Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

The COVID-19 and Cancer Consortium: A Collaborative Effort to Understand the Effects of COVID-19 on Patients with Cancer

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https://doi.org/10.1016/j.ccell.2020.04.018

National and international consortia will play a key role in understanding the effects of the coronavirus disease 2019 (COVID-19) pandemic on cancer patients. The COVID-19 and Cancer Consortium (CCC19) aims to collect and analyze observational data at scale to inform clinical practice in real-time.

Background

The rapid spread of the coronavirus disease 2019 (COVID-19) pandemic has dramatically impacted oncologic care. Current evidence suggests that the effect of the pandemic on cancer patients has been profound. Two observational studies suggest that infection rates of COVID-19 may be significantly higher in cancer patients than in the general population (Liang et al., 2020; Yu et al., 2020). Further analyses suggest that cancer patients may also be at increased risk of severe complications from COVID-19, including hospitalization, respiratory failure, and death (Dai et al., 2020; Liang et al., 2020).

Multiple factors are likely contributing to the increased prevalence and severity of COVID-19 infection seen in cancer patients. Compared to the general population, cancer patients tend to be older, are more often smokers, and have more comorbid medical conditions, all of which are reported risk factors for severe COVID-19 infection (Jordan et al., 2020). Cancer treatment also typically involves frequent and lengthy visits to healthcare facilities, which carry risks of viral transmission independent of the treatment given (Wang et al., 2020). Of major concern to medical oncologists in particular are antineoplastic therapies, which have a variety of effects that can theoretically be deleterious in the context of COVID-19. Lymphosuppression and myelosuppression directly caused by cancer itself as well as cytotoxic treatments pose an increased risk of respiratory viral infections (Vento et al., 2008); some cytotoxic agents also cause pulmonary toxicity that may prove harmful in the context of severe COVID-19. Some monoclonal antibodies (for example, anti-CD38 antibodies such as daratumumab and isatuximab) result specifically in NK-cell depletion and increase risk of lower respiratory viral infection, although it is unclear whether this applies to COVID-19 (Nahi et al., 2019). Early reports have demonstrated a hyperactive, proinflammatory T cell phenotype in severe cases of COVID-19 (Xu et al., 2020). Some clinicians have accordingly hypothesized that immune checkpoint inhibitors may promote a more severe COVID-19 phenotype and are using these drugs with some hesitation, although the subject is controversial (Bersanelli 2020). Finally, a significant proportion of cancer patients take corticosteroids for prophylaxis, treatment, and symptom control related to cancer, which might be detrimental in the management of acute respiratory distress syndrome due to COVID-19 (Russell et al., 2020).

Although many oncologists are uncertain about whether they can safely treat their patients in the face of the concerns noted above, deferring therapy poses its own risks. Delays in cancer therapy have been associated with worse outcomes in multiple settings, particularly if the intent of treatment is curative or associated with a meaningful overall survival benefit (Biagi et al., 2011; Bleicher et al., 2016; Samson et al., 2015). Prospective clinical trials of investigational antineoplastic therapy, which drive many advancements in medical oncology, are now faced with additional logistical and practical barriers in the COVID-19 era. Due to this, many cancer clinical trials are either on hold or accruing slowly. In addition, despite COVID-19-related trials accruing at record pace, no randomized data are yet available to guide practice. Notably, some antineoplastic treatments may be helpful in mitigating the harmful immune response associated with severe COVID-19 and are under active investigation as repurposed therapies for COVID-19 (Table 1). Given the above, it is imperative that real-world evidence about the effects of COVID-19 on cancer patients is collected and disseminated rapidly to inform clinical decisions.

The COVID-19 and Cancer Consortium (CCC19)

The CCC19 is a multicenter registry that was created to help bridge the knowledge gap in cancer care caused by the COVID-19 pandemic. A guiding principle of the CCC19 is that through crowdsourcing, the consortium can both reduce barriers to entry of data and leverage expertise that is broadly distributed, both in terms of geography and subject matter, as is discussed elsewhere in more detail (Desai et al., 2020). Launched in beta testing on March 16, 2020, and live on March 17, 2020, the CCC19 now includes more than 90 institutions at the time of this

Table 1. Selected FDA-Approved Antineoplastic Therapies under Study as Repurposed COVID-19 Treatments as of April 24, 2020

Antineoplastic Therapy	Mechanism of Action	Cancer-Specific FDA Indications	Trials Indexed on Clinicaltrials.gov (n)
Acalabrutinib	Small molecule irreversible Bruton tyrosine kinase (BTK) inhibitor	Chronic lymphocytic leukemia (CLL); mantle cell lymphoma	1
Bevacizumab	Monoclonal antibody targeting the vascular endothelial growth factor (VEGF) inhibitor	Various solid malignancies	2
Emapalumab	Monoclonal antibody targeting interferon gamma	Hemophagocytic Lymphohistiocytosis (HLH)	1
Imatinib	Small molecule multiple tyrosine kinase inhibitor	Chronic myelogenous leukemia (CML); dermatofibrosarcoma protuberans (DFSPs); gastrointestinal stromal tumor (GIST); acute lymphoblastic leukemia (ALL); myelodysplastic syndrome (MDS); systemic mastocytosis	1
Interferons	Cytokine, immune system activator, precise antineoplastic mechanism not known	CML; hairy cell leukemia (HCL); Kaposi sarcoma; melanoma; renal cell carcinoma	15
Nivolumab, Pembrolizumab	Monoclonal antibodies to programmed cell-death protein 1 (PD-1)	Various solid and hematologic malignancies	3
Ruxolitinib	Small molecule janus-associated kinase (JAK) 1 and JAK2 inhibitor	Primary myelofibrosis; polycythemia vera	8
Selinexor	Selective inhibitor of nuclear export (XPO-1 inhibitor)	Multiple myeloma	2
Thalidomide	Immunomodulatory drug, precise antineoplastic mechanism not known	Multiple myeloma	2

writing, in multiple practice settings across 28 states, as well as Canada and Spain (Figure 1A). Participation in the CCC19 is open and voluntary in nature. Participating sites are asked to obtain necessary institutional IRB approval and data transfer and to make the best possible effort to report data on cases of COVID-19 in cancer patients that are treated in both the inpatient and outpatient settings, to ensure data are collected on patients with both mild and severe disease. To avoid duplicate entry of patients, the CCC19 recommends that data entry be centralized either through an institutional point person with oncology domain knowledge or to professional data entry personnel.

Data are entered through a RedCAP survey (Harris et al., 2019). Survey build-out and maintenance, as well as data maintenance, analysis, and dissemination, are coordinated at Vanderbilt University Medical Center in Nashville, TN. The founding member institutions of the CCC19 are Aurora Health Care (Wisconsin), Dana-Farber Cancer Institute (Boston, MA), Fred Hutchinson Cancer Research Center (Seattle, WA), Sylvester Comprehensive Cancer Center (Miami, FL), and Vanderbilt-Ingram Cancer Center (Nashville, TN). The CCC19 is overseen by a Steering Committee (SC) comprised of established experts in the fields of clinical hematology/oncology, virology, epidemiology, biostatistics, patient advocacy, and informatics, with all SC members having equal standing.

This nature of data collection, and the absence of protected health information being collected, facilitates rapid IRB approval, often with exemptions, at participating sites, which in turn enables the CCC19 to collect large amounts of data in a short period of time. To illustrate this point, fewer than 30 days elapsed between completion of the first and the 1,000th surveys (Figure 1B). Ultimately, electronic health record integration is planned, which will augment the manually abstracted data and further accelerate data collection. Of note, a large global analysis is planned, subsequently fusing RedCAP databases with the European Society for Medical Oncology COVID-19 and Cancer Registry (ESMO-CoCARE) project. As 25% of ESMO members are located in Asia, this effort is expected to involve participating sites across three continents.

The CCC19 collects data in four primary domains: (1) deidentified demographic data and other baseline patient-level data, including medical comorbidities that are not related to cancer or to COVID-19; (2) clinical data pertaining to

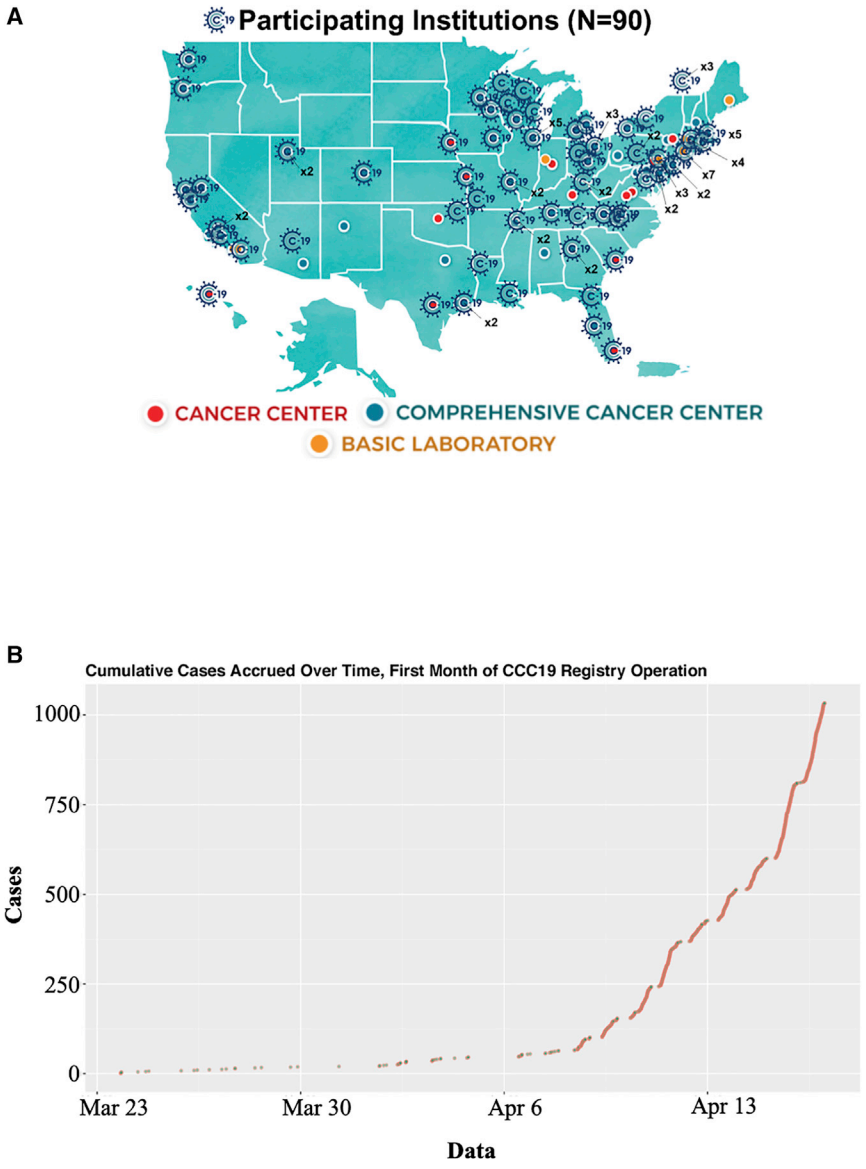

Figure 1. Geographic Participation and Patient Accrual in the CCC19

(A) Schematic indicating institutions that are participating in the CCC19 as of April 16, 2020. The sites are a combination of National Cancer Institute-designated comprehensive cancer centers, academic institutions, and community-based institutions.

(B) Chart demonstrating exponential growth in reported cases over time (n = 1,040 as of a data lock on April 16, 2020) for analysis in the first CCC19 publication.

COVID-19, including laboratory values, severity of COVID-19 presentation, and treatments received for COVID-19; (3) data pertaining to cancer diagnosis, stage, and current and prior treatment; and (4) follow-up data including outcomes related to COVID-19 . Data collection on 30-day and 90-day outcomes is also planned.

As examples, demographic data can be used to validate published data on adverse factors for COVID-19, such as age or pre-existing pulmonary or cardiovascular disease. The correlation of outcomes with the type and timing of antineoplastic therapy received can inform decisions on the risks and benefits of starting or continuing specific therapies in specific tumor types and clinical scenarios, or whether certain antineoplastic therapies may be associated with more severe COVID-19. The outcomes for patients receiving various potential anti-COVID-19 therapies are useful in determining which agents are most rational to investigate in future prospective clinical trials.

Collective Wisdom in the Era of COVID-19

The care of patients with COVID-19 and cancer is rapidly evolving and expanding around current geographic, operational, and bioinformatic boundaries. Driven by the need to harmonize data, CCC19 has the potential to collect large-scale, timely real-world data on cancer patients with COVID-19. Nevertheless, these data are observational in nature, which introduces the potential for unmeasured confounding in any analyses. Data collection is entirely cross-sectional or retrospective, although as 30-day and 90-day outcome surveys are completed, the data will develop a prospective component. Although institutions in a variety of practice patterns are participating, sites to date include a large number of tertiary care centers, which care for a population of cancer patients that are being treated with later-line therapy and suffer from higher numbers of complex medical problems than cancer patients treated in the community. This somewhat limits the external generalizability of studies conducted using CCC19 data; however, the same bias holds for most clinical trials that form the evidence base of oncology. At this time, the geographic distribution of centers and patients skews toward the Northeastern United States, which contains several cities that have particularly high caseloads. The reality of the COVID-19 era is that many of the most urgent questions for the field involve determining when it is safe or advisable to deploy the pre-COVID-19 standard of care. Observational data, such as that collected through the CCC19, can be very informative in answering these types of questions.

Through a landmark voluntary effort to crowdsource data collection as well as innovative collaboration between dedicated oncology professionals, CCC19 will shed light on the answers to some crucial questions with real-world evidence. We anticipate that the aggregate data collected through CCC19 will be harnessed to increase innovative and agile ways to answer more specific questions. In these unprecedented times, such an

initiative has the potential to improve outcomes for cancer patients in the United States and beyond.

DECLARATION OF INTERESTS

J.W. reports consulting for Westat, is a member of the IBM Health Watson Oncology and Genomics advisory council, and is cofounder of HemOnc.org LLC (no monetary value). B.I.R. reports consulting for Merck and research funding to institution for Merck, BMS, Pfizer, Aveo, AstraZeneca, and Genentech and holds stock in PTC therapeutics. S.P. has received education grants, provided consultation, attended advisory boards, and/or provided lectures for Abbvie, Amgen, AstraZeneca, Bayer, Biocartis, Bioinvent, Blueprint Medicines, Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, Eli Lilly, F. Hoffmann-La Roche, Foundation Medicine, Illumina, Janssen, Merck Sharp and Dohme, Merck Serono, Merrimack, Novartis, Pharma Mar, Pfizer, Regeneron, Sanofi, Seattle Genetics, Takeda, and Vaccibody, from whom she has received honoraria (all fees to institution). T.K.C. reports research (institutional and personal) for AstraZeneca, Alexion, Bayer, Bristol Myers-Squibb/ER Squibb and Sons LLC, Cerulean, Eisai, Foundation Medicine Inc., Exelixis, Ipsen, Tracon, Genentech, Roche, Roche Products Limited, F. Hoffmann-La Roche, GlaxoSmithKline, Lilly, Merck, Novartis, Peloton, Pfizer, Prometheus Labs, Corvus, Calithera, Analysis Group, Sanofi/Aventis, and Takeda; honoraria from AstraZeneca, Alexion, Sanofi/Aventis, Bayer, Bristol Myers-Squibb/ER Squibb and Sons LLC, Cerulean, Eisai, Foundation Medicine Inc., Exelixis, Genentech, Roche, Roche Products Limited, F. Hoffmann-La Roche, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, EMD Serono, Prometheus Labs, Corvus, Ipsen, Up-to-Date, NCCN, Analysis Group, NCCN, and Michael J. Hennessy (MJH) Associates, Inc. (Healthcare Communications Company with several brands such as OnClive, PeerView and PER); research to practice for L-path, Kidney Cancer Journal, Clinical Care Options, Platform Q, Navinata Healthcare, Harborside Press, American Society of Medical Oncology, NEJM, Lancet Oncology, Heron Therapeutics, and Lilly; consulting or advisory role for AstraZeneca, Alexion, Sanofi/Aventis, Bayer, Bristol Myers-Squibb/ER Squibb and Sons LLC, Cerulean, Eisai, Foundation Medicine Inc., Exelixis, Genentech, Heron Therapeutics, Lilly, Roche, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, EMD Serono, Prometheus Labs, Corvus, Ipsen, Up-to-Date, NCCN, Analysis Group, Pionyr, Tempest; stock ownership in Pionyr and Tempest; and other present or past leadership roles: Director of GU Oncology Division at Dana-Farber and past President of medical Staff at Dana-Farber), member of NCCN Kidney panel and the GU Steering Committee, past chairman of the Kidney Cancer Association Medical and Scientific Steering Committee); patents, royalties, or other intellectual properties: International Patent Application No. PCT/US2018/12209, entitled "PBRM1 Biomarkers Predictive of Anti-Immune Checkpoint Response," filed January 3, 2018, claiming priority to U.S. Provisional Patent Application No. 62/445,094, filed January 11, 2017; international patent application No. PCT/US2018/058430, titled "Biomarkers of Clinical Response and Benefit to Immune Checkpoint Inhibitor Therapy," filed October 31, 2018, claiming priority to U.S. Provisional Patent Application No. 62/581,175, filed November 3, 2017; medical writing and editorial assistance support may have been funded by Communications companies funded by pharmaceutical companies (ClinicalThinking, Envision Pharma Group, Fishawack Group of Companies, Health Interactions, Parexel, Oxford PharmaGenesis, and others); the institution (Dana-Farber Cancer Institute) may have received additional independent funding of drug companies or/and royalties potentially involved in research around the subject matter. Mentored several non-US citizens on research projects with potential funding (in part) from non-U.S. sources/Foreign Components. CV provided upon request for scope of clinical practice and research.

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