**Trial Watch**

**Immunostimulatory monoclonal antibodies in cancer therapy**

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**Abbreviations:** CLL, chronic lymphocytic leukemia; CTLA4, cytotoxic T lymphocyte-associated protein 4; FDA, Food and Drug Administration; GM-CSF, granulocyte macrophage colony-stimulating factor; KIR, killer cell immunoglobulin-like receptor; mAb, monoclonal antibody; NHL, non-Hodgkin’s lymphoma; NK, natural killer; NSCLC, non-small cell lung carcinoma; TNFRSF, tumor necrosis factor receptor superfamily, member; TLR, Toll-like receptor

Immunostimulatory monoclonal antibodies (mAbs) exert antineoplastic effects by eliciting a novel or reinstating a pre-existing antitumor immune response. Most often, immunostimulatory mAbs activate T lymphocytes or natural killer (NK) cells by inhibiting immunosuppressive receptors, such as cytotoxic T lymphocyte-associated protein 4 (CTLA4) or programmed cell death 1 (PDCD1, best known as PD-1), or by engaging co-stimulatory receptors, like CD40, tumor necrosis factor receptor superfamily, member 4 (TNFRSF4, best known as OX40) or TNFRSF18 (best known as GITR). The CTLA4-targeting mAb ipilimumab has been approved by the US Food and Drug Administration for use in patients with unresectable or metastatic melanoma in 2011. The therapeutic profile of ipilimumab other CTLA4-blocking mAbs, such as tremelimumab, is currently being assessed in subjects affected by a large panel of solid neoplasms. In the last few years, promising clinical results have also been obtained with nivolumab, a PD-1-targeting mAb formerly known as BMS-936558. Accordingly, the safety and efficacy of nivolumab and other PD-1-blocking molecules are being actively investigated. Finally, various clinical trials are underway to test the therapeutic potential of OX40- and GITR-activating mAbs. Here, we summarize recent findings on the therapeutic profile of immunostimulatory mAbs and discuss clinical trials that have been launched in the last 14 months to assess the therapeutic profile of these immunotherapeutic agents.

**Introduction**

A large panel of monoclonal antibodies (mAbs) is currently approved by the US Food and Drug Administration (FDA) and other international regulatory agencies, including the European Medicines Agency (EMA), for the treatment of conditions as diverse as autoimmune diseases and cancer.1,2 For illustrative purposes, antineoplastic mAbs can be subdivided into 2 large groups: (1) tumor-targeting mAbs, which directly bind to malignant cells or intercept trophic signals delivered by the tumor stroma;2 and (2) immunostimulatory mAbs, which operate by interacting with (hence modulating the function of) components of the immune system.3-5

As we have discussed in previous issues of OncoImmunology,6-8 the therapeutic potential of tumor-targeting mAbs may or may not involve immune effectors. Thus, while some of these molecules, such as the vascular endothelial growth factor (VEGF)-specific IgG1 bevacizumab,9,10 mainly exert antineoplastic effects by inhibiting pro-survival or mitogenic signaling pathways, others, such as the CD20-targeting IgG1 rituximab,11-13 near-to-completely rely on effector mechanisms of innate immunity, including antibody-dependent cell-mediated cytotoxicity (ADCC),14-17 antibody-dependent cellular phagocytosis (ADCP),18 and complement-dependent...
cytotoxicity (CDC). Of note, some tumor-targeting mAbs, such as cetuximab, a chimeric IgG1 specific for the epidermal growth factor receptor (EGFR), appear to inhibit tumor growth via both cancer cell-autonomous and immune system-dependent mechanisms. In addition, tumor-targeting mAbs can be harnessed as carriers for the selective delivery to malignant cells of toxins or radionuclides. This is the case of the CD20-targeting molecules ⁹⁰Y-ibritumomab tiuxetan and ¹³¹I-tositumomab, which are currently approved for the treatment of non-Hodgkin’s lymphoma (NHL).

| Target(s) | mAb | Aliases | Isotype | Source | Activity | Owner               |
|-----------|-----|---------|---------|--------|----------|---------------------|
| CD27      | CDX-1127 | 1F5    | n.a.    | Human  | Agonist   | Celldex             |
| CD40      | Chi Lob 7/4 | -     | IgG1    | Chimeric| Agonist   | Cancer Research UK  |
|           | CP-870,893 | -     | IgG2    | Human  | Agonist   | Pfizer              |
|           | Dacetuzumab | SGN-40 huS2C6 | IgG1 | Humanized | Agonist | Seattle Genetics    |
|           | Lucatumumab | HCD122 | IgG1    | Human  | Agonist   | Novartis Pharmaceuticals |
| CD274 (PD-L1, B7-H1) | BMS-936559 | MDX-1105 | IgG4    | Human  | Antagonist | Bristol–Myers Squibb |
|           | MEDI4736 | -     | IgG1    | Human  | Antagonist | Medimmune          |
|           | MPDL3280A | RG7446 | IgG1    | Human  | Antagonist | Genentech (Roche)   |
|           | MSB0010718C | -    | n.a.    | Human  | Antagonist | Serono (Merck)      |
| CTLA4     | Ipilimumab | BMS-734016 MDX-010 MDX-101 ‘Iervoy’ | IgG1k | Human | Antagonist | Bristol–Myers Squibb |
|           | Tremelimunab | CP-675,206 Ticilimumab | IgG2 | Human | Antagonist | Pfizer              |
| KIR       | IPH2101 | 1–7F9 | IgG4    | Human  | Antagonist | Innate Pharma       |
|           | Lirilumab | BMS-986015 IPH2102 | IgG4 | Human | Antagonist | Bristol–Myers Squibb |
| MHCIi     | IMP321 | -     | IgG1 chimera | Human | Agonist | Immutep            |
| PDCD1 (PD-1) | AMP-224 | -     | IgG1 chimera | Human | Antagonist | Amplimmune (Medimmune, AstraZeneca) |
|           | Lambrolizumab | MK-3475 | IgG4   | Humanized | Antagonist | Merck               |
|           | Nivolumab | BMS-936558 MDX1106 ONO-4538 | IgG4 | Human | Antagonist | Bristol–Myers Squibb |
|           | Pidilizumab | CT-011 | IgG1k   | Humanized | Antagonist | CureTech            |
| PDCD1LG2 (PD-L2, B7-DC) | rHlgM1287 | -     | IgM    | Human  | Agonist | Mayo Foundation     |
| TGFβ1     | Fresolimumab | GC1008 | IgG4κ | Human | Antagonist | Sanofi–Aventis      |
| TNFRSF4 (OX40) | 9B12 | -     | IgG1    | Murine | Agonist | AgonOx              |
|           | MED6469 | -     | n.a.    | Murine | Agonist | Medimmune (AstraZeneca) |
| TNFRSF9 (CD137, 4–1BB) | Urelumab | BMS-663513 | IgG4 | Human | Agonist | Bristol-Myers Squibb |
|           | PF-05082566 | -    | IgG2    | Human  | Agonist | Pfizer              |
| TNFRSF18 (GITR) | TRX518 | -     | IgG1    | Humanized | Agonist | Tolerex             |

Abbreviations: CTLA4, cytotoxic T lymphocyte-associated protein 4; KIR, killer cell immunoglobulin-like receptor; mAb, monoclonal antibody; MHCIi, MHC Class II; n.a., not available; PDCD1, programmed cell death 1; PDCD1LG2, PDCD1 ligand 2; TGFβ1, transforming growth factor β1; TNFRSF, tumor necrosis factor receptor superfamily.
The efficacy of immunostimulatory mAbs invariably relies on the elicitation of a novel or on the reactivation of a pre-existing immune response against malignant cells.\textsuperscript{3,5} So far, this has been achieved through three general strategies: (1) the blockade of inhibitory receptors such as cytotoxic T lymphocyte-associated protein 4 (CTLA4)\textsuperscript{29-31} and programmed cell death 1 (PD1D1, best known as PD-1),\textsuperscript{32-36} both of which are expressed by activated T lymphocytes, or various members of the killer cell immunoglobulin-like receptor (KIR) family, which are found on the surface of natural killer (NK) cells;\textsuperscript{37-40} (2) the activation of co-stimulatory receptors such as tumor necrosis factor receptor superfamily, member 4 (TNFRSF4, best known as OX40)\textsuperscript{41-44} and TNFRSF18 (best known as GITR),\textsuperscript{45,46} which are expressed by activated CD4\textsuperscript{+} and CD8\textsuperscript{+} T cells; (3) the neutralization of soluble immunosuppressive factors, such as transforming growth factor \(\beta\) (TGF\(\beta\)) (Table 1).\textsuperscript{47,51}

At odds with their tumor-targeting counterparts, which have attracted attention as potential anticancer agents as early as in the 1980s,\textsuperscript{52-55} immunostimulatory mAbs have been the focus of intensive preclinical and clinical investigation only with the advent of the 21st century. At least in part, this relates to the fact that tumors have long been considered as immunologically silent entities, a notion that began to change only in the late 1990s, thanks to the theoretical foundations provided by Polly Matzinger’s “danger theory.”\textsuperscript{56,57} In spite of such a delayed kickoff, however, the clinical development of immunostimulatory antibodies has proceeded at a rapid pace, culminating in 2011 with the approval of ipilimumab, a fully human CTLA4-targeting IgG1k also known as MDX-010, MDX-101, and BMS-734016 (now commercialized by Bristol–Myers Squibb under the trade mark Yervoy\textsuperscript{®}), for use in patients with unresectable or metastatic melanoma.\textsuperscript{58-60} Ipilimumab nowadays represents the sole immunostimulatory mAb licensed by regulatory agencies for use in cancer patients, whereas no less than 14 tumor-targeting mAbs are currently employed in the clinic as part of FDA-approved immunotherapeutic regimens.\textsuperscript{1,2,8}

This said, starting with the late 2000s, promising results have also been obtained in clinical trials investigating the safety and therapeutic profile of other immunostimulatory mAbs, including (1) the PD-1-targeting molecules nivolumab, a human IgG4 also known as BMS-936558, MDX-1106, and ONO-4538,\textsuperscript{61-64} and lambrolizumab, a humanized IgG4 also known as MK-3475;\textsuperscript{65} (2) BMS-936559 (also known as MDX-1105), a human IgG4 that targets the PD-1 ligand CD274 (best known as PD-L1);\textsuperscript{66} and (3) the CD40 agonist mAb CP-870,893 (a human IgG2),\textsuperscript{67} and dacetuzumab, a humanized IgG1 also known as SGN-40 and huS2C6.\textsuperscript{68,69}

Fully reflecting their immunostimulatory nature, mAbs may provoke immune reactions against self antigens that, at least potentially, may result in a life-threatening functional and/or structural damage to healthy tissues.\textsuperscript{1,4} However, these reactions most often fail to reach a clinically meaningful amplitude and can be controlled with corticosteroids or other immunosuppressants.\textsuperscript{1,4} Thus, immunostimulatory mAbs stand out as a relatively safe and well tolerated immunotherapeutic regimen, most frequently causing mild and controllable adverse effects including (but not limited to) skin rashes, pruritus, fatigue, nausea, and diarrhea.\textsuperscript{3,4} As a standalone exception, urelumab (also known as BMS-663513), which operates as an agonist of the co-stimulatory receptor TNFRSF9 (best known as CD137 or 4–1BB), has been associated with severe hepatotoxicity (in particular when employed at high doses).\textsuperscript{70,71}

We have summarized recent advances on the clinical use of tumor-targeting mAbs in the latest issue of *OncoImmunology*.\textsuperscript{8} Here, along the lines of our monthly Trial Watch series,\textsuperscript{72-75} we will restrict our focus on immunostimulatory antibodies, discussing the results of clinical trials published in the last 14 mo and commenting on studies launched in the same period to evaluate the safety and efficacy of this immunotherapeutic paradigm in cancer patients.

**Update on Clinical Reports**

During the last 14 mo, the results of no less than 19 clinical trials investigating the therapeutic potential of immunostimulatory mAbs in cancer patients have been published in peer-reviewed scientific journals (source http://www.ncbi.nlm.nih.gov/pubmed). More than half of these studies involved mAbs that antagonize the delivery of inhibitory signals to immune effector cells, including the CTLA4-targeting agents ipilimumab\textsuperscript{76-82} and tremelimumab (a human IgG2 also known as ticilimumab or CP-675,206),\textsuperscript{83-85} the PD-1-specific mAbs nivolumab and lambrolizumab,\textsuperscript{86,87} as well as IPH2101 (a KIR-inhibitory human IgG4 also known as 1-TF9)\textsuperscript{88,89} In addition, 6 studies involved mAbs that directly operate as agonists for co-stimulatory receptors, including the CD40-targeting molecules dacetuzumab, CP-870,893 and latumumab (a human IgG1 also known as HCD122),\textsuperscript{90-93} 9B12, a murine IgG1 that triggers OX40 signaling,\textsuperscript{94} as well as IMP321, an IgG- and lymphocyte-activation gene 3 (LAG3)-based chimera that binds to, hence activating, MHC Class II molecules (Table 2).\textsuperscript{95}

Ipilimumab has recently been tested (1) together with the BRAF inhibitor vemurafenib in patients with metastatic melanoma bearing a BRAF V600 mutation;\textsuperscript{78} (2) combined with paclitaxel (a microtubular inhibitor and hyperploidizing agent of the taxane family)\textsuperscript{96,97} and carboplatin (a second-generation platinum derivative)\textsuperscript{98,99} as first-line therapy in subjects bearing extensive small-cell lung cancer lesions;\textsuperscript{79} (3) alone or in combination with a granulocyte macrophage colony-stimulating factor (GM-CSF)-secreting allogeneic vaccine\textsuperscript{100,101} in pancreatic ductal adenocarcinoma patients;\textsuperscript{80} and (4) as part of a nivolumab-based immunotherapeutic regimen in patients with advanced melanoma.\textsuperscript{82} In addition, (1) Sherrill and colleagues evaluated the quality-adjusted survival of patients enrolled in study CA18/4024, a multinational, randomized, double-blind, Phase III trial testing dacarbazine (an alkylating agent currently approved by the US FDA for the treatment of Hodgkin’s lymphoma and melanoma) alone vs. dacarbazine plus ipilimumab in subjects with previously untreated metastatic melanoma;\textsuperscript{95,96} (2) Santegoets and collaborators performed an exploratory T-cell monitoring study in the context of Phase I/II dose escalation/expansion trial testing ipilimumab plus a GM-CSF-secreting allogeneic...
(3) Kwek and co-authors monitored the humoral immune responses elicited by the co-administration of ipilimumab and a fixed dose of GM-CSF in subjects with prostate cancer. In these clinical settings, ipilimumab-based immune(chemo)therapy was well tolerated and associated with promising clinical responses, with a single exception. Indeed, in 2 distinct cohorts of melanoma patients, the co-administration of ipilimumab and vemurafenib at full approved doses was associated with grade 3 elevations in circulating alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Although such hepatotoxic effects were asymptomatic and reversible upon the temporary discontinuation of treatment or the administration of glucocorticoids, this Phase I clinical trial was promptly closed to further patient accrual.

The clinical potential of tremelimumab, employed as a standalone therapeutic intervention or combined with the Toll-like receptor 9 (TLR9) agonist PF-3512676, has recently been assessed in patients affected by metastatic melanoma or other advanced neoplasms. In the context of a Phase I clinical trial, the combination of tremelimumab with PF-3512676 was well tolerated, but evoked measurable clinical responses in 2 out of 21 patients only. Along similar lines, in the context of a large, randomized, Phase III study, no statistically significant survival advantage could be documented in metastatic melanoma patients receiving tremelimumab vs. standard-of-care chemotherapy, although response duration (measured from the time of randomization) was significantly longer in the tremelimumab arm. Based on such a lack of efficacy, the A3671009 study (NCT00257205) has been discontinued.

The safety and efficacy of PD-1-targeting mAbs have recently been investigated in 2 distinct cohorts of melanoma patients, receiving either lambrolizumab as a single agent in the context of a Phase I clinical trial (NCT01295827), or nivolumab coupled to ipilimumab, again as part of a Phase I study (NCT01024231). In addition, the long-term therapeutic potential of nivolumab given as a standalone intervention has been assessed in a mixed patient cohort, encompassing melanoma, renal cell carcinoma

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**Table 2. Recently published clinical trials investigating the therapeutic profile of immunostimulatory mAbs.**

| Target | mAb | Indication(s) | Phase | Note |
|--------|-----|---------------|-------|------|
| CD40   | CP-870,893 | Pancreatic cancer | I | In combination with gemcitabine |
|        |       | Advanced solid tumors | I | In combination with paclitaxel and carboplatin |
|        | Dacetuzumab | DLBCL | Pilot | In combination with rituximab and gemcitabine |
|        | Lucatumumab | CLL | I | As single agent |
|        |       | MM | I | As single agent |
|        | Ipilimumab | Melanoma | I | As single agent |
|        |       | Pancreatic cancer | Ib | As single agent or combined with a GM-CSF-secreting vaccine |
|        |       | Prostate carcinoma | I/Ii | In combination with a GM-CSF-secreting allogeneic vaccine |
|        |       | SCLC | Ii | In combination with paclitaxel and carboplatin |
|        | Tremelimumab | Melanoma | I | As single agent |
|        |       | Pancreatic cancer | I | In combination with the TLR9 agonist PF-3512676 |
|        | KIR | IPH2101 | I | As single agent |
|        |       | MM | I | As single agent |
|        | MHCII | IMP321 | Pancreatic carcinoma | I | In combination with gemcitabine |
|        |        | Lambrolizumab | Melanoma | I | As single agent |
|        |        | Nivolumab | Melanoma | I | Combined with ipilimumab |
|        |        |       | Advanced solid tumors | I | As single agent |

**Abbreviations:** AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CTLA4, cytotoxic T lymphocyte-associated protein 4; DLBCL, diffuse large B-cell lymphoma; GM-CSF, granulocyte macrophage colony-stimulating factor; KIR, killer cell immunoglobulin-like receptor; mAb, monoclonal antibody; MHCII, MHC Class II; MM, multiple myeloma; PDCD1, programmed cell death 1; SCLC, small cell lung carcinoma; TLR9, Toll-like receptor 9; TNFRSF, tumor necrosis factor receptor superfamily. 

*between 2012, October 1st and the day of submission.*
as well as colorectal carcinoma patients. In these settings, the administration of PD-1-targeting mAbs alone was associated with relatively mild (grade 1 or 2) side effects. Conversely, the co-administration of nivolumab and ipilimumab provoked grade 3 or 4 adverse reactions in a consistent proportion of melanoma patients. Still, (1) such side effects were qualitatively similar to those previously associated with either nivolumab or ipilimumab monotherapy and were generally reversible; and (2) the combined inhibition of CTLA4- and PD-1-dependent immunosuppression was associated with an objective response in 53% of patients, invariably manifesting with a reduction in tumor burden of 80% or more.

The clinical potential of mAbs directly targeting NK cells, rather than T lymphocytes, has recently been assessed in patients affected by acute myeloid leukemia (EUDRACT 2005–005298–31) or relapsed/refractory multiple myeloma (NCT00552396). In both these Phase I sequential-cohort dose-escalation studies, IPH2101 was administered as a single agent, provoking limited side effects at doses that fully inhibit KIRs.

Finally, the safety and efficacy of immunostimulatory mAbs that operate as agonists for co-stimulatory receptors have recently been investigated (invariably in Phase I settings) (1) in patients with chronic lymphocytic leukemia (CLL) or relapsed/refractory multiple myeloma, receiving lusacatumab as a single agent in the context of sequential-cohort dose-escalation studies; (2) in patients affected by advanced pancreatic ductal adenocarcinoma, who were treated with CP-870,893 plus gemcitabine-based chemotherapy; (3) in individuals bearing advanced solid tumors, receiving CP-870,893 coupled to carboplatin and paclitaxel; (4) in patients with relapsed/refractory diffuse large B-cell lymphoma, who were given dacetuzumab in combination with rituximab and gemcitabine; (5) in individuals bearing advanced neoplasms, receiving 9B12 in combination with various adjuvants (NCT01644968); and (6) in patients with advanced pancreatic adenocarcinoma, receiving IMP321 plus gemcitabine-based chemotherapy. Globally, these immunostimulatory mAbs were well tolerated but exerted limited clinical efficacy.

In summary, the results of the clinical studies reported above suggest that immunostimulatory mAbs are well tolerated by cancer patients, especially when administered as standalone interventions, yet elicit limited clinical responses in these conditions. Conversely, combinatorial approaches such as the co-administration of nivolumab and ipilimumab are associated not only with an increased incidence and severity of adverse effects, but also with improved clinical activity.

**Update on Clinical Trials Testing Immunostimulatory Monoclonal Antibodies**

When this Trial Watch was being redacted (November 2013), official sources listed 60 clinical trials launched after 2012, October 1st to evaluate the therapeutic profile of immunostimulatory mAbs in cancer patients (source http://www.clinicaltrials.gov).

For obvious advantages related to its approval status, more than half (36) of these studies aim at investigating the clinical profile of ipilimumab, either as a standalone intervention or combined with radiotherapy, conventional chemotherapeutics, targeted anticancer drugs or other immunostimulatory agents. In particular, ipilimumab is being tested as part of immunochemotherapeutic or immunoradiotherapeutic regimens in melanoma patients (NCT01701674; NCT01703507; NCT01708941; NCT01709162; NCT01715077; NCT01730517; NCT01740297; NCT01740401; NCT01767454; NCT01769222; NCT01783938; NCT01789827; NCT01800106; NCT01827111; NCT01838200; NCT01844505; NCT01856023; NCT01866319; NCT01879306), the sole oncological indication for which this CTLA4-targeting mAb is licensed by regulatory agencies, as well as in cohorts of individuals affected by various hematological malignancies (NCT01729806; NCT01757639; NCT01769222; NCT01822509; NCT01896999; NCT01919619), prostate carcinoma (NCT01804465; NCT01832870), head and neck cancer (NCT01860430; NCT01935921), non-small cell lung carcinoma (NSCLC) (NCT01820754), cervical carcinoma (NCT01711515), Merkel cell carcinoma (NCT01913691), pancreatic cancer (NCT01896869), colorectal carcinoma (NCT01769222), and various advanced/metastatic solid tumors (NCT01738139; NCT01750580; NCT01750983; NCT01928394). Alongside, the safety and efficacy of the other CTLA4-targeting mAb tremelimumab are being assessed in cohorts of malignant mesothelioma patients, receiving tremelimumab as a single agent (NCT01843374), liver cancer patients, who are treated with a combination of tremelimumab and trans-arterial catheter chemoembolization or radiofrequency ablation (NCT01853618), and subjects affected by various solid neoplasms, who are given tremelimumab plus MEDI4736 (a human IgG1 specific for PD-L1) (NCT01975831). Of note, MEDI4736 as well as two other PD-L1 targeting mAbs, namely MPDL3280A (a human IgG1 also known as RG7446) and MSB001718C, are being investigated also as standalone therapeutic interventions in cohorts of patients affected by NSCLC (NCT01846416; NCT01903993) or various advanced solid neoplasms (NCT01772004; NCT01938612; NCT01943461) (Table 3).

As a matter of fact, targeting PD-1-dependent immunosuppression currently stands out as the experimental mAb-based immunotherapeutic paradigm most intensively investigated in clinical settings. Thus, nivolumab is being tested, most often as a standalone intervention or combined with ipilimumab, in patients with melanoma (NCT01721746; NCT01721772; NCT01783938; NCT01844505; NCT01927419), NLSLC (NCT01721759; NCT01928576), glioma (NCT01952769) or other solid neoplasms (NCT01714739; NCT01928394; NCT01968109). Alongside, the safety and therapeutic profile of lambrolizumab, most frequently employed as a single agent or together with ipilimumab, are being assessed in cohorts of subjects bearing melanoma (NCT01704287; NCT01866319), NSCLC (NCT01840579; NCT01905657), hematological malignancies (NCT01953692), colorectal carcinoma with high degrees of microsatellite instability (NCT01876511), or advanced/metastatic tumors (NCT01840579; NCT01848834) (Table 3).

Finally, some interest is growing around the possibility to harness the antineoplastic activity of NK cell-targeting mAbs as
Table 3. Clinical trials recently launched to evaluate the therapeutic profile of immunostimulatory mAbs.*

| mAb | Target(s) | Indication(s) | Phase | Status | Note | Ref. |
|-----|-----------|---------------|-------|--------|------|------|
| Anti-OX40 | TNFRSF4 (OX40) | Breast carcinoma | I/II | Recruiting | Combined with SBRT | NCT01862900 |
| | | | | | | |
| Anti-OX40 | TNFRSF4 (OX40) | AML MDS | I | Recruiting | As single agent | NCT01757639 |
| | | Cervical carcinoma | I | Recruiting | Combined with cisplatin and radiation therapy | NCT01711515 |
| | | CRC Lymphoma Melanoma | I/II | Recruiting | Combined with radiation therapy | NCT01769222 |
| | | Hematological malignancies | I | Recruiting | As single agent | NCT01822509 |
| | | HNC | I | Recruiting | Combined with cetuximab and radiation therapy | NCT01860430 |
| | | I | Recruiting | Combined with cetuximab and radiation therapy | NCT01935921 |
| | | Hodgkin's lymphoma | I | Not yet recruiting | Combined with brentuximab vedotin | NCT01896999 |
| | | Leukemia | n.a. | Not yet recruiting | Combined with lenalidomide | NCT01919619 |
| | | Lymphoma | I | Recruiting | Combined with rituximab | NCT01729806 |
| Ipilimumab | CTLA4 | Melanoma | I/II | Recruiting | As single agent or combined with oncolytic virotherapy | NCT01740297 |
| | | | II | Active not recruiting | Combined with cyclophosphamide | NCT01740401 |
| | | | II | Not yet recruiting | As single agent | NCT01879306 |
| | | | II | Recruiting | As single agent or combined with IFNα-2b | NCT01708941 |
| | | | II | Recruiting | As single agent | NCT01709162 |
| | | | II | Recruiting | Combined with nivolumab | NCT01783938 |
| | | | II | Recruiting | Combined with paclitaxel | NCT01827111 |
| | | | III | Recruiting | Combined with nivolumab | NCT01844505 |
| | | | III | Recruiting | Combined with lambrolizumab | NCT01866319 |
| | | | IV | Recruiting | Combined with high-dose IL-2 | NCT01856023 |
| | | Merkel cell carcinoma | II | Not yet recruiting | As single agent | NCT01913691 |
| Ipilimumab | CTLA4 | NSCLC | I | Recruiting | Combined with carboplatin, cisplatin and paclitaxel | NCT01820754 |
| | | Pancreatic cancer | II | Not yet recruiting | As single agent or combined with a GM-CSF-secreting vaccine | NCT01896869 |
| | | Prostate cancer | I | Recruiting | Combined with sipuleucel-T | NCT01832870 |
| | | | II | Active not recruiting | After sipuleucel-T treatment | NCT01804465 |
| | | Advanced solid tumors | I | Recruiting | Combined with imatinib | NCT01738139 |
| | | | I | Recruiting | Combined with lirilumab | NCT01750580 |
| | | | I | Recruiting | Combined with lenalidomide | NCT01750983 |
| | | | I/II | Not yet recruiting | Combined with nivolumab | NCT01928394 |
well as mAbs that operate as agonists for co-stimulatory T-cell and NK-cell receptors. In this setting, lirilumab (a human IgG4 that antagonizes KIRs, also known as IPH2102) is being tested in combination with ipilimumab or nivolumab for the treatment of patients bearing advanced solid malignancies (NCT01714739; NCT01750580). Moreover, the safety and therapeutic potential of the TNFRSF9-activating mAb urelumab and a not better specified OX40-activating mAb, combined with rituximab and stereotactic body radiation, respectively, are being assessed in cohorts of patients with

Table 3. Clinical trials recently launched to evaluate the therapeutic profile of immunostimulatory mAbs.* (continued)

| mAb          | Target(s) | Indication(s) | Phase | Status | Note                          | Ref.            |
|--------------|-----------|---------------|-------|--------|-------------------------------|-----------------|
| Lambrolizumab| PDCD1 (PD-1, CD279) | CRC | II   | Recruiting | As single agent | NCT01876511    |
|              |           | Hematological malignancies | I     | Not yet recruiting | As single agent | NCT01953692    |
|              |           | Melanoma | II   | Active recruiting | As single agent | NCT01704287    |
|              |           |         | III  | Recruiting | Combined with ipilimumab | NCT01866319    |
|              |           | NSCLC    | II/III | Recruiting | As single agent | NCT01905657    |
|              |           | Advanced solid tumors | I     | Recruiting | As single agent or combined with conventional chemotherapy | NCT01840579    |
|              |           |         | I     | Recruiting | As single agent | NCT01848834    |
| Lirilumab    | KIR       | Advanced solid tumors | I     | Recruiting | Combined with nivolumab | NCT01714739    |
|              |           |         | I     | Recruiting | Combined with ipilimumab | NCT01750580    |
| MEDI4736     | CD274 (PD-L1, B7-H1) | Advanced solid tumors | I     | Not yet recruiting | Combined with tremelimumab | NCT01975831    |
|              |           |         | I     | Recruiting | As single agent | NCT01938612    |
| MPDL3280A    | CD274 (PD-L1, B7-H1) | NSCLC | II   | Recruiting | As single agent | NCT01846416    |
|              |           |         | II   | Recruiting | As single agent | NCT01903993    |
| MS80010718C  | CD274 (PD-L1, B7-H1) | Advanced solid tumors | I     | Recruiting | As single agent | NCT01772004    |
|              |           |         | I     | Recruiting | As single agent | NCT01943461    |
| Nivolumab    | PDCD1 (PD-1, CD279) | Melanoma | II   | Recruiting | Combined with ipilimumab | NCT01783938    |
|              |           |         | II   | Recruiting | Combined with ipilimumab | NCT01927419    |
|              |           |         | III  | Recruiting | As single agent | NCT01721746    |
|              |           |         | III  | Recruiting | As single agent | NCT01721772    |
|              |           |         | III  | Recruiting | Combined with ipilimumab | NCT01844505    |
|              |           | NSCLC    | II   | Active not recruiting | As single agent | NCT01721759    |
|              |           |         | II   | Recruiting | Combined with azacitidine ± entinostat | NCT01928576    |
| Tremelimumab | CTLA4     | HCC | I     | Recruiting | Combined with RFA and TACE | NCT01853618    |
|              | Mesothelioma | II     | Recruiting | As single agent | NCT01843374    |
|              | Advanced solid tumors | I     | Not yet recruiting | Combined with MEDI4736 | NCT01975831    |
| Urelumab     | TNFRSF9 (CD137, 4-1BB) | CLL | I     | Recruiting | Combined with rituximab | NCT01775631    |
|              |           | NHL | I/II | Not yet recruiting | As single agent | NCT01952769    |

Abbreviations: aML, acute myeloid leukemia; BCG, bacillus Calmette-Guérin; CLL, chronic lymphocytic leukemia; CRC, colorectal carcinoma; CTLA4, cytotoxic T lymphocyte-associated protein 4; GM-CSF, granulocyte macrophage colony-stimulating factor; HCC, hepatocellular carcinoma; HNC, head and neck cancer; IFNα-2b, interferon α-2b; IL, interleukin; KIR, killer cell immunoglobulin-like receptor; mAb, monoclonal antibody; MDS, myelodysplastic syndrome; n.a., not available; NHL, Non-Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung carcinoma; PDCD1, programmed cell death protein 1; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; SRS, stereotactic radiosurgery; TACE, transarterial catheter chemoembolization; TIL, tumor-infiltrating lymphocyte; TNFRSF, tumor necrosis factor receptor superfamily; WBRT, whole-brain radiation therapy. *between 2012, October 1st and the day of submission.
CLL, NHL (NCT01775631) or metastatic breast carcinoma (NCT01862900) (Table 3).

As for the clinical trials listed in our previous Trial Watches dealing with this topic,6,7 only NCT01034787 has changed status. As a matter of fact, the status of NCT01034787, a Phase 2 trial testing intravenous tremelimumab in patients affected by uveal melanoma, is no longer available because the information relative to this study has not been verified recently (source http://www.clinicaltrials.gov).

Concluding Remarks

Similar to their tumor-targeting counterparts,8 immunostimulatory mAbs are being intensively investigated for their ability to mediate therapeutically relevant antineoplastic effects. However, while tumor-targeting mAbs are designed to specifically bind to malignant, stromal or endothelial components of neoplastic lesions or to neutralize trophic signals delivered by the tumor stroma,1,2 most immunostimulatory mAbs modulate general mechanisms that control innate and adaptive immune responses, de facto operating in a relatively unspecific manner.3,4

Based on this consideration, one would expect immunostimulatory mAbs to provoke more severe side effects than their tumor-targeting counterparts3,4 and to display a therapeutic activity resembling that of other relatively unspecific immunomodulatory interventions, including TLR agonists,104,105,112,113 specific cytokines,102,103 and immunogenic chemotherapeutics.74,75,114-116 Accumulating clinical evidence actually suggests that immunostimulatory mAbs are generally well tolerated by cancer patients, in particular when administered as single agent rather than a general feature of CTL4-targeting mAbs such as tremelimumab.84 The development of immunostimulatory mAb rather than a general feature of CTL4-targeting mAbs such as tremelimumab.84 The development of immunostimulatory mAbs is in its infancy and further studies are required to obtain profound insights into the pharmacodynamics and pharmacokinetic properties of molecules that are conceived to target the same immunomodulatory receptor yet exhibit differential clinical activity. As it stands, immunomodulatory mAbs hold great promise as tools to potentiate tumor-targeting immune responses elicited by active immunotherapeutic interventions, including recombinant vaccines,117,118 dendritic cell-based approaches,100,101,105,119,120 and adoptive T-cell transfer.121-124 The future will tell whether immunostimulatory mAbs other than ipilimumab will add to the growing list of FDA-approved anticancer immunotherapeutics.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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