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Preface

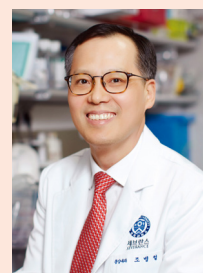
Dear Colleagues,

The ESMO Virtual Congress 2020 has attracted more than 30,000 registrants from over 150 countries to whom content presented at more than 70 sessions has been made available. The 2,137 abstracts reported at the conference included 87 late breaking abstracts. Sessions were provided for 135 proffered papers, 195 mini orals, and 1,807 ePosters. Twelve simultaneous publications of studies in peer-reviewed journals underscore the scientific significance of the analyses that were shared with the audience by over 230 invited speakers.

For us as lung cancer specialists, the ESMO 2020 congress harbored a range of notable abstracts that will most likely change our clinical practice in the years to come. In the field of early-stage lung cancer, the LungART study was the first trial to prospectively demonstrate the lack of added benefit of postoperative irradiation in patients with completely resected NSCLC and pN2 nodal involvement. Immunotherapy continues

to excel in the management of early and metastatic NSCLC, as demonstrated by long-term study updates such as those for PACIFIC and KEYNOTE-024. New checkpoint inhibitors keep arriving that show efficacy in various settings. The PIONeeR project is dedicated to improving the understanding and prediction of resistance to PD-(L)1-targeted compounds. Also, interactions between radiotherapy and immunotherapy have recently moved into the focus of research. In the treatment of malignant mesothelioma, evidence for the successful use of immune checkpoint inhibition is being built up at present.

Noteworthy insights have also been gained regarding targeted therapies. Among ALK inhibitors, lorlatinib has demonstrated convincing activity in the first-line treatment of patients with ALK-positive NSCLC. In *KRAS*^{G12C}-mutated disease, a first-in-class inhibitor is being explored, with encouraging results. Novel combination approaches are investigated in patients with *EGFR*-activating mutations. The idea is to enhance the efficacy of established therapies and to delay or prevent the emergence of resistance in a highly targetable setting where treatment



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initially works well in most patients, but responses inevitably abate over time. Current approaches include, among others, the combined administration *EGFR*-targeted agents and anti-angiogenic compounds, as well as *MET* inhibition plus *EGFR* inhibition. Also, the refined use of standard therapies can contribute to outcome optimization. Thus, the management of thoracic cancer is continuously improving together with heightened tolerability as an important part of a modern treatment approach.

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Immune checkpoint inhibition: chemotherapy-free regimens & new PD-1 inhibitors on the horizon

Monotherapy versus chemotherapy

Five-year update of KEYNOTE-024

Pembrolizumab as single agent for up to 35 cycles has been shown to be superior to 4 to 6 cycles of platinum-doublet chemotherapy in patients with metastatic non-small-cell lung cancer (NSCLC) and a PD-L1 tumor proportion score (TPS) $\geq 50\%$ in the KEYNOTE-024 trial. At a median follow-up of 11.2 months, median progression-free survival (PFS) was 10.3 vs. 6.0 months (HR, 0.50; $p < 0.001$), and median overall survival (OS) had not been reached yet in either group, with 80.2% vs. 72.4% of

patients alive at 6 months (HR, 0.60; $p = 0.005$) [1]. At the ESMO 2020 Congress, Brahmer et al. reported updated outcomes after a follow-up of 5 years [2]. Pembrolizumab and chemotherapy had been administered in 154 and 151 patients, respectively. The group of 39 patients who had received all of the 35 pembrolizumab cycles was analyzed separately, as were 12 patients who had been treated with a second course of pembrolizumab upon progression.

Pembrolizumab continued to induce meaningful OS improvement in the total group (26.3 vs. 13.4 months; HR, 0.62). Despite the 66% effective crossover rate, the 5-year OS rate was approximately doubled in the experimental arm (31.9% vs. 16.3%). Median PFS was

7.7 vs. 5.5 months, with 22.8% vs. 4.1% of patients being progression-free at 36 months. Objective responses occurred in 46.1% and 31.1%, respectively. Seven pembrolizumab-treated patients (4.5%) experienced complete remissions (vs. 0% in the chemotherapy arm). Duration of response was 29.1 vs. 6.3 months. The group of 39 patients who had received 35 cycles of pembrolizumab experienced long-term OS. At data cutoff, 46% were alive without disease progression or subsequent therapy. The 3-year OS rate from completion of treatment was 81%, and objective responses had occurred in 82%. Four patients (10%) showed complete remissions. One patient developed a secondary malignancy and was treated accordingly.

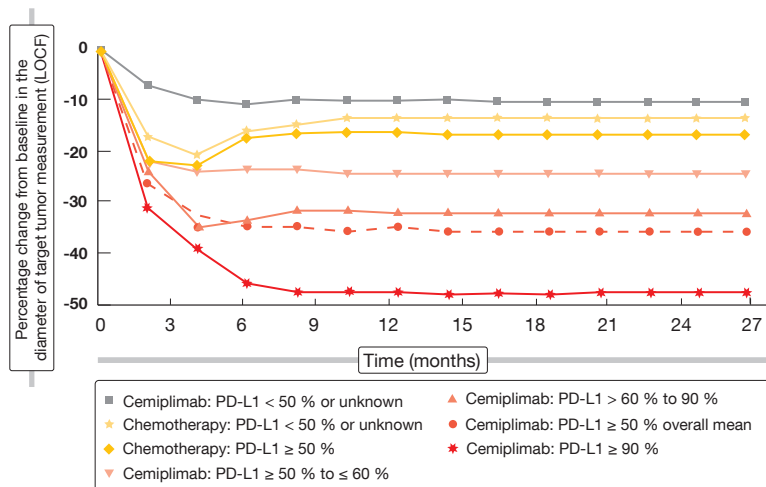


Figure 1: Correlation of changes in target tumor volume with baseline PD-L1 levels in patients receiving either cemiplimab or chemotherapy

Also, second-course pembrolizumab proved feasible and was associated with anti-tumor activity. Here, the objective response rate (ORR) during the second course amounted to 33 %, and 42 % of patients were alive without disease progression at data cutoff. Twenty-five percent of these received no subsequent treatment. The long-term administration did not give rise to new safety signals. Patients in the experimental arm developed less frequently any-grade and grade 3 to 5 treatment-related AEs than those in the control arm. Overall, these data confirmed the 5-year OS outcomes among previously untreated patients included in the single-arm KEYNOTE-001 study [3]. KEYNOTE-024 is the first phase III trial to show 5-year efficacy for first-line immunotherapy, demonstrating that pembrolizumab monotherapy is an active first-line regimen in patients with metastatic NSCLC and PD-L1 TPS \geq 50 %.

Cemiplimab in lung cancer: EMPOWER-Lung 1

A new first-line monotherapy option is the anti-PD-1 antibody cemiplimab that has already been widely approved for the treatment of cutaneous squamous cell carcinoma. Sezer et al. presented the second pre-specified interim analysis of the randomized phase III EMPOWER-Lung 1 study that compared cemiplimab monotherapy with platinum-doublet chemotherapy according to investigators' choice in untreated patients with advanced NSCLC and PD-L1 expression \geq 50 % [4]. In the ITT population, 356 and 354 patients were randomized to ce-

miplimab 350 mg three-weekly (Q3W) and 4 to 6 cycles of chemotherapy, respectively. The PD-L1 \geq 50 % ITT population consisted of 563 patients, with 283 and 280 receiving cemiplimab and chemotherapy, respectively. OS and PFS were defined as coprimary endpoints.

EMPOWER-Lung 1 met its primary and secondary endpoints. In the PD-L1 \geq 50 % ITT population, the mortality risk was reduced by 43 % (median OS, not reached vs. 14.2 months; HR, 0.57; $p = 0.0002$), and the risk of progression and death decreased by 46 % (median PFS, 8.2 vs. 5.7 months; HR, 0.54; $p < 0.0001$). At 12 months, 72.4 % vs. 53.9 % of patients were alive, and 40.7 % vs. 7.1 % were progression-free. The significant OS benefit was achieved despite a high crossover rate of 74 %. ORRs were 39.2 % vs. 20.4 %, with responses lasting longer in the experimental arm (16.7 vs. 6.0 months). Increasing PD-L1 expression levels correlated with better outcomes in the cemiplimab-treated group; this was true with respect to changes in target tumor volume (**Figure 1**), ORR, OS and PFS. No such correlations were seen for chemotherapy.

With regard to global health status and health-related quality of life, cemiplimab was shown to induce early improvement that increased over time, while patients treated with chemotherapy fared worse from the beginning and eventually deteriorated. Although exposure to cemiplimab was substantially longer than exposure to chemotherapy, a favorable safety profile of the PD-1 inhibitor was observed, with considerably lower rates of hematological and non-

hematological adverse events (AEs). Immune-related AEs led to discontinuation in 2.5 %. As the authors summarized, these data provide the rationale for cemiplimab as a new first-line monotherapy option for patients with advanced NSCLC and PD-L1 expression \geq 50 %.

Immunotherapy plus anti-angiogenesis

Nivolumab-based regimen

Combination therapies of checkpoint inhibitors, cytotoxic chemotherapy and anti-angiogenic treatment are assumed to exert synergistic effects. In the IMpower150 study, atezolizumab has shown efficacy together with chemotherapy and bevacizumab as first-line therapy for patients with advanced NSCLC [5]. Therefore, the randomized phase III ONO-4538-52/TASUKI-52 trial evaluated nivolumab 360 mg Q3W plus carboplatin/paclitaxel and bevacizumab in a treatment-naïve PD-L1 all-comer population with stage IIIB/IV non-squamous NSCLC. In the control arm, placebo was administered in addition to the chemotherapy doublet and bevacizumab. Each arm contained 275 patients.

Regarding PFS, which was defined as the primary endpoint, the interim analysis presented at ESMO 2020 demonstrated superiority of the nivolumab-based regimen (12.1 vs. 8.1 months; HR, 0.56; $p < 0.0001$) [6]. The 12-month PFS rates were 50.1 % and 30.2 % for the two arms. Almost all subgroups derived PFS benefits from the addition of nivolumab. Notably, PD-L1 expression did not affect the outcomes. However, median OS did not differ across the two arms (25.4 vs. 24.7 months; HR, 0.85). No new safety signals were detected in the experimental group. The authors noted that the addition of nivolumab to first-line chemotherapy and bevacizumab induces a significant and clinically meaningful PFS improvement, providing a potential new standard of care for these patients.

Atezolizumab plus bevacizumab

In patients with high PD-L1 expression, a chemotherapy-free regimen of atezolizumab plus bevacizumab might be sufficient to elicit substantial effects. The phase II, single-arm, open-label,

multi-institutional WJOG @Be Study tested this combination in an untreated population of 39 patients with advanced non-squamous NSCLC and PD-L1 TPS $\geq 50\%$ [7]. Atezolizumab was administered at a dose of 1,200 mg together with bevacizumab 15 mg/kg Q3W for up to 2 years. ORR constituted the primary outcome.

Overall, 64.1 % of patients developed complete or partial responses, with almost all of them experiencing tumor shrinkage (**Figure 2**). Median PFS was 15.9 months. At 12 months, 70.6 % of patients were alive, 48.2 % showed responses, and 54.9 % were progression-free. Median duration of response was 10.4 months. At the time of the data cut-off, half of the population was still receiving the study treatment. Unexpected AEs did not occur, and no grade 4/5 events were observed. Two patients discontinued treatment due to toxicity. As confirmatory evidence is called for, atezolizumab plus bevacizumab will be compared with the IMpower150 regimen and atezolizumab monotherapy in the 3-arm, phase III @Be-F1rst study.

Phase III results for emerging PD-1 inhibitors

Tislelizumab: pivotal phase III study

New PD-1 inhibitors are being developed, among them tislelizumab that was designed to minimize binding to Fc γ R on macrophages. This mechanism abrogates antibody-dependent phagocytosis, which is a potential mechanism of T cell clearance and resistance to anti-PD-1 therapy [8, 9]. Three early-phase

studies (BGB-A317-001, BGB-A317-102, BGB-A317-206) showed that tislelizumab, as a single agent and in combination with chemotherapy, was generally well tolerated and demonstrated antitumor activity in Asian and non-Asian populations with solid tumors including advanced lung cancers [10-12]. In the phase III setting, the open-label, multicenter, randomized RATIONALE 304 study investigated tislelizumab 200 mg Q3W combined with pemetrexed plus cisplatin or carboplatin ($n = 223$) versus chemotherapy alone ($n = 111$) as first-line treatment in patients with stage IIIB/IV non-squamous NSCLC [13]. After induction that comprised 4-6 cycles, the maintenance phase included three-weekly treatment with tislelizumab 200 mg plus pemetrexed 500 mg/m² in the experimental arm and pemetrexed monotherapy in the control arm. Forty-seven sites in China participated in the trial.

The addition of tislelizumab gave rise to a significant improvement in PFS (9.7 vs. 7.6 months; HR, 0.645; $p = 0.0044$; **Figure 3**) as well as higher ORR (57.4 % vs. 36.9 %) and longer duration of response (8.5 vs. 6.0 months). Consistent PFS benefits were observed across most prespecified subgroups. Median OS had not been reached yet in either arm. The tislelizumab-based regimen was generally well tolerated, with most AEs being mild or moderate and manageable. Most commonly, cytopenias were reported, followed by nausea and elevated transaminases. Immune-mediated AEs occurred in 25.7 % of patients in the experimental arm; these primarily included pneumonitis (9.0 %), hypothyroidism (8.6 %), and hyperthyroid-

ism (2.7 %). Most of them were mild to moderate in severity. Overall, these findings support tislelizumab in combination with platinum-based doublet chemotherapy as a potential new standard first-line treatment of patients with advanced non-squamous NSCLC.

Activity in squamous NSCLC

The pivotal, open-label, three-arm, phase III RATIONALE 307 trial conducted in China tested the addition of tislelizumab to paclitaxel/carboplatin or nab-paclitaxel/carboplatin in patients with stage IIIB/IV squamous NSCLC. Results presented at the ASCO 2020 Congress showed that compared to chemotherapy alone, tislelizumab plus chemotherapy Q3W gave rise to significantly improved PFS, ORR and duration of response [14]. An updated analysis of the study including assessment of the clinical significance of blood tumor mutational burden (bTMB) was reported at the ESMO 2020 Congress [15].

Median PFS was 7.6 months for both tislelizumab plus paclitaxel/carboplatin (Arm A) and tislelizumab plus nab-paclitaxel/carboplatin (Arm B) and was thus significantly superior to the PFS obtained with paclitaxel/carboplatin (Arm C; 5.5 months), with risk reductions of approximately 50 % (HR, 0.524; $p = 0.0001$ and HR, 0.478; $p < 0.0001$, respectively). The PFS benefits observed with both tislelizumab-based regimens were consistent across all subgroups including PD-L1 expression cohorts. ORRs were 73 % and 75 % in Arms A and B, respectively, vs. 50 % in Arm C. Tislelizumab plus chemotherapy evoked higher response rates irrespective of PD-

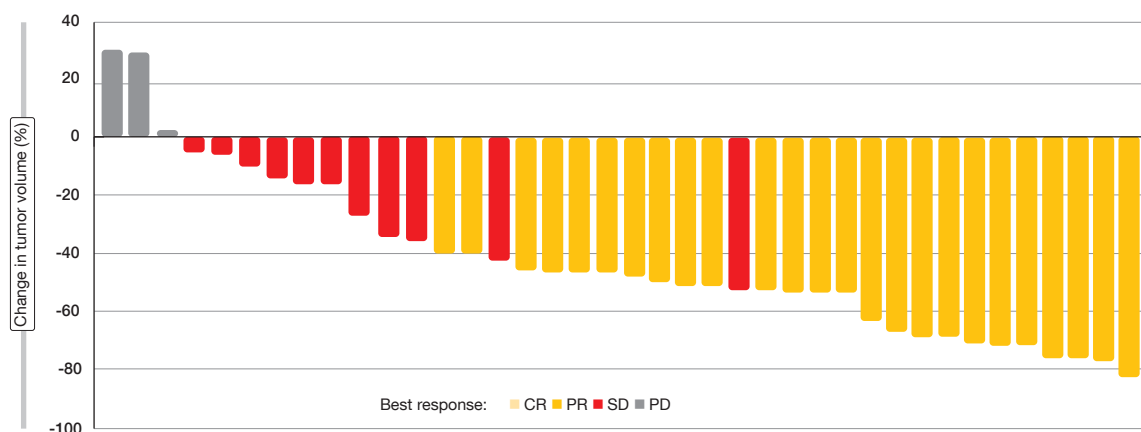


Figure 2: Atezolizumab plus bevacizumab: tumor shrinkage in almost all patients

L1 expression status. Median OS had not been reached yet.

The exploratory analysis of bTMB showed that tislelizumab plus chemotherapy demonstrated ORR and PFS benefits compared to chemotherapy in patients with both bTMB-high (i.e., ≥ 6 mutations/Mb) and bTMB-low (< 6 mutations/Mb) status. Clinical utility of bTMB as a predictive marker for PFS in the tislelizumab plus chemotherapy arms appeared to be limited according to the interactive analysis. The incidence of treatment-emergent AEs (TEAEs) including grade ≥ 3 events was similar across the arms. Most AEs were mild or moderate and manageable. The authors concluded that these results obtained in patients with squamous lung cancer address a high unmet need. The data support tislelizumab plus paclitaxel/carboplatin or nab-paclitaxel/carboplatin as a potential standard for first-line treatment of advanced squamous NSCLC.

ORIENT trials: sintilimab

Sintilimab, another new anti-PD-1 antibody, is also being evaluated in the phase III setting in both squamous and non-squamous NSCLC. In patients with advanced lung cancer of squamous histology, the randomized, double-blind, phase III ORIENT-12 trial demonstrated favorable findings with first-line sintilimab plus gemcitabine and cisplatin or carboplatin [16]. Patients with stage IIIB/C disease ineligible for surgery/local therapy or stage IV disease participated in the study regardless of their PD-L1 expression status. They were randomized to either sintilimab plus chemotherapy ($n = 179$) or placebo plus chemotherapy ($n = 178$) for 4 or 6 cycles. PFS according to independent radiologic review committee was defined as the primary endpoint.

Compared to chemotherapy only, the combination significantly improved PFS (5.5 vs. 4.9 months; HR, 0.536; $p < 0.00001$). OS was not mature yet, although the preliminary results suggested an advantage in the experimental arm (HR, 0.567; $p = 0.01701$). Objective responses occurred in 44.7% vs. 35.4%, and disease control was achieved in 86.0% vs. 80.3%. The two regimens did not differ in terms of TEAEs, grade 3 to 5 TEAEs, and AEs leading to treatment interruption or withdrawal.

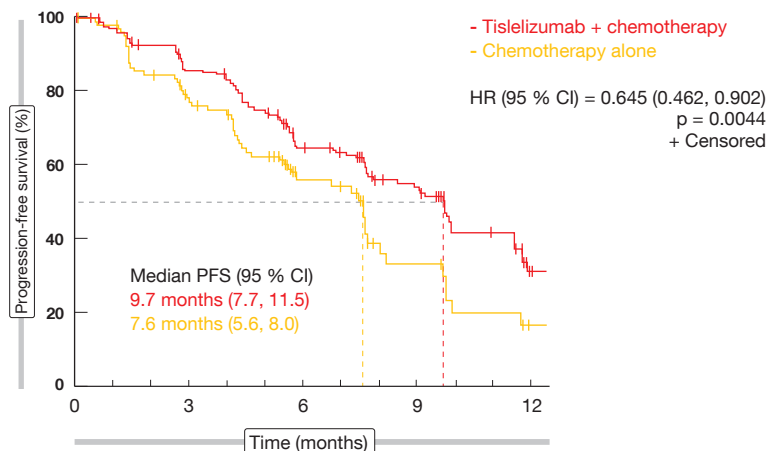


Figure 3: Progression-free survival with tislelizumab plus chemotherapy compared to chemotherapy

In patients with advanced non-squamous NSCLC, the superiority of sintilimab plus chemotherapy (pemetrexed and cisplatin or carboplatin) over placebo plus chemotherapy has been established by the randomized phase III ORIENT-11 study [17]. Median PFS was 8.9 vs. 5.0 months for the two regimens (HR, 0.482). In their analysis presented at ESMO 2020, Yang et al. identified the major histocompatibility complex (MHC)-II antigen presentation pathway as predictive for the activity of this combination [18]. The signature score of this pathway was significantly associated with clinical efficacy, as were representative genes such as *HLA-B*, *HLA-DMB*, *B2M* and *CIITA*.

Advancing insights into predictive biomarkers

The PIONeer Project

Approximately 30% and 50% of first-line and second-line patients, respectively, progress within the first 6 months after initiation of immune checkpoint inhibition. Given the lack of biomarkers to predict these events, the PIONeer Project is dedicated to improving the understanding and prediction of resistance to PD-(L)1-targeted treatment of patients with advanced NSCLC. It consists of the PIONeer Biomarkers study and the PIONeer umbrella trial that will test various targeted inhibitors in combination with durvalumab. Barlesi et al. presented results for the first 100 patients included in the PIONeer Biomarkers study [19].

Biopsies were taken before the initiation of treatment and again at 6 weeks in patients with advanced NSCLC who were receiving PD-(L)1 inhibitors as monotherapy or combined with chemotherapy in the first- and second-line settings. The biomarker program comprises more than 400 biomarkers. These relate to drug response (pharmacokinetic[PK]/pharmacodynamic[PD] modeling), immune cell infiltration, sensitivity to immune effectors (i.e., immune gene expression signatures), immune checkpoints, immune suppression and tumor foreignness (e.g. TMB). Also, peripheral markers include circulating immune cells, soluble markers, endothelial markers, ctDNA, and the microbiome.

Among the first 100 patients included in the biomarker part of the PIONeer project, the vast majority received treatment in the second line (87%). As can be expected, the ORR was 13%, and median PFS and OS were 3.0 and 11.0 months, respectively. The scientists analyzed the predictive power of certain clinical characteristics and biomarkers with respect to these clinical endpoints. None of the clinical characteristics showed a significant association with the probability of objective response, although several biomarkers did (e.g., pretreatment levels of PD-L1-positive tumor cell percentage, cytotoxic T cell CD3+/CD8+ density in the tumor, effective T cell density in the tumor, regulatory T-cell density in the stroma). At 6 weeks, the numbers of neutrophils infiltrating the stroma were also increased in responding patients compared to non-responders.

TABLE 1

Clinical characteristics and biomarkers that significantly affect the outcomes obtained with PD-(L)1-targeted treatment in patients with advanced NSCLC

Clinical characteristic/biomarker	Progression-free survival		Overall survival	
	Median PFS	Hazard ratio, p value	Median OS	Hazard ratio, p value
ECOG PS (2/3 vs. 0/1)	1.22 vs. 3.22	10.8, p = 0.002	3.09 vs. 12.78	3.9, p = 0.041
Histological subtype (others vs. adenocarcinoma)	1.51 vs. 4.63	2.24, p = 0.007	No association	
Type of PD-(L)1 inhibitor (pembrolizumab vs. nivolumab)	3.22 vs. 2.56	0.58, p = 0.049	No association	
PD-L1 TC expression (< 1 % vs. ≥ 1 %)	2.25 vs. 6.6	2.0, p = 0.004	No association	
PD-L1 expression in TC (%)		0.98, p = 0.0209	No association	
Circulating T cells	No association		0.99, p = 0.039	
Circulating activated T cells		1.06, p = 0.0008	1.07, p = 0.001	
Cytotoxic T cells in the tumor		1.00, p = 0.047	No association	
Serum IL-6		1.00, p = 0.047	1.00, p = 0.037	
Serum TNF-α	No association		1.04, p = 0.031	

PS remains the strongest predictor

For PFS, a significant correlation was found with ECOG performance status, histological subtype, the type of treatment and the PD-L1 expression of tumor cells (**Table**). At the biomarker level, there was an association with PD-L1 expression in tumor cells, circulating activated T cells, serum IL-6, and cytotoxic T cells in the tumor. With respect to OS, the only relevant clinical characteristic was ECOG PS. Among the biomarkers, circulating T cells correlated with the probability of survival, as well as circulating activated cells, serum IL-6, and serum TNF-α.

PD-L1-positive cell density in the tumor was particularly low in specimens of patients who did not respond to treat-

ment despite PD-L1 expression of ≥ 15 % on tumor cells. Also, PD-L1-positive cell density on all cell types (i.e., tumor and stroma cells), when provided with a cutoff of 546 cells/mm², showed a potent correlation with OS. Other potentially powerful biomarkers were cytotoxic T cells in the tumor and at the tumor-stroma interface.

With regard to PK/PD parameters, a large inter-patient variability existed for both peak and trough levels after exposure to atezolizumab, pembrolizumab and nivolumab. The identification of individual PK parameters and PK/PD modeling is ongoing. Finally, the evolution of the immune profile before and after 6 weeks of treatment is being assessed. This showed that all of the T cell parameters increased during treatment (i.e., PD-L1-positive cell density in the

tumor, cytotoxic T cell density in the tumor, CD8+PD-L1+ cell proximity index in the tumor, regulatory T cells in tumor parenchyma, regulatory T cells in the stroma, exhausted T cells in the tumor). Overall, PIONeER Biomarkers demonstrated that ECOG performance status remains the strongest predictor of OS and suggested a predictive value for PD-L1 tumor expression (although PD-L1-positive cell density might be superior), density of cytotoxic T cells in the tumor, and density of immunosuppressive cells such as T regulatory cells and myeloid-derived suppressor cells. The study is continuing to recruit patients. Additional analyses will provide further data to design an “immunogram” helping to drive the immunotherapy management of patients with advanced NSCLC. ■

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Early-stage lung cancer: noteworthy findings for different types of therapy

Phase III data regarding postoperative radiation

Postoperative radiotherapy (PORT) in patients with completely resected NSCLC has been a subject of debate for years. In the absence of robust data confirming the benefit of this intervention, its feasibility was additionally challenged by a multitude of changes that have taken place over the last two decades with respect to patient selection, (neo)adjuvant chemotherapy, surgery, and radiotherapy. Therefore, the large, randomized, phase III LungART study was designed to assess the role of modern mediastinal PORT in patients with completely resected NSCLC and proven N2 nodal involvement. Patients were randomized to either conformal PORT at a dose of 54 Gy delivered over 5.5 weeks (n = 252) or the control arm that went without radiotherapy (n = 249) at centers in France, UK, Germany, Switzerland, and Belgium.

In both arms, 96 % of patients received (neo)adjuvant chemotherapy. Patient selection was predominantly conducted via PET scan. Approximately 40 % had unforeseen N2 disease according to the cTNM classification. According to pTNM or ypTNM, 45 % in each arm showed 1 involved N2 station, and in 52 %, ≥ 2 stations were involved.

In each arm, approximately 80 % of patients underwent lobectomy. The main PORT technique used in the experimental arm was 3D-conformal radiation therapy (89 %). Eleven percent received intensity-modulated radiotherapy. LungART is the first European randomized study to evaluate modern PORT after complete resection in patients selected predominantly with PET who have received (neo)adjuvant chemotherapy. Disease-free survival (DFS) was defined as the primary endpoint.

Increases in cardiopulmonary toxicity

Le Péchoux et al. reported the primary endpoint analysis of LungART at the

TABLE

Causes of death in the LungART study with and without postoperative radiotherapy (PORT)

Cause of death, n (%)	PORT arm (deaths, 99)	Control arm (deaths, 102)
Progression or recurrence	68 (69.4)	87 (86.1)
Cardiopulmonary	16 (16.2)	2 (2.0)
Second primary tumor	5 (5.1)	1 (1.0)
Radiotherapy- or chemotherapy-related toxicity	3 (3.0)	0 (0)
Other	6 (6.1)	11 (10.9)
Unreported	1	1

ESMO 2020 Congress [1]. After a median follow-up of 4.8 years, median DFS was 30.5 vs. 22.8 months in the PORT and control arms, which was equivalent to a non-significant advantage (HR, 0.85; $p = 0.16$). At 3 years, DSF rates were 47.1 % vs. 43.8 %; these were higher than expected in both arms. A greater proportion of patients in the control arm had mediastinal relapse as first event (46.1 %) compared to those in the PORT arm (25.0 %), although death occurred more frequently as the first event in the PORT-treated patients than in the control patients (14.6 % vs. 5.3 %). OS did not differ across the arms, with 3-year rates of 66.5 % vs. 68.5 %. Overall death rates in the two arms were comparable (39.6 % vs. 41.5 %). However, progression or recurrence was responsible for a greater percentage of fatalities in the control arm, whereas more patients in the PORT arm died due to cardiopulmonary causes (Table).

As expected, early grade 3/4 toxicity occurred more commonly in the experimental arm (11.6 % vs. 7.7 %), as did late grade 3/4 toxicity (14.6 % vs. 8.9 %). Within the first 3 months after randomization, 3 patients in the PORT arm (1.2 %) vs. none in the control arm died due to toxicity (i.e., cardiopulmonary arrest, pneumonitis, infectious pneumonitis). In terms of late grade 5 toxicity, the arms did not differ (1.2 % vs. 0.8 %). Twenty-six patients in the PORT arm (10.8 %) vs. 12 in the control arm (4.9 %) experienced at least one cardiac/pulmo-

nary toxicity grade 3/4 event. Second cancers occurred in 11.1 % vs. 7.2 %; among these patients, second lung cancers were particularly common (39.3 % vs. 22.2 %). This issue clearly requires further analysis with respect to the location of the second tumor, patterns of failure with competing events, and other factors.

Overall, although mediastinal relapse was reduced almost by half in the PORT arm as compared to the control arm, conformal PORT cannot be recommended as a standard of care in all completely resected stage IIIA N2 NSCLC patients due to increased toxicity. Further analyses of the data obtained in the LungART study are planned.

ADAURA: 82 % reduction in CNS recurrence risk

In the double-blind, phase III ADAURA study, adjuvant use of the third-generation EGFR TKI osimertinib induced highly statistically significant and clinically meaningful DFS improvement in patients with completely resected, stage IB-IIIa, EGFR-mutant NSCLC [2]. At the ESMO 2020 Congress, Tsuboi et al. presented a pre-specified exploratory analysis of disease recurrence patterns observed in ADAURA, including CNS [3]. The type of recurrence is a key consideration in resected NSCLC due to worse prognosis in cases of distant events compared to local/regional progression and the significance of the CNS as a

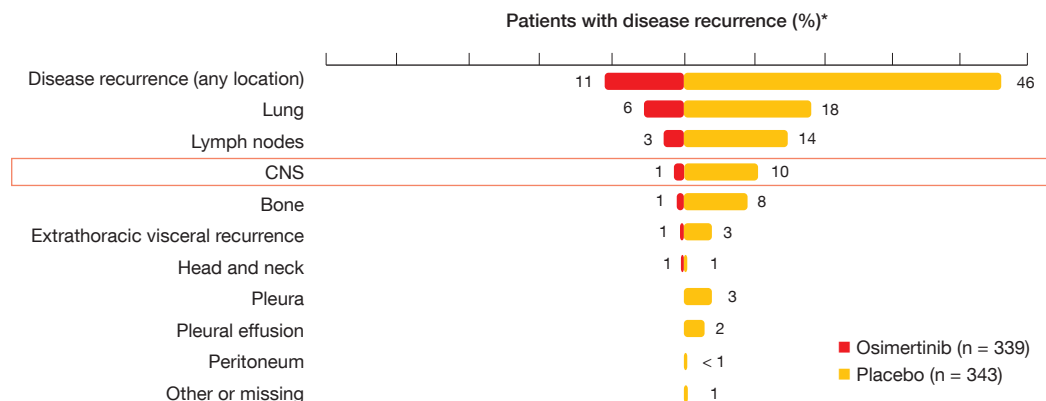


Figure 1: ADAURA trial: sites of disease recurrence in the relapsing population

common site of distant recurrence in *EGFR*-mutant disease. Osimertinib has been shown to achieve clinically significant exposure in the brain compared to other *EGFR* TKIs and has demonstrated greater penetration of the blood-brain barrier [4-6].

In total, 11 % vs. 46 % of patients treated in the osimertinib and placebo arms of ADAURA, respectively, developed disease recurrence or died. Within the group of relapsing patients in the osimertinib arm, most showed local/regional recurrence (62 %), while 38 % had distant recurrence. In the placebo arm, these proportions were reversed (39 % and 61 % for local/regional and distant recurrence, respectively). Only 1 % of osimertinib-treated patients experienced CNS recurrence, as opposed to 10 % in the control arm (**Figure 1**). Compared to placebo, the risk of CNS disease recurrence or death observed in the osimertinib arm was reduced by 82 % (HR, 0.18; $p < 0.0001$). Kaplan-Meier estimates showed a consistently lower cumulative incidence of CNS recurrence in the osimertinib arm. The conditional probability of observing CNS recurrence in the absence of non-CNS recurrence or death at 18 months was < 1 % vs. 9 %. As the authors emphasized in their summary, these results reinforce adjuvant osimertinib as a highly effective, practice-changing treatment for patients with stage IB/II/IIIA, *EGFR*-mutant NSCLC following complete tumor resection.

Preoperative atezolizumab: PRINCEPS

In patients with NSCLC, neoadjuvant immune checkpoint inhibition has been shown to induce major pathological re-

sponse rates in 17 % to 45 % [7, 8]. The phase II PRINCEPS trial tested neoadjuvant atezolizumab monotherapy in patients with stage I to IIIA NSCLC and tumor diameters ≥ 2 cm [9]. Thirty patients unselected for PD-L1 expression received one injection of atezolizumab 1,200 mg, and surgery was performed approximately 4 weeks later, on day 21 to 28. Adjuvant chemotherapy \pm radiotherapy according to local standards was possible.

The 2-month tolerance rate (i.e., the rate of patients without major toxicities or morbidities between the start of treatment and 1 month after surgery) constituted the primary endpoint. Major toxicities or morbidities included treatment toxicity leading to a ≥ 15 day delay of surgery, grade ≥ 3 toxicity occurring within 2 months after atezolizumab administration, major postoperative morbidities, any death related to the experimental treatment that occurred from the day of atezolizumab administration to postoperative day 30, and omission of surgery due to early progression.

Besides clinical endpoints, several exploratory objectives were defined that included the adaptive immune response in the microenvironment in post-surgical fresh tissue and blood, the rate of circulating immunomarkers according to liquid biopsy, and molecular profiling at resection, prior to treatment and at disease progression, among others. Negative baseline PD-L1 expression status (< 1 %) was present in 62 % of patients, while 21 % had PD-L1 ≥ 1 % and 17 % were highly PD-L1-positive (≥ 50 %).

No impairment of surgery

Surgery was conducted after a median of 24 days from the administration of

atezolizumab. Notably, the resection was not delayed by ≥ 15 days in any patient. Almost all patients underwent lobectomy. In 97 %, R0 resection was possible, while 3 % had R1 resection. Adjuvant radiotherapy was conducted in 29.7 %. Seven of 30 patients (23 %) experienced complications within 1 month after surgery, mostly atrial fibrillation and infection. The complication rate matched the rate that was to be expected in this population. No grade 4/5 complications occurred.

According to RECIST 1.1, 7 % of patients developed partial response. Major pathological responses (i.e., < 10 % residual tumor cells) were observed in 14 %. Pathological response ≥ 50 % (i.e., < 50 % residual cells) was present in 41 %. No patient developed complete pathological response. Analyses demonstrated that pathological responses did not show any correlation with RECIST 1.1 response rates nor metabolic variations according to octreoscan or 18F-FDG PET/CT. However, the researchers found a correlation between pathological response and PD-L1 expression at baseline, as increased PD-L1 levels on tumor cells were associated with more pronounced pathological regression. Quantitative results confirmed this correlation. Also, characterization of the immune infiltration on fresh tissue within 4 hours after resection was initiated. According to flow cytometry analysis, there was a clear correlation between PD-L1 expression and TIGIT expression on lymphocytes.

The authors concluded that one cycle of preoperative atezolizumab was safe and did not impair surgery. Recruitment of 30 patients who do not receive neoadjuvant therapy and who will

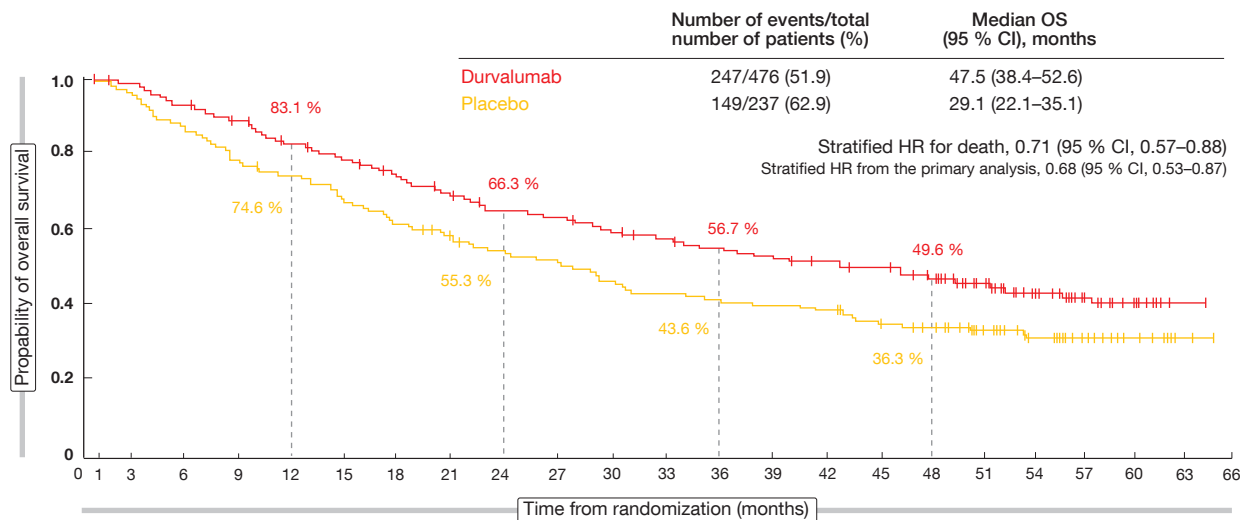


Figure 2: Long-term overall survival in the PACIFIC trial with durvalumab consolidation *versus* placebo

serve as a control group for translational research is ongoing. The final analysis of the immune contexture in blood and fresh tissue will be performed when the control group will be fully recruited.

Unprecedented OS improvement in PACIFIC at 4 years

The randomized, double-blind, phase III PACIFIC trial has demonstrated benefits of durvalumab as consolidation therapy in patients with stage III, locally advanced, unresectable NSCLC that had not progressed after platinum-based chemoradiotherapy. According to the primary analyses, durvalumab improved both PFS (16.8 vs. 5.6 months; HR, 0.52; $p < 0.001$) and OS (17.2 vs. 5.6 months; HR, 0.68; $p = 0.0025$) [10, 11]. At the same time, the PD-L1 inhibitor exhibited a manageable safety profile and did not detrimentally impact patient-re-

ported outcomes [10–12]. These findings established durvalumab after chemoradiotherapy as standard of care in unresectable stage III disease.

At ESMO 2020, Faivre-Finn et al. reported updated OS and PFS analyses from PACIFIC approximately 4 years after the last patient had been randomized [13]. The findings included the first estimate of median OS for the durvalumab arm, which was 47.5 months, translating into a 29% mortality reduction compared to placebo (29.1 months; HR, 0.71; **Figure 2**). At 48 months, OS rates were 49.6% vs. 36.3%. According to the updated PFS analysis, the risk of progression and death was reduced by 45% (17.2 vs. 5.6 months; HR, 0.55). The estimated 48-month PFS rates were 35.3% vs. 19.5%. All of the pre-specified subgroups benefited from the durvalumab treatment in terms of OS and PFS with the exception of patients with *EGFR* mu-

tations, although the small size of this subgroup and the exploratory nature of the analysis preclude definitive conclusions. The checkpoint inhibitor improved PFS in all PD-L1 subgroups as well as OS in patients with PD-L1-positive tumors, while those without PD-L1 expression did not appear to derive any OS benefit from the treatment. However, limitations need to be taken into consideration here, as this was an unplanned post-hoc analysis that was not powered for efficacy.

Overall, durvalumab consolidation after chemoradiotherapy continued to demonstrate durable PFS and sustained OS benefits at 4 years. Ongoing clinical trials are investigating concurrent immune checkpoint inhibition and chemoradiotherapy regimens and might further transform the treatment landscape for patients with unresectable stage III NSCLC. ■

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Determinants of treatment success in small-cell lung cancer

Predictive characteristics in CASPIAN ...

The randomized, controlled, open-label, phase III CASPIAN trial has assessed first-line treatment with durvalumab ± tremelimumab plus platinum/etoposide (EP) compared to EP alone in patients with extensive-stage small-cell lung cancer (ES-SCLC). Durvalumab plus EP significantly improved OS compared to EP alone (HR, 0.73; $p = 0.0047$) [1]. This benefit was maintained after more than 2 years of median follow-up (12.9 vs. 10.5 months; HR, 0.75; $p = 0.0032$) [2]. At 24 months, 22.2 % vs. 14.4 % of patients were alive. Exploratory analyses were conducted to identify clinical characteristics that might predict outcomes in patients deriving long-term benefit, as well as the relationship between tissue tumor mutational burden (tTMB) and efficacy [3]. PFS ≥ 12 months was used as a preliminary threshold to identify potential predictive parameters in treated patients.

In the durvalumab plus EP group, 45 of 265 patients (17.0 %) achieved PFS ≥ 12 months, and in the durvalumab plus tremelimumab plus EP arm, 42 of 266 patients (15.8 %). For both immunotherapy arms combined, the percentage of patients achieving PFS ≥ 12 months (87/531, 16.4 %) was more than 3 times higher than that in the EP arm (12/266, 4.5 %). Patients with PFS ≥ 12 months in all arms had improved ORR, duration of response, depth of response

and OS compared to the subgroups with PFS < 12 months (**Table 1**). The 2-year OS rates exceeded 75 %, which denotes an exceptional long-term benefit.

However, no unique clinical characteristics identified those who achieved long-term benefit. Across all treatment arms, patients with PFS ≥ 12 months showed a higher incidence of traditional favorable prognostic factors such as ECOG performance status 0 and lack of brain or liver metastases, although poor prognostic factors were also present in a meaningful percentage of patients. The groups with PFS ≥ 12 months and < 12 months did not differ with regard to use of cisplatin or overall chemotherapy exposure. Also, tTMB was not shown to predict OS improvement with durvalumab ± tremelimumab plus EP vs. EP alone at any cutoff or as a continuous variable. Despite greater exposure to durvalumab and numerically higher rates of immune-mediated AEs in the PFS ≥ 12 subgroup, rates of grade 3/4 AEs were similar to those in the PFS < 12 subgroup, as were serious AEs and AEs leading to discontinuation. Further investigation into predictive factors for long-term benefit with durvalumab is ongoing.

... and in IMpower133

Atezolizumab plus carboplatin/etoposide has been evaluated for the first-line treatment of ES-SCLC in the double-blind, placebo-controlled, phase III IMpower133 trial. Compared to placebo

plus carboplatin/etoposide, the immunotherapy-based regimen gave rise to improvements in OS (12.3 vs. 10.3 months; HR, 0.70; $p = 0.007$) and PFS (5.2 vs. 4.3 months; HR, 0.77; $p = 0.02$) [4]. Additional follow-up showed persistent OS benefit in the experimental arm with increased survival rates at 12, 18 and 24 months, establishing the IMpower133 regimen as a new standard of care [5]. As data are limited regarding the characteristics of patients who experienced long-term survival, Liu et al. presented exploratory analyses to characterize long-term survivors (LTS) defined as patients who lived ≥ 18 months since randomization [6].

The comparison across the study arms of IMpower133 showed that a greater proportion of LTS was treated with atezolizumab plus chemotherapy (61 of 182 patients, 33.5 %) than with placebo plus chemotherapy (39 of 191 patients, 20.4 %). For each of the patient characteristics (i.e., sex, age, ECOG performance status), more patients in the LTS group had received atezolizumab plus chemotherapy than chemotherapy alone. The same applied to disease characteristics (i.e., number of metastatic sites, presence of liver metastases or brain metastases, elevated LDH levels, greater sum of longest diameters of target lesions) that are typically associated with greater disease burden. With respect to each of these, LTS were more likely to have received atezolizumab rather than placebo.

TABLE 1

CASPIAN trial: improved outcomes in patients across both arms achieving PFS ≥ 12 months compared to those with PFS < 12 months

Outcome	PFS ≥ 12 months		PFS < 12 months	
	Durvalumab arms combined (n = 87)	EP (n = 12)	Durvalumab arms combined (n = 443)	EP (n = 254)
Confirmed objective response rate, %	94	100	58	57
Median duration of response, months	Not reached	20	4	5
Patients remaining in response at 24 months, %	59	48	0	0
Mean reduction from baseline in target lesion size, %	74.59	78.91	52.78	50.67
Median overall survival, months	Not reached	Not reached	10.1	10.0
24-month overall survival rates, %	82.2	83.3	11.0	10.4

According to the biomarker analysis, high blood-based TMB and PD-L1 expression using various cutoffs did not correlate with the likelihood of long-term survival. Therefore, neither TMB nor PD-L1 status appeared to have utility in patient selection. In the multivariate Cox regression analysis, only worse performance status, elevated LDH levels and highest sum of longest diameters were confirmed as poor prognostic variables (**Table 2**). The impact of atezolizumab treatment on OS was more pronounced after adjustment for other covariates in the multivariate model, with a significant HR of 0.71. As the authors concluded, these exploratory analyses suggest that patients with ES-SCLC can derive benefit from the addition of atezolizumab plus chemotherapy regardless of the patient and disease characteristics evaluated, confirming atezolizumab plus carboplatin/etoposide as a standard of care for patients with untreated ES-SCLC.

STIMULI: consolidation immunotherapy

In patients with limited-stage SCLC (LS-SCLC), chemoradiotherapy (CRT) followed by prophylactic cranial irradiation (PCI) is the standard radical strategy. The global, randomized phase II ETOP/IFCT 4-12 STIMULI trial aimed to demonstrate superiority of nivolumab plus ipilimumab as consolidation treatment in patients with LS-SCLC (stage I-IIIb) who had not progressed after CRT and PCI [7]. The induction phase comprised nivolumab 1 mg/kg and ipilimumab 3 mg/kg Q3W for 4 cycles and was followed by maintenance nivolumab 240 mg Q2W for a maximum of 12 months. Patients in the control arm did not receive any further treatment. A total of 153 patients were randomized to nivolumab plus ipilimumab (n = 78) or observation (n = 75). For administrative

TABLE 2

Multivariate Cox regression analysis performed in the ITT population included in IMpower133: correlation of certain variables with the likelihood of long-term survival

Covariate	HR (95 % CI)	p value
Treatment arm (reference: atezolizumab)	0.71	< 0.01
Sex (ref: male)	1.21	0.13
Age (ref: ≥ 65 years)	1.18	0.17
ECOG performance status (ref: 1)	1.43	0.01
Metastatic sites (ref: ≥ 3)	1.22	0.15
LDH (ref: > upper limit of normal)	1.30	0.04
Sum of longest diameters (ref: ≥ 111 mm)	1.56	< 0.01

reasons, the accrual was closed prematurely. Also, there was an unexpectedly low rate of identification of LS-SCLC cases and a high attrition rate (i.e. percentage of patients unable to complete CRT and PCI). Due to all this, the primary outcome was eventually defined as PFS after the original design had included a coprimary endpoint.

The STIMULI trial did not meet its primary endpoint (median PFS, 10.7 vs. 14.5 months for consolidation and observation, respectively; HR, 1.02; p = 0.93). Median time to treatment discontinuation in the experimental arm was as short as 1.7 months, and at 12 months, only 15.6 % of patients were still receiving treatment. This potentially explains the similar course of the curves, which crossed several times.

Benefits in certain subgroups

According to the subgroup analysis, patients with an ECOG performance status of 1 and those who received twice daily radiotherapy fractions appeared to derive a PFS benefit from nivolumab plus ipilimumab (HRs, 0.67 and 0.63, respectively). OS had not been reached in the experimental arm at the time of analysis and was 31.6 months in the control arm; this difference was not significant (HR,

1.06; p = 0.83). Again, benefits were seen for patients with ECOG PS 1 (HR, 0.44) and twice daily radiotherapy (0.41), as well as female patients (HR, 0.34).

Both treatment arms demonstrated the same pattern of progression. In the nivolumab plus ipilimumab arm, most treatment failures were due to toxicity, while in the control arm, disease progression constituted the most common reason for treatment failure. Treatment-related grade 3 to 5 AEs occurred in 51 % vs. 25 %, and most of these (49 %) led to treatment discontinuation in the experimental arm. The most frequent any-cause AEs included fatigue, anorexia, diarrhea, vomiting, pneumonitis, nausea, and cough.

In their conclusion, the authors noted that the short period on active treatment related to toxicity and treatment discontinuation has certainly impacted the efficacy results of the STIMULI trial. A longer follow-up will allow for the exploration of a possible late effect of immunotherapy consolidation on survival that was already apparent after the current short follow-up. Also, exploratory translational work is ongoing to identify biomarker-defined subgroups that could benefit from the consolidation immunotherapy treatment. ■

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Interview: Maarten Lambrecht, MD, PhD, Department of Oncology, KU Leuven – University of Leuven, Belgium

Exploring interactions between radiotherapy and the immune system

The modulation of molecular pathways that determine the patient response to radiotherapy might contribute to improving patient outcomes. What insights have been gained to date in this field of research that may be relevant in the years to come?

There is indeed a growing interest in the field of radiobiology and interactions between radiotherapy and molecular biology. In the last couple of years, there is a focus on the interaction between ionizing radiation and the immune system. We have observed that by exploiting the synergy between irradiation and the immune system, we can improve the treatment response. Furthermore, there is growing interest into the effect the immune system has on the specific toxicities caused by radiotherapy.

How can immunotherapy and radiotherapy be expected to interact?

Although radiotherapy is local treatment, it has been known for decades that there is an interaction between radiotherapy and the immune system. We know that an intact immune system is necessary for radiotherapy to be successful. In rare instances, even so-called abscopal responses can be observed where tumor responses are seen, located outside of the radiation field. However, it has been very difficult to harness this synergy. Over the last years, however, our understanding of the basic biology of this synergy has increased considerably. Now we know that radiotherapy has synergistic effects on the immune system through immunogenic cell death, release of cytokines and upregulation of major histocompatibility complex class I molecules that increase antigen presentation. On the other hand, irradiation can also have an immunosuppressive effect on the tumor microenvironment through upregulation of regulatory T cells or upregulation of the PD-L1 expression. The combination of agents such as checkpoint inhibitors with ionizing radiation is very promising because it can actually counteract the immunosuppressive features that are sometimes



Maarten Lambrecht, MD, PhD, Department of Oncology, KU Leuven – University of Leuven, Belgium

found in tumors. This way, radiotherapy can be used to prime the immune system like a sort of in-situ tumor vaccination in combination with different types of immunotherapy.

What is new with respect to non-invasive imaging biomarkers in oncology?

Generally, the major evolution in non-invasive imaging biomarkers in oncology over the last years has been the introduction of artificial intelligence. There is a lot of research going on in an attempt to identify non-invasive imaging biomarkers for both tumor response and the prediction of toxicity. Many promising data are emerging. So far, the big problem has been the validation of these results. For this we need a lot of data. Finding a standardized way to obtain these data and using all clinically relevant data to confirm certain imaging biomarkers will be the challenge in the years to come. However, these efforts can result in improving the prediction of patient outcomes.

What are your personal highlights from ESMO 2020?

For me as a radiation oncologist specializing in thoracic oncology, the ESMO Congress held three highlights. The first one was the presentation of the 4-year overall survival data of the PACIFIC trial that assessed the value of durvalumab as consolidation therapy in patients with stage III, unresectable NSCLC [1]. According to the analysis, the addition

of durvalumab increased OS, with a 4-year rate of nearly 50 % which is unprecedented in this patient population. This finding, together with manageable toxicity, is good news for this population that generally has a dismal outcome. It serves as an example where we see that the interaction between radiotherapy and immunotherapy has increased OS in patients without metastatic disease.

The second important abstract revealed rather disappointing results. The phase II STIMULI trial evaluated consolidation with nivolumab and ipilimumab in patients with limited-disease SCLC [2]. Similar to the PACIFIC trial, STIMULI tested a very promising combination of double immunotherapy with radiotherapy. However, the study failed to show any PFS benefit. This was very disappointing, as while checkpoint inhibition has demonstrated some activity in SCLC stage IV disease, the investigators did not observe the same effect in the limited-disease population. What they did see was an excess in toxicity in the consolidation arm. However, only a very limited proportion of patients in the experimental arm actually received sufficient immunotherapy, so the combination treatment was not completed in the majority of cases.

The third highlight was the LungART trial, which is an important study for radiation oncologists as it deals with the addition of postoperative radiotherapy in patients with stage III (N2), resectable NSCLC [3]. Patients were randomized to postoperative radiotherapy versus observation. We saw that this population did not derive any survival advantage from the addition of postoperative radiotherapy to standard treatment. ■

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Innovative and established approaches for patients with uncommon mutations

CROWN: first-line use of ALK inhibitor lorlatinib

The highly potent, brain-penetrant, third-generation ALK tyrosine kinase inhibitor lorlatinib has been widely approved for the treatment of patients with ALK-positive advanced NSCLC who have previously received ALK TKIs. In the first-line setting, lorlatinib was compared with crizotinib in the randomized, phase III CROWN study that included almost 300 patients with stage IIIB/IV, ALK-positive NSCLC. Solomon et al. reported results from a planned interim analysis of the trial at ESMO 2020 [1].

Overall, 104 centers in 23 countries participated in the CROWN study. In the experimental arm, 149 patients received lorlatinib 100 mg daily, and in the control arm, 147 patients were treated with crizotinib 250 mg twice daily. Asymptomatic treated or untreated CNS metastases were permitted. Approximately 25 % of patients in each arm had brain lesions at baseline. No crossover between the study arms was allowed. PFS according to blinded independent central review constituted the primary endpoint.

After a median follow-up for PFS of 18.3 and 14.8 in the lorlatinib and crizotinib arms, respectively, lorlatinib gave rise to a 72 % reduction in the risk of progression and death (median PFS, not reached vs. 9.3 months; HR, 0.28; $p < 0.001$). At 12 months, 78 % vs. 39 % of patients were progression-free. All of the pre-specified subgroups benefited from the third-generation ALK inhibitor. Specifically, the HR for patients with brain metastases was 0.20, corresponding to an 80 % risk reduction.

Intracranial remissions and CNS protection

Moreover, lorlatinib treatment resulted in significant benefits regarding ORR (76 % vs. 58 %, odds ratio, 2.25) and median duration of response (not reached vs. 11.0 months). Intracranial response rates in patients with measurable or

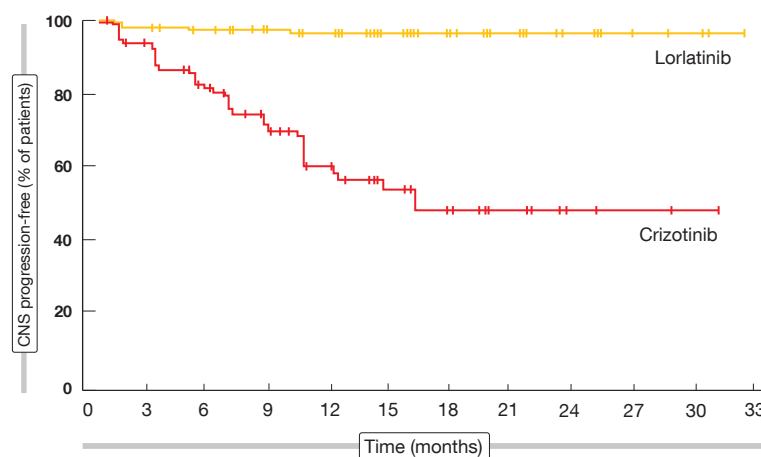


Figure 1: Time to CNS progression with lorlatinib vs. crizotinib as first-line treatment in patients with ALK-positive lung cancer

non-measurable brain metastases at baseline were higher in the experimental arm (66 % vs. 20 %; OR, 8.41). In patients with measurable brain lesions, the intracranial response rates even amounted to 82 % vs. 23 % (OR, 16.83), and a remarkable difference arose for intracranial complete remissions (71 % vs. 8 %). Time to CNS progression was significantly longer in the experimental arm (not reached vs. 16.6 months; HR, 0.07; $p < 0.001$; **Figure 1**), which translated into a risk reduction of 93 %. Notably, the curves showed a wide separation due to the paucity of intracranial progression events in the lorlatinib arm. These findings indicated the ability of lorlatinib not only to delay progression of existing brain lesions, but also to prevent the development of new ones.

Although OS data remained immature at the time of the interim analysis, the HR of 0.72 favored lorlatinib. The safety profile of lorlatinib resembled that reported in previous studies. Grade 3/4 AEs occurred more frequently with lorlatinib than with crizotinib; however, the majority of these were laboratory abnormalities that were asymptomatic and readily managed. No differences emerged across the arms in terms of AEs leading to permanent treatment discontinuation or temporary dose interruption.

According to patient-reported outcomes as assessed using the EORTC QLQ-C30 questionnaire, lorlatinib treatment led to significantly greater improvement in global quality of life from baseline ($p < 0.01$). This was seen early on and was maintained over the course of 18 cycles. As the authors noted in their summary, the results of the CROWN trial support the use of lorlatinib as a first-line therapy for patients with advanced ALK-positive NSCLC. No data on the activity of subsequent therapies after lorlatinib failure, particularly with respect to other ALK TKIs, were presented yet.

First-in-class KRAS inhibitor sotorasib

Despite the discovery of the *KRAS* oncogene almost 4 decades ago, no approved targeted therapy has been established thus far. The *KRAS*^{G12C} mutation is found in approximately 13 % of patients with NSCLC [2-4].

Sotorasib (AMG 510) is a novel, highly selective, first-in-class *KRAS*^{G12C} inhibitor that has demonstrated anticancer activity and a manageable safety profile in patients with *KRAS*^{G12C}-mutant solid tumors [4, 5]. The phase I, multicenter, open-label, dose-escalation, dose-expansion CodeBreaK100 trial assessed sotorasib in patients with

KRAS^{G12C}-mutant, locally advanced or metastatic solid tumors after prior standard therapies. Sotorasib 960 mg orally daily was identified as the recommended phase II dose. Overall, 129 patients with 13 different tumor types participated, including 59 with NSCLC.

Hong et al. presented the data obtained for the NSCLC cohort at ESMO 2020 [6]. Within this group, 34 patients received the 960 mg dose. Prior anti-PD-(L)1 therapy had been administered in 82.4 % and 89.8 % of the 960 mg dose cohort and the total NSCLC group, respectively. All patients had received platinum-based chemotherapy, and 75 % had been treated with ≥ 2 prior systemic anticancer therapy lines.

Durable disease control

According to the investigators' assessment, ORR was 35.3 % and 32.2 % for the 960 mg dose cohort and the total NSCLC group, respectively. Responses lasted for a median of 10.9 months, with 10 of the 19 responders still responding at the time of data cutoff. Disease control was obtained by 91.2 % and 88.1 % of patients, respectively. Tumor reductions were seen across all dose levels. Median PFS amounted to 6.3 months in the total group. Sotorasib demonstrated clinical activity across a range of *KRAS*^{G12C} mutational allele frequencies, PD-L1 tissue expression levels, and plasma tumor mutational burden levels. Also, clinical activity was found irrespective of tissue co-mutational profiles (e.g., *TP53*, *SMAD4*, *PTEN/PIK3CA*, *KEAP1*, *EGFR*).

Most AEs reported in the study were mild or moderate, with grade 3/4 treatment-related AEs showing an incidence of 18.6 %. Only one patient discontinued treatment due to a grade 3 AE, which was transaminase elevation. No dose-limiting toxicities and no treatment-related fatal AEs occurred. The most commonly observed any-grade AEs included diarrhea, transaminase elevations, fatigue, and nausea. In their conclusions, the authors emphasized that sotorasib showed a favorable safety profile and demonstrated durable disease control in this heavily pretreated patient population. Additional trials of the CodeBreak program evaluating sotorasib as monotherapy or in combination with other anticancer agents are underway.

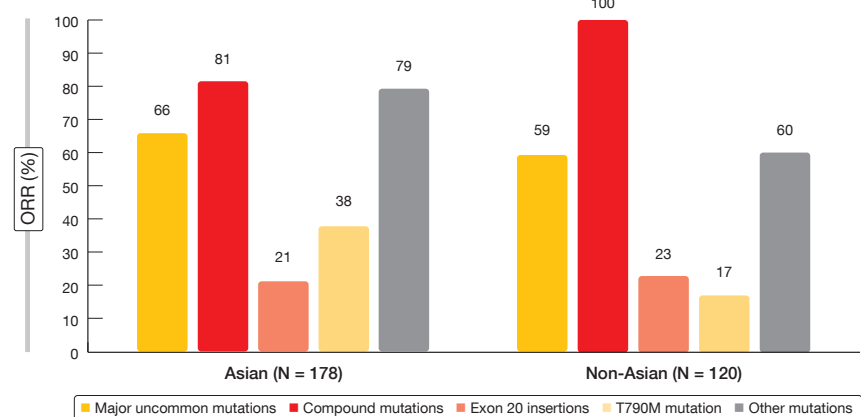


Figure 2: Objective response rates observed with afatinib in Asian and non-Asian patients harboring uncommon *EGFR* mutations

Afatinib in uncommon *EGFR* mutations

Uncommon *EGFR* mutations account for 7 % to 23 % of *EGFR*-mutated NSCLC cases and affect sensitivity to *EGFR* TKI treatment [7]. The irreversible ErbB receptor family blocker afatinib has shown clinical activity against major uncommon mutations including G719X, L861Q, and S768I [8]. However, there are few clinical data regarding the efficacy of *EGFR* TKIs against other uncommon *EGFR* mutations, and knowledge of ethnic differences in prevalence and outcomes is lacking. A pooled sub-analysis of the afatinib uncommon mutations database therefore assessed the efficacy of afatinib in the treatment of Asian (n = 178) and non-Asian (n = 120) patients with *EGFR*-mutated NSCLC harboring uncommon mutations [9]. Five mutation categories were defined: major uncommon (G719X, L861Q, S768I), compound, exon 20 insertions, T790M, and other mutations.

Asian patients were shown to have a high proportion of major uncommon mutations (61.8 %), for which afatinib has been approved. In the non-Asian group, exon 20 insertions ranked first (39.2 %), followed by major uncommon mutations (35.0 %). Afatinib showed activity in both Asian and non-Asian patients, with ORRs ranging from 17 % to 100 % (**Figure 2**). A certain percentage of patients with exon 20 insertions responded, which reflects the heterogeneity of this subgroup.

According to the assessment of duration of response and time to treatment failure, clinical activity was durable,

particularly in patients with major uncommon, compound or other uncommon mutations. The authors concluded that afatinib should be considered as a first-line option in Asian and non-Asian patients with major uncommon and compound *EGFR* mutations.

Treatment patterns of patients with *NRG1* fusions

NRG1 gene fusions are present in 0.2 % of all solid tumors, although their prevalence is higher in certain types such as invasive mucinous lung adenocarcinomas, where it has been estimated at 31 % [10, 11]. No approved therapies for patients with *NRG1* gene fusion-positive tumors are available yet. However, several reports suggest durable responses to treatment with afatinib [12–14], which might therefore represent a novel therapeutic option in patients with *NRG1*-positive cancer.

A retrospective, real-world feasibility study identified US-based patients with solid tumors harboring *NRG1* gene fusions who had received afatinib in any line of treatment or other systemic therapies without prior afatinib [15]. The objectives of the study comprised the assessment of the number of patients with *NRG1* gene fusion-positive solid tumors available for analyses and gaining insights into treatment patterns and testing. A total of 108 patients were identified 67 of whom had received afatinib.

The data support previous findings that *NRG1* gene fusions are detected across multiple tumor types [10]. In both the afatinib-treated group and the group receiving other systemic thera-

pies, NSCLC constituted the most common tumor type (40 % and 56 %, respectively), followed by gastrointestinal cancers and breast cancer. The most common *NRG1* gene fusion partners were *SDC4*, *CD74*, and *ATP1B1*. mRNA sequencing constituted the most commonly used testing methodology.

Afatinib was mainly prescribed in the second line, while other treatments dominated the first-line setting.

According to the authors, these findings provide a rationale for a larger, retrospective, chart-based cohort study evaluating treatment outcomes. The use of afatinib in *NRG1*-positive tumors is

under investigation in ongoing prospective studies including the Drug Rediscovery Protocol trial (DRUP; NCT02925234) and the Targeted Agent and Profiling Utilization Registry study (TAPUR; NCT02693535). ■

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EGFR-targeted options in a changing treatment landscape

Amivantamab plus lazertinib

The combination of amivantamab, a bispecific antibody that targets both *EGFR* and *MET*, and the potent third-generation *EGFR* TKI lazertinib is being explored in patients with advanced NSCLC. Amivantamab has demonstrated clinical activity across various types of *EGFR*-mutant NSCLC harboring both activating and resistance mutations [1] and was granted FDA Breakthrough Therapy Designation for *EGFR*-mutant NSCLC with exon 20 insertion after progression on platinum-based chemotherapy. Also, lazertinib was shown to be efficacious in NSCLC patients with activating *EGFR* mutations, T790M resistance mutation, and CNS disease [2, 3]. As with other third-generation *EGFR* inhibitors, rates of *EGFR*-related toxicity such as rash and diarrhea are low with lazertinib treatment. It was hypothesized that the com-

bination of these agents might have the potential to delay or prevent the emergence of resistance without increasing toxicity.

Patients with metastatic or unresectable *EGFR*-mutant (i.e., exon 19 deletions or L858R mutations) NSCLC were treated with amivantamab plus lazertinib in the phase I CHRYSALIS study [4]. The recommended phase II dose was found to be equivalent to the recommended monotherapy doses of each agent: amivantamab 1,050 mg in patients with body weight < 80 kg or 1,400 mg in patients weighing ≥ 80 kg, and lazertinib 240 mg. Amivantamab is administered intravenously once weekly in cycle 1 and two-weekly in subsequent cycles, while lazertinib is taken orally once daily. The dose escalation and dose expansion cohorts contained 26 and 65 patients, respectively; in the dose expansion cohort, 45 were osimertinib-resistant and chemother-

apy-naïve, while 20 were treatment-naïve. Within the total group of 91 patients, 37 % had brain metastases at baseline. The number of prior treatment lines ranged from 0 to 9. Fifty-nine percent had received first- or second-generation *EGFR* TKIs, and 58 % had been treated with third-generation TKIs.

Rapid and lasting responses

In the osimertinib-resistant, chemotherapy-naïve population, 36 % of patients obtained ORR, with one and 15 patients experiencing complete and partial remission, respectively. The clinical benefit rate was 60 %. Tumor regressions were observed regardless of the line of pretreatment with osimertinib and also occurred in patients who had progressed on prior lazertinib (Figure 1). Responses are ongoing in the majority of cases. Biomarker and CNS analyses for this group will be presented at future

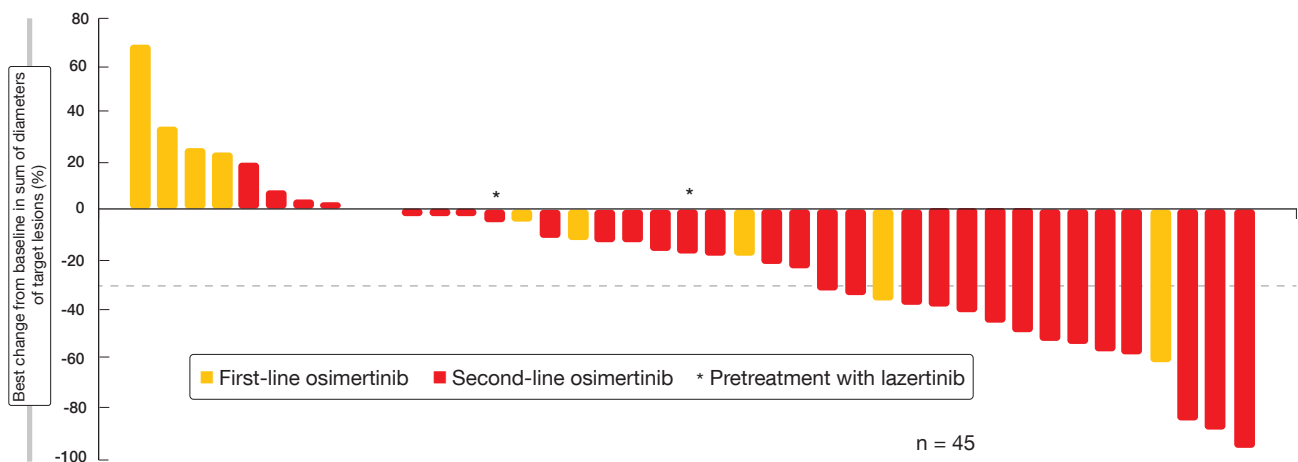


Figure 1: Changes in target lesions with amivantamab plus lazertinib in osimertinib-resistant, chemotherapy-naïve patients

meetings. In the treatment-naïve group, ORR and clinical benefit rates were 100 % each. Patients showed deep responses regardless of the *EGFR* mutation genotypes. Time to first response was short at a median of 1.5 months. After a median follow-up of 7 months, the treatment is ongoing in all patients.

The combination of amivantamab and lazertinib was safe and well tolerated. No dose-limiting toxicity occurred during escalation. AEs were predominantly grade 1 and 2; treatment-related serious AEs and grade ≥ 3 AEs were observed in 6 % and 11 %, respectively. As expected, the most common event was skin rash, which occurred in 85 %, followed by infusion-related reactions (65 %). Infusion-related reactions were mostly observed during the first administration and did not give rise to treatment discontinuations or dose modifications. In 19 % each, AEs led to dose interruption or reduction of either one or both drugs. However, discontinuation of either one or both drugs only became necessary in 6 %. The rates of AEs were similar across the dose-escalation, treatment-naïve, and osimertinib-resistant/chemotherapy-naïve groups.

According to the authors' conclusions, amivantamab can be safely combined with lazertinib and the combination is active in patients with advanced *EGFR*-mutated NSCLC. An analysis of the efficacy by mechanism of resistance is ongoing. New studies assessing amivantamab plus lazertinib have been started, including the phase III MARIPOSA trial (NCT04487080) that is comparing frontline use of the combination with osimertinib.

Antiangiogenic combination partner: apatinib

Blockage of the vascular endothelial growth factor receptor (VEGFR) pathways was demonstrated to enhance the efficacy of EGFR TKI treatment [5]. Therefore, the multicenter, randomized, double-blind, placebo-controlled, phase III ACTIVE trial evaluated the combination of the EGFR TKI gefitinib and the oral small molecule VEGFR2 TKI apatinib as first-line treatment in advanced lung cancer [6]. At 30 sites in China, chemotherapy-naïve patients with locally advanced, metastatic or recurrent non-squamous, *EGFR*-positive NSCLC were randomized to either apatinib 500 mg daily plus gefitinib 250 mg daily (n = 157) or placebo plus gefitinib (n = 156).

PFS according to independent radiology review committee, which constituted the primary endpoint, was significantly in favor of the combination (13.7 vs. 10.2 months; HR, 0.71; $p = 0.0189$; **Figure 2**). Almost all subgroups benefited from the addition of the VEGFR2 TKI. The study arms did not differ with respect to ORR (77.1 % vs. 73.7 %) or DCR (84.7 % vs. 87.8 %), although apatinib plus gefitinib significantly improved depth of response ≥ 30 % (89.2 % vs. 79.5 %; $p = 0.0209$) and depth of response ≥ 50 % (64.3 % vs. 52.6 %; $p = 0.0238$). Also, duration of response was longer in the experimental arm (12.9 vs. 9.3 months; HR, 0.64; $p = 0.005$). Apatinib plus gefitinib was generally well tolerated, with manageable toxicity. Dose interruptions of any drug due to treatment-emergent AEs (TEAEs) occurred in

59.9 % vs. 22.7 %, and dose reductions became necessary in 48.4 % vs. 4.5 %. However, only 5.1 % in the combination arm discontinued treatment due to TEAEs (vs. 3.2 % in the control arm). No unexpected safety signals were identified beyond the established safety profile of each agent.

A biomarker analysis conducted in 145 patients (73 and 72 in the experimental and control arms, respectively) showed that patients with *TP53* exon 8 mutation derived greater benefit from apatinib plus gefitinib (HR, 0.24) than those with *TP53* non-exon 8 mutation (HR, 0.79). Patients without *TP53* mutation did not experience any PFS prolongation (HR, 0.92). However, due to the small sample size, this observation requires confirmation in a large study. Similar PFS benefits were seen with *EGFR* exon 19 deletion and exon 21 L858R mutation (HRs, 0.67 and 0.72, respectively). The resistance biomarker analysis revealed that patients in both study arms developed a similar T790M resistance pattern, with T790M positivity in 37.8 % and 37.0 %, respectively. In their summary, the authors stated that apatinib plus gefitinib might become a new first-line option for advanced *EGFR*-mutant NSCLC. This dual oral regimen provides convenient treatment for patients who require long-term therapy.

No benefit of osimertinib plus bevacizumab

Less favorable results were generated for the combination of the third-generation EGFR TKI osimertinib, which is the standard option in T790-mutant

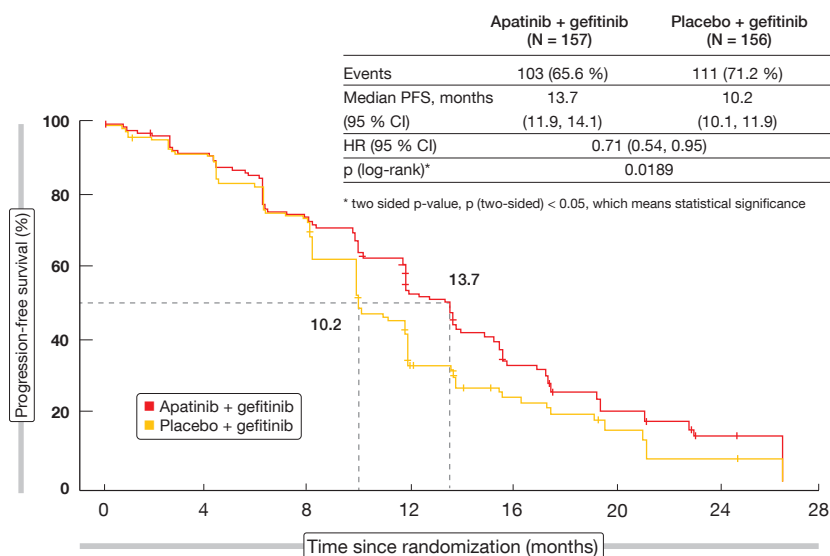


Figure 2: Superior progression-free survival with apatinib plus gefitinib compared to placebo plus gefitinib

NSCLC, with the anti-VEGF antibody bevacizumab. The randomized phase II WJOG8715L study compared osimertinib 80 mg daily plus bevacizumab 15 mg/kg Q3W (n = 40) with osimertinib 80 mg daily (n = 41) in patients with advanced, EGFR-TKI-resistant adenocarcinoma of the lung that had acquired the T790M mutation.

According to the primary analysis of the trial presented at ESMO 2020, the combination failed to improve PFS, which was defined as the primary endpoint (9.4 vs. 13.5 months; HR, 1.44; p = 0.20) [7]. This lack of efficacy was confirmed by the results of the subgroup analysis. In patients who had received prior anti-VEGF therapy, PFS was even shorter for the osimertinib plus bevacizumab combination than for the other regimens (osimertinib plus bevacizumab without anti-VEGF pretreatment, osimertinib monotherapy with and without anti-VEGF history). The ORR was higher in the combination arm than in the osimertinib monotherapy arm (71.8 % vs. 55.0 %), although no significant differences between the study arms were noted for time to treatment failure or OS. At the same time, AEs such as proteinuria and hypertension occurred significantly more frequently in the experimental arm.

Antibody drug conjugate patritumab deruxtecan

HER3 is expressed in approximately 80 % of EGFR-mutated lung cancers,

and overexpression has been linked to worse clinical outcomes [8]. The investigational HER3-directed antibody drug conjugate patritumab deruxtecan (U3-1402) was tested in patients with metastatic or unresectable EGFR-mutated NSCLC in a phase I study. The dose-escalation part included 12 patients who had progressed on osimertinib or were T790M-negative after progression on erlotinib, gefitinib, or afatinib. In the dose-expansion cohort (n = 45), patients after ≥ 1 EGFR TKI and ≥ 1 platinum-based chemotherapy were treated. Both cohorts received patritumab deruxtecan at the recommended phase II dose of 5.6 mg/kg Q3W.

Yu et al. presented updated findings of the combined cohorts [9]. This was a heavily pretreated population with a

median of 4 prior lines of therapy. Eighty-six percent had received osimertinib prior to study inclusion. Platinum-based chemotherapy had been administered in 90 %, and anti-PD-(L)-1 agents in 40 %. A history of CNS metastases was present in 47 %, as asymptomatic stable brain lesions were allowed. Patients were not selected for HER3 expression, although tumor tissue was collected prior to the initiation of study treatment for a retrospective analysis. This showed that the majority of patients had evidence of HER3 expression.

Fifty-six patients were evaluable for response. After a median follow-up of 5 months, the confirmed ORR was 25 %, which did not include 3 partial remissions yet to be confirmed (Table). One patient (2 %) achieved complete remission. Disease control resulted in 70 %. Responses emerged early on, and most patients experienced some degree of tumor shrinkage. According to next-generation sequencing on plasma or tumor tissue, clinically meaningful anti-tumor activity emerged in patients with diverse resistance mechanisms; this included confirmed partial responses in patients with EGFR C797S mutation, MET amplification, HER2 amplification, BRAF fusion, and PIK3CA mutation. Median PFS was not mature yet.

Patritumab deruxtecan 5.6 mg/kg continued to demonstrate a manageable safety profile. The most common grade ≥ 3 TEAEs were thrombocytopenia and neutropenia, although no patients discontinued treatment due to these toxicities. Three cases (5.3 %) of interstitial lung disease were reported.

TABLE
Clinical outcomes observed for patritumab deruxtecan according to blinded independent central review in heavily pretreated patients

Outcome	n = 56
Confirmed best response, n (%)	
Complete response	1 (2)
Partial response	13 (23)
Stable disease	25 (45)
Progressive disease	9 (16)
Not evaluable	8 (14)
Confirmed objective response rate, %	25
Disease control rate, %	70
Median time to response, months	2.0
Median duration of response, months	6.9

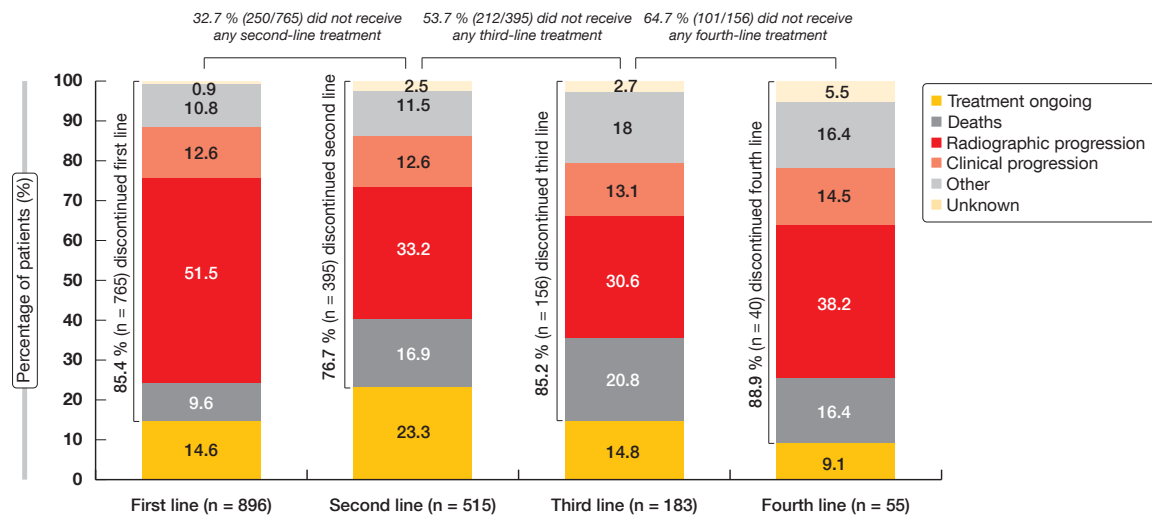


Figure 3: Attrition rates in the REFLECT study and reasons for treatment discontinuation across four treatment lines

Most TEAEs responded well to dose reduction and interruption. Collectively, these data support further clinical investigation of patritumab deruxtecan in a patient population with no available targeted therapy options. A phase II study of single-agent patritumab deruxtecan in patients after failure of EGFR TKIs and platinum-based chemotherapy is planned to start in early 2021.

Evaluation of low-dose afatinib

Although afatinib is an effective treatment option for patients with *EGFR*-positive NSCLC, its toxicities, particularly nail and skin AEs as well as diarrhea, often require dose modifications. Based on the assumption that a lower dose from the initiation of treatment might contribute to improving efficacy and safety, Noro et al. conducted a multicenter, single-arm, open-label, phase II trial assessing afatinib 20 mg daily in treatment-naïve patients with advanced NSCLC harboring common *EGFR* mutations [10]. Patients who showed complete or partial response or disease stabilization without tumor growth at 8 weeks continued the 20 mg dose, while in those with growing tumors, the dose was escalated to 30 mg or 40 mg daily. When drug-related grade ≥ 2 AEs occurred after dose increases, reductions were performed in 10-mg increments. Afatinib plasma concentrations were measured on day 9 after the start of treatment and at the time of disease progression. Fifty-three patients were enrolled at 21 institutions in Japan.

In 66.0% (n = 35), partial remissions were achieved. Thirty of these patients (56.6%) maintained their 20 mg dose over time, whereas the schedule was reduced to 20 mg every other day in five (9.4%) patients. Within the group that achieved stable disease (n = 14, 26.4%), dose escalations to 30 mg and 40 mg were performed in 4 (7.5%) and 2 (3.8%) patients, respectively. Eight patients continued the 20 mg dose. Disease progression occurred in 3 cases (5.7%), and one patient was not evaluable. Overall, afatinib 20 mg gave rise to a disease control rate of 92.5%. Median PFS and time to treatment failure were 12.6 months and 9.7 months, respectively. Median OS had not been reached yet at the time of the analysis.

Grade ≥ 3 AEs occurred in 12 patients (22.6%), including diarrhea in 4 patients (7.5%). This was lower than the rates for grade ≥ 3 AEs and diarrhea observed in the phase III setting with afatinib 40 mg (49% and 14.4%, respectively) [11]. Afatinib plasma concentrations 9 days after the start of treatment showed no correlation with ORR or time to treatment failure, performance status, smoking, clinical staging, or AEs including diarrhea. The only significant correlation was noted for the *EGFR* mutation status, with higher plasma concentrations in the exon 19 deletion group compared to the L858R mutation cohort (p = 0.03). Clinical activity was achieved even at low plasma concentrations with an average of 11.4 ng/ml. The authors pointed out that afatinib 20 mg might be considered a standard therapy

for patients with *EGFR*-mutated NSCLC based on these findings.

European use of EGFR TKI therapy

The retrospective multinational study REFLECT assessed treatment and testing patterns as well as outcomes and attrition rates in the context of first-line *EGFR* TKI therapy with first- and second-generation agents in Austria, Bulgaria, Greece, Israel, Poland, Romania, Slovenia and Switzerland [12]. Overall, 896 patients with locally advanced or metastatic *EGFR*-mutant NSCLC who started treatment with afatinib, gefitinib or erlotinib between January 1, 2015, and June 30, 2018, were included in the analysis. REFLECT is one of the largest attrition rate studies investigating first-line treatment with first- or second-generation *EGFR* TKIs that has been conducted in European patients.

Afatinib, erlotinib and gefitinib were administered in 45.4%, 27.3% and 27.2%, respectively. At the time of data collection, 85.4% of patients had discontinued treatment. Median time to discontinuation amounted to 12.6 months in the first line. Radiographic progression was the main reason for discontinuation across the treatment lines, with increasing proportions of patients not receiving any next-line treatment (Figure 3). Among patients progressing on first-line *EGFR* TKIs (n=723), only 513 (71.0%) were tested for the presence of the T790M resistance mutation. In these, the mutation was

found in 58.3 %. Osimertinib was prescribed for 94.6 % of patients with confirmed T790M mutations in any subsequent line, mostly in the second line. Additionally, osimertinib in any subsequent line was used by 41 patients (18.5 %) with negative T790M test results and by 15 (6.2 %) who had not undergone T790M testing.

Median PFS and OS from the start of the first-line EGFR TKI therapy were 13.0 and 26.2 months. As the authors noted in their summary, this study indicates suboptimal survival in patients with *EGFR*-mutant NSCLC treated with first- and second-generation EGFR TKIs. To improve outcomes, a better understanding of the efficient use of EGFR

TKIs is highly needed. However, the treatment landscape is anticipated to change after first-line approval of the third-generation EGFR TKI osimertinib, and further real-world evidence is awaited. ■

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Interview: Paul Baas, MD, PhD, Department of Thoracic Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands

Malignant mesothelioma: implementation of immunotherapy-based standards

Which outcomes can be expected in European patients with malignant mesothelioma who receive the current standard treatment?

After 4 to 6 courses of standard chemotherapy with platinum and pemetrexed, we can expect a median overall survival of around 15 or 16 months. This has hardly changed over the last 15 years. Due to patient selection, the results are a bit better than when we started with this chemotherapy regimen in 2004, but there is an urgent need to improve survival.

Where are we today regarding first-line checkpoint inhibitor treatment of mesothelioma?

Exploration of the combined modality treatment with immune checkpoint inhibitors and chemotherapy has just

been started, so we are in the process of building up evidence. In the first-line setting, CheckMate 743 is the first positive phase III study for checkpoint inhibition in patients with unresectable mesothelioma. The data presented at the WCLC Presidential Session in August 2020 showed an overall survival benefit with nivolumab plus ipilimumab compared to the standard chemotherapy in an all-comer population [1]. Nivolumab plus ipilimumab led to a median OS of 18.1, while this was 14.1 months with cisplatin or carboplatin plus pemetrexed, translating into a reduction of the risk of death of 26 %. At 2 years, 41 % compared to 27 % of patients were alive. This was the first actual prove of efficacy of an immunotherapy-based regimen over chemotherapy. Phase II trials investigating durvalumab

and chemotherapy have shown encouraging results, reinforcing the value of immunotherapy as a first-line approach in malignant mesothelioma [2, 3].

What can be said about later-line immunotherapy?

If the first-line treatment was chemotherapy, there is the possibility to use an immune checkpoint inhibitor as monotherapy or as part of a combination treatment. Single-agent nivolumab has demonstrated clinical benefits in patients with mesothelioma and has been approved in Japan in 2018 for second-line use based on the MERIT trial [4]. This was the first approval of an immuno-oncological agent in the second or later lines.

After first-line treatment with checkpoint inhibitors, especially nivolumab

plus ipilimumab, the next step depends on the condition of the patient, duration of the previous response and the availability of a study. I think that at present, after first-line combination treatment with immune checkpoint inhibitors, the patient should preferably be treated in a study.

Which regimens are currently being assessed?

Several ongoing phase III trials are evaluating immunotherapy plus chemotherapy as first-line treatment. Over the next 4 years, we can expect the results for at least 3 studies. Pembrolizumab is investigated together with cisplatin and pemetrexed (NCT02784171), as is durvalumab (NCT04334759), while atezolizumab is tested in addition to carboplatin, bevacizumab and pemetrexed (NCT03762018). The underlying biology of the disease remains to be elucidated further, and future translational studies may help to address this knowledge gap.

What is new regarding other immunotherapeutic approaches in mesothelioma?

Much research has been conducted in mesothelioma over the last 5 to 6 years. It has focused first on immunotherapeutic treatment, but of course this is not restricted to checkpoint inhibition but also includes CAR-T cells and anti-



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body-drug conjugates containing antibodies of mesothelin that are linked to a payload, which can be thorium or killer T cells. Also, vaccines are being developed. An example of this is the randomized phase II/III DENIM study that is run in Europe [5]. Immature dendritic cells are harvested from patients who have not progressed during first-line chemotherapy. These cells are exposed to epitopes of malignant mesothelial cell lines and are reinfused, in the hope that there will be an immune response. The DENIM trial is comparing dendritic cell therapy to best supportive care.

For many years, we have struggled to improve outcomes in this patient population where it was difficult to contain

the disease. I think one of the strong points to arise from the CheckMate 743 study in the future might be the emergence of a tail of the overall survival curve. This will indicate that some patients can be successfully treated for many years, just like we see it with melanoma and in some cases with NSCLC. We have to identify these patients, which is the real trick. Thus, we might not be able to actually cure mesothelioma, we might turn it into a chronic disease with considerably improved outcomes. ■

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Expert interviews at ESMO 2020

Lung Cancer



Paul Baas, MD, PhD,
Department of Thoracic Oncology,
Netherlands Cancer Institute
Amsterdam, Netherlands

Paul Baas discusses the prognosis and treatment of patients with malignant mesothelioma, relating to combined modality treatment with immune checkpoint inhibitors plus chemotherapy and talks about other immunotherapeutic approaches beyond checkpoint inhibition.



Maarten Lambrecht, MD, PhD,
Universitair Ziekenhuis Leuven
Leuven, Belgium

Maarten Lambrecht highlights aspects of radiobiology regarding interactions between radiotherapy and the immune system, non-invasive imaging biomarkers and trial results presented at ESMO 2020 that bear importance from a radiation oncologist's point of view.

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Tony S. K. Mok, MD,
Chinese University of Hong Kong
Hong Kong, China

Tony Mok summarizes insights into the immunotherapeutic management of patients with advanced lung cancer who receive PD-1 inhibitors and relates to aspects of biomarker-based treatment selection, patient prognosis, and new agents that might change the treatment landscape.



Byoung Chul Cho, MD, PhD,
Yonsei University College of Medicine
Seoul, Southkorea

Byoung Chul Cho explains about the rationale and outcomes for combined targeted treatment of lung cancer patients with an emphasis on EGFR-mutant disease and describes findings obtained for a first-in-class agent targeting the KRASG212C mutation.



WCLC CONGRESSES

Summary
WCLC
virtual Presidential
Symposium

WCLC 2020 – virtual

English

Improved median PFS for patients with late-stage non-squamous NSCLC treated with first-line sintilimab plus conventional chemotherapy regimen

Improved median PFS for patients with late-stage non-squamous NSCLC treated with first-line sintilimab plus conventional chemotherapy regime Orient-11 evaluated the efficacy and safety of the addition of sintilimab, an anti-PD-1 antibody, to conventional chemotherapy combination of platinum and pemetrexed as first-line therapy in patients with non-squamous non-small cell lung cancer (nsq NSCLC).

Ensartinib outperforms crizotinib as a treatment for patients with ALK-positive NSCLC who were naïve to ALK-targeted therapy

Ensartinib outperforms crizotinib as a treatment for patients with ALK-positive NSCLC who were naïve to ALK-targeted therapy eXalt3 was a randomized, open-label, comparator-controlled phase III trial designed to evaluate the efficacy and safety of treatment with either of two anaplastic lymphoma kinase (ALK) inhibitors alone, ensartinib or crizotinib, in the treatment of advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) patients.

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Combinational immunotherapy of nivolumab and ipilimumab prolongs survival in comparison to standard chemotherapy in malignant pleural mesothelioma

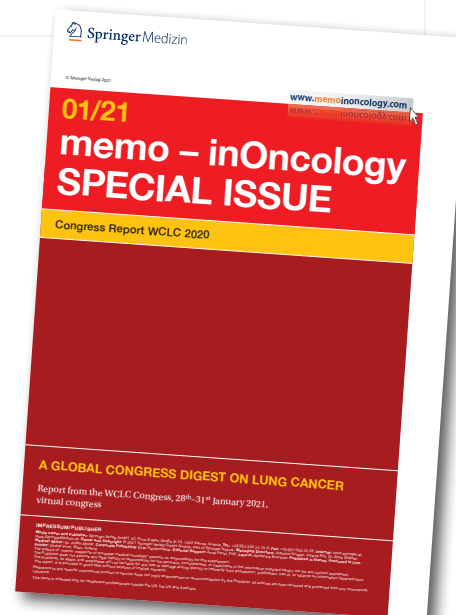
Combinational immunotherapy of nivolumab and ipilimumab prolongs survival in comparison to standard chemotherapy in malignant pleural mesothelioma CheckMate743, a randomized, open-label, phase III study evaluate the efficacy and safety of the combination treatment of two immunotherapy drugs, nivolumab (NIVO), an anti-PD-1 antibody, and ipilimumab (IPI), an anti-CTLA-4 antibody, as compared to standard chemotherapy in patients with malignant pleural mesothelioma (MPM).

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Forthcoming Special Issue

This special issue will be offering a synopsis from the WCLC 2020 that will be held in January 2021. The report promises to make for stimulating reading, as the WCLC 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.



WCLC 2020 – virtual Annual Meeting

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