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Trial watch
Monoclonal antibodies in cancer therapy

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Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; ALL, acute lymphoid leukemia; BiTE, bispecific T-cell engager; CDC, complement-dependent cytotoxicity; CLL, chronic lymphocytic leukemia; FDA, Food and Drug Administration; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; GM-CSF, granulocyte macrophage-colony stimulating factor; IFNα-2b, interferon α-2b; IGF1R, insulin-like growth factor 1 receptor; IL, interleukin; mAb, monoclonal antibody; MMAE, monomethyl auristatin E; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung carcinoma; OS, overall survival; pCR, pathological complete response; PFS, progression-free survival; PS, phosphatidylserine; RANKL, receptor activator of NFκB ligand; TRAILR2, tumor necrosis factor-related apoptosis-inducing ligand receptor 2; TBI, total body irradiation; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2

During the past 20 years, dozens—if not hundreds—of monoclonal antibodies have been developed and characterized for their capacity to mediate antineoplastic effects, either as they activate/enhance tumor-specific immune responses, either as they interrupt cancer cell-intrinsic signal transduction cascades, either as they specifically delivery toxins to malignant cells or as they block the tumor-stroma interaction. Such an intense research effort has lead to the approval by FDA of no less than 14 distinct molecules for use in humans affected by hematological or solid malignancies. In the inaugural issue of *OncoImmunology*, we briefly described the scientific rationale behind the use of monoclonal antibodies in cancer therapy and discussed recent, ongoing clinical studies investigating the safety and efficacy of this approach in patients. Here, we summarize the latest developments in this exciting area of clinical research, focusing on high impact studies that have been published during the last 15 months and clinical trials launched in the same period to investigate the therapeutic profile of promising, yet hitherto investigational, monoclonal antibodies.

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Introduction

In 1975, Georges Köhler and César Milstein described for the first time an experimental setup allowing for the cost-effective production of high quantities of antibodies exhibiting the same antigenic specificity.[1] This breakthrough discovery, which allowed Köhler and Milstein to win the 2004 Nobel Prize for Medicine or Physiology, de facto revolutionized an unbelievable number of research protocols and clinical applications.[2] During the past 30 years, the hybridoma technology originally described by Köhler and Milstein (which was purely murine and hence associated with relevant immunogenicity issues) has been consistently ameliorated, resulting in the production of ever more refined reagents for clinical applications.[3] In 1986, the US Food and Drug Administration (FDA) approved muromonab, a murine IgG1 specific for CD3, for the therapy of transplanted patients undergoing rejection.[4] Since then, dozens of monoclonal antibodies (mAbs), including murine, chimeric as well humanized reagents, have been approved by international regulatory agencies (including FDA and the European Medicines Agency, EMA) for use in humans against multiple diseases, including (but not limited to) autoimmune disorders and cancer.[2,5] Of these, no less than 14 mAbs, including naked reagents as well as mAbs coupled to antibiotics or radioactive isotopes, are nowadays authorized for use in cancer patients (**Table 1**).[5,6]

One year ago, concomitant with the launch of *OncoImmunology*, we published the first Trial Watch of what has then become a monthly series,[6–14] dealing with the use of mAbs in cancer therapy.[6] As described in details therein, mAbs that potentially exert antineoplastic effects belong to one of six, non-mutually

Table 1. Monoclonal antibodies currently approved for cancer therapy*,**

mAb	Target	Approved	Type	Indication(s)
Alemtuzumab	CD52	2001	Hzed IgG1	Chronic lymphocytic leukemia
Bevacizumab	VEGF	2004	Hzed IgG1	Glioblastoma multiforme, colorectal, renal and lung cancer
Brentuximab vedotin	CD30	2011	C IgG1	Hodgkin and anaplastic large cell lymphoma (coupled to MMAE)
Catumaxomab	CD3 EpCAM	2009	M-R hybrid	Malignant ascites in patients with $EpCAM^+$ cancer
Cetuximab	EGFR	2004	C IgG1	Head and neck and colorectal cancer
Denosumab	RANKL	2011	H IgG2	Breast and prostate carcinoma
Gemtuzumab	CD33	2000	Hzed IgG4	Acute myeloid leukemia (coupled with calicheamicin)
Ibritumomab tiuxetan	CD20	2002	M IgG1	Non-Hodgkin lymphoma (coupled with ^{90}Y or ^{111}In)
Ipilimumab	CTLA-4	2011	H IgG1	Melanoma
Panitumumab	EGFR	2006	H IgG2	Colorectal carcinoma
Ofatumumab	CD20	2009	H IgG1	Chronic lymphocytic leukemia
Rituximab	CD20	1997	C IgG1	Chronic lymphocytic leukemia and non-Hodgkin lymphoma
Tositumomab	CD20	2003	H IgG1	Non-Hodgkin lymphoma (naked or coupled with ^{131}I)
Trastuzumab	HER2	1998	Hzed IgG1	Breast carcinoma and gastric or gastresophageal junction cancer

C, chimeric; CTLA-4, cytotoxic T lymphocyte antigen 4; EGFR, epidermal growth factor receptor; EpCAM, epithelial cell adhesion molecule; H, human; Hzed, humanized; M, murine; mAb, monoclonal antibody; MMAE, monomethyl auristatin E; R, rat; RANKL, receptor activator of NFκB ligand; VEGF, vascular endothelial growth factor. *By FDA or European Medicines Agency (EMA) at the day of submission. **Updated from reference 6.

exclusive classes: (1) mAbs that target cancer cell-intrinsic pro-survival signal transduction cascades (e.g., cetuximab, which inhibits the epidermal growth factor receptor, EGFR, and is currently employed for the therapy of colorectal cancer);[15] (2) mAbs that interrupt the trophic interaction between malignant cells and their stroma, hence indirectly inhibiting tumor growth (e.g., bevacizumab, which targets the vascular endothelial growth factor, VEGF, and is currently approved for use in patients affected by breast, lung, renal and colorectal carcinoma);[16] (3) mAbs that recognize antigens expressed on the surface of tumor cells and exert antineoplastic effects by engaging immune effector mechanisms such as antibody-dependent cellular cytotoxicity (ADCC),[5,17,18] antibody-dependent cellular phagocytosis (ADCP),[19] and complement-dependent cytotoxicity (CDC)[20,21] (e.g., rituximab, a naked anti-CD20 currently approved for use in lymphoma patients);[22–24] (4) trifunctional (bispecific) mAbs, which can bind two distinct antigenic targets while retaining the ability of activating immune effector functions (e.g., catumaxomab, an anti-CD3, anti-EpCAM chimeric mAb nowadays is use for the therapy of malignant ascites in patient with $EpCAM^+$ neoplasms);[25] (5) immunoconjugates (e.g., ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab, two radionuclide-coupled anti-CD20 mAbs that are currently approved for the treatment of lymphoma patients);[26,27] and (6) immunostimulatory mAbs, i.e., mAbs that facilitate the development of an antitumor immune response by influencing the balance between the immunogenicity of malignant cells and the immunosuppressive mechanisms that they normally establish (e.g., ipilimumab, an anti-CTLA-4 mAb nowadays employed in melanoma patients).[28–31]

Here, we will summarize the latest developments in the clinical development of mAbs for cancer therapy, focusing on high impact studies that have been published during the last 15 months and clinical trials that have been launched in the same period to investigate the therapeutic profile of promising, yet hitherto experimental, mAbs. Of note, in this period, FDA has authorized one novel mAb for use in cancer patients and one oncological indication for a mAb that had previously been approved for the therapy of non-oncological patients (source www.cancer.gov/cancertopics/druginfo). Thus, brentuximab vedotin, an anti-CD30 monomethyl auristatin E (MMAE) conjugate, is now approved for the treatment of relapsed Hodgkin lymphoma and relapsed systemic anaplastic large cell lymphoma patients,[32,33] In addition, denosumab, a receptor activator of NFκB ligand (RANKL)-targeting mAb that was employed in post-menopausal women at risk for osteoporosis, can nowadays be used to increase bone mass in patients who are at high risk of fracture as they undergo androgen deprivation therapy for non-metastatic prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer.[34] Finally, the approval status of rituximab and cetuximab has recently been expanded in terms of therapeutic schedules and therapy-eligible patients subsets, respectively, while the authorization of bevacizumab as a therapeutic option for breast cancer patients has been revoked (**Table 1**).

Update on Clinical Reports

Since the submission of our previous Trial Watch on this topic (August 2011),[6] high-impact journals have published the results of no less than 50 clinical studies investigating the safety and efficacy of mAbs for cancer therapy. Obviously, a majority of these studies involved FDA-approved mAbs (**Table 1**), including bevacizumab (16 studies),[35–50] trastuzumab (11 studies),[46,51–60] rituximab (10 studies),[61–70] cetuximab (8 studies),[71–78] ipilimumab (4 studies),[79–82] alemtuzumab (2 studies),[83,84] and denosumab (1 study).[85] In addition, a few high-impact publications have reported on the clinical profile of experimental mAbs, including immunostimulatory anti-PD-1 and anti-PD-L1 mAbs,[86,87] the anti-CD22 calecheamicin conjugate inotuzumab ozogamicin,[88]

the anti-CD19 maytansinoid conjugate SAR3419,[89] cixutumumab and figitumumab, two distinct mAbs specific for insulin-like growth factor 1 receptor (IGF1R),[90,91] pertuzumab, an anti-HER2 mAb,[92,93] and the CS1-targeting mAb elotuzumab.[94,95]

Thus, the clinical potential of FDA-approved mAbs, most often combined with conventional chemotherapeutic approaches, is under intensive investigation, an effort that will presumably lead to the approval of further oncological indications for these agents in the near future. In this respect, bevacizumab has been found to prolong progression-free survival (PFS) and overall survival (OS) in ovarian cancer patients treated with carboplatin and paclitaxel, in two randomized Phase III studies,[41,42] and to improve the rate of pathological complete responses (pCRs) among HER2-negative breast carcinoma patients undergoing neoadjuvant docetaxel-based chemotherapy, again in two large randomized Phase III trials.[44,45] The clinical profile of trastuzumab has most often been evaluated in cohorts of breast cancer patients,[46,51–58,60] reflecting the indications for which it has been authorized by FDA. In particular, two distinct, randomized Phase III studies demonstrated that the combination of neoadjuvant chemotherapy, trastuzumab and a chemical inhibitor of HER2, lapatinib, is clinically superior to use of either approach alone.[58,60] Similar to trastuzumab, rituximab has most extensively been tested in clinical settings that match its FDA-approved indications, i.e., cohorts of chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL) patients.[61–67] One notable exception to this trend is represented by the study of Kluin-Nelemans et al., demonstrating that rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone is efficient in old patients affected by mantle-cell lymphoma.[70] Cetuximab has been tested in a few different clinical settings, including cohorts of non-small cell lung carcinoma (NSCLC), pancreatic cancer and colorectal carcinoma patients.[71–78] Notably, EGFR expression levels have been shown to predict a survival benefit from the addition of cetuximab to first-line conventional chemotherapy in NSCLC patients.[74] Ipilimumab has been tested in cohorts of melanoma and NSCLC patients, alone or combined with paclitaxel and cisplatin, respectively,[81,82] as well as in prostate cancer patients undergoing vaccination,[79,80] invariably providing clinical benefits, at least to some extent. Finally, alemtuzumab and denosumab have been shown to improve the therapeutic potential of fludarabine in a cohort of CLL patients,[83] and to reduce the incidence of bone metastases in subjects affected by castration-resistant prostate carcinoma.[85]

Some experimental mAbs have also generated remarkable clinical results during the last 15 months. For instance, the mAb-mediated blockade of the interaction between the inhibitory receptor PD-1 (which is expressed by T cells) and its ligand (PD-L1), undertaken as a standalone intervention with either anti-PD-1 (MDX-1106, BMS-936558) or anti-PD-L1 (MDX-1105, BMS-936559) mAbs, has been shown to induce tumor regression or disease stabilization in a relatively small (but encouraging) proportion of patients affected by NSCLC, melanoma and renal cell carcinoma (RCC).[86,87] Inotuzumab ozogamicin has been associated with a promising therapeutic profile among refractory and relapsed acute lymphocytic leukemia patients.[88] The intravenous administration of SAR3419 to relapsed CD19$^+$ B-cell lymphoma patients has been found to be safe and to elicit a consistent rate of clinical responses.[89] Along similar lines, anti-IGF1R mAbs such as cixutumumab and figitumumab have been shown to be well tolerated by children affected by refractory Ewing sarcoma, exhibiting modest antineoplastic activity as single agents.[90,91] The inclusion of pertuzumab in combinatorial regimens involving trastuzumab (alone or combined with docetaxel-based chemotherapy) have been associated with improved PFS (compared with the use of either mAb alone or chemotherapy plus trastuzumab only), in cohorts of HER2$^+$ breast cancer patients.[92,93] Finally, in two distinct Phase I clinical trials, the combination of elotuzumab and bortezomib or lenalidomide plus low-dose dexamethasone was well tolerated and exhibited a promising efficacy in patients affected by relapsed or refractory multiple myeloma.[94,95]

Focusing on recent, high-impact mAb-related translational research, we have found of particular interest the studies by Yonesaka et al., Diaz et al. and Misale et al., demonstrating that colorectal carcinoma patients become refractory to EGFR-targeting mAbs including cetuximab and panitumumab along with the emergence of *KRAS* mutations or with an increased signaling via the EGFR-related receptor HER2;[96,97] as well as the work by Prahallad et al., revealing that—at least in a fraction of cases—the unresponsiveness of colon carcinoma patients to BRAF^{V600E} inhibitors stems from a feedback hyperactivation of EGFR signaling.[98]

Update on Investigational Monoclonal Antibodies under Clinical Evaluation

When this Trial Watch was being redacted (October 2012), official sources listed 45 clinical trials launched after 2011, August 1 that would investigate the safety and therapeutic profile of hitherto investigational mAbs in cancer patients (source www.clinicaltrials.gov).

Bavituximab is a chimeric IgG1 specific for phosphatidylserine (PS), an anionic phospholipid that—under physiological conditions—is found in the inner leaflet of the plasma membrane.[99] PS translocates to the cell surface in some instances of cell death,[100–102] cell activation and malignant transformation, and has been proposed to constitute a tumor vasculature-specific marker.[103,104] Encouraging preclinical findings by Ran et al.[99] supported the evaluation of bavituximab in clinical settings. Recent results from a Phase I study indicate that bavituximab at doses up to 3 mg/Kg/week is well tolerated by patients with advanced solid tumors.[105] Recently (since 2011, August 1), one single Phase I trial has been launched to assess the tolerability and preliminary therapeutic profile of bavituximab, combined with capecitabine and radiotherapy, in rectal adenocarcinoma patients (NCT01634685) (**Table 2**).

BC8, a CD45-targeting mAb that most often is conjugated to radionuclides (e.g., ^{131}I, ^{111}In), is currently under preclinical and clinical investigation for the treatment of CD45-expressing hematological malignancies.[106] The combination of BC8 with cyclophosphamide and total body irradiation (TBI) has

Table 2. Clinical trials recently launched to evaluate the therapeutic profile of monoclonal antibodies*

mAb	Target(s)	Indication(s)	Phase	Status	Note	Ref.
Bavituximab	PS	Rectal carcinoma	I	Recruiting	Combined with chemo- and radiotherapy	NCT01634685
BC8	CD45	Lymphoid tumors	I	Not yet recruiting	Followed by ASCT	NCT01678443
		Multiple myeloma		Recruiting	Combined with fludarabine and TBI followed by transplantation	NCT01503242
Blinatumomab	CD3 CD19	B-precursor ALL	I/II	Recruiting	As single agent	NCT01471782
			II			NCT01466179
Ch14.18	GD2	Neuroblastoma	I/II	Recruiting	Combined with GM-CSF, IL-2 and isotretinoin	NCT01592045
			n.a.	Not yet recruiting	As single agent	NCT01418495
Cixutumumab	IGF1R	Brain tumors Sarcoma	II	Recruiting	Combined with temsirolimus	NCT01614795
		Melanoma		Active, not recruiting	As single agent	NCT01413191
Dalotuzumab	IGF1R	Advanced solid tumors	I	Recruiting	As single agent or combined with ridaforolimus	NCT01431547
		Breast cancer	II		Combined with exemestane and ridaforolimus	NCT01605396
		Rectal cancer			Combined with irinotecan	NCT01609231
Ganitumab	IGF1R	Advanced solid tumors	II	Recruiting	Combined with MEK inhibitors	NCT01562899
		Breast cancer	I/II	Withdrawn	Combined with trastuzumab	NCT01479179
		Pancreatic cancer	I	Active, not recruiting	Combined with gemcitabine and followed by radiotherapy	NCT01298401
			I/II	Completed	Combined with FOLFIRINOX	NCT01473303
MDX-1105	PD-L1	Hematological tumors	I	Withdrawn	As single agent	NCT01452334
MDX-1106	PD-1	Advanced solid tumors	I	Recruiting	Combined with rIL-21	NCT01629758
		Hematological tumors			As single agent	NCT01592370
		HCC		Not yet recruiting		NCT01658878
		Melanoma				NCT01621490
		NSCLC		Recruiting	Combined with bevacizumab, erlotinib or chemotherapy	NCT01454102
			III	Not yet recruiting	As single agent	NCT01642004
						NCT01673867
		Renal cell carcinoma	I	Recruiting	Combined with pazopanib or sunitinib	NCT01472081
			III	Not yet recruiting	As single agent	NCT01668784
Necitumumab	EGFR	Advanced solid tumors	II	Recruiting	As single agent	NCT01624467
		Solid tumors			Combined with cisplatin and gemcitabine	NCT01606748

ALL, acute lymphocytic leukemia; ASCT, autologous stem cell transplantation; EGFR, epidermal growth factor receptor; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan and oxaliplatin; IGF1R, insulin-like growth factor 1 receptor; GD2, ganglioside GD2; GM-CSF, granulocyte macrophage colony-stimulating factor; HCC, hepatocellular carcinoma; IL, interleukin; mAb, monoclonal antibody; MEK, MAPK/ERK kinase; n.a., not available; NSCLC, non-small cell lung carcinoma; rIL-21, recombinant interleukin-21; PD-1, programmed cell death 1; PD-L1, PD1 ligand 1; PS, phosphatidylserine; TBI, total body irradiation. *Between 2011, August 1 and the day of submission.

previously been shown to be tolerated and convey clinical benefits in a small cohort of patients affected by myelodysplastic syndrome (MDS) and acute lymphoid leukemia (ALL).[107] Recently (since 2011, August 1), two Phase I trials have been launched to test the clinical profile of BC8, one involving multiple myeloma patients treated with BC8 in combination with fludarabine and TBI (NCT01503242), and one involving patients with refractory or relapsed lymphoid malignancies receiving BC8 as a standalone

Table 2 (continued). Clinical trials recently launched to evaluate the therapeutic profile of monoclonal antibodies*

mAb	Target(s)	Indication(s)	Phase	Status	Note	Ref.
Nimotuzumab	EGFR	Esophageal cancer	II	Active, not recruiting	As single agent	NCT01463605
				Recruiting	Combined with FOLFIRI	NCT01486992
					Combined with cisplatin and paclitaxel-based chemotherapy	NCT01688700
		Head and neck cancer			Combined with 5-fluorouracil, cisplatin and docetaxel	NCT01425736
					Combined with radio- or chemotherapy	NCT01516996
					Combined with cisplatin and 5-fluorouracil	NCT01616849
		NSCLC			Combined with gefitinib	NCT01498562
Ramucirumab	VEGFR2	Breast cancer	II	Recruiting	Combined with eribulin	NCT01427933
		Solid tumors	I	Not yet recruiting	As single agent	NCT01682135
			II	Recruiting	Combined with paclitaxel	NCT01515306
					Combined with docetaxel	NCT01567163
				Not yet recruiting	Combined with FOLFIRI	NCT01634555
Siltuximab	IL-6	Myelodysplastic syndrome	II	Active, not recruiting	Combined with best supportive care	NCT01513317
		Multiple myeloma	I/II	Recruiting	Combined with bortezomib, dexamethasone and lenalidomide	NCT01531998
			II		As single agent	NCT01484275
Tigatuzumab	TRAILR2	Breast cancer	II	Active, not recruiting	Combined with protein- bound paclitaxel	NCT01307891
Tremelimumab	CTLA-4	Mesothelioma	II	Active, not recruiting	As single agent	NCT01649024
				Recruiting		NCT01655888

CTLA-4, cytotoxic T lymphocyte antigen 4; EGFR, epidermal growth factor receptor; FOLFIRI, 5-fluorouracil, leucovorin, irinotecan; IL, interleukin; mAB, monoclonal antibody; NSCLC, non-small cell lung carcinoma; TRAILR2, tumor necrosis factor-related apoptosis-inducing ligand receptor 2; VEGFR2, vascular enothelial growth factor receptor 2. *Between 2011, August 1 and the day of submission.

intervention (NCT01678443), in both cases as a pre-transplantation conditioning regimen (**Table 2**).

Blinatumomab belongs to the category of so-called BiTEs (bispecific T-cell engagers), i.e., bi-specific mAbs that invariably target CD3 (a component of the TCR signal transduction machinery expressed by T cells) and a tumor-associated antigen (in this case, CD19, a transmembrane protein mainly expressed by B cells).[108] Hence, unlike conventional monospecific mAbs, blinatumomab exerts antineoplastic effects by physically bridging malignant B cells and host T cells, hence promoting the cytotoxic activity of the latter.[108] High response rates and durable remissions have been observed in the first clinical trials testing the safety and therapeutic profile of blinatumomab among B-cell NHL and B-precursor ALL patients.[109–111] Recently (since 2011, August 1), two Phase I/II trials have been initiated to investigate the safety and efficacy of blinatumomab, given as a standalone intervention, in subjects affected by B-precursor ALL (NCT01466179, NCT01471782) (**Table 2**).

Ch14.18 is a chimeric IgG1 specific for GD2, a disialoganglioside GD2 that is often abundant at the surface neuroendocrine tumor cells.[112,113] The evaluation of the safety and efficacy of Ch14.18 as a standalone agent for the treatment of melanoma and neuroblastoma has begun in the early 1990s,[114,115] with relatively unsatisfactory results. Later on, a few clinical studies have investigated the clinical potential of combinatorial regimens consisting of Ch14.18 in association with immunostimulatory cytokines like interleukin (IL)-2 and granulocyte macrophage-colony stimulating factor (GM-CSF) or metronomic chemotherapy,[116–119] reporting rather promising findings, in particular for the use of Ch14.18 in association with GM-CSF, IL-1 and isotretinoin (a retinoid) in high-risk neuroblastoma patients.[118] Recently (since 2011, August 1), two Phase I/II trials have been launched to test the therapeutic potential of Ch14.18, alone or combined with GM-CSF, IL-1 and isotretinoin, in neuroblastoma patients (NCT01418495; NCT01592045) (**Table 2**).

Cixutumumab (a fully human IgG1), *dalotuzumab* (a humanized IgG1) and *ganitumab* (a fully human IgG1) all target IGFR1, a transmembrane receptor that is overexpressed or hyperactivated by most, if not all, malignant tissues, hence

operating as an anti-apoptotic signal transducer.[120] According to the results of early clinical trials, cixutumumab and dalotuzumab as single agents as well as the combination of cixutumumab and temsirolimus (an inhibitor of the intracellular signaling pathway elicited by IGFR1) are generally well tolerated by patients bearing advanced solid tumors,[91,121–123] with prominent adverse effects involving the dermis.[124] Conversely, dose-limiting toxicities have been reported to develop among unselected NSCLC patients treated with cixutumumab in combination with the EGFR inhibitor erlotinib at full dosage.[125] In 2012, results from 4 distinct clinical studies testing the safety and efficacy of ganitumab in patients affected by Ewing family tumors, pancreatic carcinoma or other solid malignancies have been published.[126–129] Globally, ganitumab—both as a single agent and associated with targeted agents or conventional chemotherapy—appears to be well tolerated and to exert antineoplastic activity, at least in a fraction of patients.[126–129] This said, results from less recent Phase III studies have shown that targeting the IGF1R pathway is not associated with clear clinical benefits in cancer patients.[130] Accordingly, several anti-IGF1R programs—including one large randomized Phase III study that originally aimed at testing the therapeutic potential of ganitumab among prostatic cancer patients (NCT01231347)—have lately been discontinued.[130,131] Recently (since 2011, August 1), two Phase II clinical trials have been launched to test the clinical profile of cixutumumab, either as a standalone intervention or combined with temsirolimus, in melanoma, sarcoma and brain cancer patients (NCT01413191; NCT01614795). In addition, three Phase I/II studies have been initiated to investigate the safety and efficacy of dalotuzumab, alone or in combination with ridaforolimus (a functional analog of temsirolimus) or conventional chemotherapeutics, in subjects bearing breast carcinoma, colorectal carcinoma or advanced solid tumors (NCT01431547; NCT01605396; NCT01609231). Finally, four Phase I/II studies have been initiated to assess the therapeutic potential of ganitumab, in combination with conventional chemotherapy, radiotherapy or trastuzumab, in individuals affected by breast carcinoma, pancreatic carcinoma or other advanced solid neoplasms (NCT01298401; NCT01473303; NCT01479179; NCT01562899). Of note, one of these studies (NCT01473303) is listed as complete, though results are not available, while another one (NCT01479179) has been withdrawn prior to patient enrollment, which somehow reflects current feelings about mAb-based anti-IGF1R cancer therapy (**Table 2**).

MDX-1106 is a fully human IgG4 that specifically binds PD-1, a transmembrane receptor that—upon binding by its cognate ligand PD-L1, generates immunosuppressive signals in activated T cells.[132–134] In 2012, MDX-1106 (as well as of the PD-L1-targeting antibody *MDX-1105*) has been shown to be well tolerated and to induce objective clinical responses in a relatively small (but encouraging) proportion of patients affected by advanced NSCLC, melanoma and RCC.[86,87] Recently (since 2011, August 1), no less than 10 Phase I-III clinical trials have been launched to investigate the clinical potential of MDX-1105 and MDX-1106, given as standalone agents or combined with conventional chemotherapy (e.g., carboplatin + paclitaxel or cisplatin + gemcitabine or cisplatin + paclitaxel), targeted therapy (e.g., pazopanib or sunitinib, two tyrosine kinase receptor inhibitors) or immunostimulatory agents (e.g., recombinant IL-21), in cohorts of patients affected by hematological tumors (NCT01452334; NCT01592370), melanoma (NCT01621490), NSCLC (NCT01454102; NCT01642004; NCT01673867), hepatocellular carcinoma (NCT01658878), RCC (NCT01472081; NCT01668784), and advanced solid tumors (NCT01629758) (**Table 2**). Of note, the only study involving MDX-1105 (NCT01452334) has been withdrawn prior to patient enrollment, for undeclared reasons (source www.clinicaltrials.gov).

Both *necitumumab* (a fully human IgG1) and *nimotuzumab* (a humanized IgG1) specifically bind EGFR, a transmembrane receptor with tyrosine kinase activity that is hyperactivated, due to point mutations, in a number of solid malignancies. Accordingly, a number of EGFR-targeting therapeutics have already been approved by FDA and other regulatory agencies for use in cancer patients, including the cell-permeant tyrosine kinase inhibitors erlotinib and gefinitib[135–137] and the anti-EGFR mAbs cetuximab and panitumumab (**Table 1**).[138,139] Still, the clinical interest in EGFR-targeting approaches is not decreasing, at least in part owing to the fact that most, if not all, FDA approved EGFR-targeting agents have been associated with the development of chemoresistance in a consistent fraction of patients.[96–98,140] The clinical development of nimotuzumab appears to be more advanced than that of necitumumab. Indeed, during the last 15 months, several pilot or Phase I studies investigating the safety and preliminary therapeutic profile of nimotuzumab (given as a standalone intervention or combined with standard radio- or chemotherapeutic regimens) in patients affected by various solid malignancies have been concluded, overall reporting a low incidence of tolerable adverse effects and improved disease outcome, at least in a fraction of cases.[141–154] Conversely, no reports have been published since 2010 on the clinical profile of necitumumab.[144] Recently (since 2011, August 1), a total of 9 Phase II clinical trials have been initiated to investigate the safety and efficacy of necitumumab (NCT01606748; NCT01624467) or nimotuzumab (NCT01425736; NCT01463605; NCT01486992; NCT01498562; NCT01516996; NCT01616849; NCT01688700), as single agents or associated with standard chemotherapy, in cohorts of head and neck cancer (NCT01425736, NCT01516996; NCT01616849) esophageal cancer (NCT01463605; NCT01486992; NCT01688700) and NSCLC (NCT01498562) patients, as well as of individuals affected by various solid tumors (NCT01606748; NCT01624467) (**Table 2**).

Ramucirumab (IMC-1121B) is a fully human IgG1 specific for the VEGF receptor 2 (VEGFR2). By antagonizing endogenous VEGF signaling,[155] ramucirumab inhibits of the most prominent interactions between neoplastic and stromal cells, i.e., neo-angiogenesis.[156] Early Phase I clinical trials demonstrated that ramucirumab is generally well tolerated by cancer patients,[155,157] and prompted the launch of a randomized, double-blind Phase III study to evaluate whether ramucirumab can improve the efficacy of docetaxel-based chemotherapy in subjects bearing Stage IV NSCLC (NCT01168973, registered at www.clinicaltrials.gov on July 2010).[158] This study has not yet been concluded. More

recently (since 2011, August 1), 5 distinct Phase I clinical trials have been commenced to investigate the tolerability and efficacy of ramucirumab, most often combined with conventional chemotherapeutics, in subjects affected by breast carcinoma (NCT01427933) or other solid neoplasms (NCT01515306; NCT01567163; NCT01634555; NCT01682135) (**Table 2**).

Siltuximab (CNTO-328) is a chimeric IgG1 that binds to IL-6, a pleiotropic cytokine that reportedly modulates several aspects of oncogenesis and tumor progression, including the balance between cell proliferation and cell death as well as neoangiogenesis.[159] Siltuximab-based monotherapy as well as combinatorial regimens including siltuximab and mitoxantrone + prednisone or siltuximab + docetaxel have lately been reported to be well tolerated by prostate cancer patients, although objective effects on disease outcome could not always be documented.[160–162] Since 2011, August 1, 3 Phase I/II clinical trials have been launched to assess the therapeutic profile of siltuximab, as a single agent or combined with best supportive care or bortezomib + dexamethasone + lenalidomide, in MDS (NCT01513317) and multiple myeloma (NCT01484275; NCT01531998) patients (**Table 2**). Conversely, the Phase III trial NCT01266811, which was initiated in December 2010 to test the efficacy of siltuximab + bortezomib + dexamethasone in similar patient cohorts has been withdrawn prior to patient enrollment for undeclared reasons (source www.clinicaltrials.gov).

Tigatuzumab (CS-1008) is a humanized IgG1 that functions as an agonist for tumor necrosis factor-related apoptosis-inducing ligand receptor 2 (TRAILR2), hence promoting the death of TRAILR2-expressing malignant (not non-transformed) cells.[163] Although the molecular basis underlying the selectivity of tigatuzumab remains unclear,[164,165] the results of preliminary Phase I-II studies in cancer patients were encouraging, suggesting that tigatuzumab is generally well tolerated.[166] Recently (since 2011, August 1), 1 Phase II clinical trial has been initiated to test the safety and efficacy of tigatuzumab combined with abraxane (protein-bound paclitaxel particles), in breast carcinoma patients (NCT01307891) (**Table 2**).

Tremelimumab (ticilimumab, CP-675,206) is a human IgG2 that, similar to the FDA-approved mAb ipilimumab, inhibits the development of peripheral tolerance by antagonizing the immunosuppressive receptor CTLA-4 on the surface of T cells.[167,168] Combinatorial regimens including tremelimumab + high-dose interferon α-2b (IFNα-2b) and tremelimumab + androgen deprivation have recently been shown to be well tolerated by melanoma and prostate carcinoma patients,[169,170] respectively. Since 2011, August 1), 2 Phase II studies have been launched to investigate the clinical profile of tremelimumab, invariably employed as a standalone intervention, in mesothelioma patients (NCT01649024; NCT01655888) (**Table 2**).

Concluding Remarks

In no more than 15 months, besides extending the indications of mAbs that were previously approved in oncological settings, the US FSA has authorized the use in cancer patients of two novel mAbs, brentuximab vedotin and denosumab.[32–34] In the very same period, (1) results from no less than 50 clinical studies testing the safety and antineoplastic profile of mAbs have been published in top-impact forums; and (2) approximately 50 novel mAb-based clinical trials enrolling cohorts of cancer patients have been registered at www.clinicaltrials.gov. Thus, the interest in the clinical development of mAbs for cancer therapy remains very high.

With two notable exceptions (i.e., NCT01266811 and NCT01231347), all Phase III studies that we listed in our latest Trial Watch dealing with mAbs and cancer therapy are still ongoing.[6] The results of these large, randomized clinical trials are likely to determine whether novel mAbs will soon be authorized by FDA and/or other international regulatory agencies for use in cancer patients. In addition, an intense wave of preclinical investigation is ongoing not only to discover novel mAb-druggable oncology-relevant targets, but also to generate further insights into the molecular and cellular circuitries whereby mAbs actually exert antineoplastic effects and how this knowledge can be translated into more stable and more efficient therapeutics.[6,29,171] In the mid-long term, such preclinical studies will surely generate the next generation of mAbs for clinical development.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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