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An Essential Role for the Immune System in the Mechanism of Tumor Regression Following Targeted Oncogene Inactivation

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Abstract

Tumors are genetically complex and can have a multitude of mutations. Consequently, it is surprising that the suppression of a single oncogene can result in rapid and sustained tumor regression, illustrating the concept that cancers are often “oncogene addicted.” The mechanism of oncogene addiction has been presumed to be largely cell autonomous as a consequence of the restoration of normal physiological programs that induce proliferative arrest, apoptosis, differentiation, and/or cellular senescence. Interestingly, it has recently become apparent that upon oncogene inactivation, the immune response is critical in mediating the phenotypic consequences of oncogene addiction. In particular, CD4⁺ T cells have been suggested to be essential to the remodeling of the tumor microenvironment, including the shut down of host angiogenesis and the induction of cellular senescence in the tumor. However, adaptive and innate immune cells are likely involved. Thus, the effectors of the immune system are not only involved in tumor initiation, tumor progression, and immunosurveillance, but are also involved in the mechanism of tumor regression upon targeted oncogene inactivation. Hence, oncogene inactivation may be an effective therapeutic approach because it both reverses the neoplastic state within a cancer cell and reactivates the host immune response that remodels the tumor microenvironment.

Keywords

Oncogene addiction; MYC; tumor recurrence; tumor microenvironment; tumor immunology

Introduction: oncogene addiction

Oncogene addiction describes the dramatic and sustained regression of some cancers following the targeted inactivation of a single oncogene [1–12]. Oncogene addiction has been described as a cell autonomous phenomenon that is associated with proliferative arrest, apoptosis, senescence, and/or differentiation [13]. The mechanism of oncogene addiction is not known but has been suggested to be a consequence of the restoration of physiological programs [11,14], synthetic lethality [15], and/or differential decay of survival and apoptosis

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programs [16]. The mechanisms of oncogene addiction appear to be generally similar for different oncogenes and different tumor types. The most robust oncogene targets may be the essential driver mutations that are critical for the molecular scaffolding that maintains the cancer phenotype [17,18]. However, it is not clear if an oncogene must be mutated in order to establish addiction [12]. Regardless, until recently, it has been largely presumed that the mechanisms of oncogene addiction are cell autonomous. Current literature illustrates that this is unlikely to be the case [19–26].

In the clinic, oncogene addiction has been used as a therapeutic approach. Thus, the inactivation of an oncogene with a targeted small molecule or antibody therapy can be associated with significant tumor regression, although tumors often recur [27–29]. Drugs that target oncogenes such as BCR-ABL, c-Kit, HER2/Neu, EGFR, and PML-RAR α have significant clinical activity against leukemia, breast cancer, and lung cancer [30–32]. More recently, vemurafenib, which targets the BRAF V600E mutation, has been shown to have activity against melanoma [33]. Drugs that target oncoproteins such as ALK, JAK2, MDM2, and PI3 kinase are currently in clinical trials [34–43]. However, the most important driver oncoproteins, such as K-RAS and MYC, have remained undruggable, although strategies to target RAS [44] and MYC [45,46] have been recently described.

Experimental mouse models have been a particularly tractable approach to interrogating the mechanism of oncogene addiction. Transgenic mouse models employing strategies that enable the conditional expression of oncogenes have been used to illustrate that cancers initiated by an oncogene, such as MYC, RAS, BCR-ABL, MET, and BRAF, are generally reversible upon oncogene suppression [1,2,4,5,8,47,48]. From these mouse models, insight has been gleaned into the mechanisms of oncogene addiction [49]. Oncogene inactivation has been shown to induce rapid proliferative arrest, apoptosis, differentiation, and/or senescence of tumors, as previously described [50]. The specific consequences depend upon the particular tumor type. Thus, oncogene inactivation in hematopoietic tumors induces proliferative arrest and apoptosis [4], whereas in sarcoma, it induces sustained differentiation [51], and in epithelial tumors it induces apoptosis in most but not all tumor cells (a small population can remain dormant) [52]. Genetic and cellular contexts influence the consequences of tumor regression [53].

However, it also has been appreciated that oncogene inactivation in a tumor elicits a profound influence not only on tumor cells but also on the tumor microenvironment. Oncogenes can regulate angiogenesis; MYC inactivation can result in the shut down of angiogenesis, contributing to tumor regression [54–57]. Inactivation of an oncogene recruits a marked change in the tumor microenvironment associated with the recruitment of immune effector cells, and this plays a direct role in the mechanism of oncogene addiction [12,58–61]. The innate and the adaptive immune systems are known to play a critical role in tumor initiation and progression [62–65] as well as immunosurveillance [66–69]. Hence, it appears that the immune system is integral to both the construction as well as the destruction of tumors [59]. Oncogene inactivation appears to be an unanticipated mechanism by which these immune-based mechanisms against cancer can be activated.

Immune system and the anti-tumor response

The immune system is a critical barrier to tumorigenesis [70]. Hosts with suppressed immune systems have a greatly increased incidence of cancer [71,72]. In particular, drugs that suppress host adaptive immunity are associated with multiple tumor types, including lymphoma and skin cancer [73–75]. Patients with a compromised immune system seem to have decreased overall and progression-free survival in several different solid and hematologic malignancies [76,77]. During tumorigenesis, cancers appear to be immune edited. For a tumor to arise, they must evolve to bypass immune-mediated mechanisms [78–80]. Hence, immune surveillance can prevent cancer formation and tumors that arise have learned to coexist or bypass these effector mechanisms.

Similarly, the immune system appears to play a role in the mechanism by which therapeutics prompt tumor regression [75,81]. Evidence that conventional therapeutics, such as certain chemotherapies, mediate their efficacy at least in part through immune activation has been defined [82,83]. Many immune-based therapies are emerging as efficacious treatments for cancer, including engineered antibodies that target tumor cells, such as rituximab [84] and trastuzumab [85], as well antibodies or drugs that manipulate immunostimulatory or immunoinhibitory signals that can be used to induce immune effectors to recognize cancer cells [86–88], such as anti-CTLA-4, which can enable T cell activation via stimulation of CD80 and CD86 [89], anti-PD-L1, which can reverse immunosuppression [90] or anti-CD47, which enhances phagocytosis of cancer cells [91]. Thus, a robust host immune response may be useful or necessary for the complete clearance of tumor cells [86,87]. By specifically activating effectors of the immune response, one can elicit a robust therapeutic response.

Oncogene addiction and the immune response

Multiple studies provocatively suggest that targeted oncogene inactivation and oncogene addiction are mediated in concert with immune activation against tumor cells (summarized in Table 1, Fig. 1). Hence, oncogene inactivation appears to elicit tumor regression by reversing a cancer phenotype both from within tumor cells through cell autonomous mechanisms as well as outside the tumor cells through the activation of a host immune response. Together, this results in the remodeling the tumor microenvironment (Fig. 1) [92]. Thus, following oncogene inactivation, there appear to be discrete, temporally associated changes that occur in a tumor. Initially, within the first 2 days, tumor cells undergo proliferative arrest and apoptosis. Then, CD4⁺ T cells, as well as other immune effectors, are recruited to the tumor site and this response appears to be causally required to elicit cellular senescence of tumor cells and the shut down of angiogenesis in the host. Finally, additional immune effector cells may contribute to the clearance of remaining tumor cells (Fig. 1).

Prior studies suggested that oncogenes might regulate the ability of a tumor to recruit immune cells. Thus, oncogene activation can modulate the expression of some critical immune regulatory receptors [92], perturb normal immune cell development [93], and modulate the expression of critical immune regulatory cytokines [94]. Thus, it seemed possible that oncogene inactivation could restore an immune response. Indeed, oncogene

inactivation depends upon an immune response to induce tumor regression (Table 1) through many mechanisms (Fig. 1). In conditional transgenic mouse models of MYC or BCR-ABL tumorigenesis [95], oncogene inactivation only results in sustained tumor regression in immune intact hosts [58]. Notably, the kinetics of tumor regression, the extent of tumor regression, and the ability to maintain sustained tumor regression were all perturbed by up to 1000-fold in an immune compromised host [58] (Fig. 2).

Surprisingly, in CD4^{-/-} but not CD8^{-/-} hosts, oncogene inactivation failed to elicit sustained tumor regression. In CD4^{-/-} hosts, oncogene inactivation continued to result in proliferative arrest and apoptosis, but cellular senescence and shut down of angiogenesis was impeded [58]. Reconstitution of RAG1^{-/-} hosts with CD4⁺ T cells alone was sufficient to enable oncogene inactivation to induce sustained tumor regression. The absence of immune cells, generally, and CD4⁺ T cells, specifically, was likely to suppress tumor regression through an influence on other immune effectors and the expression of cytokines. Upon oncogene inactivation, there is a dramatic recruitment of immune cells to the tumor as measured by bioluminescence imaging of luciferase-labeled effector cells [58]. Thus, CD4⁺ T cells are causally involved in the mechanism of tumor regression upon oncogene inactivation.

Changes in cytokines are also likely important in the mechanism of tumor regression. Notably, there is an induction of anti-tumor and a suppression of pro-tumor cytokines after oncogene inactivation but only in immunocompetent, not immunocompromised, hosts [58]. Although many cytokines are likely to be involved, thrombospondin-1 (TSP-1) was found to be one critical cytokine [58]. Notably, immune cells that were TSP^{-/-} could not reconstitute the ability of RAG^{-/-} mice to elicit tumor regression upon oncogene inactivation. TSP-1 has been suggested to be a key regulator of not only angiogenesis but also senescence [96]. Moreover, CD47, the receptor of TSP, is a key regulator of the immune response [97]. Finally, TSP-1 and CD47 have been suggested to regulate cellular senescence [96,98,99]. Thus, there are likely multiple mechanisms by which TSP-1 could contribute to tumor regression.

CD4⁺ T cells are likely to contribute to tumor regression through many mechanisms. Of note, CD4⁺ T cells can express a variety of cytokines that have been implicated in the regulation of cellular senescence and/or angiogenesis [100–103]. But, CD4⁺ T cells may also be working via direct cellular interactions with the tumor cells or host stromal cells resident in the tumor microenvironment. Finally, CD4⁺ T cells may recruit other immune or host cells that contribute to the mechanism of tumor regression.

How MYC inactivation results in the activation of immune effectors, and specifically CD4⁺ T cells, is not clear. There are several non-mutually exclusive possibilities. First, MYC has been suggested to regulate the expression of molecules that may be immunosuppressive and/or regulate angiogenesis [104]. Hence, MYC inactivation could lead to the direct change in expression of cytokines by tumor cells, thereby recruiting immune cells [104]. Second, MYC inactivation could activate an immune response through immunogenic cell death [105]. Third, MYC inactivation could result in such a dramatic reduction in tumor growth that immune effectors are able to effectively compete to further suppress tumor growth.

Identifying the specific mechanism of the immune activation and response could suggest important strategies for monitoring and implementing a therapeutic response [19].

Importantly, many other immune effectors are likely to contribute to the response of targeted therapies. This is potentially governed by the unique genetic and cellular context of each tumor [106,107]. In other mouse models of oncogene-induced tumors, investigators have noted that innate immune cells such as mast cells [108], macrophages [109], and other antigen-presenting cells (APCs) may function as barriers to tumor growth and facilitators of tumor regression. Thus, it would seem likely that these other innate and adaptive immune cells as well as other host cells may contribute to the mechanism of tumor regression.

Combining immune therapy with targeted therapy could cooperate to induce efficacious treatment for human cancers (Fig. 2). In an immune-competent host, oncogene-targeted therapy may result in a robust immune response that leads to a swift and thorough tumor regression (left panel). However, the lack of an immune system dampens both the kinetics and the magnitude of tumor clearance, and tumor recurrence is almost guaranteed (center panel). To prevent disease relapse, immune-targeted therapy may cooperate with oncogene-targeted therapy (right panel). There are many types of immune therapy that could be useful, including boosting NK activity [110], modulating cytokine production by T cells and cytokine signaling [111], and transferring memory T cells [112,113]. Engineering of other specific cytotoxic and T helper cells [114], NK cells [138–142], gamma delta T cells [143], and APCs such as dendritic cells [144] could also be useful. Finally, modulating the humoral immune response could be effective [145,146]. Defining the precise contributions of different effectors could be integral to designing the most efficacious strategies for utilizing the immune system to treat cancer.

Targeted oncogene inactivation and immune response in human patients

The host immune response has been shown to be essential for the optimal response to cancer therapy in human patients [115]. Select chemotherapeutics and radiotherapy mediate their anti-tumor effects in part by inducing an immune response [116,117]. Because conventional therapeutics often also impede the immune system, they may be limited in their efficacy [118]. In contrast, targeted oncogene inactivation provides a strategy to selectively target tumor cells that may not inhibit immune activation and, ideally, may cooperate with immune therapies.

Significant evidence suggests that targeted oncogene inactivation recruits an immune response (Table 1). In patients with BCR-ABL⁺ gastrointestinal stromal tumors treated with imatinib, a better prognosis has been associated with IFN- γ secretion by NK cells in the peripheral blood [119]. Similarly, CD8⁺ T cells were essential for optimal responses to imatinib, and this may be due to a reduction in the immunosuppressive enzyme indoleamine 2,3-dioxygenase (Ido) within the tumor cells. Thus, the best clinical outcomes may be obtained through combination of oncogene-targeted therapy together with immune-modulating therapy.

Oncogene inhibition appears to induce tumor regression both through direct effects on tumor cells as well as recruitment of an immune response; this is true for many oncogenes, as

summarized (Table 1). The inhibition of BRAF has a direct influence on tumor growth but also appears to activate the immune system [120]. The combination of immune therapy and vemurafenib may be synergistic [121]. Vemurafenib increased intratumoral accumulation of adoptively transferred T cells [122]. Similarly, vemurafenib increased the number of CD4⁺ or CD8⁺ T cells in tumors in Stage III and Stage IV melanoma [120]. The presence of tumor-infiltrating lymphocytes after BRAF inhibition is associated with a better clinical prognosis [120]. Lastly, targeting BRAF V600E appears to diminish the expression of immunosuppressive cytokines and chemokines [123]. Ongoing investigations will determine whether optimal combinations and doses of vemurafenib in combination with immunotherapy are more clinically efficacious [124,125]. Sunitinib, which can target PDGFR, RET, and KIT, may also recruit and/or depend on the immune response for its optimal function as a tyrosine kinase inhibitor [126]. Sunitinib treatment increases IFN- γ -producing T cells [127] and decreases regulatory T cells [127,128].

Other targeted therapies may induce an immune response in addition to their tumor-specific effects (Table 1). The combination of arsenic and all-trans-retinoic acid is used against PML-RAR α , and can modulate antigen presentation [129]. Bortezomib, an agent used for multiple myeloma that targets the proteasome and NF- κ B, can affect numbers of CD8⁺ T cells and dendritic cells [130]. Erlotinib, a successful non-small cell lung cancer therapeutic that targets EGFR, can also induce an influx of dendritic cells [131]. Lastly, the efficacy of trastuzumab, a breast and ovarian cancer therapeutic that targets HER2/neu, may depend on a robust NK cell response [132,133]. Thus, targeted inhibition of oncogenes may be efficacious via activation of an immune response and may synergize with immunotherapy (Fig. 2).

However, the targeted inactivation of oncogenes may have undesired effects on the immune response. The MAPK/extracellular signal-regulated kinase kinase (MEK) inhibitors can induce potent T cell inhibition [134]. Imatinib has been shown experimentally to influence the immune response in a multitude of ways [34,58,135–139]. Similarly, targeted inactivation of oncogenes such as MYC and RAS could have profound effects on immune activation [34]. Consequently, it will be pivotal to consider that targeted oncogene inactivation can have positive and negative influences on the contribution of the immune system to the therapeutic response.

Implications: targeted oncogene inactivation and the immune response

Generally, targeted oncogene inactivation can elicit an immune response that may be critical to tumor regression (Table 1). In preclinical identification of therapeutic agents that target oncogenes, it is important to utilize model systems that have an intact host immune system. Thus, xenograft models may underestimate the efficacy of therapeutics. Monitoring the immune response may be useful to predict the efficacy of targeted therapeutics both during preclinical and clinical studies. This could include the evaluation of immune cellular effectors as well as specific cytokines.

The immune response dynamically evolves because of interactions between the tumor and the host [140]. The immune state of a host cannot just be measured prior to therapy, but also

will have to be examined after a therapeutic response. It is likely that this response may predict the outcome. A deliberate understanding of how targeted oncogene therapies influence immune activation should enable a directed approach to combining immune and targeted therapies.

Oncogene inactivation alone appears to be able to induce tumor regression both through a direct effect on tumor cells as well as by recruiting immune effectors that can remodel the tumor microenvironment. The judicious combination of oncogene-targeted therapy with specific immunomodulatory therapy may further increase the clinical response and long-term survival of patients [124,141,142]. Pointedly, immune activation may be essential to prevent the emergence of therapy-resistant tumor cells, which can lead to tumor recurrence [143,144] (Fig. 2). Hence, the identification of the best agents to elicit oncogene addiction will require examination of the efficacy of these therapies and consideration of their ability to induce both cell autonomous and host-dependent mechanisms of tumor regression.

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References

1. Jain M, Arvanitis C, Chu K, Dewey W, Leonhardt E, Trinh M, Sundberg CD, Bishop JM, Felsher DW. Sustained loss of a neoplastic phenotype by brief inactivation of MYC. *Science*. 2002; 297:102–104. [PubMed: 12098700]
2. Shachaf CM, Kopelman AM, Arvanitis C, Karlsson A, Beer S, Mandl S, Bachmann MH, Borowsky AD, Ruebner B, Cardiff RD, et al. MYC inactivation uncovers pluripotent differentiation and tumour dormancy in hepatocellular cancer. *Nature*. 2004; 431:1112–1117. [PubMed: 15475948]
3. Hennighausen L, Wall RJ, Tillmann U, Li M, Furth PA. Conditional gene expression in secretory tissues and skin of transgenic mice using the MMTV-LTR and the tetracycline responsive system. *J Cell Biochem*. 1995; 59:463–472. [PubMed: 8749716]
4. Felsher DW, Bishop JM. Reversible tumorigenesis by MYC in hematopoietic lineages. *Mol Cell*. 1999; 4:199–207. [PubMed: 10488335]
5. Chin L, Tam A, Pomerantz J, Wong M, Holash J, Bardeesy N, Shen Q, O'Hagan R, Pantginis J, Zhou H, et al. Essential role for oncogenic Ras in tumour maintenance. *Nature*. 1999; 400:468–472. [PubMed: 10440378]
6. D'Cruz CM, Gunther EJ, Boxer RB, Hartman JL, Sintasath L, Moody SE, Cox JD, Ha SI, Belka GK, Golant A, et al. c-MYC induces mammary tumorigenesis by means of a preferred pathway involving spontaneous Kras2 mutations. *Nat Med*. 2001; 7:235–239. [PubMed: 11175856]
7. Fisher GH, Wellen SL, Klimstra D, Lenczowski JM, Tichelaar JW, Lizak MJ, Whitsett JA, Koretsky A, Varmus HE. Induction and apoptotic regression of lung adenocarcinomas by regulation of a K-Ras transgene in the presence and absence of tumor suppressor genes. *Genes Dev*. 2001; 15:3249–3262. [PubMed: 11751631]
8. Huettner CS, Zhang P, Van Etten RA, Tenen DG. Reversibility of acute B-cell leukaemia induced by BCR-ABL1. *Nat Genet*. 2000; 24:57–60. [PubMed: 10615128]
9. Marinkovic D, Marinkovic T, Mahr B, Hess J, Wirth T. Reversible lymphomagenesis in conditionally c-MYC expressing mice. *Int J Cancer*. 2004; 110:336–342. [PubMed: 15095297]

10. Karlsson A, Giuriato S, Tang F, Fung-Weier J, Levan G, Felsher DW. Genomically complex lymphomas undergo sustained tumor regression upon MYC inactivation unless they acquire novel chromosomal translocations. *Blood*. 2003; 101:2797–2803. [PubMed: 12517816]
11. Felsher DW. Cancer revoked: oncogenes as therapeutic targets. *Nat Rev Cancer*. 2003; 3:375–380. [PubMed: 12724735]
12. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011; 144:646–674. [PubMed: 21376230]
13. Weinstein IB. Cancer. Addiction to oncogenes--the Achilles heel of cancer. *Science*. 2002; 297:63–64. [PubMed: 12098689]
14. Felsher DW. Oncogene addiction versus oncogene amnesia: perhaps more than just a bad habit? *Cancer Res*. 2008; 68:3081–3086. discussion 3086. [PubMed: 18451131]
15. Kaelin WG Jr. The concept of synthetic lethality in the context of anticancer therapy. *Nat Rev Cancer*. 2005; 5:689–698. [PubMed: 16110319]
16. Sharma SV, Settleman J. Oncogene addiction: setting the stage for molecularly targeted cancer therapy. *Genes Dev*. 2007; 21:3214–3231. [PubMed: 18079171]
17. Bozic I, Antal T, Ohtsuki H, Carter H, Kim D, Chen S, Karchin R, Kinzler KW, Vogelstein B, Nowak MA. Accumulation of driver and passenger mutations during tumor progression. *Proc Natl Acad Sci U S A*. 2010; 107:18545–18550. [PubMed: 20876136]
18. Wood LD, Parsons DW, Jones S, Lin J, Sjoblom T, Leary RJ, Shen D, Boca SM, Barber T, Ptak J, et al. The genomic landscapes of human breast and colorectal cancers. *Science*. 2007; 318:1108–1113. [PubMed: 17932254]
19. Restifo NP. Can antitumor immunity help to explain "oncogene addiction"? *Cancer Cell*. 2010; 18:403–405. [PubMed: 21075303]
20. Furth PA. Cancer prevention as biomodulation: targeting the initiating stimulus and secondary adaptations. *Ann N Y Acad Sci*. 2012; 1271:1–9. [PubMed: 23050958]
21. Ding ZC, Huang L, Blazar BR, Yagita H, Mellor AL, Munn DH, Zhou G. Polyfunctional CD4(+) T cells are essential for eradicating advanced B-cell lymphoma after chemotherapy. *Blood*. 2012; 120:2229–2239. [PubMed: 22859605]
22. Ding ZC, Zhou G. Cytotoxic chemotherapy and CD4+ effector T cells: an emerging alliance for durable antitumor effects. *Clin Dev Immunol*. 2012; 2012:890178. [PubMed: 22400040]
23. Anders K, Buschow C, Herrmann A, Milojkovic A, Loddenkemper C, Kammertoens T, Daniel P, Yu H, Charo J, Blankenstein T. Oncogene-targeting T cells reject large tumors while oncogene inactivation selects escape variants in mouse models of cancer. *Cancer Cell*. 2011; 20:755–767. [PubMed: 22172721]
24. Zitvogel L, Kepp O, Kroemer G. Immune parameters affecting the efficacy of chemotherapeutic regimens. *Nat Rev Clin Oncol*. 2011; 8:151–160. [PubMed: 21364688]
25. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pages C, Tosolini M, Camus M, Berger A, Wind P, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science*. 2006; 313:1960–1964. [PubMed: 17008531]
26. Dave SS, Wright G, Tan B, Rosenwald A, Gascoyne RD, Chan WC, Fisher RI, Braziel RM, Rimsza LM, Grogan TM, et al. Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. *N Engl J Med*. 2004; 351:2159–2169. [PubMed: 15548776]
27. Shortt J, Johnstone RW. Oncogenes in cell survival and cell death. *Cold Spring Harb Perspect Biol*. 2012;4.
28. Baker SJ, Reddy EP. Targeted inhibition of kinases in cancer therapy. *Mt Sinai J Med*. 2010; 77:573–586. [PubMed: 21105121]
29. Houshmand P, Zlotnik A. Targeting tumor cells. *Curr Opin Cell Biol*. 2003; 15:640–644. [PubMed: 14519400]
30. Blay JY, Le Cesne A, Alberti L, Ray-Coquart I. Targeted cancer therapies. *Bull Cancer*. 2005; 92:E13–E18. [PubMed: 15749638]
31. Soria JC, Blay JY, Spano JP, Pivot X, Coscas Y, Khayat D. Added value of molecular targeted agents in oncology. *Ann Oncol*. 2011; 22:1703–1716. [PubMed: 21300696]

32. Nagai S, Takahashi T, Kurokawa M. The impact of molecularly targeted therapies upon the understanding of leukemogenesis and the role of hematopoietic stem cell transplantation in acute promyelocytic leukemia. *Curr Stem Cell Res Ther.* 2010; 5:372–378. [PubMed: 20528759]
33. Bollag G, Tsai J, Zhang J, Zhang C, Ibrahim P, Nolop K, Hirth P. Vemurafenib: the first drug approved for BRAF-mutant cancer. *Nat Rev Drug Discov.* 2012; 11:873–886. [PubMed: 23060265]
34. Casey SC, Bellovin DI, Felsher DW. Noncanonical roles of the immune system in eliciting oncogene addiction. *Curr Opin Immunol.* 2013; 25:246–258. [PubMed: 23571026]
35. Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, Jenkins RB, Kwiatkowski DJ, Saldivar JS, Squire J, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *Arch Pathol Lab Med.* 2013; 137:828–860. [PubMed: 23551194]
36. O'Bryant CL, Wenger SD, Kim M, Thompson LA. Crizotinib: a new treatment option for ALK-positive non-small cell lung cancer. *Ann Pharmacother.* 2013; 47:189–197. [PubMed: 23386065]
37. Casaluce F, Sgambato A, Maione P, Rossi A, Ferrara C, Napolitano A, Palazzolo G, Ciardiello F, Gridelli C. ALK inhibitors: a new targeted therapy in the treatment of advanced NSCLC. *Target Oncol.* 2013; 8:55–67. [PubMed: 23325296]
38. Younes A, Romaguera J, Fanale M, McLaughlin P, Hagemester F, Copeland A, Neelapu S, Kwak L, Shah J, de Castro Faria S, et al. Phase I study of a novel oral Janus kinase 2 inhibitor, SB1518, in patients with relapsed lymphoma: evidence of clinical and biologic activity in multiple lymphoma subtypes. *J Clin Oncol.* 2012; 30:4161–4167. [PubMed: 22965964]
39. Cheok CF, Verma CS, Baselga J, Lane DP. Translating p53 into the clinic. *Nat Rev Clin Oncol.* 2011; 8:25–37. [PubMed: 20975744]
40. Essmann F, Schulze-Osthoff K. Translational approaches targeting the p53 pathway for anti-cancer therapy. *Br J Pharmacol.* 2012; 165:328–344. [PubMed: 21718309]
41. Fruman DA, Rommel C. PI3Kdelta inhibitors in cancer: rationale and serendipity merge in the clinic. *Cancer Discov.* 2011; 1:562–572. [PubMed: 22586681]
42. Roschewski M, Farooqui M, Aue G, Wilhelm F, Wiestner A. Phase I study of ON 01910.Na (Rigosertib), a multikinase PI3K inhibitor in relapsed/refractory B-cell malignancies. *Leukemia.* 2013; 27:1920–1923. [PubMed: 23486532]
43. Hong DS, Bowles DW, Falchook GS, Messersmith WA, George GC, O'Bryant CL, Vo AC, Klucher K, Herbst RS, Eckhardt SG, et al. A multicenter phase I trial of PX-866, an oral irreversible phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors. *Clin Cancer Res.* 2012; 18:4173–4182. [PubMed: 22693357]
44. Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature.* 2013; 503:548–551. [PubMed: 24256730]
45. Ott CJ, Kopp N, Bird L, Paranal RM, Qi J, Bowman T, Rodig SJ, Kung AL, Bradner JE, Weinstock DM. BET bromodomain inhibition targets both c-Myc and IL7R in high-risk acute lymphoblastic leukemia. *Blood.* 2012; 120:2843–2852. [PubMed: 22904298]
46. Delmore JE, Issa GC, Lemieux ME, Rahl PB, Shi J, Jacobs HM, Kastiris E, Gilpatrick T, Paranal RM, Qi J, et al. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. *Cell.* 2011; 146:904–917. [PubMed: 21889194]
47. Hoeflich KP, Gray DC, Eby MT, Tien JY, Wong L, Bower J, Gogineni A, Zha J, Cole MJ, Stern HM, et al. Oncogenic BRAF is required for tumor growth and maintenance in melanoma models. *Cancer Res.* 2006; 66:999–1006. [PubMed: 16424035]
48. Boxer RB, Jang JW, Sintasath L, Chodosh LA. Lack of sustained regression of c-MYC-induced mammary adenocarcinomas following brief or prolonged MYC inactivation. *Cancer Cell.* 2004; 6:577–586. [PubMed: 15607962]
49. Giuriato S, Rabin K, Fan AC, Shachaf CM, Felsher DW. Conditional animal models: a strategy to define when oncogenes will be effective targets to treat cancer. *Semin Cancer Biol.* 2004; 14:3–11. [PubMed: 14757531]
50. Felsher DW. Reversing cancer from inside and out: oncogene addiction, cellular senescence, and the angiogenic switch. *Lymphat Res Biol.* 2008; 6:149–154. [PubMed: 19093787]

51. Shachaf CM, Felsher DW. Rehabilitation of cancer through oncogene inactivation. *Trends Mol Med.* 2005; 11:316–321. [PubMed: 15955741]
52. Shachaf CM, Felsher DW. Tumor dormancy and MYC inactivation: pushing cancer to the brink of normalcy. *Cancer Res.* 2005; 65:4471–4474. [PubMed: 15930260]
53. Bellovin DI, Das B, Felsher DW. Tumor dormancy, oncogene addiction, cellular senescence, and self-renewal programs. *Adv Exp Med Biol.* 2013; 734:91–107. [PubMed: 23143977]
54. Giuriato S, Ryeom S, Fan AC, Bachireddy P, Lynch RC, Rieth MJ, van Riggelen J, Kopelman AM, Passegue E, Tang F, et al. Sustained regression of tumors upon MYC inactivation requires p53 or thrombospondin-1 to reverse the angiogenic switch. *Proc Natl Acad Sci U S A.* 2006; 103:16266–16271. [PubMed: 17056717]
55. Baudino TA, McKay C, Pendeville-Samain H, Nilsson JA, Maclean KH, White EL, Davis AC, Ihle JN, Cleveland JL. c-Myc is essential for vasculogenesis and angiogenesis during development and tumor progression. *Genes Dev.* 2002; 16:2530–2543. [PubMed: 12368264]
56. Brandvold KA, Neiman P, Ruddell A. Angiogenesis is an early event in the generation of myc-induced lymphomas. *Oncogene.* 2000; 19:2780–2785. [PubMed: 10851079]
57. Janz A, Seignani C, Kenyon K, Ngo CV, Thomas-Tikhonenko A. Activation of the myc oncoprotein leads to increased turnover of thrombospondin-1 mRNA. *Nucleic Acids Res.* 2000; 28:2268–2275. [PubMed: 10871348]
58. Rakhra K, Bachireddy P, Zabuawala T, Zeiser R, Xu L, Kopelman A, Fan AC, Yang Q, Braunstein L, Crosby E, et al. CD4(+) T cells contribute to the remodeling of the microenvironment required for sustained tumor regression upon oncogene inactivation. *Cancer Cell.* 2010; 18:485–498. [PubMed: 21035406]
59. Albini A, Sporn MB. The tumour microenvironment as a target for chemoprevention. *Nat Rev Cancer.* 2007; 7:139–147. [PubMed: 17218951]
60. Coussens LM, Tinkle CL, Hanahan D, Werb Z. MMP-9 supplied by bone marrow-derived cells contributes to skin carcinogenesis. *Cell.* 2000; 103:481–490. [PubMed: 11081634]
61. Bissell MJ, Radisky D. Putting tumours in context. *Nat Rev Cancer.* 2001; 1:46–54. [PubMed: 11900251]
62. Shankaran V, Ikeda H, Bruce AT, White JM, Swanson PE, Old LJ, Schreiber RD. IFN γ and lymphocytes prevent primary tumour development and shape tumour immunogenicity. *Nature.* 2001; 410:1107–1111. [PubMed: 11323675]
63. de Visser KE, Korets LV, Coussens LM. De novo carcinogenesis promoted by chronic inflammation is B lymphocyte dependent. *Cancer Cell.* 2005; 7:411–423. [PubMed: 15894262]
64. Dougan M, Li D, Neuberg D, Mihm M, Googe P, Wong KK, Dranoff G. A dual role for the immune response in a mouse model of inflammation-associated lung cancer. *J Clin Invest.* 2011; 121:2436–2446. [PubMed: 21537082]
65. Ruffell B, DeNardo DG, Affara NI, Coussens LM. Lymphocytes in cancer development: polarization towards pro-tumor immunity. *Cytokine Growth Factor Rev.* 2010; 21:3–10. [PubMed: 20005150]
66. Gross E, Sunwoo JB, Bui JD. Cancer immunosurveillance and immunoediting by natural killer cells. *Cancer J.* 2013; 19:483–489. [PubMed: 24270347]
67. Torroella-Kouri M, Rodriguez D, Caso R. Alterations in macrophages and monocytes from tumor-bearing mice: evidence of local and systemic immune impairment. *Immunol Res.* 2013; 57:86–98. [PubMed: 24203436]
68. Iannello A, Raulet DH. Immune Surveillance of Unhealthy Cells by Natural Killer Cells. *Cold Spring Harb Symp Quant Biol.* 2013
69. Raj N, Attardi LD. Tumor suppression: p53 alters immune surveillance to restrain liver cancer. *Curr Biol.* 2013; 23:R527–R530. [PubMed: 23787049]
70. Gasser S, Raulet D. The DNA damage response, immunity and cancer. *Semin Cancer Biol.* 2006; 16:344–347. [PubMed: 16914325]
71. Chaturvedi AK, Pfeiffer RM, Chang L, Goedert JJ, Biggar RJ, Engels EA. Elevated risk of lung cancer among people with AIDS. *AIDS.* 2007; 21:207–213. [PubMed: 17197812]

72. Mbulaiteye SM, Biggar RJ, Goedert JJ, Engels EA. Immune deficiency and risk for malignancy among persons with AIDS. *J Acquir Immune Defic Syndr*. 2003; 32:527–533. [PubMed: 12679705]
73. Dugue PA, Rebolj M, Garred P, Lynge E. Immunosuppression and risk of cervical cancer. *Expert Rev Anticancer Ther*. 2013; 13:29–42. [PubMed: 23259425]
74. Kubica AW, Brewer JD. Melanoma in immunosuppressed patients. *Mayo Clin Proc*. 2012; 87:991–1003. [PubMed: 23036673]
75. Hoover RN. Lymphoma risks in populations with altered immunity--a search for mechanism. *Cancer Res*. 1992; 52:5477s–5478s. [PubMed: 1394157]
76. Boshoff C, Weiss R. AIDS-related malignancies. *Nat Rev Cancer*. 2002; 2:373–382. [PubMed: 12044013]
77. Ray-Coquard I, Cropet C, Van Glabbeke M, Sebban C, Le Cesne A, Judson I, Tredan O, Verweij J, Biron P, Labidi I, et al. Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. *Cancer Res*. 2009; 69:5383–5391. [PubMed: 19549917]
78. Al-Tameemi M, Chaplain M, d'Onofrio A. Evasion of tumours from the control of the immune system: consequences of brief encounters. *Biol Direct*. 2012; 7:31. [PubMed: 23009638]
79. Ribas A. Immunoediting the cancer genome--a new approach for personalized cancer therapy? *Pigment Cell Melanoma Res*. 2012; 25:297–298. [PubMed: 22629569]
80. Peggs KS, Quezada SA, Allison JP. Cell intrinsic mechanisms of T-cell inhibition and application to cancer therapy. *Immunol Rev*. 2008; 224:141–165. [PubMed: 18759925]
81. Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. *Nat Rev Immunol*. 2006; 6:715–727. [PubMed: 16977338]
82. Martins I, Wang Y, Michaud M, Ma Y, Sukkurwala AQ, Shen S, Kepp O, Metivier D, Galluzzi L, Perfettini JL, et al. Molecular mechanisms of ATP secretion during immunogenic cell death. *Cell Death Differ*. 2014; 21:79–91. [PubMed: 23852373]
83. Vacchelli E, Senovilla L, Eggermont A, Fridman WH, Galon J, Zitvogel L, Kroemer G, Galluzzi L. Trial watch: Chemotherapy with immunogenic cell death inducers. *Oncoimmunology*. 2013; 2:e23510. [PubMed: 23687621]
84. Maloney DG, Grillo-Lopez AJ, White CA, Bodkin D, Schilder RJ, Neidhart JA, Janakiraman N, Foon KA, Liles TM, Dallaire BK, et al. IDEC-C2B8 (Rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. *Blood*. 1997; 90:2188–2195. [PubMed: 9310469]
85. Pegram MD, Konecny G, Slamon DJ. The molecular and cellular biology of HER2/neu gene amplification/overexpression and the clinical development of herceptin (trastuzumab) therapy for breast cancer. *Cancer Treat Res*. 2000; 103:57–75. [PubMed: 10948442]
86. Obeid M, Tesniere A, Ghiringhelli F, Fimia GM, Apetoh L, Perfettini JL, Castedo M, Mignot G, Panaretakis T, Casares N, et al. Calreticulin exposure dictates the immunogenicity of cancer cell death. *Nat Med*. 2007; 13:54–61. [PubMed: 17187072]
87. Shiao SL, Coussens LM. The tumor-immune microenvironment and response to radiation therapy. *J Mammary Gland Biol Neoplasia*. 2010; 15:411–421. [PubMed: 21161342]
88. Pardoll DM. Immunology beats cancer: a blueprint for successful translation. *Nat Immunol*. 2012; 13:1129–1132. [PubMed: 23160205]
89. Acharya UH, Jeter JM. Use of ipilimumab in the treatment of melanoma. *Clin Pharmacol*. 2013; 5:21–27. [PubMed: 24113540]
90. Devaud C, John LB, Westwood JA, Darcy PK, Kershaw MH. Immune modulation of the tumor microenvironment for enhancing cancer immunotherapy. *Oncoimmunology*. 2013; 2:e25961. [PubMed: 24083084]
91. Chao MP, Weissman IL, Majeti R. The CD47-SIRPalpha pathway in cancer immune evasion and potential therapeutic implications. *Curr Opin Immunol*. 2012; 24:225–232. [PubMed: 22310103]
92. Parsa AT, Waldron JS, Panner A, Crane CA, Parney IF, Barry JJ, Cachola KE, Murray JC, Tihan T, Jensen MC, et al. Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma. *Nat Med*. 2007; 13:84–88. [PubMed: 17159987]

93. Mattarollo SR, West AC, Steegh K, Duret H, Paget C, Martin B, Matthews GM, Shortt J, Chesi M, Bergsagel PL, et al. NKT cell adjuvant-based tumor vaccine for treatment of myc oncogene-driven mouse B-cell lymphoma. *Blood*. 2012; 120:3019–3029. [PubMed: 22932803]
94. Kawakami Y, Yaguchi T, Sumimoto H, Kudo-Saito C, Tsukamoto N, Iwata-Kajihara T, Nakamura S, Nishio H, Satomi R, Kobayashi A, et al. Cancer-induced immunosuppressive cascades and their reversal by molecular-targeted therapy. *Ann N Y Acad Sci*. 2013; 1284:80–86. [PubMed: 23651199]
95. Gossen M, Bujard H. Tight control of gene expression in mammalian cells by tetracycline-responsive promoters. *Proc Natl Acad Sci U S A*. 1992; 89:5547–5551. [PubMed: 1319065]
96. Lawler PR, Lawler J. Molecular basis for the regulation of angiogenesis by thrombospondin-1 and-2. *Cold Spring Harb Perspect Med*. 2012; 2:a006627. [PubMed: 22553494]
97. Li SS, Liu Z, Uzunel M, Sundqvist KG. Endogenous thrombospondin-1 is a cell-surface ligand for regulation of integrin-dependent T-lymphocyte adhesion. *Blood*. 2006; 108:3112–3120. [PubMed: 16835379]
98. Baek KH, Bhang D, Zaslavsky A, Wang LC, Vachani A, Kim CF, Albelda SM, Evan GI, Ryeom S. Thrombospondin-1 mediates oncogenic Ras-induced senescence in premalignant lung tumors. *J Clin Invest*. 2013; 123:4375–4389. [PubMed: 24018559]
99. Sosale N, Discher DE. Marker-of-self becomes marker-of-senescence. *Blood*. 2012; 119:5343–5344. [PubMed: 22679336]
100. Acosta JC, O’Loghlen A, Banito A, Guijarro MV, Augert A, Raguz S, Fumagalli M, Da Costa M, Brown C, Popov N, et al. Chemokine signaling via the CXCR2 receptor reinforces senescence. *Cell*. 2008; 133:1006–1018. [PubMed: 18555777]
101. Beatty G, Paterson Y. IFN-gamma-dependent inhibition of tumor angiogenesis by tumor-infiltrating CD4+ T cells requires tumor responsiveness to IFN-gamma. *J Immunol*. 2001; 166:2276–2282. [PubMed: 11160282]
102. Kuilman T, Michaloglou C, Vredeveld LC, Douma S, van Doorn R, Desmet CJ, Aarden LA, Mooi WJ, Peepers DS. Oncogene-induced senescence relayed by an interleukin-dependent inflammatory network. *Cell*. 2008; 133:1019–1031. [PubMed: 18555778]
103. Muller-Hermelink N, Braumuller H, Pichler B, Wieder T, Mailhammer R, Schaak K, Ghoreschi K, Yazdi A, Haubner R, Sander CA, et al. TNFR1 signaling and IFN-gamma signaling determine whether T cells induce tumor dormancy or promote multistage carcinogenesis. *Cancer Cell*. 2008; 13:507–518. [PubMed: 18538734]
104. Whitfield JR, Soucek L. Tumor microenvironment: becoming sick of Myc. *Cell Mol Life Sci*. 2012; 69:931–934. [PubMed: 22033838]
105. Galluzzi L, Vitale I, Kroemer G. Past, present, and future of molecular and cellular oncology. *Front Oncol*. 2011; 1:1. [PubMed: 22655224]
106. Somasundaram R, Villanueva J, Herlyn M. Intratumoral heterogeneity as a therapy resistance mechanism: role of melanoma subpopulations. *Adv Pharmacol*. 2012; 65:335–359. [PubMed: 22959031]
107. Al-Ejeh F, Smart CE, Morrison BJ, Chenevix-Trench G, Lopez JA, Lakhani SR, Brown MP, Khanna KK. Breast cancer stem cells: treatment resistance and therapeutic opportunities. *Carcinogenesis*. 2011; 32:650–658. [PubMed: 21310941]
108. Soucek L, Lawlor ER, Soto D, Shchors K, Swigart LB, Evan GI. Mast cells are required for angiogenesis and macroscopic expansion of Myc-induced pancreatic islet tumors. *Nat Med*. 2007; 13:1211–1218. [PubMed: 17906636]
109. Reimann M, Lee S, Loddenkemper C, Dorr JR, Tabor V, Aichele P, Stein H, Dorken B, Jenuwein T, Schmitt CA. Tumor Stroma-Derived TGF-beta Limits Myc-Driven Lymphomagenesis via Suv39h1-Dependent Senescence. *Cancer Cell*. 2010; 17:262–272. [PubMed: 20227040]
110. Kerkar SP, Muranski P, Kaiser A, Boni A, Sanchez-Perez L, Yu Z, Palmer DC, Reger RN, Borman ZA, Zhang L, et al. Tumor-specific CD8+ T cells expressing interleukin-12 eradicate established cancers in lymphodepleted hosts. *Cancer Res*. 2010; 70:6725–6734. [PubMed: 20647327]

111. Zhang L, Yu Z, Muranski P, Palmer DC, Restifo NP, Rosenberg SA, Morgan RA. Inhibition of TGF-beta signaling in genetically engineered tumor antigen-reactive T cells significantly enhances tumor treatment efficacy. *Gene Ther.* 2012
112. Gattinoni L, Klebanoff CA, Restifo NP. Paths to stemness: building the ultimate antitumour T cell. *Nat Rev Cancer.* 2012; 12:671–684. [PubMed: 22996603]
113. Klebanoff CA, Gattinoni L, Restifo NP. Sorting through subsets: which T-cell populations mediate highly effective adoptive immunotherapy? *J Immunother.* 2012; 35:651–660. [PubMed: 23090074]
114. Mlecnik B, Tosolini M, Kirilovsky A, Berger A, Bindea G, Meatchi T, Bruneval P, Trajanoski Z, Fridman WH, Pages F, et al. Histopathologic-based prognostic factors of colorectal cancers are associated with the state of the local immune reaction. *J Clin Oncol.* 2011; 29:610–618. [PubMed: 21245428]
115. Prestwich RJ, Errington F, Hatfield P, Merrick AE, Ilett EJ, Selby PJ, Melcher AA. The immune system--is it relevant to cancer development, progression and treatment? *Clin Oncol (R Coll Radiol).* 2008; 20:101–112. [PubMed: 18037277]
116. Hannani D, Sistigu A, Kepp O, Galluzzi L, Kroemer G, Zitvogel L. Prerequisites for the antitumor vaccine-like effect of chemotherapy and radiotherapy. *Cancer J.* 2011; 17:351–358. [PubMed: 21952286]
117. Ma Y, Kepp O, Ghiringhelli F, Apetoh L, Aymeric L, Locher C, Tesniere A, Martins I, Ly A, Haynes NM, et al. Chemotherapy and radiotherapy: cryptic anticancer vaccines. *Semin Immunol.* 2010; 22:113–124. [PubMed: 20403709]
118. Dougan M, Dranoff G. Immune therapy for cancer. *Annu Rev Immunol.* 2009; 27:83–117. [PubMed: 19007331]
119. Menard C, Blay JY, Borg C, Michiels S, Ghiringhelli F, Robert C, Nonn C, Chaput N, Taieb J, Delahaye NF, et al. Natural killer cell IFN-gamma levels predict long-term survival with imatinib mesylate therapy in gastrointestinal stromal tumor-bearing patients. *Cancer Res.* 2009; 69:3563–3569. [PubMed: 19351841]
120. Wilmott JS, Long GV, Howle JR, Haydu LE, Sharma RN, Thompson JF, Kefford RF, Hersey P, Scolyer RA. Selective BRAF inhibitors induce marked T-cell infiltration into human metastatic melanoma. *Clin Cancer Res.* 2012; 18:1386–1394. [PubMed: 22156613]
121. Wilmott JS, Scolyer RA, Long GV, Hersey P. Combined targeted therapy and immunotherapy in the treatment of advanced melanoma. *Oncoimmunology.* 2012; 1:997–999. [PubMed: 23189245]
122. Liu C, Peng W, Xu C, Lou Y, Zhang M, Wargo JA, Chen J, Li HS, Watowich S, Yang Y, et al. BRAF Inhibition Increases Tumor Infiltration by T cells and Enhances the Anti-tumor Activity of Adoptive Immunotherapy in Mice. *Clin Cancer Res.* 2012
123. Sumimoto H, Imabayashi F, Iwata T, Kawakami Y. The BRAF-MAPK signaling pathway is essential for cancer-immune evasion in human melanoma cells. *J Exp Med.* 2006; 203:1651–1656. [PubMed: 16801397]
124. Bajor DL, Vonderheide RH. Rehabilitation for oncogene addiction: role of immunity in cellular sobriety. *Clin Cancer Res.* 2012; 18:1192–1194. [PubMed: 22266272]
125. Knight DA, Ngiew SF, Li M, Parmenter T, Mok S, Cass A, Haynes NM, Kinross K, Yagita H, Koya RC, et al. Host immunity contributes to the anti-melanoma activity of BRAF inhibitors. *J Clin Invest.* 2013; 123:1371–1381. [PubMed: 23454771]
126. Bex A, Etto T, Vyth-Dreese F, Blank C, Griffioen AW. Immunological heterogeneity of the RCC microenvironment: do targeted therapies influence immune response? *Curr Oncol Rep.* 2012; 14:230–239. [PubMed: 22362358]
127. Finke JH, Rini B, Ireland J, Rayman P, Richmond A, Golshayan A, Wood L, Elson P, Garcia J, Dreicer R, et al. Sunitinib reverses type-1 immune suppression and decreases T-regulatory cells in renal cell carcinoma patients. *Clin Cancer Res.* 2008; 14:6674–6682. [PubMed: 18927310]
128. Busse A, Asemussen AM, Nonnenmacher A, Braun F, Ochsenreither S, Stather D, Fusi A, Schmittl A, Miller K, Thiel E, et al. Immunomodulatory effects of sorafenib on peripheral immune effector cells in metastatic renal cell carcinoma. *Eur J Cancer.* 2011; 47:690–696. [PubMed: 21215610]

129. Zhang H, Melamed J, Wei P, Cox K, Frankel W, Bahnson RR, Robinson N, Pyka R, Liu Y, Zheng P. Concordant down-regulation of proto-oncogene PML and major histocompatibility antigen HLA class I expression in high-grade prostate cancer. *Cancer Immun.* 2003; 3:2. [PubMed: 12747744]
130. Chang CL, Hsu YT, Wu CC, Yang YC, Wang C, Wu TC, Hung CF. Immune mechanism of the antitumor effects generated by bortezomib. *J Immunol.* 2012; 189:3209–3220. [PubMed: 22896634]
131. Guttman-Yassky E, Mita A, De Jonge M, Matthews L, McCarthy S, Iwata KK, Verweij J, Rowinsky EK, Krueger JG. Characterisation of the cutaneous pathology in non-small cell lung cancer (NSCLC) patients treated with the EGFR tyrosine kinase inhibitor erlotinib. *Eur J Cancer.* 2010; 46:2010–2019. [PubMed: 20621734]
132. Jaime-Ramirez AC, Mundy-Bosse BL, Kondadasula S, Jones NB, Roda JM, Mani A, Parihar R, Karpa V, Papenfuss TL, LaPerle KM, et al. IL-12 enhances the antitumor actions of trastuzumab via NK cell IFN-gamma production. *J Immunol.* 2011; 186:3401–3409. [PubMed: 21321106]
133. Kohrt HE, Houot R, Weiskopf K, Goldstein MJ, Scheeren F, Czerwinski D, Colevas AD, Weng WK, Clarke MF, Carlson RW, et al. Stimulation of natural killer cells with a CD137-specific antibody enhances trastuzumab efficacy in xenotransplant models of breast cancer. *J Clin Invest.* 2012; 122:1066–1075. [PubMed: 22326955]
134. Boni A, Cogdill AP, Dang P, Udayakumar D, Njauw CN, Sloss CM, Ferrone CR, Flaherty KT, Lawrence DP, Fisher DE, et al. Selective BRAFV600E inhibition enhances T-cell recognition of melanoma without affecting lymphocyte function. *Cancer Res.* 2010; 70:5213–5219. [PubMed: 20551059]
135. Catellani S, Pierri I, Gobbi M, Poggi A, Zocchi MR. Imatinib treatment induces CD5+ B lymphocytes and IgM natural antibodies with anti-leukemic reactivity in patients with chronic myelogenous leukemia. *PLoS One.* 2011; 6:e18925. [PubMed: 21533122]
136. Krusch M, Salih HR. Effects of BCR-ABL inhibitors on anti-tumor immunity. *Curr Med Chem.* 2011; 18:5174–5184. [PubMed: 22087818]
137. Ohyashiki K, Katagiri S, Tauchi T, Ohyashiki JH, Maeda Y, Matsumura I, Kyo T. Increased natural killer cells and decreased CD3(+)CD8(+)CD62L(+) T cells in CML patients who sustained complete molecular remission after discontinuation of imatinib. *Br J Haematol.* 2012; 157:254–256. [PubMed: 22077498]
138. Kreutzman A, Juvonen V, Kairisto V, Ekblom M, Stenke L, Seggewiss R, Porkka K, Mustjoki S. Mono/oligoclonal T and NK cells are common in chronic myeloid leukemia patients at diagnosis and expand during dasatinib therapy. *Blood.* 2010; 116:772–782. [PubMed: 20413659]
139. Chen J, Schmitt A, Giannopoulos K, Chen B, Rojewski M, Dohner H, Bunjes D, Schmitt M. Imatinib impairs the proliferation and function of CD4+CD25+ regulatory T cells in a dose-dependent manner. *Int J Oncol.* 2007; 31:1133–1139. [PubMed: 17912440]
140. Blank CU, Hooijkaas AI, Haanen JB, Schumacher TN. Combination of targeted therapy and immunotherapy in melanoma. *Cancer Immunol Immunother.* 2011; 60:1359–1371. [PubMed: 21847631]
141. Wrzesinski C, Paulos CM, Kaiser A, Muranski P, Palmer DC, Gattinoni L, Yu Z, Rosenberg SA, Restifo NP. Increased intensity lymphodepletion enhances tumor treatment efficacy of adoptively transferred tumor-specific T cells. *J Immunother.* 2010; 33:1–7. [PubMed: 19952961]
142. Humphrey RW, Brockway-Lunardi LM, Bonk DT, Dohoney KM, Doroshow JH, Meech SJ, Ratain MJ, Topalian SL, Pardoll DM. Opportunities and challenges in the development of experimental drug combinations for cancer. *J Natl Cancer Inst.* 2011; 103:1222–1226. [PubMed: 21765011]
143. Vanneman M, Dranoff G. Combining immunotherapy and targeted therapies in cancer treatment. *Nat Rev Cancer.* 2012; 12:237–251. [PubMed: 22437869]
144. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature.* 2011; 480:480–489. [PubMed: 22193102]

Fig. 1. The immune system is essential to the mechanism of oncogene addiction

The interaction between tumor cell-intrinsic and immune-mediated mechanisms is crucial for sustained tumor regression upon oncogene inactivation. Following oncogene inactivation in a mouse model or targeted therapy in the clinic, the tumor (*first panel*) will initially regress via proliferative arrest, differentiation, and/or apoptosis (*second panel*). If the host immune system is activated, immune effectors are recruited to the tumor site, leading to senescence and the shutdown of angiogenesis (*third panel*). As time progresses, both an innate and an adaptive immune response result in the clearance of residual tumor cells and a potent anti-tumor memory (*fourth panel*).

Fig. 2. Oncogene inactivation combined with immune therapy may be more efficacious as a treatment for cancer

In an immune-competent host, oncogene inactivation induces an immune response that leads to more rapid, complete, and sustained tumor regression (*left*). Conversely, oncogene inactivation in the absence of an immune system impedes the kinetics and extent of tumor elimination and is associated with tumor recurrence (*center*). The combination of oncogene inactivation together with immunostimulatory therapy may cooperate to induce more sustained tumor regression, in particular in circumstances where hosts are immune compromised (*right*).

Table 1

Select Oncogenes that, when targeted, recruit immune effectors.

Target Protein(s)	Tumor Type	Mechanism of Inactivation	Immune Effectors Recruited	Refs
<i>MYC</i>	T cell acute lymphoblastic lymphoma	Conditional Animal Models	CD4 ⁺ T cells, cytokines	[58]
<i>BCR-ABL</i>	Pro-B cell acute lymphocytic leukemia, CML, GIST	Conditional Animal Models, Imatinib	CD4 ⁺ T cells, CD8 ⁺ T cells, NK cells, cytokines,	[58,119]
<i>BRAF</i>	Melanoma	Vemurafenib	CD ⁺ T cells, CD8 ⁺ T cells, reduction in immunosuppressive cytokines	[120,123]
PDGFR, RET, or KIT	Kidney Cancer	Sunitinib	T cell activation, reduction of regulatory T cells, Influencing MHC class I antigen presentation	[126–128]
<i>PML</i>	Acute promyelocytic leukemia, prostate cancer	Arsenic+All-Trans-Retinoic Acid (ATRA)	CD8 ⁺ T cells	[129]
<i>HER2/Neu</i>	Breast Cancer	Trastuzumab	NK Cells	[132,133]
<i>Proteasome, NF-κB</i>	Multiple Myeloma	Bortezomib	CD8 ⁺ T cells, Dendritic cells	[130]
<i>EGFR</i>	Non-small cell lung cancer	Erlotinib	TRAIL ⁺ Dendritic cells	[131]