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REVIEW

Durvalumab: a potential maintenance therapy in surgery-ineligible non-small-cell lung cancer

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Abstract: Lung cancer is the most common cancer worldwide and the most common cause of cancer-related death. Non-small-cell lung cancer comprises ~87% of newly diagnosed cases of lung cancer, and nearly one-third of these patients have stage III disease. Despite improvements in the treatment of stage IV lung cancer, particularly with the introduction and dissemination of checkpoint inhibitors, very little progress has been made in the treatment of stage III lung cancer. In this article, we discuss the general staging criteria and treatment options for stage III lung cancer. We review how concurrent radiation and chemotherapy can have immunomodulatory effects, supporting the rationale for incorporating immunotherapy into existing treatment paradigms. Finally, we discuss the results of the PACIFIC trial and implications for the treatment of stage III lung cancer. In the PACIFIC trial, adding durvalumab as a maintenance therapy following the completion of chemoradiotherapy improved progression-free survival in patients with locally advanced unresectable stage III lung cancer. On the strength of these results, durvalumab has been approved by the US Food and Drug Administration for use in this setting, representing the first advance in the treatment of stage III lung cancer in nearly a decade.

Keywords: non-small-cell lung cancer, maintenance therapy, staging, immunotherapy, chemoradiation, surgery-ineligible, durvalumab

Introduction

Lung cancer is the most frequent cancer worldwide, with 1.8 million new cases in 2012 when it accounted for ~20% of cancer-related mortality, amounting to the deaths of 1.59 million people.[1] The highest rates of incidence globally occur in Central and Eastern Europe among men and Northern America and Northern Europe among women.[2] In common with general trends in other Western countries,[3] 87% (~194,000) of all new lung cancers in the USA are non-small-cell lung cancers (NSCLCs) of various histological cell types.[4]

As with all cancers, the treatment recommendations for NSCLC depend on correctly identifying stage. The outlook for stage IV lung cancer patients has improved, particularly with the introduction and dissemination of checkpoint inhibitors. However, over the past decade, little progress has been made in the treatment of stage III NSCLC, which represents almost one-third of cases. We examine current staging criteria and treatment options for stage III NSCLC and review how concurrent radiation and chemotherapy can have immunomodulatory effects, supporting the rationale for incorporating immunotherapy into existing treatment paradigms. We evaluate indications from recent and ongoing clinical trials that use this approach, with a particular

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focus on the PACIFIC trial and implications for the treatment of stage III lung cancer using durvalumab combined with chemoradiation.

Staging

As defined by the eighth edition of the American Joint Committee on Cancer's tumor, node, and metastasis-based classification for lung cancer and the International Association for the Study of Lung Cancer database grouping of patients, stage III disease affects a heterogeneous population of patients, with lymph node involvement outside of the lung (N2 or N3 nodes involved) and/or primary tumors that are locally invasive, unresectable, or borderline resectable.[5–7] Nearly one-third of new NSCLCs in the USA are stage IIIA–B, which represents a population of ~62,000 new patients each year. Because of the heterogeneity of this stage, treatment recommendations are best discussed in terms of patient subgroups, as described in the Robinson Classification of N2 Disease[8] that is now used by the 2015 European Society for Medical Oncology Consensus Guidelines on Locally Advanced Stage III NSCLC.[9]

A patient has stage $IIIA_1$ disease when incidental N2 node metastases are found on the final pathologic examination of their resection specimen.[8] Despite thorough preoperative staging that includes positron emission tomography (PET) scans, this situation is reported to occur in as many as 5–16% of clinical stage I–II patients; therefore, adjuvant chemotherapy is recommended.[10] Sequential radiotherapy is suggested, although this is based on limited retrospective data.[11]

Stage $IIIA_2$ refers to the intraoperative finding of single mediastinal node metastasis on frozen section – the so-called "unsuspected" or "surprise" N2.[8] Although it is controversial, most authorities and the most recent guidelines recommend proceeding with the planned resection, so long as a "complete resection of the mediastinal nodes and the primary tumor is technically possible" (R0 resection).[9,10,12] Similar to recommendations in the guidelines for stage $IIIA_1$ patients, adjuvant chemotherapy is recommended and sequential radiotherapy suggested for stage $IIIA_2$ patients who have undergone resection. In these two subgroups, when there is a complete R0 resection of stage T1 to T2 tumors, only a single positive N2 station is present, adjuvant therapy has been given, and the 5-year survival rates are quite good, ranging from 31 to 66%, depending on the series.[12,13]

Stage $IIIA_3$ refers to patients recognized by initial clinical and/or invasive staging to have discrete mediastinal N2 nodal involvement, often called "potentially resectable" disease (a subjective determination). Despite controversy derived from the often conflicting results of multiple studies, including those of randomized Phase III trials, current guidelines recommend that patients with good performance status, non-bulky (<2 cm diameter in short axis), resectable, single-node station disease should be evaluated by a knowledgeable multidisciplinary team. They should be considered for induction chemotherapy or chemoradiotherapy followed by complete R0 resection of the primary tumor and mediastinal nodes by a thoracic surgeon experienced in complex cases.[8–10] In this subgroup, recent randomized trials have demonstrated 5-year survival rates of up to 41%.[14] Nevertheless, only ≤25–30% of stage $IIIA_3$ patients are candidates for this multimodal therapy involving surgery.[15]

Approximately two-thirds of all stage IIIA patients can be classified as stage $IIIA_4$, presenting with unresectable, bulky, infiltrative multistation mediastinal-node disease.[15] Although the optimal treatment recommendations are still evolving, chemoradiotherapy is the preferred treatment modality, with sequential chemotherapy and radiation recommended if concurrent therapy is not tolerated. A median survival of up to 17 months and an overall 5-year survival of 16% can be expected.[9,10,16,17] Chemoradiotherapy is similarly recommended for the smaller number of patients with more advanced stage IIIB disease.

Therapeutic approaches

Durvalumab in NSCLC

Durvalumab is an IgG1 monoclonal antibody that specifically targets programmed death-ligand 1 (PD-L1).[18] In normal circumstances, PD-L1 is expressed on a variety of hematopoietic cells, including T lymphocytes (T cells), B lymphocytes (B cells), and dendritic cells (DCs), where it serves to regulate inflammatory responses.[19,20] It functions through interactions with programmed cell death protein 1 (PD-1) and cluster of differentiation 80 (CD80). Both PD-1 and CD80 can be found on antigen-presenting cells (APCs) and activated T cells. A hallmark of malignancy is an inflamed tumor microenvironment, a manifestation of which is the presence of gamma interferon. Gamma interferon recruits immune cells to a tumor, enhances tumor antigen presentation, and induces PD-L1 expression.[21,22] In the context of malignancy, tumor cells that express PD-L1 can inhibit antitumor T-cell responses through interaction with PD-L1 receptors.[19,23,24] PD-L1 found on T cells and APCs can also have an inhibitory effect by binding to CD80 found on those cells. Durvalumab binds to PD-L1 with high affinity, interrupting its interaction with PD-1 and CD80 and restoring T-cell activity.[18]

Durvalumab received accelerated approval in the USA in May 2017 for second-line use in patients with locally advanced or metastatic urothelial carcinoma. A Phase I/II trial with 191 urothelial carcinoma patients reported an objective response rate (ORR) of 17.8%.[25] The ORR was 27.6% in patients with high PD-L1 expression, as determined by the Ventana SP-263 anti-PD-L1 antibody assay.[26] Immune-related adverse events (AEs) of grade 3 or 4 severity occurred among only 2.1% of patients, and treatment-related AEs leading to the discontinuation of durvalumab were reported among only 2.8% of patients. However, the following two treatment-related deaths were reported: one episode of immune-mediated hepatitis and one episode of pneumonitis.

In a cohort of 304 patients with advanced and metastatic NSCLC, safety data were similarly encouraging.[27] Treatment-related AEs led to discontinuation among only 5% of patients; grade ≥3 AEs occurred among only 10% of patients; and pneumonitis occurred among only five patients, although in one case, it was grade 4 in severity and complicated by pneumonia, which ultimately led to the death of the patient.[25,27] Safety data in the subset of patients with treatment-naive disease were similarly encouraging.[28]

The Phase II ATLANTIC trial reported results of durvalumab given to patients with two or more lines of prior therapy. In this heavily pretreated population, ORRs were as high as 30.9% among patients with PD-L1 expression ≥90%.[29] Among those with moderately high expression, defined as PD-L1 expression ≥25%, the response rate was 16.4% and fell further to 7.5% among patients with low or negative PD-L1 expression. These findings were consistent with response rates seen in earlier Phase I studies.

Antibodies targeting the PD-1/PD-L1 axis, including nivolumab given at 3 mg/kg every 2 weeks, pembrolizumab given at 2 mg/kg every 3 weeks, and atezolizumab given at 1200 mg every 3 weeks, have improved responses and overall survival (OS) rates in previously treated, advanced NSCLC.[30–33] Pembrolizumab given at 200 mg every 3 weeks also demonstrated improved progression-free survival (PFS) and OS compared to standard chemotherapy as a first-line treatment in patients with PD-L1 expression ≥50%.[34] However, avelumab given at 10 mg/kg every 2 weeks failed to meet the prespecified endpoint of improved OS compared to docetaxel in previously treated NSCLC patients with PD-L1 expression ≥1%.[35] Durvalumab is safe and has encouraging efficacy data in similar patient populations. Investigators have been interested in incorporating these agents into existing treatment paradigms for stage III NSCLC.

Evidence for concurrent chemotherapy and radiotherapy

For patients with unresectable stage IIIA or IIIB disease, treatment with concurrent, platinum-based chemotherapy and radiotherapy is the standard of care.[36] Sequential chemotherapy was first shown to be more effective than radiotherapy alone in locally advanced unresectable lung cancer.[37,38] Follow-up studies and a meta-analysis demonstrated greater improvement with concurrent treatment than with sequential approaches.[17,39–41] Attempts to augment chemoradiotherapy with additional cytotoxic chemotherapy have generally been disappointing. Induction chemotherapy added to concurrent treatment with definitive doses of chemotherapy did not improve survival with statistical significance.[42] Similarly, the use of consolidation chemotherapy following concurrent treatment with definitive doses of cisplatin and etoposide showed promise in a Phase II trial in which results were compared with historical data. However, a follow-up Phase III trial was terminated early due to futility.[43,44] In practice, concurrent treatment with radiation and weekly radiosensitizing doses of carboplatin and paclitaxel is generally followed by two cycles of consolidation chemotherapy using systemic doses. However, trials that support this regimen have not assessed the value of the additional consolidation cycles of chemotherapy.[45]

Attempts at improving the efficacy outcomes of chemoradiotherapeutic approaches have been disappointing. A trial using maintenance gefinitib in patients who did not progress following concurrent chemotherapy and radiation was negative and closed after an interim analysis.[46] The trial, however, did not select for patients with activating epidermal growth factor receptor (EGFR) mutations. A trial using chemotherapy followed by chemoradiotherapy in the control arm investigated the addition of thalidomide during cycle 1 of induction and throughout concurrent therapy in the experimental arm. There was no statistically significant difference in survival between the two arms.[47] The addition of cetuximab to chemoradiotherapy using carboplatin, paclitaxel, and either 74 or 60 Gy did not provide benefit.[48] Bevacizumab was also studied as part of a consolidation regimen following the completion of concurrent therapy in high- and low-risk cohorts. The study was closed to high-risk patients following two episodes of fatal hemoptysis, and slow accrual eventually led to termination of the low-risk cohort.[49] Given these disappointing results and the survival benefits seen in the stage IV setting with the use of checkpoint inhibitors, interest has grown in exploring the use of these agents in the stage III setting.

Immunomodulatory changes associated with chemoradiotherapy

The preclinical scientific rationale for combining checkpoint inhibitors with radiation is robust and well documented. Cancers progress in an evolving immune environment.[50] Initially, the innate and adaptive immune systems can eliminate tumor cells. However, as tumor cells become less immunogenic and develop immunosuppressive properties, equilibrium and immune escape ultimately occur, leading to the progression of disease. Perhaps the first observed evidence suggesting an immunomodulatory effect of radiotherapy, one that can restore antitumor immune function is the abscopal effect. The abscopal effect refers to treatment-related changes at tumor sites distant from the area subjected to radiation.[51,52] The mechanisms behind this observation are not entirely clear but are suggestive of T-cell-mediated processes.[53–55] Through local tumor effects and improved antigen presentation, radiotherapy can activate T cells that recirculate and reject distant metastases.[52] Delivery of ionizing radiation to one of the two identical mammary carcinomas implanted in mouse models resulted in the regression of not only the treated tumor but also the untreated tumor.[54] The DC growth factor Flt3-ligand was used to improve DC-induced T-cell activation. Importantly, B-cell lymphoma cells implanted simultaneously were not affected. These results suggest that a tumor-specific response was primed by the local effects of radiation, producing distant disease control.

It is clear that radiotherapy produces an immunogenic form of cell death.[52,56] Radiotherapy enhances major histocompatibility complex I-mediated antitumor immunity through increased protein degradation, displayed on APCs, and recognition of antigen by cytotoxic T cells.[57] Ionizing radiation and some forms of cytotoxic chemotherapy increase the expression of calreticulin on tumor cells, facilitating phagocytosis by DCs and efficient antigen presentation.[58,59] Additionally, high mobility group box 1 release in the late stages of cell death seen with radiation treatment further improves APC function through toll-like receptor 4.[60,61] First apoptosis signal (FAS) gene expression in tumor cells is upregulated with sublethal doses of radiation in an adenocarcinoma model.[62] The Fas-receptor protein mediates apoptosis in tumor cells following radiation. It can sensitize tumors to the cytotoxic effects of radiation and improve the activity of cytotoxic T lymphocytes.[63]

In addition to the immunogenic form of cell death initiated by radiotherapy, there is evidence that T-cell infiltration of tumors can be modulated by radiotherapy. Low-dose gamma irradiation given to RT5 mice resulted in an increased T-cell infiltration in tumors. The highest level of infiltration was noted at 0.5 Gy, and the authors observed declining infiltrates at higher doses, due to dose-dependent lymphopenia. The authors hypothesized that normalization of the vasculature improves T-cell recruitment into tumor tissue.[64]

Despite the evidence suggesting that radiotherapy can improve antitumor immune responses, radiation treatment can trigger changes in the tumor microenvironment that may also dampen antitumor responses. Repopulation of cells at the site of irradiation includes myeloid-derived suppressor cells (MDSCs) and macrophages.[65–67] Radiation may also cause the upregulation of PD-L1 in tumor cells through interferon gamma-mediated processes.[68]

Chemotherapy also exerts immunomodulatory changes, with effects on regulatory T cells and MDSCs.[69,70] The cytotoxic apoptotic effects of chemotherapy on tumor cells can result in the upregulation of similar pathways to those seen with radiation treatment, including calreticulin and high mobility group box 1. The effects of chemotherapy vary with the specific agents and doses administered. Cyclophosphamide can be immunosuppressive at high doses but can deplete regulatory T cells at lower doses, increasing T-cell proliferation and natural killer cell lytic activity.[71] Gemcitabine can have similar effects on regulatory T cells.[72] MDSC can be depleted by agents such as fluorouracil, gemcitabine, and cyclophosphamide. Docetaxel and doxorubicin have been observed to induce a phenotypic change in the population of MDSCs from one that is less immunosuppressive to one that supports enhanced antitumor activity.[73]

There is a clear complex interplay among cytotoxic chemotherapy, radiotherapy, and immunotherapeutic agents. However, taken together, preclinical evidence of the effects of combining chemoradiotherapy and immunotherapy is intriguing. PD-L1-targeted approaches in particular can overcome immune-evasion mechanisms elicited by radiation and augment immune-mediated tumor control.

Previous immunotherapy approaches

Prior approaches integrating immunotherapy and chemoradiotherapy have demonstrated feasibility. Clear evidence of efficacy, however, has been lacking. A recent study using ipilimumab in the neoadjuvant setting offered encouraging safety data, supporting the use of checkpoint inhibitors in the periradiotherapeutic setting. The neoadjuvant chemotherapy regimen consisted of 175 mg/m^2 of paclitaxel with either 75 mg/m^2 of cisplatin or carboplatin area under curve 6 given for 3 cycles. Ipilimumab 10 mg/kg was added for cycles 2 and 3. Sixteen patients received either surgery with

postoperative radiation or concurrent chemotherapy and radiation, if they were not surgical candidates.[74] No grade 3 toxicities were seen in any patients, and importantly, the authors did not report any episodes of pneumonitis. Grade 1 or 2 odynophagia was the most common toxicity and was reported in 38% of patients.

Tecemotide (L-BLP25) is perhaps the best-studied immunotherapeutic agent that is administered with chemoradiotherapy. Tecemotide is a mucin 1-specific immunotherapy and is a synthetic peptide designed to induce T-cell responses to the mucin 1 that is expressed on the surface of tumors.[75,76] A single dose of cyclophosphamide is administered prior to the first dose of tecemotide to boost the T-cell responses.[77] Over a decade ago, a Phase IIB randomized trial compared tecemotide with best supportive care following the completion of first-line chemotherapy alone or chemoradiotherapy in stage IIIB/IV NSCLC patients. The initial OS data favored tecemotide but did not reach statistical significance. The improvement in OS was 4.4 months, representing a hazard ratio of 0.739 (95% confidence interval [CI], 0.509–1.073). A greater treatment effect was seen among stage IIIB patients with a hazard ratio of 0.524 (95% CI, 0.261–1.052).[78] Updated survival data from this trial reinforce the implications of these outcomes.[79]

The results of a Phase III trial comparing maintenance tecemotide with placebo in stage IIIB/IV patients who had not progressed on either prior chemotherapy or chemoradiotherapy offer insights into the interplay between radiation and immunotherapy.[80] The trial did not demonstrate improvement in median OS between the maintenance and placebo arms; however, it did suggest that the patients randomized to tecemotide within 12 weeks of completion of first-line treatment had better rates of OS compared to those on placebo. Additionally, patients who received radiation as a part of first-line treatment prior to tecemotide enjoyed an OS advantage. Taken together, these findings support the ideas that the proinflammatory milieu can have antitumor benefit when combined with immunotherapy and that this benefit might be time sensitive.

The Phase III START trial randomized patients with stages IIIA and IIIB NSCLC in a 2:1 fashion to receive placebo or tecemotide in the maintenance setting following the completion of concurrent or sequential chemotherapy and radiation.[75] After confirmation of stable disease or objective response, patients randomized to the intervention arm received tecemotide weekly for eight doses followed by treatments every 6 weeks until progression. Of the 1239 patients included in the primary analyses, 806 patients received concurrent treatment. The authors determined that tecemotide was not associated with an OS benefit in the general population of unresectable stage III patients; however, the trial did show a benefit for patients receiving concurrent chemoradiotherapy. The INSPIRE trial was subsequently designed to assess OS benefit in a concurrently treated population but was terminated early when a parallel Japanese Phase I/II trial in a similar population failed to show a survival benefit for tecemotide as a maintenance therapy.[81]

Maintenance immunotherapy following chemoradiation

While previous studies demonstrated the feasibility and safety of integrating immunotherapy with concurrent chemoradiotherapy, the PACIFIC trial was the first study to show a clear benefit for the approach. The data from this recently published trial support a new role for immunotherapy in the treatment of lung cancer.[82] The PACIFIC trial was a Phase III double-blind randomized placebo-controlled trial. Patients who did not progress following definitive platinum-based chemotherapy (≥2 cycles) concurrent with radiotherapy were enrolled. Patients were randomized in a 2:1 fashion to 10 mg/kg of durvalumab every 2 weeks versus a similarly administered placebo. The coprimary endpoints were PFS and OS. Patients were enrolled regardless of PD-L1 expression, and those with EGFR mutations were also eligible. A total of 713 patients were enrolled, with 709 patients ultimately receiving treatment.

The trial had a median follow-up time of 14.5 months, and the durvalumab and placebo arms were balanced in terms of patient characteristics (P=0.05). More patients in the durvalumab arm had PD-L1 tumor-cell expression scores >25%, although this was not statistically significant. The median PFS was 5.6 months in the placebo arm and 16.8 months in the durvalumab arm. In addition to the impressive PFS data, the ORR was significantly higher in the durvalumab arm than in the placebo arm (28.4 versus 16%, respectively; P=0.001). Responses in the placebo group were attributed to continued tumor regression following radiotherapy. Treatment with durvalumab also reduced the incidence of progression with brain metastases.

All-cause grade 5 events affected 21 (4.4%) patients in the treatment arm and 13 (5.6%) patients in the placebo arm. More pneumonitis of all grades was seen in the durvalumab arm; however, only 3.4% of patients in the durvalumab and 2.6% of patients in the placebo arms experienced serious grade 3 or 4 pneumonitis, which suggests that the pneumonitis rate was not significantly greater among patients treated with durvalumab.

On the basis of this trial, durvalumab was approved by the US Food and Drug Administration for use as a maintenance therapy following the completion of platinum-based chemoradiation in unresectable lung cancer.[83] The most favorable duration of maintenance treatment remains unknown, and only 42% of the patients randomized to durvalumab maintenance completed 12 months of therapy. Due to high false-positive rates when using PET, only computed tomography (CT) imaging was used to determine whether patients met the criteria for enrollment. Patients with undetected metastatic disease could, therefore, have been enrolled. Despite these issues, a significant difference in PFS was still seen. Ongoing trials in the adjuvant and maintenance settings are testing the efficacy of checkpoint inhibitors when given for up to 12 months, and future studies may investigate shorter courses of treatment.[84–87]

The optimal timing for the initiation of maintenance therapy is also unclear. Studies with tecemotide suggest a benefit to early initiation of treatment.[80] In the PACIFIC trial, the HR for patients randomized to durvalumab or placebo within 14 days of completion of chemoradiation was 0.39 (95% CI, 0.26–0.58) compared to 0.63 when randomization occurred between 14 and 72 days afterward. These results indicate that chemoradiation may promote a time-sensitive antitumor milieu. Alternatively, selection bias may explain these differences, with healthier patients undergoing randomization sooner after the completion of concurrent therapy than less healthy patients.

Patients in the PACIFIC trial received durvalumab or placebo within 6 weeks of completing chemoradiation. Nearly a third of patients had received a regimen of weekly carboplatin at area under curve 2 and 45 mg/m^2 of paclitaxel. Although these patients received 6–7 weekly doses, consolidation cycles of chemotherapy were not permitted on this trial. Even though general practice favors giving an additional two cycles of carboplatin and paclitaxel, it is not known whether this is in fact beneficial. The durvalumab and placebo arms were fairly well balanced in terms of patients treated with carboplatin and paclitaxel; 33% of the durvalumab-treated patients and 35% of the placebo-receiving patients got the combination. The omission of consolidation cycles of these drugs would not be expected to affect the PFS difference seen in the study.

The PFS of the PACIFIC control group was 5.6 months, which was lower than PFS results in previously reported trials. In the RTOG 0617 trial, the median PFS for patients who received 60 Gy of radiotherapy with concurrent carboplatin and paclitaxel was 11.8 months (95% CI, 102.0–14.3). RTOG 0617 measured PFS at the initiation of concurrent therapy, whereas PACIFIC measured PFS from the point at which patients were randomized to a maintenance therapy.[88] The median age in both trials was 64. The PFS of the control group in the PACIFIC trial was consistent with the results of the START study, in which patients were randomized to intervention or placebo arms following chemoradiotherapy.[75] PFS measured from the randomization point in the START trial was 8.4 months in the placebo arm. However, only 65% of patients on the START trial received concurrent therapy and it may not provide a robust comparison, even indirectly.

The PACIFIC trial did not select for PD-L1 expression levels or other molecular abnormalities. Patients with PD-L1 expression ≥25% demonstrated a hazard ratio of 0.41 (95% CI, 0.26–0.65) compared to placebo-treated patients, and those with expression levels <25% had a hazard ratio of 0.59 (95% CI, 0.43–0.82) by the same comparison. PD-L1 expression is an important but imperfect biomarker in the metastatic setting, but the PACIFIC trial suggests that it should not be used to select patients for durvalumab maintenance as groups with both high and low expressions benefited.[89] The subgroup of patients with EGFR mutations did not clearly benefit from durvalumab maintenance. These patients were equally represented in the durvalumab (6%) and placebo (5.9%) arms. The hazard ratio was 0.76 in this setting, and whether because of a small sample size or true lack of efficacy, the findings were not significant (95% CI, 0.35–1.64). Nevertheless, it is known that in the second-line metastatic setting, EGFR-mutant patients treated with checkpoint inhibitors do not share the same OS benefits as wild-type patients.[90] These data suggest a role for EGFR testing in the stage III setting and for additional trials specifically targeting EGFR-mutant patients.

The OS data for the PACIFIC trial are immature at the present time; however, in addition to the encouraging PFS data, responses in the durvalumab-treated arm have shown durability. Of patients who responded to the drug, 72.8% demonstrated ongoing responses at both 12 and 18 months.[82] Given the positive preliminary data, there is optimism that PFS will translate into OS benefits.[91] The PFS data alone indicate the first significant advancement in the treatment of stage III lung cancer in nearly a decade and a new standard of care.

Ongoing studies and future directions

Several clinical trials are investigating whether other immune checkpoint inhibitors can improve outcomes in stage III, locally advanced NSCLC. Table 1 summarizes trials

Table 1 Current ongoing clinical trials incorporating immunoncology drugs with definitive treatment for unresectable, stage III non-small-cell lung cancer

Immunotherapeutic agent	Phase	Trial number	Design	Status
Nivolumab	III	NCT02768558	Maintenance nivolumab following concurrent cisplatin, etoposide, and radiation	Active, not recruiting
Nivolumab	II	NCT02434081	Concurrent nivolumab with chemoradiotherapy and nivolumab in the maintenance setting	Recruiting
AGS-003-LNG (autologous dendritic cells)	II	NCT02662634	AGS-003-LNG concurrent with or sequential to chemoradiotherapy	Recruiting
Pembrolizumab	II	NCT02343952	Maintenance pembrolizumab following chemoradiotherapy	Active, not recruiting
Tecemotide	II	NCT00828009	Concurrent tecemotide with carboplatin, paclitaxel, and bevacizumab	Active, not recruiting
Pembrolizumab	I	NCT02621398	Concurrent pembrolizumab with chemoradiotherapy and pembrolizumab in the maintenance setting	Recruiting

incorporating immunotherapeutic agents in the treatment of locally advanced unresectable NSCLC. In NCT02768558, investigators are testing whether OS and/or PFS improve with nivolumab in the maintenance setting.[85] This is an active Phase III trial that is no longer recruiting participants and is similar in design to the PACIFIC trial. A Phase II single-arm pembrolizumab trial is also active but not recruiting participants.

In addition to maintenance or consolidation-only protocols, current trials are testing the safety and efficacy of immunotherapies given concurrently with chemotherapy and radiation. NCT02434081 is a Phase II trial with a primary endpoint of grade ≥3 pneumonitis, following the radiotherapy portion of the trial.[87] Four 360 mg doses of nivolumab will be given concurrently with chemoradiotherapy, and 480 mg doses of nivolumab will be given for up to 1 year following completion of the concurrent portion. NCT02987998 is recruiting patients with stage IIIA NSCLC to test the safety of pembrolizumab combined with neoadjuvant cisplatin, etoposide, and radiation.[92] The trial will include consolidation treatment with pembrolizumab following surgical resection. Although this is a distinctly different population from the PACIFIC trial, the importance of this study is its potential to define the safety of combining pembrolizumab with chemoradiotherapy. A second Phase I trial using pembrolizumab will assess safety when combined with carboplatin, paclitaxel, and radiotherapy.[93]

Despite negative results using single-agent tecemotide in the consolidation setting, an ongoing Phase II trial is testing whether adding bevacizumab to tecemotide following concurrent chemoradiotherapy is beneficial (NCT00828009).[94] In this study, which is no longer recruiting, patients receive carboplatin and paclitaxel with concurrent radiation. Patients also receive two cycles of consolidation chemotherapy prior to cyclophosphamide conditioning and tecemotide. A clear difference between this study and the PACIFIC trial is the use of consolidation chemotherapy, which was not allowed in the PACIFIC trial.

A Phase I trial is testing the safety of novel therapeutic agent AGS-003 in patients with stage III NSCLC (NCT02662634).[95] AGS-003 consists of autologous monocyte-derived DCs obtained from patients' tumor tissues.[96] The DCs are co-electroporated using tumor RNA, which allows the DCs to present tumor antigen via class I major histocompatibility complex. Additionally, synthetic CD40L RNA is included during electroporation to improve T-cell induction via IL-12 production. The four arms in this trial will test the safety of regimens that include AGS-003 given sequentially following chemotherapy and radiation and AGS-003 given concurrently with chemoradiotherapy.

There are no studies currently underway to evaluate the combining of checkpoint inhibitor regimens. Despite a small retrospective report describing encouraging safety data with ipilimumab in the periradiotherapy timeframe, it has generally been found that combining anti-PD-L1 checkpoint inhibitors with anti-CTLA4 antibodies increases immune-related toxicities.[97]

Conclusion

Durvalumab is the first immune checkpoint inhibitor to demonstrate a positive impact on median PFS for patients with unresectable stage III NSCLC, although OS data remain to be determined. Current ongoing studies will clarify the role of other checkpoint inhibitors and define the safety

of concurrent immunotherapies with radiation. Further research should focus on whether immunotherapy or targeted approaches are the best options for patients with activating mutations or other targetable molecular abnormalities.

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