The goals of all novel therapies include improvement in overall survival, quality of life and disease control. We are fortunate to finally have two therapies that have demonstrated survival benefit in Phase III clinical trials – one, ipilimumab, a monoclonal antibody against CTLA-4, a checkpoint inhibitor, and the other, Sipuleucel-T, an autologous-based cellular therapy. Ipilimumab is the second drug that has been approved for melanoma within the last year, suggesting that there are multiple ways to achieve antitumor responses. Sipuleucel-T is the first immunotherapy approved for asymptomatic, castration-resistant prostate cancer, and while Sipuleucel-T lengthened survival modestly, there was no improvement in time to progression and no responders. While Sipuleucel-T has been well-tolerated, ipilimumab has been associated with autoimmune-related events. As single agents, these drugs have shown benefit; however, maximizing durability remains a challenge. This article provides support for our continued efforts in this area of research and clinical care.

**Keywords:** checkpoint • chemotherapy • CTLA-4 • immunotherapy • ipilimumab • PD-1 • PSA • PSMA • Sipuleucel-T • vaccines

Immunotherapy has come a long way since Coley’s toxin [1,2], an observation that bacterial toxins can elicit immunologic changes that lead to remissions in cancer. Not only have we more fully identified the players of what was termed by the late Richard Gershon as the ‘immunologic orchestra’ led by the ‘generator of diversity’ [3,4], but complex interplays between cytokines, checkpoint inhibitors and T and B cells and their respective receptors have now been elucidated. These interactions pose continuous challenges as to how these immunologic participants can be harnessed to effect antitumor responses. A continuous challenge to immune therapies is that cancer antigens are often altered ‘self-antigens’ [5], thought to be either overexpressed or underglycosylated byproducts of the malignant process. Cancer testes antigens are one of many examples including, the expression of mucins, gangliosides and glycolipids, all of which are naturally present in normal tissues but are changed by the malignant process.

The concept of cancer vaccines is not new. An article from Toronto’s The Globe in 1925 [6] reported how British researchers identified that a virus could cause cancer and that vaccines could be made against them. Through the last several decades, the field has waxed and waned with false promises of successes. A more recent success, Sipuleucel-T [7–9,101] has reawakened the field of immunotherapy by demonstrating that an autologous cellular product vaccine can impact on the disease. Similarly, ipilimumab [10,11,12] has also shown broad activity in prostate [11,12] and ovarian cancers [13]; interestingly, those patients who ultimately respond develop autoimmune-related events such as colitis, hypophysitis or rash, which demonstrate that not only is an immune target likely hit, but can be associated with bystander events that signal the complex interplay between inhibiting nature’s checkpoints and...
causing unhindered proliferation of T lymphocytes. Two other vaccines have been of interest, the first, CEA-TRICOM, a pox-virus-based vaccine that incorporates the carcinoembryonic antigen (CEA) and docetaxel, versus docetaxel alone, did not show benefit. The second therapy of interest is PSA-TRICOM, a pox-virus-based vaccine that incorporates the prostate-specific antigen (PSA), LFA, ICAM and the cytokine GM-CSF. Though initially promising when given with sunitinib in patients with metastatic prostate cancer, randomized trials using a combination of GVAX and docetaxel, versus docetaxel alone, did not show benefit. The therapy of interest is PSA-TRICOM, a pox-virus-based vaccine that incorporates the prostate-specific antigen (PSA), LFA, ICAM and the cytokine GM-CSF. Though initially promising when given with sunitinib in patients with metastatic prostate cancer, randomized trials using a combination of GVAX and docetaxel, versus docetaxel alone, did not show benefit.

Time-to-treatment effect

Observations in melanoma support a delayed response to treatment with a period of time during which the disease may worsen post-vaccination, as is ascertained [8]. This is the time during which intermediate radiographic imaging may lead to the premature discontinuation of therapy. However, in preclinical models in addition to clinical observations, support the presence of lymphocytic infiltrates that can cause the cancerous organ to appear to be transiently radiographically worse. However, when given as an adjuvant to the vaccine, the overall survival benefits to any benefit is seen radiographically. With continued close observation, the involved organ may demonstrate remission, which may be durable from months to years. Can this be demonstrated by other therapies? It is not uncommon for patients with metastatic prostate cancer to bone who are on hormonal ablation to have worsening bone scans within 3 months of initiating hormonal treatment. This is thought to be due to more rapid bone turnover cause by the healing of the bone lesions with increased metabolic activity seen on a bone scan.

With continued observation, even additional lesions not previously noted on the original bone scan will either ultimately remit or worse. To date, there are no formal recommendations to assess how long it will take for an immune therapy to exert any antitumor effects, if at all. The experience with Sipuleucel-T had shown limited radiographic benefit, but in patients the trial were not followed for an extended period of time, hence it remains unknown whether any benefit would ultimately have been seen if the patients were continued to be monitored in lieu of instituting another therapeutic intervention. Therefore, patients on these kinds of immune therapies may potentially lose immunologically-driven antitumor benefit if they go on to another therapy prematurely due to the length of time it may take for a clinical benefit to be assessed. Patient anxiety may also impact on a patient’s response. It is felt that the chronic inflammatory milieu that develops during tumor growth compromises the immune response while promoting further progression of the malignancy [35-39]. It is felt that chronic inflammation causes immune cells to release cytokines such as TNF-α, TGF-β and IL-6, which recruit myeloid-derived suppressor cells (MDSCs) and CD4+ cells toward a suppressive (Treg) phenotype. Some chemotherapeutic agents promote specific immune cell types. For example, docetaxel administered in a mouse model selectively decreased myeloid MDSCs while increasing CTL responses [40]. Docetaxel may have a relatively potent effect, but other taxanes also alter cytokine patterns and enhance lymphocyte proliferation, as well as the cytotoxic activity of natural killer and lymphocyte-activated killer cells, while reducing Treg cell populations [37,38].

Chemoimmunotherapy combinations

Chemotherapy is widely held to be immunosuppressive, but in fact it has immunomodulatory effects [35-39]. Merely debulking the tumors reverses tumor-induced immune tolerance, possibly through reducing the frequency of suppressive immune responses, as well as by malignant cells [41]. In addition, the transient lymphopenia caused by properly dosed chemotherapy activates homoeostatic mechanisms, eliminating excess suppressor cells, and stimulating tumor-specific effector T-cell proliferation as well as dendritic cell maturation [41]. Some chemotherapeutic agents promote specific immune cell types. For example, docetaxel administered in a mouse model selectively decreases myeloid MDSCs while increasing CTL responses [40]. Docetaxel may have a relatively potent effect, but other taxanes also alter cytokine patterns and enhance lymphocyte proliferation, as well as the cytotoxic activity of natural killer and lymphocyte-activated killer cells, while reducing Treg cell populations [37,38].

In another murine model, immunized mice with implanted colon tumors expressing human carcinoembryonic antigen (CEA) were studied. The vaccine was based on a poxvirus vaccine containing genes for CEA and costimulatory molecules (CEA-TRICOM) [41]. A standard course of docetaxel administered 4 days following two poxvirus immunizations improved vaccine-specific immune responses. It also induced antigen-specific T-cell responses to tumor-derived antigens such as TGF-β and VEGF. These cytokines directly reduce CTL numbers and recruit CD25+ Treg cells and MDSC that repress the immune response. Yet another mechanism employed by tumor cells may cause reduction in CTL responses. For example, CEA- and hCD4+ cells, which has been used as a surrogate marker of response, considerable evidence has been shown to indicate that prostate cancers can promote immune tolerance starting early in the disease [41-45]. However, in a transgenic mouse model of prostate cancer, CD4+ cells specific to prostate antigens infiltrate prostate tumors, but are anergic or non-functional. The encounter with tumor antigens apparently shifts CD4+ T cells toward a suppressive (Treg) phenotype. Patient biopsies show that prostate tumor infiltrating CD4+ cells include high levels of Treg cells [46]. Human prostate tumors also contain elevated populations of possibly protective Th17 cells populations, but only in low-grade tumors [47].

Efficacy of immunotherapies as single agents

**Rationale for combinatorial approaches**

The agents may worsen post-vaccination, either monovalent vaccines, DNA, or vaccine- or antibody-drug conjugates has been limited. While there are immunologic signals with these constructs, such as the expression of cancer-testis antigens, PSA and CEA, the immunogen in use, the overall impact of these approaches has been limited by not demonstrating a change in the biology of the cancer. The field of immunotherapeutics demonstrates that Phase 1 trials directed at novel tumor antigens, including PSA, PSMA, PSCA or PAP, all highly expressed antigens in prostate cancer cell lines and prostate tissue and to which therapeutic benefit is expected. Nevertheless, the durability of these antibody signals and even the induction of T-cell proliferative responses, are insufficient to affect tumor antigens, as evidenced by changes in imaging or even impacting on a new biomarker, circulating tumor cells. Therefore, efforts have long been underway to seek out other agents that can either be additive or synergistic with the vaccine/immune therapies. Although an appealing concept, chemotherapy-vaccine combinations have not been widely applied, albeit the concept has been under consideration. Much of the chemotherapy-vaccine combinations for immunosurveillance, for example preclinical and marine murine studies, or are based on small Phase I trials. In mouse models of colon and breast cancer, paclitaxel, docetaxel or cisplatin subsequent to vaccination enhanced the effectiveness of the vaccine-generated cytotoxic lymphocytes (CTLs), probably by causing an increase in tumor cell permeability to granzyme B and C. Cell death in the vaccinated and treated mouse cancer models included a desirable bystander effect in which the vaccine-induced CTLs caused apoptosis in neighboring tumor cells not expressing the vaccine antigens. It is felt that the chronic inflammatory milieu that develops during tumor growth compromises the immune response while promoting further progression of the malignancy [35-39]. It is felt that chronic inflammation causes immune cells to release cytokines such as TNF-α, TGF-β and IL-6, which recruit myeloid-derived suppressor cells (MDSCs) and directly reduce immune cell activity. These cytokines also promote metastatic transition later in the disease process. The tumor cells play their own role in compromising induction of immunologic responses. Tumor cells evade CTLs through a number of strategies, including blocking antigen presentation, loss of MHC and apoptosis [35-39]. They can also produce immunosuppressive cytokines such as TGF-β and VEGF. These cytokines directly reduce CTL numbers and recruit CD25+ Treg cells and MDSC that repress the immune response. Yet another mechanism employed by tumor cells may cause reduction in CTL responses. For example, CEA- and hCD4+ cells, which has been used as a surrogate marker of response, considerable evidence has been shown to indicate that prostate cancers can promote immune tolerance starting early in the disease [41-45]. However, in a transgenic mouse model of prostate cancer, CD4+ cells specific to prostate antigens infiltrate prostate tumors, but are anergic or non-functional. The encounter with tumor antigens apparently shifts CD4+ T cells toward a suppressive (Treg) phenotype. Patient biopsies show that prostate tumor infiltrating CD4+ cells include high levels of Treg cells [46]. Human prostate tumors also contain elevated populations of possibly protective Th17 cells populations, but only in low-grade tumors [47].

**Issues for resolution**

**Time-to-treatment effect**

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With continued observation, even additional lesions not previously noted on the original bone scan will either ultimately remit or worse. To date, there are no formal recommendations to assess how long it will take for an immune therapy to exert any antitumor effects, if at all. The experience with Sipuleucel-T had shown limited radiographic benefit, but in patients the trial were not followed for an extended period of time, hence it remains unknown whether any benefit would ultimately have been seen if the patients were continued to be monitored in lieu of instituting another therapeutic intervention. Therefore, patients on these kinds of immune therapies may potentially lose immunologically-driven antitumor benefit if they go on to another therapy prematurely due to the length of time it may take for a clinical benefit to be assessed. Patient anxiety may also impact on a patient’s response. It is felt that the chronic inflammatory milieu that develops during tumor growth compromises the immune response while promoting further progression of the malignancy [35-39]. It is felt that chronic inflammation causes immune cells to release cytokines such as TNF-α, TGF-β and IL-6, which recruit myeloid-derived suppressor cells (MDSCs) and directly reduce immune cell activity. These cytokines also promote metastatic transition later in the disease process. The tumor cells play their own role in compromising induction of immunologic responses. Tumor cells evade CTLs through a number of strategies, including blocking antigen presentation, loss of MHC and apoptosis [35-39]. They can also produce immunosuppressive cytokines such as TGF-β and VEGF. These cytokines directly reduce CTL numbers and recruit CD25+ Treg cells and MDSC that repress the immune response. Yet another mechanism employed by tumor cells may cause reduction in CTL responses. For example, CEA- and hCD4+ cells, which has been used as a surrogate marker of response, considerable evidence has been shown to indicate that prostate cancers can promote immune tolerance starting early in the disease [41-45]. However, in a transgenic mouse model of prostate cancer, CD4+ cells specific to prostate antigens infiltrate prostate tumors, but are anergic or non-functional. The encounter with tumor antigens apparently shifts CD4+ T cells toward a suppressive (Treg) phenotype. Patient biopsies show that prostate tumor infiltrating CD4+ cells include high levels of Treg cells [46]. Human prostate tumors also contain elevated populations of possibly protective Th17 cells populations, but only in low-grade tumors [47].
Clinical Trial Outcomes

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**Review:** Clinical Trial Outcomes

**Immunotherapeutic combinations for cancer:**

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Antigens from dying cells. Docetaxel was effective only when administered after immunization. If administered prior to docetaxel, inhibited cellular infection by the viral vaccine or antigen expression in the cells that did become infected [46]. How to combine chemotherapy with vaccines and the therapeutic dosing of chemotherapy agents that can be used with vaccines remains unclear. A study that investigated daily low-dose paclitaxel found that by targeting HPV E7+ implanted tumors in mice receptors, survival, survival and tumor growth delayed. The results were improved when compared with the vaccine alone, the vaccine plus high-dose paclitaxel, or high-dose, twice-weekly paclitaxel alone [40]. Daily low-dose paclitaxel did not result in the significant T-cell declines induced by high-dose paclitaxel. When administered with the vaccine, daily low-dose paclitaxel resulted in a higher CD8+ T-cell/Treg ratio than either the vaccine alone or the vaccine plus high-dose paclitaxel. Furthermore, the low-dose chemotherapy had greater antiangiogenic effects than did high-dose [41]. A chemotherapy drug, that has been studied extensively is cyclophosphamide. Low-dose cyclophosphamide also has well-documented immune modulatory effects [42,43]. It reduces the Treg cell infiltrate and the activity of Treg cells, and stimulates cell-mediated immunity [44]. The drug is now making its debut after being retired for many years in its role as an immune modulator. In a transgenic murine prostate cancer model, administering low-dose cyclophosphamide 1–2 days before immunization with a whole-cell, GM-CSF-secreting vaccine (GVAX) resulted in a tumor shrinkage effect not observed with the vaccine alone. This effect related seemed to a reduced Treg population in the tumor and its draining lymph node, as well as increased dendritic cell activation [45]. Other studies have found specific benefits from high-dose but submyeloablative chemotherapy. An adenovirus-based vaccine was found to have limited effectiveness in mice with established melanoma tumors, unless the mice were pretreated with higher doses of cyclophosphamide (Cy) [46]. The combination resulted in tumor regression due to the high frequency of vaccine antigen-specific T-cells, reflecting cyclophosphamide’s general promotion of cell-mediated immunity. This drug has been used at low dose, high-dose and on a metronomic schedule. More recently, an anti-PD-1 antibody (CT-001) with Treg cell depletion by low-dose Cy (CPM), combined with a DNA vaccine was shown to induce synergistic antigen-specific immune responses [47]. This strategy led to complete regression of established tumors with survival prolongation in a significant proportion of animals. This is the first demonstration that the combination of anti-PD-1 and high-dose vaccination, increased the number of vaccine-induced tumor infiltrating CD8+ T cells with simultaneous decrease in infiltrating Treg cells. Another chemotherapy approach was to do estramustine phosphate (initially administered as 280 mg daily in concert with a personalized peptide vaccine in HLA-A2+ or -A24+ patients with castration-resistant prostate cancer [48]. There were no preclinical studies to suggest that this drug had a direct immunomodulatory effect and the impetus for the drug was based on clinical tolerability and safety. Nevertheless, ten of 11 patients who received a combination of peptide vaccination and estramustine showed a serum PSA decrease; eight patients showed a PSA decrease of ≤50%. One of two patients with measurable disease showed a 44% decrease in lymph node metastasis; no changes were seen in patients with bone lesions. Estramustine-induced immunosuppression was analyzed in ten patients by IFN-γ production to PHA, EBV peptide stimulation and T-cell function. No changes were observed; no significant immune suppression was seen when the peptide was given along with a smaller dose of estramustine [48]. These responses were thought to be mediated by restoring T cells, memory T cells and a combination of memory and activated T cells, respectively [48]. These observations were further extended into another Phase I multicenter study [49] of 15 patients treated with low-dose estramustine and IFN-γ, 1 a peptide set consisting of 14 kinds of peptide that induced HLA-A24-restricted tumor-specific cytotoxic activity. Patients were treated with the top four peptides shown to be immunogenic based on pre-vaccination measurement of peptide-specific IgG in plasma reactive to ITK-1. While safe, in vitro analysis did not reveal any correlation between the peptide dose and the generation of specific T cells from vaccinated patients. A median survival of 23.8 months was reported with this combination regimen, albeit the exact immune mechanism, if any, that contributed to this remains unclear [49].

**Attempts to reduce or suppress the regulatory T-cell population & enhance response with nonchemotherapeutic agents**

One means of polarizing Treg cells has been through specific targeting of the T-cell checkpoint inhibitor CTLA-4 with a monoclonal antibody such as ipilimumab [48,50]. In the past few years it has become apparent that costimulation is even more complex than initially thought. After activation, T cells express CTLA-4, a close homologue to CD28. CTLA-4 binds members of the B7 family with a much higher affinity than CD28 [51]. There has been some controversy as to the role of CTLA-4 in regulating T-cell activation. It now appears that CTLA-4 down regulates T-cell responses [52]. This was based on the following in vitro observations: blockade of CTLA-4 on T cells of using low-dose estramustine enhanced T-cell responses; crosslinking of CTLA-4 with CD3 and CD28 inhibited T-cell responses, and antibodies to CTLA-4 in vivo augmented the immune response to peptide antigens or superantigens in mice [53,54]. Blocking CTLA-4–B7 interaction while preserving signalling via CD28 resulted in enhanced T-cell responses in vitro [55]. Perhaps the most convincing demonstration of the downregulatory role of CTLA-4 came from examination of mice with a null mutation [48,55,56]. CTLA-4 knockout mice appear to have spontaneously activated T cells early in development followed by rapidly progressive lymphoid proliferation consistent with a lymphomatous presentation. Mice usually die within 3 weeks either as a result of polyclonal T-cell expansion or T-cell mediated death; no other disease returned as a result of lymphokine release with ensuing shock. Thymocyte differentiation and selection proceed normally in CTLA-4-deficient mice; this suggests that CTLA-4 may contribute to downregulating peripheral T-cell responses [56].

**Immunotherapeutic combinations can impact on tumor response & survival**

Recent attempts to demonstrate improvement in overall or progression-free survival (PFS) have been shown using a poxvirus–PSA recombinant vaccine, a mixture of recombinant pot viruses expressing either or both the vaccine antigens of the remaining tumor. This DNA-based vaccine is usually administered once followed by monthly injections of low-dose–PSA recombinant virus in a prime–boost strategy. Each vaccination is administered with GM-CSF [57]. In a Phase II study, patients with metastatic castration-resistant prostate cancer (n = 28) received the poxvirus-PSA vaccine twice a week for the first month and then monthly until disease progression occurred. Half the group additionally received docetaxel/dexamethasone therapy in 3-weeks-on/1-week-off cycles [58]. In the vaccine-alone arm, 11 patients (78.6%) were changed to docetaxel upon evidence of progression. Median time to progression was 1.8 months in the vaccine-alone arm and 3.2 months in the vaccine plus docetaxel arm. Notably, patients experienced a median 6.1-month progression-free period after progressing on the vaccine alone and then switching to docetaxel. PFS was 3.7 months in an historic control group receiving docetaxel alone [59]. All evaluable vaccine recipients exhibited increased PSA-specific T-cell responses (median 3.3-fold increase in both arms). In the three vaccine-alone recipients who were examined, T-cell responses emerged, as well as responses to other prostate tumor antigens (PAP, PSA and/or MUC). Patients with PSA responses to the vaccine also demonstrated an epopeptide spreading phenomenon pursuant to the tumor cell death by the vaccine-induced PSA-specific T-cell response [59].

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References:

[18,56] Several studies in patients with metastatic castration-resistant prostate cancer (n = 8) were included in a randomized Phase III study evaluating ipilimumab alone [39,42]. In both the prostate cancer and melanoma studies, the vaccines were administered simultaneously with the course of ipilimumab; there was no attempt to evaluate sequential therapy [42,57]. Furthermore, blocking CTLA-4 function may permit the emergence of autoreactive T cells and resultant autoimmune responses in mice [40,41]. In a nonhuman primate model of autoimmune diseases such as diabetes, hypophysitis, transplant rejection, and others, it is possible to use technology such as ipilimumab [42,43]. The severity of the adverse events appeared to be related to the dose and timing of response. Although the use of ipilimumab remains controversial. Overall, the results suggest that chemotherapy, albeit at less than therapeutic doses, may induce a wide range of immune effects that may ultimately lead to tumor regressions. However, the number of patients with a good prognosis for cancer remains several weeks to months after treatment.

Another molecule, the programmed death-1 receptor (PD-1) is expressed on T cells following antigen activation. Binding of PD-1 to its ligands, programmed death ligand (PD-L1) and PD-L2, downregulates signals by the T cell receptor, thereby promoting T-cell anergy and apoptosis, and can therefore lead to immune suppression. Recent clinical trials in renal cell carcinoma and melanoma suggest significant activity of this drug, sparking additional plans for combining anti- CTLA-4 with anti-PD-1. [50] The role of PD-1 in regulating immune responses is currently being explored in several clinical trials.
It should be noted that no Phase II trials were conducted prior to VITAL-2 in order to test various docetaxel/GVAX doses and schedules. VITAL-1 results with GVAX alone, it is conceivable that the concurrent high-dose docetaxel undercut the GVAX effect. Administering GVAX before or after docetaxel therapy rather than concurrently may be a more successful result. Another possibility is that some of the study population had disease that was too advanced to benefit from the vaccine.

Unanswered questions for the next generation of immune-based therapies
There continues to be unresolved issues regarding perfecting vaccine strategies alone or given in combination with other immune modulatory agents or chemotherapies. The first issue is how to maximize immunogenic responses. As discussed, the data support the use of chemotherapy with an immune-based approach. However, it remains to be seen whether there is a ‘best’ chemotherapy agent for this application. Second, chemotherapy is sufficient for this implementation or should additional agents such as GM-CSF or IL-2 be added for synergism. Last, in what sequence should the respective agents be delivered to foster maximum benefit?

Chemotherapies with potential to induce metronomic dosing, taxanes, anthracyclines and cyclophosphamide, but it remains unclear whether newer agents that target the androgen receptor, that is, MDV-3100, or abiraterone analogs, or androgen deprivation therapy. The comparator group received standard immunotherapy in prostate cancer to date. Immunotherapeutic combinations for cancer

Impact of immunotherapy combinations
Phase III clinical trials support the further development of immunotherapeutic approaches and should include combination with other immune modulatory agents or chemotherapies as a multimodality approach in concert with radiotherapy.

Clinical trial development
Continued efforts to develop immunologic end points that are custom-tailored to the therapy under investigation should continue.

Timelines in assessing clinical/immunologic benefit
There is still much discussion about achieving survival benefits in the absence of disease control or impact on a clinical biomarker. This may be due to delayed immunologic responses, but it remains unclear as to when it can be shown that an immune therapy has truly failed and the patient needs to go on to the next therapy.

There is also need to standardize immune assays so that study results become more easily reproducible [45]. As the field of immunotherapy develops, we are faced with critical issues that may impact on the success of future trials. Among these issues may be taken with due consideration are: identifying the patient cohort that will derive maximal benefit from immunotherapy; realistic timelines by which to assess whether or not the immunologic approach has provided benefit; what agents should be used in combinatorial studies with vaccines; and, importantly, how do we go about screening immunologic agents for potential usefulness? Are neoadjuvant studies that interrogate the tumor’s natural milieu beneficial to understanding the immunotherapy or does this blunt our understanding of the therapy’s ultimately systemic usefulness? How do we evaluate the answers to all these questions in the next several years and bring into the clinical arena a wider array of effective agents?

End points & responses: still unresolved
Another reason for suboptimal results with vaccines in populations with advanced disease and low life expectations is that the timeframe needed to observe a clinical response may be delayed. Researchers have realized that responses to immunotherapies are often ‘late’ phenomena [46,47] and that the disease could remain stable or even progress for some months before prompt immune responses are apparent. Alternatively, the initial vaccine-induced inflammatory flare may be mistaken for tumor growth. Various groups have therefore proposed revised end points for cancer vaccine trials that place greater emphasis on overall survival or long-term disease stability rather than PFS. The emphasis is on minimizing premature discontinuation, and allowing patients to continue with therapy despite early, minor progression [48–54].

Future perspective
Biomarkers of immune response that reliably predict treatment outcome would simplify our issues, allowing for more rapid identification and optimization of effective regimens before trials have reached clinical end points [55–58]. These would ideally give a better advance indication of clinical benefit we might expect the long follow-up required to observe clinical end points. In general, there remains the question as to whether blood biomarkers reflect conditions within the tumor itself of within the surrounding milieu.

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Immunotherapeutic combinations for cancer


Review: Clinical Trial Outcomes

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