51 (9.8)** | **72 (5.7)** | **73 (5.5)** |
| BMI (kg/m$^2$) | 34.1 (7.7) | 36.6 (8.2) | 32 (7) | 32(6) |
| CRP (mg/L) | 29.8 (58.8) | 19.5 (17.5) | 17.2 (27.8) | 26.4 (51.9) |
| **PF Ratio**<br>**ARDS Severity (mild, moderate, severe)** | **163 (79)**<br>**17.%, 48%, 24%**<br>**(11% missing or no ARDS)** | **144 (85)**<br>**9.%, 48%, 37%**<br>**(6% missing or no ARDS)** | **132 (50)**<br>**13.%, 57%, 28%**<br>**(2% missing or no ARDS)** | **150 (54)**<br>**14%, 67%, 14%**<br>**(5% missing or no ARDS)** |
| SOFA Score | 6.3 (2.4) | 6.6 (1.8) | 6.3 (2) | 6.4 (1.9) |
| Any Steroids at Baseline<br>Dexamethasone at Baseline | 67%<br>50% | 84%<br>67% | 98%<br>78% | 93%<br>67% |
| Remdesivir at Baseline | 62% | 63% | 72% | 74% |
| Anti-IL6 at Baseline | 3% | 4% | 7% | 5% |

# Baseline Summary Data: Increased Co-Morbid Conditions in Patients ≥ 65

| All Patients - ITT | ITT Patients < 65 years | | ITT Patients ≥ 65 years | | < 65 vs ≥ 65 |
|---|---|---|---|---|---|
| | REM Mean n=58 | Control Mean n=67 | REM Mean n=54 | Control Mean n=43 | Chi-Squared P-Value |
| **Medical History** | | | | | |
| COPD | 2% | 1% | 13% | 12% | 0.0004 |
| Asthma | 10% | 10% | 6% | 9% | |
| Pulmonary Fibrosis. | 0% | 0% | 4% | 0% | |
| CF | 0% | 0% | 0% | 0% | |
| MI last 12 months | 0% | 0% | 2% | 2% | |
| CHF | 2% | 6% | 9% | 0% | |
| Cancer | 3% | 4% | 19% | 19% | 0.0002 |
| Renal Disease | 7% | 7% | 19% | 19% | 0.0047 |
| Immunological Disorder | 3% | 3% | 4% | 2% | |
| Smoker | 27% | 27% | 43% | 37% | 0.0464 |
| Hepatic | 7% | 0% | 0% | 12% | |
| Diabetes | 45% | 36% | 39% | 42% | |
| Hypertension | 50% | 49% | 67% | 70% | 0.0069 |
| Neurological | 5% | 1% | 13% | 7% | 0.0074 |

# Greater Mortality through Day 60 in Control Patients Older than 65, Consistent with Other Trials

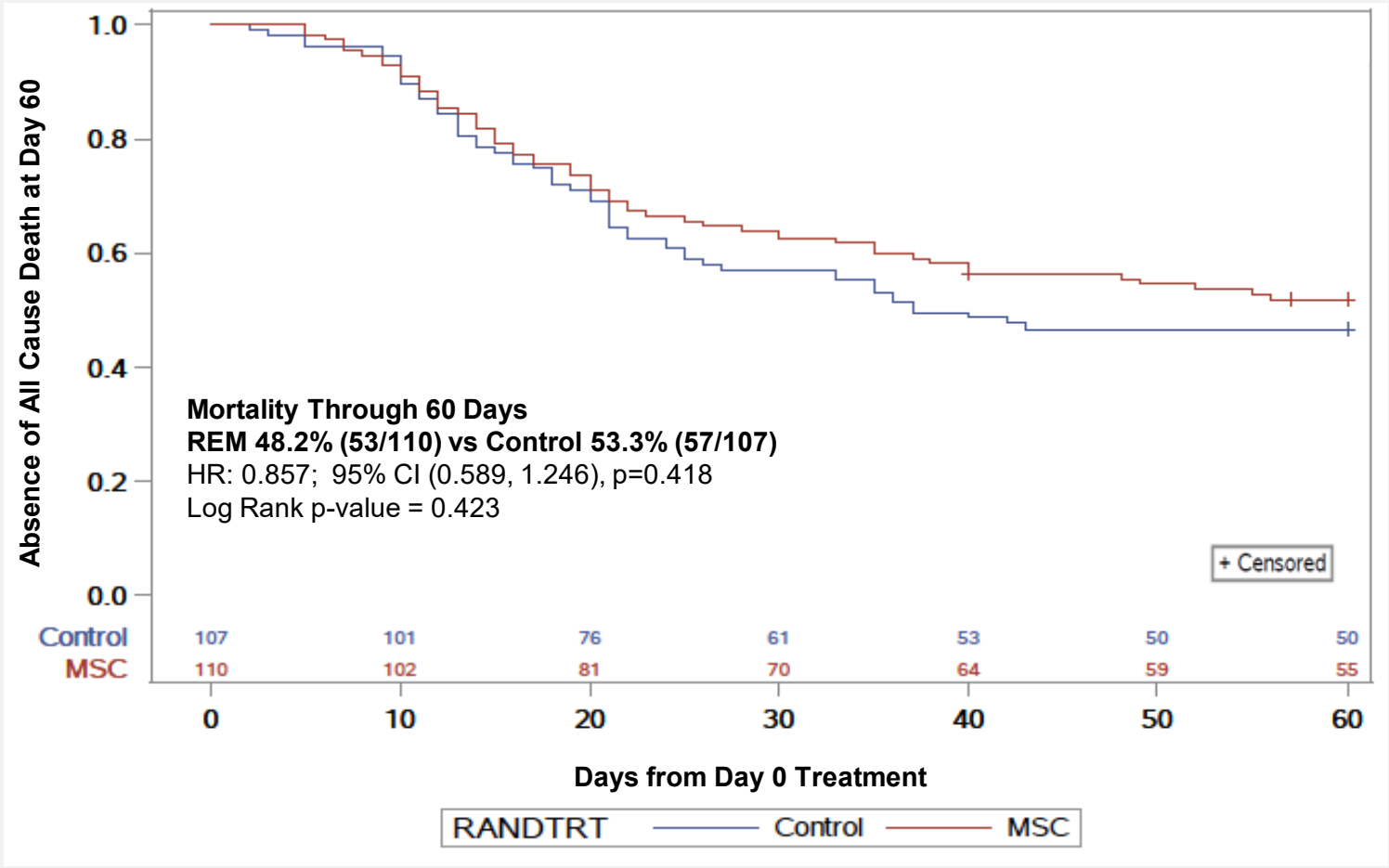
Controls Age < 65 vs ≥ 65 (n=110)



# Remestemcel-L vs Controls with COVID-19 ARDS: Mortality through 60 Days in Treated Patients

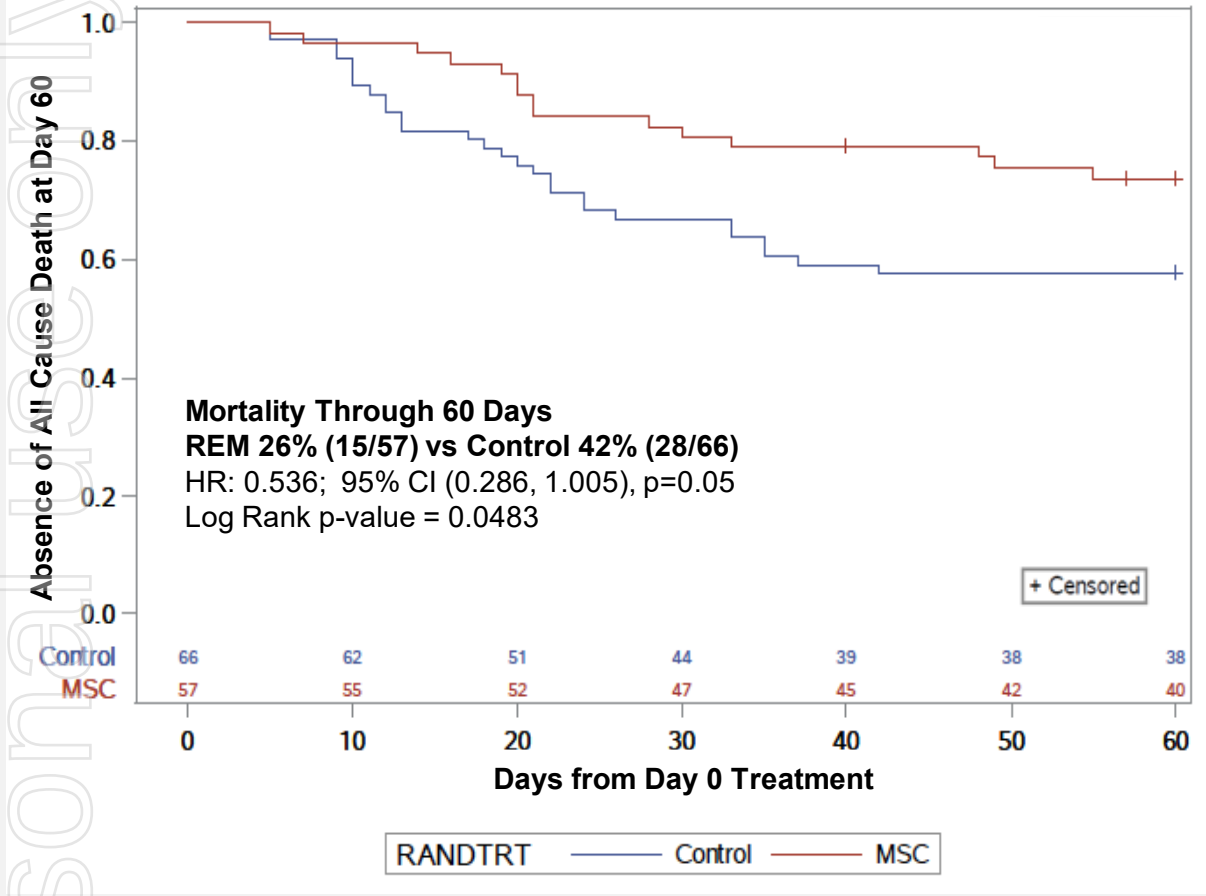


All **Modified Intent to Treat** Patients (n=217), Remestemcel-L vs Control

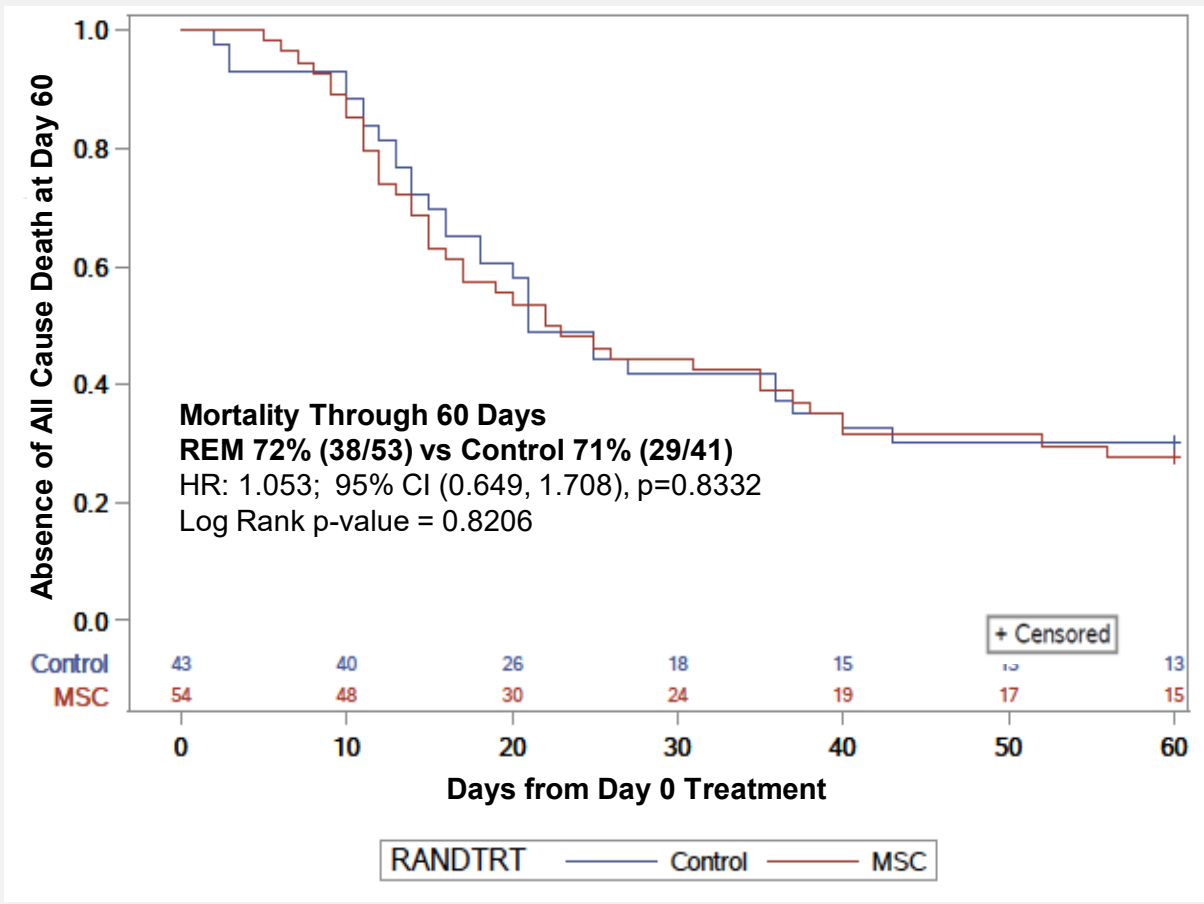


# Remestemcel-L vs Controls:
# Pre-Specified Mortality Analysis through 60 Days < or ≥ 65 Years Old

Modified Intent to Treat Patients **< 65 years old** (n=123)
REM vs Control

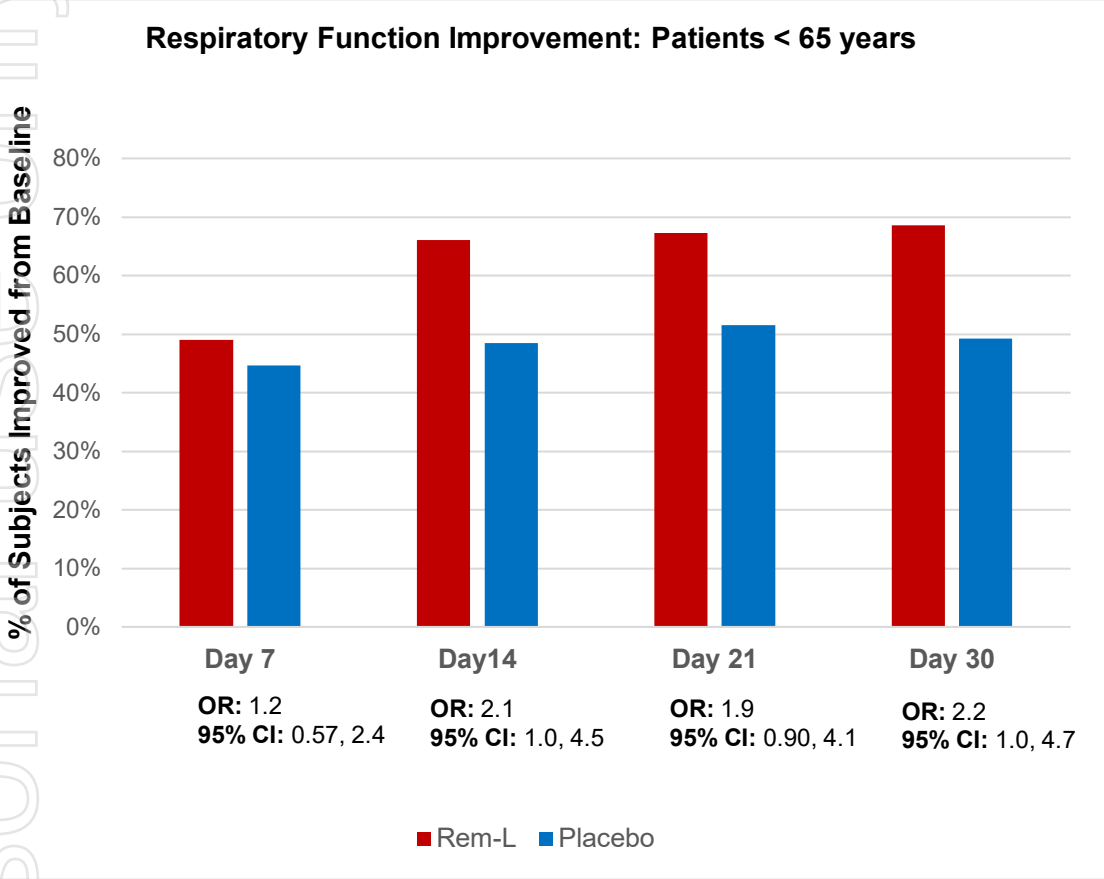



Modified Intent to Treat Patients **≥ 65 years old** (n=94)
REM vs Control

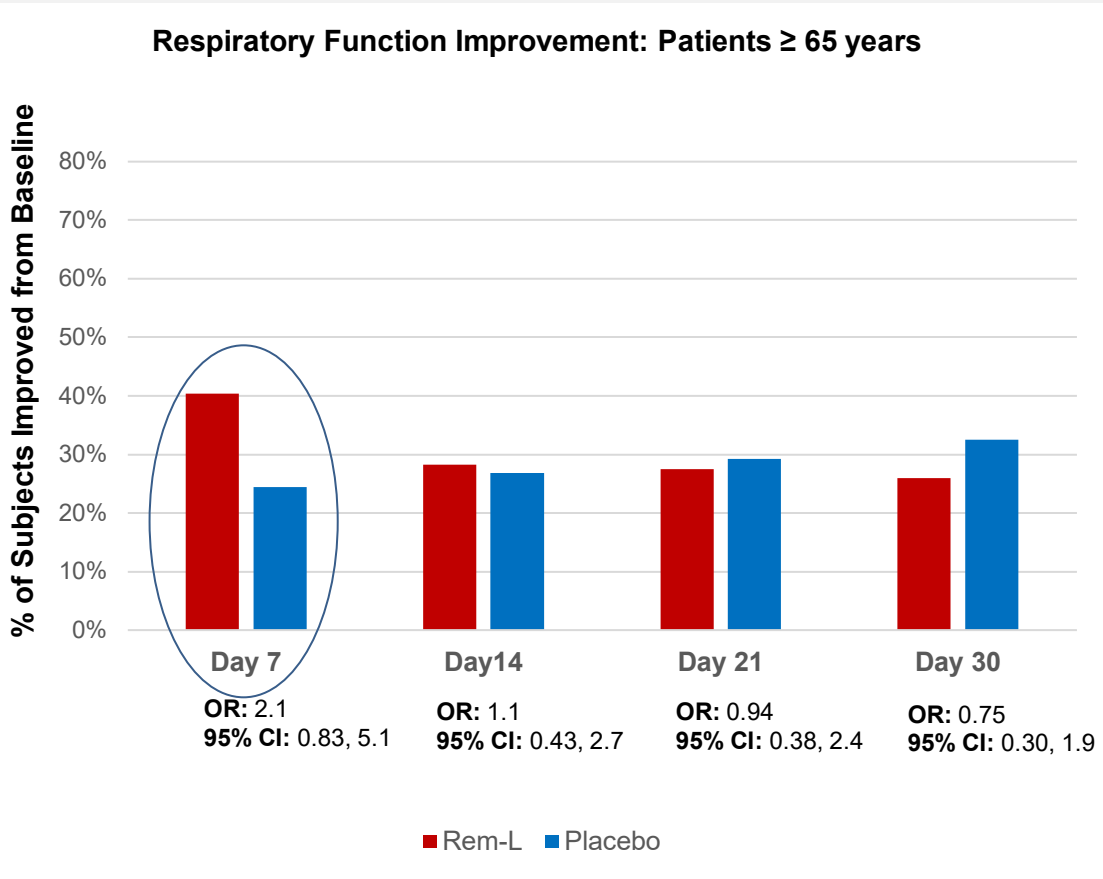


# Remestemcel-L vs Controls: Analysis of Respiratory Function Improvement*

## Treated Patients (mITT) **< 65 years old** (n=123) Remestemcel-L vs Control

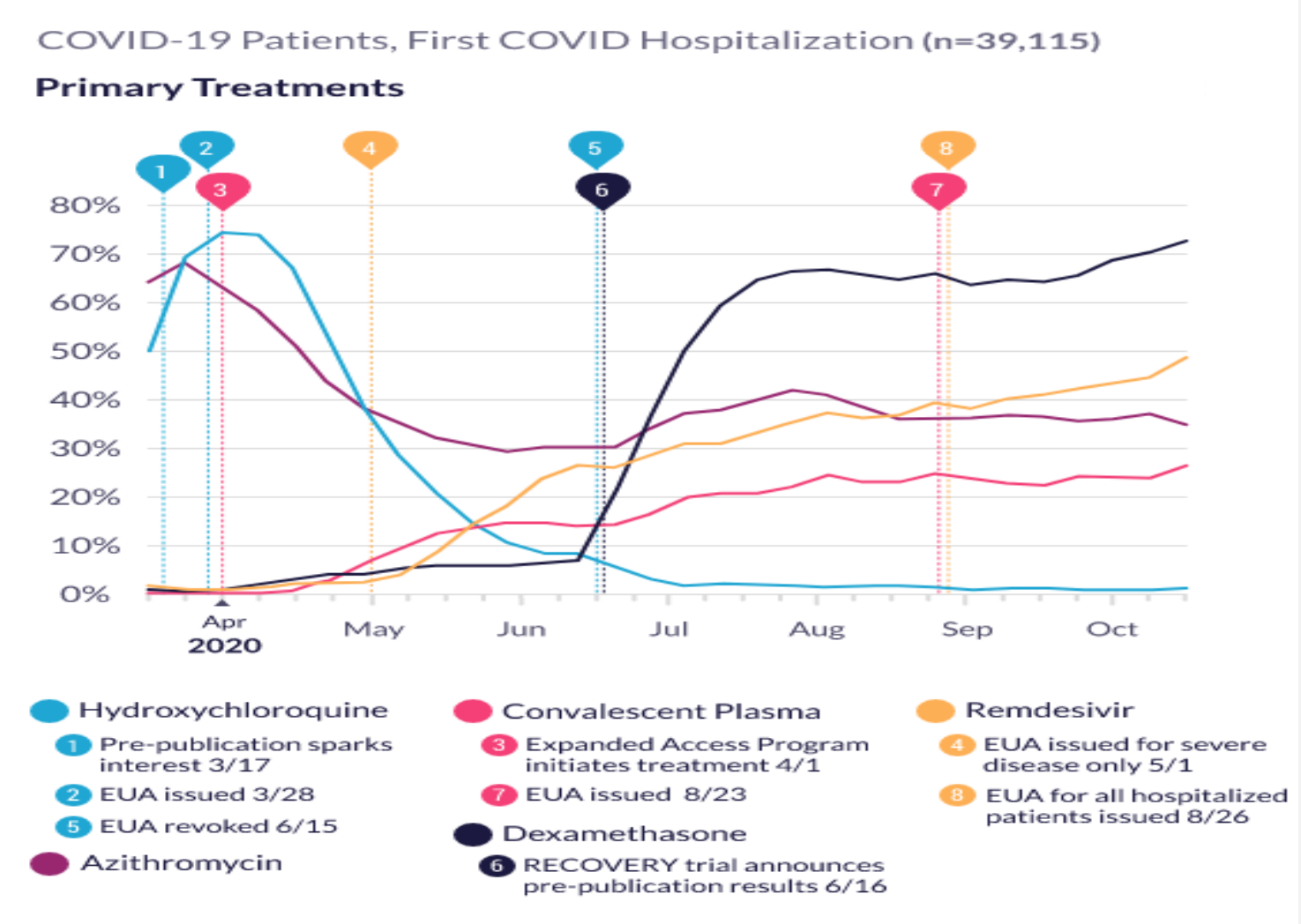



## Treated Patients (mITT) **≥ 65 years old** (n=94) Remestemcel-L vs Control




* Measured as resolution and/or improvement of ARDS as defined by the Berlin criteria at Days 7, 14, 21, and 30 post-randomizations

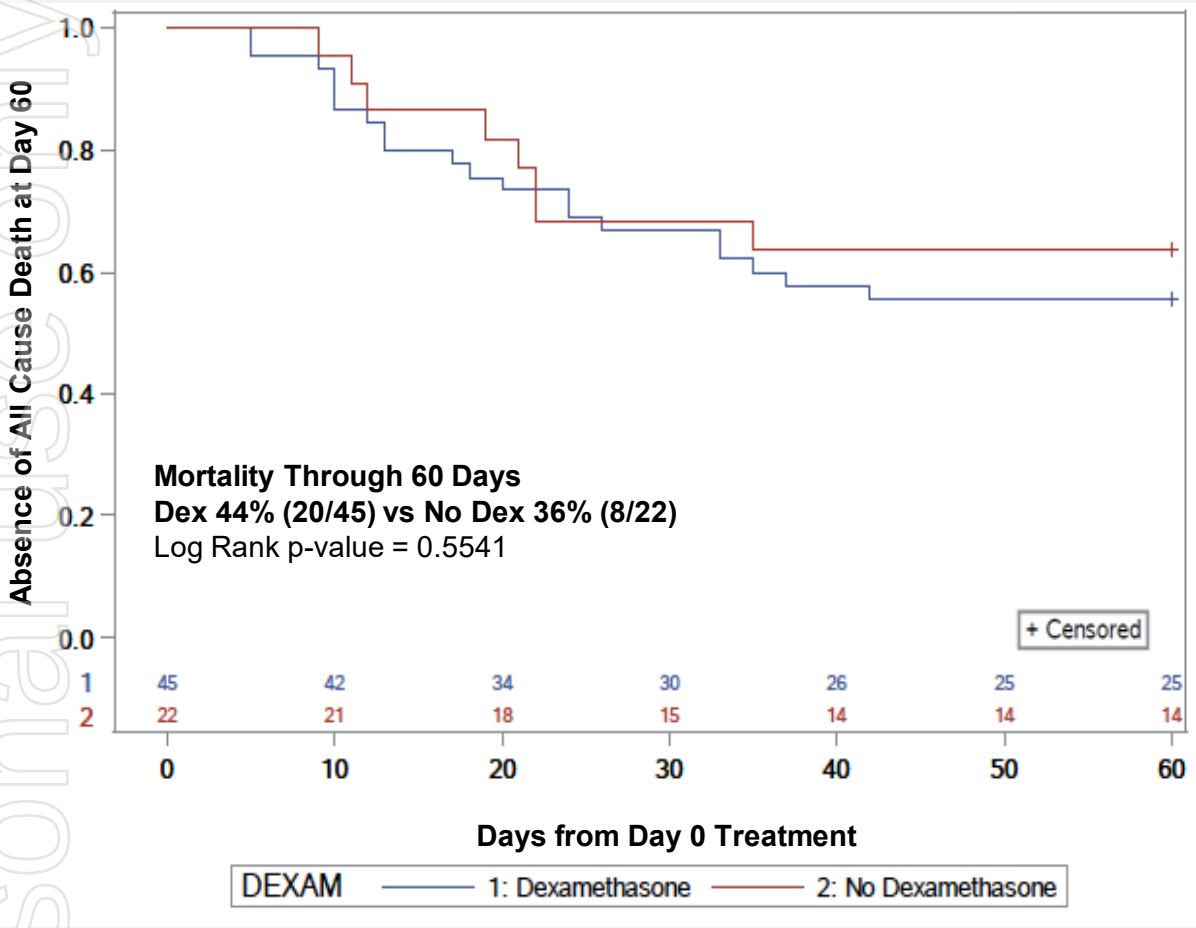
# Dynamic Changes in the Treatment Regimes During the Trial



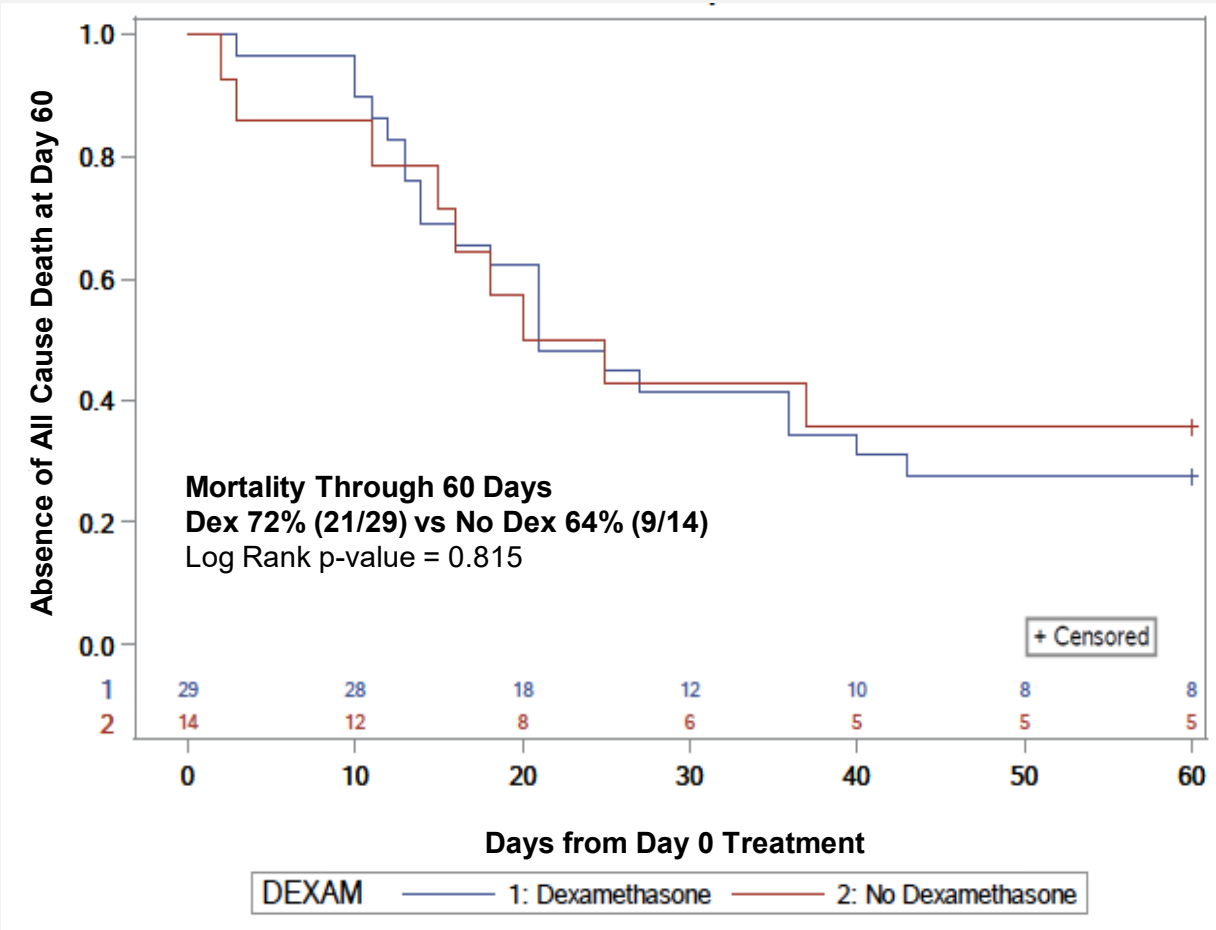

Source: Noel A. et al. Epic Health Research Network. Nov 2020

# Dexamethasone did not Reduce Mortality in Controls on Invasive Mechanical Ventilation with Moderate/Severe COVID-19 ARDS

## Controls < 65 years old +/- Dexamethasone (ITT n=67)



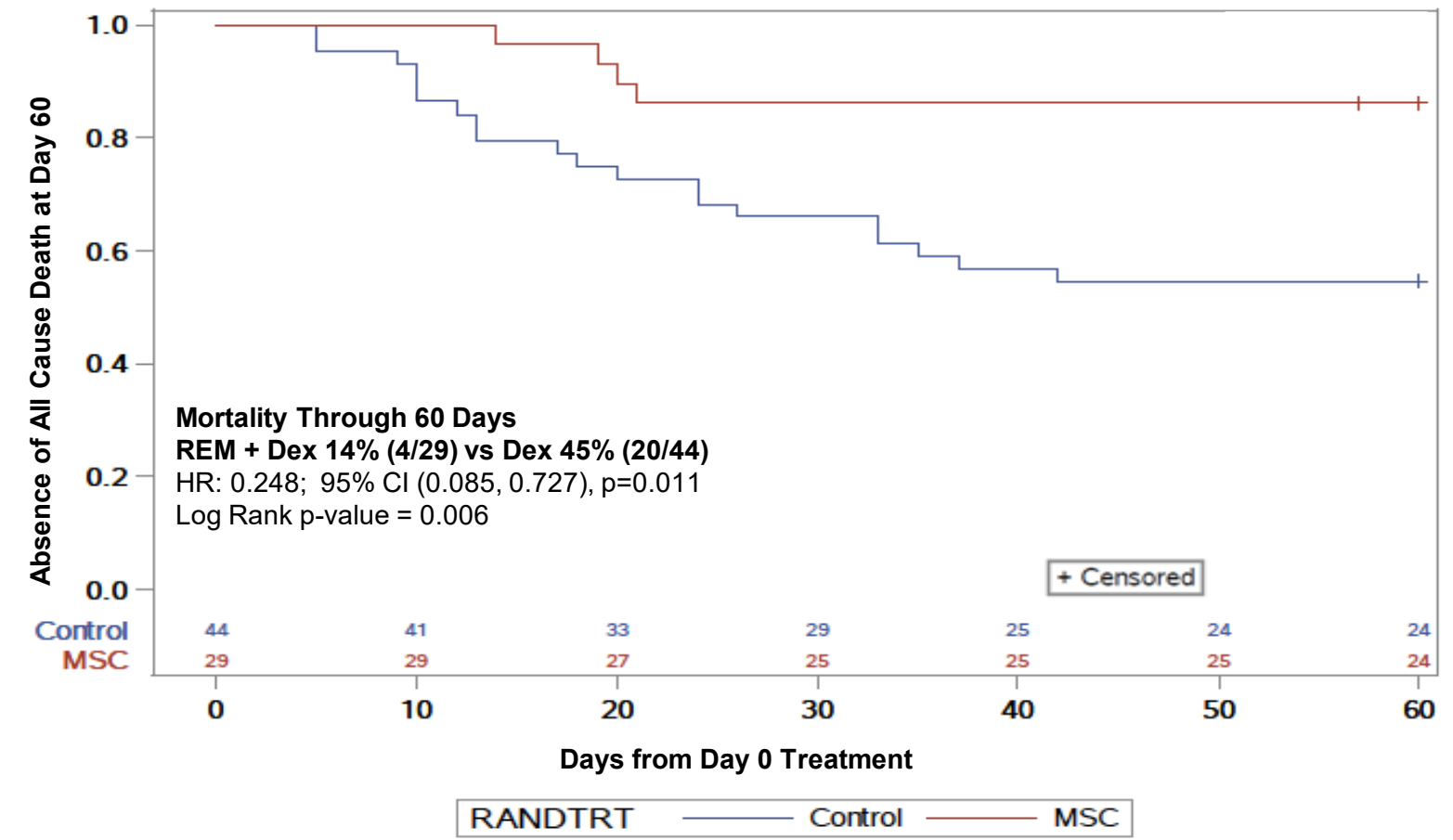

## Controls ≥ 65 years old +/- Dexamethasone (ITT n=43)



# Remestemcel-L plus Dexamethasone: Synergistic in Reducing Mortality in Exploratory Population < 65 years old



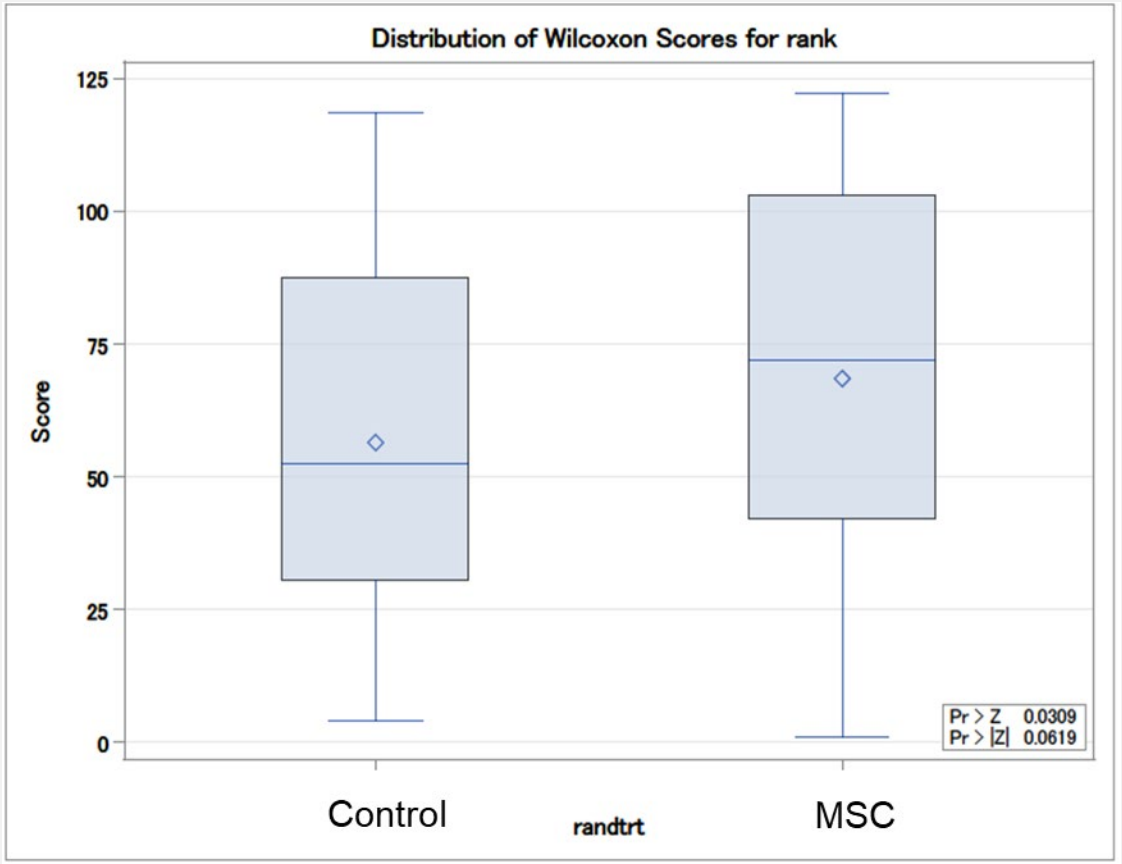
All Treated Patients < 65 years old on Dexamethasone (n=73)



# Remestemcel-L Increases Ventilator-Free Days Alive through 60 Days in Patients < 65 years old

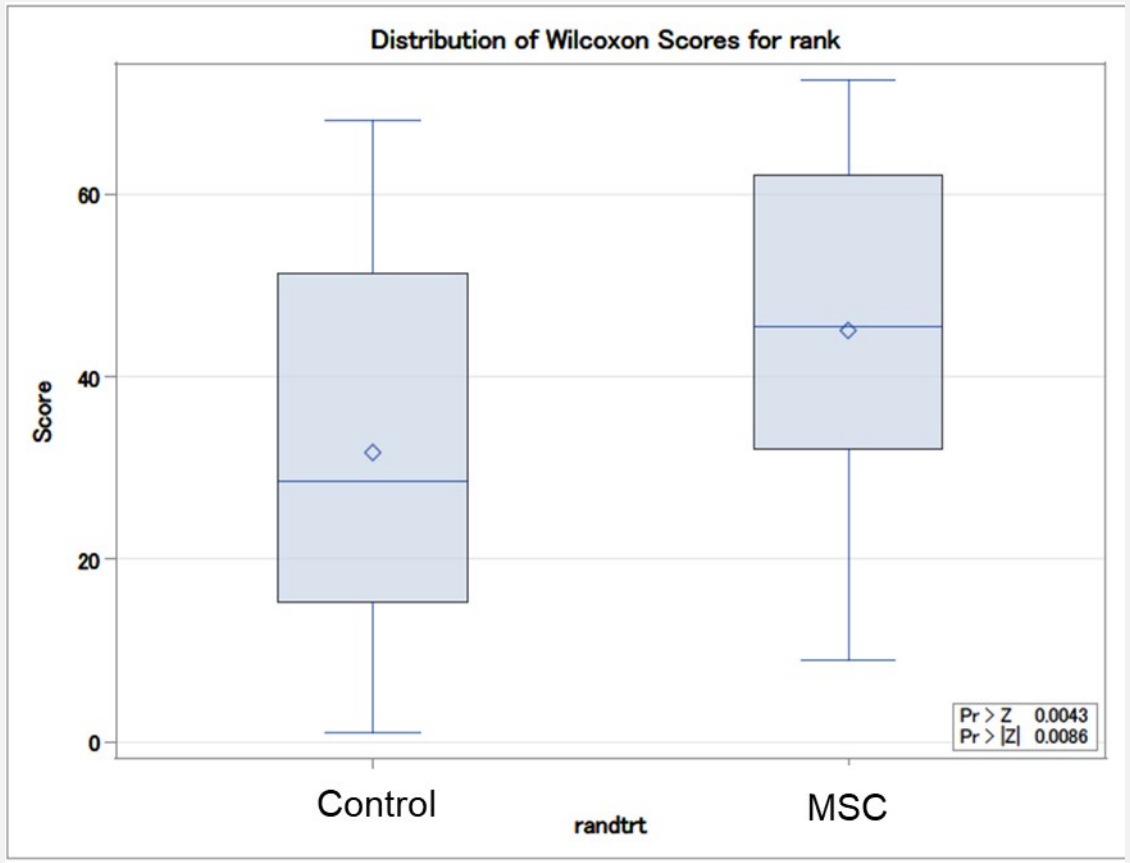


All Treated Patients < 65 years old (n=123)




Ventilator-Free Days Alive Through Day 60

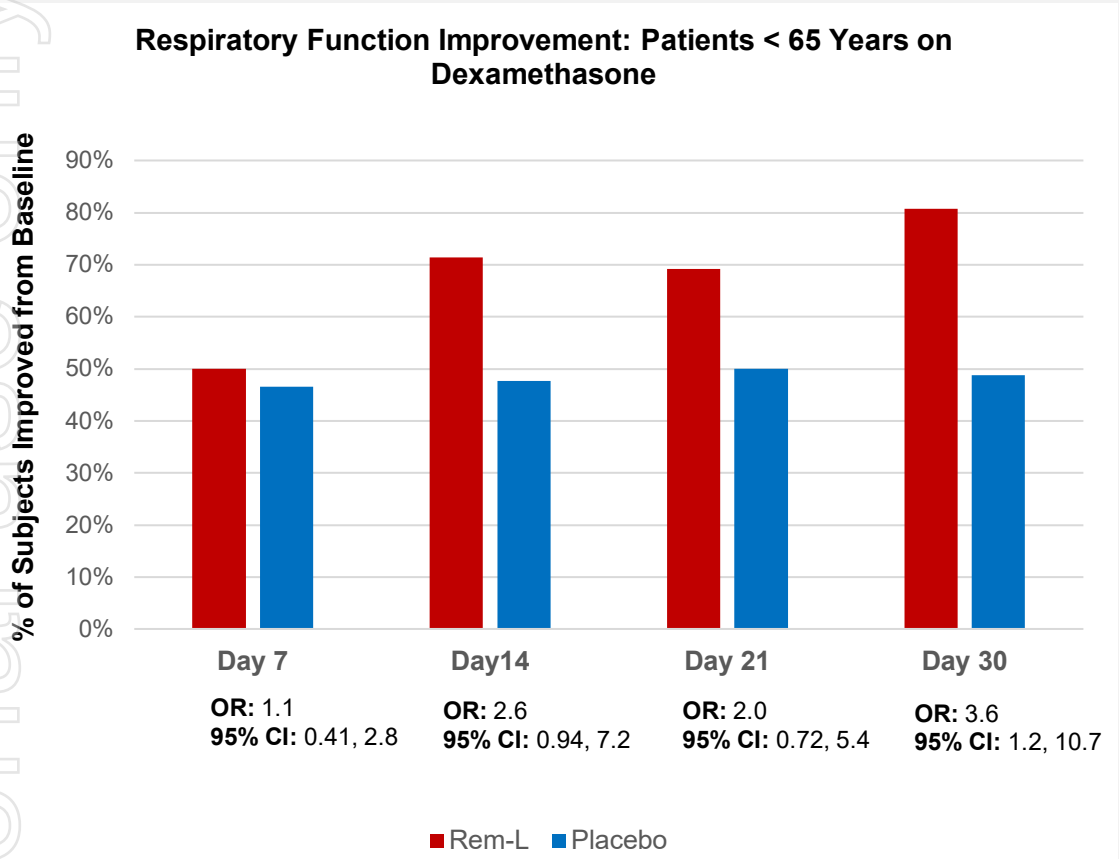
All Treated Patients < 65 years old on Dexamethasone (n=73)



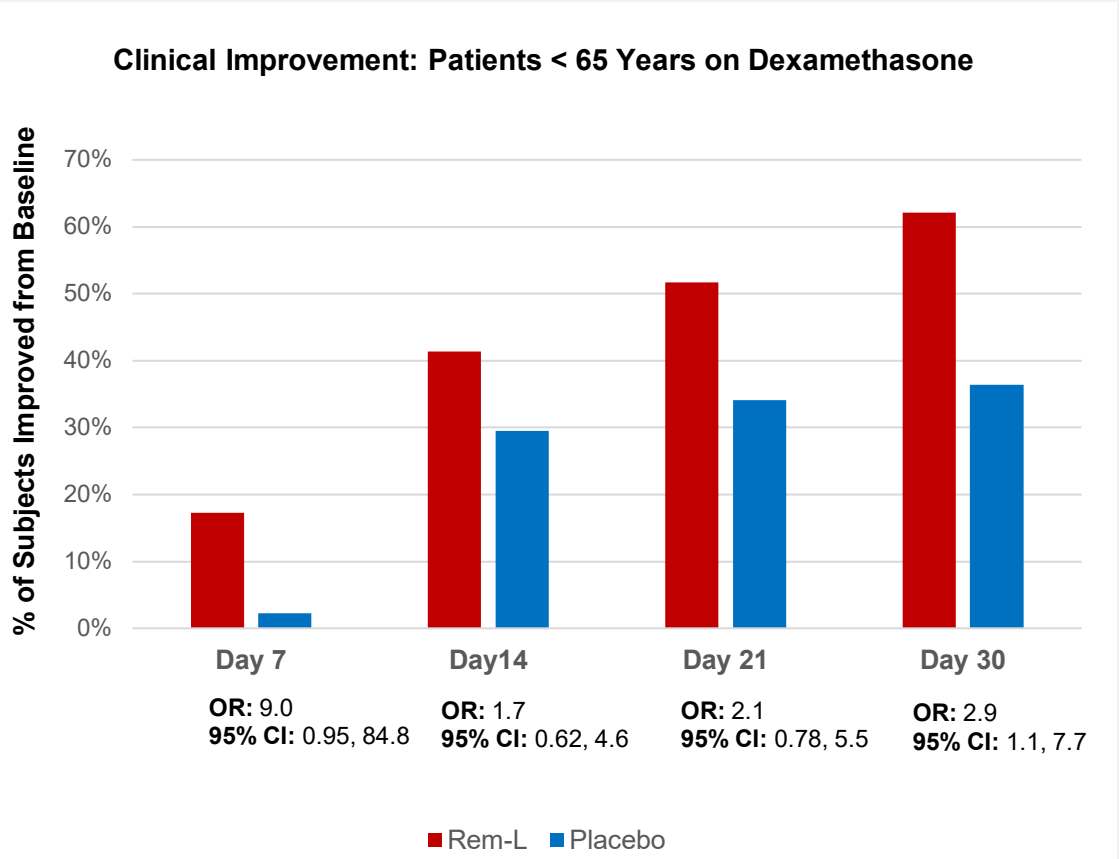

Ventilator-Free Days Alive Through Day 60

# Remestemcel-L plus Dexamethasone: Analysis of Respiratory Function and Clinical Improvement* in Exploratory Population < 65 years old

Treated Patients (mITT) **< 65 years old** on Dexamethasone (n=73)



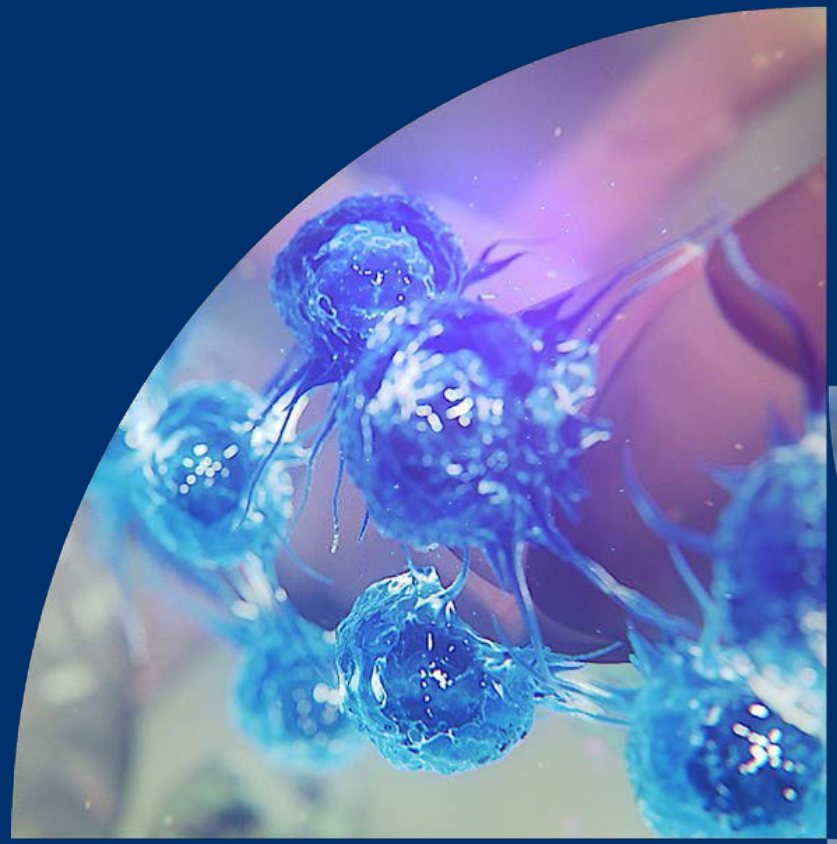

Treated Patients (mITT) **< 65 years old** on Dexamethasone (n=73)




* Respiratory Function Improvement measured as resolution and/or improvement of ARDS as defined by the Berlin criteria at Days 7, 14, 21, and 30 post-randomizations; Clinical Improvement was assessed based on a 7-point ordinal scale at baseline and on Days 7, 14, 21, and 30 and discharge from hospital

# Conclusions and Next Steps for Remestemcel-L in ARDS Due to COVID-19

- Remestemcel-L did not significantly reduce overall mortality
- Remestemcel-L reduced mortality and increased ventilator-free days through 60 Days in pre-specified patient population < 65 years old
- Addition of remestemcel-L to dexamethasone was synergistic in reducing mortality and increasing days alive off ventilator through 60 Days in exploratory analysis of patients < 65
- Plan to meet with U.S. Food and Drug Administration (FDA) to discuss potential next steps
- Confirmatory Phase 3 trial in COVID-19 ARDS patients < 65 years of age with dexamethasone, explore additional remestemcel-L dosing regimens for patients with ARDS ≥ 65 years of age

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