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NEW PATHWAYS TO SMARTER MEDICINE™

Evaluating Bempegaldesleukin for the Treatment of Adult Patients with Mild COVID-19

Investor & Analyst Call October 27, 2020

Today's Speakers

Howard Robin

President and
Chief Executive Officer
Nektar Therapeutics

Dr. Jonathan Zalevsky

Chief Research and
Development Officer
Nektar Therapeutics

Dr. Robert C. Gallo

Co-founder & Director,
Institute of Human Virology
University of Maryland
School of Medicine

Dr. Richard Bucala

Professor of Medicine,
Pathology and Epidemiology
& Public Health
Yale School of Medicine

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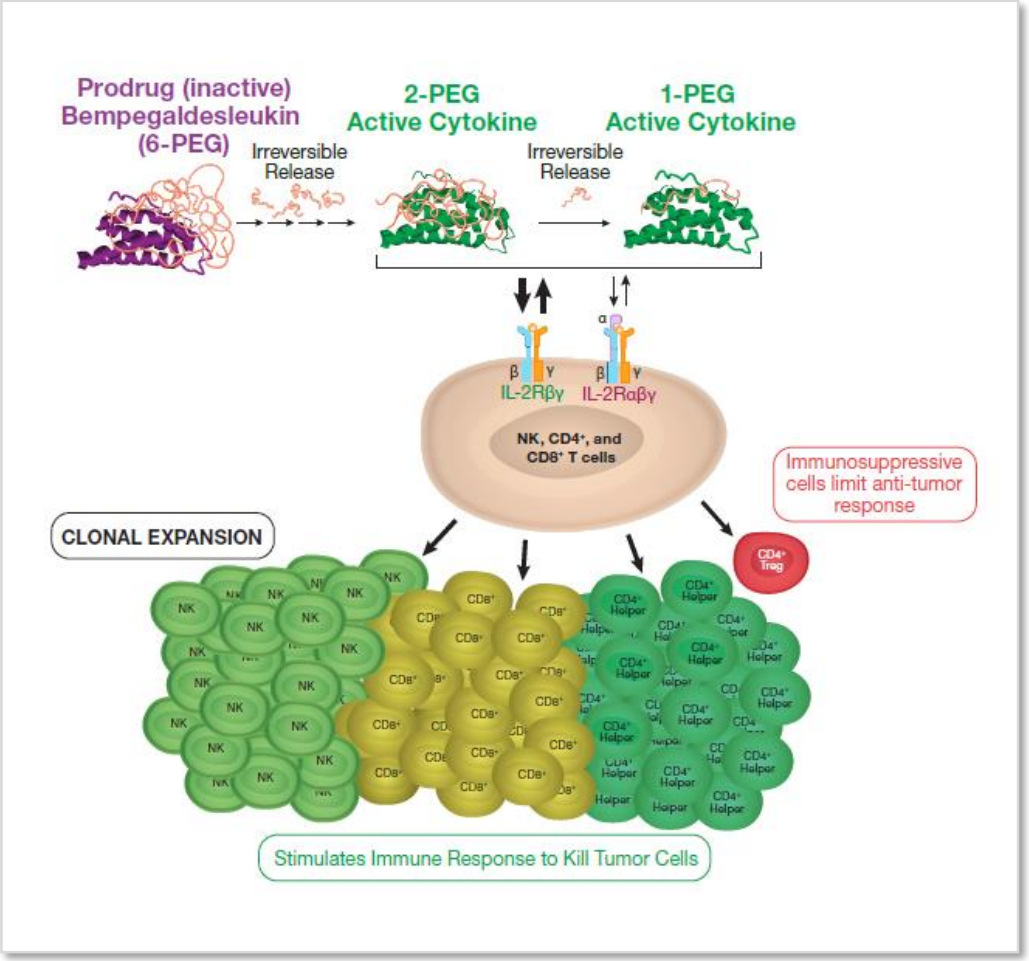
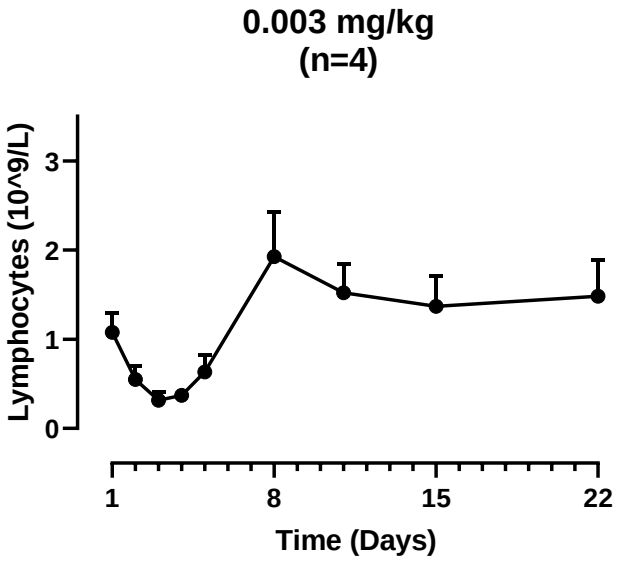
Potential Role of Bempegaldesleukin in the Treatment of Mild COVID-19

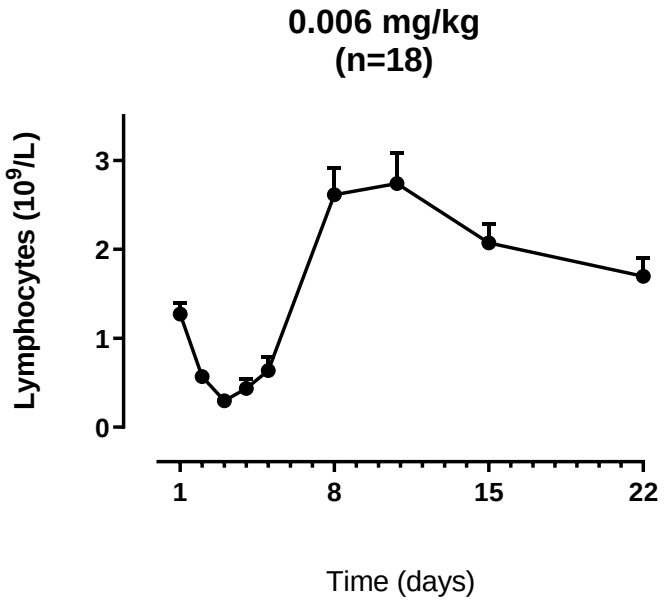


Can treatment with bempegaldesleukin increase lymphocyte production in patients with mild COVID-19, and could it improve outcomes?

- Large body of emerging data shows correlation between decreased lymphocyte levels and severity of disease in COVID patients
- Bempegaldesleukin: investigational CD122-preferential IL-2 pathway agonist
  - Stimulates the immune system through the proliferation of lymphocytes
  - Currently being evaluated in six separate late-stage clinical studies in various cancer indications
  - Large safety database with >1,000 patients dosed in multiple oncology studies

Bempegaldesleukin Promoted Increase in Absolute Lymphocyte Count (ALC)





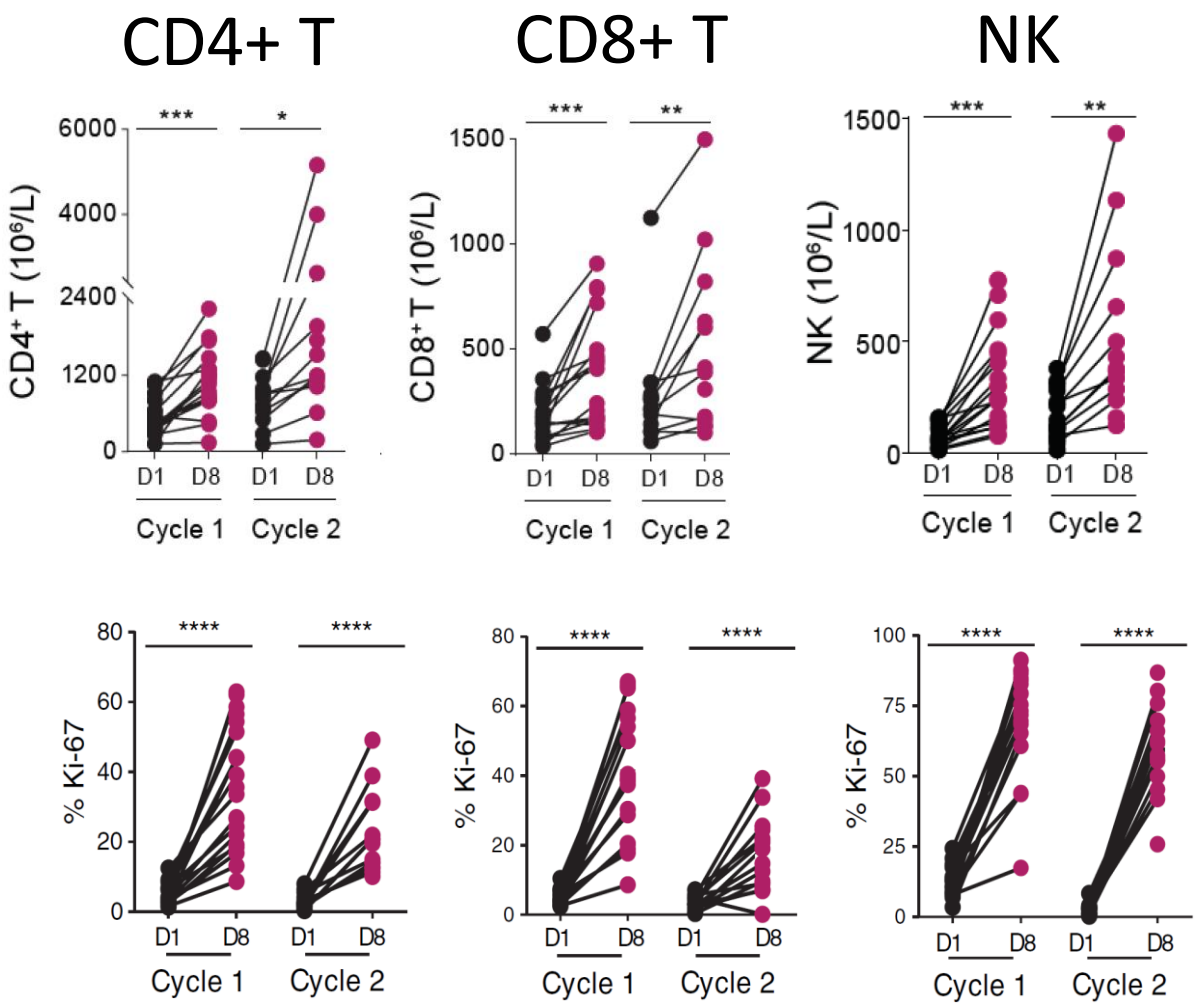
Parameter	Bempegaldesleukin Dose (mg/kg) and Time Point			
	0.003		0.006	
	C1D1	C1D8	C1D1	C1D8
Bempegaldesleukin Monotherapy				
n	4	4	18	18
ALC	1.08	1.93	1.23	2.68
Fold ↑	**179%**		**217%**	
Lymphocyte %	15%	23%	20%	33%

C1D1: Cycle 1, Day 1
C1D8: Cycle 1, Day 8

- BEMPEG rapidly raised total lymphocyte counts through lymphocyte proliferation.
  - Elevation of Ki67+ CD8, CD4, and NK cells by flow cytometry.
- Transient lymphopenia post-dose (Days 2-4) was due to lymphocyte activation and extravasation into tissues followed by lymphocytosis and new elevated baseline.
- Effect of lymphocyte mobilization was consistent and maintained with successive treatment cycles for up to 2 years.

NEKTAR Bentebibel SE, et al. *Cancer Discov* 2019;9:711–721.

Bempegaldesleukin Directly Strengthened Cellular Antiviral Immunity



- CD4+ T cells “help” B cells produce high quantities of high-affinity antibodies (**humoral** immunity).
- CD8+ T cells directly and specifically kill virus-infected cells (**adaptive cellular** immunity).
- NK cells directly kill abnormal, stressed and virus-infected cells (**innate cellular** immunity).
- BEMPEG directly increased CD4+ and CD8+ T cells and NK cells.

n=28 p-values: ****<0.0001, *** <0.001, ** < 0.01, * <0.05

Bentebibel SE, et al. *Cancer Discov* 2019;9:711–721.

Lymphocyte Count Over Time by Survivor Status in Patients with COVID-19

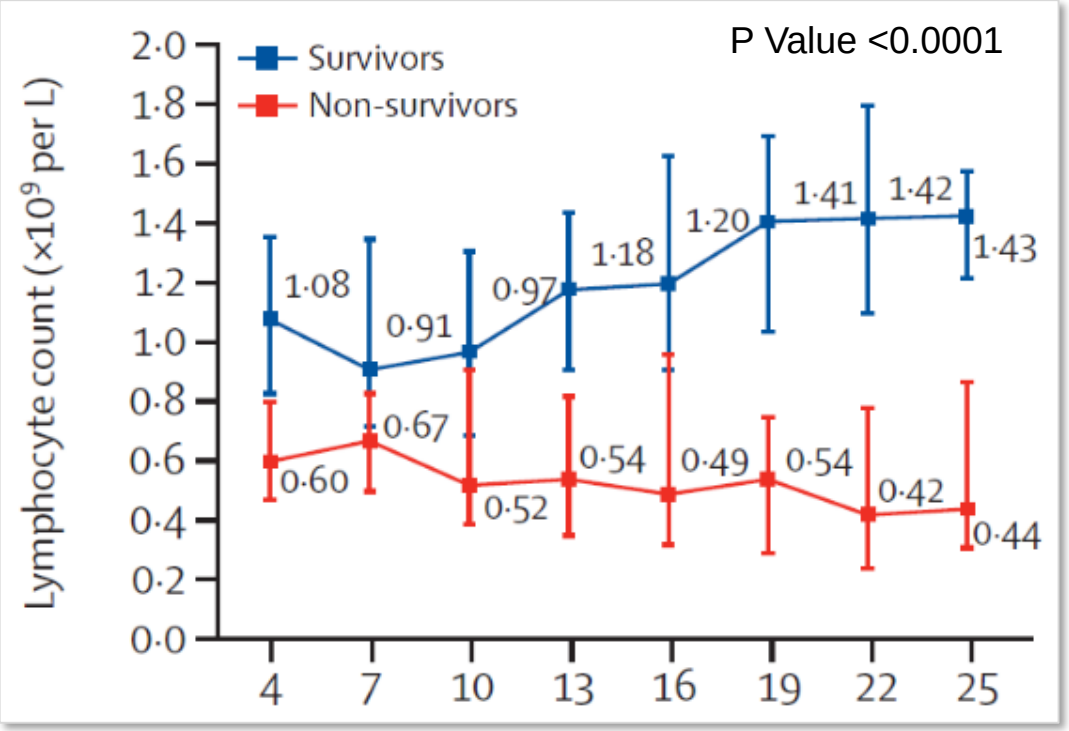
~60% OF HOSPITALIZED PATIENTS WITH COVID-19 WERE LYMPHOPENIC IN US STUDIES[1,2]

4-FOLD Increased odds of in-hospital death with **ANY** lymphopenia[3†]
OR: 3.71; 95% CI: 1.63–8.44

12-FOLD Increased odds of in-hospital death with **SEVERE** (<0.5 X 10^9/L) lymphopenia[3‡]
OR: 12.71; 95% CI: 6.00–26.90

- Blood lymphocyte percentage during SARS-CoV-2 infection associated with disease course[4]
  - In survivors, lymphocyte count was lowest on Day 7 of illness and improved during hospitalization[4]
  - Severe lymphopenia was observed until death in non-survivors[4]

Lymphocyte count over time by survivor status (N=191)[4]



OR, odds ratio.
†Severe disease was defined as a composite of: (1) respiratory distress, respiratory rate ≥30 per min; or (2) oxygen saturation on room air at rest ≤93%; or (3) partial pressure of oxygen in arterial blood/fraction of inspired oxygen ≤300 mmHg; or (4) patients requiring mechanical ventilation/vital life support/intensive care unit admission; or (5) death.
‡Composite poor outcomes were defined as included intensive care unit admission, oxygen saturation <90%, invasive mechanical ventilation utilization, severe disease, in-hospital admission and mortality.

1. Chilimuri S, et al. *West J Emerg Med* 2020;21:779–784; 2. Richardson S, et al. *JAMA* 2020;323:2052–2059; 3. Henry BM, et al. *Acta Biomed* 2020;91:e2020008;
4. Zhou F, et al. *Lancet* 2020;395:1054–1062.

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Lymphopenia is Associated with Severe COVID-19 (N=4,969)

LYMPHOPENIA* AT HOSPITAL ADMISSION WAS SIGNIFICANTLY ASSOCIATED WITH

4-FOLD Increased odds of progression to severe disease[1†]

OR: 4.20; 95% CI: 3.46–5.09

3-FOLD Increased odds of poor outcome[2‡]

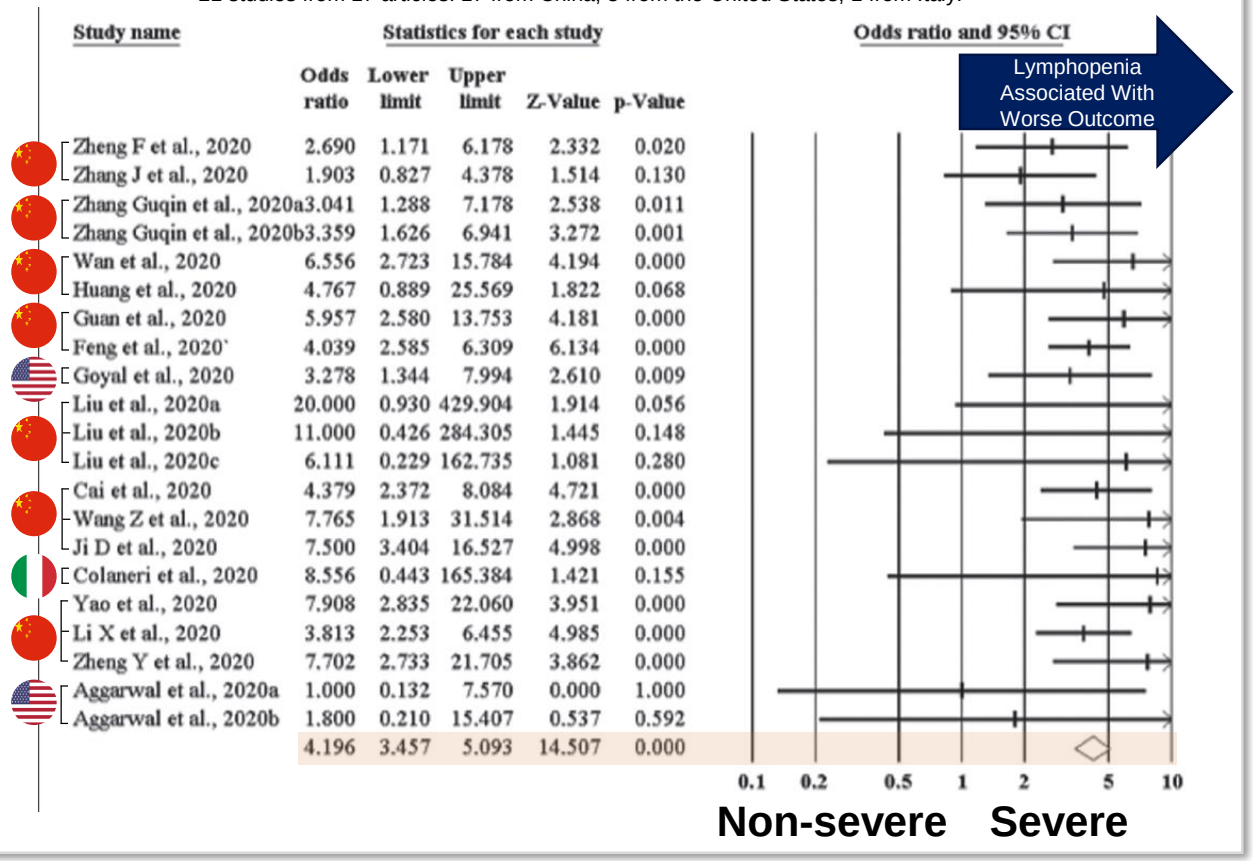
OR: 3.33; 95% CI: 2.51–4.41

12-FOLD Increased odds of mortality with severe lymphopenia (<0.5x10^9/L)[1†]

OR: 12.71; 95% CI: 6.00–26.90

Meta-analysis of 21 studies[1]

21 studies from 17 articles: 17 from China; 3 from the United States; 1 from Italy.



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Zheng F et al., 2020	2.690	1.171	6.178	2.332	0.020
Zhang J et al., 2020	1.903	0.827	4.378	1.514	0.130
Zhang Guqin et al., 2020a	3.041	1.288	7.178	2.538	0.011
Zhang Guqin et al., 2020b	3.359	1.626	6.941	3.272	0.001
Wan et al., 2020	6.556	2.723	15.784	4.194	0.000
Huang et al., 2020	4.767	0.889	25.569	1.822	0.068
Guan et al., 2020	5.957	2.580	13.753	4.181	0.000
Feng et al., 2020	4.039	2.585	6.309	6.134	0.000
Goyal et al., 2020	3.278	1.344	7.994	2.610	0.009
Liu et al., 2020a	20.000	0.930	429.904	1.914	0.056
Liu et al., 2020b	11.000	0.426	284.305	1.445	0.148
Liu et al., 2020c	6.111	0.229	162.735	1.081	0.280
Cai et al., 2020	4.379	2.372	8.084	4.721	0.000
Wang Z et al., 2020	7.765	1.913	31.514	2.868	0.004
Ji D et al., 2020	7.500	3.404	16.527	4.998	0.000
Colaneri et al., 2020	8.556	0.443	165.384	1.421	0.155
Yao et al., 2020	7.908	2.835	22.060	3.951	0.000
Li X et al., 2020	3.813	2.253	6.455	4.985	0.000
Zheng Y et al., 2020	7.702	2.733	21.705	3.862	0.000
Aggarwal et al., 2020a	1.000	0.132	7.570	0.000	1.000
Aggarwal et al., 2020b	1.800	0.210	15.407	0.537	0.592
	4.196	3.457	5.093	14.507	0.000

OR, odds ratio.

*The cut-off values for lymphopenia ranged from 0.5 to 1.5×10^9/L across studies.

†Severe disease was defined as a composite of: (1) respiratory distress, respiratory rate ≥30 per min; or (2) oxygen saturation on room air at rest ≤93%; or (3) partial pressure of oxygen in arterial blood/fraction of inspired oxygen ≤300 mmHg; or (4) patients requiring mechanical ventilation/vital life support/intensive care unit admission; or (5) death.

‡Composite poor outcomes were defined as included intensive care unit admission, oxygen saturation <90%, invasive mechanical ventilation utilization, severe disease, in-hospital admission and mortality.

1. Henry BM, et al. *Acta Biomed* 2020;91:e2020008; 21 of 22 studies included because 1 study did not include lymphopenia rate according to disease severity.
2. Malik P, et al. *BMJ Evid Based Med* 2020: doi: 10.1136/bmjebm-2020-111536 [ePub ahead of print].

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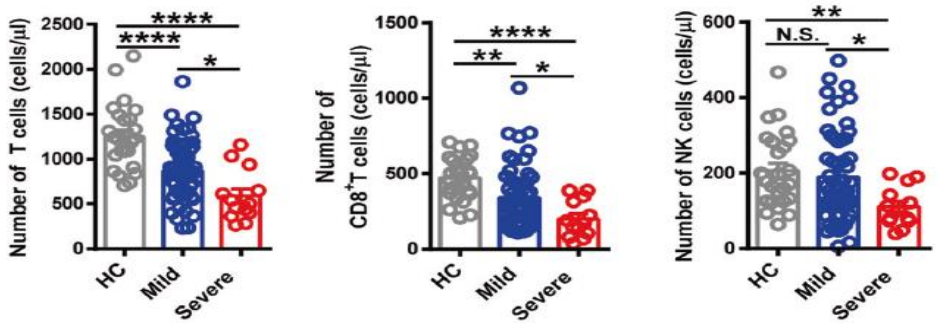
The Effects of SARS-CoV-2 Infection on T Cells

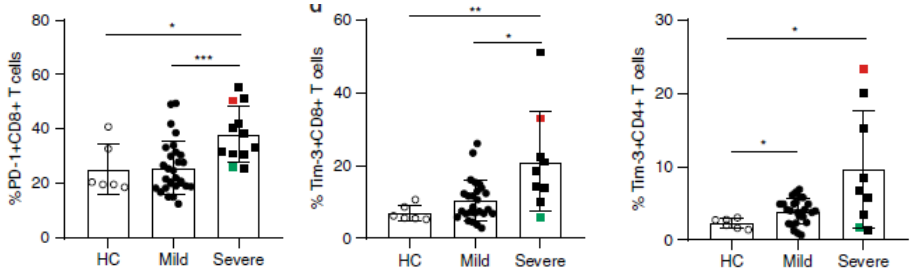
Lymphopenia[1,2]

Selective loss of CD4+ T cells, CD8+ T cells and NK cells[1,2]



Absolute T- and NK-cell numbers in healthy controls (n=25), or mild (n=55) or severe (n=13) COVID-19[1]

Functional exhaustion of T cells (high PD-1 and TIM-3 expression)[2,3]



Markers of T-cell exhaustion in healthy controls (n=6), or mild (n=29) or severe (n=12) COVID-19[2]

*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001;

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HC, healthy controls; NK, natural killer cells.

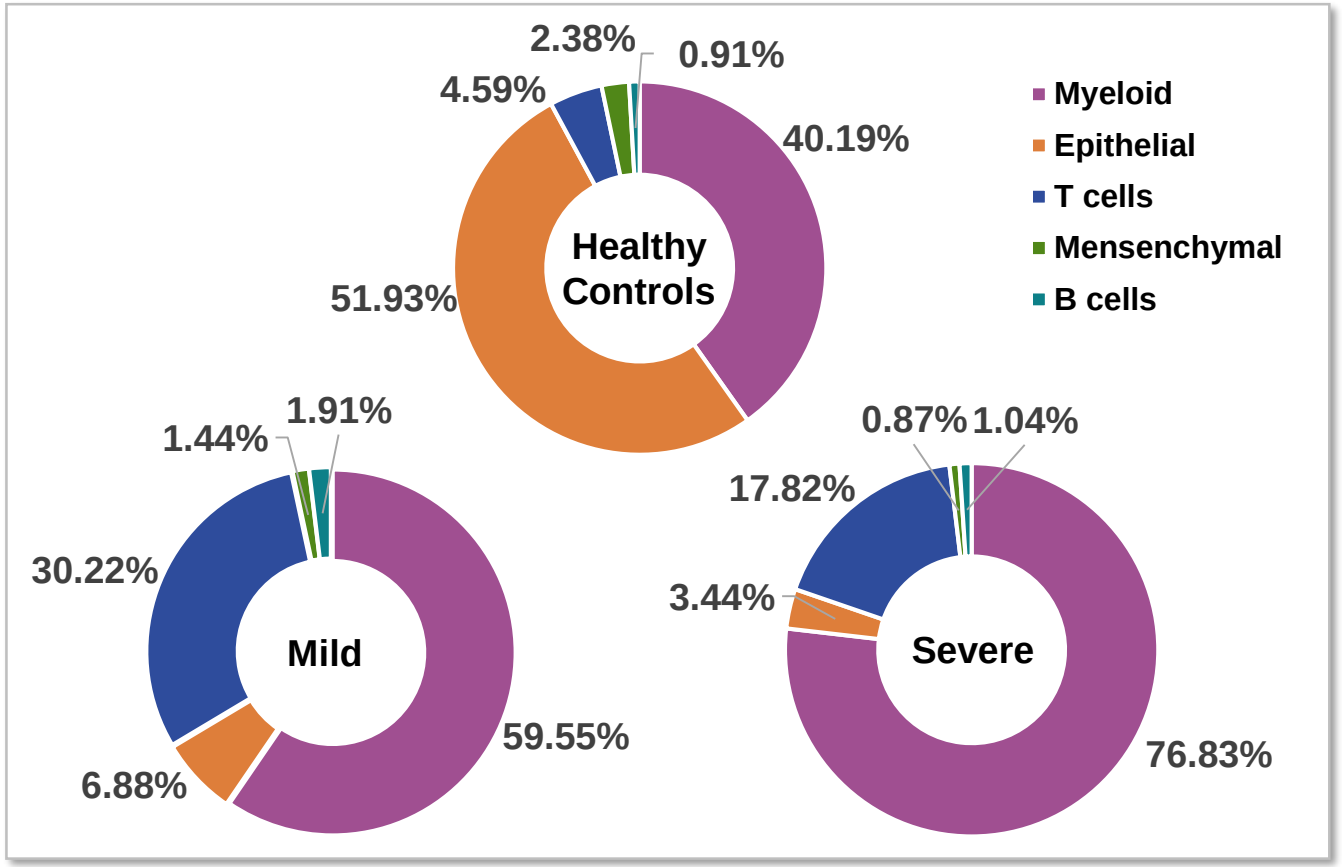
1. Zheng M, et al. *Cell Mol Immunol* 2020;17:533–535; 2. Song J-W, et al. *Nat Commun* 2020;11:3410; 3. Diao B, et al. *Front Immunol* 2020;11:827.

T-cell Responses May Play a Crucial Role in SARS-CoV-2 Clearance

- In patients with severe COVID-19, proinflammatory monocyte-derived macrophages were abundant in the bronchoalveolar lavage fluid.
- Moderate cases of COVID-19 were characterized by the presence of highly clonally expanded CD8+ T cells.

A robust adaptive immune response corresponds with better control of COVID-19[1]

Percentages of cell populations in the lung microenvironment of patients with mild or severe COVID-19, or healthy controls[1]



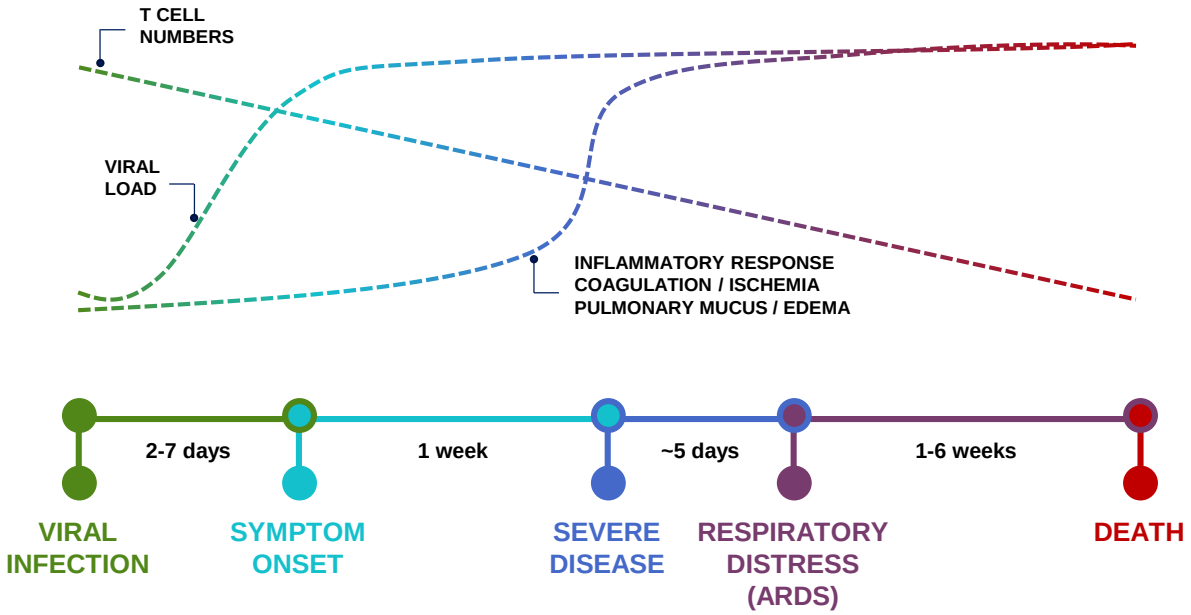
*Lung microenvironment was assessed with bronchoalveolar lavage fluid through single-cell RNA sequencing combined with TCR-sequencing.

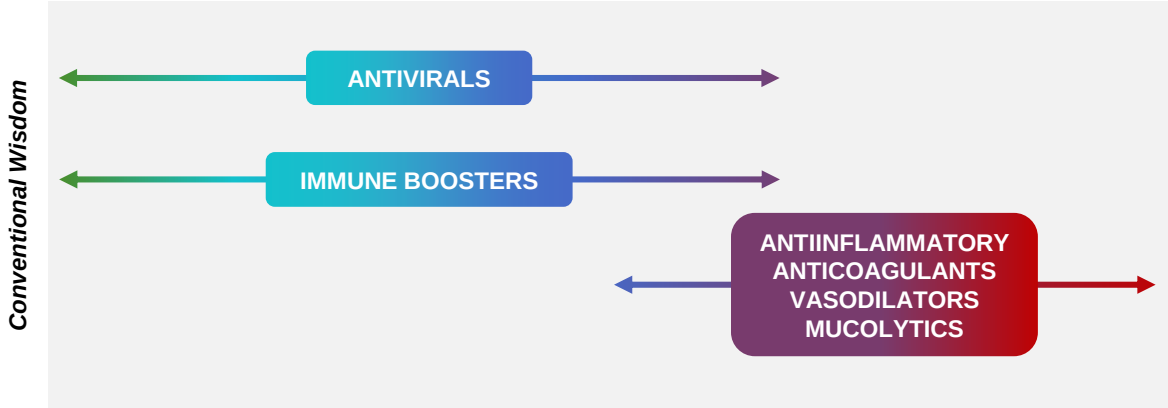
1. Liao M, et al. *Nature Med* 2020; 26:842–844.

Current Treatment of COVID Patients and Phase 1b Study Design of BEMPEG in Mild COVID-19 Patients

Dr. Richard Bucala
Yale School of Medicine

COVID-19 Treatment Paradigm





- The incubation period of the virus can be up to 2 weeks, while most people experience symptoms within 4-5 days after exposure.
- 81% of patients present with mild to moderate disease severity.[1] Early symptoms include fever or chills, cough, and shortness of breath.
- Patients with severe disease experienced dyspnea in 5-8 days after onset of symptoms and progressed to ICU admission after 10-12 days.
- In addition to a lack of understanding of certain aspects of the virus, large variability between patients has complicated treatment decisions.

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1. To KK, Tsang OT, Leung WS, et al. Lancet Infect Dis 2020.

Study Design for Phase 1b, Randomized, Double-Blind, Placebo-Controlled Trial of Bempegaldesleukin (NKTR-214) in Adults with Mild COVID-19

Screening

Patients with:

- Confirmed COVID-19 PCR CDC Criteria
- Oxygen saturation > 93% on room air
- Respiratory rate < 20 breaths per minute
- Heart rate < 90 bpm
- Admission to an in-patient facility for Days 1 to 8, inclusive

N=30

R (1:1)

Double-Blind Treatment

Dose Finding

Maximum of 3 cohorts with 10 patients per cohort.

Treatment Arm:

- Bempegaldesleukin IV:
  - Cohort 1: 0.00075 mg/kg (starting dose)
  - Cohort 2: 0.0015 mg/kg
  - Cohort 3: 0.003 mg/kg
- Standard of care

N = 5

Comparator Arm:

- Placebo
- Standard of care

N = 5

Follow-up

Primary Endpoints:

- Safety and tolerability
- PK and pharmacodynamic profiles
- Identify the RP2D
- Fold Change from Baseline ALC

Secondary Endpoints:

- Incidence of AEs/SAEs
- Patients who require supplemental oxygen
- Evaluation of clinical status (using WHO Clinical Progression Scale)
- Assess immunologic effects

Follow Up Day 30

- Safety and clinical status 30 days after discharge
- SARS-COV-2 serology, detection of SARS-CoV-2 nucleic acid in respiratory specimens, DNA/RNA sequencing, immune cell profiling, and immunogenicity assessments

Q&A Session

Howard Robin

President and
Chief Executive Officer
Nektar Therapeutics

Dr. Jonathan Zalevsky

Chief Research and
Development Officer
Nektar Therapeutics

Dr. Mary Tagliaferri

Executive Clinical
Fellow
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