REVIEW ARTICLE

IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER: A REVIEW

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Abstract

Immunotherapy has revolutionized the field of oncology by utilizing the body's immune system to target and eliminate cancer cells. In non-small cell lung cancer (NSCLC), immunotherapeutic agents such as immune checkpoint inhibitors (ICIs) have shown promising results. ICIs target receptors like PD-1, PD-L1, and CTLA-4 to enhance the immune response against tumors. However, resistance mechanisms to immunotherapy are not fully understood, and ongoing research aims to overcome these challenges. In the early-stage setting, neoadjuvant and adjuvant trials are investigating the efficacy of ICIs in combination with chemotherapy, with interesting results. Additionally, in the metastatic landscape of NSCLC the therapeutic options multiplied in recent years. The use of immunotherapy in NSCLC holds great promise, and future studies may provide more effective therapies and biomarkers for personalized treatment approaches.

Keywords: *immunotherapy, NSCLC, treatment, lung cancer, immune checkpoint inhibitors.*

Immunology and oncology have been hand in hand since the late 19th century, when a surgeon named William Coley reported that tumor shrinkage could be achieved with the injection of killed bacteria into sarcoma sites [1]. Over the past decades, enormous advances in the understanding of the tight relationship between immune surveillance and tumor growth and development have led to broad therapeutic advances that are now being studied in all types of cancers.

1) TUMOR IMMUNOLOGY

An efficient immune response against a tumor requires a complex interaction between a variety of immune cell types in the adaptive and innate immune system.

The various immune cell types involved are:

a) CD8+ and CD4+ lymphocytes: these cells initiate the distinction between self and non-self-antigens through antigen-presenting cells (APCs) such as dendritic cells. Overall, the cytotoxic activity of a CD8+ T cell is regulated by the presence and spatial orientation of a set of stimulatory and inhibitory receptors whose expression is regulated by a multitude of cytokines. This configuration is often referred to as the "immune synapse". The most important costimulatory signal in naïve T cells is CD28, which binds to B7-1 and B7-2 (CD80/86) on the APC (Figure 1). This costimulatory process is tightly regulated by both "agonist" signals (e.g., GITR, OX40, ICOS) and inhibitory signals on both the APC and T cells, often collectively referred to as "immune checkpoint" molecules. Examples of co-inhibitory or "immune checkpoint" molecules include cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death 1 (PD-1), TIM3, and LAG3. Chronic recognition of an antigen (such as that present in a malignant clone or in a chronic viral infection) may lead to feedback inhibition of effector T cell function, resulting in a phenotype termed "exhaustion".[2]

b) Natural killer (NK) cells do not require antigen

presentation by the major histocompatibility complex (MHC) for cytotoxic activity. NK cells also express various inhibitory molecules, most notably killer immunoglobulin-like receptor (KIR) subtypes.[3]

c) Macrophages present with two different phenotypes: M1 which are responsible for phagocytosis through the release of interferon (IFN) gamma; and M2 macrophages that are responsible for tolerance and diminished inflammatory response due to cytokine release such as IL-4, IL-10 and transforming growth factor beta (TGF-beta) [4].

d) Finally, additional cell types such as FoxP3+, CD25+, CD4+ T regulatory (Treg) and myeloid derived suppressor cells (MDSCs) largely inhibit cytotoxic T lymphocyte activity.[5,6]

The interaction of the cells described above is the hallmark of immune surveillance, however tumor evasion in some cases happens regardless. This current prevailing theory is called "cancer immunoediting", and it evolves in three phases (Figure 2)[7]: 1 – elimination phase consists of innate and adaptive immune responses to specific tumor-associated antigens and is characterized by T, B and NK cell effector function[8, 9]; 2 –the equilibrium phase is a balance between destruction by the adaptive immune system and persistence of rare malignant clones; 3 – the immunologic escape phase happens when malignant cells have acquired the ability to evade the immune system.

2) IMMUNOTHERAPEUTIC AGENTS

Cancer immunotherapy harnesses the body's immune system to launch an immune response against cancer cells. Immune agents like cytokines, vaccines, cell therapies, humoral and transfection agents are used to tweak the immune system. This review focuses on the immunotherapeutic interventions with efficacy in NSCLC such as monoclonal antibodies anti-PD-1/ PD-L1 agents and anti-CTLA-4 antibodies. Other agents like cancer vaccines, oncolytic viruses and adoptive T cell therapy are still in development or under clinical trials and will not be discussed here.

Immune Checkpoint Inhibitors (ICIs) target the programmed death 1 receptor (PD-1), programmed cell death receptor ligand 1 (PD-L1) and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). Targeting PD-1, PD-L1, and CTLA-4 helps the T cell population target and eliminate tumor cells.10 ICIs used in NSCLC that target PD-1 are nivolumab pembrolizumab and cemiplimab; those that are anti-PD-L1 are atezolizumab and durvalumab and the one anti-CTLA-4 is ipilimumab. (Table1)

1) PD-1 and PD-L1 inhibitors

When PD-1 (present on T cells and other immune cells) interacts with its ligands PD-L1 and PD-L2 (present on tumor cells), the number of receptors on the surface of T cells decreases, making the T cells insensitive to cancer cells. Many lung cancers overexpress PD-L1 to downregulate the T cell response. PD-1 inhibitors block the interaction of PD-1 with PD-L1 and PD-L2, but not the interaction of PD-L1 with CD80 (B7.1). Anti-PD-L1 antibodies block the interaction of PD-L1 with PD-1 and CD80 (B7.1) but allow PD-L2 to interact with PD-1 and CD80 to interact with CTLA-4.The expression of PD-L1 in NSCLC tissues serves as an important biomarker which could help one select an appropriate intervention that will reduce the overexpression of PD-L1 in tumors.

Although with similar activity these antibodies are not equal. Pembrolizumab is a fully humanized IgG4 kappa isotype monoclonal antibody; Nivolumab is a fully human immunoglobulin G4 antibody; Atezolizumab is a humanized IgG1 monoclonal, antagonistic, anti- PD-L1 antibody; Durvalumab (MEDI4736) is a high- affinity, humanized IgG1-antagonistic, PD-L1 inhibiting antibody; Cemiplimab is a recombinant human immunoglobulin G (IgG) 4 monoclonal antibody that binds to programmed cell death 1 (PD-1) and blocks its interaction with programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), countering PD-1- mediated inhibition of the immune response, including the anti-tumor immune response. [11]

2) CTLA-4 inhibitors

CTLA-4 is another inhibitory receptor that disrupts T cell function. It uses CD28, a co-stimulatory receptor to reduce T cell signaling and suppresses the immune system.[4] CTLA-4 inhibitors activate T cells and help them launch an immune response against tumors. They have also been observed to exert a synergistic anti-tumor response when combined with vaccines, chemotherapy, and radiation.

Ipilimumab is an IgG1 monoclonal antibody. It was the first anti-CTLA-4 antibody that received approval for cancer, however, it failed to bring about the desired effects in NSCLC patients.[11]

Immunotherapy resistance mechanisms

The advent of immune checkpoint inhibitors (ICIs) completely changed the therapeutic landscape of NSCLC, but most lung cancer patients eventually progress during immunotherapy.[10, 11]

Truthfully, resistance to immunotherapy is not fully understood. Wang et al. classified resistance based on the timing of its development, the characteristics of the cancer cell, and the type of immune infiltrate [12]. With respect to timing, primary resistance is defined as disease progression during first-line ICIs, and acquired resistance is defined as tumor progression after initial disease control [13]. Schoenfeld et al defined acquired resistance to PD-(L)1 blockade patients who meet the following criteria: received prior treatment that included PD-(L)1 blockade, experienced objective response on PD-(L)1 blockade, and presented with progressive disease occurring within 6 months of last anti-PD-(L)1 antibody treatment or rechallenge with anti-PD-(L)1 antibody, if not exposed to anti-PD-(L)1 in 6 months[14].

When considering the cancer cell itself, we can identify intrinsic resistance, which is related to genomic or proteomic features, and extrinsic resistance, which is modulated by the tumor microenvironment, including the immune cells. Finally, the spatial distribution of immune cells can create distinct patterns with complete absence of immune cells (immune desert), abundant intratumoral immune cells within the tumour and at the periphery (inflamed pattern), or absence of immune cells in the tumour bed, with immune cells only at the invasive margin (immune excluded tumors).[15]

Currently, the distinction between primary and secondary resistance is applicable in clinical trials and for clinical purposes but cannot be used to guide treatment selection and does not offer any mechanistic insight for the development of more effective therapies or biomarkers. However, in the future with a clear definition of these sub-populations of patients, perhaps a more tailored treatment approached can be reached with new molecules and drugs under investigation.

Immunotherapy in early stage

Patients with stage I, II, or III non-small cell lung cancer (NSCLC) are at substantial risk for recurrence and death even after complete surgical resection. Approximately 25% of patients with stage IB, 35 to 50% of stage II, and a greater percentage of those with pathologic stage III NSCLC eventually recur and die of their disease despite potentially curative surgery [16].Recently, with the revolution of immunotherapy in the advanced setting, the opportunity to exploit the possible benefit deriving from these new treatment options in earlier stages has been taken into consideration.

Concerning ICIs several trials have been designed and are currently ongoing to investigate their role in early-stage NSCLC.

a) Neoadjuvant trails

In the neoadjuvant setting, in preliminary results of Checkmate 816, among over 350 patients with stage IB to IIIA resectable NSCLC and no known EGFR/ALK genetic mutation, the addition of nivolumab to neoadjuvant platinum-doublet chemotherapy improved pathologic complete response rates (24.0% versus 2.2%; odds ratio 13.9, 99% CI 3.5-55.8) and major pathologic response in 36.9% vs. 8.9% (OR 5.70, 95% CI 3.16–10.26).There was no decrease in the percentage who underwent definitive surgery (83% versus 75%) or increase in grade ≥3 adverse events (34% versus 37%)[17]. A prespecified interim analysis for OS resulted in an HR of 0.57 (99.7% CI 0.30-1.07); although this did not cross the threshold for statistical significance, the majority of patients were still living at the time of this analysis (74%). Longer follow-up is needed but CheckMate 816 data certainly appear as practice-changing results in this setting and nivolumab combined with CT has already received FDA approval and is undergoing EMA centralized review procedure.

Many other trials are ongoing with other ICI molecules (Table 1).

IMpower-030 is a phase III trial randomizing stage II-IIIB (N2) patients to neoadjuvant atezolizumab/placebo in association with CT for 4 cycles; then, after unblinding, patients in the experimental arm will also receive adjuvant atezolizumab for 16 cycles[18]. Atezolizumab is being tested in this setting also in association with tiragolumab (an anti-TIGIT antibody) in the phase II NCT04832854 trial. Stage II-IIIB (N2) patients will receive the two antibodies and CT for 4 cycles, then the two experimental drugs will be continued for 16 more cycles in the adjuvant setting. In the NAUTIKA1 trial, 4 cycles of neoadjuvant atezolizumab are administered in patients without driver alterations and PD-L1 expression≥1%.

In the KEYNOTE-671 phase III trial, pembrolizumab is being compared to placebo in association with concomitant CT for 4 cycles, with then 13 more cycles of adjuvant pembrolizumab/placebo.[19] Pembrolizumab is being evaluated also without CT and together with lenvatinib for 6 weeks before surgery in the INNWOP1 phase II trial, and then continued in the adjuvant setting for 15 cycles.

CheckMate 77T is studying the association of nivolumab with neoadjuvant CT but, unlike CheckMate 816, patients will continue nivolumab/placebo also in the adjuvant setting.[20]

Finally, other trials are experimenting neoadjuvant durvalumab: in the NeoCOAST 2, in association with CT and either monalizumab (an ICI targeting Natural Killer Group 2A) or oleclumab (an anti-CD73 antibody); in the AEGEAN, with concomitant CT and then continued as adjuvant therapy.

b) Adjuvant trails

The use of immunotherapy in the adjuvant setting for non-small cell lung cancer (NSCLC) has evolved rapidly in recent years.

In 2018, the PACIFIC trial demonstrated that the use of durvalumab, an immune checkpoint inhibitor, as adjuvant therapy for patients with unresectable stage III NSCLC who had completed definitive chemoradiotherapy led to a significant improvement in progression-free survival compared to placebo. Based on these results, durvalumab was approved by the US FDA, as well as by EMA in the EU for this indication.

Since then, several other trials have investigated the use of immunotherapy in the adjuvant setting for NSCLC, including trials of other immune checkpoint inhibitors such as pembrolizumab and atezolizumab, as well as trials of combination therapies involving chemotherapy and immunotherapy.

The first positive results from a phase III trial in the adjuvant setting have been provided by IMpower010, in which 1280 stage IB-IIIA patients were randomized to 1 year of atezolizumab (1200 mg q21 for 16 cycles) or observation after standard cisplatin based adjuvant CT [21]. The DFS benefit was confirmed in the stage II-IIIA population independently from PD-L1 expression (HR 0.79, 95% CI 0.64–0.96,p = 0.02) and in the intention-to-treat population (HR 0.81, 95% CI 0.67–0.99, p = 0.04). It was even higher in pts

Table 1 **Pivotal Trials in NSCLC unselected by PD-L1 expression**

Clinical Trial	Phase N	Nr Patients	Estimated Primary Completion	Stage	Interventions
ACCIO (NCT04267848)	III	1210	Dec 2024	II-IIIB	CT + concomitant pembro 4 cycles, then pembro 13 cycles vs. CT + sequential pembro 17 cycles vs. CT (1:1:1)
NADIMADJU-VANT (NCT04564157)	III	210	Apr 2027	IB-IIIA	CT + nivolumab q21 4 cycles, then nivolumab q28 6 cycles vs. CT 4 cycles (1:1)
MERMAID-1 (NCT04385368)	III	332	Dec 2024	II-III	CT +durvalumab/placebo q21 for 4 cycles, then durvalumab/ placebo q28 for 1 y (1:1)
IMpower-030 (NCT03456063)	III	451	Nov 2024	II-IIIB N2	Neoadj CT + atezo 4 cycles, then adj atezo 16 cycles vs. neoadj CT + placebo and no adj treatment
NCT04832854	II	82	Feb 2027	II-IIIB N2	Neoadj CT + atezo + tiragolumab 4 cycles, then adj atezo + tiragolumab 16 cycles
KEYNOTE-671 (NCT03425643)	III	786	Jan 2024	II-IIIBN2	Neoadj CT + pembro/placebo 4 cycles, then adj pembro/placebo 13 cycles(1:1)
INNWOP1 (NCT04875585)	II	33	Dec 2023	I-IIIA	Neoadj pembro + Lenvatinib 6w, then adj pembro 15 cycles
CANOPY-N (NCT03968419)	II	88	Apr 2022	IB-IIIA (no T4 or N2)	Neoadj pembrolizumab vs. canakinumab vs. pembrolizumab + canakinumab 2 cycles
CheckMate 77T (NCT04025879)	III	452	Dec 2023	II-IIIB N2	Neoadj CT + nivolumab/placebo, then adj nivolumab/placebo
GECP 16/03_NADIM (NCT03081689)	II	46	Jun 2022	**IIIA N2**	Neoadj CT + nivolumab 3 cycles, then adj nivolumab 1 y
NADIM II (NCT03838159)	II	86	Nov 2026	**IIIA-IIIB N2**	Neoadj CT + nivolumab/placebo, then adj nivolumab/observation
NeoCOAST 2 (NCT05061550)	II	140	Feb 2026	**II-IIIA**	Neoadj CT + durvalumab + monalizumab/oleclumab q21 4 cycles, then adj monalizumab/oleclumab q28 (1:1)
AEGEAN (NCT03800134)	III	824	Apr 2023	**II-IIIB**	Neoadj CT + durvalumab/placebo q21 4 cycles, then adj durvalumab/placebo q28 12 cycles (1:1)

Ongoing clinical trials with ICI in the (neo) adjuvant setting NSCLC.

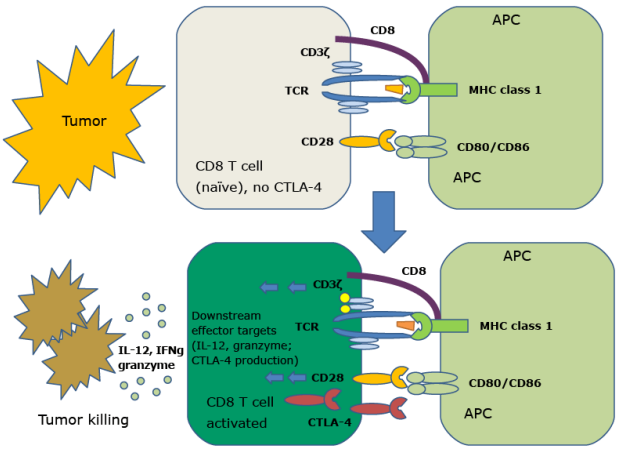

Figure 1

Immune synapse mechanism in a naïve (CD4 or) CD8 T cell and for an activated CD8+ T cell.
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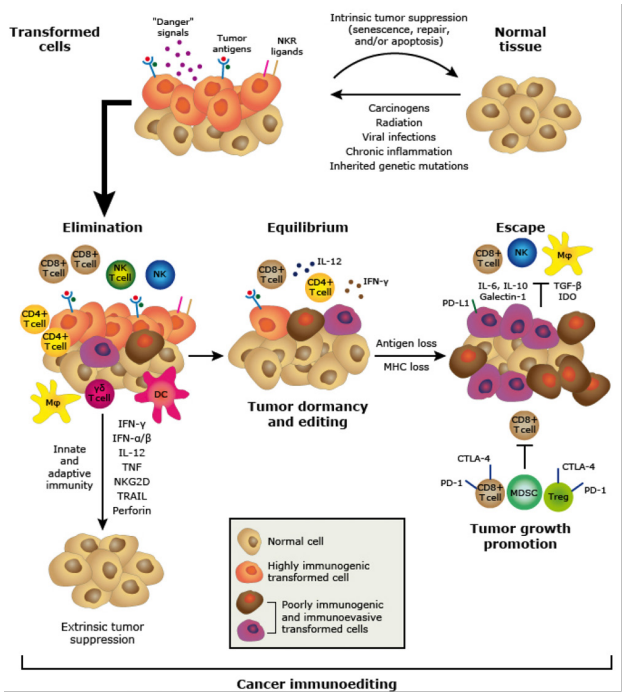

Figure 2

Cancer immunoediting. Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ. Natural Innate and Adaptive Immunity to Cancer. 2011; 29:235.
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with PD-L1≥50% (HR 0.43, 95% CI 0.27–0.68). OS data are still immature, and OS was not formally tested due to the hierarchic design of the study, though preliminary stratified HR was 0.77 (95% CI 0.51–1.17). A longer follow-up is needed to confirm the translation of DFS benefit on survival.

According to the positive reported results, atezolizumab received the FDA approval for the adjuvant treatment of PD-L1≥1% stage II-IIIA NSCLC patients. A positive opinion has also been adopted by EMA to support atezolizumab approval for high-risk NSCLC pts with PD-L1≥50% not harboring EGFR mutation or ALK rearrangement.

PEARLS/KEYNOTE-091 is another key phase III trial in the adjuvant setting in which pembrolizumab 200 mg q21 for 18 cycles has been tested against placebo in 1177 stage IB-IIIA NSCLC patients, after standard CT[22]. Also in this case, results from an interim analysis have shown a DFS benefit in the experimental arm, with a median of 53.6 vs. 42.0 m (HR 0.76, 95% CI 0.63–0.91, p = 0.0014). Surprisingly, the DFS benefit was not confirmed in the PD-L1≥50% (tumor proportion score, TPS) population (HR 0.82; 95% CI0.57–1.18, p = 0.14). OS data are still immature, with a non-significant trend in favour of the experimental arm (18-month rate 91.7% vs. 91.3%, HR 0.87, p = 0.17). Based on these preliminary data, pembrolizumab appears as another feasible option in this setting, independently from PD-L1 expression, which led to FDA approval in May 2021 for use as adjuvant therapy in patients with resected stage II or III NSCLC.

NCT04367311 is a phase II trial evaluating atezolizumab in addition to standard CT in stage IB-IIIA pts with detectable ctDNA after surgery. The primary endpoint is the percentage of patients with ctDNA negativization after treatment completion.

The ACCIO phase III trial is characterized by a design similar to PEARLS/KEYNOTE-091, with pembrolizumab evaluated in the adjuvant setting both sequentially after standard CT and concomitantly with CT, for a total of 17 cycles[23]. Another phase II trial (NCT04317534) is studying pembrolizumab as adjuvant treatment in stage I NSCLC patients.

Other trials are evaluating nivolumab in this setting. ANVIL is a large phase III trial with a design like IMpower010 and PEARLS/KEYNOTE-091, with 1year of nivolumab compared to observation after standard CT.[24] NADIM-ADJUVANT(NCT04564157, phase III) is assessing the same drug started concomitantly with CT.[25]

2) IMMUNOTHERAPY IN ADVANCED STAGE

The advent of ICIs has contributed to improved outcomes in lung cancer. So much that decision on how to treat NSCLC not harboring a genetic treatable alteration is based on the value of PD-L1 in tumor tissue. Currently, eligibility for most of the ICIs indicated for the treatment of advanced NSCLC is conditional based on PD-L1 expression above a specific cut-off.

The most used cut-off values are PD-L1 expression ≤1%, 1%–49%, and ≥50%. In real-world analyses, roughly 44% of tumors have PD-L1 expression <1%, 25% of tumors have PD-L1 expression 1%–49%, and around 31% of tumors have PD-L1 expression ≥50%.[26] At the time of manuscript

Table 2 **Pivotal Trials in NSCLC with PD-L1 expression ≥50%**

Clinical Trial	Line of therapy	Interventions	Results		
			ORR	OS	PFS
IMpower110 (NCT02409342)	First-line	Atezolizumab	38.3% (95% CI 29.1% to 48.2%)	Median OS: 20.2 months (95% CI 16.5 to NE) (HR vs chemo-therapy 0.59; 95% CI 0.40 to 0.89; p=0.01)	8.1 months (95% CI) (HR vs chemotherapy 0.63; 0.59; 95% CI 0.45 to 0.88)
		Platinum-based chemotherapy	28.6% (95% CI 19.9% to 38.6%)	Median OS: 13.1 months (95% CI 7.4 to 16.5)	5.0 months
KEYNOTE-024 (NCT02142738)	First-line	Pembrolizumab	44.8% (95% CI 36.8% to 53.0%)	Median OS: 30.0 months (95% CI 18.3 to NR) (HR vs chemotherapy 0.63; 95% CI 0.47 to 0.86; p=0.002)	10.3 months (95% CI 6.7 to NR) (HR vs chemo-therapy 0.50; 95% CI 0.37 to 0.68; p<0.001
		Platinum-based chemotherapy	27.8% (95% CI 20.8% to 35.7%)	Median OS: 14.2 months (95% CI 9.8 to 19.0)	6.0 months (95% CI 4.2 to 6.2)
EMPOWER-Lung 1 (NCT03088540)	First-line	Cemiplimab	39% (95% CI 34% to 45%)	Median OS: NR (95% CI 17.9 to NE) (HR vs che-motherapy 0.57; 95% CI 0.42 to 0.77; p=0.0002)	8.2 months (95% CI 6.1 to 8.8) (HR vs chemotherapy 0.54; 95% CI 0.43 to 0.68; p<0.0001)
		Platinum-based chemotherapy	20% (95% CI 16% to 26%)	Median OS: 14.2 months (95% CI 11.2 to 17.5)	5.7 months (95% CI 4.5 to 6.2)

Table 3 **Pivotal Trials in NSCLC with PD-L1 expression ≥1%**

Clinical Trial	Line of therapy	Interventions	Results		
			ORR	OS	PFS
KEYNOTE-010 (NCT01905657)	Second-line	Pembrolizumab	18% (95% CI 14.1% to 22.5%)	36-month OS: 22.9% (95% CI 19.8% to 26.1%) (HR vs docetaxel 0.69; 95% CI 0.60 to 0.80; p<0.00001)	4.0 months (95% CI 3.1 to 4.1) (HR vs docetaxel 0.83; 95% CI 0.72 to 0.96; p<0.005)
		Docetaxel	9.3% (95% CI 6.5% to 12.9%)	36-month OS: 11.0% (95% CI 7.9% to 14.7%)	4.1 months (95% CI 3.8 to 4.5)

Table 4 **Pivotal Trials in NSCLC unselected by PD-L1 expression**

Clinical Trial	Line of therapy	Interventions	Results		
			ORR	OS	PFS
OAK (NCT02008227)	Second-line	Atezolizumab	14.6% (95% CI 11.4% to 18.3%)	24 month OS: 30.9% (HR vs docetaxel 0.75; 95% CI 0.64 to 0.89; p=0.0006)	8.1 months (95% CI) (HR vs chemotherapy 0.63; 0.59; 95% CI 0.45 to 0.88)
		Docetaxel	13.4% (95% CI 10.3% to 17.0%)	24-month OS: 21.1%	2.8 months (95% CI 2.6 to 3.0) (HR vs docetaxel 0.93; 95% CI 0.80 to 1.08; p=0.3495)
CheckMate 017 (NCT01642004) and CheckMate 057(NCT01673867	Second-line	Nivolumab	19% (95% CI 16% to 24%) (OR vs docetaxel 1.91; 95% CI 1.28 to 2.86)	36-month OS: 17% (95% CI 14% to 21%) (HR vs docetaxel 0.70; 95% CI 0.61 to 0.81)	2.56 months (95% CI 2.20 to 3.48) (HR vs docetaxel 0.80; 95% CI 0.69 to 0.92)
		Docetaxel	11% (95% CI 8% to 15%)	36-month OS: 8% (95% CI 6% to 11%)	3.52 months (95% CI 3.15 to 4.21)
KEYNOTE-189 (NCT02578680)	First-line (Nonsquamous non-small-cell lung cancer)	Pembrolizumab + chemotherapy	48.0% (95% CI 43.1% to 53.0%)	24-month OS: 45.5% (HR vs chemotherapy 0.56; 95% CI 0.45 to 0.70)	9.0 months (95% CI 8.1 to 9.9) (HR vs chemotherapy 0.48; 95% CI 0.40 to 0.58)
		Platinum-based chemotherapy	19.4% (95% CI 14.2% to 25.5%)	24-month OS: 29.9%	4.9 months (95% CI 4.7 to 5.5)
KEYNOTE-407 (NCT02775435	First-line (Squamous non-small-cell lung cancer)	Pembrolizumab + chemotherapy	62.6% (95% CI 56.6% to 68.3%	Median OS: 17.1 months (95% CI 14.4 to 19.9) (HR vs chemotherapy 0.71; 95% CI 0.58 to 0.88)	8.0 months (95% CI 6.3 to 8.4) (HR vs chemotherapy 0.57; 95% CI 0.47 to 0.69)
		Platinum-based chemotherapy	38.4% (95% CI 32.7% to 44.4%)	Median OS: 11.4 months (95% CI 10.1 to 13.7)	5.1 months (95% CI 4.3 to 6.0)
IMpower130 † (NCT02367781)	First-line	Atezolizumab + nab- paclitaxel + carboplatin	49.2% (95% CI 44.5% to 54.0%) (OR vs nab-paclitaxel + carboplatin 2.07; 95% CI 1.48 to 2.89)	24-month OS: 30.0% (95% CI 21.7% to 38.2%)	7.0 months (95% CI 6.2 to 7.3) (HR vs chemotherapy 0.64; 95% CI 0.54 to 0.77; p<0.0001)
		Nab-paclitaxel + carboplatin	31.9% (95% CI 25.8% to 38.4%)	24-month OS: 30.0% (95% CI 21.7% to 38.2%)	5.7 months (95% CI 4.5 to 6.2)
CheckMate 9LA † (NCT03215706)	First-line	Nivolumab + ipilimumab + chemotherapy	38.2% (95% CI 33.2% to 43.5%)	Median OS: 15.6 months (95% CI 13.9 to 20.0) (HR vs chemotherapy 0.66; 95% CI 0.55 to 0.80; p=0.0006)	6.7 months (95% CI 5.6 to 7.8) (HR vs chemotherapy 0.68; 95% CI 0.57 to 0.82)
		Platinum-based chemotherapy	24.9% (95% CI 20.5% to 29.7%)	Median OS: 10.9 months (95% CI 9.5 to 12.6)	5.0 months (95% CI 4.3 to 5.6)

† Not reimbursed in Portuguese Public Health SystemDOR, duration of response; ITT, intention-to-treat; NE, not estimable; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TKI, tyrosine kinase inhibitor

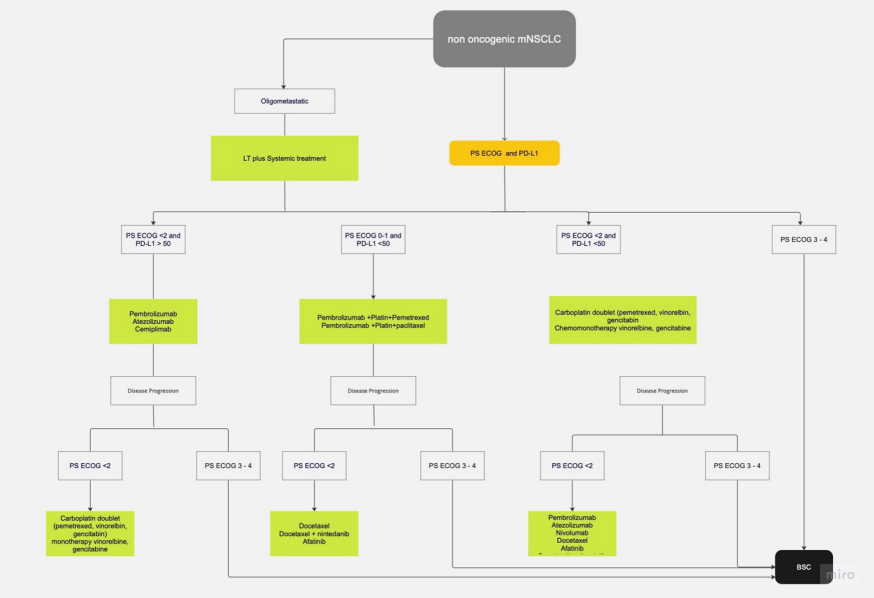

Figure 3

publication, most EMA-approved ICIs have activity as monotherapies, and in combinations with chemotherapies necessary for maximal benefit for some tumors. Additionally, the nivolumab plus ipilimumab dual-ICI regimen has been approved for NSCLC Dual ICI with 2 cycles of chemotherapy has also been approved for NSCLC. Pivotal trial outcomes data for European Medical agency (EMA) approved immunotherapies for NSCLC are in Tables 1-3. Not all regimens are reimbursed in the Portuguese Public Health System.

In NSCLC not previously treated with PD-L1 expression ≥50% pembrolizumab, atezolizumab and cemiplimab have been approved as monotherapy. Approval of pembrolizumab as monotherapy was based on results from the phase III, randomized, open-label KEYNOTE-024 Long-term efficacy results in the intention-to-treat (ITT) population show a 5-year OS rate of 31.9% (95% CI 24.5% to 39.5%) with pembrolizumab versus 16.3% (95% CI 10.6% to 23.0%) for chemotherapy. The toxicity profile was favorable for immunotherapy, where 76.6% of patients in the pembrolizumab arm developed treatment-related adverse events (TRAEs) compared with 90.0% of patients in the chemotherapy arm, 31.2% and 53.3% of which were grade 3–5 TRAEs, respectively.27,28,29 Atezolizumab monotherapy for first-line systemic therapy of metastatic PD-L1-positive disease approval was based on the phase III, randomized, open-label trial IMpower110. An interim analysis of the 572 chemotherapy-naïve patients who were enrolled and randomized to atezolizumab versus chemotherapy found benefit in median OS for patients in the PD-L1- high categories by the SP142 assay (PD-L1 staining on TCs ≥50% or ICs ≥10%). Median OS: 20.2 months (95% CI 16.5 to NE) vs 13.1 months (95% CI 7.4 to 16.5) (HR vs chemotherapy 0.59; 95% CI 0.40 to 0.89; p=0.01). TRAEs occurred in 90.2% of patients in the atezolizumab arm and 94.7% of patients in the chemotherapy arm, and grade 3–4 TRAEs occurred in 30.1% and 52.5% of patients in the respective treatment arms.30 Cemiplimab has also received approval as a first-line monotherapy based on results of the phase III, open-label EMPOWER-Lung 1 study, Patients receiving cemiplimab experienced significantly better OS and PFS compared with chemotherapy regimens. An exploratory analysis that stratified patients by PD-L1 expression (PD-L1 ≥90%; PD-L1 >60% to <90%; PD-L1 ≥50% to ≤60%) found that PD-L1 expression correlated with degree of change to tumor size, as well as with incremental improvements in OS, PFS, and ORR with a Median OS: NR (95% CI 17.9 to NE) (HR vs chemotherapy 0.57; 95% CI 0.42 to 0.77; p=0.0002).[31]

In NSCLC not previously treated, atezolizumab, pembrolizumab and nivolumab plus ipilimumab are approved in association with chemotherapy. Based on KEYNOTE-189, EMA approved the use of pembrolizumab with pemetrexed and platinum chemotherapy for first-line treatment of non-squamous NSCLC with no EGFR/ALK genetic alterations regardless of PD-L1 value. Pembrolizumab with pemetrexed and platinum treatment was associated with improved ORR, DOR, milestone OS at 24 months, and median PFS. All- cause adverse events (AEs) occurred in 99.8% of patients receiving pembrolizumab (71.9% of patients developed AEs of grade 3–5) and in 99.0% of patients receiving chemotherapy alone (66.8% of patients developed AEs of grade 3–5).[32] On KEYNOTE-407 (NCT02775435), pembrolizumab plus chemotherapy (carboplatin and paclitaxel or nab-paclitaxel) had a higher ORR, median DOR, median OS, and median PFS. OS and PFS benefit for the ICI plus chemotherapy combination was maintained across prespecified PD-L1 expression subgroups, with an OS HR of 0.61 (95% CI 0.38 to 0.98) for patients with PD-L1-negative tumors, 0.57 (95% CI 0.36 to 0.90) for patients with tumor PD-L1 expression 1%–49%, and 0.64 (95% CI 0.37 to 1.10) for patients with tumor PD-L1 expression ≥50%.Patients in the pembrolizumab arm developed AEs at a rate of 98.6%, with 74.1% developing

AEs of grade 3–5 versus AEs at a rate of 98.2%, and 69.6% developed AEs of grade 3–5 in the chemotherapy alone arm.[33] Atezolizumab plus chemotherapy was approved based on In IMpower130, that compared atezolizumab with chemotherapy (nab-paclitaxel and carboplatin) with chemotherapy alone. Patients in the atezolizumab arm with no EGFR/ALK alterations (ITT wild-type population) had longer median OS, long- term (24-month) OS, median PFS, ORR. No difference in OS was seen across pre-stratified PD-L1 expression subgroups. TRAEs were observed in 96% of patients in the atezolizumab arm and 93% of patients in the chemotherapy alone arm, with 75% of patients receiving atezolizumab with chemotherapy and 61% of patients receiving chemotherapy developing grade 3–5 TRAEs.[34] The CheckMate 9LA trial a phase III, randomized, open-label study, compared nivolumab and ipilimumab plus 2 cycles of platinum doublet chemotherapy versus platinum doublet chemotherapy alone. ORR was increased in the ICI-treated arm, as well as DOR, median OS, and median PFS. The 2-year OS rates were 38% and 26% for the ICI arm and the chemotherapy arm, respectively. Median OS was similar for the PD-L1 expression ≥1% group and the PD-L1 expression <1% group, at 15.8 months and 16.8 months, respectively (HR vs chemotherapy 0.64 (95% CI 0.50 to 0.82) for PD-L1 expression ≥1%; HR versus chemotherapy 0.62 (95% CI 0.45 to 0.85) for PD-L1 expression <1%). TRAEs of grade 3–4 were reported in 47% of patients receiving ICIs versus 38% of patients receiving chemotherapy alone.[35]

Atezolizumab, nivolumab and pembrolizumab have proven efficacy in NSCLC previously treated with different levels of PD-L1based on the following studies: In a pooled analysis of CheckMate 017 (patients with squamous NSCLC) and CheckMate 057 (patients with non-squamous NSCLC), patients treated with nivolumab exhibited improvements in ORR, median DOR, 36-month OS, and 3-year PFS rates (10% versus <1%; HR 0.80; 95% CI 0.69 to 0.92) compared with patients who received docetaxel. At 5-year update, the OS rates (13.4% vs 2.6%), and PFS rates (8% vs 0%; HR 0.79; 95% CI 0.68 to 0.92), continued to favor immunotherapy.[36,37] Atezolizumab showed benefit in the OAK trial that compared docetaxel to atezolizumab with higher median OS, milestone (24-month) OS, although there was not a statistically significant advantage in PFS or ORR. Patients receiving atezolizumab developed TRAEs at a rate of 64.0% (14.9% developed grade 3–5 TRAEs), while patients receiving docetaxel developed TRAEs at a rate of 86.2% (42.4% developed grade 3–5 TRAEs).[38] In KEYNOTE-010 pembrolizumab was compared with docetaxel in pretreated NSCLC setting.[39]

The treatment strategy for a patient with newly diagnosed, advanced NSCLC without an oncogenic driver includes consideration of histology, tumor genotype, PD-L1 expression, PS, comorbidities, and the patient's preferences.[40]

In Portugal for patients with metastatic NSCLC with no actionable mutations and PD-L1 expression or Tumor proportion score (TPS) ≥50%, not previously treated, pembrolizumab monotherapy should be used; cemiplimab is waiting evaluation by the regulatory agency.

For patients with metastatic NSCLC with no actionable mutations and TPS <50%, pembrolizumab with chemotherapy (cisplatin plus pemetrexed in nonsquamous NSCLC and cisplatin plus paclitaxel in squamous NSCLC) should be used; nivolumab with ipilimumab with or without 2 cycles of chemotherapy is waiting evaluation by the regulatory agency.

For patients with metastatic NSCLC previously treated with chemotherapy, atezolizumab and nivolumab should be used regardless of PD-L1; in metastatic NSCLC with PD-L1 expression >1% pembrolizumab should be used.

An algorithm of the treatment of advanced NSCLC without driver mutations is in Fig 3.

3) ADVERSE EVENTS

ICIs can give rise to various adverse events, the occurrences of which depend on various factors. The activation of the immune system can cause it to attack various organs like the kidneys, nervous system, liver, eyes, and even the endocrine system. The use of ICIs can also give rise to various autoimmune diseases or activate existing autoimmune diseases. There are various autoimmune mechanisms which lead to pulmonary, cardiac, renal, rheumatic, hematologic, cutaneous, vascular, and neurologic complications during lung cancer treatment, irrespective of the histology. Some of the adverse events can be so life-threatening so that discontinuing the treatment, taking corticosteroids for a long period of time to counter these effects or at times undergoing an immunosuppressor therapy becomes necessary.[41]

Conflict of interest: TS Advisory Board Lilly, MSD, BMS, Pfizer. Travel expenses from TAKEDA, MSD and Janssen.

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