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Radioimmunotherapy of Solid Tumors: Searching for the Right Target

Hong Song* and **George Sgouros**

Division of Nuclear Medicine, Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, Maryland, 21231, USA

Abstract

Radioimmunotherapy of solid tumors remains a challenge despite the tremendous success of ^{90}Y ibritumomab tiuxetan (Zevalin) and ^{131}I Tositumomab (Bexxar) in treating non-Hodgkin's lymphoma. For a variety of reasons, clinical trials of radiolabeled antibodies against solid tumors have not led to responses equivalent to those seen against lymphoma. In contrast, promising responses have been observed with unlabeled antibodies that target solid tumor receptors associated with cellular signaling pathways. These observations suggest that anti-tumor efficacy of the carrier antibody might be critical to achieving clinical responses. Here, we review and compare tumor antigens targeted by radiolabeled antibodies and unlabeled antibodies used in immunotherapy. The review shows that the trend for radiolabeled antibodies under pre-clinical development is to also target antigens associated with signaling pathways that are essential for the growth and survival of the tumor.

Keywords

Radioimmunotherapy; radiolabeled antibody; solid tumor; antigen

INTRODUCTION

In the past decade, radiolabeled antibodies have seen tremendous success in treating non-Hodgkins' lymphoma (NHL) resulting in the FDA approval of ^{90}Y ibritumomab tiuxetan (Zevalin) and ^{131}I tositumomab (Bexxar). However, limited clinical success has been achieved with radiolabeled antibodies against solid tumors. In contrast, several naked monoclonal antibodies, including Trastuzumab, Cetuximab, Panitumumab and Bevacizumab, have been approved by the FDA to treat solid tumors after showing significant clinical benefit [1]. In this review we examine the following questions: What are the challenges that have thwarted the development of radiolabeled antibodies against solid tumors? What can we learn from the development of ^{90}Y ibritumomab tiuxetan and ^{131}I tositumomab?

The majority of unlabeled antibodies in immunotherapy are targeting tumor receptor antigens that are critical to maintaining different elements of the cancer phenotypes, these include self-sufficient growth signals, insensitivity to anti-growth signals, limitless replicative potential, evasion of apoptosis and enhanced capacity for angiogenesis [2]. Here, we review the tumor specific or associated antigens that are currently under clinical trials in antibody immunotherapy and radioimmunotherapy. The trend in radioimmunotherapy also seems to target tumor antigens that are important for cancer cell growth and survival. Choosing these tumor antigen targets might help to achieve clinical response in radioimmunotherapy of solid tumors in the near future.

Mechanisms of Cancer Cell Kill by Radiolabeled Antibody

Numerous radiolabeled antibodies are under development to treat a wide variety of solid tumors, including breast, ovarian, colorectal, prostate, kidney and brain cancers. All these radiolabeled antibodies have the potential to kill cancer cells through two therapeutic components: radiation delivery and antibody action upon binding. Understanding the contributions of these two components to overall tumor response when choosing different radioisotopes, antibodies to target various tumor types could help us improve the design of radioimmunoconjugates.

Cancer Cell Kill by Radiation—Radiation kills cancer cells primarily by damaging DNA [3]. When cancer cells are irradiated, both DNA single strand breaks (SSBs) and double strand breaks (DSBs) can occur. Single strand breaks are readily repaired although sometimes point mutations can be generated. Double strand breaks are the most important lesions caused by radiation leading to chromosome aberrations that kill cells through apoptosis or mitotic death. Compared to radiosensitive non-Hodgkin's lymphoma where radiation induced apoptosis is the dominant cell death pathway, most solid tumors demonstrate little apoptotic cell death after irradiation. When non-Hodgkin's lymphoma cells are killed by radiation, the cell survival curve is typically an exponential function of total radiation dose delivered. When more radioresistant solid tumor cells are irradiated, the survival curves typically are characterized by a broad initial shoulder at a lower dose range before turning into an exponential function of dose at higher doses. As a result, a much higher radiation dose is required to kill solid tumor compared to radiosensitive non-Hodgkin's lymphoma.

Indeed, low dose radiation therapy has been found to be very effective in treating non-Hodgkin's lymphoma where doses for standard radiation therapy in the range of 30–40 Gy are typically used and doses as low as 4 Gy are effective in radiosensitive indolent lymphoma [4]. In a dosimetric study of non-Hodgkin's lymphoma patients successfully treated with ^{90}Y ibritumomab tiuxetan, tumor doses were found to be 17 Gy [5]. Similar studies have found that the mean tumor doses treated with ^{131}I -tositumomab are 3 Gy [6] and 3.7 Gy in previously untreated patients [7]. In comparison, high doses of standard radiation therapy are needed to achieve clinical responses in solid tumors such as prostate cancer (64.8–81 Gy) [8], lung cancer (40–65 Gy) [9], glioma (60 Gy) [10], breast cancer (50 Gy) [11], ovarian cancer (45 Gy) [5], colorectal cancer (70 Gy) [12] and pancreatic cancer (50.4 Gy) [13]. Based on these clinical experiences, it is generally accepted that solid tumor

doses need to reach at least 50 Gy to achieve any clinical benefits. It is also important to note, even with these high doses, the improvement in patient survival is not comparable to that observed in non-Hodgkin's lymphoma patients.

In most reported radioimmunotherapy studies of solid tumors, unfortunately, the tumor radiation doses are below 50 Gy. In a phase I trial of ^{131}I labeled anti-TAG72 mAb (CC49) to treat metastatic gastrointestinal cancers, tumor absorbed doses in metastatic sites ranged from 6.3 to 33 Gy [13]. In a similar study, the tumor doses for ^{90}Y -CC49 were found to be 1.8 to 30 Gy [14]. In another phase I trial of ^{131}I labeled anti-carcinoembryonic antigen (CEA) mAb (MN-14) to treat gastrointestinal cancers, the tumor doses were 7.4 Gy at the highest injected activity of 80 mCi [15]. Pai-Scherf *et al* found a tumor mean dose of 25.1 cGy/mCi (about 6.3 Gy at the highest injected activity of 25 mCi) in a phase I study of ^{90}Y labeled anti-Lewis^y mAb (B3) to treat breast cancer [16]. These studies bring into question whether systemic injection of radiolabeled intact monoclonal antibodies can deliver absorbed doses that are high enough to achieve objective clinical responses.

Local regional injection of radiolabeled antibody was studied with the hope that high local radiation concentration can be delivered to achieve meaningful tumor absorbed doses [17–19]. In a phase III trial of ^{90}Y labeled anti-MUC1 mAb (HMFG1) to treat ovarian cancer after a surgically defined complete remission, intraperitoneal delivery of the radiolabeled antibody did not extend survival or time to relapse [20]. Mathematical modeling estimated that radiation doses of ^{90}Y labeled mAb to small peritoneal tumors could range from 20 to 60 Gy depending on the geometrical shape and size of the tumors [21]. Radiation dose of ^{131}I labeled mAb to peritoneal tumors was estimated to be at 11 Gy/100 mCi [22]. When ^{131}I labeled anti-tenascin mAb (81C6) was injected into surgically created resection cavities of patients with glioma, the tumor absorbed doses reached 41 Gy at the MTD [23]. In a phase II trial of the same radiolabeled antibody, injecting 100 mCi of ^{131}I -81C6 in the resection cavity delivered an estimated absorbed dose that exceeded 100 Gy. The absorbed doses varied substantially (18–186 Gy), however, and were significantly affected by the size of the cavity [24].

Another approach to increase effectiveness is to use emissions with a higher relative biological effectiveness (RBE), such as alpha particles. Alpha particles are able to deposit very high energy along their short path, with a linear energy transfer 2 or 3 orders of magnitude higher than that of β -particles. Based on *in vitro* studies, the RBE values of alpha particles range from 3 to 7. Numerous alpha particle emitters, including ^{225}Ac / ^{213}Bi , ^{212}Pb / ^{212}Bi , ^{211}At , ^{223}Ra , are currently being developed for targeted therapy of leukemia, non-Hodgkin's lymphoma, brain, prostate and ovarian cancer. There are several excellent reviews of alpha particle based radioimmunotherapy [25,26].

Tumor responses, however, do not depend solely on the radiation doses delivered to the tumors. It was realized during the early development of ^{90}Y ibritumomab tiuxetan and ^{131}I tositumomab that relatively low tumor absorbed doses can lead to tumor responses. Press *et al.* has shown that overall survival and progression free survival for patients treated with ^{131}I tositumomab was 83% and 68%, better than those patients treated with external beam total body irradiation during the same period with overall survival of 53% and progression free

survival of 36% when they are combined with etoposide and cyclophosphamide [27]. On the other hand, high dose ^{131}I tositumomab radioimmunotherapy with autologous stem cell transplantation studies showed that this treatment approach can deliver 20–27 Gy to critical normal organs (liver, kidneys and lungs) compared to 12 to 15.75 Gy by standard total body irradiation [27], suggesting that normal organs can tolerate radiolabeled antibodies relatively well. Differential responses of lymphoma cells and normal organs to radiolabeled antibody and external beam radiation suggest that differences other than absorbed doses between the two modalities play an important role. Both low dose rate and bystander effects of radiation has been proposed to explain the improved efficacy of radioimmunotherapy over external beam radiation at equivalent doses [28]. The differential ability of lymphoma as compared to normal organs in DNA damage repairs after low dose rate radiation has also been suggested. Furthermore, considering that lymphoma cells are specifically targeted by the antibody while antibody accumulation in normal organs is primarily non-specific, the biological effects of antibody binding on the tumor cells must also be taken into account [28].

Cancer Cell Kill by Naked Monoclonal Antibodies—Monoclonal antibodies bound to cancer cells are capable of killing cancer cells through two basic mechanisms: immunologic and signal transduction, in many cases both mechanisms are operative. Signal transduction mechanisms involve disrupting cellular signaling pathways that are required to sustain a tumor phenotype such as growth or apoptotic signaling modulation. Immunologic mechanisms include antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC).

Antibody dependent cellular cytotoxicity is mediated through antibody binding of tumor cell antigen. The antibody Fc domains are recognized by Fc receptors on the surface of immune effector cells, such as natural killer cells and phagocytes. ADCC induced cell lysis has been demonstrated in lymphoma cells following treatment with the chimeric antibody Rituximab [29]. Enhanced Fc receptor binding to the Fc domains of Rituximab in patients with polymorphism of Fc γ RIIIa gene has been linked to better clinical responses [30]. For radiolabeled Ibritumomab tiuxetan and Tositumomab, the evidence, *in vivo*, of ADCC mediated cell lysis has been difficult to obtain and is not considered a significant component in the cell killing activity of this radiolabeled antibody. The inclusion of Rituximab in almost all therapeutic regimens of NHL may obscure this aspect of cell killing. Complement dependent cytotoxicity is also mediated through antibody binding of tumor antigen. The subsequent binding of the C1q subcomponent results in assembly of the complement complex that lyses the cancer cells. Like ADCC, CDC has been identified as a mechanism in the lysis of lymphoma cells after Rituximab treatment [31]. In solid tumors, ADCC and affinity for Fc γ RIIIa have also been found to be involved in the anti-tumor activity of naked monoclonal antibodies, such as Trastuzumab [32] and Cetuximab [33]. In radioimmunotherapy, however, it is believed that the relevance of ADCC and CDC to tumor control is limited because of the immune suppression by systemic injection of radiolabeled antibody and the weak interaction between Fc receptors on human immune cells and Fc domains on murine antibodies that are frequently employed in radioimmunotherapy.

Binding of monoclonal antibodies to tumor specific or associated antigens can also induce tumor cell kill by engaging in signaling pathways that are required to sustain tumor survival and growth. Some antibodies function by antagonizing receptor initiated signaling while other antibodies act to block ligand binding. Numerous anti-CD20 antibodies have been shown to induce apoptosis in lymphoma cells *in vitro* [34,35]. Recent studies suggest that Tositumomab is more potent than Rituximab (they differ in their ability to distribute to lipid rafts after binding) in inducing apoptosis and is more efficient in depleting lymphoma cells [36]. Such potency seems to be related to Tositumomab's ability to induce non-classical apoptotic pathways that bypass impaired apoptotic pathways frequently observed in lymphoma, such as overexpression of bcl-2 [37]. In solid tumors, both Trastuzumab and Cetuximab, targeting EGFR family antigen HER-2 and HER-1, have been shown to induce tumor cell apoptosis [38,39]. The ability of the radiolabeled antibody itself to induce apoptosis via a cell signaling pathway might be an important complement to radiation-induced cell kill since most solid tumors are resistant to radiation-induced apoptosis.

In contrast to the repeated injection of large amounts of naked antibodies, therapy with radiolabeled antibodies is typically administered using small quantities in a single or fractionated dosing schedule due to dose limiting toxicity, primarily to red marrow. For example, anti-EGFR antibody Cetuximab was given at 400 mg/m² body surface area (1.9 m² on average for men) initial dose and 250 mg/m² weekly for the duration of the study to treat colorectal cancer [40], while in clinical studies of anti-EGFR antibody radioimmunotherapy, three fractionized injection of 3.2–3.4 mg of antibody each was used [41], more than 100 times less compared to naked antibody. Similar low levels of administered radio-labeled antibody have been reported for other radioimmunotherapy studies, including ⁹⁰Y labeled anti-CEA antibody to treat colorectal cancer (1.66–2.06 mg/m²)[42], ⁹⁰Y labeled anti-MUC1 antibody to treat ovarian cancer (25 mg single dose intraperitoneal injection) [20], ¹⁷⁷Lu anti-PSMA antibody to treat prostate cancer (10 mg/m²)[43] and ⁹⁰Y labeled anti-Lewis^x antibody to treat solid tumors (5, 10, 50 mg total with both imaging and therapy) [16]. The low quantities of antibody used in radioimmunotherapy reduce the possibility of overcoming the multiple barriers to delivery of large molecules to tumor. The barriers include poor blood flow, elevated interstitial pressure and heterogeneous antigen expression [44]. In radioimmunotherapy, a pretargeting strategy has been developed to overcome the poor antibody penetration into tumor. By separating delivery of the targeting vehicle from the radionuclide, this approach enables the administration of a large quantity of antibody that is subsequently cleared from the circulation and then followed by administration of radiolabeled small molecule therapeutic agents that can bind to antibody already bound to tumor antigens. This strategy has shown great promise in delivering higher radiation dose and is actively studied in clinical trials [45, 46].

Although it is likely that the first successful radiolabeled antibody to treat solid tumor will be based on an antibody that itself demonstrates anti-tumor effects in the clinics, the injection of much smaller amount of radiolabeled antibody compared to unlabeled antibody treatment poses a serious obstacle for antibody penetration and targeting. One possible scenario to overcome this obstacle is targeting solid tumor under minimal residue disease

setting where the requirement of high antibody concentration for penetrating larger tumors can be reduced or eliminated. The other possible approach is to design combinational dosing regimen with unlabeled antibody to improve tumor penetration of radiolabeled antibody. When treating non-Hodgkin's lymphoma, pre-dosing with unlabeled antibody (450 mg Tositumomab followed by 35 mg of ^{131}I -Tositumomab) is common practice primarily because it saturates non-tumor CD20 binding sites in spleen and circulating lymphocytes, thereby allowing the radiolabeled antibody to more readily reach tumor cell antigen sites. Clinically, improved tumor uptake and efficacy were observed with Rituximab pretreatment [47–49]. In solid tumor, the clinical effects of pre-dosing with unlabeled antibodies are not clear because in most cases there is no normal tissue antigenic sink as is the case in CD20 targeting [50,51]. Whether pre-dosing with unlabeled antibody could improve efficacy of radiolabeled antibodies with their own biological activities remain to be studied. Nonetheless, few monoclonal antibodies employed in radioimmunotherapy of solid tumor so far have shown efficacy as naked antibodies themselves like Tositumomab, undermining the rationale for combination therapy with the radiolabeled antibodies.

The objective of the next section is to review and compare the tumor associated or specific antigens that are currently being studied in both radioimmunotherapy and naked monoclonal antibody therapy of solid tumors; thereby identifying antigen targets that are potential candidates for future development of radiolabeled antibody.

Tumor Antigens Targets in Antibody Immunotherapy and Radioimmunotherapy

After decades of searching for tumor associated or specific antigens that are highly expressed by solid tumors, few targets have been identified that have proved clinically useful for monoclonal antibody-based cancer immunotherapy. From the experience of a handful of successful antibodies that have entered the clinic, such as the anti-EGFR family antibodies and anti-VEGF antibodies, it has become clear that the optimal targets are not only those being highly expressed on tumors, but rather those that have a functional activity critical for the maintenance and survival of tumors. The question is whether this is also the case for tumor antigen targets in radioimmunotherapy. Here, we will review the solid tumor antigens that are actively studied in the clinic by both radioimmunotherapy and immunotherapy approaches.

Solid Tumor Antigen Targets in Radioimmunotherapy—Solid tumor antigens spanning a wide variety of tissue origin and function are currently being evaluated in clinical trials of radioimmunotherapy. Since development of novel radiolabeled antibodies involves several optimization steps, including enhancing antibody affinity, choosing optimal radionuclides, preclinical evaluation and delivery optimization, the process can be very slow. Consequently, the majority of the solid tumor antigen targets being evaluated in current clinical trials now have been investigated over the last decade.

Table 1 lists solid tumor antigens that are currently being evaluated in radioimmunotherapy. Data of clinical trials were compiled based on trials listed on clinicaltrials.gov. Only trials that are newly launched and currently still recruiting patients are included. Trials with radiolabeled peptides and trials that aim to develop antibody based solid tumor imaging and

imaging based dosimetry studies are not included. Due to the clinical success of ^{90}Y ibritumomab tiuxetan and ^{131}I tositumomab the majority of current radioimmunotherapy trials are focused on treating hematologic malignancies. There are a total of 23 clinical trials that are investigating radioimmunotherapy of solid tumors, targeting 10 solid tumor antigens and 11 cancer types. All these trials are in phase I or II and none are in phase III studies.

Solid tumor antigens that have been clinically investigated recently (complete or ongoing but not recruiting) are shown in Table 2. Earlier trials that are not included in clinicaltrials.gov are summarized by several excellent reviews [52–54]. There were a total of 34 trials targeting 12 solid tumor antigen targets. Most trials were in phase I/II and two trials were in phase III. The two phase III trials were against ovarian carcinoma using ^{90}Y labeled anti-MUC1 monoclonal antibody HMFG-1 [20] and against glioblastoma multiforme using ^{131}I -labeled anti-tenascin antibody 81C6 [24]. Most solid tumor antigens (8 out of 10) in newly launched clinical trials (Table 1) have been investigated in clinical trials previously (Table 2) and few clinical trials are launched to target novel solid tumor antigens.

Carcinoembryonic Antigen (CEA): CEA was discovered in 1968 [55] and is highly expressed in epithelial tumors from the digestive system, including colorectal, gastric, and pancreatic cancer. This antigen target has recently also been found on breast, ovarian, non small cell lung cancer and medullary thyroid carcinoma. CEA is the most extensively studied solid tumor antigen in clinical trials of radiolabeled antibodies (Table 1, 2). In an early phase I/II trial of ^{131}I labeled anti-CEA antibody for patients with small volume liver metastases, 2 out of 11 patients had partial remission and 5 patients had minor/mixed responses or stable disease [56]. More recently, when ^{131}I labeled Labetuzumab was used to treat colorectal cancer patients after resection of liver metastases, the median overall survival of treated patients was 58.0 months versus 31.0 months of the control group (95% CI) ($P = 0.032$). The median disease-free survival for treated patients was 18.0 months versus 12.0 months (95% CI) for the controls ($P = 0.565$) [57,58]. In a phase I trial of ^{90}Y -hMN-14 to treat medullary thyroid carcinoma, 1 out of 14 patients had partial response and 2 patients had minor responses [59]. In a pre-targeting study using anti-CEA bispecific antibody and ^{131}I labeled bivalent hapten, forty-seven percent of patients, defined as biologic responders by a more than 100% increase in calcitonin doubling times, experienced significantly longer survival than nonresponders (median OS, 159 v 109 months; $P < 0.035$) and untreated patients (median OS, 159 v 61 months; $P < 0.010$) [60]. In an early phase I trial with ^{131}I -MN14 in ovarian cancer patients, one out of 14 patients with diffuse peritoneal implants had complete response for 8 months and one more patient had partial response for 10 months, both at 40 mCi/m² dose [61]. In another phase I trial of ^{131}I labeled anti-CEA antibody, patients with colorectal, breast, lung, pancreatic, medullary thyroid carcinoma were treated and 1 had a partial response (pancreatic), 4 had minor/mixed responses (colorectal, breast) and 7 had stable diseases [62]. Overall, radiolabeled intact antibody has achieved modest anti-tumor effects except under minimal residual disease setting. The trend of current clinical trials is testing pretargeting strategies and combinational therapy with chemotherapeutic agents (Table 1).

Mucin 1 (MUC1): MUC1 is a membrane protein that is expressed on the apical borders of secretory epithelial cells. Overexpression of MUC1 and aberrant glycosylation has been found on many human cancers, including colorectal, pancreatic, breast and ovarian cancer. In the phase II trials of ^{90}Y labeled anti-MUC1 antibody HMFG-1, ovarian cancer patients under remission after chemotherapy were treated and significant survival improvement was found after radiolabeled antibody treatment with five year survival of 80% compared to 55% for controls ($P = 0.0035$) [63,64]. A phase III randomized multicenter trial, however, showed no difference in both survival and time to relapse between control and patients treated with ^{90}Y -HMFG-1 [20]. The negative results raised the question of whether using the long range beta emitter ^{90}Y for treatment of minimal residual disease is appropriate. In breast cancer patients, a phase I trial of ^{90}Y labeled anti-MUC1 antibody BrE3 found three of six patients had a minor and transient, but objective tumor response, and none of the patients had significant toxicity [65]. Another ^{90}Y labeled anti-MUC1 antibody M170 has been evaluated in breast and prostate cancer patients, but no objective tumor responses were observed [66,67]. Currently, ^{90}Y labeled anti-MUC1 antibody hPAM4 is being tested clinically in pancreatic cancer patients in combination with gemcitabine.

Tenascin-C: Tenascin-C is an extracellular matrix glycoprotein that can bind and block another extracellular matrix protein fibronectin from interacting with cell surface syndecans, thereby regulating cell adhesion and migration. It has elevated expression in the stroma of high grade glioma but not in normal brain tissues [68]. In a phase II trial of ^{131}I labeled anti-tenascin antibody 81C6 into surgically created resection cavities of patients with recurrent malignant glioma, median overall survival was 64 weeks (for patients with glioblastoma multiforme or gliosarcoma) and 99 weeks (for patients with anaplastic astrocytoma or anaplastic oligodendroglioma), respectively [24]. These survival data compare favorably to other salvage therapies, for example, of patients treated with temozolomide (32 weeks) and ^{125}I -brachytherapy (46 weeks). This study also found that patients receiving less than 44 Gy in the resection cavity had a higher chance of recurrence, supporting patient specific dosimetry planning in a future randomized phase III trial. Another phase I trial of the alpha particle emitter ^{211}At conjugated to 81C6 antibody also showed favorable results, with median survival of 54, 52 and 116 weeks for glioblastoma multiforme, anaplastic astrocytoma and oligodendro glioma patients, respectively [69]. A phase III trial of ^{131}I labeled 81C6 (Neuradiab) is ongoing (GLASS-ART Trial).

Carbonic Anhydrase Isotype IX (CAIX/MN): CAIX, a protein from the carbonic anhydrase family, is overexpressed on 85% renal cell carcinoma. The expression of CAIX has been linked to hypoxia [70] and correlated with poor survival and metastasis [71]. A phase I/II trial of ^{131}I labeled anti-CAIX G250 antibody to treat patients with metastatic renal cell carcinoma yielded 17 out of 33 patients with stable disease, but no objective responses [72]. Currently, clinical studies have been focused on using ^{90}Y and ^{177}Lu labeled G250 (Table 1) and dose fractionation [73].

Prostate-Specific Membrane Antigen (PSMA): PSMA is prostate restricted transmembrane protein that is highly expressed in all prostate cancer. An anti-PSMA antibody, J591, targeting the extracellular epitope of PSMA was developed for

radioimmunotherapy. In a phase I trial of ^{177}Lu -J591 in 35 patients with androgen-independent prostate cancer, none of the seven patients with measurable disease had an objective tumor response. Four patients experienced 50% declines in prostate-specific antigen (PSA) levels lasting from 3 to 8 months and 16 patients experienced PSA stabilization [43]. In another phase I trial of ^{90}Y -J591 in 29 patients with androgen-independent prostate cancer, two patients at the 20 mCi/m² dose level had objective measurable responses with a 90% and 40% decrease in the size of pelvic and retroperitoneal lymphadenopathy, respectively. Both patients also experienced 85% and 70% declines in PSA lasting 8 and 8.6 months. Six patients experienced PSA stabilization by week 12 [74]. Currently, phase II trials of ^{177}Lu -J591 alone and in combination with chemotherapeutic agents are being evaluated (Table 1).

Ganglioside 2 (GD2) and 4Ig-B7-H3: Ganglioside GD2 is a disialoganglioside expressed on all human neuroblastoma and melanoma, with highly restricted expression on cerebellum and peripheral nerves [75]. A murine monoclonal antibody, 3F8, against GD2, has been developed for radioimmunotherapy of leptomeningeal cancer. In a phase II trial of intra-Ommaya (the Ommaya reservoir is a plastic device with a catheter to deliver anti-cancer drugs directly to the cerebrospinal fluid surrounding central nervous system) ^{131}I labeled 3F8 antibody, objective responses were achieved in 3 out of 13 assessable patients. Two patients remained in remission off therapy for more than 3.5 years without any late toxicity [76]. Analysis of 51 patients who received ^{131}I -3F8 and survived more than three months has shown that 56% of the patients developed hypothyroidism. Currently, ^{131}I -3F8 is being tested in combination with chemotherapeutic agents and anti-angiogenesis antibody Bevacizumab to treat patients with central nervous system tumors (Table 1). 4Ig-B7-H3 is a member of human B7 family that acts as an immunoregulatory protein [77]. It is over-expressed on neuroblastoma cell surface and can exert a protective role from natural killer-mediated lysis [78]. In a clinical phase II trial of ^{131}I labeled anti-4Ig-B7-H3 antibody 8H9 in patients with neuroblastoma, a significant improvement in survival was observed. In all of 21 patients treated, 17 patients were treated with ^{131}I -8H9, 3 patients were treated with ^{131}I -3F8 and one patient with both ^{131}I -8H9 and ^{131}I -3F8. All radiolabeled antibodies were injected through an intraventricular Ommaya catheter placed at surgical resection. Seventeen of the 21 patients had median survival of 33 months (7 to 74 months) compared to median survival of 6 months in patients without radioimmunotherapy treatment [79].

Epidermal Growth Factor (EGFR): EGFR, from the epidermal growth factor receptor (ErbB/HER) family, is a key mediator of a tumor cell signaling pathway regulating growth and differentiation. It is highly expressed on many solid tumors and inhibition of EGFR has shown anti-tumor activity in many tumor types including colon carcinoma, non-small-cell lung cancer, head and neck cancer, ovarian carcinoma, and renal cell carcinoma [80]. Despite FDA approval of naked anti-EGFR monoclonal antibodies (Cetuximab, Panitumumab and Nimotuzumab) to treat colorectal or head/neck cancer and numerous preclinical studies of radiolabeled anti-EGFR antibodies, few clinical trials of radioimmunotherapy targeting EGFR have been launched. In a phase I study of ^{131}I labeled anti-EGFR antibody to treat 10 patients with glioma, one patient responded and continued in remission for 3 years after therapy and five patients responded initially but relapsed 6 to 9

months after therapy [81]. In a recent phase II study of ^{125}I labeled anti-EGFR antibody 425 to treat 180 patients diagnosed with astrocytoma with anaplastic foci (AAF) and glioblastoma multiforme (GBM), ^{125}I -425 demonstrated significant benefit in improving survival with overall median survival of 13.4 and 50.9 months for patients with GBM and AAF, respectively [82]. However, conflicting results were reported in another clinical trial of ^{125}I labeled 425 to treat 8 patients with grade III and IV glioma. There was no improvement in disease free or total survival in the group of patients treated with radiotherapy plus radioimmunotherapy over radiotherapy alone [41]. Currently, a phase II trial of ^{125}I labeled 425 is underway to treat patients with high grade gliomas (Table 1).

DNA/histone H1 Associated Protein (Necrotic Region): TNT-1 is a monoclonal antibody that binds a 22 kd nuclear protein associated with the DNA/histone H1 and localizes to the necrotic region of tumors [83]. A clinical trial has evaluated ^{131}I labeled chimeric antibody chTNT in 107 patients with advanced lung cancer. The overall therapeutic efficacy (ORR) was 34.6% (complete response, 3.7%; partial response, 30.8%; no change, 55.1%) [84]. Based on this study, ^{131}I -chTNT was approved in China for the treatment of advanced lung cancer refractory to chemotherapy and radiotherapy. However, a phase I trial of ^{131}I -chTNT-1/B in the US to treat colorectal cancer did not achieve complete or partial responses in 21 patients [85]. Currently, a phase I trial of ^{131}I -chTNT-1/B to treat glioblastoma multiforme patients is underway (Table 1).

Melanin: Melanin is a novel tumor antigen target for clinical evaluation of radioimmunotherapy against melanoma. It is a class of pigment compounds expressed in melanoma cells. A couple of preclinical studies have proposed and demonstrated a strategy to target this intracellular compound where tumor cell lysis caused by chemotherapeutic agents will release melanin in the tumor environment for subsequent targeting by radiolabeled anti-melanin antibody [86,87]. Currently, a phase I study is underway to evaluate safety and maximum tolerated dose of ^{188}Re labeled anti-melanin IgM antibody PTI-6D2 (Table 1).

Other tumor antigen targets that have been actively studied in radioimmunotherapy recently include TAG-72, Lewis^y, A33 (Table 2).

Tumor Associated Glycoprotein (TAG-72): TAG-72 is a mucin-like, high molecular weight glyco-protein that is expressed on a variety of solid tumors, such as ovarian, pancreatic and colorectal cancer. In a phase II trial of ^{131}I labeled anti-TAG72 antibody CC49 to treat patients with colorectal cancer, no objective responses were observed in 15 patients [88]. When ^{131}I -CC49 was combined with interferon in another phase II trial, no objective responses were observed in 14 patients [89]. In similar phase II trials in breast and prostate cancer patients, only one out of 15 breast cancer patients had a partial response. Two out of 15 breast patients and 2 out of 6 prostate cancer patients had minor responses [90,91]. In a phase I study of ^{90}Y -CC49 to treat non small cell lung cancer patients, no objective tumor responses were observed in 34 patients [92]. A recent phase I trial using a pretargeting strategy to treat patients with gastrointestinal adenocarcinoma showed 4 out of 9 patients had partial responses and 2 had stable diseases [93].

Lewis^y: Abnormal glycosylation of cell surface proteins is characteristic of many tumor cells and is frequently observed in Lewis related histo-blood group antigens. Higher expression of Lewis^y antigen has been found in breast, ovarian and colon cancers and correlated with poor survival [94–96]. In a phase I trial of ⁹⁰Y labeled murine anti-Lewis^y antibody B3 in patients with breast, ovarian, bladder and non small cell lung cancer, no objective response were observed. Six out of 24 patients had stable disease [16]. ⁹⁰Y labeled humanized anti-Lewis^y antibody hu3S193 has also been studied in a phase I trial of ovarian cancer patients (Table 2).

A33: A33 is another transmembrane glycoprotein that is expressed on colorectal cancer cells [97]. In a phase I trial of ¹³¹I labeled anti-A33 antibody huA33 in patients with colorectal cancer, 4 out of 15 treated patients had stable disease and excellent tumor localization was reported. In another phase I trial of ¹³¹I-huA33 to treat patients with gastric cancer, no objective clinical responses were observed [98].

Other solid tumor antigen targets that have been previously evaluated in clinical trials of radioimmunotherapy but have not shown significant clinical benefits include: the folate receptor, EpCAM, CA125, asialo GM1 terminal disaccharide, fibroblast activation protein (FAP), L6, and NCAM (CD56) [52,53].

Solid Tumor Antigen Targets in Antibody Immunotherapy—Monoclonal antibody based immunotherapy of solid tumors is a fast growing field of targeted therapy and four antibodies, Trastuzumab, Cetuximab, Panitumumab, Bevacizumab, have been approved to treat various types of solid tumors in the US. With the improvement of our understanding in cancer biology, novel tumor antigens are being discovered and exploited for antibody targeting and a variety of antibodies enter clinical trials every year. Clinical trials using naked monoclonal antibodies to target solid tumors are obtained from clinicaltrials.gov and shown in Table 3 and Table 4. Only trials that are currently recruiting patients are included. Trials of monoclonal antibodies directly targeting to tumor cells by engaging tumor signaling pathways are listed in Table 3, while trials of antibodies that kill tumors indirectly, such as by blocking tumor angiogenesis or activating host immune system are listed in Table 4. Antibodies with toxin conjugates and fusion antibodies targeting two tumor antigens are not included. This is not intended as a comprehensive list of antibodies currently under development for cancer therapy, rather it is compiled to compare with the tumor antigens that are currently evaluated in cancer radioimmunotherapy (Table 1 and 2).

There are a total of 420 clinical trials of monoclonal antibody based treatment of solid tumors (with open recruitment). As in radioimmunotherapy trials, the majority of the clinical trials (278 out of 420, 66%) are focused on the four FDA approved antibodies to evaluate their efficacy in other cancer types or when they are combined with various chemo- and radiation therapy regimens. One third of the clinical trials (142 trials) are evaluating novel antibodies for solid tumor, compared to 23 trials that are currently open in radioimmunotherapy (16%). Among the 142 trials, 111 clinical trials are testing antibodies directly targeting tumor cells and 31 trials involve antibodies that inhibit tumor angiogenesis or activate host anti-tumor immune system. These open trials are evaluating a total of 59 antibodies (42 direct and 17 indirect tumor targeting) targeting 32 tumor antigens (20 direct

and 12 indirect tumor targeting). Out of the 20 direct tumor antigen targets, 5 antigen targets (25%) are also being or have been evaluated in radioimmunotherapy trials (Table 1, 2). The majority of these trials are in phase I/II and 8 antibodies are in phase III trials, compared to 2 phase III trials in radioimmunotherapy studies. Out of these 8 antibodies in phase III trials, 5 antibodies are actually targeting the same tumor antigens (EGFR, HER-2 and VEGF) that are also targeted by the FDA approved antibodies.

Gains in knowledge obtained by dissecting the molecular signaling pathways underlying tumor cell growth and survival, have led to an increased emphasis in identifying and using monoclonal antibody-mediated therapy that is designed to target signaling pathways essential for tumor growth, while few radiolabeled antibodies targeting these antigens are under investigation in current clinical trials. The tumor antigens involved in these growth signal pathways and being evaluated in clinical trials (Table 3) are discussed below.

EGFR, HER-2, HER-3 (Epidermal Growth Factor Receptor Family, ErbB): EGFR receptors are tyrosine kinase receptors that are aberrantly activated in many solid tumors and lead to tumor growth and resistance to apoptosis through their downstream signaling pathways. Members of the EGFR receptor family, EGFR and HER-2, have been extensively studied for their role in tumor growth and survival. Three monoclonal antibodies, Trastuzumab for HER-2, Cetuximab and Panitumumab for EGFR, have been approved by the FDA to treat breast and colorectal cancer, respectively. Binding of antibodies to EGFR receptors on tumor cells will lead to cell cycle arrest, apoptosis and inhibition of angiogenesis and metastasis [80]. Beside further clinical evaluation of Trastuzumab, Cetuximab and Panitumumab for other types of cancer, several other antibodies targeting EGFR (Nimotuzumab, Zalutumumab, Necitumumab and RO5083945), HER-2 (Pertuzumab) or HER-3 (U3-1287, MM-121) are also being evaluated for a wide variety of cancer types (Table 3). In comparison, only one clinical trial of radiolabeled antibody is currently designed to target the EGFR receptor family (^{125}I -425) in glioma patients.

IGF-1R (Insulin-Like Growth Factor Receptor)/IGF (Insulin-Like Growth Factor): IGF-1R is a member of the insulin like growth factor system that control normal organ growth and differentiation. Aberrant upregulation of IGF-1R is detected in a variety of cancer types, such as breast, ovarian, prostate, liver and lung cancer and has been found to be responsible for abnormal tumor cell growth and, more importantly, for making cancer cells resistant to apoptotic mechanisms [99]. There are 7 antibodies currently in clinical trials and all of them are targeting IGF-1R, but not the ligand IGF-1. Among the 7 antibodies, Figitumumab (CP-751,871) is being evaluated in a phase III trial to treat non small cell lung cancer (NSCLC) patients in combination with cisplatin and gemcitabine. In a phase II trial of Figitumumab in NSCLC patients in combination with paclitaxel and carboplatin, 54% the patients treated with Figitumumab, paclitaxel and carboplatin had an objective response compared to 42% of patients treated with paclitaxel and carboplatin alone [100].

MET (Mesenchymal Epithelial Transition Factor or Hepatocyte Growth Factor Receptor)/HGF (Hepatocyte Growth Factor): MET is a proto-oncogene that has been upregulated in a variety of cancers of epithelial origin, such as head and neck cancer,

glioma, lung and breast cancer. Binding of MET by ligand, HGF, in normal cells regulates cell proliferation, migration and wound healing. The aberrant expression of MET in tumors has been shown to reduce cancer cell growth dependence on HGF binding and correlate with poor prognosis [101]. Four antibodies are in clinical trials (Table 3) to block the binding of HGF to MET, thereby, disrupting activation of the MET/HGF signaling pathway. Three antibodies (AMG 102, SCH 900105, TAK-701) function by binding to the ligand HGF and blocking its binding to MET, while one antibody MetMab functions by binding to MET directly to block HGF binding. In a phase I trial of AMG 102 to treat patients with advanced solid tumors, 16 out of 23 patients had stable disease but no patients had partial or complete responses [102]. Although tumor secreted ligands, such as HGF, can also be targeted by radiolabeled antibody, targeting tumor surface receptors, such as MET, might enhance tumor residence time and improve uptake. MetMab, therefore, could be a better candidate antibody to evaluate radioimmunotherapy of the MET/HGF pathway.

PDGFR (Platelet Derived Growth Factor Receptor)/PDGF (Platelet Derived Growth Factor): PDGFR is a tyrosine kinase receptor that promotes cell proliferation, survival and migration when activated by PDGF binding, its ligand. PDGFR has been found to be over expressed in several solid tumors, including glioblastoma, ovarian and prostate cancer. Abnormal PDGFR expression contributes to tumor growth and development via autocrine-dependent growth stimulation and angiogenesis [103]. There are currently 2 antibodies in clinical trials, IMC-3G3 and MEDI-575 (Table 3), both targeting PDGFR. In a phase I trial of another anti-PDGFR antibody CP-868,596 to treat patients with advanced solid tumors (trial completed), however, no objective responses were reported in 59 patients and eight patients achieved stable disease [104].

TRAIL-R and TWEAK-R (Tumor Necrosis Factor Family): Cancer cells typically acquire the anti-apoptotic phenotype after somatic mutation, especially after treatment by chemotherapy, thereby leading to drug resistance. There are two apoptotic pathways. One is induced by cellular damage and stress, while the other is activated upon by extracellular ligand binding to death receptors, such as TRAIL-R (Tumor necrosis factor related apoptosis inducing ligand receptors) [105] and TWEAK-R (TNF-related weak inducer of apoptosis receptor) [106], both belong to the tumor necrosis factor receptor super family. Antibodies targeting these receptors were, therefore, developed to induce apoptosis in tumor cells. There are currently 3 antibodies for TRAIL-R and 1 antibody for TWEAK-R in clinical trials. In a phase II trial of the anti-TRAIL-R antibody, Mapatumumab, against colo-rectal cancer, no objective response were observed in 38 patients and 12 patients achieved stable disease [107].

AGS-8 (Activator of G Protein Signaling 8) and AGS-16 (Activator of G Protein Signaling 16): G proteins are important cellular signaling molecules that relay cellular information from the cell surface through G protein coupled receptors. G proteins can also be activated without interaction with receptors, rather by other proteins interacting with subunits of G proteins, called activator of G protein signaling (AGS). Two AGS family proteins, AGS-8 and AGS-16, are being targeted by antibodies to treat solid tumors in clinical trials [108,109].

Other Antigen Targets: Several tumor antigens that are targeted in radioimmunotherapy trials are also being evaluated using unlabeled antibodies, such as ganglioside GD2 (CH14.18, 3F8), Lewis^y (Hu3S193), EpCAM (Adecatumumab), CAIX/MN (cG250), NCAM (BB-10901). In a phase II clinical trial of anti-GD2 antibody 3F8 in patients with neuroblastoma, tumor response was seen in bony lesions (2 of 7 pts) and marrow (3 of 8 pts) [110]. In a phase I trial of another anti-GD2 antibody CH14.18 in 9 patients with neuroblastoma, 2 complete response, 2 partial responses, 1 minor response and 1 stable disease were observed [111]. In a recent phase I trial of Ch14.18 in infants with stage IV neuroblastoma, however, no increase in event free survival or overall survival was found in the antibody treatment group [112]. When combined with GM-CSF and IL-2, Ch14.18 was evaluated in 25 patients with neuroblastoma in a phase I trial and estimated 3-year survival probability was 78% and the median follow-up time for those alive at last contact was 494 days [113]. Currently, a phase III trial of Ch14.18 in combination with GM-CSF and IL-2 is underway to treat patients with neuroblastoma (Table 3).

Unlabeled anti-Lewis^y antibody, hu3S193, has also been evaluated in clinical trials. In a phase I trial of hu3S193 in patients with Lewis^y positive epithelial cancers, no objective responses were observed and 4 out of 15 patients had stable disease [114]. In another phase I trial using hu3D193, another anti-Lewis^y antibody, in Lewis^y positive small cell lung cancer patients, all 40 patients had disease progression [115]. Clinical trials of naked antibodies targeting either EpCAM (Adecatumumab) in metastatic breast cancer patients or CAIX/MN (cG250) in renal cell carcinoma patients failed to show any objective responses [116,117].

Unlabeled antibodies are also very effectively and extensively studied in indirect tumor kill via blocking tumor angiogenesis and activating host anti-tumor immunity (Table 4). Anti-angiogenesis therapy is based on the hypothesis that killing and blocking growth and neovascularization of tumor blood vessels can deprive tumor cells of necessary nutrients and oxygen, thereby, eliminating tumor cells by starvation. By elucidating the molecular pathways (VEGFR/VEGF pathway and Notch/Delta-like ligand 4 pathway) governing tumor angiogenesis [118], numerous antibodies have been launched in clinical trials. Bevacizumab, an anti-VEGF antibody, was recently approved by the FDA to treat colorectal cancer [119] and other cancer types [120]. In addition to the extensive trials of Bevacizumab in a wide variety of cancer types (146 trials), anti-neuropilin, another ligand for VEGF, antibody is also being evaluated. Antibodies targeting extracellular matrix bound or associated vascular antigens involved in tumor angiogenesis, such as endoglin (CD105), tumor endothelial marker 1 (TEM-1), $\alpha_5\beta_1$ integrin, $\alpha_v\beta_3$ integrin and epidermal growth factor-like domain 7 (EFGL7) are also being studied clinically (Table 4). No clinical trials in radioimmunotherapy have been launched to target vascular cells directly although some targeted tumor antigens, such as CD44v6 (Bivatuzumab) or tenascin-c, might play a role in tumor angiogenesis.

Antibodies, as part of the human immune system, have demonstrated great potential in regulating and activating the host immune system against tumors. Primarily, several antibodies, such as anti-CTLA-4 and anti-PD1 antibodies, have been developed to block negative regulators of T cell receptors (TCR) on tumor antigen targeting T cells, thereby enhancing their anti-tumor activity. In a phase II trial of anti-CTLA-4 antibody in melanoma

patients, three patients had complete response and 5 patients had partial response out of 36 total patients [121]. Currently, anti-CTLA-4 antibody, Ipilimumab, is being evaluated in a phase III trial to treat melanoma patients. Since the anti-tumor efficacy of the antibody is highly related to its biological function and systemic injection of radiolabeled antibody usually causes immune suppression, the use of these antibodies in radioimmunotherapy is not foreseen in the near future. However, recent studies suggest that localized radiation might benefit subsequent immunotherapy. Radiation could alter the phenotype of tumor cells and therefore make them more susceptible to immune-mediated killing and tumor cell antigens released from radiation cell kill could result in cross-priming and effective presentation of tumor antigens to activate the immune system [122–124]. These findings might help to design novel radioimmunotherapy strategies to enhance tumor cell killing in combination with immune responses.

Solid Tumor Antigens in Pre-Clinical Development for Radioimmunotherapy—

It becomes apparent that a large proportion of tumor antigen targets evaluated in clinical trials of radioimmunotherapy are different from those studied in immunotherapy, where the trend seems to be targeting tumor cell growth signaling pathways or angiogenesis signaling pathways that are essential for the growth and survival of tumors. Considering that systemically injected intact radiolabeled antibodies are not able to deliver sufficient radiation doses to tumors, it is reasonable to ask whether the anti-tumor efficacy of the carrier antibody is critical for achieving clinical responses with radiolabeled antibodies. The success of ^{90}Y ibritumomab tiuxetan and ^{131}I tositumomab seems to show that the clinical efficacy of the anti-CD20 antibodies themselves are an important factor although radiosensitivity of lymphoma cells also plays a major role.

A review of tumor antigens studied in the past decade in preclinical animal models for radioimmunotherapy (Table 5) shows that tumor antigen targets selection also trends toward those growth signaling pathway antigens critical for tumor growth and survival. Noticeably, antibodies targeting epidermal growth factor receptor family antigens (EGFR, HER-2) and tumor angiogenesis are extensively studied in the pre-clinical models of radioimmunotherapy. Pfost *et al.* radiolabeled anti-EGFR antibody Matuzumab with the alpha particle emitter ^{213}Bi and found it very effective for the treatment of bladder cancer when the radiolabeled antibody is injected intravesically with mice surviving over 300 days compared to 89 and 41 days in unlabeled antibody treated and untreated control groups [125]. Another anti-EGFR antibody, Cetuximab, has also been investigated pre-clinically where both ^{90}Y labeled Cetuximab and the unlabeled antibody showed efficacy in a mouse model of head and neck squamous cell carcinoma [126]. In studying radioimmunotherapy of another ErbB family protein HER-2, several groups have shown significant efficacies of anti-HER-2 antibodies labeled with various radionuclides. Song *et al.* demonstrated efficacy of alpha particle ^{213}Bi , ^{225}Ac labeled anti-HER-2 antibody in treating mice bearing metastatic breast cancer [127,128]. Likewise, ^{213}Bi , ^{225}Ac labeled Trastuzumab significantly improved survival of mice with peritoneally disseminated ovarian cancer cells [129,130]. Persson *et al.* showed that radiolabeling of another anti-HER-2 antibody Pertuzumab with ^{177}Lu significantly delayed tumor progression in an ovarian cancer xenograft model, where tumor growth in 3 out of 8 mice did not reach the endpoint of 0.5

cm³ [131]. Radiolabeled Trastuzumab with another alpha emitter ²¹¹At has been shown to completely eradicate ovarian cancer xenografts when combined with unlabeled Trastuzumab [132].

Radiolabeled antibodies targeting antigens involved in tumor angiogenesis are also being developed, but only a handful of studies have demonstrated efficacy in animal models. ¹³¹I labeled antibody L19 targeting extra domain B of fibronectin was shown to significantly delay tumor growth and prolong mouse survival in an embryonal teratocarcinoma model, although a small immunoprotein (SIP) variant format of the same antibody showed better efficacy [133]. Tumor growth delay were also observed in a colorectal tumor model after treatment by ¹³¹I labeled L19-SIP [134]. Jaggi *et al.* showed that anti-vascular endothelial cadherin antibody E4G10 labeled with ²²⁵Ac was able to markedly prolong survival in a prostate xenograft model [135]. Tumor vascular normalization was observed after treatment and the efficacy was enhanced by subsequent treatment with paclitaxel. In another study of ²²⁵Ac labeled anti-thrombomodulin antibody 201B in a mouse model of breast cancer lung metastases, however, lung toxicity was observed after treatment [136].

In addition, several other novel tumor antigen targets are being studied in preclinical models of radioimmunotherapy, including tumor antigens involved in cell adhesion, antigens expressed during cell differentiation and viral origin antigens in virally induced cancer. Cheng *et al.* found that ²¹¹At labeled U36 targeting CD44v6, involved in cell binding with extracellular matrix protein hyaluronic acid, was able to inhibit tumor growth in an HNSCC xenograft model [137]. ²¹³Bi labeled anti-d9-E-cadherin, a mutant E-cadherin, antibody d9MAB was also shown to significantly prolong survival of mice bearing metastatic gastric cancer [138,139]. Mesothelin is a cell differentiation marker that is found to be specifically overexpressed in mesothelioma, ovarian and pancreatic cancers. Sato *et al.* showed that, in a pretargeting model, anti-mesothelin antibody with ⁹⁰Y-DOTA-biotin significantly prolonged survival with 86% of mice tumor free for 110 days compared to median survival of 16 days in untreated mice [140]. Radiolabeled antibody C1P5 targeting viral protein HPV 16 E6 with ¹⁸⁸Re has also been evaluated in an HPV positive cervical cancer model [141].

The identification of potential tumor antigen targets for radioimmunotherapy in the future is probably going to depend on our further understanding of other aspects of cancer pathways and mechanisms essential for tumor growth, such as metastasis and cancer metabolic abnormality. Furthermore, most tumor antigens in tumor growth signaling pathways are not unifunctional and most tumor phenotypes are not regulated by single signaling pathway or single antigens. Understanding this redundancy of tumor growth regulation can help us to design more effective combinational treatment regimens. Another lesson learned from the success of radio-immunotherapy in non-Hodgkin's lymphoma is that cancer cell radiosensitivity is also critical to obtaining clinical responses with radiolabeled antibody therapy. The development of radiosensitizers that can synergize with long-lived, low dose-rate radionuclides used in radioimmunotherapy might also help enhance the efficacy of radiolabeled antibodies in solid tumor treatment.

CONCLUSION

Radioimmunotherapy of solid tumors remains a challenge despite its success in hematological malignances. Several unlabeled antibodies successfully treat solid tumors by targeting tumor cell antigens that modulate tumor growth signaling pathways. Clinical trials are needed to determine whether choosing these antigens as targets will lead to increased efficacy of radiolabeled antibodies against solid tumors. Preclinical studies have shown promising results by targeting antigens in tumor growth signaling pathways, suggesting clinical radioimmunotherapy studies investigating such targets are likely to lead to promising results.

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Table 1

Tumor Surface Antigens Targeted in Clinical Trials (Open Recruitment) of Solid Tumor Radioimmunotherapy

Antigens	Phases	Cancer Types	Radiolabeled mAbs	Combination
CEA	I	Colorectal cancer	cT84.66- ⁹⁰ Y	Floxuridine, Gemcitabine
	I	NSCLC	cT84.66- ⁹⁰ Y	Carboplatin, paclitaxel, radiation
	I	Colorectal cancer	TF2 + IMP-288- ¹⁷⁷ Lu	No
	I	Colorectal cancer	TF2 + IMP-288- ¹³¹ I	No
	II	Medullary thyroid carcinoma	F6-734 + di-DTPA- ¹³¹ I	No
	I	CEA producing tumors	M5A- ⁹⁰ Y	No
PSMA	I	Prostate cancer	HuJ591- ¹⁷⁷ Lu	No
	II	Prostate cancer	HuJ591- ¹⁷⁷ Lu	No
	I	Prostate cancer	HuJ591- ¹⁷⁷ Lu	Docetaxel, prednisone
	II	Prostate cancer	HuJ591- ¹⁷⁷ Lu	Ketoconazole, hydrocortisone
	I	Non-prostate solid tumors	HuJ591- ¹⁷⁷ Lu	No
	I	Prostate cancer	7E11-C5.3- ¹⁷⁷ Lu	No
Tenascin-C	II	Glioblastoma multiforme	81C6- ¹³¹ I	Bevacizumab
GD2	I	Neuroblastoma	3F8- ¹³¹ I	Bevacizumab, filgrastim
	II	Brain tumors	3F8- ¹³¹ I	No
	II	Medulloblastoma	3F8- ¹³¹ I	Lomustine, vincristine, IMRT
4Ig-B7-H3	I	Brain tumors	8H9- ¹³¹ I	No
CAIX/MN	I	Renal cell carcinoma	cG250- ⁹⁰ Y	No
	I/II	Renal cell carcinoma	cG250- ¹⁷⁷ Lu	No
MUC1	I	Pancreatic cancer	hPAM4- ⁹⁰ Y	Gemcitabine
DNA/histone H1 (necrosis)	II	Glioblastoma Multiforme	chTNT-1/B- ¹³¹ I	No
EGFR	II	Glioma	425- ¹²⁵ I	No
Melanin	I	Melanoma	PTI-6D2- ¹⁸⁸ Re	No

Table 2

Tumor Surface Antigens Targeted in Clinical Trials (Without Recruitment) of Solid Tumor Radioimmunotherapy

Antigens	Phases	Cancer Types	Radiolabeled mAbs	Combination
CEA	I/II	Medullary thyroid carcinoma	Labetuzumab- ⁹⁰ Y	Doxorubicin
	I/II	Breast cancer	Labetuzumab- ⁹⁰ Y	No
	I/II	Ovarian cancer	Labetuzumab- ⁹⁰ Y	No
	I/II	Colorectal, pancreatic cancer	Labetuzumab- ⁹⁰ Y	Filgrastim
	I/II	Colorectal Cancer	Labetuzumab- ⁹⁰ Y	No
	I/II	Pancreatic Cancer	Labetuzumab- ⁹⁰ Y	No
	I	NSCLC	Labetuzumab- ⁹⁰ Y	No
	I	Small cell lung cancer	Labetuzumab- ⁹⁰ Y	No
MUC1	III	Ovarian cancer	HMFG-1- ⁹⁰ Y	No
	I	Breast cancer	BrE3- ⁹⁰ Y	ASCT
	I	Breast Cancer	M170- ⁹⁰ Y	Cyclosporine, paclitaxel
	I	Prostate Cancer	M170- ⁹⁰ Y	Filgrastim, cyclosporine, paclitaxel
	I	Breast cancer	M170- ⁹⁰ Y	Cyclosporine and ASCT
PSMA	I	Prostate cancer	J591- ¹³¹ I	No
	II	Prostate cancer	J591- ¹⁷⁷ Lu	No
CAIX/MN	I/II	Renal cell carcinoma	cG250- ¹³¹ I	No
GD2	I	Leptomeningeal Cancer	3F8- ¹³¹ I	No
TAG-72	I	Ovarian Cancer	CC49- ⁹⁰ Y/CC49- ¹⁷⁷ Lu	Paclitaxel and interferon alpha
	I	Colorectal cancer	CC49-deltaCH2- ¹³¹ I	No
	I	Gastrointestinal cancer	CC49-deltaCH2- ¹³¹ I	No
	I/II	Colorectal cancer	CC49-deltaCH2- ⁹⁰ Y	No
Tenascin-C	I/II	Primary brain cancer	81C6- ¹³¹ I	Radiation therapy
	I/II	Neuroblastoma	81C6- ²¹¹ At	No
	I/II	Neuroblastoma	81C6- ¹³¹ I	Carmustine, irinotecan
	I/II	Glioma	81C6- ¹³¹ I	No
	I/II	Primary brain tumor	81C6- ¹³¹ I	No
	III	Glioblastoma multiforme	81C6- ¹³¹ I	Radiotherapy, temozolomide
Lewis ^x	I	Breast cancer	B3- ⁹⁰ Y	ASCT
	I	Ovarian cancer	Hu3S193- ⁹⁰ Y	No
A33	I	Colorectal Cancer	A33- ¹³¹ I	No
DNA/histone H1 (necrosis)	I	Brain tumor	TNT-1/B- ¹³¹ I	No
	II	Brain tumor	TNT-1/B- ¹³¹ I	No
EGFR	I	Glioma	425- ¹²⁵ I	No
FAP	I	Colorectal cancer	F19- ¹³¹ I	No

Table 3

Monoclonal Antibodies in Clinical Trials that Directly Target Solid Tumors

Antigens	Antibodies	Cancer Types	Phases	Trials
EGFR	Cetuximab	NSCLC, colorectal, HNSCC, liver, etc.	I, II, III	66
	Panitumumab	Colorectal, pancreatic, NSCLC, etc.	I, II, III	24
	Nimotuzumab	Pancreatic, HNSCC, colorectal, etc.	I, II, III	10
	Zalutumumab	HNSCC	I, II, III	5
	Necitumumab	NSCLC	III	2
	RO5083945	HNSCC	I	2
HER-2	Trastuzumab	Breast, NSCLC, pancreatic, etc.	I, II, III	42
	Pertuzumab	Breast, colorectal, NSCLC, etc.	I, II, III	7
HER-3	U3-1287	Solid tumors	I	1
	MM-121	NSCLC	I/II	1
IGF-1R	Cixutumumab	Liver, prostate, sarcoma, breast, etc.	I, II	21
	AMG 479	NSCLC, ovarian, pancreatic, etc.	I, II	8
	Figitumumab	NSCLC, breast	I, II, III	6
	Dalotuzumab	Colorectal, NSCLC	I, II	4
	Robatumumab	Breast cancer	I	2
	SCH 717454	Solid tumors	I, II	2
	MEDI-573	Solid tumors	I	1
MET/HGF	AMG 102	Ovarian, gastric, esophageal etc.	I, II	4
	MetMab	NSCLC	II	1
	SCH 900105	NSCLC	II	1
	TAK-701	Solid tumor	I	1
PDGFR	IMC-3G3	NSCLC, brain, ovarian cancer	I, II	3
	MEDI-575	Solid tumor	I	1
TRAIL-R	Conatumumab	Colorectal, pancreatic cancer	I, II	3
	TRA-8	Colorectal, ovarian cancer	II	2
	Lexatumumab	Kidney, neuroblastoma	I	1
	Mapatumumab	Liver cancer	I, II	1
Tweak-R	PDL192	Solid tumors	I	1
AGS-8	AGS-8M4	Ovarian cancer	I	2
AGS-16	AGS-16M18	Kidney cancer	I	1
GD2	CH14.18	Neuroblastoma, melanoma	II, III	4
	3F8	Neuroblastoma	I, II	3
GD3	KW2871	Melanoma	II	1
EpCAM	Adecatumumab	Colorectal	II	1
	MOC-31	Solid tumors	I	1
CAIX/MN	cG250	Kidney cancer	I	1
Lewis ^y	Hu3S193	Ovarian cancer	I	1

Antigens	Antibodies	Cancer Types	Phases	Trials
Mesothelin	MORAb-009	Mesothelioma	II	1
PSCA	AGS-1C4D4	Pancreatic cancer	II	1
NCAM	BB-10901	Solid tumors	I	1
GC128	Claudiximab	Gastric cancer	I	1
MAGE-A3	GSK2132231A	Melanoma	II	1

Table 4

Monoclonal Antibodies in Clinical Trials that Indirectly Target Solid Tumors

Antigens	Antibodies	Cancer Types	Phases	Trials
VEGFR/VEGF	Bevacizumab	Colorectal, NSCLC, breast, brain etc.	I, II, III	146
	Ramucirumab	Gastric, solid tumor	I, II, III	3
Neuropilin-1	MNRP1685A	Solid tumors	I	2
Endoglin	TRC-105	Prostate, solid tumor	I, II	2
TEM-1	MORAb-004	Solid tumors	I	1
$\alpha_5\beta_1$ Integrin	PF-04605412	Solid tumors	I	1
$\alpha_v\beta_3$ Integrin	EMD 525797	Colorectal cancer	I, II	1
EFGL7	MEGF0444A	Solid tumors	I	1
CTLA-4	Ipilimumab	Prostate, pancreatic, melanoma	I, II, III	6
	Tremelimumab	Liver, bladder cancer, prostate	I, II	3
PD-1/PD-L1	CT-101	Liver, colorectal cancer	I/II	3
	MDX-1106	NSCLC, kidney, melanoma	I	3
	MDX-1105	Kidney, NSCLC, melanoma, etc.	I	1
CD40	CP-870,893	Pancreatic cancer	I	1
CCR-2/CCL-2	MLN1202	Solid tumors	II	1
	CNTO 888	Prostate cancer	II	1
IL-6	CNTO 328	Solid tumors	I, II	1

Table 5

Pre-Clinical Studies of Radiolabeled Antibodies Targeting Novel Tumor Antigens

Antigens	Cancer Types	Antibodies	Radionuclides	References
EGFR	Glioma, bladder cancer, colorectal, pancreatic, ovarian, prostate cancer, HNSCC	Matuzumab, Panitumumab, Cetuximab, Nimotuzumab, 425	^{213}Bi , ^{90}Y , ^{188}Re , ^{125}I , ^{111}In	[125,126,142–144]
HER-2	Breast, ovarian, pancreatic cancer	Trastuzumab, Pertuzumab, C6.5, 7.16.4	^{90}Y , ^{225}Ac , ^{213}Bi , ^{212}Pb , ^{211}At , ^{188}Re , ^{177}Lu , ^{111}In	[127–132,145–155]
FZD10	Synovial sarcoma	MAB 92-13	^{90}Y	[156]
VEGFR1	Liver cancer	Anti-VEGFR1	^{177}Lu	[157]
ED-B, fibronectin	Glioblastoma, HNSCC, teratocarcinoma, colorectal	L19-SIP	^{90}Y , ^{177}Lu , ^{131}I	[133,134,158–160]
VE cadherin	Prostate cancer	E4G10	^{225}Ac	[135]
Thrombomodulin	Breast cancer	201B	^{225}Ac	[136]
CD44v6	HNSCC	U36	^{125}I , ^{211}At	[137,161]
CK19	Cervical cancer	Cx99	^{188}Re	[162]
d9-E-cadherin	Gastric cancer	d9Mab	^{213}Bi , ^{149}Tb	[138,139,163,164]
L1-CAM	Kidney cancer	chCE7	^{177}Lu	[165]
EGP-1	Breast and lung cancer	RS7	^{90}Y , ^{131}I , ^{177}Lu	[166]
Mesothelin	Mesothelin transfected epidermoid carcinoma	SS1sc FvSA pretargeting	^{177}Lu , ^{90}Y	[140]
HPV-16 E6	Cervical cancer	C1P5	^{188}Re	[141]