

# ORAL PRESENTATIONS



## S1 - THE POWER OF PATHOLOGY - INFLUENCE OF MUTATIONAL STATUS IN NSCLC ON ONCOLOGICAL TREATMENT

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The identification of numerous gene alterations in the past decade had a major impact on the treatment of Non Small Cell Lung Cancer (NSCLC). These driver mutations lead to specific biochemical pathways, which further promote growth and survival of cancer cells. There are several important mutations which represent well established targets in the treatment of NSCLC. The first discovered drug-sensitive mutation in NSCLC was Epidermal Growth Factor Receptor (EGFR). The inhibition of EGFR has led the way for targeted therapy in the treatment of NSCLC. Erlotinib, the first anti-EGFR antibody was first approved in 2004. At first, the approval was referred to unselected patients after failure of chemotherapy, but was later proven to be superior in comparison with chemotherapy as first-line treatment of metastatic NSCLC with sensitizing EGFR mutations. Today, there are a variety of other anti-EGFR antibodies, such as gefitinib, afatinib, osimertinib or dacomitinib. The analyzes of phase 3 randomized trial FLAURA, showed superiority of osimertinib in first-line therapy with osimertinib in metastatic NSCLC with EGFR mutations regardless of T790M status. Another driver mutation, found in approximately 5% of patients with NSCLC is ALK gene rearrangement, also known as ALK fusion. This mutation is not routinely found in patients with squamous cell carcinoma, and therefore it is recommended to test for ALK fusions in patients with metastatic non-squamous NSCLC, based on the data showing efficacy of different kinase inhibitors, such as alectinib, brigatinib, ceritinib and crizotinib. ROS1 gene rearrangements (also known as ROS1 fusions) occur in about 1% to 2% of patients with NSCLC. There are different fusion partners that can be detected in NSCLC: CD74, SLC34A2, CCDC6 and FIG. The benefit of crizotinib, ceritinib and entrectinib for patients with ROS1 fusions was shown in different trials. Additionally, there are other gene alterations, such as BRAF V600E mutation. These patients have a significant benefit in the treatment with combination of BRAF and MEK inhibitors dabrafenib and trametinib. Detection of RET rearrangements is predictive for the treatment with TKIs selpercatinib and pralsetinib. Furthermore, NTRK, METex14, KRAS mutations are proven to be very efficacious molecular biomarkers in the treatment of NSCLC. Testing for the expression of immune biomarker PD-L1 is crucial predictive biomarker for the treatment with immune checkpoint inhibitors. IHC testing for PD-L1 expression should be performed before first-line treatment in all patients with metastatic NSCLC. There are different checkpoint inhibitors (pembrolizumab, atezolizumab, nivolumab, ipilimumab, cemiplimab), which showed efficacy alone or in combination with other treatment regimens. Testing of lung cancer specimens for these alterations is important for identification of potentially efficacious targeted therapies, as well as avoidance of therapies unlikely to provide clinical benefit. With the invention of targeted therapies and antibodies directed against tyrosine kinases and other specific driver mutations, the treatment options in lung cancer changed from histology-based to molecular and biomarker-based treatment. These changes in the treatment of NSCLC put in spotlight the significance of the cooperation between oncology and pathology.

**Keywords:** NSCLC, biomarkers, driver mutations

## S2 - RADIOTHERAPY OF CNS METASTASES IN HER2 POSITIVE AND TRIPLE NEGATIVE DISEASE

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Brain metastases occur in about 30- 50% of patients with HER2 positive and 40% of patients with triple negative breast cancer. Occurrence of CNS metastases is a marker of aggressive disease. Median overall survival of patients with brain metastases is 13 – 19 months in patients with HER2 positive disease and 4.4 months in patients with triple negative disease. Regarding radiotherapy, breast cancer brain metastases are treated the same as metastases from all other tumor sites. When setting up an indication for local treatment, crucial is to have information about the control of extracranial disease, possibility of further systemic therapy lines and patient's performance status. Local therapy consists of surgical treatment, with or without consolidation stereotactic radiotherapy and radiotherapy as a sole modality. Preferred method of radiotherapy would be stereotactic radiotherapy (SRT), in patients with up to 10-15 metastases, limiting factor being the volume of the disease (up to 15 mL). With STR local control can be achieved in up to 60% of patients. Fractionated stereotactic radiotherapy (FSRT), delivered in 3 to 12 fractions provides 1- year local control rate in up to 80% of patients. In case stereotactic radiotherapy is not available or possible, patients with good performance status and extracranial disease control could be referred to whole brain radiotherapy (WBRT), which palliates symptoms in about 60% of patients. Both stereotactic and whole brain radiotherapy are connected with cognitive impairment, which is more often after WBRT. WBRT induced cognitive toxicity can be lowered by using hippocampal sparing radiation techniques. WBRT after SRT or neurosurgical procedure improves local control but has no effect on overall survival and can also lead to cognitive impairment. Therefore, WBRT is not indicated after these procedures. Upon neurosurgical operation, SRT of resection cavity should be performed, as it lowers the risk if intracranial relapse of the disease. There are several ongoing trials exploring different radiotherapy techniques (SRT or WBRT), and their timing and combination with various systemic agents in breast cancer patients with brain metastases, such as lapatinib, trastuzumab emtansine, pembrolizumab. In patients with low performance status, loss of extracranial disease control and short life expectancy, it would be reasonable to omit whole brain radiotherapy since it has no effect on survival or quality of life and the same palliative effect can be achieved with corticosteroids use only.

**Keywords:** CNS metastases, HER2 positive breast cancer, triple negative breast cancer, radiotherapy, SRT, WBRT, FSRT

### **S3 - THE ROLE OF IMMUNOTHERAPY IN METASTATIC COLORECTAL CANCER TREATMENT - IS THERE A ROOM FOR IMPROVEMENT?**

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Immunotherapy has evolved recently as very promising and possibly effective treatment of several tumor types. Immunotherapy has dramatically changed treatment landscape of some entities, but benefit in colorectal cancer was so far very modest due to fact that only up to 5% of patients with mCRC have high microsatellite instability and mismatch-repair deficient genes. These features are considered as biologic markers for tumors which we expect to respond to immunotherapy. According to data obtained from early clinical studies (phase II) and last year presented phase III study, KEYNOTE-177, led to FDA-approval of pembrolizumab in first line treatment of metastatic colorectal cancer in June 2020. KEYNOTE-177 was a randomized, open-label study enrolling 307 treatment-naive patients with microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) mCRC. Randomization was 1:1 to treatment with pembrolizumab or investigator's choice of doublet chemotherapy (n=154) meaning standard of care. Dual primary endpoint were PFS and OS, and crossover was permitted at disease progression. This is very important trial, since it was the first randomized- trial evaluating first-line pembrolizumab in patients with metastatic colorectal cancer. This was especially critical for Europe, because pembrolizumab was not approved. It is worth to mention that about 25% of patients had BRAF V600E-mutant tumor sin the trial. Median PFS2 was not reached in the pembrolizumab group and was 23.5 months in the chemotherapy group (HR:0.63)(ASCO GI 2021). The 12-month rate was PFS2 76% for pembrolizumab and 67% for chemotherapy. The same tendency was at 24-month PFS2. The rate of adverse events (AEs) and treatment-related AEs was similar in both treatment arms. Grade  $\geq 3$  treatment-related AEs were much more common in the chemotherapy group, affecting 66% of the patients compared with 22% of the patients receiving pembrolizumab. Grade  $\geq 3$  diarrhea, fatigue, and neutropenia also were significantly higher in the chemotherapy group. These results were expected, as pembrolizumab is generally well-tolerated. Generally, quality of life did not decrease in pembrolizumab group (QoL scores), and pain and appetite loss also improved with pembrolizum vs chemotherapy. So, there was a clear benefit in both PFS and QoL for the use of pembrolizumab over chemotherapy. The rate of adverse events (AEs) and treatment-related AEs was similar in both treatment arms. Grade  $\geq 3$  treatment-related AEs were much more common in the chemotherapy group, affecting 66% of the patients compared with 22% of the patients receiving pembrolizumab. Grade  $\geq 3$  diarrhea, fatigue, and neutropenia also were significantly higher in the chemotherapy group. These results were expected, as pembrolizumab is generally well-tolerated. Although this results put immunotherapy as very attractive treatment modality, there are many questions still to be answered in the future. We still don't know the relationship between KRAS-mutant phenotype and immunotherapy, as well as the meaning of other biomarkers. After all, some patients do not respond to immunotherapy, so in the near future we should define which patients would be optimal for immunotherapy in first line setting and which would benefit from chemotherapy, nevertheless.

**Keywords:** immunotherapy, pembrolizumab, colorectal cancer, chemotherapy

## S4 - THE BEST APPROACH TO SYSTEMIC THERAPY IN FIRST LINE TREATMENT OF ADVANCED/METASTATIC HCC

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**Background:** Hepatocellular carcinoma is fourth leading cause of death among cancer patients. This cancer is four to eight times more common in the male population and is usually associated with chronic liver damage (hepatitis B (HBV), hepatitis C (HCV) and alcoholic cirrhosis). Cirrhosis, regardless of the cause, is present in 70-80% of HCC cases. Chronic infection with HBV and cirrhosis increases the possibility of HCC up to 100 times. 5-30% of patients with HCV infection develop chronic liver disease, > 30% progress to cirrhosis, and in that population, 1-2% of them develop HCC annually. Co-infection with HBV further increases the risk of developing the disease. Other risk factors are: alcohol abuse, autoimmune diseases (autoimmune hepatitis and primary biliary cirrhosis), metabolic diseases (diabetes mellitus, hemochromatosis, non-alcoholic steatohepatitis...) and environmental toxins (alpha-toxins, alcohol, tobacco). According to currently available epidemiological data, HCC still kills about 1,000,000 people a year, and the 5-year OS is less than 5%.

**Current treatment of HCC:** Historically, in the last few decades, systemic HCC therapy has relied on classical chemotherapy, which unfortunately has not been shown to be effective in the treatment of advanced or metastatic hepatocellular carcinoma. We see the first big leap in treatment in 2007 with the introduction of Sorafenib into clinical practice. Sorafenib, a TKI inhibitor, demonstrated in the SHARP study has been shown to have better OS and PFS for 3 months compared to the placebo group. Until 2017, Sorafenib was the only treatment option for HCC - numerous clinical studies with EGFR and VEGFR, TKI inhibitors gave negative results (BRIK FL, LIGHT and SEARCH studies). Since 2017, the revolution in the treatment of this disease has continued, with the fact that in a short period of time we suddenly have more than 10 drugs that have FDA and EMA approval for the treatment of HCC in the first and second line. The first drug to show non-inferiority to Sorafenib in the REFLECT study was Lenvatinib, thus finding its place as another option in first-line HCC treatment. At the same time, several targeted drugs show their efficacy in the second line of HCC treatment - Regorafenib (RESORCE study), Cabozantinib (CELESTIAL Study) and Remocirumab. The concept of monoimmunotherapy, after promising results from phase 2 studies - Pembrolizumab and Nivolumab, has unfortunately not been confirmed in phase 3 studies, and the concept of monoimmunotherapy is not recommended. Given the studies presented at ASCO GI (IMBRAVE150), the future of HCC treatment is most likely to be found in combinations of immunotherapy + target therapy, as well as combinations of CTLA4 inhibitors and immunotherapy. IMBRAVE150 is a study that established the combination of atezolizumab + bevacizumab as first-line therapy. The study alone included 150 patients, randomized 2: 1, and the primary goal of the study was OS and PFS. The median PFS for the combination was 6.8 months, compared with 4.3 months in the Sorafenib group. The side effects shown in the atezolizumab and bevacizumab groups corresponded to the safety profiles of drugs known from before, and 15% of patients discontinued therapy due to side effects. In contrast, 10% of patients discontinued Sorafenib therapy due to side effects. Combination therapy also resulted in a longer time to deterioration in quality of life than in patients on Sorafenib. A couple of phase two studies examining the efficacy of combinations of VEGFR inhibitors + Pembrolizumab, and a combination of CTLA4 inhibitors and immunotherapy showed promising results. The results of a phase III study of LEAP-002 - efficacy and safety of the combination of Lenvatinib and Pembrolizumab, in first-line therapy of advanced / metastatic

HCC, are currently expected. The primary objectives of the study are OS and PFS. Interesting results are also expected in the HIMALAYA phase 3 study, where the efficacy and safety of durvalumab + tremelimumab and durvalumab monotherapy are evaluated compared to sorafenib in the treatment of naive patients with unresectable HCC. The study was randomized into four groups, but it will be interesting to follow the results between the two combination groups Durvalumab + Tremelimumab, given the choice of drug dose. The COSMIC-312 study compares the efficacy of Cabozatinib + atezolizumab versus Sorafenib in first-line therapy. The CheckMATE-040 study investigated the efficacy and safety of Nivolumab, alone or in combination with immunotherapy, in patients with concomitant comorbidities.

**Conclusion:** After a long time, in the treatment of HCC in addition to chemotherapy, we have made progress in the form of targeted therapy and immunotherapy, as well as combinations of the same that are currently being investigated. In the end, the question remains how to further sequence HCC therapy? This is a question to which there is no clear answer right now, given that we have not recently had an option for a second line of therapy and now we already have over 10 approved drugs. Proper sequencing of therapy lines would greatly facilitate the treatment of patients with HCC, taking into account that patients with HCC are usually in a severe general condition, burdened with primary disease and concomitant comorbidities. Numerous clinical studies that are underway will most likely better clarify these dilemmas and thus enable better sequencing of the therapy itself.

**Keywords:** hepatocellular carcinoma - HCC, advanced, metastatic, non-resectable, sorafenib, atezolizumab, bevacizumab

## S5 - PARP INHIBITORS IN THE TREATMENT OF TRIPLE NEGATIVE BREAST CANCER

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Triple negative breast cancer (TNBC) accounts for approximately 10-15% of all breast cancers and it is associated with a poor prognosis. TNBC are characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression, therefore chemotherapy has long time been the only treatment option. This has changed in the last few years. Molecular targets and target therapy were identified, namely immunotherapy with the immune checkpoint inhibitor atezolizumab in PD-L1 positive tumors and, the oral inhibitor of poly (adenosine diphosphate-ribose) polymerase (PARP) directed against mutated BRCA genes. Approximately 5 % of all breast cancer patients are BRCA mutation carriers, and among them, more than half have the clinical TNBC subtype, showing a high association between germline (g) BRCA mutations and TNBCs. BRCA1 mutation carriers mainly develop TNBCs, whereas BRCA2 carriers are more likely to develop ER and/or PR positive tumors. For patients with advanced breast cancer (ABC) who carry gBRCA mutation PARP inhibitors has shown activity in several clinical trials. OlympiAD and EMBRACA were the pivotal phase III trials leading to the single-agent approvals of olaparib and talazoparib in gBRCA-mutated, HER2- negative ABC, previously treated with anthracyclines and taxanes. The OlympiAD randomly assigned 302 patients to receive olaparib (300 mg bid) or standard therapy of the physician's choice. Median progression-free (PFS) was significantly longer in the olaparib group than in the standard therapy group (7.0 months vs. 4.2. months). Overall survival (OS) did not differ between the two treatment groups. The subset analysis suggested that PFS improvement with olaparib appeared greater in the TNBC subgroup. The EMBRACA trial randomly assigned 431 patients to talazoparib (1 mg PO qd) or standard single-agent chemotherapy of the physician's choice. Median PFS was significantly longer in the talazoparib group than in the standard therapy group (8.6 months vs. 5.6 months). Median OS did not differ between the two groups. The phase III BROCADE3 trial evaluated carboplatin and paclitaxel, with or without the PARP inhibitor veliparib. Results showed not only improvement in PFS with the addition of veliparib (median: 14.5 months). Recently published Cochrane systematic review confirmed that PARP inhibitors offer a PFS advantage and there might be a small advantage in OS for patients with HER2-negative, gBRCA mutated ABC. Given PARP inhibitors did not have significantly increased toxicity and two studies that did look at quality of life outcomes showed an improvement. Based on these results ABC 5 guidelines included single-agent PARP inhibitor (olaparib or talazoparib) for patients with a gBRCA mutation as preferred treatment option for those with triple-negative ABC and one of treatment options in HR-positive, HER2-negative ABC. PARP inhibitors are currently being investigated in early BC, in novel combinations, and in patients without germline BRCA mutations, including those with somatic BRCA mutations and other DNA homologous recombination mutations. Ongoing phase 2/3 studies include PARP inhibitors combined with immune checkpoint inhibitors for the treatment of triple-negative BC.

**Keywords:** triple negative breast cancer, germline BRCA mutation, PARP inhibitors

## S6 - ALK /ROS1 AND BEYOND: NOVEL MOLECULARLY DRIVEN TARGETED THERAPIES IN WITH NON-SMALL CELL LUNG CANCER (NSCLC)

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With the advent of genomic medicine, in NSCLC personalized oncology has helped improve treatment outcomes and quality of life compared to traditional chemotherapy. Advances in the knowledge of pathways, technologies for detecting actionable genetic lesions, and newly developed drugs to block the activities of the pathways in recent years have allowed the physicians to tailor the treatment options. In lung adenocarcinoma, a number of targetable major pathways have been identified, such as ALK, ROS 1, MET, RAS–MAPK, and NTRK pathways. The discovery of the EML4-ALK fusion gene in a limited subset of patients affected by NSCLC and the subsequent clinical development of crizotinib in 2011 has been an impressive milestone in lung cancer research. Rearrangements in anaplastic lymphoma kinase (*ALK*) account for 3–7% of all non-small cell lung cancers (NSCLC). Modern tyrosine kinase inhibitors (TKIs), such as ceritinib, alectinib, brigatinib, and lorlatinib, have been approved for the management of anaplastic lymphoma kinase (*ALK*)-positive NSCLCs. Treatment with targeted tyrosine kinase inhibitors (TKIs) has shown impressive clinical responses. Treatment sequencing today is crucial in this patient population due to fact that these patients are living much longer with good quality of life. ROS1-rearranged NSCLC is classified as a distinct molecular subset of NSCLC with a therapeutic target. ROS1 rearrangement is most often identified in never-smokers with adenocarcinoma and EGFR and ALK receptor tyrosine kinase gene (*ALK*) wild type. ROS1 rearrangements occur in approximately 1-2% of patients with NSCLC. ROS1-positive lung cancer tends to be more aggressive form of disease. Treatment with tyrosine kinase inhibitors (TKIs), which target the ROS1 kinase domain, is considered the standard of care. TKIs have been shown to have a robust and durable response. BRAF mutations, considered as alternative oncogenic drivers in NSCLC, lead to constitutive activation of cell signaling pathways downstream of MAP kinase, are generally mutually exclusive compared to EGFR mutations and ALK and ROS1 rearrangements and, in contrast to these, are more frequent in smokers. 30% of NSCLC patients. BRAF V600E positive show a benefit if treated with a BRAF inhibitor such as vemurafenib or dabrafenib. Data also reveal that combined therapy with BRAF and MEK inhibitors, specifically dabrafenib and trametinib, doubling response rate (66.7% in previously treated patients, 64% in untreated patients) and improved disease-free survival. Gene rearrangements involving *NTRK1/2/3* can generate fusion oncoproteins containing the kinase domains of TRKA/B/C, respectively. These fusions are rare in non-small cell lung cancer (NSCLC), with frequency previously estimated to be less 1%. Inhibition of TRK signaling has led to dramatic responses across tumor types with *NTRK* fusions. *RET* fusions are oncogenic drivers in 1 to 2% of non–small-cell lung cancers (NSCLCs). In patients with *RET* fusion–positive NSCLC, the efficacy and safety of selective RET inhibition are promising. Selpercatinib and pralsetinib have durable efficacy, including intracranial activity, with mainly low-grade toxic effects in patients with *RET* fusion–positive NSCLC. Abnormalities in the MET gene have been shown to be one of key drivers in the development and growth of non-small cell lung cancer (NSCLC). These MET abnormalities frequently occur as exon-14 skipping mutations, in which the MET transcript lacks exon 14. These MET exon-14-skipping mutations (METex14) are found in approximately 3%-4 % of NSCLC patients. Capmatinib is a drug for the treatment of patients with metastatic NSCLC who are also positive for METex14. In a key clinical trial, capmatinib showed a promising overall

response rate among patients: 68%, when used as the initial treatment, and 41% when used in second- and third-line settings. In addition, capmatinib is relatively well tolerated by patients. Because NSCLC has been known to metastasize to the central nervous system, it is also important to note that capmatinib can penetrate into the central nervous system. Taken together, these results suggest that capmatinib and some other agents could be a good treatment option to consider for NSCLC patients who are positive for METex14 mutations. Nevertheless, while target therapy in NSCLC has provided disease control, the tumors inevitably develop drug resistance. Understanding resistance mechanisms and developing combi-national therapies are essential for improving the treatment outcomes.

**Keywords:** non small cell lung cancer – NSCLC, ALK, ROS 1, MET, RAS-MAPK, NTRAK, target therapy.

## **S7 - OPTIMAL SEQUENCE IN HER-2 POSITIVE METASTATIC BREAST CANCER**

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Breast cancer is the most commonly diagnosed cancer in female population worldwide. Advances in understanding tumor biology, particularly signalling pathways, have led to the development and approval of novel therapeutic agents, especially in HER2-positive and hormone receptor positive subtypes. For the decades ago there were no improvement in overall survival of patients with metastatic disease till improvement in the prognosis of HER2-positive metastatic breast cancer (MBC). It has radically changed in the recent years mainly due to broad application of targeted therapies designed to block HER2 signalling pathway like monoclonal antibodies and small molecules tyrosine kinase inhibitors. HER2 signalling pathway is an ideal target due to persistent dependency of tumor cells on this oncogene and low expression in healthy tissues. Precise delivery of cytotoxic drugs via HER2 receptor has been recently developed. The first improvement was shown in a phase 3 trial by adding trastuzumab to first line taxane chemotherapy compared to chemotherapy alone, with almost 5 months improvement in the median overall survival (OS). Further improvement was reached in CLEOPATRA Phase 3 trial with addition of pertuzumab to trastuzumab and chemotherapy in first-line treatment of metastatic disease, with almost 16 months in median OS improvement. Pertuzumab, humanized monoclonal antibody, targets different epitope of the HER2 receptor extracellular domene thus preventing hetero dimerization of HER2 with other HER receptors. Dual anti HER2 antibody blockade also stimulates antibody-dependent, cell- mediated cytotoxicity (ADCC). In the later lines of treatment there were also some improvements, particularly by using antibody-drug conjugates and small molecules tyrosine kinase inhibitors. T-DM1 represents the first antibody–drug conjugate (ADC) approved for the treatment of MBC. ADCs are drugs consisting of a monoclonal antibody covalently bound to a cytotoxic drug with synthetic linker. ADCs combine the advantages of specific targeting through the monoclonal antibody directed against HER2 receptor and high cytotoxicity by the precise delivery of chemotherapeutic drug. The phase 3 registration trials, EMILIA and THERESA, comparing T-DM1 with capecitabine plus lapatinib and with treatment according to physician’s choice, respectively, established T-DM1 as today’s standard of care for second-line treatment of HER2-positive MBC and early progressor during adjuvant therapy also. Neratinib is an orally available irreversible pan-HER TKI, targeting HER1, HER2 and HER4. The NALA phase 3 trial compared neratinib plus capecitabine with lapatinib plus capecitabine in patients with HER2-positive MBC, who have received at least two prior anti-HER2-based regimens. Progression or death was reduced by 24% in the neratinib-arm compared to the lapatinib-arm with a prolongation of PFS by 2.2 months. Based on these results, the FDA approved neratinib in combination with capecitabine for patients with advanced HER2-positive breast cancer who have received at least 2 prior anti-HER2-based regimens in the metastatic setting. Recently, the US Food and Drug Administration (FDA) approved new drugs for the treatment of HER2-positive MBC: the antibody–drug conjugate (ADC) trastuzumab deruxtecan (proven in the phase 2 study DESTINY- Breast 01) and tucatinib tested in the HER2CLIMB trial. Tucatinib is a third generation, orally available, highly selective inhibitor of the HER2 tyrosine kinase. In the HER2CLIMB phase II trial all patients had received prior treatment with trastuzumab, pertuzumab and T-DM1. Patients with brain metastases were included also. After failure of these two drugs, the new TKI tucatinib in combination with

capecitabine has prolonged PFS and OS and has achieved objective response in 40% of patients, with significant intracranial responses and a survival advantage in patients with brain metastases. In addition, new ADC trastuzumab deruxtecan has shown impressive response rates and long-lasting remissions in heavily pre-treated patients with a median of six previous treatment lines. Such rapid developments give us hope in further improvements of overall survival in metastatic breast cancer patients with HER2 positive subtype, but also complicate optimal therapy sequencing. Encouraged with these recent advances breast cancer specialists are looking forward to new upcoming options in the treatment of metastatic HER2 positive breast cancer, like CDK 4/6 inhibitor and immunotherapeutic combination options.

**Keywords:** metastatic breast cancer, HER2 positive, monoclonal antibodies, trastuzumab, pertuzumab trastuzumab deruxtecan, neratinib, tucatinib, lapatinib

## **S8 - AN UNMET NEED IN BRAF MUTANT METASTATIC MELANOMA: TREATMENT SEQUENCING AND LEPTOMENINGEAL DISEASE**

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In BRAF-mutant metastatic melanoma, there is a choice of first-line treatment with BRAFi+MEKi targeted therapy, immunotherapy (mono, or combination), and recently, in US with triple combination of vemurafenib+cobimetinib+atezolizumab. Since there are still no reliable predictive and prognostic biomarkers, the choice of treatment relies on physicians' judgment based on disease dynamics, tumor burden, and patients' preference. In most of the patients with low-tumor burden the treatment is usually started with immunotherapy, while in disease with high tumor and symptoms, BRAFi+MEKi or combination anti-PD1+anti-CTLA-4 can be initiated. More mature data from clinical studies that are underway are eagerly awaited to answer the question of best sequence in metastatic melanoma. One of the most difficult clinical scenarios is leptomeningeal disease that frequently develops as a site of failure of different systemic treatments. Through case report of the patient with leptomeningeal disease developing on progression to second-line treatment with BRAFi+MEKi, data from the existing clinical studies on treatment sequencing and treatment options for leptomeningeal disease are analyzed. Based on the recent data, leptomeningeal disease is still holding a dismal prognosis, with overall survival of 2.9 months. Radiotherapy does not affect overall survival, while short-term responses to BRAFi+MEKi were described and rare, more durable responses to immunotherapy. Clinical studies are underway with intrathecal immunotherapy. Despite the great developments in the treatment of metastatic melanoma, questions about the treatment sequencing are still a matter of debate. Also, more data on leptomeningeal disease and search for the better treatment options for this group of patients are needed.

## S9 - URINARY BLADDER CARCINOMA

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Bladder carcinoma (BC) is the most common neoplasm of the urinary system while urothelial carcinoma (UC) is the most common histologic type of BC (approximately 90%). Management of non-muscle invasive UC has its basis on the risk stratification done following transurethral resection of the bladder tumor and relies on tumor stage, number, size, pathological grade, associated CIS, lymphovascular invasion, or presence of aberrant histology. All muscle-invasive tumors are categorized as high-grade urothelial carcinomas. Management of muscle-invasive BC has its basis in the stage and whether the patient is a surgical candidate and whether the patient willing to accept the consequences of radical cystectomy which is the primary treatment for T2 and T3 tumors, with consideration for neoadjuvant chemotherapy. Clinical evidence has demonstrated a overall survival benefit of neoadjuvant chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) or gemcitabine and cisplatin compared with cystectomy alone. Neoadjuvant chemotherapy for muscle invasive UC is a validated therapeutic standard that is also in the NCCN, ESMO, EUA recommendations with the highest level of scientific evidence-IA. Current clinical data conflict on the role of adjuvant therapy in invasive bladder cancer, and additional trials are required, however, results from trials show delays of recurrence, so chemotherapy with MVAC or gemcitabine and cisplatin may be used. According to NCCN recommendations, adjuvant chemotherapy can be use in T3-4 or N + (only in patients who did not receive neoadjuvant chemotherapy) with level of evidence 2B. Patients diagnosed with metastatic urothelial carcinoma (mUC) have a poor 5-year relative survival rate. Metastatic disease is generally incurable, with a relative 5-year survival rate of ~5%. Cisplatin-containing combination chemotherapy is standard if first line (1L) chemotherapy in advanced or metastatic patients fit enough to tolerate cisplatin. A number of cisplatin-containing regimens are acceptable although gemcitabine and cisplatin is the most widely accepted than dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (ddMVAC). However, in real clinical practice about 50% patients with metastatic UC are not “fit” for cisplatin therapy. Ineligibility for the use of cisplatin refers to: creatinine clearance <60mL/min, grade  $\geq 2$  audiometric hearing loss, NYHA Class III heart failure, WHO or ECOG PS  $\geq 2$  and grade  $\geq 2$  peripheral neuropathy. Carboplatin-based chemotherapy is recommended in patients “unfit” for cisplatin chemotherapy and carboplatin and gemcitabine is the preferred regimen. Pembrolizumab or atezolizumab are second choices for patients in 1L who are programmed death-ligand 1 (PD-L1)-positive and not eligible for cisplatin-based chemotherapy. “Checkpoint” inhibitor avelumab has found its place in maintenance therapy in patients who do not have disease progression after 1L of systemic therapy. There are no definitive recommendations for second-line therapy (2L). Options for palliative therapy depends on the therapy that was used for 1L. In patients treated with platinum-based chemotherapy, ESMO recommendations in 2L list the following as a standard options: atezolizumab, pembrolizumab, nivolumab and erdafitinib (*FGFR* alterations) and as alternative options chemotherapy or enfortumab vedotin. If immunotherapy is administered as 1L, platinum-based chemotherapy should be considered in 2L as well as enfortumab vedotin and erdafitinib (if specific *FGFR* alterations present) in patients who progress after platinum based chemotherapy and immunotherapy. Until a few years ago, there was no significant improvement for 1L and 2L systemic therapy for mUC patients and for 30 years chemotherapy was therapy of choice. The therapeutic landscape has been altered and enhanced by the introduction of immunotherapy and new drugs like erdafitinib, a fibroblast growth factor receptor (*FGFR*) inhibitor and antibody-drug Enfortumab vedotin.

**Keywords:** bladder carcinoma, urothelial carcinoma, systemic therapy, immunotherapy

## S10 - NEXT GENERATION SEQUENCING

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Next generation sequencing (NGS) of tumor and inherited (germline) genomes is an DNA sequencing technology. With NGS an entire human genome can be sequenced within a single day in contrast with the previous Sanger sequencing technology, used to decipher the human genome, required over a decade to deliver the final draft. NGS has revolutionized and refined cancer treatment during the past two decades and is now vital for evaluating therapeutic opportunities in many solid and hematologic malignancies. There are a number of different NGS platforms using different sequencing technologies, but all NGS platforms perform sequencing of millions of small fragments of DNA in parallel. Bioinformatics analyses are used to piece together these fragments by mapping the individual reads to the human reference genome. Each of the three billion bases in the human genome is sequenced multiple times, providing high depth to deliver accurate data and an insight into unexpected DNA variation. NGS can be used to sequence entire genomes or constrained to specific areas of interest, including all 22 000 coding genes (a whole exome) or small numbers of individual genes. Currently, NGS panels including sets of genes are the most widespread method of rapidly identifying sequence variation in patients with cancer. NGS panels provide information for a variety of purposes, including diagnostics (eg, determination of sarcoma subtype), hereditary risk assessment (eg, Lynch syndrome), prognosis (eg, *KRAS* mutations in lung and colorectal adenocarcinoma), and treatment selection (eg, biomarkers for immunotherapy responsiveness, such as tumor mutational burden and microsatellite instability, therapeutic selection for clinically actionable alterations, such as *BRAF* V600E in melanoma, and biomarkers of resistance, such as loss of *B2M* for immunotherapy). The main disadvantage of NGS in the clinical setting is putting in place the required infrastructure, such as computer capacity and storage, and also the personnel expertise required to comprehensively analyse and interpret the subsequent data. The ESMO Translational Research and Precision Medicine Working Group in 2020 developed the recommendations on the basis of the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) ranking for genomic alterations occurring in the eight cancers responsible for the most deaths worldwide and NGS should be routinely used in patients with advanced lung adenocarcinoma, metastatic prostate and ovarian cancer and metastatic cholangiocarcinoma. Based on the data presented by Cobain et al. and others, it is evident that such precision medicine strategies are especially fruitful in cancer types without clear standard-of-care options, such as carcinoma of unknown primary and other rare tumors. In conclusion, as the cost-effectiveness of using multigene sequencing in daily practice is currently weak, the NGS should be used for subgroup of patients with advanced cancer and no standard therapeutic options.

## **S11 - DO ALL PATIENTS WITH RECURRENT OVARIAN CANCER NEED SYSTEMIC THERAPY AND WHICH IS THE OPTIMAL TREATMENT ALGORITHM**

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Ovarian cancer (OC) is the sixth most frequently diagnosed female cancer and the fifth cause of cancer death. The average life time risk for OC is 1 / 78 females, median age at diagnosis is 63 years while OC is extremely rare before age 35. Mortality is high, and almost 2/3 of patient will die of recurrent OC. The most common histological type is the most malignant one, high grade serous carcinoma, representing ~75-80% of all OC. Due to unspecific symptoms, approximately 80% of patients are diagnosed in advanced stage, and 75-80% will experience relapse after primary treatment median 3 years after primary diagnosis. Initial treatment is optimal cytoreductive surgery followed by platinum based chemotherapy and that has not been changed in the last almost 30 years. Relapse is almost always considered incurable, but with proper treatment, significant life prolongation can be achieved. The chances for the relapse of the disease are estimated taking into account several factors: the stage of the disease at the moment of establishing the diagnosis, the success of the initial surgical treatment and accomplished cytoreduction, the level and the speed of growth of cancer antigen 125 and the response to the primarily administered therapy. However, even besides the aforementioned facts, there are not any predictive recurrence markers. Even though the treatment of OC is mainly standardized and implies surgery (with the goal of complete cytoreduction) and administration of chemotherapy based on platinum derivatives, the recurrent disease is heterogenous and implies a broad spectrum of presentation in terms of the location and expansion of the very relapse as well as the length of the time interval from the primary treatment to the occurrence of relapse. All three therapy models are considered in treating recurrent OC: surgery, chemotherapy and/or targeted therapy, and radiotherapy. In reference to the time of occurrence, recurrent OC is classified into two large groups: the group where the relapse occurred 6 months or more after the primary treatment and the other group where the relapse occurred earlier than the stated period, so-called early relapse. This classification significantly affects the choice of the therapy treatment. There is a special group of patients where secondary surgical treatment is indicated. Those are primarily fit patients, with relatively long DFI, a clear, anatomically localized relapse, where a good effect of further postoperative systematic therapy is expected. In individual cases, intraperitoneal chemotherapy may also be administered. In the systematic treatment of recurrent OC, there are several therapy options. The choice of treatment is mostly affected by the performance of the patient in the first place, then the stage of the disease, the time elapsed from the last platinum therapy to the relapse, biology of the tumor, previous chemotherapy treatments and the patients' reactions to them, but also the toxicity of the previous therapies. Generally, dividing patients into platinum-sensitive and platinum-resistant groups is the solution to the treatment algorithm for these patients. Non-platinum protocols are indicated for the patients with early relapse, or the progression of the disease that occurred during administering platinum chemotherapy, or for the patients with intolerance to platinum medication. Monotherapy, primarily paclitaxel, pegylated liposomal doxorubicin (PLD), gemcitabine, or topotecan – is recommended for these patients. The patients who did not receive bevacizumab in the first line of treatment, should be given this medication along with chemotherapy. For the group of patients with platinum-sensitive disease, there are several options at disposal with the addition of the targeted therapy which implies biological agents affecting the angiogenesis and/or DNA reparation mechanisms. The

detected BRCA mutation represents a predictor of a better response to platinum and introduction of poly (adenosine diphosphate- ribose) polymerase (PARP) inhibition. PARP inhibitors and anti-angiogenic medications have a proven record as the sustainment therapy after chemotherapy, and concurrently with chemotherapy. These medications have changed the manner and outcome of recurrent OC treatment, even though a very small number of predictive biomarkers of targeted therapy are available. The patients who fall into the platinum-sensitive group and cannot receive the medication again should be treated with trabectedin and PLD, the most active non-platinum therapy in this setting. These last years, the field of interest has moved from chemotherapy to targeted therapy which is dominated by anti-angiogenic and anti-PARP agents. It is assumed that platinum-free interval will not remain the main prognostic and predictive criterion in the future and will be replaced by a multi-factorial approach. This trend for personalization of therapy has highlighted necessary neglected fields for clinical research such as multi-line ( $\geq 3$ ) relapse, frail patients including elderly and symptomatic and supportive measurements.

**Keywords:** ovarian cancer, recurrence, secondary surgery, BRCA, poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors, platinum resistance.

## S12 - SYSTEMIC TREATMENT OF MELANOMA

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The incidence of melanoma in both men and women, has been increasing over the past 40 years despite stable or even declining trends for most cancers. Melanoma accounts for about 75% of deaths from skin cancer. More than 50% of patients have a BRAF mutation, 20% NRAS and 5% c-KIT mutation. With the development of modern immunotherapy: ipilimumab, pembrolizumab and nivolumab, and targeted therapies - BRAF and MEK inhibitors, the survival of patients with melanoma has greatly improved. BRAF + MEK inhibitors are suitable for patients with the BRAF mutation, and Immunotherapy is effective regardless of the BRAF mutation. The combination of nivolumab and ipilimumab is even more effective than nivolumab or pembrolizumab alone, but it also has more side effects. Combination immunotherapy is also highly effective in BRAF mutated patients, even more than a combination of BRAF + MEK inhibitors. A series of different lines of immunotherapy or target and immunotherapy leads to further prolongation of survival. Adverse reactions associated with these new treatments are generally acceptable and mild to moderate, but care should be taken in the choice of treatment as specific adverse events are associated with these treatments. unique and serious adverse events have also been reported. Therapeutic decisions are increasingly complex, examining patient and disease characteristics, individual and treatment goals, as well as different efficacy and safety profiles of drugs with different mechanisms of action and according to their lines of treatment. The long-term survival of patients with advanced melanoma is now a realistic goal, creating an additional need to re-establish the clinical benefit assessment. The future will also bring us different combinations and answers about the sequence in the approach to treatment, which should further increase the number of patients who will benefit clinically from this type of treatment

**Keywords:** metastatic melanoma, immunotherapy, targeted therapy

## S13 - TREATMENT OF HER2 POSITIVE GASTRIC CANCER

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**Background:** Gastric cancer is the fifth most common cancer worldwide and accounts for 6.8% of all cancers excluding non-melanoma skin cancer. It is the third most common cause of cancer-related mortality worldwide. Patients diagnosed at an advanced stage has very poor prognosis with 5-year survival not exceeding 5–20%. Systemic chemotherapy based on fluoropyrimidine and a platinum agents is the standard treatment for patients with unresectable advanced gastric cancer. Role of targeted therapies is so far limited to trastuzumab in the first line treatment of HER2-positive tumors and ramucirumab in the second line.

**Treatment of HER2 positive gastric cancer:** The HER2 protein is overexpressed in 10–20% of patients with AGC. Having in mind excellent results with anti HER2 therapy in breast cancer, there was a hope that same can be achieved for patients with HER2 positive gastric cancer. First results were promising, in 2010, the phase 3 ToGA trial demonstrated the benefit of adding trastuzumab to first-line chemotherapy in patients with HER2-positive locally advanced, recurrent, or metastatic gastric or GEJ adenocarcinoma. Unfortunately, several trials in 1<sup>st</sup> and 2<sup>nd</sup> line treatment with different anti HER2 agents such as Lapatinib, Pertuzumab and TDM-1 failed to confirm positive results of ToGA trial. Explanation for these negative result lies in different biology of HER2 positive breast and gastric cancer. Mechanism of Primary Resistance to Anti-HER2 agents in gastric cancer is related to fact that, unlike breast cancer, HER2 overexpression and/or amplification by GC can be heterogeneous which could affect response to anti-HER2 therapies. Also in gastric cancer primary resistance can be explained with presence of oncogenic alterations such as PTEN deficiency and/or PI3K-activating mutations, MET amplification or EGFR overexpression that can co-exist in HER2-amplified tumors. Proposed mechanism of Secondary Resistance to Anti-HER2 Agents in gastric cancer includes: loss of HER2 positivity acquired HER2 mutations, activation of alternative pathways, protein overexpression, epithelial to mesenchymal transition, micro RNAs. Recently two trials with anti-HER2 agents showed activity in gastric cancer. In the randomized, phase II trial DESTINY-Gastric01, trastuzumab deruxtecan (T-DXd) a novel HER2 antibody–drug conjugate demonstrated a significantly higher ORR as a primary endpoint and a longer OS as a secondary endpoint in patients with pretreated HER2-positive AGC. The ORR as the primary endpoint was significantly higher in the T-DXd group compared with the physician’s choice group (51% *versus* 14%,  $p < 0.001$ ). The median duration of response was 11.3 months with T-DXd and 3.9 months with chemotherapy. This trial demonstrated a statistically significant improvement in OS as a key secondary endpoint with T-DXd (median OS 12.5 *versus* 8.4 months, HR 0.59,  $p = 0.01$ ). Regarding adverse events approximately 10% of patients experienced interstitial lung disease related to T-DXd. Another positive results are coming from PETRARCA trial which evaluated the addition of trastuzumab and pertuzumab to FLOT for HER2-positive resectable gastric cancer. In this prospective, multicenter, randomized, investigator initiated trial patients with HER2+ resectable esophago-gastric cancer ( $\geq$  cT2 or cN+) were randomized 1:1 to 4 pre- and post-operative cycles of FLOT (Arm A) or the same regimen with trastuzumab and pertuzumab, followed by 9 cycles trastuzumab/pertuzumab (arm B). Primary endpoint for the phase II part was the rate of pathological complete remission (pCR). The pCR rate was significantly improved with tras/per (A, 12%, B, 35%,  $p = 0.02$ ). Likewise, the rate of pathological lymph node negativity was higher with tras/per (A, 39%, B, 68%). R0-resection rate and surgical morbidity were comparable. DFS and OS rates [with 95% CI] at 24 months were 54% [38-71%] and 77% [63-90%] in

arm A and 70% [55-85%] and 84% [72-96%] in arm B, respectively. In terms of toxicity more  $\geq$  grade 3 adverse events were reported with trastuzumab/pertuzumab (75% vs. 85%), especially diarrhea (5% vs. 41%) and leukopenia (13% vs 23%). In conclusion, trastuzumab-based first-line therapy is Standard of care in HER2 overexpressing advanced/metastatic gastroesophageal cancer. Novel HER2 targeted approaches have shown great promise, in particular, antibody-drug conjugates with proof-of-efficacy even in trastuzumab-pretreated cancers. Promising results are also coming from PETRARCA trial in neoadjuvant setting with dual anti-HER2 therapy. Ongoing trials with of anti-PD-1 and anti-HER2 therapy may further improve treatment results for patients with HER2 positive gastric cancer.

**Keywords:** gastric cancer, HER2, Petrarca,T-DXd

## S14 - STATE OF THE ART IN TREATMENT OF mRC: A CASE REPORT

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The treatment of metastatic Renal Cell Carcinoma (RCC) has changed dramatically over the past two decades. There has been significant progress in both surgical management and development of novel therapeutic agents. Most patients with RCC are asymptomatic or only have mild symptoms which leads to an increased number of metastatic RCC at the initial diagnosis. With growing data from clinical trials and large number of monitored patients, prognostic scoring systems (The MSKCC criteria and IMDC or Heng's model) have been developed in order to define risk groups and provide optimal treatment. Novel prognostic models based on genomic and molecular signatures are being developed and tested in latest trials. In some patient, surgical management of primary tumor and oligometastatic sites may be beneficial. Some studies have showed that there is no difference in overall survival but the data is unclear so surgery should be considered. Immunologic characteristic of RCC have been recognized a long time ago, so the use of interferon-alfa and interleukin-2 resulted in so-called "cytokine era" in treatment of advanced RCC before 2005. Discovery of new molecular pathways lead to "era of targeted therapies" that greatly improved prognosis of patients with metastatic RCC. In the recent years, modulation of immune response has again found an important role in treatment of metastatic RCC. Also combination therapy has become the focus of research including combination of immunotherapy and targeted therapy. Recent studies have showed promising results especially in the first line of treatment of metastatic RCC. The ultimate aim is to personalize and optimize treatment for each patient. We will present a patient with recurrent RCC and course of his treatment during the last fifteen years. The patient is a 40-year-old male who initially presented with large tumor mass in his left kidney in 2006. After nephrectomy it was determined that it is clear cell RCC, stage III. Patient was on regular follow-up. In 2013, seven years after nephrectomy, local recurrence of RCC occurred. The patient was treated surgically and with six cycles of first line therapy with Vinblastin/ Interferon-Alpha-2a. In 2015, one year after the last cycle of therapy, patient presented with a retroperitoneal tumor mass that was surgically removed and pathohistological report determined it to be metastasis of RCC. One year after the surgery, three new tumor masses were detected on the site of the primary tumor. The masses were unresectable, so the patient started second line of therapy with Pazopanib, due to limited therapeutic options at our institution. In the following two years, the patient achieved complete remission while on Pazopanib. However, the patient decided to stop taking Pazopanib due to reduced quality of life. In 2020, two years after the patient had stopped taking Pazopanib, new relapse of disease occurred, with local tumor recurrence, enlarged lymph nodes in the retroperitoneum, liver metastases and infiltration of descendant colon that were seen on PET/CT. The patient underwent hemicolectomy, but still refused further systemic treatment. The patient continued with regular follow-up. Recently, PET/CT showed only local recurrence without dissemination of disease. Previously shown liver metastasis had no metabolic activity in the latest PET/CT. The patient is in good condition but is still reluctant to undergo any type of systemic treatment currently available. However, radiotherapy would be a reasonable option as tumor is present only locally. Possible treatment options will be discussed but taking into consideration the patient's unwillingness to receive systemic treatment, options are limited. Despite growing knowledge about biological nature of RCC, it still remains an unpredictable and aggressive disease. There is a necessity for novel therapeutic agents and regimens that would be optimized for each patient based on clinical and pathohistological characteristics.

**Keywords:** metastatic renal cell, late recurrence, pazopanib

## S15 - PARP INHIBITORS IN THE TREATMENT OF THE OVARIAN CANCER

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Treatment of the ovarian cancer was until recently based on initial cytoreductive surgery followed by chemotherapy based on carboplatin and paclitaxel. Based on the results of randomized phase III trials GOG-0218 and ICON7 which confirmed progression-free survival (PFS) benefit with addition of bevacizumab to chemotherapy, this combination become standard especially in high-risk patients with poor prognosis like stage IV disease, residual disease after suboptimal debulking or presence of ascites where quick response to the therapy is needed. The role of the bevacizumab in the neoadjuvant setting is less clear and this treatment setting still presents significant unmet patients' need. Only few years ago the recurrent ovarian cancer treatment has changed enormously due to introduction of PARP inhibitors which were found to be effective in tumors with defects in DNA damage repair. Inhibition of PARP leads to propagation of single strand DNA breaks and accumulation of double strand breaks which require repair by homologous recombination (HR) repair mechanisms. PARP inhibitors were initially developed as maintenance therapy in patients with complete or partial response to platinum-based chemotherapy for recurrent ovarian cancer. The remarkable improvement in PFS confirmed in three randomized phase III trials – NOVA/ENGOT-OV16, SOLO-2/ENGOT-OV21 and ARIEL3 – led to approval of niraparib, olaparib and rucaparib, respectively, as highly effective maintenance therapy in this setting. Platinum sensitivity seems to be the most reliable biomarker for sensitivity to PARP inhibitor in recurrent disease. The greatest benefit was seen in BRCA-mutated population. In all three studies, exploratory analysis suggested additional antitumor activity in patients with measurable disease at the beginning of the maintenance suggesting PARP inhibitor treatment role as well. PARP inhibitors changed course of disease in this setting delaying need to initiate further chemotherapy. For the illustration, 11% of patients in the Study 19 were treated by olaparib for more than 6 years. Olaparib, rucaparib and niraparib monotherapy are also approved in various treatment rather than maintenance setting for pretreated recurrent ovarian cancer patients. Further on, PARP inhibitors were investigated in randomized, altogether four, phase III trials in the front-line setting (SOLO-1, PAOLA-1/ENGOT-OV25, PRIMA/ENGOT-OV26 and VELIA/GOG-3005) and demonstrated remarkable improvements in PFS with PARP inhibitor therapy (olaparib, niraparib or veliparib) for newly diagnosed ovarian cancer. Differences in trial design, patient selection and primary analysis population influence interpretation of these trials making meaningful comparisons an almost impossible challenge. Those differences were considered in relation to the control arms (placebo versus active drug), patient populations (sensitivity to induction platinum and residual disease), timing of PARP inhibitor initiation (concomitant with chemotherapy versus maintenance only), and planned duration of PARP inhibitor therapy. The treatment choice in the first line should take into consideration clinical risk factors, comorbidities, timing of surgery (interval versus primary debulking), residual disease, need for bevacizumab, BRCA status as well as access to PARP inhibitors. Overall survival data are pending and there is limited experience regarding long-term safety. PARP inhibitors therefore play a pivotal role in the management of newly diagnosed ovarian cancer, which will then affect subsequent treatment choices. In newly

diagnosed ovarian cancer sensitivity to PARP inhibitors rely more on BRCA and HR deficiency (HRD). Approval of olaparib in maintenance after front-line chemotherapy is restricted to BRCA mutated disease if given alone and in combination with bevacizumab in HR deficient disease. Niraparib is approved as maintenance after front-line platinum-based chemotherapy irrespective of HR status. Accuracy and reliability of currently available tests leave room for improvement by developing more robust tests. Defining of testing for patient selection and identification of regimens to treat populations that benefit less from PARP inhibitors are priority. In conclusion, new data support use of PARP inhibitors earlier in the treatment algorithm.

**Keywords:** ovarian cancer, PARP inhibitor, BRCA mutation, HR deficiency

## S16 - HEAD AND NECK CARCINOMA

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Head and neck cancers are the sixth most common malignancy in the world, affecting about 830,000 people a year. Risk factors are well known and are associated with the use of nicotine, alcohol and human papillomavirus infection. This is a heterogeneous group of diseases that in 95% of cases refers to squamous cell carcinomas. The dominant mode of treatment in the early stage of the disease refers to local control by surgery or irradiation. At an advanced stage, the disease is controlled by various forms of systemic anti-neoplastic treatment, although we should not forget the importance of maintaining nutritional health, and more recently the use of radiosurgical treatment in the presence of oligometastatic disease. The basis of systemic treatment in advanced disease is a combination of cisplatin and 5-fluorouracil, to which cetuximab (EXTREME protocol) has been added since 2008. This resulted in a prolonged overall survival and an improved response rate. A data update published in 2014 showed that the addition of cetuximab to chemotherapy improved survival, regardless of p16 or HPV status. An attempt to add bevacizumab to standard combination chemotherapy has not been justified in terms of prolonging survival, despite a higher response rate and prolonging the time to disease progression. After initial knowledge of gene alterations (TCGA, Nature 2015), immunotherapy was started in this vulnerable group of patients, in whom there were no significant therapeutic shifts for years. The significance of nivolumab in second-line treatment after progression to a platinum compound within 6 months was first investigated. A shift in overall survival from 4.6 to 8.7 months was found in the group of patients with PD-L1 expression <sup>31</sup>%, with an overall improvement in quality of life according to the EORTC-QOL-C30 questionnaire compared to treatment chosen by the researchers. In a very similar study design, pembrolizumab after platinum (KEYNOTE 040) was administered compared to standard treatment (methotrexate, docetaxel, or cetuximab). There was a difference in the median OS of 8.4 vs 6.9 months, although the difference was not statistically significant. It is also worth mentioning the increase in the overall response rate from 9.2 to 26.6%. In the PD-L1 TPS <sup>3</sup> 50% patient population, the median OS was 11.6 vs 6.6 months. The reason for the impact on overall survival may also be found in the fact that 12.5% of patients who received standard treatment subsequently received immunotherapy. What was expected as a turning point in the treatment of advanced head and neck cancer was the KEYNOTE-048 study. There, in first-line treatment, pembrolizumab was directly compared in monotherapy, versus combination with chemotherapy, and versus the standard EXTREME protocol. Pembrolizumab has been shown to be more effective in OS gain, compared to EXTREME, independent of CPS, as well as in combination with chemotherapy. The results of a longer follow-up published at ESMO 2020 showed in the group pembrolizumab vs EXTREME after 48 months OS 16.7 vs 5.9 months (CPS <sup>31</sup>) and 21.6 vs 8.0 (CPS <sup>320</sup>). In the pembrolizumab group with chemotherapy vs EXTREME, the difference was 21.8 vs 4.1 (CPS <sup>31</sup>) and 28.6 vs 6.6 (CPS <sup>320</sup>). According to these results, EXTREME remains the standard therapy in patients who do not show PD-L1 expression, pembrolizumab as monotherapy becomes a therapeutic option in patients whose tumors show PD-L1 (CPS <sup>31</sup>), while the use of pembrolizumab with chemotherapy is recommended when rapid therapeutic response needed. *Trk* family proteins are encoded by *NTRK* genes, expressed in human neuronal tissue and activated by neurotrophins. Ligand binding activates downstream signal transduction pathways – MAPK, ERK, PI3K/AKT and plays a key role in CNS and PNS development and cell survival. Gene fusions involving NTRK genes

have known oncogenic potential via ligand-independent, constitutive *Trk* activation and mediate neoplastic proliferation using the same signal transduction pathways. NTRK fusions are most commonly found in papillary thyroid carcinoma and salivary gland tumors, and today valid therapeutic options in this extremely rare group of patients are larotrectinib and entrectinib with an overall response rate of 50-79%, which clearly indicates the need for their detection. In a small group of patients with oligometastatic disease, radiosurgical treatment is considered. In the case of wider application of immunotherapy, synergism with high doses of radiation could represent a new therapeutic step forward. However, regardless of therapeutic advances, it should be borne in mind that head and neck cancer patients are extremely vulnerable population of patients in whom continuous nutritional health care is required, the risk of toxicity as a consequence of immunotherapy should be well assessed, so multidisciplinary as the foundation of the approach today has gained additional importance.

**Keywords:** head and neck carcinoma, pembrolizumab, NTRK genes, radiosurgical treatment

## S17 - PARP INHIBITORS IN THE TREATMENT OF PROSTATE CANCER

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In cancer patients with *error-prone* DNA repair drug-induced PARP inhibition can lead to cellular death. Over 20% of man with metastatic castration-resistant prostate cancer (mCRPC) have loss-of-function alterations in genes that are involved in DNA repair, including homologous recombination repair. These alterations can be either hereditary or somatic. The phase III trial PROfound which evaluated olaparib demonstrated significant improvements in radiologic progression-free survival (rPFS) and overall survival (OS) among men in cohort A with mutations in *BRCA1*, *BRCA2*, and *ATM*, but not in men with alterations in other prespecified genes with a direct or indirect role in the homologous recombination repair. Similarly, phase II TRITON2 trial found benefit to rucaparib, though this was not a randomized comparison. Up until now somatic and/or germinal *BRCA 1* and *2* alterations seem to be the most predictive biomarkers of efficacy of PARP inhibitors in patients with mCRPC. While these trials provided evidence of substantial clinical benefit in an advanced patient population using a biomarker-driven study design and have changed clinical practice, there are significant limitations as these patients are not cured and many responses are not durable. Further, a large proportion of biomarker-positive patients failed to demonstrate benefit. Results of other ongoing phase III trials assessing the efficacy of a PARPi used alone or in combination are awaited, to better define their place with regard to standard treatments and platinum-based chemotherapies.

**Keywords:** prostate, cancer, tretament

## S18 -VALUE OF ANTIHER2 TREATMENT IN BREAST CANCER

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In about a fifth of breast cancer cases, it is HER 2 positive breast cancer, which means that tumor cells on their surface overexpress a HER2 receptor, one that makes them more aggressive, and for years HER2 positive breast cancer has been the most aggressive subtype of the disease in terms of frequent dissemination and death in the metastatic stage of disease. The revolution happened twenty years ago, with the introduction of targeted antiHER2 therapy. It all started with trastuzumab, which in the metastatic stage of the disease prolonged survival by several months and, in the long run, saved more than 150 000 life years. In the early stages of the disease, the use of trastuzumab has been shown to reduce the risk of disease recurrence and death by as much as a third. However, despite the use of standard one-year treatment with trastuzumab, a quarter of patients experience relapse, signaling the need to do more. The most significant success was achieved by double HER2 blockade, trastuzumab and pertuzumab, which when administered together have a synergistic effect. This success is primarily reflected in the 16-month longer overall survival of patients with metastatic disease, who were treated with double HER2 blockade in addition to chemotherapy, compared to trastuzumab alone. In the neoadjuvant setting, a number of studies have shown a higher rate of achieving a complete pathological response, if pertuzumab was used in addition to trastuzumab. Adjuvantly, double blockade with trastuzumab and pertuzumab proved to be justified in patients with positive lymph nodes. In addition to monoclonal antibodies, a valuable antiHER2 drug is trastuzumab emtansin, which acts by an antibody-drug conjugate mechanism. In metastatic disease, it has achieved valuable success in prolonging survival of patients who have progressed to previous antiHER2 therapy. In early stage, it halved the risk of recurrence of invasive disease, in those patients who did not achieve a complete response to neoadjuvant therapy. In the antiHER2 arsenal we also have several small molecules, respectively tyrosine kinase inhibitors, among which the first is lapatinib, which has been shown to be a relevant option with capecitabine chemotherapy or even with trastuzumab, in metastatic HER2 positive breast cancer. Unfortunately, after positive results from neoadjuvant studies, large adjuvant studies have not confirmed the efficacy of lapatinib in the treatment of early disease, and with non-negligible drug toxicity. Another TKi, neratinib, has been shown to be effective in the extended adjuvant treatment of early HER2-positive breast cancer, but also in pretreated patients with metastatic stage, however the results are not sufficient to change clinical practice and drug toxicity is significant. Is that all? What does the panorama of antiHER2 therapy look like today? New agents are on the horizon today, with new properties and benefits. An example of one is the tyrosine kinase inhibitor tucatinib, which has shown a significant effect on survival, again, in pretreated patients with metastatic disease, and is of particular interest in population with brain metastases. The next new drug that has aroused interest and hope for new developments and advances is trastuzumab deruxtecan, an antibody-conjugate drug, with excellent results in the pretreated population of patients with metastatic disease, and showing effect even in those with low HER2 expression. Moreover, nowadays in oncology we witness also the advent of biosimilar drugs, and trastuzumab biosimilars are of particular interest, taking into account the economic factor, namely the financial toxicity with the original drug. However, it remains to be seen what has brought to us the possibility of applying biosimilar drugs, in terms of long-term open issues, in a sensitive area such as oncology. On the other hand, the importance of financial toxicity is being balanced also through the

novelties and new benefits that the original drugs still bring, such as the fixed subcutaneous combination of trastuzumab and pertuzumab. When we look at the other side of the coin, it is gratifying that the toxic profile of these drugs, especially the main one among them, trastuzumab, is very appreciative. With trastuzumab we monitor cardiotoxicity, while with pertuzumab we can expect some diarrhea, which is somewhat more serious with tyrosine kinase inhibitors, and with the advent of new drugs it is necessary to keep in mind the possibility of new, unusual toxic manifestations. Targeted anti-HER 2 therapy, especially trastuzumab, has revolutionized and artificially completely altered the natural course of an aggressive disease, such as HER 2-positive breast cancer, providing these patients with a significantly better prognosis in the long run, in comparison to other, naturally more indolent types of breast cancer.

**Keywords:** antiHER2 targeted therapy, trastuzumab, dual blockade, pertuzumab, T-DM1

## **S19 - ADJUVANT ANTIHORMONAL TREATMENT OF EARLY BREAST CANCER**

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It is well known that estrogene stimuli enhance proliferation, and thus also hormone-dependent tumors. Among breast cancers, in over two thirds of cases, these are hormone-dependent tumors. The purpose of antihormonal treatment is to block the effect of estrogen on the progression of these tumors, by blocking the function of estrogen receptors or by blocking the production of estrogen, on the periphery or in the ovary. Relevant world recommendations, St Gallen, ESMO, NCCN, ASCO, in the instructions on the use of adjuvant antihormonal therapy in the treatment of early breast cancer somewhat differ. Certainly, it is recommended that in low-risk patients, at the earliest stage of the disease, five-year treatment be used, either with tamoxifen or aromatase inhibitor, while intensification of therapy, qualitatively or quantitatively, is recommended in higher stages of the disease or higher risk. Evidence for this lies in a number of studies and meta - analyzes, which showed that the use of tamoxifen in the treatment of breast cancer reduced the risk of recurrence of the disease and new breast cancer by half and the risk of death by about a third. Aromatase inhibitors added an additional benefit of about 4% in reducing the risk of disease recurrence, but without the additional survival benefit. How to create adjuvant antihormonal treatment for an individual patient is best examined through a complex risk analysis for each individual patient, ie the characteristics of the disease, but also the patient's toxicity, general health and willingness of the patient to continue taking the drug after five years of therapy. In premenopausal patients, it is very important, with increasing risk, to introduce ovarian suppression with tamoxifen, while the use of aromatase inhibitors in premenopausal patients, mandatorily with ovarian suppression, contributed to a reduction in the risk of disease recurrence but again, not in overall survival. Given that even after five years of adjuvant antihormonal therapy, the long-term risk of disease recurrence cannot be ignored, even in the smallest tumors, numerous studies have investigated the benefit of prolonged, so called extended adjuvant antihormonal treatment. Prolongation of tamoxifen treatment has been shown to indeed bring additional benefit. Prolonged treatment with aromatase inhibitors has been shown to be effective in reducing the risk of developing secondary cancers, possibly in reducing the risk of relapse, but without affecting survival. Due to all the above, it is very important to decide on the use of antihormonal therapy, especially its duration, in agreement with the patient, and depending on her preferences, individual risk and tolerability of therapy.

**Keywords:** adjuvant antihormonal treatment, endocrine treatment, tamoxifen, aromatase inhibitors, ovarian function supression, extended adjuvant

## **S20 - OPTIMAL SEQUENCE IN HORMON RECEPTOR POSITIVE METASTATIC BREAST CANCER**

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Hormone receptor positive breast cancer subtype accounts for approximately 70 % of advanced breast cancer patients. New targeted treatment options are emerging after more than a decade without any significant improvement in these frequent and incurable disease. Overall survival of metastatic breast cancer disease is still short about 37 months. Today there is no biomarker that meets evidence for clinical use. The special issue of endocrine treatment is resistance, primary or acquired. The CDK4/6 inhibitors are newer class of drugs used to treat HR positive Her2 negative subtypes of metastatic breast cancer. This targeted therapy inhibits specific proteins cyclin-dependent kinases 4 and 6 which can become overactive and cause fast cells grow and dividing. Inhibitors of these protein interrupt these processes in the way to slow cancer cells grow. Hormone receptor positive tumors are dependent of hormones as estrogen, progesterone, or both. HER2 negative breast cancers doesn't have human epidermal growth factor receptor 2 (HER2). The CDK4/6 inhibitors also can be used to treat locally advanced breast cancer which is not metastatic. Endocrine therapy is the preferred option for hormone receptor positive disease. If there is condition of visceral crisis defined as severe organ dysfunction or rapid progression of disease we have to treat patients with chemotherapy. Palbociclib was the first inhibitor of CDK4/6 received an approval by FDA in 2015. in combination with letrozole as initial therapy for AI sensitive metastatic breast cancer based on results from PALOMA-1 and PALOMA-2 clinical studies. PALOMA-3 trial expanded indications with fulvestrant for both postmenopausal and preperimenopausal women with AI-resistant advanced or metastatic breast cancer. Ribociclib approved in 2017. due to results of MONALEESA-2 study as first line endocrine based therapy for AI-sensitive advanced or metastatic breast cancer in addition with an aromatase inhibitor. Based on MONALEESA-7 trial, these drug combinations approved for the treatment of premenopausal women. MONALEESA-3 trial shows that ribociclib in combination with fulvestrant is effective in post-menopausal women with both AI-sensitive and AI-resistant metastatic breast cancer. In 2017. MONARCH-2 approved efficacy of abemaciclib in combination with fulvestrant in women with AI-resistant advanced or metastatic breast cancer. The MONARCH-3 study showed that abemaciclib with non-steroidal aromatase inhibitor significantly improved PFS in patients with AI-sensitive advanced or metastatic breast cancer. Abemaciclib also has indication as a monotherapy based on MONARCH-1 trial for patients with HR-positive HER2-negative metastatic breast cancer who previously received endocrine therapy or chemotherapy. These specific cell inhibitors cause side effects which are not so intense as caused by chemotherapy. Most common side effects are nausea, diarrhea, fatigue, neutropenia, anemia, thrombocytopenia ect. Also, there are alopecia, liver and cardiac toxicities. If there are high grade toxicities the procedure of stopping the drug or lowering the dose maybe useful to continue treatment and made the best efficacy of the approach. In some cases, these drugs can cause QT interval prolongation. These can influence the chosen of drug when patient has hearth comorbidities. Next step is to use these drugs in adjuvant setting when patients can be cured in the early stage of these malignant disease.

**Keywords:** breast, cancer, hormonal, CDK4/6, inhibitors

## S21 - CNS METASTASES IN HER2 POSITIVE AND TRIPLE NEGATIVE DISEASE

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Breast cancer cells have pronounced neurotropism and breast cancer is, after lung cancer, the second most common cause of brain metastases (especially HER2 positive and triple negative subtypes). The risk of developing brain metastases in breast cancer is as high as 25% with a median time from diagnosis of advanced cancer to brain dissemination of 2-3 years. Overall survival, despite therapeutic modalities involving surgery, radiation, and systemic therapy, ranges from 2–25 months, depending on prognostic factors including age, histological subtype, number of central metastases, and volume of extracranial disease. Potential systemic therapeutic options are limited by the blood-brain (BBB) and blood-tissue barrier (BTB). In HER2 positive disease, about 50% of patients develop brain metastases, and monoclonal antibodies targeting the HER2 receptor (trastuzumab, pertuzumab, T-DM1) do not pass intact BBB, however, by controlling extracranial disease, they delay time to central dissemination. Two important therapeutic options in HER2 positive disease are HER2-targeted tyrosine kinase inhibitors (lapatinib, neratinib, tucatinib) in combination with capecitabine and antibody-cytotoxic drug conjugates, trastuzumab emtansine (T-DM1) and trastuzumab-deruxtecan (T-DXd). Lapatinib monotherapy has a minimal therapeutic response with an ORR of 6%, while combination with capecitabine in pretreated HER2 positive disease has a response rate of 18-38%. Pan-TKI neratinib in combination with capecitabine (NALA trial) in the third-line treatment of patients with asymptomatic brain metastases showed a benefit in PFS of 2.2 months and a statistically insignificant benefit to OS (24 vs. 22.2 months) compared to the combination of lapatinib and capecitabine. Neratinib in combination with paclitaxel in the first-line treatment (NEfERT trial) of HER2-positive brain metastases was not superior in PFS but it slowed central disease progression and halved central events in comparison with the combination of trastuzumab and paclitaxel. Tucatinib, a selective HER2 TKI in combination with trastuzumab and capecitabine compared to trastuzumab and capecitabine in previously HER2 pretreated patients (HER2CIMB trial) met pre-determined endpoints, reducing the risk of disease progression by 46% and the risk of death by 34% with ORR 41% vs 23% in the total population. In patients with active brain metastases, the reduction in risk of death was 51% and the reduction in central progression 64% in the tucatinib arm. Trastuzumab deruxtecan (T-DXd) conjugate (DESTINY-Breast01 trial) used in heavily pretreated patients (median of 6 previous lines of therapy) showed impressive results with ORR of 61.4%, response rate of 58.3% in the brain metastases group, and the median survival without central progression of 18.1 months. New therapeutic options in the treatment of HER2 positive diseases including neratinib, tucatinib and trastuzumab deruxtecan show very promising results in patients with central disease. As for the central propagation of TNBC, it is thought that TNBC cells cause neuroinflammation, increase activity of proteolytic enzymes and directly destroy the blood-brain barrier which causes loss of integrity of the blood-brain barrier, enables entry of tumor cells into the brain parenchyma and stimulates neovascularization. VEGF expression is significantly higher in triple negative metastatic breast cancer than in HER2 positive. Also, TNBC metastases are thought to have less representation to immune cells such as CD8+ T lymphocytes, regulatory and dendritic cells, which can contribute to the immune escape of tumor cells. New therapeutic strategies over the past few years include among others PARP (poly ADP-ribose polymerase) inhibitors (talazoparib, veliparib, olaparib), VEGF

inhibitors (bevacizumab) and checkpoint inhibitors (anti PD-L1, atezolizumab). Addition of PARP inhibitor velaparib to cisplatin in SWOG1416 trial did not significantly improve PFS or OS. The BRCA mutated subset of patients had an improvement in PFS from 4.2 months to 5.9 months and in OS from 12 to 14 months. Final results (2020) of EMBRACA trial which used talazoparib in comparison to chemotherapy (capecitabine, cisplatin, gemcitabine), despite longer PFS with HR 0.54, showed no benefit in OS in the overall population as well as in patients with central disease. TNBC is the most immunogenic type of breast cancer and inhibition of cell death receptors (PD-1) and its ligand (PD-L1) is an attractive therapeutic target. The results of IMpassion 130 trial which combined anti PD-L1 drug atezolizumab and nab-paclitaxel, are a significant milestone in the treatment of advanced TNBC with the extension of PFS and OS by 9.5 months, including patients with central disease. Potential therapeutic options, including nanotechnology, which could reduce the incidence of brain metastases and prolong survival are continuously investigated.

**Keywords:** brain metastases, HER2 positive disease, triple negative breast cancer, therapeutic strategies

## S22 - TOP TEN NEWS (EXCEPT COVID) IN 2020 ONCOLOGY

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Despite the many challenges faced in 2020, we have seen impressive progress in many areas of cancer research. Twenty-one novel oncology drugs were approved by the U.S. Food and Drug Administration (FDA). Although cancer is one of the major public health problems worldwide, cancer mortality projections for 2021 confirm the persistent declines in cancer mortality in EU and US for many specific cancers. The breast cancer treatment landscape has evolved in the past year and several new drugs approved in 2020 as antibody drugs conjugates (ADC) sacituzumab in TNBC and fam-trastuzumab deruxtecan-nxki (T-DXd) in metastatic HER2 positive BC, as well as tucatinib, a small kinase inhibitor. A few very important clinical trial /RxPONDER, ADAPT, PRIME II/ presented last year support de-escalation of adjuvant chemotherapy and radiation, sparing patients from some of the side effects that can accompany treatments. *In ovarian cancer five-year follow-up data from the SOLO-1 trial continue to show progression-free survival benefit of olaparib as maintenance therapy following platinum-based chemotherapy in the frontline setting.* In the final analysis of SOLO-2 trial, maintenance olaparib provided an improvement of 12.9 months in median OS vs placebo in women with relapsed BRCA-related ovarian cancer who had responded to their most recent platinum-based chemotherapy after having received at least one more line of chemotherapy. In 2020 first new treatment for hepatocellular carcinoma approved in more than ten years according to the data from phase III IMbrave 150 trial. In that study, which includes 501 patients the combination of atezolizumab and bevacizumab provides the longest survival seen in a front-line phase III study in advanced HCC, confirming atezo + bev as a standard of care for previously untreated, unresectable HCC. In the field of thoracic oncology there were some very important news in 2020, potentially practice changing. Osimertinib, next generation EGFR-TKI, standard first line therapy in metastatic EGFR-mutated advanced NSCLC was successfully used, in ADAURA study, in adjuvant setting vs placebo (planned treatment duration three years), in resected NSCLC patients, stage IB-IIIA. Patients might had adjuvant chemotherapy also, and there was no outcome differences between these two groups. Overall, there was a 79% reduction in the risk of disease recurrence or death (DFS HR was 0.21,  $p < 0.0001$ ). Lorlatinib is the third generation of ALK-inhibitors in the treatment of advanced NSCLC. The results of CROWN study where lorlatinib was given in the first line treatment were presented at ESMO 2020. In this randomized study, comparing lorlatinib with crizotinib, lorlatinib was superior in the term of PFS, HR was 0.28,  $p < 0.001$ , this superiority was particularly pronounced in intracranial disease, where the percent of intracranial response was 82% in lorlatinib arm and only 23% in crizotinib arm, and percent of complete response per CT was 71% vs 7%. Lorlatinib has been recently approved for patients with advanced ALK-positive NSCLC, irrespectively of treatment line. Also of interest were two studies that inovatively used immunologic drugs as a combination in advanced NSCLC: in Check Mate 9LA randomized study, cytotoxic chemotherapy was given in paralell with nivolumab + ipilimumab for first two cycles, and compared with four cycles of chemoherapy. Median OS was significantly better: 15.6 vs 10.9 months, HR 0.66 and a overall response rate was 38% vs 25%. CITYSCAPE study give us inovative combination of two immuno-oncology drugs, tiragolumab as TIGIT inhibitor, and standard atezolizumab. Median PFS was particularly longer in the population of patients with high PD-L1 expression (NE vs 4.11 months, HR 0.30). In gastrointestinal oncology, last year will be remembered by introducing immunotherapy in first line treatment of metastatic colorectal cancer for

patients with MSI-H tumors. In KN177, such patients were randomized to receive pembrolizumab or standard chemotherapy+/-biologic therapy, and after second interim analysis, there was a very clear advantage for pembrolizumab in terms of mPFS (16.5 vs 8.2 months) and duration of response (at 24 months, 83% vs 35%). The results are impressive, and it is expected to be confirmed by OS advantage in future analyses. In urological oncology, JAVELIN Bladder 100 study demonstrated that the maintenance avelumab + best supportive care is superior over best supportive care alone after platinum-based first-line chemotherapy in advanced urothelial carcinoma. In overall population, OS was 21.4 vs 14.3 months, HR 0.69,  $p < 0.001$ , and the results are even better in PD-L1 positive population, with HR 0.56. These results are very probably practice changing, since cytotoxic chemotherapy have very modest achievements in the field of urothelial cancer.

**Keywords:** oncology news, breast cancer, gynecological tumors, hepatocellular carcinoma, non-small cell lung cancer, MSI-H colorectal cancer, bladder cancer