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Title: Emerging Frontiers in the Treatment of Non-small Cell Lung Cancer: Innovations and Clinical Advances

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Clinical Question Box

What are the current strategies for selecting optimal treatment regimens for patients with non-small cell lung cancer (NSCLC)?

Treatment selection for NSCLC is guided by molecular profiling, PD-L1 expression, tumor histology, and patient factors. Targeted therapies are preferred for tumors with actionable mutations like EGFR, ALK, ROS1, BRAF, MET, RET, KRAS G12C, HER2, or NTRK. If no mutations are found, PD-L1 levels guide therapy: ≥50% often leads to immunotherapy alone, while lower levels usually require chemo-immunotherapy. Chemotherapy choices depend on histology, with pemetrexed used for non-squamous tumors and taxanes or gemcitabine for squamous types. Patient fitness, comorbidities, and emerging biomarkers, such as circulating tumor DNA, further personalize treatment.

Abstract

Non-small cell lung cancer (NSCLC), which accounts for about 85% of lung cancer cases, remains a leading cause of cancer-related mortality worldwide. Over the past decade, the advent of immunotherapies, targeted agents, and molecularly guided strategies has transformed the therapeutic landscape. However, significant challenges persist: many patients still present with advanced disease, and uncertainties remain regarding treatment sequencing, integration of novel therapies, and management of cases without actionable mutations. This review highlights the evolving role of chemotherapy within the modern multimodal treatment paradigm of NSCLC and underscores its enduring relevance amidst rapid therapeutic innovation. While platinum-based chemotherapy has historically been the cornerstone of treatment, its role is now increasingly dynamic, serving as a critical component of combination regimens alongside immunotherapies and targeted approaches. Advances such as immune checkpoint inhibitors and therapies directed at oncogenic drivers like EGFR, ALK, and ROS1 have significantly improved patient outcomes, yet chemotherapy remains essential, particularly for patients without actionable mutations. Emerging strategies, including perioperative immunotherapy, antibody-drug conjugates, bispecific antibodies, and novel cytotoxic agents, promise to further enhance efficacy. In addition, molecular personalization and the use of circulating tumor DNA are opening new avenues for precision oncology.

Keywords: Non-small cell lung cancer, NSCLC, immunotherapy, targeted therapy, chemotherapy, precision oncology

Introduction

Lung cancer continues to be the leading cause of cancer-related mortality worldwide, accounting for approximately 1.8 million deaths annually.[1] Non-small cell lung cancer (NSCLC) represents about 85% of all lung cancer cases. Despite improvements in screening and preventive strategies, a significant proportion of NSCLC patients are still being diagnosed with advanced or metastatic disease.[2] Historically, platinum-based chemotherapy regimens have been the cornerstone of systemic treatment, with cisplatin- or carboplatin-based doublets providing modest improvements in overall survival (OS) and symptom palliation in both locally advanced and metastatic NSCLC.[3] Over the past decade, the therapeutic landscape of NSCLC has undergone a remarkable transformation with the advent of immunotherapy and targeted therapies. Immune checkpoint inhibitors (ICIs), such as pembrolizumab, nivolumab, and atezolizumab, have become standards of care in various clinical scenarios, improving survival outcomes and quality of life for many patients.[4] In parallel, tyrosine kinase inhibitors (TKIs) have revolutionized the management of NSCLC harboring oncogenic driver mutations, including alterations in EGFR, ALK, ROS1, and BRAF genes.[5,6]

Despite significant therapeutic advances, chemotherapy continues to be the mainstay in the management of advanced or metastatic NSCLC. It is particularly important for patients lacking actionable driver mutations or those ineligible for immunotherapy due to contraindications or toxicity concerns.[7] Furthermore, chemotherapy is a foundational component in combination regimens with ICIs and targeted therapies, underscoring its enduring relevance in contemporary treatment strategies.[8] This review provides a comprehensive and current overview of chemotherapy within the evolving NSCLC treatment landscape, exploring its conventional

applications, integration into novel combination approaches, emerging cytotoxic agents, and future directions.

Traditional Cytotoxic Chemotherapy

Since the 1990s, platinum-based chemotherapy has formed the core of NSCLC treatment. Cisplatin and carboplatin, when combined with agents like pemetrexed, gemcitabine, docetaxel, or paclitaxel, have consistently demonstrated survival advantages compared to the best supportive care.[9] In early-stage resectable NSCLC, adjuvant cisplatin-based chemotherapy improves the chances of five-year OS by approximately 4.1% and disease-free survival (DFS) by 5.1% compared to observation, as demonstrated in a randomized trial with a median follow-up of 56 months.[10] Similarly, neoadjuvant chemotherapy is known to improve the resectability and downstaging of the disease.[11]

For patients with stage III unresectable NSCLC, concurrent chemoradiotherapy using platinum doublets has long been the standard, offering median OS between 16 and 28 months in trials such as RTOG 9410.[12] In advanced and metastatic NSCLC, platinum-based chemotherapy prolongs median OS between 8 and 12 months, with response rates around 20–30% depending on histology and performance status.[13] Pemetrexed in non-squamous histology and gemcitabine or paclitaxel in squamous histology remain commonly used candidates for platinum agents.[14] Nevertheless, platinum chemotherapy is associated with significant toxicities, including nephrotoxicity, neurotoxicity, ototoxicity, and myelosuppression.[15] These side effects often require dose adjustments, growth factor support, or supportive care interventions, underscoring the need for ongoing refinement of chemotherapy regimens.

Monotherapy Immunotherapy

The development of ICI monotherapy has significantly reshaped the treatment paradigm of NSCLC, particularly in patients without actionable mutations such as EGFR or ALK. Since their initial approval, ICIs targeting PD-1 or PD-L1 have demonstrated durable survival benefits and favorable tolerability profiles in selected patient populations.[16] Figure 1 summarizes the chronological advances in ICIs for NSCLC from 2015 to 2025. It highlights the progressive introduction of agents such as nivolumab, pembrolizumab, atezolizumab, durvalumab, and cemiplimab across various treatment settings, including first-line, perioperative, adjuvant, and neoadjuvant therapies. The breakthrough came with the Food and Drug Administration (FDA) approval of nivolumab in March 2015 for patients with advanced NSCLC who progressed on or after platinum-based chemotherapy.[17] This established the role of anti–PD-1 therapy in the second-line setting. Soon after, pembrolizumab monotherapy received first-line approval in October 2016 for metastatic NSCLC with PD-L1 tumor proportion score (TPS) ≥50%, based on the KEYNOTE-024 trial, which demonstrated significant improvements in both OS and progression-free survival (PFS) compared to chemotherapy.[18] Subsequent studies, such as KEYNOTE-042, broadened pembrolizumab's indication to patients with PD-L1(TPS ≥1%), although the greatest benefit was in those with high PD-L1 expression.[19]

Similarly, atezolizumab was approved in the first-line setting for high PD-L1–expressing NSCLC based on the IMpower110 trial, confirming the efficacy of PD-L1 inhibition in monotherapy.[20] Long-term follow-up data from these trials show a subset of patients achieving sustained responses beyond 5 years, emphasizing the potential for durable disease control with monotherapy.[21] Moreover, real-world evidence has supported the use of ICI monotherapy in older or frailer patients who may not tolerate combination chemoimmunotherapy.[22] Despite these

successes, ICI monotherapy is most effective in patients with high PD-L1 expression (TPS ≥50%), and still requires predictive biomarkers beyond PD-L1.[23] Ongoing efforts also aim to optimize sequencing and re-administration strategies in patients who relapse after initial ICI therapy.[24]

ICI monotherapy has made important strides in resectable early-stage NSCLC. The IMpower010 trial led to the FDA approval of adjuvant atezolizumab in October 2021 for patients with resected Stage II–IIIA NSCLC and PD-L1 TPS ≥1%, following platinum-based chemotherapy.[25] This marked the first approval of an ICI as adjuvant monotherapy in NSCLC. In the LCMC3 study, neoadjuvant atezolizumab monotherapy demonstrated a major pathologic response rate of approximately 20%, with a promising 3-year DFS when followed by adjuvant atezolizumab.[26] It also highlights a potential path forward for monotherapy-based perioperative strategies.

As of 2025, several ICIs have FDA-approved subcutaneous formulations that offer comparable efficacy to intravenous dosing with significantly shorter administration times. Nivolumab subcutaneous (OPDIVO Qvantig) was approved in December 2024 for all previously approved indications, including perioperative use in NSCLC, and can be administered in just 3–5 minutes.[27] Atezolizumab subcutaneous was approved in September 2024 (Hybreza) and is indicated for NSCLC, SCLC, and other solid tumors.[28] Additionally, pembrolizumab subcutaneous has completed Phase III trials demonstrating non-inferior pharmacokinetics and efficacy and is expected to receive FDA approval by late 2025.[29] These subcutaneous options improve patient convenience, reduce infusion chair time, and may expand access to immunotherapy, particularly in resource-limited or outpatient settings.

Beyond clinical equivalence, these subcutaneous formulations have important practical implications for patient care. Shorter administration times can enhance treatment adherence by

reducing patient burden and improving the overall treatment experience.[30] They also increase accessibility, particularly in resource-limited or high-volume outpatient settings, by optimizing infusion chair turnover and reducing healthcare resource utilization. Moreover, subcutaneous delivery may be especially beneficial for patients with limited mobility or those living in remote areas, where minimizing hospital visits can significantly improve quality of life and facilitate continuity of care.

Combined Immunotherapy Approaches

Advanced NSCLC

CTLA-4 inhibitors such as ipilimumab and tremelimumab enhance T-cell priming in lymphoid tissues, complementing the PD-1/PD-L1 blockade in the tumor microenvironment.[31] Combining ICIs with chemotherapy or anti-VEGF agents further modulates the immune landscape, improving tumor infiltration and antigen presentation. Despite their efficacy, dual-ICI regimens may be highly toxic, leading to particularly immune-related adverse events.[32] The use of dual ICI combinations, particularly targeting PD-1/PD-L1 and CTLA-4, has emerged as a powerful approach to enhance anti-tumor immunity in NSCLC.[32] These combinations aim to overcome resistance mechanisms seen with monotherapy and provide broader, more durable responses across PD-L1 expression levels and histological subtypes.

The pivotal CheckMate 227 trial was the first to demonstrate the clinical benefit of dual ICI therapy in NSCLC. In patients with PD-L1 expression ≥1%, the combination of nivolumab and ipilimumab significantly improved OS compared to chemotherapy, with a 5-year OS rate of 24% vs. 14%.[33] This regimen received FDA approval in May 2020 as a first-line treatment for advanced NSCLC with PD-L1 ≥1% and no EGFR or ALK alterations. Building on this, the CheckMate 9LA trial combined nivolumab and ipilimumab with a limited course (two cycles) of platinum-based chemotherapy to deliver a rapid disease control benefit while preserving the durability of ICI response.[34] This approach demonstrated improved survival in both PD-L1–positive and –negative patients, and was approved by the FDA in 2021. Notably, the 9LA regimen is suitable across all PD-L1 expression levels, including patients with PD-L1 <1%, with limited monotherapy efficacy.

The POSEIDON trial evaluated durvalumab and tremelimumab in combination with chemotherapy in first-line metastatic NSCLC. The triplet regimen significantly improved OS (hazard ratio [HR] 0.77) compared to chemotherapy alone.[35] The benefit was particularly notable in patients with high tumor mutational burden and PD-L1–low tumors. Based on these findings, the FDA approved durvalumab, tremelimumab, and chemotherapy in 2023 as an alternative ICI-based regimen for metastatic NSCLC.

The integration of immunotherapy with platinum-based chemotherapy has reshaped first-line treatment paradigms in advanced NSCLC. For instance, the KEYNOTE-189 trial, examining pembrolizumab plus pemetrexed and platinum in non-squamous NSCLC, demonstrated a marked survival benefit and improved OS with an HR of 0.56, and at 5 years. A total of 19.4% patients receiving the combination survived compared with just 11.3% on chemotherapy alone.[36]Similarly, KEYNOTE-407, focused on squamous NSCLC, showed that pembrolizumab plus carboplatin and paclitaxel or nanoparticle-albumin-bound paclitaxel significantly extended median OS to 15.9 months versus 11.3 months in the chemotherapy group (HR 0.64).[37] Five-year updates confirm that these chemo-immunotherapy regimens consistently outperform standard chemotherapy, solidifying their status as the backbone of treatment in advanced NSCLC[38].

Sequential ICI and Chemoradiotherapy

While not yet standard in the resectable setting, the combination of ICIs with radiation therapy has shown significant benefit in unresectable Stage III NSCLC, most notably demonstrated in the PACIFIC trial.[39] In this pivotal phase III study, patients who had not progressed following concurrent chemoradiotherapy were randomized to receive durvalumab or placebo for up to 12 months. Durvalumab significantly improved outcomes, with a median PFS of 17.2 months vs. 5.6 months (HR 0.51) and a median OS of 47.5 months vs. 29.1 months (HR 0.72) compared to

placebo. These results led to the global adoption of durvalumab as the standard of care for unresectable Stage III NSCLC. Preclinical and early-phase clinical studies suggest that radiation may enhance anti-tumor immunity by promoting neoantigen release and modulating the tumor microenvironment, providing a strong rationale for ongoing trials exploring neoadjuvant chemoradiation plus ICIs in the perioperative setting for resectable disease.[40]

Perioperative Immunotherapy Strategies in NSCLC

Beyond the established role of immunotherapy in advanced NSCLC, a breakthrough in early-stage disease came with the CheckMate 816 trial.[41] This study evaluated neoadjuvant nivolumab combined with platinum-based chemotherapy before surgical resection. The regimen significantly increased the rate of pathologic complete response (24.0% vs. 2.2%) and improved event-free survival (EFS) (31.6 vs. 20.8 months) compared to chemotherapy alone. These benefits translated into durable survival outcomes, with a 5-year OS advantage presented at ASCO 2025.[42] Based on these findings, the FDA approved neoadjuvant nivolumab plus chemotherapy in March 2022, signaling a paradigm shift in the treatment of early-stage NSCLC. Similarly, the AEGEAN trial demonstrated that durvalumab combined with neoadjuvant chemotherapy, followed by adjuvant durvalumab, significantly improved EFS versus chemotherapy alone (HR 0.68). These results led to FDA approval in August 2024 for use in resectable Stage II–IIIB NSCLC.[43] Together, these trials underscore the value of perioperative immunotherapy to reduce tumor burden preoperatively as well as prevent micrometastatic relapse post-surgery.

Immunotherapy Combination Strategies

In advanced NSCLC, the choice and sequencing of immunotherapy combinations are increasingly guided by tumor PD-L1 expression, histological subtype, and disease burden.[44] Dual

ICI regimens, such as nivolumab plus ipilimumab or durvalumab plus tremelimumab, are preferred in patients without actionable driver mutations and with adequate performance status, particularly when a durable immune response is prioritized.[45] For tumors with PD-L1 ≥1%, nivolumab–ipilimumab, as supported by CheckMate 227, offers significant long-term survival benefit, whereas for PD-L1 <1%, combinations like CheckMate 9LA or the POSEIDON triplet provide rapid disease control alongside durable responses.[46] Chemo-immunotherapy combinations, such as those from KEYNOTE-189 and KEYNOTE-407, remain the standard backbone for most patients, especially when a quick tumor shrinkage is needed or when PD-L1 expression is low or absent.[47] Sequencing strategies are also evolving: platinum-based chemotherapy may be frontloaded in high-tumor-burden cases to debulk disease before transitioning to ICI-dominant maintenance, while perioperative settings now leverage neoadjuvant chemo-immunotherapy regimens (e.g., CheckMate 816, AEGEAN) to enhance surgical outcomes and reduce relapse risk. This nuanced, biomarker-driven approach enables clinicians to tailor regimens to maximize efficacy while balancing toxicity risks and treatment durability.

Targeted Therapy in NSCLC

Precision Medicine in NSCLC

Targeted therapy has revolutionized the management of NSCLC by tailoring treatment strategies to specific oncogenic drivers, thereby improving efficacy and reducing unnecessary toxicity. Across multiple genomic alterations, such as EGFR, ALK, ROS1, BRAF, MET, RET, KRAS, NTRK, and HER2, novel inhibitors have consistently demonstrated enhanced progression-free survival, central nervous system penetration, and improved quality of life compared to conventional chemotherapy.[48] While each mutation-driven therapy requires individualized selection based on molecular profiling, several shared principles emerge: early and comprehensive genomic testing is essential, CNS-active agents are increasingly prioritized, and resistance mechanisms frequently necessitate sequential targeted approaches or combination regimens.[49] Furthermore, the expanding role of perioperative and adjuvant targeted therapies underscores a shift toward integrating precision medicine across disease stages.[50] Together, these advancements highlight a unifying paradigm: harnessing molecular insights to deliver personalized, durable, and more effective treatment for patients with NSCLC.

EGFR Mutations

EGFR mutations are among the most well-characterized oncogenic drivers in NSCLC, most commonly appearing as exon 19 deletions and exon 21 L858R point mutations.[51] These mutations are more frequent in non-smokers, women, and individuals of East Asian descent.[52] For EGFR exon 19 Deletion or exon 21 L858R, first-line treatment options include osimertinib, which has demonstrated superior efficacy and CNS penetration compared to earlier generation EGFR TKIs.[53] Combination therapies such as osimertinib and chemotherapy[54] and amivantamab-vmjw

with lazertinib are also approved and recommended in select settings.[55] Alternative TKIs such as afatinib, dacomitinib, erlotinib, or gefitinib may be used based on availability, tolerability, and patient-specific factors.[56] Several EGFR-TKI and VEGF/VEGFR inhibitor combinations have been tested in NSCLC, with the most consistent PFS benefit seen in erlotinib plus bevacizumab, improving median PFS to 16–17 months (HR 0.60) across multiple trials like JO25567 and NEJ026, despite clear OS gains.[57,58] Gefitinib plus bevacizumab also showed a PFS of 14.4 months in Phase II studies. In contrast, osimertinib plus bevacizumab or ramucirumab failed to improve OS in advanced NSLCL.[59,60] The perioperative use of EGFR TKIs, especially adjuvant osimertinib, represents a promising advancement in the management of early-stage EGFR-mutant NSCLC. However, the role of neoadjuvant TKIs remains investigational.[61]

Subsequent therapy should involve reassessment for resistance mutations such as T790M, where osimertinib remains effective.[62] In T790M-negative cases, chemotherapy or newer EGFR bispecific antibodies may be appropriate.[63] These uncommon mutations, such as EGFR S768I, L861Q, and G719X, typically show variable sensitivity to EGFR TKIs. Afatinib has shown consistent efficacy and remains the preferred agent, although osimertinib and other TKIs may be considered.[62] Historically resistant to most EGFR TKIs, exon 20 insertions now have approved targeted options. Amivantamab-vmjw and sunvozertinib represent significant advancements, showing durable responses even in previously treated patients.[64]

ALK Rearrangement

Anaplastic lymphoma kinase (ALK) gene fusions are found in 3–7% of NSCLC cases, commonly in younger, non-smoking patients.[65] First-line treatment includes potent ALK inhibitors, such as alectinib, brigatinib, ensartinib, or lorlatinib, all of which exhibit excellent CNS penetration.[66] Upon progression, especially with CNS involvement or resistant mutations (e.g.,

G1202R), lorlatinib is often the preferred line of treatment.[67] Continued CNS surveillance and molecular re-testing guide further management.

ROS1 Rearrangement

ROS1 fusions are rare but actionable targets in NSCLC. First-line therapy includes crizotinib, entrectinib, repotrectinib, or taletrectinib.[68,69] These agents differ in CNS activity, with repotrectinib and entrectinib showing improved intracranial efficacy.[70,71] In cases of progression, alternative ROS1 inhibitors or systemic chemotherapy may be utilized, guided by resistance mutation profiling.

BRAF V600E Mutation

BRAF mutations, particularly V600E, occur in 1–3% of NSCLC cases.[72] These mutations activate the MAPK pathway and respond well to dual BRAF/MEK inhibition. The preferred first-line therapies are dabrafenib plus trametinib or encorafenib plus binimetinib.[73] For patients who progress, retreatment with another BRAF/MEK combination or standard chemotherapy is considered based on prior exposure and tolerability.

MET Exon 14 Skipping Mutation

MET exon 14 skipping mutations lead to prolonged MET signaling and occur in 3–4% of NSCLC cases.[74] Capmatinib and tepotinib are preferred first-line agents with demonstrated intracranial activity.[75] Crizotinib may also be used, but with less CNS efficacy.[76] As with other targeted therapies, progression warrants re-biopsy to identify resistance mechanisms.

RET Rearrangement

RET fusions are seen in 1–2% of NSCLC and respond well to selective RET inhibitors such as selpercatinib and pralsetinib.[77] These agents exhibit high response rates and good CNS activity. Upon progression, switching to an alternative RET inhibitor or systemic chemotherapy remains standard practice, particularly if new resistance mutations arise.[78]

KRAS G12C Mutation

KRAS mutations are among the most common in NSCLC, despite being historically considered undruggable. The G12C variant, in particular, is now targetable with small-molecule inhibitors such as sotorasib and adagrasib.[79] In the first-line setting, treatment decisions are driven by PD-L1 expression. Upon progression or if patients have previously received systemic therapy, KRAS G12C inhibitors are appropriate options, providing targeted benefit with a manageable toxicity profile.[80]

NTRK Gene Fusion (NTRK1/2/3)

Although extremely rare in NSCLC, NTRK gene fusions represent a tumor-agnostic biomarker of treatment sensitivity.[81] TRK inhibitors, such as entrectinib, larotrectinib, and repotrectinib, are highly effective.[82] Due to the potential for acquired resistance, repeat molecular profiling is crucial. Repotrectinib is particularly useful in overcoming solvent-front mutations that confer resistance to earlier TRK inhibitors.[83]

HER2 (ERBB2) Mutation

HER2 mutations, mainly insertions in exon 20, are targetable with HER2-directed therapies. Trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate (ADC), has emerged as the most effective agent with demonstrated survival benefit in previously treated HER2-mutant NSCLC.[84]

Other agents under investigation include poziotinib and pyrotinib, though clinical trial enrollment is encouraged for refractory cases.[85,86]

NRG1 Gene Fusion

NRG1 fusions are very rare and have been reported across various tumor types. Although there are no approved targeted therapies, afatinib has shown limited efficacy in small series.[87] Enrollment in clinical trials remains the most promising option. Re-biopsy and comprehensive genomic profiling are essential for these patients.

Emerging Novel Agents

Novel therapeutic agents are being explored to enhance chemotherapy efficacy while minimizing toxicity. Telisotuzumab vedotin, an ADC targeting c-Met, a receptor tyrosine kinase overexpressed in non-squamous NSCLC and associated with tumor progression and therapy resistance, has demonstrated promising activity. In the Phase 2 LUMINOSITY study, it showed encouraging efficacy in previously treated advanced NSCLC, achieving an ORR of 34.6% in patients with high c-Met expression (≥ 50% IHC), with a manageable safety profile.[88] By selectively delivering cytotoxic payloads to c-Met–positive cells, it enhances antitumor activity while sparing normal tissues. Plinabulin, a selective microtubule destabilizer, combines antimitotic activity with immune modulation by activating dendritic cells and priming T cells. It has shown potential to improve antitumor responses and reduce chemotherapy-induced neutropenia. Plinabulin is currently being evaluated in the Phase 3 DUBLIN-3 trial, often in combination with docetaxel for previously treated NSCLC.[89]

Bispecific antibodies represent another innovative approach. By simultaneously engaging tumor-associated antigens and immune effector cells, these agents promote targeted immune activation. Candidates targeting EGFR/MET or PD-L1/CD3 are in early- to mid-phase trials, aiming to overcome resistance seen with monotherapies. Additional investigational agents, such as ivonescimab, a bispecific PD-1/VEGF antibody, and spartalizumab, are being explored in combination with platinum-based doublets to further potentiate anti-tumor immune responses.[90,91] NVL-655, a next-generation ALK inhibitor, is also being evaluated with platinum chemotherapy in patients with ALK-positive NSCLC who have developed resistance to earlier-generation TKIs.[92] As chemotherapy evolves from a primary backbone to a synergistic partner, the integration of

supportive agents and innovative combination strategies will be essential for optimizing clinical outcomes.

Conclusion

Although chemotherapy is no longer the sole pillar of NSCLC management, it remains vital within the current treatment landscape. Its integration with immunotherapy and targeted therapies has transformed patient outcomes and will continue to evolve with the emergence of novel agents and biomarkers. By adapting to advances in precision medicine, chemotherapy retains its place as an essential partner in the multidisciplinary treatment of NSCLC.

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Figure 1 Advances in Immune Checkpoint Inhibitors for NSCLC