



Repurposing Cancer Immunotherapies for COVID

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Disclosure

- **Employment or Leadership Position:** None
- **Consultant/Advisory Role:** Bristol-Meyers Squibb, Roche-Genentech, Merck Sharp & Dohme, Novartis, Array, Merck Serono, Pierre-Fabre, Incyte, NewLink Genetics, Genmab, Medimmune, AstraZeneca, Syndax, Sun Pharma, Sanofi, Idera, Ultimovacs, Sandoz, Immunocore, 4SC, Alkermes, Italfarmaco, Nektar, Boehringer-Ingelheim, Eisai, Regeneron, Daiichi Sankyo, Pfizer, Oncosec.
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- **Expert Testimony:** None
- **Other Remuneration:** Travel support from MSD

What about COVID-19 pandemic and cancer patients?

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Dept. Melanoma, Cancer Immunotherapy and Development Therapeutics



The first rule during COVID-19 pandemia:

...to keep everybody safe.



To keep everybody safe ...protect

Patients



&

Health workers

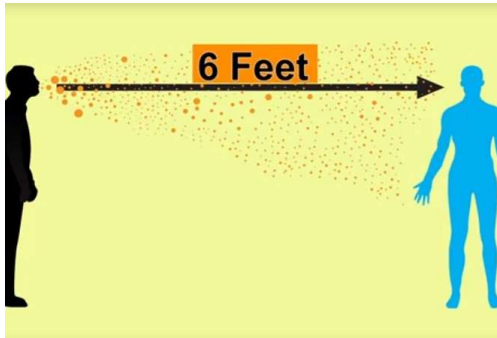


Protect Patients...

How to minimise any potential patient exposure



- Avoid Gatherings
- Triage
- Use DPI



- Prioritize Patients
- TEST

Prioritize Patients: Surgery

- High priority can be given to T3 and T4 and medium to T1 and T2. Depending on the local COVID situation, delaying surgery is acceptable as this was not shown to influence survival
- For T1a or lower, wide excision alone with medium priority
- Any curative resection for stage III melanoma
- Resection of oligo-metastatic disease
- Surgical management of complications from surgical procedures

HIGH PRIORITY

Prioritize Patients: Therapy (Adjuvant setting)



- Optimize access to Day Hospital
 - treatments can be delayed up to the 12 weeks (allowed in the adjuvant clinical trials)
- For melanoma BRAF mutated patients, depending on local hospital situation, adjuvant BRAFi/MEKi could be initiated
- Preferring longer schedule (pembrolizumab 400 mg every 6 weeks or nivolumab 480 every 4 weeks)

Prioritize Patients: Follow up




- Telemedicine
(by phone with electronic reports)
- If patients were NED... Clinical visit could be postponed

Prioritize Patients: Therapy (Metastatic setting)



No stop or delays for targeted therapies or immunotherapies for unresectable stage III or IV melanoma!

Special ISSUE: Clinical trials

- Many trials: enrollment 
- Telemedicine for control visit.
- For patients on treatment, in agreement with regulatory agencies, the pivotal principals were:
 - assuring the safety of trial participants
 - maintaining compliance with good clinical practice (GCP)
 - minimizing risks to trial integrity and quality of data.

Special warning



- Patients on IO showing signs of pneumonitis on CT scans should be tested for COVID before administering steroids
- For patients on BRAFi/MEKi affected by fever that does not resolve with treatment interruption: require a COVID test.



Immunotherapy and pneumonia

- One of main concerns relates to the possible increased risk of pneumonia in patients with cancer on immunotherapy
 - The risk was only hypothetical but cannot be ruled out



- In the **TERAVOLT registry** of patients with thoracic cancers who contract COVID-19 (n = 200)¹
 - The most common complications were pneumonia/pneumonitis (79.6%) and acute respiratory distress syndrome (26.8%)
 - 76% of patients were hospitalized, 33.3% died
 - **No reports of increased risk of pneumonitis or deaths due to COVID-19 in patients on treatment with ICI**

ICI, immune checkpoint inhibitor.

1. The ASCO Post. AACR 2020: mortality rate in patients with thoracic cancers infected with COVID-19 Available at: <https://www.ascopost.com/news/april-2020/mortality-rate-from-covid-19-in-patients-with-thoracic-cancers/> (Accessed May 2020).

The PD-1/PD-L1 axis and virus infections: a delicate balance

- Preclinical data suggest that **anti-PD-1 can increase virus clearance**¹
 - High-pathological infection with influenza A is associated with increased PD-1 expression on influenza virus-specific CD8⁺ T cells
 - Likely caused by the more highly inflamed airway microenvironment during the early days of infection
 - Blockade of PD-L1 *in vivo* led to reduced virus titres and increased CD8⁺ T cell numbers in high- but not low-pathological infection

PD-1; programmed cell death protein 1; PD-L1, programmed death-ligand 1.

1. Rutigliano JA *et al. J Virol* 2014;88:1636–51.

CPI May be also protective



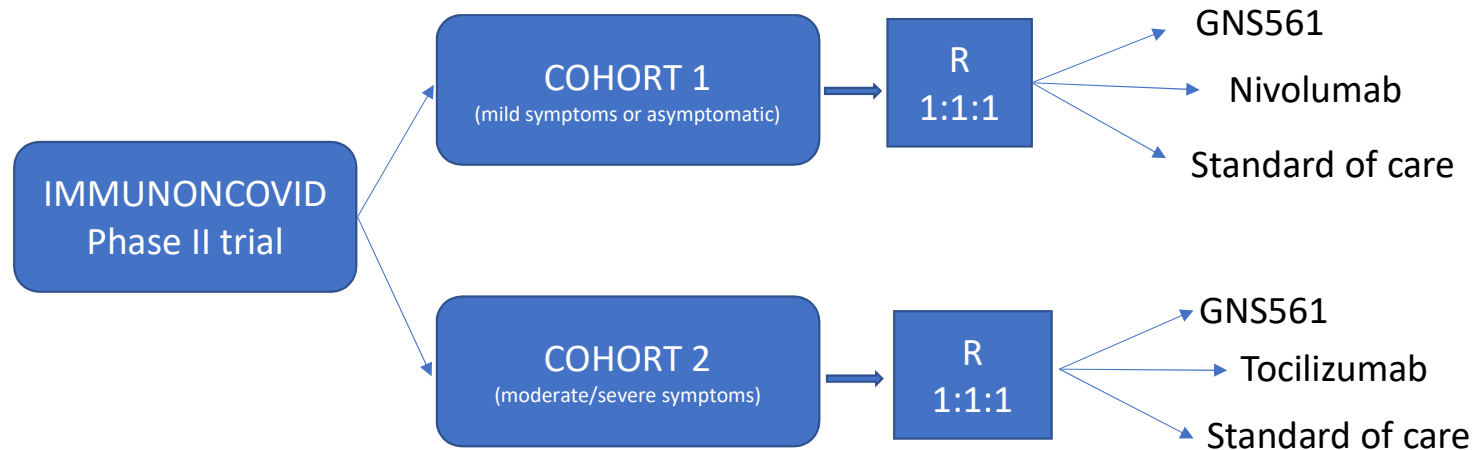
In our Unit, during the period (March-April 2020) only 2 pts/~400 pts on IO were COVID+:

- Asymptomatic
- Early recover with test negative in less than 10 days

NIH U.S. National Library of Medicine

ClinicalTrials.gov

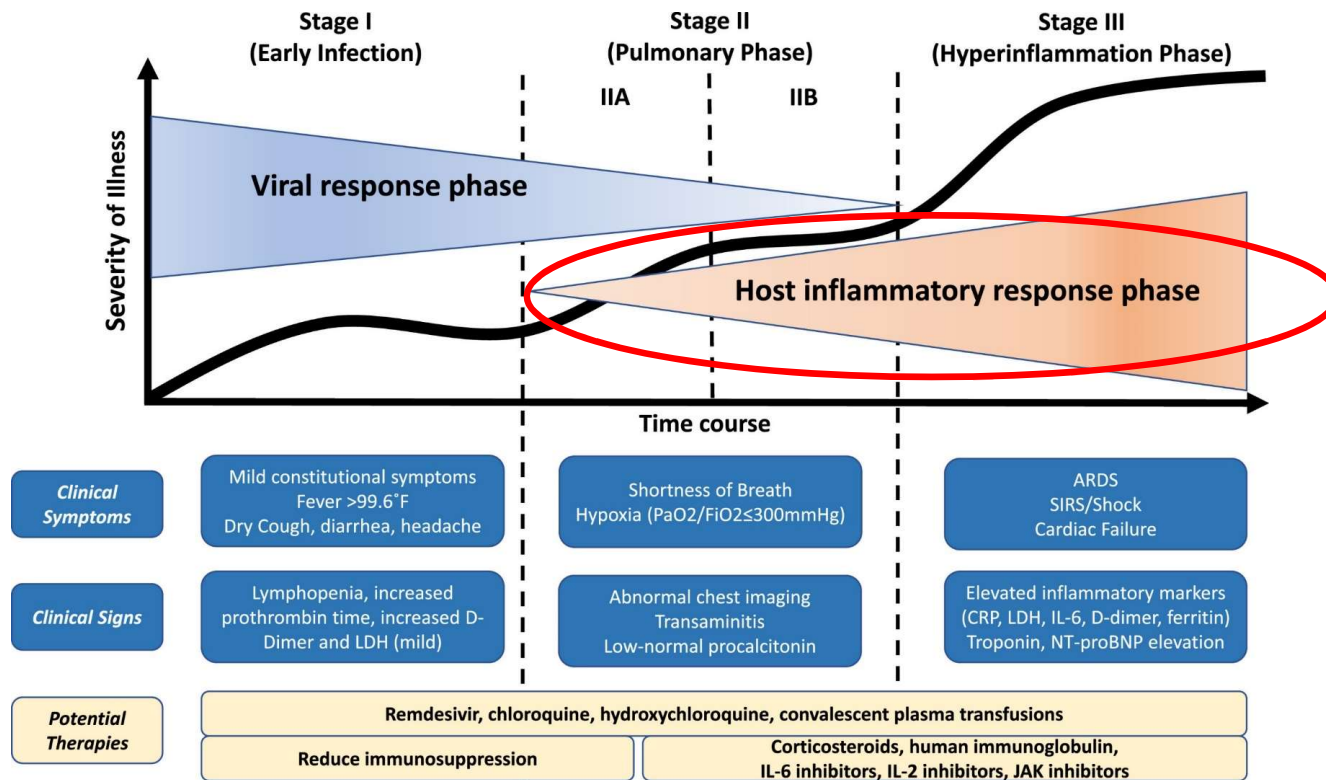
Prospective Study in Patients With Advanced or Metastatic Cancer and SARS-CoV-2 Infection (IMMUNONCOVID)



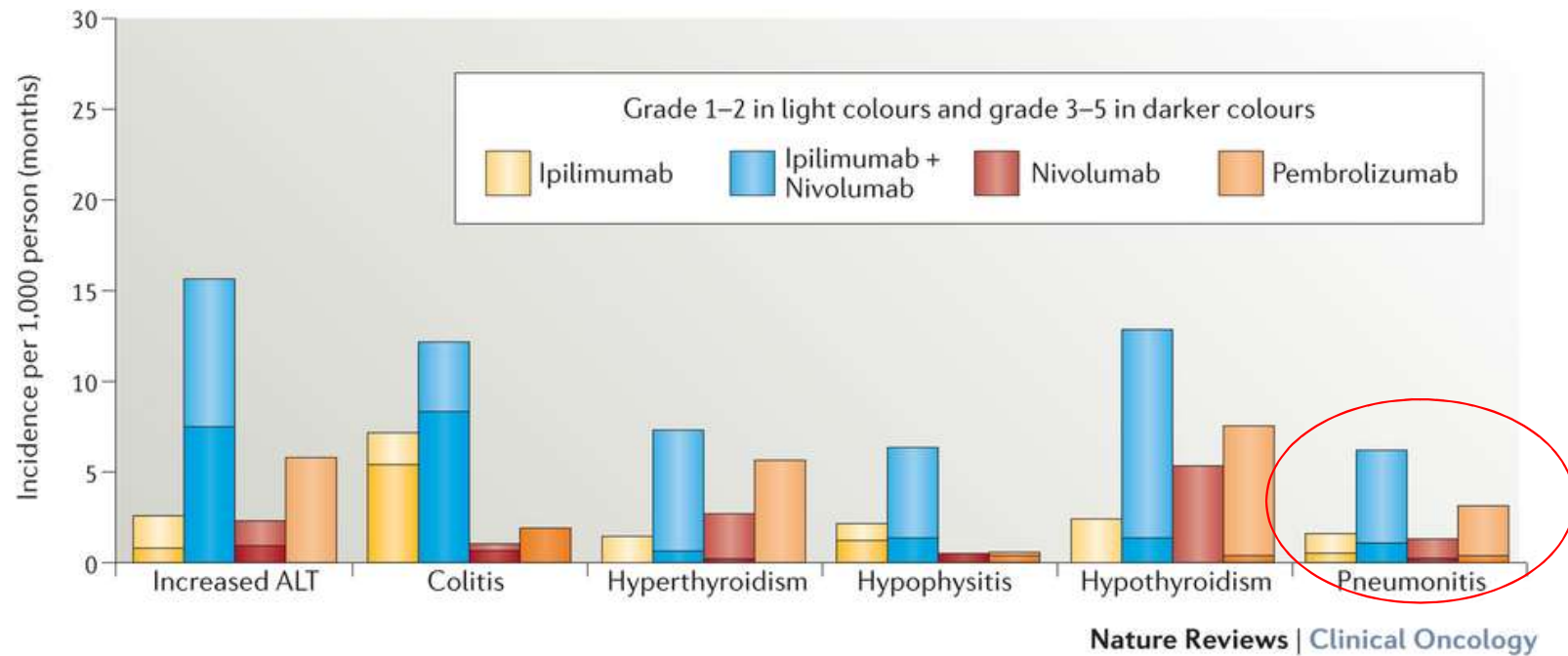
<https://clinicaltrials.gov/ct2/show/NCT04333914>

What can also do immuno-oncologists in the era of COVID-19?

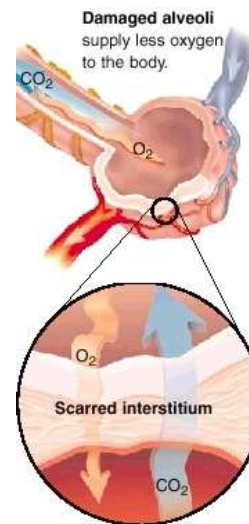
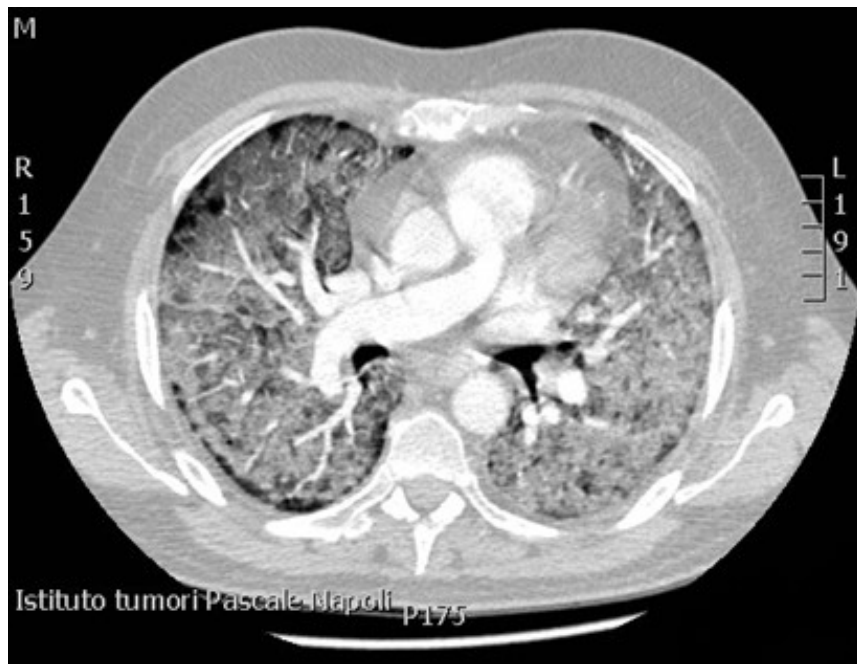
A step back



Adverse events of special interest noted with immune-checkpoint inhibitors



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

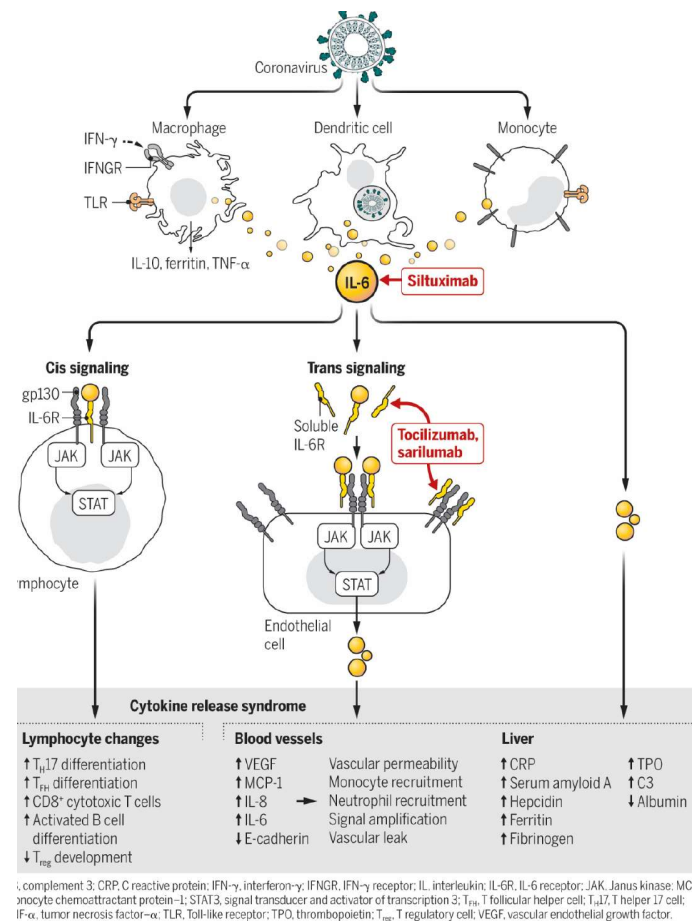
Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade

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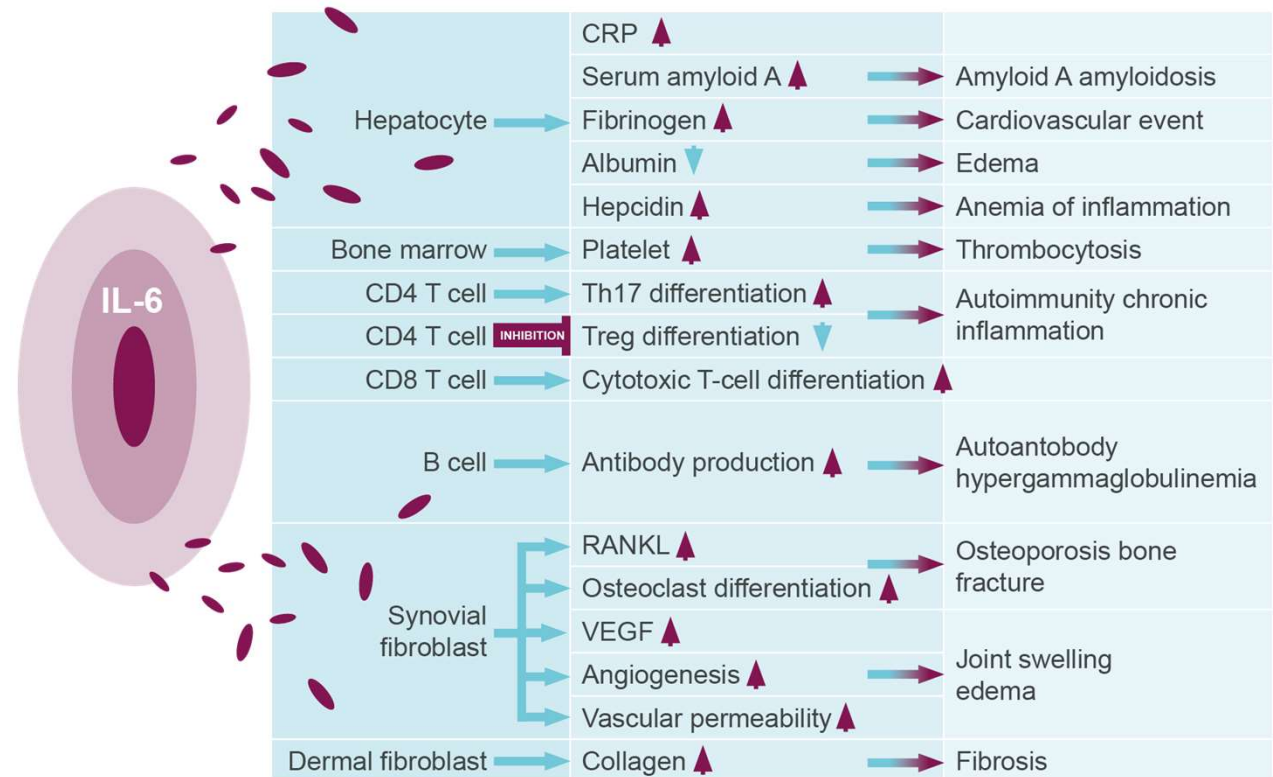
What we could suspect...CRS and COVID-19



IL-6 in inflammation, immunity and disease

IL-6 is a cytokine with pleiotropic activity¹








- IL-6 plays an important role in acquired immune response by stimulation of antibody production and of effector T-cell development
- IL-6 can promote differentiation or proliferation of several nonimmune cells
- Dysregulated continual production of IL-6 leads to the onset or development of various diseases




CRP, C-reactive protein; IL-6, interleukin-6; RANKL, receptor activator of nuclear factor kappa-B ligand; VEGF, vascular endothelial growth factor.

1. Tanaka T *et al. Cold Spring Harb Perspect Biol* 2014;6:a016295.

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

Paolo Antonio Ascierto ¹, Bernard Fox,² Walter Urba,²
Ana Carrizosa Anderson ³, Michael B Atkins ⁴, Ernest C Borden,⁵
Julie Brahmer,⁶ Lisa H Butterfield ^{7,8}, Alessandra Cesano,⁹ Daniel Chen ¹⁰,
Tanja de Gruijl,¹¹ Robert O Dillman,¹² Charles G Drake,¹³ Leisha A Emens,¹⁴
Thomas F Gajewski,¹⁵ James L Gulley ¹⁶, F Stephen Hodi,¹⁷ Patrick Hwu,¹⁸
David Kaufman,¹⁹ Howard Kaufman,²⁰ Michael Lotze,²¹ Douglas G McNeel,²²
Kim Margolin,²³ Francesco Marincola,²⁴ Michael J Mastrangelo,²⁵
Marcela V Maus,²⁶ David R Parkinson,²⁷ Pedro J Romero,²⁸ Paul M Sondel ²⁹,
Stefani Spranger,³⁰ Mario Sznol,³¹ George J Weiner,^{32,33,34} Jon M Wiggington,³⁵
Jeffrey S Weber³⁶

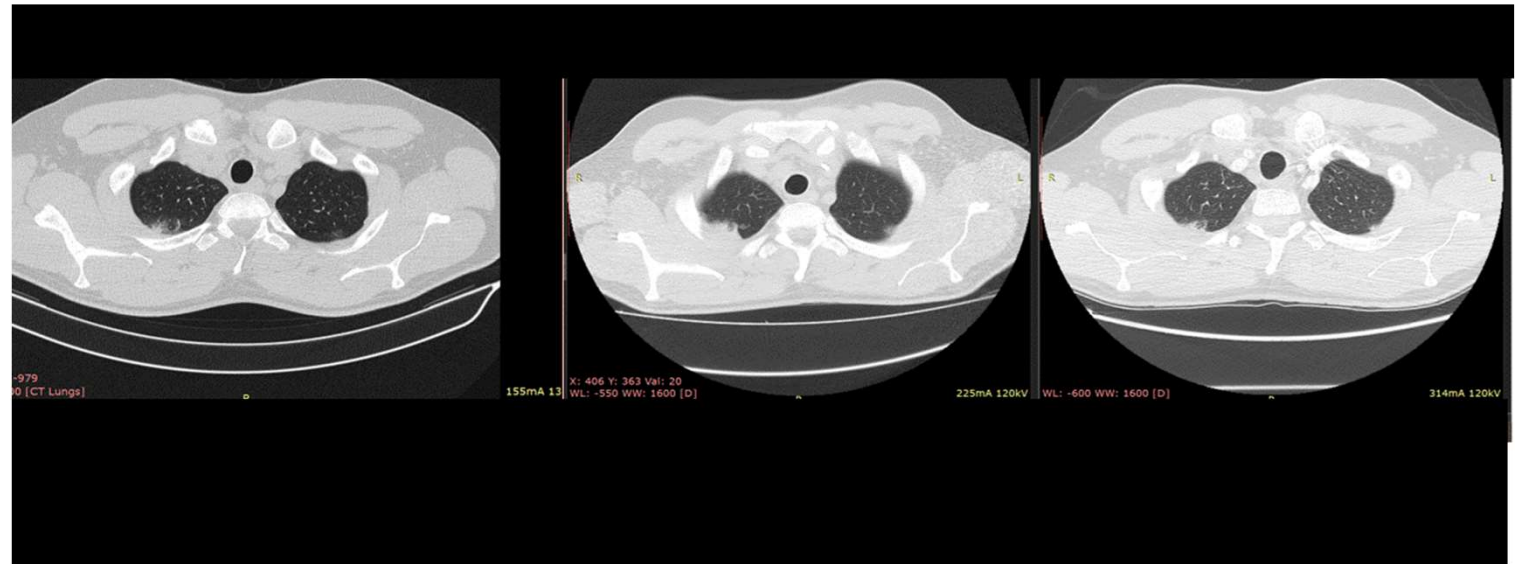
Clinical case

13 th March 2020	 Tocilizumab 18 th March	25 th March 2020	30 th March 2020
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Male

Born in 1993

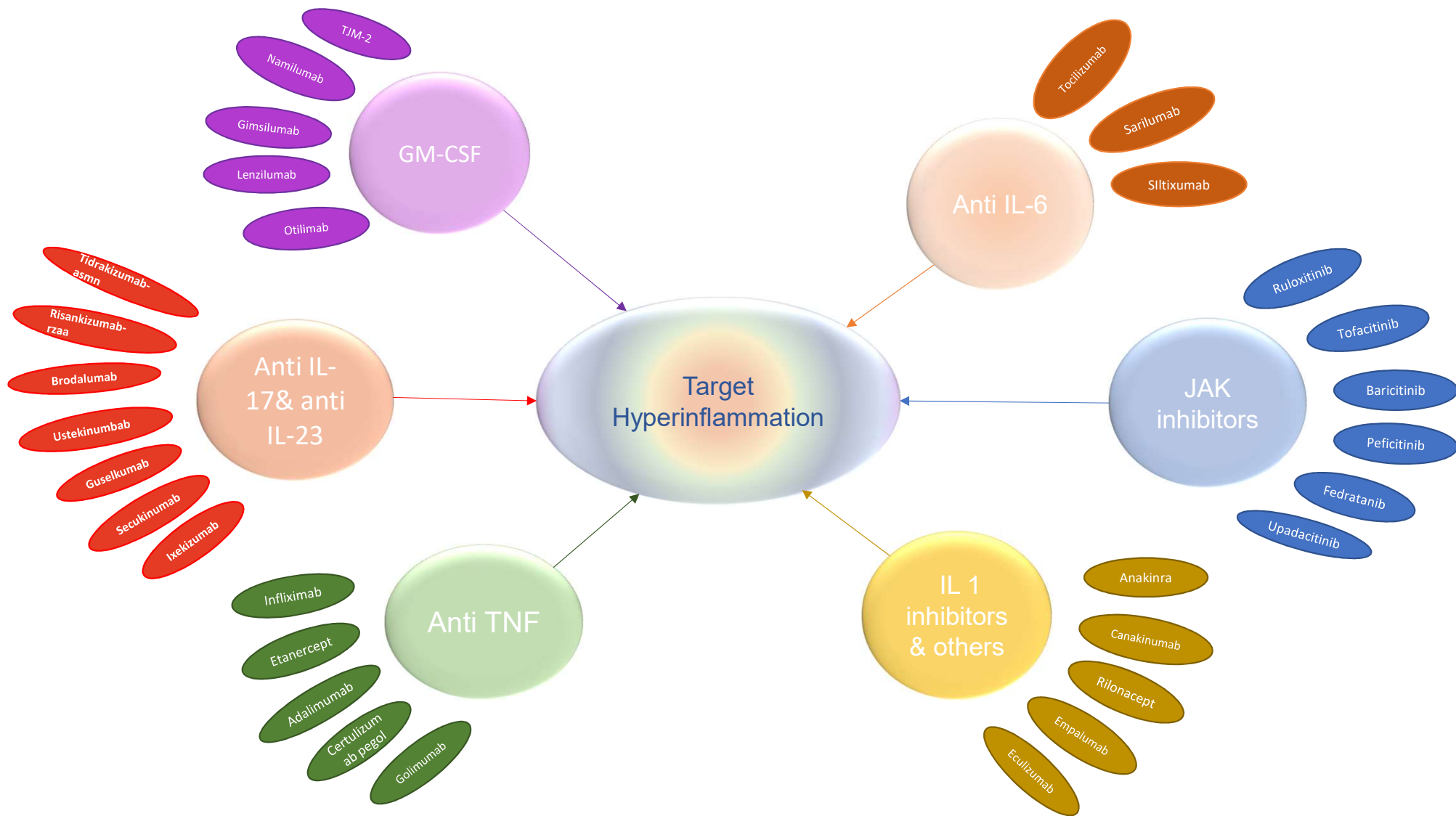
No
comorbidity



Baseline
P/F: 98
pO₂ 59 mmHg; pCO₂ 30 mmHg
CPR: 24 (ULN <1);

After Tocilizumab
P/F:250
pO₂:100 mmHg; pCO₂:39 mmHg
CPR: 4.2 (ULN <1)

Follow up
P/F:300
pO₂:100 mmHg; pCO₂:42 mmHg
CPR: 2.3 (ULN <1)





- Keep everybody safe (patients, nurses, physicians)
- Prioritize and test patients
- No increased risk for patients on treatment with CPI
- Early diagnosis and treating Cytokine storm is essential





Acknowledgment



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