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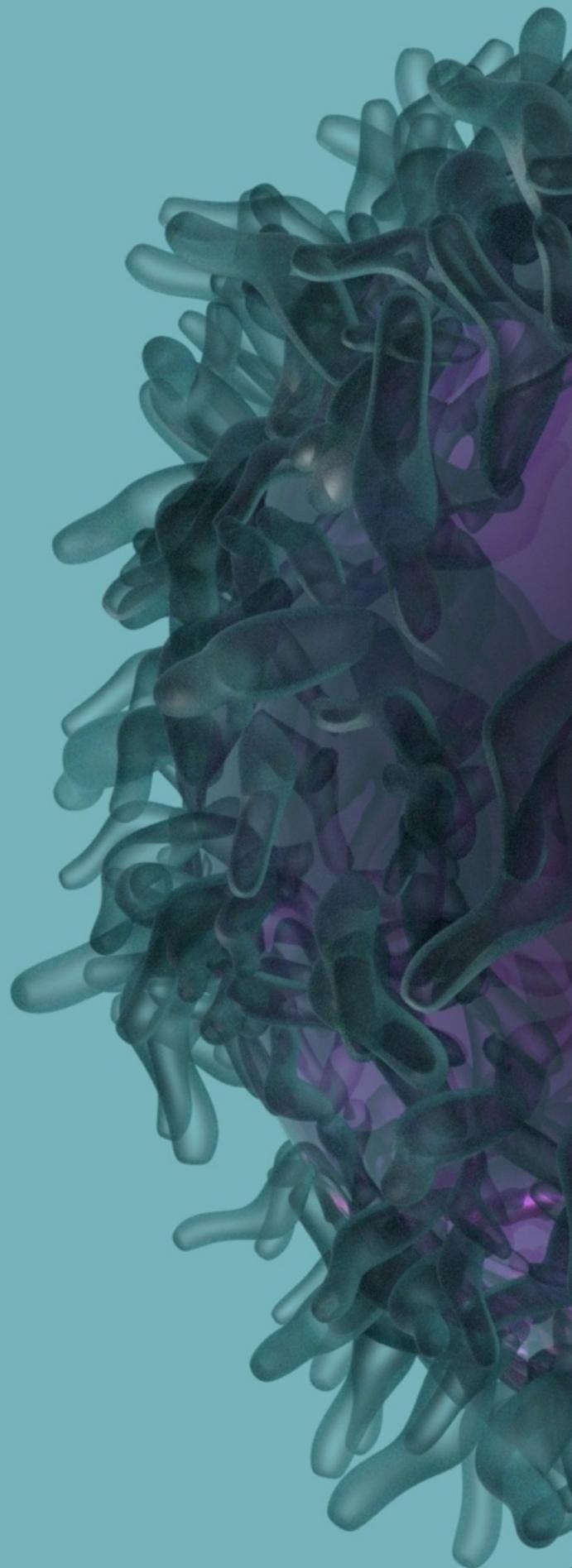
**CECOG CEE
THORACIC
NEWSLETTER**
Vol1. | Issue 01

Expert Opinion
& Scientific Events

Modern Cancer Drugs Registration &
Upcoming innovations in IO

Young Oncologists & interdisciplinarity
in lung cancer management

Personalized medicine &
combination therapies for NSCLC



CECOG CEE THORACIC NEWSLETTER

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The CECOG CEE Newsletter is built over a continuous collaborative exchange of knowledge among multidisciplinary oncology experts, paired with scientific rigor and evidence-based guidelines.

Find out what's new in lung cancer management in CEE. Deepen your understanding of the groundbreaking lifesaving therapeutic modalities for lung cancer. Discover how state-of-the-art access to drugs and the delivery of essential levels of quality care can transform the lives of cancer patients.

EDITORIAL

Dear Reader,

It is our pleasure to welcome you to the first edition of the CEE Thoracic Oncology Newsletter provided to you by CECOG.

We wish you a pleasant reading of the current compilation of country-oriented articles in our first edition of the CEE Thoracic Oncology Newsletter. We thank all contributing authors, but also AstraZeneca for the financial support to make our vision come true. ”

Lung cancer is the leading malignancy-caused reason of death and one of the most frequent cancers worldwide. It is particularly the CEE region which is unfortunately harboring one of the highest incidence of lung cancer worldwide and has an unsatisfactory mortality/incidence ratio is constantly struggling with that deadly disease. With multiple novel and very effective diagnostic and therapeutic approaches entering the field in the beginning of this century, lung cancer is changing from a type of cancer with the worst prognosis to a highly controllable and treatable disease. However, to achieve those high rates of disease control, constant efforts in the transfer of knowledge and technology into a routine clinical practice are needed. This constitutes a major challenge to CEE countries which have much less resources, as compared to countries of Western Europe. Considering all these circumstances, CECOG is organizing regular Lung Cancer and Thoracic Cancer Academies which gather leading specialists from CEE excelling in the field of thoracic oncology in order to exchange knowledge, define best practices and - most of all - to participate in common activities with the aim to improve lung cancer care in “our” CEE region.

The present first edition of the CEE Thoracic Oncology Newsletter represents a further step in CECOG’s attempt to connect and unite specialists from the CEE region dealing with this particular topic. The idea of this newsletter is to exchange top knowledge, practical skills and good practices among all stakeholders in the CEE region. Although the majority of contributions have been authored by senior oncologists, we ask you to consider the first edition only as the initiation of our goal to attract and interconnect particularly younger colleagues from the region by giving them access to high quality information and to their peers from the entire geographic region. Any ideas from such young colleagues are more than welcome and much appreciated, as **we want to build on younger generations in order to establish the CEE region as a center of gravitation in oncologic excellence.**

With best personal wishes,

Tanja Cufer, Christiane Thallinger, Christoph Zielinski
Editors-in-Chief



CECOG CEE THORACIC NEWSLETTER

CONTENTS

- 3 EDITORIAL

- 6 EXPERT OPINION
Novel reimbursed drugs in CEE, Liquid biopsy, ALK inhibitors, EGFR TKI, Access to testing, EMA and more

- 14 HIGHLIGHTS FROM SCIENTIFIC-DRIVEN EVENTS
CEE Region

- 18 YOUNG ONCOLOGISTS CORNER
Industry insights from promising young oncologists

- 22 NSCLC
Liquid biopsy, TKI, Target therapy, Immuno Therapy

- 34 CECOg CORNER
Continuous Medical Education, New Releases

- 36 INTERVIEW
Prof. Lukas Plank



OVERVIEW

MAJOR DRIVERS AND DEVELOPMENTS
IMPACTING THORACIC ONCOLOGY

Over the past decade, lung cancer has been dominating the immune-oncology market, thoracic oncology research aimed at the development of more effective therapies and the investigation of combination treatments, and the most significant industry conferences. Due to the emergency of Lung Cancer in Non-smokers (LCINs) and the rise of pollution, lung cancer has been witnessing a significant CAGR (Compound Annual Growth Rate).

Today, areas of focus for lung cancer and immunotherapy research include biomarker driven medicine, drugs that can treat multiple cancers indications, the use of T-cells to treat cancer cells and the regulatory challenges for the approval of innovative medicines that fulfil unmet needs of cancer patients. In this Newsletter Issue you will access information regarding groundbreaking developments in the field of TO and insight into the current challenges and opportunities of frontline therapies from the perspective of a multidisciplinary team of medical oncologists.



EXPERT OPINION

ACCESS TO LUNG CANCER TESTING & TREATMENT
CROATIA | [Marko Jakopovic, Prof.](#)

Lung cancer is the most common cancer in Croatia with more than 3000 new patients each year. At the same time, it is the most common cause of death among malignant diseases with more than 2900 deaths each year. Developments in the diagnosis and treatment in the last decade have led to significant improvement in treatment of non-small cell lung cancer. [Marko Jakopovic, Prof.](#) reports the situation in [Croatia](#).

Targeted agents in the treatment of lung cancer started to develop rapidly after publication of IPASS in 2009. Since then, four different EGFR TKIs were put on the market (gefitinib, erlotinib, afatinib, osimertinib) and a fifth is on the way (dacomitinib). Although, molecular testing was introduced relatively quickly after IPASS study, EGFR TKIs were not reimbursed in front-line setting until 2017. Gefitinib, erlotinib and afatinib have been reimbursed for the treatment of EGFR-positive non-small cell lung cancer since 2017.

EXPERT OPINION

ACCESS TO LUNG CANCER TESTING & TREATMENT

CROATIA | Marko Jakopovic, Prof.

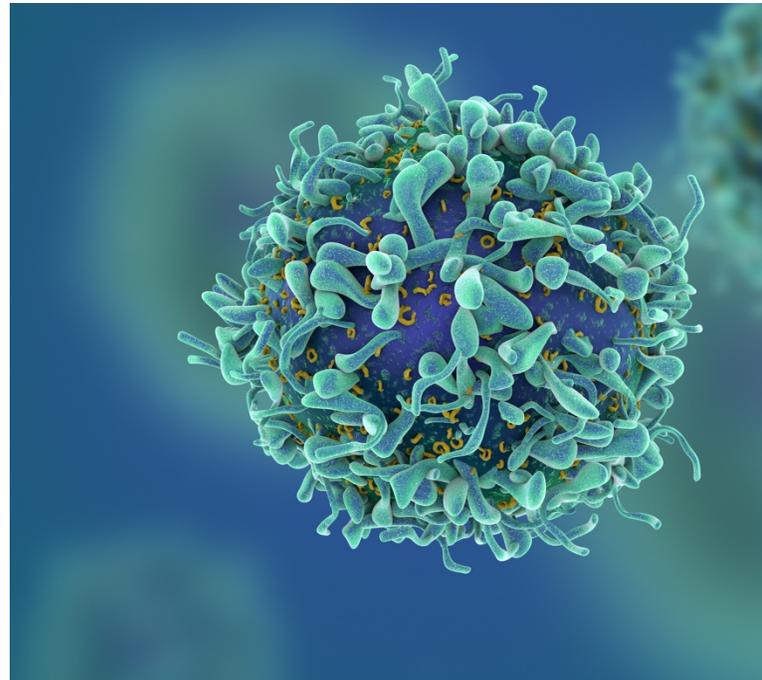
Liquid biopsy was also introduced as a routine test for patients who progress on first or second generation EGFR TKIs. In patients with T790M resistance mutation osimertinib has been available since March 2018. Based on results of FLAURA trial, osimertinib showed efficacy in front-line settings in patients with common mutation in EGFR gene. Unfortunately, osimertinib is not reimbursed in front-line setting in Croatia.

ALK inhibitors are also reimbursed in Croatia for treatment of ALK positive patients in front-line setting. Crizotinib and alectinib are both reimbursed. After the publishing of ALEX trial alectinib became first choice for the treatment of ALK positive NSCLC patients.

For ROS1-positive patients, crizotinib is available.

In recent years, **immune check-point inhibitors** have emerged in the treatment of different malignancies like melanoma, lung cancer, bladder cancer, and many others. PD-L1 testing has routinely been done for the last two years. In patients who are PD-L1 positive 50% or above, pembrolizumab as monotherapy has been reimbursed in Croatia and therefore available for Croatian patients since March last year. Combination of pembrolizumab with chemotherapy is not available (reimbursed) for patients with PD-L1 expression below 50%.

Problems with the access to drugs in the second-line setting remain because neither of immune check-point inhibitors (pembrolizumab, nivolumab, atezolizumab) are reimbursed for **second-line treatment**. The only new drug which was reimbursed in second line is nintedanib in combination with docetaxel.



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Since March 2018, the access to lung cancer drugs in Croatia has significantly improved.

Marko Jakopovic, Prof.

CECOG CEE THORACIC NEWSLETTER

EXPERT OPINION

ACCESS TO LUNG CANCER TESTING & TREATMENT

CROATIA | Marko Jakopovic, Prof.

In the last three years, we have had really extensive patient named programs for **immunotherapy** with nivolumab in second and later lines, atezolizumab and pembrolizumab in the second-line setting, and currently ongoing programs for durvalumab in consolidation setting after chemo-radiotherapy, and atezolizumab in combination with chemotherapy for patients with small-cell lung cancer.

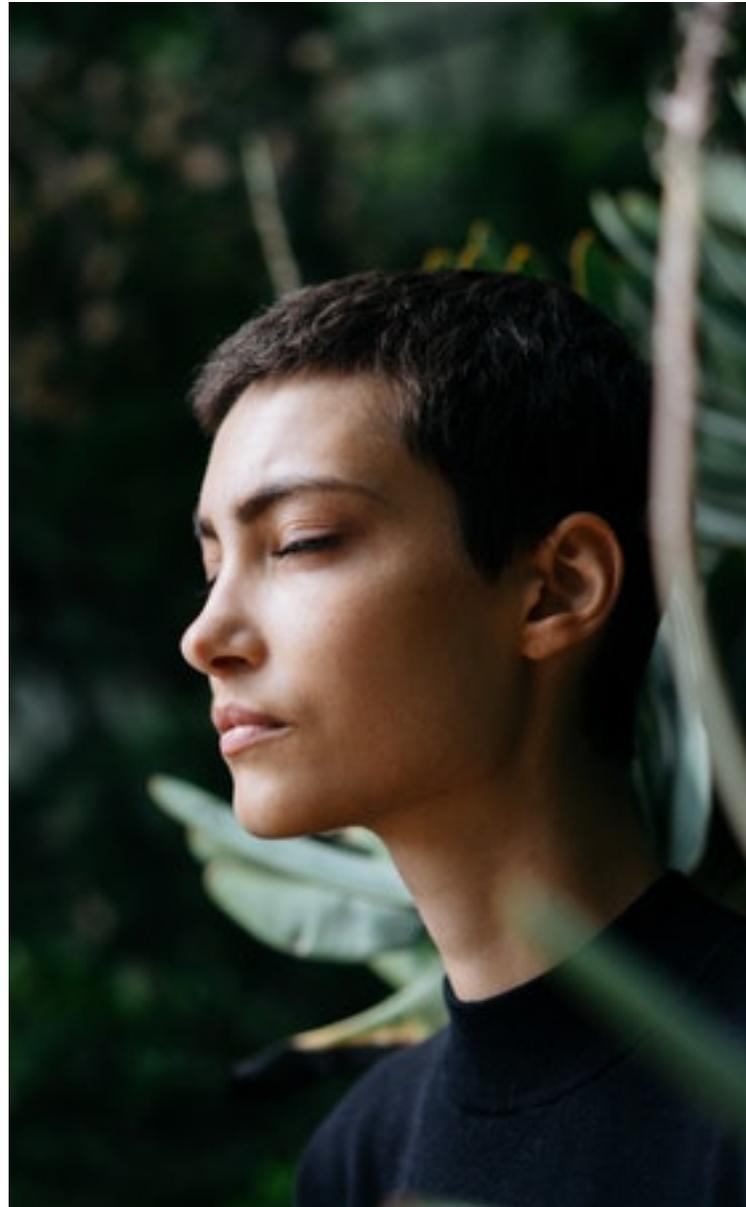
Given the above, the situation regarding the access to lung cancer drugs in Croatia has significantly improved since March 2018. However, we still have a substantial number **unmet needs** so we have to keep on working, and, with the help of patient organizations, try to expand access to the drugs.

Early detection of lung cancer is needed so that radical surgery can be performed and patients are potentially cured.

Marko Jakopovic, Prof.

Lung cancer is the most common cause of cancer deaths worldwide. Despite huge improvements in lung cancer treatments in the last decade, survival remains poor with 5 years overall survival below 20%. One of the main reasons for that is that the majority of patients are diagnosed in advanced stages of the disease (stages III and IV) when there are limited radical treatment options.

Early detection of lung cancer is needed so that radical surgery can be performed and patients are potentially cured. A lot of **screening trials** were done in the 1990s and at the beginning of the 2000s and they were all negative until presenting data of a large American NLST trial. NLST trial included more than 50 000 people who were heavy smokers aged 55 to 75. In the trial authors compared low-dose CT with chest X-ray and showed reduction of lung cancer mortality for 20%.

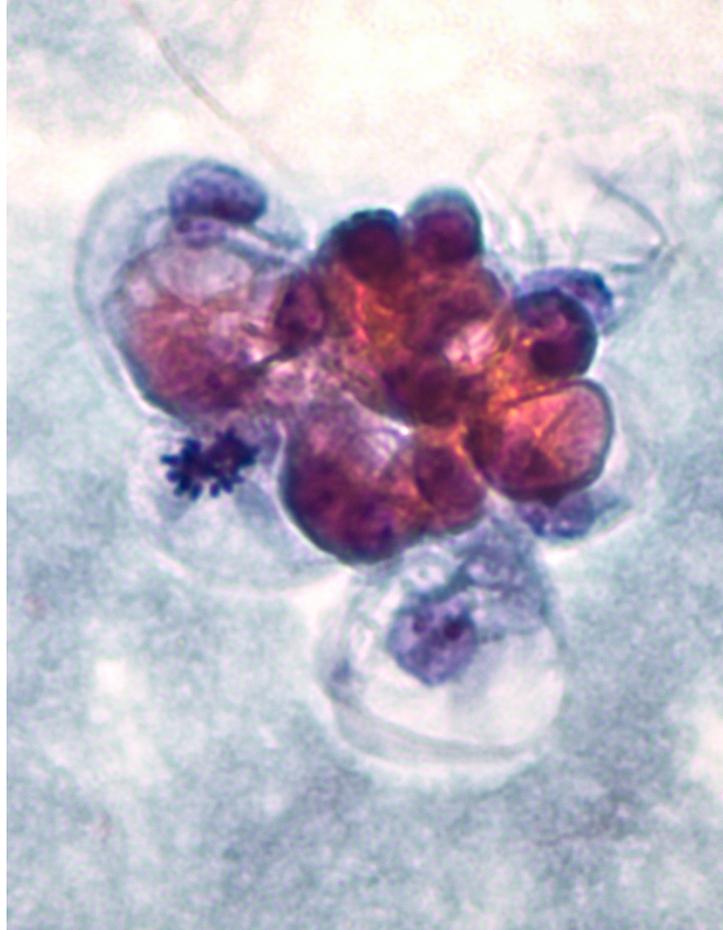
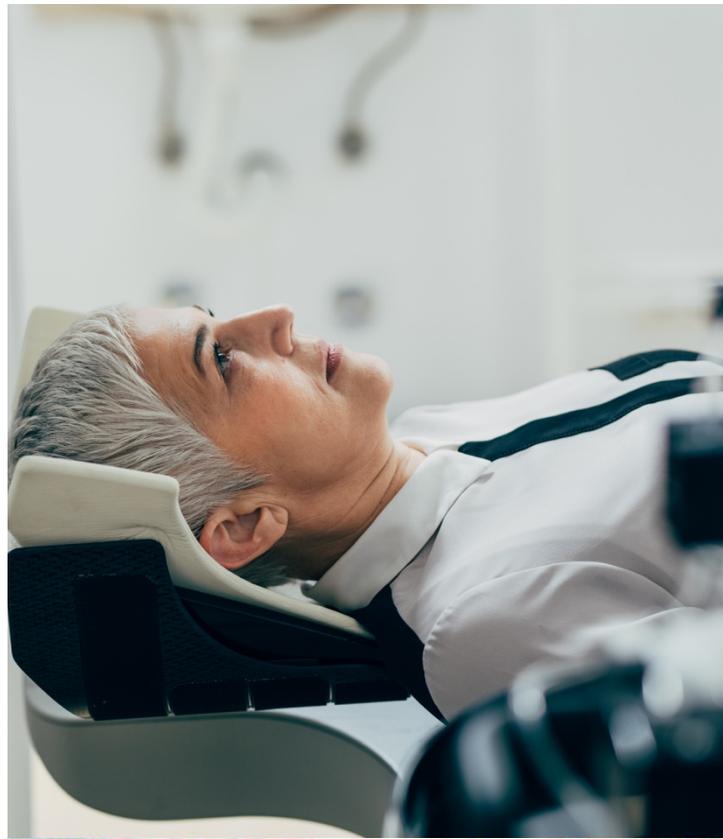


EXPERT OPINION

ACCESS TO LUNG CANCER TESTING & TREATMENT

CROATIA | Marko Jakopovic, Prof.

Just recently presented, data from European Nelson trial has shown an even larger reduction of mortality in the population at risk (heavy smokers, aged 50 to 75) who was screened with low-dose CT vs no screening (reduction in mortality from 28 to 61%). Based on these results, a national lung cancer screening program will be initiated in Croatia. The Croatian Thoracic Society and the Ministry of Health will start the **Lung Cancer Screening Program in Croatia**. It will include population, females and males, at high risk (heavy smokers, aged 50 to 75), who will go to an **annual low-dose CT scan**. Screening will be done in 14 centers throughout Croatia, and in patients with suspicious lung cancer workup will be done in 6 centers. To the best of our knowledge, this is the first national lung cancer screening program in the world.



EXPERT OPINION

ACCESS TO LUNG CANCER TESTING & TREATMENT

CZECH REPUBLIC | Petra Zemanová, MD

Algorithms of **therapy options for advanced/ metastatic NSCLC** used in the Czech Republic are based on worldwide valid recommendations. They are also slightly modified by the Czech Oncology Society according to valid payments by health insurance companies. New diagnosed non-small-cell lung cancers regardless of the clinical stage are reflexively tested for PD-L1 expression. Moreover, therapy predictive biomarkers (ALK and EGFR) are automatically tested in so-called small samples (transbronchial biopsy, transparietal biopsy, etc.) in morphologically defined subgroups (NSCLC adenocarcinoma, NSCLC NOS).

EXPERT OPINION

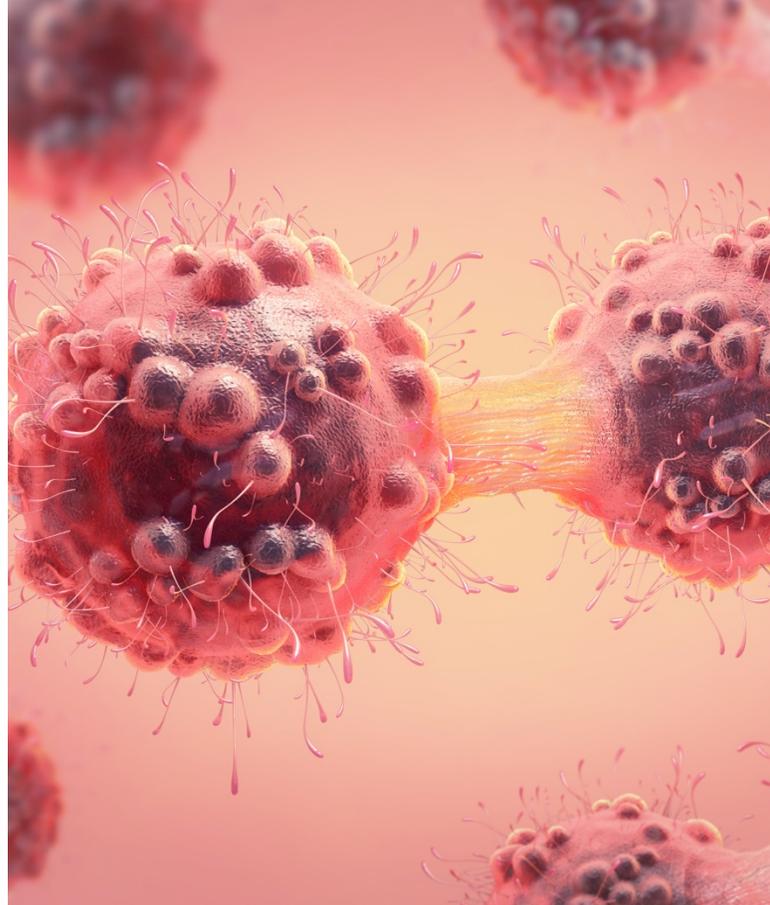
ACCESS TO LUNG CANCER TESTING & TREATMENT

CZECH REPUBLIC | Petra Zemanová, MD

Oncogenic driver genomic alterations from resections are only examined based on the oncologist's request. The acceptable approach to detect the activation of mutation in exons 18-21 of EGFR in cell-free DNA is a test of peripheral blood (called liquid biopsy) with the sensitivity surrounding 70%. Other specific molecular alterations are tested upon oncologist's request as well. Thus, the overview below is focused on the first-line treatment of advanced/metastatic NSCLC in the Czech Republic.

EGFR tyrosine kinase inhibitors of the first (erlotinib, gefitinib) and second generation (afatinib) represent a standard care of the first-line treatment for advanced/ metastatic EGFR mutated NSCLC adenocarcinoma. In contradistinction to ESMO guidelines, EGFR TKIs may be offered only to patients with a good performance status (PS 0-2). Therefore, osimertinib is approved for patients with resistance mutation of exon 20 (T790) at the time of progression on the lower generation EGFR TKI.

Furthermore, the current discussions are focused on the **sequential EGFR treatment**. A change of the treatment strategy is also noted in ALK-rearranged advanced NSCLC adenocarcinoma. To date, only crizotinib (reimbursed by the health insurance companies) or alectinib (reimbursed by pharmaceutical companies) have been used as the first-line medications for these patients. ALK inhibitor of the second generation (alectinib) is also allowed to patients previously treated with crizotinib. However, other ALK inhibitors (ceritinib, lorlatinib, brigatinib) do not receive health insurance payments.



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Therapy predictive biomarkers (ALK and EGFR) are automatically tested in NSCLC adenocarcinoma and NSCLC NOS.

Petra Zemanová, MD

In the field of **immunotherapy**, until recently, check point inhibitors (nivolumab) have been indicated in the second- and upper-line after the failure of chemotherapy, regardless of PD-L1 testing. To date, pembrolizumab has been approved as the first-line treatment of advanced NSCLC without the actionable oncologic driver and with high PD-L1 expression (TPS \geq 50%). Thus, the combination of immunotherapy and chemotherapy remains the domain of clinical trials.

The chemotherapy with platinum-based doublets and the third generation cytotoxics (taxanes, vinorelbin, gemcitabine, pemetrexed) is performed in the first-line treatment of advanced non-mutated NSCLC, NSCLC with PDL1 expression below 50% and given to patients with high expression PD-L1, but concurrently with the contraindication of immunotherapy. Bevacizumab can be added to chemotherapy (CBDCA + Paclitaxel) in the first-line treatment of NSCLC unless the general contraindications of VEGFR antibodies are present.

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EXPERT OPINION

ACCESS TO LUNG CANCER TESTING & TREATMENT

SERBIA | Jelena Spasic, MD; Fedja Djordjevic, MD;
Davorin Radosavljevic, Prof.

Access to testing is still not uniform in Serbia and in most cases not reflex. Upon diagnosis of NSCLC, patients are referred to a tertiary center where an MDT requests further molecular testing. These are performed in only three centers in Serbia, but the turnaround time is good, up to 7 work days. EGFR testing is standard, while ALK is performed in only one center at the moment.

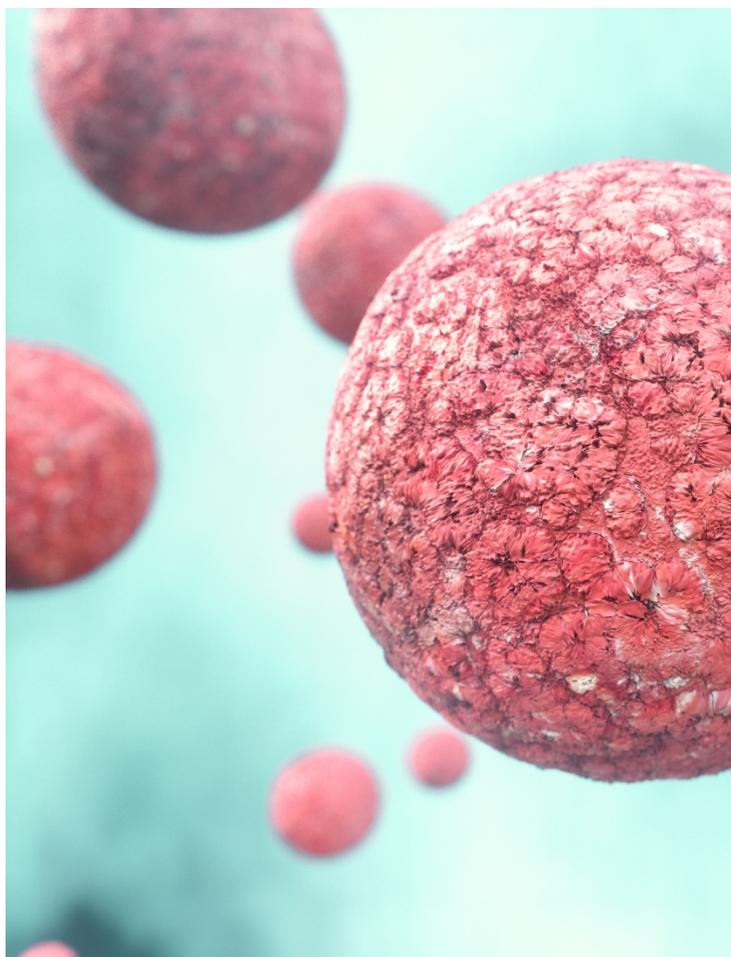
The reason for this is the fact that no **ALK inhibitors** are reimbursed by the National Insurance Fund, so testing is not standard. PD-L1 testing is performed as part of an Expanded Access Program. No other molecular testing is currently routinely performed, although we have the necessary equipment and knowledge.

At this time, **first- and second-generation EGFR TKIs** are reimbursed for first-line treatment, with erlotinib allowed for second line as well. No IO agents are currently reimbursed. As previously mentioned, no ALK inhibitors are reimbursed. Otherwise, the biggest problem remains the fact that pemetrexed is not reimbursed for adenocarcinoma, only for mesothelioma.

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Access to testing is still not uniform in Serbia.

Jelena Spasic, MD; Fedja Djordjevic, MD;
Davorin Radosavljevic, Prof.



CECOG CEE THORACIC NEWSLETTER

EXPERT OPINION

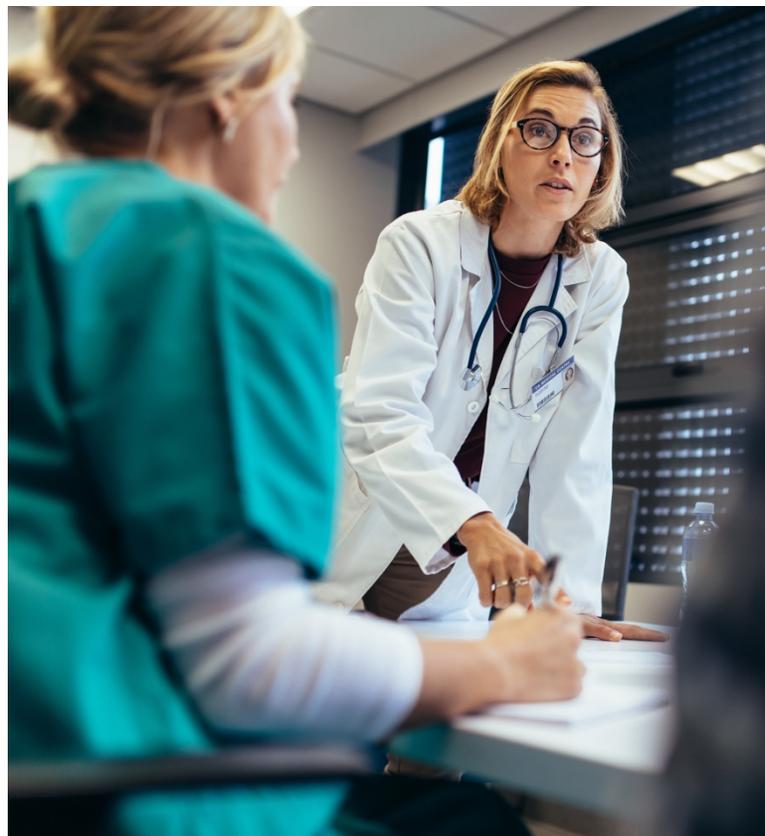
ACCESS TO NOVEL DRUGS

SLOVENIA | Tanja Cufer, MD, PhD, Prof.;
Urska Janzic, MD

Being medical oncologist in today's reality is both a privilege and a burden. Since advances in both diagnostics and treatment of oncological patients are moving forward with almost the speed of lightning and the things seemed impossible only a few years back are now essential, we begin to question ourselves how much more can we achieve? How much more knowledge, how many more improvements, how much more responsibility, and how much more expenditure to keep a sustainable healthcare system. Even though accessibility to knowledge and information is now – more than ever – at the tip of our fingers every second of every day, we cannot say the same about the accessibility of novel anticancer therapies for our patients, especially in less wealthy parts of the world, such as CEE region.

Spending on anticancer drugs

As reported by Prasad et al. (Nat Rev Clin Onc 2017), spending on anticancer drugs worldwide is in a range of \$100 billion annually and it only seems to be rising. **Novel anticancer therapies** usually come to the market with a high price tag, leaving the availability of them totally up to the economic situation of a certain country or forcing the patients to get access through out of pocket expenses. How can a CEE country compete with rising expenditures for cancer care on a global scale, when it's GDP per capita is 2 – 10 times less than that of the WE (Western European) country? When we analyzed (Vrdoljak et al., Oncologist 2019) the power ratio even further – CEE countries are dedicating a staggering 2.5 times less money to novel anticancer therapies compared to WE countries, which in turn correlates with worse cancer control in the CEE region.



“It is our mandate as medical oncologists not only to offer the best possible treatment to each individual patients; but most of all to achieve the best possible cancer control in the whole population with the available resources.”

Tanja Cufer, MD, PhD, Prof.

Slovenia is actually not doing badly in this region – our country has always been rather prosperous and fortunate in relation to other CEE countries; but still, we use about a third less resources for oncology treatment than WE countries. Nevertheless, access to novel anticancer therapies has historically been satisfactory – which is still the case; the major problem is a lag time between **EMA MA (European Medicines Agency marketing authorization)** and **NRA (national reimbursement approval)**, which is sometimes unacceptably long. In addition, in Slovenia, access to clinical trials is scarce; therefore, we are dependent on anticancer drugs being reimbursed by national government insurance.

EXPERT OPINION

ACCESS TO NOVEL DRUGS

SLOVENIA | Tanja Cufer, MD, PhD, Prof.;
Urška Janžic, MD

In the perspective of anticancer drug accessibility in European Union countries, a drug must overcome a few obstacles on its way to the patient. First, it must gain EMA MA, which is the same for all of the EU countries, including Slovenia. Then, it must gain **national reimbursement** approval, which is completely at the competence of specific country and its healthcare providers.

In Slovenia, a single entity, the National Health Insurance Institute is in charge of both, drug reimbursement and price negotiations. The drugs become actually available to all Slovenian patients after **National Health Insurance approval**. Price negotiations can substantially extend time to drug availability. Of note, Slovenia follows the charges of three WE countries when it comes to drug pricing (Austria, Germany and France) which by itself poses the question of system sustainability with Slovenian halved GDP/capita in comparison with those three countries.

Most health authority agencies rely on **health-technology assessment (HTA)** tools to make informed decisions about novel drug reimbursement, which is based on QALY (quality-adjusted life year) as a measure of health outcome of a certain treatment. In addition to that, oncological societies, such as ASCO and ESMO have developed new methods of assessment that can provide valuable information about a certain drug. One such tool is ESMO MCBS score (European Society of Medical Oncology Magnitude of Clinical Benefit Scale), developed by Cherny et al. (Ann Oncol 2015), which was established to help both physicians and patients make better and more informed treatment – related decisions.

The score does not only evaluate a certain anticancer therapy on the basis of responses to treatment or added time until disease progression or improvement in survival, but also takes into account all of the toxicities that can possibly occur during this treatment and how this affects the patient. Taking a score like this into consideration could be of great help in deciding what anticancer treatments to preferably implement into a cost – restrained healthcare system like ours.

As we reported in our study at last year's ESMO Congress (Janžic, Cufer et al. Abstract 1565PD, Ann Oncol 2018), the median time to both EMA marketing authorization and Slovenian **reimbursement approval** are above one year each (397 and 422 days, respectively) and are completely independent of the ESMO MCBS score of the drug.

That adds up to more than two years in average for an anticancer drug to be available to our cancer patients, who has to wait the same amount of time for a drug that is of limited or no clinical benefit for him as for the one that provides substantial clinical benefit. The EMA system of marketing authorization process could hardly be shortened without compromising quality and evidence based decision-making. On the other hand, national reimbursement processes have more room for improvement. In the case of lung cancer treatment, some anticancer drugs with a high ESMO MCBS score of 5 were actually reimbursed in Slovenia in a relatively short time of about half a year like pembrolizumab for first-line metastatic NSCLC with PDL1 \geq 50% while for some other drugs with equal substantial clinical benefit took around two years to get to the Slovenian market after EMA approval, as in the case of crizotinib for ALK positive NSCLC.

CECOG CEE THORACIC NEWSLETTER

EXPERT OPINION

ACCESS TO NOVEL DRUGS

Working with patients with lung cancer, where there was so many improvements and novelties in the last decade, there is a constant urge to provide patients with the latest and the most effective treatments possible. As mentioned before, in Slovenia, access to clinical trials is scarce, therefore, we are dependent on anticancer drugs being reimbursed through our national insurance company. Here, we present the actual availability of **novel targeted** and **immunology (IO) drugs**, recommended by ESMO guidelines for the treatment of advanced NSCLC (Planchard et al., Ann Oncol 2018), in Slovenia on May 2019 (Table 1).

As already mentioned, the majority of EMA approved drugs are reimbursed, excluding the latest **chemo-immunotherapy** options that are still being processed by the health authorities. Regarding targeted therapies, we are still struggling with unacceptable long decision times regarding reimbursement of some “real” targeted therapies such as crizotinib for ROS1 positive disease; while pending decisions for some targeted therapies with low ESMO scores, such as afatinib or erlotinib for molecularly unselected population are not so much of concern.

SLOVENIA | Tanja Cufer, MD, PhD, Prof.;
Urška Janžić, MD

In current situation, the glass can be viewed either half-full or half-empty. Since Slovenia still has quite good access to novel anticancer therapies, that aspect has to be seen with optimism and appreciation. On the other hand, it sometimes takes much too long for cancer patients to gain access to these treatments, which can be frustrating. Not only as medical oncologists, but also as an active member of the society,

it is clear to us that we cannot afford every possible treatment, but then again, maybe we do not have to. It is our mandate as medical oncologists not only to offer the best possible treatment to each individual patients; but most of all to achieve the best possible cancer control in the whole population with the available resources. It is probably time for each medical oncologist to be more acquainted with health-policy principles and for our teams to be not only **multidisciplinary but also multi-professional** in a way that will enable our active collaboration with health care decision and policy makers thus achieving best solutions and quicker access to therapies with meaningful clinical benefit for our patients.

NSCLC without targetable mutations				NSCLC with targetable mutations						
Any NSCLC		Non-SCC	SCC	EGFR mutation	ALK translocation	ROS1 translocation	BRAF mutation			
PD-L1 ≥ 50%		PD-L1 < 50%	PD-L1 < 50%							
1st line	Pembrolizumab 5		Platinum + pemetrexed + pembrolizumab 4	Platinum doublet + pembrolizumab NS	Gefitinib 4	Crizotinib 4	Crizotinib NS	Dabrafenib + trametinib NS		
			Platinum doublet + atezolizumab +/- bevacizumab NS	Platinum doublet + atezolizumab NS	Erlotinib 4				Alectinib NS	
					Afatinib 4				Osimertinib NS	Ceritinib NS
					Erlotinib + bevacizumab 2				Dacomitinib NS	Brigatinib NS
Subsequent lines	Docetaxel + nintedanib (non-SCC) NS	Docetaxel + nintedanib NS	Afatinib 2	Osimertinib (T790M +) 4	Alectinib NS					
	Afatinib (SCC) 2	Docetaxel + ramucirumab 1			Ceritinib 3					
		Erlotinib 1			Brigatinib NS					
	Docetaxel + ramucirumab 1	Nivolumab 5			Lorlatinib NS					
		Atezolizumab 5								
	Erlotinib 1	Pembrolizumab (PD-L1 >1%) 5								

Table 1: Current status of access to novel anticancer therapies for metastatic non-small cell lung cancer in Slovenia.

ESMO MCBS scores are shown on the right by each specific therapy, if available.

Lines in green –approved by EMA and reimbursed in Slovenia. Lines in blue –approved by EMA, but not yet reimbursed in Slovenia. Lines in red –not yet approved by EMA. NS – not scored by ESMO guidelines committee; non-SCC – non – squamous cell carcinoma; SCC – squamous cell carcinoma

HIGHLIGHTS FROM LOCAL EVENTS

CANCER IMMUNOTHERAPY CONFERENCE
TIMISOARA, FEBRUARY 21-24, 2019

ROMANIA | Serban Negru, MD
OncoHelp Cancer Center, Timisoara

More than 300 medical oncologists attended the Cancer Immunotherapy conference in Timisoara, Romania, between the 21st and 24th of February, 2019. The meeting was organized as an educational winter school by OncoHelp, the local cancer center. The first day, the conference placed emphasis on the understanding of the complex processes that govern immune responses. First lectures addressed specific subjects from the field of basic **immunology**. Mechanisms of immune destruction and malignant resistance were in the middle of debates, as well as hot topics like the influence of microbiota on the immune system and the future of anti-cancer vaccines. The afternoon discussions were divided in sessions for **tumor markers and immune side effects**. The second day was dedicated to recent advances of **immunotherapy** in the vast domain of medical oncology. Special sessions for lung and breast cancer, as well as malignant melanoma in the morning were followed by specific urogenital, digestive, gynecological and head & neck cancers in the afternoon.

Experts from each field tried to concentrate the news which sometimes overwhelmed us. **Professor Tudor Ciuleanu** assembled a formidable team to put order into the chaos of therapeutic combinations in lung cancer. **Professor Gal Markel** opened a window to the future of immunotherapy, by outlining the directions of development that emerged continuously in this area.

The last day was dedicated to **adoptive immunotherapy**. **Professor Christoph Zielinski** delighted the audience from the beginning, as he reviewed the current concepts on the function of immune compounds in cancer. The conference continued with other speakers from US and from Oncogen, a local research laboratory. They all showed the progress in the field of **CAR-T cells**, as well as potential difficulties for the years to come. Immunotherapy remains a subject of great interest for medical oncologists and this was proven once more in Timisoara. Due to the positive feedback from the participants, the next edition of this conference has already been announced to take place around the same time next year.

HIGHLIGHTS
FROM LOCAL
EVENTS

55TH ANNUAL CANCEROLOGY WEEK,
BELGRADE 31ST OCTOBER – 3RD
NOVEMBER 2018

SERBIA | Jelena Spasic, MD; Fedja Djordjevic, MD; Davorin Radosavljevic, Prof.

The 55th annual Cancerology week was held in Belgrade between October 31st and November 3rd. It is a great tradition, which has been going on since the mid 1950s, it is always multidisciplinary and gathers oncologists from Serbia and the region. This year's event covered lung cancer among other topics, specifically **access to drugs and new molecular testing**.

We are looking forward to the next one. Another important event was also held in Serbia. The Central European Lung Cancer Conference was held in Novi Sad at the end of November 2018 and it proved to be a well-visited and successful meeting.

**11TH CURRENT STATUS OF LUNG CANCER TREATMENT
CONFERENCE, SIELNICA, NOVEMBER 9, 2018**

SLOVAKIA | Michal Urda, MD
F.D. Roosevelt University Hospital

The biggest thoracic oncology meeting in Slovakia took place in Sielnica on Friday, November 9, 2018. The conference was opened by Assoc. Prof. Peter Berzinec

During the first block of presentations various topics were discussed, including the role of pathologists in NSCLC diagnosis presented by **Professor Lukas Plank**.

The next very interesting topics were the comparison between RECIST and iRECIST, the role of **radical radiotherapy in NSCLC**, and the clinical use of **Next generation sequencing in NSCLC**.

The second block of presentations was dedicated to **immunotherapy** in the first- and second- line setting of NSCLC treatment, in consideration of new ESMO Guidelines 2018. The management of immunotherapy toxicity, the role of PD-L1 as predictive biomarker, and the first experience with atezolizumab in NSCLC patients in Slovakia were also presented in this block.

The **targeted treatment** of patients with tumors harboring genetic alterations (EGFR, ALK) and the antiangiogenic treatment were covered in the last block. Attendees had the opportunity to discuss with local experts and the overall quality of the meeting was top-rated.

HIGHLIGHTS
FROM LOCAL
EVENTS

10TH ANNUAL ONCOLOGICAL COLLOQUIUM
PRAGUEONCO 2019

CZECH REPUBLIC | [Ludmila Křížová, MD](#)

The 10th annual oncological colloquium PragueOnco took place in Prague at the beginning of this year. The overarching theme of the event was multidisciplinary and its program was built on this very principle to provide a space for open discussion between professionals of different specialties who participate in taking care of oncological patients.

In the lung cancer section, [Prof. Nir Peled](#) from Israel spoke about possibilities of [screening for Lung Cancer](#). [Prof. Robert Pirker](#) from Vienna presented [Immunotherapy in Lung Cancer](#), a subject undergoing intense study, and summarized results from current clinical trials. Last but not least, [Andrea Camerini](#) from Italy illuminated the principles of using [metronomic chemotherapy](#) in Patients with NSCLC.

TOP CHOICE ARTICLE:

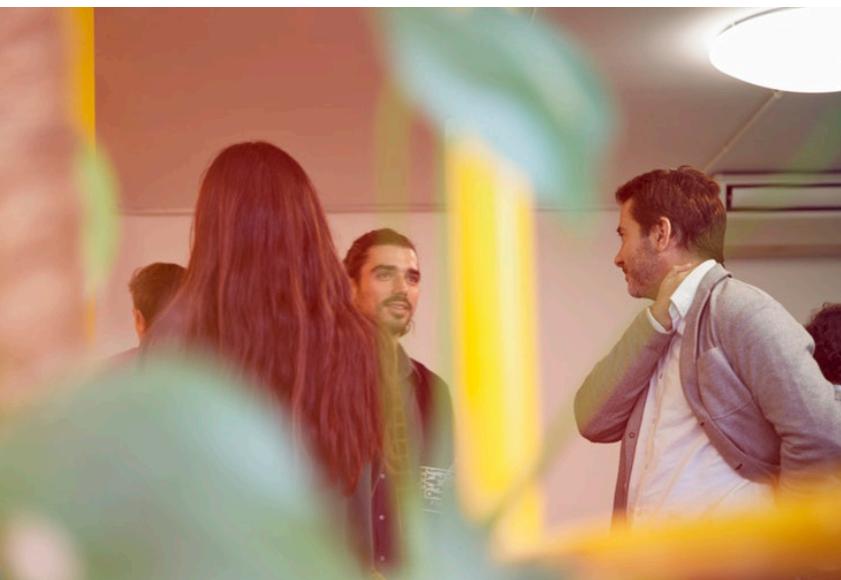
“ Ball D, Mai GT, Vinod S, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomized controlled trial. *The Lancet Oncology* [online]. 2019. DOI: 10.1016/S1470-2045(18)30896-9. ISSN 14702045

This article presents results of a multicenter, phase 3, randomized, controlled trial comparing stereotactic ablative body radiotherapy (SABR) to standard radiotherapy in inoperable stage 1 non-small-cell lung cancer. The primary endpoint of the trial is time to local treatment failure. The results show that SABR has superior local control of the primary disease without an increase in toxicity.

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[Ludmila Křížová, MD](#)

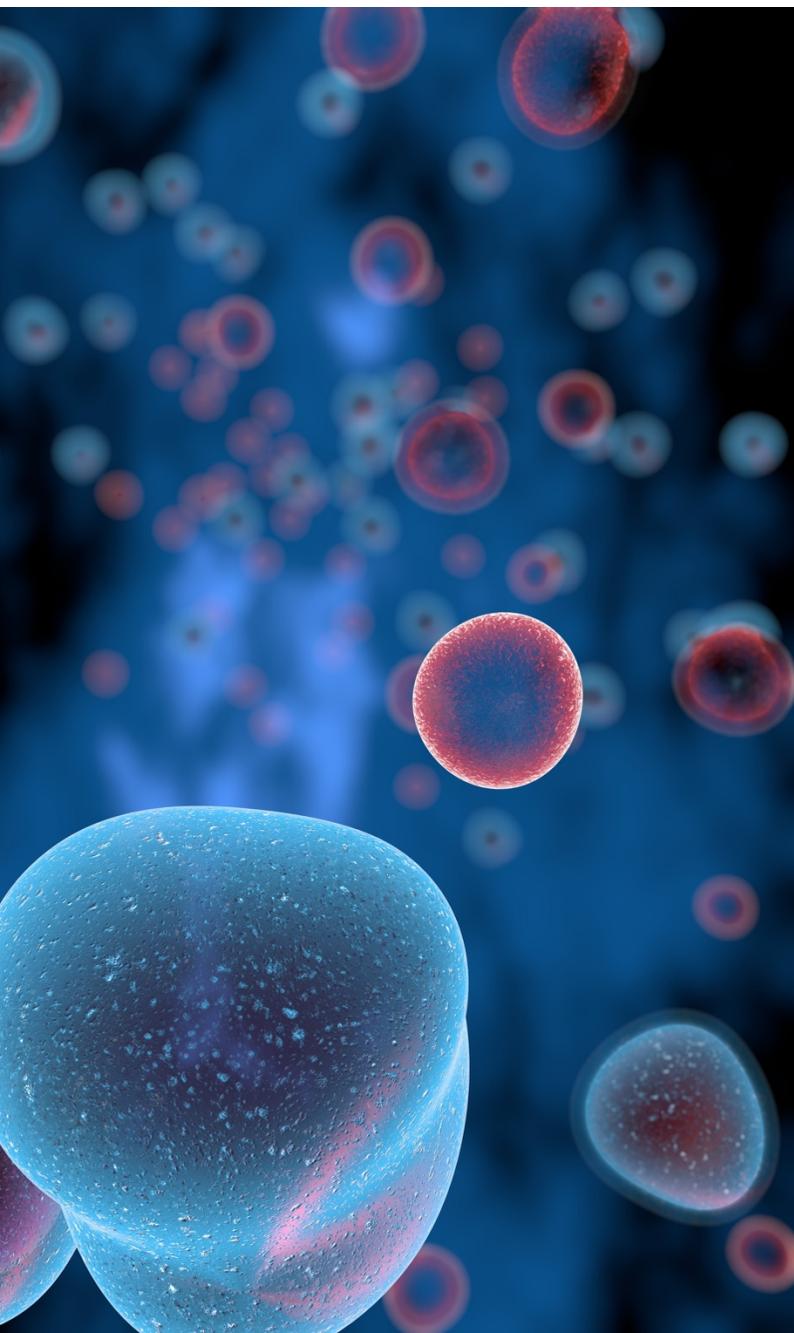


CECOG CEE THORACIC NEWSLETTER



YOUNG
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YOUNG ONCOLOGISTS CORNER

MOLECULAR MECHANISM OF SCLC TRANSFORMATION

Petra Zemanová, MD

Recently, I have been persuaded by necessity to remember that SCLC transformation can occur during EGFR TKI treatment for **NSCLC adenocarcinoma**. The pathologic mechanism of this phenomenon is based on the idea that NSCLC and SCLC might share common cell precursors. The other hypothesis presumes that NSCLC also consists of the proportion of SCLC population. Within the EGFR TKI treatment, NSCLC component decreases, whereas SCLC component becomes dominant.

Molecular mechanism of SCLC transformation includes TP53 mutations, Rb1 loss, the lack of EGFR expression and MYC amplification. The increase in the serum proGRP and NSE level during the EGFR TKI treatment can be helpful to identify SCLC transformation. Furthermore, normal-range values cannot exclude the possibility of SCLC transformation. However, repeating biopsy is recommended to rule out this phenomenon for patients with NSCLC, which progresses rapidly in spite of TKI treatment.

TOP CHOICE ARTICLE:

Rolfo C, Mack PC, Scagliotti GV at al. Liquid Biopsy for Advanced Non-Small Cell Lung Cancer (NSCLC): A Statement Paper from the IASLC. J Thorac Oncol. 2018;13(9):1248-1268.

“

A multidisciplinary panel of experts in the field of thoracic oncology evaluates currently available evidence with the aim of producing a set of recommendations for the use of liquid biopsy for molecular analysis in guiding the clinical management of advanced NSCLC patients.

Fedja Djordjevic, MD

“

YOUNG ONCOLOGISTS CORNER

PROFESSIONAL ONCOLOGY SOCIETIES

Mila Petrova, MD



The **Young Oncologists (YOs)** are becoming extremely important members of professional oncology societies, such as **ESMO**, **ASCO** and others. Since the last several years, YOs account for more than 40% of all ESMO members.



There are specific sessions dedicated to YOs at major scientific conferences like ESMO meetings. The YO forum which is already a traditional part of each ESMO meeting has been organized at ESMO 2018 in Munich, as well. The forum provides a wonderful option for networking and further discussion not only between the YOs themselves, but also with speakers who are well known and prominent oncologists with a wealth of experience. The focus of the 2018 YO forum was “Research projects: from ideas to papers”. The discussion was mainly oriented on tips how to define a proper project, to get it financed and how to deal with the obstacles faced during the project.

Multiple other sessions dedicated to YOs have been organized, such as YO fellowship and mentorship sessions which are very well attended. In addition, the Vesalius talk is carried out in a big foyer (open area) with a small stage. This is a rare opportunity for YOs to directly address and reach some of the most experienced oncologists. In 2018, the topic was “**work/life balance** at early stages of a young oncologist’s career” - an extremely intriguing discussion between **Professor Solange Peters**, **Professor Martine Piccart** and **Professor Andres Cervantes**. The duration of the session usually is 45 minutes.

With regard to specific educational sessions, three different sessions were organized in Munich, the first one on **fertility and pregnancy in cancer**, the second on breaking bad news and the third on **biosimilars**. Every topic was presented by an expert resulting in a very vivid and thoughtful discussion with the audience. Sessions with intriguing discussions and open questions.

YO clinical case discussion – the newest session in the YO track started in 2017. It is a preregistered session with three separate tables focused on different cancer types. In 2018, the session was well attended with many YOs on the waiting list.

YOUNG ONCOLOGISTS CORNER

PROFESSIONAL ONCOLOGY SOCIETIES

Mila Petrova, MD

There were three topic tables – soft tissue sarcoma, prostate cancer and lung cancer. Every table was chaired by an experienced senior medical oncologist and a young oncologist who prepared challenging clinical cases. The lung cancer cases have been prepared by [Professor Tanja Cufer](#) from University Clinic Golnik, Slovenia, and [Mila Petrova](#) from Bulgaria. Two cases, one on EGFR positive advanced NSCLC cancer and one on PD-L1 highly expressed advanced NSCLC were thoroughly discussed between attendees and presenters taking into account current oncology guidelines for diagnosis and treatment and also sharing thoughts and experience about best practice and shortages in [access to novel therapies](#) in particular regions.

Last year, the YO track was the most attended in the last years. By active participation in different sessions, YOs gain a valuable experience on how to present and discuss topics related to their career, cancer care as well as its organization. YOs from the CEE region are highly encouraged to participate in this important initiative of ESMO.

YOUNG ONCOLOGISTS CORNER

YOUNG SMOKER WITH LEFT LUNG TUMOR AND SUPERIOR VENA CAVA SYNDROME

Damian Tworek, MD

A 43-year-old man with a history of 120 pack years, not reporting any previous symptoms and chronic diseases, attended emergency unit due to facial edema, upper limb edema and dyspnea that had occurred 2 days before.

Chest X-ray showed features of emphysema and a tumorlike enlargement of the upper part of the left lung hilum (Image 1). Laboratory tests showed elevated d-dimer concentration (3420 ng/ml) as well as hypoxia (54 mmHg) with hypocapnia (29 mmHg) in capillary blood gases.

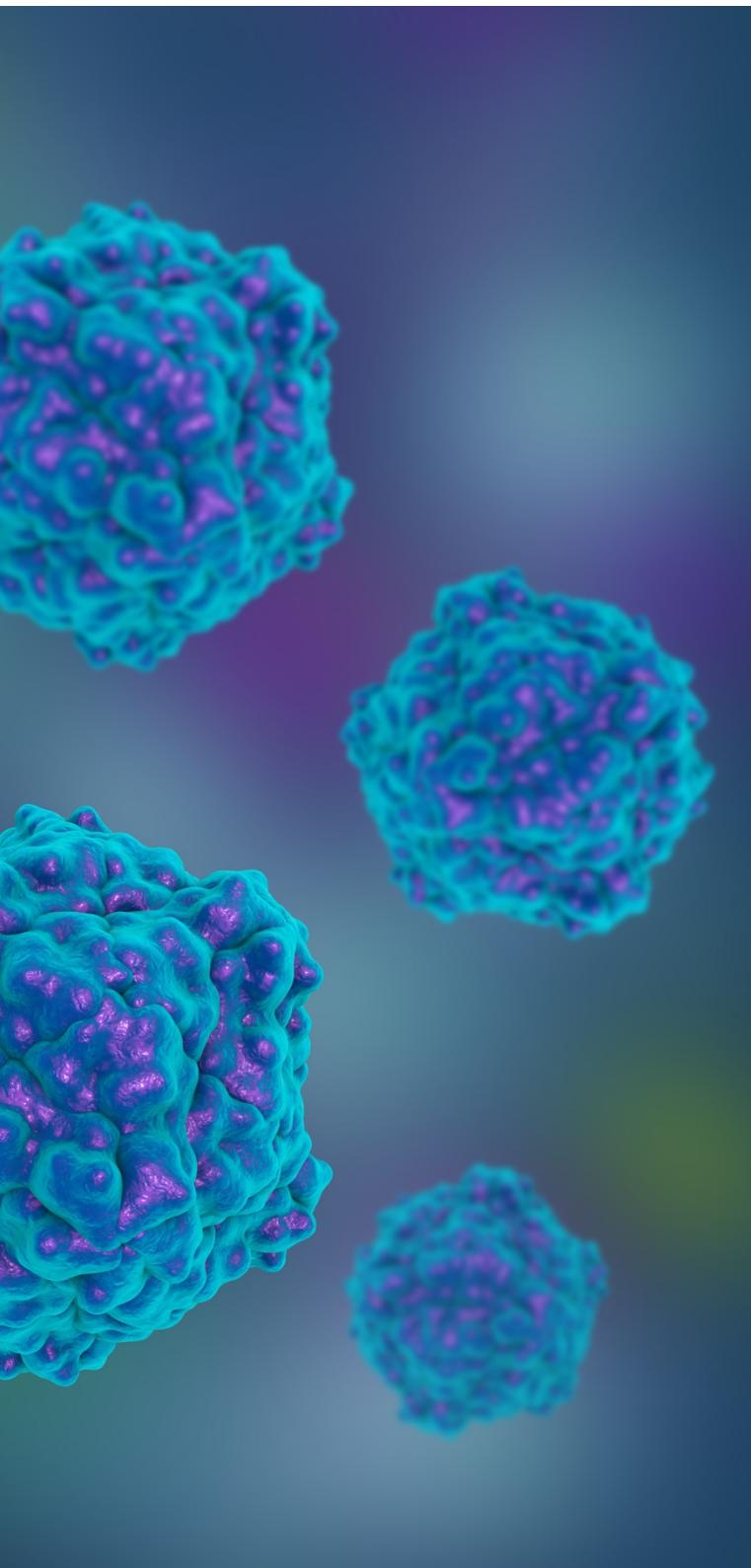




Image 1. Posterior-anterior chest radiograph. Yellow arrow indicates a tumor located in the upper part of the left lung hilum.

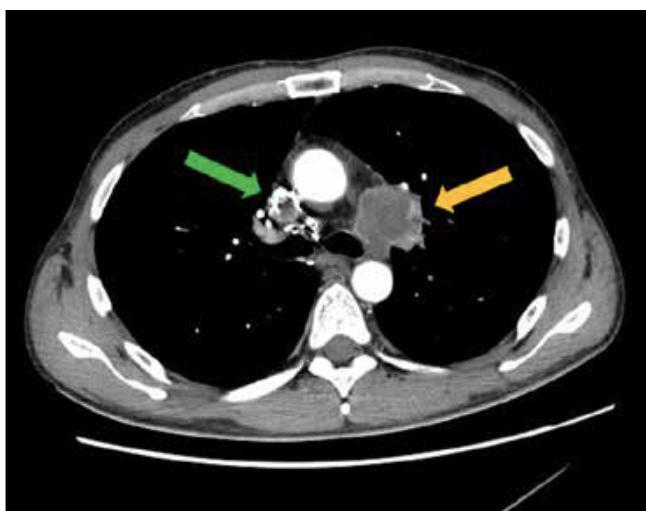


Image 2. A chest computed tomography scan below bifurcation of the trachea. Yellow arrow indicates a lung tumor. Green arrow indicates an occlusion and preserved partial contrast flow in the lumen of superior vena cava.

YOUNG ONCOLOGISTS CORNER

YOUNG SMOKER WITH LEFT LUNG TUMOR AND SUPERIOR VENA CAVA SYNDROME

Damian Tworek, MD

Physical examination revealed tachycardia (100/min), normal blood pressure (123/81 mmHg), head, neck, and upper limbs edema, widened external jugular veins, and superficial vessels of the upper chest, diminished vesicular sound on lung auscultation. On admission to the Department of General and Oncological Pulmonology, **standard treatment of superior vena cava (SVC) syndrome (systemic glucocorticosteroids, diuretics)** was initiated. In addition, low molecular weight heparin at therapeutic dose was introduced due to suspected pulmonary embolism. **Computed tomography** of the chest (Image 2) revealed a left lung tumor located under the aortic arch and adjacent to the trachea and left main bronchus. In addition, occlusions within the lumen of SVC and left pulmonary artery were noted, indicating presence of **SVC thrombosis and pulmonary embolism**. **Bronchofibroscopy** did not reveal lesions characteristic of proliferative process. Due to general condition and tumor location no surgical diagnostic procedures were recommended.

Therefore, **endobronchial ultrasound with real-time guided transbronchial needle aspiration (EBUSTBNA)** was performed. Lung squamous cell carcinoma was diagnosed based on the cytological examination of the collected tumor sample. The patient was qualified for **chemo- and radiotherapy** by a multidisciplinary team comprised of a pulmonologist, oncologist, radiotherapist, and thoracic surgeon. In this case, two clinical problems were encountered.

Firstly, the SVC syndrome was mainly caused by right sided lung tumors that compress the vasculature and ultimately lead to disturbances of the upper body blood flow.

In the described case, symptoms were caused by one of the well-known complications of malignancies, i.e. a tendency to thrombosis. The other clinical problem was the determination of **histopathological diagnosis**. In the presence of endobronchial lesions, it is possible to collect tumor biopsies for histopathological examination. In this case, the diagnosis could be made by means of the **EBUSTBNA** technique, which has become an important tool used in the diagnosis and **staging of lung cancer**.

YOUNG ONCOLOGISTS CORNER

FIRST ESO-ASCO MASTERCLASS IN CLINICAL ONCOLOGY

Aleksandra Pusica, MD; Vladimir Nikolic, MD and Fedja Djordjevic, MD

This November in Yerevan, Armenia, first ESO-ASCO Masterclass in Clinical Oncology was held. Three young oncologists from Serbia were active participants: [Aleksandra Pusica](#), [Vladimir Nikolic](#), and [Fedja Djordjevic](#). Other participants were from Caucasus region, Europe and the former Soviet Republics. The program provided a full spectrum of issues in clinical oncology and practice-oriented training, focusing on [breast](#), [gastro-intestinal](#), [gynecologic](#), [lung](#), and [prostate cancers](#), and furthermore included professional development topics. The case presentation about a lung cancer patient from Serbia by Fedja Djordjevic was selected as one of the best of the Masterclass.



NSCLC – MULTIDISCIPLINARITY INNOVATION

TUMOR MULTIDISCIPLINARY TEAM IN HUNGARY

Krisztina Bogos, MD, PhD; Gabriella Galffy MD, PhD, HUNGARY

Caring for a cancer patient is a complex task. The different specialists need to work together to organize the optimal patient paths during the investigation and after the diagnosis is made, and to recommend the best treatment option to improve the outcome of the disease.

NSCLC – MULTIDISCIPLINARITY INNOVATION

TUMOR MULTIDISCIPLINARY TEAM IN HUNGARY

Krisztina Bogos, MD, PhD; Gabriella Galffy MD, PhD, HUNGARY

The multidisciplinary team's prototype is the **oncoteam**. Oncoteam's work is regulated by EMMI (Ministry of Human Capacities) Decree (1/2012. V.31.) in Hungary. In general, the decree specifies the definite cancer patient group of the expert's specialty and the minimum professional conditions necessary for medical care and procedures. Oncoteam's tasks include the complete pathway planning, management, diagnostic tests, the setting up of the therapeutic plan and its renegotiation after disease progression, based on the new diagnostic results, with further therapeutic consequences.



The oncoteam involves specialists in clinical oncology, pathology, radiology, radiotherapy, surgery, patient's physician, and residents.

Oncoteam establishes a therapeutic plan after accurate clinical status assessment, taking into account the patient's general condition, their histological classification, comorbidities, and the existence or absence of patient's informed consent. The therapeutic plan has to detail the sequence of methods, the combination of therapies, the surgical extension, and the main characteristics of radiotherapy and medication. It reviews the effectiveness of therapy, and modifies it as needed. It also proposes participation in a clinical trial and rehabilitation. The oncoteam involves (at least): clinical oncologist, pathologist (with molecular pathological background), radiologist, radiotherapy specialist, surgical specialist of a given tumor,

patient's physician, candidate for opinion in the concerned profession, residents, oncoteam organizer.

The operating procedures of the oncoteam must be specified in the Organizational and Operational Rules of the Health Care Institutions. This should include the order and location of the meetings, the involved specialists from other institutions, the use of telemedicine and telecommunication equipment. Oncoteam's suggestion is based on the referral by the attending physician and a review of the available health documentation. The participants have to verify their recommendation with their signature and seal it.

NSCLC – MULTIDISCIPLINARITY INNOVATION

TUMOR MULTIDISCIPLINARY TEAM IN HUNGARY

Krisztina Bogos, MD, PhD; Gabriella Galffy MD, PhD, HUNGARY

One copy is placed in the patient's medical records, and a copy must be placed in the oncoteam's records. The Decree also defines the responsibilities of the oncoteam organizer.

In the last two decades, there has been a rapid development of tumor care with respect to diagnostic procedures, effective surgical, radiotherapy, and systemic treatment, the power of **IT technology** and the multidisciplinary, specialist-led care.

ONCOPULMONOLOGY

Last year, the Head of the Oncopulmonology Section organized "Good and Well" domestic practices in the operation of oncoteams' forum about the role of the multidisciplinary team and its impact on the outcome of the disease in Budapest. The oncoteam leaders involved in the **domestic lung cancer care** could share their experiences with each other at the conference, while also learning from international examples.

The creation of a single oncology reporting and follow-up sheet has been formulated, which can be the basis of accurate epidemiological data collection, by assessing rare diseases, therapeutic habits, and its effectiveness, and by showing the causes of sad mortality data in Hungary. Another goal is to shorten the **time from diagnosis to therapy** by better organizing the processes. We really want to provide unified care for lung cancer patients.

Unified care for lung cancer patients is among the primary goals of the oncoteam.

MULTIDISCIPLINARY TEAM AND INNOVATION

The summary "Identifying Critical Steps, Innovation in Tumor Care" of The European Cancer Organization Working Group draws attention to the responsibility of the multidisciplinary team to continuously integrate new procedures, treatment modalities, and improve their own internal processes, in order to make care more efficient, of course, considering the local finance.



NSCLC – TKI

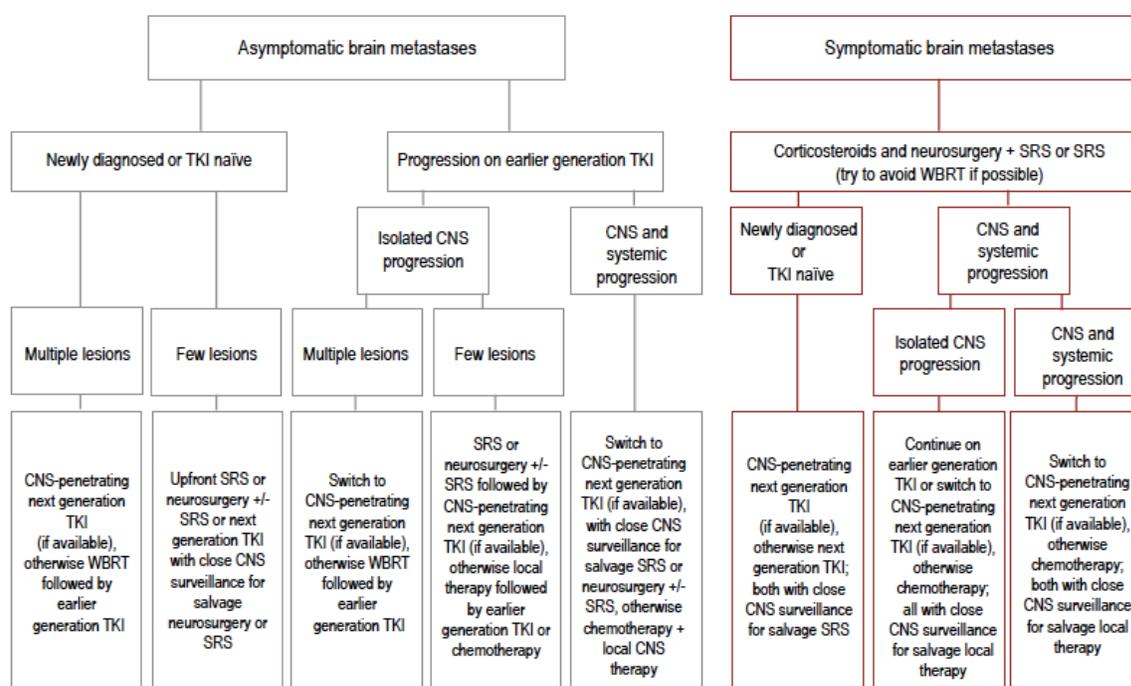
MANAGEMENT OF BRAIN METASTASES IN NON-SMALL CELL LUNG CANCER IN THE ERA OF TYROSINE KINASE INHIBITORS

 Anna Wrona, MD; Rafał Dziadziuszko, Prof.; Jacek Jassem, Prof., **POLAND**

Lung cancer represents the most common cause of brain dissemination. **Oncogene-addicted (EGFR- and ALK-positive) non-small cell lung cancers (NSCLCs)** are characterized by a unique metastatic neurotropism resulting in a particularly high incidence of **brain metastases**. The goal of optimal brain metastases management is to improve both overall survival and quality of life, with the focus on neurocognitive function preservation. Neurosurgery is offered to patients presenting with limited intracranial tumor burden located in surgically accessible un-eloquent regions of the brain, whereas **stereotactic radiosurgery (SRS)** represents the preferred radiotherapy option for patients not amenable to surgery. **Whole brain radiotherapy (WBRT)**, owing to its neurocognitive sequelae, should be reserved for patients with multiple lesions.

EGFR and ALK tyrosine kinase inhibitors (TKIs) provide significantly superior systemic response rates and progression-free survival compared to standard chemotherapy in the molecularly defined NSCLC subpopulations. An apparent intracranial activity of new generation TKIs triggered the discussion on their role in brain metastases in lieu of local therapies. Our aim is to suggest the management of brain metastases in NSCLC patients with EGFR- or ALK-sensitizing alterations in central nervous system based on the current therapeutic landscape of brain metastases management in NSCLC, with a particular focus on EGFR-mutated and ALK-rearranged NSCLC subtypes.

Fig. 1: Suggested management of brain metastases in NSCLC patients with EGFR-or ALK-sensitizing alterations. TKI, tyrosine kinase inhibitor; CNS, central nervous system; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery.



NSCLC – RADIO CHEMOTHERAPY

RADIOCHEMOTHERAPY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

Maciej Krzakowski*, Prof.

Center of Oncology-Institute Maria Skłodowska – Curie, Warsaw, POLAND

Non-small cell lung cancer (NSCLC) is diagnosed in locally advanced stage in approximately 40% of patients. Locally advanced NSCLC is a heterogeneous disease in terms of primary tumor as well as characteristics of regional lymph nodes [1]. Moreover, demographic and clinical features (e.g. age, nutritional and performance status, comorbid conditions, cardiopulmonary function) may differ in patients with locally advanced NSCLC. This situation results in a different therapeutic management in patients with locally advanced NSCLC – definite resection may be offered to some patients, whereas others are candidates for radical irradiation in combination with chemotherapy, or just systemic treatment depending on histology and molecular characteristics.

In patients who are candidates for **radio chemotherapy** concomitant use of both modalities should be considered, first based on the results of the meta-analysis of randomized trials documenting superiority of concurrent radio chemotherapy over sequential administration of chemotherapy and irradiation (e.g. the difference of about 15% for grade 3 esophageal toxicity: 18% versus 4%) [2].

Concurrent radio chemotherapy is obviously more challenging and requires knowledge of the selection of patients as well as experience in the management of side effects. It is also challenging in terms of adequate care organization (optimally – availability of radiotherapy and systemic therapy together with all options of supportive care in the same institution).

Concurrent radio chemotherapy is used in an insufficient number of patients with locally advanced NSCLC.

The outcome of NSCLC patients who receive concurrent radio chemotherapy illustrates median survival of no more than 28 months [3] – this justifies efforts to improve the results. One option is to use systemic therapy to consolidate the results of radio chemotherapy. Unfortunately, several trials of consolidation chemotherapy have proved ineffective. Recently, consolidation **immunotherapy** with durvalumab has shown substantial survival benefit in patients who had not progressed after radio chemotherapy – the use of durvalumab resulted in significant reduction in the risk of death as compared with placebo (hazard ratio – 0.64).

No new safety signals were identified during follow-up of patients in the study [4]. These results represent a real progress and an additional argument for a more frequent use of concurrent radio chemotherapy in patients with locally advanced and inoperable NSCLC.

Concurrent radio chemotherapy is being used in an insufficient number of patients with locally advanced NSCLC. Approximately 3000 patients are diagnosed with locally advanced and inoperable NSCLC.

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NSCLC – RADIO CHEMOTHERAPY

RADIOCHEMOTHERAPY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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Our estimation is that about 50% of them are candidates for concurrent use of chemotherapy and radiotherapy.

In a survey, we found that only 250 of the patients received concurrent radio chemotherapy, which represents less than 20% potential beneficiaries of combined radical treatment. The rest of the patients are either subjected to sequential chemotherapy and radiotherapy, or are given chemotherapy alone. The reasons for this inappropriate situation are complex – the lack of coordinated and comprehensive health care in lung cancer patients is the most important. It is mandatory to select the best treatment during **multidisciplinary meetings** with participation of pulmonologists, thoracic surgeons, radiation and medical oncologists.

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The meetings should be preceded by adequate pathology and molecular diagnosis as well as meticulous staging. If radiotherapy is indicated and feasible, the treatment plan should be prepared upfront; the use of radiotherapy in patients with locally advanced NSCLC without initial planning and as salvage treatment should be considered as inadequate practice.

The goal for now is to disseminate knowledge of the benefits related to combined – concurrent in particular – treatment and create better organizational solutions that will increase the use of concurrent radio chemotherapy in well-selected patients, in a safe and effective way. This will allow patients with locally advanced NSCLC to have better access to modern therapeutic approach.

References: Pg. 38

It is mandatory to select the best treatment during multidisciplinary team meetings.



NSCLC – LIQUID BIOPSY

THE CLINICAL USEFULNESS OF LIQUID BIOPSY FOR DETECTION AND DYNAMIC MONITORING OF EGFR T790M IN NSCLC PATIENTS ON EGFR-TKI THERAPY

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The greatest limitation of the I & II generation EGFR TKIs' efficacy is the resistance acquired by most treated patients through the T790M mutation present in exon 20 of EGFR gene. Non-invasive access to the tumor DNA circulating in the blood of NSCLC patients, so called **liquid biopsy**, enables the real-time monitoring of status and level of mutated EGFR gene DNA (mEGFR) during EGFR TKI treatment, instead of retrospective evaluation of tumor tissue specimens. In the present study we evaluated the feasibility and the diagnostic usefulness of quantitative EGFR mutations analysis in liquid biopsy collected from NSCLC patients during EGFR TKI treatment.

Method: The study group consists of 40 patients with advanced NSCLC treated with EGFR TKI (erlotinib, gefitinib or afatinib) in the first line. Peripheral blood was prospectively collected at the time of diagnosis (baseline) and then every month during treatment. In 10 patients (7 patients with deletion in exon 19 and 3 patients with L858R mutation in exon 21 of EGFR gene) sampling was carried on until clinical progression. The mutated EGFR DNA was analyzed quantitatively in plasma using cobas EGFR Mutation Test v2 (Roche, Germany). chemotherapy in well-selected.

Result: The mEGFR in the plasma of NSCLC patients demonstrated notable dynamics during EGFR TKI treatment. In 8 out of 10 (80%) patients followed until progression, who responded well to EGFR TKIs, the complete clearance of mEGFR in plasma in the first 2 months of treatment was observed, regardless of the type of activating EGFR mutation. The levels of mEGFR remained undetectable in plasma for several months of treatment in those patients. In 6 (60%) patients a rapid raise to or above mEGFR baseline preceded clinical progression in time, in 4 patients by at least four weeks. In 4 patients, the raising level of mEGFR in plasma was accompanied by the increasing T790M mutation level. In 2 patients, the plasma level of mEGFR was undetectable at diagnosis and during treatment.

Conclusion: The dynamic changes in levels of mutated EGFR gene DNA in plasma of NSCLC patients reflect their response to EGFR TKI treatment. The monitoring of T790M mutation levels in plasma by allele-specific qPCR assay allows observance of disease progression on EGFR TKIs much earlier than conventional imaging techniques. This is an ongoing study: at least 80 patients are to be recruited and clinical data correlated with results of molecular tests.

The liquid biopsy enables the real-time monitoring of status and level of mutated EGFR-gene DNA during EGFR TKI treatment.

Financial support: This study is financed by the investigator initiated research grant (ESR) from AstraZeneca.

NSCLC – TARGETED THERAPY

BRIEF UPDATE ON THE TARGETED THERAPY IN EGFR MUTANT NON-SMALL CELL LUNG CANCER (NSCLC)

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The discovery of the activating mutation in the EGFR domain [1] opened the way for **molecular targeted therapy** in the field of NSCLC. Since the seminal IPASS study published a decade ago [2], the EGFR tyrosine kinase inhibitors (TKI) have become the standard of care in first line for this subset of patients. Substantial improvement in response rates, progression free survival (PFS) and quality of life were recorded in phase III randomized trials, when TKI were compared with standard chemotherapy [2,3,4]. Compared with the first generation (gefitinib, erlotinib), second generation TKI (afatinib, dacomitinib) provide some benefits mainly in terms of PFS and to a lesser extent in overall survival, at the expense of a more severe toxicity profile [5,6,7].

EGFR T790M is responsible for drug resistance in approx. 50-60% cases.

Despite the initial benefit, after approximately 1 year all patients will eventually relapse. Brain as the sole site of relapse or in the context of a widespread tumor progression appears a challenging scenario in up to 30 % of patients. Occurrence of T790M, a second target mutation, was demonstrated to be responsible for drug resistance in approximately 50-60% of the cases [8]. For this pattern of progression, the third generation TKI – osimertinib, was able to induce a 71% response rate, and median PFS of 10.1 months, significantly higher than the standard chemotherapy regimen (phase III AURA trial) [9].

Moreover, substantial activity in preventing the intracerebral progression and a favorable toxicity profile was also noted [9,10]. Due to various reasons, only 70% of progressing patients were candidates for further therapy, while the other 30% might be missing a valuable second line chance. The high inhibitory potency on cell clones harboring the classical exon 19 and 21 with or without T790M mutation, along with the high brain/plasma Cmax ratio, and the favorable toxicity profile set the rationale for anticipating a favorable activity of osimertinib in first-line setting.

The randomized phase III trial, FLAURA, evaluated patients with EGFR mutation treated upfront with either osimertinib or a first generation TKI [11]. A significant improvement in PFS was noted, median 18.9 vs 10.2 months (HR=0.46, p<0.0001). The data for overall survival analysis were immature, but a superiority trend was noted in the osimertinib arm. Median CNS progression free survival in patients with measurable and/or non-measurable CNS lesions was not reached with osimertinib and was of 13.9 months with standard EGFR-TKIs (HR=0.48, p=0.14) [12]. Lower grade ≥ 3 treatment related toxicity was recorded in the osimertinib arm (18% vs 28%). Based on these results, osimertinib has been recently added in the **ESMO** and **NCCN guidelines** as a valid first line alternative, along with other first- and second-generation TKI. Further developments in this field are focused on identifying active drugs able to target the new resistance molecular events occurring upon osimertinib progression, like the C797S mutation and MET amplification [13].

NSCLC – IMMUNOTHERAPY

BRIEF INSIGHT INTO THE BENEFITS OF DURVALUMAB AFTER CHEMORADIOTHERAPY IN UNRESECTABLE, LOCALLY ADVANCED NSCLC

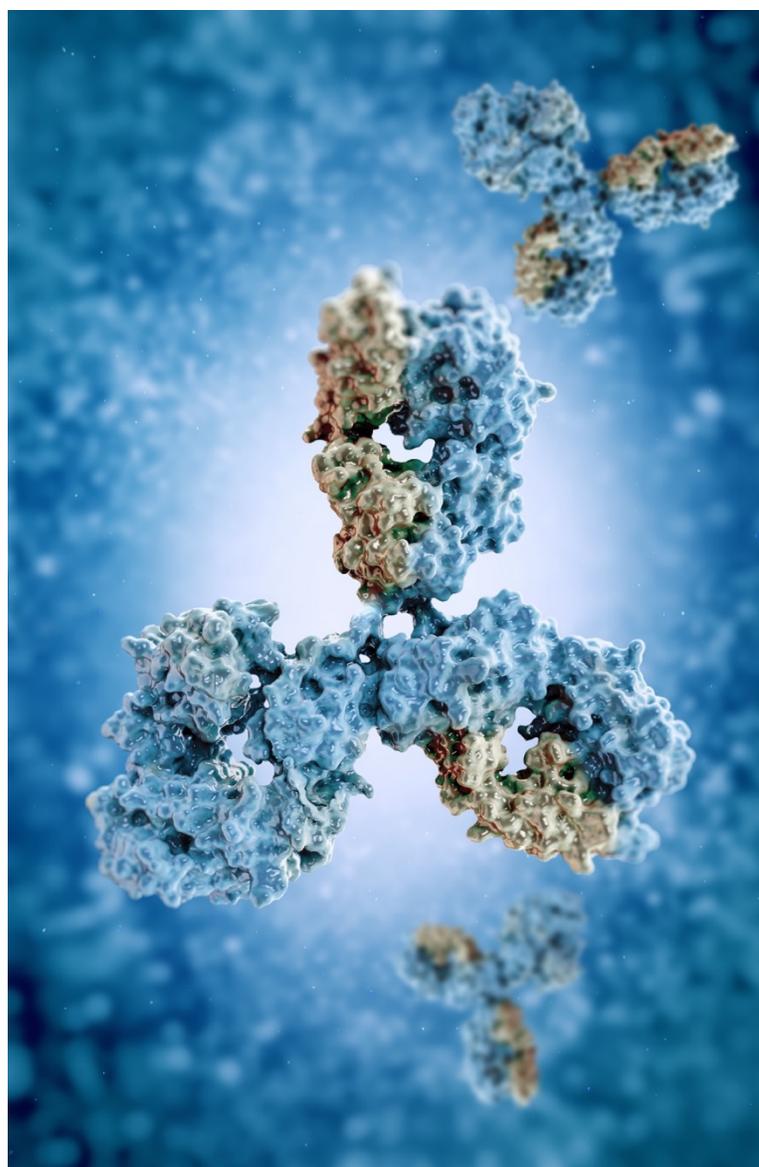
Ciuleanu Tudor, Prof.

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Approximately 14.8% to 21.8% of the patients with NSCLC initially present with locally advanced disease at diagnosis [1]. Patients with locally advanced disease make up a heterogeneous population with varying degrees of **tumor resectability** [2]. While the treatment goal for unresectable locally advanced NSCLC is cure, treatment options for patients with locally advanced NSCLC include radiation therapy (RT) and chemotherapy [2]. With a **multimodal treatment** approach, treatment planning for locally **advanced NSCLC** involves a **multidisciplinary team of specialists** [3]. Over the past 10 years, no clinical studies on patients with unresectable, locally advanced NSCLC have demonstrated a benefit in overall or progression-free survival from different treatments compared with standard chemotherapy and/or RT [4-7]. **Concurrent CRT** is the treatment of choice in patients evaluated as unresectable in stage IIIA and IIIB. If concurrent CRT is not possible—for any reason— sequential ChT followed by definitive RT represents a valid and effective alternative [3].

Consolidation therapy with Durvalumab following Concomitant chemoradiotherapy could significantly improve the outcome in patients with inoperable stage III NSCLC.

Currently, only 15-30% of patients are alive 5 years after chemoRT, and this aspect remains unchanged despite multiple phase III randomized trials integrating surgery, higher radiation dose or induction/consolidation with chemotherapy [4-7]. PACIFIC study demonstrated that consolidation immunotherapy with durvalumab following concomitant chemoradiotherapy could significantly improve the outcome in patients with inoperable stage III NSCLC [8,9].



Durvalumab significantly prolonged overall survival and PFS as compared with placebo in ITT population. The 24-month overall survival rate was 66.3% in the durvalumab group, as compared with 55.6% in the placebo group. Analysis of PFS at 24 months demonstrated a benefit of 17.2 months in the durvalumab group versus 5.6 months in the placebo group. The median time to death or distant metastasis was 28.3 months in the durvalumab group and 16.2 months in the placebo group [8,9].

NSCLC – IMMUNOTHERAPY

BRIEF INSIGHT INTO THE BENEFITS OF DURVALUMAB AFTER CHEMORADIOTHERAPY IN UNRESECTABLE, LOCALLY ADVANCED NSCLC

Ciuleanu Tudor, Prof.

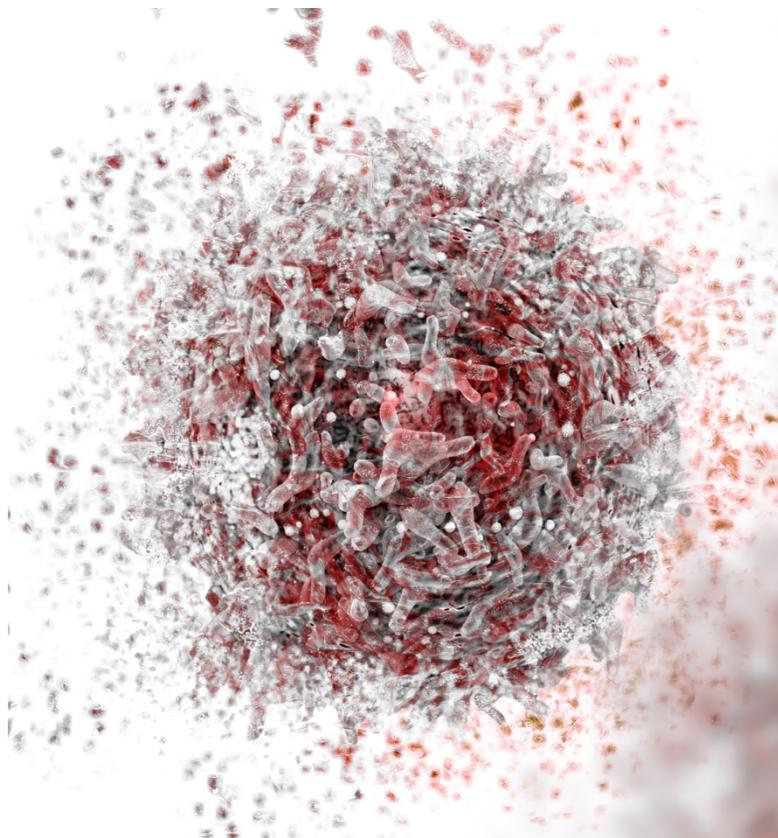
The Oncology Institute “Prof. Dr. Ion Chiricuta” , Cluj-Napoca, **ROMANIA**

Following these results, the FDA and regulatory agencies in Canada, Japan, Australia, Switzerland, Malaysia, Singapore, India have approved durvalumab as consolidation therapy after CRT in unselected unresectable stage III NSCLC. Based on unplanned, exploratory, post-hoc analysis (requested by EMA) in a small subset of patients, the European approval was limited only to patients with PD-L1 expressing tumors, (cut off for PD-L1 > 1%) [10,11]. Solange Peters from Oncology Department, Lausanne University and CHUV, Switzerland, said „Currently, EMA recommendations exclude patients with PD-L1 < 1% or unknown status, from access to durvalumab despite the fact that PD-L1 unknown subgroup demonstrated a strong survival benefit, consistent with that of the ITT population”.

A panel of international lung cancer experts wrote a Position paper after the approval decision for durvalumab in Europe; experts are „concerned that this decision will have a negative social impact creating unacceptable disparities across countries, with differential access to treatments”. In this context, we should wait for additional validation in the PD-L1 negative subgroup before drawing a definitive conclusion regarding these patients, and we, as a scientific community, are fully supportive of the need to identify appropriate **biomarkers** to individualize novel therapies for patients.

We strongly believe that in the near future we will add durvalumab to IO therapeutic armamentarium in Romania. Patients with non-targetable mutations already have several options for NSCLC metastatic disease: for the first-line treatment pembrolizumab (PD-L1 expression more than 50%) and for the second-line nivolumab (after progression on chemotherapy).

[References: Pg. 38](#)



NSCLC – STAGE III

RENAISSANCE OF STAGE III NON-SMALL CELL LUNG CANCER

Martina Vrankar, Prof.

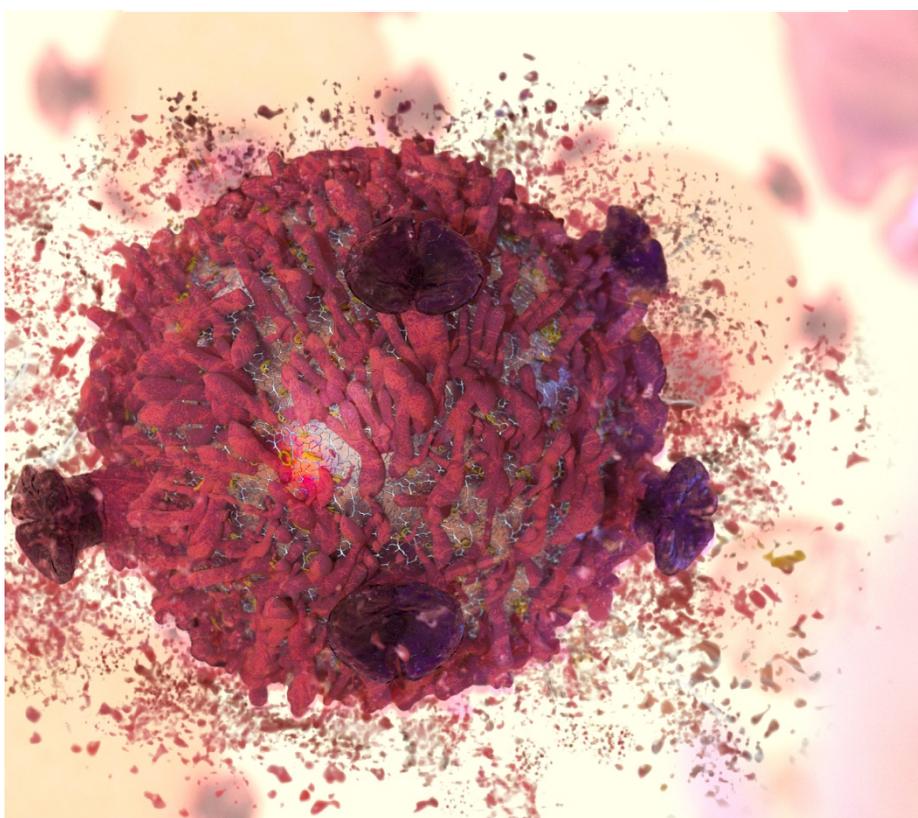
Institute of Oncology Ljubljana, SLOVENIA

Slovenia is a unique country. It lies at the heart of Europe and has a population of 2 million. Oncology in Slovenia has a long tradition. Last year, the Institute of Oncology Ljubljana, a principal national institution that supervises programs on the comprehensive management of cancer diseases, celebrated its 80th anniversary. An important part of the Institute of Oncology is Cancer Registry of the Republic of Slovenia (CRRS). It is one of the oldest population-based cancer registries in Europe. It was founded in 1950 and ever since it has been collecting data on cancer incidence and survival. Another important part of the Institute of Oncology is The Division of Radiotherapy, which is the leading radiotherapy center in Slovenia which also provides training for professional staff working in radiotherapy and has a teaching center status. In 2013 the Department of Radiotherapy was officially recognized by the International Atomic Energy Agency (IAEA) as a Centre of Competence in Radiotherapy.

As it is worldwide, lung cancer in Slovenia is also the leading cause of cancer-related death. With over 1400 new cases per year, it is the third most common cancer in males and fourth in females. 85% of all patients present with non-small cell lung cancer. The 5-year survival rate of patients diagnosed between 2011 and 2015 was 16.6%. In over 50% of the cases, patients have metastatic disease at diagnosis. Approximately 25% of all patients with lung cancer are currently treated by surgery. Locally advanced cancer patients in stage III represent almost one third of all patients with lung cancer, of which, approximately 70% have inoperable disease. Standard treatment for non-small cell lung cancer patients in stage III is **concurrent chemoradiotherapy**. Five-year overall survival rates of these subgroups are ranging between 15 and 25%. In Slovenia, according to our experience, patients with **inoperable NSCLC** in good performance status often receive 2 cycles of **platinum-based induction chemotherapy**, followed by **concomitant chemoradiotherapy**.

Inoperable locally advanced stage III NSCLC underwent a renaissance after the release of data from PACIFIC trial.

The cancer registry of the Republic of Slovenia is among the oldest population-based cancer registries in Europe



NSCLC – STAGE III

RENAISSANCE OF STAGE III NON-SMALL CELL LUNG CANCER

Martina Vrankar, Prof.

Institute of Oncology Ljubljana, SLOVENIA

This schedule is used based on a good result of the treatment in a study that was conducted in our center between 2005 and 2010. A total of 102 patients with **stage III NSCLC** were included and recently the data of long-term survival analysis have been published. The median OS of all patients was 24.8 months with a 10-year survival rate of 11.2%. 2- and 5-year survival rates were 52.0%, and 22.5%, respectively. Survival data are comparable even to reported data from studies with **trimodality treatment** that includes surgery, though far from satisfactory. Since throughout the duration of study only one **radiotherapy** center was active in Slovenia and all eligible patients were included, the present results represent the 10-year national survival data of treatment in locally advanced inoperable non-small cell lung cancer. **Inoperable locally advanced stage III non-small cell lung cancer (NSCLC)** underwent a renaissance after the release of data from PACIFIC trial. In this study, the consolidation therapy with new PD-L1 monoclonal antibody durvalumab provides 11-month improvement of PFS compared to placebo after definitive concurrent chemoradiotherapy in locally advanced inoperable non-small cell lung cancer.

This improvement was associated with a better both local and systemic control. PFS benefit resulted from a significantly higher local objective tumor response as well as from a significantly better systemic control with longer time to distant metastases and lower frequency of new lesions, including **brain metastases**. The benefit was observed irrespective of PD-L1 expression on tumor cells before treatment. Durvalumab significantly prolonged overall survival as well, as compared with placebo. After the median follow-up of 25.2 months, the 24-month overall survival rate was 66.3% in the durvalumab group, as compared with 55.6% in the placebo group. In Slovenia, we have had an opportunity to offer durvalumab to eligible patients since December 2017 in an Early Access Programme for durvalumab as monotherapy for the treatment of adults with locally advanced, unresectable non-small cell lung cancer whose disease has not progressed following platinum-based **chemoradiation therapy**. From January 2018 to date, 50 patients have been included in the program. Treatment has been well tolerated with no grade 3 or 4 toxicity so far. After decades of failures in endeavors to improve outcome of treatment in patients



CECOG CORNER

MULTIDISCIPLINARY REFRESHER COURSE ON THORACIC MALIGNANCIES | CECOG, Ljubljana, SLOVENIA on April 5-6, 2019

The Multidisciplinary Refresher Course on Thoracic Malignancies held in Brdo- Ljubljana, Slovenia on April 5-6, 2019 certified by CECOG Academy focused on lung cancer. A special emphasis was given to prognosis, diagnosis, staging, treatment and palliative care. This course was not only centered on the holistic understanding of thoracic malignancies but also on the current related trends as well as the strengths and limitations of frontline drugs and therapies. Visit our website (www.cecog.org) to read more about this course.



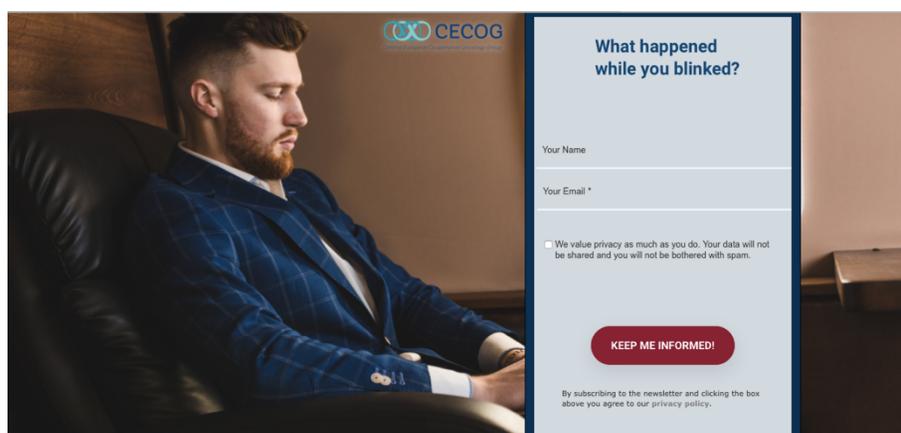
EDUCATIONAL COURSE ON LUNG CANCER | CEESO, Moscow, RUSSIA on May 24-25, 2019

Recently, CECOG Academy had the joy of being part of the Educational Course on Lung Cancer organized by the Central and East European School of Oncology (CEESO) in Moscow. From Epidemiology and Prevention to Immunotherapy of Lung Cancers, the Educational Course on Lung Cancer provided its participants with a unique opportunity to deepen the scientific understanding of lung cancer care.



NEW CECOG WEBSITE | CECOG NEWSLETTER | Multidisciplinary Course on Thoracic Malignancies Coming soon...

CECOG is turning 20! To celebrate this very special occasion CECOG is becoming more proactive and more social. 2019/2020 is a period of rebirth for CECOG. The Central European Cooperative Group is working on a new website and two newsletters. Both designed to facilitate communication, connected forms of learning and the dissemination of state-of-the-art knowledge in oncology care. For more information, please visit our website (www.cecog.org). CECOG is also preparing a new Multidisciplinary Course on Thoracic Malignancies for the first trimester of 2020. Visit our website or social media accounts to see what CECOG is doing in real-time.



CECOG ACADEMY
Multidisciplinary Refresher Course on Thoracic Malignancies

Yes, we did it again. CECOG held another two-day intensive course on Thoracic Malignancies. From investigational-driven therapies to supportive and palliative care, from diagnosis to treatment and prognosis, from multidisciplinary care to radiologic and imaging procedures, the Multidisciplinary...

[Sign up and learn more](#)



GOIA
What to expect in the next GOIA Meeting?

CECOG is leading lively discussions focused on the amelioration of access to cancer care in CEE and Southeastern Europe. Practical actions, deeper engagement and regulatory changes are required at a regional, national and international level. You can expect two more meetings this year. The first...

[Sign up and learn more](#)

CECOG CEE THORACIC NEWSLETTER

CECOG CORNER

THE DYNAMIC STORY OF LUNG CANCER TREATMENT AT THE 2018 EDITION OF CECOG CEE LUNG CANCER ACADEMY



Worldwide and in the Central and Southeastern Europe in particular, lung cancer is leading as prevalence and cause of death. This has triggered treatment advances from **chemotherapy** to **precision medicine**, through development of important compounds based on the molecular and immunologic characteristics of the various malignancies encompassed in the entity of Non- Small Cell Lung Cancer (NSCLC).

Thus, CECOG became rapidly aware of the importance of establishing a Lung Cancer Academy aiming to build a strong network of experts – clinicians, researchers, pathologists, and genetics specialists – from Central and Eastern European (CEE) countries to facilitate knowledge exchange and best practice sharing, in order to maximize the clinical benefits of the latest advances in the oncology field.

The first **CEE Lung Cancer Academy Conference** was held by CECOG on November 2-3, 2017, in Vienna, and it proved to be a successful and fruitful starting experience. Consequently, on November 16-17, 2018, CECOG hosted the 2nd edition of the CEE Lung Cancer Academy Conference under the coordination of **Prof. Christoph Zielinski**. This event gathered 86 participants from 11 countries and 22 invited speakers who discussed a broad spectrum of topics, presenting the newest scientific achievements in the field of NSCLC as well as focusing on the needs and obstacles in the diagnosis and treatment of NSCLC in our geographic area. The 2018 edition of the Lung Cancer Academy Conference brought together a large number of experts from Austria, Czech Republic, Croatia, Hungary, Poland, Romania, Slovakia, and Slovenia. Oncologists, surgeons, genetics specialists and pathologists had the opportunity to capitalize on ideas and experience of oncology centers from CEE.

The event covered a wide range of topics related to diagnosis, local treatment and systemic treatment in the advanced stages of lung cancer, **state-of-the-art NSCLC treatments**, and **access to innovative medicines in CEE countries**.

Despite differences between national health systems and heterogeneity of access patterns to the most recent therapeutic solutions, the participants provided specific examples and valuable updated information about progress in promoting the use of new medications with important clinical benefits on survival and quality of life, as well as administrative barriers and concerns in their clinical practice. Moreover, detailed discussions were held on updated recommendations of international guidelines, changes in TNM classification and the impact on the management of lung cancer, new technologies for **histologic** and **genetic diagnosis, immunophenotyping, surgical approaches** and progress in **chemo-radiation therapy**, as well as results of CECOG surveys with regard to **access to molecular testing, targeted therapy** and **immune oncology** in CEE countries.

The theoretical discussions were accompanied by case studies presented by young specialists from Poland, Slovenia and Slovakia. The 2nd edition of the CEE Lung Cancer Academy was once again a very good opportunity for scientific information and project idea sharing, as well as a strong proof of how CECOG Lung Cancer Academy grows into a very structured and well-defined project every year.



CECOG CEE THORACIC NEWSLETTER

INTERVIEW Biopsy Center SLOVAKIA

PROFESSOR LUKAS PLANK INTERVIEWED
BY PETER BERZINEC, Prof.

Professor, could you tell us a few words about
Martin's Biopsy Center?

Martins Biopsy Center was established in 2003 as a biopsy laboratory offering patients in Slovakia its expertise focused mainly on the diagnosis of oncological and hematological disorders. Due to the increasing importance of the analyses of these tumors for evaluation of prognostic and predictive factors, we have implemented new **immunohistochemical tests** and **molecular pathology analyses** in our routine practice - both the in-situ hybridization tests and the based PCR analyses on the isolation of the tumors DNA. The next step, as a reflection of the demands of the cooperating oncologists, was to also apply in our practice the analyses of the circulating tumor-free DNA isolated from patients' plasma, especially the NSCLC and colorectal

How many samples of lung cancer did you analyze in the year 2018?

Altogether, in 2018 we examined the biopsy and cytology specimen of 486 NSCLC patients, the same is true for 58 plasma samples from these patients.

The main advantage of the beaming PCR is its very high sensitivity at the level of 0.01% of DNA molecules.

Which biomarkers are you testing in lung cancer patients for the common clinical purposes?

For the biopsies of NSCLC patients with adenocarcinoma type and/or carcinoma with adenocarcinomatous component we use a reflex approach to look for EGFR gene mutations. If the result is negative, we continue with both parallel IHC and FISH tests to look for ALK and ROS1 gene rearrangement, respectively. All these cases and the biopsies of the patients with **squamous cell carcinoma** are tested by reflex approach also for the PD-L1 expression using 22C3 and/or SP-142 antibody .

The **molecular genetic testing** of the biopsies of squamous cell carcinoma patients are performed only at the oncologists request and the same is true for tests of NSCLC specimen for the MET and HER2 gene alterations. In addition, the liquid biopsies of the NSCLC patients are analyzed for all clinically relevant EGFR mutations.

Why did you decide for the "beaming" PCR - i.e. what advantage do you see using this method?

In addition to already implemented tests using the cobas. 4800 platform and related assays we have looked for more sensitive methodology. We are all very proud that we could not only accept the offer of Sysmex Inostic comp. to use the OncoBeam™ platform, as the 1st laboratory in the Central and Eastern Europe, but also fulfill all the necessary criteria for implementation of cftDNA analyses of both NSCLC and CRC patients. Although the OncoBEAM™ technology represents a very challenging method, the main advantage of the method is its very high sensitivity at the level of 0.01% of DNA molecules. In addition, it also allows a very precise quantification of mutant tumor DNA molecules for patients' follow-up and evaluation of patients therapy response in time.

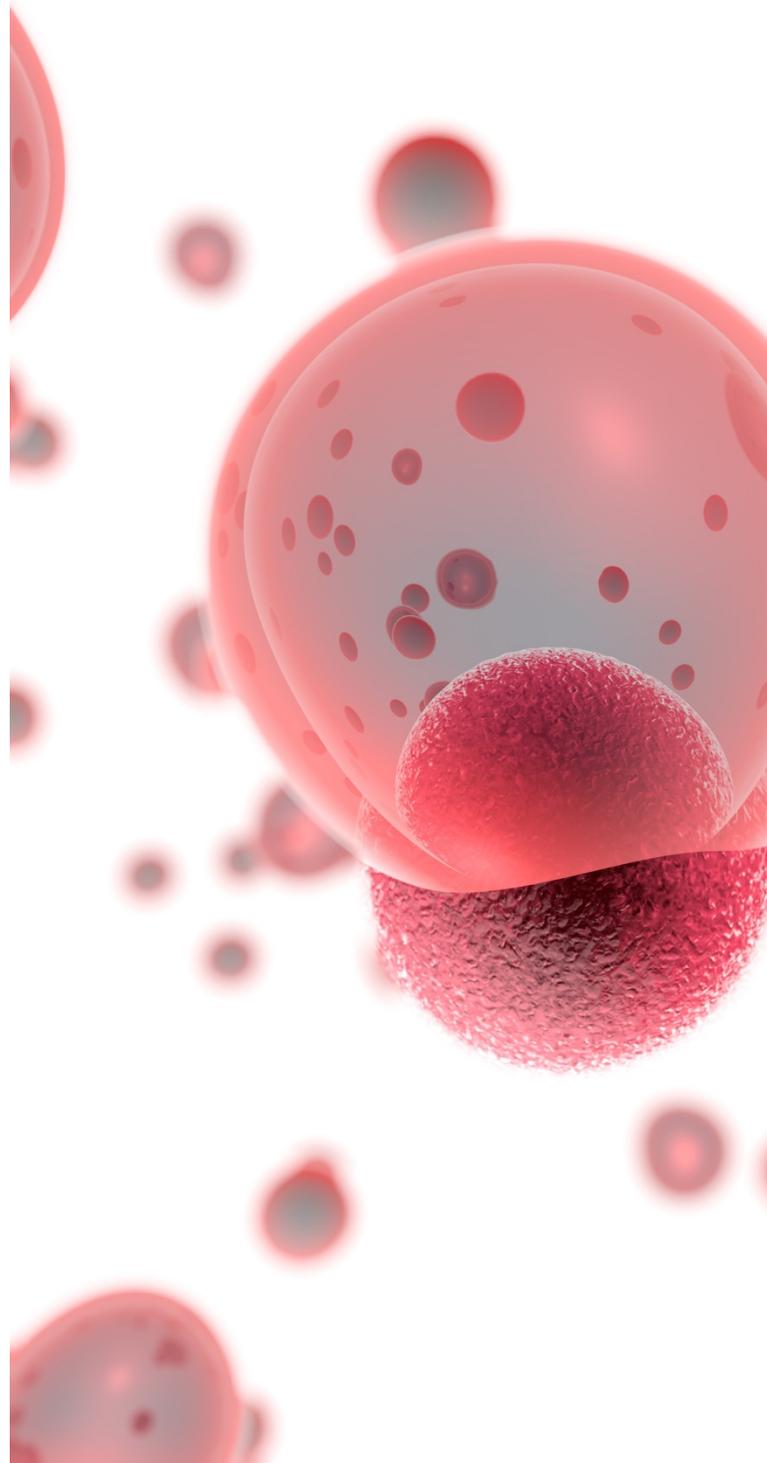
INTERVIEW
Biopsy Center
SLOVAKIA

Could you comment on the sensitivity of the digital PCR for the detection of T790M mutations in patients with metastatic NSCLC pretreated with the first or second generation EGFR-TKI? What is your experience?

It might be premature to answer very strictly. We are now running the first clinical studies, comparing the 1st analyses using cobas EGFR Mutation Test v2 with those of the 2nd analyses using OncoBEAM™ EGFR kit v2, as well as with the clinical data. Although both assays cover a very broad spectrum of clinically relevant both sensitizing and **resistant EGFR mutations**, the coverage of the mutations is not completely identical. We already showed the first preliminary data in 2018 and will be glad to refer the more complex data at the traditional autumn meeting of the Slovak pneumo-oncologists, and then at some of the European congresses.

Are there any other comments you would like to make for our readers?

Thank you for the possibility to present our work in this new **CECOG newsletter**. What I would like to add, that we are now in the transition from the described approaches to the implementation of NGS methodology for both tissue and liquid biopsies, allowing the analysis of a broad spectrum of genetic alterations and the MSI and TMB parameters as well.



CECOG CEE THORACIC NEWSLETTER

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