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Faculdade de Farmácia

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Immunomodulatory options for Lung Cancer

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Monografia orientada pelo Professor Doutor João Pedro Fidalgo Rocha, Professor Assistente.

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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Abstract

Much uncertainty remains on how to best use novel immunomodulatory therapies in oncologic patients, especially lung cancer patients. This disease's global prevalence, mortality and poor prognosis warrant fast development and application of novel therapies, capable of changing the current disease's grave paradigm. As immunotherapies, namely immune checkpoint inhibitors (ICIs), have yielded improved outcomes for lung cancer patients, but demand high expenditures for their purchases, this study looks to systemize currently published data on ICIs for lung cancer patients, to help clarify the evidence that's still lacking and the current most cost-effective methods to apply such therapies. As combinations with these options hold the potential of improving effectiveness, through the enhanced benefits of synergistic mechanisms of action, but also aggravated adverse events and high costs, these regimens were the focus of the present study.

A systematic literature review of studies analysing effectiveness, cost-effectiveness or cost-utility of ICIs in lung cancer was constructed. 175 studies were abstract screened, with 85 being selected for integral analysis and, from those, 43 being selected for inclusion in the present review.

Varied regimens with ICIs in monotherapy or in combination, either between ICIs or with other options like chemotherapy or bevacizumab, were analysed in the included studies. Although most regimens presented significantly improved outcomes in comparison to classical chemotherapy, only Pembrolizumab and Atezolizumab in monotherapy were found to be cost-effective, in biomarker-selected groups of patients. The high prices at which these medicines enter the market were found to be the biggest barrier to ICI's generalized use in lung cancer patients. Investigation of new ways to use current biomarkers for ICIs or cost-sharing and risk-sharing strategies were suggested to balance this issue, potentially allowing healthcare systems to sustainably imburse the use of these novel options in oncologic patients' subgroups that most benefit from them, while still supporting and incentivising innovation.

Keywords: Lung; cancer; Immunotherapy; Immunomodulatory; Cost-effectiveness.

Resumo

Ainda subsiste muita incerteza sobre a melhor maneira de utilizar novas terapias imunomoduladoras em doentes oncológicos, especialmente em doentes com cancro do pulmão. A prevalência global desta doença, a mortalidade e o mau prognóstico a ela associados justificam a necessidade de um rápido desenvolvimento e aplicação de novas terapias, capazes de mudar o atual paradigma complicado da doença. Dado que as imunoterapias, nomeadamente os inibidores de pontos de controlo imunitário (ICI), têm produzido resultados melhorados em doentes com cancro do pulmão, mas exigem despesas elevadas para as suas aquisições, este estudo procura sistematizar os dados atualmente publicados sobre ICIs para doentes com cancro do pulmão, de modo a ajudar a clarificar os métodos atuais mais custo-efetivo para as aplicar e a evidência que ainda falta ser gerada. As combinações com estas terapias possuem o potencial de melhorar a eficácia dos regimes, através do uso de mecanismos de ação sinérgicos, mas também representam riscos de eventos adversos agravados e custos elevados, sendo o foco do presente estudo.

Foi construída uma revisão sistemática de estudos disponíveis que analisavam a eficácia, a relação custo-eficácia ou o custo-utilidade dos ICI no cancro do pulmão. Foram analisados 175 estudos através do respetivo resumo, tendo sido selecionados 85 para análise integral e, dos quais, 43 foram selecionados para inclusão no presente trabalho.

Os estudos incluídos analisaram regimes variados com ICIs em monoterapia ou em combinação, quer entre ICIs quer com outras opções como a quimioterapia ou o bevacizumab. Embora a maioria dos regimes tenha apresentado resultados significativamente melhores em comparação com a quimioterapia clássica, apenas o Pembrolizumab e o Atezolizumab em monoterapia foram considerados custo-efetivos, em grupos de doentes selecionados por biomarcadores. Os preços elevados com que estes medicamentos entram no mercado foram considerados como a maior barreira à utilização generalizada dos ICI. Este estudo sugere a investigação de uma melhor utilização dos biomarcadores atuais ou estratégias de partilha de custos e riscos para contrariar esta dificuldade, permitindo, potencialmente, que os sistemas de cuidados de saúde possam adquirir de forma sustentável estas novas opções terapêuticas e utilizá-las nos subgrupos de doentes oncológicos que mais beneficiam com as mesmas, ao mesmo tempo que apoiam e incentivam a inovação.

Palavras-chave: Cancro; Pulmão Imunoterapia; Imunomodulador; Custo-efetividade.

Acknowledgements

Firstly, I want to thank Professor Doctor João Rocha, for enabling me to work on such an interesting topic, for his guidance and cheerfulness throughout this process and for all the teachings he passed down to me. I would also like to acknowledge all the professors that taught me throughout these 5 years and thank them for their critical part in spurring my growth.

Second, I would like to thank all who shared this journey with me, I do hope I was able to give back a little of all I got from you. I address a special thanks to Carlos Fresco, David Lopes, Luís Silva and Simone Bento, my dear friends from day 1, for being my song and dance throughout starless nights and my rhyme and reason throughout noteless laboratories. I also want to thank my fellow bohemians from T.A.F.U.L., for the unbreakable brothership and irreverent joviality.

I'm very grateful to my life partner, Ana Fernandes, for being my balance when my knees swayed, my hearth when I was far from home and my compass when my resolve faltered. Reaching this point would not be possible without her.

I also want to thank my family for all their unconditional love and support, namely my parents, for enabling me to live life to the fullest and to chase happiness without constraints, for picking me up whenever I fell and celebrate whenever I strived forward; and my grandfather, Francisco Ribeiro, for being such a noble role model and living proof that strength and valour trample any obstacles.

And lastly, I dedicate this work to my grandmother, Maria Jovita, the main reason why I chose to be a Pharmacist. I'm very fortunate to have been able to spend time with and learn from such a notable woman and phenomenal Pharmacist. I hope my course through life makes her proud and that she'll keep watching over me.

Acronyms

SCLC – Small cell lung cancer

NSCLC – Non-small cell lung cancer

ICI – Immune checkpoint inhibitors

CTLA-4 - cytotoxic T-lymphocyte-associated protein 4.

AG - ANTIGEN

TCR - T-cell receptor

PD-L1 - programmed death ligand 1

PD-1 - programmed cell death protein 1

PRO - patient reported outcomes

HRQoL - health-related quality of life

PPS – post-progression survival

PFS – progression-free survival

OS – overall survival

OR – objective response

ORR - objective response rate

RR – response ratio

TOR – time to objective response

DR – duration of response

DOR – duration of objective response

BORR - best overall response rate

DCR - disease control rate

DOC – docetaxel

PBC - Platinum-based chemotherapy~

CH - chemotherapy

PEM – pembrolizumab

ATE – atezolizumab

ABC - Atezolizumab + bevacizumab + chemotherapy

AC - atezolizumab + chemotherapy

BC - bevacizumab + chemotherapy

NIV – nivolumab

IPI – ipilimumab

DUR or D – durvalumab

DTC – durvalumab plus tremelimumab plus chemotherapy

DC – durvalumab plus chemotherapy

TRE or T – tremelimumab

BEV - bevacizumab

TPS - tumour proportion score

FDA – Food and Drugs Administration

EMA – European Medicines Agency

VEGF - vascular endothelial growth factor

CAR-T – Chimeric antigen receptor T-cell therapy

RECIST – Response Evaluation Criteria in Solid Tumors

WHO – World Health Organization

irRECIST – Imune-related Response Evaluation Criteria in Solid Tumors

IC – incremental cost

ICER – Incremental cost-effectiveness ratio

QALY – Quality-adjusted life years

WTP – Willingness-to-pay

ICUR – Incremental cost-utility ratio

LY – Life-years

LYG - Life-years gained

US or USA – United States of America

Ig – immunoglobulin

MSI-H - microsatellite instability high

CHF - Confoederatio Helvetica franc (Swiss franc)

TMB – tumour mutational burden

NHS - National Health System

GDP – gross domestic product

BR – Brazil

AR – Argentina

PE- Peru

AE – adverse events

TR – treatment related

HR – hazard ratio

Q-TWiST - quality-adjusted time without symptoms of disease progression or toxicity of treatment

ITT - Intention to Treat

EOL - end-of-life

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1 Introduction

1.1 An overview of immunotherapies in oncology

Cancer is a large group of pathologies characterized by an abnormal and uncontrolled cellular growth that may result in deviations from the cell's normal functioning processes. Originating from virtually any organ or tissue of the body, these tumours can be cancerous and have the ability to invade adjoining parts and spread throughout the organism. (1) These transformations may arise from physical, chemical or biological carcinogens, such as ionizing radiation, tobacco smoke or viruses. (2)

This group of diseases is the second leading cause of death globally, having accounted for nearly 10 million deaths in 2020, world-wide. About 70% of these deaths occurred in low- and middle-income countries, where the lack of access to diagnosis and treatment are common. The most common cancer types enlist breast cancer, with 2.26 million cases; lung cancer with 2.21 million cases; colon and rectum cancer, with 1.93 million cases; prostate cancer, with 1.41 million cases and non-melanoma skin cancer, with 1.20 million cases. Nonetheless, the leading causes of death among malignancies, for that year, were lung, colon and rectum and liver cancer with 1.80 million; 935 000 and 830 000 deaths, respectively. (2)

The development of therapies capable of achieving results for oncologic patients has been a long-lasting battle, with rare occasions of success. The first effective intervention was surgery, which, although curative, was restricted to patients with localized tumours and often left them disfigured and in pain. Radiation therapy followed as an important adjuvant, remaining clinically relevant to this day. Mid-20th century, the first chemotherapeutic agents were developed, completing the third modality of therapies that would remain as an unchallenged standard of care up until recently. Although, providing clinicians with an arsenal capable of producing positive results for oncology, the lack of specificity limited their effectiveness and safety profile. Also, they showed little to no benefit in later-stage cancers, associated with metastasis. The next generation of therapies sought to target oncogenic pathways critical to tumorous growth, in order to maximize response ratios and minimize the toxicity deeply associated with the previous options. (3)

Attempts to utilize the immune system to fight off tumour growth can be traced all the way back to the 1890's, although the tumour cells' ability to evade the immune system has hindered the clinical efficacy of cancer immunotherapy, up to the present time. The deepening

of our understanding of cancer immune evasion has opened the door to the creation of therapies able to block such mechanisms. Accumulated evidence has shown us the immune system's role as an oncogenesis inhibitor (4), through various roles, such as supressing tumour inducing viral infections, promptly resolving inflammation and directly eliminating tumour cells that co-express ligands for innate immune cells' receptors and tumour antigens that are recognizable by lymphocytes. But, if the immune system has the ability to supress and eliminate tumours, why do they develop? The answer lies in the ability of the malignant cells to escape immune elimination, through Cancer Immunoediting. (5)

Cancer Immunoediting is the process through which the immune system paradoxically also promotes tumour growth. It is divided in up to 3 sequential phases: elimination, equilibrium and escape. In its initial stages, tumour cells are supressed by the immune system's innate and adaptive response, where the malignant cells are recognized and killed. This phase lasts until an eventual subclone capable of resisting elimination is created, progressing into equilibrium. In this stage, tumour outgrowth is controlled and stalled by the adaptive immune system. Either of these 2 phases may be maintained throughout all the individual's life, avoiding the development of disease. Nevertheless, this constant pressure, coupled with the tumour cells inherent genetic instability, may also potentiate the development of subclones capable of escaping immune recognition, of being insensitive to immune effector mechanisms or of inducing immunosuppression within its environment. If these subclones emerge, the escape phase will be reached and a unrestrained growth will, in due course, lead to a clinically apparent disease.(5,6)

The immune system has the potential to specifically destroy malignant cells, without toxicity to normal tissues and to provide a long-lasting protection against recurrence. As such, Immunotherapy strives to tip the balance by empowering the patient's immune system, with various approaches such as targeting tumour antigens or immunosuppressive abilities or even by raising the number and the activity of existing immune effector cells. The most developed strategies to achieve these objectives include therapeutic cancer vaccines, nonspecific immune stimulation, transferred immune cells or targeted antibodies that promote tumour cell elimination or block cancer's immunosuppression. (3,7)

Therapeutic cancer vaccines promote tumour recognition and antitumour response through the injection of immunogenic matter. (3) They aim to jumpstart the immune system and create specific immunomodulatory effects to target suppressed innate and/or adaptive immune responses. (8) The first human therapeutic cancer vaccine Sipuleucel-T was approved

by the FDA, in 2010, for advanced prostate cancer. Since then, Talimogene laherparepvec has also been approved, this time to treat advanced melanoma skin cancer. Although this strategy has yielded positive results, evidence about cancer vaccine options is still scarce. (9)

Regarding nonspecific immune stimulation, the therapeutic aim is to stimulate the patient's immune system with the inoculation of pro-inflammatory substances such as cytokines, in order to counter malignant immunosuppression. These proteins can upregulate the innate and adaptive immune system's response, priming tumour suppression and elimination. This approach has various approved options, such as InterLeukin-2 or Interferon-a, as adjuvant oncotherapies. (3)

Looking at cell-based immunotherapies, these strategies explore the immune response's priming through transferred tumour-reacting immune cells. The endogenous cells are originally extracted from the patient and undergo *ex vivo* maturation, expansion or activation (adoptive cell transfer) rendering them able to exert potent anti-tumour activity. This enhanced immune response can be further manipulated through genetic engineering of immune effector cells, such as T-cells. This method allows the transferred T-cells to express qualities such as increased proliferation, enhanced trafficking to tumour sites or even tumour-selective T-cell receptors. The most promising approach today is the creation of chimeric antigen receptors in T-cells (CAR-T cells) targeting tumour antigens for solid and liquid tumours, which can confer increased antitumor activity due to increased proliferative capacity, survival and resistance to the inhibitory effects of Regulatory T cells. (3) With the development of improved cellular manufacturing techniques and engineering approaches, precision genome editing technologies and combination therapy strategies, CAR T cells have the potential to become a cost-effective and potentially curative treatment of human cancer. (10)

Lastly, antibody therapeutic approaches are currently the most well-established option, having already various approved molecules by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), for various indications, including pathologies outside of oncology. These strategies encompass varied targets and mechanisms such as the direct targeting and signalling of cancer cells for immune elimination; blockage of critical tumoral signalling pathways along receptors such as the vascular endothelial growth factor (VEGF), supressing tumour growth or inducing apoptosis; and lastly, immunomodulatory antibodies with the capability to potentiate immune surveillance and response, through interaction with the immune downregulating pathways. The previous category can be divided in 4 main mechanisms, illustrated by Figure 1. (3)

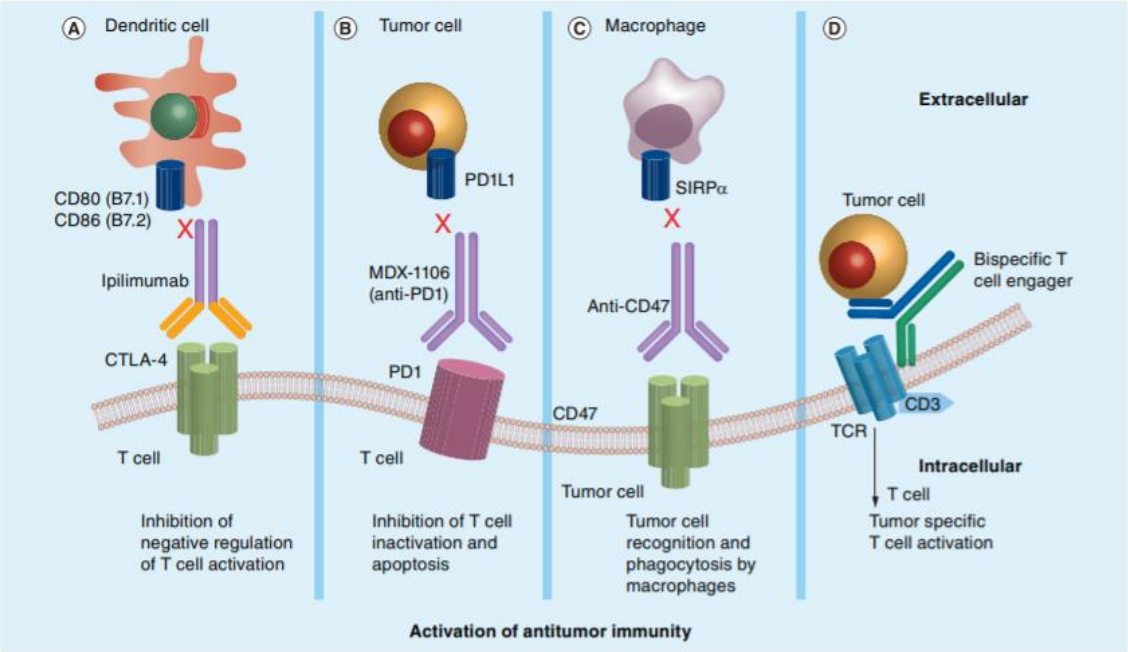

Figure 1 - Antibody-based immunomodulatory strategies for treating cancer. (A) Inhibitory T-cell CTLA-4 antagonist, there by disinhibitory of endogenous T-cells against tumours; (B) anti-PD1 antibody, blocking tumour induced T-cell apoptosis; (C) Anit-CD47 blockage, facilitating programmed cell removal by macrophages; (D) Bispecific antibodies, binding with both tumour antigens and T-cells' CD3 receptor, promoting antitumour T-cell response. (3)

The introduction of immunotherapeutic options into oncology has represented a major shift in the paradigms of many oncologic patients, providing promising clinical outcomes, with longer lasting responses and less treatment-associated toxicity when compared to classical chemotherapy, making the development of such pharmaceutical options a big landmark in cancer's treatment history. (11) Nevertheless, there are plenty of limitations associated with these therapies. Indications are still reserved to a select number of cancer types, biomarkers predictive of response ratios and effectiveness are still elusive, toxicity is still present and demands specific management, especially with combination therapeutic plans, and medicine's cost and reimbursement policies remain a major obstacle to universal access (12–14). The transition to these high-cost therapies as standard of care with the possible use of combinations, longer overall survivals and an increasingly large population of oncologic patients, poses a paramount concern to the economic sustainability of Healthcare Systems across the globe. As such, it's crucial that the disease management and therapy costs' are pondered and evaluated in order to achieve optimal allocation of resources. (15)

1.2 Introduction to lung cancer

As previously stated, lung cancer is one of the leading types of malignant diseases, toping 2020's charts in sheer number of patients and associated deaths. (1,2) The development of this disease is deeply linked with tobacco smoke exposition, with 80 to 90% of all lung cancers being attributable to this risk factor. (16) Most lung cancers are carcinomas, being malignancies that develop from the airways' epithelium cells. The pathophysiology of lung cancer is very complex and not yet completely understood. This disease is insidious, with the majority of patients affected not showing symptoms at the time of the diagnosis. When symptomatic, the patient may present worsening cough, chest pain, haemoptysis, malaise, weight loss, dyspnoea, dysphonia. (17–19)

Histologically, this type of cancer is divided in two main subtypes, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with NSCLC accounting for about 85% of all diagnosed lung carcinomas. The most commonly used tumour biomarkers for diagnosis are thyroid transcription factor-1, CD56, synaptophysin and chromogranin. (17) Nevertheless, lung cancer is considered a heterogenous group of diseases, showing significant histological and molecular differences within histological subtypes. (20) Stage at diagnosis is a key determinant of prognosis and approximately 57% of patients present a stage IV disease and about 70% of diagnosed lung cancers present in advanced stages at the time of diagnosis. (21,22)

SCLC is characterized by small cells with scant cytoplasm and no distinct nucleoli. This subtype shows a high degree malignancy, with rapid progression to later stages and poor prognosis. The 5 year survival rate rounds the 1-5%. (17,23) NSCLC is any type of epithelial lung cancer other than SCLC, presenting very heterogenous histologic characteristics and being divided into 5 major very variable subtypes. NSCLC are usually less sensitive to chemotherapy and radiation therapy than SCLC, although both types are hardly ever curable, due to very probable installed dissemination at the time of diagnosis. (17,19,24)

For both NSCLC and SCLC, at the first lines of systemic and neo/adjuvant therapy remain chemotherapeutic options such as Cisplatin and Carboplatin, Topotecan, Docetaxel and Paclitaxel. Immunotherapeutic options are reserved for patients who present PD-L1 expression superior to 1% and with no known targetable driver mutations, including antibodies like Pembrolizumab, Atezolizumab, Nivolumab and Ipilimumab, either in monotherapy or in combination (with another immune checkpoint inhibitor or chemotherapy). Even though

current guidelines use PD-L1 as the predictive biomarker to make the decision to administer immunomodulatory therapy, most studies suggest that PD-L1 expression does not completely predict benefit with immune checkpoint inhibitors. Some literature suggests that tumour mutational burden might be a more adequate indicator than PD-L1 for some therapies, like Pembrolizumab. (13,25–30)

As new lung cancer cases and related deaths steadily increase every year, there is still a need for more effective and long lasting first-line treatments for the majority of lung cancer patients and for the identification of predictive biomarkers to better determine which patients may benefit the most from new therapies. New clinical evidence and pharmacoeconomic analysis must be generated in pursuit of improving the still dauting prognosis of lung cancer patients. (2,12,13)

1.3 Immunomodulatory therapy – Monotherapy and combination approaches in lung cancer treatment

Currently approved immune checkpoint inhibitors (ICIs) for cancer treatment target either the interaction between PD-1 and PD-L1, such as atezolizumab, durvalumab, nivolumab and pembrolizumab, or the CD28/CTLA-4 system of immune modulation, with ipilimumab being the only currently approved antibody, although tremelimumab might be added to the group in the near future. (30,31)

PD-1 and PD-L1 inhibitors look to inhibit either the activated T cell's PD-1 receptor or its tumorous ligands, PD-L1 and PD-L2. Tumour cells' PD-L receptors are in part intrinsic but can also result from the immunoediting process conducted by the immune system's response. The interaction between these 2 components results in the inhibition of TCR-mediated effector functions. As tumour cells often express PD-L ligands and tumour-infiltrating lymphocytes highly express PD-1 receptors, this might be a key mechanism in cancer's immune evasion, possibly targetable and reversible by blockage of the PD-1/PD-L1 interaction. (30)

CTLA-4 inhibitors focus a receptor that although not expressed in naive and memory T cells, it's highly expressed in activated ones, where it competes with its CD28 counterpart for antigen biding through AG-presenting cells' CD80 and CD86. CD28 activation amplifies TCR signalling as a costimulatory and CTLA-4 engagement reduces the amplitude of T-cell responses. As the latter has a higher affinity for the AGs, it downregulates TCR-mediated responses, assuring immune tolerance. In cancers with high immune recognition, resulting in

large proportions of tumour reactive T cells, such as melanoma, CTLA-4 inhibitors hold most promise of clinical benefit. (30,32)

The rationale behind combination of immune checkpoint inhibitor's mechanisms lies in the synergy of dual checkpoint inhibition. In the tumour microenvironment, the CTLA-4 receptor seems to modulate immune responses early in T-cell activation, whereas PD-1 inhibits the effector phase of T-cell activity. CTLA-4 is expressed mainly on helper T-cells and its suppressor activity probably happens in the secondary lymphoid organs, where T-cell activation occurs. As for PD-1-mediated immune suppression, it occurs at the tumour microenvironment. As they have distinct but complementary mechanisms, CTL4-A and PD-1 inhibition have the potential to synergistically modulate the anti-tumour immune response by increasing activated tumour-specific T-cells, able to carry out effector mechanisms. It seems that dual checkpoint inhibition greatly improves the ratios of effector T cells to regulatory T cells and myeloid-derived suppressor cells, suggesting an improved enhancement of antitumor immunity. (30,33)

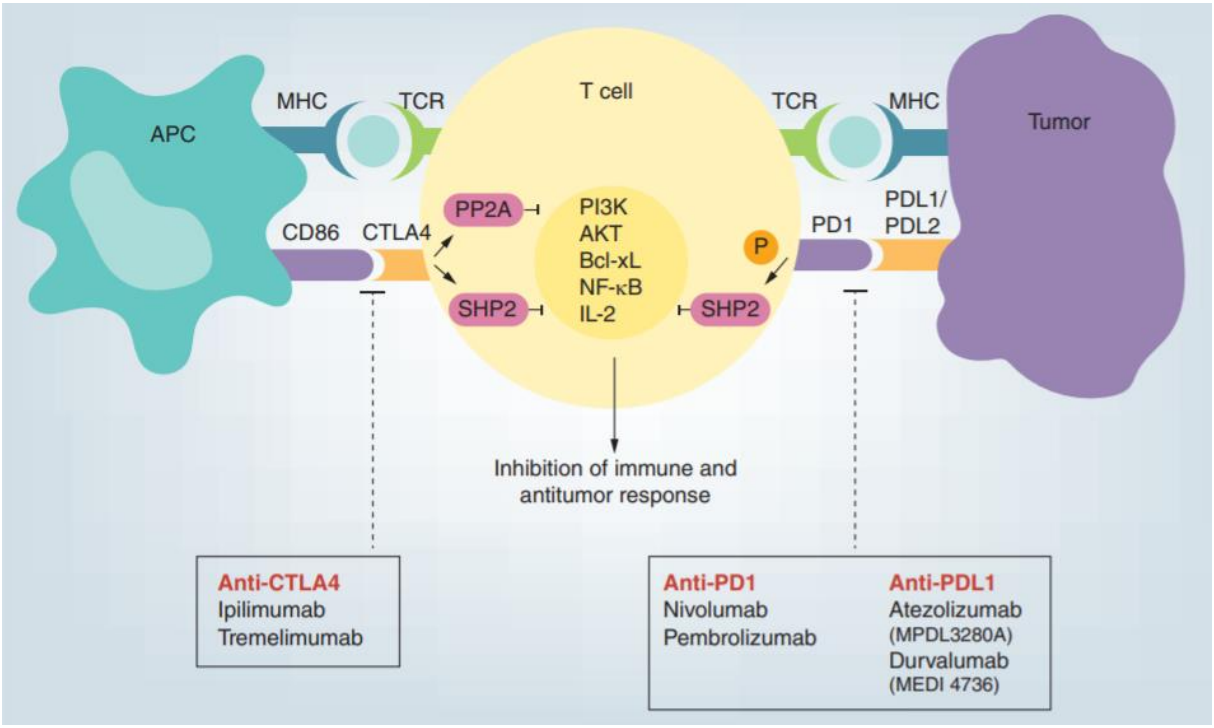

Figure 2 – Graphic representation of the synergistic mechanisms of PD-1/PD-L1 and CTLA-4 inhibitors. (34)

Nivolumab is a genetically engineered, fully human IgG4 monoclonal antibody against human PD-1 that binds to activated human T cells with high affinity. Nivolumab has been shown to inhibit the interaction of PD-1 with PD-L1 and to enhance tumour antigen-specific T-cell proliferation and cytokine secretion in vitro. There is already much clinical data about the positive outcomes this medication has achieved for lung cancer patients, having approvals for

the isolated and combined therapy of patients who present PD-L1 expression superior to 1% and with no known targetable driver mutations, since 2015. This therapy is indicated for melanoma, NSCLC, advanced renal cell carcinoma, classical Hodgkin lymphoma, squamous cell cancer of the head and neck, urothelial cancer, malignant pleural mesothelioma, microsatellite instability high (MSI-H) cancer of the colon or rectum, squamous oesophageal cancer and oesophageal cancer. (25,26,30,35–37)

Pembrolizumab is a humanized monoclonal PD-1 antibody that blocks the interaction between PD-1 and PD-L1 receptors, thereby potentiating the expression of T-cells including anti-tumour response. Pembrolizumab received approval by EMA in 2015 for metastatic NSCLC patients whose tumours express PD-L1 superior to 1% and disease progression on or after platinum-containing chemotherapy. This medication is indicated in melanoma, NSCLC, classical Hodgkin lymphoma, urothelial cancer, head and neck squamous cell carcinoma, renal cell carcinoma and microsatellite instability high (MSI-H) cancer of the colon or rectum (38,39)

Durvalumab is a selective, high-affinity, human immunoglobulin G1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80. It was recently approved (2018) for the treatment of patients with unresectable, stage III NSCLC whose disease has not progressed following platinum-based chemotherapy and radiotherapy. In recent studies, this antibody has shown promising results in monotherapy and in combination with tremelimumab. This antibody is currently used exclusively in the treatment of NSCLC. (31,40,41)

Atezolizumab is a humanized monoclonal anti-PD-L1 antibody that inhibits PD-1 and PD-L1–B7-1 signalling and restores tumour-specific T-cell immunity. This medication was recently approved by the FDA (2020), being indicated for use in urothelial carcinoma, NSCLC, triple-negative breast cancer, SCLC, hepatocellular carcinoma and melanoma. In phase 1 trials, atezolizumab monotherapy had an acceptable side-effect and safety profile, with promising durability of response in patients with relapsed or refractory SCLC. (42–44)

Ipilimumab is a fully human IgG1 monoclonal antibody that prevents CTLA-4 on activated T cells from binding to its ligands on antigen-presenting cells, has been shown to increase the percentages of circulating activated CD8+ and CD4+ T cells and to enhance humoral immunity in patients with advanced melanoma. Similar to nivolumab, ipilimumab has already shown positive results in lung cancer patients, also having approvals, dating 2011, for monotherapy and combinations (especially with nivolumab) for lung cancer patients. It’s indicated for patients facing advanced melanoma, advanced renal cell carcinoma, metastatic

NSCLC, Malignant pleural mesothelioma and microsatellite instability high (MSI-H) cancer of the colon or rectum.(15,25,26,30,45)

Tremelimumab is a human monoclonal antibody and potential new medicine that targets the activity of CTLA-4. Tremelimumab is currently being tested in clinical trials as combination therapy for NSCLC, SCLC, bladder cancer and liver cancer. Although this antibody doesn't have an approval for lung cancer yet, there are already studies defining tremelimumab potential for combination therapies in this indication, especially with durvalumab. (31,44,46)

Possible common side effects of these therapies include fatigue, cough, nausea, itching, skin rash, loss of appetite, constipation, joint pain, and diarrhoea. More serious side effects are infusion and autoimmune reactions. (47)

Important questions remain regarding the role of immunotherapy monotherapy/combinations versus immunotherapy–chemotherapy combinations and versus chemotherapy, such as the preferred sequencing of therapies and medicine's combinations, dosage and length of treatment, predictive indicators of response and how to economically sustain long term and universal access to these treatments. These inquiries translate to all types of cancer with current approvals of such medicinal substances. (15,28,35)

1.4 Endpoints for Immunotherapy's evaluation

When looking at immunotherapy's endpoints, consideration of their mechanism of action and anti-tumour activity profile is needed, as they are fundamentally different from classical chemotherapy. They show different tumour response kinetics from cytotoxic agents, which present a clear dose-response relationship and short onset effects. As such, outcomes defined need to be adjusted to novel therapies' over time disease control and modest dose-response correlation. (48,49)

Overall survival (OS), defined as the time between treatment's institution and patient's death, is the gold standard for oncology cytotoxic agents' clinical trials, as well as for immunotherapy ones. Nevertheless, this parameter requires large sample sizes and long follow-ups, especially when dealing with slow developing diseases. On the contrary, outcomes like progression-free survival (PFS), the time period between treatment's institution and disease progression or patient's death, and overall response rate (ORR), the proportion of sample patients achieving partial or complete responses to treatment, may underestimate clinical over-

time benefits of immune-oncologic medicines, rendering these parameters as limited when applied to this group. Even so, there have been many accelerated approvals based solely on ORR results, on the premise of later validation through OS and PFS data. (48,49)

When evaluating patient's outcomes with immunotherapy, it is possible to assess objective clinical results, such as tumour progression, patient reported outcomes (PRO) (which have an increasing relevance in clinical trials of the last decade, as they have been correlated with prognosis) and health related quality of life (HRQoL) parameters. Conventional response evaluation golden standard criteria is still the Response Evaluation Criteria in Solid Tumours (RECIST), developed by the World Health Organization (WHO), as it provides a provides a simple and pragmatic methodology to assess the activity and efficacy of new cancer therapeutics, across multiple tumour types. Unfortunately, this evaluation does not account for the different response mechanisms of immunotherapy, presenting shortcomings in this regard. As such, irRECIST, Immune Related Response Evaluation Criteria in Solid Tumours, was developed in order to assess more adequately these outcomes. (48,50,51)

The HRQoL can be defined as a metric the encompasses all factors that impact upon an individual's health, how well a person functions in their life and his/her perceived wellbeing in physical, mental, and social domains of health. As such a multifactorial parameter, many aspects impact patients' HRQoL like symptoms, treatment adverse effects, economic status, patients' ability to work and perform tasks. PRO is an umbrella term used to define any information of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a third party. (52,53)

When approaching PRO and HRQoL outcomes, there is a need to carefully choose assessment tools, as endpoints might not be easily quantifiable through clinical endpoints, such as symptoms and adverse effects. These outcomes are especially valuable in oncology, as survival isn't the main goal in most cases. Overall quality of life parameters take a more relevant position when assessing these treatment options, making the assessment of PRO and HRQoL key in the development of relevant endpoints for immunotherapy. Currently no tool has been specifically created for immuno-oncology. Surveying instruments such as the Functional Assessment of Cancer Therapy-General (FACT-G) or the European Organization for Research and Treatment of Cancer–Quality of Life Questionnaire-30 (EORTC QLQC30), which are often utilized to measure HRQOL, might lack sensitivity for immunotherapy, as they haven't yet been validated for these agents. (48)

1.5 Pharmacoeconomic and evaluation of novel immunotherapies

Pharmacoeconomics is the branch of economics where the most economical and efficient use of pharmaceutical products is studied, weighing health and economic consequences. This analysis is key to assure the limited resources that Healthcare Systems have at their disposal are optimally allocated. The scarcity of resources coupled with the increasing expectancies of patients requires decision-makers to utilize pharmacoeconomics as a tool to guide their decisions in order to meet patients' needs while still maintaining the Healthcare Systems' financial sustainability. (54) Economic evaluation is gaining increasing importance in decision-making for coverage and reimbursement of new medicines in many countries. As such, these must be high-end quality assessments, offering trustworthy results and enabling informed decisions. (55)

The main components for any pharmacoeconomic evaluation are: perspective (health trust, patients); time horizon; costs (direct medical costs, indirect costs, intangible costs); and outcomes (years of life saved, years of progression-free survival). (54)

The perspective of the analysis determines which costs are relevant to quantify. For instance, in the Healthcare Sector's perspective, medical costs, both current and future, related or unrelated to the considered medical condition, are the focus of the analysis. (55)

The time horizon of the evaluation has to be correctly set in order to capture not only immediate medical and economic consequences, but also the long-term ones (may them be delayed therapeutical benefits or post survival costs). (54,56)

The specific costs to be measured need to be defined from the get-go with the perspective adopted in mind. The analysis may need to focus on direct medical costs (for example pharmaceutical products), indirect medical costs (like inability to work because of illness related impairment) direct non-medical costs (for instance, transportation expenses) or intangible costs (for example patient's suffering). (54)

Regarding the treatment outcomes explored, there are four types of pharmacoeconomic studies: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA) and cost-minimisation analysis (CMA). (57) In this study, only cost-effectiveness analysis and cost-utility analysis were included, as these were considered the most useful when evaluating of immunotherapies.

Cost-effectiveness analysis is an analytic tool in which the costs and effects of a medicine and at least one alternative are calculated and presented in a ratio of incremental cost to incremental effect. In this case, effects are health outcomes, such as progression-free years or quality-adjusted life-years. This type of analysis can only be used when alternatives present different, but measurable benefits, which make them easily quantifiable. Nevertheless, comparison between cost-effectiveness studies requires attention to outcomes evaluated, as they must be the same. These analyses present their results in incremental cost per unit of outcome gained, in the form of the incremental cost-effectiveness ratio (ICER). (56)

In turn, the cost-utility analysis measures outcomes in units of utility or preference, through a not so easily quantifiable parameter - quality-adjusted life years (QALY). This outcome takes morbidity and mortality gains into account, weighing the years of life gained as well as the quality of life with which those years are experienced, making it exceptionally useful when evaluating oncologic treatments. Similarly to CEA, CUA presents its results in the form of the incremental cost-utility ratio (ICUR), establishing incremental costs per QALY gained. (57)

In both these analyses, a willingness to pay (WTP) threshold is defined as maximum incremental cost per unit of outcome gained through the intervention that's reasonable in the selected payer's perspective. For the alternative in study to be found cost-effective its ICER or ICUR needs to be under the WTP threshold. The relation between comparator medicine and in study alternative's costs and benefits is represented in Figure 3.

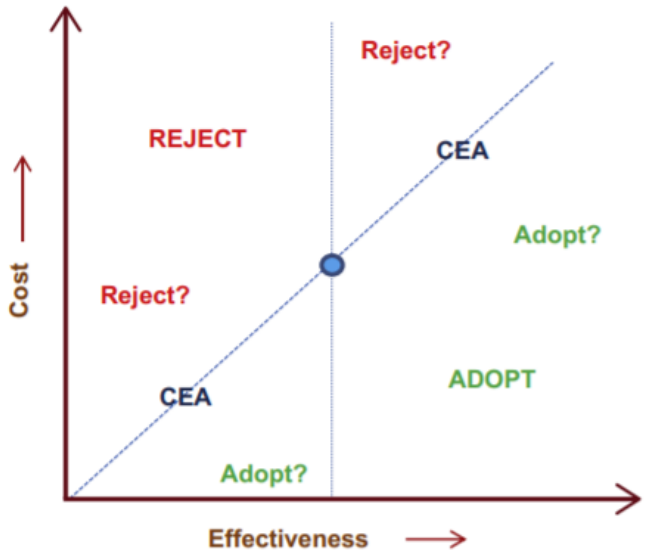

Figure 3 - Cost-effectiveness plane in decision making. When an alternative is inserted in the top left quadrant, its dominated by the comparator, as it is found to be less effective and more

expensive. On the other hand, when it is located on the bottom right quadrant, it's considered dominant, being more effective and cheaper than the comparator. (57)

When evaluating the pharmacoeconomic aspects of new immunotherapies available new challenges present themselves, in addition to the ones relative to outcomes.

Firstly, evidence shows that the cost-effectiveness of immunotherapy varies extensively, depending on therapeutic indication and biomarkers used. Also, as cost-effectiveness results describe individual gains, even when profound, they may be diluted by the outcomes calculated in the entire treated group. As immunotherapies often generate heterogenous results in studied populations, there is a minority experiencing vastly greater benefits than the median outcome, which is hard to account for, raising the question of how to balance expensive options that extensively benefit a handful of patients and the economic burden to Healthcare Systems. (58)

Relatively to adverse events, the amount that these occurrences reduce life-years gained is calculated by applying disutility weights, in accordance with AE's incidence, severity and duration. Nevertheless, disutility values found in current literature only focus chemotherapy related AEs, not accounting for the unique detriments of ICIs. (59)

Regarding WTP thresholds utilized in cost-effectiveness evaluations, there are no governmental WTP benchmarks in some countries like the US. As such, values utilized are based on the most widely used figures in published literature. For the US, the value most used by authors is $100,000US$, but if it was raised to 150,000US$ per QALY (which would be in accordance to WHO's recommendations (60)), some ICIs like nivolumab would be considered cost-effective in indications in which they currently aren't. Adding to the variability of WTP thresholds in between countries, there is also the need to account for the variations of ICIs' transversely high prices between different Healthcare Systems. (59)

Considering the current biomarkers, these identify patients who are most likely to respond to ICI treatment and guide better clinical choices, consequently increasing the QALYs gained. They include microsatellite instability (MSI), tumour mutation burden (TMB), PD-L1 expression percentage and immune cell infiltrate in/around the tumour. MSI translates deficiencies in DNA repair and, similarly to TMB, increased tumour related antigenicity. A MSI positive result indicates higher probability of clinical benefit with ICIs, but positive results are rare. High TMB levels indicates probable immune suppression by checkpoint mechanisms but does not guarantee it. PD-L1 expression is limited by the variability in testing and cut off levels used to anticipate clinical response, expressing inconsistent predictive values in different cancer types. Lastly, assessment of the degree of T cell infiltration and patterns of host immune

response using immune cell biomarkers still need further technological development to be fully understood and utilized. (59)

1.6 Study aims

Much uncertainty remains on how to best use novel immunomodulatory therapies in oncologic patients. Lung cancer patients aren't an exception and current disease poor prognosis warrants fast development and application of new options that might be a ray of hope for these patients. As immunotherapy options have presented added clinical value in both lung cancer types (NSCLC and SCLC) it is key to fully assess the most efficient way to apply these therapies. As combination therapies present the potential to achieve maximized clinical benefit, but toxicity and high costs associated may pose an exclusion criteria from clinical practice, the present study prioritized information regarding these type of regimens.

The optimal cost-effectiveness strategies still have not been clarified, although the high prices of these medicines threaten the sustainability of healthcare systems, especially if used at large scale and through long periods of time. As such, this study was designed with the goal of reviewing and assessing current available data on the cost-effectiveness and cost-utility of immunomodulatory therapies, in lung cancer patients. By systematizing currently published data, the evidence that's still lacking and the current most cost-effective methods to apply such therapies might become clearer for clinicians and decision-makers and help patients with these nefarious diseases achieve better outcomes in the future.

2 Methods

2.1 Included studies selection and data extraction

175 studies were abstract screened, with 85 being selected for integral analysis. Of these 85 studies, 43 were identified as presenting relevant information for the present review. The inclusion criteria were: focus on the 6 selected medicines – tremelimumab, nivolumab, pembrolizumab, atezolizumab, ipilimumab or durvalumab; target disease being lung cancer; inclusion of clinical benefit related outcomes, cost-effectiveness or cost-utility evaluations; if possible, inclusion of robust sample sizes, with over 50 included patients, if available data was limited, smaller samples sizes with over 10 patients were permitted; outcomes included listing at least OS or PFS and, lastly, time period of the study encapsuling over 6 months of patient monitoring. The results were treated and categorized through medicine evaluated, comparator and target lung cancer type.

The data considered as relevant for extraction included: the study's title, name of the first author and publication year; country of the studied population and costs; sample population's characteristics; time period considered; intervention/s; comparators used; clinical outcomes; costs parameters; effectiveness, cost-effectiveness or cost-utility results. Studies' identifications were named as follows: FirstAuthor'sName_PublicationDate_Country.

2.2 Data search

A search on Pubmed and Google Scholar was conducted for studies that reported cost-efectiveness or cost-utility data related to immunomodulatory therapies. The search profile used was the following: (lung cancer) AND (pharmaeconomic OR economic OR anti-PD1+anti-PDL1 OR costs OR cost+efectiveness OR cost+utility) AND (tremelimumab OR ipilimumab OR durvalumab OR atezolizumab OR pembrolizumab OR nivolumab OR nivolumab+ipilumumab OR nivolumab+tremelimumab OR nivolumab+atezolizumab OR nivolumab+pembrolizumab OR nivolumab+durvalumab OR ipilimumab+tremelimumab OR ipilimumab+durvalumab OR ipilimumab+atezolizumab OR ipilimumab+pembrolizumab OR durvalumab+atezolizumab OR durvalumab+tremelimumab OR durvalumab+pembrolizumab OR atezolizumab+pembrolizumab). The collected data was later synthetized into the Table 1.

3 Results

3.1 Nivolumab vs docetaxel

Study	Main intervention vs	Lung cancer type	Sample	Effectiveness Results	Costs	Biomarkers	Therapeutic advantage?	Cost-Efec./Uti. ?
Matter-Walstra_2018_Switzerland	Nivolumab vs Docetaxel	Advanced Nonsquamous NSCLC	CheckMate-057	Median OS : 12.25 months for NIV vs. 9.5 months for DOC Median PFS: NIV - 2.3 months vs. DOC - 4.2 months QALYs: NIV - 0.69 vs. DOC - 0.53	WTP: CHF100,000/QALY Mean cost: NIV - CHF 66,208 QALYs) vs. DOC - CHF 37,618 ICER: NIV - CHF177,478/QALY	PD-L1 testing	Yes	No
Aguiarjr_2017_USA	Nivolumab vs docetaxel	Squamous NSCLC	37 638 patients, various randomized clinical trials	Mean PFS: NIV - 7.28 vs DOC - 4.07 Post-progression survival (PPS) - NIV - 11.80 vs DOC - 6.45 Median OS: NIV - 19.08 vs DOC - 10.52 QALYs: NIV - 0.82 vs DOC - 0.40 LYs: NIV - 1.59 vs DOC - 0.88	WTP of US$100 000/QALY **NIV vs DOC:** ICER : $155 605 Cost per Incremental LYG: $91 034 PD-L1 ≥1% or TC ≥ 1: ICER by QALY - $201 461 PD-L1 ≥5%: ICER by QALY - $135 080 PD-L1 ≥10%: ICER by QALY - $131 159	PD-L1 expression	Yes	No
		Non-squamous NSCLC		Mean PFS: NIV - 6.72 vs DOC - 5.33 Post-progression survival (PPS) - NIV - 14.50 vs DOC - 9.60 Median OS: NIV - 21.22 vs DOC - 14.93 QALYs: NIV - 0.87 vs DOC - 0.59 LYs: NIV - 1.77 vs DOC - 1.24	WTP of US$100 000/QALY **NIV vs DOC:** ICER : $187 685 Cost per Incremental LYG: $102 896 PD-L1 ≥1% or TC ≥ 1: ICER by QALY - $112 311 PD-L1 ≥5%: ICER by QALY - $72 897 PD-L1 ≥10%: ICER by QALY - $78 921		Yes	Yes for PD-L1 ≥5% patients
Aguiar_2018_Brazil,Argentina,Peru	Nivolumab vs docetaxel	Squamous NSCLC	5 RCTs involving 3043 participants, Second-line	LYs: NIV - 1.59 vs DOC - 0.88 QALY gain, NIV vs DOC: PD-L1 unselect - 0.417 PD-L1 ≥ 1% - 0.322 PD-L1 ≥ 5% - 0.481 PD-L1 ≥ 10% - 0.495	NIV vs DOC - BR, AR,PE: Cost per LYS: $98,739, $131,544, $100,070 ICER by QALY : PD-L1 unselect - $168,115, $223,971, $170,383 PD-L1 ≥ 1% - $217,714, $290,050, $220,651 PD-L1 ≥ 5% - $145,746, $194,171, $147,712 PD-L1 ≥ 10% - $141,624, $188,679, $143,535	PD-L1 expression	Yes	No WTP treshold
		Non-squamous NSCLC	5 RCTs involving 3043 participants, Second-line	LYs: NIV - 1.77 vs DOC - 1.24 QALY gain, NIV vs DOC: PD-L1 unselect - 0.287 PD-L1 ≥ 1% - 0.480 PD-L1 ≥ 5% - 0.740 PD-L1 ≥ 10% - 0.683	NIV vs DOC - BR, AR,PE: Cost per LYS: $117,824, $160,881, $119,658 ICER by QALY: PD-L1 unselect - $168,115, $297,097, $220,971 PD-L1 ≥ 1% - $217,714, $177,639, $132,122 PD-L1 ≥ 5% - $145,746, $115,226, $85,701 PD-L1 ≥ 10% - $141,624, $124,842, $92,853	PD-L1 expression	Yes	No WTP treshold
Hellmann_2018_Multi	Nivolumab vs Docetaxel	Advanced NSCLC	CheckMate 227, 150 pantients with stage IV NSCLC	Patients with high TMB (≥10 mutations per megabase): Median PFS, months: NIV - 4.2 vs DOC-5.6	-	TMB	No	-

Table 1 – Summary of data extracted from included studies. (12,61–63)

Four studies compared Nivolumab with docetaxel in terms of effectiveness outcomes and three evaluated its cost-effectiveness/utility.

Matter-Walstra et al.'s analysis found that, in PD-L1 selected patients, nivolumab resulted in longer OS and 0.16 incremental QALYs, even though median PFS was longer in the docetaxel arm. This study took the perspective of Switzerland's National Health System (NHS), assuming a WTP of 100,000CHF per QALY. With this threshold, nivolumab was not considered cost-effective, having an ICER of 177,148CHF per QALY. (61)

Looking through USA's NHS perspective, Aguiar Jr. et al. found that nivolumab achieved much better outcomes in both squamous and non-squamous NSCLC, when compared with docetaxel. Even so, the author still found this ICI to be cost-effective only in the non-squamous

NSCLC with PD-L1 expression superior to 5%, with all other subpopulations ICERs far surpassing the 100,000US$ WTP established. (59)

On the other hand, Aguiar et al. (12) compared nivolumab with docetaxel in Brazil, Argentina and Peru's payers perspective, also selecting squamous and non-squamous NSCLC through PL-D1's tumour expression. Again, nivolumab demonstrated efficacy superiority, adding more life years and QALYs to treated patients. Nevertheless, ICER per QALYs achieved values very unlikely to be cost-effective, if we estimate the missing WTPs through WHO's established 3 times the respective national GDP per capita formula, for Brazil (WTP=20,388US$), Argentina (WTP=25,323US$) and Peru (WTP=18,378US$). (60,64) With the lowest ICER being 85,701US$ for PD-L1 ≥ 5%, in the non-squamous population.

Lastly, Hellman et al.'s study demonstrated that high levels of TMB might correlate with a nivolumab's diminished therapeutic efficacy, as docetaxel achieved longer PFS (plus 1.4 months) in a stage IV NSCLC, more than 10 mutations per megabase, population.

3.2 Nivolumab + erlotinib

Study	Main intervention vs Comparator	Lung cancer type	Sample	Effectiveness Results	Costs	Biomarkers	Therapeutic advantage?	Cost-efec./uti. ?
Rizvi 2014 USA	Nivolumab + erlotinib	Advanced NSCLC	Stage IIIB/IV EGFR mutant chemotherapy-naïve NSCLC, 21 patients	3 patients were observed to have partial responses, all ongoing. DR : 6.1+, 16.3+ and 27.1+ weeks. 9 patients (45%) had stable disease with 3 patients (33%) having ongoing responses. One patient was observed to have unconventional 'immune-related' response that was ongoing at the time of interim analysis.	-	EGFR MT	Yes	-
Gettinger 2018 USA	Nivolumab + erlotinib	Advanced EGFR-mutant NSCLC	20 patients with advanced EGFR-mutant NSCLC who were EGFR TKI–naive or TKI-treated but had not received chemotherapy	PR in 3 patient, 1 with CR. 24-week PFS: 48% Responses lasted 13.8, 17.6, and 38.2 months 1nonconventional immune-related response lasting 12.5 months The TKI-naive patient, who had compound EGFR mutations (L858R and S768I) achieved a complete response, had an ongoing response lasting more than 5 years based on investigator records.	-	EGFR MT	Yes	-

Table 2 - Summary of data extracted from included studies (cont.). (65,66)

Two studies were identified for the combination of nivolumab and erlotinib.

In Rizvi et al. and Gettinger et al.'s studies, the addition of nivolumab to erlotinib produced positive outcomes in Advanced EGFR-mutant NSCLC patients, with some patients achieving partial and even complete durable responses within these small samples. (65,66)

No studies using comparators or economic factors were found.

3.3 Nivolumab + chemotherapy

Study	Main intervention vs Comparator	Lung cancer type	Sample	Effectiveness Results	Costs	Biomarkers	Therapeutic advantage?	Cost-effective ?
Borghaei 2020 USA	Nivolumab + chemotherapy vs chemotherapy	Advanced NSCLC	CheckMate 227, 550 chemo-naive, stage IV/recurrent NSCLC, patients	PFS improved NIV+CH vs CH - HR = 0.74 [95% CI: 0.58, 0.94] Discontinuation TR AEs: NIV+CH - 13% vs CH - 14%	-	tumor PD-L1 expression	Yes	-
Provencio 2020 Spain	Nivolumab + chemotherapy neoadjuvant	Resectable NSCLC	Open-label, multicentre, single-arm phase 2 trial, 51 patients	PFS 1 year : NIV+CH - 95·7% PFS 2 year : NIV+CH - 77·1% OS 1 year : NIV+CH - 97·8% OS 2 year : NIV+CH - 89·9% AEs of grade ≥ 3: NIV+CH - 30%	-	-	-	-

Table 3 - Summary of data extracted from included studies (cont.). (67,68)

Looking at the published data regarding the combination of nivolumab with chemotherapy, only two studies were found, with Provencio et al.'s study lacking a comparator. In this study NIV plus CH was used as neoadjuvant therapy, with the included population achieving very positive 1- and 2-year PFS and OS. Despite indicating a good performance as a neoadjuvant, a high percentage of patients experienced serious treatment related adverse events (30%). (67) On the other hand, Borghaei et al. compared nivolumab with chemotherapy versus only chemotherapy, reporting a high hazard ratio for a higher PFS with NIV plus CH and a very similar toxicity profile, despite the combination therapy. The included population was constituted by PD-L1 selected, chemo-naive stage IV recurrent NSCLC patients. (69)

3.4 Nivolumab + ipilimumab

Study	Main intervention vs Comparator	Lung cancer type	Sample	Effectiveness Results	Costs	Biomarkers	Therapeutic advantage?	Cost-Efec./Uti.?
Hellmann 2019 USA &Spain	Nivolumab + ipilimumab vs chemotherapy	NSCLC	CheckMate 227, 1189 stage IV or recurrent NSCLC patients	Median OS, months: NIV+IPI - 17.1 vs CH - 14.9 ORR: NIV+IPI - 35.9% vs CH - 30% Median DR, months: NIV+IPI - 23.2 vs CH - 6.2 PFS at 2 years: NIV+IPI - 10.5% vs CH - 4.6% AEs of grade ≥ 3: NIV+IPI - 32.8% vs CH - 36.0%	-	-	Yes	-
	Nivolumab + ipilimumab vs nivolumab			PD-L1 ≥ 1%: OS at 2 years: NIV+IPI - 40% vs NIV - 36.2% CR: NIV+IPI - 5.8% vs NIV - 3.0% Media DR, months: NIV+IPI - 23.2 vs NIV - 15.5	-	PD-L1 expression and TMB	Yes	-
	Nivolumab + ipilimumab vs nivolumab + chemotherapy			PD-L1 ≥ 1%: ORR: NIV+IPI - 27.3% vs NIV+CH - 37.9% OS at 2 years: NIV+IPI - 40.4% vs NIV+CH - 34.7% Media DR, months: NIV+IPI - 18.0 vs NIV+CH - 8.3	-	PD-L1 expression and TMB	Yes	-
Paz-Ares 2021 Spain	Nivolumab + ipilimumab + 2 cycles of chemotherapy vs chemotherapy	Advanced NSCLC	CheckMate 9LA, 719 patients	ORR: NIV+IPI - 38.2% vs CH - 24.9% Median DR, months: NIV+IPI - 11.3 vs CH - 5.6 Median OS, months: NIV+IPI - 15.6 vs CH - 10.9 Median PFS, months: NIV+IPI - 6.7 vs CH - 5.0 AEs of grade ≥ 3: NIV+IPI - 47% vs CH - 38%	-	PD-L1 expression	Yes	-
Hellmann 2018 Multi	Nivolumab + ipilimumab vs chemotherapy	Advanced NSCLC	CheckMate 227, 1739 pantients with stage IV NSCLC	Patients with **high** TMB (≥10 mutations per megabase): ORR: NIV+IPI - 45.3% vs CH - 26.9% Ongoing response at 1 year: NIV+IPI - 68% vs CH - 25% Median PFS, months: NIV+IPI - 7.2 vs CH - 5.5 Survival at 1 year: NIV+IPI - 42.6% vs CH - 13.2%	-	TMB	Yes	-
				Patients with **low** TMB (<10 mutations per megabase): Median PFS, months: NIV+IPI - 3.2 vs CH - 5.5	-		No	-
	Nivolumab vs Chemotherapy		CheckMate 227, 150 pantients with stage IV NSCLC	Patients with high TMB (≥10 mutations per megabase): Median PFS, months: NIV - 4.2 vs CH - 5.6	-		No	-
Antonia 2016 Multi	Nivolumab + ipilimumab (2 dosages, NIV 3 mg/kg + IPI 1mg/kg and NIV 1" and IPI 3") vs nivolumab	Recurrent SCLC	CheckMate 032, 213 patients	Median OS, months: NIV - 4.4 vs NIV+IPI1 - 6.0 vs NIV+IPI3- 7.7 ORR: NIV - 10% vs NIV+IPI1 - 19% vs NIV+IPI3- 23% Time to OR (IQR),months: NIV - 2 vs NIV+IPI1 - 1.4 vs NIV+IPI3- 2.1 Median PFS, months: NIV - 1.4 vs NIV+IPI1 - 1.4 vs NIV+IPI3- 2.6	-	PD-L1 expression	Yes	-
Ready 2019 USA	Nivolumab + ipilimumab vs nivolumab	Advanced SCLC	CheckMate 032, third line or later mestatic 147 patients	ORR: NIV+IPI - 21.9% vs NIV - 11.6% Median DOR, months: NIV+IPI - 10.0 vs NIV - 15.8 Median OS: NIV+IPI - 5.7 vs NIV - 4.7 Median PFS, months: NIV+IPI - 1.4 vs NIV - 1.5 Discontinuation TR AEs: NIV+IPI - 29% vs NIV - 18%	-	TMB	Partly	-

Table 4 - Summary of data extracted from included studies (cont.). (13,35,63,70–74)

Eight studies evaluating the therapeutic advantage of nivolumab in combination with ipilimumab were found.

Hellman et al.'s study compared the combination NIV+IPI with NIV, CH and NIV plus CH. The studied population included 1189 stage IV or recurrent NSCLC, PD-L1 and TMB

selected patients, divided throughout the 3 trials. Comparing with CH, NIV plus IPI showed significant gains in median OS and PFS at the 2 years mark, inducing more and longer responses, while maintaining a similar (and better) toxicity profile. When comparing NIV monotherapy with the addition of IPI, patients achieved better outcomes with the combination, especially in the subgroup with higher PD-L1 expression (≥ 50%). Even though both regimes had better performances in this subpopulation, the gap between both outcomes was wider. Similar results were found when comparing NIV+IPI with NIV plus CH, with the distinction that the combination that included CH had much higher ORR. (27)

The second study compared NIV+IPI and 2 cycles of CH to CH alone, in the treatment of advanced NSCLC patients. Regardless of PD-L1 expression, the outcomes were superior in the combination group, although at the cost of notable increase in treatment related toxicity. (71)

The following study compared NIV+IPI versus CH, distinguishing TMB levels in stage IV NSCLC patients. When observing patients with more than 10 mutations per megabase, much more positive outcomes were observed in the combination group, regarding PFs, ORR and duration of response. On the contrary, patients with lower levels of TMB achieved poorer PFS outcomes with NIV plus IPI. (13)

Antonia et al.'s study compared clinical efficacy of NIV plus IPI, with 2 different dosages – NIV 3mg/kg plus IPI 1mg/kg and NIV 1mg/kg plus IPI 3mg/kg, versus NIV, in recurrent SCLC patients. The outcomes reported showed clinical superiority of the NIV 1mg/kg plus IPI 3mg/kg, achieving more and longer responses. (72)

In Ready et al.'s review, NIV+IPI was also compared with NIV, this time in advanced SCLC patients, but contrary to the previous study, the combination did not achieve better outcomes across the board. ORR, which was de primary endpoint, and median OS were superior in NIV plus IPI, but NIV resulted in longer median DOR and PFS, with less associated serious toxicity. (73)

Study	Main intervention vs Comparator	Lung cancer type	Sample	Effectiveness Results	Costs	Biomarkers	Therapeutic advantage?	Cost-effective ?
	Nivolumab + ipilimumab vs chemotherapy			Median OS, months: NIV+IPI - 17.1 vs CH - 14.9 ORR: NIV+IPI - 35.9% vs CH - 30% Median DR, months: NIV+IPI - 23.2 vs CH - 6.2 PFS at 2 years: NIV+IPI - 10.5% vs CH - 4.6% AEs of grade ≥ 3: NIV+IPI - 32.8% vs CH - 36.0%	-	-	Yes	-
	Nivolumab +			PD-L1 ≥ 1%: OS at 2 years: NIV+IPI - 40% vs NIV - 36.2%		PD-L1		
Hellmann2_2018_Multi	Nivolumab + ipilimumab vs nivolumab	SCLC	CheckMate 032	**High TMB:** ORR: NIV+IPI - 46.2% vs NIV - 21.3% 1 year PFS: NIV+IPI - 30.0% vs NIV - 21.2% 1 year OS: NIV+IPI - 62.4% vs NIV - 35.2% **Medium TMB:** ORR: NIV+IPI - 16.0% vs NIV - 6.8% 1 year PFS: NIV+IPI - 8.0% vs NIV - 3.1% 1 year OS: NIV+IPI - 19.6% vs NIV - 26.0%	-	TMB	Yes	-
Zhou_2020_China	Nivolumab + ipilimumab versus chemotherapy	NSCLC	KEYNOTE-024, KEYNOTE-042 and CheckMate 227,	**PD-L1 ≥ 1%:** OS HR (95% CI): 0.79 PFS HR (95% CI): 0.82 ORR RR (95% CI): 1.20 **PD-L1 = 1-49%:** OS HR: 0.94 **PD-L1 ≥ 50%:** OS HR (95% CI): 0.70 PFS HR (95% CI): 0.62 ORR RR (95% CI): 1.16	-	PD-L1 level of ≥1%,	Yes	-
				PD-L1 ≥ 1%: OS HR (95% CI): 0.98				
Ando_2020_Japan	Nivolumab + ipilumumab vs pembrolizumab + platinum-based chemotherapy vs PEM, NIV or PBC	Advanced NSCLC	KEYNOTE-189, KEYNOTE-407, KEYNOTE-042, CheckMate 227	PFS HR, ≥1% - ≥50% : NIV+IPI vs PEM+PBC - 1.784 - 1.671 NIV+IPI vs PEM - 0.770 - 0.775 PEM+PBC vs PEM - 0.436 - 0.493 NIV+IPI vs NIV - 0.832 - 0.805 PEM+PBC vs NIV - 0.474 - 0.519 PEM vs NIV - 1.091 - 1.064	-	PD-L1 level	Pem+PBC > Niv+Ipi > Pem > Niv >PBC	-
				OS HR, ≥1% - ≥50% : NIV+IPI vs PEM+PBC - 1.465- 1.423 NIV+IPI vs PEM - 0.982- 1.029 PEM+PBC vs PEM - 0.681- 0.748 NIV+IPI vs NIV - 0.903- 0.877 PEM+PBC vs NIV - 0.631- 0.648 PEM vs NIV - 0.931- 0.875	-			-
				TR AEs ≥ 3 OR: NIV+IPI vs PEM+PBC - 0.761 NIV+IPI vs PEM - 2.624 PEM+PBC vs PEM - 3.508 NIV+IPI vs NIV - 1.973 PEM+PBC vs NIV - 2.680 PEM vs NIV - 0.931- 0.777	-			-

Table 5 - Summary of data extracted from included studies (cont.). (35,63,74)

In the next study, NIV+IPI was compared with NIV in SCLC patients, selected by levels of TMB. In accordance with what previous studies reported, clinical outcomes improved in correlation with higher TMB for both NIV+IPI and NIV monotherapy arms. The incremental clinical benefit of the combination regime was also bigger in higher TMB patients. (63)

Zhou et al.'s study compared the NIV+IPI combination to CH and PEM, selecting NSCLC patients through PD-L1 expression levels. In the NIV plus IPI versus CH trial, the combination presented therapeutic advantage throughout all PD-L1 levels, however results didn't show a direct correlation between the two. Patients with expression of the tumorous ligand superior to 50% actually achieved worse clinical outcomes then the ones with lower

expression (at least 1%) and the highest OS hazard ratio was in the 1 to 49% expression population. Differently, when comparing to PEM in monotherapy, the combination of ICIs was only partly advantageous. NIV+IPI were associated with longer PFS than PEM. However, the combination was not superior in terms of OS neither of ORR, while also showcasing a worse serious toxicity profile. Increased PD-L1 expression didn't predict better results with NIV plus IPI. (74)

Lastly, a Japanese study indirectly compared NIV+IPI with: PEM plus platinum-based chemotherapy (PBC), PEM, NIV or PBC in monotherapy. The studied population was constituted by advanced NSCLC patients from 4 different clinical trials and divided by PD-L1 expression (superior to 1% or to 50%). Ando et al. reported an outcome superiority of PEM plus PBC, achieving longer PFS and OS than all other regimens, including NIV+IPI, in both PD-L1 expression subpopulations. NIV+IPI had a therapeutic advantage over the rest of the regimens. The combination therapies displayed more serious treatment related adverse events, with the toxicity profiles being similar between the two.(35)

No studies evaluating economic factors were found.

3.5 Pembrolizumab vs chemotherapy

Study	Main intervention vs Comparator	Lung cancer type	Sample	Effectiveness Results	Costs	Biomarkers	Therapeutic advantage?	Cost-Efec./Uti. ?
Huang_2016_USA	Pembrolizumab vs docetaxel	Advanced non-squamous NSCLC	KEYNOTE 010 trial - pre-treated patients with PD-L1 positive tumors (total proportion score [TPS] ≥ 50%	Mean OS: PEM - 2.25 years vs DOC - 1.07 years Median PFS: PEM - 5.0 months vs DOC - 4.1 months QALYs: PEM - 1.71 years vs DOC - 0.76 years	WTP - US: $109,000–$297,000 per QALY IC per QALY : PEMBRO vs DOC -$168,619/QALY weekly disease management cost: PEMBRO - $1,282 vs DOC - $1,623 Direct cost over 20 years: PEMBRO - $297,443 vs DOC - $136,921	-PD-L1 tumour proportion score (TPS)	Yes	Yes
Huang_2018_USA	Pembrolizumab vs platinum-based chemotherapy or docetaxel	Advanced or metastatic NSCLC	KEYNOTE (KN)-024 (305 patients) and KN010 (1034 patients) trials	PEM vs PLAT: 2.49 months greater Q-TWiST PEM vs DOC: 2.29 months greater Q-TWiST PEM superior OS vs CH: HR 0.63, 95% CI 0.47–0.86	-	-	Yes	-
Bhadhuri_2019_Switzerland	Pembrolizumab vs chemotherapy	Metastatic NSCLC	KEYNOTE-024	QALYs: PEM 3.05 vs CH 1.71	WTP: CHF 100,000 Costs: PEMBRO - CHF 223,324 vs CHEMO - CHF 146,264 PEMBRO'S ICER: CHF 57,402 per QALY gained	PD-L1 tumour proportion score (TPS) ≥50%	Yes	Yes
Huang_2017_USA	Pembrolizumab vs platinum-based chemotherapy	Stage IV NSCLC	KEYNOTE-024	PEM vs CH: gained 1.31 LYs and 1.05 QALYs	WTP: $US122,360–340,000/LYs gained $US140,392–382,536/QALYs gained PEMBRO vs CHEMO: incremental cost of $US102,439 IC = $US97,621/QALY and $US78,344/LY	PD-L1 TPS ≥50%	Yes	Yes
AguiarJr_2017_USA	Pembrolizumab vs docetaxel	NSCLC	37 638 patients, various randomized clinical trials	Mean PFS: PEM - 6.56 vs DOC - 5.06 PPS: PEM - 15.78 vs DOC - 8.95 Median OS: PEM - 22.34 vs DOC - 14.01 QALYs: PEM - 0.92 vs DOC - 0.57 LYs: PEM - 1.86 vs DOC - 1.17	WTP of US$100 000/QALY **PEM vs DOC:** ICER : $98 421 Cost per Incremental LYG: $49 007 PD-L1 ≥50% or TC 3: ICER by QALY - $80 735	PD-L1 expression	Yes	Yes
Aguiar_Brazil,Argentina,Peru_2018	Pembrolizumab vs platinum-based chemotherapy	NSCLC	5 RCTs involving 3043 participants, First-line EGFR and ALK Wt	LYs: PEM - 2.27 vs PBC- 1.54 QALY gain, PEM vs PBC: PD-L1 ≥ 10% - 0.74	PEM vs DOC - BR, AR,PE: Cost per LYS: $35,556, $78,121, $25,713 ICER by QALY : PD-L1 ≥ 10% - $63,424, $139,351, $45,866	PD-L1 expression	Yes	No WTP treshold
	Pembrolizumab vs docetaxel	NSCLC	5 RCTs involving 3043 participants, Second-line	LYs: PEM - 1.86 vs DOC - 1.17 QALY gain, PEM vs DOC: PD-L1 ≥ 1% - 0.346 PD-L1 ≥ 50% - 0.409	PEM vs DOC - BR, AR,PE: Cost per LYS: $66,005, $109,458, $65,720 ICER by QALY: PD-L1 ≥ 1% - $131,630 , $218,283, $131,060 PD-L1 ≥ 50% - $111,355, $184,660, $110,872	PD-L1 expression	Yes	No WTP treshold
Zhou_2020_China	Pembrolizumab versus chemotherapy	NSCLC	KEYNOTE-024, KEYNOTE-042 and CheckMate 227,	**PD-L1 ≥ 1%:** OS HR (95% CI): 0.81 PFS HR (95% CI): 1.07 ORR RR (95% CI): 1.03 **PD-L1 = 1-49%:** OS HR: 0.92 **PD-L1 ≥ 50%:** OS HR (95% CI): 0.63 PFS HR (95% CI): 0.50 ORR RR (95% CI): 1.35	-	PD-L1 level of ≥1%,	Yes	-

Table 6 - Summary of data extracted from included studies (cont.). (12,62,74–78)

Seven studies were identified comparing PEM effectiveness to CH options, with 5 evaluating its cost-effectiveness/utility.

Huang et al.'s study compared PEM with DOC in advanced pre-treated non-squamous NSCLC patients with PD-L1 positive tumours. PEM resulted in better outcomes across the board, achieving longer OS, PFS and more QALYs gained. Incremental cost per QALY for PEM versus DOC was 168,619US$. Adopting USA payers' perspective, the willingness to pay

threshold used was 109,000 to 297,000US$ per QALY, making PEM a cost-effective option with a clear therapeutic advantage. (75)

The second study analysed PEM effectiveness in comparison with CH (either docetaxel or PBC) in advanced or metastatic NSCLC patients. This study assessed the Quality-adjusted Time Without Symptoms of disease progression or Toxicity of treatment (Q-TWiST), finding it to be more than 2 months longer for PEM, in comparison to either of the CH options, with OS being longer as well. (76)

Bhadhuri et al.'s review compared PEM to CH in a PD-L1 selected metastatic NSCLC population, reporting 1,34 incremental QALYs. From Switzerland payers' perspective, PEM was deemed cost-effective, as its ICER per QALY gained was 57,402CHF, way under the 100,000CHF established threshold. (77)

In another study, Huang et al.'s compared PEM to PBC in stage IV NSCLC, reporting 1.31 LYs and 1.05 QALYs gained in the PEM arm. The authors adopted the USA payers' perspective and found PEM to be a cost-effective option, when utilizing a 122,360 to 340,000US$ per LY gained and 140,392 to 382,536US$ per QALY gained, as the incremental cost for this ICI was 78,344US$ per LY and 97,621US$ per QALY. (78)

Aguiar Jr et al.'s analysis reported PEM to be cost-effective in comparison with DOC, in 37 638 NSCLC, PD-L1 selected patients. Outcomes were overall better with PEM, registering longer median PFS and OS, more QALYs and LYs gained. Assuming the USA payers' perspective and utilizing a WTP limit of 100,000US$, PEM was considered cost-effective, in accordance with the calculated ICERs of 49,007US$ per LY and 80,735US$ per QALY. (12)

On the contrary, Aguiar et al. (62) compared PEM to DOC and PBC and, although no WTP thresholds were mentioned, if the missing WTPs are estimated through WHO's established 3 times the respective national GDP per capita formula, for Brazil (WTP=20,388US$), Argentina (WTP=25,323US$) and Peru (WTP=18,378US$), finding it to be cost-effective is very unlikely. (60,64) In both trials, PEM had significant improvements in LY and QALYs gained over the CH options, especially in the subgroup of the PBC trial with higher PD-L1 expression. Even so, ICERs per QALY were, respectively for Brazil, Argentina and Peru: 131,630US$, 218,283US$, 131,060US$ for the PD-L1≥1% subgroup and 111,355US$, 184,660US$, 110,872US$ for the PD-L1≥50% subgroup. (62)

Lastly, in Zhou et al.'s review PEM was compared to CH and was found to have a therapeutic advantage across all PD-L1 expression level subgroups of NSCLC patients. OS, PFS and ORR outcomes were significantly better in the PD-L1 ≥50% subpopulation. (74)

3.6 Pembrolizumab + chemotherapy

Study	Main intervention vs Comparator	Lung cancer type	Sample	Effectiveness Results	Costs	Biomarkers	Therapeutic advantage?	Cost-Efec./Uti. ?
Paz-Ares_2019_Spain	Pembrolizumab + Chemotherapy vs Chemotherapy	Untreated metastatic, squamous NSCLC	Double-blind, phase 3 trial, 559 patients	Median OS: PEM+CH - 15.9 months vs CH - 11.3 months Median PFS: PEM+CH - 6.4 months vs CH - 4.8 months Response Rate (RR): PEM+CH - 57.9% vs CH - 38.4%	-	PD-L1 status	Yes	-
Jiang_2020_China	Pembrolizumab + Chemotherapy vs Chemotherapy	Untreated metastatic, non-squamous NSCLC	KEYNOTE-189	-	WTP: $28 106/QALY Cost: PEM+CH - $139 168 vs CH - $73 081 PEM+CH ICER: $80 444/LY and $96 644/QALY IC / QALY for PD-L1 TPS: ≥50% - $90 419 1%–49% - $91 399 <1% - $109 229	PD-L1 TPS	-	No
Gandhi_2018_USA	Pembrolizumab + Chemotherapy vs Chemotherapy	Advanced NSCLC	Double-blind, phase 3 trial, 616 patients	OS at 12 months: PEM+CH - 69.2% vs CH - 49.4% Median PFS: PEM+CH - 8.8 months vs CH - 4.9 months AEs of grade ≥ 3: PEM+CH - 67.2% vs CH - 65.8%	-	PD-L1 TPS ≥50%	Yes	-

Table 7 - Summary of data extracted from included studies (cont.). (38,79,80)

The work of Paz-Ares et al. compared PEM in combination with CH to CH alone, in untreated metastatic, squamous NSCLC patient. The combination achieved significant improvements in median OS (+4.9 months), PFS (+1.6 months) and RRs (+19.5%), demonstrating a therapeutic advantage in the studied sample. (38)

Jiang et al.'s review evaluated PEM+CH cost-effectiveness, in comparison with CH, assuming the perspective of China's payers. The WTP threshold set was 28,106US$. PEM+CH ICER per LY gained was 80,444US$ and 96,644US$ per QALY gained. The incremental cost per QALY varied with PD-L1 expression subgroups, with costs per QALY diminishing in correlation with higher PD-L1 expressions: ≥50% - 90 419US$, 1%–49% - 91 399US$, <1% - 109 229US$. Even the lowest value doesn't even come close to the WTP threshold, deeming this combination hardly cost-effective. (79)

The last study reported PEM+CH effectiveness versus CH in 616 advanced NSCLC patients with PD-L1 expression superior to 50%. The combination's arm revealed significantly better OS at the 1-year mark (+19.8%) and median PFS (+3.9 months) and a similar toxicity profile (+1.4%). (80)

3.7 Pembrolizumab + ipilimumab

Study	Main intervention vs Comparator	Lung cancer type	Sample	Effectiveness Results	Costs	Biomarkers	Therapeutic advantage?	Cost-Efec./Uti. ?
Gubens_68_2018_USA	Pembrolizumab + ipilimumab	Advanced NSCLC	KEYNOTE-021, 51 patients, previously received ≥1 PBC or an appropriate targeted therapy and experienced treatment failure	PEM + IPI: ORR: 30% Median PFS: 4.1 months Median OS: 10.9 months AEs of grade ≥ 3: +64%	-	-	Insuficient data	-

Table 8 - Summary of data extracted from included studies (cont.). (68)

One study regarding the combination of PEM with IPI in lung cancer patients was found, but it lacked a comparator and economic evaluation. Gubens et al.'s work reported positive responses in pre-treated and refractory advanced NSCLC, with ORR reaching 30% and achieving median PFS and OS of 4.1 and 10.9 months, respectively. Treatment related serious adverse events had a prevalence of 64%. (68)

3.8 Durvalumab vs chemotherapy

Study	Main intervention vs Comparator	Lung cancer type	Sample	Effectiveness Results	Costs	Biomarkers	Therapeutic advantage?	Cost-Efec./Uti. ?
Witlox_2020_UK	Durvalumab vs chemotherapy	NSCLC	PACIFIC trial, locally advanced, unresectable, stage III patients	Median PFS, months: DUR - 23.9 vs CH - 5.6 Serious TR AEs: DUR - 30% vs CH - 20%	WTP: £30,000 ICER DUR vs CH: £50,238 /QALY	PD-L1 on ≥ 1%	Yes	No

Table 9 - Summary of data extracted from included studies (cont.). (81)

One study was found evaluating the cost-effectiveness/utility of DUR against classical CH, in stage III, unresectable NSCLC patients, selected by PD-L1 expression of at least 1%. This Witlox et al.'s review reports significant gains in median PFS (+18.3 months), although with a notable increase in serious TR AEs (+10%). The authors considered DUR's ICER per QALY of 50,238£ to be not cost-effective, as it far surpassed the 30,000£ threshold. (81) Nevertheless, if the WTP was calculated through WHO's formula of 3 times the GPD per capita, it can be assumed to be about 88,308£, which would result in a different evaluation. (60,64)

3.9 Durvalumab + chemotherapy +/- tremelimumab

Study	Main intervention vs Comparator	Lung cancer type	Sample	Effectiveness Results	Costs	Biomarkers	Therapeutic advantage?	Cost-Efec./Uti. ?
Zhang 2020 China and Paz-Ares 2019	Durvalumab + chemotherapy vs chemotherapy	Extensive-Stage SCLC	CASPIAN trial	Median OS, months: DUR+CH - 13.0 vs CH - 10.3 Median PFS, months: DUR+CH - 5.1 vs CH - 5.4 ORR: DUR+CH - 68% vs CH -58% LYs: DUR+CH - 0.99 vs CH - 0.57 QALYs: DUR+CH - 0.55 vs CH - 0.33	WTP threshold of $100,000 /QALY Total costs,US$: DUR+CH - 90,072.83 vs CH - 11,874.08 ICER DUR+CH vs CH: 355,448.86US$/QALY Drug cost per mg, US $: DUR-7.6179, Etoposide-0.0602, Carboplatin-0.05714, Cisplatin-0.1845, Topotecan-12.11	-	Yes	No
Goldman 2021 Multi	Durvalumab +/- tremelimumab + chemotherapy vs chemotherapy	Extensive-Stage SCLC	CASPIAN trial, 972 patients	Median OS, months: DTC - 10.4 vs DC - 12.9 vs CH -10.5 1 year OS: DTC - 48.3% vs DC - 52.8% vs CH - 39.3% 2 year OS: DTC - 23.4% vs DC - 22.2% vs CH - 14.4% ORR: DTC - 58% vs DC - 68% vs CH -58% 2 year OR: DTC - 17.2 vs DC - 13.5 vs CH - 3.9 1 year PFS: DTC - 16.9% vs DC - 17.9% vs CH - 5.3% 2 year PFS: DTC - 11.5%vs DC - 11.0% vs CH - 2.9% Serious TR AEs: DTC - 45% vs DC - 32% vs CH - 36%	-	-	Partly	-
Planchard 2020 UK	Durvalumab +/- tremelimumab vs chemotherapy	Metastic NSCLC	ARTIC trial, 126 patients	PD-L1 ≥25%: Median OS, months: DUR - 11.7 vs CH - 6.8 Median PFS: DUR - 3.8 vs CH - 2.2 ORR: DUR - 35.5% vs CH - 12.5% DR, months: DUR - 9.5 vs CH - 4.8	-	PD-L1 expression	Yes	-
			ARTIC trial, 469 patients	PD-L1 <25%: mOS, months : DT -11.5 D - 10.0 T - 6.9 CH - 8.7 1 year OS: DT - 49.5% D - 43.6% T - 41.2% CH - 38.8% mPFS, months: DT -3.5 D - 3.1 T - 2.1 CH - 3.5 2 year PFS: DT - 20.6% D - 15.0% T - 7.3% CH - 8.0% ORR: DT - 14.9% D - 15.4% T - 6.7% CH - 6.8% DR, months: DT -12.2 D - 10.0 T - 4.7 CH - 10.8	-		Yes	-

Table 10 - Summary of data extracted from included studies (cont.). (40,82–84)

Three studies were found regarding DUR in combination with CH, with the possible addition of Tremelimumab.

Both Zhang et al.'s and Paz-Ares et al.'s reviews analyse data from the CASPIAN trial and report complementary data about DUR+CH versus CH cost-effectiveness, in extensive stage SCLC patients. The combination therapy resulted in better overall outcomes, except for median PFS. Even so, considering the 100,000US$ per QALY WTP, DUR+CH's ICER was abysmally superior (3.5 times the WTP) and, consequently, not a cost-effective alternative. (82,83)

Goldman et al.'s work evaluated the effectiveness of DUR if accoupled with CH, with or without tremelimumab, compared to CH alone. It reported that DUR+CH had overall the better outcomes of the 3 arms, in the 1-year framework. When extending the considered period to 2 years, the DTC combination achieved the most promising results in all outcomes, but at the cost of a worse safety profile. As such both combinations were considered to have a therapeutic advantage over CH, but between them there wasn't a predominantly more effective regimen. (84)

Lastly, Planchard et al.'s review compares the effectiveness of DUR or TRE, in combination or not, to CH in monotherapy. Metastatic NSCLC patients were divided by the PD-L1 expression threshold of 25%, with tremelimumab being added only in the less than 25%

arm. In monotherapy, DUR showed clinical superiority to CH, achieving improved outcomes across the PD-L1 ≥25% subpopulation, demonstrating better ORR and longer DR, PFS and OS. In the PD-L1<25%, the combination of DUR+TRE showed therapeutic advantage, resulting in longer OS, PFS and DR (11.5, 3.5, 12.2 months, respectively), with DUR alone having the second longest and having the highest ORR by a small margin (+0.5%), followed by TRE and then CH. (40)

3.10 Atezolizumab vs docetaxel

Study	Main intervention vs Comparator	Lung cancer type	Sample	Effectiveness Results	Costs	Biomarkers	Therapeutic advantage?	Cost-Efec./Uti. ?
AguiarJr 2017 USA	Atezolizumab vs docetaxel	NSCLC	37 638 patients, various randomized clinical trials	Mean PFS: ATE - 6.03 vs DOC - 5.25 PPS: ATE - 16.05 vs DOC - 7.95 Median OS: ATE - 22.08 vs DOC - 13.20 QALYs: ATE - 0.90 vs DOC - 0.54 LYs: ATE - 1.84 vs DOC - 1.10	WTP of US$100 000/QALY **ATE vs DOC:** ICER : $215 802 Cost per Incremental LYG: $103 095 PD-L1 ≥1% or TC ≥ 1: ICER by QALY - $188 632 PD-L1 ≥50% or TC 3: ICER by QALY - $76 459	PD-L1 expression	Yes	Yes, if PD-L1 ≥50% or TC patients.
Rittmeyer 2019 USA	Atezolizumab vs docetaxel	Previously treated NSCLC	OAK study, a randomised, open-label, international phase 3, 850 patients, subgroups with/out biomarker	Median OS: ATE - 13.8 and 15.7 months vs DOC - 9.6 and 10.3 months Treatment-related (TR) grade 3 or 4 AEs: ATE - 15% vs CH - 43%	-	PD-L1 expression	Yes	-
Fehrenbacher 2016 USA	Atezolizumab vs docetaxel	Previously treated, advanced or metastatic NSCLC	287 patients	Median OS: ATE - 12·6 months vs DOC - 9·7 months Treatment-related grade 3 or 4 AEs: ATE - <1% vs CH - 2%	-	PD-L1 tumour proportion score (TPS)	Yes	-

Table 11 - Summary of data extracted from included studies (cont.). (12,85,86)

Three studies evaluating ATE in comparison with DOC were found.

The first one compared ATE to DOC in NSCLC patients, selected through the cancer's PD-L1 expression. Aguiar Jr's review found ATE to achieve better outcomes in the studied population, with longer PFS (+0.78 months), PPS (+8.10 months) and OS (+8.88 months), also leading to QALYs (+0.36) and LYs (0.74) gains. Assuming USA payers' perspective and a WTP value of 100,000US$ per QALY, the authors found ATE to be a cost-effective option only in the subpopulation with PD-L1 ≥50% expression, as it resulted in an incremental cost of 76,459US$ per QALY gained. In the PD-L1 ≥1% the incremental cost was way higher, amounting to 188,632US$ per QALY gained. (12)

In Rittmeyer et al.'s work, ATE was compared to DOC in a previously treated NSCLC population, dividing it in two groups – the Intention to Treat (ITT) subpopulation and the PD-L1 selected subpopulation. Achieving incremental median OS of 4.2 months and 5.4 months in ITT and PD-L1s' subgroups and demonstrating a much better toxicity profile (-28% TR AEs

of grade 3 or more), ATE was considered an effective alternative with therapeutic advantage to DOC. (85)

Accordingly, Fehrenbacher et al.'s study demonstrated ATE's improved outcomes in comparison to DOC. The sample population of 287 previously treated, with advanced or metastatic NSCLC patients achieved better results in ATE's arm, registering a median OS increment of 2.9 months, with a very similar toxicity profile to the CH option. (86)

3.11 Atezolizumab + chemotherapy vs chemotherapy

Study	Main intervention vs Comparator	Lung cancer type	Sample	Effectiveness Results	Costs	Biomarkers	Therapeutic advantage?	Cost-Efec./Uti. ?
Wang 2021 USA	Atezolizumab + chemotherapy vs. chemotherapy	Extensive-stage SCLC	IMpower133 trial	Total QALYs: ATE + CH - 0.73 vs CH - 0.63 Total LYGs: ATE + CH - 1.12 vs CH - 0.96	WTP: US$100,000/QALY Total Cost: ATE + CH -109,051 US$ vs CH - 25,556 US$ ICER ATE + CH: 785.848 US$/QALY	-	Yes	No
Horn 2018 Poland	Atezolizumab + chemotherapy vs. chemotherapy	Extensive-stage SCLC	IMpower133 trial, 403 patients	Median OS: ATE+CH - 12.3 months vs CH - 10.3 months 1-year OS rate: ATE+CH - 51.7% vs CH - 38.2% PFS: ATE+CH - 5.2 months vs CH - 4.3 months Similar toxicity profile	-	Tumor mutational burden TMB	Yes	-
Ding 2020 USA	Atezolizumab + chemotherapy vs. chemotherapy	Non-squamous NSCLC	IMpower130	Total QALYs: ATE + CH - 1.68 vs CH - 1.52 Total LYGs: ATE + CH - 2.65 vs CH - 2.33	WTP $/QALY: 150,000 US$ ICER ATE + CH vs CH: 346,646.94 US$ per LY 670,309.66 US$ per QALY	PD-L1 TPS	Yes	No
West 2019 USA	Atezolizumab + chemotherapy vs. chemotherapy	Non-squamous NSCLC	IMpower130, 723 patients	Median OS: ATE+CH - 18.6months vs CH - 13.9 months PFS: ATE+CH - 7.0 months vs CH - 5.5 months Similar toxicity profile TR grade ≥ 3 AEs: ATE+CH - 51% vs CH - 38%	-	PD-L1 TPS	Yes	-

Table 12 - Summary of data extracted from included studies (cont.). (44,68,87,88)

Four reviews comparing ATE in combination with CH to CH alone were included.

In Wang et al.'s work extensive stage SCLC patients were put through one of the regimens, with ATE+CH achieving better QALYs and LYs gained outcomes (+0.10 and +0.16, respectively). The authors also calculated ATE+CH's ICERs and values added up to 785,848US$ per additional QALY and 529,888US$ per additional LY. (42)

In the Polish study, Horn et al.'s evaluated ATE+CH effectiveness in comparison with CH, in a TMB selected, extensive stage NSCLC population. With a similar toxicity profile, the combination achieved better outcomes, with longer median OS and PFS (+2 and +0.9 months), with OS rate at 1 year of treatment being significantly higher (+13.5%). (44)

In another study, ATE+CH was compared to CH in non-squamous NSCLC and achieved total incremental QALYs and LYs of 0.16 and 0.32, respectively. In the economic analysis,

WTP threshold for USA payers was set at 150,000US$. ATE+CH's ICERs were 346,646US$ per LY gained and 670,309US$ per QALY gained. (88)

Lastly, in West et al.'s analysis ATE+CH was juxtaposed with CH, in PD-L1 selected non-squamous NSCLC patients. Median OS and PFS improvements were significant (+4.7 and 1.5 months, respectively) but with significantly higher probability of treatment related toxicity (+13%). (87)

3.12 Atezolizumab + bevacizumab + chemotherapy vs atezolizumab + chemotherapy vs bevacizumab + chemotherapy

Study	Main intervention vs Comparator	Lung cancer type	Sample	Effectiveness Results	Costs	Biomarkers	Therapeutic advantage?	Cost-Efec./Uti. ?
Reck 2019 USA	Atezolizumab + bevacizumab + chemotherapy (ABC) vs. atezolizumab + chemotherapy (AC) vs bevacizumab + chemotherapy (BC)	Non-squamous NSCLC	IMpower150, 1202 patients	Objective Response (OR): ABC - 56.4% AC - 40.6% BC - 40.2% Median duration of response, months (DR): ABC - 11.5 AC - 8.3 BC - 6.0 Median OS, months: ABC - 19.8 AC - 19.5 BC - 14.9 Median PFS, months: ABC - 8.4 AC -7.5 BC - 6.8	-	EGFR mutations, baseline liver metastases or PD-L1 expression	Yes	-

Table 13 - Summary of data extracted from included studies (cont.). (89)

A single study approaching the combination of ATE with bevacizumab (BEV) was found. In this study the ICI was combined with BEV and CH and compared to ATE+CH or BEV+CH. The studied population included non-squamous NSCLC patients, which were selected through EGFR mutation identification, existence of baseline liver metastases and PD-L1 expression. The triple combination resulted in better outcomes overall, with significant gap in ORR (+5.8%), closely followed by the ATE+CH regime and last, with a larger gap than previous two, the BEV+CH. (89)

3.13 Ipilimumab + chemotherapy

Study	Main intervention vs Comparator	Lung cancer type	Sample	Effectiveness Results	Costs	Biomarkers	Therapeutic advantage?	Cost-Efec./Uti. ?
Tomasini 2012 France	Ipilumumab + chemotherapy vs chemotherapy	Advanced NSCLC	204 patients	Median irPFS, months: IPI+CH - 5.68 vs CH - 4.63 Median OS, monts: IPI+CH - 9.7 vs CH - 8.3 Disease Control rate (DCR): IPI+CH - 72.7% vs CH - 57.1% TR grade ≥ 3 AEs: IPI+CH - 58% vs CH - 42%	-	-	Yes	-
Reck 2013 Multi	Ipilumumab + chemotherapy vs chemotherapy	Extensive disease SCLC	130 patients	Median irPFS, months: IPI+CH - 6.4 vs CH - 5.3 Median OS, monts: IPI+CH - 12.9 vs CH - 9.9 (irDCR): IPI+CH - 93% vs CH - 96% Best overall response rate (BORR): IPI+CH -71 vs CH - 53 TR grade ≥ 3 AEs: IPI+CH - 17% vs CH - 9%	-	-	Yes	-

Table 14 - Summary of data extracted from included studies (cont.). (90,91)

Only 2 studies reporting outcomes with ipilimumab plus chemotherapy were identified. Both found the combination therapeutically advantageous but did not approach an economic evaluation. Tomasini et al. described better median irPFS, OS and DCR in the combination arm, although at the cost of more probable serious treatment related adverse events, in advanced NSCLC patients. (90) On the other hand, Reck et al. studied the use of IPI plus CH in extensive SCLC patients, reporting similarly positive results and harsh toxicity profile in comparison with monotherapy CH. (91)

3.14 ICI's costs

Parameter	Squamous tumours		Non-squamous tumours		All histology		All histology	
	PD-L1 unselected		PD-L1 unselected		PD-L1 ≥1%		PD-L1 unselected	
	Nivo	Doc	Nivo	Doc	Pembro	Doc	Atezo	Doc
Median No. of cycles	15	5	14	7	9	7	8	7
Drug cost	$77 774	$12 326	$72 589	$17 256	$55 188	$17 256	$100 032	$17 256
AEs costs	$202	$6922	$1738	$7002	$1380	$3513	$749	$4415
PPS costs	$6638	$5925	$6989	$7676	$9599	$12 457	$5947	$9270
EOL costs	$7251	$8287	$7251	$8287	$6776	$8261	$7251	$8287
Adm costs	$4350	$1450	$4060	$2030	$2610	$2030	$2320	$2030
Mon costs	$8238	$3290	$8164	$4606	$6588	$4606	$5856	$4606
Total costs	$104 453	$39 516	$100 791	$46 856	$82 201	$48 182	$122 155	$45 864

Table 15 – 1 year treatment costs for second-line treatment of NSCLC in the USA Health System. Nivo, nivolumab; Doc, docetaxel; Pembro, pembrolizumab; Atezo, atezolizumab; No, number; AEs, adverse events; PPS, post-progression survival; EOL, end-of-life; Adm, administering; Mon, monitoring; PFS, progression-free survival; OS, overall survival; TC, tumour cells or infiltrating cells PD-L1 expression score. (12)

Parameter	First-line EGFR and ALK Wt		Second-linesquamous tumors		Second-linenonsquamous tumors		Second-line all histology	
	PD-L1 ≥ 50%		PD-L1 unselected		PD-L1 unselected		PD-L1 ≥ 1%	
	Pembro	PBC	Nivo	Doc	Nivo	Doc	Pembro	Doc
Number of cycles	14	8	15	5	14	7	9	7
Brazil								
Drug cost	$83,320	$10,904	$75,474	$5,785	$70,442	$8,099	$53,563	$8,099
AEs costs	$231	$1,185	$31	$1,058	$266	$1,071	$211	$537
PPS costs	$1,862	$26,781	$3,146	$2,544	$3,291	$3,091	$3,970	$3,729
EOL costs	$972	$1,276	$1,109	$1,267	$1,109	$1,267	$1,036	$1,263
Adm costs	$420	$222	$665	$222	$621	$310	$399	$310
Mon costs	$1,167	$670	$1,260	$704	$1,260	$704	$1,007	$704
Total costs	$87,972	$41,038	$81,684	$11,580	$76,989	$14,542	$60,246	$14,702
Argentina								
Drug cost	$160,249	$6,824	$122,346	$3,733	$114,190	$5,226	$103,018	$5,226
Cost per LYS	$78,121		$131,544		$160,881		$109,458	
Peru								
Drug cost	$83,849	$10,368	$76,892	$6,480	$71,765	$9,072	$53,903	$9,072
Cost per LYS	$25,713		$100,070		$119,658		$65,720	

Table 16 – 1 year treatment costs for NSCLC in Brazil, Argentina and Peru. AE: Adverse event; Adm: Administering; Doc: Docetaxel; EOL: End-of-life; LYS: Life-year saved; Mon: Monitoring; N: Number; Nivo: Nivolumab; PBC: Platinum-based chemotherapy; Pembro: Pembrolizumab; PPS: Post-progression survival; Wt: Wild-type (62)

In the Table 15 and Table 16, Nivolumab and Pembrolizumab's costs are directly compared with chemotherapy options adequate for the same populations. Differences in medicines' costs amount to sums between 80,000US$ and 30,000US$, with total costs gaps amounting to 30,000 to 70,000 US$, when looking at the USA's or Brazil's price tags. Adverse reactions related to treatment presented overall lowers prices in ICI's, contrary to administration and monitorization costs.

4 Discussion

4.1 Immunomodulatory therapy cost-effectiveness in lung cancer patients

In this study, current data on ICI's therapeutic benefit and cost-effectiveness was reviewed and congregated, in order to enable a broad evaluation of these medications' potential and shortcomings.

Evidence gathered on the comparison of NIV to CH concordantly found the ICI option to have clear therapeutical benefit in lung cancer patients, selected through PD-L1 expression and TMB. Contrary to other ICI regimes, Hellman et al.'s work showed that high TMB might predict poorer outcomes with monotherapy NIV, as this was the only instance where patients achieved shorter PFS with the ICI option in comparison to classical CH. Even so, most studies found NIV to have a very low probability of being cost-effective compared to CH, as its high price requires very significant improvements to make up for the costs associated. Aguiar Jr et al.'s study is the exception in this regard, finding NIV to be cost-effective in non-squamous NSCLC patients with tumour cells PD-L1 expression being of at least 5%, with an ICER per QALY of 72,897US$, well within USA's WTP of 100,000 US$ per QALY. In other subgroups NIV wasn't found to be a cost-effective alternative. (12) Other included studies made this comparison with the perspective of Switzerland, Brazil, Argentina and Peru's payers and all found NIV to be effective, but not cost-effective.

Looking at the NIV plus erlotinib combination, no studies were found comparing this regime with other options or evaluating its cost-effectiveness. The included studies showed positive results, but population sizes were very small, demanding more robust evidence. Even so, they hint that the combination of ICIs with targeted therapy might be a regimen with potential for added benefit.

Regarding NIV in addition to CH, one of the studies included demonstrated its significant added clinical benefit in comparison with CH. Provencio et al.'s work showed positive results with NIV+CH as neoadjuvant therapy but didn't use any comparators. Unfortunately no evidence regarding its cost-effectiveness was found, which is surprising considering it's an already approved and used in clinical practice combination. (47) As NIV in monotherapy had already high costs associated, it's highly unlikely that the addition of CH would have a better cost-effectiveness profile.

The combination of NIV+IPI demonstrated across all included studies improved clinical outcomes when compared to CH, NIV in monotherapy or even NIV in addition to CH. Considering their complementary and synergic mechanisms of action, the combination of these two ICIs was expected to yield positive results. Nevertheless, even though all studies agreed upon the therapeutical added value of NIV+IPI, reports regarding its toxicity profile were contradictory. Hellman et al.'s work (27) described the probability of serious treatment related adverse events to be lower in patients being administered NIV+IPI, than in patients with a CH regimen (32.8% versus 36%). On the other hand, Paz-Ares et al.'s study (71) reported this probability to be significantly higher in studied patients doing NIV+IPI treatment, in comparison to the ones doing CH (47% versus 38%) and Hellman et al.'s (13) review reported a much higher probability of treatment discontinuation related to adverse events in the NIV+IPI group of the population (17.4% versus 8.9%). A combination therapy is expected to represent higher probability of AEs for patients, but even so further investigation should be conducted to better define NIV+IPI's toxicity profile.

Relatively to biomarkers, Hellman et al.'s study (13) showed a correlation between TMB levels and NIV+IPI's efficacy, as the combination achieved improved outcomes over CH in high TMB patients, but underperformed in the low TMB group. In addition, Hellman et al.'s (63) review also reported better results in comparison to NIV, the higher the TMB levels of the subgroup were. These studies indicate that TMB might be a good biomarker for NIV+IPI's clinical efficacy. Zhou et al.'s analysis (74) showed that patients with higher PD-L1 expression levels achieved better outcomes with NIV+IPI, but the opposite occurred in comparison to monotherapy PEM. High levels of PD-L1 expression actually correlated with less added therapeutical value from NIV+IPI in comparison with PEM. As such, PD-L1 expression seems to be a good biomarker for NIV+IPI's efficacy, but higher levels seem to correlate better with a higher efficacy of PEM.

Lastly, Ando et al.'s study compared this ICIs combination with PEM+PBC, PEM and NIV, and reported that, although NIV+IPI achieved better results at the cost of toxicity than PEM or NIV, PEM+PBC was found to be more clinically impactful than NIV+IPI, across different PD-L1 expression levels, but also more inducing of adverse events.

No data regarding this combination's economic aspects was found, but as NIV in monotherapy had already high costs associated, it's highly unlikely that the addition of another expensive ICI will result in a better cost-effectiveness relation.

Analysing the data collected relative to PEM in comparison with CH, added therapeutical value with the ICI use was describe in every studied included. Zhou et al.'s review (74) reported that clinical results with PEM were better in patients with higher PD-L1 expression. Regarding this therapy's cost-effectiveness relation with CH, Huang et al (75) found it to be cost-effective at an IC per QALY of 168,619US$, but the WTP values of up to 297,000US$ utilized are way higher than those used by most authors (ranging from 50,000US$ to 150,000US$). The same issue arose in Huang et al.'s review analysis (78). Bhadhuri et al.'s work (77) found PEM to be a cost-effective alternative in Switzerland's perspective, as did Aguiar et al.'s (12) analysis relative to the ICI's cost-effectiveness in the USA payers' perspective. On the contrary, Aguiar Jr's work analysed PEM's cost-effectiveness in comparison with DOC and PBC, through Brazil, Argentina and Peru payers' lens, and found the ICI to be a cost-effective alternative only to PBC, in patients from Brazil and Peru with PD-L1 expression of at least 10%. It was concordant in included studies that high levels of PD-L1 expression have a strong correlation with PEM's effectiveness, proving it to be a good biomarker for this ICI. Analysing the evidence collected in this study, PEM in monotherapy seems to be the most probable ICI regimen of being cost-effective in comparison with classical chemotherapy options.

Looking at the combination of PEM with CH, studies included described significantly improved outcomes in comparison to CH alone, with similar toxicity profiles. Only Jiang et al.'s (79) work approached the cost-effectiveness of this combination and found it not to be a cost-effective alternative to CH, in China Health System's perspective and considering a WTP threshold of 28 106US$ per QALY gained. Nevertheless, IC per QALY for the subgroups with a PD-L1 expression above 1% were around 90,000US$, a value than would be considered cost-effective in the USA, for example. But it needs to be considered that medicines' costs are highly variable between different countries, making a direct extrapolation probably inaccurate. More information about the pharmacoeconomic aspects of this combination is needed in order to figure out if, similarly to PEM in monotherapy, PEM+CH is a cost-effective alternative for CH.

Regarding the combination of PEM with IPI, the only included study approaching this regimen in lung cancer described only clinical results without the usage of a comparator. As such, it's impossible to reach conclusions regarding this therapy's effectiveness and cost-effectiveness in comparison with CH. In theory, the combination of these synergic ICIs would potentiate their clinical effects (30,33), demanding further investigation to verify its potential for clinical use.

In respect of DUR in comparison to CH, only one study was included. This review (81) reported longer median PFS with DUR, although at the cost of more associated AEs. Regarding the ICI's cost-effectiveness within the British National Health System, Witlox et al. considered DUR not cost-effective, as its ICER per QALY gained was 50,238£, way above the established WTP of 30,000£. More information is needed to reach solid conclusions over DUR's cost-effectiveness in comparison to CH, even if the included study hints that DUR is not a cost-effective alternative.

About DUR in combination with CH and TRE, Zhang et al. and Paz-Ares et al. found DUR plus CH to yield improved outcomes in comparison to CH, but the combination was far from being considered cost-effective, using the established WTP of 100,000US$. The authors calculated this regimen to have an ICER per QALY gained of 355,448.86US$, a very high cost comparing to other therapies approached in the present review. Goldman et al.'s (29) review found that DUR in addition to TRE and CH yielded slightly better outcomes at 2 years post initiation of treatment when compared to DUR with CH, but had a significantly worse toxicity profile. Planchard et al.'s work reported improved clinical results with DUR+TRE compared to DUR+CH, in patients with PD-L1 expression lower than 25%, achieving longer OS and PFS, with higher ORR. The data presented by both studies in respect of the addition of TRE to DUR in comparison to DUR+CH is contradictory, demonstrating that there is a need of new evidence evaluating this ICI's combination. As TRE still hasn't been approved for lung cancer and is currently being studied in clinical trials (31), it's expectable that new information about this medicine will be published in the near future.

In regards of ATE in comparison to DOC, the three included studies reported improved outcomes and a better toxicity profile with the ATE regimen. In Aguiar Jr et al.'s review (12), ATE cost-effectiveness in comparison to DOC was evaluated, with the USA payers' perspective, establishing a WTP of 100,000US$. ATE's ICER per QALY was 188,632US$ in patients with PD-L1 expression of at least 1% and 76,459US$ in the subgroup with PD-L1 expression of at least 50%. As such, ATE was found to be cost-effective for the at least 50% PD-L1 expression group, while the ICER of the other subgroup was very far from the established WTP. These results indicate a very good predictive power from PD-L1 expression, suggesting it to be a good biomarker for ATE's efficacy.

Looking at the collected evidence relative to ATE in combination with CH, all four studies describe improved outcomes in SCLC and NSCLC patients, but Horn et al. and West et al.'s (87,92) works report distinct findings regarding the toxicity profile of this combination.

The Horn et al.'s (92) study mentions a similar profile but West et al.'s describes an added probability of serious TR AEs of 13%. Wang et al. and Ding et al.'s studies (42,88) approached the economic evaluation of ATE+CH through USA payer's perspective, with the first set of authors establishing a WTP of 100,000US$ and the second establishing a WTP of 150,000US$. Both studies found ATE+CH to be extremely far from the established cost-effectiveness thresholds, with ICERs per QALY of 785,848US$ and 670,309.66US$, respectively. Although clinical outcomes were positive, the high price tags impose a limitation to this regimen's use in clinical practice.

Regarding the triple combination of ATE with BEV and CH, Reck et al.'s described significant improvements in clinical outcomes, especially in ORR (+15.8%), when comparing this regimen to ATE+CH and BEV+CH, in non-squamous NSCLC patients, selected through EGFR mutations, baseline liver metastases or PD-L1 expression. This study shows the potential that ICIs have to be combined with different classes of oncologic treatments, like antiangiogenic agents or kinase inhibitors. Although the reported results are promising, more much robust evidence regarding these types of medicines' combinations is needed in order to reach solid conclusions that might fuel new approvals. Also, as reports for ATE+CH show this combination to be highly cost-ineffective, the probability of the addition of BEV being cost-effective is probably even lower, if new criteria for selecting patients that may most benefit isn't established.

Lastly, two studies evaluating IPI in addition to CH against CH alone were included. Both reported significant improvements in clinical outcomes, but with added treatment related toxicity (+16%(90) and +8%(91)), demonstrating some potential for its clinical use. Unfortunately, no available information regarding this combination's pharmacoeconomic aspects or IPI's use in lung cancer as monotherapy was found.

4.2 Immune checkpoint inhibitor's cost barriers and possible solutions

The abysmal disparity in treatment costs presented in Table 15 and 16, derivate mainly from immunotherapy's high market entrance prices, makes the probability of such therapies being cost-effective or cost-useful very low. Observing Table 15 and 16 reported costs, it's obvious the main setback is the medicines' costs, as differences between parameters like monitorization or administration costs present much tighter intervals. In this review, with the exception of monotherapy pembrolizumab or atezolizumab, no other therapy regimens showed

consistently a positive cost-effectiveness or cost-utility relation to CH, which is hardly surprising when clinical outcomes have to make up for a at least 30,000US$ gap. (12,62)

As such, there is a need to find strategies to compensate for these prices, in order to assure that ICI's and novel therapies are accessible to all the oncologic patients, while maintaining the balance between supporting and incentivising innovation and the sustainment of Healthcare Systems around the globe.

First suggested course of action is the improvement of biomarker selection. In immunotherapy, there are often patients that achieve great outcomes, but, as mentioned before, these results are often diluted in the heterogenous outcomes of the studied populations. Consequently, greater precision in biomarkers, related to specific aspects of regulation of the immune response and tailored to both the patient and cancer type, will improve the clinical value of both ICIs and other emerging classes of immunotherapy for cancer. There are 4 currently approved biomarkers, although studies included in this review only used mostly PD-L1 expression percentage, with a few utilizing TMB as the main biomarker. With the limitations of these biomarkers mentioned in section **1.5** in mind, it is imperative that current biomarker selection is primed and that new biomarkers are developed. (58,59) In Aguiar Jr's analysis, it was estimated that the optimization of biomarker's use to identify the subpopulations that most benefited from ICIs would resulted in costs' attenuation up to 45% of total budget impact of ICI generalized use. (62)

Second suggested approach is the negotiation of economic burden sharing tactics like discounts from the manufacturers, cost-sharing (where the pharmaceutical industry assumes therapy's costs for a certain amount of time) and patient co-participation (where patients assume part of the cost of their respective treatments). With these strategies, Healthcare Systems share the economic burden of therapy with both the laboratories and the selected patients. According to Aguiar Jr's analysis, manufacturer's discounts of 20% reduce the annual incremental cost for treating all eligible lung cancer patients with ICIs up to 22% and cost-sharing, with the manufacturer providing the first month of treatment free of charge, decreases incremental costs up to 14%. Patient co-participation has limited use, as high prices decrease the probability of most patients being able to sustain continuously even a fraction of ICI's costs. (62)

The third recommendation is the institution of risk-sharing, payment-by-results policies when approving new market entries of oncologic immunotherapies. Current mean introduction prices of new ICI's often exceed the 100,000US$ mark, even though the manufacturing and distribution costs of these medicines reside far below this value. Furthermore, information of

innovative therapies is always limited at launch, not necessarily estimating correctly the new medicines' added clinical value. (56) Implementation of indication-specific-pricings, according to ICERs' variations, and other payment-by-results policies might result, according to Aguiar Jr's study, to a up to 20% reduction of budgetary impact of ICI universal use. (62) Risk-sharing agreements are increasingly becoming common practice between pharmaceutical companies and payers, as they allow the mitigation of uncertainty in clinical and cost-effectiveness outcomes through conditional reimbursement of medicine's costs, in accordance with projected outcomes in the clinical practice context (with therapy failure meaning the reimbursement of Healthcare Systems' payments by the manufacturers). (15) These agreements can deduce up to 35% of budget impact of generalized ICI's use, according to Aguiar Jr's study. (62)

Even though some ICI's options were found to be cost-effective in this study, this metric does not directly translate into affordability. As such, it is crucial to continue generating new evidence regarding the optimal way to use these therapies, to maximise clinical benefits and to simultaneously find agreements and policies that allow immunotherapy to be more affordable and consequently broadening patients access to these therapeutic options.

5 Conclusion

This study collected information that proves ICIs to be therapies that yield added clinical benefit for lung cancer patients, both in monotherapy and in combination with another ICI or chemotherapy. In most reviews included, these approaches resulted in significantly improved outcomes, comparing to chemotherapy regimens. Even so, only pembrolizumab and atezolizumab in monotherapy were consistently shown to be cost-effective comparing to classical approaches, with other regimens studied being far from constituting cost-effective alternatives.

There is still limited published information regarding possible combinations with ICIs in lung cancer patients, like pembrolizumab plus ipilimumab or combinations with different classes of oncologic treatments like erlotinib or bevacizumab. Data regarding how to best use these combined therapies (dosages, administration intervals) is still scarce, as is evidence of the pharmacoeconomic aspects of immunotherapies, especially when used in combinations. The same applies for biomarkers and other indicators of efficacy, as PD-L1 expression and TMB, still demand for investigation on their predictive capacity and on how to best use them to define the subgroups that will most benefit from these therapies. Other biomarkers not found in the included studies, such as MSI and immune cell infiltrate in or around the tumour, might have the potential to complement PD-L1 expression and TMB in the definition of such subpopulations of patients.

Pricing is clearly the biggest barrier to the universal use of ICIs, making it crucial to develop policies and agreements with manufacturers, in order to help mitigate the high prices that these therapies exhibit upon market entrance, which are very unlikely to be lowered in the future. In this study, we suggested the exploration of strategies like cost-sharing and payment-by-results, as means to enable access for all the oncologic patients, while maintaining the balance between supporting and incentivising innovation and the sustainment of Healthcare Systems around the globe.

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