

The pandemic and non-COVID studies: The CRO Insight

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Ethics & GCP Forum

Precision Oncology Trials in the COVID Era

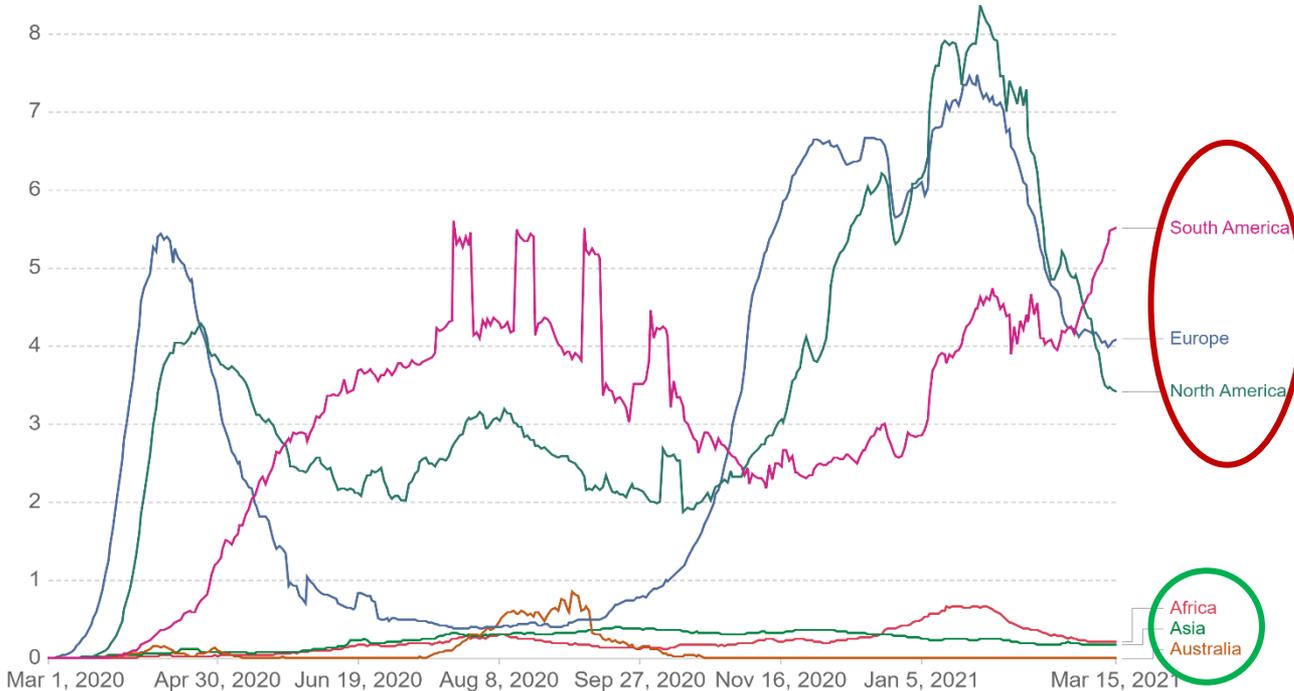
- ▶ Background
- ▶ Challenges
 - Logistic
 - Scientific and medical
 - Regulatory and ethical
- ▶ Solutions

COVID Waves; Stark Geographical Differences

Daily new confirmed COVID-19 deaths per million people

Shown is the rolling 7-day average. Limited testing and challenges in the attribution of the cause of death means that the number of confirmed deaths may not be an accurate count of the true number of deaths from COVID-19.

Our World
in Data

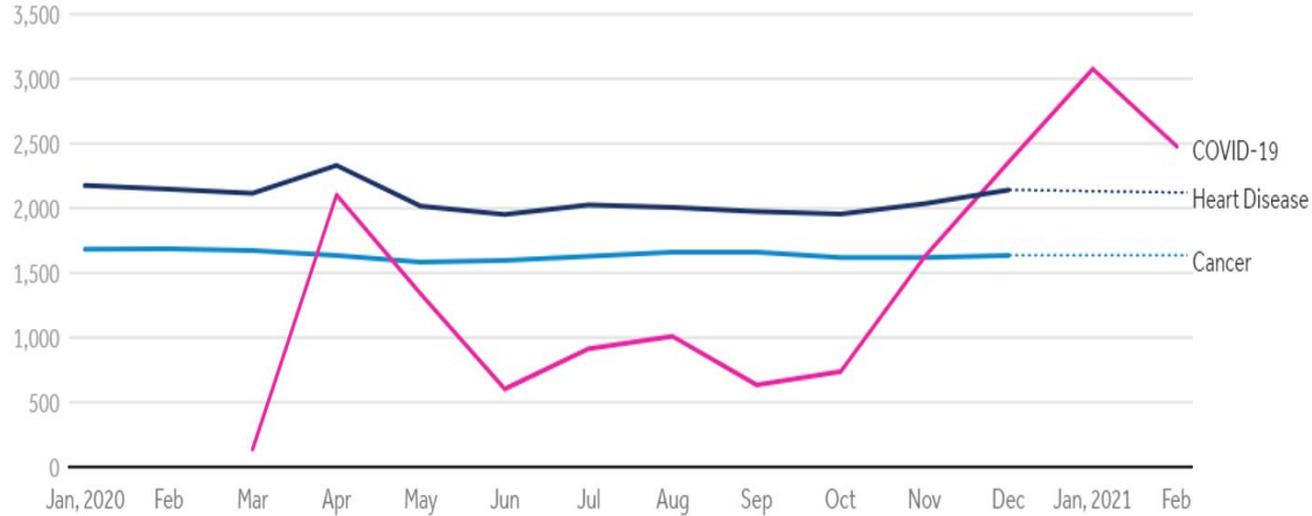


Source: Johns Hopkins University CSSE COVID-19 Data

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- ▶ Age of population?
- ▶ Obesity levels?
- ▶ Immune priming by prior/endemic infection(s)?
- ▶ Some X factor?

Average Daily Deaths (USA)



Notes: February 2021 COVID-19 deaths represent the daily average for February 2021 through February 20, 2021. COVID-19 daily average deaths are based on the KFF COVID-19 Tracker data. Death counts for 2020 represent the daily average for each month using the CDC's mortality data as of January 27, 2021. Heart disease refers to all circulatory diseases except stroke.

<https://www.healthsystemtracker.org/brief/covid-19-is-the-number-one-cause-of-death-in-the-u-s-in-early-2021/>

Three Key Similarities Between Cancer and COVID-19

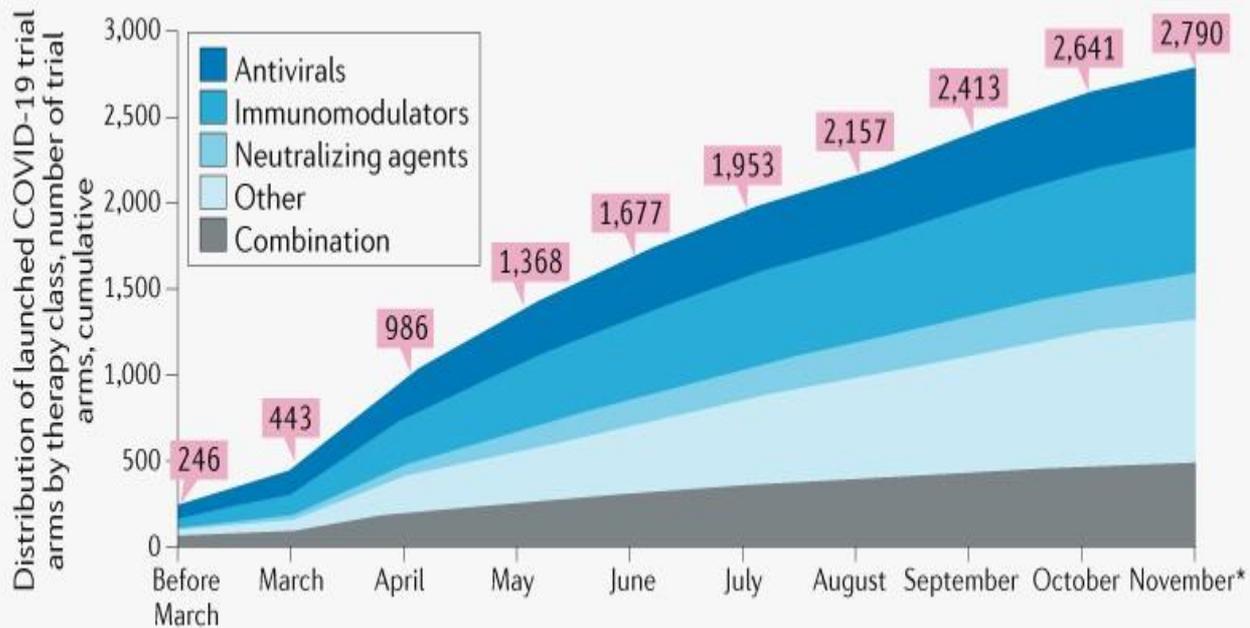
- ▶ **Inflammation:** Increased IL-6, TNF- α , IL-1 β , IL-2, IFN- γ , and IL-10 lead to vasodilation, neutrophil extravasation, and leakage of plasma into the infected tissue
- ▶ **Immune dysfunction:** Lymphopenia, decreased IFN- γ , exhaustion of cytotoxic T lymphocytes, activation of macrophages
- ▶ **Coagulopathy:** Microvascular or macrovascular thrombosis in lung, heart, intestine, kidney, or other organs, with elevated D-dimer, fibrin/fibrinogen degradation products, fibrinogen level, or DIC

Repurposing anticancer drugs for COVID-19-induced inflammation, immune dysfunction, and coagulopathy

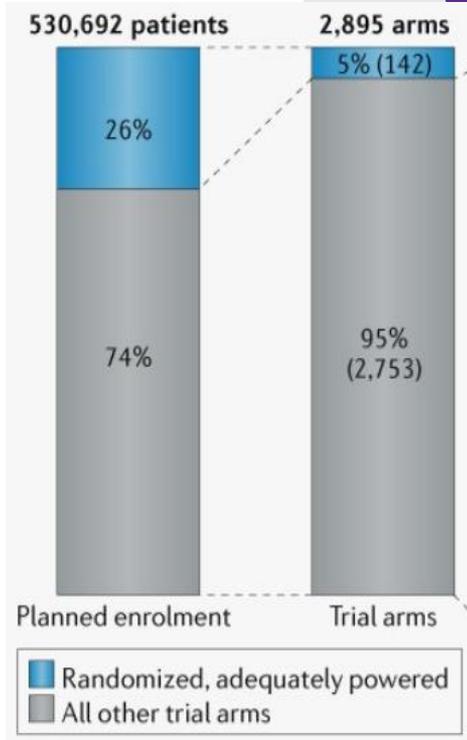
Kamal S. Saini, Carlo Lanza, Marco Romano, Evandro de Azambuja, Javier Cortes, Begoña de las Heras, Javier de Castro, Monika Lamba Saini, Sibylle Loibl, Giuseppe Curigliano, Chris Twelves, Manuela Leone & Mrinal M. Patnaik

British Journal of Cancer

COVID-19 Trials: Global Landscape



Nature Reviews | Drug Discovery



Bugin, Woodcock, Feb 2021 <https://www.nature.com/articles/d41573-021-00037-3>

Precision Oncology Trials in the COVID Era

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COVID-19: Impact on Current Cancer Trials

- ▶ Overloading hospital systems, sequestering of oncology staff
- ▶ Deferral of some routine therapy, tests, and procedures
- ▶ Reduction in recruitment to ongoing trials, delay in the planned launch of new ones
- ▶ Potential delay in data entry, increase in protocol deviations

Effect of the COVID-19 pandemic on cancer treatment and research

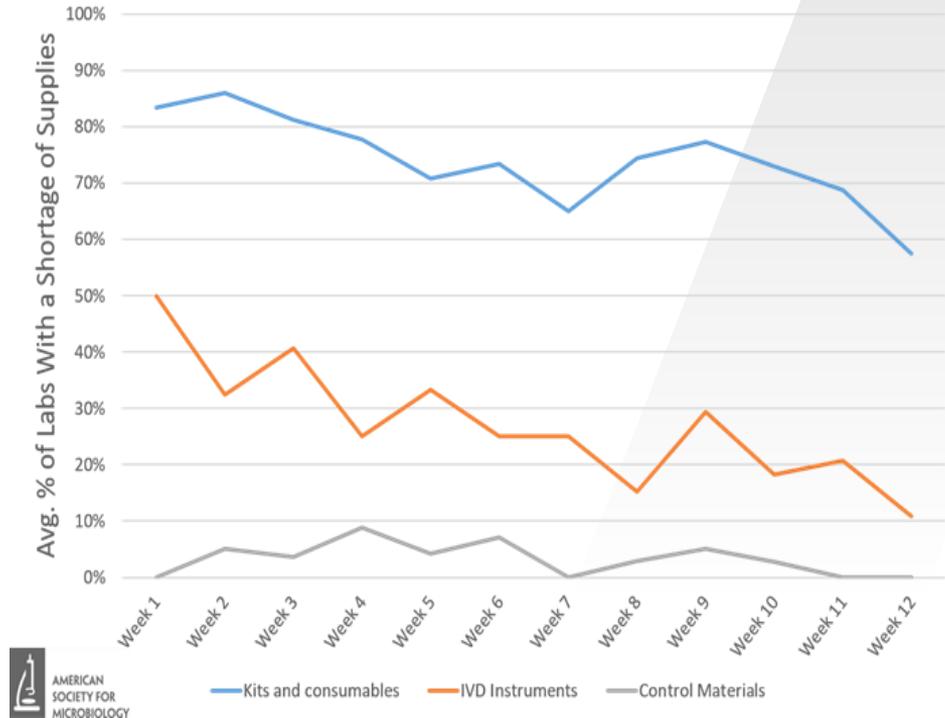
Kamal S Saini ¹, Begoña de Las Heras ², Javier de Castro ³, Ramachandran Venkitaraman ⁴, Martine Poelman ⁵, Gopalakrishnan Srinivasan ⁴, Monika Lamba Saini ⁶, Sanjeev Verma ⁷, Manuela Leone ⁵, Philippe Aftimos ⁸, Giuseppe Curigliano ⁹

THE LANCET
Haematology

[https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026\(20\)30123-X/fulltext](https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(20)30123-X/fulltext)

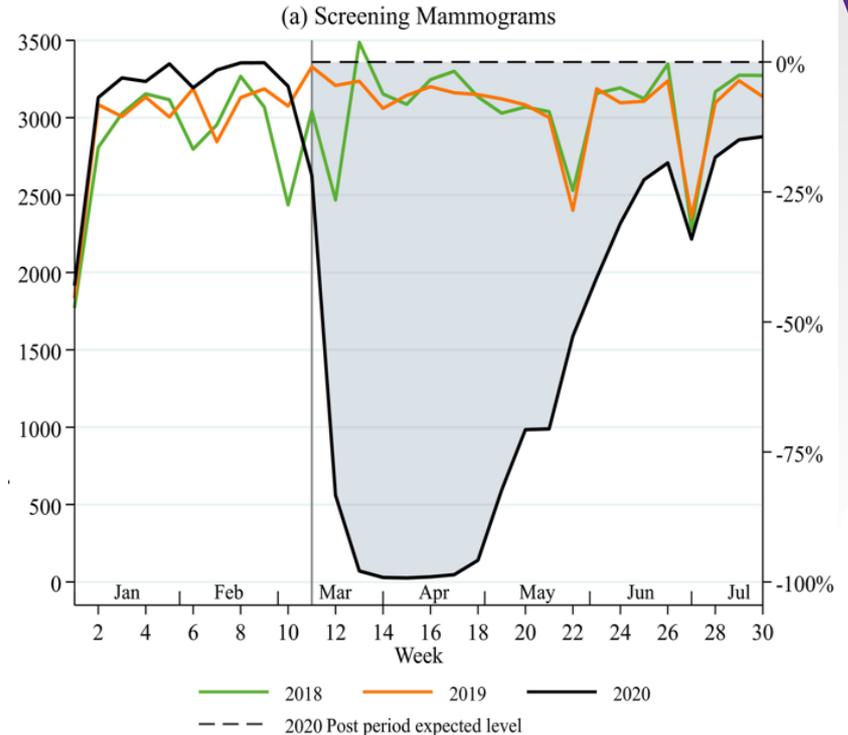
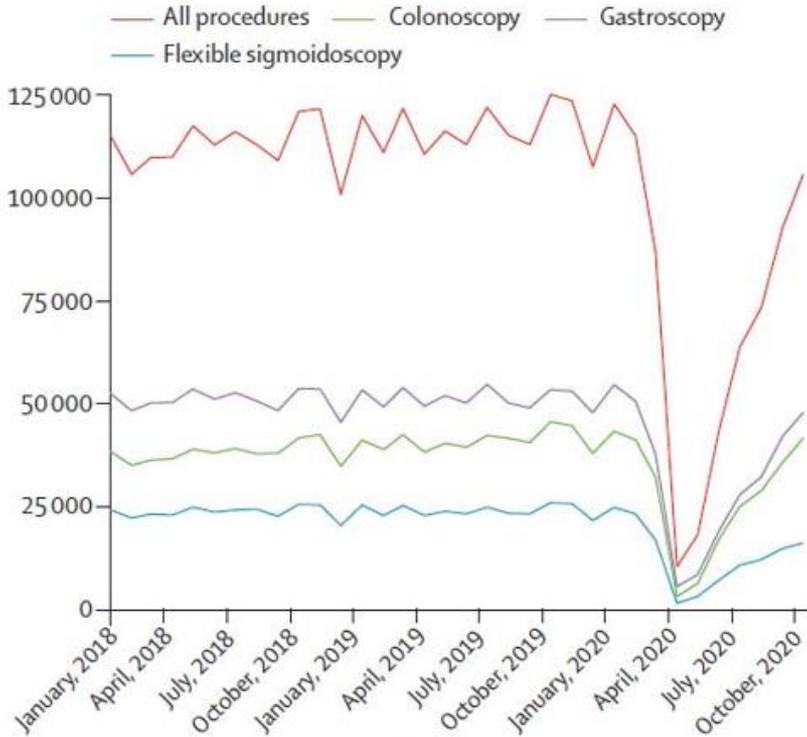
Global Shortage of Sampling Kits

- ▶ COVID-19 patients & trials prioritized
- ▶ Impact on precision cancer studies: biomarker testing for eligibility (e.g. PD-L1 or HER2 testing) and response assessment (e.g. MRD)
- ▶ Safety sampling also impacted; trial protocol amendment to allow local testing

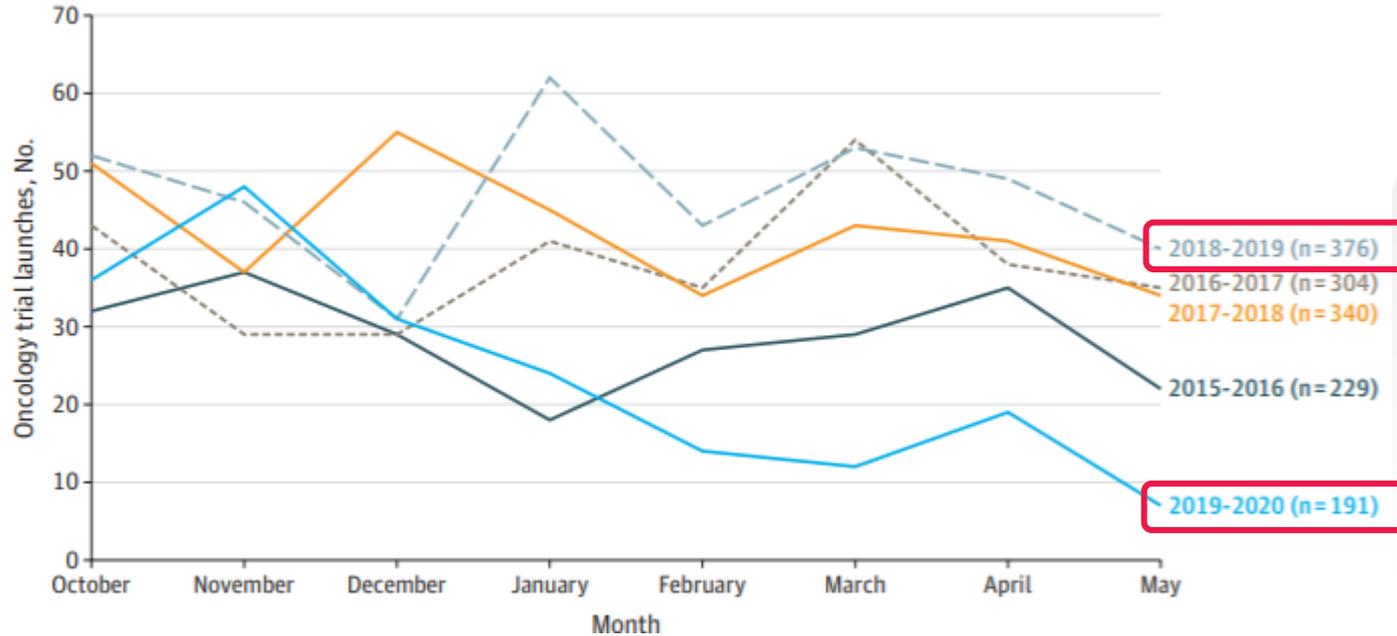


<https://asm.org/Articles/2020/September/Clinical-Microbiology-Supply-Shortage-Collecti-1>

Sudden, Severe Drop in Cancer Screening



60% Drop in Number of New Cancer Trials in 2020

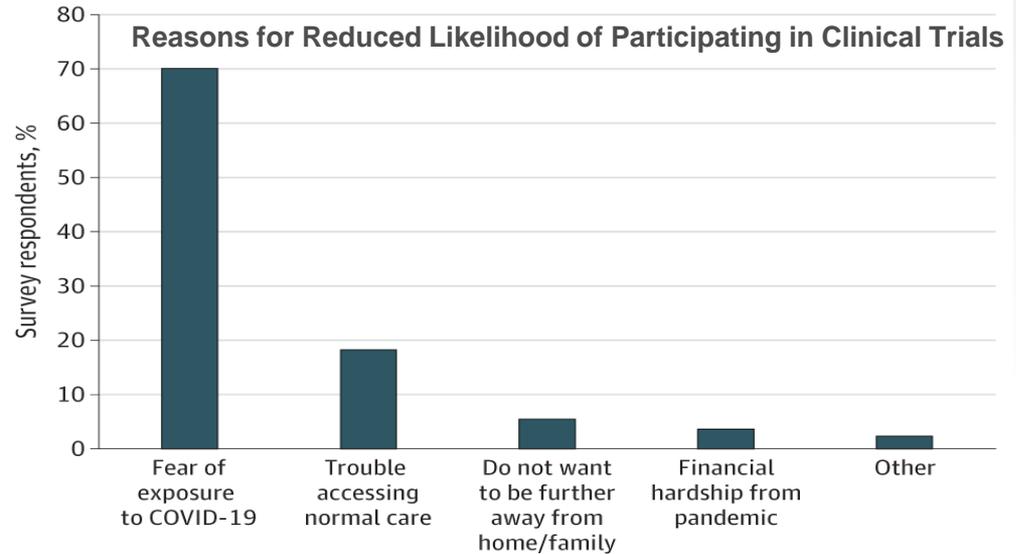


Trends in Oncology Clinical Trials Launched Before and During the COVID-19 Pandemic
(Medidata/RAVE)

Lamont et al, *JAMA Network Open*. Jan 2021

(Un)Willingness to Participate in COVID Era Cancer Trials

- ▶ US cancer patient survey: Has pandemic made you more or less likely to participate in a cancer clinical trial, or if it made no difference
- ▶ 907 respondents:
 - 79.5% indicated no difference
 - 18.1% less likely



#1 Priority in Precision Oncology Trials: Patient Safety

- ▶ Patients with underlying cancer who develop COVID-19 are highly vulnerable
- ▶ Radiotherapy, Day-care, and Trials units should be in COVID-free areas within hospitals
- ▶ Are COVID vaccines safe for patients with cancer? (Yes!)
- ▶ Are COVID vaccines effective in patients with cancer? (It's complicated!)
- ▶ What impact will COVID vaccines have on patients immune system, I-O agents, and IMPs?

25% Mortality in Patients with Cancer and COVID-19

Original Research

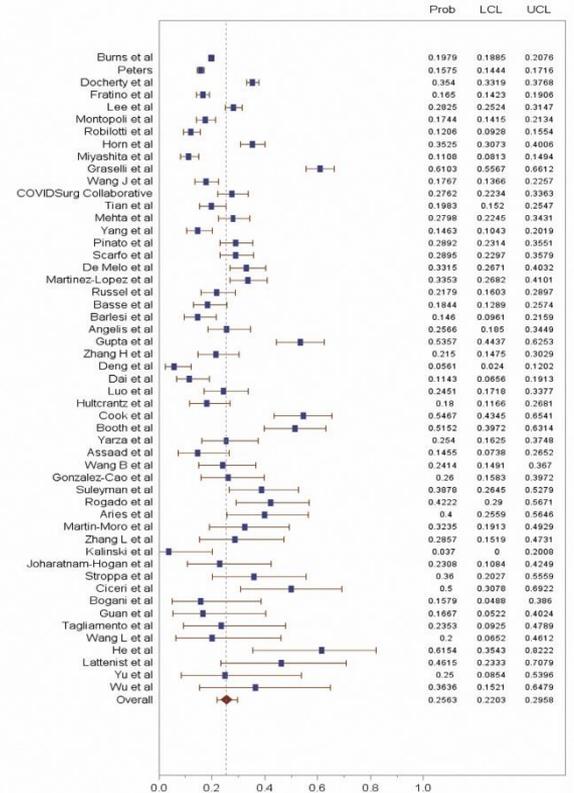
Mortality in patients with cancer and coronavirus disease 2019: A systematic review and pooled analysis of 52 studies

Kamal S. Saini ^{a, b}, Marco Tagliamento ^{c, d}, Matteo Lambertini ^{c, d}, Richard McNally ^a, Marco Romano ^a, Manuela Leone ^a, Giuseppe Curigliano ^{e, f}, Evandro de Azambuja ^{g, h, i, j}

European Journal of Cancer

Volume 139, November 2020, Pages 43-50

- ▶ Highest mortality in lung cancer and hematological malignancies
- ▶ Lower mortality in breast cancer



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7467090/>

Single Dose Pfizer Vaccine Insufficient in Cancer Patients

- ▶ SOAP study, UK: 151 cancer patients, 54 healthy controls
 - 47 patients received 2 doses, 3 weeks apart
 - rest got 1 dose with planned booster 12 weeks later
- ▶ After single dose of Pfizer vaccine BNT162b2:

Population	Immune protection at 3 weeks	Immune protection at 5 weeks
Patients with solid cancers	39%	43%
Patients with haematological cancers	13%	8%
Healthy controls	97%	100%

- ▶ Patients with solid cancer who got 2nd dose at week 3 had 95% immune protection at week 5
- ▶ 12 week interval between vaccine doses (current UK policy) may leave many cancer patients vulnerable

Optimal Timing for COVID Vaccination in Patients on Cancer Studies

Panel: Recommendations for SARS-CoV-2 vaccination and phase 1 cancer trials

Not started phase 1 trial

Avoid starting trial investigational medicinal product (IMP) until 2–4 weeks after the second dose of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine is administered safely for trial IMPs with cytokine release syndrome risk.

Already in phase 1 trial

Administer SARS-CoV-2 vaccine during the phase 1 trial but avoid vaccination on days of parenteral IMP dosing and the dose-limiting toxicity period.

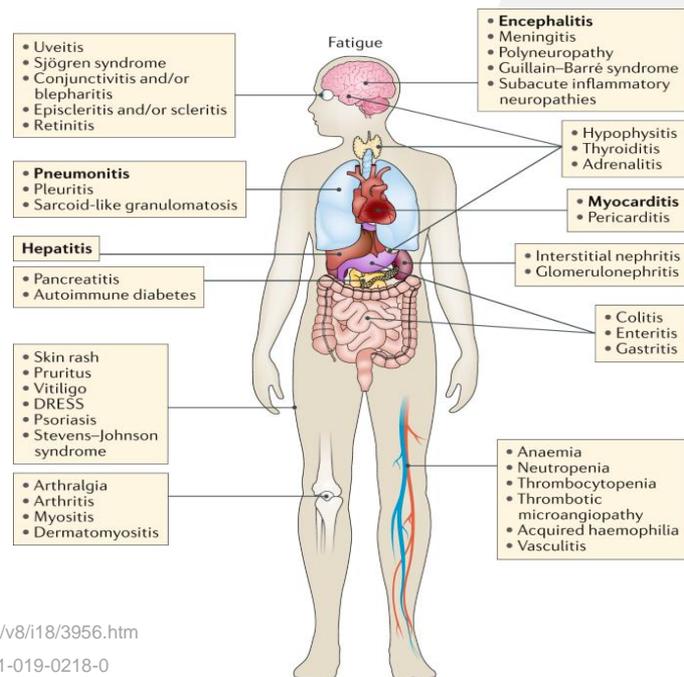
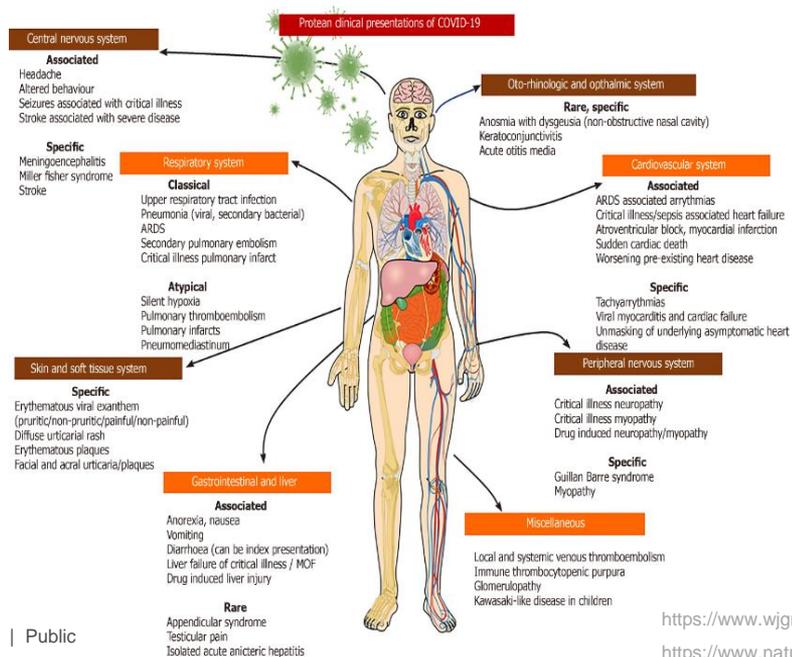
Solid tumours	
Cytotoxic chemotherapies	On vaccine availability (1–2 weeks before or 1–2 weeks after drug dose, when possible, to increase the potential for the immune system to mount a response)
Targeted therapy (e.g. TKIs)	On vaccine availability
Hormone therapy (e.g. anti-androgens or anti-oestrogen therapy)	On vaccine availability
Immunotherapy (e.g. immune-checkpoint inhibitors)	On vaccine availability
Epigenetic therapy	On vaccine availability
Haematological malignancies	
Intensive cytotoxic chemotherapies expected to result in profound and prolonged immunosuppression (e.g. anthracycline-based and/or cytarabine-based induction regimens)	Delay until absolute neutrophil count recovery
Epigenetic therapy	On vaccine availability
Targeted therapy (e.g. TKIs)	On vaccine availability
Immunotherapy (e.g. anti-CD20 antibodies)	On vaccine availability
Haematopoietic stem cell transplantation (allogenic or autologous)	>3 months after treatment
Adoptive cell therapies (for example, CART cells)	>3 months after treatment

[https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(21\)00017-6/fulltext](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00017-6/fulltext)

<https://www.nature.com/articles/s41571-021-00487-z.pdf>

Overlapping Symptoms of COVID-19, Cancer, Toxicity of I-O, and IMPs

- ▶ Cytokine release syndrome: COVID-19, lymphomas, CAR-T, bispecifics, monoclonals
- ▶ Attribution of a patients symptom tricky; case-by-case discussion between PI, CRO medical monitor, sponsor medic; formal risk assessment; distortion of efficacy and toxicity signals



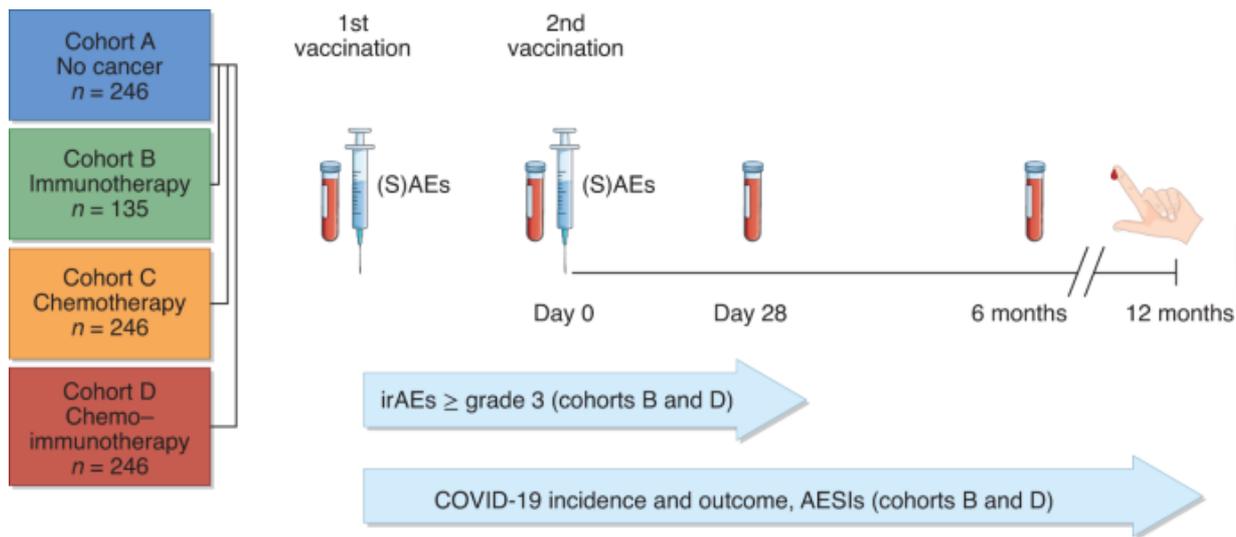
Checkpoint Inhibitors (CPI) & COVID Vaccines

- ▶ CPIs have a 5–8% risk of severe grade immune-related adverse events (irAEs)
- ▶ Concern that COVID vaccine may stimulate an overexuberant immune response in patients on CPIs
- ▶ 23 patients on ICIs who received the influenza vaccine had 52% rate of irAEs
- ▶ Other larger studies did not show higher frequencies of irAEs with vaccination
- ▶ ICIs are routinely used in patients with chronic hepatitis B, and those who have received HepB vaccines

<https://jhoonline.biomedcentral.com/articles/10.1186/s13045-021-01046-w>

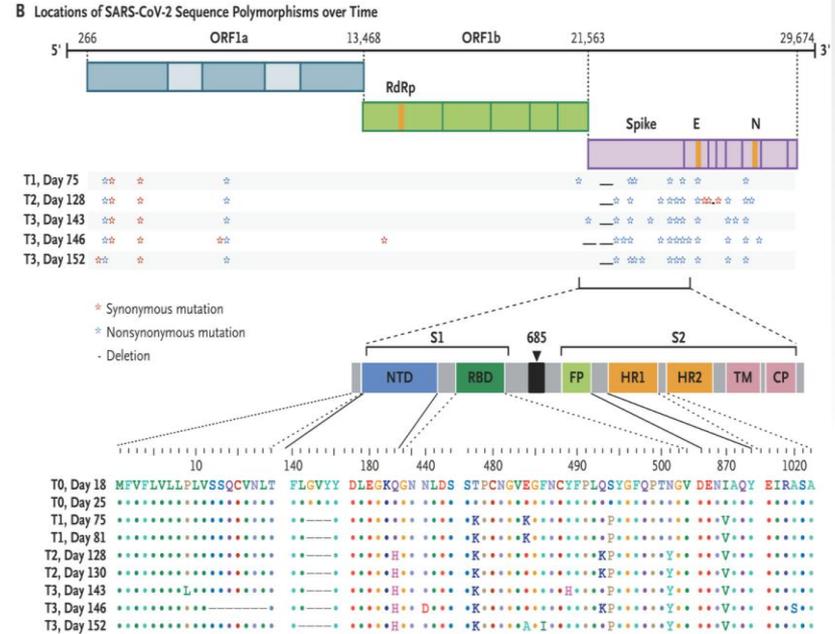
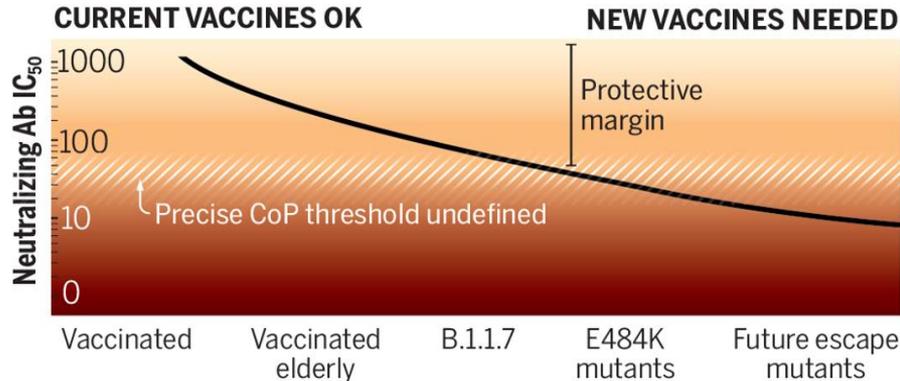
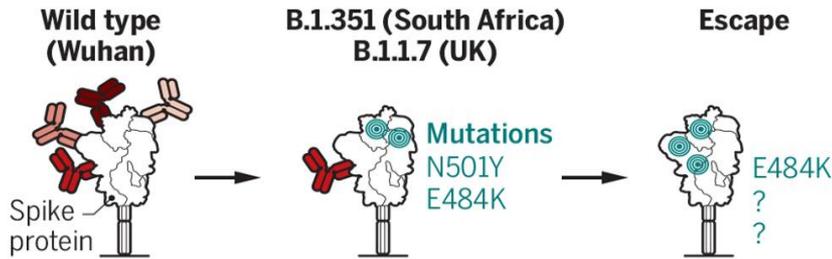
VOICE Trial, Netherlands

- ▶ Patients with cancer were largely excluded from COVID vaccine trials
- ▶ Scanty data on efficacy and safety of COVID vaccines for patients with cancer
- ▶ ASCO, AACR, ESMO, SITC: strong recommendation to vaccinate patients with cancer
- ▶ VOICE, OCTAVE will inform future precision cancer studies, esp with I-O backbone



Mutants: Need for Newer Vaccines in Future?

- ▶ Rapid evolution of SARS-CoV-2 observed in immuno-compromised pts (HIV, cancer)



<https://science.sciencemag.org/content/371/6534/1103>
<https://www.nejm.org/doi/full/10.1056/NEJMc2031364>

Regulatory Guidance: COVID Vaccines in Clinical Trial Patients

▶ Question:

- Certain clinical trial protocols disallow use of other “investigational medical product (IMP)”
- COVID-19 vaccines are currently authorized under an Emergency Use Authorization (EUA), technically making them an IMP
- **If a trial participant receives a COVID vaccine, would FDA consider the vaccine as an IMP?**

▶ Short answer: **No**

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COVID-19: Impact on Future Cancer Trials

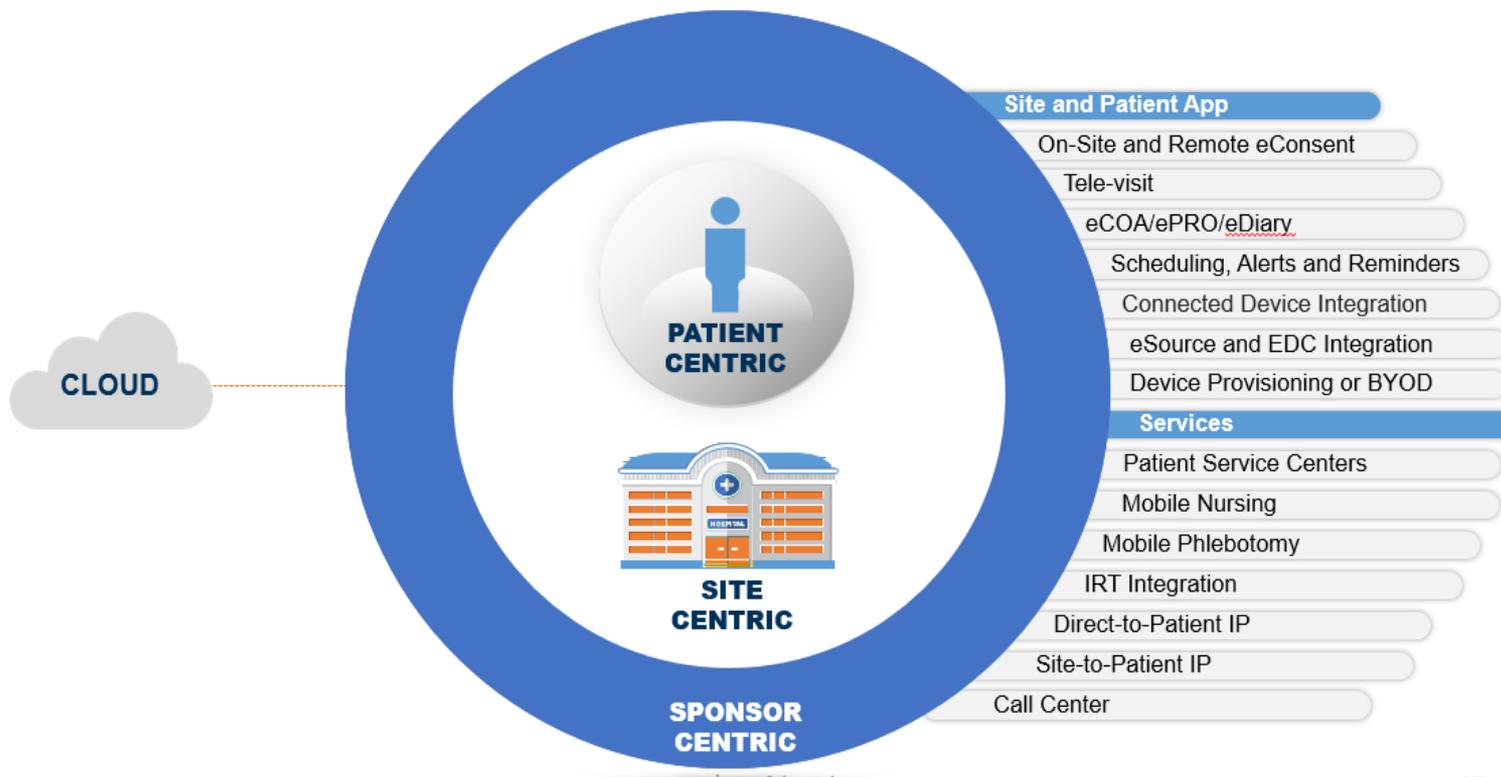
- ▶ Optimal use of technology (e-consent, telemedicine, wearables, ePRO, AI)
- ▶ Reduced paperwork and bureaucracy (ICF, data, samples)
- ▶ Speedier trial setup (regulatory and startup)
- ▶ Greater patient centricity (virtual, hybrid, decentralized studies)

Reimagining Global Oncology Clinical Trials for the Postpandemic Era: A Call to Arms

Kamal S Saini ^{1 2}, Begoña de Las Heras ^{1 3}, Ruth Plummer ⁴, Victor Moreno ⁵, Marco Romano ¹, Javier de Castro ⁶, Philippe Aftimos ⁷, Judy Fredriksson ⁸, Gouri Shankar Bhattacharyya ⁹, Martin Sebastian Olivo ¹⁰, Gaia Schiavon ¹¹, Kevin Punie ¹², Jesus Garcia-Foncillas ¹³, Ernesto Rogata ¹⁴, Richie Pfeiffer ¹, Cecilia Orbegoso ¹¹, Kenneth Morrison ¹, Giuseppe Curigliano ^{15 16}, Lynda Chin ^{17 18}, Monika Lamba Saini ¹⁹, Øystein Rekdal ²⁰, Steven Anderson ¹, Javier Cortes ²¹, Manuela Leone ¹, Janet Dancey ²², Chris Twelves ²³, Ahmad Awada ⁷

JCO® Global Oncology
An American Society of Clinical Oncology Journal

Decentralized Trial (DCT) Platform



DCT Platform: Applications for Oncology Studies



Enable Patients and Caregivers with Mobile App

- Study Information
- Study alerts and reminders
- Schedule of visits
- Collect data remotely (ePRO, at-home IP administration, medications for symptomatic care, treatment related symptoms, health outcomes, etc)



Use Televisits to Reduce Study Burden

- Replace phone calls and hold wait times with scheduled face to face conversations
- Reduce patient and caregiver burden (travel, parking waiting room, etc) by replacing some on-site visits
- Allow more family members to participate in discussions with investigator and decision making
- Enable sites to perform clinical assessments remotely



Allow for Mobile Nurses/Phlebotomy Visits

- Avoid in clinic visits by locally collecting safety lab samples
- Obtain lab samples from patient homes via mobile phlebotomists
- Utilize mobile nurses to perform clinical assessments, administer medication and obtain lab samples
- Allow patients to have samples drawn at local LabCorp patient service centers



Include Wearable Devices for Digital Biomarkers

- Track activities of daily living remotely like sleep, active time
- objective data to correlate with PROs for clinical assessments
- Monitor vital signs remotely like heart rate, heart rate variability, respiration, SPO2 for early detection of chemo related toxicities

Case study: Phase III Breast Cancer Study

20 Countries, 200 Sites, 800 Patients

COVID 19 Challenges –Site activation & Recruitment

- 50% Recruitment target behind, less patients being screened
- Site Activation delayed due to less resources at the sites, countries/hospitals in lockdown

Team Approach

- Covance medical team was in close contact with sites to discuss any burdens for recruitment, COVID 19 impact, protocol challenges
- Ongoing support from Sponsor local team in reaching out to the site
- Country online local meetings with National Coordinators and PIs
- Arranging remote SIVs
- Implement electronic signatures of the site agreements

Outcome

- Exceeded 50% site activation despite COVID 19 impact
- Recruitment on track

Case study: Phase III Breast Cancer Study

20 Countries, 200 Sites, 800 Patients

Challenges – Data Cleaning

- iDMC safety meetings every 6 month
- First iDMC safety meeting scheduled few months after start of COVID 19 pandemic
- Significant source data verification and queries backlog due to limited site staff availability, monitoring restrictions

Team Approach

- Very close communication with sites, medical team/Sponsor support
- Implementation of reduced source data verification
- Updating patient Informed Consent to allow remote SDV

Outcome

- Delivery of relevant data on time for first iDMC
- Positive iDMC outcome – study can continue and no safety concerns raised

Precision Oncology Trials in Post-Pandemic Era: Likely Trends

- ▶ Explosive growth in cancer drug pipeline - Targeted agents and immuno-oncology
- ▶ Falling costs of gene sequencing; Multi-'omics'
- ▶ Fragmented, molecularly defined populations
- ▶ Genomically-driven histology-agnostic drug approval
- ▶ Liquid biopsy
- ▶ Big data, bio-informatics and artificial intelligence

PAST	PRESENT	FUTURE
Intuition Medicine	Evidence-based Medicine	Precision Medicine
Signs and Symptoms	Clinical Trials <small>Gameiro, Clinics, 2018</small>	Algorithms



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