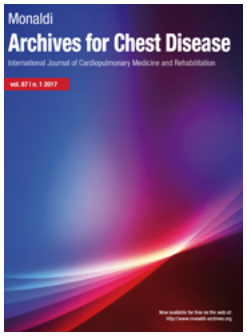

Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2024 [Online ahead of print]

To cite this Article:
Eleftheriadou ED, Saroglou M, Syrigos N, et al. **The role of immunotherapy in patients with lung cancer and brain metastases: a narrative review of the literature.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2024.2967

The role of immunotherapy in patients with lung cancer and brain metastases: a narrative review of the literature

Eleni D. Eleftheriadou,[1] Maria Saroglou,[1] Nikolaos Syrigos,[2]
Ellias Kotteas,[2] Marousa Kouvela[2]

[1]Department of Pulmonary Medicine, George Papanikolaou General Hospital, Thessaloniki; [2]Oncology Unit, 3rd Department of Internal Medicine, Medical School, National and Kapodistrian University of Athens, Greece

Correspondence: Eleni D. Eleftheriadou, Department of Pulmonary Medicine, George Papanikolaou General Hospital, Leoforos Papanikolaou, Hortiatis , 57010 , Thessaloniki, Greece. Tel.: +306983194082. E-mail: heleneleft@gmail.com

Contributions: all the authors have contributed significantly to create this review, read and approve the final version of the manuscript, and agreed to be accountable for all aspects of the work. EDE, conducted the literature review and wrote most of the article; MS, MK, helped with the initial design, made the final corrections and helped with the article's submission; EK, contributed by coming up with the initial idea and the design of the review; NS, writing - manuscript review.

Conflict of interest: no conflict of interest exists for any of the authors in relation to the research presented in this paper.

Ethics approval and consent to participate: institutional review board' approval was not required for this study as only de-identified compliant data were used in the analysis. The review involves synthesizing existing published research and does not involve collecting new data from human participants or animals.

Patient consent for publication: not applicable.

Funding: none.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Abstract

Worldwide, approximately half of the patients diagnosed with lung cancer (LC) will develop, simultaneously or asynchronously, brain metastases (BMs). The existence of BMs negatively affects the quality of life and constitutes a poor prognostic factor, linked with high mortality. Locoregional therapy with surgery or radiation is, until now, the treatment of choice, especially for symptomatic patients; however, both options are linked to a high complication rate. The question arising here is whether, in asymptomatic patients, the benefit outweighs the risk and whether an alternative method can be used to treat this special category of patients. Over the last decade, immune checkpoint inhibitors (ICIs) have represented a major breakthrough in the field of oncology, and several molecules have been approved as a treatment option for LC. This review tried to analyze the tumor microenvironment of both the primary lung tumor and the BMs in order to evaluate the intracranial activity of ICIs, outline the main challenges of including these agents in the treatment of LC with BMs, highlight the available information from the main clinical trials, and mark the potential positive effect of choosing a combination therapy. In conclusion, it appears that immunotherapy has a positive effect, inhibiting the progression of BMs, but more data should be published specifically for this category of patients.

Key words: lung cancer; brain metastases; immunotherapy.

Key Acronyms

ATB: Antibiotics
BBB: Blood-Brain Barrier
BM: Brain Metastases
CRT : Chemoradiotherapy
CT: Computed Tomography
CTLA-4: Cytotoxic T-Lymphocyte Antigen 4
DOR: Duration of Response
HZ: Hazard Ratio
HIF: Hypoxia Inducible Factor
ICI: Immune Checkpoint Inhibitors
irAEs: Immune-Related Adverse Events
iRECIST : immuno RECIST
iUPD: unconfirmed progression
LC: Lung Cancer
MSI: Microsatellite Instability

Nivo/ipi: Nivolumab/Ipilimumab
NSCLC: Non-Small Cell Lung Cancer
OS: Overall Survival
PCI: Prophylactic Cranial Irradiation
PD-L1: Programmed Death-Ligand 1
PFS: Progression Free Survival
RECIST (Response Evaluation Criteria in Solid Tumors)
SCLC: Small Cell Lung Cancer
SRS: Stereotactic Radiosurgery
TAMs: Tumor-Associated Macrophages
TILs: Tumor-Infiltrating Lymphocytes
TKB: Tyrosine Kinase Inhibitors
TMB: Tumor Mutational Burden
TME: Tumor Microenvironment
WBRT: Whole-Brain Radiotherapy

Introduction

Lung cancer (LC) is the leading cause of cancer-related mortality worldwide. Over the past 15 years, there have been tremendous advances in lung cancer evaluation, diagnosis, and management. The introduction of screening programs for high-risk individuals with low dose computed tomography (CT) helped in the diagnosis of more early-stage lung cancers. The focus of scientific study in understanding the different pathways of cell proliferation and differentiation has provided a variety of new therapies, increasing the ability to deliver personalized medical care to patients whose, until recently, treatment choices were limited [1].

However, the majority of cases are in an advanced stage at the time of diagnosis, often with distant metastases. Apart from cases of lymphogenous spread, which are particularly common in lung cancer, the most frequent sites of hematogenous metastasis are the liver, the adrenal glands, and the bones, followed by the brain [1]. At the time of the initial diagnosis, approximately 20% of patients with small-cell lung cancer (SCLC) and 10% of patients with non-small cell lung cancer (NSCLC) have detectable brain metastases, and an additional 40% will develop them sometime during the course of their disease [2].

Brain metastases can dramatically affect the quality of life, and their presence is linked with a negative impact on neurocognitive function and a poor prognosis. If untreated, BM can lead to death, with a median overall survival of only 1 to 2 months. Age, extra cranial tumor activity, the number of BMs and the initial tumor type/molecular subtype are important factors determining patients' prognosis [3]. Given that the incidence of BMs in SCLC can be as high

as 80% during the course of the disease, prophylactic cranial irradiation (PCI) is recommended in limited-stage disease. It seems that PCI reduces the risk of BM's appearance and improves the patient's quality of life. It can be applied after the patient's response to first line systemic therapy [4]. The management of BMs is a clinical challenge and requires a multidisciplinary approach, as there are several potential treatments, each with its own limitations and side effects. Characteristics such as the location and number of BMs, the presence of symptoms, actionable mutations or other extra-CNS metastases, the performance status, and the patients' preferences are important for the selection of adequate local treatment [5].

Neurosurgical resection is often the standard method of care for solitary or symptomatic BMs since resection rapidly reduces symptoms [6]. However, this is a high-risk procedure that places strict limits on the number and location of the lesions in the brain that are suitable for resection. Whole-brain radiotherapy (WBRT) and Stereotactic Radiosurgery (SRS) ,for the treatment of limited brain lesions, are also proven to be treatment options [6]. Despite the improved local control rate, there are still serious concerns about the use of these treatment options. Particularly, the importance of WBRT is decreasing due to the related neurotoxicity and deterioration in patients' quality of life, a point that is also highlighted by a phase III trial (QUARTZ) that revealed limited clinical benefit compared with best supportive care [7]. SR has better neurocognitive and/or QoL outcomes but is linked to a highest rate of intracranial relapse and its use might delay the initiation of systemic treatment, which is crucial for such a group of advanced-stage patients [5]

On the other hand, the structure of the brain, with the blood-brain barrier (BBB), makes the role of systemic treatment controversial [8]. Historically, the BBB reduces the access and activity of hydrophilic and other large agents into the Central Nervous System (CNS). Nevertheless, the presence of BMs sometimes alters this structure, resulting in increased exposure to systemic drugs.

Unfortunately, this group of patients is usually excluded from clinical trials, especially with systemic agents; hence, the real-world evidence on efficacy is limited.

Over the last decade, the approach to lung cancer treatment has changed with the introduction of immunotherapy. The tumor microenvironment is characterized by an overexpression of inhibitory ligands and receptors, which downregulates the immune system, evading the immune response. The two most common clinically targeted pathways include the cytotoxic T-lymphocyte antigen 4 (CTLA-4) and PD-1 pathways. The CTLA-4 and PD-1/PD-L1 pathways are key immune checkpoint receptors that downregulate T-cells and mediate

immunosuppression. CTLA-4 inhibits CD28 costimulation, which is required for T-cell activation. PD-1 is upregulated on active T-cells and binds to PD-L1 or PD-L2 , resulting in T-cell suppression [1].

The application of immune checkpoint inhibitors (ICIs) has revolutionized the therapeutic approach of lung cancer, significantly enhancing survival outcomes across all stages of the disease, both in NSCLC and SCLC. In the early stages of lung cancer, ICIs serve a crucial role as either a neoadjuvant or an adjuvant therapy. In the advanced stages, they are utilized in the first and second line settings, as a single- agents or in combination with chemotherapy, irrespective of the histological subtypes [9].

The question of whether ICIs are effective in brain metastases is challenging, as the available data is limited due to the underrepresentation of these patients in clinical trials. Moreover, even the selected subgroups consist of rather patients with small, asymptomatic, or previously treated BMs than a broader population; thereby, the available results are controversial.

The aim of this review is to summarize the state-of-the-art of clinical evidence for ICIs intracranial activity by exploring the details of the tumor microenvironment of the primary and metastatic sites, outline the main challenges of including these agents in the treatment of LC with BMs, highlight the available information by citing the data of the main clinical trials, and mark the possible positive effect of choosing a combination therapy.

Methods

For this review, articles from databases such as Google Scholar, Clinicaltrials.gov., and PubMed were retrieved, using the keywords “lung neoplasms”, “non-small-cell lung cancer”, “small-cell lung cancer”, “immunotherapy”, “immune checkpoint inhibitors”, “brain metastases”, “brain tumors[1], “PDL1” , “CTLA-4”. Only English articles were included, as well as clinical trials, systematic reviews and meta-analysis and some abstracts from international conferences. The references cited in the papers identified were also reviewed.

Differences in the tumor microenvironment between primary lung tumors and brain metastases

In order to assess the potential impact of immunotherapy in treating BMs, it is important to describe and compare the tumor microenvironment (TME) of both the primary tumor of the lung and the brain metastases. Each TME has unique characteristics that distinguish the primary from the metastatic site and determine the response of ICIs [10].

The brain is considered an immune-privileged organ due to the presence of the BBB and the existence of specialized cells such as microglia, astrocytes, and neurons [8]

In contrast to targeted medicationsthat act directly on tumor cells, the mechanism of ICIs is believed to involve the modification of immune cell activity rather than the direct impact of tumor cells in the brain [11].

Furthermore, it has been widely observed that in brain tumors, the balance between the tumor and the microenvironment of the brain is impaired. This frequently results in a breach in the BBB and an infiltration of immune cells from the peripheral circulation [12]. Due to its complexity, many scientific attempts have been made to investigate this microenvironment.

Microglia, as innate immune cells in the brain, play an important role in antigen presentation and immune responses. Upon activation, they release proinflammatory molecules and modulate their surface markers, facilitating the entry of immune cells into the brain through the blood-brain barrier, thereby promoting angiogenesis and metastasis [13]. Brain metastases primarily contain macrophages derived from peripheral monocytes rather than resident microglia, which are related to different phenotypes and ways of action [14]. Despite the overall reduction in immune cell abundance within brain metastatic tissue, there is an elevation in the proportion of tumor-associated macrophages (TAMs). This increase directly contributes to tumor growth by releasing specific molecules that impede T cell proliferation and antigen presentation. TAMs play an immunosuppressive role in the immune context of brain metastases, and their targeting may be a promising strategy for the approach of BMs [12].

Astrocytes is another brain-exclusive cell type . It appears that brain injury affects astrocyte by producing reactive astrocyte proliferation. Their role is intricate and multifaceted. Firstly, they produce factors like plasmin that fight against the extension of brain metastases; however, with further interaction, they trigger the release of growth factors, encouraging tumor-growth [12,15].

Ikarashi et al. used multiplex fluorescence immunohistochemical analysis to evaluate the immune characteristics of the primary lung tumors and the corresponding brain metastasis in 34 patients with NSCLC [16]. The study revealed that BMs have fewer tumor-infiltrating lymphocytes (TILs) such as CD4+ T-cells, CD8+ T-cells and CD4+Foxp3+, but despite their lower number, they were positively correlated with overall survival (OS).

Reduced T cell abundance and infiltration combined with suppression of antigen presentation (suppressed dendritic cell maturation), lymphocyte extravasation, and leukocyte adhesion

(reduced vascular cell adhesion protein 1) contribute to an immunosuppressive microenvironment in BM [12,14].

In the same context, Chen et al performed a comprehensive TME analysis using an RNA sequencing platform on 86 samples from lung tumors and matched the brain metastases of 43 individuals with NSCLC [17]. They concluded that in BMs, the enrichment of total immune cells is significantly lower, which is in line with the previous study.

Moreover, the fraction of neutrophils in brain metastases was higher compared to the primary lung tumor, while, normally, the brain has a lower density. This finding may be linked to the immunosuppressive effects of the brain TME. Since neutrophils were thought to be specialized cells with a low level of transcriptional flexibility, their role in oncogenesis and progression was underappreciated until recently [18]. Without stimulation, neutrophils undergo apoptosis, and the release of harmful enzymes is prevented. The tumor microenvironment, by reprogramming the normal neutrophils, can create tumor-associated neutrophils (TANs), which contribute to cancer growth and spread by attracting macrophages and Tregs, suppressing cytotoxic T cells and natural killer cells, and increasing angiogenesis [19]. Targeting immunosuppressive TANs may contribute to the management of brain metastases in NSCLC.

Furthermore, the study mentioned that some immune-related signatures [17], such as the scores of IFN-gamma and T cell-inflamed GEP signatures, both predictors of the clinical response to ICIs, were lower in brain metastases' tissue. IFN-γ may control various adhesion molecules (such as VCAM-1 and ICAM-1) and chemokines (such as CXCL10), mediating T cell migration and resulting in BBB disruption [11,20].

Finally, PD-L1 expression in brain metastases was found to be unrelated to matched primary lung cancers, findings that are similar to previous reports [21].

Kim et al also tried to compare the differences in the immunological TME of the two tumor sites and agreed that in the BM specimen, the density of PD-1+ TILs was markedly decreased and the infiltration was positively correlated with PD-L1 expression of tumor cells [10]. This might be linked to the contradictory efficacy of ICIs in lung cancer patients with BM.

The presence of TILs is required for the efficacy of immunotherapy. Other immune cells that are part of the brain TME and the metastatic site, such as tumor-associated macrophages, microglia, and astrocytes, are also involved in tumor progression and immune evasion [11]. The TME of the brain metastases has a lower number of lymphocytes compared to the primary tumor site; however, a significant lymphocytic response exists, presumably prompting tumor

cells to produce the PD-L1 factor [22]. So, there might be an intracranial response to ICIs despite the inadequate amount of TILs. CD8+ T cells within brain metastases exhibit reduced activity compared to those in peripheral and normal intracranial environments. This diminished activity may be attributed to the upregulation of immune suppressive signals, such as PD-1 and CTLA-4. Notably, this process presents a potential target for enhancement through immune checkpoint inhibitors Blocking PD-1 could cause immune cells to migrate to the brain and interact with the BBB by producing factors such as IFN-gamma [11,20].

In addition to the specific cell subpopulations discussed above, hypoxia is a condition consistently present in cancer, including lung cancer, and is associated with carcinogenesis and possibly with the occurrence of metastases [23]. Increasing evidence suggests that hypoxia significantly contributes to cancer dormancy and metabolism. It enhances stem cell activity, facilitating cancer initiation and progression. Hypoxia activates the hypoxia inducible factor (HIF) by silencing the RASSF1A/Hippo pathway. Recent studies evaluated the link between the presence of HIF and cancer growth. It seems that this factor promotes angiogenesis and other changes in the metabolism of cancer cells, resulting in oncogenesis. In fact, it appears that it is related to the formation of brain metastases in lung cancer [24]. There are three types of HIF. HIF-1 is a potential therapeutic target in NSCLC, offering a pathway to prevent cancer spread and improve patient prognosis [23].

The greatest limitation in these studies is the small number of patients participating, as it requires both metastasectomy and lung cancer surgery and simultaneous analysis of the samples, making it difficult to execute. In addition, the methods used for their research were not the same, as were the biomarkers evaluated.

Thusdespite significant heterogeneity between primary lung tumors and their corresponding brain metastases, patients may derive therapeutic benefits from ICI treatment, given the activation observed in both intracranial and extracranial immune systems.

Single-agent anti-PD-L1/PD-1 or anti CTLA-4 monoclonal antibodies

A non-randomised, open-label phase 2 trial enrolled 18 patients with melanoma and untreated brain metastases and 18 patients with NSCLC plus untreated or progressing brain metastases plus positive PD-L1 (PD-L1 > 1%) and established the activity and safety of pembrolizumab, a PD-1 inhibitor, in the CNS. The trial reached the primary endpoint, which was the BM response, as 22% (95% CI, 7–48) of patients with melanoma and 33% (95% CI, 14–59) of patients with NSCLC responded, and the CNS response was durable [25]. Even though this

study includes patients with melanona and only a small number with LC, it is noteworthy as it is the first to evaluate the role of immunotherapy in patients with untreated BMs.

The updated results from the NSCLC arm of the previous trial showed a CNS response in the cohort with PD-L1 expression ≥1% (29·7% [95% CI, 15·9-47·0%]) with intracranial response's duration of 5.7 months (IQR 4·0 to 17·7 months) and with no intracranial response in the PD-L1 negative cohort [26].

This was the first prospective study to demonstrate efficacy of ICI monotherapy for the management of untreated and asymptomatic BM.

A pooled analysis of KEYNOTE-001, 010, 024 and 042 also tried to retrospectively evaluate the outcomes of pembrolizumab monotherapy in patients with PD-L1 positive NSCLC and previously treated, stable brain metastases versus chemotherapy [27]. The median overall survival (OS) in patients receiving pembrolizumab with BM and PD-L1 TPS ≥50% was 19.7 months (95% CI: 12.1–31.4) with a HR of 0.67 (95% CI: 0.44–1.02). Similarly, benefit was achieved in the PD-L1 TPS ≥1%, where the OS was 13.4 months (95% CI: 10.4–18.0) with a HR of 0.83 (95% CI: 0.62–1.10). In both cohorts, the activity of pembrolizumab was higher than in the chemotherapy arm; however, patients with PD-L1 ≥50% had even greater benefit than the PD-L1 TPS ≥1%. The safety profile of pembrolizumab was more favorable than that of chemotherapy and the presence of brain metastases did not affect the incidence of adverse events (AEs).

The phase III open-label OAK study evaluated the effectiveness and safety of atezolizumab versus docetaxel as a second-line treatment in patients with PD-L1-unselected advanced or metastatic NSCLC [28]. Atezolizumab is an anti-programmed death-ligand 1 (anti–PD-L1) monoclonal antibody approved for the treatment of metastatic NSCLC with disease progression.

Using data from the OAK trial, Gadgeel et al. performed a detailed analysis, particularly for the patients with advanced NSCLC and asymptomatic, previously treated from brain metastases highlighting the benefit of atezolizumab in OS, providing a longer period until the appearance of new symptomatic brain lesions and fewer AEs compared to docetaxel [29].

Another immune checkpoint inhibitor of this category is nivolumab. The superiority of nivolumab over docetaxel as second-line treatment in patients with advanced squamous and non-squamous NSCLC has already been established by 2 phase III studies [30,31]. Various studies based on the nivolumab Italian Expanded Access Program (EAP) examined the subgroup of patients with CNS metastases. The studies involved patients with disease

progression or recurrence after systemic therapy and treated metastatic CNS lesions [32,33]. The median Progression-Free-Survival (PFS) for the squamous NSCLC was 4.9 months (95%CI=2.7-7.1) and the OS was 5.8 months (95%CI=1.8-9.8) while for the non-squamous NSCLC it was 3 (95% CI: 2.7–3.3) and 8.6 (95% CI: 6.4–10.8) months respectively.

All these findings were consistent with previous trials, emphasizing that brain metastases have similarbenefit from anti-PD-L1 therapy as the extra-cerebral disease [27,29,32-34]. The ICIs have an acceptable safety profile in advanced and metastatic NSCLC patients and their efficacy in the subgroup of patients with BMs is comparable to their efficacy in patients without a history of brain metastases.

The most important limitation is that the majority of these studies refer to stable and asymptomatic metastatic lesions, usually pretreated. Consequently, the true efficacy of these molecules in treating brain metastases cannot be truly determined. However, the encouraging rates analyzed above show that immunotherapy, even as monotherapy, compared to chemotherapy, is an effective therapeutic option for advanced NSCLC with brain metastases.

Combined immunotherapy

Due to the fact that ICI monotherapy could benefit NSCLC patients with BMs, numerous scientific groups have investigated whether combining immunotherapy agents can provide a better outcome in this group of patients. The different immune checkpoint inhibitors have different but complementary mechanisms of action. Although all ICIs contribute to removing immune system restraints, the specific pathways for restoring anti-tumor immunity are peculiar [11]. Nevertheless, data about ICI combinations in NSCLC with BM is limited.

In Part 1a of the CheckMate 227 trial [35], 1189 patients with stage IV NSCLC and PD-L1 expression level of 1% or more, were enrolled and randomized to receive first-line treatment with ICI combination with nivolumab plus ipilimumab, a fully human CTLA-4 antibody, nivolumab alone or histology-driven chemotherapy. 202 patients had baseline BMs. The study achieved its primary endpoint by demonstrating that double immunotherapy was superior in terms of overall survival compared to chemotherapy alone (p= 0.007, hazard ratio [HR] = 0.79).

It is worth mentioning that the OS with nivolumab plus ipilimumab was nearly identical in patients with PD-L1 ≥1% and <1%, suggesting that maybe the different immune effects of CTLA-4 inhibition may be important in PD-L1 negative tumors for obtaining antitumor immunity.

The 4-year outcomes from CheckMate 227 reported the durable benefit of dual immunotherapy as a first line treatment across all efficacy endpoints, regardless of the PD-L1 expression level or tumor histology [36].

A post-hoc analysis specifically for the patients with BMs confirmed the efficacy of double immunotherapy in OS (18.8 months versus 13.7 in chemotherapy with HR 0.57) and PFS (1y PFS 38% vs 21% HR 0.79) and in the duration of response (DOR 29.9 vs 8.4 months) [37]. In the same context, the 5-year follow up showed a prolonged OS (hazard ratio = 0.63; 95% confidence interval: 0.43–0.92), 5-year systemic and intracranial PFS rates at 12% and 16% respectively (0% and 6% respectively for the chemotherapy arm) and fewer incidents of new brain lesions appearance (4% versus 20% with chemotherapy) [38].

Apart from the encouraging clinical benefit, CheckMate 817 compounded the tolerable safety profile of dual immunotherapy in the special category of patients with ECOG PS 0-1 and untreated BMs with manageable treatment-related toxicity, similar to the general population [39].

Combination of immunotherapy with chemotherapy

The combination of immunotherapy with systemic therapy is a commonly selected first-line treatment for patients with metastatic NSCLC [9]. While chemotherapy's inability to penetrate the blood-brain barrier has been noted, ongoing investigations explore the presence of brain metastases and potential synergistic effects between immunotherapy and chemotherapy. Chemotherapy has demonstrated the ability to enhance the efficacy of ICI by increasing neoantigen expression, promoting immunogenic cell death, and upregulating PD-L1 expression within the tumor microenvironment. Consequently, this fosters T-cell activation and response [11,40,41].

Keynote 021, 189 and 407 tried to evaluate the efficacy of pembrolizumab plus platinum-based chemotherapy as first-line treatment for metastatic NSCLC compared to chemotherapy alone [42-44]. All these trials permitted enrollment of patients with asymptomatic, pre-treated (KEYNOTE 021) or untreated (KEYNOTE 189 and 407) brain metastases.

Powell et al. executed a pooled analysis of these trials, investigating the efficacy of immunotherapy plus chemotherapy in patients with stable, brain metastases [45]. The superiority of this combination was evident across all endpoints analyzed (OS 18.8 versus 7.6 mo for chemotherapy alone, PFS (6.9 versus 4.1 mo , ORR 39% versus 19.7%, mDOR 11.3

months versus 6.8). This benefit was consistently observed across all PD-L1 expression subgroups.

Attempting to evaluate the possibility of a faster initial disease control, scientists in CheckMate 9LA added a limited course of chemotherapy (2 cycles) to dual immunotherapy with nivolumab and ipilimumab and found that the combination regimen provided a significant and durable improvement in overall survival, with a favorable risk-benefit profile [46].

Carbone et al. focused on the 101 patients who had stable or asymptomatic BMs and concluded that the patients in the combination arm had a considerable gain in PFS and OS (1-year PFS rate: 36% vs. 8%, 1-year OS rate: 67% vs. 26%) and the benefits were consistent with the ones observed in all randomized patients from CheckMate 9LA [47].

The ATEZO-BRAIN trial, a single-arm phase II study, represents the first investigation into the efficacy of immune checkpoint inhibitor atezolizumab in combination with platinum-based chemotherapy in 40 patients with non-squamous NSCLC and untreated brain metastases, a population often excluded from trials [48]. Results showed that the combination therapy had an acceptable safety profile and achieved a 12-week PFS rate of 62.2%. Significantly, it demonstrated comparable efficacy both systemically and intracranially, suggesting the possibility to serve as a therapeutic option for this highly vulnerable patient population. However, this is a single-arm trial, which prevents the establishment of an optimal treatment approach.

Combination of Immunotherapy with radiotherapy

Concurrent administration of ICI with radiotherapy is a crucial area of investigation. It seems that radiation induces cell death and stimulates the production and release of cytokines and chemokines, particularly type I interferons, within the TME [49]. Consequently, cytotoxic T-cells and suppressive cells, like Treg, infiltrate the tumor, while immune cells such as dendritic cells, which play a crucial role in presenting antigens, migrate out of the tumor [50]. Moreover, it can also increase the permeability of the BBB. Thus, it can provide a more active immune microenvironment for ICI treatment [51].

Ikirashi et al. compared the microenvironment of the brain in patients who received localized radiation for the metastatic site before surgery, with those who did not receive such treatment [16]. The findings revealed that patients who underwent radiation prior to brain surgery had a higher concentration of TILs within the metastases. Notably, the density of CD4+ T-cells and

CD4+Foxp3+ T-cells in the radiation group was statistically higher than in the untreated group, both in the carcinoma and stromal regions.

Since radiation can potentially improve patient outcome, research has begun to explore whether it can also be used for metastatic lung cancer with BMs, elaborating efficacy and safety.

In a small phase II open labeled trial [52], 22 patients with NSCLC and 4 with renal cell carcinoma were submitted in treatment with nivolumab plus SRS, 14 days after the first dose of immunotherapy. The systematic therapy was not the first line treatment. The study revealed a clinically meaningful improvement in controlling intracranial response with an intracranial PFS (iPFS) rate at 45,2% (95% CI 29.3–69.6%) at 1 year and a median iPFS of 6.1 months (95 CI: 3.5–NA months), with intracranial progression probability of 19,5% (95 CI: 6.5–37.6%) at 1 year. However, the probability of extracranial progression was high (46% at 1 year) suggesting the possibility that the addition of an extra drug to systemic therapy is necessary, as mentioned in the trials above.

Influenced by the positive results of CheckMate 227 trial and taking into account patients with untreated BM, Jing Li et al tested the nivo/ipi combination with concurrent SRS for active [53], untreated or progressive intracranial metastases from NSCLC. The number of patients enrolled was small (13 patients); however, the results both for the intracranial and extracranial responses and for the safety-profile of this combination were encouraging.

The advantages of the combination of the two treatments became clearer with the analysis of Chen et al [54], who separated 74 patients with metastatic melanoma and metastatic NSCLC into two groups, one who underwent only radiotherapy (WBRT or SRS) and one who received radiotherapy and ICI treatment. Although patients with melanoma were also included in this study, the encouraging results were noteworthy. Both PFS and OS were significantly higher in the concurrent group, findings in agreement with those reported in other trials. The intracranial disease progression was higher in the monotherapy group, with 93% of patients who received SRS alone having new intracranial metastases compared to 53% in patients who received concurrent immunotherapy (p=0.0006, OR 17.14, 95% CI:2.97-99.1).

The timing of administration of radiation therapy is another factor that needs to be evaluated. So far, the studies mentioned used concurrent radiotherapyand ICI therapy. Schapira et al. conducted a retrospective analysis of patients treated with a combination of SRS and PD-1 pathway inhibitors, focusing on the time of administration [55]. Simultaneous administration was associated with a better OS rate compared to SRS prior or after the administration of

immunotherapy respectively (1-year OS 87.3% vs. 70.0% vs. 0%, p=0.008) and the possibility of new brain lesions' appearance was lower (1-year Distant Brain Failure 38.5% vs 65.8% vs 100%, P = .042). No grade 4 or 5 toxicities were observed.

In a multicentric retrospective study, NSCLC patients with brain metastases treated with radiotherapy and immunotherapy showed longer intracranial Local Progression-Free Survival compared to those treated with exclusive radiotherapy. Combined treatment was better tolerated and not associated with increased toxicity or radionecrosis [56].

Overall, there is agreement that the combination of immunotherapy plus radiotherapy is safe, does not increase the incidence of radiation necrosis or neurological side effects and the complications are as common as immunotherapy alone, with maximum grade 3 and 4 AEs. The different definitions of concurrent therapy used in every study make it difficult to conclude about the time of administration of radiotherapy.

Immunotherapy and targeted therapy

Immunotherapy's efficacy appears to be present in cases of individuals with targetable mutations and brain metastases, even though they are often excluded from investigations assessing immunotherapy combinations due to guidelines favoring first-line targeted therapies. Intriguingly, tyrosine kinase inhibitors (TKIs), particularly the newer generations utilized in the management of EGFR-mutant lung cancer, demonstrate a favorable impact on CNS outcomes [57,58]. However, as a secondary treatment approach, the combination of immunotherapy with chemotherapy has shown superior CNS efficacy compared to chemotherapy alone [59].

Adagrasib, a second-line treatment option in patients with KRAS G12C mutation, seems to penetrate the CNS, achieving effective concentrations in the cerebrospinal fluid [60,61]. Given the challenging nature of treating patients with KRAS mutations, preliminary findings from ongoing studies suggest that monotherapy with a KRAS inhibitor may not be sufficient, advocating for a combination therapy with immunotherapy [62]. A retrospective study examining the impact of KRAS mutational status on the efficacy of ICI in patients with NSCLC and brain metastases, concluded that administering immunotherapy in patients and KRAS mutations within 90 days of the initial diagnosis significantly enhanced overall survival compared to patients who did not receive ICI therapy [63].

Brain metastases from small cell lung cancer and immunotherapy

SCLC has several peculiarities and a different clinical behaviour in relation to NSCLC. It is a chemosencitive tumor, characterized by a rapid proliferation and expansion. In the majority of cases, it is diagnosed at an extensive stage, usually with brain metastases. If not present at the initial diagnosis, 80% of patients will develop brain lesions during the course of their disease [1].

There is no clear recommendation regarding the use of PCI at the extensive stage, however the indication remains in response to the initial treatment in patients with limited stage disease [4]. It was not until 2019 that immunotherapy was approved for use in SCLC treatment, and this approval was only for the extensive stage. Hence, now the standard of care includes chemo and immunotherapy combinations [4].

The two main clinical trials that contributed to ICI approval were the IMpower 133 and the CASPIAN study [64,65]. They both demonstrated the superiority of anti-PDL1 input in OS and PFS. However, only the latter included patients with untreated, asymptomatic brain metastases. More specifically, in the CASPIAN trial, treatment-naive patients with extensive SCLC were separated into two groups receiving platinum-based chemotherapy and etoposide with or without durvalumab. In a subgroup analysis of outcomes according to the presence of BMs, it was shown that the OS and the PFS benefits of first line combination therapy were maintained regardless of the presence of brain lesions. This data is consistent with the ones mentioned above about NSCLC, supporting the notion that the brain is an immune-provileged site.

Moreover, the CASPIAN study's 3-year OS data continue to show consistent benefits with the use of durvalumab plus chemotherapy, regardless of whether patients had baseline brain metastases [65].

Another study by Chang et al. tried to evaluate the role of additional immunotherapy in patients with extensive-SCLC and brain metastases, who had already received chemotherapy (at least 4 cycles) and radiotherapy for the BMs [66,67]. The results were promising as OS and iPFS were significantly improved compared to patients who only received chemotherapy and brain radiotherapy (median OS 13.3 months versus 33.4, 1 year OS rate was 54% versus 82%, median iPFS 6.93 months versus 10.7). The major limitation of this analysis was that different types of immunotherapies were administered while some patients had undergone PCI before. In general, it is more difficult to draw any conclusions about SCLC as the data is very limited and many decisions are based on the treating physician'stactics.

Discussion

Immunotherapy has emerged as a transformative modality in the management of lung cancer across all stages, significantly altering the treatment landscape of stage IV disease, which historically carries the poorest prognosis [68].

However, identifying reliable biomarkers for predicting the efficacy of immunotherapy, especially in patients with brain metastases, remains a major challenge. The advent of biomarkers, such as PD-L1 expression and tumor mutational burden (TMB), has facilitated the identification of patients most likely to benefit from immunotherapy, enabling personalized treatment strategies and optimizing therapeutic outcomes. However, inconsistencies in immunohistochemical tests and cut-off points have led to confusion and dissatisfaction within the medical community [68]. Additionally, the biological heterogeneity of PD-L1 expression within tumors, further complicates its predictive value [69]. Despite these challenges, studies have shown that the PD-L1 status obtained from core biopsies or fine needle aspirates is generally consistent with outcomes from paired resections, suggesting that analysis of small samples may provide reliable results [70].

It seems that the use of one single parameter as a marker is not enough because, until now, a precise, easy to detect, cheap and capable biomarker has not been identified in the particularly heterogeneous environment of tumors and tumor metastases. Probably, the combination of TIL's concentration and PD-L1 expression is a noteworthy combination.

Liquid biopsy holds significant relevance in clinical practice, offering a non-invasive meanof obtaining real-time molecular information for monitoring treatment efficacy and evaluating disease progression [71]. It can also possible provide early evidence of drug resistence, which is quite often in patients receiving immunotherapy. In addition, studies have shown that liquid biopsy, particularly in cerebrospinal fluid and blood, enables molecular characterization of brain metastases, facilitating the assessment of tumor evolution and its heterogeneity. It allows for the determination of key immune biomarkers such as PD-L1 expression,TMB, and microsatellite instability (MSI) status [72]. In the same context, a retrospective study investigating the predictive effect of peripheral blood lymphocyte subsets [73] suggests that baseline peripheral blood CD4+CD45RA- T-cell counts can be used as a biomarker to predict the efficacy of ICIs. Similarly, a study held by Shuai Liu et al. [74] added the possible value of easier-to-detect markers in the peripheral blood, such as the neutrophil-to-lymphocyte ratio.

Circulating Tumor Cells (CTCs) have an additional important role as prognostic factors in patietns with NSCLC. A prospective study by Rossi et al. has shown that an increase in their

number is associated with poorer prognosis, lower PFS and OS. In addition, there are published data supporting the ability to detect, among other factors, ALK rearrangements using CTCs. Those scientific efforts to standardize CTC characterization will soon enable routine assays for all lung cancer patients [75].

Administrating immunotherapy is associated with various adverse events while the percentage can reach 60%. In the majority, these immune-related adverse events (irAEs) are mild and easily treated without discontinuation of the systematic therapy. However, the risk of fatal conditions such as serious pneumonitis is always present [76]. Potential risks associated with the co-administration of agents, such as antibiotics, corticosteroids, proton pump inhibitors or vaccinations, that may affect the mechanisms of action of immunotherapy are often not adequately considered as risk factors for the appearance of side effects [77]. In detail, antibiotics (ATB) can negatively impact outcomes in cancer patients receiving ICIs by reducing gut microbiota diversity and eliminating immunogenic bacteria. Until more evidence is available, ATB use during immunotherapy should be carefully evaluated, especially for long or repeated courses, while ensuring necessary treatment for infections. Desicion-making is more complicated when it comes to the use of corticosteroids, as they are essential for the treatment of irAEs and for the relief of patients with BMs. Retrospective studies indicate that early corticosteroid use correlates with poor prognosis, even though this association might be influenced by other factors such as high TMB or poor ECOG performance status [76]. However, recent randomized phase III trials suggest that premedication with corticosteroids does not compromise the efficacy of ICIs in chemo-immunotherapy combinations. More prospective studies are needed to determine the impact of corticosteroids at doses above 10 mg daily of prednisone [77].

When selecting immunotherapy regimens for the treatment of lung cancer, particularly in cases involving patients with brain metastases, it is crucial to bear in mind the occurrence of pseudoprogression. This phenomenon manifests as the enlargement of existing lesions or the emergence of new ones, which may mimic tumor progression. Radiographic follow-up is more commonly utilized in order to evaluate these conditions; however, biopsy and histopathologic examination remain the gold standard for confirming pseudoprogression [78]. Understanding that movements like these are difficult to perform in everyday clinical practice, published studies suggest that ctDNA and serum IL-8 levels hold promise as biomarkers for predicting pseudo progression with high sensitivity and specificity, potentially outperforming radiographic methods. Therefore, careful consideration and vigilance are warranted in the

assessment of treatment response, necessitating diligent monitoring and accurate interpretation of imaging findings [78].

It is important to mention that the majority of these trials and protocols used specific criteria to evaluate the tumor's response to ICI treatment. RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) criteria are globally used to assess treatment response in patients under systemic therapy. However, tumors often respond differently to immunotherapy, following unique patterns such as pseudoprogression, which was discussed earlier. Consequently, the traditional RECIST 1.1 criteria may not accurately reflect responses to immunotherapies. To address this issue, iRECIST (immune-RECIST) criteria are employed in many clinical trials and protocols discussed in this review. iRECIST is based on RECIST 1.1 but includes mechanisms for confirming progression to account for atypical responses. When progression is identified based on RECIST 1.1 principles, it is classified as initial unconfirmed progression (iUPD). This requires confirmation through additional examinations that show either further increase in size or the appearance of new lesions. If the lesions are stable in subsequent examinations, the disease stage remains iUPD, and it is up to the doctor in charge to decide how to proceed. If there is tumor shrinkage, the situation is classified as complete response (iCR), partial response (iPR), or stable disease (iSD), depending on the specific characteristics. This approach helps differentiate true progression from temporary increases in tumor size or new lesions due to immune response dynamics [79].

The primary limitation of this review, as well as the broader discussion surrounding the utilization of immunotherapy in patients with lung cancer and concurrent brain metastases, lies in the underrepresentation or outright exclusion of this particular patient demographic from clinical trials. Consequently, the available data remains sparse. Even within the clinical trials that have included individuals with active brain metastases, eligibility criteria often permit the enrollment of patients with pretreated brain metastases or those undergoing concurrent corticosteroid therapy. This gap between the controlled environment of clinical trials and the real-world clinical setting underscores the necessity for further research and randomized controlled studies' accumulation to better guide clinical decision-making and optimize treatment strategies for lung cancer patients with active brain metastases. Furthermore, it is imperative that research endeavors focus on investigating the potential protective role of adjuvant immunotherapy in mitigating the onset of future brain metastases.

Overall, the era of immunotherapy has arrived for lung cancer;however, there are several questions that need to be answered in order to benefit from it in the best way possible.

Conclusions

Most studies support, with significant superiority, the use of immunotherapy-based combination therapy in patients with brain metastases. There is uncertainty concerning patients with active, symptomatic metastases as they are underepresented in the clinical trials; however, there are several ongoing ones that could provide important answers in the near future. So far, loco regional therapy stands as the treatment of choice for those patients, with several factors like age, performance status, the number of CNS lesions and the presence of symptoms guiding method selection. The type of cancer and the existence of targetable mutations can also influence treatment, and a combination of treatments is often required for optimal results. It is evident from this discussion that the issue is highly complex. More prospective trials are required to establish a more definitive and comprehensive therapeutic approach for the management of BMs.

References

1. Tanoue L., Detterbeck F. Lung cancer: a practical approach to evidence-based clinical evaluation and Management. Amsterdam, Netherlands: Elsevier; 2018.
2. Gavrilovic IT, Posner JB. Brain Metastases: epidemiology and pathophysiology. J Neuro-Oncol 2005;75:5-14.
3. Lamba N, Kearney RB, Catalano PJ, et al. Population-based estimates of survival among elderly patients with brain metastases. Neuro Oncol 2020;23:661-76.
4. NCCN clinical practice guidelines in oncology: (NCCN Guidelines®) for small cell lung cancer. Version 2.2024. National Comprehensive Cancer Network, Inc. 2024.
5. Ernani V, Stinchcombe TE. Management of brain metastases in non–small-cell lung cancer. J Oncol Pract 2019;15:563-70.
6. Khan AJ, Dicker AP. On the merits and limitations of whole-brain radiation therapy. J Clin Oncol 2013;31:11-3.
7. Mulvenna P, Nankivell M, Barton R, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. Lancet 2016;388:2004-14.
8. Boire A, Brastianos PK, Garzia L, Valiente M. Brain metastasis. Nat Rev Cancer 2019;20:4-11.

9. NCCN clinical practice guidelines in oncology: (NCCN Guidelines®) for non-small cell lung cancer. Version 2.2024. National Comprehensive Cancer Network, Inc. 2024.
10. Kim R, Keam B, Kim S, et al. Differences in tumor microenvironments between primary lung tumors and brain metastases in lung cancer patients: therapeutic implications for immune checkpoint inhibitors. BMC Cancer 2019;19:19.
11. Yang G, Xing L, Sun X. Navigate towards the immunotherapy era: value of immune checkpoint inhibitors in non-small cell lung cancer patients with brain metastases. Front Immunol 2022;13:852811.
12. Wang Y, Chen R, Wa Y, et al. Tumor immune microenvironment and immunotherapy in brain metastasis from non-small cell lung cancer. Front Immunol 2022;13:819451.
13. Lehnardt S. Innate immunity and neuroinflammation in the CNS: the role of microglia in toll-like receptor-mediated neuronal injury. Glia 2009;58:253-63.
14. Kudo Y, Haymaker C, Zhang J, et al. Suppressed immune microenvironment and repertoire in brain metastases from patients with resected non-small-cell lung cancer. Ann Oncol 2019;30:1521-30.
15. Vilariño N, Bruna J, Bosch-Barrera J, et al. Immunotherapy in NSCLC patients with brain metastases. Understanding brain tumor microenvironment and dissecting outcomes from immune checkpoint blockade in the clinic. Cancer Treat Rev 2020;89:102067.
16. Ikarashi D, Okimoto T, Shukuya T, et al. Comparison of tumor microenvironments between primary tumors and brain metastases in patients with NSCLC. JTO Clin Res Rep 2021;2:100230.
17. Li M, Hou X, Sai K, Wu L, et al. Immune suppressive microenvironment in brain metastatic non-small cell lung cancer: comprehensive immune microenvironment profiling of brain metastases versus paired primary lung tumors (GASTO 1060). OncoImmunology 2022;11:2059874.
18. Hofman P. New insights into the interaction of the immune system with non-small cell lung carcinomas. Transl Lung Cancer Res 2020;9:2199-213.
19. Tecchio C, Cassatella MA. Neutrophil-derived chemokines on the road to immunity. Semin Immunol 2016;28:119-28.
20. Peng W, Liu C, Xu C, et al. PD-1 blockade enhances T-cell migration to tumors by elevating IFN-γ inducible chemokines. Cancer Res 2012;72:5209-18.
21. Mansfield AS, Aubry MC, Moser JC, et al. Temporal and spatial discordance of programmed cell death-ligand 1 expression and lymphocyte tumor infiltration between

paired primary lesions and brain metastases in lung cancer. Ann Oncol 2016;27:1953-8.

22. Camy F, Karpathiou G, Dumollard JM, et al. Brain metastasis PD-L1 and CD8 expression is dependent on primary tumor type and its PD-L1 and CD8 status. J Immunother Cancer 2020;8:e000597.
23. Pezzuto A, Carico E. Role of HIF-1 in cancer progression: novel insights. A review. Curr Mol Med 2019;18:343-51.
24. Levallet J, Biojout T, Bazille C, et al. Hypoxia-induced activation of NDR2 underlies brain metastases from non-small cell lung cancer. Cell Death Dis 2023;14:823.
25. Parakh S, Park JJ, Mendis S, et al. Efficacy of anti-PD-1 therapy in patients with melanoma brain metastases. Br J Cancer 2017;116:1558-63.
26. Goldberg SB, Schalper KA, Gettinger SN, et al. Pembrolizumab for management of patients with NSCLC and brain metastases: long-term results and biomarker analysis from a non-randomised, open-label, phase 2 trial. Lancet Oncol 2020;21:655-63.
27. Mansfield AS, Herbst RS, de Castro G, et al. Outcomes with pembrolizumab monotherapy in patients with programmed death-ligand 1–positive NSCLC with brain metastases: pooled analysis of KEYNOTE-001, 010, 024, and 042. JTO Clin Res Rep 2021;2:100205.
28. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255-65.
29. Gadgeel SM, Lukas RV, Goldschmidt J, et al. Atezolizumab in patients with advanced non-small cell lung cancer and history of asymptomatic, treated brain metastases: Exploratory analyses of the phase III OAK study. Lung Cancer 2019;128:105-12.
30. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. N Eng J Med 2015;373:123-35.
31. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Eng J Med 2015;373:1627-39.
32. Cortinovis D, Chiari R, Catino A, et al. Italian cohort of the nivolumab EAP in squamous NSCLC: efficacy and safety in patients with CNS metastases. Anticancer Res 2019;39:4265-71.
33. Crinò L, Bronte G, Bidoli P, et al. Nivolumab and brain metastases in patients with advanced non-squamous non-small cell lung cancer. Lung Cancer 2019;129:35-40.

34. Sun L, Davis CW, Hwang W-T, et al. Outcomes in patients with non–small-cell lung cancer with brain metastases treated with pembrolizumab-based therapy. Clin Lung Cancer 2021;22:58-66.e3.
35. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in advanced non–small-cell lung cancer. N Eng J Med 2019;381:2020-31.
36. Paz-Ares LG, Ramalingam SS, Ciuleanu T-E, et al. First-line nivolumab plus ipilimumab in advanced NSCLC: 4-year outcomes from the randomized, open-label, phase 3 CheckMate 227 part 1 trial. J Thorac Oncol 2022;17:289-308.
37. Borghaei H, Pluzanski A, Caro RB, et al. Abstract CT221: nivolumab (NIVO) + ipilimumab (IPI) as first-line (1L) treatment for patients with advanced non-small cell lung cancer (NSCLC) with brain metastases: Results from CheckMate 227. Cancer Res 2020;80:CT221.
38. Reck M, Ciuleanu T-E, Lee J-S, et al. Systemic and intracranial outcomes with first-line nivolumab plus ipilimumab in patients with metastatic NSCLC and baseline brain metastases from CheckMate 227 part 1. J Thorac Oncol 2023;18:1055-69.
39. Ready NE, Audigier-Valette C, Goldman JW, et al. First-line nivolumab plus ipilimumab for metastatic non-small cell lung cancer, including patients with ECOG performance status 2 and other special populations: CheckMate 817. J Immunother Cancer 2023;11:e006127.
40. Buriolla S, Pelizzari G, Corvaja C, et al. Immunotherapy in NSCLC patients with brain metastases. Int J Mol Sci 2022;23:7068.
41. Mathew M, Enzler T, Shu CA, Rizvi NA. Combining chemotherapy with PD-1 blockade in NSCLC. Pharmacol Ther 2018;186:130-7.
42. Awad MM, Gadgeel SM, Borghaei H et al. Long-term overall survival from KEYNOTE-021 cohort G: pemetrexed and carboplatin with or without pembrolizumab as first-line therapy for advanced nonsquamous NSCLC. J Thorac Oncol 2021;16:162-8.
43. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Eng J Med 2018;378:2078-92.
44. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non–small-cell lung cancer. N Eng J Med 2018;379:2040-51.
45. Facchinetti F, Di Maio M, Perrone F, Tiseo M. First-line immunotherapy in non-small cell lung cancer patients with poor performance status: a systematic review and meta-analysis. Transl Lung Cancer Res 2021;10:2917-36.

46. Paz-Ares L, Ciuleanu T-E, Cobo M, Schenker M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:198-211.
47. Carbone D, Ciuleanu T, Cobo M, et al. OA09.01 first-line nivolumab + ipilimumab + chemo in patients with advanced NSCLC and brain metastases: results from CheckMate 9LA. J Thorac Oncol 2021;16:S862.
48. Nadal E, Rodríguez-Abreu D, Simó M, et al. Phase II trial of atezolizumab combined with carboplatin and pemetrexed for patients with advanced nonsquamous non–small-cell lung cancer with untreated brain metastases (Atezo-Brain, GECP17/05). J Clin Oncol 2023;41:4478-85.
49. Weichselbaum RR, Liang H, Deng L, Fu Y-X. Radiotherapy and immunotherapy: a beneficial liaison? Nat Rev Clin Oncol 2017;14:365-79.
50. Yu S, Zhang S, Xu H, et al. Organ-specific immune checkpoint inhibitor treatment in lung cancer: a systematic review and meta-analysis. BMJ Open 2023;13:e059457.
51. Chen Z, Duan X, Qiao S, Zhu X. Radiotherapy combined with PD-1/PD-L1 inhibitors in NSCLC brain metastases treatment: the mechanisms, advances, opportunities, and challenges. Cancer Medicine 2022;12:995-1006.
52. Wong P, Masucci L, Florescu M, et al. Phase II multicenter trial combining nivolumab and radiosurgery for NSCLC and RCC brain metastases. Neurooncol Adv 2023;5:vdad018.
53. Altan M, Wang Y, Song J, et al. Nivolumab and ipilimumab with concurrent stereotactic radiosurgery for intracranial metastases from non-small cell lung cancer: analysis of the safety cohort for non-randomized, open-label, phase I/II trial. J Immunother Cancer 2023;11:e006871.
54. Chen L, Douglass J, Walker AJ, et al. Concurrent immunotherapy and stereotactic radiosurgery for brain metastases is associated with a decreased incidence of new intracranial metastases. Int J Radiat Oncol Biol Phys 2015;93:E102.
55. Schapira E, Hubbeling H, Yeap BY, et al. Improved overall survival and locoregional disease control with concurrent PD-1 pathway inhibitors and stereotactic radiosurgery for lung cancer patients with brain metastases. Int J Radiat Oncol Biol Phys 2018;101:624-9.

56. Scoccianti S, Olmetto E, Pinzi V, et al. Immunotherapy in association with stereotactic radiotherapy for non-small cell lung cancer brain metastases: results from a multicentric retrospective study on behalf of AIRO. Neuro Oncol 2021;23:1750-64.
57. Billena C, Lobbous M, Cordova CA, et al. The role of targeted therapy and immune therapy in the management of non-small cell lung cancer brain metastases. Front Oncol 2023;13:1110440.
58. Vogelbaum MA, Brown PD, Messersmith H, et al. Treatment for brain metastases: ASCO-SNO-ASTRO guideline. J Clin Oncol 2022;40:492-516.
59. Zhou S, Ren F, Meng X. Efficacy of immune checkpoint inhibitor therapy in EGFR mutation-positive patients with NSCLC and brain metastases who have failed EGFR-TKI therapy. Front Immunol 2022;13:955944.
60. Sabari JK, Velcheti V, Shimizu K, et al. Activity of adagrasib (MRTX849) in brain metastases: preclinical models and clinical data from patients with KRASG12C-mutant non–small cell lung cancer. Clin Cancer Res 2022;28:3318-28.
61. Jänne PA, Riely GJ, Gadgeel SM, et al. Adagrasib in non–small-cell lung cancer harboring a KRASG12C mutation. N Eng J Med 2022;387:120-31.
62. Jänne PA, Smit EF, de Marinis F, Laskin J, et al. LBA4 preliminary safety and efficacy of adagrasib with pembrolizumab in treatment-naïve patients with advanced non-small cell lung cancer (NSCLC) harboring a KRASG12C mutation. IOTECH 2022;16:100360.
63. Lauko A, Kotecha R, Barnett A, et al. Impact of KRAS mutation status on the efficacy of immunotherapy in lung cancer brain metastases. Sci Rep 2021;11:18174.
64. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Eng J Med 2018;379:2220-9.
65. Paz-Ares L, Chen Y, Reinmuth N, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. ESMO Open 2022;7:100408.
66. Chang J, Jing X, Hua Y, et al. Programmed cell death 1 pathway inhibitors improve the overall survival of small cell lung cancer patients with brain metastases. J Cancer Res Clin Oncol 2023;149:1825-33.
67. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29:iv192-237.

68. Sholl LM. Biomarkers of response to checkpoint inhibitors beyond PD-L1 in lung cancer. Mod Pathol 2022;35:66-74.
69. Ng Kee Kwong F, Laggner U, McKinney O, et al. Expression of PD-L1 correlates with pleomorphic morphology and histological patterns of non-small-cell lung carcinomas. Histopathology 2018;72:1024-32.
70. Heymann JJ, Bulman WA, Swinarski D, et al. PD-L1 expression in non-small cell lung carcinoma: Comparison among cytology, small biopsy, and surgical resection specimens. Cancer Cytopathol 2017;125:896-907.
71. Brozos-Vázquez EM, Rodríguez-López C, Cortegoso-Mosquera A, et al. Immunotherapy in patients with brain metastasis: advances and challenges for the treatment and the application of circulating biomarkers. Front Immunol 2023;14:1221113.
72. Mino-Kenudson M, Schalper K, Cooper W, et al. Predictive biomarkers for immunotherapy in lung cancer: perspective from the International Association for the Study of Lung Cancer Pathology committee. J Thorac Oncol 2022;17:1335-54.
73. Miao K, Zhang X, Wang H, et al. Peripheral blood lymphocyte subsets predict the efficacy of immune checkpoint inhibitors in non–small cell lung cancer. Front Immunol 2022;13:912180.
74. Liu S, Zhao L, Zhou G. Peripheral blood markers predict immunotherapeutic efficacy in patients with advanced non-small cell lung cancer: a multicenter study. Front Genet 2022;13:1016085.
75. Rossi E, Aieta M, Tartarone A, et al. A fully automated assay to detect the expression of pan-cytokeratins and of EML4-ALK fusion protein in circulating tumour cells (CTCs) predicts outcome of non-small cell lung cancer (NSCLC) patients. Transl Lung Cancer Res 2021;10:80-92.
76. Rossi G, Pezzuto A, Sini C, et al. Concomitant medications during immune checkpoint blockage in cancer patients: novel insights in this emerging clinical scenario. Crit Rev Oncol Hematol 2019;142:26-34.
77. Ricciuti B, Dahlberg SE, Adeni A, et al. Immune checkpoint inhibitor outcomes for patients with non–small-cell lung cancer receiving baseline corticosteroids for palliative versus nonpalliative indications. J Clin Oncol 2019;37:1927-34.

78. Jia W, Gao Q, Han A, Zhu H, Yu J. The potential mechanism, recognition and clinical significance of tumor pseudoprogression after immunotherapy. Cancer Biol Med 2019;16:655-70.
79. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143-52.