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Immunotherapy and tumor microenvironment

Key words: checkpoint blockade, immune-phenotype, immunotherapy, tumor microevironment

One of the most recent development in our understanding of cancer biology is the field of immuno-oncology. The rapidly growing field of cancer immunotherapy has developed largely as result of our increased understanding of the immune system and malignancy. Recently, cancer immunotherapy, particularly immune checkpoint therapy /cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1) and programmed cell death ligands (PD-L1 and PD-L2) / which have been shown to have potent immunomodulatory effects through their function as negative regulators of T cell activation), has progressed and provided novel strategies for the treatment. Although this immunotherapy has very promising results, the percentage of patients who respond is limited, and the factors that determine a patient's respond are not well understood. There is increasing evidence demonstrating that the differences in the results of cancer immunotherapy are attributed to the heterogeneity of the tumor microenvironment/TME/. The tumor microenvironment consists of tumor cells, tumor-infiltrating immune cells, cancer-associated fibroblasts, the tumor vasculature and the extracellular matrix. Cancer cells are able to communicate with other cells and components of the TME through two mechanisms: the first being contact-dependent mechanism between the cancer cells and another cell or with the extracellular matrix and the second being contact-independent mechanism via cytokines, growth factors and lipid mediators. Modulation of the TME is now becoming an important research goal in the field of immunotherapy. There are many potential targets for cancer therapy, these including the targeting of excessive immunoregulation, angiogenesis, inflammation, and tumor cell communication with the extracellular matrix. The recruitment, differentiation and location of immune cells in the TME are variable among different tumor types, and their heterogeneity is also affected. Therefore, due to the heterogeneity if immune cells in the TME, it is considered to exist three phenotypes according to the distribution of immune cells: immune-inflamed phenotype, immune-excluded phenotype and immune-desert phenotype. By changing the immune-phenotype the TME can be modified providing a basis for personalized immunotherapy. This can be achieved by different mechanism: with immunotherapies targeted to the TME (immune checkpoint blockade), tumor metabolism regulation, tumor stroma regulation or combination with chemotherapy and radiotherapy. In the future, immunotherapy may be required to be tailored for each patient with cancer according to the TME.

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Time to anticancer drug access in Slovenia in view of ESMO MCBS

All new drugs, including anticancer drugs, must first receive EMA market approval (EMA MA), which is a centralized procedure for all EU members and then the national reimbursement approval (NRA) which is in jurisdiction of every member state separately. In Slovenia, the National Health Institute (ZZZS) is in charge of the latter. Not having a unified method of drug reimbursement leads to different lag times in drug approval and access. A scaling system was introduced by ESMO, named ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) that is set up for assis-

tance in informed treatment decision making for both oncologists and patients, but can also be used by health authorities to aid decision making. We were interested if ESMO-MCBS had any influence in time to anticancer drug approval both by EMA and Slovenia health authorities.

We reviewed anticancer drugs approved for solid cancer treatment by EMA and assessed for reimbursement in Slovenia from 2008 until 2018 that already had an ESMO-MCBS applied by the ESMO expert panel. All the dates for registration and reimbursement procedures were publically available and retrieved from corresponding websites: www.ema.europa.eu and www.zzzs.si. Data lock was March 15th 2018.

There were 51 anticancer drugs included in our analysis, each drug indication being evaluated separately; 39 targeted, 9 immunotherapy, 3 cytostatic therapies. Up until data lock, 46/51 drugs were also reimbursed in Slovenia, 1 was rejected and 4 were pending for decision. Out of the 46 reimbursed drugs, 24 had a high ESMO-MCBS score indicating a substantial clinical benefit (A-B, 4-5), and 22 had a low ESMO-MCBS score (C, 1-3). Their median time to EMA MA was 398 days with no difference between high vs low ESMO-MCBS (377 vs 398 days). Median time to NRA was 429 days; again with no difference between high vs low ESMO-MCBS (451 vs 416 days). Altogether, anticancer drugs were available to Slovenian patients in a median of 762 days (373 – 1426 days).

In conclusion, most of novel anticancer therapies are actually available in Slovenia, but the combined process of EMA MA and NRA takes about two years altogether (one year each), which is sometimes well past due for cancer patients. Neither the EMA MA, nor the NRA times seem to differ according to ESMO-MCBS. Hopefully, the score will be better integrated in the future for rational prioritizing and decision making, especially on the national level.

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Real world data: Ten years of using adjuvant trastuzumab in breast cancer in Serbia - single institution experience

The purpose of this study was to determine disease-free interval (DFI) and overall survival (OS) in HER2-positive breast cancer patients who received adjuvant trastuzumab at the University Clinic of Nis, Serbia, and to investigate the influence of clinicopathological and biological characteristics of the tumor on prognosis. The second aim was to determinate the most frequent cause for the treatment discontinuation, recurrence rate, as well as the site of most common localization of the first recurrence of disease.

This research was conducted as a retrospective study at the University Oncology Clinic, Clinical Centre in Nis. The study included 238 patients who were operated and treated for HER2-positive breast cancer between January 1st, 2007 to September 30th, 2012 and followed up until December 31st, 2016. Trastuzumab was administered concurrently with taxanes, if administered, or after the completed anthracycline-based chemotherapy.

After a median follow up of 69 months the 5-year DFI was 65.9% and 5-year OS was 81.8% and, as expected, significantly longer in the group of patients with smaller tumors, a smaller number of positive axillary lymph nodes, as well as a lower stage of disease ($p<0.0001$). Patients older than 65 years had a longer DFI compared to the 45-65 and under 45 age groups of patients ($p=0.01$). No statistical significance was found in the length of DFI in relation to the histological tumor subtype, tumor grade, or the status of hormone receptors. Unlike DFI, a longer OS was recorded in the group of patients with lower tumor grade ($p=0.03$) and there was no statistically significant difference in survival regarding the age of patients ($p=0.07$). Recurrence occurred in approximately one third of the patients (38.23%), mostly in the

form of local recurrence. Adjuvant therapy with trastuzumab was not completely carried out in 18.49% of the patients, the most common reason being the progression of disease.

A long median follow up period of 69 months indicated that anti-HER2 monoclonal antibody trastuzumab, after anthracycline-based chemotherapy or concurrently with taxanes, is efficient and safe in treating early breast cancer.

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Prognostic Value of Age-Adjusted International Prognostic Index in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma-Single Centre Experience

Key words: Lymphoma, Large B-Cell, Diffuse, recurrence, prognosis, Progression-Free Survival

Background: The research aimed to estimate the influence of aaIPI score (Age-adjusted International Prognostic Index) and time to the first relapse on overall survival (OS) and progression-free survival (PFS) in the second line of treatment in patients with relapsed/refractory diffuse large B cell lymphoma (DLBCL).

Material and methods: Research included 36 patients with relapsed/refractory DLBCL treated at Oncology Institute of Vojvodina, Serbia, from January 2013 until December 2015. Patients were stratified according to aaIPI score value at the time of relapse into: patients with low risk (aaIPI 0-1) and patients with high risk (aaIPI 2-3), as well as according to the time of the first relapse occurrence: early relapse (≤12 months) and late relapse (>12 months).

Results: In the group of patients with aaIPI 0-1 median OS was 44 months in comparison with 6 months in patients with aaIPI 2-3 HR 0,4(CI 0,16-0,99), p=0,03. In patients with early relapse, median OS was 7 months compared with 25 months in patients with late relapse, HR 0,55(CI 0,25-1,19), p=0,12.In patients with early relapse, median PFS was 0 months compared with 10 months in patients with late relapse, HR 0,34(CI 0,12-1,00), p=0,0017.

Conclusion: The value of aaIPI score significantly influences OS in patients with relapsed DLBCL. Time to the first relapse impacts PFS calculated from the time of initiation of second-line treatment in these patients.

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Efficacy comparison of pazopanib and trabectedin vs standard chemotherapy in second line treatment of patients with metastatic soft tissue sarcomas: Experience from countries with limited resources

Keywords: pazopanib, soft tissue sarcomas, STS, standard chemotherapy, trabectedin

Background: Soft tissue sarcomas (STS) are rare tumors with more than 50 histologic subtypes. Treatment outcomes for pa-

tients with STS has improved over the past few decades mostly due to the adoption of a multidisciplinary approach, but still patients with advanced disease have a poor prognosis.Our study compared efficacy of novel sarcoma therapies - pazopanib and trabectedin vs standard chemotherapy, after failure to anthracycline based therapy, in patients with metastatic STS.

Methods: In the period between 2014 and 2017 we made a retrospective analysis of 80 patients treated in Clinical Centre University of Sarajevo and University Hospital Centre Zagreb for metastatic STS. All patients received antracycline based therapy as a first line therapy. Patients were grouped in two cohorts. Patients in first cohort received pazopanib and/or trabectedin as a 2nd line treatment. In second cohort patients were treated with standard chemotherapy protocols. Efficacy was assessed in terms of RR(response rate) and PFS(progression free survival).

Results: For patients treated with pazopanib PFS in 2nd line therapy was 4.6 months and for trabectidine group 6.15 months. Patients receiving standard chemotherapy as a 2nd line treatment had PFS of 2.0 months.

Conclusions: Doxorubicin monotherapy is currently the only standard option for the first-line treatment of STS. For second-line and subsequent lines of treatment, there is no standard therapy. Results of our study confirmed superior efficacy of novel therapies pazopanib and trabectedin over standard chemotherapy. Our results are in correlation with results of pivotal trials (PALETTE and ET743-SAR-3007 trial) for pazopanib and trabectedin. Future clinical trials should adress issues such as sequential therapy, identification of biomarkers and the use of immunotherapy in sarcoma treatment.Clinical studies exploring efficacy of novel drugs in specific histologies are needed.

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What is off-label in cytotoxic therapy of solid tumors today?

Key words: chemotherapy, off-label drug use

By definition off-label use is any intentional use of an authorized drug not in accordance with the Summary of Product Characteristic. This could mean the use for a different disease, in a different dose, frequency or duration of use, in a different method of administration, or by a different patient group. According to the *Study on off-label use of medicinal products in the European Union*, off-label prescription is most common in pediatrics, rare diseases, oncology/haematology, psychiatry and in special patient groups such as pregnant women and the elderly. In oncology specifically, if a chemotherapy drug is approved for treating one type of cancer but is used to treat a different cancer, or if it is used for treatment of a type of cancer in a stage other than the approved, it is considered off-label.

There are many reasons for the common practice of off-label use in oncology: some chemotherapy agents are effective for many different types of cancer; treatment often comprises of combination of drugs, some of which may not be approved for that specific disease; for some types of cancer there are limited treatment options or it is difficult to conduct randomised trials and there are always new findings regarding the efficacy of cancer drugs. Also, cancer patients and their physicians may be more willing to try off-label drugs as a last resort. One of the main reasons for off-label use of chemotherapy drugs is the unwillingness of pharmaceutical companies to undergo the costly and time-consuming process of approval for a new indication. Another important issue is the fact that there are many cases in national and international guidelines where proposed drugs are actually off-label for that indication. A study by Saiyed et al showed that up to 71% of adult cancer patients receive a minimum one off-label chemotherapy during the disease trajectory, mostly in metastatic disease. The

most commonly administered off-label drugs were carboplatin, doxorubicin, fluorouracil, paclitaxel, docetaxel, vinorelbine, gemcitabine and oxaliplatin.

In the European Union, off-label prescription is not prohibited or even regulated by law. In governmental health care institutions in Serbia, off-label use of cancer drugs is generally discouraged, but if considered, a special approval from the institution's Ethics Board is recommended. However, the provisions of the *Law on Medicines and Medicinal Devices* indirectly indicate that off-label use of medicinal devices can be allowed if certain conditions are met, but are less clear when it comes to off-label use of medicines. Despite the insufficiently clear regulation, even when all stated conditions are met, the prescribing physician can be held professionally, even legally accountable for any inadvertent occurrences during the treatment.

Off-label use in oncology is a common occurrence and not an illegal one, but remains a poorly defined and regulated area.

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Standard chemotherapy in gastrointestinal tumors

OESOPHAGEAL CANCER: In palliative treatment patients with advanced esophageal adenocarcinoma are managed according to the recommendations for gastric cancer. Oxaliplatin/fluoropyrimidine is alternative to cisplatin/5-FU. Taxanes are recommended in first-line combinations or as monotherapy in second-line therapy. In SCC Cisplatin-based combinations increased RR but no survival gain compared with monotherapy.

GASTIC CANCER: Routine sequence for metastatic gastric cancer (mOS 16-18m) is fluoropyrimidine and platinum combinations and taxanes in second line therapy. Trastuzumab + CF in HER2-positive patients show benefit in OS 13.8 vs 11.1 (HR 0.74, p value 0.0046). For patients with ≥Stage IB gastric cancer who have surgery without preoperative chemotherapy postoperative chemoradiotherapy or adjuvant capecitabine-oxaliplatin is recommended. Perioperative chemotherapy with a platinum/fluoropyrimidine doublet or triplet is recommended for patients with ≥Stage IB resectable gastric cancer. Perioperative FLOT demonstrated higher pathological response vs ECF/X, 5 y OS 45% vs 36% (HR 0.77). Patients undergoing chemotherapy followed by surgery had similar OS and PFS regardless if they received postoperative chemotherapy or CRT.

PANCREATIC CANCER: Gemcitabine/capecitabin chemotherapy showed benefit vs gemcitabine in adjuvant setting OS 28.0 vs 25.5 m (HR 0.82) as well as mFolfirinox vs gemcitabin, OS 54.4m vs 35,0m but with significant toxicity. For borderline resectable lesions chemotherapy (gemcitabine or FOLFIRINOX) followed by chemoradiation and surgery appears to be the best option. In treatment of metastatic pancreatic cancer (patients with PS 0/1) FOLFIRINOX or gemcitabine/nab-paclitaxel should be considered or monotherapy with gemcitabine in patients with PS 2.

BILIARY TRACT: UK ABC-02 study (faze 3) established cisplatin/gemcitabine combination as a standard of care in advanced BTC,

mOS 11.7m vs 8.1m for gemcitabine alone. NCCN include various combinations of gemcitabine, oxaliplatin, fluoropyrimidine as first line therapy for metastatic disease (phase II trials).

COLON CANCER: Adjuvant treatment with FOLFOX increased DFS at 3 years versus LV/5FU. 6-year follow-up confirmed the benefit in DFS and OS but for stage III patients only. In metastatic setting for patients who have left-sided RAS wt disease doublet chemotherapy + EGFR antibody should be the treatment of choice. For right-sided RAS wt disease triplet CT + bevacizumab or doublet CT + EGFR antibody can be the treatment of choice. For RAS mutant disease doublet CT + bevacizumab or triplet CT + bevacizumab are the preferred options.

ANAL CANCER: Fit patients with symptomatic metastatic or recurrent disease not amenable to surgery (10%–20%) should be considered for chemotherapy cisplatin + 5-FU. NCCN 2018 recommended carboplatin/docetaxel as a first line therapy based on phase II InterAACT study (carboplatin+ paclitaxel vs 5FU+ cisplatin) which observed superior OS of 20m vs 12.3 m (p=.014) and fewer SAE.

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Systemic treatment of breast cancer with cytotoxic chemotherapy

Key words: chemotherapy, breast cancer, targeted therapy.

Adjuvant systemic therapies, including endocrine therapy, anti-HER2 therapy and chemotherapy, are effective in reducing the risk of distant, local recurrence and breast cancer mortality rates. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has periodically reported meta-analyses of all clinical trials with available data that have added to our knowledge about the benefits of adjuvant systemic therapy (1).

Although adjuvant treatments are routinely guided by predictive factors for endocrine therapy (hormone receptor expression) and anti-HER2 therapy (HER2 overexpression), predicting benefit from chemotherapy has been more challenging. The first randomized trial evaluating adjuvant chemotherapy in breast cancer was the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-01 trial initiated in 1958, which reported in 1968 that an adjuvant alkylating agent (thiotepa) given after radical mastectomy significantly decreased recurrence rate in pre-menopausal women with four or more positive axillary lymph nodes. Other trial showed that combination chemotherapy regimen called "CMF" including an alkylating agent (cyclophosphamide) and antimetabolites (methotrexate and 5-fluorouracil) significantly reduced the risk of recurrence, announcing modern age of adjuvant polychemotherapy regimens that are now commonly used in clinical practice. Anthracyclines and taxanes integrated into adjuvant chemotherapy regimens produce additional survival gains presenting nowadays the most effective chemotherapy for breast cancer treatment.

Although the widespread adoption of more effective systemic therapies contributed to declining breast cancer mortality rates,

it also resulted in many patients being unintentionally "overtreated" with chemotherapy who might otherwise may been cured without it. Randomized studies have shown that multiparameter gene expression assays may more accurately select patients most likely to benefit from adjuvant chemotherapy (2).

Predict v2 is a web-based decision aid commonly used in clinical practice that allows clinicians and patients to better understand the potential benefits of adjuvant therapy, especially chemotherapy. Estimates provided by Predict have been shown to correlate closely with actual clinical outcomes in population-based and hospital-based cohorts. In an era of precision oncology, accurate and validated models that predict patient outcomes are valuable clinical tools.

The treatment of advanced breast cancer has relied largely on the use of sequential single-agent chemotherapies, except in cases of severe symptomatic disease burden where it may be appropriate to use combinations (3). This is for patients who either are steroid receptor-negative and HER2-negative or patients who have had prior endocrine therapy having become endocrine-resistant. For the HER2 population, chemotherapy is the backbone of the treatment, and used in combination with effective anti-HER2 targeted therapy, makes synergies in order to get cytoreduction, strong apoptotic stimulus and reduction of tumour burden. In patients with triple-negative breast cancer, the inhibition of programmed death 1 (PD-1) and PD-L1 was proven as useful treatment strategy in combination with chemotherapy, which may enhance tumour-antigen release and antitumor responses to immune checkpoint inhibition.

Currently, open question remains regarding the optimal use of chemotherapy in clinical practice, such as accurate identification, if possible by biomarkers, of the patients who need to be treated with chemotherapy and those who can be adequately treated with targeted agents alone.

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Standards of cytotoxic chemotherapy in gynecologic oncology

Key words: ovarian cancer, endometrial cancer, cervical carcinoma

Ovarian cancer is recognised as a heterogeneous disease. The dualistic model for the pathogenesis of this disease has emerged, which divides epithelial tumours into type 1 and type 2 ovarian carcinomas. Standard chemotherapy consists of a combination of paclitaxel 175 mg/m^2 and carboplatin AUC 6-5, both administered intravenously every 3 weeks. Dose-dense scheduling to improve the effectiveness of paclitaxel chemotherapy has also been explored in ovarian cancer. A Japanese study (NOVEL–JGOG 3062) compared 3-weekly paclitaxel and carboplatin with the same dose of carboplatin every 3 weeks (AUC 6) and paclitaxel administered in a weekly dose of 80 mg/m2. Significant benefits in PFS and OS were seen at 3 years. Three trials GOG 262 , ICON 8 and MITO7 were recently completed, but in the absence of confirmatory data, dose-dense administration of paclitaxel currently can only be considered an option, and not as a standard of care.

Endometrial cancer is the most common gynecological cancer in developed countries. Historically, endometrial carcinoma has been classified into two main clinicopathological and molecular types: type I is the much more common endometrioid adenocarcinoma (80%–90%) and type II comprises non-endometrioid subtypes such as serous, clear-cell and undifferentiated carcinomas, as well as carcinosarcoma/malignant-mixed Müllerian tumour (10%–20%). Hormone therapy is the preferred front-line

systemic therapy for patients with hormone receptor-positive grade 1 or 2 tumours in the absence of rapidly progressive disease, as it provides an excellent benefit/risk ratio and convenient toxicity profile. However, patients with visceral involvement and rapidly progressive disease are not candidates for hormone therapy. The standard of care is six cycles of 3-weekly carboplatin and paclitaxel.

The most significant cause of cervical cancer is persistent papilloma virus infection. HPV is detected in 99% of cervical tumours, particularly the oncogenic subtypes such as HPV 16 and 18. The World Health Organization (WHO) recognises three categories of epithelial tumours of the cervix: squamous, adenocarcinoma and other epithelial tumours including adenosquamous carcinoma, neuroendocrine tumours and undifferentiated carcinoma. A large randomised phase III trial (GOG-204) comparing four different cisplatin-based doublets with paclitaxel, topotecan, gemcitabine or vinorelbine was unable to demonstrate the superiority of any regimen. Nevertheless, paclitaxel–cisplatin showed the highest response rate (29%), median PFS (5.8 months) and median OS (12.8 months) and was considered the preferred regimen based on the balance between efficacy and toxicity profile. Based on this observation, the GOG-240 study explored the addition of bevacizumab to chemotherapy in a randomised phase III trial. Two main conclusions were obtained from this study: first, the median OS is significantly prolonged by the addition of bevacizumab (16.8 versus 13.3 months; HR 0.765; 95%CI: 0.62–0.95;P=0.0068) and second, non-platinum doublet is not superior to cisplatin–paclitaxel, even in the population previously treated with cisplatin.

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Molecular pathology in lung cancer

Key words: adenocarcinoma, immunohistochemistry, lung, next generation sequencing, squamous cell carcinoma

Lung carcinoma is still the leading cause of cancer-related death worldwide. It is a rather heterogeneous group of tumors, with predominance of adenocarcinomas (40%) and squamous cell carcinomas (35%), followed by small cell carcinoma (15%) and other rare types. Due to the late occurrence of symptoms, it is most commonly diagnosed in an advanced stage, and overall combined 5-year survival is still around 15-17%.

However, there is no other field in pathology and oncology, where in the last decade such a big progress in precise therapy development has occurred. Especially in adenocarcinoma, where many targetable mutations have been detected, resulting in new diagnostic responsibilities for lung pathologists. According to the international recommendations, in an ideal case, all newly diagnosed adenocarcinomas, and carcinomas where adenocarcinoma cannot be excluded, should undergo reflex molecular testing. The most important mutations for analysis nowadays include EGFR, ALK, and ROS-1, with the addition of BRAF, HER2, RET and MET analysis if possible. Although there are many different methods of testing, multiplex gene analysis is recommended. It will provide the most information out of the smallest sample. The panel for testing should include EGFR, BRAF, and HER2 genes. Immunohistochemistry, if strongly positive, is the method of choice for the ALK translocation testing, while positive immunohistochemical reaction for ROS-1 must be confirmed with additional molecular testing (fluorescence in situ hybridization or PCR based methods). On the other hand, there are still no targetable and clinically important mutations in squamous cell carcinomas and small cell carcinomas.

Like in other solid tumors, immunotherapy has a very important role in lung carcinoma treatment, namely in adenocarcinomas and squamous cell carcinomas. Since there is no single ideal biomarker predictive for immunotherapy, PD-L1 expression on tumor cells is the best one available and applicable in routine praxis. However, problem is that PD-L1 is rather fluctuating in time and space. Furthermore, there are 5 different clones used in different clinical studies, with different cut-off values for positivity and different relation to the therapy response. In praxis that means that pathologist should know how good specific PD-L1 clone performs in their institution, and communicate this to the oncologist, who needs this information to make the best possible choice for the patient.

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Liquid biopsy in cancer: The future is now

Key words: liquid biopsy, next generation sequencing, NSCLC, targeted therapies

The results of many pharmacogenomics research in recent years, overcame the old paradigm of 'one size fits all' in oncology, providing a large amount of molecular data that generated the concept of 'precision medicine'. Non–small cell lung cancer (NSCLC) has become a prominent example of precision medicine among solid tumor malignancies.

Comprehensive genomic profiling of lung cancers revealed their genetic heterogeneity and complexity and identified numerous targetable oncogenic driver alterations. These molecular profiling efforts have made it possible to exploit the potential of molecularly targeted therapies. As molecular testing becomes increasingly important, preserving tissue for this purpose while rendering an accurate histologic diagnosis becomes a key consideration, especially in advanced-stage NSCLC, in which small biopsy samples are often the only specimen available. Furthermore, traditional sampling methods are usually invasive, frequently unrepeatable and cannot be performed when clinical conditions have worsened or when a tumor is inaccessible. Additionally, the molecular profiling of biopsy tissues provides a tumor picture limited to a single point in time. Numerous studies have established that the genomic landscape of tumors and metastases dynamically evolve over time in response to selective pressure of therapies that can suppress or promote the growth of different cellular clones. These limitations are particularly evident in the presence of acquired resistance to therapy or in monitoring the disease during follow up. Now, attention is turning to minimally invasive liquid biopsies, which enable analysis of tumor components (including circulating tumor cells and circulating tumor DNA) in bodily fluids such as blood. The potential of liquid biopsies is highlighted by studies that show they can track the evolutionary dynamics and heterogeneity of tumors and can detect very early emergence of therapy resistance, residual disease and recurrence. The initial limitations due to the scarcity of nucleic acid as well as the difficulty in distinguishing between normal and tumor nucleic acids have been overcome by the increased sensitivity of next-generation sequencing (NGS) techniques, which now may accurately detect genetic and epigenetic aberrations.

Although molecular profiling has traditionally relied on direct sampling of tumor tissue, blood-based diagnostics now offer the potential to provide some clinically useful information noninvasively.

The future clinical uptake of liquid biopsies will depend on the practical advantages for patients and clinicians.

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Patterns of response and progression to immunotherapy

Key words: pancreatic cancer, FOLFIRINOX, Gemcitabine, PRODIGE study

Patterns of response and progression to immunotherapy may differ from those observed with drugs such as chemotherapy and molecularly targeted agents. Specifically, some patients experience a response after progression that is retrospectively named pseudoprogression. This phenomenon of pseudoprogression, first reported in patients with melanoma who were treated with ipilimumab, has led to the development of immune-specific related response criteria, such as irRC (immune related response criteria), irRECIST (immune-related RECIST), and iRECIST (immunotherapy RECIST) that allow continued treatment beyond progression. However, the rate of pseudoprogression has never exceeded 10% of patients across tumor types. Conversely, rapid progressions after immunotherapy, called hyperprogressions occur in similarly smaller proportion of patients treated with immunotherapy. Because of the absence of control arms in these studies, it remains to be determined whether these rapid progressions reflect a detrimental effect of immunotherapy in these patients. Finally, preliminary data suggest that immunotherapy might also affect response to subsequent standard therapies. In total, given the rarity of pseudoprogressions across tumor types and the recent description of hyperprogressions, classic RECIST remains a reasonable and rational method to assess response to immunotherapy. Continuation of treatment beyond progression should be proposed only in carefully selected patients whose clinical conditions have improved and who have not experienced severe toxicities.

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Treatment of a patient with metastatic pancreatic cancer

Introduction: Pancreatic adenocarcinoma is a major cause of cancer-related death in Western countries and is anticipated to emerge as the second leading cause of cancer-related death in the United States by 2030. It remains the most lethal cancer, primarily as a result of the advanced stage at the time of diagnosis for the majority of patients and limited treatment options. Although chemotherapy regimens, including FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin), gemcitabine and nab-paclitaxel, have improved survival, there remains a paucity of effective therapeutic options beyond these combinations. Chemotherapy, however, remains the mainstay of treatment.

Case presentation: A 48-year-old female patient, was presented at the multidisciplinary medical council for the gastro-intestinal tumors, after the pancreatoduodenectomy sec Whipple due to pancreatic tumor. Pathohistological diagnosis was: Adenocarcinoma ductale gr II capitis pancreatis pT3N1 (2/18) MxR0. Adjuvant treatment was started 6 cycles of MKT Gemcitabine D1, D8, D15 q4w. Reevaluation after sixth cycle with CT scan of abdomen and pelvis showed no signs of disease. Regular FU was performed with CT scan every six months. After two years, an elevation of tumor markers CEA and CA 19-9 occurred. PET/

CT scan showed adnexal mass aprox 61mm. Surgery was performed and carcinosis of peritoneum was found and confirmed with biopsy and pathohistological finding. First line of chemotherapy for metastatic disease was started, the FOLFIRINOX. After 12 cycles disease was stable and only FOLFIRI was continued due to oxaliplatin neuropathy grade II. After 3 months of FOLFIRI protocol, reevaluation showed progression so second line of therapy for metastatic disease was started. Currently the patient is receiving her third cycle of Carboplatin D1/Gemcitabine D1, D8. Also the results of the NGS testing are expected.

Discussion: Results from PRODIGE study showed a significant improvement in median disease free survival (21.6 vs. 12.8 months) in patients receiving mFOLFIRINOX compared to those receiving standard chemotherapy with Gemcitabine as a single agent, as was the median overall survival (54.4 vs. 35.0 months). Adjuvant therapy with a modified FOLFIRINOX regimen led to significantly longer survival than Gemcitabine among patients with resected pancreatic cancer, at the expense of a higher incidence of toxic effects.

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Role of the PET-CT in defining primary origin of the metastatic disease

67-year old man presented with fatigue and microcytic anemia. More then 20 years ago he underwent nephrectomy for clear cell renal carcinoma and excision of left lower leg melanoma. Gastroenterology workup revealed no pathology. Abdominal MSCT showed possible pancreatic tumor. PET-CT showed infiltrative lesion of the pancreas resembling primary pancreatic cancer or metastasis of renal carcinoma, possible infiltration of the small bowel and paravertebral muscle resembling melanoma metastases, subcutaneous infiltration of left lower leg suggesting possible melanoma metastasis or local recidiva and marginally enlarged mesenterial lymph nodes without pathological FDG accumulation. Excision of the subcutaneous lesion of the left lower leg revealed melanoma metastasis and CT guided biopsy of pancreas revealed renal cell carcinoma metastasis. As disseminated renal cell carcinoma was confirmed and melanoma dissemination was not, treatment with sunitinib was initiated. After four cycles of sunitinib, patient developed bowel opstruction and underwent surgery. Resection of the small bowel with tumor was done and pathology revealed metastasis of the melanoma. PET-CT was done after surgery and showed stable disease in the pancreas, partial regression of mesenterial lymph nodes and complete regression of the lesion in the paravertebral muscle.

Presented patient obviously had diseminated disease of two different origins what was initially suggested by PET-CT finding. Therefore, PET-CT can be considered useful tool in the oncology treatment decision making.

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Early and locally advanced HER2-positive breast cancer

Key words: anti-HER2 therapies, early and locally advanced stage, HER2-positive breast cancer

Although HER2-positive breast cancer is an aggressive disease historically associated with high relapse and mortality rates, HER2-targeted therapies have revolutionized treatment and led to significantly improved outcomes for many patients.

Combining trastuzumab, an anti-human epidermal growth factor receptor2 (HER2) monoclonal antibody that binds close to the transmembrane domain inhibiting HER2 dimerization and inducing antibody-dependent cell-mediated cytotoxicity, with adjuvant chemotherapy has dramatically improved the prognosis for patients with early stage HER2-positive breast cancer. Several adjuvant pivotal trials demonstrated consistent DFS and OS benefit over time with one year of trastuzumab treatment and established the combination of chemotherapy and one year of trastuzumab as the standard of care for this patient population. Yet, long-term follow-up data indicate that 15-24% of patients still develop recurrent disease. Most of the research has focused on the addition of novel anti-HER2 drugs to standard therapy.

Results of APHINITY study showed that pertuzumab, a humanized monoclonal antibody that has mechanisms of action complementary to those of trastuzumab binding to the dimerization domain and inhibiting HER2 heterodimerization with other HER family receptors, significantly improved the rates of invasive-disease-free survival among patients with HER2-positive operable breast cancer when it was added to trastuzumab and chemotherapy. The study demonstrated a 1.7% absolute improvement in disease-free survival at 4 years, with more pronounced effect of adding adjuvant pertuzumab to standard trastuzumab and chemotherapy in cohorts of higher-risk patients (patients with node-positive disease or hormone-receptor negative tumors).

Improved neoadjuvant outcomes with the addition of HER2-targeted therapy to chemotherapy were demonstrated in pivotal NOAH study that inducted trastuzumab plus chemotherapy as the neoadjuvant standard of care for HER2-positive breast cancer. As part of a neoadjuvant regimen, pertuzumab added to trastuzumab plus docetaxel in NeoSphere study was shown to significantly increase the rate of pathological complete response (tpCR 39.3% vs 21.5%) and TRYPHAENA study further confirmed high pCR rates with pertuzumab and trastuzumab added to different chemotherapy regimens. Dual HER2 blockade with trastuzumab and pertuzumab plus chemotherapy is considered the current standard of care in neoadjuvant setting for early and locally advanced HER2-positive breast cancer.

ExteNET study indicated that one year of extended adjuvant therapy with neratinib, an oral irreversible pan-HER2 small-molecule tyrosine kinase inhibitor, administered after chemotherapy and trastuzumab significantly reduced the proportion of distant and locoregional relapses, with extended treatment with neratinib particularly beneficial for patients with HR-positive disease.

Among patients with HER2-positive early breast cancer who had residual invasive disease after completion of neoadjuvant therapy in KATHERINE study, the risk of recurrence of invasive breast cancer or death was 50% lower with adjuvant trastuzumab emtansine, an antibody-drug conjugate of trastuzumab and the cytotoxic agent emtansine, a maytansine derivative and microtubule inhibitor, than with trastuzumab alone.

Biological heterogeneity with HER2-positive early and locally advanced breast cancer may determine response to treatment and prognosis. Different subgroups of patients with HER2-positive breast cancer may benefit from different therapeutic approaches. Thus, there is ongoing work to optimize treatment in this patient population.

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Luminal, HER2-negative breast cancer - new targeted drugs

Keywords: Estrogene receptor (ER) positive, HER2-negative breast cancer; Cyclin-dependent kinase (CDK) 4 and 6; Mammalian target of rapamycin (mTOR); Phosphatidylinositol 3-kinases (PI3Ks)

Luminal, HER2 negative breast cancer subtype, which represents approximately 70% of all breast cancers respond well to endocrine therapy (ET). For many decades, blockade of estrogen receptor signaling was the basis for local, advanced, and metastatic HR+/HER2– breast cancer treatment. However, all advanced breast cancer patients eventually developed resistance to ET throughout the course of their disease. Drug resistance remains a clinical challenge in this disease. Recent advances in elucidating the molecular mechanisms of pathway "cross-talk" between the estrogen receptor (ER), cell-cycle regulation and intracellular signaling pathways, such as the CDK–RB–E2F pathway or the PI3K/Akt/mTOR pathway, have provided the rationale for combining endocrine therapies with targeted agents.

Cyclins and cyclin dependent kinases (CDKs), play a very important role in the cell cycle, regulating the transition from the phase G1 to the phase S. CDK4 and CDK6 bind cyclin D promoting the hyperphosphorylation, and thus deactivation of the retinoblastoma protein (pRb). Hyperphosphorylated pRb releases E2F to express genes needed to proceed to S-phase. Therefore, in its physiological role, hypophosphorylated pRb acts as a tumor suppressor by slowing the progression of the cell cycle to the S-phase. Multiple studies have shown that targeting CDK 4/6 resulted in substantial improvements in clinical response and progression-free survival (PFS) in women with metastatic ER-positive breast cancer. The CDK inhibitor story is perhaps one of the most important targeted therapy stories of the past few years. Remarkably, three new CDK 4/6 inhibitors, including palbociclib, ribociclib and abemaciclib received approvals from the EMA and FDA. These approvals were based on the initial randomized phase II study evaluating palbociclib in combination with letrozole and subsequent phase III studies (PALOMA 2 and 3, MONALEESA 2 and 3 and MONARCH 2 and 3) showing that the addition of palbociclib, ribociclib and abemaciclib in combination with aromatase inhibitors or fulvestrant.

The mTOR pathway is frequently hyperactivated in ER-positive breast cancer. Inhibitors of mTOR comprise another important chapter in the story of endocrine resistance. mTOR activates ER in a ligand-independent fashion, and hyperactivation of this pathway has been observed in endocrine-resistant breast cancer cells. Therefore, mTOR has become a rational target to enhance the efficacy of ET. The BOLERO 2 trial showed that, in patients with ER-positive metastatic breast cancer resistant to letrozole or anastrozole who were given exemestane as the next line of therapy, the mTOR inhibitor everolimus, when given with exemestane, could extend PFS.

PIK3CA (which encodes phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit α) is frequently mutated in breast cancer, and 30-40% of advanced ER-positive HER2-negative breast cancers have an activating PIK3CA mutation. The phase III trial SOLAR1 I showed that in patients with PIC3CA mutated tumors, pretreated with aromatase inhibitors +/- CDK4/6 inhibitors, addition of selective PIC3CA-alpha inhibitor alpesilib to fulvestrant prolong PFS compared with fulvestrant and placebo.

A number of ongoing clinical trials are exploring the optimal combination and sequencing of the above-mentioned therapies in ER-positive metastatic disease and at other possible therapeutic targets.

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ALK and EGFR positive lung cancer - do we have a therapeutic algorithm?

Key words: adenocarcinoma, ALK inhibitors, EGFR inhibitors, lung cancer, targeted therapy

Groundbreaking research on the molecular drivers of NSCLC has led to major therapeutic advances over the past decade. EGFR and ALK tyrosine kinase inhibitors entered the treatment guidelines for advanced stage lung adenocarcinoma after remarkable results observed through high response rate (RR) and significantly improved progression free survival (PFS). Pivotal trials in both groups of targeted therapeutics failed to show significant improvement in overall survival (OS), mainly due to cross-over and the fact that phase III TKI trials were not powered to demonstrate OS superiority. However, real world data published so far, show significant prolongation of overall survival when compared to chemotherapy, mostly because of appearance of next generation drugs directed towards resistance mutations. EGFR inhibitors evolved from first generation drugs (erlotinib, gefitinib) through second generation (afatinib, dacomitinib) to third generation (osimertinib). ALK inhibitors evolved from crizotinib as first generation, through second generation ceritinib, alectnib and brigatinib to third generation lorlatinib. Each generation shows better PFS and OS results, even in head to head trials. These results are raising the question of treatment sequencing in order to improve PFS and OS in advanced stage oncogene addicted lung adenocarcinoma. While many authors believe in the concept of "first strike" with the most potent drug, others advocate escalation approach keeping the most potent drug for "additional strike". The true evidence based sequencing algorithm will remain unknown for the time being. Large, real world metadata are needed to clarify the most viable sequence. However, new TKI's in both groups are emerging, targeting secondary and tertiary resistance mutations but also primary driver mutations what complicates the treatment decisions even more (1). The FLAURA trial (2) shifted osimertinib, the third generation TKI, into the first line treatment of EGFR positive lung adenocarcinoma, while ALEX trial (3) shifted alectinib in the first line treatment of ALK positive lung adenocarcinoma. Currently these two studies dictate standard of care in first line treatment, however with the maturation of data in forthcoming phase III trials on next generation TKI's, the tides could just as easy turn to some other compounds. One must have in mind the possibilities of combination with immunotherapy, even though the data seen so far do not encourage such concepts. So, for the time being we do have algorithm of treatment (for oncogene addicted lung cancers) as given in major guidelines, but we do not have evidence based sequencing recommendation.

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Renal cancer – biologic therapy in the treatment algorithm

Key words: Renal cancer , targeted therapy, immunotherapy , biomarker.

Renal cell carcinoma (RCC) represents 2% to 3% of all cancers, and its incidence is rising. Established risk factors include tobacco smoking, body size, and history of hypertension and chronic kidney disease. Improvement of understanding of pathways engaged in RCC pathogenesis has produced creation of molecular targeted and immunotherapy treatment options for patients with RCC. Recent adjuvant vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) trails in resected high risk RCC that compared sunitinib, sorafenib, pazopanib and axitinib with placebo demonstrated some mixed impact on DFS, but no improvement in OS and thus, are controversial. The systemic treatment of advanced RCC has experienced tremendous evolution over past 15 years. Until recently, sequential VEGF targeted therapy or VEGF followed by MTOR inhibition has been most used treatment algorithm for patients with RCC. However, newer agents such as cabozantinib and nivolumab started to change those approaches. In addition, combination treatments including nivolumab and ipilimumab and atezolizumab plus bevacizumab have transformed whole RCC treatment landscape, with other doublet combos in clinical testing will very likely continue to alter the treatment paradigm in RCC. Clinical progress in RCC treatment is evident but there is still unmet need for whole RCC treatment landscape with no Level I evidence for predictive biomarker in clinical routine use and additional strategies are warranted.

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Hormone-sensitive and castration-resistant prostate cancer today

Key words: prostate cancer, treatment, hormone-sensitivity, castration-resistance

Prostate cancer accounts for one in every five cancer diagnoses, making it the most common cancer in men. Patients presenting with advanced disease typically receive hormonal therapy using medical or surgical castration as initial treatment. However, most prostate cancer patients acquire resistance to the initial hormonal therapy over 2-3 years. Recent advances have completely transformed the therapeutic landscape in advanced prostate cancer. Novel hormonal treatments and chemotherapy have proven efficacy in earlier stages of the disease, as well.

Since docetaxel was introduced in 2004 to prolonging the survival of patients with castration-resistant prostate cancer (CRPC), there has been a rapid increase in the number of effective systemic agents for CRPC, including novel androgen receptor-directed (abiraterone-acetate, enzalutamide), immunotherapeutic (sipuleucel-T if asymptomatic or minimally symptomatic patient and without visceral or liver metastases), chemotherapeutic (cabazitaxel) and radiopharmaceutical drug (radium-223 for symptomatic bone metastases without visceral metastases). However, no consensus exists for the best additional therapy for patients with metastatic CRPC after docetaxel failure.

Concomitant docetaxel or abiraterone-acetate treatment at the beginning of hormonal therapy for metastatic castration-sensitive prostate cancer (CSPC) has resulted in longer overall surviv-

al than hormonal therapy alone. Both docetaxel and abiraterone represent a new standard of care for metastatic CSPC.

The therapeutic landscape of advanced prostate cancer is continuously changing under the light of new available treatment options and the improved understanding of the molecular characteristics of the disease. The lack of high quality evidence regarding the sequencing of these treatments along with the earlier implementation of these therapeutic approaches during the course of the disease have created issues of dispute regarding the optimal treatment of patients with advanced prostate cancer. Elucidating an appropriate treatment sequence is important for maximizing clinical benefit in CSPC and CRPC patients. Improvements in technology aimed at genomic and metabolic analysis have led to the discovery of potential new biomarkers that may be utilized in the prediction of prostate cancer outcome and response to therapy.

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Update on biologic therapy in gynecological cancers

In the last decade significant improvement in treatment of gynecological malignancies has been achieved. Today, patients with advanced cervical and ovarian cancer are living longer, as more treatment options are available in the setting of recurrent disease.

Concept of angiogenesis inhibition and use of VEGF inhibitor bevacizumab particularly, proved efficacy in patients with ovarian cancer in the front line (GOG 218 and ICON 7) and recurrent setting (AURELIA and OCEAN trial), increasing progression free survival (PFS) in considerable number of patients. For patients with cervical carcinoma addition of bevacizumab to chemotherapy (GOG 240) increased overall survival (OS) for more than 3 months compared to chemotherapy alone.

Recently, poly(ADP-ribose) polymerase (PARP) inhibitors niraparib, rucaparib and olaparib were approved for maintenance therapy following second-line platinum-based therapy in all ovarian cancer patients and have changed the standard of care in this setting. Substantial improvement in PFS in newly diagnosed patients with advanced ovarian cancer and a BRCA1/2 mutation were reported in phase III SOLO-1 trial with olaparib as maintenance therapy. As over 50% of women on the olaparib arm were still progression-free at 4 years compared to only 11% for placebo, there is a real hope that this treatment will lead to increased cure rates.

Use of immune checkpoint inhibitors for all gynecologic malignancies continue to broaden the landscape of options for women with recurrent disease. PD-1 inhibitors pembrolizumab and nivolumab have been approved for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed after previous treatment, an approval that will provide a new option for women with MSI-H recurrent endome-

trial cancer (~20% will be MSI-H) and other MSI-H gynecologic malignancies.

The future of targeted therapy and immunotherapy in the treatment of gynecologic malignancies is promising and it probably lies in the combination of these agents as well as their combination with chemotherapy. Multiple studies, both in front-line and recurrent setting, are ongoing and result are awaited. It is certain that a better understanding of the tumor microenvironment and biomarkers that will predict the responsiveness of the individual patient to a particular therapy will have great impact on survival of patients with gynecological malignancies in the future.

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Soft-tissue sarcoma - the time for biological therapy?

Key words: soft tissue sarcoma, biological therapy, olaratumab

Doxorubicin based chemotherapy was a mainstay of treatment for locally advanced and disseminated soft tissue sarcomas (STS) for many decades. Problem with subsequent lines of treatment appears anyway as a matter of debate.

Recently, in the era of new drugs called signal inhibitors, PDGFR inhibitor olaratumab combined with Doxorubicin revealed significant improvement in the overall survival without significant damage regarding adverse events of therapy. Unfortunately, those findings from phase II study were not confirmed in the phase III study according to results reported recently by FDA and EMA. Results of other studies with olaratumab combined with doxorubicin and ifosfamide and also gemcitabine and docetaxel are eagerly awaited.

In the mean time, many biological drugs proved activity in subsequent lines of advanced STS treatment. Pazopanib, a multikinase signal inhibitor, has been established in the third line of treatment since 2012. Phase III Pallete study showed longer PFS in non adipocytic STS with acceptable toxicities. Regorafenib and anlotinib as members of the same family of drugs appear to be active as well as palbocyclib, a CDK 4/6 inhibitor and NTRK fusion inhibitor larotrectinib in rare pediatrics sarcomas. Those drugs are now in enrolling phase II and III studies worldwide.

Obviously, the time for biological therapy for soft tissue sarcomas has begun. We are still waiting for a real breakthrough.

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Patient with ovarian cancer treated with PARP inhibitor olaparib

Key words: ovarian cancer, PARP inhibitor, olaparib

A 59 year old lady, without comorbidities till that time, with positive family history for ovarian cancer, was diagnosed with stage IIIA high grade serous ovarian cancer. She successfully underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy and omentectomy. Postoperatively she received 6 cycles of chemotherapy with carboplatin and paclitaxel,

which she tolerated well and without any unexpected toxicity. She achieved a complete remission with CA125 being in normal range at the end of the treatment.

After 27 months of follow-up, she presented with headache, vertigo and instability. A CT scan of the head was done, followed by an MRI, confirming three brain lesions, 33 mm, 18 mm and 11 mm in diameter. A neurosurgical resection of the biggest lesion in the right cerebellum was performed. Histology revealed it was a metastasis of high grade serous ovarian cancer. Stereotactic radiosurgery of the two remaining cerebellar metastasis was done. PET/CT showed no distant metastasis, patient received no systemic therapy at that time. After 5 months, the patient developed a new brain metastasis in the right frontoparietal lobe. She had another stereotactic radiosurgery performed, this time together with hippocampal sparing whole-brain radiotherapy. A partial response of the brain metastasis was achieved.

During follow-up, 3 months later, a CT scan of thorax and abdomen showed a systemic progression with new peritoneal and abdomino-pelvic nodal disease, all brain metastasis were stable. Level of CA125 reached 188 U/mL. The patients reported some abdominal discomfort and pain, which was well controlled with metamizole tablets, she had no neurological symptoms. At that point, genetic testing was performed, the patient was found to have a BRCA1 germ line mutation. She started with systemic therapy with chemotherapy carboplatin and pegylated liposomal doxorubicin. After 5 cycles, level of CA125 declined to 54 U/mL, patient had less pain. She then continued treatment with maintenance olaparib capsules, 400 mg twice daily. Due to anemia grade 2 in the second month of maintenance treatment the dose was reduced to 300 mg twice daily. Patient reported also some occasional fatigue and nausea. After 3 months of olaparib levels of CA125 normalized. Now, after 17 months of maintenance olaparib, patients feels well and still has normal levels of serum CA125.

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Treatment of a patient with triple-negative breast cancer

Key words: triple negative breast cancer, BRCA, mutation, PARP inhibitors, Olaparib

Introduction: Triple-negative breast cancer (TNBC) is a subtype of aggressive breast cancer characterized by a lack of the estrogen receptor expression, progesterone receptor and HER2 receptors. BRCA genes are tumor-suppressor genes that are involved in DNA damage repair, thus mutations of BRCA genes may increase the risk of developing breast cancer due to defective DNA repair mechanisms. However, the relationship between BRCA status and TNBC needs to be further investigated and validated. [1] Therefore, defects in the DNA repair pathway could represent a promising therapeutic target for this subgroup of TNBC patients. PARP inhibitors exploit this deficiency through synthetic lethality and have emerged as promising anticancer therapies, especially in BRCA1 or BRCA2 mutation carriers. Several PARP inhibitors are currently being evaluated in the adjuvant, neo-adjuvant, and metastatic setting for the treatment of breast cancer patients. [2]

Case presentation: A 31-year-old patient was referred to Clinic of oncology with tumor mass in left breast, with core biopsy showing triple negative invasive ductal cancer. MRI of the abdomen showed lesion in the liver of unclear significance. Patient received neoadjuvant therapy: 6 cycles of TAC protocol, followed by quadrantectomy and dissection of axilla that showed PCR and radiation therapy, as well as metastasectomy of the liver lesion. Afterwards patient received 4 cycles of AC protocol and 12 weakly Paclitaxel. After year of FU, MRI of the abdomen showed progression in number of liver lesions. The molecular analysis showed positive BRCA mutation, so patient was started with Olaparib.

Discussion: Results from OLYMPIAD study showed a significant improvement in median progression free survival (7.0 months vs. 4.2 months) in patients receiving olaparib as a single agent compared to those receiving standard chemotherapy. 3 Final results of OlympiAD study showed no statistically significant improvement in OS with Olaparib compared to TPC, there was the possibility of meaningful OS benefit among patients who had not received chemotherapy for metastatic disease.

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Head and neck cancers – how far have we advanced?

Key words: head and neck cancer, systemic treatment, immunotherapy.

Although being relatively rare in developed countries, squamous cell cancers of head and neck (SCHNN) are the sixth most common malignancy worldwide with a global incidence of 3-5%. Well known risk factors are tobacco smoking, alcohol abuse and human papilloma virus (HPV) infection. SCHNC is an immunosuppressive illnes distinguished by impaired excretion of cytokines as well as dysregulation of immunocompetent cells. (1) Despite the advances in multimodality treatment, the 5-year progression free survival (PFS) rates in locally advanced disease do not exceed 40-50%, and survival in reccurent or metastatic settings (R/M) remains poor.

For decades in these patients the cornerstone of medical treatment had been related to the use of antimetabolites (5fluorouracil, methotrexate) and platinum derivatives (cisplatin, carboplatin) either alone or in combination. Since 2006, cetuximab, monoclonal antibody against the EGF receptor has been approved for SCHNC treatment as a single agent in R/M disease after failure of platinum-based chemotherapy or in concurrent setting with definitive radiotherapy. In 2011 the approval of cetuximab was extended to R/M SCHNC as first line treatment in conjunction with 5FU-cisplatin doublet.

Almost 10 years after approval of cetuximab, immunotherapy is beginning to emerge as a valid therapeutic option. At present, immune checkpoint inhibitors namely CTLA-4, PD-1 and PD-L1 monoclonal antibodies have been studied in SCHNC patients pertaining to various settings of clinical use. The anti-tumour effect consists of inhibition of the activity of immune checkpoints, blockade of immunosuppression in tumour environment and reactivation of T-cell immune response. The main PD-1 targeting agents approved in SCHNC at the moment are pembrolizumab and nivolumab, both PD-1 inhibiting IgG4 monoclonal antibodies with high specificity. Both drugs have been approved (nivolumab in the USA and Europe, pembrolizumab only in USA) for the treatment of patients with R/M SCHNC with disease progression on or after platinum-containing chemotherapy. According to the results of well designed clinical studies, Check Mate-141 and Keynote 012 these drugs represent a new standard of care with clinical benefit and favourable safety profile in aforementioned subset of patients with head and neck cancers. (2,3)

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Immunotherapy in gastrointestinal cancers

Key words: microsatellite instability (MSI), immunotherapy, GI cancers

Gastrointestinal (GI) cancers are a group of highly aggressive malignancies with a huge burden worldwide. There is clearly a significant need for new biomarkers and following treatments in order to improve outcomes of GI malignancies. Immunotherapy is a novel treatment strategy that is emerging as an effective and promising treatment option against several typer of cancers. There are critical immune checkpoint molecules, like CTLA-4 and PD-1, that negatively regulate T-cell activation via distinct mechanisms. One of the most important tumor biomarker predictive for immunotherapy is frequncy of microsatellites (MSI). MSI The frequency of MSI across gastrointestinal cancers is variable, mostly about 10%, but some data suggest it can be higher in different tumor types. Microsatellites are short and repetitive DNA sequences randomly widespread throughout the genome. The mismatch repair system deficiency (MMRD) is generally caused by germline mutations or sporadic epigenetic silencing that lead to insertion or deletions of nucleotides in the microsatellite regions during DNA replication; these phenomena are known as microsatellite instability (MSI). Recently, there is increasing number of clinical trials trying to define prognostic and predictive value as well correlation between MSI and clinical and pathological features in certain GI cancers. Further on, recent studies have hypothesized that alterations in the mismatch repair (MMR) system may predict clinical benefit for treatment with immune-checkpoint inhibitors. There is very important immunotherapy trial in gastric cancer compared pembrolizumab versus chemotherapy in second line for gastroesophageal junction adenocarcinoma (KEYNOTE-181) and the study was positive, with overall survival improved. Pembrolizumab was approved for gastric cancer treatment in 2017, based on a phase 2 study, analysing patients regerdless of MSI-status. Objective repsonse was 57 percent vs only 9 percent in percent with non-MSI-high tumors. Anti-PD1-therapy for MSI-high colorectal cancer was the first immunotherapy approved for gastrointestinal cancers. In CheckMate-142-trial nivolumab has already demonstrated durable responses, sustained disease control, and encouraging survival in patients with dMMR/MSI-H mCRC. Later on, the combination of nivolumab and ipilimumab after at least two lines of previous treatment, showed even better response, owing to sinergistic effect and different mechanisms of action. An estimated 15 percent of colorectal cancers are MSI-H, and about 3% of colorectal cancers with the abnomrality occur in patients who have Lynch syndrome. The identification of clinically relevant predictive and prognostic biomarkers will therefore help define subgroups of GI cancer patients who are most liekly to benefit from various immunotherapeutic strategies.

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Immunotherapy in urothelial cancer

Key words: checkpoint inhibitors, cisplatin-ineligible, muscle-invasive bladder cancer, neoadjuvant, non-muscle-invasive bladder cancer

Urothelial carcinoma has been regarded as an immune-responsive tumor since intravesical BCG therapy was proven effective for non-muscle-invasive bladder cancer (NMIBC). It is also known that there is a high prevalence of somatic mutations in metastatic urothelial cancer (mUC), hence this represents an attractive target for immunotherapy.

Drugs targeting the programmed death receptor or ligand (PD-1, PD-L1), also known as checkpoint inhibitors (CPIs), have drastically changed the treatment of metastatic urothelial carcinoma after decades of no progress in treatment advances. Since 2016, there have been five checkpoint inhibitors approved for mUC treatment.

Atezolizumab was the first CPI approved for platinum-refractory mUC based on the results from the phase 2 IMvigor210 trial, but phase 3 study IMvigor211 did not show survival benefit.

Pembrolizumab recived approval in the post-platinum setting based on the results of the phase 3 KEYNOTE-045 trial that demonstrated statistically significant improvement in overal survival (OS) regardless of the level of PD-L1 expression, 10.3 months vs 7.4 months with chemotherapy. Nivolumab, durvalumab and avelumab were also approved for platinum-refractory mUC based on phase 2 trials.

Platinum-based chemotherapy is still the backbone of first-line therapy in most patients. However, up to 60% of mUC patients are cisplatin-ineligible due to poor performance status, renal insufficiency or other comorbidities. Atezolizumab and pembrolizumab recived approval for cisplatin-ineligible patients based on the results of the cohort1 the IMvigor210 trial and the KEYNOTE-052 trial. Recent interim reviews of the two ongoing multi-arm clinical trials IMvigor130 and KEYNOTE-361 showed that patients with low PD-L1 expression had decreased survival when treated with CPI monotherapy compared to those who received platinum-based chemotherapy. Currently, atezolizumab and pembrolizumab are only indicated for the treatment of cisplatin-ineligible mUC patients with high PD-L1 expression or those not eligible for any platinum-based chemotherapy.

Given the established efficacy of CPIs in metastatic UC in the first and second-line setting, multiple trials are evaluating the role of CPIs in non-metastaticUC.

CPIs are being tested in neoadjuvant setting in muscle-invasive bladder cancer (MIBC) in an effort to improve pathologic response at cystectomy. Preliminary date from atezolizumab trial ABACUS and pembrolizumab trial PURE01, look promising. There are also many ongoing trials in MIBC after surgery in adjuvant setting. Radical cystectomy remains the current standard therapy for patients with BCG-unresponsive non-muscle-invasive bladder cancer. We hope that results from trials with immunotherapy will improve the likelihood of bladder preservation in that setting.

There are still no predictive biomarkers with clinical utility to help select patients likely to derive benefit from a particular therapy.

Despite the promising responses with immunotherapy, majority of patients do not respond to CPI monotherapy and many trials testing imuno-immuno and immuno-chemo combinations or novel agents are under way. Promising results have been reported for fibroblast growth factor receptor inhibitors (FGFRi) erdafitinib and rogaratinib, and nectin-4 targeted agent enfortumab vedotoin. There is still a lot to be done to better understand predictive biomarkers, optimal combinations and sequences to improve clinical outcomes in patients with urothelial carcinoma.

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Melanoma immunotherapy

Key words: melanoma, checkpoint inhibitors

In recent years we have witnessed a rapid development of cancer immunotherapy first of all in melanoma. Essentially, it was a discovery of immune checkpoints pathways: cytotoxic T-lymphocyte-associated antigen 4 (CTA-4) and program death 1 (PD1) immune checkpoint. The CTLA-4 and PD1 operate at different stages of immune response, but both are negative regulators of T-cell immune function. The first to be approved in 2011 was the anti-CTLA-4 antibody ipilimumab for treatment of metastatic melanoma. Subsequently, the anti-PD-1s pembrolizumab and nivolumab were approved for melanoma.

Anti PD-1 inhibitors pembrolizumab and nivolumab showed in clinical trials superior response rates and survival with less toxicity compared with ipilimumab and have become the standard first-line immunotherapy options in treatment of metastatic melanoma. Pembrolizumab was shown to be superior to ipilimumab in the randomized phase III Keynote 006 study. After 4 years of follow-up, pembrolizumab continues to provide durable anti melanoma acitivity, with 86% of patients who are progression-free at 20 months after completing 2 years of therapy. Regarding nivolumab, phase III CheckMate 003 revealed 40% ORR in nivolumab group. A study update reported a 2-year OS of 57.7% with nivolumab therapy.

The rationale to combine anti-PD1 and anti-CTLA-4 antibodies relays in their different mechanisms of action. The combination of nivolumab and ipilimumab has shown significant activity and has been approved by FDA for the first line treatment for BRAF negative melanoma. The critical concern was immunotoxicity: grade 3 and 4 adverse event (AE) in 55% patients in the combination arm. Therefore, it is not possible to define the best choice of immunotherapy. High responses are described with combination immunotherapy, but toxicity is also higher than monotherapy. Furthermore, ipilimumab and nivolumab combination showed respectable eficacy on brain metastases, with and intracranial clinical benefit rate of 57% and the 6-months PFS was more than 60%.

Recently, nivolumab was also approved in the adjuvant setting for completely resected stage III/IV melanoma. In randomized phase III trial, in comparison to adjuvant ipilimumab, adjuvant nivolumab resulted in significantly longer reccurence-free survival and lower rate of grade 3 and 4 adverse events.

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New approach to treatment of non-melanoma skin cancer

Non-melanoma skin cancer is one of the most common cancers in the world**.** Basal cell carcinoma (BCC) represent 75%–80%, squamous cell carcinoma (SCC) about 20% of all skin cancers. BCC and SCC tend to grow slowly and are often found early. Rare types include Merkel cell carcinoma (MCC) and cutaneous T-cell lymphoma.

The majority of primary BCC are treated surgically or, in case of superficial lesions, with non-surgical methods. The risk of recurrence increases with the size of the tumor, poorly defined edges of the lesion, aggressive histologic subtype and the previous relapse. In the case of multiple local recurrence or invasion (laBCC/mBCC), when surgery and/ or radiation are not appropriate, a multidisciplinary approach to patient management is very important.

Abnormal activation of the Hedgehog signaling pathway is responsible for the occurrence of the disease in 90% of BCC. Vismodegib selectively inhibit abnormally activated signaling pathway. In a clinical trial ERIVANCE BCC, efficacy and safety results of vismodegib in patients BCC have been reported. ORR was achieved in 33.3% of mBCC and 47.6% laBCC pts. The disease control was confirmed in 94% mBCC and 83% laBCC. The median duration of objective response is longer in laBCC than in mBCC. Results showed a significant reduction in the size and number of the multiple lesions in patients with Gorlin syndrome. The most common side effects are muscle cramps, dysgeusia, hair loss and fatigue.

The majority of primary SCC are treated surgically. In around 10% of cases, SCC may progress to distant tissues. There are only limited data of systemic chemotherapy in the treatment of advanced cutaneous SCC. Cisplatin-based combinations appear to be the most active regimens. Monoclonal antibodies and oral agents that target the epidermal growth factor receptor like cetuximab, panitumumab, erlotinib and gefitinib, have limited antitumor activity in patients with advanced SCC of the skin. In a clinical cohort study phase II with anti-PD-1 antibody cemiplimab for advanced cutaneous SCC efficacy and safety were tested. The primary objective was response - observed in 47% pts with mSCC and in 60% pts with unresectable laSCC. Treatment was well tolerated, with no single grade 3 or higher toxicity present in more than 5% pts, pneumonitis was present in 3 %, while diarrhea was present in 2 %. Anti PD-1 is a new standard of care for the therapy of locally advanced/metastatic SCC in USA. This does not apply to patients developing advanced SCC of the skin as a consequence of the immunosuppression of organ transplantation.

Merkel cell carcinoma is a rare, aggressive neuroendocrine skin cancer with poor prognosis in advanced stage. Incidence is increasing. Risk factors are advanced age, immunosuppression, and ultraviolet light exposure. There are association between MCC and polyomavirus infection. For localized disease (when feasible) surgery is the recommended treatment, followed by adjuvant radiation or chemoradiation. In the metastatic setting, chemotherapy has been the standard treatment, but durable responses are rare. Trials with immune checkpoint inhibitors (avelumab, pembrolizumab and nivolumab) in first and second line showed good results with a tolerable safety profile and these are becoming the standard therapy, already included in international guidelines.

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Immunotherapy for Hodgkin lymphoma

Key words: Hodgkin lymphoma, Immunotherapy, PD-1 inhibitor

Hodgkin lymphoma (HL) is un unusual malignant disease in which neoplastic HRS (Hodgkin & Reed-Sternberg) cells represent only minority (1-2%) of tumour burden, surrounded by polymorphous inflammatory infiltrate. Although most patients with HL are cured with initial chemotherapy, 10% to 25% of patients will have relapsed or refractory (rel/ref) HL despite modern, risk-adapted approaches. The need to optimize initial therapy and improve outcomes in patients with rel/ref HL has led to the development of new drugs for HL that target its unique biology. In addition to the incorporation of brentuximab vedotin (BV), an antibody-drug conjugate directed against CD30 on HRS cells, the development of anti–programmed cell death-1 (PD-1) antibody therapy for the treatment of HL has been a major advance in the care of these patients. PD-1 blockade targets a pathway central to the pathogenesis of HL and has been a well-tolerated, highly effective treatment in patients with rel/ref HL. With the evaluation of BV and PD-1 blockade in the frontline setting in patients with advanced-stage HL, the role of PD-1 blockade in HL continues to evolve.

Nearly universal genetic alterations of chromosome 9p24.1, which include the PD-L1/PD-L2 loci, have been identified in HL, supporting the concept that the PD-1 pathway plays a key role in the host immune evasion that is central to HL pathogenesis. The genetic alterations in 9p24.1 are directly linked with increased

expression of the PD-1 ligands, programmed death-ligand 1 (PD-L1) and PD-L2, on HRS cells. In addition, the JAK2 locus is also contained within the 9p24.1 region, and JAK2 activation upregulates PD-L1 transcription and expression. Furthermore, Epstein-Barr virus infection, which is frequently observed in HL, has also been identified as a mechanism of PD-L1 upregulation and expression in HL. In addition to the PD-1 ligand expression observed on HRS cells, tumour-associated macrophages (TAMs) in the HL tumour microenvironment (TME) frequently express PD-L1.

Anti–PD-1 antibody monotherapy has been evaluated in patients with rel/ref HL and produced a high rate of objective responses in early phase studies. A notable feature of treatment with anti–PD-1 antibody therapy in patients with HL is the clinical benefit observed with continued treatment beyond disease progression. Patients who achieve a CR appear to derive the longest duration of benefit from PD-1 blockade and only a minority of patients will have a CR. There are several agents that are being combined with anti–PD-1 antibodies based on possible biological synergies with the goal of augmenting the effectiveness of PD-1 blockade, including chemotherapy, BV, anti–CTLA-4 antibody, ipilimumab. The results of ongoing clinical trials evaluating novel anti–PD-1 antibody-based combinations in newly diagnosed and rel/ref patients with HL will determine where PD-1 blockade will fit in the future.

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Common and rare anti-PD1/PD-L1 toxicities – how much do we think about them and how do we react

Key words: immunotherapy, immune checkpoint inhibitor, toxicity

Immunotherapy has changed the clinical practice of medical oncology bringing revolution in the treatment of many different types of malignancies. Checkpoint inhibitors are an exciting new category of drugs because they are nonspecific. Treatment-related adverse events in patients treated with immune checkpoint inhibitor therapy differ significantly from adverse events of all other previousely used systemic treatments. In general, immune checkpoint inhibitor use is associated with a spectrum of immune-related adverse events (irAEs) with the variety of clinical manifestations in multiple organs of the body. They can affect and are most commonly seen in the skin, GI tract, lungs and endocrine system, as well as in the musculoskeletal, renal, nervous, hematologic, cardiovascular and ocular systems. Most patients who are treated with immunotherapy are going to develop some adverse event, but it is usually mild to moderate. With single-agent immunotherapy, on average, the side effects occur about 4 to 10 weeks after the initiation of the drug. Many side effects will go away when treatment ends, but some effects can last beyond the treatment period and other effects may occur months or years later. It is very important for patients and caregivers to know what to look for, so their education is very important including detailed information about immuno-oncologic agent with toxicity information, including signs, symptoms and monitoring parameters, and also an established response plan if a side effect develops is needed.

The management approach to immune-related adverse events in a very simplified version is that for mild (grade 1) side effect

generally ICPi therapy should be continued with close monitoring and supportive care treatment (with the exception of some neurologic, hematologic, and cardiac toxicities). For most moderate (grade 2) side effect ICPi therapy may be suspended and if the side effect resolves restarting immunotherapy is considered. For a severe side effect, a grade 3 or 4, the initiation of high-dose corticosteroids is needed with suspension of ICPis. In general, permanent discontinuation of ICPis is recommended with grade 4 toxicities, but endocrinopathies controlled by hormone replacement therapy generally do not require the termination of immunotherapy. Rare but serious side effects can lead to death, especially if left untreated. Because immunotherapy is so new—and combination treatment is even newer—predicting the side effects for an individual patient is not easy. Sharing expertise, samples and data with longer clinical experience and everyday practice in expert oncology centers will certainly contribute to higher quality of patient care and will help to improve cancer immunotherapy side effects treatment as well.

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Durable response to nivolumab in pretreated patient with non-small cell lung cancer

Nivolumab was the first monoclonal antibody targeting programmed death (PD-1). Whether anti-PD-1/PD-L1 antibody therapy can provide added benefits for heavily pretreated patients with advanced NSCLC and what is the expected efficacy of anti-PD-1/PD-L1 antibody therapy depending on tumor PD-L1 expression level remain controversial. Here we present an efficacy and safety of nivolumab in a patient with previously treated NSCLC.

In 2015, 49-year old female patient came to neurologic department of our hospital due to partial motoric epileptic seizure. Brain MRI revealed multiple metastatic lesions with edema.The thorax and abdomen CT scan showed nodal lesion in left posterobasal segment of the lung and liver metastases. The patient was admitted to our Department for Thoracic Oncology where bronchoscopy and transthoracic needle aspiration biopsy did not reveal etiology of pulmonary left lower lobe lesion. Simultaneously with pulmonary diagnostic procedures, an ultrasound-guided fine needle aspiration biopsy of the thyroid gland revealed follicular thyroid tumor, and operation was proposed. Due to pulmonary diagnostic procedures, thyroidal operation was postponed. The diagnosis of lung adenocarcinoma (*EGFR* mutation and *ALK* rearrangement negative) was established after mini-thoracotomy, atypical resection of left lower lobe and biopsy of mediastinal lymph nodes.

The patient was treated with WBRT due to central metastases at the beginning, and then with platinum based chemotherapy dublet and afterwards irradiation of mediastinum (37.5Gy / 15 fr) was applied due to mediastinal residual lymph node.

PET-CT was done prospectively to monitor metabolic activity and morphological dynamic of the malignant disease. In April 2016 a metabolic progression in mediastinal and retroclavicular lymph nodes was detected and second line pemetrexed monochemotherapy started.

In September 2016, according to further PET-CT progression, patient started immunotherapy with nivolumab 3mg/kg every 2 weeks through a compassionate use program (Expanded Access Program or EAP) as a third line treatment. Within 6 weeks of nivolumab treatment thyroid disfunction (hyperthyroidism) developed. Nivolumab was discontinued and treatment with methilprednisolone and thiamazole was initiated. Thyroid dysfunction (thyreoiditis) is considered as a possible and common immune-related adverse event. Thus, it was important to test for thyroid dysfunction at baseline and once a month.

Due to further enlargement of the node in right thyroid lobe, after normalization of thyroid hormone levels, total thyreoidectomy was done in January 2017. Pathohystologic diagnosis revealed papillary thyroid carcinoma with later on radioactive iodine ablation therapy needed. Once subsequent hypothyroidism occurs, levothyroxine replacement therapy was proposed and treatment with immunotherapy continued in February 2017.

After 52 applications of nivolumab, in January 2019 PET-CT was performed, without detectable metabolic activity in lung, mediastinum, and liver, besides intensive metabolic activity in the gallbladder (SUVmax=7.2), which proved to be calculous cholecystitis. Only morphological with no metabolic activity was detected in the left lower lobe paramediastinally lesion close to aorta and thoracic wall but without infiltration, regressive in dimension. There were no detectable mediastinal lymph nodes.
Conclusion: Nivolumab was effective and safe in previously treated patient with advanced non-small cell lung cancer (NSCLC) although PD-L1 expression was unknown. The patient had very good performance status all the time and therapy with nivolumab was well tolerated.

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Immunooncology in clinical practice

Keywords: BRAF mutated malignant melanoma, immunotherapy

Four years after he was diagnosed with MM and 2.5 years after he finished with adjuvant therapy, his disease progressed. In May 2014. on his regular follow up visit surgeon palpated enlarged left supraclavicular and axillar lymph nodes (LN), LDH was normal but S100 was elevated. Cytology of the enlarged LN was positive. PET CT showed metastastasis in left supraclavucular, axillar and subpectoral LN. As the tumor was BRAF V600E mutated, he was treated with BRAF inhibitor Vemurafenib. PET CT which was done 3 months after he started Vemurafenib, showed complete response (CR). He had skin toxicity as AE. His disease progressed after 7.5 months in the same LN. He was treated with anti-CTLA4 antibody ipilimumab. He recieved 4 applications, but without any success, his disease progressed again in LN.
In June 2015 he started with anti-PD1 antibody Pembrolizumab. First PET CT was done 4 months later and showed partial response (PR)a, the next one showed CR. He was treated with Pembrolizumab for 2 years without any AE. Last application he recieved in June 2017. Since then he is seen regularly by his medical oncologist 4 times per year. Last follow up was done in February 2019, he is still in CR.
Almost 5 years after he was diagnosed with metastatic MM he is still alive.

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Immune-related adverse events: case reports from clinical practice

Key words: adverse events, immune-related, mucositis, myocarditis, pneumonitis

Pembrolizumab is the up to date strategy against various types of cancers. In Serbia pembrolizumab is registered and reimbursed for the treatment of advanced melanoma. It is registered, but not reimbursed for the treatment of advanced non-small lung cancer and is available thorough patient compassionate use programs. Pembrolizumab has a unique type of adverse events (AEs) described as immune-related AEs (irAEs) connected with excessive immune system activation and can affect any organ.
The objective of this presentation is to report three cases in which high grade and life threatening irAE´s was observed:
57-year-old male with metastatic melanoma with a recurrent immune-related oral mucositis (irOM), grade 2 irOM after the first cycle and grade 4 irOM after the second cycle of pembrolizumab. OM was judged as an irAE because of its recurrent nature and after other causes were excluded. Treatment included: parenteral high-dose corticosteroids and dexamethasone oral rinses with local and systemic analgesia and parenteral nutrition. IrOM of grade 4 was rather unresponsive to therapy: after one month it was downgraded to grade 3. However, symptom benefit re-

garding oral mucositis was observed and patient was discharged from the hospital.

66-year-old male with metastatic melanoma with a sudden worsening of respiratory symptoms with dyspnea, hypoxia and cyanosis after the second cycle of pembrolizumab. Chest X-ray and CT scan showed pneumonitis, and its severity was assessed as grade 3. Skin rash grade 3 was also observed and assessed. Treatment included: parenteral high-dose corticosteroids, parenteral antibiotics, oxygen, morphine and hydromorphone for dyspnea and local corticosteroids for the skin rash. Pneumonitis and skin rash were improved with improvement of performans status and symptoms. Patient was discharged from the hospital.

A 40-year-old female diagnosed with metastatic squamous cell lung cancer presented with chest pain, fatigue and nausea and vomiting after the sixth cycle of pembrolizumab. Diffuse ECG changes and highly elevated cardiac enzymes were registered. She was transferred to cardiac intensive care unit for further testing. Cardiac ultrasound showed enlargement of both ventricles with paradoxal septal movements. Diagnostic coronary catheterization was negative as well as pulmonary angiography. Immune-related myocarditis was suspected. She was treated with parenteral high-dose corticosteroids, inotrops, oxygen. However, due to further worsening of her condition she passed away two days after admission.

For the successful treatment of irAE´s, early recognition is very important as well as availability and accessibility to additional immunosuppressive agents which in Serbia are off-label.

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Choosing the right chemotherapy regimen with neoadjuvant dual HER2 blockade – a case report

We present a case of a 44 year old female patient with no relevant comorbidities and alergies. A year after giving birth and a few months after stopping breast feeding, she presented with pain in her right breast. Initial breast ultrasound was reported as normal. Since symptoms persisted, mamography was done: ACR4, a small group of microcalcifications detected in the lower inner quadtrant of the right breast, could be a papilomatosis, but biopsy was still performed. The histology was ductal invasive carcinoma, hg2, ng2, ER-, PR-, HER2 3+, ki67 35%. MR of the breast showed a 7x4.5cm tumor and three enlarged lymph nodes in the right axilla, up to 16mm. PET CT confirmed locally advanced disease with no distant metastases.

Chemotherapy docetaxel 100mg/m^2 with trastuzumab and pertuzumab and primary G-CSF profilaxis with between day 5 and 12. Even then, neutropenia gr.4 developed, as well as diarrhea gr.2-3 and onicholysis. After cycle 2, PET CT was performed which showed a complete metabolic response. Six cycles of the same therapy was administered altogether. Two weeks after completion of chemotherapy radical mastectomy was performed. Histology showed a complete pathological response. Postoperative irradiation was done, and adjuvant trastuzumab continued.

The dillema when choosing the right chemotherapy protocol in this group of patoents is whtere to start with targeted therapy with taxanes (as in BERENICE and NEOSPHERE) or start with antracyclines and then administer taxanes with dual HER2 blockade (NSABP-FB7). If choosing the first protocol, another dillema is whether to administer carboplatin with taxanes and dual blockade as in KRISTINE study. There is still no consensus regarding question.