What future opportunities may immuno-oncology provide for improving the treatment of patients with lung cancer?

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Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small-cell lung cancer (NSCLC) accounting for approximately 85% of all cases. Most patients with NSCLC are diagnosed at an advanced stage and have a poor prognosis, with a 5-year survival rate of <5%. Despite the introduction of new chemotherapeutic agents and molecularly targeted drugs, outcomes remain poor, emphasising the need for new treatment approaches. Inducing or potentiating immune responses via immunotherapeutic manipulation is a viable treatment approach for lung cancer. Antigen-specific, tumour-cell, and dendritic cell-based vaccines have all been evaluated in lung cancer, and some have shown promising clinical activity in phase II trials. These include liposomal BLP25 vaccine (L-BLP25), which targets mucin 1, and melanoma-associated antigen 3 (MAGE-A3) antigen-specific cancer immunotherapeutic (ASCI), which targets MAGE-A3, a peptide expressed almost exclusively on tumour cells. MAGE-A3 ASCI is being evaluated in the adjuvant setting in a phase III trial of patients with early-stage NSCLC, while a phase III trial of L-BLP25 is enrolling patients with unresectable stage III NSCLC. T-cell modulating agents (e.g. antibodies against programmed death 1 and cytotoxic T-lymphocyte-associated antigen-4 [CTLA-4]) are also being investigated. For example, in patients with NSCLC treated with paclitaxel and carboplatin, the phased administration of ipilimumab (an antibody against CTLA-4) resulted in substantial improvements in immune-related progression-free survival compared with chemotherapy alone (5.7 versus 4.6 months; P = 0.05). Immunotherapy in lung cancer is starting to deliver promising results in clinical trials. However, further research will be required to establish the optimal timing of therapy (i.e. in the adjuvant or metastatic settings). In addition, it will be important to determine if immunotherapies are most effective when used alone or in combination with other agents.

Key words: antibody, antigen-specific vaccines, extensive disease-small-cell lung cancer (ED-SCLC), immunotherapy, non-small-cell lung cancer (NSCLC), T-cell modulation

introduction

Lung cancer is the leading cause of cancer-related mortality worldwide in men, and is second only to breast cancer in women [1]. Approximately 85% of lung cancer cases are diagnosed as non-small-cell lung cancer (NSCLC), which can be histologically divided into different subtypes, the main three being squamous cell carcinoma, large cell carcinoma and adenocarcinoma [2, 3]. At the time of diagnosis, approximately 70% of NSCLC cases are locally advanced or metastatic [2]. Presently, the overall survival (OS) rates for advanced or metastatic NSCLC are poor; the 5-year survival rate is 5% for stage IIIB NSCLC (unresectable, locally advanced) and <1% for stage IV disease (distant metastases) [4].

Treatment decisions for NSCLC are driven by the patient’s clinical and tumour characteristics, including their performance status, the histological subtype of their tumour and tumour genotype or phenotype, such as mutations in epidermal growth factor receptor (EGFR) and the fusion oncogene EML4-ALK, in which the N-terminus of the echinoderm microtubule-associated protein-like 4 (EML4) is fused with the intracellular domain of anaplastic kinase (ALK) [5–7]. Platinum-based chemotherapy doublets are the standard first-line therapy for patients with advanced NSCLC [6, 8, 9]; however, in recent years, there has been much research into agents that target molecular mechanisms associated with tumour growth and proliferation. Examples of approved targeted agents include bevacizumab, a monoclonal antibody that binds to vascular endothelial growth factor-A, erlotinib and gefitinib, small molecule tyrosine kinase inhibitors (TKIs) that inhibit EGFR, and crizotinib, a TKI that inhibits EML4-ALK [10]. Despite much more progress in treatment, survival rates for advanced disease remain low and acquired resistance to targeted agents is a major clinical problem; therefore, alternative treatment options that yield durable responses and enhance OS remain an important focus of research [11].
Against this background, immunotherapeutic agents, such as cancer vaccines and antibodies that modulate T-cell activity, offer an alternative treatment approach that could potentially improve the prognosis of patients with this disease.

Immunotherapy utilises the immune system to control and potentially eradicate cancer. Despite limited success with older immunotherapies, such as interleukin-2, interferon and first-generation vaccines, treatment with novel immunotherapeutic agents has resulted in improved OS in phase III trials of patients with melanoma and prostate cancer, leading to US Food and Drug Administration approval of ipilimumab, a monoclonal antibody that modulates T-cell activity, for patients with unresectable or metastatic melanoma and sipuleucel-T, an autologous cellular vaccine, for patients with asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer [12–14].

Until recently, the field of immuno-oncology has mainly focused on melanoma and renal cell carcinoma. However, there is evidence to suggest that inducing or potentiating immune responses via immunotherapeutic manipulations may offer a viable therapeutic approach in many other tumour types, including lung cancer.

Retrospective analyses of tumour samples from lung cancer patients, for example, suggest that cellular immune responses against the tumour are associated with a favourable prognosis. In early-stage NSCLC, increased tumour infiltration of CD4+ /CD8+ T cells and/or mature dendritic cell/T-cell clusters has been shown to be independently associated with improved survival [15–19], with high expression of immunosuppressive, tumour-infiltrating T-regulatory (T_reg) cells associated with disease recurrence [20, 21]. Similarly, in an analysis of peripheral blood from 35 patients with small-cell lung cancer (SCLC), long-term survivors were shown to maintain a high immune effector T cell-to-T_reg ratio, whereas patients with recurrent disease exhibited a low ratio, suggesting that inducing T-cell responses while eliminating T_reg cells could help prevent systemic metastasis [22].

There is also evidence to suggest that chemotherapy, which is the standard treatment for patients with NSCLC, can elicit specific cellular responses that render tumour-cell death immunogenic, possibly potentiating the response to immunotherapies. Future successes may therefore include the development and clinical application of combined chemo- and immunotherapies [23, 24].

In light of this growing body of evidence, we are entering an exciting time in the field of immuno-oncology. Here, the available clinical data for several immunotherapeutic approaches in lung cancer are reviewed.

**vaccines**

Despite disappointing outcomes with early attempts to modulate the immune system via vaccine-based therapeutics, advances in our understanding of tumour immunology have sustained momentum in this area of immuno-oncology, supporting the development of more complex cancer vaccines, including antigen-specific, tumour-cell, and dendritic-cell-based vaccines (Table 1) [25]. Some of these vaccines are now in phase III development, including the liposomal BLP25 vaccine (L-BLP25) that targets mucin 1 (MUC1) and an antigen-specific strategy that targets melanoma-associated antigen 3 (MAGE-A3).

**MAGE-A3 antigen-specific cancer immunotherapeutic**

MAGE-A3 is expressed in 35–55% of NSCLC cases and is an independent predictor of poor outcomes in adenocarcinoma [26, 27]. MAGE-A3 antigen-specific cancer immunotherapeutic (ASCI) is being evaluated in the postoperative adjuvant setting, where it is thought vaccines may have the greatest clinical activity due to the minimal tumour burden [25]. Tumours can escape the immune system by establishing powerful immunosuppressive networks which allow them to grow. This tolerance towards immune responses may impede the results of therapy for advanced disease, but appears to be less of an issue for patients with reduced tumour burden. The reduction in absolute tumour volume to the level

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Table 1. Examples of immunotherapies in development for NSCLC

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<th>Immunomodulatory therapies</th>
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<tr>
<td>Phase II</td>
<td>BMS-936558 (anti-PD1 MAb)</td>
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<td>Telekin (scFv(F16) fused to IL-2)</td>
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<td>ImPrime PGG* (soluble PGG-glucan)</td>
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<td>Reolysin* (reovirus based)</td>
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<td>Phase III</td>
<td>Talactoferrin (iron-binding glycoprotein)</td>
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Source: AdisInsight, ClinicalTrials.gov.

ASCI, antigen-specific cancer immunotherapeutic; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; IL-2, interleukin 2; MAb, monoclonal antibody; mRNA, messenger ribonucleic acid; MUC1, mucin 1; PD, programmed death; PGG-glucan, polymers of poly-(1–6)-β-D-glucopyranosyl-(1–3)-β-D-glucopyranose.
of subclinical disease may therefore allow for a more stable and effective therapeutic response [28].

In a phase II trial, 182 patients with resected, MAGE-A3-positive, stage IB/II NSCLC received five doses of either MAGE-A3 ASCI or placebo every 3 weeks, followed by eight doses every 3 months [25, 27]. Patients who received MAGE-A3 ASCI had non-significant improvements in disease-free interval, disease-free survival and OS compared with patients who received placebo, with hazard ratios (HR) of 0.74 ($P = 0.107$), 0.73 ($P = 0.093$) and 0.66 ($P = 0.088$), respectively. A total of 1214 MAGE-A3 doses were given and grade 3/4 adverse events (AEs) were reported in 9.6% of patients [25].

MAGRIT (MAGE-A3 as Adjuvant non-small-cell lung Cancer ImmunoTherapy) is a phase III trial to evaluate MAGE-A3 ASCI in the adjuvant setting. With a planned enrollment of 2270 patients with resected MAGE-A3-positive NSCLC, it will be the largest ever trial in lung cancer (Figure 1) [29]. Patients will be randomly assigned 2:1 to receive either MAGE-A3 ASCI or placebo [25, 29]. The trial will also investigate the activity of MAGE-A3 ASCI in patients who have or have not received standard post-operative chemotherapy [29].

**L-BLP25**

MUC1 is a cell-surface glycoprotein known to be aberrantly expressed in various cancers, including breast, lung, pancreatic, ovarian, gastric and colon [30]. The L-BLP25 vaccine, which targets MUC1, comprises BLP25 lipopeptide, immunoadjuvant monophosphoryl lipid A and three lipids (cholesterol, dimyristoyl phosphatidylglycerol and dipalmitoyl phosphatidylcholine) to form a liposomal product [31].

In a phase IIb trial, pretreated patients with stage IIb/IV NSCLC were randomly assigned to receive treatment with either L-BLP25 plus best supportive care (BSC) or BSC alone. Three days prior to the administration of L-BLP25, patients were treated with a single, low dose of cyclophosphamide [31]. A subset analysis of patients with stage IIb locoregional NSCLC showed a trend for improved survival in those patients treated with L-BLP25 compared with BSC alone; median OS was 30.6 versus 13.3 months (HR: 0.55; $P = 0.16$) (Figure 2) [31, 32]. The most common L-BLP25-related AEs reported were grade 1 flu-like symptoms [31].

These promising results suggest vaccines may be more effective in patients with a lower tumour burden and no evidence of metastatic disease [33]. As a result, a phase III trial (Stimulating Targeted Antigenic Responses to NSCLC Trial; START) of L-BLP25 in patients with unresectable, stage III NSCLC is ongoing, with a planned enrollment of 1322 patients, making this the largest ever trial in stage III lung cancer (Figure 3) [33]. Enrolment into this phase III trial is dependent on patients achieving stable disease (SD) or objective response after first-line chemoradiotherapy (sequential or concomitant). Patients will be randomly assigned 2:1 to receive either L-BLP25 or placebo.
immunomodulatory agents
talactoferrin
Various immunomodulating agents are also being investigated in clinical trials for patients with lung cancer (Table 1). Talactoferrin (recombinant human lactoferrin) is an immunomodulatory iron-binding glycoprotein, known to activate lymphokine-activated killer cells and natural killer cells and to enhance the cytotoxicity of polymorphonuclear cells and macrophages [34]. In a recent phase II trial of 110 treatment-naive patients with locally advanced or metastatic NSCLC, patients received either talactoferrin or placebo in combination with carboplatin and paclitaxel (CP) [35]. Among 100 assessable patients, the response rate for patients receiving talactoferrin plus CP (47%) was higher than for patients receiving placebo plus CP (29%) (P = 0.05). OS was also greater for those receiving talactoferrin compared with placebo, although the difference was not significant (11.3 versus 8.5 months; HR: 0.75; P = 0.11). The most frequent grade 3/4 AEs reported were those commonly observed in patients with NSCLC undergoing treatment with chemotherapy, including myelotoxicity, gastrointestinal disorders and respiratory disorders. Significantly fewer AEs were reported in the talactoferrin group compared with the placebo group; 472 versus 569 (P = 0.003) for total AEs and 78 versus 105 (P = 0.05) for grade 3/4 AEs, possibly because talactoferrin accelerates reconstitution of the immune system and protects against chemotherapy-induced AEs such as irritant-induced enteropathy [35–38].

Two ongoing phase III trials are evaluating talactoferrin in patients with NSCLC. The design of one, FORTIS-C, is similar to the phase II trial, with treatment-naive patients receiving either talactoferrin or placebo in combination with CP (NCT00706862). The other, FORTIS-M, has been designed to investigate talactoferrin in pretreated patients compared with BSC (NCT00707304).

BMS-936558
PD1 (CD279), a member of the B7-CD28 superfamily, is a cell surface receptor that has two known ligands, PD-L1 (B7-H1) and PD-L2 (B7-DC) [39]. PD1 is inducibly expressed on activated CD4+ and CD8+ T cells, natural killer T cells, B cells, activated monocytes, and activated dendritic cells (DCs) [39–41]. The PD1 pathway is an important regulator of the induction and maintenance of peripheral tolerance, protecting tissues from autoimmune damage and maintaining a balance between T-cell activation and tolerance [42].

PD1 overexpression on CD8+ T cells has been observed in patients with NSCLC, with PD1+ CD8+ T cells having reduced capacity to produce cytokines and proliferate [43]. In addition, analysis of PD-L1 expression in patients with NSCLC identified a substantial increase in PD-L1-positive cells in tumour tissue compared with lung parenchyma adjacent to tumour (53.2% versus 4.8%, P = 0.004) [44]. In a multivariate analysis, PD-L1 expression on lung cancer cells correlated with poor prognosis and decreased OS.

It is hypothesised that blocking the PD1 pathway can restore/promote the function of chronically ‘exhausted’ tumour-specific T cells and diminish tumour-induced immune suppression [45].

In a phase I dose-escalation trial of a fully human monoclonal antibody (MAb) against PD1 (BMS-936558), patients with previously treated solid tumours, including NSCLC, received an initial 8-week treatment cycle, with the option of follow-up treatment dependent on the clinical response [46]. Results from this trial show clinical activity in some patients with NSCLC, with one patient (3 mg/kg anti-PD1) achieving a partial response for 14+ months and five patients achieving SD (10 mg/kg anti-PD1). Common AEs in the phase I trial included fatigue, pruritus, rash, diarrhoea and nausea. Grade 3/4 AEs were uncommon. These preliminary results are exciting but require further investigation to confirm the true efficacy and safety of this anti-PD1 MAb in patients with NSCLC.

Owing to the unique mechanism of action of antibodies against PD1, there is potential for synergistic activity with other anticancer therapies, including chemotherapy or other T-cell modulating agents.

ipilimumab
Another T-cell modulatory agent under investigation in lung cancer is ipilimumab, a fully human MAb against CTLA-4. Blocking the inhibitory signal from CTLA-4 potentiates T-cell activation, proliferation and infiltration into tumours, which may lead to tumour cell death [47]. In a phase II trial of ipilimumab 10 mg/kg in patients with stage IIIb/IV extensive disease (ED)-SCLC and NSCLC, patients were treated with CP either alone or in combination with ipilimumab (Figure 4) [48, 49]. Because the importance of treatment scheduling is not yet fully understood, one objective of this trial was to assess differences between the scheduling of agents relative to each other. Two dosing schedules were explored; concurrently with CP or after two rounds of CP (phased). The results of this trial showed a substantial improvement in immune-related progression-free survival (irPFS) and modified World Health Organisation PFS in patients with NSCLC who received the phased ipilimumab regimen compared with CP alone; 5.7 versus 4.6 months (HR: 0.72; P = 0.05) and 5.1 versus 4.2 months (HR: 0.69; P = 0.01).

Figure 3. The study design of the phase III trial of L-BLP25 (Stimulating Targeted Antigenic Responses to NSCLC Trial; START). ECOG PS, Eastern Cooperative Oncology Group Performance Status; L-BLP25, liposomal BLP-25 vaccine, which targets mucin 1; OR, objective response; NSCLC, non-small-cell lung cancer; PD, progressive disease; SC, subcutaneous; SD, stable disease.
months (HR: 0.69; \( P = 0.02 \)) for irPFS and modified WHO-PFS, respectively [48]. There was also a trend towards improved OS in patients with NSCLC who received the phased ipilimumab regimen compared with CP alone; 12.2 versus 8.3 months (HR: 0.87; \( P = 0.23 \)) [48]. Histological subanalysis of patients with NSCLC treated with the phased ipilimumab regimen indicated greater clinical activity in patients with squamous cell NSCLC compared with non-squamous cell NSCLC (Figure 5) although the results were not significant [48].

A phase III trial to investigate ipilimumab in combination with CP in patients with stage IV squamous cell NSCLC is open for enrolment (NCT01285609). This clinical trial has been designed to evaluate the concomitant scheduling of ipilimumab and CP and is estimated to enrol 920 patients.

Patients with ED-SCLC treated with the phased ipilimumab regimen also had a substantial improvement in irPFS: 6.4 versus 5.3 months (HR: 0.64; \( P = 0.03 \)) [49]. Although this observation needs to be confirmed in further clinical trials, it marks a potentially exciting development for patients with ED-SCLC. Despite many clinical trials, the survival of patients with ED-SCLC has not been significantly improved for nearly 30 years, highlighting the need for further development of novel agents [50]. The activity of ipilimumab plus carboplatin and etoposide chemotherapy in patients with ED-SCLC is being investigated in a phase II trial, currently open for enrolment (NCT01331525). A phase III trial is also planned to investigate the activity of etoposide and platinum therapy with or without ipilimumab in patients with ED-SCLC (NCT01450761).

The safety profile of ipilimumab in combination with CP in the phase II trial was generally consistent with other ipilimumab trials. The most common grade 3/4 treatment-related AEs experienced by patients with NSCLC treated with the phased ipilimumab regimen were anaemia (6%), diarrhoea (5%) and fatigue (5%) [48]. For patients with ED-SCLC, the most common grade 3/4 treatment-related AEs from the phased ipilimumab regimen were fatigue (12%), arthralgia (10%), diarrhoea (10%), neutropenia (10%), anaemia (10%), elevated levels of aspartate aminotransferase (7%) and thrombocytopenia (7%) [49]. Most of these AEs were managed with adequate treatments and, in general, the toxicity profile appeared better than reported in melanoma patients. This may be a result of the concomitant chemotherapy counteracting some of the AEs associated with ipilimumab.

**summary**

Preliminary evidence of clinical activity in trials of novel immunotherapeutic agents in patients with lung cancer is encouraging. In the case of cancer vaccines, phase II trials of MAGE-A3 ASCI and L-BLP25 show promising trends towards improved OS in stage Iib/II and III NSCLC, respectively. For immunomodulatory agents, phase II trials of talactoferrin plus CP and ipilimumab plus CP in patients with advanced NSCLC...
suggest OS and irPFS benefits, respectively. These promising results will hopefully be confirmed in the ongoing phase III trials; MAGRIT (MAGE-A3 ASCI), START (L-BLP25), FORTIS-C (talatocoferrin) and CA184-104 (ipilimumab).

Owing to the unique mechanisms of action of immunotherapeutic agents, there is great potential for immunotherapies to work synergistically with chemotherapies and molecularly targeted agents, making combinatorial strategies a key area of clinical research. The timing of immunotherapy and scheduling of different elements in combinatorial approaches represent ongoing challenges for outcome optimisation. This is exemplified by results from the phase II trial of ipilimumab plus CP in patients with advanced NSCLC or ED-SCLC, in which a phased regimen of ipilimumab appeared to provide greater efficacy than a concurrent regimen. In addition, understanding how patient characteristics and biomarkers may influence the choice of therapy will ensure that patients receive the most appropriate treatment and attain the maximum benefit possible. Through this we can hope to achieve what is being promised during the clinical development of immunotherapies in this setting.

disclosures

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references


