OXFORD

JNCI J Natl Cancer Inst (2021) 113(1): djaa061

doi: 10.1093/jnci/djaa061
First published online April 27, 2020
Article

The Exceptional Responders Initiative: Feasibility of a National Cancer Institute Pilot Study

Barbara A. Conley, MD,[1] Lou Staudt, MD, PhD,[2] Naoko Takebe, MD, PhD,[3] David A. Wheeler, PhD,[4] Linghua Wang, PhD,[5] Maria F. Cardenas, BS,[4] Viktoriya Korchina, MS,[4] Jean Claude Zenklusen, PhD,[2] Lisa M. McShane, PhD,[1] James V. Tricoli, PhD,[1] Paul M. Williams, PhD,[6] Irina Lubensky, MD,[1] Geraldine O'Sullivan-Coyne, MD,[3] Elise Kohn, MD,[1] Richard F. Little, MD,[1] Jeffrey White, MD,[1] Shakun Malik, MD,[1] Lyndsay N. Harris, MD,[1] Bhupinder Mann, MD,[1] Carol Weil, JD,[1] Roy Tarnuzzer, PhD,[2] Chris Karlovich, PhD,[6] Brian Rodgers, MD,[1] Lalitha Shankar, MD, PhD,[1] Paula M. Jacobs, PhD,[1] Tracy Nolan, BE,[7] Sean M. Berryman, MA,[7] Julie Gastier-Foster, PhD,[8] Jay Bowen, MS,[8] Kristen Leraas, MS,[8] Hui Shen, PhD,[9] Peter W. Laird, PhD,[9] Manel Esteller, MD, PhD,[10] Vincent Miller, MD,[11] Adrienne Johnson, MS,[11] Elijah F. Edmondson, DVM, PhD,[12] Thomas J. Giordano, MD,[13] Benjamin Kim, MS,[1] S. Percy Ivy, MD[1,*]

[1]Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA; [2]Center for Cancer Genomics, National Cancer Institute, Bethesda, MD, USA; [3]Developmental Therapeutics Clinic, National Cancer Institute, Bethesda, MD, USA; [4]Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, USA; [5]Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]Frederick National Laboratory for Cancer Research, Frederick, MD, USA; [7]Department of Biomedical Informatics, University of Arkansas for Medical Sciences, Little Rock, AR, USA; [8]Nationwide Children's Hospital, Columbus, OH, USA; Van Andel Research Institute, Grand Rapids, MI, USA; [9]Van Andel Research Institute, Grand Rapids, MI, USA; [10]Josep Carreras Leukaemia Research Institute, Badalona, Barcelona, Catalonia, Spain; [11]Foundation Medicine Inc, Cambridge, MA, USA; [12]Pathology and Histology Laboratory, Leidos Biomedical Research, Inc, Frederick National Laboratory for Cancer Research, Frederick, MD, USA and [13]Department of Pathology, University of Michigan, Ann Arbor, MI, USA

*Correspondence to: S. Percy Ivy, MD, National Cancer Institute, 9609 Medical Center Dr. Room 5W458, Bethesda, MD 20852, USA (e-mail: ivyp@ctep.nci.nih.gov).

Abstract

Background: Tumor molecular profiling from patients experiencing exceptional responses to systemic therapy may provide insights into cancer biology and improve treatment tailoring. This pilot study evaluates the feasibility of identifying exceptional responders retrospectively, obtaining pre-exceptional response treatment tumor tissues, and analyzing them with state-of-the-art molecular analysis tools to identify potential molecular explanations for responses. **Methods:** Exceptional response was defined as partial (PR) or complete (CR) response to a systemic treatment with population PR or CR rate less than 10% or an unusually long response (eg, duration >3 times published median). Cases proposed by patients' clinicians were reviewed by clinical and translational experts. Tumor and normal tissue (if possible) were profiled with whole exome sequencing and, if possible, targeted deep sequencing, RNA sequencing, methylation arrays, and immunohistochemistry. Potential germline mutations were tracked for relevance to disease. **Results:** Cases reflected a variety of tumors and standard and investigational treatments. Of 520 cases, 476 (91.5%) were accepted for further review, and 222 of 476 (46.6%) proposed cases met requirements as exceptional responders. Clinical data were obtained from 168 of 222 cases (75.7%). Tumor was provided from 130 of 168 cases (77.4%). Of 117 of the 130 (90.0%) cases with sufficient nucleic acids, 109 (93.2%) were successfully analyzed; 6 patients had potentially actionable germline mutations. **Conclusion:** Exceptional responses occur with standard and investigational treatment. Retrospective identification of exceptional responders, accessioning, and sequencing of pretreatment archived tissue is feasible. Data from molecular analyses of tumors, particularly when combining results from patients who received similar treatments, may elucidate molecular bases for exceptional responses.

Received: June 12, 2019; **Revised:** February 27, 2020; **Accepted:** April 20, 2020

Rare exceptional responses are recognized in clinical studies with or without molecular patient selection criteria (1–4). For example, in a phase II clinical trial of the mTOR inhibitor everolimus (without molecular selection criteria) for metastatic bladder cancer, whole exome sequencing (WES) of the tumor of a patient who sustained an exceptional durable complete response revealed loss of function mutations in *TSC1* and *NF2*, which were associated preclinically with mTORC1 pathway dependence, explaining this unique favorable response (1,2). In a phase I study of everolimus plus anti-angiogenesis agent pazopanib, sequencing of the tumor of a patient with metastatic urothelial cancer who sustained a prolonged complete response revealed 2 mutations in the mTOR pathway (3).

Based on these and other reports (4,5), the National Cancer Institute (NCI) Exceptional Responders Initiative pilot study opened in August 2014. The goal was to assess the feasibility and potential usefulness of sequencing DNA and RNA from clinical tumor specimens from patients who had had unusually profound or durable responses to systemic anticancer therapy (6).

Methods

Case Selection

Eligible cases were proposed by cancer clinicians, primarily from NCI-supported clinical trials sites (7,8).

Exceptional response (ER) eligibility criteria, developed by informal consensus after several meetings at NCI involving experts from across the United States, were defined as partial response (PR) greater than 6 months or complete response (CR) using RECIST 1.1 or other relevant criteria (9,10) expected to occur in fewer than 10% of patients who received the treatment. Responses were adjudicated by a team of expert clinicians for inclusion based on the CR or PR rate found in literature review of the same or similar regimens, including standard regimens and regimens of systemic therapy and radiation and/or surgery. Unusually long PRs or CRs were also considered exceptional (eg, more than 3 times longer than the regimen's published median response duration in a similar patient population and/or on expert opinion if there were no applicable publications), even if criteria of CR or PR greater than 6 months in at most 10% of patients were not met. Any systemic antineoplastic treatment, standard or investigational, with or without concurrent radiotherapy was eligible. Cases proposed without patient identifiers were reviewed by a committee comprising medical oncologists, radiologists, pathologists, and molecular scientists (Supplementary Table 1, available online). If provisionally accepted, the clinical site submitted additional clinical data (pathology and imaging reports, any molecular tests, and, if requested, radiographic images), which were reviewed centrally to confirm eligibility prior to requesting specimens.

Clinical sites submitted baseline imaging reports from prior to the treatment that resulted in the exceptional response, imaging reports associated with best response, and reports from either the progression scan or the latest scan if no progression had occurred. These follow-up scans served as the "subsequent scans" required (9,10), and the elapsed time from these assessments was used as response duration. We reviewed the reports and graded the responses by noting the size of the lesions at each time point by description in the report. For those patients treated with systemic and local modalities, response was assessed based on sites that were not subjected to the local modality. If size was not mentioned, and in most cases proffered as PRs, we requested the images themselves for central review. Nonmeasurable lesions were acceptable if they were considered by reviewers to be evidence of malignancy and could be assessed to have responded.

Submitted clinical imaging studies were placed in The Cancer Imaging Archive (11). Participating sites were reimbursed for submitting clinical and imaging data.

After study analyses are completed, all clinical and molecular data (including images) will be deposited in the NCI Genomic Data Commons (12) and made available to other investigators, except those data subject to confidentiality agreements from certain clinical trials (which can be obtained with appropriate permissions).

Human Subjects' Protection

Clinical sites obtained institutional review board (IRB) approval. The protocol (clinicaltrials.gov identifier NCT02243592) was approved by an NCI central IRB, which could be used as the responsible IRB by participating sites. Living patients signed a written consent form. If the patient had died or was lost to follow-up, we used the consent approach defined in Supplementary Table 2 (available online). Clinical data were submitted without patient identifiers.

Molecular results were not returned. However, if potential clinically significant likely germline alterations (eg, as described in the American College of Medical Genetics and Genomics guidelines) were detected in tumor by these research grade assays (13), the site clinician was contacted and could consider genetic counseling and clinical confirmatory testing.

Specimens

Tumor tissues were required from prior to the initiation of the treatment that produced the exceptional response. Submission of germline specimens was encouraged. Decalcified bone or bone marrow aspirate specimens were not accepted. Multiple specimens were encouraged, particularly matched primary tumor and metastases.

Pathology review at the treating site described percent tumor nuclei and percent necrosis. Formalin-fixed paraffin-embedded (FFPE) or frozen specimens were submitted to the central Biospecimen Core Resource at Nationwide Children's Hospital (Columbus, OH). Sites were reimbursed for provision of specimens.

Molecular Characterization

Successful WES or targeted sequencing was required. The two platforms complemented each other: the targeted panel sequences are deeper and thus more sensitive over a selected core cancer driver set; the exome sequencing is an unbiased broad look across the genome. Most clonal driver genes should be detected by both. Other molecular analyses were conducted if enough sample was available.

WES (performed at Baylor College of Medicine [BCM], Houston, TX) provided approximately 100X coverage. Standard algorithms were used to identify clonal heterozygous or homozygous mutations (14). RNA sequencing was performed at BCM and employed the Illumina Nextera Rapid Capture Exome v 1.2 protocol, which includes a total target length of 45 Mb of selected exonic content and is compatible with low-input (50 ng of total RNA) and degraded FFPE samples. The CIBERSORT (15) and

microenvironment cell populations–counter (16) immune deconvolution algorithms were applied to normalized expression data to estimate the relative cellular fraction and population abundance of tumor-infiltrating immune and stromal cell populations. Proliferation score was calculated using a list of proliferation-related signature genes.

Targeted sequencing (Foundation Medicine, Inc, Cambridge, MA) was accomplished with FoundationOne hybrid capture based next generation sequencing clinical cancer assay for solid tumors (gene list can be found online at https://assets.ctfassets.net/vhribv12lmne/4ZHUEfEiI8iOCk2Q6saGcU/11dd3b532e30c34f56cb8e9b4a896783/F1CDx_TechSpecs_10-06_digital.pdf) (17), which sequences the coding region of more than 300 cancer-related genes plus introns from 28 genes often rearranged or altered in cancer to a typical median coverage depth of 500X. The assay detects base substitutions, insertions and deletions (indels), copy number alterations, and rearrangements. Tumor mutation burden, microsatellite instability, and homologous recombination deficiency score were calculated.

DNA methylation status was determined by Van Andel Research Institute (Grand Rapids, MI) and the Josep Carreras Leukaemia Research Institute (Badalona, Barcelona, Catalonia, Spain) using bisulfite-converted DNA processed by the Infinium FFPE restoration process and then hybridized on an Infinium Methylation EPIC BeadChip array (18).

Immunohistochemistry staining and tumor infiltrating lymphocytes were performed by the Pathology and Histology Laboratory at Frederick National Laboratory for Cancer Research, NCI (Frederick, MD) by standard laboratory methods.

For each case, the goal was to assess and tabulate mutations, copy number alterations, gene translocations and transcript fusions, epigenetic alterations, aberrant transcriptional regulation, immune cell infiltration, summary measures including tumor mutation burden, microsatellite instability, aneuploidy, and signatures based on immune-related genes or pathways. Each molecular alteration was categorized by its involvement in known pathways relevant to cancer (eg, growth factor receptor, MAPKinase pathway, DNA damage response and repair pathway, PI3Kinase pathway, cell cycle) and according to potential therapeutic relevance (responsiveness or resistance to an investigational or approved drug, drug combination, or radiotherapy), using literature and available databases.

If results on tumor or germline tissue indicated a likely potentially actionable germline mutation, we communicated these results to the proposing clinician, with advice to seek a clinical assay if indicated for the patient's care.

Statistical Considerations

The overall study goal was to collect interpretable WES or FoundationOne results on approximately 100 ER cases and to explore the relationship between those results and the treatment(s) received. The first aim was to show that exceptional responders can be identified who also have relevant stored tumor from which enough DNA and RNA can be harvested to perform high-quality genomic analyses to detect and characterize the tumor's molecular changes. The second aim was to explore associations between identified tumor molecular alterations, immune features, and the putative mechanisms of action of the treatments associated with response, or with the biology of the cancer. For this paper, we focused on the first aim and assessed the feasibility of obtaining interpretable molecular results on approximately 100 exceptional responder cases. If 20 of the 100 cases yielding interpretable molecular results are judged to have at least one promising discovery, a 95% confidence for the promising discovery rate (among successfully performed assays) is 12.7% to 29.2%. Results pertinent to the second aim are the subject of another report in preparation.

Planned primary descriptive statistical analyses to assess feasibility were number of cases identified as potential ER; percentage of identified potential cases confirmed as ER; percentage of confirmed ER cases for whom adequate tissues with appropriate informed consent were acquired; and percentage of acquired cases with tissues for which at least the minimum molecular characterization was obtained.

All estimated percentages include exact 95% confidence intervals (CI) (19). For this feasibility assessment, no statistical adjustment is made for the fact that multiple confidence intervals are computed.

Table 1. Demographics of analyzable cases (updated March 13, 2019)

Case descriptions	Number of Cases
Total	117
Male	57
Female	60
Age at diagnosis, mean (range), y	59 (22–89)
On clinical trial (%)	31 (26.5)
Alive at time of case proposal	107
Consent approach as in Supplementary Table 2 (available online)	10
Tumor histology	
Colorectal	22
Esophagogastric adenocarcinoma	18
Lung	
Adenocarcinoma	8
Squamous carcinoma	1
Small cell carcinoma	1
Large cell neuroendocrine	1
Central nervous system	10
Breast	10
Ovary	9
Other gynecologic cancer	6
Melanoma	6
Renal	5
Urothelial cancer bladder	4
Pancreas	3
Other	13[a]

[a]2 each: squamous cancer of head and neck, gastrointestinal stromal tumor, adenocarcinoma unknown primary. 1 each: cholangiocarcinoma, small cell cancer of colon, squamous anal cancer, papillary thyroid, Merkel cell cancer, prostate cancer, soft tissue sarcoma.

Results

Patient Demographics

Demographics for 117 patients with analyzable tissue are shown in Table 1. Most ER cases (107 of 117, 91.4%) were living at the time of case proposal. Median age was 59 (range 22–89) years. Patients treated on a clinical trial represented 26.5% of cases (31 of 117).

Types of Exceptional Response

Type of response, tumor type, and treatment regimen for patients whose tumors had sequencing attempted are shown in

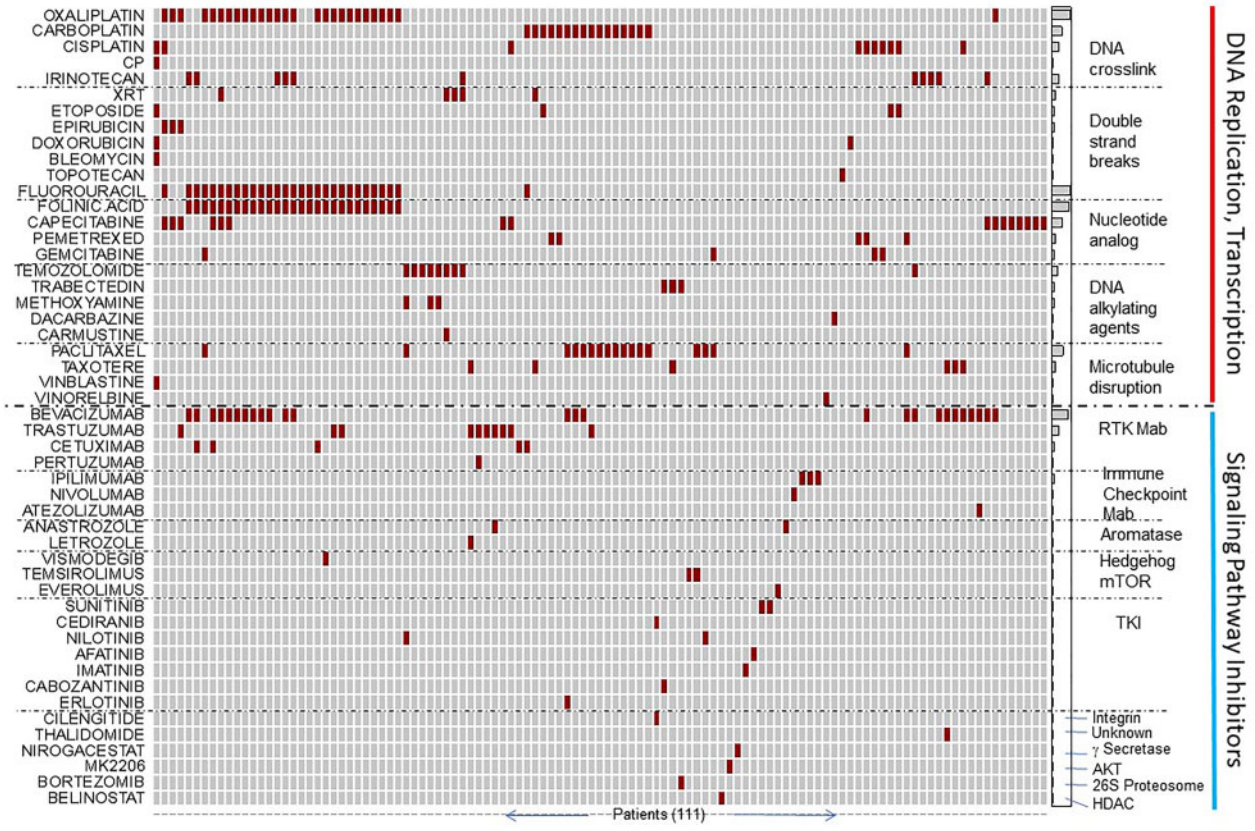

Figure 1. Antineoplastic agents used in treatments leading to exceptional response. Treatment agents are listed on the left and categorized by mechanism of action as indicated on the right. It is administered infused in a biodegradable, Gliadel, wafer layered onto the site from which the brain tumor was resected. Treatments involving standard combinations of drugs are evident from systematic correlation across multiple patients: FOLFOX, 5-FU, folinic acid, oxaliplatin; FOLFIRI, 5-FU, folinic acid, Irinotecan; FOLFIRINOX, 5-FU, folinic acid, Irinotecan, Oxaliplatin; EOX, Epirubicin, Oxiplatin, Capecitabine (Xeloda). Some agents could be classified in more than one category, for example, Carmustine alkylates N1 of G and N3 of C but also forms interstrand crosslinks. Note, methoxyamine binds to apurinic/apyrimidinic and blocks base excision repair leading to double-stranded breaks. It is classified with the alkylating agents because it is often given in combination with alkylating agents. The mechanism of action of Thalidomide is unknown. CP = cyclophosphamide.

ARTICLE

Supplementary Table 3 (available online) (20–109). Of the 117 cases, 37 (31.6%) cases were considered exceptional responses based only on whether CR or PR was expected to be less than 10%, 54 (46.2%) cases met criteria only for exceptionally long response, and 26 cases met criteria for both response and duration (22.2%).

Most (80 of 117, 68.4%) ER occurred with combination chemotherapy regimens. Figure 1 depicts the frequency with which an antineoplastic drug or combination was associated with an ER. Of the 117 patients, 34 (29.0%) were treated with one or more anti-angiogenesis agents, with or without additional chemotherapy: 29 patients with bevacizumab, 1 with cediranib, 3 with sunitinib, and 1 with cabozantinib. Six patients had ER after treatment with immune checkpoint inhibitors (nivolumab, atezolizumab, or ipilumumab). Examples of exceptional CRs to standard therapies include a man with metastatic clear cell kidney cancer (Supplementary Table 3, available online, case 94), who sustained a CR (expected CR rate <10%) of at least 74 months to sunitinib (Figure 2A). An exceptional 41-month CR (expected CR rate <10%) occurred in a woman with metastatic squamous lung cancer treated with paclitaxel and carboplatin (Supplementary Table 3, available online, case 46) (Figure 2B). A remarkably long 128-month PR to docetaxel and cisplatin (reported median response duration 24 months) occurred in a man with esophageal adenocarcinoma. The tumor recurred and responded for the second time to concurrent chemoradiation using the same drugs (Supplementary Table 3, available online, case 37). A woman with metastatic lung adenocarcinoma had an exceptional 61-month PR (Supplementary Table 3, available online, case 48) to cisplatin and pemetrexed (expected duration is 4.1 months). Several patients with brain tumors (Supplemental Table 3, available online, cases 67–76) treated after maximal resection were considered ER cases because their progression-free survival was at least 3 times longer than the median overall survival with these types of tumors (110).

Feasibility

Between August 2014 and July 2017, 520 cases were proposed, 476 (91.5%) were accepted for further review, and 222 of 476 (46.6%) proposed cases met eligibility requirements. Clinical data were obtained from 168 of 222 cases (75.7%). Tumor was provided from 130 of 168 cases (77.4%). Of 117 of 130 (90.0%) cases with sufficient nucleic acids, 109 of 117 (93.2%) were successfully analyzed (Figure 3, CONSORT diagram). Most ER patients (207 of 222, 93.2%, 95% CI = 89.2% to 96.2%) supplied written informed consent. The remainder (6.8%) was accepted based on criteria for those patients who had died (Supplementary Table 2, available online). Of 476 proposed

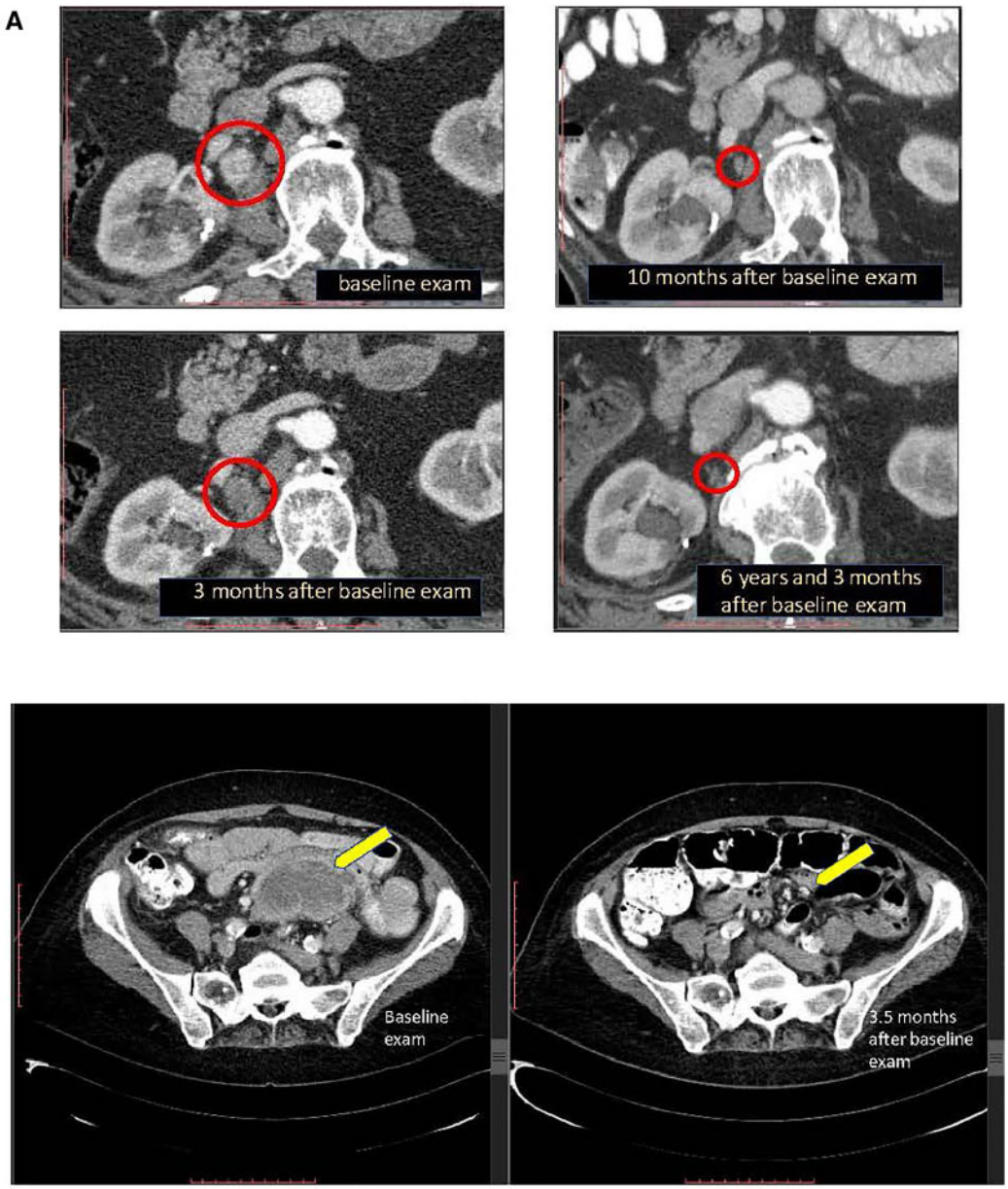

Figure 2. Computerized Axial Tomography (CT) images from 2 cases evaluating exceptional response to therapy. **A)** Case 94 (Supplementary Table 3, available online) with metastatic clear cell carcinoma of kidney, treated with sunitinib continuously beginning approximately 2 weeks after baseline imaging exam. Contrast enhanced CT scans of the abdomen, soft tissue windows; axial images at the level of the takeoff of the right renal artery. Baseline exam: 1.7 × 2.1 cm retroperitoneal mass and/or lymph node (mass highlighted in circle) posterior to the mid-right renal artery and immediately lateral to the right iliopsoas muscle. Three months later, the mass highlighted in circle is smaller, 1.3 × 2.0 cm and does not enhance. Ten months after baseline exam, the same mass is 0.6 × 1.0 cm. Six years and 3 months after baseline exam, the mass is 0.3 × 1.2 cm without evidence of additional metastatic disease (residual stable imaging changes considered CR). **B)** Case 46 (Supplementary Table 3, available online) with metastatic squamous cell lung cancer and biopsy proven metastasis to cecum treated with weekly paclitaxel and carboplatin for 10 months. Baseline imaging also showed metastases in lung, liver, kidney, and mesentery (arrow). Contrast-enhanced CT scans of the abdomen, soft tissue windows; large mid-upper pelvic mass with lower-density center. Baseline exam (image on left): 5.8 × 8.4 cm with lower density in the center of the mass (arrow). CT scan 3.5 months later (image on right): This partially necrotic mass was not seen. Repeat CT of chest, abdomen and pelvis more than 3 years after the 3.5-month scan demonstrated no evidence of disease.

cases, 184 (38.7%) were ineligible: 120 patients did not meet ER criteria for CR or PR rate or duration, 38 patients had no or inadequate tumor tissues, 12 patients had no measurable disease (includes cases treated with adjuvant therapy), 12 patients had indolent disease or no response documentation, and 2 patients had no systemic treatment. In 70 of 476 (14.7%) cases, sites did not respond to queries for clarifying information.

Molecular Characterization Success Rate

Of the 117 patients with adequate nucleic acids for shipment to analysis sites, 13 cases had tissue from both primary and metastatic diseases, 1 had tissues from both primary and recurrence, and 30 had matched germline specimens. Six failed to generate high-quality sequencing libraries. A matched normal sample was sent for 27 of 111 (24.3%) tumors successfully sequenced.

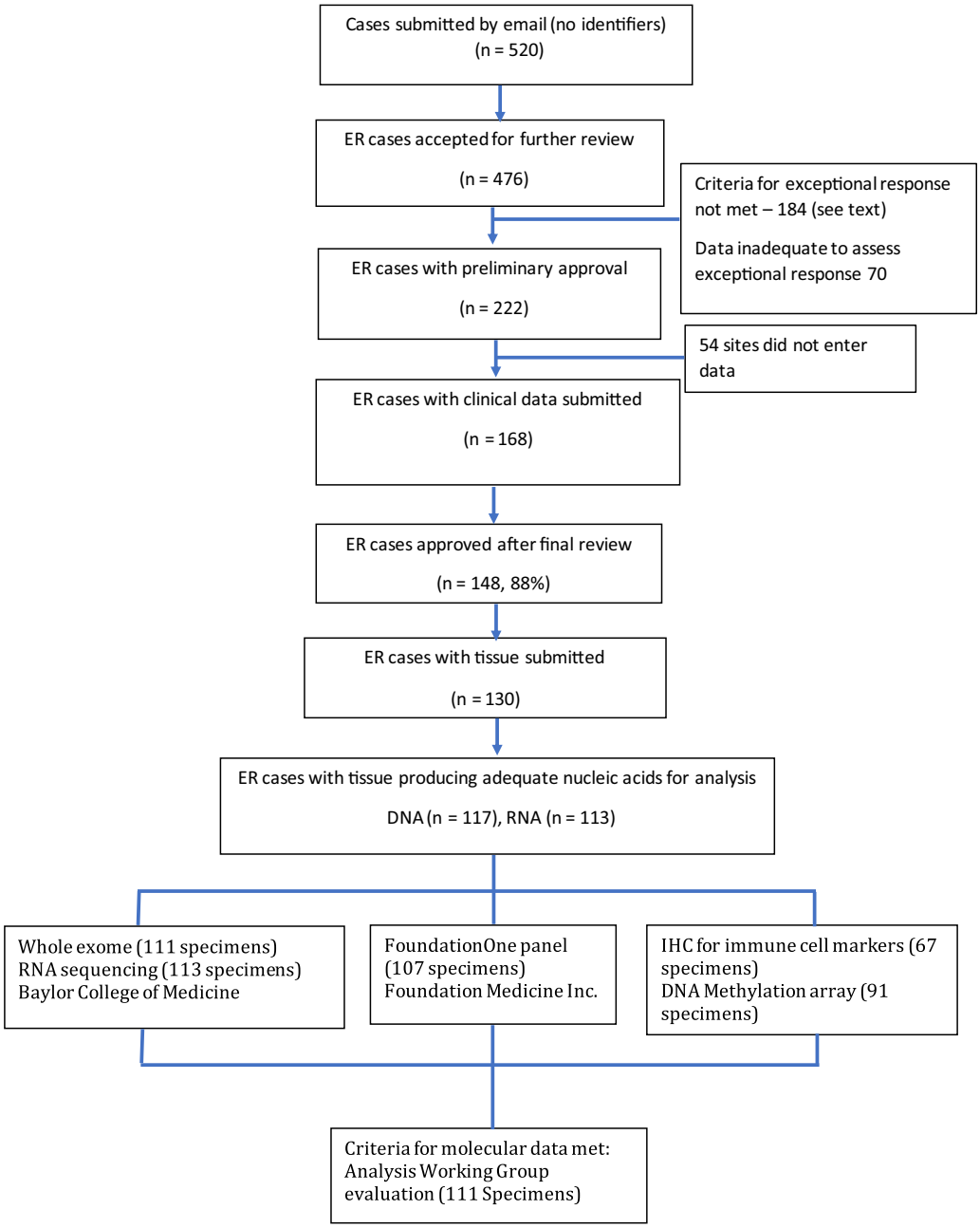

Figure 3. CONSORT diagram for the exceptional responders pilot study. ER = exceptional response; IHC = immunohistochemistry.

Table 2 and Supplementary Figure 1 (available online) show the success rates for the various molecular analyses platforms.

Imaging Results Concordance

In 34 of 40 (85%, 95% CI = 70.2% to 94.3%) cases reviewed, a definite assessment of stable disease (1 case), PR (17 cases), or CR (16 cases) was made. One case was discordant between local imaging assessment and study review (concordance rate 33 of 34 [97.1%, 95% CI = 84.7% to 99.9%]).

Incidental Findings

Potential clinically relevant germline (American College of Medical Genetics and Genomics guidelines) mutations were found in 6 tumors. Pathogenic *BRCA1* or *BRCA2* mutations were found in 2 breast cancer patients, 1 non-small cell lung cancer patient, and 1 rectal cancer patient. One of the breast cancer patients had a known pathogenic *BRCA1* germline mutation. Another patient with breast cancer had a likely germline mutation in *CHEK2*. One patient with a poorly differentiated lung cancer and history of breast cancer had a *PALB2* mutation.

Discussion

This study met its main feasibility goal to identify at least 100 analyzable ER cases in less than 3 years. Proposed and accepted ER cases represent a variety of malignancies and treatments (eg, standard cytotoxic chemotherapy, including multi-agent chemotherapy) or chemotherapy and radiation combinations,

Table 2. Numbers of specimens sequenced and success rate for each platform

Platform	No. of samples tested	No. of samples passed (%)	Minimum tumor purity, %
WES	119	111 (93.3)	5
Targeted NGS	107	97 (90.6)	10[a]
mRNA sequencing	113	99 (87.6)	—
Methylation array	91	77 (84.6)	—
IHC/TIL	67	67 (100)	—

[a]Computational purity assessment. IHC = immunohistochemistry; Targeted NGS = FoundationOne targeted next-generation sequencing; TIL = tumor-infiltrating lymphocytes; WES = whole exome sequencing

as well as some who had single agent or investigational treatment. Only 6 patients were treated with immunotherapy, perhaps reflecting that accrual ended in 2017, when such treatment had been approved for relatively few tumor types. Several cases with exceptionally durable PRs (eg, more than 100 months) may represent actual CRs or tumors with indolent clinical course. Prolonged responses may suggest an immune system role (111–113). As analysis proceeds, grouping cases treated with drugs having similar mechanisms of action may increase confidence in observed associations between molecular alterations and response to drugs within a class.

Study limitations include that we did not molecularly characterize tumors from patients who responded poorly to the same treatment that an ER patient received. We chose not to do so because the pilot study's goal was to evaluate the feasibility of acquiring tumor tissues and identifying relevant molecular features as a first step. It was unknown which types of tumors or treatments would be represented in the cases submitted. For a true comparison, clinical features of nonresponders to the same regimen, such as primary tumor, performance status, additional medications, and line of treatment, would need to be matched to those in exceptional responders. This level of effort could not be justified if the pilot study was not feasible. An additional limitation is that we may not be able to distinguish molecular alterations that are prognostic for indolent course from those that truly predict treatment-related prolonged response duration. We also included patients who had exceptional responses to multiagent and multimodality treatment, which may confound definition of molecular determinants of response. Acceptance of such cases relied on results from trials of similar or identical treatments in published clinical trials for the most part and, for PRs, evaluation of lesions on imaging that had not been subjected to radiation or surgery.

Although feasible, only about 20%–25% of proposed cases were able to be analyzed. For improved efficiency, future studies could utilize completed clinical trials in which tumor and ideally normal tissue were collected prior to treatment and in which clinical variables are more uniform (114) and could analyze both responders and nonresponders. Clinical trials randomizing patients to different treatments would inform about molecular alterations correlating with a more indolent or more aggressive disease course (prognostic alterations) as well as alterations that predict a very good or very poor response (predictive alterations). A commitment to sharing the data will accelerate the ability to discern predictive molecular features that can guide treatment, as suggested by the recent overview manuscript by Saner et al. (115). For example, results from current clinical studies of exceptional responses in ovarian cancer (NCT02321735), glioblastoma multiforme (NCT03770468), or tumors that either had exceptionally good or exceptionally poor responses to treatment (NCT03740503) may increase the chance of finding predictive alterations.

Collaboration between several exceptional responder initiatives would allow development of solid hypothesis-generating data and validation of results from individual studies, as well as exploration of different types of response (eg, exceptionally good, recurrent responses, exceptionally poor) (115). A potential registry would require common infrastructure, established preanalytic and accessioning procedures, harmonized agreements, and standard operating procedures for storage of sequencing data prior to characterization and analysis. Consideration should be given to 1) harmonization of eligibility criteria and definitions of exceptional response, 2) reasonable time frame, 3) identification of sustainable funding, and 4) dedicated clinicians, imagers, molecular biologists, computational biologists, and molecular pathologists to review and confirm all cases.

The value of the NCI Exceptional Responder Initiative lies in the potential to yield clinically important insights into molecular features associated with favorable response or outcome from specific treatments and awaits the completion of the ongoing analysis of each case and potential grouping of similar treatments or similar tumors. The hypotheses generated by this study will require testing in preclinical studies or in larger patient cohorts with the same and different histologies and treatments to validate associations between molecular features and response. Importantly, all data will be made available to researchers for generation of new hypotheses or to validate other findings.

Funding

This project has been funded in whole or in part with federal funds from the NCI, National Institutes of Health, under grants and contracts. BCM was supported by Grant No. 5U24CA143843 and then LEIDOS Subcontract No. HHSN261200800001E/17X184TO1, Nationwide Children's Hospital on LEIDOS Subcontract No. HHSN261200800001E/14X242TO1 and then NCI contract No. HHSN2612017000051/TO1, IMS on NCI Contract No. HHSN26120150002B/TO10, and University of Chicago (Genomic Data Center) on NCI contract HHSN261200800001E/17X147TO2.

Notes

Role of the funders: Personnel employed by NCI, NIH (funding agency) participated in the design and implementation of the study, in collaboration with personnel from the funded institutions.

Conflicts of interest: S. Percy Ivy, MD—None; Barbara A. Conley, MD—None; Lou Staudt, MD, PhD—None; Naoko Takebe, MD, PhD—None; David A. Wheeler, PhD—None; Linghua Wang, PhD—None; Maria F. Cardenas, BS—None; Viktoriya Korchina, MS—None; Jean Claude Zenklusen, PhD—None; Lisa M. McShane, PhD—None; James V. Tricoli, PhD—None; Paul M. Williams, PhD—None; Irina Lubensky, MD—None; Geraldine O'Sullivan-Coyne, MD—None; Elise Kohn, MD—None; Richard Little, MD—None; Jeffrey White, MD—None; Shakun Malik, MD—None; Lyndsay N. Harris, MD—None; Bhupinder Mann, MD—None; Carol Weil, JD—None; Roy Tarnuzzer, PhD—None; Chris Karlovich, PhD—Clovis Oncology; Brian Rodgers, MD—None; Lalitha Shankar, MD, PhD—None; Paula M. Jacobs, PhD—

None; Tracy Nolan, BE—None; Sean M. Berryman, MA—None; Julie Gastier-Foster, PhD—Bristol-Myers Squibb; Incyte Corporation; Jay Bowen, MS—None; Kristen Leraas, MS—None; Hui Shen, PhD—AnchorDx; Progenity; Peter W. Laird, PhD—AnchorDx; Progenity; Manel Esteller, MD, PhD—Ferrer Internacional; Quimatryx; Vincent Miller, MD—Foundation Medicine, Inc; Revolution Medicines; Memorial Sloan Kettering, Inc; Adrienne Johnson, MS—Foundation Medicine, Inc; Elijah F. Edmondson, DVM, PhD—None; Thomas J. Giordano, MD—None; Benjamin Kim, MS—None.

Author contributions: BAC: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing. LS: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Supervision; Validation; Writing—review & editing. NT: Data curation; Formal analysis; Investigation; Validation; Writing—review & editing. DAW: Data curation; Formal analysis; Investigation; Methodology; Software; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing. LW: Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing—review & editing. MFC: Data curation; Formal analysis; Investigation; Validation; Visualization. VK: Data curation; Formal analysis; Investigation; Validation. JCZ: Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Validation; Visualization; Writing—review & editing. LMM: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Supervision; Validation; Visualization; Writing—review & editing. JVT: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Writing—review & editing. PMW: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing—review & editing. IL: Data curation; Formal analysis; Investigation; Methodology; Writing—review & editing. **GOS-C:** Data curation; Formal analysis; Investigation; Methodology; Writing—review & editing. EK: Data curation; Formal analysis; Investigation; Methodology; Writing—review & editing. RFL: Data curation; Formal analysis; Investigation; Methodology; Writing—review & editing. JW: Data curation; Formal analysis; Investigation; Methodology; Writing—review & editing. SM: Data curation; Formal analysis; Investigation; Methodology; Writing—review & editing. LNH: Data curation; Formal analysis; Investigation; Methodology; Writing—review & editing. BM: Data curation; Formal analysis; Investigation; Methodology; Writing—review & editing. CW: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing—review & editing. RT: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Writing—review & editing. CK: Data curation; Formal analysis; Writing—review & editing. BR: Data curation; Formal analysis; Investigation; Methodology; Writing—review & editing. LS: Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Writing—review & editing. PMJ: Funding acquisition; Investigation; Methodology; Resources; Supervision; Writing—review & editing. TN: Data curation; Investigation; Methodology; Resources; Visualization; Writing—review & editing. SMB: Data curation; Investigation; Methodology; Resources; Visualization; Writing—review & editing. **JG-F:** Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing—review & editing. JB: Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing—review & editing. KL: Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing—review & editing. HS: Data curation; Formal analysis; Investigation; Methodology; Validation; Writing—review & editing. PWL: Data curation; Formal analysis; Investigation; Methodology; Validation; Writing—review & editing. ME: Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing—review & editing. VM: Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Resources; Supervision; Validation; Writing—review & editing. AJ: Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing—review & editing. EFE: Data curation; Formal analysis; Investigation; Methodology; Writing—review & editing. TJG: Investigation; Methodology; Resources. BK: Data curation; Methodology; Project administration; Resources; Validation; Writing—review & editing. SPI: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administrations; Resources; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing.

Acknowledgments: We would like to acknowledge the contributions of the following: Paul Fishkin, MD; Robin K. Kelley, MD; Dr Terrence Cescon; Dr James L. Wade III; Karen Hoelzer, MD; Mark A. Meadors, DO; William E. Luginbuhl, MD; Christopher B. Sanders, MSEd; Bryan A. Faller, MD; Timothy Wassenaar, MD; Jay W. Carlson, DO; Jose E. Najera, MD; Mohamed Tejani, MD; H. Ian Robins, MD, PhD; Anthony Elias; Benjamin Musher, MsD; Anthony F. Shields, MD, PhD; Philip J. Stella, MD; Tareq Al-Baghdadi, MD; Erik Carson, MD; Kathleen Beekman, MD; Niklas Mackler, MD; Dr Charles Landen; Melody Cobleigh; Dr Robert Bloom; Robin K. Kelley, MD; Preston Steen, MD; Aine Clements, MD; Grant W. Harrer, MD, FACP, CPI; Michele Britto, RN, MS; Gustavo Rodriguez, MD; Ramya Varadarajan, MD; Laura Tenner, MD; Ignacio Garrido-Laguna, MD, PhD; Dr Preston Steen; Ignacio Garrido-Laguna, MD, PhD; Abdul-Hai Mansoor, MD; Kathleen Yost, MD; Erin Souhan; Suhela Pandit; Kathleen Paul; Lucille Patrichuk; Kathi Celli; Michael Montello; Sherry Ansher, PhD; Sara Coppens; and Erik Zmuda.

Prior presentation: This work was presented in part at the 2015 annual meeting of the American Association for Cancer Research.

References

1. Milowsky MI, Iyer G, Regazzi AM, et al. Phase II study of everolimus in metastatic urothelial cancer. *BJU Int*. 2013;112(4):462–470.
2. Iyer G, Hanrahan AJ, Milowsky MI, et al. Genome sequencing identifies a basis for everolimus sensitivity. *Science*. 2012;338(6104):221–223.
3. Wagle N, Grabiner BC, Van Allen EM, et al. Activating mTOR mutations in a patient with an extraordinary response on a phase I trial of everolimus and pazopanib. *Cancer Discov*. 2014;4(5):546–553.
4. Nishikawa G, Luo J, Prasad V. A comprehensive review of exceptional responders to anticancer drugs in the biomedical literature. *Eur J Cancer*. 2018; 101:143–151.
5. Hoppenot C, Eckert MA, Tienda SM, Lengyel E. Who are the long-term survivors of high grade serous ovarian cancer? *Gynecol Oncol*. 2018;148(1):204–212.
6. Takebe N, McShane LM, Conley B. Exceptional responders: discovering predictive biomarkers. *Nat Rev Clin Oncol*. 2015;12(3):132–134.
7. National Academies Press. *Implementing a National Cancer Clinical Trials System for the 21st Century*. Second Workshop Summary. Washington, DC: Institute of Medicine, National Academies Press; 2013.
8. Wade JL 3rd, Petrelli NJ, McCaskill-Stevens W. Cooperative group trials in the community setting. *Semin Oncol*. 2015;42(5):686–692.

ARTICLE

9. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009; 45(2):228–247.
10. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol*. 2010;28(11):1963–1972.
11. Clark K, Vendt B, Smith K, et al. The cancer imaging archive: maintaining and operating a public information repository. *J Digit Imaging*. 2013;26(6):1045–1057.
12. Grossman RL, Heath AP, Ferretti V, et al. Toward a shared vision of cancer genomic data. *N Engl J Med*. 2016;375(12):1109–1112.
13. Kalia S, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v 2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med*. 2017;19(2):249–255.
14. Carter SL, Cibulskis K, Helman E, et al. Absolute quantification of somatic DNA alterations in human cancer. *Nat Biotechnol*. 2012;30(5):413–421.
15. Newman AM, Liu CL, Green MR, et al. Robust enumeration of cell subsets from tissue expression profiles. *Nat Methods*. 2015;12(5):453–457.
16. Becht E, Giraldo NA, Lacroix L, et al. Estimating the population abundance of tissue-infiltrating immune and stromal cell populations using gene expression. *Genome Biol*. 2016;17(1):218–238.
17. Frampton GM, Fichtenholtz A, Otto GA, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. *Nat Biotechnol*. 2013;31(11):1023–1031.
18. Moran S, Arribas C, Esteller M. Validation of a DNA methylation microarray for 850,000 CpG sites of the human genome enriched in enhancer sequences. *Epigenomics*. 2016;8(3):389–399.
19. Korn EL, Graubard BI. *Analysis of Health Surveys*. Chapter 3: Sample Weights and Imputation. New York: Wiley; 1999:64–65.
20. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350(23):2335–2342.
21. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group study E3200*J*. *J Clin Oncol*. 2007;25(12):1539–1544.
22. Souglakos J, Ziras N, Kakolyris S, et al. Randomised phase-II trial of CAPIRI (capecitabine, irinotecan) plus bevacizumab vs FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) plus bevacizumab as first-line treatment of patients with unresectable/metastatic colorectal cancer (mCRC). *Br J Cancer*. 2012; 106(3):453–459.
23. Heinemann V, Fischer von Weikersthal L, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2014;15(10):1065–1075.
24. Ducreux M, Bennouna J, Hebbar M, et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX-6) as first-line treatment for metastatic colorectal cancer. *Int J Cancer*. 2011;128(3): 682–690.
25. Hurwitz H, Mitchell EP, Cartwright T, et al. A randomized, phase III trial of standard triweekly compared with dose-dense biweekly capecitabine plus oxaliplatin plus bevacizumab as first-line treatment for metastatic colorectal cancer: XELOX-A-DVS (dense versus standard). *Oncologist*. 2012;17(7): 937–946.
26. Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol*. 2008;26(12):2013–2019.
27. Rougier P, Lepere C. Second-line treatment of patients with metastatic colorectal cancer. *Semin Oncol*. 2005;32(9):S48–S54.
28. Tabernero J, Van Cutsem E, Díaz-Rubio E, et al. Phase II trial of cetuximab in combination with fluorouracil, leucovorin, and oxaliplatin in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol*. 2007;25(33):5225–5232.
29. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*. 2000;18(16):2938–2947.
30. Falcone A, Ricci S, Brunetti I, et al. Phase III Trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol*. 2007;25(13):1670–1676.
31. van Hazel GA, Heinemann V, Sharma NK, et al. SIRFLOX: randomized phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. *J Clin Oncol*. 2016; 34(15):1723–1731.
32. Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol*. 2001;19(21): 4097–4106.
33. Martens MH, Maas M, Heijnen LA, et al. Long-term outcome of an organ preservation program after neoadjuvant treatment for rectal cancer. *J Natl Cancer Inst*. 2016;108(12):djw171.
34. Lièvre A, Samalin E, Mitry E, et al. Bevacizumab plus FOLFIRI or FOLFOX in chemotherapy-refractory patients with metastatic colorectal cancer: a retrospective study. *BMC Cancer*. 2009;9(1):347–354.
35. Ramanathan RK, McDonough SL, Kennecke HF, et al. Phase 2 study of MK-2206, an allosteric inhibitor of AKT, as second-line therapy for advanced gastric and gastroesophageal junction cancer: a SWOG Cooperative Group trial (S1005). *Cancer*. 2015;121(13):2193–2197.
36. Prithviraj GK, Baksh K, Fulp W, et al. Carboplatin and paclitaxel as first-line treatment of unresectable or metastatic esophageal or gastric cancer. *Dis Esophagus*. 2015;28(8):782–787.
37. Sumpter K, Harper-Wynne C, Cunningham D, et al. Report of two protocol planned interim analyses in a randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer receiving ECF. *Br J Cancer*. 2005;92(11):1976–1983.
38. Al-Batran S-E, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol*. 2008;26(9):1435–1442.
39. Bang Y-J, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010;376(9742): 687–697.
40. Ajani J. Review of capecitabine as oral treatment of gastric, gastroesophageal or esophageal cancer. *Cancer*. 2006;107(2):221–231.
41. Haller B, Schuster T, Pauligk C, et al. Impact of pathologic complete response on disease-free survival in patients with esophagogastric adenocarcinoma receiving preoperative docetaxel-based chemotherapy. *Ann Oncol*. 2013; 24(8):2068–2073.
42. Kurishima K, Watanabe H, Ishikawa H, Satoh H, Hizawa N. A retrospective study of docetaxel and bevacizumab as a second- or later-line chemotherapy for non-small cell lung cancer. *Mol Clin Oncol*. 2017;7(1):131–134.
43. Zinner RG, Obasaju CK, Spigel DR, et al. PRONOUNCE: randomized, open-label, phase III study of first-line pemetrexed + carboplatin followed by maintenance pemetrexed versus paclitaxel + carboplatin + bevacizumab followed by maintenance bevacizumab in patients with advanced nonsquamous non-small-cell lung cancer. *J Thorac Oncol*. 2015;10(1):134–142.
44. Sequist LV, Yang JC-H, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013;31(27):3327–3334.
45. Pietanza CM, Hellmann MD, Fiore JJ, et al. Phase II study of a non-platinum-containing doublet of paclitaxel and pemetrexed with bevacizumab (PPB) as initial therapy for patients with advanced lung adenocarcinomas. *J Thorac Oncol*. 2016;11(6):890–899.
46. Gatzemeier U, Pluzanska A, Szczesna A, et al. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. *J Clin Oncol*. 2007; 25(12):1545–1552.
47. Govindan R, Szczesna A, Ahn M-J, et al. Phase III trial of ipilimumab combined with paclitaxel and carboplatin in advanced squamous non-small-cell lung cancer. *J Clin Oncol*. 2017;35(30):3449–3457.
48. Lo Russo G, Pusceddu S, Proto C, et al. Treatment of lung large cell neuroendocrine carcinoma. *Tumor Biol*. 2016;37(6):7047–7057.
49. Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol*. 2012;13(3): 247–255.
50. Patel JD, Socinski MA, Garon EB, et al. PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2013; 31(34):4349–4357.
51. Barlesi F, Scherpereel A, Gorbunova V, et al. Maintenance bevacizumab–pemetrexed after first-line cisplatin–pemetrexed–bevacizumab for advanced nonsquamous non-small-cell lung cancer: updated survival analysis of the AVAPERL (MO22089) randomized phase III trial. *Ann Oncol*. 2014; 25(5):1044–1052.
52. Lara PN Jr, Natale R, Crowley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. *J Clin Oncol*. 2009;27(15):2530–2535.
53. Monk BJ, Sill MW, Hanjani P, et al. Docetaxel plus trabectedin appears active in recurrent or persistent ovarian and primary peritoneal cancer after up to three prior regimens: a phase II study of the Gynecologic Oncology Group. *Gyn Oncol*. 2011;120(3):459–463.
54. Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2018;379(26): 2495–2505.

55. Orr B, Edwards RP. Diagnosis and treatment of ovarian cancer. *Hematol Oncol Clin North Am*. 2018;32(6):943–964.
56. Aghajanian C, Blessing JA, Darcy KM, et al. A phase II evaluation of bortezomib in the treatment of recurrent platinum-sensitive ovarian or primary peritoneal cancer: a Gynecologic Oncology Group study. *Gyn Oncol*. 2009; 115(2):215–220.
57. Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2007;25(33): 5165–5171.
58. Pautier P, Ribrag V, Duvillard P, et al. Results of a prospective dose-intensive regimen in 27 patients with small cell carcinoma of the ovary of the hypercalcemic type. *Ann Oncol*. 2007;18(12):1985–1989.
59. Hoskins PJ, Swenerton KD, Pike JA, et al. Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: a phase II study. *J Clin Oncol*. 2001;19(20):4048–4053.
60. Mahdi H, Rizzo A, Rose PG. Outcome of recurrent uterine papillary serous carcinoma treated with platinum-based chemotherapy. *Int J Gynecol Cancer*. 2015;25(3):467–473.
61. Rose PG, Ali S, Moslemi-Kebria M, Simpkins F. Paclitaxel, carboplatin, and bevacizumab in advanced and recurrent endometrial carcinoma. *Int J Gynecol Cancer*. 2017;27(3):452–458.
62. Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel paclitaxeli.nlm.nih.gov/pubmed/28187088cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017;18(6):779–791.
63. Hirte H, Kennedy EB, Elit L, Fung M. Systemic therapy for recurrent, persistent, or metastatic cervical cancer: a clinical practice guideline. *Curr Oncol*. 2015;22(3):211–219.
64. Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. *Gynecol Oncol*. 2008;109(3): 329–334.
65. Vredenburgh JJ, Desjardins A, Reardon DA, Friedman HS. Experience with irinotecan for the treatment of malignant glioma. *Neuro-Oncology*. 2009; 11(1):80–91.
66. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol*. 2009;27(28): 4733–4740.
67. Wen PY, Drappatz J, de Groot J, et al. Phase II study of cabozantinib in patients with progressive glioblastoma: subset analysis of patients naive to antiangiogenic therapy. *Neuro-Oncology*. 2018;20(2):249–258.
68. Batchelor TT, Mulholland P, Neyns B, et al. Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma. *J Clin Oncol*. 2013;31(26):3212–3218.
69. Gerstner ER, Ye X, Duda DG, et al. A phase I study of cediranib in combination with cilengitide in patients with recurrent glioblastoma. *Neuro Oncol*. 2015;17(10):1386–1392.
70. Rock K, McArdle O, Forde P, et al. A clinical review of treatment outcomes in glioblastoma multiforme—ultivalidation in a non-trial population of the results of a randomised phase III clinical trial: has a more radical approach improved survival? *Br J Radiol*. 2012;85(1017):e729–e733.
71. Gilbert MR, Pugh SL, Aldape K, et al. NRG oncology RTOG 0625: a randomized phase II trial of bevacizumab with either irinotecan or dose-dense temozolomide in recurrent glioblastoma. *J Neurooncol*. 2017;131(1):193–199.
72. Lambertini M, Ferreira AR, Di Meglio A, et al. Patterns of care and clinical outcomes of HER2-positive metastatic breast cancer patients with newly diagnosed stage IV or recurrent disease undergoing first-line trastuzumab-based therapy: a multicenter retrospective cohort study. *Clin Breast Cancer*. 2017;17(8):601–610.
73. Swain SM, Kim S-B, Cortés J, et al. Overall survival benefit with pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer in CLEOPATRA, a randomised phase 3 study. *Lancet Oncol*. 2013;14(6):461–471.
74. Rimawi M, Ferrero J-M, de la Haba-Rodriguez J, et al. First-line trastuzumab plus an aromatase inhibitor, with or without pertuzumab, in human epidermal growth factor receptor 2receptor 2b, in human epidermal growth factortatic or locally advanced breast cancer (PERTAIN): a randomized, open-label phase II trial. *J Clin Oncol*. 2018;36(28):2826–2835.
75. Aapro M, Finek J. Oral vinorelbine in metastatic breast cancer: a review of current clinical trial results. *Cancer Treat Rev*. 2012;38(2):120–126.
76. Vogel CL, Cobleigh MA, Tripathy D, et al. First-Line Herceptin® monotherapy in metastatic breast cancer. *Oncology*. 2001;61(2):37–42.
77. Robertson JFR, Lindemann JPO, Llombart-Cussac A, et al. Fulvestrant 50 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized First study. *Breast Cancer Res Treat*. 2012;136(2):503–511.
78. Dickler MN, Barry WT, Cirrincione CT, et al. Phase III Trial Evaluating Letrozole As First-Line Endocrine Therapy With or Without Bevacizumab for the Treatment of Postmenopausal Women With Hormone Receptor–Positive Advanced-Stage Breast Cancer: CALGB 40503 (Alliance). *J Clin Oncol*. 2016;34(22):2602–2609.
79. Perez DG, Suman VJ, Fitch TR, et al. Phase II trial of carboplatin, weekly paclitaxel and biweekly bevacizumab in patients with unresectable stage IV melanoma: a North Central Cancer Treatment Group (NCCTG) study, N047. *Cancer*. 2009;115(1):119–127.
80. McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAFV600E and BRAFV600K mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. *Lancet Oncol*. 2014;15(3):323–332.
81. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711–723.
82. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*. 2007;356(2):115–124.
83. McDermott DF, Huseni MA, Atkins MB, et al. Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. *Nat Med*. 2018;24(6): 749–757.
84. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med*. 2007;356(22): 2271–2281.
85. Motzer RJ, Barrios CH, Kim TM, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2014;32(25):2765–2772.
86. Agarwal N, McPherson JP, Bailey H, et al. A phase I clinical trial of the effect of belinostat on the pharmacokinetics and pharmacodynamics of warfarin. *Cancer Chemother Pharmacol*. 2016;77(2):299–308.
87. Hussain M, Daignault S, Agarwal N, et al. A randomized phase 2 trial of gemcitabine/cisplatin with or without cetuximab in patients with advanced urothelial carcinoma. *Cancer*. 2014;120(17):2684–2693.
88. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2017;18(3):312–322.
89. Lynch SP, Shen Y, Kamat A, et al. Neoadjuvant chemotherapy in small cell urothelial cancer improves pathologic downstaging and long-term outcomes: results from a retrospective study at the MD Anderson Cancer Center. *Eur Urol*. 2013;64(2):1–16.
90. Amin MB. Histological variants of urothelial carcinoma: diagnostic, therapeutic and prognostic implications. *Mod Pathol*. 2009;22(S2):S96–S118.
91. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817–1825.
92. Yoo C, Hwang JY, Kim J-E, et al. A randomised phase II study of modified FOLFIRI.3 vs modified FOLFOX as second-line therapy in patients with gemcitabine-refractory advanced pancreatic cancer. *Br J Cancer*. 2009; 101(10):1658–1663.
93. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet*. 2017;389(10073):1011–1024.
94. Schinzari G, Rossi E, Mambella G, et al. First-line treatment of advanced biliary ducts carcinoma: a randomized phase II study evaluating 5-FU/LV plus oxaliplatin (Folfox 4) versus 5-FU/LV (de Gramont Regimen). *Anticancer Res*. 2017;37(9):5193–5197.
95. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010;362(14):1273–1281.
96. Valle JW, Wasan H, Johnson P, et al. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study: the UK ABC-01 Study. *Br J Cancer*. 2009;101(4):621–627.
97. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non- randomised, open-label phase 2 trial. *Lancet Oncol*. 2018;19(7): 940–952.
98. Moertel CG, Kvols LK, O'Connell MJ, Rubin J. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer*. 1991; 68(2):227–232.
99. Mitry E, Baudin E, Ducreux M, et al. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. *Br J Cancer*. 1999;81(8): 1351–1355.
100. Sclafani R, Morano F, Cunningham D, et al. Platinum-fluoropyrimidine and paclitaxel-based chemotherapy in the treatment of advanced anal cancer patients. *Oncologist*. 2017;22(4):402–408.
101. Goodman VL, Rock EP, Dagher R, et al. Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. *Clin Cancer Res*. 2007;13(5): 1367–1373.
102. Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *J Clin Oncol*. 2008;26(4):620–625.
103. Messersmith WA, Shapiro GI, Cleary JM, et al. A phase I, dose-finding study in patients with advanced solid malignancies of the oral g-secretase inhibitor PF-03084014. *Clin Cancer Res*. 2015;21(1):60–67.

104. Cowey CL, Mahnke L, Espirito J, Helwig C, Oksen D, Bharmal M. Real-world treatment outcomes in patients with metastatic Merkel cell carcinoma treated with chemotherapy in the USA. *Future Oncol*. 2017;13(19):1699–1710.
105. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med*. 2008;359(11):1116–1127.
106. Caponigro F, Longo F, Perri F, Ionna F. Docetaxel in the management of head and neck cancer. *Anticancer Drugs*. 2009;20(8):639–645.
107. Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. *Lancet*. 2012; 379(9824):1428–1435.
108. Nakabayashi M, Sartor O, Jacobus S, et al. Response to docetaxel/carboplatin-based chemotherapy as first- and second-line therapy in patients with metastatic hormone-refractory prostate cancer. *BJU Int*. 2008;101(3):308–312.
109. Young RJ, Natukunda A, Litière S, Woll PJ, Wardelmann E, van der Graaf WTA. First-line anthracycline-based chemotherapy for angiosarcoma and other soft tissue sarcoma subtypes: pooled analysis of eleven European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group trials. *Eur J Cancer*. 2014;50(18):3178–3186.
110. Wipfler K, Cornish AS, Guda C. Comparative molecular characterization of typical and exceptional responders in glioblastoma. *Oncotarget*. 2018;9(47): 28421–28433.
111. Woo S-R, Corrales L, Gajewski TF. Innate immune recognition of cancer. *Annu Rev Immunol*. 2015;33(1):445–474.
112. Ding L, Kim H-J, Wang Q, et al. PARP inhibition elicits STING-dependent antitumor immunity in BRCA1-deficient ovarian cancer. *Cell Rep*. 2018; 25(11):2972–2980.
113. Shen J, Zhao W, Ju Z, et al. PARPi triggers STING-dependent immune response and enhances therapeutic efficacy of immune checkpoint blockade independent of BRCAness. *Cancer Res*. 2019;79(2):311–319.
114. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. *J Natl Cancer Inst*. 2009;101(21):1446–1452.
115. Saner FAM, Herschtal A, Nelson BH, et al. Going to extremes: determinants of extraordinary response and survival in patients with cancer. *Nat Rev Cancer*. 2019;19(6):339–348.