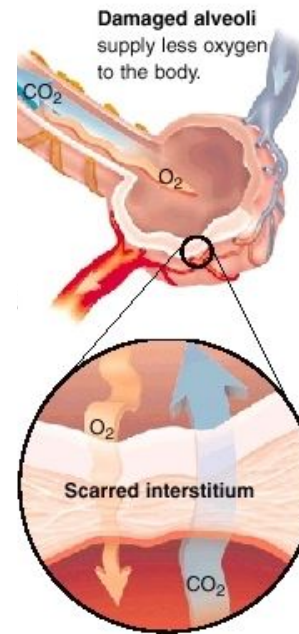
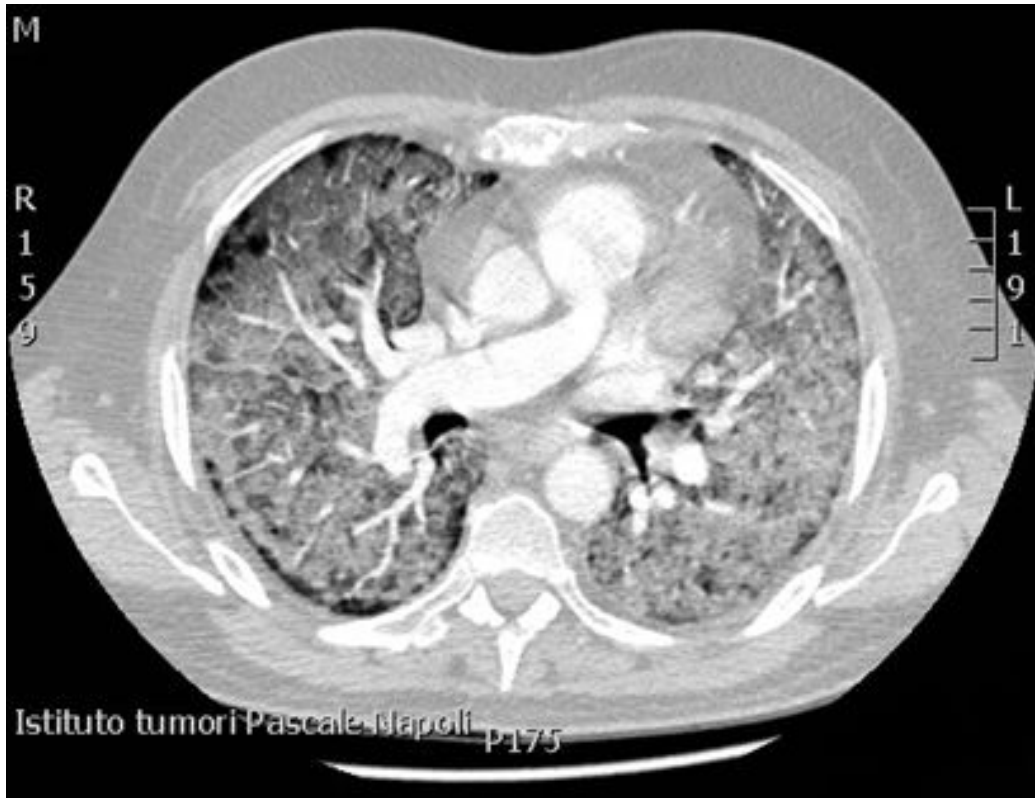


# **Neutralizzare la tempesta di citochine nella polmonite da COVID-19**

**Paolo A. Ascierto, MD**

**Unit Melanoma, Cancer Immunotherapy and Innovative Therapies  
Istituto Nazionale Tumori – Fondazione “G. Pascale”, Napoli**

# What we already know...irAE



## 1) First line treatment of irAE

- High-dose steroids

## 2) Management of steroids-refractory irAE

- Infliximab
- Mycophenolate mofetil
- Tocilizumab

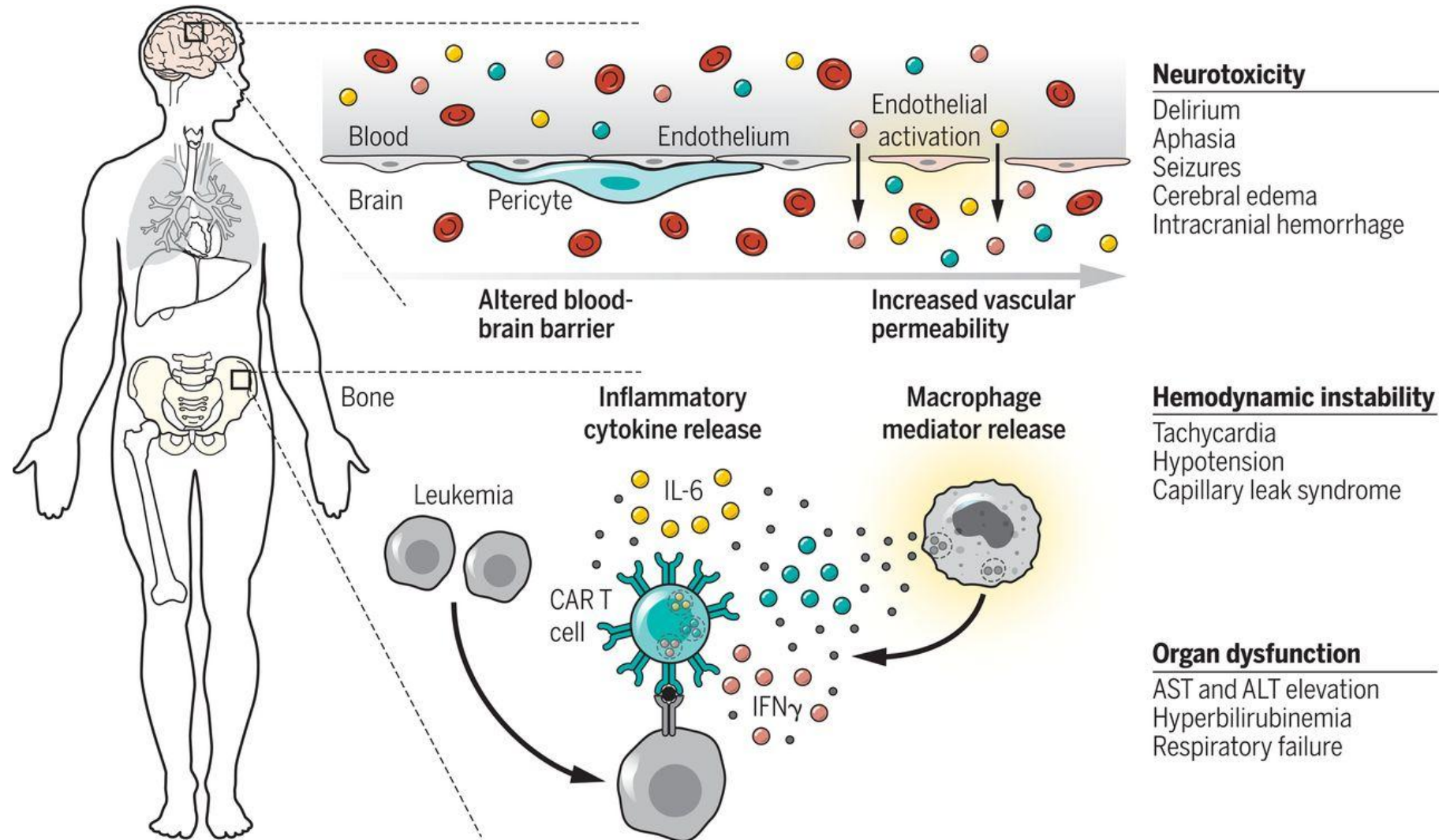
Original Article

### Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade

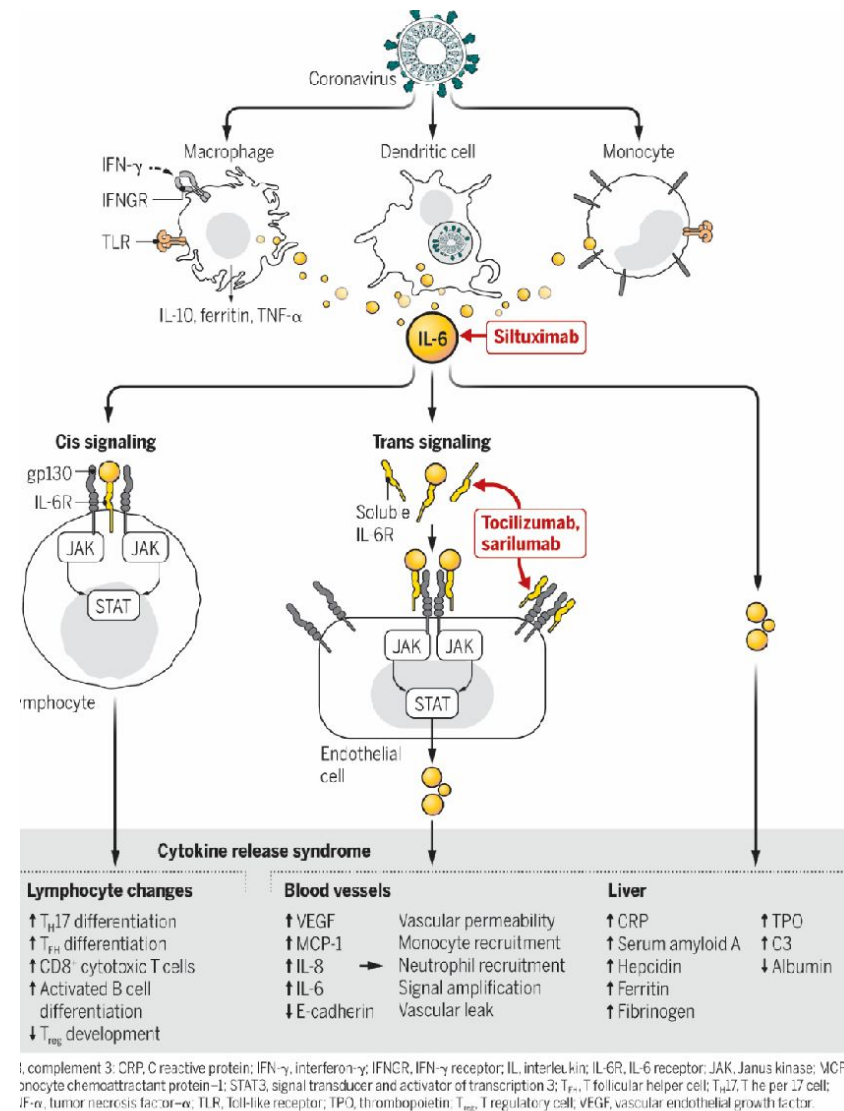
Chipman RG Stroud, Aparna Hegde, Cynthia Cherry, Abdul R Naqash, Nitika Sharma, Srikala Addepalli, Sulochana Cherukuri, Teresa Parent, Jessica Hardin and Paul Walker

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# What we already know...CRS and CAR T



# What we could suspect...CRS and COVID-19



# Anti IL-6 agents








- TOCILIZUMAB
- SARILUMAB
- SILTIXUMAB

Open access

Editorial



## Insights from immuno-oncology: the Society for Immunotherapy of Cancer Statement on access to IL-6-targeting therapies for COVID-19

Paolo Antonio Ascierto <sup>1</sup>, Bernard Fox,<sup>2</sup> Walter Urba,<sup>2</sup>  
Ana Carrizosa Anderson <sup>3</sup>, Michael B Atkins <sup>4</sup>, Ernest C Borden,<sup>5</sup>  
Julie Brahmer,<sup>6</sup> Lisa H Butterfield <sup>7,8</sup>, Alessandra Cesano,<sup>9</sup> Daniel Chen <sup>10</sup>,  
Tanja de Gruijl,<sup>11</sup> Robert O Dillman,<sup>12</sup> Charles G Drake,<sup>13</sup> Leisha A Emens,<sup>14</sup>  
Thomas F Gajewski,<sup>15</sup> James L Gulley <sup>16</sup>, F Stephen Hodi,<sup>17</sup> Patrick Hwu,<sup>18</sup>  
David Kaufman,<sup>19</sup> Howard Kaufman,<sup>20</sup> Michael Lotze,<sup>21</sup> Douglas G McNeel,<sup>22</sup>  
Kim Margolin,<sup>23</sup> Francesco Marincola,<sup>24</sup> Michael J Mastrangelo,<sup>25</sup>  
Marcela V Maus,<sup>26</sup> David R Parkinson,<sup>27</sup> Pedro J Romero,<sup>28</sup> Paul M Sondel <sup>29</sup>,  
Stefani Spranger,<sup>30</sup> Mario Sznol,<sup>31</sup> George J Weiner,<sup>32,33,34</sup> Jon M Wiggington,<sup>35</sup>  
Jeffrey S Weber<sup>36</sup>




COMMENTARY

Open Access



# Why tocilizumab could be an effective treatment for severe COVID-19?

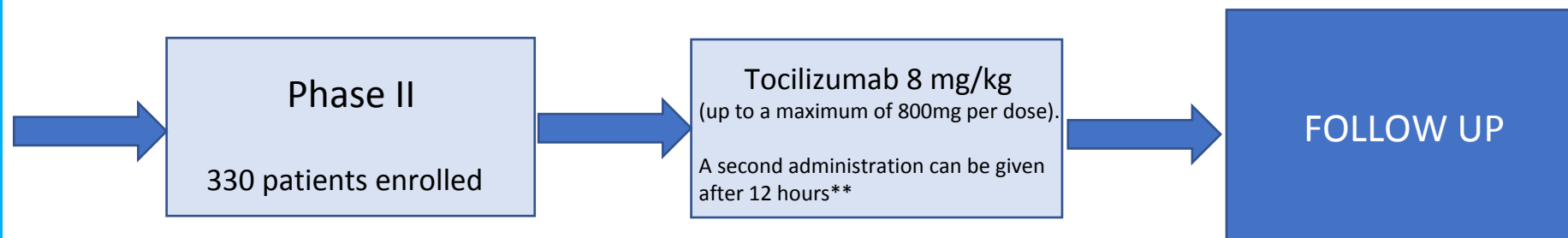
Binqing Fu<sup>1,2,3</sup>, Xiaoling Xu<sup>3</sup> and Haiming Wei<sup>1,2,3\*</sup> 

20/21 patients recovered from COVID-19 ARDS after a single dose of tocilizumab in 24-48 h

# TOCIVID-19 Study design

## Main inclusion criteria:

- Hospitalized due to clinical/instrumental diagnosis of pneumonia COVID-19
- Oxygen saturation at rest in ambient air  $\leq 93\%$
- Intubated less than 24 hours before registration



## Primary endpoint:

- Lethality rate two weeks after registration in the ITT phase 2 population
- Lethality rate one month after registration in the ITT phase 2 population

## Hypothesis:

$P_0$ : two-week and 1-month lethality rates for the population defined by the selection criteria is around 20% and 35%, respectively .

$P_1$ : the experimental drug may produce a 10% reduction of the lethality (from 20% to 10% at two weeks and from 35% to 25% at one month from registration in the study,  $P_1$ ), 330 patients will provide 99% and 95% power, respectively, with a 2.5% bilateral alpha error for each test.

	Centri che hanno aderito e si sono iscritti	Centri che hanno arruolato almeno 1 paziente
<b>NORD</b>	<b>241</b>	<b>122</b>
Lombardia	94	52
Emilia-Romagna	40	25
Veneto	43	20
Piemonte	43	16
Liguria	8	4
Trentino Alto Adige	8	3
Friuli Venezia Giulia	4	2
Valle d'Aosta	1	0
<b>CENTRO</b>	<b>103</b>	<b>41</b>
Toscana	38	19
Lazio	32	12
Umbria	5	3
Marche	28	7
<b>SUD ED ISOLE</b>	<b>120</b>	<b>46</b>
Campania	38	15
Puglia	20	12
Sicilia	38	13
Abruzzo	8	4
Calabria	8	1
Sardegna	5	1
Molise	2	0
Basilicata	1	0
<b>ITALIA</b>	<b>464</b>	<b>209</b>



## Hypothesis:

$P_0$ : **two-week** and 1-month lethality rates for the population defined by the selection criteria is around **20%** and 35%, respectively .

$P_1$ : **the experimental drug may produce a 10% reduction** of the lethality (from 20% to 10% at two weeks and from 35% to 25% at one month from registration in the study,  $P_1$ ), 330 patients will provide 99% and 95% power, respectively, with a 2.5% bilateral alpha error for each test.

	Phase 2
14 days intention-to-treat, n	301
N. of patients dead/available outcome data	55/299
Lethality rate, % (97.5% CI)	18.4% (13.6-24.0)
P value ( $P_0=20\%$ )	0.52
14 days modified intention-to-treat, n	180
N. of patients dead/available outcome data	28/180
Lethality rate, % (95% CI)	15.6% (10.6-21.7)

Please, do NOT post!!!



## Hypothesis:

$P_0$ : two-week and **1-month** lethality rates for the population defined by the selection criteria is around 20% and **35%**, respectively .

$P_1$ : **the experimental drug may produce a 10% reduction** of the lethality (from 20% to 10% at two weeks and from 35% to 25% at one month from registration in the study,  $P_1$ ), 330 patients will provide 99% and 95% power, respectively, with a 2.5% bilateral alpha error for each test.

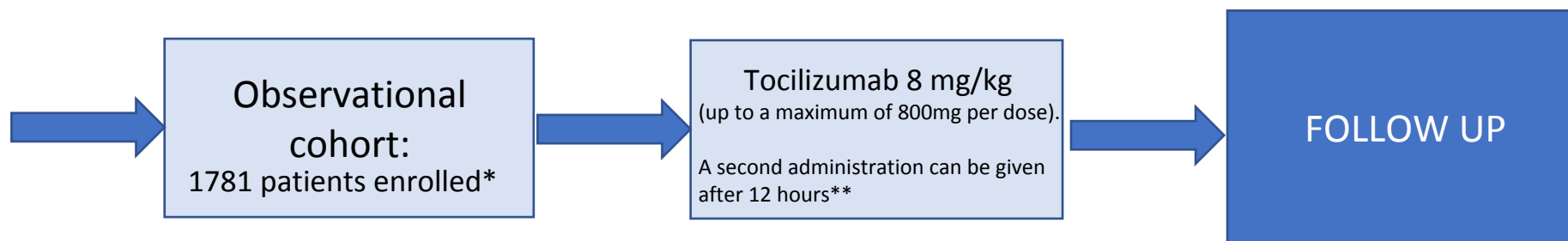
30 days intention-to-treat, n	301
N. of patients dead/available outcome data	67/299
Lethality rate, % (97.5% CI)	22.4% (17.2-28.3)
P value (P0=35%)	<0.001
Median time of death, days (IQR)	8 (4-14)
30 days modified intention-to-treat, n	180
N. of patients dead/available outcome data	36/180
Lethality rate, % (95% CI)	20.0% (14.4-26.6)

Please, do NOT post!!!

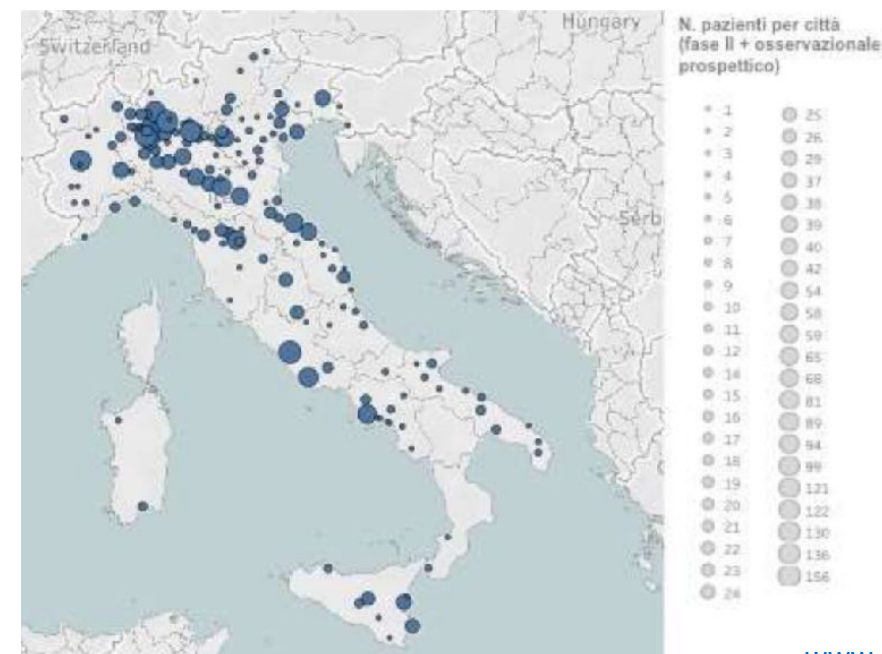
# TOCIVID-19 Study design

## Main inclusion criteria:

- emergency conditions or infrastructural or operational limits prevented registration before the administration of the experimental drug or
- Pts intubated more than 24 hours before registration




	Centri registrati	Pazienti registrati prospetticamente* (fase II + osservazionale)
<b>NORD</b>	<b>321</b>	<b>1499</b>
Lombardia	131	821
Emilia-Romagna	48	345
Veneto	49	166
Piemonte	54	111
Liguria	20	27
Trentino Alto Adige	12	17
Valle d'Aosta	1	7
Friuli Venezia Giulia	6	5
<b>CENTRO</b>	<b>126</b>	<b>356</b>
Lazio	39	157
Toscana	48	90
Marche	32	63
Umbria	7	46
<b>SUD ED ISOLE</b>	<b>153</b>	<b>256</b>
Sicilia	46	100
Campania	51	66
Puglia	22	54
Abruzzo	12	13
Sardegna	8	12
Calabria	10	6
Molise	2	5
Basilicata	2	0
<b>ITALIA</b>	<b>600</b>	<b>2111</b>



\* descriptive analysis ; \*\* by clinical judgment

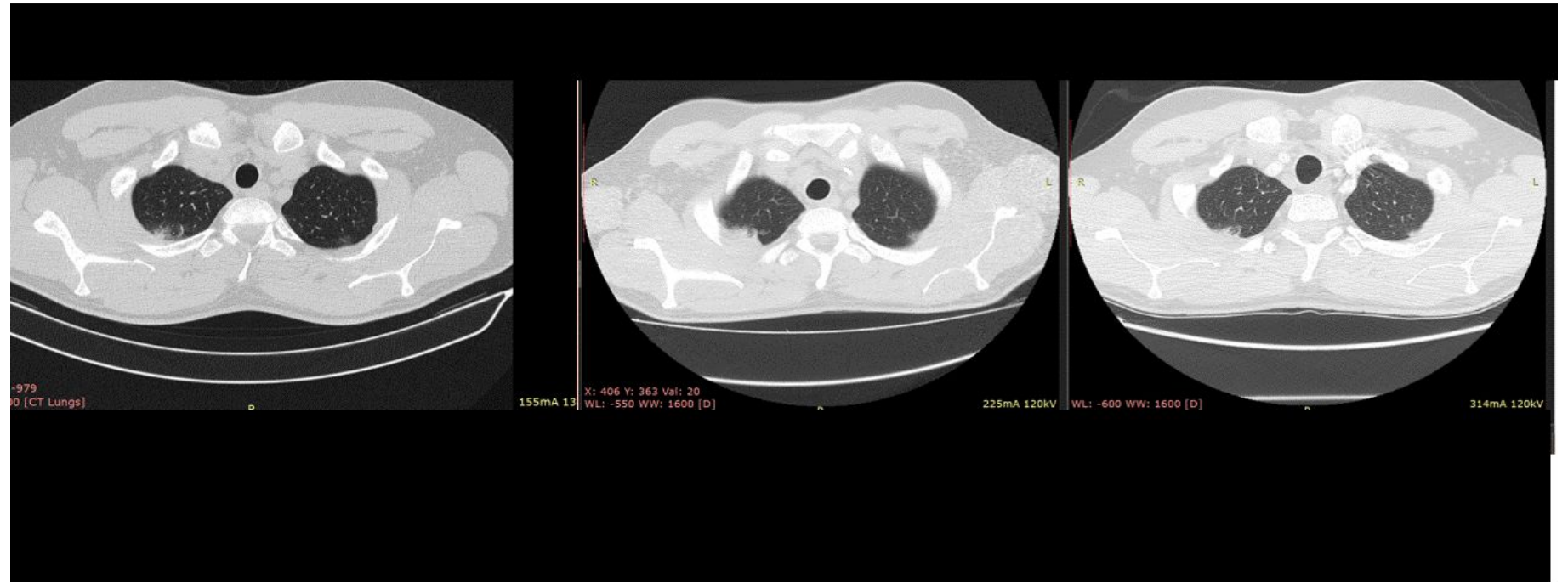
# Clinical case

13 <sup>th</sup> March 2020	 Tocilizumab 18 <sup>th</sup> March	25 <sup>th</sup> March 2020	30 <sup>th</sup> March 2020
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Male

Born in 1993

No  
comorbidity



Baseline

P/F: 98

pO<sub>2</sub>: 59 mmHg; pCO<sub>2</sub>: 30 mmHg  
CPR: 24 (ULN <1);

After Tocilizumab

P/F: 250

pO<sub>2</sub>: 100 mmHg; pCO<sub>2</sub>: 39 mmHg  
CPR: 4.2 (ULN <1)

Follow up

P/F: 300

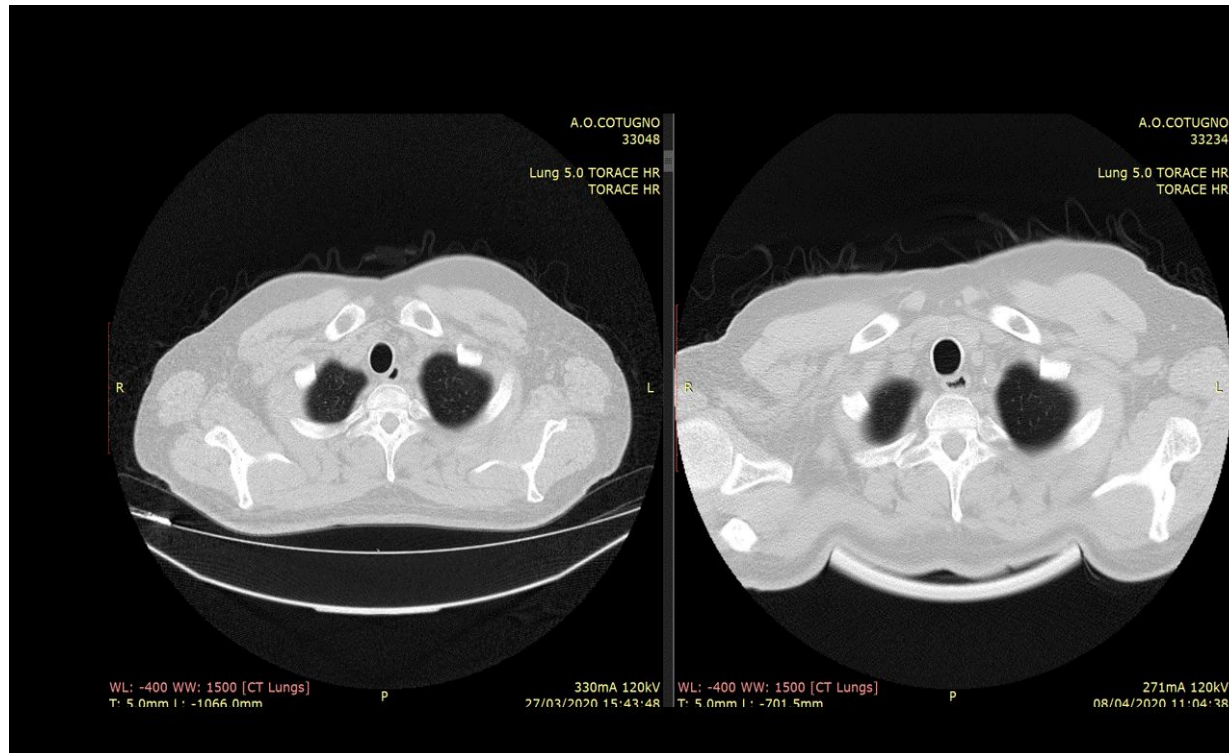
pO<sub>2</sub>: 100 mmHg; pCO<sub>2</sub>: 42 mmHg  
CPR: 2.3 (ULN <1)

# Anecdotal case of treatment with sarilumab

Sarilumab 400 mg SQ, single administration

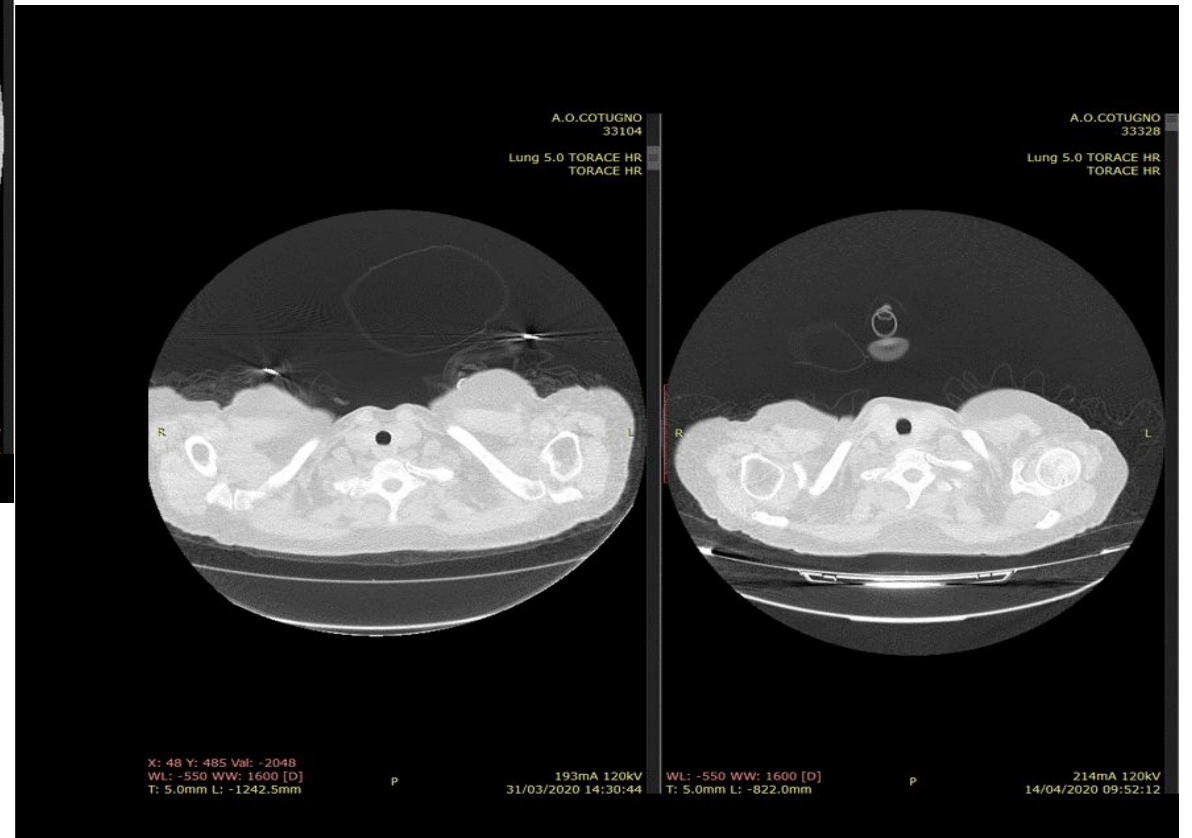
Patients characteristics	N = 15
<b>Gender:</b> Female/Male, N(%)	3(20)/12(80)
Median <b>age</b>	59 (range 53-75)
Median <b>PaO2/FiO2</b>	207 (139-290)
Median <b>BMI</b>	28.7 (range 23-45)
Normal weight, (BMI ≤25), N(%)	2 (13.3)
Overweight (BMI >25), N(%)	5 (33.3)
Obese (BMI >30), N(%)	3 (20)
NA, N(%)	5 (33.3)
<b>Intubated</b> , N(%)	8 (53.3)
<b>Not intubated</b> , N(%)	7 (46.7)
<b>Deaths</b> , N(%)	5 (33.3)

# Clinical cases



Male; Date of birth: 1960  
Baseline 27.03.2020: P/F 94  
Sarilumab 30.03.2020  
After 24 h: P/F 124; After 72h: P/F 198

Female; Date of birth: 1957  
Baseline 31.03.2020: P/F 83  
Sarilumab 01.04.2020  
After 24 h: P/F 135; After 72h: P/F 185





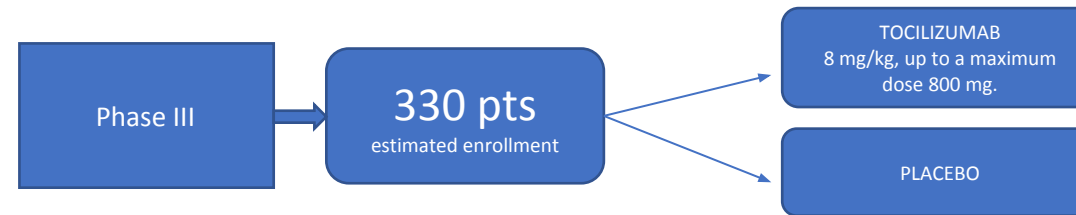
# Waiting for...

## A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA)

ClinicalTrials.gov Identifier: NCT04320615

### Main inclusion criteria:

-COVID-19 positive patients and evidenced by chest X-ray or CT scan;  
-SPO2  $\leq$  93% or PaO<sub>2</sub>/FIO<sub>2</sub> <300 mmHg



### Primary endpoint:

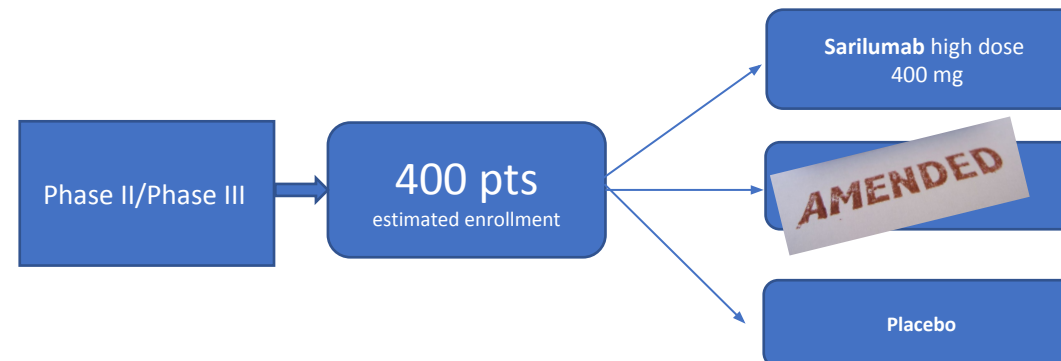
Clinical Status Assessed  
Using a 7-Category Ordinal  
Scale

## Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19

ClinicalTrials.gov Identifier: NCT04315298

### Main inclusion criteria:

-SARS-CoV-2 infection as determined by polymerase chain reaction (PCR), result from any specimen (or other commercial or public health assay) within 2 weeks prior to randomization and no alternative explanation for current clinical condition



**Phase 2 primary endpoint:**  
Percent change in C-reactive protein (CRP) levels

**Phase 3 primary endpoint:**  
Time to improvement (2 points) in clinical status assessment using the 7-point ordinal scale in patients with serum IL-6 levels greater than the upper limit of normal



# Acknowledgment



## IRCCS Pascale: Melanoma, Cancer Immunotherapy and Innovative Therapies

## A.O.R.N. dei COLLI "Ospedali Monaldi-Cotugno-CTO"



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**Gaetano Rea**

**Luigi Atripaldi**

**Elio Manzillo**

**Maurizio D'Abbraccio**

**Cristiana Palumbo**

**Patrizia Murino**

**Rosanna De Rosa**

**Physicians and nurses who saved lives by putting their own at risk, patients who consented to these studies**