Published in final edited form as:
Update Cancer Ther. 2007 June 1; 2(2): 61–65. doi:10.1016/j.uct.2007.06.001.

Anti-CD40 agonist antibodies: preclinical and clinical experience

Magi Khalil and **Robert H. Vonderheide***
Abramson Family Cancer Research Institute; Abramson Cancer Center; Division of Hematology-Oncology, Department of Medicine; University of Pennsylvania School of Medicine, Philadelphia, PA

Abstract

The cell-surface molecule CD40, a member of the tumor necrosis factor receptor superfamily, broadly regulates immune activation and mediates tumor apoptosis. CD40 is expressed by antigen-presenting cells (APC) and engagement of its natural ligand on T cells activates APC including dendritic cells and B cells. Agonistic CD40 antibodies have been shown to substitute for T cell help provided by CD4+ lymphocytes in murine models of T cell-mediated immunity. In tumor-bearing hosts, CD40 agonists trigger effective immune responses against tumor-associated antigens. In contrast, CD40 is also expressed on many tumor cells and its ligation in this setting mediates a direct cytotoxic effect. Engagement of CD40 on tumor cells results in apoptosis *in vitro* and impaired tumor growth *in vivo*. These observations have prompted efforts to use agonistic CD40 antibodies for the treatment of cancer patients and initial clinical results have been promising.

Keywords

CD40; monoclonal antibody; tumor immunology; cancer

Introduction

CD40 is a transmembrane protein that is a member of the TNF receptor superfamily. It is expressed on a variety of normal cells such as B cells, macrophages, dendritic cells, epithelial, stromal, and endothelial cells as well as platelets. It is also found on a large portion of melanomas and carcinomas of the lung, breast, colon, prostate, pancreas, kidney, ovary, and head and neck as well as all of B cell malignancies (1–4). The ligand for CD40 (CD154 or CD40L) is expressed on activated T cells and platelets (3,5).

Ligation of CD40 on the surface of antigen presenting cells (APC) enhances the expression of MHC and costimulatory molecules such as CD86, stimulates the production of pro-inflammatroy cytokines such as IL-12 and induces T cell activation, all of which are essential to cell-mediated immune responses (1,3). Patients with germline mutations in either CD40 or CD40L are markedly immunosuppressed, susceptible to opportunistic infections, and have deficient T cell-dependent immune reactions including IgG production, germinal center formation, and memory B cell induction (6–8). In murine models of T cell-mediated immunity, agonist CD40 antibodies have been shown to mimic the signal of CD40L and substitute for

*Corresponding author: Robert H. Vonderheide, MD, DPhil, University of Pennsylvania School of Medicine, 551 BRB II/III, 421 Curie Blvd, Philadelphia, PA 19104; Email address: E-mail: rhv@mail.med.upenn.edu.

the function of CD4+ lymphocytes (9–11). Agonist CD40 antibodies can also overcome T cell tolerance in tumor-bearing mice, evoke effective cytotoxic T cell responses, and enhance the efficacy of anti-tumor vaccines (12–14).

These findings are in counter-distinction to ligation of CD40 on the surface of tumor cells, which in many cases mediates a direct cytotoxic effect resulting in tumor regression through apoptosis and necrosis (1,3). Although the exact function of CD40 on tumor cells is unclear (2), engagement of CD40 *in vitro* inhibits the growth of solid tumor cells and high-grade B cell lymphoma lines (15–20). In addition, CD40-mediated tumor inhibition has also been observed *in vivo*, including inhibition of breast carcinoma or B cell lymphoma xenografts in immunocomprised mice (15,21–23).

These diverse roles for CD40 provide an opportunity where activation of CD40 in a tumor-bearing animal has the potential of (i) a direct cytotoxic effect on the tumor, and (ii) provision of tumor antigens to APC simultaneously activated by CD40. Agonist monoclonal antibodies (mAb) to CD40 have already shown therapeutic activity in a range of preclinical models (24). These findings, along with the dual functionality of CD40, have made CD40 an attractive target for cancer therapy and form the rationale for the clinical development of agonist anti-CD40 antibodies.

Clinical trials of CD40 agonists

Several CD40 agonists have undergone phase 1 clinical evaluation in patients with advanced stage cancer and have yielded promising results (Table 1) (24). The first such agent to be tested was a trimeric form of a recombinant human CD40-ligand (rhuCD40L) (25). In this study 32 patients with advanced solid tumors or non-Hodgkin's lymphoma were treated with rhuCD40L subcutaneously daily for 5 days of each cycle (25). Transient elevations in serum transaminases defined the maximum tolerated dose, and serum half-life was about 24 hrs. Two patients had an objective partial response (PR), one of whom was subsequently found to have a complete response several months after discontinuing rhuCD40L therapy in the absence of additional anti-cancer therapy.

Despite promising results with this initial study, it was not until several years later with the development of anti-CD40 mAbs that interest in targeting CD40 for anti-cancer therapy resurfaced. CP-870,893 (Pfizer) is a fully human CD40 agonist IgG2 mAb that exhibits immune-mediated and non-immune mediated effects on tumor cell death (26,27). Antibodies of the IgG2 subclass do not fix complement or bind Fc receptors effectively, insuring that most observed biological effects of antibody administration are a function of the antigenic specificity of the antibody, in this case CD40 signaling, rather than of its constant region. We recently completed a first-in-human, dose-escalation trial of 29 patients with advanced solid tumors given single doses of CP-870,893 intravenously (28). The most common adverse event was cytokine release syndrome (CRS) manifesting as transient chills, rigors, and fevers on the day of infusion and associated with elevations of serum TNF-alpha and IL-6. Four PRs were observed, all of which were in patients with melanoma. With repeated dosing every 6–8 weeks, one patient had a continued PR ongoing at 18 months, associated with complete resolution of abnormal tracer activity on PET scan.

A single infusion of CP-870,893 led to a marked, rapid, and dose-dependent decrease in the percentage and absolute number of peripheral blood B cells. Among B cells remaining in the blood, we observed upregulation of cell surface CD86, a costimulatory molecule fundamental to T cell activation (28). At the highest dose levels, the percentage of CD86+ B cells increased >8-fold. From these and other findings, we hypothesize that CP-870,893 infusion activates peripheral blood B cells, leading to the extravasation and/or margination of most B cells from the blood. It is not yet known whether CD40-activated B cells alone or in combination with

other CD40-activated APC drive anti-tumor T cell responses in patients, but *in vitro* CD40-activated B cells are highly potent APC (29,30). In the one melanoma patient with continued response to CP-870,893, treatment was associated with the induction of cellular tumor-specific immunity to a panel of known melanoma antigens. A study of weekly doses of CP-870,893 is currently nearing completion.

A second CD40 mAb, SGN-40 (Seattle Genetics), has been evaluated in phase 1, dose-escalation studies in patients with relapsed or refractory non-Hodgkins lymphoma (NHL) and multiple myeloma. Both these malignancies uniformly express CD40. SGN-40 is a humanized IgG1 immunoglobulin and a partial agonist of CD40 that induces apoptosis and antibody-dependent cellular cytotoxicity against a panel of malignant B cell lines *in vitro* and results in tumor regression in human multiple myeloma and lymphoma xenograft models *in vivo* (31–33). In a phase 1 study of 35 patients with relapsed NHL, weekly doses of SGN-40 were administered over 4–5 weeks (34). Like CP-870,893, SGN-40 is associated with CRS, most pronounced with the first infusion and becoming less prominent with subsequent dosing. Five NHL patients achieved objective tumor responses with 3 patients experiencing a PR and 2 with a complete response (CR). A second phase 1 study of SGN-40 administered to 32 patients with relapsed or refractory multiple myeloma demonstrated decreased M-protein and improvement in subjective symptoms in several patients but no patients met criteria for objective response. Five patients had stable disease (35) (Table 1). Pharmacodynamic studies of SGN-40 in monkeys show marked, dose-dependent, and persistent depletion of peripheral CD20+ B lymphocytes.

No serious toxicities have been reported in these initial clinical trials despite the potential for CD40-mediated systemic inflammation and autoimmunity (36). In our studies with an agonist CD40 mAb, no episodes of enterocolitis, dermatitis, or hypophysitis have been observed, although these events have been observed with other immunomodulatory agents such as blocking anti-CTLA4 mAb (37). Although CRS has been observed with agonist CD40 mAb, the effects have been moderate and transient, and clinically and mechanistically distinct from the serious syndrome observed in subjects recently given a single dose of anti-CD28 agonist mAb (38). It has also been suggested that CD40 plays a role in tumor angiogenesis, such that cancer prone mice lacking CD40 have diminished tumor formation compared to controls (39). These findings prompted certain authors to suggest that the use of a CD40-based therapy for cancer is premature at this stage (40), but the unexpected rate of objective clinical responses in phase 1 studies with CP-870,893 and SGN-40 suggests otherwise.

Combination therapy with CD40 agonists

The greatest potential for CD40 agonists will no doubt be in combination with other agents (Table 2). Data from multiple preclinical models suggest the prospect of synergistically enhancing immune activation with such combinations as chemotherapy, radiotherapy, tumor vaccines, toll-like receptor agonists, cytokines, and other TNF receptor family agonists such as DR5 and CD137 mAb (13,14,20,41–43).

The basic premise of some of these combinations is that tumor-specific induction of T cells plays a crucial role in the successful anti-tumor effects of CD40 agonist antibodies and that combining strategies to induce tumor-cell apoptosis with T cell activation results in greater anti-tumor responses. CD40-mediated tumor cell death appears at least additive and possibly synergic with chemotherapy both *in vitro* and *in vivo* (17,23,41). In a mouse model of established tumor implants, the combination of an anti-CD40 agonist antibody and the chemotherapeutic agent gemcitabine cures most mice, which are then resistant to tumor rechallenge (41). This effect is dependent on CD8 T cells and independent of CD4 T cells, is only seen *in vivo* in the setting of tumor cell death and only when immunotherapy follows

chemotherapy. These findings provide evidence that chemotherapy has the capacity to augment cellular anti-tumor immunity. In the case of gemcitabine, this augmentation likely results from antigen cross-presentation, T lymphocyte expansion, and infiltration of the tumor. Given these observations, the combination of cytotoxic chemotherapy and activating anti-CD40 antibodies will be the subject of very interesting future clinical trials.

It is likely that the potential priming effect observed with gemcitabine is shared by other drugs that cause tumor cell death. In mice with multi-organ metastasis from primary fibrosarcoma, therapy with an agonistic mAb to DR5, the apoptosis-inducing receptor for TNF-related apoptosis-inducing ligand, combined with T cell activation by agonistic mAb to CD40 and the costimulatory molecule CD137, potently and rapidly stimulated tumor-specific effector CD8 + T cells capable of eradicating an established tumor burden (43).

There is also the notion that the immune system can be overwhelmed by a rapidly growing tumor in such a way that an animal can succumb to malignancy before immunotherapy with anti-CD40 can promote an effective T cell response. Combining anti-CD40 with an effective debulking cancer treatment appears to be a promising way to overcome this limitation. To this end, the interaction between an anti-CD40 mAb antibody following external beam irradiation was investigated in two B cell lymphoma models (44). It was found that doses of antibody and irradiation that were ineffective individually were capable of providing long-term protection when used in combination. This result was dependent on the generation of CD8+ T cells at levels 10–15 times that found in animals given either treatment modality alone. The biphasic decrease observed in tumor burden in these animals corresponded to an initial direct cytotoxic effect of the radiation on the tumor followed by formation of a CTL response promoted by the CD40 antibody that did not occur in non-tumor bearing animals treated similarly. This was in contrast to animals receiving irradiation alone in which there was rebound of tumor burden to the pre-treatment levels 10–12 days after treatment. Therefore radiation-induced tumor apoptosis alone is inadequate in generating long-term tumor clearance and an anti-CD40 driven CD8+ T cell activation is required to achieve long-term survival.

Another approach to incorporating CD40 agonists in the treatment of solid tumors would be use as an adjuvant with other agents that stimulate a host immune system. It has been established that the immune system of tumor-bearing hosts develops tolerance to tumor antigens, shows alterations in T cell signal transduction, and that tumor can induce suppressor cells (45). In a lung metastasis model of renal cell carcinoma, Sotomayor et al were able to show that the tumor antigen-specific T cell tolerance that normally limits the efficacy of therapeutic cancer vaccines was overcome by co-administration of an agonistic antibody to CD40 (14). In addition, Diehl et al showed that CD40 activation can convert a tolerizing peptide vaccine into one capable of inducing strong CTL priming and can enhance the therapeutic efficacy of a vaccine capable of inducing protective anti-tumor immunity (13). In combination with toll-like receptors (TLR) agonists, which are potent activators of innate immunity, CD40 agonists synergize to stimulate antigen specific CD8+ T cell responses 10–20 fold greater than the use of either agonist alone. This treatment approach generated memory T cells capable of expansion upon rechallenge with antigen in the absence of the agonists (42). CD40 agonists could also be combined with agents that block negative immune checkpoints such as anti-CTLA4 mAb. CTLA-4 is a negative regulator of T cell activation. Blockade of the B7-CTLA-4 pathway with anti-CTLA-4 mAb enhances anti-tumor T cell responses and leads to tumor rejection (46,47). *In vivo* animal studies have shown that anti-CD40 mAb and anti-CTLA-4 mAb can function as potent and safe immunomodulators that can enhance induction of CTL to tumor associated antigen vaccines and significantly improve survival in a tumor mouse model (48).

Clinical trial designs testing these hypotheses will require careful consideration of both the basic immunology involved and the pharmacology and pharmacodynamics of the agents being

investigated. The above examples all confirm the notion that modulation of APC activation by CD40 agonist antibodies may be useful in enhancing the efficacy of both existing treatment options for cancer as well as novel immunotherapeutic modalities. It is likely that as we go forward with novel immunotherapeutic agents such as CD40 agonists, the tumor heterogeneity that develops during carcinogenesis and natural immune selection will necessitate a role for all of these treatment modalities in various combinations.

Acknowledgments

Supported by National Cancer Institute grant P50 CA093372. Dr. Vonderheide reports receiving research funds from Pfizer Corp.

References

1. Grewal IS, Flavell RA. CD40 and CD154 in cell-mediated immunity. Annu Rev Immunol 1998;16:111–35. [PubMed: 9597126]
2. Young LS, Eliopoulos AG, Gallagher NJ, Dawson CW. CD40 and epithelial cells: across the great divide. Immunol Today 1998;19(11):502–6. [PubMed: 9818543]
3. van Kooten C, Banchereau J. CD40-CD40 ligand. J Leukoc Biol 2000;67(1):2–17. [PubMed: 10647992]
4. Quezada SA, Jarvinen LZ, Lind EF, Noelle RJ. CD40/CD154 interactions at the interface of tolerance and immunity. Annu Rev Immunol 2004;22:307–28. [PubMed: 15032580]
5. Armitage RJ, Fanslow WC, Strockbine L, et al. Molecular and biological characterization of a murine ligand for CD40. Nature 1992;357:80–2. [PubMed: 1374165]
6. Allen RC, Armitage RJ, Conley ME, et al. CD40 ligand gene defects responsible for X-linked hyper-IgM syndrome. Science 1993;259(5097):990–3. [PubMed: 7679801]
7. Ferrari S, Giliani S, Insalaco A, et al. Mutations of CD40 gene cause an autosomal recessive form of immunodeficiency with hyper IgM. Proc Natl Acad Sci USA 2001;98(22):12614–9. [PubMed: 11675497]
8. Etzioni A, Ochs HD. The hyper IgM syndrome--an evolving story. Pediatr Res 2004;56(4):519–25. [PubMed: 15319456]
9. Bennett SR, Carbone FR, Karamalis F, Flavell RA, Miller JF, Heath WR. Help for cytotoxic-T-cell responses is mediated by CD40 signalling. Nature 1998;393(6684):478–80. [PubMed: 9624004]
10. Ridge JP, Di Rosa F, Matzinger P. A conditioned dendritic cell can be a temporal bridge between a CD4+ T- helper and a T-killer cell. Nature 1998;393(6684):474–8. [PubMed: 9624003]
11. Schoenberger SP, Toes RE, van der Voort EI, Offringa R, Melief CJ. T-cell help for cytotoxic T lymphocytes is mediated by CD40-CD40L interactions. Nature 1998;393(6684):480–3. [PubMed: 9624005]
12. French RR, Chan HT, Tutt AL, Glennie MJ. CD40 antibody evokes a cytotoxic T-cell response that eradicates lymphoma and bypasses T-cell help. Nat Med 1999;5(5):548–53. [PubMed: 10229232]
13. Diehl L, den Boer AT, Schoenberger SP, et al. CD40 activation in vivo overcomes peptide-induced peripheral cytotoxic T-lymphocyte tolerance and augments anti-tumor vaccine efficacy. Nat Med 1999;5(7):774–9. [PubMed: 10395322]
14. Sotomayor EM, Borrello I, Tubb E, et al. Conversion of tumor-specific CD4+ T-cell tolerance to T-cell priming through in vivo ligation of CD40. Nat Med 1999;5(7):780–7. [PubMed: 10395323]
15. Funakoshi S, Longo DL, Beckwith M, et al. Inhibition of human B-cell lymphoma growth by CD40 stimulation. Blood 1994;83(10):2787–94. [PubMed: 7514045]
16. Hess S, Engelmann H. A novel function of CD40: induction of cell death in transformed cells. J Exp Med 1996;183(1):159–67. [PubMed: 8551219]
17. Eliopoulos AG, Dawson CW, Mosialos G, et al. CD40-induced growth inhibition in epithelial cells is mimicked by Epstein-Barr Virus-encoded LMP1: involvement of TRAF3 as a common mediator. Oncogene 1996;13(10):2243–54. [PubMed: 8950992]

18. von Leoprechting A, van der Bruggen P, Pahl HL, Aruffo A, Simon JC. Stimulation of CD40 on immunogenic human malignant melanomas augments their cytotoxic T lymphocyte-mediated lysis and induces apoptosis. Cancer Res 1999;59(6):1287–94. [PubMed: 10096561]
19. Eliopoulos AG, Davies C, Knox PG, et al. CD40 induces apoptosis in carcinoma cells through activation of cytotoxic ligands of the tumor necrosis factor superfamily. Mol Cell Biol 2000;20(15): 5503–15. [PubMed: 10891490]
20. Tong AW, Papayoti MH, Netto G, et al. Growth-inhibitory effects of CD40 ligand (CD154) and its endogenous expression in human breast cancer. Clin Cancer Res 2001;7(3):691–703. [PubMed: 11297266]
21. Wingett DG, Vestal RE, Forcier K, Hadjokas N, Nielson CP. CD40 is functionally expressed on human breast carcinomas: variable inducibility by cytokines and enhancement of Fas-mediated apoptosis. Breast Cancer Res Treat 1998;50(1):27–36. [PubMed: 9802617]
22. Hirano A, Longo DL, Taub DD, et al. Inhibition of human breast carcinoma growth by a soluble recombinant human CD40 ligand. Blood 1999;93(9):2999–3007. [PubMed: 10216096]
23. Ghamande S, Hylander BL, Oflazoglu E, Lele S, Fanslow W, Repasky EA. Recombinant CD40 ligand therapy has significant antitumor effects on CD40-positive ovarian tumor xenografts grown in SCID mice and demonstrates an augmented effect with cisplatin. Cancer Res 2001;61(20):7556–62. [PubMed: 11606394]
24. Vonderheide RH. Prospect of targeting the CD40 pathway for cancer therapy. Clin Cancer Res 2007;13(4):1083–8. [PubMed: 17317815]
25. Vonderheide RH, Dutcher JP, Anderson JE, et al. Phase I study of recombinant human CD40 ligand in cancer patients. J Clin Oncol 2001;19(13):3280–7. [PubMed: 11432896]
26. Gladue R, Cole S, Donovan C, et al. In vivo efficacy of the CD40 agonist antibody CP-870,893 against a broad range of tumor types: impact of tumor CD40 expression, dendritic cells, and chemotherapy. J Clin Oncol 2006;24 (18S):103s.
27. Bedian V, Donovan C, Garder J, et al. In vitro characterization and pre-clinical pharmacokinetics of CP-870,893, a human anti-CD40 agonist antibody. J Clin Oncol 2006;24 (18S):109s.
28. Vonderheide RH, Flaherty KT, Khalil M, et al. Clinical activity and immune modulation in cancer patients treated with CP-870,893, a novel CD40 agonist monoclonal antibody. J Clin Oncol 2007;25 (7):876–83. [PubMed: 17327609]
29. Coughlin CM, Fleming MD, Carroll RG, et al. Immunosurveillance and survivin-specific T cell immunity in patients with high-risk neuroblastoma. J Clin Onc 2006;24(36):5725–5734.
30. Schultze JL, Michalak S, Seamon MJ, et al. CD40 activated human B cells: an alternative source of highly efficient antigen presenting cells to generate autologous antigen-specific T cells for adoptive immunotherapy. J Clin Invest 1997;100:2757–65. [PubMed: 9389740]
31. Tai YT, Catley LP, Mitsiades CS, et al. Mechanisms by which SGN-40, a humanized anti-CD40 antibody, induces cytotoxicity in human multiple myeloma cells: clinical implications. Cancer Res 2004;64(8):2846–52. [PubMed: 15087402]
32. Law CL, Gordon KA, Collier J, et al. Preclinical antilymphoma activity of a humanized anti-CD40 monoclonal antibody, SGN-40. Cancer Res 2005;65(18):8331–8. [PubMed: 16166310]
33. Kelley SK, Gelzleichter T, Xie D, et al. Preclinical pharmacokinetics, pharmacodynamics, and activity of a humanized anti-CD40 antibody (SGN-40) in rodents and non-human primates. Br J Pharmacol 2006;148(8):1116–23. [PubMed: 16847437]
34. Advani R, Forero-Torres A, Furman RR, Rosenblatt JD, Younes A, Shankles B, Harrop K, Drachman JG. SGN-40 (anti-huCD40 mAb) monotherapy induces durable objective responses in patients with relapsed aggressive non-Hodgkin's lymphoma: evidence of anti-tumor activity from a phase 1 study. Blood 2006:108.[abstract 695]
35. Hussein MA, Berenson JR, Niesvizky R, Munshi NC, Matous J, Harrop K, Drachman JG. Results of a phase 1 trial of SGN-40 (anti-huCD40 mAb) in patients with relapsed multiple myeloma. Blood 2006:108.[abstract 3576]
36. Tong AW, Stone MJ. Prospects for CD40-directed experimental therapy of human cancer. Cancer Gene Ther 2003;10(1):1–13. [PubMed: 12489023]
37. Kapadia D, Fong L. CTLA-4 blockade: autoimmunity as treatment. J Clin Oncol 2005;23(35):8926–8. [PubMed: 16204008]

38. Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, Panoskaltsis N. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. New Engl J of Med 2006;355(10):1018–28. [PubMed: 16908486]

39. Chiodoni C, Iezzi M, Guiducci C, et al. Triggering CD40 on endothelial cells contributes to tumor growth. J Exp Med 2006;203(11):2441–50. [PubMed: 17043144]

40. Bergmann S, Pandolfi PP. Giving blood: a new role for CD40 in tumorigenesis. J Exp Med 2006;203 (11):2409–12. [PubMed: 17043147]

41. Nowak AK, Robinson BW, Lake RA. Synergy between chemotherapy and immunotherapy in the treatment of established murine solid tumors. Cancer Res 2003;63(15):4490–6. [PubMed: 12907622]

42. Ahonen CL, Doxsee CL, McGurran SM, et al. Combined TLR and CD40 triggering induces potent CD8+ T cell expansion with variable dependence on type I IFN. J Exp Med 2004;199(6):775–84. [PubMed: 15007094]

43. Uno T, Takeda K, Kojima Y, et al. Eradication of established tumors in mice by a combination antibody-based therapy. Nat Med 2006;12(6):693–8. [PubMed: 16680149]

44. Honeychurch J, Glennie MJ, Johnson PW, Illidge TM. Anti-CD40 monoclonal antibody therapy in combination with irradiation results in a CD8 T-cell-dependent immunity to B-cell lymphoma. Blood 2003;102:1449–57. [PubMed: 12714523]

45. Drake CG, Jaffee E, Pardoll DM. Mechanisms of immune evasion by tumors. Adv Immunol 2006;90:51–81. [PubMed: 16730261]

46. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. Science 1996;271(5256):1734–6. [PubMed: 8596936]

47. Yang YF, Zou JP, Mu J, et al. Enhanced induction of antitumor T-cell responses by cytotoxic T lymphocyte-associated molecule-4 blockade: the effect is manifested only at the restricted tumor-bearing stages. Cancer Res 1997;57(18):4036–41. [PubMed: 9307290]

48. Ito D, Ogasawara K, Iwabuchi K, Inuyama Y, Onoe K. Induction of CTL responses by simultaneous administration of liposomal peptide vaccine with anti-CD40 and anti-CTLA-4 mAb. J Immunol 2000;164(3):1230–5. [PubMed: 10640735]

Table 1

Phase 1 studies of CD40 agonist therapy in cancer patients

Drug	Formulation	CD40 signaling	Patient population	Clinical trial findings	References
Recombinant CD40L	Recombinant human trimer	Agonist	Solid tumors or NHL N=32	• Increased AST/ALT • Injection site reactions • 2 PR	Vonderheide et al. J Clin Oncol, 2001
CP-870,893	Fully human IgG2 mAb	Agonist	Solid tumors N=29	• CRS • 4 PR	Vonderheide et al. J Clin Oncol, 2007
SGN-40	Humanized IgG1 mAb	Weak agonist	NHL N=35	• CRS • 3 PR, 2 CR	Advani et al. Blood 2006
			Multiple myeloma N=32 (ongoing)	• CRS • No clinical responses	Husein et al. Blood 2006

NHL, Non-Hodgkins lymphoma; PR, partial response; CR, complete response; CRS, cytokine release syndrome

Update Cancer Ther. Author manuscript; available in PMC 2009 July 7.

Table 2

Pre-clinical data on combination cancer therapy with CD40 agonists

Anti-CD40 agonist and…	Rationale	References
Chemotherapy	Induce tumor death while stimulating immune system	Nowak et al. Can Res, 2003
Radiation	Induce tumor death while stimulating immune system	Honeychurch et al., Blood, 2003
Cancer vaccine	Reverse T cell tolerance Substitute for T cell help	Sotomayor et al. Nat Med, 1999 Diehl et Al., Nat Med, 1999
Blocking anti-CTLA-4 mAb	Inhibit negative immune regulation while triggering immune activation	Ito et al., JI, 2000
TLR agonists	Synergistic activation of both innate and acquired immunity	Ahonen et al., JEM, 2004
DR5 and CD137 agonist mAb	Induce apoptosis while fully stimulating immune system	Uno et al., Nat Med, 2006