# Table of Contents

| Page | Title |
|------|-------|
| S68  | Preface |
| S68  | NSCLC with *MET* alterations: molecular insights and innovative treatments |
| S72  | Immune checkpoint inhibition: comprehensive benefits, but not devoid of risks |
| S75  | *EGFR*-mutated disease: early combinations and new approaches in exon 20 insertion-positive lung cancer |
| S78  | Improving outcomes in the early-stage setting with (neo)adjuvant strategies |
| S81  | Present and future perspectives of anti-angiogenic therapy |
| S84  | COVID-19 in patients with thoracic cancers: TERAVOLT |
| S84  | Rare mutations: HER2, RET, ALK, BRAF |
| S87  | Small-cell lung cancer: moving the limits further |

## Editorial Board:

Alex A. Adjei, MD, PhD, Mayo Clinic, Department of Oncology, Rochester, Minnesota, USA  
Maria Rosario Garcia Campelo, MD, Lung Cancer and Thoracic Tumors, University Hospital Quirón A Coruña, La Coruña, Spain  
Federico Cappuzzo, MD, Medical Oncology Department, Ospedale Civile di Livorno, Livorno, Italy  
Wolfgang Hilbe, MD, Departement of Oncology, Hematology and Palliative Care, Wilhelminenspital, Vienna, Austria  
Frau Vera Hirsh, MD, McGill University, Health Centre, Montreal, Quebec, Canada  
Maximilian Hochmair, MD, Department of Respiratory and Critical Care Medicine, KH Nord, Vienna, Austria  
Herbert H F Loong, MD, The Chinese University of Hong Kong, Department of Clinical Oncology, Hong Kong  
Massimo Di Maio, MD, National Institute of Tumor Research and Therapy, Foundation G. Pascale, Napoli, Italy  
Filippo de Marinis, MD, PhD, Director of the Thoracic Oncology Division at the European Institute of Oncology (IEO), Milan, Italy  
Barbara Melosky, MD, FRCP, University of British Columbia and British Columbia Cancer Agency, Vancouver, Canada  
Nir Peled, MD, PhD, Pulmonologist & Medical Oncologist, Thoracic Cancer Unit, Petach Tiqwa, Israel  
Robert Pirker, MD, Medical University of Vienna, Vienna, Austria  
Martin Reck, MD, Lungen Clinic Grosshansdorf, Grosshansdorf, Germany  
Matthias Scheffler, MD, Lung Cancer Group Cologne, Universitätsklinikum Köln, Cologne, Germany  
Riyaz Shah, PhD, FRCP, Kent Oncology Centre, Maidstone Hospital, Maidstone, UK  
Yu Shyr, PhD, Department of Biostatistics, Biomedical Informatics, Cancer Biology, and Health Policy, Nashville, TN, USA  
Masahiro Tsuboi, MD, Kanagawa Cancer Center, Yokohama, Japan  
Gustavo Werutsky, MD, Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil  
Yi-Long Wu, MD, FACS, Guangdong Lung Cancer Institute, Guangzhou, PR China

Lecture Board for this issue:  
D. Ross Camidge, MD, PhD; Maximilian Hochmair, MD

---

Supported by Boehringer Ingelheim in the form of an unrestricted grant
Preface

Dear Colleagues,

Although the COVID-19 pandemic has prevented on-site attendance of the world’s largest cancer conference this year, the experts’ avid interest in advances in their respective areas of specialization remains unchanged. Approximately 40,000 oncology professionals participated in the three-day virtual ASCO scientific meeting that was held online from Friday, May 29, through Sunday, May 31. The program contained almost 5,300 abstracts and more than 100 on-demand and broadcast sessions featuring over 2,300 oral and poster presentations, opening and plenary sessions, cancer-specific highlights sessions, and clinical cancer symposia. Until June 4, the content was viewed more than 2.5 million times. It can be said that the global oncology community has risen magnificently to the occasion.

A range of relevant and potentially practice-changing findings was presented in the field of lung cancer. Immunotherapy and targeted-therapy strategies are now being explored either before or after surgery for early stage disease, with multiple challenges in determining what is and is not a transformative approach. In addition, combinations with radiation therapy continue to be explored in different clinical settings. Moreover, patient care in the setting of rare oncogenic drivers is an important focus of lung cancer research. Significant progress has been made with regard to various aberrations including ALK, MET, HER2, and RET alterations, as well as EGFR exon 20 insertions. All of these occur only in a few percent of patients but make for excellent therapeutic targets. A considerable part of this publication is dedicated to MET aberrations and the agents that have been developed to tackle them with precision. Molecular insights play an important role here as MET alterations have many faces. Also, results for drugs that enable targeting of EGFR exon 20 insertions are promising in this difficult-to-treat subtype of EGFR-positive lung cancer.

Clinical studies and their updates presented at the conference continue to confirm the importance of immune checkpoint inhibition with the next barriers being the determination of unequivocally active combinations of immune agents and the patients/tumor characteristics in whom they may be most effective. Of course, the COVID-19 pandemic itself was addressed in the context of thoracic cancer care this year. Findings obtained from the TERA-VOLT study contribute to the identification of lung cancer patients at risk for fatal COVID-19 infections, while data collection is ongoing and additional analyses will expand our knowledge in this area. Overall, data in this publication are presented together with the conclusions of the authors. We welcome you to question the data and these conclusions yourself.

D. Ross Camidge, MD, PhD
Director of Thoracic Oncology,
University of Colorado,
Aurora, Colorado, USA
National Medical Director of the Academic Thoracic Oncology Medical Investigators Consortium (ATOMIC)

NSCLC with MET alterations: molecular insights and innovative treatments

Oncogenic alterations of the exon 14 of the mesenchymal-epithelial transition (MET) gene occur in 3 % to 4 % of patients with adenocarcinoma of the lung and in 2 % of those with squamous-cell lung cancer [1, 2]. MET exon 14 (METex14) mutations tend to coexist with MET amplifications. Multiple agents are in development for the treatment of lung cancer patients with these alterations. The highly selective, oral MET tyrosine kinase inhibitors (TKIs) capmatinib and tepotinib have already gained regulatory approval.

Capmatinib is being investigated in patients with stage IIIIB/IV non-small-cell lung cancer (NSCLC) and METex14 skipping mutations or MET amplifications in the ongoing, international, open-label, phase II GEOMETRY mono-1 study. This trial has revealed rapid, deep, and durable responses with capmatinib when administered under fasting conditions in patients harboring METex14 skipping mutations [3]. Based on this, capmatinib has received accelerated approval by the US Food and Drug Administration for the treatment of patients with METex14-mutant metastatic NSCLC in May 2020.

GEOMETRY mono-1: high-level MET-amplified NSCLC

High-level MET amplification (i.e., gene copy number ≥ 10) has emerged as a potential predictive biomarker for MET-directed therapies. At the ASCO 2020 Congress, Wolf et al. reported the results for capmatinib 400 mg BID (twice daily) in patients included in GEOMETRY mono-1 who had high-level MET-amplified NSCLC without METex14 mutations [4]. These were either pretreated with one or two lines of systemic therapy (Cohort 1a; n = 69), or treatment-
naïve (Cohort 5a; n = 15). Compared to patients with METex14 mutations, who are predominantly female and never smokers, this population with high-level MET amplifications tended to be male and to have a history of smoking. Overall response rate (ORR) was defined as the primary endpoint. According to blinded independent review, ORRs were 29.0 % and 40.0 % for Cohorts 1a and 5a, respectively (Table 1). One patient in Cohort 1a achieved complete response. Disease control was obtained in 71.0 % and 66.7 %, respectively. The treatment line appeared to determine ORR but not the other outcomes, which were fairly similar across cohorts. Responses lasted for a median of approximately 8 months for both pretreated and treatment-naïve patients. Progression-free survival (PFS) was 4.07 and 4.17 months, respectively, and overall survival (OS) was 10.61 and 9.56 months, respectively. Capmatinib showed a favorable safety profile that matched previous reports. The majority of treatment-related adverse events (AEs) were grades 1 and 2.

The authors concluded that the analysis demonstrated evidence of activity of capmatinib in patients with high-level MET-amplified advanced NSCLC, although response rates were moderate compared to those achieved in the first and second/third treatment lines in the METex14-mutated cohorts of GEOMETRY mono-1 (67.9 % and 40.6 %, respectively) [6]. It can be assumed that a subgroup within the high-level MET-amplified population derives distinct benefit from MET-directed therapy. This group should be characterized more precisely in the future.

Capmatinib use without fasting restrictions

Efficacy and safety results from Cohort 6 of the GEOMETRY mono-1 study were presented by Groen et al. [5]. This expansion group received capmatinib 400 mg BID in the second-line setting and was the first cohort not to include fasting restrictions. It included patients with high-level MET amplification and no METex14 mutations (group 1; n = 31) and METex14 mutations with any MET gene copy number (group 2; n = 31).

Only patients in group 2 responded, with an ORR of 48.4 % based on partial responses according to blinded independent review, although all of the patients included in group 1 achieved disease stabilization. Duration of response in group 2 was 6.93 months. Median PFS was 8.11 months in group 2 and not evaluable in group 1 due to the limited number of patients. Overall, the safety profile proved manageable and was consistent with the safety profile observed under fasting conditions. Notably, there was a numerical trend towards fewer gastrointestinal AEs of any grade when capmatinib was taken without fasting restrictions compared to the administration during a fasted state.

In their summary, the authors concluded that capmatinib demonstrated efficacy as a second-line agent. Taken together with previously reported results, the activity of capmatinib was confirmed irrespective of the line of treatment, with higher ORR in patients treated in earlier lines.

### MET-directed antibody mixture

Sym015 is a synergistic mixture of two recombinant humanized monoclonal antibodies against non-overlapping epitopes of MET. This antibody approach was developed to improve MET selectivity avoiding off-target toxicity and to circumvent intracellular acquired resistance mechanisms to MET TKIs, such as kinase domain mutations. In the phase Ila setting, Sym015 was tested in a total of 45 patients at a loading dose of 18 mg/kg on day 1 of cycle 1 followed by a maintenance dose of 12 mg/kg two-weekly [6]. Twenty of these patients had NSCLC with MET amplifications or METex14 deletions. In this cohort, treatment with prior MET- and/or EGFR-targeting agents was permitted, with 10 patients each being MET-TKI-naïve and MET-TKI-pre-treated. Each of these groups contained both patients with MET amplifications and METex14 deletions.

Responses in lung cancer patients occurred in treatment-naïve individuals only (n = 5; 25 %), with a median duration of 13.8 months. None of the pre-treated patients developed complete or partial responses, although the data suggest minor responses and prolonged stabilization of disease in some cases. The disease control rate (DCR) was 100 % for MET-TKI-naïve patients and 60 % for the MET-TKI-pretreated ones. Median OS had not been reached yet in the overall NSCLC cohort, and PFS was 7.4 vs. 5.4 months. The response rate obtained in the MET-TKI-naïve population was similar to that observed with METTKI treatment in METex14-mutant and MET-amplified NSCLC.

Sym015 showed a favorable safety profile, with peripheral edema, asthenia, decreased appetite constituting the most common treatment-related AEs. Six patients in the overall population of 45 individuals experienced grade ≥ 3 AEs, but only one lung cancer patient required a dose reduction. No patient discontinued treatment due to AEs. Moreover, the analysis suggested that liquid biopsy is a viable option for the selection of patients with METex14 deletions, as there was a 100 % concordance between local tumor and blood circulating tumor DNA (ctDNA).

### Table 1

Responses in the GEOMETRY mono-1 study in patients with high-level MET-amplified NSCLC according to blinded independent review

| Response Category | Cohort 1a (second/third line) | Cohort 5a (first line) |
|------------------|-------------------------------|------------------------|
| Complete response (CR) | 1 (1.4) | 0 |
| Partial response (PR) | 19 (27.5) | 6 (40.0) |
| Stable disease (SD) | 28 (40.6) | 4 (26.7) |
| Non-CR/non-PD | 1 (1.4) | 0 |
| Progressive disease (PD) | 12 (17.4) | 4 (26.7) |
| Not evaluable | 8 (11.6) | 1 (6.7) |
| Overall response rate, % (95 % CI) | 29.0 (18.7-41.2) | 40.0 (16.3-67.7) |
| Disease control rate, % (95 % CI) | 71.0 (58.8-81.3) | 66.7 (38.4-88.2) |
for this aberration in nine evaluable patients. On the other hand, the concordance for the detection of MET amplification was low at 29%, which might be due to factors such as low tumor shedding or tumor evolution. Evaluation of Symb15 in combination with MET TKI treatment to delay or treat resistance is planned.

Subtypes of METex14 alterations

Exon 14 skipping is caused by the range of genomic alterations in exon 14 and its flanking introns. Awad et al. analyzed samples from NSCLC patients to characterize potential differences across various METex14 alteration subtypes and to assess co-occurring alterations as well as immunotherapy biomarkers that might impact treatment efficacy and inform combination strategies [7]. NGS-based hybrid-capture genomic profiling of tumor DNA from 60,495 NSCLC patients revealed METex14 alterations in 2.3% (n = 1,387) at multiple functional site subsets resulting in exon 14 skipping, deletion, or mutation at Y1003. METex14-altered lung tumors showed significantly lower tumor mutational burden (TMB) than those with METex14 wildtype (p < 0.001). Moreover, they were enriched for high (≥50%) PD-L1 expression compared with wildtype samples (48% vs. 29%; Figure 1). PD-L1 positivity was relatively similar across METex14 alteration functional site subsets. None of the cases demonstrated an association between TMB and PD-L1 expression. Additional data are required to determine the predictive role of these biomarkers for immunotherapy response.

Also, the frequency of co-alterations such as MDM2, CDK4 and MET amplification was largely consistent across splicing functional sites. Concurrent drivers including KRAS and EGFR mutations were rare at 3.2% and 0.65%, respectively. No concurrent BRAP/NVME mutations or ALK/ROS1/NTRK fusions emerged.

According to the analysis of 36 paired cases, potential acquired resistance mechanisms appeared to be essentially independent of the primary METex14 alteration subtype. Resistance alterations included recurrent secondary MET mutations (25% of pairs), MET amplification (8% of pairs), and individual cases with EGFR/ErbB2 activation, KRAS amplification, and PI3K mutations.

DNA- vs. RNA-based assays

Assuming that DNA-based assays alone might be suboptimal for the detection of METex14 mutations, Jurkiewicz et al. examined profiling data of lung adenocarcinomas determined by NGS to compare the performance of DNA- and RNA-based assays for the detection of METex14 variants [8]. The tumors of 644 patients were profiled by a custom targeted DNA-based panel that targets MET exons 2, 14, 16, 18, and 19. Cases without DNA-based driver mutations were reflexed to an NGS-based RNA fusion panel.

Over a 21-month period, DNA profiling detected METex14 skipping events in 2.5% of patients. However, RNA analysis of driver-negative cases identified nine additional METex14 mutations, which made for a total of 3.9% events. Thus, 36% of METex14 mutations were missed by the DNA panel. The variants identified only by the RNA panel tended to be present at the intron 13 splice acceptor site or other sites relevant to splicing. These were not covered by the DNA panel, while the intron 14 splice donor site was. The authors noted that mutations can occur in the splice acceptor site, branching site A and polypyrimidine tracks. Custom DNA panels that cover these areas could increase assay sensitivity but require deeper intronic coverage, which poses a technical challenge.

Overall, DNA-based NGS panels can potentially miss METex14 skipping events in lung adenocarcinomas when the panel primers do not target both the 3’ splice site of intron 13 and the 5’ splice site of intron 14. A reflex workflow testing for RNA fusions in cases without DNA-detected driver mutations can potentially capture such events. With respect to future research, histological, clinical and molecular characterization of the variants detected only by RNA assays warrants further exploration.

The VISION trial: tepotinib

The phase II VISION trial assessed the efficacy and tolerability of the MET TKI tepotinib at a daily dose of 500 mg in patients with locally advanced or metastatic NSCLC harboring METex14 skipping mutations after ≤2 lines of therapy. Based on these results, tepotinib and its companion diagnostic were approved in Japan in March 2020. MET alterations had been detected through liquid biopsy or tissue biopsy before trial inclusion. Patients with asymptomatic brain metastases were allowed to enroll. Le et al. reported the primary efficacy, safety, and biomarker results of the VISION trial [9].

ORR according to independent review, which was defined as the primary endpoint, was 48.5% in the liquid-biopsy-positive group, 50.0% in the tissue-biopsy-positive group, and 46.5% in the combined group that was liquid- and/or tissue-biopsy-positive (Table 2). Tumor shrinkage occurred in 89% of all patients. In the combined group, median PFS and OS were 8.5 and 17.1 months, respectively. Outcomes in patients with baseline brain metastases (n = 11), all of which were non-target lesions, were comparable to those in the
overall population, with an ORR of 54.5% and median PFS of 10.9 months.

Sixty-seven percent of patients achieved molecular ctDNA responses, i.e., reductions in METex14 mutant allelic frequency. Among these, high response rates were observed, with 71% and 88% experiencing radiographic response and disease control, respectively. Tepotinib had a manageable tolerability profile. Peripheral edema, nausea and diarrhea were the most common AEs. Grade ≥ 3 treatment-related AEs occurred in 27.6% of patients. Dose reductions became necessary in 32.9%, and permanent discontinuations in 11.2%.

The authors concluded that tepotinib is a promising targeted therapy with durable clinical activity in NSCLC patients with METex14 skipping mutations identified by liquid or tissue biopsy.

**Quality-of-life data from VISION**

Findings on health-related quality of life in the VISION trial were reported separately at the ASCO Congress [10]. This outcome was assessed using the EORTC QLQ-LC13, EORTC QLQ-C30 and EQ-5D-5L questionnaires, as well as the Visual Analog Scale (VAS). At study entry, almost all patients had metastatic disease; they were older than patients with other actionable molecular alterations (median age, 74.0 years), and the majority had an ECOG performance status of 1. Baseline scores showed moderate-to-high functioning and quality of life, and a moderate lung cancer symptom burden.

For the QLQ-LC13 symptoms, mean changes from baseline indicated a meaningful improvement in cough and numerical improvement in dyspnea and chest pain. Mean changes in the QLQ-C30 global health and functional scale scores and EQ-5D-5L VAS scores demonstrated stability in quality of life over time. These findings, together with the efficacy and safety results from the VISION study, support tepotinib as a promising treatment option in NSCLC patients with METex14 skipping mutations.

**Robust activity of savolitinib**

A Chinese multicenter, single-arm phase II study evaluated the highly selective, oral MET TKI savolitinib in patients with unresectable or metastatic METex14-skipping–positive pulmonary sarcomatoid carcinoma (PSC; n = 25) and other types of NSCLC (n = 45) [11]. Patients were unfit for chemotherapy or had not responded to it. PSC is a rare type of NSCLC with particularly aggressive clinical behavior and poor prognosis that is often resistant to chemotherapy. Savolitinib was prescribed in a weight-adjusted manner, with daily doses of 600 mg and 400 mg for patients weighing ≥ 50 kg and < 50 kg, respectively.

Savolitinib showed robust and durable activity with an ORR of 49.2% in the efficacy-evaluable set. Responses lasted for a median of 9.6 months. Median PFS was 6.9 months; patients with PSC showed shorter PFS than those with other NSCLC types (5.5 months and 9.7 months, respectively). Also, PFS was longer in the previously treated group (13.8 months) than in the treatment-naïve cohort (5.6 months), although this reflects the fact that nearly half of patients in the treatment-naïve cohort had PSC. Median OS was 14.0 months.

Treatment-related serious AEs including hepatic dysfunction, drug hypersensitivity and pyrexia occurred in 25.7% of patients. One patient died of tumor lysis syndrome. Treatment discontinuation due to AEs became necessary in 14.3%. Overall, savolitinib demonstrated promising anti-tumor activity and acceptable tolerability.

**Characteristics of early-stage METex14-mutant lung cancer**

Clinical and genomic features of METex14-mutant NSCLC have been characterized in the metastatic setting, while less is known about this molecular subtype in early-stage disease. Therefore, Recondo et al. retrospectively assessed various features of METex14-mutant lung cancer in a cohort of 613
patients with resected stage I-III NSCLC and compared them to stage IV lung cancer [12]. The prevalence of METex14 mutations was 2.8 % in this group; nonsquamous tumors showed a higher frequency (2.9 %; Figure 2) than those with squamous histology (1.4 %).

Regarding genomic co- alterations, MET amplifications, TP53 mutations and CDKN2A/B loss were significantly less prevalent in stages I-III than in stage IV NSCLC. The difference for MDM2 and CDK4/6 amplification was not significant, while KRAS mutation/amplification and EGFR mutation/amplification occurred in stage IV tumors only. High PD-L1 expression with tumor proportion scores (TPS) of ≥50 % was infrequent in stages I and II (13.5 % and 14.3 %, respectively) but considerably more prevalent in stage III (36.0 %), although this was still lower than the prevalence of PD-L1 TPS ≥50 % observed in stage IV (48.7 %).

With respect to clinical outcomes, the analysis showed that approximately 46 % of patients with stage II or III disease experienced recurrence after resection with curative intent. Median disease-free survival (DFS) from surgery in these groups was only 2.6 and 2.1 years, respectively. On the other hand, DFS for patients with stage I disease was 8.3 years (p = 0.017). The investigators emphasized that clinical trials exploring the role of adjuvant and neoadjuvant MET-targeted therapy in this population might be warranted.

REFERENCES

1 Drilon A et al., Targeting MET in lung cancer: will expectations finally be met? J Thorac Oncol 2017; 12; 15-26
2 Tong JH et al., MET amplification and exon 14 splice site mutation define unique molecular subgroups of non-small cell lung carcinoma with poor prognosis. Clin Cancer Res 2016; 22: 3048-3056
3 Wolf J et al., Capmatinib (INC280) in METex14-mutated advanced non-small cell lung cancer (NSCLC): Efficacy data from the phase II GEOMETRY mono-1 study. J Clin Oncol 37, 2019 (suppl; abstr 9004)
4 Wolf J et al., Capmatinib in patients with high-level MET-amplified advanced non-small cell lung cancer (NSCLC): results from the phase 2 GEOMETRY mono-1 study. J Clin Oncol 38: 2020 (suppl; abstr 9058)
5 Groen HJM et al., Capmatinib in patients with METex14-mutated or high-level MET-amplified advanced non-small-cell lung cancer (NSCLC): results from cohort 6 of the phase 2 GEOMETRY mono-1 study. J Clin Oncol 38: 2020 (suppl; abstr 9520)
6 Camidge DR et al., Safety and preliminary clinical activity of the MET antibody mixture Sym015 in advanced non-small cell lung cancer (NSCLC) patients with MET amplification/exon 14 deletion (MET(DD/HS)). J Clin Oncol 38: 2020 (suppl; abstr 9519)
7 Awad M et al., Characterization of 1,387 NSCLCs with MET exon 14 (METex14) skipping alterations (SA) and potential acquired resistance (AR) mechanisms. J Clin Oncol 38: 2020 (suppl; abstr 9511)
8 Jurkiewicz M et al., Efficacy of DNA vs. RNA NGS based methods in MET Exon 14 skipping mutation detection. J Clin Oncol 38: 2020 (suppl; abstr 9036)
9 Le X et al., Primary efficacy and biomarker analyses from the VISION study of tepotinib in patients with NSCLC with MET exon 14 skipping. J Clin Oncol 38: 2020 (suppl; abstr 9556)
10 Paik PK et al., Tepotinib in NSCLC patients with MET exon 14 skipping: health-related quality of life. J Clin Oncol 38: 2020 (suppl; abstr 9575)
11 Lu S et al., Phase II study of savolitinib in patients with pulmonary sarcomatoid carcinoma and other types of non-small cell lung cancer harboring MET exon 14 skipping mutations. J Clin Oncol 38: 2020 (suppl; abstr 9519)
12 Recondo G et al., Clinical characteristics, genomic features, and recurrence risk of early-stage MET exon 14 mutant non-small cell lung cancer (NSCLC). J Clin Oncol 38: 2020 (suppl; abstr 9040)

Immune checkpoint inhibition: comprehensive benefits, but not devoid of risks

Three-year findings in CheckMate 227

First-line nivolumab plus ipilimumab (NI) was shown to significantly prolong OS compared to chemotherapy in patients with advanced NSCLC irrespective of tumor PD-L1 expression in the randomized, phase III CheckMate 227 study [1]. At the ASCO Congress, Ramalingam et al. presented the updated 3-year efficacy and safety results from Part 1 of the trial [2]. Part 1 consisted of Part 1a that compared NI (n = 396) with chemotherapy (n = 397) and nivolumab monotherapy (n = 396), as well as Part 1b which assessed NI (n = 187) vs. chemotherapy (n = 186) and nivolumab plus chemotherapy (n = 177). Patients in Part 1a showed PD-L1 expression ≥1 %, while those in Part 1b tested PD-L1-negative (<1 %).

At three years, first-line NI continued to provide long-term benefits compared to chemotherapy regardless of PD-L1 expression. In Part 1a, 3-year OS rates were 33 % vs. 22 % with the combination and chemotherapy, respectively (HR, 0.79). For Part 1b, these were 34 % vs. 15 % (HR, 0.64). More than one third of all responders remained in response after three years with NI (38 % and 34 % for PD-L1 expressors ≥1 % and <1 %, respectively), while the respective rates in the chemotherapy group ranged below 5 %. Also, the combination showed lasting superiority over both nivolumab monotherapy and nivolumab plus chemotherapy independent of PD-L1 expression.

An exploratory landmark analysis assessed the impact of response at six months on long-term OS. This showed that among patients with PD-L1 ≥1 %, 70 % of those achieving complete or partial responses at six months with NI were alive at three years; in the chemotherapy arm, this applied only to 39 %. Similar results were observed for the group with PD-L1 <1 % (82 % vs. 25 %). The extended safety follow-up over at least 36.3 months did not reveal any new signals for the combination. Treatment-related select AEs of NI affecting the skin, gastrointestinal tract, endocrine system and other areas decreased over time. The authors concluded that NI is a novel chemotherapy-sparing first-line treatment option for patients with advanced NSCLC. In May 2020, the
regimen has received approval in the USA in this indication, while the European application was withdrawn four months earlier.

**Two cycles of chemotherapy plus checkpoint blockade: CheckMate 9LA**

The phase III, randomized CheckMate 9LA trial was conducted based on the assumption that adding a limited course of chemotherapy to first-line NI might provide rapid disease control while building on the durable OS benefit observed with NI in CheckMate 227. Among 719 patients with stage-IV or recurrent NSCLC, 361 received NI combined with two cycles of chemotherapy. In the control arm (n = 358), four cycles of chemotherapy were administered, followed by optional pemetrexed maintenance in patients with non-squamous tumors. OS was defined as the primary endpoint.

After a minimum follow-up of 8.1 months, CheckMate 9LA met its primary endpoint at the time of the pre-planned interim OS analysis, with a statistically significant benefit for the immunotherapy-based regimen compared to chemotherapy only (14.1 vs. 10.7 months; HR, 0.69; p = 0.0006) [3]. The OS advantage increased over time; according to updated results obtained after a follow-up of 12.7 months, median OS was 15.6 vs. 10.9 months (HR, 0.66; Figure 1). Patients fared better regarding survival with the immunotherapy-based approach regardless of histology (squamous vs. non-squamous) and PD-L1 expression (<1 %, ≥1 %, 1-49 %, ≥50 %). At 12 months, PFS rates were 33 % vs. 18 % (HR, 0.68), and 49 % vs. 24 % patients responded to treatment. The combination did not induce any new AEs; any-grade treatment-related AEs mainly included nausea, anemia, asthenia, and diarrhea. Immune-related AEs were mostly grades 1 and 2. Overall, the CheckMate 9LA study demonstrated that NI plus a limited course of chemotherapy should be considered as a new first-line treatment option for patients with advanced NSCLC. Indeed, approval in the USA has been granted by the Food and Drug Administration in May 2020.

**Durvalumab/tremelimumab ± chemotherapy**

Another trial to assess the combined first-line approach of dual checkpoint inhibition and chemotherapy in stage IV NSCLC is the international, randomized phase II CCTG BR.34 study [4]. Patients were allocated to either durvalumab plus tremelimumab followed by durvalumab maintenance (n = 150) or the same regimen plus platinum doublet chemotherapy followed by durvalumab alone or combined with pemetrexed, depending on histology (n = 151). Although the addition of chemotherapy did not prolong OS (HR, 0.88), the combined strategy led to significant benefits compared to the immunotherapy-only approach with respect to PFS (7.7 vs. 3.2 months; HR, 0.67; p = 0.0035) and ORR (p = 0.033).

The effect of the addition of chemotherapy appeared to be greater in patients with blood tumor mutational burden (bTMB) < 20 mutations/Mb; however, the interaction test was negative. According to the investigators, this finding warrants further evaluation in randomized studies. Irrespective of the type of treatment, patients with bTMB ≥ 20 mut/Mb had longer OS and PFS than those with bTMB < 20 mut/Mb, which suggested a prognostic (rather than a predictive) effect. PD-L1 levels were not associated with differential benefit from the addition of chemotherapy. More patients experienced serious AEs in the experimental arm, although the incidence of immune-related AEs was similar between the two groups.

Analyses of quality of life, plasma genomics and cost in this trial are ongoing.

**Final analysis of KEYNOTE-189**

In the randomized, double-blind, phase III KEYNOTE-189 trial, pembrolizumab plus platinum-based chemotherapy first demonstrated significantly improved OS and PFS over placebo plus chemotherapy in untreated patients with metastatic non-squamous NSCLC regardless of PD-L1 expression [5, 6]. At ASCO 2020, Rodriguez-Arueu et al. presented the protocol-specified final analysis of KEYNOTE-189 after a median of 31.0 months from randomization to data cut-off [7].

With long-term follow-up, pembrolizumab plus pemetrexed/platinum continued to improve the efficacy outcomes over chemotherapy alone. Median OS

![Figure 1: CheckMate 9LA: sustained overall survival benefit of nivolumab plus ipilimumab and chemotherapy versus chemotherapy](image_url)
was approximately twice as long in the experimental arm as in the control arm (22.0 vs. 10.6 months; HR, 0.56). This also applied to PFS (9.0 vs. 4.9 months; HR, 0.49) and PFS2, i.e. PFS after the next line of therapy (17.0 vs. 9.0 months; HR, 0.50). Objective responses resulted in 48.3% vs. 19.9%. PD-L1 expression did not affect any of these outcomes. ORR was high at 85.7% in the group of patients in the experimental arm who completed 35 cycles of pembrolizumab (n = 56); this included four complete responders. Median OS had not been reached in this cohort yet.

The authors concluded that pembrolizumab plus pemetrexed/platinum is a standard-of-care therapy for patients with newly diagnosed metastatic non-squamous NSCLC.

**Anti-TIGIT antibody tiragolumab**

The co-inhibitory receptor TIGIT is expressed on multiple immune cells and inhibits T cells as well as NK cells by binding to its ligand on tumor and antigen-presenting cells [8-10]. It was hypothesized that anti-TIGIT antibodies preventing this binding reaction might restore the anti-tumor response and complement the activity of anti-PD-(L)1 antibodies. Indeed, the anti-TIGIT monoclonal antibody tiragolumab showed activity in combination with atezolizumab in the phase I GO30103 trial (NCT02794571). Based on these observations, the randomized, double-blind, phase II CITYSCAPE study assessed tiragolumab plus atezolizumab (n = 67) compared to placebo plus atezolizumab (n = 68) in the first-line treatment of patients with stage IV, PD-L1-expressing NSCLC [11].

ORR and PFS were defined as the co-primary endpoints. After a median follow-up of 10.9 months, tiragolumab plus atezolizumab, as compared to placebo and atezolizumab, induced clinically meaningful improvements in ORR (37% vs. 21%) and PFS (5.55 vs. 3.88 months; HR, 0.56) in the ITT population. Of note, both ORR and PFS benefits were observed in patients with PD-L1 tumor proportion scores (TPS) ≥ 50%, but not in those with TPS 1-49% (Table). Duration of response and OS are not yet mature.

Tiragolumab plus atezolizumab was well tolerated, with a safety profile similar to that of the comparator regimen. Although immune-mediated toxicity occurred more frequently in the experimental arm, these AEs were primarily grades 1 or 2 and were manageable. SKYSCRAPER-01, an ongoing phase III study, is aiming to confirm the observed activity and safety of tiragolumab plus atezolizumab in untreated patients with PD-L1-expressing (TPS ≥ 50%) NSCLC.

**Pneumonitis as an underreported AE**

Although immunotherapy is of increasing importance in the treatment of patients with advanced NSCLC, potentially life-threatening AEs such as checkpoint inhibitor pneumonitis (CIP) need to be dealt with and might deserve more consideration. Spieler et al. hypothesized that CIP might be underreported in patients with advanced NSCLC receiving nivolumab monotherapy and that radiomics features can identify CIP which has been clinically misclassified [12]. Within an Institutional Review Board-approved database, 9 of 159 nivolumab-treated NSCLC patients (5%) had been diagnosed with any-grade CIP. Forty additional patients without a CIP diagnosis were randomly selected from the same population by the investigators. In all 49 cases, uninvolved lung in the last pre-immunotherapy CT imaging study was segmented, delineated, and analyzed for radiomics features associated with CIP. A logistic regression model incorporating radiomics assigned a CIP probability score to each patient.

Six radiomics features were shown to correlate with CIP. The radiomics-based probability model assigned seven out of 40 patients (17.5%) without a clinical diagnosis of CIP a > 50% probability of CIP. The chart review revealed that six of these seven patients exhibited symptoms or radiographic features highly suggestive of CIP. Therefore, it appears that the incidence of CIP is underreported and radiomics features can

![Figure 2](image-url)

**Table: ORR and PFS outcomes with first-line tiragolumab plus atezolizumab compared to atezolizumab alone**

|                     | Tiragolumab + atezolizumab | Placebo + atezolizumab |
|---------------------|----------------------------|------------------------|
| **Overall response rate (%)** |                           |                        |
| ITT population      | 37                         | 21                     |
| PD-L1 TPS ≥ 50%     | 66                         | 24                     |
| PD-L1 TPS 1-49%     | 16                         | 18                     |
| **Progression-free survival (months)** |                       |                        |
| ITT population      | 5.55                       | 3.88                   |
| PD-L1 TPS ≥ 50%     | Not reached                | 4.11                   |
| PD-L1 TPS 1-49%     | 4.04                       | 3.58                   |

**Figure 2:** Incidence and severity of pneumonitis in patients with stage III NSCLC treated with chemoradiation and durvalumab consolidation.
help to identify cases that have been clinically misclassified. Future directions for research include expansion of this study across the full database, correlation of radiomics features with blood biomarkers, and the inclusion of tumor burden and radiotherapy as additional covariates in the analysis.

**Durvalumab rechallenge after pneumonitis**

Saito et al. investigated the timing, clinical course, severity, management, and clinical outcomes of pneumonitis/radiation pneumonitis among patients with locally advanced NSCLC who received chemoradiotherapy after the approval of durvalumab in the real-world setting [13]. This retrospective study conducted at 17 Japanese centers involved consecutive patients who started concurrent chemoradiotherapy between May 2018 and May 2019. The analysis population comprised 275 individuals. Durvalumab consolidation was performed in 74.2% of cases.

More than 80% of patients developed pneumonitis that was mostly grades 1 (48.7%) and 2 (26.5%), although in 1.5%, pneumonitis was fatal (Figure 2). Thirty-three percent of patients experienced pneumonitis with any symptoms (≥ grade 2); here, the lung volume receiving doses of ≥ 20 Gy (V20) was identified as an independent risk factor. In 6%, grade ≥ 3 pneumonitis occurred. Thirteen patients (5%) required home oxygen therapy after pneumonitis. Median onset of pneumonitis was 14 weeks after the initiation of chemoradiotherapy and approximately four to seven weeks after the initiation of durvalumab treatment.

Among patients who developed pneumonitis during durvalumab consolidation, steroid therapy was administered in 25%. In this group, a durvalumab rechallenge was performed in 41%, with the majority of patients experiencing no relapse of pneumonitis. Half of those who did relapse did not require treatment interruption and had no fatal relapse or chronic respiratory failure. The authors noted that with careful consideration, durvalumab rechallenge might be an option after corticosteroid therapy for pneumonitis.

**REFERENCES**

1. Hellmann MD et al., Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. N Engl J Med 2018; 381: 2020-2031
2. Ramalingam SS et al., Nivolumab + ipilimumab versus platinum-doublet chemotherapy as first-line treatment for advanced non-small cell lung cancer: Three-year update from CheckMate 227 Part 1. J Clin Oncol 38: 2020 (suppl; abstr 9500)
3. Reck M et al., Nivolumab + ipilimumab + 2 cycles of platinum-doublet chemotherapy vs. 4 cycles chemoradiotherapy as first-line treatment for stage IV unresectable non-small cell lung cancer (NSCLC): CheckMate 9LA. J Clin Oncol 38: 2020 (suppl; abstr 9501)
4. Leight NB et al., CCGT BR:34: A randomized trial of durvalumab and tremelimumab +/- platinum-based chemotherapy in patients with metastatic (stage IV) squamous or nonsquamous non-small cell lung cancer (NSCLC). J Clin Oncol 38: 2020 (suppl; abstr 9502)
5. Gandhi L et al., Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018; 378(22): 2078-2092
6. Gadgeel S et al., Updated analysis from KEYNOTE-189: Pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer. J Clin Oncol 2020; 38(14): 1505-1517
7. Rodriguez-Abreu D et al., Protocol-specified final analysis of KEYNOTE-189: pemetrexed-platinum chemotherapy with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC. J Clin Oncol 38: 2020 (suppl; abstr 9802)
8. Manieri NA et al., TIGIT: A key inhibitor of the cancer immunity cycle. Trends Immunol 2017; 38(1): 20-28
9. Rotte A et al., Mechanistic overview of immune checkpoints to support the rational design of their combinations in cancer immunotherapy. Ann Oncol 2018; 29(1): 71-83
10. Yu X et al., The surface protein TIGIT suppresses T cell activation by promoting the generation of mature immunoregulatory dendritic cells. Nat Immunol 2009; 10: 48-57
11. Rodriguez-Abreus D et al., CITYSCAPE: Primary analysis of a randomized, double-blind, phase II study of the anti-TIGIT antibody tiragolumab plus atezolizumab versus placebo plus atezol as first-line treatment in patients with PD-L1-selected NSCLC. J Clin Oncol 38: 2020 (suppl; abstr 9503)
12. Spieler B et al., Is checkpoint inhibitor pneumonitis underreported in patients with advanced non-small cell lung cancer (NSCLC) on PD-1 inhibitor monotherapy? J Clin Oncol 38: 2020 (suppl; abstr 9579)
13. Saito G et al., Real-world survey of pneumonitis/radiation pneumonitis among locally advanced NSCLC with chemoradiotherapy after the approval of durvalumab: A multicenter retrospective cohort study (HOPE-005/CRIMSON). J Clin Oncol 38: 2020 (suppl; abstr 9039)

**EGFR-mutated disease: early combinations and new approaches in exon 20 insertion-positive lung cancer**

**Upfront radiation plus TKI in the oligometastatic setting**

Oligometastatic disease is generally defined by one to five metastatic lesions. As progression occurs most frequently in sites of the original disease, it is surmised that aggressive local treatment might prevent further dissemination. Based on this rationale, the open-label, randomized, phase III SINDAS trial conducted in China explored the use of concurrent stereotactic body radiotherapy (SBRT) and EGFR TKI therapy in patients with oligometastatic, EGFR-mutant NSCLC [1]. Patients had no more than two metastatic lesions in any one organ and a maximum of five metastases in total. In the experimental arm (n = 68), SBRT was administered at doses of 25 to 40 Gy in five fractions, while patients in the control arm (n = 65) received TKI treatment (i.e., gefitinib, erlotinib, icotinib) only.

PFS was defined as the primary endpoint. Here, the combined regimen gave rise to a significant benefit with a 38% reduction in the risk of progression or death (HR, 0.618; p = 0.001; Figure 1). Also, the addition of radiotherapy prolonged OS in a significant manner (HR, 0.682; p < 0.001). At the same time, the incidence of grade-3 AEs including
rash, severe liver injury, pneumonitis, esophagitis, and pathological rib fractures did not differ significantly across the treatment arms. Overall, these findings confirmed previous hypotheses assuming a benefit of consolidative SBRT for limited metastatic NSCLC. The authors concluded that aggressive upfront local therapy should be investigated further in large phase III trials as a standard option in this clinical scenario.

First-line dual TKI therapy: osimertinib plus gefitinib

As is known, the first-generation EGFR TKI gefitinib and the third-generation EGFR TKI osimertinib give rise to different predominant second-site EGFR resistance mutations (i.e., T790M and C797S with gefitinib and osimertinib, respectively). Each agent retains activity against the main resistance mechanism observed with the other one. Based on the assumption that treatment response might be prolonged with a combined strategy, a phase I/II study is currently evaluating the first-line regimen of gefitinib plus osimertinib in patients with EGFR-mutant (i.e., EGFR L858R mutation or exon 19 deletion), stage IV NSCLC. Twenty-seven patients were included in the analysis presented at the ASCO Congress [2]. Most of these were Caucasian (81 %), and more than half had never smoked. Treated or asymptomatic untreated CNS disease was permitted; 33 % and 26 % of patients had treated and untreated brain lesions, respectively, while in 41 %, CNS metastases were absent. Primary endpoints included the maximum tolerated dose and the feasibility of treatment, which was defined as receipt of the combination therapy for at least six 28-day cycles. No dose-limiting toxicities occurred with gefitinib 250 mg and osimertinib 80 mg daily during the dose escalation phase, and AEs were consistent with the known toxicity profile for EGFR TKI therapy. Rash (96 %), diarrhea (85 %) and dry skin (70 %) represented the most common events. None of the patients experienced pneumonitis.

During the dose expansion phase, the feasibility endpoint was met by 81.5 % of patients who received at least six cycles. Objective responses and disease control resulted in 88.9 % and 100 %, respectively. Median PFS was 22.5 months, although these data are still immature, as are those for OS. Moreover, the combination induced rapid and near-universal plasma clearance of the mutant EGFR allele, with 88 % of patients showing undetectable mutation status at two weeks. In terms of acquired resistance, next-generation sequencing at disease progression revealed no known pathogenic EGFR second-site mutations in seven patients. Also, no patient experienced histologic transformation.

In their summary, the investigators pointed out that the observed ORR of 88.9 % is comparable to response rates obtained for first-line use of osimertinib. Further analyses of PFS and OS will facilitate understanding of the clinical utility of first-line dual EGFR TKI therapy.

Mobocertinib in NSCLC with EGFR exon 20 insertions

Among activating EGFR mutations, exon 20 insertions mark a type of NSCLC that is difficult to treat and associated with poor prognosis. These tumors are generally insensitive to EGFR TKI therapy, and treatment options are limited after progression on platinum-based chemotherapy.

The novel EGFR TKI mobocertinib (TAK-788) is currently in development for lung cancer with exon 20 insertions and has already received Breakthrough Therapy Designation by the US Food and Drug Administration for the treatment of patients with metastatic NSCLC harboring EGFR exon 20 insertions whose disease has progressed on or after platinum-based chemotherapy.

![Figure 1: Progression-free survival with radiotherapy plus EGFR TKI treatment vs. TKI therapy alone in oligometastatic, EGFR-mutant lung cancer.](image1)

**Figure 1:** Progression-free survival with radiotherapy plus EGFR TKI treatment vs. TKI therapy alone in oligometastatic, EGFR-mutant lung cancer

![Figure 2: Improvement in progression-free survival with mobocertinib compared to real-world findings in NSCLC patients harboring EGFR exon 20 insertions.](image2)

**Figure 2:** Improvement in progression-free survival with mobocertinib compared to real-world findings in NSCLC patients harboring EGFR exon 20 insertions
In the absence of head-to-head evidence, Horn et al. indirectly compared clinical trial data for mobocertinib obtained in a single-arm, phase I/II study with real-world outcomes [3]. Real-world data that had been generated to understand the natural history and treatment patterns in patients with exon 20 insertions were obtained from the US Flatiron Health HER-derived de-identified database. In the ongoing phase I/II trial, mobocertinib is being administered orally at a daily dose of 160 mg. A total of 99 patients with locally advanced or metastatic NSCLC harboring EGFR exon 20 insertions (n = 28 and n = 71 for mobocertinib and real-world patients, respectively) were included in the analysis; data were reported for the second-line setting. Treatments in the real-world population included chemotherapy, immunotherapy, EGFR TKI treatment and combinations of these; also, combinations of chemotherapy and/or EGFR TKIs with monoclonal antibodies were used. Immunotherapies were most prevalent, at 29.6 %, followed by EGFR TKI treatment (25.4 %) and docetaxel (10.0 %).

Even with baseline propensity matching, mobocertinib performed better than the comparator regimens. Patients in the mobocertinib group achieved superior ORR (43 % vs. 14 %; p = 0.003) and PFS (7.3 vs. 3.7 months; p = 0.0235; Figure 2). A trial comparing first-line mobocertinib with platinum-based chemotherapy in NSCLC patients with EGFR exon 20 insertions is currently recruiting (NCT04129502).

Poziotinib: Cohort 1 of the ZENITH20 study

Similarly, the oral, irreversible EGFR TKI poziotinib has been developed to target EGFR and HER2 exon 20 insertions. At the ASCO Congress, Le et al. presented the results for Cohort 1 of the multicenter, phase II ZENITH20 trial that assessed poziotinib in a total of seven cohorts including previously treated and treatment-naive NSCLC patients [4]. Brain metastases were permitted if the lesions were stable.

Cohort 1 contained 88 evaluable patients with EGFR exon 20 insertions who received poziotinib after pretreatment. In this group, the TKI gave rise to an ORR of 19.3 % and DCR of 80.7 %. Duration of response was 7.4 months. Assessment of response according to prior therapy showed that after ≥3 lines of treatment, patients obtained even slightly better ORR (22.2 %) than after one line (18.5 %) or two lines (16.7 %). The investigators concluded that multiple prior lines of therapy did not impair response. EGFR insertion location had a certain effect on the efficacy of treatment: exon 20 near-loop insertions were the most prevalent alterations (>50 %), and these patients benefited most from poziotinib.

Tumor shrinkage occurred in 84 % of evaluable patients. Freedom from progression was maintained for a median of 4.1 months. Twelve patients had stable CNS disease at baseline. Among these, 83 % did not experience progression during treatment, and only 3 % of patients without baseline brain lesions developed new CNS metastases. Common grade-3 treatment-related AEs events comprised diarrhea (25 %), rash (28 %), stomatitis (9 %), and paronychia (6 %).

EGFR-MET-bispecific antibody amivantamab

A novel treatment approach with broad application in EGFR-mutant NSCLC is the EGFR-MET-bispecific antibody amivantamab that targets both activating and resistance EGFR mutations and MET mutations/amplifications. This agent inhibits aberrant EGFR and MET signaling through binding to the extracellular domains of these receptors, rather than targeting the kinase active site.

Amivantamab is being investigated in the ongoing phase I CHRYSLAS trial in patients with metastatic or unresectable NSCLC and activating EGFR or MET mutations or amplifications. Park et al. reported preliminary results for patients with EGFR exon 20 insertions who had received the recommended phase II dose of 1,050 mg (1,400 mg for patients weighing ≥80 kg) intravenously once weekly for the first cycle and biweekly thereafter [5]. Fifty and 39 patients constituted the safety and response-evaluable populations, respectively. In the response-evaluable group, 29 (74 %) had been treated with platinum-based chemotherapy in the metastatic setting prior to inclusion, while six were treatment-naïve and four had received other therapies including EGFR TKIs and/or VEGF inhibition.

Responses were observed in both treatment-naïve and post-platinum patients. ORRs amounted to 36 % and 41 % in the overall group and in the post-platinum cohort, respectively (Figure 3). In the total population, 67 % of patients derived clinical benefit; for the post-platinum group, this was 72 %. Activity of treatment was observed across all 13 distinct EGFR exon 20 insertion alterations identified. Responses were durable, with a median duration of 10 months for all evaluable patients and 7 months for the post-platinum group. Median PFS was 8.3 and 8.6 months, respectively.

Amivantamab was shown to have a manageable safety profile, with rash, infusion-related reaction and paronychia occurring as the most common adverse events. Toxicities were mostly grade 1 and 2. Dose reductions and discontinuations due to AEs were infrequent, at 10 % and 6 %. Based on these data, amivantamab has received FDA Breakthrough Therapy Designation for
the treatment of patients with EGFR exon 20 insertion-mutant NSCLC whose disease has progressed on or after platinum-based chemotherapy.

High-dose osimertinib as another option

The activity of third-generation EGFR TKIs such as osimertinib in NSCLC with EGFR exon 20 insertions is unknown. Preclinical studies suggest that the favorable therapeutic window of these agents might allow for inhibition at clinically achievable doses [6]. Therefore, the single-arm, phase II EA5162 trial assessed osimertinib 160 mg in 17 patients with advanced NSCLC harboring EGFR exon 20 insertions who had received at least one prior treatment line [7]. Notably, the dose used in this trial was double the approved osimertinib dose.

Osimertinib 160 mg daily showed clinical activity in exon 20 insertion-mutant NSCLC, with a confirmed ORR of 24%. Eighty-two percent of patients achieved disease control. Median duration of response had not been reached yet, and median PFS was 9.6 months. AEs were consistent with previous reports. Diarrhea, fatigue, cytopenia and anorexia occurred as the most common toxicities, with low rates of grade ≥3 events. Skin toxicities were restricted to grade 1 AEs. One patient experienced grade 4 respiratory failure, and another discontinued study treatment due to grade 3 anemia. Further study of osimertinib in patients with EGFR exon 20 insertions is planned.

**REFERENCES**

1 Wang XS et al., First-line tyrosine kinase inhibitor with or without aggressive upfront local radiation therapy in patients with EGFRm oligometastatic non-small-cell lung cancer: interim results of a randomized phase III, open-label clinical trial (SINDAS). J Clin Oncol 38: 2020 (suppl; abstr 9508)
2 Rotow JK et al., Concurrent osimertinib plus gefitinib for first-line treatment of EGFR-mutated non-small cell lung cancer (NSCLC). J Clin Oncol 38: 2020 (suppl; abstr 9507)
3 Horn L et al., Indirect comparison of moctecitinib (TAK-788) vs real-world data outcomes in refractory NSCLC with EGFR exon 20 insertions. J Clin Oncol 38: 2020 (suppl; abstr 9580)
4 Le X et al., Pozotinib shows activity and durability of responses in subgroups of previously treated EGFR exon 20 NSCLC patients. J Clin Oncol 38: 2020 (suppl; abstr 9514)
5 Park K et al., Amivantamab (JNJ-61186372), an anti-EGFR-MET bispecific antibody, in patients with EGFR exon 20 insertion (Exon20Ins)-mutated non-small-cell lung cancer (NSCLC). J Clin Oncol 38: 2020 (suppl; abstr 9515)
6 Hirano T et al., In vitro modeling to determine mutation specificity of EGFR tyrosine kinase inhibitors against clinically relevant EGFR mutants in non-small-cell lung cancer. Oncotarget 2015; 6(36): 38789-903
7 Piotrowska Z et al., ECOG-ACRIN EAS162: A phase II study of high-dose osimertinib in NSCLC with EGFR exon 20 insertions. J Clin Oncol 38: 2020 (suppl; abstr 9513)

---

**Improving outcomes in the early-stage setting with (neo)adjuvant strategies**

Approximately 30 % of NSCLC patients present with resectable disease at diagnosis [1-3]. Surgery is the primary treatment for early-stage NSCLC; after resection, adjuvant cisplatin-based chemotherapy is recommended for patients with stage II/IIIA lung cancer and select patients with stage IB disease [4]. However, the rates for disease recurrence or death following surgery and adjuvant chemotherapy remain high, ranging from 45 % in stage IB to 76 % in stage III [5]. Clearly, there is an unmet need for novel and effective therapies to improve clinical outcomes.

**ADAURA: adjuvant use of osimertinib**

The third-generation EGFR TKI osimertinib has been established as a standard-of-care first- and second-line treatment option in patients with EGFR-mutant advanced NSCLC. Based on the observation that the efficacy and safety profile of this agent suggest activity in early-stage disease [6], the double-blind, randomized, phase III ADAURA trial compared osimertinib 80 mg daily (n = 339) with placebo (n = 343) in patients who had undergone complete resection of EGFR-mutant (i.e., exon 19 deletion or L858R mutation), non-squamous lung cancer. Histology had shown negative resection margins, and imaging including brain CT or MRI scans demonstrated the absence of disease. Delivery of post-operative standard adjuvant chemotherapy was allowed prior to randomization, while radiotherapy was not. The maximum interval between surgery and randomization comprised 10 or 26 weeks without or with adjuvant chemotherapy, respectively. The planned treatment duration was three years. Approximately one third of patients each belonged to stages IB, II, and IIIA in both arms, and 55 % had received adjuvant chemotherapy. Disease-free survival in stage II/IIIA patients was defined as the primary endpoint.

Following a recommendation by the independent data monitoring committee, the study was unblinded two years early due to an overwhelming benefit of the osimertinib treatment. At the ASCO Congress, Herbst et al. reported an unplanned interim analysis of the ADAURA trial [7]. At the time of unblinding, the study had completed enrollment, and all patients had been followed up for at least one year.
Substantial risk reductions

For the primary endpoint, osimertinib treatment induced an 83% reduction in the risk of disease recurrence or death in patients with stage II/IIIA disease. Median DFS had not been reached in the experimental arm and was 20.4 months in the control arm (HR, 0.17; p < 0.0001; Figure 1). The key secondary endpoint of DFS in the overall population was also met. Even with the addition of lower-risk patients with stage IB disease, the risk reduction amounted to 79% (not reached vs. 28.1 months; HR, 0.21; p < 0.0001). At two years, DFS rates were 89% vs. 53%, respectively.

All of the pre-specified subgroups benefited from osimertinib treatment; notably, DFS was improved regardless of whether patients had received prior adjuvant chemotherapy. An analysis conducted according to disease stage showed that in the osimertinib arm, 2-year DFS rates remained high across stages IB (87%), II (91%) and IIIA (88%), whereas they decreased rapidly in the placebo arm with increasing stage. The hazard ratios therefore indicated the greatest risk reductions in stages II (0.17) and IIIA (0.12). OS results were immature, but the interim analysis already suggested a 60% benefit (HR, 0.40). The safety profile of adjuvant osimertinib matched the established safety profile. Diarrhea occurred as the most common AE in 46% of patients, followed by paronychia (25%) and dry skin (23%). AEs were generally mild. Grade-1/2 interstitial lung disease was reported in 10 osimertinib-treated patients (3%), and QTc prolongation emerged in 22 (7%) vs. 4 (1%) patients.

In their summary, the authors pointed out that adjuvant osimertinib is the first targeted agent in a global trial to show a statistically significant and clinically meaningful improvement in DFS in patients with stage IB/II/IIIA, EGFR-mutated NSCLC. Osimertinib therefore represents a highly effective, practice-changing treatment after complete tumor resection.

CTONG1104: OS for gefitinib vs. chemotherapy

The randomized, phase III CTONG 1104 trial has established a significant DFS benefit of adjuvant treatment with the first-generation EGFR TKI gefitinib 250 mg daily compared to standard doublet chemotherapy consisting of vinorelbine plus cisplatin in EGFR-mutant, completely resected stage II/IIIA NSCLC [8]. Wu et al. presented the final OS results after a median follow-up of 80.0 months at the ASCO Congress [9]. The intent-to-treat (ITT) population included 111 patients in each treatment arm, while the per-protocol (PP) population included 106 and 87 patients in the gefitinib and chemotherapy arms, respectively.

According to the analysis, gefitinib gave rise to survival benefits compared to chemotherapy with median OS of 75.5 vs. 62.8 months in both populations, although this difference was not significant (HR, 0.92). Five-year OS rates were 53.2% vs. 51.2% in the ITT group, with similar results for the PP population. The authors noted that the OS finding for the gefitinib arm was among the best observed in completely resected IIB/IIIA NSCLC compared to historical data [10]. Updated findings for DFS showed a significant benefit for gefitinib (30.8 vs. 19.8 months), with reductions in the risk of recurrence and death of 44% and 49% in the ITT and PP populations, respectively (p = 0.001 and < 0.001, respectively). However, this advantage did not translate into a significant OS difference.

According to a post-hoc analysis, the patients in the gefitinib arm who received subsequent TKI treatment achieved the longest OS compared to patients with other or no subsequent therapies across the two arms (p < 0.0001). At 55.6%, the response rate was highest in individuals treated with gefitinib followed by osimertinib. Moreover, patients receiving gefitinib for at least 18 months experienced significantly better OS than those with a treatment duration < 18 months (HR, 0.38; p < 0.001; Figure 2). The authors concluded that adjuvant EGFR TKI therapy should be considered as the optimal modality to improve DFS and achieve potentially prolonged OS in patients with completely resected, EGFR-mutated, stage II/IIIA NSCLC.

Atezolizumab prior to chemoradiation

Neoadjuvant PD-1/PD-L1 blockade in early-stage NSCLC has been shown to be feasible and associated with high...
SABR in conjunction with atezolizumab

Stereotactic ablative radiotherapy (SABR) is used in inoperable, early-stage NSCLC, although regional and distant failures remain an issue [16]. Data have demonstrated synergy between radiation and immune checkpoint inhibition, suggesting that neoadjuvant delivery of checkpoint blockade might be superior to adjuvant-only delivery [17, 18]. Based on these observations, Kelly et al. conducted a phase I study to assess the safety and maximum tolerated dose of neoadjuvant, concurrent, and adjuvant atezolizumab with SABR in high-risk, early-stage NSCLC [19]. Patients with inoperable NSCLC (T1-3 N0 M0) and at least one feature predictive of high recurrence risk, such as certain tumor diameters or poorly differentiated histology, received six cycles of atezolizumab at three dose levels, while five fractions of SABR at doses of 10 Gy to 12.5 Gy per fraction were delivered concurrently during cycle 3. Fifteen out of 20 patients completed all six cycles.

Atezolizumab 1,200 mg/kg was identified as the recommended phase II dose. Re-staging after the initial two cycles of atezolizumab already showed signs of anti-tumor activity, with unconfirmed partial remissions in 22 %. Median PFS in the total cohort of 20 patients was 25.5 months. In those with PD-L1-positive tumors, PFS was almost double that observed in the PD-L1-negative group (30.0 and 16.3 months, respectively). Overall, atezolizumab administered before, during, and after SABR proved feasible and well tolerable. Treatment-related AEs, such as cytopenia, fatigue, rash, and diarrhea were mainly limited to grade 1 and 2 events. Two cases of pneumonitis were graded as 1 and 2. Additional blood and tissue biomarker analyses are ongoing, as an inflamed tumor microenvironment might be associated with response. Moreover, the combination of atezolizumab and SABR is presently being tested in the randomized phase III SWOG/NRG S1914 trial.

Perioperative durvalumab

Neoadjuvant chemotherapy with three cycles of cisplatin and docetaxel followed by two cycles of durvalumab 750 mg/m² two-weekly prior to surgery was investigated by the multicenter, single-arm, phase II SAKK 16/14 trial [20]. After surgery, durvalumab treatment continued for one year. Sixty-seven patients with resectable stage IIA NSCLC (T1-3 N2 M0) were included in the study. Event-free survival (EFS) at 12 months was defined as the primary endpoint.

Fifty-eight patients completed neoadjuvant immunotherapy, and 55 underwent surgery. In 91 % of cases, R0 resection was achieved. Pathologic complete responses resulted in 18.2 % of patients, and nodal downstaging was obtained in 67.3 % (Table). Also, the analysis revealed a high rate of major pathological responses. EFS at 12 months amounted to 73.3 %, with median EFS not having been reached at the time of the analysis. Likewise, median OS had not been reached yet. The 30-day postoperative mortality rate was 1.8 %.

According to the authors, the addition of perioperative durvalumab to standard-of-care cisplatin/docetaxel is safe and resulted in an encouraging 1-year EFS rate, which exceeded historical data of chemotherapy alone. Perioperative PD-L1 inhibition in addition to standard neoadjuvant chemotherapy forms the backbone of the SAKK 16/18 study that will evaluate the benefit of neoadjuvant immunomodulatory radiotherapy.

Induction chemotherapy plus radiation or bevacizumab

The randomized phase II PTH-1 study assessed platinum doublet chemotherapy plus concurrent thoracic radiation ther-

TABLE Pathologic responses with perioperative administration of durvalumab

| Response | n (%) |
|----------|-------|
| Pathological complete response | 10 (18.2) |
| Major pathological response | 33 (60.0) |
| Nodal downstaging | 37 (67.3) |
| - ypN0 | 26 (47.3) |
| - ypN1 | 11 (20.0) |
apy (TRT) or bevacizumab followed by surgery in 88 patients with stage IIIA (N2) non-squamous NSCLC [21]. In the TRT and bevacizumab arms, 37 and 38 patients, respectively, underwent surgery. R0 resection was possible in 97% and 89%, respectively.

Regarding the 2-year PFS rate, which constituted the primary endpoint, the analysis demonstrated a 50% benefit with the TRT regimen that was superior to the rate of 36.8% obtained in the bevacizumab arm. Also, major pathological responses occurred more frequently in the TRT group (49 % vs. 14 %). Two-year OS rates were 80% in both arms. Most of the treatment-related AEs were well balanced, although grade 1-3 hypertension occurred more often with bevacizumab, while grade 1/2 esophagitis and dermatitis were restricted to the TRT-based regimen. Fatal surgical complications due to bronchopleural fistula were only observed in the bevacizumab group (two cases). Based on these findings, the authors chose pemetrexed/cisplatin plus concurrent TRT as the investigational induction regimen for a future phase III study.

REFERENCES

1. Datta D, Lahiri B, Preoperative evaluation of patients undergoing lung resection surgery. Chest 2003; 123(6): 2096-2103
2. Le Chevalier T, Adjuvant chemotherapy for resectable non-small-cell lung cancer: where is it going? Ann Oncol 2010; 21 Suppl 7: vi196-vi198
3. Cagle PT et al., Lung cancer biomarkers: Present status and future developments. Arch Pathol Lab Med 2013; 137(8): 1191-1198
4. Kris MG et al., Adjuvant systemic therapy and adjuvant radiation therapy for stage I to IIIA completely resected non-small-cell lung cancers: American Society of Clinical Oncology Cancer Care Canada Clinical Practice Guidelines update. J Clin Oncol 2017; 35(25): 2960-2974
5. Pignon JP et al., Lung Adjuvant Siplogen Evaluation: A pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008; 26(21): 4552-3559
6. Soria JC et al., Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018; 378(15): 139-148
7. Herbst RS et al., Osimertinib as adjuvant therapy in patients with stage IB-IIIA EGFR mutation-positive NSCLC after complete tumor resection: ADJUVANT. J Clin Oncol 38; 2020 (supp; abstr LB53)
8. Zhong WZ et al., Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): A randomised, open-label, phase 3 study. Lancet Oncol 2018; 19(1): 139-148
9. Wu YL et al., CTONG1104: Adjuvant gefitinib versus chemotherapy for resected N1-N2 NSCLC with EGFR mutation – final overall survival analysis of the randomized phase 3 trial. J Clin Oncol 38; 2020 (supp; abstr 9005)
10. Goldstraw P et al., The IASLC Lung Cancer Staging Project: Proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. J Thorac Oncol 2016; 11(1): 39-51
11. Forde PM et al., Neo-adjuvant PD-1 blockade in resectable lung cancer. N Engl J Med 2018; 378(21): 1976-1986
12. Kwikstowski DJ et al., Neo-adjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): interim analysis and biomarker data from a multicenter study (LCMC3). J Clin Oncol 37; 2019 (supp; abstr 8504)
13. Cascione T et al., Neo-adjuvant nivolumab or nivolumab plus ipilimumab for resectable non-small cell lung cancer (NSCLC): Clinical and correlative results from the NEOSTAR study. J Clin Oncol 37; 2019 (supp; abstr 8504)
14. Provencio M et al., NEO-adjuvant chemo-immunotherapy for the treatment of stage II-IIIA resectable non-small-cell lung cancer (NSCLC): A phase II multicenter exploratory study - final data of patients who underwent surgical assessment. J Clin Oncol 37; 2019 (supp; abstr 8505)
15. Ross HJ et al., AFT-16: Phase II trial of atezolizumab before and after definitive chemoradiation (CRT) for unresectable stage III non-small cell lung cancer (NSCLC). J Clin Oncol 38; 2020 (supp; abstr 9045)
16. Timmerman R et al., Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010; 303(11): 1070-1076
17. Young KH et al., Optimizing timing of immunotherapy improves control of tumors by hypofractionated radiation therapy. PLoS One 2016; 11(9): e0157164
18. Dovedi SJ et al., Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res 2014; (74)(19): 5458-5468
19. Kelly K et al., Atezolizumab plus stereotactic ablative therapy for medically inoperable patients with early-stage non-small cell lung cancer. J Clin Oncol 38; 2020 (supp; abstr 9011)
20. Rothchild SI et al., SAKK 16/14: Anti-PD-L1 antibody durvalumab in addition to neo-adjuvant chemotherapy in patients with stage IIIA(N2) non-small cell lung cancer (NSCLC) – a multicenter single-arm phase II trial. J Clin Oncol 38; 2020 (supp; abstr 9016)
21. Takamochi K et al., PIT-1: Randomized phase II trial of pemetrexed-cisplatin plus bevacizumab or concurrent thoracic radiation therapy followed by surgery in stage IIA (N2) nonsquamous non-small cell lung cancer. J Clin Oncol 38; 2020 (supp; abstr 9014)

Present and future perspectives of anti-angiogenic therapy

The oral, triple angio kinase inhibitor nintedanib has been approved in the European Union and other countries in combination with docetaxel for the treatment of advanced adenocarcinoma of the lung after first-line chemotherapy. It works by targeting vascular endothelial growth factor (VEGF) receptors 1-3, platelet-derived growth factor (PDGF) receptors α/β and fibroblast growth factor (FGF) receptors 1-3, as well as RET [1, 2].

Given the changing treatment landscape in advanced NSCLC, the activity of nintedanib plus docetaxel is of particular interest in patients who have previously received immune checkpoint inhibitor (ICI) therapy. The optimal sequence after progression on this therapy has not yet been elucidated, although the underlying tumor biology can contribute to guiding the selection of treatment.

Angiogenesis plays a role in ICI resistance as excessive VEGF release can create an immunosuppressive tumor microenvironment [3, 4]. Therefore, anti-angiogenic strategies involving the inhibition of VEGF, PDGF and FGF might support vessel normalization and improve access of immune cells to the tumor. This might tip the balance towards an immunosupportive tumor microenvironment in the so-called angio-immunogenic switch.

Nintedanib plus docetaxel after ICI therapy

At the ASCO Congress, Grobé et al. reported updated results from 57 patients included in the Cohort B of the ongoing, non-interventional, prospective VARGADO trial [5]. In this cohort, patients with locally advanced, metastatic or loco-
cally recurrent adenocarcinoma of the lung received nintedanib plus docetaxel after first-line chemotherapy and second-line ICI treatment.

The updated analysis continued to demonstrate encouraging clinical benefit and a manageable safety profile of nintedanib plus docetaxel. From the start of third-line therapy, patients remained progression-free for a median of 6.5 months and survived for a median of 12.4 months. OS from the start of first-line therapy was 34.5 months. Twenty patients responded to the treatment, which translated to an ORR of 50% (Table). One patient experienced a complete response. In 65%, treatment-related AEs occurred, with the most common events being diarrhea (all grades, 37%) stomatitis (12%) and decreased white blood cell count (11%). At least one dose reduction was performed in 26% and 19% for nintedanib and docetaxel, respectively. Treatment-emergent AEs led to discontinuation of study treatment in 30% of patients.

As the authors noted, these data are consistent with the ICI-pretreated subgroup analysis of the LUME-BioNIs study evaluating nintedanib plus docetaxel after failure of bevacizumab to erlotinib provided no OS benefit with bevacizumab plus erlotinib alone in the first-line treatment of advanced NSCLC harboring *EGFR* mutations [16]. The analysis included the NEJ026, ARTEMIS, RELAY, and JCO5567 studies, as well as the US-based trial by Stinchcombe et al. RELAY was conducted with ramucirumab in addition to erlotinib, while all of the others used bevacizumab as the anti-angiogenic partner of the *EGFR* TKI. For all studies, PFS had been defined as the primary endpoint.

According to the results, the combined inhibition of *VEGF* and *EGFR* is associated with significantly improved PFS and duration of response compared to erlotinib alone. However, mature data for OS are required to confirm the benefit of this strategy. Moreover, the outcomes suggested that the combination might slow the emergence of resistance to *EGFR* TKIs. In the ARTEMIS trial, at the time of progression, patients in the combination arm showed fewer acquired resistance mutations, such as *T790M*, than the patients in the monotherapy arm. The same trend was observed in RELAY.

### VEGFR inhibition with anlotinib

The TKI anlotinib is an anti-angiogenic drug that targets multiple receptor tyrosine kinases including *VEGFR*2 and *VEGFR*3. Due to its oral route of administration, anlotinib offers advantages over bevacizumab and ramucirumab.
which are administered intravenously. Huang et al. conducted a single-arm study to investigate the activity of anlotinib combined with the oral EGFR TKI icotinib in untreated patients with EGFR-mutated, IIIb, IIC or IV non-squamous NSCLC [17]. Thirty-five patients were evaluated for toxicity, and 30 of these were evaluated for efficacy. Anlotinib plus icotinib demonstrated encouraging efficacy in the first-line setting. Overall, 21 patients (70.0%) responded, with all of them achieving partial remission. PRs were obtained by 11 patients with exon 19 deletions (73.3%) and 10 of those with L858R mutations (66.7%). Figure). Disease control resulted in 96.7%, as another eight patients experienced disease stabilization. Eighteen patients harbored additional aberrations regarding oncopgenic drivers (PIK3CA or AKT1) and/or tumor suppressors (TP53, RBI, PTEN); here, the ORR was 83.3%. Anlotinib plus icotinib was well tolerated, and AEs proved manageable. The most common AEs included hypercholesterolemia, hypertriglyceridermia, hypertension, diarrhea, and rash. Among grade-3 AEs, hypertension (17%) and hypertriglyceridermia (6%) occurred most frequently. The only grade-4 event was hypertriglyceridermia (6%). PFS and OS outcomes are awaited as longer follow-up is required for further evaluation.

**VEGF/Ang-2 blockade and checkpoint inhibition**

Another potential combination strategy based on anti-angiogenesis consists in the inhibition of VEGF/Angiopoietin-2 (Ang-2) together with an immunotherapeutic approach. A phase Ib trial established preliminary antitumor activity of the VEGF/Ang2-blocking nanobody® BI 836880 combined with the anti-PD-1 antibody BI 754091 at doses of 720 mg and 240 mg, respectively, three-weekly [18]. Ten of 12 patients with locally advanced or metastatic non-squamous NSCLC achieved partial remissions or disease stabilization. Two thirds of them had already received ICI therapy prior to enrollment. Changes in target lesions were observed in both ICI-pretreated and ICI-naïve patients.

The combination showed a manageable safety profile. All-grade AEs comprised hypertension, vomiting, nausea, and asthenia. No grade-4 events occurred. Expansion cohorts are ongoing, and further results can be expected.

**REFERENCES**

1 Hilberg F et al., BIBF 1120: Triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res 2006; 66(12): 4774-4782
2 Hilberg F et al., Triple angiokinase inhibitor nintedanib directly inhibits tumor cell growth and induces tumor shrinkage via blocking oncopgenic receptor tyrosine kinases. J Pharmacol Exp Ther 2018; 364(3): 494-503
3 Fukumura D et al., Enhancing cancer immuno-therapy using antiangiogenics: Opportunities and challenges. Nat Rev Clin Oncol 2018; 15(5): 325-340
4 van der Woude LL et al., Migrating into the tumor: A roadmap for T cells. Trends Cancer 2017; 3(11): 797-808
5 Grohé C et al., Nintedanib plus docetaxel in lung adenocarcinoma patients following treatment with immune checkpoint inhibitors: updated efficacy and safety results of the ongoing non-interventional study VARIOGADO (NCT02932455). J Clin Oncol 38: 2020 (suppl; abstr 9004)
6 Rock M et al., Nintedanib + docetaxel after immunotherapy in adenocarcinoma non-small-cell lung cancer: first results from the non-interventional LUME-BioNS study. Ann Oncol 2019; 30(Suppl. 1): abstract 180
7 Corral J et al., Efficacy of nintedanib and docetaxel in patients with advanced lung adenocarcinoma treated with first-line chemotherapy and second-line immunotherapy in the nintedanib NPU Program. Clin Transl Oncol 2019; 21(9): 1270-1279
8 Seito T et al., Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harboring EGFR mutations (JO25567): An open-label, randomised, multicentre, phase 2 study. Lancet Oncol 2014; 15(11): 1236-1244
9 Ichihara E et al., Phase II trial of gefitinib in combination with bevacizumab as first-line therapy for advanced non-small cell lung cancer with activating EGFR gene mutations: The Okayama Lung Cancer Study Group Trial 1001. J Thorac Oncol 2015; 10(3): 486-491
10 Saio H et al., Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ028): Interim analysis of an open-label, randomised, multicentre, phase 3 Trial. Lancet Oncol 2019; 20(5): 625-635
11 Byers LA, Heymach JV, Dual targeting of the vascular endothelial growth factor and epidermal growth factor receptor pathways: Rationale and clinical applications for non-small-cell lung cancer. Clin Lung Cancer 2007; 8(Suppl 2): S79-S85
12 Nakagawa K et al., Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019; 20(12): 1655-1669
13 Nishio M et al., RELAY+: Exploratory study of ramucirumab plus gefitinib in untreated patients with epidermal growth factor receptor (EGFR)-mutated metastatic non-small cell lung cancer (NSCLC). J Clin Oncol 38: 2020 (suppl; abstr 9564)
14 Maemondo M et al., NEJ026: final overall survival analysis of bevacizumab plus erlotinib treatment for NSCLC patients harboring activating EGFR mutations. J Clin Oncol 38: 2020 (suppl; abstr 9506)
15 Yamamoto N et al., Erlotinib plus bevacizumab (EB) versus erlotinib alone (E) as first-line treatment for advanced EGFR-mutation-positive non-squamous non-small-cell lung cancer (NSCLC): Survival follow-up results of JO25567. J Clin Oncol 36, 2018 (suppl; abstr 9007)
16 Landre T et al., Angiogenesis inhibitor plus erlotinib versus erlotinib alone as first-line for advanced non-small cell lung cancer harboring EGFR mutation. J Clin Oncol 38: 2020 (suppl; abstr 9569)
17 Huang D et al., Study of anlotinib combined with icotinib as the first-line treatment in NSCLC patients harboring activating EGFR mutations (AL-TER-L004). J Clin Oncol 38: 2020 (suppl; abstr 9573)
18 Girard N et al., Phase Ib study of BI 836880, a VEGF/Ang2-blocking nanobody®, in combination with BI 754091, an anti-PD-1 antibody: initial results in patients with advanced non-small cell lung cancer. J Clin Oncol 38: 2020 (suppl; abstr 9566)
COVID-19 in patients with thoracic cancers: TERAVOLT

The global consortium TERAVOLT was established to determine factors that place patients with thoracic malignancies who develop COVID-19 at risk for hospitalization and death, to elucidate the clinical course of these patients and to identify therapeutic strategies that might impact survival. Thoracic cancer patients with a COVID-19 diagnosis, i.e. cases of confirmed infection according to RT-PCR techniques and suspected COVID-19 cases, are being entered into the database. The latter are defined by either clinical criteria (known exposure to a person with confirmed COVID-19 and symptoms such as fever > 37.5 °C, cough, diarrhea etc.) or lung imaging features consistent with coronavirus pneumonia and symptoms.

The analysis presented at ASCO 2020 included a global population of 400 patients with a median follow-up of 33 days from the COVID-19 diagnosis [1]. At the time of data cut-off, 169 of patients had recovered, while 141 had died (35.5 %) and the infection was ongoing in 118. The median age across these groups ranged from 67 to 70 years. Most patients were male and current or former smokers.

Chemotherapy increases mortality

Presenting COVID-19 symptoms mainly included fever, cough, and dyspnea. In 78.3 % and 8.3 %, hospital and ICU admissions, respectively, became necessary. The median length of stay at hospital was 10 days. Among the patients who died, COVID-19 was the cause of death in 79.4 %, while only 10.6 % of fatalities were attributed to cancer. The most common complications in the deceased group comprised pneumonitis/pneumonia (71.0 %), acute respiratory distress syndrome (49.6 %), multiorgan failure (14.9 %), and sepsis (12.1 %).

Baseline risk factors for mortality from COVID-19 included age ≥ 65 years, performance status of 1 and presence of comorbidities (e.g., hypertension, COPD, vascular disease), while other factors such as gender, body mass index, smoking status, and stage or type of cancer did not affect the risk of death. Steroids (> 10 mg of prednisone or equivalent) or anticoagulation prior to the diagnosis of COVID-19 increased the risk, as did prior administration of chemotherapy alone or combined with immunotherapy, while immunotherapy and TKI treatment had no adverse effect on survival (Figure). No particular treatment for COVID-19 was associated with increased chances of recovery from the infection. Data collection is ongoing, and additional analyses are planned.

REFERENCES

1 Horn L et al., TERAVOLT: Thoracic cancERs international coVid 19 COLlaboraTion: impact of cancer therapy and COVID therapy on survival. J Clin Oncol 38: 2020 (suppl; abstr LBA111)

Rare mutations: HER2, RET, ALK, BRAF

DESTINY-Lung01: trastuzumab deruxtecan

Trastuzumab deruxtecan (T-DXd) is a novel antibody-drug conjugate containing a humanized anti-HER2 monoclonal antibody linked to a topoisomerase I inhibitor exatecan derivative. The open-label, multicenter, phase II DESTINY-Lung01 study tested T-DXd 6.4 mg/kg 3-weekly in patients with relapsed or refractory advanced NSCLC that expressed HER2 (Cohort 1; n = 42) or carried HER2-activating mutations (Cohort 2; n = 42). At the ASCO Congress, Smit et al. reported the interim results for Cohort 2 [1]. In terms of confirmed ORR according to independent central review, which was the primary endpoint, T-DXd demonstrated pronounced clinical activity. Almost 62 % of patients re-
sponded, and 2.4% achieved complete remissions (Table). At the time of the analysis, the median duration of response had not been reached yet; this also applied to OS. Median PFS was 14.0 months.

The safety profile observed in this HER2-mutated cohort was generally consistent with previously reports. Nausea, alopecia, anemia, neutropenia and decreased appetite represented the most common treatment-emergent AEs. Fatigue and nausea primarily prompted dose reductions, while dose interruptions were predominantly due to neutropenia (19.0%) and lung infection (7.1%). Five patients developed grade-2 interstitial lung disease (ILD). The authors noted that ILD remains a concern and requires careful monitoring and management. Overall, these data show the potential of T-DXd as a new treatment option in the setting of HER2-mutated NSCLC. Meanwhile, enrollment in the HER2-mutated cohort has been expanded to better characterize the risk-benefit ratio of T-DXd.

### CNS effects of selpercatinib in RET-positive lung cancer

RET fusions have been identified in approximately 2% of NSCLC patients [2, 3]. The ongoing registrational, international, phase I/II LIBRETTO-001 trial is assessing the efficacy of the selective, CNS-active RET inhibitor selpercatinib (LOXO-292). LIBRETTO-001 is being conducted in patients with advanced RET-fusion-positive solid tumors; 253 of these have NSCLC. In the primary analysis set, the ORR was 68%, and responses lasted for a median of 20.3 months [4].

Data from the NSCLC CNS population with measurable CNS disease (n = 22) presented by Subbiah et al. shed more light on the intracranial activity of selpercatinib [5]. Overall, the CNS ORR was 81.8%, with CRs occurring in 22.7%. Patients without prior irradiation to the brain fared somewhat better than those who had received radiotherapy (ORR, 85.7% vs. 75.0%; CR, 28.6% vs. 12.5%). Both patients with and without prior anti-PD-(L)1 treatment responded intracranially; also, this was not affected by the prior use of multi-targeted kinase inhibitor therapy. Median duration of CNS response was 9.4 in the total group. The authors concluded that selpercatinib shows marked and durable intracranial anti-tumor activity in patients with RET-fusion-positive NSCLC and CNS metastases. A randomized, global, phase III study of selpercatinib versus platinum-based chemotherapy with or without pembrolizumab in treatment-naïve RET-fusion-positive NSCLC including patients with asymptomatic brain metastases is ongoing.

### RET kinase inhibitor pralsetinib

Another investigational, selective RET kinase inhibitor that is currently being developed is pralsetinib (BLU-667). The ongoing pivotal, global, phase I/II ARROW trial is testing pralsetinib in patients with advanced solid, RET-altered tumors including RET-fusion-positive NSCLC. Gainor et al. reported data for the intent-to-treat (ITT) efficacy population of 132 NSCLC patients that included 116 response-evaluable individuals [6]. In the ITT population, 92 and 29 patients had received prior platinum and were treatment-naïve, respectively.

Pralsetinib gave rise to rapid and durable responses. According to blinded independent centralised review, the ORR in the response-evaluable group was 65%, with 6% obtaining CRs. Disease control resulted in 93%. The median duration of response had not been reached yet. All treatment-naïve patients in the evaluable cohort achieved tumor reductions, and 12% experienced CRs. Furthermore, pralsetinib showed robust activity in the CNS, with intracranial ORR and CR rates of 56% and 33%, respectively.

The RET inhibitor therapy was well tolerated. Treatment-related AEs included mainly transamnise elevations, cytopenia, constipation and hypertension, and were predominantly grades 1 and 2. In their summary, the authors emphasized that pralsetinib has the potential to change the standard of care for patients with RET-fusion-positive NSCLC.

### Survival update of ALEX

Previous analyses of the global, randomized, phase III ALEX study have established the superiority of alectinib over crizotinib in patients with untreated, advanced ALK-positive NSCLC. The mature PFS data confirmed significant improvement for this endpoint (34.8 vs. 10.9 months) [7], while the OS results remained immature. After another 12 months of follow-up, Peters et al. presented updated OS and other outcomes [8].

The OS data were still immature at that time, with five-year OS rates of 62.5% vs. 45.5% for alectinib and crizotinib, respectively (HR, 0.67; p = 0.0376; Figure). Among patients who experienced disease progression, subsequent therapy was administered in more than 60% in both arms. Follow-up treatment with other ALK TKIs was prescribed to 38.1% and 53.5% of alectinib- and crizotinib-treated patients with progressive disease. No new safety signals occurred after almost three-times longer median treatment duration with alectinib (28.1 months) than crizotinib (10.8 months). The investigators concluded that ALEX is the first global, randomized trial of a next-generation ALK TKI to
demonstrate a clinically meaningful OS improvement compared to crizotinib in treatment-naive, advanced ALK-positive NSCLC.

Impact of biomarkers in ALTA-1L

The open-label, randomized, multicenter, phase III ALTA-1L study evaluated brigatinib in patients with ALK-TKI-naive, ALK-positive advanced NSCLC, demonstrating superior efficacy compared to crizotinib with acceptable tolerability at the second interim analysis [9]. Camidge et al. evaluated the impact of EML4-ALK fusion variants and other baseline variables on the activity of brigatinib vs. crizotinib in the ALTA-1L trial [10].

Brigatinib was superior to crizotinib with respect to ORR and PFS regardless of EML4-ALK fusion variant or TP53 mutation status. EML4-ALK fusion variant 3 (V3) appeared to be prognostic, as patients with this variant had worse PFS than those harboring V1 or V2, irrespective of treatment. Brigatinib demonstrated superior PFS particularly in this poor-prognosis group of patients with V3 (HR, 0.30). Also, there was a trend indicating that TP53 mutations are an independent biomarker of poor prognosis which persisted in multivariate analyses and warrants further investigation in a larger sample size. Defining higher-risk ALK-positive advanced NSCLC might impact future clinical trial designs and treatment options.

BRAFV600E-mutant disease: dabrafenib & trametinib

Dabrafenib as a monotherapy and combined with trametinib was assessed in a non-randomized, multicenter, open-label phase II trial in patients with BRAFV600E-mutant metastatic NSCLC. The primary analysis has revealed robust clinical activity for dabrafenib plus trametinib with a manageable safety profile [11]. At the ASCO Congress, Planchard et al. updated the presented OS and genomic analysis data for the combination therapy population in Cohorts B (pretreated patients) and C (treatment-naive patients) [12].

Dabrafenib plus trametinib provided combined CR and PR rates of 68.4 % and 63.9 % in Cohorts B and C, respectively. Responses lasted for 9.8 and 10.2 months, respectively. OS was 18.2 months in Cohort B and 17.3 months in Cohort 3. The genomic analysis suggested that co-occurring genetic alterations influence clinical outcomes, as patients with PI3K pathway alterations showed a trend towards decreased OS. Toxicities of the combined treatment were manageable; the safety profile matched that reported for patients with melanoma who receive dabrafenib and trametinib. Overall, the combination provided durable clinical benefit with a favorable risk/benefit ratio regardless of prior treatment.

REFERENCES

1 Smit E et al., Trastuzumab deruxtecan in patients with HER2-mutated metastatic non-small cell lung cancer: interim results of DESTINY-Lung01. J Clin Oncol 38: 2020 (suppl; abstr 9504)
2 Takeuchi K, Discovery stories of RET fusions in lung cancer: a mini-review. Frontiers Physiol 2019; 10: 216
3 Tsuta K et al., RET-rearranged non-small-cell lung carcinoma: a clinicopathological and molecular analysis. Br J Cancer 2014; 110(6): 1571-1579
4 Drilon A et al., L-BRETT0-001: a phase 1/2 trial of selpercatinib (LOXO-203) in patients with RET-fusion-positive lung cancer: initial results. WCLC 2019, abstract #PL02.08
5 Subbiah V et al., Intracranial activity of selpercatinib (LOXO-203) in RET-fusion-positive non-small cell lung cancer (NSCLC) patients on the L-BRETT0-001 trial. J Clin Oncol 38: 2020 (suppl; abstr 9516)
6 Gainer JF et al., Registration dataset from the phase 1/2 ARROW trial of pralsetinib (BLU-667) in patients with advanced RET fusion+ non-small cell lung cancer (NSCLC). J Clin Oncol 38: 2020 (suppl; abstr 9515)
7 Mok T et al., Updated overall survival and final progression-free survival data for patients with treatment-naïve advanced ALK-positive non-small-cell lung cancer in the ALEX study. Ann Oncol 2020; S0923-7534(20)39796-9
8 Peters S et al., Updated overall survival and safety data from the randomized, phase III ALLEX study of alecinitib vs crizotinib in untreated advanced ALK+ NSCLC. J Clin Oncol 38: 2020 (suppl; abstr 9518)
9 Camidge DR et al., Brigatinib vs. crizotinib in patients with ALK inhibitor-naive advanced ALK+ NSCLC: update results from the phase III ALTA-1L trial. Ann Oncol 2019; 30 (suppl_9): ix183-ix202
10 Camidge DR et al., Correlation of baseline molecular and clinical variables with ALK inhibitor efficacy in ALTA-1L. J Clin Oncol 38: 2020 (suppl; abstr 9517)
11 Planchard D et al., Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol 2017; 18(10): 1307-1316
12 Planchard D et al., The updated overall survival and genomic analysis from a single-arm phase 2 study of dabrafenib plus trametinib in patients with BRAFV600E mutant metastatic non-small cell lung cancer. J Clin Oncol 38: 2020 (suppl; abstr 9593)
Small-cell lung cancer: moving the limits further

High-dose irradiation proves feasible

Concurrent chemotherapy and thoracic radiotherapy (TRT) have been the standard treatment for limited-stage small-cell lung cancer (SCLC) since the early 1990s, with twice-daily TRT at a dose of 45 Gy being the most commonly recommended schedule. However, less than one third of patients are cured after chemoradiotherapy. In up to 50 %, local failure occurs that is associated with inferior survival [1, 2]. Hallqvist et al. showed that high-dose, twice-daily TRT of 60 Gy is feasible and safe [3]. Based on the hypothesis that this strategy is tolerable and improves local control and survival, the randomized phase II trial by Grønberg et al. compared 60 Gy in 40 fractions with 45 Gy in 30 fractions twice daily (10 fractions per week) [4]. Four courses of chemotherapy with cisplatin or carboplatin plus etoposide (EP) were administered in weeks 0, 3, 6, and 9. All patients started TRT along with the second chemotherapy course. Prophylactic cranial irradiation (PCI) was offered to anyone who responded to chemoradiotherapy. Importantly, the higher dose did not cause more radiotoxicity than the standard dose. Grade-3/4 AE rates for cytopenia, neutropenic infections, esophagitis and pneumonitis were similar across the treatment arms.

ES-SCLC: new findings from the CASPIAN trial

After more than three decades of limited progress in extended-stage SCLC (ES-SCLC), the addition of immunotherapy to platinum-based chemotherapy has improved OS in the first-line setting [5, 6]. The global, open-label, randomized, multicenter phase III CASPIAN study demonstrated that first-line treatment with the PD-L1 inhibitor durvalumab plus EP gave rise to a significant OS improvement compared to EP alone (HR, 0.73; p = 0.0047) [5]. In the control arm, PCI was optional. Durvalumab plus EP was approved for ES-SCLC by the US authorities in March 2020 and is under review by other health authorities globally. The CASPIAN study contained another experimental arm assessing the CTLA-4 inhibitor tremelimumab in addition to durvalumab and EP 3-weekly for 4 cycles followed by durvalumab maintenance. At the ASCO Congress, Paz-Ares et al. presented the primary analysis for the comparison between this group and the EP-only control patients [7]. According to this, the addition of tremelimumab to durvalumab and EP did not significantly improve OS over EP alone (10.4 vs. 10.5 months; HR, 0.82). Moreover, the investigators reported the results of planned updated analyses for durvalumab plus EP vs. EP. After an additional follow-up of 11 months, durvalumab in combination with chemotherapy continued to demonstrate OS improvement compared to a robust control arm that allowed up to 6 cycles and EP and the use of PCI (12.9 vs. 10.5 months; HR, 0.75; nominal p = 0.0032). The OS curves showed a sustained separation, with 22 % vs. 14.4 % of patients alive at 24 months. Durvalumab-related benefits were observed across all pre-

![Figure 1: Survival after 1 and 2 years with thoracic irradiation at doses of 60 Gy vs. 45 Gy in limited-stage SCLC](image-url)
specified subgroups and key secondary efficacy outcomes including PFS (24-month rates, 11.0 % vs. 2.9 %), objective response rates (67.9 % vs. 58.0 %; OR 1.53) and duration of response (24-month rates, 13.5 % vs. 3.9 %). The safety findings in all arms remained consistent with the known safety profiles of all agents. These results further support the administration of durvalumab plus EP as a new standard-of-care treatment for first-line ES-SCLC, offering the flexibility of platinum choice (cisplatin vs. carboplatin).

**KEYNOTE-604: pembrolizumab plus chemotherapy**

Pembrolizumab has been approved in the third or later lines for patients with metastatic SCLC in several countries based on the KEYNOTE-028 and KEYNOTE-158 studies [8]. The randomized, placebo-controlled KEYNOTE-604 trial assessed pembrolizumab plus EP for four 3-weekly cycles in 228 treatment-naive patients with stage IV SCLC [9]. This regimen was followed by pembrolizumab maintenance for up to 31 cycles. In the control group (n = 225), patients received EP plus placebo followed by placebo maintenance. Unstable brain metastases were not allowed.

The addition of pembrolizumab to EP as first-line therapy significantly improved PFS compared to EP alone at the time of the second interim analysis that provided the final PFS analysis per protocol (4.5 vs. 4.3 months; HR, 0.75; p = 0.0023). According to the final analysis of the trial, the 18-month PFS rates were 10.8 % vs. 2.1 % (HR, 0.73). OS findings in the ITT population showed a 20 % reduction in the mortality risk (10.8 vs. 9.7 months; HR, 0.80; p = 0.0164), although the significance threshold was missed (p = 0.0128). At 24 months, 22.5 % vs. 11.2 % of patients were alive. Both PFS and OS subgroup analyses suggested improved results across subgroups in the experimental arm with the exception of patients with baseline brain metastases. The ORRs were 70.6 % vs. 61.8 % for pembrolizumab plus EP and EP, respectively. Complete responses resulted in 1.8 % vs. 0.9 %. Responses appeared to be durable in a subset of pembrolizumab-treated participants, with 18-month rates of 16.3 % vs. 1.3 % (Figure 2).

AEs of the combination were as expected and manageable. The rates for any-grade immune-mediated AEs were 24.7 % vs. 10.3 % in the as-treated population, with 5.8 % vs. 0.9 % leading to discontinuation. According to the authors, these data support the benefit of pembrolizumab and the value of immunotherapy in the treatment of SCLC.

**Evaluation of nivolumab in ECOG-ACRIN EA5161**

The ECOG-ACRIN EA5161 trial was conducted to assess the role of nivolumab in ES-SCLC [10]. Patients who had not received prior chemotherapy were randomized to EP plus nivolumab followed by nivolumab maintenance (n = 75) or chemotherapy only followed by observation (n = 70). The inclusion of patients with treated brain metastases was allowed.

For PFS, which was defined as the primary endpoint, the nivolumab-based regimen showed superiority with a median PFS of 5.5 vs. 4.7 months (HR, 0.68; p = 0.047). OS, as a secondary endpoint, was also in favor of the experimental arm, although not significantly so (11.3 vs. 9.3 months; HR, 0.73; p = 0.14). Objective responses resulted in 52 % vs. 47 %, with a median duration of response of 5.6 vs. 3.3 months. The combination of nivolumab and chemotherapy was well tolerated, and toxicities were manageable. Grade 3/4 AEs occurred across the treatment arms with similar frequency. In their conclusion, the investigators noted that ECOG-ACRIN EA5161 confirms the efficacy of nivolumab in ES-SCLC.

**REFERENCES**

1. Turrisi AT et al., Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 1999; 340(4): 205-271
2. Kubota K et al., Etoposide and cisplatin versus irinotecan and cisplatin in patients with limited-stage small-cell lung cancer treated with etoposide and cisplatin plus concurrent accelerated hyperfractionated thoracic radiotherapy (COCOG2002): a randomised phase 3 study. Lancet 2014; 15(1): 106-113
3. Hallqvist A et al., Accelerated hyperfractionated radiotherapy and concomitant chemotherapy in small-cell lung cancer limited-disease. Dose response, feasibility and outcome for patients treated in western Sweden, 1998-2004. Acta Oncol 2007; 46(7): 869-874
4. Gronberg BH et al., Randomized phase II study comparing the efficacy of standard-dose with high-dose twice-daily thoracic radiotherapy in limited stage small-cell lung cancer. J Clin Oncol 38: 2020 (suppl; abstr 9007)
5. Paz-Ares L et al., Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019; 394: 1929-1939
6. Horn L et al., First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 2018; 379: 2220-2229
7. Paz-Ares L et al., Durvalumab ± tremelimumab ± platinum-etoposide in first-line extensive-stage SCLC: updated results from the phase 3 CASPIAN study. J Clin Oncol 38: 2020 (suppl; abstr 9002)
8. Chung JC et al., Pembrolizumab after two or more lines of previous therapy in patients with recurrent or metastatic SCLC: results from the KEYNOTE-028 and KEYNOTE-158 studies. J Thorac Oncol 2020; 15: 618-627
9. Rudin CM et al., KEYNOTE-604: pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer. J Clin Oncol 38: 2020 (suppl; abstr 9001)
10. Leal TA et al., Randomized phase II clinical trial of cisplatin/carboplatin and etoposide alone or in combination with nivolumab as frontline therapy for extensive stage small-cell lung cancer: ECOG-ACRIN EA5161. J Clin Oncol 38: 2020 (suppl; abstr 9001)
Expert interviews at ASCO 2020

Victor Moreno provides insight into new investigational immune checkpoint inhibitors, safety profiles of combinational therapies and the importance of HLA B44 supertype in the context of lung cancer treatment. Moreover, he discusses the increased vulnerability of clinical research units during the COVID-19 crisis and their protection.

Helmut Prosch gives an overview on clinical and radiological response assessment of immunotherapy in lung cancer patients, specifically with regards to pneumonitis and atypical pulmonary findings.

For more expert interviews and educational materials around lung cancer please visit our memo InOncology webpage (www.memoinoncology.com).

Here you will find the latest memo inOncology issues reporting on ASCO, ELCC and ESMO 2019 and previous years in English, Japanese and Mandarin!

Read memo inOncology congress reports of ASCO, EHA and ESMO 2020 and watch video interviews with Key Opinion Leaders!

Learn about the new memo inOncology - medical educational series, which provides information from preceptorships to clinical trials trainings.

Sign up for the memo inOncology Newsletter on memoinoncology.com to keep yourself updated on all exciting news and developments in lung cancer.

Forthcoming Special Issue

This special issue will be offering a synopsis from the ESMO 2020 that will be held in September 2020. The report promises to make for stimulating reading, as the ESMO Congress itself draws on the input from a number of partner organizations, representing a multidisciplinary approach to cancer treatment and care. Again, lung cancer will be at the heart of this special issue.

ESMO 2020
Annual Meeting
SEPTEMBER 19–21, 2020