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Preface

Dear Colleagues,

As physicians and researchers, we are fortunate to be part of the dramatic innovation in cancer research and treatment brought about by precision medicine. Although the success of precision medicine may seem like an overnight success, it has actually been a thoughtful, strategic approach based upon decades of hard, disciplined work by dedicated scientists from around the world. In lung cancer, this has resulted in identifying oncogenes that can effectively be treated with targeted therapies, as well as the rise of immunotherapy, which is now playing a pivotal role in the treatment of many patients, within the last 10 to 15 years. The cumulative effect of these efforts has been transformative. Today, nearly half of all patients presenting with advanced lung cancer can receive initial treatment with oral targeted agents or immunotherapy, rather than chemotherapy. I am optimistic that a subset of our lung cancer patients might actually be cured with checkpoint inhibitor therapy. It has been the holy grail of oncology to develop potentially curative treatments for advanced common solid tumours, and this may now be on our doorstep, at least for some of our patients.

Of course, this issue of memo inOncology summarising results in the field of lung cancer care that were presented at the 2018 ASCO Congress focuses to a considerable extent on immunotherapeutic approaches. Combination treatment is currently being explored on a large scale to improve patient outcomes, which also applies to small-cell lung cancer. Another important field of research is determinants of the treatment success obtained with immunotherapy. Nonetheless, targeted therapy continues to play an essential role, which was reflected by the plethora of data presented at the conference. Some of these findings are outlined in the articles on EGFR- and ALK-directed treatment presented in this issue.

However, expanding the reach of precision medicine still requires ongoing effort. It is important to note that precision medicine aims at improving the lives of our patients, not only in terms of survival, but also with regard to their quality of life. As researchers, we are constantly exposed to response rates and survival curves, but the ultimate test should be whether these

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agents make our patients feel better while living longer. At this pivotal time in cancer research and cancer care, we need to extensively characterise our patients' tumours, treat them with our most effective agents, and support a robust research infrastructure to improve the efficacy of drugs.

Bruce E. Johnson, MD
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PD-(L)1 inhibition alone and in combination: recent insights into immunotherapy

First-line, single-agent pembrolizumab: KEYNOTE-042

Monotherapy with the anti-PD-1 monoclonal antibody pembrolizumab has significantly improved clinical endpoints compared to chemotherapy in patients with metastatic non–small-cell lung cancer (NSCLC) [1, 2]. KEYNOTE-024 showed overall survival (OS) improvement in addition to a progression-free survival (PFS) benefit; moreover, patients treated with pembrolizumab had a better safety profile than those receiving chemotherapy [2].

As there is an unmet need with regard to more effective and tolerable first-line regimens for metastatic NSCLC, KEYNOTE-042 investigated the role of pembrolizumab in patients with previously untreated, locally advanced or metastatic lung tumours of any histology that expressed PD-L1 (tumour proportion score [TPS] ≥ 1 %) but showed no sensitising *EGFR* or *ALK* alterations [3]. They received either pembrolizumab 200 mg every 3 weeks (Q3W) for up to 35 cycles or one of two platinum-based chemotherapy regimens for up to 6 cycles: carboplatin AUC 5 or 6 Q3W plus paclitaxel 200 mg/m^2 Q3W or carboplatin AUC 5 or 6 Q3W plus pemetrexed 500 mg/m^2 Q3W. There was no protocol-defined crossover.

Each arm contained 637 patients of whom almost 40 % had squamous histology. PD-L1 TPS was ≥ 50 % in nearly 50 % of cases, while approximately one third had TPS 1 % to 19 %. PD-L1 ex-

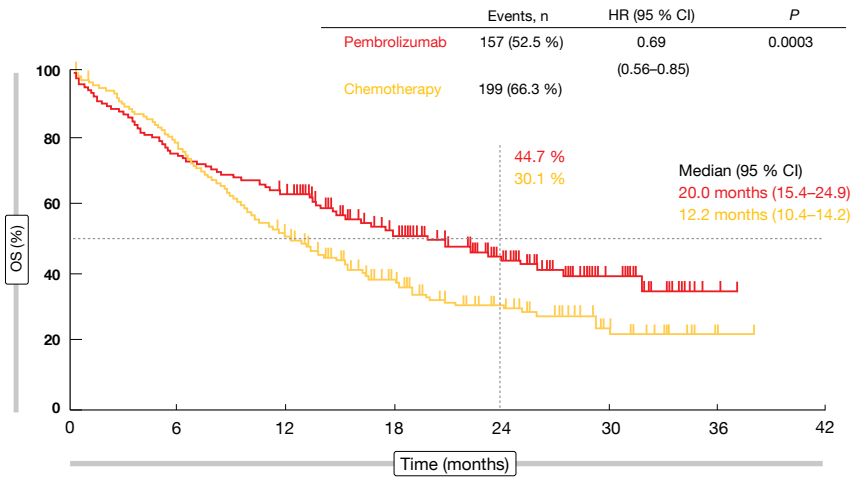

Figure 1: Overall survival obtained with pembrolizumab vs. chemotherapy in the TPS ≥ 50 % cohort of KEYNOTE-042

pression of 20 % to 49 % was present in approximately 17 % in each group. OS in the PD-L1 TPS subgroups of ≥ 50 %, ≥ 20 %, and ≥ 1 % constituted the primary endpoint.

Benefits related to PD-L1 expression

KEYNOTE-042 is the first study with a primary endpoint of OS to demonstrate superiority of pembrolizumab over platinum-based chemotherapy in the population described above. In all of the predefined TPS groups, the administration of pembrolizumab significantly improved survival. As for previous trials in metastatic NSCLC, the analysis yielded a greater magnitude of pembrolizumab-related benefits at higher levels of PD-L1 expression. The HRs for OS were 0.69, 0.77 and 0.81 for PD-L1 TPS ≥ 50 %, ≥ 20 %, and ≥ 1. In the TPS ≥ 50 % group, median OS was 20.0 vs. 12.2 months with pembrolizumab and chemotherapy, respectively (p = 0.0003; **Figure 1**). At 24 months, 44.7 % vs. 30.1 % of patients, respectively, were alive. For PFS, the difference did not meet the protocol-specified significance boundary. This outcome will be re-assessed based on additional follow-up, as the study is continuing.

Response rates did not differ to a meaningful extent between the pembrolizumab and chemotherapy arms (TPS ≥ 50 %, 39.5 % vs. 32.0 %; TPS 1 % to 49 %, 16.6 % vs. 21.7 %), although duration of response (DOR) was longer in the pembrolizumab-treated arm (20.2 vs. 8.3 months). This was true for all levels of PD-L1 expression.

Despite longer treatment exposure, treatment-related adverse events (AEs) occurred less frequently with immunotherapy than with chemotherapy. The superior safety profile suggests that pembrolizumab is an appropriate treatment option for any level of PD-L1 positivity. Overall, these data confirm and potentially extend the role of pembrolizumab monotherapy as a standard first-line treatment for patients with PD-L1–expressing tumours.

Assessment of pembrolizumab in squamous tumours

As add-on pembrolizumab significantly improved OS over chemotherapy alone in non-squamous NSCLC [4], evaluation in squamous tumours was a logical next step. The KEYNOTE-407 trial tested pembrolizumab 200 mg Q3W plus carboplatin AUC 6 Q3W and paclitaxel 200 mg/m² Q3W or nab-paclitaxel 100 mg/m² Q1W for 4 cycles compared to placebo plus the same chemotherapy regimen in untreated patients with stage IV NSCLC and squamous histology. After completion of this treatment, either pembrolizumab or placebo maintenance was administered for up to 31 cycles. The data of 278 and 281 patients who received pembrolizumab plus chemotherapy or placebo plus chemotherapy, respectively, were included in the second interim analysis, which was the first analysis of PFS and OS [5]. In both arms, approximately 35 % of patients showed a PD-L1 TPS of < 1 %, and in 37 %, TPS was 1 % to 49 %. Higher PD-L1 expression (≥ 50 %) was recorded in only 26 % of cases in each treatment arm.

The addition of pembrolizumab significantly improved OS over chemotherapy alone (15.9 vs. 11.3 months; HR, 0.64; p = 0.0008). Survival benefits occurred irrespective of PD-L1 expression, with similar HRs of approximately 60 % across all of the TPS categories. Consistently, patients receiving the checkpoint inhibitor therapy fared better with respect to PFS (6.4 vs. 4.8 months in the ITT population; HR, 0.56; p < 0.0001), objective response rates (ORR; 57.9 % vs. 38.4 %), and DOR (7.7 vs. 4.8 months). For PFS, the magnitude of benefit correlated with PD-L1 expression, with patients in the TPS ≥ 50 % group showing the highest risk reduction of 63 %.

The incidence and severity of AEs were similar in the two treatment groups, although immune-related AEs occurred more frequently in the experimental arm, which also applied to treatment discontinuations. Frequency and severity of immune-mediated AEs matched the known profile for pembrolizumab monotherapy. The authors concluded that these data suggest that pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel should become a new standard of care for first-line treatment of metastatic squamous NSCLC independent of PD-L1 expression.

Atezolizumab-based treatment for squamous NSCLC: IMpower 131

In analogy to KEYNOTE-407, the IMpower 131 trial evaluated the PD-L1 inhibitor atezolizumab plus chemotherapy compared to chemotherapy alone for 4 or 6 cycles in chemotherapy-naïve patients with stage IV NSCLC of squamous histology and any PD-L1 status. Arm A received atezolizumab together with carboplatin plus paclitaxel, while Arm B used a slightly different chemotherapy regimen (carboplatin plus nab-paclitaxel) in addition to atezolizumab. Patients randomised to Arm C (i.e., the control arm) were treated with carboplatin plus nab-paclitaxel. Maintenance therapy in the experimental arms consisted of atezolizumab, whereas Arm C received best supportive care. Each arm contained approximately 340 patients. The results presented at the ASCO Con-

gress related exclusively to comparisons across Arms B and C [6].

Investigator-assessed PFS in the ITT population was in favour of the atezolizumab-based combination (6.3 vs. 5.6 months; HR, 0.71; p = 0.0001). At 12 months, the PFS rate in the experimental arm was twice as high as the one in the control arm (24.7 % vs. 12.0 %). All of the pre-defined subgroups fared better with the addition of atezolizumab. This included the PD-L1 expression cohorts, even though the PFS benefit was enriched in those with higher expression (**Figure 2**). Similarly, responses were more pronounced in Arm B, particularly in the group expressing PD-L1 to the highest degree (ORR, 60 % vs. 33 %). DOR was longer in all of the PD-L1 subgroups, with the largest difference resulting in the PD-L1 high group (18.7 vs. 5.3 months). Most of the atezolizumab-treated patients in this cohort had ongoing responses at the time of evaluation.

The first interim OS analysis showed no difference between the two arms (14.0 vs. 13.9 months for Arms B and C, respectively). When analysed according to PD-L1 expression status, there was an OS advantage for the atezolizumab-based treatment in patients with high expression, while those with low expression fared better with the chemotherapy-only regimen. Possible causes for this are being investigated. Patients without PD-L1 expression experienced no difference between the two treatments. The safety analysis demonstrated that atezolizumab plus chemotherapy has a manageable safety profile. No new safety signals were identified.

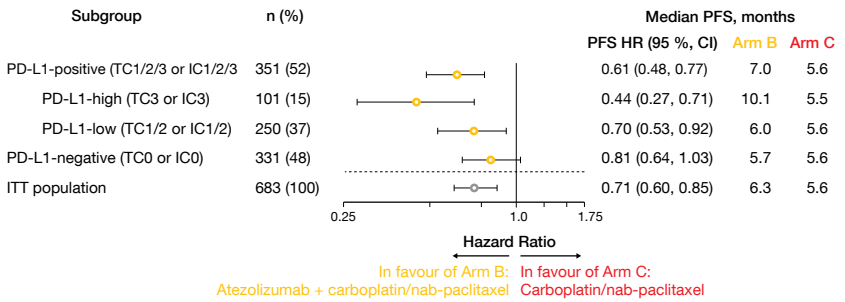

Figure 2: IMpower131: investigator-assessed progression-free survival in pre-defined PD-L1 expression subgroups

OS continues to be followed, with the next interim analysis anticipated later in 2018.

VEGF inhibition plus anti-PD-L1 activity

Immune checkpoint inhibition, chemotherapy and anti-angiogenesis are hypothesised to exert synergistic effects. For instance, the T-cell–mediated cancer cell killing brought about by atezolizumab might be enhanced by the VEGF inhibitor bevacizumab that exerts immunomodulatory effects [7].

The IMpower150 study therefore compared atezolizumab plus carboplatin and paclitaxel (Arm A) with a regimen consisting of atezolizumab, chemotherapy and bevacizumab (Arm B), and chemotherapy plus bevacizumab (control arm, Arm C). Each of the treatments was administered for 4 or 6 cycles. Maintenance therapy included atezolizumab (Arm A), atezolizumab plus bevacizumab (Arm B), or bevacizumab (Arm C). Four hundred chemotherapy-naïve patients with stage IV or recurrent metastatic non-squamous NSCLC of any PD-L1 status participated in each arm. Out of all randomised patients (ITT population), 87 % had no *EGFR* or *ALK* aberrations (ITT-WT population). Various co-primary and secondary endpoints have been defined. In 2017, the IMpower150 trial was reported as positive with respect to PFS outcomes across Arms B vs. C [8], and in March 2018, another analysis relating to OS showed positive results [9].

A new treatment standard in certain subgroups

The updated PFS analysis in the ITT-WT population presented at the ASCO 2018 Congress revealed median results of 8.3 vs. 6.8 months for Arms B vs. C (HR, 0.59; p < 0.0001) [10]. At 12 months, PFS rates were 38 % vs. 20 %, and at 18 months, 27 % vs. 8 %. Likewise, the regimen featuring atezolizumab in addition to chemotherapy and bevacizumab gave rise to a significant and clinically meaningful survival benefit in the ITT-WT population, with a risk reduction of 22 % (median OS, 19.2 vs. 14.7 months; HR, 0.78; p = 0.0164). OS rates at 24 months were 43 % vs. 34 %.

Analyses of key subgroups demonstrated that the survival benefit occurred across all of the PD-L1 expression cohorts (**Figure 3**). Moreover, the addition of bevacizumab prolonged OS in patients with liver metastases and in all key subgroups regarding *EGFR*/*ALK* aberrations. For the OS comparison between Arm A (atezolizumab plus chemotherapy) and Arm C, a trend favouring Arm A was observed (19.4 vs. 14.7 months; HR, 0.88). This outcome will be tested again at the time of the final analysis. Further comparisons between

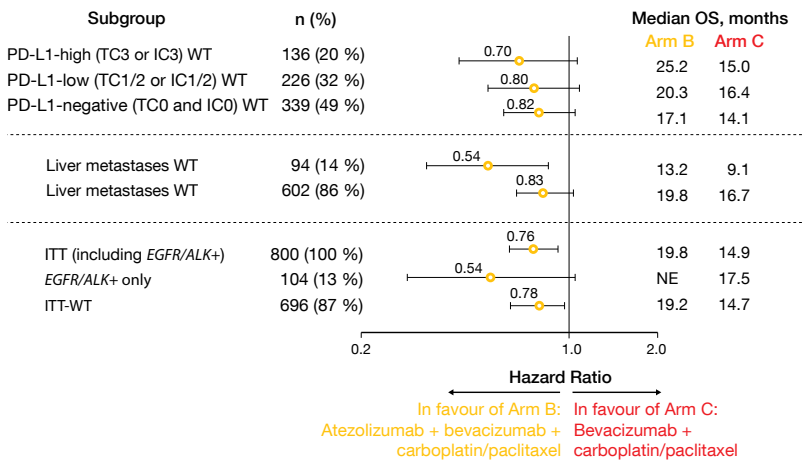

Figure 3: Comparison of overall survival results in key subgroups of IMpower150 across Arms B and C: consistent advantage due to the addition of atezolizumab

Arms A and C in the ITT-WT population did not show any significant survival benefits in the presence of liver metastases or *EGFR*/*ALK* positivity. These results appear to be due to the interplay between the anti-VEGF treatment and the anti-PD-L1 therapy.

For ORR, Arm B outperformed the other two arms, with the highest response rate of 69 % occurring in the cohort of patients showing high PD-L1 expression. According to the authors, the data generated by the IMpower150 trial demonstrate that the combination of atezolizumab plus bevacizumab and chemotherapy provides a new standard of care, particularly for key populations studied in this trial.

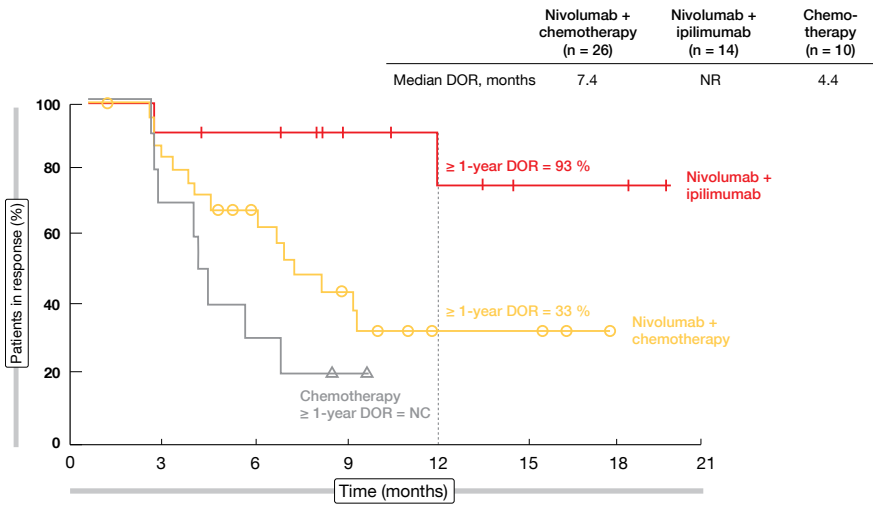

Figure 4: Duration of response with nivolumab plus ipilimumab, nivolumab plus chemotherapy, and chemotherapy only in patients with PD-L1 expression < 1 % and high TMB

CheckMate 227: nivolumab in PD-L1–negative patients

The large, randomised, phase III, multipart CheckMate 227 trial compared first-line nivolumab-based therapy to chemotherapy in advanced NSCLC. The co-primary endpoint was met, with nivolumab plus ipilimumab prolonging PFS in patients showing a high tumour mutational burden (TMB) of ≥ 10 mutations per megabase (mut/Mb) [11]. In patients with PD-L1 expression of < 1 %, two studies recently demonstrated that the addition of anti-PD-(L)1 therapy to chemotherapy improves outcomes compared to chemotherapy alone, with HRs for PFS of 0.75 and 0.77 [4, 12].

Therefore, an analysis of the CheckMate 227 trial presented at the ASCO Congress 2018 focused on comparing nivolumab 360 mg Q3W plus histology-based chemotherapy (n = 177) with histology-based chemotherapy alone (n = 186) in the PD-L1–negative cohort (PD-L1 expression < 1 %) [13]. Patients with both squamous and non-squamous tumours were included.

TMB as a predictor

Indeed, the PFS gain observed in the total population was consistent with the aforementioned studies (median PFS, 5.6 vs. 4.7 months for nivolumab plus chemotherapy vs. chemotherapy; HR, 0.74). At 1 year, PFS rates were 26 % and 14 %, respectively. Also, the addition of the PD-1 inhibitor led to an improvement in ORR (36.7 % vs. 23.1 %), even though responses did not appear to be more durable, with 28 % vs. 24 % of patients experiencing treatment effects beyond 1 year. The subgroup analyses suggested that the combination was particularly beneficial in patients with non-squamous histology and in those with high TMB (≥ 10 mut/Mb).

For patients with high TMB, 1-year PFS rates were 27 % vs. 8 % for nivolumab plus chemotherapy and chemotherapy, respectively (HR, 0.56). However, when juxtaposed in an exploratory analysis, the PFS obtained with the double checkpoint inhibitor regimen of nivolumab plus ipilimumab in CheckMate 227 outperformed these results (1-year PFS rate, 45 %; HR, 0.48 vs. chemotherapy). Importantly, responses in patients receiving both immune checkpoint inhibitors proved extremely durable, as median DOR had not been reached at the time of the analysis. DOR rates beyond 1 year were 93 % and 33 % for nivolumab plus ipilimumab and nivolumab plus chemotherapy, respectively (**Figure 4**). In patients with low TMB, on the other hand, the addition of any immunotherapy (i.e., nivolumab alone or nivolumab plus ipilimumab) did not correlate with a PFS benefit.

In their conclusions, the authors noted that TMB testing might be clinically relevant for patient selection in the PD-L1–negative group, as the PFS benefit resulting from the addition of nivolumab was enhanced in the setting of high TMB. At the same time, patients with low TMB did not appear to benefit from nivolumab in combination with either chemotherapy or ipilimumab.

Early and sustained PRO improvements

Reck et al. presented the initial patient-reported outcomes (PROs) in patients with TMB ≥ 10 mut/Mb treated with nivolumab plus ipilimumab versus chemotherapy in CheckMate 227 [14]. PROs were assessed as an exploratory endpoint using lung-cancer–specific and generic instruments including the Average Symptom Burden Index (ASBI), Lung Cancer Symptom Scale (LCSS), minimally important difference (MID), and visual analog scale (VAS). Moreover, the safety profile of the checkpoint inhibitor combination was characterised further to inform clinical practice.

The analysis showed that patients treated with nivolumab plus ipilimumab experienced rapid, durable, and clinically meaningful improvements in symptoms and overall health status. According to LCSS ASBI, these patients, while on treatment, had a longer time to deterioration in disease-related symptoms than those receiving chemotherapy (not reached vs. 6.3 months, HR, 0.43). The proportion of patients with a clinically meaningful deterioration in disease-related symptoms on or off treatment by week 12 was lower with the checkpoint inhibitor combination than with chemotherapy (22.3 % vs. 35.0 % by LCSS ASBI). Symptoms improved with nivolumab plus ip-

ilimumab within the first 12 weeks, and the decrease in symptom burden from baseline exceeded the MID for most of the on-treatment period. With chemotherapy, on the other hand, symptoms remained similar to baseline on average. The patients' overall health status as per EQ-5D VAS improved with the immunotherapy regimen within the first 12 weeks and was maintained over the on-treatment period. In contrast, patients receiving chemotherapy did not experience any improvement of health status within the first 12 weeks but only after completion of 4 cycles of chemotherapy.

Toxicities observed with nivolumab plus low-dose ipilimumab across three studies (CheckMate 227, CheckMate 012, CheckMate 568; n = 941) were consistent and manageable. Treatment-related AEs gave rise to low discontinuation rates. Among patients with treatment-related select AEs, the majority of events resolved, with a median time to resolution of < 10 weeks.

NICOLAS: safety of checkpoint inhibition plus chemo-RT

The feasibility of combined chemo-radiotherapy (chemo-RT) and concurrent PD-1 inhibition is of high scientific interest. As concurrent immune checkpoint inhibition and radical thoracic radiotherapy (RT) had never been assessed in a clinical trial, the single-arm, phase II NICOLAS study was the first one to evaluate the safety of the addition of nivolumab to first-line chemo-RT in patients with unresectable, locally advanced stage IIIA/B NSCLC.

Three cycles of chemotherapy (i.e., cisplatin plus vinorelbine, cisplatin plus etoposide, or cisplatin plus pemetrexed) were administered, as well as RT with a physical dose of ≥ 60 Gy. The first four doses of nivolumab consisted of 360 mg Q3W. Thereafter, the dosage was 480 mg Q4W for up to 1 year from the start of nivolumab treatment. The pneumonitis-free rate (grade ≥ 3) observed at any time during 6 months post-RT was defined as the primary endpoint.

At the time of the interim safety analysis, which was performed in September 2017 and included 21 patients who had reached 3 months of follow-up after completion of RT, no pneumonitis grade ≥ 3 had occurred [15]. In the safety cohort followed up to February 2018 (n = 62), no unexpected AEs or increased safety risks were observed. The most frequent AEs comprised fatigue, anaemia, and nausea. The 1-year PFS will be evaluated in the expanded cohort of 74 patients in 2019.

Ongoing studies

A promising approach in tackling lung tumours with squamous histology is the combination of pembrolizumab with the ErbB family inhibitor afatinib, as *EGFR* overexpression is more common in squamous tumours than in adenocarcinomas. Preclinical evidence suggests that both the immune microenvironment and tumour expression of PD-L1 might be modulated by EGFR signaling in *EGFR*-mutant NSCLC [16, 17]. The phase II, open-label, non-randomised, single-arm LUX-Lung IO/KEYNOTE 497 study has been initiated with the aim of assessing afatinib plus pembrolizumab in patients with locally advanced or metastatic squamous NSCLC whose disease progressed during or after first-line platinum-based treatment [18]. ORR constitutes the primary endpoint.

Against the background of growing evidence suggesting that the tumour microenvironment might interfere with effective immune recognition even in the presence of checkpoint inhibitors [19], an ongoing phase I/II trial is evaluating the triple kinase inhibitor nintedanib in combination with nivolumab and ipilimumab in patients with advanced NSCLC [20]. The rationale for this study results from the fact that cancer-associated fibroblasts, which are inhibited by nintedanib, represent an important component of the tumour microenvironment and are known to promote metastasis by modifying immune cell infiltration [21]. Apart from determination of the maximum tolerated dose and the required phase II dose in the phase I part, the study aims to confirm whether concurrent nivolumab, ipilimumab and nintedanib administration is efficacious with regard to ORR in treatment-naïve and pretreated patients. ■

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Immune checkpoint blockade: determinants of treatment success

Various clinical factors beyond PD-L1 expression have been explored as predictors of response to immune checkpoint inhibition. Specifically, analyses have associated lack of tobacco exposure with diminished responsiveness to PD-1 pathway blockade in NSCLC [1, 2]. One possible explanation for this is that lung cancers arising in never or minimal smokers generally show low TMB [3]. As smoking exposure increases, the number of mutations per megabase rises as well. TMB has been established as an independent predictive biomarker of response to immune checkpoint inhibitors, with high TMB indicating more favourable responses [4, 5].

In their retrospective review, Gainor et al. explored the role of PD-(L)1 inhibition among never or light smokers with advanced NSCLC and high PD-L1 expression (TPS ≥ 50 %) [6]. This has not been well defined to date due to limited enrolment of never/light smokers in randomised studies and routine exclusion of certain molecular subsets (e.g., *EGFR* or *ALK* aberrations) in first-line clinical trials of PD-(L)1 inhibitors. Overall, 283 patients treated with checkpoint inhibitors from 4 institutions were evaluated; out of these, 69 were defined as never or light smokers, with 33 classified as never smokers (< 100 lifetime cigarettes) and 36 classified as light smokers (≤ 10 pack years; median number of pack years, 1.13). The majority of patients received PD-(L)1 inhibitors in the first-line setting.

Smoking habits influence DOR

The most common oncogenic driver mutations in never/light smokers included *KRAS* and *EGFR* mutations as well as *MET* exon 14 skipping. PD-L1 expression did not differ between never/light smokers and heavy smokers. TMB was assessed based upon smoking status; as expected, TMB was higher in heavy smokers (8.2 mut/Mb) than in never/light smokers (4.1 mut/Mb; p = 0.002), with median TMB being identical for never and light smokers.

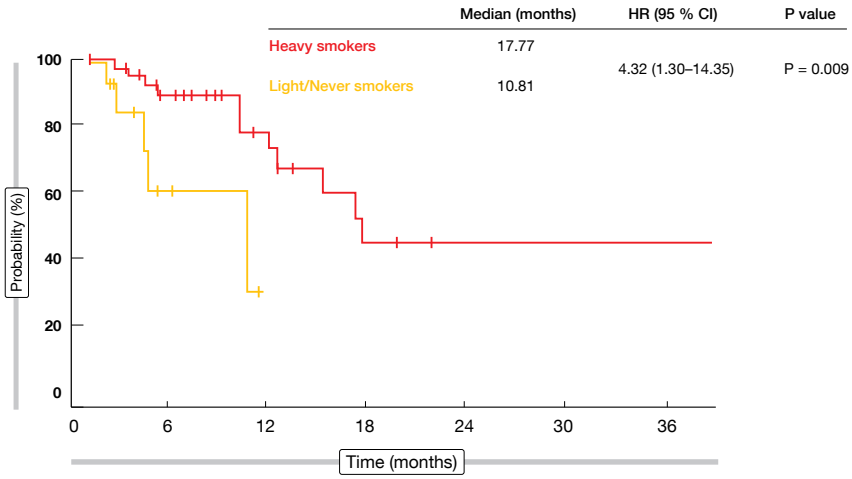

Figure 1: Significantly prolonged duration of response in heavy smokers *versus* light/never smokers

In terms of anti-tumour activity of the anti-PD-(L)1 treatment, there was no statistically significant ORR difference between never/light smokers and heavy smokers (31.9 % vs. 39.6 %; p = 0.386). In 24 never smokers with measureable disease at baseline, the ORR was numerically lower at 25 %, although this was not statistically significant. Responses occurred across multiple oncogenic driver mutations, even though only 1 out of 8 patients with *EGFR*-mutant NSCLC responded (12.5 %), while this was the case for 4 out of 11 patients with *KRAS*-mutant disease (36.3 %). However, these results should be viewed cautiously, as the numbers of patients in this series were small. TMB did not affect responses to checkpoint inhibitors among never/light smokers. The PFS analysis showed a slight trend in favour of heavy smokers (4.8 vs. 3.29 months in never/light smokers; HR, 1.32; p = 0.105).

A conspicuous result, however, was the significant improvement in DOR observed with heavy smokers compared to never/light smokers (17.77 vs. 10.81 months; HR 4.32; p = 0.009; **Figure 1**) despite similar ORRs. The authors summarised that the immunobiological features determining initial response *versus* durability of response might be distinct. Given the shorter DOR with PD-(L)1 monotherapy, chemotherapy plus PD-1 combinations should be considered in never/light smokers with high PD-L1 expression.

What does baseline steroid use do?

Corticosteroids are commonly employed in cancer care, as they can palliate and provide rapid relief of numerous cancer-related symptoms, and they are the mainstay of treatment for immune-related AEs. In this setting, steroids do not appear to diminish the activity of immune checkpoint blockade. However, the efficacy of PD-(L)1 inhibitors in patients receiving baseline steroids used to be unknown, as these patients were usually not eligible for clinical trials investigating immunotherapies.

Arbour et al. performed a retrospective review of the data of 455 and 185 patients from the Memorial Sloan Kettering Cancer Center (MSKCC) and the Gustave Roussy Cancer Center (GRCC), respectively, with the aim of evaluating the efficacy of PD-(L)1 inhibition in patients receiving baseline steroids (≥ 10 mg prednisone or equivalent on day 1 of treatment) [7]. At the two institutions, a total of 90 patients had been treated with steroids at the time of initiation of their PD-(L)1-inhibitory therapy.

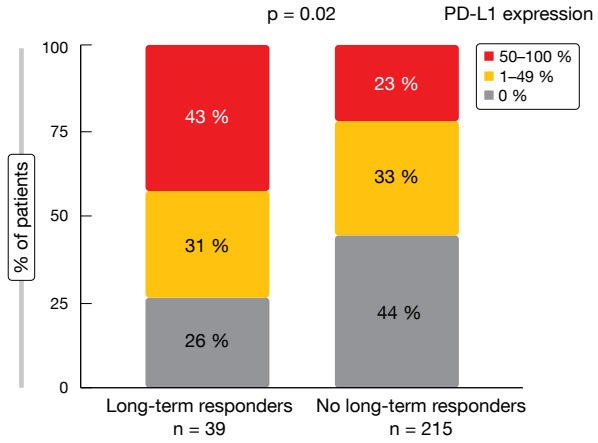

Figure 2: Greater proportion of high PD-L1 expression in patients with LTR

Diminished activity in two independent cohorts

The data clearly demonstrated the deleterious effect of baseline steroid treatment on the PD-(L)1 blockade, such as lower ORR. In the MSKCC Cohort, complete and partial responses occurred in 6 % vs. 19 % in the steroid group and the group without steroids, respectively ($p = 0.02$). For the GRCC Cohort, the analysis revealed a similar distribution, with 8 % vs. 18 % ($p = 0.2$). Inferior PFS outcomes in patients receiving baseline steroids were observed in both cohorts (MSKCC: HR, 1.7; $p < 0.0001$; GRCC: HR, 1.5; $p < 0.0001$). Similarly, OS from the start of PD-(L)1 blockade therapy was significantly lower in the steroid groups at both institutions (MSKCC: HR, 2.1; $p < 0.0001$; GRCC: HR, 2.0; $p < 0.001$). Subgroup analyses using pooled data from both cohorts showed worse PFS and OS outcomes for patients receiving baseline steroids in nearly every subgroup. Of course, steroids are frequently used in a palliative setting for patients with brain metastases or poor performance status. According to a multivariate analysis, however, the deleterious PFS and OS effects of baseline steroid use remained after adjusting for negative prognostic variables.

The investigators pointed out that it is still uncertain whether the observed effect is predictive and/or prognostic. Based on these results, they recommended prudent use of steroids in patients for whom PD-(L)1 inhibition therapy is planned. This includes the consideration of non-steroid alternatives for the management of cancer symptoms, whereas medically necessary steroids (e.g., for the treatment of brain metastases) should not be withheld. As this analysis only incorporated patients on single-agent PD-(L)1 inhibition, the implications for those receiving chemotherapy and combinations with checkpoint inhibitors are uncertain.

Features predicting long-term response

Responses obtained with anti-PD-(L)1 therapy may last years in selected cases, but the features predicting long-term response (LTR) have not been described yet. Therefore, Rizvi et al. analysed 766 patients with advanced NSCLC who received anti-PD-(L)1 therapy at the MSKCC from 2011 through 2016 [8]. LTR was defined as PFS lasting longer than 18 months. This was true for 62 patients (8 % of the total cohort). Of these, 47 (76 %) achieved complete or partial responses, and 15 (24 %) achieved disease stabilisation. At the time of the analysis, 68 % remained progression-free.

The authors identified several features typical of LTR. Long-term responders had significantly higher TMB that those without LTR (12.24 vs. 6.34 mut/Mb; $p < 0.001$), and the proportion of patients with high PD-L1 expression was greater ($p = 0.02$; **Figure 2**). Moreover, ever-smokers constituted the vast majority of those with LTR, whereas never-smokers were the exception; for patients without LTR, this distribution was more balanced. The analysis yielded a significant difference between the two groups in this respect ($p = 0.03$). *EGFR* mutation status showed a negative association with LTR: none of the long-term responders carried an *EGFR* mutation, while this was the case for 12 % of patients without LTR ($p = 0.002$).

The direct comparison of long-term and short-term responders revealed that TMB, but not PD-L1 expression differed significantly between the two groups. Also, it was shown that the depth of response correlated with LTR, but not tumour burden. Baseline tumour burden was similar in long-term and short-term responders.

The authors concluded that the features predicting durable response might indeed be distinct from the features predicting initial response on which biomarkers usually focus. ■

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New data on EGFR-directed TKIs across 3 generations

Erlotinib plus bevacizumab

EGFR TKI treatment has become a standard first-line strategy for patients with advanced, *EGFR*-mutation–positive NSCLC. Established agents include the first-generation drugs gefitinib and erlotinib, the second-generation agents afatinib and dacomitinib, and the third-generation TKI osimertinib. Combinations of EGFR TKIs with other drug classes might lead to outcome optimisation, for instance the additional administration of anti-angiogenic drugs, such as bevacizumab and ramucirumab.

The NEJ026 trial was the first phase III study to investigate first-line erlotinib in combination with the anti-VEGF antibody bevacizumab [1]. In the phase II setting, the randomised JO25567 trial already showed a significant PFS benefit of erlotinib plus bevacizumab compared to erlotinib monotherapy [2]. The NEJ026 study was conducted to confirm these results. Japanese patients with non-squamous, stage IIIB/IV or postoperatively recurrent NSCLC with activating *EGFR* mutations received either bevacizumab 15 mg/kg Q3W plus erlotinib 150 mg once daily (QD; n = 112) or erlotinib alone (n = 112). After disease progression, patients in the experimental arm were treated with platinum and pemetrexed, followed by pemetrexed maintenance, while those in the control arm received platinum plus pemetrexed and bevacizumab, followed by maintenance with pemetrexed and bevacizumab. Asymptomatic central nervous system (CNS) metastases were allowed and present in 32.1 % in each arm.

PFS by independent review committee constituted the primary endpoint. According to the pre-planned interim analysis for PFS, the addition of bevacizumab led to a significant PFS prolongation (16.9 vs. 13.3 months; HR, 0.605; p = 0.01573) [1]. Patients with both exon 19 deletion and exon 21 L858R mutation benefited from the combination. ORR by independent review did not differ significantly across the treatment arms (72.3 %. vs. 66.1 %). Hypertension, proteinuria and haemorrhages occurred more frequently in the bevacizumab arm, but proved manageable. As the investigators pointed out, erlotinib plus bevacizumab represents a new standard first-line treatment in the setting of *EGFR*-mutant NSCLC. Biomarker analyses and OS follow-up are ongoing.

Concurrent use of gefitinib and chemotherapy

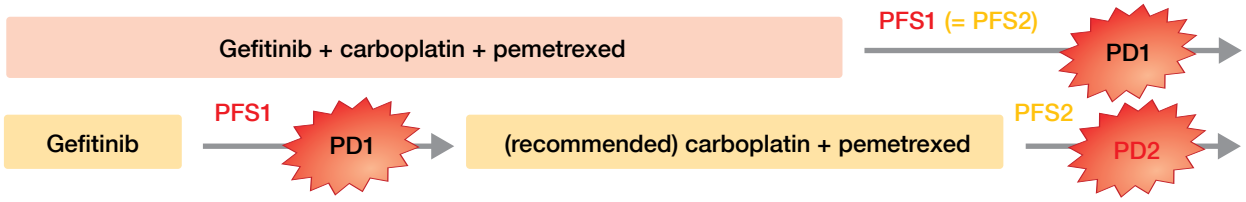
In the NEJ002 trial, gefitinib treatment gave rise to a PFS benefit compared to standard chemotherapy (10.8 vs. 5.4 months; HR, 0.30; p < 0.001) [3], although no significant difference resulted for OS. Also, only 70 % of patients in the gefitinib arm received platinum-doublet chemotherapy, which is a standard post-TKI treatment. Therefore, a thorough use of both EGFR TKI treatment and chemotherapy was expected to improve OS.

Indeed, the phase II NEJ005 study suggested promising efficacy of the concurrent use of gefitinib and chemotherapy compared to a sequential regimen [4]. In the phase III setting, the NEJ009 trial evaluated the concurrent administration of gefitinib QD plus carboplatin and pemetrexed for 4 to 6 cycles [5]. Maintenance treatment after the induction phase contained daily gefitinib plus pemetrexed Q3W until progression. Patients in the control arm, on the other hand, received gefitinib QD until progression; at that time, a platinum-based second-line regimen was recommended.

Multiple primary endpoints were evaluated; these included PFS, PFS2 (i.e., a PFS comparison at the time of the second disease progression [PD2] in the reference arm and the first progression [PD1] in the experimental arm; **Figure**), and OS. Across Japan, 345 patients with non-squamous, previously untreated stage IIIB/IV or recurrent NSCLC were enrolled at 47 institutions.

Time to first progression counts

As expected, the combination treatment was superior by a wide margin with regard to PFS1 (20.9 vs. 11.2 months; HR, 0.494; p < 0.001) and ORR (84.0 % vs. 67.4 %). These effects are most likely due to the considerably longer gefitinib treatment exposure in the experimental arm (730 vs. 462 days). At the time of PD1, the clinical status of patients (i.e., ECOG PS, number of metastatic organs, brain metastasis) was comparable across the trials arms. This was not the case at PD2, however; here, patients treated sequentially fared much worse. The PFS2 analysis yielded no difference between the two regimens (20.9 vs. 20.7 months; HR, 0.966; p = 0.774).



PD1, first disease progression; PD2, second disease progression

Figure: PFS outcomes as defined in the NEJ009 study

TABLE 1
Comparison across first-line trials of second- and third-generation EGFR TKIs

	LUX-Lung 7	ARCHER 1050	FLAURA
Median OS	27.9 vs. 24.5 months	34.1 vs. 26.8 months	Immature
Phase	IIb (n = 319)	III (n = 452)	III (n = 556)
Arms	Afatinib vs. gefitinib	Dacomitinib vs. gefitinib	Osimertinib vs. gefitinib/erlotinib
RR	70 % vs. 56 %	75 % vs. 71.2 %	80 % vs. 76 %
PFS (all comers)	11 vs. 10.9 months (BIRC) HR, 0.73 (0.57-0.95) p = 0.017	14.7 vs. 9.2 months (BIRC; no patients with brain metastases) HR, 0.59 (0.47-0.74) p < 0.0001	17.7 vs. 9.7 months (BIRC) HR, 0.45 (0.36-0.57) p < 0.001
PFS (patients without brain metastases)		16.6 vs. 11.0 months (INV) HR, 0.62 (0.50-0.78) p < 0.0001	19.1 vs. 10.9 months (INV) HR, 0.46 (0.36-0.59) p < 0.001

BIRC, blinded independent review committee; INV, investigator

An additional OS analysis revealed a significant advantage of the combination regimen (52.2 vs. 38.8 months; HR, 0.695; p = 0.013). No difference resulted for survival from PD1 (19.3 vs. 23.0 months; HR, 1.037; p = 0.812) even though the majority of patients in the gefitinib-alone arm had received a platinum regimen after the first progression. This indicates that OS in this study is closely related to PFS1, rather than to PFS2. The authors concluded that prolongation of the time until the first progression is critical for patients with *EGFR*-mutant NSCLC, and that PFS is a good surrogate marker for OS.

Haematological AEs were more common in the combination arm. However, only few patients discontinued treatment due to toxicities in both treatment groups. Overall, the addition of carboplatin and pemetrexed to gefitinib significantly improved PFS and OS in untreated advanced *EGFR*-mutant NSCLC, with acceptable toxicity. The combined regimen might therefore be an effective first-line option in this setting.

OS results obtained in ARCHER 1050

The second-generation, irreversible EGFR TKI dacomitinib was investigated in the phase III, randomised, open-label ARCHER 1050 study. Wu et al. reported significant PFS improvement with dacomitinib *versus* gefitinib as first-line treatment in patients with *EGFR*-mutant, advanced NSCLC (14.7 vs. 9.2 months; HR, 0.59; p < 0.0001) [6]. A total of 452 patients received either dacomitinib 45 mg QD or gefitinib 250 mg QD. Pre-existing CNS metastases were not allowed in this trial, as the efficacy of dacomitinib in patients with brain lesions was unknown at the time of study inclusion. Seventy to 80 % of the population in both arms were Asian. Approximately 60 % were younger than 65 years.

The pre-specified final OS analysis of ARCHER 1050 presented at the ASCO 2018 Congress showed that this is the first randomised phase III trial comparing two first-line EGFR TKIs to demonstrate OS improvement [7]. Median OS results were 34.1 vs. 26.8 months for dacomitinib and gefitinib, respectively (HR, 0.76; p = 0.0438). At 30 months, 56.2 % vs. 46.3 % of patients were alive. The subgroup analysis yielded no OS differences between the two treatments in patients with exon 19 deletion (HR, 0.88; p = 0.4862) or exon 21 L858R mutation (HR, 0.707; p = 0.0805), although the study was not powered to capture survival differences in these subgroups. Likewise, the OS analysis for Asian patients did not show a significant treatment benefit (HR, 0.812; p = 0.1879). Median OS in the dacomitinib-treated patients who went on to receive third-generation EGFR TKI treatment (9.7 % of the population) was 36.7 months. Other EGFR TKIs as subsequent therapy led to an OS of 34.7 months.

The increased EGFR-inhibitory activity of dacomitinib caused typical AEs, with grade ≥ 3 acneiform dermatitis occurring in 13.7 %, grade ≥ 3 diarrhoea in 8.8 %, and grade ≥ 3 paronychia in 7.5 %. Gefitinib, on the other hand, only gave rise to slightly higher rates of grade ≥ 3 liver enzyme elevations. AEs frequently made dose modifications necessary in the experimental arm (66.5 % vs. 8.0 % with gefitinib). The authors concluded that dacomitinib should be considered as a new option for the first-line management of patients with *EGFR*-mutant advanced NSCLC.

Putting the ARCHER 1050 data into perspective

As Dr. Daniel Tan, National Cancer Centre Singapore, pointed out in his discussion of the ARCHER 1050 and NEJ009 data, here are two phase III trials finally demonstrating OS benefit over a standard EGFR TKI, although questions remain [8]. All of the prior EGFR TKIs were approved for first-line treatment based on PFS, but showed no significant differences in OS, which was potentially due to crossover. When comparing ARCHER 1050 with the other key first-line trials investigating second- and third-generation EGFR TKIs, Dr. Tan noted that the LUX-Lung 7 study, which tested afatinib against gefitinib [9], had a smaller sample size (n = 319) than ARCHER 1050 (n = 452; **Table 1**). Also, this was a phase IIb study, which might have confounded its ability to detect an OS difference. While patients with brain metastases were included in LUX-Lung 7, this was not the case for ARCHER 1050. Long-term tolerability of dacomitinib is a potential concern, raising the need to define the optimal pharmacologically active dose. Another unsolved issue is sequencing of second- and third-generation TKIs.

TABLE 2
Pathological responses among surgical patients who received neoadjuvant afatinib in the ASCENT trial

Surgical patient	TNM stage preoperatively	TNM stage postoperatively	% cellularity or similar comments
1	T2N2	ypT1N0	< 5 %
2	T1N2	ypT1N0	Foci of tumour cells
3	T3N2	ypT1N0	< 1 %
4	T2N2	ypT2N1	50 %
5	T2N2	ypT1N2	Scattered cells
6	T3N2	ypT0N0	Complete response
7	T3N3	ypT3N1	Scattered cells

Also, the question remains of where osimertinib fits. OS data from the FLAURA trial are not mature yet, and resistance mechanisms are still incompletely characterised, with uncertain druggability. Dr. Tan emphasised that *EGFR*-mutant lung cancer is a clinically and genomically heterogeneous disease. Initial upfront therapy can augment its natural history; therefore, it is increasingly important to ascertain the individual risk of disease progression with a view to rationalising upfront therapy. According to Dr. Tan, there is a need to critically evaluate the risk-benefit ratio of these potential standards of care and to tailor them to individual patient preference.

Real-world evidence on afatinib

Tolerability-guided dose adjustment of afatinib reduced the incidence and severity of AEs without affecting efficacy in the LUX-Lung studies. Halmos et al. reported the impact of afatinib dose modifications on the efficacy and safety of this treatment in a real-world setting [10]. A total of 228 patients from 13 countries who received first-line afatinib were included in this non-interventional, observational study.

As in the LUX Lung trials, afatinib dose adjustments reduced the frequency and intensity of AEs without impacting efficacy. Time on treatment and time to progression were similar regardless of dose modifications or reduced starting dose. Sixty-seven percent of patients who started on doses of ≥ 40 mg underwent reductions, with 86 % of these occurring in the first 6 months. In 12 %, doses were increased. AEs constituted the main reason for modifications. Dose adjustments were more frequent in females, older patients, Eastern Asian patients, and those with lower body weight. The analysis revealed no new safety signals. These results highlighted the benefit of tailoring afatinib dose based on individual patient characteristics and AEs to optimise outcomes.

Clinical outcomes obtained with afatinib in real-world practice were the focus of a Japanese analysis of 128 patients 76 of whom received first-line afatinib, while 52 were treated in the re-challenge setting [11]. The use of afatinib gave rise to comparable or even better outcomes than in previous trials. In the first-line setting, PFS and OS were 17.8 months and 39.5 months, respectively. Although dose reductions became necessary in 58 patients (76.3 %) due to AEs, this did not affect OS outcomes (39.5 months in the reduction group vs. not yet reached in the group without reduction; $p = 0.37$). Moreover, patients whose doses were reduced even experienced longer PFS than those in whom this was not the case (18.0 vs. 7.9 months; $p = 0.016$). The ORR was 64 %. In the re-challenge setting, the analysis yielded an ORR of 24 %.

Afatinib in uncommon *EGFR* mutations

A retrospective, multicentre study evaluated the efficacy of afatinib in patients with lung adenocarcinoma harbouring uncommon *EGFR* mutations in Spanish clinical practice [12]. Medical records of 67 NSCLC patients who had been treated with afatinib between 2012 and 2017 at 23 Spanish institutions were reviewed. Eighty percent of patients had received afatinib as first-line therapy. Uncommon *EGFR* mutations were analysed as complex mutations (Group A; n = 20), exon 20 insertion (Group B; n = 23), or single mutations (Group C; n = 24).

No differences in clinical characteristics emerged across the three groups. Eighteen percent of patients started afatinib at reduced doses, and 24 % required dose reductions. Responses to afatinib were significantly higher in Groups A and C (70 % and 54 %, respectively) than in Group B (13 %; pairwise comparison $p < 0.001$ and $p = 0.013$, respectively). Median OS for the entire cohort was 19.9 months, with HRs of 0.27 ($p = 0.009$) and 0.40 ($p = 0.037$) for Groups A and C compared to Group B, respectively. As the authors stated in their conclusion, afatinib was active in NSCLC with uncommon *EGFR* mutations in clinical practice, particularly in complex and single mutations. Further strategies, however, are called for in patients with exon 20 insertion.

Neoadjuvant use: the ASCENT trial

Afatinib in the neoadjuvant setting was assessed in the phase II ASCENT study conducted in patients with stage III, *EGFR*-mutant NSCLC whose disease burden was feasible for chemoradiation [13]. After treatment with afatinib 40 mg QD for 2 months, patients received chemoradiation and went on to undergo resection or adjuvant therapy with afatinib 40 mg QD for 2 years, provided no disease progression had occurred with the neoadjuvant TKI use. After surgery, adjuvant chemotherapy was optional, followed by adjuvant afatinib.

Although only 13 patients were included in this analysis, it showed a favourable neoadjuvant response rate of 75 %. The delivery of chemoradiation with or without surgery was not impeded by the neoadjuvant afatinib administration. Six out of 7 patients who underwent surgery experienced clinically significant pathological responses (i.e., scant cells, < 5 % cellularity; **Table 2**). Median PFS was 34.8 months, with 7 patients staying recurrence-free at the time of the analysis. This result compares favourably to the 16.8-month PFS outcome observed in the immunotherapy arm of the PACIFIC study [14], supporting the genotype-directed approach. PACIFIC had tested sequential treatment with the PD-L1 inhibitor durvalumab *versus* placebo in locally advanced, unresectable stage III NSCLC. The investigators noted that the feasibility of 2 months of neoadjuvant afatinib administration might exceed adjuvant TKI use. Accrual to the ASCENT trial is continuing.

Significance of TMB for anti-EGFR treatment

Tumour mutation burden (TMB) might have multiple biological implications that depend on the specific treatment and disease setting. For immunotherapy, the relationship between TMB and improved treatment benefit has been described. Offin et al. hypothesised that TMB might have a distinct (and inverse) relationship with outcomes in the setting of targeted therapies, where TMB might be a surrogate for the presence of resistance pathways [15]. The researchers identified 153 patients with *EGFR*-mutant (exon 19 deletion and exon 21 L858R mutation) lung cancer treated with first- and second-generation EGFR TKIs, who had next generation sequencing with the tumour-profiling multiplex panel MSK-IMPACT™ performed on pre-treatment tissue. OS and time to treatment discontinuation (TTD) with the initial EGFR TKI therapy were evaluated according to TMB in univariate and multivariate analyses.

The results indicated that *EGFR*-mutant lung cancers have a broad molecular heterogeneity with a wide range of TMB even within this specific oncogene-defined disease. As the investigators had surmised, TMB was inversely associated with the efficacy of the EGFR TKI treatment. Both OS and TTD were shortest in the group showing high TMB, with HRs of 0.49 and 0.57, respectively, according to multivariate analysis ($p = 0.025$ and 0.009, respectively). This relationship is in contrast to that seen with immunotherapy, which highlights the varied and context-specific implications of TMB.

Resistance to osimertinib: what's new?

The third-generation EGFR TKI osimertinib has shown significant clinical activity in the phase III AURA3 study when compared to platinum-pemetrexed chemotherapy for patients with T790M-positive NSCLC after progression on first- or second-generation EGFR TKI treatment [16]. Moreover, in comparison to erlotinib or gefitinib in the first-line setting, osimertinib gave rise to a significant PFS benefit in the phase III FLAURA trial [17].

Despite the increasing role of osimertinib for treatment of NSCLC, there is limited data regarding resistance mechanisms to this agent. However, a comprehensive understanding of these mechanisms is required in order to develop strategies to overcome osimertinib resistance. Le et al. therefore performed an analysis based on the MD Anderson Lung Cancer Moon Shot GEMINI database and the Moffitt electronic health record, Clinical Genomic Action Committee database and pyrosequencing database for NSCLC patients with *EGFR* T790M mutation, isolating those who were treated with osimertinib [18]. A total of 118 patients met the study criteria. Almost all of them (95 %) had received previous EGFR TKI treatment, mostly erlotinib.

Genomic profiling showed that resistance mechanisms are diverse, with T790M preservation and T790M loss each prevailing in approximately half of cases. In T790M-preserved samples, C797S/L792H mutations were found (58 %), as well as *MET* amplifications. This means that tertiary mutation of *EGFR* is a common mechanism in this group. In those with T790M loss, the resistance mechanisms were largely EGFR-independent and non-oncogene-driver–mediated (i.e., *PIK3CA* mutation, *MET* amplification, SCLC

TABLE 3
PFS and ORR results obtained with osimertinib at weeks 3 and 6 according to the clearance of *EGFR* mutations

	Events, n	Median PFS, months (95 % CI)	HR (95 % CI)	ORR, % (95 % CI)
At 3 months				
Undetectable plasma EGFRm (n = 81)	43	10.9 (8.3, 12.7)	2.05 (1.30, 3.22)	81 (71, 89)
Detectable plasma EGFRm (n = 48)	34	5.7 (4.1, 9.7)		50 (35, 65)
At 6 months				
Undetectable plasma EGFRm (n = 88)	46	10.9 (9.5, 12.7)	2.65 (1.70, 4.14)	81 (71, 88)
Detectable plasma EGFRm (n = 45)	35	4.6 (3.9, 6.9)		51 (35, 65)

EGFRm, *EGFR*-activating mutations

transformation). Cell cycle gene alterations showed an association with inferior clinical outcomes.

Zhang et al., when analysing differences relating to the mutation spectrum in 110 patients with activating *EGFR* mutations who were clinically osimertinib-resistant, observed that acquired mutations leading to osimertinib resistance were more likely to be identified in the group with deletion 19 than in patients with L8585R mutation (62.5 % vs. 39.1 %; p = 0.015) [19].

Prediction of response to osimertinib

Previous longitudinal analyses from the AURA programme suggested that early clearance of plasma *EGFR* mutations in patients with T790M-positive advanced NSCLC receiving osimertinib is a prognostic marker for improved PFS [20]. Shepherd et al. investigated whether the presence of plasma *EGFR* mutations in patients from AURA3 at 3 and 6 weeks after starting osimertinib therapy is associated with clinical outcomes [21].

It was shown that osimertinib-treated patients with detectable *EGFR* mutations in their baseline plasma samples, which are indicative of tumour shedding, had less favourable outcomes than those without shedding regarding both PFS (8.3 vs. 14.0 months) and ORR (68 % vs. 75 %). The researchers concluded that detectable tumour shedding might reflect increased disease burden and could be a prognostic biomarker for poorer outcome.

Also, early dynamic changes of plasma *EGFR* mutations might predict PFS in patients receiving treatment for T790M-positive NSCLC, as continued presence of circulating tumour DNA (ctDNA) for *EGFR* mutations at weeks 3 and 6 was associated with less favourable PFS and ORR results (**Table 3**). Thus, patients with T790M-positive NSCLC who might experience sub-optimal clinical outcomes could be identified as early as 3 weeks after initiation of osimertinib treatment. Monitoring of ctDNA for *EGFR* mutations might allow for modification of treatment with the aim of outcome optimisation.

Another potential early marker for the prediction of responses to osimertinib is ^{18}F-fluorodeoxyglucose (FDG) PET. Yoon et al. conducted a prospective, open-label, single-centre pilot study in 25 patients who had shown disease progression on first-generation EGFR TKI treatment [22]. ORR was 76 %, with the metabolic response (defined as ≥ 20 % decrease of ΔSUVmax) being significantly related to median PFS and ORR. Osimertinib showed anti-tumour activity even in patients harbouring no T790M mutation.

Ramucirumab as a combination partner

The ongoing phase I JVDL trial is assessing the combination of osimertinib with the monoclonal anti-VEGFR-2 antibody ramucirumab in *EGFR*-mutant, T790M-positive NSCLC after progression on first-line EGFR TKI treatment. In their analysis of 25 patients, Planchard et al. showed that the safety profile of the combination was consistent with the safety profile of each drug as monotherapy, with no additive toxicities [23]. Hypertension, diarrhoea, stomatitis, rash, and thrombocytopenia constituted the most common AEs. Discontinuation due to AEs occurred only in 4 %.

Furthermore, the results suggest encouraging anti-tumour activity. Complete or partial responses were achieved in 76 %, and disease control in 92 %.

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Median DOR had not been reached at the time of the analysis, which also applied to median PFS. At 12 months, 57.5 % of patients were alive and progression-free.

New kid on the block: nazartinib

Nazartinib is an investigational third-generation, irreversible EGFR TKI selective for activating *EGFR* mutations and T790M mutations while sparing wild-type *EGFR*. According to the preliminary phase II results of a multicentre, open-label phase I/II first-in-human study, nazartinib shows a tolerable safety profile and promising efficacy in treatment-naïve patients with *EGFR*-mutant, stage IIIB/IV NSCLC [24]. Forty percent of patients had brain metastases at screening.

Nazartinib was well tolerated, with the majority of AEs being grade 1 or 2. Overall, the safety profile appeared favourable in terms of all typical toxicities, such as diarrhoea, acneiform rash, dry skin, stomatitis, and paronychia. Maculopapular rash was the most frequent AE, but proved manageable. Despite the high proportion of patients with brain lesions at baseline, the new TKI elicited an ORR of 66.7 % according to the blinded independent review committee. Disease control occurred in 95.8 %. The majority of patients experienced reductions in the size of target lesions. Nazartinib was effective in patients both with and without brain metastases (**Table 4**). PFS and DOR data were still immature at the data cut-off. A phase III study investigating nazartinib in the treatment-naïve setting is projected to start in July 2018. ■

TABLE 4
Best overall responses to treatment with nazartinib in 24 patients with and without brain metastases at baseline

	Brain metastases present	Brain metastases absent
Evaluable patients, n (%)	10 (41.7)	14 (58.3)
Best overall response, n (%)		
Complete response	0	1 (7.1)
Partial response	5 (50.0)	10 (71.4)
Stable disease	4 (40.0)	2 (14.3)
Progressive disease	1 (10.0)	0
Non-CR/non-PD	0	1 (7.1)
Disease control rate, n (%) [95 % CI]	9 (90.0) [55.5-99.7]	14 (100) [76.8-100]
Overall response rate, n (%) [95 % CI]	5 (50.0) [18.7-81.3]	11 (78.6) [49.2-95.3]

CR, complete response; PD, disease progression

Interview: Barbara Melosky, MD, FRCPC, University of British Columbia and British Columbia Cancer Agency, Vancouver, Canada

"The sequencing question remains"

Afatinib has been licensed for the second-line treatment of patients with squamous-cell carcinoma of the lung. A combination trial is ongoing that is testing afatinib plus pembrolizumab. What can we expect from this regimen?
I think this is a highly interesting regimen. We know that afatinib does play a role in squamous-cell carcinoma of the lung. The LUX-Lung 8 trial has shown an improvement in PFS and OS over erlotinib [1]. Our Canadian trial demonstrated that erlotinib does have activity in squamous-cell carcinoma in the second-line setting [2]. We know that afatinib is a very useful drug, and we also know that pembrolizumab has efficacy in squamous-cell carcinoma after platinum-doublet therapy in patients whose tumours express PD-L1. Therefore, I think that combining these two agents will be very interesting. The ongoing study is a phase II trial that is looking at reduction in tumour size [3]. The combination should be well tolerated, and I hope we see an improvement in response rates.


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Are there further combinations of anti-EGFR agents with other drug classes that might be worth exploring?
The addition of anti-angiogenesis to EGFR TKI treatment is certainly worth exploring. At this year's ASCO Congress, we saw exciting data obtained with the combination of erlotinib and the anti-VEGF antibody bevacizumab [4]. This phase III study demonstrated the supe-

riority of erlotinib plus bevacizumab over erlotinib alone, with a PFS benefit of more than 3 months.

Based on the ARCHER 1050 trial, can dacomitinib be regarded as a first-line standard option in patients with *EGFR*-mutation–positive NSCLC?
The ARCHER 1050 study caught us all by surprise last year. At that time, Dr. Mok presented the PFS results, demonstrating a benefit of dacomitinib over gefitinib [5]. Now the pre-specified final OS analysis of ARCHER 1050 was presented, which was positive [6]. This means that we now have the first EGFR TKI study showing an OS benefit. There was no significant OS difference in any other trial, so I think dacomitinib can be regarded as a first-line standard option in *EGFR*-mutant NSCLC, if the patient has no brain metastases at baseline as the ARCHER 1050 study did not include these patients.

From a clinical point of view, how do you rate the sequence of afatinib followed by osimertinib as compared to first-line osimertinib?
With the positive results of the FLAURA trial [7], oncologists will soon have to decide if they use osimertinib upfront or use it after progression in patients on first-generation or second-generation EGFR TKIs who are found to have an acquired T790 mutation. With an investigator-assessed PFS of over 18 months and a favourable toxicity profile, osimertinib might be ideal for patients whose treatment goal is not necessarily OS. FLAURA will not answer the sequencing question, as patients in the control arm were only randomised to first-generation EGFR TKIs, and crossover, although allowed, was not ideal in this design. Without the OS known for the osimertinib arm of FLAURA or the osimertinib arm of AURA3 [8], the sequencing question remains.

We now have second-generation TKIs like afatinib, which showed an impressive statistically significant OS advantage of 33 months compared to chemotherapy in patients with deletion 19 included in the LUX-Lung 3 trial [9]. At this year's ASCO Congress, the ARCHER 1050 study illustrated a statistical OS benefit of dacomitinib compared to gefitinib [6]. There is no perfect trial. Do we start with osimertinib for all patients, or do we sequence it after first-generation or second-generation EGFR TKIs in only a subset? The question remains. We will likely use individual patient factors such as age, type of mutation, performance status, or brain metastases to make such decisions. The good news is that with debate, other questions arise and the person who most benefits is the patient. ■

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ALK-positive disease: pushing the borders of treatability

CNS and non-CNS efficacy of alectinib confirmed in ALEX

Standard treatment for patients with *ALK*-positive, advanced NSCLC includes the first-generation ALK inhibitor crizotinib and, more recently, second-generation ALK TKIs such as ceritinib and alectinib. The global, phase III ALEX trial tested the highly selective, CNS-active ALK inhibitor alectinib as first-line agent compared to crizotinib in patients with stage IIIB/IV *ALK*-positive NSCLC. Asymptomatic brain metastases were allowed in this study. According to the primary analysis, alectinib treatment gave rise to improved investigator-assessed PFS (not estimable vs. 11.1 months; HR, 0.47; $p < 0.0001$) [1]. PFS was also superior when estimated by the independent review committee (IRC; 25.7 vs. 10.4 months). Moreover, the patients in the experimental arm experienced prolonged DOR (not estimable vs. 11.1 months; HR, 0.36) and an improved safety profile.

The updated efficacy and safety analysis of ALEX presented at the ASCO 2018 Congress confirmed the superiority of alectinib over crizotinib with respect to investigator-assessed PFS (34.8 vs. 10.9 months; HR, 0.43) [2]. PFS benefits occurred irrespective of the presence of baseline CNS metastases. Median PFS was 27.7 vs. 7.4 months (HR,

0.35) in patients with brain lesions and 34.8 vs. 14.7 months (HR, 0.47) in those without. In spite of similar ORRs across the two arms (82.9 % vs. 75.5 %), alectinib-treated patients with and without CNS metastases showed longer duration and greater depth of response. Overall, responses lasted 33.1 vs. 11.1 months with alectinib and crizotinib, respectively. In the ITT population, 43.7 % vs. 25.4 % of responders treated with alectinib and crizotinib, respectively, demonstrated tumour reductions > 75 % **(Table 1)**. Both patients with and without CNS lesions experienced more pronounced tumour reductions in the experimental arm.

Alectinib showed consistently better tolerability compared to crizotinib despite longer treatment duration. OS data are still immature. These data consolidate alectinib as the standard of care for the first-line treatment of patients with *ALK*-positive NSCLC.

TABLE 1
ALEX trial: tumour reductions in responders (ITT and CNS subgroups)

Responders, n (%)	**Alectinib (n = 126)**	**Crizotinib (n = 114)**
> 50 % tumour reduction	114 (90.5)	73 (64.0)
> 75 % tumour reduction	55 (43.7)	29 (25.4)
Responders with measurable and/or non-measurable CNS lesions at baseline	**Alectinib (n = 52)**	**Crizotinib (n = 38)**
> 50 % tumour reduction	45 (86.5)	20 (52.6)
> 75 % tumour reduction	18 (34.6)	10 (26.3)
Responders without CNS lesions at baseline	**Alectinib (n = 74)**	**Crizotinib (n = 76)**
> 50 % tumour reduction	69 (93.2)	53 (69.7)
> 75 % tumour reduction	37 (50.0)	19 (25.0)

ALTA: update on brigatinib

However, the emergence of resistance and progression despite the use of second-generation agents necessitated the development of further agents. The next-generation ALK inhibitor brigatinib is being tested in the ongoing, randomised, phase II ALTA trial that includes 222 patients with advanced *ALK*-positive NSCLC who have experienced disease progression on crizotinib. Patients are receiving either brigatinib 90 mg QD (Arm A) or brigatinib 90 mg followed by 180 mg QD (Arm B). Updated data and exploratory analyses of the ALTA study presented at the ASCO 2018 Congress highlighted the continued efficacy of this treatment [3].

Confirmed ORRs as assessed by the investigator, which constituted the primary endpoint, were 46 % and 56 % in Arms A and B. Disease control occurred in 81 % and 86 %, respectively. In patients with ≥ 1 baseline CNS target lesion, ORRs were 43 % and 61 %. Systemic PFS according to IRC amounted to 9.2 and 16.7 months. At one year, 45 % and 61 % of patients were progression-free and alive. For OS, the analysis yielded median results of 29.5 and 34.1 months. Two-year OS probability was 55 % and 66 %.

The treatment induced similar depth of response in target lesions both in the CNS and outside of the CNS. Confirmed intracranial responses per IRC in patients with measurable baseline brain metastases occurred in 50 % and 67 %, and intracranial disease control rates were 85 % and 83 %. Intracranial responses lasted for 9.4 and 16.6 months. In patients with any brain metastases at baseline, intracranial PFS was 12.8 and 18.4 months.

The authors noted that the median PFS of 16.7 months in Arm B is highly comparable to the 16.3-month PFS seen in patients with crizotinib-treated, *ALK*-positive NSCLC who received the same regimen in the phase I/II trial of brigatinib [4]. Although cross-trial comparisons are limited by differing patient characteristics and assessment methods, this remains the longest median PFS in the post-crizotinib setting for any next-generation ALK inhibitor reported to date. The randomised phase III ALTA-1L trial that is evaluating brigatinib 180 mg (with lead-in) as compared to crizotinib in patients with ALK-inhibitor-naïve, advanced, *ALK*-positive NSCLC has already completed accrual.

TABLE 2
Efficacy of lorlatinib in *ALK*-positive patients after pre-treatment with ≥ 1 ALK TKI

	Prior crizotinib ± chemotherapy	**Prior non-crizotinib ALK-TKI ± chemotherapy**	**≥ 2 prior ALK TKIs ± chemotherapy**
Overall			
N	59	28	111
Overall response rate, %	72.9	42.9	39.6
Time to tumour response, months	1.4	1.4	1.4
Duration of response, months	Not reached	5.6	9.9
Progression-free survival, months	11.1	5.5	6.9
Intracranial			
N	37	13	81
Intracranial overall response rate, %	70.3	46.2	48.1
Time to intracranial response, months	1.4	1.4	1.4
Duration of intracranial response, months	Not reached	Not reached	14.5

Lorlatinib: deep and durable benefits in the phase II

An ongoing, multicentre, open-label, single-arm phase I/II study is testing the third-generation ALK and ROS1 TKI lorlatinib in patients with metastatic, *ALK*- or *ROS1*-positive NSCLC. Lorlatinib is CNS-active and shows broad-spectrum potency against most known *ALK* resistance mutations that develop during treatment with first- and second-generations TKIs. Asymptomatic untreated or treated CNS metastases at baseline are permitted in this trial. In the phase I part, lorlatinib showed clinically meaningful and durable responses (ORR, 46 %; DOR, 12.4 months) among patients with *ALK*-positive disease, many of whom had CNS lesions and disease progression after previous ALK TKI therapy [5].

Besse et al. reported updated efficacy findings from the phase II portion that investigated lorlatinib among patients with *ALK*-positive NSCLC who had been pre-treated with ≥ 1 ALK TKI (n = 198) [6]. Of these 198 patients, 131 (66 %) showed CNS involvement. Safety data were presented for all treated phase II patients, i.e., those with both *ALK*-positive and *ROS1*-positive disease; these were both pre-treated and treatment-naïve (n = 275).

Lorlatinib gave rise to clinically meaningful benefit in pre-treated patients, including those who had received prior crizotinib, only 1 second-generation ALK TKI, or up to 3 prior ALK TKIs **(Table 2)**. Rapid, deep and durable systemic and intracranial responses were observed. Translational analyses demonstrated that 45 patients had ≥ 1 detectable *ALK* kinase domain mutation. Lorlatinib showed anti-tumour activity across a variety of *ALK* kinase domain resistance mutations, including the *G1202R/del* mutation that was most frequently found. Responses also occurred in patients without detectable *ALK* kinase domain mutations. The treatment generally proved tolerable, with a low incidence of permanent discontinuations due to toxicity. AEs were manageable through dose modifications and/or supportive therapy. ■

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Recent benchmarks in the management of small-cell tumours

KEYNOTE-158

Extensive-disease small-cell lung cancer (ED-SCLC) is highly responsive to first-line therapy, but early relapses commonly occur, and prognosis is poor. To date, no biomarker-driven therapies have been established.

Based on the involvement of the immune system in the pathophysiology of SCLC and the high mutational burden of this disease, immunotherapy has potential as a novel treatment option [1-3]. KEYNOTE-158, a phase II basket study conducted in 10 tumour types including cancer with high microsatellite instability (MSI-H), assessed the anti-PD1 antibody pembrolizumab in advanced SCLC regardless of biomarker status [4]. Pre-treated patients with unresectable and/or metastatic SCLC who had experienced progression on or intolerance to standard therapy received pembrolizumab 200 mg Q3W for 2 years or until progression. ORR constituted the primary endpoint. Out of 107 patients, 16 (15 %) had stable brain metastases. The cohort included one patient with carcinoid histology and seven patients with neuroendocrine tumours.

One third of the population had already received 2 treatment lines, and in 23 %, ≥ 3 therapies had been administered. At baseline, 39 % and 47 % of tumours were PD-L1–positive and PD-L1–negative, respectively, with 14 % being not evaluable. Furthermore, the biomarker analysis yielded non–MSI-H status (i.e., microsatellite stability and low microsatellite instability) in 91 %, with 9 % being not evaluable.

Superior results in the PD-L1–positive group

Overall, responses occurred in 18.7 %, and disease control was observed in 30 %. Patients with PD-L1–positive tumours responded in 35.7 %, while in the PD-L1–negative group, this was only the case in 6.0 %. Disease control rates amounted to 43 % and 20 %, respectively. The authors pointed out that these findings are consistent with those

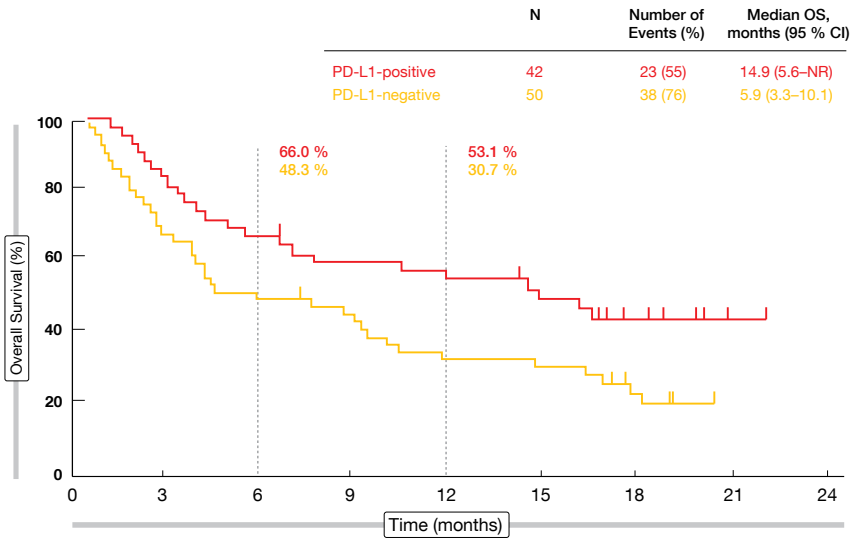


Figure 1: Promising survival results in the PD-L1–positive patient group treated with pembrolizumab

from the SCLC cohort of the phase IB KEYNOTE-028 trial that evaluated pembrolizumab in patients with previously treated extensive-stage tumours expressing PD-L1 [5]. Importantly, responses proved durable; their median duration had not been reached at the time of the analysis, and 12 patients (73 %) responded for ≥ 1 year. Median PFS was 2.1 and 1.9 months for PD-L1–positive and PD-L1–negative patients, respectively. The respective OS results were 14.9 and 5.9 months **(Figure 1)**. At 12 months, 53.1 % and 30.7 % of patients, respectively, were alive.

The safety profile matched the previous experience for pembrolizumab monotherapy in other tumour types. Pembrolizumab plus standard-of-care chemotherapy (i.e., etoposide/platinum) is being evaluated in the ongoing phase III KEYNOTE-604 study in patients with newly diagnosed ED-SCLC.

Durvalumab alone and together with tremelimumab

Another checkpoint inhibitor investigated in SCLC is the anti-PD-L1 antibody durvalumab. This agent showed activity both as a single agent and in combination with the anti-CTLA-4 antibody tremelimumab. In the monotherapy trial, which was the multicentre, open-label ED-SCLC expansion cohort of Study 1108, durvalumab 10 mg/kg Q2W for up to 12 months demonstrated durable clinical activity in certain patients [6]. Only 2 out of 21 patients responded (ORR, 9.5 %), but these responses lasted 14.6 and 29.5+ months, respectively. The second patient was platinum-refractory and had received 3 prior treatment lines. Median PFS and OS were 1.5 and 4.8 months, respectively. The 12-month OS rate amounted to 27.6 %. Durvalumab was well tolerated, with no grade-3/4 AEs observed.

In the multicentre, open-label combination trial, which was a phase I dose exploration/expansion study, durvalumab 20 mg/kg Q4W and tremelimumab 1 mg/kg Q4W for 4 doses were tested in previously treated patients with select advanced solid tumours. After the combination phase, patients received durvalumab 10 mg/kg Q2W to complete 12 months. At the ASCO 2018 Congress, Cho et al. presented the first report of clinical activity and safety in the ED-SCLC dose-expansion cohort (n = 30) [7].

Consistent with findings in NSCLC [8], durvalumab plus tremelimumab demonstrated promising activity. Confirmed ORR was 13.3 %, including 2 complete and 2 partial responses. Three platinum-resistant/-refractory patients responded to the treatment. Responses occurred early on and were durable (median DOR, 18.9 months). The 6-month PFS rate was 16.3 %, and the 12-month OS rate was 41.7 %. There were no discontinuations or deaths due to treatment-related AEs. Grade-3/4 treatment-related AEs occurred in 23.3 %. The authors concluded that together with the monotherapy data, these results indicate activity of durvalumab in patients with ED-SCLC. Ongoing trials include the phase II, open-label BALTIC study investigating durvalumab plus tremelimumab in platinum-refractory patients and the phase III CASPIAN trial into first-line durvalumab with or without tremelimumab plus platinum-based chemotherapy *versus* chemotherapy alone.

Compelling activity of second-line lurbectedin monotherapy

Lurbinectedin is a new anti-cancer drug that blocks transcription and induces DNA double-strand breaks, leading to apoptosis. Trigo et al. presented the results of 61 SCLC patients treated in a multicentre phase II basket trial that is assessing the efficacy and safety of lurbinectedin 3.2 mg/m^2 Q3W in several types of advanced solid tumours [9]. The SCLC group had received one prior chemotherapy line. Brain metastases

TABLE
Outcomes obtained with lurbenectedin according to chemotherapy-free interval

Response	CTFI < 90 days (n = 27)	CTFI ≥ 90 days (n = 34)	Total (n = 61)
ORR (95 % CI; %)	33.3 (16.5-54)	44.1 (27.2-62.1)	39.3 (27.1-52.7)
Clinical benefit (95 % CI; %)	44.4 (25.5-64.7)	55.9 (37.9-72.8)	50.8 (37.7-63.9)
DCR (95% CI; %)	63 (42.4-80.6)	82.4 (65.5-93.2)	73.8 (60.9-84.2)
DOR (95 % CI; %)	4.1 (1.3-5.1)	6.2 (5.3-NR)	6.2 (3.0-8.8)
PFS (95 % CI; %)	3.4 (1.2-5.7)	4.2 (2.6-7.4)	4.1 (2.6-5.7)
OS (95% CI; %)	8.1 (4.4-14.0)	15.8 (9.6-17.6)	11.8 (9.6-15.9)

CTFI, chemotherapy-free interval; ORR, overall response rate; DCR, disease control rate; DOR, duration of response; PFS, progression-free survival; OS, overall survival; NR, not reached

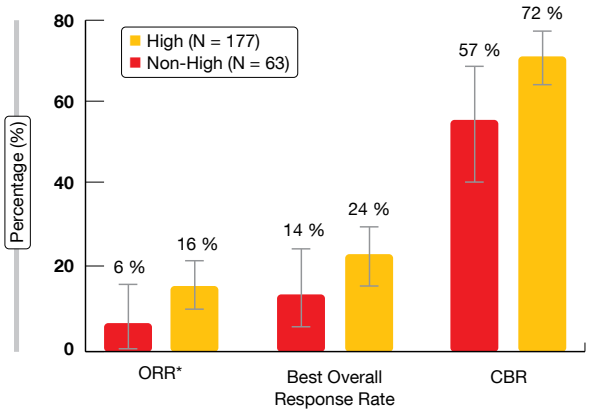
were not allowed. For this analysis, the population was split up according to the chemotherapy-free interval (CTFI); 34 and 27 patients had a CTFI of ≥ 90 and < 90 days, respectively.

The group with prolonged CTFI was shown to fare better with respect to ORR, clinical benefit, disease control rate, DOR, PFS, and OS **(Table)**. At 6 months, 36.3 % of patients in the overall population were alive and progression-free; these proportions were 42.8 % and 28.1 % for CTFI ≥ 90 and < 90 days, respectively. Likewise, OS rates at 12 months were 59.1 % and 22.9 %. The safety profile observed in this population was acceptable and well tolerated, with no unexpected toxicity or drug-related deaths. According to the investigators, these results suggest that single-agent lurbinectedin can be considered as an alternative therapy for patients with relapsed SCLC.

Rova-T in the third-line setting

A novel target in neuroendocrine tumours is the atypical inhibitory Notch ligand delta-like protein 3 (DLL 3). It is expressed on both cancer stem cells and tumour cells, but not on normal adult tissues. More than 85 % of SCLC express DLL3, although it is not prognostic of outcomes on standard therapy. The antibody-drug conjugate rovalpituzumab tesirine (Rova-T™) has been developed to target DLL3. A phase I study demonstrated an ORR of 16 % in 56 patients with recurrent SCLC; here, those with the highest DLL3 expression responded in 31 % and experienced a median OS of 5.8 months [10].

The phase II, single-arm TRINITY trial tested Rova-T 0.3 mg/kg (2 doses, 6 weeks apart) in 339 patients with DLL3-expressing, relapsed or refractory SCLC who had already been treated with ≥ 2 previous regimens containing at least 1 platinum-based regimen [11]. Re-treatment was permitted at progression. Seventy percent of the patients participating in TRINITY were defined as DLL3-high, i.e. ≥ 75 % of cells in their tumours expressed DLL3. Stable CNS metastases were allowed. Among the 339 patients enrolled, 23 % were resistant or refractory to first-line platinum therapy. Seventy-seven percent had been pre-treated with 2 lines. Brain metastases were present in 40 %, and 25 % had a history of pleural effusions.



ORR, overall response rate; CBR, clinical benefit rate

Figure 2: ORR, best overall responses and clinical benefits in DLL3-high and DLL3–non-high patients

Clinical benefits in > 70 %

ORR constituted the primary endpoint. According to the investigators, ORR was 18.0 % in the entire cohort and 19.7 % in the DLL3-high subgroup. These results were 12.4 % and 14.3 % per IRC. Median OS amounted to 5.6 and 5.7 months for the overall group and the DLL3-high patients, respectively. Response rates appeared to be higher in the third- and fourth-line settings (29 % and 23 % for third and fourth line, respectively, according to investigator). Importantly, clinical benefit rates (complete and partial responses plus disease stabilisations) were > 70 % in the third and fourth line according to both investigator and IRC. The responses seemed to be enriched in the group with high DLL3 expression. There was a tendency to improvement in ORR, best overall response rate and clinical benefit rate in the DLL3-high patients as opposed to those with non-high, but positive DLL3 expression **(Figure 2)**. Approximately 40 % of responses occurred after 10 weeks of treatment initiation. DOR by IRC was 4.1 and 2.8 months in the third- and fourth-line setting, respectively. IRC-assessed PFS and OS among DLL3-high patients in all lines were 3.8 and 5.7 months, respectively.

Drug-related serious AEs occurred in 30 %, and grade ≥ 3 AEs in 40 %. Ten fatal AEs (3 %) occurred during the study due to generalised oedema, pneumonitis, ascites, drug-induced liver injury, pleural effusion, pneumothorax, respiratory failure, and sepsis. In 5 %, AEs led to discontinuation. The most common AEs included photosensitivity reactions (35 %), pleural effusions (28 %), fatigue (28 %), peripheral oedema (26 %), and thrombocytopenia (22 %). The risk of high-grade serosal effusions appeared to be increased in patients who had already developed effusions before treatment.

The investigators concluded that Rova-T is an active agent in SCLC beyond the second treatment line, where currently no therapies are approved. Rova-T is being evaluated in the MERU and TAHOE phase III studies that are assessing this drug in frontline maintenance and in the second-line setting, respectively. Multiple phase I trials are also ongoing; these are testing Rova-T in combination with chemotherapy, nivolumab, and nivolumab/ipilimumab.

What happens after SCLC transformation?

Three to 10 % of *EGFR*-mutant adenocarcinomas transform to high-grade neuroendocrine carcinoma, including SCLC, at acquired resistance to TKI treatment [12]. Cases of *de novo* SCLC harbouring an *EGFR* mutation have been reported [13]. As characteristics and clinical course of SCLC-transformed *EGFR*-positive lung cancer were largely unknown, Marcoux et al. retrospectively reviewed 67 patients with *EGFR*-mutant SCLC [14]. At initial diagnosis of metastatic cancer, 58 (87 %) had pathology consistent with NSCLC, and 9 (13 %) had evidence of SCLC. Five had pure SCLC, and 4 had mixed histology that included a SCLC component. The patients received a median of 2 systemic treatment lines before transformation.

At the time of transformation, 93 % were treated with an EGFR TKI. Median time between the initial diagnosis of metastatic NSCLC and the first evidence of SCLC was 17.8 months.

All genotyped patients kept their founder *EGFR* mutation at transformation. The majority of previously T790M-positive patients (79 %) no longer had T790M detected at the time of transformation. *TP53*, *RB1* and *PIK3CA* mutations were the next most frequently observed genetic alterations. Median OS from initial diagnosis of metastatic lung cancer (31.5 months) was similar to the expected OS in *EGFR*-mutant patients that never transform to SCLC, and median OS from first evidence of *EGFR*-mutant SCLC (10.9 months) was similar to what is seen with *de novo* SCLC. Responses to platinum-etoposide and taxanes were frequent, but transient. Importantly, the analysis revealed no responses to checkpoint inhibitor therapy. The authors summarised that further investigation is required to better elucidate the optimal diagnostic and therapeutic approach for these *EGFR*-mutant tumours. ■

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Comprehensive sequencing of plasma cell-free DNA permits non-invasive cancer detection

Early detection of lung cancer is a highly unmet medical need. Even though low-dose computed tomography (LDCT) has been shown to improve lung cancer mortality in high-risk individuals [1], the rate of clinical adoption remains low at 1.9 % [2, 3]. Cell-free DNA (cfDNA) testing might substitute LDCT as a screening tool, according to preliminary results of the Circulating Cell-free Genome Atlas (CCGA) Study presented at the ASCO Congress [4].

CCGA is a prospective longitudinal cohort study designed for early cancer detection. Approximately 15,000 participants will be enrolled, 70 % of whom have cancer, while 30 % do not. In the non-cancer participants, benign comorbid conditions are not excluded, making it a real-world population. The cancer patients have been diagnosed with any malignancy. Non-cancer and cancer participants are enrolled from the same institutions to control for pre-analytical variability due to geographic distribution. Blood samples and clinical data are collected from all participants; tissue samples are obtained from the cancer patients.

Characterisation of cancer-specific cfDNA signals

Genome-based screening calls for a broad approach. The researchers apply extensive sequencing of blood samples, including targeted and whole-genome sequencing of cfDNA and white blood cells (WBCs), targeted and whole-genome bisulfite sequencing of cfDNA, and whole transcriptome sequencing of cell-free RNA. This allows for characterisation of all major somatic and epigenetic cfDNA features. Correction for WBC variants is performed, as these are a major source of interference. Tumour tissue undergoes whole genome sequencing. During the 5-year follow-up, patients with cancer are followed up with regard to treatment, recurrence and mortality; in the non-cancer group, any new cancer diagnosis is assessed, as well as treatment and mortality.

More than 12,000 participants have been enrolled at 142 sites in the USA and Canada to date. At the ASCO Congress, the results obtained in a pre-specified case-control sub-study comprising 2,800 participants were presented. This population was divided into a training set (n = 1,406; 118 patients with lung cancer) and an independent test set (n = 834; 46 patients with lung cancer) intended for verification of the findings. Indeed, comprehensive sequencing of plasma cfDNA was shown to generate high-quality data across the spectrum of genomic features, permitting non-invasive cancer detection. The assays used detected lung cancer across stages, histologies, and populations. Importantly, WBC-derived mutations and copy num-

ber variations proved a major source of potential false positives and must be accounted for to achieve high specificity. Together, these early results support the promise of using cfDNA-based sequencing to develop an early cancer detection test with high specificity. Further assay and clinical development in large-scale clinical studies is ongoing. ■

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Distinct somatic genome variations in young lung cancer patients

Lung cancer in young adults is relatively rare, but it is considered a unique subgroup with distinct biology [1]. In patients aged ≤ 40 years, the incidence of lung cancer has been found to be 4 % [2], and in those aged ≤ 45 years, 5.3 % [3]. Characteristically, women are more often affected than men; adenocarcinoma prevails, and the stage of disease is frequently advanced at the time of the diagnosis. Of course, these patients usually receive aggressive treatment.

According to recent studies in young lung cancer patients, actionable genomic targets such as *EGFR* and *ALK* aberrations might be more enriched in this population [2]. There was also a trend with regard to *HER2* and *ROS1* alterations. Hsu et al. found no significant difference in survival between young lung cancer patients with and without *EGFR* mutation [4]. However, the broader genomic landscape and related oncogenic pathways are not fully understood yet.

Overlap with TCGA genes

Therefore, Wu et al. performed whole exome sequencing based upon paired normal blood DNA and formalin-fixed, paraffin-embedded genomic DNA in 27 Chinese NSCLC patients aged ≤ 45 years (median, 40; range, 31–45) [5]. Adenocarcinoma was present in 18 patients, and 21 were female. All of them had never smoked or did not smoke at the time of diagnosis. The investigators identified adenocarcinoma (AD) and squamous-cell carcinoma (SC) somatic variants, ending up with 288 and 151 AD and SC variants, respectively. Among genomic variant types, frameshift variants and missense variants predominated in both AD and SC **(Figure)**. For both histologies, insertion or deletion polymorphisms (indels) were present in approximately 60 % and SNPs in approximately 40 %. The majority of mutated genes in both cohorts overlapped with the mutated genes obtained in the young NSCLC The Cancer Genome Atlas (TCGA) cohort for each disease subtype (i.e., 86 of 94 AD mutated genes and 41 of 48 SC mutated genes).

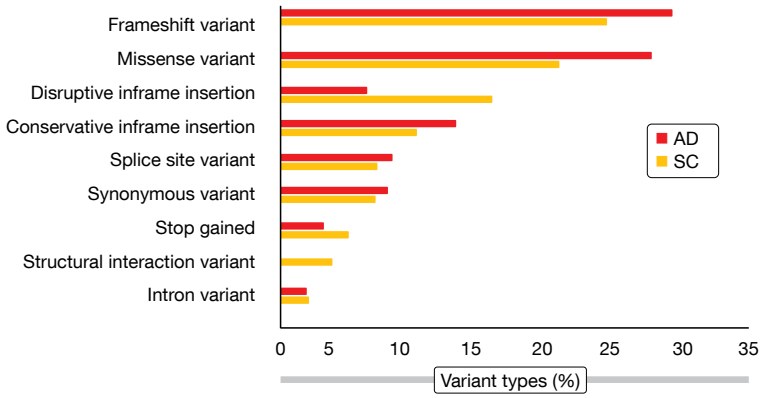

Figure: Genomic variant types in young patients with adenocarcinoma (AD) or squamous-cell carcinoma (SC) of the lung

Genes with predicted high-impact mutations were selected for the pathway analysis, which yielded somatically altered candidate pathways that differed across histologies. For example, ERK/MAPK signaling and PTEN cell cycle arrest were altered in AD, but not in SC. Conversely, this was true for Trk/PI3K signaling and ADP ribosylation/DNA repair, among others, in SC, but not in AD. Further bioinformatic analyses are ongoing to compare the mutated genes and pathways in young patients with older TCGA cohorts. ■

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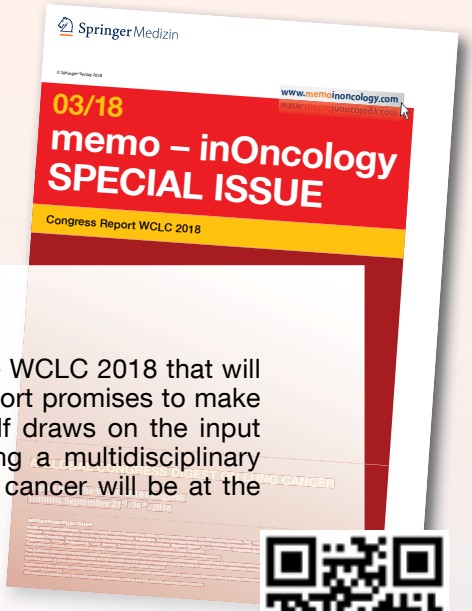

Forthcoming Special Issue

This special issue will be offering a synopsis from the WCLC 2018 that will be held in Toronto, in September of this year. The report promises to make for stimulating reading, as the WCLC 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.

WCLC 2018
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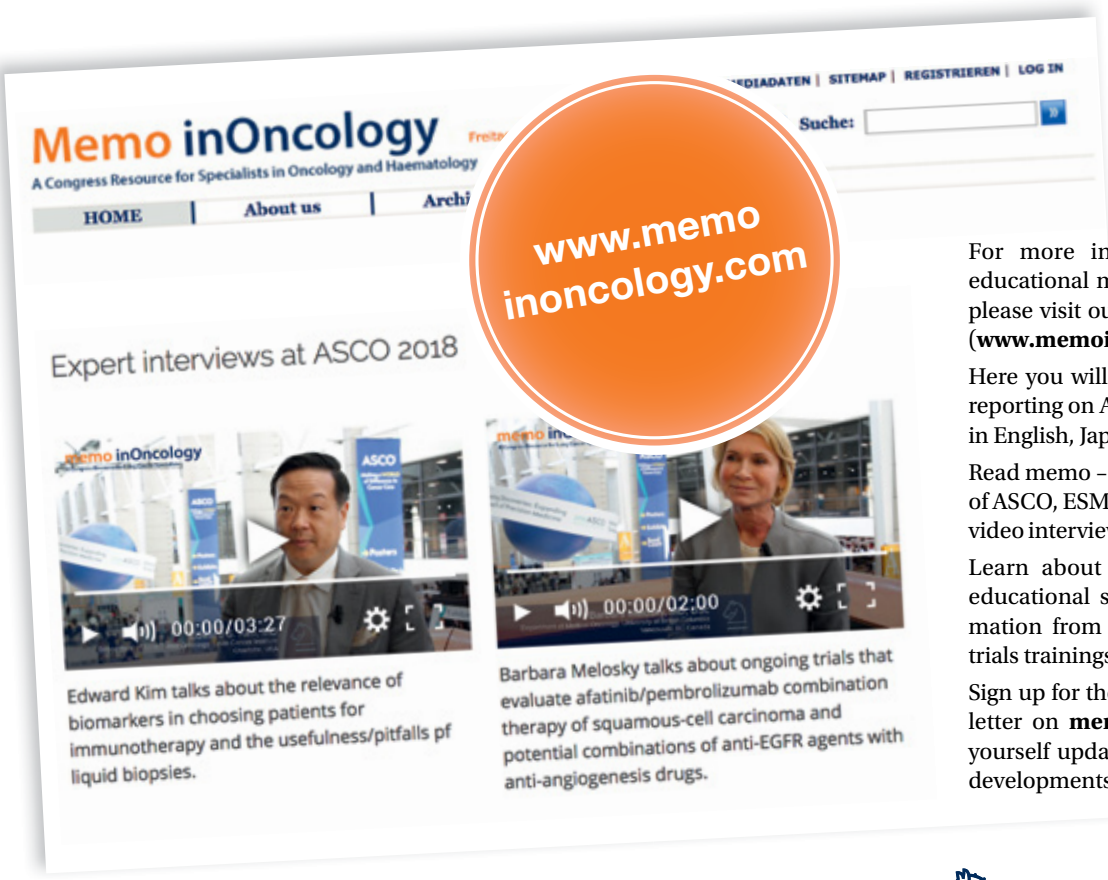
TORONTO, CANADA, SEPTEMBER 23–26, 2018



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