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Congress Report WCLC 2017

A GLOBAL CONGRESS DIGEST ON LUNG CANCER

Report from the International Association for the Study of Lung Cancer (IASLC) 18th World Conference on Lung Cancer, October 15th–18th, 2017, Yokohama, Japan

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Preface

Dear Colleagues,

Throughout the last decades, the treatment of non–small-cell lung cancer has undergone enormous advancements that make keeping up with the latest developments a challenge for physicians. For purposes of providing continual education to health care professionals involved in lung cancer care, the World Conference on Lung Cancer (WCLC) of the International Association for the Study of Lung Cancer (IASLC) is now being held annually. With delegates from more than 100 countries attending, this conference has become the premier international forum in the field of lung cancer and thoracic malignancies.

From 15th to 18th October, the 18th WCLC took place in Yokohama, Japan. The programme offered more than 2,000 oral, mini oral and poster abstract presentations, and more than 400 renowned speakers, session chairs and abstract discussants shared their knowledge with the audience. In a way, the choice of the congress location might mirror the fact that much of the recent lung cancer research that has succeeded in actually improving patient outcomes has taken place in Asian countries. Clinical trials conducted in Asia have contributed considerably to the development of targeted therapies, such as EGFR or ALK tyrosine kinase inhibitors, and immunotherapies, but also to the implementation of cytotoxic drugs. Particularly in lung cancer, Eastern Asia has evolved into a stronghold of cancer research over the previous years.

The WCLC 2017 issue of memo inOncology covers various topics ranging from thoracic surgery to targeted therapy, immunotherapy, chemotherapy, and mesothelioma treatment. Overall, the data presented at the conference highlighted the steady progress that is being made in all of these areas, as new targets, new biomarkers and novel ways to apply the established interventions are moving into the focus of scientific research. Of course, screening for lung cancer is another important area that can contribute greatly to rendering lung cancer a controllable disease. Nationwide screening programmes are currently ongoing in various countries and might provide answers to open questions as they are conducted on a large scale. We hope that early detection, further drug development as well as innovative combinations and the identification of reliable biomarkers will make cure a feasible goal for many of our patients in the foreseeable future.

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What is new in surgery? Redefining current options

In 2005, the International Association for the Study of Lung Cancer (IASLC) Staging Committee proposed the definition of complete resection of lung cancer, which included the criteria of uncertain resection [1]. Uncertain resection was defined by the criteria detailed in the **Table**. On behalf of the IASLC Staging and Prognostic Factors Committee, Edwards et al. conducted a retrospective analysis of the resection margin status using the data of 14,712 patients obtained from the 8th Edition Database who underwent NSCLC surgery [2]. Full resection status and survival data were available for these patients. Neoadjuvant therapy cases were excluded. Cases were reassigned to R (uncertain) [R(un)], if any of the following applied:

+ Less than 3 N1 or N2 node examined
+ Less than lobe-specific systematic lymph node dissection
+ Extra-capsular invasion of N2 nodes
+ Positive highest lymph node station (status of highest node unavailable)
+ *Carcinoma in situ* at bronchial resection margin (currently R1 [i. s.])
+ Positive pleural lavage cytology (currently R1 [cy+])

Importance of high-quality surgical staging

Survival curves according to the conventional resection status showed a significant difference between R0 and R1, but no significant difference between R1 and R2. Upon reassignment, 55.8 % of cases (n = 8,203) became R(un) cases. Among the reasons for assignment to the R(un) category, less rigorous intraoperative staging compared to systematic lymph node dissection prevailed in the vast majority of cases, although there was a reasonable number of cases

TABLE
Definition of an uncertain resection

(a) Resection margins are proved to be free of disease microscopically, but one of the following applies:
(b) The intraoperative lymph node evaluation has been less rigorous than systemic nodal dissection or lobe-specific systematic nodal dissection.
(c) The highest mediastinal node removed is positive.
(d) The bronchial margin shows carcinoma in situ.
(e) Pleural lavage cytology is positive (R1 cy+).

with ‚highest station positive only'. In pN2 cases with positivity of the highest station, median survival was 14 months shorter than in the patients who were highest-station–negative (41.0 vs. 55.0 months; HR, 1.45; p < 0.0001). The survival curves according to resection status in N0 cases did separate, but not significantly. In node-positive cases, median survival was 20 months less for patients with R(un) compared to R0 (50.0 vs. 70.0 months; HR, 1.27; p < 0,0001). However, the numbers in the other proposed R(un) categories were small.

The authors concluded that the IASLC Proposed Definition for Complete Resection has relevance. It is important to acknowledge that high-quality surgical staging gives the most accurate assignment of stage group and the most favourable survival data, stage by stage, in association with stage migration. However, it is essential that clinical trials take into account the quality standard of surgery, which can be assessed systematically using these criteria. Optimal staging data also allows the most appropriate decision making for routine adjuvant therapy and accurate interpretation of survival in adjuvant therapy clinical trials. The R Domain Sub-Committee will continue work to refine the proposed R status descriptors.

How to handle screen-detected lung cancer

Dr. Shun-ichi Watanabe, Department of Thoracic Surgery, National Cancer Center Hospital, Tokyo, Japan, discussed the optimal management of small tumours detected using CT screening [3]. He reported that the first series of successful segmentectomy was reported in 1973 [4], but the results of the only randomised controlled trial comparing lobectomy with sublobar resection significantly favoured lobectomy [5], thus rendering it the standard surgical approach for more than half a century.

Today, however, many small subsolid tumours are being detected using CT screening. "The ideal procedure, i.e., observation, segmentectomy, or lobectomy, is controversial for some nodules at the moment," Dr. Watanabe emphasised. In Japan, the type of surgery is selected based on tumour size and C/T ratio, i.e., the maximum consolidation diameter divided by the maximum tumour diameter. "Based on the JCOG0201 trial, a C/T ratio < 0.25 was considered non-invasive," Dr. Watanabe said [6].

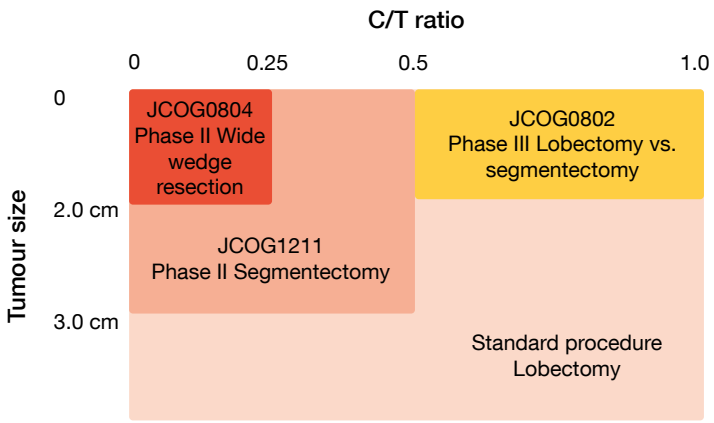

Figure 1: Ongoing trials exploring sublobar resection

When performing sublobar resection, a choice must be made between segmentectomy and wedge resection. If segmentectomy is performed, the regional lymphatic pathways are removed, which means that anatomic segmentectomy could be applied even for invasive tumours. However, non-anatomic wedge resection should be restricted to non-invasive tumours, as tumour cells might persist within the lymphatic pathways.

Trial results to come

Dr. Watanabe pointed out that in the context of sublobar resection, points of attention relate to ensuring adequate resection margins and the exclusion of tumours with pleural invasion. "Surgical margins should exceed the tumour diameter, which can of course be difficult, particularly in the apical parts of the lung." In the setting of pleural invasion, skip metastasis is possible.

In 2009, the Japan Clinical Oncology Group (JCOG) initiated two clinical trials exploring different surgical approaches for small-sized (≤ 2 cm) lung tumours **(Figure 1)**. The one-arm, phase II JCOG0804 study investigated wide wedge resection, and the phase III JCOG0802 trial compared lobectomy with segmentectomy. "Enrolment has already been completed in both studies, and patients are being followed up."

JCOG is conducting another phase III trial, JCOG1211, for segmentectomy in patients with T1c tumours sized > 2 cm (C/T ratio < 0.5). This study was initiated based on the survival outcomes of JCOG0201 that showed very good prognosis in tumours with a diameter of ≤ 2 cm (C/T ratio < 0.25) and ≤ 3 cm (C/T ratio < 0.5) [7]. Five-year overall survival (OS) rates were 97.1 % and 96.7 %, respectively. JCOG1211 has already completed enrolment. Overall, the three trials on sublobar resection comprise 1,836 cases. These results will be likely to change the textbooks, as Dr. Watanabe concluded.

Bilateral mediastinal lymphadenectomy

Experimental studies have shown that lymphatic drainage occurs from the left

lower lobe to the contralateral mediastinal nodes [8]. To date, level I evidence on the survival effect of wide mediastinal resection is not available, and the role of bilateral mediastinal lymph node dissection in lung cancer remains unknown. Therefore, the aim of a randomised, controlled study was to analyse the impact of bilateral mediastinal lymphadenectomy (BML) on survival in NSCLC patients [9]. Between 2010 and 2013, 89 patients with NSCLC stage I to IIIa were randomised to standard pulmonary resection with either systematic lymph node dissection (SLND; n = 49) or BML (n = 40).

After a mean follow-up of 66.5 months, the 4-year survival rate was significantly higher in the BML group than in the SLND group (72.5 % vs. 51 %; p = 0.039). Separate comparisons were performed for different lobar locations of the tumour, showing no significant differences for 4-year survival rates and mean survival time between the two groups for tumours located in the right lung and those located in the left upper lobe. However, analysis of the left lower lobe revealed significantly improved 4-year survival in the BML cohort (90.9 % vs. 25 %; p = 0.003; **Figure 2**). Accordingly, mean survival was significantly longer (1,923 vs. 1,244 days; p = 0.027).

These findings indicated that for NSCLC located in the left lower lobe, removal of the contralateral mediastinal lymph nodes might be associated with a significant survival benefit. As patient numbers were low, the trial results should be confirmed in larger randomised controlled studies. A large international trial based on a similar protocol with the aim of validating these findings has recently been launched.

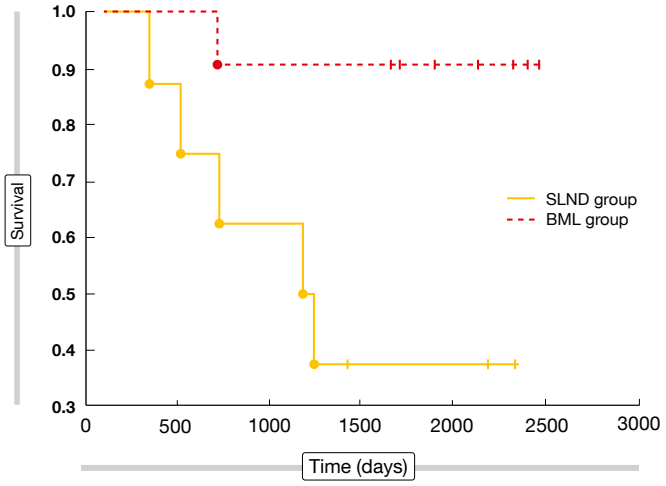

Figure 2: Long-term survival in patients who received standard pulmonary resection with either bilateral mediastinal lymphadenectomy (BML) or systematic lymph node dissection (SLND)

Primary tumour resection in metastatic NSCLC

Oligometastatic NSCLC may represent an indolent phenotype that might benefit from locally ablative treatments such as surgery or radiotherapy. Kang et al. evaluated the potential effect of primary tumour resection and an aggressive local consolidative therapy on 3-year OS and PFS in patients with metastatic OS and progression-free survival (PFS) [10]. Moreover, the objectives included the assessment of surgical outcomes in the treatment of patients with metastatic NSCLC and the identification of clinical factors that predict OS and PFS, in order to improve patient selection for surgery.

Consecutively treated patients with stage IV disease and ≤ 3 metastatic sites were analysed in a retrospective manner. They had received standard first-line systemic therapy (i.e., ≥ 4 cycles of platinum-based doublet chemotherapy) or approved first-line EGFR TKI therapy for ≥ 3 months if the tumour was known to harbour *EGFR* mutation. According to the extent of pulmonary resection, the patients were divided into two subgroups: intent to cure (ITC; removal of total or primary pulmonary lesions) and intent to biopsy (ITB; preservation of major lesions, only diagnostic biopsy via minimally invasive approach). The primary endpoint was 3-year OS and PFS.

Between 2000 and 2015, 115 patients were enrolled. The analysis showed that primary tumour resection in combination with systemic therapy was feasible, tolerable, and significantly extended OS and PFS compared to maintenance therapy or observation alone. Median OS was not reached vs. 23 months with ITC and ITB, respectively (HR, 0.38; p < 0.0001), and median PFS was 36 vs. 10 months (HR, 0.35; p < 0.0001). The ITC cohort experienced both longer OS and PFS across the M1a, M1b and M1c subgroups. Among characteristics evaluated for association with OS and PFS in the multivariate Cox proportional regression analysis, only the clinical M stage and the treatment type (ITC vs. ITB) were identified as significant factors. No patient in either group had grade 4 adverse events (AEs) or died due to an AE. The authors pointed out that these results are exploratory, but worthy of further evaluation. Identification of subgroups of patients who are most likely to benefit is necessary.

Advantages of less invasive surgery

In elderly patients with stage I NSCLC, sublobar resection was shown to be an alternative to standard lobectomy [11]. Laohathai et al. assumed that this approach might be preferable because of reduced operative risk and better preservation of pulmonary function. From 2003 to 2016, 77 octagenarians who underwent curative resection for stage I NSCLC were enrolled. Fifty-three and 24 received lobar and sublobar resection, respectively. The two groups did not differ with regard to sex, smoking history, performance status and comorbidities except for COPD, which was more prevalent in the group treated with sublobar resection. Clinical data were collected retrospectively. OS and recurrence-free survival (RFS) constituted the outcomes, as well as complication rates.

Indeed, OS did not differ significantly between the two groups, with 5-year rates of 51 % and 68 % for lobar and sublobar resection, respectively (p = 0.354). This also applied to RFS (recurrence rates, 57.14 % and 42.86 %, respectively; p = 0.623). At the same time, complications occurred less frequently

with sublobar resection than with lobar resection (13 % vs. 26 %). Pneumonia and persistent air leak were the predominant AEs in the lobar resection group. The length of hospital stay (LOS) was significantly shorter in patients who received sublobar resection (p = 0.011).

VATS *versus* OT

Likewise, a retrospective analysis demonstrated equivalence of video-assisted thoracic surgery (VATS) and open thoracotomy (OT) with regard to survival outcomes while revealing a LOS advantage of the less invasive approach [12]. VATS has become the recommended approach for treatment of early-stage lung cancer, but no large randomised clinical trial has formally compared it to OT thus far, although the VIOLET study in the UK is nearing accrual.

This single-institution chart review included a total of 235 patients diagnosed with stage I-III lung cancer who received either VATS or OT between 2005 and 2015. In this group, VATS and OT was performed in 101 and 134 cases, respectively. Age at diagnosis, sex, tobacco use, tumour location, and tumour size were comparable across the groups.

No significant difference occurred with respect to the risk of positive resection margins for VATS vs. OT. OS and RFS were similar for both techniques (p = 0.68 and p = 0.23, respectively), while median LOS was significantly shorter in patients receiving VATS (4 vs. 6 days; p = 0.002). These favourable outcomes were achieved regardless of tumour stage at diagnosis. ■

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EGFR TKI therapy in specific populations and settings

The first-generation EGFR TKIs erlotinib and gefitinib as well as the second-generation EGFR TKI afatinib have become the standard first-line treatment options for advanced *EGFR*-mutation–positive NSCLC. All three drugs improved PFS and objective response rate (ORR) compared to chemotherapy in phase III studies [1-4]. Afatinib induced prolongation of OS *versus* chemotherapy in patients with deletion 19 in the LUX-Lung 3 and 6 phase III studies [5]. In the phase II LUX-Lung 7 trial, afatinib, compared to gefitinib, gave rise to improvements in PFS, ORR, and time to treatment failure. [6]

Post-hoc analyses of the LUX-Lung trials

According to an analysis of the LUX-Lung 3 and 6 trials, tolerability-guided dose adjustment of afatinib is an effective measure to reduce treatment-related AEs without affecting therapeutic efficacy [7]. It diminished the interpatient variability of afatinib exposure and decreased the incidence and severity of AEs, while efficacy outcomes were similar across patients with and without dose reductions. Efficacious plasma levels were maintained, and patient-reported outcomes (PROs) did not change to a clinically meaningful extent.

Schuler et al. performed a post-hoc analysis of afatinib long-term responders (LTRs) in the LUX-Lung 3, 6 and 7 studies [8]. In these three trials, 10 %, 10 % and 12 % of afatinib-treated patients, respectively, were LTRs. This equalled a total population of 66 individuals. Median treatment duration was 50, 56 and 42 months, respectively. Baseline patient characteristics were generally consistent with the overall study populations, with the exception of greater proportions of women and patients with deletion 19 among LTRs.

Median OS could not be estimated due to few deaths. Ranging from 71 % to 89 %, ORRs were higher in LTRs than in the overall LUX-Lung 3, 6 and 7 populations **(Figure 1)**. Five patients (8 %) experienced CR. PR occurred in 47 patients (71 %) and SD in nine patients (14 %). LTRs tolerated afatinib treatment well. Long-term treatment was independent of tolerability-guided dose adjustment or baseline brain metastases. Also, it had no detrimental impact on subsequent therapies, which resembled those in the overall study populations. Likewise, PROs appeared stable between weeks 24 and 160; they even

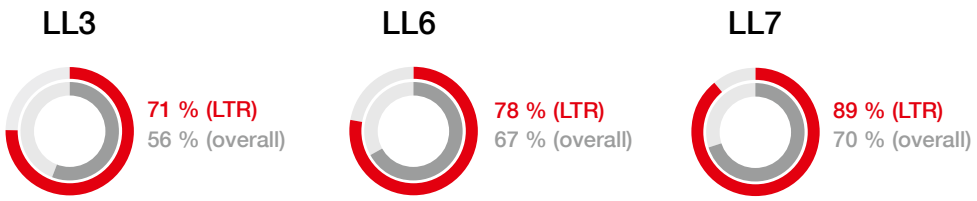

Figure 1: Response rates in the afatinib-treated overall populations of the LUX-Lung 3, 6 and 7 trials, and in long-term responders (LTRs) in these studies

improved slightly after approximately 3 years of afatinib treatment compared to the start of therapy.

Real-world data of afatinib in a large-scale Asian population

A large phase IIIb, open-label study is currently evaluating afatinib treatment in a broad Asian population of EGFR-TKI–naïve patients with locally advanced or metastatic *EGFR*-mutated NSCLC. An interim analysis of the data of 479 patients enrolled in five Asian countries was presented at the WCLC [9]. Two thirds of the population were chemotherapy-naïve. Thirty percent had received one prior line of chemotherapy, and 10 % had received ≥ 2 prior lines. Common mutations (deletion 19 and L858R mutation) were found in 86.0% of patients. Almost 20 % had asymptomatic brain metastases.

Median time to symptomatic progression (TTSP) and PFS in the overall cohort were 15.3 and 12.1 months, respectively. The fact that TTSP was 3 months longer than PFS suggests that afatinib therapy can be continued beyond progression, reflecting real-world clinical practice and treatment guidelines. TTSP and PFS were encouraging in patients with both common and uncommon *EGFR* mutations and in those with and without prior chemotherapy.

The safety data were consistent with those from the LUX-Lung 3, 6 and 7 studies. However, dose reductions occurred less often, confirming that in real-world practice, most afatinib-related AEs are manageable and result in few treatment discontinuations.

Efficacy in brain metastases and uncommon mutations

Likewise, in a retrospective Korean real-world analysis of 165 patients, first-line afatinib showed similar or even better PFS and OS outcomes compared with the clinical trials [10]. Median PFS was 19.1 months, and median OS had not been reached. At 12 and 24 months, 91.0 % and 70.7 % of patients were alive, respectively. The data also demonstrated the efficacy of afatinib in patients who had brain metastases before initiation of treatment. This cohort constituted almost half of the population (43.0 %). In those without any CNS irradiation, PFS was 15.7 months, which resembled PFS in patients who underwent Gamma Knife surgery (15.6 months). Those with whole brain radiotherapy experienced a median PFS of 11.5 months. Overall, CNS response rate was 75.9 %. In addition, the data showed that tumours harbouring uncommon *EGFR* mutations other than T790M also responded to afatinib treatment **(Figure 2)**. In these patients, median PFS had not been reached at the time of the analysis. Compared to the clinical trials, more patients required dose reductions due to AEs, but this did not affect efficacy outcomes.

A case report underscores the activity of afatinib in uncommon mutations [11]. Lorandi et al. described the case of a 39-year-old female patient with adenocarcinoma of the lung that had already spread extensively to the bone and lymph nodes. Testing revealed an insertion of exon 20. While patients with deletion 19 and L858R point mutation generally benefit from TKI therapy, those with other mutations such as exon 20 insertions do not. However, the patient was offered afatinib treatment after she had received platinum-based chemotherapy and requested an alternative treatment, as she was not inclined to accept chemotherapy maintenance. After the initiation of afatinib treatment, the patient achieved a long-lasting partial response.

Potential combinations

Based on preclinical data suggesting a synergistic effect of afatinib and the anti-VEGF antibody bevacizumab [12], Kuyama et al. conducted a phase I trial evaluating afatinib plus bevacizumab as first-line treatment in 19 chemotherapy-naïve patients with advanced *EGFR*-mutant NSCLC [13]. Afatinib was tested at two dose levels (40 mg/day or 30 mg/day).

The analysis identified afatinib 30 mg/day and bevacizumab 15 mg/kg as the recommended regimen. This

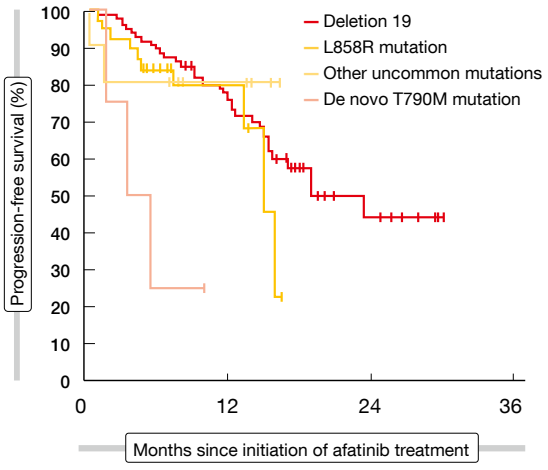

Figure 2: Activity of afatinib in patients with common and uncommon *EGFR* mutations

combination therapy was well tolerated and showed evidence of clinical activity. The ORR was 81.3 % for 16 evaluable patients, and all of them achieved disease control.

Another phase I trial assessed the combination of afatinib with carboplatin and pemetrexed in patients with *EGFR*-mutant metastatic NSCLC who had developed progression after first-line EGFR TKI treatment with gefitinib or erlotinib [14]. The combined administration of afatinib 20 mg/d (days 8 to 18) and pemetrexed 500 mg/m^2 plus carboplatin AUC 5 (on day 1 every 21 days) demonstrated clinical activity. Median PFS was 16.2 months, and and disease control rate (DCR) was 100 %.

Dacomitinib: activity by *EGFR* mutation subtype

The randomised, open-label, phase III ARCHER 1050 trial tested the investigational second-generation EGFR TKI dacomitinib in the first-line setting. Patients with advanced *EGFR*-mutated NSCLC received either dacomitinib or gefitinib. Brain metastases were not allowed in this trial. Compared to gefitinib, dacomitinib showed significantly improved PFS (14.7 vs. 9.2 months; $p < 0.0001$) [15].

A prospective subgroup analysis of the ARCHER 1050 study assessing the activity of treatment by *EGFR* mutation subtype showed that dacomitinib was effective in patients with both exon 19 deletions and L858R mutations [16]. Compared to gefitinib, PFS was prolonged in both patient populations (exon 19 deletion, 16.5 vs. 9.2 months; HR, 055; $p < 0.0001$; L858R mutation, 12.3 vs. 9.8 months; HR, 0.63; $p = 0.0034$). While ORRs were comparable across EGFR TKI treatment (i.e., approximately 70 % in all cohorts), patients receiving dacomitinib achieved significantly longer duration of response in both genetic subgroups (exon 19 deletion, 15.6 vs. 8.3 months; HR, 0.454; $p < 0.0001$; L858R mutation, 13.7 vs. 7.5 months; HR, 0.403; $p < 0.0001$). ■

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Interview: Keunchil Park, MD, PhD; Division of Hematology/Oncology, Innovative Cancer Medicine Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

"We are making steady progress toward better lung cancer control"

The motto of this year's WCLC is "Synergy to Conquer Lung Cancer". What types of synergy would be required to provide optimal care for lung cancer patients?

In a way, synergy is another expression for the multidisciplinary team approach, but the term ‚multidisciplinary' is not necessarily restricted to medical doctors. It also includes nursing staff and others such as the supportive care team, including the rehabilitation team and patient advocates. At the same time, the bottom line of that concept is having the patient at the centre of the overall care plan. The team members cooperate to provide the patient with the best, most advanced care.

In which areas of lung cancer research do you presently see the most relevant advancements from a clinical point of view?

Especially in lung cancer, the treatment paradigm has shifted dramatically throughout the past one and half decades. Until the dawn of the new millennium in 2000, the standard of care for

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patients with advanced lung cancer has been platinum-based chemotherapy, which gave rise to very limited benefits, resulting in a median survival in the range of 10 months. Treatments never even touched the one-year milestone. However, with the introduction of the molecularly targeted agents, particularly EGFR TKIs, the management of advanced NSCLC has totally changed, at least in patients with oncogene-driven tumours. As of 2017, reports estimate the median survival of *EGFR*-mutant patients treated with the correct targeted drug at 3 years or more. This is remarkable progress that has been made in the last 10 to 15 years. At the same time, patients with the other major oncogene-driven cancer, i.e., *ALK*-positive tumours, have experienced dramatic improvements in survival as well. Next-generation targeted kinase inhibitors that allow for salvage treatment in the second or third line after failure of previous drugs are being implemented. Overall, we are making steady progress toward better control of the disease. Of course, lung cancer is not curable yet, but at least in some subsets of patients, we can turn it into a chronic disease.

In addition to targeted agents, another important advancement in the treatment of lung cancer recently arose due to the introduction of checkpoint inhibitors. Here, too, newer agents are constantly being evaluated. We are living in an era of evolving new tools, and we expect even more benefits for our patients.

How do you rate the situation regarding screening and prevention of lung cancer in South Korea and Japan?
This is a rather important area of investigation. Of course, some Asian countries only have limited resources, but fortunately, nationwide screening programmes are ongoing now in Japan, Korea and some other Asian countries. At least some subsets of the Korean population are enabled to undergo a nationwide low-dose spiral CT screening programme. We are very excited about that, and we expect some answers from this screening programme as it is conducted on a nationwide scale. If it is shown to provide benefit, this will represent another big step forward in the management of lung cancer. ■

Taking anti-EGFR drug treatment further: later lines

Osimertinib after prior EGFR TKI therapy

Acquired resistance usually follows first-line EGFR TKI therapy, with the gatekeeper T790M mutation being the most common mechanism. The third-generation irreversible EGFR TKI osimertinib has been licensed for the treatment of patients whose tumours have been shown to carry this mutation. Retrospective data presented by Tan et al. demonstrated the activity of later-line osimertinib in 52 patients who participated in an early access program in Singapore [1]. Osimertinib was administered after progression on prior EGFR TKI therapy, from the second through the ninth treatment line (median, third line). Fifty-three percent of patients had brain metastases at initiation of treatment.

The independently assessed ORR was 46 %, with a median duration of response of 8.7 months. Complete responses (CRs) and partial responses (PRs) were achieved in 7.7 % and 38.5 %, respectively. Stable disease occurred in 40.4 %. Median PFS was 10.3 months; OS data were not mature at the time of the analysis. Osimertinib showed efficacy beyond the second line of therapy as well as regardless of the presence of CNS metastases.

Data on CNS control

Osimertinib is known to be CNS-active, which was confirmed by analyses presented at the WCLC. Zhu et al. assessed the efficacy of osimertinib 80 mg after first-generation TKI therapy in 10 patients with symptomatic brain lesions [2]. Two patients achieved PR in the CNS, and seven obtained stable disease (SD). Similarly, second-line osimertinib therapy exerted significant CNS control in Korean patients with measurable baseline brain metastases who participated in the open-label, multinational, real-world ASTRIS treatment study [3]. In the group of 16 patients evaluable for response, intracranial ORR was 81.3 %, with all of the patients achieving PR. The median duration of intracranial response had not been reached yet. Osimertinib showed clinical CNS efficacy irrespective of radiation history.

The single-arm, phase II TREM trial assessed the activity of osimertinib in T790M-positive and T790M-negative patients who had progressed after at least one EGFR TKI [4]. Thirty-four patients with brain metastases were included. The results indicated that osimertinib has similar efficacy in patients with CNS disease as in those without, whereas the benefit in T790M-negative patients appeared to be substantially lower. Overall, 75 % of patients experi-

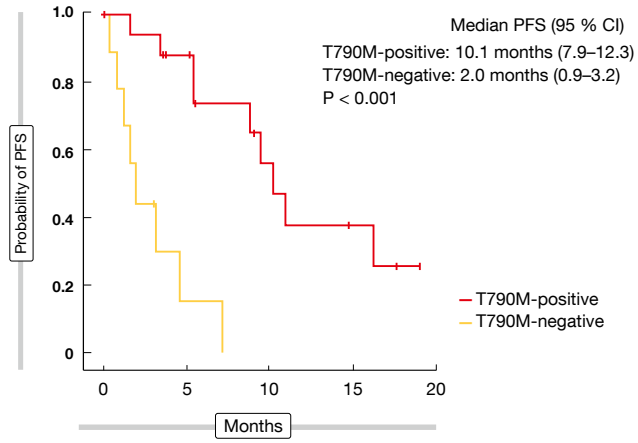


Figure 1: Osimertinib in patients with brain metastases: progression-free survival according to T790M mutation status

enced disease control, but this percentage was considerably higher in the T790M-positive cohort than in the T790M-negative group (88 % vs. 38 %). PFS was 10.1 vs. 2.0 months in these two cohorts (p < 0,001; **Figure 1**), while there was no significant PFS difference between the patients with brain metastases and those without (7.2 vs. 9.7 months; p = 0.300).

Prevalence of T790M mutation after afatinib

In patients who acquired resistance to first-line treatment with erlotinib and gefitinib, the T790M mutation showed prevalence rates of 49 % to 69 % [5-7]. However, data on resistance mechanisms to afatinib are lacking, particularly in Caucasian patients. Available evidence suggests that the development of the T790M mutation is also the predominant mechanism of afatinib resistance, with rates of 48 % to 68 % [7, 8].

In their single-centre, retrospective analysis, Hochmair et al. assessed the prevalence of the *EGFR* T790M mutation in patients who had progressed on afatinib treatment, as well as the response to osimertinib in this group [9]. Osimertinib has shown favourable results as second-line treatment after failure of first-generation or second-generation EGFR TKI therapy in the AURA3 study, but only 7 % of patients included in this trial had received first-line afatinib [10]. At the same time, emerging data suggest favourable clinical outcomes in patients who are prescribed the sequence of afatinib followed by osimertinib. According to a retrospective analysis of the LUX-Lung 3, 6 and 7 trials, median duration of osimertinib treatment after failure of afatinib was 20.2 months, and median OS had not yet been reached [11].

Consistent mutation rate & excellent response

Forty-eight patients who had progressed after initially achieving ≥ 3 months' disease control with afatinib were included in this analysis. In 75 %, afatinib had been used in the first-line setting, whereas 19 % and 6 % of patients, respectively, had received the TKI as a second-line or third-line agent. Testing showed that 56 % (n = 27) had developed the *EGFR* T790M mutation, which is consistent with the available prevalence rates from previous analyses [7, 8] and the T790M mutation rates in patients who progressed on erlotinib or gefitinib treatment [5–7].

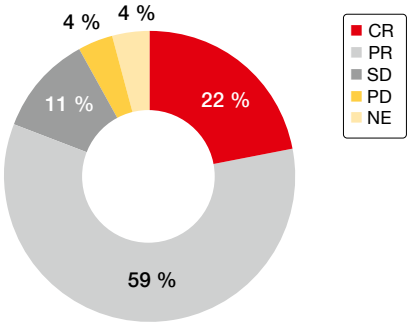
Additional tissue re-biopsy was performed in 34 patients to confirm liquid biopsy findings, giving a concordance rate of 91 % between the two tests. Emergence of the T790M mutation did not appear to correlate with baseline characteristics or other parameters such as the duration of response to afatinib. For patients receiving afatinib in the second or third line, it is not known when the T790M mutation emerged, as testing took place only after failure of afatinib therapy.

In the 27 patients who had developed T790M mutation, treatment with osimertinib elicited a high ORR of 81 %, with 22 % of patients achieving CR **(Figure 2)**. Data on the duration of response to osimertinib were immature at the time of the analysis. Osimertinib treatment was ongoing in 11 (41 %) of patients. Median time on sequential treatment with afatinib and osimertinib was 25.0 months.

Mechanisms of resistance to osimertinib

Based on the phase III FLAURA trial, osimertinib is an emerging standard of care for the first-line treatment of metastatic *EGFR*-mutation–positive NSCLC [12]. However, acquired resistance to osimertinib represents a challenge, even more so as it has not been systematically characterised to date. Understanding the mechanisms of resistance to third-generation EGFR TKIs is pivotal for the future development of next-generation EGFR TKIs and drug combinations.

Therefore, Puri et al. retrospectively reviewed the genomic profiles of 51 patients with metastatic NSCLC and T790M mutation to identify the potential mechanisms of resistance to osimertinib [13]. Among the 51 patients, 35 had been treated with osimertinib; as expected, they showed significantly longer OS than the group of 16 patients who had not received osimertinib (25.8 vs. 4.34 months; p = 0.019). According to the genomic profiling of 10 patients who developed progressive disease on osimertinib, *EGFR*-dependent mechanisms, such as C797S or C797G muta-



CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable

Figure 2: Response to osimertinib in patients who developed T790M mutation after initially achieving ≥ 3 months' disease control with afatinib

tion, loss of *EGFR* T790M and *EGFR* amplification, were most common (80 %). In addition, *EGFR*-independent mechanisms occurred in 60 %. These included *HER2* and *MET* amplification, activation of accessory pathways (e.g., MAPK/ERK pathway), and others (e.g., *RET NCOA4* fusion, *MYC* amplification). Each patient showed multiple mechanisms of resistance at the time of genomic testing.

Loss of T790M does not indicate resensitisation

Oxnard et al. also focussed on describing mechanisms of resistance to osimertinib [14]. The scientists performed tumour and plasma genotyping from patients who received single-agent osimertinib for T790M-positive NSCLC after acquired resistance to prior EGFR TKI treatment, using plasma from the AURA trial for purposes of validation. Among 33 patients who progressed on osimertinib treatment, 11 maintained T790M, and 22 lost it. The *EGFR* C797S mutation, which is deemed characteristic of osimertinib-resistant tumours, was detected only in patients who maintained T790M mutation. In those who lost it, competing resistance mechanisms occurred, including histologic transformation to SCLC, *MET* amplification or *PIK3CA* mutation. Patients with loss of T790M showed early resistance to osimertinib; here, median time to treatment failure was 6.9 months. In contrast, resistance due to the C797S mutation is frequently observed later on in the treatment course. At the same time, loss of T790M mutation is difficult to predict from baseline plasma genotyping. The relative T790M allelic fraction was only slightly lower for patients with loss of T790M than for those with maintained T790M.

The authors concluded that loss of T790M does not indicate resensitisation to first-generation EGFR TKI treatment, but often indicates overgrowth of a competing resistance mutation. The range of rare genetic resistance mechanisms to look out for includes *KRAS* mutations, *RET* fusions, and *EGFR* fusions. Retesting for T790M at progression might help to elucidate the biology of resistance. The authors suggested considering a trial of osimertinib combined with alternate pathway inhibitors (e.g., a MET inhibitor) in case of early resistance; for patients with late resistance, a study of osimertinib plus an additional EGFR inhibitor might be appropriate, as resistance with maintained EGFR addiction can be suspected. ■

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Immunotherapy: novel biomarkers on the horizon & news from pivotal trials

Is tumour mutation burden relevant in SCLC?

Only limited treatment options are available for patients with recurrent small-cell lung cancer (SCLC). The CheckMate 032 trial evaluated the anti-PD-1 antibody nivolumab with or without the anti-CTLA-4 antibody ipilimumab in a PD-L1–unselected cohort of SCLC patients who had received at least one prior platinum-based chemotherapy regimen. Both nivolumab alone and the combination showed impressive activity in this setting: 2-year OS rates were 26 % and 14 %, respectively [1]. Responses occurred regardless of PD-L1 status.

As PD-L1 expression is uncommon in SCLC, improved biomarkers are needed for immunotherapy in this tumour type. The randomised, phase III CheckMate 026 trial that compared frontline nivolumab with chemotherapy has identified tumour mutation burden (TMB) as a predictive biomarker for the use of nivolumab [2]. Antonia et

al. therefore conducted an exploratory TMB analysis of the CheckMate 032 trial data with the aim of assessing if this observation holds true for SCLC [3].

The TMB-evaluable group included 211 patients, 133 and 78 of whom received single-agent nivolumab and nivolumab plus ipilimumab, respectively. TMB was determined by whole-exome sequencing, and was calculated as the total number of missense mutations in the tumour. For the analysis, patients were divided into 3 subgroups based on the TMB tertile. The TMB-evaluable patients were representative of the overall population, with comparable PFS and OS outcomes in both treatment arms.

Improved activity with high TMB

According to the ORR analysis by TMB subgroup, an incremental increase was observed for nivolumab treatment, ranging from 4.8 % to 21.3 % across the groups with low, medium and high TMB **(Figure 1)**. The combination of nivolumab and ipilimumab, on the other hand, gave rise to similar response rates in the low and medium TMB cohorts, while the high TMB group showed an impressive ORR of 46.2 %.

In a similar vein, there was a differential benefit for PFS, with the high TMB cohort experiencing considerably longer progression-free intervals with both treatments. At 1 year, PFS rates were 21.2 % and 30.0 % for nivolumab and the combination, respectively. As opposed to this, patients with low and medium TMB showed PFS rates in the single-digit range. The OS analysis revealed an incremental survival effect of rising TMB for nivolumab monotherapy; here, 1-year OS rates were 22.1 %, 26.0 % and 35.2 % for patients with low, medium, and high TMB, respectively. In contrast, patients receiving both nivolumab and ipilimumab fared considerably better when they had high TMB (1-year OS rate, 62.4 %) compared with low or medium TMB (23.4 % and 19.6 %, respectively).

Overall, as for the NSCLC setting, patients with SCLC were shown to respond differently to immunotherapeutic treatment according to their tumour mutation load. In those with high TMB, improved outcomes resulted for both nivolumab monotherapy and nivolumab plus ipilimumab, but the findings were clearly more robust for the combination. Optimisation of the TMB cut-off and prospective investigation of TMB are warranted. As the authors concluded, TMB might be a relevant predictive biomarker across all lung cancers.

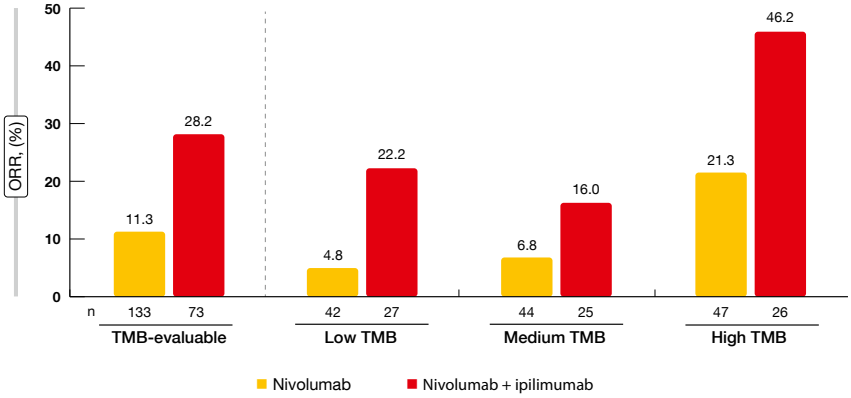

Figure 1: CheckMate 032: response rates according to tumour mutation burden

OAK: analysis according to Teff gene expression

High expression of the T-effector (Teff) gene signature, which is a marker of pre-existing immunity, has been demonstrated to correlate with improved survival in patients treated with the anti-PD-L1 antibody atezolizumab in the phase II POPLAR study [4]. Therefore, a retrospective, exploratory analysis of the phase III OAK study was conducted to assess the association between Teff gene expression and the clinical benefit achieved with atezolizumab in this trial [5]. Patients included in the OAK trial had received either atezolizumab or docetaxel in the second-line or later-line settings. The primary analysis showed significantly improved median OS with atezolizumab compared to docetaxel (13.8 vs. 9.6 months; HR, 0.73; p = 0.0003), but a PFS benefit with atezolizumab was only observed in patients with high PD-L1 expression [6].

In the primary OAK population, 753 patients had tumour tissue sufficient for the evaluation of Teff gene expression. For the purposes of this analysis, the Teff signature was defined by mRNA expression of three genes (*PDL1*, *CXCL9*, *IFNG*). There was a partial overlap between the Teff gene signature and PD-L1 expression according to immunohistochemistry (IHC), but at the same time, the Teff gene signature identified a unique patient subset within the PD-L1–negative population.

Higher accuracy of PFS prediction

The results of the study imply that the Teff gene signature is a more sensitive biomarker of PFS than PD-L1 expression. Three different Teff gene expression levels were assessed. The analysis showed a significant association between higher expression levels and the atezolizumab-mediated PFS benefit. PFS HR was 0.73 for patients with high Teff gene expression (≥ 50 %), but 1.30 for those with low expression (< 50 %).

TABLE
Progression-free survival HRs achieved with atezolizumab in subgroups defined by PD-L1 IHC and Teff gene signature in the OAK study

	PD-L1 IHC TC 1/2/3 or IC1/2/3	Teff signature ≥ median
Population prevalence of the marker	55 %	51 %
HR (95 % CI)	0.93 (0.76, 1.15)	0.73 (0.58, 0.91)
HR (95 % CI) Biomarker-evaluable population (n = 753)	0.94 (0.81, 1.10)	

TC, tumour cells; IC, immune cells

Compared to PD-L1 status according to IHC, the Teff signature identified a larger number of patients who experienced a significant PFS benefit with atezolizumab therapy at a comparable population prevalence of the two biomarkers **(Table)**. For OS, the atezolizumab-mediated benefit resembled that observed in the entire biomarker-evaluable population, although the Teff signature also enriched for improved results at all expression cut-offs.

These findings suggest that pre-existing immunity could be an important biological aspect determining the efficacy of immunotherapeutic agents in lung cancer patients. Ongoing studies are designed to further validate a role for the Teff gene signature as a potential predictive biomarker of immunotherapy efficacy in first-line NSCLC treatment.

PACIFIC study: function and quality of life

The double-blind, placebo-controlled, international, phase III PACIFIC trial compared the anti-PD-L1 antibody durvalumab 10 mg/kg every 2 weeks for up to 12 months (n = 476) with placebo (n = 237) in patients with stage III, locally advanced, unresectable NSCLC who had not progressed following definitive platinum-based concurrent chemoradiation. Patients were not selected according to PD-L1 expression status. The interim PFS analysis yielded significantly superior findings with durvalumab compared to placebo (median PFS, 16.8 vs. 5.6 months; HR, 0.52; p < 0.0001) [7].

At the WCLC, Hui et al. presented patient-reported outcomes (PROs), which were a pre-specified secondary endpoint of the PACIFIC study [8]. Symptoms, physical function and global health status/ quality of life were evaluated using the EORTC QLQ-C30 v3 questionnaire and its lung cancer module, QLQ-LC13. According to this, the scores for key symptoms as well as functioning and global health status remained stable throughout the study with both durvalumab and placebo. There were no significant differences between arms with regard to changes from baseline. Clinically relevant improvements within each arm from baseline were observed at week 48 for dysphagia and alopecia, which suggests resolution of toxicities related to the concurrent chemoradiation therapy that all patients received. Odds of improvement of the item ‚appetite loss' were greater with durvalumab, while no between-arm differences in improvement rates existed for functioning or other symptoms. For time to deterioration of functioning and symptoms, the analysis showed no differences between durvalumab and placebo with regard to most of the items. Only time to deterioration of ‚other pain' was longer with durvalumab (HR, 0.72). This difference, however, was not reflected in any additional ‚pain' terms.

Overall, this analysis showed that adding durvalumab for 12 months after chemoradiation did not compromise quality of life in patients with locally advanced, unresectable NSCLC. Alongside the positive efficacy and safety data from PACIFIC, these findings further support the clinical value of durvalumab in the early-stage setting.

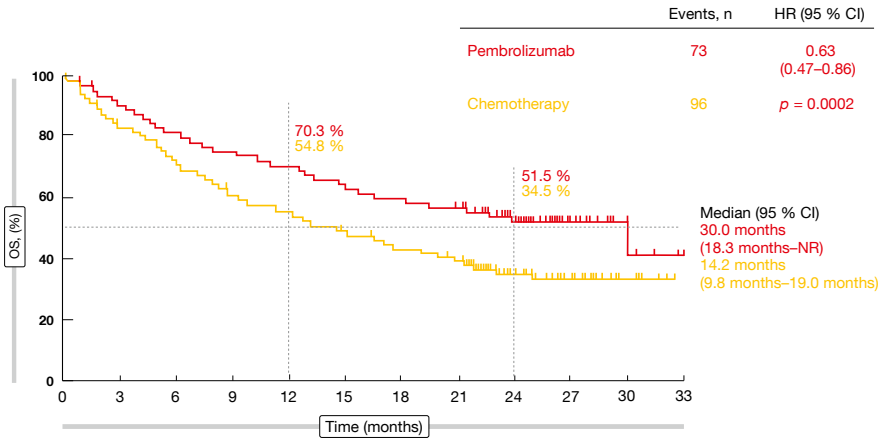

Figure 2: Updated overall survival outcomes in the KEYNOTE-024 trial

First-line pembrolizumab: update of KEYNOTE-024

Brahmer et al. presented the updated analysis of the international, randomised, open-label, phase III KEYNOTE-024 trial that compared pembrolizumab and platinum-based chemotherapy in 305 untreated patients with stage IV NSCLC expressing PD-L1 (tumour proportion score [TPS] ≥ 50 %) [9]. The primary analysis has revealed significant superiority of pembrolizumab over chemotherapy with respect to PFS (HR, 0.50) and OS (HR, 0.60), but median OS in the pembrolizumab arm had not been reached at that time [10].

After a median follow-up of 25.2 months, the updated OS analysis showed a significant benefit for pembrolizumab with a remarkable median survival outcome of 30.0 months (vs. 14.2 months in the chemotherapy arm; HR, 0.63; p = 0.002; **Figure 2**). 24-month OS rates were 51.5 % and 34.5 % for patients treated with pembrolizumab and chemotherapy, respectively. This improvement was maintained in spite of a significant effective crossover rate to anti-PD-1 treatment in the chemotherapy arm that amounted to 63 %.

ORRs were 45.5 % vs. 29.8 % for pembrolizumab and chemotherapy, respectively (p = 0.0031). Patients who crossed over to pembrolizumab experienced an ORR of 20.7 %. In all pembrolizumab-treated patients, median duration of response had not been reached yet (vs. 7.1 months in the chemotherapy arm). After a median exposure of 7.9 months, which was more than double that in the chemotherapy arm, pembrolizumab continued to demonstrate a favourable safety profile. The authors concluded that pembrolizumab remains a standard of care for the first-line therapy of patients with NSCLC and high PD-L1 expression (TPS ≥ 50 %).

Nivolumab in patients with brain metastasis

An Italian expanded access programme offered the opportunity to evaluate nivolumab 3 mg/kg every 2 weeks for a maximum of 24 months in patients with stage IIIB/IV, non-squamous NSCLC and CNS metastases outside of a controlled clinical trial [11]. Patients with brain lesions were eligible if they

had no neurologic symptoms at least 2 weeks before enrolment and did not require systemic corticosteroid treatment or were on a stable or decreasing dose of ≤ 10mg/day of prednisone or prednisone equivalent. Among the total population of 1,588 patients who participated at 153 centres, 409 (26 %) had asymptomatic and controlled brain metastases. Twenty-nine percent were receiving steroid therapy at baseline, and 18 % had concomitant radiotherapy.

Efficacy and safety of nivolumab therapy in this group appeared similar to that observed in the overall cohort and the CheckMate 057 trial population [12]. ORR and DCR were 17 % and 40 %, respectively. CR occurred in four patients (1 %), PR in 64 patients (16 %), and SD in 96 patients (23 %). Median OS was 8.6 months for patients with CNS metastasis, compared with 11.3 months for all patients. At 1 year, 43 % and 48 % of patients in the CNS metastasis and overall cohorts, respectively, were alive. Both the CNS cohort and the overall population showed a median PFS of 3.0 months. PFS 1-year rates were 20 % and 22 %. These results suggested that patients with CNS metastasis could benefit from immunotherapy with nivolumab. ■

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Approaching squamous-cell carcinoma in a targeted manner

Possible benefit from afatinib

The *EGFR* mutation status is not routinely examined in NSCLC patients with squamous cell cancer (SCC) histology due to the low incidence of *EGFR* mutations in these tumours and poor clinical response to first-generation EGFR TKI treatment. Taniguchi et al. retrospectively reviewed 441 consecutive patients in 23 of whom the *EGFR* mutation status was assessed, in order to explore the clinical features of SCC with sensitive *EGFR* mutation, and to select the optimal indications for afatinib treatment [1].

Five patients tested positive for sensitising *EGFR* mutations (exon 19 deletion and L858R mutation). All of these were female and never smokers. Four had normal lung function, and only one had underlying emphysema/ fibrosis. Four patients received TKI treatment; gefitinib and afatinib were administered in two patients each. While gefitinib did not elicit any clinical responses, the afatinib-treated patients responded well, achieving partial remissions. At the time of the analysis, they were still alive, whereas the gefitinib-treated patients had died. In their conclusion, the authors noted that patients with SCC might benefit from afatinib treatment. Patient selection using baseline characteristics could contribute to identifying a population with greater sensitivity to afatinib.

ErbB mutation status counts

A genetic analysis of patients who participated in the LUX-Lung 8 trial was conducted with the aim of establishing the frequency of *ErbB* family mutations and the patient outcomes according to mutation status [2]. LUX-Lung 8 compared second-line afatinib and erlotinib in patients with SCC, revealing significant benefits in the afatinib-treated group [3]. Tissue samples were retrospectively selected and enriched for patients with PFS ≥ 2 months to reflect a range of responsiveness to EGFR TKIs. The tumour genetic analysis subset consisted of 245 patients, 132 of whom had received afatinib. This cohort was representative of the overall LUX-Lung 8 population; both PFS and OS favoured afatinib over erlotinib.

As the analysis showed, 53 patients (21.6 %) had at least one *ErbB* family mutation. In both wild-type and *ErbB*-mutation-positive cohorts, afatinib gave rise to superior PFS **(Figure)** and OS

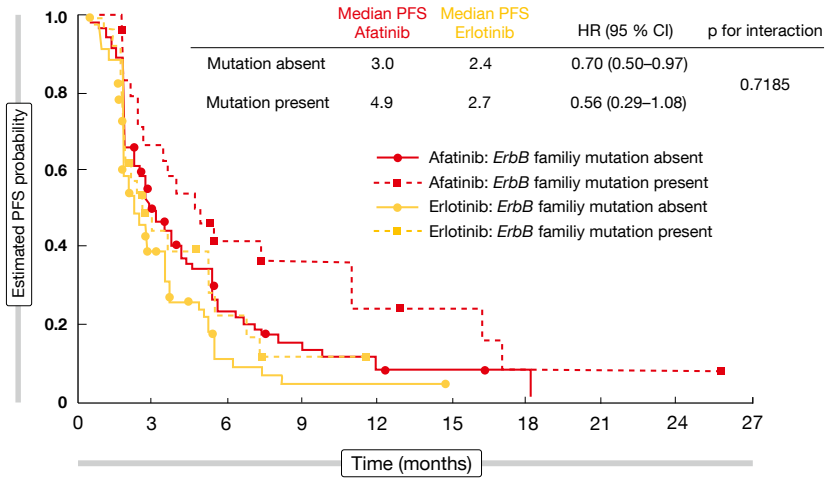

Figure: Progression-free survival obtained with afatinib vs. erlotinib in LUX-Lung 8 according to *ErbB* family mutation status

compared to erlotinib, although this effect was more pronounced in the mutant group. For erlotinib, on the other hand, PFS and OS did not differ according to *ErbB* mutation status. OS achieved with afatinib was 10.6 months in the *ErbB*-mutation-positive group and 8.1 months in the wild-type population.

The accentuated benefit of afatinib over erlotinib in patients with *ErbB* mutations did not appear to be driven by *EGFR*, as the largest benefits were observed with *HER3*, *HER4*, and, in particular, *HER2* mutations. No apparent correlation emerged between *ErbB* amplification or EGFR expression and clinical outcomes. The authors concluded that next-generation sequencing might help to identify patients with SCC of the lung who could derive additional benefit from afatinib or erlotinib. The role of *ErbB* mutations, particularly *HER2* mutations, as predictive markers for afatinib warrants further evaluation.

Ongoing trial of afatinib plus pembrolizumab

Preclinical evidence suggests that both the immune microenvironment and tumour expression of PD-L1 can be modulated by EGFR signaling in *EGFR*-mutant NSCLC [4, 5]. Afatinib is currently being tested in combination with the anti-PD-1 antibody pembrolizumab based on the assumption that concurrent inhibition of the EGFR and PD-1 pathways represents a rational and promising approach for treatment of SCC of the lung, to improve responses and delay the onset of resistance [6]. Recruitment into the open-label, single-arm phase II trial named LUX-Lung IO/ KEYNOTE 497 started in October 2017 in the USA, Spain, France, South Korea, and Turkey (NCT03157089). Objective response has been defined as the primary endpoint. The target population comprises 50 to 60 patients. ■

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Malignant mesothelioma: recent data on nintedanib and checkpoint inhibitors

Malignant pleural mesothelioma (MPM) is an aggressive tumour that, if left untreated, shows a median survival of 7–9 months [1]. The front-line standard treatment for patients with unresectable MPM consists of combination doublet therapy with cisplatin and pemetrexed, which yields a median OS of approximately 1 year.

Biomarker analysis of the LUME-Meso trial

The angiokinase inhibitor nintedanib has been tested successfully in MPM patients in the randomised, double blind, placebo-controlled phase II/III LUME-Meso trial. In the phase II part of the study, 87 chemotherapy-naïve patients with unresectable epithelioid or biphasic MPM received either nintedanib plus pemetrexed/ cisplatin or placebo plus chemotherapy. Here, the addition of nintedanib to chemotherapy improved PFS to a clinically meaningful extent (9.4 vs. 5.7 months; HR, 0.54; p = 0.010), and there was a trend towards improvement in OS (18.3 vs. 14.2

TABLE
Anti-tumour activity of tremelimumab plus durvalumab in malignant mesothelioma (ITT population)

Tumour response	Patients (n = 40)
ir-ORR, % (95 % CI)	27.5 (14.6-43.9)
- ir-CR, %	0
- ir-PR, %	27.5
- ir-SD, %	37.5
- ir-PD, %	35.0
ir-DCR, % (95 % CI)	65.0 (48.3-79.4)
Median duration of ir-OR, months	Not reached
Median duration of disease control, months (95 % CI)	14.1 (12.1-16.1)

months; HR, 0.77; p = 0.319) [2]. The efficacy of treatment was most pronounced in patients with epithelioid histology.

Nowak et al. conducted an exploratory biomarker analysis in the epithelioid population that covered plasma levels of 58 angiogenic factors, SNPs in genes for mesothelin, VEGFR1 and VEGFR3, and microvessel density [3]. Predictive and prognostic analyses were performed for OS and PFS. However, none of these biomarkers showed a clear association with treatment benefit after false discovery rate adjustment, although the analyses were limited by the small sample size. The only marker that was predictive for both OS and PFS was plasma endoglin, with higher levels suggesting smaller benefits from the addition of nintedanib. VEGF-D appeared to have a certain predictive value for OS, but this did not hold true for PFS. For SNPs, there was a signal that two VEGFR3 polymorphisms might be predictive of lesser benefit of nintedanib. These findings will be evaluated further in the phase III part of the study.

The confirmatory phase III part of the LUME-Meso trial is currently enrolling patients with unresected epithelioid MPM at approximately 140 centres worldwide [4]. Nintedanib plus pemetrexed/ cisplatin followed by nintedanib maintenance is being compared with placebo plus chemotherapy followed by placebo maintenance. PFS constitutes the primary endpoint.

Immunotherapeutic approaches

Goto et al. assessed the use of the checkpoint inhibitor nivolumab in the second-line or third-line setting [5]. Thirty-four patients with advanced or metastatic MPM who were resistant or intolerant to platinum-based combination therapy with pemetrexed participated in the MERIT trial. ORR was 29.4 % in the total population. Patients with all histologies responded to treatment: ORRs for epithelioid, sarcomatoid and biphasic histology were 25.9 %, 66.7 %, and 25.0 %, respectively. The DCR amounted to 67.6 %. Median PFS was 6.1 months; at 6 months, half of the patients remained progression-free. Median OS had not been reached at the time of the analysis, with a 6-month OS rate of 85.3 %. The toxicity profile proved manageable. Grade 3/4 AEs occurred in 11.8 % of patients, and AEs necessitated treatment discontinuation in 5.9 %.

The NIBIT-MESO-1 trial investigated the combination of the anti-CTLA-4 antibody tremelimumab with the anti-PD-L1 antibody durvalumab in 40 mesothelioma patients who were refractory to or had relapsed after first-line chemotherapy, or had refused it [6]. The study met its primary objective, which was defined as immune-related (ir) ORR. In the ITT population, ir-ORR was 27.5 %, and an additional 37.5 % of patients achieved ir-SD **(Table)**. This translated into an ir-DCR of 65.0 %. Median duration of ir-OR had not been reached at the time of the analysis, and median duration of disease control was 14.1 months.

Immune-related AEs of any grade occurred in 75 % of patients; grade 3/4 AEs were observed in 17.5 %. Treatment-related AEs were generally manageable and reversible. The authors concluded that the combination of tremelimumab and durvalumab is active and shows a good safety profile in malignant mesothelioma. Further exploration is warranted. ■

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Chemotherapy: new approaches, new settings

SCAT: customising adjuvant chemotherapy using BRCA1

Current guidelines recommend postoperative platinum-based chemotherapy in completely resected NSCLC with nodal involvement (stage II-IIIA) [1]. However, survival outcomes remain limited, and compliance is lower than for adjuvant therapy in other neoplasms. There are no direct comparisons between different chemotherapy regimens.

The analysis of expression of genes involved in DNA repair could be used to individualise the choice of optimal chemotherapy agents and schedules [2]. Here, the *BRCA1* gene has significance as it plays a role in the homologous recombination pathway and functions as a differential regulator of response to cisplatin and antimicrotubule agents. It has prognostic and predictive relevance; low levels translate into low risk and cisplatin sensitivity, while high levels indicate high risk and cisplatin resistance, which implies that the patient is sensitive to taxane-based chemotherapy.

A BRCA1-guided treatment approach was tested by the randomised SCAT trial, which contained patients with resected NSCLC R0 pN1/ pN2 [3]. While the control arm received docetaxel plus cisplatin, patients randomised to the experimental arm were treated according to BRCA1 expression levels. Patients with low BRCA1 expression received gemcitabine/ cisplatin, those with medium levels, cisplatin/ docetaxel, and those with high levels, docetaxel alone. Four cycles were administered every 21 days. Chemotherapy was started within 8 weeks after surgery. The per-protocol treatment population included 102 patients in the control arm and 354 in the experimental arm. OS constituted the primary endpoint.

Single-agent docetaxel appears sufficient in high expressors

Low levels of BRCA1 expression were significantly associated with female sex, never-smoking status, adenocarcinoma histology, and mediastinal lymph node involvement. Higher levels, on the other hand, correlated with male sex, squamous histology, and current or former smoker status.

According to the primary analysis, customisation of adjuvant chemotherapy according to BRCA1 levels did not induce a significant OS difference between the experimental arm and the control arm (82.4 vs. 69.3 months; HR, 0.946). Five-year survival rates exceeded 50 % in both arms (56 % and 54 %, respectively). In the experimental group, there was no striking variation of median OS, which ranged from 74 to 80.5 months. In contrast, patients treated in the control cohort fared worst when expressing high BRCA1 levels (OS, 40.1 months), whereas outcomes were markedly improved for those with intermediate and high levels (not reached and 82.4 months, respectively). In a multivariate Cox analysis, BRCA1 levels were found to be prognostic in the control group.

When analysed across the two treatment arms according to BRCA1 subgroup, patients with low expression levels were shown to benefit from cisplatin/ gemcitabine compared to cisplatin/ docetaxel (74 vs. 40.1 months; HR, 0.622; **Figure**). However, for the BRCA1 high expression group, there was no difference between the experimental and control regimens, i.e. survival achieved with docetaxel alone resembled the OS outcomes in the docetaxel/ cisplatin cohort. The compliance relating to planned treatment was significantly improved for the group without cisplatin in the experimental arm. Patients treated

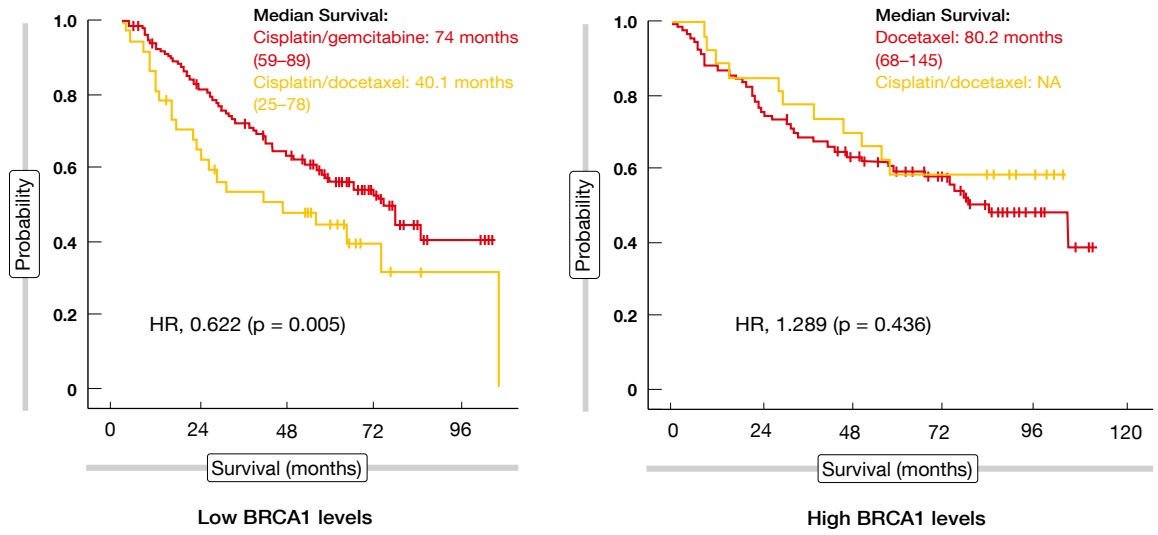

Figure: SCAT trial: progression-free survival analysis according to BRCA1 subgroups across treatment arms

TABLE
Response outcomes in the ABOUND.2L+ trial for nab-paclitaxel plus durvalumab

Response outcome, n (%)	Nab-paclitaxel + durvalumab (n = 79)	Nab-paclitaxel + durvalumab (non-squamous) (n = 55)	Nab-paclitaxel + durvalumab (squamous) (n = 23)
Overall response	21 (26.6)	13 (23.6)	8 (34.8)
- Complete response	1 (1.3)	1 (1.8)	0
- Partial response	20 (25.3)	12 (21.8)	8 (34.8)
Stable disease	35 (44.3)	26 (47.3)	9 (39.1)
Disease control rate (≥ stable disease)	56 (70.9)	39 (70.9)	17 (73.9)
Progressive disease	11 (13.9)	10 (18.2)	1 (4.3)
Response data pending	12 (15.2)	6 (10.9)	5 (21.7)

without cisplatin showed a trend to lower non–cancer-related mortality. Overall, the authors concluded that adjuvant taxane treatment without a platinum component might be assessed in patients with high BRCA1 expression levels. Here, it should be possible to avoid short-term and long-term platinum toxicity.

Surprisingly good second-line activity of nab-paclitaxel

Efficacious and tolerable chemotherapy options are called for in the second-line setting of advanced NSCLC. The randomised, open-label, multicentre phase II ABOUND.2L+ trial compared single-agent nab-paclitaxel with nab-paclitaxel plus oral azacitidine (CC-486) in 161 patients with advanced non-squamous NSCLC who had already undergone one platinum-based chemotherapy, but no prior taxane treatment [4]. Eighty patients received nab-paclitaxel monotherapy at a dose of 100 mg/m^2 on days 1 and 8 of a 21-day cycle, while 80 were treated with the combination of nab-paclitaxel (days 8 and 15 of a 21-day cycle) and CC-486 (200 mg orally on days 1 to 14 of a 21-day cycle).

The study did not meet its primary endpoint, as nab-paclitaxel plus CC-486 did not demonstrate superiority regarding PFS. Patients in the control arm fared surprisingly well, experiencing even better PFS than those in the experimental arm (4.2 vs. 3.2 months; HR, 1.3). This was also true for OS (13.6 vs. 8.1 months; HR, 1.5) and ORRs (15.0 % vs. 13.6 %). Disease control, which was defined as the combination of CR, PR and SD, occurred in 67.5 % vs. 65.4 %. According to the quality-of-life analysis, nab-paclitaxel gave rise to improved outcomes for respiratory symptom, symptom burden index, and global quality-of-life scores. Both regimens were well tolerated. Grade ≥ 3 adverse events (AEs) remained in the single-digit range for both arms.

After all patients had been recruited, the investigators were advised to discontinue CC-486 treatment. Although the combination had not brought about any added benefit, single-agent nab-paclitaxel showed promise as a second-line drug in the treatment of advanced non-squamous NSCLC. Results from ongoing trials will provide further insight into the role of nab-paclitaxel in this setting.

Immunotherapy plus chemotherapy

A third treatment arm was implemented in the ABOUND.2L+ trial in March 2016, with the objective of investigating the addition of the anti-PD-L1 antibody durvalumab to nab-paclitaxel [5]. Seventy-nine patients with advanced non-squamous or squamous NSCLC received nab-paclitaxel 100 mg/m^2 on days 1 and 8 of a 21-day cycle plus durvalumab 1,125 mg on day 15 of a 21-day cycle. Approximately one third showed squamous histology. As with the other two arms of ABOUND.2L+, one prior platinum-based chemotherapy was allowed, while prior taxanes were not, but patients could have had immune checkpoint inhibitor therapy before trial inclusion. This was the case for 11.4 % of the population. PFS was defined as the primary endpoint.

The combined treatment with paclitaxel plus durvalumab gave rise to a median PFS of 4.5 months. Median OS had not been reached yet. Somewhat unexpectedly, patients who had received immune checkpoint inhibitor treatment before enrolment experienced superior PFS compared with the checkpoint-inhibitor–naïve group (6.9 vs. 4.4 months), but these results must be regarded with caution due to the small number of pretreated patients. Also, patients with squamous histology achieved longer PFS than those with non-squamous histology (5.9 vs. 4.2 months). ORR was 26.6 % in the overall population **(Table)**, which compares favourably to outcomes achieved with other therapies in the second-line setting. Again, the subgroup analysis revealed comparatively better findings in patients with squamous NSCLC than in those with non-squamous tumours (34.8 % vs. 23.6 %). Overall, the trial yielded a commendable DCR of 70.9 %.

Toxicity proved predictable, with peripheral sensory neuropathy, dyspnoea, neutropenia and anaemia reported as the most common AEs. Febrile neutropenia did not occur. The authors concluded that the combination of nab-paclitaxel and durvalumab demonstrated anti-tumour activity with manageable toxicity in the second-line or third-line treatment of patients with advanced NSCLC. These data provide further support for the use of nab-paclitaxel as a chemotherapy partner for immune checkpoint inhibitors in NSCLC.

Nab-paclitaxel in squamous-cell carcinoma

As therapeutic options for squamous-cell lung cancer remain limited, the phase II trial presented by Paik et al. is currently testing nab-paclitaxel plus

gemcitabine in patients with untreated stage IV squamous NSCLC. The findings presented at the WCLC showed that nab-paclitaxel plus gemcitabine has promising efficacy and is well tolerated compared to platinum-based regimens [6]. Twenty-one patients were enrolled and treated with one of two dosing regimens.

ORR is defined as the primary objective of the trial. At the time of the analysis, this was 58 %, with a duration of response of 7.5 months. PFS was 6.1 months, and OS was 13.9 months. In comparison, platinum-based chemotherapies, which have been the standard first-line agents for almost 20 years, are known to induce ORRs of 30 % to 40 %, median PFS of 4 to 5.7 months, and median OS of 9 to 11.5 months [7-9]. Fatigue, oedema, peripheral neuropathy and nausea predominated among AEs, the majority of which were grade 1. Serious AEs included leukopenia, diarrhoea, and lung infection. Accrual to the trial is ongoing with a focus on PD-L1–negative patients.

Adjuvant doublet chemotherapy including nedaplatin

Nedaplatin is a cisplatin derivative developed in Japan. A prospective, multi-institutional phase II study evaluated the feasibility of combination chemotherapy with docetaxel and nedaplatin in the adjuvant treatment of 34 patients with NSCLC stage IB-IIIA, who had undergone radical surgery including lobectomy and lymph node dissection [10]. On day 1 of 4 cycles, docetaxel and nedaplatin were administered at 60 mg/m² and 80 mg/m², respectively. Feasibility (i.e., the proportion of patients who completed 4 cycles) was defined as the primary endpoint, and toxicity and relapse-free survival (RFS) constituted the secondary endpoints.

The results demonstrated that adjuvant chemotherapy with docetaxel plus nedaplatin is feasible and tolerable for patients with completely resected NSCLC. Overall, 76.5 % of patients completed all of the 4 cycles. Median RFS had not been reached at the time of the analysis, and the 5-year RFS rate was 65.8 %. The incidence of haematologic and non-haematologic AEs was lower than for the combination chemotherapy of cisplatin plus vinorelbine tested in the ANITA trial [11]. ■

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Interview: Fred R. Hirsch, MD, PhD; CEO of the IASLC, Professor, University of Colorado School of Medicine, Denver, Colorado, USA

Survival is the result of lung cancer screening

During Lung Cancer Awareness Month (LCAM) in November, memo inOncology spoke with Dr. Fred Hirsch, who is CEO of the International Association for the Study of Lung Cancer (IASLC) and professor at the University of Colorado School of Medicine in Denver, USA. The Lung Cancer Awareness Month Coalition (LCAMC) is a group of more than 20 global non-profit organisations focused on improving outcomes for patients with thoracic cancers, led by the IASLC.

What are the reasons why lung cancer screening is only implemented in a fraction of high-risk individuals who would qualify for it?
The US Preventive Services Task Force recommends that patients aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit smoking within the past 15 years are screened for lung cancer using low-dose CT scans. These guidelines are also supported by the Centers for Medicaid and Medicare Services (CMS). The basis for that recommendation was the randomised National Lung Screening Trial (NLST) study, which compared low-

dose CT screening with conventional chest X-ray screening, showing a reduction in lung cancer mortality of 20 % for CT scans *versus* X-ray scans.

However, implementation of these screening guidelines in the United States has been very slow. The reason for that can be multifold; one main reason is a lack of education about guidelines among the general public and health care personnel. Another reason might be the high false-positive rate that can occur with CT scans (most CT detected nodules are not malignant, and some individuals have to undergo further diagnostic work-up to discover that their nodules are benign). Physicians might be wary of using low-dose CT scans given the false-positive rate.

In many other countries, screening guidelines do not yet exist, as they wait for more scientific evidence based on other studies. Regardless of the country, we need to encourage the creation and implementation of comprehensive guidelines so that we can detect lung cancer in earlier stages when treatment is most effective. It is critical to educate physicians on the tremendous impact of implementing guidelines, as well as the public on risk factors that make them eligible for screening. If successful, we can significantly reduce the mortality rate from lung cancer around the world.

What can be done to educate community physicians about the range of modern treatment options that have emerged in rapid succession over the last few years?

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Fred R. Hirsch, MD, PhD
CEO of the IASLC, Professor, University of Colorado School of Medicine, Denver, Colorado, USA

In recent years, we have seen tremendous success with new treatment methods like precision medicine and immunotherapies. Through research of tumor cells, scientists are identifying specific abnormalities that fuel the growth of tumours. With that knowledge, doctors are developing unique, precision treatments that target abnormalities. We are also seeing the development of exciting medicines that activate patients' immune systems to better identify and attack cancer cells. While these treatments are still emerging, results from clinical trials have been very promising. Unfortunately, these successes are often limited to specific countries and academic centers where the research community is vibrant. It is critical that we are sharing the newest advances with physicians across the world and giving them the latest scientific knowledge that they can leverage with their own patients.

Where do you see obstacles to setting up clinical lung cancer trials?

One of the biggest challenges we face in setting up more clinical trials is a lack of patient participation. In fact, only 3 to 5 % of lung cancer patients in the US participate in clinical trials. Often times, patients and their physicians are not aware of potential trials – either because they simply do not know of their existence or because they are not up-to-speed on the latest applicable research. Some patients only become aware of clinical trial options after they have undergone other treatments, which in many cases, disqualifies them from trials in the future.

Another major obstacle is the lack of sufficient funding and research for lung cancer across the globe. Even though lung cancer is responsible for 32 % of cancer deaths, it only receives 10 % of cancer research funding. This gap in funding results in too few clinical studies initiated by clinical investigators. ■

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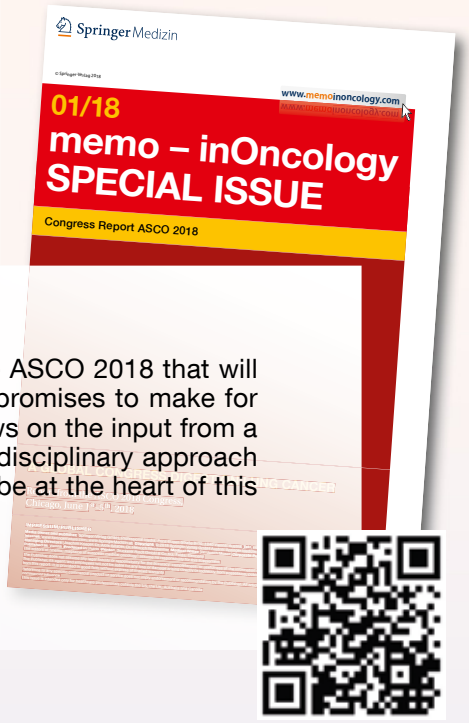

Forthcoming Special Issue

This special issue will be offering a synopsis from the ASCO 2018 that will be held in Chicago, in June of next year. The report promises to make for stimulating reading, as the ASCO Congress itself draws on the input from a number of partner organizations, representing a multidisciplinary approach to cancer treatment and care. Again, lung cancer will be at the heart of this special issue.

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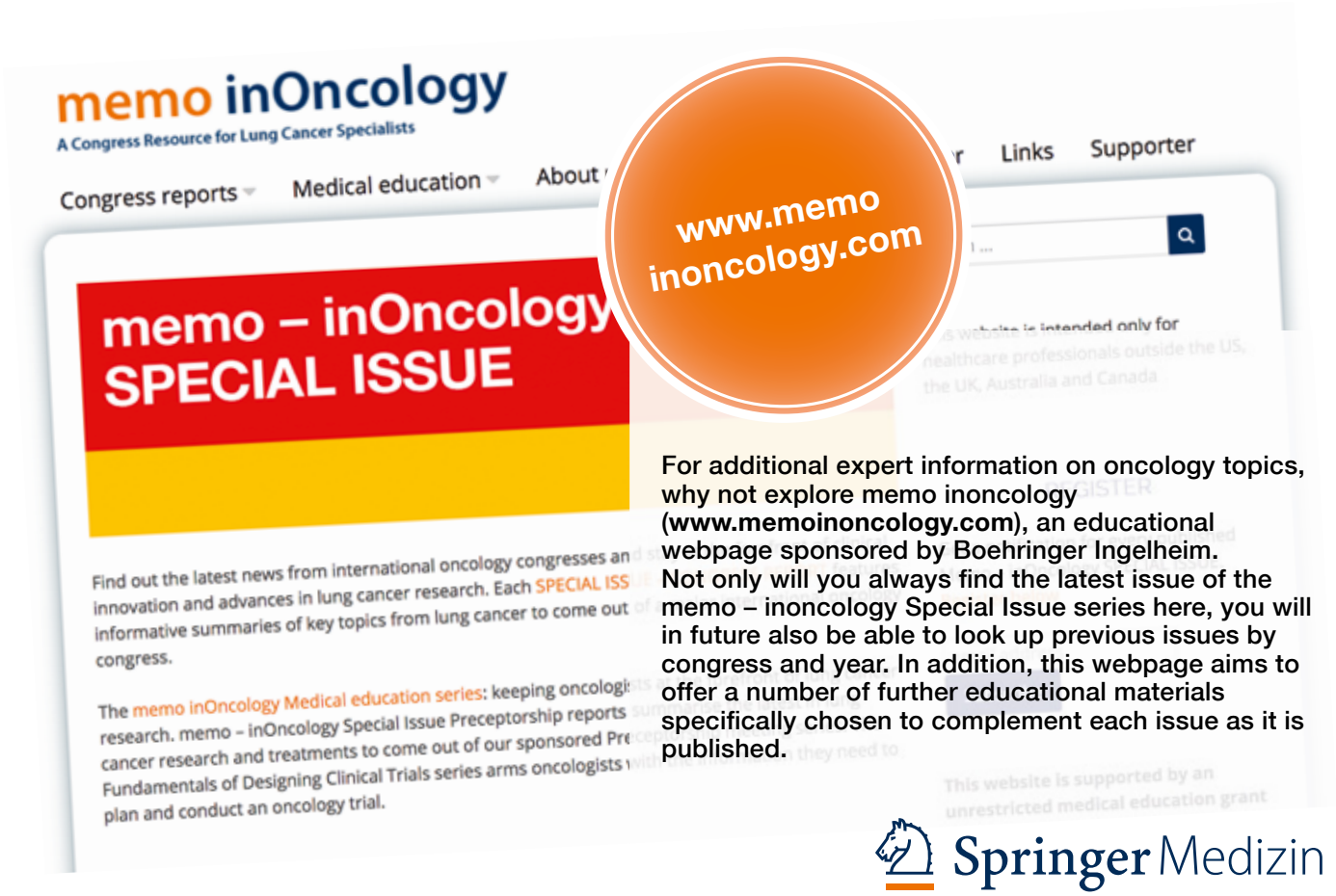

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