Meeting Report

Cancer Immunology Research

Cancer Immunotherapy Highlights from the 2014 ASCO Meeting

Lauren C. Harshman[1], Charles G. Drake[2], Jennifer A. Wargo[3], Padmanee Sharma[3], and Nina Bhardwaj[4]

Abstract

The promise of cancer immunotherapy was validated officially in March 2011 when the FDA approved Yervoy (ipilimumab; Bristol-Myers Squibb) for the treatment of unresectable or metastatic melanoma. The approval was based on results of a randomized, double-blind clinical trial establishing that ipilimumab (a humanized anti-CTLA-4 monoclonal antibody) treatment extended the overall survival of patients with advanced melanoma. CTLA-4 is a member of the so-called family of checkpoint regulators, which are expressed on immune cells that activate or inhibit an immune response. An increasing number of immune checkpoint regulators are now being identified and targeted for immunotherapy. At the 2014 meeting of the American Society of Clinical Oncology (ASCO), it was reported that checkpoint blockade as a monotherapy or combination therapy was used successfully to treat advanced melanoma and non–small cell lung cancer. Checkpoint blockade immunotherapy was also used successfully for the treatment of other cancers, most notably genitourinary cancers such as urothelial bladder cancer and metastatic renal cell carcinoma. This report is a compiled summary of cancer immunotherapy highlights presented at the 2014 ASCO meeting by various investigators. *Cancer Immunol Res; 2(8); 714–9. ©2014 AACR.*

Introduction

The current progress in cancer immunotherapy can be traced back over a century, beginning with the prediction by Nobel laureate Paul Ehrlich that host immunity should protect against cancer, to studies by Lloyd Old and colleagues on tumor immunity and on developing immune-based solutions for cancer. The promise of cancer immunotherapy was validated officially in March 2011 by the FDA approval of Yervoy (ipilimumab; Bristol-Myers Squibb) for the treatment of unresectable or metastatic melanoma. This approval was based on the results of a randomized, double-blind clinical trial establishing that ipilimumab treatment extended the overall survival (OS) of patients with advanced melanoma. Ipilimumab is a humanized mAb that suppresses the immune-inhibitory receptor CTLA-4, which is a member of the so-called family of negative checkpoint regulators. Immune checkpoint regulators are receptors expressed on immune cells that activate or inhibit an immune response. Increasing numbers of immune checkpoint regulators are now being identified and targeted for immunotherapy.

At the 2013 meeting of the American Society of Clinical Oncology (ASCO), a great deal of excitement was expressed about the development and efficacy of various immune checkpoint blockade therapies for advanced melanoma and non–small cell lung cancer (NSCLC). These reports included results from clinical trials on the safety, dosing, pharmacodynamics, and efficacy of ipilimumab and the targeting of other negative checkpoint regulators, such as PD-1/PD-L1/PD-L2 for advanced melanoma and NSCLC. There were also preliminary reports on the use of combined regimens of checkpoint blockade with cytokines or other chemotherapy agents. At the 2014 ASCO meeting, in addition to advanced melanoma and NSCLC, reports on the successful use of checkpoint blockade therapy in other types of cancer were presented, most notably genitourinary cancers such as urothelial bladder cancer and metastatic renal cell carcinoma. The following are summaries provided by various investigators on cancer immunotherapy highlights from the 2014 ASCO presentations.

PD-1 Blockade in the Treatment of Renal Cell Carcinoma

Lauren C. Harshman and Charles G. Drake

ASCO was abuzz with the results of studies testing PD-1 blockade in renal cell carcinoma (RCC) this year. A set of interesting early-phase studies (I–III) clearly demonstrated the clinical activity of the PD-1-blocking antibody nivolumab in RCC. After the last 2 to 3 years of excitement over this strategy

Authors' Affiliations: [1]Dana-Farber Cancer Institute, Boston, Massachusetts; [2]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland; [3]The University of Texas MD Anderson Cancer Center, Houston, Texas; and [4]Icahn School of Medicine at Mount Sinai, New York, New York

L.C. Harshman, C.G. Drake, and J.A. Wargo contributed equally to this meeting report.

Corresponding Authors: Padmanee Sharma, The University of Texas MD Anderson Cancer Center, Genitourinary Medical Oncology 1515 Holcombe Boulevard, Houston, TX 77030. Phone: 713-792-2830 or 713-713-563-7227; Fax: 713-792-4198. E-mail: PadSharma@mdanderson.org; and Nina Bhardwaj, Mount Sinai School of Medicine, Department of Hematology/Oncology Hess Center for Science and Medicine, 1470 Madison Avenue, Room 116, New York, NY 10029. Phone: 212-824-8427; Fax: 646-537-9571. E-mail: Nina.Bhardwaj@mssm.edu

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based on the intriguing responses and survival data from a small 34-patient phase I cohort, the results of the dose-ranging monotherapy trial (1) in patients who had received two to four lines of prior systemic therapy were perhaps somewhat disappointing in terms of the median progression-free survival (PFS) of 2.7 to 4.2 months and the low rate of complete responses. However, objective responses (OR) occurred in 20% to 22% of patients, which is higher than what is typically observed with standard targeted therapies against the VEGF and mTOR axes in treatment-refractory patients. Another interesting facet of these data, which is in sharp contrast to findings with tyrosine kinase inhibitors (TKI) therapy, was the lack of a clear dose–response relationship, suggesting that even low doses of anti–PD-1 may elicit significant clinical benefit. Most noteworthy was the encouraging durability of responses even when the patients were off drug, with the overall tolerability and median OS durations of approximately 2 years.

However, monotherapy is rarely a panacea in cancer, and results of the phase I combination study of nivolumab with established effective agents in the clinic, the VEGF receptor TKIs pazopanib and sunitinib, as well as the anti-CTLA-4 antibody ipilimumab, were also presented (2). Combining anti–PD-1 with VEGF inhibition is rational not only for additive antitumor activity but also because these agents may induce a more hospitable immune environment by decreasing immunosuppressive cell populations such as regulatory T cells (Treg) and myeloid-derived suppressor cells, and by reversing the suppressive effects of VEGF on dendritic cell function. While the nivolumab/pazopanib combination proved intolerable secondary to dose-limiting liver toxicity, both TKI combination arms achieved a high clinical benefit rate with some degree of tumor elimination in almost all patients. The sunitinib arm was dose escalated to a higher nivolumab dose and enrolled treatment-naïve patients. Median PFS was encouraging at around 12 months but included mostly treatment-naïve patients. However, one should keep in mind that sunitinib monotherapy can induce OR at a rate of 25% to 47% along with a median PFS of 9.5 to 11 months in the first-line setting. Thus, we must question whether this combination is indeed additive and whether it merits the significant additional toxicity observed. That being said, and with the caveat of the dangers of comparing across trials, there appeared to be less primary treatment-refractory disease to the TKI/nivolumab combinations than was observed in the phase II nivolumab monotherapy trial or the phase III sunitinib trials, supporting the principle of combining TKIs with immunotherapy. Several ongoing and planned trials, including two interesting three-arm studies investigating different combinations of PD-1 and VEGF blockade, such as with bevacizumab and anti–PD-L1 (MPDL3280A) as well as pazopanib with pembrolizumab (MK-3475), will eventually provide additional insight into combining VEGF-targeted therapy with PD-1/PD-L1 blockade.

The first results of combined checkpoint inhibition in RCC were also presented (3). Nivolumab was combined with ipilimumab at varying doses of both agents. In this mostly treatment-refractory patient population, likely more than additive effects were observed with OR in greater than 40% of patients and median PFS rates ranging from 9 to 10 months. However, the remarkable efficacy comes at the expense of toxicity, namely in the form of colitis and liver dysfunction. A phase III study is planned to further evaluate this combination in the treatment-naïve setting against a VEGFR TKI control with an OS endpoint.

The results of these two exciting combination studies reinforce several important points regarding PD-1 blockade in RCC: (i) we should continue to build upon the durability of responses. (ii) Continued responses and/or disease stabilization is common even off therapy, suggesting the induction of a tumor-specific memory response. (iii) Unconventional or delayed immune-mediated responses can occur despite the appearance of new lesions early in the treatment course. (iv) The overall tolerability as a monotherapy is good, making PD-1 blocking agents excellent partners for combination regimens. (v) So far, toxicity appears to be both noncumulative and generally manageable. Anti–PD-1 is one of the most promising new agents in the battle against kidney cancer, and we eagerly await the results of the maturing phase III nivolumab registration study, which will assess definitively its ability to improve survival as a monotherapy. Further, multiple ongoing and planned studies will assess the synergy of combining PD-1 pathway blockade with other established targeted therapies, immune checkpoint inhibitors, and immune stimulants that have high potential to enhance outcomes and increase the already impressive rate of durable partial and complete responses.

PD-1 Blockade in the Treatment of Bladder Cancer and Metastatic Renal Cell Carcinoma

Padmanee Sharma

Thomas Powles and colleagues (4) reported data from a phase Ia trial, in which patients with bladder cancer (urothelial carcinoma) received MPDL3280A (anti–PD-L1 antibody) in the second-line setting after prior chemotherapy. The treatment was well tolerated with 4% grade 3–4 adverse events. The response rate was reported according to PD-L1 status, in which the expression of PD-L1 was evaluated on patients' tumor samples by immunohistochemistry (IHC). The IHC assay consisted of evaluating PD-L1 expression on immune cells within the tumor microenvironment (TME) and graded positive expression as those samples that had greater than or equal to 5% of immune cells that were PD-L1$^+$ (IHC 2), or IHC 3 for those that were greater than or equal to 10% PD-L1$^+$; samples that had less than 5% (IHC 1) or less than 1% PD-L1$^+$ cells (IHC 0) were deemed PD-L1$^-$. Patients were categorized as PD-L1$^+$ or PD-L1$^-$ based on these definitions of the PD-L1 status of their tumor-infiltrating immune cells, and the authors reported a 43% response rate for PD-L1$^+$ patients and an 11% response rate for PD-L1$^-$ patients. These data are promising for patients with bladder cancer, for whom there are no approved therapies in the second-line setting, and the median OS averages 6 to 7 months. Anti–PD-L1 immunotherapy and other immunotherapy strategies should be developed for patients with bladder cancer. However, PD-L1 expression status will not be an appropriate predictive biomarker to select patients for treatment because PD-L1 is a dynamic marker that changes over time; therefore, a biopsy at a single time point

may not accurately reflect the PD-L1 status of that patient's tumor-infiltrating immune cells. Moreover, 11% of patients who were deemed to be PD-L1$^-$ did have clinical responses to anti–PD-L1 treatment, which is further evidence that PD-L1 expression should not be used as a predictive marker to select patients for treatment.

Toni Choueiri and colleagues (5) reported that patients with metastatic renal cell carcinoma who received treatment with nivolumab (anti–PD-1 antibody) had measurable clinical responses, which seemed to correlate with PD-L1 expression. In this study, PD-L1 expression was measured on tumor cells, as opposed to immune cells within the TME analyzed by Powles and colleagues. Choueiri and colleagues reported a response rate of 22% (4/18) in patients who were deemed to be PD-L1$^+$ and 8% (3/38) in patients who were deemed to be PD-L1$^-$. The authors also reported that additional biomarkers were evaluated for correlation with clinical responses. They found that CD3 and CD8 T-cell infiltration in tumor tissues appeared to correlate with clinical responses, suggesting that these and other biomarkers need to be evaluated in additional studies.

In summary, treatment with anti–PD-1 and anti–PD-L1 immunotherapy agents was reported to lead to clinical responses, and these results support further development of these agents for the treatment of patients with cancer. However, a predictive biomarker that can be used to select patients for treatment with these agents has not been identified. Expression of PD-L1 on immune cells or tumor cells cannot serve as a predictive biomarker because a subset of patients who were deemed to be PD-L1 were found to have clinical responses, which is probably due to the dynamic nature of the immune system and PD-L1 expression. It should be noted that upon T-cell activation, T cells will produce IFNγ, which will lead to upregulation of PD-L1 on both immune cells and tumor cells. Therefore, evaluation of PD-L1 expression at a single time point may not accurately reflect an evolving immune response, making it difficult to implement PD-L1 expression as a predictive biomarker.

Developmental Therapeutics Poster Highlights on Immunologic Correlates of Response

Jennifer A. Wargo

Several posters at ASCO focused on immunologic correlates of response, and included insights gained from large data sets as well as from deeper studies performed in smaller sets of patients. These abstracts were organized into three categories: (i) pretreatment biomarkers of response; (ii) on-treatment biomarkers or response; and (iii) strategies to modulate responses with combination therapy.

Pretreatment biomarkers of response

Richard Joseph and colleagues (6) reported baseline tumor size as a strong predictor of OS in patients with advanced melanoma treated with the anti–PD-1 humanized IgG4 mAb pembrolizumab (MK-3475) in the context of the KEYNOTE-001 trial (NCT01295827). In this study, baseline tumor size was quantified as the sum of the longest dimensions of a maximum of 10 target lesions (maximum of 5 per organ) as assessed by RECIST v1.1. The median tumor size was 97.8 mm, and patients who had a baseline tumor size below the median had a significantly improved survival compared with those with a larger baseline tumor size. However, patients with baseline tumor size above the median still derived clinical benefit, with durable responses noted. The authors concluded that baseline tumor size is the strongest prognostic factor in this trial, and should be used when randomizing patients with advanced melanoma for treatment with immune checkpoint blockade.

Yanyan Lou and colleagues (7) reported a strong association between epithelial–mesenchymal transition status and immunophenotypes in patients with NSCLC. These investigators analyzed two large data sets of lung cancer patients [from The Cancer Genome Atlas (TCGA) and the PROSPECT database at the University of Texas MD Anderson Cancer Center] via gene expression profiling and found significant differences in the immunophenotype between tumors with a mesenchymal versus an epithelial phenotype. They found that mesenchymal tumors had higher levels of immune-activating and immunomodulatory molecules. However, they did not report an association with response to immune checkpoint blockade, and these studies are currently under way.

On-treatment biomarkers or response

Lawrence Fong and colleagues (8) described the use of next-generation mRNA sequencing to track changes in the T-cell repertoire of the peripheral blood mononuclear cells (PBMC) in 46 patients with metastatic castration-resistant prostate cancer (CRPC) or metastatic melanoma prior to and during treatment with anti-CTLA-4 blockade. They showed the importance of memory T-cell phenotype in responses to immune checkpoint inhibition, and that maintenance of pre-existing memory T-cell responses was associated with improved survival in these patients. These investigators demonstrated that improved clinical response was associated with persistence of pre-existing, high-frequency T-cell clonotypes. Antigen specificity is not known, but these findings highlight the potential use of this technology to follow responses in patients. Insights gained from such analyses could lead to mechanisms to guide treatment.

Cariad Chester and colleagues (9) described the use of mass cytometry for immunomonitoring in patients receiving urelumab (BMS-663513), an agonist of CD-137 (4-1BB). These patients had advanced solid tumors and refractory or relapsed B-cell non-Hodgkin lymphoma. This technology enabled the investigators to discern changes in immune profiles in circulating CD4 and CD8 T cells during the course of treatment, with increased production of IFN, TNF, and IL2. Although the sample size was limited (4 patients), the study provides a proof of concept that mass cytometry may be utilized for immune monitoring. Limitations of this technology at present include its cost and tissue requirements.

Jon Bjoern and colleagues (10) described the effects of ipilimumab on tumor-infiltrating lymphocytes (TIL) in patients with stage IV melanoma. This study was performed in light of clinical observations that patients who receive ipilimumab have improved responses to TIL therapy. These investigators found no difference in the number of infiltrating T cells in

patients who received ipilimumab prior to TIL harvest and those who did not. Patients who received prior ipilimumab had higher levels of CD27, TIM3, LAG3, and CTLA-4. In addition, differences were seen in the ability of the TILs to recognize common melanoma antigens (TILs from patients who received prior ipilimumab had better antigen recognition). The findings of increased memory T cells with higher levels of exhaustion markers has impact and raises potential questions about sequence of therapy as well as strategies to augment TIL-based therapy.

Strategies to modulate responses with combination therapy

Anuj Bapodra and colleagues (11) analyzed clinical outcomes and CD4 T cells in patients treated with the combined regimen of CTLA-4 blockade with ipilimumab and radiation. They found that patients treated with this combined regimen had improved survival compared with those treated with ipilimumab alone. They also analyzed cytokine production in peripheral blood lymphocytes over the course of therapy and noted an increase in IFN and TNF, suggesting a skewing toward a more pro-inflammatory response. In addition, the authors showed that patients who required steroids for toxicity had improved responses, which is supported by the observation that patients with higher autoimmune toxicity have better responses to therapy (i.e., the steroids were a marker for those patients who developed autoimmune toxicity). These findings highlight the notion that tumor immunity is autoimmunity.

David Page and colleagues (12) described studies in which T-cell receptor sequencing was used to evaluate the clonality of TILs in patients with early-stage breast cancer treated with preoperative cryoablation and/or ipilimumab. They studied breast cancer patients with different mutational status and observed a trend toward a more inflammatory environment in poorly differentiated tumors, which is reminiscent of the results shown in abstract 3017, which described different immunophenotypes based on epithelial versus mensenchymal phenotype in NSCLC. However, the main objective of this study was to look at clonality in the setting of treatment, and they showed that treatment with cryoablation alone or in combination with ipilimumab results in a more polyclonal response than treatment with ipilimumab alone. The authors analyzed the top five dominant clones and demonstrated a step-wise enhancement in proliferation of dominant clones in ipilimumab alone, cryoablation alone, and combined ipilimumab and cryoablation. Together, these data suggest that differentiation status may have an impact on immunophenotype, and that combined therapy with ipilimumab and local ablative therapies such as cryoablation may result in a more polyclonal T-cell response.

Developmental Therapeutics: Oral Abstract Session on Immunotherapy

Nina Bhardwaj

This session was organized in three parts: (i) PD-1/PD-L1 checkpoint blockade immunotherapy responses in clinical trials; (ii) studies on the biology underlying responses to immunotherapy; and (iii) new targets in immunotherapy.

(i) PD-1/PD-L1 checkpoint blockade immunotherapy responses in clinical trials

Results from the clinical trial KEYNOTE-001 (NCT01295827) on the use of anti–PD-1 humanized IgG4 mAb pembrolizumab (MK-3475) for patients with ipilimumab-refractory (IPI-R) and IPI-naïve (IPI-N) melanoma were presented by Omid Hamid and colleagues (13, 14). In addition to five nonrandomized arms, the trial compared two doses of MK-3475 (2 mg/kg and 10 mg/kg) administered every 3 weeks for IPI-R and IPI-N melanoma patients in a randomized fashion (13). The trial included 103 patients for the IPI-N cohort and 173 patients for the IPI-R cohort. No differences in OR rates between the two doses in either the IPI-N or IPI-R cohorts were found. The responses are durable, ranging from 6+ to 39+ weeks, with the median duration of responses not yet reached for either cohort, and with 88% to 91% of responses ongoing. Thus far, the PFS and OS are similar between these two cohorts. Pembrolizumab, therefore, appears to be a promising treatment in both IPI-N and IPI-R melanoma. Stephen Hodi and colleagues presented the immune-related response criteria in the study patients (14). There were multiple patterns of response, and a subset that by RECIST would be considered a poorer response was actually found to do better clinically. Thus, alternative ways to measure treatment responses for these new types of immunotherapies were proposed.

Results from a phase I multi-arm expansion study of the anti–PD-L1 mAb MEDI4736 in patients with advanced solid tumors were presented (15, 16). Jose Lutzky and colleagues reported that the dose-escalation phase has been completed for doses of 0.1 to 10 mg/kg every 2 weeks with extension to 15 mg/kg every 3 weeks (15). MEDI4736 was well tolerated at all doses tested, with no treatment-related serious adverse events such as colitis, hyperglycemia, or pneumonitis at any grade. Neil Segal and colleagues (16) presented preliminary data on the ongoing study of MEDI4736 at a dosage of 10 mg/kg every 2 weeks for 1 year for 346 patients with solid tumors, including 143 with NSCLC, 54 with head and neck squamous cancer (SCCHN), 44 with uveal and cutaneous melanoma, 24 with triple-negative breast cancer, 26 with gastroesophageal tumors, 19 with hepatocellular carcinoma, 32 with pancreatic adenocarcinoma, and 4 patients with other cancers. The median duration of treatment was 8 weeks. As of May 18, 2014, there were very few (6%) grade 3/4 drug-related serious adverse events. Clinical activity was observed as early as 6 weeks, with maintenance for over 67 weeks and off active therapy; OR rates in NSCLC were 13% and 14% in SCCHN with more responders in the PD-L1$^+$ subsets of patients. There is also emerging clinical evidence in GI$^+$ pancreatic cancers.

(ii) Studies on the biology underlying responses to immunotherapy

Alexandra Snyder and colleagues outlined the exome analysis pipeline strategy used to identify candidate neoantigens in patients with metastatic melanoma treated with

ipilimumab (17). Briefly, they performed whole exome and RNA sequencing of tumor genomes, looked for tumor-specific mutations that function as neoantigens with high affinity for HLA and likelihood of interacting with T-cell receptors, and found that the exon missense mutational load correlates with clinical benefit. They have identified a neo-epitope signature for clinical benefit from ipilimumab in the discovery set, and this neo-epitope signature will need to be tested in a large prospective study. They have tested and validated one of these peptides in an *in vitro* priming assay using patient PBMCs.

Christina Adaniel and colleagues presented results from studies evaluating germline SNPs from patients with metastatic melanoma treated with ipilimumab (18). They identified CCR2, CCL2, and CCR5, proteins that are important for immune cell chemotaxis as variants associated with responses to anti-CTLA-4. They concluded that the chemokine receptor locus in 3p21 strongly associates with anti-CTLA-4 responses with variants associated with resistance to ipilimumab. Again, this association will need to be tested in a large prospective study to determine if these polymorphisms alter protein function.

Richard Kefford and colleagues presented studies evaluating clinical efficacy and correlation with tumor PD-L1 expression in patients with melanoma treated with anti–PD-1 mAb MK-3475 (19). They found that the tumor PD-L1$^+$ status correlates with OR rates (49% in PD-L1$^+$ versus 13% in PD-L1$^-$ tumors.) However, PD-L1 is a dynamic marker heterogeneously expressed on tumor cells, and PD-L1$^-$ patients are able to respond to checkpoint blockade monotherapy and combination therapy. Furthermore, OS was not different between the two groups. Therefore, PD-L1 status should not be used to exclude patients from checkpoint blockade therapy.

(iii) New targets in immunotherapy

Neil Segal and colleagues presented preliminary results from a phase I dose-escalation study (20) of agonistic anti-41BB (PF-05082566) in patients with advanced solid tumors including colorectal cancer, melanoma, non-Hodgkin lymphoma, pancreatic adenocarcinoma, follicular lymphoma, lymphocytic lymphoma, nasopharyngeal cancer, breast cancer, and Merkel cell carcinoma. Although still early, they have found positive clinical activity with no grade 2 or higher adverse events. Combination studies are planned with rituximab in B-cell lymphoma and with MK-3475 in solid tumors.

Christian Hinrichs and colleagues presented studies on HPV E6- and HPV E7-targeted TILs for cervical cancer (21). Eight patients with HPV18$^+$ cervical cancer were treated with TILs isolated from their tumors, expanded *ex vivo*, and reinfused back into the patients. To date, 3 of these patients had clinical responses, and 2 are in complete remission. These patients have HPV reactivity in their TILs, and the 2 patients in complete remission have long-term circulating HPV reactivity in their blood following infusion. However, not all T cells in TILs were HPV reactive, and the role of lymphodepletion is not clear in this setting.

New Vaccines and Antibodies

Charles G. Drake

The 2014 ASCO meeting highlighted some of the important recent advances in immunotherapy, perhaps most notably the ongoing interest in immune checkpoint blockade as an emerging treatment modality. However, as data accumulate, it is becoming abundantly clear that, even with combined immune checkpoint blockade, a substantial proportion of patients fail to derive clinical benefit. Because checkpoint blockade is thought to function when a patient already has an ongoing antitumor response, there has been a resurgence in interest in cancer vaccines as a means to awaken antitumor immunity, and to help checkpoint blockade work in patients in whom it otherwise would not. One particularly interesting vaccine approach involves intratumoral (i.t.) injection of a natural pathogen in an effort to induce immunogenic cell death and a resultant immune response. Robert Ingemar Andtbacka and colleagues (22) presented data from a phase II study showing in which i.t. injection of a bioselected strain of oncolytic Coxsackievirus A21 (CVA21) into melanoma lesions resulted in OR in approximately 25% of the 54 treated patients with advanced-stage melanoma. Some of the responders had tumor regression at distant sites, indicating that local oncolytic virus vaccine delivery elicited a systemic antitumor immune response. Based on this demonstration of activity, CVA21 will likely be moved into combination studies with PD-1 or other checkpoint blocking antibodies.

Another interesting vaccine approach now in a latestage clinical development is based on data from decades of studies in solid organ transplantation showing that hyperacute rejection of xenotransplants is mediated by preexisting antibodies to foreign α(1,3)galactosyltransferase (α-gal) carbohydrate molecules on the xenograft, and that anti-α-gal antibodies are a component of the inherent preexisting immunity in humans. To generate a vaccine using this technology, cancer cells have been transfected with murine α-gal; this approach has been applied to lung cancer, pancreatic cancer, and kidney cancer. Once injected into patients, the allogeneic α-gal vaccines rapidly undergo immunogenic cell death, releasing cellular contents and presumably inducing an immune response to multiple tumor antigens. Because one of the proteins released is calreticulin, a calcium-binding chaperone protein that functions in the folding of MHC class I molecules, one might hypothesize that vaccination with these α-gal–expressing, cell-based vaccines could lead to the induction of antibodies against calreticulin, and that antibody induction might correlate with patient outcome. Data presented by Gabriela Rossi and colleagues (23) confirmed that this was indeed the case; in a phase II trial of the pancreatic cancer vaccine Algenpantucel-L (pancreatic cancer cells engineered to express α-gal), titers of anticalreticulin antibodies correlated positively with OS. A randomized phase III trial using this vaccine completed its accrual in September 2013, so the clinical benefit of this vaccine may be apparent before the end of 2014.

Finally, tumor-targeted antibodies continue to garner significant interest. Alexander Starodub and colleagues (24) introduced a new antibody-drug conjugate (ADC), IMMU-132, which comprises antibody hRS7 conjugated by a pH-sensitive linker to SN38, the active metabolite of CPT-11, which, in turn, causes DNA breaks and inhibits DNA synthesis. IMMU-132 recognizes a molecule known as Trop-2, which is a transmembrane, calcium-transducing protein expressed on multiple human carcinoma tumor types This ADC localizes the chemotherapy agent SN-38 to the tumor site. Partial responses and stable disease were noted in patients with various tumor types, including triple-negative breast cancer, NSCLC, and colorectal cancer. Based on these data, as well as on good tolerability, a phase II dose-expansion study is ongoing. In summary, these emerging data reflect ongoing interest in ADCs and a potentially expanding interest in the field of cancer vaccines.

Disclosure of Potential Conflicts of Interest

L.C. Harshman has served as a consultant/advisory board member for Aveo, Pfizer, Bristol-Myers Squibb, and Dendreon. C.G. Drake has received research support from Janssen and Bristol-Myers Squibb. He is a coinventor on a patent related to LAG-3, which is currently unlicensed. He also serves as a consultant/advisory board member for Bristol-Myers Squibb, Compugen, Dendreon, ImmunExcite, Merck, Pfizer, and Roche/Genentech. J.A. Wargo serves on the speakers' bureau for Dava Oncology. P. Sharma has an ownership interest (including patents) in Jounce and is a consultant/advisory board member for GlaxoSmithKline, Bristol-Myers Squibb, and MedImmune. N. Bhardwaj serves as a consultant/advisory board member for Dendreon and Merck.

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References

1. Motzer RJ, Rini BI, McDermott DF, Redman BG, Kuzel T, Harrison MR, et al. Nivolumab for metastatic renal cell carcinoma: Results of a randomized, dose-ranging phase II trial. J Clin Oncol 2014;32:5s, abst5009.
2. Amin A, Plimack ER, Infante JR, Ernstoff MS, Rini BI, McDermott DF, et al. Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with sunitinib or pazopanib in patients with metastatic renal cell carcinoma. J Clin Oncol 2014;32:5s,abst5010.
3. Hammers HJ, Plimack ER, Infante JR, Ernstoff MS, Rini BI, McDermott DF, et al. Phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma. J Clin Oncol 2014;32:5s,abst4504.
4. Powles T, Vogelzang NJ, Fine GD, Eder JP, Braiteh FS, Loriot Y, et al. Inhibition of PD-L1 by MPDL3280A and clinical activity in patients with metastatic urothelial bladder cancer (UBC). J Clin Oncol 2014;32:5s, abst5011.
5. Choueiri TK, Fishman MN, Escudier BJ, Kim JJ, Kluger HM, Stadler WM, et al. Immunomodulatory activity of nivolumab in previously treated and untreated mRCC: Biomarker-based results from a randomized clinical trial. J Clin Oncol 2014;32:5s,abst5012.
6. Joseph RW, Elassaiss-Schaap J, Wolchok JD, Joshua AM, Ribas A, Hodi FS, et al. Baseline tumor size as an independent prognostic factor for overall survival in patients with metastatic melanoma treated with the anti-PD-1 monoclonal antibody MK-3475. J Clin Oncol 2014; 32:5s,abst3015.
7. Lou Y, Diao L, Byers LA, Gibbons DL, Denning W, Wang J, et al. Association of epithelia-mesenchymal transition status with PD1/PDL1 expression and a distinct immunophenotype in non-small cell lung cancer: implications for immunotherapy biomarkers. J Clin Oncol 2014;32:5s,abst3018.
8. Fong L, Cha E, Klinger M, Hou Y, Cummings C, Ribas A, et al. Association of maintenance of pre-existing memory T-cell responses following anti-CTLA-4 antibody treatment with improved overall survival. J Clin Oncol 2014;32:5s,abst3016.
9. Chester C, Chang S, Kurland F, Sagiv-Barfi I, Czerwinski D, Rajapaksa A, et al. Biomarker characterization using mass cytometry in a phase I trial of urelumab (BMS-663513) in subjects with advanced solid tumors and relapsed/refractory B-cell non-Hodgkin lymphoma. J Clin Oncol 2014;32:5s,abst3017.
10. Bjoern J, Donia M, Andersen R, Reker Hadrup S, Lyngaa R, Svane I. Effects of ipilimumab on expanded tumor-infiltrating lymphocytes in patients with stage IV malignant melanoma. J Clin Oncol 2014;32:5s, abst3020.
11. Bapodra A, Pires Da Silva IE, Lui KP, Pavlick AC, Zhong J, Osman I, et al. Clinical outcome and CD4+ differentiation in anti-CTLA-4/radiation and anti-CTLA-4/steroid therapy. J Clin Oncol 2014;32:5s, abst3019.
12. Page DB, Diab A, Yuan J, Dong Z, Emerson R, Robins H, et al. T-cell receptor (TCR) DNA deep sequencing to evaluate clonality of tumor-infiltrating lymphocytes (TILs) in early-stage breast cancer patients receiving preoperative cryoablation (cryo) and/or ipilimumab. J Clin Oncol 2014;32:5s,abst3021.
13. Hamid O, Robert C, Ribas A, Wolchok JD, Hodi FS, Kefford R, et al. Randomized comparison of two doses of the anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) for ipilimumab-refractory (IPI-R) and IPI-naïve (IPI-N) melanoma (MEL). J Clin Oncol 2014;32:5s, abst3000.
14. Hodi FS, Ribas A, Daud A, Hamid O, Robert c, Kefford R, et al. Evaluation of immune-related response criteria (irRC) in patients with advanced melanoma treated with anti-PD-1 monoclonal antibody MJ-3475. J Clin Oncol 2014;32:5s,abst3006.
15. Lutzky J, Antonia SJ, Blake-Haskins A, Li X, Robbins PB, Shalabi AM, et al. A phase 1 study of MEDI4736, an anti-PD-L1 antibody, in patients with advanced solid tumors. J Clin Oncol 2014;32:5s,abst3001.
16. Segal NH, Antonia SJ, Brahmer JR, Maio M, Blake-Haskins A, Li X, et al. Preliminary data from a multi-arm expansion study of MEDI4736, an anti-PD-L1 antibody. J Clin Oncol 2014;32:5s,abst3002.
17. Snyder Charen A, Makarov V, Merghoub T, Walsh L, Yuan J, Miller M, et al. The neoantigen landscape underlying clinical response to ipilimumab. J Clin Oncol 2014;32:5s,abst3003.
18. Adaniel C, Rendleman J, Polsky D, Berman RS, Shapiro RL, Shao Y, et al. Germline genetic determinants of immunotherapy response in metastatic melanoma. J Clin Oncol 2014;32:5s,abst3004.
19. Kefford R, Ribas A, Hamid O, Robert A, Daud A, Wolchok JD, et al. Clinical efficacy and correlation with tumor PD-L1 expression in patients with melanoma treated with the anti-PD-L1 monoclonal antibody MK-3475. J Clin Oncol 2014;32:5s,abst3005.
20. Segal NH, Gopal AK, Bhatia S, Kohrt HE, Levy R, Pishvaian MJ, et al. A phase I study of PF-05082566 (anti-4-1BB) in patients with advanced cancer. J Clin Oncol 2014;32:5s,abst3007.
21. Hinrichs CS, Stevanovic S, Draper L, Somerville R, Wunderlich J, Restifo NP, et al. HPV-targeted tumor-infiltrating lymphocytes for cervical cancer. J Clin Oncol 2014;32:5s,abst3008.
22. Andtbacka RI, Curti BD, Kaufman H, Daniels GA, Nemunaitis JJ, Spitler LE, et al. CALM study: A phase II study of an intratumorally delivered oncolytic immunotherapeutic agent, coxsackievirus A21, in patients with stage IIIc and stage IV malignant melanomas. J Clin Oncol 2014;32:5s,abst3031.
23. Rossi GR, Rocha Lima CS, Hardacre JM, Mulcahy MF, Talamonti MS, Obel JC, et al. Correlation of anti-calreticulin antibody titers with improved overall survival in a phase 2 clinical trial of algenpantucel-L immunotherapy for patients with resected pancreatic cancer. J Clin Oncol 2014;32:5s,abst3029.
24. Starodub A, Ocean AJ, Guarino MJ, Picozzi VJ, Thomas SS, Messersmith WA, et al. IMMU-132 ADC targeting Trop-2 as novel therapy platform for metastatic solid cancers. J Clin Oncol 2014;32:5s, abst3033.