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A GLOBAL CONGRESS DIGEST ON LUNG CANCER

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Table of Contents

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Preface

Dear Colleagues,

The demands in lung cancer care are changing as we proceed in our efforts to improve outcomes. Besides investigating the optimal succession of agents to prolong survival in the best possible way, we need to learn to manage toxicity, and strategies must be found to limit treatment costs to a range that can be afforded by healthcare systems in the long run. Trial data presented at the 19th World Conference on Lung Cancer that was held in Toronto, Canada, from 23rd to 26th September, 2018, demonstrated huge steps forward, such as the survival-prolonging effect of atezolizumab as an add-on to chemotherapy in patients with extensive-stage small-cell lung cancer. This is the first study in more than 20 years to show a clinically meaningful survival improvement over the current first-line standard of care in this setting.

A singular survival benefit has also been obtained with durvalumab in unresectable, stage III non–small-cell lung cancer. Patients with *ALK*-positive disease were shown to benefit from the next-generation, CNS-active ALK inhibitor brigatinib when administered in the first line. Various oncogene driver mutations represent targets for potent agents; taken together, these enable us to treat a considerable percentage of patients with advanced disease today. Finally, new and exciting data were reported on the screening of lung cancer that has been under debate due to a lack of convincing evidence. Volume CT screening gave rise to substantial reductions in lung cancer mortality in both men and women.

However, we have to keep in mind that in the setting of advanced lung cancer, only 2 % of patients will achieve cure, which renders therapy essentially palliative in this large patient group. Quality of life and all aspects tied to it therefore merit great attention and should not be neglected in daily routine care. It is up to us to ensure that patients do not only live longer but also experience better quality of life than they would without treatment. Here, the patient perspective matters more than any laboratory or imaging findings, although of course these represent necessary information. Instruments have been developed to assess quality of life and patient-reported outcomes in a fast and very effective manner, and these data tell us a lot about patient needs, but also provide amazingly accurate information on the individual prognosis. The comprehensive use of the available means in each case will contribute to giving patients hope and providing them with quality time in the face of a serious disease.

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New data on PD-L1 inhibitor activity and determinants of outcomes in immunotherapy-treated patients

Superior survival with durvalumab in the PACIFIC trial

Traditionally, the standard-of-care treatment for patients with unresectable, stage III non–small-cell lung cancer (NSCLC) used to be platinum-based chemoradiotherapy. However, outcomes have been poor, which provided the rationale for the phase III PACIFIC trial. PACIFIC investigated the anti-PD-L1 antibody durvalumab 10 mg/kg every 2 weeks (Q2W) for up to 12 months (n = 476) *versus* placebo (n = 237) in patients who had remained progression-free after definitive platinum-based concurrent chemoradiotherapy. These patients had been recruited irrespective of their PD-L1 status. The superiority of durvalumab concerning progression-free survival (PFS) was shown at the time of the first planned interim analysis, which yielded a PFS improvement of 11.2 months [1].

At the WCLC 2018, Antonia et al. reported the second primary endpoint of overall survival (OS) as well as updated results for PFS and other secondary endpoints [2]. For OS, durvalumab showed statistically significant and clinically meaningful improvement over placebo in the intent-to-treat (ITT) population. While the median OS had not yet been reached in the experimental arm, it was 28.7 months in the placebo group (HR, 0.68; p = 0.00251; **Figure 1**). At 24 months, 66.3 % vs. 55.6 % of patients were alive. As in the first interim analysis, the PFS difference in favour of

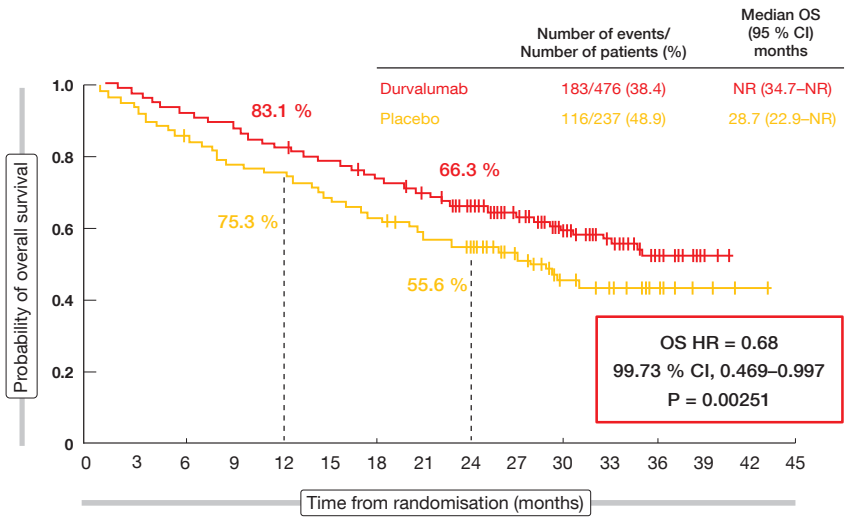

Figure 1: Significant reduction of mortality risk with durvalumab compared to placebo in patients with unresectable, stage III NSCLC after chemoradiotherapy

durvalumab amounted to 11 months (17.2 vs. 5.6 months; HR, 0.51). Likewise, improvements *versus* placebo with respect to time to death or distant metastasis as well as incidence of new lesions were maintained.

Both OS and PFS results favoured durvalumab across a range of patient subgroups. Two PD-L1 analyses were performed, with one being pre-specified and the other one being an unplanned post-hoc analysis. The cut points differed between the analyses (25 % and 1 %, respectively). Patients whose tumours were PD-L1-negative according to the post-hoc analysis did not benefit from durvalumab treatment with regard to OS or PFS. No new safety signals were identified after longer follow-up. The authors noted that PACIFIC is the first study to demonstrate a survival advantage for unresectable, stage III NSCLC, supporting chemoradiotherapy followed by durvalumab for 1 year as a standard of care.

IMpower133: atezolizumab plus SCLC standard treatment

There has been little progress in the first-line management of patients with small-cell lung cancer (SCLC) for more than 20 years. The majority of patients present with extensive-stage SCLC (ES-SCLC); here, the standard of care is platinum plus etoposide. In spite of high initial response rates, outcomes remain poor.

The global, phase I/III, double-blind, randomised, placebo-controlled IMpower133 study evaluated first-line treatment with the anti-PD-L1 antibody atezolizumab plus carboplatin and etoposide (n = 201) compared to placebo plus carboplatin and etoposide (n = 202) in patients with ES-SCLC [3]. Indeed, IMpower133 was the first study in more than 20 years to show a clinically meaningful improvement in OS over the current first-line standard of care. The addition of atezolizumab significantly prolonged both OS (12.3 vs. 10.3 months; HR, 0.70; p = 0.0069) and investigator-assessed PFS (5.2 vs. 4.3 months; HR, 0.77; p = 0.017) that were defined as the co-primary endpoints. At 12 months, 51.7 % vs. 38.2 % of patients were alive, and 12.6 % vs. 5.4 % were progression-free. Except for patients with brain metastases, the OS subgroup analysis favoured the atezolizumab-based regimen across all of the subgroups, which means that the benefit of treatment was not limited to patients with high tumour mutational burden (TMB) **(Figure 2)**. Response rates did not differ across the two arms, although duration of response favoured the experimental arm (4.2 vs. 3.9 months; HR, 0.70). The atezolizumab combination also gave rise to greatly improved results with respect to event-free rates at 6 months (32.2 % vs. 17.1 %) and 12 months (14.9 % vs. 6.2 %). A greater proportion of patients in the experimental arm had ongoing responses (14.9 % vs. 5.4 %). Possible correlations of survival outcomes with the PD-L1 status have not been established yet, but will be assessed in the future.

Rates of AEs were similar across the two arms. Haematological toxicity occurred most commonly in the entire population, with the addition of atezolizumab not altering the incidence. The median number of carboplatin and etoposide doses received was identical in the two groups, which implies that atezolizumab treatment did not interfere with dose delivery. No new safety signals were identified. Overall, these data suggest that atezolizumab plus carboplatin and etoposide is a new standard-of-care first-line treatment for patients with ES-SCLC.

Promising activity of neoadjuvant atezolizumab

The multicentre, open-label, single-arm, phase II LCMC3 study tested the neoadjuvant use of atezolizumab in patients with resectable NSCLC. Preliminary efficacy and safety data obtained in Part 1 of the trial have been reported at the ASCO 2018 Congress [4].

At the WCLC 2018, Rusch et al. presented updated safety and efficacy results in 54 patients [5]. Forty-five individuals without *EGFR* or *ALK* aberrations underwent surgical resection. Ten of these (22 %) achieved major pathological responses, which were defined as ≤ 10 % viable tumour cells. Three patients (7 %) had pathological complete remissions. Changes in lesion size from baseline appeared not to correlate with the amount of viable tumour cells. The neoadjuvant administration of atezolizumab proved tolerable and did not cause any major delays in surgery or interfere with the surgical resection. A follow-up interim analysis in 90 patients is planned.

Second-line avelumab: negative trial according to primary analysis

No OS benefit was detected in the randomised, open-label, phase III JAVELIN Lung 200 trial that tested the anti-PD-L1 antibody avelumab 10 mg/kg Q2W against docetaxel in the pre-treated setting [6]. These patients had experienced disease progression after platinum doublet therapy. The primary analysis population comprised 529 patients who showed PD-L1 expression levels ≥ 1 %.

In this group, there was no difference regarding the primary endpoint of OS

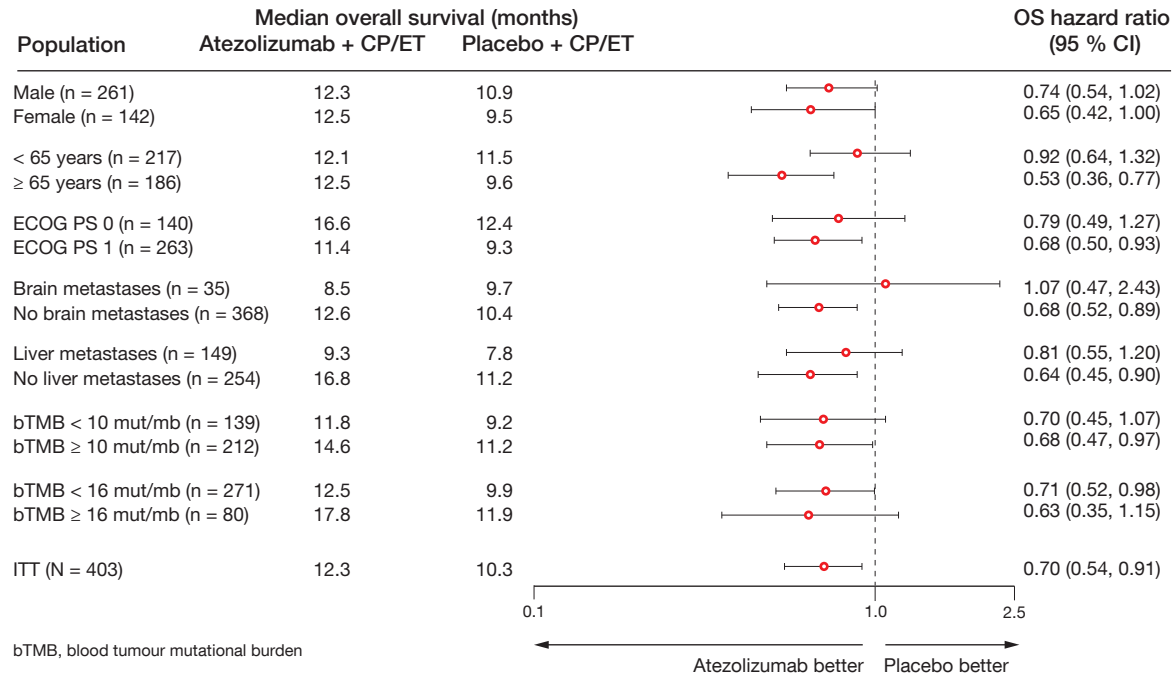

Figure 2: IMpower133: overall survival benefits in all subgroups including those with low tumour mutational burden, except for patients with brain metastases

(11.4 vs. 10.3 months; HR, 0.90; p = 0.1627); however, as the authors pointed out, OS findings in this trial might have been impacted by high use of subsequent immune checkpoint inhibitor (ICI) treatment in the docetaxel arm. Prespecified exploratory subgroup analyses showed increasing clinical activity of avelumab compared to docetaxel in patients with higher PD-L1 expression; for instance, in those with ≥ 80 % expression, median OS was 17.1 vs. 9.3 months (HR, 0.59; p = 0.0022). This group also experienced the greatest benefits with regard to PFS (5.6 vs. 2.8 months; HR, 0.58; p = 0.0021) and objective response rate (ORR; 31 % vs. 10 %; p = 0.0002). Avelumab had an overall favourable AE profile relative to docetaxel. Several trials assessing avelumab in NSCLC patients are ongoing, including JAVELIN Lung 100, which is a phase III trial of first-line avelumab monotherapy for PD-L1-positive NSCLC (NCT02576574).

Effect of antibiotic treatment on survival endpoints

Retrospective data suggest that the use of antibiotics alters patient response to ICIs in different types of cancer including NSCLC [7, 8]. This may be due to the fact that antibiotics affect the gut microbiota, which plays an essential role in the development and maturation of the immune system [9].

A multicentre, retrospective study conducted in 168 consecutive NSCLC patients who received nivolumab or pembrolizumab in the second line or beyond revealed that the use of antibiotics appeared to have a negative impact on survival outcomes [10]. Antibiotics were administered 2 months before or within the first month after the beginning of ICI treatment in almost half of the patients. Median OS was significantly shorter in patients who received antibiotics compared to those who did not (8.1 vs. 11.9 months; HR, 1.55; p = 0.027).

The investigators also determined if OS was affected by the route of administration of antibiotics. They found that patients treated intravenously fared markedly worse than those on oral treatment (HRs, 3.62 and 1.17, respectively). The multivariate analysis confirmed intravenous application as an independent risk factor. Consistent results were obtained with regard to both antibiotic use and route of administration for the endpoint of PFS.

Moreover, the type of infection might also affect the outcomes, as patients with lower respiratory tract and urinary infections experienced considerably shorter median OS than those with other infections (6 vs. 26 months; p = 0.006). In light of the retrospective nature of this analysis, the results need further prospective confirmation. For the time being, the authors recommended a rational use of antibiotics in ICI-treated patients.

Driver mutations and outcomes with ICI therapy

ICIs are thought to be less effective in patients whose lung tumours harbour oncogenic driver mutations, but data are limited due to low mutation frequency and exclusion of these patients from clinical trials. Vokes et al. therefore assessed clinical outcomes in 82 ICI-treated patients with targetable driver mutations, including *EGFR* aberrations (L858R mutation, exon 19 deletion, exon 20 insertion, missense mutation in OncoKB), *ALK*, *ROS1* and *RET* rearrangements, *MET* exon 14 skipping mutations (*METΔ14*), and *BRAF* V600E missense mutations [11]. These patients received immunotherapy in the third or later lines. The TMB was calculated as the number of non-synonymous mutations per megabase of genome covered.

PFS in this group of patients did not differ from PFS in a wild-type population. Considering the low numbers,

TABLE
Progression-free survival in patients treated with immunotherapies according to the type of oncogenic driver aberration

	EGFR (n = 44)	ALK (n = 5)	ROS1 (n = 6)	RET (n = 4)	BRAF (n = 8)	METΔ14 (n = 15)	None (n = 410)
6-month PFS rate (%)	24	20	17	0	38	39	31
12-month PFS rate (%)	9	0	0	0	38	21	21
Maximum PFS (months)	26.5	9.4	7.8	4.2	16.5	13.8	48.8

however, a trend was observed towards worse outcomes in patients with *EGFR*, *RET*, *ROS1* and *ALK* aberrations **(Table)**. Conversely, PFS in patients with *BRAF* and *METΔ14* appeared similar to that obtained in the wild-type setting. Except for the group with *RET*-mutant tumours, at least one patient in each subtype group achieved PFS of > 6 months. PFS results of > 12 months occurred in at least one individual with *EGFR*, *BRAF* or *METΔ14* aberrations, which indicates that some of these patients derived significant clinical benefit from ICI treatment. Likewise, response rates did not differ significantly between patients with driver mutations and those without, although a trend was observed towards lower response rates in patients with *EGFR*, *ALK* and *RET* aberrations. An exploratory analysis according to *EGFR*-mutant subtypes demonstrated that fewer patients in the groups with L858R mutation and exon 20 insertion responded compared to those in the other groups. As expected, TMB was lower in the population with driver mutations than in the wild-type population. This marker did not correlate with response in the group with driver mutations, neither in the entire cohort nor in different mutation subtypes.

The investigators concluded that even though response rates may be lower in certain mutation subtypes, neither the presence of oncogenic driver mutations nor low TMB should preclude offering these patients therapeutic trials of ICI therapy. Further retrospective and prospective studies are necessary. ■

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Emerging standards in tumours with rare genetic drivers

First-line brigatinib: ALTA-1L

In the setting of *ALK*-positive NSCLC, the first-generation ALK inhibitor crizotinib is currently being replaced as the first-line standard by next-generation agents. The open-label, randomised, multicentre, phase III ALTA-1L trial investigated the ALK/ROS1 inhibitor brigatinib in untreated patients. Brigatinib, which has excellent CNS activity, was administered at a daily dose of 180 mg after a 7-day lead-in at 90 mg in the experimental arm (n = 137), whereas patients enrolled in the control arm received crizotinib 250 mg twice daily (n = 138). *ALK* positivity was defined using multiple ALK diagnostic tests, which reflects the real-world setting. Approximately 30 % of patients in each arm had asymptomatic brain metastases at baseline. One line of prior chemotherapy was allowed. Overall, 27 % of patients had received chemotherapy in the locally advanced or metastatic setting.

At the WCLC 2018, Camidge et al. presented the first pre-planned interim analysis of the ALTA-1L trial [1]. After a follow-up of 9 to 11 months, the study had already met its primary endpoint. Brigatinib was superior to crizotinib with respect to PFS according to a blinded independent review committee (not reached vs. 9.8 months; HR, 0.49; p = 0.0007; **Figure 1**). At 12 months, 67 % vs. 43 % of patients were progression-free. Brigatinib treatment gave rise to more favourable PFS in both patients

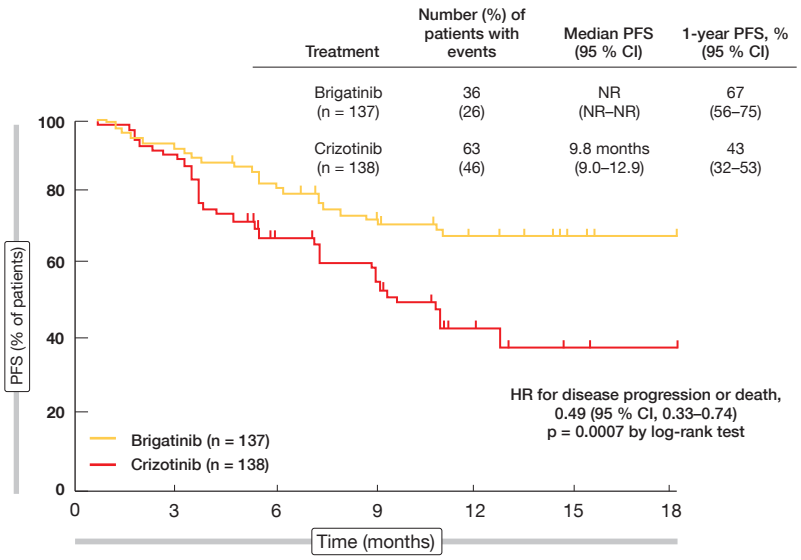

Figure 1: Progression-free survival by blinded independent review committee with brigatinib vs. crizotinib in ALTA-L1

with prior chemotherapy (not reached vs. 11.0 months; HR, 0.35; p = 0.0207) and those without (not reached vs. 9.8 months; HR, 0.55; p = 0.0095).

CNS activity of brigatinib

The subgroup analysis suggested that reductions in the risk of progression or death were greater for patients with baseline CNS disease than for those without (HRs, 0.20 and 0.72, respectively). However, as the PFS dataset was more mature in patients with brain lesions, particularly for the crizotinib arm that had a greater number of CNS events, this finding preferentially emphasised CNS progression among patients with baseline brain disease as an earlier differentiating event. Additional follow-up will reveal the full differential impact of the two drugs on both early and later-onset progression events.

ORRs did not differ significantly between the two treatment arms (71 % vs. 60 %; p = 0.0678). The median duration of response had not been reached for brigatinib (vs. 11.1 months), with a 12-month probability of maintaining response of 75 % vs. 41 %. Among patients with measurable CNS lesions, brigatinib demonstrated a significantly higher intracranial response rate of 78 % (vs. 29 %; OR, 10.42; p = 0.0028). When including those with non-measurable CNS disease, the odds ratio improved to 13.00 (67 % vs. 17 %; p < 0.0001). Also, intracranial PFS differed to a highly statistically significant degree in favour of brigatinib (not reached vs. 5.6 months; HR, 0.27; p < 0.0001).

Brigatinib was well tolerated, with dose reductions being mainly protocol-mandated for asymptomatic laboratory abnormalities such as elevations of creatine phosphokinase, lipase, and amylase. Excess AEs observed with crizotinib treatment, on the other hand, included gastrointestinal effects, transaminase elevations, bradycardia, oedema, and visual effects. Although interstitial lung disease or pneumonitis occurred in both arms, early-onset pneumonitis that emerged within 14 days of treatment initiation appears to be a unique side effect of brigatinib, but only occurred in 3 %, which is half the rate seen in the post-crizotinib setting [2]. The authors concluded that brigatinib represents a promising new first-line treatment option for *ALK*-positive NSCLC.

MET exon 14-positive NSCLC: tepotinib

Approximately 3 % of NSCLC cases harbour *MET* proto-oncogene that causes exon 14 to be skipped during processing of mRNA [3, 4]. Tepotinib has been developed as a highly selective oral inhibitor of MET. Interim data from the single-arm, phase II VISION trial investigating tepotinib in patients with advanced NSCLC and *MET* exon skipping 14 alterations suggest encouraging activity of tepotinib 500 mg daily [5]. Patients were treated in the first, second and third lines. The efficacy and safety analyses included 40 and 46 patients, respectively. *MET* exon skipping 14 mutation status was positive in liquid biopsy in 60.9 %, in tumour biopsy in 80.4 %, and in both in 43.5 %.

Objective responses occurred in 35.0 % and 57.5 % according to independent review committee and investigator, respectively. Disease control was achieved in 62.5 % and 72.5 %, respectively. Responses lasted for a median of 14.3 months, although these data are not mature yet. Teponitib was well tolerated, with a median time on treatment of 4.7 months. The most common AEs included peripheral oedema and diarrhoea, which were of mild or moderate intensity in the majority of cases. In 15.2 %, patients discontinued treatment due to AEs. Recruitment to the trial is ongoing.

Crizotinib in *MET* exon 14-alterations

Apart from its effects on ALK and ROS1, crizotinib is also a potent MET inhibitor. The multicentre phase I PROFILE 1001 trial examined crizotinib 250 mg twice daily in an expansion cohort of patients with *MET* exon 14-altered advanced NSCLC without prior exposure to MET-directed targeted therapy. According to an updated analysis conducted in 65 patients, crizotinib treatment proved active with an ORR of 32 % [6]. Three patients (5 %) developed complete responses. Median duration of response was 9.1 months, and median PFS amounted to 7.3 months. OS data were not mature at the time of data cut-off.

A vital part of the analysis was an exploratory analysis of local molecular profiling results, as *MET* exon 14-positive cancers are molecularly diverse, with a wide array of different mutation types occurring at different sites. Up to 20 % harbour concurrent *MET* amplification. This analysis demonstrated therapeutic benefits despite heterogeneity with respect to both mutation type and absence or presence of concurrent *MET* amplification, which was found in 7 %. The overall safety profile of crizotinib in this subset was consistent with that previously described for *ALK*- and *ROS1*-rearranged lung cancer. The investiga-

tors noted that screening for *MET* exon 14 alterations in the clinic is important. As shown in this trial, alterations can be detected successfully using comprehensive tumour or plasma profiling. Crizotinib recently received Breakthrough Designation by the US Food and Drug Administration (FDA) for the treatment of *MET* exon 14-altered lung cancers.

Entrectinib as a new option for *ROS1*-positive cancer

ROS1 fusions are driver mutations in 1 % to 2 % of NSCLC cases [7, 8]. CNS disease represents an unmet need in *ROS1*-positive patients; crizotinib is the current standard of care, but progression commonly develops in the CNS as the first site in treated patients. The oral ROS1/NTRK/ALK TKI entrectinib was designed to cross the blood-brain barrier and remain within the CNS. Moreover, preclinical studies showed that entrectinib inhibits ROS1 more potently than crizotinib [9].

An integrated analysis of 3 studies (STARTRK-2, STARTRK-1, ALKA-372-001) conducted with entrectinib in a total of 53 patients with *ROS1*-positive NSCLC illustrates the efficacy of this treatment [10]. In patients with and without CNS metastases at baseline, clinically meaningful, deep and durable systemic responses were obtained. The ORR amounted to 77.4 %; for patients with and without CNS disease, this was 73.9 % and 80.0 %, respectively **(Table)**. Median duration of response was 24.6 months. Intracranial responses occurred in 55 % of patients with brain metastases and lasted for a median of 12.9 months; here, 20 % experienced complete responses. In the total cohort, PFS was 19.0 months. Patients with and without CNS lesions had a PFS of 13.6 and 26.3 months, respectively. Entrectinib was tolerable, with a manageable safety profile. Most of the AEs were managed with dose interruption or dose reduction. Only 3.9 % of treatment-related AEs led to discontinuation.

BRAF-positive tumours: vemurafenib monotherapy

Approximately 2 % of NSCLC cases carry *BRAF* mutations as their driver aberration [11]. BRAF inhibitors are recommended for these patients in most guidelines. In addition to combination therapy consisting of dabrafenib and trametinib, single-agent treatment with the BRAF inhibitors dabrafenib or vemurafenib is an option for patients who do not tolerate combination therapy. In this context, the French National Cancer Institute launched a programme permitting nationwide access to vemurafenib for patients with *BRAF*-mutated tumours. At the WCLC 2018, Mazières et al. reported the findings obtained in the NSCLC cohort that included patients with metastatic NSCLC progressing after ≥ 1 standard treatment [12]. They had *BRAF* V600 or other *BRAF* mutations as assessed by direct sequencing or next-generation sequencing in authorised molecular genetic centres and had not received any prior BRAF- or MEK-targeted treatment. Hundred patients with V600 mutations were analysed; the group with non-V600 mutations comprised 15 individuals. Overall, this cohort resembled a real-world population due to pronounced pre-treatment and reduced performance status in a considerable percentage of patients. Brain metastases were allowed if treated.

ORR, the primary endpoint, was analysed using a sequential Bayesian approach. In the *BRAF* V600 cohort, the analysis showed that vemurafenib 960 mg twice daily provided reasonable responses with a mean Bayesian estimated success rate of 44.9 %. Responses lasted for 6.4 months. PFS and OS were 5.2 and 9.3 months, respectively. Patients with non-V600 mutations, on the other hand, did not benefit from the vemurafenib treatment (mean Bayesian estimated success rate, 5.9 %; median PFS, 1.8 months; median OS, 5.2 months). The safety profile proved manageable, with asthenia, decreased appetite, acneiform dermatitis and nausea constituting the most common AEs. Twenty-seven patients stopped the treatment due to toxicity.

Based on these findings, the authors concluded that single-agent vemurafenib can be considered if the combination of dabrafenib and trametinib, which remains the preferred option due to comparatively higher response rates, is not well tolerated or cannot be used in countries where the combination has not yet been approved. These results emphasise the need of integrating *BRAF* V600 in routine biomarker screening.

Robust activity of RET inhibitor in heavily pre-treated patients

In solid tumours, *RET* is an established oncogene that is activated by either fu-

TABLE 1
Entrectinib in *ROS1*-positive tumours: objective response rates

n (%)	Total (n = 53)	CNS disease at baseline (n = 23)	No CNS disease at baseline (n = 30)
Objective response rate (95 % CI)	**41 (77.4)** (63.8, 87.7)	**17 (73.9)** (51.6, 89.8)	**24 (80.0)** (61.4, 92.3)
Complete responses (CR)	3 (5.7)	0	3 (10.0)
Partial responses	38 (71.7)	17 (73.9)	21 (70.0)
Disease stabilisation	1 (1.9)	0	1 (3.3)
Disease progression (PD)	4 (7.5)	4 (17.4)	0
Non-CR/PD	3 (5.7)	0	2 (10.0)
Missing or unevaluable	4 (7.5)	2 (8.7)	2 (6.7)
Clinical benefit rate (95 % CI)	41 (77.4) (63.8, 87.7)		

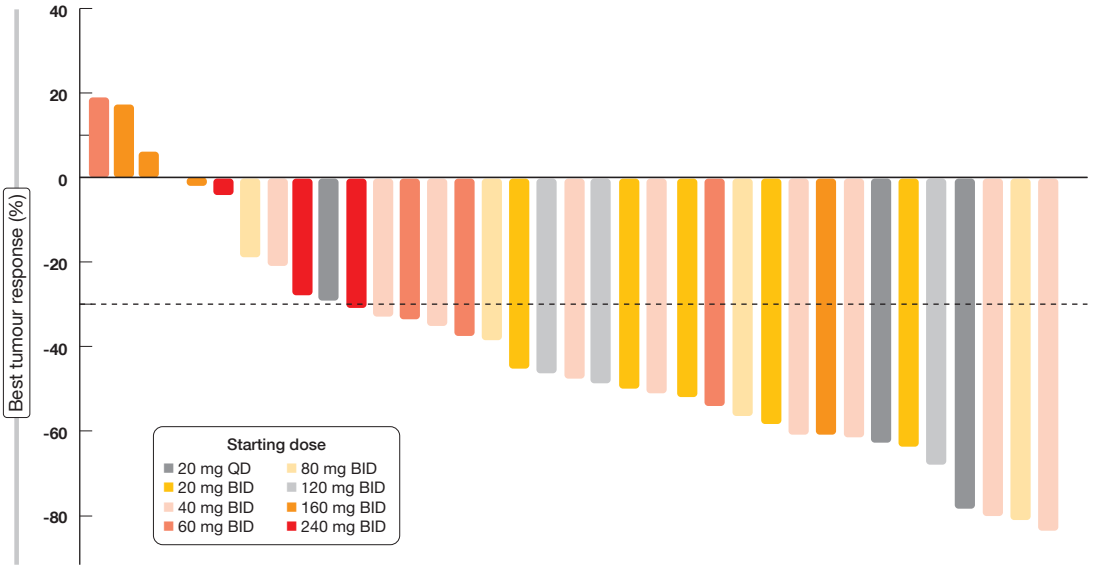

Figure 2: Responses to treatment with LOXO-292 in patients with *RET*-fusion–positive NSCLC

sions or mutations. In NSCLC, *RET* fusions are present in approximately 2 % of patients. The potent and selective RET inhibitor LOXO-292 showed robust anti-tumour activity in *RET*-fusion-positive, locally advanced or metastatic NSCLC in the phase I LIBRETTO-001 trial that enrolled 38 NSCLC patients across 8 dose levels [13]. Most of them had received prior chemotherapy or immunotherapy, or both. The median number of prior systemic regimens was 3.

Sixty-eight percent of patients responded to LOXO-292. RECIST 1.1 responses occurred at all starting dose levels prior to any intra-patient dose escalation **(Figure 2)**. Treatment activity was independent of prior therapy. Four patients with measurable CNS disease participated in the trial; all of them experienced intracranial responses. At the time of the analysis, almost all of the responding patients remained on therapy, with 92 % of responses ongoing. The majority of these had been ongoing for ≥ 6 months. Consistent with the highly selective drug design, the treatment showed high safety and tolerability. LOXO-292 was granted Breakthrough Therapy Designation by the FDA in September 2018. Phase II assessments are currently ongoing in multiple cohorts. ■

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Anti-EGFR treatment: real-world experience and clinical trial insights

Factors determining treatment selection

As the treatment landscape for *EGFR*-mutant stage IIIB/IV NSCLC has significantly changed over the past years, Hirsh et al. assessed current attitudes among physicians towards decision making for EGFR tyrosine kinase inhibitor (TKI) sequencing [1]. Between April and May 2018, the investigators conducted a representative online survey of 310 healthcare professionals including oncologists, pulmonologists, thoracic surgeons and internal respiratory specialists across the USA, Germany, Japan and China.

Irrespective of treatment line, the physicians' most important treatment ambitions when prescribing TKIs included increasing OS, followed by improvement in quality of life. While clinically meaningful OS stood out for the US, Germany and Japan, offering a clinically meaningful PFS, OS and improved health-related quality of life appeared to be of equal importance to Chinese doctors **(Table 1)**. Predictability of treatment outcome in the first-line setting was another important factor influencing treatment choices. In terms of sequencing of TKIs, 55 % of participants strongly preferred a treatment sequence offering the patients maximum time on targeted therapies.

Physicians across all countries expressed a strong need for information on potential resistance mutations before changing their current treatment practice. Thirty-six percent of all health care professionals agreed that they do not feel they have all the data required to make informed decisions on how to sequence EGFR-targeted NSCLC treatments.

TABLE 1
Criteria for EGFR TKI treatment selection in the first line: survey among healthcare professionals in four countries (mentions > 5 %)

Criterion for EGFR TKI selection	USA (n = 100)	Germany (n = 70)	Japan (n = 70)	China (n = 70)
Offers a clinically meaningful OS (%)	42	38	43	16
Offers a clinically meaningful PFS (%)		16	14	18
Provides a clinically meaningful ORR (%)	9	7		
Strongly improves health-related quality of life (%)	14	11	9	16
Strongly improves disease-related symptoms (%)		8		9
Effective in specific *EGFR*-mutation subtypes (%)				7
Is part of standard protocols and treatment guidelines (%)			7	

Real-world data on afatinib and feasibility in elderly patients

The irreversible ErbB family inhibitor afatinib is approved in several countries worldwide for the treatment of patients with *EGFR*-mutant NSCLC. Real-world data presented at the WCLC 2018 corroborated the efficacy of afatinib in everyday clinical practice. A multicentre retrospective study of 128 patients conducted at five institutions in Japan revealed comparable or even better efficacy compared to previous clinical trials [2]. In the first-line and re-challenge settings, median PFS was 17.8 and 8.0 months, respectively. Median OS for first-line patients amounted to 39.5 months. Dose reductions did not diminish treatment efficacy, but even significantly prolonged PFS compared to patients without dose reductions (18.5 vs. 7.9 months; p = 0.018). Another retrospective observational study conducted in 22 patients showed a median PFS of 13.1 months, an ORR of 86.3 % and a disease control rate of 95.5 % [3]. At 12 months, 81.8 % of patients were alive.

An open-label, multicentre, single-arm phase II study identified first-line afatinib at a daily dose of 30 mg as a preferable treatment option in the elderly [4]. Substantial activity of this regimen was observed in 40 patients aged 70 years or older, with an ORR of 72.5 % and a 100 % disease control rate. Twenty-eight patients (70 %) achieved partial responses, and complete response occurred in one case (2.5 %). PFS and OS were 15.2 and 30.2 months, respectively. Most of the AEs observed in the study were rated as low-grade.

RealGiDo

In the LUX-Lung clinical trials assessing afatinib in patients with *EGFR*-mutation–positive NSCLC, the incidence and severity of AEs was reduced by the use of tolerability-guided dose adjustments, which did not compromise efficacy [5, 6]. Real-world data from the non-interventional, observational RealGiDo study confirmed that outcomes in afatinib-treated NSCLC patients can be optimised by tailoring afatinib doses based on individual patient characteristics and adverse drug reactions (ADRs) [7]. Dose adjustments reduced the frequency and intensity of ARDs without impacting treatment efficacy. RealGiDo was conducted at 29 sites across 13 countries worldwide and included 228 patients. Compared to the pivotal LUX-Lung 3 trial [8], the cohort contained more patients with deletion 19 (78 % vs. 49 %), fewer Asian patients (44 % vs. 72 %) and a greater proportion of individuals with poor performance status, as 12 % had ECOG PS 2-3 compared to none in LUX-Lung 3.

Overall, 78 % of patients had a dose modification in the course of RealGiDo. Thirty-one percent received a starting dose of < 40 mg. In 20 % of these, dose increases were implemented during the study. ADRs constituted the main reason for dose modifications. Consistent with LUX-Lung 3, most dose reductions

TABLE 2
Time to treatment failure and time to progression obtained with afatinib in RealGiDo according to dose groups

	Afatinib ≥ 40 mg in the first 6 months (n = 66)	Dose reduction to < 40 mg within the first 6 months (n = 91)	Starting dose ≤ 30 mg (n = 71)
Time to treatment failure (TTF)			
Median TTF (months), 95 % CI	19.5 (13.4-NR)	17.7 (14.5-21.5)	19.4 (12.9-NR)
Estimated 12/18-month TTF rates (%)	70/53	74/50	66/53
Time to progression (TTP)			
Median TTP (months), 95 % CI	29.0 (17.9-NR)	20.0 (14.7-23.0)	25.9 (17.3-NR)
Estimated 12/18-month TTP rates (%)	79/65	84/60	86/64

in patients who started on a dose of 40 mg occurred within the first 6 months of treatment. The rate of dose reductions was numerically higher in RealGiDo (67 % vs. 53 % in LUX-Lung 3).

Nevertheless, afatinib demonstrated consistent activity regardless of dose reductions or modification of starting doses. Time to treatment failure (TTF) was 18.7 months in the total population and did not differ significantly across the groups with and without dose modifications **(Table 2)**. This also applied to time to progression, which amounted to 20.8 months in the total population **(Table 2)**. In patients starting on doses ≤ 30 mg, the overall ADR incidence was similar to that in patients using starting doses ≥ 40 mg, with fewer grade-3 and no grade-4 ADRs.

Mechanisms of afatinib resistance

Approximately half of the patients progressing on treatment with first- or second-generation EGFR TKIs are expected to have *EGFR* T790M resistance mutations. For afatinib, data are lacking even though it is assumed that resistance mechanisms might differ from those found in first-generation EGFR TKIs due to the irreversible and pan-HER nature of inhibition.

Nakamura et al. analysed 20 patients with acquired afatinib resistance, including resistance during EGFR TKI rechallenge [9]. As with first-generation EGFR TKIs, T790M mutation was associated with acquired resistance to afatinib, albeit with somewhat lower frequency. Among the patients who were T790M-negative before the start of afatinib treatment, 40 % became positive at the time of progression. C797S emerged in 3 patients, although with very low allele frequency. While *BRAF* V600E mutation was detected in 1 patient, no *MET* amplification occurred.

In their prospective assessment of 25 previously afatinib-treated patients, Iwama et al. identified T790M as a putative mechanism of resistance in 44 % [10]. The cause was unknown in another 40 %. Apart from these groups, only 1 patient each showed other mutations or combined aberrations that have also been reported in the setting of other-generation EGFR TKIs (i.e., *MET* copy number gains [CNGs], *NRAS* CNGs, T790M plus *EGFR* CNGs, T790M plus *PIK3CA* CNGs plus *PIK3CA* E545K).

ASTRIS: osimertinib in everyday clinical practice

Wu et al. reported results from the second interim analysis of the ongoing ASTRIS trial, which is the largest international, real-world treatment study investigating the third-generation EGFR TKI osimertinib in *EGFR* T790M-positive, locally advanced or metastatic NSCLC [11]. Before receiving osimertinib 80 mg daily, the patients had been treated with at least one prior EGFR TKI. Asymptomatic stable CNS metastases were allowed. The patients were identified using a wide range of clinically employed molecular tests and specimens.

According to the findings, the clinical activity and safety of osimertinib as assessed in this real-world population were in line with the results observed in the AURA clinical trial programme. In the overall population of the ASTRIS trial, the response rate was 56.1 %, and median PFS amounted to 11.0 months. Time to treatment discontinuation was 12.6 months. OS data were immature at the time of the analysis, with an 18-month OS rate of 63.4 %.

Subgroup analyses showed consistent efficacy in patients aged ≥ 75 years and < 75 years; here, PFS was 11.8 and 10.9 months, respectively. Moreover, osimertinib provided clinical benefit in patients with poor performance status (PS 2), although this group experienced shorter PFS than the population with PS 0 or 1 (6.9 vs. 11.1 months for PS 2 and PS 0/1, respectively), which is not surprising. Also, the data corroborated the CNS activity of osimertinib. Median PFS results for patients with and without brain metastases were 9.7 and 11.9 months, respectively.

Uncommon mutations: activity of osimertinib

Approximately 10 % of *EGFR* mutants harbour uncommon mutations, which represent a heterogeneous group of rare molecular alterations within exons 18 to 21. There has been a paucity of data regarding the sensitivity of these tumours to EGFR TKI therapies [12].

According to a phase II, open-label, single-arm, multicentre study, osimertinib is active in NSCLC with uncommon mutations [13]. Thirty-five EGFR-TKI–naïve patients with stage IV NSCLC and activating *EGFR* mutations other than exon 19 deletion, L858R mutation, T790M mutation, and exon 20 insertion were included. G719X mutation was most prevalent in this population (54 %), followed by L861Q (26 %) and S768I (23 %). When treated with osimertinib 80 mg daily, 51 % of patients experienced objective responses, and disease control occurred in 89 %. Median PFS and duration of response were 8.2 and 9.8 months, respectively.

A separate analysis according to the most frequent uncommon mutations revealed the highest response rate in the

presence of the L861Q mutation (77.8 %) compared to G719X and S768I (57.9 % and 37.5 %, respectively). Activity was also observed in some patients with CNS metastases. Nine patients had brain lesions at baseline. After initiation of osimertinib treatment, one of these achieved complete intracranial response, and two had partial responses. Osimertinib demonstrated a manageable safety profile consistent with previous reports.

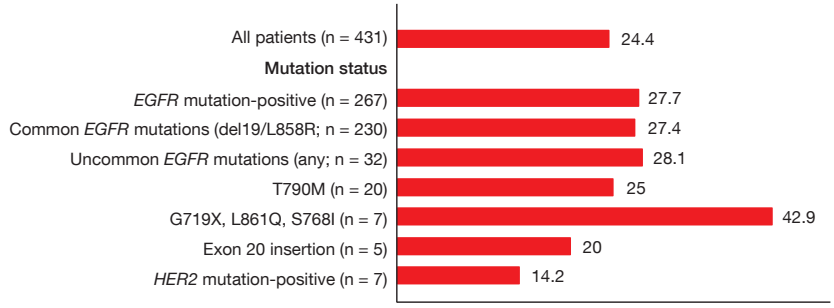

Figure 1: Afatinib in common and uncommon mutations: response rates (%)

Mutation-independent effects of afatinib

Likewise, results obtained from a global named-patient-use programme underscore the efficacy of afatinib in patients with advanced NSCLC harbouring uncommon mutations [14]. Almost all of 2,242 patients included in 10 Asian countries had received previous lines of treatment (median, 3) that involved erlotinib or gefitinib. Ninety-seven percent of patients with known tumour mutation status were *EGFR*-positive. Among those with specified mutations, 93.9 % had common mutations, while 10.6 % had uncommon mutations (e.g., exon 20 insertion, G719X, L861Q, S768I, T790M). In some cases, multiple mutations were observed. Twelve patients had *HER2* mutations, but no *EGFR* mutations.

Overall, 24.4 % of patients responded to the afatinib treatment, with 77.7 % achieving disease control. Activity of afatinib was evident in patients with both common and uncommon *EGFR* mutations **(Figure 1)**. Response rates for these two groups were 27.4 % and 28.1 %, respectively. When analysed according to the type of uncommon mutation, ORRs amounted to 42.9 % in patients with G719X, L861Q and S768I mutations, and to 20 % in those with *EGFR* exon 20 insertion. Patients with *HER2* mutation responded in 14.2 %.

Median TTF was 7.6 months in the total cohort and 7.2 months in the *EGFR*-positive group. Again, patients with uncommon mutations fared at least as well as those with common mutations; TTF was 8.4 and 6.4 months for these two groups, respectively. Patients with exon 20 insertions even showed a median TTF of 18.9 months. In the *HER2*-positive patient population, this was 12.2 months.

Poziotinib in exon 20-positive patients

The pan-epidermal growth factor receptor inhibitor poziotinib was designed as a potent and selective inhibitor of *EGFR* and *HER2* exon 20 mutations. Targeting this rare, difficult-to-treat mutation became possible because the size and shape of pozitinib enable the molecule to fit into the sterically hindered exon 20 binding pocket.

An open-label, phase II trial presented at the WCLC 2018 demonstrated pronounced anti-tumour activity for poziotinib in metastatic, heavily pretreated *EGFR* exon 20-mutant NSCLC [15]. The ORR achieved in 50 patients was 55 %, with 43 % having been confirmed to date. This compares favourably to historical ORR rates obtained with approved EGFR TKIs and standard-of-care second-line agents including docetaxel and immune checkpoint inhibitors. Durable responses were observed. At the time of the analysis, 6 patients had been receiving treatment for > 1 year. Median PFS was 5.5 months.

Moreover, the trial contained 13 patients with *HER2* exon 20-mutant NSCLC who also derived significant benefits. Initial responses occurred in 50 % of evaluable patients (n = 12), and median PFS was 5.1 months. EGFR-related toxicity proved manageable. Dose reductions became necessary in 60 %, but discontinuations due to AEs were rare at 3 %. A confirmatory, international, multicentre study evaluating poziotinib in *EGFR* and *HER2* exon 20-mutant NSCLC patients is currently enrolling (NCT03318939).

Rationale for combinations with immunotherapy

Experimental data support the combination of EGFR-targeted therapy with immune checkpoint inhibitors [16]. EGFR TKI treatment was found to alter the tumour microenvironment by way of indirect effects on immune cells. A phase I study examined the immunomodulatory effects of combining afatinib 40 mg daily with pembrolizumab 200 mg Q3W in 11 patients with advanced, *EGFR*-mutant NSCLC that had progressed on front-line EGFR TKI therapy [17]. The combination showed modest activity with an ORR of 18 % and a median PFS > 6 months in 4 patients. It induced dynamic changes in the immune microenvironment in patients who showed clinical benefit, such as increases in CD3-positive T cell counts and decreases in tumour Ki-67.

All patients with partial responses and/or PFS > 6 months experienced immune-related AEs (irAEs) that necessitated eventual discontinuation of pembrolizumab. Patients who derived clinical benefit but developed irAEs had a distinct circulating and tumour immune cell profile including increased CD4/CD8 T cell ratio and increased soluble B- and T-lymphocyte attenuator. Larger data sets are needed to further support these findings.

Promising activity of third-generation TKI lazertinib

The potent, highly mutant-selective and irreversible third-generation EGFR TKI lazertinib targets both the T790M mutation and activating *EGFR* mutations while sparing wild-type *EGFR*. Lazertinib is able to penetrate the blood-brain barrier. In an open-label, multicentre, phase I/II study, patients with locally advanced or metastatic NSCLC and acquired resistance to prior EGFR TKI treatment received lazertinib once daily. Cho et al. presented the findings obtained in the dose escalation and

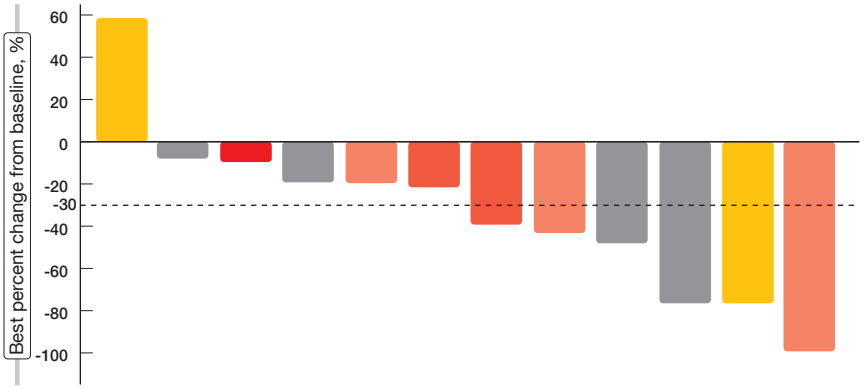

Figure 2: : Intracranial responses to lazertinib in patients with measureable brain metastases

dose expansion parts of the trial; these included a total of 127 patients [18].

In the dose escalation part, no dose-limiting toxicity was observed up to a dose of 320 mg. The most common AEs comprised pruritus, rash, constipation, and decreased appetite. Across the entire dose range, the confirmed ORR amounted to 61 %, and disease control resulted in 89 %. For patients with T790M mutation, these were 66 % and 93 %, respectively. Lazertinib also showed activity in patients with measurable brain metastases, with an intracranial ORR of 50 % (**Figure 2**). Responses lasted for extended periods, with the longest duration of response exceeding 12.5 months. At the time of the data cut-off, median PFS had not yet been calculated.

As the authors noted, lazertinib demonstrated promising anti-tumour activity in patients with acquired resistance to prior EGFR TKI treatment. Based on the risk-benefit profile and pharmacokinetics, 240 mg is the recommended phase II dose. A global phase III clinical trial investigating first-line lazertinib will commence in 2019. ■

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Interview: Herbert Ho Fung Loong, MD, Clinical Assistant Professor, Department of Clinical Oncology, Deputy Medical Director, Phase 1 Clinical Trials Centre, The Chinese University of Hong Kong, China

Modern agents enable dramatic responses even in phase I trials

Looking at phase I clinical trials that are ongoing at the moment, which novel approaches in advanced lung cancer do you deem most promising?
At present, a lot of developments for many types of cancer are being tested in phase I trials, not only for lung cancer. I think that in the past we were very agnostic about whether or not the mechanism of a phase I drug will work for a particular cancer. Today, however, with many drugs being targeted therapies, we have a pretty good idea already in the preclinical setting about which specific targets may be useful. Particularly in lung cancer, a lot of the new molecularly targeted agents have shown promise; this applies for example to the very small subgroup of tumours with *RET* alterations. Results in this area were announced at this meeting including the

phase I trial on the RET inhibitor LOXO-292 that was further updated by Geoffrey Oxnard and showed very dramatic responses [1]. Two or three years ago, we did not see such dramatic responses in a phase I clinical trial.

What are the peculiarities of lung cancer research compared to other areas of cancer research?

The peculiarities of lung cancer research are severalfold. One is the patient population. Lung cancer is a very big cancer in terms of patient numbers, and there is a large variety of tumours within lung cancer itself. While some are molecularly driven and the treatment approaches would be addressing these targets, we do not know the molecular targets for others, and immunotherapy is a very big avenue here. It is the balance between the two; balancing which patients should go into trials, identifying the molecular drivers and looking at them. On the other hand, what is the role of immunotherapy even in patients with molecular drivers? The greatest challenge is how to combine these two. I think these are issues we do not have good answers for yet.

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Which areas within lung cancer research would require more attention, given that this disease needs to be tackled at the level of both prevention and treatment?

With regard to prevention, a very good abstract on screening has been presented at the WCLC 2018 [2]. Certainly there is a proportion of lung cancers for which prevention itself is the best way of treatment in the sense of preventing tumours completely by removing the risk factor, as for small-cell lung cancer. This requires a lot of work, however.

On the other hand, I think that one of the biggest challenges in terms of drug development for lung cancer is the necessity to obtain considerable amounts of tumour tissue as a biomaterial for further analysis. Many times, the initial biopsy is very small. Another issue is the combination of different types of treatment, molecularly targeted therapies as well as immunotherapies, but also the combinations of other modalities of cancer treatment like radiation, surgery and so on. It is a growing field with a lot to learn, but I think we are moving in the right direction. ■

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To watch additional expert interviews, use the link at the end of this report on page 19.

Substantial reduction in lung cancer mortality using volume CT screening: the NELSON trial

Years ago, the large National Lung Screening Trial that was published in 2011 demonstrated a 20 % relative reduction in lung cancer mortality due to annual screening over 3 years with low-dose CT compared to chest radiography [1]. However, no other randomised, controlled trial has shown any mortality benefits to date.

In the Netherlands and Belgium, the randomised, controlled NELSON trial compared volume CT screening vs. no screening in high-risk individuals who were recruited through population-based registries [2]. Out of 606,409 men and women aged 50-74 years, 30,959 were found to be eligible based on questionnaires. They had a smoking history of > 10 cigarettes/day for > 30 years or > 15 cigarettes/day for > 25 years. Also, smoking cessation during the last 10 years was an inclusion criterion. Eventually, 15,792 persons entered the screen arm (n = 7,900) or the control arm (n = 7,892). More than 80 % were males, with a median age of just under 60 years and approximately 40 pack years. A little more than half were current smokers. Volume and volume doubling time of nodules were used for measurements. Screening took place at 1 year, 2 years, 4 years, and 6.5 years. Acceptance was high for several years and decreased only later on.

In the course of all of the 4 rounds, indeterminate test results were found in 9.3 %. The study showed a referral rate for further investigation as low as 2.3 %. Ultimately, the rate of positive results was 2.2 %, leading to a lung cancer detection rate of 0.9 %. This corresponded to a 41 % probability of lung cancer detection in case of a positive result (i.e., positive predictive value). According to the stage distribution analysis, screening gave rise to a massively higher detection rate of stage Ia tumours compared to the later stages, which contrasted with the findings in the control arm that matched those in the Dutch Cancer Registry.

At year 10, the lung cancer mortality rate ratio was 0.74 in males (p = 0.003) and 0.61 in females (p = 0.0543); thus, volume CT screening had reduced the lung cancer-related risk of dying by 26 % in men and by 39 % in women. While the risk reduction proved stable in men, women showed consistently better results with risk reductions of 61 % and 53 % at years 8 and 9, respectively. Overall, these results were more favourable than the NLST findings and demonstrated a substantial reduction in lung cancer mortality in both genders.

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The patient perspective: assessment of quality of life and lung cancer stigma

TABLE 1
Relationship between baseline PRO factors using the LCSS 3-item global index and survival in patients with NSCLC

Number of negative PRO factors*	Median survival, months (n = 620)	1-year survival rates (%)	2-year survival rates (%)
0	16 (p = 0.0003)**	64	36
1, 2	13 (p = 0.007)***	54	30
3	9	38	13

* Negative PRO factor: value below the median
** 0 versus 3 factors
*** 1 versus 3 factors

Burden of illness

Even though quality-of-life (QoL) assessments are highly valued by patients and constitute a necessary component of cancer care evaluation, they generally receive too little attention in both daily routine and the clinical trial setting [1]. "QoL evaluation can provide information that is unique and not available otherwise," emphasised Richard J. Gralla, MD, Department of Medicine, Albert Einstein College of Medicine, Bronx, New York, USA.

According to a survey conducted in 1998 among 154 oncologists, 87 % believed that QoL data and patient-reported outcomes (PROs) are important for patients with advanced cancer [2]. However, fewer than 50 % of these physicians always or frequently formally obtained such data at baseline, and fewer than 45 % used them in following or monitoring patients. "There is absolutely no indication that we are doing better today," Dr. Gralla stressed. Additionally, instead of assessments of the actual patient QoL or symptoms, surrogate markers such as laboratory findings that represent symptoms are often resorted to. Another possibility is derivative endpoints, such as time to deterioration.

In essence, the assessment of QoL and PROs aims at the quantification of the individual patient burden of illness. "We do not sufficiently assess the burden of illness and its impact on prognosis, or the effects of treatment on this burden," Dr. Gralla pointed out. Imaging, clinical laboratory testing and molecular testing cannot replace the direct patient input. Likewise, ECOG performance status (PS) does not fully capture the burden of illness and is not a PRO. QoL measurements are frequently not included in the design of clinical trials. In larger studies, they often represent secondary endpoints, but physicians tend to neglect them during follow-up.

Questionnaires: available and practical instruments

Three validated lung-cancer-specific QoL assessment instruments are currently available. The Lung Cancer Symptoms Scale (LCSS) contains patient and observer forms and has been developed for clinical trials and patient management, while both EORTC QLQ-C30 and FACT-L contain general and lung cancer modules and have been developed for general use. As Dr. Gralla noted, these questionnaires are inexpensive, have extremely high patient acceptance, and are easy to apply. "Using electronic assistance, it takes as little as 2 minutes to complete them." QoL and PROs should be assessed every 3 weeks in patients with lung cancer.

Important prognostic information can be obtained through these instruments. For instance, data demonstrated an association between baseline PRO factors according to the LCSS 3-item global index and survival **(Table 1)** [3]. The 3-item global index includes symptom distress, interference with the activity level, and health-related quality of life. These clusters are a more reliable measure than symptoms whose patterns vary individually [4]. Dr. Gralla pointed out that PS does not reflect this information to a sufficient degree, as several prognostic groups can be present within the same PS category.

This is illustrated by data on hospitalisation rates. Hospital admissions in patients with advanced lung cancer are due to either the disease and its complications (73 %) or toxicity (27 %) [5]. Among 160 patients with advanced NSCLC included in a prospective assessment, one-third were hospitalised in the first 90 days. The LCSS 3-item global index baseline score was found to be highly predictive for cancer-related hospitalisations (p = 0.0001). The separate analysis of a patient cohort with ECOG PS 1 showed that the same relation exists within this group, which indicates that PS itself is not an accurate predictive measure. At 90 days, there was a 4:1 difference between the patient cohorts with the highest and the least risk according to the 3-item global index (48 % vs. 12 %; p = 0.025; **Table 2**).

TABLE 2
Hospitalisation rates according to the LCSS 3-item global index at baseline in patients with ECOG performance status 1 (n = 90)

Time from baseline	Least risk group (%)	Medium risk group (%)	Highest risk group (%)
At 30 days	0	12	8
At 60 days	10	15	37
At 90 days	12	15	48

Early determination of treatment benefits

Dr. Gralla concluded that QoL and PRO assessments have multiple roles in tho-

TABLE 3
Lung Cancer Stigma Inventory (LCSI; Cronbach's alpha = 0.89)

+ Factor 1 (Internalised Stigma; 9 items; α = 0.90)	
-	I have felt guilty about my lung cancer.
-	Having lung cancer has made me feel like I have made mistakes.
-	I have blamed myself for having lung cancer.
+ Factor 2 (Perceived Stigma; 10 items; α = 0.74)	
-	My family or friends have blamed me for having lung cancer.
-	People have assumed that lung cancer is always caused by smoking.
-	People have said that those with lung cancer get what they deserve.
+ Factor 3 (Constrained Disclosure; 6 items; α = 0.82)	
-	I have had an urge to keep my lung cancer a secret.
-	I have been careful who I have told about my lung cancer.
-	I have stopped spending time with some people since my lung cancer diagnosis.

racic oncology. "Currently, they are secondary endpoints in large randomised trials and serve for informal assessment in daily practice." Enhanced roles, however, might include identification of patients at increased risk, which allows for addressing their needs and reducing hospitalisation rates. More accurate baseline prognostic data than PS at the outset of clinical trials renders improvements in study design possible. Assuring high completion of practical QoL/PRO assessment of appropriate endpoints is mandatory.

Finally, evaluations might enable earlier determination of the benefit of a certain treatment in an individual patient. In this context, significant survival differences have been shown based on a 20 % decline in the 3-item prognostic index in NSCLC patients already after 2 cycles of chemotherapy (p = 0.01) [6]. "If we evaluated PROs and QoL early on, we would get much more information that is very valuable both in clinical trials and in patient management," Dr. Gralla concluded.

Lung cancer stigma affects all levels of care

The concept of health-related stigma is not new but highly relevant in the context of lung cancer. "We found that as many as 95 % of lung cancer patients feel stigmatised by other people," reported Heidi A. Hamann, PhD, Department of Psychology, Department of Family and Community Medicine, University of Arizona Cancer Canter, Tucson, Arizona, USA [7]. This stigma is often linked to the belief that behaviour, such as smoking, has caused the person's illness, and is likely associated with several negative psychosocial and behavioural outcomes such as depression, poor treatment adherence, and underreporting of symptoms.

Dr. Hamann pointed out that stigma is relevant across the continuum of lung cancer care [8]. "This includes prevention, detection, diagnosis, treatment, and survivorship." Moreover, implications of stigma need to be dealt with on many levels of lung cancer care ranging from the individual patients to families, practice settings and even the national level, where policies and financial/political structures are provided [9].

LCSI

The Lung Cancer Stigma Inventory (LCSI) has been developed in three phases that entailed interviews, generating and refining of items, and multisite field testing among lung cancer survivors [10]. Three factors related to patient-reported stigma were identified: internalised stigma, perceived stigma, and constrained disclosure **(Table 3)**. The LCSI Measure is available for download on the NCI GEM database. "In terms of other psychometrics associated with this measure, a high test-retest correlation was found, as well as good convergent validity with the Cataldo Lung Cancer Stigma Scale, although the two tests were not completely overlapping," explained Dr. Hamann. Ever smokers reported higher internalised stigma scores than never smokers, while these two groups did not differ with respect to perceived stigma. Also, there was a positive correlation between different aspects of stigma and the depression scale: higher levels of stigma correlated with higher levels of depression.

"Patient-reported stigma has multifaceted psychosocial impact and potentially affects multiple levels of lung cancer care," Dr. Hamann summarised. "Addressing it is very important." Further research is required regarding the care-related impact of stigma. "We need more data to truly understand how stigma affects treatment decisions, patient adherence, and clinical trial involvement." Moreover, interventions, including those at the patient level, should be tested with a focus on internalised stigma and constrained disclosure. ■

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Multiple approaches for the treatment and prevention of CNS metastases

Activity of afatinib and osimertinib in the *EGFR*-mutant setting

More than 40 % of NSCLC patients develop CNS metastasis in their lifetime [1, 2]. As the burden of brain lesions affects both quality of life and survival, the development of therapies that are able to penetrate the blood-brain barrier is an important focus of research.

Among the EGFR TKIs, the second-generation agent afatinib and the third-generation drug osimertinib have shown particular CNS activity in patients with *EGFR*-mutant NSCLC. Additional evidence on afatinib in this respect is provided by the analysis of a large, open-label, single-arm phase IIIb study conducted in EGFR TKI-naïve Asian patients in conditions similar to real-world clinical practice [3]. Among 479 patients, 92 had CNS lesions. PFS was numerically shorter in those with brain metastases compared to those without (10.9 vs. 12.4 months), but median time to symptomatic progression did not differ across the groups (14.8 vs. 15.4 months). In accordance with previous observations, the analysis of the total cohort confirmed that the use of tolerability-guided dose adjustments reduces the rates of commonly occurring AEs, while therapeutic efficacy of afatinib was maintained.

Kang et al. reported data on the activity of osimertinib in patients with brain lesions included in the Korean subset of the open-label, single-arm, real-world treatment ASTRIS trial [4]. ASTRIS investigated osimertinib 80 mg daily in a global population of patients with T790M-positive advanced NSCLC after previous EGFR TKI treatment. Patients with asymptomatic, stable CNS metastases who did not require increasing doses of corticosteroids within 2 weeks prior to initiation of osimertinib were allowed to enroll. This applied to 211 individuals.

The findings strongly supported the clinical benefits of osimertinib in patients with *EGFR*-mutant NSCLC and CNS metastases. Median PFS was 10.8 and 11 months, respectively, with 1-year PFS rates of 39.6 % vs. 47.3 %. Sixty-eight percent and 79.6 % of patients responded, and time to treatment discontinuation was 11.2 vs. 14.7 months.

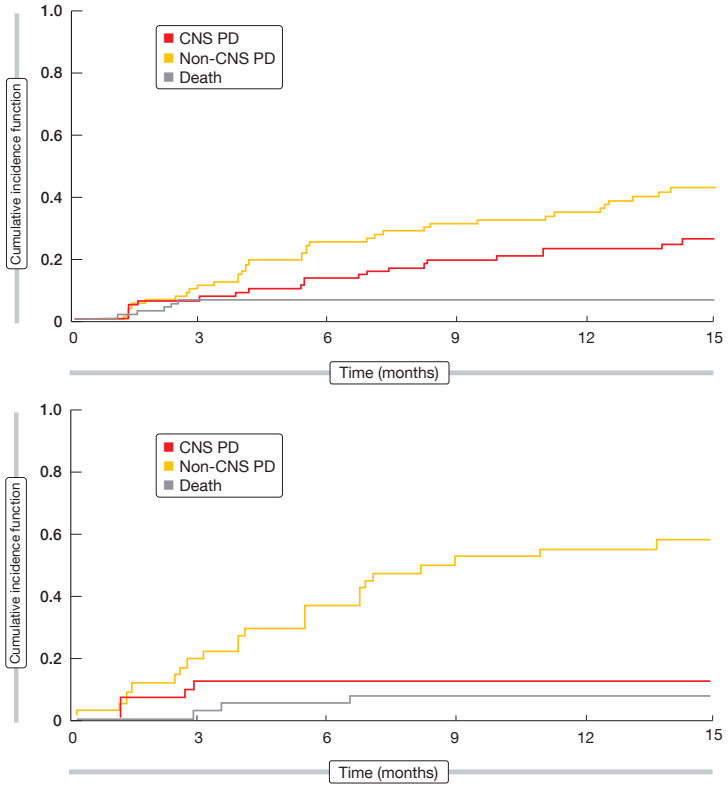

Figure: Cumulative incidence of CNS progression, non-CNS progression, and death after ≥ 1 prior second-generation ALK TKI in lorlatinib-treated patients with (above) and without (below) baseline CNS metastases

ALK-positive pre-treated NSCLC: lorlatinib

The selective, potent ALK/ROS1 TKI lorlatinib was designed to penetrate the blood-brain barrier. In a phase I/II study, lorlatinib showed robust clinical activity in patients with *ALK*-positive NSCLC most of whom had CNS disease and had failed ≥ 1 ALK TKI [5, 6]. Cerebrospinal fluid sampling revealed a mean lorlatinib CSF-to-unbound plasma concentration ratio of 0.73, indicating high CNS penetration of the drug. Bauer et al. analysed the patients for progressive disease (PD), which was categorised as either CNS or non-CNS progression based on independent central review, or death [7]. The cumulative incidence rates were calculated using competing risks methodology in pooled cohorts in the ongoing phase II study that contains multiple subsets.

The analysis demonstrated pronounced activity of lorlatinib100 mg daily in the treatment of brain lesions in patients with and without baseline CSN metastases after progression on crizotinib and/or second-generation ALK TKIs. In the group of crizotinib-pretreated patients, the intracranial ORR (IC-ORR) was 70 %, and median duration of intracranial responses (IC-DOR) had not been reached yet. For patients with baseline CNS metastases, the probabilities of both CNS and non-CNS PD were 22 % at 12 months. Those without brain lesions had a higher probability of non-CNS PD than CNS PD (43 % vs. 9 % at 12 months). Similarly, the patient group that had received one prior non-

TABLE
Intracerebral responses according to the interval between radiotherapy and initiation of nivolumab treatment

	< 3 months n = 20	> 3 months n = 30
Complete response	1	0
Partial response	5	2
Stable disease	5	12
Progressive disease	4	8
Not evaluable	5	8
Intracerebral RR	30.0 %	6.7 %

crizotinib TKI had an IC-ORR of 46 %, and median IC-DOR had not been reached. In those with two or three prior TKIs, IC-ORR and IC-DOR were 48 % and 15 months, respectively. Pooled data of those after a non-crizotinib TKI and those after two or three TKIs revealed that both patients with and without baseline CNS lesions showed a higher likelihood of extracranial PD compared to CNS PD (35 % vs. 23 % at 12 months for patients with baseline CNS metastases, and 55 % vs. 12 % for those without; **Figure**). This was also true for patients who had been treated with a second-generation ALK TKI as their last prior TKI therapy. Taken together, these findings underscore the activity of lorlatinib against CNS metastases and suggest that lorlatinib might also prevent the spread of the disease to the brain. To date, these are the only available prospective data on sequencing after progression on second-generation ALK TKI therapy.

Prophylactic cranial radiotherapy in high-risk patients

The role of prophylactic cranial irradiation (PCI) in patients with NSCLC remains controversial because of concerns about radiation-induced neurological morbidity and lack of OS gain. Arrieta et al. presented results showing that PCI is beneficial in patients with a high risk of developing brain metastases [8]. These were defined as patients showing a target mutation (e.g. either sensitising *EGFR* mutations or *ALK* rearrangement) and/or elevated CEA levels (> 20 pg/ml) at the time of diagnosis. In addition to treatment with first- and second-generation TKIs, they were randomised to receive either PCI (25 Gy in 10 fractions, 5 days per week; n = 41) or were followed up only (n = 43). Intracranial PFS constituted the primary outcome. After an amendment, patients who were treated with PCI after January 2016 had hippocampal sparing.

According to the multivariate analysis, PCI reduced the risk of intracranial progression and death by 60 % (p = 0.006). Patients treated with PCI showed a 22 % cumulative incidence of CNS progression at 24 months, while those in the control arm experienced CNS progression in 52 %. Similar trajectories were observed for OS (median OS, 42.8 vs. 25.9 months; HR, 0.47; p = 0.035). Cognitive function was assessed using Mini Mental State Examination (MMSE), and quality of life was evaluated through the EORTC-QLQ-30 questionnaire [9]. MMSE scores and median score values for global quality of life, fatigue and cognitive functioning did not differ across groups or between baseline and follow-up. Long-term assessments are necessary, however.

Overall, these results highlight the benefit of PCI particularly in patients at high risk of developing brain metastases. The authors noted that these findings can be extrapolated for patients treated with third-generation TKIs, which have higher CNS penetration but are often not accessible in developing countries.

Does immunotherapy work in the brain?

The multicentre, non-interventional, retrospective cohort IMMUNOBrainZH study was designed to evaluate the PD-1 inhibitor nivolumab 3 mg/kg Q2W in patients with advanced NSCLC and brain metastases who had failed ≥ 1 line of chemotherapy [10]. Fifty out of 77 eligible patients had received either stereotactic radiotherapy (SRT, n = 17) or whole-brain radiotherapy (WBRT, n = 33), while in 27 cases, no previous intracranial local treatment had been administered. PD-L1 expression levels were unknown.

For intracerebral response, which was defined as the primary endpoint, the analysis yielded a rate of 20.8 %. Extracerebral responses occurred in 22.1 %, and the ORR was 23.4 %. When analysed according to prior local treatment, intracerebral response rates were higher in patients without previous radiotherapy (29.6 %) and those after SRT (23.5 %) than in those after WBRT (12.1 %). Patients who had received radiotherapy less than 3 months before nivolumab initiation responded considerably better than those with a longer interval (intracerebral RRs, 30.0 % vs. 6.7 %; **Table**). Intracerebral PFS was 8.0 months for the entire cohort, and OS was 9.0 months.

The authors concluded that intra- and extracerebral efficacy of nivolumab appears to be similar. Prior radiotherapy within 3 months of the beginning of nivolumab therapy might have a synergistic anti-tumour effect. Immunotherapy, as other systemic therapies, demonstrates promising efficacy on brain metastases due to NSCLC. ■

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James Ho talks about novel diagnostic approaches, monitoring of lung cancer patients as well as the potential for the use of antioxidants in lung cancer.

Herbert Loong on peculiarities of lung cancer research with a focus on phase I studies.

Maximilian Hochmair on the future of combinations of immunotherapies with other drugs as well as his recommendations for treatment sequencing in *ALK*-positive and *EGFR*-positive lung cancer.

Vera Hirsh discusses the latest clinical achievements using *EGFR*-targeted therapy in patients with advanced NSCLC and the role of patient quality of life.

Virote Sriuranpong talks about new agents in the area of *EGFR*-targeted therapy as well as the results obtained with afatinib in a named patient program at Asian centers.

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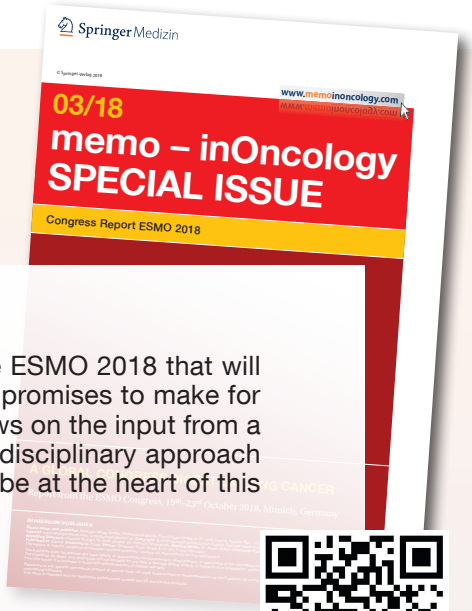

Forthcoming Special Issue

This special issue will be offering a synopsis from the ESMO 2018 that will be held in Munich, in October 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.

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