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Review

Monoclonal Antibodies for the Treatment of Cancer

JOSEPH THOMAS PENTO

Department of Pharmaceutical Sciences, College of Pharmacy, University of Oklahoma, Health Sciences Center, Oklahoma, OK, U.S.A.

Abstract. *The ability of cancer cells to evade the immune system is one of the most deadly characteristics of the majority of malignant tumours. Accordingly, the recent development of antibodies which target tumor cell evasion of immune checkpoints such as the cytotoxic T lymphocyte associated antigen-4 (CTLA-4) as well as the programmed cell death protein (PD-1) and the PD-1 ligand (PD-L1) has been a major and apparently highly effective approach in the treatment and/or eradication of a variety of highly malignant forms of cancers. The US Food and Drug Administration (FDA) has recently approved the application of lpilimumab (which targets CTLA-4) and pembrolizumab (targeting PD-1) for the treatment of advanced gastric cancer. Indeed, various checkpoint blockade antibodies have been approved or have been under clinical investigation. An indication of the renewed interest and importance of cancer immunotherapy is that James Allison was awarded the Lasker-DeBakey Clinical Research Award in 2015 for his discovery that antibody blockade of CTLA-4 enhances the immune response to cancer. Further, this discovery has stimulated the development of multiple immune checkpoint approaches to the treatment of cancer. In addition, a number of monoclonal antibodies (MAB) have been created to specifically target antigens on cancer cells and/or to selectively deliver radiotherapy to them. These immunotherapeutic approaches and advances will be reviewed in this article.*

Correspondence to: Joseph Thomas Pento, Department of Pharmaceutical Sciences, College of Pharmacy, University of Oklahoma, Health Sciences Center, Oklahoma City, Oklahoma 73117, U.S.A. Tel: +1 4052716593, Fax: +1 4052717505, e-mail: tom-pento@ouhsc.edu

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Cancer metastasis is responsible for most of the morbidity and mortality associated with cancer. Cancer metastatic progression is a multiple step process which includes enhanced cell proliferation, release of proteolytic enzymes, cell motility and invasion, angiogenesis and establishment of a supportive microenvironment at the sites of metastatic growth (1, 2).

Traditional cancer therapy has focused on removal or destruction of tumour cells by surgery, radiation and rather non-selective types of chemotherapy. Surgery and radiation are often effective with tumours which are localized and have not metastasized to multiple sites throughout the body. Chemotherapy appears to be most effective in the treatment of metastatic cancer; however, typical chemotherapeutic agents such as cisplatin, methotrexate, vincristine, 5-fluorouracil among many others, focus on rapidly growing tissues since cancer cells are relatively rapidly growing. Thus, cancer chemotherapy often results in a high incidence of unwanted and damaging side-effects in rapidly-dividing normal tissues, such as blood cells and cells lining gastrointestinal tract.

With a greater understanding of cellular chemistry and genomics during the past twenty years, cellular targets that are unique to cancer cells have been identified and chemotherapeutic agents which specifically bind to, destroy or otherwise inactivate these unique cellular targets have been developed. These agents which impede these unique or overexpressed cancer targets tend to be more selective, -thus more effective with fewer side-effects than traditional, non-selective chemotherapy. They target critical checkpoints which are often overexpressed on rapidly growing and malignant cancer cells, such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and tyrosine kinase. Therefore, cancer Immunotherapy is an exciting and relatively new method to selectively block critical checkpoints in the process of cancer development (3, 4).

Anticancer Immune Checkpoint Targeting

It is commonly known that cancer cells are resistant to the body's immune system; however, in the late 1800's William

Coley and other clinical investigators observed that some solid tumors regressed or were totally eliminated in patients that suffered streptococcal skin infections or were injected with bacterial extracts (3, 5). Unfortunately Coley's work did not have adequate controls and other investigators of that period were unable to duplicate his observations. Thus, this concept was not actively studies or pursued for approximately the next fifty years. However, the encouraging results of Sherman and Allison have stimulated new enthusiasm for targeting critical checkpoints of the immune regulatory system in order to enhance immune responsiveness in tumours cells (4). Since Sharma and Allison (4) demonstrated that CTLA-4, which turns off the response to T-cells, could be targeted, and thereby enhance the killing of tumour cells, these observations led the way to the study and identification of several other pathways or checkpoints which were typically deactivated or activated in malignant tumors (6, 7). The main check point inhibitors used for the treatment of cancer included lipilimumab (which targets CTLA-4) and pembrolizumab (targeting PD-1) (8, 9). Indeed, antibodies from unique checkpoint targets were employed in immunohistochemical staining for determining cancer cells (10). In addition, novel checkpoint inhibitors and co-stimulators are currently under study such as LAG-3 (11), TIM-3 (12), VISTA (13), ICOS (14), OX40 (15) and 4-1BB (16). Further many of the checkpoint inhibitors are being developed and some of these are currently under clinical study (4). The FDA recently approved the first therapeutic vaccine for advanced prostate cancer (17).

Antitumor Monoclonal Antibodies (MABs)

Several of specially engineered humanized or chimeric MABs have been approved recently by the FDA. These MABs are used to target and kill cancer cells. The novel MABs include the following: (i) Alemtuzumab which is a humanized IgG1 which targets CD52 and is often overexpressed on malignant lymphocytes, granulocytes, macrophages and natural killer cells. This agent has been approved for therapy in patients with lymphocytic leukemia who have not responded to alkylating agents (18, 19); (ii) Bevacizumab which is also a humanized IgG1 MAB that binds to VEGF and blocks its binding to the VEFG receptor on cancer cells. This action inhibits the formation and growth of tumor blood vessels; thus, restricts the growth and metastatic development of tumor cells. It has been approved for the treatment of metastatic colon cancer and metastatic kidney cancer as well as non-small cell lung cancer and glioblastoma. Due to the antiangiogenic mechanism of this agent it may reduce wound healing and should not be used soon after surgery (20-22); (iii) Panitumumab which is a human IgG2 kappa MAB is used to eradicate metastatic colon cancer expressing epidermal growth factor receptor (EGFR) which has been unresponsive to traditional chemotherapy (23-25); (iv) Cetuximab a human/mouse chimeric MAB, which also binds to and inactivates the EGFR, is used in the treatment of EGFR-positive colon cancer and also for head and neck cancers (24-26); (v) Ofatumumab is a human IgG1 MAB used in patients with chronic lymphocytic leukemia who are unresponsive to chemotherapy (27-30) ; (vi) Trastuzumab is a humanized MAB that acts at extracellular HER-2/neu which impedes ERGR activity. This agent is used in patients with HER-2/neu-positive breast cancer and metastatic gastrointestinal (GI) cancers and in patients with other forms of cancer that express HER-2/neu (31-34); (vii) Rituximab is a human/murine MAB that has been approved for the treatment of non-Hodgkin's lymphoma and also lymphocytic leukemia. It may also be effective for the treatment of other tumours and autoimmune diseases such as lupus erythematosus (27, 35-38) .

In addition to the use of MABs in the direct treatment of various cancers, MABs are also used to deliver radioisotopes selectively to cancer cells. Examples of the delivery MABs include: (i) Arcitumomab which is a murine antibody fragment that is labeled with technetium 99m. This agent is administered to patients with metastatic colorectal cancer to view the extent of metastatic development (39-42); (ii) Ibritumomab tiuxetan is a murine MAB which is labeled with yttrium 90 or Indium 111. These radioactive agents are used for the treatment of patients with non-Hodgkin's lymphoma and often used together with Rituximab which was discussed above (43-45); (iii) Capromab pendetide, a murine MAB, targets prostate membranes and is used to diagnose prostate cancer or determine the extent of cancer eradication following prostatectomy (46-48); (iv) Tositumomab is a MAB labeled with iodine 131 and is used to treat patients with non-Hodgkin's lymphoma who are unresponsive to standard chemotherapy (49-52) .

The Future of MAB Immunotherapy

One of the major problems with the use of MAB treatment is that cancer cells are constantly mutating which often leads to resistance or complete lack of responsiveness to targeted therapy. However, as tumour cells mutate, they develop new antigens and checkpoint targets and the current system of rapid cancer genome sequencing can be employed to identify these novel targets for MAB immunotherapy. Accordingly, this process may lead to the expansion and development of new and more effective MABs' inhibitors (4, 53-55).

The relatively recent appreciation of the effectiveness of MAB immunotherapy has led to a major consideration of new therapeutic combinations that employ standard chemotherapy together with immunotherapy to provide a combination approach which may enhance therapeutic responsiveness while reducing adverse side effects (4, 56-59).

References

1 Kohn EC and Liotta LA: Molecular insights into cancer invasion: strategies for prevention and intervention. Cancer Res *55*: 1856-1862, 1995.

2 Poste G and Fidler IJ: The pathogenesis of cancer metastasis. Nature *283*: 139-146, 1980.

3 Littman DR: Releasing the Brakes on Cancer Immunotherapy. Cell *162*: 1186-1190, 2015.

4 Sharma P and Allison JP: Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. Cell *161*: 205-214, 2015.

5 Coley WB: II. Contribution to the Knowledge of Sarcoma. Ann Surg *14*: 199-220, 1891.

6 Krummel MF and Allison JP: CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. J Exp Med *182*: 459-465, 1995.

7 Ishida Y, Agata Y, Shibahara K and Honjo T: Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J *11*: 3887-3895, 1992.

8 Azoury SC, Straughan DM and Shukla V: Immune Checkpoint Inhibitors for Cancer Therapy: Clinical Efficacy and Safety. Curr Cancer Drug Targets *15*: 452-462, 2015.

9 Mahoney KM, Freeman GJ, and McDermott DF: The Next Immune-Checkpoint Inhibitors: PD-1/PD-L1 Blockade in Melanoma. Clin Ther *37*: 764-782, 2015.

10 Mahoney KM, Sun H, Liao X, Hua P, Callea M, Greenfield EA, Hodi FS, Sharpe AH, Signoretti S, Rodig SJ and Freeman GJ: PD-L1 Antibodies to Its Cytoplasmic Domain Most Clearly Delineate Cell Membranes in Immunohistochemical Staining of Tumor Cells. Cancer Immunol Res *3*: 1308-1315, 2015.

11 Triebel F, Jitsukawa S, Baixeras E, Roman-Roman S, Genevee C, Viegas-Pequignot E and Hercend T: LAG-3, a novel lymphocyte activation gene closely related to CD4. J Exp Med *171*: 1393-1405, 1990.

12 Sakuishi K, Apetoh L, Sullivan JM, Blazar BR, Kuchroo VK and Anderson AC: Targeting Tim-3 and PD-1 pathways to reverse T cell exhaustion and restore anti-tumor immunity. J Exp Med *207*: 2187-2194, 2010.

13 Wang L, Rubinstein R, Lines JL, Wasiuk A, Ahonen C, Guo Y, Lu LF, Gondek D, Wang Y, Fava RA, Fiser A, Almo S and Noelle RJ: VISTA, a novel mouse Ig superfamily ligand that negatively regulates T cell responses. J Exp Med *208*: 577-592, 2011.

14 Fan X, Quezada SA, Sepulveda MA, Sharma P and Allison JP: Engagement of the ICOS pathway markedly enhances efficacy of CTLA-4 blockade in cancer immunotherapy. J Exp Med *211*: 715-725, 2014.

15 Curti BD, Kovacsovics-Bankowski M, Morris N, Walker E, Chisholm L, Floyd K, Walker J, Gonzalez I, Meeuwsen T, Fox BA, Moudgil T, Miller W, Haley D, Coffey T, Fisher B, Delanty-Miller L, Rymarchyk N, Kelly T, Crocenzi T, Bernstein E, Sanborn R, Urba WJ and Weinberg AD: OX40 is a potent immune-stimulating target in late-stage cancer patients. Cancer Res *73*: 7189-7198, 2013.

16 Melero I, Shuford WW, Newby SA, Aruffo A, Ledbetter JA, Hellstrom KE, Mittler RS and Chen L: Monoclonal antibodies against the 4-1BB T-cell activation molecule eradicate established tumors. Nat Med *3*: 682-685, 1997.

17 McGranahan N, Furness AJ, Rosenthal R, Ramskov S, Lyngaa R, Saini SK, Jamal-Hanjani M, Wilson GA, Birkbak NJ, Hiley CT, Watkins TB, Shafi S, Murugaesu N, Mitter R, Akarca AU, Linares J, Marafioti T, Henry JY, Van Allen EM, Miao D, Schilling B, Schadendorf D, Garraway LA, Makarov V, Rizvi NA, Snyder A, Hellmann MD, Merghoub T, Wolchok JD, Shukla SA, Wu CJ, Peggs KS, Chan TA, Hadrup SR, Quezada SA and Swanton C: Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science *351*: 1463-1469, 2016.

18 Marsh RA, Lane A, Mehta PA, Neumeier L, Jodele S, Davies SM and Filipovich AH: Alemtuzumab levels impact acute GVHD, mixed chimerism, and lymphocyte recovery following alemtuzumab, fludarabine, and melphalan RIC HCT. Blood *127*: 503-512, 2016.

19 Schmidt K, Kleinschnitz K, Rakocevic G, Dalakas MC and Schmidt J: Molecular treatment effects of alemtuzumab in skeletal muscles of patients with IBM. BMC Neurol *16*: 48, 2016.

20 Alidzanovic L, Starlinger P, Schauer D, Maier T, Feldman A, Buchberger E, Stift J, Koeck U, Pop L, Gruenberger B, Gruenberger T and Brostjan C: The VEGF rise in blood of bevacizumab patients is not based on tumor escape but a host-blockade of VEGF clearance. Oncotarget *7*: 57197-57212, 2016.

21 Arjaans M, Schroder CP, Oosting SF, Dafni U, Kleibeuker JE and de Vries EG: VEGF pathway targeting agents, vessel normalization and tumor drug uptake: from bench to bedside. Oncotarget *7*: 21247-21258, 2016.

22 Lee D, Kim D, Choi YB, Kang K, Sung ES, Ahn JH, Goo J, Yeom DH, Jang HS, Moon KD, Lee SH and You WK: Simultaneous blockade of VEGF and Dll4 by HD105, a bispecific antibody, inhibits tumor progression and angiogenesis. MAbs *8*: 892-904, 2016.

23 Lo Nigro C, Ricci V, Vivenza D, Granetto C, Fabozzi T, Miraglio E and Merlano MC: Prognostic and predictive biomarkers in metastatic colorectal cancer anti-EGFR therapy. World J Gastroenterol *22*: 6944-6954, 2016.

24 Rosati G, Aprile G, Cardellino GG and Avallone A: A review and assessment of currently available data of the EGFR antibodies in elderly patients with metastatic colorectal cancer. J Geriatr Oncol *7*: 134-141, 2016.

25 Yang J, Li S, Wang B, Wu Y, Chen Z, Lv M, Lin Y and Yang J: Potential biomarkers for anti-EGFR therapy in metastatic colorectal cancer. Tumour Biol *37*: 11645-11655, 2016.

26 Kassouf E, Tabchi S and Tehfe M: Anti-EGFR Therapy for Metastatic Colorectal Cancer in the Era of Extended RAS Gene Mutational Analysis. BioDrugs *30*: 95-104, 2016.

27 Church AK, VanDerMeid KR, Baig NA, Baran AM, Witzig TE, Nowakowski GS and Zent CS: Anti-CD20 monoclonal antibody-dependent phagocytosis of chronic lymphocytic leukaemia cells by autologous macrophages. Clin Exp Immunol *183*: 90-101, 2016.

28 Strati P, Lanasa M, Call TG, Leis JF, Brander DM, LaPlant BR, Pettinger AM, Ding W, Parikh SA, Hanson CA, Chanan-Khan AA, Bowen DA, Conte M, Kay NE and Shanafelt TD: Ofatumumab monotherapy as a consolidation strategy in patients with previously untreated chronic lymphocytic leukaemia: a phase 2 trial. Lancet Haematol *3*: e407-414, 2016.

29 Tempescul A, Bagacean C, Riou C, Bendaoud B, Hillion S, Debant M, Buors C, Berthou C and Renaudineau Y: Ofatumumab capacity to deplete B cells from chronic lymphocytic leukaemia is affected by C4 complement exhaustion. Eur J Haematol *96*: 229-235, 2016.

30 Vela CM, McBride A, Jaglowski SM and Andritsos LA: Ibrutinib for treatment of chronic lymphocytic leukemia. Am J Health Syst Pharm *73*: 367-375, 2016.
31 Ingthorsson S, Andersen K, Hilmarsdottir B, Maelandsmo GM, Magnusson MK and Gudjonsson T: HER2 induced EMT and tumorigenicity in breast epithelial progenitor cells is inhibited by coexpression of EGFR. Oncogene *35*: 4244-4255, 2016.
32 Kim Y, Kim H, Park D, Han M, Lee H, Lee YS, Choe J, Kim YM and Jeoung D: miR-217 and CAGE form feedback loop and regulates the response to anti-cancer drugs through EGFR and HER2. Oncotarget *7*: 10297-10321, 2016.
33 Privitera G, Luca T, Musso N, Vancheri C, Crimi N, Barresi V, Condorelli D and Castorina S: In vitro antiproliferative effect of trastuzumab (Herceptin((R))) combined with cetuximab (Erbitux((R))) in a model of human non-small cell lung cancer expressing EGFR and HER2. Clin Exp Med *16*: 161-168, 2016.
34 Razumienko EJ, Chen JC, Cai Z, Chan C and Reilly RM: Dual-Receptor-Targeted Radioimmunotherapy of Human Breast Cancer Xenografts in Athymic Mice Coexpressing HER2 and EGFR Using ^{177}Lu- or ^{111}In-Labeled Bispecific Radioimmunoconjugates. J Nucl Med *57*: 444-452, 2016.
35 Cramer P, Hallek M and Eichhorst B: State-of-the-Art Treatment and Novel Agents in Chronic Lymphocytic Leukemia. Oncol Res Treat *39*: 25-32, 2016.
36 Maury S, Chevret S, Thomas X, Heim D, Leguay T, Huguet F, Chevallier P, Hunault M, Boissel N, Escoffre-Barbe M, Hess U, Vey N, Pignon JM, Braun T, Marolleau JP, Cahn JY, Chalandon Y, Lheritier V, Beldjord K, Bene MC, Ifrah N and Dombret H: Rituximab in B-Lineage Adult Acute Lymphoblastic Leukemia. N Engl J Med *375*: 1044-1053, 2016.
37 Sikaria S, Aldoss I and Akhtari M: Monoclonal antibodies and immune therapies for adult precursor B-acute lymphoblastic leukemia. Immunol Lett *172*: 113-123, 2016.
38 Smolej L: Therapeutic approach to patients with chronic lymphocytic leukemia and significant comorbid conditions. Curr Cancer Drug Targets *16*: 710-720, 2016.
39 Cheng KT: ^{99m}Tc-Arcitumomab. *In*: Molecular Imaging and Contrast Agent Database (MICAD). Bethesda (MD), 2004.
40 Fuster D, Maurel J, Muxi A, Setoain X, Ayuso C, Martin F, Ortega ML, Fuertes S and Pons F: Is there a role for (99m)Tc-anti-CEA monoclonal antibody imaging in the diagnosis of recurrent colorectal carcinoma? Q J Nucl Med *47*: 109-115, 2003.
41 Hladik P, Vizda J, Bedrna J, Simkovic D, Strnad L, Smejkal K and Voboril Z: Immunoscintigraphy and intra-operative radioimmunodetection in the treatment of colorectal carcinoma. Colorectal Dis *3*: 380-386, 2001.
42 Hughes K, Pinsky CM, Petrelli NJ, Moffat FL, Patt YZ, Hammershaimb L and Goldenberg DM: Use of carcinoembryonic antigen radioimmunodetection and computed tomography for predicting the resectability of recurrent colorectal cancer. Ann Surg *226*: 621-631, 1997.
43 Casadei B, Pellegrini C, Pulsoni A, Annechini G, De Renzo A, Stefoni V, Broccoli A, Gandolfi L, Quirini F, Tonialini L, Morigi A, Argnani L and Zinzani PL: 90-yttrium-ibritumomab tiuxetan consolidation of fludarabine, mitoxantrone, rituximab in intermediate/high-risk follicular lymphoma: updated long-term results after a median follow-up of 7 years. Cancer Med *5*: 1093-1097, 2016.
44 Martinez A, Martinez-Ramirez M, Martinez-Caballero D, Beneit P, Clavel J, Figueroa G and Verdu J: Radioimmunotherapy for non-Hodgkin's lymphoma; positioning, safety, and efficacy of 90Y-Ibritumomab. 10 years of experience and follow-up. Rev Esp Med Nucl Imagen Mol *36*: 13-19, 2016.
45 Rizzieri D: Zevalin ((R)) (ibritumomab tiuxetan): After more than a decade of treatment experience, what have we learned? Crit Rev Oncol Hematol *105*: 5-17, 2016.
46 Ren J, Yuan L, Wen G and Yang J: The value of anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid PET/CT in the diagnosis of recurrent prostate carcinoma: a meta-analysis. Acta Radiol *57*: 487-493, 2016.
47 Lutje S, van Rij CM, Franssen GM, Fracasso G, Helfrich W, Eek A, Oyen WJ, Colombatti M and Boerman OC: Targeting human prostate cancer with ^{111}In-labeled D2B IgG, F(ab')2 and Fab fragments in nude mice with PSMA-expressing xenografts. Contrast Media Mol Imaging *10*: 28-36, 2015.
48 Rizvi T, Deng C and Rehm PK: Indium-111 Capromab Pendetide (ProstaScint((R))) Demonstrates Renal Cell Carcinoma and Aortocaval Nodal Metastases from Prostate Adenocarcinoma. World J Nucl Med *14*: 209-211, 2015.
49 Friedberg JW, Unger JM, Burack WR, Gopal AK, Raju RN, Nademanee AP, Kaminski MS, Li H, Press OW, Miller TP and Fisher RI: R-CHOP with iodine-131 tositumomab consolidation for advanced stage diffuse large B-cell lymphoma (DLBCL): SWOG S0433. Br J Haematol *166*: 382-389, 2014.
50 Gopal AK, Gooley TA, Rajendran JG, Pagel JM, Fisher DR, Maloney DG, Appelbaum FR, Cassaday RD, Shields A and Press OW: Myeloablative I-131-tositumomab with escalating doses of fludarabine and autologous hematopoietic transplantation for adults age >/= 60 years with B cell lymphoma. Biol Blood Marrow Transplant *20*: 770-775, 2014.
51 Kraeber-Bodere F, Bodet-Milin C, Rousseau C, Eugene T, Pallardy A, Frampas E, Carlier T, Ferrer L, Gaschet J, Davodeau F, Gestin JF, Faivre-Chauvet A, Barbet J and Cherel M: Radioimmunoconjugates for the treatment of cancer. Semin Oncol *41*: 613-622, 2014.
52 Shadman M, Gopal AK, Kammerer B, Becker PS, Maloney DG, Pender B, Shustov AR, Press OW and Pagel JM: Radioimmunotherapy consolidation using ^{131}I-tositumomab for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma in first remission. Leuk Lymphoma *57*: 572-576, 2016.
53 Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, Walsh LA, Postow MA, Wong P, Ho TS, Hollmann TJ, Bruggeman C, Kannan K, Li Y, Elipenahli C, Liu C, Harbison CT, Wang L, Ribas A, Wolchok JD and Chan TA: Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med *371*: 2189-2199, 2014.
54 Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, Miller ML, Rekhtman N, Moreira AL, Ibrahim F, Bruggeman C, Gasmi B, Zappasodi R, Maeda Y, Sander C, Garon EB, Merghoub T, Wolchok JD, Schumacher TN and Chan TA: Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science *348*: 124-128, 2015.
55 Van Allen EM, Miao D, Schilling B, Shukla SA, Blank C, Zimmer L, Sucker A, Hillen U, Geukes Foppen MH, Goldinger SM, Utikal J, Hassel JC, Weide B, Kaehler KC, Loquai C, Mohr P, Gutzmer R, Dummer R, Gabriel S, Wu CJ, Schadendorf D and Garraway LA: Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science *350*: 207-211, 2015.

56 Minn AJ and Wherry EJ: Combination Cancer Therapies with Immune Checkpoint Blockade: Convergence on Interferon Signaling. Cell *165*: 272-275, 2016.

57 Fu J, Kanne DB, Leong M, Glickman LH, McWhirter SM, Lemmens E, Mechette K, Leong JJ, Lauer P, Liu W, Sivick KE, Zeng Q, Soares KC, Zheng L, Portnoy DA, Woodward JJ, Pardoll DM, Dubensky TW Jr. and Kim Y: STING agonist formulated cancer vaccines can cure established tumors resistant to PD-1 blockade. Sci Transl Med *7*: 283ra252, 2015.

58 Twyman-Saint Victor C, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, Benci JL, Xu B, Dada H, Odorizzi PM, Herati RS, Mansfield KD, Patsch D, Amaravadi RK, Schuchter LM, Ishwaran H, Mick R, Pryma DA, Xu X, Feldman MD, Gangadhar TC, Hahn SM, Wherry EJ, Vonderheide RH and Minn AJ: Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature *520*: 373-377, 2015.

59 Pisansky TM, Hunt D, Gomella LG, Amin MB, Balogh AG, Chinn DM, Seider MJ, Duclos M, Rosenthal SA, Bauman GS, Gore EM, Rotman MZ, Lukka HR, Shipley WU, Dignam JJ and Sandler HM: Duration of androgen suppression before radiotherapy for localized prostate cancer: radiation therapy oncology group randomized clinical trial 9910. J Clin Oncol *33*: 332-339, 2015.

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