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# Management of Non-Small Cell Lung Cancer: Updates from the European Lung Cancer Congress 2022

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**ABSTRACT**

The recently concluded European Lung Cancer Congress 2022 (ELCC22) showcased some very exciting data, with more than 200 abstracts presented during the meeting. Through this review, we focus on selected clinically relevant abstracts that in our opinion represent significant updates in the current management of non-small cell lung cancer (NSCLC). Here, we summarize the updates in surgical management, adjuvant therapy and therapy for advanced stage NSCLC and put these advances in the context of the current clinical standard of care.

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## Introduction

Non-small cell lung cancer (NSCLC) is a major molecular and histologic subtype of lung cancer representing 76% of all lung cancer cases in the United States (1). The incidence of NSCLC though has been steadily declining over the past decade. The United States witnessed a decrease in the number of new cases from 46.4 per 100,000 in 2010 to 40.9 per 100,000 people in 2017 (2).

Interestingly, this has also been accompanied by a significant decline in NSCLC-associated mortality even when adjusted for the decreasing incidence. A study by Howlader et al. (3) demonstrated an improvement in lung cancer-specific survival from 26% when diagnosed in 2001 to 35% when diagnosed in 2014. This has been attributed to the major advances and improvements in NSCLC screening and therapy that have emerged in the past decade (4). The identification of driver mutations in oncogenes such as anaplastic lymphoma kinase (ALK), epidermal growth factor receptor (EGFR), mesenchymal epidermal transition factor (MET), and receptor tyrosine kinase 1 (ROS1), with the emergence of targeted treatments could, at least in part, account for this decrease in mortality (5).

As the therapeutic landscape of NSCLC continues to advance rapidly, some exciting data were presented at the recently concluded European Lung Cancer Congress 2022 (ELCC22). ELCC22 was held virtually from 30 March 2022 to 2 April 2022. Participants from more than 95 countries attended the meeting with a total of 201 presentations (6). Herein, we review some of the studies of clinical relevance, that in our opinion represent significant updates in the current management of NSCLC. We summarize the updates in surgical management, adjuvant therapy and therapy for advanced stage NSCLC and put these advances in the context of the current clinical standard of care.

### *Updates in surgical management*

About 40% of patients with lung cancer are candidates for potentially curative resection based on clinical factors such as tumor staging, performance status and comorbidities. Anatomic lobectomy, sleeve resection, bilobectomy, and

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pneumonectomy constitute the standard surgical procedures used in the treatment of NSCLC. Even with the improvement in surgical techniques and perioperative management over time, postoperative complications may occur in up to 30% of patients (7,8). Bilobectomy is a radical procedure considered for patients with lung cancer involving either both superior and middle or lower and middle lobes (9).

Data comparing perioperative survival outcomes between bilobectomy and other lung resection procedures are limited. The findings from the retrospective analysis of the Society for Thoracic Surgeons General Thoracic Surgery Database assessing 30-day peri-operative mortality in patients with lung cancer (2009–2017) who underwent elective lobectomy ($n = 65{,}506$), bilobectomy ($n = 2{,}911$) or pneumonectomy ($n = 3{,}024$) were presented at the ELCC 2022 meeting (10). The adjusted 30-day mortality of bilobectomy was worse than both right lobectomy [HR: 0.47; 95% CI: 0.36–0.60 ($p \leq 0.0001$)] or left lobectomy [HR: 0.44; 95% CI: 0.34–0.56 ($p = 0.0001$)], however better than right pneumectomy [HR: 2.76; 95% CI: 2.01–3.81 ($p \leq 0.0001$)]. When compared to left pneumectomy, this outcome for bilobectomy was comparable [HR: 1.32; 95% CI: 0.95–1.85 ($p = 0.10$)]. Bilobectomy was also associated with worse 30-day morbidity than lobectomy. Hence, this data suggests that careful pre-operative risk stratification is required prior to the addition of middle lobectomy to lung resection, given the risks associated with this procedure.

Given the advancements in thoracic surgery and with increasing utilization of minimally invasive procedures, a comparison of outcomes in more recent years may be helpful. Further analysis of the exact techniques used and whether sleeve techniques were applied is also warranted. However, this data does inform the need for careful pre-operative risk stratification and highlights the importance of shared decision making.

## Updates in adjuvant therapy

### IMPower010 trial

Curative surgery remains the treatment of choice for early stage (I and II) and select cases of stage III NSCLC. However, despite this treatment, 5-survival rates decrease significantly in stage IIIA disease when compared to Stage IA1 disease, suggesting the presence of micro metastasis (11). Hence, adjuvant treatment with systemic chemotherapy was the standard of care, until recently, for completely resected early-stage NSCLC (Stage IB – Stage IIIA) (12). Adjuvant platinum-based chemotherapy results only in modest improvement (5% improvement in survival at 5 years) when compared to observation. With the advent of immunotherapy and clinical benefit of the programmed death-ligand 1 (PD-L1) inhibitor atezolizumab in metastatic NSCLC, its use in early-stage NSCLC was assessed in the randomized open-label, phase 3 IMPower010 trial. The IMPower010 showed a disease-free survival (DFS) benefit with atezolizumab when compared to best supportive care (BSC) after adjuvant chemotherapy in patients with resected stage II-IIIA NSCLC (HR: 0.79;0.64–0.96; $p = 0.020$), especially in the subgroup whose tumors expressed PD-L1 on $\geq$ 1% of tumor cells (HR 0.66; 95% CI 0.50–0.88; $p = 0.0039$). The greatest benefit was seen in the PD-L1 tumor cell (TC) $\geq$ 50% subgroup (unstratified HR, 0.43; 95% CI: 0.27, 0.68) (13). This subsequently led to FDA approval of atezolizumab for adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II to IIIA NSCLC whose tumors have PD-L1 expression on $\geq$1%of tumor cells on October 15, 2021 (14).

The results of further exploratory analysis of the PD-L1 TC $\geq$50% stage II-IIIA NSCLC patients in the IMPower010 study were discussed at the ELCC 2022 (15). When compared to BSC, addition of atezolizumab resulted in improved DFS in both age $<$ 65 years [HR: 0.49, 95% CI 0.27–0.89] and $\geq$ 65 years [HR: 0.36, 95% CI 0.17–0.75], both female [HR: 0.34, 95% CI 0.15–0.76] and male [HR: 0.50, 95% CI 0.28–0.89], non-squamous histology [HR: 0.36, 95% CI 0.20–0.65], stage IIIA [HR: 0.38, 95% CI 0.20–0.72], nodal stage N1 [HR: 0.29, 95% CI 0.12–0.72] and N2 [HR: 0.35, 95% CI 0.18–0.68], current or former smokers [HR: 0.40, 95% CI 0.24–0.68], and undetected [HR: 0.41, 95% CI 0.20–0.84] or unknown EGFR/ALK mutation [HR: 0.45, 95% CI 0.23–0.91]. Subgroup analysis

did not show any apparent benefit of atezolizumab over BSC for patients with squamous histology [HR: 0.60, 95% CI 0.29–1.26], stage II disease [HR: 0.51, 95% CI 0.26–1.00], N0 node status [HR: 1.09, 95% CI 0.39–3.07], never smoker [HR: 0.46, 95% CI 0.17–1.25], and detectable EGFR/ALK mutation [HR: 0.26, 95% CI 0.06–1.02].

The relapsed disease occurred in 44% of patients in the BSC arm and 22% of patients in the atezolizumab arm. In terms of patterns of relapse in the atezolizumab arm, 13% of patients had a locoregional only relapse, 5% had a distant only relapse with just 1% experienced CNS only relapse. In comparison, patients in the BSC arm had higher rates of locoregional only (15%), distant only (18%) and CNS only (6%) relapse.

Overall, there was little heterogeneity in the efficacy of atezolizumab among the high PD-L1 expressers. The study is limited by the small patient population in some subgroups. Interestingly, the pattern of distant and CNS relapse was higher in the BCS arm as compared to the atezolizumab arm indicating that perhaps atezolizumab use may alter the pattern of disease progression. These findings could be significant from a therapeutic standpoint, as locoregional recurrence may be amenable to more aggressive measures which have a better chance of achieving a cure.

Interestingly, in the PEARLS/KEYNOTE-091 phase III clinical trial which compared the programmed cell death-1 (PD-1) inhibitor pembrolizumab to placebo in patients with early-stage NSCLC, there was no statistically significant improvement noted in median DFS compared to placebo in the subgroup of patients with PD-L1 tumor proportion score (TPS) $\geq$50% (median DFS not reached, [HR 0.82; 95% CI 0.57–1.18; $P = 0.14$]) (16). Therefore, more mature data and probably also data from more studies are needed to evaluate the effect of immunotherapy in NSCLC patients with high PD-L1 expression, with some experts questioning the true predictive value of PD-L1 expression, especially in the early stage setting. A longer follow-up along with a greater number of events may help elucidate the pattern of relapse in patients treated with immunotherapy in the early-stage setting, and its implications on clinical outcomes.

### *PACIFIC-6 trial*

Historically, the standard of care for patients with unresectable stage III NSCLC with a good performance status was platinum-based doublet chemotherapy with concurrent radiotherapy (concurrent chemoradiotherapy/cCRT). However, the addition of durvalumab as consolidation therapy in the PACIFIC trial for patients that had not progressed after platinum-based cCRT showed improvement in both progression-free survival (PFS) and overall survival (OS) when compared to placebo and was established as a standard of care in this setting (17,18). However, some patients who are older or frail may not be ideal candidates for cCRT based on their functional status, where sequential CRT (sCRT) is an alternate treatment option.

The results from the phase II PACIFIC-6 trial that aimed to assess safety with durvalumab in patients with stage III unresectable cancer who did not progress after sCRT were presented in the ELCC 2022 meeting (19). In this study, 117 patients were enrolled, with a median age of 68 years. The majority of patients were males (62.4%) and most patients had stage IIIB disease (50.4%) followed by stage IIIA (37.6%). About 98.3% patients had past or current medical conditions including vascular (59.0%), respiratory (53.8%) and metabolic (51.3%) disorders. Although PS2 was allowed, almost no patients with PS2 were enrolled. The primary endpoint was the incidence of grade 3/4 possibly related adverse events (PRAEs) within 6 months of starting durvalumab. This was seen in only 5 (4.3%) patients with the majority of patients tolerating the treatment well. Two of these events were grade 3–4 pneumonitis. All grade 3–4 PRAEs reported in this trial happened within 6 months of therapy initiation. The median total treatment duration was 32.0 weeks, and during this time, 94.9% of patients had any adverse effects and 76.9% of patients had any-grade PRAEs. The incidence of grade 3–4 AEs and grade 3–4 PRAEs was 18.8% and 4.3% respectively. AEs and PRAEs resulted in treatment discontinuation in 21.4% and 16.2% of patients, respectively.

Pneumonitis was attributed as the most common AE causing treatment discontinuation (10.3%). Overall, there were two fatal AEs, one of which was due to pneumonitis. In terms of secondary outcomes, the objective response rate was reported to be 17.1% [95% CI 11.1%–25.8%]. The median PFS was 10.9 months [95% CI 7.3–15.6] and the 12-month PFS rate was 49.6% [95% CI 39.5%–58.9%]. Median OS was 25.0 months (95% CI 25.0–not calculable), with a 12-month OS rate of 84.1% [95% CI 75.6%–89.9%].

The incidence of toxicities was comparable to that of the PACIFIC trial. The encouraging result of this study demonstrates benefits from durvalumab after sCRT and could be an alternative for frail and older patients, although reasons for administering sCRT instead of cCRT were not provided (i.e. patient receiving sCRT due to logistical issues probably has a different prognosis compared with a frail or PS2 patient). Furthermore, the study is limited by the small sample size and notable coexistent comorbidities that may affect outcomes. Similar findings were reported with the use of a different PD-L1 antibody sugemalimab in the GEMSTONE-301 study. This was a placebo-controlled phase 3 trial that compared sugemalimab as consolidation therapy to placebo for patients with stage III NSCLC whose disease did not progress after sCRT or cCRT. The sugemalimab group had a higher mPFS (9 months [95% CI 8.1–14.1] vs 5.8 months [95% CI 4.2–6.6]; $p = 0.0026$) compared to the placebo group (20).

## Updates in non-oncogene addicted advanced NSCLC

### CameL-sq study

The updated findings of the CameL-sq study from China were presented at the ELCC 2022 meeting. This was a phase III clinical trial that evaluated the use of PD-1 inhibitor camrelizumab (21) as a first-line agent in combination with chemotherapy in patients with advanced squamous NSCLC. The initial results from the study demonstrated improved PFS with the addition of camrelizumab to chemotherapy vs placebo (22). With this update (23), the authors presented OS data after a longer period of follow-up. The study consisted of 389 patients who were randomized to 2 arms, camrelizumab 200 mg with chemotherapy (carboplatin plus paclitaxel) every 3 weeks for 4–6 cycles followed by camrelizumab maintenance ($n = 193$) vs placebo with chemotherapy every 3 weeks for 4–6 cycles followed by maintenance with placebo ($n = 196$). The study design also allowed for crossover to the camrelizumab arm after disease progression in the placebo arm.

Outcomes included OS and survival rate at 24 and 36 months. After a median follow up of 23.7 months in the camrelizumab arm and 15.2 months in the placebo arm, the camrelizumab arm had improved OS (median, 27.4 mo. [95% CI 22.1-not reached (NR)] vs 15.5 mo. [95% CI 13.4–18.4]; HR 0.57 [95% CI 0.44–0.75]; 1-sided log-rank $P < 0.0001$); survival rate was 53.9% (95% CI 46.5–60.8) vs 35.0% (95% CI 28.3–41.7) at 24 months and 42.8% (95% CI 34.0–51.4) vs 25.7% (95% CI 18.6–33.4) at 36 months. Around 56% of patients crossed over to the camrelizumab arm following disease progression in the placebo arm. On adjusting for the crossover, the camrelizumab arm continued to show significant improvement in median OS compared to the placebo [27.4 months vs 12.4 months (HR, 0.41; 95% CI, 0.30–0.56; $P <$ .0001)]. The study did not report any new safety signals.

### Orient – 11 study

The orient-11 study evaluated the use of Sintilimab as a first-line treatment option in combination with chemotherapy in patients with stage IIIb-IV non-squamous NSCLC (24). Sintilimab is a human IgG4 antibody against PD-1 which initially gained approval for use in classical Hodgkin's lymphoma (25). This phase 3 clinical trial had a sample size of 397 patients who were randomized 2:1 to receive Sintilimab ($n = 266$) in combination with chemotherapy (cisplatin/carboplatin plus pemetrexed) vs placebo ($n = 131$) with chemotherapy for up to 4 cycles, followed by maintenance therapy with pemetrexed plus Sintilimab/placebo. Crossover to the Sintilimab arm from the placebo arm was allowed following disease progression. After a median follow-up period of 30.8 months, the Sintilimab plus chemotherapy arm had a longer mOS compared

to the placebo with the chemotherapy arm (24.2 mo. vs 16.8 (hazard ratio [HR], 0.65; 95% CI, 0.50–0.85). When adjusting for a crossover rate of 47%, the HR further improved to 0.52 (95% CI 0.38–0.69).

The above studies (ORIENT-11 and Camel-sq) have shown promising efficacy of new immunotherapeutic agents Sintilimab and carmelizumab as a first-line treatment in combination with chemotherapy in advanced stage non-squamous NSCLC and squamous NSCLC respectively. However, it remains to be seen what added advantage these agents offer in the treatment of advanced NSCLC over the other already established immune-chemotherapy combinations and the focus should be either on reduction in health care costs due to these new agents or on new combinations.

For example, in advanced squamous NSCLC, improved survival outcomes from chemotherapy combined with immunotherapeutic agents such as pembrolizumab (KEYNOTE-407) (26), cemiplimab (EMPOWERLung3) (27), nivolumab-ipilimumab (Checkmate 9LA) (28) and durvalumab-tremelimumab (POSEIDON) (29) have already been demonstrated. Furthermore, since the above studies were predominantly done in Asia, there is a concern about the potential lack of generalizability of the data in the population of the US and other nations. However, we hope these agents may prove to be an opportunity to improve access and affordability of immunotherapies in low-middle income countries, which has been an ongoing issue (30,31).

#### *POSEIDON trial*

The POSEIDON trial (29) is a randomized phase III study that evaluated the addition of immunotherapies Durvalumab (D) with/without Tremelimumab (T) to investigator choice chemotherapy (CT) as first-line treatment in patients with stage IV NSCLC. This study included 1013 patients who were randomized patients into 3 groups receiving D + T + CT, D + CT and CT alone. The initial results of this study were presented at the 2021 World Conference of Lung Cancer and demonstrated a survival benefit with D + T + CT (significantly improved mPFS and mOS) and D + CT (significantly improved mPFS) compared to CT only arm.

The additional data from this trial presented in the ELCC 2022 meeting compared Patient-reported outcomes (PROs): global health status/quality of life (QoL), physical functioning and symptoms (loss of appetite, dyspnea, chest pain, cough, fatigue between D + T + CT ($n = 338$)/D + CT ($n = 338$) and CT only ($n = 337$) groups (32). The median Time to deterioration (TTD) of each of these PROs was assessed. Median TTD (HR [95% CI]) in the D + T + CT group were significantly longer compared to the CT only group in the following outcomes: global health status: 8.3 vs 5.6 months (0.78 [0.63, 0.96]), physical functioning: 7.7 vs 5.3 months (0.75 [0.61, 0.92]), and dyspnea 5.4 vs 3.6 months (0.77 [0.63, 0.94]). Similarly, median TTD in the D + CT group were significantly longer compared to the CT only group in the following outcomes: Global health status: 7.8 vs 5.6 months (0.79 [0.64, 0.96]), physical functioning: 8.3 vs 5.3 months (0.70 [0.57, 0.87]), and dyspnea 5 vs 3.6 months (0.81 [0.67, 0.98]).

This additional data indicates that the survival benefit of the addition of durvalumab with/without tremelimumab to standard chemotherapy also translates to improved patient-reported outcomes, making it a possible option as a first-line treatment of metastatic NSCLC.

### *Updates in the management of advanced oncogene addicted NSCLC*

#### *EGFR mutated NSCLC*

Mutations in the epidermal growth factor receptor (EGFR) occur in about 28% of patients with advanced NSCLC (33). While it varies in different parts of the world, a metanalysis by Zhang et al. (34) estimated the overall pooled prevalence to be 32.3% (95% CI 30.9%–33.7%). The 2 most common types of EGFR mutations seen are L858R (leucine to arginine substitution at position 858) and exon19del (deletion at exon 19) which lead to constitutive activation of tyrosine kinase (35). The presence of this oncogene allowed for the use of tyrosine kinase inhibitors (TKIs) in the management of NSCLC (36). Since then, these agents have become the standard of

care as first-line treatment for metastatic EGFR mutated NSCLC (37). Newer generation TKIs are also being developed and employed in clinical trials with the promise of improved outcomes and tolerability.

The FURLONG trial (38) presented at the ELCC 2022 focused on evaluating the use of a new EGFR inhibitor called furmonertinib. This randomized double-blind phase III study compared furmonertinib versus gefitinib as first-line treatment in patients with advanced stage (IIIB/IIIC/IV) NSCLC who carried an exon19del or L858R EGFR mutation. A total of 358 patients were randomized to receive either furmonertinib 80 mg/day ($n = 178$) or gefitinib 250 mg/day ($n = 180$). The primary endpoint of the study was median PFS. With a median follow-up of 21 months, furmonertinib had a longer median PFS compared to gefitinib (20.8 vs 11.1 months; HR 0.44 [95% CI 0.34–0.58]; $p < 0.0001$). In terms of tolerability, 11% of grade $\geq$ 3 TRAEs were reported in the furmonertinib group whereas 18% of grade $\geq$ 3 TRAEs were reported in gefitinib group.

In the above study, furmonertinib was shown to confer a higher PFS benefit and was also better tolerated than gefitinib. Similar conclusions were drawn for another 3rd generation of TKI, Osimertinib, in the recent FLAURA trial (39). This was a phase 3 randomized clinical trial that compared the irreversible third generation tyrosine kinase inhibitor Osimertinib (40) with gefitinib or erlotinib (then standard of care treatment) as first-line treatment for EGFR mutated locally advanced or metastatic NSCLC. Osimertinib was shown to have a significantly longer mPFS compared to standard of care treatment (18.9 months vs 10.2 months, HR 0.46, 95% CI 0.37–0.57; $p < 0.001$). Grade $\geq$ 3 adverse events were also lesser with Osimertinib compared to standard of care treatment (34% vs 45%). Since then, Osimertinib has also been studied and approved for adjuvant therapy after tumor resection in patients with NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations (41). Osimertinib also has been shown to benefit patients with central nervous system metastases given its demonstrated ability to penetrate the blood-brain barrier (42).

With multiple third-generation EGFR TKIs in the pipeline, it will be interesting to see if this again can affect the pricing, access, and affordability of these novel agents for patients with NSCLC (30). A head-to-head comparison of these two agents will be warranted in the future to define the optimal first-line standard of care approaches, including good CNS efficacy.

### *ROS positive NSCLC*

The ROS receptor tyrosine kinase 1(ROS1) has been identified as another oncogene in lung cancers with rearrangement in the ROS1 gene occurring in an estimated 1–2% of all NSCLC (43). On March 11, 2016, Crizotinib became the first ROS1 tyrosine kinase inhibitor approved by the FDA for the treatment of metastatic ROS1 positive NSCLC (44). The phase 1 PROFILE 1001 (45) study reported an ORR of 72% (95% CI, 58%–83%) with crizotinib in patients with ROS1 rearranged metastatic NSCLC. With a median follow-up of 62.6 months, median PFS was 19.3 months (95% CI, 15.2–39.1) and median OS was 51.4 months (95% CI, 29-NR). Another TKI, entrectinib was approved by the FDA in 2019 for metastatic ROS1 positive NSCLC (46). An integrated analysis of three phases 1/2 studies evaluating the use of entrectinib for this indication (47) demonstrated an ORR of 67% (95% CI, 59.3–74.3) and median PFS of 15.7 months. Entrectinib was also shown to be effective in patients with CNS metastases, with an intracranial ORR of 79.2% (95% CI, 57.9–92.9). In terms of safety data, TRAEs led to dose reduction in 29% of patients, treatment interruption in 30.5% of patients and discontinuation in 4.3% of patients. Common TRAEs with entrectinib included dysgeusia, dizziness, constipation fatigue and diarrhoea.

At ELCC22, data from a phase 2 study (48) using a novel receptor tyrosine inhibitor, TQ-B3101 (49) in patients with ROS positive advanced NSCLC were presented. The study included 111 patients who received TQ-B3101 as first-line treatment at a dose of 300 mg twice a day in 28-day cycles. The treatment was stopped in cases of severe toxicity and/or disease progression. Of note, out of the 111 patients included, about 93% of patients had stage IV disease. With

**Table 1.** Overview of advances in NSCLC management presented at ELCC 2022 meeting.

| Study name | Study design | Clinical setting | Disease stage targeted | Sample size | Intervention | Primary outcome | Results |
|---|---|---|---|---|---|---|---|
| STS Surgical Database (10) | Retrospective Database analysis | Surgical treatment | Not specified | 71,441 | Elective Lobectomy, Bilobectomy, Pneumonectomy | 30-day perioperative mortality | Adjusted 30-day mortality: bilobectomy worse than both right lobectomy and left lobectomy; better than right pneumectomy; comparable to left pneumonectomy |
| IMPower010 trial (15) | Phase III clinical trial | Adjuvant treatment | Stage II-IIIA | 229 | Intervention Arm: atezolizumab<br><br>Control Arm: BSC | DFS | Atezolizumab – improved DFS across all age groups, both female and male sex, non-squamous histology, Stage IIIA, nodal stage N1 and N2, current or former smokers, and undetected or unknown AGFR/ ALK mutation. |
| PACIFIC-6 trial (19) | Phase II clinical trial | Consolidative | Non-Resectable Stage III | 117 | Single arm: Durvalumab after sCRT | Incidence of grade 3 or 4 PRAEs within 6 months of starting durvalumab | 5/117 (4.3%) patients experienced grade 3 or 4 PRAEs within 6 months of starting durvalumab. |
| CameL-sq (23) | Phase III clinical trial | First-line treatment | Stage IIIB-IV Squamous NSCLC | 389 | Intervention arm: Camrelizumab plus chemotherapy<br><br>Control arm: placebo with chemotherapy | mOS | Camrelizumab plus chemotherapy group had prolonged mOS compared to the placebo plus chemo group. (27.4 mo vs 15.5 mo; HR 0.57; 1-sided log-rank $P < 0.0001$) |
| ORIENT-11 (24) | Phase III clinical trial | First-line treatment | Stage IIIB-IV Non-squamous NSCLC | 397 | Intervention arm: Sintilimab plus chemotherapy<br><br>Control arm: placebo with chemotherapy | mOS | Sintilimab plus chemotherapy had a longer mOS compared to placebo with chemotherapy (24.2 mo vs 16.8 (hazard ratio [HR], 0.65; 95% CI, 0.50–0.85) |
| POSEIDON Trial: Patient reported outcomes (PRO) (32) | Phase III clinical trial | First line treatment | Stage IV NSCLC | 1013 | Arm 1: Durvalumab + Tremelimumab + Chemotherapy<br><br>Arm 2: Durvalumamb + chemotherapy<br><br>Arm 3: Chemotherapy only | PRO: median TTD of Global health status, physical functioning, symptoms (chest pain, dyspnea, cough, appetite loss, and fatigue) | Arm 1 and arm 2 had significantly longer median TTD of global health status, physical functioning and dyspnea compared to arm 3. |
| FURLONG Trial (38) | Phase III Clinical trial | First line treatment | EGFR mutated Stage IIIB-IV NSCLC | 358 | Arm 1: furmonertinib therapy<br><br>Arm 2: gefitinib therapy | mPFS | Furmonertinib arm had longer mPFS compared to the gefitinib arm (20.8 vs 11.1 months; HR 0.44 [95% CI 0.34–0.58]; $p < 0.0001$). |

(*continued*)

**Table 1.** Continued.

| Study name | Study design | Clinical setting | Disease stage targeted | Sample size | Intervention | Primary outcome | Results |
|---|---|---|---|---|---|---|---|
| ORI TQ- B3101 (48) | Phase II clinical trial | First-line treatment | ROS-1 positive locally advanced/ metastatic NSCLC | 111 | Single arm: TQ-B3101 treatment | ORR | ORR was 78.4% (95% CI, 69.6%–85.6%) |
| GEOMETRY mono-1 study (Cohort 7) (55) | Phase II clinical trial | First-line treatment | METex 14 positive Stage IIIB-IV NSCLC | 32 | Single arm: Capmatinib therapy | ORR | ORR was 68.8% (95% CI, 50–83.9) |
| VISION Trail (Asian patients) (59) | Phase II clinical trial | Both first line and salvage treatment | METex 14 positive Locally advanced, metastatic NSCLC | 106 | Single arm: Tepotinib therapy | ORR | ORR was 54.4% (95%.CI: 42.8–56.7) |
| Savolitinib (62) | Phase II clinical trial | Both first line and salvage treatment | METex 14 positive Metastatic PSC and NSCLC | 70 | Single arm: Savolitinib therapy | mOS | With a median follow up of 28.4 months, mOS was 12.5 mo (95% CI 10.5–21.4) |

STS: Society for thoracic surgeons; DFS: Disease free survival; BSC: Best supportive care; sCRT: Sequential chemoradiotherapy; PRAE: Possibly related adverse event; mOS: Median overall survival; PRO: Patient reported outcomes; TTD: Time to deterioration; mPFS: Median progression free survival; ORR: Overall response rate.

a median follow-up of 12.1 months, the independent review committee (IRC) assessed ORR was 78.4% (95% CI, 69.6%–85.6%); the complete response was achieved in 1 patient, 86 patients achieved a partial response. IRC assessed disease control rate (DCR) was 87.4% (95% CI, 79.7%–92.9%). Median PFS was 15.6 months (95% CI, 10.2–27.0), the median duration of response (DoR) was 20.3% (95% CI, 11.0–26.1) and the median OS was not reached. 99.1% of patients had treatment related adverse events (TRAE), but only 1.8% of patients had to discontinue treatment due to the same. Common TRAEs with TQ-B3101 therapy were nausea, diarrhea, sinus bradycardia, increases in aspartate transaminase (AST), alanine transaminase (ALT), leukopenia, and neutropenia.

Overall, based on the data presented in the above study, TQ-B3101 has been shown to have at least comparable efficacy and safety to already approved agents (crizotinib and entrectinib). It will be interesting to see if TQ-B3101 is found to be effective in intracranial disease, which is one of the major advantages of entrectinib.

### *MET-exon14 mutated NSCLC*

C-mesenchymal-epithelial transition factor (c-MET) is oncogene coding for MET tyrosine kinase receptor, dysregulation of which has been shown to drive NSCLC. One very common mechanism of MET dysregulation identified in NSCLC is MET exon 14 skipping mutation (METex positive), which results in decreased degradation of the MET receptor and has a prevalence of 3% among all NSCLC (50,51). Capmatinib and Tepotinib are currently the two MET inhibitors granted accelerated approval from the FDA for treatment of METex positive metastatic NSCLC (52,53). Updated results from studies evaluating these two drugs for this indication, and an additional new MET inhibitor Savolitinib, were presented at ELCC22.

***GEOMETRY Mono-1 study.*** The GEOMETRY mono- 1 study evaluated the use of the selective small molecule MET inhibitor Capmatinib (54) in patients with advanced (stage IIIB or IV) NSCLC who had MET gene dysregulation (including MET gene amplification and MET

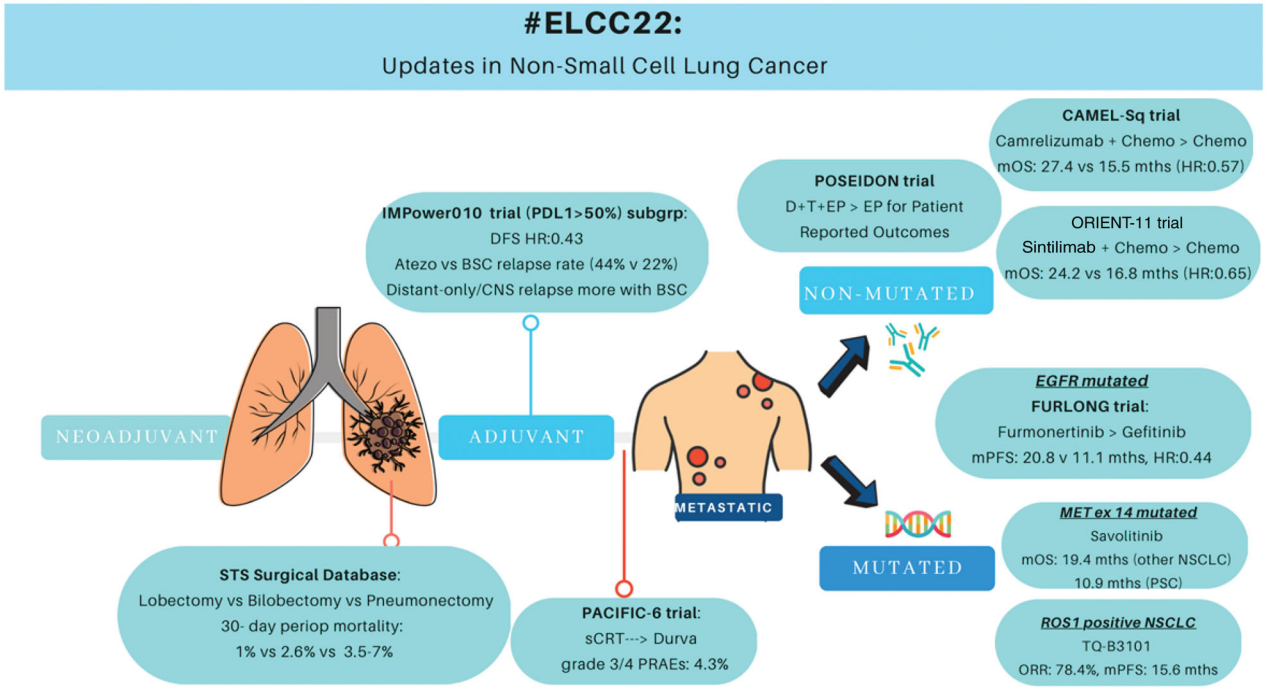


**Figure 1.** Advances in NSCLC management presented at ELCC 2022 meeting.

exon14 skipping mutation). Data from this study published in 2020 revealed capmatinib to be an effective option in patients with MET exon 14 skipping mutation (68% ORR [95% CI 48–84] as first-line therapy [cohort 5 b], 41% ORR [95% CI 29–53] as salvage therapy) (55).

Updated results from cohort 7 of this study consisting of treatment naïve patients were presented at the ELCC 2022 (56). The primary endpoint was ORR. The 32 patients included in cohort 7 received capmatinib 400 mg twice daily with an ORR of 68.8% (95% CI, 50–83.9), and the median duration of response (mDOR) of 16.59 months (95% CI, 8.34 – not estimable [NE]). mOS was not reached, and mPFS was 12.45 months (95% CI, 6.87–20.50). TRAEs occurred in 90.6% of patients and required treatment interruption and discontinuation in 71.9% and 18.8% of patients respectively. Peripheral edema, nausea and increased blood creatinine were the most reported TRAEs. These updated findings further support the use of capmatinib as a first-line option in patients with advanced NSCLC who carry the MET exon 14 skipping mutation. In addition to the FDA approval as mentioned above, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) has also recently recommended authorization of capmatinib for the treatment of advanced NSCLC with METex14 skipping mutations (57).

***VISION study.*** The VISION study is a single arm phase II study evaluating the use of the selective MET tyrosine inhibitor tepotinib (58) in patients with locally advanced or metastatic NSCLC who carry MET gene mutations. The updated results of this study focusing on Asian patients with MET exon 14 skipping mutations were presented at the ELCC22 meeting (59). A total of 106 Asian patients were included and received tepotinib 500 mg once a day. 79 of these patients had at least 3 months of follow-up and were included in the efficacy analysis (27 received tepotinib as a first line, 52 as salvage). ORR was 54.4% (95%.CI: 42.8–56.7), mDOR 18.5 months (8.3-NE), mPFS of 12 months (6.9-NE), and mOS 20.4 months (19.1-NE). Regarding TRAE's (assessed in 88 patients): Grade 3 or more occurred in 29.5% of patients. Dose reduction, temporary interruption and permanent discontinuation occurred in 29.5%, 43.2% and 14.8% of patients respectively. Peripheral edema, increase in creatinine and diarrhea were the most common side effects seen.

***Savolitinib.*** Savolitinib is a selective MET tyrosine kinase inhibitor (60) which was shown to be effective against METex positive metastatic pulmonary sarcomatoid carcinoma (PSC) and other NSCLC in a phase 2 study by Lu et al (61). Out of the 70 patients treated in this study, 25 had PSC while 45 had other NSCLCs; 61 patients were efficacy evaluable. The study reported an ORR of 47.5% (95% CI, 34.6–60.7) and a median PFS of 6.8 months (95% CI 4.2–13.8). In terms of safety data, grade 3 or more TRAEs were reported in 41.4% of patients, and TRAEs necessitated treatment discontinuation in 14.3% of patients. The most common TRAEs were peripheral edema, nausea, increased AST/ALT, vomiting and hypoalbuminemia. Further updates from this study, including long-term OS and subgroup analysis results were presented at ELCC 2022 (62). With a median follow-up of 28.4 months (Interquartile range 26.2–36.3), mOS was 12.5 mo. (95% CI 10.5–21.4). Out of the 70 patients who received savolitinib, 28 patients received it as the first line (treatment naïve group), whereas 42 patients were pre-treated. CNS lesions were present in 15 patients prior to treatment with savolitinib. mOS was 19.4 months (95% CI 10.5–31.3) and 10.9 months (95% CI 7.5–14) respectively in pretreated and treatment naïve groups. Patients with PSC had an mOS of 10.6 months (95% CI 4.6–14), while patients with other NSCLC had mOS of 17.3 months (95% CI 10.6–23.6). Patients with CNS metastases also responded well to treatment with savolitinib with an mOS of 17.7 months (95% CI 10.48-NR). TRAEs were like that reported previously. This update further demonstrates the efficacy of savolitinib in METex14 positive metastatic NSCLC across multiple specific sub-groups, including those with CNS metastases.

## Conclusion

We saw interesting data presented at the ELCC22 conference which further reinforced the importance of immunotherapy in the management of NSCLC in early stage, unresectable Stage III and Stage IV disease. Data on various newer targeted agents showed encouraging efficacy, giving us a problem of plenty in the management of oncogene addicted NSCLC. Our hope is that this increased competition with many similar me-too agents will continue to present therapeutic options to patients worldwide, making these life-saving therapies available at an affordable price.

## Disclosure statement

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