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Trial Watch

Tumor-targeting monoclonal antibodies in cancer therapy

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Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; CLL, chronic lymphocytic leukemia; CRC, colorectal carcinoma; DLBCL, diffuse large B-cell lymphoma; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; EPCAM, epithelial cell adhesion molecule; FDA, Food and Drug Administration; HNSCC, head and neck squamous cell carcinoma; IGF1R, insulin-like growth factor 1 receptor; IL, interleukin; mAb, monoclonal antibody; MMAE, monomethyl auristatin E; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung carcinoma; TAA, tumor-associated antigen; TNFα, tumor necrosis factor α; VEGF, vascular endothelial growth factor

In 1997, for the first time in history, a monoclonal antibody (mAb), i.e., the chimeric anti-CD20 molecule rituximab, was approved by the US Food and Drug Administration for use in cancer patients. Since then, the panel of mAbs that are approved by international regulatory agencies for the treatment of hematopoietic and solid malignancies has not stopped to expand, nowadays encompassing a stunning amount of 15 distinct molecules. This therapeutic armamentarium includes mAbs that target tumor-associated antigens, as well as molecules that interfere with tumor-stroma interactions or exert direct immunostimulatory effects. These three classes of mAbs exert antineoplastic activity via distinct mechanisms, which may or may not involve immune effectors other than the mAbs themselves. In previous issues of *OncoImmunology*, we provided a brief scientific background to the use of mAbs, all types confounded, in cancer therapy, and discussed the results of recent clinical trials investigating the safety and efficacy of this approach. Here, we focus on mAbs that primarily target malignant cells or their interactions with stromal components, as opposed to mAbs that mediate antineoplastic effects by activating the immune system. In particular, we discuss relevant clinical findings that have been published during the last 13 months as well as clinical trials that have been launched in the same period to investigate the therapeutic profile of hitherto investigational tumor-targeting mAbs.

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Introduction

The proof-of-concept that high amounts of antibodies exhibiting the same antigen specificity can be produced in a cost-effective manner has been first been provided in 1975 by the German biologist Georges Köhler and the Argentinian biochemist César Milstein.[1] This milestone discovery, which granted to Köhler and Milstein the 1984 Nobel Prize for Medicine or Physiology, not only has revolutionized countless experimental applications and diagnostic procedures, but also has generated a growing armamentarium of highly specific therapeutic agents.[2,3] Indeed, a large panel of monoclonal antibodies (mAbs) is nowadays approved by the US Food and Drug Administration (FDA) and other international regulatory agencies, including the European Medicines Agency (EMA), for the treatment of disorders as diverse as autoimmune diseases and cancer.[2,3] In 1997, rituximab, a chimeric (meaning that it contains both human and murine domains) molecule specific for the B-cell lineage marker CD20 was the first mAb to be licensed for use in cancer patients, i.e., individuals with non-Hodgkin's lymphoma (NHL) relapsing upon conventional chemotherapy.[4] Since then, no less than 15 distinct mAbs have been approved for the treatment of hematopoietic and solid neoplasms, encompassing: (1) mAbs that exert an antineoplastic activity as they primarily bind to

Table 1. Tumor-targeting mAbs 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'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
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 (emtansine)	HER2	1998	Hzed IgG1	Breast carcinoma (naked or coupled to mertansine) and gastric or gastresophageal junction cancer

Abbreviations: C, chimeric; EGFR, epidermal growth factor receptor; EPCAM, epithelial cell adhesion molecule; H, human; HNC, head and neck cancer; Hzed, humanized; M, murine; mAb, monoclonal antibody; MMAE, monomethyl auristatin E; R, rat; RANKL, receptor activator of NF-κB ligand; VEGF, vascular endothelial growth factor. *by the US Food and Drug Administration or European Medicines Agency at the day of submission. **updated from ref. 12

proteins preferentially expressed on the surface of neoplastic, as opposed to non-malignant, cells; (2) mAbs that neutralize trophic signals provided by the tumor stroma; and (3) so-called immunostimulatory mAbs, i.e., mAbs that mediate therapeutic effects as they bind to, and hence modulate the activity of, cells of the immune system, de facto eliciting a novel or reactivating a pre-existing immune response against malignant cells. In 2 previous issues of *OncoImmunology*,[5,6] we have discussed the scientific rationale behind the use of mAbs, all types confounded, in cancer therapy, as well as the clinical development of (1) mAbs that have not yet been approved by the US FDA for use in humans, and (2) FDA-approved mAbs employed as off-label therapeutic interventions. As this area of clinical investigation is continuously expanding, here we will maintain the approach that we adopt in our Trial Watch series,[7-10] but we will restrict our attention on mAbs that mediate antineoplastic effects by primarily targeting cancer cells and/or the trophic support that they receive from the tumor stroma, which we cumulatively refer to as "tumor-targeting" mAbs (**Table 1**). Recent advances on the use of immunostimulatory antibodies in cancer therapy[11-16] will be discussed in the next Trial Watch.

For illustrative purposes, tumor-targeting mAbs can be sub-grouped into 6 non-mutually exclusive classes,[17] based on functional considerations: (1) mAbs that inhibit cancer cell-intrinsic signal transduction pathways that are required for survival and/or proliferation, such as cetuximab, a chimeric IgG1 specific for the epidermal growth factor receptor (EGFR), which is currently approved for the treatment of head and neck cancer and colorectal carcinoma (CRC);[18,19] (2) mAbs that activate cytotoxic receptors expressed by cancer cells (e.g., tumor necrosis factor receptor superfamily, member 10B, TNFRSF10B, best known as TRAILR2 or DR5), hence actively triggering their apoptotic demise, such as the fully human TRAILR2-specific IgG1 conatumumab;[20] (3) mAbs that bind (but not necessarily inhibit the activity of) tumor-associated antigens (TAAs) and exert antineoplastic effects as they engage effector mechanisms of innate immunity, including antibody-dependent cell-mediated cytotoxicity (ADCC),[3,21-24] antibody-dependent cellular phagocytosis (ADCP),[25] and complement-dependent cytotoxicity (CDC),[26,27] such as rituximab, which is widely employed for the treatment of chronic lymphocytic leukemia (CLL) and NHL;[28-30] (4) trifunctional (bispecific) mAbs, which can crosslink 2 distinct antigens (generally, one TAA and one T-cell marker) while preserving the capacity of activating immune effector functions via their constant fragment, such as catumaxomab, a chimeric (mouse and rat) mAb specific for CD3 and epithelial cell adhesion molecule (EPCAM) that is currently licensed for the therapy of malignant ascites in patients with $EPCAM^+$ tumors;[31,32] (5) immunoconjugates, i.e., TAA-specific mAbs coupled to toxins or radionuclides, such as the CD20-targeting molecules ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab, which are nowadays used in the treatment of NHL;[33,34] and (6) mAbs that interfere with the trophic interaction between neoplastic cells and the tumor stroma, such as the vascular endothelial growth factor (VEGF)-directed mAb bevacizumab, which is currently approved for use in patients affected by CRC as well as lung and renal cancer.[35,36] It should be kept in mind that several

tumor-targeting mAbs exert antineoplastic effects via multiple of these mechanisms. For instance, cetuximab not only inhibits EGFR signaling, but also triggers ADCC,[37] and has a direct immunostimulatory activity.[38]

Since the submission of our latest Trial Watch on this topic (October 2012),[5] the US FDA has approved bevacizumab for use in combination with fluoropyrimidine/irinotecan- or fluoropyrimidine/oxaliplatin-based chemotherapy for the treatment of patients with metastatic CRC whose disease has progressed in spite of first-line bevacizumab-based therapy.[39] Of note, bevacizumab had been licensed by the US FDA as first- or second-line therapeutic intervention in subjects affected by metastatic CRC as early as in 2004 and 2006, respectively.[40-42] During the last 13 mo, the US FDA has also extended the approval of denosumab, a human IgG2 specific for receptor activator of NF-κB ligand (RANKL), to unresectable giant cell tumors of the bone in adults and skeletally mature adolescents.[43,44] Besides being employed in postmenopausal women at risk for osteoporosis, denosumab is licensed by the US FDA since 2011 for use in patients at high risk of bone fracture as they undergo androgen-deprivation therapy for non-metastatic prostate cancer, or adjuvant aromatase inhibitor therapy for breast cancer.[45] On 2013, February, 22nd, the US FDA approved trastuzumab emtansine, a humanized IgG1 specific for *v-erb-b2* avian erythroblastic leukemia viral oncogene homolog 2 (ERBB2, best known as HER2) coupled to the cytotoxic agent mertansine, for use in women bearing $HER2^+$ metastatic breast carcinoma who previously received naked trastuzumab (which is approved for use in breast carcinoma patients since 1998) and a taxane, separately or in combination.[46,47] Finally, no earlier than on 2013, September 30th, the US FDA granted accelerated approval to pertuzumab (a humanized IgG1 specific for HER2) for use in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with $HER2^+$, locally advanced, inflammatory, or early-stage breast cancer.[48] Of note, pertuzumab had previously (on 2012, June 8th) been licensed for use in combination with trastuzumab and docetaxel for the treatment of patients with metastatic $HER2^+$ breast carcinoma who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.[49] However, the recent regulatory extension granted to this tumor-targeting mAB is relevant as pertuzumab in combination with trastuzumab and docetaxel has now become the first FDA-approved neoadjuvant treatment for patients with breast cancer (source http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm370393.htm).

Update on Clinical Reports

Since the submission of our previous Trial Watch dealing with this topic (October 2012),[5] the preclinical and clinical development of mAbs for cancer therapy has proceeded at an unprecedented speed. Indeed, querying PubMed with the string "antibody AND cancer AND patients" as of 2013, October 21st returned more than 3200 entries indexed later than 2012, October 1st. Narrowing down the search to "antibody AND cancer AND patients AND trial" resulted in approximately 600 entries (source http://www.ncbi.nlm.nih.gov/pubmed). Although this figure (1) refers to mAbs all types confounded and (2) is expected to comprise a number of review articles, commentaries and false-positive hits (i.e., scientific reports that do not deal with the clinical development of mAb although they do contain all these keywords), it is representative of the huge interest that this therapeutic modality continues to attract. Obviously, a significant fraction of the clinical reports published during the last 13 mo on the use of tumor-targeting mAbs in cancer patients refers to the use of FDA-approved molecules as on-label interventions. This is the case of studies comparing experimental interventions to gold standard therapeutic approaches, when the latter involves a tumor-targeting mAb, as well as of studies that investigated whether some FDA-approved tumor-targeting mAbs can be safely and effectively administered at different doses and/or via different routes and/or according to alternative schedules. In line with the scope of our Trial Watch (see above), we will not consider these studies further. Rather, we will focus on experimental mAbs or FDA-approved mAbs employed as off-label interventions.

Experimental mAbs

The results of no less than 33 clinical studies investigating the safety and efficacy of hitherto experimental tumor-targeting mAbs in cancer patients have been published during the last 13 mo (**Table 2**). The therapeutic paradigms investigated by these studies are relatively heterogeneous, encompassing the inhibition of cancer cell-intrinsic survival pathways, the active elicitation of endogenous signal transduction cascades with pro-apoptotic effects, the engagement of immune effectors, the selective delivery to neoplastic cells of cytotoxic agents or radionuclides as well as the blockade of trophic molecules produced by the tumor stroma and/or their receptors. Among the strategies that nowadays appear to attract more interest is the mAb-mediated inhibition of insulin-like growth factor 1 receptor (IGF1R), an anti-apoptotic signal transducer that is overexpressed by a large panel of tumors.[50] Thus, 3 distinct IGF1R-specific mAbs, namely, ganitumab (a fully human IgG1 also known as AMG 479),[51] cixutumumab (a fully human IgG1 also known as IMC-A12),[52] and AVE1642 (a humanized IgG1),[53,54] have recently been tested, either as a standalone intervention, either combined with conventional chemotherapeutic agents (e.g., docetaxel, doxorubicin, and gemcitabine), or given together with temsirolimus (an inhibitor of the mammalian target of rapamycin currently approved by FDA for the treatment of renal cell carcinoma),[55] in cohorts of patients affected by bone and soft tissue sarcomas,[56] pancreatic tumors,[57] locally advanced or metastatic breast carcinomas,[58] and advanced solid tumors.[59-61] In all these studies, anti-IGF1R antibodies were well tolerated and displayed promising clinic activity, at least in a subset of patients.

Another approach that has been investigated in several recent clinical studies is the therapeutic activation of TRAILR2.[62] Indeed, although both normal and malignant cells express TRAILR2, the latter appear to be more susceptible to TRAILR2 agonists than the former, for hitherto unclear reasons.[62,63] During the last 13 mo, the results of 5 distinct studies investigating the

Table 2. Recently published clinical trials assessing the therapeutic profile of hitherto investigational tumor-targeting mAbs.[*,***]

mAb	Target(s)	Indication(s)	Phase	Note	Ref.
1D09C3	HLA-DR	CLL Lymphoma	I	As single agent	94
AGS-1C4D4	PSCA	Pancreatic cancer	II	Combined with gemcitabine	95
AVE1642	IGF1R	Solid tumors	I	Combined with docetaxel	60
			I	Combined with docetaxel, gemcitabine, erlotinib or doxorubicin	59
Blinatumomab (MEDI-538)	CD3 CD19	Acute lymphoblastic leukemia	II	As single agent or followed by HSCT	96
Carlumab (CNTO 888)	CCL2	Prostate cancer	II	As single agent	88
		Solid tumors	I	As single agent	86
Cixutumumab (IMC-A12)	IGF1R	Bone or soft-tissue sarcomas	II	Combined with temsirolimus	56
		Renal cell carcinoma	I	Combined with temsirolimus	249
Clivatuzumab tetraxetan	MUC1	Pancreatic cancer	I	Coupled with ^{90}Y and combined with low-dose gemcitabine	117
Conatumumab (AMG 655)	TRAILR2	Colorectal carcinoma	II	Combined with bevacizumab plus folinic acid-, 5-FU- and oxaliplatin-based chemotherapy	65
		Lung cancer	II	Combined with paclitaxel plus carboplatin	64
		Pancreatic cancer	II	Combined with ganitumab and gemcitabine	57
Drozitumab (PRO95780)	TRAILR2	Colorectal carcinoma	Ib	Combined with bevacizumab plus folinic acid-, 5-FU- and oxaliplatin-based chemotherapy	67
Farletuzumab (MORAb-003)	FOLR1	Ovarian carcinoma	II	As single agent or combined with platinum- or taxane-based chemotherapy	97
GC33 (RO5137382)	GPC3	Hepatocellular carcinoma	I	As single agent	98
Ganitumab (AMG 479)	IGF1R	Breast carcinoma	II	As single agent	58
		Pancreatic cancer	II	Combined with conatumumab and gemcitabine	57
Inotuzumab ozogamicin (CMC-544)	CD22	Non-Hodgkin's lymphoma	I/II	Combined with rituximab	99
Intetumumab (CNTO 95)	ITGA5	Prostate cancer	II	Combined with docetaxel and prednisone	100
KRN330	GPA33	Colorectal cancer	I	As single agent	101
L19	FN1	Solid tumors	I/II	As a shuttle to deliver TNFα to the tumor vasculature	120
Lexatumumab (HGS-ETR2)	TRAILR2	Solid tumors	I	As single agent	66
Lintuzumab (SGN-33)	CD33	Acute myeloid leukemia	IIb	Combined with low-dose cytarabine	108
MIK-β1 (MA1–35896)	IL2RB	T-LGL leukemia	I	As single agent	93
Nimotuzumab (h-R3)	EGFR	NSCLC	I	Combined with gefitinib	102
Obinutuzumab (GA101)	CD20	Non-Hodgkin's lymphoma	I	As single agent	103
Rilotumumab (AMG 102)	HGF	Prostate cancer	II	Combined with mitoxantrone plus prednisone	91

Table 2. Recently published clinical trials assessing the therapeutic profile of hitherto investigational tumor-targeting mAbs.*,** (continued)					
mAb	**Target(s)**	**Indication(s)**	**Phase**	**Note**	**Ref.**
Ramucirumab (IMC-1121B)	VEGFR2	Hepatocellular carcinoma	II	As single agent	77
		Gastresophageal adenocarcinoma	III	As single agent	76
		Lung cancer	III	Combined with docetaxel	78
Trebananib (AMG 386)	ANGPT1 ANGPT2	Solid tumors	I	As single agent	87
Volociximab (M200)	ITGA5 ITGB1	NSCLC	Ib	Combined with carboplatin and paclitax	107

Abbreviations: 5-FU, 5-fluorouracil; ANGPT, angiopoietin; CCL2, chemokine (C-C motif) ligand 2; CLL; chronic lymphocytic leukemia; EGFR, epidermal growth factor receptor; FN1, fibronectin 1; FOLR1, folate receptor 1 (adult); GPA33, glycoprotein A33; GPC3, glypican 3; HGF, hepatocyte growth factor; HSCT, hematopoietic stem cell transplantation; IGF1R, insulin-like growth factor 1 receptor; IL2RB, IL-2 receptor β; ITGA5, integrin α5; ITGB1, integrin β1; mAb, monoclonal antibody; MUC1, mucin 1; NSCLC, non-small cell lung carcinoma; PSCA, prostate stem cell antigen; T-LGL, T-cell large granular lymphocytic; TRAILR2, TNFα-related apoptosis-inducing ligand receptor 2; VEGFR2, vascular endothelial growth factor receptor 2. *between 2012, October 1st and the day of submission. **refers to mAbs that directly bind cancer cells or block trophic signals provided by the tumor stroma.

safety and clinical profile of TRAILR2-activating mAbs in cancer patients have been published.[57,64-67] In particular, these studies tested (1) conatumumab (a human IgG1 also known as AMG 655)[20,68,69] in combination with gemcitabine-based chemotherapy for the treatment of pancreatic cancer,[57] with paclitaxel plus carboplatin for the first-line treatment of advanced non-small-cell lung carcinoma (NSCLC),[64] or with bevacizumab plus a folinic acid-, 5-fluorouracil, and oxaliplatin-based chemotherapeutic regimen (generally known as mFOLFOX6) for the first-line treatment of metastatic CRC;[65] (2) drozitumab (a human IgG1 also known as PRO95780)[70,71] in combination with bevacizumab plus mFOLFOX6 as a first-line intervention against metastatic CRC;[67] and (3) lexatumumab (a human IgG1 also known as HGS-ETR2)[72-74] as a standalone intervention in pediatric patients affected by solid tumors.[66] In these clinical cohorts, TRAILR2-activating mAbs were well tolerated. The therapeutic potential of this approach, however, seems limited, as poor (if any) clinical responses have been documented among patients receiving TRAILR2-activating mAbs.

There are several means for blocking the trophic support that stromal cells normally provide to their malignant counterparts. By antagonizing VEGF receptor 2 (VEGFR2) signaling, ramucirumab (a human IgG1 also known as IMC-1121B), blocks perhaps the most prominent of these interactions, *i.e.*, neoangiogenesis.[75] Ramucirumab has recently been tested as a standalone intervention in patients affected by advanced gastric or gastresophageal junction adenocarcinoma and hepatocellular carcinoma,[76,77] as well as in combination with docetaxel for the treatment of stage IV NSCLC patients progressing upon one cycle of platinum-based therapy.[78] More frequently, however, mAbs are devised to block the crosstalk between neoplastic cells and their stroma by neutralizing soluble mediators. The precursor of this class of tumor-targeting mAbs is bevacizumab (which targets VEGF), but several other molecules operate in a similar fashion, including carlumab (a human IgG1 also known CNTO 888), which neutralizes chemokine (C-C motif) ligand 2 (CCL2);[79] trebananib (also known AMG 386), a peptibody (*i.e.*, a fusion between a biologically active peptide and the constant fragment of a mAb) that blocks angiopoietin 1 and 2;[80-82] and rilotumumab (a human IgG2 also known as AMG 102), which binds to—hence neutralizing—hepatocyte growth factor (HGF).[83-85] During the last 13 mo, carlumab and trebananib have been employed for dose-escalation studies in patients affected by advanced solid tumors,[86-88] while rilotumumab has been tested in combination with mitoxantrone (an anthracycline that induces the immunogenic demise of cancer cells)[8,89,90] and prednisone in patients with progressive, taxane-refractory castration-resistant prostate cancer.[91,92] All these agents were well tolerated, yet only trebananib was associated with durable antitumor activity in a fraction of patients.[87]

Among several other therapeutic strategies based on hitherto experimental tumor-targeting mAbs,[93-108] great interest is attracted by immunoconjugate-based regimens. This approach is very flexible, as it can be harnessed to shuttle chemicals,[109] radionuclides,[110] as well as biologically active factors (e.g., cytokines)[111-113] to virtually any cellular component of neoplastic lesions, provided that these components express (ideally in a restricted manner) an antigenic moiety on their surface.[114] Recently, ^{90}Y-conjugated clivatuzumab tetraxetan, a humanized mAb specific for mucin 1 (MUC1, which is frequently overexpressed or aberrantly glycosylated in multiple carcinomas),[115,116] has been employed in combination with low-dose gemcitabine (an immunostimulatory therapeutic regimen)[11,12] in patients bearing advanced pancreatic neoplasms.[117] On a slightly different note, a tumor necrosis factor α (TNFα)-armed variant of L19, a human single chain variable fragment targeting the extra domain B (EDB) of fibronectin (which is predominantly expressed by the tumor-associated vasculature),[118,119] has been tested as a standalone therapeutic intervention in patients with advanced solid tumors.[120] Interestingly, these studies demonstrated some clinical activity for ^{90}Y-conjugated clivatuzumab tetraxetan,[117] but not for the TNFα-L19 fusion.[120] However, the maximal tolerated dose of TNFα-L19 was not attained in this trial, leaving room for further tests at increased doses and/or in combination with conventional therapeutic regimens.

Table 3. Recently published clinical trials assessing the therapeutic profile of FDA-approved tumor-targeting mAbs employed as off-label anticancer interventions.*,**

mAb	Target(s)	Indication(s)	Phase	Note	Ref.
Bevacizumab	VEGF	Angiosarcoma and epithelioid hemangioendotheliomas	II	As a single agent	154
		Breast carcinoma	n.a.	Coupled to ^{89}Zr as a diagnostic tool	155
			II	Combined with docetaxel plus capecitabine	126
			II	Combined with docetaxel plus cisplatin	128
			II	Combined with gemcitabine	129
			II	Combined with trastuzumab plus docetaxel	48
			III	Combined with docetaxel	125
			III	Combined with capecitabine or paclitaxel	130
			III	Combined with capecitabine or paclitaxel	127
			III	Combined with trastuzumab plus docetaxel	156
		Cervical cancer	II	Combined with topotecan plus cisplatin	147
		Colorectal carcinoma	II/III	Combined with folinic acid, 5-FU, oxaliplatin and irinotecan	145
		Endometrial carcinoma	II	Combined with temsirolimus	150
		Gastresophageal adenocarcinoma	II/III	Combined with epirubicin, cisplatin and capecitabine	152
		Hepatocellular carcinoma	n.a.	Combined with erlotinib	133
			I	Combined with rapamycin	132
			II	Combined with erlotinib	135
			II	Combined with erlotinib	134
			II	After transhepatic arterial chemoembolization	136
		HNSCC	II	Combined with cisplatin plus IRMT	123
			II	Combined with cetuximab	124
		Leukemia	II	Combined with cytarabine	121
		Melanoma	II	Combined with temozolomide or albumin-bound paclitaxel plus carboplatin	131
		Multiple myeloma	II	Combined with bortezomib	122
		Ovarian carcinoma	n.a.	As a single agent	139
			n.a.	Combined with gemcitabine plus oxaliplatin	140
			II	Combined with docetaxel within 12 months of platinum-based therapy	138
			II	Combined with PLD	143
			II	Combined with albumin-bound paclitaxel	142
			III	Combined with carboplatin plus paclitaxel	141
		Pancreatic cancer	II	Combined with gemcitabine plus 5-FU	137
		Prostate cancer	II	Combined with docetaxel	144
		Urothelial carcinoma	II	Combined with gemcitabine plus carboplatin	149
		Metastatic solid tumors	I	Combined with vincristine, irinotecan and temozolomide	146
			I	Combined with albumin-bound paclitaxel plus gemcitabine	148
			I	Combined with sorafenib plus low-dose cyclophosphamide	151
			I	Combined with temsirolimus plus liposomal doxorubicin	153

Table 3. Recently published clinical trials assessing the therapeutic profile of FDA-approved tumor-targeting mAbs employed as off-label anticancer interventions.*,** (continued)

mAb	Target(s)	Indication(s)	Phase	Note	Ref.
Cetuximab	EGFR	Bone or soft-tissue sarcomas	II	As a single agent	179
		Breast carcinoma	II	Combined with cisplatin	166
		Cervical cancer	I	Combined with cisplatin	177
		Esophageal cancer	I	As part of a chemoradiotherapeutic regimen	168
			II/III	As part of a chemoradiotherapeutic regimen	167
		Gastric cancer	III	Combined with capecitabine plus cisplatin	169
		Lung cancer	I	Combined with bevacizumab plus erlotinib	170
			II	Combined with bevacizumab, paclitaxel and carboplatin	171
		Pancreatic cancer	n.a.	Combined with gemcitabine plus IRMT	172
			II	Combined with gemcitabine plus oxaliplatin	173
			I/II	Combined with everolimus plus capecitabine	174
		Prostate cancer	II	Combined with docetaxel	176
		Urothelial carcinoma	II	Combined with paclitaxel	178
		Solid tumors	n.a.	As a single agent	175
			I	As a carrier for doxorubicin-loaded immunoliposomes	180
Denosumab	RANKL	Lung cancer	III	As a single agent	181
Ofatumumab	CD20	Small lymphocytic lymphoma	I	As single agent	186
Panitumumab	EGFR	Gastresophagic cancer	III	Combined with epirubicin, oxaliplatin and capecitabine	185
		HNSCC	III	Combined with cisplatin plus 5-FU	182
		Ovarian carcinoma	II	Combined with PLD	183
Pertuzumab	HER2	NSCLC	Ib	Combined with erlotinib	104
		Ovarian carcinoma	II	Combined with carboplatin	105
Rituximab	CD20	B-cell malignancies	I	Combined with rIL-21	184

Abbreviations: 5-FU, 5-fluorouracil; EGFR, epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; IL, interleukin; IMRT, intensity-modulated radiation therapy; mAb, monoclonal antibody; n.a., not available; NSCLC, non-small cell lung carcinoma; PLD, pegylated liposomal doxorubicin; r, recombinant; RANKL, receptor activator of NF-κB ligand; VEGF, vascular endothelial growth factor. *between 2012, October 1st and the day of submission. **refers to mAbs that directly bind cancer cells or block trophic signals provided by the tumor stroma.

FDA-approved mAbs tested as off-label interventions

Testing FDA-approved drugs on indications for which they have not yet been licensed is advantageous in that safety concerns are generally limited. Accordingly, there is an intense wave of clinical investigation that aims at determining whether FDA-approved tumor-targeting mAbs employed as off-label interventions may provide clinical benefits to cancer patients. During the last 13 mo, the results of no less than 60 clinical trials of this type have been published in peer-reviewed scientific journals (**Table 3**). The largest fraction of these studies involved the VEGF-targeting mAb bevacizumab, which has been tested, most often in combination with conventional chemotherapy and/or targeted anticancer agents, in cohorts of patients affected by acute myeloid leukemia,[121] multiple myeloma,[122] head and neck squamous cell carcinoma (HNSCC),[123,124] breast carcinoma,[48,125-130] melanoma,[131] hepatocellular carcinoma,[132-136] pancreatic cancer,[137] ovarian carcinoma,[138-143] prostate cancer,[144] and several other advanced or metastatic solid tumors.[145-154] Moreover, ^{89}Zr-conjugated bevacizumab has been investigated as a means to visualize neoplastic lesions by positron emission tomography (PET) in women with primary breast carcinomas, which often secrete high levels of VEGF.[155] In the context of a randomized Phase III clinical trial, the addition of bevacizumab to docetaxel and trastuzumab failed to improve the progression-free survival of HER2$^+$ metastatic breast cancer patients.[156] Along similar lines, in patients with HER2$^-$ metastatic or locally recurrent breast carcinoma, the combination of bevacizumab with capecitabine (a precursor of 5-fluorouracil) failed to meet the non-inferiority criterion as compared with a therapeutic regimen involving bevacizumab and paclitaxel (a microtubular poison of the taxane family).[127] Earlier, the addition of bevacizumab had been suggested to improve the efficacy of multiple taxanes, including paclitaxel and docetaxel, against breast carcinoma.[157,158] Thus, the clinical profile of specific, but not all, chemotherapeutics employed for the treatment of breast carcinoma may be ameliorated from the co-administration of bevacizumab. Nonetheless, on 2011,

Table 4. Clinical trials recently launched to evaluate the therapeutic profile of tumor-targeting monoclonal antibodies in investigational settings.[***]

mAb	Target(s)	Indication(s)	Phase	Status	Note	Ref.
Alemtuzumab	CD52	Hematological malignancies	I/II	Not yet recruiting	In combination with genetically modified T cells	NCT01875237
		Peripheral T-cell lymphoma	II	Completed	As a consolidation regimen upon cyclophosphamide-based chemotherapy	NCT01806337
BC8	CD45	Hematological malignancies	I/II	Not yet recruiting	Followed by BEAM chemotherapy and ASCT	NCT01921387
Bevacizumab	VEGF	Brain tumors	II	Recruiting	As single agent	NCT01767792
		Breast carcinoma	0	Not yet recruiting	As ^{89}Zr-bevacizumab radiotracer	NCT01894451
			II	Not yet recruiting	Combined with carboplatin, cyclophosphamide or paclitaxel	NCT01898117
			II	Not yet recruiting	Combined with eribulin	NCT01941407
			II	Not yet recruiting	Combined with cyclophosphamide, doxorubicin and paclitaxel	NCT01959490
			II	Recruiting	Combined with paclitaxel	NCT01722968
		Glioma	I/II	Recruiting	Combined with temozolomide and vitamin C	NCT01891747
			II	Recruiting	Combined with radiation therapy	NCT01743950
		Lymphoma	II	Recruiting	Combined with gemcitabine-based chemotherapy	NCT01921790
		Melanoma	II	Not yet recruiting	Combined with paclitaxel-based chemotherapy	NCT01879306
			II	Not yet recruiting	Combined with ipilimumab	NCT01950390
		MM	n.a.	Recruiting	As ^{89}Zr-bevacizumab radiotracer	NCT01859234
		Ovarian cancer	II	Not yet recruiting	Combined with trabectedin ± carboplatin	NCT01735071
			II	Recruiting	Combined with carboplatin and paclitaxel	NCT01739218
			II	Recruiting	Combined with paclitaxel	NCT01770301
			II	Recruiting	Combined with carboplatin and paclitaxel	NCT01838538
			II	Recruiting	Combined with carboplatin and paclitaxel	NCT01847677
			III	Active not recruiting	Combined with carboplatin and PLD	NCT01837251
			III	Not yet recruiting	Combined with carboplatin and gemcitabine or paclitaxel or PLD	NCT01802749
		Reproductive tract cancers	II	Recruiting	Combined with carboplatin and paclitaxel	NCT01770171
			II	Recruiting	Combined with gemcitabine ± platinum based chemotherapy	NCT01936974
			II	Terminated with results	Followed by abraxane infusion	NCT01821859
		Rhabdomyosarcoma	II	Recruiting	Combined with cyclophosphamide-based chemotherapy	NCT01871766
		Sarcoma	I	Recruiting	Combined with doxorubicin and radiation therapy	NCT01746238
		Sarcoma and neuroectodermal tumors	II	Not yet recruiting	Combined with cyclophosphamide-based chemotherapy	NCT01946529
		Advanced or metastatic solid tumors	I	Not yet recruiting	Combined with lurbinectedin and paclitaxel	NCT01831089
			I	Recruiting	Combined with tivantinib	NCT01749384
			I	Recruiting	As single agent	NCT01847118
			II	Not yet recruiting	As single agent	NCT01898130
			II	Recruiting	Combined with cisplatin and pemetrexed	NCT01951482
Blinatumomab	CD3 CD19	DLBCL	II	Recruiting	As single agent	NCT01741792

Table 4. Clinical trials recently launched to evaluate the therapeutic profile of tumor-targeting monoclonal antibodies in investigational settings.[***] (continued)

mAb	Target(s)	Indication(s)	Phase	Status	Note	Ref.
Brentuximab vedotin	CD30	AML	I	Recruiting	Combined with immunogenic chemotherapy	NCT01830777
		DLBCL	II	Recruiting	Combined with cyclophosphamide-based chemotherapy	NCT01925612
		Germ cell tumors	II	Not yet recruiting	As single agent	NCT01851200
		Lymphoma	I/II	Recruiting	Combined with rituximab	NCT01805037
			III	Recruiting	Combined with cyclophosphamide-based chemotherapy	NCT01777152
		Mast cell leukemia	n.a.	Not yet recruiting	As single agent	NCT01807598
		Peripheral T-cell lymphoma	n.a.	Not yet recruiting	As single agent	NCT01841021
Catumaxomab	CD3 EPCAM	Gastric peritoneal carcinomatosis	II	Recruiting	As single agent	NCT01784900
		Ovarian cancer	II	Recruiting	As single agent	NCT01815528
Cetuximab	EGFR	Brain tumors	I/II	Recruiting	Combined with bevacizumab	NCT01884740
		Esophageal cancer Gastric cancer	II	Recruiting	Combined with cisplatin, 5-FU and radiotherapy	NCT01787006
			II	Completed	Combined with carboplatin, paclitaxel and radiotherapy	NCT01904435
		Advanced solid tumors	I	Recruiting	Combined with erlotinib	NCT01727869
			I	Recruiting	Combined with irinotecan and vemurafenib	NCT01787500
Ch14.18	GD2	Neuroblastoma	II	Recruiting	Combined with irinotecan and temozolomide	NCT01767194
Conatumumab	TRAILR2	Reproductive tract cancers	I	Not yet recruiting	Combined with birinapant	NCT01940172
Denosumab	RANKL	NSCLC	II	Not yet recruiting	As single agent	NCT01951586
Lintuzumab	CD33	Leukemia	I/II	Recruiting	Combined with cytarabine	NCT01756677
Necitumumab	EGFR	NSCLC	I/II	Recruiting	Combined with cisplatin and gemcitabine	NCT01763788
			II	Recruiting	Combined with carboplatin and paclitaxel	NCT01769391
			II	Recruiting	Combined with cisplatin and gemcitabine	NCT01788566
Nimotuzumab	EGFR	Breast carcinoma	II	Not yet recruiting	Combined with capecitabine and docetaxel	NCT01939054
		Cervical cancer	II	Recruiting	Combined with chemoradiotherapy	NCT01938105
		Gastric cancer	III	Recruiting	Combined with irinotecan	NCT01813253
		NSCLC	I/II	Not yet recruiting	Combined with afatinib	NCT01861223
		Rectal cancer	II	Recruiting	Combined with radiotherapy, capecitabine and oxaliplatin	NCT01899118
Ofatumumab	CD20	Leukemia	II	Not yet recruiting	Combined with cyclophosphamide and fludarabine	NCT01762202
		NHL	I	Recruiting	Combined with rIL-18	NCT01768338
Panitumumab	EGFR	Anal cancer	II	Recruiting	Combined with capecitabine, mitomycin and radiotherapy	NCT01843452
		Bladder cancer	II	Recruiting	Combined with carboplatin and gemcitabine	NCT01916109
Pertuzumab	HER2	Gastric cancer Gastresophageal cancer	III	Recruiting	Combined with capecitabine, cisplatin, 5-FU and trastuzumab	NCT01774786
Rituximab	CD20	B-cell malignancies	I	Recruiting	Combined with a PI3K inhibitor	NCT01905813
		Hodgkin's lymphoma	0	Not yet recruiting	Combined with brentuximab vedotin	NCT01900496
		Neuroblastoma	III	Recruiting	Combined with dexamethasone	NCT01868269
		Prostate cancer	0	Recruiting	As single agent	NCT01804712

Table 4. Clinical trials recently launched to evaluate the therapeutic profile of tumor-targeting monoclonal antibodies in investigational settings.*** (continued)

mAb	Target(s)	Indication(s)	Phase	Status	Note	Ref.
SAR650984	CD38	MM	I	Recruiting	Combined with lenalidomide and dexamethasone	NCT01749969
TF2	CEA	Breast cancer	I/II	Recruiting	As single agent	NCT01730612
		Medullary thyroid carcinoma	I/II	Recruiting	As single agent	NCT01730638
Trastuzumab	HER2	Bladder cancer	II	Active, not recruiting	Combined with carboplatin, cisplatin and gemcitabine	NCT01828736
		Recurrent or metastatic tumors	II	Recruiting	Combined with lapatinib	NCT01771458

Abbreviations: 5-FU, 5-fluorouracil; AML, acute myeloid leukemia; ASCT, autologous stem cell transplantation; BEAM, carmustine + etoposide + cytarabine + melphalan; CEA, carcinoembryonic antigen; DLBCL, diffuse large B-cell lymphoma; EGFR, epidermal growth factor receptor; EPCAM, epithelial cell adhesion molecule; IL, interleukin; mAb, monoclonal antibody; MM, multiple myeloma; n.a., not available; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung carcinoma; PI3K, phosphoinositide-3-kinase; PLD, pegylated liposomal doxorubicin; r, recombinant; RANKL, receptor activator of NF-κB ligand; TRAILR2, TNFα-related apoptosis-inducing ligand receptor 2; VEGF, vascular endothelial growth factor. *between 2012, October 1st and the day of submission. **refers to hitherto investigational tumor-targeting mAbs as well as to FDA-approved tumor-targeting mAbs employed as off-label interventions.

November 18th, the US FDA revoked the authorization that was given to bevacizumab for use in metastatic breast cancer patients (in combination with paclitaxel) in February 2008 (which was originally granted under the FDA accelerated approval program) (source http://www.cancer.gov/cancertopics/druginfo). Of note, plasmatic VEGF may constitute a predictive biomarker for bevacizumab efficacy among breast cancer patients.[125,156] This finding is being prospectively validated in the context of the MERiDiAN trial, a study in which patients will be treated with bevacizumab and paclitaxel upon stratification based on the circulating levels of short VEGF-A isoforms.[159] Finally, the addition of bevacizumab to cytotoxic chemotherapeutics including paclitaxel and carboplatin (a DNA-damaging platinum derivative),[160-162] has been associated with a small but quantifiable decrease in the quality of life of ovarian carcinoma patients.[141] This combinatorial regimen had previously been shown to prolong the disease-free survival of ovarian cancer patients (in particular individuals at high risk for progression) as compared with conventional paclitaxel- or carboplatin-based chemotherapy.[163] Thus, clinicians will have to carefully consider on a per-patient basis whether such a prolongation in disease-free survival is warranted in exchange of a decline in quality of life.

Recently, the safety and efficacy of cetuximab as an off-label therapeutic intervention, most often in combination with conventional chemotherapeutic agents, chemical EGFR inhibitors (such as erlotinib),[164,165] or radiation therapy, have been investigated in patients affected by a large panel of neoplasms, including breast carcinoma,[166] esophageal and gastric cancer,[167-169] NSCLC,[170,171] pancreatic carcinoma,[172-174] and other solid tumors.[175-179] In addition, the tolerability, safety, pharmacokinetics, and efficacy of doxorubicin-loaded liposomes coupled to the antigen-binding fragment of cetuximab have been evaluated in patients with EGFR-overexpressing advanced solid tumors what were no longer amenable to standard treatments.[180] Only one of these studies was a large, open-label randomized Phase III trial, assessing the addition of cetuximab to capecitabine/cisplatin-based chemotherapy in patients with advanced gastric or gastresophageal junction cancer (EXPAND trial).[169] In this context, 904 patients (followed at 164 cancer centers in 25 distinct countries) were randomized at a 1:1 ratio to receive 3-wk cycles of twice-daily capecitabine (on days 1–14) plus intravenous cisplatin (on day 1), with or without weekly cetuximab (starting on day 1).[169] Grade 3–4 adverse events were significantly more frequent among patients treated with cetuximab than among individuals receiving chemotherapy only. Moreover, the addition of cetuximab to chemotherapy provided no additional benefits to advanced gastric cancer patients as compared with the use of capecitabine plus cisplatin alone.[169]

The results of a few other clinical trials testing FDA-approved tumor-targeting mAbs in off-label indications have been published during the last 13 mo.[181-186] In particular, denosumab has been shown to improve the overall survival of lung cancer patients with bone metastases as compared with zoledronic acid.[181] The addition of panitumumab (a EGFR-specific human IgG2 currently approved for the treatment of CRC)[187-189] to cisplatin- or 5-fluorouracil-based chemotherapy has been demonstrated to improve the progression-free survival (but not the overall) survival of unselected HNSCC patients.[182] Along similar lines, the combination of panitumumab with pegylated liposomal doxorubicin has been associated with clinical efficacy in patients with platinum-refractory ovarian carcinoma, though skin toxicity was considerable.[183] Conversely, panitumumab failed to improve the therapeutic profile of conventional chemotherapy in an unselected population of patients with advanced gastresophagic adenocarcinoma.[185] Finally, the co-administration of rituximab and recombinant interleukin (IL)-21 to patients with indolent B-cell malignancies has been reported to be well tolerated and clinically active, warranting further investigation.[184]

Additional studies

Although in our Trial Watch series we never discuss clinical studies that evaluate the therapeutic profile of anticancer agents employed as on-label interventions, a mention here goes to the CLEOPATRA trial, a randomized, double-blind, placebo-controlled, Phase 3 study investigating the safety and efficacy of pertuzumab,[49,190] in combination with trastuzumab and docetaxel, in patients with HER2$^+$ first-line metastatic breast carcinoma.[106]

In the context of this study, 808 women with HER2+ metastatic breast cancer who had not received previous chemotherapy or biological treatments (enrolled at 204 distinct cancer centers in 25 countries) were randomized at a 1:1 ratio to receive either pertuzumab, trastuzumab, and docetaxel or the same regimen with a matching placebo replacing pertuzumab.[106] At data cutoff (when the median follow-up was 30 mo for both groups), intention-to-treat analyses revealed a significant improvement in both disease-free and overall survival among patients receiving pertuzumab, trastuzumab, and docetaxel as compared with patients treated with trastuzumab and docetaxel only, with no marked differences in the incidence and severity of side effects.[106] As it stands, the first wave of results from the CLEOPATRA trial (which has been published in January 2012) underpinned the approval of pertuzumab in combination with trastuzumab and docetaxel for the treatment of patients with HER2+ metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.[49] Conversely, the recent approval of pertuzumab for use in patients with HER2+, locally advanced, inflammatory, or early-stage breast cancer (see above) was supported by the results of the NeoSphere study, a Phase II, randomized clinical trial involving no less than 417 patients.[48]

Taken together, the findings of recently published clinical studies testing the safety and efficacy of tumor-targeting mAbs reinforce the notion that this approach is generally well tolerated and has the potential to elicit robust therapeutic responses, at least in subsets of patients. Among a huge amount of preclinical studies demonstrating the efficacy of tumor-targeting mAbs in a large panel of experimental paradigms (source http://www.ncbi.nlm.nih.gov/pubmed), we have found of particular interest the work by Boross and colleagues, demonstrating that IgAs and the corresponding Fc receptor (CD89) may be harnessed to achieve robust antineoplastic effects in vivo.[191] These observations pave the way to the development of novel tumor-targeting mAbs of the IgA, rather than IgG, isotype and strategies for the therapeutic targeting of CD89.

Update on Clinical Trials Testing Tumor-Targeting Monoclonal Antibodies

When this Trial Watch was being redacted (October 2013), official sources listed 74 clinical trials launched after 2012, October 1st to evaluate the therapeutic profile of hitherto investigational tumor-targeting mAbs in cancer patients (16 studies) or the efficacy of FDA-approved tumor-targeting mAbs employed as off-label anticancer interventions (58 studies) (source http://www.clinicaltrials.gov).

Among the investigational tumor-targeting mAbs that continue to attract considerable clinical interest are nimotuzumab and necitumumab. Nimotuzumab (a humanized IgG1) and necitumumab (a fully human IgG1) target the EGFR and have been the subject of an intense wave of clinical investigation[192-205] During the last 13 mo, no less than 8 clinical trials have been launched to evaluate the safety and therapeutic potential of these EGFR-targeting mAbs, including 7 Phase I-II studies testing nimotuzumab or necitumumab in combination with conventional chemo(radio)therapeutic regimens in patients with breast carcinoma (NCT01939054); NSCLC (NCT01763788; NCT01769391; NCT01788566; NCT01861223), cervical carcinoma (NCT01938105) and rectal cancer (NCT01899118), as well as 1 Phase III trial assessing the therapeutic potential of nimotuzumab plus irinotecan (an inhibitor of topoisomerase I) in individuals with EGFR-overexpressing gastric or gastresophageal junction cancer (NCT01813253).

Alongside, multiple clinical studies have recently been initiated to investigate the therapeutic profile of a relatively heterogeneous group of investigational tumor-targeting mAbs. These mAbs include (1) BC8, a CD45-targeting murine IgG1 usually coupled to radionuclides,[206,207] which is now being tested (in its ^{90}Y-conjugated form) together with combinatorial chemotherapy in patients with high-risk lymphoid malignancies allocated to undergo hematopoietic stem cells transplantation (NCT01921387); (2) blinatumomab, a bispecific T-cell engager (BiTE) targeting CD3 and CD19 (also known as MEDI-538),[96,208-210] now under evaluation as a standalone therapeutic measure in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) (NCT01741792); (3) Ch14.18, a chimeric IgG1 specific for disialoganglioside GD2,[211-216] which is currently being assessed in combination with irinotecan and temozolomide (an alkylating agent) in young patients with relapsed or refractory neuroblastoma (NCT01767194); (4) conatumumab (see above), which is now being investigated in combination with a small SMAC peptidomimetic[217,218] in women with relapsed ovarian cancer (NCT01940172); (5) lintuzumab, a humanized IgG1 targeting the cell surface myelomonocytic differentiation antigen CD33,[219,220] which is currently being tested (as an ^{225}Ac conjugate) in combination with cytarabine (an inhibitor of DNA synthesis) in old leukemia patients (NCT01756677); (6) SAR650984, a humanized IgG1 targeting CD38,[221] now under evaluation together with lenalidomide and dexamethasone[222] in patients with relapsed or refractory multiple myeloma (NCT01749969); and (7) TF2, a bispecific molecule that binds carcinoembryonic antigen (CEA) while providing a platform for the highly targeted delivery of a second, radionuclide (^{68}Ga)-coupled peptide,[223-225] which is currently being tested as a diagnostic tool in subjects affected by HER2- breast carcinoma (NCT01730612) or medullary thyroid carcinoma (NCT01730638) (**Table 4**).

For obvious safety reasons, the largest fraction of clinical trials initiated during the last 13 mo to test tumor-targeting mAbs aims at determining whether FDA-approved molecules might exert therapeutic effects in off-label indications. Thus, bevacizumab is currently being tested as a diagnostic tool (in its ^{89}Zr-conjugated form) or as a therapeutic intervention, most frequently in combination with standard chemo(radio) therapeutic regimens, in patients with hematological malignancies (NCT01859234; NCT01921790), various forms of sarcoma (NCT01746238; NCT01871766; NCT01946529), glioma (NCT01743950; NCT01891747), breast carcinoma (NCT01722968; NCT01894451; NCT01898117; NCT01941407; NCT01959490), melanoma (NCT01879306;

NCT01950390), ovarian carcinoma (NCT01735071; NCT01739218; NCT01770301; NCT01802749; NCT01837251; NCT01838538; NCT01847677), neoplasms of the reproductive tract (NCT01770171; NCT01821859; NCT01936974), and other (advanced or metastatic) solid tumors (NCT01749384; NCT01767792; NCT01831089; NCT01847118; NCT01898130; NCT01951482; NCT01946529). Brentuximab vedotin, an anti-CD30 monomethyl auristatin E (MMAE) conjugate approved for the treatment of relapsed Hodgkin's lymphoma and relapsed systemic anaplastic large cell lymphoma,[226,227] is being investigated, either as a single therapeutic agent or combined with (often cyclophosphamide-based) chemotherapy, in patients affected by acute myeloid leukemia (NCT01830777), mast cell leukemia or systemic mastocytosis (NCT01807598); DLBCL or other forms of lymphoma (NCT01777152; NCT01805037; NCT01841021; NCT01925612), and $CD30^+$ germ cell tumors (NCT01851200). The clinical profile of cetuximab, invariably in combination with chemotherapy or multimodal therapy, is being evaluated in subjects bearing esophageal or gastric carcinoma (NCT01787006; NCT01904435), brain neoplasms (NCT01884740) or other advanced solid tumors (NCT01727869; NCT01787500). Rituximab, given as a standalone therapeutic regimen or combined with brentuximab vedotin, dexamethasone or INCB040093 (an orally available inhibitor of the δ isoform of the 110 kDa catalytic subunit of class I phosphoinositide-3-kinases)[228,229] is under investigation for its therapeutic potential in cohorts of individuals with various B-cell malignancies (NCT01905813), Hodgkin's lymphoma (NCT01900496), neuroblastoma-associated opsoclonus myoclonus syndrome (a rare neurological disorder of unclear origin)[230] (NCT01868269), and prostate carcinoma (NCT01804712). The clinical profile of trastuzumab, in combination with either conventional chemotherapy or lapatinib (a tyrosine kinase inhibitor currently approved for use in $HER2^+$ breast carcinoma patients),[231] is being assessed in patients bearing bladder neoplasms (NCT01828736) or other solid tumors (NCT01771458). Pertuzumab is being tested in combination with trastuzumab as a first-line therapeutic intervention in patients with gastric or gastresophageal carcinoma (NCT01774786). Catumaxomab is now being evaluated as a standalone therapeutic agent in patients with gastric peritoneal carcinomatosis (NCT01784900) or ovarian carcinoma (NCT01815528). Denosumab plus standard chemotherapy is under investigation as a first-line intervention against metastatic NSCLC (NCT01951586). Ofatumumab, a human IgG1 targeting CD20 that is approved by FDA for the treatment of CLL,[232,233] is currently being tested, in combination with cyclophosphamide-based chemotherapy or human recombinant IL-18,[234] in patients with other forms of leukemia (NCT01762202) or NHL (NCT01768338). Alemtuzumab, a CD52-specific humanized IgG1 that is licensed for use in CLL patients,[235,236] is being evaluated as a consolidation regimen upon cyclophosphamide-based chemotherapy in patients with peripheral T-cell lymphoma (NCT01806337) or in combination with donor lymphocyte infusions in subjects with multiple hematological malignancies (NCT01875237). Finally, panitumumab, an EGFR-specific humanized IgG2 currently licensed for use in CRC patients,[237,238] is under investigation as a therapeutic measure against anal cancer (NCT01843452) and bladder carcinoma (NCT01916109) (**Table 4**).

As for the clinical trials listed in our previous Trial Watches dealing with this topic,[5,6] the following studies have changed status: NCT00560794, NCT00848926, NCT00866047, and NCT00986674, now listed as "Active, not recruiting"; NCT00563680, NCT00947856, NCT00778167, and NCT00838201, now listed as "Completed"; NCT01614795, now listed as "Temporarily closed to accrual"; NCT00385827, NCT01335204, and NCT01513317, now listed as "Terminated"; and NCT01034787, whose status is now "Unknown." NCT01513317, comparing siltuximab (a chimeric mAb that neutralizes IL-6, also known as CNTO 328)[239,240] plus best supportive care to placebo plus best supportive care in anemic patients with low/intermediate-risk myelodysplastic syndrome, has been stopped after the interim analysis, based on lack of efficacy (although there were no safety concerns). Conversely, the reasons underlying the suspension of NCT01614795 and the termination of both NCT00385827 and NCT01335204 are not available. Among "Active, not recruiting" and "Completed" studies, (preliminary or definitive) results appear to be available for NCT00560794;[241] NCT00778167; NCT00838201; NCT00848926; NCT00866047; NCT00947856;[242] and NCT00986674 (source http://www.clinicaltrials.gov).

Concluding Remarks

The interest of clinicians in harnessing the specificity of mAbs for cancer therapy remains very high, as demonstrated by the consistent number of clinical trials that have been initiated during the last 13 mo to test this immunotherapeutic paradigm in oncological settings. As discussed here, a large fraction of these studies involves tumor-targeting mAbs, i.e., mAbs that primarily bind to malignant cells or interrupt the trophic support provided to developing tumors by the stroma. Such an intense wave of clinical development is paralleled by the relatively frequent approval by FDA of (1) novel tumor-targeting mAbs, or (2) novel oncological indications for previously licensed molecules. As some (but not all) tumor-targeting mAbs exert antineoplastic effects by engaging immune effector functions, it will be interesting to see whether and in which circumstances the clinical benefits of mAbs can be improved by combining these immunotherapeutic agents with broad or targeted immunostimulatory interventions, including selected cytokines,[111,112] Toll-like receptor agonists,[243-245] immunogenic chemotherapy;[246-248] and irradiation.[110]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Köhler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature 1975; 256:495-7; PMID:1172191; http://dx.doi.org/10.1038/256495a0
2. Alkan SS. Monoclonal antibodies: the story of a discovery that revolutionized science and medicine. Nat Rev Immunol 2004; 4:153-6; PMID:15040588; http://dx.doi.org/10.1038/nri1265
3. Weiner LM, Surana R, Wang S. Monoclonal antibodies: versatile platforms for cancer immunotherapy. Nat Rev Immunol 2010; 10:317-27; PMID:20414205; http://dx.doi.org/10.1038/nri2744
4. Scott SD. Rituximab: a new therapeutic monoclonal antibody for non-Hodgkin's lymphoma. Cancer Pract 1998; 6:195-7; PMID:9652253; http://dx.doi.org/10.1046/j.1523-5394.1998.006003195.x
5. Vacchelli E, Eggermont A, Galon J, Sautès-Fridman C, Zitvogel L, Kroemer G, Galluzzi L. Trial watch: Monoclonal antibodies in cancer therapy. Oncoimmunology 2013; 2:e22789; PMID:23482847; http://dx.doi.org/10.4161/onci.22789
6. Galluzzi L, Vacchelli E, Fridman WH, Galon J, Sautès-Fridman C, Tartour E, Zucman-Rossi J, Zitvogel L, Kroemer G. Trial Watch: Monoclonal antibodies in cancer therapy. Oncoimmunology 2012; 1:28-37; PMID:22720209; http://dx.doi.org/10.4161/onci.1.1.17938
7. Vacchelli E, Eggermont A, Fridman WH, Galon J, Tartour E, Zitvogel L, Kroemer G, Galluzzi L. Trial Watch: Adoptive cell transfer for anticancer immunotherapy. Oncoimmunology 2013; 2:e24238; PMID:23762803; http://dx.doi.org/10.4161/onci.24238
8. Vacchelli E, Senovilla L, Eggermont A, Fridman WH, Galon J, Zitvogel L, Kroemer G, Galluzzi L. Trial watch: Chemotherapy with immunogenic cell death inducers. Oncoimmunology 2013; 2:e23510; PMID:23687621; http://dx.doi.org/10.4161/onci.23510
9. Senovilla L, Vacchelli E, Garcia P, Eggermont A, Fridman WH, Galon J, Zitvogel L, Kroemer G, Galluzzi L. Trial watch: DNA vaccines for cancer therapy. Oncoimmunology 2013; 2:e23803; PMID:23734328; http://dx.doi.org/10.4161/onci.23803
10. Aranda F, Vacchelli E, Eggermont A, Galon J, Sautes-Fridman C, Tartour E, et al. Trial Watch: Peptide vaccines in cancer therapy. OncoImmunology 2013; 2:e26621
11. Zitvogel L, Galluzzi L, Smyth MJ, Kroemer G. Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. Immunity 2013; 39:74-88; PMID:23890065; http://dx.doi.org/10.1016/j.immuni.2013.06.014
12. Galluzzi L, Senovilla L, Zitvogel L, Kroemer G. The secret al.y: immunostimulation by anticancer drugs. Nat Rev Drug Discov 2012; 11:215-33; PMID:22301798; http://dx.doi.org/10.1038/nrd3626
13. Zitvogel L, Kroemer G. Targeting PD-1/PD-L1 interactions for cancer immunotherapy. Oncoimmunology 2012; 1:1223-5; PMID:23243584; http://dx.doi.org/10.4161/onci.21335
14. Margolin K. Ipilimumab in a Phase II trial of melanoma patients with brain metastases. Oncoimmunology 2012; 1:1197-9; PMID:23170278; http://dx.doi.org/10.4161/onci.20687
15. Mansfield AS, Nevala WK, Lieser EA, Leontovich AA, Markovic SN. The immunomodulatory effects of bevacizumab on systemic immunity in patients with metastatic melanoma. Oncoimmunology 2013; 2:e24436; PMID:23762809; http://dx.doi.org/10.4161/onci.24436
16. Zitvogel L, Kepp O, Kroemer G. Immune parameters affecting the efficacy of chemotherapeutic regimens. Nat Rev Clin Oncol 2011; 8:151-60; PMID:21364688; http://dx.doi.org/10.1038/nrclinonc.2010.223
17. Derer S, Lohse S, Valerius T. EGFR expression levels affect the mode of action of EGFR-targeting monoclonal antibodies. Oncoimmunology 2013; 2:e24052; PMID:23762793; http://dx.doi.org/10.4161/onci.24052
18. Weiner LM, Belldegrun AS, Crawford J, Tolcher AW, Lockbaum P, Arends RH, Navale L, Amado RG, Schwab G, Figlin RA. Dose and schedule study of panitumumab monotherapy in patients with advanced solid malignancies. Clin Cancer Res 2008; 14:502-8; PMID:18223225; http://dx.doi.org/10.1158/1078-0432.CCR-07-1509
19. Ming Lim C, Stephenson R, Salazar AM, Ferris RL. TLR3 agonists improve the immunostimulatory potential of cetuximab against EGFR(+) head and neck cancer cells. Oncoimmunology 2013; 2:e24677; PMID:23894722; http://dx.doi.org/10.4161/onci.24677
20. Kaplan-Lefko PJ, Graves JD, Zoog SJ, Pan Y, Wall J, Branstetter DG, Moriguchi J, Coxon A, Huard JN, Xu R, et al. Conatumumab, a fully human agonist antibody to death receptor 5, induces apoptosis via caspase activation in multiple tumor types. Cancer Biol Ther 2010; 9:618-31; PMID:20150762; http://dx.doi.org/10.4161/cbt.9.8.11264
21. Nimmerjahn F, Ravetch JV. Fcgamma receptors: old friends and new family members. Immunity 2006; 24:19-28; PMID:16413920; http://dx.doi.org/10.1016/j.immuni.2005.11.010
22. Hubert P, Amigorena S. Antibody-dependent cell cytotoxicity in monoclonal antibody-mediated tumor immunotherapy. Oncoimmunology 2012; 1:103-5; PMID:22720225; http://dx.doi.org/10.4161/onci.1.1.17963
23. Houot R, Kohrt H, Levy R. Boosting antibody-dependant cellular cytotoxicity against tumor cells with a CD137 stimulatory antibody. Oncoimmunology 2012; 1:957-8; PMID:23162770; http://dx.doi.org/10.4161/onci.19974
24. Kute T, Stehle JR Jr., Ornelles D, Walker N, Delbono O, Vaughn JP. Understanding key assay parameters that affect measurements of trastuzumab-mediated ADCC against Her2 positive breast cancer cells. Oncoimmunology 2012; 1:810-21; PMID:23162748; http://dx.doi.org/10.4161/onci.20447
25. Winiarska M, Glodkowska-Mrowka E, Bil J, Golab J. Molecular mechanisms of the antitumor effects of anti-CD20 antibodies. Front Biosci (Landmark Ed) 2011; 16:277-306; PMID:21196171; http://dx.doi.org/10.2741/3688
26. Dunkelberger JR, Song WC. Complement and its role in innate and adaptive immune responses. Cell Res 2010; 20:34-50; PMID:20010915; http://dx.doi.org/10.1038/cr.2009.139
27. Zipfel PF, Skerka C. Complement regulators and inhibitory proteins. Nat Rev Immunol 2009; 9:729-40; PMID:19730437
28. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002; 346:235-42; PMID:11807147; http://dx.doi.org/10.1056/NEJMoa011795
29. McLaughlin P, Grillo-López AJ, Link BK, Levy R, Czuczman MS, Williams ME, Heyman MR, Bence-Bruckler I, White CA, Cabanillas F, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998; 16:2825-33; PMID:9704735
30. Sorbye SW, Kilvaer T, Valkov A, Donnem T, Smeland E, Al-Shibli K, Bremnes RM, Busund LT. High expression of CD20+ lymphocytes in soft tissue sarcomas is a positive prognostic indicator. Oncoimmunology 2012; 1:75-7; PMID:22720216; http://dx.doi.org/10.4161/onci.1.1.17825
31. Seimetz D. Novel monoclonal antibodies for cancer treatment: the trifunctional antibody catumaxomab (removab). J Cancer 2011; 2:309-16; PMID:21716847; http://dx.doi.org/10.7150/jca.2.309
32. Armeanu-Ebinger S, Hoh A, Wenz J, Fuchs J. Targeting EpCAM (CD326) for immunotherapy in hepatoblastoma. Oncoimmunology 2013; 2:e22620; PMID:23482411; http://dx.doi.org/10.4161/onci.22620
33. Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmanouilides C, Joyce R, Pohlman BL, Bartlett NL, Wiseman GA, Padre N, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002; 20:2453-63; PMID:12011122; http://dx.doi.org/10.1200/JCO.2002.11.076
34. Kaminski MS, Estes J, Zasadny KR, Francis IR, Ross CW, Tuck M, Regan D, Fisher S, Gutierrez J, Kroll S, et al. Radioimmunotherapy with iodine (131)I tositumomab for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience. Blood 2000; 96:1259-66; PMID:10942366
35. Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discov 2004; 3:391-400; PMID:15136787; http://dx.doi.org/10.1038/nrd1381
36. Michielsen AJ, Ryan EJ, O'Sullivan JN. Dendritic cell inhibition correlates with survival of colorectal cancer patients on bevacizumab treatment. Oncoimmunology 2012; 1:1445-7; PMID:23243624; http://dx.doi.org/10.4161/onci.21318
37. Kawaguchi Y, Kono K, Mimura K, Sugai H, Akaike H, Fujii H. Cetuximab induce antibody-dependent cellular cytotoxicity against EGFR-expressing esophageal squamous cell carcinoma. Int J Cancer 2007; 120:781-7; PMID:17096332; http://dx.doi.org/10.1002/ijc.22370
38. Srivastava RM, Lee SC, Andrade Filho PA, Lord CA, Jie HB, Davidson HC, López-Albaitero A, Gibson SP, Gooding WE, Ferrone S, et al. Cetuximab-activated natural killer and dendritic cells collaborate to trigger tumor antigen-specific T-cell immunity in head and neck cancer patients. Clin Cancer Res 2013; 19:1858-72; PMID:23444227; http://dx.doi.org/10.1158/1078-0432.CCR-12-2426

39. Bennouna J, Sastre J, Arnold D, Österlund P, Greil R, Van Cutsem E, von Moos R, Viéitez JM, Bouché O, Borg C, et al.; ML18147 Study Investigators. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol 2013; 14:29-37; PMID:23168366; http://dx.doi.org/10.1016/S1470-2045(12)70477-1
40. Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA, Benson AB 3rd; Eastern Cooperative Oncology Group Study E3200. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007; 25:1539-44; PMID:17442997; http://dx.doi.org/10.1200/JCO.2006.09.6305
41. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D, Davidson NE. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007; 357:2666-76; PMID:18160686; http://dx.doi.org/10.1056/NEJMoa072113
42. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350:2335-42; PMID:15175435; http://dx.doi.org/10.1056/NEJMoa032691
43. Chawla S, Henshaw R, Seeger L, Choy E, Blay JY, Ferrari S, Kroep J, Grimer R, Reichardt P, Rutkowski P, et al. Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study. Lancet Oncol 2013; 14:901-8; PMID:23867211; http://dx.doi.org/10.1016/S1470-2045(13)70277-8
44. Branstetter DG, Nelson SD, Manivel JC, Blay JY, Chawla S, Thomas DM, Jun S, Jacobs I. Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone. Clin Cancer Res 2012; 18:4415-24; PMID:22711702; http://dx.doi.org/10.1158/1078-0432.CCR-12-0578
45. Coleman RE. Bone cancer in 2011: Prevention and treatment of bone metastases. Nat Rev Clin Oncol 2011; 9:76-8; PMID:22182971; http://dx.doi.org/10.1038/nrclinonc.2011.198
46. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, Pegram M, Oh DY, Diéras V, Guardino E, et al.; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012; 367:1783-91; PMID:23020162; http://dx.doi.org/10.1056/NEJMoa1209124
47. Mavilio D, Galluzzi L, Lugli E. Novel multifunctional antibody approved for the treatment of breast cancer. Oncoimmunology 2013; 2:e24567; PMID:23802090; http://dx.doi.org/10.4161/onci.24567
48. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, Lluch A, Staroslawska E, de la Haba-Rodriguez J, Im SA, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012; 13:25-32; PMID:22153890; http://dx.doi.org/10.1016/S1470-2045(11)70336-9
49. Baselga J, Cortés J, Kim SB, Im SA, Hegg R, Im YH, Roman L, Pedrini JL, Pienkowski T, Knott A, et al.; CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012; 366:109-19; PMID:22149875; http://dx.doi.org/10.1056/NEJMoa1113216
50. Rosenfeld RG. Insulin-like growth factors and the basis of growth. N Engl J Med 2003; 349:2184-6; PMID:14657423; http://dx.doi.org/10.1056/NEJMp038156
51. Beltran PJ, Mitchell P, Chung YA, Cajulis E, Lu J, Belmontes B, Ho J, Tsai MM, Zhu M, Vonderfecht S, et al. AMG 479, a fully human anti-insulin-like growth factor receptor type I monoclonal antibody, inhibits the growth and survival of pancreatic carcinoma cells. Mol Cancer Ther 2009; 8:1095-105; PMID:19366899; http://dx.doi.org/10.1158/1535-7163.MCT-08-1171
52. McKian KP, Haluska P. Cixutumumab. Expert Opin Investig Drugs 2009; 18:1025-33; PMID:19548856; http://dx.doi.org/10.1517/13543780903055049
53. Desbois-Mouthon C, Baron A, Blivet-Van Eggelpoël MJ, Fartoux L, Venot C, Bladt F, Housset C, Rosmorduc O. Insulin-like growth factor-1 receptor inhibition induces a resistance mechanism via the epidermal growth factor receptor/HER3/AKT signaling pathway: rational basis for cotargeting insulin-like growth factor-1 receptor and epidermal growth factor receptor in hepatocellular carcinoma. Clin Cancer Res 2009; 15:5445-56; PMID:19706799; http://dx.doi.org/10.1158/1078-0432.CCR-08-2980
54. Descamps G, Gomez-Bougie P, Venot C, Moreau P, Bataille R, Amiot M. A humanised anti-IGF-1R monoclonal antibody (AVE1642) enhances Bortezomib-induced apoptosis in myeloma cells lacking CD45. Br J Cancer 2009; 100:366-9; PMID:19165200; http://dx.doi.org/10.1038/sj.bjc.6604839
55. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, Staroslawska E, Sosman J, McDermott D, Bodrogi I, et al.; Global ARCC Trial. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007; 356:2271-81; PMID:17538086; http://dx.doi.org/10.1056/NEJMoa066838
56. Schwartz GK, Tap WD, Qin LX, Livingston MB, Undevia SD, Chmielowski B, Agulnik M, Schuetze SM, Reed DR, Okuno SH, et al. Cixutumumab and temsirolimus for patients with bone and soft-tissue sarcoma: a multicentre, open-label, phase 2 trial. Lancet Oncol 2013; 14:371-82; PMID:23477833; http://dx.doi.org/10.1016/S1470-2045(13)70049-4
57. Kindler HL, Richards DA, Garbo LE, Garon EB, Stephenson JJ Jr., Rocha-Lima CM, Safran H, Chan D, Kocs DM, Galimi F, et al. A randomized, placebo-controlled phase 2 study of ganitumab (AMG 479) or conatumumab (AMG 655) in combination with gemcitabine in patients with metastatic pancreatic cancer. Ann Oncol 2012; 23:2834-42; PMID:22700995; http://dx.doi.org/10.1093/annonc/mds142
58. Robertson JF, Ferrero JM, Bourgeois H, Kennecke H, de Boer RH, Jacot W, McGreivy J, Suzuki S, Zhu M, McCaffery I, et al. Ganitumab with either exemestane or fulvestrant for postmenopausal women with advanced, hormone-receptor-positive breast cancer: a randomised, controlled, double-blind, phase 2 trial. Lancet Oncol 2013; 14:228-35; PMID:23414585; http://dx.doi.org/10.1016/S1470-2045(13)70026-3
59. Macaulay VM, Middleton MR, Protheroe AS, Tolcher A, Dieras V, Sessa C, Bahleda R, Blay JY, LoRusso P, Mery-Mignard D, et al. Phase I study of humanized monoclonal antibody AVE1642 directed against the type 1 insulin-like growth factor receptor (IGF-1R), administered in combination with anticancer therapies to patients with advanced solid tumors. Ann Oncol 2013; 24:784-91; PMID:23104723; http://dx.doi.org/10.1093/annonc/mds511
60. Soria JC, Massard C, Lazar V, Ozoux ML, Mery-Mignard D, Deslandes A, Tolcher AW. A dose finding, safety and pharmacokinetic study of AVE1642, an anti-insulin-like growth factor-1 receptor (IGF-1R/CD221) monoclonal antibody, administered as a single agent and in combination with docetaxel in patients with advanced solid tumours. Eur J Cancer 2013; 49:1799-807; PMID:23485230; http://dx.doi.org/10.1016/j.ejca.2013.01.003
61. Naing A, Kurzrock R, Burger A, Gupta S, Lei X, Busaidy N, Hong D, Chen HX, Doyle LA, Heilbrun LK, et al. Phase I trial of cixutumumab combined with temsirolimus in patients with advanced cancer. Clin Cancer Res 2011; 17:6052-60; PMID:21750201; http://dx.doi.org/10.1158/1078-0432.CCR-10-2979
62. Takeda K, Stagg J, Yagita H, Okumura K, Smyth MJ. Targeting death-inducing receptors in cancer therapy. Oncogene 2007; 26:3745-57; PMID:17530027; http://dx.doi.org/10.1038/sj.onc.1210374
63. Rahman M, Pumphrey JG, Lipkowitz S. The TRAIL to targeted therapy of breast cancer. Adv Cancer Res 2009; 103:43-73; PMID:19854352; http://dx.doi.org/10.1016/S0065-230X(09)03003-6
64. Paz-Ares L, Bálint B, de Boer RH, van Meerbeeck JP, Wierzbicki R, De Souza P, Galimi F, Haddad V, Sabin T, Hei YJ, et al. A randomized phase 2 study of paclitaxel and carboplatin with or without conatumumab for first-line treatment of advanced non-small-cell lung cancer. J Thorac Oncol 2013; 8:329-37; PMID:23370314
65. Fuchs CS, Fakih M, Schwartzberg L, Cohn AL, Yee L, Dreisbach L, Kozloff MF, Hei YJ, Galimi F, Pan Y, et al. TRAIL receptor agonist conatumumab with modified FOLFOX6 plus bevacizumab for first-line treatment of metastatic colorectal cancer: A randomized phase 1b/2 trial. Cancer 2013; 119:4290-8; PMID:24122767; http://dx.doi.org/10.1002/cncr.28353
66. Merchant MS, Geller JI, Baird K, Chou AJ, Galli S, Charles A, Amaoko M, Rhee EH, Price A, Wexler LH, et al. Phase I trial and pharmacokinetic study of lexatumumab in pediatric patients with solid tumors. J Clin Oncol 2012; 30:4141-7; PMID:23071222; http://dx.doi.org/10.1200/JCO.2012.44.1055
67. Rocha Lima CM, Bayraktar S, Flores AM, MacIntyre J, Montero A, Baranda JC, Wallmark J, Portera C, Raja R, Stern H, et al. Phase Ib study of drozitumab combined with first-line mFOLFOX6 plus bevacizumab in patients with metastatic colorectal cancer. Cancer Invest 2012; 30:727-31; PMID:23061802; http://dx.doi.org/10.3109/07357907.2012.732163
68. Doi T, Murakami H, Ohtsu A, Fuse N, Yoshino T, Yamamoto N, Boku N, Onozawa Y, Hsu CP, Gorski KS, et al. Phase 1 study of conatumumab, a pro-apoptotic death receptor 5 agonist antibody, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol 2011; 68:733-41; PMID:21161528; http://dx.doi.org/10.1007/s00280-010-1544-1
69. Herbst RS, Kurzrock R, Hong DS, Valdivieso M, Hsu CP, Goyal L, Juan G, Hwang YC, Wong S, Hill JS, et al. A first-in-human study of conatumumab in adult patients with advanced solid tumors. Clin Cancer Res 2010; 16:5883-91; PMID:20947515; http://dx.doi.org/10.1158/1078-0432.CCR-10-0631
70. Camidge DR, Herbst RS, Gordon MS, Eckhardt SG, Kurzrock R, Durbin B, Ing J, Tohnya TM, Sager J, Ashkenazi A, et al. A phase I safety and pharmacokinetic study of the death receptor 5 agonistic antibody PRO95780 in patients with advanced malignancies. Clin Cancer Res 2010; 16:1256-63; PMID:20145186; http://dx.doi.org/10.1158/1078-0432.CCR-09-1267

71. Kang Z, Chen JJ, Yu Y, Li B, Sun SY, Zhang B, Cao L. Drozitumab, a human antibody to death receptor 5, has potent antitumor activity against rhabdomyosarcoma with the expression of caspase-8 predictive of response. Clin Cancer Res 2011; 17:3181-92; PMID:21385927; http://dx.doi.org/10.1158/1078-0432.CCR-10-2874
72. Wakelee HA, Patnaik A, Sikic BI, Mita M, Fox NL, Miceli R, Ullrich SJ, Fisher GA, Tolcher AW. Phase I and pharmacokinetic study of lexatumumab (HGS-ETR2) given every 2 weeks in patients with advanced solid tumors. Ann Oncol 2010; 21:376-81; PMID:19633048; http://dx.doi.org/10.1093/annonc/mdp292
73. Zhang L, Zhang X, Barrisford GW, Olumi AF. Lexatumumab (TRAIL-receptor 2 mAb) induces expression of DR5 and promotes apoptosis in primary and metastatic renal cell carcinoma in a mouse orthotopic model. Cancer Lett 2007; 251:146-57; PMID:17184908; http://dx.doi.org/10.1016/j.canlet.2006.11.013
74. Zeng Y, Wu XX, Fiscella M, Shimada O, Humphreys R, Albert V, Kakehi Y. Monoclonal antibody to tumor necrosis factor-related apoptosis-inducing ligand receptor 2 (TRAIL-R2) induces apoptosis in primary renal cell carcinoma cells in vitro and inhibits tumor growth in vivo. Int J Oncol 2006; 28:421-30; PMID:16391797
75. Krupitskaya Y, Wakelee HA. Ramucirumab, a fully human mAb to the transmembrane signaling tyrosine kinase VEGFR-2 for the potential treatment of cancer. Curr Opin Investig Drugs 2009; 10:597-605; PMID:19513949
76. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, Safran H, Dos Santos LV, Aprile G, Ferry DR, et al.; for the REGARD Trial Investigators. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2013;Forthcoming; PMID:24094768; http://dx.doi.org/10.1016/S0140-6736(13)61719-5
77. Zhu AX, Finn RS, Mulcahy M, Gurtler J, Sun W, Schwartz JD, Dalal RP, Joshi A, Hozak RR, Xu Y, et al. A Phase II and Biomarker Study of Ramucirumab, a Human Monoclonal Antibody Targeting the VEGF Receptor-2, as First-Line Monotherapy in Patients with Advanced Hepatocellular Cancer. Clin Cancer Res 2013; 19:6614-23; PMID:24088738; http://dx.doi.org/10.1158/1078-0432.CCR-13-1442
78. Garon EB, Cao D, Alexandris E, John WJ, Yurasov S, Perol M. A randomized, double-blind, phase III study of Docetaxel and Ramucirumab versus Docetaxel and placebo in the treatment of stage IV non-small-cell lung cancer after disease progression after 1 previous platinum-based therapy (REVEL): treatment rationale and study design. Clin Lung Cancer 2012; 13:505-9; PMID:22853980; http://dx.doi.org/10.1016/j.cllc.2012.06.007
79. Obmolova G, Teplyakov A, Malia TJ, Grygiel TL, Sweet R, Snyder LA, Gilliland GL. Structural basis for high selectivity of anti-CCL2 neutralizing antibody CNTO 888. Mol Immunol 2012; 51:227-33; PMID:22487721; http://dx.doi.org/10.1016/j.molimm.2012.03.022
80. Neal J, Wakelee H. AMG-386, a selective angiopoietin-1/-2-neutralizing peptibody for the potential treatment of cancer. Curr Opin Mol Ther 2010; 12:487-95; PMID:20677100
81. Mita AC, Takimoto CH, Mita M, Tolcher A, Sankhala K, Sarantopoulos J, Valdivieso M, Wood L, Rasmussen E, Sun YN, et al. Phase 1 study of AMG 386, a selective angiopoietin 1/2-neutralizing peptibody, in combination with chemotherapy in adults with advanced solid tumors. Clin Cancer Res 2010; 16:3044-56; PMID:20501621; http://dx.doi.org/10.1158/1078-0432.CCR-09-3368
82. Herbst RS, Hong D, Chap L, Kurzrock R, Jackson E, Silverman JM, Rasmussen E, Sun YN, Zhong D, Hwang YC, et al. Safety, pharmacokinetics, and antitumor activity of AMG 386, a selective angiopoietin inhibitor, in adult patients with advanced solid tumors. J Clin Oncol 2009; 27:3557-65; PMID:19546406; http://dx.doi.org/10.1200/JCO.2008.19.6683
83. Gordon MS, Sweeney CS, Mendelson DS, Eckhardt SG, Anderson A, Beaupre DM, Branstetter D, Burgess TL, Coxon A, Deng H, et al. Safety, pharmacokinetics, and pharmacodynamics of AMG 102, a fully human hepatocyte growth factor-neutralizing monoclonal antibody, in a first-in-human study of patients with advanced solid tumors. Clin Cancer Res 2010; 16:699-710; PMID:20068101; http://dx.doi.org/10.1158/1078-0432.CCR-09-1365
84. Jun HT, Sun J, Rex K, Radinsky R, Kendall R, Coxon A, Burgess TL. AMG 102, a fully human anti-hepatocyte growth factor/scatter factor neutralizing antibody, enhances the efficacy of temozolomide or docetaxel in U-87 MG cells and xenografts. Clin Cancer Res 2007; 13:6735-42; PMID:18006775; http://dx.doi.org/10.1158/1078-0432.CCR-06-2969
85. Kakkar T, Ma M, Zhuang Y, Patton A, Hu Z, Mounho B. Pharmacokinetics and safety of a fully human hepatocyte growth factor antibody, AMG 102, in cynomolgus monkeys. Pharm Res 2007; 24:1910-8; PMID:17520181; http://dx.doi.org/10.1007/s11095-007-9316-2
86. Sandhu SK, Papadopoulos K, Fong PC, Patnaik A, Messiou C, Olmos D, Wang G, Tromp BJ, Puchalski TA, Balkwill F, et al. A first-in-human, first-in-class, phase I study of carlumab (CNTO 888), a human monoclonal antibody against CC-chemokine ligand 2 in patients with solid tumors. Cancer Chemother Pharmacol 2013; 71:1041-50; PMID:23385782; http://dx.doi.org/10.1007/s00280-013-2099-8
87. Doi T, Ohtsu A, Fuse N, Yoshino T, Tahara M, Shibayama K, Takubo T, Weinreich DM. Phase 1 study of trebananib (AMG 386), an angiogenesis targeting angiopoietin-1/2 antagonist, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol 2013; 71:227-35; PMID:23124648; http://dx.doi.org/10.1007/s00280-012-2000-1
88. Pienta KJ, Machiels JP, Schrijvers D, Alekseev B, Shkolnik M, Crabb SJ, Li S, Seetharam S, Puchalski TA, Takimoto C, et al. Phase 2 study of carlumab (CNTO 888), a human monoclonal antibody against CC-chemokine ligand 2 (CCL2), in metastatic castration-resistant prostate cancer. Invest New Drugs 2013; 31:760-8; PMID:22907596; http://dx.doi.org/10.1007/s10637-012-9869-8
89. Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic cell death in cancer therapy. Annu Rev Immunol 2013; 31:51-72; PMID:23157435; http://dx.doi.org/10.1146/annurev-immunol-032712-100008
90. Vacchelli E, Galluzzi L, Fridman WH, Galon J, Sautès-Fridman C, Tartour E, Kroemer G. Trial watch: Chemotherapy with immunogenic cell death inducers. Oncoimmunology 2012; 1:179-88; PMID:22720239; http://dx.doi.org/10.4161/onci.1.2.19026
91. Ryan CJ, Rosenthal M, Ng S, Alumkal J, Picus J, Gravis G, Fizazi K, Forget F, Machiels JP, Srinivas S, et al. Targeted MET inhibition in castration-resistant prostate cancer: a randomized phase II study and biomarker analysis with rilotumumab plus mitoxantrone and prednisone. Clin Cancer Res 2013; 19:215-24; PMID:23136195; http://dx.doi.org/10.1158/1078-0432.CCR-12-2605
92. Galluzzi L. New immunotherapeutic paradigms for castration-resistant prostate cancer. OncoImmunology 2013; 2:e26084; http://dx.doi.org/10.4161/onci.26084
93. Waldmann TA, Conlon KC, Stewart DM, Worthy TA, Janik JE, Fleisher TA, Albert PS, Fig. WD, Spencer SD, Raffeld M, et al. Phase 1 trial of IL-15 trans presentation blockade using humanized Mikβ1 mAb in patients with T-cell large granular lymphocytic leukemia. Blood 2013; 121:476-84; PMID:23212516; http://dx.doi.org/10.1182/blood-2012-08-450585
94. Schweighofer CD, Tuchscherer A, Sperka S, Meyer T, Rattel B, Stein S, Ismail S, Elter T, Staib P, Reiser M, et al. Clinical safety and pharmacological profile of the HLA-DR antibody 1D09C3 in patients with B cell chronic lymphocytic leukemia and lymphoma: results from a phase I study. Cancer Immunol Immunother 2012; 61:2367-73; PMID:23090290; http://dx.doi.org/10.1007/s00262-012-1362-x
95. Wolpin BM, O'Reilly EM, Ko YJ, Blaszkowsky LS, Rarick M, Rocha-Lima CM, Ritch P, Chan E, Spratlin J, Macarulla T, et al. Global, multicenter, randomized, phase II trial of gemcitabine and gemcitabine plus AGS-1C4D4 in patients with previously untreated, metastatic pancreatic cancer. Ann Oncol 2013; 24:1792-801; PMID:23448807; http://dx.doi.org/10.1093/annonc/mdt066
96. Topp MS, Gökbuget N, Zugmaier G, Degenhard E, Goebeler ME, Klinger M, Neumann SA, Horst HA, Raff T, Viardot A, et al. Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL. Blood 2012; 120:5185-7; PMID:23024237; http://dx.doi.org/10.1182/blood-2012-07-441030
97. Armstrong DK, White AJ, Weil SC, Phillips M, Coleman RL. Farletuzumab (a monoclonal antibody against folate receptor alpha) in relapsed platinum-sensitive ovarian cancer. Gynecol Oncol 2013; 129:452-8; PMID:23474348; http://dx.doi.org/10.1016/j.ygyno.2013.03.002
98. Zhu AX, Gold PJ, El-Khoueiry AB, Abrams TA, Morikawa H, Ohishi N, Ohtomo T, Philip PA. First-in-man phase I study of GC33, a novel recombinant humanized antibody against glypican-3, in patients with advanced hepatocellular carcinoma. Clin Cancer Res 2013; 19:920-8; PMID:23362325; http://dx.doi.org/10.1158/1078-0432.CCR-12-2616
99. Fayad L, Offner F, Smith MR, Verhoef G, Johnson P, Kaufman JL, Rohatiner A, Advani A, Foran J, Hess G, et al. Safety and clinical activity of a combination therapy comprising two antibody-based targeting agents for the treatment of non-Hodgkin lymphoma: results of a phase I/II study evaluating the immunoconjugate inotuzumab ozogamicin with rituximab. J Clin Oncol 2013; 31:573-83; PMID:23295790; http://dx.doi.org/10.1200/JCO.2012.42.7211
100. Heidenreich A, Rawal SK, Szkarlat K, Bogdanova N, Dirix L, Stenzl A, Welslau M, Wang G, Dawkins F, de Boer CJ, et al. A randomized, double-blind, multicenter, phase 2 study of a human monoclonal antibody to human αv integrins (intetumumab) in combination with docetaxel and prednisone for the first-line treatment of patients with metastatic castration-resistant prostate cancer. Ann Oncol 2013; 24:329-36; PMID:23104724; http://dx.doi.org/10.1093/annonc/mds505
101. Infante JR, Bendell JC, Goff LW, Jones SF, Chan E, Sudo T, Burris HA, Berlin JD. Safety, pharmacokinetics and pharmacodynamics of the anti-A33 fully-human monoclonal antibody, KRN330, in patients with advanced colorectal cancer. Eur J Cancer 2013; 49:1169-75; PMID:23294608; http://dx.doi.org/10.1016/j.ejca.2012.11.033
102. Kim SH, Shim HS, Cho J, Jeong JH, Kim SM, Hong YK, Sung JH, Ha SJ, Kim HR, Chang H, et al. A phase I trial of gefitinib and nimotuzumab in patients with advanced non-small cell lung cancer (NSCLC). Lung Cancer 2013; 79:270-5; PMID:23261229; http://dx.doi.org/10.1016/j.lungcan.2012.11.017

103. Ogura M, Tobinai K, Hatake K, Uchida T, Suzuki T, Kobayashi Y, Mori M, Terui Y, Yokoyama M, Hotta T. Phase I study of obinutuzumab (GA101) in Japanese patients with relapsed or refractory B-cell non-Hodgkin lymphoma. Cancer Sci 2013; 104:105-10; PMID:23046388; http://dx.doi.org/10.1111/cas.12040

104. Felip E, Ranson M, Cedrés S, Dean E, Brewster M, Martínez P, McNally V, Ross G, Galdermans D. A phase Ib, dose-finding study of erlotinib in combination with a fixed dose of pertuzumab in patients with advanced non-small-cell lung cancer. Clin Lung Cancer 2012; 13:432-41; PMID:22609229; http://dx.doi.org/10.1016/j.cllc.2012.03.004

105. Kaye SB, Poole CJ, Dańska-Bidzińska A, Gianni L, Del Conte G, Gorbunova V, Novikova E, Strauss A, Moczko M, McNally VA, et al. A randomized phase II study evaluating the combination of carboplatin-based chemotherapy with pertuzumab versus carboplatin-based therapy alone in patients with relapsed, platinum-sensitive ovarian cancer. Ann Oncol 2013; 24:145-52; PMID:23002282; http://dx.doi.org/10.1093/annonc/mds282

106. Swain SM, Kim SB, Cortés J, Ro J, Semiglazov V, Campone M, Ciruelos E, Ferrero JM, Schneeweiss A, Knott A, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2013; 14:461-71; PMID:23602601; http://dx.doi.org/10.1016/S1470-2045(13)70130-X

107. Besse B, Tsao LC, Chao DT, Fang Y, Soria JC, Almokadem S, Belani CP. Phase Ib safety and pharmacokinetic study of volociximab, an anti-α5β1 integrin antibody, in combination with carboplatin and paclitaxel in advanced non-small-cell lung cancer. Ann Oncol 2013; 24:90-6; PMID:22904239; http://dx.doi.org/10.1093/annonc/mds281

108. Sekeres MA, Lancet JE, Wood BL, Grove LE, Sandalic L, Sievers EL, Jurcic JG. Randomized, phase IIb study of low-dose cytarabine and lintuzumab versus low-dose cytarabine and placebo in older adults with untreated acute myeloid leukemia. Haematologica 2013; 98:119-28; PMID:22801961; http://dx.doi.org/10.3324/haematol.2012.066613

109. Kato J, O'Donnell RT, Abuhay M, Tuscano JM. Efficacy and toxicity of a CD22-targeted antibody-saporin conjugate in a xenograft model of non-Hodgkin's lymphoma. Oncoimmunology 2012; 1:1469-75; PMID:23264893; http://dx.doi.org/10.4161/onci.21815

110. Vacchelli E, Vitale I, Tartour E, Eggermont A, Sautès-Fridman C, Galon J, Zitvogel L, Kroemer G, Galluzzi L. Trial Watch: Anticancer radioimmunotherapy. Oncoimmunology 2013; 2:e25595; PMID:24319634; http://dx.doi.org/10.4161/onci.25595

111. Vacchelli E, Eggermont A, Fridman WH, Galon J, Zitvogel L, Kroemer G, Galluzzi L. Trial Watch: Immunostimulatory cytokines. Oncoimmunology 2013; 2:e24850; PMID:24073369; http://dx.doi.org/10.4161/onci.24850

112. Vacchelli E, Galluzzi L, Eggermont A, Galon J, Tartour E, Zitvogel L, Kroemer G. Trial Watch: Immunostimulatory cytokines. Oncoimmunology 2012; 1:493-506; PMID:22754768; http://dx.doi.org/10.4161/onci.20459

113. Chen P, Balachandran S. Development of interferon γ-based immunocytokines targeting renal cancer. Oncoimmunology 2013; 2:e24964; PMID:24073376; http://dx.doi.org/10.4161/onci.24964

114. Pasquetto MV, Vecchia L, Covini D, Digilio R, Scotti C. Targeted drug delivery using immunoconjugates: principles and applications. J Immunother 2011; 34:611-28; PMID:21989410; http://dx.doi.org/10.1097/CJI.0b013e318234ecf5

115. Gulec SA, Cohen SJ, Pennington KL, Zuckier LS, Hauke RJ, Horne H, Wegener WA, Teoh N, Gold DV, Sharkey RM, et al. Treatment of advanced pancreatic carcinoma with 90Y-Clivatuzumab Tetraxetan: a phase I single-dose escalation trial. Clin Cancer Res 2011; 17:4091-100; PMID:21527562; http://dx.doi.org/10.1158/1078-0432.CCR-10-2579

116. Sharkey RM, Karacay H, Govindan SV, Goldenberg DM. Combination radioimmunotherapy and chemoimmunotherapy involving different or the same targets improves therapy of human pancreatic carcinoma xenograft models. Mol Cancer Ther 2011; 10:1072-81; PMID:21467164; http://dx.doi.org/10.1158/1535-7163.MCT-11-0115

117. Ocean AJ, Pennington KL, Guarino MJ, Sheikh A, Bekaii-Saab T, Serafini AN, Lee D, Sung MW, Gulec SA, Goldsmith SJ, et al. Fractionated radioimmunotherapy with (90) Y-clivatuzumab tetraxetan and low-dose gemcitabine is active in advanced pancreatic cancer: A phase 1 trial. Cancer 2012; 118:5497-506; PMID:22569804; http://dx.doi.org/10.1002/cncr.27592

118. Tarli L, Balza E, Viti F, Borsi L, Castellani P, Berndorff D, Dinkelborg L, Neri D, Zardi L. A high-affinity human antibody that targets tumoral blood vessels. Blood 1999; 94:192-8; PMID:10381513

119. Viti F, Tarli L, Giovannoni L, Zardi L, Neri D. Increased binding affinity and valence of recombinant antibody fragments lead to improved targeting of tumoral angiogenesis. Cancer Res 1999; 59:347-52; PMID:9927045

120. Spitaleri G, Berardi R, Pierantoni C, De Pas T, Noberasco C, Libbra C, González-Iglesias R, Giovannoni L, Tasciotti A, Neri D, et al. Phase I/II study of the tumour-targeting human monoclonal antibody-cytokine fusion protein L19-TNF in patients with advanced solid tumours. J Cancer Res Clin Oncol 2013; 139:447-55; PMID:23160853; http://dx.doi.org/10.1007/s00432-012-1327-7

121. Ossenkoppele GJ, Stussi G, Maertens J, van Montfort K, Biemond BJ, Breems D, Ferrant A, Graux C, de Greef GE, Halkes CJ, et al. Addition of bevacizumab to chemotherapy in acute myeloid leukemia at older age: a randomized phase 2 trial of the Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON) and the Swiss Group for Clinical Cancer Research (SAKK). Blood 2012; 120:4706-11; PMID:23047822; http://dx.doi.org/10.1182/blood-2012-04-420596

122. White D, Kassim A, Bhaskar B, Yi J, Wamstad K, Paton VE. Results from AMBER, a randomized phase 2 study of bevacizumab and bortezomib versus bortezomib in relapsed or refractory multiple myeloma. Cancer 2013; 119:339-47; PMID:22811009; http://dx.doi.org/10.1002/cncr.27745

123. Fury MG, Lee NY, Sherman E, Lisa D, Kelly K, Lipson B, Carlson D, Stambuk H, Haque S, Shen R, et al. A phase 2 study of bevacizumab with cisplatin plus intensity-modulated radiation therapy for stage III/IVB head and neck squamous cell cancer. Cancer 2012; 118:5008-14; PMID:22415650; http://dx.doi.org/10.1002/cncr.27498

124. Argiris A, Kotsakis AP, Hoang T, Worden FP, Savvides P, Gibson MK, Gyanchandani R, Blumenschein GR Jr., Chen HX, Grandis JR, et al. Cetuximab and bevacizumab: preclinical data and phase II trial in recurrent or metastatic squamous cell carcinoma of the head and neck. Ann Oncol 2013; 24:220-5; PMID:22898037; http://dx.doi.org/10.1093/annonc/mds245

125. Miles DW, de Haas SL, Dirix LY, Romieu G, Chan A, Pivot X, Tomczak P, Provencher L, Cortés J, Delmar PR, et al. Biomarker results from the AVADO phase 3 trial of first-line bevacizumab plus docetaxel for HER2-negative metastatic breast cancer. Br J Cancer 2013; 108:1052-60; PMID:23422754; http://dx.doi.org/10.1038/bjc.2013.69

126. Bisagni G, Musolino A, Panebianco M, De Matteis A, Nuzzo F, Ardizzoni A, Gori S, Gamucci T, Passalacqua R, Gnoni R, et al. The Breast Avastin Trial: phase II study of bevacizumab maintenance therapy after induction chemotherapy with docetaxel and capecitabine for the first-line treatment of patients with locally recurrent or metastatic breast cancer. Cancer Chemother Pharmacol 2013; 71:1051-7; PMID:23377310; http://dx.doi.org/10.1007/s00280-013-2100-6

127. Lang I, Brodowicz T, Ryvo L, Kahan Z, Greil R, Beslija S, Stemmer SM, Kaufman B, Zvirbule Z, Steger GG, et al.; Central European Cooperative Oncology Group. Bevacizumab plus paclitaxel versus bevacizumab plus capecitabine as first-line treatment for HER2-negative metastatic breast cancer: interim efficacy results of the randomised, open-label, non-inferiority, phase 3 TURANDOT trial. Lancet Oncol 2013; 14:125-33; PMID:23312888; http://dx.doi.org/10.1016/S1470-2045(12)70566-1

128. Tai CJ, Chen CS, Hung CS, Kuo LJ, Wei PL, Chiou JF, Hsu CH, Chiou HY, Wu CH. Bevacizumab plus docetaxel and cisplatin for metastatic breast cancer: a pilot phase II study. Anticancer Res 2012; 32:5501-6; PMID:23225458

129. Borson R, Harker G, Reeves J, Beck T, Hager S, Horvath W, Jones M, Tillinghast G, Arrowsmith E, Harrer G, et al. Phase II study of gemcitabine and bevacizumab as first-line treatment in taxane-pretreated, HER2-negative, locally recurrent or metastatic breast cancer. Clin Breast Cancer 2012; 12:322-30; PMID:23040000; http://dx.doi.org/10.1016/j.clbc.2012.07.004

130. Lang I, Inbar MJ, Kahán Z, Greil R, Beslija S, Stemmer SM, Kaufman B, Zvirbule Z, Steger GG, Messinger D, et al. Safety results from a phase III study (TURANDOT trial by CECOG) of first-line bevacizumab in combination with capecitabine or paclitaxel for HER-2-negative locally recurrent or metastatic breast cancer. Eur J Cancer 2012; 48:3140-9; PMID:22640829; http://dx.doi.org/10.1016/j.ejca.2012.04.022

131. Kottschade LA, Suman VJ, Perez DG, McWilliams RR, Kaur JS, Amatruda TT 3rd, Geoffroy FJ, Gross HM, Cohen PA, Jaslowski AJ, et al. A randomized phase 2 study of temozolomide and bevacizumab or nab-paclitaxel, carboplatin, and bevacizumab in patients with unresectable stage IV melanoma : a North Central Cancer Treatment Group study, N0775. Cancer 2013; 119:586-92; PMID:22915053; http://dx.doi.org/10.1002/cncr.27760

132. Choo SP, Chowbay B, Ng QS, Thng CH, Lim C, Hartono S, Koh TS, Huynh H, Poon D, Ang MK, et al. A Phase 1 dose-finding and pharmacodynamic study of rapamycin in combination with bevacizumab in patients with unresectable hepatocellular carcinoma. Eur J Cancer 2013; 49:999-1008; PMID:23265712; http://dx.doi.org/10.1016/j.ejca.2012.11.008

133. Govindarajan R, Siegel E, Makhoul I, Williamson S. Bevacizumab and erlotinib in previously untreated inoperable and metastatic hepatocellular carcinoma. Am J Clin Oncol 2013; 36:254-7; PMID:22643560; http://dx.doi.org/10.1097/COC.0b013e318248d83f

134. Hsu CH, Kang YK, Yang TS, Shun CT, Shao YY, Su WC, Sandoval-Tan J, Chiou TJ, Jin K, Hsu C, et al. Bevacizumab with erlotinib as first-line therapy in Asian patients with advanced hepatocellular carcinoma: a multicenter phase II study. Oncology 2013; 85:44-52; PMID:23838576; http://dx.doi.org/10.1159/000350841

135. Yau T, Wong H, Chan P, Yao TJ, Pang R, Cheung TT, Fan ST, Poon RT. Phase II study of bevacizumab and erlotinib in the treatment of advanced hepatocellular carcinoma patients with sorafenib-refractory disease. Invest New Drugs 2012; 30:2384-90; PMID:22402942; http://dx.doi.org/10.1007/s10637-012-9808-8

136. Buijs M, Reyes DK, Pawlik TM, Blackford AL, Salem R, Messersmith WA, Weekes CD, Mulcahy M, Kamel IR, Geschwind JF. Phase 2 trial of concurrent bevacizumab and transhepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. Cancer 2013; 119:1042-9; PMID:23132335; http://dx.doi.org/10.1002/cncr.27859

137. Martin LK, Li X, Kleiber B, Ellison EC, Bloomston M, Zalupski M, Bekaii-Saab TS. VEGF remains an interesting target in advanced pancreas cancer (APCA): results of a multi-institutional phase II study of bevacizumab, gemcitabine, and infusional 5-fluorouracil in patients with APCA. Ann Oncol 2012; 23:2812-20; PMID:22767582; http://dx.doi.org/10.1093/annonc/mds134

138. Wenham RM, Lapolla J, Lin HY, Apte SM, Lancaster JM, Judson PL, Gonzalez-Bosquet J, Herschberger A, Havrilesky LJ, Secord AA. A phase II trial of docetaxel and bevacizumab in recurrent ovarian cancer within 12 months of prior platinum-based chemotherapy. Gynecol Oncol 2013; 130:19-24; PMID:23623830; http://dx.doi.org/10.1016/j.ygyno.2013.04.049

139. Emile G, Chauvenet L, Tigaud JM, Chidiac J, Pujade Lauraine E, Alexandre J. A clinical experience of single agent bevacizumab in relapsing ovarian cancer. Gynecol Oncol 2013; 129:459-62; PMID:23474345; http://dx.doi.org/10.1016/j.ygyno.2013.02.035

140. Ikeda Y, Takano M, Oda K, Kouta H, Goto T, Kudoh K, Sasaki N, Kita T, Kikuchi Y. Weekly administration of bevacizumab, gemcitabine, and oxaliplatin in patients with recurrent and refractory ovarian cancer: a preliminary result of 19 cases. Int J Gynecol Cancer 2013; 23:355-60; PMID:23358182; http://dx.doi.org/10.1097/IGC.0b013e31827de69e

141. Stark D, Nankivell M, Pujade-Lauraine E, Kristensen G, Elit L, Stockler M, Hilpert F, Cervantes A, Brown J, Lanceley A, et al. Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phase 3 randomised trial. Lancet Oncol 2013; 14:236-43; PMID:23333117; http://dx.doi.org/10.1016/S1470-2045(12)70567-3

142. Tillmanns TD, Lowe MP, Walker MS, Stepanski EJ, Schwartzberg LS. Phase II clinical trial of bevacizumab with albumin-bound paclitaxel in patients with recurrent, platinum-resistant primary epithelial ovarian or primary peritoneal carcinoma. Gynecol Oncol 2013; 128:221-8; PMID:22960352; http://dx.doi.org/10.1016/j.ygyno.2012.08.039

143. Verschraegen CF, Czok S, Muller CY, Boyd L, Lee SJ, Rutledge T, Blank S, Pothuri B, Eberhardt S, Muggia F. Phase II study of bevacizumab with liposomal doxorubicin for patients with platinum- and taxane-resistant ovarian cancer. Ann Oncol 2012; 23:3104-10; PMID:22851407; http://dx.doi.org/10.1093/annonc/mds172

144. Ross RW, Galsky MD, Febbo P, Barry M, Richie JP, Xie W, Fennessy FM, Bhatt RS, Hayes J, Choueiri TK, et al. Phase 2 study of neoadjuvant docetaxel plus bevacizumab in patients with high-risk localized prostate cancer: a Prostate Cancer Clinical Trials Consortium trial. Cancer 2012; 118:4777-84; PMID:22282219; http://dx.doi.org/10.1002/cncr.27416

145. Loupakis F, Schirripa M, Caparello C, Funel N, Pollina L, Vasile E, Cremolini C, Salvatore L, Morvillo M, Antoniotti C, et al. Histopathologic evaluation of liver metastases from colorectal cancer in patients treated with FOLFOXIRI plus bevacizumab. Br J Cancer 2013; 108:2549-56; PMID:23703247; http://dx.doi.org/10.1038/bjc.2013.245

146. Wagner L, Turpin B, Nagarajan R, Weiss B, Cripe T, Geller J. Pilot study of vincristine, oral irinotecan, and temozolomide (VOIT regimen) combined with bevacizumab in pediatric patients with recurrent solid tumors or brain tumors. Pediatr Blood Cancer 2013; 60:1447-51; PMID:23630159; http://dx.doi.org/10.1002/pbc.24547

147. Zighelboim I, Wright JD, Gao F, Case AS, Massad LS, Mutch DG, Powell MA, Thaker PH, Eisenhauer EL, Cohn DE, et al. Multicenter phase II trial of topotecan, cisplatin and bevacizumab for recurrent or persistent cervical cancer. Gynecol Oncol 2013; 130:64-8; PMID:23591400; http://dx.doi.org/10.1016/j.ygyno.2013.04.009

148. Tsimberidou AM, Ye Y, Wheler J, Naing A, Hong D, Nwosu U, Hess KR, Wolff RA. A phase I study of hepatic arterial infusion of nab-paclitaxel in combination with intravenous gemcitabine and bevacizumab for patients with advanced cancers and predominant liver metastases. Cancer Chemother Pharmacol 2013; 71:955-63; PMID:23377373; http://dx.doi.org/10.1007/s00280-013-2088-y

149. Balar AV, Apolo AB, Ostrovnaya I, Mironov S, Iasonos A, Trout A, Regazzi AM, Garcia-Grossman IR, Gallagher DJ, Milowsky MI, et al. Phase II study of gemcitabine, carboplatin, and bevacizumab in patients with advanced unresectable or metastatic urothelial cancer. J Clin Oncol 2013; 31:724-30; PMID:23341513; http://dx.doi.org/10.1200/JCO.2012.42.5215

150. Alvarez EA, Brady WE, Walker JL, Rotmensch J, Zhou XC, Kendrick JE, Yamada SD, Schilder JM, Cohn DE, Harrison CR, et al. Phase II trial of combination bevacizumab and temsirolimus in the treatment of recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2013; 129:22-7; PMID:23262204; http://dx.doi.org/10.1016/j.ygyno.2012.12.022

151. Navid F, Baker SD, McCarville MB, Stewart CF, Billups CA, Wu J, Davidoff AM, Spunt SL, Furman WL, McGregor LM, et al. Phase I and clinical pharmacology study of bevacizumab, sorafenib, and low-dose cyclophosphamide in children and young adults with refractory/recurrent solid tumors. Clin Cancer Res 2013; 19:236-46; PMID:23143218; http://dx.doi.org/10.1158/1078-0432.CCR-12-1897

152. Okines AF, Langley RE, Thompson LC, Stenning SP, Stevenson L, Falk S, Seymour M, Coxon F, Middleton GW, Smith D, et al. Bevacizumab with peri-operative epirubicin, cisplatin and capecitabine (ECX) in localised gastro-oesophageal adenocarcinoma: a safety report. Ann Oncol 2013; 24:702-9; PMID:23108952; http://dx.doi.org/10.1093/annonc/mds533

153. Moroney J, Fu S, Moulder S, Falchook G, Helgason T, Levenback C, Hong D, Naing A, Wheler J, Kurzrock R. Phase I study of the antiangiogenic antibody bevacizumab and the mTOR/hypoxia-inducible factor inhibitor temsirolimus combined with liposomal doxorubicin: tolerance and biological activity. Clin Cancer Res 2012; 18:5796-805; PMID:22927482; http://dx.doi.org/10.1158/1078-0432.CCR-12-1158

154. Agulnik M, Yarber JL, Okuno SH, von Mehren M, Jovanovic BD, Brockstein BE, Evens AM, Benjamin RS. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. Ann Oncol 2013; 24:257-63; PMID:22910841; http://dx.doi.org/10.1093/annonc/mds237

155. Gaykema SB, Brouwers AH, Lub-de Hooge MN, Pleijhuis RG, Timmer-Bosscha H, Pot L, van Dam GM, van der Meulen SB, de Jong JR, Bart J, et al. 89Zr-bevacizumab PET imaging in primary breast cancer. J Nucl Med 2013; 54:1014-8; PMID:23651946; http://dx.doi.org/10.2967/jnumed.112.117218

156. Gianni L, Romieu GH, Lichinitser M, Serrano SV, Mansutti M, Pivot X, Mariani P, Andre F, Chan A, Lipatov O, et al. AVEREL: a randomized phase III Trial evaluating bevacizumab in combination with docetaxel and trastuzumab as first-line therapy for HER2-positive locally recurrent/metastatic breast cancer. J Clin Oncol 2013; 31:1719-25; PMID:23569311; http://dx.doi.org/10.1200/JCO.2012.44.7912

157. Brufsky AM, Hurvitz S, Perez E, Swamy R, Valero V, O'Neill V, Rugo HS. RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 2011; 29:4286-93; PMID:21990397; http://dx.doi.org/10.1200/JCO.2010.34.1255

158. Robert NJ, Diéras V, Glaspy J, Brufsky AM, Bondarenko I, Lipatov ON, Perez EA, Yardley DA, Chan SY, Zhou X, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol 2011; 29:1252-60; PMID:21383283; http://dx.doi.org/10.1200/JCO.2010.28.0982

159. Lambrechts D, Lenz HJ, de Haas S, Carmeliet P, Scherer SJ. Markers of response for the antiangiogenic agent bevacizumab. J Clin Oncol 2013; 31:1219-30; PMID:23401453; http://dx.doi.org/10.1200/JCO.2012.46.2762

160. Galluzzi L, Vitale I, Senovilla L, Olaussen KA, Pinna G, Eisenberg T, Goubar A, Martins I, Michels J, Kratassiouk G, et al. Prognostic impact of vitamin B6 metabolism in lung cancer. Cell Rep 2012; 2:257-69; PMID:22854025; http://dx.doi.org/10.1016/j.celrep.2012.06.017

161. Galluzzi L, Senovilla L, Vitale I, Michels J, Martins I, Kepp O, Castedo M, Kroemer G. Molecular mechanisms of cisplatin resistance. Oncogene 2012; 31:1869-83; PMID:21892204; http://dx.doi.org/10.1038/onc.2011.384

162. Galluzzi L, Morselli E, Vitale I, Kepp O, Senovilla L, Criollo A, Servant N, Paccard C, Hupé P, Robert T, et al. miR-181a and miR-630 regulate cisplatin-induced cancer cell death. Cancer Res 2010; 70:1793-803; PMID:20145152; http://dx.doi.org/10.1158/0008-5472.CAN-09-3112

163. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, Carey MS, Beale P, Cervantes A, Kurzeder C, et al.; ICON7 Investigators. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011; 365:2484-96; PMID:22204725; http://dx.doi.org/10.1056/NEJMoa1103799

164. Boehrer S, Adès L, Braun T, Galluzzi L, Grosjean J, Fabre C, Le Roux G, Gardin C, Martin A, de Botton S, et al. Erlotinib exhibits antineoplastic off-target effects in AML and MDS: a preclinical study. Blood 2008; 111:2170-80; PMID:17925489; http://dx.doi.org/10.1182/blood-2007-07-100362

165. de La Motte Rouge T, Galluzzi L, Olaussen KA, Zermati Y, Tasdemir E, Robert T, Ripoche H, Lazar V, Dessen P, Harper F, et al. A novel epidermal growth factor receptor inhibitor promotes apoptosis in non-small cell lung cancer cells resistant to erlotinib. Cancer Res 2007; 67:6253-62; PMID:17616683; http://dx.doi.org/10.1158/0008-5472.CAN-07-0538

166. Baselga J, Gómez P, Greil R, Braga S, Climent MA, Wardley AM, Kaufman B, Stemmer SM, Pêgo A, Chan A, et al. Randomized phase II study of the anti-epidermal growth factor receptor monoclonal antibody cetuximab with cisplatin versus cisplatin alone in patients with metastatic triple-negative breast cancer. J Clin Oncol 2013; 31:2586-92; PMID:23733761; http://dx.doi.org/10.1200/JCO.2012.46.2408

167. Crosby T, Hurt CN, Falk S, Gollins S, Mukherjee S, Staffurth J, Ray R, Bashir N, Bridgewater JA, Geh JI, et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. Lancet Oncol 2013; 14:627-37; PMID:23623280; http://dx.doi.org/10.1016/S1470-2045(13)70136-0

168. Chen Y, Wu X, Bu S, He C, Wang W, Liu J, Guo W, Tan B, Wang Y, Wang J. Promising outcomes of definitive chemoradiation and cetuximab for patients with esophageal squamous cell carcinoma. Cancer Sci 2012; 103:1979-84; PMID:22845557; http://dx.doi.org/10.1111/j.1349-7006.2012.02393.x

169. Lordick F, Kang YK, Chung HC, Salman P, Oh SC, Bodoky G, Kurteva G, Volovat C, Moiseyenko VM, Gorbunova V, et al.; Arbeitsgemeinschaft Internistische Onkologie and EXPAND Investigators. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol 2013; 14:490-9; PMID:23594786; http://dx.doi.org/10.1016/S1470-2045(13)70102-5

170. Falchook GS, Naing A, Hong DS, Zinner R, Fu S, Piha-Paul SA, Tsimberidou AM, Morgan-Linnell SK, Jiang Y, Bastida C, et al. Dual EGFR inhibition in combination with anti-VEGF treatment: a phase I clinical trial in non-small cell lung cancer. Oncotarget 2013; 4:118-27; PMID:23435217

171. Bonomi PD, Mace J, Mandanas RA, Min M, Olsen M, Youssoufian H, Katz TL, Sheth G, Lee HJ. Randomized phase II study of cetuximab and bevacizumab in combination with two regimens of paclitaxel and carboplatin in chemonaive patients with stage IIIB/IV non-small-cell lung cancer. J Thorac Oncol 2013; 8:338-45; PMID:23370316

172. Pipas JM, Zaki BI, McGowan MM, Tsapakos MJ, Ripple GH, Suriawinata AA, Tsongalis GJ, Colacchio TA, Gordon SR, Sutton JE, et al. Neoadjuvant cetuximab, twice-weekly gemcitabine, and intensity-modulated radiotherapy (IMRT) in patients with pancreatic adenocarcinoma. Ann Oncol 2012; 23:2820-7; PMID:22571859; http://dx.doi.org/10.1093/annonc/mds109

173. Merchan JR, Ferrell A, Macintyre J, Ciombor KK, Levi J, Ribeiro A, Sleeman D, Flores A, Lopes G, Rocha-Lima CM. Phase II study of gemcitabine, oxaliplatin, and cetuximab in advanced pancreatic cancer. Am J Clin Oncol 2012; 35:446-50; PMID:21552097; http://dx.doi.org/10.1097/COC.0b013e31821862fb

174. Kordes S, Richel DJ, Klümpen HJ, Weterman MJ, Stevens AJ, Wilmink JW. A phase I/II, non-randomized, feasibility/safety and efficacy study of the combination of everolimus, cetuximab and capecitabine in patients with advanced pancreatic cancer. Invest New Drugs 2013; 31:85-91; PMID:22367239; http://dx.doi.org/10.1007/s10637-012-9802-1

175. Deeken JF, Shimkus B, Liem A, Hill D, Gurtler J, Berghorn E, Townes L, Lu H, Trifan O, Zhang S. Evaluation of the relationship between cetuximab therapy and corrected QT interval changes in patients with advanced malignancies from solid tumors. Cancer Chemother Pharmacol 2013; 71:1473-83; PMID:23589315; http://dx.doi.org/10.1007/s00280-013-2146-5

176. Cathomas R, Rothermundt C, Klingbiel D, Bubendorf L, Jaggi R, Betticher DC, Brauchli P, Cotting D, Droege C, Winterhalder R, et al.; Swiss Group for Clinical Cancer Research SAKK. Efficacy of cetuximab in metastatic castration-resistant prostate cancer might depend on EGFR and PTEN expression: results from a phase II trial (SAKK 08/07). Clin Cancer Res 2012; 18:6049-57; PMID:22977195; http://dx.doi.org/10.1158/1078-0432.CCR-12-2219

177. Moore KN, Sill MW, Miller DS, McCourt C, De Geest K, Rose PG, Cardenes HR, Mannel RS, Farley JH, Schilder RJ, et al. A phase I trial of tailored radiation therapy with concomitant cetuximab and cisplatin in the treatment of patients with cervical cancer: A gynecologic oncology group study. Gynecol Oncol 2012; 127:456-61; PMID:22960004; http://dx.doi.org/10.1016/j.ygyno.2012.08.030

178. Wong YN, Litwin S, Vaughn D, Cohen S, Plimack ER, Lee J, Song W, Dabrow M, Brody M, Tuttle H, et al. Phase II trial of cetuximab with or without paclitaxel in patients with advanced urothelial tract carcinoma. J Clin Oncol 2012; 30:3545-51; PMID:22927525; http://dx.doi.org/10.1200/JCO.2012.41.9572

179. Ha HT, Griffith KA, Zalupski MM, Schuetze SM, Thomas DG, Lucas DR, Baker LH, Chugh R. Phase II trial of cetuximab in patients with metastatic or locally advanced soft tissue or bone sarcoma. Am J Clin Oncol 2013; 36:77-82; PMID:22237145; http://dx.doi.org/10.1097/COC.0b013e31823a4970

180. Mamot C, Ritschard R, Wicki A, Stehle G, Dieterle T, Bubendorf L, Hilker C, Deuster S, Herrmann R, Rochlitz C. Tolerability, safety, pharmacokinetics, and efficacy of doxorubicin-loaded anti-EGFR immunoliposomes in advanced solid tumours: a phase 1 dose-escalation study. Lancet Oncol 2012; 13:1234-41; PMID:23153506; http://dx.doi.org/10.1016/S1470-2045(12)70476-X

181. Scagliotti GV, Hirsh V, Siena S, Henry DH, Woll PJ, Manegold C, Solal-Celigny P, Rodriguez G, Krzakowski M, Mehta ND, et al. Overall survival improvement in patients with lung cancer and bone metastases treated with denosumab versus zoledronic acid: subgroup analysis from a randomized phase 3 study. J Thorac Oncol 2012; 7:1823-9; PMID:23154554; http://dx.doi.org/10.1097/JTO.0b013e31826aec2b

182. Vermorken JB, Stöhlmacher-Williams J, Davidenko I, Licitra L, Winquist E, Villanueva C, Foa P, Rottey S, Skladowski K, Tahara M, et al.; SPECTRUM investigators. Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial. Lancet Oncol 2013; 14:697-710; PMID:23746666; http://dx.doi.org/10.1016/S1470-2045(13)70181-5

183. Steffensen KD, Waldstrøm M, Pallisgård N, Lund B, Bergfeldt K, Wihl J, Keldsen N, Marth C, Vergote I, Jakobsen A. Panitumumab and pegylated liposomal doxorubicin in platinum-resistant epithelial ovarian cancer with KRAS wild-type: the PaLiDo study, a phase II nonrandomized multicenter study. Int J Gynecol Cancer 2013; 23:73-80; PMID:23211422; http://dx.doi.org/10.1097/IGC.0b013e3182775fae

184. Timmerman JM, Byrd JC, Andorsky DJ, Yamada RE, Kramer J, Muthusamy N, Hunder N, Pagel JM. A phase I dose-finding trial of recombinant interleukin-21 and rituximab in relapsed and refractory low grade B-cell lymphoproliferative disorders. Clin Cancer Res 2012; 18:5752-60; PMID:22893631; http://dx.doi.org/10.1158/1078-0432.CCR-12-0456

185. Waddell T, Chau I, Cunningham D, Gonzalez D, Okines AF, Okines C, Wotherspoon A, Saffery C, Middleton G, Wadsley J, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol 2013; 14:481-9; PMID:23594787; http://dx.doi.org/10.1016/S1470-2045(13)70096-2

186. Ogura M, Hatake K, Tobinai K, Uchida T, Suzuki T, Terui Y, Yokoyama M, Maruyama D, Mori M, Jewell RC, et al. Phase I study of ofatumumab, a human anti-CD20 antibody, in Japanese patients with relapsed or refractory chronic lymphocytic leukemia and small lymphocytic lymphoma. Jpn J Clin Oncol 2013; 43:466-75; PMID:23456745; http://dx.doi.org/10.1093/jjco/hyt022

187. Giusti RM, Shastri K, Pilaro AM, Fuchs C, Cordoba-Rodriguez R, Koti K, Rothmann M, Men AY, Zhao H, Hughes M, et al. U.S. Food and Drug Administration approval: panitumumab for epidermal growth factor receptor-expressing metastatic colorectal carcinoma with progression following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Clin Cancer Res 2008; 14:1296-302; PMID:18316547; http://dx.doi.org/10.1158/1078-0432.CCR-07-1354

188. Hecht JR, Mitchell E, Chidiac T, Scroggin C, Hagenstad C, Spigel D, Marshall J, Cohn A, McCollum D, Stella P, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol 2009; 27:672-80; PMID:19114685; http://dx.doi.org/10.1200/JCO.2008.19.8135

189. Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, Juan T, Sikorski R, Suggs S, Radinsky R, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008; 26:1626-34; PMID:18316791; http://dx.doi.org/10.1200/JCO.2007.14.7116

190. Cortés J, Fumoleau P, Bianchi GV, Petrella TM, Gelmon K, Pivot X, Verma S, Albanell J, Conte P, Lluch A, et al. Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 2012; 30:1594-600; PMID:22393084; http://dx.doi.org/10.1200/JCO.2011.37.4207

191. Boross P, Lohse S, Nederend M, Jansen JH, van Tetering G, Dechant M, Peipp M, Royle L, Liew LP, Boon L, et al. IgA EGFR antibodies mediate tumour killing in vivo. EMBO Mol Med 2013; 5:1213-26; PMID:23918228; http://dx.doi.org/10.1002/emmm.201201929

192. Bebb G, Smith C, Rorke S, Boland W, Nicacio L, Sukhoo R, Brade A. Phase I clinical trial of the anti-EGFR monoclonal antibody nimotuzumab with concurrent external thoracic radiotherapy in Canadian patients diagnosed with stage IIb, III or IV non-small cell lung cancer unsuitable for radical therapy. Cancer Chemother Pharmacol 2011; 67:837-45; PMID:20563810; http://dx.doi.org/10.1007/s00280-010-1379-9

193. Choi HJ, Sohn JH, Lee CG, Shim HS, Lee IJ, Yang WI, Kwon JE, Kim SK, Park MS, Lee JH, et al. A phase I study of nimotuzumab in combination with radiotherapy in stages IIB-IV non-small cell lung cancer unsuitable for radical therapy: Korean results. Lung Cancer 2011; 71:55-9; PMID:20451284; http://dx.doi.org/10.1016/j.lungcan.2010.04.010

194. Hong J, Peng Y, Liao Y, Jiang W, Wei R, Huo L, Han Z, Duan C, Zhong M. Nimotuzumab prolongs survival in patients with malignant gliomas: A phase I/II clinical study of concomitant radiochemotherapy with or without nimotuzumab. Exp Ther Med 2012; 4:151-7; PMID:23060940

195. Kuenen B, Witteveen PO, Ruijter R, Giaccone G, Dontabhaktuni A, Fox F, Katz T, Youssoufian H, Zhu J, Rowinsky EK, et al. A phase I pharmacologic study of necitumumab (IMC-11F8), a fully human IgG1 monoclonal antibody directed against EGFR in patients with advanced solid malignancies. Clin Cancer Res 2010; 16:1915-23; PMID:20197484; http://dx.doi.org/10.1158/1078-0432.CCR-09-2425

196. Li LF, Wang HQ, Liu XM, Zhang HL, Qiu LH, Qian ZZ, Li W. [Nimotuzumab in combination with chemotherapy in patients with advanced non-small cell lung cancer]. Zhonghua Zhong Liu Za Zhi 2011; 33:626-8; PMID:22325226
197. Ling Y, Chen J, Tao M, Chu X, Zhang X. A pilot study of nimotuzumab combined with cisplatin and 5-FU in patients with advanced esophageal squamous cell carcinoma. J Thorac Dis 2012; 4:58-62; PMID:22295168
198. Qi DL, Wang HQ, Li Y, Huang CB, Wang QS, Xu L, Yang YZ, Cui Y, Xin L. [Efficacy and adverse effets of nimotuzumab plus palitaxel liposome and carboplatin in the treatment for advanced non-small cell lung cancer]. Zhonghua Zhong Liu Za Zhi 2012; 34:152-5; PMID:22780937
199. Ramos-Suzarte M, Lorenzo-Luaces P, Lazo NG, Perez ML, Soriano JL, Gonzalez CE, Hernadez IM, Albuerne YÁ, Moreno BP, Alvarez ES, et al. Treatment of malignant, non-resectable, epithelial origin esophageal tumours with the humanized anti-epidermal growth factor antibody nimotuzumab combined with radiation therapy and chemotherapy. Cancer Biol Ther 2012; 13:600-5; PMID:22555809; http://dx.doi.org/10.4161/cbt.19849
200. Strumberg D, Schultheis B, Scheulen ME, Hilger RA, Krauss J, Marschner N, Lordick F, Bach F, Reuter D, Edler L, et al. Phase II study of nimotuzumab, a humanized monoclonal anti-epidermal growth factor receptor (EGFR) antibody, in patients with locally advanced or metastatic pancreatic cancer. Invest New Drugs 2012; 30:1138-43; PMID:21170759; http://dx.doi.org/10.1007/s10637-010-9619-8
201. Verduzco-Rodríguez L, Aguirre-González EH, Verduzco-Aguirre HC. Durable complete response induced by paclitaxel-nimotuzumab-methotrexate chemotherapy in a patient with metastatic head and neck squamous cell carcinoma. Hematol Oncol Stem Cell Ther 2011; 4:182-4; PMID:22198189
202. Yang QY, Shen D, Sai K, Mu YG, Jiang XB, Zhang XH, Chen ZP. [Nimotuzumab in combination with chemotherapy for patients with malignant gliomas]. Zhonghua Zhong Liu Za Zhi 2011; 33:232-5; PMID:21575527
203. You B, Brade A, Magalhaes JM, Siu LL, Oza A, Lovell S, Wang L, Hedley DW, Nicacio LV, Chen EX. A dose-escalation phase I trial of nimotuzumab, an antibody against the epidermal growth factor receptor, in patients with advanced solid malignancies. Invest New Drugs 2011; 29:996-1003; PMID:20454832; http://dx.doi.org/10.1007/s10637-010-9444-0
204. Zhao KL, Hu XC, Wu XH, Fu XL, Fan M, Jiang GL. A phase I dose escalation study of Nimotuzumab in combination with concurrent chemoradiation for patients with locally advanced squamous cell carcinoma of esophagus. Invest New Drugs 2012; 30:1585-90; PMID:21901403; http://dx.doi.org/10.1007/s10637-011-9735-0
205. Zhao XY, Guo Y, Zhu YX, Wang Y, Zhu GP, Hu CS, Ji QH. [Clinical analysis of nimotuzumab plus cisplatin and fluorouracil regimen as induction treatment in resectable head and neck squamous cell carcinoma]. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2012; 47:536-9; PMID:22932235
206. Gopal AK, Pagel JM, Fromm JR, Wilbur S, Press OW. 131I anti-CD45 radioimmunotherapy effectively targets and treats T-cell non-Hodgkin lymphoma. Blood 2009; 113:5905-10; PMID:19332764; http://dx.doi.org/10.1182/blood-2009-02-205476
207. Matthews DC, Appelbaum FR, Eary JF, Fisher DR, Durack LD, Hui TE, Martin PJ, Mitchell D, Press OW, Storb R, et al. Phase I study of (131)I-anti-CD45 antibody plus cyclophosphamide and total body irradiation for advanced acute leukemia and myelodysplastic syndrome. Blood 1999; 94:1237-47; PMID:10438711
208. Nagorsen D, Kufer P, Baeuerle PA, Bargou R. Blinatumomab: a historical perspective. Pharmacol Ther 2012; 136:334-42; PMID:22940266; http://dx.doi.org/10.1016/j.pharmthera.2012.07.013
209. Nagorsen D, Baeuerle PA. Immunomodulatory therapy of cancer with T cell-engaging BiTE antibody blinatumomab. Exp Cell Res 2011; 317:1255-60; PMID:21419116; http://dx.doi.org/10.1016/j.yexcr.2011.03.010
210. Topp MS, Kufer P, Gökbuget N, Goebeler M, Klinger M, Neumann S, Horst HA, Raff T, Viardot A, Schmid M, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J Clin Oncol 2011; 29:2493-8; PMID:21576633; http://dx.doi.org/10.1200/JCO.2010.32.7270
211. Murray JL, Kleinerman ES, Jia SF, Rosenblum MG, Eton O, Buzaid A, Legha S, Ross MI, Thompson L, Mujoo K, et al. Phase Ia/Ib trial of anti-GD2 chimeric monoclonal antibody 14.18 (ch14.18) and recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) in metastatic melanoma. J Immunother Emphasis Tumor Immunol 1996; 19:206-17; PMID:8811495; http://dx.doi.org/10.1097/00002371-199605000-00005
212. Ozkaynak MF, Sondel PM, Krailo MD, Gan J, Javorsky B, Reisfeld RA, Matthay KK, Reaman GH, Seeger RC. Phase I study of chimeric human/murine anti-ganglioside G(D2) monoclonal antibody (ch14.18) with granulocyte-macrophage colony-stimulating factor in children with neuroblastoma immediately after hematopoietic stem-cell transplantation: a Children's Cancer Group Study. J Clin Oncol 2000; 18:4077-85; PMID:11118469
213. Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, Smith M, Anderson B, Villablanca JG, Matthay KK, et al.; Children's Oncology Group. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med 2010; 363:1324-34; PMID:20879881; http://dx.doi.org/10.1056/NEJMoa0911123
214. Simon T, Hero B, Faldum A, Handgretinger R, Schrappe M, Klingebiel T, Berthold F. Long term outcome of high-risk neuroblastoma patients after immunotherapy with antibody ch14.18 or oral metronomic chemotherapy. BMC Cancer 2011; 11:21; PMID:21244693; http://dx.doi.org/10.1186/1471-2407-11-21
215. Modak S, Kushner BH, Kramer K, Vickers A, Cheung IY, Cheung NK. Anti-GD2 antibody 3F8 and barley-derived (1 ® 3),(1 ® 4)-β-D-glucan: A Phase I study in patients with chemoresistant neuroblastoma. Oncoimmunology 2013; 2:e23402; PMID:23802080; http://dx.doi.org/10.4161/onci.23402
216. Cheung NK, Guo H, Hu J, Tassev DV, Cheung IY. Humanizing murine IgG3 anti-GD2 antibody m3F8 substantially improves antibody-dependent cell-mediated cytotoxicity while retaining targeting in vivo. Oncoimmunology 2012; 1:477-86; PMID:22754766; http://dx.doi.org/10.4161/onci.19864
217. Nguyen QD, Lavdas I, Gubbins J, Smith G, Fortt R, Carroll LS, Graham MA, Aboagye EO. Temporal and spatial evolution of therapy-induced tumor apoptosis detected by caspase-3-selective molecular imaging. Clin Cancer Res 2013; 19:3914-24; PMID:23729364; http://dx.doi.org/10.1158/1078-0432.CCR-12-3814
218. Krepler C, Chunduru SK, Halloran MB, He X, Xiao M, Vultur A, Villanueva J, Mitsuuchi Y, Neiman EM, Benetatos C, et al. The novel SMAC mimetic birinapant exhibits potent activity against human melanoma cells. Clin Cancer Res 2013; 19:1784-94; PMID:23403634; http://dx.doi.org/10.1158/1078-0432.CCR-12-2518
219. Sutherland MK, Yu C, Anderson M, Zeng W, van Rooijen N, Sievers EL, Grewal IS, Law CL. 5-azacytidine enhances the anti-leukemic activity of lintuzumab (SGN-33) in preclinical models of acute myeloid leukemia. MAbs 2010; 2:2; PMID:20495353
220. Raza A, Jurcic JG, Roboz GJ, Maris M, Stephenson JJ, Wood BL, Feldman EJ, Galili N, Grove LE, Drachman JG, et al. Complete remissions observed in acute myeloid leukemia following prolonged exposure to lintuzumab: a phase 1 trial. Leuk Lymphoma 2009; 50:1336-44; PMID:19557623; http://dx.doi.org/10.1080/10428190903050013
221. Chillemi A, Zaccarello G, Quarona V, Ferracin M, Ghimenti C, Massaia M, Horenstein AL, Malavasi F. Anti-CD38 antibody therapy: windows of opportunity yielded by the functional characteristics of the target molecule. Mol Med 2013; 19:99-108; PMID:23615966; http://dx.doi.org/10.2119/molmed.2013.00009
222. Semeraro M, Vacchelli E, Eggermont A, Galon J, Zitvogel L, Kroemer G, et al. Trial Watch: Lenalidomide-based immunochemotherapy. OncoImmunology 2013; 2: e26494; http://dx.doi.org/10.4161/onci.26494
223. Sharkey RM, Karacay H, Vallabhajosula S, McBride WJ, Rossi EA, Chang CH, Goldsmith SJ, Goldenberg DM. Metastatic human colonic carcinoma: molecular imaging with pretargeted SPECT and PET in a mouse model. Radiology 2008; 246:497-507; PMID:18227543; http://dx.doi.org/10.1148/radiol.2462070229
224. Schoffelen R, van der Graaf WT, Franssen G, Sharkey RM, Goldenberg DM, McBride WJ, Rossi EA, Eek A, Oyen WJ, Boerman OC. Pretargeted 177Lu radioimmunotherapy of carcinoembryonic antigen-expressing human colonic tumors in mice. J Nucl Med 2010; 51:1780-7; PMID:21051650; http://dx.doi.org/10.2967/jnumed.110.079376
225. Schoffelen R, Boerman OC, Goldenberg DM, Sharkey RM, van Herpen CM, Franssen GM, McBride WJ, Chang CH, Rossi EA, van der Graaf WT, et al. Development of an imaging-guided CEA-pretargeted radionuclide treatment of advanced colorectal cancer: first clinical results. Br J Cancer 2013; 109:934-42; PMID:23860529; http://dx.doi.org/10.1038/bjc.2013.376
226. Younes A, Yasothan U, Kirkpatrick P. Brentuximab vedotin. Nat Rev Drug Discov 2012; 11:19-20; PMID:22212672; http://dx.doi.org/10.1038/nrd3629
227. Senter PD, Sievers EL. The discovery and development of brentuximab vedotin for use in relapsed Hodgkin lymphoma and systemic anaplastic large cell lymphoma. Nat Biotechnol 2012; 30:631-7; PMID:22781692; http://dx.doi.org/10.1038/nbt.2289
228. Fruman DA, Rommel C. PI3Kδ inhibitors in cancer: rationale and serendipity merge in the clinic. Cancer Discov 2011; 1:562-72; PMID:22586681; http://dx.doi.org/10.1158/2159-8290.CD-11-0249
229. Subramaniam PS, Whye DW, Efimenko E, Chen J, Tosello V, De Keersmaecker K, Kashishian A, Thompson MA, Castillo M, Cordon-Cardo C, et al. Targeting nonclassical oncogenes for therapy in T-ALL. Cancer Cell 2012; 21:459-72; PMID:22516257; http://dx.doi.org/10.1016/j.ccr.2012.02.029
230. Sahu JK, Prasad K. The opsoclonus–myoclonus syndrome. Pract Neurol 2011; 11:160-6; PMID:21551110; http://dx.doi.org/10.1136/practneurol-2011-000017
231. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, Jagiello-Gruszfeld A, Crown J, Chan A, Kaufman B, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006; 355:2733-43; PMID:17192538; http://dx.doi.org/10.1056/NEJMoa064320

232. Cheson BD. Ofatumumab, a novel anti-CD20 monoclonal antibody for the treatment of B-cell malignancies. J Clin Oncol 2010; 28:3525-30; PMID:20458041; http://dx.doi.org/10.1200/JCO.2010.27.9836

233. Wierda WG, Kipps TJ, Mayer J, Stilgenbauer S, Williams CD, Hellmann A, Robak T, Furman RR, Hillmen P, Trneny M, et al.; Hx-CD20-406 Study Investigators. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 2010; 28:1749-55; PMID:20194866; http://dx.doi.org/10.1200/JCO.2009.25.3187

234. Tarhini AA, Millward M, Mainwaring P, Kefford R, Logan T, Pavlick A, Kathman SJ, Laubscher KH, Dar MM, Kirkwood JM. A phase 2, randomized study of SB-485232, rhIL-18, in patients with previously untreated metastatic melanoma. Cancer 2009; 115:859-68; PMID:19140204; http://dx.doi.org/10.1002/cncr.24100

235. Uppenkamp M, Engert A, Diehl V, Bunjes D, Huhn D, Brittinger G. Monoclonal antibody therapy with CAMPATH-1H in patients with relapsed high- and low-grade non-Hodgkin's lymphomas: a multicenter phase I/II study. Ann Hematol 2002; 81:26-32; PMID:11807632; http://dx.doi.org/10.1007/s00277-001-0394-7

236. Schmitt B, Wendtner CM, Bergmann M, Busch R, Franke A, Pasold R, Schlag R, Hopfinger G, Hiddemann W, Emmerich B, et al. Fludarabine combination therapy for the treatment of chronic lymphocytic leukemia. Clin Lymphoma 2002; 3:26-35; PMID:12141952; http://dx.doi.org/10.3816/CLM.2002.n.008

237. Gibson TB, Ranganathan A, Grothey A. Randomized phase III trial results of panitumumab, a fully human anti-epidermal growth factor receptor monoclonal antibody, in metastatic colorectal cancer. Clin Colorectal Cancer 2006; 6:29-31; PMID:16796788; http://dx.doi.org/10.3816/CCC.2006.n.01

238. Gould P. Monoclonal antibody aids colorectal-cancer treatment. Lancet Oncol 2006; 7:370; PMID:16696165; http://dx.doi.org/10.1016/S1470-2045(06)70681-7

239. Rossi JF, Négrier S, James ND, Kocak I, Hawkins R, Davis H, Prabhakar U, Qin X, Mulders P, Berns B. A phase I/II study of siltuximab (CNTO 328), an anti-interleukin-6 monoclonal antibody, in metastatic renal cell cancer. Br J Cancer 2010; 103:1154-62; PMID:20808314; http://dx.doi.org/10.1038/sj.bjc.6605872

240. Hunsucker SA, Magarotto V, Kuhn DJ, Kornblau SM, Wang M, Weber DM, Thomas SK, Shah JJ, Voorhees PM, Xie H, et al. Blockade of interleukin-6 signalling with siltuximab enhances melphalan cytotoxicity in preclinical models of multiple myeloma. Br J Haematol 2011; 152:579-92; PMID:21241278; http://dx.doi.org/10.1111/j.1365-2141.2010.08533.x

241. Klinger M, Brandl C, Zugmaier G, Hijazi Y, Bargou RC, Topp MS, Gökbuget N, Neumann S, Goebeler M, Viardot A, et al. Immunopharmacologic response of patients with B-lineage acute lymphoblastic leukemia to continuous infusion of T cell-engaging CD19/CD3-bispecific BiTE antibody blinatumomab. Blood 2012; 119:6226-33; PMID:22592608; http://dx.doi.org/10.1182/blood-2012-01-400515

242. Gopal AK, Ramchandren R, O'Connor OA, Berryman RB, Advani RH, Chen R, Smith SE, Cooper M, Rothe A, Matous JV, et al. Safety and efficacy of brentuximab vedotin for Hodgkin lymphoma recurring after allogeneic stem cell transplantation. Blood 2012; 120:560-8; PMID:22510871; http://dx.doi.org/10.1182/blood-2011-12-397893

243. Galluzzi L, Vacchelli E, Eggermont A, Fridman WH, Galon J, Sautès-Fridman C, Tartour E, Zitvogel L, Kroemer G. Trial Watch: Experimental Toll-like receptor agonists for cancer therapy. Oncoimmunology 2012; 1:699-716; PMID:22934262; http://dx.doi.org/10.4161/onci.20696

244. Vacchelli E, Galluzzi L, Eggermont A, Fridman WH, Galon J, Sautès-Fridman C, Tartour E, Zitvogel L, Kroemer G. Trial watch: FDA-approved Toll-like receptor agonists for cancer therapy. Oncoimmunology 2012; 1:894-907; PMID:23162757; http://dx.doi.org/10.4161/onci.20931

245. Vacchelli E, Eggermont A, Sautès-Fridman C, Galon J, Zitvogel L, Kroemer G, Galluzzi L. Trial Watch: Toll-like receptor agonists for cancer therapy. Oncoimmunology 2013; 2:e25238; PMID:24083080; http://dx.doi.org/10.4161/onci.25238

246. Ma Y, Adjemian S, Mattarollo SR, Yamazaki T, Aymeric L, Yang H, Portela Catani JP, Hannani D, Duret H, Steegh K, et al. Anticancer chemotherapy-induced intratumoral recruitment and differentiation of antigen-presenting cells. Immunity 2013; 38:729-41; PMID:23562161; http://dx.doi.org/10.1016/j.immuni.2013.03.003

247. Senovilla L, Vitale I, Martins I, Kepp O, Galluzzi L, Zitvogel L, Castedo M, Kroemer G. An anticancer therapy-elicited immunosurveillance system that eliminates tetraploid cells. Oncoimmunology 2013; 2:e22409; PMID:23482968; http://dx.doi.org/10.4161/onci.22409

248. Senovilla L, Vitale I, Martins I, Tailler M, Pailleret C, Michaud M, Galluzzi L, Adjemian S, Kepp O, Niso-Santano M, et al. An immunosurveillance mechanism controls cancer cell ploidy. Science 2012; 337:1678-84; PMID:23019653; http://dx.doi.org/10.1126/science.1224922

249. Naing A, Lorusso P, Fu S, Hong D, Chen HX, Doyle LA, Phan AT, Habra MA, Kurzrock R. Insulin growth factor receptor (IGF-1R) antibody cixutumumab combined with the mTOR inhibitor temsirolimus in patients with metastatic adrenocortical carcinoma. Br J Cancer 2013; 108:826-30; PMID:23412108; http://dx.doi.org/10.1038/bjc.2013.46