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Congress Report ESMO 2016

A GLOBAL CONGRESS DIGEST ON LUNG CANCER

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Preface

Dear Colleagues,

According to an estimate by the World Health Organization, 1.37 million people worldwide die of lung cancer every year. Both incidence and lung-cancer–related mortality are substantial: to date, primary lung cancer remains the most common malignancy after non-melanocytic skin cancer, and the global numbers of patients dying from it exceed those linked to any other malignancy.

However, profound changes have been a notable development with respect to lung cancer over the last years. For one thing, shifts with regard to histology can be observed across the globe. The proportion of patients with small-cell lung cancer has been decreasing in frequency in many countries over the past two decades. Non-small lung cancer has undergone transformation concerning the relative importance of its predominant subtypes during the same period. In the USA, squamous cell carcinoma has decreased, while adenocarcinoma has increased in both genders. Similar trends apply to European men, while in women, both squamous-cell carcinoma and adenocarcinoma are currently on the rise.

Of course, from a clinician's point of view, therapeutic innovation is the more spectacular part of lung-cancer–related changes. Novel approaches address targets that are not confined to the tumour cell, which had been at the centre of treatment considerations for a long time. Once again, immunotherapy was a hot topic at the ESMO 2016 Congress that took place in Copenhagen from 7th to 11th October. Renowned speakers presented four late-breaking abstracts on immunotherapeutic agents in advanced lung cancer at the second Presidential Symposium, which drew throngs of congress attendees. The results of these trials are presented in this publication, along with other findings in the field of immunotherapy.

Meanwhile, research has been ongoing with regard to druggable genetic aberrations within the tumour cell. Tyrosine kinase inhibitors like vandetanib and lenvatinib have shown promising clinical activity in *RET*-positive tumours, and convincing results were obtained with the next-generation ALK inhibitors ceritinib, alectinib and brigatinib. Recent

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insights into the EGFR landscape shed light on the refined use of EGFR-targeted drugs. At the same time, patients with small-cell histology find themselves entitled to share in the benefits conferred by molecularly targeted therapy. Aurora kinase A inhibition is a promising approach here, as is the PD-L1 antibody atezolizumab. Finally, the disruption of tumour angiogenesis contributes to tailoring treatment to each patient's needs. Individualised therapy has become a reality for the benefit of a large number of present and future patients.

Silvia Novello, MD, PhD,
University of Turin, Italy

Immune checkpoint inhibition: the picture is slowly completing itself

KEYNOTE-024: first-line, PD-L1–enriched population

The anti–PD-1 antibody pembrolizumab has been approved for treatment of patients with PD-L1–expressing, advanced NSCLC. The KEYNOTE-024 study focused on the first-line comparison of pembrolizumab with platinum-doublet chemotherapy [1]. Chemotherapy regimens comprised five options, two of which (pemetrexed plus carboplatin; pemetrexed plus cisplatin) were used with non-squamous non-small–cell lung cancer (NSCLC) only. In all, 305 patients were randomised across 142 sites in 16 countries. The population was enriched for PD-L1 expression, as a key eligibility criterion was PD-L1 tumour proportion score (TPS) ≥ 50 % (i. e., PD-L1 expression on at least 50 % of tumour cells). Approximately 20 % of patients had tumours with squamous histology.

The progression-free survival (PFS) obtained with pembrolizumab was significantly greater than that with the platinum-doublet chemotherapy, which translated into a risk reduction of 50 % (10.3 vs. 6.0 months; HR; 0.50; $p < 0.001$; **Figure 1**). PFS at 12 months was 48 % *versus* 15 % for patients with pembrolizumab and chemotherapy, respectively. Patients treated with pembrolizumab also experienced significant OS benefit despite 50 % total crossover from chemotherapy (HR, 0.60; $p = 0.005$). Median OS had not been reached in either arm. At 12 months, 70 % *versus* 54 % of the patients, respectively, were alive. Likewise, the confirmed objective response rate (ORR) differed by 17 % in favour of pembrolizumab (45 % vs. 28 %; $p = 0.0011$).

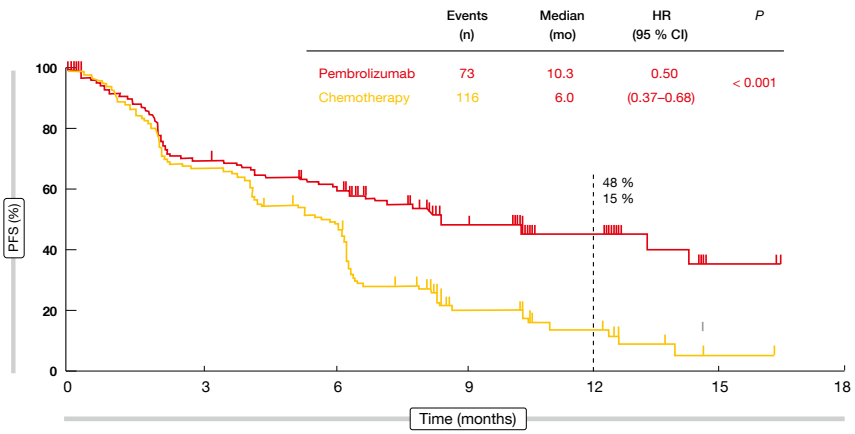


Figure 1: Progression-free survival in KEYNOTE-024: benefit obtained with pembrolizumab compared to chemotherapy

Six complete responses were observed with the anti-PD-1 antibody. Despite longer exposure to pembrolizumab (7.0 vs. 3.5 months), adverse event (AE) rates of all grades were lower in the experimental arm. The Data Monitoring Committee recommended stopping the trial because of this superior efficacy with pembrolizumab.

According to the authors, a PD-L1 TPS ≥ 50 % is detected in approximately one third of patients with advanced NSCLC, and this identifies those most likely to benefit from anti-PD-1 therapy. Pembrolizumab should become a new standard of care as first-line therapy for advanced NSCLC with high levels of PD-L1 expression.

Pembrolizumab plus chemotherapy: KEYNOTE-021

There is a rationale for combining chemotherapy and immunotherapy, as chemotherapy itself has several immunological effects and can induce PD-L1 expression on tumour cells. Clinical data in this area were provided by the multi-cohort phase I/II KEYNOTE-021 trial that evaluated pembrolizumab-based combination therapy for patients with advanced NSCLC [2]. The patients in Cohort G of this study, who had untreated stage IIIB or IV non-squamous NSCLC, were randomised to either pembrolizumab 200 mg every 3 weeks for 2 years plus carboplatin and pemetrexed (n = 60), or carboplatin plus pemetrexed only (n = 63). Pemetrexed maintenance therapy was permitted.

The objective response rate (ORR) according to blinded independent central review, which was defined as the primary endpoint, was almost doubled with the addition of pembrolizumab to chemotherapy (55 % vs. 29 %; p = 0.0016; **Figure 2**). In the responding population, the time to response was shorter in the experimental arm than in the control arm (1.5 vs. 2.7 months), and a higher percentage of patients showed ongoing responses in the experimental arm (88 % vs. 78 %). Of note, only two pembrolizumab-treated patients experienced primary progression of disease at the initial assessment of 6 weeks (i. e., 3 % vs. 17 % in the control arm). The ORRs were similar for PD-L1 expression of < 1 % and ≥ 1 % in the pembrolizumab arm.

Progression-free survival favoured the pembrolizumab combination, and here the risk of progression or death was nearly halved, with PFS for pembrolizumab plus chemotherapy exceeding 1 year (13.0 vs. 8.9 months; HR, 053; p = 0.0102). OS did not differ between

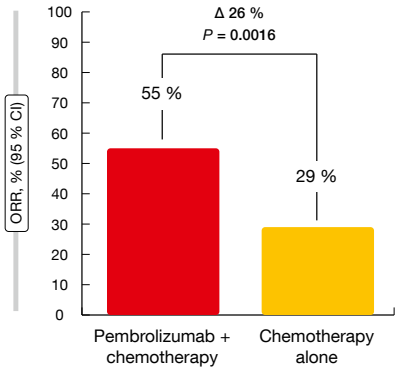


Figure 2: Confirmed objective response rates in KEYNOTE-021

the two arms. At 6 months, 92 % of patients were alive with both treatment regimens. Grade 3/4 AEs were more frequent with the pembrolizumab combination, but this did not translate into higher discontinuation rates. Overall, pembrolizumab in combination with carboplatin and pemetrexed appears to be an effective treatment option for patients with chemotherapy-naïve, advanced non-squamous NSCLC.

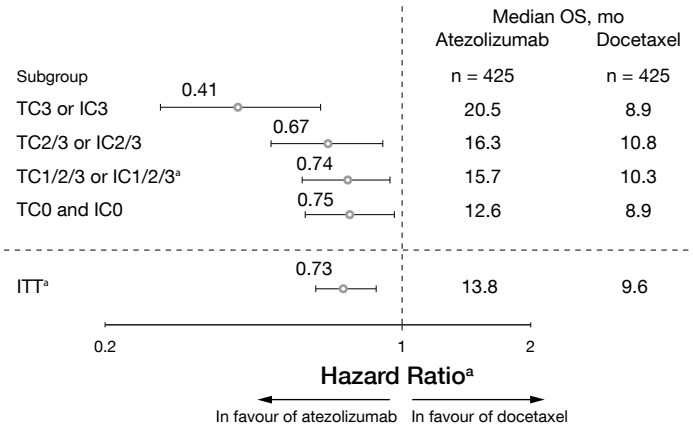
OS improvement of 4 months with atezolizumab in OAK

The anti–PD-L1 antibody atezolizumab showed superiority with regard to OS over docetaxel in patients with advanced NSCLC in the phase II POPLAR study [3, 4]. In the randomised phase III setting, the OAK trial compared atezolizumab 1,200 mg every 3 weeks with docetaxel 75 mg/m^2 every 3 weeks, in patients with locally advanced or metastatic NSCLC who had received one or two prior lines of chemotherapy, including at least one platinum-based regimen [5]. Patients were recruited regardless of their PD-L1 expression status. Crossover was not allowed. The co-primary endpoint consisted of OS in the ITT population and OS in patients with PD-L1 expression on ≥ 1 % of their tumour cells (TCs) or immune cells (ICs). The OAK data are the first phase III results obtained for a PD-L1–directed antibody, with a total of 1,225 patients projected to be recruited into the study.

The analysis of the first 850 patients showed that OAK met its co-primary endpoint. In the ITT population, atezolizumab treatment was associated with significant and clinically meaningful OS benefit (13.8 vs. 9.6 months; HR, 0.73; p = 0.0003). The survival curves separated early on, at 3 months, and remained separated over time. At 18 months, almost twice as many patients were alive in the atezolizumab arm as in the docetaxel arm (40 % vs. 27 %). A comparable OS benefit was observed for the 55 % of the patient population with PD-L1 expression on ≥ 1 % of their TCs or ICs (TC1/2/3 or IC1/2/3) (15.7 vs. 10.3 months; HR, 0.74, p = 0.0102). However, the subgroups of patients with no or minimal PD-L1 expression (< 1 %; TC0 and IC0) also benefited, with a similar HR of 0.75 (12.6 vs. 8.9 months; p = 0.0205). The greatest OS improve-

ment occurred in the group with the highest PD-L1 expression (on ≥ 50 % of TCs or ≥ 10 % of ICs; TC3 or IC3), which made up 16 % of the total population. Here, the OS benefit achieved with atezolizumab treatment translated into 59 % reduction in mortality risk (median OS, 20.5 vs. 8.9 months; HR, 0.41; p < 0.0001).

As the forest plot for OS by PD-L1 expression shows **(Figure 3)**, the HRs were comparable across all of the subgroups, except for those with the highest expression, where the patients experienced even greater benefit. The OS benefit conferred by atezolizumab is further supported by the 17 % of patients who were randomised into the chemotherapy arm who subsequently received immunotherapy.



[a]Stratified HR for ITT and TC1/2/3 or IC1/2/3. Unstratified HR for subgroups.

Figure 3: OAK trial: OS according to PD-L1 expression for atezolizumab and docetaxel

Additional analyses

As patients with both non-squamous and squamous histological subtypes were included in the OAK trial, the investigators also assessed the OS effects of the treatments in these subgroups. In both cohorts, the HRs were 0.73 in favour of atezolizumab. A similar OS advantage was seen across most subgroups irrespective of gender, age, ECOG performance status, number of prior treatment lines, smoking history, and baseline CNS metastasis. The only exception to this were patients with *EGFR*-activating mutations, who did not benefit from this treatment with the anti–PD-L1 antibody. This phenomenon has already been observed with other PD-L1 inhibitors.

As in previous trials assessing immunotherapy, significant PFS benefit was only seen for the group of patients with the highest PD-L1 expression. Accordingly, response rates only showed benefit for atezolizumab in this high-expression subgroup. Generally, responses lasted considerably longer in the atezolizumab arm than in the docetaxel arm (median duration of response for ITT population, 16.3 vs. 6.2 months). This effect was seen across all of the PD-L1 subgroups.

In spite of the prolonged duration of therapy, atezolizumab was well tolerated. Grade 3/4 AEs were less frequent in the experimental arm, which also applied to AEs that led to withdrawal, dose modification, delays or interruptions. Only musculoskeletal pain and pruritus occurred more frequently with atezolizumab than with docetaxel; for all of the other AEs, the reverse was the case. Immune-mediated AEs were reported with low incidence rates, at below 1 %.

News from the pivotal pembrolizumab trial

The phase III KEYNOTE-010 study demonstrated the efficacy and safety of pembrolizumab in comparison with docetaxel in 1,034 previously treated patients with PD-L1–expressing, advanced NSCLC [6]. This thus provided the basis for European approval of pembrolizumab for this indication. An updated analysis after six additional months of follow-up showed that OS continued to be superior with pembrolizumab 2 mg/kg and 10 mg/kg compared to docetaxel in the TPS ≥ 50 % and ≥ 1 % populations [7]. PFS was similar to that previously observed, and responses continued to be durable. Overall, these findings confirm pembrolizumab as a standard of care in patients with pre-treated, PD-L1–expressing, advanced NSCLC.

Barlesi et al. assessed the effects of pembrolizumab and docetaxel on health-related quality of life in KEYNOTE-010 using the EORTC QLQ-C30, EORTC QLQ-LC13 and EuroQoL-5D-3L instruments [8]. For changes from baseline to week 12, there were either numeric or significant improvements in the EORTC QLQ-C30 global health status/quality of life scores for pembrolizumab compared to docetaxel. Compared with docetaxel, pembrolizumab also prolonged the time to deterioration for the EORTC QLQ-LC13 composite endpoint of cough, dyspnoea and chest pain. Along with results from the supportive patient-reported outcome analyses, these findings suggest that the patient health-related quality of life and symptoms were maintained or improved to a greater degree with pembrolizumab than with docetaxel in this population.

Two-year data: CheckMate 017 and 057

Nivolumab is a standard of care for previously treated NSCLC patients based on the results of the global, randomised, open-label, phase III CheckMate 017 and 057 trials. In both studies, nivolumab significantly prolonged OS compared with docetaxel in previously treated patients with squamous NSCLC (CheckMate 017) [9] or with non-squamous NSCLC (CheckMate 057) [10].

The updated efficacy and safety data after ≥ 2 years of follow-up were presented at the ESMO Congress [11]. These showed that in both trials, the improved OS rates for nivolumab over docetaxel remained consistent from year 1 to year 2. Among responders, approximately one third of the nivolumab-treated patients (but none of the docetaxel-treated patients) had ongoing responses. Durable responses occurred regardless of PD-L1 expression levels. No new safety signals were identified for nivolumab therapy. Treatment-related selected AEs were managed using protocol-defined toxicity management algorithms, and these were resolved in the majority of patients.

Reck et al. presented data on the impact of nivolumab *versus* docetaxel on

the overall health status of the patients treated in CheckMate 057 [12]. Both the EQ-5D VAS and the Lung Cancer Symptom Scale indicated better preservation of health status, health-related quality of life, and symptom control with nivolumab compared to docetaxel. Also, both of these assessments hinted at relative improvements in patient-reported outcomes for nivolumab over docetaxel, and suggested that the onset of the benefit occurred prior to the separation of the survival curves, which again favoured nivolumab.

Hardly any first-line benefits in CheckMate 026

Negative results were obtained for first-line nivolumab in patients with stage IV or recurrent PD-L1–positive NSCLC. The open-label, international, phase III, CheckMate 026 study compared first-line nivolumab with platinum-based doublet chemotherapy in this population [13]. PD-L1 expression of ≥ 1 % was mandatory. Crossover to nivolumab in the case of progression was optional.
The results for the primary endpoint, which was PFS by independent radiological review in the ≥ 5 % PD-L1–positive population, did not differ significantly between the two regimens (4.2 vs. 5.9 months, for nivolumab and chemotherapy, respectively). This also applied to OS (14.4 vs. 13.2 months). Progressive disease was more common in the nivolumab arm (27.5 % vs. 9.9 %), but when responses were seen, they lasted more than twice as long with nivolumab than in the chemotherapy-treated population (12.1 vs. 5.7 months).

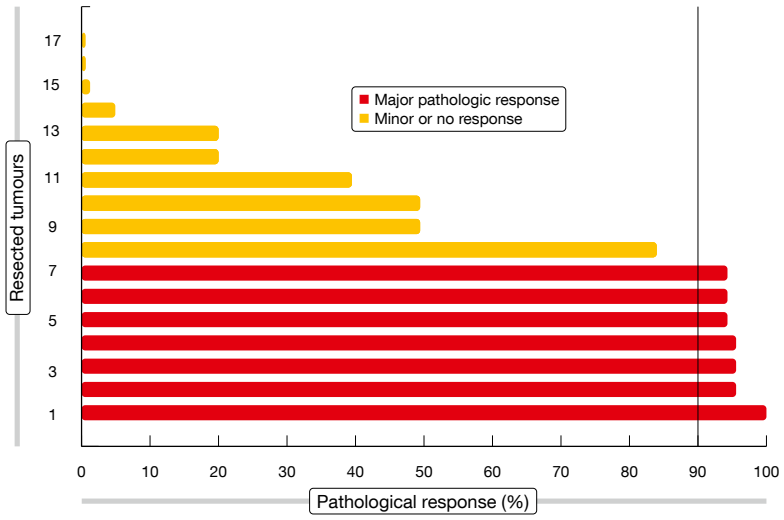


Figure 4: Pathological responses in tumours of 17 patients with early NSCLC after neoadjuvant administration of two nivolumab doses

In general, the subgroups mirrored the overall study population. Whereas patients with squamous histology appeared to fare better with regard to PFS and OS when treated with nivolumab, the opposite appeared to be the case for the non-squamous population; however, definite conclusions cannot be drawn due to the overlapping confidence intervals. The CheckMate 227 trial continues to evaluate the role of nivolumab as monotherapy and in combination with ipilimumab or standard chemotherapy in the first-line setting of stage IV or recurrent NSCLC.

Neoadjuvant use of nivolumab

Preliminary, but aspirational, data have been generated with neoadjuvant nivolumab in a trial that enrolled 18 patients with newly diagnosed, resectable stage I (> 2 cm)/II/IIIA NSCLC [14]. The rationale for neoadjuvant use of anti–PD-1 strategies in early-stage NSCLC results from the fact that stage I to III NSCLC, albeit considered early-stage disease, has poor prognosis, and only modest benefits are seen with adjuvant chemotherapy. Nivolumab was administered at a dose of 3 mg/kg at 4 weeks and 2 weeks prior to surgical resection. The primary endpoint was safety and tolerability. Exploratory endpoints included various correlative analyses of blood and the tumour, as well as other clinical outcome parameters, such as pathological response.

These two neoadjuvant doses of nivolumab did not delay or interfere with the surgical resection in any of the patients. According to exploratory anal-

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yses of the responses, 22 % of the patients had radiographic response, and seven patients showed pathological down-staging from the pre-treatment clinical stage. Major pathological response was defined as < 10 % residual viable tumour cells at resection. One of the seven patients with a major pathological response experienced a pathological complete response **(Figure 4)**. The tumours of these patients showed immune cell infiltration. Toxicity was consistent with the safety profile observed in other studies with nivolumab, and the treatment was well tolerated. One third of patients experienced treatment-related AEs of any grade, but there was only one grade 3/4 AE. Comprehensive studies on aspects such as genomics and functionality of tumour-infiltrating lymphocytes are ongoing, and larger follow-up clinical studies are planned. ■

Next-generation ALK inhibitors excel after crizotinib failure

ALK fusion-gene–positive lung cancer occurs in approximately 5 % of patients with advanced NSCLC [1]. The ALK inhibitor crizotinib demonstrates significant initial efficacy in patients with *ALK*-positive advanced NSCLC.

However, most patients eventually develop resistance, with the central nervous system (CNS) being one of the most common sites of first progression. Approximately half of these patients develop CNS metastases during crizotinib treatment. Next-generation ALK inhibitors represent efficacious options for patients who have progressed on crizotinib.

ASCEND-5

Ceritinib is a next-generation ALK inhibitor with 20-fold greater potency than crizotinib [2]. Anti-tumour effects of ceritinib in pre-treated patients were demonstrated in the ASCEND-1 and ASCEND-2 trials [3–5]. In ASCEND-2, ceritinib treatment promoted durable responses in an *ALK*-positive NSCLC population that had progressed on chemotherapy and crizotinib, including patients with brain metastases [5].

At the ESMO Congress, Scagliotti et al. presented the confirmatory phase III ASCEND-5 study, which compared ceritinib with second-line chemotherapy in the crizotinib-pretreated setting [6]. In this global, randomised, open-label trial, a total of 231 patients with locally advanced or metastatic *ALK*-positive NSCLC were randomised at 99 sites in 20 countries. Prior to study entry, they had received one or two chemotherapy regimens for advanced disease, as well as crizotinib (at any time). The treatment consisted of either ceritinib 750 mg/day or chemotherapy with pemetrexed or docetaxel. PFS was defined as the primary study endpoint. In each arm, more than half of the patients had metastatic brain disease, and radiotherapy had been administered to the CNS in one third of these cases.

Ample benefits with ceritinib treatment

This ALK inhibitor therapy proved highly efficient, promoting statistically significant and clinically meaningful improvement in PFS according to the blinded independent review committee (BIRC; 5.4 vs. 1.6 months; HR, 0.49; p < 0.001). This effect was robust and consistent across a number of subgroups. Clinical benefit was further supported by ORR (39.1 % vs. 6.9 %) and DCR (76.5 % vs. 36.2 %). OS data were immature at the data cut-off. The safety profile matched the observations in prior ceritinib studies, which featured primarily diarrhoea, nausea, vomiting, and transaminase elevation.

The analysis of patient-reported outcomes showed that compared with chemotherapy, ceritinib significantly improved lung-cancer specific symptoms and overall health status. While the majority of symptoms assessed with the QLQ-C30 questionnaire improved with ceritinib treatment, some deterioration was observed with the ALK inhibitor according to two scales for gastrointestinal symptoms (i.e., diarrhoea, nausea and vomiting). The authors concluded that these results establish ceritinib as a preferred treatment option in patients with crizotinib-resistant *ALK*-positive NSCLC.

Long-term follow-up of ASCEND-3: remarkable findings

Felip et al. presented the long-term follow-up of the global, phase II, single-arm, open-label ASCEND-3 study, which assessed ceritinib in 124 patients with metastatic *ALK*-positive NSCLC who had received no prior ALK inhibitor treatment [7]. They were either chemotherapy-naïve (although only two patients) or had been treated with up to three lines of chemotherapy and had experienced progression during or after the last chemotherapy regimen. Asymptomatic or neurologically stable brain metastases at baseline were allowed. Forty percent of patients had brain lesions at study entry; local radiotherapy had been applied in 53.1 %. The primary endpoint was ORR according to the investigator.

After a median follow-up of 25.9 months, 48.4 % of patients remained on treatment. With regard to whole-body

TABLE
Whole-body efficacy observed with ceritinib in the ASCEND-3 study, according to the investigator and the blinded independent review committee (BIRC)

	Investigator	BIRC
ORR, n (%)	84 (67.7)	79 (63.7)
Best overall response, n (%)		
CR	1 (0.8)	1 (0.8)
PR	83 (66.9)	78 (62.9)
SD	27 (21.8)	20 (16.1)
Non-CR/non-PD*	1 (0.8)	8 (6.5)
PD	5 (4.0)	9 (7.3)
Unknown	7 (5.6)	8 (6.5)
DCR (CR + PR + SD + non-CR/non-PD*), n (%)	112 (90.3)	107 (86.3)
Median DOR, months	22.1	23.9
Estimated 18-month DOR rate, %	55.7	60.4
Median PFS, months	16.6	18.4
Estimated 18-month PFS rate, %	49.1	51.7
Median OS	Not yet reached at data cut-off	

* Includes patients who did not have target lesions at baseline per BIRC assessment and who qualify for neither CR nor progressive disease.
BIRC, blinded independent review committee; ORR, objective response rate; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; DOR, duration of response

efficacy, the analysis yielded robust ORR findings of 67.7 % according to the investigator, and 63.7 % according to the BIRC **(Table)**. Decreases in tumour burden from baseline occurred in 94.7 % of patients. Disease control was obtained in 90.3 % and 86.3 % according to the investigator and the BIRC, respectively. The study revealed remarkable results with regard to median PFS (16.6 and 18.4 months according to the investigator and the BIRC, respectively) and OS: at 24 months, 67.5 % of the patients were alive, and median OS had not been reached yet. Ceritinib also showed activity in patients with brain metastases. Those with CNS lesions at baseline achieved a whole-body ORR of 57.1 % and a median PFS of 10.8 months. Overall intracranial responses were obtained in 61.5 %.

Updated patient-reported outcomes at a follow-up of up to 29 cycles were consistent with those previously reported. The patients showed improvements in symptoms burden from baseline with a mean change in the overall Lung Cancer Symptom Scale score that ranged from -3.39 to -14.83. Quality of life was maintained on treatment.

Alectinib: update on pivotal data

The highly selective and potent oral ALK inhibitor alectinib has been approved by the FDA for the treatment of patients who have progressed on, or are intolerant to, crizotinib. Two pivotal phase II studies, the global NP28673 trial and the North American NP28761 trial, formed the basis of this approval [8–11]. They enrolled a total of 225 previously treated patients with locally advanced or metastatic *ALK*-positive NSCLC, who had progressed after prior crizotinib treatment. All patients received alectinib 600 mg orally twice daily.

The updated safety and efficacy analysis of the NP28673 study was presented at ESMO 2016, and these demonstrated robust efficacy and good tolerability of alectinib, both systemically and in the CNS [12]. ORR in response-evaluable patients was 50.8 % according to the independent review committee. Chemotherapy-naïve patients benefited to a greater extent than those who had received prior chemotherapy (ORR, 73.1 % and 44.8 %, respectively). DCR was 78.7 % in response-evaluable individuals. Median PFS was 8.9 months in the intention-to-treat population, and median OS was 26.0 months. The patients with measurable CNS disease at baseline had a CNS ORR of 58.8 %.

An exploratory analysis assessed the time to response in both NP28673 and NP28761 [13]. Determination of how rapidly patients can benefit from alectinib was rated as important for both symptomatic patients and patients at the point of developing symptoms, particularly within the CNS. In addition, rapidity of response is of relevance for those with active CNS disease, as an area of high unmet medical need. The findings showed that alectinib therapy can achieve a rapid response. Most patients in all populations showed a RECIST response by the first assessment (8 weeks in NP28673, and 6 weeks in NP28761). This also applied to time to CNS response in patients with measurable and/or non-measurable CNS disease at baseline, irrespective of prior radiotherapy. Further investigation into the early clinical benefit (<6 weeks) is warranted, to evaluate alectinib for initial treatment of CNS metastases, with the potential for sparing radiation therapy.

Substantial anti-tumour activity of brigatinib

An ongoing phase I/II, single-arm, multicenter dose-escalation, dose-expansion trial is evaluating the investigational next-generation ALK inhibitor brigatinib in patients with advanced malignancies, which includes 79 *ALK*-positive NSCLC patients. Ninety percent of them had received prior crizotinib therapy.

Updated data on the activity and safety of brigatinib in *ALK*-positive NSCLC patients after a median time on treatment of 20 months showed that tumour reductions with brigatinib were obtained in almost all of the cases [14]. Thirty-three percent of 72 evaluable patients had a 100 % decrease in target lesions. The confirmed ORR amounted to 62 % with all doses of brigatinib. One-hundred percent of crizotinib-naïve patients achieved confirmed objective responses, including three complete remissions. Disease control was achieved in 87 %. Median PFS had not yet been reached in the crizotinib-naïve population, and was 12.9 months in patients after prior crizotinib. For OS, the

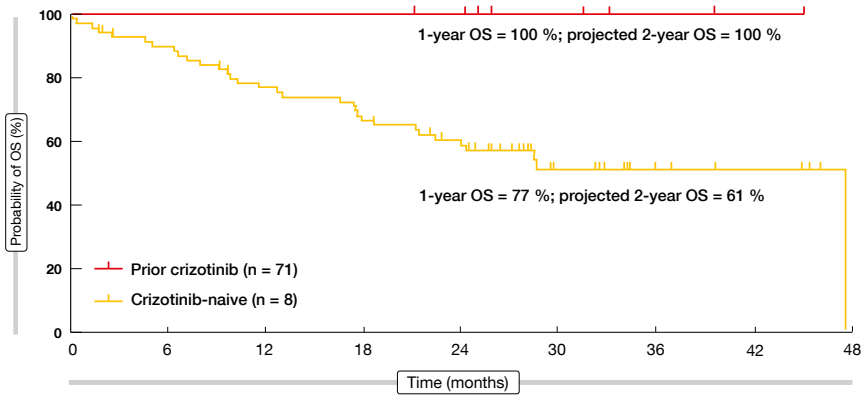

Figure: Overall survival obtained with brigatinib (ITT population)

1-year rates were 100 % and 77 % for these two groups, respectively **(Figure)**. According to the analysis of patients with brain metastases (n = 50), brigatinib was highly active in the CNS. The intracranial ORR was 67 % in patients with measurable baseline disease. Most common treatment-emergent adverse events were nausea, fatigue, diarrhoea, headache and cough.

The results from this phase I/II study support further evaluation of brigatinib at 90 mg/day and 180 mg/day. The international, randomised, dose-evaluation ALTA trial showed that brigantinib has potential as a new treatment option in the crizotinib-resistant setting [15]. A randomised phase III trial of brigatinib *versus* crizotinib has been initiated in ALK inhibitor-naïve patients with advanced *ALK*-positive NSCLC (ALTA-1L; NCT02737501). ■

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Interview: Anders Mellemgaard, MD, PhD, Clinical Associate Professor, Department of Oncology, Herlev University Hospital, Copenhagen, Denmark

"Targeting angiogenesis can prolong life"

How important is anti-angiogenesis in the treatment concept of lung cancer?
Angiogenesis is a very important driver for cancer progression. Some cancers are particularly dependent on the development of new vasculature in order to grow and metastasise. Targeting the vasculature is therefore very useful. Anti-angiogenic compounds are available, such as bevacizumab, which is used primarily in first-line treatment, but now we also have second-line drugs that are applied together with chemotherapy, thus improving its efficacy. When the anti–VEGFR-2 antibody ramucirumab and the triple angiokinase inhibitor nintedanib are added to a common chemotherapeutic agent like docetaxel, they can actually improve OS. There are differences in terms of administration and toxicity profiles between these two compounds, but they are also a proof of concept that targeting angiogenesis is important, and that it

can prolong the life of patients with metastatic lung cancer.

Where do you see anti-angiogenic drugs in the future, considering the plethora of new treatments, such as immunotherapies?

That is a good question, because when everybody was thinking ahead two years ago, I do not think anybody anticipated that today we would be talking about immunotherapies that much. However, I believe that what we need to realize is that any cancer, and this is certainly true for lung cancer, has many subgroups that differ from a biological point of view. Some of these are amenable to immunotherapy, while for others, other kinds of therapy are more suitable. It appears that in the case of rapid progression after first-line therapy, immunotherapies do not work too well. In the CheckMate 057 trial [1], nivolumab was most effective in patients with a longer time interval since their last prior treatment. On the other hand, an analysis of the LUME-Lung 1 study showed that the OS effect of nintedanib plus docetaxel was stronger in patients who had experienced a shorter disease-free interval after first-line treatment **(Table)** [2]. There was a pronounced OS benefit

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watch video

in the group who only showed progressive disease as best response or who were chemo-refractory in the first-line setting. In my opinion, the time interval from first-line to second-line therapy is therefore quite important for the selection of treatment. This has to be considered when discussing the further courses of action with the patient. Immunotherapy might be the best option if the interval is long, and antiangiogenic compounds are preferable if the interval is short.

Are there any biomarkers for anti-angiogenic drugs in the molecular sense yet?

Research is still ongoing to identify biomarkers, but thus far there are no classical markers in the sense of parameters that can be tested in the laboratory. The problem is that angiogenesis is a normal function of the body and is just up-regulated in cancers. We cannot look for biomarkers in the cancer cell itself, because the cell is not involved in the mechanism of action of these agents, but rather the tumour microenvironment. What we do have is a clinical marker, which is the interval from first-line to second-line therapy. ■

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TABLE

Overall survival for the adenocarcinoma population with nintedanib plus docetaxel vs. placebo plus docetaxel according to time from first-line therapy

	OS with nintedanib plus docetaxel (months)	OS with placebo plus docetaxel (months)	OS difference (months)	HR	P-value
All patients	12.6	10.3	2.3	0.83	0.0359
Time from start of first-line therapy*					
< 9 months	10,9	7.9	3.0	0.75	0.0073
< 6 months	9.5	7.5	2.0	0.73	0.0327
Early progressors					
Chemorefractory patients**	9.1	6.9	2.2	0.72	0.0456
PD-FLT	9.8	6.3	3.5	0.62	0.0246
Time from end of first-line therapy*					
< 3 months	11.0	8.0	3.0	0.74	0.0120
3–6 months	12.0	10.6	1.4	0.84	0.3768
> 6 months	18.2	15.8	2.4	0.94	0.7321
≤ 6 months	11.3	8.2	3.1	0.75	0.0047

* Information on the time since first-line therapy was missing for 7 adenocarcinoma patients (4 in the nintedanib arm and 3 in the placebo arm).
** Defined as patients with adenocarcinoma who were randomised within 5 months from start of first-line therapy; this cut-off was based on approximate median PFS and 95% CIs of standard first-line chemotherapy from published studies.
PD-FLT, progressive disease as best response to first-line therapy

EGFR-targeted therapy: at the right time in the right patient

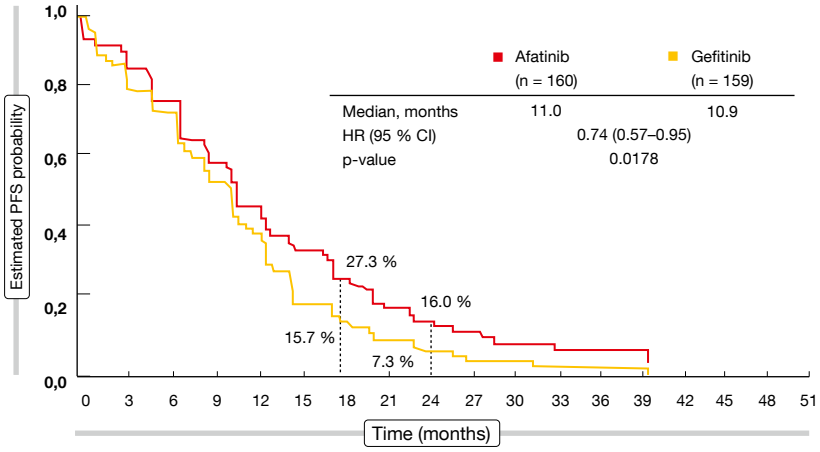

Figure: Progression-free survival according to independent data review with afatinib versus gefitinib in LUX-Lung 7

Approximately 11 % of Caucasian patients with NSCLC have tumours that harbour *EGFR* mutations [1], which occur in exons 18, 19, 20 and 21 of the *EGFR* gene. Common mutations include exon 19 in-frame deletions and the exon 21 Leu858Arg point mutation (L858R) [2]. Exon 20 insertions are known to mediate resistance [3]. Little data are available for the other more uncommon mutations.

The activating *EGFR* mutations sensitise lung tumours to EGFR tyrosine kinase inhibitor (TKI) therapies. The irreversible ErbB family blocker afatinib and the reversible EGFR TKIs gefitinib and erlotinib have been approved for first-line therapy of patients with advanced, *EGFR*-mutation–positive NSCLC. The phase IIb LUX-Lung 7 study is the first prospective, global, randomised trial to compare two EGFR-directed therapies (afatinib, gefitinib) in a head-to-head manner in this setting. A total of 319 patients with *EGFR*-mutated, stage IIIB/IV adenocarcinoma of the lung who had not received any prior treatments for advanced or metastatic disease were randomised to either afatinib 40 mg/day or gefitinib 250 mg/day. According to the primary analysis, when compared to gefitinib, afatinib significantly improved the co-primary endpoints of PFS (hazard ratio [HR], 0.73; p = 0.017) and time to treatment failure (TTF; HR, 0.73; p = 0.007) [4]. Correspondingly, ORR was significantly superior in the afatinib arm (p = 0.008).

LUX-Lung 7: OS analysis and other updated outcomes

At the ESMO Congress, Paz-Ares et al. presented the primary OS analysis of LUX-Lung 7, which yielded a difference of 3 months between these two TKIs in favour of afatinib (27.9 vs. 24.5 months), although this difference did not reach statistical significance (HR, 0.86; p = 0.2580) [5]. Most of the prespecified subgroups derived greater OS benefit from afatinib than gefitinib. The median OS for afatinib was similar across the age subgroups. Also, the OS analyses by mutation subtype favoured afatinib in patients with both deletion 19 and the L858R mutation, although without reaching statistical significance. Forty-six percent in the afatinib arm and 56 % in the gefitinib arm received subsequent EGFR TKI therapy. In those treated with a subsequent third-generation EGFR TKI, median OS was similar for afatinib and gefitinib.

The updated results on PFS and ORR were consistent with the initial data. Relative to gefitinib, afatinib significantly improved PFS (11.0 vs. 10.9 months; HR, 0.74; p = 0.0178; **Figure**) and ORR (73 % vs. 56 %; p = 0.002). At 24 months, PFS rates were 16.0 % *versus* 7.3 %. In patients with the L858R mutation, ORR significantly favoured afatinib (69 % vs. 42 %; p = 0.003), while in those with deletion 19, afatinib gave rise to a numerical ORR advantage (75 % vs. 66 %; p = 0.150). AEs were predictable and manageable, with both TKIs showing equally low rates of treatment discontinuation. Updated quality-of-life data remained similar between the arms. The investigators concluded that the overall data, which were largely positive across multiple clinically relevant endpoints, suggest that afatinib is a more effective treatment option than gefitinib in the first-line setting.

TTF in LUX-Lung 7

Schuler et al. reported results for the co-primary endpoint of time to treatment failure (TTF), which was chosen to reflect real-world clinical practice and treatment guidelines [6]. TTF was defined as the time from randomisation to the time of treatment discontinuation for any reason, including disease progression, treatment toxicity, and death. Patients could remain on treatment beyond progression if deemed beneficial by the physician. Thirty-five percent of patients in the afatinib arm and 29.6 % of those in the gefitinib arm who obtained clinical benefit continued their TKI treatment beyond radiological progression, for median durations of 2.7 and 2.0 months, respectively.

In the overall LUX-Lung 7 population, afatinib provided superior TTF compared to gefitinib (13.7 vs. 11.5 months; HR, 0.73; p = 0.0073). These TTF benefits were generally consistent across the prespecified subgroups (i.e., type of *EGFR* mutation, presence of brain metastases, baseline ECOG performance status, gender, age, ethnicity, smoking history). Significantly greater percentages of patients in the afatinib arm were free of treatment failure at 24 months (25 % vs. 13 %) and at 30 months (15 % vs. 5 %)."

These results are complementary to the PFS and ORR findings in LUX-Lung 7. According to the authors, improved TTF

TABLE 1
Tumour responses obtained with afatinib in pre-treated patients participating in a global named patient use programme

Population	N (%)
Patients with available data[1]	2,862 (72.2[2])
Patients with response assessment reported	1,141 (39.9[3])
- CR	7 (0.6[4])
- PR	260 (22.8[4])
- MR	8 (0.7[4])
- SD	506 (44.4[4])
- PD	360 (31.6[4])
DCR[5]	773 (67.8[4])

1 Same subset as for TTF; 2 Percentage of the total 3,966 patients; 3 Percentage of the subset with TTF reported; 4 Percentage of the subset with response assessment reported; 5 Patients with PR, CR or SD
CR, complete response; PR, partial response; MR, mixed response; SD, stable disease; PD, progressive disease

with afatinib testifies to its general tolerability and the manageability of the associated AEs, and suggests that this drug can confer additional clinical benefit in patients who continue treatment beyond radiological disease progression.

VeriStrat® stratification of afatinib-treated patients

The phase III, global, open-label, LUX-Lung 8 study compared afatinib with erlotinib in patients with stage IIIB/IV squamous-cell NSCLC who had progressed after first-line platinum-doublet chemotherapy. In this trial, afatinib significantly improved OS, PFS and disease control rate (DCR) compared to erlotinib [7].

Goss et al. evaluated the predictive value of the VeriStrat® serum protein test in LUX-Lung 8, using OS as the primary efficacy variable [8]. VeriStrat® can be used to identify patient responses to their tumour by measuring several acute-phase reactant proteins in the blood. This test categorises patients according to a distinct classification algorithm that distinguishes between 'good' (VS-G) and 'poor' (VS-P). Clinical outcomes were analysed with respect to the patient VeriStrat® status in the overall population and in the pre-defined subgroups. Results were obtained for 675 patient samples. Of these, 412 and 263 fell into the VS-G and VS-P categories, respectively.

The VeriStrat® test was shown to have a strong independent stratification effect with these afatinib-treated patients. In the VS-G group, as compared to erlotinib, afatinib gave rise to significant improvements in OS (11.5 vs. 8.9 months; HR, 0.79) and PFS (3.3 vs. 2.0 months; HR, 0.73). In the VS-P group, on the other hand, the OS and PFS did not differ significantly between these two TKIs. The patients who received afatinib experienced significant OS and PFS benefits based on the VS-G group *versus* the VS-P group ($p < 0.0001$ for each). Multivariate analysis showed that VeriStrat® was an independent predictor of OS and PFS in these afatinib-treated patients, regardless of ECOG performance status, best response to first-line therapy, ethnicity, and age. However, there was no significant interaction between the VeriStrat® classification and treatment group for OS or PFS.

Real-world evidence for afatinib in later lines

The named patient use (NPU) programme, which was initiated in May 2010, provides real-world evidence of afatinib use in global clinical practice [9]. Eligibility criteria included advanced or metastatic NSCLC, progression after clinical benefit on erlotinib/gefitinib and/or presence of an activating *EGFR*/*HER2* mutation, exhaustion of all other treatment options, and ineligibility for actively recruiting afatinib trials.

As of January 2016, data were available for 3,966 NSCLC patients from 41 countries across six continents. The patients were heavily pre-treated. Approximately 50 % received afatinib as their fourth or later lines.

Median TTF was 4.4 months for all of these patients for whom the data were available. Similar TTF findings were seen for patients with any *EGFR* mutation, common or uncommon *EGFR* mutations, and *HER2* mutations. The ORR was 23.4 % for all of the patients, with a DCR of 67.8 % **(Table 1)**. Of note, the patients with any *EGFR* mutation and those with common and uncommon *EGFR* mutations showed similar ORRs. Response rates of 19 % and 35 % were seen for the patients with NSCLC harbouring the T790M and exon 20 insertion mutations, respectively. No new or unexpected safety findings were observed in the NPU programme.

Effects in patients with leptomeningeal disease

The central nervous system (CNS) is a common site of recurrence in patients with NSCLC, probably owing to the low penetration of agents into the CNS. Cerebrospinal fluid (CSF) concentration rates of the EGFR TKIs gefitinib and erlotinib were found to be low [10]. However, the combined analysis of patients with brain metastases in the LUX-Lung 3 and 6 trials suggests that afatinib works in the brain [11].

As Tamiya et al. noted in their prospective multi-centre trial including 11 patients with *EGFR*-positive NSCLC and leptomeningeal carcinomatosis [12], treatment with afatinib at the recommended daily dose of 40 mg shows a higher median cerebrospinal fluid (CSF) penetration rate than previously reported. The median blood and CSF levels were 88.2 ng/mL and 1.4 ng/mL, respectively, and the median CSF penetration rate was 1.65 %. Overall, median PFS and OS were 2.0 and 3.8 months, respectively. Particularly patients harbouring uncommon *EGFR* mutations appeared to benefit from afatinib with regard to clinical outcomes.

IMPRESS: gefitinib continuation has detrimental effects

After progression on EGFR TKI therapy, the continuation of this treatment in combination with platinum-based doublet chemotherapy was suggested to be beneficial because of potential tumour heterogeneity at the time of resistance.

TABLE 2
Characteristics of patients with *EGFR* mutations: histology, smoking history, and first-line treatment by subtype

	All patients (n = 1,837)	Exon 18 (n = 102)	Exon 19 (n = 931)	Exon 20 (n = 102)	Exon 21 (n = 702)	p
Histology (n = 1,837)						
Squamous	23 (1.3 %)	0	14 (1.5 %)	2 (2.0 %)	7 (1.0 %)	NS
Adenocarcinoma	1,563 (85.1 %)	87 (85.3 %)	791 (85.0 %)	88 (86.3 %)	597 (85.0 %)	
Large cell	26 (1.4 %)	3 (2.9 %)	14 (1.5 %)	1 (1.0%)	8 (1.1 %)	
NOS	225 (12.2 %)	12 (11.8 %)	112 (12.0 %)	11 (10.8 %)	90 (12.8 %)	
Smoking history (n = 1,158)						
Smoker	142 (12.3 %)	9 (20 %)	68 (11.5 %)	10 (19.2 %)	55 (11.8 %)	0.02
Former smoker	323 (27.9 %)	19 (42.2 %)	152 (25.6 %)	17 (32.7 %)	135 (28.8 %)	
Never-smoker	693 (59.8 %)	17 (37.8 %)	373 (62.9 %)	25 (48.1 %)	278 (59.4 %)	
First-line treatment (all patients, 1,173)						
Adapted to mutation	686 (59 %)	20 (43 %)	350 (59 %)	26 (47 %)	290 (61 %)	0.07
EGFR-TKI	530 (45 %)	11 (23 %)	275 (46%)	8 (15 %)	236 (49 %)	< 0.0001
Chemotherapy	292 (25 %)	16 (34 %)	149 (25 %)	23 (42 %)	104 (22 %)	0.01
Other	351 (30 %)	20 (43 %)	169 (28 %)	24 (44 %)	138 (29 %)	

This prompted the design of the IMPRESS trial. IMPRESS was the first randomised, phase III, multi-national study that investigated continued application of gefitinib plus chemotherapy *versus* chemotherapy alone in patients with *EGFR*-mutated advanced NSCLC who had acquired resistance to first-line gefitinib treatment after initial response. The primary analysis had already shown no statistically significant differences between the two strategies for PFS, ORR and DCR [13].

In agreement with the preliminary OS analysis, the final OS data demonstrated significant inferiority of the gefitinib combination [14]. Median OS was 13.4 months in the gefitinib arm and 19.5 months in the control arm, which translated into an increase in mortality risk of almost 50 % with the addition of gefitinib (HR, 1.44; p = 0.016). Furthermore, all of the subgroup categories favoured the chemotherapy-only treatment. A larger proportion of the patients in the chemotherapy-only arm received EGFR TKI therapy after discontinuation, which might have contributed to their longer survival.

Exploratory plasma biomarker analyses suggested that this OS decrease associated with gefitinib continuation is driven by T790M-positive status. In the T790M-positive subgroup, median OS was 10.8 and 14.1 months with gefitinib and chemotherapy only, respectively (HR, 1.49). Results for the T790M-negative subgroup were inconclusive, however. Caution must be exercised here, because T790M status according to circulating tumour DNA is not always informative. The authors concluded that this first-generation EGFR TKI therapy needs to be stopped at the time of radiological disease progression, due to the risk of survival deterioration seen here for treatment continuation. Patients with T790M-positive status should be

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considered for third-generation EGFR TKI treatment.

Activity of gefitinib and erlotinib in uncommon mutations

A meta-analysis investigated the efficacy of the first-generation EGFR-TKIs gefitinib and erlotinib in patients with uncommon *EGFR* mutations (S768I, L861Q, G719X, R705K, and others) [15]. Out of 6,404 patients from the 13 trials included, 466 (7.3 %) were diagnosed as having uncommon *EGFR* mutations. These patients had received gefitinib and erlotinib as any line of treatment.

In single-arm synthesis, the overall ORRs for uncommon and common mutations were 34 % and 71 %, respectively. Direct comparisons indicated significantly lower responses in patients with uncommon mutations (odds ratio, 0.30). Also, they showed an inferior 6-month PFS rate (odds ratio, 0.44; $p < 0.001$). ORRs were still considerable, however, particularly in complex mutations, i.e., mutations at two or more uncommon mutant sites (64.2 %). The authors therefore stated that first-generation EGFR-TKIs remain an option for the treatment of patients with uncommon mutations, but the decision-making needs to be cautious. The specific efficacies related to each mutation site merit future studies with larger sample sizes.

EGFR mutations: characteristics in a large French cohort

As different molecular properties of *EGFR* mutation subtypes might affect responses to EGFR TKIs and patient outcomes, an observational ancillary study of the French nationwide programme "Biomarkers France" assessed the characteristics of non-small cell lung tumours harbouring *EGFR* mutations on the basis of 18,679 analyses that represented 17,664 patients [16]. After exclusion of *EGFR* wild-type and the T790M mutation, a total of 1,837 patients with *EGFR* mutations were analysed.

Fifty-two percent and 38 % had exon 19 and exon 21 mutations, respectively. Exon 18 and exon 20 mutations were found in 5 % each. Two thirds of the patients were female, and 85.1 % had adenocarcinoma **(Table 2)**. Sixty percent of those with exon 19 mutations and exon 21 mutations were never-smokers, while these proportions were smaller in the populations with uncommon mutations. Patients with exon 19 mutations and exon 21 mutations were more likely to receive first-line EGFR TKI therapy than the other two groups.

The investigators concluded that *EGFR* mutations should be screened regardless of smoking status. Precision of the specific sequence of the mutation at diagnosis is crucial for the selection of the appropriate treatment. In the subgroup with uncommon mutations, results differed considerably: while patients with exon 18 mutations derived benefit from first-line EGFR TKIs (median PFS, 7.8 months; DCR, 80 %), this did not apply to those whose tumours harboured exon 20 mutations, which were equivalent to *EGFR* wild-type in this respect (median PFS, 2.7 months; DCR, 20 %). For exon 21 mutations, OS and PFS were longer with EGFR-TKI therapy for L858R compared to the other mutations.

PFS and OS obtained with TKI treatment for patients with exon 19 mutations were superior to all of the other mutations, and the median OS was significantly longer even when compared to patients with exon 21 mutations ($p = 0.045$). EGFR-TKIs should therefore be a part of the treatment plan, although not necessarily the first-line strategy. ■

Rare driver mutations: encouraging results in small patient populations

As well as *ALK* fusion mutations and *EGFR* mutations, studies of the genetic profiles of patients with NSCLC have identified other mutations that might be used for additional targeted therapies. Among these, *ROS1* and *RET* rearrangements both occur in 1 % to 2 % of patients with NSCLC.

Update of PROFILE 1001

Crizotinib is known to target not only ALK, but also ROS1, among others. Patients with *ROS1*-positive advanced NSCLC are being treated with crizotinib 250 mg twice daily in the ongoing phase I, open-label, PROFILE 1001 study. Initial findings confirm that targeting ROS1 is a viable strategy in *ROS1*-rearranged NSCLC [1]. In 2016, crizotinib was approved for the treatment of patients with metastatic/ advanced *ROS1*-positive NSCLC in the United States and Europe. Shaw et al. presented the up-dated results on safety and antitumour activity from the expansion phase of PROFILE 1001 [2]. Fifty-three patients were included in this analysis. The population contained three patients with *ALK*-negative NSCLC who were retrospectively determined to be *ROS1*-positive. Adenocarcinoma was the most common NSCLC histology (96.2 %), and the majority of patients (75.5 %) had no history of smoking.

According to the analysis, the crizotinib treatment gave rise to a clinically meaningful ORR rate of 69.8 %. The patients experienced rapid responses, with median time to response of 7.9 weeks, which corresponded to the approximate time of the first on-treatment tumour scan. Responses were durable and consistent across a variety of patient demographics and baseline characteristics. Almost all of the patients had some degree of tumour shrinkage during the study **(Figure)**. Crizotinib was

generally well tolerated, with the safety profile being consistent with that observed in *ALK*-positive NSCLC.

RET-positive NSCLC: Japanese data on vandetanib

In patients with *RET* fusion mutations, clinical trials are underway in Japan and the United States to evaluate specific agents, including vandetanib, alectinib and cabozantinib.

Vandetanib is an oral receptor TKI that potently inhibits RET, EGFR, and VEGFR. Horiike et al. conducted a multicentre phase II trial of vandetanib 300 mg/day in patients with advanced, non-squamous, *RET*-rearranged NSCLC [3]. These patients had received at least one prior chemotherapy. ORR according to the Independent Radiological Review Committee was defined as the primary endpoint. Out of 1,536 patients screened, 34 (2 %) had *RET* fusion. Of these, 19 patients constituted the ITT population. In this group, ORR was 47 % with vandetanib, and disease control was achieved in 90 %. Responses lasted for 5.6 months. Median PFS was 4.7 months, and 47 % of patients were alive at 1 year.

According to exploratory subgroup analyses, the type of *RET* fusion made a difference, as patients with CCDC6-RET (n = 6) appeared to benefit to a greater extent from vandetanib treatment than those with KIF5B-RET (n = 10), for ORR (83 % vs. 20 %, respectively), median PFS (8.3 vs. 2.9 months), and 1-year OS rate (67 % vs. 42 %). The safety profile corresponded to previous experience with vandetanib. The main AEs were hypertension, diarrhoea and acneiform rash.

The authors concluded that vandetanib showed clinical antitumor activity in patients with advanced *RET*-rearranged NSCLC, although large screening programmes are now required. One of these programmes is a nationwide genomic screening project called LC-SCRUM-Japan. It was initiated in Japan in conjunction with this study, and it involves the identification of *RET* rearrangements using multiplex RT-PCR and a break-apart FISH assay. By August 2016, more than 200 institutions and 14 drug companies were participating in LC-SCRUM-Japan.

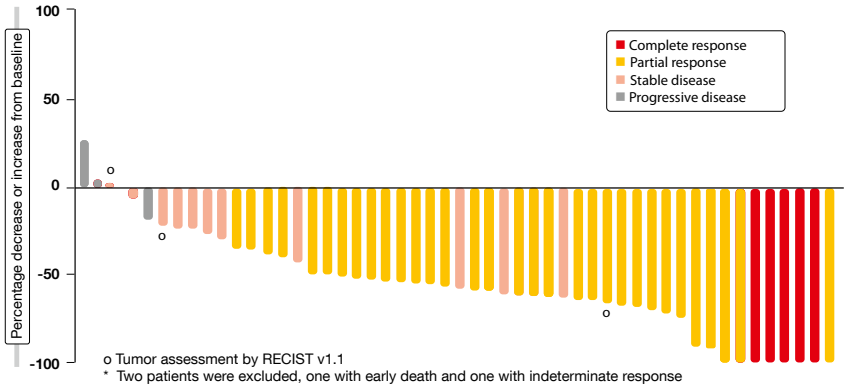

Figure: PROFILE 1001: best percentage change from baseline in size of target lesions obtained with crizotinib in patients with *ROS1*-rearranged NSCLC*

Lenvatinib in *RET*-positive tumours

The oral multikinase inhibitor lenvatinib targets VEGFR, FGFR and PDGFR-α, and the *RET* and *KIT* proto-oncogenes. In 2015, lenvatinib was approved for treatment of radioiodine-refractory, differentiated, thyroid cancer. As RET kinase is a target of lenvatinib, this appeared to be a therapeutic option for patients with *RET*-positive adenocarcinoma of the lung.

Indeed, a phase II, open-label, global, proof-of-concept study presented at the ESMO Congress showed promising clinical activity of lenvatinib 24 mg/day in 25 patients with *RET*-positive NSCLC [4]. The patients had received a maximum of three previous systemic therapies, with those with more than three treatments enrolled on a case-by-case basis. ORR was defined as the primary outcome, and was seen as 16 %; all of these were confirmed partial responses. Disease control (CR plus PR plus SD at ≥7 weeks) was obtained in 76 %, and clinical benefit (CR plus PR plus SD at ≥23 weeks) in 48 %. Tumour shrinkage occurred in the majority of patients. Importantly, patients showed similar ORRs, disease control rates, and clinical benefit rates irrespective of whether they had received previous RET-targeted therapy with cabozantinib or vandetanib **(Table)**. Median PFS was 7.3 months.

For most patients, the lenvatinib toxicities were manageable with dose modifications. The most common AEs included hypertension, nausea, decreased appetite, diarrhoea, proteinuria, and vomiting. These data provide support for further studies with lenvatinib in the treatment of *RET*-positive adenocarcinoma of the lung. ■

TABLE
Efficacy outcomes with lenvatinib according to use of previous RET-targeted therapy

Previous RET-targeted therapy	n	Outcome [n (%)]		
		Objective response*	Disease control**	Clinical benefit***
Yes	7	1 (14.3)	6 (85.7)	4 (57.1)
No	18	3 (16.7)	13 (72.2)	8 (44.4)

*Objective response: all confirmed responses
**Disease control: CR plus PR plus SD at ≥ 7 weeks
***Clinical benefit: CR plus PR plus SD at ≥ 23 weeks

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SCLC: genomic alterations pave the way to targeted approaches

Rapid growth and early development of metastatic disease are characteristic of small-cell lung cancer (SCLC), which constitutes approximately 15 % of all lung cancer cases [1]. In limited-stage disease, a cure is possible with chemoradiotherapy. However, 68 % of patients present with extensive-stage SCLC (ES-SCLC). Although high initial responses to platinum-based chemotherapy and radiotherapy are observed, recurrence of chemo-refractory disease takes place as a rule.

At present, the lack of effective therapies for relapsed SCLC is one of the greatest unmet needs in the management of lung cancer patients. Nearly all SCLC cases are attributable to cigarette smoking, which has implications for the mutational landscape of these cases, and thus for the potential use of certain treatments.

Genomic profiling of SCLC patients

Ali et al. reviewed 883 patients with SCLC using a comprehensive genomic profiling approach [2]. Importantly, all types of genomic alterations were identified (i.e., base-pair substitutions, insertions/deletions, copy number alterations, rearrangements). This study is the largest to date that describes the genomic profiles of SCLC patients through the course of their clinical care.

The results here showed that frequent genomic alterations are present in SCLC. Genomic alterations, which included *MYCL1* fusions, were consistent with those in the published literature. The most commonly altered genes were *TP53* (90 %), *RB1* (69 %), *MLL2* (12.0 %), *LRP1B* (10.9 %), *PTEN* (8.5 %), *MYCL1* (8.0 %), *RICTOR* (6.5 %), and *MYC* (6.1 %). Focal amplifications were frequent, and included *RICTOR*/*FGF10* on chromosome 8 and *MYCL1* on chromosome 1. *MYCL1* amplification was found in 68 (7.8 %) of the patients. Seven patients harboured *MYCL1* fusions, and five of these also had *MYCL1* amplification.

These patients included the unique index case of a never-smoker whose tumour harboured *JAZF1-MYCL1* without amplification of *MYCL1*. This patient experienced durable complete remission over 18 months when treated with the investigational aurora A kinase inhibitor alisertib (MLN8237), and durable partial response to nivolumab. The biological implication of this is that *JAZF1-MYCL1* might ectopically stabilise functional MYCL1 expression, thus hyper-activating the downstream target aurora kinase, as well as hyper-inhibiting the downstream target PD-L1. *MYCL1* amplifications might represent a less dramatic elevation of downstream activity, but they still confer sensitivity to aurora kinase inhibitors and PD-1 inhibitors. Therefore, some patients, and particularly those harbouring *MYCL1* amplifications, might benefit from the combination of an aurora kinase inhibitor and an immunotherapeutic drug.

The tumour mutational burden (TMB) in SCLC was calculated at 9.9 mutations/megabase. In comparison, the TMB for melanoma is 12.6 mutations/megabase, while it is lower in other tumours. Assuming that the TMB correlates with the efficacy of PD-1/PD-L1 inhibitors, the distribution of the TMB in SCLC suggests a similar response to immunotherapy as seen in NSCLC.

Aurora A kinase inhibition plus paclitaxel

Aurora A kinase (AAK) is a key regulator of mitosis. It can be overexpressed or amplified in a range of solid tumours and haematological malignancies. Inhibition of AAK leads to disrupted mitosis and cell death, which makes AAK a potential target for anti-cancer therapies. AAK inhibitors appear to be effective in SCLC cell lines, and especially in those with amplification and/or high expression of *Myc* [3, 4], which is a main driving oncogene in many cancers. *Myc* amplification of overexpression occurs in 18 % to 31 % of SCLCs, and is more common in chemo-refractory disease [3].

The investigational, orally available, selective, small-molecule, AAK inhibitor alisertib was tested in combination with paclitaxel in a randomised phase II study [5]. Patients with SCLC participated who had previously been treated with one platinum-based chemotherapy regimen and had experienced relapses earlier than 180 days of completion. The patients in the control arm received placebo plus paclitaxel. Eighty-eight individuals were enrolled in each study arm.

Activity in c-Myc–expressing tumours

For PFS in the ITT population, which was defined as the primary endpoint, the analysis revealed a significant advantage of the alisertib combination (3.32 vs. 2.17 months; HR, 0.71; p = 0.038). Patients with resistant or refractory relapses also experienced significant PFS benefit (2.86 vs. 1.64 months; HR, 0.659; p = 0.037). For OS, DCR and ORR, the results hinted at favourable outcomes with the alisertib combination, although the differences did not reach significance.

Alisertib and paclitaxel have overlapping toxicities. Grade ≥ 3 AEs occurred more frequently with alisertib plus paclitaxel (76 % vs. 51%), as did drug-related serious AEs (32 % vs. 7 %). The most common AEs with the alisertib combination included diarrhoea, fatigue, neutropenia, anaemia and stomatitis. Neutropenia dominated among the grade ≥ 3 AEs (38 % vs. 6 %). All of the grade ≥ 3 AEs were at least two-fold more frequent in the experimental arm than in the control arm. AE-related drug discontinuation occurred more frequently in the experimental arm (15 % vs. 6%), as also seen for dose reductions due to AEs (38 % vs. 10 %).

With c-Myc protein expression believed to serve as a biomarker, a prespecified exploratory analysis yielded a strong association with PFS. Here, the addition of alisertib led to a marked clinical PFS benefit over paclitaxel alone in c-Myc–positive patients (HR, 0.29),

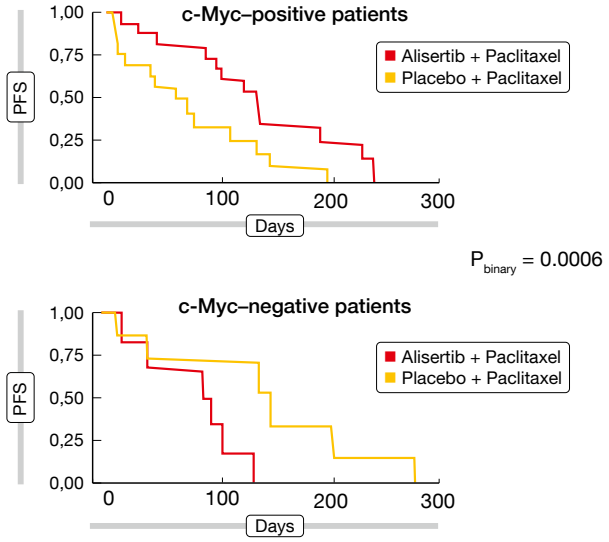

Figure 1: Effect on PFS of addition of alisertib to paclitaxel, according to c-Myc protein expression

whereas the opposite pattern was observed in the c-Myc–negative subgroup (HR, 11.8; **Figure 1**). A prospective study is needed to further validate the predictive value of c-Myc.

Preliminary results with atezolizumab

The humanised monoclonal anti–PD-L1 antibody atezolizumab has demonstrated promising clinical activity and a tolerable safety profile in a number of NSCLC clinical trials. As SCLC shows a high frequency of somatic mutations, these tumours might be amenable to treatment with PD-1/PD-L1 inhibitors. Sequist et al. presented the results obtained for an ES-SCLC cohort that was part of a larger phase Ia clinical trial investigating atezolizumab in locally advanced or metastatic solid tumours [6]. The first five patients were PD-L1–selected; after that, the enrolment continued regardless of PD-L1 expression status. Seventeen patients were evaluated in the safety and efficacy analyses.

Treatment with atezolizumab was generally well tolerated, with the majority of AEs as grades 1 or 2. Atezolizumab showed encouraging single-agent activity. The spider plot depicted in **Figure 2** illustrates the responses achieved according to the immune-related response criteria (irRC). Objective responses per irRC occurred in 17.6 %. Disease control was obtained in 41.2 %. Median PFS was 2.9 months per irRC across all of the patients, and median OS was 5.9 months. In tumours expressing PD-L1, higher expression of *PD-L1* mRNA and T-effector gene signature corresponded to a trend towards improved PFS (per irRC) and OS. The clinical benefit of atezolizumab continued beyond classical radiographic progression. A phase III randomised study of atezolizumab or placebo plus carboplatin/ etoposide in patients with ES-SCLC is currently recruiting (NCT02763579).

Other novel agents

Chu et al. presented encouraging data on the monoclonal antibody BMS-986012 that targets fucosyl-GM1, which is a chemically defined monosialoganglioside that shows limited expression in normal tissues, but is highly expressed on the surface of tumour cells in SCLC [7]. BMS-986012 was developed as a first-in-class fully human immunoglobulin G1 monoclonal antibody. The anti-tumour activity of this agent is based on antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cellular phagocytosis.

The phase I/II dose-escalation and dose-expansion CA001-030 study was initiated in patients with relapsed and refractory SCLC. According to the preliminary data from the phase I monotherapy portion of this trial, BMS-986012 was well tolerated, and patients responded to treatment. However, due to the small number of patients in this part of the study and their heterogeneity, no firm conclusions regarding the efficacy of BMS-986012 can be drawn yet. The BMS-986012 pharmacokinetics were consistent with what might be expected for a monoclonal antibody, and no anti-drug antibodies were detected in treated patients. Enrolment in the phase II monotherapy portion of this trial is ongoing. Further studies are currently investigating BMS-986012 as part of the combination regimens with nivolumab and chemotherapy.

In contrast, negative trial results were obtained with roniciclib, an oral, highly potent, small-molecule inhibitor of cyclin-dependent kinases [8]. A phase II, randomised, double-blind, placebo-controlled study conducted in patients with ES-SCLC compared cis-

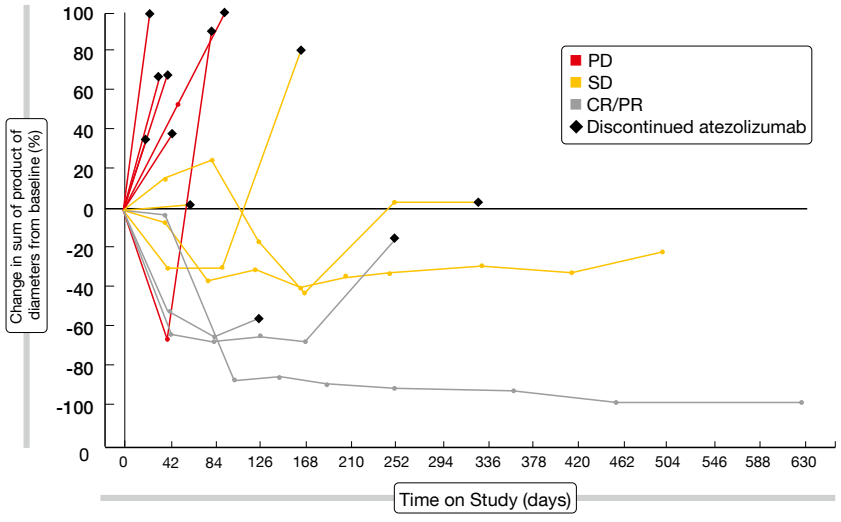

Figure 2: Confirmed responses to atezolizumab in patients with ES-SCLC (according to irRC)

platin/ etoposide with carboplatin/ etoposide as first-line therapy in combination with roniciclib or placebo. No improvements were observed for the addition of roniciclib with regard to PFS, OS, ORR and time to progression. Moreover, the combination was not well tolerated, as patients who received roniciclib showed higher incidence of clinically important AEs and fatal AEs than those in the control group. The study was terminated following primary completion. ■

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No phase III benefit with selumetinib in *KRAS*-mutant NSCLC

Oncogenic mutations of *KRAS* define the largest genomic subset of NSCLC **(Figure)**. This patient group appears to derive less clinical benefit from chemotherapy than the overall NSCLC population. There are currently no targeted treatments specifically for patients with *KRAS*-mutant tumours of the lung. However, *KRAS* mutations are associated with activation of the RAS/RAF/MEK/ERK pathway, which converges at MEK1/2, making *KRAS* mutation in NSCLC a potential target of the oral MEK1/2 inhibitor selumetinib. Indeed, in a phase II trial, selumetinib has shown encouraging activity in combination with docetaxel, improving PFS and ORR to a significant extent compared to placebo plus docetaxel [1].

The phase III SELECT-1 study therefore tested selumetinib 75 mg twice daily plus docetaxel against placebo plus docetaxel in patients with *KRAS*-mutated advanced NSCLC (stage IIIB-IV) after failure of first-line therapy [2]. PFS by investigator assessment was defined as the primary endpoint. Overall, 510 patients were randomised. SELECT-1 was the first and largest prospective phase III, randomised, double-blind trial of second-line treatment for patients with *KRAS*-mutant NSCLC.

However, PFS did not differ significantly between the treatment arms (3.9 vs. 2.8 months with selumetinib plus docetaxel and docetaxel alone, respectively; HR, 0.93). This also applied to OS (8.7 and 7.9 months, respectively; HR, 1.05). There was no evidence of a statistically significant interaction of treatment by subgroup with regard to both PFS and OS. ORR was numerically improved in the experimental arm (confirmed responses, 13 % vs. 9 %); however, responses lasted only 2.9 months (vs. 4.5 months in the control arm). The safety profile of selumentinib plus docetaxel was consistent with historical data for docetaxel and emerging data for selumetinib.

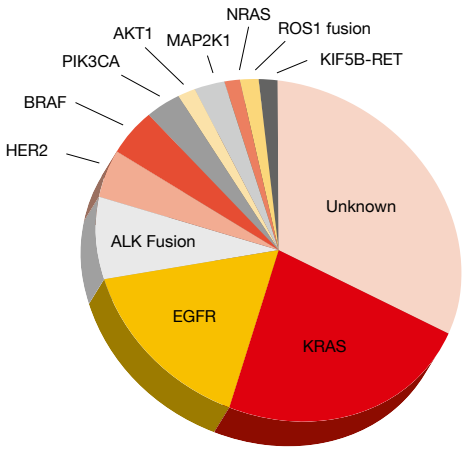

Figure: Molecular subsets of adenocarcinoma of the lung

At present, there is no clear reason why the phase II results did not translate into a positive phase III study. Exploratory analyses are ongoing or planned for different *KRAS* codon mutations, as well as for PD-L1, LKB1 and TP53 status. ■

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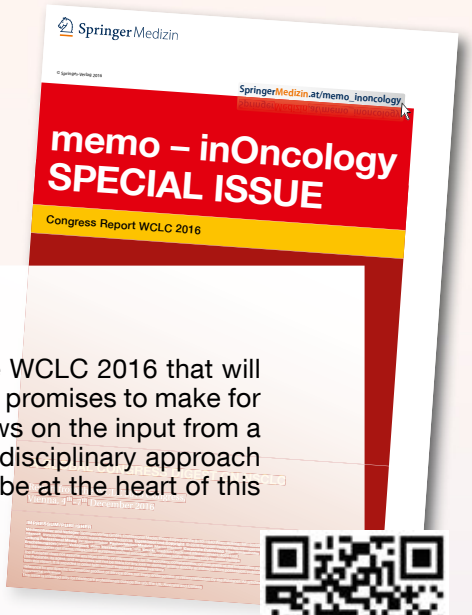

Forthcoming Special Issue

This special issue will be offering a synopsis from the WCLC 2016 that will be held in Vienna, in December 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.

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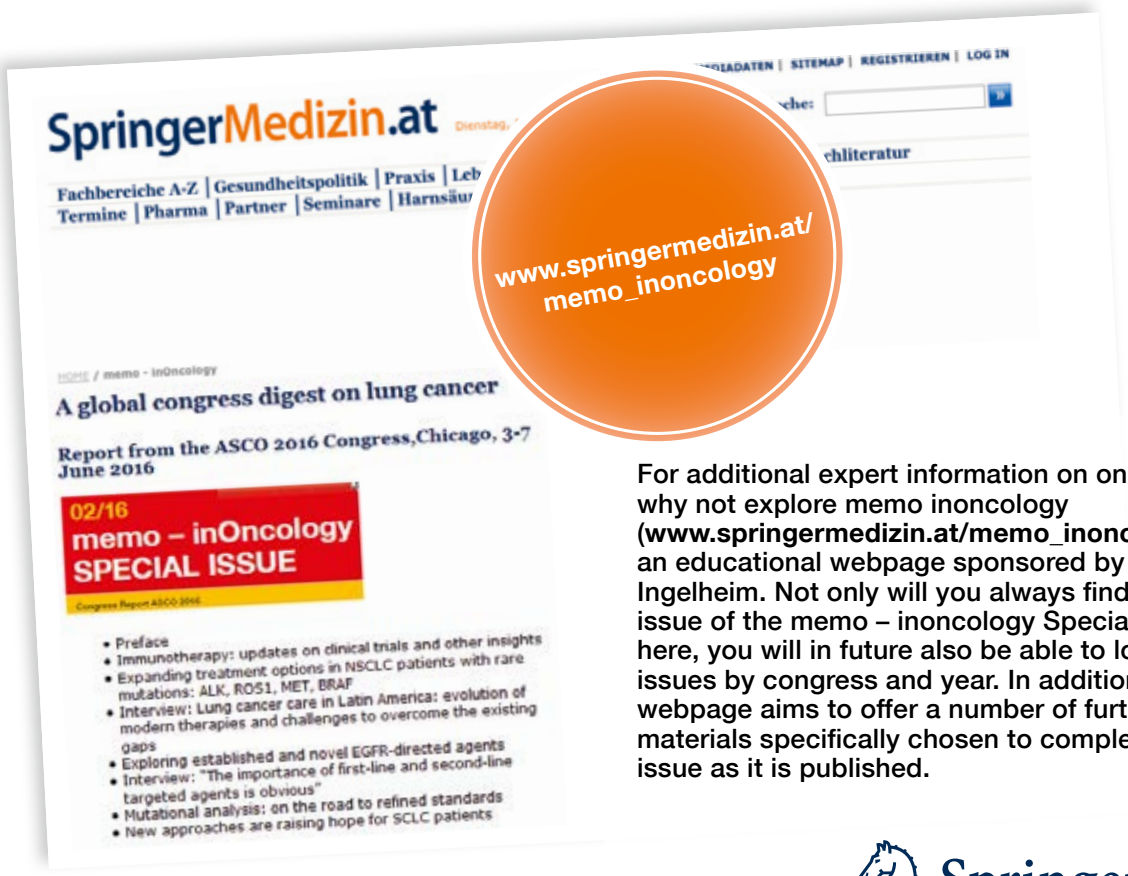

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