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Immunotherapy in Kidney Cancer: The Past, Present and Future

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Name: Hans Hammers, MD, PhD
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Research/ Academic Interest: The primary interest is to develop novel effective therapies for kidney cancer patients. Dr, Hammers has extensive experience in emerging immunotherapies for kidney cancer and has had leadership roles on several immunotherapy trials ranging from monotherapies targeting the PD1/PDL1 pathway to combination therapies with PD1 inhibitors and VEGF and CTLA4 inhibitors. Dr. Hammers has a particular interest in studying the ability of stereotactic radiation, TLR and STING agonists to potentiate the immune response seen with combined immune checkpoint inhibition using the PD1 inhibitor nivolumab and the CTLA4 inhibitor ipilimumab. Dr. Hammers is the PI of an investigator-initiated pilot trial studying this approach in kidney cancer.

Purpose and Overview: The purpose of the presentation is to highlight the development of immunotherapy for renal cell carcinoma. The audience will be introduced to some basic preclinical and clinical concepts of tumor immunotherapy. Long considered one of the more “immunogenic” tumors we will review the early experience with first generation immunotherapies, i.e. cytokine like interferon alpha and interleukin 2 and then discuss the current state of kidney cancer immunotherapy with immune checkpoint inhibitors like nivolumab. Lastly, we will point out strategies to maximize the benefit of immunotherapy in kidney cancer with rationally designed treatment approaches.

Educational Objectives: At the conclusion of this lecture, the listener should be able to:

1. Describe the required components necessary for a successful anti-tumor immune response
2. Explain the expected efficacy and side effect profile of the recently approved anti-PD1 immune checkpoint inhibitor nivolumab
3. Outline therapeutic strategies to further increase the potential of immunotherapies in kidney cancer

1. Introduction

In 2016, we expect to diagnose 62,700 patients with kidney cancer/renal cell carcinoma (RCC) and around 14,240 patients are expected to die from metastatic RCC (mRCC) (SEER). Kidney cancer is different from other epithelial tumors in that it is inherently resistant to cytotoxic chemotherapy and effective systemic treatments have been elusive for a long period of time. However, insights into the genetic characteristics of clear-cell renal cell carcinoma, the most common form of kidney cancer, has led to an unprecedented success of small molecule tyrosine kinase inhibitors and monoclonal antibodies targeting the vascular-endothelial growth factor pathway, which suppresses tumor angiogenesis. The sequential use of these targeted therapies has led to an impressive improvement in life expectancy for patients with metastatic kidney cancer[1].

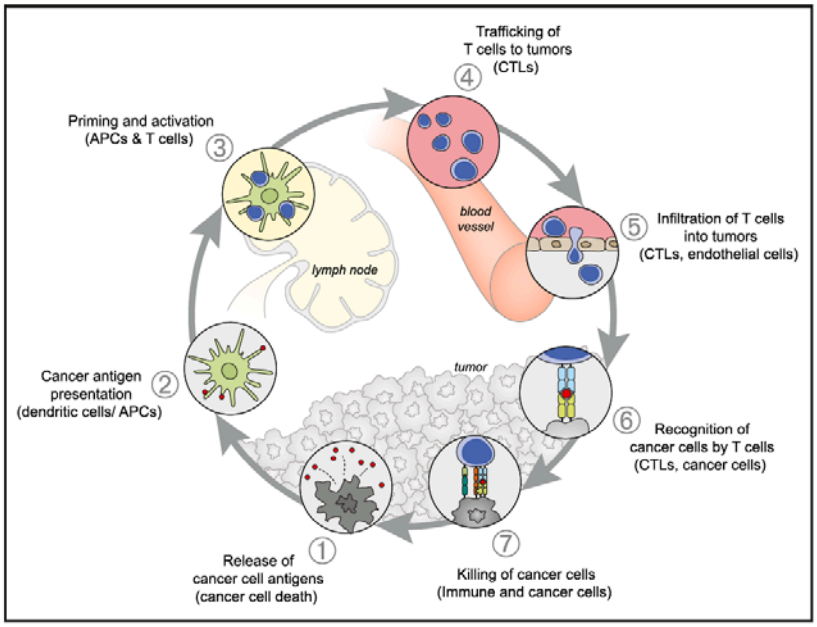
Another distinguishing feature of clear cell renal cell carcinoma (ccRCC) is the perceived immunogenicity of this histology. Albeit rare, tumor regressions of metastatic deposits after nephrectomy have been described and ccRCC is the only other tumor type for which interleukin-2 has been approved for since 1992[1].

The goal is to review some basic principles in tumor immunology and provide an overview of a.) first-generation immunotherapies such as high dose IL-2 and IFN-alpha, b.) the current state of immune checkpoint inhibition with PD1 and PD-L1 inhibitors in RCC and c.) a look at potential strategies for improving immunotherapies for the treatment of kidney cancer.

2. Basic Immunological Principles

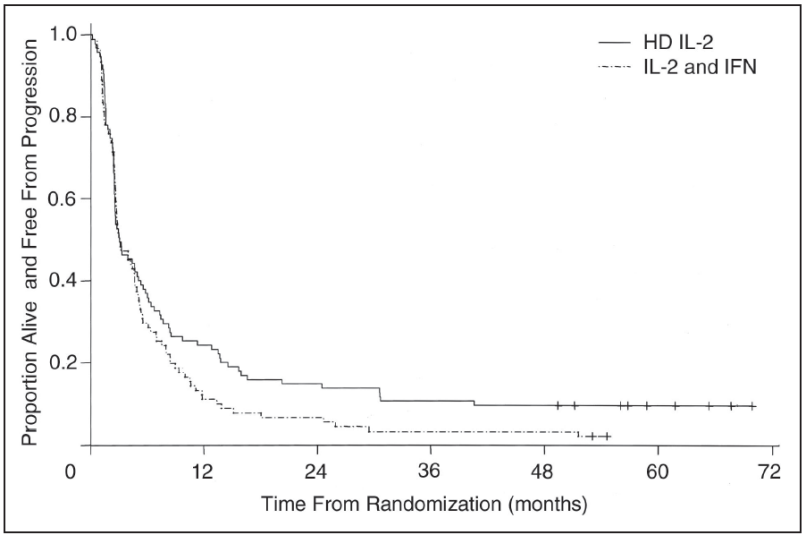
A lot has been learned in the field of cancer immunology over recent decades and has been captured well in the Cancer Immunity Cycle as described by David Chen and Ira Mellman[2]:

The adaptive immune response requires education about the target. Cancer cell death leads to the release of tumor associated antigens, typically overexpressed or mutated proteins, which are then captured by professional antigen presenting cells, the dendritic cells. These cells migrate to secondary lymphoid organs where effector T cells are being educated and activated, which in turn will traffic throughout the host, infiltrate tumors and recognize and kill cancer cells expressing specific tumor associated antigens or mutated proteins. They do so by recognizing respective peptides which are presented through the MHC I complex to the cognate T cell receptor. This leads to further activation and expansion of reactive T cell clones which engage their targets release an arsenal of cytotoxic molecules like granzyme and perforin in close proximity. This can release further antigens which in the best case scenario leads to the detection of several tumor specific epitopes ("epitope spreading"), broadening of the immune response and potential elimination of the tumor cells. Importantly, however, at virtually each point of the immunity cycle counter-regulatory mechanisms exist which can dampen or suppress the immune response to keep us protected from an overshooting immune response. These breaks of the immune system, often referred to as "immune checkpoints" can be usurped by the tumor and its associated microenvironment to protect it from an effective immune response. Interestingly, the recent revolution in immuno-oncology has been primarily achieved by targeting and releasing the breaks of the immune system (immune-checkpoint inhibitors). The opposite, activating the immune system with tumor vaccines for example, has been met primarily with failures, although sipuleucel T, a dendritic cell based vaccine has been approved for the treatment of prostate cancer. Other agents, like the cytokine interferon alpha and interleukin have T cell activating functions and been used with moderate success for the treatment of renal cell carcinoma.



3. “The Past”

Before the advent of targeted therapy, i.e. VEGF pathway inhibitors, cytokines dominated the treatment for metastatic ccRCC. The most widely used agent was interferon alpha (IFNa) which produced a moderate response rate and a moderate effect on median overall survival (mOS) when compared to chemotherapy or progesterone and remained around one year. Most responses to IFNa were of limited duration and complete responses were only seen in a small number of patients.

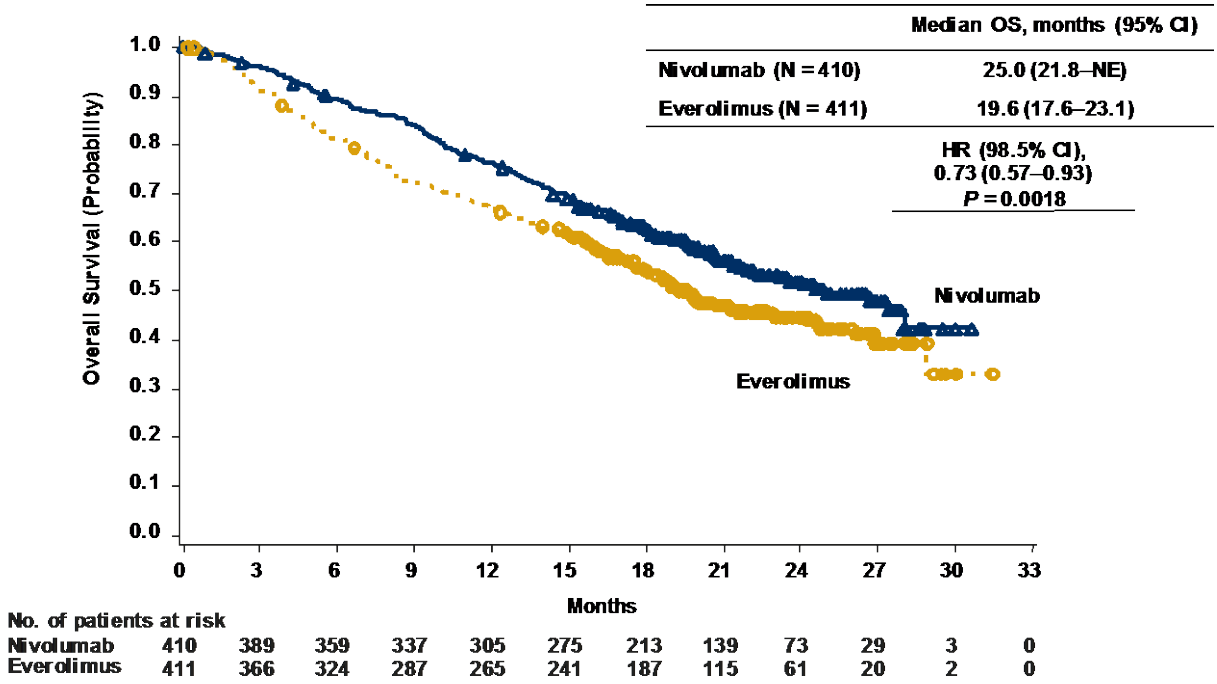


The other cytokine, which has been approved for kidney cancer in 1992, is interleukin 2. This cytokine, when given intravenously in high doses can produce an overall responses rate of 20-25% with 8-10% of complete responses[3]. Clinical benefit was mostly limited to responders and an improvement in mOS or median progression-free survival (mPFS) has not been observed. However, the duration of responses and the lack of recurrence for most complete responders has led to the approval of this agent for kidney cancer and melanoma alike. The major drawback of interleukin 2, which performs best when administered intravenously in high doses is its acute toxicity. The administration requires inpatient ,often intensive care unit, support for the management of edema, capillary leak, severe hypotension and multiorgan failure. Thus, the administration of this potentially curative treatment is typically restricted specialized academic center and is only offered to 2 percent of patients with metastatic kidney cancer in the US.

4. “The Present”

Modern immunotherapy, specifically immune checkpoint inhibitors such as anti-PD1 and anti-PDL1 antibodies are challenging the current treatment paradigm of most solid tumors, and in particular kidney cancer[4]. One of these drugs, the anti-PD1 antibody nivolumab, has been FDA approved for kidney cancer at the end of 2015.

The primary endpoint of the pivotal 821 patient trial leading to approval of this agent for kidney cancer was median overall survival. Patients treated with nivolumab experienced a mOS of 25 months vs 19.6 months for patients treated with everolimus. 70% of patients were treated in the second line[4].



- Minimum follow-up was 14 months

Additionally, nivoliumab was very well tolerated and the immune related side effects typically responded well to the treatment with corticosteroids. In fact, quality of life scores improved for patients treated with nivolumab and were superior to the treatment with everolimus, an mTOR inhibitor. The success of PD1/PDL1 pathway inhibitors has established immunotherapy as an indisputable pillar for the treatment of metastatic kidney cancer and immune checkpoint inhibitors like nivolumab will form the backbone of future, more effective combination therapies[7,8].

Interestingly, patients whose tumor tissue stained positive for the PD1 ligand PDL1 or were negative for PDL1 expression, both benefitted from the treatment of nivolumab.

5. “The Future”

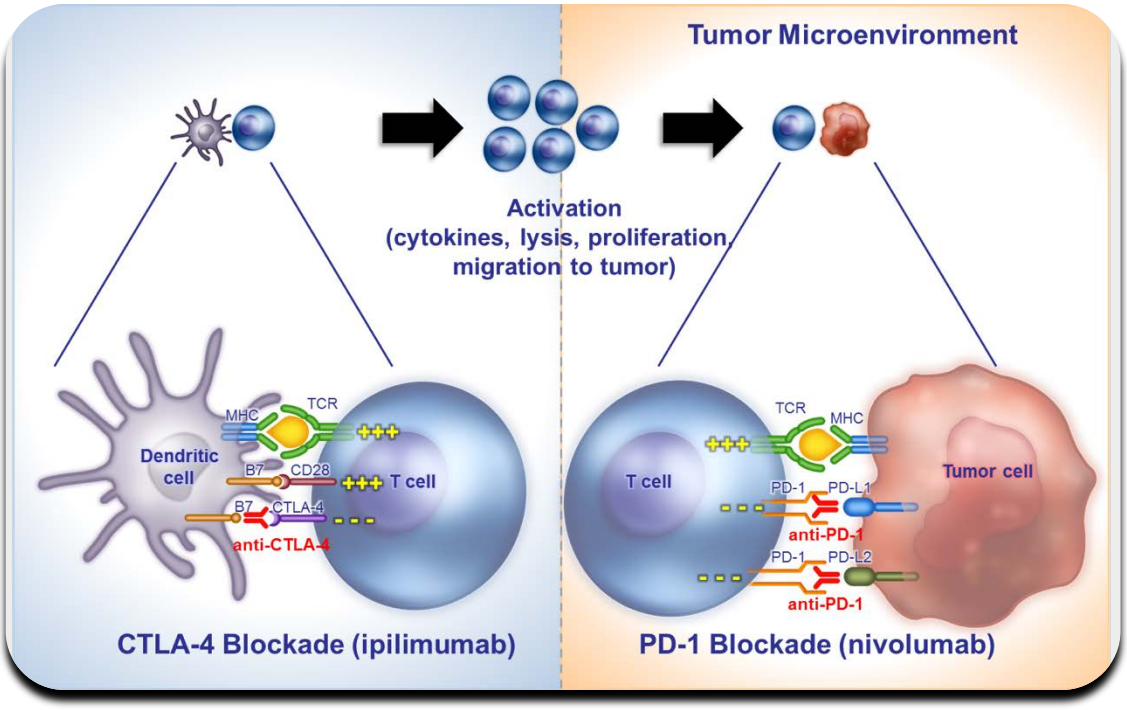
The most promising combination therapies will fall into one of three categories[5,6]:

- PD1/PDL1 inhibition plus other checkpoint inhibitors, T cell agonists or microenvironment modifying agents

- PD1/PDL1 inhibition plus (personalized) vaccination approaches

- PD1/PDL1 inhibition plus adoptive T cell therapy

Checkpoint Inhibitor Combination Therapies
Over the next decade, the immunotherapy trials in kidney cancer will be dominated by combination studies of PD1/PDL1 inhibitors with other immune modifying agents such as CTLA4, IDO, TGF beta, LAG3 and, TIM3 inhibitors, most of which are largely driven by the industry[4,7].



For example, the dual immune checkpoint inhibition with the PD1 inhibitor nivolumab (Nivo) and the CTLA4 inhibitor ipilimumab (Ipi) is demonstrating encouraging activity in ccRCC and other solid tumors. Nivolumab and Ipilimumab target different compartments of the immune response and thus synergize in their ability to unleash the immune response. In melanoma, this combination has led to unprecedented response rates, mPFS and mOS benefit. We have treated almost 100 patients in two different

dosing cohorts with nivolumab and ipilimumab[7,8]. Both dosing cohorts (3 mg/kg Nivo, 1 mg/kg Ipi (N3I1) and 1 mg/kg Nivo, 3 mg/kg Ipi (N1I3)) have shown a remarkable activity with 40% of patients experiencing durable responses in both arms. However, the treatment arm with the lower dose of ipilimumab was better tolerated with on third of patients experiencing grade 3/4 treatment related toxicity vs. two-thirds of patients on the N1I3 arm. A large phase III has accrued and pivoted this combination against sunitinib in the first line setting. Results are expected as early as 2017.

Vaccination strategies

It has become increasingly clear that immune checkpoint inhibitors essentially require a pre-established immune response. In the past, vaccination strategies alone have not produced the desired results in the treatment of cancer, however, they do have the potential to synergize with immune checkpoint inhibitor therapy. This hypothesis will undoubtedly lead to a renaissance of these approaches across solid and liquid tumors. Two principal approaches can be pursued. The first approach is designed to turn a cancer deposit into an *in situ vaccine* by using focally ablative techniques such stereotactic radiation or cryotherapy[9]. The other approach is exogenous and makes use of either peptides, RNA or tumor cell lysates. In the future these approaches will be tailored to the patients mutanome and tumor associated antigen profile in an attempt to individualize treatments.

In situ vaccination approach with focal therapies and concurrent immune checkpoint inhibition

The new era of immunoncology allows us to ask new and better questions. One of the questions we are particularly interested in is whether focal therapy under conditions of maximal immune checkpoint blockade can unleash a clinically significant abscopal effect[10].

We are currently launching an investigator-initiated clinical trial that combines ablative stereotactic radiation as a personalized in situ vaccination strategy with dual immune checkpoint inhibition (nivolumab and ipilimumab). Dual immune checkpoint inhibition has led to an impressive response rate of 40% and has been suggested to maximally enhance the abscopal effect[10].

Most vaccination attempts in the clinic represent "off-the shelf", allogeneic approaches since they target common "self" tumor antigens, shared among different patients. In contrast, personalized approaches of vaccination are tailor-made for each patient and in spite of being laborious, hold great potential[11-16]. Recent technical advancements has enabled the immunotherapy community to identify immunogenic peptides from the mutanome, or deliver RNA vaccines, Such vaccines could induce enhanced tumor-specific immune response since neo-antigens are mutation-derived antigens that can be recognized by high affinity T cells, not limited by central tolerance. Autologous tumor cells/lysates could be used as well and adjuvants like TLR or STING agonists[16], or cells modified to express GM-CSF can increase the likelihood of the initial, critical immune

response. Whole cell vaccines can provide a source for the full repertoire of the patient-specific tumor antigens, ranging from overexpressed, non-mutated proteins, including cancer testis antigens, to private, mutation-driven neo-antigens.

Adoptive T cell therapies for renal cancer

Other emerging opportunities for the immunotherapy of kidney cancer are based on the cellular therapy with either genetically modified and redirected T cells (e.g. CAR T-Cells) or expanded tumor infiltrating lymphocytes[17]. While CAR T-cells are showing potent antitumor activity in hematological malignancies, their utility in solid tumors, which typically lack highly specific or exclusive antigens (like CD19) and expendable target tissues (B cells), is somewhat questionable. For example, a clinical trial with CA9 redirected T cells showed limiting, on-target, biliary toxicity in renal cell carcinoma patients and its development has been abandoned[18]. However, “natural” tumor specific T-cells, which recognize (often unknown) tumor antigens, can be expanded and adoptively transferred thus offering considerable opportunities for kidney cancer patients[19].

The classic, adoptive T cells transfer requires the resection of metastatic lesions and the culture and expansion of the tumor-infiltrating lymphocytes[19-22]. While this approach has historically been a complex and resource intensive undertaking that has been primarily restricted to the NCI (Dr. Rosenberg, melanoma patients), but the opportunity is emerging to outsource the production of the cellular product to a commercial partners (Lion Biotechnologies). This could greatly facilitate and expand the implementation of this approach to other institutions.

Studies in cancer patients have defined the human bone marrow as a harbor and reservoir for tumor Ag-specific memory CD8 T cells with potent effector function in a variety of diseases ranging from breast cancer, pancreatic cancer and melanoma to multiple myeloma. The quality of these memory cells with regards to their polyclonal, endogenous, tumor specificity differs significantly from regular expanded peripheral blood lymphocytes, which lack intrinsic tumor specificity.

Concluding Remarks:

The rapidly evolving field of immuno-oncology is producing already significant clinical benefits for patients with kidney cancer. However, the full potential of immunotherapy has not been reached and will require the assessment of the host anti-tumor immune response the tailored, rational design of combination therapies. While immunotherapy, like any therapy, will not work for everyone, its potential is enormous and will likely dominate therapeutic approaches in the future.

Questions/Statements (Right or wrong ?)

1. High dose Interleukin 2 is obsolete in the treatment for kidney cancer given its high toxicity profile and it's low progression free survival benefit?

   FALSE: IL2 is still offering the potential for durable responses in up to 20% of selected patients.

2. Nivolumab has impressed with its median progression-free survival benefit in previously treated kidney cancer patients which has led to approval by the FDA.

   FALSE: Nivolumab has no median PFS benefit, but a median overall survival benefit which led to expedited FDA approval.

3. Vaccines have the potential to synergize with immune checkpoint inhibitors.

   CORRECT: Immune checkpoint inhibitors are probably the reason why vaccination approaches have failed in the past. Combination approaches will promising.

References:

1. Motzer RJ. New perspectives on the treatment of metastatic renal cellcarcinoma: an introduction and historical overview. Oncologist. 2011;16 Suppl 2:1-3.
2. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013 Jul 25;39(1):1-10.
3. McDermott DF, et, al. The high-dose aldesleukin "select" trial: a trial to prospectively validate predictive models of response to treatment in patients with metastatic renal cell carcinoma. Clin Cancer Res. 2015 Feb 1;21(3):561-8.
4. Motzer RJ et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015 Nov 5;373(19):1803-13.
5. Mahoney KM, Rennert PD, Freeman GJ. Combination cancer immunotherapy and new immunomodulatory targets. Nat Rev Drug Discov. 2015 Jul 31;14(8):561-84.
6. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell. 2015 Apr 13;27(4):450-61.
7. Hammers H, Plimack ER, Infante JR, Ernstoff MS, Rini B, McDermott DF, Razak A, Pal SK, Voss MH, Sharma P, Kollmannsberger C, Heng D, Spratlin J, Shen Y, Kurland JF, Gagnier P, Amin A. Phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC). ASCO 2014, Abstract #4504
8. Hammers H, Plimack ER, Infante JR, Rini BI, McDermott DF, Ernstoff MS, Voss MH, Sharma P, Pal SK, Razak A, Kollmannsberger C, Heng DYC, Spratlin J, Shen Y, Gagnier P, Amin A. Expanded Cohort Results From CheckMate 016: A Phase I Study of Nivolumab in Combination With Ipilimumab in Metastatic Renal Cell Carcinoma (mRCC). ASCO 2015, Abstract #4516
9. Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. J Natl Cancer Inst. 2013 Feb 20;105(4):256-65.
10. 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, Minn AJ. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 2015 Apr 16;520(7547):373-7.
11. Keenan BP, Jaffee EM. Whole cell vaccines--past progress and future strategies. Semin Oncol. 2012 Jun;39(3):276-86.
12. Ophir E, Bobisse S, Coukos G, Harari A, Kandalaft LE. Personalized approaches to active immunotherapy in cancer. Biochim Biophys Acta. 2015 Aug 1.
13. Fritsch EF, Hacohen N, Wu CJ. Personal neoantigen cancer vaccines: The momentum builds. Oncoimmunology. 2014 Jun 25;3:e29311.
14. Simons JW, Jaffee EM, Weber CE, Levitsky HI, Nelson WG, Carducci MA, Lazenby AJ, Cohen LK, Finn CC, Clift SM, Hauda KM, Beck LA, Leiferman KM, Owens AH Jr, Piantadosi S, Dranoff G, Mulligan RC, Pardoll DM, Marshall FF. Bioactivity of autologous irradiated renal cell carcinoma vaccines generated by ex vivo granulocyte-macrophage colony-stimulating factor gene transfer. Cancer Res. 1997 Apr 15;57(8):1537-46.
15. Borrello I, Sotomayor EM, Cooke S, Levitsky HI. A universal granulocyte-macrophage colony-stimulating factor-producing bystander cell line for use in the formulation of autologous tumor cell-based vaccines. Hum Gene Ther. 1999 Aug 10;10(12):1983-91.
16. 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, Kim Y. STING agonist formulated cancer

vaccines can cure established tumors resistant to PD-1 blockade. Sci Transl Med. 2015 Apr 15;7(283):283ra52.
17. June CH, Riddell SR, Schumacher TN. Adoptive cellular therapy: a race to the finish line. Sci Transl Med. 2015 Mar 25;7(280):280ps7.
18. Lamers CH, Sleijfer S, Vulto AG, Kruit WH, Kliffen M, Debets R, Gratama JW, Stoter G,Oosterwijk E. Treatment of metastatic renal cell carcinoma with autologous T-lymphocytes genetically retargeted against carbonic anhydrase IX: first clinical experience. J Clin Oncol. 2006; 24:e20–e22.
19. Baldan V, Griffiths R, Hawkins RE, Gilham DE. Efficient and reproducible generation of tumour-infiltrating lymphocytes for renal cell carcinoma. Br J Cancer. 2015 Apr 28;112(9):1510-8.
20. Feuerer M, Beckhove P, Bai L, Solomayer EF, Bastert G, Diel IJ, et al. Therapy of human tumors in NOD/SCID mice with patient-derived reactivated memory T cells from bone marrow. Nat Med. 2001; 7:452–8.
21. Schirrmacher V, Feuerer M, Fournier P, Ahlert T, Umansky V, Beckhove P. T-cell priming in bone marrow: the potential for long-lasting protective anti-tumor immunity. Trends Mol Med. 2003 Dec;9(12):526-34.
22. Zhang X, Dong H, Lin W, Voss S, Hinkley L, Westergren M, et al. Human Bone Marrow: A Reservoir for “Enhanced Effector Memory” CD8+ T Cells with Potent Recall Function. J Immunol. 2006; 177:6730–7.