

# The Evolving War on Cancer

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**Building on years of basic scientific discovery, recent advances in the fields of cancer genetics and medicinal chemistry are now converging to revolutionize the treatment of cancer. Starting with serendipitous observations in rare subsets of cancer, a paradigm shift in clinical research is poised to ensure that new molecular insights are rapidly applied to shape emerging cancer therapies. Could this mark a turning point in the “War on Cancer”?**

In the past year, a startling series of clinical studies has brought molecularly targeted therapies to the treatment of diverse cancers. An inhibitor that blocks a specific mutant of the serine/threonine kinase B-RAF (V600E-B-RAF) demonstrated dramatic efficacy in treating metastatic melanoma, a cancer that was long thought to be among the most refractory (Flaherty et al., 2010). An inhibitor of the anaplastic lymphoma kinase (ALK) proved highly effective against a subset of nonsmall cell lung cancers that had been prescreened for an oncogenic EML4-ALK translocation (Kwak et al., 2010). A Janus kinase 2 (JAK2) inhibitor proved beneficial against a form of preleukemia, myelodysplastic syndrome, that harbors an activating JAK2 mutation (Verstovsek et al., 2010). In B cell hematological malignancies, which selectively express the class I phosphatidylinositol 3-kinase (PI3K)  $\delta$  isoform, a PI3K  $\delta$ -specific inhibitor has shown remarkable activity in refractory tumors (Furman et al., 2010). Even the immunology front, after years of setbacks, made significant strides when antibodies abrogating anticytotoxic T lymphocyte antigen (CTLA)-4 improved survival in patients with advanced melanoma (O’Day et al., 2010). In addition, we anticipate promising results from approaches that combine known treatments, such as using both mitogen-activated protein kinase kinase (MEK) and PI3K inhibitors to treat cancers with mutations in K-RAS (Engelman et al., 2008) and combining antibodies and kinase inhibitors to treat breast cancers with the *HER2* gene amplified (Baselga et al., 2010).

Most impressive, however, is the sense that the timeline of translating molecular studies into the clinic is accelerating. For example, it took 6–8 years to demonstrate the efficacy of B-RAF and epidermal growth factor receptor (EGFR) inhibitors in appropriate clinical studies (Davies et al., 2002; Flaherty et al., 2010; Lynch et al., 2004; Mok et al., 2009; Paez et al., 2004). In contrast, it took just more than 1 year for researchers to demonstrate clinical responses to ALK inhibition in a cohort of genotyped patients, after the initial discovery of the EML4-ALK translocations in a subset of lung cancers (Soda et al., 2007; Kwak et al., 2010).

In this Essay, we explore the important advances in cancer genetics, medicinal chemistry, and clinical strategies contributing to these recent successes and enhanced pace. Then, we discuss the key challenges and objectives for continual success. Clearly, the future of targeted therapies depends upon a detailed understanding of the molecular genetic abnormalities that drive different subsets of cancer, a rich pipeline of promising compounds targeting such lesions, and the appropriate use of companion diagnostics, both to prescreen patients that are likely to respond and to detect early signs of either drug response or acquired resistance.

## Breaking the Cancer War Stalemate

The “War on Cancer,” now 40 years old, has been declared a failure, both in the medical literature (Bailar and Gornik, 1997) and in the general press (Leaf,

2004). In contrast to the marked success of cholesterol-lowering drugs and antihypertensives in reducing the risk of cardiovascular disease, the decline in cancer mortality has been relatively modest. This decrease has been attributed primarily to screening for breast and colon cancer and preventive measures, such as a reduction in smoking and the declining use of postmenopausal estrogen replacement. Could the new forms of cancer treatment provide hope for reduced mortality? And what are the critical components that are required to achieve a sustained impact on the disease?

It is perhaps ironic that the bill signed by President Richard M. Nixon in 1971, which was ultimately labeled the War on Cancer, triggered a massive investment in basic science. The research was undertaken with the assumption that unbiased fundamental research would hold the key to unlocking the secrets of cancer cells, and indeed, our current knowledge about cellular biology and molecular genetics owes much to this national investment.

Although the anticipated timeline for clinical applications of basic research may have been optimistic, recent successes in targeted therapies are based on the accumulated knowledge generated by years of fundamental research in genetics, signaling, cellular, and molecular biology. In particular, we have learned that the genesis of cancer mirrors the process of mutation and selection underlying our own evolution, and the signals that drive or suppress

proliferation, apoptosis, differentiation, and quiescence in cancer cells mimic those of normal development.

We are finally capable of manipulating these signals in some cancers to achieve a profound initial response in the tumor. However, the acquisition of resistance by cancer cells prompts the need for even greater understanding of cellular mechanisms underlying cancer cells' plasticity and adaptation. Single driving genetic lesions may provide clear therapeutic targets in some cancers, but a more profound understanding of interconnected signaling pathways may be required to tackle the majority of tumors.

### Drawing from Somatic Cancer Genetics to Find Therapeutic Targets

Early cancer genetic studies focused on inherited cancer syndromes in which a single germline mutation is responsible for cancer susceptibility within a family. Such studies provide clear and compelling evidence for the one lesion, typically in a tumor suppressor gene, that is capable of initiating tumorigenesis, as opposed to a vast number of somatic aberrations accumulating during cancer progression. Directed genotyping studies uncovered additional somatic mutations, chromosome translocations, and loss of heterozygosity patterns, pointing to recurrent (and hence probably significant) lesions in many cancers. Functional studies of introduced oncogenes and tumor suppressor genes in cells and model organisms readily demonstrated the powerful impact of mutating a single gene in triggering malignancy.

However, it was the decision to undertake whole-scale sequencing of cancer genomes, first by the Sanger Center and then by US and international consortia, that provided a comprehensive view of somatic mutational landscapes in cancer and potential therapeutic targets. Important successes of genome-scale sequencing included the discovery of highly recurrent and specific mutations in BRAF and PI3K (Davies et al., 2002; Samuels et al., 2004). However, most mutations identified in such analyses appear to be relatively rare and are not shared across multiple cancers (Beroukhim et al., 2010). Although such mutations may be grouped within large functional pathways,

predominant therapeutic targets have yet to emerge for the majority of epithelial cancers, which constitute ~85% of all cancers. Thus, although large cancer genome sequencing projects are underway for many different cancer types, the identification of promising drug targets may ultimately require detailed biological insights to complement mutational analyses.

Given that numerous mutations in human cancers occur at low frequency, it is essential to distinguish the mutations that constitute essential "drivers" of tumorigenesis from those that are "passengers" without functional significance (for more on driver and passenger mutations, see Ashworth et al., 2011 in this issue). Of course, the response of cancers to a targeted inhibitor is ultimately the most compelling evidence for the relevance of a given target. For example, the dramatic clinical response to EGFR inhibitors by patients whose lung cancers harbor an activating EGFR mutation clearly demonstrates that these EGFR mutations are not simply bystanders of mutational load, but rather drivers of malignant proliferation (Lynch et al., 2004; Paez et al., 2004). In fact, the EGFR inhibitors trigger massive tumor apoptosis in these lung cancers, suggesting that these cells are "addicted" to the EGFR signaling pathway for survival.

The concept of "oncogene addiction" emphasizes the critical role played by the "wiring" of signaling pathways in a cancer cell; specifically, a cancer cell's signaling networks may depend on a single mutationally activated driving pathway that, when disrupted, triggers cell death (in effect, its "Achilles heel") (Weinstein, 2002). However, identifying such extraordinary drug targets and translating these into effective therapy is not always straightforward, as illustrated by the development of B-RAF inhibitors against melanoma. The failure of sorafenib, an inhibitor of B-RAF, in clinical trials of metastatic melanoma challenged the validity of V600E-B-RAF as a good drug target until PLX4032, a more potent and specific inhibitor against V600E B-RAF, showed dramatic efficacy (Eisen et al., 2006; Flaherty et al., 2010). It is in this setting that preclinical modeling of oncogene addiction, using large panels of cancer-derived cell lines, is emerging as

an effective approach to validating both target and inhibitor. Individual cell lines have limited predictive value. However, when they are studied in large aggregates, they recapitulate much of the genetic heterogeneity of human cancers, as well as their specific hypersensitivity profiles to inhibitors of EGFR, ALK, MET, FGFR, and B-RAF (McDermott et al., 2007).

Preclinical efforts at target identification and validation have also relied on strategies that suppress gene expression using interference RNA (RNAi), although clinically validated targets have not yet emerged from such genome-wide screens. Instead of matching a single compound against the entire genetic heterogeneity of human cancers, RNAi screens have typically focused on screening the entire kinome against a selected cell type. Important applications of this strategy include: searching for new targets for which RNAi-induced knockdown may reverse acquired resistance to first-line targeted inhibitors, and screens for "synthetic lethality," in which a target only becomes essential within a specific genetic context (Berns et al., 2004). For instance, the clinical effectiveness of poly-ADP ribose polymerase (PARP) inhibitors in breast and ovarian cancers with BRCA gene mutations is attributable to their inhibition of a parallel DNA repair pathway that becomes critical for cell viability only in the setting of BRCA gene inactivation. Finally, both RNAi and drug screens are essential to model effective combinations of agents required to block interdependent cellular pathways implicated in intrinsic and acquired drug resistance. Drug resistance has been attributed to numerous mechanisms, including the appearance of additional or "second site" mutations within drug-binding sites (Kobayashi et al., 2005; Pao et al., 2005; Talpaz et al., 2006; Zhou et al., 2009), the activation of parallel signaling pathways (Engelman et al., 2007), or even the induction of drug resistance quiescence states (Sharma et al., 2010). To counter all these mechanisms requires an even better understanding of the wiring diagram of cancer cells.

### Challenging Medicinal Chemistry to Design New Classes of Inhibitors

The history of targeted cancer therapy is now intricately linked with the success of

imatinib (Gleevec) to treat chronic myeloid leukemia (CML). The prototype kinase inhibitor imatinib blocks the ABL kinase, which is activated in the BCR-ABL chimeric fusion. From its first identification as the Philadelphia chromosome (Nowell and Hungerford, 1960) to its molecular characterization as the sole genetic driver of CML, BCR-ABL is the perfect drug target (Druker, 2004). The development of imatinib was the result of a structure-activity relationship-guided optimization of a phenylaminopyrimidine lead compound that was originally identified as an inhibitor of protein kinase C (Capdeville et al., 2002). Indeed, imatinib's eventual application as a BCR-ABL inhibitor owes much to serendipity, intuition, and the dedication of individual scientists.

The success of imatinib resolved numerous concerns about using ATP-mimics as kinase inhibitors. It demonstrated that these inhibitors can compete effectively for binding with the abundant pool of cellular ATP and that they can achieve selectivity despite closely related catalytic pockets in other kinases. In addition, it proved that a class of signaling molecules with broad expression patterns in multiple normal tissues could indeed be successful drug targets, given the exceptional sensitivity of genetically defined subsets of cancer. Imatinib was initially aimed at suppressing PDGFR signaling that is implicated in the proliferation of coronary endothelial cells; its fortuitous "off-target" effects on the ABL and c-KIT kinases launched a revolution in cancer therapy, and its anti-PDGFR effects ultimately found their place in the treatment of rare leukemias with PDGFR-dependent translocations (Druker, 2004). The admittedly serendipitous saga of imatinib spawned a broad and systematic effort throughout the pharmaceutical industry that is now poised to radically change the essential tools for cancer treatment.

Tremendous investment in medicinal chemistry, primarily from the pharmaceutical sector, has resulted in the development of numerous efficient strategies for designing potent and selective kinase inhibitors. For example, PLX4720 was developed by an innovative approach called "fragment-based screening," in which small molecular fragments with low affinity for V600E B-RAF were identi-

fied and then optimized using rational structure-guided drug design (Tsai et al., 2008). In addition, structural biology of kinases has become an integral part of drug optimization, with large-scale initiatives such as the Structural Genomics Consortium providing an increasingly large fraction of new depositions (Marsden and Knapp, 2008).

Nonetheless, serendipity still plays a major part in successful drug discovery. For example, crizotinib was originally designed as a c-MET inhibitor, but its fortuitous off-target activity against ALK drove its efficacy in EML4-ALK-dependent lung cancer (Kwak et al., 2010). Significant developmental hurdles still exist for kinase inhibitors, including the high interspecies variation in their toxic side effects and the difficulty in deciphering which of these are on-target versus off-target effects of the inhibitor. Despite their large investment, commercial enterprises have been reluctant to develop inhibitors against kinases that have not already been subject to intense biological investigation. This has resulted in an abundance of drugs against a relatively small number of well-validated targets but a dearth of inhibitors with sufficient selectivity to validate the vast majority of the kinome pharmacologically (Fedorov et al., 2010). Although there are remarkable examples of how broadly active kinase inhibitors, such as sunitinib, may be well tolerated, recent trends have focused more on inhibition of specific mutant targets. These include targeting the specific B-RAF mutant V600E in melanoma, mutationally activated forms of EGFR in lung cancer, and imatinib-resistant T315I-BCR-ABL in CML (Flaherty et al., 2010; Zhou et al., 2009).

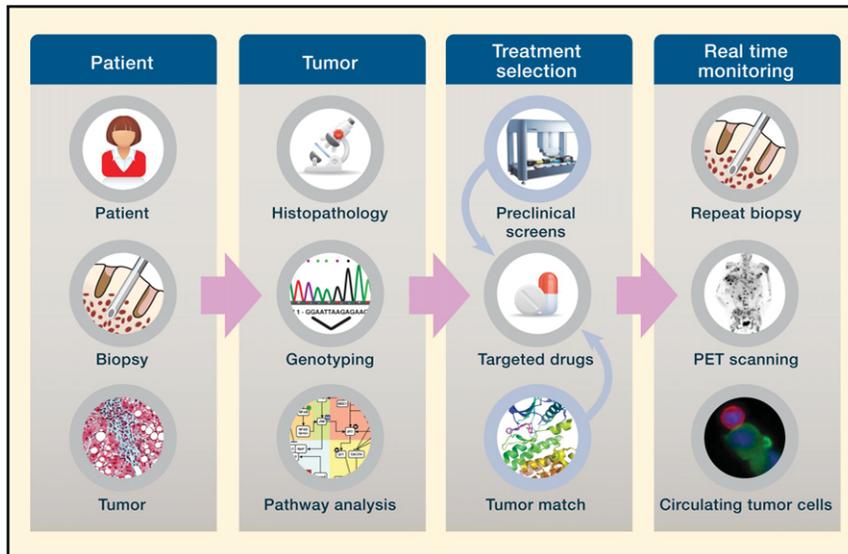
Although many potential cancer therapies remain in the pool of untargeted kinases, new classes of cancer drugs on the horizon are reaching outside of the kinome to target modulators of protein turnover and folding, phosphatases, chromatin-modifying enzymes, and regulators of cellular metabolism. Transcription factors and adaptor proteins with relatively large interaction surfaces remain a major challenge for drug design. From a biological standpoint, tumor suppressor genes, which commonly sustain loss-of-function mutations in cancer, are only druggable through pathway components that display

synthetic lethality. Moreover, the most common villains of cancer cells, mutations in the oncogene K-RAS and the tumor suppressor p53, have remained recalcitrant to direct targeting approaches. Many of these targets will require chemists to invent entirely new classes of compounds or develop novel approaches for modulating their activity.

Targeted inhibitors stand to benefit from integrated development within the appropriate biological and genetic contexts. Preclinical screens need to test inhibition of an oncogenic target within the appropriate cancer cells, in which the targeted gene is biologically relevant. When possible, biomarkers that identify the responsive subset of cancers should be selected during early preclinical development, rather than awaiting retrospective analyses of clinical trials. As with cancer cell line studies, animal models used to optimize drug dosing and toxicity profiles are most informative if they recapitulate the genetic context of the relevant subset of human cancer. These approaches mark a departure from classical drug testing paradigms that have typically relied on testing a small number of nonannotated cancer cell lines and xenograft mouse models matched to tissue type, rather than underlying genetic lesion. However, the increasing cost of testing large numbers of new agents that may be highly selective for subsets of cancer necessitates detailed information to match the drug, disease subtype, and biomarker before entry into clinical trials.

### Redesigning Cancer Clinical Trials: Genotype First, Monitor in Real Time

There is a growing consensus that traditional designs of cancer clinical trial are not well suited to address the current needs of drug development. These clinical trials typically begin with a phase one, in which the maximally tolerated dose of a new drug is defined by increasing dosage in a small number of patients (who have failed standard therapies and are willing to be treated with a new untested compound with uncertain benefits). This is followed by a phase two trial in a larger patient cohort with a specific cancer type (without regard to the cancer's genotype or biomarkers); this phase aims at defining efficacy at the



**Figure 1. Matching Each Cancer with Individually Targeted Therapy: Steps toward Implementing a New Clinical Strategy**

In genotype-directed cancer therapy, the malignant tumor specimen is subjected to detailed biomarker analysis, including immunohistochemical as well as DNA-based markers. These biomarkers are interpreted within the relevant signaling pathway to identify a potential vulnerability for the cancer. Selection of an appropriate therapy (often oral agents of limited toxicity) is dependent upon prior preclinical validation of drug/genotype pairing and detailed analysis of drug/target interactions. Early drug response and development of acquired resistance are monitored by repeat biopsy of the tumor or, noninvasively, by functional imaging or circulating tumor cell analysis.

appropriate drug dose. Eventually, if clinical activity has been observed in the phase two trial, a large randomized phase three trial is conducted in which the new drug, either alone or in combination with currently used drugs, is directly compared with the standard regimen. If successful, phase three leads to FDA registration for the new drug.

This strategy has resulted in a high failure rate, and even in studies with a positive outcome, the benefits are mostly incremental in nonselected patient populations. Besides time and expense, the underlying premise of such trial designs is not suited to the new world of targeted cancer therapy. In particular, defining the maximal tolerated dose for selective inhibitors in patients whose tumor does not carry biomarkers predictive of response for that inhibitor is far less relevant than preselecting tumors that are likely to respond to the inhibitor and defining the therapeutic index within these relevant cases. Traditional multi-institutional clinical trials have relied on enrolling large numbers of unselected patients, followed by retrospective analysis of tumor markers in a fraction of

cases enrolled. Thus, they do not readily lend themselves to detailed pretreatment genotyping and may be underpowered to assess drug effectiveness against rare tumor subsets. Given the early and dramatic responses in genotype-selected cancers, the need and even the ethics of large clinical trials—such as the one randomizing V600E-positive melanoma patients between highly effective PLX4032 and minimally effective cytotoxic chemotherapy—is being vigorously debated. For all of these reasons, a new model is emerging, one with an extended phase one that seeks from the beginning to build upon preclinical information and enrich trial populations for the genetic marker of interest (Figure 1).

Changes in both method and expected outcome do not come easily, either for physicians or for pharmaceutical companies. The fragmentation of a market among many subtypes of cancer, each requiring a different treatment, means the end of blockbuster compounds for companies. However, it is worth noting that a highly effective drug such as imatinib, administered daily for many years to patients throughout the world, can still

provide major financial returns to its manufacturer. For clinicians, targeted cancer therapy requires breaking down traditional barriers in clinical medicine. Phase one and novel drug testing teams are no longer focused exclusively on patients with advanced refractory disease, irrespective of tumor characteristics. Instead, early drug testing is being integrated into the initial care of patients, with the expressed goal of trying to match the drug under study with specific subsets of cancers, within a timeline that may derive real benefit for patients participating in such trials.

Most importantly, the pathologist is now in the critical position of going beyond the standard histopathological diagnosis of cancer, providing the oncologist with the key biomarkers that direct appropriate targeted therapy. In some cases, this may involve prescreening tumors to enable a successful clinical trial. For example, even for a common cancer, such as non-small cell lung cancer, genotype-drug combinations require testing a large number of cases to enrich for EGFR mutations (10% of all cases), EML4-ALK rearrangements (4%), or MET, HER2, and B-RAF abnormalities (1%–2% each). In the landmark clinical trial of crizotinib for EML4-ALK-translocated lung cancer, 1500 patients were prescreened to identify 82 cases with the translocation. These patients were then selected for treatment with crizotinib, producing benefit in 90% of cases (57% responses and 33% stable disease) (Kwak et al., 2010).

Despite dramatic initial responses in genotype-selected clinical trials of epithelial cancers and melanoma, acquired resistance to targeted agents has emerged as a primary challenge. We are beginning only now to understand the underlying mechanisms of this resistance. Some tumors acquire second-site mutations in the target, which interferes with drug binding (Kobayashi et al., 2005; Pao et al., 2005; Talpaz et al., 2006), whereas other tumors evolve alternative signaling pathways, which compensate for the disrupted oncogenic signal (Chandralapaty et al., 2011; O'Reilly et al., 2006; Tabernero et al., 2008). Achieving long-lasting control of malignancy in this setting may require sequential treatments while monitoring the evolution of tumor genotypes during therapy.

In some cases, signaling feedback loops immediately activate alternative pathways, which must be suppressed at the outset by using a combination of targeted therapies. For example, the initial observation that mammalian target of rapamycin (mTOR) inhibitors have limited anticancer activity in the clinic resulted in the identification of compensatory activation of insulin growth factor 1 receptor (IGF-1R) when mTOR is blocked (O'Reilly et al., 2006; Tabernero et al., 2008). This led to a phase one clinical study in which both mTOR and IGF-1R are inhibited. Indeed, this combination treatment has shown notable clinical efficacy in breast cancer (Di Cosimo et al., 2010). Similarly, the combined use of inhibitors against the two critically important PI3K and ERK pathways has shown remarkable activity in preclinical models of cells harboring K-RAS activating mutations (Engelman et al., 2008). These and other approaches that rationally combine therapies are currently being explored in clinical trials. Though very promising, these trials may elicit a number of regulatory challenges because they typically involve the combined use of investigational agents, each of which may have a separate path to regulatory approval.

Innovative clinical trial platforms are needed to address the opportunities and challenges posed by the array of targeted agents and their appropriate clinical deployment. In addition to biomarkers for preselection of responsive cancers, early markers of clinical benefit are needed to rapidly assess effectiveness and inform ongoing monitoring of clinical trials. The most promising approaches include: repeat biopsies of tumor sites to measure the impact of new therapies on the degree of target inhibition; functional tumor imaging through positron emissions tomography (PET) or functional magnetic resonance imaging (fMRI); and molecular analysis of both genotypes and signaling pathways within circulating tumor cells in the blood (Maheswaran et al., 2008). Together, these approaches may provide early warnings of acquired drug resistance and identify specific resistance pathways that may direct the choice of second line therapy (Figure 1).

Early tumor interrogation may also result in a dynamic “real-time” measurement of response or failure to the drug

under study, allowing for rapid adjustments within clinical trial settings. For example, in breast cancer, the testing of new agents immediately prior to surgery (known as “neo-adjuvant therapy”) allows for monitoring of tumor response at the time of surgical resection. Compared to the large number of patients and prolonged clinical follow-up required for traditional postsurgery (or “adjuvant”) trials in breast cancer, neo-adjuvant trials allow for rapid testing of multiple drug combinations within small and affordable trials. These new designs rely upon surrogate markers, such as changes in proliferation or apoptosis markers, or even absence of visible tumor at the time of surgery, which will then be correlated with endpoints of clinical benefit, such as time free of disease or improved overall survival.

### The Next Steps in the War on Cancer

The War on Cancer has not been lost, nor is it won. Instead, we are now at a turning point, where fundamental knowledge gathered over the past 40 years can, for the first time, be applied directly to the care of patients with cancer. Early results in selected types of cancer are exciting in themselves and in what they forecast for the future of cancer treatment. However, the rush for translational applications of these initial breakthroughs should not be interpreted as evidence that we now know all we need to know about the pathogenesis, progression, and vulnerabilities of cancer. Far from it, basic research in cancer biology is progressing as never before. New and unpredicted discoveries continue to shed light on fundamental mechanisms, from new insights into long-studied genes like *p53*, to advances that are transforming the fields of cancer metabolism, chromatin regulation, and noncoding RNA biology. There is still much to discover, and continued support for basic research is essential to continue the progress in the War on Cancer.

Although the early successes in translating scientific discoveries into targeted treatments are full of promise, they also point to important future challenges. The development of resistance by cancer cells, even to the most dramatically effective therapies, underscores the need for a detailed understanding of these resis-

tance pathways. In addition, we need tools to monitor the emergence of resistance pathways in “real time” and new generations of second line drugs to suppress them. For the majority of cancers, we still have not identified molecular drivers as targets for treatment, and common drivers, such as K-RAS, are currently “undruggable.” Both of these facts point to the need for further analyses of genetic and epigenetic changes that drive different cancers, as well as the need for innovative approaches to drug design. Finally, “smaller and smarter” clinical trials are necessary to rapidly capitalize on credible therapeutic signals and apply these to the treatment of early cancers, for which major improvements in long-term survival may be expected (Smith et al., 2007).

Ironically, at this time of unparalleled promise in cancer biology, the biggest risk to progress may be economic. Shrinking support for basic research threatens the very foundation of the success that we are now witnessing in the clinic. Uncertainties in healthcare delivery models may emphasize more uniform and economical application of the “standard of care,” prompting the pharmaceutical industry and medical community to shy away from developing and testing innovative and initially expensive new therapies. Public support and enthusiasm are not enhanced by the application of costly targeted therapies in a nontargeted setting, where the measurable clinical impact is often marginal.

Despite these immediate and serious concerns, we remain optimistic that the next 10 years will witness unprecedented progress in the fight against cancer, both in terms of our fundamental understanding and direct clinical applications. The extraordinary complexity of pathways driving malignant proliferation may be daunting, but the clinical impact of a focused strategy targeted at susceptible nodes within a cancer are compelling. This is a time of exceptional promise and a great reward for cancer researchers. It comes none too soon for patients with cancer.

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## REFERENCES

- Ashworth, A., Lord, C.J., and Reis-Filho, J.S. (2011). *Cell* 145, this issue, 30–38.
- Bailar, J.C., III, and Gornik, H.L. (1997). *N. Engl. J. Med.* 336, 1569–1574.
- Baselga, J., Bradbury, I., Eidtmann, H., Di Cosimo, S., Aura, C., De Azambuja, E., Gomez, H., Dinh, P., Fauria, K., Van Dooren, V., et al. (2010). San Antonio Breast Cancer Symposium. Abstract S3-3. Presented December 10, 2010.
- Berns, K., Hijmans, E.M., Mullenders, J., Brummelkamp, T.R., Velds, A., Heimerikx, M., Kerkhoven, R.M., Madiredjo, M., Nijkamp, W., Weigelt, B., et al. (2004). *Nature* 428, 431–437.
- Beroukhi, R., Mermel, C.H., Porter, D., Wei, G., Raychaudhuri, S., Donovan, J., Barretina, J., Boehm, J.S., Dobson, J., Urashima, M., et al. (2010). *Nature* 463, 899–905.
- Capdeville, R., Buchdunger, E., Zimmermann, J., and Matter, A. (2002). *Nat. Rev. Drug Discov.* 1, 493–502.
- Chandarlapaty, S., Sawai, A., Scaltriti, M., Rodrik-Outmezguine, V., Grbovic-Huezo, O., Serra, V., Majumder, P.K., Baselga, J., and Rosen, N. (2011). *Cancer Cell* 19, 58–71.
- Davies, H., Bignell, G.R., Cox, C., Stephens, P., Edkins, S., Clegg, S., Teague, J., Woffendin, H., Garnett, M.J., Bottomley, W., et al. (2002). *Nature* 417, 949–954.
- Di Cosimo, S., Bendell, J.C., Cervantes-Ruiperez, A., Roda, D., Prudkin, L., Stein, M.N., Leighton-Swayze, A., Song, Y., Ebbinghaus, S., and Baselga, J. (2010). ASCO Meeting Abstracts 28, 3008.
- Druker, B.J. (2004). *Adv. Cancer Res.* 91, 1–30.
- Eisen, T., Ahmad, T., Flaherty, K.T., Gore, M., Kaye, S., Marais, R., Gibbens, I., Hackett, S., James, M., Schuchter, L.M., et al. (2006). *Br. J. Cancer* 95, 581–586.
- Engelman, J.A., Zejnullahu, K., Mitsudomi, T., Song, Y., Hyland, C., Park, J.O., Lindeman, N., Gale, C.M., Zhao, X., Christensen, J., et al. (2007). *Science* 316, 1039–1043.
- Engelmaras, J.A., Chen, L., Tan, X., Crosby, K., Guimaraes, A.R., Upadhyay, R., Maira, M., McNamara, K., Perera, S.A., Song, Y., et al. (2008). *Nat. Med.* 14, 1351–1356.
- Fedorov, O., Müller, S., and Knapp, S. (2010). *Nat. Chem. Biol.* 6, 166–169.
- Flaherty, K.T., Puzanov, I., Kim, K.B., Ribas, A., McArthur, G.A., Sosman, J.A., O'Dwyer, P.J., Lee, R.J., Grippo, J.F., Nolop, K., and Chapman, P.B. (2010). *N. Engl. J. Med.* 363, 809–819.
- Furman, R.R., Byrd, J.C., Flinn, I.W., Coutre, S.E., Benson, D.M., Jr., Brown, J.R., Kahl, B.S., Wagner-Johnston, N.D., Giese, N.A., and Yu, A.S. (2010). ASCO Meeting Abstracts 28, 3032.
- Kobayashi, S., Boggon, T.J., Dayaram, T., Jänne, P.A., Kocher, O., Meyerson, M., Johnson, B.E., Eck, M.J., Tenen, D.G., and Halmos, B. (2005). *N. Engl. J. Med.* 352, 786–792.
- Kwak, E.L., Bang, Y.J., Camidge, D.R., Shaw, A.T., Solomon, B., Maki, R.G., Ou, S.H., Dezube, B.J., Jänne, P.A., Costa, D.B., et al. (2010). *N. Engl. J. Med.* 363, 1693–1703.
- Leaf, C. (2004). *Fortune Magazine*. March 22 issue, 365076.
- Lynch, T.J., Bell, D.W., Sordella, R., Gurubhagavata, S., Okimoto, R.A., Brannigan, B.W., Harris, P.L., Haserlat, S.M., Supko, J.G., Haluska, F.G., et al. (2004). *N. Engl. J. Med.* 350, 2129–2139.
- Maheswaran, S., Sequist, L.V., Nagrath, S., Ullkus, L., Brannigan, B., Collura, C.V., Inserra, E., Diederichs, S., Iafrate, A.J., Bell, D.W., et al. (2008). *N. Engl. J. Med.* 359, 366–377.
- Marsden, B.D., and Knapp, S. (2008). *Curr. Opin. Chem. Biol.* 12, 40–45.
- McDermott, U., Sharma, S.V., Dowell, L., Greninger, P., Montagut, C., Lamb, J., Archibald, H., Raudales, R., Tam, A., Lee, D., et al. (2007). *Proc. Natl. Acad. Sci. USA* 104, 19936–19941.
- Mok, T.S., Wu, Y.L., Thongprasert, S., Yang, C.H., Chu, D.T., Saijo, N., Sunpaweravong, P., Han, B., Margono, B., Ichinose, Y., et al. (2009). *N. Engl. J. Med.* 361, 947–957.
- Nowell, P., and Hungerford, D. (1960). *Science* 132, 1497.
- O'Day, S., Hodi, F.S., McDermott, D.F., Weber, R.W., Sosman, J.A., Haanen, J.B., Zhu, X., Yellin, M.J., Hoos, A., and Urba, W.J. (2010). ASCO Meeting Abstracts 28, 4.
- O'Reilly, K.E., Rojo, F., She, Q.-B., Solit, D., Mills, G.B., Smith, D., Lane, H., Hofmann, F., Hicklin, D.J., Ludwig, D.L., et al. (2006). *Cancer Res.* 66, 1500–1508.
- Paez, J.G., Jänne, P.A., Lee, J.C., Tracy, S., Greulich, H., Gabriel, S., Herman, P., Kaye, F.J., Lindeman, N., Boggon, T.J., et al. (2004). *Science* 304, 1497–1500.
- Pao, W., Miller, V.A., Politi, K.A., Riely, G.J., Somwar, R., Zakowski, M.F., Kris, M.G., and Varmus, H. (2005). *PLoS Med.* 2, e73.
- Samuels, Y., Wang, Z., Bardelli, A., Silliman, N., Ptak, J., Szabo, S., Yan, H., Gazdar, A., Powell, S.M., Riggins, G.J., et al. (2004). *Science* 304, 554.
- Sharma, S.V., Lee, D.Y., Li, B., Quinlan, M.P., Takahashi, F., Maheswaran, S., McDermott, U., Azizian, N., Zou, L., Fischbach, M.A., et al. (2010). *Cell* 141, 69–80.
- Smith, I., Procter, M., Gelber, R.D., Guillaume, S., Feyereislova, A., Dowsett, M., Goldhirsch, A., Untch, M., Mariani, G., Baselga, J., et al. (2007). *Lancet* 369, 29–36.
- Soda, M., Choi, Y.L., Enomoto, M., Takada, S., Yamashita, Y., Ishikawa, S., Fujiwara, S., Watanabe, H., Kurashina, K., Hatanaka, H., et al. (2007). *Nature* 448, 561–566.
- Taberero, J., Rojo, F., Calvo, E., Burris, H., Judson, I., Hazell, K., Martinelli, E., Ramon y Cajal, S., Jones, S., Vidal, L., et al. (2008). *J. Clin. Oncol.* 26, 1603–1610.
- Talpa, M., Shah, N.P., Kantarjian, H., Donato, N., Nicoll, J., Paquette, R., Cortes, J., O'Brien, S., Nicaise, C., Bleickardt, E., et al. (2006). *N. Engl. J. Med.* 354, 2531–2541.
- Tsai, J., Lee, J.T., Wang, W., Zhang, J., Cho, H., Mamo, S., Bremer, R., Gillette, S., Kong, J., Haass, N.K., et al. (2008). *Proc. Natl. Acad. Sci. USA* 105, 3041–3046.
- Verstovsek, S., Kantarjian, H., Mesa, R.A., Pardanani, A.D., Cortes-Franco, J., Thomas, D.A., Estrov, Z., Fridman, J.S., Bradley, E.C., Erickson-Viitanen, S., et al. (2010). *N. Engl. J. Med.* 363, 1117–1127.
- Weinstein, I.B. (2002). *Cancer Sci.* 297, 63–64.
- Zhou, W., Ercan, D., Chen, L., Yun, C.H., Li, D., Capelletti, M., Cortot, A.B., Chirieac, L., Iacob, R.E., Padera, R., et al. (2009). *Nature* 462, 1070–1074.