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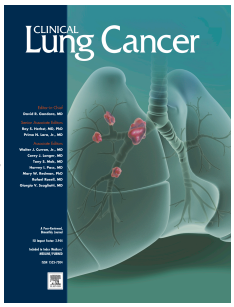

Evolution and Increasing Complexity of the Therapeutic Landscape in Advanced Non-Small Cell Lung Cancer

D.R. Gandara, J.W. Riess, K. Kelly, T. Li, P.C. Mack, P.N. Lara

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Perspective

Evolution and Increasing Complexity of the Therapeutic Landscape in Advanced Non-Small Cell Lung Cancer

D. R. Gandara[1], J. W. Riess[1], K. Kelly[1], T. Li[1], P. C. Mack[1], P. N. Lara[1]

[1]University of California Davis Comprehensive Cancer Center, Sacramento, CA

Periodically, clinical trials data emerge which alter standards of care and change the decision-making process within a given tumor type. Such advances led us to propose an overall treatment algorithm in 2009 to account for histology- and oncogene-related advances in the therapeutic strategy toward advanced non-small cell lung cancer (NSCLC). (1) For the vast majority of patients, platinum doublet chemotherapy remained the standard of care, as it had been for over a decade. (2, 3) Distinctions within the algorithm in 2009 were largely reflective of contraindications, such as those for pemetrexed and bevacizumab in squamous lung cancer or enrichment strategies, such as those for 1st-line therapy with epidermal growth factor receptor (EGFR)-directed tyrosine kinase inhibitors (TKIs) for EGFR-mutated cancers. (4, 5)

Remarkably, there have been a series of rapid and dramatic transformations in this therapeutic landscape since that time. Never in the history of oncology have so many changes of such magnitude occurred at such a rapid pace as those witnessed over the last 2 years. Advances from 2014 to date highlight the recognition that NSCLC represents a multitude of different malignancies, defined not only by tumor histologic subtype and genomic makeup, but also now by the interaction of these factors with tumor immunophenotype. (6, 7) The therapeutic implications of these findings cannot be over-emphasized, as they increasingly provide a rationale and pathway toward personalizing therapy between one patient and the next.

By 2014 (Figure 1), treatment paradigms for advanced NSCLC were increasingly distinguished by histologic subtype and the presence of oncogenic drivers such as EGFR mutation and anaplastic lymphoma kinase (ALK) translocation. (8, 9) Within each of these categories, the practicing oncologist could draw upon evidence-based medicine to determine the most appropriate approach in 1st-line, 2nd-line and 3rd-line therapy. Maintenance therapy strategies, using pemetrexed with or without bevacizumab or with erlotinib, became acceptable therapeutic options. (10, 11) So-called second generation TKIs in EGFR-mutated cancers (afatinib) and ALK-translocated cancers (ceritinib) were in use. (12, 13) Regardless, platinum-based combination chemotherapy remained the best 1st-line option for most patients.

In stark contrast, the proposed treatment paradigm for 2016-2017 (Figure 2) is dramatically more complex, accounting for new drugs, including third generation TKIs in the oncogene-driven subtypes, a new EGFR monoclonal antibody-chemotherapy combination, a new anti-angiogenic agent-chemotherapy regimen, integration of a new EGFR TKI in squamous cancers, and new drug classes, most prominently the checkpoint immunotherapies directed against PD-1 and PD-L1. To briefly summarize changes within the last year or so, necitumumab plus gemcitabine-cisplatin became the first addition to