DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
12th VIRTUAL NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
February 11, 2020

Virtual
Conference Room TE406, East Wing, Shady Grove Campus
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
Summary of Meeting
11 February 2020

The National Cancer Advisory Board (NCAB) convened for its 12th virtual regular meeting on 11 February 2020. NCAB members attended virtually, and National Cancer Institute (NCI) staff attended in Conference Room TE406, East Wing, Shady Grove Campus, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 11 February 2020 from 1:00 p.m. to 3:08 p.m., and closed to the public from 3:20 p.m. to 4:47 p.m. The NCAB Chair, Dr. Elizabeth M. Jaffee, Deputy Director, The Sidney Kimmel Comprehensive Cancer Center, Co-Director, Skip Viragh Center for Pancreas Cancer, The Dana and Albert "Cubby" Broccoli Professor of Oncology, Johns Hopkins University, presided during both the open and closed sessions.

NCAB Members

Dr. Elizabeth M. Jaffee (Chair, attended in person)
Dr. Peter C. Adamson
Dr. Francis Ali-Osman
Dr. Deborah Watkins Bruner
Dr. Yuan Chang
Dr. David C. Christiani
Dr. Judy E. Garber
Mr. Lawrence O. Gostin
Dr. Scott W. Hiebert
Dr. Beth Y. Karlan
Dr. Timothy J. Ley
Dr. Electra D. Paskett
Dr. Nancy J. Raab-Traub
Dr. Mack Roach III
Dr. Charles L. Sawyers (absent)
Dr. Margaret R. Spitz
Dr. Max S. Wicha

Members, Scientific Program Leaders, National Cancer Institute, NIH

Dr. Norman E. Sharpless, Director, National Cancer Institute
Dr. L. Michelle Bennett, Director, Center for Research Strategy
Dr. Oliver Bogler, Director, Center for Cancer Training
Dr. Stephen J. Chanock, Director, Division of Cancer Epidemiology and Genetics
Dr. Henry P. Ciolino, Director, Office of Cancer Centers
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences
Dr. William Dahut, Scientific Director for Clinical Research, Center for Cancer Research
Dr. James H. Doroshow, Deputy Director for Clinical and Translational Research
Dr. Dan Gallahan, Acting Director, Division of Cancer Biology
Mr. Peter Garrett, Director, Office of Communications and Public Liaison
Dr. Satish Gopal, Director, Center for Global Health
Dr. Paulette S. Gray, Director, Division of Extramural Activities
Dr. Ed Harlow, Special Advisor to the NCI Director
Dr. Toby T. Hecht, Deputy Director, Division of Cancer Treatment and Diagnosis
Dr. Sara Hook, Director, Office of Scientific Operations, NCI Campus at Frederick
Dr. Tony Kerlavage, Director, Center for Biomedical Informatics and Information Technology
Dr. Douglas R. Lowy, Principal Deputy Director, National Cancer Institute
Dr. Glenn Merlino, Scientific Director for Basic Research, Center for Cancer Research
Dr. Tom Misteli, Director, Center for Cancer Research
Dr. Margaret Mooney, Associate Director, Cancer Therapy Evaluation Program
Dr. Henry Rodriguez, Acting Deputy Director, Center for Strategic Scientific Initiatives
Mr. Jeff Shilling, Chief Information Officer and Chief of Infrastructure and Information Technology Services Branch, Center for Bioinformatics and Information Technology
Ms. Donna Siegle, Executive Officer and Deputy Director for Management, Office of the Director
Dr. Dinah Singer, Deputy Director, Science Strategy and Development
Dr. Sanya Springfield, Director, Center to Reduce Cancer Health Disparities
Dr. Louis M. Staudt, Director, Center for Cancer Genomics
Mr. Michael Weingarten, Director, Small Business Innovation Research and Small Business Technology Transfer Programs
Dr. Deborah M. Winn, Acting Director, Division of Cancer Prevention
Dr. Robert Yarchoan, Director, Office of HIV and AIDS Malignancy
Dr. Maureen Johnson, Executive Secretary, Office of the Director

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TUESDAY, 11 FEBRUARY 2020

I. CALL TO ORDER AND OPENING REMARKS—DR. ELIZABETH M. JAFFEE

Dr. Elizabeth M. Jaffee called to order the 12th virtual National Cancer Advisory Board (NCAB) meeting. She welcomed members of the Board, staff, and guests. Members of the public were welcomed and invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), National Cancer Institute (NCI), in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Jaffee reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations. She also thanked NCI Information Technology and DEA Committee Management Office staff for setting up the infrastructure for the virtual meeting.

Motion. A motion to accept the minutes of the 3 December 2019 Joint Meeting of the Board of Scientific Advisors (BSA) and the NCAB was approved unanimously.

II. FUTURE BOARD MEETING DATES—DR. ELIZABETH M. JAFFEE

Dr. Jaffee called Board members' attention to the future meeting dates listed on the agenda.

III. NCI DIRECTOR'S REPORT—DR. NORMAN E. SHARPLESS

Dr. Norman E. Sharpless, Director, NCI, welcomed NCAB members and attendees to the 12th virtual meeting and provided an update on the evidence of progress against cancer, NCI budget, leadership, and recent topics of interest receiving significant publicity.

Evidence of Progress Against Cancer. Dr. Sharpless remarked that this is an exceptional time in cancer research because of the rate of progress being made. The strongest evidence of progress in cancer research can be measured by the significant number of U.S. Food and Drug Administration (FDA) oncology drug approvals and the declines in cancer mortality reported annually since the mid-1990s. In fact, the American Cancer Society (ACS) *Cancer Facts & Figures 2020* (generated using the NCI Surveillance, Epidemiology, and End Results [SEER] data) reported the largest 1-year decrease (2.2 percent) in cancer mortality from 2016 to 2017, with the most rapid declines in melanoma and non-small cell lung cancer (NSCLC). Although no single research area can be attributed to these decades of progress, the advances are undoubtedly reflective of improvements in prevention and diagnosis, screening, treatment of rare abnormalities, and survivorship. Decades of sophisticated and painstaking science have led to these unprecedented therapies and diagnostics for cancer patients.

Dr. Sharpless elaborated on this exciting time for cancer research but explained that progress in cancer has brought new challenges to the NCI. For example, the increased biological understanding of cancer and heightened awareness of progress in cancer research are two main contributors to the high influx of grant applications to the NCI during the past 5 to 6 years. With the new investigator-initiated research applications, specifically R01s, data on cancer health disparities show improvements, but the rural versus urban disparity remains, primarily because of barriers to access to care. Another challenge is that the progress in cancer is uneven, significant in some areas and less notable in others. In addition, the progress in cancer research has brought about conflict-of-interest and undisclosed support from entities other than the NIH/NCI as well as issues in clinical trial prioritization and patient accrual. Last, new therapies have led to high personal costs for patients (e.g., financial toxicity). The NCI is considering ways to address all of these newfound challenges.

Despite the advances and progress, the fact remains that too many patients are still dying of cancer in the United States, and those cured experience survivorship toxicities related to care. Lung cancer mortality is a major factor in the overall U. S. cancer statistics at which the NCI has been looking

more closely. In the 2018 report, *Smoking and Lung Cancer Mortality in the United States from 2015 to 2065: A Comparative Modeling Approach*, the Cancer Intervention and Surveillance Modeling Network (CISNET) modelers of tobacco control and lung cancer predicts a 50 percent decrease in lung cancer deaths by 2040 for both men and women based on the status quo trends. Dr. Sharpless remarked on how these projected trends are reflective of the efforts of the NCI and other agencies to implement tobacco control policies and noted that lung cancer kills more people than breast, prostate, and colon cancers combined. The 2019 *Annual Report to the Nation on the Status of Cancer*, a collaborative effort of the NCI, Centers for Disease Control and Prevention, ACS, and North American Association of Central Cancer Registries, reveals that lung cancer mortality is decreasing faster than the incidence. Two possible explanations, Dr. Sharpless suggested, are the advent of new therapies for lung cancer (e.g., epidermal growth factor receptor inhibitors) and screening for early stage lung cancer, although the latter has yet to be implemented broadly across the United States. Finally, SEER data from 2001 to 2016 reveal significant improvements in the 2-year survival of NSCLC in women but little to no change in small cell lung cancer (SCLC) survival. Improvements in chemotherapy, surgery, and radiation are credited with the increased survival for NSCLC, none of which have changed for SCLC in the past 30 years. Dr. Sharpless reiterated that the new lung cancer therapies have improved the outcome of NSCLC and noted that the NCI is continuing to analyze these data.

NCI Budget. Members were informed that the fiscal year (FY) 2020 appropriation includes a significant increase in the base appropriations for the NCI above the FY 2019 enacted budget, $195 million (M) for the Cancer Moonshot SM, and $50 M for the Childhood Cancer Data Initiative (CCDI). The President's FY 2021 Budget proposal released on 10 February 2020 includes a 9 percent decrease for the NCI. In the next step of the NIH/NCI budget process for regular appropriations, Congressional appropriations committees will consider the President's proposal and prepare legislation. Dr. Sharpless highlighted that the FY 2020 appropriations bill for the first time includes language directing the NCI to spend $212.5 M to: (1) prioritize competing grants, which entails increasing paylines for most grants (e.g., Type 2) from the 8th to the 10th percentile, and (2) sustain the commitments, translating to restoring the 3 percent reduction in continuing grants (i.e., Noncompeting Continuation [Type 5] awards). This speaks to the continued commitment and bipartisan support in Congress for biomedical research, particularly cancer research, and conveys the legislators' confidence that the NCI, in its mission, is making their constituents' lives better with these investments.

Dr. Sharpless reminded the NCAB members of the report presented at the June 2019 Joint BSA and NCAB meeting by then-NCI Acting Director, Dr. Douglas R. Lowy, detailing the projected Research Program Project (RPG) pool additional funds that would be necessary in FY 2020 for NCI commitments to competing and noncompeting grants. In FY 2019, the NCI also supported more than $1.1 billion (B) of extramural research grants through non-RPG mechanisms, such as clinical trials (U10), NCI-Designated Cancer Centers (P30), Specialized Programs of Research Excellence (SPOREs (P50), Specialized Center (U54), and training (K awards). Because of Congress' support, the NCI will be able to restore the paylines in FY 2020 and continue to fund meritorious research. Dr. Sharpless called attention the NCI blog, "NCI Bottom Line: A Blog About Grants and More", launched in September 2019 to communicate to the investigator community details on NCI paylines and funding plans. The blog features one to two posts monthly addressing budget and funding-related milestones, funding trends and patterns, emerging policy or fiscal issues, and analyses of the NCI's grants portfolio.

Leadership Updates. Dr. Sharpless announced two recent appointments: Dr. Oliver Bogler is Director, Cancer Center for Training (CCT) and Dr. Satish Gopal is Director, Center for Global Health (CGH). He also noted the NCI's ongoing recruitment efforts for directors of the Division of Cancer Prevention (DCP) and Division of Cancer Biology (DCB) and expressed appreciation to Drs. Deborah M. Winn, Acting Director, DCP, and Daniel Gallahan, Acting Director, DCB, for their continued support in filling these roles.

Topics of Interest in the News. Dr. Sharpless updated the NCAB members on two recent news items of interest to the NCI: undisclosed support and women in science. The topic of undisclosed support pertains to financial conflicts of interest involving undisclosed payments (or arrangements) that can lead to the perception of biased research and foreign influence relating to shadow laboratories, misbehavior in peer review, ghost-written applications, and transfer of intellectual property. The common theme from NIH's perspective is scientists' receipt of support that is not disclosed on NIH grant applications, thereby violating the disclosure rule. Visible examples of wrongdoing are being revealed at some academic institutions resulting in consequences, and scientists are being terminated from their positions and subsequently fined, all translating to a loss of trust. This type of misbehavior from a small number of scientists is problematic for the cancer research enterprise, especially in terms of the commercially developable science of which the NCI is at the forefront. The NCI is working closely with the NIH Office of Extramural Research (OER), which, in turn, is addressing these issues with the Federal Bureau of Investigation, other federal agencies, and non-federal organizations. The NIH and NCI will not be able to solve all of the problems of undisclosed support alone and need the academic institutions' assistance to clarify their policies for their investigators and ensure compliance.

Dr. Sharpless outlined how the NCI plans to assist in solving these problems. For the vast majority of grantees who want to report their information, complying with the disclosure rules at academic institutions is confusing because of the lack of harmonization in the information needed and in reporting requirements across institutions and journals, as well as the changing policies. The NCI is actively discussing with journal editors and cancer research and professional organizations, including the American Association for Cancer Research, American Society of Clinical Oncology, Association of American Cancer Institutes, and Association of American Medical Colleges, about the option of a voluntary database that could be queried for grant submissions. Dr. James H. Doroshow, Deputy Director for Clinical and Translational Research, is leading this effort, and further details will be forthcoming. Dr. Sharpless explained that the reviews are ongoing. To date, the OER has contacted more than 70 institutions concerning 180 scientists across the United States; a significant number are NCI grantees.

Dr. Sharpless noted that women in science is a topic that the NCI strongly supports and highlighted that 11 February is designated as the United Nations International Day of Women and Girls in Science. Any experience with the work-life balance brings about an appreciation of the difficulty of having a family and a successful career. The NCI is indebted to women in science in cancer research, two of whom are well known in the cancer research community, i.e., Dr. Janet Rowley, a geneticist and the first to discover chromosomal translocation as causative to cancers, and Dr. Gertrude B. Elion, a biochemist, pharmacologist, and Nobel Prize recipient,. He highlighted the story of Dr. Alma Levant Hayden, an African-American chemist who worked at the NIH in the 1950s and then moved to the FDA. Dr. Hayden, using spectrophotometry, is credited with uncovering that Krebiozen, promoted as a successful anti-cancer agent being sold for thousands of dollars, was a harmless non-cancer agent (creatine). Her work in exposing this fraud led to a court trial resulting in criminal charges against the drug promoters. Dr. Sharpless emphasized that women have played a leading role in cancer research, a trend that the NCI aims to continue through its funding practices, training, and workforce development initiatives. He closed by adding that the impact of the NIH and NCI reaches internationally and is capturing the attention of young girls from as far as Japan who are asking questions about a cure for cancer and aiming to become scientists.

Recognition of Retiring Members. On behalf of the NCI, Dr. Sharpless recognized the contributions made by members of the NCAB whose terms of office have expired. He expressed appreciation for their service and dedication over the course of their terms. The following NCAB members are retiring: Dr. David C. Christiani, Elkan Blout Professor of Environmental Genetics, Department of Environmental Health, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Professor of Medicine, Harvard Medical School; Dr. Judy E. Garber, Susan F. Smith Chair, Director, Division of Cancer Genetics and Prevention, Dana–Farber Cancer Institute, Professor of

Medicine, Harvard Medical School; Dr. Beth Y. Karlan, Vice Chair, Women's Health Research, Professor, Department of Obstetrics and Gynecology, Director, Cancer Population Genetics, Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at the University of California, Los Angeles; Dr. Mack Roach III, Professor of Radiation Oncology and Urology, Director, Particle Therapy Research Program and Outreach, Department of Radiation Oncology, University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center; and Dr. Charles L. Sawyers, Chairman, Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, Investigator, Howard Hughes Medical Institute, Professor of Medicine, Weill Cornell Medical College.

IV. ANNUAL DELEGATIONS OF AUTHORITY—DR. PAULETTE S. GRAY

Dr. Paulette S. Gray, Director, DEA, requested concurrence by the NCAB on two Delegations of Authority to the Director of the NCI. She described the delegations and provisions in the Statement of Understanding. Delegation A allows the Director to obtain the services of not more than 151 special experts or consultants who have scientific or professional qualifications. Dr. Gray also explained that Delegation B specifies that the NCAB delegates authority to the NCI Director to appoint one or more advisory committees composed of private citizens and officials of Federal, state, and local governments to advise the Director with respect to his or her functions.

The Statement of Understanding with NCI Staff on Operating Principles in Extramural Grants also falls within the Delegations of Authority to the Director, NCI. NCAB operations are conducted in accordance with management and review procedures described in the NIH Manual Issuance 4513. Concurrence of the NCAB with recommendations of initial review groups will be required, except for the following: (1) Training grants and fellowships and other non-research grant applications are not subject to NCAB review and approval and, without other concerns, may be awarded without presentation to the NCAB for concurrence, with the exception of Ruth L. Kirschstein National Research Service Awards. (2) Applications above the 20th percentile will not have summary statements presented to the NCAB unless the Institute is considering an award of such an application or other special consideration is requested or required by NCI or NIH policy or for special consideration by an appointed member of the Board. (3) For applications assigned raw scores that are not percentiled, the cutoff will be a priority impact score of 50 for all mechanisms except R41, R42, R43, and R44 awards; for the latter, all scored applications will be included.

Expedited Concurrence: (1) For R01 and R21 applications with percentiled or raw scores that fall within the NCI paylines for that mechanism, a process of expedited concurrence will be used and (2) the Executive Secretary will alert Board members with responsibility for expedited concurrence when review outcomes for eligible applications are available on the Electronic Expedited Concurrence portion of the Electronic Council Book.

Administrative Adjustments: (1) Permission is delegated to the Director, NCI, to allow staff to negotiate appropriate adjustments in dollars or other terms and conditions of grant and cooperative agreement awards. (2) Administrative requests for increases in direct costs that are the result of marked expansion or significant change in the scientific content of a program after formal peer review will be referred to the Board for advice and recommendation. (3) Actions not requiring Board review or advice, such as change of institution, change of principal investigator (PI), phase-out of interim support, or additional support, need not be reported to the Board. (4) NCI staff may restore requested time and support that were deleted by the initial review group when justified by the PI in an appeal letter or when restoration is in the best interest of the NCI and the project is of high NCI programmatic relevance.

To continue responsible stewardship of public funds, the NIH has instituted a policy of Special Council Review of applications from well-funded investigators. Applications from PIs who have $1 M or more in direct costs from active NIH RPGs must be given additional consideration.

Questions and Answers

Dr. Gray confirmed that the language of the Delegations of Authority has not changed since the 2019 approvals.

Motion. A motion to approve the NCI Annual Delegations of Authority was approved unanimously.

V. EXCEPTIONAL RESPONDERS PROGRAM—DR. LOUIS M. STAUDT

Dr. Louis M. Staudt, Director, Center for Cancer Genomics (CCG), provided an update on the 6-year Exceptional Responders initiative, the Phenotype to Genotype trial, including clinical success stories and new insights in cancer biology. Dr. Staudt elaborated on the successful team science effort at the NCI in support of the Exceptional Responder initiative and acknowledged the multidisciplinary team for case review and analysis comprising the NCI Division of Cancer Treatment and Diagnosis (DCTD), CCG, and Frederick National Laboratory for Cancer Research staff; extramural collaborators; and industry partners. He expressed appreciation to the patients who donated their clinical and genomic data and tissue samples to the project and noted that all data presented during today's meeting are shared through the NCI Genomic Data Commons (GDC).

In terms of the rationale for an Exceptional Responders program, 10 percent of patients respond well to drugs that do not advance to receiving FDA approval. Certain cancer agents believed to be inactive are actually effective in a subset of patients. Dr. Staudt and the CCG hypothesize that specific genomic lesions or gene expression patterns might explain these exceptional responses in some cases, enabling the ability to prospectively identify this subset of patients and resulting in new therapeutic opportunities. Exceptional responders are robustly defined as patients having (1) a complete response (CR) to a regimen in which such a response is expected in less than 10 percent of similarly treated patients, (2) a partial response (PR) involving more than 6 months duration in which the length of a PR is also found in less than 10 percent of similarly treated patients, or (3) a response to standard treatment lasting three times longer than the median response duration in clinical trials of that agent.

After a rigorous screening process to identify patients for the Phenotype to Genotype trial, 478 exceptional responder cases were accepted for further review, their samples requested, and data added to the Medidata Rave® database. Of the 478 cases, 119 were approved for in-depth analysis; the distribution was nearly equal in men and women patients, and the median age was 57 years. Thirty percent of the patients were currently enrolled in an existing clinical trial and the remainder were receiving standard therapy, both representing a wide range of tumor histologies. Building on the previous exceptional responder studies by leading investigators in this field consisting of exome and amplicon sequencing, the CCG integrated RNA sequencing, immune profiling using the NanoString technology, and DNA methylation profiling using the Infinium array technology. Using this multi-platform approach, three levels of exceptional responder evidence were revealed in the 119 cases: Level 1, molecular evidence relevant to therapy and plausible hypothesis from the literature; Level 2, molecular evidence possibly relevant to therapy with little to no literature support; and Level 3, genomic analysis uninformative.

Dr. Staudt described the molecular characterizations of Level 1 exceptional responder cases, which were stratified into four broad groups based on the type of treatment received: DNA damage or standard of care, signaling inhibitors, immune-related, and prognostic genetics. For exceptional responses to DNA damage agents, one clinical case involved a female 48 years of age who was diagnosed with stage IV glioblastoma multiforme (GBM), had received standard treatment of carmustine, radiation, and temozolomide, and has been in CR for 84 months. The second case was a male 66 years of age, diagnosed with stage III B colorectal carcinoma (CRC), who relapsed following standard 5-fluorouracil (FU) and

oxaliplatin (commonly called FOLFOX) and 5-FU/irinotecan (commonly called FOLFIRI) regimens and was then treated with temozolomide plus a new drug, TRC102 (methoxyamine), in a clinical trial, resulting in ongoing PR for more than 48 months. GBM molecular characterizations revealed a somatic translocation involving base excision repair (BER) enzyme, APEX1 (apurinic/apyrimidinic endodeoxyribonuclease 1), and ACTN4 (alpha-actinin-4) resulting in low *APEX1* expression levels and low expressions of the direct DNA repair *MGMT* (O-6-methylguanine-DNA methyltransferase) gene resulting from promoter hypermethylation. Because this modified DNA is not repairable, these data speak to the synthetic lethality of carmustine and temozolomide in tumors with defective BER and direct repair pathways. CRC molecular characterizations also revealed low expressions of the *MGMT* gene and high expression of topoisomerase 2A/B. Again, results point to synthetic lethality of temozolomide and TRC102 in a tumor with *MGMT* silencing.

In exceptional responses to signaling inhibitors, a female patient 63 years of age, diagnosed with metastatic breast cancer, was treated with carboplatin, docetaxel, and trastuzumab for a tumor that was estrogen and progesterone receptor and human epidermal growth factor receptor 2 (HER2) positive. The patient achieved a CR for 84 months post treatment. Dr. Staudt emphasized that only 17 percent of similarly treated patients achieve a CR; even then, the median duration is 9.4 months. Molecular characterization revealed somatic breast cancer type 2 susceptibility protein (BRCA2) and BRCA1-interacting protein 1 (BRIP1) deleterious mutations, BRCA1 homozygous deletion, and HER2 amplification and overexpression. This molecular signature (BRCA2, BRIP1, and BRCA1), a component in the Fanconi anemia DNA damage pathway, is found in only a small percentage of invasive breast cancer cases in The Cancer Genome Atlas (TCGA) and never in the same tumor. Another patient, female, 63 years of age, diagnosed with breast adenocarcinoma stage IV, treated with trastuzumab and anastrozole, has had a PR for more than 35 months. Molecular characterizations showed high *HER2* amplification, but surprisingly, *HER2* expression was silenced and the anastrozole target, aromatase (i.e., cytochrome P450 19A1), expression was very high. The mechanism suggests that the response to anastrozole results from the hyperaddiction of the tumor to estrogen derived from the high expression of aromatase.

Many of the exceptional responders cases could be attributed to immune engagement and were evaluated against the 18-panel Nanostring array and compared with existing TCGA data. Overall, the mature natural killer (NK) cells, previously linked to the adaptive immune response, were statistically significantly higher in exceptional responder cases. The B cell enrichment was higher compared to TCGA cases, but to a lesser extent. In a stage IV bladder carcinoma case, a male patient, 75 years of age, who had undergone surgery and nivolumab treatment, was in ongoing CR for more than 16 months. The molecular characterization revealed high expression of programmed death 1 (*PD-1*) and interferon gamma (*IFNG*) genes and modest expression of PD ligand 1 (*PD-L1*), all translating to the hypothesis that an exceptional response results from immune checkpoint inhibitor in a tumor with hyperproduction of IFNG and PD-1 positive T cells.

For exceptional responses to attributable to prognostic genetics, the data showed frequent activating mutations in IDH1 (isocitrate dehydrogenase 1) and inactivating mutations in ATRX (chromatin remodeler) and TP53 (tumor protein p53) in GBMs that were significantly higher than TCGA GBM cases. An early molecular diagnosis could possibly inform patients with similar high-grade gliomas of the hope for a positive response. Dr. Staudt highlighted that several cases were outside the scope of a single category and explained that exceptional responses could be attributed to two or more interactions. For example, a female patient, 55 years of age, diagnosed with stage IV B endometrial adenocarcinoma, treated with carboplatin, paclitaxel, and temsirolimus, has been in ongoing CR for more than 70 months. The molecular characterizations revealed activating PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) and inactivating PTEN (phosphatase and tensin homolog) mutations; MLH1 (mutL homolog 1) methylation and low expression; and microsatellite instability. The patient also had the highest immune mRNA signature score yet seen in clinical samples and infiltration of CD8

T cells. The mechanism suggests sensitivity to temsirolimus resulting from PI3 kinase pathway activation and immune recognition as a result of microsatellite instability high mutational burden, translating to a favorable prognosis of microsatellite instability in endometrial cancer, aligning with the TCGA data.

Dr. Staudt summarized the lessons learned. A multi-platform genomics approach is necessary to understand exceptional responses; even then, roughly 75 percent remain not well understood. Some responses occur in tumors that appear aggressive pathologically but have the genetics of an indolent cancer. The immune system appears to play an important role in exceptional responders treated with standard therapies (not just immunotherapies). Multiple lesions in the same pathway generate synthetic lethality. He called attention to the need to develop a much better pathway-based understanding of therapeutic response and resistance.

Questions and Answers

Dr. Max S. Wicha, Madeline and Sidney Forbes Professor of Oncology, Director, Forbes Institute for Cancer Discovery, Founding Director Emeritus, University of Michigan Rogel Cancer Center Professor, Internal Medicine, Division of Hematology and Oncology, observed that although epigenetic regulation is a broad approach in the Exceptional Responders initiative, most of the emphasis has been on genetic mutations. Dr. Wicha also suggested expanding the scope to include solid tumors and noted two areas of missing emphasis: tumor heterogeneity and cell plasticity. Dr. Staudt explained that the exceptional responder researchers are merging ideas on genetic and epigenetic heterogeneity, which he anticipates will result in enhanced pathway-based understanding of therapeutic response and resistance, a dynamic process.

Dr. Jaffee asked whether the NK cells and B cells were distinct in some patients or whether the response could be attributed to antibody-dependent cell-mediated cytotoxicity. Dr. Staudt explained that some tumors, which they classified as immune high, displayed a signature clustering of the different types of lymphocytes, including NK and B cells. He added that the hypotheses generated were pre-formed based on the Nanostring panels; 18 were tested, and those results were presented during today's meeting. Single-cell analysis of tumors in the future would be optimal.

Dr. Garber suggested developing approaches to identify the non-responders early and determining ways to convert them to exceptional responders.

Dr. Sharpless commented on the 75 percent of exceptional responders and asked whether other research groups would make similar conclusions. Dr. Staudt pointed out that the Exceptional Responder initiative data are uploaded to the GDC and available to the research community. He speculated that in-depth proteomics on the existing data would be insightful.

VI. INTRAMURAL RESEARCH PROGRAM NEUROFIBROMATOSIS TYPE-1 PROGRAM—DR. BRIGITTE C. WIDEMANN

Dr. Brigitte C. Widemann, Chief, Pediatric Oncology Branch (POB), Center for Cancer Research, highlighted ways that the NCI Intramural Research Program (IRP) has contributed to advances in improving the outcome of neurofibromatosis type-1 (NF1). A common, single gene disorder and RASopathy, NF1 affects 1 in 3,500 people in the United States, is manifested in cutaneous stigmata (e.g., skin freckling) and tumor development, and has an effect on all organ systems in the body. Dr. Widemann's research focuses on NF1 peripheral nerve sheath tumors (PNST) of which there are several types, all resulting from the biallelic loss of *NF1*. The cutaneous tumors are benign but severely disfiguring; plexiform neurofibromas (PN) occur more frequently in younger patients; atypical neurofibromas (AN) are characterized by loss of cyclin-dependent kinase inhibitor 2A/B (CKDN2A/B); and malignant PNST (MPNST) tumors are presented with additional genetic changes. Because no

effective medical therapies for NF1 PNST exist, the POB's goal has been to develop therapies targeted for PN that also would extend to the other tumor types.

The most significant contribution in the timeline of IRP NF1 PN research was the development of the semiautomated volumetric magnetic resonance imaging (MRI) analysis for PN in 1999 in collaboration with Dr. Jeffrey Solomon, who was then a Ph.D. candidate working at Sensor Systems, Inc., and POB researchers that enabled a series of clinical trials beginning in 2001 conducted with extramural researchers. Other benchmarks include the POB NF1 Natural History Study that opened in 2008, the subsequent validated NF animal models developed in collaboration with preclinical investigators, and the first active treatment for NF1, selumetinib, as well as its FDA new drug application (NDA).

Many PN are congenital and histologically benign tumors, but they cause severe morbidity in patients. Approximately 10 to 15 percent of PN transform to MPNST and surgical resection is the only potentially curative treatment. The semiautomated volumetric MRI technique identifies and precisely marks the tumor border, encasing small segments of the surrounding normal tissue (e.g., negative disease margin) and allowing measurement of small PN changes and timely detection of any disease progression. Compared with the one-dimensional Response Evaluation Criteria in Solid Tumors (commonly called RECIST) and two-dimensional World Health Organization tumor burden measurements, the POB three-dimensional (3-D) volumetric MRI is more sensitive and reproducible in detecting progression (i.e., more than 20 percent increase in tumor volume) and response (i.e., less than 20 percent decrease in tumor volume) in PN. Dr. Widemann emphasized that volumetric MRI analysis has enabled the determination of central responses in most NF clinical trials conducted nationwide, including multisite studies. In the PN Natural History Study, volumetric MRI characterizations revealed that PN grows more rapidly in younger patients and that growth of distinct nodular lesions, many of which are AN, occurs independent of patient age.

Dr. Widemann detailed some of the IRP NF1 program clinical trial findings testing active PN therapies. The Phase II double-blind, placebo-controlled, flexible cross-over design multisite trial evaluated tipifarnib in children with PN. In phase A, patients with operable progressive PN were treated with either tipifarnib or placebo and treatments crossed in phase B. The data showed that tipifarnib did not improve the 3-year progression-free survival (PFS) and no patient had a tumor response of more than a 10 percent decrease in tumor volume. Dr. Widemann pointed out that although the findings were not positive, without the 3-D analysis disease progression would not have been possible to detect within a relatively short time period. After a series of studies evaluating potential PN treatments, the POB discovered, with limited preclinical data, a novel mitogen-activated protein kinase (MEK) 1 inhibitor, selumetinib, that showed promise. The Cancer Therapy Evaluation Program (CTEP) sponsored and the POB coordinated a Phase I trial. The primary objective was to determine the maximum tolerated dose of selumetinib in a small-scale study in children with NF1 PN. The results showed a PR in 71 percent of patients and significant improvement in disfigurement. The FDA requested additional studies beyond anecdotal clinical benefit and to include external controls.

In collaboration with AstraZeneca and CTEP, the POB designed the multisite Phase II registration trial of selumetinib for PN (commonly called SPRINT) and enrolled patients ages 2 to 18 who had one or more PN morbidity. The primary objective was to assess confirmed response rate with evaluations of pain, quality of life, and function as key secondary outcome measures. A total of 50 patients were enrolled during a 1-year period from August 2015 to August 2016. Of the 50 patients, 74 percent had a PR, 56 percent had a durable PR, and 8 percent had progressive disease. Regarding outcome measures, 78 percent of patients and 82 percent of parents of patients treated reported improvements in pain. Functional morbidities, such as range of motion, strength, and pulmonary complications, also improved. Compared to the NFI Natural History Study (external control), which did not demonstrate spontaneous PN volume decrease (≥ 20% per year), the aged-matched cohort in SPRINT showed modest but sustained decrease in PN volume (e.g., ≥ 20% per year). In addition, the median PFS for patients on

the natural history trial was 1.3 years compared to an 84 percent PFS after 3 years of observation for age-matched patients treated with selumetinib.

The SPRINT trial led to the FDA's granting selumetinib breakthrough discovery designation for PN treatment in pediatric patients 3 years of age and older and the NCI's filing the NDA. A decision is expected by summer 2020. Dr. Widemann acknowledged collaborations with Dr. Nancy Ratner at the Cincinnati Children's Hospital and Dr. Wade Clapp, the Developmental and HyperActive RAS Tumor SPORE principal investigator, resulting in the development of NF1 genetically engineered mouse models capable of predicting the activity of MEK inhibitors for PN. The POB, in collaboration with the Developmental Therapeutics Clinic, DCTD, designed a Phase II trial to investigate selumetinib in adults with growing or asymptomatic PN. To date, 21 patients have been enrolled in the trial. Preliminary results show a PR in 71 percent of patients and improvements in pain. The study is ongoing; DCTD collaborators will analyze patient biopsies for functional responses, and further objective responses are soon to be reported.

Dr. Widemann described efforts to determine the extent of AN as precursor of the aggressive MPNST. The POB and collaborators in Belgium and England characterized 63 patients with AN and discovered that 33 percent had MPNST, which is a higher incidence than the general population. The question remains whether all AN transforms to MPNST and at what stage. To address this challenge, three strategies were implemented. The POB convened a MPNST state-of-the-science conference and invited six world-class pathologists to review borderline lesions, make recommendations, and develop a tool for assessing patients. Biomarkers of malignant transformation from serial blood samples are being developed. A Phase I/II trial evaluating the CKD4/6 inhibitor, abemaciclib, in inoperable AN will soon open. Future considerations for the NCI IRP NF1 program will be to design clinical trials to assess the effect of selumetinib on asymptomatic but growing PN and other NF1 manifestations, develop tools for NF1 trials and patients, and evaluate MEK inhibitors and other RAS targeted agents in other conditions.

VII. ONGOING AND NEW BUSINESS—DR. ELIZABETH M. JAFFEE

Policy on Percent Effort on Grants. Dr. Dinah Singer, Deputy Director, Science Strategy and Development, presented the NCI's new policy addressing the level of effort principal investigators (PIs) devote to grant activities. Grants being proposed in the Special Council for Review of PIs that have more than $1 M of support have raised concerns regarding the level of effort devoted to the research effort. The NCI has reviewed a limited number of cases in which the percent effort has been 5 percent for significant grant mechanisms. Aside from a few cases (e.g., the R35 Outstanding Investigator Initiative (OIA) and P50 grants), no general NCI policies requiring a minimum percent effort for the standard grant mechanisms exist.

Historical data on the number of R01 grants per principal investigator show that 87 percent of NCI R01 recipients have fewer than four R01s, with some exceptions having six or seven. Although these exceptions do not present a major problem, Dr. Singer conveyed NCI's concern that if the R01 principal investigators request too little percent effort for a particular project, they are not likely to have sufficient time to provide satisfactory scientific and mentoring leadership. The NCI is therefore proposing a policy on the adoption of minimal effort requirements for the major funding mechanisms, including the R01, U01, R21, and P01 grants. This policy would ensure that the appropriate effort and attention are devoted to grant leadership and impose minimal effort requirements across all grants of similar size at NCI.

Dr. Singer described the principles guiding the Policy on Percent Effort on Grants. Required effort should be assigned for grants that provide substantial support for a laboratory's research efforts (e.g., R01s, U01s.); support for projects and core facilities within e complex research grants (e.g., P01s or U54s); or have a major leadership role within a complex research grant, such as a program project (P010)

or a SPORE (P50). Grants that are higher risk, have shorter durations, or those in which the researchers contribute to the community effort (e.g., R03s or training grants) should not have a required minimum. Required effort should be maintained for the duration of the award, and researchers should be able to request exceptions that are well justified.

Regarding the PI's level of effort by major grant mechanism, the NCI leadership and program staff are proposing a minimum 15 percent effort for the PI of an R01/U01; a 10 percent effort for the PI of multiple PI R01s; a 10 percent effort for the P01 PI,, a 15 percent effort for a P01 project leader and a 5 to 10 percent effort for a core leader; and 5 percent for the R21 PI. The percent effort for the P50, P30, and R35 mechanisms will be maintained at the current policy level. Levels of effort for such cooperative mechanisms as U54, U56, and UM1 will be stipulated in the respective request for applications.

Questions and Answers

Dr. Timothy J. Ley, Professor of Medicine and Genetics, Division of Oncology, Department of Medicine, Washington University School of Medicine in St. Louis, lauded the NCI for developing a policy that addresses an ongoing concern about NCI investigators who have a large number of grants and establishes a limit of six R01s per investigator, which he indicated appears to be reasonable. Dr. Ley asked about the circumstances in which an investigator would appeal a 50 percent minimum effort. Dr. Singer could not speak to a specific scenario but noted that the NCI would not rule out the possibility of such a request.

Dr. Peter C. Adamson, Chair, Children's Oncology Group, Alan R. Cohen Endowed Chair in Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania, suggested specifying in the proposed policy that the percentages indicated are the minimum amount of time a PI could spend on activities and that adjustments can be considered on a case-by-case basis.

Dr. Roach called attention to the unintended consequences of having a policy on required minimum effort, particularly in cases when junior level investigators, who need the financial support, are performing the work under the leadership of senior investigators. Dr. Singer explained that a 10 percent effort would be required for senior level investigator oversight and mentoring to a project and noted that the NCI will stay vigilant for any unintended consequences as the policy is implemented.

Dr. Wicha sought clarity about the change to the NCI-Designated Cancer Center Support Grants from 50 percent to 25 percent of effort. Dr. Henry P. Ciolino, Director, Office of Cancer Centers, clarified that the Cancer Center Support Grants percent effort was not a requirement but represented the typical amount of time a Cancer Center director would devote to grant-related activities.

In response to a query by Dr. Ley on the data showing the level of effort of NCI R01s by PI, Dr. Singer noted that these data are generally not recorded in a manner that is readily searchable but noted that the NCI could look into performing an analysis of the existing data.

Dr. Singer clarified that the policy, after approval, will take effect with new submissions in the June 2020 funding cycle, be communicated via the *NIH Guide for Grants and Contracts*, and will not be retroactive to grant applications already received in the NCI.

Dr. Electra D. Paskett, Marion N. Rowley Professor of Cancer Research, Director, Division of Cancer Prevention and Control, Department of Internal Medicine, College of Medicine, The Ohio State University, expressed concern that having the percent effort of established investigators outlined in the policy would be an issue for some disciplines, especially the population sciences in which the budgets are close to the upper limit for a project. Dr. Singer noted that the 15 percent requirement reflects a compromise; the NCI is aware of the potential effects on some groups, including the population scientists,

and will wait to hear back from the investigator community.

Motion. A motion to concur on the NCI Policy on Percent Effort on Grants was approved unanimously.

Establish an *ad hoc* Working Group on Clinical Trials Enrollment and Retention. Dr. Jaffee stated that the NCAB will need to concur on establishing an NCI Council of Research Advocates *ad hoc* Working Group. An overview of the expectations and the mission statement were provided to members prior to the meeting and were included in the Board book**.**

Questions and Answers

Dr. Paskett suggested expanding the focus and mission of the NCI Council of Research Advocates *ad hoc* Working Group on Clinical Trials Enrollment and Retention to include multiple perspectives on the financial costs of participation in clinical trials.

Motion. A motion to concur with establishing an NCI Council of Research Advocates *ad hoc* Working Group on Clinical Trials Enrollment and Retention, with modification to expand the focus and mission statement, was approved unanimously.

VIII. ADJOURNMENT OF OPEN SESSION—DR. ELIZABETH M. JAFFEE

Dr. Jaffee adjourned the open session. Only Board members and designated NCI staff remained for the closed session.

IX. CLOSED SESSION—DR. ELIZABETH M. JAFFEE

"This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 552b(c) (6), Title 5 U.S. code and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2)."

There was a discussion of personnel and proprietary issues. Members absented themselves from the meeting during discussions for which there was a potential conflict of interest, real or apparent.

There was a review of grants and a discussion of personnel and proprietary issues. Members absented themselves from the meeting during discussions for which there was potential conflict of interest, real or apparent.

The Board was informed that a comprehensive listing of all grant applications to be included in the **en bloc** vote was in the Special Actions package. Those grant applications, as well as those announced during the closed session, could be considered for funding by the Institute.

The NCAB **en bloc** motion to concur with IRG recommendations was unanimously approved. During the closed session, a total of 2,456 NCI applications were reviewed requesting direct cost support of $925,858,633 and 2 FDA applications requesting direct cost support of $928,376.

X. ADJOURNMENT—DR. ELIZABETH M. JAFFEE

Dr. Jaffee thanked all the Board members, as well as the visitors and observers, for attending.

There being no further business, the 12th virtual meeting of the NCAB was adjourned at 4:47 p.m. on Tuesday, 11 February 2020.

Date	Elizabeth M. Jaffee, M.D., Chair
Date	Paulette S. Gray, Ph.D., Executive Secretary