Review Article

Redefining Lung Cancer Therapy — A Long-Awaited Shift in Strategy

Kenji Sato [1]*, Ayaka Suzuki [2]

1. Kyoto University Faculty of Medicine, Kyoto, Japan.
2. Tohoku University School of Medicine, Sendai, Japan.

* Correspondence: kenji.sato.jp@gmail.com

Abstract: Lung cancer has long been regarded as one of the most formidable challenges in oncology, characterized by its late-stage diagnosis, aggressive biology, and historically poor prognosis. Traditional therapeutic paradigms, dominated by cytotoxic chemotherapy and radiation, provided only modest improvements in survival while inflicting substantial toxicity. Over the last two decades, however, the field has undergone a paradigm shift, fueled by insights into tumor biology, advances in molecular diagnostics, and the rise of precision medicine. Targeted therapies and immune checkpoint inhibitors have redefined treatment landscapes, transforming subsets of lung cancer into chronic, manageable conditions. Moreover, the incorporation of next-generation sequencing, liquid biopsy technologies, and biomarker-driven clinical decision-making has ushered in an era of individualized therapy. This review article recent breakthroughs, examines the transformative impact of immunotherapy and molecularly targeted agents, and reflects on the promise and challenges of next-generation approaches such as cellular therapies, antibody–drug conjugates, and artificial intelligence–enabled treatment strategies. By critically analyzing the evidence and identifying ongoing gaps, this discussion underscores how lung cancer therapy is finally experiencing a long-awaited strategic redefinition, one that emphasizes precision, personalization, and survivorship.

Keywords: lung cancer, immunotherapy, targeted therapy, personalized medicine, biomarkers

1. INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality worldwide, accounting for approximately 1.8 million deaths annually. Despite advances in screening and awareness, the disease is often diagnosed at advanced stages, where curative interventions are limited [1]. For much of the 20th century, treatment revolved around surgery for localized disease and systemic chemotherapy or radiotherapy for advanced stages. These modalities, though occasionally effective, offered only incremental gains and were hampered by substantial toxicity [2]. Median survival for metastatic non-small cell lung cancer (NSCLC)—the most prevalent histological subtype—rarely exceeded one year in the pre-targeted therapy era. The past two decades have redefined this bleak narrative. With the discovery of oncogenic driver mutations, the development of targeted therapies, and the advent of immune checkpoint inhibitors (ICIs), lung cancer therapy has transitioned from a "one-size-fits-all" approach to an era of precision medicine [3]. Molecular stratification now guides frontline therapy, enabling tailored regimens that yield longer survival and improved quality of life. These editorial traces the historical trajectory of lung cancer treatment, explores the biological rationale underpinning modern therapies, examines real-world clinical outcomes, and discusses future strategies poised to further revolutionize the field [4].

2. HISTORICAL PARADIGM: CHEMOTHERAPY AND RADIATION

Chemotherapy and radiation therapy once defined the therapeutic standard. Platinum-based doublet chemotherapy—cisplatin or carboplatin combined with agents such as paclitaxel, gemcitabine, or vinorelbine—remained the backbone of treatment for decades. Though this approach modestly improved survival and palliation of symptoms, outcomes were limited [5]. Objective response rates hovered around 20–30%, and median overall survival rarely surpassed 12 months in metastatic NSCLC. Toxicities—including nephrotoxicity, myelosuppression, and neuropathy—further diminished patient quality of life. Radiation therapy, while curative in selected localized settings, was primarily used for palliation in advanced disease. Innovations such as stereotactic body radiotherapy (SBRT) have expanded its role in oligometastatic disease, but historically, radiation was constrained by collateral damage to normal lung tissue [6]. The limits of cytotoxic approaches underscored the urgent need for new strategies, setting the stage for a molecular revolution.

3. THE MOLECULAR REVOLUTION: TARGETED THERAPIES

The identification of driver mutations marked a turning point in lung cancer therapy. Genetic alterations such as epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) rearrangements, and ROS1 fusions were discovered to drive tumorigenesis in distinct subsets of NSCLC. These findings highlighted the heterogeneity of lung cancer and suggested that therapy could be guided by molecular characteristics rather than histology alone [7].

4. EGFR INHIBITORS

EGFR mutations, particularly exon 19 deletions and exon 21 L858R substitutions, occur in 10–15% of NSCLC cases in Western populations and up to 40% in East Asian patients. First-generation EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib demonstrated dramatic responses in patients with these mutations, often producing response rates above 70% and progression-free survival (PFS) of 9–12 months [8]. The development of resistance, commonly through the T790M mutation, spurred second- and third-generation TKIs like Osimertinib, which not only overcame resistance but also improved central nervous system penetration. The FLAURA trial established Osimertinib as the standard first-line therapy, with median overall survival exceeding 38 months, a remarkable improvement over chemotherapy [9].

5. ALK AND ROS1 REARRANGEMENTS

The discovery of ALK rearrangements further reshaped the therapeutic landscape. Crizotinib, the first ALK inhibitor, demonstrated unprecedented activity with response rates above 60% in ALK-positive patients. Resistance and central nervous system (CNS) progression, however, remained challenges [10]. Subsequent generations of ALK inhibitors—ceritinib, alectinib, brigatinib, and lorlatinib—offered improved potency and CNS activity, dramatically extending survival for this subgroup. Similarly, ROS1-positive patients, comprising about 1–2% of NSCLC, benefited from crizotinib and newer agents like entrectinib.

6. EXPANDING THE SPECTRUM OF TARGETED THERAPIES

Beyond EGFR, ALK, and ROS1, additional oncogenic drivers have emerged as therapeutic targets:

- BRAF V600E mutations, targeted by dabrafenib plus trametinib.
- MET exon 14 skipping mutations, treated with capmatinib and tepotinib.
- RET fusions, treated with selective RET inhibitors such as selpercatinib and pralsetinib.
- KRAS G12C mutations, historically "undruggable," now targetable with sotorasib and adagrasib.

The growing spectrum of targetable alterations underscores the necessity of comprehensive molecular testing at diagnosis, a practice that has become the foundation of modern NSCLC management.

7. IMMUNOTHERAPY: A PARADIGM SHIFT

While targeted therapies transformed outcomes for molecularly defined subsets, the introduction of immunotherapy redefined treatment for a broader population. Immune checkpoint inhibitors (ICIs), particularly those targeting programmed cell death-1 (PD-1) and programmed death-ligand 1 (PD-L1), have fundamentally altered the treatment of NSCLC [11].

8. PD-1/PD-L1 INHIBITORS

Clinical trials such as KEYNOTE-024 demonstrated that pembrolizumab, a PD-1 inhibitor, significantly improved survival compared with chemotherapy in patients with PD-L1 expression ≥50%. Median overall survival extended beyond 26 months, with a substantial proportion of patients achieving long-term remission [12]. Subsequent trials validated benefits even in patients with lower PD-L1 expression, particularly when ICIs were combined with chemotherapy. Nivolumab and atezolizumab further expanded options across treatment settings.

9. CTLA-4 AND COMBINATION STRATEGIES

Beyond PD-1/PD-L1, inhibition of cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) has shown synergy when combined with PD-1 blockade. The Check Mate 227 trial demonstrated that nivolumab plus ipilimumab improved overall survival compared to chemotherapy in advanced NSCLC, highlighting the potential of dual-checkpoint inhibition [13].

10. LONG-TERM SURVIVORS AND THE IMMUNOTHERAPY PLATEAU

Perhaps the most striking feature of immunotherapy is the emergence of a survival plateau. A subset of patients achieves durable responses lasting years, effectively transforming metastatic NSCLC into a chronic condition. This phenomenon, previously unimaginable in lung cancer, represents a true paradigm shift [14]. However, the challenge remains that only 20–30% of patients derive durable benefit, underscoring the need for predictive biomarkers and rational combination strategies.

11. INTEGRATION OF BIOMARKERS INTO CLINICAL DECISION-MAKING

The success of targeted therapies and immunotherapy has elevated the role of biomarkers in lung cancer management. PD-L1 expression serves as a biomarker for ICI eligibility, though its predictive accuracy is imperfect. Tumor mutational burden (TMB), microsatellite instability (MSI), and gene-expression signatures are under investigation as additional predictors of immunotherapy response [15]. Comprehensive genomic profiling via next-generation sequencing (NGS) has become indispensable, enabling identification of rare but actionable alterations. Liquid biopsies using circulating tumor DNA (ctDNA) provide minimally invasive tools for diagnosis, monitoring, and detection of resistance mutations, enhancing real-time treatment adaptation.

12. OVERCOMING RESISTANCE: A PERSISTENT CHALLENGE

Despite remarkable advances, resistance remains inevitable. For targeted therapies, secondary mutations, bypass signaling, and histologic transformation drive progression. Strategies to overcome resistance include:

- Next-generation inhibitors designed for specific resistance mutations.
- Combination therapies targeting multiple pathways simultaneously.
- Adaptive trial designs that allow rapid testing of new strategies as resistance mechanisms are uncovered.

In immunotherapy, primary resistance (lack of response) and acquired resistance (progression after initial benefit) pose challenges. Research is focused on combination regimens, novel checkpoint targets (e.g., LAG-3, TIGIT), and cellular therapies to extend immunotherapy's reach.

13. FUTURE HORIZONS IN LUNG CANCER THERAPY

ADCs represent a promising therapeutic class that links cytotoxic payloads to monoclonal antibodies targeting tumor-specific antigens. Agents such as trastuzumab deruxtecan (targeting HER2 mutations) and datopotamab deruxtecan (targeting TROP2) have demonstrated encouraging activity in NSCLC. By delivering potent cytotoxins directly to cancer cells, ADCs offer targeted efficacy with reduced systemic toxicity.Chimeric antigen receptor T-cell (CAR-T) therapy has transformed hematologic malignancies and is being explored in solid tumors, including lung cancer. Challenges such as the immunosuppressive tumor microenvironment, antigen heterogeneity, and toxicity remain barriers, but early trials show feasibility. AI-driven algorithms are being deployed to analyze radiologic imaging, pathology slides, and genomic datasets, facilitating earlier diagnosis, better risk stratification, and optimized treatment selection. Machine learning models may help predict resistance mechanisms and identify patients most likely to benefit from emerging therapies. Low-dose CT screening has improved early detection of lung cancer, enabling curative interventions in earlier stages. Future efforts integrating molecular biomarkers into screening programs may further enhance detection and reduce mortality.

14. THE PATIENT PERSPECTIVE: QUALITY OF LIFE AND SURVIVORSHIP

The redefinition of lung cancer therapy extends beyond survival statistics to encompass patient-reported outcomes and survivorship care. Targeted therapies and immunotherapies, while generally more tolerable than chemotherapy, present unique toxicity profiles—such as immune-related adverse events, dermatologic manifestations, and pulmonary toxicity. Long-term survivors now require comprehensive follow-up care that addresses physical, psychological, and social dimensions of health. Integrating palliative care, psychosocial support, and survivorship programs is crucial to ensuring holistic care.

15. GLOBAL AND EQUITY CONSIDERATIONS

While therapeutic advances are impressive, access disparities remain profound. High costs of targeted agents and immunotherapies limit availability in low- and middle-income countries. Molecular diagnostics, essential for precision medicine, are not universally accessible. Efforts to democratize access—through generic production, tiered pricing, and global clinical trials—are necessary to ensure that the redefined strategies benefit patients worldwide.

16. ETHICAL CONSIDERATIONS AND POLICY IMPLICATIONS

The rapid pace of innovation in lung cancer therapy raises ethical and policy questions. Should access to life-prolonging therapies depend on biomarker status when testing is unavailable? How should healthcare systems allocate resources to balance cost-effectiveness with equity? What safeguards are

needed to ensure transparency in industry-sponsored research and guideline development? Addressing these issues will be central to sustaining the progress made in lung cancer care.

17. CONCLUSION

Lung cancer therapy is undergoing a long-awaited redefinition, propelled by advances in molecular oncology, immunotherapy, and precision medicine. The transition from empiric cytotoxic regimens to biomarker-driven, personalized strategies has fundamentally changed the trajectory of the disease, offering unprecedented survival and quality of life improvements for subsets of patients. Yet challenges remain: resistance, cost, access, and the need for more durable, broadly effective therapies. The future of lung cancer care lies in continued integration of cutting-edge science with patient-centered, equitable, and ethically grounded approaches. If the momentum of recent years persists, lung cancer—once synonymous with therapeutic futility—may increasingly resemble a chronic, manageable disease, marking a profound and long-awaited shift in oncology.

REFERENCES

[1] Heigener, D. F., Kerr, K. M., Laing, G. M., Mok, T. S., Moiseyenko, F. V., & Reck, M. (2019). Redefining treatment paradigms in first-line advanced non–small-cell lung cancer. *Clinical Cancer Research*, *25*(16), 4881-4887.

[2] Michel Brown (2025). Inherited Mitochondrial Genetics as a Predictor of Immune Checkpoint Inhibition Efficacy in Melanoma: A Narrow Review. Journal of Medical Innovations, 4(07):489-497.

[3] Bertolaccini, L., Casiraghi, M., Mazzella, A., & Spaggiari, L. (2025). Redefining resectability: Bridging perspectives in stage III NSCLC management. *Lung Cancer*, *202*.

[4] Calvo, V. (2025). Redefining Lung Cancer Therapy—A Long-Awaited Shift in Strategy. *New England Journal of Medicine*, *393*(8), 809-810.

[5] Kemper, M., Reitnauer, L. E., Lenz, G., Evers, G., & Bleckmann, A. (2025). Redefining the Fight Against SCLC: Standards, Innovations, and New Horizons. *Cancers*, *17*(13), 2256.

[6] Pradhan, A., Pattnaik, G., Das, S., Acharya, B., & Patra, C. N. (2025). Advancements in lung cancer: molecular insights, innovative therapies, and future prospects. *Medical Oncology*, *42*(9), 383.

[7] de Matos, M. F., de Freitas, G. C., dos Santos, V. R. L., Lopes, A. C., Maior, F. F. S., Aquino, R. D. S. S., ... & Bedone, J. A. F. (2025). ADVANCES IN IMMUNE THERAPY: REDEFINING THE FUTURE OF CANCER CARE. *ARACÊ*, *7*(7).

[8] Noor Alam Ansari, Sanjay Prasad Sah, Susanta Kumar Paul, Pratik Wagley, Shamim Ahmed & Mohammed Atiqur Rahman (2025). Assessment of Vitamin D 25(OH)D Status in Patients with Tuberculous Pleural Effusion in a Tertiary Care Hospital: A Cross-Sectional Study. Dinkum Journal of Medical Innovations, 4(01):15-28.

[9] Zhong, R., Dong, J., Liang, H., & He, J. (2025). Redefining the role of surgery in advanced lung cancer: a new paradigm of adjuvant lung surgery to systemic therapy. *Translational Lung Cancer Research*, *14*(6), 1892.

[10] Gul, M. H., Wardak, A. B., & Waheed, A. Navigating a paradigm shift; food and drug administration approved Tarlatamab-dlle redefining the landscape of small cell lung cancer therapy.

[11] Doerr, F., Stange, S., Michel, M., Schlachtenberger, G., Menghesha, H., Wahlers, T., ... & Heldwein, M. B. (2022). Redefining the role of surgery in early small-cell lung cancer. *Langenbeck's Archives of Surgery*, *407*(7), 2663-2671.

[12] Go, S. I., Yang, J. W., Jeong, E. J., Lee, W. J., Park, S., Song, D. H., & Lee, G. W. (2024). Redefining YAP1 in small cell lung cancer: shifting from a dominant subtype marker to a favorable prognostic indicator. *Translational Lung Cancer Research*, *13*(8), 1768.

[13] Terrie D.Taylor (2025). Critical Analysis of the Phase 3 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis . Dinkum Journal of Medical Innovations, 4(02):63-68.

[14] Sagun Baral (2025). Evaluation of Predictors of Outcome in Patients with Tubercular Meningitis. Dinkum Journal of Medical Innovations, 4(03):81-103.

[15] Pakkala, S., & Ramalingam, S. S. (2018). Personalized therapy for lung cancer: striking a moving target. *JCI insight*, *3*(15), e120858.

