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A GLOBAL CONGRESS DIGEST ON NSCLC

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Table of Contents

3 Preface

4 Metastatic NSCLC: new drugs and updates on well-known agents

8 Interview: “EGFR testing is a reality in central and eastern European countries”

9 Immunotherapy: effective treatments gathering on the horizon

12 Statement: “Select the patients who will be able to benefit”

12 Novel approaches in small-cell lung cancer

15 Further analyses of biomarkers

16 Interview: “These findings will change the standard-of-care”

17 Phase III results in local and regional lung cancer

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Preface

Dear Colleagues,

As for many other oncological diseases, the management of lung cancer has undergone major changes in the last few years with the rise of targeted therapies, and more lately, of immunotherapy. These advances are reflected in the results of experimental research and clinical trials that were presented at the Annual Meeting of the American Society of Clinical Oncology that took place in Chicago, from 29th May to 2nd June, 2015.

Patient improvement is of paramount importance, especially with respect to lung cancer, and particularly in the second-line setting, considering the poor prognosis that is still linked to this disease. The majority of patients are diagnosed at advanced stages. Not too long ago, there was little left to offer them except for chemotherapy of mediocre activity in terms of prolongation of life and sometimes even symptom relief. Nowadays, the physician faces a vast range of available therapies to choose from. Many of these agents have proven to be highly effective, giving hope to both patients and physicians even in settings in which the decline of the patient's condition used to be inevitable. Time and again, cases are being reported at meetings and congresses that demonstrate disease control in the metastatic situation. The abbreviation "NED", which stands for "no evidence of disease", is slowly but surely making its way into the files of oncology patients.

However, quite a few of the new drugs require genetic testing prior to use, as only certain subsets of patients can be expected to benefit. Even therapies that are not restricted to particular groups frequently do not work alike in all patients, as they might greatly improve the course of the disease in one patient but not in another, without any recognizable features to explain these differences. Moreover, specific toxicities need to be kept in mind, thus massively increasing the complexity of side-effect management. Thus, in modern practice, a considerable proportion of the time used on patient care is dedicated to this aspect of treatment.

The chapters presented in this publication summarise the recent findings in the fields of metastatic non–small-cell lung cancer (NSCLC), immunotherapy, SCLC, biomarkers, and local and regional lung cancer. Naturally, targeted agents are the 'stars' of the coverage, but other long-standing strategies, such as chemotherapy and radiotherapy, enter the stage as well.

In metastatic NSCLC, EGFR tyrosine kinase inhibition has become a mainstay of treatment in patients with activating EGFR mutations, although resistance frequently develops. This need is addressed by the development of mutant-selective EGFR inhibitors, which show promising activities. Other genetic anomalies that constitute therapeutic targets include RET and ALK rearrangements as well as BRAF mutations, with the prevailing armamentarium being constantly expanded. However, a second-generation platinum compound that offers reduced toxicity has also been found to provide advantages when tested in patients with squamous-cell carcinoma.

Research in immunotherapy is currently proceeding beyond the first PD-1 antibody nivolumab, which has shown highly favourable effects. New agents are already being tested with success. Great hopes in the treatment of SCLC are also being pinned on immunotherapy, as this disease responds poorly to standard approaches. No final answers have yet been found to the question of biomarker expression in the context of immunotherapy. So far, various analyses have generally revealed conflicting results on the predictive power of biomarkers. More research is called for in this field.

For local and regional lung cancer, in terms of overall survival, chemoradiotherapy followed by pemetrexed consolidation was not superior to commonly used chemoradiation regimens followed by consolidation regimens of choice, although at the same time it showed higher tolerability. BRCA1 expression is gaining importance as a prognostic and potentially predictive factor in the adjuvant setting. Customisation of chemotherapy according to BRCA1 levels has been demonstrated to be feasible in node-positive resected NSCLC.

All of these findings will hopefully contribute to further improvements to our daily management of lung cancer patients. Although the defeat of cancer remains a long-term goal, the progress that has been made is truly encouraging, making us look forward to further data that will be presented at the upcoming congresses.

We are going through an exciting time in lung cancer.

Barbara Melosky, MD, FRCPC,
University of British Columbia and
British Columbia Cancer Agency,
Vancouver, Canada

Metastatic NSCLC: new drugs and updates on well-known agents

Squamous-cell carcinoma: nedaplatin

Tumours with squamous histology account for 20 % to 30 % of cases of non–small-cell lung cancer (NSCLC). Despite this substantial proportion, only limited progress has been made in the treatment of advanced squamous-cell carcinoma (SCC) compared to non-squamous NSCLC, and thus SCC of the lung is a disease with a high unmet medical need.

In the field of chemotherapy, cisplatin plus docetaxel is standard-of-care in patients with advanced SCC of the lung. Nedaplatin is a second-generation platinum compound with reduced toxicity. Based on the WJOG5208L trial, it can be considered as a new standard treatment for advanced or relapsed SCC [1]. This study compared docetaxel 60 mg/m² plus nedaplatin 100 mg/m² every 3 weeks for 4 to 6 cycles with the standard regimen of docetaxel and cisplatin. A total of 349 chemo-naïve patients with stage IIIb/IV or recurrent SCC who were not amenable to curative-intent radiation therapy participated in the trial.

For the primary endpoint of overall survival (OS) in the WJOG5208L trial, the new combination regimen showed significant benefit over the control arm (13.6 vs. 11.4 months; hazard ratio [HR] 0.81; p = 0.037). However, progression-free survival (PFS) did not differ between the two arms, as also seen for objective response rate (ORR) and disease control rate (DCR). Grade ≥3 adverse events (AEs) occurred to a similar extent in both treatment arms, whereas AEs leading to discontinuation of the study drug were more frequent in the control arm (15.3 % vs. 23.3 %). The experimental arm showed advantages regarding incidence of nausea/vomiting and electrolyte imbalance, whereas myelosuppression was more frequent and more severe than in the patients in the control arm. This increase did not translate into higher rates of febrile neutropenia or bleeding, however.

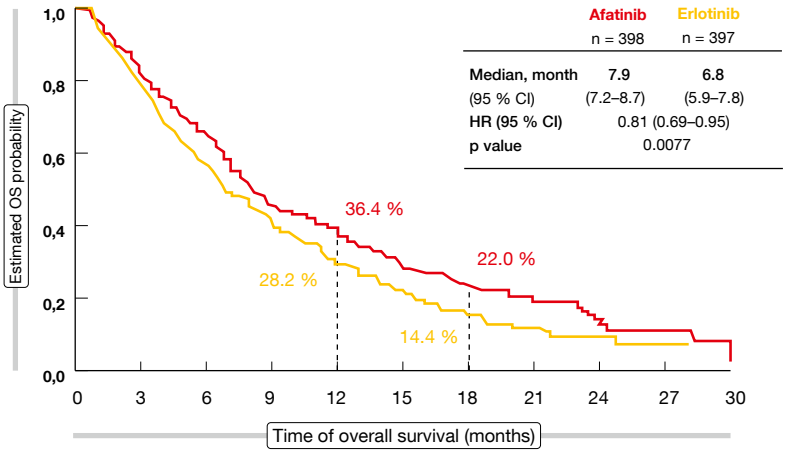

Figure 1: Significant OS benefit with afatinib over erlotinib in the LUX-Lung 8 trial for pre-treated patients with squamous-cell histology

Afatinib-mediated survival benefit

Activating epidermal growth factor receptor (EGFR) mutations including the exon 21 L858R mutation and exon 19 deletions are key drivers of NSCLC in 10 % to 15 % of patients of European descent, and in 30 % to 35 % of those of Asian descent. EGFR tyrosine kinase inhibitors (TKIs) are recommended as first-line therapy in EGFR-mutation-positive advanced NSCLC. Among these agents, afatinib appears to be the TKI of choice in the second-line treatment of patients with SCC of the lung. This insight is derived from the LUX-Lung 8 global phase III trial, the largest phase III trial ever conducted in the second-line treatment setting of SCC of the lung. Here, the reversible EGFR TKI erlotinib was compared with afatinib. In contrast to erlotinib, afatinib is an irreversible TKI, and its effects extend to ErbB1 (EGFR), HER2 and HER4. The study authors hypothesised that afatinib would confer additional benefits over erlotinib due to its broader signal-transduction inhibition. Thus, for LUX-Lung 8, a total of 795 patients with SCC of the lung (stage IIIB/IV) who had progressed after at least 4 cycles of a first-line platinum doublet were randomised to either afatinib 40 mg daily (QD) or erlotinib 150 mg QD.

The primary endpoint was defined as PFS by independent review. This outcome was met according to the primary PFS analysis that was presented at the ESMO Congress 2014 [2]. At the ASCO Congress 2015, the median OS (key secondary endpoint) with afatinib and erlotinib was shown to be 7.9 months and 6.8 months, respectively, which translated into a 19 % reduction in mortality risk (HR, 0.81; p = 0.0077; Figure 1) [3]. The survival curves separated early on, which reflects a consistent advantage of afatinib. Landmark analyses at 12 and 18 months demonstrated higher percentages of patients alive in the afatinib arm (36.4 % vs. 28.2 %, 22.0 % vs. 14.4 %, respectively). All subgroup analyses favoured afatinib over erlotinib, independent of age, gender, ethnicity, smoking history, histology, and best response to first-line chemotherapy.

LUX-Lung 8: patient-reported outcomes and adverse events

The updated PFS analysis of LUX-Lung 8 was in keeping with the data obtained at the first analysis, with a 19 % reduction in the risk of progression (median PFS, 2.6 vs. 1.9 months; HR, 0.81; p = 0.0103).

The ORR favoured afatinib numerically (5.5 % vs. 2.8 %; p = 0.055). However, the benefit gained by afatinib therapy is basically due to disease stabilisation. The DCR was 50.5 % vs. 39.5 % for afatinib and erlotinib, respectively, and this difference was significant (p = 0.002). Patient-reported outcomes were acquired by means of standard European Organisation for Research and Treatment of Cancer (EORTC) questionnaires that focussed on dyspnoea, cough, and pain, with global health status also evaluated [4]. Symptom relief and quality of life improvement were more pronounced with afatinib than erlotinib. This also applied to the time to deterioration.

Overall, AEs were balanced between both arms. The AEs that led to dose reduction were more frequent with afatinib as compared to erlotinib, but the proportions of AEs prompting discontinuation were similar. The most common drug-related AEs matched the overall safety profiles that have been described for these two treatments. Diarrhoea and stomatitis occurred predominantly with afatinib, whereas grade 3 rash was observed more frequently with erlotinib.

A tumour genomic analysis is ongoing. So far, 238 patients have been analysed. The results show that EGFR aberrations are infrequent and are balanced between the two arms.

No correlations of EGFR aberrations with PFS or OS were found. Therefore, the EGFR mutation status cannot explain the added benefit of afatinib over erlotinib.

Mutant-selective EGFR inhibition

Patients with activating EGFR mutations typically experience good initial responses to therapy with first-generation EGFR TKIs (e.g., erlotinib, gefitinib) and with the second-generation TKI afatinib. However, after 9 months to 14 months of treatment, disease progression invariably ensues. In 50 % to 60 % of patients, this is driven by a secondary T790M 'gatekeeper' mutation in exon 20. Furthermore, approximately 2 % to 3 % of patients with EGFR-mutant NSCLC have this T790M mutation at baseline. For this group of patients, no approved therapies exist, and they show very poor outcomes with the currently available TKIs.

Third-generation EGFR TKIs that address this need have been developed. AZD9291 is an oral irreversible EGFR TKI that shows selectivity for sensitising and for T790M resistance mutations. The AURA phase I dose-escalation/expansion study demonstrated encouraging clinical activity of AZD9291 as first-line treatment in 160 patients with EGFR-mutation-positive, locally advanced or metastatic NSCLC [5]. With AZD9291 80 mg QD and 160 mg QD, the ORRs were 63 % and 83 %, respectively. Although these data were still too immature to estimate the median PFS, the PFS analysis at 12 months yielded a high rate of 72 %. The tolerability profile also proved manageable. AZD9291 80 mg is currently being tested in the phase III FLAURA study, in comparison with gefinitib 250 mg QD and erlotinib 150 mg QD.

Compelling activity of rociletinib

Rociletinib is another orally administered third-generation EGFR TKI, which irreversibly inhibits activating EGFR mutations as well as the T790M mutation, while wild-type EGFR is spared. The phase I/II TIGER-X trial assessed rociletinib in patients with advanced or recurrent NSCLC who had received prior treatments with EGFR-directed therapy and showed documented activating EGFR mutations [6]. The phase II expansion cohort contained second-line patients after progression on EGFR-directed therapy, as well as patients beyond second line, who had progressed on two or more TKIs or chemotherapy. Their biopsies had to be positive for the T790M mutation at study entry. Treatment was administered at four different doses: 500 mg twice daily (BID), 625 mg BID, 750 mg BID, and 1,000 mg BID.

In the 243 patients included with centrally confirmed T790M mutation, the ORR and DCR were 53 % and 85 %, respectively (Table). The response rates did not vary significantly by dose. PFS estimates are immature, as the study is still ongoing. At the time of the analysis, median PFS was 8.0 months in patients with centrally confirmed T790M mutation. In the group without central nervous system (CNS) disease at baseline, it was 10.3 months. Rociletinib was also shown to have activity in T790M-negative patients, with an ORR of 37 %. Furthermore, TIGER-X demonstrated that T790M plasma testing using the quantitative and sensitive BEAMing Test is a viable alternative to tissue testing. The ORRs obtained with both methods were similar.

Table: Response rates obtained with rociletinib at four doses in 243 patients with centrally confirmed tissue T790M mutation

	500 mg BID	625 mg BID	750 mg BID	1,000 mg BID	Total
Number of patients	48	114	77	4	243
ORR (%)	60	54	46	75	53
DCR (%)	90	84	82	100	85

Hyperglycaemia with rociletinib: frequent, but manageable

Rociletinib was generally well tolerated, with the primary side effect being hyperglycaemia, which was often accompanied by diarrhoea, nausea and decreased appetite. The 500 mg dose level showed an improved safety profile compared to the higher dose levels. In this group, the rate of grade 3/4 hyperglycaemia was lowest at 17 %. Also, no cases of interstitial lung disease have been observed in the 500 mg dose group, although seven cases occurred in TIGER-X overall. Treatment-related AEs that led to drug discontinuation were less frequent with 500 mg BID than in the total cohort (2.5 % vs. 4 %).

Hyperglycaemia is caused by iatrogenic insulin resistance due to a rociletinib metabolite. It can be managed through a monitoring and treatment algorithm that uses oral agents. These are very successful in treating the hyperglycaemia as well as in relieving the associated gastrointestinal symptoms.

On the grounds of the assumption that early targeting of the T790M mutation along with initial activating mutations is a rational approach to impeding disease progression, the randomised, open-label, phase II/III study TIGER-1 is currently investigating rociletinib in

the first-line setting as compared to erlotinib, in patients with EGFR-mutant NSCLC [7]. The phase III, open-label, randomised TIGER-3 trial is comparing rociletinib with single-agent cytotoxic chemotherapy in patients with EGFR-mutant NSCLC who have shown progression on at least one previous EGFR TKI therapy and platinum-based doublet chemotherapy [8]. The rationale for the TIGER-3 trial is that patients who fail on chemotherapy and first-generation EGFR TKIs have limited treatment options.

EGFR wild-type NSCLC

As erlotinib has only modest activity in unmutated EGFR NSCLC, administration of the oral small-molecule multikinase inhibitor cabozantinib alone or in combination with erlotinib might improve efficacy in these patients. The randomised phase II E1512 trial tested erlotinib 150 mg QD, cabozantinib 60 mg QD, and erlotinib 150 mg QD plus cabozatinib 40 mg QD, as second-line or third-line therapy in 125 patients with EGFR-mutation-negative, metastatic non-squamous NSCLC [9]. The median PFS in each cabozantinib arm in comparison to the erlotinib-only control arm was defined as the primary endpoint.

Indeed, the PFS results were improved with cabozantinib monotherapy as well as with the erlotinib plus cabozantinib combination, compared to erlotinib monotherapy (median PFS, 4.2 vs. 4.7 vs. 1.9 months, respectively; Figure 2). The differences between the two experimental arms and the erlotinib arm were statistically significant (p = 0.0004, 0.0005, respectively) and these translated into risk reductions of > 60 %. Similarly, for OS, the cabozantinib-treated patients fared significantly better. This was particularly true for the combination group, whereby the median OS was 4.1 months for the control arm, but as high as 13.3 months for the erlotinib plus cabozantinib arm (p = 0.004) and 9.2 months for the cabozantinib-only arm (p = 0.03). Thus, compared to erlotinib, the mortality risk was reduced by 56 % and 41 %, respectively. However, the follow-up is currently short on the combination arm, so that the results might change with further analysis. Responses were noted relatively infrequently across the three arms, ranging from 3 % to 14 %. However, disease stabilisation was much more common with the combination and with cabozantinib alone than with erlotinib monotherapy (42 % and 45 % vs. 17 %, respectively).

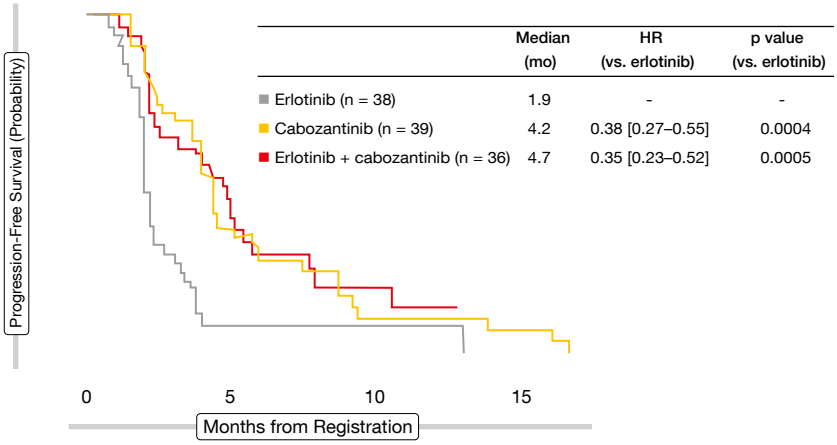

Figure 2: Superior PFS with cabozantinib and cabozantinib vs. erlotinib in non-squamous NSCLC without EGFR mutation

Tissue was collected in all patients with the intention of MET immunohistochemistry (IHC) testing. The comparison of the treatment effects on MET-positive tumours was defined as a secondary outcome. According to this analysis, the total MET IHC status did not appear to be predictive of PFS for cabozantinib treatment. A follow-up study is currently being planned.

Efficacy of cabozantinib in RET rearrangement

Cabozantinib also appears to be active in tumours that show RET rearrangements, which are characterised by fusions of intact tyrosine kinase domains to upstream gene partners. These aberrations are found in 1 % to 2 % of NSCLCs, and they are drivers of cell growth in vitro and in vivo. Clinical features of patients with RET rearrangements comprise young age and never-smoking status, or former light smoking. Adenocarcinoma is the most common histology.

A phase II, open-label trial evaluated cabozantinib 60 mg daily in patients with stage IV NSCLC with RET rearrangements [10]. In stage 1 of the trial, 16 patients were included, with one response required to move on to stage 2, which is currently accruing nine additional patients. Here, responses in five cases are required to meet the primary endpoint of overall response.

At the completion of stage 1, the ORR was 38 %, and another 56 % of patients experienced disease stabilisation. The median duration of response was 8 months, the median PFS was 7 months, and the median OS was 10 months. The most common AEs included transaminase elevations, diarrhoea, fatigue, mucositis, skin and hair hypopigmentation, palmar-plantar erythrodysaesthesia, and decreased platelet counts. While the overall rates of AEs were high, grade 3 events were rare. The majority of patients required at least one dose reduction during the course of therapy; however, clinical benefit was maintained in spite of these dose reductions.

BRAF-mutated tumours: dabrafenib and trametinib

Another genetic aberration to be found in NSCLC is BRAF mutations. These mutations are present in approximately 2 % of patients. BRAFV600E-mutated tumours typically show histologic features that are suggestive of aggressive tumour biology, and the patients affected have less-favourable outcomes when treated with platinum-based chemotherapy.

The small molecules dabrafenib and trametinib both inhibit the MAP kinase (MAPK) pathway by targeting BRAF V600 kinase and MEK signalling, respectively, thus antagonising cell proliferation, growth and survival in different tumour types. A multicentre, open-label, phase II study (BRF113928) tested dabrafenib as monotherapy (n = 60) and

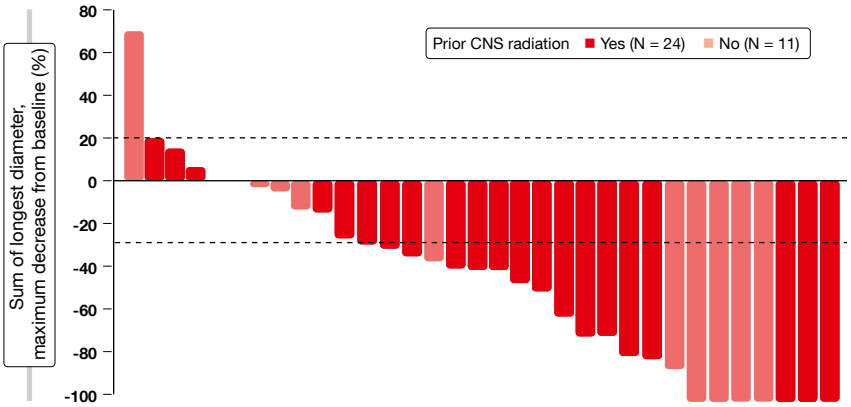

Figure 3: Marked activity of alectinib in ALK-positive NSCLC patients with measurable CNS disease

in combination with trametinib (n = 40) in patients with BRAFV600E-mutated, stage IV NSCLC who had received at least one previous platinum-based chemotherapy [11].

At the time of the interim analysis of BRF113928, 82 % of the patients were still on study treatment, and dabrafenib plus trametinib showed clinically meaningful anti-tumour activity. In the combination group, 63 % and 25 % of patients achieved partial responses and stable disease, respectively, giving a DCR of 88 %. With monotherapy, the ORR and DCR were 32 % and 56 %, respectively. The median duration of response had not been reached in the second-line setting and beyond. The safety profile proved manageable and similar to previous studies in melanoma. AEs leading to dose reduction occurred in 27 % of patients, and dose interruptions were necessary in 52 %. A third cohort that is investigating dabrafenib plus trametinib in previously untreated BRAF-mutated, stage IV NSCLC is actively recruiting at present.

ALK rearrangements as a therapeutic target

The ALK-specific TKI crizotinib is an established option in pre-treated patients with ALK-rearranged NSCLC. However, acquired resistance mutations in the ALK gene are a common cause of progression. Also, in spite of potential CNS disease control, approximately half of the patients develop brain metastases during crizotinib treatment.

The highly selective oral ALK inhibitor alectinib is active against most clinically relevant acquired ALK-resistance mutations. In the phase II NP28673 trial, patients with ALK-positive NSCLC who did not respond to or had progressed on prior crizotinib treatment received alectinib 600 mg BID [12]. Overall, 138 people participated in this study, and the response-evaluable cohort comprised 122 patients. The co-primary endpoint was ORR by Independent Review Committee in two populations: in all of the patients, and in those who had received prior chemotherapy.

The analysis yielded a robust response rate of 50 %. For the chemotherapy-naïve and chemotherapy-treated patients, the rates were 69.2 % and 44.8 %, respectively. Disease control was obtained in 78.7 % in the total population; also, the duration of response was remarkably long, at 11.2 months. Median PFS was 8.9 months. Alectinib showed considerable activity in patients with measurable brain metastases, irrespective of prior irradiation (Figure 3). In this cohort, the analysis revealed an excellent DCR of 85.7 %. Objective CNS response was observed in 57.1 %, and complete remission occurred in 20.0 %. CNS response lasted for 10.3 months. Alectinib also demonstrated a favourable safety and tolerability profile. Most common AEs included constipation, fatigue, peripheral oedema, and myalgia. There were only a few reported grade 3/4 AEs. The ALEX phase III study is currently investigating first-line alectinib 600 mg BID compared to crizotinib 250 mg BID in patients with stage IIIb/IV or recurrent NSCLC.

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Omission of whole-brain radiotherapy

After radical treatment of primary NSCLC, the brain remains a frequent and early site of distant relapse, with CNS metastases affecting up to 40 % of patients. Patients with NSCLC and brain metastases fare poorly, even if irradiated. In spite of a lack of randomised, controlled data, whole-brain radiotherapy (WBRT) plus steroid therapy is the present standard of care.

The randomised, controlled, non-inferiority QUARTZ trial investigated the omission of WBRT in patients with NSCLC and brain metastases who were unsuitable for resection or stereotactic radiosurgery [13]. While the control arm received optimal supportive care (OSC), including dexamethasone and WBRT 20 Gy/5f, patients in the investigational arm were treated with OSC and dexamethasone only. The primary outcome was quality-adjusted life years (QALYS). Each arm contained 269 patients from the UK and Australia, and >70 % of the patients in both arms suffered from moderate or severe symptoms, with the majority requiring steroid treatment.

The analysis showed that the OS did not differ between the two arms (9.3 vs. 8.1 weeks in the OSC plus WBRT group and the OSC alone group, respectively; HR, 1.05; p = 0.52). For the primary outcome measure, there was a difference in QALYS of 1.9 days that favoured the WBRT arm, which stayed below the non-inferiority boundary. According to the conclusion of the authors, this suggests that WBRT provides no additional clinically significant benefit in this group of patients. Also, WBRT did not appear to be a steroid-sparing treatment modality. ■

Interview: Robert Pirker, MD, Medical University of Vienna, Vienna, Austria

"EGFR testing is a reality in European countries"

Robert Pirker, MD, Medical University of Vienna, Vienna, Austria

Which of the recent advances in the field of NSCLC would you deem most important from the clinical point of view?
Medical science in oncology has moved on to specific, molecularly targeted treatments. Personalised medicine is based on molecular alterations of the tumour cells. Chemotherapy has been around for decades, and I believe that it will stay on for many more decades to come. However, in the long run, targeted agents will be increasingly available, either as a single modality or in combination with chemotherapy. The classification of lung cancer has changed markedly. Besides histology, subtyping of histology has been included, and more importantly, there are molecular parameters we should assess.

Are new treatments being implemented in the clinic to a sufficient degree?
Here I would like to refer to a study we did in Central and Eastern European countries. We evaluated whether patients with advanced NSCLC receive testing for EGFR mutations in a real-world setting, and the kind of treatment strategy prescribed in those with EFGR-mutation-positive disease. The study shows that EGFR testing is a reality in these countries. EGFR-mutation positivity was present in 14% of patients with advanced NSCLC; these were of course mainly patients with adenocarcinomas. Also, importantly, we have shown that the treatment is conducted according to the guidelines. This means that the majority of the EGFR-mutation-positive patients will receive EGFR-directed TKIs, such as afatinib, erlotinib or gefitinib, in the first-line setting. Moreover, patients without EGFR mutations are treated with chemotherapy rather than with EGFR-directed TKIs.

Will findings presented at the ASCO Congress change the future of NSCLC therapy?
In some areas, they will. For example, second-generation TKIs are already in use in patients with EGFR-mutation-positive disease, but in the future, third-generation TKIs will be available as well, particularly for patients with resistance mutations. Also, because of the LUX-Lung 8 trial that has clearly demonstrated benefits from afatinib compared to erlotinib in squamous cell carcinoma, we will probably be able to prescribe second-line afatinib for our patients with advanced squamous cell tumours. The difference observed between the two arms of the trial is statistically significant, but I think that it is also of clinical relevance. One of the next steps will be the identification of those patients who benefit most. There will be research efforts with respect to predictive factors in afatinib-treated patients with squamous cell carcinoma. In general, predictive factors are an important future area of research.

Another trial evaluated the value of whole brain radiotherapy in addition to stereotactic radiotherapy in patients with brain metastases. This is a simple question, but it is clinically relevant. The study demonstrated that there is no survival benefit by adding whole brain radiotherapy to stereotactic radiotherapy in patients with up to three brain metastases. In the clinic, we already go along these lines in the vast majority of patients.

The major news is that immunotherapy that is actually working is now available. Attempts were made in this field in the past, but they always failed. Immune checkpoint inhibitors now have demonstrated that they can improve outcomes in patients with NSCLC. Two trials have shown a survival benefit in patients with advanced NSCLC, who had previously been treated with chemotherapy. From my point of view, this is an important improvement. ■

Immunotherapy: effective treatments gathering on the horizon

EGFR mutations and ALK rearrangements are well-established therapeutic targets in NSCLC, with EGFR TKIs and ALK TKIs representing the first-line standard of care for these molecular subsets of patients. However, resistance to first-generation inhibitors invariably develops, which calls for strategies to improve upon the durability of any response. Moreover, targeted agents are available only for a limited group of patients, while chemotherapy with or without anti-angiogenic treatments still remains the cornerstone in the majority of cases. Docetaxel is the standard second-line therapy in NSCLC, but its use is hampered by important toxicity.

Two anti-angiogenic agents have recently been shown to enhance docetaxel efficacy and to improve patient survival. Ramucirumab proved beneficial in the REVEL trial in patients with all histologies [1]. In the LUME-Lung 1 study, nintedanib demonstrated activity in patients with adenocarcinoma [2]. In 2015, immunotherapeutic agents targeting the PD-L1/PD-1 pathway are about to change the management of NSCLC.

CheckMate 057: nivolumab in non-squamous NSCLC

Nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, is active in pre-treated patients with advanced or metastatic NSCLC across different histologies. PD-1 expression on tumour-infiltrating lymphocytes is associated with decreased cytokine production and effector function. Nivolumab binds PD-1 receptors on T-cells and disrupts the negative signalling triggered by PD-L1/PD-L2, to thus restore T-cell antitumour function.

The randomised, global, phase III CheckMate 057 trial assessed the efficacy and safety of nivolumab 3 mg/kg every 2 weeks until progression (n = 292) compared to docetaxel 75 mg/m^2 every 3 weeks until progression (n = 290) in patients with advanced non-squamous NSCLC (stage IIIb/IV), after failure of one platinum-based doublet chemotherapy [3]. PD-L1 expression was measured using IHC. The rationale for this trial was based on the concept that patients with advanced non-squamous NSCLC who progress after platinum-based doublet chemotherapy only have limited effective options.

Outcomes according to PD-L1 expression

The CheckMate 057 trial showed that nivolumab-treated patients benefited significantly in terms of OS, compared to the docetaxel arm (12.2 vs. 9.4 months; HR, 0.73; p = 0.0015). The 1-year OS rates were 51 % and 39 % for nivolumab and docetaxel, respectively. The OS analysis favoured nivolumab in almost all of the predefined subgroups. Nivolumab is the first PD-1 inhibitor to significantly improve OS over docetaxel in previously treated patients with advanced non-squamous NSCLC.

There was also significant advantage for the ORR in the experimental arm (19 % vs. 12 %; p = 0.0246), and the responses lasted conspicuously longer in the nivolumab-treated group (17.2 vs. 5.6 months). The PFS did not differ significantly between the two arms. Also, nivolumab showed a more favourable safety profile than its comparator.

According to the biomarker analysis, both OS and PFS were significantly prolonged in the nivolumab patients with marked PD-L1 expression. This correlation was evident already at the lowest expression levels. The median OS nearly doubled with nivolumab versus docetaxel across the PD-L1 expression continuum. On the other hand, no differences in OS were seen in patients whose tumours did not express PD-L1. The ORR almost tripled in the PD-L1 expressors.

However, when compared indirectly to pooled data of ramucirumab plus docetaxel and nintedanib plus docetaxel, these results are not robust enough to be able to state that nivolumab can outperform the combination of docetaxel and the anti-angiogenics. Only a head-to-head trial will answer this question fully.

CheckMate 017: nivolumab in patients with squamous histology

As compared to patients with non-squamous tumours, those with squamous

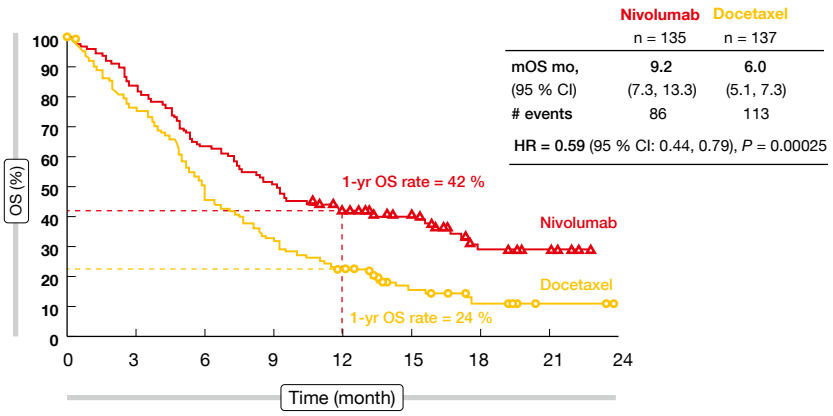

Figure 1: Overall survival in CheckMate 017

cell histology have a worse prognosis. Indeed, the therapeutic options after front-line chemotherapy are meagre in this group. Second-line therapy with docetaxel has only modest clinical activity and is associated with significant toxicity.

The phase II, single-arm trial CheckMate 063 demonstrated clinical activity of nivolumab in refractory squamous-cell carcinoma with a median OS of 8.2 months, a 1-year OS rate of 41 %, and an ORR of 15 % [4]. In the head-to-head setting, the randomised global phase III study CheckMate 017 tested the efficacy and safety of nivolumab compared to docetaxel in patients with advanced squamous-cell carcinoma after failure of platinum-based chemotherapy [5]. Patients with stage IIIb/IV squamous NSCLC who had already received one previous platinum-doublet-based chemotherapy were randomised to either nivolumab 3 mg/kg every 2 weeks until progression (n = 135) or docetaxel 75 mg/m² every 3 weeks until progression (n = 137). Pre-treatment tumour samples were required for the PD-L1 analysis. 83 % of patients showed quantifiable PD-L1 expression.

Superiority across all endpoints

Regarding the OS, which was defined as the primary endpoint of the CheckMate 017 trial, nivolumab did significantly better than docetaxel. Survival was 9.2 months versus 6.0 months with nivolumab and docetaxel, respectively, which translated to a reduction in the risk of death of 41 % (HR, 0.59; p = 0.00025; Figure 1). At 1 year, the OS rates were 42 % and 24 %, respectively (Figure 1). Nivolumab demonstrated superiority over docetaxel across all of the secondary efficacy endpoints. The PFS was significantly longer with nivolumab (3.5 vs. 2.8 months; HR, 0.62; p = 0.0004). 21 % of patients were progression-free in the nivolumab arm at 1 year, while this proportion was much lower in the control arm (6.4 %). Objective response rates were 20 % and 9 %, respectively (p = 0.0083).

The OS and PFS were also investigated according to PD-L1 expression. This analysis showed, however, that the survival benefit obtained with nivolumab was independent of PD-L1 expression levels. This was also true for the ORR, which was also consistently higher with nivolumab than with docetaxel. Moreover, according to the Lung Cancer Symptom Scale (LCSS) Average Symptom Burden Index, the symptoms were reduced more efficiently with nivolumab treatment.

Treatment-related AEs occurred more frequently with docetaxel than with nivolumab (any grade: 86 % vs. 58 %). Correspondingly, AEs predominantly led to discontinuation in the docetaxel arm (10 % vs. 3 %). Nivolumab showed a favourable safety profile that was consistent with prior studies. Fatigue, decreased appetite, and asthenia were the most common AEs reported in the nivolumab arm. Docetaxel, on the other hand, gave rise to fatigue, neutropenia, anaemia, nausea, diarrhoea, and alopecia. Among the select AEs, however, pneumonitis occurred in 5 % of the nivolumab-treated patients (docetaxel: 0 %), and was severe in 1 %. Nivolumab is the first PD-1 inhibitor to demonstrate a survival benefit compared to standard-of-care docetaxel therapy in previously treated patients with advanced squamous NSCLC.

However, as for CheckMate 057, the follow-up period is still relatively short. An indirect comparison of the REVEL and CheckMate 017 trials shows a larger risk reduction between the two arms regarding OS with nivolumab versus docetaxel than with docetaxel plus ramucirumab versus docetaxel monotherapy, which suggests that nivolumab could outperform not only docetaxel, but also the combination of docetaxel and ramucirumab. Nevertheless, a randomised trial is called for to clarify this.

POPLAR: favourable results with atezolizumab

Atezolizumab (MPDL3280A) is a humanised anti-PD-L1 antibody that inhibits the binding of PD-L1 to PD-1 and B7.1. The inhibition of the PD-L1/PD-1 and PD-L1/B7.1 interactions can restore antitumour T-cell activity and enhance T-cell priming. Targeting PD-L1 leaves the PD-L2/PD-1 interaction intact, thereby potentially preserving peripheral immune homeostasis. PD-L2 expression on tumour cells and immune cells is potentially predictive for the activity of atezolizumab in NSCLC.
In the POPLAR randomised, all-comer, phase II study, 287 patients with metastatic or locally advanced NSCLC who showed disease progression on a prior platinum therapy were randomised to either atezolizumab 1,200 mg IV every 3 weeks until loss of clinical benefit or docetaxel 75 mg/m² IV every 3 weeks until progression [6]. PD-L1 expression (0 vs. 1 vs. 2 vs. 3) was one of the stratification factors. The primary study objective was the estimated OS in the PD-L1-selected and the intention-to-treat (ITT) patient populations.

After a minimum of 10 months of follow-up, an interim analysis was performed according to which the OS favours atezolizumab in most of the PD-L1 expression subgroups (Figure 2). The pattern of improved survival correlated with increasing PD-L1 expression. Whereas the patients with the highest PD-L1 expression (i.e., tumour cell 'TC3' or immune cell 'IC3') experienced a reduction in mortality of 54 %, those in the 'TC0' and 'IC0' cohorts, with PD-L1 expression < 1 %, did not derive any

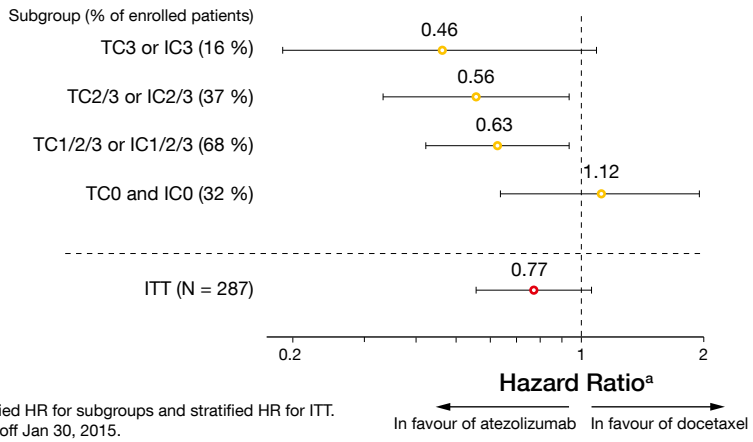

Figure 2: POPLAR: Increasing overall survival benefit with atezolizumab treatment relative to PD-L1 expression

benefit relative to docetaxel. This correlation between PD-L1 expression and risk reduction also applies to the PFS analysis. In the ITT population, the OS was longer in the atezolizumab-treated arm than in the docetaxel-treated arm, although not significantly so (11.4 vs. 9.5 months; HR, 0.77; p = 0.11). Also, the response rates achieved with atezolizumab were highest in the 'TC3' and 'IC3' subgroups (38 %). In the ITT population, there was no difference between the two treatment arms regarding the response rates (15 % each). The median duration of response had not been reached in the experimental arm at the time of the analysis, while it was 7.8 months for the control arm.

Atezolizumab was well tolerated, and its safety profile was consistent with previous studies. Compared with docetaxel, the atezolizumab AE rates were lower, which also applied to grade 3/4 AEs. The median treatment duration with atezolizumab exceeded that in the docetaxel group (3.7 vs. 2.1 months), and the proportion of patients treated beyond progression was greater by far (38 % vs. 2 %). This trial also demonstrated that the highly sensitive and specific IHC SP142 assay that measures PD-L1 on both tumour cells and immune cells is a predictive diagnostic biomarker for the efficacy of atezolizumab treatment in NSCLC. A phase III randomised study of atezolizumab monotherapy in second-line and third-line NSCLC patients is ongoing at present.

Preliminary evidence on pembrolizumab: KEYNOTE-021

Robust antitumour activity and manageable toxicity in multiple tumour types has been shown for pembrolizumab, a potent, humanised monoclonal antibody against PD-1. In the KEYNOTE-001 trial, pembrolizumab was effective in treatment-naïve patients with advanced NSCLC [7]. The KEYNOTE-021 trial tested the combination of pembrolizumab and the CTLA-4 antibody ipilimumab [8]. Anti-PD-1 and anti-CTLA-4 combination therapy is feasible because of the complementary mechanisms of action: CTLA-4 functions at the activation stage of the anticancer immune response, while PD-1 shows activity at the effector stage.

Patients with advanced or metastatic NSCLC of any histology participated in KEYNOTE-021. They had to have received at least one prior therapy that included ≥ 1 platinum-doublet chemotherapy. Any PD-L1 status was allowed, as well as any EGFR and ALK status. In the dose-finding part of this study, pembrolizumab 2 mg/kg plus ipilimumab 1 mg/kg was shown to have a manageable toxicity profile. The most frequent treatment-related AEs were fatigue, de-

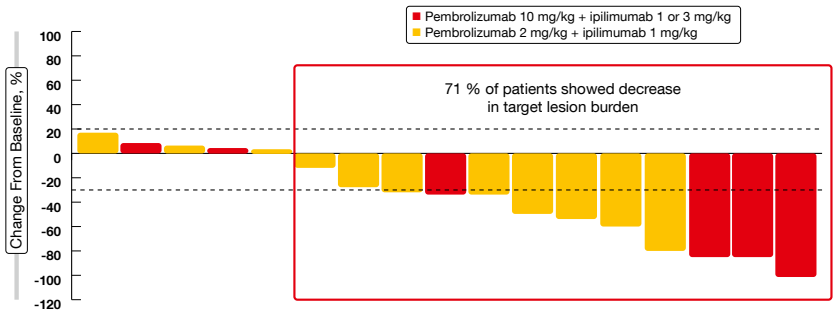

Figure 3: Reductions in target lesions with pembrolizumab plus ipilimumab in KEYNOTE-021

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creased appetite, myalgia, pruritus and rash.

The preliminary evidence on efficacy has indicated robust, durable antitumour activity in an unselected population. In the pembrolizumab 2 mg/kg plus ipilimumab 1 mg/kg dose group, an ORR of 33 % was achieved. Partial responses were 33 %, and disease stabilisation for at least 6 weeks was achieved in 42 %. The DCR was 75 %. 71 % of patients showed decreases in target-lesion burden (Figure 3). All of the responses were ongoing at the time of data cut-off. The combination will be further characterised in a currently enrolling dose-expansion cohort of 32 patients. ■

Statement: Alex A. Adjei, MD, PhD, FACP, Roswell Park Cancer Institute, New York, USA

"Select the patients who will be able to benefit"

Alex A. Adjei, MD, PhD, FACP, Roswell Park Cancer Institute, New York, USA

At this ASCO Congress, the biggest news in the field of NSCLC was the effects of the checkpoint inhibitors in the treatment of this disease. This applies especially to the results of the CheckMate 057 trial. The PD-1 inhibitor nivolumab is one of the first checkpoint inhibitors to be approved in lung cancer; it was approved in the United States for the treatment of squamous NSCLC early in 2015. CheckMate 057 assessed nivolumab in the non-squamous patient group. This trial was conducted in the second-line setting. The study revealed a significant survival benefit of nivolumab as compared to standard second-line chemotherapy with docetaxel. Nivolumab was well tolerated. These results are certainly going to change our practice.

One interesting facet of the study consisted of the evaluation of PD-L1 expression by means of immunohistochemistry. If this assay is validated, it will be a very important predictive tool. The study showed that nivolumab-treated patients whose tumours highly express PD-L1 had a significant survival advantage. These are patients in the second line whose median survival exceeds 19 months, compared to only 8 months for chemotherapy. In contrast, the outcomes of nivolumab-treated patients whose tumours did not express PD-L1 were identical to those of chemotherapy-treated patients.

One of the aspects we do not address to a sufficient degree, but which is certainly going to be of concern, is that many of these novel agents are very expensive. Therefore, being able to select the patients who will be able to benefit from the treatment is advantageous for the patients themselves, because they do not receive therapies that do not work for them. On the other hand, there is an advantage for society at large, as money will not be spent on futile treatments. ■

Novel approaches in small-cell lung cancer

Small-cell lung cancer (SCLC) accounts for approximately 15 % of all lung cancers, and it is associated with poor outcomes [1]. 70 % of these patients present with extensive disease. Their treatment remains a significant challenge for oncologists. The median survival in the extensive disease stage is 7 months to 9 months, and only 2 % of patients survive for 5 years [2]. So far, many attempts to improve upon these results in the first-line setting have failed.

Patients with SCLC usually respond to initial platinum-based chemotherapy, but the response is rapidly followed by progression. After that, treatment options become limited. At the ASCO Congress, the results obtained with two new

chemotherapy approaches were presented, as well as data on two trials that explored immunotherapeutic agents in relapsed disease.

Toxicity-adjusted chemotherapy dosing: STAD-1

The STAD-1 trial attempted to optimise chemotherapy by comparing toxicity-adjusted dosing of cisplatin and etoposide with fixed dosing of the same drugs in patients with advanced SCLC [3]. This concept is based on the observation that haematological toxicity due to cytotoxic agents might serve as a surrogate biomarker of drug activity. Between 2008 and 2014, 11 Italian centres participated in this trial. A total of 161 chemotherapy-naïve patients were randomly assigned to either fixed-dose cisplatin 80 mg/m² on day 1 plus etoposide 100 mg/m² on days 1 to 3, every 3 weeks (n = 81), or to dose adjustment of both cisplatin and etoposide within a range of eight dosing levels (level -2 to level +5; Table 1) according to the toxicity after the start of the treatments (n = 80). If grade 2 to grade 4 neutropenia or unacceptable toxicity were not present in a given cycle, the dose level had to be escalated for the next cycle. De-escalation occurred for unacceptable toxicity. The ORR was defined as the primary endpoint of the trial.

As expected, the side effects increased considerably in the experimental arm, where there was a predominance of severe AEs (grade ≥ 3) at 30 % over the control arm (90 % vs. 60 %; p < 0.0001). Six deaths occurred during treatment, one in the control arm (for unknown reasons), and five in the experimental arm (3 infections, 1 febrile neutropenia, 1 vascular death). However, no differences between the two approaches were observed regarding the ORR (57 % vs. 54 %, for the toxicity-adjusted and fixed-dose therapies, respectively), PFS (5.6 vs. 6.0 months) and OS (9.2 vs. 9.6 months). There was a higher range of doses in the experimental group, but the median dose intensities did not differ between these treatment arms.

Table 1: STAD-1: Dose escalation algorithm used in the absence of toxicity

	Cisplatin (mg/m²)	Etoposide (mg/m²)
Level - 2	stop	stop
Level - 1	60 (- 25 %)	80 (- 25 %)
Level 0	80	100
Level + 1	100 (+ 20 %)	120 (+ 20 %)
Level + 2	110 (+ 10 %)	120 (-)
Level + 3	110 (-)	135 (+ 12.5 %)
Level + 4	120 (+ 9 %)	135 (-)
Level + 5	120 (-)	150 (+ 11 %)

MATISSE: palifosfamide as part of the team

Another strategy that was aimed at improving standard platinum chemotherapy for extensive-stage SCLC was tested in the MATISSE trial [4]. A prior phase III study demonstrated improved survival with etoposide plus cisplatin and ifosfamide over etoposide plus cisplatin alone [5]. However, increased toxicity occurred. Also, the administration of ifosfamide requires hospitalisation and the administration of mesna for the prevention of drug-induced haemorrhagic cystitis. Therefore, research efforts focused on the identification of an equally effective but less toxic third drug.

The multi-centre, open-label, MATISSE study tested the addition of palifosfamide 130 mg/m² on days 1 to 3 to etoposide 100 mg/m² on days 1 to 3 and cisplatin AUC 4 on day 1 as compared to etoposide 100 mg/m² on days 1 to 3 plus cisplatin AUC 5 on day 1, for 4 to 6 cycles. Overall, 118 chemotherapy-naïve patients participated in the study, with OS defined as the primary outcome.

The addition of palifosfamide indeed added little toxicity to this comparator regimen, but it did not give rise to any improvement in the OS either. On the contrary, survival was numerically inferior in the experimental arm (10.0 vs. 10.4 months). MATISSE was closed prematurely, and palifosfamide is no longer being developed for the treatment of SCLC.

Preliminary results on pembrolizumab: KEYNOTE-028

Pembrolizumab, an anti-PD-1 monoclonal antibody, has shown antitumour activity in multiple advanced malignancies. The KEYNOTE programme is investigating pembrolizumab in a variety of tumour types. Patients with SCLC have been included in the ongoing KEYNOTE-028 phase Ib multicohort study that is assessing pembrolizumab monotherapy in PD-L1–positive solid tumours [6]. In the SCLC cohort, 20 patients who were not able to receive standard therapy or who had experienced treatment failure were treated with pembrolizumab 10 mg/kg IV every 2 weeks. If complete or partial responses or stable disease was achieved, the therapy was continued for 24 months or until progression.

Pembrolizumab was shown to be generally well tolerated and to have promising antitumour activity. The overall response rate was 35 %, and stable disease occurred in 5 % of these patients. At the time of the data cut-off, six of seven responses were ongoing. However, as the authors pointed out, these results are still early. The safety and toxicity profiles are consistent with previous observations for pembrolizumab in patients with other tumour types.

CheckMate 032: concurrent nivolumab and ipilimumab

Combined block of the PD-1 and CTLA-4 immune checkpoint pathways shows solid antitumour activity, with a manageable safety profile. The open-label, randomised, CheckMate 032 phase I/II study investigated the fully human IgG4 PD-1 immune checkpoint inhibitor nivolumab with or without the CTLA-4 checkpoint inhibitor ipilimumab for the treatment of recurrent SCLC [7].

Platinum-sensitive and platinum-refractory patients with progressive disease after at least one prior line of therapy (including a platinum-based regimen in the first line) participated regardless of their tumour PD-L1 status or number of prior chemotherapy regimens. They were randomised to either nivolumab monotherapy at a dose of 3 mg/kg every 2 weeks or to the combination of nivolumab and ip-

Table 2: Clinical activities of nivolumab monotherapy and nivolumab plus ipilimumab

	Nivolumab (n = 40)	Nivolumab + ipilimumab (n = 46)
ORR, n (%)	7 (18)	15 (32.6)
CR, n (%)	0	1 (2.2)
PR, n (%)	7 (18)	14 (30.4)
SD, n (%)	8 (20)	17 (37)
DCR, n (%)	15 (38)	25 (54.3)
PD, n (%)	21 (53)	17 (37)
Death prior to first response assessment, n (%)	4 (10)	3 (6.5)
Not evaluable (no tumour assessment follow-up)	0	1 (2.2)
Median time to objective response, months	1.6	2.1
Median duration of response (95 % CI) Range	NR 4.1-11+	6.9 (1.5, NR) 1.5-11.1+

ORR, objective response rate; CR, complete response; PR, partial response; SD, stable disease; DCR, disease control rate; PD, progressive disease.

ilimumab IV. While 40 patients received nivolumab alone, 50 were treated with nivolumab 1 mg/kg plus ipilimumab 1 mg/kg IV or nivolumab 1 mg/kg plus ipiliumumab 3 mg/kg IV, every 3 weeks, for 4 cycles. After these 4 cycles of the combination, all of the patients received nivolumab 3 mg/kg every 2 weeks, as maintenance therapy.

Approximately half of the patients in the combination arm and one third of those in the monotherapy arm were treated in the second-line setting. The other trial participants were treated in the third line and beyond. One third of the entire cohort were platinum-refractory. At the time of assessment of clinical activity, the experimental arm consisted of 46 patients, as four had not reached the first tumour assessment at the database lock.

Immunotherapy shows promise

As the primary objective, the ORR was higher for the combination than for nivolumab monotherapy (32.6 % vs. 17.4 %; Table 2). Partial responses occurred in 30.4 % vs. 18.0 % of the patients in the experimental and control arms, respectively. Importantly, durable responses were observed. Overall, DCR achieved with nivolumab plus ipilimumab was superior to nivolumab monotherapy (54.4 % vs. 38 %). The median OS was 8.2 months and 4.4 months, respectively. A subset analysis of the second-line patients demonstrated that even patients with platinum-refractory disease experienced profound responses to both of these therapies. The onset of responses was generally rapid. Occasional pseudo-progression was followed by tumour regression. PD-L1 expression did not appear to be predictive for the responses, as many PD-L1-negative patients responded well to both combination therapy and monotherapy.

The safety profiles of both of these treatment regimens were consistent with those seen in other tumour types, and these were managed according to the established safety guidelines. Treatment-related AEs occurred more frequently in the combination arm (77 % vs. 53 %). This was also true for grade 3/4 AEs (34 % vs. 15 %). Of note, diarrhoea, rash, hypothyroidism, hyperthyroidism, and lipase elevations were seen mainly in the experimental arm. There were no grade 3/4 cases of pneumonitis in the nivolumab arm, while one patient was affected in the combination cohort. Development of autoimmune disease (myasthenia gravis) or paraneoplastic syndromes is a possible issue, however. Three patients developed limbic encephalitis, which was resolved under immunosuppressive treatment in two cases.

Based on these encouraging results, nivolumab monotherapy and the combination therapy with ipilimumab will be explored in future SCLC trials. ■

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Further analyses of biomarkers

Immune checkpoint inhibitors have become established as standard therapy for certain subsets of NSCLC patients. Efforts are ongoing to optimise the benefits gained through these drugs, by identification of reliable prognostic and predictive biomarkers, such as PD-L1 expression in tumour cells or infiltrating immune cells, CD8-positive tumour-infiltrating lymphocytes, smoking status, and mutation burden. The necessity for collaboration in this field is obvious; as yet, progress in the area of immuno-oncological biomarkers has been impeded by marked variations with regard to development and reporting (e.g., different cut-offs).

Targets of immune checkpoint inhibitors

An analysis of the tumour samples of 208 patients with NSCLC assessed the prognostic relevance of PD-L1, PD-1 and CTLA-4 [1]. PD-L1 protein expression in tissue microarrays of archival tumour samples was tested using IHC. Mutations, expression, and copy-number variations in the PD1, PD-L1 and CTLA-4 genes were retrieved from the publicly available The Cancer Genome Atlas (TCGA) database. The scientists estimated the differences in disease-free survival and OS between patients with high and low PD-L1 protein expression, using univariate and multivariate survival analyses. The prognostic impact of genetic alterations was assessed in the overall population and in subsets of adenocarcinoma, squamous cell carcinoma, smokers and non-smokers.

The analysis showed that there is higher PD-L1 expression in smokers, non-squamous carcinoma, and females, with no significant differences found according to race and tumour stage or grade. Higher normalised PD-1 gene expression correlated with improved patient survival. Mutations of the PD-1, PD-L1 and CTLA4 genes were very rare in NSCLC and showed no association with survival. According to the conclusions of the authors, the PD-L1 protein, but not PD-L1 gene expression, might have value as a prognostic marker in early-stage NSCLC.

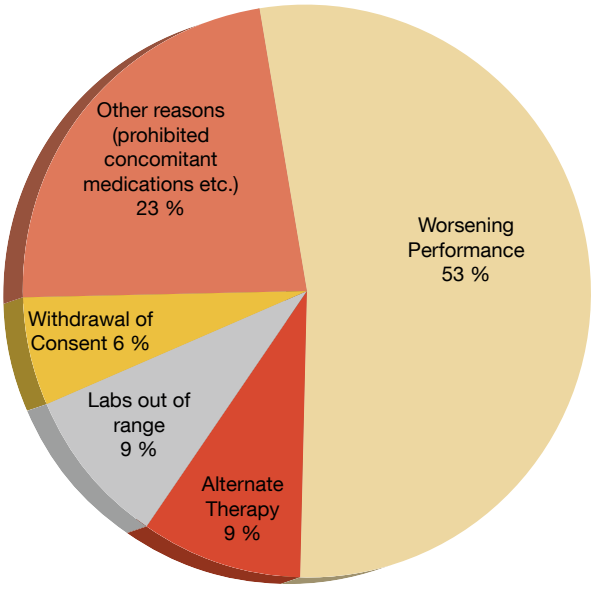

Figure: Reasons for screening failure in patients who had consented to trials involving bioptic biomarker sampling and were eligible according to biomarker status

PD-L1 and immune infiltrates

There has been interest in combining PD-1/PD-L1 inhibitors with EGFR or ALK TKIs in NSCLC, because data has suggested that there are links between the underlying molecular principles. For instance, a PD-1 block can improve survival in EGFR-mutant mouse models [2]. Several trials involving EGFR TKIs or ALK TKIs and PD-1/PD-L1 inhibitors are currently ongoing.

Therefore, a retrospective analysis investigated PD-L1 expression patterns and immune infiltrates in NSCLC patients with EGFR mutations (n = 68) and ALK rearrangements (n = 26) [3]. This showed that EGFR-mutant and ALK-positive lung cancers can express PD-L1 and have CD8+ immune infiltrates, although most of these tumours do not have both. As the authors noted, this might underlie the low response rates that were seen with PD-1 pathway inhibition in never smokers and light smokers in the CheckMate 057 trial [4]. In a subset of patients, there were changes in PD-L1 expression and immune infiltrates over time and/or following treatment. Future studies with early, 'on-treatment' biopsies would be necessary to determine whether immune cells can be recruited to the tumour environment following the initial treatment with TKIs.

Reasons for screening failure

As trials for NSCLC increasingly involve small patient populations expressing specific molecular abnormalities, many studies now require evaluation of a fresh biopsy prior to enrolment. This is not feasible for all research sites. Moreover, the implications of potentially increased screening duration on the interpretation of clinical outcomes have not been completely explored yet.

To identify factors associated with lack of enrolment, researchers reviewed the charts of 268 patients with NSCLC who had consented to participate in a total of 26 trials requiring biopsies for

evaluation of certain biomarkers as part of the patient eligibility. Out of these 268 patients, 141 failed this screening and were thus included in the analysis. 24 % of these were eligible based on biomarker status. The results demonstrated that apart from the presence or absence of a specific biomarker, many factors can lead to screening failure. The reasons included worsening performance status in 52.9 %, pursuit of alternate therapy in 8.8%, out-of-range screening laboratory values in 8.8 %, withdrawal of consent in 5.8 %, and other reasons in 23.5% (Figure).

Due to disease progression, many patients had worsening performance status at the time of initiation of the study, as well as abnormal laboratory values. The time that elapsed between the signing of the informed consent and the beginning of the trial was approximately 35 days. Whether such a delay in enrolment based on the duration of the screening either excludes patients who would have been more likely to experience early decline or enrols patients who have become more ill during screening needs to be fully explored. ■

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Interview: Barbara Melosky, MD, FRCPC, University of British Columbia and British Columbia Cancer Agency, Vancouver, Canada

"These findings will change the standard-of-care"

Barbara Melosky, MD, FRCPC, University of British Columbia and British Columbia Cancer Agency, Vancouver, Canada

Will findings presented here at ASCO change the future of NSCLC therapy?
This year's ASCO Congress was very interesting. The findings will definitely change the standard-of-care in non–small-cell and small-cell carcinoma. Immune checkpoint inhibitors are the biggest news at this year's ASCO Congress. They are showing survival advantages in small-cell cancer, and advantages have also been proven in squamous and non-squamous NSCLC in the second line. This is going to change the landscape and the standard-of-care, especially in the second-line setting, in both squamous and non-squamous NSCLC. Nivolumab has now been accepted by the FDA for the treatment of squamous cell carcinoma in the second-line setting.

Which molecular targets deserve the greatest attention at present?
There are many molecular targets and many ways to define molecular targets. We learnt that RET is an interesting target to look at; we learnt that new drugs are available for ALK; also, EGFR continues to be an extremely important issue with the emergence of third-generation EGFR inhibitors. Immunotherapy as a sort of targeted therapy against the immune system is also emerging as a major player in NSCLC and in SCC.

Should lung cancer in women be considered a "different disease"?
Lung cancer in women is an extremely important issue. We used to think that it was a different disease. I think what we are learning is that it is a different disease molecularly, because of issues like smoking. If we thus were to equalise patients for some of those other issues like smoking, we might find that we should treat male and female patients alike.

What potential promises and pitfalls are currently associated with immune checkpoint blockade in cancer treatment?
The biggest pitfall is the PD-1 or PD-L1 biomarker expression. One has to face questions as to which kit one should use, whether to assess the expression in the T cells or in the tissue or in the stroma, and which cut-off percentage to use – 1, greater than 5, greater than 10, or none? Therefore, the biggest pitfalls are the application of biomarkers, and of course the cost. ■

Phase III results in local and regional lung cancer

PROCLAIM: chemoradiotherapy followed by pemetrexed consolidation

The standard-of-care for inoperable stage III NSCLC is concurrent chemoradiotherapy. However, the role of consolidation chemotherapy remains controversial. The multi-targeted antifolate pemetrexed shows selective activity in non-squamous NSCLC. Choy et al. demonstrated that pemetrexed-platinum combinations can be administered at full systemic doses with concurrent thoracic radiotherapy (TRT) [1].

The randomised phase III PROCLAIM study was initiated to determine whether the concurrent administration of pemetrexed/cisplatin and TRT followed by consolidation treatment with pemetrexed provides any survival advantage compared to a commonly used chemoradiation regimen followed by a consolidation regimen of choice. Previously untreated patients with stage IIIA or IIIB non-squamous NSCLC were randomised to either pemetrexed/cisplatin plus TRT for 3 cycles (n = 301), or to etoposide/cisplatin plus TRT for 2 cycles (n = 297). This concurrent phase was followed by a recovery period lasting 3 weeks to 5 weeks.

Patients who achieved partial response, complete response or stable disease moved on to the consolidation phase. Here, the experimental arm received pemetrexed for 4 cycles (n = 229), whereas the control arm was treated with consolidation according to the investigator's choice (etoposide/cisplatin, or vinorelbine/cisplatin, or paclitaxel/carboplatin) for 2 cycles (n = 202). The OS was defined as the primary outcome. At the ASCO Congress, the final overall results were presented [2].

Acceptable safety findings

PROCLAIM did not demonstrate superiority of the pemetrexed-based regimen with regard to OS. No differences were noted for the median outcomes (26.8 vs. 25.0 months with pemetrexed/cisplatin and etoposide/cisplatin, respectively; p = 0.831). This was also true for OS rates at 2 years (52 % each) and 3 years (40 %, 37 %, respectively). The subgroup analysis did not clearly favour any of the two regimens. For PFS, there was a trend in favour of the experimental treatment (11.4 vs. 9.8). The risk of progression was lower by 14 % in the experimental arm, but this difference was not statistically significant (p = 0.130).

Table: PROCLAIM: Response rates observed in the study

Response (%)	Experimental arm	Control arm	p value
Complete response (CR)	1.3	0	
Partial response (PR)	34.6	33.0	
Stable disease (SD)	44.9	37.7	
Progressive disease	3.7	6.4	
Unknown/ not assessed	15.6	22.9	
ORR (CR + PR)	35.9	33.0	0.458
DCR (CR + PR + SD)	80.7	70.0	0.004

Furthermore, ORRs did not differ significantly between the two regimens (35.9 % vs. 33.0 %; p = 0.458). For DCR, however, the pemetrexed-treated patients experienced a significant benefit (80.7 % vs. 70.7 %; p = 0.004; Table), which was mostly due to a higher rate of stable disease (44.9 % vs. 37.7 %). For local relapse, both within the radiation field and inside the thorax but outside of the radiation field, there were no significant differences between the two treatment arms. This also applied to distant relapse and CNS disease.

In terms of safety, the pemetrexed-based regimen showed higher tolerability. The proportion of patients experiencing at least one drug-related grade 3 to 5 AE was markedly lower at 67.8 %, versus 79.4 % in the control arm. Administration of the control regimen was more frequently associated with neutropenia, thrombocytopenia, and alopecia. In contrast, the experimental treatment gave rise to higher rates of mucositis and stomatitis, as well as pneumonitis, which counted among the radiation-related toxicities. Grade 3/4 pneumonitis was more frequent in the control arm, however (1.8 % vs. 2.6 %). Grade 3/4 oesophagitis, as another radiation-related toxicity, was also more common in the control group (15.5 % vs. 20.6 %). The authors noted that pemetrexed/cisplatin combined with radiotherapy and followed by consolidation treatment with pemetrexed showed an acceptable safety profile.

SCAT: adjuvant chemotherapy according to BRCA1

Post-operative platinum-based chemotherapy improves outcomes in completely resected NSCLC with nodal involvement (stage II to IIIA). Survival outcomes remain limited, however. Also, the compliance issue can be vital in the adjuvant setting, and patient compliance was lower with this treatment than with adjuvant therapy in other tumour types.

Attempts to optimise results are based on the rationale that the analysis of expression of genes involved in DNA repair might be used to individualise optimal chemotherapy drug use. BRCA1 is known to have a role in the homologous recombination nucleotide excision repair pathway and to function as a differential regulator of response to cisplatin and anti-microtubule agents. BRCA1 levels can serve as both prognostic and potentially predictive factors. Low levels signify low risk and cisplatin sensitivity, while high levels are indicative of high risk and cisplatin resistance.

In the randomised, phase III, adjuvant SCAT trial, treatment was customised to BRCA1 status [3]. Patients with resected NSCLC and node involvement (R0 pN1/

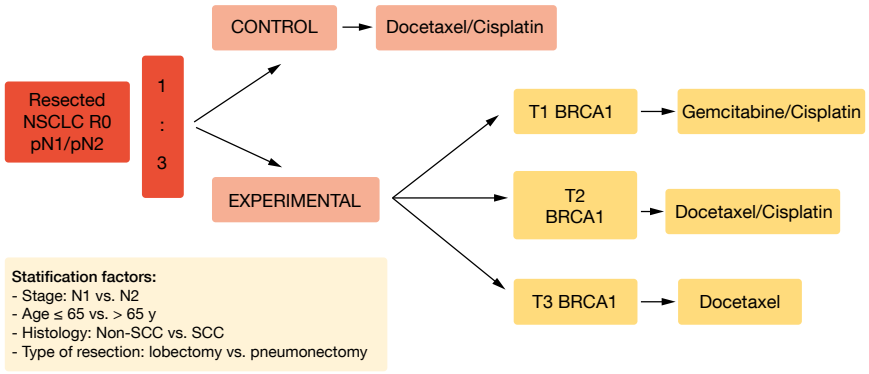

Figure: Design of the SCAT trial

pN2) were randomly assigned to either docetaxel plus cisplatin (n = 108) or experimental therapy that was administered according to the BRCA1 levels (n = 392; Figure). Patients with low levels received gemcitabine/cisplatin; patients with intermediate levels were treated with docetaxel/cisplatin, and those with high levels received single-agent docetaxel. Post-operative radiotherapy was applied in patients with N2 disease. The primary endpoint was OS.

Differential effects according to BRCA1 levels

BRCA1 expression levels were higher in tumours with squamous histology than in those with adenocarcinoma histology. For OS, a trend favoured experimental therapy over control therapy (HR, 0.86). In the subgroup with high BRCA1 levels, DFS and OS were inferior in the experimental arm that had received no cisplatin. Opposite results were noted in the group of patients with low BRCA1 levels: Here, the outcomes were better for those who had been treated with cisplatin/gemcitabine in the experimental arm than for patients receiving cisplatin/docetaxel in the control arm, with a HR for OS of 0.50. With regard to histology, no differences between the groups were seen for OS in squamous carcinoma, while in the adenocarcinoma group, there was a clear trend that indicated benefit in the experimental arm (HR, 0.66).

The full dose of planned treatment conferred a survival advantage (HR, 0.63; p = 0.04). Patients treated in the experimental arm required fewer dose reductions. No differential effects of the tested treatments were observed according to lymph node status.

Overall, this customisation of adjuvant chemotherapy according to BRCA1 levels was demonstrated to be feasible in node-positive resected NSCLC, although it did not significantly improve OS. The authors emphasised that longer follow-up is needed to confirm these data, as the median survival has not been reached yet. ■

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Forthcoming Special Issue

This special issue will be offering a synopsis from the biennial European Cancer Congress that will be held in Vienna, Austria, in September of this year. The report promises to make for stimulating reading, as the ECC 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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*** Indication and usage:** VARGATEF® is indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.

Note: The information presented here is intended for NON-US, NON-UK, NON-Canadian healthcare professionals only. To allow quick identification of new safety information, please report any suspected adverse reactions. Please refer to the Summary of Product Characteristics (SmPC) for detailed information.

Procedure ID: 4247 - August 2015. Brief prescribing information page 18.

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