AG iHO INFEKTIONEN IN DER HÄMATOLOGIE UND ONKOLOGIE
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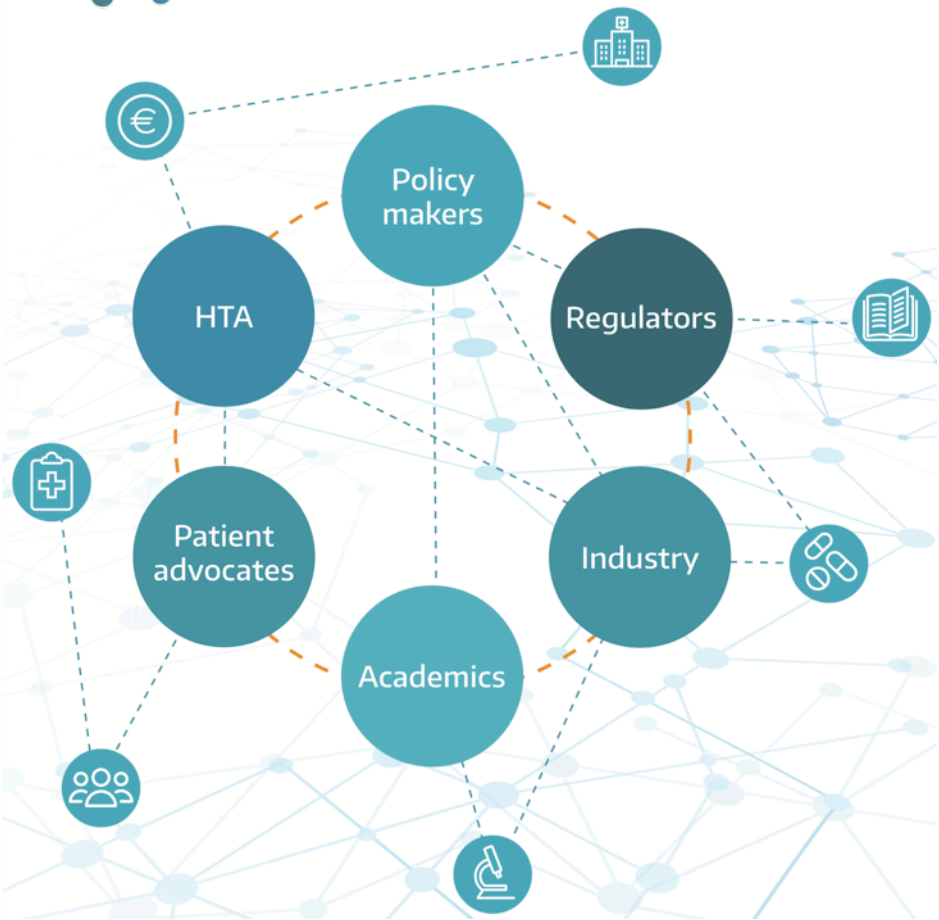
Zoom Webinar

Treatment of Cancer Patients during the SARS-CoV2 Pandemic: *Implications for Clinical Trials*

What is the CDDF?



- The **Cancer Drug Development Forum** is an international not-for-profit organization providing a platform for all stakeholders to accelerate the delivery of effective oncology agents to patients.
- The CDDF, based in Brussels, unites experts from academia, the pharmaceutical industry, regulatory authorities (including the EMA and FDA), health technology assessors and patient advocates.
- Please visit our website: **www.cddf.org**
- **The meeting is co-sponsored by Catenion** (https://catenion.com)

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Today's Agenda

Introduction	**Prof. Dr. Axel Glasmacher, CDDF**
Presentation (20-25 min)	**Prof. Dr. Marie von Lilienfeld-Toal, Univ. Jena, Germany**
Q&A (30 min)	**Moderators: Prof. Dr. Jaap Verweij, CDDF Prof. Dr. Axel Glasmacher,**
CDDF	

CDDF
Cancer Drug Development Forum

Today's Presenter: Marie von Lilienfeld-Toal

Professor of Medicine at the University Clinic of Jena, Germany

Clinical and scientific focus on

- **Haematological malignancies *and***
- **Infectious Diseases in immunocompromised patients with a focus on virology**

Lead author of the

- **COVID-19 Guidelines of the German, Austrian and Swiss Societies of Hematology-Oncology**
- **EHA SWG Infections in Hematology FAQ Recommendations**

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SARS-CoV-2 in Haematology and Oncology

Marie von Lilienfeld-Toal
Universitätsklinikum Jena

Offenlegung potentieller Interessenkonflikte

Anstellungsverhältnis oder Führungsposition:

keine

Beratungs- bzw. Gutachtertätigkeit:

MSD, Oncopeptides, Chugai, Janssen

Besitz von Geschäftsanteilen, Aktien oder Fonds:

keine

Patent, Urheberrecht, Verkaufslizenz:

keine

Honorare:

MSD, Gilead, Celgene, Janssen Cilag, Takeda, Oncopeptides, medac, BMS

Finanzierung wissenschaftlicher Untersuchungen:

BMBF, Deutsche Jose Carreras Leukämie-Stiftung, IZKF Jena, DFG, Novartis, Gilead, Deutsche Krebshilfe

Andere finanzielle Beziehungen:

…

Immaterielle Interessenkonflikte:

…

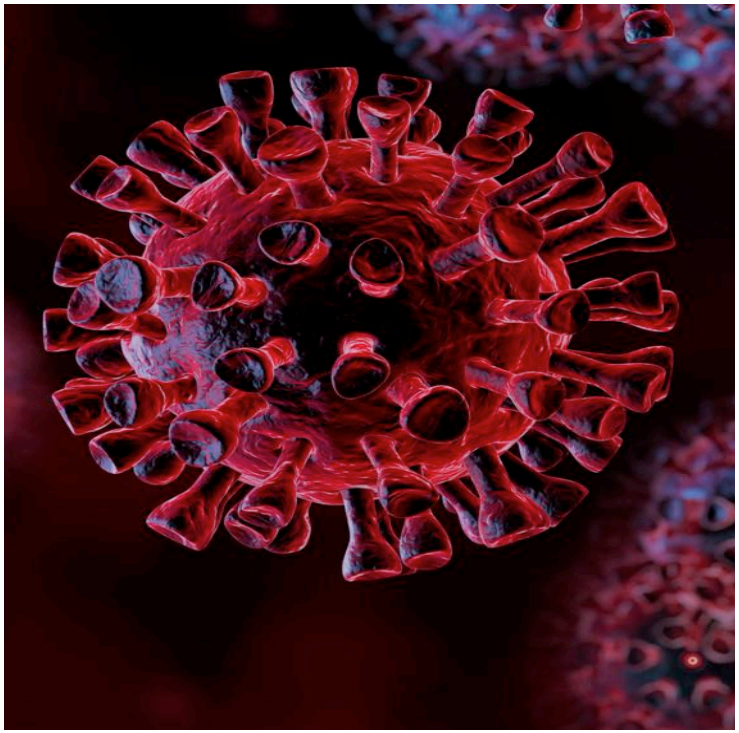
SARS-CoV-2

RNA-Virus

belongs to the CARV (Community Acquired Resp. Viruses)

Similarity with SARS-Virus

First observed in China 2019



SARS-CoV-2: Name of the virus
CoVID-19: Coronavirus Infectious Disease – name of disease

Definitions in CARV infections

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Upper respiratory tract infectious disease (URTID)

Diagnosed, if one of the following:

- Cough
- Coryza
- Sore throat
- Shortness of breath

AND a systemic symptom such as:

- Fever/malaise/myalgia

AND

- Confirmed by nucleic acid testing (NAAT)

Lower respiratory tract infectious disease (LRTID)

Diagnosed in patients with:

- Tracheitis and/or bronchitis
- Dyspnea

and/or

- Declined O_2 saturation at ambient air
- Bilateral ground glass infiltrates on CT

→ Viral pneumonia

- May progress to respiratory failure

SARS-CoV-2 infections are typically associated with “strange” symptoms like myalgia or **disturbance in taste**

Clinical Course of SARS-CoV-2 Infection

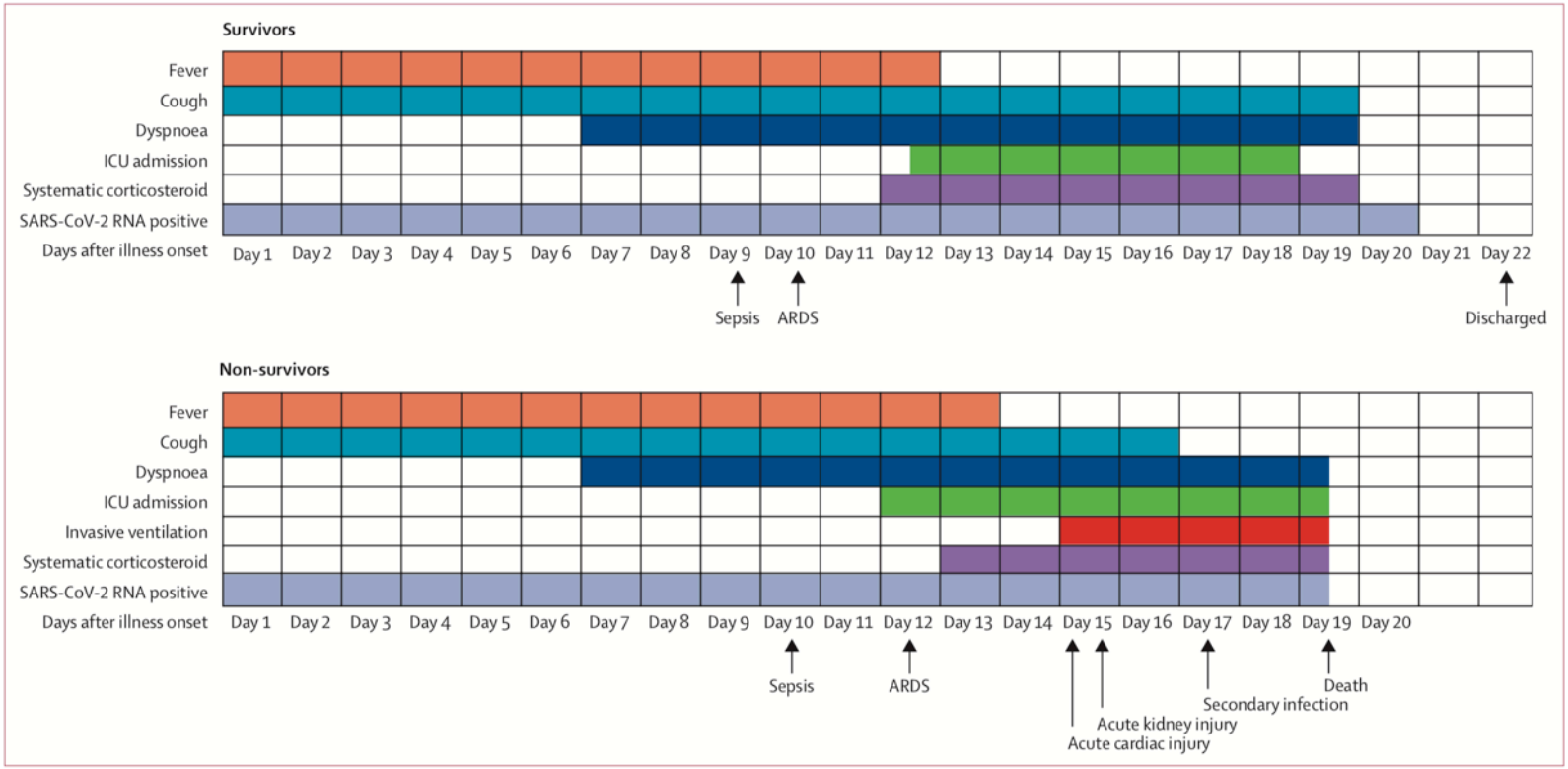
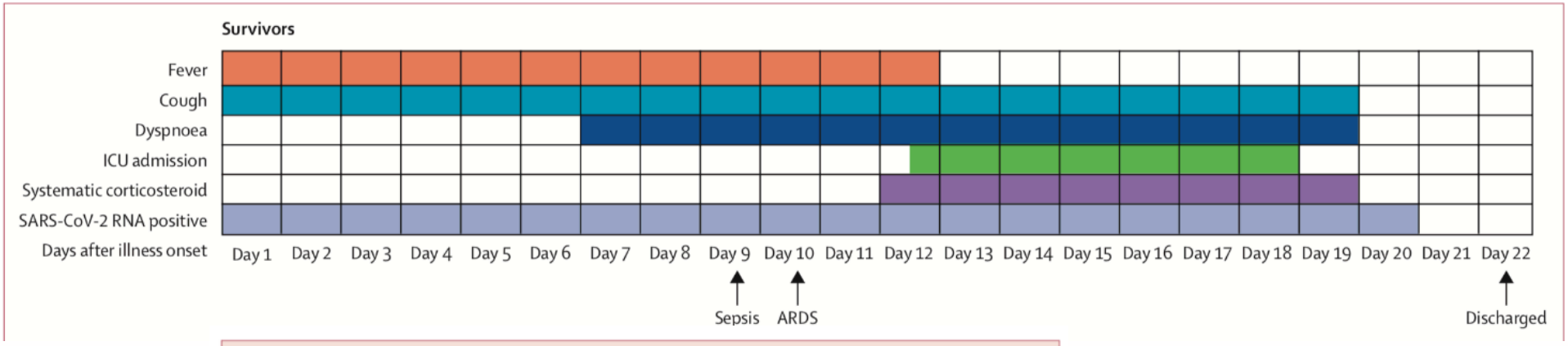


Figure 1: **Clinical courses of major symptoms and outcomes and duration of viral shedding from illness onset in patients hospitalised with COVID-19**
Figure shows median duration of symptoms and onset of complications and outcomes. ICU=intensive care unit. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ARDS=acute respiratory distress syndrome. COVID-19=coronavirus disease 2019.

Zhou et al., Lancet 2020

Clinical Course of SARS-CoV-2 Infection



	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
D-dimer, µg/mL	0·8 (0·4–3·2)	5·2 (1·5–21·1)	0·6 (0·3–1·0)	<0·0001
≤0·5	55/172 (32%)	4 (7%)	51/118 (43%)	<0·0001*
>0·5 to ≤1	45/172 (26%)	6 (11%)	39/118 (33%)	..
>1	72/172 (42%)	44 (81%)	28/118 (24%)	..
Serum ferritin, µg/L	722·0 (377·2–1435·3)	1435·3 (728·9–2000·0)	503·2 (264·0–921·5)	<0·0001
>300	102/128 (80%)	44/46 (96%)	58/82 (71%)	0·0008
IL-6, pg/mL	7·4 (5·3–10·8)	11·0 (7·5–14·4)	6·3 (5·0–7·9)	<0·0001

Zhou et al., Lancet 2020

Clinical Course of SARS-CoV-2 Infection

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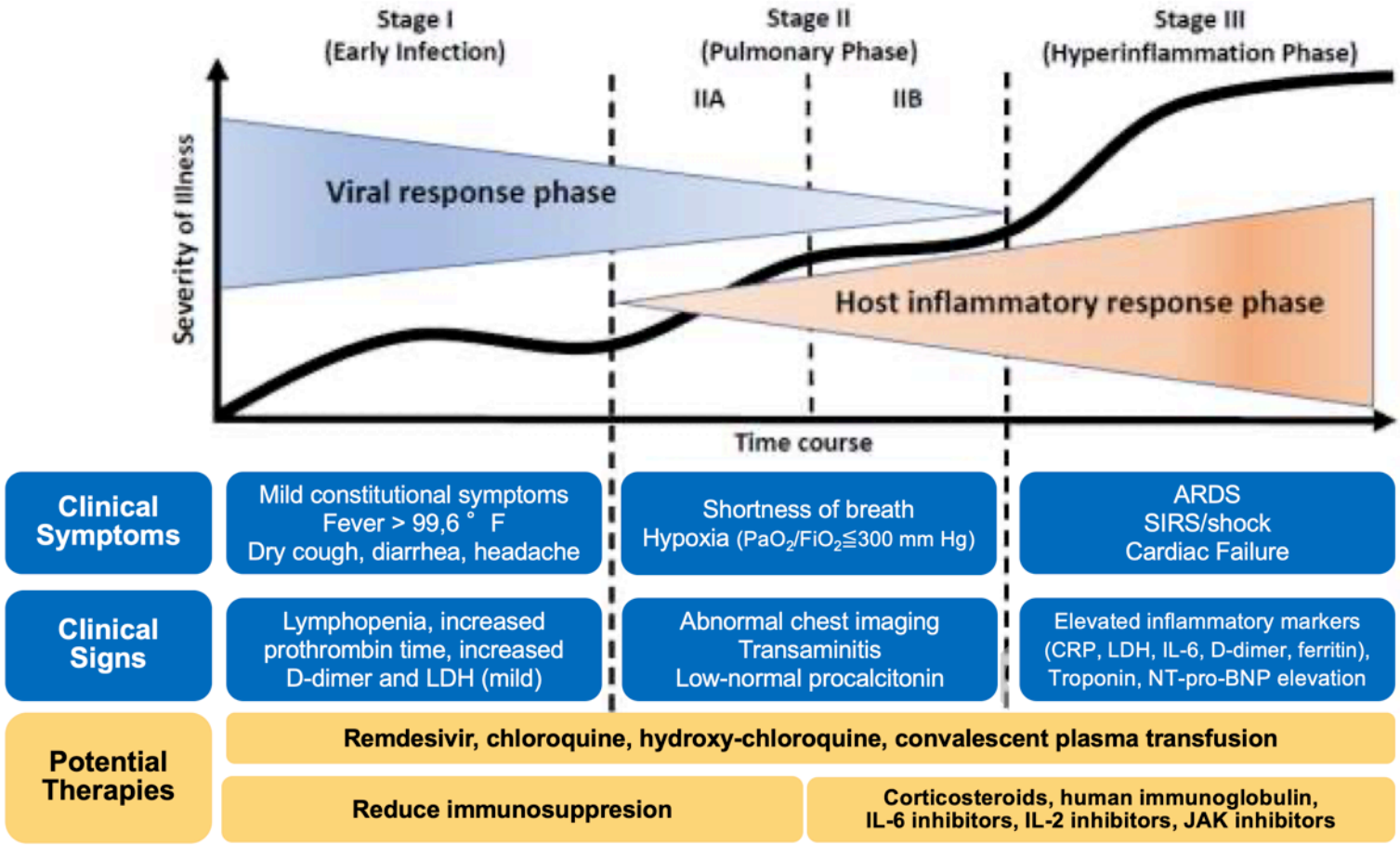

Cytokine storm?

Hemophagocytic Lymphohistiocytosis?

Vasculitis/Thrombosis?

Treatment options:

Steroids
JAK-inhibition
Cytokine-blockage (e.g. IL-1, IL-6)

Siddiqi & Mehra. J Heart Lung Transplant 2020 (in press); Zhang et al., Clinical Immunol 2020

Risk factors for severe course

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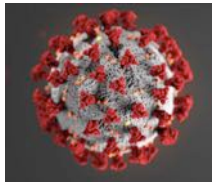

- Risk factors for worse outcome: advanced age, hypertension, and diabetes
- Cancer patients should be assumed to have worse prognosis
- Prone to bacterial/fungal superinfection or co-infections
- Preliminary data suggest mortality of 20% in hematological patients (Livio Pagano, Rom)

Guan *N Engl J Med* 2020; Zhou *Lancet* 2020; Hirsch HH *Clin Infect Dis.* 2013;56(2):258-266

Published Data on CoVID-19 and cancer

18 (1%; 95% CI 0·61–1·65) of 1590 hospitalised COVID-19 cases from 575 hospitals

Lung cancer frequent type (5/18 [28%]).

4/16 (25%) chemotherapy or surgery within the past month
12/16 (75%) cancer survivors in routine follow- up, 2 unknown

Compared with patients without cancer, patients with cancer were:
older (mean age 63·1 years [SD 12·1] *vs* 48·7 years [16·2]),
more likely to smoke (4/18 [22%] *vs* 107/1572 [7%]),
had more polypnea (8/17 [47%] *vs* 323/1377 [23%]),
had more severe baseline CT (17/18 [94%] *vs* 1113/1572 [71%]),

adverse outcome (ICU or death): **7/18 (39%),** associated with recent therapy

Liang et al., Lancet 2020

Published Data on CoVID-19 and cancer

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28 Patients with solid tumours hospitalised with COVID-19

Characteristics
17 (61%) male,
mediane age 65 years (IQR:56.0-70.0).

Lungcancer 7 (25%),
GI-tumours 9 (32%),
gyn. tumours 5,
Head/Neck, test. Ca and Prostate-Ca

8 (29%) acquired the infection in the hospital

Symptoms:
fever (23, 82.1%),
dry cough (22, 81%)
dyspnoea (14, 50.0%),

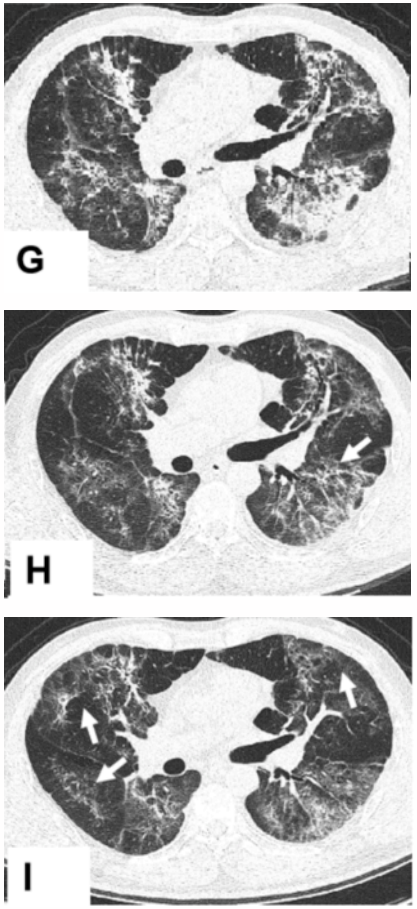
Lab-Results:
Lymphopenia (23, 82.1%),
Raised CRP (23, 82.1%),
Anaemia (21, 75.0%)
Hypoproteinaemia (25, 89.3%).

Severe Course
15 (53.6%)

Mortality
8/28 (29%)

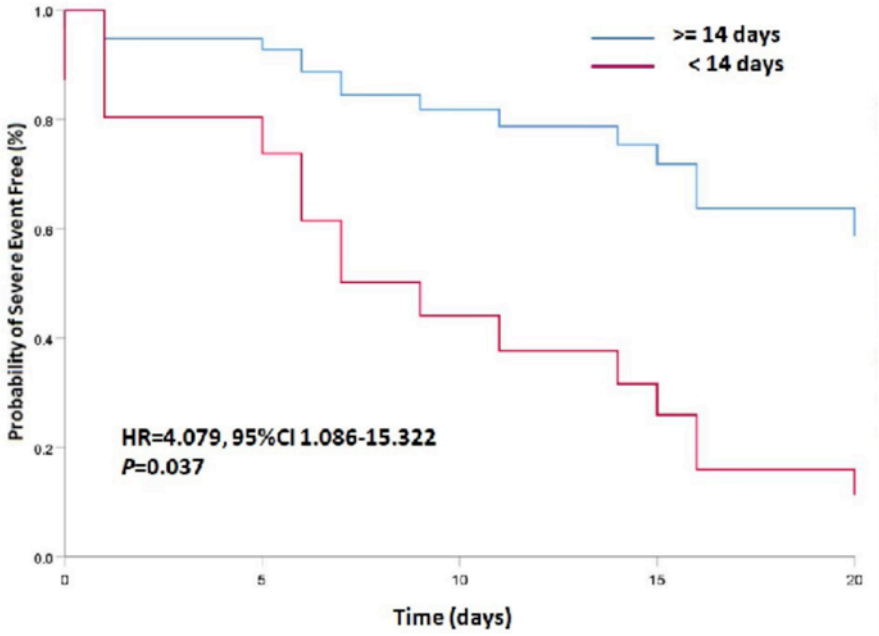
Zhang et al., Ann Oncol 2020

Published Data on CoVID-19 and cancer



Riskfactors for adverse outcome:

1. patchy consolidation on CT
2. recent cancer therapy



Zhang et al., Ann Oncol 2020

Prevention of CoVID-19 in cancer patients

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- General contact precautions including hand hygiene
- Symptomatic family members should stay away from cancer patients
- Face masks for situations when contact isolation is difficult
- Good general health should be reinforced

Jefferson *Cochrane Database Syst Rev.* 2011(7):Cd006207; EMA 2018; Ogimi *Biol Blood Marrow Transplant.* 2018;24(11):2293-2301; Mikulska *J Infect.* 2018;76(1):20-37; Neumann S *Ann Hematol.* 2013;92(4):433-442; Vehreschild *Ann Oncol.* 2014;25(9):1709-1718.

Prevention of CoVID-19 in cancer patients

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- Intravenous immunoglobulins (ivIg) as recommended by EMA
- Strong recommendation not to implement additional antimicrobial prophylaxis concerning use of antibiotics and G-CSF
- Vaccination against seasonal influenza and pneumococci

Jefferson *Cochrane Database Syst Rev.* 2011(7):Cd006207; EMA 2018; Ogimi *Biol Blood Marrow Transplant.* 2018;24(11):2293-2301; Mikulska *J Infect.* 2018;76(1):20-37; Neumann S *Ann Hematol.* 2013;92(4):433-442; Vehreschild *Ann Oncol.* 2014;25(9):1709-1718.

Prevention of CoVID-19 in cancer patients – organisational aspects

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- Patient education regarding hygiene
- All patients under active cancer therapy should practise social isolation – that also means restructuring waiting areas
- Try to reduce patient contact as much as possible, telemedicine?
- Dedicated areas for CoVID-19 and cancer therapy (inpatient and outpatient), possibly dedicated teams
- Enough personal protective equipment for staff

Prevention of CoVID-19 in cancer patients – organisational aspects

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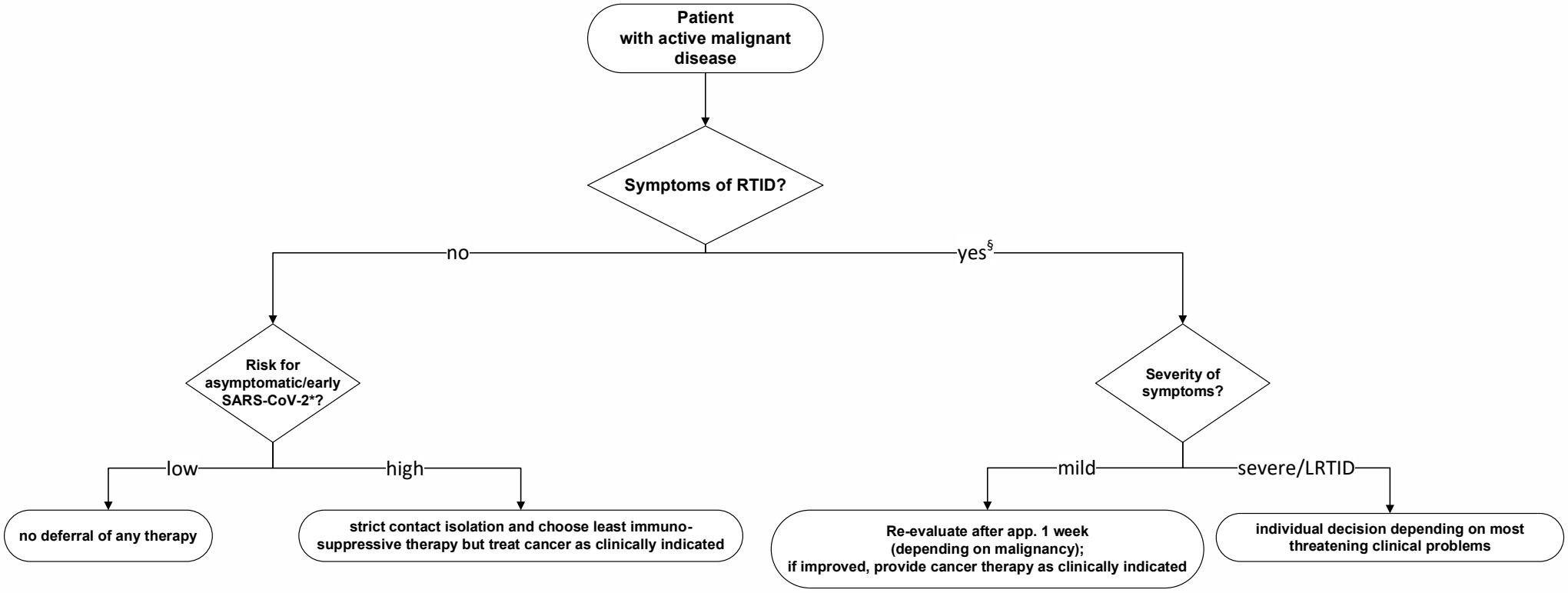
- Challenges due to a massively changed work environment
- Significant rate of infected care-givers
- Appropriate cancer therapy has to be ensured
- Therefore many organisational changes

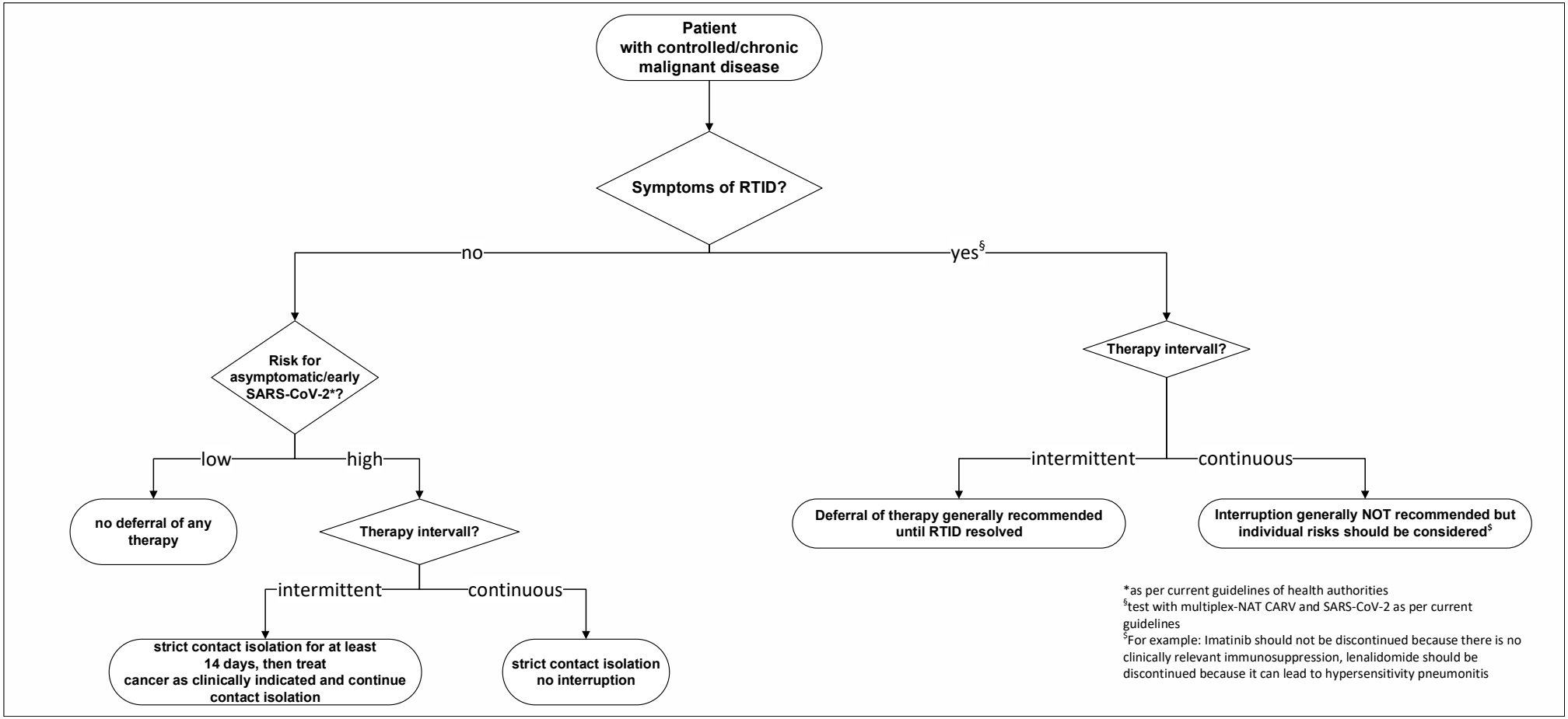
Deferral of Therapy



*as per current guideline of health authorities
§test with multiplex-NAT CARV and SARS-CoV-2 as per current guidelines

von Lilienfeld-Toal et al., Leukemia in press

Deferral of Therapy



von Lilienfeld-Toal et al., Leukemia in press

Therapy of CoVID-19

- no antiviral prophylaxis

- Antivirals (need to be given early)
  - Hydroxychloroquine 2x400mg/2x200mg ggbfs. plus Azithromycin
  - Remdesivir
  - Lopinavir/Ritonavir (first randomized trial negative!)

- Close collaboration with infectious disease specialists regarding indication of therapy, starting point of therapy and currently available drugs!

Therapy of CoVID-19

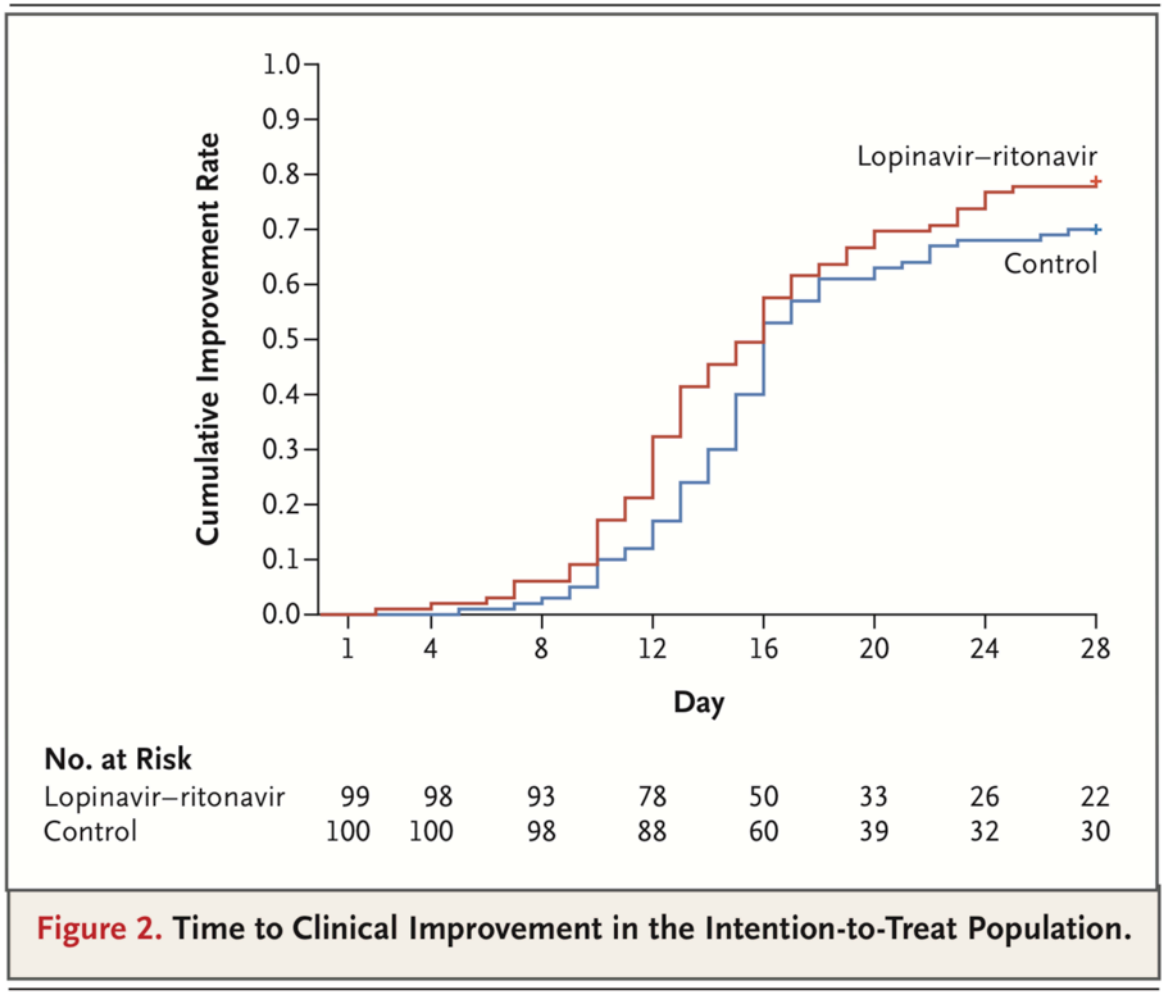


Figure 2. Time to Clinical Improvement in the Intention-to-Treat Population.

Problems:

- very late start (day13 after onset)
- underpowered

Cao et al., New Engl J Med 2020

Therapy of CoVID-19

- Immunosuppression:
  - Steroids
  - Cytokine-inhibition (for example anti-IL6 or anti-IL1)
  - JAK-inhibition

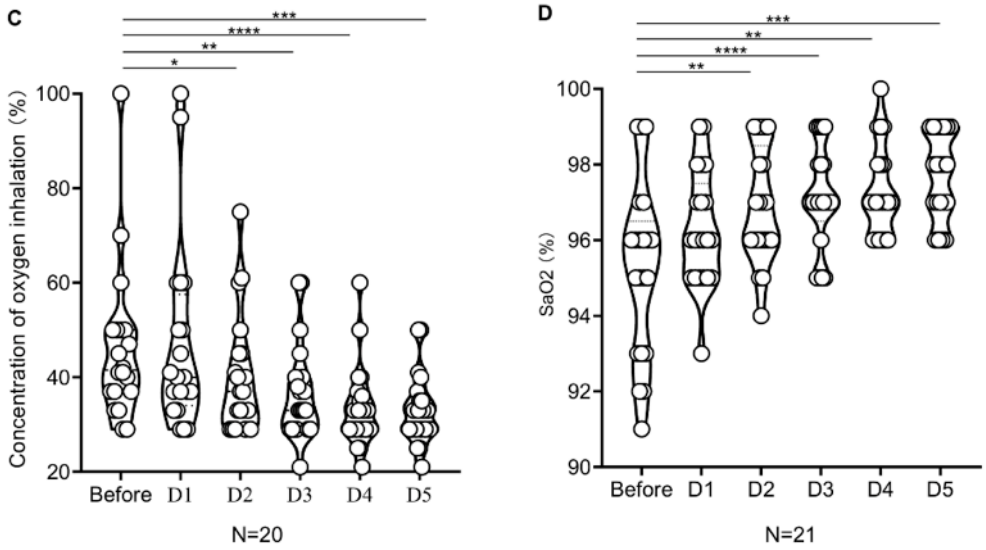
- Close collaboration with infectious disease specialists regarding indication of therapy, starting point of therapy and currently available drugs!

Therapy of CoVID-19

Tocilizumab:

21 patients with ARDS due to SARS-CoV-2

Tocilizumab 400mg iv
n=18 one dose
n=3 two doses



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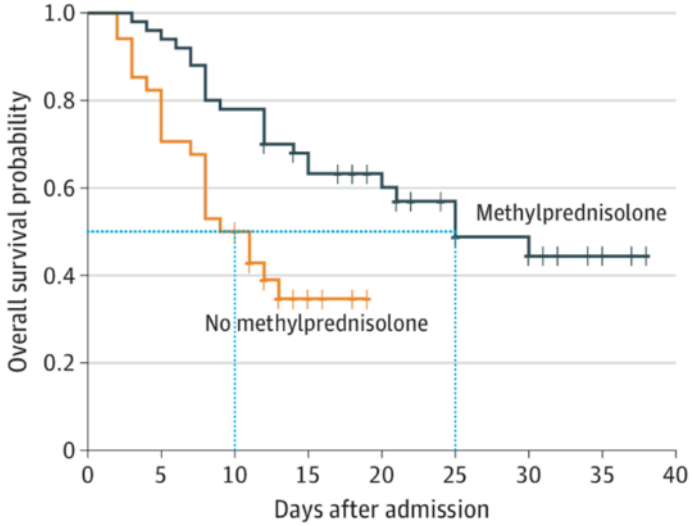
Xu et al., chinaXiv:202003.00026v1

Therapy of CoVID-19

84 patients with ARDS due to SARS-CoV-2

Dose of methylprednisolone not reported, likely to be <1mg/kg/d

Figure. Survival Curve in Patients With Acute Respiratory Distress Syndrome Who Did and Did Not Receive Methylprednisolone Treatment



No. at risk

No methylprednisolone	34	28	17	4	0	0	0	0	0
Methylprednisolone	50	48	39	29	20	14	11	4	0

Administration of methylprednisolone reduced the risk of death (hazard ratio, 0.38; 95% CI, 0.20-0.72; P = .003).

Wu et al., JAMA Intern Med *2020*

Therapy of CoVID-19

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- Supportive Therapy with O_2 and continuous positive airway pressure, discuss with intensivists

- **Anticoagulation** (Heparin)
- Diagnostics regarding superinfection
- Therapy of superinfection as per standard

Clinical Trials for CoVID-19

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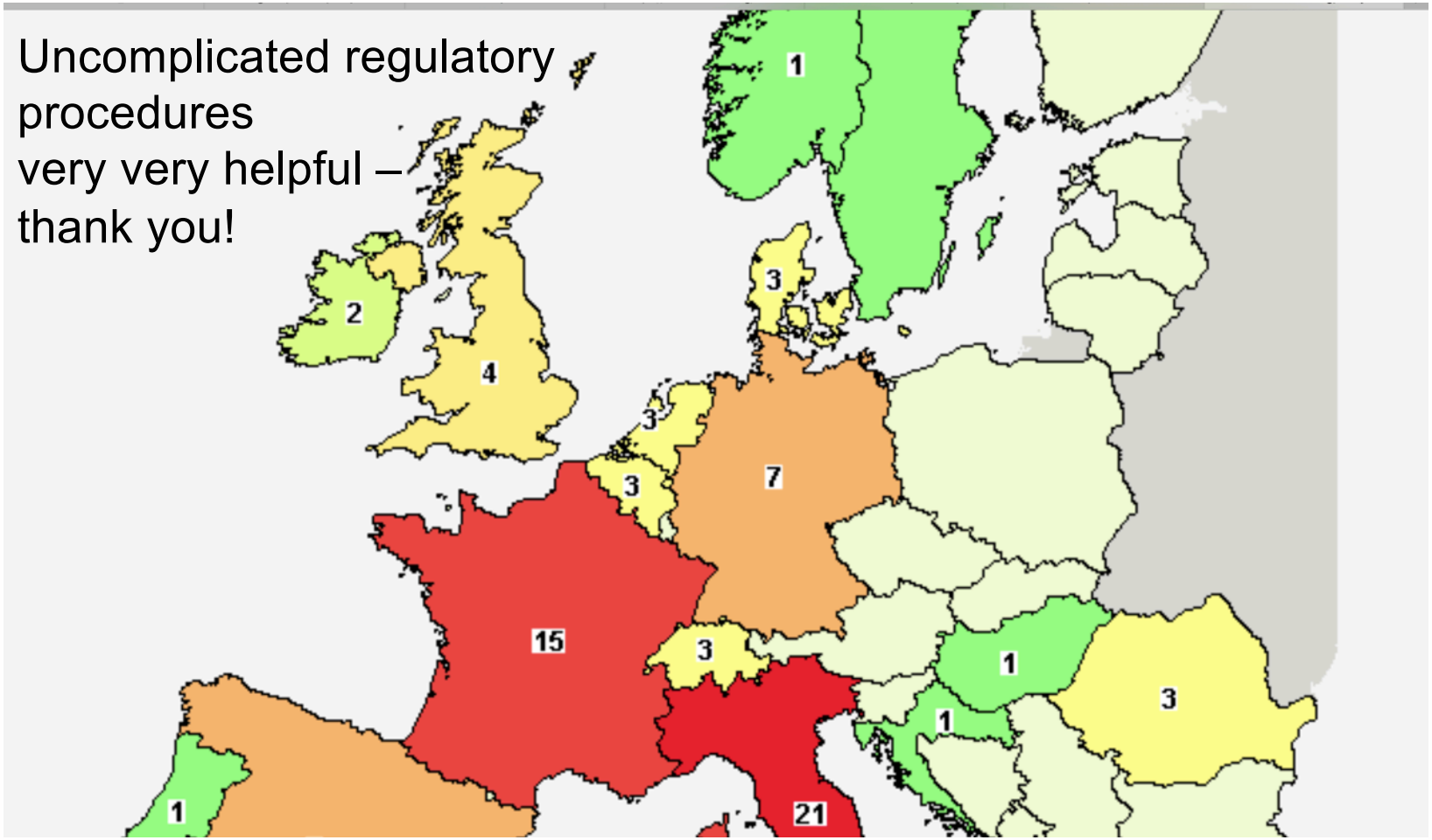
Uncomplicated regulatory procedures
very very helpful –
thank you!



clinicaltrials.gov

Clinical Trials for Cancer in the Era of CoVID-19

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- Try to carry on as much as possible, please!
- Make study conduct more flexible, allow for:
  - Reduction of visits, reduction of physical examinations, etc.
- Be more lenient with regard to who is allowed to perform study tasks (for example involvement of GPs)
- Find a way to reduce paper work resulting from deviations from study protocol (for example defining what is absolutely vital in terms of procedures, so documentation of deviations is reduced to a minimum)
- Consider reducing translational parts

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Thank you!