

How I Treat Stage IV Non–Small Cell Lung Cancer in the Absence of Any Actionable Oncogenic Driver



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Overview

- Testing for several genetic alterations as well as programmed death ligand 1 (PD-L1) expression is paramount in the management of advanced, metastatic non–small cell lung cancer.
- Immunotherapy is the standard of care for patients with high PD-L1 expression.
- Platinum-based doublets remain the standard of care in the majority of patients.
- Bevacizumab is appropriate in selected patients with nonsquamous histology.
- Consider the use of necitumumab plus cisplatin/gemcitabine in selected patients with squamous histology.
- Pembrolizumab added to chemotherapy is an option for selected patients but the role of this approach will be defined in ongoing phase 3 trials.
- Maintenance therapy is an option but not a mandate.

Introduction

Non–small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality in the United States.¹ NSCLC is a heterogeneous disease that comprises 2 main histologic subtypes: adenocarcinoma and squamous cell carcinoma.² Most commonly, patients have stage IV disease at the time of diagnosis. Stage IV NSCLC is considered treatable in patients who retain a good performance status, but it is not considered curable.

The management of stage IV NSCLC has become increasingly complex over the last decade for 2 main reasons. The first is the discovery of several oncogenic drivers that most often occur in patients with adenocarcinoma;

targeted therapies are used in place of standard platinum-based therapies in these patients.³ The second is the establishment of immunotherapy as superior to platinum-based therapies in patients whose tumors stain intensely for programmed death ligand 1 (PD-L1).⁴ The discussion that follows focuses on my approach to the first-line management of stage IV NSCLC in the absence of actionable oncogenic molecular alterations.

Initial Evaluation: Staging and Diagnosis

Accurate staging at the time of diagnosis is critically important. The details of the appropriate staging evaluation vary depending on the patient's initial presentation. The initial diagnostic test should be dedicated computed tomography (CT) of the chest and abdomen. If the initial CT evaluation suggests stage IV disease (eg, presence of liver metastases or bilateral lung nodules) or bone metastases are suspected, additional testing may include a bone scan. Positron emission tomography (PET) may be useful for staging but is not necessary in all cases. If the initial CT evaluation suggests that the stage of disease is less advanced than stage IV, PET can be very helpful in identifying the cases that actually are stage IV. Also, PET is more sensitive than standard technetium scanning for detecting bone metastases.⁵

Evaluation of the brain is also important—particularly in patients with known adenocarcinoma histology, in whom brain metastases are significantly more frequent than in patients with squamous histology.⁶ Magnetic resonance imaging (MRI) is the standard for evaluating suspected brain metastases. After the initial chest/abdominal CT, the staging evaluation I do most commonly includes PET/CT and brain MRI.

It should be noted that diagnostic biopsies should also confirm stage IV disease when possible. Bone biopsies should be avoided, however, owing to the requirement for decalcification, which makes molecular testing unreliable.

A final point is the importance of confirming stage IV disease when a solitary site of metastatic disease is detected outside the chest. Up to half of these solitary lesions represent a process different from NSCLC, which will obviously change the patient's management.

A monumental change has taken place in the approach to the diagnosis of NSCLC when stage IV disease is suspected. Two decades ago, the only information needed from the initial diagnostic biopsy was a confirmation of lung cancer and the differentiation of NSCLC from the less-common small cell lung carcinoma (SCLC). This information was most often obtained with fine-needle aspiration (FNA) of the most accessible site of metastasis. Pathologists diagnosed lung cancer and differentiated NSCLC from SCLC with a high degree of confidence in almost all cases.⁷

With the discoveries of a growing list of actionable genotypes in NSCLC and the need to establish the PD-L1 status of the tumor, the amount of tissue and the nature and quality of the tissue required have changed dramatically. PD-L1 immunohistochemistry (IHC) testing has been validated only on core biopsy specimens, not on FNA specimens. In my practice, the interventional radiologists, pulmonologists, and thoracic surgeons all know to obtain core biopsy specimens as well as FNA specimens whenever possible. In this way, enough tissue is available for both PD-L1 staining and molecular testing. The genetic alterations I believe clinicians should test for in the initial evaluation of patients with stage IV NSCLC are listed in Table 1. I believe it is necessary to obtain this information from every patient in whom stage IV adenocarcinoma is diagnosed and from selected patients with squamous cell carcinoma (ie, never smokers or former light smokers, patients whose tumors are of uncertain or mixed histology, and patients whose biopsy specimens are small). A detailed review of the tissue requirements is beyond the scope of this discussion. As noted earlier, we focus here on those patients who have been adequately evaluated for a molecular alteration but have not been found to have one.

Immunotherapy as First-Line Treatment for Stage IV NSCLC

The results of KEYNOTE-024 (Study of Pembrolizumab Compared to Platinum-Based Chemotherapies in Participants With Metastatic Non-Small Cell Lung Cancer) changed the management of stage IV NSCLC,⁴ as well as the diagnostic evaluation (Table 2). This phase 3 trial selected patients whose tumors had a PD-L1 tumor proportion score (TPS) of at least 50% and randomly assigned them to either standard platinum-based doublet chemotherapy or single-agent pembrolizumab (Keytruda,

Table 1. Oncogenic Drivers That Should Be Included in Molecular and IHC Testing in Stage IV NSCLC at the Time of Initial Diagnosis

Adenocarcinoma
• <i>EGFR</i> mutations
• <i>ALK</i> translocations
• <i>ROS1</i> translocations
• <i>BRAF</i> mutations
• <i>MET</i> alterations (high-level amplification, exon 14 skip mutations)
• <i>RET</i> translocations
• <i>HER2</i> alterations (high-level amplification, mutations)
• <i>KRAS</i> mutations
• Elevated PD-L1 expression
Squamous Cell Carcinoma ^a
• Elevated PD-L1 expression

IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1.

^aPatients with squamous histology should be assessed with the same panel of molecular markers if they have a history of never or light smoking, if they have a mixed histology, or if there is uncertainty about the histologic diagnosis (eg, a small biopsy specimen).

Merck). The primary endpoint was progression-free survival (PFS). A total of 1934 patients were enrolled or screened, but only 305 (15.8%) were randomized. The trial met its endpoint, with a significant improvement in PFS for pembrolizumab vs platinum-based chemotherapy (10.3 vs 6.0 months; hazard ratio [HR], 0.50; $P < .001$). The overall response rate (ORR) was 45% for pembrolizumab vs 28% for chemotherapy ($P < .0011$). Overall survival (OS) also favored pembrolizumab (HR, 0.60; $P = .005$). No unexpected toxicities were noted in this trial, and in general, the side effect profile reported favored pembrolizumab. These results instantly changed the standard of care in this setting.

A second trial, CheckMate 026 (An Open-Label, Randomized, Phase 3 Trial of Nivolumab Versus Investigator's Choice Chemotherapy as First-Line Therapy for Stage IV or Recurrent PD-L1+ Non-Small Cell Lung Cancer), compared nivolumab (Opdivo, Bristol-Myers Squibb) with platinum-based chemotherapy; the trial design was similar to that of KEYNOTE-024, but with a very different selection strategy (Table 2).⁸ This trial enrolled patients whose PD-L1 expression was at least 1%. However, the primary endpoint—PFS—was evaluated in a population whose PD-L1 expression was at least 5%. (It should be noted that these 2 trials used different antibodies for PD-L1 testing: PD-L1 IHC 22C3

Table 2. Randomized Trials Evaluating Anti-PD-1/Anti-PD-L1 Antibodies in the First-Line Treatment of Advanced NSCLC

Parameter	Trials		
	KEYNOTE-024 ⁴	CheckMate 026 ⁸	KEYNOTE-021 (Cohort G) ⁹
Inclusion criterion	≥50% PD-L1+	≥1% PD-L1+	All comers
No. of patients	305	541	123
Comparison	Pembrolizumab vs chemotherapy	Nivolumab vs chemotherapy	Chemotherapy ± pembrolizumab
Phase	3	3	2
Primary endpoint	PFS	PFS	ORR
ORR, %	44.8 vs 27.8	26 vs 33	55 vs 29
PFS, mo	10.3 vs 6.0 (HR, 0.50; <i>P</i> <.001)	4.2 vs 5.9 (HR, 1.15; <i>P</i> =0.25)	13.0 vs 8.9 (HR, 0.53; <i>P</i> =.01)
OS, mo	NR (HR, 0.60; <i>P</i> =.005)	14.4 vs 13.2 (HR, 1.02; <i>P</i> =NS)	<i>P</i> =NS

HR, hazard ratio; mo, month(s); NR, not reached; NS, not significant; ORR, overall response rate; OS, overall survival; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PFS, progression-free survival.

Sources: Reck M et al. *N Engl J Med.* 2016;375(19):1823-1833⁴; Carbone DP et al. *N Engl J Med.* 2017;376(25):2415-2426⁸; Langer CJ et al. *Lancet Oncol.* 2016;17(11):1497-1508⁹.

pharmDx (Dako) in KEYNOTE-024 and PD-L1 IHC 28-8 (Dako) in CheckMate 026.) CheckMate 026 did not meet its endpoint, nor did it show any significant differences in ORR or OS.

These 2 trials of similar design but different selection criteria led to 2 different results. Imbalances in known prognostic baseline patient characteristics in CheckMate 026 seemingly favored the chemotherapy arm (ie, more female patients, fewer patients with liver metastases, and a higher percentage of patients with tumors strongly positive for PD-L1), complicating the interpretation of the trial data. Nevertheless, the results of KEYNOTE-024 clearly changed the standard of care for the minority of patients with strong PD-L1 positivity (TPS ≥50% with the 22C3 antibody), mandating the practice of obtaining the PD-L1 IHC status of all patients.

Recently, the US Food and Drug Administration (FDA) granted accelerated approval to pembrolizumab in combination with carboplatin/pemetrexed (Alimta, Lilly; CbPemx) in nonsquamous NSCLC regardless of the patient's PD-L1 status.⁹ This was based on the data from cohort G of KEYNOTE-021 (A Study of Pembrolizumab in Combination With Chemotherapy or Immunotherapy in Participants With Lung Cancer), which was a randomized phase 2 trial in which 123 patients were randomly assigned to CbPemx alone or in combination with pembrolizumab (Table 2). The primary endpoint of this trial was ORR. The triplet combination showed an ORR of 55% vs 29% for CbPemx (*P*=.0016). There was also a benefit in PFS (13.0 months for the triplet combination vs 8.9 months for CbPemx; HR, 0.53; *P*=.01) but no difference in OS. Toxicity that was

mostly grade 1 to 2 and consisted of fatigue, rash, and gastrointestinal side effects was increased with the triplet combination. Immune-related toxicities were as expected and consisted largely of thyroid dysfunction, pneumonitis, and skin disorders.

In my practice, I have not fully adopted the strategy of using pembrolizumab plus CbPemx given that KEYNOTE-021 was a small phase 2 trial with no OS benefit. Multiple phase 3 trials are ongoing that will define the role of combining immunotherapy agents with standard platinum-based doublets. For now, I think this combination is an option for highly selected patients but do not see it as the standard of care in all eligible patients.

Selection of Chemotherapy Doublets in the First-Line Setting

Historically, all platinum-based doublets were felt to lead to similar outcomes.¹⁰ This idea changed with the trial conducted by Scagliotti and colleagues (Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients With Advanced-Stage Non-Small-Cell Lung Cancer),¹¹ in which cisplatin/pemetrexed (CsPemx) was compared with cisplatin/gemcitabine (CsGem) in advanced NSCLC. This was a randomized phase 3 trial comparing the 2 doublets in 1725 patients with stage IV NSCLC. The trial had a noninferiority design, with OS as the primary endpoint. The trial met its endpoint, showing a median OS time of 10.3 months for both arms (HR, 0.94; *P*=not significant). A prespecified analysis based on histology was included in this trial owing

to the hypothesis that the activity of pemetrexed may vary according to the expression of thymidylate synthase, which differs between squamous vs nonsquamous histology.¹² In patients who had nonsquamous NSCLC, the OS was better with CsPemx than with CsGem (median OS, 12.6 months for CsPemx vs 10.9 months for CsGem; HR, 0.81, $P < .05$). Conversely, in patients who had squamous histology, the OS favored CsGem compared with CsPemx (median OS, 10.8 months for CsGem vs 9.4 months for CsPemx; HR, 1.23).

This trial influenced the FDA and led to an indication for CsPemx only in patients with nonsquamous NSCLC. The real lesson of this trial, in my view, is that CsPemx should not be used in patients with squamous histology. It should be remembered that although this trial used CsGem as the control arm, this does not mean that CsGem is the standard for patients with squamous histology. Taxanes are commonly used in this setting and are my preferred agents for patients with squamous histology.¹³ The same is true for patients with nonsquamous NSCLC, in whom taxane-based regimens remain perfectly appropriate rather than the platinum/pemetrexed combination (see later discussion of the PointBreak trial). We do not have a definitive trial comparing platinum/pemetrexed with platinum/taxane. However, this trial did establish platinum/pemetrexed as a standard, and it remains the most commonly used doublet in the setting of nonsquamous histology. I think this is largely because of its convenient infusion schedule and favorable toxicity profile.

In patients with squamous histology, either taxane- or gemcitabine-based platinum doublets are appropriate choices in the first-line setting. As previously noted, I favor taxane-based combinations. The choice of taxane remains controversial. A trial comparing solvent-based paclitaxel/carboplatin (sb-CbP) with nanoparticle albumin-bound paclitaxel (Abraxane, Celgene)/carboplatin (nab-CbP)¹⁴ showed a higher ORR for nab-CbP than for sb-CbP (33% vs 25%; $P = .005$) that was seemingly driven by patients with squamous histology (41% for nab-CbP vs 24% for sb-CbP; $P < .001$).¹⁵ No differences in PFS or OS were noted, although this trial was not powered to evaluate the effect of the 2 formulations on these endpoints relative to histologic subtype. I think we tend to underestimate the value of an improved ORR in the absence of a PFS or OS benefit. Most patients with stage IV squamous NSCLC have disease-related symptoms. Tumor shrinkage is the best way to palliate symptoms, which is the argument for the use of a doublet associated with a higher ORR.

In summary, multiple choices exist for the treatment of both squamous and nonsquamous NSCLC. The ultimate treatment decision can factor in toxicity profiles, administration schedules, patient comorbidities, and financial costs.

Regarding duration of therapy, I stop platinum-based doublet therapy after 4 cycles given the lack of demonstrated OS benefit for therapy extended beyond 4 cycles and the risk for cumulative toxicity.¹⁶ Patients should be fully informed of the differences between the options and should participate in the decision-making process.

Antiangiogenic Therapy in Stage IV Nonsquamous NSCLC: The Case for Bevacizumab

Angiogenesis is a critical pathway in the biology of cancer, and the ability to induce angiogenesis is one of the hallmarks of cancer.¹⁷ Bevacizumab (Avastin, Genentech) is a monoclonal antibody to various isoforms of vascular endothelial growth factor (VEGF).¹⁸ Binding these ligands to block their binding to VEGF receptors inhibits angiogenesis. Early in the development of bevacizumab, a prohibitive risk for pulmonary hemorrhage in patients with squamous histology was identified, and these patients were subsequently excluded from trials evaluating bevacizumab.¹⁹ The pivotal trial evaluating bevacizumab grafted onto CbP was reported by Sandler and colleagues.²⁰ This trial showed better ORR, PFS, and OS in patients treated with CbP plus bevacizumab than in those treated with CbP alone. Although the risk for certain toxicities was increased (eg, neutropenia, febrile neutropenia, hypertension, and proteinuria), these side effects were not viewed as outweighing the clinical benefit demonstrated in the trial. Table 3 summarizes the four phase 2/3 trials in which bevacizumab was added to platinum-based doublets.²⁰⁻²³ All of these trials met their primary endpoint. On the basis of these data, bevacizumab remains an option for patients in whom its use is not contraindicated. The biological effect on stage IV nonsquamous cancer cannot be denied, and treatment with bevacizumab should be considered in the first-line setting.²⁴ I consider this agent routinely in my practice but realize it is appropriate in only a minority of patients because there are many absolute and relative contraindications to its use, including age.^{25,26}

The phase 3 trial PointBreak (A Study of Pemetrexed, Carboplatin and Bevacizumab in Participants With Nonsquamous Non-Small Cell Lung Cancer) evaluated CbP plus bevacizumab vs CbPemx plus bevacizumab in an attempt to establish superiority of the latter over the former.²⁷ There were 2 variables in this design: (1) the substitution of pemetrexed for paclitaxel in the induction phase (initial 4 cycles) and (2) the use of dual-agent maintenance in the pemetrexed arm (pemetrexed/bevacizumab) vs bevacizumab alone in the paclitaxel arm. The primary endpoint was OS, which was similar in the

Table 3. Key Results of Randomized Trials of Bevacizumab in Nonsquamous NSCLC

Parameter	Trials and Regimens								
	E4599 ²⁰		AVAIL ²¹			JO19907 ²²		BEYOND ²³	
	CbPB	CbP	CsGemB (7.5 mg/kg) ^a	CsGemB (15 mg/kg) ^a	CbP	CbPB	CbP	CbPB	CbP
ORR, %	35	15	34.1	30.4	20.1	60.7	31.0	54	26
	(P<.001)		(P<.0001)	(P=.0002)		(P<.001)			
HR for PFS	0.66 (P<.001)		0.75 (P=.003)	0.82 (P=.03)		0.61 (P=.009)		0.40 (P<.001)	
Median PFS, mo	6.2	4.5	6.7	6.5	6.1	6.9	5.9	9.2	5.65
HR for OS	0.79 (P=.003)		0.93 (NS)	1.03 (NS)		0.00 (P=.95)		0.68 (P=.0154)	
Median OS, mo	12.3	10.3	13.6	13.4	13.1	22.8	23.4	23.4	17.7

CbP, paclitaxel and carboplatin; CbPB, paclitaxel, carboplatin, and bevacizumab; CsGemB, cisplatin, gemcitabine, and bevacizumab; HR, hazard ratio; mo, months; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

^aDose of bevacizumab.

Sources: Sandler A et al. *N Engl J Med.* 2006;355(24):2542-2550²⁰; Reck M et al. *J Clin Oncol.* 2009;27(8):1227-1234²¹; Niho S et al. *Lung Cancer.* 2012;76(3):362-367²²; Zhou C et al. *J Clin Oncol.* 2015;33(19):2197-2204.²³

2 arms (median OS, 13.4 months in the paclitaxel arm vs 12.6 months in the pemetrexed arm; HR, 1.0; P=.949). The ORRs also were similar in the 2 arms (median ORR, 33% in the paclitaxel arm vs 34% in the pemetrexed arm). There was a statistically significant benefit in PFS that was clinically underwhelming (median PFS, 5.6 months in the paclitaxel arm vs 6.0 months in the pemetrexed arm; HR, 0.83; P=.012). As expected, the toxicity profiles of the 2 approaches were different, with more alopecia, neuropathy, neutropenia, and febrile neutropenia in the paclitaxel arm and more fatigue, anemia, and thrombocytopenia in the pemetrexed arm. My take-home messages from this trial are that either regimen is reasonable in a bevacizumab-eligible patient, that pemetrexed does not seem to be a more active agent than paclitaxel in this combination, and that even though dual maintenance seemed to affect PFS, it was not clinically meaningful in the absence of an OS benefit.

Anti-EGFR Antibodies in Stage IV NSCLC

The role of anti-endothelial growth factor receptor (EGFR) antibodies in stage IV NSCLC remains controversial. Cetuximab (Erbix, Lilly) was the first such antibody tested in this setting.²⁸ A phase 3 trial that evaluated cetuximab plus cisplatin/vinorelbine (CsVino) vs CsVino alone in 1125 patients with stage IV NSCLC did show a modest OS benefit (median OS, 11.3 months

for CsVino plus cetuximab vs 10.1 months for CsVino alone; HR, 0.871; P=.044).²⁹ This combination never gained FDA approval and was not widely used.

Necitumumab (Portrazza, Lilly) is a fully humanized anti-EGFR antibody that has shown a survival benefit in patients with stage IV squamous histology in combination with CsGem (median OS, 11.5 months for CsGem plus necitumumab vs 9.9 months for CsGem alone; HR, 0.84; P=.01).³⁰ The FDA has approved the combination of CsGem plus necitumumab in this setting. In my practice, I consider using this triplet regimen in highly selected patients with stage IV squamous NSCLC (ie, patients who are younger and have good performance status, are cisplatin-eligible, and have no comorbidities). I do not use it very often, however, because of the modest benefit demonstrated in the phase 3 trial and the risk for greater toxicity associated with cisplatin-based therapy. Necitumumab remains the only targeted agent for use in the first-line setting in patients with stage IV squamous NSCLC, so I think it does have a role in selected patients. Necitumumab was tested in the nonsquamous setting in combination with CsPemx, but this trial was stopped early owing to toxicity concerns in the necitumumab arm.³¹ A total of 633 patients with nonsquamous NSCLC were randomly assigned with no suggestion of a survival benefit (median OS, 11.3 months for necitumumab plus CsPemx vs 11.5 months for CsPemx alone; HR, 1.01; P=.96).

Maintenance Therapy

In my practice, maintenance therapy is an option but not a mandate. The use of maintenance therapy is largely confined to the patients with nonsquamous NSCLC. The initial strategy with bevacizumab was to continue it until disease progression; this approach was later termed *continuation maintenance*. When I use bevacizumab in the first-line setting, I tend to continue it until progression. I also tend to use it as monotherapy, even if pemetrexed was part of the initial induction regimen.

Dual maintenance has been evaluated in at least two phase 3 trials,^{27,32} both of which showed a benefit in PFS but not in OS. Because pemetrexed can be used as a second-line drug, I often reinitiate treatment with pemetrexed, particularly if the PFS has been at least 6 months (ideally, it will be longer). In those patients who are not eligible to receive bevacizumab and who receive pemetrexed-based treatment in the first-line setting, I generally continue pemetrexed as maintenance therapy on the basis of the two phase 3 trials that evaluated pemetrexed as a switch³³ as well as a continuation³⁴ maintenance agent. Both bevacizumab and pemetrexed are generally well tolerated as single agents, but cumulative toxicity with either can become an issue. I often work in treatment breaks or extend the cycle length to 4 weeks to help mitigate cumulative toxicity, particularly if disease control is continuing.

The options for maintenance therapy in patients with squamous histology are limited. Other than necitumumab, no agents are currently approved for maintenance therapy in this setting. Erlotinib (Tarceva, Genentech/Astellas) once had a role as a maintenance agent in patients with squamous histology, but its indication in advanced NSCLC was recently revoked.³⁵ A few trials evaluating switch or continuation maintenance with cytotoxic agents (gemcitabine, paclitaxel, and docetaxel) that included patients with squamous histology have been reported.³⁶ Most show a modest effect on PFS with no significant benefit in OS, along with greater toxicity associated with prolonged therapy. In my practice, I generally stop after 4 cycles of therapy in patients with stage IV squamous carcinoma and employ second-line therapy once disease progression occurs.

Summary

The management of advanced NSCLC in the absence of an actionable oncogenic driver has become more complex over the past decade. The era of immunotherapy is clearly here, and routine testing for PD-L1 is now the standard of care in stage IV NSCLC. In those patients with high-level expression of PD-L1, pembrolizumab monotherapy

is currently the optimal treatment. In those patients with low-level (<50%) or no expression of PD-L1, platinum-based doublets according to histologic subtype remain the standard of care. The addition of anti-VEGF or anti-EGFR monoclonal antibodies in appropriately selected patients does improve survival with acceptable toxicity. Although initial studies regarding the addition of anti-programmed death 1/anti-PD-L1 therapy to chemotherapy appear promising, mature survival data from phase 3 trials will be necessary before we accept this as a standard of care. Although incremental progress has been slower than desired, real gains have been made, and we should continue to offer patients the opportunity to participate in well-designed clinical trials exploring novel approaches in this disease.

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