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Trial watch: Tumor-targeting monoclonal antibodies for oncological indications

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Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; ALCL, anaplastic large-cell lymphoma; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BiTE, bispecific T-cell engager; CDC, complement-dependent cytotoxicity; CLL, chronic lymphocytic leukemia; CRC, colorectal carcinoma; DLBCL, diffuse large B-cell lymphoma; EGFR, epidermal growth factor receptor; F3, coagulation factor III; FDA, Food and Drug Administration; FOLFIRI, folinic acid, 5-fluorouracil, irinotecan; FOLFOX, folinic acid, 5-fluorouracil, oxaliplatin; HCC, hepatocellular carcinoma; HHV-8, human herpesvirus-8; IL, interleukin; mAb, monoclonal antibody; MMAE, monomethyl auristatin E; MCL, mantle cell lymphoma; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung carcinoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphoinositide-3-kinase; RCC, renal cell carcinoma; SLL, small lymphocytic leukemia; TAA, tumor-associated antigen.

An expanding panel of monoclonal antibodies (mAbs) that specifically target malignant cells or intercept trophic factors delivered by the tumor stroma is now available for cancer therapy. These mAbs can exert direct antiproliferative/cytotoxic effects as they inhibit pro-survival signal transduction cascades or activate lethal receptors at the plasma membrane of cancer cells, they can opsonize neoplastic cells to initiate a tumor-targeting immune response, or they can be harnessed to specifically deliver toxins or radionuclides to transformed cells. As an indication of the success of this immunotherapeutic paradigm, international regulatory agencies approve new tumor-targeting mAbs for use in cancer patients every year. Moreover, the list of indications for previously licensed molecules is frequently expanded to other neoplastic disorders as the results of large, randomized clinical trials become available. Here, we discuss recent advances in the preclinical and clinical development of tumor-targeting mAbs for oncological indications.

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Introduction

One of the most successful immunotherapeutic paradigms developed so far for the treatment of malignant conditions relies on tumor-targeting mAbs.[1,2] Immunostimulatory mAbs, which lately have also been associated with impressive clinical responses among cancer patients, function by specifically binding to, hence activating, effector or regulatory components of the immune system.[3,4] Conversely, tumor-targeting mAbs exert antineoplastic effects upon binding to transformed cells or upon neutralizing trophic signals delivered by the tumor stroma.[5,6] Thus, several mechanisms may underlie the clinical efficacy of this class of immunotherapeutics: (1) the inhibition of cancer cell-intrinsic signal transduction pathways that are necessary for survival and/or proliferation;[7,8] (2) the activation of pro-apoptotic receptors preferentially expressed by neoplastic cells (e.g., tumor necrosis factor receptor superfamily, member 10B, TNFRSF10B, best known as TRAILR2 or DR5);[9] (3) the selective opsonization of malignant cells, resulting in the engagement of an innate immune response based upon antibody-dependent cell-mediated cytotoxicity (ADCC),[2,10-13] antibody-dependent cellular phagocytosis,[14] and complement-dependent cytotoxicity (CDC),[15,16] (4) the recruitment of T lymphocytes in the proximity of cancer cells and or their activation, relying on mAbs specific for one tumor-associated antigen (TAA) and one T-cell marker;[17,18] (5) the targeted delivery of toxins or radionuclides to neoplastic lesions;[19-22] or (6) the neutralization of trophic factors released by stromal or

malignant components of the tumor mass.[23,24] Often, these mechanisms are not mutually exclusive, and the clinical activity of many mAbs may indeed reflect some degree of functional diversity. This applies to cetuximab, a chimeric IgG1 specific for the epidermal growth factor receptor (EGFR). Cetuximab does not only inhibit the trophic signal transduction cascade elicited by the EGFR,[25,26] but also promotes ADCC,[27] and mediates immunostimulatory effects.[28,29] A particular class of mAb-related therapeutic agents is represented by bispecific T-cell engagers (BiTEs), fusion proteins consisting of two single-chain variable fragments from distinct mAbs, one targeting a TAA and one specific for a T-cell surface antigen, most often CD3.[30,31] BiTEs, such as the CD3- and CD19-targeting molecule blinatumomab,[32-35] exert antineoplastic effects by promoting the interaction between malignant cells and T lymphocytes, resulting in the activation of the latter against the former.[33,36] In thus far, BiTEs operate as mixed tumor-targeting and immunostimulatory mAbs.

Since the submission of our latest trial watch dealing with this topic (October 2013),[6] several tumor-targeting mAbs have been approved by the US Food and Drug Administration (FDA) for use in cancer patients (source http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm). In particular: (1) siltuximab (Sylvant®, Janssen Biotech, Inc.), a chimeric IgG1 that neutralizes interleukin (IL)-6[37,38] has been approved for the treatment of multicentric Castleman's disease (an uncommon lymphoproliferative disorder of lymph nodes)[39-41] in HIV- and human herpesvirus-8 (HHV-8)-negative individuals;[42] (2) ramucirumab (Cyramza®, Eli Lilly and Company), a fully human IgG1 specific for kinase insert domain receptor (KDR, best known as VEGFR2),[43] has been licensed for use in patients with advanced or metastatic, gastric or gastroesophageal junction adenocarcinoma experiencing disease progression on or after fluoropyrimidine- or platinum-containing chemotherapy;[44-46] and (3) obinutuzumab (Gazyva®, Genentech, Inc.), a fully human IgG1 specific for CD20,[47-49] has been approved for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) in combination with chlorambucil (an alkylating agent).[50-52] In addition, during the last 13 mo the US FDA has extended the approved indications of two tumor-targeting mAbs previously licensed for use in humans (source http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm). Bevacizumab (Avastin®, Genentech, Inc.), a humanized vascular endothelial growth factor A (VEGFA)-targeting IgG1 that was previously approved for the treatment of some forms of glioblastoma, colorectal carcinoma (CRC), renal cell carcinoma (RCC) and non-small cell lung carcinoma (NSCLC),[23,53-55] is now indicated for the therapy of persistent, recurrent or metastatic cervical cancer, in combination with paclitaxel (a microtubular poison of the taxane family),[56-58] and cisplatin (a DNA-damaging agent) or paclitaxel and topotecan (a topoisomerase inhibitor).[59] Moreover, ofatumumab (Arzerra®, GlaxoSmithKline), a CD20-specific human IgG1 licensed in 2009 for the treatment of previously treated CLL patients,[60-63] can now be used also in treatment-naïve CLL patients for whom fludarabine-based therapy is considered inappropriate.[64,65] Overall, this raises the number of tumor-targeting mAbs currently approved for oncological indications to 17 (**Table 1**).

Along the lines of our monthly trial watch series,[66-68] here we present recent advances in the preclinical and clinical development of tumor-targeting mAbs for oncological indications. Immunostimulatory mAbs and radionuclide-conjugated mAbs will not be treated in further details here but will be discussed in dedicated Trial Watches of the series. Of note, both ipilimumab (a human IgG1 specific for cytotoxic T lymphocyte-associated protein 4, CTLA4, also known as Yervoy®) and pembrolizumab (a humanized IgG4 targeting programmed cell death 1, PDCD1,

Table 1. Tumor-targeting mAbs currently approved for cancer therapy*,†

mAb	Target	First approved	Type	Indication(s)
Alemtuzumab	CD52	2001	Hzed IgG1	Chronic lymphocytic leukemia
Bevacizumab	VEGFA	2004	Hzed IgG1	Glioblastoma multiforme, cervical, colorectal, renal, and lung cancer
Brentuximab vedotin	CD30	2011	C IgG1	Hodgkin's 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	HNC and colorectal carcinoma
Denosumab	RANKL	2011	H IgG2	Breast cancer, prostate carcinoma, and giant cell tumors of the bone
Gemtuzumab ozogamicin	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)
Panitumumab	EGFR	2006	H IgG2	Colorectal carcinoma
Pertuzumab	HER2	2012	Hzed IgG1	Breast carcinoma
Obinutuzumab	CD20	2013	H IgG1	Chronic lymphocytic leukemia
Ofatumumab	CD20	2009	H IgG1	Chronic lymphocytic leukemia
Ramucirumab	VEGFR2	2014	H IgG1	Gastric or gastroesophageal junction adenocarcinoma
Rituximab	CD20	1997	C IgG1	Chronic lymphocytic leukemia and non-Hodgkin lymphoma
Siltuximab	IL-6	2014	C IgG1	Multicentric Castleman's disease
Tositumomab	CD20	2003	H IgG1	Non-Hodgkin lymphoma (naked or coupled with ^{131}I)
Trastuzumab (emtansine)	HER2	1998 (2013)	Hzed IgG1	Breast carcinoma (naked or coupled to mertansine) and gastric or gastroesophageal junction cancer

Abbreviations: C, chimeric; EGFR, epidermal growth factor receptor; EPCAM, epithelial cell adhesion molecule; H, human; HNC, head and neck cancer; Hzed, humanized; IL-6, interleukin-6; M, murine; mAb, monoclonal antibody; MMAE, monomethyl auristatin E; R, rat; RANKL, receptor activator of NF-κB ligand; VEGFA, vascular endothelial growth factor A. *by the US Food and Drug Administration on the day of submission. †updated from Ref.[6]

also known as Keytruda®) are licensed for use in humans by various regulatory agencies worldwide, and may be harnessed, at least hypothetically, as tumor-targeting mAbs against T-cell lymphoma.[69] However, both these mAbs are currently employed as immunostimulatory agents for the therapy of unresectable or metastatic melanoma,[4,70-77] and hence will not be discussed further here. Finally, owing to the high number of clinical studies dealing with this immunotherapeutic paradigm that has been published or initiated during the last 13 mo, here we will focus on hitherto experimental mAbs and FDA-approved mAbs employed as off-label interventions only.

Update on the Development of Tumor-Targeting Monoclonal Antibodies

Completed clinical trials

On 2014 October 20th, we queried PubMed with various strings in the attempt to identify all clinical studies published since the submission of our latest trial watch about tumor-targeting mAbs (October 2013),[6] retrieving more than 1,400 entries all types confounded (source http://www.ncbi.nlm.nih.gov/pubmed). Although a fraction of this figure corresponds to preclinical studies, reviews and commentaries, such an amount of scientific publications is a reliable sign of the clinical success achieved by tumor-targeting mAbs since the approval of rituximab, a CD20-specific agent licensed for use in humans as early as in 1997.[78,79] Among the clinical trials testing the efficacy of hitherto investigational tumor-targeting mAbs or FDA-approved tumor-targeting mAbs employed in off-label indications, we found several of particular interest.

Siltuximab

Van Rhee et al. (University of Arkansas for Medical Sciences; Little Rock, AR, US) performed a randomized, double-blind, placebo-controlled Phase II clinical trial to test the safety and efficacy of siltuximab in subjects with multicentric Castleman's disease (NCT01024036), which reportedly rely on the overproduction of IL-6.[80] In this setting, 79 patients were randomly assigned to receive 11 mg/Kg siltuximab i.v. every 3 weeks ($n = 53$) or placebo ($n = 26$). Objective responses occurred in 18/53 (34%) patients treated with siltuximab and 0/26 patients treated with placebo. The incidence of Grade 3–4 adverse events (the most common being fatigue, night sweats and anemia) did not differ between groups, and only three patients experienced serious toxicity related to siltuximab administration.[42] Based on the results of this study, the US FDA approved siltuximab for the treatment of multicentric Castleman's disease in HIV- and HHV-8-negative patients.

Ramucirumab

Wilke et al. (Kliniken Essen-Mitte; Essen, Germany) ran a randomized, placebo-controlled, double-blind, Phase III clinical trial to assess whether ramucirumab would increase the therapeutic efficacy of paclitaxel, measured in terms of overall survival (OS), among patients with previously treated advanced gastric or gastroesophageal junction adenocarcinoma (NCT01170663). In this setting, 665 patients were randomly assigned to receive 8 mg/Kg ramucirumab or placebo i.v. on days 1 and 15 plus 80 mg/m^2 paclitaxel i.v. on days 1, 8, and 15 of a 28-d cycle. Median OS was 9.6 mo in patients receiving ramucirumab plus paclitaxel, while it was 7.4 mo in patients treated with paclitaxel only. Grade 3–4 side effects that were significantly more frequent in subjects administered with ramucirumab included neutropenia, leucopenia, hypertension, fatigue, anemia, and abdominal pain.[46] The findings of this study led to the regulatory approval of ramucirumab for use in subjects with advanced or metastatic, gastric or gastroesophageal junction adenocarcinoma experiencing disease progression on or after fluoropyrimidine- or platinum-containing chemotherapy.

Garon et al. (University of California; Los Angeles, CA, US) assessed the safety and efficacy of docetaxel plus ramucirumab or placebo as second-line treatment for subjects with Stage IV NSCLC after platinum-based therapy (NCT01168973). In this double-blind, randomized, Phase III clinical trial, 1,253 patients were randomly allocated to receive 75 mg/m^2 docetaxel and either 10 mg/kg ramucirumab or placebo on day 1 of 21-d cycles (until disease progression, unacceptable toxicity, withdrawal, or death). Median OS (PFS) was 10.5 (4.5) and 9.1 (3.0) mo for patients receiving ramucirumab plus docetaxel and placebo plus docetaxel, respectively. Treatment-related adverse events emerged in more than 95% of the patient cohort, the most common Grade 3–4 toxicities being neutropenia, fatigue, leucopenia, and hypertension. These adverse events were manageable with dose reductions and supportive care.[81]

Obinutuzumab

Goede et al. (University of Cologne; Cologne, Germany) compared the safety and therapeutic potential of obinutuzumab and rituximab, each combined with chlorambucil, in 781 patients with previously untreated CLL and coexisting conditions (NCT01010061). Both obinutuzumab and rituximab ameliorated progression-free survival (PFS) and response rates associated with chlorambucil monotherapy, but only the addition of obinutuzumab prolonged OS among chlorambucil-treated patients (hazard ratio for death = 0.41; 95% CI, 0.23–0.74; $p = 0.002$). The administration of obinutuzumab plus chlorambucil was associated with a slightly increased incidence of infusion-related toxicities and neutropenia, but not with an accrued percentage of infections.[52] Based on these data, the US FDA licensed obinutuzumab for the therapy of previously untreated CLL patients in combination with chlorambucil.

Ofatumumab

Hillmen et al. (St. James's University Hospital; Leeds, UK) evaluated the therapeutic profile of ofatumumab plus chlorambucil, as compared to that of chlorambucil alone, in CLL patients who were considered inappropriate for fludarabine-based therapy due to advanced age and/or co-morbidities (NCT00748189). In this multicenter, open-label, Phase III clinical trial, 447 patients from 16 countries were randomized to receive either chlorambucil alone (10 mg/m^2 p.o., on days 1–7 of 28-d cycles) or

chlorambucil plus ofatumumab (300 mg i.v. on day 1, 1000 mg i.v. on day 8, and 1000 mg i.v. on day 1 of each subsequent cycle). Median PFS and response rates at 29 mo median follow-up were significantly higher among patients receiving chlorambucil plus ofatumumab (22.4 mo, 82%) than among individuals treated with chlorambucil alone (13.1 mo, 69%). Grade 3–4 adverse events were experienced by 50% of patients receiving chlorambucil plus ofatumumab and by 43% of patients receiving chlorambucil monotherapy, but the incidence of severe infections did not differ between the study arms. No fatal infusion reactions were reported.[65] These results led the US FDA to extend the approval of ofatumumab (combined with chlorambucil) to CLL patients for whom fludarabine-based therapy is considered inappropriate.

Byrd et al. (Ohio State University Comprehensive Cancer Center; Columbus, OH, US) evaluated the efficacy of ibrutinib (an FDA-approved inhibitor of Bruton agammaglobulinemia tyrosine kinase, BTK)[82,83] or ofatumumab in CLL or small lymphocytic leukemia (SLL) patients at risk for poor outcome (NCT01578707). In this open-label, randomized Phase III clinical study, 391 patients were randomly assigned to receive ibrutinib (*p.o.*, 420 mg once daily) or ofatumumab (i.v., 300 mg on week 1, 2000 mg weekly for 7 weeks, 2000 mg monthly for 4 mo). As compared to ofatumumab-based monotherapy, the administration of ibrutinib as a standalone therapeutic intervention was associated with improved PFS (median PFS not reached *vs.* 8.1 mo, at a median follow-up of 9.4 mo), OS rate (90% vs. 81%, at 12 mo) and overall response rate (ORR, 43% vs. 4%). Frequent non-hematological adverse events were diarrhea, fatigue, pyrexia, and nausea among ibrutinib-receiving patients, and fatigue, infusion-related reactions, and cough among subjects treated with ofatumumab.[84] These results suggest that ibrutinib may be more efficient than ofatumumab for the treatment of CLL and SLL.

Cetuximab

Kim et al. (Levine Cancer Institute; Charlotte, NC, USA) tested whether the addition of cetuximab to chemotherapy would improve PFS in subjects with recurrent or progressive NSCLC after platinum-based therapy (NCT00095199). In this setting (an open-label, randomized, Phase III study), 605 patients were allocated to receive the antimetabolite pemetrexed (of which 301 in combination with cetuximab) and 333 to receive the microtubular poison docetaxel (of which 167 in combination with cetuximab). The addition of cetuximab did not improve the PFS associated with pemetrexed-based chemotherapy, yet it significantly increased the incidence and severity of adverse effects.[85] These data suggest that cetuximab is not indicated for co-administration with pemetrexed in NSCLC previously treated with platinum-based chemotherapy.

Bevacizumab

Tewari et al. (University of California; Irvine, CA, US) tested the efficacy of bevacizumab plus paclitaxel-based chemotherapy in subjects with recurrent, persistent, or metastatic cervical cancer (NCT00803062). In this setting, 452 patients were randomly assigned to chemotherapy alone or combined with bevacizumab (15 mg/kg). The addition of bevacizumab to paclitaxel-based chemotherapy was associated with increased median OS (17.0 vs. 13.3 mo) and response rates (48% vs. 36%). Moreover, the combinatorial administration of bevacizumab plus paclitaxel increased the incidence of moderate to severe hypertension, as well as that of severe thromboembolic events and gastrointestinal fistulas.[59] Based on these findings, the US FDA extended the approval of bevacizumab (in combination with paclitaxel plus cisplatin of paclitaxel plus topotecan) to the treatment of persistent, recurrent or metastatic cervical cancer.

Pujade-Lauraine et al. (Université Paris Descartes; Paris, France) investigated the safety and therapeutic potential of bevacizumab plus single-agent, standard chemotherapy in ovarian carcinoma patients refractory to platinum derivatives (NCT00976911). This randomized, Phase III clinical trial enrolled a total of 361 patients. The addition of bevacizumab to chemotherapy improved PFS (6.7 vs. 3.4 mo), OS (16.6 vs. 13.4 mo) and ORR (27.3% vs. 11.8%). Common Grade 2–3 adverse effects that were more frequent among bevacizumab-receiving patients included hypertension and proteinuria.[86] These results support the addition of bevacizumab to standard chemotherapy for the treatment of platinum-reflactory ovarian carcinoma.

Von Minckwitz et al. (University Women's Hospital; Frankfurt, Germany) assessed the therapeutic profile of second-line bevacizumab plus chemotherapy or chemotherapy alone in patients with $HER2^-$ locally recurrent or metastatic breast carcinoma previously treated with bevacizumab plus chemotherapy (NCT01250379). In this open-label, randomized, Phase III clinical trial, 494 patients were randomly assigned to second-line single-agent chemotherapy alone or combined with bevacizumab (15 mg/kg every 3 weeks or 10 mg/kg every 2 weeks). Median PFS was significantly longer among bevacizumab-receiving patients (6.3 vs. 4.2 mo). Serious adverse events were reported in 25% of 245 individuals receiving bevacizumab and in 18% of subjects treated with chemotherapy alone. Seventeen subjects (7%) treated with the combinatorial immunochemotherapy experienced Grade 3 proteinuria, while the most common Grade 3–4 adverse events involving both study arms were hypertension, neutropenia and hand-foot syndrome.[87] These findings indicate that bevacizumab may be a useful addition to single-agent chemotherapy for the second line treatment of $HER2^-$ breast carcinoma.

A clinical research team coordinated by the same physician investigated whether carboplatin is a useful addition to neoadjuvant chemotherapy (involving, among other agents, bevacizumab or trastuzumab) for the treatment of triple-negative and $HER2^+$ breast carcinoma (NCT01426880). In this setting (a randomized Phase II clinical trial), 296 patients were randomly assigned to receive multimodal chemoimmunotherapy (depending on the molecular features of the tumor) alone or combined with carboplatin. In general, carboplatin increased the percentage of pathological complete responses only among patients with triple-negative tumors (53.3% vs. 36.9%). Serious adverse effects that were more common among carboplatin receivers were neutropenia, anemia, thrombocytopenia and diarrhea.[88] Thus, the

addition of neoadjuvant carboplatin to multimodal, trastuzumab- or bevacizumab-containing immunochemotherapy appears to increase the proportion of breast carcinoma patients experiencing a pathological complete response, in particular among individuals with triple-negative neoplasms.

hu14.18^{K322A}

Navid et al. (St Jude Children's Research Hospital; Memphis, TN, US) tested the safety and pharmacokinetics of hu14.18^{K322A}, a humanized mAb targeting ganglioside GD2 and genetically endowed with limited CDC-inducing potential, in children with neuroblastoma (NCT00743496). In the context of this Phase I clinical trial, a total of 38 subjects with refractory or recurrent neuroblastoma received escalating doses of hu14.18^{K322A} (from 2 to 70 mg/m^2 per day) for 4 consecutive days every 28 d. Dose-limiting adverse effects (including cough, asthenia, sensory neuropathy, anorexia, serum sickness, and hypertensive encephalopathy) occurred in 4 out of 36 evaluable individuals. Of note, 6 of 31 evaluable patients experienced objective responses.[89]

Preclinical development

Among the vast amount of preclinical literature dealing with tumor-targeting mAbs published during the last 13 mo, we found of particular interest the works of: (1) Desnoyers et al. (CytomX Therapeutics Inc.; San Francisco, CA, US), who demonstrated that a variant of cetuximab that is specifically activated within the tumor microenvironment (a so-called "probody") exhibits an improved therapeutic index as compared to the parental mAb;[90] (2) Spring et al. (Harvard Medical School; Boston, MA, US), who developed TAA-specific mAbs conjugated to a self-quenched chromophore that is activated (and hence become cytotoxic) upon lysosomal proteolysis;[91] (3) Pearce et al. (University of California, San Diego; La Jolla, CA, US), who proved that (at least some) TAA-targeting mAbs administered at low doses can promote, rather than inhibit, tumor growth;[92] (4) the research teams headed by Marjolein van Egmond (University Medical Center; Amsterdam, the Netherlands) and Philippe Bousso (Institut Pasteur; Paris, France), who provided significant insights into the mechanisms that account for the elimination of opsonized cancer cells (which is mostly mediated by hepatic Kupffer cells);[93,94] (5) Li et al. (Shanghai Jiao Tong University; Shanghai, Republic of China), who designed a bispecific mAb targeting *v-erb-b2* avian erythroblastic leukemia viral oncogene homolog 2 (ERBB2, best known as HER2) that is able to revert (at least in part) the resistance of malignant cells to trastuzumab (a HER2-specific humanized IgG1 approved for use in patients with HER2$^+$ breast carcinoma),[95] (6) Kudo et al. (National University of Singapore; Singapore), who engineered T lymphocytes to express a chimeric receptor specific for the constant region of immunoglobulins coupled to intracellular signaling domains from CD3 and tumor necrosis factor receptor superfamily, member 9 (TNFRSF9, best known as 4-1BB),[96] consistently improving their ability to mediate ADCC in the presence of tumor-targeting mABs;[97] (7) the research teams headed by Ronald Levy (Stanford University; Stanford, CA, US) and Pascal André (Innate Pharma; Marseille, France), who demonstrated that boosting the activity of natural killer cells with immunostimulatory Abs can significantly improve the therapeutic profile of rituximab and cetuximab;[98,99] (8) Gondi et al. (Helmholtz Zentrum München; Munich, Germany), who demonstrated that carbonic anhydrase XI, a plasma membrane enzyme frequently overexpressed by neoplastic cells,[100,101] can be harnessed as a target for mAb-based immunotherapy;[102] (9) the research teams headed by Seth A. Ettenberg (Novartis Institutes for Biomedical Research; Cambridge, MA, US), Carlos L. Arteaga (Vanderbilt University; Nashville, TN, US) and Maurizio Scaltriti (Memorial Sloan Kettering Cancer Center, New York, NY, US) who proved that ERBB3 (best known as HER3) may constitute a druggable target for HER2$^+$ and triple negative breast carcinomas;[103-105] (10) Breij et al. (Genmab; Utrecht, The Netherlands), who demonstrated that a coagulation factor III (F3)-specific mAb conjugated to monomethyl auristatin E (MMAE) exerts potent antineoplastic effects in vitro and in vivo against F3-expressing tumors;[106] (11) Graves et al. (Amgen Inc.; Cambridge, MA, US), who established the synergistic anticancer activity of recombinant tumor necrosis factor (ligand) superfamily, member 10 (TNFSF10, best known as TRAIL) plus a mAb that activates TRAILR2;[107] (12) Klitgaard et al. (Symphogen A/S; Lyngby, Denmark), who demonstrated that two distinct mAbs specific for CD5 synergistically induce CDC, thus exerting standalone antileukemic activity and significantly improving the efficacy of other mAbs or chemotherapy;[108] and Junttila et al. (Genentech Inc.; San Francisco, CA, US), who developed a HER2-targeting BiTE mediating potent therapeutic effects in various tumor models.[109]

Recently initiated clinical trials

Since the submission of our latest trial watch dealing with this topic (October 2013),[6] no less than 304 clinical studies have been initiated to test the safety and/or efficacy of tumor-targeting mAbs in cancer patients and have not been prematurely terminated. Two hundred and fourteen of these studies involve FDA-approved mAbs employed as on label interventions (and hence will not be discussed in further detail here). Moreover, 66 studies have been launched during the last 13 mo to investigate the therapeutic profile of FDA-approved mAbs in off-label oncological indications (**Table 2**), and 24 to assess the safety and efficacy of hitherto experimental mAbs (**Table 3**) (source http://clinicaltrials.gov/).

Bevacizumab is being tested (most often in combination with conventional chemotherapeutic regimens) in patients affected by breast carcinoma (NCT01989780; NCT02005549; NCT02175446; NCT02185352), tumors of the central nervous system (NCT01999270; NCT02234050), esophageal, gastric or gastrointestinal carcinomas (NCT02024607; NCT02048540; NCT02072720; NCT02129933), melanoma (NCT02020707; NCT02023710; NCT02065466; NCT02158520), hepatocellular carcinoma (HCC) (NCT02013830), NSCLC (NCT02054052; NCT02162537; NCT02200354), RCC (NCT01984242; NCT02208128), ovarian carcinoma or other gynecological malignancies (NCT01995188; NCT02022917; NCT02121990; NCT02217956), and advanced neoplasms

Table 2. Clinical trials recently started to evaluate the therapeutic profile of FDA-approved tumor-targeting mAbs in off-label indications*

mAb	Indication(s)	Phase	Status	Notes	Ref.
Alemtuzumab	Hematological malignancies	I/II	Recruiting	As part of conditioning followed by HSCT	NCT02061800
	Lymphoma	n.a.	Recruiting	As part of conditioning followed by HSCT	NCT02059239
Bevacizumab	Breast carcinoma	II	Not yet recruiting	BEEP regimen	NCT02185352
			Recruiting	Combined with eribulin	NCT02175446
			Recruiting	Combined with paclitaxel ± hormonotherapy	NCT01989780
			Completed with results	Combined with capecitabine and docetaxel	NCT02005549
	CNS cancer	0	Recruiting	Combined with irinotecan	NCT01999270
	Esophageal carcinoma	0	Recruiting	As single agent	NCT02072720
		I	Recruiting	As single agent	NCT02129933
	Gastric carcinoma	I/II	Completed	Combined with DOF regimen	NCT02048540
	Gastrointestinal cancers	I	Recruiting	Combined with FOLFOX6- or FOLFIRI-based chemotherapy	NCT02024607
	Gynecological tumors	I	Recruiting	Combined with cisplatin	NCT02217956
		I	Recruiting	Combined with cisplatin, olaparib and paclitaxel	NCT02121990
	HCC	II	Completed with results	Combined with capecitabine	NCT02013830
	Malignant pleural effusion	II	Recruiting	As single agent	NCT02054078
	Melanoma	I	Recruiting	Combined with paclitaxel nanoparticles	NCT02020707
		I/II	Recruiting	Combined with paclitaxel and temozolomide	NCT02065466
		II	Recruiting	Combined with carboplatin and paclitaxel	NCT02023710
				Combined with paclitaxel	NCT02158520
	Meningioma	II	Not yet recruiting	Combined with trabectedin	NCT02234050
	NSCLC	II	Not yet recruiting	Combined with pemetrexed	NCT02200354
			Recruiting	As single agent	NCT02054052
		III	Recruiting	Combined with chemoradiotherapy	NCT02162537
	Ovarian carcinoma	I	Recruiting	Combined with immunochemotherapy	NCT01995188
		II	Enrolling by invitation	As single agent	NCT02022917
	RCC	n.a.	Recruiting	As single agent	NCT02208128
		II	Recruiting	Combined with anti-CD274 mAb	NCT01984242
Brentuximab vedotin	AML	I/II	Recruiting	As single agent or coupled to 5-azacytidine	NCT02096042
	DLBCL	I	Recruiting	Combined with lenalidomide	NCT02086604
	Hematological malignancies	I/II	Recruiting	Combined with standard chemotherapy	NCT01994850
Cetuximab	Esophageal carcinoma	II	Recruiting	Combined with radiotherapy	NCT02123381
	Pancreatic adenocarcinoma	n.a.	Recruiting	Combined with pegylated hyaluronidase	NCT02241187
	Penis SCC	II	Not yet recruiting	Combined with TIP regimen	NCT02014831
	Advanced solid tumors	I	Recruiting	Combined with regorafenib	NCT02095054
				Combined with temsirolimus	NCT02215720
				Combined with afatinib	NCT02020577
				Combined with regorafenib	NCT01973868
		II	Recruiting	As single agent	NCT02142036
Denosumab	NSCLC	III	Not yet recruiting	Combined with standard chemotherapy	NCT02129699
	Advanced solid tumors	IV	Recruiting	Combined with pamidronate	NCT02101164
Gemtuzumab ozogamicin	MDS	II	Recruiting	As single agent	NCT02117297
					NCT02221310
Obinutuzumab	DLBCL	I	Not yet recruiting	Combined with anti-CD274 mAb	NCT02220842
	NHL	I	Recruiting	Combined with CHOP and BCL2 inhibitor	NCT02055820
		I/II	Recruiting	Combined with lenalidomide	NCT01995669

Ofatumumab	Burkitt leukemia	II	Not yet recruiting	As DA-EPOCH regimen	NCT02199184
	CLL SLL	II	Recruiting	Combined with idelalisib	NCT02135133
		III	Recruiting	As single agent	NCT02004522
					NCT02049515
Panitumumab	CRC HNSCC	I/II	Recruiting	Combined with cetuximab	NCT02205398
	Advanced solid tumors	II	Recruiting	As single agent	NCT02142036
Pertuzumab	Gastric carcinoma	II	Not yet recruiting	Combined with cisplatin and trastuzumab ± capecitabine	NCT02205047
	Esophageal carcinoma	I/II	Recruiting	Combined with carboplatin, paclitaxel and trastuzumab	NCT02120911
	Ovarian carcinoma	II	Completed	Combined with carboplatin, gemcitabine and paclitaxel	NCT02004093
Ramucirumab	HCC	I	Recruiting	Combined with FOLFOX regimen	NCT02069041
	NSCLC	I	Recruiting	Combined with LY2835219	NCT02079636
Rituximab	Acute leukemia	II	Not yet recruiting	Combined with cytarabine, clofarabine, idarubicin and vincristine	NCT02135874
	ALL NHL	II	Recruiting	As a part of cytarabine-based chemotherapy	NCT02043587
	DLBCL and Advanced tumors	I/II	Recruiting	Combined with anti-CD274 mAb	NCT02205333
	HCL	II	Completed	Combined with cladribine	NCT02157181
	Hematological malignancies	I/II	Active not recruiting	As a part of myeloablative chemotherapy followed by UCBT	NCT01983761
		II	Not yet recruiting	As conditioning regimen followed by HSCT and NK cell transfer	NCT02259348
	Melanoma	II	Recruiting	Combined with abraxane	NCT02142335
	Waldenstrom's macroglobulinemia	III	Recruiting	As single agent or combined with ibrutinib	NCT02165397
Trastuzumab	NSCLC	II	Not yet recruiting	Combined with paclitaxel	NCT02226757
	Urothelial cancer	II	Completed	Combined with cisplatin and gemcitabine	NCT02006667
	Advanced solid tumors	II	Recruiting	As single agent	NCT02048059
					NCT02142036

Abbreviations: 5-FU, 5-fluorouracil; ALL, acute myeloid leukemia; AML, acute myeloid leukemia; BEEP, bevacizumab, etoposide, cisplatin; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CLL, chronic lymphocytic leukemia; CNS, central nervous system; CRC, colorectal carcinoma; DA-EPOCH, dose adjusted-etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; DLBCL, diffuse large B-cell lymphoma; DOF, docetaxel, oxaliplatin, 5-FU; FDA, Food and Drug Administration; FOLFIRI, folinic acid, 5-FU, irinotecan; FOLFOX, folinic acid, 5-FU, oxaliplatin; HCC, hepatocellular carcinoma; HCL, hairy cell leukemia, HNSCC, head and neck squamous cell carcinoma; HSCT, hematopoietic stem cell transplantation; mAb, monoclonal antibody; MDS, myelodysplastic syndrome; n.a., not available; NHL, non-Hodgkin's lymphoma; NK, natural killer; NSCLC, non-small cell lung carcinoma; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; SLL, small lymphocytic lymphoma; TIP, paclitaxel, ifosfamide, cisplatin; UCBT, umbilical cord blood transplantation. *initiated after 2013, October 1st and not withdrawn, terminated or suspended on the day of submission.

associated with malignant pleural effusions (NCT02054078). Cetuximab is being tested as a single agent or combined with radiotherapy or chemotherapeutics including the FDA-approved small molecule kinase inhibitors afatinib and regorafenib[110-113] in individuals with esophageal carcinoma (NCT02123381), pancreatic adenocarcinoma (NCT02241187), squamous cell carcinoma of the penis (NCT02014831), and other advanced solid neoplasms (NCT01973868; NCT02020577; NCT02095054; NCT02142036; NCT02215720). Obinutuzumab is being evaluated in combination with lenalidomide, an immunostimulatory mAb targeting CD274 (best known as PD-L1),[114-116] or a chemotherapeutic regimen comprising a chemical inhibitor of BCL2[117-119] in patients with various forms of lymphoma (NCT01995669; NCT02055820; NCT02220842). Ofatumumab is being tested as a standalone therapeutic agent, in combination with an experimental phosphoinositide-3-kinase (PI3K) inhibitor (i.e., idelalisib), or in the context of chemotherapeutic cocktail involving rituximab,[78,79] in subjects with Burkitt leukemia or small lymphocytic lymphoma (NCT02004522; NCT02049515; NCT02135133; NCT02199184). Rituximab is being investigated as part of conditioning regimens followed by hematopoietic stem cell transplantation or in the context of combinatorial induction chemotherapy in subjects with a broad panel of hematological malignancies or advanced $CD20^+$ solid tumors (NCT01983761; NCT02043587; NCT02135874; NCT02142335; NCT02157181; NCT02165397; NCT02205333; NCT02259348). Ramucirumab is being tested in combination with the so-called FOLFOX4 regimen (involving folinic acid, 5-fluorouracil, and oxaliplatin)[120] or with a chemotherapeutic cocktail including an experimental inhibitor of cyclin-dependent kinases (i.e., LY2835219)[121,122] in patients with advanced HCC or NSCLC, respectively (NCT02069041; NCT02079636). Alemtuzumab, an anti-CD52 humanized IgG1 that is approved for use in CLL patients,[123,124] is being evaluated as part of an intensive chemotherapeutic regimen followed by allogeneic transplantation in patients with various hematological malignancies (NCT02059239; NCT02061800). Brentuximab vedotin, a CD30-specific, MMAE conjugate approved for the treatment of relapsed Hodgkin's lymphoma and relapsed systemic anaplastic large cell lymphoma,[125,126] is being tested, either as a single agent or in combination with 5-azacytidine (a nucleoside analog mainly employed for the treatment of myelodysplastic syndromes, MDSs)[127-129] or lenalidomide (an immunomodulatory drug),[130,131] in subjects with acute myeloid leukemia (AML) (NCT02096042) or various forms of lymphoma (NCT01994850; NCT02086604). Panitumumab, an EGFR-specific human IgG2 currently approved for the treatment of CRC,[132-134] is being tested as a single agent or in combination with cetuximab for the treatment of advanced tumors, including head and neck squamous cell carcinoma (HNSCC) (NCT02142036; NCT02205398). Pertuzumab, a humanized HER2-targeting IgG1 approved for the treatment of $HER2^+$ breast carcinoma,[135,136] is being investigated in combination with chemotherapeutic regimens that include platinum salts (i.e., cisplatin or oxaliplatin)[137,138] in subjects with gastric, esophageal or ovarian carcinoma (NCT02004093; NCT02120911; NCT02205047). Trastuzumab is being tested as a single agent, combined with paclitaxel or in the context of cisplatin-based chemotherapy in patients with NSCLC or various metastatic tumors (NCT02006667; NCT02048059; NCT02142036; NCT02226757). Denosumab, a human IgG2 specific for receptor activator of NF-κB ligand (RANKL) approved for use in patients affected by breast carcinoma, prostate carcinoma or unresectable giant cell tumors with bone involvement,[139-141] is being evaluated as a support to standard chemotherapy in subjects with metastatic NSCLC (NCT02129699), or combined with pamidronate (a nitrogen-containing bisphosphonate employed for the treatment of osteoporosis)[142,143] in individuals affected by various metastatic cancers (NCT02101164). Finally, gemtuzumab ozogamicin, a CD33-specific calicheamicin conjugate approved in 2000 for the treatment of AML,[144-146] is being assessed as a standalone therapeutic intervention in two cohorts that also contain MDS patients (NCT02117297; NCT02221310). Blinatumomab is currently under evaluation as a standalone therapeutic agent or combined with other chemotherapeutic agents in subjects with acute lymphocytic leukemia (ALL) (NCT02000427; NCT02003222; NCT02013167; NCT02101853; NCT02143414). AFM11, a bispecific tandem mAb (TandAb®)[147] that also targets CD3 and CD19,[148,149] is being tested as a standalone therapeutic intervention in patients with B-cell ALL and non-Hodgkin's lymphoma (NHL) (NCT02106091). Nimotuzumab, a humanized IgG1 targeting the EGFR,[150-152] is being assessed (most often in the context of standard, cisplatin-based chemotherapy) in patients with nasopharyngeal carcinoma (NCT02012062), esophageal carcinoma (NCT02011594; NCT02034968; NCT02041819) or cervical carcinoma (NCT02039791; NCT02083211; NCT02095119). Rilotumumab, a human IgG2 that neutralizes hepatocyte growth factor (HGF),[153-155] is being evaluated in combination with conventional chemotherapeutics or targeted anticancer agents (such as the EGFR inhibitor erlotinib)[156,157] in subjects with gastric carcinoma (NCT02137343; NCT02213289) or NSCLC (NCT02154490). Ublituximab, a chimeric IgG1 targeting CD20,[158,159] is being tested together with ibrutinib and/or an orally available PI3Kδ inhibitor (TGR-1202) in patients with CLL, NHL and mantle cell lymphoma (MCL) (NCT02006485; NCT02013128). LY2875358, a bivalent humanized IgG4 specific for MET,[160] is being evaluated in combination with ramucirumab-containing chemotherapy for the treatment of NSCLC (NCT02082210). Polatuzumab vedotin, an MMAE conjugate specific for CD79B,[161,162] is being assessed in combination with obinutuzumab, rituximab and bendamustine (an FDA-approved alkylating agent)[163] for the treatment of lymphoma (NCT02257567). Dinutuximab, a chimeric IgG1 specific for disialoganglioside GD2,[164-169] is being tested together with isotretinoin (a retinoid), IL-2 and granulocyte macrophage colony-stimulating factor[170,171] in neuroblastoma patients (NCT02169609). SCT400, a chimeric anti-CD20 mAb, is under evaluation as a standalone therapeutic measure in subjects with NHL (NCT02206308). SGN-CD70A, a CD70-targeting pyrrolobenzodiazepine conjugate,[172] is being assessed as single therapeutic intervention in various $CD70^+$ malignancies,

Table 3. Clinical trials recently started to evaluate the therapeutic profile of experimental tumor-targeting mAbs*

mAb	Indication(s)	Phase	Status	Notes	Ref.
ABBV-399	Advanced solid tumors	I	Recruiting	Combined with bevacizumab, carboplatin, cetuximab or erlotinib	NCT02099058
AFM11	B-ALL NHL	I	Recruiting	As single agent	NCT02106091
Blinatumomab	ALL	II	Not yet recruiting	Combined with dasatinib and prednisone or POMP	NCT02143414
			Recruiting	As single agent	NCT02000427
		III	Not yet recruiting	Combined with other chemotherapeutics and followed by allogeneic HSCT	NCT02101853
			Recruiting	As single agent	NCT02013167
				Combined with standard chemotherapy	NCT02003222
Dinutuximab	Neuroblastoma	II	Not yet recruiting	Combined with IL-2, rGM-CSF and isotretinoin	NCT02169609
LY2875358	HCC RCC	I/II	Recruiting	Combined with ramucirumab	NCT02082210
Nimotuzumab	Cervical carcinoma	I/II	Active not recruiting	Combined with cisplatin and gemcitabine	NCT02095119
		II	Recruiting	Combined with chemoradiotherapy	NCT02039791
		III	Enrolling by invitation	Combined with standard chemotherapy	NCT02083211
	Esophageal carcinoma	II	Not yet recruiting	Combined with cisplatin and paclitaxel	NCT02034968
			Recruiting	As single agent	NCT02041819
					NCT02011594
	NPC	III	Recruiting	Following neoadjuvant TPF	NCT02012062
Polatuzumab	Lymphoma	II	Recruiting	Combined with bendamustine, obinutuzumab ± rituximab	NCT02257567
Rilotumumab	Gastric carcinoma	I/II	Not yet recruiting	Combined with FOLFIRI, FOLFOX or FOLTAX-based chemotherapy	NCT02213289
		III	Recruiting	Combined with capecitabine and cisplatin	NCT02137343
	NSCLC	II/III	Recruiting	Combined with erlotinib	NCT02154490
SCT400	NHL	I	Completed	As single agent	NCT02206308
SGN-CD70A	$CD70^+$ tumors	I	Recruiting	As single agent	NCT02216890
Ublituximab	CLL MCL	I	Recruiting	Combined with ibrutinib	NCT02013128
	CLL NHL	I	Recruiting	Combined with PI3Kδ inhibitor	NCT02006485

Abbreviations: 5-FU, 5-fluorouracil; ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; FOLFIRI, folinic acid, 5-FU, irinotecan; FOLFOX, folinic acid, 5-FU, oxaliplatin; FOLTAX, 5-FU, docetaxel; HCC, hepatocellular carcinoma; HSCT, hematopoietic stem cell transplantation; IL, interleukin; mAb, monoclonal antibody; MCL, mantle cell lymphoma; NHL, non-Hodgkin's lymphoma; NPC, nasopharingeal carcinoma; NSCLC, non-small cell lung carcinoma; PI3K, phosphoinositide-3-kinase; POMP, prednisone, vincristine, methotrexate, 6-mercaptopurine; RCC, renal cell carcinoma; rGM-CSF, recombinant granulocyte-macrophage colony-stimulating factor; TPF, docetaxel, cisplatin, 5-FU. *initiated after 2013, October 1st and not withdrawn, terminated or suspended on the day of submission.

including RCC, MCL, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (NCT02216890). Finally, ABBV-399, an antibody drug conjugate with undisclosed specificity, is being tested in combination with cetuximab, bevacizumab, erlotinib or carboplatin in patients with advanced solid tumors (NCT02099058).

Of note, although all these studies have been launched during the last 13 mo, some of them have already been completed, including NCT02004093, NCT02006667, NCT02048540, NCT02157181, and NCT02206308 (whose results have not yet been disseminated, to the best of our knowledge) as well as NCT02005549 and NCT02013830 (for which results are available). NCT02005549 (a Phase II study) tested neoadjuvant bevacizumab in combination with docetaxel[173,174] and capecitabine in 18 women with primary breast carcinoma. Although five patients (27.78%) were affected by serious adverse reactions, 13 or them (72.22%) experienced a pathological complete response, clinical complete response or clinical partial response. Moreover, 15 patients (83%) could undergo breast-conserving surgery as opposed to radical mastectomy at the end of treatment. NCT02013830 (a Phase II study) intended to investigate the safety and efficacy of bevacizumab plus capecitabine in 45 chemotherapy-naïve patients with advanced or metastatic HCC. Only 15 patients completed the 6 cycles of therapy originally planned as per study design without unacceptable toxicity or disease progression, but all of them were affected by serious adverse events. Four patients out of 44 that could be evaluated (9.1%) experienced an objective response, while 23 (52.3%) achieved disease control lasting no less than 4 weeks (source http://clinicaltrials.gov/).

As for the clinical studies listed in our previous Trial Watches dealing with tumor-targeting mAbs,[5,6,175] the following trials have changed status during the last 13 mo: NCT00866047, NCT01168973, NCT01461538, NCT01466179, NCT01471782, NCT01472081, NCT01508312, NCT01515306, NCT01562899, NCT01605396, NCT01606748, NCT01609231, NCT01614795, NCT01624467, NCT01629758, NCT01634555, NCT01642004, NCT01668784, NCT01673867, NCT01741792, NCT01749969, NCT01769391, NCT01788566, which are now listed as "Active, not recruiting;" NCT01079780, NCT01545648, NCT01621490,

NCT01658878, NCT01678443, NCT01682135, NCT01735071, NCT01762202, NCT01807598, NCT01837251, NCT01841021, NCT01851200, NCT01861223, NCT01875237, NCT01879306, NCT01898117, NCT01900496, NCT01921387, NCT01940172, NCT01950390, NCT01951586 and NCT01959490, which are now listed as "Recruiting;" NCT01463605, NCT01486992, NCT01498562, NCT01616849 and NCT01649024, whose status now is now "Unknown;" NCT01473303, NCT01620229 and NCT01671813, which are now listed as "Withdrawn;" NCT00385827 and NCT01513317, which have been "Terminated;" as well as NCT00627042, NCT00639509, NCT00683475, NCT00791011, NCT00862784, NCT00947856, NCT00986674, NCT01005355, NCT01026415, NCT01253525, NCT01286818, NCT01298401, NCT01413191, NCT01418495, NCT01425736, NCT01427933, NCT01431547, NCT01531998, NCT01567163 and NCT01592045, which have been "Completed" (source http://www.clinicaltrials.gov).

NCT01473303, a Phase I/II study testing the therapeutic profile of ganitumab (a fully human IgG1 specific for insulin-like growth factor 1 receptor, IGF1R)[176] plus standardized chemotherapy in patients with advanced pancreatic adenocarcinoma, has been closed prior to enrollment owing to financial issues. NCT01671813, testing brentuximab vedotin (an anti-CD30 MMAE conjugate approved for the treatment of some forms of lymphoma)[125,126] as a standalone therapeutic intervention in subjects with DLBCL, has been terminated due to poor accrual. The reasons underlying the termination of NCT01620229, a Phase I/II trial assessing the therapeutic profile of brentuximab vedotin in subjects with hematological malignancies subjected to allogenic stem cell transplantation, have not been disclosed. Both NCT00385827, a Phase II trial testing siltuximab plus prednisone (a glucocorticoid) and mitoxantrone (an anthracycline that promotes immunogenic cell death),[177,178] and NCT01513317, evaluating the clinical profile of siltuximab plus best supportive care in low- or intermediate-1-risk MDS patients, have been prematurely terminated owing to lack of efficacy (source http://www.clinicaltrials.gov).

Although NCT00866047, NCT01515306, and NCT01634555 are currently listed by official source as "Active, not recruiting," results are available. NCT00866047, a Phase II study, tested brentuximab vedotin as a standalone immunotherapeutic intervention in 58 patients with relapsed or refractory systemic anaplastic large-cell lymphoma (ALCL).[179] Grade 3–4 adverse events affecting <10% of patients were neutropenia (21%), thrombocytopenia (14%), and peripheral sensory neuropathy (12%). Moreover, 50 patients (86%) achieved an objective response, 33 patients (57%) achieved a complete remission (CR), and 17 patients (29%) achieved a partial remission, warranting further investigation of brentuximab vedotin as a therapeutic intervention for ALCL.[179] NCT01515306 and NCT01634555, two Phase II trials, aimed at testing pharmacokinetic and immunological parameters in patients with advanced solid tumors receiving ramucirumab alone or combined with other chemotherapeutics. Of 65 individuals cumulatively enrolled in these studies, only 9 experienced severe adverse events in response to therapy, including acute renal failure, elevations in circulating hepatic enzymes and neurological/psychiatric problems (source http://www.clinicaltrials.gov).

NCT00947856, a Phase II study, investigated the efficacy of brentuximab vedotin in 110 patients with $CD30^+$ hematological malignancies previously treated with the same tumor-targeting mAb, either as a treatment extension or as a retreatment upon relapse. Twenty-five of these patients experiences serious adverse effects, most of which required treatment discontinuation. However, objective responses were recorded in 68% of participants retreated with brentuximab vedotin upon disease relapse. NCT00639509, NCT00683475 and NCT00986674, three Phase II studies, tested cixutumumab (a fully human IgG1 targeting IGF1R)[180] alone or combined with chemo- or immunochemotherapy, in patients with HCC, NSCLC or prostate carcinoma. Of 24 HCC patients treated with cixutumumab only, 11 (45.83%) experienced serious adverse effects, including 4 deaths, progression-free rate at 4 mo being 30%. Of 90 NSCLC individuals receiving cixutumumab in the context of combinatorial chemotherapy, 63 (70.00%) experienced severe toxicities, median PFS and OS being 4.2 and 7.7 mo, respectively, for patients administered with cixutumumab, carboplatin and paclitaxel, and 4.0 and 8.8 mo, respectively, for patients treated with cixutumumab, carboplatin, paclitaxel and cetuximab. Of 66 patients treated with cixutumumab plus mitoxantrone and prednisone, 40 (60.61%) were affected by serious adverse events, including 4 deaths, median PFS and OS being 4.1 and 10.8 months, respectively.

NCT00683475 also evaluated ramucirumab in combination with mitoxantrone and prednisone in prostate carcinoma patients. Of 66 individuals receiving this immunochemotherapeutic regimen, 36 (54.55%) experienced severe side effects, including 1 death, median PFS and OS being 6.7 and 13.0 mo, respectively. NCT00627042, a Phase II trial, tested ramucirumab as a standalone intervention in 42 chemotherapy-naïve HCC patients. Severe adverse reactions were recorded in 24 patients (57.14%), median PFS and OS being 4.0 and 12.0 mo, respectively. NCT00862784, a Phase II study, evaluated the therapeutic profile of ramucirumab administered in the context of the mFOLFOX6 regimen in 48 subjects with CRC. Eighteen of these patients experienced serious side effects, median PFS was 11.5 mo, and 1-y ORR 85%.[181] NCT01005355, a Phase I study, tested the safety of three distinct doses of ramucirumab, given as a standalone therapeutic intervention, in 15 patients with advanced solid tumors. Only 1 out of 6 patients treated with 10 mg/kg ramucirumab experienced Grade 3–4 side effects. NCT01253525, a Phase I trial, investigated the safety and pharmacokinetic profile of ramucirumab administered in combination with paclitaxel in six subjects with advanced gastric adenocarcinoma. None of these individuals was affected by dose-limiting toxicities. NCT01286818, a Phase 1 study, tested ramucirumab combined with folinic acid, 5-fluorouracil and irinotecan (FOLFIRI) in six CRC patients progressing on bevacizumab, oxaliplatin, and a fluoropyrimidine. All patients experienced at

least one Grade 3 adverse event, and five of them had to be temporarily withdrawn from ramucirumab or FOLFIRI to manage such toxicities. Median PFS was 7.3 mo.[182] NCT01427933, a Phase II trial, evaluated the efficacy of ramucirumab plus eribulin (an FDA-approved mitotic inhibitor)[183,184] vs. eribulin alone in a total of 141 metastatic breast carcinoma patients. The addition of ramucirumab to eribulin-based chemotherapy did not significantly improve PFS, but increased the incidence of various side effects, including fatigue, headache, hypertension, diarrhea, and bleeding.[185] NCT01567163, a Phase II study, evaluated the pharmacokinetic profile of ramucirumab administered in combination with docetaxel in 22 subjects with advanced solid tumors. Of these patients, 18 completed at least two cycles of treatment and were therefore amenable to evaluation. The co-administration of ramucirumab appeared not to influence the pharmacokinetics of docetaxel.[186] Finally, to the best of our knowledge, the results of NCT00791011, NCT01026415, NCT01298401, NCT01413191, NCT01418495, NCT01425736, NCT01431547, NCT01531998, and NCT01592045 have not been disseminated yet (source http://www.clinicaltrials.gov).

Concluding Remarks

The huge number of clinical trials recently initiated to assess the safety or efficacy of tumor-targeting mAbs indicates that the interest of oncologists and pharmaceutical companies in this immunotherapeutic paradigm remains very high. Indeed, enormous human and economic resources are still being invested in the preclinical and clinical development of tumor-targeting mAbs. Only in the last few months, such an effort led to the approval of three novel molecules of this class for use in cancer patients. As it stands, it is difficult to predict for how long tumor-targeting mAbs will be under the limelight and how they will impact the clinical management of cancer on the long term. Production-associated costs undoubtedly limit the number of patients to which these immunotherapeutic agents are accessible.[187] Moreover, as for many other forms of immunotherapy,[68,188,189] the insurgence of antigen loss variants may underlie the development of resistance,[190-192] especially when tumor-targeting mAbs block dispensable TAAs or interrupt replaceable trophic circuitries. Finally, potent mAbs (e.g., trastuzumab) as well as some BiTEs and mAb-drug conjugates are associated (in a fraction of patients) with non-negligible off-target effects, which generally require treatment discontinuation.[193] The development of technological platforms allowing for the production of clinical grade mAbs at reduced costs, the identification of highly specific and targetable TAAs to which malignant cells are obligatorily addicted, and the optimization of first-generation molecules that have already been introduced into the clinical practice in spite of some degree of toxicity is expected to expand further the benefits of this immunotherapeutic paradigm.

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