Highlights in respiratory oncology

J. Vansteenkiste, MD, PhD, E. Wauters, MD,
University Hospital KU Leuven and Leuven Lung Cancer Group, Leuven, Belgium

In this article, the ten key messages with respect to thoracic oncology presented at ASCO 2019, are summarized.

EARLY STAGE NSCLC: ADJUVANT CHEMOTHERAPY

Current ESMO guidelines recommend adjuvant chemotherapy with a two-drug combination with cisplatin in resected stage II and IIIA NSCLC. The cisplatin-pemetrexed (cis-pem) regimen – superior in stage IV non-squamous NSCLC – until now had only been studied in the adjuvant phase II randomized TREAT trial where it was better tolerated and achieved better dose delivery.[1]

In a phase III randomized controlled trial (RCT) cisplatin-pemetrexed versus cisplatin-vinorelbine is compared in resected stage II-IIIA non-squamous NSCLC (JIPANG study, UMIN000006737).[2] With 784 patients in the efficacy analysis and a median follow-up of 45 months, median relapse-free survival was similar: 38.9 months for cis-pem and 37.3 months for cis-vino (hazard ratio (HR) 0.98, p= 0.948) (*Figure 1*). Overall survival (OS) rates at 3 years were comparable: 83.5% *vs.* 87.2%. Cis-pem was better tolerated (e.g. grade 3-4 febrile neutropenia 0.3% *vs.* 11.6%, p<0.001), and more patients could complete treatment with cis-pem (87.9% *vs.* 72.7%, p<0.001). This trial thus confirms the TREAT findings and adds phase III data, showing that the efficacy of cis-pem is similar to cis-vino. Therefore, cis-pem can also be considered as a possible regimen for non-squamous tumors.

Neoadjuvant immunotherapy (IO) in upfront resectable stage I-IIIA NSCLC recently gained a lot of attention based on a feasibility trial in which all resectable patients could proceed to surgery, with a major pathological response (MPR) in 45% of the resection specimens.[3] Updates were presented on other trials with neoadjuvant IO. Of caution, in the atezolizumab trial (LCMC3), 11 out of 101 patients (11%) did not make it to surgery (all stage III), and MPR was seen in 15 out of 90 (17%) resected patients.[4] In the trial with nivolumab ± ipilimumab (NEOSTAR), 7 out of 44 patients (16%) did not go to surgical resection, and MPR was seen in 24% of the ITT population.[5]

LOCALLY ADVANCED NSCLC: ROLE OF IO

Current ESMO guidelines recommend concurrent chemo-radiotherapy (cCRT) for fit patients with unresectable stage III NSCLC. Not yet added to these guidelines is the substantial benefit in OS when one year of consolidation IO with durvalumab is added in patients without progression after cCRT (PACFIC trial). In this setting with curative intent, long-term OS benefits are crucial.

Gray *et al*. reported on mature 3-year OS data in the PACIFIC trial.[6] After a median duration of follow-up of 33.3 months, updated OS curves remain clearly separated: HR 0.69 (95%CI: 0.55-0.86), with 3-year OS rates 57% *vs.* 43.5%. This long-term clinical benefit with durvalumab following cCRT reinforces the PACIFIC regimen as the standard of care in this population. Ongoing studies are investigating an earlier start of IO during the cCRT phase in unresectable stage III NSCLC. Feasibility of this approach is being revealed, however with a higher incidence of grade ≥2 pneumonitis than in PACIFIC.[7,8]

In resectable stage IIIA (N2 or T4N0), Provencio *et al*. presented the final data of patients who underwent surgical resection in the Spanish phase II NADIM study with neoadjuvant chemo + IO (carboplatin-paclitaxel and nivolumab) 3 cycles, with nivolumab post-surgery for up to one year.[9] 41 of the

Please send all correspondence to: J. Vansteenkiste, MD, PhD, Pneumology, Respiratory Oncology Unit, Leuven University Hospital, Herestraat 49, 3000 Leuven, Belgium, Tel: +32 16 34 68 01, E-mail: johan.vansteenkiste@uzleuven.be

Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

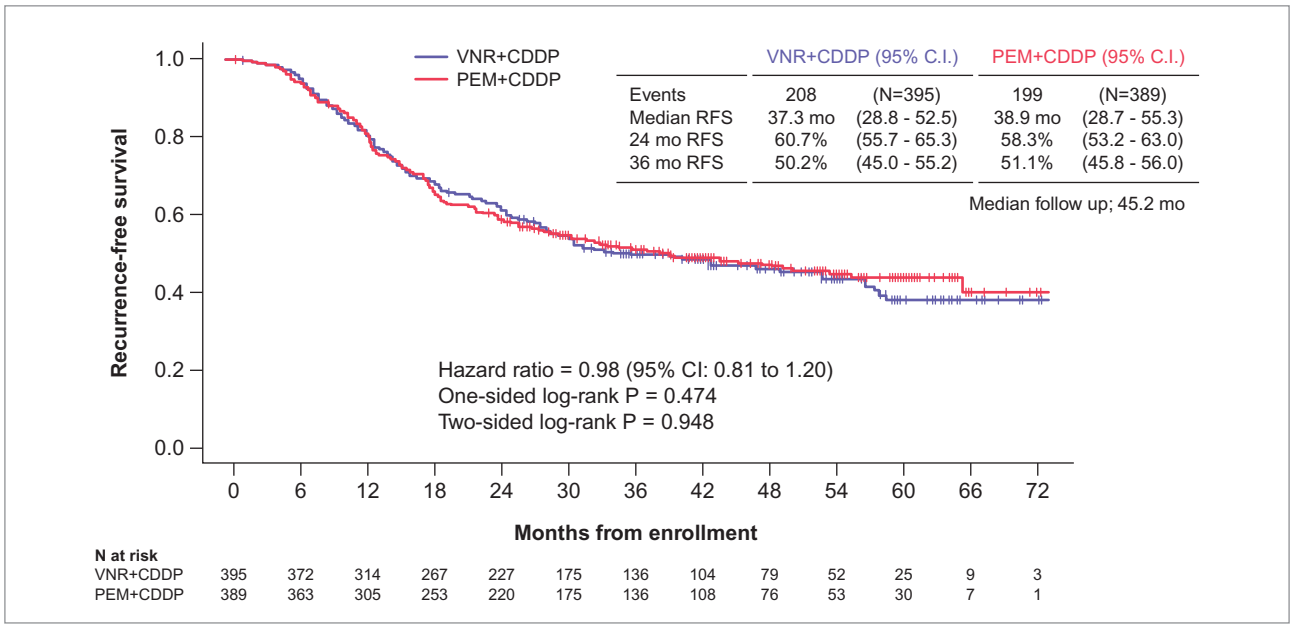

FIGURE 1. Similar RFS with cisplatin-pemetrexed and cisplatin-vinorelbine in resected stage II-IIIA non-squamous NSCLC.[2]

46 included patients had R0 resection. 34 out of 41 (83%) patients achieved MPR and 58% of the patients had a complete pathologic response. These major and complete pathologic response rates are unprecedented and promising for long-term outcomes. The results also indicate that neoadjuvant chemo + IO is probably a better research strategy than neoadjuvant IO alone, certainly in patients with node positive disease.

ADVANCED NSCLC: EGFR-TKI – ANTI-ANGIOGENIC DRUG COMBINATION FOR EGFR-MUTATED DISEASE

The focus of upcoming treatment strategies for EGFR-mutated advanced NSCLC is on delaying and overcoming resistance to EGFR TKIs. A synergistic role for dual EGFR and tumor angiogenesis blockade has been suggested for a longer time. The recently published interim analysis of the Japanese phase III NEJ026 trial showed a significant improvement in progression-free survival (PFS) with the upfront combination of the first generation EGFR TKI erlotinib and the VEGF-A blocking monoclonal antibody bevacizumab (16.9 months *vs.* 13.3 months, HR=0.60).[10] Toxicity was substantial in the experimental arm, leading to discontinuation of bevacizumab in 30% of cases. Improvement in OS still has to be confirmed.

A study presented a double-blinded placebo-controlled phase III trial (RELAY, N=449) that evaluated the superiority of "***1L erlotinib + ramucirumab vs. 1L erlotinib + placebo***" in a mainly Asian population (77%).[11] Patients with central nervous system (CNS) involvement were excluded. The addition of ramucirumab, a monoclonal antibody blocking VEGFR2, significantly prolonged investigator-assessed PFS: 19.4 months *vs.* 12.4 months (HR 0.59, p<0.0001). This was not driven by a difference in objective response rate (ORR), but by a significantly longer duration of response. As expected, the improved outcome was at the cost of increased toxicity: grade ≥3 AEs in 72% *vs.* 53%, leading to a discontinuation rate of 33% for ramucirumab. OS data are not yet mature. Incidence of the T790M resistance mutation was similar in both treatment arms (42% *vs.* 47%), as was the frequency of patients that received second-line osimertinib (28% *vs.* 30%).

Although the improvement in PFS with the upfront combination of erlotinib and ramucirumab is clinically relevant, erlotinib can no longer be regarded as an appropriate comparator in first-line setting given the FLAURA data.[12] Indeed, the FLAURA trial established the 3rd generation EGFR TKI osimertinib as the current standard of care upfront treatment. Superiority of osimertinib is not only based on the significantly longer PFS compared with 1st generation TKIs (18.9 months *vs.* 10.2 months, HR=0.46) - an improvement that is actually in the same range as that observed with erlotinib and ramucirumab - but also on the very favorable toxicity profile, good CNS activity and better quality of life (QoL). OS data for upfront osimertinib are now eagerly awaited. Meanwhile, a study reported a phase II trial (N=49) on the safety and efficacy of combining osimertinib and bevacizumab in first-line.[13] PFS at one year (primary endpoint) was 76%. All patients with measurable CNS disease had a partial response (5/5). Treatment was largely well tolerat-

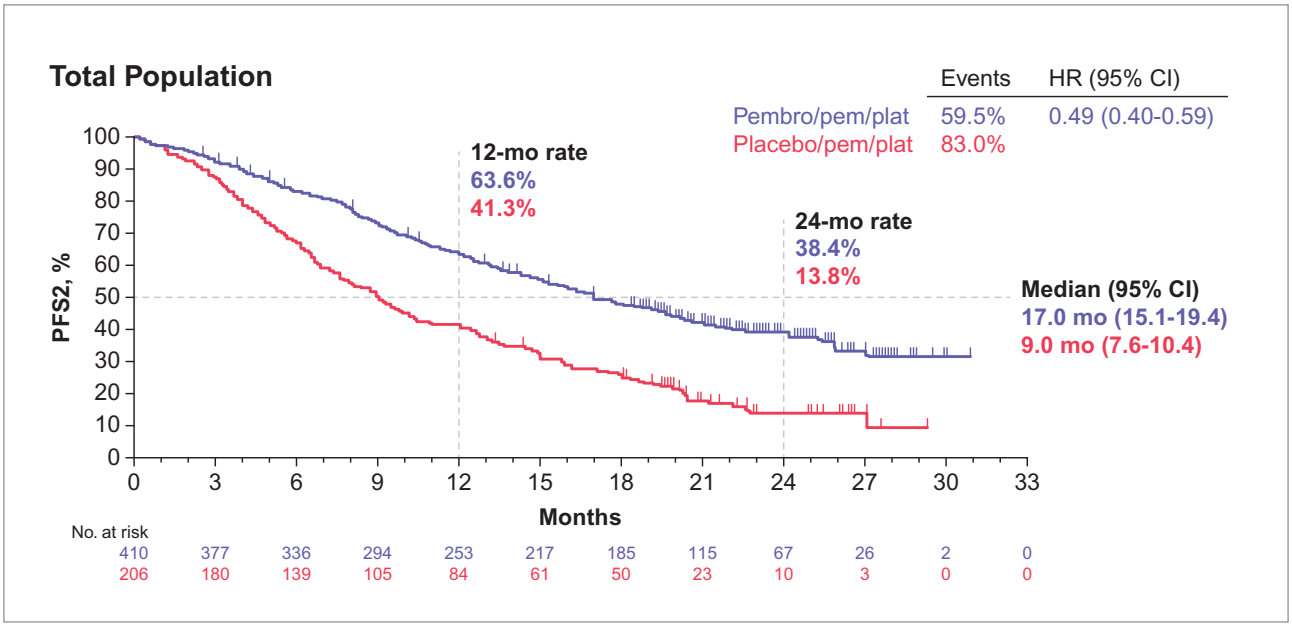

FIGURE 2. Significantly longer PFS on subsequent therapy for patients treated with pembrolizumab-chemotherapy vs. chemotherapy alone in the phase III Keynote-189 trial.[29]

ed, with toxicity as expected. In total, 18% of patients had to discontinue bevacizumab and 24% needed a dose reduction of osimertinib. A randomized study of osimertinib compared to osimertinib and bevacizumab as initial treatment is planned.

ADVANCED NSCLC: EGFR TKI – CHEMOTHERAPY COMBINATION FOR EGFR-MUTATED DISEASE

All previously published phase III RCTs comparing a 1st/2nd generation EGFR-TKI to chemotherapy could not demonstrate an OS benefit for the TKI, which was attributed to crossover in subsequent treatment line. At ASCO 2018, two phase III trials (NEJ009 and ARCHER1050) demonstrated an OS benefit of the experimental regimen over the 1st generation TKI gefitinib. In particular, the NEJ009 trial showed a clear OS benefit with the upfront combination of gefitinib and chemotherapy *vs.* gefitinib followed by chemotherapy at progression (52.2 months *vs.* 38.3months). An early effect of chemotherapy on 'TKI tolerant' cells was hypothesized to drive the OS benefit.

Noronha *et al.* reported on a phase III trial that randomly assigned 350 untreated *EGFR*-mutant advanced NSCLC patients (including 21% of PS2 patients) to "1L gefitinib in combination with carboplatin-pemetrexed *vs.* gefitinib alone".[14] Patients with stable brain metastasis were allowed in the study (17% *vs.* 19%) and the majority of them received prior whole brain RT (13% *vs.* 18%). ORRs and depth of response were increased in the combination arm, leading to a significantly longer investigator-assessed median PFS (16 months *vs.* 8 months, HR 0.51, p<0.0001). OS was improved (median NR *vs.* 17 months, HR 0.45, p<0.0001) was confirmed, hereby corroborating the findings of NEJ009. Of note in the current trial is that few patients received second-line therapy: only 24% received platinum-doublet chemotherapy in the gefitinib arm. Eleven % *vs.* fifteen % of the patients received osimertinib. As expected, toxicity was significantly increased with the combination (grade ≥3 AEs in 51% *vs.* 25%). As mentioned above, osimertinib is now considered as the standard of care first-line treatment in EGFR-mutated advanced NSCLC based on the best mix of PFS improvement, mild toxicity profile, CNS control, QoL and practicality. However, chemotherapy still plays a role in the treatment of EGFR-mutated patients. Currently, platinum-doublet chemotherapy is the standard second-line treatment after osimertinib resistance. Neal *et al.* reported retrospectively on the addition of chemotherapy to osimertinib (used in ≥2L) at osimertinib resistance.[15] The combination appeared tolerable, with need of treatment discontinuation in only 8 % of the patients. Prospective data of this approach are needed to confirm safety and efficacy in front-line setting.

At ESMO 2018 (Ramalingam *et al.*), resistance mechanisms to upfront osimertinib identified in ctDNA of FLAURA patients were presented, including both on-target (e.g. *EGFR* C797S) and off-target genetic events (e.g. *MET* amplification).[16] These data are now stimulating the development of more targeted strategies to overcome acquired osimertinib resistance. During ASCO 2019, Oxnard *et al.* introduced the upcom-

ing phase II trial evaluating the combination of osimertinib and savolitinib (MET inhibitor) in *MET*-amplified patients, a combination that resulted in a partial response (PR) of 25% in the prior phase Ib TATTON trial.[17] Very early data (phase I) on two monoclonal antibodies after progression on osimertinib were also presented: a first one revealed a PR of 28% with an EGFR- and cMET-bispecific antibody (JNJ-372)[18], while the second one revealed a PR of 31% with a HER3 antibody drug conjugate (U3-1402).[19] More data on targeted strategies to overcome osimertinib resistance are expected in the near future.

ADVANCED NSCLC: ACTIVITY AND RESISTANCE TO MET TKIS

MET exon 14 (*MET*ex14) skipping mutations are present in 3-4% of cases with stage IV non-squamous NSCLC and are mutually exclusive with other established driver mutations. Although controversial for quite some time, they by now have been established as primary oncogenes that can effectively be targeted in advanced NSCLC. At the 2018 ESMO meeting, data of the GEOMETRY mono-1 trial showed high response rates to capmatinib, an oral highly selective MET inhibitor.[20]

Wolf *et al.* now presented results on duration of response (DoR) and PFS, as well as updated results for ORRs of GEOMETRY mono-1 in previously treated (cohort 4, N=69) and untreated (cohort 5b, N=28) patients.[21] Although immature at the time of data analysis, data on DoR and PFS by an independent review committee (IRC) are promising. In cohort 4, ORR, median DoR, and median PFS were 40.6%, 9.7 months, and 5.4 months respectively. For cohort 5b, this was 67.9%, 11.1 months and 9.7 months.

ORR in both cohorts were confirmed. In the subgroup of patients with brain metastasis at inclusion (N=13), intracranial responses were confirmed by IRC in 54%. The safety profile remained favorable. These data establish capmatinib as a promising treatment option for patients with *MET* exon 14-mutated stage IV NSCLC, for which it was granted Breakthrough Therapy Designation by the FDA.

Paik *et al.* presented an update on the phase II study of tepotinib, another highly selective MET inhibitor (VISION trial).[22] In this study, *MET*ex14 skipping mutations could have been identified in a liquid (DNA-based assay) or a tissue biopsy (RNA-based assay). Overall ORR by IRC was 50% in patients with the driver mutation detected in a liquid biopsy (with highest ORRs in first-line setting), and 45.1% in those selected based on a tissue biopsy. Median PFS by IRC was 9.5 months and 10.8 months in the liquid and tissue biopsy group, respectively. No data on intracranial responses were provided. Grade 3 treatment-related adverse events occurred in 19.5% of cases.

The consistently higher ORRs to MET-directed therapy in the first-line setting support the routine testing of MET exon 14 skipping mutations at diagnosis. Testing is preferably performed as part of a broader DNA sequencing panel. However, as exemplified by [22], RNA-based approaches are now being assessed to more comprehensively capture MET exon 14 skipping events, given the various genomic locations of exon 14 skipping alterations.

Guo *et al.* presented an early report on resistance mechanisms to MET TKIs in METex14-mutated disease, mainly (91%) with crizotinib, a non-specific MET inhibitor with ORR of 32%.[23] Primary resistance appeared to correlate with MET protein expression: ORR 0% in the absence of MET expression *vs.* 54% with MET expression in the tumor. Acquired resistance was analyzed by use of 14 paired pre- and post-treatment biopsies and revealed on-target or off-target resistance mechanisms in 50% of cases. Data on resistance mechanisms to the newer more specific MET TKIs are needed to further guide MET-directed therapy.

ADVANCED NSCLC: KNOWN TARGETS, NEW DRUGS

EGFR exon 20 insertions are present in about 6% of EGFR-mutated advanced NSCLC patients, however, currently approved EGFR TKIs are largely ineffective in these patients. Janne *et al.* presented an update on a phase I/II trial exploring the safety and efficacy of the selective TAK-788 in 28 pretreated patients.[24] Overall ORR was 43% and was higher in patients without brain metastasis at baseline: 56% *vs.* 25%. Median PFS was 7.3 months, and longer in patients with no CNS involvement at baseline (8.1 months *vs.* 3.7 months). Grade 3 or higher treatment-related AEs occurred in 40% of cases, mainly diarrhea.

In RET fusions, few responses to multikinase inhibitors have been observed. At ASCO 2018, phase I data on the selective RET inhibitor LOXO-292 showed an ORR of 77%.[25] This year, Gainor *et al.* discussed a phase II trial with the selective RET inhibitor BLU-667 (ARROW trial).[26] Overall ORR was 58%: 71% in treatment-naïve patients and 60% in patients previously treated with platinum-based chemotherapy. Responses were seen regardless of the presence of CNS metastases. The drug was well tolerated with mainly low-grade treatment-related AEs. The FDA granted Breakthrough Therapy Designation to BLUE-667 for RET-driven NSCLC with progression after platinum-based chemotherapy.

KRAS G12C mutations are prevalent in advanced NSCLC, however, not yet effectively targeted by a drug. These mutations are present in 13% of cases and are selectively and irreversibly inhibited by AMG510. Fakih *et al.* reported on the phase I first-in-human study with AMG 510.[27] Responses

were promising in 5 out of 10 NSCLC patients that were previously treated with standard therapy. The drug was generally well tolerated with no serious drug-related AEs. The phase II part of the study will soon start enrollment.

For the ROS1 fusions, crizotinib is currently approved for ROS1-mutated NSCLC, with an ORR of 72% and median PFS of 19.3 months. Repotrectinib is developed specifically to overcome the most common resistance mutation G2032R. Cho *et al.* reported preliminary results of the TRIDENT-1 trial with repotrectinib.[28] Confirmed ORR was 82% in treatment-naïve patients and 55% in pretreated patients (ORR influenced by the dose). Activity against G2032R was confirmed with an ORR of 40%. Promising CNS activity was present in 100% of untreated patients and 75% of pretreated patients. Overall, the drug was well tolerated. Outcome data, as well as the recommended phase II dose, are awaited.

ADVANCED NSCLC: OUTCOME AFTER COMBINED CHEMO-IO IN FIRST-LINE

KEYNOTE-189 (platinum-pemetrexed plus pembrolizumab) has revolutionized the approach to stage IV non-squamous NSCLC. ASCO 2019 featured updated OS data and the first data on post-study therapy and PFS2 (progression after the Keynote-189 therapy and the next line of therapy).[29] With a median follow-up of 18.7 months, OS remained strongly in favor of the triplet: HR 0.56 (95CI: 0.45-0.70, p <0.00001, median 22.0 *vs.* 10.7 months). Second-line therapy was received by 45% in the chemotherapy/pembrolizumab arm and 59% (54% IO) in the chemotherapy arm. Even with 54% crossover to 2L IO, PFS2 was longer for 1L chemotherapy/pembrolizumab: HR 0.49, 95%CI: 0.40-0.59, p <0.00001; median 17.0 *vs.* 9.0 months) (*Figure 2*), and this in all PD-L1 cohorts.

ADVANCED NSCLC: RESPONSE PREDICTION WITH IO

While PD-L1 expression on tumor cells now is universally recognized as an enrichment biomarker of single agent anti-PD-(L)1 IO, further refinement of response prediction is a high need.

In a science symposium, Skoulidis reported on how next-generation sequencing (NGS) may help with the identification of genomic predictors of IO response.[30] It has already been reported that STK11/LKB1 gene alterations predict resistance to single agent IO. The new data now reported the findings for response to platinum-pemetrexed + pembrolizumab.

STK11/LKB1 genomic alterations were present in 102 out of 377 patients treated with platinum-pemetrexed + pembrolizumab, and were associated with significantly shorter PFS (median 4.8 *vs.* 7.2 months, p= 0.0063) and OS (median 10.6 *vs.* 16.7 months, p = 0.0083). Importantly, this was not only prognostic, but predictive as well: in patients with STK11/LKB1-mutant NSCLC, addition of pembrolizumab to platinum-pemetrexed did not improve PFS or OS (median 4.8 *vs.* 4.3 months, p= 0.75, and median 10.6 *vs.* 10.3 months, p= 0.79, respectively). This information also reinforces the evidence that broad NGS profiling is to be preferred for molecular analysis of NSCLC, rather than single gene PCR tests.

FOR YOUR CALENDAR

Respiratory Oncology Update 2019: 19/10/2019 in La Hulpe. https://www.update-respiratoryonco.be/

ADVANCED NSCLC: IO IN PATIENTS WITH AUTOIMMUNE DISORDERS

Patients with active autoimmune disorders (AD), or even those with a history of AD, have in general been excluded from clinical trials with IO in lung cancer. Nevertheless, in clinical practice, they are estimated to represent about 13.5% of patients with lung cancer.[31]

Khozin *et al.* presented a retrospective real-world study of IO in NSCLC patients with AD. Among 2425 patients, AD was present in 22% (N=538).[32] There was no association between AD status and outcomes: median OS in all patients was 12.4 months (95%CI: 11.3-13.5). Time-to-treatment-discontinuation (3.68 *vs.* 4.24 months, p= 0.10) and OS (11.5 *vs.* 12.8 months, p= 0.20) did not differ between the two cohorts. There was no overall increased incidence of AEs in the AD group, but sub-analysis in patients with active AD showed higher rates of select AEs including endocrine, GI and blood disorders.

SCLC: NEW AGENTS

Over the last decades, the only progress in systemic therapy for metastatic SCLC was the addition of atezolizumab to carboplatin-etoposide, resulting in a (modest) improvement in survival.[33]

Paz-Ares *et al.* reported on the relapsed SCLC cohort of a multicenter phase II basket trial with lurbinectedin (N=105).[34] Lurbinectedin is a novel anti-cancer drug that inhibits activated transcription and induces DNA double-strand breaks, leading to apoptosis. Response rate was 35%: 21% in platinum-resistant relapse (<90 days), 47% in platinum-sensitive relapse (≥90 days). Median duration of response was 5.3 months: 4.7 months in resistant and 6.2 months in sensitive

patients. Median OS was 10.8 months: 5.1 months in resistant and 15.2 months in sensitive relapse. These data are comparable, or even slightly superior, to Topotecan, but with an improved tolerability profile (febrile neutropenia in 3.8%, treatment-related discontinuations in 3.8%). These promising data have been further explored in a phase III trial comparing doxorubicin + lurbinectedin *vs.* standard second line chemotherapy. Data are awaited.

REFERENCES

1. Kreuter M, Vansteenkiste J, Fischer JR, et al. Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: the TREAT study. Ann Oncology, 2013.

2. Kenmotsu H, Yamamoto N, Yamanaka T, et al. Randomized phase III study of pemetrexed/cisplatin (Pem/Cis) versus vinorelbine /cisplatin (Vnr/Cis) for completely resected stage II-IIIA non-squamous non-small-cell lung cancer (Ns-NSCLC): The JIPANG study. Presented at ASCO 2019; Abstract 8501.

3. Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. N Eng J Med, 2018.

4. Kwiatkowski DJ, Rusch VW, Chaft JE, et al. Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): Interim analysis and biomarker data from a multicenter study (LCMC3). Presented at ASCO 2019; Abstract 8503.

5. Cascone T, Nassib W, Weissferdt A, et al. Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC): Clinical and correlative results from the NEOSTAR study. Presented at ASCO 2019; Abstract 8504.

6. Gray JE, Villegas AE, Daniel DB, et al. Three-year overall survival update from the PACIFIC trial.Presented at ASCO 2019; Abstract 8526.

7. Jabbour SK, Berman AT, Decker RH, et al. Prospective phase I multi-institutional trial of PD-1 blockade with pembrolizumab during concurrent chemoradiation for locally advanced, unresectable non-small cell lung cancer.Presented at ASCO 2019; Abstract 8511.

8. Lin SH, Lin Y, Mok I, et al. Phase II trial combining atezolizumab concurrently with chemoradiation therapy in locally advanced non-small cell lung cancer. Presented at ASCO 2019; Abstract 8512.

9. Provencio M, Nadal E, Insa A, et al. NEO-adjuvant chemo-immunotherapy for the treatment of STAGE IIIA resectable non-small-cell lung cancer (NSCLC): A phase II multicenter exploratory study—Final data of patients who underwent surgical assessment. Presented at ASCO 2019; Abstract 8509.

10. Saito H, Fukuhara T, Furuya N, et al. Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial. Lancet Oncol 2019.

11. Nakagawa K, Garon EB, Seto T, et al. RELAY: A multinational, double-blind, randomized Phase 3 study of erlotinib (ERL) in combination with ramucirumab (RAM) or placebo (PL) in previously untreated patients with epidermal growth factor receptor mutation-positive (EGFRm) metastatic non-small cell lung cancer (NSCLC). Presented at ASCO 2019; Abstract 9000.

12. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Eng J Med, 2018.

13. Yu HA, Kim R, Makhnin A, et al. A phase 1/2 study of osimertinib and bevacizumab as initial treatment for patients with metastatic EGFR-mutant lung cancers. Presented at ASCO 2019; Abstract 9086.

14. Noronha V, Joshi A, Patil VM, et al. Phase III randomized trial comparing gefitinib to gefitinib with pemetrexed-carboplatin chemotherapy in patients with advanced untreated EGFR mutant non-small cell lung cancer (gef vs gef+C). Presented at ASCO 2019; Abstract 9001.

15. Neal JW, Hausrath D,Wakelee HA, et al. Osimertinib with chemotherapy for EGFR-mutant NSCLC at progression: Safety profile and survival analysis. Presented at ASCO 2019; Abstract 9083.

16. Ramalingam S, Cheng Y, Zhou C, et al. Mechanisms of acquired resistance to first-line osimertinib: preliminary data from the phase III FLAURA study. Presented at ESMO 2018; Abstract LBA50.

17. Oxnard G, Cantarini M, Frewer P, et al. SAVANNAH: A Phase II trial of osimertinib plus savolitinib for patients (pts) with EGFR-mutant, MET-driven (MET+), locally advanced or metastatic non-small cell lung cancer (NSCLC), following disease progression on osimertinib. Presented at ASCO 2019; Abstract TPS9119

18. Haura EB, Cho BC, Lee JS, et al. JNJ-61186372 (JNJ-372), an EGFR-cMet bispecific antibody, in EGFR-driven advanced non-small cell lung cancer (NSCLC). Presented at ASCO 2019; Abstract 9009.

19. Janne PA, Yu HA, Johnson ML, et al. Safety and preliminary antitumor activity of U3-1402: A HER3-targeted antibody drug conjugate in EGFR TKI-resistant, EGFRm NSCLC. Presented at ASCO 2019; Abstract 9010.

20. Wolf J, Seto T, Han J-Y, et al. Results of the GEOMETRY mono-1 phase II study for evaluation of the MET inhibitor capmatinib (INC280) in patients (pts) with METΔex14 mutated advanced non-small cell lung cancer (NSCLC). Presented at ESMO 2018; Abstract LBA52.

21. Wolf J, Seto T, Han JY, et al. Capmatinib (INC280) in METΔex14-mutated advanced non-small cell lung cancer (NSCLC): Efficacy data from the phase II GEOMETRY mono-1 study. Presented at ASCO 2019; Abstract 9004.

22. Paik PK,Veillon R, Cortot AB, et al. Phase II study of tepotinib in NSCLC patients with METex14 mutations. Presented at ASCO 2019; Abstract 9005.

23. Guo R, Offin M, Brannon AR, et al. MET inhibitor resistance in patients with MET exon 14-altered lung cancers. Presented at ASCO 2019; Abstract 9006.

24. Janne PA, Neal JW, Camidge DR, et al. Antitumor activity of TAK-788 in NSCLC with EGFR exon 20 insertions. Presented at ASCO 2019; Abstract 9007.

25. Drilon AE, Subbiah V, Oxnard GR, et al. A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with RET-altered cancers. Presented at ASCO 2018; Abstract 102.

26. Gainor JF, Lee DH, Curigliano G, et al. Clinical activity and tolerability of BLU-667, a highly potent and selective RET inhibitor, in patients (pts) with advanced RET-fusion+ non-small cell lung cancer (NSCLC). Presented at ASCO 2019; Abstract 9008.

27. Fakih M, O'Neil B, Price TJ, et al. Phase 1 study evaluating the safety, tolerability, pharmacokinetics (PK), and efficacy of AMG 510, a novel small molecule KRASG12C inhibitor, in advanced solid tumors. Presented at ASCO 2019; Abstract 3003.

28. Cho BC, Drilon AE, Doebele RC, et al. Safety and preliminary clinical activity of repotrectinib in patients with advanced ROS1 fusion-positive non-small cell lung cancer (TRIDENT-1 study). Presented at ASCO 2019; Abstract 9011.

29. Gadgeel SM, Garassino MC, Esteban E, et al. KEYNOTE-189: Updated OS and progression after the next line of therapy (PFS2) with pembrolizumab (pembro) plus chemo with pemetrexed and platinum vs placebo plus chemo for metastatic nonsquamous NSCLC. Presented at ASCO 2019; Abstract 9013.

30. Skoulidis F, Arbour KC, Hellmann MD, et al. Association of STK11/LKB1 genomic alterations with lack of benefit from the addition of pembrolizumab to platinum doublet chemotherapy in non-squamous non-small cell lung cancer. Presented at ASCO 2019; Abstract 102.

31. Khan SA, Pruitt SL, Xuan L, et al. How does autoimmune disease impact treatment and outcomes among patients with lung cancer? A national SEER-Medicare analysis. Lung Cancer, 2018.

32. Khozin S, Walker MS, Jun M, et al. Real-world outcomes of patients with advanced non-small cell lung cancer (aNSCLC) and autoimmune disease (AD) receiving immune checkpoint inhibitors (ICIs). Presented at ASCO 2019; Abstract 110.

33. Horn L, Mansfield AS, Szczęsna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med 2018.

34. Paz-Ares LG, Perez JMT, Besse B, et al. Efficacy and safety profile of lurbinectedin in second-line SCLC patients: Results from a phase II single-agent trial. Presented at ASCO 2019; Abstract 8506.