special articles

OncoKB: A Precision Oncology Knowledge Base

Debyani Chakravarty
Jianjiong Gao
Sarah Phillips
Ritika Kundra
Hongxin Zhang
Jiaojiao Wang
Julia E. Rudolph
Rona Yaeger
Tara Soumerai
Moriah H. Nissan
Matthew T. Chang
Sarat Chandarlapaty
Tiffany A. Traina
Paul K. Paik
Alan L. Ho
Feras M. Hantash
Andrew Grupe
Shrujal S. Baxi
Margaret K. Callahan
Alexandra Snyder
Ping Chi
Daniel C. Danila
Mrinal Gounder
James J. Harding
Matthew D. Hellmann
Gopa Iyer
Yelena Y. Janjigian
Thomas Kaley
Douglas A. Levine
Maeve Lowery
Antonio Omuro
Michael A. Postow
Dana Rathkopf
Alexander N. Shoushtari
Neerav Shukla
Martin H. Voss
(continued)

executive summary

Purpose With prospective clinical sequencing of tumors emerging as a mainstay in cancer care, an urgent need exists for a clinical support tool that distills the clinical implications associated with specific mutation events into a standardized and easily interpretable format. To this end, we developed OncoKB, an expert-guided precision oncology knowledge base.

Methods OncoKB annotates the biologic and oncogenic effects and prognostic and predictive significance of somatic molecular alterations. Potential treatment implications are stratified by the level of evidence that a specific molecular alteration is predictive of drug response on the basis of US Food and Drug Administration labeling, National Comprehensive Cancer Network guidelines, disease-focused expert group recommendations, and scientific literature.

Results To date, > 3,000 unique mutations, fusions, and copy number alterations in 418 cancer-associated genes have been annotated. To test the utility of OncoKB, we annotated all genomic events in 5,983 primary tumor samples in 19 cancer types. Forty-one percent of samples harbored at least one potentially actionable alteration, of which 7.5% were predictive of clinical benefit from a standard treatment. OncoKB annotations are available through a public Web resource (http://oncokb.org) and are incorporated into the cBioPortal for Cancer Genomics to facilitate the interpretation of genomic alterations by physicians and researchers.

Conclusion OncoKB, a comprehensive and curated precision oncology knowledge base, offers oncologists detailed, evidence-based information about individual somatic mutations and structural alterations present in patient tumors with the goal of supporting optimal treatment decisions.

INTRODUCTION

The past decade witnessed accelerated growth in understanding the genomic landscape of common and rare cancer types, and prospective clinical sequencing of patient tumors is now increasingly recognized as a component of routine cancer care.[1,2] Tumor sequencing also is being applied more broadly as an investigational tool, with the goal of matching patients to treatments that target the mutations or downstream pathways that drive the growth and/or progression of individual tumors. With the shift from single analyte tests and small hotspot panels to larger gene panels and whole-exome and -genome platforms, interpretation of the clinical significance of the increasing number of genomic alterations identified in individual tumors has become a challenge. Most somatic alterations identified by whole-exome and large gene panel sequencing are likely passenger events with no influence on the patient's prognosis or response to therapy. A smaller subset are known or suspected functionally significant mutations with no clear therapeutic implications, and the smallest subset consists of known driver mutations that are clinically actionable.

The information that discriminates whether an alteration is clinically actionable can reside in various silos, including US Food and Drug Administration (FDA) labeling, National Comprehensive Cancer Network (NCCN) guidelines, conference proceedings, disease-focused expert group recommendations, and the scientific literature. Therefore, an urgent need exists for a clinical support tool that distills this information into a standardized and easily interpretable format that democratizes its access to clinicians of all knowledge levels and at all centers. Such a support tool would help clinicians interpret genomic alterations detected in patient tumor samples and enable them to make optimal treatment decisions for each individual patient with cancer.

Several knowledge base efforts exist, including My Cancer Genome,[3] CIViC,[4,5] the Precision Medicine Knowledge Base,[6,7] The Jackson Laboratory Clinical Knowledgebase,[8,9] Cancer Genome

Ederlinda Paraiso
Ahmet Zehir
Michael F. Berger
Barry S. Taylor
Leonard B. Saltz
Gregory J. Riely
Marc Ladanyi
David M. Hyman
José Baselga
Paul Sabbatini
David B. Solit
Nikolaus Schultz

Author affiliations and support information appear at the end of this article.

D.C. and J.G. contributed equally to this work.

Corresponding authors: Nikolaus Schultz, PhD, and David B. Solit, MD, Kravis Center for Molecular Oncology, Memorial Sloan Kettering Cancer Center, 1275 York Ave, Box 20, New York, NY 10065; e-mail: schultz@cbio.mskcc.org; solitd@mskcc.org.

Interpreter,[10] Cancer Driver Log,[11,12] Tumor Portal,[13,14] Targeted Cancer Care,[15] and Personalized Cancer Therapy.[16,17] Some of these databases are in their early stages of development; do not yet contain sufficient breadth or detail to be used in clinical decision support; and vary in the methods by which data are collected, stored, or accessed. To address these limitations, we describe OncoKB, a comprehensive precision oncology knowledge base that offers oncologists detailed, evidence-based information about individual somatic mutations and structural alterations present in patient tumors to support optimal treatment decisions. OncoKB content is supervised by a dedicated panel of physicians and cancer biologists who review and edit biomarker-associated investigational therapeutic strategies (Data Supplement). Through continual dialogue with the scientific and medical community, OncoKB integrates clinical best practices as defined by institution-wide, multidisciplinary disease management teams (Fig 1). OncoKB communicates information on the biomarker-guided use of FDA-approved therapies and investigational agents under evaluation in clinical trials and highlights negative clinical results to discourage off-label use of expensive targeted therapies shown to be ineffective in specific mutational contexts.

METHODS

OncoKB includes biologic, clinical, and therapeutic information curated from multiple unstructured information resources, including guidelines and recommendations derived from FDA labeling, NCCN guidelines, other disease-specific expert and advocacy group recommendations, and the medical literature (Fig 1). With recognition that clinical implications vary substantially on the basis of specific alterations within a gene and tumor context, information in OncoKB is hierarchically organized by gene, alteration, tumor type, and clinical implication (Fig 1). OncoKB information is publicly available through an interactive Web site[19] and incorporated into the cBioPortal for Cancer Genomics,[20-22] where patient genomic alterations are annotated with information from OncoKB and their biologic effects and clinical implications are summarized, which facilitates cancer researcher and clinician interpretation of complex genomic data (Fig 1). To date, OncoKB has annotated > 3,000 alterations in 418 cancer-associated genes (Table 1).

Levels of Evidence

To communicate the clinical utility of individual mutant alleles consistently, a level of evidence classification system was developed (Fig 2) that takes into account the site of tumor origin by recognizing that the effects of targeted inhibitors vary by tumor lineage, even in cancers that share the same mutant allele (Fig 3). Potentially actionable alterations in a specific cancer type are assigned to one of four levels that are based on the strength of evidence that the mutation is a predictive biomarker of drug sensitivity to FDA-approved or investigational agents for a specific indication. OncoKB currently has annotated 3,405 alterations in 418 genes (Table 1), including those in genes with standard therapeutic implications (either level 1 or 2A), such as the *ALK*-, *BRAF*-, *EGFR*-, and *ERBB2*-targetable kinases and genes that play a role in maintaining DNA integrity, such as *BRCA1* and *BRCA2*.

RESULTS

Level 1. Level 1 includes genes for which specific alterations have been recognized by the FDA as predictive of response to an FDA-approved drug in a particular disease context (Data Supplement). Examples include *BRAF* V600E and either vemurafenib or dabrafenib as monotherapy or in combination with the MEK inhibitors cobimetinib or trametinib in melanoma; *EGFR* L858R and erlotinib, afatinib, or gefitinib in non–small-cell lung cancer (NSCLC); and mutations in exons 9 and 11 of *KIT* and imatinib, sunitinib, and regorafenib in GI stromal tumors. In total, 82 alterations in 12 genes are considered level 1 (Data Supplement). In recognition that some alterations in what would be considered a level 1 gene are intrinsically resistant to currently available FDA-approved drugs or fall outside explicit FDA approval, OncoKB assigns individual alterations to a level of evidence as opposed to the entire gene. For example, *BRAF* K601E has been shown to be pharmacologically resistant to the RAF inhibitors vemurafenib and dabrafenib,[23] whereas compelling preclinical data associate this biomarker as predictive of response to MEK inhibitors; the use of MEK inhibitors in patients with *BRAF* K601E mutant tumors remains investigational.[24] Therefore, intrinsically RAF inhibitor–resistant *BRAF* mutations, although oncogenic, are not designated as level 1, and *BRAF* K601E is assigned level 3A on the basis of emerging clinical data that support this

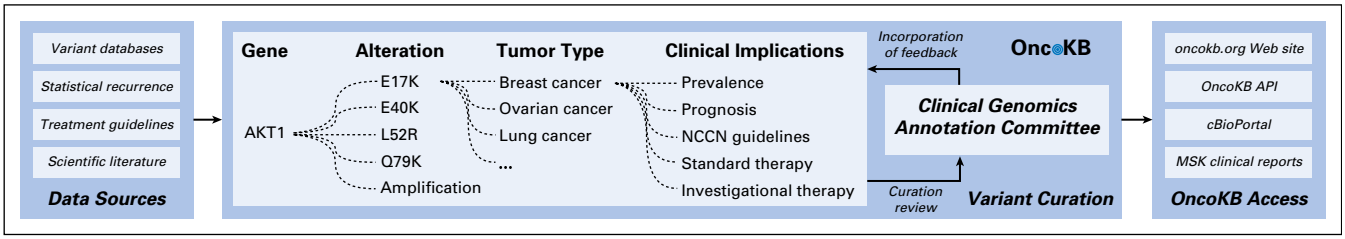

Fig 1. OncoKB workflow. Data sources: Alterations are identified by their recurrence[18] from public variant databases (cBioPortal, COSMIC [Catalogue of Somatic Mutations in Cancer], the Memorial Sloan Kettering [MSK] IMPACT internal clinical sequencing cohort), and by prior knowledge available in the literature. Biologic and clinical therapeutic implications of alterations are curated from several public resources, including disease-specific treatment guidelines; abstracts from major conference proceedings, such as ASCO, European Society of Medical Oncology, and American Association for Cancer Research; and the scientific literature through PubMed. Variant curation: This information is entered into the curation interface as structured data elements organized in a hierarchy of gene, alteration, and tumor type. Within each tumor type, clinical implications, including prevalence, prognostic implications, and standard or investigational therapeutic implications, are individually curated and stored. Clinical Genomics Annotation Committee (CGAC): OncoKB annotation is vetted by selected clinicians and physician-scientists across 22 disease management teams who make up the CGAC. Curation review occurs in the form of sample medical reports sent every 3 months to CGAC members and monthly e-mails that request feedback. CGAC recommendations and feedback are incorporated

biomarker as predictive of response to the MEK inhibitor trametinib[25,26] (Fig 3).

Levels 2A and 2B. Level 2A includes alterations that are not FDA-recognized biomarkers but are considered standard care predictive biomarkers of response to an FDA-approved therapy in specific cancer types. These alterations are highlighted in expert panel guidelines, such as the NCCN compendium and ASCO clinical practice guidelines. Several level 2A associations involve rare cancer types (eg, *BRAF* V600E mutant histiocytosis) or small subpopulations of common cancers (eg, *BRAF* V600E mutant lung cancer), and therefore, accrual to a prospective randomized phase III clinical study may not be feasible. However, administration of a targeted agent to patients whose tumors harbor the biomarker demonstrated sufficient clinical activity to have changed standard practice. Because the total number of patients affected often is small, an application for an FDA indication may never be filed, but disease experts consider the biomarker-drug association as a standard off-label use. In total, 11 genes with 85 alterations are currently considered level 2A (Data Supplement).

As an example, *MET* exon 14 alterations are present in approximately 3% of NSCLC[27] and represent a distinct, molecularly defined subpopulation of lung adenocarcinomas that are mutually exclusive with tumors that harbor activating mutations in *EGFR* and *KRAS* and fusions of *ALK*, *ROS1*, and *RET*.[28-30] An adequately powered randomized trial that compares the MET inhibitor crizotinib with other standard approaches, such as chemotherapy and immunotherapy, has not yet been performed partly because of the rarity of these alterations. However, durable complete or partial responses to crizotinib and cabozantinib in patients with *MET* exon 14–altered lung cancers have been reported.[27,31] Although widely available as a result of its FDA approval for use in *ALK* fusion–positive NSCLC, crizotinib is not explicitly FDA approved in the setting of MET exon 14–altered NSCLC. Because the NCCN guidelines consider off-label prescription of crizotinib a standard treatment approach for patients with lung cancer with *MET* exon 14 alterations,[32] they are classified as level 2A (Fig 2). Another example of a level 2A alteration is *BRAF* V600E as a predictive biomarker for BRAF inhibitor sensitivity in NSCLC and malignant histiocytosis. Although vemurafenib is not FDA approved for use in patients with these specific *BRAF* V600E mutant indications, the off-label use of vemurafenib is a well-supported treatment option included in the NCCN guidelines on the basis of compelling clinical data[33-35] (Fig 3).

Level 2B includes alterations that are standard predictive biomarkers of drug sensitivity in other tumor types but for which data in the tumor in question are either lacking or negative to date. For example, *BRAF* V600E mutations have been identified in several cancer types, including urothelial carcinomas and germ cell tumors,[36,37] for which no clinical response data are reported in the literature. In these tumors, the use of RAF inhibitors in patients with *BRAF* mutant tumors remains investigational, and *BRAF* V600E is therefore classified as level 2B[36] (Fig 3). In patients with *BRAF* V600E mutant colorectal cancer, BRAF inhibitors, such as vemurafenib, have been tested with disappointing results.[38] Such negative data are referenced in OncoKB and argue against the use of RAF inhibitor monotherapy in patients with *BRAF* V600E colorectal cancers. Level 2B also takes into account that early results in investigational clinical trials with RAF inhibitors as part of combination regimens appear promising.[39]

Levels 3A and 3B. Level 3A includes mutations that are candidate predictive biomarkers of drug response on the basis of off-label use of FDA-approved drugs or investigational agents not yet FDA approved for any indication. For the former, the evidence that supports the predictive value of the alteration is not considered sufficient to warrant a change in standard clinical practice, and disease experts would consider the use of the FDA-approved drug in this context to be investigational. The OncoKB level 3A classification only applies to tumor types in which clinical

into OncoKB in real time. OncoKB access: OncoKB data are available for public use through an interactive Web site[19] and the cBioPortal for Cancer Genomics[22] and are used internally to annotate MSK clinical reports. API, application program interface; NCCN, National Comprehensive Cancer Network.

activity has been reported, and the mutation-drug association is classified as level 3B in all other tumor types. Fifty-five alterations in 25 genes are considered level 3 (Data Supplement).

A representative example of a level 3 alteration is *AKT1* E17K (Fig 3). Promising clinical activity consistent with preclinical studies of this compound has been reported with the investigational pan-AKT inhibitor AZD5363 in patients with *AKT1* E17K mutant breast, lung, cervical squamous, and endometrial cancers.[40-42] On the basis of these emerging clinical data, *AKT1* E17K is classified as a level 3A mutation in breast, cervical, endometrial, ovarian, and lung cancers. With the lack of disease-specific data, *AKT1* E17K is classified as a level 3B mutation in all other cancer types (Fig 3). A more complex example of level 3 alterations are *ERBB2* missense mutations that are present in a minority of a broad range of human cancers[43] and that often arise in patients without *ERBB2* amplification or human epidermal growth factor receptor 2 (HER2) protein overexpression.[44] These *ERBB2* mutants demonstrate varying degrees of sensitivity to HER2-selective kinase inhibitors, such as lapatinib and neratinib[44] (Fig 3). Because the FDA does not recognize *ERBB2* mutations as a predictive biomarker of response to HER2-targeted therapies and the clinical utility of such agents is promising[45] but not yet established, activating missense mutations in *ERBB2* are classified as level 3A in breast cancer and 3B in other cancer types (Fig 3).

Level 4. Level 4 alterations are candidate predictive biomarkers of response to either FDA-approved or investigational agents on the basis of compelling laboratory data and an absence of substantiating compelling clinical data. Although anecdotal responses to targeted agents may have been demonstrated in individual patients whose tumor harbored a level 4 alteration, the data are not sufficiently robust to indicate that the presence of the mutation is associated with significantly greater activity than tumors that lack the alteration. For example, although studies in mouse- and patient-derived xenograft models have suggested that mammalian target of rapamycin– or AKT-targeted inhibitors may be effective in PTEN-null tumors,[46] the clinical data that support PTEN loss as a predictive biomarker of response to phosphatidylinositol 3-kinase, AKT, or mammalian target of rapamycin inhibitors in patients are limited and conflicting.[47-52] Therefore, classification of loss-of-function PTEN alterations as a level 4 alteration indicates that patients with PTEN-deficient tumors would be rational candidates for a clinical trial of investigational phosphatidylinositol 3-kinase pathway inhibitors alone or in combination with other agents, but that the use of such agents outside the context of a clinical trial is not yet supported by the sum of the clinical data. Additional examples of level 4 alterations include *NF1* inactivating alterations, which may be predictive of response to MEK1/2 inhibitors,[53] and *EGFR* exon 20 insertions in lung adenocarcinomas that respond poorly to erlotinib[54,55] but which may be sensitive to AP32788, an investigational inhibitor of EGFR and HER2[56] (Fig 3). As of this publication, 47 alterations in 17 genes are considered level 4 (Data Supplement). Because OncoKB levels are dynamic, mutations currently classified as level 4 may be reclassified as level 3 or higher if additional compelling clinical data emerge.

Levels of Resistance (Levels R1 to R3). OncoKB classifies mutations that have been shown to confer resistance to specific targeted therapies into one of three levels on the basis of the strength of the evidence that the mutation is predictive of treatment resistance (Fig 2). Level R1 includes mutational events for which there is sufficient evidence to recommend routine testing for the mutation to identify, with a high likelihood, patients who will not respond to a standard therapy. Identification of R1 mutations, therefore, would lead to a recommendation that the associated therapy be withheld in patients whose tumors harbor the mutation. By definition, level R1 mutations predict for resistance to FDA-approved drugs, and testing for such mutations is typically recommended by expert guidelines, such as those published by the NCCN. Level R1 alterations include activating RAS mutations in colorectal cancer, which predict for resistance to the EGFR-targeted monoclonal antibodies cetuximab and panitumumab[57,57a]; *EGFR* T790M mutations in NSCLC, which predict for intrinsic and acquired resistance to the EGFR tyrosine kinase inhibitors (TKIs) erlotinib, afatinib, and gefitinib[58]; and *PDGFRA* D842V, which predicts for

Table 1. OncoKB Results

OncoKB Annotation Metric	No. of Genes	No. of Alterations
Total No.	418	3,405
FDA approved (level 1)	12	82
Standard care (level 2A)	11	85
Emerging clinical evidence (level 3A)	25	55
Biologic evidence (level 4)	16	38
Oncogenic without a level of evidence	375	3,199

Abbreviations: FDA, Food and Drug Administration.

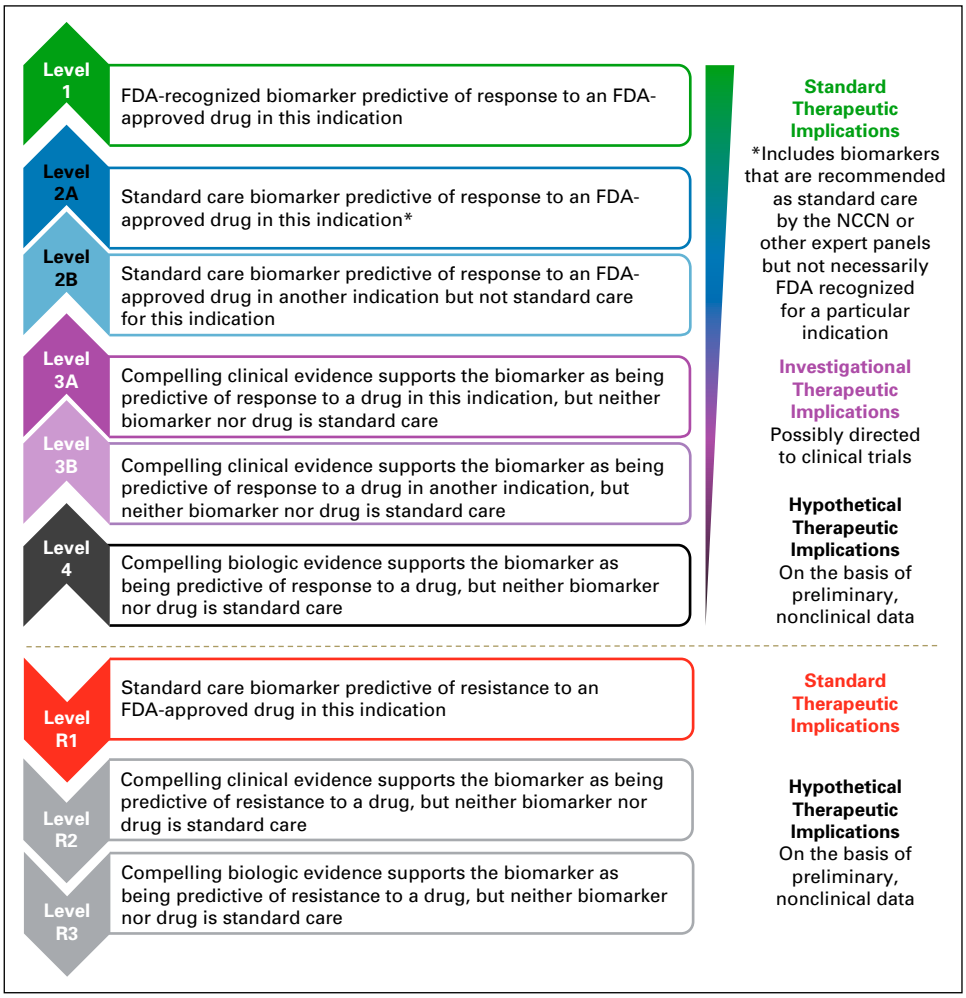

Fig 2. Levels of evidence. Individual mutational events are annotated by the level of evidence that supports the use of a certain drug in an indication that harbors that mutation. Standard therapeutic implications include Food and Drug Administration (FDA)–recognized biomarkers that are predictive of response to an FDA-approved drug in a specific indication (level 1) and standard care biomarkers that are predictive of response to an FDA-approved drug in a specific indication (level 2A). Investigational therapeutic implications include FDA-approved biomarkers predictive of response to an FDA-approved drug detected in an off-label indication (level 2B), FDA- or non–FDA-recognized biomarkers that are predictive of response to novel targeted agents that have shown promising results in clinical trials (level 3A), and non–FDA-recognized biomarkers that are predictive of response to novel targeted agents on the basis of compelling biologic data (level 4). NCCN, National Comprehensive Cancer Network.

resistance to imatinib in patients with GI stromal tumors.[59] Alterations classified as levels R2 and R3 have hypothetical therapeutic implications and include alterations that are predictive of drug resistance on the basis of clinical and biologic data, respectively, but their use in guiding treatment decisions is considered investigational (Fig 2). In some cases, alternative targeted therapies specifically target an alteration predictive of resistance to first- or second-line targeted therapies. For example, *EGFR* T790M is level R1 for erlotinib, gefitinib, and afatinib but is also classified as level 1 because it predicts sensitivity to the EGFR inhibitor osimertinib, which was recently approved for use in patients with NSCLC who progress on first-line EGFR TKI therapy and whose tumors harbor the *EGFR* T790M mutation.[60]

Functional Alterations Without Compelling Treatment Implications

Many genes are critical mediators of tumorigenesis, but compelling targeted therapeutic strategies have yet to be developed. For example, although multiple strategies to reverse the oncogenic effects of *TP53* loss have been explored in laboratory studies and early-phase clinical trials,[61,62] the agents tested do not directly target *TP53*, their activity is typically not restricted to *TP53* mutant models, and clinical trials that test these agents either have been aborted because of lack of efficacy or do not use *TP53* status as a selection criterion.[63] Thus, although genomic alterations in *TP53* are typically oncogenic, OncoKB does not consider them therapeutically actionable. In fact, > 90% of alterations in OncoKB have curated biologic effects and are classified as oncogenic but are not associated with actionability.

Actionable Alterations Across Cancer Types

Although targeted inhibitors have been shown to improve clinical outcomes in melanoma and lung cancer among others,[64] the broader clinical utility of large panel or whole-exome testing remains undefined. To assess the potential clinical impact

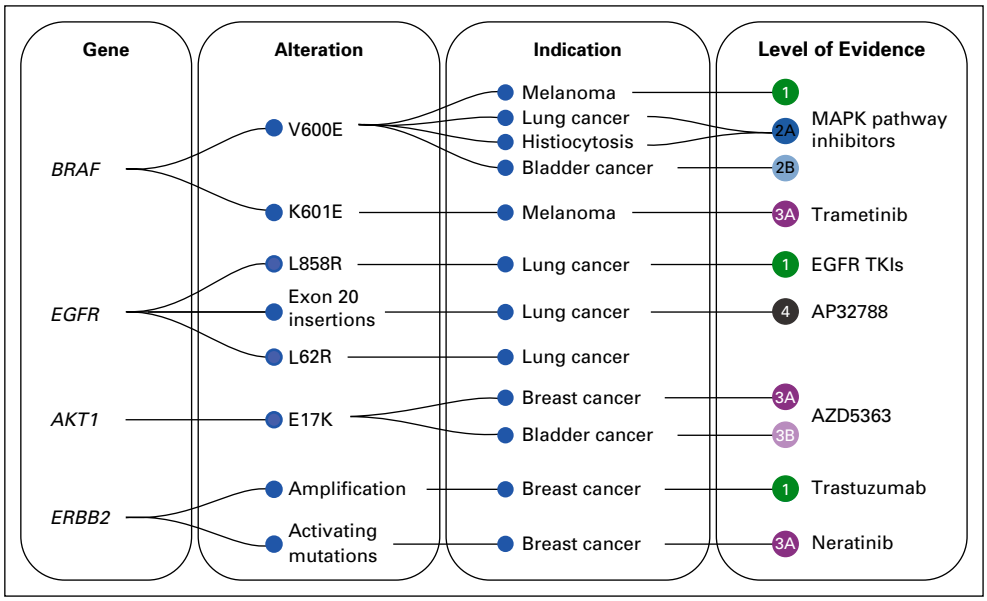

Fig 3. Examples for the OncoKB levels of evidence system. Information in OncoKB is organized hierarchically by gene, alteration, indication, and level of evidence. Implicit in the designation of a level of evidence for each branch is whether the biomarker is Food and Drug Administration (FDA)–recognized standard care or investigational and whether it is predictive of response to a drug that is FDA approved or currently being tested in clinical trials. Examples shown are *BRAF*, *EGFR*, *AKT1*, and *ERBB2*. MAPK, mitogen-activated protein kinase; TKI, tyrosine kinase inhibitor.

of prospective broad tumor genomic testing, we used the OncoKB levels of evidence classification to annotate mutations, copy number alterations, and gene fusions in a publicly available data set of 5,983 primary tumor samples that represent 19 cancer types profiled by whole-exome and RNA sequencing by the Cancer Genome Atlas.[1] Although > 90% of samples harbored at least one known oncogenic mutation, only 41% had one or more alterations for which compelling clinical data currently exist to justify the use of a standard or an investigational agent (levels 1 to 3B) (Fig 4A). Overall, 7.5% of all samples harbored alterations that predict for response to a standard therapy in that disease context (levels 1 and 2A) (Fig 4A). Level 1 and 2A alterations were most common in melanoma (44%), ovarian cancer (21%, which includes 65 of 312 samples that have either germline or somatic *BRCA1*- or *BRCA2*-inactivating mutations), soft tissue sarcomas (19% on the basis of *CDK4* amplifications, which predict response to palbociclib in well-differentiated and dedifferentiated liposarcomas but not in other soft tissue sarcomas), NSCLC (14%), esophagogastric cancer (13%), and breast cancer (12%). Low-grade gliomas (LGGs) and melanomas had the highest proportion of actionable alterations. However, whereas 44% of melanomas had mutations that predict for clinical benefit with standard therapies in patients with melanoma, the majority of actionable alterations in LGG were associated with only investigational implications, with the most common mutation being *IDH1* R132C (77% of LGG samples), a level 3B alteration that is based on promising clinical data with the IDH1 inhibitor AG-120 in patients with acute myeloid leukemia (Figs 4A and 4B). In total, just over 10% of all samples had a level 3A mutation as their highest actionable alteration, a cohort of patients for which enrollment in a clinical trial would represent a compelling treatment option after standard treatments. In addition, approximately 15% of samples had level 3B alterations as their highest actionable event, ie, alterations for which promising clinical data have been observed in an investigational setting in another cancer type.

On average, there were approximately three oncogenic mutations per sample, and the number of known oncogenic mutations per sample in tumor types was independent of overall mutation burden (Fig 4C). The number of actionable and oncogenic mutations varied greatly across cancer types. For example, although renal cell cancers had, on average, one oncogenic mutation per sample, these mutations were typically inactivating in tumor suppressors, such as *VHL* and *PBRM1*, which are not clinically actionable at this time. Therefore, 95% of renal cell cancers had no actionable alteration (Fig 4D). In contrast, although thyroid cancers also on average had approximately one oncogenic mutation per sample (Fig 4C), these alterations were typically actionable, such as *RET* fusions and *BRAF* and *NRAS* mutations. Therefore, 60% of thyroid samples had at least one actionable alteration (Fig 4D). Breast, colorectal, and esophagogastric cancers were found to have a large fraction of samples with two or more actionable

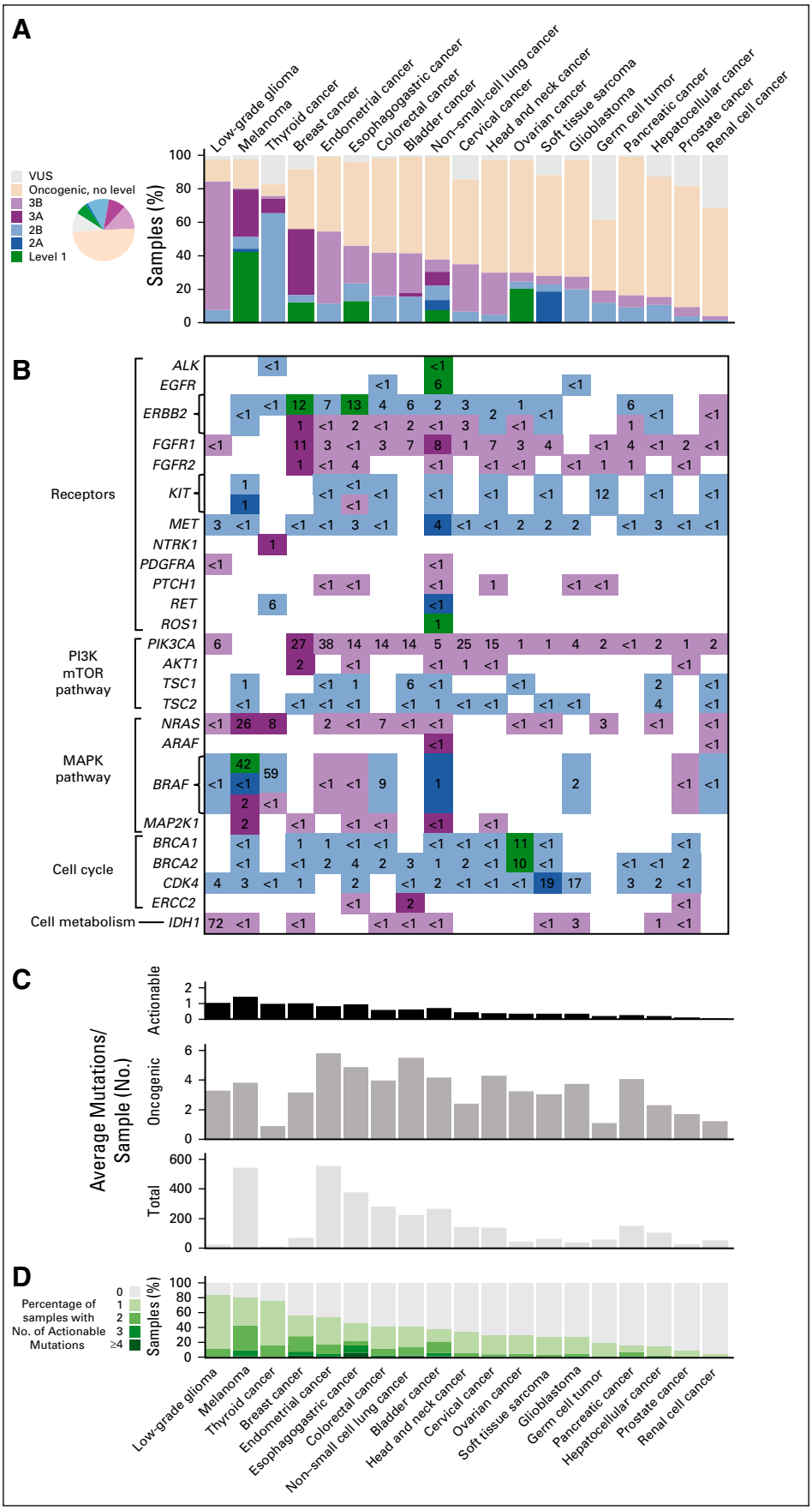

Fig 4. Frequencies of level of evidence 1 to 3 assignments in the Cancer Genome Atlas cohorts. Patient samples from 19 cancer types (The Cancer Genome Atlas) are classified by the alteration that carries the highest level of evidence. (A) Inset pie chart: Fraction of samples across all cancer types that carry a mutation considered actionable according to the levels of evidence, oncogenic but not actionable, or variants of unknown significance (VUS). Stacked bar graph: Similar analysis as inset pie chart. Tumor type–specific samples are analyzed by variants considered actionable, oncogenic but not actionable, or VUS. (B) Highest level of evidence by tumor type and gene. Cell color as shown in the key for the inset pie chart (A). Columns indicate sample tumor type, rows indicate gene alteration present in sample, and numbers indicate the percentage of samples per tumor type that harbor an alteration in each gene. (C) Each patient sample was classified by the number of oncogenic alterations or the number of actionable alterations. Shown is the mean number of actionable (black), oncogenic (dark gray), or total (gray) mutations per sample per tumor type. (D) Each tumor type was evaluated for the percentage of samples that carry zero, one, two, three, or four or more actionable mutations per sample (indicated in shades of blue). MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase.

mutations (31%, 25%, and 22%, respectively), which is consistent with data that demonstrate that these tumor types are driven by multiple oncogenic mutations in nonredundant pathways[65-68] (Fig 4D) and may explain why targeted monotherapies have shown disappointing results to date in some of these cancer types.[69,70]

DISCUSSION

Since the introduction of imatinib for chronic myeloid leukemia more than a decade ago,[71,72] a growing number of drugs that target specific genetic alterations required for tumor initiation and progression have been shown to significantly improve outcomes in molecularly defined populations of patients with cancer.[64,73-74a] Although tumor genetic testing is now part of routine patient care in an increasing number of tumor types, interpretation of variants remains an important challenge, and in major academic cancer centers, a significant proportion of physicians report low confidence in their ability to make optimal treatment recommendations on the basis of genomic information.[75]

Although multiple classification systems exist for the annotation of germline variants,[76,77] efforts to define the clinical utility of somatic alterations have been limited to established biomarkers,[78-80] and prior efforts often have classified actionability as a binary variable that results in the grouping of biomarkers that are FDA recognized with those that are nonactionable but oncogenic. To this end, we assigned each mutation to one of four levels that are based on available clinical and laboratory data that support the use of the mutation as a predictive biomarker. Standard therapeutic implications are classified as either level 1 or 2A to recognize that not all mutation-drug associations used in standard practice have been recognized by the FDA. Levels 2B, 3, and 4 include mutations for which the biomarker-drug association remains investigational and may be useful in guiding the use of an FDA-approved therapy in an off-label setting or, preferably, in prompting consideration for enrollment in appropriate clinical trials. The latter is particularly relevant because clinical trials are increasingly incorporating into their eligibility criteria the molecular profiles of patient tumors, including basket studies, such as the Roche VE-BASKET (A Study of Zelboraf [vemurafenib] in Patients With *BRAF* V600 Mutation-Positive Cancers; ClinicalTrials.gov identifier NCT01524978), Puma Biotechnology SUMMIT (An Open-Label, Phase 2 Study of Neratinib in Patients With Solid Tumors With Somatic Human Epidermal Growth Factor Receptor [EGFR, HER2, HER3] Mutations or EGFR Gene Amplification; ClinicalTrials.gov identifier NCT01953926), and Loxo Oncology NAVIGATE (A Phase II Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects With NTRK Fusion-Positive Tumors; ClinicalTrials.gov identifier NCT02576431) trials, and master or umbrella studies, such as the NCI-MATCH (National Cancer Institute Molecular Analysis for Therapy Choice; ClinicalTrials.gov identifier NCT02465060), ASCO TAPUR (Targeted Agent and Profiling Utilization Registry; ClinicalTrials.gov identifier NCT02693535), Genentech MyPathway (ClinicalTrials.gov identifier NCT02091141), and Novartis SIGNATURE (Ceritinib [LDK378] for Patients Whose Tumors Have Aberrations in ALK or ROS1; ClinicalTrials.gov identifier NCT02186821) trials.

Off-label use of cancer drugs in oncology has a long history,[81-83] particularly in patients with rare cancer types for whom randomized clinical trials may not be feasible. Access to drugs for off-label use is becoming increasingly difficult because of high drug costs and variations in reimbursement among individual insurance providers. Moreover, there are cases where off-label use of an FDA-approved drug is explicitly not warranted because of existing data that argue against the use of a targeted agent in a specific cancer type. For example, although the BRAF inhibitor vemurafenib is a standard treatment option for patients with *BRAF* V600E mutant melanoma or NSCLC, robust clinical reports from multiple independent centers demonstrated that patients with *BRAF* V600E mutant colorectal cancer do not respond to RAF inhibitors, at least as monotherapy.[38,84] Similarly, although *ERBB2* amplification predicts for the clinical utility of HER2-targeted therapies in breast and esophagogastric cancers, the clinical activity of trastuzumab in *ERBB2*-amplified lung cancers has been disappointing.[85] *BRAF* V600E and *ERBB2* amplification are, therefore, level 2B when detected in colorectal cancers. A level 2B designation should encourage consideration of a clinical trial. In the case of *BRAF* V600E mutant colorectal cancers, somewhat more encouraging results have been observed with BRAF-EGFR inhibitor combinations[39]; however, given that thus far this approach is nonstandard and that expensive agents are involved, access to these drugs outside a clinical trial in this scenario may be difficult.

Individual mutant alleles within a single gene may be functionally distinct, with different predictive value and, therefore, individual therapeutic implications, which complicates the development of clinical decision support tools, particularly in the context of often-vague FDA labeling and expert guidelines, such as those provided by the NCCN, that may not define at a granular level whether specific mutations within a gene are predictive of drug response. To address this complexity, OncoKB groups mutations in level 1 genes, such as *EGFR* and *KIT*, according to whether they are biologically active, whether there are preclinical data to suggest that the allele is sensitive or resistant to the matched targeted agents, and whether there are clinical data to suggest clinical sensitivity or intrinsic resistance to the approved targeted therapy. Consequently, less common *EGFR* mutations, such as L861Q and G719A, are classified as level 1, whereas *EGFR* exon 20 insertions are classified as level 4.[85a] A limitation of this approach is that the response rate of erlotinib in patients with these mutations may prove to be lower relative to the more common EGFR TKI–sensitizing alleles, such as L858R, after more clinical data on these rare alleles become available. We therefore anticipate further refinement of OncoKB classifications as additional clinical data emerge for rare targetable alleles. The challenge of rare drug-sensitive variants in level 1 genes also highlights the need for consortia efforts, such as the American Association for Cancer Research Project GENIE (Genomics Evidence Neoplasia Information Exchange), which should allow for the collection of clinical response data for rare alleles to help to guide the treatment of patients with these less common mutations.

Although new laboratory and clinical data are continually generated, FDA labels and professional guidelines are updated at irregular intervals. Thus, the level of evidence assigned to an annotated alteration may change, with immediate implications for patients with active disease. For example, although explicit FDA approval of crizotinib in *ROS1*-rearranged NSCLC did not occur until March 2016, off-label use of crizotinib in patients with *ROS1* fusion-positive lung cancers has been considered standard of care by several expert groups for some time.[86-88] As another example, whereas *KRAS* was initially considered a level 3A alteration in NSCLC on the basis of promising data from the randomized phase II study that supplemented standard chemotherapy with a MEK inhibitor,[89] the subsequent phase III trial showed no survival benefit with this combination,[90] which is consistent with negative data associated with MEK inhibitor use in *KRAS* mutant pancreatic and colorectal cancers.[91,92] Nonetheless, anecdotal clinical and compelling preclinical data support the use of *KRAS* as a predictive biomarker of sensitivity to novel MEK and ERK inhibitors alone or in combination with other agents.[93-97] OncoKB thus recognizes and reassigns the level of evidence of mutational events, if appropriate, on the basis of newer, more-definitive, and negative randomized clinical data, which take precedence over prior preliminary clinical findings.

To incorporate new clinical and research findings, we have made the OncoKB annotation available publically through an interactive Web site[19] and through the cBioPortal for Cancer Genomics.[22] Both systems include a comment feature to facilitate crowdsourcing curation of this knowledge base. User suggestions are evaluated by the scientific team and incorporated into OncoKB through periodic updates. OncoKB is also an active member in efforts to promote harmonization of variant annotation across existent knowledge bases and is participating in both ClinGen and the Global Alliance for Genomic Health through the Variant Interpretation Cancer Consortium.

In the future, we will curate information about mutational signatures, such as overall mutation burden and the possible link to immunotherapy, mutational clonality, and the impact on drug sensitivity of co-occurrence of specific oncogenic and actionable mutations. Additional prospective and retrospective clinical studies will further define the proportion of patients with cancer and the specific patient subsets that would benefit from targeted therapies. Toward this goal, clinical and scientific researchers must establish standards and aggregate scientific knowledge for the benefit of clinicians and patients. A curated database such as OncoKB can play an important role in realizing the promise of precision medicine by helping physicians to identify potentially actionable variants to ensure that patients receive appropriate standard therapies or are directed to the most appropriate clinical trials.

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AUTHOR CONTRIBUTIONS

Conception and design: Debyani Chakravarty, Jianjiong Gao, Sarah Phillips, Ritika Kundra, Hongxin Zhang, Julia E. Rudolph, Ederlinda Paraiso, David M. Hyman, José Baselga, Paul Sabbatini, David B. Solit, Nikolaus Schultz

Financial support: Ederlinda Paraiso, Nikolaus Schultz

Administrative support: Julia E. Rudolph, Ederlinda Paraiso

Collection and assembly of data: Debyani Chakravarty, Jianjiong Gao, Sarah Phillips, Ritika Kundra, Hongxin Zhang, Tara Soumerai, Moriah H. Nissan, Matthew T. Chang, Sarat Chandarlapaty, Tiffany A. Traina, Paul K. Paik, Alan L. Ho, Shrujal S. Baxi, Margaret K. Callahan, Alexandra Snyder, Ping Chi, Daniel C. Danila, Mrinal Gounder, James J. Harding, Matthew D. Hellmann, Gopa Iyer, Yelena Y. Janjigian, Thomas Kaley, Douglas A. Levine, Maeve Lowery, Antonio Omuro, Michael A. Postow, Dana Rathkopf, Alexander N. Shoushtari, Neerav Shukla, Martin H. Voss, Leonard B. Saltz, Gregory J. Riely, Marc Ladanyi, David M. Hyman, Nikolaus Schultz

Data analysis and interpretation: Debyani Chakravarty, Jianjiong Gao, Sarah Phillips, Ritika Kundra, Hongxin Zhang, Matthew T. Chang, David B. Solit, Nikolaus Schultz

Manuscript writing: All authors

Final approval of the manuscript: All authors

Accountable for all aspects of the work: All authors

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Debyani Chakravarty
No relationship to disclose

Jianjiong Gao
No relationship to disclose

Sarah Phillips
No relationship to disclose

Ritika Kundra
No relationship to disclose

Hongxin Zhang
No relationship to disclose

Jiaojiao Wang
No relationship to disclose

Julia E. Rudolph
No relationship to disclose

Rona Yaeger
Consulting or Advisory Role: GlaxoSmithKline, Advaxis

Tara Soumerai
No relationship to disclose

Moriah H. Nissan
No relationship to disclose

Matthew T. Chang
No relationship to disclose

Sarat Chandarlapaty
Honoraria: Chugai Pharmaceutical, Foresite Capital, AstraZeneca, Sermonix Pharmaceuticals, MacroGenics, Agendia
Research Funding: Eli Lilly (Inst), Novartis (Inst)
Travel, Accommodations, Expenses: Chugai Pharmaceutical, MacroGenics, AstraZeneca

Tiffany A. Traina
Consulting or Advisory Role: Genentech, Roche, Eisai, Mundipharma, Medivation, Pfizer, AstraZeneca, Bayer AG, Immunomedics, Merck
Research Funding: Medivation, Eisai, Pfizer, Novartis, Myriad Genetics, Innocrin Pharmaceuticals, AstraZeneca

Paul K. Paik
Honoraria: Celgene, Bristol-Myers Squibb, Eli Lilly, ARIAD Pharmaceuticals
Consulting or Advisory Role: Celgene, Eli Lilly, ARIAD Pharmaceuticals, Bristol-Myers Squibb, Celgene
Research Funding: Celgene, EMD Serono
Travel, Accommodations, Expenses: EMD Serono

Alan L. Ho
Consulting or Advisory Role: Oncology Consortium, Bristol-Myers Squibb, Eisai, Genzyme, Merck, Novartis, Sun Pharmaceutical Industries, Kura Oncology
Speakers' Bureau: Medscape, Omniprex America, Eli Lilly, Genentech, Roche, AstraZeneca, Bayer AG, Kura Oncology, Kolltan Pharmaceuticals, Eisai, AstraZeneca
Travel, Accommodations, Expenses: Janssen Pharmaceuticals, Merck, Kura Oncology

Feras M. Hantash
Employment: Quest Diagnostics
Stock and Other Ownership Interests: Quest Diagnostics
Patents, Royalties, Other Intellectual Property: Patents on molecular methods, but not related to manuscript

Andrew Grupe
Employment: Quest Diagnostics
Stock and Other Ownership Interests: Quest Diagnostics
Patents, Royalties, Other Intellectual Property: Patents or patent applications
Travel, Accommodations, Expenses: Quest Diagnostics

Shrujal S. Baxi
Consulting or Advisory Role: Bristol-Myers Squibb, AstraZeneca
Travel, Accommodations, Expenses: AstraZeneca

Margaret K. Callahan
Employment: Bristol-Myers Squibb (I), Celgene (I), Kleo Pharmaceuticals (I)
Consulting or Advisory Role: AstraZeneca, Moderna
Research Funding: Bristol-Myers Squibb (Inst)
Other Relationship: Clinical Care Options, Potomac Center for Medical Education

Alexandra Snyder
Consulting or Advisory Role: Third Rock Ventures, Driver Group
Research Funding: Bristol-Myers Squibb
Travel, Accommodations, Expenses: Genentech, Roche, Bristol-Myers Squibb

Ping Chi
Honoraria: Novartis

Daniel C. Danila
Honoraria: Astellas Pharma, Angle, Bayer AG, Janssen Pharmaceuticals
Consulting or Advisory Role: Angle, Bayer AG
Research Funding: Prostate Cancer Foundation, Genentech, Janssen Pharmaceuticals (Inst)
Patents, Royalties, Other Intellectual Property: Gene expression profile associated with prostate cancer
Travel, Accommodations, Expenses: Cambridge Healthtech Institute, Prostate Cancer Foundation, Angle, Bayer AG, American Austrian Foundation Open Medical Institute, Global Technology Community, Janssen Pharmaceuticals, Oncology Education

Mrinal Gounder
Honoraria: Amgen, Daiichi Sankyo, Karyopharm Therapeutics, TRACON Pharmaceuticals, Amgen
Consulting or Advisory Role: Daiichi Sankyo, Karyopharm Therapeutics, Epizyme
Speakers' Bureau: Amgen
Travel, Accommodations, Expenses: Amgen
Travel, Accommodations, Expenses: Daiichi Sankyo, Karyopharm Therapeutics

James J. Harding
No relationship to disclose

Matthew D. Hellmann
Consulting or Advisory Role: Bristol-Myers Squibb, Merck, Genentech, AstraZeneca, MedImmune, Novartis, Janssen Pharmaceuticals
Research Funding: Bristol-Myers Squibb, Genentech, Roche

Gopa Iyer
No relationship to disclose

Yelena Y. Janjigian
Consulting or Advisory Role: Eli Lilly, Pfizer
Research Funding: Boehringer Ingelheim, Bayer AG, Eli Lilly, Amgen, Roche, Genentech

Thomas Kaley
No relationship to disclose

Douglas A. Levine
Stock and Other Ownership Interests: Critical Outcome Technologies
Consulting or Advisory Role: Clovis Oncology, MTrap, Biodesix, TESARO

Maeve Lowery
Consulting or Advisory Role: Agios, Celgene

Antonio Omuro
Consulting or Advisory Role: Stemline Therapeutics, Juno Therapeutics, Bristol-Myers Squibb, OXiGENE, Alexion Pharmaceuticals, AstraZeneca, Inovio Pharmaceuticals, Merck

Michael A. Postow
Honoraria: Bristol-Myers Squibb, Merck
Consulting or Advisory Role: Amgen, Bristol-Myers Squibb, Novartis
Research Funding: Bristol-Myers Squibb (Inst), Novartis (Inst), Array BioPharma (Inst), Infinity Pharmaceuticals (Inst)
Travel, Accommodations, Expenses: Bristol-Myers Squibb

Dana Rathkopf
Consulting or Advisory Role: Janssen Pharmaceuticals
Research Funding: Janssen Pharmaceuticals (Inst), Medivation (Inst), Celgene (Inst), Takeda Pharmaceuticals (Inst), Millennium Pharmaceuticals (Inst), Ferring Pharmaceuticals (Inst), Novartis (Inst), Taiho Pharmaceutical (Inst), AstraZeneca (Inst), Genentech (Inst), Roche (Inst), TRACON Pharmaceuticals (Inst)

Alexander N. Shoushtari
Consulting or Advisory Role: Vaccinex, Castle Biosciences, Immunocore
Research Funding: Bristol-Myers Squibb, Immunocore
Travel, Accommodations, Expenses: Bristol-Myers Squibb

Neerav Shukla
No relationship to disclose

Martin H. Voss
Honoraria: Novartis
Consulting or Advisory Role: Novartis, Calithera Biosciences, Natera, GlaxoSmithKline, Exelixis, Pfizer, Alexion Pharmaceuticals
Research Funding: Pfizer, Bristol-Myers Squibb, Genentech, Roche
Travel, Accommodations, Expenses: Novartis, Takeda Pharmaceuticals

Ederlinda Paraiso
No relationship to disclose

Ahmet Zehir
No relationship to disclose

Michael F. Berger
Consulting or Advisory Role: Cancer Genetics, Sequenom

Barry S. Taylor
No relationship to disclose

Leonard B. Saltz
Consulting or Advisory Role: Eli Lilly, McNeil (I), AbbVie
Research Funding: Taiho Pharmaceutical

Gregory J. Riely
Consulting or Advisory Role: Novartis, Genentech
Research Funding: Novartis (Inst), Roche (Inst), Genentech (Inst), Millennium Pharmaceuticals (Inst), GlaxoSmithKline (Inst), Pfizer (Inst), Infinity Pharmaceuticals (Inst), ARIAD Pharmaceuticals (Inst)
Patents, Royalties, Other Intellectual Property: Patent application submitted that covers pulsatile use of erlotinib to treat or prevent brain metastases (Inst)
Travel, Accommodations, Expenses: Novartis

Marc Ladanyi
Honoraria: Merck (I)
Consulting or Advisory Role: National Comprehensive Cancer Network, Boehringer Ingelheim, AstraZeneca
Research Funding: Loxo Oncology (Inst)

David M. Hyman
Consulting or Advisory Role: Atara Biotherapeutics, Chugai Pharmaceutical, CytomX Therapeutics
Research Funding: AstraZeneca, Puma Biotechnology

José Baselga

Leadership: Infinity Pharmaceuticals, Varian Medical Systems, GRAIL, Foghorn

Stock or Other Ownership: PMV Pharma, Juno Therapeutics, Infinity Pharmaceuticals, GRAIL, Varian Medical Systems, Tango, Foghorn, Aura Biomedical, Apogen, Northern Biologics

Honoraria: PMV Pharma, Juno Therapeutics, Infinity Pharmaceuticals, GRAIL, Northern Biologics

Consulting or Advisory Role: Eli Lilly, Novartis, GRAIL

Patents, Royalties, Other Intellectual Property: Combination therapy using PDK1 and PI3K inhibitors. Pending. MSK owned, listed as investigator. Jul 16 Use of phosphoinositide 3- kinase inhibitors for treatment of vascular malformations. Licensed. MSK owned, listed as investigator. May 16

Travel, Accommodations, Expenses: Roche/Genentech

Paul Sabbatini

Research Funding: Bristol-Myers Squibb (Inst), Ludwig Institute for Cancer Research (Inst)

David B. Solit

Honoraria: Loxo Oncology, Pfizer

Consulting or Advisory Role: Pfizer, Loxo Oncology

Nikolaus Schultz

No relationship to disclose

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Affiliations

Debyani Chakravarty, **Jianjiong Gao**, **Sarah Phillips**, **Ritika Kundra**, **Hongxin Zhang**, **Jiaojiao Wang**, **Julia E. Rudolph**, **Rona Yaeger**, **Tara Soumerai**, **Moriah H. Nissan**, **Matthew T. Chang**, **Sarat Chandarlapaty**, **Tiffany A. Traina**, **Paul K. Paik**, **Alan L. Ho**, **Shrujal S. Baxi**, **Margaret K. Callahan**, **Alexandra Snyder**, **Ping Chi**, **Daniel C. Danila**, **Mrinal Gounder**, **James J. Harding**, **Matthew D. Hellmann**, **Gopa Iyer**, **Yelena Y. Janjigian**, **Thomas Kaley**, **Douglas A. Levine**, **Maeve Lowery**, **Antonio Omuro**, **Michael A. Postow**, **Dana Rathkopf**, **Alexander N. Shoushtari**, **Neerav Shukla**, **Martin H. Voss**, **Ederlinda Paraiso**, **Ahmet Zehir**, **Michael F. Berger**, **Barry S. Taylor**, **Leonard B. Saltz**, **Gregory J. Riely**, **Marc Ladanyi**, **David M. Hyman**, **José Baselga**, **Paul Sabbatini**, **David B. Solit**, and **Nikolaus Schultz**, Memorial Sloan Kettering Cancer Center; **Sarat Chandarlapaty**, **Paul K. Paik**, **Shrujal S. Baxi**, **Margaret K. Callahan**, **Alexandra Snyder**, **Ping Chi**, **Daniel C. Danila**, **Mrinal Gounder**, **James J. Harding**, **Matthew D. Hellmann**, **Gopa Iyer**, **Yelena Y. Janjigian**, **Maeve Lowery**, **Michael A. Postow**, **Dana Rathkopf**, **Alexander N. Shoushtari**, **Michael F. Berger**, **Leonard B. Saltz**, **Gregory J. Riely**, **José Baselga**, and **David B. Solit**, Weill Cornell Medical College, New York, NY; and **Feras M. Hantash** and **Andrew Grupe**, Quest Diagnostics Nichols Institute, San Juan Capistrano, CA.

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