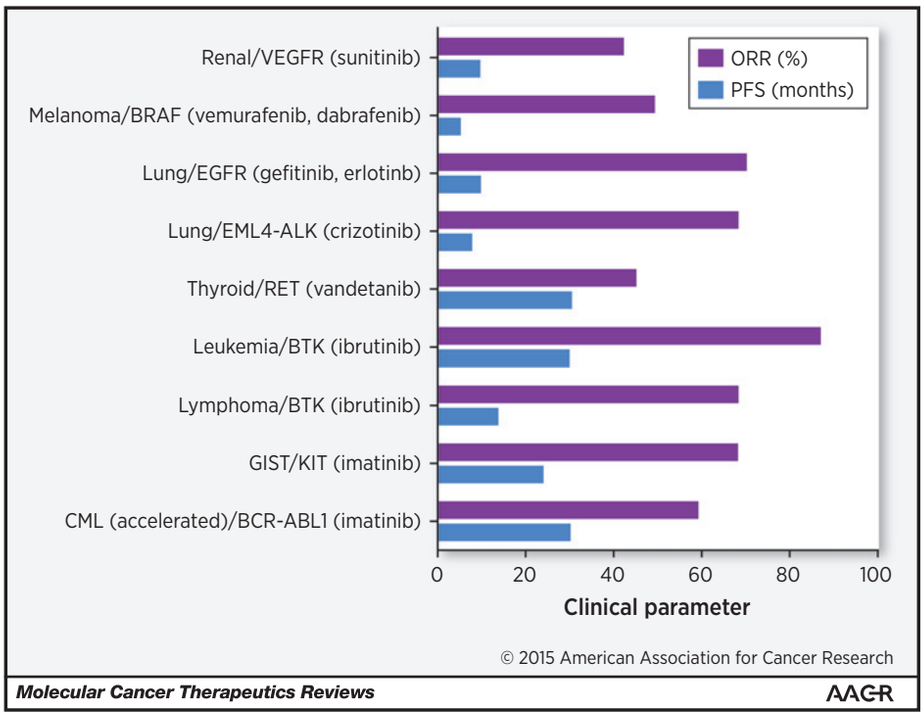

Figure 1.
Evaluation of the durability of response to approved kinase-targeted therapies for patients with advanced disease. Overall response rates (ORR, purple bars) to kinase-directed therapies is plotted relative to the durability of response as measured by PFS (blue bars)—sunitinib, VEGFR/renal cell carcinoma (99); vemurafenib, BRAF-V600E/melanoma (46); erlotinib and gefitinib, oncogenic EGFR/NSCLC (100, 101); crizotinib, EML4-ALK/NSCLC (102); vandetanib, RET/medullary thyroid cancer (103); ibrutinib, BTK/chronic lymphocytic leukemia (104); ibrutinib, BTK/mantle cell lymphoma (105); imatinib, KIT/gastrointestinal stromal tumors (106); imatinib, BCR-ABL1/blast crisis, chronic myeloid leukemia (90).

whereas others (e.g., EGFR) invoke an allosteric, intermolecular mechanism (3). Catalytic domain structural dynamics is also regulated by hydrophobic spines—internal amino acid residues that transverse the two subdomains (4). In addition, kinases have noncatalytic domains that facilitate substrate docking, subcellular trafficking, and recruitment of other signaling proteins (5–7). Taken together, sophisticated mechanisms have evolved to regulate protein kinases that can be coopted by tumor cells to evade kinase-directed therapies.

Multidimensional arrays of protein kinases create signaling networks with modular subunits and hierarchical structures that squelch unnecessary signaling (robustness), yet can respond to environmental changes (evolvability; ref. 8). Ingrained in these networks are essential behaviors that enable complex properties such as ultrasensitivity (switch-like behavior), bistability (two stable states which store one bit of information), and hysteresis (dependence on current and previous inputs). Many processes work in concert to create these network properties (e.g., feedback regulation, multistep activation, and trafficking). With such an intricate signaling fabric, the role of a kinase in a given network will define the effects from drug modulation. Protein kinases mutated in oncogenesis (e.g., BRAF-V600E, BCR-ABL1, BCR-ABL-T315I, and EGFR-L858R) have higher evolvability scores because they are central to the dysregulation that causes a phenotypic change in cell behavior. Nononcogenic driver kinases (e.g., stromal VEGFR2) are also important for cancer progression (9) and typically score higher in robustness because redundancy is built into the signaling network. Patient-specific network biology is also important because therapies that target a specific oncogenic kinase (e.g., BRAF-V600E) have a spectrum of clinical responses from robust, prolong responders to nonresponders (innate/endogenous resistance; refs. 10–12). As such, the network context of the targeted protein kinase is critical to identifying patients "wired" to respond as well as mechanisms that can be engaged to evade therapy.

Intrinsic Mechanisms of Drug Response and Resistance

Clinical response and resistance to kinase-directed therapies depend on properties of the targeted kinase (intrinsic factors). Altered protein kinases (e.g., mutated, amplified) are known to be critical to tumor cell signaling through their modified structures, activities, and molecular associations (Fig. 3). The strong dependence on these kinases for tumor cell survival is thought to be from either required oncogenic signaling ("oncogene addiction"; refs. 13, 14) or as counter balances to proapoptotic pressure ("oncogenic shock"; ref. 15). In addition, the properties of an altered kinase can cause "highly optimized tolerance"—acquired tolerance to conventional perturbations (e.g., hypoxia) but fragility to other perturbations (16). For example, the fusion of BCR to ABL1 that fundamentally changes the capabilities of a chronic myelogenous leukemia (CML) cell. When BCR-ABL1 function is lost for a short time (20–60 minutes), the tumor cell commits to apoptosis (17, 18). The presence of an altered kinase in a tumor can, but not always, enables an innate response toward the associated kinase-directed drug. For example, single-agent targeted therapies to BRAF-V600E in melanoma have high response rates and significant clinical benefit (19). In contrast, BRAF-V600E mutations also occur in colorectal cancer but BRAF-targeted therapies are not clinically effective (discussed later in this review in the context of extrinsic resistance; refs. 20, 21). Identification of sensitizing on-target mutations can stratify patient populations and accelerate clinical trials. Initial clinical studies of EGFR drugs toward unselected non–small cell lung cancer (NSCLC) patient