

Immunomodulation to manage COVID-19

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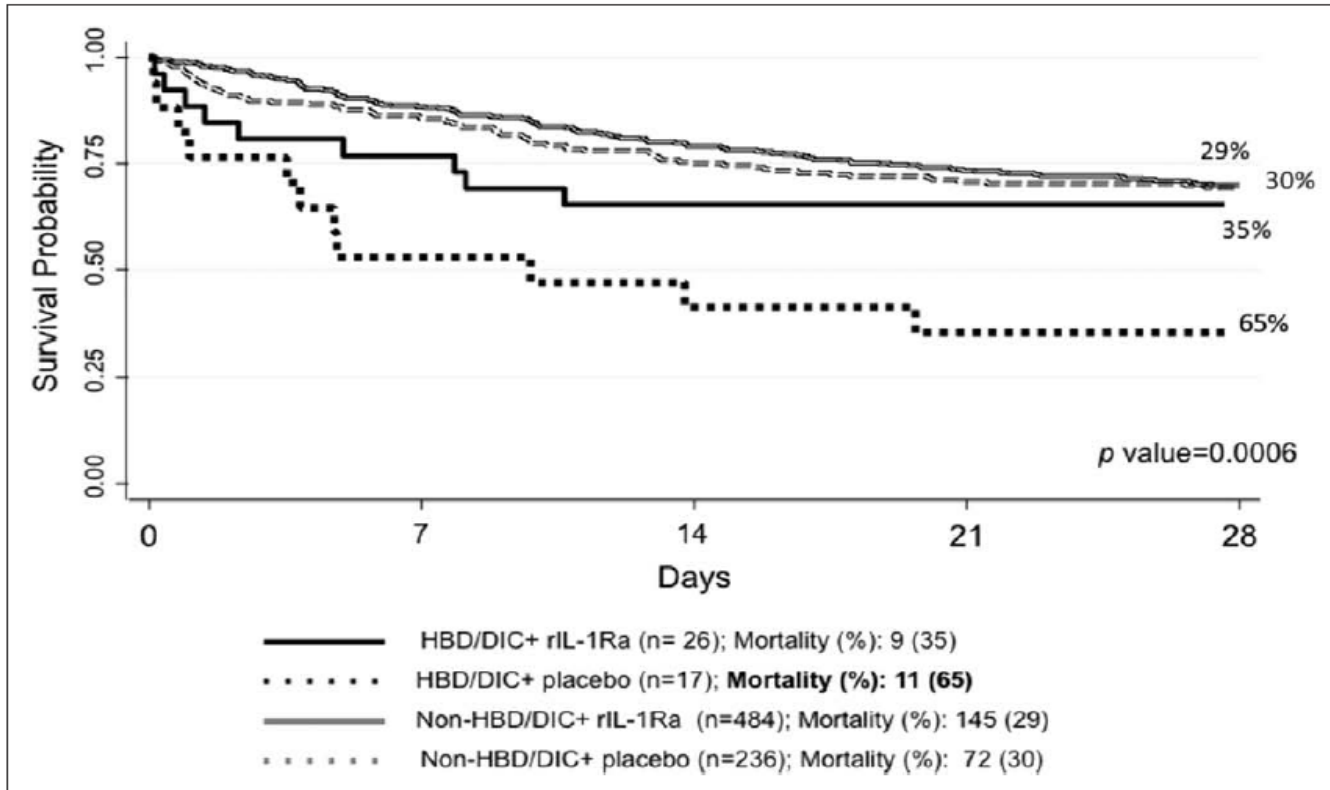
President: Hellenic Institute for the Study of Sepsis

Chairman: European Sepsis Alliance

Past-President: European Shock Society

POSITIVE ANAKINRA OUTCOMES IN SEVERE SEPSIS

(Shakoory B, et al. *Crit Care Med* 2016; 44: 275)



STRATEGIES FOR IMMUNO-MODULATION

Patients AT RISK
for Severe Respiratory Failure



Biomarker= informs on

- Risk of unfavorable outcome
- Mechanism of progression



ANAKINRA

Patients ALREADY critical
with Severe Respiratory Failure



Block excess cytokine production
Unsafe on kinetics # outcome

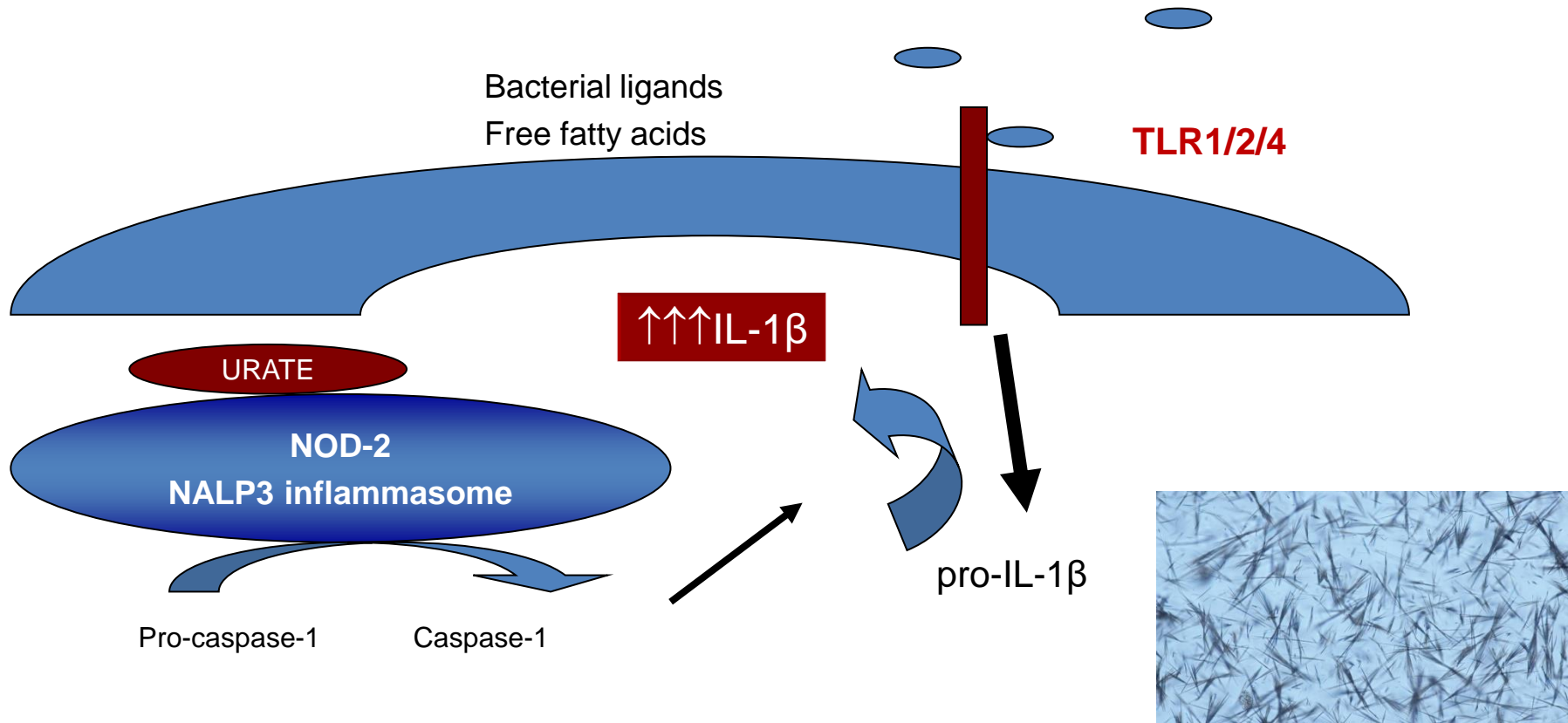


Dexamethasone
Tocilizumab
Anakinra

OVER-PRODUCTION OF IL-1 β MANDATES PRIMING

(Giamarellos-Bourboulis EJ, et al. *Ann Rheum Dis* 2009; 68: 273

Mylona EE, et al. *Arthritis Res Ther* 2012; 14: R158)



IL-1 β OVER-PRODUCTION AND GENETIC MODULATION OF NLRP3 SENSITIVITY

(Jamilloux Y, et al. *Rheumatology* 2018; 57: 100)

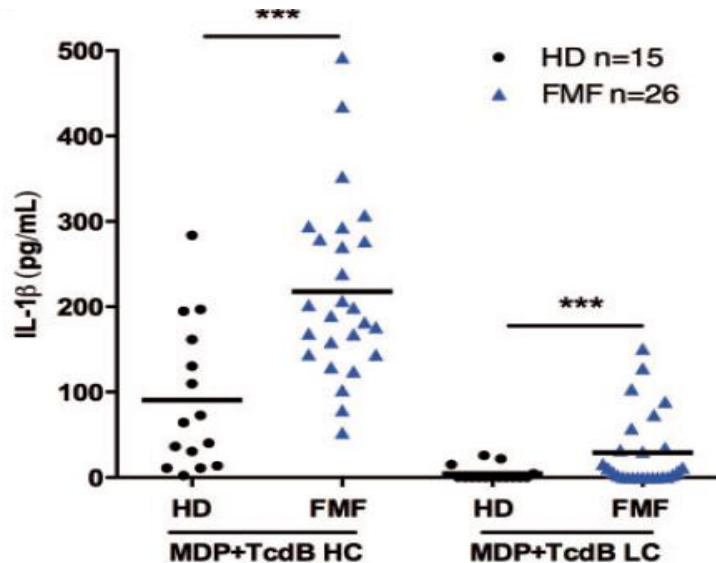
HD: healthy donors

CAPS: cryopyrin-associated periodic syndrome

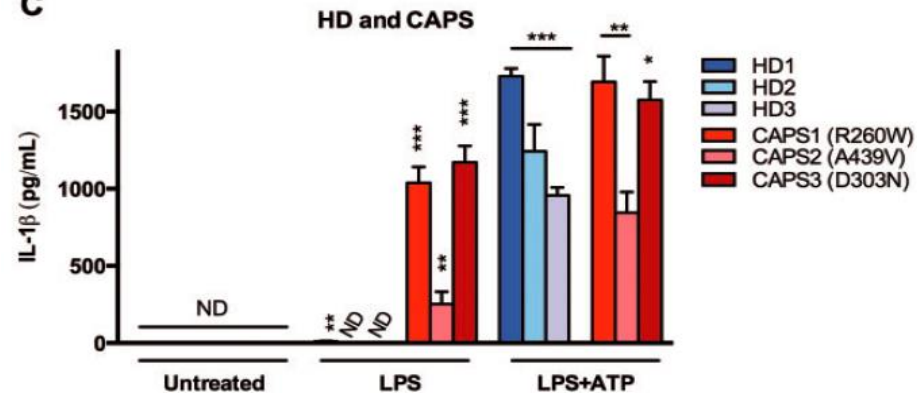
FMF: Familial Mediterranean Fever

MDP: muramyl dipeptide

TcdB: *C.difficile* toxin B



C



MAIN FEATURES

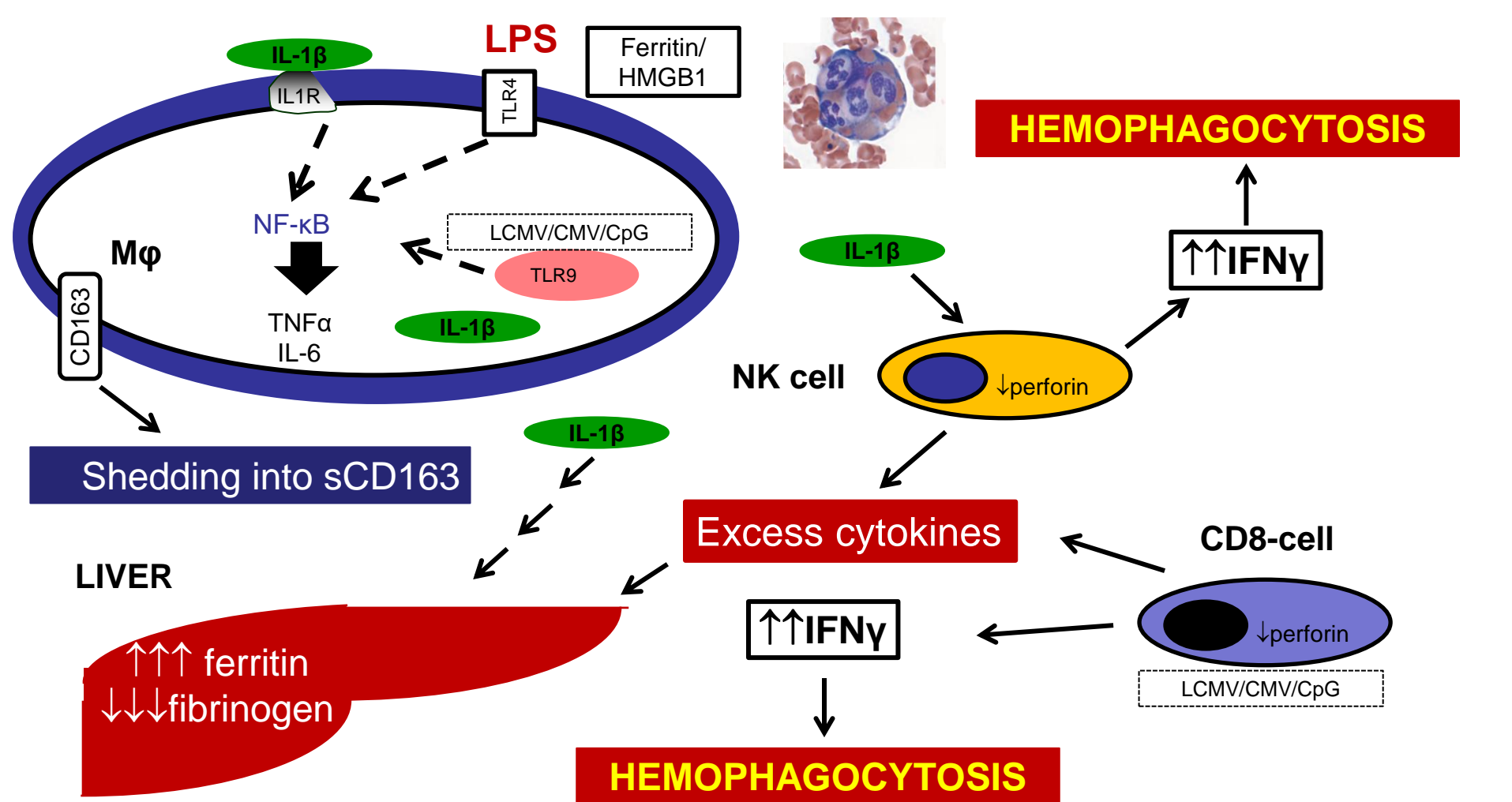
Ref.	No pts	Main clinical /laboratory signs	Mortality (%)
1	71 ICU admissions	Fever, hepatomegaly, splenomegaly, thrombocytopenia , hemophagocytosis	38.1
2	17 with SLE and acute pancreatitis	Fever, hepatomegaly, thrombocytopenia, leukopenia, ↑ TGs	23
3	32 with SLE	Fever, splenomegaly, anemia, thrombocytopenia, neutropenia, ↑ TGs, ↑ALT, hemophagocytosis	12.5
4	68	Fever, splenomegaly, anemia, thrombocytopenia, neutropenia, ↑ TGs, ↑ bilirubin, ↓ fibrinogen, ↑ALT, hemophagocytosis	21

ALT: alanine aminotransferase

SLE: systemic lupus erythematosus

TGs: triglycerides

1. Barba T, et al. *Medicine* 2015; 94: e2318
2. Gormezano N, et al. *Semin Arthr Rheum* 2016; 45: 706
3. Liu A C, et al. *Clin Rheumatol* 2018; 37: 93-100
4. Schraam AM, et al. *Br J Haematol* 2016; 72: 412-419.



MALS AND 10-DAY MORTALITY

(Kyriazopoulou E, et al. *BMC Med* 2017; 15: 172)

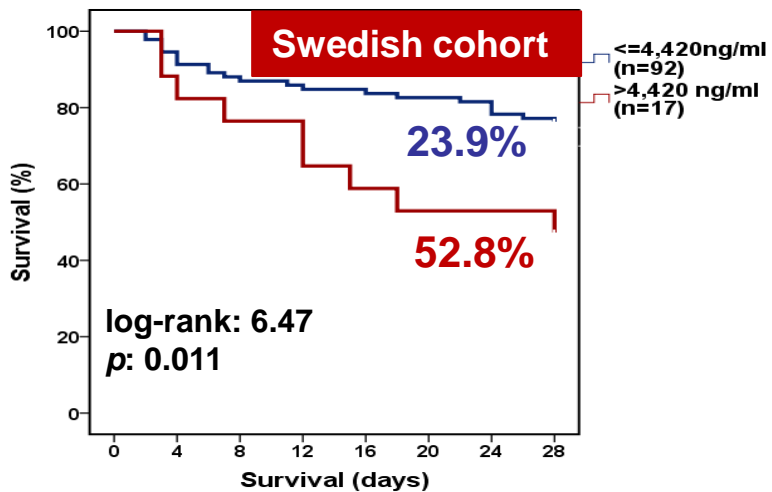
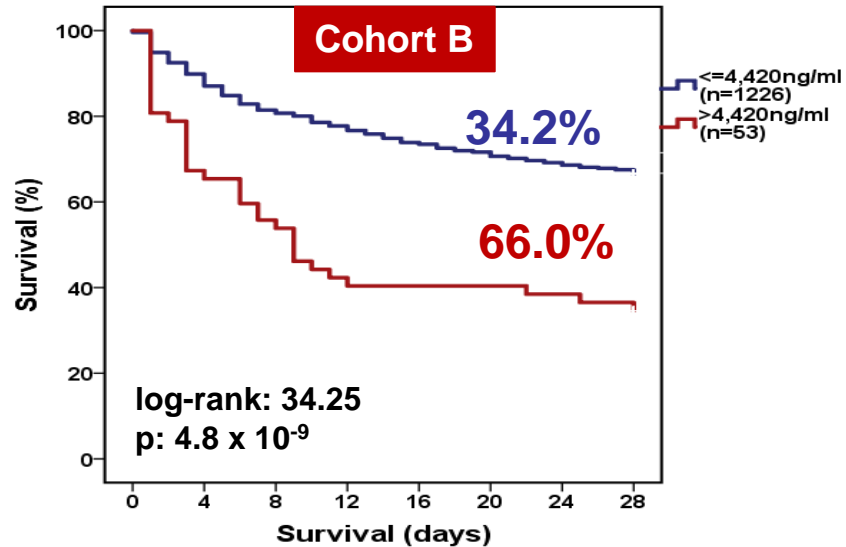
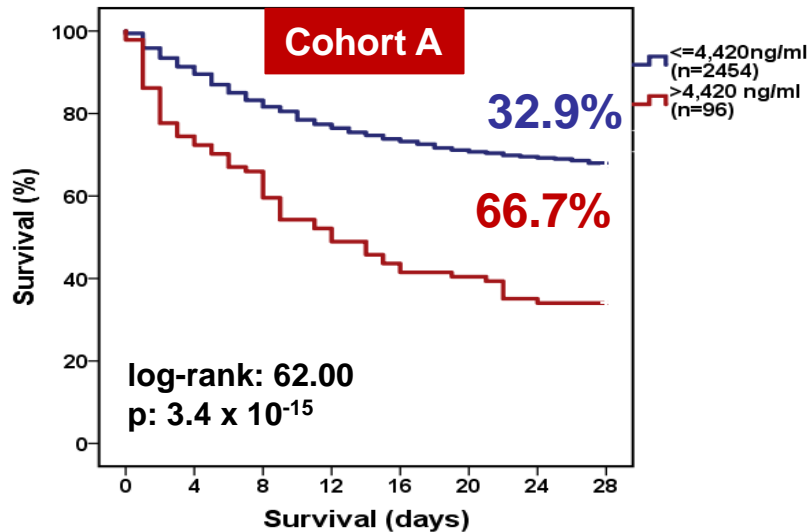
	Cohort A		Cohort B	
	OR	p	OR	p
MALS	1.86	0.003	2.81	<0.0001
ARDS	1.72	<0.0001	1.81	<0.0001
AKI	3.12	<0.0001	3.79	<0.0001
Shock	3.45	<0.0001	4.16	<0.0001

AKI: acute kidney injury

ARDS: acute respiratory distress syndrome

MALS: macrophage-activation like syndrome

OR: odds ratio

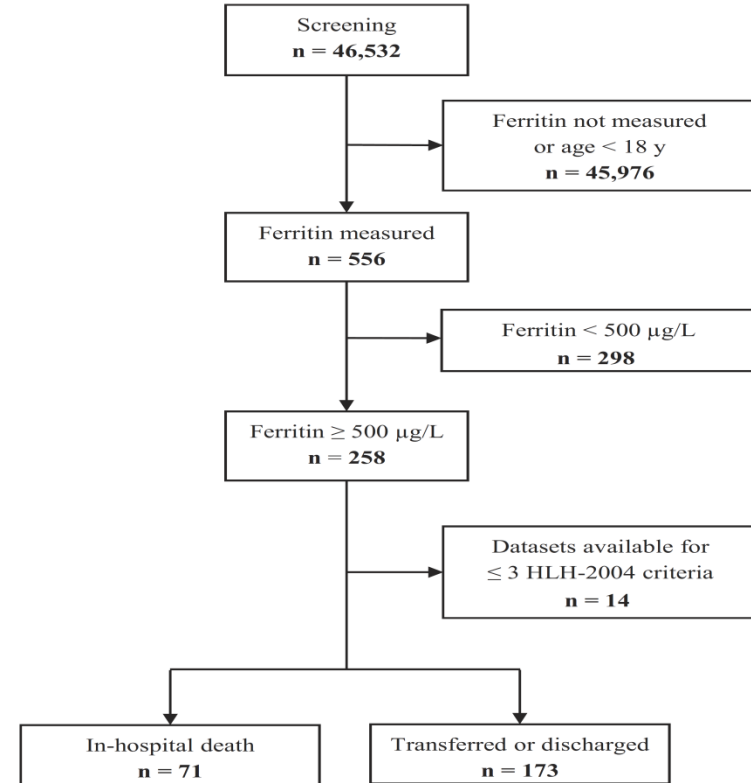


Ferritin > 4,420 ng/ml
 Specificity 97.1%
 Negative predictive value 98%

HYPERFERRITINEMIA IN THE ICU: CHARITÉ GERMANY 2006-2013

(Lachmann G, et al. *Shock* 2018; 50: 149)

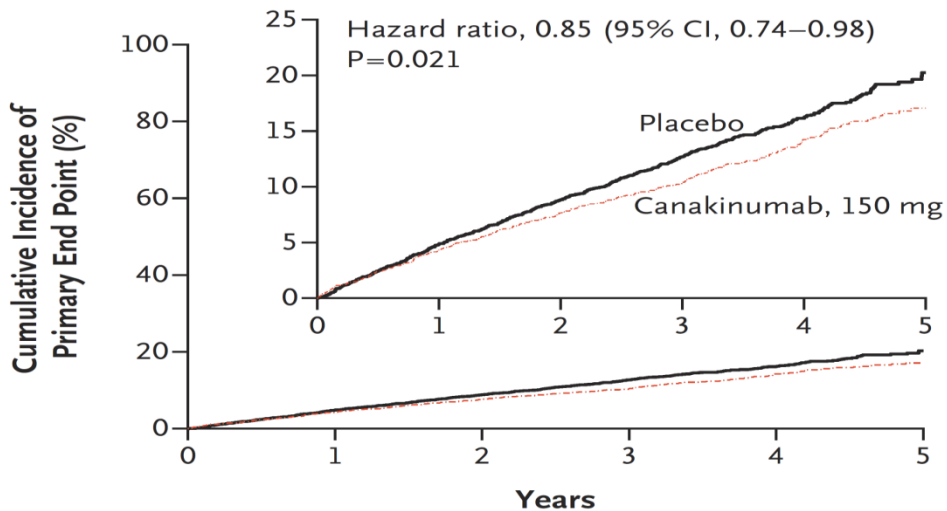
9 patients with
positive HScore



CHRONIC MACROPHAGE ACTIVATION & CARDIOVASCULAR RISK

(Ridker PM, et al. *N Engl J Med* 2017; 377: 1119)

Primary End Point with Canakinumab, 150 mg, vs. Placebo



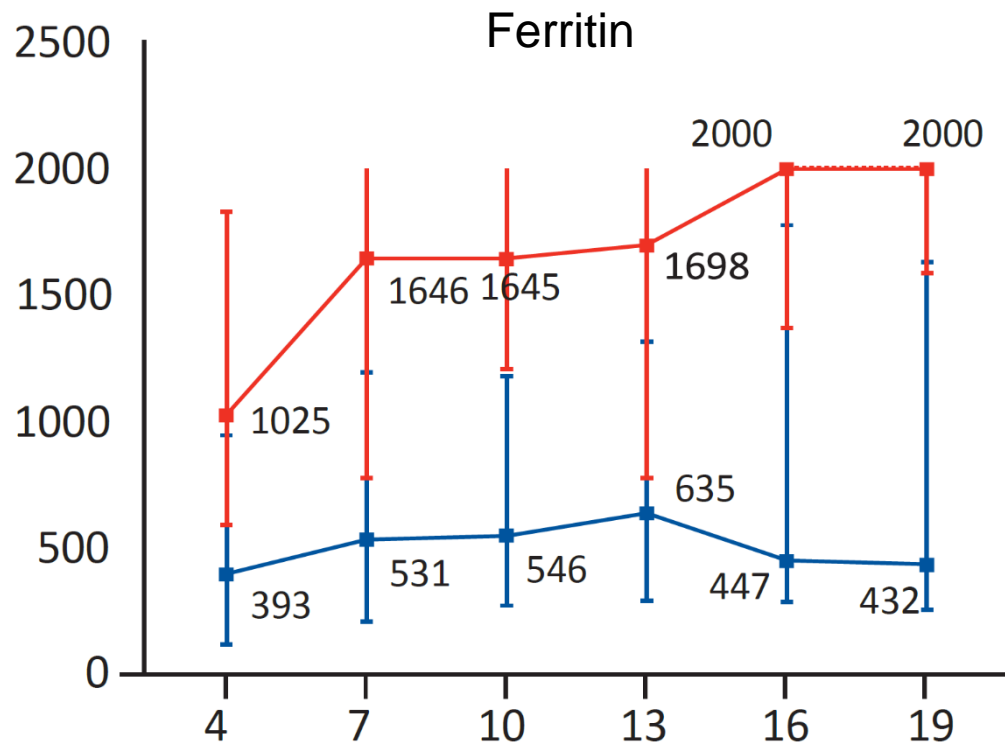
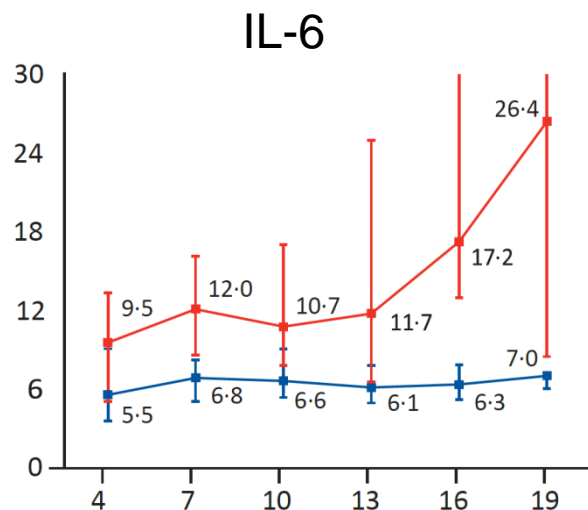
No. at Risk

Placebo	3344	3141	2973	2632	1266	210
Canakinumab	2284	2151	2057	1849	907	207

- Canakinumab
Antiinflammatory
Thrombosis Outcome
Study (CANTOS)
- First myocardial infarct
survivors + CRP>2mg/l

THE FIRST INDICATION FOR THE PRESENCE OF MAS IN SEVERE COVID-19

(Zhou F, et al. *Lancet* 2020; doi: 10.1016/S0140-6736(20)30566-3)



Survivors (n=137)

Non-survivors (n=54)

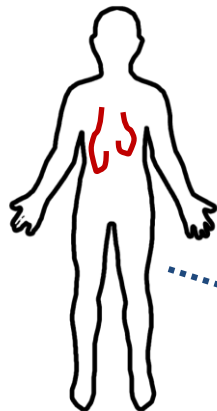
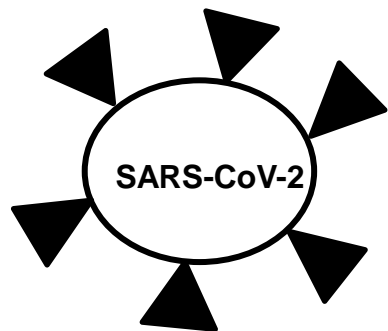
HOW CAN MACROPHAGE ACTIVATION SYNDROME BE DIAGNOSED?

Ferritin >4,420 ng/ml

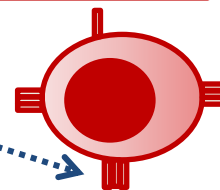
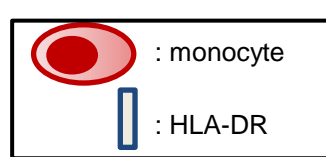


Count

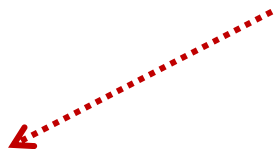
- ✓ ↑↑ temperature (0 to 49 pts)
- ✓ Hepato-/splenomegaly (0 to 38 pts)
- ✓ ↓↓ blood cell counts (0 to 34 pts)
- ✓ ↑↑ triglycerides (0 to 64 pts)
- ✓ ↓ fibrinogen (0 to 38 pts)
- ✓ ↑↑ ferritin (0 to 50 pts)
- ✓ ↑ AST (0 to 19 pts)
- ✓ BM hemophagocytosis (0 to 35 pts)
- ✓ Immunosuppression (0 to 18 pts)



Infiltrates
↑CRP
↑D-dimers
↑AST/ALT

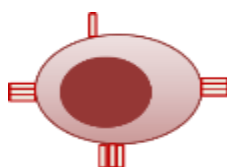
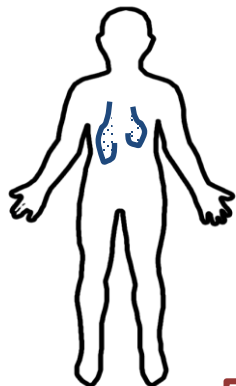


Vivid antigen-
presentation



Macrophage activation: IL-1 β (25%)

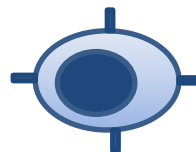
Immune dysregulation: IL-6 (75%)



↑↑↑CRP/ferritin/TGs
↑↑D-dimers
↑↑AST/ALT

↑↑TNF α
↑↑IL-1 β
↑↑IL-6

Moderate antigen-
presentation



↑↑CRP
↑↑D-dimers
↑↑AST/ALT

Weak antigen-
presentation

↑↑TNF α
↑↑IL-6

↓↓ CD4-/CD8-/T17-
lymphocytes
↓ B-lymphocytes, ↓IgGs
↓↓ NKT-/NK-cells

CASE-SERIES OF 8 PATIENTS

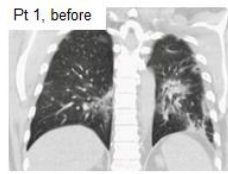
(Dimopoulos G, et al. *Cell Host Microbe* 2020; doi: 10.1016/j.chom.2020.05.007)

- Eight patients; 7 male
- Charlson's comorbidity index: 1-10
- Seven intubated: IV anakinra 200mg three times daily for 7 days
- Criterion for treatment HScore ≥ 169
- One non-intubated: IV 300 mg once daily for four days + 100 mg subcutaneously one daily until discharge

HScore: THE SELECTION TOOL

(Dimopoulos G, et al. *Cell Host Microbe* 2020; doi: 10.1016/j.chom.2020.05.007)

Pt	T (°C)	Organomegaly	Number of cytopenias	TGs (mmol/l)	Fibrinogen (g/l)	Ferritin (ng/ml)	AST (IU/l)	Hemo-phagocytosis	Immuno-suppression	HScore
1	39.8 (49)	None (0)	Hb 8.5 g/dl; WBC 2890/mm ³ (24)	2.28 (44)	0.78 (0)	5002 (35)	55 (19)	N/A	No	171
2	40.0 (49)	H & S (38)	Nil lineage (0)	4.89 (64)	0.48 (0)	1924 (0)	71 (19)	N/A	No	170
3	38.5 (33)	H & S (38)	Nil lineage (0)	1.84 (44)	0.38 (0)	3582 (35)	34 (19)	N/A	No	169
4	37.5 (0)	S (23)	Hb 8.5 g/dl; WBC 3200/mm ³ (24)	1.53 (44)	0.80 (0)	6032 (50)	36 (19)	N/A	Non-Hodgkin Lymphoma (18)	178
5	39.5 (49)	H (23)	WBC 3200/mm ³ (0)	2.32 (44)	0.64 (0)	6786 (50)	241 (19)	N/A	No	185
6	37.7 (0)	H & S (38)	Nil lineage (0)	4.22 (64)	0.57 (0)	7389 (50)	265 (19)	N/A	No	171
7	38.6 (33)	H & S (38)	Hb 8.3 g/dl; WBC 4200/mm ³ ; PLT 48,000/mm ³ (34)	3.29 (44)	0.77 (0)	10500 (50)	332 (19)	N/A	No	218
8	38.5 (33)	N/A	Hb 6.0 g/dl; WBC 1800/mm ³ ; PLT 31,000/mm ³ (34)	1.80 (44)	0.76 (0)	>6000 (50)	615 (19)	N/A	Chemotherapy (18)	198



Pt 1, before
Infiltrates of lower right and left lobes
 pO_2/FiO_2 : 88mmHg, AKI(-)



Pt 1, EOT
Worsening of infiltrates
 pO_2/FiO_2 : 160mmHg, AKI(-)



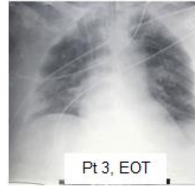
Pt 2, before
Diffuse parenchymal and peribronchial infiltrates
 pO_2/FiO_2 : 78mmHg, AKI(+)



Pt 2, EOT
↓ Infiltrates
 pO_2/FiO_2 : 115mmHg, AKI(+)



Pt 3, before
Diffuse infiltrates
 pO_2/FiO_2 : 68mmHg, AKI(-)



Pt 3, EOT
↓ infiltrates; ↑ aeration
 pO_2/FiO_2 : 125mmHg, AKI(-)



Pt 4, before
Diffuse infiltrates
 pO_2/FiO_2 : 89mmHg, AKI(-)



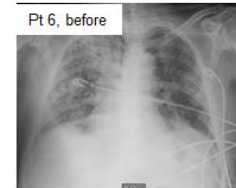
Pt 4, EOT
Unchanging Infiltrates
 pO_2/FiO_2 : 141mmHg, AKI(+)



Pt 5, before
Diffuse infiltrates
 pO_2/FiO_2 : 88mmHg, AKI(-)



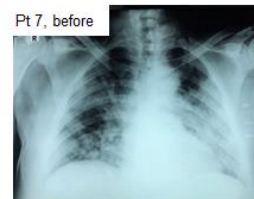
Pt 5, EOT
↓ infiltrates; ↑ aeration
 pO_2/FiO_2 : 92mmHg, AKI(-)



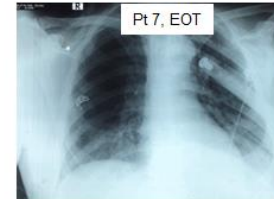
Pt 6, before
Diffuse infiltrates, predominantly right
 pO_2/FiO_2 : 92mmHg, AKI(-)



Pt 6, EOT
↓ Infiltrates
 pO_2/FiO_2 : 198mmHg, AKI(+)



Pt 7, before
Diffuse infiltrates, predominantly left
 pO_2/FiO_2 : 87mmHg, AKI(-)

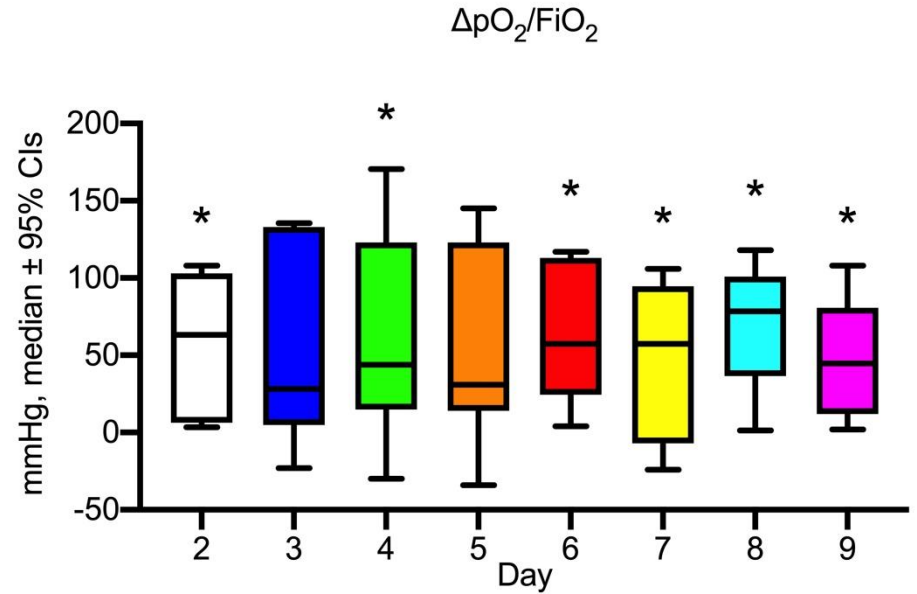
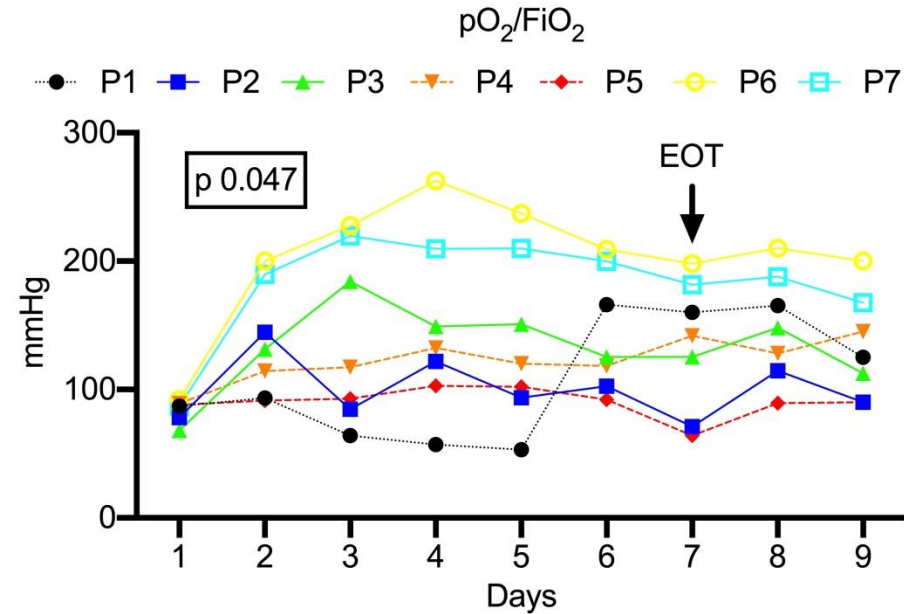


Pt 7, EOT
↓ infiltrates; ↑ aeration
 pO_2/FiO_2 : 182mmHg, AKI (-)

EOT: end of treatment

APPARENT BENEFIT ON RESPIRATORY FUNCTION

(Dimopoulos G, et al. *Cell Host Microbe* 2020; doi: 10.1016/j.chom.2020.05.007)



EOT: end of treatment

Efficiency in management of organ dysfunction associated with infection by the novel SARS-Cov-2 virus through A Personalized immunotherapy approach

ESCAPE

- Adults of both genders
- Confirmed infection by SARS-CoV-2 virus using molecular techniques
- Total SOFA score ≥ 2 or ARDS
- Laboratory documentation of MAS or immune dysregulation.

Macrophage activation syndrome (MAS): serum ferritin $>4,420\text{ng/ml}$.

Immune dysregulation as the combination of : a) serum ferritin $\leq 4,420\text{ng/ml}$; and b) $<5,000$ receptors of the membrane molecule of HLA-DR on CD14-monocytes or <30 MFI of HLA-DR on CD14-monocytes by flow cytometry.

ARDS: acute respiratory distress syndrome

MAS: macrophage activation syndrome

SOFA: sequential organ failure assessment

INTERVENTION

Patients with MAS

- IV anakinra 200mg q8h for 7 days.
- If creatinine clearance < 30 ml/min adjustment to 100mg anakinra q8h for 7days.

Patients with complex immune dysregulation

- IV tocilizumab 8mg/kg once (maximum 800mg)
- IV anakinra when:
Absolute neutrophil count <2,500/mm³
Absolute platelet count < 100,000/mm³
AST or ALT >1.5 x the upper normal limit

ALT: alanine aminotransferase

AST: aspartate aminotransferase

IV: intravenous

MAS: macrophage activation syndrome

q8h: every 8 hours

Efficiency in management of organ dysfunction associated with infection by the novel SARS-Cov-2 virus through A Personalized immunotherapy approach-ESCAPE

EudraCT number 2020-001039-29
Clinicaltrials.gov NCT04339712

Screened for eligibility= 144

- Excluded= 42
- Failed immune classification= 19
 - No increase of SOFA= 8
 - Not meeting category 2 or 3 criteria of LRTI involvement= 5
 - Corticosteroid intake= 4
 - Stage IV malignancy= 3
 - Withdrew consent= 3

Allocated to personalized treatment (ITT)= 102

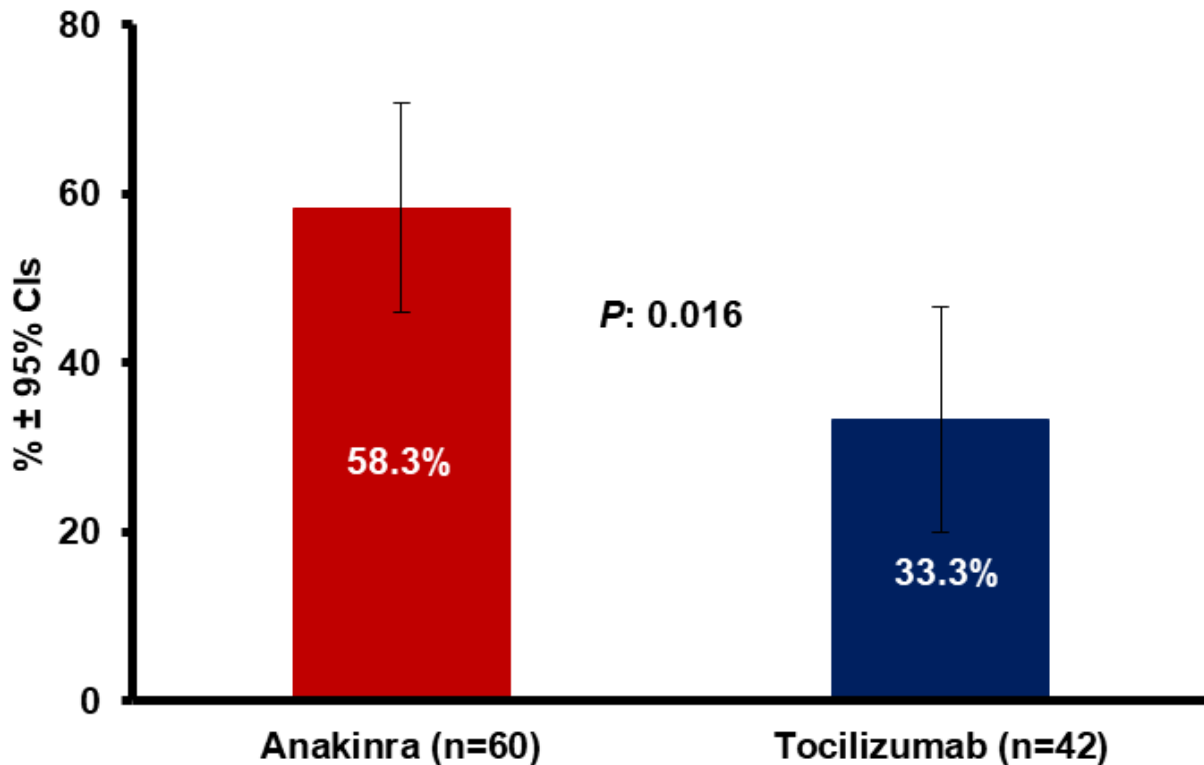
Tocilizumab= 42
Dysregulation with normal PMNs, AST/ALT, PLT

Anakinra= 60
• MAS= 14
• Dysregulation with ↑AST/ALT= 46

ALT: alanine aminotransferase
AST: aspartate aminotransferase
ITT: intent-to-treat
LRTI: lower respiratory tract infection
MAS: macrophage activation syndrome
PLT: platelets
PMNs: neutrophils
SOFA: sequential organ failure assessment

PRIMARY STUDY ENDPOINT

$\geq 25\%$ decrease of baseline total SOFA score AND/OR $\geq 50\%$ increase of the baseline pO_2/FiO_2

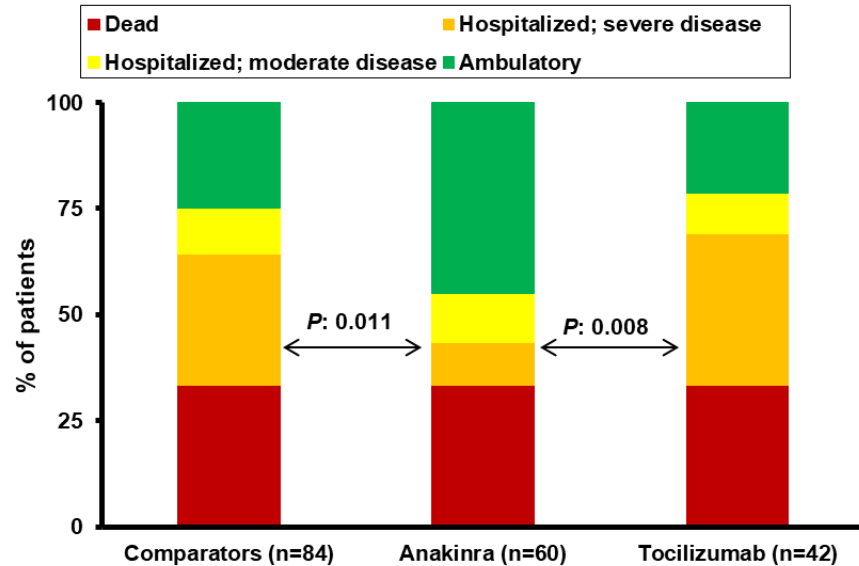


CI: confidence interval

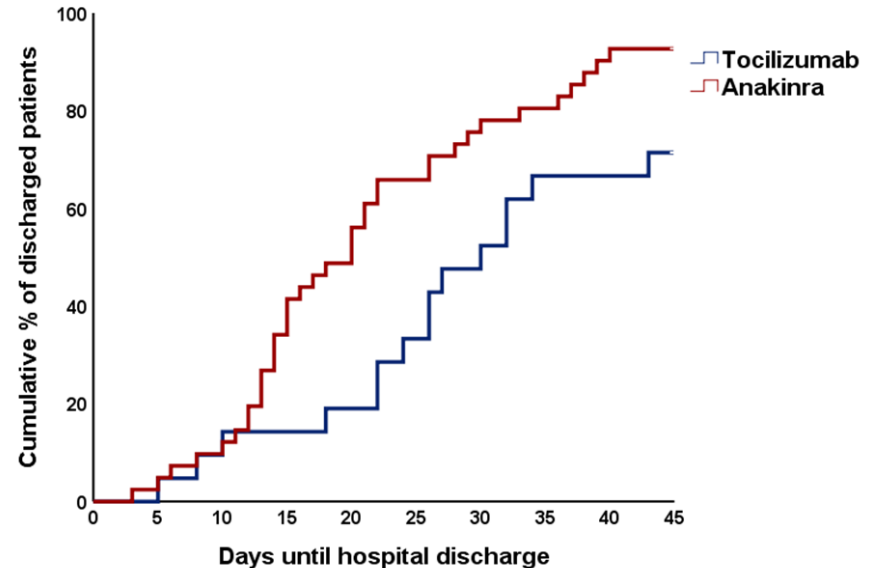
SECONDARY ENDPOINTS

(Karakike E, et al. *J Innate Immun* doi 10.1159/000519090)

WHO Clinical Progression Scale Day 28



Length of Hospital Stay

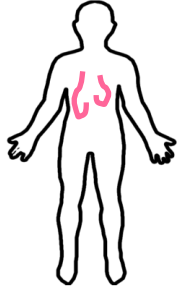
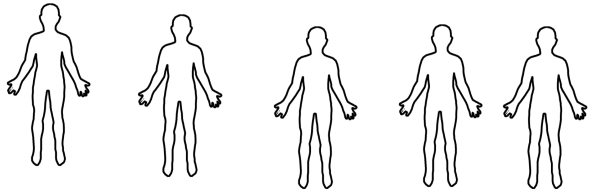


SERIOUS ADVERSE EVENTS (n, %)

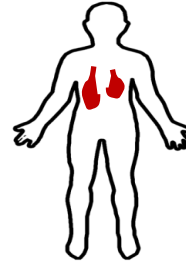
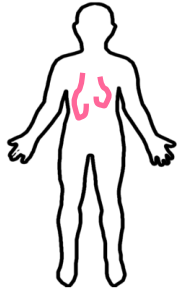
(Karakike E, et al. *J Innate Immun* doi 10.1159/000519090)

	Anakinra (n=60)	Tocilizumab (n=42)	P -value
Pneumothorax	2 (3.3)	6 (14.3)	0.062
Pulmonary embolism	1 (1.7)	0 (0)	1.00
Deep venous thrombosis	1 (1.7)	0 (0)	1.00
Acute kidney injury	7 (11.7)	5 (11.9)	1.00
Shock	17 (28.3)	10 (23.8)	0.655
Infections			
Ventilator-associated pneumonia	9 (15.0)	15 (15.7)	0.019
Catheter-related bloodstream infection	4 (6.7)	4 (9.5)	0.714
Bloodstream infection	13 (21.7)	17 (40.5)	0.049
Clostridioides difficile infection	3 (5.0)	1 (2.4)	0.641
Arrhythmias			
Ventricular tachycardia	3 (5.0)	0 (0)	0.266
Atrial fibrillation	6 (10.0)	4 (9.5)	1.00
Bradycardia	0 (0)	4 (9.5)	0.026
Grade 4 laboratory investigation	4 (6.7)	5 (11.9)	0.572
Thrombocytopenia	3 (5.0)	4 (9.5)	0.442
Increase of aminotransferases	0 (0)	3 (7.1)	0.067
Increase of CPK	1 (1.7)	2 (4.8)	0.567

TIME COURSE OF COVID-19 PNEUMONIA

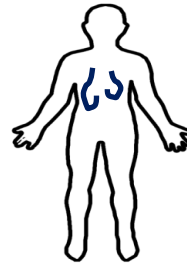


60% ARE AT RISK



1st scenario:
Severe Respiratory Failure

- Mechanical Ventilation
- Death?



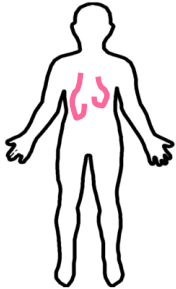
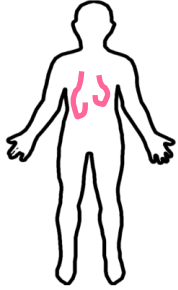
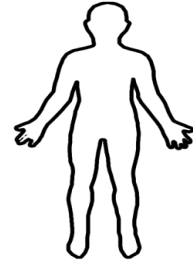
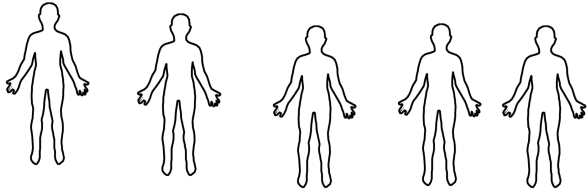
2nd scenario:

- Persistent symptoms/problems
- Work abstinence
- Loss of work productivity
- Long-term morbidity/mortality

PATIENTS ARRIVING
AT HOSPITAL

THERAPY
STARTS

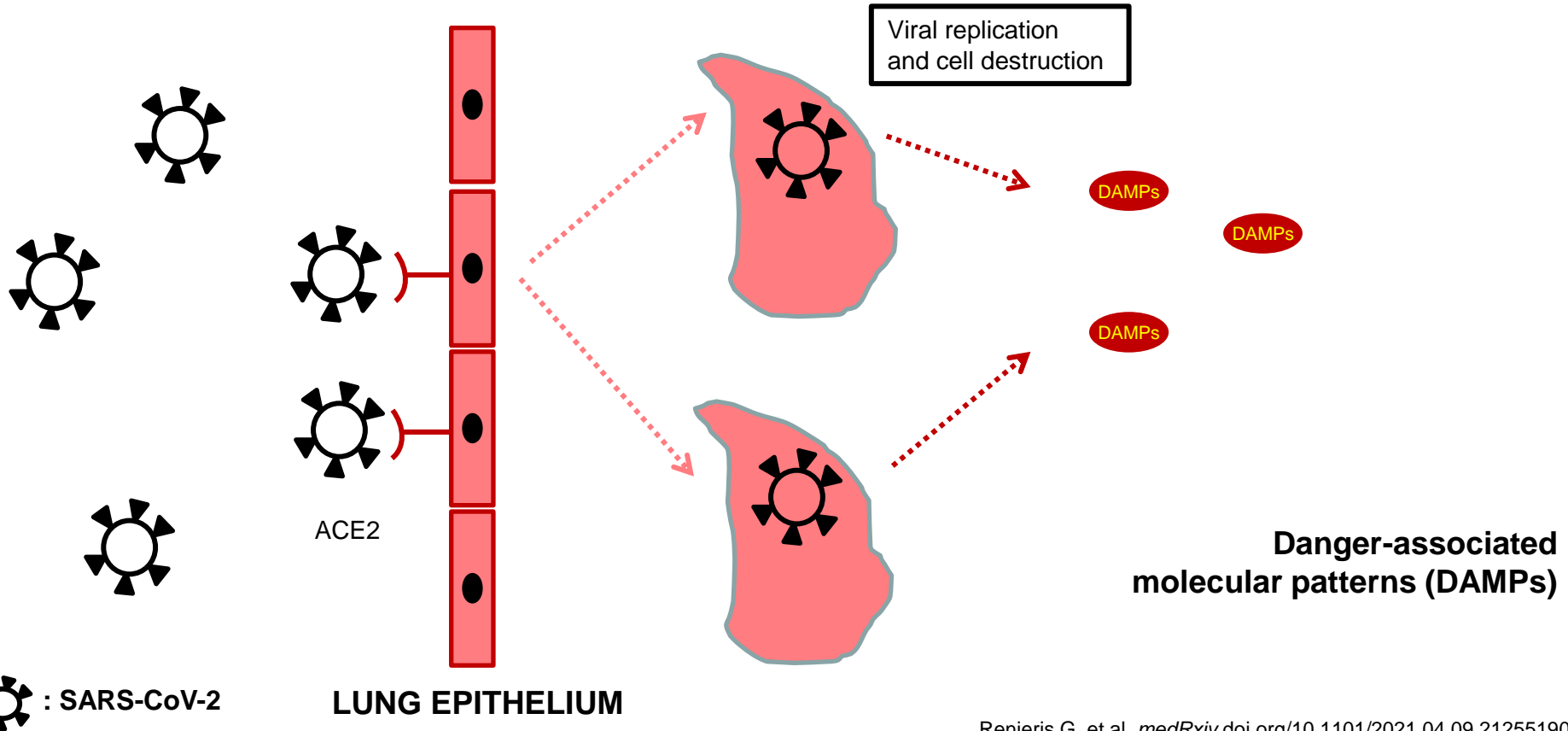
WHAT WE SHOULD DO?



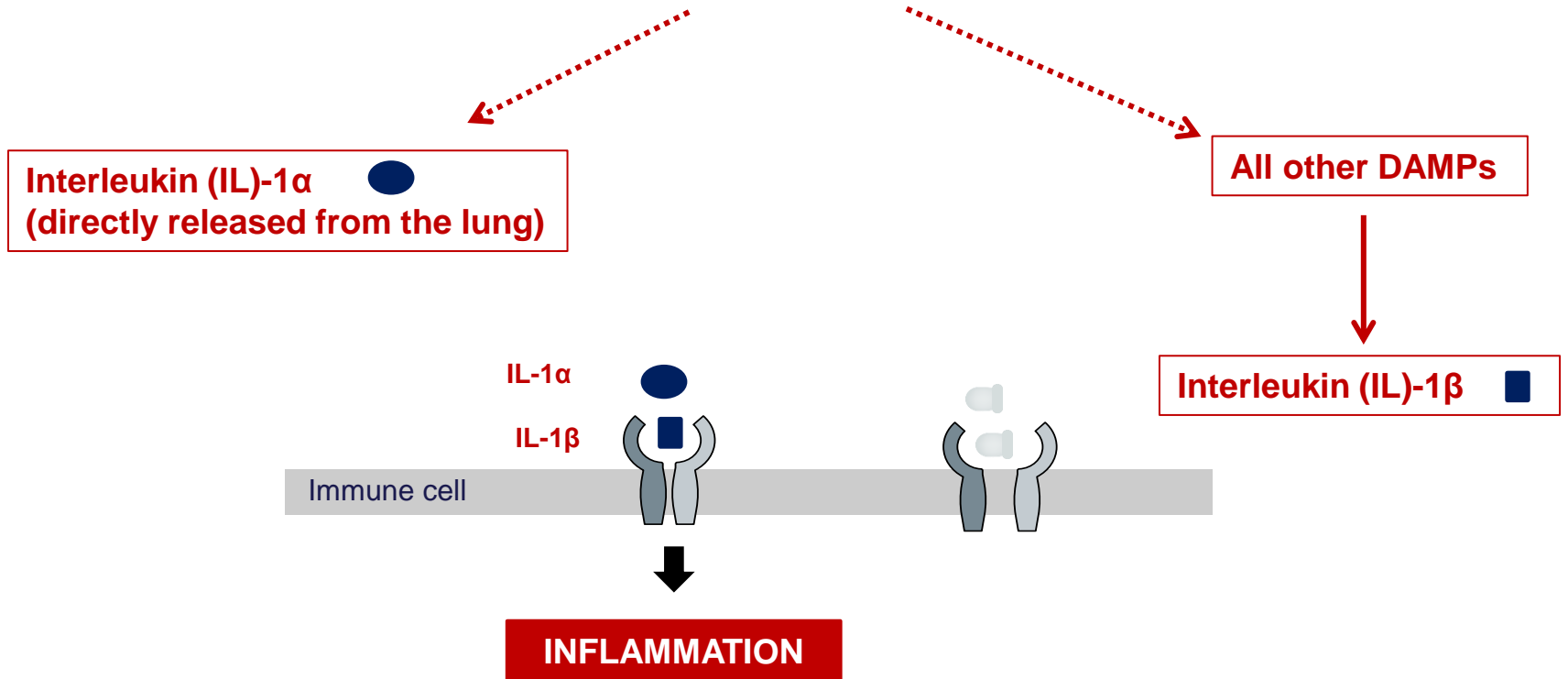
- ↓ admission in the ICU
- ↓ Mortality
- ↑ Cure rate



EARLY INITIATION OF BAD OUTCOME

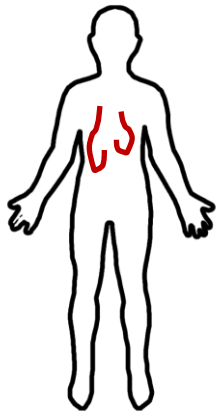


DANGER-ASSOCIATED MOLECULAR PATTERNS (DAMPs) IN COVID-19



suPAR-GUIDED ANAKINRA TREATMENT FOR VALIDATION OF THE RISK AND EARLY MANAGEMENT OF SEVERE RESPIRATORY FAILURE BY COVID-19

THE SAVE STRATEGY



STOP
IL-1 α
IL-1 β



PREVENT
Unfavorable outcome



Pneumonia

- Hospitalization
- pO₂/FiO₂: 150-400
- Oxygen mask/nasal oxygen/high-flow oxygen
- suPAR \geq 6 ng/ml

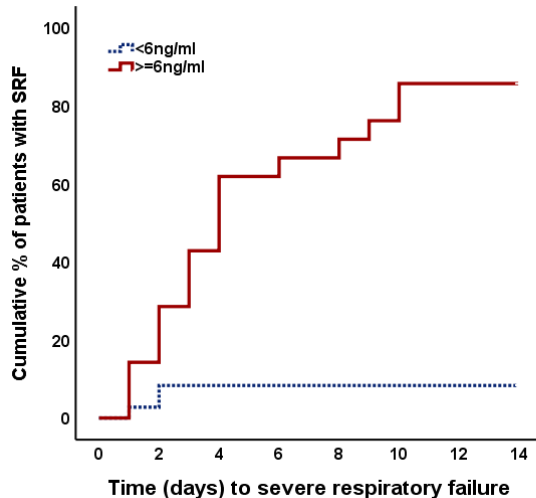
Anakinra

- Recombinant human receptor antagonist
- Blocks the action of IL-1 α and IL-1 β

suPAR FOR EARLY PROGNOSTICATION (Rovina N, et al. *Crit Care* 2020; 24: 187)

TEST SET

(Rovina N, et al. *Crit Care* 2020; 24: 187)



Validation cohort 1: ISIC

(Azan TU et al. *J Am Soc Nephrol* 2020; 31: 2725-35)

352 patients

Progression into severe respiratory failure

- suPAR <4.6ng/ml: 2.6%
- suPAR 4.6-6.8 ng/ml: 17.9%
- suPAR >6.8 ng/ml: 44.9%

Validation cohort 2: ISIC

(Vasbinder A, et al. *Diabetes Care* 2022; dc212102)

n = 2,044 patients

- suPAR among patients with DM2
- Independent predictor of respiratory failure
odds ratio 1.94 (1.36-2.75); p<0.0001

IL: interleukin

ISIC: International Study of Inflammation in COVID-19

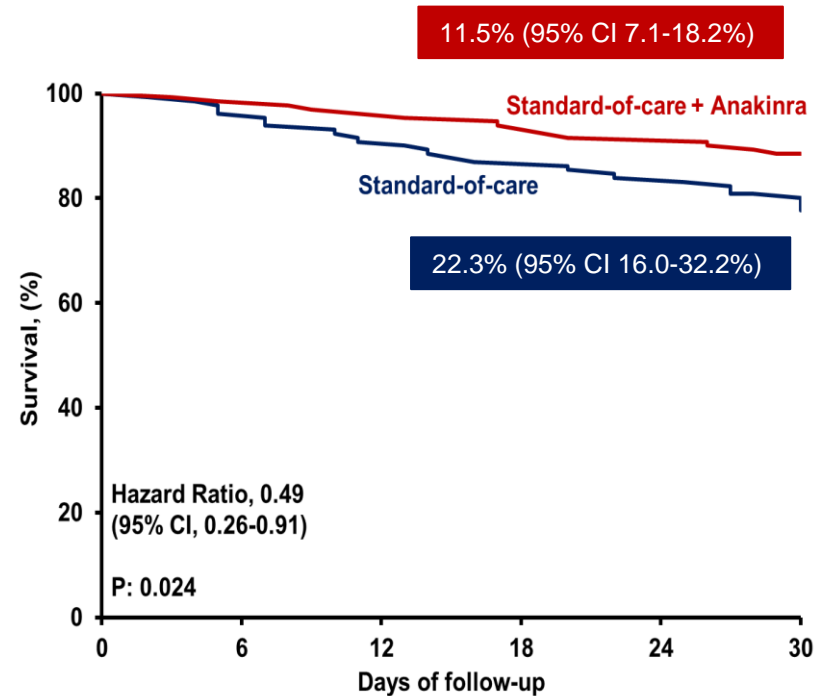
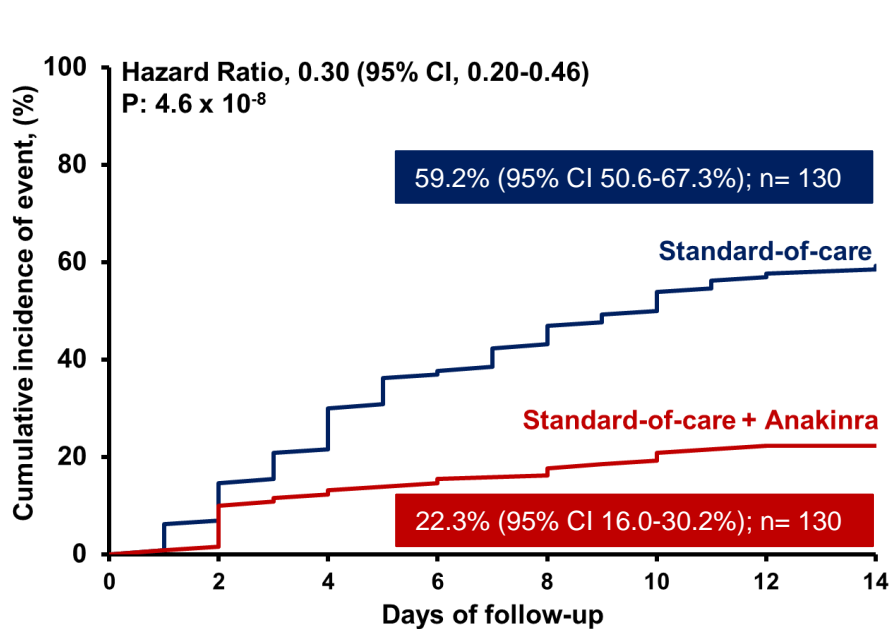
LDH: lactate dehydrogenase

ROC: receiver operator characteristics

suPAR: soluble urokinase plasminogen activator receptor

SAVE PHASE 2 TRIAL: ANAKINRA EFFICACY

(Kyriazopoulou E, et al. *eLife* 2021; 10: e66125)





OPEN

Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial

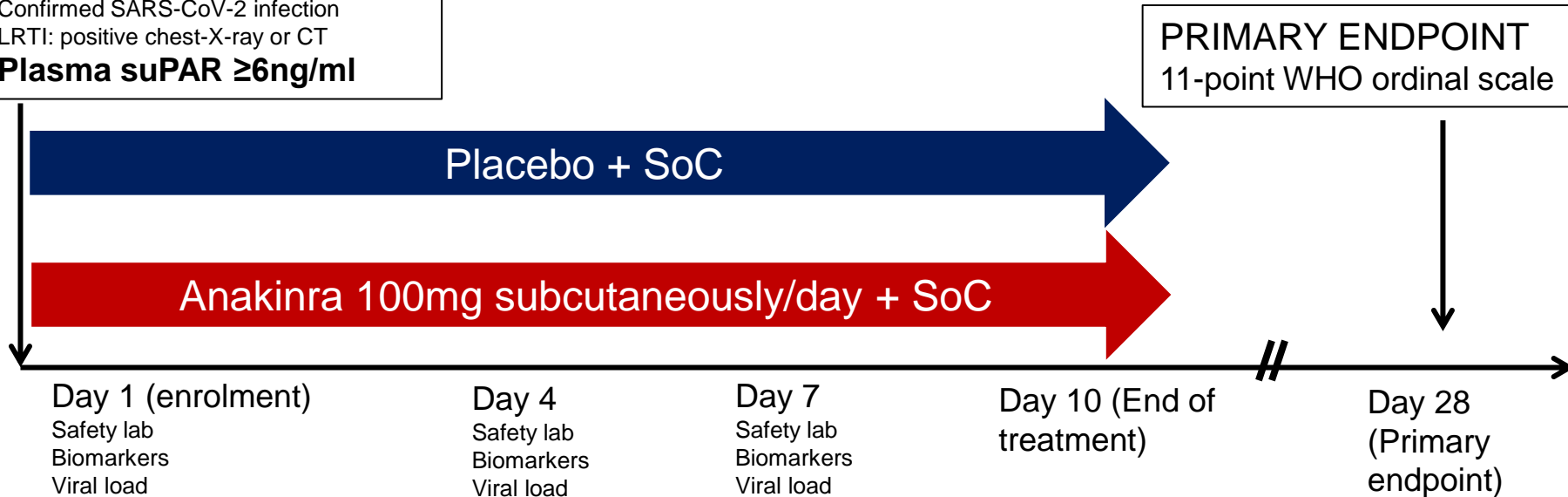
Evdoxia Kyriazopoulou¹, Garyfallia Poulakou², Haralampos Milionis³, Simeon Metallidis⁴, Georgios Adamis⁵, Konstantinos Tsiakos⁶, Archontoula Fragkou⁷, Aggeliki Rapti⁶, Christina Damoulari¹, Massimo Fantoni⁸, Ioannis Kalomenidis⁹, Georgios Chrysos¹⁰, Andrea Angheben¹¹, Ilias Kainis¹², Zoi Alexiou¹³, Francesco Castelli¹⁴, Francesco Saverio Serino¹⁵, Maria Tsilika¹, Petros Bakakos¹⁶, Emanuele Nicastrì¹⁷, Vassiliki Tzavara¹⁸, Evangelos Kostis¹⁹, Lorenzo Dagna²⁰, Panagiotis Koufargyris¹, Katerina Dimakou²¹, Spyridon Savvanis⁷, Glykeria Tzatzagou²², Maria Chini²³, Giulio Cavalli²⁰, Matteo Bassetti²⁴, Konstantina Katrini¹, Vasileios Kotsis²⁵, George Tsoukalas²⁶, Carlo Selmi²⁷, Ioannis Bliziotis²⁸, Michael Samarkos²⁹, Michael Doulas³⁰, Sofia Ktena¹, Aikaterini Masgala³¹, Ilias Papanikolaou³², Maria Kosmidou³, Dimitra-Melia Myrodi², Aikaterini Argyraki³³, Chiara Simona Cardellino¹¹, Katerina Koliakou³⁴, Eleni-Ioanna Katsigianni³⁴, Vassiliki Rapti², Efthymia Giannitsioti¹⁰, Antonella Cingolani⁸, Styliani Micha³⁴, Karolina Akinosoglou³⁵, Orestis Liatsis-Douvitsas³⁴, Styliani Symbardi³⁶, Nikolaos Gatselis³⁷, Maria Mouktaroudi^{1,34}, Giuseppe Ippolito¹⁷, Eleni Florou³⁴, Antigone Kotsaki¹, Mihai G. Netea^{38,39}, Jesper Eugen-Olsen⁴⁰, Miltiades Kyprianou³⁴, Periklis Panagopoulos⁴¹, George N. Dalekos³⁷ and Evangelos J. Giamarellos-Bourboulis^{1,34} ✉

THE SAVE-MORE, PIVOTAL RCT

(Kyriazopoulou E, et al. *Nature Medicine* 2021; 27: 1752)

Inclusion criteria

- Age ≥ 18 years, both genders, ICF
- Confirmed SARS-CoV-2 infection
- LRTI: positive chest-X-ray or CT
- **Plasma suPAR ≥ 6 ng/ml**



suPAR-guided Anakinra treatment for Validation of the risk and Early Management
Of severe respiratory failure by COVID-19 (EudraCT number: 2020-005828-11)

National Ethics Committee of Greece approval 161/20

Comitato etico dell'istituto nazionale per le malattie infettive "LAZZARO SPALLANZANI" IRCCS of 01.02.2021

www.clinicaltrials.gov NCT04680949

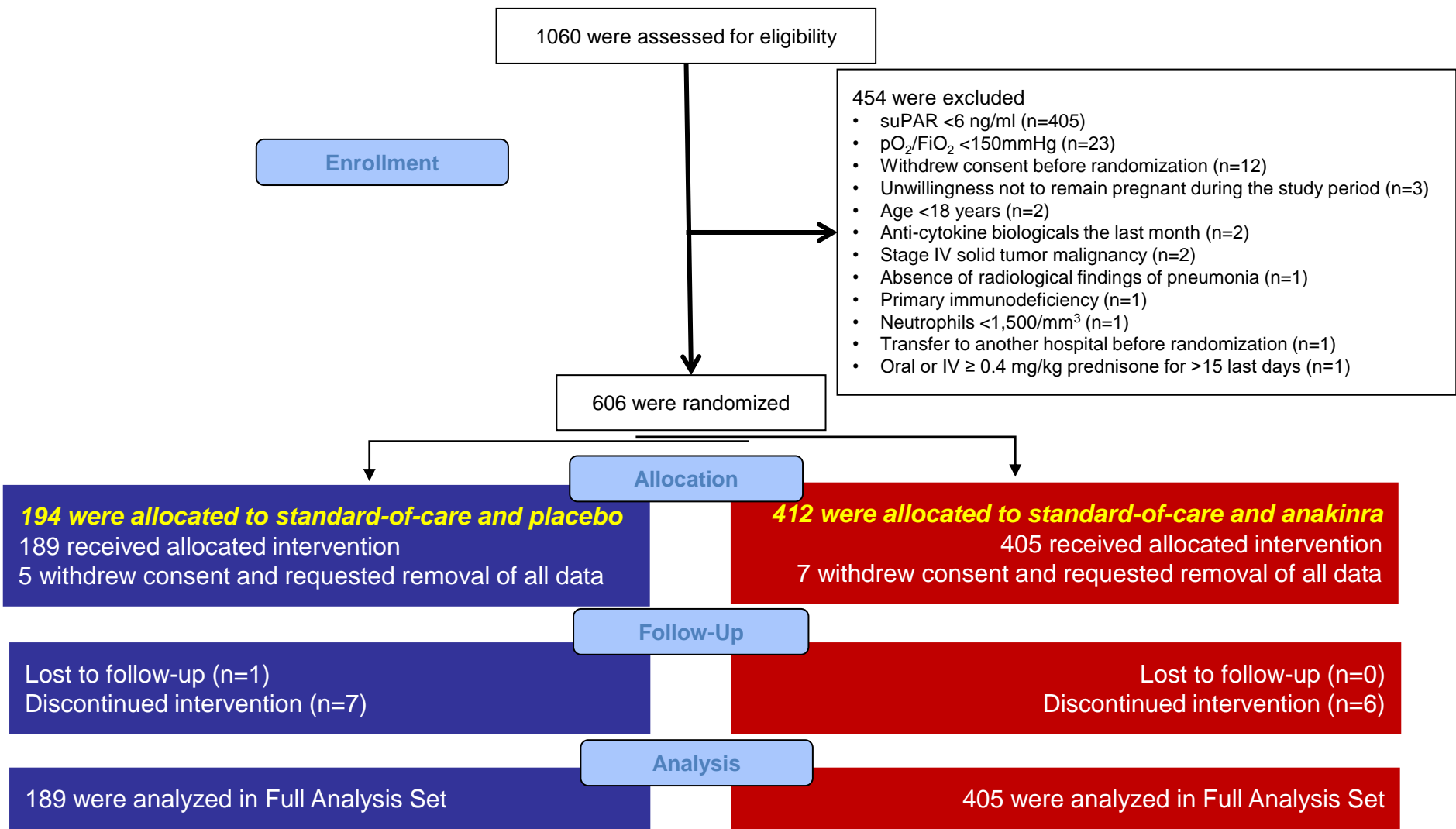
CT: computed tomography

ICF: written informed consent form

LRTI: lower respiratory tract infection

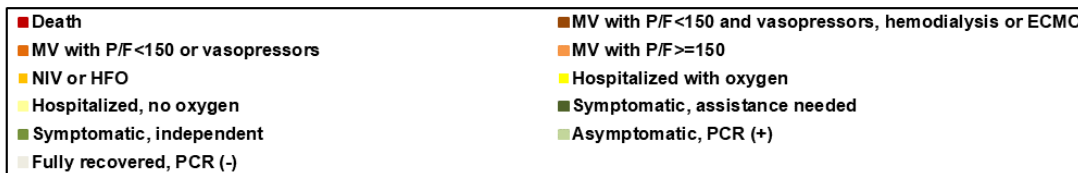
SOC: standard-of-care

suPAR: soluble urokinase Plasminogen Activator Receptor



PRIMARY ENDPOINT

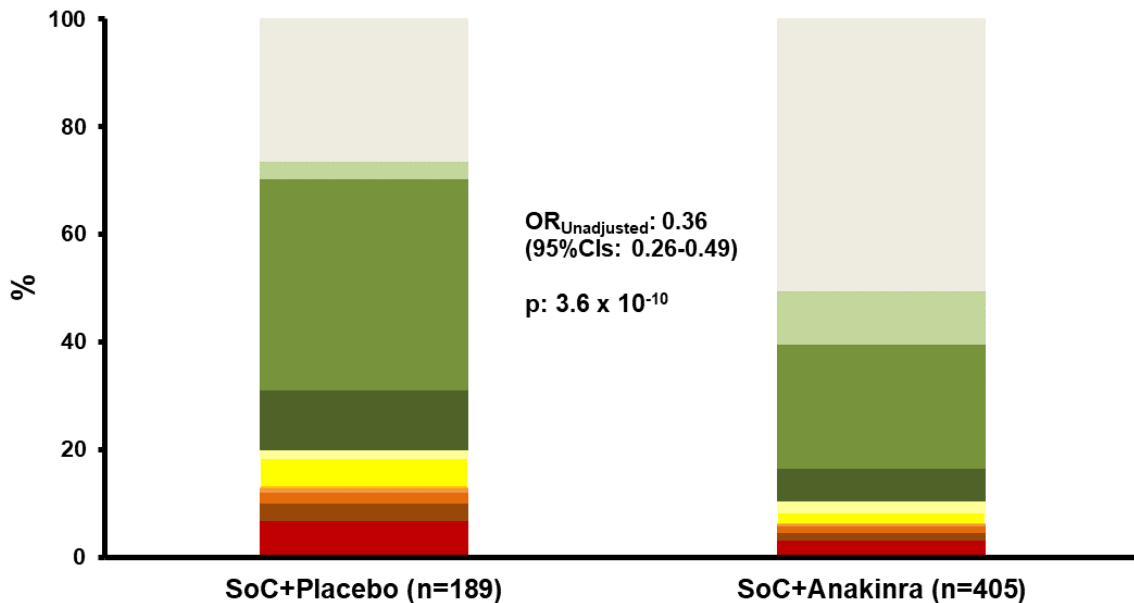
11-point WHO Clinical Progression ordinal Scale by day 28



Assumption of ordinal regression analysis

Goodness-of-fit test
(Pearson's chi-square test)
p: 0.172

Assumption of proportional odds
(test of parallel lines)
p: 0.131



CIs: confidence intervals
OR: odds ratio
SoC: standard-of-care

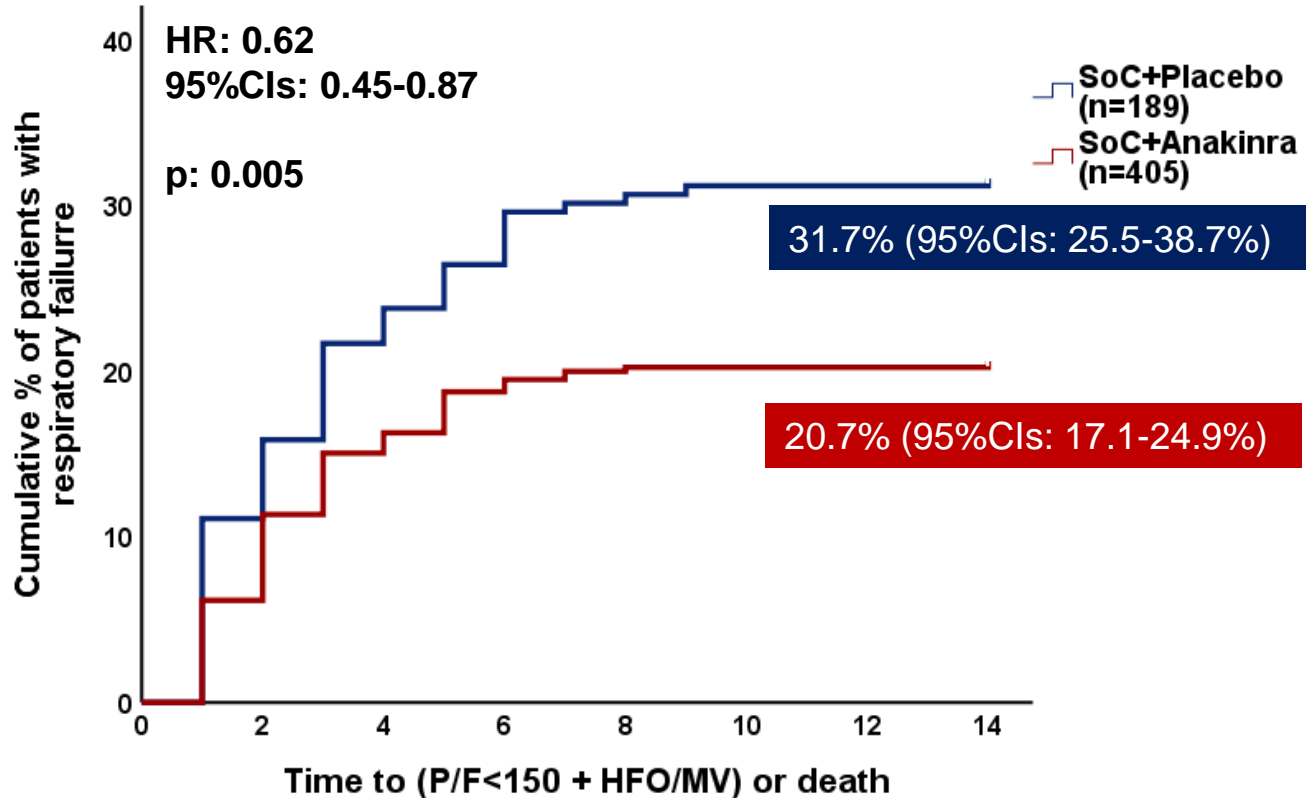
PRIMARY ENDPOINT

ORDINAL LOGISTIC REGRESSION OF WHO-CPS BY DAY 28

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CIs	p-value	Odds ratio	95% CIs	p-value
Group of treatment (Anakinra vs placebo)	0.36	0.26-0.49	3.59×10^{-10}	0.36	0.26-0.50	7.74×10^{-10}
Intake of dexamethasone (Yes/No)	1.90	1.28-2.83	0.002	1.49	0.59-3.80	0.395
Severe COVID-19 by WHO (Yes/No)	1.95	1.31-2.90	0.001	1.29	0.51-3.27	0.582
BMI >30 kg/m ² (Yes/No)	1.27	0.87-1.61	0.267	1.10	0.81-1.50	0.530
Country (Italy vs Greece)	1.18	0.74-1.88	0.482	1.25	0.77-2.03	0.350

CIs: confidence intervals

TIME TO RESPIRATORY FAILURE



CI: confidence interval
HFO: high-flow oxygen
HR: hazard ratio
MV: mechanical ventilation
SoC: standard-of-care













MOST COMMON SERIOUS TREATMENT-EMERGENT ADVERSE EVENTS

	Placebo (n=189)	Anakinra (n=405)	P-value
At least one serious TEAE, n (%)	41 (21.7)	65 (16.0)	0.107
Type of serious TEAE, n (%)			
Infections and infestations, total	30 (15.9)	34 (8.4)	0.010
Ventilator-associated pneumonia	15 (7.9)	9 (2.2)	0.003
Septic Shock and multiple organ dysfunction	7 (3.7)	6 (1.5)	0.128
Bloodstream infection	6 (3.2)	12 (3.0)	1.000
Probable hospital-acquired infections	7 (3.7)	11 (2.7)	0.608
Hospital-acquired pneumonia	5 (2.6)	6 (1.5)	0.339
Acute pyelonephritis	4 (2.1)	5 (1.2)	0.476
Pulmonary embolism	4 (2.1)	6 (1.5)	0.733

Adding anakinra to current Standard-of-Care (SoC)

2.8 times more likely to improve overall clinical status

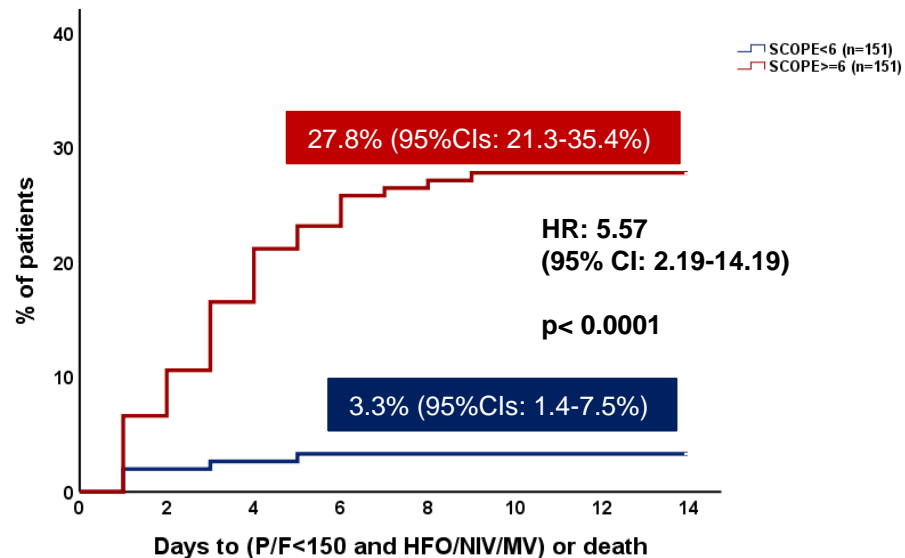
towards completely resolving the viral infection and preventing severe respiratory failure/death

Patient state	SoC + Placebo	SoC + Anakinra
Fully recovered, PCR(-)	 26.5%	 50.4%
Asymptomatic, PCR (+)	 3.2%	 9.9%
Ambulatory, with symptoms	 50.3%	 29.3%
Hospitalized, moderate disease	 6.9%	 4.2%
Hospitalized, severe disease	 6.3%	 3.1%
Dead	 6.9%	 3.2%

SCOPE (Severe Covid Predictor Estimate) Score

(Giamarellos-Bourboulis EJ, et al. *Cell Reports Medicine* 2022; 3: 100560)

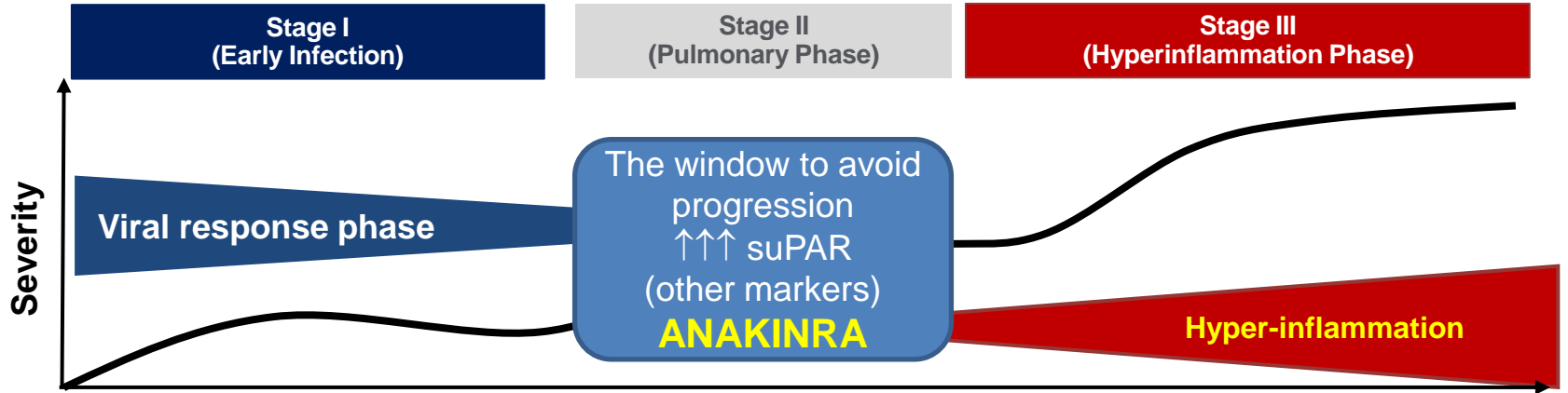
Points	D-dimers (mg/l)	CRP (mg/l)	Ferritin (ng/ml)	IL-6 (pg/ml)
0	0.10-0.40	0.3-25.0	10-225.0	0.7-5.0
1	>0.4-0.57	>25.0-45.0	>225.0-450.0	>5.0-12.0
2	>0.57-0.90	>45.0-85.0	>450.0-750.0	>12.0-30.0
3	>0.90	>85	>750	>30



CI: confidence interval
CRP: C-reactive protein
HFO: high-flow oxygen
HR: hazard ratio
IL: interleukin
NIV: non-invasive ventilation
MV: mechanical ventilation

DRUG POSITIONING IN COVID-19 PNEUMONIA

(van de Veerdonk FL, et al. *Nat Med* 2022; 28: 39-50)



Clinical Symptoms	Constitutional symptoms Fever, Cough	$\text{PaO}_2/\text{FiO}_2 \leq 150\text{-}300\text{mmHg}$	ARDS, Shock, Cardiac Failure
Potential Therapies	Monoclonals, molnupiravir	Dexamethasone	Dexamethasone, tocilizumab, baricitinib

Anakinra (SAVE-MORE)		Tocilizumab (REMAP-CAP, RECOVERY)
Achieve cure	Avoid being severe/dead	Avoid death
NNT= 4	NNT= 15	NNT= 12 NNT= 25

NNT: number needed to treat