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A GLOBAL CONGRESS DIGEST ON NSCLC

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Preface

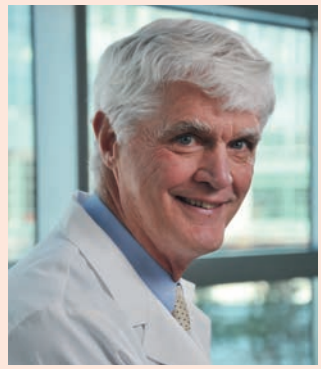
Dear Colleagues,

Lung cancer mortality rates for both men and women have been declining in recent years. Early detection, refined understanding of tumour biology, and a variety of novel treatment options have made these advances possible. Nevertheless, lung cancer is still the leading cause of cancer death in the United States and worldwide, prompting the scientific community to persevere in their research efforts and to extend them to areas that have traditionally been marked by little progress, such as small-cell lung cancer (SCLC).

At the Annual Meeting of the American Society of Clinical Oncology (ASCO) that took place in Chicago, 3rd–7th June, 2016, promising results were presented that have been achieved using immunotherapeutic approaches in the setting of SCLC. As in non-SCLC (NSCLC), it appears that a certain proportion of treated patients can hope for long-term survival. Also, phase I data on the DLL3-targeted antibody–drug conjugate rovalpituzumab tesirine suggest that it has clinically relevant activity in the SCLC population.

One quarter of the abstracts submitted for this year's ASCO Congress were focussed on the topic of immunotherapy. According to updates of pivotal trials, sustained benefits can be expected in a minority of patients with these drugs. Combination immunotherapy consisting of nivolumab and ipilimumab may provide benefits over nivolumab monotherapy in advanced NSCLC of any histology. However, molecularly targeted therapies remain the preferred therapeutic choice in the first line for patients with driver alterations. ALK inhibitors such as alectinib and brigantinib have shown efficacy in tumours with *ALK*-resistance mutations, and the novel agents lorlatinib and olmutinib are being tested in *ALK/ROS1*-positive and *EGFR*-T790M-mutated NSCLC, respectively.

Continual refinement in the field of molecular diagnostics is a cornerstone of this evolution. According to a large analysis, targeted therapy conferred survival improvements when all driver mutations were considered. Minimally invasive techniques are gaining ground, due to their obvious advantages. The assessment of circulating tumour DNA, which is obtained through conventional blood sampling, enables profiling of solid tumours and adds to the accuracy of tissue typing.



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Immunotherapy: updates on clinical trials and other insights

Nivolumab plus ipilimumab: CheckMate 012

Besides targeted drugs for driver mutations, immunotherapies represent one of the two recent major advancements of the past decade for the treatment of metastatic non–small-cell lung cancer (NSCLC). Nivolumab and ipilimumab enhance T-cell antitumour activity through distinct and complementary mechanisms. The combination of these two agents has already been approved in the US and EU for metastatic melanoma. In NSCLC, nivolumab monotherapy is approved as a second-line treatment for locally advanced or metastatic disease, while first-line standard treatment still consists of platinum-doublet chemotherapy. Progress towards improved first-line treatment options has plateaued over the last decade, and the need for improvement in this clinical setting is critical.

Therefore, the 3-arm, randomised, phase I, CheckMate 012 trial examined the role of combination immunotherapy in patients with advanced NSCLC (stage IIIB/IV) of any histology. Treatment consisted of nivolumab 1 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks, nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 12 weeks, or nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks. Previous data had indicated that efficacy was greatest in the two arms that received nivolumab 3 mg/kg. The updated analysis presented at the ASCO Congress was performed after an extended follow-up in these two groups, which comprised 38 patients

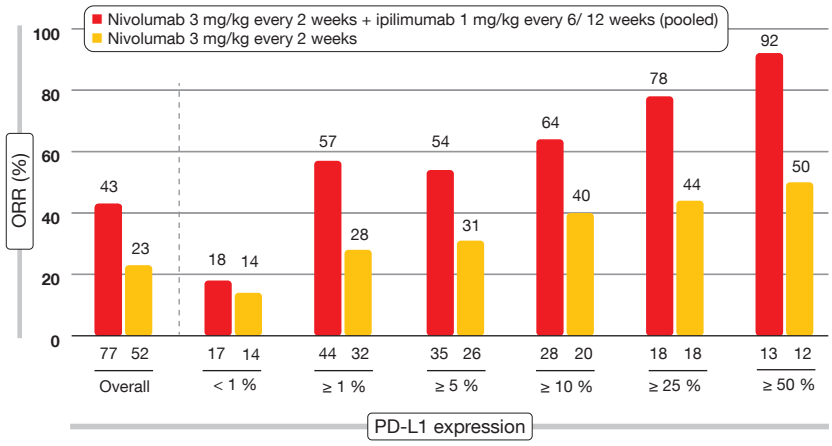

Figure 1: CheckMate 012: pooled ORR analysis of two schedules of nivolumab plus ipilimumab across different PD-L1 expression levels, as compared to nivolumab monotherapy

(nivolumab plus ipilimumab every 12 weeks) and 39 patients (nivolumab plus ipilimumab every 6 weeks), respectively [1]. Safety and tolerability were defined as the primary endpoints.

Improved tolerability and promising efficacy

As compared to older combination regimens included in the CheckMate 012 trial that used higher or more frequent doses of ipilimumab, these dosing schedules showed improved tolerability and a manageable safety profile. Treatment-related grade 3/4 adverse events (AEs) occurred in 37 % and 33 %, respectively, and led to discontinuation at a third of the rate seen with the older study arms (5 % and 8 %, respectively). No treatment-related deaths were observed. Reassuringly, the overall incidence of grade 3/4 immune-related AEs was low across all treatment arms. These data were similar to a separate arm of the CheckMate 012 trial that used nivolumab monotherapy 3 mg/kg every 2 weeks.

The analysis yielded promising efficacy, with overall response rates (ORRs) of 47 % and 39 %, respectively. These ORRs exceed those obtained with nivolumab monotherapy (23 %). The median duration of response was not yet reached. According to a pooled biomarker analysis, efficacy was enhanced with increasing PD-L1 expression, and patients treated with the combination fared better than the historical nivolumab-only group across all PD-L1 expression levels (**Figure 1**). Also, superiority of the combination over nivolumab monotherapy was observed in never smokers and current/ former smokers alike. Patients with *EGFR* mutations showed markedly higher ORRs with nivolumab plus ipilimumab than with nivolumab alone. Responses obtained with the combination tended to be both deep and durable, and were achieved early in most cases. The schedule containing nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks is being evaluated in further studies, including the phase III CheckMate 227 trial.

Durable survival benefit of nivolumab in CheckMate 017 and 057

Nivolumab monotherapy demonstrated a significant overall survival (OS) benefit compared with docetaxel in advanced NSCLC in the phase III CheckMate 017 (squamous histology) [2] and CheckMate 057 (non-squamous histology) trials [3]. Borghaei et al. presented the updated OS and safety results from these two studies, based on a follow-up of ≥ 2 years [4]. Also, exploratory analyses of the association between baseline serum cytokine profiles and OS were conducted for both histologies.

In both trials, nivolumab demonstrated durable, long-term OS and progression-free survival (PFS) compared with docetaxel. The differences in OS and PFS rates between the nivolumab and docetaxel arms remained consistent from 1 to 2 years. At two years, 23 % vs. 8 % of patients in the nivolumab and docetaxel arms, respectively, were alive in the CheckMate 017 trial (HR, 0.62). For CheckMate 057, these percentages were 29 % vs. 16 % (HR, 0.75). In CheckMate 057, as in the primary analysis, PD-L1 expression level was associated with magnitude of OS benefit. Treatment-related AEs were reported in fewer nivolumab-treated patients than in docetaxel-treated patients in both studies. Overall, AE rates at 2 years resembled those at 1 year.

The cytoscores, which reflect the cytokine profile at baseline, appeared to be associated with prognosis in both squamous and non-squamous disease, but these results are only hypothesis-generating and require prospective validation. Cytoscores were not associated with treatment effects of nivolumab over docetaxel.

Long-term results for pembrolizumab

Based on the findings obtained in the large multi-cohort phase Ib KEYNOTE-001 study [5, 6], pembrolizumab received accelerated approval in the United States for the treatment of advanced NSCLC that expresses PD-L1 and has progressed after platinum-containing chemotherapy and (in the case of *EGFR* or *ALK* positivity) an approved EGFR or ALK inhibitor. KEYNOTE-001 demonstrated a correlation between higher PD-L1 expression and improved outcomes.

The long-term analysis of the KEYNOTE-001 trial showed that pembrolizumab monotherapy provides sustained OS benefit in patients with advanced NSCLC [7]. Increased PD-L1 expression was associated with increased survival benefit. Pembrolizumab continued to have a manageable safety profile; no unexpected toxicities occurred during the long-term follow-up. Along with the KEYNOTE-010 trial, which demonstrated OS improvement with pembrolizumab in patients with previously treated NSCLC and PD-L1 expression of ≥1 % on tumour cells [8], these data support PD-L1 as a predictive biomarker for pembrolizumab, and confirm the manageable safety profile of this agent.

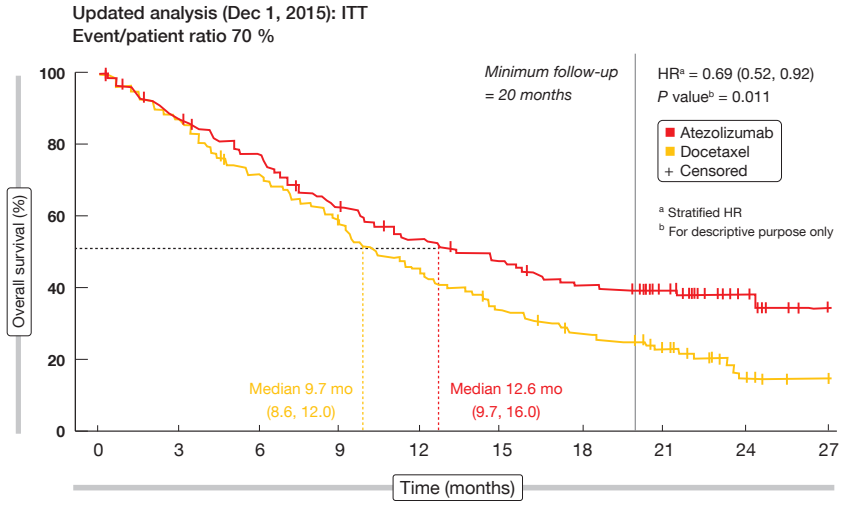

Figure 2: Updated OS findings with atezolizumab vs. docetaxel in the POPLAR trial

OS improvement with atezolizumab becomes apparent over time

The engineered and humanised anti-PD-L1 antibody atezolizumab was compared to docetaxel in the multi-centre, randomised, open-label, phase II, POPLAR study in patients with previously treated locally advanced or metastatic NSCLC who progressed during or after platinum-based therapy. At a minimum follow-up of 13 months, the primary analysis was conducted, which revealed an OS benefit of atezolizumab over docetaxel in both unselected and PD-L1-selected patients [9, 10]. Increasing PD-L1 expression on tumour cells and/ or immune cells was associated with increasing OS benefit. The survival curves showed late separation, underscoring the need for long-term follow-up to fully capture the benefit of this anti-PD-L1 therapy.

Therefore, Smith et al. presented an updated analysis after a minimum follow-up of 20 months [11]. This showed further separation of the survival curves in the ITT population (**Figure 2**). Consistent with the previous pattern, OS hazard ratios (HRs) improved in favour of atezolizumab over time. The OS benefit was observed in all PD-L1 subgroups. Also, survival curves for histology subgroups showed continued separation over time, with the improvement in HRs more pronounced in the squamous NSCLC subgroup. PFS and ORR were similar across the atezolizumab and docetaxel arms in the ITT population; here, the data did not change significantly from the primary analysis.

As the authors noted, the lack of correlation between the OS benefit and the PFS and ORR findings implies that OS improvement with atezolizumab might extend beyond disease progression by RECIST. Responses observed with atezolizumab were durable, however (median, 18.6 vs. 7.2 months with atezolizumab and docetaxel, respectively). Together, these results provide further evidence that survival benefits with atezolizumab extend to all patients with NSCLC.

Durvalumab shows efficacy in squamous and non-squamous disease

A multicentre, open-label, dose-escalation and dose-expansion, phase I/II trial investigated the safety and clinical efficacy of durvalumab in patients with advanced, treatment-naïve NSCLC [12]. Durvalumab is a selective, high-affinity, engineered human monoclonal anti-PD-L1 antibody. PD-L1 expression was prospectively evaluated (high: ≥ 25 % tumour cell staining; low or negative: < 25 % tumour cell staining). Fifty-nine patients who had not received prior systemic therapy for advanced disease were treated. Forty-nine of these showed high PD-L1 expression.

Durvalumab 10 mg/kg every 2 weeks was demonstrated to have a manageable safety profile. ORR was 27 %; in patients with high PD-L1 expression, responses occurred in 29 %, and in those with low or negative expression, in 11 %. One patient with high expression experienced complete remission. Reductions of target lesions were observed in patients with both high and low/ negative PD-L1 expression and in one patient with an unknown PD-L1 expression status (**Figure 3**). ORR was similar regardless of histology (squamous vs. non-squamous) for patients with high PD-L1 expression. In three patients who had non-squamous disease and low or negative PD-L1 expression, no responses occurred. Current or former smokers with high expression showed an ORR of > 30 %. Responses were gen-

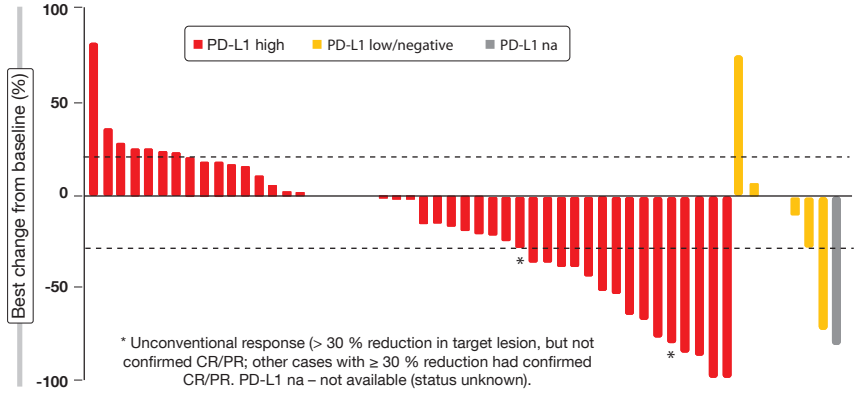

Figure 3: Best changes from baseline in tumour size by PD-L1 expression obtained with durvalumab

erally rapid and durable; at data cut-off, they were ongoing in 69 %. Durvalumab is currently being investigated across a range of studies in treatment-naïve patients with advanced NSCLC.

JAVELIN: avelumab in chemotherapy-refractory mesothelioma

Approximately 3,000 cases of malignant mesothelioma are diagnosed each year in the US. There are no FDA-approved treatment options for patients who progress after first-line chemotherapy. The international, multi-cohort, dose-escalation and dose-expansion, phase Ib, JAVELIN trial investigated the fully human anti-PD-L1 antibody avelumab in mesothelioma on the basis that PD-L1 is expressed on the surface of mesothelioma cells [13]. JAVELIN enrolled a total of 1,600 patients with different tumour types. Fifty-three patients with advanced, unresectable, pleural or peritoneal mesothelioma, who had progressed after treatment with platinum and pemetrexed, received avelumab 10 mg/kg every 2 weeks. PD-L1 expression status was assessed, revealing the presence of any staining intensity (≥ 1 % of tumour cells) in 51.3 % of cases.

Avelumab monotherapy led to a disease control rate of 56.6 %, which was mainly due to disease stabilisation (47.2 %). Five patients developed partial responses (9.4 %), which were ongoing in four of them at last follow-up. The median duration of response was not reached. ORR and PFS did not differ according to PD-L1 expression levels. Overall, median PFS was 17.1 weeks. Avelumab showed an acceptable safety profile. Most treatment-related AEs were grades 1 or 2. Immune-mediated AEs of any grade were seen in 13.2 %, but grade 3 events occurred in only 1.9 %. Ongoing follow-up will further characterise the durability of the clinical activity.

Is treatment beyond RECIST progression feasible?

In the context of immunotherapy, there is uncertainty around tumour reductions according to RECIST as an endpoint, because the assessment of shrinkage appears to underestimate the true magnitude of benefit in terms of survival. This might be justified, as conventional response criteria are based on traditional cytotoxic chemotherapy, and tumour flare or pseudo-progression can lead to early treatment discontinuation. Anecdotal cases of decreases in tumour size after initial RECIST-defined progression have led to trials allowing for treatment past RECIST-defined first progression.

A retrospective exploratory analysis presented at the ASCO Congress described findings in patients with metastatic NSCLC who were treated with anti-PD-1 therapy past conventional progression (treatment past progression, TPP) [14]. The investigators pooled three multi-centre clinical trials that had been submitted to the FDA, which evaluated anti-PD-1 monotherapy in 535 patients who progressed after initial therapy. From these, 121 patients receiving TPP were identified. Changes in tumour burden from radiographic tumour measurement data following RECIST-defined progression were evaluated.

Compared to all anti-PD-1-treated patients (n = 535), the subgroup with TPP showed a slightly higher frequency of non-squamous histology (59 % vs. 54 %). Most patients had only had one prior line of chemotherapy, and all of them had an ECOG performance status of 0 or 1, although ECOG 0 was more frequent in the TPP group (36 % vs. 25 %). Patients who received TPP initially progressed per RECIST due to unequivocal progression of non-target lesions (38 %), appearance of new lesions (32 %), or increases of ≥ 20 % from nadir in target lesions (30 %). Overlaps of 2 causes or all 3 causes were observed.

A small, but not negligible effect

Of the 121 patients who received TPP, 10 (8.3 %) experienced additional tumour shrinkage, which was defined as a subsequent decrease in target lesions of ≥ 30 %, as compared to baseline. The **Table** summarises the characteristics of these patients. This group represents 1.9 % of all patients treated with anti-PD-1 agents in these trials. The best tu-

TABLE
Characteristics of the ten patients who achieved additional tumour shrinkage with continuation of anti-PD-1 therapy past RECIST progression

Patient	Prior best overall response	Reason for RECIST progression	PD-L1 expression (%)	Best change from baseline with TPP (%)	New duration of response (months)
1	SD	Target lesion ≥ 20 %	0	-56	1.5
2	PR	New lesion	0	-56	14.0
3	SD	Target lesion ≥ 20 %	50	-58	1.4
4	PR	Non-target lesion progression	0	-73	14.2
5	PD	New lesion and non-target lesion	80	-50	1.3
6	PD	New lesion	90	-71	14.0
7	PR	New lesion	40	-100	1.4
8	PR	Target lesion ≥ 20 %	0	-95	7.1
9	PD	Non-target lesion progression	0	-35	5.8
10	PD	Unknown; received radiation	n/a	-57	10.2

mour reductions compared to baseline during TPP ranged from 35 % to 100 % (median, 58 %). With TPP, the median duration of responses after a ≥ 30 % reduction was not reached. At the time of data capture, at least 5 of 10 patients had responses of at least 6 months, and 3 patients had ongoing responses of over 1 year.

Moreover, the best reductions in target lesions were in patients who attained at least 30 % reduction, compared to the overall nadir measurements. Seven of the 10 patients met these criteria. The best tumour shrinkage compared to nadir ranged from 13 % to 100 %, with a median reduction of 35 %. Durations of new responses showed a wide range, from 1.3 months to > 1 year.

According to the authors' conclusions, it is unclear whether the observed tumour reductions were due to TTP or to a delayed effect of the immunotherapy the patients had received previously. This implies that the risk of continued treatment (immune-related adverse reactions) after first progression should be balanced against the possibility of further tumour shrinkage. As more knowledge is gained with the use of immunotherapies, it might be possible to better identify patients who are more likely to benefit from TPP (e. g., biomarkers, patient characteristics). Randomised controlled trials are needed to prospectively establish any benefit of treating patients past first progression. However, TPP is unlikely to significantly change major FDA regulatory endpoint results or benefit/ risk determination. ■

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Expanding treatment options in NSCLC patients with rare mutations: *ALK, ROS1, MET, BRAF*

ALK gene rearrangements occur in approximately 4 %to 5 % of all Caucasian and Asian patients with advanced NSCLC. Crizotinib was the first approved ALK inhibitor and is the current front-line standard treatment for *ALK*-positive NSCLC. However, despite initial responses to TKI treatment, all of these patients relapse in the long run. This is mainly due to secondary mutations in the *ALK* or *ROS1* kinase domains, or poor CNS drug penetration. Secondary mutations have been observed in approximately 25 % of patients with resistance to crizotinib [1, 2]. Research is focussing on the development of new options for both first-line and resistant settings.

The J-ALEX frontline trial: alectinib *versus* crizotinib

Alectinib is a potent, highly selective, CNS-active ALK inhibitor with activity against *ALK*-resistance mutations. The J-ALEX phase III study compared alectinib 300 mg BID (n = 103) with crizotinib 250 mg BID (n = 104) in ALK-inhibitor-naïve patients with stage IIIB/IV or recurrent *ALK*-positive NSCLC [3]. Patients with treated or asymptomatic brain metastases were eligible.

J-ALEX has already met the primary endpoint, which was PFS, at a preplanned interim analysis, as assessed by an independent review facility. These findings suggested a highly significant difference in favour of alectinib (median PFS, not reached vs. 10.2 months; HR, 0.34; p > 0.0001; **Figure**). Almost all of the patients derived a PFS benefit from the alectinib treatment, according

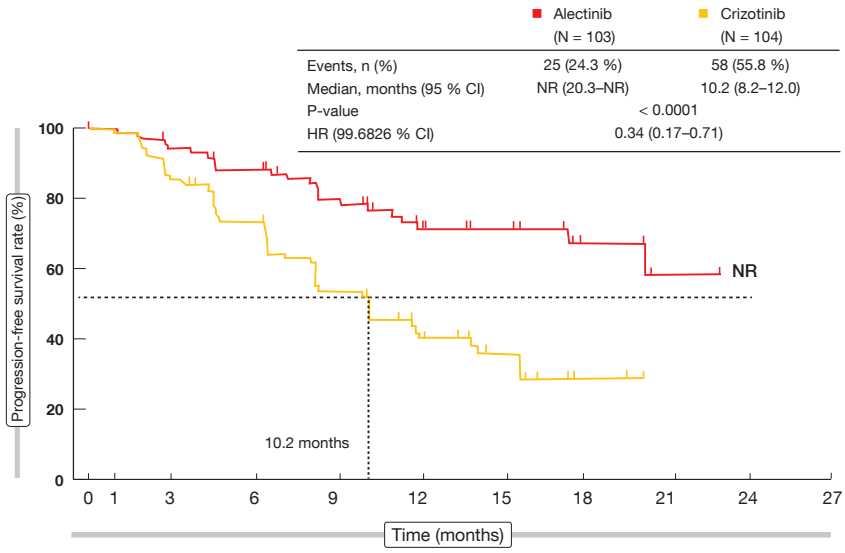

Figure: J-ALEX-study: superiority of alectinib over crizotinib with regard to PFS (ITT population)

to a subgroup analysis. ORRs assessed through the independent review facility were 91.6 % and 78.9 % for alectinib and crizotinib, respectively. The waterfall plots indicated greater tumour shrinkage in the alectinib arm.

Alectinib was well tolerated, and showed a favourable AE profile. Patients in both arms reported constipation, nasopharyngitis, dysgeusia, nausea, pyrexia, diarrhoea and vomiting. All of these AEs occurred less frequently with alectinib than with crizotinib, and sometimes by a very large margin. This was also true for elevation of the liver enzymes. Grade 3/4 AE rates were halved with alectinib compared to crizotinib (26.2 % vs. 51.9 %), and the AEs necessitated both discontinuations and dose interruptions to markedly lower levels in the experimental arm than the control arm. Overall, these results suggest that alectinib has the potential to be a new first-line standard for patients with *ALK*-positive NSCLC.

Brigantinib in crizotinib-refractory patients: ALTA

Brigantinib is an investigational next-generation ALK TKI, which was designed to have potent and broad activity against resistant *ALK* mutations. Phase II data presented at the ASCO Congress demonstrated activity of this agent after progression on crizotinib. The international, randomised, dose-evaluation ALTA trial evaluated brigantinib in patients with locally advanced or metastatic *ALK*-positive NSCLC [4]. The patients received brigantinib at two doses in a randomised manner: 180 mg OD (n = 110), which was preceded by a 7-day lead-in at 90 mg, or 90 mg OD (n = 112). The primary endpoint was ORR according to the RECIST criteria.

Patients in the 180 mg and 90 mg brigantinib groups achieved confirmed ORRs of 54 % and 45 %, respectively. The majority experienced PR. Confirmed CRs occurred in 4 and 1 patients, respectively. ORRs did not differ by history of chemotherapy. Most of the patients in both groups showed reductions in tumour size. Disease control was achieved in 86 % and 82 %, respectively. Median PFS exceeded 1 year in the 180 mg dose group (12.9 months), while it was only 9.2 months in the 90 mg dose group. At 1 year, 54 % and 39 % of patients were alive and progression free, respectively. Median OS had not yet been reached in either group. The proportions of patients alive at 1 year were 80 % and 71 %, respectively.

Activity against brain lesions

Intracranial responses occurred in both dose groups, as assessed by an independent review committee. In patients with measurable (≥ 10 mm) lesions, the confirmed intracranial ORRs were 67 % *versus* 36 % with the 180 mg and 90 mg doses, respectively. Intracranial disease control occurred in 83 % and 88 %, respectively **(Table 1)**. Patients with measurable, active brain metastases (with no prior radiotherapy, or progression after radiotherapy) at baseline attained intracranial ORRs of 73 % and 37 %, respectively. Intracranial PFS had not been reached with the 180 mg treatment, and was 15.6 months with the 90 mg schedule.

Brigantinib demonstrated an acceptable safety profile in both arms. Nausea, diarrhoea, headache, cough and fatigue were reported most frequently. Grade 3/4 AE rates were low. The authors concluded that brigantinib has the potential to be a new treatment option for patients with crizotinib-resistant *ALK*-positive NSCLC. The efficacy and safety findings support the choice of the 180-mg regimen for further trials. A randomised phase III study is currently comparing brigantinib 180 mg with crizotinib in ALK-inhibitor-naïve patients.

TABLE 1
Intracranial responses obtained with brigantinib in patients with measureable brain metastases (≥ 10 mm) in the ALTA trial

IRC-assessed efficacy parameter	180 mg OD (n = 18)	90 mg OD (n = 25)
Confirmed intracranial ORR, n (%) [95 % CI]	12 (67) [41–87]	9 (36) [18–58]
Best overall response, n (%)		
- Confirmed intracranial CR	0	2 (8)
- Confirmed intracranial PR	12 (67)	7 (28)
- Intracranial CR awaiting confirmation	0	0
- Intracranial PR awaiting confirmation	0	3 (12)
Intracranial disease control rate, n (%) [95 % CI]	15 (83) [59–96]	22 (88) [69–98]

IRC, independent review committee

Novel ALK- and ROS1-inhibiting compound: lorlatinib

Lorlatinib is a novel macrocyclic ALK inhibitor that is able to penetrate into the CNS. It has shown activity against a wide range of mutations that confer resistance to ALK inhibitors, and it is also a potent inhibitor of ROS1.

Solomon et al. presented the dose escalation component of an ongoing phase I/II study evaluating lorlatinib OD or BID in 54 patients with advanced, *ALK*/*ROS1*-positive NSCLC [5]. These patients were either treatment-naïve or had experienced disease progression after at least one prior ALK/ROS1 TKI. Any prior chemotherapy was allowed. Measureable extracranial disease had to be present. Asymptomatic CNS metastases (treated or untreated) were allowed; 72 % of the patients had brain metastases. The intracranial activity of lorlatinib was prospectively assessed using MRI.

Lorlatinib showed robust clinical activity in both *ALK*-positive and *ROS1*-positive patients. This treatment gave rise to three CRs and 16 PRs, resulting in an ORR of 46 %. Patients who had received one prior ALK TKI showed an ORR of 57 %, while those after at least two ALK TKIs achieved an ORR of 42 %. The majority developed decreases in target lesion size. In 20 patients, the responses were ongoing at the time of the data cut-off. Median PFS was 11.4 months for the entire cohort. At one year, 41 % were free of progression. As for ORR, the group that had previously received only one ALK TKI fared better with regard to PFS than those who had been treated with two or more TKIs (PFS, 13.5 vs. 9.2 months).

Lorlatinib treatment prompted significant intracranial responses. According to the prospective intracranial assessment, five CRs and two confirmed PRs occurred in 18 patients with measurable intracranial disease, which amounted to a confirmed intracranial response rate of 39 %. Three of four *ROS1*-positive patients with measureable intracranial disease experienced tumour reductions. Responses also occurred in patients with leptomeningeal disease.

Hypercholesterolaemia was the most frequent treatment-related AE, but it was asymptomatic and readily managed with statin therapy. At the recommended phase II dose of 100 mg OD, other AEs were seen, included peripheral oedema, hypertriglyceridaemia, and slowing of speech. The phase II portion of this study is ongoing in 57 centres worldwide.

Crizotinib in NSCLC with *MET* alterations

Mutations in the known proto-oncogene *MET* that lead to decreased MET degradation occur in approximately 3 % to 4 % of patients with non-squamous NSCLC. *MET* exon 14 alterations represent a heterogeneous group of mutations. While many of these result in *MET* exon 14 skipping, select point mutations or deletions create the same biology without causing exon skipping. Concurrent *MET* amplification can be identified in 15 % to 20 % of cases.

Crizotinib was initially developed as a MET inhibitor, and it is currently being tested in patients with advanced *MET* exon-14-altered NSCLC in the open-label, multi-centre, phase I PROFILE 1001 study. Results presented at the ASCO Congress showed that in these patients, crizotinib has anti-tumour activity and a generally tolerable AE profile, which is consistent with that previously reported for patients with *ALK*-positive or *ROS1*-rearranged NSCLC [6].

Twenty-one patients were enrolled and received crizotinib at a starting dose of 250 mg BID. None of their tumours harboured concurrent *ALK* or *ROS1* aberrations. Crizotinib therapy prompted an ORR of 44 % in the PROFILE 1001 trial. Almost all of the patients achieved disease shrinkage. Responses were usually observed early on, and most patients remained on study, with the longest ongoing response of approximately 1 year. Median PFS and OS could not be calculated, as no deaths or disease progressions had occurred at the time of the data cut-off.

The predominant treatment-related AEs were oedema, nausea, diarrhoea, and vision disorder, with the majority of these being rated as grade 1 or 2. According to the trial authors, further study of crizotinib in this patient population is warranted.

BRAF mutation as a target

BRAF V600E mutations occur in 1 % to 2 % of patients with adenocarcinoma of the lung. Among these mutations, 70 % are of the *BRAF* V600E type. NSCLC that shows *BRAF* V600E mutation has histological features that are suggestive of an aggressive tumour, and patients demonstrate less favourable outcomes when treated with platinum-based chemotherapy.

An efficient targeted approach in this group includes the BRAF-inhibiting small molecule dabrafenib in combination with the small molecule trametinib, which acts as an allosteric inhibitor of MEK1 and MEK2. Together, these drugs confer dual inhibition of the MAPK pathway. In the multi-cohort, non-randomised, open-label phase II BRF113928 study, which involved 78 patients with *BRAF* V600E-mutated stage IV NSCLC, dabrafenib monotherapy yielded an ORR of 33 % and a median PFS of 5.5

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TABLE 2
Greater clinical activity of dabrafenib plus trametinib compared with dabrafenib monotherapy in *BRAF* V600E-mutant NSCLC

	Dabrafenib + Trametinib (n = 57)	Dabrafenib monotherapy (n = 78)
ORR (95 % CI), %	63 (49–76)	33 (23–45)
Disease control rate (95 % CI), %	79 (66–87)	58 (46–67)
PFS, median (95 % CI), months	9.7 (6.9–19.6)	5.5 (3.4–7.3)
Duration of response, median (95 % CI), months	9.0 (6.9–18.3)	9.6 (5.4–15.2)

months after failure of ≥ 1 prior platinum-based therapy for advanced disease (Cohort A) [7]. At the ASCO Congress, Planchard et al. presented their primary analysis of Cohort B of this trial; these patients were treated with the combination of dabrafenib 150 mg BID and trametinib 2 mg OD after at least one platinum-based chemotherapy and not more than three previous lines of treatment [8]. The primary objective was investigator-assessed ORR.

Fifty-seven patients were evaluable for response, all of whom had non-squamous histology. In this group, ORR was 63 %, with a disease control rate of 79 %. Responses lasted for a median interval of 9.0 months, and half of the confirmed responses were ongoing at the time of analysis. For median PFS, the analysis yielded 9.7 months. As compared to dabrafenib monotherapy (Cohort A of the BRF113928 study), dabrafenib plus trametinib showed greater clinical activity **(Table 2)**.

The AE profile was manageable and similar to previous observations obtained with the treatment of melanoma patients. AEs included pyrexia, nausea, vomiting, diarrhoea, asthenia, decreased appetite, chills, peripheral oedema, and dry skin. Overall, the combination of dabrafenib and trametinib was found to provide an important treatment option for patients with *BRAF* V600E-mutant NSCLC. ■

Interview: Gustavo Werutsky, MD, Latin American Cooperative Oncology Group, Hospital São Lucas PUCRS University, Porto Alegre, Brazil

Lung cancer care in Latin America: evolution of modern therapies and challenges to overcome the existing gaps

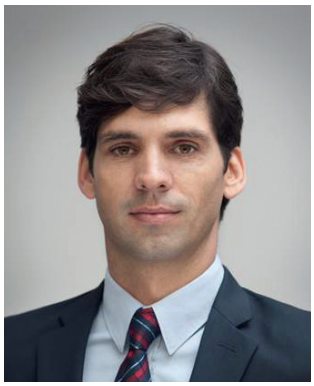
What are the specific challenges that Latin American physicians and governments are facing regarding the management of lung cancer patients?
It is important to understand that Latin America is a large continent with approximately 600 million inhabitants. The four most-populated cities are Mexico City, Rio de Janeiro, São Paulo, and Buenos Aires, where the number of people living in just these four cities is equal to the total number of inhabitants of France.

Today, approximately 85,000 new cases of lung cancer are reported in Latin America per year. Smoking is increasing in Latin America in general, and especially in women, which is why we expect rising lung cancer incidence rates in the years ahead. Overall, even in the poorer countries, people in Latin America are not dying of infectious diseases any more, but rather of non-communicable disorders, such as lung cancer. It is estimated that 70 % of new cancer cases will occur in developing countries over the coming decades. Therefore, dealing with the increasing incidence of cancers in this region will be an enormous challenge for the governments in the near future, especially for lung cancer, which is the main cause of cancer deaths in Latin America. To date, Latin America is investing 10 to 20 times less money than developed countries in the fight against cancer.

About 70 % to 90 % of patients with lung cancer have advanced or metastatic disease at the time of diagnosis. In the United States, stage I lung cancer is diagnosed in approximately 15 % of cases, whereas in Brazil, this proportion is only 8 % to 9 %. This means that many patients require treatment for advanced disease, which is more costly because these patients need more assistance, drugs and hospitalisation, and the death toll is higher. This is very difficult for the economies of the Latin American countries.

Is smoking cessation being promoted?
Brazil has been conducting smoking cessation campaigns and it has been successful here. Over the last 20 years, the rate of smokers has decreased from approximately 40 % to 15 %. However, the efforts made in this area are very heterogeneous within Latin America. In some other countries, smoking continues to increase.

How is the diagnostic situation?
With respect to imaging, CT scans and PET CT scans are not widely available in Latin America. These devices are mainly to be found in big cities, and they are not equally distributed, as there are not sufficient numbers in public hospitals. Many patients living in rural areas do not have access to these tests, and this delays their diagnosis by a considerable degree. At the time of diagnosis, half of the patients with lung cancer have an ECOG Performance Status of 2 or higher. This affects their treatment, because many of them will not receive systemic therapy. Therefore, it is very important to raise public awareness about lung cancer and the symptoms of this disease, as well as other aspects, so that pa-



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tients are encouraged to seek assistance early on. At the same time, the health authorities need to streamline and facilitate the process and the access for rapid diagnosis.

For targeted therapies, it is important to understand that their use depends on molecular diagnosis. Having access to these tests is a real challenge in Latin America. In many countries, medical care is provided either by the public health system, which is free of charge, or by the so-called private sector, where patients pay for health insurance. There is a large discrepancy between the services provided by these two systems. In Brazil, for example, the *EGFR* mutation testing rate in the public system ranges from 20 % to 30 %, while it is 60 % in the private sector. These numbers can basically be extrapolated to other countries. Obviously, the demand for molecular tests will depend on access to the targeted drugs. Again, there are only a few laboratories that perform these tests, as the equipment is expensive. *ALK* testing is not commonly requested by physicians, because ALK-targeted drugs are not approved in our countries, or have only recently been approved. *ROS-1* testing is almost non-existent. Currently, tests are basically offered free of charge through voucher programmes by pharmaceutical companies.

Are there shortages concerning treatment?

The discrepancy due to the different health systems holds true for the treatment. For example, EGFR inhibitors have already been approved in the Latin American countries, but some are not available for a large proportion of patients. In an important country like Brazil, which is the sixth or seventh largest pharmaceutical market in the world, these agents were approved some years ago, but only patients in the private sector have access to them. In Brazil, for example, ALK inhibitors and immunotherapy agents will be approved this year, but again not for the patients in the public system. This means that while the technology improves at a very fast rate in Latin America, a discrepancy in access to these new agents is created at the same pace. There are huge gaps between the countries, as well as within the cities. The Latin American governments will have to face this problem rapidly and draw up strategies for lung cancer care in general, such as conducting screening programmes, optimising the diagnosis and treatment of early/ locally advanced disease stage, and facilitating access to molecular testing and treatment for metastatic disease. Enabling patients to receive the best therapies for fighting lung cancer will be the main challenge over the next 10 years. ■

Exploring established and novel EGFR-directed agents

PROs & dose modifications in LUX-Lung 7

The phase IIb LUX-Lung 7 trial was a head-to-head comparison of the second-generation ErbB family blocker afatinib and the first-generation reversible EGFR TKI gefitinib in patients with treatment-naïve, *EGFR*-mutation-positive, advanced (stage IIIB/IV) adenocarcinoma of the lung. According to the primary analysis, patients treated with afatinib derived significant PFS, ORR and time-to-treatment-failure benefits compared to those who received gefitinib [1]. The OS data are currently immature.

Patient-reported outcomes (PROs) as well as *post-hoc* analyses of the impact of afatinib dose adjustments on PFS, management of AEs, and PROs were presented at the ASCO Congress by Hirsh et al. [2]. Afatinib dose escalation or reduction was permitted according to a pre-specified dose adjustment scheme. The incidence and severity of common AEs before and after dose reductions from 40 mg were assessed. Also, the investigators compared PROs and PFS between patients who had dose reductions within 6 months and those who received at least 40 mg for the first 6 months.

Preserved efficacy with dose reductions

Dose reductions occurred more often with afatinib than with gefitinib. Gefitinib is available in only one dose strength, as opposed to afatinib (20 mg, 30 mg, 40 mg, 50 mg). Thirty-nine percent of patients treated with afatinib 40 mg had dose reductions to 30 mg; 13 % had further dose reductions to 20 mg. However, the rates of drug-related discontinuations due to AEs were similar across arms, which suggested that dose reductions effectively managed AEs. Indeed, dose adjustments led to decreases in the incidence and severity of drug-related AEs **(Figure)**.

With regard to PROs, according to the EQ-5D™ health status self-assessment questionnaire, similar improvements were observed in both study groups. There were no significant or clinically meaningful differences between the afatinib and gefitinib treatment arms with respect to mean EQ-5D

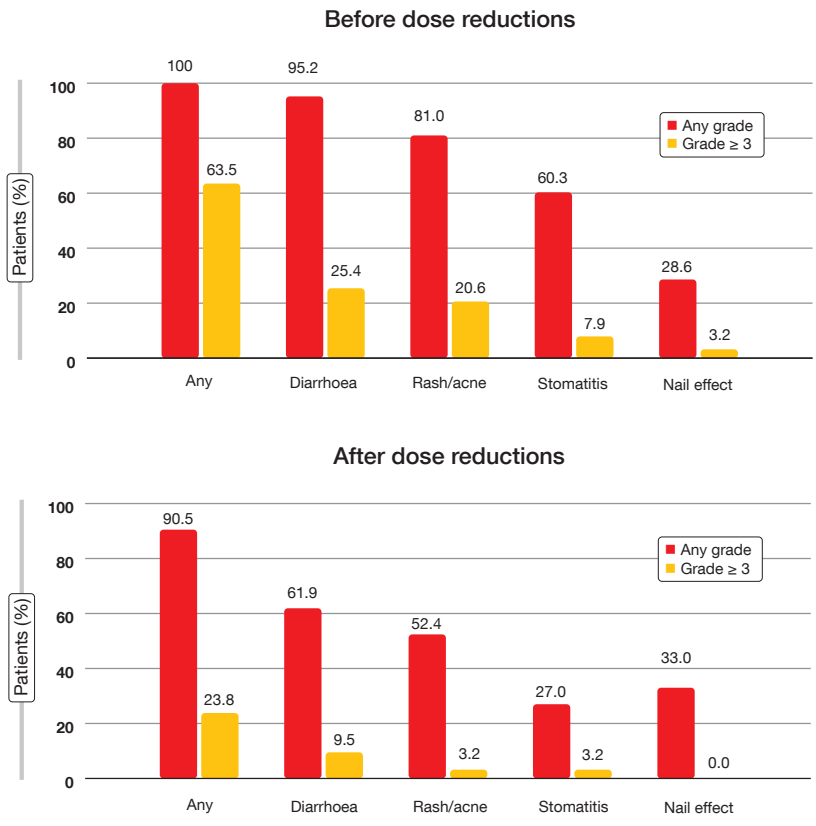

Figure: Reduction in incidence and severity of treatment-related AEs through dose modifications of afatinib

or EQ-VAS scores. Reductions in the afatinib doses did not diminish the treatment effects on PROs. Also, PFS did not differ between patients receiving doses of < 40 mg or ≥ 40 mg during the first 6 months of treatment. Median PFS was 12.8 and 11.0 months in patients with and without dose reductions, respectively. In comparison, median PFS for the gefitinib arm was 10.9 months, according to the primary analysis [1].

Overall, the afitinib dose adjustments enabled patients to remain on treatment. As observed in the LUX-Lung 3 and LUX-Lung 6 trials [3], tolerability-guided reductions in afatinib doses constituted an effective measure to reduce treatment-related AEs without affecting therapeutic efficacy.

VeriStrat analysis of the LUX-Lung 8 trial

Afatinib was compared with erlotinib in the open-label, phase III LUX-Lung 8 trial that enrolled 795 patients with advanced squamous-cell carcinoma of the lung, who had progressed after at least four cycles of platinum-based chemotherapy. Patients treated with afatinib showed significant benefits for OS, PFS and disease control [4]. Goss et al. presented data obtained with VeriStrat [5], a serum-protein mass spectrometry test that has demonstrated prognostic and predictive utility for EGFR-targeted therapies in NSCLC [6]. The investigators assessed the predictive ability of VeriStrat in LUX-Lung 8, using OS as the primary efficacy variable. To that end, serum pre-treatment samples from 675 patients were classified as 'good' (VS-G) or 'poor' (VS-P) based on pre-defined reference groups. Clinical outcomes were analysed with respect to the VeriStrat status in the overall population and in pre-defined subgroups.

In the VS-G group (n = 412), median OS was 11.5 and 8.9 months for afatinib and erlotinib, respectively (HR, 0.79; p = 0.03); median PFS was 3.3 and 2.0 months, respectively (HR, 0.73; p = 0.005). For patients classified as VS-P (n = 263), median OS was 4.7 and 4.8 months, respectively (HR, 0.90; not significant), and median PFS was 1.9 months for both afatinib and erlotinib (HR, 0.96; not significant). In patients treated with afatinib, both OS and PFS were longer in the VS-G group than in the VS-P group (OS: HR, 0.40; p < 0.0001; PFS: HR, 0.56; p < 0.0001). According to multivariate analysis, VeriStrat is an independent predictor of OS and PFS in afatinib-treated patients regardless of ECOG performance status, best response to first-line therapy, age, and ethnicity. However, no interactions were demonstrated between VeriStrat classification and treatment group for OS or PFS.

Overall, VeriStrat conferred a strong independent stratification effect in patients with relapsed/ refractory squamous-cell carcinoma of the lung treated with afatinib in the LUX-Lung 8 trial. In these difficult-to-treat patients, afatinib therapy gave rise to significantly superior OS and PFS, as compared to erlotinib in the VS-G group.

Updated data on rociletinib: TIGER-X

TKIs that inhibit mutant forms of the *EGFR* gene have two important limitations: the inhibition of wild-type *EGFR* leads to cutaneous toxicity and diarrhoea, and the efficacy of treatment is limited by the emergence of the *EGFR* T790M acquired resistance mutation in approximately 60 % of patients. Rociletinib was therefore designed as an oral, irreversible inhibitor of the activating mutation exon 19 and the L858R point mutation in exon 21, as well as of the acquired resistance mutation T790M. It has only minimal activity against wild-type *EGFR*.

Goldman et al. reported updated results from the phase I/II TIGER-X study that investigated rociletinib in patients with advanced or recurrent, centrally confirmed T790M-positive NSCLC [7]. After the dose-expansion phase I part of the trial, patients who had progressed on one or two EGFR TKIs entered the expansion cohort (phase II). Rociletinib was tested at three doses (500 mg BID, 625 mg BID, 750 mg BID) in 548 patients. N-acetyl transferase 2 (NAT2) genotype polymorphism was assessed for a subgroup in all three dosing cohorts.

According to the investigators, rociletinib therapy led to a confirmed ORR of 33.9 %. This is lower than the response rates reported previously [8, 9].

In the three dosing groups, responses proved durable, at a median of 8.9, 9.0, and 7.1 months, respectively. PFS was 5.7, 5.0, and 4.3 months, respectively.

The most common AEs of any grade across all doses included hyperglycaemia, diarrhoea, nausea, fatigue, and decreased appetite. Hyperglycaemia, QTc prolongation, and fatigue counted among the most frequently reported grade-3/4 AEs. Cataracts were found to be common in patients receiving rociletinib for prolonged periods of time, which is why visual symptoms should be investigated promptly. Based on the NAT2 genotype results, patients were classified as having a slow (n = 196), intermediate (n = 148), or rapid (n = 38) acetylator phenotype. Slow acetylators showed a tendency to develop hyperglycaemia, QTc prolongation, or other cardiac disorders. The clinical development of rocilitinib has recently been stopped by Clovis Inc.

Innovative 3rd-generation *EGFR*-mutant-specific TKI: olmutinib

Olmutinib is an oral, third-generation TKI with *EGFR*-mutant-specific activity against deletion 19, L858R, and T790M. It does not inhibit wild-type *EGFR*. The safety, tolerability, pharmacokinetics and preliminary activity of olmutinib were evaluated in an open-label, multicentre phase I/II trial in Korean patients with EGFR-TKI-pretreated NSCLC. Seventy-six patients with T790M mutation received olmutinib 800 mg OD in the phase II part of the study. These patients had experienced progression on at least one prior EGFR TKI.

TABLE
Response rates obtained with olmutinib in patients with the T790M mutation

	Response, n (%)
Objective response (confirmed and unconfirmed)	43 (61)
Disease control	63 (90)
Confirmed objective response	38 (54)
Disease stabilisation/ unconfirmed partial response	20 (29) / 5 (7)
Progressive disease	3 (4)
Not evaluable	4 (6)

Sixty-one percent of patients achieved tumour shrinkage that qualified for objective response **(Table)**. In 84 %, onset of tumour response occurred by week 6. Disease control was seen for 90 %. The median duration of response was 8.3 months. Patients with one prior systemic treatment obtained a median PFS of 8.8 months, while in those with two or more prior regimens, PFS was 6.8 months. With regard to tolerability, patients most commonly reported diarrhoea, pruritus, rash, and nausea, which were mainly of mild-to-moderate in intensity. Four patients discontinued treatment due to AEs (upper abdominal pain and vomiting, interstitial lung disease, peripheral neuropathy, skin exfoliation). QT prolongation and hyperglycaemia were not observed.

The authors concluded that olmutinib showed meaningful clinical activity with a favourable safety profile at the recommended phase II dose of 800 mg OD. An ongoing global phase II trial, ELUXA 1, is further assessing the efficacy and safety of olmutinib in patients with T790M-positive NSCLC. ■

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Interview: Nir Peled MD, PhD, FCCP, Head of the Thoracic Cancer Unit, Davidoff Cancer Center, Petah Tikva, Israel

"The importance of first-line and second-line targeted agents is obvious"

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Which parameters should be taken into consideration regarding the choice of EGFR TKIs in a lung cancer patient with an activating *EGFR* mutation?

When *EGFR* mutations are diagnosed in the first-line setting, we have the luxury of having three options today. However, it is important to discriminate between the different types. *EGFR* mutations normally occur on exons 18 to 21. Most of the activating mutations will respond to all EGFR TKIs; however, the uncommon locations, for example exon 18, tend to respond more strongly to afatinib than to the other first-line TKIs, gefitinib and erlotinib. Aberrations on exon 20 are normally associated with a lack of response to the current drugs. Providing therapeutic options for patients with exon 20 mutations is a true unmet need, because they do not respond well to the new immunotherapies either, which means that they can only receive chemotherapy. These patients make up 4 % to 9 % of the *EGFR*-positive population, which accounts for approximately 17 % of lung cancer cases, thus constituting a considerable proportion of patients.

As the EGFR TKIs showed comparable PFS results in the big studies, toxicity is a selection criterion. Gefitinib, erlotinib and afatinib have similar toxicity profiles, but according to our daily experience, diarrhoea tends to occur more often with afatinib, as well as nail abnormalities, which can become a significant burden for many patients. We can control both diarrhoea and skin eruptions, but nail issues and paronychia are less well controlled; indeed, often they force us to decrease the afatinib doses. Patients can switch to another EGFR TKI if they are in need of increased tolerability. However, the LUX-Lung 7 trial, which was a direct comparison of afatinib and gefitinib, revealed a 27 % reduction in the risk of progression or death with afatinib over gefitinib [1]. Another aspect is that a combined study analysis showed that patients with exon 19 abnormalities derive an OS benefit from afatinib treatment over chemotherapy [2], whereas the trials conducted with the other EGFR TKIs were not able to show OS improvement compared to chemotherapy in the first-line setting. This might also be a consideration.

In our daily practice, we take into account the type of mutation and the physical appearance of the patient. If the patient is an old lady with a body weight of 50 kg, afatinib would not be my first choice, but a young or middle-aged person with exon 19 mutation or other mutations can benefit from this treatment. Some of our patients also have *HER2* aberrations, such as amplifications or mutations, on top of *EGFR*-activating mutations. These patients might experience an advantage due to the dual HER2 and EGFR blockade conferred by afatinib. Also, afatinib covers uncommon mutations, especially those in exon 18. Another consideration are brain metastases. Afatinib shows a favourable response rate of approximately 30 % with regard to brain lesions. I would consider afatinib for patients with brain metastases, rather than other EGFR TKIs. The other TKIs elicit brain responses too, but not as well as afatinib.

What about the second-line setting?

The most common resistance mutation is the T790M mutation, which occurs in approximately 60 % to 66 % of EGFR-TKI-treated patients. To date, only osimertinib has been approved for this patient population. This drug is very well tolerated, with less adverse events in comparison to previous drugs. The response rate was 66 % in T790M-positive patients [3], and brain responses have also been reported in a small series [4]. The PFS is approximately 10 months, so the results of the first-line therapy are duplicated. Studies on other drugs are ongoing. Interestingly, I have observed that a few cycles of chemotherapy can sometimes restore the sensitivity of patients who have progressed on anti-EGFR therapy, towards their previous EGFR TKI treatment. Obviously, the resistant clones are eradicated by chemotherapy, and re-challenge is then rendered possible. This is not an approved approach, of course. Recommendations on the optimisation of the management of *EGFR*-mutation-positive NSCLC have recently been released by the International Association for the Study of Lung Cancer [5].

What are the current recommendations with respect to the management of brain metastasis?

Brain metastasis is a big issue. Many of our lung cancer patients develop brain lesions, especially the ones with *EGFR* and *ALK* abnormalities, and many of them die due to leptomeningeal spread and brain involvement. Currently we are trying to avoid whole-brain radiation because of the long-term adverse effects of this treatment. If up to 10 or 12 isolated lesions are present, we perform stereotactic radiosurgery. Until 2 years ago, the upper limit used to be only three lesions. If imaging reveals more lesions and if they are asymptomatic, we might start EGFR or ALK TKI therapy and monitor the patient. If the metastases are symptomatic, we perform radiation of the single lesion that causes the symptoms. Whole-brain radiation therapy is only considered if the patient does not respond to TKI therapy and progression occurs.

If we observe responses of the extracranial lesions, and at the same time, cerebral progression, this means that the

drug does not penetrate the blood-brain barrier well enough. In this situation, the administration of bevacizumab is an option, as well as radiation of the brain. An interesting phase II study yielded a median PFS of 16 months with first-line bevacizumab plus erlotinib in patients with advanced *EGFR*-mutation-positive NSCLC [6]. Another phase II first-line trial showed a median PFS of 14.4 months with the combination of bevacizumab and gefitinib [7]. These results exceed those obtained with any of the EGFR TKIs as a single agent. For the time being, this approach is based on phase II data only, but I hope it is going to be approved by the FDA soon. It is a very interesting option for many patients.

How is the role of re-biopsy currently defined?

Re-biopsy is a relevant topic, because the patients dislike being punctured; the procedure is painful and invasive. Many times, disease progresses in a heterogeneous way, which is why single-site biopsies do not reflect progression well enough. Liquid biopsy, on the other hand, offers advantages in the detection of resistant mutations. The sensitivity of the technology is not 100 % yet, but we are improving on it every day. If no tissue is available, liquid biopsy is a very good choice, also in the up-front setting, especially in the case of positive *EGFR* mutation testing. Liquid biopsy works well for the main mutations; it is less accurate for amplification and translocation. Personally, I have had very good experience with liquid biopsy. At our clinic in Israel, we use it as a routine assessment for patients who have progressed after first-line EGFR TKI therapy. I would even say that it should not be restricted to the second line, but that it can also be used in the first line. Normally, we only do re-biopsy if two negative liquid biopsy results have been obtained. Biopsy would be performed according to the PET scan results, to isolate the most resistant site.

What notable advances have recently been made in the field of molecular diagnostics?

It is the lung cancer patients who benefit most from the considerable advances in the field of molecular profiling. Due to increased sensitivity and knowledge accumulated over the years, TKIs can nowadays be offered to almost 30 % of these patients. Next generation sequencing increases the number of patients who are diagnosed with *EGFR*-positive mutations. Polymerase chain reaction misses many of the positive cases. In addition to abnormalities of *EGFR*, *ALK* and *ROS-1*, *cMET* amplifications and mutations (as exon 14 skipping) can be diagnosed, which are as common as *ALK* rearrangement, at approximately 4 % to 5 % of the adenocarcinoma population. It is possible to detect *RET* translocation and *HER2*-positivity. *BRAF* mutation is common not only in melanoma, but also in lung cancer. For *ALK* testing, we used to perform a FISH-based analysis, but now we are shifting towards immunostaining, which is much more sensitive, for many reasons. Next-generation sequencing allows us to diagnose more patients with a target-to-treat approach, and therefore we can serve the community in a better way. The importance of treatment with first-line and second-line targeted agents is obvious, as it has already been shown in many studies that not only quality of life is improved, but also response rates and overall survival. We do our best to profile the tumour properly before deciding upon chemotherapy.

A technology I expect to be implemented in many countries in the next 1 or 2 years is droplet digital PCR. This works via automated systems, requires a much smaller amount of tissue than the other methods, and is highly sensitive, highly specific, and has low cost. For the time being, liquid biopsy is only used at the time of progression. In the future, we might perform repeated liquid biopsies during monitoring and change therapy as soon as different clones occur, but this approach is still subject to research. ■

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Mutational analysis: on the road to refined standards

LCMC II

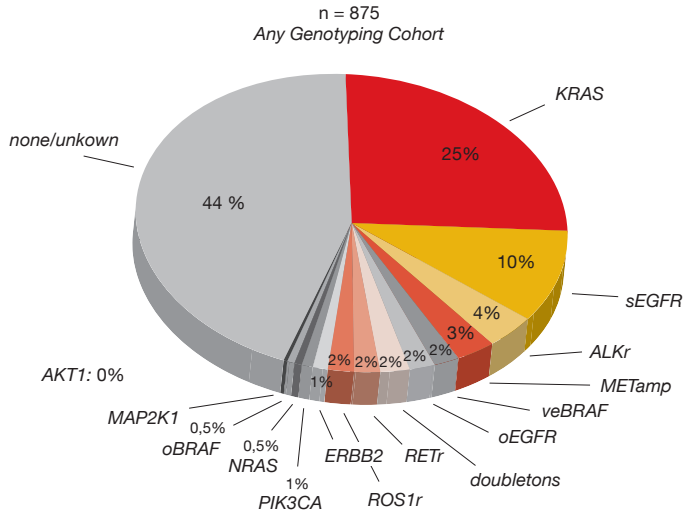
The Lung Cancer Mutation Consortium (LCMC) is a multi-institutional consortium for the study of driver mutations of lung adenocarcinoma. The cooperating sites enable the identification of relatively large numbers of patients with uncommon and rare alterations, facilitate the analysis of their clinical characteristics, and lay the ground for targeted therapy trials.

LCMC II, which is the second round for LCMC, started in 2012 [1]. The first round, LCMC I, was initiated in 2009 and demonstrated that genomic profiling can work as a multi-institutional effort for patient benefit. Sixteen sites participated in LCMC II, and 14 selected gene alterations were analysed. By the end of the project, all of the sites had accomplished the transition to next-generation sequencing for mutation identification, which was one of the goals of LCMC II.

The genes studied in LCMC II included point mutations in *AKT1*, *BRAF*, *EGFR*, *HER2*, *KRAS*, *MAP2K1* (*MEK*), *PIK3CA* and *NRAS*, as well as rearrangements in *ALK*, *RET* and *ROS1*, and other alterations, including *METamp*, PTEN-exp and METexp. Patients with stage-IV adenocarcinoma of the lung participated in the project. The results of the gene analyses were reported to the LCMC Virtual Database, as well as to the treating physicians, who could use them to select therapies, either as standard-of-care, or to recommend clinical, agent-specific trials, or off-label therapies. Subsequently, the patient outcomes obtained were reported back to the LCMC Database. Genotyping was performed in 875 patients; 242 of these showed targetable driver alterations. Finally, 131 patients went on to targeted therapy.

Improved survival due to expanded genomic analysis

The **Figure** shows the distribution of the mutations as defined in LCMC II. PTEN loss and MET expression are not included; for these, 15 % and 59 % of cases were positive, respectively. As previously described, overlapping alterations occurred infrequently (4.1 % of total cases).



sEGFR = sensitizing, oEGFR = other, veBRAF = V600E, oBRAF = other, r = rearrangement

Figure: Mutation frequencies observed in LCMC II in 875 patients with adenocarcinoma of the lung

Many of the known associations with patient outcomes, such as benefits due to EGFR TKI therapy in the *EGFR*-mutated population, were observed in LCMC II. Also, smoking status and specific gene alterations correlated with each other, as expected. When all driver mutations were considered, targeted therapy gave rise to survival improvement. On the whole, concomitant mutations in *TP53* and/or *PTEN* and/or *PIK3CA* did not influence the effects of targeted therapy. Some modulators were identified, however. In the group of *EGFR*-positive patients treated with TKI therapy, the presence of *TP53* had modulatory effects on the benefit of the targeted therapy. Survival probability was higher if the mutation was absent. *KRAS* mutations were demonstrated to confer worse prognosis in never-smokers.

The authors concluded that expanded molecular testing and associated targeted therapy provides survival benefit, but the assay systems represent an important aspect. Mutation rates obtained with different testing systems can vary widely. For example, *TP53* mutation status is most likely under-observed, which limits the ability to detect the affected patients and to develop treatment options. As testing and therapies co-evolve, additional improvements can be expected.

Circulating tumour cells mirror reality

Next-generation sequencing (NGS) of circulating tumour DNA (ctDNA) enables non-invasive profiling of solid tumours. To date, liquid biopsy studies have been limited to modest-sized cohorts and case studies. A large-scale genomic analysis has now established that patterns of genetic changes detected via liquid biopsies can closely mirror changes identified via traditional tumour biopsies [2]. Blood samples were obtained from more than 15,000 patients with advanced-stage cancer of 50 different types. Thirty-seven percent of patients had lung cancer. Somatic genomic profiling was performed using a highly accurate, deep-coverage ctDNA

NGS test targeting 70 genes. This is one of the largest cancer genomics studies ever conducted.

With the exception of resistance mutations such as *EGFR* T790M, the cancer-type-specific frequencies and mutual exclusivity patterns among major driver alterations (as assessed by ctDNA) largely resembled the tissue alteration patterns. When ctDNA was positive for key abnormalities in *EGFR*, *BRAF*, *KRAS*, *ALK*, *RET* and *ROS1*, the same mutations were reported in tissue in 94 % to 100 %. Most ctDNA alterations were detected at very low levels. Half of these occurred at a frequency below 0.4 % of the total DNA in circulation. Even at those low levels, the accuracy of the liquid biopsy remained high. Overall, ctDNA testing revealed a potential targeted treatment option for almost two thirds of the patients tested.

In the NSCLC subset, 51 cases of driver aberrations were detected using ctDNA NGS, in addition to those detected by tissue genotyping. The actionable biomarker yield was thus increased by 42 %. Overall, this analysis illustrated the ability of plasma mutation detection to enhance or complement tissue analysis.

ctDNA as a prognostic marker

Lin et al. hypothesised that tumour-specific alterations in ctDNA quantify tumour heterogeneity and can serve as a non-invasive means to determine prognosis and recurrence in patients with unresectable stage III NSCLC who are treated with curative-intent chemoradiotherapy [3]. Tumour heterogeneity is correlated with therapeutic resistance and poor prognosis. The investigators assessed ctDNA in 156 patients with unresectable NSCLC who were receiving definitive radiotherapy (XRT) or chemo-XRT. Blood was taken before, during, and after therapy. An NGS assay was used to detect single nucleotide variants in 70 genes, amplifications in 16 genes, as well as select fusions and indels.

According to the interim analysis, four main patterns of ctDNA changes were found across serial time-points: specific alterations persistent throughout XRT (n = 9), no alterations in the post-XRT sample (n = 14), increased levels from baseline (n = 10), and alterations that fluctuated throughout therapy (n = 11). No significant associations were observed between PFS/ OS and these patterns of ctDNA changes. This also applied to PFS/ OS and percent changes in ctDNA levels pre-XRT to post-XRT. These results are limited by sample size, however.

Nevertheless, the presence of specific mutations appeared to correlate with outcome. The reappearance of the driver mutations post-therapy was associated with shorter PFS. *APC*/*ARID1A* mutations present in the post-XRT blood sample correlated with shorter PFS after adjustment for tumour histology and stage. Likewise, *NF1* mutations identified in post-XRT samples were associated with shorter OS after adjustment of tumour histology and stage. The final analysis of the larger cohort might be required to achieve significance for additional prognostic patterns. ■

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New approaches are raising hope for SCLC patients

Only minor progress has been made over the past 30 to 40 years in the treatment of small-cell lung cancer (SCLC), which accounts for 10 % to 15 % of lung cancer cases. SCLC is radiosensitive, but approximately 70 % of patients present with extended disease that cannot be included within one radiotherapy field. The majority of patients respond to first-line chemotherapy. However, these responses are almost always transient, and outcomes with second-line treatments are generally poor. In extensive disease, median survival from the time of diagnosis does not usually exceed 10 months.

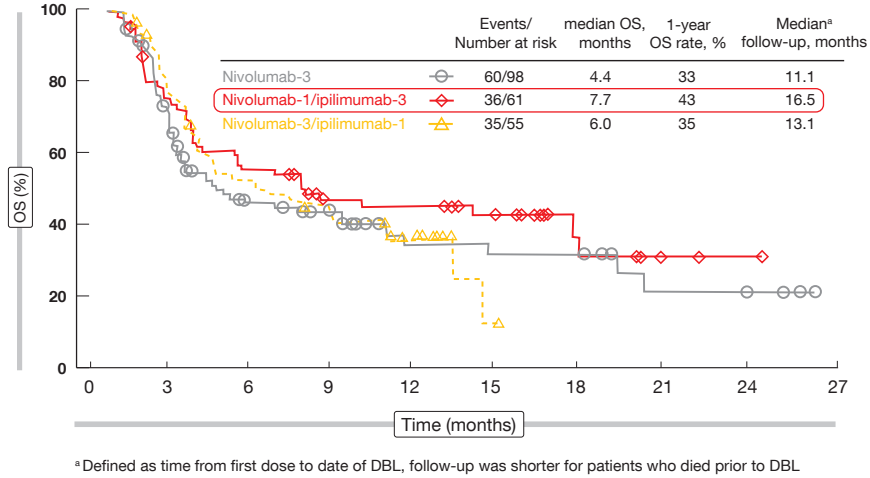
The current treatment paradigm for extensive-stage SCLC is combination chemotherapy in the first line (platinum–etoposide), followed by chemotherapy with topotecan, irinotecan, paclitaxel, docetaxel, and a variety of other drug choices for the recurrent/ progressive setting. All of these drugs elicit meagre responses. To date, topotecan is the only FDA-approved drug for recurrent disease. Alternatively, patients are enrolled into clinical trials, or receive only supportive care. No biomarker-driven therapies have been defined for this patient population yet.

There is an unmet need for the development of new active therapeutic options, particularly in relapsed disease. Meanwhile, however, improved understanding of SCLC biology has led to the identification of druggable targets; for the first time in decades, appropriate agents might start to change the course of the disease.

CheckMate 032

From the point of view of immunotherapy, SCLC is a 'cold' tumour, because the number of tumour-infiltrating T cells is low. This basically limits the efficacy of PD-1 antibodies, such as nivolumab, but it can be overcome by use of a combination strategy. The anti-CTLA-4 antibody ipilimumab increases the number of tumour-reactive T cells, thus enhancing the activity of nivolumab.

The 3-arm CheckMate 032 trial enrolled 216 patients with SCLC and progressive disease after at least one prior line of therapy, including a first-line platinum-based regimen [1]. Patients were not selected on the basis of PD-L1 expression. They were randomised to either nivolumab 3 mg/kg i. v. every 2 weeks as monotherapy (n = 98), nivolumab 1 mg/kg plus ipilimumab 3 mg/kg i.v. every 3 weeks for 4 cycles (n = 61), or nivolumab 3 mg/kg plus ipilimumab 1 mg/kg i.v. every 3 weeks for 4 cycles (n = 54). Thereafter, single-agent nivolumab 3 mg/kg every 2 weeks was administered as maintenance therapy.



[a] Defined as time from first dose to date of DBL, follow-up was shorter for patients who died prior to DBL

Figure 1: Superiority of nivolumab-1/ipilimumab-3 for overall survival in patients with recurrent SCLC, as compared to nivolumab-3/ipilimumab-1 and nivolumab monotherapy

Best results with nivolumab plus ipilimumab

Nivolumab plus ipilimumab demonstrated greater efficacy than nivolumab alone. The ORR was 10 % with single-agent nivolumab, and twice as high with nivolumab-1 plus ipilimumab-3 (23 %) and nivolumab-3 plus ipilimumab-1 (19 %). As for patients with NSCLC, the responses were rapid and durable and occurred even in patients with bulky disease. They depended neither on platinum sensitivity nor on PD-L1 expression. For OS, the nivolumab-1/ipilimumab-3 combination appeared to have the most potent effects, with a median OS of 7.7 months (vs. 6.0 months for nivolumab-3/ipilimumab-1, and 4.4 months for nivolumab alone; **Figure 1**). Although a longer follow-up period is required, the analysis already indicates that a certain percentage of patients appears to experience long-term survival, which is a known effect of immunotherapeutic agents.

The safety profiles here were similar to those seen with nivolumab and ipilimumab in other diseases. Higher rates of AEs occurred with combination therapy; there were also three treatment-related deaths (pneumonitis, myasthenia gravis, worsening of renal failure). Immune-related AEs were managed using established safety guidelines. However, only 10 % of patients discontinued treatment because of toxicity.

Nivolumab 1mg/kg plus ipilimumab 3 mg/kg was selected for the phase III investigations. Three studies are expected to confirm and extend these data. Apart from the CheckMate 032 expansion study, which is currently ongoing, CheckMate 331 will be comparing nivolumab and chemotherapy in patients with relapsed SCLC, and CheckMate 451 will test nivolumab alone *versus* nivolumab plus ipilimumab *versus* placebo as consolidation/ maintenance therapy after platinum-based first-line treatment in patients with extensive disease.

Rova-T: the first biomarker-directed strategy in SCLC

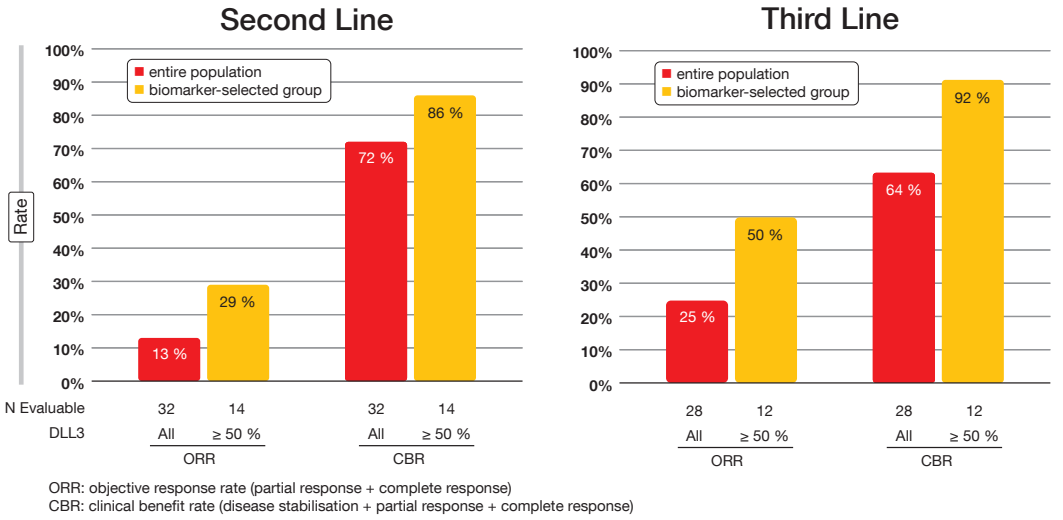
Delta-like protein 3 (DLL3) has been established as a novel target in neuroendocrine tumours. It is an atypical inhibitory Notch ligand, which is induced by the key neuroendocrine transcription factor, ASCL1. In SCLC, DLL3 is highly up-regulated and overexpressed; there is cell surface expression on both cancer stem cells and tumour cells (but not in normal adult tissue), which makes it amenable to an antibody–drug conjugate (ADC) approach. DLL3 is not a prognostic marker and does not predict response to cytotoxic chemotherapy.

Rovalpituzumab tesirine (Rova-T™, SC16LD6.5) was designed as a DLL3-targeted ADC. Within this molecule, an anti-DLL3 monoclonal antibody is linked to the pyrrolobenzodiazepine (PBD) dimer toxin, which causes DNA strand breaks and is highly cytotoxic in a cell-cycle-independent manner. Due to selective binding of the antibody, the toxin is released within the cancer cells only.

The first-in-human, phase I, dose-escalation SCRX16-001 trial included 74 patients with SCLC [2]. Two expansion cohorts received 0.2 mg/kg every 3 weeks or 0.3 mg/kg every 6 weeks. Finally, the trial defined 0.3 mg/kg twice every 6 weeks as the recommended phase II dose. DLL3 expression was assessed using immunohistochemistry and was graded as low (≥ 1 % of tumour cells, 88 % of patients) or high (≥ 50 % of tumour cells, 67 % of patients).

Benefit irrespective of the number of prior lines

The SCRX16-001 trial showed substantial clinical activity of Rova-T, with DLL3 expression being predictive of response. RECIST-confirmed response rates per investigator were 18 % in the entire population and 39 % in the biomarker-selected group; the latter comprised patients with DLL3 expression of ≥ 50 %. Clinical benefit rates were 68 % and 89 %, respectively. In a subset of patients, a central review was performed that confirmed the per-investigator responses. The analysis revealed substantial benefit irrespective of the number of prior lines, with response rates comparable in the second-line and third-line settings (**Figure 2**). According to the waterfall plot, all of the responses occurred in the group with high DLL3 expression. The population with high DLL3 expression showed a median OS of 5.8 months and a 1-year survival rate of 32 %. Overall, the safety profile proved manageable. Among the grade 3 or higher AEs, thrombocytopenia occurred in 12 % of patients, serosal effusions in 11 %, and skin reactions in 8 %.



ORR: objective response rate (partial response + complete response)
CBR: clinical benefit rate (disease stabilisation + partial response + complete response)

Figure 2: Comparable confirmed responses with Rova-T in the second-line and third-line setting of recurrent/ refractory SCLC

Historical comparisons illustrate that second-line and third-line results gained with Rova-T are superior to standard-of-care therapy. However, the numbers of patients involved in the SCRX16-001 trial are small; for the time being, these data are only hypothesis generating, but they are promising, and they justify further clinical development. The phase II, single-arm TRINITY trial is currently enrolling in the third-line setting, and this will be the confirmatory trial for SCRX16-001. Additional studies, such as a first-line basket trial investigating the activity of Rova-T in other tumour types that express DLL3, are in the planning phases.

PARP inhibition in addition to chemotherapy

A multi-centre, randomised, double-blind, phase II study tested the oral PARP-1/2 inhibitor veliparib at a dose of 40 mg twice daily for 7 days in addition to temozolomide, in patients with relapsed sensitive and refractory SCLC after failure of one or two prior regimens [3]. Sensitive disease was defined as relapse 60 days after completion of first-line platinum-based chemotherapy, whereas refractory patients had shown no response to initial platinum-based therapy or had experienced progression within 60 days after completing treatment; furthermore, this definition included any patient in need of third-line therapy. Fifty-five patients received veliparib in addition to temozolomide, and 40 patients were treated with placebo plus temozolomide. Veliparib was chosen because SCLC has been characterised by aberrant expression of genes and proteins implicated in DNA damage repair. Therefore, DNA repair pathways represent an attractive target in SCLC.

PFS and OS did not differ significantly between the veliparib and placebo arms, but there was a significant difference regarding the ORR (39 % vs. 14 %; p = 0.016). Expression of proteins involved in DNA repair, such as PARP-1, SLFN11 and MGMT, was assessed and correlated with outcome. Here, a trend towards better OS was observed with high SLFN11 expression in the veliparib arm. The analysis for additional biomarkers is ongoing. Moreover, these findings indicate that increased numbers of circulating tumour cells at baseline and after cycle 1 are associated with poorer survival. The improved ORR observed in this study supports further trials of PARP1 inhibitors and temozolomide in SCLC.

Anti-angiogenesis with bevacizumab and pazopanib

As angiogenesis is abundant in SCLC and associated with poor prognosis, another promising approach consists of inhibition of VEGF using the anti-VEGF antibody bevacizumab. In a multi-centre, phase III study, the addition of bevacizumab to platinum and etoposide in the first-line treatment of extensive-stage SCLC gave rise to a significant improvement in PFS, compared to the control regimen, which consisted of cisplatin and etoposide only (1-year PFS rates, 18.4 % vs. 11.5 %; HR, 0.72) [4]. Approximately 100 patients were treated in each arm. For OS, which was defined as the primary outcome, the analysis demonstrated a non-significant advantage of the bevacizumab-based therapy (1-year OS rate, 36.7 % vs. 24.9 %; HR, 0.78). Response rates did not differ significantly between the two groups. Time-dependent analysis revealed a significant effect of the maintenance treatment on OS (HR, 0.60). The toxicity profile was acceptable. As the authors noted, further research in the area of anti-angiogenetic treatments of SCLC is warranted.

Anti-angiogenic effects are also elicited by the multikinase inhibitor pazopanib, which is directed against VEGFR, PDGFR, FGFR and c-KIT. The Hellenic Oncology Research Group conducted a non-randomised, open-label, phase II trial on single-agent pazopanib at a dose of 800 mg/day as second-line treatment in patients with both chemoresistant/ chemorefractory and chemosensitive SCLC [5]. Patients with sensitive relapse were included in Cohort A (n = 39), and those with resistant or refractory disease were included in Cohort B (n = 19). The primary objective was the progression-free rate (PFR) at week 8.

This trial met its primary endpoint for Cohort A; here, PFR was 59 %. Recruitment in Cohort B was terminated early due to lack of efficacy at the interim analysis (PFR, 26.3 %). In Cohort A, median PFS and median OS were 3.7

and 8.0 months, respectively. At 1 year, 26.5 % of these patients were alive. Pazopanib was well tolerated.

This was the first study to demonstrate substantial and clinically relevant efficacy of a tyrosine kinase anti-angiogenic inhibitor as a salvage treatment in patients with SCLC. The authors concluded that pazopanib should be evaluated further as monotherapy or in combination with other agents.

CONVERT: chemoradiotherapy in limited disease

Approximately one third of patients with SCLC present with limited-stage disease. In those with good performance status, the standard of care is concurrent chemoradiotherapy (CTRT). The best outcomes have been documented for twice-daily (BD) CTRT; however, only one fifth of the patients actually use BD treatment routinely, due to toxicity and logistic issues. There has been a lack of consensus on the standard radiotherapy regimens in limited-stage SCLC, which led to the development of the multinational, phase III CONVERT trial [6].

Here, patients were randomly assigned to receive either 45 Gy in 30 fractions BD for 3 weeks (n = 274), or 66 Gy in 33 fractions once daily (OD) for 6.5 weeks (n = 273). Chemotherapy consisted of 4 to 6 cycles of cisplatin and etoposide. Radiotherapy started on day 22 of cycle 1. OS was defined as the primary endpoint of the CONVERT trial.

TABLE
Once-daily vs. twice-daily chemoradiotherapy in limited disease: survival rates at 1, 2 and 3 years

Overall survival (n = 543)	Twice daily	Once daily	Log-rank
Median (months)	30 (24-34)	25 (21-31)	p = 0.15
1-year (%)	83 (78-87)	76 (71-81)	
2-year (%)	56 (50-61)	51 (45-57)	
3-year (%)	43 (37-49)	39 (33-45)	

Even though the radiotherapy treatment delivery was higher in the BD arm, OS was comparable across these two groups, with 2-year survival rates of 56 % and 51 % for the BD and OD arms, respectively (HR 1.17; p = 0.15; **Table**). OD radiotherapy did not result in worse toxicity than BD radiotherapy. Toxicities were comparable, except for significantly higher rates of grade 3/4 neutropenia with BD treatment. Grade 3/4 acute oesophagitis occurred in 19 % in both arms, and grade 3/4 acute radiation pneumonitis was generally rare (2.5 % and 2.2 % with BD and OD treatments, respectively). Overall, radiation-related toxicity arose less frequently than expected, which is probably due to the use of modern radiotherapy techniques. The results of CONVERT support the use of either regimen as the standard-of-care treatment of limited-stage SCLC patients with good performance status. ■

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ULTIMATE: chemotherapy plus bevacizumab beyond first line

As chemotherapy in the second-line or third-line settings of NSCLC shows limited efficacy, the phase III, randomised ULTIMATE trial tested the combination of chemotherapy and bevacizumab in patients with advanced NSCLC of non-squamous histology, who had progressed after one or two lines of treatment. Prior platinum-based and pemetrexed therapies were mandatory, and prior bevacizumab was allowed. While the control patients received docetaxel every three weeks (n = 55), those in the experimental arm were treated with paclitaxel weekly plus bevacizumab every four weeks (n = 109). Treatment continued until progression or toxicity.

Weekly paclitaxel plus bevacizumab showed highly significant superiority over docetaxel monotherapy for both ORR at week 8 (22.5 % vs. 5.5 %; p = 0.006) and median PFS (5.4 vs. 3.9 months; p = 0.006). With the addition of bevacizumab, the risk of progression or death was reduced by 38 %. The PFS curves separated early on (**Figure**). According to the subgroup analysis, only patients with prior exposure to bevacizumab and those with performance status score of 2 did not benefit from the combined treatment. OS was similar across the two groups.

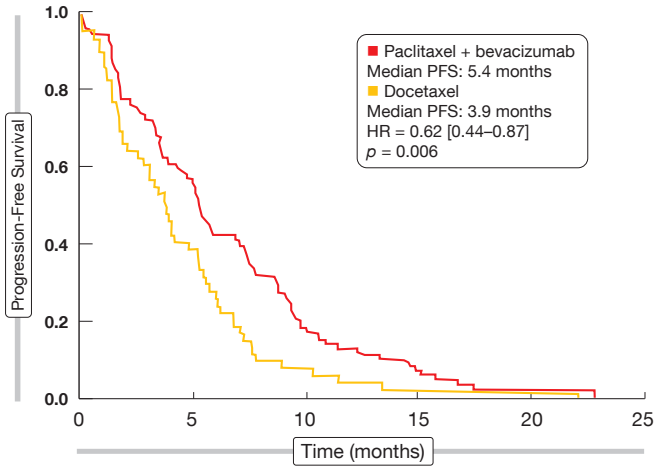

Figure: Progression-free survival with paclitaxel plus bevacizumab *versus* docetaxel

At the same time, the bevacizumab-based regimen showed significantly less haematological toxicity compared to docetaxel, and the patient quality of life was preserved. As the authors concluded, ULTIMATE introduces weekly paclitaxel and bevacizumab as a new second-line or third-line treatment option for NSCLC patients with non-squamous tumours. ■

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Locally advanced NSCLC: oral vinorelbine shows better safety profile than etoposide

The randomised, multicentre, open-label, phase II RENO trial was conducted with the objective of establishing a standard chemotherapy regimen in the setting of chemo-radiotherapy of locally advanced NSCLC. A total of 134 patients with inoperable stage III NSCLC received either oral vinorelbine plus cisplatin or etoposide plus cisplatin.

Although the analysis revealed no differences regarding both PFS (primary endpoint; 11.4 vs. 11.8 months with vinorelbine and etoposide, respectively) and response (ORR, 64 % vs. 66.7 %, respectively), vinorelbine showed a better safety profile. Grade-3/4 events were significantly reduced in the vinorelbine arm (19.7 % vs. 62.6 %; $p < 0.001$) due to higher tolerability with regard to both haematological and non-haematological events. The latter included oesophagitis, pneumonia, and sepsis. The RENO trial is currently maturing to assess the impact of these regimens on overall survival. ■

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PFS improvement due to local therapy in oligometastatic NSCLC

Evidence suggests the existence of a ‚limited metastatic' NSCLC phenotype. However, the type of optimal treatment and the role of aggressive local therapy in these patients remain controversial.

Gomez et al. presented the first prospective, randomised trial to address this question. Patients had stage IV disease without RECIST progression and a maximum of three metastases after front-line systemic therapy (FLST). Malignant pleural effusion was an exclusion criterion. FLST was defined as ≥ 4 cycles of platinum-doublet chemotherapy, ≥ 3 months of erlotinib, afatinib, or gefitinib therapy in case of *EGFR* mutation, or ≥ 3 months of crizotinib therapy for those with *EML4-ALK* fusion. The patients were randomised to either local consolidative therapy (LCT; surgery ± radiation to primary and metastases followed by standard maintenance or surveillance according to the physician's choice) or no LCT (standard mainte-

nance or surveillance according to the physician's choice). PFS was defined as the primary outcome. Twenty-four patients were evaluable in each group.

Patients treated with LCT fared significantly better than the no-LCT group. Median PFS was 11.9 vs. 3.9 months, respectively (p = 0.005). At the same time, toxicity did not differ substantially. There were differences in patterns of failure that trended towards significance (p = 0.09) **(Figure)**. Patients in the no-LCT arm experienced a comparatively higher proportion of locoregional-only and known (vs. new-site) failures, whereas those in the LCT arm showed comparatively higher percentages of metastatic-only and new failures. Both locoregional and metastatic failures were more common in the no-LCT Arm (29 % vs. 8 %). The time to new-site failure significantly favoured LCT (11.9 vs. 5.7 months; p = 0.0497), which suggests reductions in the metastatic spread.

In the entire cohort, two other factors associated with PFS were identified: patients with two to three metastases after FLST had worse outcomes than those with only one lesion (p = 0.043), as did those without *EGFR*/*ALK* alterations as compared to patients who were either *EGFR*-positive or *ALK*-positive (p = 0.035). Median OS was not reached in either arm. As the data are not yet mature, patients continue to be followed for this endpoint. ■

LCT: local consolidative therapy, LR: local recurrence

Figure: Differences in the patterns of failure by treatment arm (local consolidative therapy or no local consolidative therapy)

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Similar outcomes obtained with four adjuvant cisplatin-based chemotherapy regimens

The phase III E1505 trial was designed to investigate the addition of bevacizumab to adjuvant chemotherapy in patients with early-stage, completely resected NSCLC. It was based on the rationale that the benefit of adjuvant cisplatin-based chemotherapy is modest in this population. E1505 included 1,501 patients with completely resected, stage IB NSCLC. They were randomised to either 4 cycles of cisplatin-based chemotherapy only or the same chemotherapy plus bevacizumab for up to one year. Four chemotherapy regimens per investigator choice were allowed: cisplatin/ vinorelbine, cisplatin/ docetaxel, cisplatin/ gemcitabine, and cisplatin/ pemetrexed.

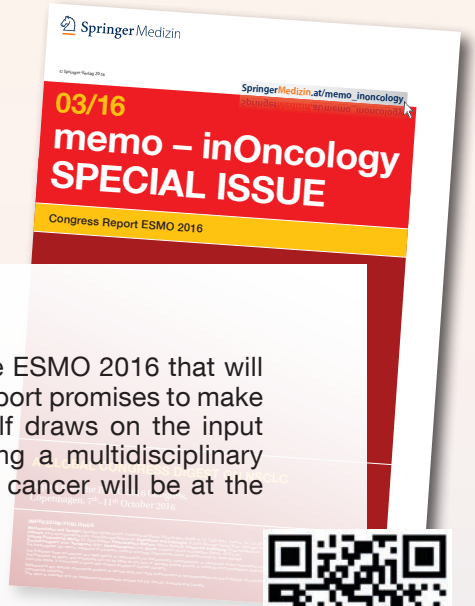
E1505 was powered for the primary endpoint of OS only and was stopped early for futility. The updated results presented at the ASCO Congress confirm the lack of difference between the two treatment arms with regard to OS and DFS; the hazard ratio was 0.99 for both endpoints.

This analysis also focussed on outcomes based on chemotherapy subsets. Patients were pooled with respect to the regimen used regardless of treatment arm (with or without bevacizumab) and divided into non-squamous and squamous cohorts to account for the restriction of pemetrexed administration to patients with non-squamous histology. DFS and OS were calculated for each chemotherapy group.

This *post-hoc*, non-randomised subset analysis yielded no differences for OS and DFS across all four adjuvant cisplatin-based chemotherapy regimens in both squamous and non-squamous tumours. Moreover, hazard ratios were calculated using vinorelbine as a reference, because cisplatin/ vinorelbine had been the regimen used in prior adjuvant trials. Again, no significant differences were noted for patients with both histologies. ■

REFERENCES

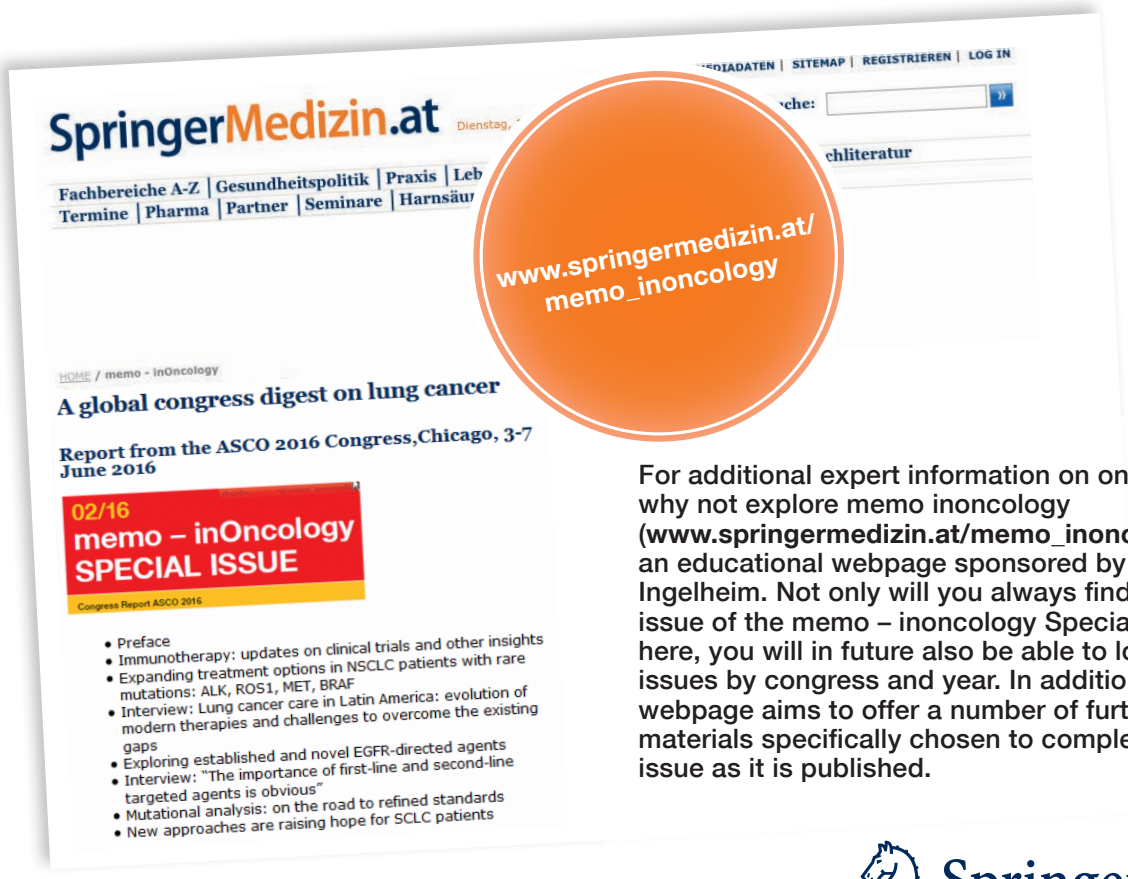
Wakelee HA et al., Adjuvant chemotherapy bevacizumab for early stage NSCLC: Outcomes based on chemotherapy subsets. J Clin Oncol 34, 2016 (suppl; abstr 8507)



Forthcoming Special Issue

This special issue will be offering a synopsis from the ESMO 2016 that will be held in Copenhagen, 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.

ESMO 2016
Annual Meeting
COPENHAGEN, 7–11 OCTOBER 2016



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