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03/18

memo – inOncology SPECIAL ISSUE

Congress Report ESMO 2018

A GLOBAL CONGRESS DIGEST ON LUNG CANCER

Report from the European Society for Medical Oncology (ESMO) Congress, 19th–23rd October 2018, Munich, Germany

IMPRESSUM/PUBLISHER

Media owner and publisher: Springer-Verlag GmbH, Professional Media, Prinz-Eugen-Straße 8–10, 1040 Vienna, Austria, **Tel.:** +43(0)1/330 24 15-0, **Fax:** +43(0)1/330 24 26, **Internet:** www.springernature.com, www.SpringerMedizin.at. **Copyright:** © 2018 Springer-Verlag GmbH Austria. Springer Medizin is a Part of Springer Nature. **Managing Directors:** Joachim Krieger, Dr. Alois Sillaber, Dr. Heinrich Weinheimer. **Medical Writer:** Dr. Judith Moser. **Corporate Publishing:** Elise Haidenthaller. **Editorial Support:** Stefanie Wurm, PhD. **Layout:** Katharina Bruckner. **Published in:** Vienna. **Produced in:** Fulda. **Printer:** Druckerei Rindt GmbH & Co KG, Fulda, Germany; The editors of "memo, magazine of european medical oncology" assume no responsibility for this supplement.

Table of Contents

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Supported by Boehringer Ingelheim in the form of an unrestricted grant

Preface

Dear Colleagues,

The ESMO Congress represents the leading international oncology event in Europe. This year's conference that took place from 19th to 23rd October in Munich, Germany, was held under the tagline "Securing access to optimal cancer care". Approximately 25,000 participants including experts from various oncology disciplines, healthcare policy makers, and patient advocates convened from all over the world to discuss innovations and the major challenge of turning new insights into actual improvements in cancer patient care. Various obstacles of structural and financial nature still tend to impede this process in many countries, and joint efforts need to be put into the task of overcoming them.

This volume of memo inOncology summarises important new data presented at the ESMO Congress in the field of lung cancer treatment. Great progress has been made over the last years in terms of immunotherapeutic approaches as well as targeted therapies, and emerging trial findings underscore the refinement that is going on as treatments are being established in different settings and appropriate patient populations that will derive the greatest benefit from them. Notable outcome improvements can be achieved in the small but important group of patients whose tumours show *ALK* fusions; today, the armamentarium comprises a number of drugs such as alectinib whose activity has been demonstrated in both Asian patients and a global population, in separate trials. Brigatinib and ceritinib additionally give rise to long-lasting responses, but new compounds are already on the doorstep. In the *EGFR*-mutant field, there are a number of active agents, and the important question of sequencing these agents is addressed in this issue as trial evidence emerges and contributes to completing the picture. While thoracic oncologists can choose among agents from three generations, considerations are required concerning resistance mechanisms and their implications for subsequent treatment.

Finally, immunotherapy of lung cancer was of course a prominent topic at the ESMO Congress, with data demonstrating effects in the neoadjuvant and radical stage III settings as well as in the palliative situation. Besides the PD-L1 expression status, tumour mutational burden is gaining momentum as a new predictive marker for checkpoint inhibitor therapy and additional data were presented. Once more, the multitude of new and exciting data suggests that our journey towards controlling lung cancer continues at a marked pace.

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Checkpoint inhibition excels in all treatment lines

Neoadjuvant therapy: NEOSTAR

Patients with early and locally advanced (stage I-IIIA) non–small-cell lung cancer (NSCLC) usually undergo surgery, but long-term outcomes leave much to be desired. After surgery alone, the recurrence rate is substantial at more than 50 % [1]. Perioperative chemotherapy as a means to prevent disease recurrence only confers a 5 % improvement in 5-year survival compared to sole surgery [2, 3]. Based on these observations, anti-PD-1 therapy is being tested in the neoadjuvant setting with the goal of priming a specific anti-tumour response and eradicating micrometastases [4].

In the open-label, randomised, phase II NEOSTAR trial, 36 patients with stage I-IIIA NSCLC who were amenable to resection received either nivolumab monotherapy 3 mg/kg for 3 doses (Arm A) or nivolumab 3 mg/kg for 3 doses plus ipilimumab 1 mg/kg for 1 dose (Arm B) prior to surgery [5]. Major pathological response (MPR; i.e., ≤ 10 % viable tumour cells) in both arms was defined as the primary endpoint. MPR is used as a surrogate for survival after neoadjuvant therapy. It was assumed that induction nivolumab and/or nivolumab plus ipilimumab would produce an MPR rate of at least 40 %, which exceeds the rate achieved with induction platinum-based chemotherapy. The study was not powered for an MPR comparison across the treatment arms.

Biomarker findings confirm activity

Neoadjuvant therapy was completed by 89 % of patients, and 84 % underwent surgery. In the resected group, the MPR

TABLE
Radiographic responses to neoadjuvant treatment with nivolumab monotherapy and nivolumab plus ipilimumab

Evaluable*	n = 32*	Nivolumab n = 16	Nivolumab + ipilimumab n = 16
Complete responses, n (%)	1 (3)	0 (0)	1 (6)
Partial responses, n (%)	6 (19)	5 (31)	1 (6)
Disease stabilisation, n (%)	19 (59)	8 (50)	11 (69)
Disease progression, n (%)	6 (19)	3 (19)	3 (19)
Not yet evaluable, n (%)	4	2*	2**

* 1 pending, 1 on therapy, ** 2 on therapy

rate was 31 %. With nivolumab and nivolumab plus ipilimumab, 28 % and 33 % of patients, respectively, achieved MPR. Nineteen percent of the patients in the resected group showed no viable tumour cells in their specimens (14 % and 25 % with nivolumab alone and the combination, respectively). Objective radiographic responses occurred in 22 % (31 % and 12 %, respectively; **Table**). A positive association was observed between radiographic responses and MPR ($p < 0.002$). Overall, neoadjuvant treatment with nivolumab and nivolumab plus ipilimumab was well tolerated.

According to biomarker analyses, both regimens significantly increased the percentages of proliferative and activated effector tumour-infiltrating lymphocytes (TILs) compared to untreated lung tumours. Moreover, compared to uninvolved lungs, the treatment increased T-cell receptor diversity in the tumours ($p = 0.021$). The combination appeared to induce greater proliferation of different T cell subsets than nivolumab alone, although the differences were not significant for CD8-positive TILs and CD4-positive regulatory T cells. Nivolumab plus ipilimumab was also shown to increase T-cell receptor homology in tumours compared to the uninvolved adjacent lung tissue ($p = 0.048$).

In their conclusion, the authors noted that this study adds to the growing neoadjuvant monotherapy data set and expands the neoadjuvant experience with a combination strategy. Limitations result from the small sample size in each arm. Exploratory biomarker analyses are ongoing.

Post-hoc analyses of PACIFIC

The phase III PACIFIC trial has established durvalumab as a standard of care in patients with unresectable, stage III NSCLC who had not experienced progression after definitive chemoradiotherapy. They were randomised to receive either durvalumab 10 mg/kg every 2 weeks (Q2W) for up to 12 months (n = 476), or placebo (n = 237). Significant benefits have been observed with the active treatment for both progression-free survival (PFS; 16.8 vs. 5.6 months; HR, 0.52; $p < 0.001$) [6] and overall survival (OS; not reached vs. 28.7 months; HR, 0.68; $p = 0.0025$) [7]. PACIFIC has been designed to evaluate durvalumab in all-comers, with PD-L1 testing not being mandatory. The PD-L1 status was unknown for 37 % of patients. Based on this trial, durvalumab has been globally approved for an all-comers population, including in the US and Japan, with the exception of the European Union where approval is limited to patients whose tumour cells express PD-L1 ≥ 1 %.

A post-hoc analysis reported at the ESMO 2018 Congress investigated outcomes in PACIFIC based on PD-L1 expression on one hand and components of the preceding concurrent chemoradiation on the other [8]. The PD-L1 analyses demonstrated that in patients whose tumour cells showed a PD-L1 expression ≥ 1 %, durvalumab gave rise to benefits with regard to PFS (17.8 vs. 5.6 months; HR, 0.46; **Figure 1**) and OS (not reached vs. 29.1 months; HR, 0.53). In those with PD-L1 expression < 1 %, PFS improvement was noted (10.7 vs. 5.6 months; HR, 0.73), whereas the results for OS were confounded by the performance of the placebo arm. In this group, the trajectory of the survival curves favoured durvalumab during the first 12 months, which corresponds to the time when the patients were on treatment, whereas the placebo-treated patients fared better during the remaining follow-up (HR, 1.36). Factors that might explain the over-performance of the placebo arm include the small number of events and the limited size of the subgroup, as well as imbalances in the baseline characteristics. Importantly, similar safety profiles were observed irrespective of PD-L1 expression. According to the authors, definite conclusions on outcomes by PD-L1 status cannot be drawn due to the limitations around the post-hoc exploratory subgroup analyses.

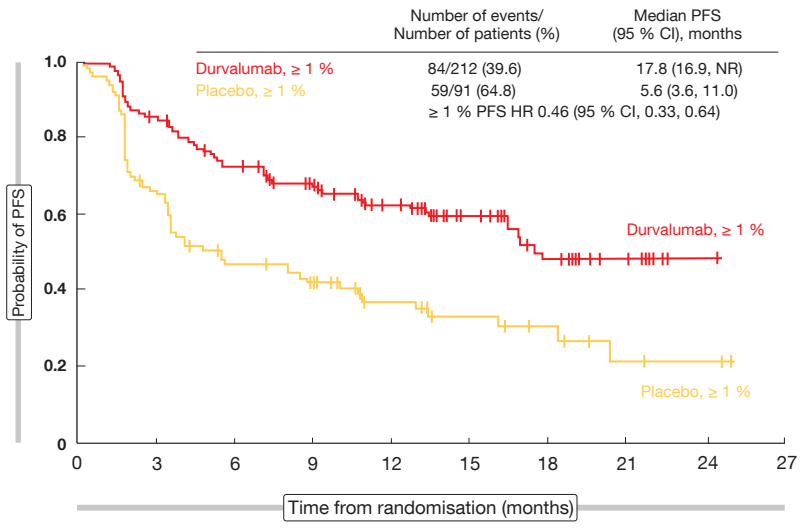

Figure 1: Improvement in progression-free survival in the PD-L1 ≥ 1 % expression group treated with durvalumab in the PACIFIC trial

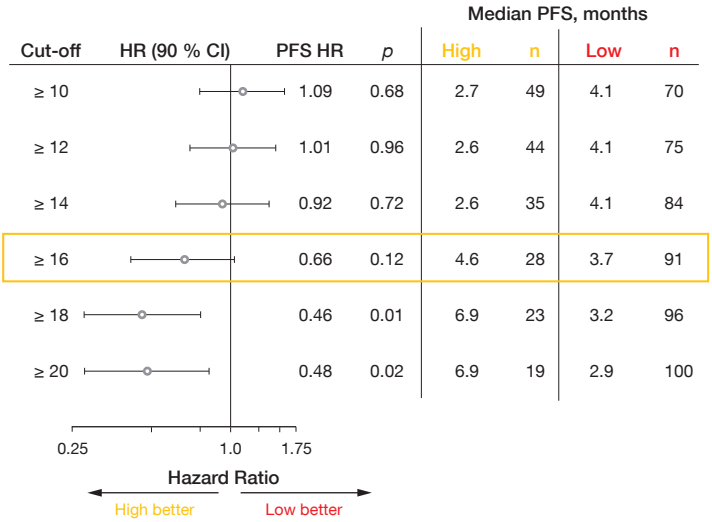

Figure 2: B-F1RST study: progression-free survival forest plot according to bTMB scores

Furthermore, analyses tested the impact of the preceding treatments with respect to both chemotherapy and radiation dose. These data revealed consistent benefits of durvalumab regarding both PFS and OS irrespective of the type of chemotherapy, radiation dose used or the time from the end of radiation to randomisation. Likewise, toxicity profiles were similar regardless of the time from radiation. Overall, these data support the PACIFIC regimen of durvalumab following chemoradiation as the new standard of care in unresectable, stage III NSCLC.

IMpower130: atezolizumab plus chemotherapy

First-line treatment of non-squamous stage IV NSCLC using atezolizumab as an add-on to chemotherapy was investigated in the randomised, open-label, phase III IMpower130 trial [9]. Carboplatin plus nab-paclitaxel constituted the chemotherapy backbone that was combined with atezolizumab in the experimental arm (n = 451) and administered alone in the control arm (n = 228). The findings support atezolizumab plus chemotherapy as a treatment option for advanced non-squamous NSCLC regardless of PD-L1 status. IMpower130 met its co-primary endpoints of PFS and OS in the intent-to treat wildtype population that comprised randomised patients excluding those with *EGFR* or *ALK* genomic alterations. The atezolizumab combination led to a 36 % reduction in the risk of progression and death (median PFS, 7.0 vs. 5.5 months; HR, 0.64; p < 0.0001). For mortality, this risk reduction amounted to 21 %, with a statistically significant and clinically relevant 4.7-month OS benefit (18.6 vs. 13.9 months; HR, 0.79 %; p = 0.033). PFS rates at 12 months were double with the atezolizumab-based treatment compared to the control arm (29.1 % vs. 14.1 %). Also, the analysis revealed a higher objective response rate (ORR) with the atezolizumab-based treatment (49.2 % vs. 31.9 %) and significantly prolonged median duration of response (8.4 vs. 6.1 months; p = 0.0004). At the time of the analysis, 36.8 % vs. 19.4 % of patients had ongoing responses.

Overall survival and PFS benefits occurred across all subgroups except for patients who had liver metastases at enrolment. Likewise, the addition of atezolizumab gave rise to PFS benefits across all PD-L1 cohorts (PD-L1–high, PD-L1–low, and PD-L1–negative). For OS, the results obtained in the PD-L1 subgroups favoured the experimental arm as well, although the differences between the treatment arms were not significant. The *EGFR*-/*ALK*-positive subgroup did not derive any statistically significant PFS or OS advantages. Atezolizumab plus chemotherapy had a safety profile consistent with the adverse events observed in the setting of single-agent therapy. The study yielded no new safety signals.

bTMB as a predictive marker

Tumour mutational burden (TMB) is an emerging predictive marker for checkpoint inhibitor therapy. However, adequate tumour tissue for TMB testing cannot always be obtained at diagnosis. Blood-based TMB (bTMB) therefore constitutes a non-invasive alternative that has recently been under evaluation. Kim et al. reported the primary efficacy results from the single-arm phase II B-F1RST study, which was the first prospective trial to test bTMB as a predictive biomarker for atezolizumab monotherapy in first-line NSCLC [10]. PD-L1–unselected patients with stage IIIB/IVA NSCLC of any histology (n = 152) received atezolizumab 1,200 mg Q3W until progression. The prespecified bTMB cut-off was defined at a score of 16. A total of 119 patients made up the biomarker-evaluable population (BEP), i.e. those with baseline evaluable blood samples showing adequate tumour content for testing. Ninety-one and 28 patients had low bTMB (< 16) and high bTMB (≥ 16), respectively.

Investigator-assessed ORR, which was the efficacy endpoint, added up to 10.1 % in the BEP, with patients in the high bTMB subgroup showing significantly improved response rate compared with those in the low bTMB group (28.6 % vs. 4.4 %; p = 0.0002). An exploratory analysis revealed improving responses with higher cut-offs. When the cut-off was set at ≥ 20, the difference between the two groups was even larger at 36.8 % vs. 5.0 % (p < 0.0001). Median duration of response had not been reached in patients with bTMB scores ≥ 16. Similarly, patients with high bTMB fared better than those with low bTMB concerning PFS, although not significantly so (4.6 vs. 3.7 months; HR, 0.66; p = 0.12). At 9 months, PFS rates were 37.4 % vs. 9.7 %. For OS, the data were not mature yet. When analysed by various bTMB cut-offs (≥ 10, ≥ 16, ≥ 20), both PFS and OS improved with increasing scores **(Figure 2)**. For both endpoints, the ≥ 16 prespecified score appeared to be an inflection point that clearly separated out efficacy. Atezolizumab was well tolerated. bTMB is currently being validated in a prospective, randomised phase III trial.

Long-term outcomes with pembrolizumab: KEYNOTE-010

The randomised, open-label, phase II/III KEYNOTE-010 study has shown superior OS activity of pembrolizumab

monotherapy at two doses compared to docetaxel in patients with previously treated, PD-L1–expressing advanced NSCLC [11]. At the ESMO 2018 Congress, Herbst et al. presented updated OS and safety results with 30 additional months of follow-up as well as outcomes for patients who completed 35 cycles or 2 years of pembrolizumab treatment [12].

According to this analysis, pembrolizumab continued to prolong OS compared to docetaxel. In the population with a PD-L1 tumour proportion score (TPS) ≥ 50 %, 35 % vs. 13 % of patients were alive at 36 months (median OS, 16.9 vs. 8.2 months; HR, 0.53; p < 0.00001). For those with TPS ≥ 1 %, the respective proportions were 23 % and 11 % (median OS, 11.8 vs. 8.4 months; HR, 0.69; p < 0.00001).

Seventy-nine patients completed 35 cycles or 2 years of treatment. In this group, 95 % had complete or partial responses according to independent central review. Responses were ongoing in 64 % at the time of the analysis. Median duration of response had not been reached yet; this also applied to median PFS and median OS. At 36 months, 98.7 % of patients were alive, and 70.3 % were both alive and progression-free. Twenty-five patients experienced disease progression after stopping 35 cycles or 2 years of treatment. Of these, 14 were able to start a second course of pembrolizumab therapy, with partial responses resulting in 43 %. Stable disease occurred in 36 %. The long-term safety profile of pembrolizumab treatment including in patients who completed 35 cycles or 2 years of treatment proved manageable. ■

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EGFR-mutant lung cancer: what's new with respect to activity and resistance?

Erlotinib as a neoadjuvant strategy

In patients with stage IIIA-N2 NSCLC, current multimodal treatment options include definitive chemoradiotherapy, surgery followed by adjuvant chemotherapy, or neoadjuvant treatment followed by surgical resection. The standard first-line EGFR tyrosine kinase inhibitor (TKI) erlotinib has already demonstrated feasibility in the neoadjuvant treatment setting of stage IIIA-N2 NSCLC [1]. Therefore, the open-label, randomised, phase II CTONG-1103 trial compared erlotinib with cisplatin-based chemotherapy as neoadjuvant/adjuvant treatment in patients with locally advanced, *EGFR*-mutant NSCLC [2]. The patients were randomised to either erlotinib 150 mg/d for 42 days (n = 37) or gemcitabine plus cisplatin three-weekly for 2 cycles (n = 35) prior to surgery. After the operation, patients in the experimental arm went on to receive erlotinib 150 mg/d for 12 months, while those in the control arm were treated with another 2 cycles of chemotherapy. ORR constituted the primary endpoint.

Neoadjuvant erlotinib indeed increased ORR, although not to a significant degree (54.1 % vs. 34.3 %; p = 0.092). The surgical outcomes favoured erlotinib numerically: a greater percentage of patients in the experimental group underwent surgery (83.8 % vs. 68.6 %; p = 0.129), and complete resections were more frequent in the erlotinib-treated arm (73.0 % vs. 62.9 %; p = 0.358), as was lymph node down-staging (10.8 % vs. 2.9 %; p = 0.185). Fifty surgically resected specimens were available. In both groups, no pathological complete responses occurred, but major pathological responses were obtained more often with erlotinib (10.7 % vs. 0 %). Erlotinib led to a significant improvement in PFS, which was defined as a secondary endpoint (21.5 vs. 11.9 months; HR, 0.42; p = 0.003; **Figure 1**). OS data had not yet reached maturity at the time of the analysis. Postoperative complications were balanced across the two groups, and adverse events associated with neoadjuvant/adjuvant therapy corresponded to those reported previously. As the authors concluded, the regimen warrants further exploration in the neoadjuvant setting.

First-line gefitinib combined with chemotherapy

Single-agent EGFR TKI treatment has become a standard first-line strategy in

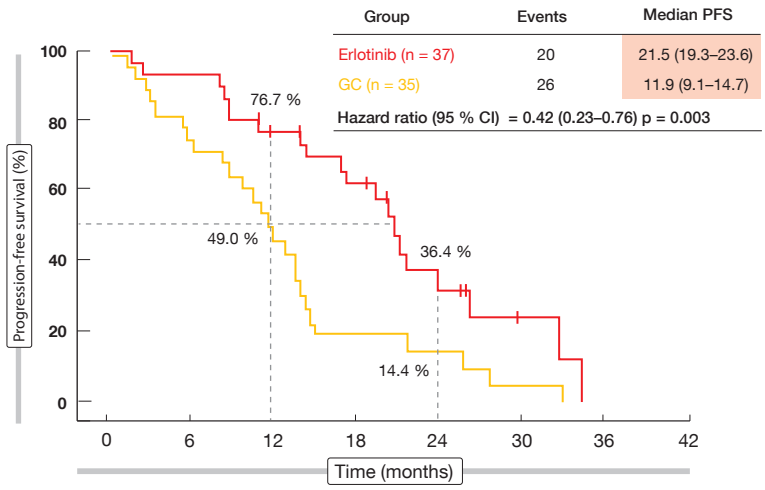

Figure 1: Erlotinib *versus* chemotherapy in the neoadjuvant setting: progression-free survival advantage observed with the EGFR TKI therapy

patients with advanced *EGFR*-mutant NSCLC, but it was hypothesised that adding chemotherapy might improve outcomes further. The phase III NEJ009 trial tested the combination of carboplatin plus pemetrexed with gefitinib compared to gefitinib alone in a total of 342 patients with previously untreated, stage IIIB/IV, non-squamous, *EGFR*-mutant NSCLC [3]. In the experimental arm, gefitinib plus chemotherapy was administered for 4 to 6 cycles, followed by maintenance with gefitinib plus pemetrexed until progression. Patients in the control arm received gefitinib continuously; when they progressed, the protocol recommended switching to a platinum-based regimen.

Compared with gefitinib monotherapy, the combination gave rise to significantly superior PFS (20.9 vs. 11.2 months; HR, 0.490; p < 0.001). No significant difference was seen for PFS2, which was defined as the comparison of the time to second progression in the control arm with the time to first progression in the experimental arm. Nevertheless, the combination also provided significantly prolonged OS (50.9 vs. 38.8 months; HR; 0.72; p = 0.02). ORR was higher with the combination (84.0 % vs. 68.0 %). The assessment of the clinical status at the first and second disease progression indicated that the patient performance status was better in the combination arm than in the monotherapy arm when the planned regimen failed.

Not surprisingly, haematological toxicities occurred more commonly in the combination arm, although few patients discontinued treatment due to toxicities in both arms (11.2 % vs. 9.4 %). A quality-of-life analysis suggested no difference across the two groups in the course of the study. The investigators stated that gefitinib combined with carboplatin and pemetrexed is an effective option for first-line treatment of patients with advanced *EGFR*-mutant NSCLC.

Final analysis of LUX-Lung 8: afatinib in squamous NSCLC

Based on the open-label, phase III LUX-Lung 8 trial, afatinib has been approved for the treatment of patients with stage IIIB/IV lung cancer of squamous histology who have progressed on or after platinum-based chemotherapy. The primary analysis of LUX-Lung 8 that compared afatinib with erlotinib showed significant improvements in the experimental arm with regard to PFS (2.6 vs. 1.9 months; HR, 0.81; p = 0.0103) and disease control rate (50.5 % vs. 39.5 %; p = 0.002) [4]. PFS and OS benefits appeared even greater for patients with ErbB-mutation–positive tumours compared to ErbB wild-type tumours [5].

The final analysis of the LUX-Lung 8 trial that was presented at the ESMO 2018 Congress confirmed these results [6]. Updated OS was significantly longer with afatinib than with erlotinib (7.8 vs. 6.8 months; HR, 0.84; p = 0.0193). Twenty-one patients in the experimental arm had long-term disease control (≥ 12 months' treatment). In this group, certain genetic aberrations, particularly in the ErbB family, were more common than in the overall afatinib-treated population. These patients were on treatment for a median of 19.0 months; their median PFS and OS amounted to 12.9 and 27.5 months, respectively. Partial responses were achieved in 29 %.

Long-term treatment was well tolerated, with a predictable tolerability profile that was manageable with supportive care and tolerability-guided dose reductions. According to the conclusion of the authors, these data position afatinib as a treatment option for patients with squamous-cell carcinoma of the lung progressing on chemotherapy, particularly those with ErbB family genetic aberrations.

GIDEON & NEJ027

Brueckl et al. reported the first interim analysis of GIDEON, a prospective non-interventional study that was conducted in Germany to investigate the activity and tolerability of first-line afatinib in routine clinical care [7]. Among 151 treated patients, the majority (72.8 %) started treatment at an afatinib dose of ≥ 40 mg; 61.8 % of these had dose reductions. In the group of patients starting at < 40 mg, 46.2 % had dose reductions, while dose increases were performed in 33.3 %. The safety profile of afatinib was consistent with the known safety profile identified by the clinical trials.

In spite of relatively high proportions of patients with brain metastases (approximately 30 %) and uncommon *EGFR* mutations (approximately 13 %), the results corroborated the clinical data for afatinib in the routine setting. Median PFS was 12.9 months, with a 12-month PFS rate of 54.6 %. Seventy-three percent of patients responded, and 90 % obtained disease control. Both ORRs and disease control rates (DCR) were independent of the type of *EGFR* mutation, the presence of baseline brain metastases, and starting dose **(Figure 2)**. Afatinib proved efficacious in the elderly population that is underrepresented in clinical trials. Patients aged < 75 years and ≥ 75 benefited equally from the treatment with regard to median PFS (12.2 and 14.2 months, respectively). The preliminary OS analysis revealed an overall median OS of over 33 months. Final results of the

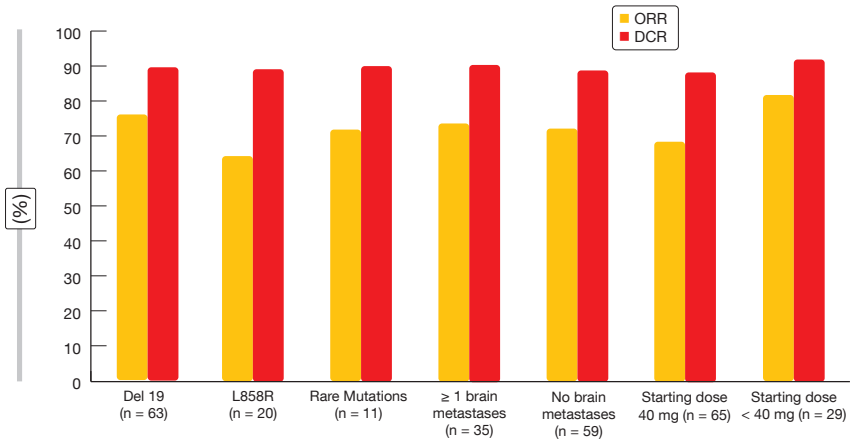

Figure 2: Overall response rates and disease control rates obtained with first-line afatinib in the non-interventional GIDEON study

GIDEON trial are expected for 2019.

Likewise, the open-label, single-arm, phase II NEJ027 study established the efficacy and safety of afatinib in elderly patients (≥ 75 years) with *EGFR*-mutant advanced NSCLC (n = 37) [8]. ORR and DCR were 75.7 % and 89.2 %, respectively. Median PFS was 14.3 months, with 64.3 % of patients showing freedom from progression at 1 year. OS follow-up is ongoing; the 1-year survival rate amounted to 83.6 %. Dose reductions and temporary withdrawal became necessary in 78.9 % and 73.7 %, respectively. Overall, the patients were treated for 368.0 days at a mean daily dose of 28.4 mg.

Osimertinib: resistance data from FLAURA …

The third-generation, CNS-active EGFR TKI osimertinib has shown superior efficacy compared with gefitinib and erlotinib as first-line treatment in patients with advanced *EGFR*-mutated NSCLC in the phase III FLAURA study [9]. Published data concerning the mechanisms of acquired resistance to first-line osimertinib are limited to date. However, increased understanding is essential here to inform future therapeutic development. At the ESMO 2018 Congress, Ramalingam et al. presented candidate mechanisms of acquired resistance to first-line osimertinib detected in plasma samples from patients who progressed or discontinued treatment during FLAURA [10]. The analysis focussed on genomic alterations detectable in circulating tumour DNA (ctDNA). Non-genetic mechanisms of resistance, including SCLC transformation and protein expression changes, were not captured. Also, amplification events might be underrepresented in plasma analyses.

Paired plasma samples obtained at baseline and at the time of progression or discontinuation were analysed used next-generation sequencing (NGS). Among 272 patients with paired NGS data, 129 and 91 who were treated with the comparator EGFR TKIs and osimertinib, respectively, had *EGFR* mutations in their baseline plasma samples and therefore were included in the analysis. This showed that the most common acquired resistance mechanism in the comparator-treated group was, as expected, the *EGFR* T790M mutation (47 %). Furthermore, *MET* amplification (4 %), and *HER2* amplification (4 %) were present. *PIK3CA* mutations occurred in 3 %. Two percent of patients developed *RET* fusion gene abnormalities.

With osimertinib treatment, no patient showed evidence of T790M-mediated acquired resistance. The most common mechanisms included *MET* amplification (15 %) and *EGFR* C797S mutation (7 %). Three percent of patients developed other secondary *EGFR* mutations, such as L718Q. *PIK3CA* mutations occurred in 7 %, *HER2* amplification in 2 %, *HER2* mutation in 1 %, and *BRAF* and *KRAS* mutations in 3 % each. Various alterations in the cell-cycle–related genes were observed in a total of 10 %. Approximately 14 % of the patients had concurrent candidate resistance mutations, which indicates that more than one pathway is involved in the development of resistance.

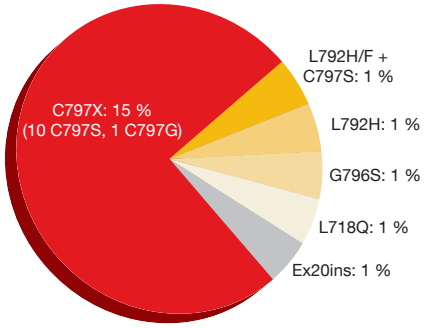

Figure 3: Acquired *EGFR* mutations after osimertinib treatment in AURA3

Overall, these results did not suggest new mechanisms of osimertinib resistance in the first-line treatment setting that give rise to aggressive disease biology. However, tissue-based testing is required to understand the full spectrum of resistance aberrations. Ongoing research will therefore address tissue analysis for mechanisms of resistance to first-line osimertinib.

… and AURA3

Similar data on acquired resistance mechanisms in osimertinib-treated patients have been obtained from the randomised AURA3 trial [11]. AURA3 established the superiority of osimertinib over chemotherapy in T790M-positive advanced NSCLC following progression on first-line EGFR TKI therapy [12]. The plasma ctDNA genomic profile was investigated in patients who progressed on osimertinib treatment during the AURA3 trial, with a focus on acquired mutations. As for the FLAURA analysis, paired plasma samples from baseline and the time of progression/discontinuation were collected and assessed using NGS. Seventy-three and 24 patients in the osimertinib and chemotherapy arms, respectively, were included. Again, the analysis did not capture non-genetic mechanisms of resistance, and most likely it did not fully reflect amplification events.

Loss of the T790M resistance mutation had occurred in 49 % of samples at the time of progression/discontinuation, which was consistent with previous studies [13-15]. It has been observed that the elimination of T790M-harbouring clones frequently co-occurs with the emergence of other competing resistance mechanisms. Acquired *EGFR* mutations, most commonly the C797S mutation, were

TABLE
Best overall response to nazartinib treatment per blinded independent review committee in patients with and without brain metastases

	Brain metastases absent (n = 27) n (%)	Brain metastases present (n = 18) n (%)
Complete response (CR)	1 (3.7)	0
Partial response (PR)	16 (59.3)	12 (66.7)
Stable disease (SD)	6 (22.2)	6 (33.3)
Progressive disease (PD)	2 (7.4)	0
Non-CR/Non-PD	1 (3.7)	0
Unknown	1 (3.7)	0
ORR (CR + PR), n (%) (95 % CI)	17 (63.0) (42.40, 80.60)	12 (66.7) (41.00, 86.70)
DCR (CR + PR + SD + Non-CR/Non-PD), n (%) (95 % CI)	24 (88.9) (70.80, 97.60)	18 (100) (81.50, 100)

seen in 21 % of patients **(Figure 3)**. All of the patients with acquired *EGFR* mutations retained T790M. *MET* amplification was found in approximately 19 % and co-occurred with *EGFR* C797S mutation (7 %) as well as *EGFR* G796S mutation and *HER2* amplification (1 %). Both T790M loss and preservation prevailed in *MET*-amplified samples. Cell cycle gene alterations emerged in 12 %. *HER2* amplifications were identified in 5 % of patients, oncogenic fusions in 3 %, and *BRAF*V600E mutations in 3 %. The analysis yielded more than one resistance-related alteration in 19 % of patients.

Progression-free survival was assessed preliminarily according to the candidate resistance mechanisms. However, due to the heterogeneity of these, the numbers for each event were small. Loss of T790M showed a correlation with slightly shorter median PFS (5.54 months) compared to preservation of T790M (7.06 months).

The authors noted in their conclusion that the overlap of targetable alterations has clinical implications when determining subsequent treatments. Research into the novel mechanisms of resistance to osimertinib and appropriate therapeutic strategies is ongoing. For instance, a prospective single-arm phase II study will assess the combination of afatinib and bevacizumab in patients after osimertinib failure [16]. It is hypothesised that this regimen might overcome resistance mechanism implicated in osimertinib failure, including uncommon *EGFR* mutations and *MET* amplification.

First-line nazartinib: phase II results

Like osimertinib, nazartinib is an oral third-generation EGFR TKI that selectively targets activating *EGFR* mutations as well as resistant mutants such as T790M while sparing wild-type *EGFR*. A phase I/II, multicentre study conducted in patients with advanced *EGFR*-mutant NSCLC who had received ≤ 3 prior lines of systemic therapy established 150 mg once daily as the recommended phase II dose [17]. Preliminary results of the phase II part of the study in treatment-naïve patients showed promising efficacy despite a high proportion of patients with brain metastases at baseline [18]. At the ESMO 2018 Congress, Tan et al. reported the primary efficacy and safety findings obtained with nazartinib

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150 mg daily as first-line therapy until progression in 45 patients with *EGFR*-mutant, locally advanced or metastatic NSCLC [19]. Treated and stable brain metastases were allowed.

The confirmed ORR by blinded independent review was 64.4 % including one confirmed complete response and 28 confirmed partial responses. Disease control resulted in 93.3 %. Most of the patients experienced reductions in the size of their target lesions. PFS and duration of response data were still immature at the time of data cut-off.

Moreover, nazartinib showed activity in patients with CNS lesions at baseline. Confirmed ORRs were 66.7 % and 63 % in those with and without brain metastases, respectively, and DCRs were 100 % and 88.9 %, respectively **(Table)**. Among 18 patients with baseline brain lesions, absence or normalisation of lesions was observed in 52.9 % of those with brain non-target lesions. Patients with brain target lesions obtained a 38.5 % decrease in size from baseline. Only two patients experienced cerebral progression with new CNS metastases. Nazartinib showed a tolerable safety profile. ■

Interview: Maximilian Hochmair, MD, Respiratory Oncology Unit, Department of Respiratory and Critical Care Medicine, Otto Wagner Spital, Vienna, Austria

Several reasons support sequencing of EGFR TKI treatment

The first-line EGFR TKI choice in patients with *EGFR*-mutated NSCLC has been under debate ever since the results of the FLAURA were reported. From the current point of view, what are the limitations of this study?

The FLAURA trial has demonstrated a survival benefit of first-line osimertinib compared to gefitinib and erlotinib [1], but the fact that afatinib was not included in the control arm diminishes the insights that can be obtained based on this trial. Also, it cannot answer the question of sequencing, as T790M mutation testing was not mandatory in patients progressing on erlotinib or gefitinib, and osimertinib was not provided as a subsequent treatment. Only approximately 25 % of patients received osimertinib. We will therefore not be able to draw any conclusions here.

In Austria, afatinib is generally prescribed in the first-line setting in patients with *EGFR*-mutant NSCLC. A particular survival benefit has been demonstrated in patients with deletion 19 in the LUX Lung 3 and 6 studies [2]. We also know that afatinib doses can be reduced without loss of efficacy. On the other hand, if first-line osimertinib is used, resistance frequently poses a problem. Druggable targets are much rarer after failure of osimertinib than after failure of afatinib [3, 4]. In 60 %, no driver mutations are found at all. After the emergence of resistance to osimertinib, chemotherapy is the only option in most of the patients.

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What would be the ideal sequence in a patient with *EGFR*-mutant NSCLC?

There are several reasons that support the sequence of afatinib followed by osimertinib. One is the prevalence of the resistance mutation T790M at the time of progression on first- or second-generation EGFR TKIs, which is as high as 60 % to 75 %. There is no question about the benefit of osimertinib in patients who have developed the T790M mutation. Another reason is the favourable long-term outcomes. At my centre, afatinib followed by osimertinib is routinely used, and we have seen many patients who derived great benefits. Patients generally tend to remain on afatinib and osimertinib treatment for extended periods of time.

Data presented at the ESMO Congress also emphasise the significance of afatinib as an effective first-line drug. A retrospective study showed that afatinib followed by osimertinib in any line provides significantly improved response rates and disease control rates compared to first-generation EGFR TKIs followed by osimertinib [5]. This is in keeping with a Japanese real-world analysis of 1,354 patients who were treated with either gefitinib, erlotinib, or afatinib [6]. The investigators noted a trend towards longer OS for afatinib compared to first-generation EGFR TKIs even after adjustment by propensity score.

What can be expected from the sequence in terms of treatment duration?

A retrospective analysis of the LUX-Lung 3, 6 and 7 studies showed that in patients who received osimertinib after afatinib, median time on osimertinib in any treatment line was 20.2 months [7]. According to a soon-to-be-published analysis conducted at our institution, 67 patients received afatinib and osimertinib for 12 months each, and half of them were still on osimertinib treatment at the time of the analysis. The global GioTag trial that was recently published assessed the time on treatment with first-

line afatinib followed by osimertinib in a real-world setting [8]. Data were only collected in patients who had started osimertinib 10 months prior to data entry. Overall, 204 patients from ten countries received the sequence, and in 48 %, the treatment is still ongoing. The results were very encouraging. In the entire population, median time on treatment with the sequence was 27.6 months. Time to treatment failure was 11.9 months with first-line afatinib and 14.3 months with second-line osimertinib. This confirms our observations in smaller patient cohorts. At 24 and 30 months, 79 % and 69 % of patients, respectively, were alive. Time on treatment with the sequence was longer in patients with deletion 19 than in those with L858R mutation (30.3 vs. 19.1 months). Also, good baseline performance status, i.e., ECOG PS 0/1, was associated with longer treatment duration of 31.3 months compared to 22.2 months in patients with ECOG PS ≥ 2. Cerebral control was achieved with frontline afatinib and with the introduction of osimertinib upon progression.

How do you rate the CNS activity of afatinib compared to the CNS effects of osimertinib?

Brain metastases can be treated very well with both afatinib and osimertinib. Actually the majority of data on the effects of EGFR TKIs in patients with CNS lesions have been obtained for these two drugs. Afatinib enters the cerebrospinal fluid and accumulates in relevant concentrations [9]. At our institution, we observed complete and long-lasting cerebral remissions with afatinib treatment in a number of patients [10]. Afatinib also appears to have protective effects against CNS metastases, as patients without brain lesions have been shown to develop mainly non-CNS progression on treatment [11]. ■

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Potent treatment options in *ALK*- and *MET*-positive disease

ALESIA: confirming findings obtained in ALEX

The highly selective, CNS-active ALK inhibitor alectinib has demonstrated superiority over crizotinib in the first-line setting of *ALK*-positive NSCLC both in the global phase III ALEX study [1] and the phase III J-ALEX trial, which was conducted in Japanese patients [2]. Alectinib has been approved in the US and Europe and has recently received priority approval in China. At the ESMO 2018 Congress, Zhou et al. reported the primary results from the phase III ALESIA study that evaluated first-line alectinib compared to crizotinib in Asian patients with advanced *ALK*-positive NSCLC using the globally approved alectinib dose [3]. The primary objective of the study was the proof of consistency with the PFS benefit of alectinib observed in the ALEX trial. Consistency was defined as maintaining ≥ 50 % of the risk reduction observed in ALEX, where PFS amounted to 34.8 months for alectinib *versus* 10.9 months for crizotinib (HR, 0.43) [1]. A total of 187 patients were randomised at 21 sites in China, South Korea, and Thailand. In the experimental arm, 125 patients received alectinib 600 mg twice daily, while 62 patients in the control arm were treated with crizotinib 250 mg twice daily. PFS as determined by the investigators constituted the primary endpoint.

ALESIA did meet its primary outcome, thus further confirming alectinib as a standard of care in the first-line treatment of *ALK*-positive NSCLC. PFS was significantly improved compared to crizotinib according to the investigators (not reached vs. 11.1 months; HR, 0.22; $p < 0.0001$; **Figure 1**). This was also true for PFS according to independent review committee (not reached vs. 10.7 months; HR, 0.37; $p < 0.0001$), which

was defined as a secondary endpoint. All of the subgroups favoured alectinib treatment. Additional benefits were noted for ORR (91.2 % vs. 77.4 %) and duration of response (not reached vs. 9.3 months; HR, 0.22; p < 0.0001). Intracranial response rates obtained with alectinib exceeded those with crizotinib in both patients with measurable baseline CNS lesions (94.1 % vs. 28.6 %) and those with both measurable and non-measurable brain metastases (72.7 % vs. 21.7 %). According to a competing risk analysis, CNS progression without prior non-CNS progression or death was significantly lower with alectinib than with crizotinib (7.3 % vs. 35.5 %; cause-specific HR, 0.14; p < 0.0001). OS data were still immature. The safety results in this Asian population generally matched the known safety profile of alectinib.

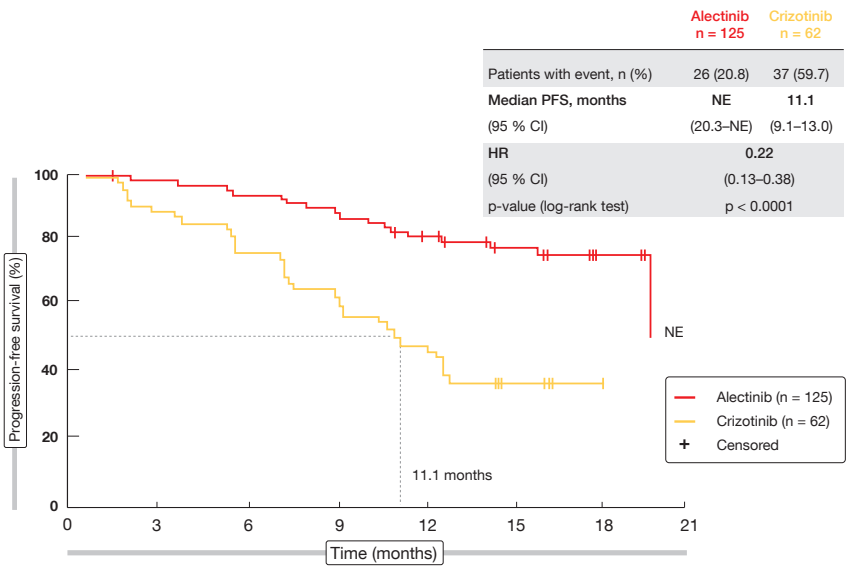

Figure 1: Primary endpoint of the ALESIA trial: progression-free survival according to investigator

Intracranial effects of brigatinib

Another option that has shown convincing results in ALK-inhibitor–naïve patients is the next-generation ALK/ROS1 inhibitor brigatinib. Compared to crizotinib, brigatinib gave rise to superior PFS in the open-label, randomised, phase III ALTA-1L study at the first planned interim analysis (HR, 0.49; p = 0.0007) [4]. Detailed intracranial efficacy data from this analysis were reported at the ESMO Congress [5]. At baseline, one third of patients in both treatment arms showed CNS lesions.

In patients with baseline brain metastases, whole-body PFS HR was 0.20 and therefore one of the lowest HRs noted among subgroups analysed. For those without CNS lesions, the PFS HR did not reach significance presumably due to short follow-up, which might preferentially emphasise CNS progression among patients with brain lesions as an earlier differentiating event. Brigatinib significantly improved confirmed intracranial ORR in both patients with measurable brain metastases at baseline (78 % vs. 29 %; OR, 10.42; p = 0.0028) and those with any brain metastases at baseline (67 % vs. 17 %; OR, 13.00; p < 0.0001). Intracranial PFS was significantly longer with brigatinib than with crizotinib in the intent-to-treat (ITT) population (HR, 0.42; p = 0.0006) and the group with baseline brain metastases (HR, 0.27; p < 0.0001). In those without brain metastases at baseline, intracranial PFS was immature.

An exploratory competing risk analysis was performed to estimate the cumulative incidence for CNS progression, systemic progression, and death by treatment group in the ITT population. This analysis revealed that the treatment with brigatinib significantly delayed both time to CNS progression (without prior systemic progression) and time to systemic progression (without prior CNS progression) compared with crizotinib.

Final results from ASCEND-3

In similar vein, the final efficacy and safety analysis of the single-arm, multicentre phase II ASCEND-3 trial confirmed the positive benefit-risk profile of the next-generation ALK inhibitor ceritinib in *ALK*-positive NSCLC [6]. ASCEND-3 has already demonstrated clinically relevant ORR (67.6 %) and PFS (16.6 months) results with ceritinib 750 mg/day in 124 ALK-naïve patients who had received ≤ 3 prior lines of chemotherapy and had progressed dur-

TABLE
Whole-body response to ceritinib according to investigator in the full analysis set of the ASCEND-3 trial (n = 124)

ORR, n (%) (95 % CI)	84 (67.7) (58.8, 75.9)
Best overall response, n (%)	
- Complete response (CR)	2 (1.6)
- Partial response (PR)	82 (66.1)
- Stable disease (SD)	27 (21.8)
- Progressive disease (PD)	5 (4.0)
- Non-CR/non-PD*	1 (0.8)
- Unknown	7 (5.6)
DCR, n (%) (95 % CI)	112 (90.3) (83.7, 94.9)
Median duration of response, months (95 % CI)	M† = 84 24.0 (14.8, 37.5)
Median PFS, months (95 % CI)	16.6 (11.0, 23.2)
Median time to first response (range), months	M† = 84 1.8 (1.6-18.4)

* Non-CR/non-PD refers to best overall responses that are neither CR nor PR per RECIST 1.1 criteria for patients with non-measurable disease only at baseline
† Total number of patients with confirmed complete or partial response

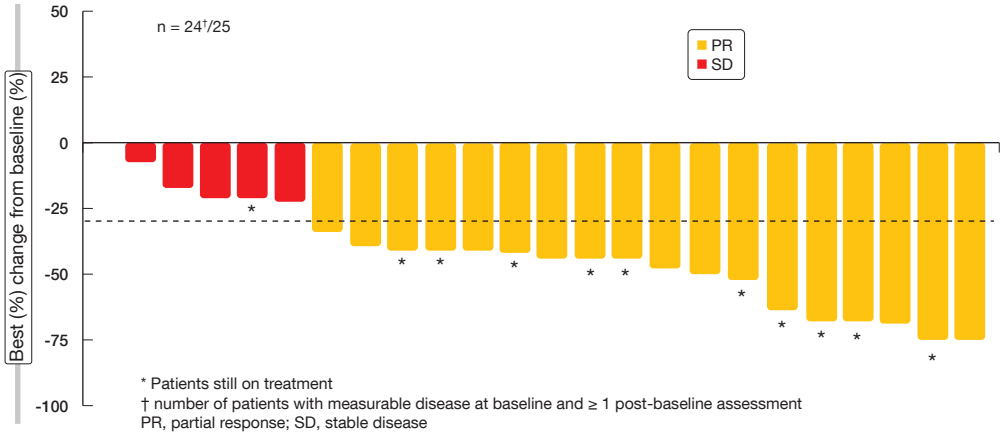

Figure 2: Tumour responses to capmatinib in the treatment-naïve cohort by blinded independent review committee

ing or after the last chemotherapy regimen [7]. Asymptomatic or neurologically stable brain metastases at baseline were permitted. In total, 49 patients (39.5 %) presented with CNS lesions at study entry.

After a median follow-up of 52.1 months, ORR according to investigator, which constituted the primary endpoint, was 67.7 % **(Table)**. Disease control occurred in 90.3 %. Responses lasted for a median of 24.0 months. The presence of brain metastases did not affect outcomes; for patients with and without brain lesions, disease control rate was 87.8 % and 92.0 %, respectively. In the overall group, median PFS and OS amounted to 16.6 and 51.3 months, respectively.

The authors summarised that ceritinib gave rise to a clinically relevant prolonged OS outcome in a heavily pretreated population, as 55 % of patients had received ≥ 2 prior antineoplastic regimens. At 18 months, 65.5 % and 78.4 % of patients with and without brain metastases, respectively, were alive. No new safety signals occurred, and the safety profile was consistent with the known data. The study included an analysis of patient-reported outcomes, according to which qualify of life was generally maintained during ceritinib treatment.

Intake of ceritinib: fed or fasted?

Ceritinib was initially approved at the recommended dose of 750 mg/day fasted for the treatment of *ALK*-positive NSCLC in the first line or after crizotinib failure. The randomised, open-label phase I ASCEND-8 trial tested ceritinib at three different doses, with 450 mg/day and 600 mg/day administered together with a low-fat meal and 750 mg/day administered under fasted conditions. After this study had yielded similar steady-state exposure and a more favourable gastrointestinal safety profile in the 450 mg fed arm compared to the 750 mg fasted arm, the recommended starting dose of ceritinib was changed to 450 mg/day with food in the US, European Union, and other countries worldwide [8]. Cho et al. presented the primary efficacy findings in treatment-naïve patients and the updated safety in the overall population treated with ceritinib 450 mg (n = 108) or 600 mg (n = 87) with food compared to 750 mg fasted (n = 111) [9].

The results confirmed that ceritinib 450 mg with food shows similar pharmacokinetics, efficacy and a more favourable gastrointestinal safety profile than 750 mg fasted. ORRs with 450 mg fed, 600 mg fed and 750 mg fasted were 78.1 %, 72.5 %, and 75.7 %, respectively. Median PFS was not estimable, 17.0 months, and 12.2 months, respectively. During the on-treatment period, the 450 mg arm showed the highest median relative dose intensity and the lowest proportion of patients with dose reductions among the three treatment arms. Fewer patients treated with 450 mg experienced gastrointestinal toxicities of all grades when compared to the 750 mg arm.

GEOMETRY: capmatinib

METexon-14 skipping mutations represent a novel oncogenic driver and occur in 3 % to 4 % of NSCLC cases [10-12]. They have been recognised as a poor prognostic factor in advanced disease [13]. Preliminary data indicated poor response to standard therapies including immunotherapy, even in the setting of pronounced PD-L1 expression and mutation load [14, 15]. The orally available, highly selective, reversible MET inhibitor capmatinib (INC280) has been shown to be the most potent inhibitor of *METΔexon-14* [16]. Capmatinib also crosses the blood-brain-barrier, and preliminary brain activity has been reported [17, 18].

The phase II GEOMETRY mono-1 trial investigated capmatinib 400 mg twice daily in patients with stage IIIB/IV NSCLC with *MET*-amplification and/or *METΔexon-14* mutation [19]. These aberration subtypes were analysed separately, which also applied to pre-treatment status (i. e., treatment-naïve patients; pre-treated patients after one or two lines). Patients with neurologically stable or asymptomatic brain metastases were allowed to enter the trial.

In the *METΔexon-14* mutation population, Cohorts 4 (n = 69) and 5b (n = 28) consisted of pre-treated and treatment-naïve patients, respectively. At the ESMO 2018 Congress, Wolf et al. reported the results obtained in these two cohorts that are fully enrolled and closed [19]. ORR by blinded independent review committee (BIRC) constituted the primary endpoint. Each cohort was analysed separately.

Impressive activity in treatment-naïve patients

For the pre-treated Cohort 4, ORR according to BIRC was 39.1 %, with disease control occurring 78.3 %. In the treatment-naïve patients from Cohort

5b, these were 72.0 % and 96.0 %, respectively. This suggests almost complete tumour control conferred by capmatinib in the first-line setting. Median duration of response could not be reported for both cohorts, as this outcome was not mature yet. Particularly in the treatment-naïve cohort, most of the patients showed deep responses **(Figure 2)**. Preliminary activity in the brain was demonstrated as exemplified by the case of 80-year-old patient who had multiple untreated CNS metastases at study entry. The patient achieved complete resolution of the brain lesions at the first post-baseline CT scan. She responded for 11.3 months and finally discontinued capmatinib treatment due to extra-cranial progressive disease.

The most common side effects of capmatinib treatment included peripheral oedema, nausea, increases in blood creatinine levels, diarrhoea, decreased appetite, and fatigue. Increases in creatinine levels do not suggest impaired renal function, but rather reduced function of the serum creatinine transporter. Overall, 10.3 % of patients discontinued treatment due to toxicity suspected to be related to capmatinib.

In their conclusion, the investigators pointed out that capmatinib has demonstrated a clinically meaningful response rate and manageable toxicity profile in patients with *METΔexon-14*–mutated, advanced NSCLC regardless of the line of therapy. The differential benefit observed between patients treated in the first line on one hand and the second or third line on the other highlight the need of early diagnosis and prompt targeted treatment.

Tepotinib plus gefitinib in *MET-/EGFR*-positive NSCLC

Dual MET and EGFR inhibition is thought to have therapeutic potential in patients with EGFR-TKI–resistant NSCLC [20]. The orally available, highly selective MET TKI tepotinib was shown to be able to overcome acquired resistance to EGFR TKIs due to aberrant *MET* activation in preclinical models [21]. At the ESMO 2018 Congress, randomised phase II data were presented from a phase Ib/II trial of tepotinib plus gefitinib in patients with relapsed *EGFR*-mutant, *MET*-positive NSCLC [22]. The open-label, single-arm, phase Ib dose escalation part had established tepotinib 500 mg/day in combination with gefitinib 250 mg/day as the recommended phase II dose [23]. In the phase II part, Asian patients with *EGFR*-positive, T790M-negative, locally advanced or metastatic NSCLC that showed *MET* overexpression (MET2+ or 3+ by immunohistochemistry) and/or *MET* amplification by in-situ hybridisation received either tepotinib 500 mg/day plus gefitinib 250 mg/day or pemetrexed plus cisplatin and carboplatin. Resistance to prior EGFR TKI treatment was an inclusion criterion. The patients had not received any prior HGF/MET-pathway–directed therapy. Overall, 55 patients were identified 31 of whom received the experimental treatment. Enrolment was halted early due to low recruitment.

Progression-free survival according to the investigators did not differ between the two treatment arms (4.9 vs. 4.4 months with tepotinib plus gefitinib and chemotherapy, respectively; HR, 0.71). However, in the group of patients with high *MET* expression (IHC3+), PFS was almost double in the experimental arm (8.3 vs. 4.4 months; HR, 0.35). The greatest difference occurred in the cohort showing *MET* amplification, as PFS was 21.2 vs. 4.2 months here (HR, 0.17). Also, there was considerable benefit with respect to ORR in patients with high *MET* expression (68.4 % vs. 33.3 %) and *MET* amplification (66.7 % vs. 42.9 %). In the overall cohort, 45.2 % vs. 33.3 % of patients responded. Treatment with the combination of tepotinib and gefitinib was generally well tolerated, with most AEs showing mild or moderate intensity. ■

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Dr. Sanjay Popat talks about modern chemotherapeutic treatment options for patients with squamous NSCLC, the benefits of combining immunotherapies with chemotherapy and the use of liquid biopsy for metastatic NSCLC in clinical practice today.

Dr. Luis Paz-Ares explains new principles of treatment using bifunctional fusion proteins, their advantages compared to the existing therapies and preliminary results in NSCLC patients.

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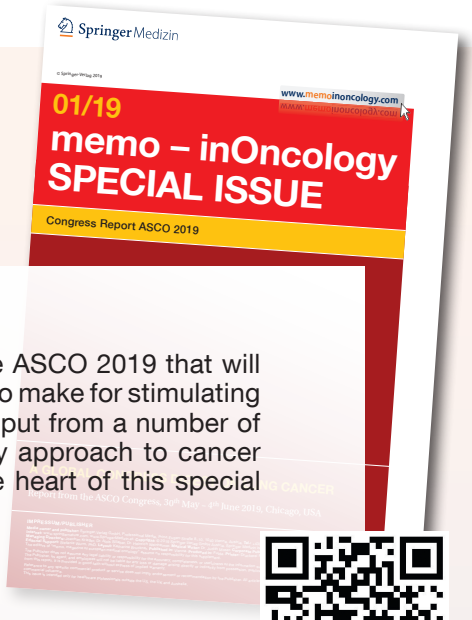

Forthcoming Special Issue

This special issue will be offering a synopsis from the ASCO 2019 that will be held in Chicago, in June 2019. The report promises to make for stimulating reading, as the ASCO Congress itself draws on the input from a number of partner organizations, representing a multidisciplinary approach to cancer treatment and care. Again, lung cancer will be at the heart of this special issue.

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