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Review article

Immune checkpoint inhibitors in non-small cell lung cancer: A bird's eye view

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ABSTRACT

Lung cancer is the leading cause of cancer-related mortality worldwide. Treatment with immunotherapy has made a significant impact on the outcomes for those patients suffering from lung cancer and its usage is currently an established treatment modality. Immune checkpoint inhibition that has blocking antibodies which target cytotoxic T-lymphocyte antigen-4 (CTLA-4) along with the programmed cell death protein 1 (PD-1) pathway [programmed death - 1/programmed death-ligand 1 (PD-L1)] have shown promising results for numerous malignancies. Nivolumab and pembrolizumab have been approved as PD-1 blocking antibodies while atezolizumab, avelumab, and durvalumab are approved as PD-L1 blocking antibodies by 'US Food and Drug Administration'. Immune checkpoint inhibitors have been found to statistically improve the survival of patients with lung cancer and have emerged as the primary immunotherapy in lung cancer and have changed the treatment paradigm for advanced disease. Despite such benefits, treatment with immune checkpoint inhibitors is associated with a unique pattern of immune-related adverse effects or side effects. Also, resistance is routinely developing in patients treated with immune checkpoint inhibitors. The current review provides an overview of immune checkpoint inhibitor treatment in lung cancer, its resistance, and adverse effects.

1. Introduction

Lung Cancer is a leading cause of death worldwide, accounting for an estimated 2.09 million new cases in 2018 according to WHO. It is the most commonly occurring cancer in men and the third most commonly occurring cancer in women. In men, 1,368,524 new cases of lung cancer were diagnosed and in women, 725,352 were reported [[145]American Institute for Cancer Research]. Chance of developing lung cancer in male is about 1 in 15 and for women, the risk is about 1 in 17.

The standard treatment for lung cancer includes surgery, adjuvant therapy, radiation therapy, chemotherapy, and immunotherapy. Surgery, as well as radiation therapy, cannot be used to treat widespread cancer. For better efficacy, a combination of two or more chemo drugs is used. However, chemotherapy may also damage healthy cells in the body, including blood cells, skin cells, and nerve cells. Moreover, chemotherapy may lead to relapse and development of resistance leading to lethality and mortality. Thus, because of several disadvantages of chemotherapy and recent advantages being offered by immunotherapy, it is used as novel approaches for lung cancer. Immunotherapy, also called biologic therapy, is designed to boost the body's natural defenses to fight cancer.

For cancer cells, there are several ways using which both the immune responses can be avoided. As cancer cells are the body's own mutated cells our immune system cannot identify them as malignant cells. T-cells have proteins on them that acts as "Off" switches called as "Checkpoints" that prevent T-cells from attacking other cells in the body. To inhibit T-cell activity, the inhibitory signals are initiated by immune-checkpoint molecules (inhibitory ligands and their related receptors). Cancer cells may over power innate cells, or they generate deceptive signals at some "checkpoints" that inform the adaptive T-cells that they aren't dangerous. Because of these checkpoints, the cancerous cell can remain undetected in the body and spread to other parts of the body.

Enhanced expression of multiple immune checkpoints, such as Cytotoxic T-lymphocyte antigen 4 (CTLA-4), Programed cell death 1 receptor (PD-1), T-cell immunoglobulin and ITIM domain (TIGIT),

Abbreviations: AE, adverse effect; CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte antigen-4; EGFR, endothelial growth factor receptor; FDA, Food and Drug Administration; HR, hazard ratio; ICIs, immune checkpoint inhibitors; IgG, immunoglobulin G; IRAEs, immune-related adverse events; LAG3, lymphocyte-activation gene 3; MHC, major histocompatibility complex; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death ligand 1; PFS, progression-free survival; RR, response rate; TIM-3, T cell immunoglobulin and mucin-domain containing-3

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lymphocyte activation gene-3 (LAG-3), and T-cell immunoglobulin-3 (TIM-3) are major hallmark of T-cell exhaustion [1]. Studies demonstrate the fact that the functioning of T-cell reduces with enhanced expression of these checkpoints [1]. The inter-link of immune checkpoints with their ligands seems quite complex. It is prone to arise at various stages of T-cell activation or function. For instance, during the priming stage of T-cell, TIM-3, TIGIT, LAG-3 and CTLA-4 initially communicate with their ligands, thereby limiting the activation of T-cell [2]. On the other hand, the PD-1 expression is upregulated on T-cell which is activated and binds with PD-L1 or PD-L2. This results in the reduction of activated T cells at the effector phase [3].

Checkpoint inhibitors are found to be suppressing, or rather, blocking the checkpoint activities. This entire mechanism is designed so that the body can effectively recognize the cancerous cells, thereby triggering the immune system to attack and destroy the cancerous cells. For most of these inhibitory receptors, antibodies have been developed and tested in clinical trials and pre-clinical models and few of them have now been recognized to be licensed for use in humans. Several agents like nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, tremelimumab and ipilimumab have been accepted by US Food and Drug Administration. And currently are being used in combination with chemotherapy agents for treatment of lung cancer. The details of evolution and major developments in discovery of immune checkpoint inhibitors are depicted in Fig. 1.

As robust biomarkers to predict resistance are difficult to track, the mechanisms are concluded from pre-clinical studies and some of the available correlative clinical data that can be used for primary and secondary resistance. With the introduction to the acquaintances of molecular and immunologic mechanisms of immune checkpoint inhibitors, the outcomes do not simply recognize the novel predictive or extrapolative biomarkers, rather it also guides the optimal sequencing or combination of immune checkpoint inhibitors treatments in the clinics [4]. The present review shall give a descriptive insight into the immune checkpoint inhibitors for lung cancer, their side effect profiles and resistance to these novel agents.

2. Immune checkpoints inhibitors in lung cancer

Immune checkpoint molecules that suppress the T-cell activity in lung cancer include PD-1/PD-L1 and CD28/cytotoxic T-lymphocyte antigen 4 (CTLA-4). These are evolved as significant druggable targets, which are discussed in the forthcoming sections [Prantesh et al. 2017].

2.1. Agents acting through PD-1/PD-L1 pathway

The programed cell death 1 receptor (PD-1) is a coinhibitory surface receptor (checkpoint protein) expressed on activated T-cells. Apart from this, immune cells like natural killer cells, B lymphocytes and myeloid derived suppressor cells also express PD-1. The ligands of PD-1 viz. Programmed death- ligands PD-L1 and PD-L2 are usually expressed on tumor cells [5–7]. In tumor, the down-regulation of T-cell response is the outcome of micro-environment association of PD-1 with its ligands, PD-L1 and PD-L2 on malignant cells [8,9]. As a mechanism for suppressing T-cell response, several lung cancer cells overexpress PD-L1 [8,10].

In the recent years, the treatment of cancer has attained a new phase with the introduction to the inhibitory receptor PD-1 and its ligand PD-L1; it has increased importance as well as acceptance of numerous antibodies that block PD-1 or PD-L1 [11]. By antigen stimulation, PD-1 expression on T cells is induced [12]. PD-1 generally exhibits its down-regulating effects over T-cells in the surroundings where PD-1 ligands are encountered by T-cells. However, such is not the case with CTLA-4 as they prohibit the initial activation of T-cell [3]. Expressed by a wide range of cell types including T cells, tumor cells, B cells, epithelial cells, monocyte-derived myeloid dendritic cells and tumor cells; PD-L1 and PD-L2 are two recognized ligands of PD-1 [13,14]. In case of cancer, these two types of ligands are considered as the essential cell types that mediate the suppression of T-cell by PD-1 ligation [15]. Fig. 2 depicts the mechanism of action of different checkpoint inhibitors viz. CTLA-4 along with PD-1.

CTLA-4 and PD-1 are immunologic checkpoints present on T-cells. The interaction between PD-1 and its ligands PD-L1 and PD-L2 which are expressed on tumor cells leads to the down regulation of immune response. This downregulation can be suppressed by blocking PD-1 by Nivolumab and Pembrolizumab and by blocking PD-L1 and PD-L2 ligands by Atezolizumab, Avelumab and Durvalumab. And the interaction between CTLA-4 and CD-80 and CD-86 which are present on antigen presenting cells also leads to downregulation of immune response. CTLA-4 can be blocked by agents Ipilimumab and Tremelimumab.

2.1.1. PD-1 blocking antibodies

PD-1 interaction with its ligands PD-L1 and PD -L2 has been accounted to be blocked by PD-1 antibodies. However, it does not prevent the PD-L1 interaction with CD80 [5]. CD80 is a membrane receptor that is activated by the binding of CD28 or CTLA-4. The activated protein CD80 induces T-cell proliferation and cytokine production.

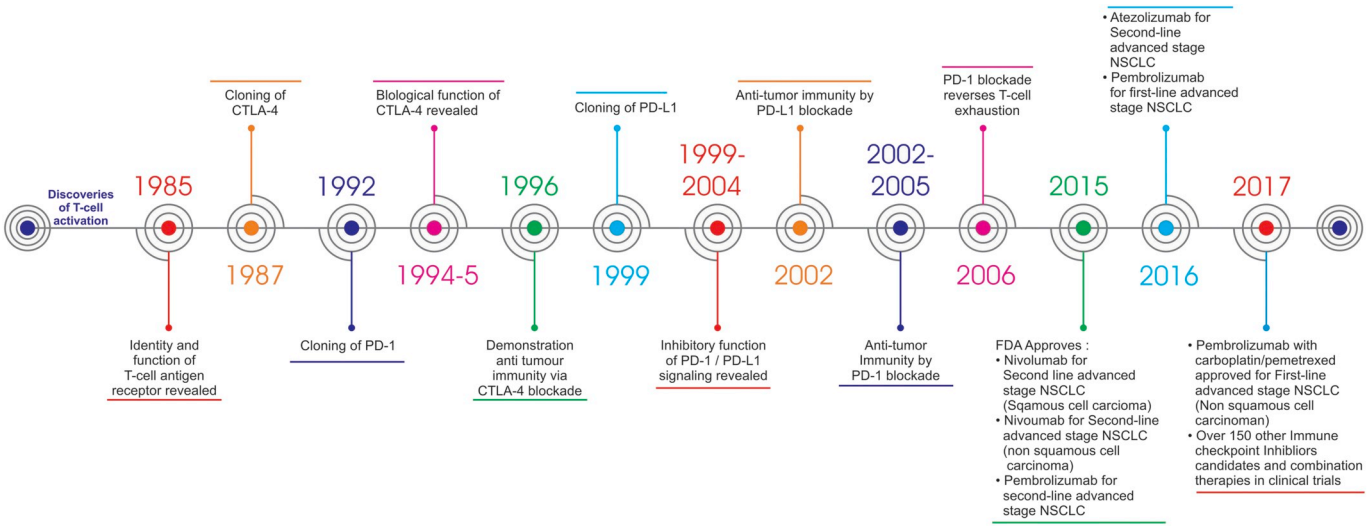

Fig. 1. History, evolution and milestones in the development of immune checkpoint inhibitors since last 35 years. The figure shows the history of cloning of PD-1, PD-L1, CTLA-4 and the history of various FDA approved immune check point inhibitors such as Nivolumab, Pembrolizumab and Atezolizumab for NSCLC.

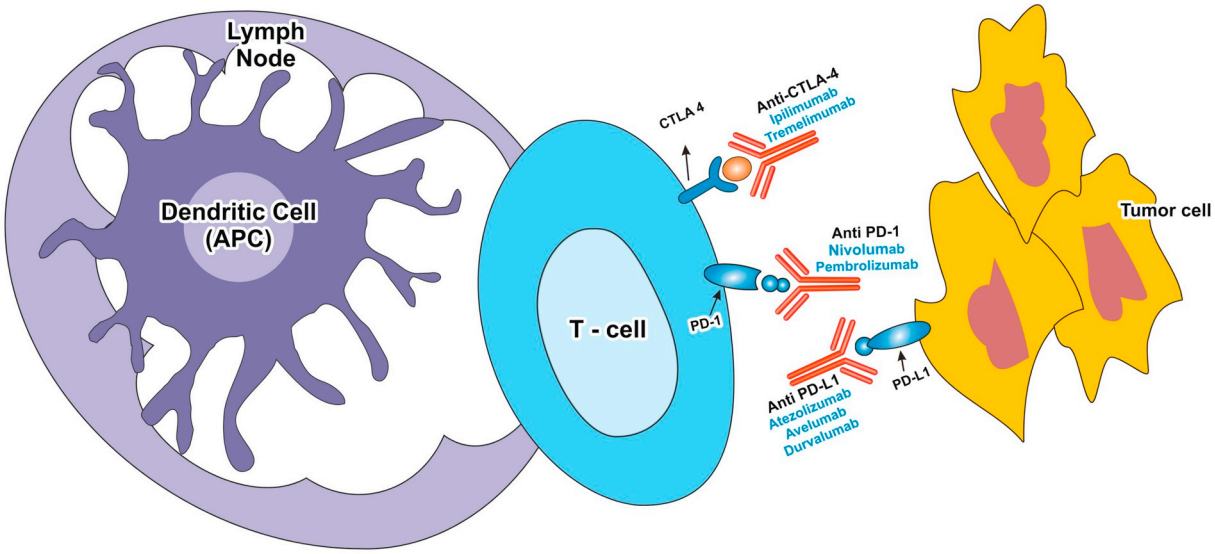

Fig. 2. Mechanism of action of immune check point inhibitors: APC, Antigen presenting cells; PD-1, programmed-death 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte associated protein 4.

2.1.1.1. Nivolumab. Nivolumab is recognized as a completely human immunoglobulin G4 (IgG4) monoclonal antibody. By binding with PD-1, it inhibits PD-1 activation by its ligand. Nivolumab is accepted as a first-line monotherapy or in combination with ipilimumab for progressive melanoma and also for metastatic renal clear-cell carcinoma as well as for advanced NSCLC approved as second-line therapy [16].

A trial was carried out on 129 NSCLC patients who entered the first phase of cohort expansion trial of dose escalation of nivolumab. Long-term follow-up result of pretreated patients state that, when nivolumab given in dose of 1, 3, or 10 mg/kg intravenously (IV), once every 2 weeks the overall survival (OS) rate outcome of 1-, 2-, and 3-year were 42%, 24%, and 18%, respectively. Whereas, the same at 3 mg/kg dose (n = 37) were 56%, 42%, and 27%, respectively. This dose was then chosen for further clinical development [17]. Response rates in squamous (Sq) (16.7%) as well as non-squamous (non-Sq) (17.6%) NSCLC were observed to be similar. In countries like Germany, USA, France and Italy, a phase-II trial of Sq. NSCLC was carried out. Nivolumab (3 mg/kg) was administered every 14 days to Sq. NSCLC patients who were previously treated with two or more treatments till progression or objectionable toxic effects were detected. In the year 2012 and 2013, 117 patients were enrolled [18,19]. Out of 117, 17 (14.5%) patients were detected with an objective response. In the patients with tumor PD-L1 expression, the response rate was found to be 14% among the patients having tumor PD-L1 expression < 5%; whereas it was 24% in those having expression ≥5% [20].

Nivolumab was initially accepted for advanced Sq. NSCLC in March 2015, based on CheckMate 017. CheckMate 017 [16,21] was an open-label, multicenter, randomized phase-III trial carried out on 272 Sq. NSCLC patients detected with disease throughout or following the 1st line chemotherapy. Randomized patients were administered docetaxel 75 mg/m^2 every 21 days or nivolumab 3 mg/kg once in 14 days. 9.2 months was the median OS with nivolumab whereas, with docetaxel it was observed to be 6 months (HR = 0.59, p < 0.001). The rate of survival that was exhibited by 42% of the patients treated with nivolumab was merely one year which was same for 24% patients administered with docetaxel. 20% with nivolumab versus 9% with docetaxel (p = 0.008) was the response rate. With nivolumab the median PFS was observed to be 3.5 months whereas, it was 2.8 months with docetaxel (p < 0.001, HR = 0.62). Acceptance of nivolumab for the treatment of metastatic Sq. NSCLC patients having progression during or following the platinum-based chemotherapy was granted by US FDA in 2015.

In October 2015, Nivolumab was stated to be approved for CheckMate 057 for non-Sq. NSCLC [20,22]. In this trial, patients with non-Sq NSCLC that had progressed during or after platinum-based chemotherapy were randomized to receive nivolumab or docetaxel. The median overall survival of 292 enrolled patient in the nivolumab arm was 12.2 months and that of 290 patients enrolled in docetaxel arm was 9.4 months (p = 0.002, HR = 0.73). The survival rate of 12 months of nivolumab was comparatively high (51%) to that of docetaxel (39%). The response rate of nivolumab was 19%, while that of docetaxel was 12% (p = 0.02). Analyzing this data, nivolumab was approved by FDA for treating the metastatic NSCLC patients, with progression on or after platinum-based chemotherapy. This acceptance authorizes the exhibition of nivolumab to enroll non-squamous histology in NSCLC.

An open label, phase 3 trial CheckMate 026 carried out on previously treated NSCLC patients where, 423 patients out of 540 enrolled patients with 5% or more PD-L1 expression level, which resulted into the conclusion of nivolumab not been related with considerably longer PFS as compared to chemotherapy (4.2 vs. 5.9 months with chemotherapy, HR 1.15; P = 0.25). Among these groups, similar overall survival was reported (HR 1.02; 14.4 vs. 13.2 months). 196/423 patients having PD-L1 > 5%, (around 43% of the patients) were above the age of 65. However for age groups of above as well as under 65 years, the results of nivolumab was equivalent that of the platinum-based chemotherapy, in context with PFS as well as OS (HR 1.30; median PFS was 4.2 in age group ≥65 years, while it was 5.7 months along chemotherapy, median OS 14.7 and that of 11 months along chemotherapy, HR 0.98) [23,24].

An ongoing trial CheckMate 153 is totally community-based. It is a phase IIIB/IV safety study of nivolumab which is conducted for pretreated patients with advanced NSCLC in the United States/Canada. The interim analysis suggests that 520 (40%) patients out of 1308, belonged to the age group ≥70 years and when they were evaluated for 6-months, their survival (63%; 95% CI, 58–67%) was related with that for the patients who were of the age < 70 years (63%; 95% CI, 59–67%). Additionally, wellbeing profile of nivolumab proved to be same in both the age subgroups of < 70 - any grade AEs: 62%; grade 3–4 AEs: 12% and in age ≥ 70 years, any grade AEs: 59%; grade 3–4 AEs: 11%. And grade 5 AEs: < 1% each one [24,25].

2.1.1.2. Pembrolizumab. Pembrolizumab (MK-3475) is recognized as an IgG4-engineered humanized antibody which acts as a blockage to

the PD-1 receptor. As a part of initial therapy, it was approved for unresectable or metastatic melanoma. Based on the results of KEYNOTE-010, a randomized phase II/III trial, pembrolizumab was approved for both Sq. as well as non-Sq NSCLC. This trial enrolled the advanced NSCLC pretreated patients who were detected with PD-L1 +ve in malignant cells with immunohistochemistry [16,26].

There were three major arms in this trial, pembrolizumab received 2 mg/kg (number of patients = 345), docetaxel received 75 mg/m2 (number of patients = 343) and pembrolizumab received 10 mg/kg (number of patients = 346), administered at a frequency of once every 3 weeks. 10.4 months was the median OS for the lower dose of pembrolizumab, whereas it was 12.7 months at a higher dose, and it was 8.5 months in case of docetaxel. Overall survival was considerably more for both doses of pembrolizumab, unlike docetaxel (with pembrolizumab 2 mg/kg: HR, 0.71; 95% CI, 0.58–0.88; $p = 0.0008$) (pembrolizumab 10 mg/kg: HR, 0.61; 95% CI, 0.49–0.75; $p < 0.0001$). For both the pembrolizumab groups, the response rate was recorded to be 18% as compared to that for the docetaxel group which was 9% [16]. In contrast with nivolumab, pembrolizumab is scheduled to be administered once every 3 weeks, which is slightly more convenient, rather than every 2 weeks. KEYNOTE-010 was introduced for patients with PD-L +ve tumors. For the approval from FDA, this became a requirement, as it certainly reduces the drug eligibility, since the PD-L1 expression although shows considerable variation among the recorded datasets (13–70%), found in less than half of the detected tumors among majority of the patients [27]. Further, another biopsy of the tumor is suggested to be necessarily required, as it is evident that expression of PD-L1 by malignant cells is an adaptive maneuver and it deceives immune response, subsequently linked with rather resistant line of cells.

In KEYNOTE-001, an international phase 1 trial, 495 patients with NSCLC were administered pembrolizumab at a dose of either 2 or 10 mg/kg every 21 days or 10 mg/kg every 14 days [20,28]. Among all these NSCLC patients, the median duration of response was 12.5 months and the objective RR was found to be 19.4%. The median duration of OS was 12.0 months. The RR was 45.2% among the patients with a PD-L1 proportion score of at least 50%. Median PFS was 6.3 months among all the patients with a proportion score of at least 50%. For metastatic NSCLC patient's treatment with disease progression during or after platinum-containing chemotherapy, the increased approval to pembrolizumab in patients with expressed PD-L1 tumors was granted by the Food and Drug Administration, US in the year 2015 [[136]www.fda.gov].

KEYNOTE-021 trial was primarily conducted for advanced NSCLC treatment-naïve patients, with an objective to assess the clinical activity, tolerability and safety of the pembrolizumab with platinum-based doublet chemotherapy [20,29]. The affected patients were randomized 1:1 to pembrolizumab 2 mg/kg or 10 mg/kg at an interval of 21 days, in combination with carboplatin and paclitaxel (Cohort A; any histology), else pemetrexed with carboplatin (Cohort C). Those patients were administered with pembrolizumab plus chemotherapy followed by maintenance therapy with pembrolizumab in Cohort A and in Cohort C pembrolizumab combined with pemetrexed as a therapy for maintenance, for consecutive four cycles. 44 patients were treated in December 2014. The preliminary response rate in Cohort A was 30% and for Cohort C was 58%.

Studying the reports of patients with melanoma, potent effectiveness and manageable toxicity have been found as a result of combined anti-CTLA-4 and anti-PD-1 treatment. In NSCLC patients, a phase 1 study analyzing pembrolizumab with ipilimumab was carried out [30]. Pembrolizumab was administered with ipilimumab for every 3 weeks for four cycles. It was carried ahead by maintenance pembrolizumab therapy in NSCLC patients. It reappears after more than two prior regimens. The preliminary data of KEYNOTE-021 demonstrates an adequate toxicity profile along with a potent antitumor action for pembrolizumab with ipilimumab for the patients recorded with persistent NSCLC.

Records from the trial of Keynote-024 recently shifted pembrolizumab to front-line therapy for the patients whose tumors expressed PD-L1 ≥ 50%. It is open label phase 3 pivotal trial carried out on 305 untreated advanced NSCLC patients. Patients randomly received pembrolizumab (a flat dosage of 200 mg every 21 days for up to 24 months) or platinum-based doublet chemotherapy. On completion of 11.2 months of a median follow up, the records reflect that the PFS as primary end-point was significantly longer in the pembrolizumab (HR 0.50, 10.3 vs. 6.0 months of chemotherapy), and the trial was terminated after second interim observation of the greater efficacy of pembrolizumab (HR 0.60, $P = 0.005$; overall survival rate at 6 months: 80.2% vs. 72.4%). Among all these subgroups, with the 164 patients having an age of 65 or more (which sums up to 54% of the total population) the improvements were evidently observed since the HR was 0.45 for OS in those administering pembrolizumab [24,31].

2.1.2. PD-L1 blocking antibodies

The interaction of PD-L1 with PD-1 and CD80 (B7.1) is hindered by the antibodies of anti-PD-L1. They, however, do not promise to block the PD-1 interaction with PD-L2 and CD80 with CTLA-4 [5].

2.1.2.1. Atezolizumab. Atezolizumab (MPDL3280A) is directed against PD-L1. It is a monoclonal antibody of IgG1 that is humanized engineered. As a part of the analysis, two randomized trials of phase II were carried out on NSCLC patients. POPLAR ($n = 287$) was one of those two studies, using docetaxel as the control arm. The results prove that OS was notably increased by atezolizumab [20,32]. In this presented analysis, earlier treated NSCLC patients were randomized and administered docetaxel 75 mg/m2 IV every 21 days or atezolizumab 1200 mg IV every 21 days. With increasing PD-L1 expression, effectiveness was found to be improved, PFS: HR = 0.56; OS: HR = 0.47; Response rate = 38% versus 13% in patients for atezolizumab as compared to docetaxel, whereas advantage from atezolizumab did not report in patients with the least levels of PD-L1 (OS: HR = 1.22). With atezolizumab, median overall survival was recorded to be 12.6 months whereas, with docetaxel, it was found to be 9.7 months ($p = 0.04$, HR = 0.73). There was no specific difference with docetaxel and atezolizumab, among the patients having slight or no PD-L1 expression (9.7 months of median OS in both arms) [32].

A single-arm study known as BIRCH proposed that with PD-L1 positive found in the advanced NSCLC individuals, atezolizumab was used [20,33]. Both, PD-L1 expression as well as POPLAR study was analyzed in similar ways. Into three cohorts' patients were divided: Cohort 1 patients were administered with no previous treatment, Cohort 2 patients were administered 1 chemotherapy prior, and Cohort 3 patients were administered no < 2 systemic therapies previously. For these cohorts of patients who were observed to have escalated PD-L1 expression, 26%, 24%, and 27% were the primary endpoint RR, respectively. With the patients who had intermediated to elevated expression of PD-L1, 19%, 17%, and 17% were the respectively recorded response rates.

Based on PD-L1 expression in stage IIIB/IV patients with NSCLC, one more phase II study was reported for atezolizumab (FIR). Chemo naïve patients were included in Cohort 1; patients who administered at least 2 systemic treatment lines with no brain metastasis were included in second Cohort, and patients who administered at least 2 lines of systemic treatment but treated through asymptomatic brain metastasis were a part of Cohort 3. Parameters like scoring method, expression of PD-L1 and atezolizumab dose were identified as that in BIRCH and POPLAR. Individuals who reported PD-L1 with IC 2/3 and TC 2/3 tumors are also included. Response rate of 138 patients involved in the first Cohort was 29%, in the second Cohort was 17% and was also 17% in Cohort 3. Apparently, for the patients having PD-L1 with IC3 or TC3 tumors, the highest response rates (29%, 26%, and 25%) were observed respectively. In NSCLC, the patients with elevated PD-L1 expression atezolizumab demonstrated a promising activity, without considering

the treatment mode [34].

For patients who entered the advanced NSCLC stage, after the progression on platinum-based chemotherapy, a confirmatory phase III (OAK) trial compared atezolizumab with docetaxel. In contrast to the result of docetaxel, the overall survival was remarkably augmented with atezolizumab [median OS 13.8 months (95% CI 11.8–15.7) as compared to the 9.6 months (8.6–11.2); $p = 0.0003$ and HR 0.73 (95% CI 0.62–0.87)] like POPLAR results. PD-L1 expression on cancer cells (TC1/2/3) or on immune cells (IC1/2/3) (greater than or equal to 1% PD-L1 by VENTANA SP142 assay) anticipated the atezolizumab advantages. Advanced NSCLC individuals having IC1/2/3 or TC1/2/3 PD-L1 expression the overall survival result was enhanced with atezolizumab for 15.7 months of median overall survival (95% CI 12.6–18.0) and 10.3 months with docetaxel (8.8–12.0) [$p = 0.0102$; HR 0.74 (95% CI 0.58–0.93)]. Nevertheless, patients with no PD-L1 expression (IC0 as well as TC0) augmented the existence of atezolizumab [OS 12.6 months versus 8.9 months; HR 0.75 (95% CI 0.59–0.96)] [Prantesh et al. 2017, [35]]. These reports accounted for the acceptance of atezolizumab in the second-line setting for advanced stage NSCLC patients by the FDA.

2.1.2.2. Durvalumab. Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Recognized as FDA-approved immunotherapy for cancer, durvalumab was developed by MedImmune/AstraZeneca. It is reported to exhibit a high degree of safety and clinical activity in previous treatment-naïve individuals along with advanced non-small-cell lung cancer [16].

In phase I/II multicenter study, its safety, and efficacy was reported analyzing extremely pretreated NSCLC patients [18]. Durvalumab was given for up to 12 months at a dosage of 10 mg/kg every 14 days till the time they reported intolerable toxicity or disease progression. A total of 149 patients were estimated for the outcome of this treatment; disease control rate (DCR) after 24 weeks was observed to be 24% and 14% was overall response rate (ORR) (23% in PD-L1-positive tumors). ORR reported greater in Sq. (21%) as compared to non-Sq (10%) histology. The response was durable as it was 76% ongoing during reporting duration.

Study of dose-escalation and dose-expansion of phase I/II with durvalumab for front-line treatment [36] reported its preliminary results. In 59 patients, 11/12 patients responded with PD-L1 appearance (the study was intended to limit the administration of PD-L1 +ve tumors later the preliminary low response with the PD-L1-negative patients) demonstrated 25% of an ORR. 56% of DCR was found. Additionally, these responses observed to be long lasting, with nine ongoing responses (The responses were recorded over the duration of 5.7+ to 70.1+ weeks).

In phase I/II study carried out on 304 patients, durvalumab displayed quite promising activity as a first- or consequent line of treatment. As an outcome of this study, 50 confirmed responses were noticed with surprisingly positive response rates among those with greater PD-L1 expression, reported as no < 25% of tumor cells staining for PD-L1. The observed ORR was 25% in high PD-L1 and 6% low PD-L1 expression respectively. Apparently, a large number of the pre-treated population with high PD-L1 expression was alive after 12 months by administering durvalumab as second-line (56%) and also as third-line treatment (51%) [37].

Analyzing these records, durvalumab was studied as third-line or higher in advanced NSCLC patients in the ATLANTIC phase II trial. This accumulation earlier was irrespective of PD-L1 status and later on, it was restricted to PD-L1 expression with higher level, with a cutoff margin of 25%. Records of more than three hundred EGRF wild-type and ALK not-rearranged, heavily-pretreated NSCLC patients proved RR to durvalumab proportionally with PD-L1 levels, in patients having PD-L1 ≥ 25% and ≥ 90% having ORR of 16.4% and 30.9%, respectively included in cohort 2 and 3. Likewise, for PD-L1 ≥ 25%, and for PD-L1 ≥ 90%, 12 months' OS rates were 47% and 50.8%. Out of 101 patients above the age of 65, 20% was the ORR in PD-L1 (≥25% of the population) and in PD-L1 (< 25%) was 3%, as compared to 13% and 11% reported among the youth, respectively. This study was found to be age-specific as it was observed that for the individuals having lower levels of PD-L1 expression, the records demonstrated a significant role of age on immune response and impact factor [38].

A phase III trial MYSTIC [[142]ClinicalTrials.gov identifier: NCT02453282] is currently recruiting stage IV NSCLC patients with no prior treatment. These patients are to be randomized with durvalumab and with tremelimumab (anti-CTLA-4), standard-of-care platinum-based chemotherapy or durvalumab as monotherapy. Further, one more phase III open-label study named NEPTUNE [[143]ClinicalTrials.gov identifier: NCT02542293] is recruiting patients to administer any one of the standard-of-care chemotherapies or tremelimumab plus durvalumab. In these III phase trials, durvalumab is also being studied for stages Ib, II or IIIA NSCLC in the adjuvant settings. [[140]ClinicalTrials.gov identifier: NCT02273375]. Further, it is studied with stage III unresectable NSCLC following concurrent chemoradiation in patients [[139]ClinicalTrials.gov identifier: NCT02125461] [38].

2.1.2.3. Avelumab. Avelumab is a fully human anti-PD-L1 IgG1 monoclonal antibody. Avelumab is also able to induce antibody-dependent cell-mediated cytotoxicity, by holding a native Fc-region [20].

A preliminary phase Ib expansion trial was carried out with an aim to access the clinical activity and wellbeing of advanced NSCLC patients developing after the platinum-based chemotherapy. Till the time the disease progression, the complete response, or intolerable toxicity was evident the individuals were administered avelumab at 10 mg/kg every 15 days. A follow-up estimation of 184 patients was recorded. In 22 (12%) patients, objective responses were reported, and 11.6 weeks of a median PFS [39]. PD-L1 negative RR = 10% ($n = 20$) and PD-L1 positive RR = 14.4% ($n = 118$).

Data from the large phase I multi-cohort dose expansion and dose escalation JAVELIN trial, reported that avelumab administration results in promising effect in front-line NSCLC patients for the PD-L1 expression who were not preselected. It was also found that biweekly consumption of avelumab at 10 mg/kg had acceptable tolerability among 156 untreated patients with advanced NSCLC, with an impressive 22.4% ORR and 17.6 weeks median PFS. The study was conducted specifically on 105 patients (> 50%), were beyond the age of 65. They were observed to be developing 25% of ORR, consistently to the overall population [24,40].

In another heterogeneous cohort carried out for 184 extremely pretreated patients of advanced NSCLC (33% of patients were ≥ 3rd third line of therapy) PD-L1 unselected [anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR)/KRAS mutated translocated] avelumab demonstrated an antitumor activity and a toxicity profile same as that of other immuno-agents: 12% was the ORR (latest to be 14.1%). OS and 1-year PFS rates were reported as 36% and 18%, respectively, with an 8 months median OS. Analyzing the exploratory evaluation, a PFS advantage resulted for PD-L1 +ve patients (more than or equal to 1% as cutoff for tumor cell staining) comparing with PD-L1 −ve counterparts (12.0 vs. 5.9 months, HR 0.27–0.75), however at 1 year survival curves are approached (one-year overall survival: 39% vs. 36% for PD-L1 +ve and −ve, respectively) [41].

Two currently ongoing randomized phase III trials for patients with NSCLC having PL-1 expression of 1%, compared avelumab to first-line chemotherapy [JAVELIN Lung 100 phase III trial; ([144]ClinicalTrials.gov identifier: NCT02576574)], and after platinum-based doublet chemotherapy failure comparing to docetaxel in the second-line setting [JAVELIN Lung 200; ([141]ClinicalTrials.gov identifier: NCT02395172)] [24].

2.2. Agents acting through CD28/CTLA-4 immune modulation system

CTLA-4 is largely introduced on T cells (killer T cells, CD4 + , CD8 + and helper) having nearly few expressions on different immune cells like fibroblast and B lymphocytes. To bind with the same ligands B7–1 (CD80) and B7–2 (CD86), CTLA-4 needs to compete with the costimulatory receptor CD28 on the surface of APCs. The outcome of this is a blockage in intracellular signaling which results downregulation of immune response. Clinical activities have been observed in advanced melanoma therapeutic anti-CTLA-4 monoclonal antibodies, as a result of the exhaustion of regulatory T cells in the microenvironment of tumor and most prominently by disrupting activation of CD28 on T cells [5].

Through multiple accepted mechanisms, immune checkpoints suppress T-cell function and they possess distinct ligands. Primarily, the inhibitory receptor CTLA-4 is reported to participate in the T-cell suppression responses [42]. The mandatory signal for activation of T-cell is the identification of peptide antigen presented by MHC (signal 1) also expressed by APCs, co-stimulation for CD28 subsequent interaction to CD86 or CD80 (signal 2). CTLA-4 is structurally alike with CD28 and it interacts with CD86 and CD80 at a greater affinity than CD28 [43]. Also, the expression of CTLA-4 hinders with T-cell activation by decreasing CD28 co-stimulation [44,45]. T cells release a differently spliced variant of CTLA-4 and show its inhibitory functions that are not dependent on the interaction of one cell with another. CTLA-4 is fundamentally secreted on regulatory T cells. It even expresses on T effector cells followed by its initiation [44,46]. However, CTLA-4 is prominently expressed intracellularly by the activated T cells, whereas it is expressed on the surface of the Treg cells [47]. Such expression indicates the dual functionality of CTLA-4. Excessive T-cell responses are suppressed by CTLA-4 expression by regulatory T cells and this behaves as a mechanism for regulatory T cells, whereas the intracellular CTLA-4 reservoirs avoid tissue damage by self-reactive pathogenic T cells [48].

It's been recorded that high CTLA-4 expression on CD4 + T cells can be critical for the Treg cells' suppressive features [49]. In vivo, blocking of CTLA-4 has been resulted to increase anti-tumor immunity. It was recorded by suppressing the regulatory T cells along with improving the effector T-cell working in a melanoma mouse model [50].

2.2.1.1. Ipilimumab. Ipilimumab is the most well-known CTLA-4 inhibitor. Being fully humanized IgG1 anti-cytotoxic T-lymphocyte antigen CTLA-4 monoclonal antibody; it has the capacity for hindering the CTLA-4 binding with its ligand. Ipilimumab permits immune system to fight against the tumor cells by arresting the regulatory mechanisms of the T cell regulator CTLA-4 [51,52]. For the treatment of cancer, ipilimumab is the initial checkpoint inhibitor that has ever been approved clinically.

A phase II trial combined carboplatin/paclitaxel doublet chemotherapy and ipilimumab, was conducted for chemotherapy-naïve stage IIIB/IV NSCLC patients. In this case, the disease for curative treatment was not amenable. It was a 3-arm (1:1:1) study conducted on 204 patients. For up to six cycles, the control arm was the doublet of carboplatin and paclitaxel. Experimental arms consisted of ipilimumab at 10 mg/kg administered concurrently along with the paclitaxel or carboplatin for 4 cycles and then 2 placebo doses; or 2 placebo doses accompanied with paclitaxel or carboplatin followed by ipilimumab with the combination of carboplatin/paclitaxel for 4 cycles. The patients without disease progression and/or without limiting toxicity were suggested to administer ipilimumab/placebo treatment as a part of maintenance therapy at every 12 weeks, following the regular end of treatment. For this trial, irPFS was the primary endpoint and, overall survival, progression-free survival, immune-related best overall response rate, best overall response rate, and safety were secondary endpoints.

Using the criteria of immune-related RECIST, the primary endpoint irPFS was not achieved for the combination of concurrent ipilimumab along with chemotherapy (4 ipilimumab doses along with carboplatin and paclitaxel followed by 2 placebo doses with carboplatin and paclitaxel) (HR 0.83, $p = 0.13$). However, it became successful for the phased ipilimumab along with chemotherapy doublet (2 doses of placebo with paclitaxel and carboplatin followed by 4 doses of ipilimumab with paclitaxel and carboplatin) (HR 0.72, $p = 0.05$). Median irPFS of the carboplatin with paclitaxel combination was 4.6 months, when administering concurrent ipilimumab it was 5.5 months, and with administering phased ipilimumab regimen, it was 5.7 months. Referring to the modifications of criteria stated by WHO, PFS was considerably reported positive for the phased ipilimumab arm related to control arm, however it wasn't the case for concurrent ipilimumab arm. 8.3 months of median survival was recorded for the control arm and 12.2 months for the phased group. ($p = 0.23$, 0.87 HR). But the survival benefits were not observed in the concurrent ipilimumab group (0.99 HR, $p = 0.48$; 9.7 months). This study carried out on the subgroups indicates the benefits in patients with squamous histology enrolled in the phased arm as compared with the non-squamous histology in overall survival and in irPFS. Considering toxicity in the three arms, grade 3 and 4 adverse effects were same: control arm - 37%, concurrent arm-41%, and phased arm- 39%. 2 deaths were associated with the treatment; out of which one was in the concurrent and the other in the group control group [53].

Observing the impact and safety of 1st line ipilimumab or placebo with carboplatin and paclitaxel, a phase III study was conducted in advanced Sq. NSCLC. Patients going through the fourth stage or recurrent chemotherapy-naïve sq. NSCLC were treated (1:1) with placebo or carboplatin and paclitaxel with ipilimumab 10 mg/kg for every 21 days on an induction schedule including 6 cycles of chemotherapy, ipilimumab or placebo from cycles three to six, followed by ipilimumab or placebo maintenance every twelve weeks for patients having stable disease or response. Overall survival was the primary endpoint. Conducted for 956 patients, in which 749 received minimum 1 dose therapy (ipilimumab with chemotherapy, $n = 388$; placebo with chemotherapy, $n = 361$). Median OS for chemotherapy with ipilimumab was 13.4 months and for chemotherapy with placebo, it was observed to be 12.4 months (hazard ratio, 0.91; 95% CI, 0.77–1.07; $p = 0.25$) [54].

One more study is currently ongoing, which is clinical trial of phase 1 that associates with crizotinib or erlotinib, plus ipilimumab ([137]ClinicalTrials.gov identifier: NCT01998126), relying upon whether the patients demonstrate ALK or EGFR mutated status. Outcomes from both trials will be very significant in Sq. NSCLC to check the dominant advantages of the combination of ipilimumab plus cytotoxic chemotherapy, or in NSCLC patients with an ALK translocation or an EGFR common mutation administering ipilimumab with target therapies [51].

2.2.1.2. Tremelimumab. Tremelimumab (formerly ticilimumab) is a fully human IgG2 monoclonal antibody, which is directed against human cytotoxic T lymphocyte-associated antigen 4 (CTLA4) [51,55]. This antibody was developed by Pfizer. Tremelimumab is currently under clinical development for the treatment of various cancers.

In NSCLC patients, tremelimumab has not exhibited any specific benefit as a monotherapy, even though it has a mechanism of action which resembles that of ipilimumab. In clinical trial of phase 2 for metastatic or locally advanced NSCLC patients having impressive outcomes status that were given 4 or more platinum-based chemotherapy cycles and the responses were randomized to tremelimumab or the best supportive care. Among those patients in the treated group, PFS the primary endpoint of this trial could not be achieved, with a disappointing 4% of an objective response rate. Adverse effects of grade 3 to 4 were noted in one-fifth of the total patients (with 9% toxicities that were immune-related) and versus none with best supportive care arm

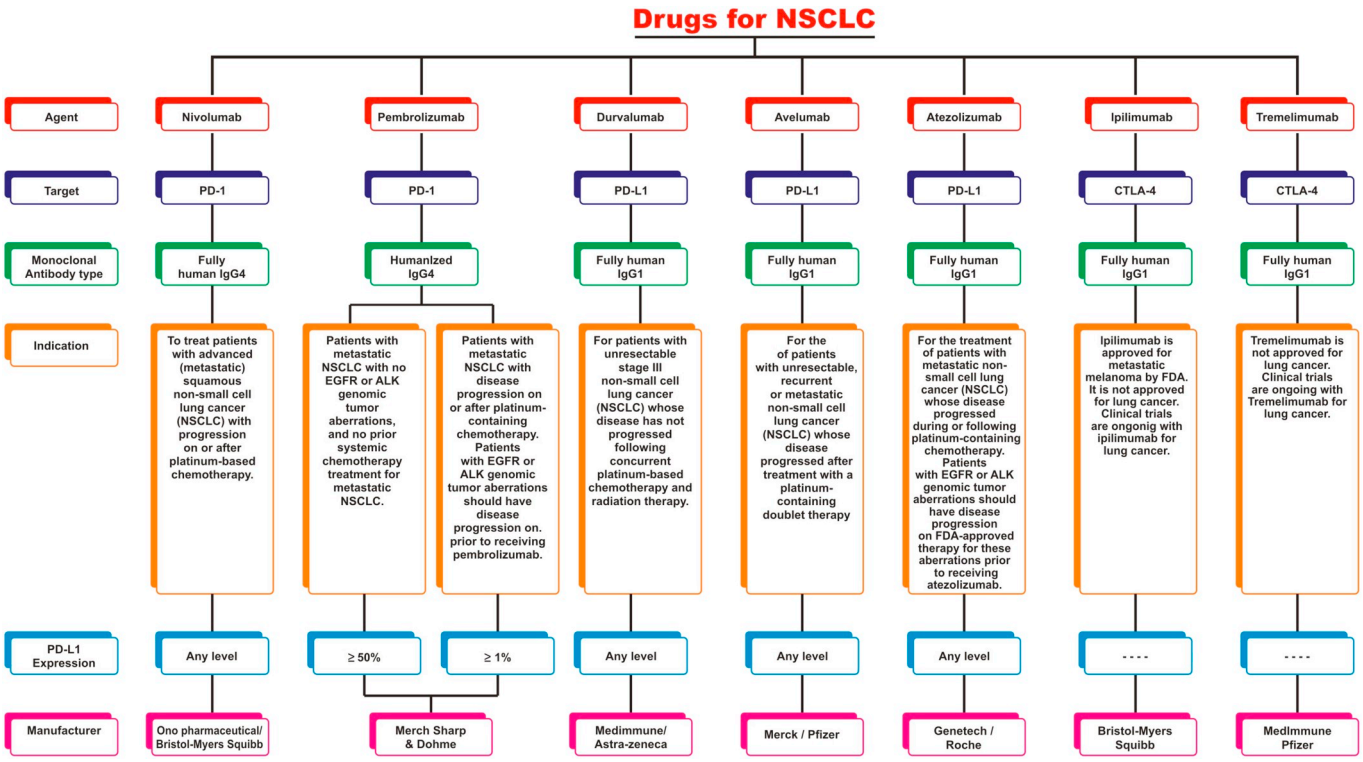

Fig. 3. Different immune checkpoint inhibitors are approved for NSCLC. The PD-1 target on T-cells are blocked by Nivolumab and Pembrolizumab with different PD-L1 expressions on it and the PD-L1 target are blocked by agents Durvalumab, Pembrolizumab and Avelumab. Clinical trials for CTLA-4 inhibitors Ipilimumab and Tremelimumab are still ongoing because of their promising effect on NSCLC.

[56]. As of now, a phase 1 clinical trial of tremelimumab in addition with gefitinib is under process for previously treated individuals with EGFR-mutated NSCLC stage IIIB and IV ([138]ClinicalTrials.gov identifier: NCT02040064). A summary of various check point inhibitors approved for NSCLC is provided in Fig. 3.

3. Resistance to checkpoint inhibitors

Mechanisms of primary and secondary resistance to immune checkpoint inhibitors treatment are not completely evident, attributed in relation with the inadequate knowledge of the complete complement of immunologic, molecular and clinical factors linked with clinical response as well as long-term advantages to immune checkpoint inhibitors treatment [57,58]. Further, there are some immune competent pre-clinical models wherein immune checkpoint inhibitors induce tumor regression that limits the capability to restate the tumor-immune interactions diversity in the patients. For justifying this observation for acquired and primary resistance, initial the model of 'response' to immune checkpoint inhibitors to concentrate on crucial steps has to be considered so that it can be blocked, inhibited or else bypassed by tumor, or co-opted by immune as well as stromal elements of the tumor microenvironment, to restrain tumor growth by subverting the efforts of the immune system.

It is globally proven that efficacious anti-tumor immune responses followed by PD-1/PD-L1 obstruction need clonal-proliferation as well as reactivation of antigen-experienced T cells found in tumor microenvironments [59,60]. Proven exhibition and processing by antigen-presenting cells, for tumor-associated peptide antigens (APCs, e.g., dendritic cells) is essential for the generation of tumor-reactive CD8 T cells and MHC I/II displaces the recognition of these antigenic peptides. MHC-bound tumor antigen is identified by a unique T-cell receptor giving the first signal for activation of T-cell. Later, the full activation of T-cell surveys the interaction on T cells of the co-stimulatory CD28 receptor by B7 on APC [61]. Effector T-cells are being predominantly distinguished from the tumor-specific CD8 T cells, through clonal expansion, traffic to the TME, and eventually release the cytolytic effector molecules to kill the cells showing tumor-associated antigen on HLA (e.g., granzyme A/B and perforin) [59].

For immunologic memory over a long duration (along with the disease control which is presumably durable), effector T-memory cells (TEM) must be differentiated from a subgroup of effector T cells [62] which are preserved for life as they respond to re-challenge with antigen [63,64]. From all the above stated defects, failure of immune checkpoint inhibition therapy occurs due to the three key reasons: (1) lack of anti-tumor T cells generation, (2) inadequate tumor-specific T cells function [65,66] and (3) development of T-cell memory impairments [59,60]. Impaired neoantigen processing, lack of sufficient or suitable neoantigens and/or impaired presentation of neoantigens might lead to impairments in the development of tumor-reactive T cells [59]. Tumor-extrinsic immune suppressive components and diverse tumor-intrinsic components of the tumor microenvironment can lead to inadequate T-cell function [67]. The detailed mechanism of resistance is provided in Fig. 4.

Analyzing patients beneath the treatment of immune checkpoint inhibitor, it is quite evident that the innate and adaptive resistance of immunotherapy can arise and as a result of it, the effectiveness of immunotherapy treatment can be restricted. This directs for the idea to augment the clinical advantages of immune checkpoint inhibitor regimen by blending radiotherapy and chemotherapy, with either other immunotherapy, or using the tyrosine kinase inhibitors with targeted therapies. Several clinical trials are ongoing, that detects the therapeutic approaches in an abundance of ailments and clinical cases. The target is not only to raise the activity and functioning of immune cell-associated destruction of tumor cell, but even the implementation of this stated concept for other immune cells like, neutrophils, myeloid-derived suppressor cells, T regulatory cells as well as induced tumor infiltration by immunocompetent cells and ultimately make them more immunogenic [68]. For obtaining an enhanced immunotherapy efficacy

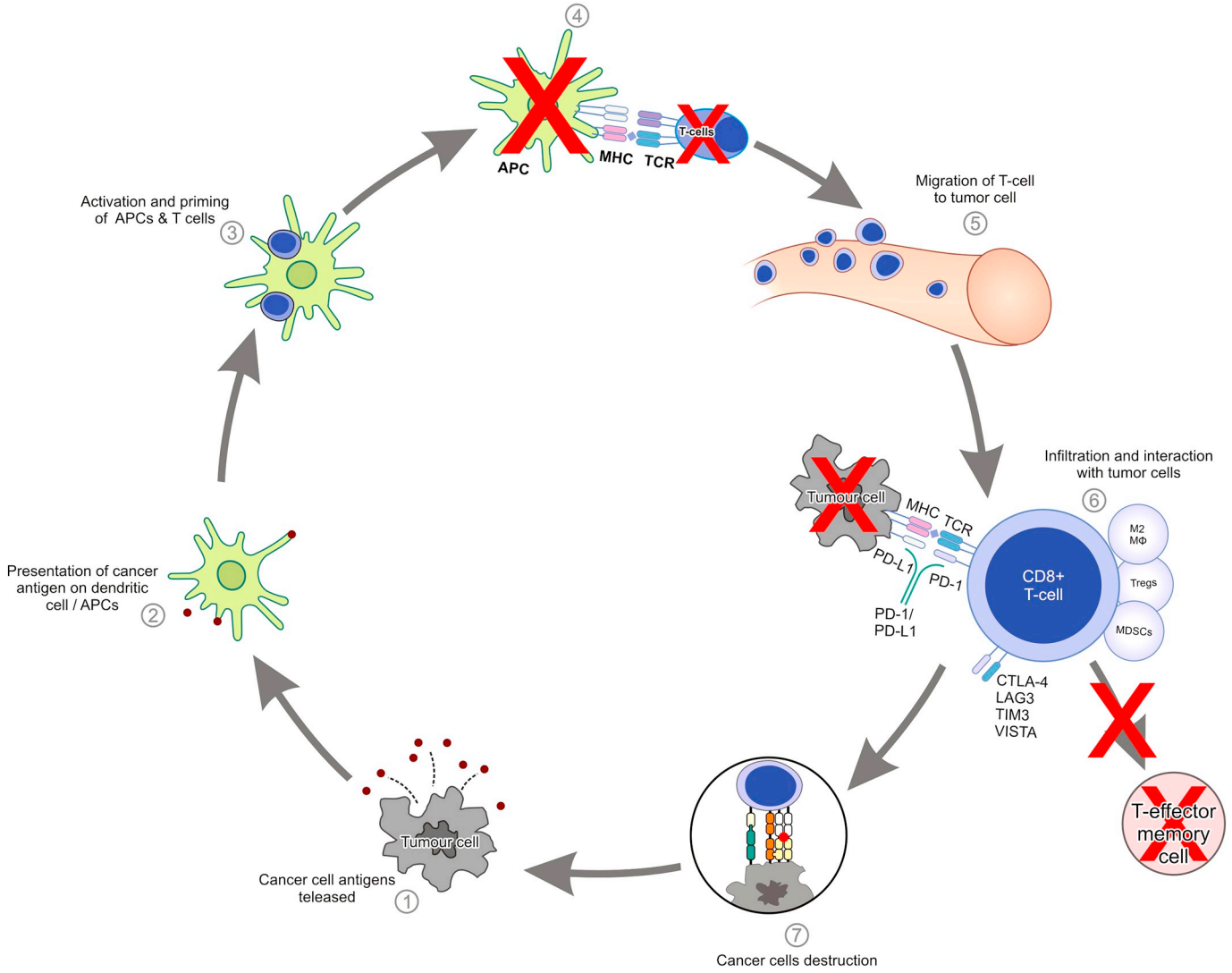

Fig. 4. Schematic representation of generation of tumor-specific T cells, effector T-cell function, and formation of memory T cells along with details of resistance to immunotherapy. Once the tumor cells are formed, cancer antigens are released from tumor cells and bind to the APCs or dendritic cells. And results into the activation and priming of APCs and T-cells. The tumor reactive T-cells are formed and migrate into the tumor cells and activate the effector T-cell function and leads to the killing of tumor cells and formation of effector memory T-cells. The red crosses in Fig. 4 shows the resistance in cancer cells destruction. The resistance occurs by impaired processing or presentation of tumor antigens and impaired intratumoural immune infiltration (step-4). The resistance also occurs by impaired tumor cell signaling and destruction of formation of effector memory T-cells which controls the tumor (step-6). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

for cancer, the key parameter is dealing effectively with the resistance mechanisms. Eventually, future strategies like the merging of immune checkpoint inhibitors with different immunotherapies, with chemotherapy, tyrosine kinase inhibitors or with radiotherapy should focus the malignant cells as well as their immunocompetent cells functioning and microenvironment [69,70].

3.1. Overcoming treatment resistance

It became clear that primary and adaptive resistance to immunotherapy might occur which limits the efficacy of treatment by following patients under immune checkpoint inhibitor treatment. This calls for concepts to maximize the clinical benefit of immune checkpoint inhibitor treatment by the combination with either other immunotherapy, with radiotherapy, with chemotherapy or using tyrosine kinase inhibitors with targeted therapies. An abundance of clinical trials in a similar abundance of clinical scenarios and diseases are underway for all of these therapeutic approaches. Goals are to not only increase the activation and function of immune cell-associated tumor cell destruction, but also to widen the current concept to other immune cells including T regulatory cells, neutrophils, and myeloid-derived suppressor cells, and induce tumor infiltration by immunocompetent cells and finally make them more immunogenic. For obtaining an enhanced efficacy of immunotherapy in cancer overcoming resistance mechanisms will be the key. Thus, future strategies should not only address the malignant cells themselves but also their microenvironment and the function of immunocompetent cells. These strategies are described in upcoming section.

3.2. Combinations of other immunotherapies with immune checkpoint inhibitor treatment

In the Checkmate 012 study, for first line treatment of stage IV NSCLC the idea of addressing the immune response and the tumor microenvironment has been studied, as CTLA-4 inhibition by ipilimumab is directed at the microenvironment, which should increase the efficacy of nivolumab seen in this disease. The proof of this concept was generated by the fact that in a subgroup of patients, a partial response

Table 1
Summary of various adverse effects of Checkpoint Inhibitors used for lung cancer.

Sr. No	Type of Toxicity	Major Symptoms	Targets	Drugs	References
1.	Endocrinological Disturbance				
	a. Hypothyroidism	Fatigue, constipation, weight gain or bradypsychia.	PD-1/PD-L1 and CTLA-4	Ipilimumab, nivolumab, Pembrolizumab and atezolizumab	[74,75]
	b. Hyperthyroidism	diarrhea, tachycardia, hyperhidrosis, tremors or even exophthalmos.	PD-1/PD-L1 and CTLA-4	Ipilimumab, nivolumab, pembrolizumab or the combination of ipilimumab and nivolumab	[75,76]
	c. Hypophysis	Nausea/vomiting, loss of libido, fatigue, muscle weakness, mild hyponatremia, orthostatic hypotension and headache	PD-1/PD-L1 and CTLA-4	Ipilimumab, nivolumab, Pembrolizumab and atezolizumab	[75,78,79]
	d. Adrenal Gland Alterations	Nausea/vomiting, skin hyperpigmentation, weight loss and fatigue.	PD-1/PD-L1	Nivolumab and Pembrolizumab	[77]
	e. Diabetes	Polydipsia with an elevated in urine output frequency.	PD-1/PD-L1	Nivolumab and Pembrolizumab	[80]
2.	Dermatologic Manifestations				
	a. Rash	Erythematous macules with or without papules, Lesions along with signs of lichenoid dermatitis, pruritus, and spongiotic dermatitis.	PD-1/PD-L1	Nivolumab and Pembrolizumab	[81,82]
	b. Other Skin Disturbances	Bullous pemphigoid, Stevens–Johnson syndrome or psoriasis	PD-1/PD-L1 and CTLA-4	Ipilimumab, nivolumab, Pembrolizumab, Durvalumab	[83–85]
3.	Cardiac Toxicity				
	a. Myocarditis	Palpitations, dyspnea or chest pain, arrhythmias, pericardial/pleural effusion, elevation in serum troponin levels, increase in BNP (Brain Natriuretic Peptide)	PD-1/PD-L1 and CTLA-4	Nivolumab and pembrolizumab and more frequent and severe with the combination of ipilimumab and nivolumab	[86–88]
	b. Pericarditis	Fever, chest pain, shortness of breath and pericardial friction rub.	PD-1/PD-L1	Nivolumab	[89]
4.	Pulmonary Toxicity	Dry cough, dyspnea, pneumonitis, infectious pneumonitis, pneumonitis may result to respiratory failure.	PD-1/PD-L1	Nivolumab, Pembrolizumab and Atezolizumab	[90–92]
5.	Gastrointestinal Disturbances				
	a. Colitis	Abdominal pain, Bloody or watery diarrhea, lamina propria expansion, villous blunting, fever, normal mucosa, acute inflammation, friability, mild erythema to severe inflammation with mucosal granularity and ulceration.	PD-1/PD-L1 and CTLA-4	More in ipilimumab alone or in combination, than in those treated with single-agent Pembrolizumab, Nivolumab and Atezolizumab	[34,75,93,100]
		Crohn's disease, intraepithelial lymphocytes, infectious diarrhea, ulcerativeand pseudomembranous colitis	CTLA-4	Ipilimumab	[95,96]
	b. Hepatitis	Increase of serum levels of hepatic alanine aminotransferase, elevation of aspartate aminotransferase enzymes, fatigue, fever, fulminant hepatitis, malaise and death	PD-1/PD-L1 and CTLA-4	Pembrolizumab, Nivolumab, Atezolizumab and ipilimumab.	[93,97,101]
		Acidophilic bodies, lobular hepatitis with scattered foci of patchy necrosis, bile ductular proliferation, focal endothelialitis, cholangiolitis, and bile duct injury, confluent necrosis and histiocytic aggregates.	PD-1/PD-L1 and CTLA-4	Pembrolizumab, Nivolumab, Atezolizumab and ipilimumab	[98,100]
	c. Pancreatitis	Elevated lipase, increase of serum amylase, swollen pancreas, decreased tissue contrast enhancement and lobulation	PD-1/PD-L1	Nivolumab, pembrolizumab, atezolizumab, durvalumab and avelumab.	[101–105]
6.	Haematologic Disturbances				
	a. Aplastic Anaemia	Pancytopenia and hypocellularity with stromal edema.	PD-Ll and CTLA-4	Pembrolizumab, Nivolumab and Nivolumab in combination with ipilimumab	[97,106–109]
	b. Autoimmune HaemolyticAnaemia	Increased bilirubin, reticulocyte count and decreased haptoglobin, elevated lactate dehydrogenase, and spherocytosis.	PD-1	Nivolumab	[110]
	c. Immune Thrombocytopenic Purpura	Elevated levels of platelet-associated igg, decreased platelet count increased normal white blood cell count, elevated number of megakaryocytes and elevated hemoglobin levels.	PD-1/PD-L1 and CTLA-4	Nivolumab,Pembrolizumab, durvalumab, Atezolizumab and combined nivolumab and ipilimumab.	[111–113].
7.	Nephrological Alterations				
	a. Acute interstitial nephritis (AIN)	Haematuria, oliguria and/or hypertension, fever, eosinophilia, and skin rash, creatinine increase, eosinophilia, inflammatory infiltrates (diffuse or patchy) and mild hyponatraemia, interstitial edema.	PD-1/PD-L1 and CTLA-4	Ipilimumab, nivolumab, pembrolizumab	[114–116]

(*continued on next page*)

Table 1 (*continued*)

Sr. No	Type of Toxicity	Major Symptoms	Targets	Drugs	References
8.	Ocular Syndromes				
	a. Uveitis	Conjunctival redness, photophobia, floaters, blurry vision and eye pain.	PD-1/PD-L1 and CTLA-4	Nivolumab, atezolizumab, pembrolizumab, durvalumab, Avelumab and ipilimumab	[117,118]
	b. Vogt–Koyanagi–Harada Syndrome (uveomeningitis syndrome)	Blurry vision, exudative retinal detachments with bilateral uveitis, cutaneous and neurologic manifestations.	PD-1	Nivolumab	[119]
	c. Other Ocular toxicity				
	a. Uveal effusion	Blurry vision, redness and ocular, serous choroidal detachment, including the fovea presence of subretinal and intraretinal fluid.	PD-1/PD-L1	Nivolumab, atezolizumab and pembrolizumab	[120]
	b. Retinopathy	Causing blurry vision	Secondary to anti-PD-1/PD-L1 agents	Nivolumab, atezolizumab and pembrolizumab	[118,121]
9.	Rheumatologic Disorders				
	a. Arthralgia/Myalgia	Arthritis or myositis	PD-1/PD-L1 and CTLA-4	Nivolumab, Pembrolizumab and Ipilimumab and combined nivolumab and ipilimumab.	[122]
	b. Arthritis	Arthralgia, joint tenderness, swelling, warmth, morning stiffness, redness and signs of inflammation in joint.	PD-1/PD-L1 and CTLA-4	Nivolumab, Pembrolizumab, durvalumab, Atezolizumab and ipilimumab.	[123–125]
	c. Myositis	Mild myalgia, myocarditis or accompanying myasthenia-like features and weakness to life-threatening rhabdomyolysis.	PD-1/PD-L1 and CTLA-4	Nivolumab, Pembrolizumab, durvalumab and combined nivolumab and ipilimumab.	[126,127]
10.	Neurological Disorders				
	a. Acute/Chronic Demyelinating Polyradiculoneuropathy	Sensory loss, paresthesia, loss of taste, decreased visual acuity, diplopia, dysarthria and weakness	PD-1	Nivolumab	[120,128,129]
	b. Encephalitis	Vomiting, fatigue, fever, Confusion, mononuclear pleocytosis, Dominance of cerebellar symptoms may occur, spastic tremors, altered movements, gait disturbance and tremor.	CTLA-4 and PD-1/PD-L1	Nivolumab, Atezolizumab and Ipilimumab.	[130–132]
	c. Myasthenia Gravis and Myasthenia-Like Syndromes	Thymoma, affect respiratory musculature.	PD-1/PD-L1 and CTLA-4	Nivolumab, Pembrolizumab and Ipilimumab	[133–135]

was observed in 39% with PFS at 24 weeks seen in 63% of patients; however, an abundance of other immunomodulating compounds, such as vaccines in combination with immune checkpoint inhibitors and antagonistic antibodies directed against proteins, such as LAG-3 or activating antibodies against such peptides as OX-40 are in current clinical testing.

3.3. Combinations of chemotherapy with immune checkpoint inhibitors

Checkpoint inhibition plus chemotherapy may show supplementary benefits as cytotoxic drugs have more effects than only causing death of malignant cells thereby setting free cancer-associated antigens but also by interfering with the function of a series of immunocompetent cells. Thus, as examples dendritic cell activation increased by anthracyclines, anti-tumor CD4+ cells elevated by cyclophosphamide and by CD8+ cells cell recognition and lysis are carried out, and the activity of T-regulatory cells and myeloid-derived suppressor cells is revoked by cisplatin.

3.4. Combination of tyrosine kinase inhibitors with immune checkpoint inhibitors

In the combination of targeted therapies with immune checkpoint inhibition, early studies using ipilimumab and vemurafenib have shown that care has to be taken regarding potential severe toxicities, particularly hepatotoxicity. This seems to depend on the drugs of choice and the sequence of their application as, for an impressive example, the number and function of T-regulatory cells decreases by the combination of nivolumab with VEGF inhibitors or TKIs.

3.5. Combination of radiotherapy with immune checkpoint inhibitors

The effect of a combination of checkpoint inhibitors with radiotherapy is determine by abundance clinical trials which are underway, the effect have been primarily observed by the induction of abscopal effect resulting from antigen exposure originating from destroyed cancer cells and the induction of a type I IFN response.

4. Adverse effects

Every coin has two sides. Adverse effects and development of resistance are other two sides of check point inhibitors. No drug comes without some side effects or adverse effects. Immune checkpoint blockade might lead to immune-related adverse events (irAEs) in a significant figure because of the initiation of over immune reactivity stimulation, else due to the induction of absolute autoimmune phenomena [71,72]. These adverse effects are noticed among 7\10 patients with CTLA-4-inhibition, while these occur in only 2–3 out of 10 with PD-(L)1 inhibitor treatment [73]. Other than that, endocrinological disturbance, dermatological manifestation, cardiac toxicity, pulmonary toxicity, gastrointestinal disturbances are some additional effects observed with immune checkpoint inhibitors [74]. The detail of such adverse effects is given in forthcoming sections.

4.1. Endocrinological disturbance

Endocrinological disturbances are the most frequent adverse events reported with immune checkpoint inhibitors.

4.1.1. Hypothyroidism

Hypothyroidism has been reported in patients receiving anti-PD-1/PD-L1 agents such as nivolumab, pembrolizumab or atezolizumab and also with anti CTLA-4 agents such as ipilimumab according to recent meta-analysis. Patients with hypothyroidism usually present with symptoms such as fatigue, constipation, weight gain or bradypsychia [74,75].

4.1.2. Hyperthyroidism

Hyperthyroidism has been observed with anti-PD-1/PD-L1 agents and CTLA-4 agents, even though it is less frequent than hypothyroidism. It is observed with nivolumab, pembrolizumab, ipilimumab or with combination of nivolumab and ipilimumab. Patients who develop hyperthyroidism usually present with symptoms like diarrhea, tachycardia, hyperhidrosis, tremors or even exophthalmos [75,76].

4.1.3. Adrenal gland alterations

The incidence of adrenal gland alterations has been rarely observed with anti-PD-1/PD-L1 agents such as nivolumab and pembrolizumab. Patients with adrenal gland alterations usually present with symptoms like nausea/vomiting, skin hyperpigmentation, weight loss, and fatigue [77].

4.1.4. Hypophysis

In patients receiving anti-CTLA-4 agents such as ipilimumab, hypophysitis is more prone to being developed. Hypophysitis is also observed with anti PD-1/anti PD-L1 agents such as nivolumab, pembrolizumab and atezolizumab. Hypophysis is usually manifested by nausea/vomiting, loss of libido, fatigue, muscle weakness, mild hyponatremia, orthostatic hypotension and headache [75,78,79].

4.1.5. Diabetes

Type 1 diabetes may develop in patients receiving anti-PD-1/PD-L1 agents such as nivolumab and pembrolizumab. Symptoms such as polydipsia with an elevated in urine output frequency should be ruled out [80].

4.2. Dermatologic manifestations

Skin toxicity is one of the most common adverse effects seen in patients receiving anti-PD-1/PD-L1 and anti- CTLA-4 agents.

4.2.1. Rash

Rash constitutes the most frequent cutaneous toxicity in patients treated with anti-PD-1/PD-L1 agents such as nivolumab and pembrolizumab. Patients with rash usually present with symptoms such as erythematous macules with or without papules, lesions along with signs of lichenoid dermatitis, pruritus, and spongiotic dermatitis [81,82].

4.2.2. Other skin disturbances

With anti-PD-1/PD-L1 agents like nivolumab, pembrolizumab or durvalumab and anti- CTLA agents such as ipilimumab many other dermatologic alterations have been diagnosed. And entities with other skin disorders such as Bullous pemphigoid, Stevens–Johnson syndrome or psoriasis have been described [83–85].

4.3. Cardiac toxicity

Cardiological events may occur using anti- CTLA-4 agents and anti-PD-1/PD-L1 agents. These events may be life-threatening and lead to fulminant situations.

4.3.1. Myocarditis

Myocarditis has been described with anti- CTLA-4 agents and anti-PD-1/PD-L1 agents. With agents such as nivolumab, pembrolizumab or with the combination of ipilimumab and nivolumab myocarditis is more frequent and severe. Symptoms may vary like palpitations, dyspnea or chest pain, arrhythmias, pericardial/pleural effusion, elevation in serum troponin levels, increase in BNP (Brain Natriuretic Peptide) [86–88].

4.3.2. Pericarditis

Autoimmune pericarditis is rarely associated with patients receiving anti-PD-1/PD-L1 agents such as nivolumab. Patients with pericarditis usually present with symptoms like fever, chest pain, shortness of breath and pericardial friction rub [89].

4.4. Pulmonary toxicity

In a recent meta-analysis, patients receiving anti-PD-1/PD-L1 agents like nivolumab, pembrolizumab, and atezolizumab may develop pulmonary toxicity. Symptoms such as dry cough, dyspnea, pneumonitis, infectious pneumonitis, pneumonitis may result in respiratory failure are diagnosed [90–92].

4.5. Gastrointestinal disturbances

Gastrointestinal tract disorders are one of the most common toxicities derived from immunotherapy.

4.5.1. Colitis

Colitis is more common in patients receiving anti- CTLA-4 agents like ipilimumab, alone or in combination, than in those treated with single anti-PD-1/PD-L1 agents such as nivolumab, pembrolizumab, and atezolizumab. Symptoms like abdominal pain, bloody or watery diarrhea, lamina propria expansion, villous blunting, fever, normal mucosa, acute inflammation, friability, mild erythema to severe inflammation with mucosal granularity and ulceration are observed. Patients receiving anti-CTLA-4 agents like ipilimumab are also diagnosed with crohn's disease, intraepithelial lymphocytes, infectious diarrhea, ulcerative and pseudomembranous colitis [75,9–96,100].

4.5.2. Hepatitis

Hepatitis is observed with patients receiving anti-CTLA-4 agents such as ipilimumab and also with anti-D-1/PD-L1 agents like nivolumab, pembrolizumab and atezolizumab. Symptoms like increase of serum levels of hepatic alanine aminotransferase, elevation of aspartate aminotransferase enzymes, fatigue, fever, fulminant hepatitis, malaise and death are observed with hepatitis. Acidophilic bodies, lobular hepatitis with scattered foci of patchy necrosis, bile ductular proliferation, focal endothelialitis, cholangiolitis, and bile duct injury, confluent necrosis and histiocytic aggregates like symptoms are also diagnosed [93,97–101].

4.5.3. Pancreatitis

In patients receiving anti-PD-1/PD-L1 agents like nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab pancreatitis is more common. Patients with pancreatitis usually present with symptoms such as elevated lipase, increase of serum amylase, swollen pancreas, decreased tissue contrast enhancement and lobulation [101–105].

4.6. Haematologic disturbances

Haematologic disorders are rarely associated with anti-PD-1/PD-L1 therapy and anti- CTLA-4 agents.

4.6.1. Aplastic anaemia

Aplastic anaemia has been observed with anti-PD-1 agents like nivolumab and pembrolizumab or in combination of nivolumab with ipilimumab which is an anti-CTLA-4 agent. Symptoms such as pancytopenia and hypocellularity with stromal edema are observed with aplastic anaemia [97,106–109].

4.6.2. Autoimmune haemolytic anaemia

In patients receiving anti-PD-1 agents like nivolumab, autoimmune haemolytic anaemia has been diagnosed. Patients with AHIA usually present with symptoms such as increased bilirubin, reticulocyte count and decreased haptoglobin, elevated lactate dehydrogenase, and spherocytosis [110].

4.6.3. Immune thrombocytopenic purpura (ITP)

In patients receiving anti-PD-1/PD-L1 agents like nivolumab, pembrolizumab, atezolizumab and durvalumab, ITP has been reported. ITP has also been diagnosed with a combination of nivolumab and ipilimumab which is an anti-CTLA-4 agent. Patients with ITP usually present with symptoms such as elevated levels of platelet-associated igg, decreased platelet counts increased normal white blood cell count, elevated number of megakaryocytes and elevated hemoglobin levels [111–113].

4.7. Nephrological alterations

Nephrological Alterations are usually associated with anti- PD-1/PD-L1 and anti- CTLA-4 agents.

4.7.1. Acute interstitial nephritis

Acute interstitial nephritis is an inflammatory disease usually associated with anti- PD-1/PD-L1 and CTLA-4 agents like nivolumab, pembrolizumab, and ipilimumab. Patients with acute interstitial nephritis usually presents with symptoms such as haematuria, oliguria and/or hypertension, fever, eosinophilia, and skin rash, creatinine increase, eosinophilia, inflammatory infiltrates (diffuse or patchy) and mild hyponatraemia, interstitial edema [114–116].

4.8. Ocular syndromes

Ophthalmologic immune-related adverse events are infrequent.

4.8.1. Uveitis

Uveitis is associated with anti-PD-1/PD-L1 and anti-CTLA-4 agents like nivolumab, atezolizumab, pembrolizumab, durvalumab, avelumab and ipilimumab. Symptoms like conjunctival redness, photophobia, floaters, blurry vision and eye pain are observed with uveitis [117,118].

4.8.2. Vogt–Koyanagi–Harada syndrome

Vogt–Koyanagi–Harada-like syndrome, also known as uveomeningitis syndrome, is diagnosed in patients receiving anti PD-1 agents like nivolumab. Symptoms such as blurry vision, exudative retinal detachments with bilateral uveitis, cutaneous and neurologic manifestations are observed with Vogt–Koyanagi–Harada Syndrome [119].

4.8.3. Other ocular toxicity

4.8.3.1. Uveal effusion. Uveal effusion has been reported with patients receiving anti- PD-1/PD-L1 like nivolumab, atezolizumab and pembrolizumab. Patients with uveal diffusion usually present with symptoms such as Blurry vision, redness and ocular, serous choroidal detachment, including the fovea presence of subretinal and intraretinal fluid [120].

4.8.3.2. Retinopathy. Retinopathy like adverse effects is associated secondary to anti-PD-1/PD-L1 agents like nivolumab, atezolizumab and pembrolizumab. Diagnosed with symptoms like causing blurry vision [118,121].

4.9. Rheumatologic disorders

Immune-mediated rheumatologic adverse events are underestimated as many clinical studies did not report this type of adverse event.

4.9.1. Arthralgia/myalgia

Arthralgia/Myalgia have been widely reported with anti-PD-1/PD-L1 such as nivolumab, pembrolizumab, with anti-CTLA-4 agents like ipilimumab and also been reported with combination of nivolumab and ipilimumab. It is especially been associated with anti PD-1 drugs. Inflammatory signs either arthritis or myositis should be ruled out [122].

4.9.2. Arthritis

Arthritis is reported in patients treated with anti-PD-1/PD-L1 agents in monotherapy such as nivolumab, pembrolizumab, atezolizumab or durvalumab and in combination with anti-CTLA-4 agents like ipilimumab. Patients with arthritis usually presents with symptoms such as arthralgia, joint tenderness, swelling, warmth, morning stiffness, redness and signs of inflammation in joint [123–125].

4.9.3. Myositis

Myositis is observed with patients treated with anti- PD-1/PD-L1 agents like nivolumab, pembrolizumab or durvalumab or in combination with anti-CTLA-4 agents like ipilimumab. Symptoms like mild myalgia, myocarditis or accompanying myasthenia-like features and weakness to life-threatening rhabdomyolysis should be ruled out [126,127].

4.10. Neurological disorders

The incidence of neurotoxicity is rare and only a few cases of immune-related neurotoxicity have been reported with anti-PD-1/PD-L1 and anti- CTLA-4 agents.

4.10.1. Acute/chronic demyelinating polyradiculoneuropathy

Acute/Chronic Demyelinating Polyradiculoneuropathy is reported with patients receiving anti-PD-1 agents like nivolumab. Patients with Acute/Chronic Demyelinating Polyradiculoneuropathy usually presents with symptoms such as sensory loss, paresthesia, loss of taste, decreased visual acuity, diplopia, dysarthria and weakness [120,128,129].

4.10.2. Encephalitis

In a recent meta-analysis, encephalitis has been reported in patients receiving anti- PD-1/PD-L1 agents such as nivolumab or atezolizumab and also with anti- CTLA-4 agents like ipilimumab. Symptoms like vomiting, fatigue, fever, confusion, mononuclear pleocytosis, dominance of cerebellar symptoms may occur, spastic tremors, altered movements, gait disturbance and tremor should be ruled out [130–132].

4.10.3. Myasthenia gravis and myasthenia-like syndromes

Myasthenia Gravis and Myasthenia-Like Syndromes are associated with patients treated with anti-PD-1/PD-L1 agents like nivolumab and pembrolizumab. It has also been reported with anti-CTLA-4 agents like ipilimumab. Patients with myasthenia gravis and myasthenia-like syndromes usually present with symptoms such as thymoma or affecting respiratory musculature [133–135].

A comprehensive list of adverse effects of various checkpoint inhibitors used for lung cancer is provided in Table 1.

5. Conclusions

Researches and study directed around the immunotherapy technique have been quickly drawing a vital path in developing a promising therapy to deal with lung cancer, thereby resulting in the improvement of outcomes in lung cancer histologies. Immune checkpoint inhibitors have made a noteworthy impact on the reports of those individuals diagnosed with lung cancer and led to majestic clinical activity and durable responses. Checkpoint inhibitors immunotherapy has modified lung cancer treatment and enhanced patient survival records. Despite such impressive advantages, resistance has been developed in patients who are treated with immune checkpoint inhibitors. Immunotherapy using the inhibition of checkpoint may lead to immune-related adverse events (irAEs) in a notable group of reported individuals because of the introduction of over immune reactivity stimulation or else to development of complete autoimmune occurrence. Future studies for

developing the new drugs or therapies such as immune checkpoint inhibitors should be carried out for improving the overall response rate or to overcome the response rate and deal with their side effects.

Declaration of competing interest

None.

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