

Recent Advances Relating to the Clinical Application of Naked Monoclonal Antibodies in Solid Tumors

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This review focuses on the recent advances in clinical data regarding antibody-based therapy in the management of solid tumors. We also discuss perspectives on antibody-based therapy in the future. Thorough understanding of the complex interactions between components of the immunological response has led to interest in the concept of immune-mediated therapy for solid tumors. Over the last few years, several humanized and chimeric monoclonal antibodies (MAbs) targeting human epidermal receptor 2 (HER2), epidermal growth factor receptor (EGFR), and vascular endothelial growth factor (VEGF) have been employed in treating solid tumors, including breast, colorectal, lung, head and neck, and gynecologic cancers. Trastuzumab, bevacizumab, cetuximab, and panitumumab are MAbs that are most widely used in clinical practice with acceptable rates of adverse events. Combination of MAbs with small-molecule inhibitors of the same pathway could potentially increase the efficacy and specificity of antibody-based treatment. Immune-mediated effects may be further exploited with the use of bivalent molecules.

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INTRODUCTION

Over the last few years, molecular biology has played a major role in the development of treatments for solid tumors. Advances in isolating, defining, and measuring appropriate targets for innovative targeted therapies have led to the production of naked and conjugated monoclonal antibodies (MAbs) against molecules, which orchestrate pathophysiological mechanisms of cancer genesis. Naked MAbs are those without any drug or radioactive material attached to them, whereas conjugated MAbs are those joined to a chemotherapy drug, radioactive isotope, or toxin (1). In this report we review and discuss recent advances in preclinical and clinical data regarding

antibody-based therapy in the management of solid tumors. We also discuss perspectives on antibody-based therapy in the future.

MECHANISM OF MAb ACTION

The mechanisms of MAb action, including the role of host and cellular factors and their influence on the response to MAbs, have not been completely elucidated. There are many potential mechanisms through which MAbs act. Briefly, the interaction between antibody and tumor antigen may induce apoptosis by activating mechanisms of complement-mediated cell death in the tumor cell (2). Some cells rely on continued stimulation by growth factors for proliferation, dif-

ferentiation, interaction with other cells, growth, and survival. These factors are also involved in invasion, metastatic spread, and angiogenesis through the activation of intracellular signaling pathways. Inhibition of ligand-receptor interaction with MAbs can lead to cell death because cells are deprived of tumorigenic stimuli (3).

Furthermore, the formation of an entire antiidiotype network induces immunological responses against cancer cells. Thus, the development of antiidiotype antibodies (Ab2) against Ab1-binding sites is another important way of MAb action. The amount of antigen on tumor cells, the subclass of the antibody, and the type of effector cell are some additional factors that regulate the ability of MAbs to induce antibody-dependent cell cytotoxicity (4). Bispecific MAbs increase this effect because bivalent MAbs contain two binding domains. The first targets the tumor antigen, and the other binds to Fc receptors on effector cells, thereby increasing the probability of tumor lysis (5).

Conjugated antibodies have a different mechanism of action than that of naked

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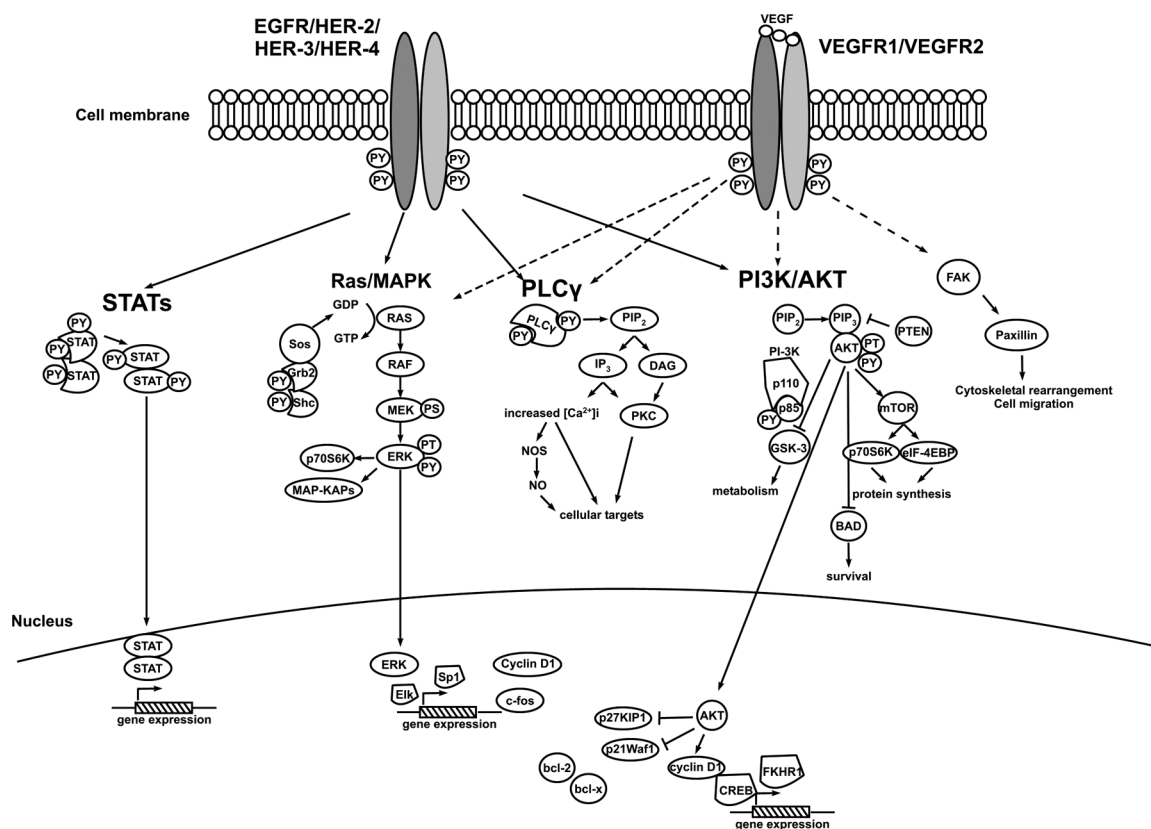


Figure 1. EGFR and VEGFR signaling share common pathways. The network of both family receptors may control pathways that affect cell proliferation, survival, differentiation, and migration.

MAbs. Interaction between antibody and tumor antigen can either facilitate toxin delivery to tumor cells, which potentially causes cell death, or contribute to targeted radioimmunotherapy (6). In the first case, the mechanism of toxic effect depends on the structure and function of the toxin. In the second setting, the administration of focused doses of radiation to tumor cells is regarded as a pioneer endeavor, attempting to specifically target cancer cells and reduce radiotoxicity in normal tissues (1).

EPIDERMAL GROWTH FACTOR RECEPTOR BIOLOGY AND ROLE

The epidermal growth factor receptor (EGFR) is a glycoprotein consisting of an extracellular ligand-binding domain, a transmembranic domain, and an intracellular cytoplasmic protein domain with tyrosine kinase activity. Briefly, EGFR belongs to the human epidermal receptor

(HER) family of receptor tyrosine kinases that are implicated in cell proliferation, growth, and survival. HER1 (EGFR, erb-B1), HER2 (neu-erb-B2), HER3 (erb-B3), and HER4 (erb-B4) are receptors comprising the HER family (7).

Elevated expression and cross-phosphorylation of EGFR, increased ligand levels, heterodimerization, and cross-talk between EGFR and other membrane-bound receptors are implicated in solid-tumor aggression. Understanding of the essential role EGFR plays in carcinogenesis has led to the development of MAbs that are capable of blocking the extracellular domain of the receptor and small-molecule inhibition of the intracellular tyrosine kinase domain (8). Table 1 summarizes the MAbs that are currently employed in clinical trials, and Figure 1 shows the signaling pathways that are downstream of EGFR and VEGFR (vascular

endothelial growth factor receptor), with emphasis on HER tyrosine kinases.

TRASTUZUMAB

Trastuzumab, a recombinant humanized MAb that targets the HER2 receptor, inhibits cell proliferation and DNA repair, induces apoptosis, and promotes DNA damage and immune modulation, thus causing cell-cycle arrest. Trastuzumab also exerts antiangiogenic effects, by both induction of antiangiogenic factors and repression of proangiogenic factors (9). Trastuzumab has been approved by the US Food and Drug Administration (FDA) for the treatment of metastatic breast cancer (MBC) with HER2 overexpression and is currently applied either alone or in an adjuvant setting in combination with chemotherapeutic agents in early breast cancer.

Several phase II studies have attempted to confirm the clinical efficacy

Table 1. Monoclonal antibodies for the treatment of solid tumors.

MAb	Trade name	Molecular target	Tumor target	Status
Trastuzumab	Herceptin	HER2/neu	Breast	FDA approved
Cetuximab	Erbix	EGFR	CRC, SCCHN, NSCLC	FDA approved for CRC, SCCHN; phase I/II for NSCLC
Bevacizumab	Avastin	VEGF-A	CRC, NSCLC, breast, renal, pancreatic, prostatic, melanoma	FDA approved for CRC, NSCLC; phase II/III for others
Panitumumab	Vectibix	EGFR	CRC, Renal	FDA approved for CRC; phase II/III for others
Matuzumab	—	EGFR	Pancreatic, NSCLC, peritoneal	Phase I/II
Nimotuzumab	TheraCIM	EGFR	SCCHN, NSCLC, glioma	Phase I/II
MDX-447	—	EGFR	SCCHN	Phase I/II
Oregovomab	OvaRex	CA125	Ovarian	Phase I/II
Pertuzumab	—	EGFR	Ovarian, NSCLC, prostatic	Phase I/II
Ipilimumab	—	CTLA-4	Melanoma	Phase I/II

Abbreviations: CRC, colorectal cancer; SCCHN, squamous cell carcinoma of the head and neck; NSCLC, non-small cell lung carcinoma; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; VEGF, vascular endothelial growth factor.

and safety of trastuzumab either as monotherapy or combined with other cytotoxic agents.

In a phase II trial, 114 women with HER2-overexpressing MBC were randomized to receive first-line weekly monotherapy with trastuzumab (4 mg/kg loading dose, followed by 2 mg/kg weekly, or a higher 8 mg/kg loading dose, followed by 4 mg/kg weekly treatment). Trastuzumab activity against MBC was demonstrated by the objective response rate of 26%, with 7 complete responses (CRs) and 23 partial responses (10). In another phase II study, 105 women with MBC received a loading dose of trastuzumab, 8 mg/kg intravenously (IV) and then 6 mg/kg IV at 3-week intervals until disease progression or patient withdrawal. The overall response rate (ORR) was 19%, and the clinical benefit rate was 33%. The median time to disease progression (mTDP) was 3.4 months. Trastuzumab was well tolerated. This study suggested that a 3-week trastuzumab treatment course may be a convenient regimen alternative to weekly administration (11).

Several studies have evaluated the synergistic effects between trastuzumab and other cytotoxic agents. In the TRAVIOTA (Trastuzumab and Vinorelbine or Taxane) study, the use of trastuzumab either with vinorelbine or taxanes was compared in 81 HER2-

overexpressing MBC patients who were chemotherapy-naïve for advanced disease. Patients were randomized to receive either trastuzumab with weekly vinorelbine therapy (arm 1, $n = 41$) or weekly taxane therapy (arm 2, $n = 40$). ORR was 51% and 40% for arms 1 and 2, respectively. The mTDP was 8.5 months and 6 months for arms 1 and 2, respectively. Similar rates of neurologic and gastrointestinal toxicity were observed with either regimen (12).

The results of another phase II trial that evaluated the efficacy and safety of trastuzumab plus docetaxel in 40 patients with HER2-positive MBC were recently published. In this study, the primary endpoint of tumor response has been reached. The ORR was 65% and the mTDP was 6.8 months. Concerning safety, of the 40 patients, 35 (88%) had grade 3 or 4 leukopenia, and 33 (83%) had grade 3 or 4 neutropenia. Otherwise, the combination of docetaxel and trastuzumab was well tolerated (13).

Other regimens (14,15) combine trastuzumab with anthracyclines (ORR: 71%), capecitabine (ORR: 47%), and gemcitabine alone or with paclitaxel (ORR: 37%–44%), paclitaxel plus docetaxel in various dosing regimens (ORR: 36–63%), and platinum/paclitaxel/docetaxel (ORR: 50%–82%). Large phase III studies are in progress to further evaluate the efficacy of such combinations.

Trastuzumab in the Adjuvant Setting

Trastuzumab has also been investigated in the adjuvant setting, and results from a number of clinical trials are sufficiently compelling to consider 1 year of adjuvant trastuzumab treatment for women with HER2-positive early breast cancer. This view was recently supported by a metaanalysis of clinical trials testing trastuzumab in the adjuvant setting. Pooled results from existing randomized trials showed a significant reduction of mortality ($P = 0.000$), recurrence ($P = 0.000$), and metastases rates ($P = 0.000$) in patients who received adjuvant trastuzumab compared with those who did not. There were more cases of grade III or IV cardiotoxicity after trastuzumab (203 of 4555 = 4.5%) versus no trastuzumab (86 of 4562 = 1.8%) (16). In addition, the HERA (Herceptin Adjuvant) trial also showed that the incidence of cardiotoxicity was higher in the trastuzumab group compared with controls. However, most patients with cardiac dysfunction recovered in less than 6 months (17). In a recent study, weekly trastuzumab administration and menopausal status have been proposed as independent prognostic factors for manifestation of left ventricular ejection fraction decrease and dermatitis, respectively, whereas a higher cumulative dose of trastuzumab was also borderline linked to acute esophagitis toxicity (18).

Trastuzumab in the Neoadjuvant Setting

Available data on the activity and safety of trastuzumab-containing neoadjuvant chemotherapy for the management of localized, irresectable, or resectable breast cancer are in keeping with a pathologic complete response (pCR) of 7%–78%, with a favorable adverse event profile. It was recently reported by Arnould *et al.* that pCR to trastuzumab-based neoadjuvant therapy is related to the level of HER-2 amplification. In this study, 35 of 93 patients (37.6%) treated with trastuzumab-based neoadjuvant therapy achieved pCR (19).

In a recent phase II study, 70 patients with HER-2-positive, stage II/III breast cancer received trastuzumab 4 mg/kg, followed by 2 mg/kg weekly, plus docetaxel 75 mg/m², and carboplatin (AUC6) for six cycles before surgery. A complete or partial objective clinical response occurred in 95% of patients (85% and 10%, respectively). In an intent-to-treat analysis, tumor and nodal pCR were seen in 27 of 70 (39%) patients. Treatment was well tolerated (20).

Finally, in the NeOAdjuvant Herceptin (NOAH) phase III trial, 228 patients with centrally confirmed HER2-positive locally advanced breast cancer received 3 cycles of doxorubicin-paclitaxel, 4 cycles of paclitaxel, and 3 cycles of CMF (cyclophosphamide/methotrexate/5-fluorouracil), with (n = 115) or without (n = 113) concomitant trastuzumab before surgery. The addition of trastuzumab improved ORR (81% versus 73%; *P* = 0.18) and significantly increased the pCR rate (43% versus 23%; *P* = 0.002). Treatment was well tolerated with acceptable cardiac safety (21).

CETUXIMAB

Cetuximab (C225), a chimeric MAb raised against EGFR, inhibits endogenous ligand binding, cell motility, invasiveness, metastasis, and the promotion of apoptosis (9). Combined administration of cetuximab with various chemotherapeutic agents showed significant growth inhibition in various cancer cell

lines, such as colon, head and neck, breast, renal, and bladder (22,23). Combination therapy of cetuximab plus irinotecan demonstrated inhibition of growth and progression of orthotopic anaplastic thyroid carcinoma xenografts in nude mice (24).

Cetuximab is FDA approved for treating advanced colorectal cancer (CRC) and squamous cell carcinoma of the head and neck (SCCHN). It has also been tested in phase I/II trials against other solid tumors. In a phase I study, cetuximab was administered in combination with paclitaxel/carboplatin in previously untreated patients with stage IV non-small cell lung cancer (NSCLC). The most common dose-limiting toxicity was acneiform rash in 84% of patients (grade 3 in 13%). An objective response was observed in eight patients (26%). With a median follow-up of 19 months, the mTDP was 5 months, median overall survival (mOS) was 11 months, and the 1- and 2-year survival rates were 40% and 16%, respectively (25).

However, the results of a recently published multicenter, phase II study indicate that the combination of cetuximab with docetaxel and carboplatin has demonstrated modest activity in 80 patients with advanced and metastatic NSCLC, because the ORR was 15.2% and the mOS was 10.3 months (26). Also of note are the disappointing results of a phase I trial that evaluated the combination of cetuximab/paclitaxel in patients with MBC. In this study and because of prohibitive grade 3 rash combined with disappointing preliminary efficacy, the combination tested was not considered promising (27). Preoperative chemoradiotherapy with cetuximab, capecitabine, and weekly irinotecan has been shown in a phase I trial to be feasible and well tolerated in patients with locally advanced rectal cancer (28).

In a large phase III trial, 572 pretreated patients with EGFR-overexpressing CRC were randomized to receive either cetuximab plus best supportive care (BSC) (287 patients) or BSC alone (285 patients). The primary end point was over-

all survival. The mOS was 6.1 months in the cetuximab group and 4.6 months in the group assigned to BSC alone. Partial responses occurred in 23 patients (8.0%) in the cetuximab group but in none in the group assigned to BSC alone (*P* < 0.001); the disease was stable in an additional 31.4% of patients assigned to cetuximab versus 10.9% of patients assigned to BSC alone (*P* < 0.001). The incidence of any adverse event of grade 3/4 was higher (78.5% versus 59.1%; *P* < 0.001) in the cetuximab group (29).

A phase II study investigated the efficacy and safety of cetuximab (initial dose 400 mg/m² during week 1, then 250 mg/m² weekly) followed by the FOLFOX-4 regimen (infusional 5-fluorouracil plus leucovorin/bevacizumab) in the treatment of 43 patients with EGFR-expressing metastatic CRC (mCRC). Confirmed ORR was 72% with 95% disease control. Median progression-free survival (PFS) and median duration of response were 12.3 and 10.8 months, respectively. Cetuximab did not increase the toxicity of FOLFOX-4 and was well tolerated (30).

For recurrent/metastatic SCCHN, treatment comprising cetuximab in combination with either cisplatin or carboplatin each in combination with fluorouracil was also tested in 53 patients in another phase II study. The ORR among patients was 36% (31). Another phase II study assessing the efficacy of cetuximab monotherapy in 346 patients with refractory mCRC demonstrated an ORR of 12.4% and mOS of 6.6 months. Grade 3 rash was observed in 4.9% of patients (32). Results of the BOND-2 (cetuximab/bevacizumab plus or minus irinotecan in patients with metastatic colorectal cancer) study, which evaluated the efficacy and safety of cetuximab and bevacizumab with (CBI arm) and without irinotecan (CB arm) in refractory CRC, demonstrated that the mTDP was 7.3 months and the ORR was 37% for the CBI arm versus mTDP of 4.9 months and ORR of 20% for the CB arm. The mOS for the CBI arm was 14.5 months versus 11.4 months for the CB-alone arm (33).

The combination of cisplatin plus cetuximab has been tested in a phase III trial aiming to increase PFS in 117 patients with SCCHN and was found to be reasonably well tolerated and active. Patients were randomly assigned to receive cisplatin every 4 weeks, with weekly cetuximab (arm A) or placebo (arm B). The mPFS was 2.7 months for arm B and 4.2 months for arm A; mOS was 8 months for arm B and 9.2 months for arm A ($P = 0.21$); ORR was 26% for arm A and 10% for arm B (34). Another phase III study enrolling 424 patients with locoregionally advanced SCCHN has demonstrated that cetuximab plus radiotherapy can significantly improve locoregional control ($P = 0.005$) and mOS ($P = 0.03$) compared with radiotherapy alone, without increasing radiotherapy-associated adverse events (35).

The mutation status of the *K-ras* gene in the tumor has been recently proposed to be a surrogate marker of response to cetuximab and may also have treatment-independent prognostic value. This important study demonstrated that patients with a colorectal tumor bearing mutated *K-ras* did not benefit from cetuximab, whereas cetuximab is effective in patients with a tumor bearing wild-type *K-ras* (36). In addition, the wild-type of the serine-threonine kinase BRAF, which is the principal effector of *K-ras* has also been proposed as being an independent factor of response to cetuximab therapy (37).

BEVACIZUMAB

Bevacizumab is a humanized MAb that inhibits the biological activities of VEGF and blocks binding of VEGF to its receptor on vascular endothelium. Combined with cetuximab, bevacizumab administration resulted in the stabilization and suppression of tumor lines in animal studies (23).

Bevacizumab in CRC

Since 2004, bevacizumab has been FDA approved as first-line therapy in metastatic CRC (mCRC). In a recent phase III study that compared the safety and efficacy of different irinotecan-

containing regimens as first-line treatment of mCRC, 117 patients were randomly assigned to either irinotecan (FOLFIRI) plus bevacizumab (FOLFIRI/Bev; $n = 57$) or irinotecan plus bolus fluorouracil and leucovorin (mIFL) plus bevacizumab (mIFL/Bev; $n = 60$). The mOS has not yet been reported for FOLFIRI/Bev and was 19.2 months for mIFL + Bev. FOLFIRI/Bev was associated with a higher rate of grade 3/4 hypertension than mIFL/Bev (38).

In another, larger phase III trial, 809 pretreated mCRC patients were randomly assigned to either FOLFOX4 (arm 1), FOLFOX4 without bevacizumab (arm 2), or bevacizumab alone (arm 3). The mOS for arm 1 was 12.9 months versus 10.8 months for arm 2, and 10.2 months for arm 3. The median PFS for the FOLFOX4/bevacizumab arm was 7.3 months, compared with 4.7 months for arm 2, and 2.7 months for arm 3. The corresponding ORRs were 22.7%, 8.6%, and 3.3%, respectively (39).

Finally, a recently published pooled analysis of two large randomized controlled trials attempted to address the issue of whether the regimen consisting of bevacizumab plus fluorouracil-based chemotherapy exerts a similar clinical benefit in 439 elderly patients (older than 65 years) with mCRC compared with younger patients. The results were persuasive enough to demonstrate that adding bevacizumab to fluorouracil-based chemotherapy improves OS and PFS and benefits in a similar degree both older and younger patients (40). In any case, it seems that continued therapy with bevacizumab beyond initial disease progression might improve the overall success of therapy in patients with mCRC (41).

Bevacizumab in Breast Cancer

Observations that angiogenesis is a component of disease progression in breast cancer have led to the investigation of bevacizumab. Current data from phase III trials are supportive; however, this did not translate into improved PFS or mOS. A recent randomized phase III

trial compared the efficacy and safety of capecitabine with or without bevacizumab (15 mg/kg) in 462 pretreated patients with MBC. Combination therapy significantly increased the ORRs (19.8% versus 9.1%; $P = 0.001$); however, this did not result in a longer PFS (4.86 versus 4.17 months). The mOS (15.1 versus 14.5 months) was comparable in both treatment groups (42). Recent results from a phase II trial of bevacizumab in combination with weekly docetaxel in 27 MBC patients showed that the ORR was 52%, the median response duration was 6.0 months, and the median PFS was 7.5 months (43).

Bevacizumab in NSCLC

A large trial, conducted by the Eastern Cooperative Oncology Group, evaluated bevacizumab plus carboplatin/paclitaxel (BV/CP, $n = 434$) versus carboplatin/paclitaxel alone (CP, $n = 444$) in chemotherapy-naïve patients with stage IIIB/IV nonsquamous NSCLC. The mOS was significantly longer in patients receiving BV/CP than in those receiving CP alone (12.3 versus 10.3 months). Severe and life-threatening adverse events, occurring more frequently in patients receiving BV/CP, were neutropenia (27% versus 17%) and hypertension (8% versus 0.7%). Fatal, treatment-related adverse events in patients receiving bevacizumab were pulmonary and gastrointestinal hemorrhage. Rates of clinically significant bleeding were 4.4% and 0.7%, respectively; $P < 0.001$ (44).

Recently, a randomized phase II trial evaluated the safety of combining bevacizumab with either chemotherapy or erlotinib, an EGFR tyrosine kinase inhibitor, in 120 patients with nonsquamous NSCLC that had progressed during or after one platinum-based regimen. The one-year survival rate was 57.4% for bevacizumab/erlotinib versus 53.8% for bevacizumab/chemotherapy compared with 33.1% for chemotherapy alone. The toxicity profile of the bevacizumab/erlotinib combination was favorable compared with either chemotherapy-containing regimen (45).

Bevacizumab in Renal Cancer

The clinical efficacy of the combination of bevacizumab plus erlotinib in refractory metastatic clear cell renal cancer was investigated in a recent phase II trial, in which 104 patients received intravenous bevacizumab (10 mg/kg) every 2 weeks in combination with 150 mg of oral Erlotinib (B + E) versus placebo daily. ORR was 14% for B + E versus 13% for bevacizumab. One complete response occurred in the B + E group. The mOS was 20 months for B + E, but not reached for bevacizumab. The most common grade 3/4 adverse events were hypertension, rash, proteinuria, diarrhea, and hemorrhage. This trial demonstrated that a regimen consisting of B + E did not provide additional clinical benefit compared with bevacizumab alone (46).

In a prospective, randomized phase III trial, 732 patients with previously untreated, metastatic renal cell carcinoma were randomly assigned to receive either bevacizumab (10 mg/kg intravenously every 2 weeks) plus interferon- α (IFN- α) (9 million U subcutaneously three times weekly) or IFN monotherapy. The median PFS was 8.5 months in patients receiving bevacizumab plus IFN versus 5.2 months in patients receiving IFN monotherapy ($P < 0.0001$), suggesting that bevacizumab plus IFN significantly prolongs PFS and is more active than IFN monotherapy in patients with metastatic renal cell carcinoma (47).

Bevacizumab in Other Tumors

A phase II study has investigated the combination of gemcitabine/bevacizumab in 52 patients with metastatic pancreatic cancer. In this study, partial response has been noted in 21% and stable disease in 46%, the mOS was 8.8 months and mean time to progression was 5.4 months (48). In another phase II study, combination immunotherapy with prostatic acid phosphatase-pulsed antigen-presenting cells plus bevacizumab in patients with serologic progression of prostate cancer was associated with induction of an immune response against PA2024 and modulation of prostate-

specific antigen (49). A randomized phase II trial of bevacizumab with or without daily low-dose IFN- α -2b in metastatic malignant melanoma showed that this regimen resulted in prolonged disease stabilization in 8 of 32 (25%) of patients enrolled (50).

PANITUMUMAB

Panitumumab (ABX-EGF) is a human IgG2 MAb that binds to EGFR, thus being an antagonist of both TGF- α and EGF. Panitumumab was FDA approved in 2006 for the treatment of EGFR-expressing mCRC with disease progression despite prior treatment. In a recent phase III trial, panitumumab significantly improved PFS with manageable toxicity in 463 patients with chemorefractory CRC. In this trial, the mPFS was 13.8 weeks for panitumumab versus 8.5 weeks for best BSC. ORRs also favored panitumumab over BSC. Panitumumab was well tolerated (51). Likewise, panitumumab given as monotherapy in a phase II trial in mCRC has been associated with an ORR of 9%, mPFS of 14 weeks, and mOS of 9 months. Toxicities were manageable, with grade 3/4 skin toxicity occurring in 5% of patients (52).

Alarming data became evident from a recently published randomized phase IIIb trial in patients with metastatic CRC, because the addition of panitumumab to chemotherapy resulted in increased toxicity and decreased PFS (53). Therefore, its combined use with other chemotherapeutic drugs in mCRC cannot be recommended.

MATUZUMAB

Matuzumab (EMD 72000) is a humanized IgG1 MAb that has shown great affinity and specificity for EGFR. Possible mechanisms of action include inhibition of the EGFR-stimulated pathway and antibody-dependent cell cytotoxicity. Recently, matuzumab activity was investigated in two phase I trials. In the first setting, combination therapy with matuzumab/gemcitabine was associated with partial response or stable disease in 8 of 12 (66.7%) of evaluated patients

with advanced pancreatic cancer (54). In the other trial, matuzumab in combination with paclitaxel was administered in 18 patients with stage IIIB or IV EGFR-positive NSCLC. Responses occurred in 4 of 18 patients and included one complete response. The combination regimen was well tolerated, with acceptable rates of toxicities (55).

However, in a phase II trial of 37 heavily pretreated patients with recurrent, EGFR-positive ovarian or primary peritoneal cancer, treatment with matuzumab (EMD 72000) failed to demonstrate evidence of significant clinical activity. No formal responses were observed in this trial (56).

NIMOTUZUMAB

Nimotuzumab (h-R3), a humanized anti-EGFR MAb, has also been used in clinical practice against brain malignancies and SCCHN. A phase I/II trial was conducted to assess the use of nimotuzumab in SCCHN. In this study, 24 patients received weekly infusions of nimotuzumab at four dose levels in combination with radiotherapy. The combination of h-R3 and radiotherapy was well tolerated, whereas mOS significantly increased after the use of the higher antibody doses (57). More recent results on the efficacy of nimotuzumab are not available.

MDX-447

MDX-447 is a bispecific antibody directed against EGFR and the high affinity Fc-receptor. The use of MDX-447, given either as monotherapy ($n = 41$) or combined with granulocyte colony-stimulating factor ($n = 23$), has been tested in a recent phase I trial that enrolled 64 patients with advanced solid tumors. In this study, MDX-447 alone was generally well tolerated, but did not achieve objective tumor responses. There were no objective complete or partial responses in either group (58).

OREGOVOMAB

Oregovomab, a murine MAb that targets the circulating tumor-associated

antigen CA 125, has been used for the treatment of ovarian cancer and showed promising results. A phase II study examined the clinical and immunologic effects of oregovomab (OvaRex) in 13 heavily pretreated patients with recurrent ovarian cancer. This study supported immunologic activity and safety of oregovomab in recurrent ovarian cancer (59). However, in another phase II study, consolidation therapy with oregovomab did not significantly improve time to relapse or median survival time in patients with advanced ovarian cancer (60,61). Considering the small sample size of studies testing the efficacy of oregovomab and the conflicting results, further studies are definitely warranted before definite conclusions can be drawn.

PERTUZUMAB

Pertuzumab (rhuMAB 2C4), a humanized HER2 antibody, represents a new class of targeted therapeutics that inhibits dimerization of HER2 with ligand-activated EGFR (HER1), HER3, and HER4. Pertuzumab has been recently tested in a phase II trial in patients with NSCLC. Of 43 patients treated with pertuzumab, no responses were seen; 18 of 43 (41.9%) and 9 of 43 (20.9%) of patients had stable disease at 6 and 12 weeks, respectively. The median and 3-month PFS were 6.1 weeks and 28.4%, respectively. Four patients (9.3%) experienced a grade 3/4 adverse event judged related to pertuzumab (62). Furthermore, pertuzumab has also recently been tested in treating 61 patients with relapsed ovarian cancer; mPFS was 6.6 weeks. Pertuzumab was well tolerated, with diarrhea occurring in 69.1% of patients (63). Pertuzumab monotherapy was well tolerated but resulted in no objective responses in castration-resistant prostate cancer after progression from taxane-based therapy (64). Overall the efficacy and safety of pertuzumab should be further tested in large phase III trials.

IPILIMUMAB

Ipilimumab (MDX-010 or MDX-101), a human MAb that blocks the activity of

cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is believed to play a critical role in sustaining an active immune response in its attack on cancer cells. Ipilimumab is currently used mainly to treat melanoma. Thus far, several phase I and II pivotal trials have been conducted to evaluate the safety and efficacy of ipilimumab monotherapy or in combination with chemotherapy in patients with advanced melanoma (65). Preliminary results show that the ipilimumab-mediated objective response occurs in about 15% of patients and tends to be long lasting (65).

The results of a recently published phase I/II study assessing, among other things, the clinical activity of either transfectoma- or hybridoma-derived ipilimumab, advocated in favor of the view that ipilimumab might be active in patients with metastatic melanoma. In this study 89 patients with unresectable stage III or IV melanoma were enrolled. Therapy with multiple doses, up to 10 mg/kg of ipilimumab, resulted in one partial response and one CR. The stabilization of disease has been demonstrated in 7 patients (66). To our knowledge, a phase I/II dose-escalation clinical trial of ipilimumab in metastatic hormone-refractory prostate cancer is currently ongoing.

CONCLUSION AND PERSPECTIVES FOR FUTURE RESEARCH

Thorough understanding of the complex interactions between components of the immunological response has led to interest in antibody-based therapy for solid tumors. A number of theories have emerged attempting to describe possible mechanisms through which certain antibodies may exert therapeutic effects through interference with cancer cell biology. Some MAbs have increased the efficacy of treatment of certain tumors, with acceptable safety profiles. Stabilization of disease and inhibition of metastases have been observed in some studies, validating the significance of MAb application in clinical practice.

Issues to be addressed include dosing strategies, timing, and schedule of anti-

body administration; duration of treatment; need for tailoring; and further testing under specific circumstances. The discovery of effective combinations with other biologic agents would be very useful. Multimodality approaches, based on synergistic effects observed with the combination of antibodies with chemotherapeutic drugs and/or radiotherapy also merit further investigation. Immune-mediated effects may be further exploited with the use of bispecific molecules. Stratification of patient subpopulations with tumors overexpressing disease-related clinical biomarkers could result in improving both efficacy and specificity of antibody-based treatment for solid tumors.

DISCLOSURE

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