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02/17

memo – inOncology SPECIAL ISSUE

Congress Report ASCO 2017

A GLOBAL CONGRESS DIGEST ON LUNG CANCER

Report from the ASCO 2017 Congress,
Chicago, June 2nd–6th, 2017

IMPRESSUM/PUBLISHER

Media owner and publisher: Springer-Verlag GmbH, Professional Media, Prinz-Eugen-Straße 8–10, 1040 Vienna, Austria, **Tel.:** +43(0)1/330 24 15-0, **Fax:** +43(0)1/330 24 26-260, **Internet:** www.springernature.com, www.SpringerMedizin.at. **Copyright:** © 2017 Springer-Verlag GmbH Austria. Springer Medizin is a Part of Springer Nature. **Managing Directors:** Joachim Krieger, Dr. Alois Sillaber, Dr. Heinrich Weinheimer. **Medical Writer:** Dr. Judith Moser. **Corporate Publishing:** Elise Haidenthaller. **Layout:** Katharina Bruckner. **Published in:** Vienna. **Produced in:** Fulda. **Printer:** Druckerei Rindt GmbH & Co KG, Fulda, Germany;
The editors of "memo, magazine of european medical oncology" assume no responsibility for this supplement.

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Supported by Boehringer Ingelheim in the form of an unrestricted grant

Preface

Dear Colleagues,

From the point of view of thoracic oncology, the 2017 ASCO Congress that took place from 2nd to 6th June, 2017, in Chicago, Illinois, offered no major highlights, but a range of interesting news. You will find a summary of selected presentations and posters in this issue of memo – inOncology that covers various targeted approaches as well as immunotherapy and mesothelioma.

Malignant pleural mesothelioma represents a difficult-to-treat entity with a generally poor prognosis. The management of these patients used to be limited by a paucity of therapeutic options, but there have recently been considerable steps forward. Novel agents including the angiokinase inhibitor nintedanib and immune checkpoint inhibitors have been tested in mesothelioma patients with encouraging results, although further research efforts are required, and confirmatory clinical studies are ongoing.

Immunotherapy is an emerging standard in lung cancer management, which is corroborated by the trial updates presented at ASCO 2017, many revealing durable treatment benefit over extended periods. Moreover, checkpoint inhibitors are being assessed in areas of unmet need such as the neoadjuvant and post-progression settings. Another important topic, which is being tackled from various directions, is the identification of determinants of response and resistance to immunotherapy. Genomic markers of course have an important role here, but also other parameters such as tumour burden dynamics.

In the field of EGFR-targeted therapies, research is increasingly moving towards overcoming acquired resistance, which as a rule limits initial responses to tyrosine kinase inhibitors. Laboratory studies are elucidating molecular mechanisms of resistance to individual therapies. Treatment of early stage patients with *EGFR*-mutant lung cancer is still under study. The adjuvant use of first-generation EGFR tyrosine kinase inhibitors might be discussed in the future, and the first-line armamentarium will most likely be augmented by the addition of another agent.

New treatment standards have been defined for patients whose lung tumours show *EML4-ALK* rearrangement, while HER2-targeted treatments are currently subject to clinical research. An issue deserving particular attention is metastatic disease to the central nervous system,

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which poses a major challenge in the management of lung cancer patients. Drugs that can penetrate the blood-brain barrier offer advantages, and the role of prophylactic cranial irradiation continues to be defined. Further evaluation of modern treatment options in this indication is vital.

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EGFR-targeted treatments: insights from the adjuvant to the resistant setting

Gefitinib after complete resection

Approximately 20 % to 25 % of non–small-cell lung cancer (NSCLC) patients are eligible for surgical resection with curative intent [1]. To date, cisplatin-based chemotherapy constitutes the adjuvant standard of care for patients with stage II-IIIA completely resected NSCLC. The first-generation EGFR tyrosine kinase inhibitor (TKI) gefitinib is used as standard first-line treatment in patients with advanced *EGFR*-mutant NSCLC. Gefitinib showed promising results as an adjuvant strategy in the phase III ADJUVANT trial. ADJUVANT was the first prospective randomised study to compare gefitinib with vinorelbine plus cisplatin in patients with completely resected stage II-IIIA (N1/N2) *EGFR*-mutant NSCLC [2]. In all, 220 patients were randomised to either gefitinib 250 mg/d for 24 months or vinorelbine plus cisplatin every 3 weeks for up to 4 cycles.

For the primary endpoint, which was disease-free survival (DFS), gefitinib showed significant superiority over the chemotherapy regimen (28.7 vs. 18.0 months; HR, 0.60; p = 0.005). Three-year DFS rates were 34 % *versus* 27 %, and all of the subgroups favoured the TKI therapy. The adverse event (AE) profile was in keeping with that reported previously, with no cases of interstitial lung disease in the ADJUVANT trial. Significantly greater proportions of gefitinib-treated patients experienced clinically relevant improvements in health-related quality of life during the study. The authors concluded that adjuvant gefi-

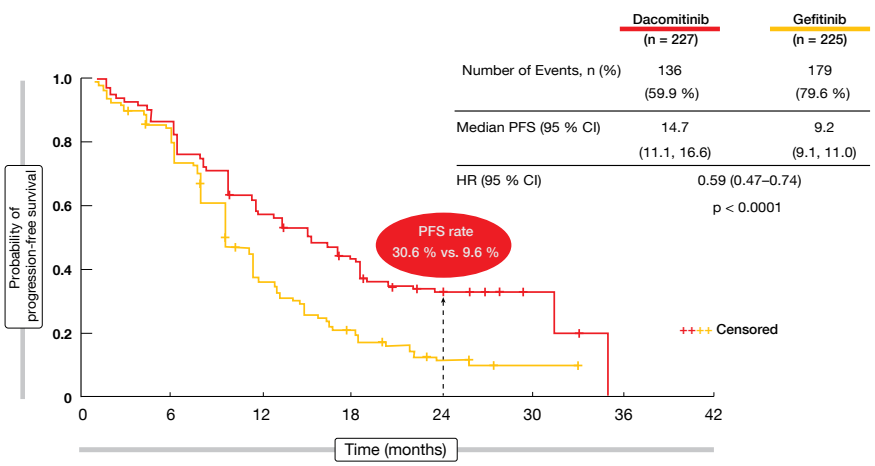

Figure 1: Dacomitinib *versus* gefitinib: PFS according to blinded independent review

tinib could become the preferred approach in the adjuvant setting; the 2-year treatment duration for gefitinib appears to be rational and safe. For overall survival (OS), the outcomes are still immature.

Alternative first-line agent: dacomitinib

At the same time, gefitinib might be superseded as a first-line agent by the second-generation, irreversible, ErbB family inhibitor dacomitinib. The randomised, open-label, phase III ARCHER 1050 trial compared dacomitinib 45 mg/d with gefitinib 250 mg/d in 452 untreated patients with advanced NSCLC and *EGFR*-activating mutations [3]. Seventy-one centres in seven countries participated in this study. The majority of the patients in both arms were of Asian origin.

For the primary endpoint of progression-free survival (PFS) according to blinded independent review, dacomitinib outperformed gefitinib significantly (14.7 vs. 9.2 months; HR, 0.59; p < 0.0001; **Figure 1**). These curves only started to separate after approximately 6 months of treatment, but then they kept separating throughout the entire observation period. At 24 months, PFS rates were 30.6 % *versus* 9.6 %. Distinct dacomitinib-related benefits were observed for all of the subgroups, with the exception of non-Asians, which might be due in part to the smaller sample size. An exploratory analysis addressed the question of whether non-Asians who responded to treatment (n = 72) indeed performed worse than Asians. Here, the PFS curves showed the same shape as in the total population, with a HR of 0.547.

Greater depth of response in the dacomitinib arm

Objective response rates (ORRs) did not differ between the study groups, although the duration of response was significantly longer in responders who received dacomitinib (14.8 vs. 8.3 months; p < 0.0001). This discrepancy can be explained by the greater depth of response in the experimental arm.

With regard to AEs, dacomitinib treatment gave rise to higher rates of diarrhoea, paronychia, rash and stomatitis, but there were only a few more grade 3 events than in the gefitinib arm. Gefitinib, on the other hand, tended to elicit alanine transaminase (ALT) increases, with markedly higher grade 3 rates (8.5 % vs. 0.9 %). Treatment discontinuations due to AEs occurred in 9.7 % *versus* 6.7 % for dacomitinib and gefitinib, respectively, and dose modification rates were 66.1 % *versus* 8.0 %. Dose modifications of dacomitinib were possible at two dose levels, while gefitinib allowed for only one dose reduction.

Patient-reported outcomes according to EORTC-QLQ-C30 and LC13 constituted a secondary endpoint. Here, the two agents induced similar improvements in key disease-associated symptoms. The authors concluded that dacomitinib should be considered as a new treatment option for first-line management of advanced *EGFR*-mutated NSCLC.

Delaying acquired resistance with anti-MET treatment

Patients treated with first-generation EGFR TKIs typically develop resistance within 10 to 14 months [4, 5]. In *EGFR*-mutant NSCLC, the receptor tyrosine kinase MET is expressed in approximately 25 % to 75 % of cases and represents a mechanism of acquired resistance to EGFR inhibition. The bivalent MET antibody emibetuzumab was tested in a phase II study that evaluated addition of emibetuzumab to first-line erlotinib, with the purpose being to delay acquired resistance to erlotinib in *EGFR*-mutant, metastatic NSCLC patients [6]. Only patients who showed disease control after an 8-week erlotinib lead-in were randomised to either emibetuzumab plus erlotinib (n = 71) or erlotinib alone (n = 70).

With regard to the primary endpoint of the study, there was no PFS difference in the intention-to-treat populations (9.3 vs. 9.5 months with the combination and erlotinib, respectively). Response rates and OS did not differ, either. However, the exploratory MET biomarker analysis indicated a clinically meaningful PFS benefit of the combination in the subgroup of patients with the highest MET expression (≥ 90 % cells with MET 3+ staining). Here, median PFS was 20.7 *versus* 5.4 months with erlotinib plus emibetuzumab and erlotinib, respectively (HR, 0.39).

Median OS results in this group were immature, but suggested a positive trend (not reached vs. 20.6 months; HR, 0.32). This was not explained by imbalances in baseline characteristics or molecular aberrations. AEs occurred with similar frequency in both treatment arms.

Dynamics of T790M-positive tumours

The secondary *EGFR* T790M mutation in exon 20 accounts for more than 50 % of acquired TKI resistance [7]. Gaut et al. examined patients with T790M mutations in terms of their response to treatment with TKIs and chemotherapy, with the aim to further characterise this important subset [8]. The patient cohort was acquired from patients who were enrolled but failed screening for the TIGER-2 and TIGER-X clinical trials that assessed the third-generation EGFR TKI rociletinib. These patients had evidence of a T790M mutation following disease

progression on most recent prior EGFR-directed therapy. In the group of patients with stage IV disease at the time of treatment (n = 97), 69 patients were T790M-positive, and 28 were T790M-negative.

This study confirmed that tumours that expressed T790M had a more indolent progression of disease than their T790M-negative counterparts. PFS was superior in the T790M-positive group, for both first-line TKI therapy (12.0 vs. 9.0 months; p = 0.021; **Table**) and initial chemotherapy (5.0 vs. 4.0 months; p = 0.025). For TKI rechallenge, the analysis showed no statistically significant PFS difference. Response rates did not differ to any significant degree between the two groups, although there was a trend towards higher ORRs in the T790M-positive cohort in the TKI rechallenge and chemotherapy settings.

Afatinib plus bevacizumab as a successful strategy

When the second-generation irreversible EGFR TKI afatinib was used as monotherapy, it had only modest activity in patients progressing on erlotinib or gefitinib [9]. However, data presented at the ASCO Congress indicated that the combination of afatinib and the VEGF antibody bevacizumab shows clinical efficacy and safety after acquired resistance to EGFR TKIs [10]. The prospective, multicentre, single-arm, phase II ABC trial evaluated the clinical efficacy and safety of afatinib 30 mg/d plus bevacizumab 15 mg/kg tri-weekly in *EGFR*-mutant NSCLC after acquired resistance to EGFR TKIs.

Thirty-two patients were analysed, among whom 6 (18.8 %) achieved partial responses **(Figure 2)**. Stable disease was achieved in 71.9 %, which provided a disease control rate (DCR) of 90.7 %. Patients with both T790M-positive and T790M-negative status responded to the therapy. Median PFS was 6.3 months, and median OS had not been reached at the time of analysis. PFS did not differ across patients with T790M-positive and T790M-negative disease (6.3 vs. 7.1 months, respectively; p = 0.7910). This was also true for the comparison between tumours expressing deletion 19 and those expressing the L858R mutation (6.3 vs. 5.1 months; p = 0.7777). The authors noted that afatinib plus bevacizumab might serve as a salvage option in patients with T790M-negative tumours.

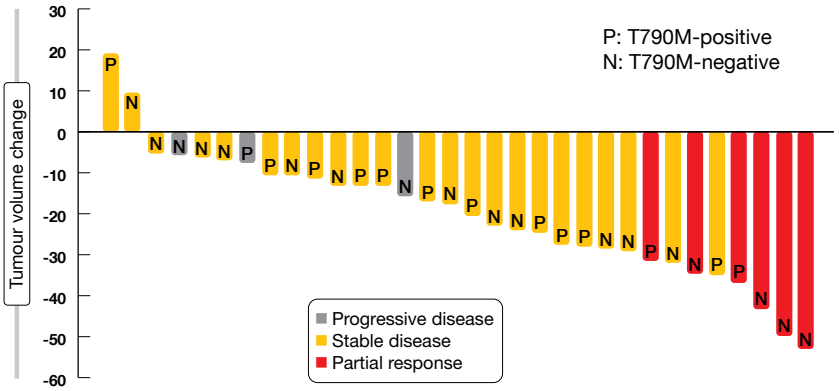

Figure 2: Responses to afatinib plus bevacizumab

Osimertinib *versus* docetaxel plus bevacizumab

Patients with T790M-positive resistance to prior EGFR TKI therapy are eligible for treatment with the third-generation, CNS-active, EGFR TKI osimertinib, which irreversibly inhibits both *EGFR*-activating mutations and the T790M resistance mutation. An open-label, randomised, phase III trial demonstrated superiority of osimertinib over docetaxel plus bevacizumab as third-line treatment in 147 NSCLC patients whose tumours had acquired the *EGFR* T790M mutation. Almost all of the outcomes favoured the EGFR TKI [11]. The osimertinib-treated arm fared better regarding PFS (10.2 vs. 2.3 months; HR, 0.23; p < 0.0001), ORR (61.6 % vs. 8.3 %) and clinical benefit rate (CBR; 87.6 % vs. 43.0 %). Grade 3 or 4 toxicities occurred considerably less frequently with osimertinib than with docetaxel plus bevacizumab. The median OS had not been reached in either group. Analyses according to the *EGFR* mutation subtype that was present in the tumours in addition to the T790M mutation revealed that PFS and OS were both similar in patients with exon 19 deletions and L858R mutations.

ASTRIS: real-world data on osimertinib

The open-label, single-arm, multinational ASTRIS trial is the largest real-world treatment study of osimertinib to date. Osimertinib 80 mg/d is being assessed in a global population of patients with T790M-positive advanced NSCLC, who had previously received an EGFR TKI. Patients with asymptomatic, stable CNS metastases that did not require increasing doses of corticosteroids within 2 weeks were enrolled.

At the time of the interim analysis in November 2016, 1,217 patients had received at least one dose of osimertinib [12]. In the majority of patients, T790M co-occurred with one other *EGFR* mutation. These were mostly exon 19 deletion, L858R mutation, and exon 20 insertion. The investigator-assessed response rate was 64 % for patients evaluable for response. Twenty-nine percent had achieved stable disease. Data on OS, PFS and time to treatment discontinuation were immature. The investigators summarised that clinical activity of osimertinib resembled that observed

TABLE
PFS with TKI therapy and chemotherapy based on T790M mutation status

Treatment	PFS (months)		HR	p-value
	T790M-positive patients	T790M-negative patients		
First-line TKI	12.0	9.0	1.75	0.021
TKI rechallenge	4.0	3.0	0.97	0.94
Chemotherapy	5.0	4.0	1.95	0.025

in the clinical trial programme. No new safety signals occurred. According to preliminary safety findings, 4 % of patients had AEs leading to discontinuation of osimertinib, and 2 % had fatal AEs. Interstitial lung disease/ pneumonitis-like events were reported in 2 % and QTc prolongation in 1 %. The second ASTRIS predefined interim analysis is planned for late 2017, and this will include more than 2,900 patients. ■

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New standards of care for *ALK*-positive disease

The first-generation ALK inhibitor crizotinib is the current standard option for patients with newly diagnosed, advanced *ALK*-positive NSCLC. However, patients invariably relapse on crizotinib treatment, with the central nervous system (CNS) being one of the most common and challenging sites of relapse. The second-generation ALK inhibitor alectinib is more potent than crizotinib [1, 2] and shows clinical activity in crizotinib-resistant NSCLC [3-6]. Notably, trial data have indicated significant CNS activity. Alectinib has become a standard therapy for patients with crizotinib pre-treated *ALK*-positive NSCLC, but research efforts are ongoing to establish it as a first-line option.

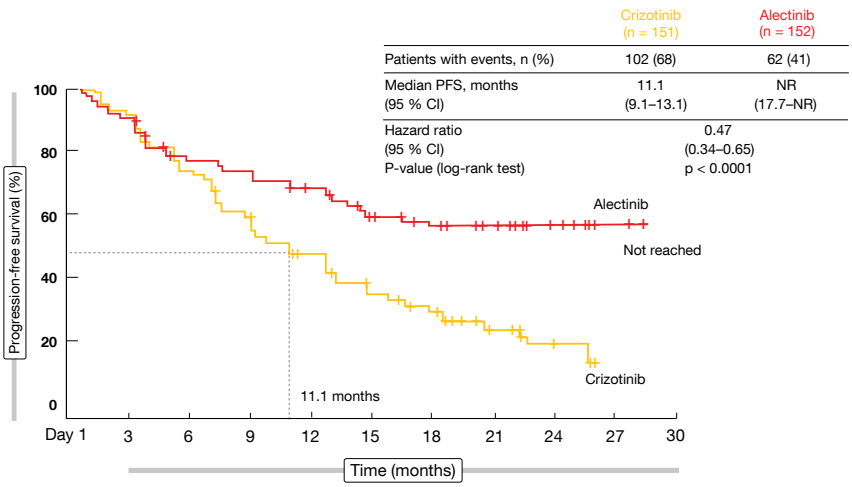

Figure 1: Primary endpoint of the ALEX trial: PFS for alectinib and crizotinib

Superiority of alectinib in ALEX

The ALEX trial evaluated alectinib 600 mg twice daily compared to crizotinib 250 mg twice daily in untreated patients with advanced or metastatic *ALK*-positive NSCLC [7]. ALEX was the first global randomised phase III study to compare a next-generation ALK TKI with a first-generation ALK TKI in the first-line setting. In all, 303 patients were randomised in a 1:1 fashion across 98 sites in 29 countries. Patients with asymptomatic, treated or untreated brain metastases were also enrolled. Approximately 40 % of individuals in each arm harboured CNS metastases, which were untreated in 60 % of cases. Investigator-assessed PFS was defined as the primary endpoint.

The study met its primary objective. At the time of the analysis, median PFS had not been reached in the alectinib-treated arm, while it was 11.1 months in the crizotinib arm (**Figure 1**). This translated into a risk reduction of 53 % (HR, 0.47; p < 0.0001). PFS according to

the Independent Review Committee, which was a secondary endpoint, was also significantly longer with alectinib (25.7 vs. 10.4 months; HR, 0.50; p < 0.0001). Objective responses occurred in 83 % *versus* 76 % of each arm, although this difference did not reach statistical significance (p = 0.09). However, duration of response was significantly longer with alectinib (not reached vs. 11.1 months; HR, 0.36). Median OS had not been reached in either treatment arm.

Alectinib showed a more favourable AE profile than crizotinib, with lower rates of nausea, diarrhoea, vomiting, peripheral oedema, dysgeusia, transaminase elevations, and visual impairment. The AE profile of alectinib included increased bilirubin levels, myalgia, anaemia, and weight. Dose reductions and treatment discontinuations were less frequent in the experimental arm, and the duration of treatment was longer with alectinib than with crizotinib.

Findings on intracranial activity

Almost all of the subgroups derived greater PFS benefit from alectinib than from crizotinib. This implies that patients both with and without brain metastases fared better with the new ALK TKI. For patients with CNS metastases at baseline, median PFS was not reached vs. 7.4 months (HR, 0.40), and for those without CNS metastases at baseline, it was not reached vs. 14.8 months (HR, 0.51).

Time to CNS progression in the total population represented a key secondary endpoint. According to a competing risk analysis with CNS progression, non-CNS progression and death as competing events, the risk of having CNS progression as the first event was reduced by as much as 84 % in the alectinib-treated arm (cause-specific HR, 0.16). At 12 months, only 9.4 % of alectinib-treated patients showed CNS progression, whereas this was 41.4 % in the crizotinib arm. The CNS ORR, as opposed to the overall ORR, demonstrated significant benefit of alectinib therapy. For patients with measurable lesions at baseline, response rates were 81 % vs. 50 % with alectinib and crizotinib, and for those with measurable and non-measurable CNS lesions, 59 % vs. 26 %. Complete remissions occurred in 38 % vs. 5 % for measurable, and 45 % vs. 9 % for non-measurable CNS lesions. The median duration of response in the brain was 17.3 vs. 5.5 months and not reached vs. 3.7 months, respectively.

As the authors summarise, the large magnitude of benefit observed with alectinib suggests that first-line alectinib will be superior to the sequential treatment of crizotinib followed by alectinib. Overall, these results establish alectinib as the new standard of care for patients with previously untreated, advanced, *ALK*-positive NSCLC.

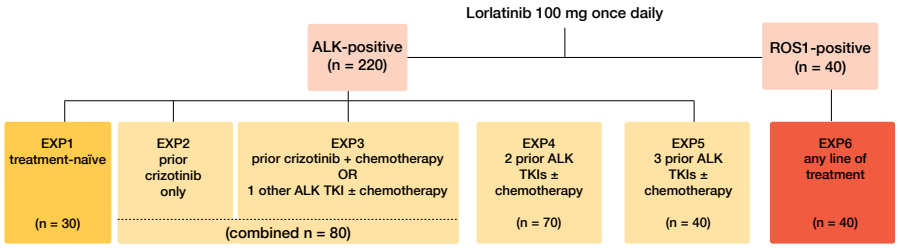

Figure 2: Phase II design and patient populations of an ongoing phase I/II study investigating lorlatinib in *ALK*-positive and *ROS1*-positive NSCLC

Third-generation agent lorlatinib

Secondary mutations in the *ALK* domain can induce resistance to first-generation and second-generation ALK TKIs, which calls for yet other treatment options. The potent third-generation TKI lorlatinib is a selective inhibitor of ALK and ROS1, with broad-spectrum effects against most known *ALK* resistance mutations, including G1202R [8, 9]. Also, lorlatinib can cross the blood–brain barrier to achieve clinically meaningful CNS activity. Indeed, a phase I trial showed intracranial efficacy for lorlatinib, which included deep responses in patients with measurable disease [10].

At present, lorlatinib 100 mg/d is being evaluated in an ongoing phase I/II study in 220 patients with *ALK*-positive NSCLC and 40 patients with *ROS1*-positive disease. In the phase II portion of the trial, patients with *ALK* rearrangement were divided into five expansion cohorts according to their pre-treatment **(Figure 2)**. One cohort was treatment-naïve (EXP1), while groups EXP2 to EXP5 had received prior crizotinib only (EXP2), prior crizotinib plus chemotherapy or one other ALK TKI with or without chemotherapy (EXP3), two prior ALK TKIs with or without chemotherapy (EXP4), or three prior ALK TKIs with or without chemotherapy (EXP5). Patients with *ROS1* rearrangement are receiving lorlatinib as any line (EXP6).

The data presented at the ASCO Congress related to groups EXP2 to EXP5; i.e., the *ALK*-positive cohort that had been treated with at least one ALK TKI prior to study entry [11]. Together, EXP2 and EXP3 included 80 patients, while EXP4 consisted of 70 patients, and EXP5 of 40 patients. Brain metastases were present in 55 % to 71 % of cases across these cohorts at the time of study entry. The primary endpoint was ORR/ intracranial ORR, according to the Independent Review Committee.

Meaningful and durable responses in heavily pre-treated patients

In the total cohort, ORR was 32.9 %. Complete responses occurred in 1.2 %, partial responses in 31.7 %, and disease stabilisation in 32.9 %. At week 12, the DCR was 56.1 %. For cohorts EXP2, EXP3, EXP4 and EXP5, ORRs were 57.1 %, 44.4 %, 25.0 % and 30.8 %, respectively. The majority of patients experienced decrease in target lesion size. There was one complete remission in the EXP4 cohort.

In addition, lorlatinib therapy evoked robust and clinically meaningful intracranial activity, which included complete intracranial responses, irrespective of prior lines of therapy. Target lesions plus non-target lesions together showed ORR of 48.1 %; for target lesions only, this was 51.4 %. Complete responses occurred in 26.9 % and 20.0 % in these two groups. Disease control was 75.0 % at 12 weeks for patients with target lesions plus non-target lesions. With regard to the systemic and intracranial activities, the re-

sponses proved durable. At data cut-off, the longest duration of treatment was more than 300 days, and the longest duration of intracranial response was 7 months.

In the entire group incorporating cohorts EXP1 to EXP6, the safety analysis identified hyperlipidaemia as the most common AE, although this was successfully managed with lipid-lowering agents. Cognitive effects occurred in 19.0 % (across all grades) and were generally mild and rapidly reversible upon dose modification. Dose delays became necessary in 29.3 %, and dose reductions in 19.8 %. Only 3.4 % of patients discontinued treatment due to AEs.

Based on these data, lorlatinib has received Breakthrough Therapy designation from the US Food and Drug Administration for use in patients with *ALK*-positive metastatic NSCLC previously treated with at least one ALK TKI. The phase III CROWN study, which is comparing first-line lorlatinib to crizotinib, is presently recruiting patients.

Analysis of *EML4-ALK* variants

Ou et al. investigated the association of *ALK* resistance mutations with specific variants of the *EML4-ALK* rearrangement [12]. Samples from 634 patients with *ALK*-positive NSCLC collected in the FoundationCORE database were analysed. The most common variants were *EML4-ALK* v1 and *EML4-ALK* v3a/b, each of which was found in 32 % of cases. *EML4-ALK* v2 occurred in 8 %, other *EML4-ALK* variants in 12 %, and non-*EML4-ALK* rearrangements in 16 %.

The presence of known *ALK* resistance mutations was significantly associated with v3 as compared to v1 ($p = 0.0002$). G1202R was the most frequent *ALK* resistance mutation in this dataset. This mutation also showed significant association with v3 compared to all non-v3 variants ($p = 0.0004$). Drop-out, switching, and evolution of multiple *ALK* resistance mutations occurred over the course of sequential ALK inhibitor treatment.

The authors concluded that the use of tissue-based and blood-based next generation sequencing allows for detection of specific *ALK* fusion variants and increases the understanding of the biology of *ALK*-positive NSCLC. In addition, it might have value to predict potential mechanisms of resistance and inform the selection of ALK inhibitor therapy. Non-*ALK* mechanisms of acquired resistance should be considered, especially in tumours with *ALK* rearrangements that are non-variant 3. For instance, MET kinase domain duplication was identified as a novel mechanism of acquired resistance after crizotinib and ceritinib treatment in a patient harbouring *EML4-ALK* v1. ■

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Reducing the danger that arises from the CNS as a site of progression

Brain metastases and leptomeningeal disease represent major clinical challenges in the management of patients with NSCLC. They are generally associated with poor prognosis, and their treatment is difficult due to the paucity of effective therapeutic options. Moreover, patients with CNS lesions are frequently excluded from clinical trials. Progress in this area is therefore slow, and more treatments are urgently needed.

NVALT-11: prophylactic irradiation

In patients with stage III NSCLC, the brain is the most important site of treatment failure. Prophylactic cranial irradi-

ation (PCI) has been shown to reduce the incidence of brain metastases in patients with NSCLC, but the exact value of PCI in stage III NSCLC patients receiving contemporary chemoradiation schedules with or without surgery remains uncertain. The investigators in the phase III NVALT-11 trial hypothesised that PCI reduces the incidence of symptomatic CNS lesions in radically treated stage III NSCLC [1].

Patients underwent concurrent or sequential chemoradiation, or concurrent chemoradiation with or without induction chemotherapy and resection before trial inclusion. If they had WHO performance status 0–2 after 2 to 3 weeks of completion of radical therapy, plus no clinical signs of disease progression, they were randomised to either PCI (36 Gy in 18 fractions; 30 Gy in 12 fractions; 30 Gy in 10 fractions) or observation. PCI was started within 4 weeks of completion of radical therapy. The proportion of patients who developed symptomatic brain metastases was defined as the primary endpoint. While 86 patients received PCI, 88 made up the observation cohort.

Indeed, a smaller proportion of patients treated with PCI developed symptomatic brain metastases compared to observation (4.6 % vs. 28.4 %; $p < 0.001$). PCI also significantly increased the time to development of symptomatic brain metastases (HR, 0.25; $p = 0.001$). This was also true for the time to development of brain metastases irrespective of symptoms (HR, 0.26). However, PCI did not prolong OS, and the experimental treatment significantly decreased global quality of life 3 months after PCI, compared to observation ($p = 0.02$). Thereafter, no differences in quality of life were noted. Time to all neurological symptoms did not differ across these study groups.

Afatinib penetration into brain metastases

Up to 40 % of patients with *EGFR*-mutation-positive NSCLC develop brain metastases over the course of their disease [2]. Failure of drugs to penetrate the blood–brain barrier (BBB) can be a major reason for treatment failure in brain disease. The investigator-initiated CamBMT1 trial is currently exploring the extent to which the small-molecule, irreversible, ErbB family blocker afatinib crosses the BBB, and is attempting to answer the question of whether the delivery of afatinib into brain metastases can be improved by radiotherapy, as it has been suggested that low-dose radiotherapy might disrupt the BBB.

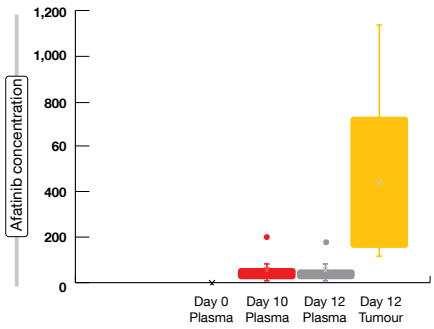

Figure 1: Afatinib levels in plasma and resected brain metastases after pre-operative treatment enhanced by radiotherapy

Patients with operable brain metastases from breast or lung origin are participating in this window-of-opportunity study that has a two-phase design. The main trial, which is currently recruiting patients, is a three-arm randomised phase II study to compare preoperative afatinib alone with afatinib plus a single fraction of radiotherapy administered as either 2 Gy or 4 Gy. This was preceded by a safety run-in phase Ib trial to test afatinib over 11 days. On day 10, a single fraction of radiotherapy at either 2 Gy (Arm A) or 4 Gy (Arm B) was applied, because afatinib was expected to be at steady-state levels at that time. Neurosurgery was performed on day 12.

At the ASCO Congress, Baird et al. presented the phase Ib results [3]. This part of the trial used an accelerated titration design with three pre-planned dose levels of afatinib. In each of the 2 Gy and 4 Gy cohorts, 1 patient was treated at the 20 mg dose level, 1 patient at 30 mg, and 3 patients at 40 mg, for a total population of 10 patients. Six patients had brain metastases from lung cancer origin. The objective of the phase Ib study was to establish feasibility and the recommended phase II dose for this combination with radiotherapy.

Distinct cerebral accumulation

The recommended phase II dose of afatinib with a single 2 or 4 Gy fraction of radiotherapy given pre-operatively was established as 40 mg daily. Pharmacokinetic results for both cohorts combined showed that afatinib concentrations in resected brain lesions were on average more than 15-fold higher than those in the plasma. On day 12, the median plasma and tumour afatinib concentrations were 22.7 ng/ml and 405 ng/g, respectively **(Figure 1)**. The treatments were well tolerated, and no dose-limiting toxicities occurred.

As the authors conceded, the number of patients included in this trial was small, and it is not yet certain that high afatinib concentrations in brain metastases might have been achieved without radiotherapy. However, preclinical studies in rats have suggested that afatinib accumulates in tissues, although afatinib concentrations in the rat brain were 20-fold to 50-fold lower than in other tissues, which suggests an effect of the BBB [4]. Moreover, the afatinib concentration in normal brain tissue of rats was only 3-fold to 4-fold higher compared to the plasma levels. Phase II of the CamBMT1 study, which is presently ongoing, will provide direct determination of the enhancement of delivery of afatinib into brain metastases by radiotherapy.

Intracranial activity of osimertinib in AURA3

The AURA3 trial demonstrated significantly greater efficacy of osimertinib 80 mg/d compared to platinum-based chemotherapy in the T790M-positive setting following progression after first-line EGFR TKI treatment [5]. Based on the AURA3 data, Mok et al. presented the first comparative evidence of osimertinib activity in CNS metastases from a randomised phase III study [6]. Patients with stable asymptomatic brain lesions were eligible for AURA3.

Two analyses were performed. The first one was the ‘CNS full analysis set’; i.e., patients with measurable and/or non-measurable CNS disease. These represented 28 % of the overall population. Here, 75 and 41 subjects received osimertinib and platinum-pemetrexed chemotherapy, respectively. The endpoint for this full analysis set was CNS PFS. The second cohort included only those with at least one measurable CNS lesion (11 % of the overall population). Thirty and 16 patients in this group were treated with osimertinib and chemotherapy, respectively. CNS objective re-

sponse rate and CNS duration of response constituted the objectives for this cohort, which was designated as the 'CNS evaluable for response set'.

Longer CNS PFS and higher CNS ORR

In this evaluable for the response set, CNS ORRs were 70 % and 31 % for patients treated with osimertinib and chemotherapy, respectively (odds ratio, 5.13; p = 0.015). Responses lasted 8.9 and 5.7 months, respectively. CNS disease control was achieved in 93 % *versus* 63 %. CNS responses to osimertinib started at 6.1 weeks, which corresponded to the first radiological evaluation. The effects of treatment were observed regardless of prior brain radiotherapy status. In osimertinib-treated patients, CNS ORR was 64 % *versus* 34 % in those who had received radiotherapy within 6 months of randomisation *versus* those without prior brain radiation or radiotherapy ≥ 6 months before randomisation. For chemotherapy, this was 22 % *versus* 16 %. The majority of patients experienced shrinkage of brain metastases, although responses appeared to be more frequent and deeper in the osimertinib group.

The full analysis set derived a statistically significant PFS benefit from osimertinib treatment, as compared to chemotherapy (11.7 vs. 5.6 months; HR, 0.32; p = 0.004). According to a competing risk analysis for this patient cohort, the probability of experiencing a CNS progression event was lower for osimertinib than for chemotherapy at both 3 and 6 months **(Figure 2)**. At 6 months, the cumulative incidence of brain metastases was 11.5 % vs. 28.2 % for osimertinib and chemotherapy, respectively. A similar reduction of risk occurred in terms of the pattern of non-CNS progression. Furthermore, encouraging activity was seen for patients with leptomeningeal disease; here, 4 out of 7 subjects experienced responses, with two achieving complete remission.

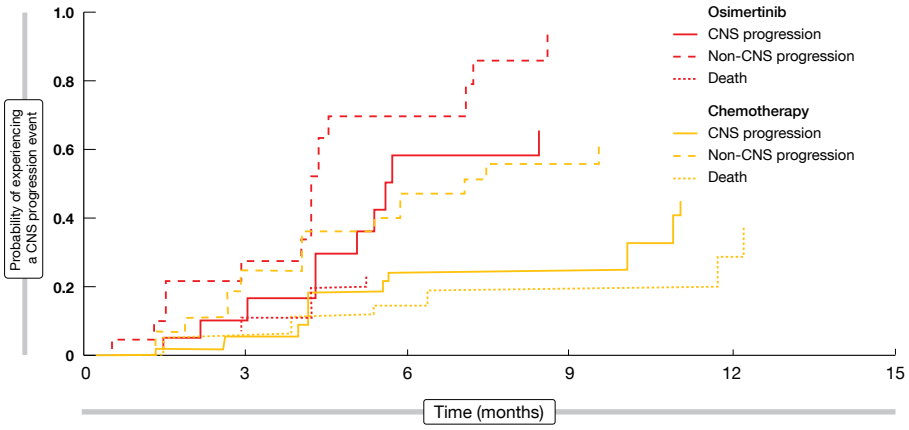

Figure 2: Competing risk analysis for osimertinib *versus* chemotherapy in terms of the probability of CNS progression

BLOOM trial: osimertinib in leptomeningeal disease

Yang et al. presented updated data from the phase I BLOOM study that investigated osimertinib 160 mg/d in patients with advanced, *EGFR*-mutation-positive NSCLC who had progressed on prior EGFR TKI therapy and showed leptomeningeal disease [7]. Patients were recruited either into a T790M-positive cohort or a T790M-unselected cohort. The results presented at ASCO referred to the unselected population only (n = 21), as those from the T790M-positive cohort were not mature yet.

Overall leptomeningeal responses by investigator assessment were found in 43 % of these 21 patients, and median duration of response was 18.9 months. All of the patients underwent neurological examinations. Of the 11 patients with 'normal' baseline assessment, 10 had no change in neurological findings, and one worsened (change from 'normal' to 'mildly abnormal'). Of the 10 patients with 'abnormal' baseline neurological assessment, seven experienced improvement. Data were recorded as 'missing' for 3 patients.

According to the evaluation of cerebrospinal fluid (CSF) after the exclusion of 1 patient, 30 % of patients had confirmed CSF response. Pharmacokinetic analysis revealed that osimertinib 160 mg/d penetrates the BBB, which resulted in mean CSF osimertinib concentration of 7.5 nM. The CSF:free plasma ratio was 16.4 %. The safety and tolerability profile matched the known profile of osimertinib 160 mg/d. Overall, these data suggest that osimertinib has the potential for use in patients with leptomeningeal disease, although further evaluation in larger clinical studies is needed to confirm these findings. ■

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Diagnostics of *EGFR*-mutant disease: biomarkers with significant clinical implications

Alterations in multiple oncogenic pathways drive progression

The clinical relevance of additional genetic alterations in advanced *EGFR*-mutant NSCLC is not clear. Blakely et al. hypothesised that co-occurring genomic alterations in cancer-related genes can cooperate with the mutant *EGFR* to drive *de-novo* resistance to EGFR TKI treatments [1]. The investigators performed targeted exome sequencing of plasma cell-free DNA (cfDNA) in 86 samples collected from 81 patients with known clinical history. They found alterations in multiple concurrent oncogenic pathways, including *TP53*, *WNT*, *PI3K* and *MYC*, and in cell-cycle genes (e.g., *CDK4/6*, *Cyclin D/E*), which appeared to function collaboratively in tumour progression and drug resistance. Co-occurring aberrations were more frequently observed in EGFR-TKI non-responders and they increased with each line of therapy. A proposed new model of *EGFR*-mutant NSCLC pathogenesis that arises from these findings suggests that *TP53*, *RTK* and *RAS-MAPK* are the most commonly co-altered functional genes. Alterations in cell-cycle genes showed the strongest correlations with non-response to EGFR TKI treatments, which warrants further investigation. As the authors noted, these findings call for re-evaluation of the prevailing paradigm of monogenic-based molecular stratification to monotherapy, and they highlight an alternative model of genetic collectives as a determinant of lung cancer progression and therapy resistance.

Predictive impact of early plasma clearance

Liquid biopsy has been approved as an alternative method for the detection of clinically relevant *EGFR* mutations in NSCLC. Two analyses evaluated whether the early assessment of molecular responses in plasma can predict the clinical benefit of EGFR-targeted therapy. Otsubo et al. conducted a prospective, multi-institutional study of liquid biopsies with 57 patients who received afatinib monotherapy 40 mg/d [2]. Complete molecular response (CMR) was defined as mutant allele event/ frequency of exon 19 deletion or exon 21 L858R that was below the cut-off for positivity by digital PCR. Among the patients who were positive for *EGFR* mutation in plasma at baseline, 60.6 % and 87.5 % achieved CMR at 2 and 4 weeks, respectively. Patients with CMR at 2 weeks had longer PFS than those without (13.6 vs. 7.5 months; p = 0.11). There was a significant PFS benefit that favoured the group that obtained CMR at 4 weeks, compared to the population who did not (13.6 vs. 5.1 months; p = 0.03; **Figure 1**).

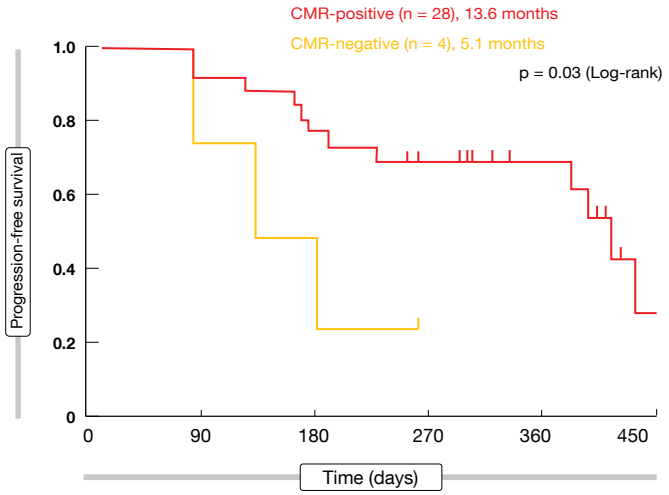

Figure 1: PFS difference between patients with and without complete molecular response (CMR) after 4 weeks of afatinib therapy

According to an exploratory analysis by Thress et al., the absence or presence of plasma *EGFR* mutations within 6 weeks of initiation of osimertinib therapy can be used to predict subsequent outcomes in patients with T790M-positive advanced NSCLC [3]. Plasma samples from 143 patients who were participating in the phase I AURA trial were analysed for detectable *EGFR* mutations at baseline and 6 weeks after osimertinib treatment. The patients for whom both *EGFR*-sensitising and T790M mutations had disappeared at 6 weeks experienced significantly longer PFS than those with detectable mutations (10.8 vs. 4.2 months; p < 0.0001). This also applied to ORR (74 % vs. 41 %; p < 0.0001).

These results were also validated in an independent cohort of patients from the AURA2 and AURA3 studies who received osimertinib as second-line therapy. Again, patients with plasma *EGFR* mutation clearance at 6 weeks showed significant improvements with regard to both PFS (11.1 vs. 5.7 months; p = 0.001) and ORR (87 % vs. 53 %; p = 0.001). Further research will improve the understanding of whether continued detection of mutations at 6 weeks might indicate the presence of heterogeneous resistance mechanisms, which have the potential to be targeted by combination therapies.

EGFR T790M detection in exhaled breath condensate

The *EGFR* T790M somatic mutation is the most common mechanism of resistance to EGFR TKIs in NSCLC. As patients with advanced disease are not always amenable to repeated tissue biopsy for further molecular analysis, the development of minimally invasive methods to detect T790M mutation in cfDNA in the absence of tissue is being actively pursued. A pilot study explored the potential of exhaled breath condensate analysis as a novel method of T790M detection [4]. Exhaled breath condensate is an easily

collected sample source and is known to contain cfDNA, including lung cancer mutations. Twenty-six patients were enrolled, who were either receiving first-generation or second-generation EGFR TKI therapy or had already developed T790M mutation before or during osimertinib treatment.

Indeed, it was possible to detect the T790M mutation in the exhaled breath condensate using a commercially available targeted assay. These results suggest that exhaled breath condensate testing is responsive to recognised dynamic molecular changes that occur on TKI treatment. The authors suggested that exhaled breath condensate analysis might be an attractive alternative for future research to optimise the detection of the T790M mutation in liquid biopsies.

Resistance to third-generation TKIs: osimertinib …

Acquired *EGFR* C797S/G mutations have been identified as a major resistance mechanism to the third-generation EGFR TKI osimertinib, but other mechanisms relating to osimertinib are still largely unknown. Zhou et al. therefore conducted targeted next-generation-sequencing-based mutational profiling and *in-vitro* testing for osimertinib resistance mutations in 93 patients [5]. Most of these had adenocarcinoma and stage-IV disease. Twenty-nine percent of osimertinib-resistant tumours showed secondary mutations on the C797, L792 or L718 residues of *EGFR*. The *in-vitro* data demonstrated that the L792 and L718 mutations induce resistance to osimertinib. Thus, these mutations represent alternative resistance mechanisms in addition to the well-known C797S mutation. The authors noted that in patients with C797, L792 and L718 wild-type, *MET* and *KRAS* copy number gains might serve as bypass resistance mechanisms.

Indeed, as demonstrated by a retrospective analysis of 23 patients from the phase I AURA trial, *MET* amplifications represent a major resistance mechanism to osimertinib treatment [6]. All patients underwent tissue biopsy and/or analysis for plasma circulating tumour DNA at the time of progression on osimertinib. None of them had shown *MET* amplification prior to the start of osimertinib therapy. According to this analysis, all of the patients retained the initial *EGFR* mutation on post-osimertinib testing. *MET* amplification was observed in 30 % of cases by tissue or plasma analysis, and was the most common resistance mechanism in this cohort **(Figure 2)**. *EGFR* T790M/C797S mutation emerged in 22 % of cases. T790M 'loss' was also commonly seen (26 %), typically with no identified resistance mechanism. The authors noted that patients with *MET* amplification responded to subsequent therapies containing MET inhibitors. Clinical trials testing both MET and EGFR inhibitors are ongoing. However, a substantial minority of patients in this study had no identifiable drivers of resistance to osimertinib, which calls for further research efforts in this area.

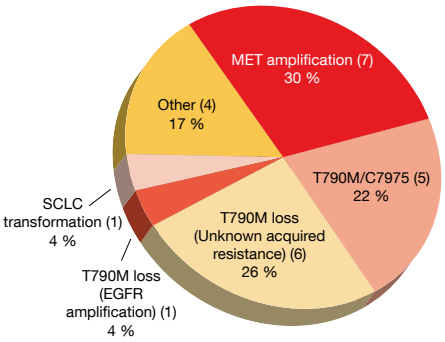

Figure 2: Distribution of resistance mechanisms to osimertinib

… and nazartinib

The third-generation EGFR TKI nazartinib is highly effective against *EGFR*-activating mutations and T790M resistance mutations. A phase I dose-escalation trial yielded favourable results, with an ORR of 47 %, DCR of 87 %, and a median PFS of 9.7 months [7]. However, resistance invariably arose. The analysis conducted by Tan et al. assessed the genetic characteristics of tumour biopsies obtained at baseline and upon tumour progression from patients treated with nazartinib in the phase I/II study, to identify mechanisms of resistance [8]. The data presented at the ASCO Congress were from the phase I dose-escalation part.

At baseline, the most frequent genetic alterations included *TP53* mutations and loss of *CDKN2A/2B*. No relationship was observed between the allelic frequency fraction of T790M and the depth or duration of response. There were no correlations between any genetic alteration and PFS. After progression, T790M was not detectable in five out of eight cases (62.5 %) in tumours that had been T790M-positive at baseline, which suggests that nazartinib is a highly active inhibitor of T790M-positive clones. In this population, however, concomitant mutations were detected, including potential resistance alterations, such as *EGFR* G724S mutation, *MET* amplification, *BRAF* fusions, and *mTOR* deletion alteration. Thirty-seven percent of patients remained T790M-positive, with one individual acquiring *EGFR* C797S mutation. These genetic alterations provide hypotheses to guide future combination treatments with nazartinib to prevent or delay the emergence of resistance. ■

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Established targeted agents taking root in the *HER2*-positive setting

HER2 aberrations in lung cancer are being increasingly identified due to the use of sensitive testing procedures, such as multiplexed testing and next-generation sequencing. Mutations of the *HER2* gene need to be distinguished from *HER2* amplifications and HER2 protein overexpression. In contrast to breast and gastric cancer, HER2 overexpression in NSCLC does not always occur with *HER2* amplification, while amplifications and *HER2* mutations are generally mutually exclusive [1]. As the various types of aberrations represent distinct molecular targets, tumours need to be precisely characterised at the molecular level prior to treatment decisions. To date, however, there is no approved treatment for patients with *HER2*-positive NSCLC.

Trastuzumab after progression on EGFR TKIs

Patients with *EGFR*-mutated NSCLC who develop EGFR TKI resistance tend to undergo activation of a HER2 bypass track. HER2 overexpression and *HER2* amplification are found in up to 17 % of these tumour biopsies [2, 3]. A single-arm, open-label, phase II trial determined whether 24 patients with *EGFR*-mutated, non-squamous, stage IV lung cancer who showed HER2 overexpression after progression on EGFR TKI monotherapy derived any benefit from the HER2 antibody trastuzumab (2 mg/kg weekly, after a loading dose of 4 mg/kg) in combination with paclitaxel 60 mg/m^2 [4].

Trastuzumab plus paclitaxel was well tolerated and induced durable tumour responses in a considerable proportion of patients. The objective response rate was 46 %, and 63 % achieved disease control at 6 weeks. Median survival in the intention-to-treat group was 3 years. The findings implied a positive correlation between response rates/disease control rates and both HER2 expression levels and *HER2* gene copy numbers. However, the regimen appeared to have limited activity against brain metastases, as isolated brain progression with extra-cerebral stable disease or partial response was observed in 21 % of cases. Extra-cerebral responses occurred in 58 %.

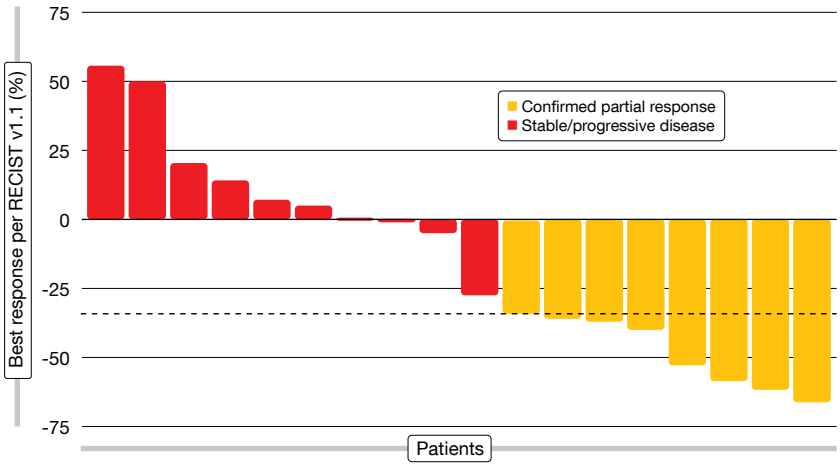

Figure 1: Activity of T-DM1 in *HER2*-mutant advanced lung cancer

Results with T-DM1 in *HER2*-mutated tumours

HER2 mutations have been identified as oncogenic drivers in approximately 3 % of lung cancers [5]. A phase II basket trial explored the antibody-drug conjugate ado-trastuzumab, also known as T-DM1, in patients with *HER2*-amplified and *HER2*-mutant advanced solid cancers, at 3.6 mg/kg every 3 weeks until disease progression [6]. T-DM1 consists of trastuzumab and the cytotoxic agent emtansine, and it has already been approved for the treatment of *HER2*-positive breast cancer. After HER2-targeted binding, the emtansine released in the tumour cell induces apoptosis.

The basket trial contained separate cohorts for *HER2*-amplified lung cancers and *HER2*-mutant lung cancers. At the ASCO Congress, the results were presented for the *HER2*-mutant cohort, which comprised 18 patients. T-DM1 was active and well tolerated in this group. For the primary endpoint, the ORR was 44 %, with eight patients responding **(Figure 1)**. There was no relationship between prior therapy and response, as six of the eight responders were heavily pre-treated, including prior HER2-targeted therapy. Responses lasted for a median of 5 months. Median PFS was 4 months. Treatment-related AEs were mainly rated as grades 1 and 2. AEs did not require any dose reductions or treatment discontinuations. According to the molecular analysis, these responses occurred across various mutation subtypes. HER2 protein levels were low in the eight responders, who therefore benefited from T-DM1 treatment even though their HER2 expression was not pronounced. These results justify a confirmatory multicentre study for patients with *HER2*-mutated lung cancers.

T-DM1 and HER2 overexpression

A study presented by Stinchcombe et al. was the first trial to report on the clinical activity of T-DM1 in HER2-overexpressing metastatic NSCLC [7]. HER2 overexpression was used as an inclusion criterion here. Forty patients with lung cancer of any histology that was *HER2*-positive according to central prospective immunohistochemistry (IHC) testing received T-DM1 3.6 mg/kg every 3 weeks until disease progression. The

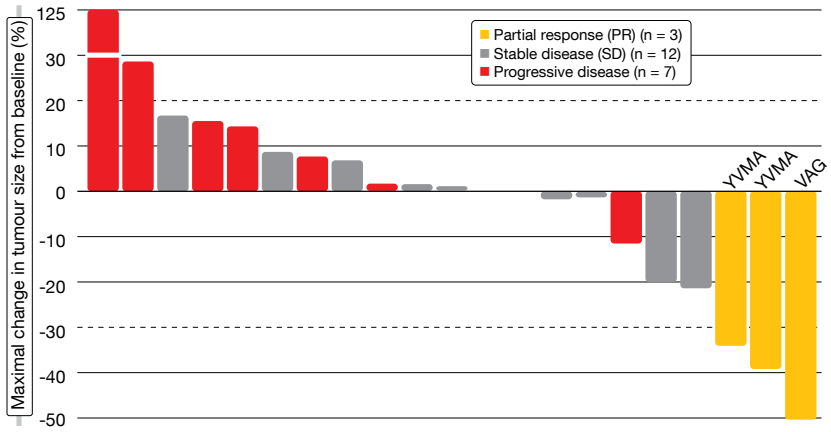

Figure 2: Responses to afatinib in patients with metastatic *HER2*-mutant lung cancer

study included two cohorts with 20 patients in each: those with HER2 IHC 2+ staining, and those with HER2 IHC 3+ staining. Patients had received at least one prior platinum-based chemotherapy. ORR was defined as the primary endpoint.

Four patients in the IHC 3+ group responded to T-DM1 treatment (20 %), three of whom responded rapidly. The median duration of response was 7.3 months. On the other hand, no objective responses occurred in the IHC 2+ cohort, although several patients achieved stable disease (SD) for 6 months, and one patient had SD for over 20 months. Median PFS in the IHC 3+ and IHC 2+ cohorts was 2.7 and 2.6 months, respectively, and median OS was 12.1 and 12.2 months, respectively. No new safety signals were observed. According to the exploratory biomarker analysis, a higher percentage of patients in the IHC 3+ cohort, compared to the IHC 2+ cohort, showed *HER2*-amplified tumours, high gene copy numbers, and HER2 mRNA. Additional investigations into improved detection of *HER2* amplification and other biomarkers might help to refine the patient population that is most likely to benefit from T-DM1 in future studies.

What can afatinib do?

To explore the effects of the irreversible ErbB family blocker afatinib in the *HER2*-positive setting, Lai et al. retrospectively reviewed clinicopathological data from patients with metastatic, *HER2*-mutated lung cancer who were treated with afatinib across seven institutions between 2009 and 2017 [8]. The primary endpoint was investigator-assessed overall response. Before afatinib therapy, the patients had received a median of two lines of treatment.

Partial responses occurred in three of the 27 patients (11 %; **Figure 2**), with a mean duration of response of 6 months. Two of these patients had the YVMA mutation, and one patient had the VAG mutation. SD was observed in 16 cases. Five patients received afatinib treatment for more than 6 months. Of these, four had the YVMA mutation, and one had the S310F mutation. One patient with SD as best response remained on afatinib beyond 30 months. Median OS was 23 months.

Overall, these findings provide data supporting the use of afatinib in *HER2*-mutant lung cancers. The authors noted that afatinib can still be considered as a treatment option when patients have previously progressed on HER2-targeted therapies. Two phase II trials investigating afatinib in the *HER2*-positive setting are ongoing: the ETOP NICHE trial in Europe, and the NCI-MATCH trial in the USA.

ETOP NICHE

The primary objective of the single-arm, phase II ETOP NICHE trial is to determine the disease control obtained with afatinib in pre-treated patients with stage IIIB/IV NSCLC harbouring *HER2* exon 20 mutations [9]. The primary endpoint is complete or partial response, or SD, for at least 12 weeks. Thirteen patients are participating in this trial.

Overall, afatinib therapy resulted in a lower disease control rate than expected in this Simon's two-stage design trial [10]. At the time of the interim analysis, five out of the first nine patients failed to maintain SD for 12 weeks. Accrual was closed, because the stopping threshold had been reached. The treatment and follow-up of the enrolled patients continued based on the judgement of the treating physicians.

Although this approach failed to meet the defined criteria for further clinical testing, signs of activity were observed in the full analysis set. Median PFS was 15.9 months, and the 12-weeks PFS rate was 53.8 %. Descriptive molecular analysis of the tumours suggests that patients with A775-G776insYV *HER2* mutations experienced prolonged disease stabilisation, but the small number of patients limits any clear pattern of association with the molecular data. ■

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Further defining the optimal use of immune checkpoint inhibitors

Neoadjuvant evaluation of nivolumab

As the anti-PD-1 antibody nivolumab is known to induce deep and durable responses in a subset of lung cancer patients, this agent was investigated in the neoadjuvant setting, which is an area of unmet need. There have been no advances in systemic treatment of resectable lung cancer since 2004. Chaft et al. hypothesised that neoadjuvant nivolumab treatment might induce immunity against micrometastases [1]. Newly diagnosed patients with resectable stage I (> 2 cm)/II/IIIA NSCLC received two doses of nivolumab 3 mg/kg, on days 14 and 28, followed by surgical resection. In the post-operative setting, standard-of-care treatment was administered. Safety and feasibility constituted the primary endpoints of this study. Out of 22 patients enrolled, 21 received neoadjuvant treatment, and tumour resection was performed for 20, as one patient was non-resectable due to tracheal invasion.

For the primary endpoint of feasibility, this trial demonstrated that nivolumab treatment did not delay or interfere with surgery in any of these patients. No unexpected safety signals occurred. Drug-related adverse events were restricted to grades 1 and 2, with the exception of one case of pneumonia that led to cancellation of the second dose of nivolumab. However, surgery was not delayed in this patient. One death in the postoperative safety period was unrelated to the study drug (sequelae of a traumatic fall).

Induction of T cells specific for mutation-associated neoantigen

Four weeks after neoadjuvant nivolumab treatment, radiographic evaluation per RECIST v1.1 showed that out of 21 patients, two (10 %) and 18 (85 %) obtained partial responses and stable disease, respectively. Only one (5 %) developed progression. Assessment of pathological responses in the surgery specimens revealed major pathological response (MPR; defined as ≤ 10 % viable tumour cells) in 9 out of 21 cases (43 %). PD-L1 positivity prior to treatment did not correlate with MPR. To date, median postoperative follow-up is 12 months. Two of 20 resected patients have recurred (one solitary brain metastasis, one systemic relapse), but none of the patients with MPR experienced relapse. One patient who was not resected died of lung cancer.

Correlative studies were conducted in a subset of tumours. These showed that mutation burden and neoantigen density are associated with pathological response to the neoadjuvant treatment. T cells specific for dominant mutation-associated neoantigen (MANA) were identified in the blood and the tumour. They expanded in the blood upon neoadjuvant administration of nivolumab. The authors concluded that temporal increases in MANA-specific T-cell receptors in the peripheral blood after nivolumab treatment might be a biomarker of nivolumab response.

Nivolumab plus ipilimumab: two-year update of CheckMate 012

The multicohort CheckMate 012 trial evaluated nivolumab alone or in combination with other agents, including ipilimumab, as first-line treatment of advanced NSCLC. It demonstrated encouraging clinical activity; for instance, patients experienced high response rate and durable responses [2, 3]. Goldman et al. presented the 2-year OS results and other up-dated findings from the nivolumab plus ipilimumab combination cohorts [4]. In these arms, patients received nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg either every 6 weeks (n = 39) or every 12 weeks (n = 38).

The pooled results from the two cohorts showed continued clinical benefit with nivolumab plus ipilimumab in all of the patients and in those with ≥ 1 %

TABLE
Median OS and OS rates at 36 months with pembrolizumab monotherapy according to PD-L1 expression

PD-L1 subgroup	Treatment-naïve (n = 101)		Previously treated (n = 449)	
	Median OS [months (95 % CI)]	36-month OS rate [% (95 % CI)]	Median OS [months (95 % CI)]	36-month OS rate [% (95 % CI)]
TPS ≥ 1 %	22.2 (16.7-31.5)	16.4 (4.0-36.3)	11.1 (8.3-14.0)	21.1 (16.1-26.6)
TPS ≥ 50 %	34.9 (20.3-NR)	25.2 (5.0-53.1)	15.4 (10.5-18.5)	29.7 (21.9-37.9)
TPS 1-49 %	19.5 (10.7-26.3)	NR[a] (NR)	8.5 (6.0-12.7)	13.5 (7.8-20.9)
TPS < 1 %	Not reported[b]	Not reported[b]	8.6 (5.5-10.6)	8.5 (2.9-18.1)

NR, not reached
[a] Due to censoring, 36-month OS was not assessable in this subgroup.
[b] PD-L1 TPS < 1 % group not presented owing to small patient numbers (n = 12)

and ≥ 50 % PD-L1 expression. For all of the treated patients, the 2-year OS rate was 49 %, and for those with ≥ 1 % PD-L1 expression, 58 %. The 2-year PFS rates for these groups were 29 % and 38 %, respectively. A total of 34 (44 %) patients in the cohorts receiving nivolumab plus ipilimumab every 6 and 12 weeks lived for at least 2 years. This was achieved in patients with diverse histology, smoking status, *EGFR* mutation status, PD-L1 expression, and best overall response to treatment. However, efficacy was enhanced with increasing PD-L1 expression. It was noted that a subset of patients who discontinued therapy had sustained responses in the absence of treatment. Nivolumab plus ipilimumab remained tolerable, and most treatment-related AEs were manageable. No new safety concerns occurred with longer follow-up.

Three-year survival with pembrolizumab as a single agent

The effects of the PD-1 antibody pembrolizumab were first demonstrated in the large multicohort phase Ib KEYNOTE-001 study that assessed pembrolizumab monotherapy for previously treated and treatment-naïve patients with melanoma and advanced NSCLC [5, 6]. Overall, 550 NSCLC patients were enrolled. Of these, 101 were treatment-naïve, and 449 had received previous therapy.

As the 3-year analysis of KEYNOTE-001 showed, pembrolizumab at 2 mg/kg or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks provided long-term OS benefit for both first-line and pre-treated patients with advanced NSCLC expressing PD-L1 [7]. At 36 months, 26.4 % and 19.0 % of first-line and pre-treated patients, respectively, were alive. For PD-L1 expression status, the subgroup with tumour proportion score (TPS) ≥ 50 % derived greater benefits from treatment than the cohorts with lower PD-L1 expression **(Table)**. Pembrolizumab therapy had favourable effects across subgroups, as defined by various baseline clinical characteristics (i.e., smoking history, histology, *EGFR* mutation status, prior radiation). The long-term findings did not suggest any cumulative immune-mediated toxicity or late-onset grade 3 to 5 AEs. These data represent the longest efficacy and safety follow-up for patients with advanced NSCLC who have received pembrolizumab treatment.

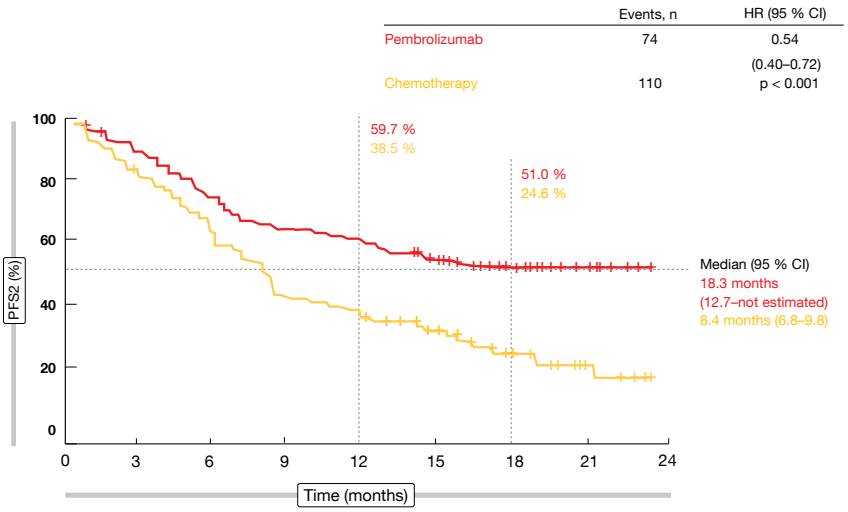


Figure 1: Significant benefit of pembrolizumab with respect to PFS2, as compared to chemotherapy

PFS2 in KEYNOTE-024

The KEYNOTE-024 trial tested fixed-dose pembrolizumab (200 mg every 3 weeks for 2 years) in patients with untreated stage IV NSCLC and a PD-L1 TPS ≥ 50 %, compared to platinum-doublet chemotherapy. Overall, 305 patients were randomised. According to the primary analysis that was conducted after a median follow-up of 11.2 months, both PFS and OS were highly significantly in favour of the immunotherapeutic agent, with HRs of 0.50 and 0.60, respectively ($p < 0.001$, $p = 0.005$, respectively) [8].

The analysis presented at the ASCO Congress related to the PFS in the second line (PFS2); i.e., the time from randomisation to progression of disease (PD) per investigator review after the start of second-line therapy or death, whichever occurred first [9]. Patients who were alive without PD on second-line therapy were censored at the time of the last known survival without PD, while those who died without PD and those who discontinued the second-line therapy were counted as events. In KEYNOTE-024, 79 chemotherapy-treated patients crossed over to pembrolizumab on study, and 12 received anti-PD-1 treatment outside of the crossover, which made for a 60.3 % effective crossover rate. Forty-eight and 97 patients in the pembrolizumab and chemotherapy arms, respectively, received subsequent therapy of any type. Median duration of second-line therapy was 3.6 and 3.5 months, respectively.

Pembrolizumab-treated patients experienced significantly better outcomes, with a median PFS2 of 18.3 months (vs. 8.4 months; HR, 0.54; $p < 0.001$; **Figure 1**). At 18 months, PFS2 rates were 51.0 % and 24.6 %, respectively. This means that patients with PD-L1 expression ≥ 50 % have better survival if the treatment is started with pembrolizumab rather than with a platinum-doublet chemotherapy. The analysis also included updated OS outcomes. Here, pembrolizumab continued to show significantly improved results (median OS, not reached vs. 14.5 months; HR, 0.63; $p = 0.003$). At 18 months, 61.2 % *versus* 43.0 % of patients were alive in the two treatment arms. As was noted, a high degree of separation of the OS curves was maintained despite the effective crossover rate of 60 %. Along with a favourable safety profile, the findings of the current analysis support pembrolizumab as a standard-of-care for first-line treatment of NSCLC with PD-L1 TPS ≥ 50 %.

Incorporating pembrolizumab into first-line chemotherapy

The addition of pembrolizumab to first-line chemotherapy with pemetrexed and carboplatin showed favourable ORR and PFS when compared with chemotherapy alone in cohort G of the

open-label, randomised, phase I/II KEYNOTE-021 trial [10]. At the time of the primary analysis, the HR for OS was 0.90.

Based on 5 months of additional follow-up, pembrolizumab plus chemotherapy continued to be more effective than standard chemotherapy in patients with treatment-naïve, advanced, non-squamous NSCLC, irrespective of PD-L1 expression [11]. ORR was almost doubled (56.7 % vs. 30.2 %; p = 0.0016), and the risk of progression or death was halved (not reached vs. 8.9 months; HR, 0.50; p = 0.0038). Furthermore, a trend towards a greater OS benefit emerged with longer follow-up in spite of the high crossover rate of 75 %. The reduction in mortality risk due to the addition of pembrolizumab was 31 % (HR, 0.69; p = 0.13), and the 12-month OS rates amounted to 76.0 % and 69.3 %. The combination proved tolerable, with readily manageable safety profile.

According to the investigators, pembrolizumab plus chemotherapy with pemetrexed and carboplatin represents an effective and tolerable treatment option as initial therapy for patients with advanced non-squamous NSCLC. Consequently, this combination has been granted accelerated approval by the US Food and Drug Administration.

OAK: atezolizumab beyond disease progression

The randomised phase III OAK study evaluated the PD-L1 antibody atezolizumab in the second-line setting [12]. Patients with locally advanced or metastatic NSCLC after one to two lines of chemotherapy that included at least one platinum-based regimen and any PD-L1 status received either atezolizumab (n = 425) or docetaxel (n = 425). Treatment beyond progression was allowed in the atezolizumab arm, as long as the patients were deriving clinical benefit, based on the protocol-defined criteria. The objective of the analysis presented at the ASCO Congress was the determination of the benefit–risk profile of atezolizumab treatment beyond progression according to RECIST v1.1 [13]. This was based on the consideration that RECIST v1.1-based endpoints such as ORR and PFS tend to underestimate the potential OS benefit of checkpoint inhibitors. There had been discordance regarding endpoints in the OAK trial, which demonstrated OS benefit of atezolizumab, but no improvements in ORR or PFS. The investigators hypothesised that immunotherapy might alter tumour biology in a way that extends survival benefit beyond radiographic progression. Overall, 78 % and 68 % of patients treated in the experimental and control arms, respectively, experienced progression per RECIST **(Figure 2)**.

Prolongation of post-PD OS

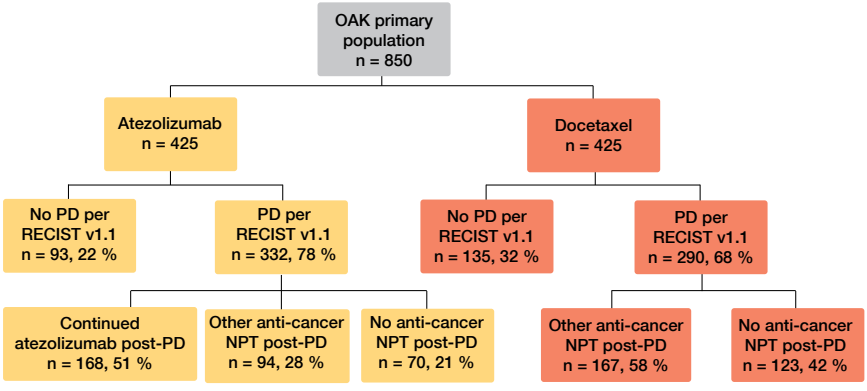
This analysis, which included the first treatment-beyond-progression OS from a phase III study of immunotherapy in advanced NSCLC, indicated clinical benefit of continued atezolizumab administration. Among atezolizumab-treated patients experiencing PD per RECIST, 51 % (n = 168) received atezolizumab therapy beyond progression, while 28 % (n = 94) were treated with other anticancer therapies, and 21 % (n = 70) with no anticancer therapy **(Figure 2)**. According to the analysis, 7 % of patients who continued to receive atezolizumab had subsequent responses in target lesions (i. e., ≥ 30 % reduction post-PD), and 49 % had stable target lesions (i.e., best change between + 20 % and – 30 %). Post-PD tumour reduction or stability was observed across all of the PD-L1 expression subgroups. Atezolizumab treatment beyond progression showed a tolerable safety profile.

Within the group of patients with PD, those who continued to receive atezolizumab fared best with regard to post-PD OS. At 18 months, their OS rate was 37 % compared to 20 % in the group undergoing other anti-cancer therapies and 9 % in the patients who were not treated with anti-cancer agents. Median OS for these 3 groups was 12.7 months, 8.8 months and 2.2 months, respectively. In the docetaxel arm, patients who had post-PD immunotherapy showed better OS outcomes than those without immunotherapy (median, 17.3 vs. 7.5 months). Here, at 18 months, the OS rates were 42 % *versus* 12 %.

The researchers concluded that these findings support the concept of post-progression prolongation of survival and they highlight the inadequacy of RECIST v1.1 to capture the full clinical benefit of cancer immunotherapy. As these findings might be biased, they are no more than hypothesis generating, and confirmation in a randomised clinical trial is needed.

Determinants of response to immune checkpoint inhibitors

As anti-PD-(L)1 therapies are revolutionising treatment and outcomes for lung cancer patients, determinants of response and resistance are eagerly sought, with the objective to improve patient selection. Hellmann et al. used targeted next-generation sequencing with MSK-IMPACT to generate molecular profiling data for 240 patients [14]. These showed that tumour mutation burden correlated with improved benefit through anti-PD-(L)1 agents, particularly at higher thresholds. Moreover, the fraction of genome altered (i. e., quantified normalised percentage of genes with copy number loss or amplification) showed an inverse association with therapeutic benefit. This also applied to



NPT: non-protocol therapy

Figure 2: Patient disposition in the OAK trial

variants in individual genes, such as *EGFR* and *STK11*. Both tumour mutation burden and fraction of genome altered were reasonably estimated by the MSK-IMPACT test, while whole exome sequencing appeared to be better suited for the assessment of molecular signatures and various other molecular features.

Nishino et al. evaluated tumour burden dynamics in 160 patients with advanced NSCLC who received nivolumab or pembrolizumab monotherapy, with the purpose being to identify imaging markers for clinical benefit of this treatment [15]. Here, 25 % of patients achieved objective responses or durable disease control. Using an 8-week landmark analysis, the researchers demonstrated that patients with < 20 % tumour burden increase from baseline had longer OS than patients with increases of ≥ 20 % **(Figure 3)**. According to Cox models, patients whose tumour burden stayed below a 20 % increase from baseline throughout therapy had significantly reduced mortality risk (HR, 0.24; p < 0.0001), after adjusting for smoking and baseline tumour burden. Tumour burden increase of < 20 % might therefore be a practical marker of clinical benefit that can be validated prospectively in a larger cohort. ■

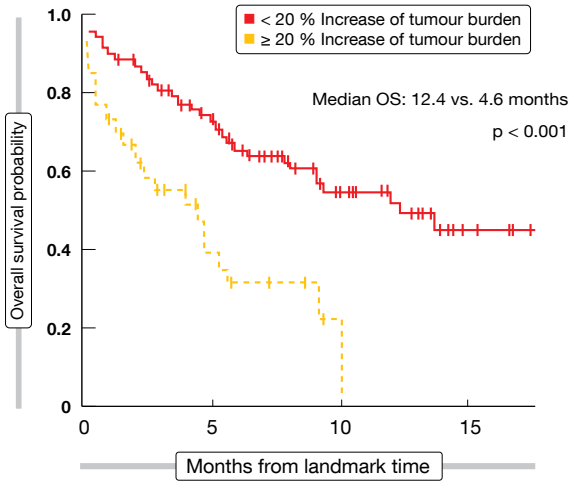


Figure 3: Association between the increase in tumour burden relative to baseline and OS obtained with commercial PD-1 inhibitors

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Real-world utility of ctDNA NGS to identify matched targeted therapy

Liquid biopsy for plasma circulating tumour DNA (ctDNA) next generation sequencing (NGS) is a rapidly evolving science. Plasma ctDNA assays are now commercially available, and are increasingly adopted in the community with a paucity of evidence-based guidance on timing and value of this test. Sabari et al. sought to determine the feasibility and utility of plasma ctDNA NGS to identify matched targeted therapy in a real-world clinical setting. At two sites, a total of 27 patients with metastatic adenocarcinoma of the lung and unknown driver mutation or unknown resistance mechanism were enrolled.

Plasma ctDNA NGS identified a variety of oncogenic drivers with a short median turnaround time of 6 days (vs. 21 days for tissue NGS; p < 0.0001) and matched them to targeted therapy in 14 % of cases. Plasma ctDNA was more frequently detected at diagnosis of metastatic disease or at progression. In patients on therapy, ctDNA detection rate was 46 %, and in those off therapy, 73 % (odds ratio, 0.31; p = 0.02). The plasma NGS concordance rate with tissue NGS regarding driver mutations was 96 %; for tissue NGS concordance with plasma NGS, this was 60 %. The authors concluded that a positive finding in plasma is highly specific and can immediately guide treatment, whereas a negative finding might still require tissue biopsy.

Sabari JK et al., Liquid biopsy in the clinic: a prospective study of plasma ctDNA NGS in patients with advanced NSCLCs to matched targeted therapy. ASCO 2017, abstract 11536

Interview: Yi-Long Wu, MD, Guangdon Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China

Lung cancer in China: hurdles and progress

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watch video

How would you describe the current situation regarding the management of lung cancer patients in China?

Lung cancer is a considerable issue in China. Every year, we have 700,000 new cases. There is a need to perform clinical trials and to launch innovative drugs. With regard to the introduction of targeted therapies, China lags 3 to 4 years behind when compared to the western countries. Two months ago, the EGFR TKI afatinib was launched, offering Chinese patients with *EGFR*-mutant lung cancer an effective treatment option. I hope that China can catch up over the next few years, and that drugs such as immune checkpoint inhibitors will become available. Other drugs targeting rare mutations including c-MET, HER2 and RET are being explored in clinical trials, in which Chinese centres are participating.

Which are the hurdles in everyday practice?

All of the targeted agents are very expensive for Chinese patients, because people in China are required to pay this type of treatment themselves. This is the reason why many lung cancer patients could not make use of targeted therapies so far. Hopefully, these drugs will be reimbursed by the Chinese health care system in the near future. Also, it would be welcome if the pharmaceutical companies reduced drug prices.

What activities is the Chinese Society of Clinical Oncology (CSCO) engaging in?

CSCO is one of the biggest medical societies in China. At present, it has more than 10,000 members. The CSCO Annual Meeting takes place every year in September. This year, we will be celebrating our 20-year anniversary, as CSCO was founded in 1997. The Annual Meeting will take place in Xiamen from 26th to 30th September. CSCO has conducted numerous clinical trials and is putting a focus on education. Clinical practice guidelines for the management of various cancer types such as lung cancer, gastric cancer and colorectal cancer have been published this year. I hope that CSCO will guide the Chinese oncology forward in the future and will determine standards of treatment for all types of cancer. ■

Anti-angiogenic and immunotherapeutic approaches in mesothelioma

The LUME-Meso trial

Malignant pleural mesothelioma (MPM) is a rare tumour that is often diagnosed at an advanced stage. Limited efficacy of the available therapies contributes to the generally poor prognosis for MPM patients. Since 2003, the only approved regimen for MPM treatment has been chemotherapy with pemetrexed and cisplatin, with median survival of approximately 12 months [1].

The oral multikinase inhibitor nintedanib strongly inhibits MPM tumour growth in human xenograft models and reduces the colony-forming capacity and migratory activity of MPM cell lines [2, 3]. Based on these observations, the randomised, double-blind, phase II LUME Meso study investigated pemetrexed/cisplatin plus either nintedanib or placebo in 87 patients with unresectable MPM who had not received prior chemotherapy. Patients who completed up to six cycles of chemotherapy without progression were able to continue with nintedanib or placebo maintenance therapy until progression. The primary analysis, which was presented in 2016, showed that the addition of nintedanib to chemotherapy induced clinically meaningful PFS improvement (9.4 vs. 5.7 months; HR, 0.56; p = 0.017) [4]. At that time, there was a trend for OS prolongation (18.3 vs. 14.5 months; HR, 0.78).

First-line benefit particularly in the epithelioid subgroup

According to the primary OS analysis reported at the ASCO Congress, patients treated with nintedanib in the intention-to-treat (ITT) population derived a 4.1-month OS gain compared to the control arm (18.3 vs. 14.2 months; HR, 0.77; p = 0.319) [5]. A pre-planned subset analysis of patients whose tumours had epithelioid histology showed a survival advantage of 5.4 months (20.6 vs. 15.2 months; HR, 0.70; p = 0.197). Like-

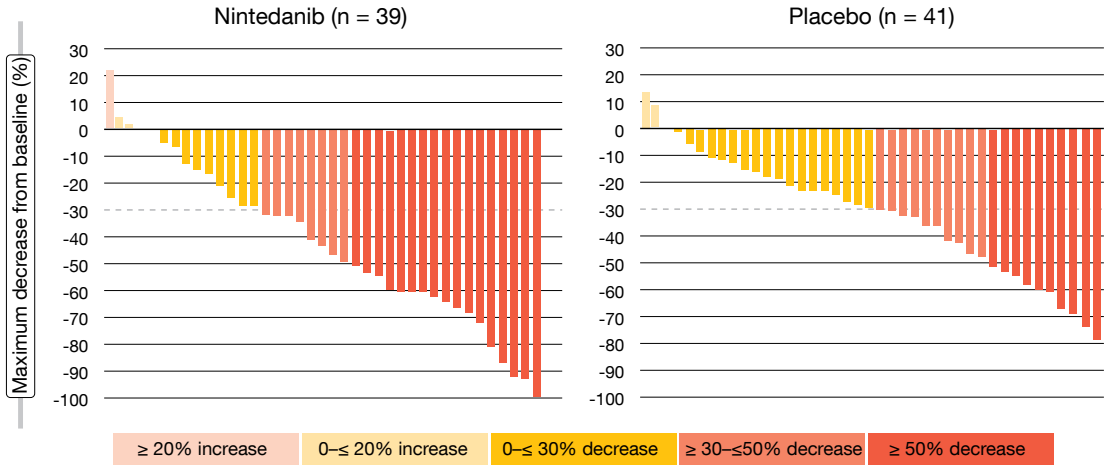

Figure 1: Greater tumour shrinkage with nintedanib plus chemotherapy compared to placebo plus chemotherapy in LUME-Meso

wise, the PFS benefit according to the updated PFS analysis was greater for the cohort with epithelioid tumours (9.7 vs. 5.7 months; HR, 0.49; p = 0.006) than for the ITT population (9.4 vs. 5.7 months; HR, 0.54; p = 0.010). The addition of nintedanib led to deeper responses **(Figure 1)**, with corresponding improvements in ORR (57 % vs. 44 %) and median duration of response (6.0 vs. 4.0 months). Importantly, nintedanib did not compromise delivery of the backbone chemotherapy. The safety profile of nintedanib was manageable and consistent with previous studies. Nintedanib-treated patients showed no excess of all-grade bleeding, thromboembolism or hypertension, although higher rates were noted in the experimental arm with respect to grade ≥ 3 hypertension. The ongoing LUME-Meso phase III trial is comparing nintedanib plus chemotherapy with chemotherapy alone in patients with epithelioid histology only.

Activity of second-line trabectedin: ATREUS

Validated treatment options beyond the failure of pemetrexed-based chemotherapy are lacking at present. As inflammation is a fundamental characteristic of MPM, there might be a rationale for the use of the alkylating agent trabectedin. Responses to trabectedin have been related to modulation of cytokines and chemokines, among others. Therefore, the single-arm, multi-centre, phase II ATREUS trial was designed to determine the activity of trabectedin in MPM patients. ATREUS included a pre-treated cohort with epithelioid histology, and a treatment-naïve and pre-treated cohort with biphasic/sarcomatoid histology. Patient enrollment in the biphasic/sarcomatoid cohort is ongoing. Preliminary results obtained in the epithelioid group, for which recruitment is complete, suggest that trabectedin can be considered as a new option in patients with epithelioid MPM that has relapsed after platinum–pemetrexed therapy [6].

The proportion of patients free from progression or death at 12 weeks constituted the primary endpoint of the preliminary analysis. Twenty-five patients met this criteria which represented 42.4 % of patients in the per-protocol analysis set (n = 58), and 38.5 % of those in the 'withdrawn considered failure' group (n = 65). This latter group included all of the patients withdrawn before 12 weeks, with these considered as failures. Here, median PFS was 2.5 months, and OS was 9.4 months. At the end of the 18-month treatment period, one patient was free of progression, and 11 were still alive.

Transaminase elevations were the major concern observed with trabectedin treatment, but they were mild and recovered after treatment delay or dose reduction in the majority of cases. Other frequent AEs included fatigue, nausea, and respiratory toxicity. Most events were transient and manageable. Only a limited number of patients interrupted treatment due to toxicity. Based on these encouraging results, a phase III trial to evaluate trabectedin in pre-treated epithelioid MPM appears warranted.

Meaningful disease control through checkpoint inhibition

Another approach worth investigating is immunotherapeutic treatment, as MPM has been shown to be potentially immunogenic. PD-L1 expression is associated with poor prognosis in MPM patients [7, 8]. Conversely, those with high levels of intra-tumour cytotoxic CD8-positive T cells in resected MPM samples were shown to have better prognosis [9].

The randomised, non-comparative, phase II MAPS-2 study evaluated nivolumab 3 mg/kg every 2 weeks (n = 63) alone or in combination with ipilimumab 1 mg/kg every 6 weeks (n = 62) in patients with unresectable MPM that had progressed after a maximum of one or two previous lines of chemotherapy, including a pemetrexed/platinum doublet [10]. The primary endpoint was DCR at 12 weeks, as centrally assessed by an independent and blinded expert panel of radiologists, according to the modified RECIST-meso criteria.

Both the nivolumab-alone regimen and the nivolumab plus ipilimumab regimen induced clinically meaningful disease control. DCR at 12 weeks for the first 108 eligible patients (i.e., the primary endpoint based on the statistical plan) was 44.4 % and 50.0 % for nivolumab and nivolumab plus ipilimumab, respectively. For the ITT population, which included 125 patients, the respective rates were 39.7 % and 51.6 %, and median PFS amounted to 4.0 and 5.6 months, respectively. Remarkably, these results resemble those generally

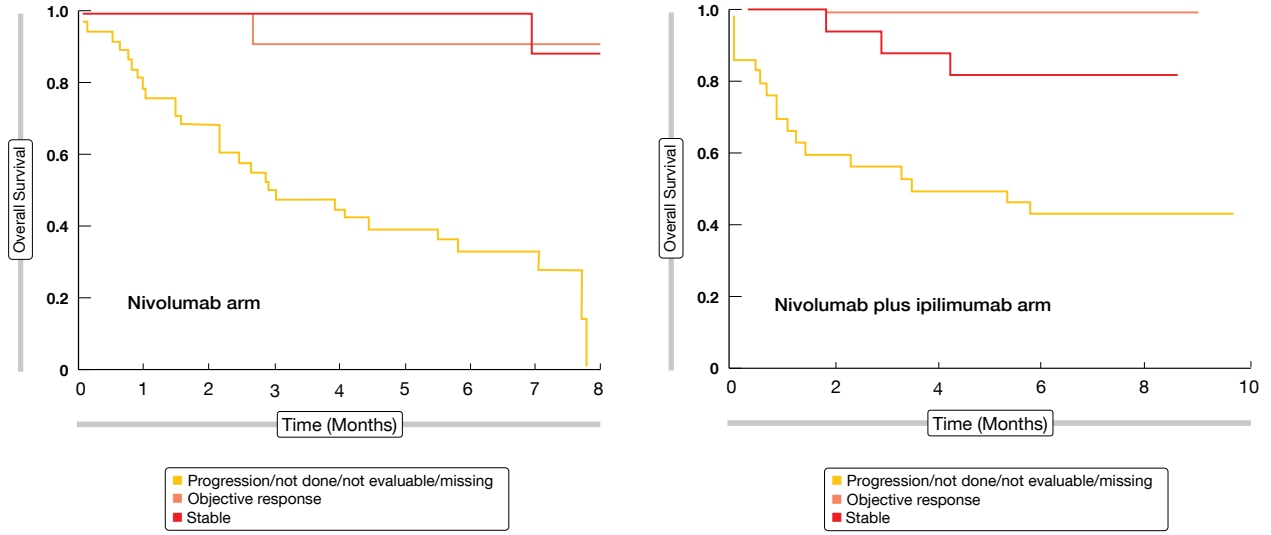

Figure 2: MAPS-2: OS curves according to the responses obtained with nivolumab (left) and nivolumab plus ipilimumab (right)

achieved in the first-line setting. Preliminary OS in the ITT cohort was 10.4 months and not reached, respectively. Thus, patients from both arms of this study appeared to have prolonged median OS compared to all of the previous reports in the second-line/third-line treatment setting of MPM. An OS analysis according to response showed that patients who achieved disease control had excellent survival in both arms **(Figure 2)**.

Toxicity was globally manageable, although three treatment-related deaths occurred in the combination arm due to fulminant hepatitis, encephalitis, and acute renal failure. The authors concluded that immunotherapy with nivolumab and ipilimumab might provide a new therapeutic option as second-line or third-line treatment for relapsing MPM patients. The randomised, open-label, phase III CheckMate 743 trial is currently investigating first-line nivolumab plus ipilimumab compared to pemetrexed plus cisplatin or carboplatin in unresectable MPM [11]. The primary results of this study should become available in October 2020.

PD-L1 expression and beyond

Rivalland et al. evaluated the effects of PD-L1 expression on clinical outcomes in 46 patients with unresectable pleural or peritoneal malignant mesothelioma who received treatment with anti-PD-1 antibodies [12]. PD-1 inhibition demonstrated clinically meaningful activity. Disease control was achieved in 48 %, and median PFS and OS were 3.1 and 8.0 months, respectively. The initial analysis suggested that PD-L1 expression correlates with improved response and survival, especially in cases with TPS > 50 %. Thirty-six percent of patients expressed PD-L1 at > 5 % (PD-L1+), and 23 % at ≥ 50 % (PD-L1^{hi}). In PD-L1+ cases, ORR and OS were 38 % and 8.9 months, respectively. For those with PD-L1^{hi}, these were 60 % and not yet reached, respectively. On the other hand, patients with PD-L1^{low} (< 50 % staining) demonstrated lower ORR and OS (12 % and 4.8 months, respectively). As well as PD-L1, the expression of other checkpoint receptors and their interplay in the MPM tumour microenvironment might affect the design of trials to evaluate single or combination checkpoint inhibition. In an assessment of 329 MPM cases, Thapa et al. showed significant expression of PD-L1, PD-L2, and TIM3 [13]. The expression of these markers was mutually exclusive in a significant proportion of samples. As the authors noted, a comprehensive assessment of multiple immunosuppressive pathways might be necessary to truly gauge the immunosuppressive environment to allow tailoring of immunotherapy for individual cases. ■

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Enhancing the profile of *KRAS*-mutant lung cancer

Characteristics and outcomes

KRAS mutations constitute the largest subset of oncogene-driven lung adenocarcinomas, at approximately 30 %. Patients with *KRAS*-mutant metastatic lung cancer have heterogeneous clinical outcomes depending on the mutation subtype and associated co-mutations. El Osta et al. analysed the Lung Cancer Mutation Consortium (LCMC) database to evaluate the characteristics of these patients and the effect of *KRAS* mutation features on their outcomes [1]. In all, data from 1,655 patients who consented to participate in LCMC between 2009 and 2015 were analysed for baseline characteristics, mutations status/subtypes/co-mutations, OS (calculated from date of distant metastasis to death), and association of patient *KRAS* data with OS. Median follow-up was 2.15 years.

In this population, the incidence of *KRAS* mutations was 27 %. The presence of *KRAS* mutation predicted short OS **(Table)**. Compared to patients with other mutations, average patient age was slightly higher in the *KRAS*-positive cohort, and there was a greater proportion of ever smokers. OS did not differ across *KRAS* mutations subtypes (i.e., *KRAS* G12C, G12D, and G12V), with 2-year OS rates of 46.5 %, 47.4 %, and 51.4 %, respectively. However, never smokers were more likely to have *KRAS* mutant subtype G12D. *TP53* mutation occurred as the most common co-mutation (52 %), followed by *STK-11* alterations (18 %), *MET* amplification (4 %), and *PIK3CA* mutation (3 %). With respect to outcome, *STK-11* co-mutation was shown to be associated with shorter OS.

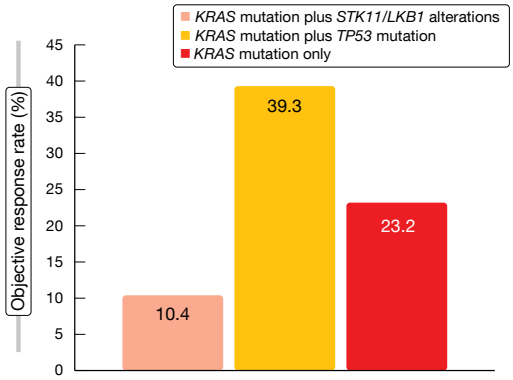

Figure: Responses to PD-1 axis blockade according to the presence of co-alterations

Intrinsic primary resistance to immunotherapy

Skoulidis et al. retrospectively assessed clinical responses to PD-1/PD-L1 therapy in co-mutation-defined subsets of *KRAS*-mutant NSCLC patients [2]. The rationale for this was the fact that the identification of molecular predictors of response to immunotherapy is deemed critical in order to maximise the therapeutic potential of immune checkpoint inhibitors. Previously, patients with *KRAS*-mutant lung cancer and co-occurring genetic events in *STK11/LKB1* or *TP53* had been defined as subgroups that showed marked differences in immune contexture. The present cohort included 162 patients harbouring metastatic *KRAS*-mutant NSCLC who received at least one cycle of PD-1/PD-L1 therapy (i.e., nivolumab, pembrolizumab, durvalumab, anti-PD-1 plus anti-CTLA-4 therapy) and had available molecular profiling.

STK11 genetic alterations were demonstrated to be associated with poor response to PD-1 axis blockade. Patients with this co-mutation experienced significantly shorter PFS and OS following PD-1/PD-L1 therapy than those with *TP53* mutation and *KRAS* mutation only. There were also significant differences with regard to response rates **(Figure)**. The authors concluded that genetic alterations in the *STK11/LKB1* tumour suppressor gene represent a novel, prevalent, tumour-cell-intrinsic mediator of primary resistance to PD-1/PD-L1 blockade in *KRAS*-mutant NSCLC. Therefore, in addition to PD-L1 expression and tumour mutational burden, personalised immunotherapy approaches should take the co-mutation status of individual tumours into consideration. ■

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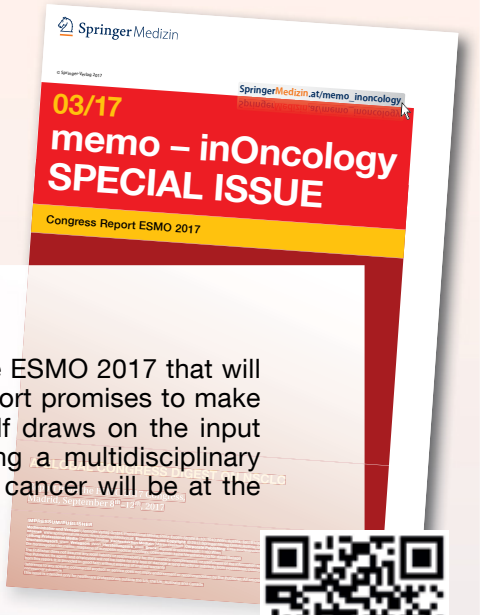
TABLE

OS results and characteristics of patients with *KRAS* mutations compared those with *KRAS*-negative tumours, pan-negative tumours or other mutations

Characteristics	*KRAS*-positive (n = 450)	*KRAS*-negative/other mutation (n = 495)	Pan-negative (n = 706)	p-value
Median OS, years	1.96	2.93	1.95	< 0.001
2-year OS, %	49.1	63.6	48.7	< 0.001
Median age, years	65	61	64	< 0.001
White ethnicity, %	93.91	83.48	88.94	< 0.001
Ever smoker, %	92.86	46.76	75.86	< 0.001



Forthcoming Special Issue

This special issue will be offering a synopsis from the ESMO 2017 that will be held in Madrid, in September of this year. The report promises to make for stimulating reading, as the ESMO 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.

ESMO 2017
Annual Meeting
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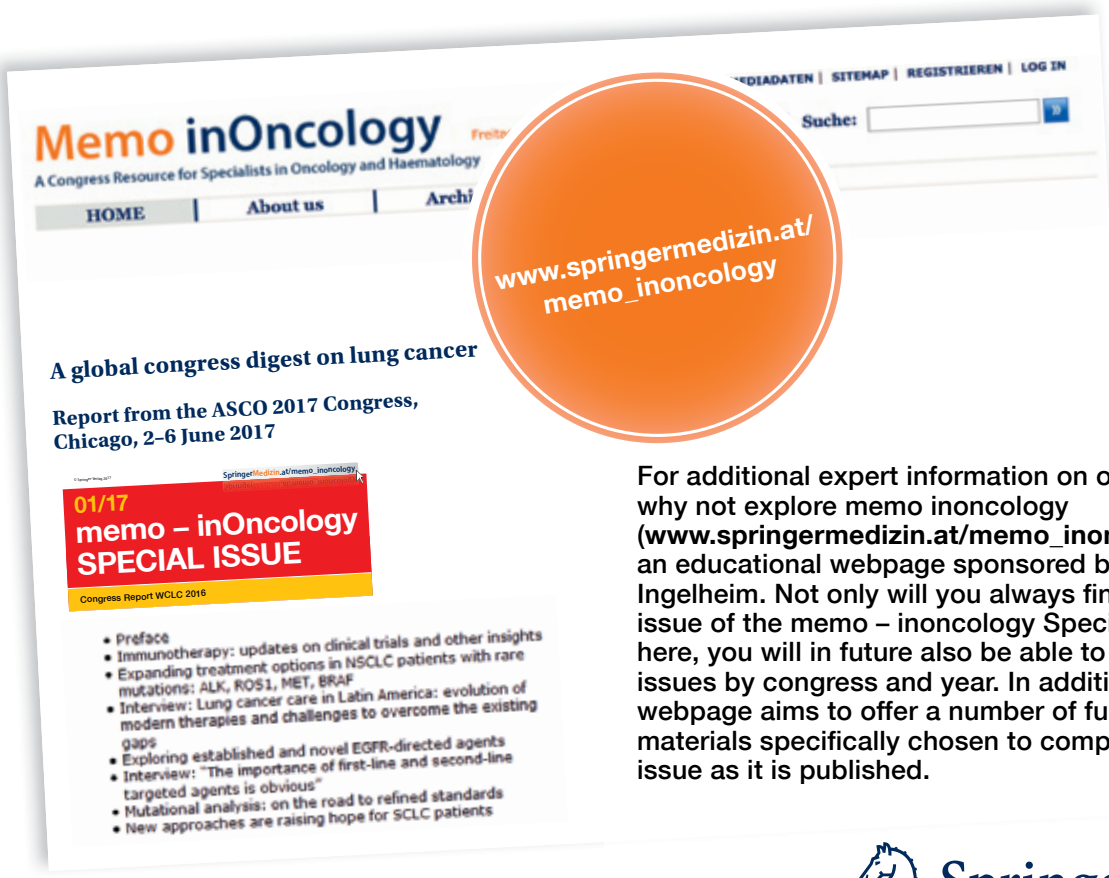

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