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Current Research on Perioperative Systemic Therapy in Resectable Non-Small Cell Lung Cancer

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Abstract

For patients with lung cancer, there is yet to be an ideal clinical treatment, with surgical resection still being the preferred treatment choice. Compared to the clinical efficacy in patients with advanced non-small cell lung cancer (NSCLC), the recurrence rate remains high for early-stage resectable disease. In recent years, immune checkpoint inhibitors and targeted therapies have shown promise as two clinical treatment approaches. Many clinical studies are evaluating perioperative immunotherapy or targeted therapy, and recent trials such as CheckMate 816, CheckMate 77T, and bispecific nanoparticle BCGN introduce new concepts while demonstrating the clinical potential of these approaches. This review addresses recent and ongoing trials of neoadjuvant and adjuvant systemic therapies for NSCLC, and potential developments in this area in the near future.

Keywords

Non-Small Cell Lung Cancer, Perioperative, Neoadjuvant Therapy, Immunotherapy, Targeted Therapy

1. Background

Lung cancer has become the leading cause of cancer-related death in humans [1] [2]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. Clinically, the majority of NSCLC patients are diagnosed at an advanced stage; however, surgical resection alone is not a curative treatment for many early-stage NSCLC cases, with recurrence rates rising as the disease progresses [3]-[7].

Clinically, platinum-based adjuvant chemotherapy has long been the standard treatment for resectable stage II-IIIA NSCLC patients, although the improvement in survival probability is limited, with an approximate 5% increase in overall survival (OS) following treatment [8] [9]. Over nearly the past decade, perioperative systemic therapy (neoadjuvant or adjuvant) for NSCLC patients has seen no significant advancements in clinical practice [10]. However, the widespread clinical use of immunotherapy and targeted therapy has greatly improved the treatment of metastatic or unresectable NSCLC. These successes have encouraged research and application of these therapies in potentially curable early-stage NSCLC with the aim of improving patient survival rates. This review provides an overview of key studies and data on neoadjuvant and adjuvant systemic therapies and highlights some ongoing trials.

2. Perioperative Chemotherapy

Since the early 2000s, platinum-based adjuvant chemotherapy has become the standard treatment for completely resected stage II-IIIA NSCLC patients [11]. A 2008 meta-analysis of the Lung Adjuvant Cisplatin Evaluation (LACE) showed a 5-year absolute survival benefit of 5.4% for all patients (hazard ratio [HR], 0.89; P = 0.005). When analyzed by stage, stage IB disease showed no significant improvement in overall survival (OS) (HR, 0.93; 95% CI, 0.78 - 1.10), while stage IA disease actually showed a decrease in OS (HR, 1.41; 95% CI, 0.96 - 2.09). For stage II and III diseases, OS improved (HR, 0.83; 95% CI, 0.73 - 0.95, and HR, 0.83; 95% CI, 0.72 - 0.94) [8]. Although the meta-analysis shows absolute survival benefits for adjuvant chemotherapy in certain stages, neoadjuvant chemotherapy is typically limited in clinical practice to patients with stage IIIA or IIIB N2 disease, with the goal of downstaging the tumor to make it more resectable [9] [12]-[14].

3. Perioperative Adjuvant Therapy

Immune checkpoint inhibitors (ICIs) have greatly changed the management of advanced NSCLC in clinical practice and have become an essential part of first-line treatment for patients without driver gene mutations. Checking the PD-L1 status of tumors has become a necessary part of the workflow for metastatic NSCLC, followed by assessments to determine the most effective treatment strategy. Molecular testing is also used to exclude patients who may not benefit from immunotherapy (e.g., EGFR, ALK). With the recent approval of neoadjuvant and adjuvant ICIs in the United States, immunotherapy has now been included in the NCCN Clinical Practice Guidelines: Oncology (NCCN Guidelines) for the management of early-stage NSCLC [9]. However, there are still many ongoing trials further exploring the efficacy of ICIs in perioperative treatment, either as monotherapy or in combination with chemotherapy [15].

4. Neoadjuvant Immunotherapy

Similar to neoadjuvant chemotherapy, neoadjuvant immunotherapy aims to

shrink tumors, improve resectability, and eliminate micrometastases. Its advantages include protecting the lymphatic system and increasing the exposure of novel antigens to the immune system. However, its drawbacks include potential side effects that could delay surgery, increase the risk of disease progression, and possibly compromise the complete removal of the tumor [15].

4.1. Neoadjuvant Immunotherapy as Monotherapy

CheckMate 159 is one of the earliest pilot studies to evaluate the safety and feasibility of neoadjuvant immunotherapy as monotherapy for NSCLC. This phase II trial evaluated 21 patients with stage I-IIIA NSCLC who received preoperative nivolumab treatment. All 21 patients underwent timely resection, with 20 achieving complete resection (R0), and only one patient did not receive the planned two doses of nivolumab before surgery [14] [16]. In the CheckMate 159 study, the major pathological response (MPR), defined as ≤10% tumor activity in the surgical specimen, was observed in 45% of cases, which is a significant increase compared to the historical MPR rates of 16% to 21% in neoadjuvant chemotherapy [16]-[19]. A similar related study is a recently published phase III, randomized, double-blind clinical trial evaluating the perioperative efficacy of pembrolizumab in early-stage non-small cell lung cancer (NSCLC). This trial recruited 797 patients with resectable stage II, IIIA, or stage IIIB NSCLC with N2 lymph node metastasis, who were randomly assigned 1:1 to the pembrolizumab group (397 patients) and the control group (400 patients). The experimental group received neoadjuvant pembrolizumab (200 mg every 3 weeks) combined with a platinum-based chemotherapy regimen for 4 cycles, followed by tumor resection and continued adjuvant pembrolizumab treatment for up to 13 cycles. The control group received the same chemotherapy and surgical regimen, but with a placebo during the neoadjuvant treatment phase. After a median follow-up of 25.2 months, the 24-month event-free survival (EFS) rate in the pembrolizumab group was significantly higher than in the control group (62.4% vs. 40.6%, $P < 0.00001$). The major pathological response (MPR) rate and pathological complete response (pCR) rate were also significantly higher in the pembrolizumab group compared to the control group (MPR: 30.2% vs. 11.0%, pCR: 18.1% vs. 4.0%, $P < 0.00001$). The study results suggest that adding pembrolizumab to neoadjuvant chemotherapy, followed by surgery and adjuvant pembrolizumab treatment, significantly improves EFS, MPR, and pCR in resectable early-stage NSCLC patients, providing strong evidence for the further exploration of pembrolizumab's potential in the treatment of early NSCLC [20]-[22].

4.2. Neoadjuvant Immunotherapy Combined with Chemotherapy

The CheckMate 816 trial, as the first study to facilitate the approval of neoadjuvant immunotherapy by the U.S. Food and Drug Administration (FDA), marks a milestone in the field. This phase III clinical trial included 358 patients with resectable stage IB (tumor size > 4 cm) to IIIA non-small cell lung cancer (NSCLC), all of whom had no EGFR or ALK gene mutations. Patients were randomly assigned to

two groups: one group received neoadjuvant nivolumab combined with platinum-based chemotherapy, while the other group received chemotherapy alone. The CheckMate 816 trial had two primary endpoints: event-free survival (EFS) and pathological complete response (pCR), both of which were significantly improved in the combination therapy group. The median EFS in the combination therapy group was extended to 31.6 months compared to 20.8 months in the control group (97.38% confidence interval, 0.43 - 0.91, P = 0.005). In terms of pCR, 24% of patients in the combination therapy group achieved this standard, compared to only 2.2% in the control group (99% confidence interval, 3.49 - 55.75, P = 0.001). There was no significant difference in surgical outcomes between the two groups. Furthermore, the addition of nivolumab did not affect treatment tolerability, feasibility, or surgery duration [23]. The FDA's approval extends to all resectable NSCLC patients with various PD-L1 expression statuses, but the most significant benefits were mainly observed in patients with stage IIIA or PD-L1 expression ≥ 50%. For IB-III stage patients with PD-L1 expression < 1%, the combination therapy did not show a noticeable EFS benefit, which may indicate that these patients have limited benefit from the combination treatment. Although the study did not deeply analyze subgroups, the pCR rates were significantly increased in all subgroups. A recent phase III randomized double-blind trial (CheckMate 77T, NCT04025879) investigated the efficacy and safety of neoadjuvant nivolumab combined with chemotherapy versus neoadjuvant chemotherapy alone in resectable stage IIA to IIIB NSCLC patients during the perioperative period. The primary endpoint was event-free survival, and secondary endpoints included pathological complete response, major pathological response, overall survival, and safety. At a median follow-up of 25.4 months, the nivolumab group had a significantly higher 18-month event-free survival rate than the chemotherapy group (70.2% vs. 50.0%; hazard ratio = 0.58; 97.36% confidence interval: 0.42 to 0.81; P < 0.001), with similar rates of grade 3 or 4 treatment-related adverse events (32.5% vs. 25.2%). The study concluded that for resectable NSCLC patients, the use of nivolumab during the perioperative period can significantly prolong event-free survival, and no new safety signals were observed. Neoadjuvant immunotherapy, when used alone, shows some potential in stimulating tumor responses and does not adversely affect surgical outcomes. However, to accurately assess its pathological response rate and survival outcomes, larger studies are necessary to further confirm its real benefits. So far, compared to the efficacy of neoadjuvant immunotherapy combined with chemotherapy in unselected patient populations, the response rate for neoadjuvant immunotherapy alone seems lower, which may limit its application in some cases. At the same time, the application of neoadjuvant immunotherapy is also somewhat restricted and requires comprehensive consideration of the patient's specific condition and tumor characteristics to choose the appropriate clinical treatment plan [24]-[28].

5. Perioperative Adjuvant Targeted Therapy

For metastatic non-small cell lung cancer (NSCLC) patients with treatable genetic

mutations such as EGFR mutations, oral tyrosine kinase inhibitors (TKIs) are the first-line treatment due to their greater effectiveness compared to traditional chemotherapy. Immunotherapy (ICIs) is effective in some lung cancers, but its effect is limited in oncogene-driven lung cancers [29]. The success of TKIs has prompted researchers to explore their application in the perioperative setting. The ADAURA study included 682 patients with EGFR-mutant non-small cell lung cancer (EGFRm NSCLC) in stages IB to IIIA. They were randomly assigned to receive 3 years of adjuvant osimertinib treatment or a placebo, setting a record for treatment duration in similar studies. Compared to first-generation TKIs, osimertinib has lower toxicity and increased activity against the central nervous system (CNS). The study found that the osimertinib group had a significantly better 24-month disease-free survival (DFS) compared to the placebo group, with rates of 89% and 52%, respectively (hazard ratio HR = 0.20; 99.12% confidence interval CI: 0.14 - 0.30; $P < 0.001$). Additionally, the study found a significant reduction in central nervous system (CNS) relapse in the TKI group [10]. Although overall survival (OS) data is not yet available, due to the significant difference in DFS, the U.S. Food and Drug Administration (FDA) has approved adjuvant osimertinib for resected EGFR-mutant NSCLC patients. The optimal duration of adjuvant osimertinib therapy is not yet defined. Currently, the standard treatment duration is 3 years (a recommendation based on previous studies), which indicate that the first 2 years after surgery are a high-risk period for recurrence. However, further research is needed to determine the best treatment duration for osimertinib, particularly by analyzing relapse patterns after discontinuation of osimertinib in the ADAURA study [30] [31]. While there is a risk of overtreatment in patients who may achieve similar efficacy with just 1 or 2 years of osimertinib, longer or indefinite treatment may also be required [13] [32] [33]. Future studies should explore the effectiveness of different treatment durations and consider risk-adjusted treatment strategies based on circulating tumor DNA (ctDNA) and minimal residual disease (MRD) [34]-[37]. The ADAURA trial marks an important breakthrough in perioperative treatment for NSCLC. These studies showcase the potential of TKIs and underscore the critical role of clinical trials. Future studies are anticipated to offer more effective and personalized treatment options for a broader range of NSCLC patients.

In the recently published experimental report titled "Dual-responsive Nanoparticles Loading Bevacizumab and Gefitinib for NSCLC", the innovative application and notable efficacy of dual-responsive nanoparticles, BCGN, in the treatment of non-small cell lung cancer (NSCLC) were elaborated in detail. The focal point of this study was to explore a novel nanomedicine carrier, BCGN, which integrates precise delivery with synergistic therapy. The uniqueness of BCGN lies in its ability to simultaneously encapsulate bevacizumab, an anti-angiogenic agent, and gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor. This dual-drug encapsulation aims to enhance the therapeutic efficacy against NSCLC through the synergistic action of the two drugs. The design of BCGN cleverly

combines environmental responsiveness with biological responsiveness. Through specific synthetic processes, the nanoparticles are engineered to release their encapsulated drugs under specific physiological conditions, such as acidic pH values or specific enzyme concentrations in the tumor microenvironment. This mechanism ensures efficient drug accumulation and release at the tumor site while minimizing nonspecific exposure to normal tissues, thereby improving treatment safety and effectiveness. Additionally, BCGN may further potentiate its antitumor effect by modulating cellular apoptosis pathways, inhibiting tumor angiogenesis, and potentially synergizing with immunotherapy. The potential benefits of this study primarily lie in precise delivery, where the dual-responsive characteristics of BCGN enable precise drug delivery, increasing drug concentration in tumor tissue and enhancing therapeutic efficacy. Another benefit is synergistic therapy, where the simultaneous encapsulation of bevacizumab and gefitinib effectively inhibits tumor cell proliferation and angiogenesis through the synergistic action of different mechanisms, improving treatment efficiency. The reduction in side effects during the entire treatment process is also significant, as precise delivery minimizes drug damage to normal tissues, reducing the side effects associated with traditional chemotherapy and thus improving patients' quality of life.

Meanwhile, it is important to consider the limitations of this technology in clinical application. Firstly, the complexity of drug preparation is a major concern: the synthesis process of BCGN is complex and requires precise control of multiple parameters to ensure its stability and responsiveness, which increases production costs and time. Secondly, biological safety is another consideration: although in vitro and in vivo experiments have demonstrated the good safety of BCGN, the potential for long-term application to cause bioaccumulation and toxicity still needs further evaluation. Furthermore, individual differences cannot be ignored. Variations in tumor microenvironments and drug metabolism rates among different patients may affect the therapeutic efficacy of BCGN, necessitating the development of individualized treatment plans.

Regarding research challenges and future directions, simplifying the synthesis steps of BCGN, improving production efficiency, and reducing costs are important research areas for the future. Additionally, further in-depth studies on the metabolic pathways, long-term toxicity, and potential immunogenicity of BCGN in vivo are necessary to ensure its safety in clinical application. Combining patients' genomic and proteomic information to develop individualized treatment plans based on BCGN can improve the precision and effectiveness of treatment. Exploring multimodal treatment strategies by combining BCGN with other therapeutic methods, such as photodynamic therapy and immunotherapy, can further enhance the therapeutic effect of NSCLC.

In summary, BCGN, as a novel dual-responsive nanoparticle, demonstrates significant antitumor efficacy and a unique mechanism of action in the treatment of NSCLC, with potential clinical application value. However, challenges such as complexity in preparation, biological safety, and the formulation of individualized

treatment plans remain. In the future, with continuous advancements in materials science, biotechnology, and precision medicine, BCGN is expected to provide more efficient and safe treatment options for NSCLC patients [38]-[40].

In addition, significant progress has been made in the field of immunotherapy. The positive results of atezolizumab in the adjuvant setting of the IMpower010 study were encouraging [41] [42], and subsequently, nivolumab also showed promising results in the neoadjuvant phase of the CheckMate 816 trial. This presents us with a challenge: how to choose between neoadjuvant chemotherapy combined with immunotherapy or adjuvant immunotherapy in the absence of direct comparisons. Notably, some immunotherapy trials (such as KEYNOTE-786) have incorporated both neoadjuvant and adjuvant immunotherapy, which undoubtedly increases the complexity of perioperative management. Based on the currently available information, we tend to recommend the neoadjuvant nivolumab combined with chemotherapy regimen to patients with stage II-IIIA disease and PD-L1 expression ≥ 1%, rather than adjuvant atezolizumab, as this combination may provide greater benefits [23] [41]. For patients with PD-L1 expression < 1%, neoadjuvant chemotherapy combined with immunotherapy may be considered, but this must be done after a thorough discussion of the potential risks, as the benefits for these patients may be relatively limited [23] [25]-[27] [43].

A significant advantage of neoadjuvant therapy is that it allows for direct assessment of the tumor, thereby enabling the evaluation of treatment efficacy. In the exploratory analysis of the CheckMate 816 trial, we found a strong correlation between pathological complete response (pCR) and longer event-free survival (EFS), which further emphasizes the importance of neoadjuvant therapy in evaluating treatment efficacy. Subsequently, for patients with different PD-L1 expression levels, we should provide personalized treatment recommendations, taking into account the potential of neoadjuvant therapy in evaluating efficacy and extending survival. The advantage of this neoadjuvant treatment regimen is that it requires only three cycles of chemotherapy combined with immunotherapy, which is much shorter than the one-year course of atezolizumab treatment following adjuvant chemotherapy. At the same time, neoadjuvant therapy also addresses issues where some patients are unable to receive adjuvant therapy due to poor postoperative recovery or difficulties with follow-up after surgery. Concerns about neoadjuvant therapy potentially causing delays in surgery or cancellation due to disease progression do not appear to be significant at present. We continue to believe that adjuvant immunotherapy could hold a place in the treatment strategy for early-stage non-small cell lung cancer (NSCLC) patients, although its precise application scope and optimal practices are still under investigation [44]-[46]. In the future, adjuvant immunotherapy may advance in tandem with neoadjuvant immunotherapy, and the combined application of these two strategies is expected to enhance immune system antitumor effects, thereby improving efficacy and providing patients with more durable and significant survival benefits. We anticipate more high-quality research results to emerge, allowing for a deeper exploration

of the limitless potential of this combination therapy.

6. Conclusion

With the advancement of medical research and continuous progress in technology, the treatment of early-stage non-small cell lung cancer (NSCLC) is undergoing rapid transformation. From traditional surgical resection, radiotherapy, and chemotherapy to current targeted therapy, immunotherapy, and combination therapies, the diversity and complexity of treatment strategies are increasing. This shift has not only enhanced therapeutic outcomes but also imposed higher demands on formulating personalized treatment plans. In developing personalized treatment plans, it is essential to consider multiple patient factors, and such dynamic adjustments to treatment strategies are vital for ensuring optimal treatment outcomes and maintaining the patient's quality of life. In conclusion, as treatment methods for early-stage NSCLC continue to improve and their efficacy increases, the development of treatment strategies must become more intricate and precise. Personalized treatment plans should be formulated based on the patient's specific condition, with close monitoring and evaluation throughout the treatment process to ensure the best therapeutic outcomes and quality of life for the patient. At the same time, we also look forward to the emergence of more innovative treatment methods and technologies in the future, bringing more hope and blessings to NSCLC patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Hendriks, L.E.L., Remon, J., Faivre-Finn, C., Garassino, M.C., Heymach, J.V., Kerr, K.M., *et al.* (2024) Non-Small-Cell Lung Cancer. *Nature Reviews Disease Primers*, **10**, Article No. 71. https://doi.org/10.1038/s41572-024-00551-9

[2] Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., *et al.* (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **71**, 209-249. https://doi.org/10.3322/caac.21660

[3] Majeed, U., Manochakian, R., Zhao, Y. and Lou, Y. (2021) Targeted Therapy in Advanced Non-Small Cell Lung Cancer: Current Advances and Future Trends. *Journal of Hematology & Oncology*, **14**, Article No. 108. https://doi.org/10.1186/s13045-021-01121-2

[4] Luo, Y., Luo, L., Wampfler, J.A., Wang, Y., Liu, D., Chen, Y., *et al.* (2019) 5-Year Overall Survival in Patients with Lung Cancer Eligible or Ineligible for Screening According to US Preventive Services Task Force Criteria: A Prospective, Observational Cohort Study. *The Lancet Oncology*, **20**, 1098-1108. https://doi.org/10.1016/s1470-2045(19)30329-8

[5] Chaft, J.E., Rimner, A., Weder, W., Azzoli, C.G., Kris, M.G. and Cascone, T. (2021) Evolution of Systemic Therapy for Stages I-III Non-Metastatic Non-Small-Cell Lung Cancer. *Nature Reviews Clinical Oncology*, **18**, 547-557.

https://doi.org/10.1038/s41571-021-00501-4

[6] Matsuyama, R., Reddy, S. and Smith, T.J. (2006) Why Do Patients Choose Chemotherapy near the End of Life? A Review of the Perspective of Those Facing Death from Cancer. *Journal of Clinical Oncology*, **24**, 3490-3496. https://doi.org/10.1200/jco.2005.03.6236

[7] Goldstraw, P., Chansky, K., Crowley, J., Rami-Porta, R., Asamura, H., Eberhardt, W.E.E., *et al.* (2016) The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. *Journal of Thoracic Oncology*, **11**, 39-51. https://doi.org/10.1016/j.jtho.2015.09.009

[8] Pignon, J., Tribodet, H., Scagliotti, G.V., Douillard, J., Shepherd, F.A., Stephens, R.J., *et al.* (2008) Lung Adjuvant Cisplatin Evaluation: A Pooled Analysis by the LACE Collaborative Group. *Journal of Clinical Oncology*, **26**, 3552-3559. https://doi.org/10.1200/jco.2007.13.9030

[9] Ettinger, D.S., Wood, D.E., Aisner, D.L., Akerley, W., Bauman, J.R., Bharat, A., *et al.* (2022) Non-Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*, **20**, 497-530. https://doi.org/10.6004/jnccn.2022.0025

[10] Wu, Y., Tsuboi, M., He, J., John, T., Grohe, C., Majem, M., *et al.* (2020) Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. *New England Journal of Medicine*, **383**, 1711-1723. https://doi.org/10.1056/nejmoa2027071

[11] Li, J., Li, B., Guo, X., *et al.* (2022) The Clinical Significance of Tumor Mutation Burden in Non-Small Cell Lung Cancer Patients Receiving Platinum-Based Adjuvant Chemotherapy after Surgery. *Practical Journal of Medicine*, **38**, 1804-1808.

[12] Burdett, S., Stewart, L. and Rydzewska, L. (2007) Chemotherapy and Surgery versus Surgery Alone in Non-Small Cell Lung Cancer. *Cochrane Database of Systematic Reviews*, No. 3, CD006157. https://doi.org/10.1002/14651858.cd006157.pub2

[13] Mouillet, G., Monnet, E., Milleron, B., Puyraveau, M., Quoix, E., David, P., *et al.* (2012) Pathologic Complete Response to Preoperative Chemotherapy Predicts Cure in Early-Stage Non-Small-Cell Lung Cancer: Combined Analysis of Two IFCT Randomized Trials. *Journal of Thoracic Oncology*, **7**, 841-849. https://doi.org/10.1097/jto.0b013e31824c7d92

[14] Hellmann, M.D., Chaft, J.E., William, W.N., Rusch, V., Pisters, K.M.W., Kalhor, N., *et al.* (2014) Pathological Response after Neoadjuvant Chemotherapy in Resectable Non-Small-Cell Lung Cancers: Proposal for the Use of Major Pathological Response as a Surrogate Endpoint. *The Lancet Oncology*, **15**, e42-e50. https://doi.org/10.1016/s1470-2045(13)70334-6

[15] Pisters, K., Kris, M.G., Gaspar, L.E. and Ismaila, N. (2022) Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I-IIIA Completely Resected Non-Small-Cell Lung Cancer: ASCO Guideline Rapid Recommendation Update. *Journal of Clinical Oncology*, **40**, 1127-1129. https://doi.org/10.1200/jco.22.00051

[16] Pataer, A., Kalhor, N., Correa, A.M., Raso, M.G., Erasmus, J.J., Kim, E.S., *et al.* (2012) Histopathologic Response Criteria Predict Survival of Patients with Resected Lung Cancer after Neoadjuvant Chemotherapy. *Journal of Thoracic Oncology*, **7**, 825-832. https://doi.org/10.1097/jto.0b013e318247504a

[17] Cascone, T., Gold, K.A., Swisher, S.G., Liu, D.D., Fossella, F.V., Sepesi, B., *et al.* (2018) Induction Cisplatin Docetaxel Followed by Surgery and Erlotinib in Non-Small Cell Lung Cancer. *The Annals of Thoracic Surgery*, **105**, 418-424. https://doi.org/10.1016/j.athoracsur.2017.08.052

[18] Weissferdt, A., Pataer, A., Vaporciyan, A.A., Correa, A.M., Sepesi, B., Moran, C.A., *et al.* (2020) Agreement on Major Pathological Response in NSCLC Patients Receiving Neoadjuvant Chemotherapy. *Clinical Lung Cancer*, **21**, 341-348. https://doi.org/10.1016/j.cllc.2019.11.003

[19] Qu, Y., Emoto, K., Eguchi, T., Aly, R.G., Zheng, H., Chaft, J.E., *et al.* (2019) Pathologic Assessment after Neoadjuvant Chemotherapy for NSCLC: Importance and Implications of Distinguishing Adenocarcinoma from Squamous Cell Carcinoma. *Journal of Thoracic Oncology*, **14**, 482-493. https://doi.org/10.1016/j.jtho.2018.11.017

[20] Wakelee, H., Liberman, M., Kato, T., Tsuboi, M., Lee, S., Gao, S., *et al.* (2023) Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. *New England Journal of Medicine*, **389**, 491-503. https://doi.org/10.1056/nejmoa2302983

[21] Garassino, M.C., Wakelee, H.A., Spicer, J., Liberman, M., Kato, T., Tsuboi, M., *et al.* (2024) Health-Related Quality of Life (HRQOL) Outcomes from the Randomized, Double-Blind Phase 3 KEYNOTE-671 Study of Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer (NSCLC). *Journal of Clinical Oncology*, **42**, 8012. https://doi.org/10.1200/jco.2024.42.16_suppl.8012

[22] Bastin, T. and Thomas, Q.D. (2024) Traitement péri-opératoire avec pembrolizumab et chimiothérapie néoadjuvante pour les CBNPC. *Bulletin du Cancer*, **111**, 1000-1002. https://doi.org/10.1016/j.bulcan.2024.08.011

[23] Forde, P.M., Spicer, J., Lu, S., Provencio, M., Mitsudomi, T., Awad, M.M., *et al.* (2022) Neoadjuvant Nivolumab Plus Chemotherapy in Resectable Lung Cancer. *New England Journal of Medicine*, **386**, 1973-1985. https://doi.org/10.1056/nejmoa2202170

[24] Cascone, T., Awad, M.M., Spicer, J.D., He, J., Lu, S., Sepesi, B., *et al.* (2024) Perioperative Nivolumab in Resectable Lung Cancer. *New England Journal of Medicine*, **390**, 1756-1769. https://doi.org/10.1056/nejmoa2311926

[25] Yang, Z., Wang, S., Yang, H., Jiang, Y., Zhu, L., Zheng, B., *et al.* (2024) Treatment Patterns and Clinical Outcomes of Patients with Resectable Non-small Cell Lung Cancer Receiving Neoadjuvant Immunochemotherapy: A Large-Scale, Multicenter, Real-World Study (Neor-World). *The Journal of Thoracic and Cardiovascular Surgery*, **168**, 1245-1258.e17. https://doi.org/10.1016/j.jtcvs.2024.02.006

[26] Lee, J.M. (2024) Neoadjuvant, Perioperative, or Adjuvant Immunotherapy in Resectable Non-Small Cell Lung Cancer: How Do I Choose? Importance of Immune Biomarkers and Molecular Testing. *The Journal of Thoracic and Cardiovascular Surgery*, **168**, 1281-1288. https://doi.org/10.1016/j.jtcvs.2024.03.034

[27] Hansen, T., Hill, J., Tincknell, G., Siu, D., Brungs, D., Clingan, P., *et al.* (2024) Evidence for the Evolving Role of Neoadjuvant and Perioperative Immunotherapy in Resectable Non-Small Cell Lung Cancer. *Exploration of Targeted Anti-Tumor Therapy*, **5**, 1247-1260. https://doi.org/10.37349/etat.2024.00273

[28] Zhang, X., Zhu, Y., Zeng, Y., *et al.* (2023) Chemotherapy Combined with Immunotherapy and Recombinant Human Endostatin in the Treatment of Advanced Non-small Cell Lung Cancer: Efficacy and Safety Analysis. *Practical Journal of Medicine*, **39**, 2112-2115.

[29] Mazieres, J., Drilon, A., Lusque, A., Mhanna, L., Cortot, A.B., Mezquita, L., *et al.* (2019) Immune Checkpoint Inhibitors for Patients with Advanced Lung Cancer and Oncogenic Driver Alterations: Results from the IMMUNOTARGET Registry. *Annals of Oncology*, **30**, 1321-1328. https://doi.org/10.1093/annonc/mdz167

[30] Wu, Y., Herbst, R.S., Mann, H., Rukazenkov, Y., Marotti, M. and Tsuboi, M. (2018) ADAURA: Phase III, Double-Blind, Randomized Study of Osimertinib versus Placebo in EGFR Mutation-Positive Early-Stage NSCLC after Complete Surgical

Resection. *Clinical Lung Cancer*, **19**, e533-e536. https://doi.org/10.1016/j.cllc.2018.04.004

[31] Joensuu, H., Eriksson, M., Sundby Hall, K., Reichardt, A., Hermes, B., Schütte, J., *et al.* (2020) Survival Outcomes Associated with 3 Years vs 1 Year of Adjuvant Imatinib for Patients with High-Risk Gastrointestinal Stromal Tumors: An Analysis of a Randomized Clinical Trial after 10-Year Follow-Up. *JAMA Oncology*, **6**, Article No. 1241. https://doi.org/10.1001/jamaoncol.2020.2091

[32] Betticher, D.C., Hsu Schmitz, S., Tötsch, M., Hansen, E., Joss, C., von Briel, C., *et al.* (2006) Prognostic Factors Affecting Long-Term Outcomes in Patients with Resected Stage IIIA Pn2 Non-Small-Cell Lung Cancer: 5-Year Follow-Up of a Phase II Study. *British Journal of Cancer*, **94**, 1099-1106. https://doi.org/10.1038/sj.bjc.6603075

[33] Blumenthal, G.M., Bunn, P.A., Chaft, J.E., McCoach, C.E., Perez, E.A., Scagliotti, G.V., *et al.* (2018) Current Status and Future Perspectives on Neoadjuvant Therapy in Lung Cancer. *Journal of Thoracic Oncology*, **13**, 1818-1831. https://doi.org/10.1016/j.jtho.2018.09.017

[34] Chaudhuri, A.A., Chabon, J.J., Lovejoy, A.F., Newman, A.M., Stehr, H., Azad, T.D., *et al.* (2017) Early Detection of Molecular Residual Disease in Localized Lung Cancer by Circulating Tumor DNA Profiling. *Cancer Discovery*, **7**, 1394-1403. https://doi.org/10.1158/2159-8290.cd-17-0716

[35] Waldeck, S., Mitschke, J., Wiesemann, S., Rassner, M., Andrieux, G., Deuter, M., *et al.* (2021) Early Assessment of Circulating Tumor DNA after Curative-Intent Resection Predicts Tumor Recurrence in Early-Stage and Locally Advanced Non-Small-Cell Lung Cancer. *Molecular Oncology*, **16**, 527-537. https://doi.org/10.1002/1878-0261.13116

[36] Abbosh, C., Birkbak, N.J., Wilson, G.A., Jamal-Hanjani, M., Constantin, T., Salari, R., *et al.* (2017) Phylogenetic ctDNA Analysis Depicts Early-Stage Lung Cancer Evolution. *Nature*, **545**, 446-451. https://doi.org/10.1038/nature22364

[37] Liu, S., Erazo, T., Jee, J., Arfe, A., Gupta, A., Pike, L.R.G., *et al.* (2024) Optimal Systemic Treatment and Real-World Clinical Application of ctDNA in Patients with Metastatic Her2-Mutant Lung Cancer. *European Journal of Cancer*, **210**, Article ID: 114257. https://doi.org/10.1016/j.ejca.2024.114257

[38] Zhao, Z., Wang, J., Fang, L., Qian, X., Cai, Y., Cao, H., *et al.* (2022) Dual-Responsive Nanoparticles Loading Bevacizumab and Gefitinib for Molecular Targeted Therapy against Non-Small Cell Lung Cancer. *Acta Pharmacologica Sinica*, **44**, 244-254. https://doi.org/10.1038/s41401-022-00930-6

[39] Li, M.S.C., Mok, K.K.S. and Mok, T.S.K. (2023) Developments in Targeted Therapy & Immunotherapy—How Non-Small Cell Lung Cancer Management Will Change in the Next Decade: A Narrative Review. *Annals of Translational Medicine*, **11**, 358. https://doi.org/10.21037/atm-22-4444

[40] Liu, S., Zhang, J., Zeng, K. and Wu, Y. (2022) Perioperative Targeted Therapy for Oncogene-Driven NSCLC. *Lung Cancer*, **172**, 160-169. https://doi.org/10.1016/j.lungcan.2022.05.007

[41] Felip, E., Altorki, N., Zhou, C., Csőszi, T., Vynnychenko, I., Goloborodko, O., *et al.* (2021) Adjuvant Atezolizumab after Adjuvant Chemotherapy in Resected Stage IB-IIIA Non-Small-Cell Lung Cancer (impower010): A Randomised, Multicentre, Open-Label, Phase 3 Trial. *The Lancet*, **398**, 1344-1357. https://doi.org/10.1016/s0140-6736(21)02098-5

[42] Fury, M.G., Solit, D.B., Su, Y.B., Rosen, N., Sirotnak, F.M., Smith, R.P., *et al.* (2006) A Phase I Trial of Intermittent High-Dose Gefitinib and Fixed-Dose Docetaxel in

Patients with Advanced Solid Tumors. *Cancer Chemotherapy and Pharmacology*, **59**, 467-475. https://doi.org/10.1007/s00280-006-0286-6

[43] Han, Y., Xiao, X., Qin, T., Yao, S., Liu, X., Feng, Y., *et al.* (2024) Efficacy and Safety of Perioperative Immunotherapy Combinations for Resectable Non-Small Cell Lung Cancer: A Systematic Review and Network Meta-Analysis. *Cancer Immunology, Immunotherapy*, **73**, Article No. 262. https://doi.org/10.1007/s00262-024-03844-w

[44] Cortazar, P., Zhang, L., Untch, M., Mehta, K., Costantino, J.P., Wolmark, N., *et al.* (2014) Pathological Complete Response and Long-Term Clinical Benefit in Breast Cancer: The CTNeoBC Pooled Analysis. *The Lancet*, **384**, 164-172. https://doi.org/10.1016/s0140-6736(13)62422-8

[45] Kilickap, S., Demirci, U., Karadurmus, N., *et al.* (2018) Endpoints in Oncology Clinical Trials. *Journal of BUON*, **23**, S1-S6.

[46] Menzies, A.M., Amaria, R.N., Rozeman, E.A., Huang, A.C., Tetzlaff, M.T., van de Wiel, B.A., *et al.* (2021) Pathological Response and Survival with Neoadjuvant Therapy in Melanoma: A Pooled Analysis from the International Neoadjuvant Melanoma Consortium (INMC). *Nature Medicine*, **27**, 301-309. https://doi.org/10.1038/s41591-020-01188-3