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Congress Report ELCC 2019

A GLOBAL CONGRESS DIGEST ON LUNG CANCER

Report from the European Lung Cancer Congress (ELCC), 10th–13th April, Geneva, Switzerland

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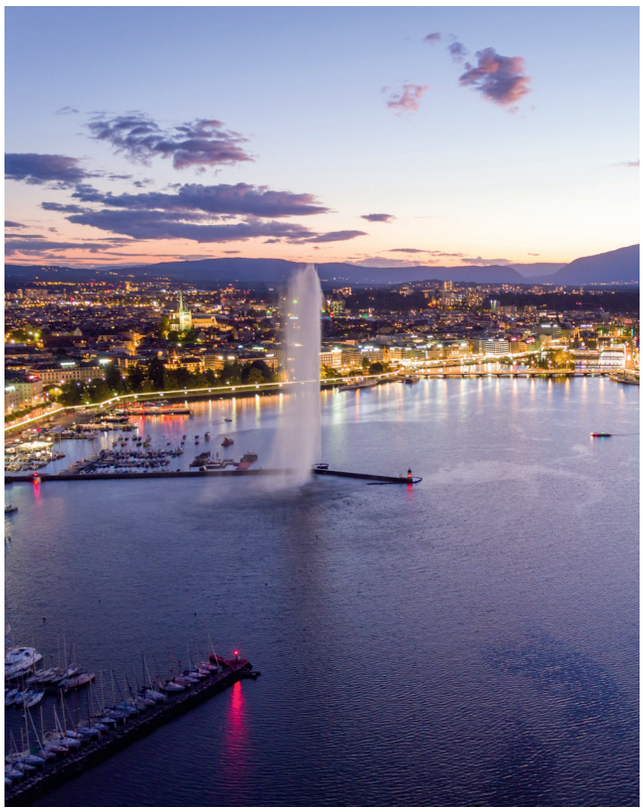

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Preface

Dear Colleagues,

The annual European Lung Cancer Congress has become a global conference attracting experts in the field of lung cancer from all over the world. At this year's conference, which took place in Geneva from 10th to 13th April, more than 120 speakers shared their knowledge with around 1,600 delegates from 75 countries. The comprehensive program that included a wide range of session types and the presentation of 210 abstracts aimed at conveying a broad view of the current knowledge ranging from screening and the very early disease to current and potential future treatment approaches for different types of thoracic tumors. Interdisciplinarity is called for in a setting where patient management requires a multitude of treatment strategies and thus the joint efforts of experts in various fields. This is mirrored by the variety of societies for thoracic oncology that contributed to the congress. The European Society for Medical Oncology (ESMO) and the International Association for the Study of Lung Cancer (IASLC) organized the conference in collaboration with the European Society for Radiotherapy and Oncology (ESTRO), the European Society of Thoracic Surgeons (ESTS), and the European Thoracic Oncology Platform (ETOP).

This publication summarizes a selection of abstracts presented at ELCC 2019 in the areas of targeted therapy and immunotherapy for both non–small-cell and small-cell tumors of the lung. New targets are gaining importance in view of the availability of efficacious therapies. Moreover, established targeted agents have been shown to improve outcomes in tumors with rare oncogene drivers to a clinically significant extent even in the pretreated setting. Updated results in *ROS1*-rearranged lung cancer demonstrate unprecedented survival rates that might announce the dawn of chronic disease courses as it has been observed for other types of cancer. Several analyses of studies investigating PD-1 and PD-L1 inhibition presented at the congress confirmed the clinical utility of immune checkpoint inhibitors particularly in patients without oncogene-addict tumors.

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Finally, two interviews with renowned experts will elaborate on markers that can increase the accuracy of lung cancer screening and will debate about the potential role of chemotherapy in the era of novel approaches that have changed the outlook for our patients so profoundly as to strike up a new age of lung cancer treatment.

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Current perspectives in EGFR-targeted therapy

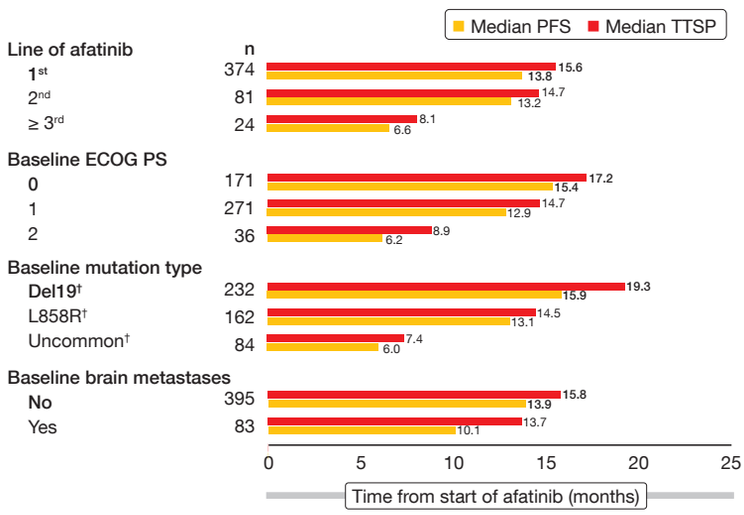
Global phase IIIb study assessing afatinib

The second-generation, irreversible ErbB family blocker afatinib has been established as a first-line standard option in patients with *EGFR*-mutant NSCLC based on the phase III LUX-Lung 3 and 6 trials that revealed significant progression-free survival (PFS) and objective response rate (ORR) improvement compared to platinum-doublet chemotherapy [1, 2]. Moreover, the phase IIb LUX-Lung 7 study showed significant benefits regarding PFS, ORR and time to treatment failure with afatinib compared to the first-generation EGFR tyrosine kinase inhibitor (TKI) gefitinib [3]. An open-label, multicenter, phase IIIb trial conducted in Europe, Israel and Australia is currently assessing afatinib 40 mg/day until disease progression in the real-world setting. Two dose reductions to 30 mg or 20 mg/day can be performed based on individual tolerability. Asymptomatic brain metastases are allowed.

A total of 479 patients were included in the interim analysis presented at ELCC 2019 [4]. Seventeen percent of these had brain metastases, 18 % had uncommon *EGFR* mutations, with exon 20 insertions representing the most frequent type, and the ECOG performance status was 1 and 2 in 57 % and 8 %, respectively. Seventy-eight percent and 17 % received afatinib as first- and second-line therapy, respectively. Thus, the population reflected real-life conditions. Safety was defined as the primary endpoint of the interim analysis, with PFS, time to symptomatic progression (TTSP), ORR and disease control rate (DCR) defined as efficacy endpoints.

Overall, the results were consistent with those observed for afatinib in the LUX-Lung 3, 6 and 7 trials. Afatinib showed a predictable and manageable

safety profile. Diarrhea and rash were the most common adverse events (AEs) and the main reasons for dose reductions, which became necessary in 54 %. In 8 %, patients had AEs leading to treatment discontinuation, most commonly diarrhea. Each of the other AEs causing discontinuation accounted for < 1 % of these cases. Also, the interim analysis revealed encouraging efficacy findings, with median PFS of 13.37 months and TTSP of 14.91 months. The activity of afatinib in patients with brain metastases was confirmed; this group had median PFS and TTSP of 10.1 and 13.7 months, respectively (**Figure 1**).



PFS, progression-free survival
TTSP, time to symptomatic progression

Figure 1: Median PFS and TTSP with afatinib in real-world practice according to line of treatment, performance status, mutation type, and presence of brain metastases

GIDEON: real-world evidence from Germany

The prospective, non-interventional GIDEON study investigated the efficacy and tolerability of first-line afatinib when used in routine clinical practice in Germany. GIDEON enrolled a high proportion of patients aged ≥ 70 years, thus providing an opportunity to study the real-world use of afatinib in older individuals. PFS at 12 months constituted the primary endpoint, while PFS, overall survival (OS), ORR and DCR were secondary outcomes. Overall, 151 patients were treated, 67 (44 %) of whom were ≥ 70 years old. Among these elderly patients, 22 % had brain metastases at inclusion, and rare mutations were present in 18 %.

Brückl et al. reported the results from a post-hoc analysis of older patients included in the first interim analysis of the study [5]. These findings supported the use of afatinib in the elderly, as the outcomes even exceeded those obtained in the overall study population. The 12-month PFS rate amounted to 62 % (12-month PFS in the entire population, 54.6 %), with median PFS of 17.3 months (vs. 12.9 months). ORR and DCR were 78 % and 93 %, respectively (vs. 73 % and 90 %, respectively).

Furthermore, the safety profile of afatinib in elderly patients was comparable to that seen in the younger subgroup. Grade ≥ 3 treatment-emergent AEs were similar in patients aged ≥ 70 years and < 70 years, with diarrhea occurring most commonly. There was a trend towards lower starting doses in older patients, with 40 mg used as initial treatment in 62 % vs. 83 % for the younger cohort, although the percentages of patients requiring dose reductions appeared comparable across age groups (55 % vs. 58 %).

First-line outcomes for osimertinib

Two phase I expansion cohorts of the AURA study evaluating first-line treatment with the third-generation, irreversible EGFR TKI osimertinib have yielded robust ORR and prolonged PFS in patients with locally advanced or metastatic *EGFR*-mutant NSCLC [6]. Sequential patient cohorts of 30 patients each received osimertinib 80 mg or 160 mg/day until progression. The final efficacy and safety data from these expansion cohorts were presented by Yang et al. at ELCC 2019 [7].

Osimertinib 80 mg showed durable clinical activity and manageable tolerability. Confirmed ORRs were 67 % and 87 % for the 80 mg and 160 mg cohorts, respectively. Median duration of response was 19.3 and 16.7 months, respectively, and median PFS 22.1 and 19.3 months, respectively. The safety profile of osimertinib 80 mg was consistent with previous reports. AEs prompting dose reductions occurred in 35 % of patients overall and were more common in the 160 mg cohort than in the 80 mg cohort (53 % vs. 17 %). In total, 12 % of patients discontinued treatment due to AEs. The investigators concluded that the final results support the use of osimertinib as first-line therapy for patients with *EGFR*-mutant NSCLC. The 80 mg dose was confirmed as the optimal and therefore recommended dose.

Four-drug activity after EGFR TKI failure

There is an urgent unmet need after failure of first-line EGFR TKIs, as these patients have limited treatment options. A potential approach is the concomitant use of anti-angiogenic agents and immunotherapy in addition to chemotherapy. The randomized, three-arm IMpower150 trial assessed the combination of the anti-PD-L1 antibody atezolizumab, carboplatin/paclitaxel and the anti-VEGF antibody bevacizumab (Arm B) compared to atezolizumab plus chemotherapy (Arm A) and chemotherapy plus bevacizumab (Arm C). IMpower150 was conducted in an all-comer population with stage IV or recurrent metastatic non-squamous NSCLC (n = 1,202) and showed significant benefits for both PFS and OS in Arm B vs. Arm C [8, 9].

The study included patients with *EGFR* mutations who had experienced progression or intolerance to treatment with at least one approved targeted agent (n = 124). Out of these, 45, 34, and 45 were treated in Arms A, B, and C, respectively. At ELCC 2019, Reck et al. presented an exploratory analysis of efficacy outcomes in *EGFR*-positive patients [10]. This showed that the four-drug

combination of atezolizumab, carboplatin, paclitaxel and bevacizumab improved clinical outcomes in the *EGFR*-mutant group. Arm B experienced prolonged PFS compared to Arm C (10.2 vs. 6.9 months), which also applied to OS (median OS, not reached vs. 18.7 months). The addition of atezolizumab to bevacizumab and chemotherapy increased both PFS and OS benefits across all subgroups of *EGFR*-positive patients. Moreover, patients in Arm B fared best with respect to ORR (71 % vs. 36 % and 42 % in Arms A and C, respectively; **Figure 2**) and duration of response (11.1 vs. 5.6 and 4.7 months, respectively). In contrast, comparisons across Arms A and C did not yield any significant differences regarding PFS or OS.

The safety profile observed in the *EGFR*-positive patients was comparable to that seen in the ITT population, which was also true for immune-related AEs. Treatment-related AEs occurred slightly more often in Arm B compared to Arms A and C. According to these results, the combination of atezolizumab, bevacizumab and platinum-based chemotherapy might represent a potential new option for patients with *EGFR*-mutant lung cancer in whom EGFR TKI treatment has failed.

Mechanisms of resistance

PD-L1 not only negatively regulates T cell function, but also leads to acquired resistance to EGFR TKIs in the NSCLC setting. Zhang et al. evaluated the mechanistic role of PD-L1 in primary resistance to EGFR TKI treatment [11]. Based on in-vitro studies and a xenograft mouse model, the researchers found that PD-L1 is responsible for primary resistance to gefitinib. Overexpression of PD-L1 attenuated sensitivity to gefitinib in vivo. In all, it appeared that PD-L1 contributes to primary resistance to EGFR TKIs in *EGFR*-mutant NSCLC, which might be mediated through induction of epithelial-mesenchymal transition. This data suggested that PD-L1–targeting immunotherapies are a promising strategy to restore sensitivity to EGFR TKI treatment in primary resistance.

Anlotinib is a novel multi-target receptor TKI that shows activity in the inhibition of tumor angiogenesis and growth. A subset of patients with advanced NSCLC who are refractory to EGFR TKIs are sensitive to anlotinib treatment. Using different types of lung cancer cell lines and a xenograft model, Lian et al. elucidated the mechanisms underlying this effect [12]. They found that FGFR1 contributes to acquired resistance, while anlotinib suppresses proliferation, apoptosis and cell cycles by inhibiting the FGFR1 signaling pathway. FGFR1 might therefore be a potential therapeutic target in patients with *EGFR*-mutant NSCLC and acquired resistance.

Resistance to third-generation treatment

Fassunke et al. provided new insights into acquired resistance mechanisms to third-generation EGFR TKI therapy [13]. The investigators analyzed pre- and post-treatment samples of 124 patients who had developed the T790M resistance on early-generation EGFR TKI therapy and were treated with third-generation TKIs. There was a high prevalence of additional genetic aberrations potentially mediating innate and acquired resistance to third-generation agents. Co-occurring aberrations were found in 75 % of the samples. *TP53* mutations were most frequent among these but had no impact on third-generation TKI treatment.

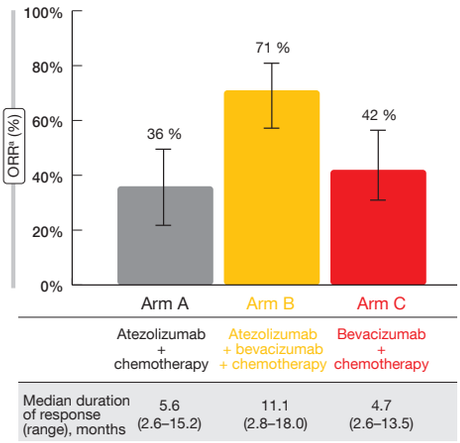


Figure 2: Doubling of response rates and duration of response with atezolizumab plus bevacizumab and chemotherapy compared to the other treatment arms

Genetic changes in the samples with acquired resistance to third-generation EGFR TKIs emerged in the *EGFR* gene (e.g., T790M loss, acquisition of C797S) and in other genes (e.g., *MET* amplification, KRAS mutations). Amplification of *MET* showed a strong association with primary treatment failure and was thus the strongest factor of innate resistance. Loss of T790M and *MET* amplification represented the most common aberrations after third-generation TKI treatment. A new *EGFR* resistance mutation after third-generation TKI therapy is G724S. The authors noted that acquired resistance due to G724S can possibly be overcome using second-generation EGFR tyrosine kinase inhibitors. ■

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Immunotherapy: analyses elucidating durvalumab & pembrolizumab activity

PACIFIC: OS after subsequent immunotherapies

The phase III, randomized, double-blind, international PACIFIC trial established durvalumab in the treatment of patients with stage III, unresectable NSCLC without progression after definitive platinum-based concurrent chemoradiotherapy. Within 6 weeks of chemoradiation, patients were randomized to either durvalumab 10 mg/kg every 2 weeks (Q2W) for up to 12 months (n = 476) or matching placebo (n = 237). PFS and OS were defined as the primary endpoints. Durvalumab provided unprecedented clinical improvement for both outcomes. At the time of the primary analysis, median OS had not been reached in the experimental arm and was 28.7 months in the control arm (HR, 0.68; p = 0.0025) [1, 2]. The survival curves separated early on and remained separated despite the limited treatment duration, which suggests long-term benefit of the PD-L1 inhibitor.

Ouwens et al. explored the question of whether subsequent immunotherapy influenced OS findings in the PACIFIC trial [3]. In the durvalumab and placebo arms, 8 % and 22 % of patients, respectively, received immunotherapy after discontinuation of the study treatment. Other anticancer treatments were administered in 33 % and 32 %, respectively. No subsequent therapy was given in 59 % and 46 %, respectively. The rank-preserving structure failure time model (RPSFTM) was used to adjust OS for subsequent immunotherapy in PACIFIC.

After statistical removal of subsequent immunotherapy, the OS results were consistent with the intent-to-treat (ITT) analysis. The curves were virtually superimposable, and the HRs for the differences between durvalumab and placebo varied only by 0.1 (0.67 and 0.68 for RPSFTM and ITT, respectively; **Figure 1**). Overall, this exploratory analysis of the PACIFIC trial added to the robustness of the data demonstrating durvalumab activity in patients with unresectable, stage III NSCLC.

Effect of PD-L1 expression on PROs

In the PACIFIC study, durvalumab treatment did not cause deterioration of patient symptoms, functioning or global health/quality of life compared to placebo in the ITT population [4]. A retrospective analysis presented at ELCC 2019 investigated the impact of tumor PD-L1 expression on patient-reported outcomes (PROs) to improve the understanding of the benefit/risk profile of durvalumab across all PD-L1 subgroups [5]. PROs (i.e., symptoms, functioning and global health status/quality of life) were assessed using the EORTC QLQ-C30 and QLQ-LC13 questionnaires. A clinically meaningful difference in PROs was defined as a 10-point change in score. Of 713 randomized patients, 451 (63 %) were evaluable for PD-L1 status; among these, 303 (67.2 %) had PD-L1 expression ≥ 1 %, while 148 (32.8 %) were PD-L1–negative. In 262 patients (37 %), the PD-L1 status was unknown.

Similar to the ITT population, the majority of PROs remained stable over time from baseline across all PD-L1 subgroups including those with unknown PD-L1 status, with no clinically meaningful differences for durvalumab vs. placebo. The consistency of results for the PD-L1 subgroups with those of the ITT population suggests that symptoms, functioning and global health status/quality of life were maintained regardless of PD-L1 expression. The authors concluded that these data further support the use of durvalumab after concomitant chemoradiation as the standard of care.

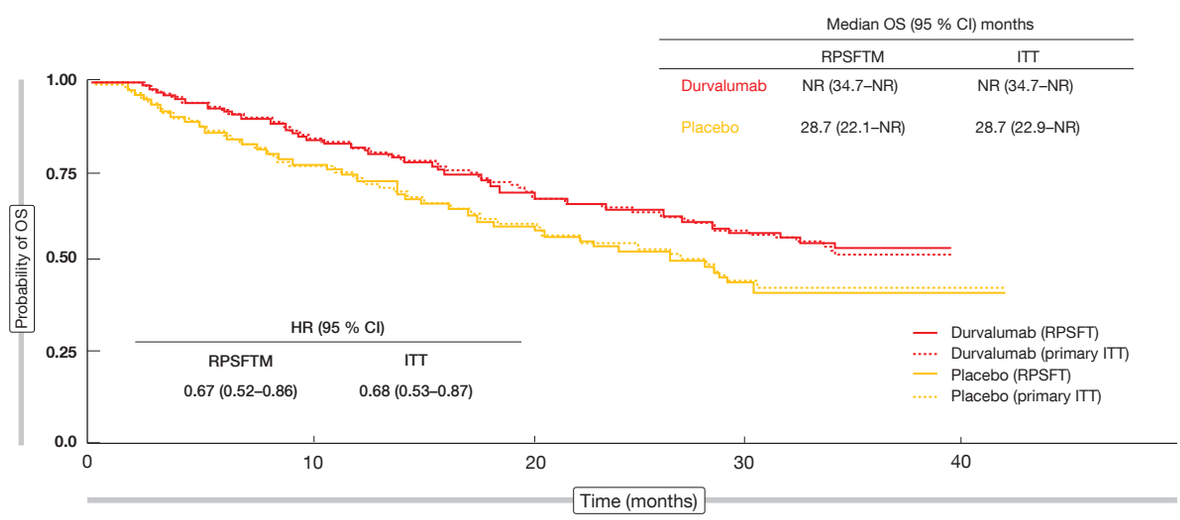

Figure 1: Overall survival adjusted for subsequent immunotherapy in the PACIFIC trial: superimposable curves for durvalumab and placebo according to the ITT and RPSFT analyses

MYSTIC: adjusted survival

The global, randomized, open-label phase III MYSTIC trial evaluated first-line durvalumab (n = 374), durvalumab plus tremelimumab (n = 372), and platinum-based chemotherapy (n = 372) in patients with metastatic NSCLC irrespective of their PD-L1 expression status. The primary endpoints were assessed in patients with PD-L1 expression ≥ 25 % and included PFS for the combination vs. chemotherapy, OS for durvalumab vs. chemotherapy, and OS for the combination vs. chemotherapy. Even though the OS difference for durvalumab vs. chemotherapy did not reach statistical significance due to multiple testing, it was clinically meaningful, with an HR of 0.76 (16.3 vs. 12.9 months; p = 0.036) [6]. At two years, 38.3 % vs. 22.7 % of patients were alive. Likewise, durvalumab plus tremelimumab did not induce a significant OS benefit over chemotherapy (11.9 vs. 12.9 months; HR, 0.85), although the 2-year OS rates were in favor of the combination (35.4 % vs. 22.7 %).

Reinmuth et al. explored the effect of subsequent immunotherapy on the OS outcome with durvalumab compared to chemotherapy in the population with PD-L1 expression ≥ 25 % enrolled in MYSTIC [7]. Subsequent immunotherapy had been administered in 14 % and 67 % of durvalumab- and chemotherapy-treated patients, respectively. Using the 2-stage model to adjust for these imbalances, the investigators found that the OS benefit of durvalumab over chemotherapy was even more pronounced than in the primary analysis, with an HR of 0.66 (median OS, 16.2 vs. 11.5 months; p = 0.002).

Thus, this exploratory analysis suggests that the high rate of subsequent immunotherapy in the control arm confounded the primary OS findings obtained in the MYSTIC study.

Outcomes according to patient characteristics

Another analysis of the MYSTIC trial presented at ELCC related to the treatment efficacy in clinically relevant patient subgroups (i.e., sex, age, percentage of tumor-associated immune cells expressing PD-L1 ≥ 25 % vs. < 25 %, histology, smoking history, ethnicity, ECOG performance status) [8]. Patients with a tumor cell PD-L1 expression ≥ 25 % were included in the OS analyses, which consistently showed favorable HRs for durvalumab *versus* chemotherapy in the defined subgroups. This was in keeping with the primary analysis. For durvalumab plus tremelimumab, the HRs compared to chemotherapy were less favorable across the subgroups. The interpretation of the findings according to immune cell PD-L1 expression was limited due to the restriction to patients with tumor cell PD-L1 expression ≥ 25 % and small sample sizes; here, further investigation is required.

Also, a safety analysis that specifically evaluated higher-grade treatment-related AEs revealed higher rates of these AEs with chemotherapy than with durvalumab or the combination. AEs leading to discontinuation of treatment were slightly more common with durvalumab plus tremelimumab than with durvalumab alone or chemotherapy. Any-grade immune-mediated AEs occurred more frequently with the combination than with durvalumab monotherapy (28.3 % vs. 13.6 %). The authors noted that the safety profile of durvalumab monotherapy and durvalumab plus tremelimumab was manageable and in line with previous results.

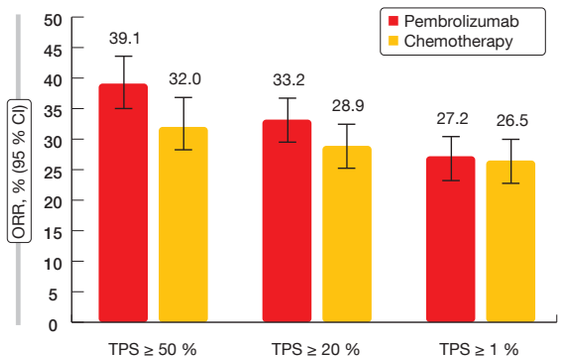

Figure 2: Response rates observed in KEYNOTE-042 according to PD-L1 expression

Final analysis of KEYNOTE-042

Mok et al. reported the final analysis of the KEYNOTE-042 study that tested pembrolizumab vs. platinum-based chemotherapy in patients with PD-L1–expressing locally advanced or metastatic NSCLC [9]. Both treatment arms contained 637 patients. The primary analysis had revealed OS improvement with pembrolizumab 200 mg Q3W for up to 35 cycles compared to carboplatin plus paclitaxel or carboplatin plus pemetrexed for up to 6 cycles at all prespecified PD-L1 cut points (i.e., tumor proportion score [TPS] ≥ 50 %, ≥ 20 %, ≥ 1 %) [10].

After an additional follow-up of 6 months, pembrolizumab treatment continued to confer significant OS improvement over chemotherapy independent of PD-L1 expression. Median OS was longer in patients with PD-L1 TPS ≥ 50 % (20.0 vs. 12.2 months; HR, 0.70), ≥ 20 % (18.0 vs. 13.0 months; HR, 0.77), and ≥ 1 % (16.4 vs. 12.1 months; HR, 0.82). However, the analysis of patients with TPS 1 % to 49 % showed no statistically significant OS benefit (13.4 vs. 12.1 months; HR, 0.91), which implies that the benefit was mostly driven by the group with the highest PD-L1 expression.

No PFS improvement was seen with pembrolizumab vs. chemotherapy for any PD-L1 expression subgroup. In terms of response rates, the results suggested a pembrolizumab-associated advantage in patients with high PD-L1 expression **(Figure 2)**. Duration of response was longer in the experimental arm compared to the control arm across all PD-L1 expression subgroups. This means that once patients benefit from treatment, a durable response of approximately 20 months can be expected irrespective of PD-L1 status. No new safety signals were identified. Overall, these results support the first-line use of pembrolizumab monotherapy in patients with PD-L1–expressing NSCLC.

Pooled KEYNOTE data in the elderly

In view of the fact that patients aged ≥ 75 years are generally underrepresented in

clinical studies, Nosaki et al. conducted a pooled analysis of the efficacy and safety of pembrolizumab in elderly patients included in the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 trials [11]. KEYNOTE-010 had assessed pembrolizumab 2 mg/kg or 10 mg/kg Q3W *versus* docetaxel in previously treated advanced NSCLC [12], while both KEYNOTE-024 [13] and KEYNOTE-042 [10] had evaluated pembrolizumab 200 mg Q3W compared to platinum-based chemotherapy in the first-line setting, with the required PD-L1 TPS defined at ≥ 50 % and ≥ 1 % in KEYNOTE-024 and KEYNOTE-042, respectively. Overall, 149 patients aged ≥ 75 years had received pembrolizumab in these studies, while 115 had been treated with chemotherapy. Median age was 77 years in both arms. Among younger patients, pembrolizumab and chemotherapy had been administered in 1,332 and 1,016 individuals, respectively.

Older patients showed clinically relevant OS improvements with pembrolizumab compared to chemotherapy in both treatment-naïve and previously treated settings. The OS benefit observed for the PD-L1 TPS groups ≥ 1 % and ≥ 50 % was consistent with the benefits seen in other populations included in the three studies and among the younger patients enrolled in these trials. In the group with PD-L1 TPS ≥ 1 %, both patients aged ≥ 75 and < 75 years derived a 24 % reduction in mortality risk with pembrolizumab treatment (HR, 0.76). For those with PD-L1 TPS ≥ 50 %, HRs were 0.40 and 0.67 for the older and younger groups, respectively. Elderly patients also fared better according to the analysis of the treatment-naïve, highly PD-L1–expressing population (i.e., TPS ≥ 50 %); this revealed HRs of 0.41 and 0.71 for the older and younger patients, respectively.

Pembrolizumab showed a comparable and favorable safety profile independent of age. Among the older patients, there were no increases in toxicity, and the majority of immune-mediated AEs and infusion reactions were grade 1/2. No grade 5 immune-mediated AEs occurred in this cohort. Median treatment duration with pembrolizumab was even longer in patients aged ≥ 75 years than in those aged < 75 years (5.6 vs. 4.3 months, respectively). ■

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Encouraging findings in *NTRK*-, *ROS1*- and *ALK*-positive lung cancer

TRK inhibition: larotrectinib

Neutrotrophic receptor tyrosine kinase (*NTRK*) gene fusions occur in a wide array of different cancers including rare entities such as infantile fibrosarcoma, but also in common tumors including melanoma, colon cancer, and lung cancer [1]. Their incidence in lung cancer is estimated at 0.2 % to 3.3 % [1, 2]. The highly selective, oral, CNS-active TRK inhibitor larotrectinib has already been approved by the US Food and Drug Administration for the treatment of adult and pediatric patients with solid tumors showing *NTRK* fusions. Drilon et al. presented pooled data from 11 patients with *TRK*-fusion–positive lung cancer who had received larotrectinib in a phase I study and a phase II basket trial conducted in advanced solid tumors [3]. Five patients had previously undergone 1 or 2 systemic therapies, and in 5 cases, 3 or more therapies had been administered. The treatment consisted of larotrectinib 100 mg BID continuously.

Indeed, the analysis demonstrated activity of larotrectinib in advanced lung cancers harboring *TRK* fusions. Seven patients (71 %) responded, with one and four experiencing complete remissions (CR) and partial remissions (PR), respectively. In two cases, disease stabilization occurred. None of the patients developed primary progressive disease. The median duration of re-

sponse had not been reached at the time of the analysis. Furthermore, larotrectinib showed intracranial activity. A female patient who experienced confirmed PR developed near complete intracranial remission of multiple cerebral lesions.

Larotrectinib was well tolerated in the entire data set including patients without lung cancer. Fatigue, dizziness and nausea occurred most frequently. The majority of AEs were low-grade events. Dose reductions became necessary in no more than 9 % of the total study population, and the discontinuation rate was low at < 1 %. Overall, these results support the routine molecular testing for *TRK* fusions in patients with NSCLC.

Meaningful responses with entrectinib

Another oral, selective, CNS-active TRK inhibitor is entrectinib that also targets ROS1 and ALK. Paz-Ares et al. reported an integrated analysis of adult patients with *NTRK*-fusion–positive, TRK-inhibitor–naïve solid tumors included in the ALKA-372-001, STARTRK-1 and STARTRK-2 trials [4]. ALKA-372-001 and STARTRK-1 were phase I dose-escalation studies, while the global phase II STARTRK-2 trial assessed entrectinib 600 mg/day. Out of 54 patients with various *NTRK*-fusion–positive solid tumors enrolled in these trials, 10 had lung cancer. Among these, six patients showed brain metastases at the time of study inclusion. Three had received one prior systemic treatment line and another 3 had been treated with ≥ 2 lines.

Entrectinib induced clinically meaningful, durable systemic and intracranial responses. According to blinded independent central review, ORR was 57.4 % in the total population with different *NTRK*-fusion–positive solid tumors. For those with NSCLC, ORR was 70.0 %, and median duration of response had not been reached yet. One patient achieved CR, while 6 obtained PR, and disease stabilized in one case. Median PFS was 14.9 months. The analysis of the patients with brain metastases at baseline showed an intracranial response rate of 66.7 %. Two obtained CR **(Table 1)**.

Entrectinib was well tolerated; AEs were mainly graded as 1 or 2. Dysgeusia occurred as the most common toxicity with an incidence rate of 47.1 %, followed by constipation, fatigue, and diarrhea. Most AEs were managed with dose interruptions or reductions, and at 4.4 %, the discontinuation rate was low.

TABLE 1
Intracranial responses with entrectinib in *NTRK*-positive patients with CNS lesions at baseline (n = 6)

Intracranial response per BICR, n (%)	4 (66.7)
Complete remissions, n (%)	2 (33.3)
Partial remissions, n (%)	2 (33.3)
Stable disease, n (%)	1 (16.7)
Not evaluable	1 (16.7)

BICR, blinded independent central review

Entrectinib activity in *ROS1*-positive disease

In *ROS1*-positive lung cancer, the ALK/ROS1/MET inhibitor crizotinib has been established as the standard of care. However, an unmet need results from the fact that CNS is a common first site of progression in crizotinib-treated patients with *ROS1*-positive NSCLC [5]. Therefore, the introduction of a CNS-penetrant ROS1 inhibitor in the first-line setting appears desirable. Compared to crizotinib, entrectinib has shown higher potency regarding ROS1 inhibition in preclinical studies [6]. Entrectinib demonstrated clinical activity in multiple tumor histologies including primary brain tumors and secondary CNS metastases [7].

The ALKA-372-001, STARTRK-1 and STARTRK-2 trials evaluating entrectinib included a total of 53 ROS1-inhibitor–naïve patients with *ROS1*-positive NSCLC. Out of these, 23 had CNS lesions at baseline. An integrated analysis of these 53 patients revealed clinically meaningful and durable systemic and intracranial responses with entrectinib [8]. The systemic response was independent of the presence of baseline brain metastases. Objective response rates were 73.9 % and 80 % in patients with and without CNS lesions, respectively. Median duration of response was 12.6 and 24.6 months, respectively, and median PFS was 13.6 and 26.3 months, respectively. Three patients (10.0 %) of those without CNS disease achieved CR. For intracranial activity according to independent central review, it was shown that 55 % of 20 patients with baseline brain metastases responded, with 20 % and 35 % obtaining CR and PR, respectively. Intracranial responses lasted for a median of 12.9 months. Median OS had not been reached yet.

The pooled safety population included 134 patients who received entrectinib without necessarily being TKI-naïve. Entrectinib proved tolerable in the *ROS1*-positive setting, with predominantly low-grade AEs that showed amenability to successful management by means of dose interruptions/reductions. The most common treatment-related AEs included dysgeusia, dizziness and constipation. In 4.5 % only, treatment had to be discontinued due to AEs.

PROFILE 1001: a new benchmark for OS

Updated results for crizotinib in *ROS1*-rearranged disease from the ROS1 expansion cohort of the PROFILE 1001 study were presented at ELCC 2019 by Shaw et al. [9]. The primary analysis of the PROFILE 1001 trial that was published in 2014 after a median follow-up of 16 months had shown marked antitumor activity [10]. Crizotinib 250 mg BID led to an ORR of 72 %, median duration of response of 17.6 months, and median PFS of 19.2 months. Median OS had not been reached yet. Based on these data, crizotinib was approved for *ROS1*-rearranged advanced NSCLC in many countries.

After a median follow-up of 62.6 months for OS, median OS in the expansion cohort of PROFILE 1001 was 51.4 months in a total of 53 patients most of whom had received at least one prior treatment in the advanced setting. One-year and 4-year OS rates amounted to 79 % and 51 %, respectively. Survival did not differ according to *ROS1* fusion

TABLE 2
Updated anti-tumor activity of crizotinib in *ROS1*-rearranged NSCLC

	Updated analysis (n = 53)	Primary analysis (n = 50)
Best overall response, n (%)		
Complete remissions	6 (11.3)	3 (6)
Partial remissions	32 (60.4)	33 (66)
Stable disease	10 (18.9)	9 (18)
Progressive disease	3 (5.7)	3 (6)
Not evaluable	2 (3.8)	2 (4)
Objective response rate, %	71.7	72
95 % CI	57.7-83.2	58-84
Median progression-free survival, months	19.3	19.2
95 % CI	15.2-39.1	14.4-not reached
Median time to response, weeks	7.9	7.9
Range	4.3-103.6	4.3-32.0
Median duration of response, months	24.7	17.6
95 % CI	15.2-45.3	14.5-not reached

partners, although the number of patients with each type of *ROS1* rearrangement was small, and further studies are needed. Updated ORR was consistent with the results obtained at the time of the primary analysis, as was updated PFS (**Table 2**). However, updated duration of response, at 24.7 months, exceeded the result previously reported. Moreover, a greater proportion of patients had achieved CR compared to the primary analysis, probably due to longer exposure. Long-term crizotinib treatment did not give rise to any new safety signals. No patient developed treatment-related AEs requiring permanent treatment discontinuation.

The authors noted that this analysis provides a new benchmark for OS in *ROS1*-rearranged advanced NSCLC. Considering the outstanding survival rate, this might be one of the few types of lung cancer that could be considered a chronic disease. Also, the data support the continued use of crizotinib in the treatment of patients with this molecular subtype of lung cancer.

First interim analysis of the ALTA-1L study

The randomized, phase III ALTA-1L trial tested the next-generation ALK/ROS1 inhibitor brigatinib against the first-generation TKI crizotinib in patients with advanced *ALK*-positive NSCLC who were ALK-inhibitor–naïve. One line of prior systemic therapy in the advanced setting was allowed. Brigatinib was administered at a dose of 180 mg/day after a 7-day lead-in at 90 mg (n = 137). In the control arm, 138 patients received crizotinib 250 mg BID. Califano et al. presented the first interim analysis at ELCC 2019 [11].

PFS according to blinded independent review committee, which was defined as the primary endpoint, was highly in favor of brigatinib (not reached vs. 9.8 months; HR, 0.49; p = 0.0007). At one year, 67 % vs. 43 % of patients were progression-free. The subgroup analysis demonstrated consistent PFS benefits with brigatinib across all subgroups. ORR was numerically higher for brigatinib compared to crizotinib (71 % vs. 60 %); median duration of response had not been reached in the experimental arm and was 11.1 months in the control arm.

In patients with measurable brain metastases at baseline, confirmed intracranial responses occurred in 78 % vs. 29 % (OR, 10.42; p = 0.0028). In those with any brain lesions at baseline, confirmed intracranial ORR was 67 % vs. 17 % (OR, 13.00; p < 0.0001). All patients treated with brigatinib achieved shrinkage of measurable CNS metastases, which did not apply to the crizotinib-treated cohort (**Figure**). Accordingly, intracranial PFS was significantly improved in the ITT population (HR, 0.42; p = 0.0006) and in patients with any brain metastases at baseline (not reached vs. 5.6 months; HR, 0.27; p < 0.0001). For those without baseline brain metastases, results for intracranial PFS are still immature.

Significant delay of CNS progression

According to a competing risk analysis, brigatinib induced significant improvements of the time to intracranial CNS progression without prior systemic progression (cause-specific HR for CNS progression, 0.30; p < 0.001) and the time to systemic progression without prior intracranial CNS progression (cause-specific HR for systemic progression, 0.51; p = 0.017). Thus, brigatinib significantly delayed both CNS and systemic progression compared to crizotinib.

While excess AEs observed with crizotinib were dominated by gastrointestinal symptoms, transaminitis, bradycardia, edema, and visual effects, brigatinib-associated excess AEs comprised mainly asymptomatic increases of CPK, lipase, and amylase. Dose reductions were largely protocol-mandated due to these laboratory abnormalities. No clinical cases of pancreatitis occurred in either arm. Early-onset interstitial lung disease/pneumonitis within 2 weeks of treatment initiation appears to be unique to brigatinib among the ALK TKIs, but was rare at 3 %, with a lower event rate compared to later-line trials [12]. Based on this data, brigatinib was shown to be a promising first-line treatment option for *ALK*-positive advanced NSCLC.

Treatment duration with brigatinib

The international Expanded Access Program (EAP) for brigatinib that was opened in July 2016 includes patients with *ALK*-positive, locally advanced or metastatic NSCLC who have exhausted available therapies or are unable to participate in a clinical study. Between July 2016 and November 2018, 604 patients in 21 countries across Western Europe, the Asian-Pacific region, and South America entered the EAP. They received brigatinib across all treatment lines.

The analysis of patient outcomes presented at ELCC was conducted with the objective to evaluate the real-world activity of brigatinib in *ALK*-rearranged NSCLC [13]. As no clinical outcome endpoints have been defined in the EAP, time to treatment discontinuation, which is highly correlated to PFS particularly in TKIs, was used as a proxy for the tolerability and efficacy of treatment.

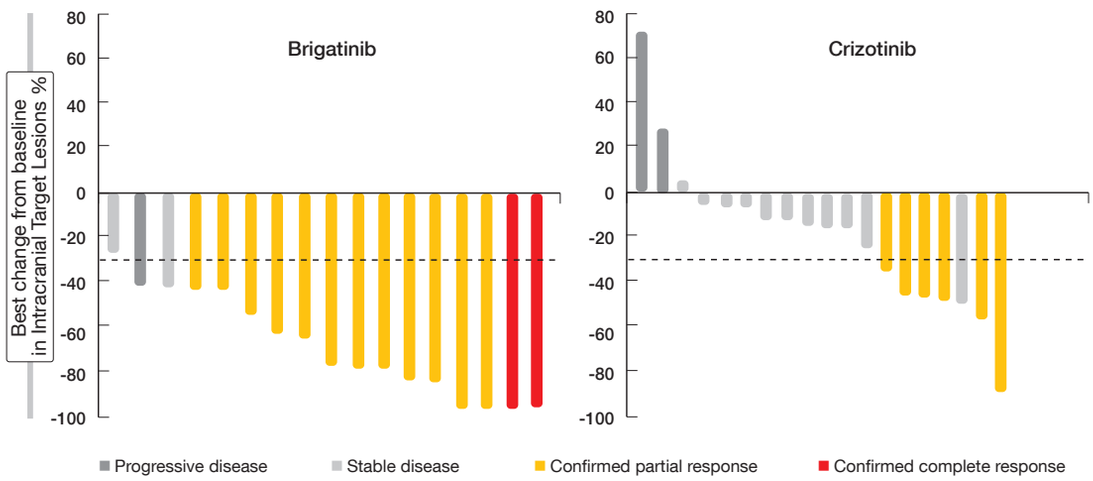

Figure: ALTA-1L: intracranial best target lesion responses in patients with measurable brain disease

Patients included in the analysis were resistant or intolerant to ≥ 1 prior ALK TKI. In the majority of cases (67.2 %), brigatinib was administered in the third or later lines. Among ALK TKIs, ceritinib, crizotinib and alectinib had been used most frequently prior to brigatinib. Despite this heterogeneity, median time to discontinuation amounted to almost one year (10.95 months) across all lines of treatment. The probability of continued use at 6 and 12 months was 67.1 % and 48.6 %, respectively. When analyzed by type of prior ALK TKI therapy, continuous use of brigatinib was seen after alectinib (n = 111; median time to discontinuation of brigatinib, 8.72 months) and ceritinib (n = 249; median time to discontinuation, 10.33 months). Brigatinib was also used post-lorlatinib, with a median time to discontinuation of 7.5 months. Both the probability of continued use of brigatinib and the median time to brigatinib discontinuation decreased with increasing prior ALK TKI treatment lines.

A total of 260 patients discontinued treatment. Only 4 of these (0.7 %) reported discontinuation due to AEs. The main reason for brigatinib treatment discontinuation was lack of efficacy (9.6 %). Overall, the treatment duration observed for brigatinib in a real-world setting was encouraging irrespective of prior ALK inhibitor treatment, and the safety profile proved manageable. ■

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Interview: Nir Peled, MD PhD, The Legacy Heritage Oncology Center & Dr. Larry Norton Institute, Soroka Medical Center & Ben-Gurion University, Beer-Sheva, Israel

Improving accuracy of lung cancer screening

Which biomarkers for early detection of lung cancer might play a role in the future?

Of course, smoking cessation is the goal in the setting of primary prevention, but once the patient is a smoker or ex-smoker, early detection should be promoted as much as possible. One of the current proven platforms for this purpose is low-dose computed tomography. However, it is our goal to add molecular biomarkers to this platform to improve specificity and even sensitivity. There is a range of promising biomarkers from different body compartments.

We recently published a review covering all types of biomarkers including microRNAs, circulating tumor DNA, blood protein profiling, and also exhaled breath biomarkers [1]. The patient could breathe into a device or even talk over the phone, and at that time the volatile compounds could be detected based on chemical responses. This generates a signal that might alarm the patient to the possible presence of cancer and prompts clinical evaluation.
However, at present, we have several platforms that mostly work based on markers obtained from the blood, such as a combination of tumoral biomarkers including protein and circulating DNA. Recently, it was shown that combining tumoral DNA and protein biomarkers gives rise to a very high sensitivity to support these efforts [2]

How can early detection of lung cancer be implemented even in poorer countries?
Early detection of lung cancer by low-dose CT is not only efficient, but it is also important to reduce expenses. When we detect lung cancer very early, we can skip the expenses related to the treatment of the advanced disease. Basically, I would say that poorer countries should go for screening even more than richer countries, because the costs of immunotherapies and the associated expenses are much higher than those of low-dose CT scans.

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Nir Peled, MD PhD, The Legacy Heritage Oncology Center & Dr. Larry Norton Institute, Soroka Medical Center & Ben-Gurion University, Beer-Sheva, Israel

However, there is still room for improvement with respect to reducing the number needed to screen to rescue one lung cancer patient. I would mainly focus on age to increase the pretest probability. Presently, it is recommended to screen from the age of 55 years in a patient with 30 pack years. If the bar would be raised to 60 years, especially in poorer countries, the expenses could be reduced. In my opinion, the age of 60 is the oldest cutoff for screening, because the average age at the time of lung cancer diagnosis is 67 years. Therefore, in poorer countries, 60 is a good cutoff that would increase the availability of screening for the patients who are in need of it. ■

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Extensive-disease small-cell tumors: signals of activity

CheckMate 451: immunotherapeutic maintenance

Most of the patients with small-cell lung cancer (SCLC) are diagnosed in the extensive-disease stage (ED-SCLC). They generally respond well to first-line platinum-based chemotherapy; however, responses are not durable, and prognosis is poor [1, 2]. In the second line and beyond, the NCCN guidelines recommend patient inclusion in a clinical trial, systemic therapy depending on the patient performance status and the duration of the relapse-free interval, or palliative symptom management [1].

No maintenance treatment is currently available to prolong the effects obtained with first-line chemotherapy. The CheckMate 451 trial was designed to assess an immunotherapeutic approach in this setting [3]. A total of 834 patients with ED-SCLC who had ongoing responses in the form of CR, PR or SD following 4 cycles of platinum-based first-line chemotherapy were randomized to either nivolumab plus ipilimumab (n = 279), nivolumab 240 mg Q2W (n = 280), or placebo (n = 275). In the combination arm, nivolumab was administered in a weight-based manner (1 mg/kg Q3W) together with ipilimumab 3 mg/kg Q3W for a maximum of 4 doses, followed by nivolumab 240 mg Q2W. The treatment continued until progression or unacceptable toxicity for a maximum of 2 years.

CheckMate 451 failed to show a significant OS improvement for nivolumab plus ipilimumab compared to placebo, which was defined as the primary endpoint (median OS, 9.2 vs. 9.6 months; HR, 0.92). This was also true for the landmark analysis at 12 months (41 % vs. 40 %).

Benefit after short treatment-free interval

Due to the hierarchical testing requirement of the study, the other endpoints were not tested for statistical significance but only analyzed for descriptive purposes. With nivolumab monotherapy vs. placebo, as for the combination, there was no OS difference in the total population (10.4 vs. 9.6 months; HR, 0.84). However, the subgroup analysis implied a significant benefit compared to placebo in patients who started immunotherapy within 5 weeks after their last doses of frontline chemotherapy (median OS, 12.1 vs. 8.9 months; HR, 0.66; **Figure**). Nivolumab plus ipilimumab did not elicit any OS advantage in this cohort (HR, 0.88). Patients who received immunotherapy after an interval of more than 5 weeks, on the other hand, showed no sur-

vival benefit with either nivolumab alone or the combination (HR for both, 0.96).

The PFS analysis hinted at improved outcomes compared to placebo with both nivolumab plus ipilimumab (HR, 0.72; 6-month PFS rates, 20 % vs. 10 %) and nivolumab alone (HR, 0.67; 6-month PFS rates, 21 % vs. 10 %). Likewise, responses were more favorable in the experimental arms. Clinical benefits (i.e., CR plus PR plus SD) occurred in 45 %, 47 %, and 35 % of patients treated with the combination, nivolumab, and placebo, respectively. Median duration of response was 10, 11, and 8 months, respectively. The safety profiles of the immunotherapeutic regimens corresponded to previous reports for the same doses and schedules. Nivolumab monotherapy proved more tolerable than the combination.

The authors concluded that PFS and response rate data suggest activity of immunotherapy in the maintenance setting of ED-SCLC. Nivolumab might provide improved OS in patients with a shorter interval from the last dose of first-line chemotherapy to initiation of treatment.

Rova-T: third-line setting

To date, no drug has been approved for the third-line treatment of ED-SCLC. The antibody-drug conjugate rovalpituzumab tesirine (Rova-T) targets the delta-like protein 3 (DLL3), which is highly expressed in SCLC and neuroendocrine carcinoma (NEC) [4]. Single-agent Rova-T has shown encouraging anti-tumor activity and a manageable safety profile in SCLC patients treated in phase I and II studies [5, 6].

	Nivolumab + ipilimumab (n = 116)	Nivolumab (n = 107)	Placebo (n = 118)
Events, n (%)	79 (68)	68 (64)	93 (79)
Median OS (95 % CI), months	9.1 (7.3–12.1)	12.1 (9.6–16.1)	8.9 (7.3–11.0)
HR (vs. placebo) (95 % CI)	**0.88** (0.65–1.18)	**0.66** (0.49–0.91)	

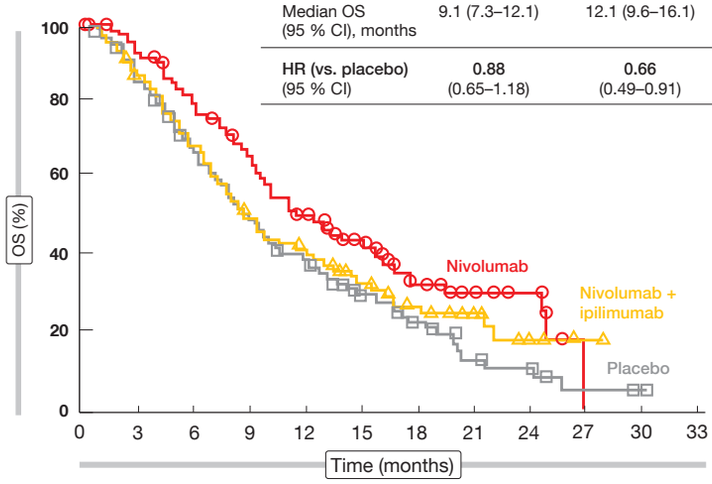

Figure: Reduction in mortality with nivolumab vs. placebo in patients who started immunotherapy within 5 weeks after frontline chemotherapy

A retrospective analysis presented at ELCC 2019 evaluated DLL3 test results and clinical experience with Rova-T in patients after failure of at least two cycles of systemic treatment in a real-life setting [7]. DLL3 immunohistochemistry was performed in 68 patients with high-grade NEC including 61 SCLC and 7 large-cell NEC cases. Most of the samples showed DLL3 staining. Forty-nine specimens (72.1 %) were classified as highly positive, 10 (14.7 %) as positive, and 9 (13.2 %) as negative. Sixteen patients who had no other treatment options left received at least one of two planned cycles of Rova-T 0.3 mg/kg. In this group, 2 patients were DLL3-negative, 4 were DLL3-positive, and 10 were highly DLL3-positive.

Both treatment cycles were administered in 7 patients, while 9 received only one cycle due to disease progression or the occurrence of AEs. Four patients (25 %) experienced partial responses, while 4 (25 %) had stable disease, and 8 developed disease progression (50 %). Common drug-related AEs included fatigue, photosensitivity, pleural effusion, peripheral edema, and thrombocytopenia. AEs were generally manageable.

The authors concluded that Rova-T gave rise to clinical benefit in selected patients and therefore appears to be an option for ED-SCLC in later lines. A large proportion of SCLC patients tested DLL3-positive, although further studies are needed to assess the feasibility of DLL3 as a biomarker in this setting. ■

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Interview: Anne-Marie C. Dingemans, MD, PhD, Department of Pulmonology, Maastricht University Medical Center, Maastricht, Netherlands

"We need chemotherapy when rapid responses are required"

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Anne-Marie C. Dingemans, MD, PhD,
Department of Pulmonology, Maastricht University Medical Center, Maastricht, Netherlands

As the relative importance of chemotherapy in NSCLC management is changing, how can chemotherapeutic agents contribute to increasing efficacy in the context of new treatments?
Over the last years, the treatment of lung cancer patients has improved greatly due to the introduction of new drugs such as targeted agents and immunotherapies. However, all of the data show that these treatments do not work for all patients. Therefore, we still need chemotherapy. For example, chemotherapy can be necessary to induce a systemic response in patients with driver mutations at the time of multiple resistance after several lines of treatment. We have also seen in the area of immunotherapy that a proportion of these patients do not respond at all or do not respond very rapidly. Chemotherapy can be very helpful in patients with a low PD-L1 expression or in those with a high burden of disease and especially a high symptom burden, who are in need of a rapid response.

Will chemotherapy be replaced completely in the long run?
No, I do not think so. We need chemotherapy together with radiotherapy, and we need chemotherapy when rapid responses are required in a patient. It is always being said that immunotherapies have fewer side effects. Indeed, this is true for grade 3/4 adverse events on a numerical level. However, with chemotherapy, grade 3/4 toxicity mainly consists of neutropenia, the burden of which is not very severe for the patient. Also, these side effects are short-lived. Rare side effects of immunotherapies can be long-lived, and the patient can have long-term problems. Therefore, I think that we will always need chemotherapy as a combination partner, particularly together with radiotherapy, and in patients for whom no targeted agents are available.

What combination of chemotherapeutic agents with other drug classes do appear promising at present?
Combinations of chemotherapy with immunotherapy appear promising, although we need to determine what types of chemotherapy are ideal for this, because it is not known whether every combination has the same efficacy. For example, it might be possible to administer chemotherapy regimens that do not contain platinum, and thus toxicity could be diminished. This might be an interesting focus of research. ■

Anti-angiogenic combinations excel in later lines

VARGADO: nintedanib after immunotherapy

The ongoing, prospective, non-interventional VARGADO study is assessing the angiokinase inhibitor nintedanib plus docetaxel in patients with advanced adenocarcinoma of the lung after first-line chemotherapy in routine clinical practice. VARGADO is conducted at approximately 100 sites across Germany and includes 3 cohorts. Cohort A is receiving chemotherapy and nintedanib plus docetaxel in the first- and second-line settings, respectively; for Cohort B, immune checkpoint inhibition (ICI) constitutes the second-line treatment after chemotherapy and is followed by the nintedanib combination; in Cohort C, chemotherapy plus ICI treatment is administered in the first line and nintedanib plus docetaxel in the second line **(Figure 1)**.

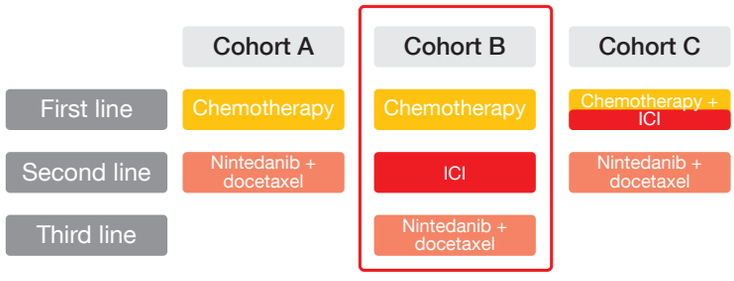

Figure 1: Design of the non-interventional VARGADO trial

At ELCC 2019, Grohé et al. presented the initial analysis of 22 patients included in Cohort B [1]. The results support the clinical benefit and manageable safety profile of nintedanib plus

docetaxel in patients who have progressed after ICI treatment. Ten of 12 patients who responded achieved disease control (83 %), with PR occurring in 7 individuals (58 %) and SD in 3 (25 %). The observed clinical benefit of nintedanib plus docetaxel was consistent across responses and median PFS, which was 5.5 months. Also, the safety profile matched the known profile for the nintedanib combination. Drug-related treatment-emergent AEs comprised mainly stomatitis, decreased white blood cell counts, and nausea.

Effects on the microenvironment

It was hypothesized that an angio-immunogenic switch might represent the underlying mechanism of the treatment activity observed in VARGADO. It has been shown that an immunosuppressive tumor microenvironment, which is closely linked to resistance to ICIs, is associated with VEGF-mediated angiogenesis [2]. Abnormal vasculature might contribute to ICI resistance. In this setting, anti-angiogenic therapy can support vessel normalization and improve access of immune cells to the tumor, tipping the balance towards an immunosupportive tumor microenvironment [3]. Targeting the microenvironment in this manner might reactivate and even enhance the effect of the ICI therapy.

The authors noted that these initial data provide valuable clinical insights in an advanced lung cancer population for which only very little clinical evidence exists to date. VARGADO is ongoing, and patient recruitment has been expanded.

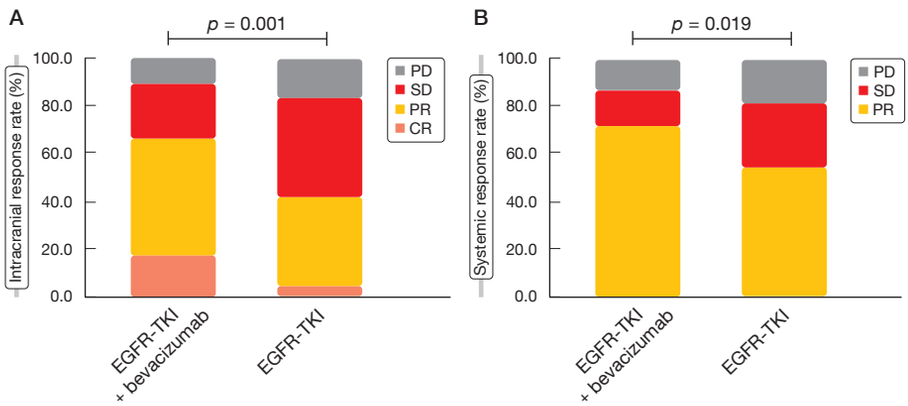

Figure 2: Intracranial (left) and systemic (right) responses with the addition of bevacizumab to EGFR TKI treatment compared to EGFR TKIs alone

Bevacizumab plus EGFR TKIs

The combination of the anti-VEGF antibody bevacizumab with the first-generation EGFR TKI erlotinib has shown promising efficacy in the phase II JO25567 trial [4] and in the phase III NEJ026 study [5] that were performed in the first-line setting. However, the efficacy of EGFR TKI treatment plus bevacizumab in patients with *EGFR*-mutant NSCLC and brain metastases remains undetermined. Therefore, Jiang et al. conducted a multi-center, retrospective study to investigate whether the administration of the first-generation EGFR TKIs erlotinib, gefitinib and icotinib together with bevacizumab could improve survival compared to the TKIs alone in patients with multiple (i.e., > 3) brain metastases [6]. Overall, 208 patients with *EGFR*-mutant NSCLC and CNS disease were included in the analysis. Of these, 59 had been treated with a TKI and bevacizumab, while 149 had received TKI monotherapy. Erlotinib was the most commonly used EGFR TKI.

Intracranial PFS, systemic PFS and OS were defined as the primary endpoints. For all of these outcomes, the combination brought about significantly superior results compared to TKI monotherapy. Median intracranial PFS was 14.0 months with bevacizumab plus TKI treatment *versus* 8.2 months with TKIs alone (HR, 0.56; p < 0.001); for systemic PFS, this was 14.4 vs. 9.0 months (HR, 0.55; p < 0.001). More importantly, the addition of bevacizumab led to a reduction in the mortality risk of almost 50 %, with median OS of 29.6 vs. 21.7 months (HR, 0.51; p < 0.001). Likewise, the combination group derived greater benefits regarding both intracranial responses (p = 0.001) and systemic responses (n = 0.019; **Figure 2**).

Overall, these findings suggested that EGFR TKIs combined with bevacizumab are an option for patients with *EGFR*-mutant NSCLC and multiple brain metastases. This might even apply to the first-line setting, although prospective data are required here. ■

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