IA03 Systems approaches reveal shared pathways affected in SARS-CoV-2 infection and cancer. Nevan Krogan. University of California San Francisco, San Francisco, CA. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of the coronavirus disease 2019 (COVID-19) pandemic, has infected millions and killed hundreds of thousands of people worldwide. Clinicians are fighting the battle against the virus with a limited arsenal of drugs that have been shown to be safe and efficacious in treating SARS-CoV-2 infection. We thus rely on gaining a deeper understanding of the molecular mechanisms of this virus, and desperately need new strategies to get drugs to patients in need quickly. To combine both of these aims, my lab has focused much of our recent work on applying systems biology approaches to identify the cellular pathways hijacked by SARS-CoV-2, with the aim of pinpointing promising clinically available drugs for rapid repurposing to treat COVID-19. Identifying which cellular pathways and mechanisms are affected across different diseases will open the existing toolbox of drug treatment for COVID-19. Cancer drugs are a particularly promising set of drugs in this regard: During the process of virus replication, viruses rely on a multitude of interactions with their host cell, and hijack similar pathways that are affected in cancer cells. For example, viruses manipulate the cell cycle for their own benefit, recruit host DNA-damage machinery to viral replication sites, rely on the host translation machinery for viral protein production, and interfere with several signaling pathways, for example, to suppress cellular antiviral defenses. This list, while not comprehensive, makes apparent the commonalities between the exploitation of molecular mechanisms by cancer and virus infection. To get a full picture of cellular pathways targeted by SARS-CoV-2, we recently generated two virus-host interaction networks using systems biology approaches. First, we used affinity-purification mass spectrometry to create a virus-host protein-protein interaction (PPI) map. We cloned, tagged, and expressed 26 of the 29 SARS-CoV-2 proteins in human cells and identified the human proteins and complexes that physically associate with the individual viral proteins. Our map revealed 332 high-confidence PPIs with human proteins involved in a wide spectrum of cell biology, highlighting several oncogenic pathways. We identified 66 druggable human proteins at the virus-host interface, targeted by 69 compounds (of which 29 drugs are approved by the US Food and Drug Administration, 12 are in clinical trials, and 28 are preclinical compounds). We screened a subset of these in multiple viral assays and found that, for example, inhibitors of mRNA translation displayed antiviral activity. In a separate study building on these results, we created a quantitative mass spectrometry-based phosphoproteomics survey of SARS-CoV-2 infection in cell culture. Focusing on phosphorylation events, which are also highly misregulated in cancer, showed stark changes for both host and viral proteins and revealed dramatic rewiring of a number of signaling pathways. For example, SARS-CoV 2 infection

promoted casein kinase II (CK2) and p38 MAP kinase activation and shutdown of mitotic kinases. We identified 87 drugs and compounds by mapping global phosphorylation profiles to dysregulated kinases and pathways. Pharmacologic inhibition of p38, CK2, CDKs, AXL, and PIKFYVE kinases possessed antiviral efficacy, representing potential COVID-19 therapies. Clinical trials with some drugs and compounds implicated by our studies are currently being discussed or are already under way. To prepare for future outbreaks, we need to further increase our knowledge of cellular pathways targeted during virus infection. To this end, in addition to a number of infectious agents my lab has studied previously, we are currently performing similar studies on the closely related coronaviruses responsible for outbreaks of SARS and Middle East respiratory syndrome (MERS) in 2003 and 2012, respectively. Combined with the results discussed above, we hope to position the health care community to successfully fight this and potential future outbreaks of novel infectious diseases. Importantly, the input of physicians and experts from other fields will be crucial to leverage the knowledge gained from our studies about the pathways targeted across diseases.

IA04 COVID-19 in patients with lung cancers in New York City. Jia Luo[1], Hira Rizvi[1], Isabel R. Preeshagul[1], Jacklynn V. Egger[1], David Hoyos[1], Chaitanya Bandlamudi[1], Mark T.A. Donoghue[1], Marta Łuksza[2], Benjamin D. Greenbaum[1], Jedd D. Wolchok[1], Mark G. Kris[1], Matthew D. Hellmann[1]. [1]Memorial Sloan Kettering Cancer Center, New York, NY, [2]Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Patients with lung cancers may have distinct vulnerability to severe COVID-19. Understanding the patient-specific and cancer-specific features that impact severity of COVID-19 may inform optimal cancer care during this pandemic. A key question is whether PD-1 blockade therapy impacts COVID-19 severity.

Methods: We identified consecutive patients with lung cancer and a positive SARS-CoV-2 RT-PCR test seen at a single cancer center in New York City. We performed detailed manual review of the disease course, medical and oncologic history. COVID-19 severity outcomes were predefined, including need for hospitalization, ICU/intubation/transition to DNI-status, or death. We examined clinical features associated with severity using single and multivariable analyses. Regarding the impact of PD-1 blockade, we prespecified several bio-plausible comparisons of PD-1 exposure. HLA alleles were inferred from NGS and compared to controls with lung cancer and no known COVID-19.

Results: We identified 102 patients with lung cancers and a SARS-CoV-2 positive swab between March 12, 2020 and May 6, 2020. Patients were followed until May 11, 2020. COVID-19 was severe in patients with lung cancers (62% hospitalized, 25% died), but accounted for only 11% of deaths among patients with lung cancer during the pandemic. Determinants of COVID-19 severity were largely patient specific, including smoking status and chronic obstructive pulmonary disease. Cancer-specific features, including prior thoracic surgery/radiation and recent systemic therapies, did not impact severity. Likelihood of severe COVID-19 was generally similar across HLA class I supertypes. We found no significant differences in the impact of PD-1 blockade on COVID-19 severity. Modest numerical increases in severity of COVID-19 associated with prior PD-1 blockade were diminished (Odds ratio 0.86-1.01) after adjusting for expected imbalances in prior smoking history. Most patients recovered from COVID-19, including 25% of patients initially requiring intubation.

Conclusion: COVID-19 is associated with a high burden of severity in patients with lung cancers. Patient-specific features, rather than cancer-specific features or treatments, were the greatest determinants of severity. In particular, PD-1 blockade did not appear to impact severity of COVID-19 in patients with lung cancers.

IA09 A phase II trial to promote recovery from COVID-19 with endocrine therapy. Catherine H. Marshall, Srinivasan Yegnasubramanian, Hao Wang, Jennifer Durham, Ting Wang, Rachel Damico, Franco R. D'Alessio, Venkataramana K. Sidhaye, Andrew Pekosz, Joseph L. Mankowski, Sabra L. Klein, Sumati Murli, Elizabeth M. Jaffee, Samuel R. Denmeade. Johns Hopkins School of Medicine, Baltimore, MD.
Background: Death from COVID-19 disproportionately affects men, with up to 80% of deaths in severe COVID-19 cases being in men. There are a number of potential differences that might contribute to these sex differences. TMPRSS2 is a serine protease that primes the spike protein of SARS-CoV-2, a critical step in viral entry. TMPRSS2 is most highly expressed in the prostate where it is under androgen control, upregulated by testosterone and downregulated by antiandrogens. ACE2, the receptor used for entry into the host cell, is located on the X chromosome and may also have levels that are altered by hormones, with estradiol downregulating its expression. Previous research on acute lung injury demonstrated that estradiol seems to have beneficial effects on repair of lung injury. Therefore, our central hypothesis is that hormones may partially contribute to the gender disparity seen in COVID-19 patients, with high levels of testosterone being harmful and high levels of estrogen being helpful. Bicalutamide is a nonsteroidal antiandrogen that inhibits the action of androgens and, via feedback on the hypothalamic-pituitary axis, upregulates estradiol. We are conducting a phase II clinical trial to determine if bicalutamide improves the percentage of COVID+ patients with clinical improvement by 7 days.

Methods: We will enroll 40 patients who are hospitalized for COVID-19 with minimal respiratory symptoms (respiratory rate <30 and < 6L oxygen by nasal canula). Patients with more severe symptoms or oxygen requirements, who have taken hormones within the past month, or have pre-existing liver or cardiac disease will be excluded. Patients will be randomized 1:1 (20 in each arm) to bicalutamide or standard of care and will be stratified by gender. The primary outcome is comparing the percentage of patients with clinical improvement at day 7, compared to historical controls based on the World Health Organization categorical scale of clinical improvement. Key secondary clinical endpoints include all-cause mortality at 28 and 60 days, need for mechanical ventilation or ICU care, and safety of bicalutamide in this population. We will also determine the impact of bicalutamide therapy on viral infectivity by studying the reduction in viral load, hormone modulation and engagement of the endocrine axis, and immune response modulation promoting pro-repair immune function in patients with COVID-19. Clinical trial registration number: NCT04374279.

IA13 Treatment of COVID-19 pulmonary failure by targeting BTK. Steven Peter Treon. Dana-Farber Cancer Institute, Boston, MA.

Pulmonary failure is the main cause of mortality related to COVID-19 infection. Up to 80% of patients hospitalized for COVID-19 infection require supplemental oxygenation, of whom 30-40% may require mechanical ventilation. SARS-CoV-2 binds via the ACE2-receptor that is highly expressed on alveolar type II (ATII) cells in the lung. ATII cells constitute 5-15% of the lung epithelium. While alveolar type I cells are highly adapted for gas exchange, alveolar type II cells have a specialized role in innate immune response. ATII cells express Toll receptors (TLRs) and can trigger inflammatory cytokines and chemoattractants in response to pathogens that recruit and activate other immune cells, including macrophages and neutrophils. We and others previously showed that BTK, and its upstream activator HCK, were involved in TLR-mediated signaling. Both BTK and HCK are triggered by MYD88, a TLR-adaptor protein that signals for all Toll receptors except TLR3 in response to viral and bacterial pathogens, including coronaviruses. ATII cells express TLRs, as do alveolar macrophages that coordinate inflammatory responses with ATII cells. As components of TLR/MYD88 signaling, BTK and HCK can drive inflammatory cytokine production through ERK1/2. The potential for BTK inhibitors to abrogate lung injury and death was demonstrated in an experimental model wherein mice challenged with a lethal intranasal inoculum of a mouse-adapted strain of H1N1 influenza virus were protected against lung injury. Control mice developed respiratory failure, along with histologic and CT findings consistent with lung injury in sharp contrast to the mice that received ibrutinib. Control mice also lost weight and died, whereas those treated with ibrutinib recovered their weight after a brief loss and all survived. Mice treated with ibrutinib also showed decreased inflammatory cell infiltration as well as proinflammatory cytokines in lung tissues that included proinflammatory and chemoattractant cytokines such as IL-1β, IL-6, KC/CXCL1, TNFα, and MCP-1 observed in SARS-Cov-1 and SARS-CoV-2 patients. In a series of Waldenstrom's macroglobulinemia (WM) patients who were on full-dose ibrutinib (420 mg/day) and contracted COVID-19, none experienced dyspnea. In this series, one WM patient who contracted COVID-19 on reduced-dose ibrutinib (140 mg/day) experienced dyspnea and became hypoxic when ibrutinib was stopped and required mechanical ventilation. He was started on full-dose ibrutinib and showed rapid improvement, was extubated the next day, and did not require any oxygen supplementation two days later. Consistent with his rapid course of improvement on ibrutinib, his C-reactive protein level showed a marked decrease. In a subsequent and larger experience, Roschewski and colleagues administered acalabrutinib to 19 COVID-19 patients, 11 on supplemental oxygenation and 8 on mechanical ventilation. Eight of 11 (73%) and 2/8 (25%) on supplemental oxygenation and mechanical ventilation

were discharged on room air, respectively. Ex vivo analysis of peripheral blood samples showed attenuation of activated monocyte BTK expression and IL-6 production following acalabrutinib. Serially collected blood samples from patients with chronic lymphocytic leukemia (CLL), WM, and chronic graft-versus-host disease (cGVHD) on ibrutinib monotherapy also showed marked reductions in proinflammatory and chemoattractant cytokines that greatly overlapped with those reported elevated in the plasma of SARS-Cov-1 and SARS-COV-2 patients, and in ACE2+ cells from lung tissue of SARS-CoV-1 patients. In the iLLUMINATE randomized study, CLL subjects treated with ibrutinib immediately prior to infusion with obinutuzumab also showed significantly decreased levels of inflammatory cytokines associated with infusion related reactions (a cytokine release syndrome). These findings are consistent with a shift from an M1 to M2 polarized macrophage response following ibrutinib and are supported by preclinical and clinical studies showing dependence of macrophage lineage commitment on BTK function. BTK-inhibitors may therefore provide protection against lung injury and even improve pulmonary function in hypoxic patients with COVID-19. Randomized clinical trials to examine the benefit of BTK-inhibitors in COVID-19 patients in pulmonary distress and/or accompanying corollary studies to identify response biomarkers have been initiated: NCT04439006, NCT04382586, NCT04346199, NCT04380688.

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IA15 Continuing cancer care through a coordinated disease outbreak response system. Lim Soon Thye. National Cancer Center, Singapore, Singapore.
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulting in COVID-19, imposes unprecedented challenges to health care systems globally. Delivering cancer care during COVID 19 is particularly challenging for several reasons. Cancer therapy is complex, and success is intricately linked to timely access to appropriate care. The cancer patient's journey, which invariably involves multiple touchpoints and multiple set of specialists, increases the risk of virus transmission. Cancer patients on active treatment who developed COVID-19 infection are also at risk of increased morbidity and mortality. Currently, health care facilities are facing significant resource constraints both in terms of infrastructure and manpower as these resources are increasingly redeployed to COVID-19 facilities. The need for appropriate social distancing to reduce risk of infection puts further pressure on limited resources. These challenges disrupt cancer care and significantly impact the delivery holistic care from diagnosis to workup evaluation, treatment, surveillance, psychosocial support, palliative care, and research. Cancer centers around the world are struggling to develop a dynamic response with a strong focus on protecting patients with cancers and health care workers while simultaneously contributing efforts to combat COVID-19 in the community. Approaches adopted include appropriate triaging of patients with suspected symptoms, reconfiguring of outpatient journey and infrastructure leveraging on technology, introducing "segregated team models," developing inpatient policies on staff and patient movement, ethically adapting treatment decisions in accordance to best available consensus guidelines developed by professional bodies such ASCO and ESMO, and proactive efforts to address the physical and emotional well-being of employees, among many others. Leadership is crucial and "command structures comprising multiple stakeholders" are instituted to provide early coordination of institution-wide efforts as well as to consolidate and centralize all information disseminated to staff, patients, and the public. Of paramount importance, successful restoration and continuation of care requires a "whole-of-government, whole-of-society" approach to combat COVID-19 beyond its impact on health. Best government practices in containment strategies, leadership in coordinating the entire health care sector, effective communication, and building trust are key for health care institutions to operate effectively in this pandemic. Singapore, a densely populated city-state of 5.7 million and a global travel hub, is particularly vulnerable to the importation of communicable disease and was one of the earliest countries to detect COVID-19 in January 2020. Having experienced severe acute respiratory syndrome (SARS) in 2003, Singapore enhanced its pandemic preparedness response and these measures are now being put to the test. This presentation describes the coordinated approach

adopted by the National Cancer Centre Singapore within the framework of a National Disease Outbreak Response System to combat COVID-19. We were able to avoid nosocomial SARS-2 COV-2 transmissions among patients and staffs without compromising on cancer care. This COVID-19 pandemic also presented unique learning opportunities and an impetus to radically transform cancer care delivery going forward.

IA16 COVID-19 pandemic and its effect on the psychological status of cancer patients and oncologists. Gabriella Pravettoni. University of Milan, Milan, Italy.
On the 11th of March, the Word Health Organization declared COVID-19 a pandemic. This unprecedented emergency caused some unexpected effects on the health care system. During the pandemic, the attention focused on keeping cancer patients safe from COVID-19. This infection could have a detrimental effect on the physical and mental health of cancer patients; patients who have a suspension of cancer care suffer more from anxiety and/or depression. One of the worst side effects of COVID-19 is the fact that family members could not visit patients; social support in cancer patients is an important factor for a healthy mental condition. With no social support, their normal coping strategies have to adapt and the feeling of helplessness is overwhelming. These aspects are highlighted by a case report of a European Institute of Oncology patient. After a surgical intervention due to oral tongue cancer, he was diagnosed with COVID-19 infection and this caused anxiety and depression symptoms. During the pandemic, health care professionals' (HCP) role has been pivotal: HCP had to cope with a stressful working environment, facing physical and psychological challenges. Oncologists, in particular, in their daily practice are at risk of developing burnout symptoms and post-traumatic stress disorder symptoms and this could be exacerbated by the pandemic. During pandemic phase 1, we evaluated emotional distress and mental health of oncologists all over the world. Our results showed a low mental health status and distress regarding emotional status; oncologists revealed that fear is one of the most diffuse emotions during pandemic. They are afraid for their patients during the hospital hours, and, when they leave the hospital ward, they feel fear for their family members and cohabitants, in a never-ending feeling of dread. This condition, if prolonged, could be a stressor that could lead to burnout syndrome and post-traumatic stress disorder. For these reasons, it is important to care for the oncologists who had cared for their patients, often prioritizing it over their own well-being. In these particular times, new technologies can help both patients and oncologists. In this complex scenario, the role of the oncologists becomes more and more important; new technologies' output must be interpreted and technologies have to be at the service of humans, not vice versa. This should help oncologists to perform the integration of a big amount of diverse data otherwise impossible to put together meaningfully.

IA17 Ethics, cancer, and COVID. Arthur Caplan. New York University Langone Medical Center, New York, NY.

This talk will review (1) the impact of the covid-19 outbreak on treating cancer patients who were infected with the virus with unapproved and off-label agents under a philosophy of compassionate use including disclosure of conflicts of interest; (2) the ethics of withholding diagnosis and treatment from patients with cancer or who might have acquired cancer in the USA once social isolation, quarantines, and restriction of “nonessential” services began; (3) decisions about how to define “essential” services during the onset of the pandemic in severely impacted areas of the U.S.; (4) the management of those who died during the pandemic as lessons for future clinical care of cancer patients; (5) decisions about how to decide how much risk to permit those involved in clinical care for cancer or for reassigned duties to assume during an ongoing pandemic; and (6) how to prioritize future cancer research as the viral outbreak continues and resources remain restricted.

IA20 Potential insights into COVID-19 disparities from the science of cancer health disparities. John M. Carethers. University of Michigan, Ann Arbor, MI.

Older age as well as health comorbidities that include metabolic syndrome, cardiovascular disease, hypertension, asthma, and chronic kidney disease are listed by the Centers for Diseases Control and Prevention (CDC) as strong risk factors for severe disease and mortality from COVID-19. Since the outbreak began throughout the world and the United States, both gender and race/ethnicity have additionally become associated with infection and severe COVID-10 disease and mortality. While all humans lacked immunity at its onset to the new SARS-CoV-2 virus, the cause of COVID-19, older-age individuals are likely more susceptible due to age-weakened immune systems, the presence of health comorbidities, and are the most likely group to be housed within skilled nursing facilities (SNFs) where outbreaks and death from COVID-19 have been frequent. SNFs often lacked isolation protocols, initial viral testing, and lacked personalized protection equipment (PPE) that was prioritized to hospitals. People with health comorbidities regardless of age are more susceptible to severe COVID-19 likely because of weakened health and immunity. Indeed, patients on immunosuppression for medical conditions were among the first susceptible to severe infection when the outbreak began. The association of severe COVID-19 and race/ethnicity shows the strongest rationale with socioeconomic inequalities. Those from minority-population backgrounds are often in more urban crowded areas where mitigating factors of social distancing and opportunities to avoid virus exposure are less realized. Many minority populations, as a result of socioeconomic inequality, have more difficult access to health care, hold lower-paying jobs, reside in lower-income neighborhoods with grocery store deserts, have higher use of tobacco and alcohol and demonstrate lower physical activity, and have lower use of preventive medicine. This in turn has the physiologic consequences of alteration of the gut microbiome, increased localized inflammation, and compromised immunity, leading to higher frequencies of health comorbidities, the exact conditions that have been shown to place an individual at much higher risk for mortality from COVID-19. Other COVID-19 risk factors such as blood group type A and the use of angiotensin-converting enzyme (ACE) inhibitors for the high prevalence of essential hypertension and cardiovascular disease in racial populations appear not to play a role. Specific spike protein variants that have proved to be more virulent have not been evaluated among racial groups. The use of hydroxychloroquine might play a role in sudden death if used for treatment or prophylaxis of COVID-19 in some African Americans because of the common presence of a cardiac sodium channel polymorphism. The higher risk for men over women for severe COVID-19 disease is intriguing; the SARS-CoV-2 virus requires the use of cell ACE2 receptors and the cell serine protease TMPRSS2, both regulated by androgens for expression. Differences in expression

levels as well as trials of antiandrogen therapy are both being explored to assess if these permissive cell factors are the cause for gender differences.