Why has active immunotherapy not worked in lung cancer?
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Vaccines that rely on active specific stimulation of the host immune system have the potential to trigger durable antitumor responses with minimal toxicity. However, in nonsmall-cell lung cancer (NSCLC), several large phase III trials of vaccines reported within the last year have yielded disappointing results. Compared with placebo, belagenpumatucel-L (an allogenic tumor cell vaccine), tecemotide (a peptide vaccine targeting MUC-1) and melanoma-associated antigen-A3 (a protein-based vaccine) did not improve outcomes in NSCLC. The lack of clinically significant outcomes, despite their ability to prime and expand tumor antigen-specific T cells could at least partly be attributed to the inability of vaccine-induced T-cell responses to overcome the tumoral mechanisms of immune escape which limit the clonal expansion of T cells following vaccination. A number of such mechanisms have been recognized including reduced antigen presentation, antigenic loss, cytokines, immunosuppressive cells and immune checkpoints. Strategies aimed at modulating the immune checkpoints have shown promise and are on the verge of revolutionizing the therapeutic landscape of metastatic NSCLC. Overcoming immune tolerance and improving the activation of antitumor T cells via combinatorial approaches may represent a new and more promising therapeutic application for active immunotherapies in NSCLC.

Key words: active immunotherapy, vaccines, nonsmall-cell lung cancer, immune checkpoint, tumor-mediated immunosuppression

introduction
The significant and durable responses induced by antibodies blocking the programmed cell death-1 (PD-1) checkpoint have led to a renewed interest in immunotherapy for nonsmall-cell lung cancer (NSCLC) [1, 2]. These results are particularly encouraging given the many unsuccessful attempts at immunotherapy in NSCLC over the last several years. In general, these have included active immunotherapies which rely on the ability of the patient’s own immune system to mount an immune response specific to tumor-associated antigens, passive immunotherapy which uses exogenous lymphocytes or antibodies to mediate an immune response and nonspecific immune stimulation which should be effective regardless of the tumor antigen which stimulates the immune response [3, 4].

Active specific stimulation of the host immune system has the potential to cause durable antitumor responses with minimal toxicity. This promise of antigen-specific immunotherapy has borne out in prostate cancer where the use of sipuleucel-T, an autologous active cellular immunotherapy prolonged overall survival (OS) among men with metastatic castration-resistant prostate cancer [5]. However, in NSCLC, several agents whose large phase III trial results have been reported within the last year have yielded no significant benefit. Given the dire need for better therapies and the cost of drug development, it is imperative to try to understand these failures. In this article, we will review the phase III trial results of recently reported antigen-specific immunotherapeutic approaches in NSCLC, explore the potential reasons behind their failure and discuss strategies for the future.

antigen-specific immunotherapeutic approaches in NSCLC
belagenpumatucel-L
Belagenpumatucel-L (Lucanix) is an allogeneic tumor cell vaccine, which consists of four irradiated NSCLC cell lines that...
have been modified with transforming growth factor-β2 (TGF-β2) antisense gene plasmid. TGF-β inhibits T-cell, B-cell and dendritic cell activation, induces immunosuppressive T regulatory (Treg) cells and inhibits immune effector cell activation [6]. In a phase II study of patients with low-volume disease, belagenpumatucel-L was well tolerated, induced antibody-mediated response to vaccine human leukocyte antigens (HLA) and demonstrated a dose-dependent improvement in survival and response [7].

A phase III trial compared the efficacy of belagenpumatucel-L with placebo as a maintenance therapy in patients with stages IIIA (T3, N2 only), IIIB and IV NSCLC without progression after up to six cycles of first-line platinum-based chemotherapy (which had to be completed 4–17 weeks before randomization) [8]. Belagenpumatucel-L (2.5 × 10^7 cells/injection intradermally) or placebo were administered every month for 18 months followed by additional two quarterly injections. The primary end point was OS. Maintenance belagenpumatucel-L did not result in improvement in OS over placebo [median OS 20.3 months with belagenpumatucel-L (n = 270) and 17.8 months with placebo (n = 262); P = 0.59]. Of interest, however, in a preplanned subgroup analysis, among patients who received prior radiation therapy and enrolled within 12 weeks, belagenpumatucel-L resulted in significantly improved OS [median OS 40.1 months with belagenpumatucel-L (n = 43) and 10.3 months with placebo (n = 36); P = 0.014].

tecemotide

Tecemotide (Liposomal BLP25; L-BLP25) is a peptide vaccine, which targets the exposed core peptide of MUC-1, a membrane-associated glycoprotein differentially overexpressed and aberrantly glycosylated in cancer cells [9, 10]. Tecemotide consists of the MUC1-derived 25-aminoacid BLP25 lipopeptide, the immunoadjuvant monophosphoryl lipid A and three liposome-forming lipids. Tecemotide was well tolerated and induced T-cell responses to MUC1 in phase I and II studies [11–13].

A phase III trial compared the efficacy of tecemotide with placebo (2:1 randomization) as a maintenance therapy in patients with unresectable stage III NSCLC who had responded to or had stable disease after primary chemoradiotherapy (which had to be completed within 4–12 weeks before randomization) [14]. One dose of cyclophosphamide (300 mg/m^2 i.v., maximum dose 600 mg) or placebo was administered before treatment. Eight consecutive weekly subcutaneous injections of tecemotide or placebo were followed in the absence of progressive disease by maintenance tecemotide or placebo every 6 weeks until disease progression. The primary end point was OS. Maintenance tecemotide did not result in improvement in OS over placebo [median OS 25.6 months with tecemotide (n = 829) and 22.3 months with placebo (n = 410) [hazard ratio (HR) 0.88, 0.75–1.03; P = 0.123]]. In a preplanned subgroup analysis, however, among patients who received concurrent chemoradiotherapy, OS was significantly longer with tecemotide than placebo [median OS 30.8 months [95% confidence interval (CI) 25.6–36.8] with tecemotide (n = 538) and 20.6 months (95% CI 17.4–23.9) with placebo (n = 268)]. However, in patients who received previous sequential chemoradiotherapy, OS was worse in patients in the tecemotide group [median OS 19.4 months (95% CI 17.6–23.1; n = 291) and 24.6 months (95% CI 18.8–33.0) with placebo (n = 142) (HR 1.12, 0.87–1.44; P = 0.38)]. Based on these results, an ongoing trial is studying the effect of tecemotide or placebo on OS of patients with unresectable stage III NSCLC with either stable disease or objective response following primary concurrent chemoradiotherapy (ClinicalTrials.gov identifier: NCT02049151).

melanoma-associated antigen-A3 vaccine

Melanoma-associated antigen-A3 (MAGE-A3) vaccine is a protein-based vaccine consisting of the recombinant antigen ProtD-MAGE-A3/His (a fusion protein containing Protein D, a lipoprotein present on the surface of haemophilus influenzae B, MAGE-A3 protein and a polyhistidine tail) and a proprietary immunological adjuvant. MAGEs are tumor-specific shared antigens which are differentially overexpressed in many cancers including NSCLC. In a phase II trial of patients with completely resected, MAGE-A3-expressing early-stage NSCLC, humoral and cellular immune responses to MAGE-A3 and statistically nonsignificant improvements in disease-free intervals were observed [15, 16].

A phase III trial compared the efficacy of MAGE-A3 vaccine with placebo (2:1 randomization) in patients with completely resected MAGE-A3-expressing stage IB, II or IIIA NSCLC. Up to four cycles of adjuvant chemotherapy could be administered at the investigators’ discretion. Thirteen doses of the vaccine were administered intramuscularly over 27 months. The primary objectives were disease-free survival (DFS) in the overall population and in those who did not receive adjuvant chemotherapy (co-primary end points). The trial enrolled 2312 MAGE-A3-positive patients (33% of patients screened had MAGE-A3-expressing tumors). The study was terminated by an independent data monitoring committee as MAGE-A3 vaccine did not significantly extend DFS compared with placebo either in the overall MAGE-A3-positive population or in those MAGE-A3-positive patients who did not receive chemotherapy [17].

considerations for active immunotherapy in NSCLC

While a number of factors are important in clinical translation of successful active immunotherapy (Figure 1), we will discuss some which are more relevant in the context of the above described negative large phase III trials.

humoral and cellular immune dysregulation in lung cancer

In the first step of an adaptive immune response, effector T cells recognize antigenic peptides of tumor cells presented by antigen-presenting cells (APC) in the context of major histocompatibility complex (MHC) class I or class II molecules expressed on the APC surface. Additional co-stimulatory signals mediated through constitutively expressed co-stimulatory molecules on the T cell and the APC are also necessary for T-cell activation. The presence of both signals trigger intracellular events resulting in the activation and interleukin (IL)-2-dependent clonal proliferation of T cells. Expansion of T cells in sufficient
numbers results in recognition and elimination of tumor cells. However, immune responses are dysregulated in cancer.

A number of mechanisms are employed by tumors to escape the host immune response and promote immune tolerance. These are perhaps the most important hurdles that need to be overcome for successful antigen-specific immunotherapy in NSCLC. The better understood immune resistance mechanisms in NSCLC are outlined in Figure 2.

Suppression of antigen-presenting machinery is one of several mechanisms of immune escape. Multiple molecular mechanisms can lead to altered HLA expression within lung cancer. These include deficiencies in expression of antigen-processing genes [18–21], and haplotype loss of HLA class I antigens [22–24]. In small retrospective studies, absence HLA class I expression was associated with poor prognosis suggesting that downregulation of HLA class I expression may play a critical role in immune surveillance of patients with NSCLC [25, 26]. The reversibility of some of the aberrations in antigen processing by interferon (IFN)-γ indicates that it is possible to overcome the suppression of antigen-presenting machinery and may be of therapeutic relevance [21, 27]. Considering the critical role of antigen presentation in immune recognition of tumor cells, these mechanisms may be of potential therapeutic importance.

In addition to reduced antigen presentation, immune inhibitory cytokines secreted by the tumor cells can impair T-cell survival and help them avoid T-cell-mediated immune responses. Soluble factors derived from NSCLC cell-line supernatants have been described to markedly enhanced apoptosis of activated T cells [28]. TGF-β enables tumor evasion of immune surveillance through various mechanisms most of which converge on the impairment of tumor cell killing by immune effector cells [29]. In addition to inhibiting proliferation and differentiation of normal bronchial epithelial cells, TGF-β mediates conversion of CD4+CD25– T cells to Tregs [30, 31]. Serum TGF-β levels are elevated in patients with lung cancer compared with normal individuals. Elevated plasma levels of TGF-β confer a poorer prognosis for patients with lung cancer [32]. IL-10 is a potent immunosuppressive cytokine that promotes lung cancer growth by suppressing T-cell and macrophage function and enabling tumors to escape immune detection [33–35].

Yet another mechanism of immunosuppression involves immune checkpoints which are molecules expressed on the surface of T lymphocytes and modulates the immune response to antigens via inhibitory or stimulatory signaling to T cells. Two most extensively studied immune inhibitory checkpoints in NSCLC are cytotoxic T-lymphocyte antigen-4 (CTLA-4) and PD-1. Activation of both receptors causes downregulation and inhibition of immune responses. PD-1 functions primarily in peripheral tissues where T cells may encounter the immunosuppressive PD-1 ligands, PD-L1 (B7-H1) and PD-L2 (B7-DC), which are expressed by tumor cells, stromal cells or both [36]. CTLA-4 mediates immune inhibitory signals which are distinct from PD-1 [37]. Clinical trial results of antibody-mediated blocking of CTLA-4 and PD-1 pathways indicate that this strategy is feasible and effective in NSCLC [1, 38].

A number of cells in the tumor microenvironment including Tregs, myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages have immunosuppressive properties. Tumor-infiltrating lymphocytes which are CD4+CD25+, the activated phenotype of Tregs, mediate potent inhibition of autologous T-cell proliferation and prevent the host from mounting an immune response to tumor antigens [39]. Tregs of a similar phenotype (CD4+CD25+) with marked immunosuppressive activity are elevated in peripheral blood of NSCLC patients [40]. MDSCs are a heterogeneous population of cells of myeloid origin that are characterized by their immature state and ability to suppress T-cell responses [41]. In lung cancer, antibody-mediated MDSC depletion increased APC activity and

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Figure 1. Important considerations in clinical translation of successful active immunotherapy.
augmented the activity of effector T cells leading to reduced tumor growth and enhanced therapeutic vaccination responses [42]. The prognostic significance of MDSCs in the tumor microenvironment is not established in NSCLC.

A number of metabolic enzymes including those associated with the catabolism of the amino acids arginine and tryptophan are associated with the suppressive activity of myeloid cells. Indoleamine 2,3-dioxygenase-1 (IDO1) is an enzyme which is expressed by a subset of dendritic cells that catalyzes the degradation of the amino acid tryptophan to kynurenine. IDO1 is thought to be an important regulator of the immunosuppressive mechanisms responsible for tumor escape from host immune surveillance and blockade of IDO activity increases the ability of tumor-bearing mice to reject tumors [43].

In summary, a number of mechanisms including reduced antigen presentation, antigenic loss, cytokines, immune checkpoints, immunosuppressive cells and enzymes are employed by tumors to escape the host immune response and promote immune tolerance.

**trial design**

With the benefit of hindsight, the negative results of these large phase III trials (with a combined accrual of over 4000) should come as no surprise. All three trials were initiated based on results of negative or at best inconclusive phase II data (Table 1) and post hoc analysis of small subgroups which showed positive results.

For example, a randomized, open-label, phase II trial failed to show significant improvement in OS of patients who received tecemotide over those who received best supportive care. In the small subset of patients with stage IIIB-LR (locoregional) disease (n = 65), those who received tecemotide had a 17.3-month improvement in median OS (30.6 versus 13.3 months) [12].

In another instance, the phase III trial of belagenpumatucel-L was initiated based on a dose-related improvement in survival and response in the phase II trial. However, the phase II trial itself had small numbers of patients in the individual treatment arms (~20 patients each in the three cohorts) who had low-
volume disease. Furthermore, the phase II trial did not have a control arm [7, 8].

In a third instance, the randomized, placebo-controlled phase II trial of MAGE-A3 vaccine, which led to the larger phase III trial, had a limited sample size. With 182 patients, and an estimated power of 50% to detect a difference of 10% in absolute recurrence after 30 months, the study was unlikely to demonstrate improvements in efficacy. A related issue, emphasized by the phase II–III transition of this drug is the lack of adequate follow-up. Trends of activity observed in earlier analysis were not confirmed with more mature follow-up data [15, 16]. A number of factors including commercial pressures and misguided enthusiasm of investigators based on early trends may explain these failures.

While it is true that investigators would not initiate a trial if they did not think it had a reasonable chance of a statistically significant and clinically meaningful benefit, some have argued that the investigators frequently use overly optimistic assumptions of treatment benefits [44]. Unfortunately, this may have been true in the transition from phase II to phase III trials of antigen-specific immunotherapies in NSCLC.

**future of antigen-specific immunotherapy in NSCLC**

The failure of vaccines in NSCLC, despite their ability to prime and expand tumor antigen-specific T cells, could at least partly be attributed to the inability of vaccine-induced T-cell responses to overcome the tumoral mechanisms of immune escape. These mechanisms probably limit the clonal expansion of T cells following vaccination.

Many of the immunosuppressive mechanisms discussed above are potentially amenable to therapeutic modulation. Low doses of cyclophosphamide have been shown to selectively decrease circulating Tregs and suppress their inhibitory functions leading to a restoration of peripheral T-cell proliferation and innate killing activity [45]. Other drugs including chemotherapies and signal transduction inhibitors have also been shown to selectively target immunosuppressive cells in the tumor microenvironment [46, 47]. Metabolic enzymes and cytokines involved in the induction of tumor immune tolerance can also be inhibited pharmacologically [42, 48]. MDSC differentiation can be blocked in a number of ways including cyclooxygenase inhibitors, which prevent the production of prostaglandin [49].

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**Table 1.** Phase II and phase III studies of selected antigen-specific immunotherapeutic approaches in nonsmall-cell lung cancer

<table>
<thead>
<tr>
<th>Investigational agent</th>
<th>Phase of study</th>
<th>N</th>
<th>Patients</th>
<th>Primary end point</th>
<th>Primary end point outcome</th>
<th>Significance of differences between treatment group and control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecemotide (Butts and Maksymiuk et al. [12])</td>
<td>Randomized phase II</td>
<td>171</td>
<td>IIIB or IV NSCLC</td>
<td>OS</td>
<td>17.2 m</td>
<td>13 m</td>
</tr>
<tr>
<td>Belagenpumatucel-L (Nemunaitis et al. [7])</td>
<td>Randomized, dose-variable phase II</td>
<td>75</td>
<td>II, IIIA, IIIIB and IV; low tumor burden</td>
<td>OS</td>
<td>20.3</td>
<td>17.8</td>
</tr>
<tr>
<td>Belagenpumatucel-L (Giaccone et al. [8])</td>
<td>Randomized, double-blind placebo-controlled phase III</td>
<td>532</td>
<td>III (T3, N2 only), IIIIB and IV</td>
<td>OS</td>
<td>Dose-related improvements in survival in three treatment arms*</td>
<td>NA</td>
</tr>
<tr>
<td>Melanoma-associated antigen-A3 vaccine (Vansteenkiste [15])</td>
<td>Randomized phase II</td>
<td>182</td>
<td>Completely resected IB/II MAGE-A3-expressing tumor</td>
<td>DFS</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Melanoma-associated antigen-A3 vaccine (release 2014)</td>
<td>Randomized, double-blind placebo-controlled phase III</td>
<td>2312</td>
<td>Completely resected IB, II, or IIIA MAGE-A3-expressing tumor</td>
<td>DFS</td>
<td>Not available</td>
<td>Not available</td>
</tr>
</tbody>
</table>

*Three doses (1.25, 2.5 or 5.0 × 10^7 cells/injection) of belagenpumatucel-L were studied in three cohorts of 25, 26 and 24 patients each.  
bHR in favor of the MAGE-A3 group.
Recent studies have demonstrated that immune checkpoints can be successfully modulated [1, 2]. An anti-PD-1 antibody, nivolumab was evaluated in a phase I trial in patients with advanced previously treated cancers [1]. Doses of 1, 3 and 10 mg/kg were administered i.v. once every 2 weeks with immune response assessment every 8 weeks. In the NSCLC expansion cohort, across all doses and histologies (squamous and nonsquamous), the objective response rate was 17% (22 of 129 patients) and median response duration 17 months [50]. Median OS was 9.2–14.9 months and 1-year OS rates 32% to 56%. In March 2015, nivolumab was approved by the FDA for use in patients with metastatic squamous cell lung cancer with progression on or after platinum-based chemotherapy. Its efficacy was established in a phase III, open-label, study that randomized previously treated patients (n = 272) with advanced squamous cell lung cancer to receive nivolumab 3 mg/kg i.v. every 2 weeks or docetaxel 75 mg/m² i.v. every 3 weeks. OS, the primary end point of the trial, was prolonged by 3.2 months at the median in patients who received nivolumab compared with those who received docetaxel. Several other agents targeting PD-1 pathway are in clinical development, including pembrolizumab (MK-3475, anti PD1), MEDIA4736 (anti-PD1), BMS-936559 (anti-PDL1) and MPDL-3280 (anti-PDL1). Despite the promise of immune checkpoint inhibitors, it is clear that responses are limited, restricted presumably to patients with a pre-existing tumor-reactive T-cell response. Investigations of ways to select patients (e.g. PD-L1 expression in the tumor or infiltrating immune cells or both) are underway. There is growing interest in modulating the multiple inhibitory and co-stimulatory pathways in the tumor microenvironment by combining inhibitors of the PD-1 pathway with other immune checkpoints antibodies, including antagonist antibodies to KIR, LAG-3 and CTLA-4.

Antigen-specific vaccines offer an opportunity to potentially extend the responses with immune checkpoint inhibitors to a greater percentage of patients. A recent study showed that tumors resistant to anti PD-1 antibodies could be eradicated by combining them with vaccines containing tumor-specific peptides with high MHCI-binding affinity [51]. In the study, melanomas that contained a high percentage of dysfunctional endogenous PD-1+ tumor-specific CD8+ T cells were treated with a PD-1 inhibitor and an exogenous tumor-specific antigen using attenuated Salmonella typhimurium. The combination rescued the endogenous tumor-specific CD8+ T-cell response and resulted in tumor regressions. A combinatorial strategy of vaccines and immune checkpoint inhibitors could rescue T cells which become dysfunctional after infiltrating long-established suppressive tumors, thereby overcoming one of the major obstacles to clinical benefit from vaccines. Most of these strategies are still in preclinical evaluation in NSCLC. While there is strong rationale to combine vaccines with other immunomodulatory strategies, important considerations in clinical testing of these combinations include determining the sequence of administration of drugs, and metrics of response assessment.

While the above-discussed approaches aim to overcome tumor-mediated immunosuppression, other approaches seek to enhance cellular immune responses through a number of different mechanisms. These include induction of immunogenic cell death with radiotherapy [52] and combination with adoptive T-cell transfer to prime T cells and amplify antitumor T-cell responses [53]. Immunogenic cell death is different from apoptotic cell death in the generation of specific molecular signals that are sensed by APC which stimulate their maturation and ability to cross-present tumor-derived antigens to T cells [54]. In addition to immunogenic cell death, radiation causes MHC I upregulation and release of antigens which are taken up by dendritic cells and presented to T cells that in turn migrate back to the tumor and provide local control, thus serving as an intrinsic vaccine priming adaptive immunity [55]. The ongoing process of killing of tumor cells by cytotoxic T lymphocytes sustains release of more tumor antigens and possibly promotes antigenic spread, i.e. the activation of a broader T-cell repertoire. Antigenic spread has been reported in some patients with prostate cancer who were treated with the combination of a vaccine and local radiotherapy [56].

Possible beneficial effects observed in subsets of patients on active immunotherapy trials indicates the need for better patient selection [8, 14]. While it is generally believed that these therapies are most active in patients with minimal volume of disease, no predictive markers have been identified to date. Better measures are needed to assess tumor-specific immune responses and understand the relationship between immune induction and clinical responses. The failure of phase III trials which were initiated based on ‘promising’ phase II trials also indicate the need to temper our optimism, particularly when making the expensive leap from phase II to phase III trials.

Finally, a better understanding of the immune dysregulation specific to NSCLC is needed. The immune evasion mechanisms in lung cancer are likely different from other tumors [57] due to the proinflammatory and immunosuppressive effects of tobacco smoke. Chronic inhalation of cigarette smoke is known to alter a wide range of immunological functions, including innate and adaptive immune responses [58]. In the context of active immunotherapy, the effect of smoking on T-cell responsiveness and proliferative capacity are important considerations. In animal models, chronic exposure to cigarette smoke affects adaptive immune responses [58]. In the context of active immunotherapy, the effect of smoking on T-cell responsiveness and decreases T-cell proliferative and T-cell dependent antibody responses [59]. Yet there are limited data on the effects of cigarette smoke on immune dysregulation in lung cancer patients. Challenges to this field of study include the multiparticle nature of cigarette smoke and the significant variability in smoking patterns which makes it difficult to study its effect in experimental systems [60]. Recent data indicating that smoking-associated NSCLC may respond better to immune checkpoint blockade [61] also suggests the distinctive influence of tobacco smoke on the tumor microenvironment. To our knowledge, clinical reports of active specific immunostimulatory agents have not assessed the effect if any of smoking on the clinical or immune outcomes.

Heterogeneity within NSCLC between the primary tumor and metastatic sites and between tumors from different patients is well described [62]. However, our understanding of the association between oncogenes and immune escape and the differential influences of different oncogenic drivers on the immune milieu are still preliminary [63]. A study of PD-L1 expression by immunohistochemistry in surgically resected NSCLC samples showed a significant association between PD-L1 expression and the presence of EGFR mutations independent of other clinical factors studied [64]. In preclinical models, EGFR mutation-
positive NSCLC may preferentially use PD-1/PD-L1-mediated mechanisms to evade immune surveillance [63]. In mouse models of lung cancer, tumors with different oncogenic drivers were characterized by distinct immune infiltrates [65]. Taken together, these data suggest the potentially distinctive effects on the immune microenvironment in individual genetic subsets of NSCLC. Further understanding of how NSCLCs with different genetic backgrounds shape the tumor immune milieu will help refine the use of active specific immunotherapy in NSCLC.

In conclusion, despite their ability to prime and expand tumor antigen-specific T cells, large phase III trials of several active specific immunostimulatory agents have yielded disappointing results in NSCLC. Several important issues need to be addressed to fully harness the therapeutic potential of antitumor immune responses induced by active immunotherapy. Strategies aimed at overcoming immune tolerance and improving the activation of antitumor T cells via combinatorial approaches may represent a new and more promising therapeutic application for active immunotherapies in NSCLC.

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**references**

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