# Key Highlights from the Latest Clinical Trials in Lung Cancer

**Introduction**

Recently, 2 lung cancer experts, Mark A. Socinski, MD, Executive Medical Director of the Florida Hospital Cancer Institute, and Tarek M. Mekhail, MD, MSC, FRCSI, FRCSEd, President of the Cancer Institute of Florida, held a lively discussion regarding the practical aspects of relevant results from lung cancer–based clinical studies presented at the European Society for Medical Oncology (ESMO) Asia Congress 2019, which was held in Singapore in November.

**Table 1: KEYNOTE-407 China Extension Trial (NCT03875092) Endpoints**

| Study Endpoint | Pembro plus Chemo Doublet | Placebo plus Chemo Doublet | Hazard Ratio |
|---|---|---|---|
| OS, median (months) | 17.3 (95% CI: 14.1–not reached) | 12.6 (95% CI: 9.6–not reached) | 0.44 (95% CI: 0.24–0.81) |
| PFS, median (months) | 8.2 (95% CI: 6.2–10.3) | 4.2 (95% CI: 4.0–4.4) | 0.32 (95% CI: 0.21–0.49) |
| ORR (%) | 78.5 (95% CI: 66.5–87.7) | 41.7 (95% CI: 29.1–55.1) | |

CI: confidence interval; ORR: objective response rate; OS: overall survival; PFS: progression-free survival

In the initial part of their conversation, the participants discussed results from KEYNOTE-407 (Table 1), which is evaluating the use of pembrolizumab plus carboplatin, in combination with either paclitaxel or nab-paclitaxel, on overall survival (OS) and progression-free survival (PFS) endpoints in patients with metastatic, squamous, non-small cell lung cancer (NSCLC).[1] When noting the differences in results between patients in mainland China vs other population groups, Dr. Mekhail stated, "I don't think we learned much; the results were very reminiscent of those for the main KEYNOTE-407." He added:

> The triplet with pembrolizumab, paclitaxel, and carboplatin that has been used on the Chinese extension, vs the doublet alone, [the] triplet is superior, displaying a better OS than the doublet. The hazard ratio (HR) seems to be better than even the original study (KEYNOTE-407, NCT02775435); ideally that has a ratio of 0.44, [and the] response rate is higher. The median OS in this analysis for patients in China was 17.3 months (HR = 0.44), which compared favorably to the figures for the overall population, where a median OS of 15.9 months (HR = 0.64) was obtained.[2]

Summarizing, Dr. Mekhail stated, "So I don't think we learned much; the triplet combination established itself as the standard of care." To this assessment, Dr. Socinski commented, "I agree, and I think one of the observations we saw from this trial is that Asian populations, in general, tend to do better." Dr. Mekhail said, "I think triplet remains the standard of care; however, it's not the only standard of care, especially for patients with PD-L1 expression levels greater than 50%."

**Table 2: RELAY Trial (NCT02411448) Endpoints**

| Study Endpoint | Hazard Ratio |
|---|---|
| TtD, LCSS Total Score | 0.96 (95% CI: 0.69–1.34) |
| TtD, Average Burden Index | 1.01 (95% CI: 0.73–1.40) |

LCSS-Lung Cancer Symptom Scale; TtD: time to deterioration

Next, the topic of the conversation turned to the phase 3 RELAY study (Table 2), which evaluated the anti–vascular endothelial growth factor receptor 2 (VEGFR2) monoclonal antibody ramucirumab in patients with epidermal growth factor receptor (*EGFR*) mutation–positive metastatic NSCLC.[3] Dr. Mekhail stated, "We know that adding ramucirumab to erlotinib was better than erlotinib plus placebo in patients with activating *EGFR* mutations; what this study is talking about is patient-focused outcomes." To this, Dr. Socinski added:

> So this is another study in a series of 3 trials with bevacizumab added to an EGFR tyrosine kinase inhibitor (TKI), and this is the first one that I'm aware of with ramucirumab. And all of them showed the same benefit in PFS. We have to remember that *EGFR* mutation–positive disease is a very VEGF-driven situation; so, it's surprising that VEGF inhibitors, both bevacizumab and ramucirumab, do this. We haven't yet seen a convincing survival benefit in any of these trials, and, although the data suggest there were really no negative effects, I didn't get the sense there were really any positive effects like better symptom control, and there was actually more hemoptysis on the ramucirumab arm.

"I don't know that it necessarily changes my standard of care, because it does change the treatment paradigm from taking a pill once a day to adding an IV [intravenous] agent that does have some toxicity," Dr. Socinski said. When asked by Dr. Mekhail what his standard of care was, Dr. Socinski replied, "Osimertinib is my standard."

**Table 3: PACIFIC Trial (NCT02125461)**

| Study Endpoint | Durvalumab | Placebo | Hazard Ratio |
|---|---|---|---|
| OS, median (months) | NR (95% CI: 38.4–NR) | 29.1 (95% CI: 22.1–35.1) | 0.69 (95% CI: 0.55–0.86) |
| 12 Month OS Rate (%) | 83.1 | 74.6 | |
| 24 Month OS Rate (%) | 66.3 | 55.3 | |
| 36 Month OS Rate (%) | 57.0 | 43.5 | |

NR: not reached

Next, the lung cancer experts discussed the 3-year follow-up analysis of the PACIFIC trial (Table 3).[5] Dr. Socinski said:

> This was a rehash of the data that we saw at ASCO, where the 3-year survival update was following chemoradiotherapy for stage 3 disease; those patients who did not progress were randomized to either durvalumab for a year or placebo. The nice thing about the presentation at ASCO and this presentation is that there didn't seem to be any decay in the survival benefit, meaning that the survival curves stayed consistently separated by 12%–13% or so, absolute difference. The HR was the same as we saw from the 2-year endpoint, which really solidified the fact that we have a new therapeutic option for patients, as well as, I think, the standard of care. We're hoping these changes, which seem to be persisting beyond 3 years, are going to really change the 4- to 5-year overall survival, and we're really curing more of these patients.

Dr. Mekhail then asked, “So does this data so far mean that we actually cured more people?” Dr. Socinski replied, “I’d like to wait a little longer, although I’m not quite sure how many more analyses we’re going to see of this particular database. The other thing that I’ll point out is that there was some initial concern that immunotherapy given after chemoradiotherapy might set up patients for more lung toxicity; however, we saw a little more grade 1/2 toxicity, but really no difference in rate of grade 3/4 toxicity, which is actually really reassuring from this population.” Summarizing this trial’s results, Dr. Socinski stated, “I think it’s an important study that has really changed all of our practices; it’s a beachhead in terms of incorporating immunotherapy.”

**Table 4: ALTA-1L Trial (NCT02737501) Endpoints**

| Study Endpoint | Brigatinib | Crizotinib | p Value |
|---|---|---|---|
| Confirmed ORR (%) | 74 (95% CI: 66–81) | 62 (95% CI: 53–70) | 0.0342 |
| Confirmed iORR(%) | 78 (95% CI: 52–94) | 26 (95% CI: 10–48) | 0.0014 |

iORR: intracranial objective response rate

The panel then discussed the data from the ALTA-1L study (Table 4).[6]

About the presented data, Dr. Socinski said, “I was hoping for a little better median PFS number; however, we have to remember that even in earlier follow-up, the number might have been in roughly the same range. This patient population lives for many years, with a median survival now greater than 5 years, and so I think we still have to kind of wait a little longer before we have any final results.” When asked if he had any toxicity concerns with brigatinib, Dr. Mekhail noted that ”we need to recognize that there is a slight increase in the incidence of ILD [interstitial lung disease].”

**Table 5: FLAURA Trial (NCT02296125) Endpoints**

| Study Endpoint | Osimertinib | Comparator EGFR TKI | Hazard Ratio | p Value |
|---|---|---|---|---|
| OS, median (months) | 38.6 (95% CI: 34.5–41.8) | 31.8 (95% CI: 26.6–36.0) | 0.799 (95% CI: 0.641–0.997) | 0.0462 |
| 12 Month Survival rate (%) | 89 (95% CI: 85–92) | 83 (95% CI: 87–77) | | |
| 24 Month Survival rate (%) | 74 (95% CI: 69–79) | 59 (95% CI: 53–65) | | |
| 36 Month Survival rate (%) | 54 (95% CI: 48–60) | 44 (95% CI: 38–50) | | |

TKI: tyrosine kinase inhibitor

Next, the experts commented on the final results of the phase 3 FLAURA study, which compared osimertinib vs. an EGFR TKI (in this trial, either gefitinib or erlotinib) (Table 5).[7]

For the FLAURA trial, Dr. Socinski noted, “This is a standard of care–changing phase 3 trial; osimertinib, a third-generation drug.” He then noted, “Its main advantage is that it is good for treating disease with sensitizing mutations; in addition, it is also very good for treating T790M-mutant disease, which is where erlotinib, gefitinib, and dacomitinib kind of fall off, at least in clinically achievable doses. There was a clear advantage in OS in this population that was, to me, not only clinically significant, but it just reminds

us that with our cancer patients, we really need to give the best drug first. You can't delay on giving your best drug or wait to use your best drug, and this was a nice example."

"However," Dr. Socinski continued, "the results don't address the issue of how osimertinib compares to second-generation drugs. I'm not aware of any trials that are doing that, and I don't think we should be doing that. The nice thing about osimertinib too is that it has a very nice toxicity profile because of the lack of … wild-type inhibitions that we would tend to see with the first- and second-generation drugs. So I think this has changed practice, it has changed guidelines in the United States, and I think it is a new standard based on the FLAURA data."

Dr. Mekhail concurred with this assessment, saying, "I agree 100%. … The other exciting thing about osimertinib is its activity in CNS [central nervous system]-based metastases. I think this is very relevant in patients with *EGFR*, who are living 4 years almost, as we have on that study."

Dr. Socinski then observed, "We didn't focus on this in the *ALK* population, but then that's another advantage of the new ALK drugs, is that they have really good CNS activity, like osimertinib has in the *EGFR* space. We had a nice story after the first-generation agents; that was the T790M story, osimertinib was a good second-line drug, although it is actually a better first-line drug [in] this population."

**TATTON Trial (NCT02143466)**

Regarding the TATTON study, Dr. Socinski stated, "I think [this] was a very nice abstract, as we are beginning to understand that *MET* amplification is a mechanism of resistance to the first- and second-generation [drugs], and also is part of a resistance to osimertinib.[8] This … added a MET inhibitor to osimertinib. It was tolerable, it was active; however, it needs further study before we consider it the standard of care. But it does reinforce the concept that retesting to understand the mechanism of resistance may open up specific options for patients in this setting."

**Table 6: STARTRK-1 (NCT02097810)/STARTRK-2 (NCT02568267)/ALKA-372-001 Trial Endpoints**

| Study Endpoint | Value |
|---|---|
| ORR (%) | 59.3 (95% CI: 45.0–72.4) |
| iORR (%) | 54.5 (95% CI: 23.4–83.3) |

Dr. Mekhail then commented on the combined data from the 3 studies (STARTRK-1/2 and ALKA-372-001) that utilized entrectinib (Table 6).[9,10] "It's a selective NTRK inhibitor for *NTRK* fusion-positive tumors as well as *ROS1*." Dr. Mekhail explained, "This particular abstract looked at the activity of entrectinib in patients with *NTRK* fusion, based on RNA testing, regardless of … the type of the tumor, including several types of solid tumors. In the study, patients had a 59% response rate, and a 54.5% intracranial overall response rate, thus showing the drug crosses the blood-brain barrier; this is a new standard of care for patients with *NTRK* fusion-positive tumors."

**Conclusion**

Dr. Socinski noted that the "key takeaways from me for the 2019 ESMO Asia population are [that] it's important to do comprehensive genomic testing to identify these subsets of patients. We have a growing number of active, targeted agents, and we've talked about *ALK* and *EGFR* here. We have immunotherapy incorporated in stage 3 NSCLC. So, compared to when we started in lung cancer, this has become a very complex disease with lots more therapeutic options, and I think in my personal experience, we are just seeing longer longevity in survival and better quality of life as a result of these therapeutic options in the general lung cancer population."

"I second that," Dr. Mekhail stated. "My takeaway from this particular meeting is that we can't have enough meetings to talk about new data in lung [cancer], which is great. We'll talk about the incorporation of immunotherapy, and targeted therapy (precision medicine); we're not talking about chemotherapy anymore, and that's very exciting."

Concluding, Dr. Socinski said, "I want to reinforce that you can't use a targeted therapeutic agent unless you find the target, thus proving the importance of comprehensive genomic testing at the time of diagnosis in the advanced stage of disease."

**References**


1. Cheng Y, Zhang L, Hu J, et al. KEYNOTE-407 China extension study: pembrolizumab (pembro) plus chemotherapy in Chinese patients with metastatic squamous NSCLC. *Ann Oncol*. 2019;30(suppl_9):ix201-ix202.
2. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non–small-cell lung cancer. *N Engl J Med.* 2018;379:2040-2051.
3. Yoh K, Atagi S, Reck M, et al. Patient-focused outcomes in RELAY, a phase III trial of ramucirumab plus erlotinib (RamErl) versus placebo plus ERL (PboErl) in untreated EGFR-mutated metastatic NSCLC (EGFR+ MNSCLC). *Ann Oncol*. 2019;30(suppl_9):ix160.
4. Nishio M, Ji JH, Hotta K, et al. Overall survival with first-line durvalumab plus platinum-etoposide in patients with extensive-stage (ES)-SCLC in CASPIAN: subgroup findings from Asia. *Ann Oncol*. 2019;30(suppl_9):ix197-ix198.
5. Wu Y, Gray JE, Villegas A, et al. Three-year overall survival update from the PACIFIC trial. *Ann Oncol*. 2019;30(suppl_9):ix108-ix109.
6. Camidge R, Kim HR, Ahn M, et al. Brigatinib vs crizotinib in patients with ALK inhibitor-naive advanced ALK+ NSCLC: updated results from the phase III ALTA-1L trial. *Ann Oncol*. 2019;30(suppl_9): ix195-ix196.
7. Cho BC, Ohe Y, Zhou C, et al. Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC (FLAURA): final overall survival analysis. *Ann Oncol*. 2019;30(suppl_9):ix198-ix199.
8. Han J, Sequist LV, Ahn M, et al. TATTON expansion cohorts: A phase Ib study of osimertinib plus savolitinib in patients (pts) with EGFR-mutant, MET-positive NSCLC following disease progression on a prior EGFR-TKI. *Ann Oncol*. 2019;30(suppl_9):ix196-ix197.
9. De Braud FGM, Siena S, Barlesi F, et al. Entrectinib in locally advanced/metastatic ROS1 and NTRK fusion-positive non-small cell lung cancer (NSCLC): updated integrated analysis of STARTRK-2, STARTRK-1 and ALKA-372-001. *Ann Oncol*. 2019;30(suppl_5):v600.
10. Rolfo C, Dziadziuszko R, Doebele RC, et al. Updated efficacy and safety of entrectinib in patients with NTRK fusion-positive tumours: integrated analysis of STARTRK-2, STARTRK-1 and ALKA-372-001. *Ann Oncol*. 2019;30(suppl_9):ix25.