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A GLOBAL CONGRESS DIGEST ON LUNG CANCER

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Preface

Dear Colleagues,

The 2020 World Conference of Lung Cancer (WCLC) originally scheduled for August 2020 in Singapore had to be postponed to January 2021 due to the COVID-19 pandemic and was finally held as a worldwide virtual conference from 28th to 31st January. WCLC, which is the leading gathering of international scientists, researchers and patient advocates in the field of lung cancer and thoracic malignancies, continues to provide a forum to connect, share knowledge and learn about the latest developments in the research and treatment of these diseases.

This publication summarizes content reported at the conference in various areas of clinical interest ranging from early-stage disease to the metastatic setting. Targeted therapies have succeeded in improving disease-free survival in patients diagnosed with early-stage lung cancer who tended to experience recurrence regardless of postoperative chemotherapy use. At the same time, customization of adjuvant chemotherapy based on genomic profiling did not contribute to survival prolongation. In advanced lung cancer, targeted therapy is gaining ground as various molecular aberrations are becoming amenable to treatment, including the *KRAS* p.G12C mutation which is found in approximately 13 % of lung adenocarcinomas. Convincing findings have been obtained for a first-in-class $KRAS^{G12C}$ inhibitor. Furthermore, refined treatment of *HER* aberrations offers new possibilities, and in *EGFR*-mutant lung cancer, innovative agents and regimens have demonstrated antitumor efficacy in difficult-to-treat settings including resistant disease. Among others, antibody-drug conjugates represent a versatile new technology that certainly meets the expectations regarding a 21st-century individualized approach.

Immunotherapy has become a mainstay of lung cancer treatment in various settings. Important analyses presented at WCLC 2020 related to findings obtained with a range of combination regimens not all of which proved successful, although checkpoint inhibition generally opens up the road to chemotherapy-free treatment. Combinations with targeted agents allow for tackling the disease from different directions and might enhance the efficacy of immunotherapy. Nevertheless, early detection of lung cancer undoubtedly provides unique advantages, even though the implementation of low-dose computed tomography screening still faces obstacles in many countries. Biomarkers might help to improve the selection of high-risk individuals who can be expected to benefit from screening programs.

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Pushing the bounds in early-stage lung cancer

ADAURA: role of adjuvant chemotherapy

Approximately 30 % of patients with non-small-cell lung cancer (NSCLC) present with resectable disease at diagnosis [1-3]. Surgery with curative intent is the recommended treatment here, followed by adjuvant cisplatin-based chemotherapy in stage II/IIIA and select cases of stage IB disease [4-6]. However, recurrence rates remain high across disease stages, regardless of postoperative chemotherapy use [7]. The randomized, double-blind, phase III ADAURA study has revealed a highly statistically significant and clinically meaningful improvement in disease-free survival (DFS) with the adjuvant administration of the third-generation EGFR tyrosine kinase inhibitor (TKI) osimertinib (HR, 0.20; $p < 0.0001$) in patients with completely resected stage IB-IIIA, *EGFR*-mutated NSCLC [8, 9]. Osimertinib ($n = 339$) was compared to placebo ($n = 343$) with and without concomitant use of adjuvant chemotherapy. In both treatment arms, 60 % of patients received chemotherapy for a median of 4 cycles prior to randomization. At WCLC 2020, Wu et al. reported an exploratory analysis relating to adjuvant chemotherapy use and outcomes observed in ADAURA [10].

As expected, higher-stage disease and younger age (< 70 years) were generally associated with increased adjuvant chemotherapy use as compared to lower disease stage and older age, while WHO performance status (0 or 1) did not affect the treatment decision. Overall, chemotherapy use was in keeping with observations from previous studies and clinical practice [11, 12]. DFS benefits obtained with osimertinib vs. placebo did not depend on whether chemotherapy had been administered or not. Patients after adjuvant chemo-

TABLE 1
Disease-free survival in ADAURA according to disease stage and use of adjuvant chemotherapy

Stage	Study treatment	Median DFS, months	HR	Median DFS, months	HR
		With adjuvant chemotherapy		Without adjuvant chemotherapy	
Overall	Osimertinib	Not reached	0.16	Not reached	0.23
	Placebo	22.1		33.1	
IB	Osimertinib	Not reached	Not calculable	Not reached	0.38
	Placebo	48.2		Not reached	
II	Osimertinib	Not reached	0.15	Not reached	0.20
	Placebo	29.4		22.1	
IIIA	Osimertinib	38.8	0.13	38.6	0.10
	Placebo	12.9		11.2	

therapy achieved an 84 % risk reduction (median DFS, not reached vs. 22.1 months; HR, 0.16; **Table 1**); 24-month DFS rates were 89 % vs. 49 %. For those without adjuvant chemotherapy, the risk reduction amounted to 77 % (not reached vs. 33.1 months; HR, 0.23), with 24-month DFS rates of 89 % vs. 58 %.

Osimertinib consistently improved DFS across disease stages **(Table 1)**. In the subgroup of patients with stage IB disease who received chemotherapy, the hazard ratio was not calculable due to the small sample size and low number of events. Higher recurrence rates observed among placebo-treated patients who received adjuvant chemotherapy compared with those who did not were likely driven by the large proportion of patients with stage II/IIIA disease, as disease stage is a prognostic factor for clinical outcome [4]. The authors concluded that these data support adjuvant osimertinib as a highly effective treatment for patients with stage IB/II/IIIA *EGFR*-mutant NSCLC after resection with or without adjuvant chemotherapy.

Patient-reported outcomes from ADAURA

An important goal of adjuvant treatment is to improve efficacy outcomes while also maintaining health-related quality of life (HRQoL). Limited HRQoL data are available in the adjuvant NSCLC setting to date. ADAURA is the first global, randomized, phase III trial in patients with resected *EGFR*-mutant NSCLC to evaluate HRQoL outcomes with adjuvant EGFR TKI treatment compared to placebo, with or without prior adjuvant chemotherapy [13-17]. HRQoL was measured using the health survey SF-36 until disease recurrence, treatment completion at 3 years or treatment discontinuation, whichever came first. At data cutoff, median duration of total exposure was 22.5 months for osimertinib and 18.7 months for placebo.

The findings presented at WCLC 2020 showed that HRQoL was not affected by osimertinib treatment with and without chemotherapy in completely resected and disease-free patients [18]. No clinically meaningful differences between osimertinib and placebo were observed from baseline to week 96 for physical and mental component summary T-scores or health domain T-scores (i.e., physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health).

During the disease-free period, > 80 % of patients across both arms did not experience any clinically meaningful deterioration in physical or mental component summary scores. For those who had deterioration, there were no differences in time to deterioration for any of the two summary scores between osimertinib and placebo. Moreover, time to deterioration of the SF-36 health domains did not differ across the treatment groups. Overall, despite prolonged treatment in the experimental arm of ADAURA, HRQoL was maintained, which further corroborates the significance of osimertinib as a new treatment strategy in this setting.

Interim findings for icotinib

The ongoing randomized, open-label, phase III EVIDENCE study is assessing the first-generation EGFR TKI icotinib, which has been approved for first-line monotherapy of *EGFR*-mutated NSCLC in China, in the adjuvant setting. Patients with completely resected, stage II-IIIA NSCLC were randomized to either icotinib 125 mg 3 times daily for 2 years (n = 161) or chemotherapy with cisplatin plus vinorelbine or pemetrexed depending on histology for 4 cycles (n = 161). DFS constitutes the primary endpoint. Approximately two thirds and one third of patients in each arm belong to the tumor stage categories IIA and IIIA, respectively, while only a minority has IIB disease. Lobectomy was performed in approximately 90 %.

As the interim analysis reported at WCLC 2020 showed, adjuvant icotinib significantly prolonged DFS compared to chemotherapy, with a risk reduction of 64 % (46.95 vs. 22.11 months; HR, 0.36; $p < 0.0001$) [19]. OS results were not mature yet. After a median duration of treatment of 22.2 months and 2.8 months with icotinib and chemotherapy, respectively, the safety analysis yielded no new signals. The most common grade 3/4 treatment-related adverse events (AEs) in the icotinib arm were rash (1.9 %), diarrhea (0.6 %) and dry skin (0.6 %). In the chemotherapy arm, these were neutropenia (41.0 %), leucopenia (19.4 %), vomiting (12.9 %) and nausea (7.2 %). No cases of interstitial lung disease occurred in either group. In their summary, the authors

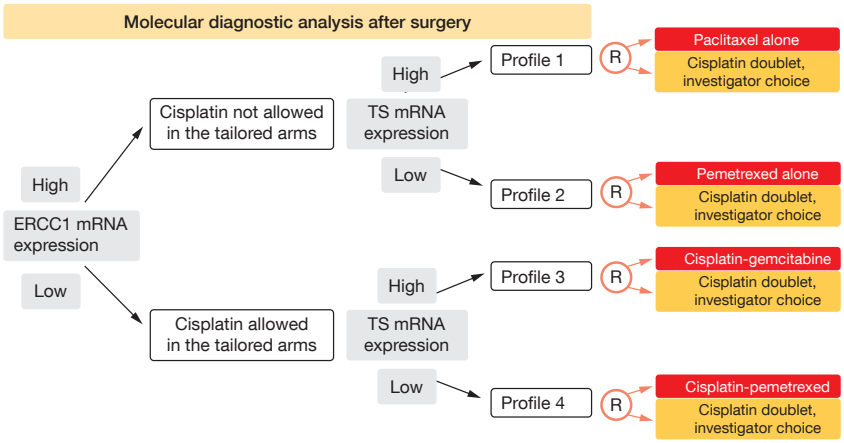

Figure 1: Design of the ITACA trial: randomization in four patient groups that have been allocated using ERCC1 and TS mRNA expression

emphasized that adjuvant icotinib might provide a new treatment option for patients with *EGFR*-mutant, early-stage NSCLC who have undergone complete tumor resection.

ITACA: chemotherapy customization

As the OS benefit of adjuvant platinum-based chemotherapy in early-stage NSCLC is modest, there is a clear need to better define patients most likely to derive survival improvement from this treatment while sparing those who do not need adjuvant chemotherapy. Based on the observation that mRNA expression of different genes has been correlated with the sensitivity or resistance to specific anticancer agents [20, 21], the phase III adjuvant ITACA trial aimed to evaluate the predictive utility of the mRNA expression levels of the molecular markers excision repair cross complementation 1 (ERCC1) and thymidylate synthase (TS) [22]. Randomization was performed following centralized assessment of ERCC1 and TS levels by real-time PCR on samples from completely resected, stage II-IIIA NSCLC. The first allocation pertained to high vs. low ERCC1 mRNA expression, which was followed by allocation to high vs. low TS mRNA expression in each of the ERCC1 groups **(Figure 1)**.

This resulted in four groups characterized by distinct genomic profiles within which the patients were randomized to treatment. All patients in the four control arms received standard chemotherapy with cisplatin doublets according to investigator's choice. In the ERCC1-high part of the population, cisplatin was not allowed in the tailored arms. TS mRNA expression was relevant for the decision between paclitaxel and pemetrexed in the tailored ERCC1-high groups and gemcitabine vs. pemetrexed in the tailored ERCC1-low groups. A total of 31 centers in Italy, Germany and Poland participated in the trial.

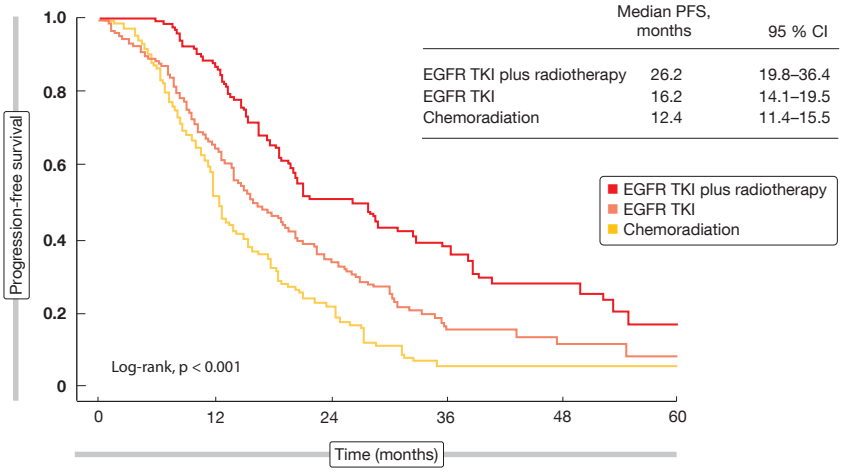

Figure 2: Progression-free survival for chemoradiation, EGFR TKI therapy and EGFR TKI plus radiotherapy after IPTW analysis

No significant results in an underpowered sample

Between 2008 and 2014, 773 patients were randomized. For statistical purposes, all pharmacogenomic-driven arms were grouped together as the tailored arm (n = 344), and all control arms were grouped together as the standard arm (n = 346). OS was defined as the primary endpoint. In both arms, patients received a median of four cycles.

Adjuvant chemotherapy customization based on the primary tumor tissue mRNA expression of ERCC1 and TS did not result in significant OS improvement. A trend favoring the tailored approach was observed in the ITT population (96.4 vs. 83.5 months; HR, 0.76). At the time of the final analysis, the study was underpowered; only 46 % of expected events had occurred. No heterogeneity existed regarding OS between different genomic profiles, although the statistical power was very low. Likewise, recurrence-free survival did not differ significantly across the arms (64.4 vs. 41.5 months; HR, 0.94).

At the same time, treatment customization significantly improved the toxicity profile of treatment without compromising efficacy; this difference mainly related to hematological AEs. The odds ratio of ≥ 1 grade 3-4 event was 0.57 for the comparison between the tailored and control arms ($p < 0.001$). Considering the insufficient statistical power of the analysis, the authors concluded that more comprehensive and high-throughput diagnostic techniques will be needed to tailor adjuvant chemotherapy with or without immunotherapy in completely resected NSCLC.

EGFR TKI therapy for stage III *EGFR*-mutant disease

In the setting of unresectable, locally advanced NSCLC harboring *EGFR* mutations, the efficacy of early use of EGFR

TKIs is unclear. A retrospective analysis investigated first-line treatment patterns in 440 patients with unresectable stage IIIA/IIIB NSCLC treated at 12 Chinese academic cancer institutions [23]. Group 1 received concurrent or sequential chemoradiation; group 2 underwent radiotherapy plus EGFR TKIs with or without chemotherapy; and group 3 had upfront TKI treatment alone until tumor progression. For their analysis, the researchers used inverse-probability of treatment weighting (IPTW) based on a multinomial propensity score model to reduce the effects of potential confounding factors while maximizing the effective sample sizes.

According to the IPTW analysis, TKI treatment plus radiotherapy with or without chemotherapy proved superior to both the standard chemoradiation approach and the TKI-only approach with respect to overall survival (OS) and progression-free survival (PFS). Median OS was 67.4 months with TKI plus radiotherapy vs. 51.0 months with chemoradiation (HR, 0.61; p = 0.039) and 49.3 months with TKI monotherapy. For PFS, this was 26.2 months vs. 12.4 months (HR, 0.40; p < 0.001) and 16.2 months **(Figure 2)**. The OS benefit might be explained by the effective control of both local-regional and distant disease. Concerning locoregional failure, patients treated with TKI plus radiotherapy had the lowest risk compared to the other groups, with a 52 % risk reduction *versus* chemoradiation (HR, 0.48; p = 0.002). For distant progression, both patients receiving TKI plus radiotherapy and TKI monotherapy fared better than those in the chemoradiation group (HRs, 0.62 and 0.56, respectively; p = 0.013 and < 0.001, respectively).

The authors noted in their conclusion that the combination of treatment modalities will provide health benefits for a greater number of patients with unresectable, locally advanced NSCLC. Randomized, controlled trials with the aim of exploring irradiation plus EGFR TKI treatment with or without chemotherapy are warranted.

LCMC3: neoadjuvant atezolizumab

The neoadjuvant use of atezolizumab was investigated by the LCMC3 trial that included untreated patients with resectable NSCLC (i.e., unselected stage IB-IIIA and select stage IIIB). Prior to surgery, two cycles of atezolizumab were administered. Thereafter, the protocol permitted optional adjuvant atezolizumab for 12 months or stage-appropriate therapy according to investigator's choice. At WCLC 2020, Lee et al. presented the primary analysis of the trial [24]. Out of 181 patients who constituted the safety population, 159 underwent surgery. A total of 144 individuals made up the primary efficacy population.

TABLE 2
Immune-related adverse events (irAEs) observed with neoadjuvant atezolizumab in the LCMC3 study

Patients with ≥ 1 AE, n (%)	Preoperative irAEs (n = 181)	Postoperative irAEs (n = 159)
Grade 1	22 (12)	18 (11)
Grade 2	16 (9)	12 (8)
Grade 3	3 (2)	11 (7)
Grade 4	0	1 (1)
Grade 5	0	1 (1)

The primary endpoint of major pathologic response (MPR; defined as ≤ 10 % viable tumor cells) was met, with a rate of 21 % in the primary efficacy population. Seven percent of these patients achieved pathological complete response. Downstaging following atezolizumab therapy resulted in 43 %, while 19 % of patients upstaged. Resection was performed within the narrow protocol-defined window of ± 10 days from the completion of atezolizumab therapy in 88 % of cases. Median time from the end of cycle 2 to surgery was 22 days. Most patient underwent lobectomy (79 %); R0 resection was achieved in as many as 92 %.

Perioperative morbidity and mortality were low. Intraoperative events occurred in 4 %, and all complications were successfully treated. One patient died within 30 after surgery due to sudden death, and another within the time window of 30–90 days after surgery due to pneumonitis. The median length of hospitalization was 7.5 days. Pre- and postoperative immune-related AEs were mostly grade 1 and 2 **(Table 2)**.

Exploratory endpoints included efficacy outcomes in the primary efficacy population. DFS rates at 1.5 years were 79 % and 77 % for patients with stage I/II and stage III disease, respectively, while OS rates amounted to 91 % and 87 %, respectively. According to an analysis of clinical and biomarker data from LCMC3, patients who achieved MPR showed a trend towards OS and DFS improvement [25]. Also, better pathological responses were associated with *STK11* wildtype, higher tumor mutational burden and a greater amount of activated immune cells and CD68-positive cells in the tumor microenvironment at baseline.

Overall, LCMC3 provides additional evidence for the ongoing placebo-controlled phase III IMpower030 study evaluating atezolizumab plus platinum-based chemotherapy.

Update of KEYNOTE-799

The standard of care for patients with stage III unresectable NSCLC includes concurrent chemoradiation (cCRT) and durvalumab as consolidation therapy in patients who have not progressed after ≥ 2 cycles of cCRT [26]. However, up to one third of patients might not be eligible for consolidation therapy with durvalumab [27, 28]. Therefore, the non-randomized phase II KEYNOTE-799 study investigated pembrolizumab plus cCRT in patients with stage IIIA-C, unresectable, previously untreated NSCLC. Cohort A that consisted of patients with both squamous and non-squamous NSCLC received pembrolizumab plus paclitaxel/carboplatin alone (cycle 1) and together with thoracic radiotherapy (cycles 2-3), which was followed by pembrolizumab monotherapy (cycles 4-17). Cohort B was restricted to patients with non-squamous NSCLC. Here, pembrolizumab plus pemetrexed/cisplatin was administered alone (cycle 1) and together with radiotherapy (cycle 2-3). In cycle 4-17, the patients received pembrolizumab monotherapy. At the time of the primary

TABLE 3
Objective response rates according to PD-L1 status and histology in KEYNOTE-799

	Cohort A (n = 112)		Cohort B (n = 61)	
ORR overall, n (%)	78 (69.6)		43 (70.5)	
PD-L1 Status	*TPS < 1 % (n = 21)*	*TPS ≥ 1 % (n = 66)*	*TPS < 1 % (n = 17)*	*TPS ≥ 1 % (n = 26)*
ORR, n (%)	14 (66.7)	49 (74.2)	11 (64.7)	18 (60.2)
Histology	*Non-squamous (n = 39)*	*Squamous (n = 73)*	*Non-squamous (n = 61)*	*Squamous (n = 0)*
ORR, n (%)	27 (69.2)	51 (69.9)	43 (70.5)	Not assessable

analysis, ORR was 67.0 % in cohort A and 56.6 % in cohort B [29]. Reck et al. reported the results of the study after an additional follow-up of 6 months [30].

Pembrolizumab plus cCRT continued to show promising antitumor activity. In cohort A (n = 112), ORR was 69.6 %, and in cohort B (n = 61), 70.5 %. Similar percentages were observed across the subgroups determined by PD-L1 tumor proportion score (< 1 % vs. ≥ 1 %) and histology (non-squamous vs. squamous; **Table 3**). Median duration of response had not been reached yet in either cohort. In 82.2 % and 72.1 % in cohorts A and B, respectively, responses lasted for ≥ 12 months. Likewise, median PFS had not been reached in both arms, with 12-month PFS rates of 67.7 % and 65.2 %, respectively. Twelve-month OS rates amounted to 81.2 % and 88.0 %. Median OS was immature.

The incidence of AEs among patients who received pembrolizumab plus cCRT was consistent with the established toxicity profiles of cCRT for stage III NSCLC and pembrolizumab monotherapy [31, 32]. Grade ≥3 pneumonitis occurred in 8.0 % and 7.9 %, respectively, and was thus within the expected range for immunotherapy combined with cCRT [33]. ■

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KRAS, HER2 & ALK: targeted options and sequencing issues

Deep responses with sotorasib: CodeBreak 100

The *KRAS* p.G12C mutation is a key oncogenic driver occurring in approximately 13 % of lung adenocarcinomas [1] and is associated with poor patient outcomes. The first-in-class, highly selective and irreversible $KRAS^{G12C}$ inhibitor sotorasib has shown durable clinical benefit in a cohort of 59 heavily pretreated patients with NSCLC included in phase I of the CodeBreaK 100 study [2]. Li et al. presented the results from the NSCLC cohort of the registrational, open-label, single-arm, phase II CodeBreaK 100 trial at the WCLC 2020 Congress [3]. In this part of the study, 126 patients from 11 countries with *KRAS* p.G12C-mutated, locally advanced or metastatic NSCLC who had progressed on prior standard therapies were treated with sotorasib 960 mg daily orally until disease progression. Almost all of them were current or former smokers. One prior line of systemic anticancer therapy had been administered in 42.9 %, while 34.9 % of patients had received two lines and 22.2 % three lines. Notably, 81 % had progressed on platinum-based chemotherapy and PD-(L)1 inhibitor treatment. The objective response rate (ORR) constituted the primary endpoint.

After a median follow-up of 12.2 months, confirmed ORR was 37.1 %, with 2.4 % and 34.7 % of patients achieving complete and partial responses, respectively. The disease control rate was 80.6 %. Tumor shrinkage of any magnitude occurred in 81 %; among responders, the median percentage of best tumor shrinkage amounted to 60 %. Moreover, the trial demonstrated early and durable responses to sotorasib. Median time to objective response and median duration of response were 1.4 and 10.0 months, respectively. Forty-three percent of responders remained on treatment without progression as of the data cutoff. Median progression-free survival was estimated at 6.8 months.

Treatment-related adverse events were generally mild and manageable, with low rates of grade 3 and 4 events (19.8 % and 0.8 %, respectively). Treatment discontinuation and dose modifications became necessary in 7.1 % and 22.2 %, respectively. The most commonly reported AEs comprised diarrhea, nausea as well as increases in ALT and AST levels. According to the exploratory biomarker analyses included in CodeBreaK 100, responses to sotorasib occurred in patients with low or negative PD-L1 expression **(Figure 1)** and independently of the *STK11*/*KEAP1* mutation status. The confirmatory phase III CodeBreaK 200 trial comparing sotorasib with second-line docetaxel is currently enrolling (NCT04303780).

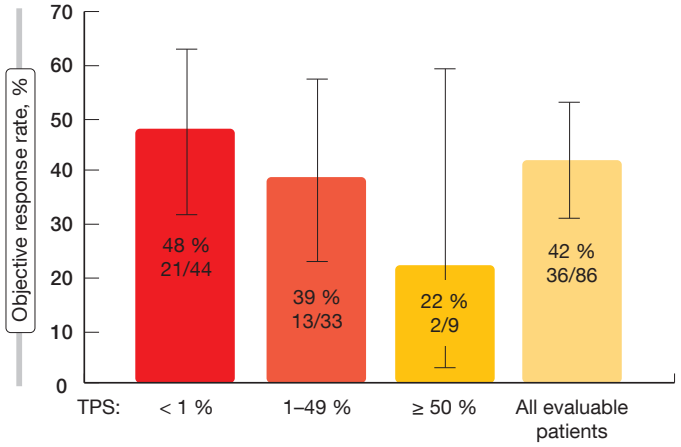

Figure 1: Responses to sotorasib therapy according to PD-L1 expression levels

DESTINY-Lung01

Somatic *HER2* mutations are seen at relatively low frequencies across multiple tumor types [4]. Preclinical models demonstrated that a subset of these mutations result in constitutive kinase signaling, oncogenic transformation and enhanced tumor growth [5]. The open-label, multicenter, phase II DESTINY-Lung01 study was designed to assess the novel antibody-drug conjugate trastuzumab deruxtecan (T-DXd) in patients with *HER2*-positive, unresectable/metastatic non-squamous NSCLC who had relapsed on or were refractory to standard treatment. DESTINY-Lung01 consisted of Cohort 1 that included patients with HER2-overexpressing tumors (n = 49) and Cohort 2 comprising patients with *HER2*-mutated disease (n = 42). Patients in both cohorts received T-DXd 6.4 mg/kg 3-weekly. At WCLC 2020, Nakagawa et al. presented the interim results for Cohort 1 [6].

In this group of extensively pretreated patients with HER2-overexpressing NSCLC who had received a median of three lines of therapy, T-DXd showed evidence of anti-tumor activity. The overall ORR was 24.5 %, without any apparent difference by HER expression; for patients with IHC 3+ and IHC 2+, ORRs were 20.0 % and 25.6 %, respectively **(Table)**. One patient developed CR (2.0 %), and disease control was achieved in 69.4 %. Responses lasted for a median of 6.0 months. Median PFS and OS were 5.4 months and 11.3 months, respectively.

Interstitial lung disease as a relevant issue

The safety profile was generally consistent with the observations from previous trials [7-11]. Drug-related treatment-emergent AEs (TEAEs) led to dose reductions in 32.7 %, while dose discontinuation due to the study drug became necessary in 12.2 %. Decreased neutrophil counts were the most common grade ≥ 3 TEAEs (20.4 %) and the main reason for dose reductions and interruptions (10.2 % each). Eight cases (16.3 %) of interstitial lung disease

TABLE 1
Trastuzumab deruxtecan in HER2-overexpressing lung tumors: responses and duration of response overall and by HER2 expression status

Response assessment by independent central review	IHC 3+ (n = 10)	IHC 2+ (n = 39)	Overall (n = 49)
Confirmed ORR, n (%)	2 (20.0)	10 (25.6)	12 (24.5)
Complete response, n (%)	0	1 (2.6)	1 (2.0)
Partial response, n (%)	2 (20.0)	9 (23.1)	11 (22.4)
Stable disease, n (%)	6 (60.0)	16 (41.0)	22 (44.9)
Progressive disease, n (%)	1 (10.0)	10 (25.6)	11 (22.4)
Not evaluable, n (%)	1 (10.0)	3 (7.7)	4 (8.2)
Disease control rate, n (%)	8 (80)	26 (66.7)	34 (69.4)
Median duration of response, months	6.0	5.8	6.0

(ILD) occurred, with grade 1, 2 and 5 cases observed in 4.1 %, 6.1 %, and 6.1 %, respectively. Among the three fatalities reported in the context of ILD, pneumonitis was the cause of death in one patient. Overall, median time to onset of drug-related ILD was 64.5 days. The treatment was withdrawn in all cases, and steroids were used in the patients with grade 2 and 5 ILD. In their conclusion, the authors noted that the encouraging efficacy results noted in DESTINY-Lung01 support the ongoing exploration of T-DXd in patients with *HER2*-overexpressing NSCLC. ILD continues to be closely monitored and proactively managed in the study, with further investigation as more follow-up data are becoming available.

Smit et al. reported the findings for the Cohort 2 of the DESTINY-Lung01 trial that included 42 patients with *HER2*-mutated advanced NSCLC [12]. In this group, the ORR was 61.9 %, and disease control was obtained in 90.5 %. Responses proved durable, with median duration of response not having been reached at the time of the analysis. Median PFS was 14.0 months. As for Cohort 1, the safety profile generally corresponded with previous reports. No high-grade ILD events occurred. According to the authors, these data demonstrated the potential of T-DXd as a new treatment option in patients with *HER2*-mutated NSCLC, which is a patient population with a high unmet need. Enrollment in the *HER2*-mutated cohort was expanded with an additional 50 patients to better characterize T-DXd in this group and further support the ongoing clinical trial program.

Neratinib alone and in combination

The oral, irreversible TKI neratinib targets EGFR, HER2, and HER4 [13]. It has been shown to display clinical activity across a spectrum of *HER2* mutations and tumor types, with sensitivity being both histology- and mutation-context–dependent [14]. Two international phase II trials assessed the activity of neratinib in patients with *HER2*-mutant lung cancers. PUMA-NER-4201 compared neratinib 240 mg/d (n = 17) in a randomized manner with neratinib 240 mg/d together with the mTOR inhibitor temsirolimus 8 mg/week (n = 43) in untreated or pretreated patients with stage IIIB/IV, *HER2*-mutated NSCLC. The open-label basket SUMMIT trial (PUMA-NER-5201) contained sequential open-label cohorts of patients with *HER2*-mutated lung cancers for which no curative therapy existed; they received neratinib alone (n = 26) or plus trastuzumab 8 mg/kg followed by 6 mg/kg 3-weekly (n = 52). Small in-frame insertions in exon 20 were the most frequent type of *HER2* mutation in both studies (95 % and 67 % in PUMA-NER-4201 and SUMMIT, respectively). Li et al. presented the outcomes obtained in the trials [15].
The analyses indicated that single-agent neratinib has limited activity in *HER2*-mutated NSCLC. ORRs were 0 % and 4 % for the monotherapy cohorts included in 4201 and SUMMIT, respectively. The combinations with temsirolimus and trastuzumab gave rise to numerically higher ORRs of 14 % and 8 %, respectively. Here, responses proved durable in a subset of pretreated patients, lasting for up to 22.6 and 18.3 months, respectively. Median OS was longest with neratinib plus temsirolimus, at 15.1 months.

Diarrhea constituted the most common AE, with any-grade events occurring in > 80 % of patients across all cohorts. Grade ≥ 3 diarrhea was reported in up to 40 %. However, dose reductions and permanent treatment discontinuation were rare. Other AEs included nausea, vomiting, constipation and fatigue. The authors noted that additional novel combinations of neratinib with other HER2-directed therapies in *HER2*-mutant NSCLC are being considered.

ARIA

In *ALK*-positive NSCLC patients, the detection of resistance mechanisms to ALK TKI therapy might help to select the subsequent treatment. The ARIA study investigated the activity of next-generation ALK TKIs based on the presence of *ALK* resistance mutations in circulating tumor DNA (ctDNA) obtained by liquid biopsy [16]. This analysis included 58 patients at 9 European sites who had *ALK*-positive, advanced NSCLC pretreated with first- and/or second-generation ALK TKIs. Liquid biopsy was collected immediately before the initiation of brigatinib or lorlatinib therapy. The activity of these two drugs was evaluated based on three ctDNA molecular groups:

- those with *ALK* mutations (only 1 mutation: single; ≥ 2 mutations: complex)

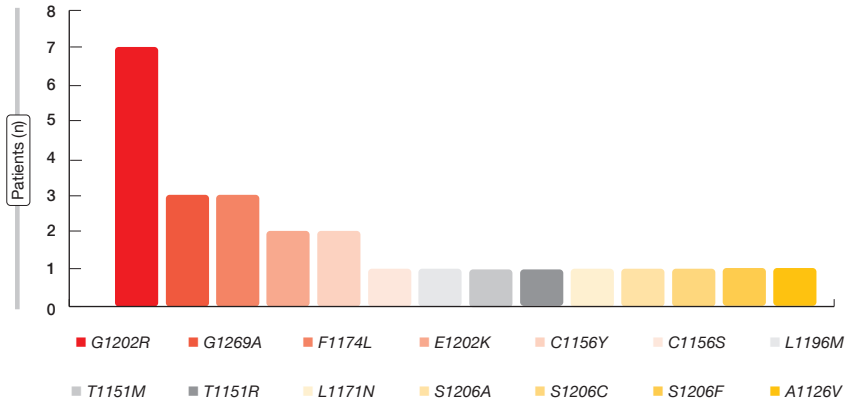

Figure 2: Subtypes of *ALK* mutations as assessed by liquid biopsy

- those with non-*ALK* mutations
- those without detectable mutations.

Among the 58 evaluable patients, 16 and 42 received brigatinib and lorlatinib, respectively. In these subgroups, 94 % and 74 % had previously been treated with crizotinib; the respective percentages for previous second-generation ALK TKI treatment were 69 % and 98 %. Most patients showed more than two metastatic sites, with intracranial lesions present in 88 % and 71 %, respectively.

Overall, *ALK* mutations were detected in 16 (28 %) patients; 9 of these were single, and 7 were complex. Other mutations were seen in 17 %, and 55 % of patients showed no mutations. The *ALK* mutations included a wide spectrum, with G1202R occurring most commonly, followed by G1269A and F1174L **(Figure 2)**. Per sample, 1–6 mutations were found. Five of the 16 patients with *ALK* mutations had previously received alectinib, another 5 had been treated with ceritinib, and 6 had received brigatinib.

Outcomes according to *ALK* resistance mutations

The subsequent treatment with lorlatinib demonstrated activity regardless of the ctDNA molecular groups. Median PFS was comparable across patients with *ALK* mutations (n = 13; 6.5 months), other mutations (n = 7; 7.6 months), and no mutations (n = 22; 7.3 months). ORRs amounted to 46 %, 71 %, and 23 %, respectively, and ORRs in the CNS were 56 %, 60 %, and 67 %, respectively. Median OS in the three groups was 62.6 months, 45.0 months, and had not been reached yet, respectively.

In contrast, outcomes observed for brigatinib in the *ALK*-mutated group were poor, although conclusions pertaining to this cohort are limited as it only comprised three individuals and patient numbers were low in general. Median PFS was 3.5 months compared to 6.2 months in the group with other mutations (n = 3) and 8.1 months in those without any mutations (n = 10). ORRs were 0 %, 67 %, and 22 %, respectively, and CNS responses occurred in 0 %, 100 %, and 50 %, respectively. Median OS amounted to 38.4 months, 62.6 months, and had not been reached yet, respectively. Summarizing these results, the authors emphasized that the recent upfront use of second-generation TKI therapy calls for similar studies to confirm if ctDNA might be a biomarker for guiding sequential therapy. ■

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Specific treatment approaches in the *EGFR*-mutated setting

Exon 20 insertions: phase I/II data for mobocertinib

EGFR exon 20 insertion mutations are found in approximately 5 % to 12 % of *EGFR*-mutated NSCLC tumors, i.e., in 2 % of all NSCLC cases [1, 2]. They represent the third most common *EGFR* mutation after L858R and exon 19 deletion [1, 3]. However, EGFR TKIs cannot be used to treat lung cancer with exon 20 insertions as they are insensitive to these drugs due to steric hindrance at the TKI-binding site [4]. No specific targeted therapies have been approved for the treatment of these patients to date. First- and second-generation EGFR TKIs or chemotherapy provide objective response rates of approximately 10 % to 15 % and median PFS of 3 to 5 months [5-10].

Mobocertinib (TAK-788) is a first-in-class, potent, oral TKI targeting *EGFR* exon 20 in-frame insertion mutations. Based on preliminary results from a phase I/II study, mobocertinib was granted a Breakthrough Therapy Designation in the USA and China for the treatment of NSCLC patients with exon 20 insertion in whom chemotherapy has failed [11]. At WCLC 2020, Zhou et al. reported findings obtained with mobocertinib in patients with metastatic NSCLC and *EGFR* exon 20 insertion mutations from the platinum-pretreated group (PPP cohort) included in the phase I/II study and the extension cohort (EXCLAIM) [12]. The PPP and EXCLAIM cohorts comprised 114 and 96 patients, respectively.

Long-lasting improvements

In both groups, treatment with mobocertinib demonstrated meaningful benefits. ORR per independent review committee (IRC) was 26 % in the PPP cohort, and responses lasted for a median of 17.5 months **(Table)**. Median PFS was 7.3 months. For the EXCLAIM cohort, ORR and median PFS were 23 % and 7.3 months, respectively, while median duration of response had not been reached yet. Although numerical differences were seen between the IRC and investigator assessments in both groups, similar disease control rates and PFS suggested that the magnitude of clinical benefit was the same with both assessments.

TABLE
Clinical outcomes with mobicertinib in the PPP and EXCLAIM cohorts

Parameter	PPP Cohort (n = 114)	EXCLAIM Cohort (n = 96)
Confirmed ORR per IRC, n (%)	30 (26)	22 (23)
Confirmed ORR per investigator, n (%)	40 (35)	31 (32)
Median duration of response per IRC, months	17.5	Not estimable
Median duration of response per investigator, months	13.9	Not estimable
Disease control rate per IRC, n (%)	89 (78)	73 (76)
Disease control rate per investigator, n (%)	89 (78)	72 (75)
Median PFS per IRC, months	7.3	7.3
Median PFS per investigator, months	7.3	7.1

Duration of response > 6 months was observed in 78 % and 84 % of patients in the PPP and EXCLAIM cohorts, respectively. At the time of data cutoff, over 50 % of responses were ongoing in the entire population. Reductions in the sum of target lesion diameter from baseline resulted in 82 % and 80 %, respectively. Confirmed responses with mobocertinib were similar among all prespecified subgroups (i. e., Asian vs. non-Asian, pretreatment with immunotherapy or EGFR TKI, presence of brain metastases at baseline).

The safety profile was consistent with the known profile of EGFR TKIs. Diarrhea and rash occurred as the most common treatment-related AEs. Grade 3/4 diarrhea was observed in 21 % and 16 % in the PPP and EXCLAIM cohorts, respectively. Nausea and diarrhea emerged as the most common AEs leading to treatment discontinuation. Overall, the treatment discontinuation rates due to AEs in the two cohorts amounted to 17 % and 10 %, respectively. Dose reductions became necessary in 25 % and 21 %, respectively. One treatment-related death occurred due to cardiac failure in a platinum-pretreated patient in the EXCLAIM cohort.

The analysis included an assessment of symptom scores. In the EXCLAIM cohort, mobocertinib gave rise to clinically meaningful improvements in core lung cancer symptoms (i.e., ≥ 10-point decrease in the EORTC QLQ-LC13 symptom score) from cycle 2 that were maintained throughout the treatment period. Meaningful changes were evident for dyspnea (54.4 % of patients), cough (44.4 %), and chest pain (37.8 %).

Robust efficacy of amivantamab

Another agent that has received Breakthrough Therapy Designation for exon 20 insertion-positive NSCLC in the USA and China is the bispecific antibody amivantamab that targets activating and resistance *EGFR* mutations as well as *MET* mutations and amplifications [13, 14]. The CHRYSALIS trial established the recommended phase II dose for antivantamab at 1,050 mg and 1,400 mg in patients with a body weight of < 80 kg and ≥ 80 kg, respectively. In the dose expansion part of the study, the safety and efficacy of this regimen was tested in patients with metastatic/unresectable NSCLC and *EGFR* exon 20 insertion mutations after progression on platinum-based chemotherapy. Sabari et al. presented the findings for the efficacy population who had undergone at least three disease assessments at clinical

cutoff (n = 81) and the safety population treated with the recommended phase II dose (n = 114) [15]. The median number of prior treatment lines was 2 in the efficacy population. Twenty-five percent were EGFR-TKI–pretreated, and immunotherapy had been administered in 46 %.

Amivantamab showed robust efficacy with an ORR of 40 % according to blinded IRC. The clinical benefit rate (i. e., complete or partial response or stable disease for ≥ 2 assessments) was 74 %. Median duration of response amounted to 11.1 months. At the time of data cutoff, 47 % of patients remained on treatment. Median PFS and OS were 8.3 and 22.8 months, respectively. Antitumor activity of the treatment was observed in all subgroups and across different insertion regions of the *EGFR* exon 20 (i. e., helical region, near loop, far loop). Overall, the efficacy of avivantamab compared favorably to currently available treatment options for NSCLC patients with exon 20 insertion mutations [16].

Also, the bispecific antibody showed a tolerable safety profile that was consistent with the known profiles observed in the setting of EGFR and MET pathway inhibition. Rash and infusion-related reactions occurred as the most common TEAEs. However, only 2 % of patients discontinued treatment because of rash, and almost all of the infusion-related reactions were observed at the first administration and rarely impacted the ability to continue the therapy. Treatment-related grade ≥ 3 AEs emerged in 16 % and led to discontinuation in 4 %. Based on these results, the combined use of amivantamab with other drug classes is currently being evaluated.

PCR testing fails in 50 %

As new drugs are being developed for the treatment of patients with exon 20 insertion-positive NSCLC, reliable identification of exon 20 insertion mutations, which are molecularly heterogeneous, is gaining importance. The most commonly used testing methods are polymerase chain reaction (PCR) and next-generation sequencing (NGS). However, as Bauml et al. showed, many cases tend to go undetected with PCR testing [17]. The researchers assessed the ability of PCR and NGS tests to comprehensively identify *EGFR* exon 20 insertion variants in US patients with NSCLC. To this end, two real-world databases were analyzed, which were the AACR Project Genomics Evidence Neoplasia Information Exchange database and the FoundationInsights database.

Results from both databases demonstrated that PCR missed approximately half of patients with exon 20 insertions identified by NGS. There was a wide range of unique exon 20 variants according to NGS (40-102), which suggests that NGS platforms, academic or commercially available, would improve their detection rate by capturing the full breadth of variants.

HER3-directed ADC patritumab deruxtecan

Most lung cancers, including > 80 % of *EGFR*-mutated NSCLC, express HER3, which represents a promising therapeutic target. Overexpression of HER3 has been associated with worse clinical outcomes [18-20]. To date, no HER3-directed therapies have been approved. The novel, investigational HER3-directed antibody-drug conjugate patritumab deruxtecan has been designed to contain an anti-HER3 IgG1 monoclonal antibody covalently linked to a topoisomerase I inhibitor payload. It is being evaluated in a global, multicenter, open-label phase I study conducted in patients with *EGFR*-mutant, metastatic/unresectable NSCLC.

The dose escalation part of the trial included patients who were either progressive after osimertinib or T790M-negative after progression on erlotinib, gefitinib, or afatinib. Here, the recommended dose for expansion was determined at 5.6 mg/kg i. v. every 3 weeks. Patients in the dose expansion portion of the study were enrolled into 3 cohorts; data for those in cohort 1 were included in the analysis presented at WCLC 2020 by Yu et al. [21]. This group had previously been treated with ≥ 1 EGFR TKI and ≥ 1 platinum-based chemotherapy regimen.

As of April 30, 2020, 57 patients from both parts of the study had received 5.6 mg/kg of patritumab deruxtecan, with 56 being evaluable for response. The median number of prior therapies for advanced or metastatic disease was 4. Forty-seven percent of patients had a history of CNS metastases.

Early benefits irrespective of resistance aberrations

After a median follow-up of 5 months, patritumab deruxtecan 5.6 mg/kg demonstrated clinically meaningful antitumor activity in this heavily pretreated population with *EGFR*-mutated NSCLC and various TKI resistance mechanisms. These included *EGFR* C797S mutation, *MET* amplification, *HER2* mutation, *BRAF* fusion, and *PIK3CA* mutation. Overall, 25 % of patients responded and 70 % achieved disease control, although 3 partial responses had not been confirmed yet and 6 patients had undergone only one tumor evaluation at the time of the analysis. One patient (2 %) obtained complete response. Decreases in tumor size occurred within 3 months **(Figure 1)**. Median duration of response was 6.9 months.

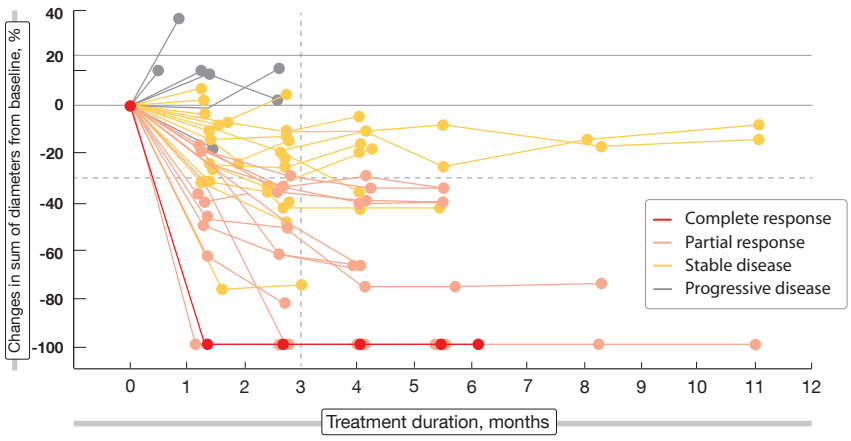

Figure 1: Patritumab deruxtecan: changes in tumor size over time (n = 49)

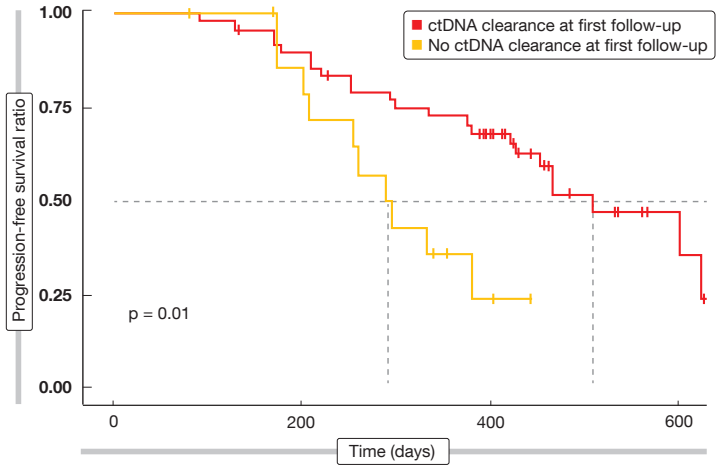

Figure 2: Association between ctDNA clearance at first follow-up on mefatinib treatment and progression-free survival

Patritumab deruxtecan showed a manageable safety profile, with thrombocytopenia and neutropenia being the most common grade ≥ 3 TEAEs. In 9 %, TEAEs led to treatment discontinuation. Three interstitial lung disease events (5.3 %) were adjudicated by an IRC as being related to treatment. No grade 5 AEs occurred. In their entirety, these insights support further clinical investigation of patritumab deruxtecan in a patient population with no available targeted options, as the authors noted in their summary. The phase II HERTHENA-Lung01 study investigating single-agent patritumab deruxtecan is currently enrolling patients after failure of EGFR TKIs and platinum-based chemotherapy (NCT04619004).

Impressive activity of front-line mefatinib

The second-generation EGFR TKI mefatinib that binds irreversibly to mutated *EGFR* inhibits EGFR- and HER2-overexpressing, *EGFR*-mutant and *KRAS*-mutant lung cancer, as well as other HER2- and EGFR-overexpressing cancer types. A randomized, open-label phase II study involving 106 patients with *EGFR*-mutant stage IIIB/IV NSCLC was conducted to assess the efficacy and safety of first-line mefatinib 60 mg and 80 mg orally once daily [22]. The analysis yielded a substantial ORR of 84.9 % in the total population; for the 60 mg and 80 mg doses, this was 80.4 % and 89.1 %, respectively. Disease control resulted in 97.2 % overall. Median PFS and OS amounted to 16.3 and 26.6 months in the total population. Mefatinib was well tolerated. Any-grade AEs mainly included diarrhea (94.3 %) and rash (86.8 %). Among grade ≥ 3 events, the most common AEs were diarrhea (19.8 %), rash (17 %), mouth ulceration (4.7 %), and stomatitis (4.7 %).

The trial included a biomarker study aimed at exploring predictive biomarkers and potential molecular mechanisms of acquired resistance to mefatinib. Circulating tumor DNA (ctDNA) clearance was defined as the absence of any mutation on a panel of 168 lung-cancer-related genes. Patients who experienced clearance of ctDNA at the first follow-up 6 weeks from starting mefatinib therapy had significantly longer PFS (p = 0.01; **Figure 2**) and OS (p = 0.005) than mutation-positive individuals. As of data cutoff, 38 patients experienced disease progression. Here, the most prevalent mechanism of acquired resistance to mefatinib was the *EGFR* T790M mutation (42.1 %). Three patients with *EGFR* T790M also acquired concurrent bypass resistance mechanisms, which were *BRAF*V600E mutation (n = 2) and *MET* amplification (n = 1). In 18 cases (48 %), no known resistance mechanism was detected.

ORCHARD

First-line treatment with the third-generation EGFR TKI osimertinib offers favorable outcomes in patients with *EGFR*-mutant NSCLC. However, most patients develop resistance. Subsequent therapies according to the specific molecular resistance mechanisms might enable personalized alternatives to standard cytotoxic chemotherapy. The most common acquired resistance mechanisms to first-line osimertinib identified to date include SCLC transformation (15 %), *MET* amplification (7-15 %), *EGFR* C797X mutation (7-11 %), and secondary *EGFR* alterations (11-12 %) **(Figure 3)** [23, 24].

The ongoing phase II platform ORCHARD study is evaluating biomarker-targeted treatments in patients with *EGFR*-mutant advanced NSCLC who have progressed on first-line osimertinib therapy and in whom actionable mutations have been identified [25]. Also, the study is assessing novel treatment strategies for patients without actionable mutations. Enrollment started in June 2019, and study completion is expected for November 2023.

RET fusions: osimertinib plus selpercatinib

Acquired oncogenic *RET* fusions are present in approximately 5 % of patients developing resistance to first-line osimertinib [26]. Rotow et al. systematically characterized the clinical response to osimertinib plus the selective RET inhibitor selpercatinib in patients with *EGFR*-mutant NSCLC who had acquired *RET* fusions on osimertinib treatment [27]. Data for 11 patients were collected across all selpercatinib compassionate access programs.

In this group, osimertinib plus selpercatinib proved active, with an ORR of 50 % and a disease control rate of 80 %. Only one patient developed progressive

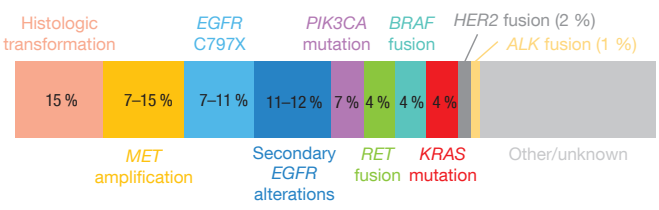

Figure 3: The most common acquired resistance mechanisms identified in patients treated with first-line osimertinib

disease. For responders, the median treatment duration was 11 months. The combination therapy was generally well tolerated. Adverse effects were consistent with the known profiles of the two drugs. One patient discontinued treatment due to grade 2 pneumonitis. Dose reductions for selpercatinib and osimertinib became necessary in one patient each. Grade 3 treatment-related AEs included hypertension, QTc prolongation, neutropenia and leukopenia. Formal AE reporting was voluntary with the exception of serious AEs.

The results for acquired resistance to osimertinib plus selpercatinib were heterogeneous and mirrored those seen in the setting of acquired resistance to TKI monotherapy. Aberrations included the second-site resistance mutations *EGFR* C797S and *RET* G810S. At present, osimertinib plus selpercatinib is prospectively assessed in the ORCHARD study in *EGFR*-positive NSCLC patients with acquired *RET* fusion [25].

Afatinib in *EGFR* G724S-positive disease

EGFR exon 18 G724S is a rare mutation mediating resistance to third-generation EGFR TKI treatment, although it retains sensitivity for second-generation EGFR TKIs including afatinib [28, 29]. Zhao et al. investigated afatinib in patients with G724S-positive NSCLC whose data were retrieved from a database comprising 42,316 individuals with lung cancer [30]. Twenty-three patients entered the survival analysis. In addition, an analysis of concurrent mutations in *EGFR* and other genes was conducted in 52 patients. This showed that 75 % harbored concurrent *EGFR* exon 19 deletions, with the rare variant E746_S752 delinsV being the most common one (55 %). Fifteen percent harbored concomitant exon 20 point mutations. The authors concluded that *EGFR* G724S, as a resistance mutation, emerges preferentially in the context of E746_S752delinsV, while G724S co-occurring with the *EGFR* exon 20 mutation is more likely a primary mutation.

All afatinib-treated patients with the G724S mutation (n = 8) achieved stable disease, which resulted in a disease control rate of 100 %. Compared to non-afatinib therapies (n = 15), PFS was significantly longer (4.5 vs. 1.7 months; HR, 0.33; p = 0.04). In the subset of patients who had progressed on osimertinib, afatinib (n = 5), compared to non-afatinib therapies (n = 8), also induced superior PFS (6.2 vs. 1.0 months; HR, 0.04; p = 0.006). According to the authors, afatinib monotherapy is a potential therapeutic option for NSCLC patients with the *EGFR* G724S mutation. The *EGFR* T790M mutation re-emerged as a major resistance mechanism to afatinib in two osimertinib-treated patients, while *MET* amplification mediated resistance in one patient treated with first-line afatinib.

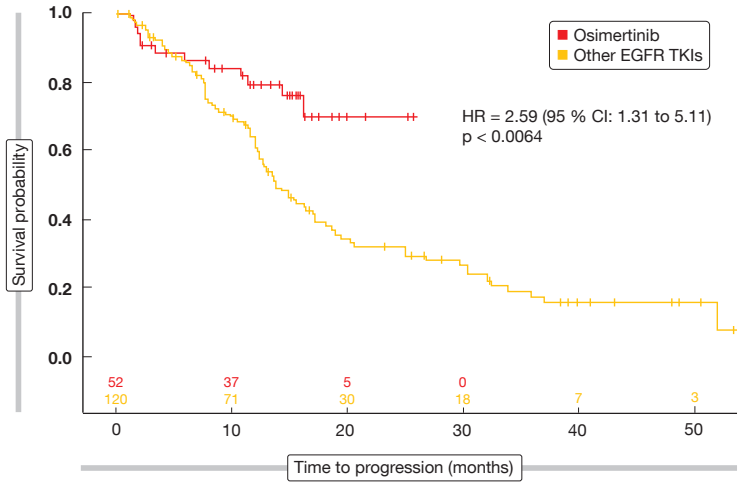

Figure 4: Real-world progression-free survival with osimertinib vs. other EGFR TKIs as first-line agents in *EGFR*-mutant NSCLC

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First- and second-line EGFR TKIs vs. osimertinib

Compared to first-generation EGFR TKIs, the FLAURA study has shown PFS and OS benefits of osimertinib as first-line therapy in patients with *EGFR*-mutated, advanced NSCLC [31]. A US-based, multicenter, retrospective review assessed the outcomes of patients treated with first/second-generation EGFR TKIs or osimertinib in the front-line setting between 2014 and 2019 [32]. Overall, 172 patients were included; among these, 52 (30.2 %) had received osimertinib, while 120 (69.8 %) had been treated with either afatinib (n = 25; 14.5 %), gefitinib (n = 1; 0.6 %), or erlotinib (n = 94; 54.7 %).

For the analysis, the population was dichotomized (osimertinib vs. all other EGFR TKIs). All of the baseline characteristics were comparable across the two groups with the exception of total bilirubin levels that were higher in the cohort receiving other EGFR TKIs. Osimertinib gave rise to improved PFS compared to the other EGFR TKIs at 12 and 18 months (HR, 2.59; $p < 0.0064$; **Figure 4**), while OS did not differ significantly between the groups (HR, 0.95; $p < 0.9128$). As the authors noted, additional studies and longer follow-up are needed to solidify the real-world OS benefit of osimertinib. ■

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Interview: Alexander Spira, MD, PhD, US Oncology Research, Virginia Cancer Specialists, Fairfax, Virginia, USA

Antibody-drug conjugates: the age of almost unlimited possibilities has just begun

Which advantages do antibody-drug conjugates (ADCs) offer over other treatment approaches?

Antibody-drug conjugates have opened up an entirely new paradigm. Targeted therapy requires specific mutations, and immunotherapy only works if the tumor expresses neoantigens or is essentially able to respond to these agents. As we know, these two approaches do not work forever, not every patient responds to them, and certainly not every patient has a targetable mutation. It is therefore nice to have something new and different. An ADC consists of an antibody, a linker that sits next to it, and the drug, which is usually chemotherapy-based. Therefore, in theory, they should show enhanced efficacy compared to mere antibodies such as trastuzumab or rituximab.

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What may be shortcomings such as particular adverse events in comparison to other drug classes?

With ADCs, we need to get used to a new toxicity profile. ADCs are designed to be very specific. The chemotherapy part is internalized into the tumor cell, but systemic toxicity can emerge if leakage or spillage occurs. These toxicities typically include cytopenias and diarrhea. Moreover, specific events such as ocular toxicity are not uncommon depending on the type of antibody or linker. Several clinical trials are elucidating that. Also, many ADCs involve some pulmonary toxicity as this is a class effect. Pulmonary adverse events are rare but can be devastating.

Which emerging ADCs do you consider particularly promising for future routine use?
From my perspective, there are three drugs on which to put the focus that were also discussed at WCLC 2020. The Trop-2-directed ADC datopotamab deruxtecan is a very exciting and promising agent, because the transmembrane glycoprotein Trop-2 is a relatively new target. In the phase I TROPION-PanTumor01 study, datopotamab deruxtecan has shown highly encouraging antitumor activity with disease control rates of up to 80 % and a manageable safety profile in heavily pretreated NSCLC patients [1]. Based on these insights, the randomized, phase III TROPION-Lung01 study is currently comparing datopotamab deruxtecan with docetaxel in patients with stage IIIB/IV NSCLC who have previously been treated with immunotherapy and platinum-based chemotherapy. Another Trop-2-directed ADC, sacituzumab govitecan, has already received FDA approval for the treatment of triple-negative breast cancer.

Moreover, the HER2-directed ADC trastuzumab deruxtecan has shown activity in HER2-overexpressing and *HER2*-mutated lung cancer in the phase II DESTINY-Lung01 trial [2, 3]. We are looking forward to the FDA approval of trastuzumab deruxtecan in this indication. Lastly, phase I data obtained in an *EGFR*-mutated population demonstrated antitumor activity of the HER3-directed ADC patritumab deruxtecan [4]. These were patients who had received at least one EGFR inhibitor and at least one platinum-based chemotherapy regimen. Patritumab deruxtecan is currently being evaluated in the phase II HERTHENA-Lung01 trial after failure of EGFR TKI treatment and platinum-based chemotherapy. From my point of view, these are the three ADCs that might become game changers in the future.

Where do you see the ADC approach three years from now?
I think the ADCs I mentioned will receive FDA approval in the next months or years, as well as many others. Numerous ADCs are being developed in multiple tumor types. We are excited about this new technology as it is almost unlimited. Any antigen on the tumor surface can be targeted as long as it is not overly expressed on normal cells. In the management of breast cancer, the ADC technology has enabled the reinvention of an established HER2-targeted treatment. I was recently involved with phase I assessments in the field of leukemia and lymphoma, where we expect FDA approvals in the near future. Many tumor-specific antigens can be used for the design of ADCs against leukemia and lymphoma, but this also applies to solid tumors. The possibilities are almost endless. ■

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What is new in SCLC?

Lurbinectedin plus irinotecan

A novel approach for targeting lung tumors with small-cell histology consists in the inhibition of transactivated transcription, as small-cell lung cancer (SCLC) has been found to be a transcription-addicted malignancy [1]. Rudin et al. defined four molecular SCLC subtypes according to their differential expression of four key transcription regulators [2]. Lurbinectedin, which acts by selectively inhibiting oncogenic transcription and modulating the tumor microenvironment, has been granted accelerated approval by the US FDA in June 2020 for the treatment of patients with metastatic SCLC who experienced disease progression on or after platinum-based chemotherapy based on the results of a phase II study [3].

As preclinical observations suggested synergism of lurbinectedin and irinotecan, a phase IB/II trial investigating escalating dose regimens was initiated in patients with various cancer types. At WCLC 2020, Ponce et al. presented the findings for 21 SCLC patients included in Cohort A who received lurbinectedin 2 mg/m^2 on day 1 plus irinotecan 75 mg/m^2 on days 1 and 8 [4]. In addition, G-CSF support was administered. Eighty-one percent of these 21 patients had extensive-stage SCLC. Bulky disease was present in 29 %, and 24 % showed CNS metastases. Thirty-eight percent had received two prior lines of treatment for advanced disease. While 71 % of patients had developed complete or partial responses to prior platinum therapy, 19 % had been refractory to this treatment.

Particular benefits in poor-prognosis settings

Lurbinectedin plus irinotecan demonstrated remarkable anti-tumor activity. Sixty-two percent of patients experienced partial remissions, and disease control resulted in 90 % **(Table)**. Median PFS and median duration of response were 6.2 and 6.7 months, respectively. Notable efficacy was observed in patients with poor prognosis, such as those with resistant disease, as indicated by a short chemotherapy-free in-

TABLE
Efficacy outcomes obtained with lurbinectedin plus irinotecan

	All patients (n = 21)	Chemotherapy-free interval		Setting	
		≥ 90 days (n = 13)	< 90 days (n = 8)	2nd line (n = 13)	3rd line (n = 8)
Objective response rate (partial responses), %	62	69	50	77	38
Clinical benefit rate (partial response + stable disease > 4 months), %	81	92.3	62.5	92.3	62.5
Disease control rate (partial response + stable disease), %	90	100	75	100	75
Median duration of response, months	6.7+	7.5+	3.7+	6.7+	3.0+
Median progression-free survival, months	6.2+	8.1+	4.8+	8.5+	4.2+

terval, and those treated in the third-line setting **(Table)**. Also, patients with brain metastases responded to the combination.

Toxicity was shown to be transient and manageable. AEs included mostly grade 1 and 2 events, although grade 3/4 neutropenia occurred in 61.9 %, and grade 3/4 febrile neutropenia was reported in 9.5 % despite G-CSF prophylaxis. Apart from hematological abnormalities, diarrhea frequently emerged (all grades, 33.3 %; grade 3/4, 28.6 %), as did fatigue (all grades, 66.7 %; grade 3/4, 23.8 %). No patient discontinued treatment due to toxicity, and there were no drug-related deaths. Dose reductions were required in 52.4 %. Considering these findings, the authors noted that further development of lurbinectedin plus irinotecan is warranted in patients with SCLC. The SCLC cohort of this phase I/II study is currently being expanded to 47 patients.

IMpower133: patients reaching maintenance

In the phase I/III IMpower133 study, atezolizumab plus carboplatin/etoposide (CP/ET) followed by maintenance therapy with atezolizumab has given rise to significant improvements in OS and PFS compared to placebo plus CP/ET followed by placebo maintenance [5]. The exploratory analysis reported at WCLC 2020 assessed the benefit of atezolizumab vs. placebo in the group that reached the maintenance phase of IMpower133 [6].

This population included patients who received at least the first dose of maintenance therapy regardless of the number of chemotherapy cycles administered. Similar proportions of patients met this criterion in the two arms (experimental arm: n = 154, 77 %; control arm: n = 164, 81 %). The baseline characteristics were balanced between these groups. A generalized linear model was used to identify characteristics that might be prognostic or predictive of reaching the maintenance phase. Also, the researchers used a multivariate Cox model from the start of maintenance treatment to evaluate the treatment effect on OS and PFS to account for potential lead-time bias.

Three prognostic factors for reaching the maintenance phase were identified. These included younger age (odds ratio, 0.459), favorable ECOG performance status (OR, 0.439), and lower LDH levels (OR, 0.589). Moreover, a significant treatment interaction was demonstrated for age (p = 0.004). The mortality risk was reduced by 41 % in the experimental arm compared to the chemotherapy-only arm (HR, 0.59). Median OS from the start of maintenance amounted to 12.5 vs. 8.4 months; when assessed from the start of randomization, this was 15.7 vs. 11.3 months. Likewise, median PFS was longer from the start of maintenance (2.6 vs. 1.8 months) and from randomization (5.5 vs. 4.5 months), with a 36 % risk reduction (HR, 0.64). Patients across the treatment arms showed similar safety results despite the continuation of atezolizumab monotherapy in the maintenance phase. In their conclusion, the authors stated that both the induction treatment with atezolizumab plus CP/ET and the atezolizumab maintenance appeared to contribute to the OS benefit observed in IMpower133. ■

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Immunotherapy: combination regimens and new data on the significance of mutations

KEYNOTE-189 update after 46.3 months

Substantial OS and PFS improvements have led to the implementation of the regimen evaluated in the KEYNOTE-189 trial as standard first-line approach for stage IV non-squamous NSCLC without sensitizing *EGFR*/*ALK* alterations [1]. Pembrolizumab plus platinum/pemetrexed for up to 4 cycles followed by pembrolizumab for up to 31 cycles plus pemetrexed (n = 410) was tested against placebo plus platinum/pemetrexed followed by placebo plus pemetrexed (n = 206). Risk reductions of approximately 50 % were achieved with the immunotherapy-based strategy for both OS and PFS (HRs, 0.49 and 0.52, respectively). After a median follow-up of 46.3 months, Gray et al. presented updated efficacy and safety outcomes for the overall study population (intent-to-treat, ITT) as well as for patients who completed 35 cycles, i.e., 2 years of pembrolizumab (n = 56) [2].

Pembrolizumab plus platinum/pemetrexed continued to provide OS and PFS benefits compared to placebo plus chemotherapy, while showing a manageable safety profile. Median OS was 22.0 vs. 10.6 months in the ITT population, with the 3-year OS rate being almost doubled in the experimental arm (31.3 % vs. 17.4 %; HR, 0.60; **Figure 1**). Median PFS was 9.0 vs. 4.9 months (HR, 0.50). At 36 months, 11.8 % vs. 1.3 % of patients were progression-free. OS and PFS benefits emerged irrespective of PD-L1 baseline expression. PFS2, which was defined as the time from randomization to investigator-assessed disease progression that led to cessation of second-line therapy, start of third-line therapy, or death, was 17.0 vs. 9.0 months (HR, 0.52). The ORR amounted to 48.3 % vs. 19.9 %, and responses lasted for a median of 12.6 vs. 7.1 months.

In the group of patients who completed 35 cycles of pembrolizumab, the 2-year OS rate from completion of this treatment was 79.6 %. Objective responses occurred in 87.5 %, with complete responses resulting in 10.7 %. Forty-five patients (80.4 %) were alive at data cut-off; 28 of them showed no signs of disease progression.

Pembrolizumab plus ipilimumab: KEYNOTE-598

Negative results were obtained in the KEYNOTE-598 study for pembrolizumab plus ipilimumab as first-line therapy of patients with stage IV NSCLC and PD-L1 TPS ≥ 50 % who had no targetable *EGFR*/*ALK* alterations [3]. KEYNOTE-598 tested this approach based on the fact that dual immunotherapy with the PD-1 inhibitor nivolumab and the CTLA-4 inhibitor ipilimumab is a standard of care for advanced melanoma and renal cell carcinoma [4, 5]. Appropriately powered, controlled comparisons of anti–PD-1 monotherapy *versus* dual PD-1 and CTLA-4 inhibition as first-line treatment for NSCLC had been lacking to date. The KEYNOTE-598 study included 284 patients in each arm; those in the experimental arm received pembrolizumab for up to 35 doses plus ipilimumab for up to 18 doses, while those in the control arm were treated with pembrolizumab plus placebo.

However, adding ipilimumab to pembrolizumab did not improve efficacy compared with pembrolizumab alone. No differences were observed regarding OS (21.4 vs. 21.9 months; HR, 1.08; p = 0.74), PFS (8.2 vs. 8.4 months; HR, 1.06; p = 0.72), ORR (45.4 % in both arms), and duration of response (16.1 vs. 17.3 months). KEYNOTE-598 was stopped for futility based on the recommendation of the data monitoring committee. Moreover, the combination of pembrolizumab and ipilimumab gave rise to greater toxicity than pembrolizumab alone. As the authors summarized, pembrolizumab monotherapy remains a standard-of-care first-line

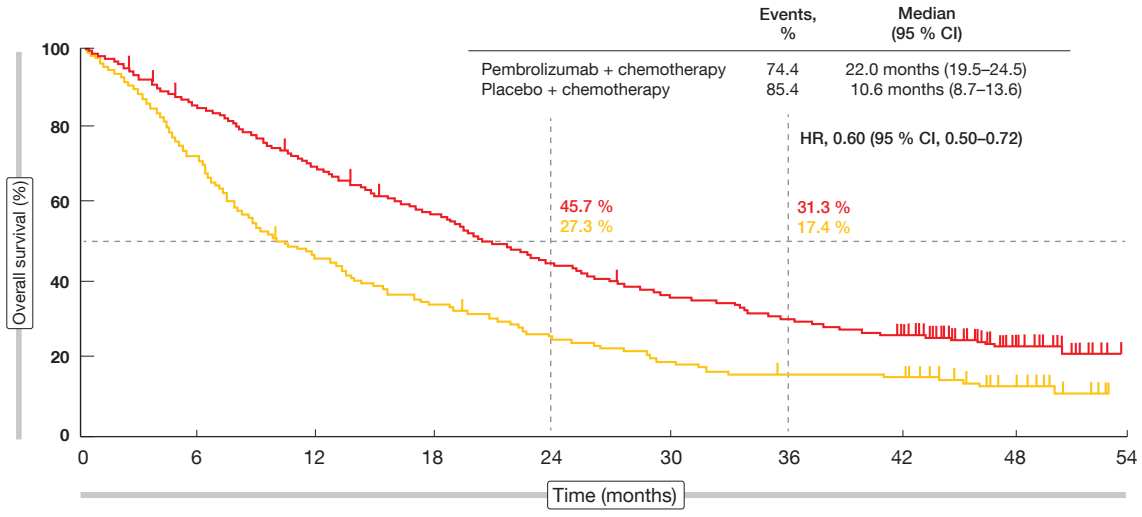

Figure 1: Sustained overall survival benefit for pembrolizumab plus chemotherapy vs. placebo plus chemotherapy: KEYNOTE-189

treatment for NSCLC patients with TPS ≥ 50 % who do not harbor *EGFR*/*ALK* aberrations.

KRAS & TP53 mutations: predicting IO efficacy

Genetic aberrations in the *KRAS* and *TP53* genes are common in NSCLC. Using a meta-cohort analysis of 8 cohorts including a total of 1,129 patients, Li et al. investigated the interrelation between these two gene mutations with respect to the prediction of immune checkpoint inhibition efficacy in *EGFR*/*ALK* wildtype, non-squamous NSCLC [6].

TP53 mutations were shown to be associated with higher ORR and PFS in patients with *KRAS* mutations, but not in the *KRAS* wildtype population. Conversely, *KRAS* mutations were associated with better ORR and PFS in *TP53*-mutant but not in *TP53*-wildtype patients. *TP53-KRAS* co-mutations predicted longer PFS on immunotherapy whereas either *TP53* or *KRAS* mutations alone did not **(Figure 2)**. In chemotherapy-treated patients, the presence of the *TP53-KRAS* co-mutation had no effect on PFS. The co-mutation was demonstrated to predict benefit from atezolizumab over docetaxel, regardless of tumor mutational burden, PD-L1 expression, significant clinicopathological features, and immunotherapy-related mutational events.

In their conclusion, the authors emphasized the interdependence of *KRAS* and *TP53* mutations in predicting the benefit of immune checkpoint inhibition. Considering this, future researchers probing into predictors of immunotherapy were advised to focus on the mutual influence between distinct biomarkers.

No nivo/ipi benefit in *EGFR*-mutant disease

In patients with *EGFR*-mutant NSCLC, monotherapy PD-1 inhibition has been shown to be associated with low clinical efficacy [7, 8]. Lai et al. conducted an open-label, randomized, phase II study to test combination immune checkpoint inhibition in patients with advanced *EGFR*-mutant NSCLC who had failed one line of standard EGFR TKI treatment and ≤ 1 line of chemotherapy [9]. Arm A received nivolumab monotherapy (n = 15), while Arm B was treated with nivolumab plus ipilimumab (n = 16). Treated or stable metastases were allowed. On disease progression, patients from Arm A could cross over to Arm B. Biomarker evaluations including exome sequencing and plasma cytokine analysis, among others, were part of the proceedings.

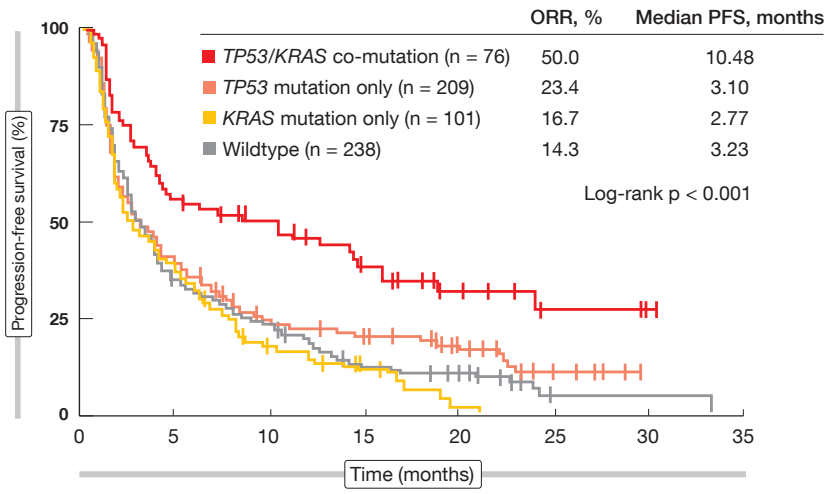

Figure 2: Progression-free survival in immunotherapy-treated patients: *TP53/KRAS* co-mutation vs. *TP53* and *KRAS* single mutations and wildtype

Combined immune checkpoint inhibition did not result in clinical benefit. The study was terminated early after 31 patients due to futility. An ORR of 3.2 % was observed in the overall cohort, with one patient attaining partial response in the combination arm and none responding in the monotherapy arm. Stable disease occurred in 6 patients each (40.0 % and 37.5 %, respectively). PFS was similar across the groups (median, 1.31 and 1.22 months, respectively). Five patients derived clinical benefit in the form of ongoing partial response/stable disease at 6 months or best response of partial response. All of these had *EGFR* exon 19 deletion, and one had a T790M mutation. No association existed between PD-L1 status and response to immune checkpoint inhibition. None of the three patients who progressed and crossed over from monotherapy to combination therapy achieved salvage. The use of immunotherapy did not result in increased safety concerns. Immune-related AEs occurred with similar rates as observed in the CheckMate 227 trial [10].

According to the biomarker analysis, tumor mutational burden was generally low, even in patients who achieved clinical benefit. Likewise, no clear pattern became evident between the Gene Expression Profiling Test (GEP) score and response to immunotherapy. However, patients who derived clinical benefit were either "immune-hot" at baseline or became "hot" on treatment. Additionally, they tended to have lower numbers of myeloid-derived suppressor cells over time. The authors noted that lack of intracranial control might have been a major factor contributing to the poor outcomes in this study. Intracranial failure should therefore be an important consideration when choosing immunotherapy for *EGFR*-mutant NSCLC patients. Combinatorial approaches might be a solution, although further research is required.

Nivolumab plus MET inhibition

Concurrent treatment with the MET inhibitor capmatinib and the PD-1 inhibitor nivolumab was assessed in a study based on the rationale that dysregulation of the MET pathway might modulate the immune cell function, leading to suppression of anticancer immune responses [11]. In mouse models, capmatinib has been shown to enhance the efficacy of immunotherapy irrespective of tumor-cell–intrinsic MET dependence [12]. The multicenter, global, open-label, phase II trial reported at WCLC included patients with advanced/metastatic, *EGFR*-wildtype, PD-(L)1-inhibitor–naïve NSCLC and documented disease progression after standard-of-care treatment [13].

Capmatinib 400 mg BID was administered together with nivolumab 3 mg/

TABLE
Survival outcomes with the combined administration of capmatinib and nivolumab according to MET expression

Efficacy parameter	High MET (n = 16)	Low MET (n = 30)
Progression-free survival		
Median PFS, months	6.2	3.1
Estimated PFS rates, %		
6 months	55.2	42.0
12 months	47.3	24.5
18 months	28.4	19.6
24 months	18.9	14.7
Overall survival		
Median OS, months	28.0	10.2
Estimated OS rates, %		
3 months	93.8	86.7
6 months	81.3	72.0
9 months	81.3	56.9
12 months	73.1	32.5

kg every 2 weeks. The patients were stratified according to MET expression, with 16 individuals meeting high-MET criteria (i.e., MET IHC 3+ in ≥ 50 % of tumor cells regardless of gene copy number [GCN], or IHC 2+ in ≥ 50 % of tumor cells and GCN ≥ 5, or *MET*ex14-positive disease) and 30 patients meeting low-MET criteria (i.e., *MET*ex14-negative or unknown status and one of the following: MET IHC 2+ in ≥ 50 % of tumor cells and GCN < 5; IHC 2+ in < 50 % of tumor cells regardless of GCN; IHC 0 or 1+ regardless of GCN). PFS at 6 months was defined as the primary endpoint. Felip et al. presented the results after a median follow-up of 22.9 and 30.4 months for the high-MET and low-MET cohorts, respectively [13].

This first report showed clinical activity of capmatinib plus nivolumab in both high-MET and low-MET patients. ORRs were 25.0 % and 16.7 %, respectively, with disease control rates of 81.3 % and 40.0 %, respectively. Median duration of response was 22.89 and 24.99 months, respectively. Tumor shrinkage occurred in both high-MET and low-MET patients. Median PFS was 6.2 and 3.1 months, respectively, with 6-month PFS rates of 55.2 % and 42.0 %, respectively **(Table)**. Median OS had been reached after 28.0 and 10.2 months, respectively. At 12 months, 73.1 % and 32.5 % of patients were alive. The authors noted that in this study with a limited sample size, the endpoints numerically favored capmatinib plus nivolumab in the high-MET group over the low-MET group, with overlapping 95 % confidence intervals.

The combination showed a manageable safety profile. Among grade 3/4 treatment-related AEs, increases in amylase (15.2 %) and lipase (10.9 %) were most commonly observed, followed by vomiting (8.7 %), nausea, asthenia, and peripheral edema (6.5 % each). Treatment-related AEs led to study drug discontinuation in 39.1 % and 19.6 %, respectively, across the two cohorts. Dose adjustments or interruptions became necessary in 80.4 % and 60.9 %, respectively, and additional therapy due to AEs was required in 93.5 % and 58.7 %, respectively.

Anti-angiogenic combination partner

The chemotherapy-free combination of the anti–PD-1 antibody sintilimab and the multi-target anti-angiogenic TKI anlotinib was evaluated in a phase I study conducted in treatment-naïve patients with stage IIIB/IV NSCLC without driver aberrations. The primary analysis has shown encouraging ORR regardless of PD-L1 expression [14]. At WCLC 2020, Han et al. reported the final analysis for the primary endpoints that demonstrated durable efficacy and good tolerability [15]. Overall, 72.7 % of patients (n = 22) responded, with 100 % achieving disease control. Median duration of response had not been reached yet. Median PFS was 15 months, while OS data were still immature. At 12 months, 95.5 % of patients were alive, and 71.4 % were progression-free.

Responses and freedom from progression occurred irrespective of tumor mutational burden, PD-L1 expression, or histology. With longer follow-up, sintilimab plus anlotinib did not give rise to any unexpected toxicities. The authors pointed out that this novel combination offers potential efficacy for a broader range of NSCLC patients regardless of histologic subtype or PD-L1 status. A randomized phase II trial is currently ongoing to further investigate sintilimab plus anlotinib (NCT04124731).

Long-term AEs in long-term survivors

Hsu et al. presented a retrospective analysis of immunotherapy survivors, i.e., patients with stage III/IV NSCLC alive at > 1 year after the initiation of PD-(L)1 treatment [16]. Overall, 317 patients treated between November 2009 and February 2020 were identified. In this group, 114 (36 %) had survived for > 1 year. Approximately half of them were aged ≥ 65 years, and > 80 % were current or former smokers. Adenocarcinoma prevailed as the most common histology in 66 %. Sixty-one percent had unknown PD-L1 status; in 21 % PD-L1 expression exceeded 50 %. The median number of doses received was 13 (range, 1-121). Two thirds and one third of patients had received monotherapy and combination therapy, respectively.

Immune-related AEs (irAEs) occurred in 59 long-term survivors (52 %), with pulmonary events (pneumonitis) and dermatologic events (dermatitis, pruritus, psoriasis) emerging most commonly, followed by endocrine (hypothyroidism, thyroiditis, hypophysitis, type 1 diabetes, fatigue), rheumatologic (inflammatory arthritis, Sicca syndrome, xerostomia, dry eye, costochondritis) and gastrointestinal (colitis, diarrhea, hepatitis, pancreatitis) AEs.

Among the 59 affected patients, 39 had a single irAE, whereas 20 developed more than one. The most common multi-system irAEs included combinations of pneumonitis with dermatitis (n = 4), inflammatory arthritis (n = 3), and Sicca syndrome (n = 2). Median time to single and multi-system irAEs was 22 and 9 weeks, respectively. The authors noted that 31 (27 %) of long-term survivors required ongoing irAE management at one year. Overall, NSCLC survivors treated with immune checkpoint inhibition represent a group with unique long-term needs. ■

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Interview: Luis M. Montuenga, PhD, Centro de Investigación Médica Aplicada (CIMA); Department of Pathology, Anatomy and Physiology, Schools of Medicine and Sciences; University of Navarra, Pamplona, Spain. IdisNa, Pamplona Spain. CIBERONC, Madrid, Spain

Lung cancer screening: hurdles in daily routine and in the research laboratory

Which factors are impeding the implementation of low-dose computed tomography (LDCT) lung cancer screening at the global level?

All of us agree that LDCT is effective and should be widely implemented. I would say that cost and awareness are the two major issues that are impeding the implementation of LDCT all over the world. Cost-effectiveness of LDCT has been demonstrated by many publications; and there are even other arguments in favor of the cost-effectiveness of this technology. We are screening for lung cancer, but we can also simultaneously identify patients with other conditions, such as cardiovascular disease (through coronary artery calcification determination) and emphysema. The awareness issue is probably due to the fact that LDCT-based lung cancer screening has been a seemingly controversial topic for decades. It still has some remnants of a controversial label, although current evidence clearly supports screening of patients who fit the National Lung Screening Trial (NLST) and other criteria [1-3]. In addition, the stigma associated with lung cancer may have had some role in the slow implementation of LDCT.

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How can new biomarkers improve the effectiveness of screening?

We must distinguish two concepts here. One is the concept of prognostic biomarkers that enable determination of the patient outcome after a diagnosis of lung cancer. The staging committee of the International Association for the Study of Lung Cancer (IASLC) has a subcommittee that focuses on identifying molecular markers for prognostication to improve the efficacy of TNM staging. In my laboratory, we are also working on finding molecular prognostic markers for early lung cancer.

The other area relates to biomarkers that can help in the process of LDCT screening. Firstly, they can improve the selection of high-risk individuals who should be advised to participate in a screening program. These markers might refine the risk models that are already in use. We have genetic biomarkers and others based on environmental exposure and smoking habits, as well as

phenotypic circulating biomarkers. The other aspect regarding biomarkers that can help in the process of screening relates to nodules of indeterminate risk. LDCT identifies nodules that clearly belong to the low-risk category, while others are clearly high-risk lesions and call for quick intervention. However, in approximately 70 % of cases, nodules are not clearly characterizable in terms of risk. Biomarkers can help here by providing information to improve risk stratification, thus contributing to avoiding unnecessary interventions such as PET scan or biopsy.

Which biomarkers are promising with respect to early detection of lung cancer?

This is a difficult question, as there are many biomarkers. Numerous publications reporting the discovery of markers have been released. Promising molecular candidates include autoantibodies, blood protein profiling, complement fragments, microRNAs, circulating tumor DNA methylation, and RNA airway or nasal signatures [4]. Other emerging biomarkers or new technologies to follow are exhaled breath biomarkers, metabolomics, sputum cell imaging, genetic predisposition studies or the integration of next generation sequencing in circulating DNA.

However, these biomarkers need to be validated. Validation is the key issue. The most promising markers will be the ones that reach clinical utility validation, and this has not been achieved in the screening context by any of these yet. A number of them have undergone some type of validation in the clinical setting, such as case control studies including samples obtained from screening cohorts. However, we need to design trials showing that these biomarkers work and improve the management of high-risk individuals or not otherwise specified patients in the setting of screening cohorts. This is a bottle neck which is very difficult to solve, because not many screening programs are collecting biospecimens. Moreover, we need collaboration between all of these programs, as well as standardization and good trial design. This is the course of action that will tell us which markers are the most promising ones. At this point, we even have commercially available biomarkers that work well for a variety of questions, but the key will be to have something that improves the gold standard management in the context of screening. ■

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Nivolumab as a new option in patients with relapsed malignant mesothelioma

Until recently, no randomized phase III trials have demonstrated OS improvement in patients with relapsed malignant mesothelioma [1, 2]. PD-1 inhibition with single-agent nivolumab has shown activity in three phase II studies, one of which led to the approval of nivolumab in Japan [3-5]. The CONFIRM trial is the first placebo-controlled, randomized, phase III trial investigating an anti-PD-1 antibody in relapsed mesothelioma. Patients after > 1 prior line of standard chemotherapy were randomized to either nivolumab 240 mg on day 1 of a 14-day cycle (n = 221) or placebo (n = 111). Approximately 60 % in each arm were treated in the third line. In 37 % and 29 %, respectively, PD-L1 assessment revealed TPS ≥ 1 %. OS and investigator-reported PFS constituted the co-primary endpoint. At WCLC 2020, Fennell et al. reported the preliminary results [6].

OS difference of almost 3 months

The study met its primary endpoint. Nivolumab therapy gave rise to a 28 % reduction in mortality risk, with median OS of 9.2 vs. 6.6 months (HR, 0.72; p = 0.018). At 12 months, 39.5 % vs. 26.9 % of patients were alive. Median PFS was 3.0 vs. 1.8 months (HR, 0.61; p < 0.001), with 12-month rates of 14.5 % vs. 4.9 %. Subgroup analyses according to PD-L1 TPS demonstrated that this biomarker did not predict OS. In contrast, histology mattered, as patients with the epithelioid subtype derived a significant survival benefit from nivolumab treatment (9.4 vs. 6.6 months; HR, 0.71; p = 0.021), whereas those with the non-epithelioid type showed similar outcomes across the arms (5.9 vs. 6.7 months; HR, 0.79; p = 0.572).

Favorable safety results

Median duration of treatment was 84 and 43 days for nivolumab and placebo, respectively. Grade ≥ 3 AEs were observed in 45 % vs. 42 %, and serious grade ≥ 3 AEs in 36 % vs. 39 %. Deaths attributable to serious AEs occurred in 3.6 % vs. 5.3 %. Overall, the findings obtained in the CONFIRM study identified nivolumab as safe and effective in patients with relapsed mesothelioma. The authors emphasized that the PD-1 inhibitor should be considered a new treatment option in this setting.

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J-AXEL: nab-paclitaxel at least equal to docetaxel in pretreated NSCLC

Various advantages have been described for nab-paclitaxel, the albumin-bound, solvent-free, nanoparticle formulation of paclitaxel [1-3]. Phase II data showed favorable results in patients with pretreated advanced NSCLC who obtained an ORR of 32 % and median PFS of 5 months [4]. Therefore, the randomized, phase III study reported by Nakamura et al. compared nab-paclitaxel 100 mg/m^2 on days 1, 8 and 15 three-weekly with docetaxel 60 mg/m^2 every three weeks in patients with stage IIIB/IV or recurrent NSCLC previously treated with cytotoxic chemotherapy [5]. The analysis aimed to demonstrate non-inferiority of nab-paclitaxel with respect to OS. Both arms included approximately 250 patients.

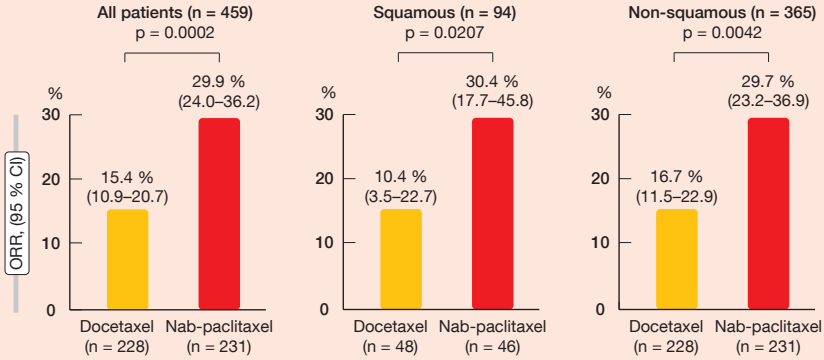

Figure: Objective responses rates achieved with nab-paclitaxel vs. docetaxel in the ITT population and according to histology

Significant PFS and ORR benefits

Non-inferiority of nab-paclitaxel in terms of OS was confirmed with the protocol-specified margin of 1.25 in the intent-to-treat population (HR, 0.85; 95.2 % CI, 0.68–1.070). Median OS amounted to 16.2 and 13.6 months with nab-paclitaxel and docetaxel, respectively. As specified by the protocol, superiority of nab-paclitaxel over docetaxel for OS was tested after non-inferiority had been shown. However, nab-paclitaxel did not significantly improve survival, although this was the case for both PFS and ORR. Median PFS was 4.2 vs. 3.4 months with nab-paclitaxel and docetaxel (HR, 0.76; p = 0.0042). In the total group (n = 459), 29.9 % vs. 15.4 % of patients responded to treatment (p = 0.0002; **Figure**). For the patients with squamous histology (n = 94), this was 30.4 % vs. 10.4 % (p = 0.0207), and for those with non-squamous NSCLC (n = 365), 29.7 % vs. 16.7 % (p = 0.0042). The results for both PFS and OS favored nab-paclitaxel across various subgroups pertaining to age, sex, ECOG performance status, histology, smoking status, disease stage, *EGFR* mutation status, and pretreatment.

Hematologic toxicity with docetaxel and neuropathy with nab-paclitaxel

Among AEs, leukopenia and neutropenia occurred significantly more often with docetaxel than with nab-paclitaxel (p < 0.0001 for both comparisons); correspondingly, docetaxel conferred a significantly higher incidence of febrile neutropenia (22.1 % vs 2.0 %). On the other hand, peripheral sensory neuropathy was more frequent with nab-paclitaxel (55.5 % vs. 20.1 %, p < 0.0001). The authors stressed in their summary that nab-paclitaxel should be considered a standard option for previously treated patients with advanced NSCLC.

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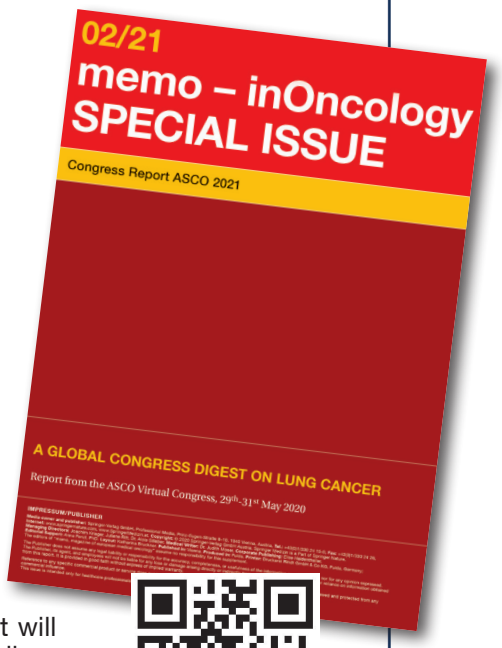
WCLC 2020 – virtual

Luis M. Montuenga talks about factors that are impeding the implementation of low-dose computed tomography lung cancer screening at the global level and describes biomarkers/molecular technologies that are promising with respect to early detection of lung cancer. Moreover, he summarizes advantages and drawbacks of pan-cancer ctDNA analysis in liquid biopsy.

Alex Spira highlights the advantages, shortcomings and the future potential of antibody-drug conjugates, the balance between pro- and anti-inflammatory cytokines within the tumor microenvironment, and the preclinical evidence for targeting inflammatory cytokines in advanced or metastatic non-small-cell lung cancer.

Ming Tsao relates to the innovations of the 5th edition of the WHO classification of lung tumors in terms of additional chapters, new tumor types and grading systems. Additionally, he discusses the use of organoids as potential platforms for drug testing and biomarker validation, as well as miRNAs for early lung cancer detection.



Forthcoming Special Issue

This special issue will be offering a synopsis from the ASCO 2021 that will be held in June 2021. The report promises to make for stimulating reading, as the ASCO Congress itself draws on the input from a number of partner organisations, representing a multidisciplinary approach to cancer treatment and care. Again, lung cancer will be at the heart of this special issue.

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