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Principles of Kinase Inhibitor Therapy for Solid Tumors

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STRUCTURED ABSTRACT

Objective—We aimed to identify key principles of targeted therapy of protein kinases and their application to the management of solid tumors.

Background—Concurrent advances in tumor genomic analysis and molecular inhibitor development have dramatically impacted the diagnosis and treatment of solid tumors and common themes regarding the use of kinase inhibitors are developing.

Methods—The list of kinase inhibitors that have been approved by the FDA was reviewed and articles related to the agents were searched in the PubMed database up until December 2015. We included pivotal, randomized, controlled phase 2 and 3 trials as well as pertinent preclinical studies.

Results—Small molecule inhibitors targeted against driver kinases, overactive in selected subsets of solid tumors, elicit improved response rates and survival compared with standard chemotherapy. Disease control has been proven in the metastatic and, to a limited extent, the adjuvant setting. However, tumor eradication is rare, and duration of treatment response is limited by the development of drug resistance.

Conclusions—Kinase inhibitors induce response in diverse types of solid tumors. While the agents are often effective in defined molecular subsets, cure is rare and resistance is common. This broad review provides rationale for further investigation of multimodality therapy combining kinase inhibitors with additional systemic and local therapies, including surgery.

Over the past 15 years, the application of kinase inhibitors has revolutionized the therapy of cancer. The ability to attack specific molecular defects in solid tumors has resulted in personalized and rational tumor therapy that goes beyond the less precise approach of using cytotoxic chemotherapy to target DNA and the cell cycle. Here, we define the basic principles of kinase inhibition using small molecule inhibitors, which share the suffix “-ib.” Consideration is given to the mechanism of action, patient selection, radiologic assessment of tumor response, efficacy in the metastatic versus adjuvant setting, acquired resistance to therapy, and multimodality therapy. Examples are provided to illustrate the major concepts. Comprehensive reviews of kinase inhibitors are available elsewhere [1–3].

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Mechanism of Action

Advances in tumor genomic analysis and drug development have dramatically impacted our management of solid tumors as diverse as gastrointestinal stromal tumor (GIST), melanoma, non-small cell lung cancer (NSCLC), medullary thyroid cancer, renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), breast cancer, and pancreatic neuroendocrine tumor (PNET). Such tumors are associated with abnormal activation of protein kinases. Kinases are a class of tightly regulated cellular enzymes that catalyze the transfer of phosphate residues from ATP molecules to specific protein substrates, thereby turning on and off key signaling pathways involved in cell growth, survival, and, when dysregulated, malignancy. To date, more than 20 small molecule inhibitors have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced solid tumors harboring activating mutations, amplifications, or overexpression of oncogenes encoding “druggable” kinases involved in neoplastic cell signaling (Table 1) [2, 3]. These novel agents are low molecular weight, orally bioavailable drugs that traverse the cell membrane, bind selectively to target kinases, and interfere with ATP binding and substrate phosphorylation (Fig. 1) [2].

There are about 500 protein kinases in humans [4]. Kinase targets within the cancer cell can be divided into two broad biologic categories: (1) receptor tyrosine kinases (RTKs), which are located on the cell surface and normally transduce extracellular ligand or growth factor signals into the cell, and (2) intracellular serine/threonine or dual specificity tyrosine/threonine kinases, which serve as downstream mediators of growth factor receptors. RTKs include epidermal growth factor receptor (EGFR), anaplastic lymphoma receptor tyrosine kinase (ALK), stem cell factor receptor (KIT), platelet derived growth factor receptor (PDGFR), rearranged during transfection (RET), human epidermal growth factor receptor 2 (HER2), and hepatocyte growth factor receptor (MET). Meanwhile, the second category includes BRAF, MEK, and mammalian target of rapamycin (mTOR). Most kinase targets converge on one or more of the following downstream signaling pathways: PI3K/AKT/mTOR, JAK/STAT, PLC/PKC, and RAS/RAF/MEK/ERK (ERK is a member of the mitogen-activated protein kinase [MAPK] family) (Fig. 1) [1, 5]. The end result is coordinated phosphorylation and nuclear translocation of transcription factor proteins, which together regulate gene expression and the ultimate balance of proliferative and death signals within the cell. Despite the complexity of these intracellular pathways, kinase inhibitors have achieved impressive tumor responses, most notably in patients whose tumors are presumed to be oncogene-addicted and thus highly dependent on a single driving kinase [6].

Patient Selection – New Tumor Subsets Based on Molecular Classification

As the list of clinically available kinase inhibitors grows, it is clear that molecular classification is necessary to optimize their application to selected patients. In the current genomic era, tumors are increasingly being classified not only by traditional anatomic and histologic categories, but also by molecular subtypes, which have varying sensitivity to targeted agents. For example, NSCLC adenocarcinoma can now be subdivided into at least 10 different genotypes. The most common genetic subtype of NSCLC is a *KRAS* mutation [7]. *KRAS* encodes a GTPase involved in signal transduction, and there is intense investigation to develop effective inhibitors to treat *KRAS*-mutated NSCLC, colorectal

cancer, pancreas cancer, and other tumors. Approximately 10–15% of NSCLC instead harbor an activating mutation in the *EGFR* oncogene [8, 9] (Fig. 2). Initial studies demonstrated low objective response rates to targeted inhibitors in the general NSCLC population, but subsequent phase 3 clinical trials in selected NSCLC subgroups showed improved survival. A large randomized, controlled phase 3 trial was enriched for patients with *EGFR* mutations and compared the *EGFR* inhibitor gefitinib against carboplatin-paclitaxel chemotherapy [10]. Among patients treated with gefitinib, those with *EGFR* mutations had a higher objective response rate than those without mutations (71 vs. 1%). Mutation-positive patients had better progression-free survival (PFS) on gefitinib compared with standard chemotherapy (hazard ratio for progression, HR, 0.48, 95% confidence interval 0.36 to 0.64). Notably, those patients without *EGFR* mutations had worse outcomes when treated with gefitinib rather than chemotherapy (HR 2.85, 95% confidence interval 2.05 to 3.98) [10]. In another phase 3 trial of patients with NSCLC containing an *EGFR* mutation, the *EGFR* inhibitor erlotinib achieved similar improvement in objective response rate and PFS compared with standard cytotoxic chemotherapy (9.7 vs. 5.2 months) [11]. Interestingly, patients with NSCLC and an *EGFR* mutation tend to be female, Asian, nonsmokers [9]. Meanwhile, another 1–7% of NSCLC contain a chromosomal rearrangement involving the *ALK* oncogene [8, 12]. In these patients, a phase 3 trial of the *ALK* inhibitor crizotinib demonstrated a 65% objective response rate and improved PFS (7.7 vs. 3 months) compared with standard chemotherapy [13].

Molecular classification has similarly impacted the management of other cancers, such as melanoma and GIST. Tumor genotyping now allows for the selection of patients with *BRAF*-mutated melanoma who will benefit from *BRAF* inhibitors, such as vemurafenib [14, 15]. Furthermore, the presence and specific type of *KIT* mutation in GIST correlates with imatinib response in metastatic disease [16]. In a phase 3 trial of imatinib in patients with advanced GIST, patients with *KIT* exon 11 mutations had significantly improved overall survival (OS), objective response rate, and time to tumor progression, compared to patients with *KIT* exon 9 mutations or wild-type tumors, regardless of imatinib dose [16]. Overall, these results underscore the importance of utilizing molecular classification to refine patient and tumor selection for targeted therapy.

For the majority of solid tumors other than NSCLC, melanoma, and GIST, genomic heterogeneity and rare frequencies of actionable mutations make it difficult to stratify patients by tumor genotype and test new targeted agents. To overcome such obstacles, “basket” or “bucket” clinical trials, such as the National Cancer Institute’s multicenter Molecular Analysis for Therapy Choice (NCI-MATCH, NCT02465060), seek to test molecular therapies in patients based solely on tumor genomic alterations rather than histology or anatomic site [17]. Such trials have the potential to identify relevant therapeutic targets across diverse tumor types. New “umbrella” trials, such as the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST), are designed to test various targeted agents in patients based on genomic subtype within a given tumor type (e.g., NSCLC harboring an *EGFR* mutation or *ALK* gene rearrangement) [18]. Overall, such trials may change the paradigm of cancer classification and hasten drug development.

Radiologic Assessment of Tumor Response - Beyond RECIST

Cancer therapies have historically been assessed by the reduction in tumor size as determined by radiologic imaging. Initially, the World Health Organization (WHO) criteria were used based on bi-dimensional measurements of target lesions [19]. Currently, the Response Evaluation Criteria In Solid Tumors (RECIST [20], RECIST 1.1 [21]) are employed, which use the sum of the single longest diameter of up to 5 target lesions to define partial response (PR, 30% decrease in the sum of diameters), progressive disease (PD, 20% increase in the sum of diameters, or the appearance of new lesions), and stable disease (SD, neither PR nor PD). Although radiologic tumor regression correlates with clinical response to cytotoxic chemotherapy, RECIST criteria may underestimate the efficacy of kinase inhibitors. Many targeted therapies actually fail to induce tumor shrinkage but nevertheless cause tumor destruction or slow disease progression, indicating the need for better radiologic correlates of drug efficacy. For example, sorafenib is a multi-kinase inhibitor that inhibits RAF and the downstream ERK/MAPK signaling pathway that is implicated in hepatocellular carcinoma (HCC). In a phase 2 trial of sorafenib in 137 patients with inoperable HCC, objective response rate by modified WHO criteria was low, with only 8% of patients achieving minor or partial response (25% decrease in the sum of bi-dimensional measurements of target lesions) [22]. Nevertheless, some tumors that increased in size had increased central necrosis on intravenous contrast-enhanced CT, suggesting better drug efficacy than estimated by RECIST (Fig. 3) [22]. In a phase 3 randomized, placebo-controlled trial of sorafenib in patients with advanced HCC, the objective response rate was similarly low by RECIST (no complete responses [CR] and 2% PR), but 71% of sorafenib-treated patients demonstrated SD, and sorafenib delayed the time to tumor progression and elicited a modest improvement in overall survival (OS, 10.7 vs. 7.9 months), suggesting that RECIST underestimated drug efficacy [23]. These results may simply reflect tumoristatic rather than tumoricidal effects of some kinase inhibitors like sorafenib. However, it is also possible that alternative radiologic criteria are required to measure drug response and estimate survival benefit. The modified RECIST assessment for HCC (mRECIST), proposed by the American Association for the Study of Liver Diseases, incorporates treatment-induced tumor necrosis into response definitions, including measurements of only the viable, arterially-enhancing regions of target lesions on contrast-enhanced axial imaging [24]. Preliminary studies suggest improved correlation of mRECIST over purely size-based imaging criteria with clinical outcomes in HCC patients on targeted therapy [25].

Decreased tumor attenuation on contrast-enhanced CT has similarly been investigated as a marker of drug effect in other cancers such as GIST and RCC. For example, the Choi criteria for GIST incorporate both tumor size by RECIST and tumor density by Hounsfield units (HU). After imatinib therapy in GIST, Choi criteria outperform RECIST as they better correlate with tumor response, metabolic activity on ¹⁸fluoro-deoxyglucose positron emission tomography (FDG-PET), and PFS [26]. The Size and Attenuation in CT (SACT) criteria, which combine unidimensional tumor measurements and volumetric mean tumor attenuation by HU, have similarly been shown to predict RCC response to sorafenib or sunitinib better than RECIST, mRECIST, or Choi criteria [27]. Newer imaging technologies,

such as dynamic contrast-enhanced (DCE) CT, MRI, and ultrasound, theoretically offer the benefit of assessing tumor vascularity and perfusion, but remain to be validated in the clinical setting [28]. Ultimately, different combinations of tumor size, viability, and perfusion may be required to accurately assess different tumor types in their response to kinase inhibitors. Optimal assessment of drug efficacy will be critical to patient selection in the clinic, as well as the evaluation and timely approval of new inhibitors in clinical trials.

Efficacy in Advanced Disease

The efficacy of kinase inhibitors has now been demonstrated in multiple cancers (Table 1) [14, 15, 29–33]. Perhaps, the most dramatic results have been seen in GIST, a gastrointestinal sarcoma driven primarily by the *KIT* oncogene and less frequently by a *PDGFR alpha* mutation. Historically, patients with unresectable metastatic GIST had a dismal prognosis, with a median survival less than a year [34], since conventional cytotoxic chemotherapy was ineffective [35]. A phase 3 trial compared 2 doses of the KIT and PDGFR inhibitor imatinib in patients with unresectable or metastatic GIST. Patients in both treatment arms had about a 40% partial response rate and median PFS was 18–20 months [32]. The results were similar in another phase 3 trial and markedly better than historical outcomes with cytotoxic chemotherapy (Fig. 4A) [33]. We now know that the median survival in metastatic GIST is 5 years [36], which again demonstrates the inadequacy of RECIST criteria in determining tumor response. In fact, some GISTs that respond to tyrosine kinase inhibitors may transiently enlarge. Furthermore, small tumors may only become visible on cross-sectional imaging after therapy, when their tumor density changes as discussed above.

While imatinib is clearly effective in advanced GIST, it is important to realize that it is rarely curative, and nearly all patients will eventually develop tumor progression, even after 10 years of therapy. In a phase 3 trial, patients with advanced GIST who had received 1 year of imatinib therapy and had responsive disease were randomly assigned to continue imatinib or suspend treatment [37]. Of 26 patients assigned to continue imatinib treatment, only 8 patients (31%) experienced disease progression compared to 26 of 32 patients (81%) who stopped imatinib therapy. The median time to progression after cessation of imatinib therapy was 6 months, but most (92%) responded after restarting imatinib. Thus, tumors can respond after premature stoppage of kinase inhibition, but also can acquire resistance (*vide infra*) during chronic therapy. These phenomena have also been observed in NSCLC and other tumors.

Efficacy as Adjuvant Therapy

Given the efficacy of imatinib in patients with advanced GIST [32, 33, 36, 38], and the historical disease-specific survival of 54% in patients with primary GIST who underwent complete resection [34], imatinib was tested in the adjuvant setting [39]. In the initial phase 3 trial, 1 year of imatinib was compared to placebo following the resection of localized, primary GIST. One-year recurrence-free survival (RFS) was improved in the imatinib arm compared to the placebo arm (98 vs. 83%) (Fig. 4B) [40]. However, there was no difference in OS, even after long-term follow-up [41], likely due to the rescue effect of imatinib in

patients on the placebo arm who developed recurrence that was detected early with serial radiologic imaging. Multivariate analysis of variables associated with decreased RFS identified tumor size, mitotic index, and primary tumor location. Notably, mutation subtype was not found to be an independent prognostic factor on multivariate analysis, which is likely due to the small number of patients per group. In subgroup analysis, patients with *KIT* exon 11 deletions had improved RFS with adjuvant imatinib therapy versus placebo, whereas patients with wild-type tumors did not [41]. It is known that the *PDGFR alpha* D842V mutation found in about 5% of primary GISTs is not sensitive to imatinib. Consistent with the rarity of cure in advanced GIST, 1 year of adjuvant imatinib therapy did not alter long-term RFS [41]. Another trial compared 1 and 3 years of adjuvant imatinib in patients at high risk of recurrence [42]. In patients who received 3 years of imatinib, the 5-year RFS was increased (66 vs. 48%), as was OS (92 vs. 82%). Importantly, though, there was no difference in disease-specific survival.

Thus, adjuvant imatinib may delay tumor recurrence by suppressing tumor growth. This finding raises important questions about the optimal use and timing of adjuvant molecular therapy. If the goal is to increase RFS, then chronic (> 3 years) therapy should be considered. Currently, a phase 2 trial of 5 years of adjuvant imatinib is ongoing [43]. Alternatively, patients could be followed carefully with serial radiologic imaging and started on therapy only if tumor recurrence occurs. Since over 70% of patients are cured with surgery alone, better indicators of the likelihood of recurrence, such as a nomogram [44], can assist with decision-making.

Acquired Resistance to Targeted Therapy

Despite the efficacy of targeted therapy, acquired resistance occurs frequently. Genetic changes that alter the structure of the target enzyme and compensatory signaling within the cancer cell represent the major mechanisms of acquired resistance to kinase inhibitors, whereas pharmacokinetic changes in drug delivery and metabolism are less well characterized (Fig. 5).

We highlight several mechanisms of acquired resistance using *EGFR*-mutant NSCLC as an example. Exon 19 deletions and the point mutation L858R account for approximately 90% of primary *EGFR* mutations [45]. Kinase inhibitors targeting EGFR are effective against this subset of tumors, but the median time to erlotinib or gefitinib resistance is only 12 months [10, 46]. The predominant resistance mechanism (50–60%) is a secondary mutation in *EGFR*, emphasizing its importance in tumor maintenance. About 90% of secondary mutations occur in exon 20 and encode the substitution of methionine for threonine at position 790 (T790M), the so-called gatekeeper residue at the opening of the ATP-binding pocket that is essential for kinase activity and which is conserved across many receptor tyrosine kinases [47]. Structural modeling of the T790M secondary mutation demonstrates an alteration of the ATP-binding pocket of EGFR likely resulting in steric hindrance to erlotinib and gefitinib binding, due to the larger size of methionine as compared to threonine [48]. ATP binding remains intact, leading to persistent oncogenic EGFR signaling.

Approximately 20% of patients with acquired resistance to EGFR kinase inhibitors instead demonstrate activation of accessory intracellular signaling pathways. Multiple mechanisms have been reported, emphasizing the remarkable plasticity of cancer. Amplification of *MET*, which encodes a receptor tyrosine kinase that activates the PI3K and MAPK pathways, confers resistance to EGFR kinase inhibitors [49, 50]. An EGFR to MET “kinase-switch” has been shown with MET activation of the PI3K pathway through ERBB3 signaling [50]. Overexpression of hepatocyte growth factor, the natural ligand of MET, has also been found to confer EGFR kinase inhibitor resistance through MET-induced restoration of PI3K pathway signaling [51]. Similarly, overexpression of *AXL*, which encodes the AXL receptor tyrosine kinase, and its ligand GAS6, can cause EGFR inhibitor resistance by activating the PI3K and MAPK pathways [52]. Mutations downstream of EGFR, within the PI3K/AKT and MAPK signaling pathways, also confer decreased sensitivity to EGFR kinase inhibitors. These include activating mutations of *PIK3CA*, *KRAS*, and *BRAF*V600E, and loss-of-function mutations of the tumor suppressor gene *PTEN* [52].

Another mechanism of acquired resistance to EGFR kinase inhibitors in NSCLC is histologic transformation. In a study analyzing pre- and post-treatment biopsies of 37 patients who developed resistance to gefitinib or erlotinib, 5 patients experienced a transformation of their tumor to a small cell lung cancer histology and 2 other patients demonstrated epithelial-to-mesenchymal transition [53]. All tumors maintained their original *EGFR* mutation [53]. The molecular events responsible for these histologic changes remain to be elucidated.

Similar mechanisms of acquired resistance to targeted agents have been revealed in other tumors. Secondary *KIT* mutations account for imatinib resistance in over half of GIST patients [54]. MET activation has also been shown in GIST [55]. In patients with advanced *BRAF*-mutated melanoma, BRAF inhibitors are initially effective, but disease progression occurs at approximately 6 months [14, 15, 31, 56]. Reactivation of the MAPK signaling pathway occurs in a variety of ways, including expression of the MAPK agonist COT, upregulation of *RAS*, kinase switching, and alternative splicing of *BRAF* leading to enhanced BRAF dimerization [57, 58].

Multimodality Therapy

Because acquired resistance to single-agent kinase inhibitor therapy is a frequent occurrence and limits therapeutic durability, attention has turned to combination approaches. Here, we will highlight combination therapy in *BRAF*-mutated melanoma, including surgery for patients with previously unresectable or metastatic disease. Combination of kinase inhibitors with other types of therapy, such as cytotoxic chemotherapy or radiation, is also under investigation but beyond the scope of this review.

Approximately 50% of malignant melanomas harbor a *BRAF* mutation, most commonly a substitution of valine to glutamic acid at position 600 (V600E) [59]. Multiple phase 3 trials have demonstrated increased response rates, PFS, and OS in patients with advanced *BRAF* V600-mutated melanoma treated with the BRAF inhibitors vemurafenib or dabrafenib compared to dacarbazine [14, 15, 31, 56, 60–62]. Despite initial efficacy, disease progression

occurs at 6 months [14, 15, 31, 56]. Under normal circumstances, BRAF phosphorylates the MAPKs MEK1 and MEK2, which activate downstream signaling. One mechanism of resistance to BRAF inhibition, mentioned above, is reactivation of the MAPK pathway via BRAF-independent, MEK-dependent signaling [57]. A phase 3 trial comparing the MEK inhibitor trametinib to conventional cytotoxic chemotherapy in patients with advanced *BRAF*V600-mutated melanoma found a >50% relative risk reduction of disease progression and death with trametinib [63]. Similar to patients treated with BRAF inhibitors, however, median time to disease progression was 5 months [14, 15, 31, 56, 63].

Given the transient efficacy of single-agent BRAF and MEK inhibition, multiple studies were conducted combining the approaches. A phase 3 trial showed that dabrafenib plus trametinib had a higher overall response rate (67 vs. 51%) and 25% relative risk reduction in disease progression compared with dabrafenib monotherapy [64]. Another phase 3 trial indicated that dabrafenib plus trametinib had greater PFS (11.4 vs. 7.3 months) and OS (not reached vs. 17.2 months) than vemurafenib monotherapy (Fig. 6) [65]. A phase 3 trial comparing combined vemurafenib plus cobimetinib (another MEK inhibitor) resulted in a higher objective response rate (68 vs. 45%) and longer median PFS (9.9 vs. 6.2 months) than vemurafenib monotherapy [66]. Dose-limiting toxic events in the monotherapy and combination therapy groups in the above studies were similar [64, 65, 67]. Notably, patients treated with BRAF inhibitor monotherapy experienced higher rates of cutaneous squamous cell carcinoma, due to activation of the MAPK pathway, compared to patients treated with combined BRAF and MEK inhibition [14, 67]. Overall, these trials demonstrate modest improvement of combination BRAF and MEK inhibitor therapy over monotherapy in advanced *BRAF*-mutated melanoma.

While kinase inhibitors are effective, their limited duration of response has prompted investigation of alternative approaches, such as immune therapy. Melanomas are notable for their high mutational burden and immunogenicity. In a subset of patients with advanced melanoma, the T cell-activating checkpoint inhibitors anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab, pembrolizumab) have demonstrated long-lasting responses [68–71]. The goal of combining these immune therapies with molecular agents is to achieve durable responses in a larger proportion of patients. Preclinical and translational studies support this approach. In mouse models of *BRAF*-mutated melanoma, BRAF and MEK inhibition were more effective at controlling tumor growth when combined with checkpoint inhibition [72, 73]. In melanoma patients, BRAF inhibition led to increased intratumoral expression of the T cell exhaustion markers TIM-3 and PD-1, as well as the immunosuppressive ligand PD-L1, suggesting an immune-mediated mechanism of BRAF inhibitor resistance [74]. Based on these data, clinical trials are now investigating the combination of kinase and immune checkpoint inhibitors. A phase 1 trial was initiated to test vemurafenib plus ipilimumab in patients with untreated *BRAF*V600-mutated advanced melanoma, but the study was closed early due to grade 3 hepatotoxicity [75]. Preliminary data from phase 1 trials testing alternative BRAF and MEK inhibitors (dabrafenib, trametinib) with ipilimumab or anti-PD-L1 (MEDI4736) demonstrate more favorable toxicity profiles [76, 77]. Studies are ongoing to evaluate efficacy [78, 79].

Combining molecular therapy with surgery remains poorly defined. Historically, resection of advanced melanoma has been reserved for patients with local recurrence and in-transit, satellite, and oligometastatic disease, with improvement in OS [80, 81]. Retrospective data suggest that patients with metastatic melanoma who respond to BRAF inhibition but have an isolated focus of residual or progressive disease may benefit from metastatectomy [82]. Similarly, patients with metastatic GIST may benefit from metastatectomy after response or disease stabilization with imatinib [83]. However, randomized clinical trials are lacking and have been difficult to conduct. Nevertheless, surgery may serve as an “adjuvant therapy” to kinase inhibition in highly selected patients. Additionally, patients with advanced melanoma treated with neoadjuvant BRAF inhibition have been reported [84], and the role of neoadjuvant combination targeted therapy in patients with resectable, high-risk metastatic melanoma is under formal investigation [85].

CONCLUSIONS

Kinase inhibitors have revolutionized cancer therapy and are effective in selected patients with advanced solid tumors. Despite initial efficacy, however, kinase inhibitors are not curative. Development of resistance is common, emphasizing the urgency to identify new therapeutic targets and more effective treatment strategies. Molecular subclassification of tumors is needed to better select patients and predict treatment response. Combination therapy is anticipated to improve outcomes in many tumor types, and surgery remains a relevant part of the shifting treatment paradigm.

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References

1. Gschwind A, Fischer OM, Ullrich A. The discovery of receptor tyrosine kinases: targets for cancer therapy. *Nat Rev Cancer*. 2004; 4:361–370. [PubMed: 15122207]
2. Rask-Andersen M, Zhang J, Fabbro D, Schiøth HB. Advances in kinase targeting: current clinical use and clinical trials. *Trends Pharmacol Sci*. 2014; 35:604–620. [PubMed: 25312588]
3. Fabbro D. 25 years of small molecular weight kinase inhibitors: potentials and limitations. *Mol Pharmacol*. 2015; 87:766–775. [PubMed: 25549667]
4. Manning G, Whyte DB, Martinez R, et al. The protein kinase complement of the human genome. *Science*. 2002; 298:1912–1934. [PubMed: 12471243]
5. Zhang J, Hochwald SN. Targeting receptor tyrosine kinases in solid tumors. *Surg Oncol Clin N Am*. 2013; 22:685–703. [PubMed: 24012395]
6. Weinstein IB. Cancer. Addiction to oncogenes--the Achilles heel of cancer. *Science*. 2002; 297:63–64. [PubMed: 12098689]
7. Lovly, CM.; Horn, L.; Pao, W. My Cancer Genome. 2015. Jun 17. 2015 Molecular Profiling of Lung Cancer.
8. Cancer Genome Atlas Research N. Comprehensive molecular profiling of lung adenocarcinoma. *Nature*. 2014; 511:543–550. [PubMed: 25079552]
9. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from “never smokers” and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci USA*. 2004; 101:13306–13311. [PubMed: 15329413]
10. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009; 361:947–957. [PubMed: 19692680]

11. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* 2012; 13:239–246. [PubMed: 22285168]
12. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature.* 2007; 448:561–566. [PubMed: 17625570]
13. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med.* 2013; 368:2385–2394. [PubMed: 23724913]
14. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med.* 2011; 364:2507–2516. [PubMed: 21639808]
15. McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. *Lancet Oncol.* 2014; 15:323–332. [PubMed: 24508103]
16. Heinrich MC, Owzar K, Corless CL, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. *J Clin Oncol.* 2008; 26:5360–5367. [PubMed: 18955451]
17. Conley BA, Doroshow JH. Molecular analysis for therapy choice: NCI MATCH. *Semin Oncol.* 2014; 41:297–299. [PubMed: 25023344]
18. Govindan R, Mandrekar SJ, Gerber DE, et al. ALCHEMIST Trials: A Golden Opportunity to Transform Outcomes in Early-Stage Non-Small Cell Lung Cancer. *Clin Cancer Res.* 2015; 21:5439–5444. [PubMed: 26672084]
19. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer.* 1981; 47:207–214. [PubMed: 7459811]
20. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000; 92:205–216. [PubMed: 10655437]
21. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1. 1). *Eur J Cancer.* 2009; 45:228–247. [PubMed: 19097774]
22. Abou-Alfa GK, Schwartz L, Ricci S, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol.* 2006; 24:4293–4300. [PubMed: 16908937]
23. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008; 359:378–390. [PubMed: 18650514]
24. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis.* 2010; 30:52–60. [PubMed: 20175033]
25. Kim MN, Kim BK, Han KH, Kim SU. Evolution from WHO to EASL and mRECIST for hepatocellular carcinoma: considerations for tumor response assessment. *Expert Rev Gastroenterol Hepatol.* 2015; 9:335–348. [PubMed: 25370168]
26. Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. *J Clin Oncol.* 2007; 25:1753–1759. [PubMed: 17470865]
27. Smith AD, Lieber ML, Shah SN. Assessing tumor response and detecting recurrence in metastatic renal cell carcinoma on targeted therapy: importance of size and attenuation on contrast-enhanced CT. *AJR Am J Roentgenol.* 2010; 194:157–165. [PubMed: 20028918]
28. Ammari S, Thiam R, Cuenod CA, et al. Radiological evaluation of response to treatment: application to metastatic renal cancers receiving anti-angiogenic treatment. *Diagn Interv Imaging.* 2014; 95:527–539. [PubMed: 24906810]
29. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med.* 2010; 362:2380–2388. [PubMed: 20573926]
30. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med.* 2007; 356:115–124. [PubMed: 17215529]

31. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2012; 380:358–365. [PubMed: 22735384]
32. Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. *J Clin Oncol*. 2008; 26:626–632. [PubMed: 18235122]
33. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet*. 2004; 364:1127–1134. [PubMed: 15451219]
34. DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg*. 2000; 231:51–58. [PubMed: 10636102]
35. Dematteo RP, Heinrich MC, El-Rifai WM, Demetri G. Clinical management of gastrointestinal stromal tumors: before and after STI-571. *Hum Pathol*. 2002; 33:466–477. [PubMed: 12094371]
36. 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; 26:620–625. [PubMed: 18235121]
37. Blay JY, Le Cesne A, Ray-Coquard I, et al. Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the French Sarcoma Group. *J Clin Oncol*. 2007; 25:1107–1113. [PubMed: 17369574]
38. Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med*. 2001; 344:1052–1056. [PubMed: 11287975]
39. DeMatteo RP, Ballman KV, Antonescu CR, et al. Long-term results of adjuvant imatinib mesylate in localized, high-risk, primary gastrointestinal stromal tumor: ACOSOG Z9000 (Alliance) intergroup phase 2 trial. *Ann Surg*. 2013; 258:422–429. [PubMed: 23860199]
40. Dematteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2009; 373:1097–1104. [PubMed: 19303137]
41. Corless CL, Ballman KV, Antonescu CR, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. *J Clin Oncol*. 2014; 32:1563–1570. [PubMed: 24638003]
42. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA*. 2012; 307:1265–1272. [PubMed: 22453568]
43. Raut CP, Espat NJ, Maki RG, et al. Adjuvant imatinib (IM) for patients (pts) with primary gastrointestinal stromal tumor (GIST) at significant risk of recurrence: PERSIST-5 planned 3-year interim analysis. *ASCO Meeting Abstracts*. 2015; 33:10537.
44. Gold JS, Gonen M, Gutierrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. *Lancet Oncol*. 2009; 10:1045–1052. [PubMed: 19793678]
45. Mitsudomi T, Yatabe Y. Epidermal growth factor receptor in relation to tumor development: EGFR gene and cancer. *FEBS J*. 2010; 277:301–308. [PubMed: 19922469]
46. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med*. 2009; 361:958–967. [PubMed: 19692684]
47. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res*. 2013; 19:2240–2247. [PubMed: 23470965]
48. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2005; 352:786–792. [PubMed: 15728811]

49. Bean J, Brennan C, Shih JY, et al. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. *Proc Natl Acad Sci USA*. 2007; 104:20932–20937. [PubMed: 18093943]
50. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science*. 2007; 316:1039–1043. [PubMed: 17463250]
51. Yano S, Wang W, Li Q, et al. Hepatocyte growth factor induces gefitinib resistance of lung adenocarcinoma with epidermal growth factor receptor-activating mutations. *Cancer Res*. 2008; 68:9479–9487. [PubMed: 19010923]
52. Huang L, Fu L. Mechanisms of resistance to EGFR tyrosine kinase inhibitors. *Acta Pharm Sin B*. 2015; 5:390–401. [PubMed: 26579470]
53. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med*. 2011; 3:75ra26.
54. Antonescu CR, Besmer P, Guo T, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. *Clin Cancer Res*. 2005; 11:4182–4190. [PubMed: 15930355]
55. Cohen NA, Zeng S, Seifert AM, et al. Pharmacological Inhibition of KIT Activates MET Signaling in Gastrointestinal Stromal Tumors. *Cancer Res*. 2015; 75:2061–2070. [PubMed: 25836719]
56. Hauschild A, Grob JJ, Demidov LV, et al. An update on BREAK-3, a phase III, randomized trial: Dabrafenib (DAB) versus dacarbazine (DTIC) in patients with BRAF V600E-positive mutation metastatic melanoma (MM). *ASCO Meeting Abstracts*. 2013; 31:9013.
57. Johannessen CM, Boehm JS, Kim SY, et al. COT drives resistance to RAF inhibition through MAP kinase pathway reactivation. *Nature*. 2010; 468:968–972. [PubMed: 21107320]
58. Johnson DB, Menzies AM, Zimmer L, et al. Acquired BRAF inhibitor resistance: A multicenter meta-analysis of the spectrum and frequencies, clinical behaviour, and phenotypic associations of resistance mechanisms. *Eur J Cancer*. 2015; 51:2792–2799. [PubMed: 26608120]
59. Hodi E, Watson IR, Kryukov GV, et al. A landscape of driver mutations in melanoma. *Cell*. 2012; 150:251–263. [PubMed: 22817889]
60. Joseph EW, Pratilas CA, Poulikakos PI, et al. The RAF inhibitor PLX4032 inhibits ERK signaling and tumor cell proliferation in a V600E BRAF-selective manner. *Proc Natl Acad Sci USA*. 2010; 107:14903–14908. [PubMed: 20668238]
61. Bollag G, Hirth P, Tsai J, et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. *Nature*. 2010; 467:596–599. [PubMed: 20823850]
62. Larkin J, Del Vecchio M, Ascierto PA, et al. Vemurafenib in patients with BRAF(V600) mutated metastatic melanoma: an open-label, multicentre, safety study. *Lancet Oncol*. 2014; 15:436–444. [PubMed: 24582505]
63. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med*. 2012; 367:107–114. [PubMed: 22663011]
64. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med*. 2014; 371:1877–1888. [PubMed: 25265492]
65. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med*. 2015; 372:30–39. [PubMed: 25399551]
66. Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med*. 2014; 371:1867–1876. [PubMed: 25265494]
67. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med*. 2012; 367:1694–1703. [PubMed: 23020132]
68. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010; 363:711–723. [PubMed: 20525992]
69. Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med*. 2013; 369:134–144. [PubMed: 23724846]
70. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2015; 16:375–384. [PubMed: 25795410]

71. Larkin J, Lao CD, Urba WJ, et al. Efficacy and Safety of Nivolumab in Patients With BRAF V600 Mutant and BRAF Wild-Type Advanced Melanoma: A Pooled Analysis of 4 Clinical Trials. *JAMA Oncol.* 2015; 1:433–440. [PubMed: 26181250]
72. Cooper ZA, Juneja VR, Sage PT, et al. Response to BRAF inhibition in melanoma is enhanced when combined with immune checkpoint blockade. *Cancer Immunol Res.* 2014; 2:643–654. [PubMed: 24903021]
73. Hu-Lieskovan S, Mok S, Homet Moreno B, et al. Improved antitumor activity of immunotherapy with BRAF and MEK inhibitors in BRAF(V600E) melanoma. *Sci Transl Med.* 2015; 7:279ra241.
74. Frederick DT, Piris A, Cogdill AP, et al. BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma. *Clin Cancer Res.* 2013; 19:1225–1231. [PubMed: 23307859]
75. Ribas A, Hodi FS, Callahan M, et al. Hepatotoxicity with combination of vemurafenib and ipilimumab. *N Engl J Med.* 2013; 368:1365–1366. [PubMed: 23550685]
76. Puzanov I, Callahan MK, Linette GP, et al. Phase 1 study of the BRAF inhibitor dabrafenib (D) with or without the MEK inhibitor trametinib (T) in combination with ipilimumab (Ipi) for V600E/K mutation-positive unresectable or metastatic melanoma (MM). *ASCO Meeting Abstracts.* 2014; 32:2511.
77. Ribas A, Butler M, Lutzky J, et al. Phase I study combining anti-PD-L1 (MEDI4736) with BRAF (dabrafenib) and/or MEK (trametinib) inhibitors in advanced melanoma. *ASCO Meeting Abstracts.* 2015; 33:3003.
78. Hu-Lieskovan S, Robert L, Homet Moreno B, Ribas A. Combining targeted therapy with immunotherapy in BRAF-mutant melanoma: promise and challenges. *J Clin Oncol.* 2014; 32:2248–2254. [PubMed: 24958825]
79. Kim T, Amaria RN, Spencer C, et al. Combining targeted therapy and immune checkpoint inhibitors in the treatment of metastatic melanoma. *Cancer Biol Med.* 2014; 11:237–246. [PubMed: 25610709]
80. Sosman JA, Moon J, Tuthill RJ, et al. A phase 2 trial of complete resection for stage IV melanoma: results of Southwest Oncology Group Clinical Trial S9430. *Cancer.* 2011; 117:4740–4706. [PubMed: 21455999]
81. Karakousis CP, Velez A, Driscoll DL, Takita H. Metastasectomy in malignant melanoma. *Surgery.* 1994; 115:295–302. [PubMed: 8128354]
82. Schlumberger, MJ.; Elisei, R.; Muller, SP., et al. Final overall survival analysis of EXAM, an international, double-blind, randomized, placebo-controlled phase III trial of cabozantinib (Cabo) in medullary thyroid carcinoma (MTC) patients with documented RECIST progression at baseline. 2015 ASCO Annual Meeting; Chicago, IL. 2015.
83. DeMatteo RP, Maki RG, Singer S, et al. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. *Ann Surg.* 2007; 245:347–352. [PubMed: 17435539]
84. Laks S, Brueske KA, Hsueh EC. Neoadjuvant treatment of melanoma: case reports and review. *Exp Hematol Oncol.* 2013; 2:30. [PubMed: 24499550]
85. Wargo JA, Amaria RN, Ross MI, et al. Neoadjuvant BRAF (dabrafenib) and MEK (trametinib) inhibition for high-risk resectable stage III and IV melanoma. *ASCO Meeting Abstracts.* 2015:33.
86. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet.* 2006; 368:1329–1338. [PubMed: 17046465]
87. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013; 381:295–302. [PubMed: 23177515]
88. Douillard JY, Ostoros G, Cobo M, et al. First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study. *Br J Cancer.* 2014; 110:55–62. [PubMed: 24263064]

89. Sequist LV, Yang JC, 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; 31:3327–3334. [PubMed: 23816960]
90. Mitsudomi T, Tsai CM, Shepherd F, et al. AZD9291 in pre-treated T790M positive advanced NSCLC: AURA2 Phase II study. 16th World Conference on Lung Cancer; Denver, CO. 2015.
91. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med.* 2014; 371:2167–2177. [PubMed: 25470694]
92. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. *N Engl J Med.* 2014; 370:1189–1197. [PubMed: 24670165]
93. Gandhi L, Shaw AT, Gadgeel SM, et al. A phase II, open-label, multicenter study of the ALK inhibitor alectinib in an ALK+ non-small-cell lung cancer (NSCLC) U.S./Canadian population who had progressed on crizotinib (NP28761). 2015 ASCO Annual Meeting; Chicago, IL. 2015.
94. Wells SA Jr, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol.* 2012; 30:134–141. [PubMed: 22025146]
95. Elisei R, Schlumberger MJ, Muller SP, et al. Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol.* 2013; 31:3639–3646. [PubMed: 24002501]
96. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med.* 2007; 356:125–134. [PubMed: 17215530]
97. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol.* 2009; 27:3312–3318. [PubMed: 19451442]
98. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2009; 27:3584–3590. [PubMed: 19487381]
99. Motzer RJ, Hutson TE, McCann L, et al. Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. *N Engl J Med.* 2014; 370:1769–1770. [PubMed: 24785224]
100. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med.* 2013; 369:722–731. [PubMed: 23964934]
101. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol.* 2013; 14:552–562. [PubMed: 23598172]
102. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med.* 2007; 356:2271–2281. [PubMed: 17538086]
103. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. *Cancer.* 2010; 116:4256–4265. [PubMed: 20549832]
104. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med.* 2006; 355:2733–2743. [PubMed: 17192538]
105. Cameron D, Casey M, Oliva C, et al. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. *Oncologist.* 2010; 15:924–934. [PubMed: 20736298]
106. Johnston S, Pippin J Jr, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol.* 2009; 27:5538–5546. [PubMed: 19786658]
107. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med.* 2011; 364:514–523. [PubMed: 21306238]
108. Pavel ME, Lombard-Bohas C, Van Cutsem E, et al. Everolimus in patients with advanced, progressive pancreatic neuroendocrine tumors: Overall survival results from the phase III RADIANT-3 study after adjusting for crossover bias. 2015 ASCO Annual Meeting; Chicago, IL. 2015.
109. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med.* 2011; 364:501–513. [PubMed: 21306237]

Figure 1. Common cell signaling pathways activated in cancer

Depiction of dysregulated oncogenic receptor tyrosine kinases (RTKs) and intracellular downstream mediators (green boxes). RTKs transduce signals from the binding of extracellular ligands and growth factors resulting in activation of downstream PI3K, JAK/STAT, PLC/PKC, and MAPK pathway mediators, causing nuclear translocation of transcription factor proteins, which regulate gene expression and the balance of proliferative and death signals within the cell. Molecular targets and their inhibitors are indicated (red boxes). Note that crizotinib and cabozantinib also target MET.

Figure 2. Genomic analysis identifies numerous molecular subsets of lung adenocarcinoma, a histologic subset of non-small cell lung cancer (NSCLC)

Based on 230 cases of lung adenocarcinoma analyzed by the Cancer Genome Atlas Research Network [8], almost two-thirds of the tumors had activating mutations, amplifications, or chromosomal rearrangements of kinase-encoding genes involved in the receptor tyrosine kinase/RAS/RAF/MEK/ERK, or MAP kinase, cell signaling pathway (red/orange). Another 14% of tumors were discovered to have novel genetic changes (i.e., *ERBB2* or *MET* amplification) or loss-of-function mutations of the *NF1* tumor suppressor gene, which have not been previously characterized in NSCLC patients (blue). Finally, about one quarter of tumors had no identifiable, targetable genetic changes (gray).

Figure 3. Targeted therapy causes tumor necrosis in the absence of tumor shrinkage
Contrast-enhanced computed tomography scan of a patient with HCC before (A) and after (B, C) treatment with sorafenib showing an increase in tumor volume and central necrosis in response to treatment. This demonstrates the limitation of relying only on RECIST criteria to evaluate tumor response to targeted therapy. (From Abou-Alfa G, Schwartz L, Ricci S, et al. Phase II Study of Sorafenib in Patients With Advanced Hepatocellular Carcinoma. J Clin Oncol 2006; 24(26):4293–4300; with permission [22].)

A **B**

Figure 4. Efficacy of imatinib in (A) metastatic and (B) resected localized, primary GIST
(A) Overall survival in patients with metastatic GIST treated with imatinib once or twice daily compared to historical controls in the EORTC database treated with doxorubicin (*From Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004; 364: 1127–1134; with permission [33].*) **(B)** Recurrence-free survival in patients with high-risk, resected primary GIST randomized to 1 year of imatinib or placebo. The 1-year estimated recurrence-free survival was 98% (95% CI 96–100) in the imatinib group vs. 83% (78–88) in the placebo group. (*From Dematteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet 2009; 373: 1097–1104; with permission [40].*)

Figure 5. Mechanisms of resistance against kinase inhibitors

(A) Depiction of common mechanisms of acquired resistance (green boxes), including secondary mutations that hinder drug binding to target receptor tyrosine kinases (RTKs), and compensatory signaling. Compensatory signaling includes kinase switching, upregulation of downstream pathways (i.e. MAPK and PI3K pathways), and extracellular signaling from the tumor microenvironment. Pharmacokinetic changes in drug delivery and metabolism are less well characterized. (B) Representation of *EGFR*-mutated NSCLC resulting in activation of downstream mediators, *left panel*. Targeting EGFR with a tyrosine kinase inhibitor (TKI) blocks downstream signaling, *center panel*. Upregulation of alternative RTKs (i.e. MET) causes a “kinase switch” and reactivates oncogenic signaling, *right panel*.

Figure 6. Combined BRAF and MEK inhibition is more effective than BRAF inhibition alone
Kaplan-Meier estimates of overall survival in the intention-to-treat population of patients with advanced melanoma treated with combination dabrafenib and trametinib compared to vemurafenib monotherapy. (From Robert C, Karaszewska B, Schachter J et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015; 372: 30–39; with permission [65].)

Table 1

Summary and efficacy of FDA-approved molecular inhibitors in advanced solid tumors.

Tumor	Target	Agent	PFS (mo)	OS (mo)	FDA Approval	Comments	Ref.
GIST	KIT, PDGFR	Imatinib (Gleevec, Novartis)	18–20	51–55	2002	400 mg qd vs. bid	[32]
		Imatinib	RFS 48	Not reached after 7.7 yr median f/u	2008	Adjuvant × 1 yr, similar results with 1 vs. 3 yrs	[39, 42]
		Sunitinib (Sutent, Pfizer)	6.3	NR	2006	Failed imatinib	[86]
		Regorafenib (Stivarga, Bayer)	4.8	NR	2013	Failed imatinib, sunitinib	[87]
Melanoma	BRAF	Vemurafenib (Zelboraf, Hoffmann-La Roche)	6.9	13.6	2011	<i>BRAF^{V600E}</i>	[15]
		Dabrafenib (Tafinlar, GlaxoSmithKline)	5.1	NR	2013	<i>BRAF^{V600E}</i> / <i>BRAF^{V600K}</i>	[31]
	MEK	Trametinib (Mekinist, GlaxoSmithKline)	4.8	Not reached	2013	<i>BRAF^{V600E}</i> / <i>BRAF^{V600K}</i>	[63]
	BRAF + MEK	Dabrafenib + Trametinib	11.4	Not reached	2014	<i>BRAF^{V600E}</i> / <i>BRAF^{V600K}</i>	[65]
		Vemurafenib + Cobimetinib (Cotellic, Genentech)	9.9	Not reached	2015	<i>BRAF^{V600E}</i> / <i>BRAF^{V600K}</i>	[66]
NSCLC	EGFR	Gefitinib (Iressa, AstraZeneca)	9.7	19.2	2003, 2015	Updated approval 1 st line for <i>EGFR</i> exon 19 deletion, exon 21 L858R substitution	[88]
		Erlotinib (Tarceva, Astellas)	9.7	19.3	2004, 2013	Updated approval 1 st line for <i>EGFR</i> exon 19 deletion, exon 21 L858R substitution	[11]
		Afatinib (Gilotrif, Boehringer Ingelheim)	11.1	Not reached	2013	<i>EGFR</i> exon 19 deletion, exon 21 L858R substitution	[89]
		Osimertinib (Tagrisso, AstraZeneca)	8.6	NR	2015	<i>EGFR^{T790M}</i> , failed other EGFR inhibitors	[90]
	ALK	Crizotinib (Xalkori, Pfizer)	10.9	Estimated 1-yr OS 84%	2011	<i>ALK</i> -positive	[91]
		Ceritinib (Zykadia, Novartis)	7.0	NR	2013	<i>ALK</i> -positive, failed crizotinib	[92]
		Alectinib (Alecensa, Hoffman-La Roche)	6.3	NR	2015	<i>ALK</i> -positive, failed crizotinib	[93]
MTC	RET	Vandetanib (Caprelsa, AstraZeneca)	~30.5	Not reached	2011	Median PFS not reached	[94]
		Cabozantinib (Cometriq, Exelixis)	11.2	26.6, 44.3 with <i>RET</i> mutation	2012		[82, 95]
RCC	Multiple RTKs	Sorafenib (Nexavar, Bayer)	5.5	17.8	2005		[96, 97]
		Sunitinib (Sutent, Pfizer)	11	26.4	2007		[30, 98]
		Pazopanib (Votrient, GlaxoSmithKline)	8.4	28.3	2009	vs. Sunitinib	[99, 100]
		Axitinib (Inlyta, Pfizer)	8.3	20.1	2012	vs. Sorafenib	[101]

Tumor	Target	Agent	PFS (mo)	OS (mo)	FDA Approval	Comments	Ref.
	mTOR	Temsirolimus (Torisel, Wyeth)	3.8	10.9	2007		[102]
		Everolimus (Afinitor, Novartis)	4.9	14.8	2009	Failed sunitinib, sorafenib	[103]
HCC	Multiple RTKs	Sorafenib (Nexavar, Bayer)	5.5 [*]	10.7	2007		[23]
Breast cancer	HER2	Lapatinib (Tykerb, GlaxoSmithKline)	8.4 [*]	~17.2	2007	HER2 overexpression, failed anthracycline, taxane, trastuzumab, with capecitabine	[104, 105]
		Lapatinib	8.2	33.3	2010	HER2 overexpression and hormone receptor-positive, with letrozole	[106]
PNET	mTOR	Everolimus (Afinitor, Novartis)	11.0	44.0	2011		[107, 108]
	Multiple RTKs	Sunitinib	11.4	Not reached	2011	~1/3 received somatostatin analogue	[109]

GIST – gastrointestinal stromal tumor, NSCLC – non-small cell lung cancer, MTC – medullary thyroid cancer, RCC – renal cell carcinoma, HCC – hepatocellular carcinoma, PNET – pancreatic neuroendocrine tumor, RTKs – receptor tyrosine kinases, *fu* – follow up,

^{*} time to progression,

NR, not reported, ref. - reference