



An Update on the Immune Landscape in Lung and Head and Neck Cancers

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Abstract: Immunotherapy has dramatically changed the treatment landscape for patients with cancer. Programmed death–ligand 1/programmed death-1 checkpoint inhibitors have been in the forefront of this clinical revolution. Currently, there are 6 US Food and Drug Administration–approved checkpoint inhibitors for approximately 18 different histologic types of cancer. Lung cancer and head and neck squamous cell carcinoma (HNSCC) are 2 diseases that have led the way in the development of immunotherapy. Atezolizumab, durvalumab, nivolumab, and pembrolizumab are all currently used as part of standard-of-care treatment for different stages of lung cancer. Similarly, nivolumab and pembrolizumab have US regulatory approval as treatment for advanced metastatic HNSCC. This is significant because lung cancer represents the most common and most fatal cancer globally, and HNSCC is the sixth most common. Currently, most of the approvals for the use of immunotherapy agents are for patients diagnosed in the metastatic setting. However, research is ongoing to evaluate these drugs in earlier stage disease. There is plausible biological rationale to expect that pharmacologic activation of the immune system will be effective for early-stage and smaller tumors. In addition, selecting patients who are more likely to respond to immunotherapy and understanding why resistance develops are crucial areas of ongoing research. The objective of this review was to provide an overview of the current immune landscape and future directions in lung cancer and HNSCC. *CA Cancer J Clin* 2020;0:1-13. © 2020 American Cancer Society.

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Introduction

The function of the programmed death-1 (PD-1) system is to provide negative feedback to prevent overactivation of T cells, thereby maintaining homeostatic control and preventing autoimmunity.¹ Developing tumors take advantage of this and other inhibitory immune mechanisms to escape immune destruction. Checkpoint blockade by monoclonal antibodies inactivate this inhibitory signaling pathway, functionally reinvigorating a hobbled T-cell immune response to the tumor. Importantly, autoreactive T cells can be unleashed, leading to inflammation in normal tissues, termed immune-related adverse events (irAEs).² One way the immune system may recognize tumor cells is through neoantigens, which are peptides expressed by major histocompatibility complex (MHC) molecules on the cell surface that result from DNA damage. Smoking-related mutations are associated with tumor mutational burden (TMB) and response to checkpoint blockade and, as such, may underlie some of the responses to PD-1 pathway blockade in both lung cancer and head and neck cancer.³ In addition, some head and neck cancers are virally mediated, such as the human papillomavirus (HPV)–induced oropharyngeal carcinomas, and thus provide a basis for a better understanding of virally triggered immune-oncology mechanisms.

Non–Small Cell Lung Cancer: Advanced/ Metastatic Disease

Immunotherapy is widely used in the care of patients with non–small cell lung cancer (NSCLC), and multiple standard-of-care (SOC) regimens are approved in locally advanced and metastatic disease (Table 1).⁴ The earliest studies of immunotherapy in NSCLC evaluated single-agent PD-(L)1 blockade in previously treated, advanced NSCLC and showed improved efficacy over standard chemotherapy with docetaxel. Thus nivolumab, pembrolizumab, and atezolizumab were approved based on results of the CheckMate 017 (ClinicalTrials.gov identifier NCT16420054), CheckMate 057 (ClinicalTrials.gov identifier NCT01673867), KEYNOTE-010 (ClinicalTrials.gov identifier NCT01905657), and OAK (ClinicalTrials.gov identifier NCT02008227) trials, respectively.^{5–8} The hazard ratio (HR) for overall survival (OS) for the checkpoint inhibitor, compared with chemotherapy, ranged from 0.59 to 0.73 in these trials. Importantly, this significant improvement in OS came with notable reductions in toxicity; serious or life-threatening adverse events (grade 3 or higher according to the Common Terminology Criteria for Adverse Events) ranged from 7% to 15% with the checkpoint inhibitor versus 35% to 55% with docetaxel.^{5–8} These regimens were rapidly adopted into standard clinical practice and thus launched the era of immunotherapy for lung cancer and the attendant management challenges related to immune-mediated toxicities.^{9,10}

The proven efficacy of immunotherapy in the postfrontline setting and the recognition that PD-L1 expression could serve as a predictive biomarker to identify likely responders facilitated the frontline testing of these agents.¹¹ Treatment with PD-(L)1 blockade has now become firmly established as an initial therapy, starting with the KEYNOTE-024 (NCT02142738) study in which patients with high expression of PD-L1, tumor proportion scores (TPS) >50% and without targetable alterations in the epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genes were randomized to receive either pembrolizumab or platinum doublet chemotherapy.¹² The median progression-free survival (PFS) was significantly longer in the group treated with pembrolizumab than in the group treated with standard platinum doublet chemotherapy (10.3 vs 6 months; HR, 0.50 [95% CI, 0.37–0.68; $P < .001$]). With more mature data from longer term follow-up, the median OS for the pembrolizumab group was 30 months compared with 14.2 months for the chemotherapy group (HR, 0.49; 95% CI, 0.34–0.69).¹³ Single-agent pembrolizumab remains a preferred regimen in patients with metastatic NSCLC and high PD-L1 expression, now with an unprecedented 5-year OS rate of

25% in patients who were previously treated and 29.6% in treatment-naïve patients reported from the phase 1 KEYNOTE-001 study.¹⁴ For those patients who may not tolerate chemotherapy and have at least 1% PD-L1 expression, single-agent pembrolizumab may be considered based on KEYNOTE-042 (ClinicalTrials.gov identifier NCT02220894), although the benefit of this approach was largely driven by patients with high levels of PD-L1 expression.¹⁵ Conversely, patients with a high symptom burden or evidence of rapidly progressive disease may be treated with combination chemoimmunotherapy, as discussed below.

Next followed the development of frontline chemoimmunotherapy options for patients with advanced NSCLC regardless of PD-L1 expression. KEYNOTE-189 (ClinicalTrials.gov identifier NCT02578680) studied previously untreated patients with non-*EGFR*-driven or *ALK*-driven, nonsquamous NSCLC and randomized patients to receive either platinum and pemetrexed plus pembrolizumab or placebo.¹⁶ Although the study allowed for cross-over to pembrolizumab monotherapy from the placebo arm, the 12-month OS was still significantly improved for the pembrolizumab-containing arm, with an HR for death of 0.49 (95% CI, 0.38–0.64; $P < .001$). Impower150 (ClinicalTrials.gov identifier NCT02366143) was the second study of chemoimmunotherapy that compared the addition of atezolizumab to bevacizumab, carboplatin, and paclitaxel in patients with nonsquamous NSCLC regardless of mutation status.¹⁷ Patients were not allowed prior chemotherapy, but a subset of patients with *EGFR* mutations or *ALK* translocations was included who already had progressed on targeted therapy. The primary endpoints of PFS in the wild-type group without *EGFR*-targetable or *ALK*-targetable alterations, as well as median OS in the entire wild-type population, were both in favor of the atezolizumab arm (median PFS, 8.3 vs 6.8 months; HR, 0.62 [95% CI, 0.52–0.74; $P < .001$]); the median OS was longer in the group that received combined atezolizumab, bevacizumab, carboplatin, and paclitaxel at 19.2 months than that in the group that received combined bevacizumab, carboplatin, and paclitaxel at 14.7 months (HR for death, 0.78; 95% CI, 0.64–0.96 [$P = .02$]).¹⁷

The importance of identifying targetable driver mutations before immunotherapy-based regimens in patients with newly diagnosed nonsquamous NSCLC cannot be overemphasized because of both toxicity and efficacy concerns. This is especially true of *EGFR*-mutated NSCLC. In a retrospective study, patients with *EGFR*-mutant NSCLC who were treated with PD-L1 blockade within 3 months before osimertinib, a third-generation *EGFR*

TABLE 1. Phase 3 Immunotherapy Trials in Lung Cancer

POPULATION	TRIALS	DRUG	DETAILS	PRIMARY OUTCOME: HR (95% CI)
Metastatic NSCLC Frontline	KEYNOTE-407	Pembrolizumab vs placebo + carboplatin and paclitaxel or nab-paclitaxel	Squamous	OS: 0.64 (0.49-0.85); PFS: 0.56 (0.45-0.70)
	KEYNOTE-024	Pembrolizumab vs platinum-based chemotherapy	PD-L1 ≥ 50%	PFS: 0.50 (0.37-0.68)
	KEYNOTE-042	Pembrolizumab vs platinum-based chemotherapy	PD-L1 ≥ 1%	OS in TPS ≥ 50%: 0.69 (0.56-0.85); OS in TPS > 20%: 0.77 (0.64-0.92); OS in TPS > 1%: 0.81 (0.71-0.93)
	KEYNOTE-189	Pembrolizumab vs placebo + platinum and pemetrexed	Nonsquamous	OS: 0.49 (0.38-0.64); PFS: 0.52 (0.43-0.64)
	CheckMate 026	Nivolumab vs platinum-based chemotherapy	PD-L1 ≥ 1%	PFS in PD-L1 ≥ 5%: 1.15 (0.91-1.45)
	CheckMate 227	Nivolumab + ipilimumab (NI) vs nivolumab + chemotherapy (NC) vs chemotherapy (C)		PFS in TMB high NI vs C: 0.58 (0.41-0.81); OS in PD-L1 ≥ 1% NI vs C: 0.79 (97.72% CI, 0.65-0.96) ^b
	CheckMate 9LA	Nivolumab + opilimumab + chemotherapy vs chemotherapy		OS endpoint met; details pending
	IMpower150	Atezolizumab + carboplatin + paclitaxel (ACP) vs bevacizumab + carboplatin + paclitaxel (BCP) vs atezolizumab + BCP (ABCP)	Nonsquamous; wild-type (WT) population had no EGFR or ALK alteration	PFS WT ABCP vs BCP: 0.62 (0.52-0.74); OS WT ABCP vs BCP: 0.78 (0.64-0.96)
	IMpower130	Atezolizumab + carboplatin + nab-paclitaxel vs chemotherapy	Nonsquamous; WT had no EGFR or ALK alteration	PFS WT: 0.64 (0.54-0.77); OS WT: 0.79 (0.64-0.98)
	IMpower110	Atezolizumab vs platinum-based chemotherapy	PD-L1 ≥ 1%; WT had no EGFR or ALK alteration	OS in TC3/IC3 WT: 0.595 (0.398-0.890); OS in TC2/TC3-IC2/IC3 WT: 0.717 (0.520-0.989); OS in TC1/TC2/TC3-IC1/IC2/IC3 WT: 0.832 (0.649-1.067)
Second-line and beyond	CheckMate 057	Nivolumab vs docetaxel	Nonsquamous	OS: 0.73 (0.59-0.89)
	CheckMate 017	Nivolumab vs docetaxel	Squamous	OS: 0.59 (0.44-0.79)
	OAK	Atezolizumab vs docetaxel		OS: 0.73 (0.62-0.87); OS TC1/TC2/TC3 or IC1/IC2/IC3: 0.74 (0.58-0.93)
	POPLAR	Atezolizumab vs docetaxel		OS: 0.73 (0.53-0.99); OS TC3/IC3: 0.49 (0.22-1.07); OS TC2/TC3 or IC2/IC3: 0.54 (0.33-0.89); OS TC1/TC2/TC3 or IC1/TC2/TC3: 0.59 (0.40-0.85)
Locally advanced NSCLC	PACIFIC	Durvalumab vs placebo		PFS: 0.52 (0.42-0.65); OS: 0.68 (99.73% CI, 0.47-0.997)
	CASPIAN	Durvalumab + platinum and etoposide vs platinum and etoposide	Frontline	OS: 0.73 (0.59-0.91)
Extensive-stage SCLC	IMpower133	Atezolizumab vs placebo + platinum and etoposide	Frontline	OS: 0.70 (0.54-0.91)
	KEYNOTE-604	Pembrolizumab vs placebo + platinum and etoposide	Frontline	OS endpoint not met; details pending
	CheckMate 451	Nivolumab + ipilimumab (NI) vs nivolumab (N) vs placebo (PI)	Maintenance	OS NI vs PI: 0.92 (0.75-1.12); OS N vs PI: 0.84 (0.69-1.02) ^b

Abbreviations: CASPIAN (ClinicalTrials.gov identifier NCT03043872); CheckMate 017 (ClinicalTrials.gov identifier NCT16420054); CheckMate 026 (ClinicalTrials.gov identifier NCT02041533); Checkmate 057 (ClinicalTrials.gov identifier NCT01673867); CheckMate 227 (ClinicalTrials.gov identifier NCT02477826); CheckMate 451 (ClinicalTrials.gov identifier NCT02538666); CheckMate 9LA (ClinicalTrials.gov identifier NCT03215706); HR, hazard ratio; IC2/IC3, ≥ 5% PD-L1-positive tumor-infiltrating immune cells; IMpower133 (ClinicalTrials.gov identifier NCT02763579); IMpower150 (ClinicalTrials.gov identifier NCT02336143); IMpower110 (ClinicalTrials.gov identifier NCT02409342); IMpower130 (ClinicalTrials.gov identifier NCT02367781); KEYNOTE-024 (ClinicalTrials.gov identifier NCT02142738); KEYNOTE-042 (ClinicalTrials.gov identifier NCT02220894); KEYNOTE-189 (ClinicalTrials.gov identifier NCT02578680); KEYNOTE-407 (ClinicalTrials.gov identifier NCT02774535); KEYNOTE-604 (ClinicalTrials.gov identifier NCT03066778); nab-paclitaxel, nanoparticle-bound paclitaxel; NSCLC, nonsmall cell lung cancer; OAK (ClinicalTrials.gov identifier NCT02008227); OS, overall survival; PACIFIC (ClinicalTrials.gov identifier NCT02125461); PD-L1, programmed death ligand 1; PFS, progression-free survival; POPLAR (ClinicalTrials.gov identifier NCT01903993); SCLC, small cell lung cancer; TC1, ≥ 1% PD-L1-positive cells tumor cells; TC2/TC3, ≥ 5% PD-L1-positive cells; TMB, tumor mutational burden; TPS, tumor proportion score.

^aThe proportional hazards assumption was not met.

^bThis was not formally tested because of statistical hierarchy (see Siu 2019⁴).

tyrosine kinase inhibitor (TKI), had a risk of serious irAEs of 24% (95% CI, 10%-45%), whereas no patients (0%) who were treated with osimertinib before PD(L)-1 therapy had severe irAEs (95% CI, 0%-14%).¹⁸ The rate of interstitial pneumonitis was of particular concern because it was the defining toxicity in 4 of 6 patients with grade 3 or higher irAEs, all of whom required hospitalization. Two combination trials of osimertinib plus durvalumab were terminated before full accrual because of an increased rate of interstitial lung disease seen in 13 of 38 patients (38%) who received the combination compared with an incidence of 2% to 3% seen in those who received osimertinib monotherapy.^{19,20} Along with an increased risk of toxicity was the lack of efficacy with this strategy. In a phase 2 study of single-agent pembrolizumab in TKI-naïve patients with PD-L1-positive (>1%) and *EGFR*-mutant NSCLC, single-agent pembrolizumab produced no objective responses.²¹ The impact of these small studies on practice has been profound such that, for patients with lung adenocarcinoma and pending molecular studies, the preferred option is to wait until their full molecular profile is available.²² If pressed to initiate treatment because of disease burden and/or symptoms, we advise temporarily withholding immunotherapy from the regimen. This is to ensure adequate safety for the patient should the need arise to transition to targeted therapy for an *EGFR* mutation or an *ALK* translocation. Immunotherapy-containing regimens remain an option for patients who develop TKI resistance, with careful attention to irAEs. Further study of salvage systemic therapies, including immunotherapy, are needed for when targeted options are exhausted, as currently available data are limited to subset analysis of the IMpower150 trial.¹⁷

Immunotherapy similarly benefitted patients with advanced squamous NSCLC. In KEYNOTE-407 (ClinicalTrials.gov identifier NCT02774535), patients were randomized to a chemotherapy backbone of carboplatin and investigator's choice of either paclitaxel or nanoparticle-bound paclitaxel plus pembrolizumab or placebo.²³ The median OS was 15.9 months with pembrolizumab plus chemotherapy versus 11.3 months with placebo plus chemotherapy (HR for death, 0.64; 95% CI, 0.49-0.85 [$P < .001$]). This combination is applicable to patients with both squamous and nonsquamous histologies regardless of PD-L1 expression status.

With multiple approved frontline regimens for patients with NSCLC, optimal sequencing of therapy is an open question in the field. Considering patients with high PD-L1 expression (>50%), proponents of single-agent immunotherapy cite a good objective response rate (ORR) of 44.8%, coupled with low toxicity rates, with grade 3 through 5 adverse events seen in 26.6% of patients treated with pembrolizumab monotherapy.¹² Conversely,

combination chemotherapy-immunotherapy in the subset of patients with high PD-L1 levels in the KEYNOTE-189, KEYNOTE-407, and IMpower150 trials led to ORRs surpassing 60%. The addition of chemotherapy to immunotherapy may prevent both rapid progression and early crossing of the PFS curves, but the effect on long-term survival is unknown. Notably, increased toxicity was seen with the addition of chemotherapy to immunotherapy, with grade 3 through 5 adverse events in the range of 58% to 68% among the 3 aforementioned trials.^{16,17,23} It is important to emphasize that, whereas the rate of toxicity is higher with combined chemoimmunotherapy over single-agent immunotherapy, the overall safety and tolerability of chemoimmunotherapy are comparable to those of chemotherapy alone. Therefore, the clinical consideration is whether or not a patient who has an adequate performance status to tolerate combined therapy truly requires immediate chemoimmunotherapy for optimal disease control and improved efficacy rather than a sequential approach of single-agent immunotherapy followed by chemotherapy at progression. The currently ongoing INSIGNA (ClinicalTrials.gov identifier NCT03793179) is a large, randomized, phase 3 clinical trial seeking to address the question of sequencing in patients with nonsquamous NSCLC and PD-L1 expression >1% with correlative immune biomarker analysis to understand which patients may benefit from each sequence of therapy.

Other approaches to combination therapy incorporating immunotherapy include strategies to limit chemotherapy exposure for the patient. Frontline nivolumab plus ipilimumab (a monoclonal antibody inhibiting CTLA-4) was compared with chemotherapy in the CheckMate 227 trial (ClinicalTrials.gov identifier NCT02477826) and showed that this could be an option for patients who desire to avoid chemotherapy but are not optimal candidates for single-agent anti-PD1.²⁴ Combination immunotherapy may also improve long-term OS over single-agent immunotherapy through enhanced immune activation, as has been seen in other malignancies.^{25,26} The study enrolled patients with advanced, metastatic NSCLC stratified by PD-L1 expression $\geq 1\%$ versus $< 1\%$ and randomized 1:1:1 to nivolumab plus ipilimumab, nivolumab alone, or platinum doublet chemotherapy. An earlier report of the first coprimary endpoint of the study highlighted high TMB (≥ 10 mutations per megabase) as a biomarker predicting longer PFS with the use of combination immunotherapy; however, this result did not persist in the OS analysis.²⁷ In the second co-primary endpoint, across PD-L1 expression levels, the median OS was longer in the immunotherapy group than in the chemotherapy group.²⁴ Specifically, in patients with PD-L1 expression $\geq 1\%$, the median OS was 17.1 months (95% CI, 15.0-20.1 months) with nivolumab plus ipilimumab

versus 14.9 months (95% CI, 12.7-16.7 months) with chemotherapy, whereas in the PD-L1 <1% group, the median OS was 17.2 months (95% CI, 12.8-22.0 months) versus 12.2 months (95% CI, 9.2-14.3 months), respectively. The other chemotherapy-limiting strategy was tested in CheckMate 9LA (ClinicalTrials.gov identifier NCT03215706), a randomized phase 3 trial that evaluated nivolumab (360 mg every 3 weeks) plus low-dose ipilimumab (1 mg/kg every 6 weeks) along with only 2 cycles of chemotherapy versus a standard schedule of chemotherapy alone (up to 4 cycles followed by maintenance therapy if eligible) as a first-line treatment in patients with advanced NSCLC regardless of PD-L1 expression and histology. Patients in the experimental arm were treated for up to 2 years or until they developed disease progression or unacceptable toxicity. A preliminary report indicated that the study met its primary endpoint of improved OS in the intent-to-treat population. Notably, the increased rate of irAEs seen with the addition of ipilimumab is an important factor that will affect how well this strategy can be incorporated into regular clinical practice.

NSCLC: Locally Advanced and Early Stage Disease

Until recently, the treatment of unresectable stage III NSCLC had remained the same for years using SOC concurrent platinum doublet chemotherapy and radiation (CRT) with or without additional consolidative chemotherapy, resulting in a 5-year OS rate <20%.²⁸ The PACIFIC trial (ClinicalTrials.gov identifier NCT02125461) randomized patients who had completed definitive CRT for locally advanced NSCLC in a 2:1 fashion to receive either consolidative durvalumab (an anti-PD-L1 monoclonal antibody) or placebo. The study demonstrated a significant prolongation of PFS (HR, 0.52 [95% CI, 0.42-0.65; $P < .00$]), with an improvement in median PFS from 5.6 months with placebo (95% CI, 4.6-7.8 months) to 16.8 months with durvalumab (95% CI, 13.0-18.1 months).²⁹ The coprimary endpoint of OS was also significantly prolonged in the durvalumab group compared with the placebo group, with a stratified HR for death of 0.68 (99.73% CI, 0.47-0.997; $P = .0025$).³⁰ Patients in the durvalumab-treated group had median time to distant metastases or death of 28.3 months compared with 16.2 months in the placebo group (stratified HR, 0.53; 95% CI, 0.41-0.68). Of note, the trial prospectively assessed efficacy in patients with PD-L1 levels $\geq 25\%$ or $< 25\%$ and was efficacious in both groups; however, a post hoc analysis of patients with PD-L1 <1% numerically favored the placebo group.³¹ Because the trial did not require PD-L1 testing (nearly 40% of patients had unknown PD-L1

expression levels) and heterogenous PD-L1 expression has been well documented, PD-L1 expression is not required to initiate durvalumab after CRT.²⁹ In practice, this regimen is well tolerated, although pneumonitis attributable to radiation and/or immunotherapy can be serious and led to treatment discontinuation in 5% of patients who received durvalumab on the trial.³⁰

Building on the success of the PACIFIC trial, ongoing studies are now seeking to test how harnessing the immune system could lead to improved outcomes by preventing recurrence in earlier stages of NSCLC. The current SOC for resected NSCLC remains perioperative cisplatin-based doublet chemotherapy, which improved OS by approximately 5% compared with surgery alone in a large meta-analysis.³² This innovation is desperately needed because, even among patients who are fortunate to be diagnosed with clinical stage I disease, 5-year survival may be as low as 77%, whereas those with clinical stage IIIA disease have 5-year survival estimates of only 36%.³³ Large phase 2 and 3 studies are underway investigating 1 year of single-agent adjuvant immunotherapy after surgical resection with nivolumab, atezolizumab, durvalumab, and pembrolizumab.³⁴ Recurrence-free survival and OS data are maturing and are anticipated in the middle to late 2020s.

Numerous neoadjuvant single-agent and combination trials are ongoing following on the heels of the promising results seen with 2 cycles of nivolumab before surgical resection.³⁵ In that pilot study, a 4-week immunotherapy treatment period before surgery was safe and well tolerated, with 20 of 21 patients undergoing subsequent complete resection. Initial signs of the efficacy of neoadjuvant immunotherapy in resectable disease were quite promising based on the major pathologic response (MPR), defined as <10% viable tumor in the resected surgical specimen, with an MPR of 45% (9 of 21 patients).^{35,36} In LCMC3 (ClinicalTrials.gov identifier NCT02927301), an ongoing Lung Cancer Mutation Consortium trial of neoadjuvant atezolizumab for 2 cycles followed by surgical resection and an optional year of adjuvant atezolizumab, the MPR rate in the initial 21 patients was 24%.³⁷ Other neoadjuvant regimens under active investigation are nivolumab plus ipilimumab and chemoimmunotherapy with nivolumab, carboplatin, and paclitaxel.^{38,39} Although pathologic response rates provide an early efficacy read-out, the crucial OS data from large randomized studies are still lacking at this point.

The optimal management of mutation-driven NSCLC in either the surgically resectable or the CRT setting also remains an active area of investigation. In the post-CRT setting, although patients with *EGFR*-mutated and *ALK*-translocated NSCLC were included in the PACIFIC trial, low numbers have limited the ability to reach definitive conclusions. Several clinical trials are currently

ongoing to assess the role of adjuvant TKIs in this setting. In EGFR-mutated NSCLC, the ADAURA clinical trial (ClinicalTrials.gov identifier NCT02511106) is investigating osimertinib versus placebo after complete surgical resection, whereas the LAURA trial (ClinicalTrials.gov identifier NCT03521154) is comparing osimertinib versus placebo after CRT.^{40,41} Similarly, the ALINA trial (ClinicalTrials.gov identifier NCT03456076) is randomizing patients with ALK-driven NSCLC to the TKI alectinib versus doublet chemotherapy after complete surgical resection.⁴²

Small Cell Lung Cancer Extensive-Stage Disease

The addition of immunotherapy to the armamentarium of treatment options for small cell lung cancer (SCLC) has provided the most consequential advancement in decades for this aggressive disease. Frontline SOC for extensive-stage SCLC now includes PD-1–targeted immunotherapy combined with the platinum etoposide chemotherapy backbone. The IMpower133 trial (ClinicalTrials.gov identifier NCT02763579) randomized patients 1:1 to receive atezolizumab or placebo concurrent with 4 cycles of carboplatin and etoposide, followed by maintenance atezolizumab or placebo until progression or unacceptable toxicity.⁴³ Combination chemoimmunotherapy was well tolerated and improved the median OS from 10.3 months (95% CI, 9.3–11.3 months) in the placebo group to 12.3 months (95% CI, 10.8–15.9 months) in the atezolizumab group (HR for death, 0.70; 95% CI, 0.54–0.91 [$P = .007$]). Similarly, the CASPIAN study (ClinicalTrials.gov identifier NCT03043872) was a 3-arm trial that randomized patients with extensive-stage SCLC to platinum-etoposide, platinum-etoposide plus durvalumab, or platinum-etoposide plus durvalumab and tremelimumab (a monoclonal antibody against CTLA-4).⁴⁴ At a planned interim analysis, standard platinum-etoposide chemotherapy for up to 6 cycles versus durvalumab in combination with a maximum of 4 cycles of doublet chemotherapy followed by maintenance durvalumab led to a significant improvement in OS (HR, 0.73, 95% CI, 0.59–0.91 [$P = .0047$]), with a median OS of 13 months (95% CI, 11.5–14.8 months) in the durvalumab plus platinum-etoposide arm versus 10.3 months in the control arm (95% CI, 9.3–11.2 months).⁴⁴ The durvalumab, tremelimumab, and chemotherapy arm was not yet mature in terms of the number of events needed at the time of the interim analysis. KEYNOTE-604 (ClinicalTrials.gov identifier NCT03066778) is a similar trial of pembrolizumab plus chemotherapy compared with chemotherapy in treatment-naïve patients with extensive-stage SCLC. Preliminary information in a press release from the study sponsor indicated that the trial met its PFS endpoint but failed to improve OS.

Limited-Stage SCLC

One-quarter of patients with SCLC are diagnosed with limited-stage disease, for which SOC therapy is CRT followed by prophylactic cranial radiation. With this approach, the 5-year OS rate remains at 20% to 25%.⁴⁵ Clinical trials are currently investigating whether the incorporation of checkpoint blockade during or after CRT will improve outcome.⁴⁶ The ACHILES trial (ClinicalTrials.gov identifier NCT03540420) is evaluating 12 months of treatment with atezolizumab, whereas STIMULI (ClinicalTrials.gov identifier NCT02046733) is testing nivolumab plus ipilimumab for 4 cycles followed by nivolumab for 12 months as consolidation post-CRT. The ADRIATIC trial (ClinicalTrials.gov identifier NCT03703297) is a 3-arm phase 3 study investigating consolidation therapy post-CRT using durvalumab with placebo or with tremelimumab for 4 cycles followed by durvalumab compared with placebo. A CRT-immunotherapy approach using atezolizumab followed by maintenance atezolizumab is the focus of NRG-LU005 (ClinicalTrials.gov identifier NCT03811002), and the CLOVER trial (ClinicalTrials.gov identifier NCT03509012) is studying durvalumab with or without tremelimumab added to CRT.

Relapsed SCLC

The role of immunotherapy in relapsed SCLC is evolving, as reported in initial studies of the safety and efficacy of checkpoint inhibitors in relapsed patients who were not exposed to immunotherapy in the frontline setting. CheckMate 032 (ClinicalTrials.gov identifier NCT01928394) assigned patients who had relapsed after at least 1 platinum-containing regimen to either single-agent nivolumab or different dose combinations of nivolumab plus 4 cycles ipilimumab every 3 weeks followed by single-agent nivolumab.⁴⁷ The primary endpoint of an investigator-assessed, objective response was met by 10 of 98 patients (10%) who received nivolumab at a dose of 3 mg/kg every 2 weeks, 14 of 61 patients (23%) who received nivolumab at a dose of 1 mg/kg plus ipilimumab at a dose of 3 mg/kg, and 10 of 54 patients (19%) who received nivolumab at a dose of 3 mg/kg plus ipilimumab at a dose of 1 mg/kg. CheckMate 331 (ClinicalTrials.gov identifier NCT02481830) is a global, open-label, phase 3 trial that randomized patients who had recurrence after frontline platinum chemotherapy to nivolumab or chemotherapy with either topotecan or amrubicin, stratified by platinum sensitivity and central nervous system metastasis.⁴⁸ The primary endpoint of OS was not met, with a median OS of 7.5 months (95% CI, 5.7–9.2 months) in the nivolumab group compared with 8.4 months (95% CI, 7.0–10.0 months) in the chemotherapy group. In patients with platinum-resistant SCLC, there was a significant improvement in OS (HR, 0.71; 95% CI, 0.54–0.94).

Single-agent pembrolizumab was tested in 24 patients with relapsed SCLC as part of the phase 1b KEYNOTE-028 clinical trial (ClinicalTrials.gov identifier NCT02054806).⁴⁹ All patients had PD-L1 expression of at least 1% and 87.5% had received 2 or more lines of prior therapy. The investigator-assessed ORR was 33%, with a single complete response and 7 partial responses noted. Subsequently, a phase 2 basket study KEYNOTE-158 (ClinicalTrials.gov identifier NCT02054806) enrolled 107 patients with relapsed SCLC, including 39% with a combined positive score (CPS) of $\geq 1\%$ (PD-L1 positive) and 47% with PD-L1 negative disease.⁵⁰ Patients with PD-L1-positive disease had an ORR of 35.7% (95% CI, 21.6-52.0), whereas PD-L1-negative patients had an ORR of 6% (95% CI, 1.3%-16.5%). OS was a secondary endpoint and also was prolonged in PD-L1-positive patients with a median OS of 14.6 months (95% CI, 5.6 months to not estimable) versus 7.7 months (95% CI, 3.9-10.4 months) in patients with PD-L-negative tumors. On the basis of these studies, single-agent pembrolizumab and nivolumab remain approved for third-line treatment of SCLC. Ongoing clinical trials are assessing other immunologic and disease-specific targets for patients with relapsed checkpoint therapy refractory disease.

Head and Neck Cancer

Immunotherapy has transformed the treatment landscape of HNSCC (Table 2). KEYNOTE-012 (ClinicalTrials.gov identifier NCT01848834) was the first trial to demonstrate the efficacy of checkpoint inhibitors in this disease. This phase 1b study examined the safety and efficacy of pembrolizumab in patients with a variety of recurrent metastatic solid tumor types, including 192 patients with HNSCC. Patients in the initial phase were required to have PD-L1 expression and were treated with pembrolizumab at a dose of 10 mg/kg every 2 weeks, whereas patients in the expansion phase were not required to have expression of PD-L1 and were treated with pembrolizumab at a dose of 200 mg every 3 weeks. Within the HNSCC cohort, 74% of patients had received at least 2 prior lines of therapy. In addition, HPV-associated HNSCC constituted 24% of HNSCC cases. Pembrolizumab was overall safe and tolerable, demonstrated an ORR of 18%, and 71% of the patients maintained their response for >1 year. The PFS was 2.1 months, and the 1-year OS rate was 38%.^{51,52} On the basis of the ORR and duration of response, the US Food and Drug Administration approved pembrolizumab for HNSCC in 2016 for platinum-refractory patients.⁵³ The subsequent KEYNOTE-055 trial (ClinicalTrials.gov identifier NCT02255097) enrolled a similar HNSCC population in a nonrandomized, single phase 2 trial, but mandated that patients be refractory to platinum-based

chemotherapy and cetuximab. The study also used pembrolizumab at a dose of 200 mg every 3 weeks. Among the 171 patients who were enrolled, 82% expressed PD-L1, and 22% were HPV positive. The results were similar to those of KEYNOTE-012, with pembrolizumab having an ORR of 16%, a duration of response of 8 months, and no new safety concerns.⁵⁴

Advances the treatment of advanced HNSCC were needed. Before the checkpoint inhibitors, the last systemic agent approved in platinum-refractory metastatic HNSCC was cetuximab in 2006, based on a single-arm trial of 103 patients demonstrating an ORR of 13%.⁵⁵ However, both KEYNOTE-012 and KEYNOTE-055 were single-arm studies, and randomized, phase 3 data were needed to truly determine the role of immunotherapy in this population. The first phase 3 randomized study showing the superiority of immunotherapy to chemotherapy in the recurrent metastatic HNSCC population was the CheckMate 141 trial (ClinicalTrials.gov identifier NCT02105636). Patients were enrolled if they recurred or progressed within 6 months of completing standard platinum-based chemotherapy. Patients were enrolled and randomized in a 2:1 fashion to either receive either nivolumab or investigator's-choice SOC (cetuximab, methotrexate, or docetaxel). Nivolumab was shown to be less toxic than SOC, with grade 3 and 4 AEs reported in 13.1% of patients versus 35.1%, respectively. The trial met its primary endpoint because OS was superior with nivolumab compared with SOC, with an HR of 0.70 ($P = .01$) and a 1-year survival rate of 36.0% versus 16.6%, respectively. There was no difference in PFS, and the ORR was 13.3% versus 5.8%, respectively. In a secondary analysis, there was a trend toward improved efficacy with nivolumab in patients that who PD-L1 positive (PD-L1 expression $\geq 1\%$; HR, 0.55) compared with those who were PD-L1 negative (HR, 0.89).⁵⁶ A separate subgroup analysis also showed that, regardless of HPV status, age, or whether patients on study had received prior cetuximab, the benefit of nivolumab was maintained.^{57,58}

KEYNOTE-040 (ClinicalTrials.gov identifier NCT02358031) was similar in design to CheckMate 141, a phase 3 study in platinum-failure, metastatic HNSCC comparing pembrolizumab with SOC chemotherapy (cetuximab, docetaxel, or methotrexate). There were 495 patients enrolled to the study across 20 countries. The safety of pembrolizumab was consistent with the earlier KEYNOTE-012 and KEYNOTE-055 studies, and there were fewer grade 3 through 5 AEs with pembrolizumab than with chemotherapy (13% vs 36%, respectively). Pembrolizumab was more effective, with a median OS of 8.4 versus 6.9 months (HR, 0.80; $P = .0161$) compared with chemotherapy.⁵⁹ These data firmly established nivolumab and pembrolizumab as the SOC for the second-line

TABLE 2. Immunotherapy Trials in Metastatic Head and Neck Squamous Cell Carcinoma

POPULATION	TRIAL	DRUGS	DETAILS	PRIMARY OUTCOME: HR (95% CI)
First-line	KEYNOTE-048	Pembrolizumab (P) ± chemotherapy (PC) vs chemotherapy + cetuximab (CC)		OS P vs CC, CPS ≥1: 0.78 (0.64-0.96); OS PC vs CC: 0.77 (0.63-0.93)
	Active8	Chemotherapy + cetuximab ± motolimod		PFS: 0.99 (90% CI, 0.00-1.22)
Second-line and beyond	KEYNOTE-040	Pembrolizumab vs chemotherapy		OS: 0.80 (0.65-0.98)
	CheckMate 141	Nivolumab vs chemotherapy		OS: 0.70 (0.51 to 0.96)
	EAGLE	Durvalumab (D) ± tremelimumab (DT) vs chemotherapy (C)		OS D vs C: 0.88 (0.72-1.08); OS DT vs C: 1.04 (0.85-1.26)
	KEYNOTE-012	Pembrolizumab	PD-L1 ≥ 1%	ORR, 18% (8%-32%)
	KEYNOTE-055	Pembrolizumab		ORR, 16% (11%-23%)
	CONDOR	Durvalumab (D) D + tremelimumab (DT) Tremelimumab (T)		ORR D: 9.2% (3.46%-19.02%)
				ORR DT: 7.8% (3.78%-13.79%) ORR T: 1.6% (0.04%-8.53%)

Abbreviations: Active8 (ClinicalTrials.gov identifier NCT01836029); CheckMate 141 (ClinicalTrials.gov identifier NCT02105636); CONDOR (ClinicalTrials.gov identifier NCT02319044); CPS, combined positive score; EAGLE, Environment and Genetics in Lung Cancer Etiology; HR, hazard ratio; KEYNOTE-012 (ClinicalTrials.gov identifier NCT01848834); KEYNOTE-048 (ClinicalTrials.gov identifier NCT02358031); KEYNOTE-055 (ClinicalTrials.gov identifier NCT02255097); ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival.

treatment of metastatic HNSCC. However, not all studies of checkpoint inhibitors have been positive in recurrent HNSCC. Whereas the phase 2 CONDOR study (ClinicalTrials.gov identifier NCT02319044) showed that durvalumab plus tremilumab was safe and had some early efficacy, the phase 3 EAGLE study (Environment and Genetics in Lung Cancer Etiology) did not show an improvement in OS of with either durvalumab or durvalumab plus tremilumab compared with chemotherapy for platinum-refractory HNSCC (7.6 months vs 6.5 months vs 8.3 months, respectively).^{4,60}

In the frontline, recurrent, metastatic setting, the long-standing SOC has been the EXTREME regimen, consisting of platinum, 5-fluorouracil (5-FU), and cetuximab.⁶¹ Fortunately, the treatment of HNSCC has recently evolved, and a recent trial examined pembrolizumab in the frontline setting for metastatic disease, challenging the long-held EXTREME frontline standard. KEYNOTE-048 was a large, international phase 3 study comparing chemotherapy, chemotherapy and pembrolizumab, and pembrolizumab alone for patients who either had newly diagnosed metastatic HNSCC or had progressed after 6 months of receiving systemic therapy for locally advanced disease. The chemotherapy was the EXTREME regimen in the SOC arm and platinum plus 5-FU without cetuximab in the chemotherapy-pembrolizumab arm. Tissue was provided for PD-L1 testing. As opposed to the more common PD-L1 TPS obtained in KEYNOTE-040, the CPS was used, which assesses PD-L1 staining on both the tumor and the immune cells, in KEYNOTE-048. The primary

endpoint was OS, comparing each of the experimental arms with the SOC arm, whereas safety, PFS, and the ORR were secondary endpoints. There was also a prespecified analysis of the endpoints stratified by PD-L1 CPS scores (≥20, ≥1, and the total population). Overall, 882 patients were enrolled: 85% were PD-L1–positive, and 43% had a CPS ≥20. In comparing pembrolizumab alone versus SOC, there was a significant improvement in the median OS for the CPS ≥20 group (14.9 months vs 10.7 months; HR, 0.61 [$P = .0007$]) and the CPS ≥1 group (12.3 months vs 10.3 months; HR, 0.78 [$P = .0086$]). OS was noninferior to SOC for the overall population. For chemotherapy plus immunotherapy versus SOC, there was a significant improvement in median OS for the total population (13 months vs 10.7 months; HR, 0.77 [$P = .0034$]) and in the other PD-L1 subgroups. There was no difference in PFS between the experimental cohorts and SOC, and the ORRs were slightly higher in the chemotherapy-containing arms than in the pembrolizumab-alone arm. As expected, toxicity was less in the pembrolizumab alone arm compared with the pembrolizumab-chemotherapy and SOC arms (grade 3-5 AEs, respectively: 55%, 85%, and 83%).⁶² To summarize, KEYNOTE-048 established that immunotherapy with or without chemotherapy is now the SOC for the first-line treatment of metastatic HNSCC. Whether the initiation of immune checkpoint inhibitors in the first-line setting would be preferable to chemoimmunotherapy remains unanswered in HNSCC given that KEYNOTE-048 was not designed to compare its 2 experimental arms. On the basis of KEYNOTE-048, the US

Food and Drug Administration has currently approved pembrolizumab monotherapy as first-line treatment for patients with CPS scores ≥ 1 and chemotherapy plus immunotherapy regardless of CPS score. Other anticipated immunotherapy frontline studies include KESTREL (ClinicalTrials.gov identifier NCT02551159), comparing the efficacy of durvalumab or durvalumab plus tremilimumab versus the EXTREME regimen, and CheckMate 651 (ClinicalTrials.gov identifier NCT02741570), comparing nivolumab and ipilimumab also versus the EXTREME regimen. CheckMate 714 (ClinicalTrials.gov identifier NCT02823574), a companion study to CheckMate 651, is a phase 2 trial comparing nivolumab versus nivolumab plus ipilimumab in HNSCC. A recent press notification reported that the study did not meet its primary endpoint in the response rate. This, in addition to the negative results of the EAGLE study, has shed some doubt regarding the clinical efficacy of CTLA-4 inhibitors and combination of these agents with PD-1/PD-L1 inhibitors in HNSCC.

Oropharyngeal HNSCC is a unique entity in that 70% of tumors in this location are biologically driven by HPV. One of the main carcinogenic mechanisms that HPV uses is overexpressing oncoproteins, such as E6 and E7, which inactivate tumor suppressors such as TP53 and RB, and thereby allow for unregulated growth.⁶³ This is distinct from the molecular mechanisms of tobacco-related and other carcinogen-related malignancies. Patients (especially nonsmokers) with locally advanced, HPV-related HNSCC tumors have a significantly better prognosis than those with HPV-negative HNSCC, with 3-year survival rates of approximately 83% versus 57%, respectively.⁶⁴ Given the biologic differences, questions have arisen as to whether immunotherapy efficacy is affected by HPV status. A systematic review of clinical trials using immunotherapy in HNSCC found no significant difference in ORR, stable disease, progressive disease, or OS when the results were stratified by HPV status.⁶⁵ As a whole, immunotherapy has proven to be effective for both HPV-related and HPV-unrelated HNSCC; therefore, as of the publication of this article, HPV status should not play a role in the decision to use these agents in clinical practice. Research focusing on the targeting of HPV-related HNSCC is eagerly awaited given its implications on the field of immunotherapy in virally mediated tumors.

In addition, given the excellent outcomes seen with definitive therapy for nonmetastatic HPV-positive oropharyngeal squamous cell carcinoma (OPSCC), there is significant interest in *de-escalating* care for this population, with the goal of maintaining efficacy and decreasing toxicity. One recently evolving treatment modality in low-risk HPV-related HNSCC is transoral robotic surgery with or without radiation/chemotherapy. This needs

to be compared with the current standard of primary CRT. Given the biologic rationale, efficacy in the metastatic setting, and safety profile, immunotherapy is considered a rational option for de-escalation. Data have suggested that radiation can sensitize HNSCC to immunotherapy through a variety of mechanisms, including increased MHC class I and other immune ligands, increased immune cell infiltration, etc.⁶⁶ HN005 (ClinicalTrials.gov identifier NCT03952585) is a trial aimed at de-intensifying therapy for low-risk HPV-related OPSCC comparing standard CRT with lower dose radiation/chemotherapy versus lower dose radiation with nivolumab. Radiation Therapy Oncology Group (RTOG) 3504 (ClinicalTrials.gov identifier NCT02764593) is a completed phase 1 study of high-risk or intermediate-risk HNSCC examining the safety of nivolumab in combination with cisplatin, both weekly and every 3 weeks, and cetuximab followed by adjuvant nivolumab. Early reported data show that the combinations with nivolumab are feasible, with promising early oncologic outcomes.⁶⁷ De-escalation using immunotherapy is worthy goal in OPSCC but should be done carefully because several recent nonimmunotherapy-based de-escalation trials were negative.^{68,69}

There are a multitude of other studies currently examining immunotherapy in locally advanced HNSCC. For example, Javelin Head and Neck 100 (ClinicalTrials.gov identifier NCT02952586) is currently examining the addition of avelumab to CRT (with a lead in, concurrent, and maintenance dosing schedule) with cisplatin for high-risk HPV- HNSCC. Unfortunately, a recent press release has indicated that the statistical boundary for futility was crossed, thereby shedding doubt as to the most appropriate approach for adding checkpoint inhibitors to the CRT backbone. More information is needed to better understand possible factors that resulted in a lack of benefit in this study. Eastern Cooperative Oncology Group (ECOG 3161) (ClinicalTrials.gov identifier NCT03811015) is following a different approach of adding immunotherapy after the completion of CRT. This trial is also focused on intermediate-risk, HPV-related OPSCC and examining the role of maintenance nivolumab. Typically, patients with intermediate-risk disease would not be candidates for de-escalation as is the case with low-risk disease. Given the potential for long-term relapse with distant metastases in this disease, a maintenance immune approach as offered by EA3161 is attractive. In addition, a randomized phase 3 study evaluating atezolizumab (ClinicalTrials.gov identifier NCT03452137) as adjuvant therapy after definitive treatment has completed accrual. The patient population in NCT03452137 is predominantly HPV-unrelated and thus is unlikely to provide a definitive answer as to the role of maintenance checkpoint inhibitors for

HPV-related OPSCC. Small institution trials are also examining novel agents in a window of opportunity designs. An example is a currently accruing trial of the semaphorin 4D inhibitor pepinemb (ClinicalTrials.gov identifier NCT03690986).⁷⁰ Finally, trials of immunotherapy in combination with reirradiation (ClinicalTrials.gov identifier NCT03521570) and with stereotactic body radiation therapy (ClinicalTrials.gov identifier NCT03546582) are also ongoing.

Research on the role of immunotherapy in HNSCC is ongoing, with significant interest in combinations and vaccine-based studies. The HPV biology of oropharyngeal HNSCC allows for unique drug development in this disease. MEDI0457 is a plasmid recombinant interleukin (IL) 2–based immunotherapy targeting the unique E6 and E7 oncoproteins of HPV-positive HNSCC. In a small phase 1b/2 study, the investigators demonstrated that, when delivered by electroporation, MEDI0457 showed sustained induction of HPV-specific, immune-specific responses and was demonstrated to be safe. Final efficacy results are awaited.⁷¹ The CUE-101 study (ClinicalTrials.gov identifier NCT03978689) used a compound that combined IL-2 and a peptide-MHC composed of HLA-A 02:01 and protein from E7, with the goal of developing an immune response to HPV-positive HNSCC. The stimulator of interferon genes (STING) pathway plays an important part in immune activation, and the ADU-S100 molecule was designed as a STING activator and is currently being studied by direct tumoral injection in combination with pembrolizumab in HNSCC.⁷² In addition, immune therapy in combination with targeted therapy is being studied, as exemplified by accruing trials in HNSCC combining immunotherapy with cabozantinib (ClinicalTrials.gov identifier NCT03468218), cetuximab (ClinicalTrials.gov identifier NCT03370276), and lenvatinib.⁷³

Resistance to Immunotherapy and Biomarkers of Response

Cancer immunotherapy relies on the ability of the immune system to recognize cancer cells and mount a tumor-specific response, with immunologic memory leading to potentially durable disease control. PD-(L)1–targeted regimens can fail patients because of primary resistance, when a cancer does not respond to immunotherapy, or acquired resistance, when a cancer initially responds but then progresses. Adaptive immune mechanisms may underlie both of these scenarios and evolve, as the interaction between the immune system and the tumor is dynamic both temporally and regionally within the body.⁷⁴ T-cell-mediated mechanisms of resistance include an absence of antigenic proteins or their presentation to the immune system. Cytotoxic T cells may be functionally

silenced by the tumor, as with oncogenic PD-L1 expression, or by other inhibitory cells, such as regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages. Alternatively, T cells may be excluded from the tumor microenvironment altogether either by the tumor-mediated, tissue-specific, or acquired microenvironment signaling pathways.⁷⁴

In a system this complex, it is perhaps not surprising that our understanding of predictive and prognostic biomarkers remains limited. PD-L1 expression by immunohistochemistry is the most widely used biomarker and is predictive of response to PD-(L)1 blockade in lung cancer and HNSCC. But each PD(L)-1–targeting antibody was developed alongside its own companion diagnostic, each of which has different sensitivities and grading scales.⁷⁵ In addition to changing PD-L1 expression levels over time, there is intratumoral heterogeneity, and expression may differ depending on which metastatic site is sampled.⁴ In NSCLC, it was shown that metastatic sites tend to differ with higher expression levels in liver and adrenal metastases than in bone or brain metastases.^{76,77} Interestingly, in patients with HNSCC, the CPS score, which accounts for the immune milieu, is more predictive than the TPS score for response to PD-1 blockade, as described above. TMB is another investigational surrogate biomarker of response to immunotherapy. The current thought is that mutations leading to neoantigens, or novel immunogenic peptides, underlie this association, but this may be a simplistic view of a genome-wide finding.⁷⁸ Among tumor types known to respond to immunotherapy, specifically NSCLC, melanoma, and mismatch repair-deficient tumors, TMB is associated with response to checkpoint blockade.^{3,79,80} Similar to PD-L1, the measurement of TMB varies by testing platform and is dynamic; to date, TMB assessment is not currently an integral part of the clinical treatment algorithm for lung cancer or HNSCC. The search for better prognostic and predictive biomarkers is ongoing and will be essential to improving patient selection for the growing list of therapeutic options.

Summary

Now that checkpoint inhibitor therapy has reached the frontline setting in both lung cancer and HNSCC, clinical trials need to address treatment options at progression because only traditional cytotoxic chemotherapy options remain as the SOC. This highlights the gaping area of need for treatment options in the setting of innate or acquired resistance to checkpoint inhibitor therapy. Strategies to resensitize patients to immunotherapy include high-dose radiation, which is being studied by the NRG cooperative group. Novel sequencing paradigms between chemotherapy and immunotherapy need investigation. The immunomodulatory effects of systemic chemotherapy need to be

further investigated. The optimal sequencing depends on the cytotoxic as well as immune-modulatory agents at stake and likely will depend on the disease. As noted, tyrosine kinases are being studied as single agents or in combination with immunomodulatory approaches. Promising drugs in phase 3 clinical trials in NSCLC include canakinumab, a monoclonal antibody targeting IL-1B, which led to a significant reduction in the risk of developing lung cancer in a large cardiovascular disease clinical trial.⁸¹ Large cooperative

efforts that enable the study of multiple genomic alterations, such as Lung-MAP (ClinicalTrials.gov identifier NCT02154490) have been designed to specifically address this need. In conclusion, immunotherapy has changed the SOC for aerodigestive malignancies, including lung cancer and HNSCC, and has paved the way for a new treatment paradigm. Despite these advances, monumental efforts are still needed to significantly affect the outcome of patients with these challenging diseases. ■

References

- Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov*. 2018;8:1069-1086.
- Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378:158-168.
- Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*. 2015;348:124-128.
- Siu LL, Even C, Mesia R, et al. Safety and efficacy of durvalumab with or without tremelimumab in patients with PD-L1-low/negative recurrent or metastatic HNSCC: the phase 2 CONDOR randomized clinical trial. *JAMA Oncol*. 2019;5:195-203.
- Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373:1627-1639.
- Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373:123-135.
- Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387:1540-1550.
- Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017;389:255-265.
- Borcman E, Nandikolla A, Long G, Goel S, Le Tourneau C. Patterns of response and progression to immunotherapy. *Am Soc Clin Oncol Educ Book*. 2018;38:169-178.
- Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2018;36:1714-1768.
- Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372:2018-2028.
- Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823-1833.
- Reck M, Rodriguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. *J Clin Oncol*. 2019;37:537-546.
- Garon EB, Hellmann MD, Rizvi NA, et al. Five-year overall survival for patients with advanced nonsmall-cell lung cancer treated with pembrolizumab: results from the phase I KEYNOTE-001 study. *J Clin Oncol*. 2019;37:2518-2527.
- Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393:1819-1830.
- Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078-2092.
- Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378:2288-2301.
- Schoenfeld AJ, Arbour KC, Rizvi H, et al. Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib. *Ann Oncol*. 2019;30:839-844.
- Yang JC, Shepherd FA, Kim DW, et al. Osimertinib plus durvalumab versus osimertinib monotherapy in EGFR T790M-positive NSCLC following previous EGFR TKI therapy: CAURAL brief report. *J Thorac Oncol*. 2019;14:933-939.
- Ahn M, Han J, Sequist L, et al. OA 09.03 TATTON ph Ib expansion cohort: osimertinib plus savolitinib for pts with EGFR-mutant MET-amplified NSCLC after progression on prior EGFR-TKI [abstract]. *J Thorac Oncol*. 2017;12(suppl 2):S1768.
- Lisberg A, Cummings A, Goldman JW, et al. A phase II study of pembrolizumab in EGFR-mutant, PD-L1+, tyrosine kinase inhibitor naive patients with advanced NSCLC. *J Thorac Oncol*. 2018;13:1138-1145.
- National Comprehensive Cancer Network. NCCN Guidelines, Version 3.2020: Non-Small Cell Lung Cancer. National Comprehensive Cancer Network; 2020.
- Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379:2040-2051.
- Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med*. 2019;381:2020-2031.
- Munhoz RR, Postow MA. Clinical development of PD-1 in advanced melanoma. *Cancer J*. 2018;24:7-14.
- Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2019;20:1370-1385.
- Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med*. 2018;378:2093-2104.
- Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol*. 2010;28:2181-2190.
- Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377:1919-1929.
- Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379:2342-2350.
- Gray JE, Villegas A, Daniel D, et al. Three-year overall survival with durvalumab after chemoradiotherapy in stage III NSCLC—update from PACIFIC. *J Thorac Oncol*. 2020;15:288-293.

32. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 2008;26:3552-3559.
33. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM Classification for Lung Cancer. *J Thorac Oncol*. 2016;11:39-51.
34. Owen D, Chaft JE. Immunotherapy in surgically resectable non-small cell lung cancer. *J Thorac Dis*. 2018;10(suppl 3):S404-S411.
35. Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. *N Engl J Med*. 2018;378:1976-1986.
36. Hellmann MD, Chaft JE, William WN Jr, et al. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. *Lancet Oncol*. 2014;15:e42-e50.
37. Rusch VW, Chaft JE, Johnson B, et al. Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): initial results from a multicenter study (LCMC3) [abstract]. *J Clin Oncol*. 2018;36(15 suppl):8541.
38. Cascone T, William WN, Weissferdt A, et al. Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC): clinical and correlative results from the NEOSTAR study [abstract]. *J Clin Oncol*. 2019;37(15 suppl):8504.
39. Provencio M, Nadal E, Insa A, et al. Neoadjuvant chemo-immunotherapy for the treatment of stage IIIA resectable non-small-cell lung cancer (NSCLC): a phase II multicenter exploratory study—final data of patients who underwent surgical assessment [abstract]. *J Clin Oncol*. 2019;37:8509.
40. Wu YL, Herbst RS, Mann H, Rukazenkov Y, Marotti M, Tsuboi M. ADAURA: phase III, double-blind, randomized study of osimertinib versus placebo in EGFR mutation-positive early-stage NSCLC after complete surgical resection. *Clin Lung Cancer*. 2018;19:e533-e536.
41. Carlisle JW, Ramalingam SS. Role of osimertinib in the treatment of EGFR-mutation positive non-small-cell lung cancer. *Future Oncol*. 2019;15:805-816.
42. Solomon BJ, Ahn JS, Barlesi F, et al. ALINA: a phase III study of alectinib versus chemotherapy as adjuvant therapy in patients with stage IB-IIIa anaplastic lymphoma kinase-positive (ALK+) non-small cell lung cancer (NSCLC) [abstract]. *J Clin Oncol*. 2019;37(15 suppl):TPS8569.
43. Horn L, Mansfield AS, Szczesna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379:2220-2229.
44. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394:1929-1939.
45. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med*. 1999;340:265-271.
46. Hann CL, Scherpereel A, Hellyer JA, Wakelee HA. Role of immunotherapy in small cell lung cancer, thymic epithelial tumors, and mesothelioma. *Am Soc Clin Oncol Educ Book*. 2019;39:543-552.
47. Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol*. 2016;17:883-895.
48. Reck M, Vicente D, Ciuleanu T, et al. Efficacy and safety of nivolumab (nivo) monotherapy versus chemotherapy (chemo) in recurrent small cell lung cancer (SCLC): results from CheckMate 331. *Ann Oncol*. 2018;29(suppl 10):mdy511-0004.
49. Ott PA, Elez E, Hirt S, et al. Pembrolizumab in patients with extensive-stage small-cell lung cancer: results from the phase Ib KEYNOTE-028 study. *J Clin Oncol*. 2017;35:3823-3829.
50. Chung HC, Lopez-Martin JA, Kao SCH, et al. Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158 [abstract]. *J Clin Oncol*. 2018;36(15 suppl):8506.
51. Mehra R, Seiwert TY, Gupta S, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: pooled analyses after long-term follow-up in KEYNOTE-012. *Br J Cancer*. 2018;119:153-159.
52. Seiwert TY, Burtneß B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol*. 2016;17:956-965.
53. Larkins E, Blumenthal GM, Yuan W, et al. FDA approval summary: pembrolizumab for the treatment of recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy. *Oncologist*. 2017;22:873-878.
54. Bauml J, Seiwert TY, Pfister DG, et al. Pembrolizumab for platinum- and cetuximab-refractory head and neck cancer: results from a single-arm, phase II study. *J Clin Oncol*. 2017;35:1542-1549.
55. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *J Clin Oncol*. 2007;25:2171-2177.
56. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2016;375:1856-1867.
57. Ferris RL, Licitra L, Fayette J, et al. Nivolumab in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: efficacy and safety in CheckMate 141 by prior cetuximab use. *Clin Cancer Res*. 2019;25:5221-5230.
58. Saba NF, Blumenschein G Jr, Guigay J, et al. Nivolumab versus investigator's choice in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: efficacy and safety in CheckMate 141 by age. *Oral Oncol*. 2019;96:7-14.
59. Cohen EEW, Soulieres D, Le Tourneau C, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *Lancet*. 2019;393:156-167.
60. Licitra LF, Haddad RI, Even C, et al. EAGLE: a phase 3, randomized, open-label study of durvalumab (D) with or without tremelimumab (T) in patients (pts) with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) [abstract]. *J Clin Oncol*. 2019;37(15 suppl):6012.
61. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med*. 2008;359:1116-1127.
62. Burtneß B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet*. 2019;394:1915-1928.
63. Miller DL, Puricelli MD, Stack MS. Virology and molecular pathogenesis of HPV (human papillomavirus)-associated oropharyngeal squamous cell carcinoma. *Biochem J*. 2012;443:339-353.
64. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363:24-35.

65. Patel JJ, Levy DA, Nguyen SA, Knochelmann HM, Day TA. Impact of PD-L1 expression and human papillomavirus status in anti-PD1/PDL1 immunotherapy for head and neck squamous cell carcinoma—systematic review and meta-analysis. *Head Neck*. 2020;42:774-786.
66. Karam SD, Raben D. Radioimmunotherapy for the treatment of head and neck cancer. *Lancet Oncol*. 2019;20:e404-e416.
67. Ferris RL, Gillison ML, Harris J, et al. Safety evaluation of nivolumab (Nivo) concomitant with cetuximab-radiotherapy for intermediate (IR) and high-risk (HR) local-regionally advanced head and neck squamous cell carcinoma (HNSCC): RTOG 3504 [abstract]. *J Clin Oncol*. 2018;36(15 suppl):6010.
68. Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet*. 2019;393:40-50.
69. Mehanna H, Robinson M, Hartley A, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. *Lancet*. 2019;393:51-60.
70. Palackdharry S, Gillison M, Worden F, et al. Neoadjuvant pembrolizumab is active in surgically resected head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2018;100:1365.
71. Aggarwal C, Cohen RB, Morrow MP, et al. Immunotherapy targeting HPV16/18 generates potent immune responses in HPV-associated head and neck cancer. *Clin Cancer Res*. 2019;25:110-124.
72. Corrales L, Desbien AL, Gauthier KES, et al. Abstract 1202: tumor cell intrinsic STING signaling demonstrates minimal contribution to the anti-tumor response elicited by the STING agonist ADU-S100 (MIW815). *Cancer Res*. 2019;79(13 suppl):1202.
73. Taylor MH, Rasco DW, Brose MS, et al. A phase 1b/2 trial of lenvatinib plus pembrolizumab in patients with squamous cell carcinoma of the head and neck [abstract]. *J Clin Oncol*. 2018;36(15 suppl):6016.
74. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. *Cell*. 2017;168:707-723.
75. Mino-Kenudson M. Programmed cell death ligand-1 (PD-L1) expression by immunohistochemistry: could it be predictive and/or prognostic in non-small cell lung cancer? *Cancer Biol Med*. 2016;13:157-170.
76. McLaughlin J, Han G, Schalper KA, et al. Quantitative assessment of the heterogeneity of PD-L1 expression in non-small-cell lung cancer. *JAMA Oncol*. 2016;2:46-54.
77. Hong L, Dibaj S, Negrao MV, et al. Spatial and temporal heterogeneity of PD-L1 and its impact on benefit from immune checkpoint blockade in non-small cell lung cancer (NSCLC) [abstract]. *J Clin Oncol*. 2019;37(15 suppl):9017.
78. Chan TA, Yarchoan M, Jaffee E, et al. Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic. *Ann Oncol*. 2019;30:44-56.
79. Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N Engl J Med*. 2014;371:2189-2199.
80. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372:2509-2520.
81. Ridker PM, MacFadyen JG, Thuren T, et al. Effect of interleukin-1beta inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;390:1833-1842.