Special Edition

Highlights in thoracic oncology

B.I. Hiddinga, MD, J.P. van Meerbeeck, MD, PhD

This report will highlight 10 important studies presented during ESMO 2014, and 4 small but promising future directions in the treatment of NSCLC. The presidential symposium featured two negative studies in a large cohort of non-small cell lung cancer (NSCLC) patients: the MAGRIT and IMPRESS. The other topics include immunotherapy, targeted treatment and biomarkers, development of new drugs in ALK-EML rearranged NSCLC, and prevention of cachexia in NSCLC. Lastly, an important study in malignant pleural mesothelioma (MPM) was presented.

(Belg J Med Oncol 2014;8(4):152-7)

MAGRIT: Adjuvant treatment with the MAGE-A3 cancer immunotherapeutic does not improve disease free survival in resected early stage non-small cell lung cancer

The MAGRIT phase III trial assessed the efficacy of the recMAGE-A3 + AS15 cancer immunotherapeutic as adjuvant treatment for patients with resected MAGE-A3-positive non-small cell lung cancer (NSCLC). Adjuvant chemotherapy is standard of care for resected stage II, IIIA and high risk IB NSCLC. However, the 5-year disease free survival (DFS) remains poor with 35 – 50% and half of the patients will not receive adjuvant chemotherapy. Tolerability of the cisplatin doublet is suboptimal.

MAGE-A3 is a tumour-specific antigen that is expressed in several tumour types, including NSCLC. In NSCLC, expression can be demonstrated in 35% of early-stage tumours. The normal function of MAGE-A3 is unknown, but its presence on tumour cells have been associated with a worse prognosis. MAGE-A3 was assessed in the primary tumour by RT-PCR testing on formalin-fixed paraffin embedded tissue. MAGE-A3 cancer immunotherapeutic is delivered as a recombinant protein, combined with immunostimulants. Phase II data showed a 25% reduction in the relative risk of lung cancer recurrence and the vaccine was very well tolerated.

MAGRIT was a randomised, double-blind, placebo-controlled phase III trial that investigated whether the rec-MAGE-A3+AS15 cancer immunotherapy as adjuvant therapy improved DFS in patients with completely resected (R0) MAGE-A3 positive NSCLC (stages IB, II and IIIA) who did or did not receive adjuvant chemotherapy (up to 4 cycles of platinum-based therapy). More than 2,000 patients were randomly assigned (2:1) to receive either 13 intramuscular injections of MAGE-A3 cancer immunothera-peutic or placebo over a 27-months period. Patients were stratified for treatment with or without chemotherapy. Overall, 52% of the patients received adjuvant chemotherapy. Stage IB disease in 47% of the patients, stage II 36% and stage IIIA 17%. Median age was 63 years, and 76% of the patients were male. The mean relative dose intensity was above 98% in both groups. The medication was well tolerated, with a limited incidence of grade ≥3 adverse events that didn't differ between the treatment groups. Median follow-up at the time of the final analysis was 38.8 months. In the overall study population, the median DFS was 60.5 months for the MAGE-A3 cancer immunotherapeutic and 57.9 months for the placebo (HR: 1.024, p = 0.737) (*Figure 1*). In patients who didn't receive adjuvant chemotherapy the DFS was 58.0 months and 56.9 months for the MAGE-A3 cancer immunotherapeutic and placebo, respectively (HR: 0.97,

Thoracic Oncology, MOCA, Antwerp University Hospital, Belgium

Please send all correspondence to: B.I. Hiddinga MD, Department of Thoracic Oncology, MOCA, Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem, Antwerp, Tel: +32 (0)3 821 45 46, Email birgitta.hiddinga@uza.be

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

Keywords: Non-small cell lung cancer, malignant pleural mesothelioma, immunotherapy, ALK inhibitor, EGFR TKI, chemotherapy, biomarker.

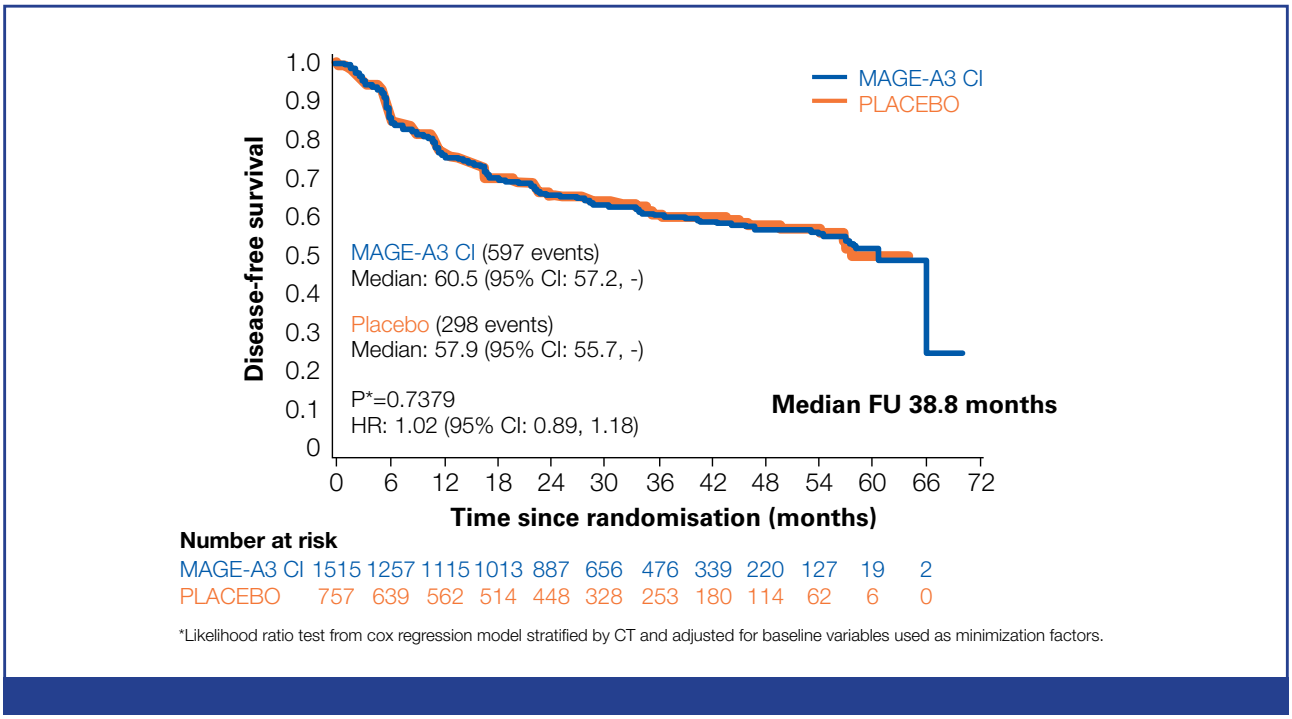

Figure 1. Maintenance MAGE-A3 does not improve the disease free survival in the phase III MAGRIT trial.

p= 0.76). Secondary endpoints included overall survival (OS), lung cancer specific survival, disease free specific survival, immunogenicity, safety, and health related quality of life. OS in the overall population was not reached, but it might be expected to exceed a median value of 5 years. No predictive gene signature was identified in the training set.

The authors concluded that adjuvant treatment with the MAGE-A3 cancer immunotherapeutic did not improve DFS compared to placebo in the resected early stage NSCLC. The study was performed in an adequate setting with an appropriate design and power. Possible reasons for failure of the study are that the retrospective subset analysis may be deceiving. Probably, monovalent molecularly defined vaccines are too weak. It can be that metastatic or progressive tumours are immune escape variants, or it could be due to epigenetic mechanisms. Future opportunities for vaccines in NSCLC are polyvalent vaccines or personalised molecular vaccines based on mutanome analysis.[1]

Immunotherapy: a new treatment strategy in thoracic oncology?

The research on the targeted monoclonal antibody pembrolizumab, which prevents PD-1 ligand (PD-L1) binding to T cells, allowing them to differentiate and destroy cancer cells, continues. Data from 282 patients in the randomised phase II and the non-randomised phase I KEYNOTE-001 were presented. Patients with treatment-naïve or previously treated advanced NSCLC received pembrolizumab 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks. The reported ORR for all patients was 21% (assessed by RECIST 1.1) or 23% (assessed by immune-related response criteria, irRECIST). The response was highest in patients with strong PD-L1 expression (≥ 50% staining): 39% (RECIST) and 47% (irRECIST) compared with 16% and 9% in patients with weak or negative PD-L1 expression. Grade ≥3 treatment-related adverse events occurred in 24 patients (9%), with pneumonitis being the most common (n=5).[2]

The randomised phase II trial of the immune modulator imprime PGG (PGG) in patients with stage IV NSCLC receiving carboplatin/paclitaxel and the vascular endothelial growth factor-targeting antibody bevacizumab failed to show any improved clinical outcome. Although numerical increases in ORR (60.4% versus 43.5%) and OS (16.1 *vs.* 11.6 months) in patients receiving PGG, these results were statistically not significant.[3]

IMPRESS: doublet chemotherapy remains the standard of care 2nd line treatment for patients with EGFR mutation positive NSCLC refractory to first-line first generation TKI

Most patients with *EGFR* mutation positive NSCLC respond to first-line EGFR tyrosine kinase inhibitors

(TKIs), but later acquire resistance. Optimal treatment strategies in patients with acquired resistance are not clear and can include discontinuing EGFR TKI and start a platinum-based doublet chemotherapy or continuation of EGFR TKI in combination with a platinum-doublet chemotherapy. The double blind Iressa Mutation Positive multicentre treatment beyond proRESsion Study (IMPRESS) evaluated the efficacy and safety of continuing gefitinib plus pemetrexed/cisplatin versus placebo plus pemetrexed/cisplatin in patients with acquired resistance to first-line gefitinib. Patients who received prior chemotherapy were excluded. The primary endpoint was PFS. Secondary endpoints included OS, objective response rate (ORR), disease control rate (DCR), safety and tolerability and health-related quality of life. The median follow-up of 265 patients was 11.2 months. Randomisation did not include stratification factors, but analysis was adjusted for two covariates: age (< 65 versus ≥ 65 years) and prior response to gefitinib (stable disease versus partial response plus complete response). There was no statistically significant improvement in PFS for gefitinib versus placebo with a HR of 0.86 (p=0.273). Median PFS was 5.4 months in each arm. The OS was immature (33% of the patients had died), with better OS for placebo than gefitinib (HR: 1.62; p= 0.029). No treatment differences were found in ORR and DCR. The safety profile for gefitinib plus chemotherapy was in line with the expectations. Common adverse events were nausea and decreased appetite. Gefitinib was associated with increased grade 1/2 gastrointestinal toxicities. Post-discontinuation therapy in the intent-to-treat population was higher in the placebo arm, where 17% of patients received platinum based regimens compared to 5% in the gefitinib arm, and 44% received EGFR TKI versus 30% of patients in the gefitinib arm. In conclusion, that continuation of gefitinib in addition to pemetrexed/cisplatin is of no clinical benefit for patients with acquired resistance to gefitinib. A doublet chemotherapy remains the standard of care for patients refractory to first-line gefitinib.[4]

LUX-Lung 8: the small benefit of afatinib is not clinically significant compared to its increased toxicity in relapsed or refractory squamous cell lung cancer

LUX-Lung 8 is a randomised, open-label, prospective phase III trial comparing the EGFR TKI erlotinib with the irreversible EGFR TKI afatinib in relapsed or refractory squamous cell NSCLC. Afatinib is an irreversible ErbB-family that inhibits all kinase-active members. In the study, 669 patients received afatinib or erlotinib after failing first-line platinum based therapy. The primary endpoint was PFS. The median PFS for afatinib was 2.4 months *vs.* 1.9 months for erlotinib (p=0.043). The disease control rate was 45.7% *vs.* 36.8%, p=0.02 with a greater tumour shrinkage. Grade 3 or more toxicity in diarrhoea and stomatitis were more common in afatinib compared to erlotinib. The small benefit of afatinib is not clinically significant compared to its increased toxicity. The clinical implications are limited since chemotherapy is generally more effective in squamous cell lung cancer.[5]

Targeting rare driver mutations

Activating BRAF-mutations are present in 1.5% of NSCLC, primarily adenocarcinomas and are mutually exclusive to other driver alterations. Dabrafenib is the first drug that shows activity in a prospective trial of NSCLC with BRAF V600E mutations Treatment with dabrafenib in this single-arm, 2-stage design, phase II study demonstrated significant activity with durable objective responses and an acceptable safety profile. The ORR for 78 patients with more than one line of prior chemotherapy was 32%. For these 25 patients experienced partial response (PR). DCR longer than 12 weeks was 56%. Median duration of response was 11.8 months with 48% of the responders progressed. Most common adverse events were pyrexia (36%), asthenia (30%), hyperkeratosis (30%), decreased appetite (29%), nausea (27%), cough (26%), fatigue (26%) and skin papilloma (26%). Cutaneous squamous-cell carcinomas, including keratoacanthoma, were reported in 18%.[6]

Somatic HER2 mutations occur in approximately 2% of patients with NSCLC. The suggestion is that combination of HER2 inhibition and mTOR inhibition has synergistic effects in HER2-driven lung tumours. A randomised 2-stage phase II study compared neratinib, an irreversible pan-HER tyrosine kinase inhibitor, and neratinib plus temsirolimus. Patients with HER2-positive NSCLC were randomised between neratinib with or without temsirolimus. The primary endpoint was ORR. Secondary endpoints included clinical benefit rate, PFS and safety. In stage 1, 27 patients were enrolled. The ORR was 21% in the neratinib/temsirolimus arm versus 0% in the neratinib arm. A partial response was observed in 3 patients in the combined arm and none in the neratinib arm. Median PFS was 4.0 months in the combined arm and 2.9 months in the neratinib arm. Most common grade 3/4 adverse events were dyspnoea, diarrhoea, vomiting and nausea. As such, the neratinib/temsirolimus combination deserves further development in

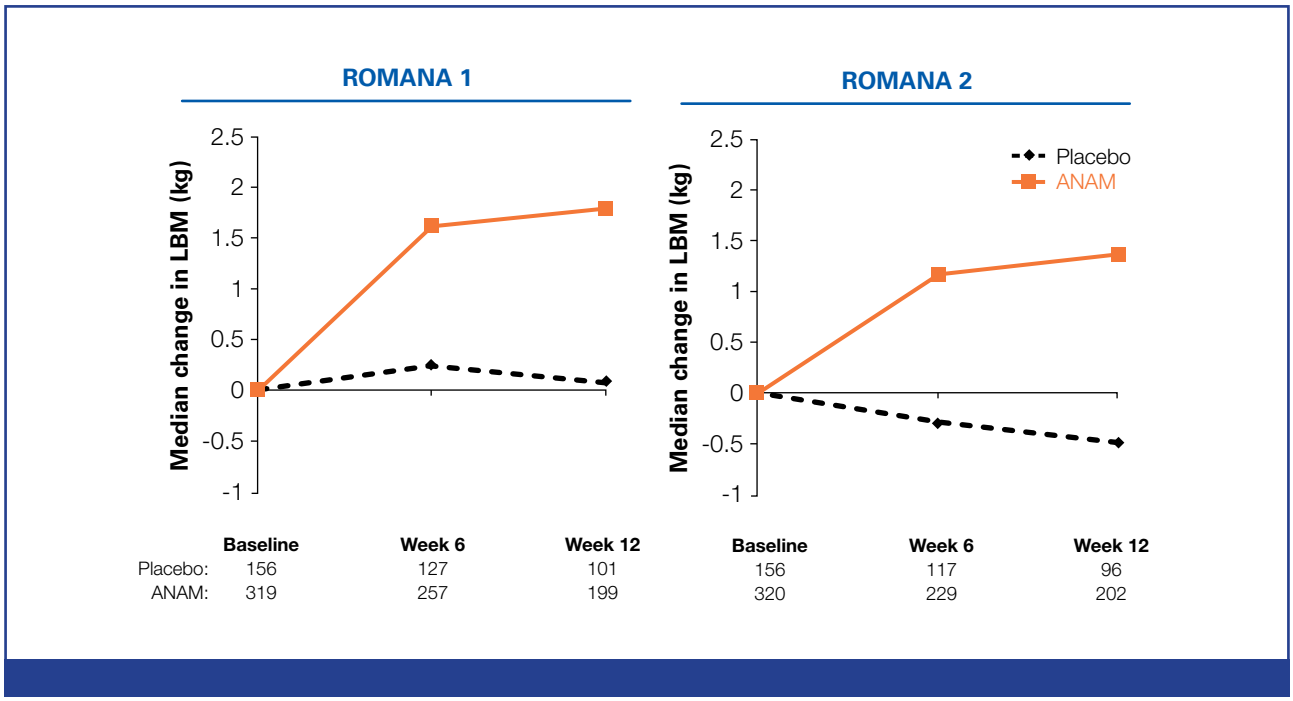

Figure 2. Anamorelin significantly increased lean body mass in ROMANA-1 and ROMANA-2.

HER2 mutated NSCLC.[7]

Promising new treatment options for patients with resistance to first generation ALK inhibitors

Crizotinib is approved for treatment in second-line metastatic ALK-EML translocation positive NSCLC. The phase III PROFILE 1014 evaluated if first-line treatment of crizotinib is better than standard treatment with a platinum-doublet in 343 patients. Treatment-naïve patients with an ALK-EML translocation were randomised between crizotinib and platinum/pemetrexed. The primary endpoint of PFS was 10.9 months for crizotinib and 7.0 months for chemotherapy (HR[95%CI]: 0.45[0.35-0.60]). Data are immature to evaluate the secondary endpoint of OS. Additional data showed a numerically reduced time to progression compared with chemotherapy (HR: 0.60) and in the 79 patients with brain metastases at baseline (HR: 0.45), both not statistically significant. In addition, the time to deterioration of symptoms was around four times longer in the crizotinib arm than in the chemotherapy arm (median 2.1 *vs.* 0.5 months, p = 0.0004). These findings support the use of crizotinib as first-line therapy in ALK-translocation positive NSCLC patients.[8]

One third of the patients with resistance to crizotinib remain ALK sensitive. A new drug is ceritinib, a second generation ALK inhibitor. In the ASCEND-1 trial, ceritinib showed activity in patients with brain metastases. Responses were prolonged and PFS was 6.9 months in patients with pre-treatment of another ALK inhibitor. Ceritinib is currently evaluated in phase III versus standard 1st and second line chemotherapy.[9]

The second-generation ALK inhibitor alectinib is a promising new treatment option for patients resistant to crizotinib. In a small pharmacological study in 24 patients with target lesions, alectinib led to a confirmed response rate of 58.3%. At a median follow-up of 141 days, 13 of 19 (68.4%) patients with brain metastases at baseline remained on study without disease progression. Gastrointestinal and visual side effects were reported with alectinib but were usually mild and manageable. None of the patients discontinued treatment due to safety concerns.[10]

Further studies are needed to define the optimal sequence of those different ALK inhibitors in the treatment of ALK-EML translocated NSCLC.

Personalised medicine: biomarkers as target for patient selection for chemotherapy?

Thymidylate synthase (TS) expression may be a useful biomarker in predicting which patients with advanced NSCLC benefit most from a treatment with cisplatin/pemetrexed. In 315 patients with advanced NSCLC, TS-negativity by immunohistochemistry was associated

with higher response rates, 38% *vs.* 21% and an improved PFS, 6.4 *vs.* 5.5 months in patients receiving pemetrexed/cisplatin compared with gemcitabine/cisplatin (p=0.013). Although there was no in-between-treatment difference in OS with regard to TS expression (not reached *vs.* 28.3 months), TS-negativity was an independent, favourable prognostic factor for OS (HR[95%CI]: 0.64[0.45-0.90]).[11] The biomarker folate receptor (FR) overexpression may be useful in therapy selection. In TARGET, a phase II trial of 199 patients whose NSCLC express the FR, the addition of the FR-targeted drug vintafolide to second-line docetaxel significantly improved OS compared to docetaxel alone in a subgroup of patients with adenocarcinoma (HR: 0.51; p= 0.0147). However, no benefit of vintafolide was seen when assessing the results of all patients.[12]

Routine use of hemithoracic radiotherapy after neoadjuvant chemotherapy and extrapleural pneumonectomy (EPP) in malignant pleural mesothelioma (MPM) not outside a clinical trial

The objectives of the SAKK17/04 trial was to evaluate the time to local-regional relapse of MPM with or without high dose hemithoracic radiotherapy in a prospective multicentre randomized phase II trial in patients with R0 and R1 resection after neoadjuvant chemotherapy and EPP. The trial had a phase II design in two parts. Part 1 included surgically resectable patients (T1-3 N0-2 M0) given neoadjuvant chemotherapy with 3 cycles of cisplatin/pemetrexed followed by restaging and EPP. The primary endpoint of part 1 was complete macroscopic resection (R0-1). Part 2 randomised the patients with complete macroscopic resection into two parallel arms (control arm A and radiotherapy arm B). The primary endpoint of part 2 was loco-regional relapse-free survival (RFS).

In total 153 patients entered the study and due to slow accrual the study was stopped early in 2013. Of 153 patients, 125 underwent surgery and 99 had complete macroscopic resection. In part 2 only 54 patients were randomized, 25 patients completed the planned radiotherapy. For part 1 the median RFS was 8.8 (95% CI: 7.3 – 10.7) and median OS was 15.0 months (95% CI: 12.1 – 19.3). For part 2 the median local RFS was 7.6 months for group A and 9.4 months for group B. The study did not reach the primary endpoint which was defined as one-year increase in loco-regional RFS and does not support the routine use of hemithoracic radiotherapy after neoadjuvant chemotherapy and EPP in MPM.[13]

Palliative care: anamorelin significantly improves lean body mass and weight in patients with cancer cachexia

Cachexia, a substantial loss of skeletal muscle and fat, is common in cancer patients particularly in advanced disease. Cachexia is thought to be responsible for 20% cancer death 20% of death. Anamorelin, a selective ghrelin receptor antagonist with appetite-enhancing and anabolic activity was evaluated in the randomised phase III ROMANA 1 and ROMANA 2 studies. Nearly 1,000 patients with NSCLC with a weight-loss of ≥ 5% within the prior 6 months or a BMI < 20 kg/m^2 were randomised 2:1 between anamorelin 100 mg or placebo, given daily orally for 12 weeks. Anamorelin significantly increased lean body mass, 1.5 kg difference between the median change from baseline for anamorelin and placebo, and body weight (p<0.0001, each) compared with placebo over 12 weeks (*Figure 2*). Significant improvements in patient symptoms and concerns of patients about anorexia – cachexia were reported. However, no improvement in the co-primary endpoint of handgrip strength in either study was noted. Side-effects related to anamorelin included hyperglycaemia and diabetes, but toxicity was usually mild.[14]

Adding ramucirumab to docetaxel improves clinical outcome without compromising the quality of life in patients with metastatic NSCLC

Previous results of the phase III REVEL study demonstrated that ramucirumab plus docetaxel significantly improves the OS and PFS in patients with locally advanced or metastatic NSCLC with progression after platinum based chemotherapy. During ESMO 2014 results of the quality of life analysis of the REVEL study were presented. The lung cancer symptom scale (LCSS) and the ECOG performance status (PS) data were collected at baseline, every cycle, and at 30-day follow up after which the LCSS total score and average symptom burden index (ASBI) were calculated.[15]

The mean baseline LCSS total score was 27.3 and 29.6 on ramucirumab plus docetaxel and placebo plus docetaxel, respectively. During treatment, the symptom burden appeared similar between treatment arms and at 30-day follow-up, the mean total LCSS score was 32.0 in the ramucirumab arm and 32.5 on placebo, which reflects a similar increase in symptom burden for both arms. Furthermore, the time to deterioration for all LCSS scores was similar between treatment arms. Stratified hazard ratios for the LCSS total score

and ASBI were 0.99 (p= 0.932) and 0.93 (p= 0.514) respectively.[15]

In summary, the addition of ramucirumab to docetaxel in the second line treatment of metastatic NSCLC improved the clinical outcomes in REVEL, while the primary QoL analyses suggests no detrimental effect on detriment in QoL.

Conclusion

Whether immunotherapy is a new treatment strategy in thoracic oncology remains debatable. Adjuvant treatment with the MAGE-A3 cancer immunotherapeutic did not improve the disease free survival in resected early stage NSCLC. Predicting improvement of the prognosis based on biomarkers, can select patients that benefit from certain chemotherapy. With respect to further personalised medicine, targeting rare driver mutations can improve survival in NSCLC.

Doublet chemotherapy remains the standard of care 2nd line treatment for patients with EGFR mutation positive NSCLC refractory to first-line first generation TKI. Promising new treatment options for patients with resistance to first generation ALK inhibitors are available. In palliative care: anamorelin significantly improves lean body mass and weight in patients with cancer cachexia. In MPM routine use of hemithoracic radiotherapy after neoadjuvant chemotherapy and EPP is not indicated outside a clinical trial.

References

1. Vansteenkiste JF, Cho B, Vanakesa T, De Pas T, Zielinksi M, Kim MS, et al. MAGRIT, a double-blind, randomized placebo-controlled phase III study to assess the efficacy of the recMAGE-A3 AS15 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small cell lung cancer (NSCLC). Ann Oncol 2014;25;suppl 4; abstract 1173O

2. Garon E, Gandhi L, Rizvi N, Hui R, Balmanoukian A, Patnaik A, et al. Antitumor activity of pembrolizumab and correlation with programmed death ligand 1 (PD-L1) expression in a pooled analysis of patients with advanced non-small cell lung carcinoma (NSCLC). Ann Oncol 2014;25;suppl 4;abstract LBA43

3. Engel-Riedel W, Schneller F, Wolf M, Schuette W, Lowe J, Mattson P, et al. Imprime PGG, a novel immune modulator, in the 1st-line treatment of stage IV NSCLC: results from a randomized, controlled, multicenter phase 2 study. Ann Oncol 2014;25;suppl 4;abstract LBA32.

4. Mok T, Wu Y, Nakagawa K, Kim S, Yang J, Ahn M, et al. Gefitinib/chemotherapy vs chemotherapy in epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC) after progression on first-line gefitinib: the phase III randomized IMPRESS study. Ann Oncol 2014;25;suppl 4;abstract LBA2_PR

5. Goss G, Felip E, Cobo M, Lu S, Syrigos KN, Lee KH, et al. A randomized, open-label, phase III trial of afatinib vs erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung following first-line platinum-based chemotherapy: LUX-Lung 8. Ann Oncol 2014;25;suppl 4;abstract 1222O.

6. Planchard D, Kim TM, Mazieres J, Quoix E, Riely G, Barlesi F, et al. Dabrafenib in patients with BRAF V600E-mutant advanced non-small cell lung cancer (NSCLC): a multicenter, open-label, phase II trial (BFR113928). Ann Oncol 2014m25;suppl 4;abstract LBA38_PR.

7. Besse B, Soria J, Yao B, Kris M, Chao B, Cortot A, et al. Neritinib with or without temsirolimus in patients with non-small cell lung cancer (NSCLC) carrying HER2 somatic mutations: an international randomized phase II study. Ann Oncol 2014;25;suppl 4;abstract LBA39_PR.

8. Solomon B, Felip E, Blackhall F, Mok T, Kim D, Wu Y, et al. Overall and intracranial efficacy results and time to symptom deterioration in PROFILE 1014: 1st-line crizotinib vs pemetrexed – platinum chemotherapy in patients with advanced ALK-positive non-squamous non-small cell lung cancer (NSCLC). Ann Oncol 2014;25;suppl 4;abstract 1225O.

9. Felip E, Kim D, Mehra R, Tan D, Chow L, Camidge D, et al. Efficacy and safety of ceritinib in patients with advanced anaplastic lymphoma kinase (ALK)-rearranged NSCLC: an update of ASCEND-1. Ann Oncol 2014;25;suppl 4;abstract1295P.

10. Seto T, Hida T, Nakagawa K, Satouchi M, Nishio M, Hotta K, et al. Anti-tumor activity of alectinib in crizotinib pre-treated ALK-rearranged NSCLC in JP28927 study. Ann Oncol 2014;25;suppl 4;abstract 1224O.

11. Ahn M, Sun J, Ahn J, Jung S, Park K. Cisplatin plus pemetrexed versus cisplatin plus gemcitabine according to thymidylate synthase expression in non-squamous NSCLC: a biomarker-stratified randomized phase II trial. Ann Oncol 2014;25;suppl 4;abstract LBA42_PR.

12. Hanna N, Juhász E, Cainap C, Gladkov O, Ramlau R, Juan-Vidal O, et al. TARGET: a randomized, phase II trial comparing vintafolide versus vintafolide plus docetaxel, versus docetaxel alone in second-line treatment of folate-receptor-positive NSCLC patients. Ann Oncol 2014;25;suppl 4;abstract LBA40_PR.

13. Stahel R, Riesterer O, Alexandros X, Opitz I, Beyeler M, Ochsenbein A, et al. Neoadjuvant chemotherapy and extrapleural pneumonectomy (EPP) of malignant pleural mesothelioma (MPM) with or without hemithoracic radiotherapy: final results of the randomized multicenter phase II trial SAKK17/04. Ann Oncol 2014;25;suppl 4;abstract LBA37_PR.

14. Temel J, Currow D, Fearon K, Gleich L, Yan Y, Friend J, et al. Anamorelin for the treatment of cancer anorexia-cachexia in NSCLC: results from the phase 3 studies ROMANA 1 and ROMANA 2. Ann Oncol 2014;25;suppl 4;abstract 1483O.

15. Garon E, Ciuleanu T, Arrieta O et al. Quality of life (QoL) results from the phase 3 REVEL study of ramucirumab + docetaxel (RAM + DTX) versus placebo + docetaxel (PL + DTX) in advanced/metastatic NSCLC patients (pts) with progression after platinum based chemotherapy. Ann Oncol 2014;25;suppl 4;abstract 1266PD.