Trial Watch: Immunomodulatory monoclonal antibodies for oncological indications

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Abbreviations: CRC, colorectal carcinoma; CTLA4, cytotoxic T lymphocyte-associated protein 4; FDA, Food and Drug Administration; IL, interleukin; KIR, killer cell immunoglobulin-like receptor; mAb, monoclonal antibody; NK, natural killer; NSCLC, non-small cell lung carcinoma; PD-1, programmed cell death 1; RCC, renal cell carcinoma; TGFβ1, transforming growth factor β1; TLR, Toll-like receptor; TNFRSF, tumor necrosis factor receptor superfamily; Treg, regulatory T cell

Immunomodulatory monoclonal antibodies (mAbs) differ from their tumor-targeting counterparts because they exert therapeutic effects by directly interacting with soluble or (most often) cellular components of the immune system. Besides holding promise for the treatment of autoimmune and inflammatory disorders, immunomodulatory mAbs have recently been shown to constitute a potent therapeutic weapon against neoplastic conditions. One class of immunomodulatory mAbs operates by inhibiting safeguard mechanisms that are frequently harnessed by cancer cells to establish immunological tolerance, the so-called “immune checkpoints.” No less than 3 checkpoint-blocking mAbs have been approved worldwide for use in oncological indications, 2 of which during the past 12 months. These molecules not only mediate single-agent clinical activity in patients affected by specific neoplasms, but also significantly boost the efficacy of several anticancer chemo-, radio-, and immunotherapies. Here, we summarize recent advances in the development of checkpoint-blocking mAbs, as well as of immunomodulatory mAbs with distinct mechanisms of action.

Introduction

Initially conceived as a means to treat autoimmune diseases and inflammatory conditions,1,2 immunomodulatory monoclonal antibodies (mAbs), i.e., mAbs that bind to (hence altering the function of) soluble or cellular component of the immune system,3,4 have been increasingly recognized as a promising tool for cancer therapy.5-7 Indeed, virtually all solid tumors and at least some hematological malignancies fail to respond to chemo-, radio-, and immunotherapy owing to the establishment of potent immunosuppressive networks that operate locally (i.e., within the tumor mass) and systemically (i.e., in the circulation and bone marrow).8-12 Importantly, some (but not all) of these immunosuppressive mechanisms are the same that operate to terminate immune responses and/or prevent autoimmune reactions in physiological scenarios.13,14 Thus, in the course of tumor progression malignant cells acquire the ability to harness immunosuppressive mechanisms to their own benefit, hence avoiding recognition and elimination by the host immune system.15,16

These considerations have driven the development of several immunomodulatory mAbs aimed at activating novel, or reinstating existing, tumor-targeting immune responses. At least hypothetically, these objectives can be achieved by at least 3 distinct strategies corresponding to 3 classes of immunomodulatory mAbs potentially useful for anticancer therapy. First, tumor-targeting immune responses can be elicited by means of mAbs that inhibit immunosuppressive receptors expressed on the surface of activated T lymphocytes or natural killer (NK) cells, such as cytotoxic T lymphocyte-associated protein 4 (CTLA4), programmed cell death 1 (PDCD1, best known as PD-1), and various members of the killer cell immunoglobulin-like receptor (KIR) family; or their ligands, like the PD-1-binding partner CD274 (best known as PD-L1 or B7-H1).17-20 CTLA4 and PD-1 are critically involved in so-called “immune checkpoints,” safeguard systems...
that control the physiological extinction of immune responses and the maintenance of peripheral tolerance (hence avoiding autoimmune reactions).\textsuperscript{30,31} Moreover, potential tumor-reactive lymphocytes are often kept in check by CTLA- and/or PD-1-transduced signals, reflecting the ability of many cancers to express increased levels of their ligands.\textsuperscript{27,32-35} Some KIRs deliver inhibitory signals to NK cells upon binding to MHC Class I molecules, hence preventing unwarranted innate immune responses against healthy cells (which generally express high levels of MHC Class I molecules).\textsuperscript{24,25} Cancer cells generally preserve the expression of MHC Class I molecules, hence evading NK cell-dependent anticancer immunosurveillance.

Second, anticancer immune responses can be (re-)established by mAbs that activate co-stimulatory receptors expressed on the surface of T lymphocytes and/or NK cells, such as tumor necrosis factor receptor superfamily, member 4 (TNFRSF4, best known as OX40),\textsuperscript{36-40} TNFRSF9 (best known as CD137 or 4-1BB),\textsuperscript{41-43} and TNFRSF18 (best known as GITR).\textsuperscript{44-46} Most immune cells require several signals for acquiring full-blown effector functions, constituting yet another safeguard mechanism against autoimmunity or disproportioned immune reactions.\textsuperscript{3,4} Such signals are generally not provided within the tumor micro-environment, often as a consequence of functional alterations of the myeloid cell compartment.\textsuperscript{8-12}

Third, tumor-specific immune responses can be initiated or restored by mAbs that neutralize immunosuppressive factors released in the tumor microenvironment, such as transforming growth factor \(\beta1\) (TGF\(\beta1\)) and interleukin-10 (IL-10).\textsuperscript{47,48} Tumor-infiltrating myeloid cells, including “alternatively-activated” M2 macrophages, secrete immunosuppressive factors in considerable amounts.\textsuperscript{10} These molecules promote the functional impairment of potentially tumor-reactive immune effector cells, both directly and via indirect circuitries involving other immunosuppressive cell populations like CD4\(^+\)CD25\(^+\)FOXP3\(^+\) regulatory T cells (Tregs).\textsuperscript{49-51}

Immunomodulatory mAbs that target CTLA4-like receptors and their ligands are cumulatively referred to as “checkpoint blockers” or “checkpoint-blocking mAbs.”\textsuperscript{52} Several mAbs of this class are relatively well tolerated and mediate antineoplastic effects, either as standalone immunotherapeutic interventions or in combination with other anticancer agents, in patients affected by a wide panel of solid neoplasms.\textsuperscript{52-54} In line with this notion, 3 checkpoint blockers have already been approved by the US Food and Drug Administration (FDA) and/or equivalent regulatory agencies worldwide for use in oncological indications (Table 1): (1) ipilimumab (Yervoy\textsuperscript{TM}), an anti-CTLA4 mAb originally approved by the US FDA for the treatment of unresectable or metastatic melanoma on 2011, March 25th;\textsuperscript{55-59} pembrolizumab (Keytruda\textsuperscript{TM}), a PD-1-targeting mAb that received accelerated approval by the US FDA for use in subjects with advanced or unresectable melanoma who fail to respond to other therapies on 2014, September 4th;\textsuperscript{52,60-64} and nivolumab (Opvido\textsuperscript{TM}), yet another PD-1-targeting mAb first licensed by the Japanese Ministry of Health and Welfare for use in humans on 2014, July 07th (and obtaining accelerated approval by the US FDA on 2014, December 22nd).\textsuperscript{65,66} Conversely, no co-stimulatory mAb has been approved by the US FDA or equivalent regulatory agency worldwide for use in cancer patients yet, despite the promising clinical results achieved by some molecules, including the CD137-targeting mAbs urelumab and PF-0582566.\textsuperscript{3,67,68} Similarly, no TGF\(\beta1\)-neutralizing mAb is licensed for use in humans today (source http://www.fda.gov).

Along the lines of our monthly Trial Watch series,\textsuperscript{69,70} here we discuss recent advances in the development of immunomodulatory mAbs for cancer therapy.

### Update on the Development of Immunomodulatory Monoclonal Antibodies

#### Completed clinical trials

Since the submission of our latest Trial Watch dealing with this topic (November 2013),\textsuperscript{53} the results of more than 120 studies assessing the safety and/or efficacy of immunomodulatory mAbs (or biomarkers associated with their clinical profile) have been published in the peer-reviewed scientific literature (source http://www.ncbi.nlm.nih.gov/pubmed) or presented at international meetings (sources http://meetinglibrary.asco.org/, http://aacrmeeetingabstracts.org/ and http://www.hematology.org/Annual-Meeting/Abstracts/). The largest fraction of these studies involved ipilimumab,\textsuperscript{71-125} pembrolizumab,\textsuperscript{53,83,126-140} or nivolumab,\textsuperscript{66,71,76,84,86,106,112,115,141-154} employed either as on-label or by label.

| mAb     | Target | First approved | Type         | Indication(s)                                                                 |
|---------|--------|----------------|--------------|-------------------------------------------------------------------------------|
| Ipilimumab | CTLA   | 2011           | Human IgG1κ  | Unresectable or metastatic melanoma                                           |
| Nivolumab | PD-1   | 2014           | Human IgG4   | Unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF\textsuperscript{V600E} mutation positive, a BRAF inhibitor |
| Pembrolizumab | PD-1   | 2014           | Humanized IgG4 | Unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF\textsuperscript{V600E} mutation positive, a BRAF inhibitor |

**Abbreviations:** BRAF, B-Raf proto-oncogene, serine/threonine kinase; CTLA4, cytotoxic T lymphocyte-associated protein 4; PD-1, programmed cell death 1.

*By the US Food and Drug Administration or equivalent regulatory agency worldwide on the day of submission.*
off-label immunotherapeutic interventions. Moreover, several publications/abstracts released during the last 13 months reported the results of clinical trials involving (1) additional checkpoint blockers, such as the CTLA4-targeting mAb tremelimumab,\textsuperscript{155-161} the PD-1-targeting mAb pidilizumab,\textsuperscript{162,163} and the PD-L1-targeting mAbs MEDI4736,\textsuperscript{156,159,164-168} MPDL3280A,\textsuperscript{169,171} and MSB0010718C,\textsuperscript{172} (2) the KIR-inhibitory mAbs lirilumab and IPH2101,\textsuperscript{151,173} (3) co-stimulatory mAbs, such as the CD137-targeting mAbs PF-05082566 and urelumab,\textsuperscript{174,175} the CD27-targeting mAb CDX-1127,\textsuperscript{176,177} the CD40-targeting mAbs Chilob 7/4, dacetuzumab and lucatumumab,\textsuperscript{178,179} and an OX40-targeting molecule;\textsuperscript{180} and (4) the TGFβ1-neutralizing mAb feresolimab.\textsuperscript{181} Taken together, these studies involved patients affected by a relatively large and heterogeneous panel of neoplasms, including (but not limited to): melanoma\textsuperscript{65,66,72,75,77,78,81-83,86,88-92,95-97,101-105,108-110,112,114,116-119,121,122,124,125,129-131,135,152,153,162,166,181-185} non-small cell lung carcinoma (NSCLC),\textsuperscript{127,128,136,142,144,159,170,186,187} renal cell carcinoma (RCC);\textsuperscript{84,133,141,145,148,188,189} and breast carcinoma.\textsuperscript{79,98,99,140,171,190}

Taken together, the results of these studies demonstrate that first generation immunomodulatory mAbs used as monotherapeutic agents are well tolerated by cancer patients or cause side effects that are generally manageable with treatment discontinuation and/or corticoids. Moreover, when employed as standalone therapeutic interventions, these immunomodulatory mAbs induce objective clinical responses in 10-90% of patients, depending on the specific scenario (i.e., immunomodulatory paradigm, cancer type, disease stage, etc.). The clinical profile of immunomodulatory mAbs combined with conventional chemotherapeutics, targeted anticancer agents, irradiation (in one of its variants) or other immunotherapies is being intensively investigated. Some of these combinatorial regimens, including the administration of ipilimumab plus nivolumab or vemurafenib (a chemical inhibitor of mutant BRAF)\textsuperscript{191} to melanoma patients, as well as the administration of ipilimumab plus pazopanib or sunitinib (2 multi-targeted receptor tyrosine kinase inhibitors) to RCC patients, have already been associated with very high objective response rates.\textsuperscript{141,192,193} However, all these combinations also provoke severe (Grade 3-4) adverse effects in a consistent (>50%) fraction of patients,\textsuperscript{141,192,193} constituting a big obstacle against their further development.

From the abundant clinical literature published during the last 13 month on immunomodulatory mAbs, we would like to highlight the work of (1) Kwon and colleagues (Mayo Clinic Comprehensive Cancer Center; Rochester, MN, US), who reported that the administration of ipilimumab after radiotherapy fails to improve the overall survival of patients with metastatic castration-resistant prostate cancer progressing after docetaxel chemotherapy, although it may beneficial for a sub-group of patients showing no visceral involvement;\textsuperscript{125} (2) Hodi and co-authors (Dana-Farber Cancer Institute; Boston, MA, US), who demonstrated that the addition of recombinant granulocyte macrophage colony-stimulating factor (GM-CSF, also known as sargramostim) to ipilimumab-based immunotherapy limits side effects while improving overall, but not progression-free, survival in patients with unresectable Stage III or IV melanoma;\textsuperscript{125} (3) Lebbé and collaborators (Hôpital Saint-Louis; Paris, France), who reported not only that the responses of subjects with advanced melanoma to ipilimumab are durable (lasting up to 5-6 years in some cases), but also that in some patients the re-administration of ipilimumab can re-establish disease control upon progression on induction ipilimumab-based immunotherapy;\textsuperscript{124} (4) Weber et al. (Moffitt Cancer Center; Tampa, FL, US), who demonstrated the favorable clinical profile of nivolumab administered in combination with a multi-epitope-based vaccine to individuals with ipilimumab-refractory or -naive melanoma;\textsuperscript{152} (5) Topalian and colleagues (Smilow Cancer Center; New Haven, CT, US), who reported long-term safety and efficacy data from a clinical trial testing the therapeutic profile of nivolumab in advanced melanoma patients;\textsuperscript{153} (6) Robert and collaborators (Gustave Roussy Cancer Campus; Villejuif, France), who demonstrated not only that nivolumab ameliorates disease outcome among previously untreated subjects with BRAF\textsuperscript{WT} melanoma, but also that pembrolizumab constitutes an effective therapeutic option for melanoma patients progressing on ipilimumab-based immunotherapy,\textsuperscript{63,66} (7) Westin and co-authors (MD Anderson Cancer Center; Houston, TX, US), who proved that pidilizumab is well tolerated and improves the clinical activity of the CD20-targeting mAb rituximab in patients with relapsed follicular lymphoma;\textsuperscript{163} as well as (8) Ansell et al. (Mayo Clinic Comprehensive Cancer Center; Rochester, MN, US) and Moskowitz et al. (Memorial Sloan Kettering Cancer Center; New York, NY, US), who reported that nivolumab or pembrolizumab employed as standalone therapeutic interventions induced a high rate of objective clinical responses among relapsed or refractory Hodgkin’s lymphoma patients.\textsuperscript{139,194}

**Preclinical and translational advances**

Reflecting the ever-increasing interest of clinicians and pharmaceutical companies in this paradigm of active immunotherapy, a high number of preclinical/translational papers dealing with the use of immunomodulatory mAbs for cancer therapy have been published in peer-reviewed scientific journals during the last 13 months. From such an abundant literature, we found of particular interest the works of: (1) Gubin and colleagues (Washington University School of Medicine; St. Louis, MO, US), who used genomic and bioinformatic approaches to identify cancer-specific mutant proteins as a major class of T-cell rejection antigens in mice bearing progressively growing sarcomas treated with CTLA4- or PD-1-targeting mAbs;\textsuperscript{195} (2) Snyder and co-authors (Weill Cornell Medical College; New York, NY, US), who defined a genetic basis for benefit from CTLA4 blockade in melanoma patients, providing a rationale for examining the exomes of individuals for whom CTLA4-targeting mAbs agents are being considered as a therapeutic option;\textsuperscript{196} (3) Herbst and collaborators (Yale Comprehensive Cancer Center; New Haven, CT, US), who demonstrated that MPDL3280A is most effective in patients in which pre-existing immunity is suppressed by PD-L1;\textsuperscript{197} (4) Tumeh et al. (University of California Los Angeles; Los Angeles, CA, US), who proved that tumor regression in response to PD-1-targeting mAbs relies on pre-existing tumor-targeting
CD8⁺ T lymphocytes that are kept in check by PD-1/PD-L1-dependent immunosuppression;⁶⁰ (5) Noman and colleagues (Gustave Roussy Cancer Campus; Villejuif, France), who discovered that tumor-infiltrating myeloid cells express increased amounts of PD-L1, a phenotype reflecting the activation of hypoxia-inducible factor 1 (HIF-1) by the tumor microenvironment;¹⁹⁸ (6) Fan and co-authors (MD Anderson Cancer Center; Houston, TX, US), who reported that simultaneously blocking CTLA4 and promoting inducible co-stimulator (ICOS) signaling mediates superior antineoplastic effects in mice bearing established melanomas or prostate carcinoma;¹⁹⁹ (7) Madireddi and collaborators (La Jolla Institute for Allergy and Immunology; La Jolla, CA, US), who found that lectin, galactoside-binding, soluble, 9 (LGALS9, best known as galectin-9) physically interacts with CD137, hence regulating its co-stimulatory activity;²⁰⁰ (8) Kong et al. (La Jolla Institute for Allergy and Immunology; La Jolla, CA, US), who demonstrated that protein kinase C, eta (PRKCH) operates downstream of CTLA4 to control the immunosuppressive activity of Tregs;²⁰¹ (9) Hermann and colleagues (Beckman Research Institute at City of Hope, Comprehensive Cancer Center; Duarte, CA, US), who designed CTLA4-targeting aptamers that are capable of delivering signal transducer and activator of transcription 3 (STAT3)-specific siRNAs to tumor-infiltrating CD8⁺ T lymphocytes, hence unleashing their effector functions;²⁰² (10) Deng and collaborators (The Ludwig Center for Metastasis Research; Chicago, IL, US), who demonstrated that combining PD-L1-targeting mAbs with radiation therapy exerts superior antineoplastic effects in tumor-bearing mice as it robustly alters (qualitatively and quantitatively) the tumor-infiltrating myeloid cell compartment;²⁰³ (11) Hannani and co-authors (Gustave Roussy Cancer Campus; Villejuif, France), who showed an opposite role for IL-2 and soluble IL-2 receptor α (sIL2RA, best known as sCD25) in antitumor responses elicited by ipilimumab in mice and melanoma patients, identifying the circulating levels of sCD25 and lactate dehydrogenase as biomarkers of ipilimumab resistance;²⁰⁴ and (12) Voron et al. (Hôpital Européen Georges Pompidou; Paris, France) who showed that vascular endothelial growth factor A (VEGFA) promotes the expression of PD-1 and other molecules involved in immunological checkpoints, delineating a therapeutically relevant, immunosuppressive response to hypoxia that can be reverted by anti-angiogenic agents targeting VEGFA or its receptors.²⁰⁵

Recently initiated clinical trials

Since the submission of our latest Trial Watch dealing with this topic (November 2013),⁵³ no less than 117 clinical studies have been initiated to investigate the safety and/or efficacy of immunomodulatory mAbs in cancer patients (source http://clinicaltrials.gov/). Although a significant proportion of these studies are intended to test molecules approved by the US FDA or similar regulatory agencies (ipilimumab, 43 studies; pembrolizumab, 28 studies; nivolumab, 22 studies), these mAbs are employed as on-label immunostimulatory interventions in a relatively limited number of trials (ipilimumab, 27 studies; pembrolizumab, 7 studies; nivolumab, 2 studies). Thus, most clinical trials that have been initiated during the last 13 months that involve ipilimumab, pembrolizumab and nivolumab enroll patients with neoplasms other than melanoma (ipilimumab, 19 studies; pembrolizumab, 24 studies; nivolumab, 20 studies). In addition, multiple trials have recently been launched to test the clinical profile of hitherto experimental immunomodulatory mAbs, including (1) the CD40-targeting co-stimulatory mAb CP-870,893 (2 studies);²⁰⁶ (2) the OX40-targeting co-stimulatory mAb MEDI6469 (2 studies);³⁹,²⁰⁷,²⁰⁸ (3) the CD137-targeting co-stimulatory mAbs PF-05082566 (1 study) and uralumab (3 studies);⁴⁶,²⁰⁹ ²¹¹ (4) the CTLA4-targeting checkpoint-blocking mAb tremelimumab (8 studies);²¹² ²¹⁴ (5) the PD-1-targeting checkpoint-blocking mAbs MEDI0680 (1 study) and pidilizumab (1 study);²¹⁵ (6) the PD-L1-targeting checkpoint-blocking mAbs MEDI4736 (16 studies), MPDL3280A (8 studies), and MSB0010718C (1 study);²¹⁵ and (7) the KIR-inhibitory mAb lirilumab (1 study).²¹⁶ Ninety-eight of these trials are early Phase I/II studies, while 17 of them are advanced Phase III-IV studies. The latter obviously encompass multiple trials evaluating the clinical profile of ipilimumab (6 studies), pembrolizumab (4 studies) and nivolumab (7 studies) (Table 2).

The cohorts of patients enrolled in the context of these clinical trials are relatively heterogeneous (source http://clinicaltrials.gov/). No less than 36 studies involve subjects with melanoma, near-to-invariably as an on-label indication for ipilimumab-, pembrolizumab-, or nivolumab-based immunotherapy. In addition, the safety and efficacy of immunomodulatory mAbs are being assessed in cohorts of patients with NSCLC (19 studies) or other pulmonary neoplasms (4 studies), various hematological malignancies (14 studies), head and neck cancer (8 studies), renal cancer (7 studies), colorectal carcinoma (CRC, 4 studies), prostate carcinoma (3 studies), Merkel cell carcinoma (2 studies), hepatocellular carcinoma (2 studies), gastric or gastrointestinal tumors (2 studies), and several other solid malignancies (23 studies). Along similar lines, it is difficult to identify a therapeutic paradigm that attracts considerably more attention than others, with the obvious exceptions of immunomodulatory mAbs employed as standalone immunotherapeutic interventions (58 studies). Thus, immunomodulatory mAbs are currently being tested in combination with a wide panel of chemo-, radio-, and immunotherapeutic regimens, including (but not limited to): (1) conventional and immunogenetic chemotherapeutics (7 studies),²¹⁷-²²² (2) targeted anticancer agents (19 studies),²²³,²²⁴ (3) radiation therapy, in one of its variants (6 studies),²²⁵,²²⁶ (4) hormone therapy (1 study),²²⁷-²²⁹ (5) surgery (1 study),²³⁰-²³² (6) tumor-targeting mAbs (10 studies),²³³-²³⁵ (7) immunostimulatory cytokines (5 studies),²³⁶,²³⁷,²³⁸-²⁴⁰ (8) anticancer vaccines (3 studies),²⁴¹-²⁴⁸ (9) Toll-like receptor (TLR) agonists (1 study),²⁴⁹,²⁵⁰ (10) adoptive cell transfer (3 studies),²⁵¹-²⁵³ (11) oncolytic virotherapy (2 studies),²⁵⁴,²⁵⁵ (12) idoximelamine 2,3-dioxynine 1 (IDO1)-targeting strategies (3 studies),²⁵⁷ (13) so-called immunomodulatory drugs, i.e., thalidomide, lenalidomide or pomalidomide (3 studies),²⁵⁸ and (14) immunomodulatory mAbs with a distinct mechanism of action (17 studies)²⁵⁹ (Table 2).

Of note, all these studies are active (NCT status: “Active, not recruiting,” “Not yet recruiting” or “Recruiting”), with 4 notable
Table 2. Clinical trials recently started to evaluate the therapeutic profile of immunomodulatory mAbs in oncological indications

| mAb          | Indication(s) | Phase | Status       | Notes                                      | Ref.            |
|--------------|---------------|-------|--------------|--------------------------------------------|-----------------|
| CP-870,893   | Solid tumors  | O     | Completed    | As single agent                            | NCT02157831     |
| Ipilimumab   | HCC, lung carcinoma | I     | Completed    | As single agent                            | NCT02225002     |
|              | HCC, melanoma | II    | Recruiting   | Combined with radiation therapy           | NCT02239900     |
|              | Lung carcinoma| III   | Not yet recruiting | Combined with carboplatin and paclitaxel  | NCT02279732     |
|              | Lymphoma, MCC | I/II  | Recruiting   | Combined with TLR9 agonist                | NCT02254772     |
|              |               | II    | Recruiting   | As single agent                            | NCT02196961     |
|              |               | I     | Completed    | Combined with IDO1-targeting vaccine       | NCT02077114     |
|              |               |       | Recruiting   | Combined with a galectin inhibitor         | NCT02117362     |
|              |               |       |              | Combined with panobinostat                | NCT01996202     |
|              |               |       |              | Combined with radiation therapy           | NCT0215243      |
|              |               |       |              | Combined with GM-CSF                      | NCT02009397     |
|              |               |       |              | Combined with indoximod                   | NCT02073123     |
|              |               |       |              | Combined with RTA 408                     | NCT02259231     |
|              |               |       |              | Combined with peptide-based vaccine and GM-CSF | NCT02275416     |
|              |               |       | Terminated   | Combined with vemurafenib and a PI3K inhibitor | NCT02095652     |
|              |               |       | II           | Active, not recruiting                     | NCT01990859     |
|              |               |       | Recruiting   | As single agent                            | NCT02115139     |
|              |               |       |              | Combined with a galectin inhibitor         | NCT02094391     |
|              |               |       |              | Combined with panobinostat                | NCT0209384      |
|              |               |       |              | Combined with radiation therapy           | NCT02054520     |
|              | Melanoma, sarcoma | I     | Not yet recruiting | Combined with adoptively transferred CD8+ T cells | NCT02158520     |
|              | NSCLC         | II    | Recruiting   | Combined with radiation therapy           | NCT02221739     |
|              | Prostate carcinoma | II   | Recruiting   | Combined with degarelix                   | NCT02020070     |
|              | SCLC          | II    | Recruiting   | As single agent                            | NCT02278887     |
|              | Solid tumors  | I     | Recruiting   | As single agent                            | NCT02068196     |
|              |               |       |              | Combined with adoptively transferred CD8+ T cells | NCT02210104     |
|              | Lirilumab     | I     | Not yet recruiting | Combined with elotuzumab                   | NCT02252263     |
|              | MEDI0680      | I     | Recruiting   | Combined with MEDI4736                     | NCT02118337     |
|              | MEDI4736      | II    | Not yet recruiting | As single agent                           | NCT02227667     |
|              | CRC           | II    | Not yet recruiting | As single agent                          | NCT02207530     |
|              | HNC           | II    | Not yet recruiting | As single agent                          | NCT02117219     |
|              | MDS           | I     | Recruiting   | As single agent                            | NCT02070406     |
|              | Melanoma      | I/II  | Recruiting   | Combined with adoptively transferred T cells and peptide-loaded DCs | NCT02252263 |
Table 2. Clinical trials recently started to evaluate the therapeutic profile of immunomodulatory mAbs in oncological indications (Continued)

| mAb                | Indication(s)                  | Phase | Status       | Notes                                                                 | Ref.       |
|--------------------|--------------------------------|-------|--------------|----------------------------------------------------------------------|------------|
| NSCLC              | I Recruiting                   |       | Combined with AZD9291 and selumetinib | NCT02143466 |                         |
|                    | I Recruiting                   |       | Combined with gefitinib                  | NCT02088112 |                         |
|                    | II Recruiting                  |       | As single agent                           | NCT02087423 |                         |
|                    | II/III Recruiting              |       | As single agent                           | NCT02154490 |                         |
|                    | III Recruiting                 |       | As single agent                           | NCT02125461 |                         |
| MEDI6469           | B-cell lymphoma, solid tumors  | I/II  | Recruiting | As single agent or combined with tremelimumab, MEDI4736 or rituximab | NCT02205333 |
|                    | HNC                            | I     | Recruiting | As single agent                                                       | NCT02274155 |
|                    | Bladder carcinoma              | II    | Recruiting | As single agent                                                       | NCT02108652 |
|                    | Lymphoma                       | I     | Not yet recruiting | Combined with obinutuzumab                                         | NCT02220842 |
|                    | NSCLC                          | I     | Recruiting | Combined with erlotinib                                               | NCT02013219 |
|                    | I Recruiting                   |       | Combined with EGF inhibitors              | NCT02100116  |
|                    | II Recruiting                  |       | Combined with erlotinib and selumetinib  | NCT02108113  |
|                    | III Recruiting                 |       | As single agent                           | NCT02031458  |
|                    | RCC                            | II    | Recruiting | Combined with bevacizumab and/or sunitinib                           | NCT01984242 |
|                    | Solid tumors                   | I     | Recruiting | Combined with cobimetinib and ipilimumab                             | NCT02174172 |
|                    | MCC                            | II    | Recruiting | Combined with cobimetinib and ipilimumab                             | NCT02155647 |
|                    | AML                            | II    | Not yet recruiting | As single agent                                                     | NCT02275533 |
|                    | Cervical carcinoma             | II    | Not yet recruiting | As single agent                                                      | NCT02257528 |
|                    | NSCLC                          | I     | Recruiting | Combined with dasatinib                                              | NCT02019145 |
|                    | CRC                            | I/II  | Recruiting | Combined with ipilimumab                                             | NCT02060188 |
|                    | Gastric carcinoma              | III   | Not yet recruiting | As single agent                                                      | NCT02267343 |
|                    | Glioblastoma                   | III   | Recruiting | As single agent or combined with ipilimumab and bevacizumab         | NCT02017717 |
|                    | HNC                            | III   | Recruiting | As single agent                                                       | NCT02105636 |
|                    | Hodgkin’s lymphoma             | II    | Recruiting | As single agent                                                       | NCT02181738 |
|                    | Lymphoma                       | II    | Recruiting | As single agent                                                       | NCT02038946 |
|                    | Melanoma                       | II    | Recruiting | As single agent                                                       | NCT02156804 |
|                    | I Recruiting                   |       | Combined with ipilimumab, dabrafenib and trametinib                   | NCT02224781 |
|                    | III Not yet recruiting          |       | Combined with ipilimumab, dabrafenib and trametinib                   | NCT02224781 |
|                    | NHL                            | II    | Recruiting | As single agent                                                       | NCT02038933 |
|                    | NSCLC                          | II    | Recruiting | As single agent                                                       | NCT02175017 |
|                    | III Recruiting                 |       | As single agent or combined with multimodal chemotherapy              | NCT0206636 |
|                    | Solid tumors                   | I     | Not yet recruiting | Combined with multimodal immunotherapy    | NCT02243371 |
|                    | Pancreatic carcinoma           | II    | Not yet recruiting | Combined with multimodal immunotherapy | NCT02243371 |
|                    | RCC                            | II    | Not yet recruiting | As single agent or combined with bevacizumab or ipilimumab           | NCT02210117 |
|                    | III Recruiting                 |       | As single agent or combined with multimodal chemotherapy             | NCT02041533 |
|                    |                              |       | Combined with multimodal immunotherapy | NCT02224371 |
| Pembrolizumab      | Breast carcinoma               | I/II  | Not yet recruiting | As single agent                                                      | NCT02129556 |
|                    | CRC                            | II    | Not yet recruiting | Combined with azacitidine                                           | NCT02260440 |
|                    | Gastrointestinal tumors        | II    | Not yet recruiting | Combined with erlotinib                                              | NCT02268825 |
|                    | HNC                            | II    | Not yet recruiting | Combined with radiation therapy                                      | NCT02289209 |
|                    | Melanoma                       | I     | Recruiting | As single agent                                                       | NCT02252042 |
|                    | II Recruiting                  |       | Combined with oncolytic virotherapy                                   | NCT02263508 |
|                    | III Not yet recruiting          |       | Combined with trametinib and dabrafenib                              | NCT02130466 |
|                    | Melanoma, NSCLC                | II    | Recruiting | As single agent                                                       | NCT02085070 |
|                    | Melanoma, RCC                  | I     | Recruiting | Combined with pazopanib                                               | NCT02014636 |

(continued on next page)
exceptions. NCT02157831 (a Phase 0 study) and NCT02225002 (a Phase I study), both of which assessed the therapeutic profile of a single infusion of CP-870,893 in patients with advanced solid tumors, are listed as “Completed.” To the best of our knowledge, however, the results of these studies have not yet been released. Similarly, NCT02077114, a Phase I clinical trial investigating the safety and efficacy of an IDO1-targeting vaccine combined with ipilimumab in Stage III/IV melanoma patients, appears as “Completed,” but the results are not yet available. Finally, NCT01721746, a Phase I/II clinical trial testing ipilimumab plus radiation therapy in patients with recurrent melanoma, non-Hodgkin’s lymphoma and CRC, has been suspended based on the results of a Data and Safety Monitoring Committee audit. NCT01913691, a Phase II clinical trial investigating the safety and efficacy of ipilimumab in Merkel cell carcinoma patients, has been withdrawn prior to

| mAb               | Indication(s)          | Phase | Status                  | Notes                                                | Ref.               |
|-------------------|------------------------|-------|-------------------------|------------------------------------------------------|-------------------|
| Multiple myeloma  | I                      | Recruiting | Combined with pegIFNα-2b or ipilimumab | NCT02089685     |
|                    | I                      | Recruiting | Combined with lenalidomide and dexamethasone | NCT02036502     |
|                    | I/II                   | Not yet recruiting | Combined with ponatalidomide and dexamethasone | NCT02289222     |
| Mycosis fungoides | II                     | Recruiting | As single agent         | NCT02243579     |
| Sezary syndrome   | II                     | Not yet recruiting | As single agent         | NCT02267603     |
| Neuroendocrine skin carcinoma | II | Not yet recruiting | As single agent         | NCT02341864     |
| NSCLC             | I                      | Active, not recruiting | As single agent         | NCT02007070     |
|                   | I/II                   | Recruiting | Combined with multimodal chemotherapy | NCT02039674     |
|                   | III                    | Recruiting | As single agent or combined with carboplatin or cisplatin | NCT02220894     |
|                   |                        |         |                         | NCT02142738     |
|                    |                        |         |                         | NCT02212730     |
|                   |                        |         |                         | NCT02133742     |
| Solid tumors      | I/II                   | Recruiting | Combined with INCB024360 | NCT02178722     |
|                   |                        |         |                         | NCT02256436     |
|                   |                        |         |                         | NCT02179918     |
|                   |                        |         |                         | NCT020077959    |
|                   |                        |         |                         | NCT02622741     |
|                   |                        |         |                         | NCT02261220     |
|                   |                        |         |                         | NCT02141347     |
|                   |                        |         |                         | NCT02253992     |
| Urothelial carcinoma | III                    | Recruiting | Combined with gemcitabine and docetaxel | NCT02101762     |
|                   |                        |         |                         | NCT02193682     |
|                   |                        |         |                         | NCT02009695     |
|                   |                        |         |                         | NCT02141347     |
|                   |                        |         |                         | NCT02255226     |
| Lung carcinoma    | I                      | Recruiting | Combined with MEDI4736 | NCT02000947     |
| Melanoma          | I                      | Recruiting | Combined with MEDI3617 | NCT02141542     |
| NSCLC             | I                      | Recruiting | Combined with gefitinib | NCT02040064     |
|                   | II                     | Recruiting | Combined with multimodal immunochemotherapy | NCT02179671     |
|                   |                        |         |                         | NCT02261220     |
|                   |                        |         |                         | NCT02141347     |
|                   |                        |         |                         | NCT02253992     |
|                   |                        |         |                         | NCT02110082     |
|                   |                        |         |                         | NCT02212547     |
|                   |                        |         |                         | NCT02141347     |
|                   |                        |         |                         | NCT02255226     |
| Urelumab          | B-cell NHL, Solid tumors | I/II         | Recruiting | Combined with nivolumab | NCT02253992     |
|                   |                        |         |                         | NCT02110082     |
|                   |                        |         |                         | NCT02225226     |

**Abbreviations:** AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CRC, colorectal carcinoma; GM-CSF, granulocyte macrophage colony-stimulating factor; HCC, hepatocellular carcinoma; HNC, head and neck cancer; IDO1, indoleamine 2,3-dioxygenase 1; IFNα-2b, interferon α2b; MCC, Merkel cell carcinoma; MDS, myelodysplastic syndrome; NHL, non-Hodgkin’s lymphoma; NSCLC, non-small cell lung carcinoma; PI3K, phosphoinositide-3-kinase; RCC, renal cell carcinoma; SCLC, small cell lung carcinoma; TLR9, Toll-like receptor 9. *Initiated after November 1st 2013.*
enrollment for undisclosed reasons. Finally, to the best of our knowledge, the results of NCT01165391, a Phase 2 study comparing fresolimumab to placebo in subjects with a pseudo-malignant renal disease, and NCT01709162, a Phase II study comparing ipilimumab re-administration to standard chemotherapy in subjects with advanced melanoma who progressed on induction ipilimumab-based immunotherapy following initial disease stabilization, have yet to be disclosed (source http://www.clinicaltrials.gov).

Concluding Remarks

One year ago, the Editors of Science Magazine designed anti-cancer immunotherapy “Breakthrough of the Year,” celebrating the extraordinary clinical success achieved by this therapeutic paradigm throughout the past decade. Immunomodulatory mAbs, and in particular checkpoint blockers, enacted a major part in this play. Accumulating lines of evidence indicate that checkpoint-blocking mAbs indeed not only represent a promising means to induce robust and durable responses when employed as single agents, but also can be harnessed to boost the activity of several (immuno)therapeutic regimens. These include (but are not limited to) tumor-targeting mAbs, adoptive cell transfer, dendritic cell-, peptide- and DNA-based anticancer vaccines, oncolytic viruses, TLR agonists, immunostimulatory cytokines, radiation therapy, and immunomodulatory drugs (e.g., lenalidomide), as well as conventional and targeted chemotherapeutics (in particular when these also mediate immunomodulatory effects).

Combinatorial strategies that simultaneously inhibit distinct immunological checkpoints, such as the co-administration of PD-1- and CTLA-targeting mAbs, also appear to mediate superior clinical activity, especially in the treatment of neoplasms such as melanoma and RCC, which are particularly sensitive to immunotherapy. Along similar lines, combining checkpoint blockers like ipilimumab or nivolumab with co-stimulatory mAbs such as MEDI6469 may be clinically advantageous as compared to monotherapeutic regimens. Therapeutic paradigms of this type, involving the co-administration of immunomodulatory mAbs with distinct mechanisms of action, are being intensively investigated in both preclinical and clinical scenarios.

Importantly, the use of some checkpoint blockers like ipilimumab has been associated with a limited, but non-negligible, rate of severe/fatal autoimmune reactions. One of the strategies currently under investigation to limit the toxicity of checkpoint-blocking mAbs has yielded promising results (at least in preclinical settings), relies on local, as opposed to systemic, administration. Interestingly, this approach appears to resemble radiation therapy in that it provokes an abscessal effect, i.e., it elicits a tumor-targeting immune response that attacks distant, non-treated lesions. Additional approaches for uncoupling the efficacy of checkpoint blockers from their toxicity may involve the gut microbiota. Of note, the clinical profile of the intratumoral co-administration of ipilimumab and a TLR9 agonist (i.e., SD-101) combined with local radiation therapy is currently being evaluated in patients affected by low-grade, recurrent B-cell lymphoma (NCT02254772).

Similar to their tumor-targeting counterparts, immunomodulatory mAbs are expensive (the use of pembrolizumab is expected to cost 12,500 USD per month) (source http://www.nytimes.com/2014/09/05/business/merck-wins-approval-of-novel-immune-system-drug-for-cancer.html?_r=0). Thus, it now imperative to identify biomarkers that predict the efficacy of immunomodulatory mAbs and hence allow for the identification of patients who are likely to obtain actual benefits from this type of immunotherapy.

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No potential conflicts of interest were disclosed.

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References

1. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Lichtenstein D, Lichtenstein SH, De Haens G, Diamond RH, Brousseau DL, et al. Infliximab, azathiprine, or combination therapy for Crohn's disease. N Engl J Med 2000; 343:1594–602; PMID:11096166; http://dx.doi.org/10.1056/NEJM200011303432202
2. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, Smolen JS, Weissman M, Emery P, Feldmann M, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study group. N Engl J Med 2000; 343:1594–602; PMID:11096166; http://dx.doi.org/10.1056/NEJM200011303432202
3. Melero I, Grimaldi AM, Perez-Gracia JL, Ascierto PA. Clinical development of immunomodulatory monoclonal antibodies and opportunities for combination. Clin Cancer Res 2013; 19:997–1008; PMID:23460531; http://dx.doi.org/10.1158/1078-0432.CCR-12-2214
4. Melero I, Herras-Stuha S, Glennie M, Pardoll DM, Chen L. Immunostimulatory monoclonal antibodies for cancer therapy. Nat Rev Cancer 2007; 7:95-106; PMID:17251916; http://dx.doi.org/10.1038/nrc2051
5. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012; 12:252-64; PMID:22437870; http://dx.doi.org/10.1038/nrc3239
6. Chawla A, Philips AV, Alatrash G, Mittendorf E. Immune checkpoints: a therapeutic target in triple negative breast cancer. Oncoimmunology 2014; 3:
7. Nowak AK. Immunological checkpoint inhibitors enter adolescence. Lancet Oncol 2013; 14:1035-7; PMID:24018650; http://dx.doi.org/10.1016/S1470-2045(13)70401-7

8. Lo S. Tumor-infiltrating lymphocytes, breast cancer subtypes and therapeutic efficacy. Oncoimmunology 2013; 2:e24720; PMID:20473665; http://dx.doi.org/10.4161/onci.20473; PMID:20473665

9. Senovilla L, Vecchelli E, Galon J, Adjemian S, Effermont A, Fridman WH, Sautès-Fridman C, Ma Y, Tartour E, Zvölgel L, et al. Trial watch: prognostic and predictive value of the immune infiltrate in cancer. PLoS One 2012; 7:e32434; PMID:22343596; http://dx.doi.org/10.1371/journal.pone.0022434

10. Senovilla L, Aranda F, Gallucci L, Kroemer G. Impact of myeloid cells on the efficacy of antitumor chemotherapy. Curr Opin Immunol 2014; 39:264-31; PMID:24295501; http://dx.doi.org/10.1016/j.coi.2014.05.009

11. de Visser KE, Koren LV, Coussens LM. De novo carcinogenesis promoted by chronic inflammation is B lymphocyte dependent. Cancer Cell 2005; 7:411-23; PMID:15894262; http://dx.doi.org/10.1016/j.ccr.2005.04.014

12. Schiotta T, Moore R, Thompson RG, Rosser EC, Kullikov S, Haas OA, Purohit S, Mauri C, Coussens LM, Ballwick FR. B regulatory cells and the tumor-promoting actions of TNF-alpha during squamous carcinogenesis. Proc Natl Acad Sci U S A 2011; 108:10662-7; PMID:2167004; http://dx.doi.org/10.1073/pnas.1100994108

13. Burt AA, Mills KH. Immunosuppressive networks and checkpoints controlling antitumor immunity and their blockade in the development of cancer immunotherapeutics and vaccines. Oncogene 2014; 33:4623-31; PMID:24314774; http://dx.doi.org/10.1038/2014.432

14. Mueller DL. Mechanisms maintaining peripheral tolerance. Nat Immunol 2010; 11:21-7; PMID:2006506; http://dx.doi.org/10.1038/2010.187

15. Dunn GP, Koelbl CM, Schreiber RD. Interferons, the immune checkpoint regulator PD-L1 is a specific target for naturally occurring CD4 T cells. Oncoimmunology 2013; 2:e23991; PMID:23774343; http://dx.doi.org/10.4161/onci.23991

16. Zitvogel L, Kroemer G. Targeting PD-1/PD-1 interactions for cancer immunotherapy. Oncoimmunology 2012; 1:1125-5; PMID:23424584; http://dx.doi.org/10.4161/onci.23424584

17. Fife BT, Paulsen KE, Eagar TN, Obu T, Wu J, Tang Q, Azuma M, Krummel MF, Bluestone JA. Interactions between PD-1 and PD-L1 promote tolerance by blocking the TCR-induced stop signal. Nat Immunol 2009; 10:1855-92; PMID:19783989; http://dx.doi.org/10.1038/ni.1790

18. Lipson EJ. Re-orienting the immune system: durable tumor regression and successful re-induction therapy using anti-PD1 antibodies. Oncoimmunology 2013; 2:e23661; PMID:23734322; http://dx.doi.org/10.4161/onci.23734322

19. Raeder DH, Guerra N. Oncogenic stress sensed by the immune system: role of natural killer cell receptors. Rev Immunol 2009; 9:568-80; PMID:19629084; http://dx.doi.org/10.1038/reird0604

20. Joncker NT, Raeder DH. Regulation of NK cell responsiveness to achieve self-tolerance and maximal responses to diseased target cells. Immunol Rev 2008; 224:85-97; PMID:18759922; http://dx.doi.org/10.1111/j.1600-065X.2008.00656.x

21. Long EO. Negative signaling by inhibitory receptors: the NK cell paradigm. Immunol Rev 2008; 227:70-84; PMID:18759921; http://dx.doi.org/10.1111/j.1600-065X.2008.00660.x

22. Schalper KA. PD-L1 expression and tumor-infiltrating lymphocytes: revisiting the antitumor immune response potential in breast cancer. Oncoimmunology 2014; 3:e29288; PMID:25083339; http://dx.doi.org/10.4161/onci.29288

23. Gutel J, Wei S, Dong H, Alvarez X, Cheng P, Moroz- tram P, Krzysiek R, Knutson KL, Daniel B, Zimmerman MC, et al. Blockade of B7-1H1 improves myeloid dendritic cell-mediated antitumor immunity. Nat Med 2003; 9:562-7; PMID:12704383; http://dx.doi.org/10.1038/nm863

24. Zou W, Chen L. Inhibitory B7-family molecules in the tumor microenvironment. Nat Rev Immunol 2004; 4:336-47; PMID:15122199; http://dx.doi.org/10.1038/nri1342

25. Keir ME, Liang SC, Guleria I, Latchman YE, Qipo A, Roncarolo MG. Continuous 4-1BB co-stimulatory signals for the tumor-infiltrating lymphocytes: revisiting the antitumor immune responsiveness to achieve self-tolerance and maximal effector CD4(+) T-cell function. Oncoimmunology 2012; 1:1323-43; PMID:23424596; http://dx.doi.org/10.4161/onci.23661

26. Zou W, Chen L. Inhibitory B7-family molecules in the tumor microenvironment. Nat Rev Immunol 2004; 4:336-47; PMID:15122199; http://dx.doi.org/10.1038/nri1342

27. Melero I, Shulford NW, Newby SA, Aruffo A, Led better JA, Hillestrom KE, Mittler RS, Chen L. Monon cleon antibodies against the 4-1BB T-cell activation molecule eradicate established tumors. Nat Med 1997; 3:682-5; PMID:9176498; http://dx.doi.org/10.1038/nm0607-682

28. Hamsb W, Ye M, Barrett JC, Levy R. Boosting antibody-dependent cellular cytotoxicity against tumor cells with a CD137 stimulatory antibody. Oncoimmunity 2012; 1:957-8; PMID:23162770; http://dx.doi.org/10.1038/1979

29. Senovilla L, Vacchelli E, Galon J, Adjemian S, Eggerger Q, Azuma M, Krummel MF, Bluestone JA. Interactions between PD-1 and PD-L1 promote tolerance by "tuning" regulatory T cells. Oncoimmunology 2012; 1:1323-43; PMID:23424596; http://dx.doi.org/10.4161/onci.22837

30. Senovilla L, Aranda F, Gallucci L, Kroemer G. Impact of myeloid cells on the efficacy of antitumor chemotherapy. Curr Opin Immunol 2014; 39:264-31; PMID:24295501; http://dx.doi.org/10.1016/j.coi.2014.05.009

31. Schiotta T, Moore R, Thompson RG, Rosser EC, Kullikov S, Haas OA, Purohit S, Mauri C, Coussens LM, Ballwick FR. B regulatory cells and the tumor-promoting actions of TNF-alpha during squamous carcinogenesis. Proc Natl Acad Sci U S A 2011; 108:10662-7; PMID:2167004; http://dx.doi.org/10.1073/pnas.1100994108

32. Burt AA, Mills KH. Immunosuppressive networks and checkpoints controlling antitumor immunity and their blockade in the development of cancer immunotherapeutics and vaccines. Oncogene 2014; 33:4623-31; PMID:24314774; http://dx.doi.org/10.1038/2014.432

33. Mueller DL. Mechanisms maintaining peripheral tolerance. Nat Immunol 2010; 11:21-7; PMID:2006506; http://dx.doi.org/10.1038/2010.187

34. Dunn GP, Koelbl CM, Schreiber RD. Interferons, McGovern. The immune checkpoint regulator PD-L1 is a specific target for naturally occurring CD4 T cells. Oncoimmunology 2013; 2:e23991; PMID:23774343; http://dx.doi.org/10.4161/onci.23991

35. Zitvogel L, Kroemer G. Targeting PD-1/PD-1 interactions for cancer immunotherapy. Oncoimmunology 2012; 1:1125-5; PMID:23424584; http://dx.doi.org/10.4161/onci.23424584

36. Fife BT, Paulsen KE, Eagar TN, Obu T, Wu J, Tang Q, Azuma M, Krummel MF, Bluestone JA. Interactions between PD-1 and PD-L1 promote tolerance by blocking the TCR-induced stop signal. Nat Immunol 2009; 10:1855-92; PMID:19783989; http://dx.doi.org/10.1038/ni.1790
61. PD-1 Inhibitor Approved for Melanoma. Cancer Dis-
2045(14)70348-1

65. Hodi FS, O'Day SJ, McDermott DF, Weber RW,
2014; 32:8023

63. Robert C, Ribas A, Wolchok JD, Hodi FS, Gangad-
2014; 3:e27297; http://dx.doi.org/10.4161/onci.22789

62. Callahan MK, Bendell JC, Chan E, Morse M, Pillai
21624011.2014.967147

52. Galluzzi L, Kroemer G, Eggermont A, Cirocchi R, Zitvogel L, Kroemer G, Galluzzi L. Trial
64. Robert C, Long GV, Brady B, Dutriaux C, Maio M,

55. Hodi FS, O'Day SJ, McDermott DF, Weber RW,
2045(09)70334-1

51. Vigneri S, Gallo A, Forlani G. Targeted therapy: oncolytic viruses for cancer ther-
2014; 3:e29030; http://dx.doi.org/10.4161/onci.28694

49. Lheureux S, Butler MO, Fleming GF, Hirte HW,
2014; 32:TP59107

48. Deo MA. Long-term survival benefit from ipilimu-
2014; 32:12034

47. Lee K, Kim TH, Kim Y, Kang BI, Park H, Park HJ, Shin YJ, Kang JW, Lee JH, et al. A phase I/II open-label study of nivolumab (anti-
2014; 32:90307

46. Callahan MK, Bendell JC, Chan E, Morse M, Pillai
2045(09)70334-1

45. van der Heyden PF, Sartor O, Gore ME, Czernobilsky AJ, et al. Phase I/II of nivolumab (anti-PD-1) in combination with ipilimumab in patients with advanced melanoma. ASCO Meeting Abstracts 2014; 32:TP59107

44. Lheureux S, Butler MO, Fleming GF, Hirte HW,
2014; 32:TP59107

43. Deo MA. Long-term survival benefit from ipilimu-
2014; 32:12034

42. Lee K, Kim TH, Kim Y, Kang BI, Park H, Park HJ, Shin YJ, Kang JW, Lee JH, et al. A phase I/II open-label study of nivolumab (anti-
2014; 32:90307

41. Vigneri S, Gallo A, Forlani G. Targeted therapy: oncolytic viruses for cancer ther-
2014; 3:e29030; http://dx.doi.org/10.4161/onci.28694

40. Deo MA. Long-term survival benefit from ipilimu-
2014; 32:12034

39. van der Heyden PF, Sartor O, Gore ME, Czernobilsky AJ, et al. Phase I/II of nivolumab (anti-PD-1) in combination with ipilimumab in patients with advanced melanoma. ASCO Meeting Abstracts 2014; 32:TP59107

38. Deo MA. Long-term survival benefit from ipilimu-
2014; 32:12034

37. Lee K, Kim TH, Kim Y, Kang BI, Park H, Park HJ, Shin YJ, Kang JW, Lee JH, et al. A phase I/II open-label study of nivolumab (anti-
2014; 32:90307

36. Deo MA. Long-term survival benefit from ipilimu-
2014; 32:12034

35. van der Heyden PF, Sartor O, Gore ME, Czernobilsky AJ, et al. Phase I/II of nivolumab (anti-PD-1) in combination with ipilimumab in patients with advanced melanoma. ASCO Meeting Abstracts 2014; 32:TP59107

34. Deo MA. Long-term survival benefit from ipilimu-
2014; 32:12034

33. Lee K, Kim TH, Kim Y, Kang BI, Park H, Park HJ, Shin YJ, Kang JW, Lee JH, et al. A phase I/II open-label study of nivolumab (anti-
2014; 32:90307

32. Hodi FS, O'Day SJ, McDermott DF, Weber RW,
2014; 32:8023

31. Antonia SJ, Gettinger SN, Chow LQM, Juergens RA,
2014; 3:e22789; PMID:23482847; http://dx.doi.org/10.4161/onci.22789

30. Pol J, Bloy N, Obsir F, Eggermont A, Galon J, Cramer L, Vegh K, Kroemer G, Galluzzi L. Trial
64. Robert C, Long GV, Brady B, Dutriaux C, Maio M,

29. Diederichs S, Witzig J, Zambotti G, Hengstler JG, Ponzoni M, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2014; 372:320-30; PMID:25399952; http://dx.doi.org/10.1056/NEJMoa1412082

28. Dai M, Tip YH, Hellstrom I, Hellstrom KE. Curing mice with large tumors by locally delivering combina-

tions of immunomodulatory antibodies. Clin Cancer Res 2014; PMID:25124124; http://dx.doi.org/10.1158/1078-0432.CCR-14-1339

27. Wei H, Zhao L, Hellstrom I, Hellstrom KE, Guo Y. Dual targeting of CD137 co-stimulatory and PD-1 co-inhibitory pathways for oncolytic virus-driven immune- therapy. Oncology 2014; 3:e28248; http://dx.doi.org/10.4161/onci.28248

26. Vacchelli E, Rappia RA, Panigada SE, di Pietro A, Sica A, Gobert G, et al. Nivolumab in combination with ipilimumab in melanoma patients: a phase II study. ASCO Meeting Abstracts 2014; 32:TP59107

25. Jaffee EM, Batsal AS, Wachsmuth H. IP-10 Inhibitors in combination with immunotherapy. Oncoimmunology 2014; 3:e27297; http://dx.doi.org/10.4161/onci.27297

24. Tumeh PC, Harvengt CL, Yearly JH, Ishikawa TK, Taylor EJ, Robert L, Chmielowski B, Spasic M, Henry C, Cihaner V, et al. PD-1 blockade induces responses in inhibiting adaptive immune resistance. Nature 2014; 515:568-71; PMID:25428505; http://dx.doi.org/10.1038/nature13954

23. Borden EC, Ascierto PA, Richards JM, et al. Ipilimumab for Melanoma. Cancer Dis-
2014; 32:52

22. Bjorn J, Donia M, Anderssen R, Reker Hadrup S, Junga R, Thorsen L, et al. Phase I/II open-label study of nivolumab (anti-
2014; 32:90307

21. Callahan MK, Bendell JC, Chan E, Morse M, Pillai
2014; 32:TP59107

20. Chassot P, Pages C, Biard L, Roux J, Sidana I, Made-
2014; 32:TP59107

19. Delea ED. Nivolumab: a review of its use in patients
2014; 32:TP59107

18. Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O,
2014; 32:TP59107

17. Delea ED. Nivolumab: a review of its use in patients with malignant melanoma. Drugui 2014; 74:1233-9; PMID:25205250; http://dx.doi.org/10.1016/j.drugui.2014-01-02544

16. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, Hassel JC, Rutkowski P, McNeil C, Kalinka-Warczonek E, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2014; 372:320-30; PMID:25399952; http://dx.doi.org/10.1056/NEJMoa1412082

15. Bacciotti S. Pembrolizumab for treatment of refractory melanoma. Lancet Oncol 2014; 15:e189; PMID:25238942; http://dx.doi.org/10.1016/S1470-2045(14)70348-1

14. Deo MA. Long-term survival benefit from ipilimu-
2014; 32:12034
melanoma (MELO) treated with the anti-PD-1 monochonal antibody MK-3475. ASCO Meeting Abstracts 2014; 32:3006

130. Joseph RW, Elsasser-Schaaf J, Wolchok JD, Joshua AM, Ribas A, Homer CR, Hamid O, Redel C, Daud A, Hwu W-J, et al. Baseline tumor size as an independent prognostic factor for overall survival in patients with metastatic melanoma treated with the anti-PD-1 monochonal antibody MK-3475. ASCO Meeting Abstracts 2014; 32:3010

131. Kefford R, Ribas A, Hamid O, Durden C, Daud A, Wolchok JD, Joshua AM, Hodi FS, Gangadhar TC, Hersey P, et al. Clinical efficacy and correlation with tumor PD-L1 expression in patients (pts) with melanoma (MELO) treated with the anti-PD-1 monochonal antibody MK-3475. ASCO Meeting Abstracts 2014; 32:3005

132. Randa N, Pлимак ER, Dees EC, Gupta S, Berger R, Elifyk A, Puxral L, Buissier L, Geva R, Pai SI, et al. A phase Ib multicohort study of MK-3475 in patients with advanced solid tumors. ASCO Meeting Abstracts 2014; 32:TPS3105

133. Ribas A, Hodi FS, Hamid O, Durden C, Daud A, Wolchok JD, Hwu W-J, Gangadhar TC, Pattnaik A, Joshua AM, et al. Efficacy and safety of the anti-PD-1 monochonal antibody MK-3475 in 411 patients (pts) with relapsed/refractory multiple myeloma (MM). ASCO Meeting Abstracts 2014; 32:LB19000

134. Rivi NA, Garon EB, Patnaik A, Gandhi L, Leigh NB, Balmanoukian AS, Goldman JW, Eder JP, Johnson E, Blumenschein GR, et al. Safety and clinical activity of MK-3475 as initial therapy in patients with advanced renal cell cancer. ASCO Meeting Abstracts 2014; 32:TPS3119

135. Segal NH, Hodi FS, Sanborn RE, Gajewski T, Wolchok JD, Carvajal RD, Sharfman WH, Brahmer JR, Lawrence DP, Atkins MB, Powderly JD, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol 2014; 32:1020-30; PMID:24590637; http://dx.doi.org/10.1200/JCO.2013.51.4802

136. Leskalin AM, Ansell SM, Armand P, Scott EC, Halwani A, Gutierrez M, Millerson MM, Cohen AD, Schuster SJ, Lebovic D, et al. Preliminary results of a Phase I study of nivolumab (BMS-936558) in patients with relapsed or refractory lymphoid malignancies. ASH Annual Meeting Abstracts 2014; Session 624: Abstract 291

137. Lessin AM, Chen J, Terreno M, Corral M, Mercado F, Wang H, Amin A, Plimack ER, Infante JR, Ernstoff MS, Rini BI, McDermott DF, Kluger HM, Carvajal RD, Shafman WH, Brahmer JR, Lawrence DP, Atkins MB, Powderly JD, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol 2014; 32:1020-30; PMID:24590637; http://dx.doi.org/10.1200/JCO.2013.53.1105

138. Moskowitz CH, Ribrag V, Michot JM, Martinelli G, Seiwert TY, Burtness B, Weiss J, Gluck I, Eder JP, Pai SI, et al. Safety of nivolumab with vaccine in ipilimumab-refractory metastatic melanoma (NCT01407772). ASCO Meeting Abstracts 2014; 32:TPS3120

139. Choueiri TK, Fishman MN, Escudier BJ, Kim JJ, Kluger HM, Stadler WM, Perez-Gracia JL, McNeil DG, Caridi BD, Harrison MR, et al. Immunomodulatory activity of nivolumab in previously treated and untreated metastatic melanoma (mRCC): biomarker-based results from a randomized clinical trial. ASCO Meeting Abstracts 2014; 32:5012

140. Reck M, Herr ADC, Carvajal RD, Hodi FS, Brahmer JR, Durden C, Daud A, Wolchok JD, Hwu W-J, et al. A multicohort study of MK-3475 in patients with advanced renal cell cancer. ASCO Meeting Abstracts 2014; 32:TPS3120

141. Rabinowitz J, Le DT, Azad NS, Laheru D, Browner IS, Wang H, Wang J, et al. Immunomodulatory activity of nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with tremelimumab in patients with advanced renal cell cancer (NSCLC). ASCO Meeting Abstracts 2014; 32:TPS3120

142. Hamid O, Kefford R, Ribas A, Hamid O, Robert C, Daud A, Wolchok JD, Hwu W-J, Ylinen R, Luedy CE, et al. Safety of nivolumab with vaccine in ipilimumab-refractory metastatic melanoma (NCT01407772). ASCO Meeting Abstracts 2014; 32:TPS3120

143. Cao J, Carvajal RD, Thomas G, Brahmer JR, Hamid O, Kefford R, Furmaniak JM, Aziz K, et al. A randomized, open-label, phase III study of nivolumab (BMS-936558) versus ipilimumab (Yervoy) in patients with metastatic renal cell carcinoma (mRCC). ASCO Meeting Abstracts 2014; 32:5012

144. Carbone DP, Scocinski MA, Chen AC, Bhagavatheswaran P, Reck M, Ponz-Ares L. A phase III, randomized, open-label study of tremelimumab versus nivolumab as monotherapy in patients with advanced non-small cell lung cancer (NSCLC). ASCO Meeting Abstracts 2014; 32:TPS3120

145. Carbone DP, Socinski MA, Chen AC, Bhagavatheswaran P, Reck M, Ponz-Ares L. A phase III, randomized, open-label study of tremelimumab versus nivolumab as monotherapy in patients with advanced non-small cell lung cancer (NSCLC). ASCO Meeting Abstracts 2014; 32:TPS3120

146. Bajrami I, Paleta J, Zhao X, Martinez AJ, Wang H, Amin A, Plimack ER, Infante JR, Ernstoff MS, Rini BI, McDermott DF, Kluger HM, Carvajal RD, Shafman WH, Brahmer JR, Lawrence DP, Atkins MB, Powderly JD, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol 2014; 32:1020-30; PMID:24590637; http://dx.doi.org/10.1200/JCO.2013.51.4802

147. Hamanishi J, Mandai M, Ikeda T, Minami M, Kawashima K, Numa H, et al. Safety and efficacy of nivolumab and MK-3475 in patients with metastatic melanoma treated with the anti-PD-1 monochonal antibody (anti-PD-1; BMS-936558, ONO-4538) monotherapy in patients with metastatic melanoma treated with the anti-PD-1 monochonal antibody (anti-PD-1; BMS-936558, ONO-4538) in combination with tremelimumab in patients with advanced renal cell cancer (NSCLC). ASCO Meeting Abstracts 2014; 32:TPS3120

148. Motzer RJ, Rini BI, McDermott DF, Redman BG, Escudier BJ, Kim JJ, Kluger HM, Stadler WM, Perez-Gracia JL, McNeil DG, Caridi BD, Harrison MR, et al. Immunomodulatory activity of nivolumab in previously treated and untreated metastatic melanoma (mRCC): biomarker-based results from a randomized clinical trial. ASCO Meeting Abstracts 2014; 32:5012

149. Seiwert TY, Burtness B, Weiss J, Gluck I, Eder JP, Pai SI, et al. A phase Ib multicohort study of MK-3475 in patients with advanced solid tumors. ASCO Meeting Abstracts 2014; 32:TPS3120

150. Seiwert TY, Burtness B, Weiss J, Gluck I, Eder JP, Pai SI, et al. A phase Ib multicohort study of MK-3475 in patients with advanced solid tumors. ASCO Meeting Abstracts 2014; 32:TPS3120
with advanced hematologic malignancies. ASCO Meeting Abstracts 2014; 32:3002

177. Infante JR, Burris HA, Ansell SM, Nemunaitis JJ, Weiss GR, Villalobos VM, Sikic BI, Taylor MH, Nordhoff DW, Caron WE, et-al. Immunostaining activity of an activating anti-CD27 antibody (CDX-1127) in patients (pts) with solid tumors. ASCO Meeting Abstracts 2014; 32:3002

178. Chowdhury F, Johnson PW, Glennie MJ, Williams AP, Ex vivo analysis of dendritic cell (DC) cytokine profiles as predictors of in vivo effects in an anti-human CD40 monoclonal antibody ChLoB 7/4 phase i trial. Cancer Immunol Res 2014; 2:229-40; PMID:2477819; http://dx.doi.org/10.1158/2166-0866.CIR-13-0079

179. de Vos S, Forero-Torres A, Ansell SM, Kalh B, Che- son BD, Bartlett NL, Furman RR, Winter JN, Kaplan H, Timmerman J, et-al. A phase ii study of dactumabin (SGN-40) in patients with relapsed diffuse large B-cell lymphoma (DLBCL). ASCO Meeting Abstracts 2014; 32:3002

180. Madireddi S, Eun SY, Lee SW, Nemcovicova I, Noman MZ, Desantis G, Janji B, Hasmim M, Karray M, et-al. A phase 1 study of pan-3/4 inhibition in patients with advanced solid tumors and relapsed/refractory B-cell non-Hodgkin lymphoma. ASCO Meeting Abstracts 2014; 32;3007

181. Chester C, Chang S, Kurland JP, Sagiv-Barz I, Czar- winski PA, D’Ambrosia R, Waller E, Sadaraz A, Richards L, Cohen LJ, et-al. Biomarker characterization using mass cytometry in a phase 1 trial of urelumab (MBS-665513) in subjects with advanced solid tumors and relapsed/refractory B-cell non-Hodgkin lymphoma. ASCO Meeting Abstracts 2014; 32:3007

182. Noman MZ, Desantis G, Janji B, Hasmim M, Karray M, et-al. Phase 1 of a 2 phase i trial of pan-KIR2D blockade with IPI1101 in smoldering multiple mye- loma. Haematologica 2014; 99:813-3; PMID:24658821; http://dx.doi.org/10.3324/haematol.2013.103085

183. Sedg NH, Gopal AK, Khleif S, Kohrt HE, Levy R, Nordhoff DW, Caron WE, et-al. Immuno-stimulatory activity of an activating anti-CD27 antibody (CDX-1127) in patients (pts) with solid tumors. ASCO Meeting Abstracts 2014; 32:3002

184. Chowdhury F, Johnson PW, Glennie MJ, Williams AP, Ex vivo analysis of dendritic cell (DC) cytokine profiles as predictors of in vivo effects in an anti-human CD40 monoclonal antibody ChLoB 7/4 phase i trial. Cancer Immunol Res 2014; 2:229-40; PMID:2477819; http://dx.doi.org/10.1158/2166-0866.CIR-13-0079

185. Morris JC, Tan AR, Olencki TE, Shapiro GJ, Denzhe BJ, Reiu M, Husi FJ, Berzofsky JA, Lawrence DP. Phase I study of GC1008 (frenolimumab): a human anti transforming growth factor-beta (TGFbeta) monoclonal antibody in patients with advanced malignant melanoma or renal cell carcinoma. PLoS One 2014; 9:e90533; PMID:24618589; http://dx.doi.org/10.1371/journal.pone.0090533

186. Junker N, Sun BC, Ahmad R, et-al. Inhibition of PD-L1 by MPDL3280A (anti-PD-L1) in patients with advanced solid tumors and relapsed/refractory B-cell non-Hodgkin lymphoma. ASCO Meeting Abstracts 2014; 32:3002

187. Heery CR, O’Sullivan Coyne GH, Madireddi S, Eun SY, Lee SW, Nemcovicova I, Noman MZ, Desantis G, Janji B, Hasmim M, Karray M, et-al. A phase 1 study of pan-3/4 inhibition in patients with advanced solid tumors and relapsed/refractory B-cell non-Hodgkin lymphoma. ASCO Meeting Abstracts 2014; 32:3002

188. Corde N, Carlsten M, Lee MJ, Minter A, Tan E, Kwok M, Manasanch E, Bhutani M, Tageja N, et-al. Clinical trials of MPDL3280A (anti-PD-L1) in patients (pts) with non-small cell lung cancer (NSCLC). ASCO Meeting Abstracts 2014; 32;TPS1825

189. Emonts LA, Brainis FS, Cassoer P, Delord JP, Eder JP, Shen Y, Ling B, Xiuan W, Hedge PG, Chen DS, et-al. Inhibition of PD-L1 by MPDL3280A leads to clinical activity in pts with metastatic urothelial bladder cancer (UBC). ASCO Meeting Abstracts 2014; 32:5011

190. Riawi NZ, Chow LQM, Diris LY, Gettying SN, Gordon MS, Kabbaznan FF, Von Powell J, Soria J-C, Gospodarowicz M, et-al. Clinical trials of MPDL3280A (anti-PDL1) in patients with advanced hematologic malignancies. ASCO Meeting Abstracts 2014; 32:3002

191. Heery CR, O’Sullivan Coyne GH, Madiran RA, von Heydecke A, Cuillerot J-M, Saba- vari H, Gullly JL. Phase I open-label, multiple ascending dose trial of MSB001718C, an anti- PD-L1 monoclonal antibody, in advanced solid malignancies. ASCO Meeting Abstracts 2014; 32:3006

192. Corde N, Carlsten M, Lee MJ, Minter A, Tan E, Kwok M, Manasanch E, Bhutani M, Tageja N, Roschewski M, et-al. A phase ii trial of pan-KIR2D blockade with IPI1101 in smoldering multiple mye- loma. Haematologica 2014; 99:813-3; PMID:24658821; http://dx.doi.org/10.3324/haematol.2013.103085

193. Sedg NH, Gopal AK, Khleif S, Kohrt HE, Levy R, Nordhoff DW, Caron WE, et-al. Immuno-stimulatory activity of an activating anti-CD27 antibody (CDX-1127) in patients (pts) with solid tumors. ASCO Meeting Abstracts 2014; 32:3002

194. Sedg NH, Gopal AK, Khleif S, Kohrt HE, Levy R, Nordhoff DW, Caron WE, et-al. Immuno-stimulatory activity of an activating anti-CD27 antibody (CDX-1127) in patients (pts) with solid tumors. ASCO Meeting Abstracts 2014; 32:3002

195. Corde N, Carlsten M, Lee MJ, Minter A, Tan E, Kwok M, Manasanch E, Bhutani M, Tageja N, Roschewski M, et-al. A phase ii trial of pan-KIR2D blockade with IPI1101 in smoldering multiple mye- loma. Haematologica 2014; 99:813-3; PMID:24658821; http://dx.doi.org/10.3324/haematol.2013.103085

196. Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JP, Noguchi T, Ivanova T, Hundal J, Arthur CD, Krebber WJ, et-al. Checkpoint blockade cancer immunotherapy targets tumour-specific mutant anti-gens. Nature 2014; 515:577-81; PMID:25414572; http://dx.doi.org/10.1038/nature14108

197. Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Infante JR, Cebon JS, Brockmann M, Stoelben E, Groen HJM, Timens W, Leyvraz S1, et-al. MART-1 peptide vaccination plus ipilimumab in patients with pretreated advanced melanoma: the phase 2 MDR2001 study. J Transl Med 2014; 12:97; PMID:25492060; http://dx.doi.org/10.1056/NEJMoa1302338

198. Noman MZ, Desantis G, Borrelli I, Haliwan A, Scott EC, Guterrez M, Schuster MJ, Millerson MM, Carthy D, Freeman GJ, et-al. PD-1 blockade with nivolumab in relapsing or refractory Hodgkin’s lym- phoma. N Engl J Med 2014; 372:311-9; PMID:24778419; doi.org/10.1056/NEJMoa1404514

199. GuimB MB, et-al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2013; 368:1595-601; PMID:23550685; http://dx.doi.org/10.1056/NEJMoa1302338

200. Madireddi S, Eun SY, Lee SW, Nemcovicova I, Noman MZ, Desantis G, Janji B, Hasmim M, Karray M, et-al. A phase 1 study of pan-3/4 inhibition in patients with advanced solid tumors and relapsed/refractory B-cell non-Hodgkin lymphoma. ASCO Meeting Abstracts 2014; 32:3007
Kroeningberg M, et-al. Protein kinase Ceta controls CTLA-4-mediated regulatory T cell function. Nat Immunol 2014; 15:465-72; PMID:24705298; http://dx.doi.org/10.1038/nm.3086.

Herrmann A, Kaelin WG Jr, Sujkowski M, Xin H, Chernyholmes GA, Zhang W, Zhang C, Lahtz C, Kowolik C, Forman SJ, et-al. CTLA-4 aptamer delivers STAT3 sRNA to tumor-associated and malignant T cells. J Clin Invest 2014; 124:2977-87; PMID:25099287; http://dx.doi.org/10.1172/JCI73174.

Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, Fu YX. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in vivo. J Clin Invest 2014; 124:687-95; PMID:24382348; http://dx.doi.org/10.1172/JCI76313.

Hanani D, Vezou M, Enot D, Rusakiewicz S, Desbois M, Chapat N, Klarmann D, Jacobnet Q, Vimichno-Chernova S, et-al. IL-2-dependent antitumor activity of inhibitory checkpoints on CD8 T cells. J Immunol 2014; 193:4297-307; PMID:25106796; http://dx.doi.org/10.4049/jimmunol.1302055.

Voron T, Colussi O, Marcheteau E, Pernot S, Nizard H, Riccardi C, et-al. Phase III randomised clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. J Clin Oncol 2013; 31:616-22; PMID:23295794; http://dx.doi.org/10.1200/JCO.2012.44.6112.

Hirschhorn-Cymerman D, Rizzuto G, Merghoub T, Moran AE, Kovacsovics-Bankowski M, Weinberg Vonderheide RH, Flaherty KT, Khalil M, Stumacher J, Ribas A, Chesney JA, Gordon MS, Abernethy AP, Rajasekhar K, Brem H, Weller S, et-al. Polyfunctional CD8α+ T cell responses in response to cancer therapy. Cancer Immunol Immunother 2013; 62:1191-8; PMID:24045386; http://dx.doi.org/10.1007/s00262-013-15416-9.

Vacchelli E, Aranda F, Eggemont A, Galon J, Sautes-Fridman C, Cremer I, Zitvogel L, Kroemer G, Galuzzi L. Trial watch: chemotherapy with immunogenic cell death inducers. Oncoimmunology 2014; 3:1307-88; http://dx.doi.org/10.4161/onci.2790.

Fridman WH, Cremer I, Zitvogel L, Kroemer G, Galluzzi L. Trial watch: tumor-targeting monoclonal antibodies in cancer therapy. Oncoimmunology 2014; 3:327048; PMID:24605265.

Feuring BM. Building better magic bullets–improving unconjugated monoclonal antibody therapy for cancer. Nat Rev Cancer 2007; 7:701-6; PMID:17721434; http://dx.doi.org/10.1038/nrc2209.

Strabelli K, Ulrich A. Paul Ehrlch’s magic bullet concept: 100 years of progress. Nat Rev Cancer 2008; 8:473-80; PMID:18469827; http://dx.doi.org/10.1038/nrclinonc.2008.239.

Hughes C. Adoptive cell therapy: honing that killer instinct. Nat Biotechnol 2013; 31:503-5; PMID:23542359; http://dx.doi.org/10.1038/504513a.

Mauv MF, Fraietta JA, Levine BL, Kals M, Zhao Y, June CH. Adoptive immunotherapy for cancer or viruses. Annu Rev Immunol 2014; 32:189-225; PMID:24433116; http://dx.doi.org/10.1146/annurev-immunol-032712-100008.

Munir J, Tartour E, Spisek F, Saez-Rodriguez J, Kefford R, Marshall MA, Punt CJ, Haenem JB, Marmol M, Garbe C, Gogas H, Schachtur J, Linee C, et-al. Phase II randomised clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. J Clin Oncol 2013; 31:616-22; PMID:23295794; http://dx.doi.org/10.1200/JCO.2012.44.6112.

Ribas A, Kefford R, Marshall MA, Punt CJ, Haenem JB, Marmol M, Garbe C, Gogas H, Schachtur J, Linee C, et-al. Phase III randomised clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. J Clin Oncol 2013; 31:616-22; PMID:23295794; http://dx.doi.org/10.1200/JCO.2012.44.6112.

Hannani D, Vezou M, Enot D, Rusakiewicz S, Desbois M, Chapat N, Klarmann D, Jacobnet Q, Vimichno-Chernova S, et-al. IL-2-dependent antitumor immunity of inhibitory checkpoints on CD8 T cells. J Immunol 2014; 193:4297-307; PMID:25106796; http://dx.doi.org/10.4049/jimmunol.1302055.
247. Rice J, Ottensmeier CH, Stevenson FK. DNA vaccines: precision tools for activating effective immunity against cancer. Nat Rev Cancer 2008; 8:106-20; PMID:18219306; http://dx.doi.org/10.1038/ntc3256.

248. Palucka K, Banchereau J. Cancer immunotherapy via dendritic cells. Nat Rev Cancer 2012; 12:265-77; PMID:22437871; http://dx.doi.org/10.1038/nc13258.

249. Vacchelli E, Eggermont A, Galon J, Sautes-Fridman C, Tartour E, Zitvogel L, Kromer G, et al. Trial watch: peptide-based anticancer vaccines. Oncoimmunology 2014; 3:e29179; doi:10.4161/onci.28344.

250. Vacchelli E, Aranda F, Eggermont A, Galon J, Sautes-Fridman C, Tartour E, Zitvogel L, Kromer G, et al. Trial watch: adoptive cell transfer for cancer immunotherapy. Oncoimmunology 2014; 3:e28344; PMID:25050207; http://dx.doi.org/10.4161/onci.29179.

251. Aranda F, Vacchelli E, Obrist F, Eggermont A, Galon J, Herve Fridman W, Tartour E, Zitvogel L, Kromer G, et al. Trial watch: adoptive cell transfer for anticancer immunotherapy. Oncoimmunology 2014; 3:e28344; PMID:25050207; http://dx.doi.org/10.4161/onci.29179.

252. Vacchelli E, Eggermont A, Sautes-Fridman C, Galon J, Herve Fridman W, Tartour E, Zitvogel L, Kromer G, et al. Trial watch: adoptive cell transfer for cancer immunotherapy. Oncoimmunology 2013; 2:e24238; PMID:23762803; http://dx.doi.org/10.4161/onci.24238.

253. Restifo NP, Dudley ME, Rosenberg SA. Adoptive cell transfer therapy. Nat Rev Immunol 2012; 12:260-81; PMID:22437939; http://dx.doi.org/10.1038/nii3191.

254. Vacchelli E, Eggermont A, Sautes-Fridman C, Galon J, Zitvogel L, Kromer G, Galluzzi L, Zitvogel L, Kromer G, et al. Trial watch: adoptive cell transfer for anticancer immunotherapy. Oncoimmunology 2013; 2:e24238; PMID:23762803; http://dx.doi.org/10.4161/onci.24238.

255. Restifo NP, Dudley ME, Rosenberg SA. Adoptive immunotherapy for cancer: harnessing the T cell repertoire. Nat Rev Immunol 2012; 12:260-81; PMID:22437939; http://dx.doi.org/10.1038/nii3191.

256. Vacchelli E, Eggermont A, Sautes-Fridman C, Galon J, Zitvogel L, Kromer G, Galluzzi L, Zitvogel L, Kromer G, et al. Trial watch: adoptive cell transfer for anticancer immunotherapy. Oncoimmunology 2013; 2:e24238; PMID:23762803; http://dx.doi.org/10.4161/onci.24238.

257. Vacchelli E, Eggermont A, Sautes-Fridman C, Galon J, Zitvogel L, Kromer G, Galluzzi L, Trial watch: lenalidomide-based immunotherapeutic approach. Oncoimmunology 2013; 2:e24238; PMID:23762803; http://dx.doi.org/10.4161/onci.24238.

258. Morales-Kastrenas A, Labiano S, Gutgemann I, Melero I. Combinations of immunomodulatory antibodies with synergistic effects against spontaneous tumors. Oncoimmunology 2014; 3:e27812.
286. Hiniker SM, Chen DS, Knox SJ. Abscopal effect in a patient with melanoma. N Engl J Med 2012; 366:2035; author reply –6; PMID:22621637; http://dx.doi.org/10.1056/NEJMoa1203984

287. Ponow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kianian S, Ma Z, Raatian A, Adamow M, Ritter E, et al. Depleting tumor-specific Tregs at a single site eradicates disseminated tumors. J Clin Invest 2013; 123:2447-63; PMID:23728179; http://dx.doi.org/10.1172/JCI64859

288. Demaria S, Pilones KA, Formenti SC, Dustin ML. Exploiting the stress response to radiation to sensitize poorly immunogenic tumors to anti-CTLA-4 treatment. Oncoimmunology 2013; 2:e23127; PMID:23802069; http://dx.doi.org/10.4161/onci.23127

289. Amin A, Ernstoff MS, Infante JR, Heng DYC, Rini BI, Plimack ER, McDermott DF, Kollmannsberger CK, Reaume MN, Spratlin JL, et-al. A phase I study of nivolumab (anti-PD-1) in combination with sunitinib, pazopanib, or ipilimumab in patients (pts) with metastatic renal cell carcinoma (mRCC). ASCO Meeting Abstracts 2013; 31:TPS4593

290. Eichberger JM, Klein A, Brahmer JR, Xu H, Pan X, Kim JH, Chen L, Pardoll DM, Topalian SL, Anders RA. Association of PD-1, PD-1 Ligands, and Other Features of the Tumor Immune Microenvironment with Response to Anti-PD-1 Therapy. Clin Cancer Res 2014; 20:5864-74; PMID:24714771; http://dx.doi.org/10.1158/1078-0432.CCR-13-3271

291. Kakavand H, Scolyer RA, Thompson JF, Mann GJ. Identification of new prognostic biomarkers for Stage III metastatic melanoma patients. Oncoimmunology 2013; 2:e25564; PMID:24228228; http://dx.doi.org/10.4161/onci.25564

292. Rodolfo M, Carelli C, Rivoltini L. Immune response markers in sentinel nodes may predict melanoma progression. Oncoimmunology 2014; 3:e28498; PMID:25050216; http://dx.doi.org/10.4161/onci.28498

293. Morse MA, OSDa T, Hobelka A, Patel S, Lyruly HK. Biomarkers and correlative endpoints for immuno-therapy trials. Am Soc Clin Oncol Educ Book 2013; PMID:23714525

294. Malyguine A, Umansky V, Kodan B, Aptsiauri N, Shurin MR. Conference overview: cancer immunotherapy and immunomonitoring (CITIM): moving forward. J Immunother 2012; 35:23-5; PMID:22639903; http://dx.doi.org/10.1007/s12117-012-0693-0

295. Butinda G, Milenic B, Angell HK, Galan J. The immune landscape of human tumors: implications for cancer immunotherapy. Oncoimmunology 2014; 3; e27456; PMID:24800163; http://dx.doi.org/10.4161/onci.27456

296. Malghina A, Umanosky V, Kodan B, Aptsiauri N, Shurin MR. Conference overview: cancer immunotherapy and immunomonitoring (CITIM): moving forward. J Immunother 2012; 35:23-5; PMID:22639903; http://dx.doi.org/10.1007/s12117-012-0693-0

297. Cao D, Anegon I, Barten D, Eibel H, Giese T, Marits P, Martinez-Caceres E, Mascart F, Nestle F, Pupil-Borell R, et-al. Predictive immunomonitoring – the COST ENTIRE initiative. Clin Immunol 2013; 147:23-6; PMID:23544893; http://dx.doi.org/10.1016/j.clim.2013.01.013