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The Evolving Role of PD-L1 Inhibition in Non-Small Cell Lung Cancer: A Review of Durvalumab and Avelumab

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ABSTRACT

Non-small cell lung cancer (NSCLC) was traditionally associated with a poor prognosis. Between 2010 and 2016, the 5-years overall survival for all stages combined was about 25 percent. However, the recent use of immunotherapy has led to significant improvements in progression free survival (PFS) and overall survival (OS). Immune check point inhibitors enable the host immune system to mount a lethal response against tumor cells. Both PD-1 (nivolumab, pembrolizumab, cemipilimab) and PD-L1 inhibitors (atezolizumab and durvalumab) have been approved by the FDA for use in NSCLC, either as individual agents or in combination with platinum-based chemotherapy, radiation therapy, or other agents. As the future of immunotherapy for lung cancer continues to evolve, with multiple agents approved or in various stages of clinical research, it is imperative that we understand the mechanism of action, clinical activity, ongoing clinical trials, indications for use and toxicity for individual agents in addition to having general, basic knowledge about this new class of cancer therapeutics. In this review, we focus on two of the newer PD-L1 inhibitors, durvalumab and avelumab.

KEYOWRDS

Non-small cell lung cancer; Atezolizumab; Durvalumab; Avelumab; PD-1 inhibitor; PD-L1 inhibitor; Immune checkpoint inhibitor

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in the US alone with 136,000 deaths in 2020 [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases, with a combined stage 5-years survival of 25% [2]. For many decades, treatment for NSCLC included platinum-based frontline chemotherapy, which provided a median overall survival (OS) of 13.2 to 14.8 months for unresectable Stage III disease and 8 to 13 months for Stage IV disease [3,4]. Recently, immune checkpoint inhibitors (ICIs) have taken center stage for treatment in advanced NSCLC with significant improvements in progression-free survival (PFS), overall response rate (ORR), OS, and a more favorable toxicity

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profile when compared to chemotherapy [5].

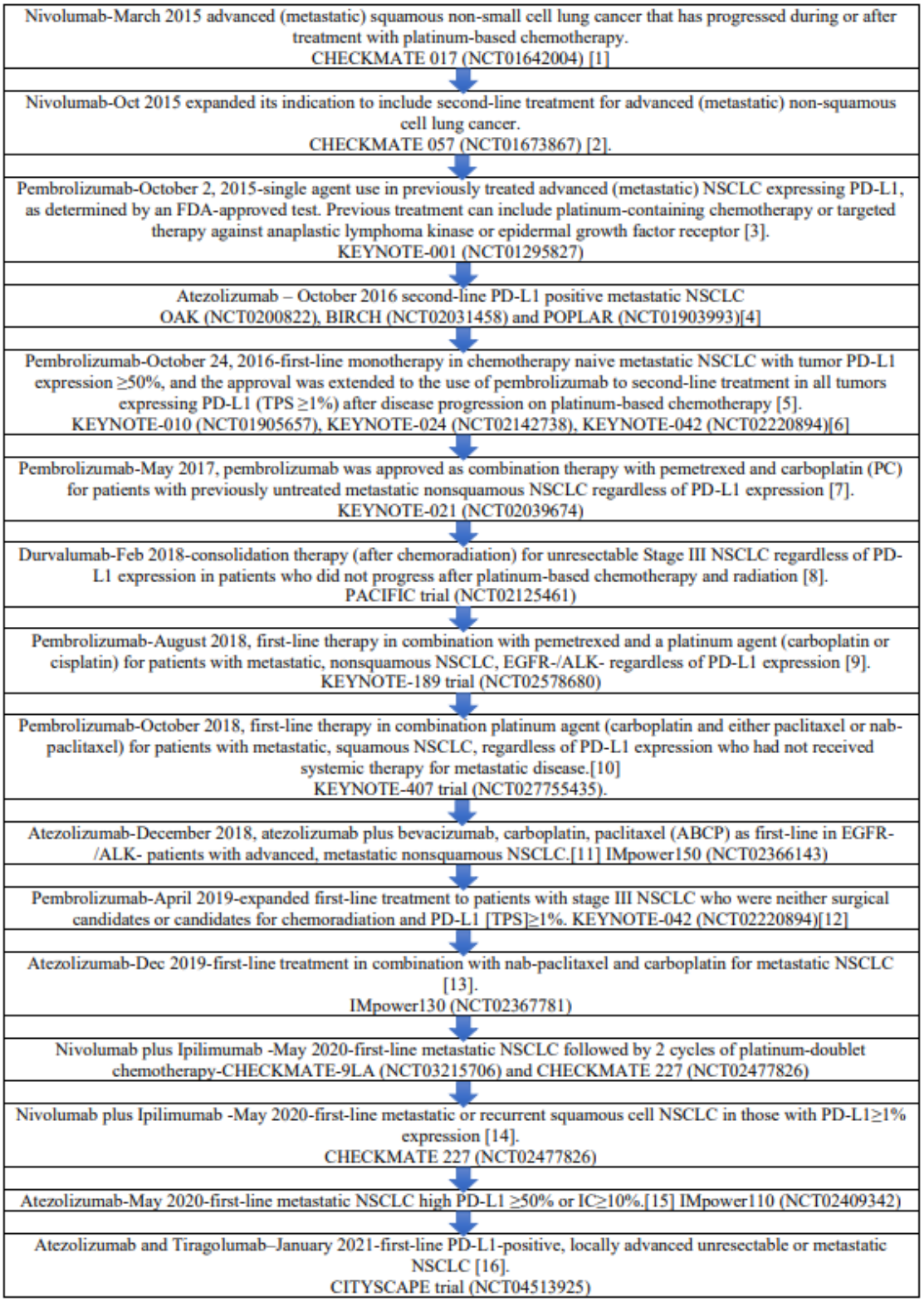

Figure 1: FDA approved ICIs in lung cancer: Timeline of drug-FDA approval date-indication-trial.
Abbreviation: TC: Tumor Cells; IC Tumor: Infiltrating Immune Cells; ICI: Immune Checkpoint Inhibitors

These agents stimulate the immune system to identify cancer cells as foreign and relieve immune-tolerance, and cause tumor cell death [6]. In particular, disengagement of programmed death ligand (PD-L1) and its receptor, programmed death protein (PD-1) using monoclonal antibodies to these molecules has been shown to be an effective strategy. PD-1 antagonists such as nivolumab, pembrolizumab, dostarlimab, cemipilimab and PD-L1 inhibitors such as atezolizumab, durvalumab, and avelumab are now widely used in treatment of various cancers. Figure 1 includes a timeline of the FDA approvals for PD-1 and PD-L1 inhibitors. This present review focuses on the newer PD-L1 inhibitors, durvalumab and avelumab.

COMPARISON OF MECHANISMS OF PD-1 AND PD-L1 INHIBITORS

PD-L1 receptors are often overexpressed on tumor cells and PD-1 receptors are present on T-cells. PD-L1 binding to PD-1 suppresses T-cell activation. ICI prevents this suppression by either blocking PD-L1 or PD-1. PD-1 inhibitors (nivolumab and pembrolizumab) have IgG4 receptors, whereas PD-L1 inhibitors (atezolizumab, durvalumab, avelumab) have IgG1 receptors. PD-L1 (also known as B7-H1 and CD274) and PD-L2 (also known as B7-DC or CD273), as demonstrated in Figure 2, are expressed on antigen presenting cells (APCs), T cells, B cells, monocytes, and epithelial cells and are upregulated in a number of cells responding to pro-inflammatory cytokines. PD-1 is inducibly expressed on T cells after activation by T-cell Receptor (TCR)-antigen-loaded Major Histocompatibility Complex (MHC) and CD28/B7 interaction. Activation of PD-1 on T cells dampens T cell response affecting IFN-, TNF- and IL-2 generation. Tumor cells express PD-L1, and through binding to PD-1 on T cells are able to escape immune surveillance. Inhibitors of PD-L1, such as durvalumab and avelumab, block the interaction between PD-L1 and PD-1, and PD-L1 with B7 (CD80, CD86), preventing suppression of T cell response, as shown in Figure 2.

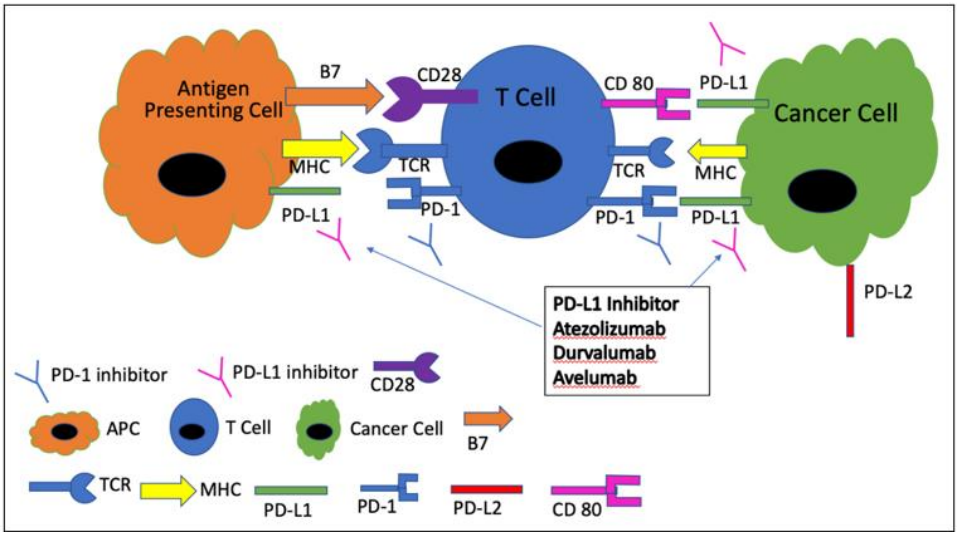

Figure 2: Inhibition of the programmed death pathway-mAbs against PD-1 and PD-L1.

Notes: PD-1 are expressed on T cells and inhibit the immune response after engagement with PD-L1 and PD-L2, expressed on APCs and/or tumor cells. PD-L1 also binds CD-80 receptors on activated T cells, further dampening the immune response. mABs bind PD-L1 receptors on APCs and tumor cells and limit the interaction of PD-L1 with PD-1 and CD-80 receptors on T cells. As a result, antigens released from tumor cells and presented on MHC on APCs and tumor cells activate T cells and subsequently alert the immune system to destroy the tumor cells.

COMPARISON OF AEs

Compared with chemotherapy, PD-1 and PD-L1 inhibitors have lower risk of AEs, such as high-grade fatigue, sensory neuropathy, diarrhea, nausea, and constipation. However, there is an increased risk of auto-immune reactions with PD-1 and PD-L1 inhibitors compared to chemotherapy, including rash, pruritis, aminotransferase elevations, colitis, hypo- and hyper-thyroidism and pneumonitis [7]. In general, adverse effects from checkpoint inhibitors PD-1/PD-L1 are related to the activation of autoimmune pathophysiological processes. These side effects are more often mild and may involve many organs; these include fatigue, encephalitis, uveitis, myocarditis, hepatitis, glomerulonephritis, thrombocytopenia, pancreatitis, colitis, vasculitis, enteritis, dermatomyositis, myositis, and arthritis [8]. The most common side effects of checkpoint inhibitors are diarrhea, pneumonitis, rash, hormone imbalances, and infections [9]. Pillai et al. conducted a systematic review comparing the adverse effects of PD-1 inhibitors (nivolumab and pembrolizumab) versus PD-L1 (atezolizumab, durvalumab and avelumab) inhibitors used as monotherapy to treat NSCLC. 23 studies were included, excluding phase I trials with less than ten patients and trials using ICIs in combination with chemotherapy [10]. Overall, 5,744 patients were included and evaluated for toxicity; 3,284 were treated with PD-1 and 2,460 were treated with PD-L1 inhibitors. Fatigue was the most commonly reported adverse effect in both groups while the most common immune-related adverse event (irAE) was hypothyroidism (6.7% *vs.* 4.2%; $p = 0.07$). The authors did not find any significant difference in overall adverse effects or immune-related adverse effects; however, it is worth noting that the incidence of pneumonitis was higher in the PD-1 treatment group (4% *vs.* 2%; $p = 0.01$). Additionally, any grade of immune related adverse events (irAEs) was slightly higher in the PD-1 treatment group vs PD-L1 group (16% *vs.* 11%; $p = 0.07$), even though the difference was not statistically different in this study. There was also a higher incidence of pneumonitis with the use of PD-1 inhibitors compared with PD-L1 inhibitors [11].

PD-L1 INHIBITORS IN NSCLC

Several PD-L1 inhibitors have been explored in clinical trials for the treatment of NSCLC (Figure 1). Only two agents have thus far obtained approval from FDA for this indication, namely atezolizumab and durvalumab.

Atezolizumab was the first PD-L1 inhibitor to be approved by the FDA for previously treated NSCLC patients, as demonstrated in Figure 1. It was approved as monotherapy for patients with NSCLC who had progressed on platinum doublet in October 2016, as a result of three studies: The Phase III POPLAR randomized control trial (RCT), which explored its use in patients with advanced NSCLC who progressed after chemotherapy [12], the OAK trial, a Phase III open-label RCT, which examined atezolizumab as second- or third-line treatment in patients with advanced NSCLC [13], and the Phase II BIRCH trial, which explored using atezolizumab in patients with advanced NSCLC with PD-L1 expression >5% as monotherapy [14]. Subsequently, Atezolizumab was approved in December 2018 as first-line in metastatic non-squamous NSCLC when combined with bevacizumab, carboplatin, and paclitaxel. In December 2019 its approval extended to first line use in combination with nab-paclitaxel and carboplatin for metastatic NSCLC. Its approval was expanded in May 2020 as monotherapy in first-line treatment in metastatic NSCLC in those with high PD-L1 (PD-L1 ≥50%). With this background information, we now turn to the two PD-L1 inhibitors, durvalumab and avelumab, which are the focus of this review.

DURVALUMAB

Durvalumab (MEDI4736, IMFINZI) is a high-affinity IgG1-kappa human monoclonal antibody (mAb) against PD-L1, that blocks PD-L1 binding to PD-1 and CD80 (aka B7-1). It is constitutively expressed on immune cells of

myeloid lineages and is inducibly expressed on activated T cells, NK and B lymphocytes, epithelial and endothelial cells once stimulated by inflammatory factors; it thereby suppresses both the adaptive and innate immune responses [15]. PD-L1 is also expressed on tumor cells and tumor-infiltrating cells. Like atezolizumab, durvalumab is designed to eliminate Fc-gamma-receptor-binding (FCγR) and effector functions (Table 1). Its Fc domain has a triple mutation designed to reduce antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [16]. ADCC is part of our innate immune system, whereby antibodies bind to membrane-surface antigens, permitting an effector cell (such as natural killer cells, macrophages, neutrophils and eosinophils) to lyse a target cell. By minimizing the interaction of its Fc with FCγR on effector cells, it avoids effector cells secretion of cytolytic enzymes. Additionally, the mutation of the Fc-portion minimizes interaction with C1q (the subcomponent of the C1 complex in the classical complement pathway) thereby preventing activation of complement-dependent cytotoxicity (CDC). This is thought to result in fewer immune related toxicities.

METABOLISM

Monoclonal antibodies, especially those targeting membrane receptors like durvalumab, undergo target-mediated drug disposition (TMDD). TMDD, which is a dose-dependent process, occurs when drug-target binding (complex with receptors, enzymes and transporters) ensues with subsequent dissociation and drug-target complex degradation. In early phase studies, durvalumab exhibited TMDD at doses <3 mg/kg and linearity was approached at doses ≥3 mg/kg [17].

	Mechanism of Action	Metabolism	Pharmacokinetics	FDA Approvals for NSCLC
Durvalumab	Triple mutation on the Fc Portion Designed to Reduce Antibody-Dependent Cellular Cytotoxicity (ADCC) and Complement-Dependent Cytotoxicity (CDC).	Like other mAb, Proteolytic Degradation to Small Peptides and Individual Amino Acids and Receptor-Mediated Clearance	**Durvalumab:** 10 mg/kg Every 2 Weeks Intravenous Dosing would Result in Optimal Exposure Levels of Above 50 µg/mL Over the Entire Dosing Interval. In Addition, Two Flat Dosing Regimens (750 mg Every 2 Weeks and 1500 mg Every 4 Weeks). Estimated Half-Life of 17 days.	- **February 2018:** Consolidation Immunotherapy for Eligible Patients (Performance Status 0-1), Regardless of PD-L1 Status, For Patients with Unresectable Stage III NSCLC who have not Progressed after 2 Cycles of Platinum-Based Chemotherapy
Atezolizumab	Same as Above	Same as Above	**Atezolizumab:** 0.01 mg/kg - 20 mg/kg Administered Every 3 Weeks Including the Fixed Prescribing Dose of 1200 Mg. Dose range of 1 mg/kg - 20 mg/kg. Estimated Half-Life of 27 Days.	- **October 2016:** Monotherapy for Patients with NSCLC who had Progressed on Platinum Doublet in October 2016 - **December 2018:** First Line in Metastatic Non-squamous NSCLC when Combined with Bevacizumab, Carboplatin, and Paclitaxel. - **December 2019:** First Line Use in Combination with Nab-Paclitaxel and Carboplatin for Metastatic NSCLC. - **May 2020:** Monotherapy in First-Line Treatment in Metastatic NSCLC in those with High PD-L1 (PD-L1 ≥50%) or IC ≥10%. - **January 2021:** In Combination with Tiragolumab as First Line PD-L1-Positive, Locally Advanced Unresectable or Metastatic NSCLC
Avelumab	No Mutation on the Fc Portion.	Same as Above	**Avelumab:** 10 mg/kg as an IV Infusion Over 60 Minutes Every 2 Weeks Until Disease Progression or Unacceptable Toxicity. Steady-State Concentrations are Reached after Approximately 4 Weeks to 6 Weeks of Repeated Dosing. The Half-Life of Avelumab is Approximately 6.1 Days	No FDA Approvals

Table 1: Differences between atezolizumab, durvalumab, and avelumab.

PHARMACOKINETICS

The estimated geometric mean terminal half-life of durvalumab is 17 days. Pharmacokinetic models in adult patients have established that 10 mg/kg every 2 weeks intravenous dosing would result in optimal exposure levels of above 50 µg/mL over the entire dosing interval, with the majority of patients achieving complete saturation of both soluble and membrane-bound PD-L1 in serum. In addition, two flat dosing regimens (750 mg every 2 weeks and 1500 mg every 4 weeks) have been established to be comparable to 10 mg/kg dosing.

EARLY-PHASE TRIALS

Durvalumab was first tested in a phase I/II study on patients with advanced solid tumors, which included those with advanced NSCLC (NCT01693562) [18,19]. 304 patients received durvalumab 10 mg/kg IV every two weeks for up to 12 months (or until disease progression or unacceptable toxicity) with an ORR of 17.5% (ORR of 27.1% for treatment-naive compared to 13.0% in heavily pretreated patients). For those with ≥25% PD-L1 expression, ORR were 25.3% compared with 6.1% for those with PD-L1<25%. Another Phase I/II study evaluated durvalumab in front-line as well as subsequent treatment in patients with stage IIIB/IV NSCLC and the results were presented at ESMO in 2016 (NCT02572843) [20,21]. High expression of PD-L1 was defined as at least 25% of tumor cells (TC) staining for PD-L1. 304 patients with NSCLC were enrolled, with 53% having squamous cell and 47% non-squamous cell histology. Fifty patients had responses, including 25% of those with high PD-L1 expression and 6% of those with low PD-L1 expression. OS at 1 year was 56% for high PD-L1 patients receiving durvalumab as second line and 37% for low expressors. For those receiving the drug as third-line, OS at 1 year was 51% in PD-L1 high expressors and 37% in low expressors. mOS for second line use in high expressors was 17.8 months compared to 8.2 months in low expressors; and mOS for third-line treatment was 13 months compared to 7.6 months for high and low expressors, respectively.

PHASE II TRIALS

The Phase II ATLANTIC study (NCT02087423) investigated durvalumab as third-line or later in NSCLC and its results were first presented at the International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer in 2016 [22]. Cohort 1 patients had EGFR+/ALK+ NSCLC with high and low PD-L1 tumor expression. Cohorts 2 and 3 were patients with EGFR-/ALK- NSCLC. Cohort 2 included 146 patients with high PD-L1 expression of ≥25% and 93 patients with low expression of <25% PD-L1 expression, and Cohort 3 patients included high expressors with ≥90% PD-L1 tumor expression. Cohorts 2 and 3 achieved higher response than Cohort 1. Cohort 2 patients receiving durvalumab had a median ORR of 16.4% and 7.5% and disease control rate (DCR) of 28.8% and 20.4% for high and low expressors, respectively. The mOS was 10.9 months compared to 9.3 months, mPFS 3.3 months vs 1.9 months, and 1 year OS 47.7% *vs.* 34.5% for high versus low expressors, respectively. Cohort 3 included 68 patients with ≥90% TC staining and achieved an ORR of 30.9%, DCR 38.2%, mPFS of 2.4 months and 1 year OS 50.8%. mOS was not reached. In the ATLANTIC study, 12 months and 24 months OS rates were increased with higher PD-L1 expression, regardless of EGFR/ALK status [23].

PHASE III TRIALS AND FDA APPROVALS

The strategy of combining radiation with checkpoint inhibitors has robust preclinical data [24]. As cancer evolves, immune escape through loss of antigen presentation enables it to evade the immune system from elimination. Radiation may ‘unmask’ tumor antigens and induce tumor recognition, especially when combined with immunotherapy which increases the potential for immune cells to recognize tumor antigens [25]. The PACIFIC trial (NCT02125461) was a phase III, 2:1 randomized, double-blind, placebo controlled,

multi-center trial which exploited this strategy in locally advanced NSCLC. The study assessed durvalumab as consolidation after chemoradiation in patients with Stage III NSCLC who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy [26]. PD-L1 expression was tested, but expression status was not mandatory for inclusion. 473 patients received durvalumab 10 mg/kg IV every 2 weeks and 236 patients received placebo. mPFS was 16.8 months with durvalumab compared to 5.6 months with placebo (hazard ratio 0.52; 95% CI 0.42-0.65; p <0.001). ORR was 28.4% with durvalumab compared to 16% for placebo. 12 months PFS was 55.9% *vs.* 35.3% and 18-month PFS was 44.2% compared with 27%. Median time to death or distant metastasis was 28.3 months with durvalumab compared to 17.1 months with placebo. The safety profile of durvalumab was consistent with that of other immunotherapies, although the incidence of pneumonitis was increased with both placebo and durvalumab; this was expected after treatment with definitive chemoradiotherapy.

In a more recent publication analyzing the PACIFIC trial's second primary endpoint (OS), 12 months OS was 83.1% in the durvalumab arm compared to 75.3% in the placebo arm [27]. 24 months OS was 66.3% compared to 55.6% in the placebo arm. There was a lower incidence of new brain metastases of 6.3% compared to 11.8% in placebo. At the 2019 American Society of Clinical Oncology (ASCO) meeting, updated study data was presented, which showed continued improvement of OS with durvalumab with median OS was 38.4 months in durvalumab arm compared with 29.1 months with the placebo arm [28]. Consolidation immunotherapy with durvalumab following CRT has revolutionized treatment for patients with advanced NSCLC. This was a practice-changing study and on February 16th 2018, FDA approved durvalumab; the indication of approval was for consolidation immunotherapy for eligible patients (performance status 0-1), regardless of PD-L1 status, for patients with unresectable Stage III NSCLC who have not progressed after 2 cycles of platinum-based chemotherapy [29]. National Comprehensive Cancer Network (NCCN) and the European Medicines Agency (EMA) have updated their guidelines to include durvalumab as consolidation therapy in Stage III disease after CRT, with PD-L1 ≥1% in tumor cells [19].

Durvalumab has also been studied as front-line therapy in patients with metastatic NSCLC. The MYSTIC study (NCT02453282) examined durvalumab as monotherapy or in combination with the CTLA-4 inhibitor tremelimumab (MEDI14736) and compared it with standard platinum-based doublet chemotherapy [30]. CTLA-4 is an inhibitory surface receptor expressed on activated dendritic cells and cytotoxic T-cells. It has a high affinity for B7 expressed on APCs, which binds to CD28 found on T cells, thereby competing for B7 binding and restoring CD28/B7 interactions. This in turn stimulates T-cell and IL-2 secretion. The study failed to reach its primary endpoint of OS for durvalumab versus chemotherapy when assessed in patients with ≥25% tumor cells expressing PD-L1. mOS was 16.3 months with durvalumab *vs.* 12.9 months with chemotherapy (HR, 0.76; 97.54% CI, 0.56-1.02; P = 0.4). In addition, the primary end point of OS and PFS for durvalumab and tremelimumab versus chemotherapy was also not achieved with a mOS for durvalumab plus tremelimumab of 11.9 months (HR, 0.85, 98.77% CI, 0.61-1.17; P = 0.20). However, in patients with blood tumor mutational burden (bTMB) ≥20 mutation per mega base, durvalumab and tremelimumab improved OS compared with chemotherapy at 22 months versus 10 months (HR 0.49, 95% CI, 0.32-0.74). Ongoing Phase III trials that continue to evaluate durvalumab as monotherapy and in combination with tremelimumab as first-time treatment for advanced NSCLC include PEARL (NCT03003962), POSEIDON (NCT03164616) and NEPTUNE (NCT02542293).

Study Name/Phase	Disease/Setting	Treatment Arms	Details	NCT Number
PACIFIC-2 Phase III	Locally Advanced, Unresectable NSCLC (Stage III)	Durvalumab + Platinum-based CRT *vs.* Placebo + Platinum-based CRT	Randomized, Placebo-Controlled, Double-Blind, Multi-Center, International Study of Durvalumab or Placebo in Combination with RT and One of the Following Chemotherapeutic Agents: Cisplatin/Etoposide, Carboplatin/Paclitaxel, Pemetrexed/Cisplatin or Pemetrexed/Carboplatin Primary Outcome: PFS	NCT03519971
Phase 1/phase 1b	Advanced Solid Malignancy in NSCLC, Gastric, Breast and Ovarian Cancer	Ceralasertib vs Ceralasertib + Olaparib *vs*. Durvalumab + Ceralasertib	Modular, Phase I, Open-Label, Multi-Center, 3-Arm Study of Ceralasertib in Combination with Carboplatin, Ceralasertib with Olaparib, and Ceralasertib with Durvalumab Primary Outcome: Safety and Tolerability AE and SAE (Including Death	NCT02264678
NEPTUNE/Phase III	Advanced or Metastatic NSCLC	Durvalumab + Tremelimumab *vs*. Chemotherapy SoC	Phase III, Randomized, Open-Label, Multi-Center, Global Study Comparing the Combination of Durvalumab Plus Tremelimumab (CTLA-4 inhibitor) Compared with Chemotherapy Standard of Care Primary Outcome: OS	NCT02542293
Phase I/II	Stage IV NSCLC	Durvalumab + Tremelimumab + Intermittent or Continuous Selumetinib	Phase I, Dose-Escalation Study of Selumetinib Followed by a Phase II Study with 2-Arms: Selumetinib BID on Days 1-7 and on Days 15-21 + Durvalumab + Tremelimumab in Arm 1, Selumetinib BID on Days 1-28 + Durvalumab + Tremelimumab in Arm 2 Primary Outcome: To determine the maximum tolerated dose, PFS	NCT03581487
HUDSON/Phase II	Metastatic NSCLC who have Progressed on an PD-1/PD-L1 Containing Therapy	Durvalumab + Olaparib, Durvalumab + AZD9150, Durvalumab + AZD6738, Durvalumab + Vistusertib, Durvalumab + Oleclumab, Durvalumab + Trastuzumab	Open-Label, Multicentre, umbrella Phase II of Patient who Progressed on ICI and Platinum-Doublet Therapies Primary Outcome: To Determine the Efficacy, Safety and Tolerability of Multiple Treatment Arms	NCT03334617
Phase 1B and Phase 2	**S**elected Advanced or Metastatic Solid Tumors Including NSCLC	Obinutuzumab + Durvalumab, Naptumomab Estafenatox + Durvalumab	Phase 1b, Open-Label, Multicentre, Prospective, Dose-Finding and MTD Cohort Expansion Study with Previously Treated Solid Tumors with High Likelihood of 5T4 Antigen Expression on Tumor Cells Including NSCLC Primary Outcome: To Determine the Efficacy, Safety and Tolerability of Multiple Treatment Arms	NCT03983954
Phase III	Locally Advanced, Unresectable Stage III NSCLC not Progressed after Concurrent Platinum-based Chemoradiation	Atezolizumab + Tiragolumab *vs*. Durvalumab	Open-Label, Randomized Primary Outcome: PFS	NCT04513925
Phase 1B	Stage I-IIIA NSCLC	Sirolimus + Durvalumab	Open-Label, Single Group Assignment Neoadjuvant Therapy of Sirolimus Followed by Durvalumab In Resectable NSCLC Primary Outcome: Evaluate the Efficacy of this Combined Treatment as Neoadjuvant Treatment for Stage I, II, and IIIA NSCLC and to Evaluate Response in Patients with PD-L1 Positive Versus PD-L1 Negative Tumors	NCT04348292
ASTEROID/Phase 2	Stage I NSCLC	Ablative Stereotactic Radiotherapy with Durvalumab	Randomized, Open-Label with Durvalumab Following Stereotactic Body Radiotherapy in Patients with Stage I NSCLC Primary Outcome: Time to Progression	NCT03446547
QUILT-3.55/Phase IIB	Advanced NSCLC	Stereotactic Body Radiotherapy (SBRT) + Follow-up *vs.* SBRT Followed by Durvalumab	Randomized, Open-Label Multicentre Study of Durvalumab Following SBRT. Primary Outcome: Time to Progression	NCT03228667
JAVELIN Medley/Phase 1B/II	Locally Advanced or Metastatic Solid Tumors (Such as NSCLC)	Avelumab + Utomilumab (4-1BB Agonist mAb), Avelumab + Plus PF-04518600 (OX40 Agonist mAb), Avelumab + PD 0360324 (M-CSF-mAb), Avelumab + Utomilumab Plus PF-04518600, Avelumab + CMP-001 (TLR9 Agonist) and these Agents in other Combinations	Open-Label Multicentre, Multiple-Dose, Safety, Clinical Activity, PK, and PD Study of Avelumab in Combination with Other Immune Modulators with Locally Advanced or Metastatic Solid Tumors (including NSCLC). Primary Outcome: Dose-Limiting Toxicities (DLT) and Objective Response	NCT02554812
Other Currently Recruiting Trials for Durvalumab not Listed in the Table: NCT04716946, NCT04612751, NCT04392505, NCT04385368, NCT04351256, NCT04348292, NCT04202809, NCT04163432, NCT04026412, NCT03975114, NCT03955198, NCT03944772, NCT03819465, NCT03800134, NCT03732274, NCT03706690, NCT03620669, NCT03345810, NCT03228667, NCT03164616, NCT02879617				

Table 2: Selected trials with durvalumab and avelumab currently recruiting patients.

OTHER ONGOING CLINICAL TRIALS

Although durvalumab has only been FDA approved for consolidation therapy (after chemoradiation) for unresectable Stage III NSCLC, there are >60 active clinical trials recruiting patients for various scenarios in NSCLC. Many of these are exploring its use in Stage III and Stage IV NSCLC, either as monotherapy or in combination with chemoradiotherapy or other agents. The PACIFIC-2 trial (NCT03519971), a Phase III study, is examining the concurrent use of durvalumab with chemoradiation [31]. Other trials are combining durvalumab with agents including the serine/threonine protein kinase ATR Ceralasertib (AZD6738) (NCT02264678) [32] the CTLA-4 inhibitor Tremelimumab (NCT02542293) [33] (NCT02352948) [34] the mitogen-activated protein kinase inhibitor Selumetinib (AZD6244) (NCT03581487) [35] the poly ADP ribose polymerase inhibitor Olaparib (NCT03334617) [36] and the 5T4 tumor antigen activator Naptumomab (NCT03983954) [37] as highlighted in Table 2.

ADVERSE EFFECTS OF DURVALUMAB

Side effect profile of durvalumab is similar to that of other checkpoint inhibitors. Antonia et al. demonstrated that 57% of patients experienced adverse events which included fatigue (17%), hyporexia (9%) and diarrhea (9%), leading to discontinuation in 5% of patients [20]. These results were similar to what were observed in the ATLANTIC and the PACIFIC trials confirming the excellent tolerability profile of the drug. In the PACIFIC trial, grade 3-4 adverse event rate in the durvalumab arm was comparable to the placebo arm (29.9% *vs.* 26.1%). Pneumonitis which occurred in 6.3% of patient compared to 4.3% in placebo and pneumonia which was reported in 1.1% of patients in durvalumab arm and 1.3% in placebo arm were the most frequent adverse effects resulting in discontinuation of the treatment. Death from adverse events occurred in 4.4% of the durvalumab group compared with 5.6% of the placebo group.

AVELUMAB

Avelumab (MSB0010718C) is a fully human IgG1 anti-PD-L1 monoclonal antibody. Avelumab effectively blocks PD-1/PD-L1 interaction, but unlike durvalumab and atezolizumab it retains a native constant fragment (Fc) region which enables ADCC inducing NK cell-mediated tumor cell lysis. As a result, avelumab activates both the adaptive and innate immune function.

METABOLISM

Avelumab undergoes nonspecific proteolytic degradation, which is typically catalyzed by protease enzymes.

PHARMACOKINETICS

The recommended dose of avelumab is 10 mg/kg as an IV infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. Patients should be premedicated with an antihistamine and acetaminophen prior to the first 4 infusions, and continuation of premedication is based upon clinical judgement. Steady-state concentrations are reached after approximately 4 weeks to 6 weeks of repeated dosing. The half-life of avelumab is approximately 6.1 days in patients receiving the 10 mg/kg dose [38].

EARLY-PHASE TRIALS

The Phase IB JAVELIN trial investigated avelumab as first-line therapy for NSCLC irrespective of PD-L1 expression with results published at IASLC World Conference on Lung Cancer in 2016 (JAVELIN Solid Tumor; NCT01772004) [39]. The trial included 145 pre-treated patients with histologically confirmed stage IV or recurrent NSCLC and no activating EGFR mutation or ALK fusion. 63% patients had adenocarcinoma and 27% had squamous cell carcinoma. Patients received avelumab 10 mg/kg every 2 weeks until disease progression or

unacceptable toxicity or withdrawal. Between March 2015 and November 2015, 156 patients were enrolled. 79.3% had PD-L1-positive tumors based on ≥1% expression. There was an ORR of 19.9% (95% CI, 13.9% - 27.0%) with an ORR of 17.4% for patients with squamous and 20.9% for patients with non-squamous histology. The ORR was 19.3% in PD-L1-positive and 8.7% in PD-L1-negative patients. 45% of patients had stable disease with a DCR of 64%. In this study, avelumab showed an acceptable safety profile and clinical activity, and was well-tolerated at doses ranging from 1 to 20 mg/kg every 2 weeks.

PHASE II TRIALS

A phase 1B/II study is currently evaluating the safety and efficacy of combined pepinemab (5 mg/kg, 10 mg/kg, 20 mg/kg) and avelumab (10 mg/kg) in 62 patients with advanced (Stage IIIB/IV) NSCLC (NCT03268057) [40]. Pepinemab is an IgG4 human monoclonal antibody targeting semaphorin 4D (SEMA4D). This study was based on data from previous studies combining anti-SEMA4D with immunotherapy, which demonstrated enhanced T cell activity and tumor regression. In the preliminary results presented at American Society of Clinical Oncology (ASCO) in 2019, the DCR for patients treated for more than 2 months was 90%. The most common adverse events were Grade 1 or Grade 2 fatigue, pyrexia or chills. Interim results presented at the American Association of Cancer Research (AACR) 2020 conference demonstrated a DCR of 81%.

PHASE III TRIALS

A Phase III multicenter, open-label (JAVELIN Lung 200; NCT02395172) RCT compared avelumab with docetaxel in patients with advanced NSCLC (stage IIIB or IV or recurrent NSCLC) following progression on platinum-based doublet chemotherapy [41]. 792 patients received either avelumab (n = 396) 10 mg/kg every 2 weeks or docetaxel (n = 396) 75 mg/m^2 every 3 weeks. Patients were stratified by staining using the 73 assay - 10 assay for PD-L1 expression (≥1% *vs.* <1% of cancer cells) and histology (squamous *vs.* non-squamous). mOS did not differ between groups (11.4 months [95% CI 9.4-13.9] *vs.* 10.3 months [8.5-13.0] (HR 0.9, 96% CI 0.72-1.12; one-sided p = 0.16). However, avelumab had a favorable safety profile with serious treatment-related adverse events occurring in 9% of patients treated with avelumab compared with 21% of patients in the docetaxel group.

FDA APPROVAL

Avelumab does not have any approved indications in NSCLC. However, it is approved as monotherapy for metastatic Merkel cell carcinoma based on results from the JAVELIN Merkel 200 trial (NCT02155647) in patients with stage IV chemotherapy refractory MCC [42]. Avelumab was also given accelerated approval as monotherapy for advanced urothelial carcinoma which did not progress with platinum-based chemotherapy as maintenance therapy or after disease progression, or for locally advanced disease based on the data from phase IB JAVELIN Solid Tumor trial (NCT01772004) [43]. It is also approved in combination with a VEGF receptor inhibitor, axitinib, for first-line treatment in advanced renal cell carcinoma based on the phase IB study and phase III JAVELIN Renal 101 trial (NCT02684006) [44-46].

The discordant activity of avelumab against various tumors has been discussed by experts. One theory is that the Fc region may interact with the immune system of the lung less effectively than in other organs. However, the apparent lack of activity may simply be a result of relatively fewer studies with this agent compared to other checkpoint inhibitors or a function of sub-optimal study design [47].

ONGOING CLINICAL TRIALS

There are currently 11 actively recruiting clinical trials exploring avelumab's use in NSCLC. A first-line, open-label, randomized, multi-center Phase III trial comparing avelumab to platinum-based doublet chemotherapy in patients with

metastatic NSCLC (JAVELIN Lung 100; NCT02576574) is ongoing. The phase IB/II JAVELIN Lung 101 (NCT02584634) is evaluating the safety and efficacy of avelumab combined with either crizotinib or lorlatinib in patients with advanced or metastatic NSCLC (no longer currently recruiting, results pending). The phase IB/II JAVELIN Medley (NCT02554812) is exploring avelumab combined with other ICIs in patients with locally advanced metastatic solid tumors, including ALK+ NSCLC (Table 2).

Treatment-related adverse effects for avelumab are similar to that of other ICIs and have a more favorable side effects profile than standard chemotherapy. In the JAVELIN Lung 200 study, adverse events occurred in 64% of the avelumab-treated patients compared to 86% of the docetaxel-treated patients, with grade 3 events - 5 events in 10% and 49%, respectively. The most common avelumab-related 3-5 grade adverse events were infusion-related reaction (2%) and increased lipase (1%). Treatment deaths occurred in 1% of participants in the avelumab group, two due to interstitial lung disease, one acute kidney injury and one from autoimmune myocarditis, acute cardiac failure and respiratory failure. This compares to 14% of treatment-related deaths in the docetaxel group. It can be hypothesized that avelumab may have a slightly different toxicity profile since its Fc portion of the monoclonal antibody is not modified to prevent ADCC and CDC, unlike atezolizumab and durvalumab. However, head-to-head studies will be needed to determine if and how this differential formulation specifically alters avelumab's toxicity profile.

OTHER PD-L1 INHIBITORS

Other PD-L1 ICIs are being investigated as cancer therapeutics, including Envafolimab (KN035/ASC22), CK-301, and CS-1001 [48]. Envafolimab is a first-in-class nanobody (single domain antibody) created by the fusion of anti-PD-L1 domain and Fc fragment of human IgG1 mAb. It binds with high affinity and specificity to PD-L1. Unlike other PD-L1 inhibitors which are administered intravenously, KN035 is administered subcutaneously and has better penetration into tumor tissue in animal studies. In a phase I trial, KN035 had a favorable safety profile and encouraging results against advanced solid tumors [49]. CK-301 is an IgG1 anti-PD-L1 mAb. Similar to avelumab, it has a functional Fc domain, capable of inducing ADCC and CDC-mediated killing. A phase I, open-label, multicenter study for advanced cancers (NCT03212404) is currently enrolling patients. CS-1001 is another IgG4 mAb that selectively binds to PD-L1. A Phase I study exhibited anti-tumor activity in advanced tumors with a DCR of 58% [48]. There are two phase III studies investigating CS-1001 for patients with stage IV NSCLC (NCT03789604) and locally advanced/unresectable stage III NSCLC (NCT03728556) after prior concurrent or sequential CRT.

CONCLUSION

There has been a paradigm shift in the treatment of lung cancer over the past few years, with ICIs being used in first line as well as subsequent-line treatment for advanced squamous and non-squamous NSCLC. With a multitude of approved agents, the choice of treatment depends on stage of disease; tissue-based biomarkers such as PD-L1 expression and TMB; performance status of the patient; co-morbidities and patient preference; institutional pathways; and sometimes insurance specifications. At this time, PD-L1 inhibitors occupy important positions in treatment pathways for NSCLC. Durvalumab has established its role as consolidation therapy in patients with unresectable stage III NSCLC, as demonstrated in the PACIFIC study. Avelumab has yet to make its mark in NSCLC, but there are a multitude of ongoing clinical trials assessing avelumab and novel combination strategies. As the future of lung cancer immunotherapy continues to evolve, all eyes are turned towards novel combinations, specifically those not involving cytotoxic agents and those that address primary and secondary resistance. The use of PD-L1 inhibitors will continue to play an essential role in improving outcomes for NSCLC patients ([50-65] (Figure 1)).

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