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RESEARCH BRIEF

Real-World Data Shows Stark Deviation From Standard of Care for Non-Small Cell Lung Cancer Patients

40% of Lung Cancer Patients With PD-L1 Expression and an EGFR Mutation Received Immunotherapy as a First-Line Treatment Against National Comprehensive Cancer Network (NCCN) Guidelines.

KEY FINDINGS:

- 40% of dual expressor patients were treated against NCCN guidelines by receiving a PD-L1 agent before an EGFR agent.
- Those patients treated in accordance with NCCN guidelines lived an average of 51 days longer than those treated against guidelines.
- Black patients were twice as likely as White patients to be treated against NCCN guidelines.

EXECUTIVE SUMMARY:

Immunotherapies such as PD-L1 inhibitors, which block the binding of key proteins to boost the human body's natural immune response to cancer cells, have revolutionized cancer care since the approval of pembrolizumab for melanoma in 2014. This breakthrough was hailed as an "entirely new principle for cancer therapy" when its seminal researchers, James P. Allison and Tasuku Honjo, were awarded the Nobel Prize in Medicine in 2018. Since then, the approach has spawned a tidal wave of drug development and inspired countless patients with the promise of an effective new weapon in the fight against cancer. Currently, PD-L1 immunotherapies are being used to treat 15 types of cancer.

Despite this amazing progress, however, the use of PD-L1 inhibitors is not recommended as the standard of care for all cancer patients. Notably, NCCN guidelines for lung cancer patients categorized as "dual expressors" — those who have the biomarker for an epidermal growth factor receptor (EGFR) mutation and PD-L1 expression — that patients should receive the appropriate targeted therapy first, and not immunotherapy.

John V. Heymach, MD, PhD, Chair of Thoracic/Head and Neck Medical Oncology at MD Anderson Cancer, recently explained this on an OncLive webcast. "As unequivocally as I can say it: First-line patients, no matter what their PD-L1 level is, if they have an EGFR/ALK alteration, they should get the appropriate targeted therapy first and not immunotherapy." The NCCN guidelines and Dr. Heymach's comments are informed by a 2019 study of 125 EGFR-mutated patients and a 2016 study of 58 EGFR-mutated patients. More recently, the 2023 AUDURA clinical trial highlighted the importance of treating EGFR-mutated patients with EGFR-targeted therapies, as patients who received osimertinib had a significantly higher survival rate than those who received a placebo.

According to our new real-world evidence (RWE) analysis of the healthcare journeys of approximately 520 dual expressor lung cancer patients, those guidelines are routinely not being followed in the real-world clinical setting. More than one-third of dual expressor lung cancer patients (40%) were treated against NCCN guidelines by receiving a PD-L1 agent before an EGFR agent. Moreover, our analysis found that patients treated in this manner died 51 days sooner, on average, after starting treatment than those whose treatment followed NCCN guidelines (310 days vs. 361 days).

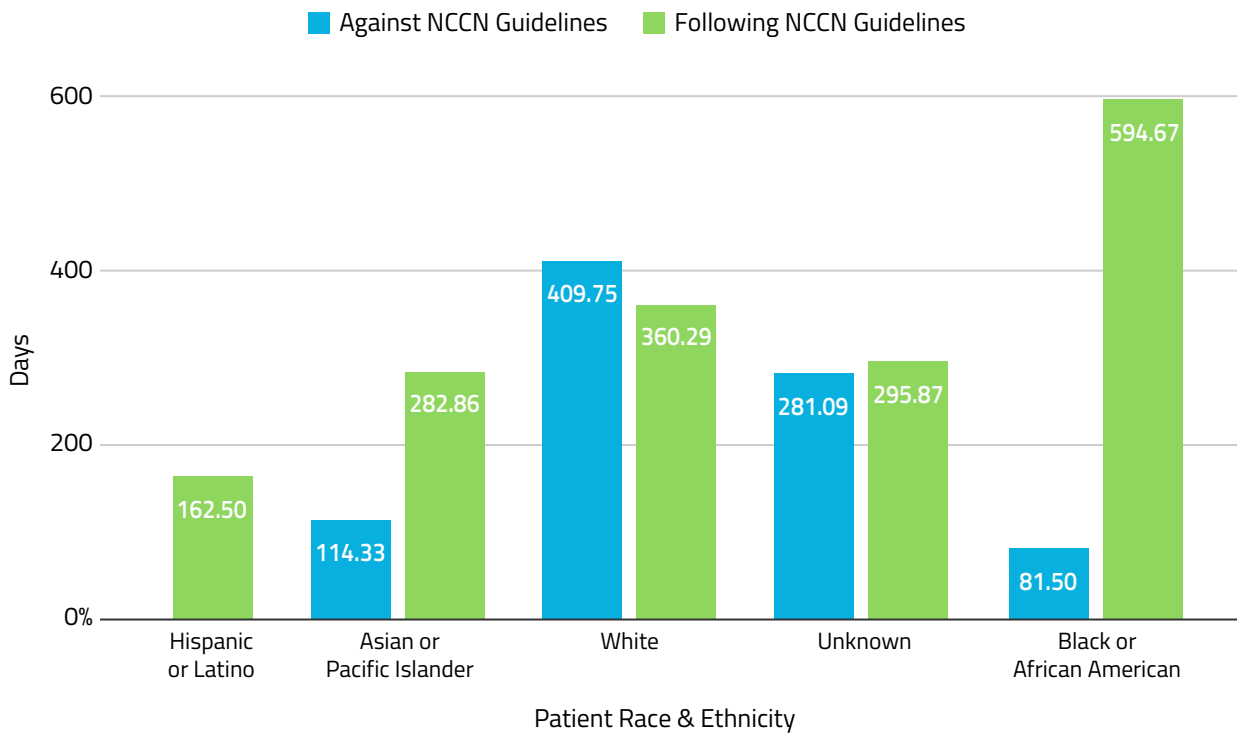
METHODOLOGY:

Using Komodo's Healthcare Map™ in combination with NeoGenomics Laboratories' genomic testing data, researchers identified over 3,400 dual expressor lung cancer patients (positive for an EGFR mutation and showing any level of PD-L1 expression) who had any history of being treated with either an EGFR and/or PD-L1 agent from November 2018 to December 2023. Of those, approximately 1,800 patients were first treated with an anti-EGFR or anti-PD-L1 agent on or after the date of being identified as a dual expressor. To allow for variability in the amount of time it took physicians to become aware of the final biomarker status, researchers focused on a subset of this patient population who received their first treatment of either a PD-L1 inhibitor or an EGFR-targeted agent at least 30 days after the treating physician received confirmation of dual-expressor status. We factored this in with the understanding that PD-L1 results are often received sometimes two to three weeks in advance of EGFR and/or NGS results. This group of approximately 520 patients was the foundation for the deeper analysis, which examined treatment types, race and ethnicity, insurance type, and mortality rates.

KEY FINDINGS:

- **40% of patients were treated against NCCN guidelines.** Of all dual-expressor patients who received treatment at least 30 days after finding an EGFR mutation and any expression of PDL1, 40% were treated against NCCN guidelines by receiving a PD-L1 agent before an EGFR agent.
- **Patients treated in accordance with NCCN guidelines live longer.** Of the approximately 140 patients with available mortality data, 54% were treated following NCCN guidelines and 46% were treated against NCCN guidelines. On average, those patients treated in accordance with guidelines lived an average of 51 days longer than those treated against guidelines.

PATIENT MORTALITY BY RACE

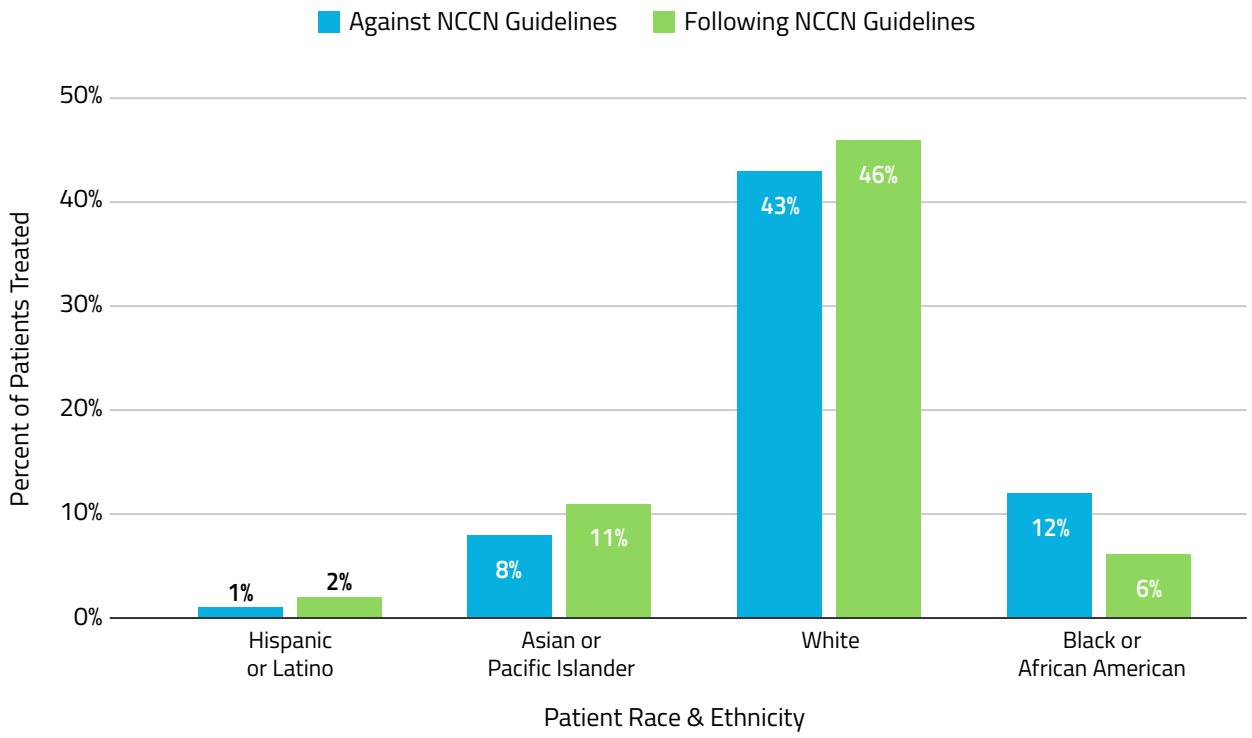


It's important to note that, although this analysis is one of the largest, if not *the* largest, conducted on this topic, the sample size for mortality data could influence the outcomes.

Patients With Mortality Data	Followed NCCN Guidelines	Did Not Follow NCCN Guidelines
White	45	32
Unknown/Other	19	23
Asian or Pacific Islander	7	6
Black or African American	3	6
Hispanic or Latino	2	0

- **Black patients were twice as likely to be treated against guidelines as compared with White patients.** Among patients treated against NCCN guidelines, 43% were White, 12% were Black, 8% were Asian or Pacific Islander, and 1% were Hispanic. Among those treated following NCCN guidelines, 46% were White, 6% were Black, 11% were Asian or Pacific Islander, and 2% were Hispanic.

FREQUENCY OF GUIDELINE-CONCORDANT CARE BY PATIENT RACE



- **Determinants such as HCO type, payer type, site of care, or age showed no significant influence on the course of treatment.** The analysis also screened results by insurance payer type, age, and center of care but found no significant variation.

DISCUSSION:

The findings of this analysis raise several important questions about the standard of care for lung cancer patients who have the EGFR mutation and PD-L1 expression. Chief among them is that such a significant proportion of NSCLC patients are receiving treatment that is directly counter to well-established guidelines. While further research is required — and warranted — to determine potential causes for this breach in the standard of care, there are some essential variables to consider that could be playing a role in this trend.

It is important to consider the reimbursement mechanisms associated with PD-L1 immunotherapies versus EGFR agents. EGFR drugs are typically covered by the patient's prescription drug benefit, while PD-L1 therapies generally are reimbursed through the patient's medical benefit. Each of these involves distinct processes for securing prior authorization, and each

comes with notably different reimbursement rates. Physician reimbursement for PD-L1 immunotherapy is significantly higher than the standard EGFR reimbursement rate. A combination of ease of reimbursement, financial incentive, and potential lack of understanding about how to treat dual expressors, may provide misaligned incentives for how these patients are being treated.

Additionally, it is important to acknowledge the increase in overall consumer awareness of PD-L1 immunotherapies over the past few years with the proliferation of direct-to-consumer (DTC) advertising campaigns. According to a recent study published in the *Journal of the American Medical Association*, immunomodulating agents were the top-advertised drugs between 2015 and 2021, accounting for a total of 31% of all DTC drug advertising in that period. Patients are asking their providers about immunotherapy options, which may be driving demand. It is possible that mainstream consumer awareness of PD-L1 immunotherapies is greater than provider awareness of the guidelines for treating dual expressor patients.

The entire field of PD-L1 immunotherapy treatment is rapidly advancing and expanding, and new studies are being published frequently. For example, a 2021 study published in *The Oncologist* found that Black patients may experience better outcomes with PD-L1 therapies. While this research did not account for dual-biomarker status, it could help explain why Black patients are receiving PD-L1 treatments against guidelines at a greater frequency than White patients. It is clear that there remains a lack of proper understanding of the most effective treatments in this population. Additional education among physicians, especially community-based physicians, could benefit and improve patient care and outcomes.

Individual patient-specific variables, such as specific PD-L1 expression levels, disease stage at diagnosis, patient medical history, and response to previous treatments, could all play roles in the specific course of treatment chosen. This analysis represents a first step in using RWE to identify potential gaps in care. Further research is necessary to understand why those gaps are emerging and the detailed outcomes associated with those examples.

The landscape of medicine, particularly in oncology, thrives on complexity and individuality. By marrying the patient journey with the intricate details of a patient's genomic profile, a fuller picture emerges— one that provides the insights necessary to build personalized medicine at scale and, ultimately, help reduce the burden of disease.

AUTHORS:

Scott Phillips, Vice President, Data Strategy, Komodo Health

Lindsey Gasparini, Vice President, Informatics, NeoGenomics

About Komodo Health

Komodo Health is a technology platform company creating the new standard for real-world data and analytics by pairing the industry's most complete view of patient encounters with enterprise software and machine learning to connect the dots between individual patient journeys and large-scale health outcomes. Across Life Sciences, payers, providers, and developers, Komodo helps its customers unearth patient-centric insights at scale — marrying clinical data with advanced algorithms and AI-powered software solutions to inform decision-making, close gaps in care, address disease burden, and help enterprises create a more cost-effective, value-driven healthcare system. For more information, visit Komodohealth.com.

About NeoGenomics, Inc:

NeoGenomics, Inc. specializes in cancer genetics testing and information services, providing one of the most comprehensive oncology-focused testing menus for physicians to help them diagnose and treat cancer. The Company's Advanced Diagnostics Division serves pharmaceutical clients in clinical trials and drug development.

Headquartered in Fort Myers, FL, NeoGenomics operates CAP accredited and CLIA certified laboratories for full-service sample processing in Fort Myers, Florida; Aliso Viejo and San Diego, California; Research Triangle Park, North Carolina; and Houston, Texas; and a CAP accredited full-service, sample-processing laboratory in Cambridge, United Kingdom. NeoGenomics also has several, small, non-processing laboratory locations across the United States for providing analysis services. NeoGenomics serves the needs of pathologists, oncologists, academic centers, hospital systems, pharmaceutical firms, integrated service delivery networks, and managed care organizations throughout the United States, and pharmaceutical firms in Europe and Asia.