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CONSENSUS STATEMENT

Clinical strategies for lung cancer management: Recommendations from the Bridging the Gaps Lung Cancer Consensus Conference 2024

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Abstract

Clinical practice guidelines for nonsmall cell lung cancer (NSCLC) and small cell lung cancer include recommendations based on high-level clinical trial evidence, but complex clinical questions are frequently seen in real-world practice that are not clearly answered by prospective trial data. To address these questions, the *Bridging the Gaps Lung Cancer Consensus Conference 2024* (BtG LCCC 2024) convened to develop US-focused expert guidance for clinical situations in which level 1 evidence is lacking. At BtG LCCC 2024, a multidisciplinary expert panel discussed ongoing clinical issues in small cell lung cancer management, targeted therapy in *EGFR*-mutated NSCLC, management of early stage NSCLC, identification and management of non-*EGFR* oncogene-driven NSCLC, and use of immunotherapy in advanced/metastatic NSCLC. By using a modified Delphi process, 12 consensus recommendations were developed with the goal of providing guidance on the use of novel diagnostic methods and treatments for clinicians who manage lung cancer. This report reviews these areas of consensus and discusses ongoing questions about ways to apply current clinical evidence.

KEYWORDS
consensus recommendations, nonsmall cell lung cancer (NSCLC), small cell lung cancer (SCLC), targeted therapy, uncommon mutations

INTRODUCTION

Evidence-based options for the management of lung cancer have expanded rapidly, with multiple recent drug approvals and management strategies across the spectrum of nonsmall cell lung cancer (NSCLC) and small cell lung cancer (SCLC). This rapid expansion has increased the complexity of the treatment landscape and has presented ongoing questions about decision-making for clinicians and patients.

Clinical practice guidelines from organizations in the United States, such as the National Comprehensive Cancer Network (NCCN), the American Society for Clinical Oncology, the American Society for Radiation Oncology, and the American College of Chest Physicians, along with the global International Association for the Study of Lung Cancer, use high-level evidence—which is often based on a clinical trial populations that may differ from the real-world population—to develop general recommendations for diagnosis, management, and surveillance of NSCLC and SCLC.[1–5] However, these guidelines are often not able to clearly answer clinical questions about nuanced and patient-specific clinical scenarios (e.g., the optimal targeted therapy for lung cancers with uncommon mutations or multiple co-mutated genes) or emerging diagnostic and treatment methods. Consensus panels provide valuable insight from experts and are useful for addressing these clinical questions.

The *Bridging the Gaps Lung Cancer Consensus Conference* (BtG LCCC) was convened to provide US-focused expert guidance on clinical decision making in situations that lack randomized clinical trial level 1 evidence to support.[1–5] This article reports the consensus recommendations and ongoing questions for management that were generated at the BtG LCCC.

METHODS

The BtG LCCC, held on July 23–24, 2024, was attended by 29 predominantly US-based academic and community lung cancer experts and investigators who specialize in medical oncology ($n = 24$), radiation oncology ($n = 2$), thoracic surgery ($n = 2$), or pure translational research ($n = 1$). Presentations delivered at the meeting by topic experts were used to prompt discussion and debate, and panelists voted on 49 consensus questions that were developed by a group of lung cancer experts using a modified Delphi process. If a panelist did not vote because they lacked expertise on a specific question or section, had prohibitive conflicts of interest, or for another reason, their lack of response was counted as *abstain*. When calculating the percentage results to determine consensus, the abstain votes were excluded from the denominator. Responses were used to develop 12 expert consensus recommendations, with a predefined consensus

criterion of ≥75% (to view all the questions and results, see the Supporting Materials and Tables S1–S5).

RESULTS AND DISCUSSION

Small cell lung cancer: Beyond first-line therapy

In 2019, chemoimmunotherapy became the standard of care for the first-line treatment of extensive-stage SCLC (ES-SCLC) based on findings from the IMpower133 (ClinicalTrials.gov identifier NCT02763579) and CASPIAN (ClinicalTrials.gov identifier NCT03043872) trials, which demonstrated improved median overall survival (OS) with the addition of an immune checkpoint inhibitor (ICI) to platinum–etoposide doublet chemotherapy.[6,7] However, the majority of patients experience disease relapse, and survival outcomes are poor with current treatment options in the second-line setting.[8] Additional treatment options and identification of biomarkers that guide therapeutic selection are needed to improve outcomes in these patients. Experts at the BtG LCCC generated four consensus recommendations for SCLC (Box 1).

Box 1 Consensus recommendations for SCLC management.

1.1 Chemoradiation therapy followed by 2 years of durvalumab is preferred for patients with limited-stage SCLC receiving radiation therapy.
1.2 An immune checkpoint inhibitor should be combined with etoposide and platinum chemotherapy for second-line treatment of patients previously treated for limited-stage disease with chemotherapy and radiation therapy (or surgical resection and chemotherapy).
1.3 Lurbinectedin or tarlatamab should be considered for second-line or beyond treatment of extensive-stage SCLC.
1.4 Magnetic resonance imaging of the brain every 3 months is preferred over prophylactic cranial irradiation for extensive-stage SCLC.

Recommendation 1.1: Chemoradiation therapy followed by 2 years of durvalumab is preferred for patients with limited-stage SCLC receiving radiation therapy

ICIs have been increasingly used in clinical trials of limited-stage SCLC (LS-SCLC) and now have data demonstrating improved OS with the addition of consolidative durvalumab after concurrent chemoradiation (CCRT).[1,9] In the ADRIATIC trial (ClinicalTrials.gov identifier NCT03703297), durvalumab given as consolidative therapy for up to 24 months after definitive CCRT significantly improved progression-free survival (PFS) and OS over placebo in patients with LS-SCLC who had not progressed after completion of curative-intent CCRT.[9,10] Implementation of ICIs earlier in the treatment sequence for LS-SCLC is a practice-changing addition to the treatment landscape; however, it also raises questions about the sequencing of treatments if recurrence occurs.

Recommendation 1.2: ICI plus platinum–etoposide is preferred for second-line treatment of patients previously treated for limited-stage SCLC with chemotherapy and radiation therapy (or surgical resection and chemotherapy)

Although chemotherapy with radiation or surgical resection yields responses in the majority of patients with limited-stage SCLC, many patients experience relapse within 2 years of completion of definitive treatment.[11] The PFS and OS benefit of adding atezolizumab to platinum-etoposide in the IMpower133 trial, which allowed enrollment of patients who previously received chemoradiotherapy with curative intent for limited-stage SCLC at least 6 months before diagnosis of ES-SCLC, supports the use of carboplatin, etoposide, and a programmed cell death ligand 1 (PD-L1) inhibitor in patients who previously received chemotherapy with radiation therapy or underwent surgical resection and experienced subsequent disease relapse.[6] However, the aforementioned results of the ADRIATIC trial are likely to increase use of ICIs in the limited-stage setting, highlighting the need for further research to optimize the management of patients with SCLC who relapse on ICI therapy. Rechallenging with the original platinum-based regimen (without ICI) may be appropriate for patients with disease relapse >6 months after the completion of initial chemotherapy.[12,13] However, the panelists noted that treatment decisions are influenced by the extent and location of recurrence as well as the presence of brain metastases. Although a small proportion of experts stated that they sometimes use single-agent ICI at metastatic relapse of LS-SCLC in patients not previously treated with ICI (e.g., previously treated with platinum-based chemotherapy and radiation), US Food and Drug Administration (FDA) approvals for monotherapy with nivolumab and pembrolizumab, respectively, were withdrawn in 2021 because of negative registrational trials in the first-line setting when given with chemotherapy.[1,14]

Recommendation 1.3: Lurbinectedin or tarlatamab should be considered for second-line or beyond treatment of extensive-stage SCLC

Although rechallenge with platinum chemotherapy is recommended by the NCCN guidelines for relapsed SCLC with a chemotherapy platinum-free interval suggestive of at least 6 months of platinum sensitivity, the limited PFS and OS with this strategy highlight the need

for better treatment options.[12] The FDA granted accelerated approval to lurbinectedin in 2020 based on findings from a phase 2 basket trial (ClinicalTrials.gov identifier NCT02454972), which demonstrated clinical activity and acceptable safety and tolerability in patients with SCLC previously treated with one chemotherapy-containing regimen.[15,16] The median OS was 16.2 months in a small subset of patients with a chemotherapy platinum-free interval of at least 180 days who were censored for survival analysis, suggesting that it may extend survival beyond that seen with chemotherapy rechallenge.[17] However, experts noted that not all patients with SCLC respond to lurbinectedin, and central nervous system (CNS) metastases could be a concern because the intracranial activity with the semisynthetic compound of lurbinectedin is unclear (the phase 2 trial leading to approval excluded patients with intracranial metastases).[16]

Tarlatamab, a DLL3-directed, bispecific CD3 T-cell engager, received accelerated FDA approval in 2024 based on findings from the DeLLphi-301 trial (ClinicalTrials.gov identifier NCT05060016), which produced an objective response rate of 40% in patients with previously treated, ES-SCLC (the majority of patients had received two prior lines of therapy).[18–20] Response duration was at least 6 months in 59% and at least 9 months in 29% of those with responses.[20] However, tarlatamab and other DLL3-directed bispecific CD3 T-cell engagers carry risks for cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, thereby requiring administration in a health care facility equipped to manage cytokine release syndrome, which may limit access for patients who do not have these resources.[21]

Although some experts prefer to use tarlatamab if the necessary resources are available, data comparing tarlatamab and lurbinectedin in a head-to-head trial were not available at the time of the BtG LCCC meeting. Since the meeting, findings from the DeLLphi-304 trial (ClinicalTrials.gov identifier NCT05060016) have been published and demonstrated longer OS with tarlatamab compared with chemotherapy (topotecan, lurbinectedin, or amrubicin) in patients with SCLC that relapsed after platinum-based chemotherapy.[22] Based on these findings, some panelists recommended tarlatamab for patients able to tolerate the treatment and lurbinectedin for those with poorer performance status or who are unable to access resources for tarlatamab.

The panelists also noted that rechallenge with platinum chemotherapy may be a suitable option in select patients, notably those with a large initial response and a PFS of at least 6 months after the last use of platinum chemotherapy. A retrospective study indicated that second-line platinum rechallenge yielded longer PFS and OS compared with lurbinectedin in patients with ES-SCLC who were initially treated with platinum chemotherapy.[23] However, patients in the platinum rechallenge group tended to be younger with a longer chemotherapy-free interval, and a significantly greater proportion of them discontinued because of tolerability.[23] The panelists concluded that, given the different characteristics of patients who received platinum rechallenge versus lurbinectedin as well as the increased use of immunotherapy for first-line management of SCLC, patient selection for platinum rechallenge is important.[24]

Recommendation 1.4: Magnetic resonance imaging of the brain every 3 months is preferred over prophylactic cranial irradiation for extensive-stage SCLC

Prophylactic cranial irradiation (PCI) was historically recommended for patients with ES-SCLC who responded to systemic therapy after trials demonstrated an improvement in OS. Still, those studies did not include magnetic resonance imaging (MRI) of the brain at baseline to evaluate for intracranial disease.[1,25,26] The phase 3 randomized trial from the European Organization for Research and Treatment of Cancer (ClinicalTrials.gov identifier NCT00016211) indicated that patients with ES-SCLC and no brain metastases who received PCI after a response to systemic therapy had longer improvements in OS and survival without disease progression compared with those who received no further therapy (control group).[25] Prior routine brain MRI was not required in that study unless the patient had symptoms suggesting brain metastases, which introduces the question of whether some patients had occult brain metastases before starting brain-directed radiation therapy.[25] By contrast, a phase 3 trial of a similar patient population conducted in Japan found no improvement in OS among patients who received PCI compared with those who underwent regular MRI surveillance with irradiation of asymptomatic brain metastases upon detection.[26] That study required brain MRI before enrollment and randomization to ensure the absence of visible brain metastases. A systematic review and meta-analysis performed a subgroup analysis of nine studies and reported no OS benefit of PCI when MRI was used to exclude patients who had brain metastases at restaging.[27] PCI can also lead to chronic neurotoxicity and decreased quality of life, particularly in patients older than 60 years and those who receive high radiation doses. These factors should be considered in the decision-making process.[28] The panelists concurred that a brain MRI study with contrast should be obtained every 3 months if PCI is not given to ensure that early salvage radiation can be given if CNS progression does develop.

Ongoing questions in SCLC management

Table 1 highlights outstanding questions from the meeting for which consensus was not reached. Although a nonconsensus majority of BtG LCCC experts stated that they consider retreatment with platinum-based chemotherapy the in second-line, chemotherapy-sensitive ES-SCLC setting, nearly one third of experts stated that they either avoid platinum chemotherapy in the second-line setting or only use it in rare scenarios (Table 1). The experts differed in opinion regarding when to use tarlatamab in ES-SCLC, with 25% of BtG LCCC experts saying they base their decision on clinical factors (e.g., those who can afford to wait for a response and are not at high risk for severe complications) rather than the line of treatment.

Approximately one half of the experts prefer MRI monitoring every 3 months over PCI for patients with LS-SCLC. However, this clinical scenario has limited data upon which to base clinical decisions based on the extensive-stage data with brain MRI at

TABLE 1 Remaining questions in small cell lung cancer management.

Topic	Answers: Responses	No. (%)	No vote/ abstain, no.
Treatment			
Do you consider re-treatment with platinum-based therapy in the second-line setting?	Yes, if the chemotherapy-free interval is >6 months.	17 (60.7)	1
	Yes, if the chemotherapy-free interval is >3 months.	2 (7.1)	
	No, I do not typically give platinum-based therapy in the second-line and beyond.	6 (21.4)	
	Rarely in outlier scenarios	3 (10.7)	
Do you use SCLC subtypes in clinical practice, or would you use them if available?	Yes, the IHC stains are done at my institution, and I take it into account in clinical decision making.	3 (10.7)	1
	Yes, the IHC stains are NOT done at my institution, but I would use the information if available.	5 (17.9)	
	No, I do not think this is yet ready for clinical practice beyond clinical trials.	20 (71.4)	
What is the ideal line of therapy to use tarlatamab as a standard treatment option?	I will use tarlatamab in the third line, according to the trial that led to submission to the FDA.	9 (32.1)	1
	I will use tarlatamab in the second line given the outcomes demonstrated in the third line.	11 (39.3)	
	I am not yet sure where this will fit into my clinical practice because I would like to see more mature trial data	1 (3.6)	
	I will use tarlatamab in patients with specific clinical factors rather than in a particular line of treatment	7 (25.0)	
	I don't plan to use tarlatamab until I see the experience in standard practice because of the hospitalization requirement demonstrated in the trial.	0 (0.0)	
Use of PCI for limited-stage SCLC	No, I prefer a brain MRI every 3 months rather than PCI.	14 (50.0)	1
	Yes, I prefer that patients receive PCI.	9 (32.1)	
	I prefer to request a radiation oncology consultation.	6 (21.4)	
Use of another DLL3-directed therapy with a different mechanism in a patient previously treated with a DLL3-directed treatment	No, I anticipate that DLL3 expression would be lost as the mechanism of resistance.	6 (21.4)	1
	Yes, I anticipate that DLL3 expression would remain with a different mechanism of resistance.	10 (35.7)	
	I would consider enrolment pending a biopsy demonstrating the presence of DLL3.	12 (41.9)	

Note: At the time of writing, the authors note that their July 2024 consensus recommendations may need to be reconsidered and updated to reflect FDA approvals since the time of voting in July 2024, in addition to promising trials with potential for expanded indications/practice-changing data.
Abbreviations: FDA, US Food and Drug Administration; IHC, immunohistochemistry; MRI, magnetic resonance imaging; PCI, prophylactic cranial irradiation; SCLC, small cell lung cancer.

baseline. The phase 3 MAVERICK trial (ClinicalTrials.gov identifier NCT04155034) is currently comparing PCI with surveillance MRI after the completion of first-line treatment in limited stage SCLC and ES-SCLC.

EGFR mutations and targeted therapy in NSCLC

Although a multitude of first-generation, second-generation, and third-generation EGFR-targeted tyrosine kinase inhibitors (TKIs) have been developed and have improved OS outcomes for patients with *EGFR*-mutated NSCLC, primary and secondary resistance mutations limit the effectiveness and durability of these targeted therapies across all *EGFR* mutation subtypes, including *EGFR* Del19, *L858R*, and *exon 20 insertion* mutations.[29] The development of therapeutic combinations and TKIs that target bypass resistance mechanisms (e.g., the EGFR-MET bispecific antibody amivantamab) may help address treatment resistance and improve outcomes in these patients.[30,31] Areas of consensus for *EGFR*-mutated NSCLC are listed in Box 2.

Box 2 Consensus recommendations for management of EGFR-mutated NSCLC

2.1 Osimertinib, carboplatin, and pemetrexed is a preferred first-line regimen for newly diagnosed metastatic NSCLC with an *EGFR* L858R mutation, multiple intracranial and extracranial metastases, and an Eastern Cooperative Oncology Group performance score ≤2.

2.2 Carboplatin, pemetrexed, and amivantamab is a preferred first-line treatment regimen for newly diagnosed stage IV lung adenocarcinoma with an *EGFR* exon 20 insertion mutation.

Recommendation 2.1: Osimertinib, carboplatin, and pemetrexed is the preferred first-line regimen for newly diagnosed metastatic NSCLC with an *EGFR* L858R mutation, multiple intracranial and extracranial metastases, and an Eastern Cooperative Oncology Group performance score of ≤2

Three potential regimens for the first-line management of *EGFR*-mutated lung cancer were discussed: osimertinib monotherapy, osimertinib with carboplatin and pemetrexed (FLAURA2; ClinicalTrials.gov identifier NCT04035486), and amivantamab and lazertinib (MARIPOSA; ClinicalTrials.gov identifier NCT04487080). Of note, mature OS data were not available for the FLAURA2 or MARIPOSA studies at the time of discussion. Subgroup analyses from these studies revealed potential benefits of combination therapy over osimertinib monotherapy, such as *EGFR* exon 19 deletions versus EGFR L858R mutations, the presence of CNS metastases, and overall disease burden. The adverse event (AE) profiles of each regimen were also discussed thoroughly. In the FLAURA2 trial, PFS was significantly longer with the addition of carboplatin and pemetrexed to osimertinib compared with osimertinib monotherapy in patients with previously untreated, *EGFR*-mutated (exon 19 deletion or L858R mutation), advanced NSCLC.[30] Experts also noted that osimertinib is generally well tolerated (the most common AEs with osimertinib monotherapy in FLAURA2 were diarrhea, paronychia, and rash, with most events being grade 1 or 2).[30] The higher rate of grade 3 or higher AEs (particularly hematologic toxicities, such as anemia and neutropenia) in the osimertinib–chemotherapy group in FLAURA2 was attributed primarily to the chemotherapy component, although clinicians must weigh the toxicities and necessity for the addition of intravenous therapy against the observed PFS benefits.[30] The combination of amivantamab plus lazertinib has also shown superior PFS and OS compared with osimertinib monotherapy in the MARIPOSA trial, and a final OS analysis further confirmed superior OS with the combination.[31–33] However, many oncologists are more familiar with managing chemotherapy-related AEs than they are with AEs associated with amivantamab–lazertinib (e.g., paronychia, rash, infusion-related reactions, hypoalbuminemia, and edema with amivantamab), and the cutaneous toxicities associated with amivantamab remain a concern for many experts. Furthermore, the increased rate of venous thromboembolism with the amivantamab–lazertinib combination, necessitating the use of prophylactic antithrombotic therapy, may make this agent a less favorable option for certain populations, such as those who are at higher risk of bleeding-related complications. The selection of first-line treatment at the time of the consensus meeting was a patient discussion on their preferences and consideration of patient and tumor characteristics in making a recommendation.

Recommendation 2.2: Carboplatin, pemetrexed, and amivantamab is the preferred first-line treatment regimen for newly diagnosed stage IV lung adenocarcinoma with an *EGFR* exon 20 insertion

EGFR exon 20 insertion mutations, which account for approximately 10%–12% of NSCLC EGFR mutations, often respond poorly to EGFR inhibitors because of steric hindrance in the drug-binding pocket that reduces affinity for most currently available TKIs.[29] Amivantamab has mechanisms of action that circumvent binding site resistance to TKIs, target bypass resistance mechanism through MET, and bring in effector cells to employ an antitumor effect.[34] Unlike most agents used for *EGFR* exon 20 insertion mutations that have limited CNS penetration, some experts noted the CNS antitumor activity of amivantamab in further supporting its efficacy. In 2024, the FDA approved amivantamab with carboplatin and pemetrexed for locally advanced or metastatic NSCLC (mNSCLC) with an *EGFR* exon 20 insertion mutation in the first-line setting.[31] In the phase 3 PAPILLION trial (ClinicalTrials.gov identifier NCT04538664), the addition of amivantamab to carboplatin and pemetrexed reduced the risk for progression by 60% and the risk for death by 33% compared with carboplatin-pemetrexed alone.[34] The NCCN guidelines recommend this regimen as the preferred first-line option but also note that responsiveness to available therapies varies among rare *EGFR* exon 20 alteration sequences, and further research into specific sequences of exon 20 insertion mutations may be important for guiding treatment selection in the future.[2]

Ongoing questions in management of *EGFR*-mutated NSCLC

Many unresolved questions pertain to the preferred management of metastatic lung adenocarcinomas with *EGFR* exon 19 deletion and L858R mutations, with differences among experts on whether to add agents or switch therapies in patients who progress on osimertinib (Table 2). Although tumor PD-L1 expression ≥50% often guides ICI use, a nonconsensus majority strongly suggests

TABLE 2 Remaining questions in *EGFR*-mutant nonsmall cell lung cancer management.

Topic	Answers: Responses	Answers: No. (%)	No vote/ abstain, no.
Treatment			
What would you recommend for second-line treatment for a woman aged 62 years with metastatic NSCLC harboring an *EGFR* Del19 who is widely progressing on first-line osimertinib and has a history of brain metastases, if no newly acquired resistance mutations are identified on tissue and liquid biopsies?	Carboplatin and pemetrexed, with or without osimertinib	6 (22.2)	2
	Add amivantamab to osimertinib	2 (7.4)	
	Switch to amivantamab, carboplatin, and pemetrexed	16 (59.2)	
	Switch to lazertinib and amivantamab	3 (11.1)	
A man age 53 years with no tobacco use history has a history of stage IIB lung NSCLC with an *EGFR* L858R mutation, and he underwent a right lower lobe lobectomy followed by adjuvant osimertinib. While on adjuvant osimertinib at the 2-year mark, his recent imaging shows new liver metastases but no brain metastases. Biopsy from the liver reveals *EGFR* L858R and *MET* amplifications. What treatment would you choose next?	Continue osimertinib and add carboplatin and pemetrexed	2 (7.1)	1
	Stop osimertinib and start carboplatin and pemetrexed	2 (7.1)	
	Continue osimertinib and start amivantamab	4 (14.3)	
	Stop osimertinib and start lazertinib and amivantamab	7 (25.0)	
	Continue osimertinib and add tepotinib or capmatinib	11 (39.3)	
	Other	2 (7.1)	
Do you use serial ctDNA for disease response monitoring in patients with metastatic lung NSCLC harboring an *EGFR* mutation?	Always	3 (10.7)	1
	Sometimes	10 (35.3)	
	Never	4 (14.3)	
	Only at disease progression	11 (39.3)	
A patient with stage IV lung adenocarcinoma who has an *EGFR* L858R mutation and a history of brain metastases is on front-line osimertinib but develops leptomeningeal disease based on radiographic imaging. What would be your next step?	Confirm leptomeningeal disease by lumbar puncture and cytology	12 (42.9)	1
	Increase osimertinib to 160 mg daily	10 (35.7)	
	Whole-brain radiation	2 (7.1)	
	Cranial-spinal radiation	1 (3.6)	
	Intrathecal chemotherapy	1 (3.6)	
	Other	2 (7.1)	
How often do you monitor the brain using MRI in a patient with no brain metastases and stage IV lung adenocarcinoma with *EGFR* mutations?	Every 3 months	7 (25.0)	1
	Every 6 months	11 (39.3)	
	Every 12 months	9 (32.1)	
	Only if the patient develops symptoms	1 (3.6)	
	Other	0 (0.0)	
When would you incorporate immunotherapy in the treatment regimen for a metastatic *EGFR*-mutated lung adenocarcinoma with *PD-L1* expression ≥50%?	Second-line carboplatin, paclitaxel, atezolizumab, and bevacizumab	2 (7.1)	1
	Second-line carboplatin, pemetrexed, and pembrolizumab	1 (3.6)	
	Third-line or beyond pembrolizumab alone	5 (17.9)	
	Never	16 (57.1)	
	Other	4 (14.3)	

(Continues)

TABLE 2 (Continued)

Topic	Answers: Responses	Answers: No. (%)	No vote/ abstain, no.
At time of radiographic progression on EGFR-targeted therapy, what test(s) do you order?	Liquid biopsy only	4 (14.3)	1
	If liquid biopsy unrevealing, then refer for tissue biopsy	13 (46.4)	
	Concurrent liquid biopsy and tissue biopsy	11 (39.3)	
	Start next line of treatment	0 (0.0)	

Note: At the time of writing, the authors note that their July 2024 consensus recommendations may need to be reconsidered and updated to reflect US Food and Drug Administration approvals since the time of voting in July 2024, in addition to promising trials with potential for expanded indications/practice-changing data.

Abbreviations: ctDNA, circulating tumor DNA; MRI, magnetic resonance imaging; NSCLC, nonsmall cell lung cancer; PD-L1, programmed cell death ligand-1.

avoiding ICIs in patients with *EGFR* mutations and tumor PD-L1 expression ≥50% because of the lack of benefit seen in some studies.

Experts differed in their recommendations on whether and when to use serial circulating tumor DNA (ctDNA) for disease response monitoring in patients with *EGFR*-mutated mNSCLC, with slightly more than one half of respondents stating that they never or only use ctDNA monitoring at disease progression. Responses were also mixed on whether to obtain tissue with or after liquid biopsy at the time of radiographic progression on EGFR-targeted therapy, with nearly one half preferring to refer for tissue biopsy only if liquid biopsy did not yield actionable information. Experts also differed in recommendations for optimal management of new-onset leptomeningeal disease while receiving osimertinib in patients with stage IV *EGFR*-mutated NSCLC and brain metastases, with most respondents choosing to confirm the presence of leptomeningeal disease with lumbar puncture and cytology or increase the osimertinib dose to 160 mg.

Early stage NSCLC

Multiple treatments that have been studied in metastatic disease have shown benefit in the neoadjuvant and adjuvant settings for early stage NSCLC.[35,36] Experts noted that establishing the utility of a pathologic complete response (pCR), a major pathologic response (mPR), and ctDNA clearance to identify patients who are likely to benefit from perioperative (neoadjuvant and adjuvant) therapy and detect recurrence will require further research. Consensus was reached around two general areas of early stage NSCLC management (Box 3).

Box 3 Consensus recommendations for management of early stage NSCLC

3.1 A clinical trial is needed to answer whether additional adjuvant immune checkpoint inhibitor therapy is beneficial for a patient with a pathologic complete response after neoadjuvant chemoimmunotherapy.

3.2 Current circulating tumor DNA minimal residual disease assays are inadequate for clinical decision making in early stage NSCLC.

Recommendation 3.1: A clinical trial is needed to answer whether additional adjuvant immune checkpoint inhibitor therapy is beneficial for a patient with a pathologic complete response after neoadjuvant chemoimmunotherapy

Although neoadjuvant chemoimmunotherapy is often preferred for eligible patients, experts question whether adding adjuvant immunotherapy can be beneficial, particularly because a pCR after neoadjuvant chemoimmunotherapy and surgery only occurs in a minority of patients.[35] Patients in the CheckMate 77T trial (ClinicalTrial.gov identifier NCT04025879) who received neoadjuvant nivolumab plus chemotherapy followed by adjuvant nivolumab had better event-free survival compared with those who received neoadjuvant chemotherapy followed by adjuvant placebo.[36] In addition, a patient-level data analysis comparing participants in the CheckMate 77T trial and the CheckMate 816 trial (ClinicalTrials.gov

identifier NCT02998528) indicated that the perioperative nivolumab regimen in CheckMate 77T yielded better event-free survival compared with neoadjuvant nivolumab and chemotherapy in CheckMate 816.[37] However, that analysis compared patients who underwent surgery on CheckMate816 with patients who underwent surgery and were fit enough to receive a dose of adjuvant therapy on CheckMate77T, thus excluding patients who completed surgery but did poorly and somewhat biasing the analysis.[37] However, the BtG LCCC experts noted that current data comparing perioperative with neoadjuvant chemoimmunotherapy are limited to cross-trial comparisons, and alternative study designs (e.g., four-arm factorial trial design, three-arm trial design, trial design with rerandomization for resectable NSCLC) intended to parse out the relative contributions of neoadjuvant and adjuvant therapy are needed. In addition, finding biomarkers beyond PD-L1 expression that can identify patients who are most likely to benefit from additional adjuvant immunotherapy and should be enrolled in these clinical trials is important.

Recommendation 3.2: Current circulating tumor DNA assays for minimal residual disease are inadequate for clinical decision making in early stage NSCLC

In exploratory analyses from the AEGEAN trial (ClinicalTrials.gov identifier NCT03800134) and CheckMate 816 trial, a pCR was more common in patients who achieved ctDNA clearance than in those who did not.[38,39] The AEGEAN study authors also reported that, of the patients who had ctDNA detected at baseline, all of those who had a pCR as well as greater than 90% of those who had an mPR had ctDNA clearance by the first day of treatment cycle 4.[38] However, the BtG LCCC experts concurred that data are insufficient to support ctDNA clearance as a surrogate for pCR or mPR or to guide the use of adjuvant therapy. They added that ctDNA clearance holds great promise as a marker or response, but the currently available assays lack the sensitivity to guide treatment decisions. Although a positive result can be interpreted as a clear signal of persistent disease, a negative result is not sufficient to confirm lack of residual disease or the probability of a later recurrence.

Ongoing questions in management of early-stage NSCLC

The BtG LCCC experts did not reach consensus on several questions related to perioperative treatment for early stage NSCLC (Table 3), including whether additional adjuvant immunotherapy is beneficial for patients with or without an mPR after neoadjuvant chemoimmunotherapy, the optimal duration of adjuvant immunotherapy or targeted therapy, the interchangeability of different programmed cell death 1 (PD-1)/PD-L1 inhibitors for the treatment of early stage NSCLC, and the use of targeted therapy in the neoadjuvant setting. Expert responses were also mixed on the minimum testing results (e.g., molecular analysis/mutation status, *PD-L1* status) needed before the initiation of neoadjuvant therapy and the clinical situations in which radiation oncology should be considered for treatment of early stage NSCLC.

Management of NSCLC driven by non-EGFR oncogenes

Targeted therapies for several oncogenic drivers other than EGFR, such as KRAS, ALK, BRAF, MET, ROS, HER2, NRG1, and NTRK, have increased therapeutic options for the subsets of patients with NSCLC driven by these oncogenes, highlighting the importance of molecular analysis to detect targetable alterations.[40] The BtG LCCC experts arrived at two general recommendations around molecular testing (Box 4) and noted that additional research is needed to optimize treatment sequences and therapeutic combinations for many of these difficult-to-treat oncogenic drivers.

Box 4 Consensus recommendations for management of non-EGFR oncogene-driven NSCLC

4.1 Next-generation sequencing that incorporates RNA-based testing is the preferred testing platform to detect *NTRK* fusions in NSCLC.[a]

4.2 Tissue and liquid biopsy should be performed (if feasible) to detect resistance mutations after progression of non-EGFR oncogene-driven NSCLC.

[a]The BtG LCCC panel also supports the 2024 National Comprehensive Cancer Network guideline recommendations about the benefit of next-generation sequencing for fusions in other oncogenes, including *ROS1*, *ALK*, and *RET*.[2]

Recommendation 4.1: Next-generation sequencing is the preferred testing platform to detect *NTRK* fusions in NSCLC

Testing for *NTRK* fusions, which occur in 0.1%–3.3% of NSCLC cases, is recommended by the NCCN because of the availability of targeted therapies (larotrectinib and entrectinib).[2,41] The experts noted how next-generation sequencing (NGS) is advantageous over other testing methods (e.g., fluorescence in situ hybridization, immunohistochemistry) for detecting *NTRK* fusions because of its high sensitivity, specificity, and ability to detect novel fusion partners.[41] RNA-based NGS is more sensitive than DNA-based NGS because it can cover large intronic regions in *NTRK1* and *NTRK3*, identify in-frame and functionally transcribed genes, and identify new fusion partners that may not be on a commercial DNA-based NGS panel.[2,41] Because RNA-based NGS is more labor-intensive to preserve

TABLE 3 Ongoing questions for management of early stage nonsmall cell lung cancer.

Topic	Answers		No vote/ abstain, no.
	Responses	**No. (%)**	
Treatment			
For a patient with an mPR after neoadjuvant chemo-IO, is additional adjuvant ICI therapy necessary?	No, the maximum benefit has likely been achieved.	2 (6.9)	0
	Yes, some benefit was seen and more would likely be helpful.	16 (55.2)	
	Not sure and would like clinical trial data	11 (37.9)	
For a patient who has not achieved mPR after neoadjuvant chemo-IO, is additional adjuvant ICI therapy helpful?	No, it's unlikely to help given the poor initial response.	2 (6.9)	0
	Yes, this is the most likely scenario for additional adjuvant benefit.	12 (41.4)	
	A clinical trial would be critical to answer this question.	15 (51.7)	
Are all PD-1/PD-L1 inhibitors the same for early stage NSCLC?	Yes, and market focus should determine use.	11 (37.9)	0
	No, we should only use each agent according to its label.	18 (62.1)	
What is the optimal duration of adjuvant ICI therapy?	1 year	21 (72.4)	0
	2 years	2 (6.9)	
	6 months	1 (3.4)	
	Until ctDNA clearance	5 (17.2)	
What is the optimal duration of adjuvant-targeted therapy?	Lifelong	6 (20.7)	0
	3 years	16 (55.2)	
	6 months to 1 year	2 (6.9)	
	2 years	1 (3.4)	
	Until ctDNA clearance	4 (13.8)	
When should radiation oncology be considered for the treatment of early stage NSCLC?	After R1 resection	4 (13.8)	0
	Patients with positive margins	12 (41.4)	
	Patients who did not have a complete pathologic response	0 (0.0)	
	Patients with bulky N2 disease or N3 disease	1 (3.4)	
	All the above	12 (41.4)	
Should targeted therapies be used as neoadjuvant therapy?	They should not be used before prospective data are available in resectable disease.	20 (69.0)	0
	Yes	5 (17.2)	
	No, subsets from KEYNOTE-671 (ClinicalTrials.gov identifier NCT03425643) and other trials indicate that driver mutation status does not significantly impact outcomes.	4 (13.8)	
What are the minimum results you need before initiation of neoadjuvant therapy?	Complete molecular analysis and PD-L1	10 (34.5)	0
	EGFR mutation status, ALK status, and PD-L1	8 (27.6)	
	Limited panel with otherwise actionable mutations and PD-L1	11 (37.9)	

Note: At the time of writing, the authors note that their July 2024 consensus recommendations may need to be reconsidered and updated to reflect US Food and Drug Administration approvals since the time of voting in July 2024, in addition to promising trials with potential for expanded indications/practice-changing data.

Abbreviations: chemo-IO, chemoimmunotherapy; ctDNA, circulating tumor DNA; ICI, immune checkpoint inhibitor; mPR, major pathologic response; NSCLC, nonsmall cell lung cancer; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1.

specimens due to the higher lability of RNA, the NCCN recommends RNA-based NGS only for individuals who do not have identifiable driver oncogenes on broad-panel, DNA-based NGS.[2,41] The BtG LCCC panel also supports the 2024 NCCN guideline recommendations about the benefit of NGS for fusions in other oncogenes, including *ROS1*, *ALK*, and *RET*.[2]

Recommendation 4.2: Tissue and liquid biopsy should be performed (if feasible) to detect resistance mutations after progression of non-EGFR oncogene-driven NSCLC

Molecular analysis is often clinically useful in oncogene-driven NSCLC that progressed on targeted therapy because it can identify molecular mechanisms of resistance to targeted therapy.[2] The use of both ctDNA and tissue testing to identify a targetable resistance mutation is ideal because false-negative results can occur with both tests.[2] Researchers of a multicancer cohort study reported that 29.0% and 5.3% of actionable variants for NSCLC were detected solely in solid tissue and blood-based ctDNA tests, respectively, suggesting that opportunities to treat with a therapy targeting these actionable variants could be missed if only one test is used.[41] However, experts acknowledged how availability and capacity to perform both tests may be limited in some practices.

Tissue and liquid biopsies can also help with identification of targetable non-*EGFR* resistance mutations that occur after osimertinib monotherapy, and ongoing clinical trials are studying the efficacy and safety of adding an MET inhibitor (SAFFRON; ClinicalTrials.gov identifier NCT05261399) or a TROP2-targeted antibody–drug conjugate (ORCHARD; ClinicalTrials.gov identifier NCT03944772) to osimertinib to bypass this treatment resistance. Preliminary research also suggests that paired tissue and liquid biopsies can identify a wide breadth of multiple polyclonal resistance mutations affecting multiple genes after anti-EGFR therapy, which can inform on the dynamic patterns of resistance and assist with the development of therapeutic strategies to target these resistance mutations.[42,43]

Ongoing questions in management of NSCLC driven by non-EGFR oncogenes

The BtG LCCC experts had many areas of uncertainty around optimal first-line therapies for non-EGFR oncogene–driven NSCLC (Table 4). Responses were mixed on the optimal first-line therapy of choice for *BRAF*-mutated NSCLC and the preferred first-line MET TKI for nonexon 14 *MET* fusions. The experts noted that, although the clinical efficacy of MET TKIs for nonexon 14 *MET* fusions appears to be promising and addresses a previously unmet clinical need, the drugs have on-target vascular effects that produce dependent edema, which does not respond effectively to diuretic therapy and may limit tolerability for some patients. The BtG LCCC experts suggested that optimizing potential comorbid medical conditions that increase risk for vascular effects (e.g., venous stasis, volume overload, nutritional status) and investigating other mechanisms to minimize these on-target effects, such as intermittent targeting, development of agents with a shorter half-life, or blockade of downstream efforts in the vasculature, should be studied further. At the time of writing, we note that these July 2024 consensus recommendations may need to be reconsidered and updated to reflect FDA approvals since the time of voting in July 2024 in addition to promising trials with potential for expanded indications/practice-changing data.

Responses were also mixed on the optimal targeted therapy to use first in *ROS1*-fusion NSCLC. Both repotrectinib and entrectinib have high tumor response rates, including intracranial responses, in patients with *ROS1*-fusion NSCLC.[44] Although the agents have not been compared directly, a population-adjusted, indirect comparison of patients with TKI-naive, *ROS*-fusion–positive NSCLC who received repotrectinib in TRIDENT-1 (ClinicalTrials.gov identifier NCT03093116) or received entrectinib in or STARTRK-1 and 2 (ClinicalTrials.gov identifiers NCT02097810 and NCT02568267. respectively) indicated that repotrectinib was associated with longer PFS and a nonstatistical trend toward a better overall response rate.[45] Experts noted that off-target side effects (e.g., dizziness, weight gain, withdrawal pain, and paresthesias) can make both of these agents difficult to manage.[44]

Immunotherapy in advanced/metastatic NSCLC

ICIs have revolutionized the management of advanced and metastatic NSCLC; notably, pembrolizumab yielded durable responses and prolonged OS when used as monotherapy in high PD-L1-expressing disease and improved OS when combined with chemotherapy in all comers who did not have oncogene-driven disease.[46,47] However, many patients do not respond to pembrolizumab, and approximately one third of patients have progressive disease at the first assessment, highlighting the need to identify ICI-containing combinations that improve response, biomarkers that predict response, and optimal second-line and beyond treatments for these patients.[46–48] Areas that reached consensus are included in Box 5.

TABLE 4 Ongoing questions for management of non-EGFR oncogene-driven nonsmall cell lung cancer.

Topic	Answers		No vote/ abstain, no.
	Responses	**No. (%)**	
Treatment			
For *KRAS*-mutated NSCLC, what co-mutations do you take into consideration to determine first-line therapy?	*KEAP1*	0 (0.0)	0
	STK11	3 (10.3)	
	TP53	0 (0.0)	
	NFE2L2	1 (3.4)	
	All the above	5 (17.2)	
	KEAP1 and *STK11*	20 (69.0)	
For *KRAS* G12C-mutated NSCLC, what is your preferred third-line therapy after progression on a KRAS inhibitor and first-line chemo-IO?	Another KRAS inhibitor	5 (17.2)	0
	Dual immunotherapy	5 (17.2)	
	Docetaxel + ramucirumab	17 (58.6)	
	Immunotherapy and chemo combination	2 (6.9)	
What is your first-line therapy of choice for *BRAF*-mutated NSCLC?	Dabrafenib + trametinib	9 (31.0)	0
	Encorafenib + binimetinib	15 (51.7)	
	Immunotherapy with or without chemotherapy	3(10.3)	
	Immunotherapy, but only for non-BRAF V600E	2 (6.9)	
For *MET* fusions, nonexon 14, what would be your preferred first-line therapy?	Crizotinib	0 (0.0)	0
	Capmatinib	9 (31.0)	
	Chemo-IO	9 (31.0)	
	Immunotherapy monotherapy	1 (3.4)	
	Tepotinib	10 (34.5)	
Do you take into consideration *ALK* variant subgroups in your treatment decision-making?	Yes, I only use it in the front-line setting.	1 (3.4)	0
	Yes, I only use it in the resistance setting.	5 (17.2)	
	Yes, I use it in both the front-line and resistance settings.	9 (31.0)	
	No, I do not use it in my decision making.	14 (48.3)	
What is the optimal sequence of therapies in *ROS1*-fusion NSCLC?	Entrectinib, then repotrectinib, then chemo	6 (20.7)	0
	Entrectinib, then repotrectinib, then chemo-IO	4 (13.8)	
	Entrectinib, then chemo-IO	0 (0.0)	
	Entrectinib, then chemo alone	2 (6.9)	
	Repotrectinib, then chemo-IO	2 (6.9)	
	Repotrectinib, then chemo alone	10 (34.5)	
	Repotrectinib, then entrectinib, then chemo	3 (10.3)	
	Repotrectinib, then entrectinib, then chemo-IO	2 (6.9)	

TABLE 4 (Continued)

Topic	Answers		No vote/ abstain, no.
	Responses	No. (%)	
Do you combine any of the targeted therapies (outside EGFR) with chemotherapy in the front-line setting?	Yes, I do, depending on the patient's tumor burden	1 (3.4)	0
	Yes, I do, depending on the oncogenic mutation type	2 (6.9)	
	No, but I consider it upon progression.	18 (62.1)	
	No, monotherapy is the preferred option.	8 (27.6)	

Note: At the time of writing, the authors note that their July 2024 consensus recommendations may need to be reconsidered and updated to reflect US Food and Drug Administration approvals since the time of voting in July 2024 in addition to promising trials with potential for expanded indications/practice-changing data.

Abbreviations: chemo, chemotherapy; chemo-IO, chemoimmunotherapy; NSCLC, nonsmall cell lung cancer.

Box 5 Consensus recommendations for management of immunotherapy in advanced/metastatic NSCLC

5.1 Administration of anti-CTLA4 therapy with anti–PD-1/anti–PD-L1 therapy (with or without chemotherapy) can be considered in patients who have metastatic NSCLC with PD-L1 tumor expression <1%, no actionable frontline driver mutation, and high-risk clinical or genomic features (e.g., *KEAP1* or *STK11* mutations).

5.2 Stereotactic body radiotherapy should be considered for patients with metastatic NSCLC who experience oligoprogression after first-line chemoimmunotherapy.

Abbreviations: CTLA4, cytotoxic T-lymphocyte–associated protein 4; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.

Recommendation 5.1: Administration of anti-CTLA4 therapy in combination with anti-PD-1/PD-L1 therapy, with or without chemotherapy, can be considered in patients who have metastatic NSCLC with PD-L1 expression <1%, no actionable frontline driver mutation, and high-risk clinical or genomic features

Patients with mNSCLC who have PD-L1 expression ≥50% have longer OS with anti–PD-1/anti–PD-L1 monotherapy compared with patients who have lower levels of PD-L1 expression.[46] Thus studies have investigated therapeutic combinations that include anti–PD-1/anti–PD-L1 to improve OS in patients who have mNSCLC with no or lower levels of tumor PD-L1.[49–51] In the POSEIDON trial (ClinicalTrials.gov identifier NCT03164616), the addition of tremelimumab and durvalumab to chemotherapy led to PFS and OS benefits across all PD-L1 expression levels.[49] Similar findings were observed with nivolumab plus ipilimumab in the CheckMate 227 (ClinicalTrials.gov identifier NCT02477826) and CheckMate 9LA trials (ClinicalTrials.gov identifier NCT03215706), with 5-year OS benefits observed using this combination versus chemotherapy regardless of PD-L1 expression levels, generating consensus regarding this approach.[50,51] Subgroup analysis of the POSEIDON trial revealed that the dual immune checkpoint blockade was associated with a sustained OS improvement in patients who had *STK11*, *KEAP1*, and *KRAS* mutations.[52] The TRITON trial (ClinicalTrials.gov identifier NCT06008093) is ongoing and is comparing tremelimumab, durvalumab, and chemotherapy with pembrolizumab plus chemotherapy in patients who have *STK11*, *KEAP1*, or *KRAS* mutations.[52] However, some experts noted that no data are available to demonstrate the superiority of a combination immuno-oncology approach, with or without chemotherapy, over a PD-1/PD-L1 inhibitor–chemotherapy approach.

Recommendation 5.2: Stereotactic body radiotherapy should be considered for patients with metastatic NSCLC who experience oligoprogression after first-line chemoimmunotherapy

In the phase 2 CURB trial (ClinicalTrials.gov identifier NCT03808662), the median PFS was greater than four-fold longer with the addition of stereotactic body radiotherapy (SBRT) to standard of care treatment in patients with mNSCLC who experienced oligoprogression (defined in this study as five or fewer progressive lesions on a positron emission tomography-computed tomography or computed tomography scan) after one or more lines of systemic therapy.[53] However, the BtG LCCC experts highlighted the lack of consensus across studies and institutions around the definition of oligoprogression in terms of the number and location of progression sites, noting that these variables likely affect the response to SBRT. Molecular heterogeneity can develop across oligoprogressive lesions that develop after an initial response to chemoimmunotherapy, and these lesions may have various responses to SBRT. The experts added that the site of oligoprogression is also an important consideration when deciding whether to perform SBRT; for example, neurotoxicity may be a concern when using SBRT for CNS oligoprogression, and SBRT targeting lung tissue near the esophagus can cause odynophagia.

TABLE 5 Ongoing questions for management of immunotherapy in advanced/metastatic nonsmall cell lung cancer.

Topic	Answers		No vote/ abstain, no.
	Response	No. (%)	
Treatment			
Should ICIs be continued after disease progression on first-line ICI therapy and as an add-on to the next cytotoxic therapy?	Yes, continue ICIs	10 (34.5)	0
	No, discontinue ICI; no role because of progression	4 (13.8)	
	Only for oligoprogression (not systemic progression	15 (51.7)	
Would you use chemotherapy with an anti–PD-1/anti–PD-L1 agent for a fit patient who desires aggressive therapy for PD-L1 expression >50% for first-line metastatic nonsmall cell lung cancer (mNSCLC) with no actionable frontline driver?	Yes, administer it for all fit patients	7 (24.1)	0
	Yes, administer it if there are high-risk clinical or genomic features	20 (69.0)	
	No, the patient should receive anti–PD-1/anti–PD-L1 monotherapy	2 (6.9)	
Should depth and duration of radiographic response identify immunotherapy primary vs. secondary resistance?	Yes, these are two different populations to study in refractory ICI clinical trials	21 (72.4)	0
	No, it's a biomarker-based classification (i.e., MRD/cfDNA or baseline mutations STK11/KEAP1)	8 (27.6)	
Should ICIs be discontinued routinely at the 2-year mark in the first-line mNSCLC setting?	Yes, studies discontinued at the 2-year mark and allowed for ICI rechallenge	12 (41.4)	0
	No, some patients require continued treatment (PR, PET + residual)	15 (51.7)	
	No, lifelong treatment is necessary in metastatic disease	2 (6.9)	
For patients who receive chemotherapy with ICIs in the curative-intent setting (neoadjuvant/perioperative/ adjuvant/post-RT) and who relapse 18 months after completion of therapy, what should be their initial systemic therapeutic strategy, assuming no actionable driver mutation?	Chemoimmunotherapy	20 (69.0)	0
	Chemotherapy alone	4 (13.8)	
	ADC	2 (6.9)	
	Clinical trials only	3 (10.3)	
	Palliative care or switch to best supportive care	0 (0.0)	
Which of the following biomarkers is required in treatment decision making for you before initiating ICI-based treatment in first-line mNSCLC (aside from actionable drivers)?	STK11/KEAP1	12 (41.4)	0
	SMARCA4	0 (0.0)	
	TMB	1 (3.4)	
	TP53	1 (3.4)	
	None	15 (51.7)	
Does ctDNA/MRD play a role in guiding treatment decision-making for patients receiving ICIs, with or without chemotherapy, in first-line mNSCLC?	Yes, in showing an early peak of efficacy relative to chemotherapy	0 (0.0)	0
	Yes, in showing radiographic mixed response/ pseudoprogression	3 (10.3)	
	Yes, in prognostication but not in therapeutic decision making yet	11 (37.9)	
	No, does not add to imaging and clinical assessment	12 (41.4)	
	Don't know	3 (10.3)	

Note: At the time of writing, the authors note that their July 2024 consensus recommendations may need to be reconsidered and updated to reflect US Food and Drug Administration approvals since the time of voting in July 2024 in addition to promising trials with potential for expanded indications/ practice-changing data.

Abbreviations: ADC, antibody-drug conjugate; cfDNA, cell-free DNA; ICI, immune checkpoint inhibitor; mNSCLC, metastatic NSCLC; MRD, minimal residual disease; PD-1, programmed cell death protein-1; PD-L1, programmed cell death-ligand 1; PET, positron emission tomography; PR, partial response; RT, radiation therapy.

Ongoing questions in the use of immunotherapy in advanced NSCLC

The BtG LCCC experts did not reach consensus on several details related to immunotherapy, including whether primary versus secondary resistance to immunotherapy should be identified by the depth and duration of radiographic response and whether to use ICIs after disease progression and as an add-on to the next cytotoxic therapy (Table 5). None of the combinations of ICIs with multitargeted TKIs studied in the CONTACT-01 (ClinicalTrials.gov identifier NCT04471428), SAPPHIRE (ClinicalTrials.gov identifier NCT03906071), or LEAP-008 (ClinicalTrials.gov identifier NCT03976375) trials had an OS benefit over docetaxel in patients with NSCLC that progressed on first-line chemoimmunotherapy, highlighting the need to identify biomarkers that predict response to combinations and to standardize the definitions of immunotherapy resistance.[54–56]

The experts also did not reach consensus on whether to use chemotherapy with an anti–PD-1/anti–PD-L1 agent as first-line treatment for a fit patient with mNSCLC, tumor PD-L1 expression >50%, and no actionable frontline driver mutation, although a nonconsensus majority recommended including chemotherapy if high-risk genomic features (e.g., *STK11*, *KEAP1*, or *TP53* mutations) were present. Some data suggest that the addition of chemotherapy to PD-1/PD-L1 inhibitors in NSCLC with PD-L1 expression >50% may yield OS benefits in women and never-smokers; and tremelimumab, durvalumab, plus chemotherapy improved OS versus chemotherapy alone in patients with *STK11* or *KEAP1* mutations.[57–59] Thus the experts noted that identifying these and other patient characteristics and biomarkers that predict benefit from the addition of chemotherapy and/or potentially CTLA4 inhibitors to PD-1/PD-L1–targeted agents in high PD-L1–expressing NSCLC would be beneficial for guiding treatment selection.

The BtG LCCC experts did not reach consensus on whether ICIs should be discontinued at the 2-year mark or continued indefinitely in the first-line mNSCLC setting. An exploratory analysis of the CheckMate 153 trial (ClinicalTrials.gov identifier NCT02066636) suggests OS benefits with the continuation of nivolumab versus a fixed 1-year duration of nivolumab treatment.[60] However, results from the CheckMate 227, Keynote 024 (ClinicalTrials.gov identifier NCT02142738), and Keynote 189 (ClinicalTrials.gov identifier NCT02578680) trials demonstrating continued OS benefits over platinum-based chemotherapy at 5 years—after the immunotherapy agents were discontinued at 2 years according to study protocol—suggest that the benefits persist beyond active administration.[48,50,61]

Conclusions

The BtG LCCC was held to develop expert guidance for clinical situations in which novel advances in management have outpaced level 1 evidence. Lung cancer experts created recommendations related to NSCLC and SCLC diagnosis, management, and surveillance and identified several areas of consensus related to best practices. They also highlighted multiple other areas in which consensus was not reached and additional research is needed. Future studies should focus on identifying patients who are likely to benefit from a given treatment, monitoring patients for disease progression and treatment resistance, and developing rational and safe treatment combinations and sequences. BtG experts intend to reconvene on an annual basis to review updated evidence and revise Consensus Recommendations to establish up-to-date guidance.

AUTHOR CONTRIBUTIONS

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The data that support the findings of this study are available in the supporting information of this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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