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Title

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Permalink

https://escholarship.org/uc/item/0ng648xh

Journal

Clinical lung cancer, 18(1)

ISSN

1525-7304

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Publication Date

2017

DOI

10.1016/j.cllc.2016.12.011

Peer reviewed

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

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Abstract

The therapeutic landscape in advanced non−small-cell lung cancer (NSCLC) is rapidly changing. Never have so many changes of major importance occurred within so short a time. The present perspective describes this rapid evolution and resultant increasing complexity in the therapeutic decision-making process for the practicing oncologist.

Periodically, clinical trials data emerge that alter the 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 the histologic- 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, just as it had been for > 1 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 first-line therapy with epidermal growth factor receptor (EGFR)-directed tyrosine kinase inhibitors (TKIs) for EGFR-mutated cancer.[4,5]

Remarkably, a series of rapid and dramatic transformations have occurred in this therapeutic landscape since 2009. Never in the history of oncology have so many changes of such magnitude occurred at such a rapid pace as those witnessed during the past 2 years. Advances from 2014 to 2016 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 overemphasized, because they increasingly provide a rationale and
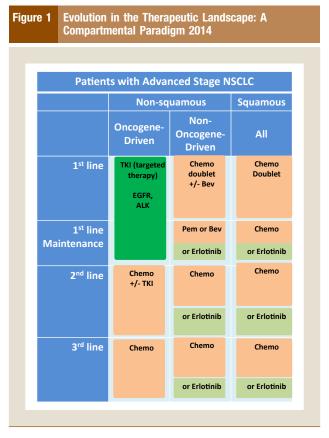
pathway toward personalizing therapy between 1 patient and the next.

By 2014 (Figure 1), the 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 on evidence-based medicine to determine the most appropriate approach for first-, second-, and third-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 first-line option for most patients.

In stark contrast, the proposed treatment paradigm for 2016 to 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 antiangiogenic agent−chemotherapy regimen, integration of a new EGFR TKI for squamous cancers, and new drug classes, most prominently the checkpoint immunotherapies directed against programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1). To briefly summarize the changes within the past year or so, necitumumab plus gemcitabine−cisplatin became the first addition to the therapeutic armamentarium in first-line therapy for squamous lung cancer in 15 years.[14] In actionable oncogene-driven lung cancer, new-generation agents were approved in EGFR-mutated (osimertinib), ALK-positive (alectinib), and ROS-1 positive (crizotinib) NSCLC subsets.[15-17] In the second-line

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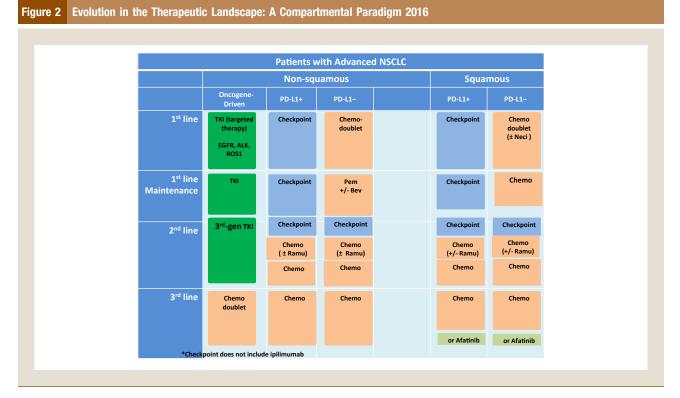E-mail contact: drgandara@ucdavis.edu

Figure 1 Evolution in the Therapeutic Landscape: A Compartmental Paradigm 2014

Abbreviations: ALK = anaplastic lymphoma kinase; Bev = bevacizumab; Chemo = chemotherapy; EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor.

setting, the antiangiogenic agent ramicirumab plus docetaxel proved superior to docetaxel alone in both nonsquamous and squamous histologic type lung cancers.[18] Additionally, the pan-HER-targeted EGFR inhibitor afatinib was shown to result in superior progression-free survival and overall survival compared with erlotinib in squamous cancers in the second- and third-line settings.[19] Of note, subtractions, as well as additions, occurred, with regulatory approval removed for erlotinib for patients with wild-type EGFR-expressing cancer, despite previous landmark phase III trials demonstrating an overall survival benefit for both adenocarcinoma and squamous histologic type subsets, with a hazard ratio of 0.71 and 066, respectively.[20]

However, it is the new drug class of PD-1/PD-L1 therapies in which the most profound advances were made, sometimes reemphasizing long held distinctions such as histologic subtype and in other cases blurring such distinctions (Table 1). A case in point can be made for the second-line approval of nivolumab by the Food and Drug Administration without a requirement for biomarker selection by PD-L1 status for both squamous and nonsquamous cancers using an "all comer strategy," despite embedded retrospective analyses in those studies showing major differences between these histologic subtypes.[21,22] Since then, both pembrolizumab and atezolizumab have gained approval within this clinical setting, each using a "biomarker-positive" strategy, albeit with different PD-L1 assay approaches and also varying in the definition and importance of PD-L1 positivity.[23,24] These complexities have left the practicing oncologist to decide who to test, how to test, or even whether to test when using these agents to treat patients with NSCLC previously treated with platinum-based therapy.

Figure 2 Evolution in the Therapeutic Landscape: A Compartmental Paradigm 2016

Abbreviations: ALK = anaplastic lymphoma kinase; Bev = bevacizumab; Checkpoint = checkpoint immunotherapy against PD-1/PD-L1; Chemo = chemotherapy; EGFR = epidermal growth factor receptor; Neci = necitumumab; Ramu = ramucirumab; ROS1 = ROS proto-oncogene 1; TKI = tyrosine kinase inhibitor.

Table 1 Phase III Trials of PD-1/PD-L1 Agents for Advanced NSCLC

Trial	Line of Therapy	Study Design	Patients (n)	Drug Comparison	Primary Endpoint	Outcome
CHECKMATE-017[21]	Second	All comers	272	Nivolumab vs. docetaxel	OS	Positive; HR, 0.59 (95% CI, 0.44-0.79); $P < .001$
CHECKMATE-057[22]	Second	All comers	582	Nivolumab vs. docetaxel	OS	Positive; HR, 0.73 (95% CI, 0.59-0.89); $P = .002$
KEYNOTE-010[23]	Second	Biomarker driven	1034	Pembrolizumab vs. docetaxel	OS	Positive; HR, 0.71 (95% CI, 0.58-0.88); $P = .0008$
OAK[24]	Second	Biomarker driven	850	Atezolizumab vs. docetaxel	OS	Positive; HR, 0.73 (95% CI, 0.62-0.87); $P = .0003$
KEYNOTE-024[25]	First	Biomarker driven	305	Pembrolizumab vs. platinum doublet	PFS	Positive; HR, 0.50 (95% CI, 0.37-0.68); $P < .001$
CHECKMATE-026[26]	First	Biomarker driven	541	Nivolumab vs. platinum doublet	PFS	Negative; HR, 1.15 (95% CI, 0.91-1.45); $P = .2511$

Abbreviations: CI = confidence interval; HR = hazard ratio; NSCLC = non—small-cell lung cancer; OS = overall survival; PD-1 = programmed cell death 1; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival.

The last change, and the most transformative, is the recent publication of KEYNOTE-024, demonstrating increased progression-free survival and overall survival for patients with advanced NSCLC expressing a high PD-L1 level of ≥ 50% when treated with pembrolizumab versus platinum doublet chemotherapy.[25] That a trial of similar design in the first-line setting with nivolumab, CHECKMATE-026, resulted in completely negative findings creates even more confusion about when and how to test for PD-L1 status.[26] With the recent approval of pembrolizumab in the first-line setting for patients with cancer expressing ≥ 50% PD-L1, it is increasingly likely that all NSCLC patients with advanced-stage disease will be tested at baseline, using the 22C3 assay used in KEYNOTE-024. For this positive subset, representing about 30% of NSCLC patients, pembrolizumab constitutes a new standard of care, replacing platinum doublet chemotherapy. However, which PD-L1 test, if any, to use and what level of positivity is indicative of likely benefit when treating with nivolumab or atezolizumab in the second-line setting remains unsettled.

A few additional points regarding other uncertainties are worthy of comment. It is notable that in every phase III trial of a PD-1 agent described in previous paragraphs, patients with cancers harboring EGFR mutations, or even never-smoking patients without a known EGFR mutation or ALK fusion, have uniformly fared poorly with these checkpoint immunotherapies, as demonstrated by hazard ratios of ≥ 1 compared with chemotherapy. These cancers in never-smoking patients, absent tobacco carcinogenesis, likely have a lower mutational burden and lower levels of neo-antigenicity, both plausible explanations for this phenomenon. The one possible exception to date for this finding is the recently reported OAK trial of atezolizumab versus docetaxel, in which a favorable hazard ratio was observed in never-smoking patients. It is intriguing to postulate that, in contrast to PD-1 agents, atezolizumab, the first PD-L1 targeted agent approved for NSCLC, might be capable of stimulating immunogenicity by virtue of its dual effects on B7-1.[27] Atezolizumab blocks the interaction of PD-L1 with PD-1 and B7-1 (CD80), potentially augmenting tumor-specific T-cell immunity and contributing to the therapeutic response in a patient population with a low mutational load, such as never-smokers with lung cancer. One other topic of future interest is whether a patent benefit exists for continuing treatment with checkpoint immuno-therapy after determination of progressive disease, because other issues are pertinent, such as determining the optimal dose schedule and the duration of therapy. For those patients whose tumors have low to absent PD-L1 expression and no identified oncogenic driver in the frontline setting, cytotoxic chemotherapy remains the treatment of choice, by default.

Finally, how to combine PD-1/PD-L1 agents with other drug classes is an area of intense research focus. Whether checkpoint immunotherapy should be given concurrently with chemotherapy or targeted therapies, or sequenced before or after, remains unclear. The study of immunotherapy combinations of PD-1/PD-L1 agents with drugs targeting CTLA-4 is already well underway, having been proved successful in melanoma therapy.[28] Immunotherapy agonist—antagonist combinations or priming strategies to make cancers more responsive to immunotherapy are critical for diversification of the therapeutic armamentarium. Thus, although the 2016 to 2017 paradigm we have presented represents the current state of affairs in the therapy for advanced-stage NSCLC, for all the reasons described, it is likely to continue to evolve, in both the short and the long term, as new studies are completed and new preclinical data help to explain the underlying biology beneath the clinical outcomes observed.

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