ORAL PRESENTATIONS

S1 – How far we have come with immuno-oncology in GU cancers?

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The immune system has a fundamental role in controlling the development and progression of cancer cells. A deeper understanding of the cellular and molecular composition of tumor environment, as well as the mechanisms controlling the immune system, has made possible the devolopment and clinical investigation of many innovative cancer therapies. Immunotherapy is a therapeutic approach that targets or manipulates the immune system. Over the past several decades, immunotherapy has emerged as a treatment option in various malignancies including urologic cancers. Genitourinary (GU) malignancies including prostate, kidney and bladder cancer are common disease. Despite advances in traditional treatment modalities, sequential cellular mutations often lead to resistance and disease progression and new therapy was unmet need.

The roots of immunotherapy in urologic cancers began with the introduction of Bacillus Calmette-Gueren (BCG) for non-muscle invasive bladder cancer (NMIBC) in 1976 and this was followed in the 1990s by the introduction of cytokines, such as interferon and interleukin-2 (IL-2) for metastatic renal cell carcinoma (mRCC). Recently, new immune therapies, including inhibition of programmed death 1(PD-1), programmed death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) have been developed. Blocking interaction of CTLA-4 and B7 on the T cell and dendritic cell, and PD-1 and PD-L1 on the T cell and tumor, respectively, releases the brakes on the immune system and permits T-cell activation against cancer cells. A new frontier of great interest in urologic cancers is based on the combination of immune checkpoint inhibitors (ICIs) with other anticancer strategies, an approach which has provided remarkable results especially in metastatic RCC.

Immunotherapy in renal cell carcinoma

Over the past decade, the management of metastatic RCC has undergone rapid evolution. After the era of targeted anti-angiogenic agents – tyrosine kinase inhibitors (TKIs), immunotherapy has become a cornerstone of the RCC treatment. Currently, doublet combination therapy with either two immune checkpoint inhibitors (ICIs) or combination of an immune checkpoint and tyrosine kinase inhibitor is considered the standard of care. Recently, triplet therapy such as ipilumumab/nivolumab plus cabozantinib, is being investigated and showed eficacy in treatment-naive mRCC patients, but overall survival (OS) data is still pending. In addition, some other doublet and triplet combinations trials such as with a hypoxia-inducible factor inhibitor belzutifan are ongoing.

There still exists an unmet need for the predictive biomarkers to guide the best initial choice of therapy and to optimize the sequential use of available therapeutic agents. In addition, ICIs are also beeing investigated in localized RCC and the efficacy of adjuvant pembrolizumab was confirmed in patients with resected RCC at increased risk of recurrence.

Immunotherapy in urothelial carcinoma

The standard first-line treatment in metastatic urothelial cancer (UC) has been cisplatin-based combination chemotherapy for more than 20 years. However, a substantial proportion of patients, up to approximately 50%, are deemed ineligible for cisplatin-based regimens and a carboplatin-based option has been widely adopted. Despite the relatively high response rates from platinum-based chemotherapy, the median progression-free survival (PFS) and overall survival (OS) are only 8 and 14 months. In recent years,

systemic treatment options for patients with metastatic urothelial cancer have increased, particularly with the introduction of immune checkpoint inhibitors and more recently, with the emergence of antibody drug conjugates (ADC). Currently, a switch maintenance immunotherapy with avelumab to keep the response achieved immediately following platinum-based chemotherapy is the first-line standard of care. In addition, immunotherapy has demonstrated some benefit in the first-line for platinum-ineligible patients and in second-line treatment. Recently, the combination of pembrolizumab and an ADC enfortumab vedotin (EF) has been approved in the first-line cisplatin ineligible mUC. Neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy with lymph node dissection is the standard of care for localized muscle-invasive bladder cancer (MIBC). However, relapse rates are high, and many patients are considered cisplatin ineligible and there is an unmet need to develop novel treatment options. Neoadjuvant immunotherapy with ICIs, has emerged as a promising approach, but it is crucial to identify predictive biomarkers to improve patient selection. In addition, immunotherapy is also beeing investigated in the earlier stages of bladder cancer and nivolumab is approved as adjuvant therapy for high-risk MIBC but the OS data is still immature. Recently, pembrolizumab demonstrated the benefit for treating high-risk NMIBC unresponsive to BCG.

Immunotherapy in prostate cancer

Despite prostate cancer (PC) has been traditionally considered an immunologically „cold" malignancy, with not encouraging findings in early trials, numerous further trials are investigating ICIs alone or in combination with other immunotherapies, chemotherapy or loco-regional treatments. An autologous vaccine sipuleucel-T was the first, and still the only approved immunotherapy for prostate cancer, except in a selected group of patients. PD-1 inhibition has only been shown to be effective in MSI-H/dMMR refractory disseminated castration-resistant prostate cancer and its treatment is tumor agnostic.

Immunotherapy in testicular cancer

Testes are considered immunologically privileged sites and that is thought to be driven by a constitutive expression of PD-L1 in normal testis. However, immune-based therapy in patients with refractory testicular cancer has demonstrated early signs of activity but tend to be short lived.

Immunotherapy in penile cancer

In penile cancer, PD-L1 expression has been reported in ~60% of primary tumors and that provided rational support for application of ICIs. However, current evidence regarding the efficacy of immune-based therapies is limited in penile cancer, but a number of clinical studies are ongoing based on promising results from studies in other squamous cell carcinoma.

Conclusions

A true revolution in the management of advanced genitourinary cancers has occured with the discovery and adoption of immunotherapy. ICIs are now at the forefront of cancer therapy, especially in front-line metastatic RCC and in multiple settings of urothelial cancer. The use of ICIs in prostate cancer, testicular cancer and penile cancer has not been as heavily explored. The therapeutic benefits of immunotherapy were also observed in select patients with localized genitourinary neoplasms. We should expect even more progress that will dramatically change our treatment strategies in the months and years to come.

Keywords: immunotherapy; renal cell carcinoma; urothelial cancer; prostate cancer; testicular cancer; penile cancer

S2 – Onco-nephrology: The current concept and future perspectives

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Onco-nephrology is a new, multidisciplinary field that integrates the areas of oncology and nephrology. The number of cancer patients with kidney disease has been increasing, probably due to more effective anticancer systemic treatments and related procedures. These novel therapies however can also be nephrotoxic and e because of the effective treatment of patients with end-stage renal disease, we are facing a higher incidence and prevalence of various cancer types, some of them closely associated with replacement therapy and other related conditions. A decline of kidney function and the presence of chronic kidney disease (CKD) both have a negative impact on oncological and non-oncological outcomes in patients who have solid as well as lymphoproliferative cancers, and efforts to preserve renal function are essential for the optimal management of cancer patients. The goal of the holistic management of onco-nephrological patients is to increase the efficacy and safety of their treatment. Since patients with renal impairment have often been excluded from prospective oncologic randomized trials evaluating novel treatments, there is no available high-evidence data about the efficacy and safety of available treatments in these patients. There is also a lack of evidence regarding the cut-off values of biomarkers, that could guide the treatment of onco-nephrological patients. In clinical practice, the management of onco-nephrological patients is based on clinical experience, data from retrospective analyses, case series, case reports, and recommendations supported by a multidisciplinary expert consensus. Close cooperation between an oncologist and a nephrologist is crucial, and a multidisciplinary consultation is often needed for the optimal management of onco-nephrological patients. The physician who is responsible for the treatment plan must have not only a basic knowledge of nephrology but also a good knowledge of the limitations of oncology treatment. An approach to onco-nephrological patients can be presented through the following:

1. Acute kidney injury, CKD, and CKD-related conditions in cancer patients.
2. Nephrotoxicity and additional risk factors for kidney impairment in cancer patients.
3. Estimation of kidney function in cancer patients.
4. Kidney injury related to paraneoplastic syndrome.
5. Approach to cancer patients with a solitary kidney.
6. Approach to cancer patients with renal failure who are on chronic dialysis.
7. Cancer in patients with a transplanted kidney.

Due to the increasing number of onco-nephrological patients and new anti-cancer treatment options, an onco-nephrology outpatient clinic began operating at the Institute of Oncology Ljubljana more than ten years ago. An onco-nephrology multidisciplinary team (MDT) has been established, and a clinical pathway guiding an approach to patients managed by the onco-nephrology MDT has been developed. Furthermore, the Working Group on Onco-nephrology at the Section of Medical Oncology periodically organizes an onco-nephrology school, where views of different experts on a certain clinical problem are presented and discussed. One of the priorities of onco-nephrology is to advance research in the field. As active

members of the Research Committee of the American Association of Onco-nephrology (ASON), we meet periodically with members of the committee and are involved in various collaborative research projects. Specifically, at the present time we are involved in various onco-nephrology collaborative research projects with Memorial Sloan Kettering Cancer Center in New York.

Keywords: onco-nephrology, estimation of kidney function, acute kidney injury, nephrotoxicity, solitary kidney, kidney transplantation.

S3 – How to decide to omit chemotherapy in early HR+/HER2- breast cancer

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Hormone receptor-positive/HER2-negative (HR+/HER2-) tumors are the most commonly diagnosed breast cancer subtypes. Administering (neo)adjuvant endocrine therapy, with or without chemotherapy, significantly reduces the risk of relapse and mortality in this patient subgroup, becoming the cornerstone of treatment. While endocrine therapy is recommended for all patients with HR+/ HER2- breast cancer, the decision regarding chemotherapy hinges on tumor characteristics. Defining what constitutes "high" and "low" risk for HR+/HER2- early breast cancer (EBC) remains uncertain. Traditionally, risk assessment for relapse in HR+/HER2- EBC relied on clinicopathological factors such as age, menopausal status, tumor size, nodal status, histologic type, tumor grade, expression levels of estrogen receptor (ER) and progesterone receptor (PR), as well as proliferation markers like Ki67/MIB-1. All these variables influence the prognosis of HR+/HER2- EBC patients and are commonly used in clinical practice to determine the need for adjuvant chemotherapy alongside endocrine therapy. Numerous trials have aimed at optimizing adjuvant treatment, exploring both escalation and de-escalation approaches. Tailored strategies involving the escalation of endocrine therapy and de-escalation of chemotherapy have shown feasibility and are associated with reduced relapse risk and improved toxicity profiles. Nevertheless, defining "high" and "low" risk and quantifying individual risk levels remain challenging. While many patients categorized as "low-risk" could likely achieve a cure through endocrine therapy alone, a significant subset of HR+/HER2- EBC patients still face local and/or systemic relapses despite receiving chemotherapy and optimal adjuvant endocrine therapy.

To offer an easily accessible tool for daily oncology practice, several of these variables have been incorporated into multiparametric scoring systems. These systems generate relatively accurate estimations of recurrence and death probabilities from breast cancer for each patient. Notable risk assessment tools include the Nottingham Prognostic Index (NPI), PREDICT, and Adjuvant Online!. These tools aid healthcare providers in deciding about adjuvant chemotherapy for HR+/HER2- BC patients. In 2000, Perou et al. introduced a molecular classification of breast cancer based on gene-expression profiling, identifying six transcriptomic subtypes: Luminal-A, Luminal-B, HER2-enriched, basal-like, normal breast-like, and claudin-low. Subsequently, numerous genomic signatures were developed to enhance prognostication and risk stratification for HR+/HER2- EBC patients. Multigene assays enabled better characterization of tumor prognosis and recurrence risk, revealing that select patients at low genomic risk could safely forego chemotherapy despite having a clinically high risk of recurrence. Commercially available genomic assays

based on these signatures include Oncotype DX and Mammaprint, as well as Prosigna, Breast Cancer Index (BCI), and Endopredict. Gene signature guides adjuvant endocrine and chemotherapy in patients postmenopausal or age > 50 years with HR+, HER2- EBC, node-negative or with 1-3 positive nodes. In premenopausal patients, Oncotype DX in patients with node-negative ER+ HER2– EMB could help to decide to omit chemotherapy. Current data suggest that premenopausal patients with 1-3 positive nodes benefit from chemotherapy regardless of genomic assay result. There is no data on using genomic tests to guide adjuvant chemotherapy in patients with ≥ 4 positive nodes.

Keywords: HR+/Her2- breast cancer, chemotherapy, prognostic factors, gene signature

S4 – Tailoring extended adjuvant endocrine therapy in early-stage HR + breast cancer

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One of the most controversial issue nowadays is how to identify patients who will benefit from extended adjuvant endocrine therapy (ET). After standard 5 years of tamoxifen, more than two thirds of patients will remain disease free even after 15 years of follow-up demonstrating that an important subgroup of patients are cured with a shorter course of ET. There are currently no algorithms based on efficient biomarkers that identify patients who benefit from longer exposure to ET. However, based on evidence-based data some prognostic factors might be used in our daily clinical practice for decision when to extend ET. Among classical clinico-pathological factors, nodal status at primary diagnosis is the best predictor of both, early and late relapse. Patients with node positive breast cancer remain at sufficient high risk, even after 5 years of ET to justify extension of ET. The MA.17 trial demonstrated that the greatest benefit of extended letrozole was seen in node positive subgroup. Additionally, some evidence-based data suggest that patients with node positive invasive lobular breast carcinoma are at particular high risk for late relapses. Further studies will hopefuly give us an explanation of underlying biological mechanisms for these findings. Other patient characteristics that influence the decision about extended ET are comorbidities, biological, rather than chronological age, life expectancy and risk factors for second cancers. Extended ET should systematically be considered in any fit patient, regardless of her/his chronological age. Tailoring ET and its duration will in near future also have to include pharmacogenetic information. Evidence for the possible detrimental effect of CYP 2D6 inhibition in tamoxifen-treated women already exist. Studies have shown patients with variant CYP 2D6 genotype do not benefit from tamoxifen as much as those with wild-type CYP 2D6 however negative studies were also found, so CYP 2D6 is not ready for clinical use. There is also variability seen in terms of musculoskeletal symptoms among patients treated with AIs. Some patients have absolutely no musculoskeletal symptoms, where others are disabled from them. Ingle and colleagues identified single nucleotide polymorphisms (SNPs) near the T cell leukemia 1A gene (TCL1A) that were associated with the AI-dependent musculoskeletal pain. Elucidation of the mechanisms underlying adverse events is very important to be able to prevent and/or treat them, as well as better select treatment for an individual patient. Gene expression profiling represents a next step to an individualized breast cancer management. It helps us predict the risk of relapse in an individual patient.

First generation gene signatures such as Oncotype Dx, Mammaprint and the Rotterdam gene signature proved to be efficient especially in predicting early distant relapse. It has been shown that a higher expression of genes that contribute to cell cycle proliferation is associated with higher rates of distant metastases during the first 5 years but not later, while genes associated with ER-signaling pathway seem to predict better late distant relapses. Therefore, second generation gene signatures, which include more genes of the ER-signaling pathway, have been developed; PAM 50, Breast Cancer Index (BCI), Endopredict (EP/EP Clin). Dubsky and colleagues found in the retrospective study including 1702 postmenopausal women with ER + HER-2 – early breast cancer, that EP gene signature combined with clinical data (EP Clin) provides a significant, independent prognostic model for both, early and late relapses. The identification of patients with an extremely low risk of late relapse who can be spared a full decade of ET is an important goal of clinical research. The EP Clin (the combination of EP with the nodal status and tumor size) stratified 64% of patients into a low risk subgroup with an absolute risk of late distant metastases of only 1.8% between years 5 to 10. These studies were retrospectively designed and therefore currently there is no »standard« gene signature in routine clinical practice that would help us select patients who might benefit from longer duration of ET. Randomized prospective trials designed specifically for the utility of second generation gene signatures are urgently needed. Based on all data described above, both, tumor bology and tumor burden are important determinators for late distant relapses. The Breast Cancer Index (BCI) which consists of two independent markers: HOXB13/IL17BR (H/I) gene expression ratio and molecular grade index (MGI) (a set of cell cycle-related genes) has been shown to predict the 10-year distant recurrence rate in ER positive node negative BC patients. In the MA.17 trial it was found that BCI and H:I index but not MGI were preditive of late relapse and HOXB13 expression at diagnosis was predictive of benefit from extended letrozole therapy. SGroi and colleagues reported the results of their study which compared 3 assays for the ability to predict early and late recurrences in 665 women with ER-positive, node negative BC given either tamoxifen or anastrozole monotherapy in Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial. Only BCI, using a linear combination of its component variables, did so for late relapses. Two other molecular assays have also been shown to predict late relapses: Endopredict in ABCSG6 and ABCSG8 trials, and PAM50 risk of recurrence (ROR score) in the ABCSG8 and ATAC trial.

Keywords: HR+ early-stage breast cancer, extended endocrine therapy, second generation gene expression profiling.

S5 – Optimal treatment in early HER2 positive BC

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Treatment of Her2 positive early breast cancer (EBC) continues to evolve with neoadjuvant and adjuvant Her2-targeted therapies as standard of care. First decision point in management of patients involves deciding between neoadjuvant therapy or proceeding directly to surgery. Neoadjuvant chemotherapy plus pertuzumab-trastuzumab is appropriate for patients with high-risk Her2 positive EBC (tumour diameter ≥ 2 cm, and node positive disease). Patients with node negative disease and tumour diameter < 2 cm are candidates for upfront surgery followed by paclitaxel for 12 weeks plus 18 cycles of trastuzumab. A

frequent clinical question is whether some patients with clinically node-negative disease and tumours smaller than 2 cm could benefit from neoadjuvant chemotherapy. Importantly, up to 24.7% of patients with T1c and clinically node-negative disease are found to have lymph node metastases at the time of surgery. These patients could potentially benefit from neoadjuvant therapy; therefore, in selected patients with larger T1c tumours (1.5–2 cm) and high-risk features, neoadjuvant chemotherapy with HER2-targeted therapies could be considered. Second decision point in the management of Her2 positive EBC involves pathohistological result at surgery after neoadjuvant therapy. Pathological complete response (pCR) is associated with improved survival endpoints. For patients with invasive residual disease, 14 cycles of post-neoadjuvant trastuzumab emtansine (T-DM1) therapy significantly increases invasive disease-free survival (DFS) compared with trastuzumab. Pertuzumab in combination with trastuzumab is the standard therapy for patients who had nodal involvement at the time of the diagnosis and who achieve a pCR with neoadjuvant therapy. First generation adjuvant trials establishing trastuzumab as the standard of care mostly included anthracycline and taxane chemotherapy backbone. BCIRG 006 showed that the anthracycline-free regimen TCH was associated with good DFS and overal survival (OS) outcomes and with lower rates of cardiomyopathy. TRYPHENA showed that the anthracycline free-regimen TCHP was associated with high pCR rates and a lower incidence of cardiac events when compared with anthracycline-containing regimens. More recently, the phase III, TRAIN-2 study assessed whether adding anthracyclines improved pCR rates in patients with HER2 positive EBC. No significant difference in pCR rates was observed with the two regimens. Additionally, at a median follow-up of 3 years, the event-free survival rate was 93% in those treated with and 94% in those treated without anthracyclines; the results were irrespective of hormone receptor or nodal status. Based on these findings and anthracycline risk of long-term toxicities, it seems reasonable to consider anthracycline-free chemotherapy regimens in some patients. Less agressive chemotherapy regimens are recommended in populations with lower risk of recurrence (patients with small tumours without axillary involvement). The optimal endocrine therapy for premenopausal patients with tumours that express hormone receptors and HER2 remains unclear. A recent analysis from the Short-HER trial showed that out of the 853 patients enrolled in the study, 40% were premenopausal showed that the DFS was better for premenopausal patients who received aromatase inhibitors compared with those who received tamoxifen or combination therapy. SOFT and TEXT studies, that included small numbers of patients with HER2 positive disease (n=695, 10.3%), have demonstrated improved outcomes with ovarian function supression (OFS) and endocrine therapy for premenopausal women with high-risk disease. The landscape of the treatment of HER2 positive breast cancer is evolving. Currently, we mainly tailor treatment based on tumour size, lymph node status and response to neoadjuvant therapy. However, future research is needed, including other predictive and prognostic biomarkers with the goal of continuing to improve patient outcomes and decrease exposure to unnecessary treatments for patients with a good prognosis.

Keywords: Her2 positive, early breast cancer, treatment optimization

S6 – Post-neoadjuvant therapy in triple-negative breast cancer

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Patients who do not have a pathological complete response after neoadjuvant taxane and anthracycline chemotherapy have a 20% to 30% risk of relapse. Currently, there are two options for additional treatment after neoadjuvant chemotherapy for triple-negative breast cancer (TNBC). The first option that became available in this setting was capecitabine, which was studied in phase 3 clinical trial CREATE X. The trial was conducted in 910 patients with HER2-negative breast cancer (30% of patients had TNBC) who had invasive residual disease after neoadjuvant chemotherapy with anthracyclines, taxanes, or both and were randomly assigned in a 1:1 ratio to either capecitabine plus standard therapy or standard therapy alone. The addition of adjuvant capecitabine prolonged disease-free survival (DFS) and overall survival (OS). The prolongation of DFS and OS (hazard ratio for death, 0.52) was particularly notable in patients with TNBC. Capecitabine therapy was safe, with hand–foot syndrome being the most common side effect, occurring in nearly 75% of patients receiving capecitabine. Recently, adjuvant olaparib therapy was evaluated in the phase 3 OlympiA clinical trial. The poly (adenosine diphosphate ribose) polymerase (PARP) inhibitor was evaluated as adjuvant therapy in BRCA1 or BRCA2 germline mutation–associated early breast cancer. 1836 patients with high-risk clinicopathological factors were randomized 1:1 to receive oral olaparib or placebo for 1 year. The 3-year invasive DFS was 85.9% in the olaparib group and 77.1% in the placebo group. In addition, there was a benefit for distant DFS. Olaparib was associated with fewer deaths than placebo, although the difference was not statistically significant. Serious adverse events occurred in 8.7% of patients receiving olaparib, with anemia being the most common grade 3 or higher AE. Adverse events of particular interest included MDS and AML. KEYNOTE-522 was a phase 3 trial in which previously untreated stage II or stage III TNBC patients were randomized (2:1 ratio) to receive either a combination of chemotherapy and pembrolizumab or chemotherapy and placebo in the neoadjuvant phase. In the adjuvant phase, patients received adjuvant pembrolizumab or placebo every 3 weeks for up to nine cycles. Pathological complete response (64.8% vs. 51.2%) and event-free survival (EFS) were improved in the pembrolizumab–chemotherapy group. The incidence of grade 3 or higher treatment-related adverse events of grade 3 or higher was 78.0% in the pembrolizumab–chemotherapy group and 73.0% in the placebo chemotherapy group. The most appropriate duration of pembrolizumab therapy is uncertain because the study was not designed to identify the relative contributions of neoadjuvant and adjuvant treatment phases.

Keywords: TNBC, olaparib, capecitabine, pembrolizumab, post-neoadjuvant treatment

S7 – Adjuvant systemic therapy for patients with germline BRCA1/2 mutations

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Approximately 10% to 15% of all breast cancers are related to either high-penetrant or intermediate- to low-penetrant genes. Hereditary breast and ovarian cancer syndrome is clinically defined by family history criteria, and moleculary defined by identification of germline pathogenic variants in clinically validated hereditary breast and ovarian cancer syndrome genes. The genetic basis of about half of clinical hereditary breast and ovarian cancer syndrome is currently unknown or unexplained by single gene variants, and conversely, approximately half of individuals who harbour pathogenic variants in genes do not have a suggestive family history. Approximately 5% of unseletcted patients with breast cancer carry germline BRCA1 or BRCA2 variants that are either pathogenic or likely pathogenic. Such variants are more likely in patients who have a strong family history of breast cancer, are younger, have synchronous or metachronous contralateral breast cancer and ovarian cancer, or are from ethnic groups with known variants. Patients with BRCA1 pathogenic or likely pathogenic variant have a particular predisposition to breast cancer that is triple-negative, whereas hormone-receptor-positive tumors often develop in patients with BRCA2 pathogenic or likely pathogenic variant. Triple-negative breast cancer accounts for 15–20% of all breast cancers. Approximately 70% of *BRCA1*-mutant and 20% of *BRCA2*-mutant breast tumours present as triple-negative breast cancer. BRCA1 and BRCA2 are tumor-suppressor genes that encode proteins involved in the repair of DNA double-strand by way of the homologous recombination repair pathway. To remain viable, cancer cells must maintain some ability to repair DNA, so they become dependent on an alternative repair pathway in which poly (adenosine diphosphate-ribose) polymerase (PARP) family of enzymes have a central role. BRCA1 or BRCA2 mutation, resulting in a lack of homologous recombination, sensitizes cells to inhibition of PARP activity, which in turn leads to chromosomal instability, cell-cycle arrest, and subsequent apoptosis. If PARP is inhibited in these cells, the worsening genomic instability induces apoptosis. The most-compelling evidence of the efficacy of PARP inhibitors in the treatment of cancer comes from studies that involved patients with BRCA1 or BRCA2 mutations. After initial phase II studies confirmed the activity of the PARP inhibitor olaparib in patients with pathogenic variants in BRCA1 or BRCA2 and metastatic breast cancer, phase III trials in metastatic disease were initiated comparing monotherapy with a PARP inhibitor with single-agent chemotherapy (olaparib in OlympiAD and talazoparib in EMBRACA). Positive results of these trials were published and led to the approval of both PARP inhibitors as single agents in patients with metastatic breast cancer and pathogenic variants in germline BRCA1 or BRCA2. Adjuvant olaparib in the early breast cancer setting was evaluated in phase III OlympiA trial. This double-blind, randomized trial involved 1836 patients HER2-negative early breast cancer with BRCA1 and BRCA2 germline patogenic or likely patogenic variants and high-risk clinicopatological factors who had received local treatment and neoadjuvant or adjuvant chemotherapy. Patients were randomly assigned to one year of oral olaparib or placebo. At a interim anaysis with a median follow-up of 2.5 years, the 3-year invasive disese-free survival was 85.9% in the olaparib group and 77.1% in the placebo group (hazard ratio 0.58; P<0.001). The 3-year distant disease-free survival was 87.5% in the olaparib group and 80.4% in the placebo group (HR 0.57; P<0.001). Olaparib was associated with fewer deaths than placebo, however the difference was not statistically significant at an interim-analysis. At the planned second interim analysis for overall survival, statistically significant improvement was demonstrated in the intention-to-treat population. The hazard ratio was 0.68 and was statistically significant. The improvement

amounted to an absolute benefit of 3.4% at 4 years. At present drugs other than olaparib are available in adjuvant setting for high-risk hormone-receptor-positive and triple-negative breast cancer. Agents like abemaciclib, ribociclib, capecitabine and pembrolizumab were not included in in the OlympiA trial. Choosing between different treatment options represents an ongoing challenge.

Keywords: High risk early breast cancer, Hereditary breast and ovarian cancer syndrome, germline BRCA1 and BRCA2 variants, PARP inhibitor, Adjuvant olaparib, OlympiA trial

S8 – Treatment beyond CDK4/6 inhibitor in HR+ HER2- ABC

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The management of hormone-receptor-positive (HR+), HER2-negative (HER2-) breast cancer has changed considerably with the introduction of CDK4/6 inhibitors (iCDK4/6) such as palbociclib, ribociclib and abemaciclib as standard first-line systemic treatment. They have demonstrated remarkable efficacy in combination with endocrine therapies (ET), leading to prolonged progression-free survival (PFS) and improved overall survival (OS). However, despite these advances, a proportion of patients eventually progress or develop resistance to iCDK4/6s, posing a clinical challenge. The search for effective next-line systemic treatments in this setting is therefore of paramount importance. Several therapeutic strategies have emerged as potential options for patients facing disease progression on iCDK4/6s. These include the use of ETs with or without targeted agents to overcome resistance mechanisms.

Firstly, it is important to determine whether the patient is at risk of organ failure and how long the response to current therapy has been. Second, comprehensive molecular profiling and genomic testing are essential to effectively guide treatment decisions following progression on iCDK4/6s. These approaches can help identify specific targetable molecular and genomic alterations, such as germline BRCA1/2 and PALB2 mutations, PIK3CA mutations and ESR1 mutations, and guide the selection of targeted therapies most likely to benefit individual patients. In cases without identified molecular or genomic alterations and without imminent organ failure, switching to ET with or without the addition of targeted treatment is the preferred option. The BOLERO-2 trial showed that the combination of everolimus plus exemestane significantly prolonged PFS compared with exemestane alone. Everolimus can also be combined with fulvestrant. However, OS or quality of life benefits were not confirmed. Switching ET and adding an iCDK4/6 is an option if the patient did not receive it in the first line. It should be noted that based on the recently presented results of SONIA study, the use of iCDK4/6s plus ET in the first line did not provide a statistically significant or clinically meaningful PFS benefit compared to the use of ET in the second line. Fulvestrant monotherapy is also an option. Guidelines recommend the use of the PIK3CA inhibitor alpelizib in combination with fulvestrant in patients with PIK3CA-mutated tumours. In SOLAR-1, alpelizib provided a PFS benefit without an OS benefit. Notably, there was a significant increase in toxicity in the alpelizib group. Elacestrant is an option for patients with ER+ HER2-, ESR1-mutated breast cancer that has progressed after at least one line of ET, according to results from the EMERALD trial. ESMO guidelines recommend testing for this mutation, although the drug is not yet approved by the EMA. PARP inhibitors, monotherapy, olaparib or talazoparib, should be

considered for patients with germline pathogenic BRCA1/2 mutations and as an option for patients with somatic pathogenic or likely pathogenic BRCA1/2 or germline PALB2 mutations. OlympiAD and EMBRACA both show a PFS benefit without an OS benefit. Is capecitabine an option after disease progression on iCDK4/6s? Based on the results of BOLLERO-6, capecitabine is a valid option for patients who are unlikely to tolerate exemestane and everolimus combination, as PFS and OS were not significantly different for these agents. Capecitabine would be a preferred treatment option in the setting of shorter PFS on prior ET or imminent organ failure. Systemic chemotherapy (ChT) should be considered for patients with imminent organ failure and endocrine-resistant tumours. Single agent ChT is generally preferred to combinations, which are reserved for patients with rapidly progressive disease. Available drugs for single-agent ChT include anthracyclines, taxanes, capecitabine, eribulin, vinorelbine, platinum and other agents. The optimal sequence of ChT has not been established. As a third or subsequent line of treatment, some new effective therapies are available, e.g. trastuzumab-deruxtecan for HER2-low tumours, sacituzumab-govitecan. Several studies have investigated the continuation of iCDK4/6s beyond progression. So far, we have results from three phase II trials. PACE and PALMIRA, which evaluated palbociclib beyond progression, did not show positive results. The MAINTAIN study evaluated switching ET and continuing ribociclib, and the results were positive in terms of PFS prolongation, but the follow-up was short. Results from the phase III postMONARCH trial with abemaciclib are still awaited. In conclusion, despite the clinical benefits achieved with iCDK4/6s as first-line therapy for HR+ HER2- breast cancer, the emergence of resistance remains an obstacle. Next-line systemic treatments, including targeted therapies, offer hope to patients in need of alternative therapeutic options. The evolving landscape of precision medicine and ongoing clinical research will undoubtedly shape the future of treatment strategies for iCDK4/6 resistant breast cancer, with the aim of improving outcomes and quality of life for these patients, even more so now that iCDK4/6s are being used in the adjuvant setting.

Keywords: cyclin-dependent kinases 4 and 6 inhibitors, breast cancer, metastatic, treatment

S9 – Management of breast cancer patients with brain metastases

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Breast cancer (BC) is the second most common cause of brain metastases (BrM), with different reports indicating incidence between 10% to 30% among all BC patients. The risk of BrM is subtype specific, with higher incidence among patients with human epidermal growth factor receptor 2-positive (HER2+) and triple-negative breast cancer (TNBC). In the HER2+ subtype, a diagnosis of BrM is common, affecting 25% to 50% of women with advanced disease. Systemic treatment has been so far relatively ineffective at treating BrM overall due to its lower central nervous system (CNS) penetrance. Local treatment such as whole-brain radiotherapy (WBRT), stereotactic radiotherapy/radiosurgery (SRS) and neurosurgery has been the mainstay of BrM treatment in the past. But nowdays, especially in HER2+ BC subgroup, where the new sytemic therapy options appear to be more active intracranially, systemic therapy will probably become more attractive alternative to radiotherapy, aiming to prevent neurocognitive decline associated with radiotherapy. Current practice issues in the treatment of BrM in HER2+ BC will be provided in further text as most advances regarding this topic have emerged lately in this BC patient subgroup.

Clinical management of BrM in HER2 + BC

Current guidelines recommend local therapy to the existing BrM as initial treatment and to continue on current HER2-targeted systemic therapy if extracranial disease is stable or absent.

With new evidence of improved intracranial activity of new systemic anti-HER2 targeted agent, the treatment course for second and third intracranial recurrence is highly patient-specific, and there is no single consensus on local therapy or systemic treatment recommendations. Multidisciplinary evaluation is recommended.

Studies, mostly exploratory retrospective analysis, confirmed intracranial response to trastuzumab, pertuzumab and lapatinib. However, we now have several good options beyond the second-line setting for patients with HER2+ BCBrMs as the combinations of tucatinib/trastuzumab/ capecitabine and trastuzumab deruxtecan (TDXd) have shown impressive extra- and intracranial results. Practice-changing results were reported for the phase II HER2CLIMB trial which included 47% of patients with stable untreated, treated progressive, and stable treated brain metastases. The addition of tucatinib improved both PFS and OS in the intention-to-treat population as well as in the population with BrMs.Tucatinib is now approved in combination with trastuzumab and capecitabine, for the treatment of patients with HER2+ MBC, including patients with BrM who have received 2 or more prior anti-HER2 agents by EMA. The PFS and OS benefits demonstrated in patients with active or stable BrM warrants consideration of its second-line use for selected patients with known BMs-already FDA approved. Based on the impressive results of DESTINY-Breast-03 trial, TDXd may be used as second-line therapy.Trial also enrolled patients with stable and treated BrM. TUXEDO-1 study was specifically designed to evaluate efficacy and safety of TDXd in patients with HER2+BC with newly diagnosed BrM or progressing after prior local treatment and also as proof-of-principle for the intracranial activity of antibody drug conjugates.

Clinical practice issues

In the past radiotherapy was a default choice for all patients with BrM. But nowdays, especially in HER2+ BC patients with more potent systemic therapy, we now increasingly will have to make a choice between systemic and local therapy. In patients, who present with small burden of BrM which are amneble to SRS, we will probably choose local therapy. However, in patients, who are progressing after prior local therapy or have higher BrM burden, which are occuring at highher velocity over time, we will probably consider systemic therapy. Also with broadened arsenal of systemic treatment options, oncologists are now left with uncertainty about which agent to choose and how to best sequence therapies for patients with HER2+ BCBrMs that will optimize both intracranial and extracranial PFS and OS, especially in the third-line setting and beyond. Factors paramount in determining which agent to select and when, include both extracranial disease status and the status of intracranial disease—stable and treated, treated and progressive, or asymptomatic and untreated. For patients with stable brain metastases after local therapy who are progressing extracranially, tucatinib/trastuzumab/capecitabine or TDXd are both reasonable choices. For patients with rapid, visceral progression in need of a robust response, the overall response rate of TDXd is superior to HER2-directed TKIs. Trastuzumab deruxtecan has yet to be formally studied in patients with treated, but progressive, or previously untreated brain metastases and intracranial response remains unknown.

Keywords: brain metastasis, breast cancer, systemic therapies, local therapies

S10 – HER2-low breast cancer – definition, dilemmas and new systemic therapy options

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The landscape of advanced breast cancer (BC) has rapidly changed in recent years with the emergence of novel antibody-drug conjugates (ADCs). While the classification of HER-2 status in BC has traditionally been binary – positive or negative – now a new field has emerged – HER2-low breast cancer – with new therapeutic options. Among the HER2-targeted therapies, trastuzumab deruxtecan (T-DXd) was the first ADC approved for treating advanced HER2-low BC. Many new agents are currently being investigated in clinical trials and preclinical development.

Definition

HER2-low BC is defined as HER2 staining with immunohistochemistry (IHC) 1+ or 2+, without amplification through in situ hybridization. The definition has shifted from clinical trials, largely focused on emerging ADCs, to pathology laboratories. Approximately 45-55% of BC cases fall within this definition, with the recognition that this is not a distinct molecular entity but a heterogeneous group of BC with biological behaviour primarily driven by hormone receptor status.

Dilemmas

Three major dilemmas arise when discussing HER2-low BC. First, whether it constitutes a new clinical subtype with a specific pattern of relapse/metastasis and/or therapeutic response. Many retrospective trials have not demonstrated distinct clinical evolution when adjusted for hormone receptor status, regardless of the setting they were conducted in (early, inflammatory, or advanced BC). Second, the question of whether approved ADCs are truly effective only in HER2 IHC+ scenarios or also in HER2 IHC 0 clinical scenarios. The Phase II clinical trial DAISY exhibited an overall response rate of 30% in the HER2 IHC 0 cohort, with no statistically significant survival difference on treatment compared to the HER2-low cohort, despite shorter progression-free survival for HER2 IHC 0 cohort. The Phase III trial DESTINY-Breast-06 is expected to provide more clarity on this matter. Third, the reliability of discriminating between HER2 IHC 0 and 1 with established assays, considering that the test was originally designed to differentiate between HER2-positive and HER2-negative BC. The distinction between HER2 IHC 1+ and 0 is often subtle, and concordance among pathologists is low. The fluidity of HER2 status has been demonstrated during disease evolution, with 40% of cases switching between HER2 IHC 0 and HER2-low results when primary and metastatic results are compared.

New systemic therapy options

The Phase III clinical trial DESTINY-Breast04 compared ADC T-DXd with physician's choice of chemotherapy in patients with advanced HER-2-low BC after at least one line of chemotherapy (patients with hormone receptor-positive disease needed to receive one line of endocrine therapy before; 65-70% were previously treated with cyclin-dependent kinase inhibitors). The trial demonstrated improved progression-free and overall survival in patients treated with T-DXd. The drug's toxicity profile is favorable, with special attention to nausea prevention using a three-drug regimen and the need for careful monitoring for interstitial lung disease/pneumonitis. The initiation of T-DXd treatment can be based on the HER2 status of the primary

or repeated biopsies during the evolution of metastatic disease. Several other new ADCs have shown promising activity in Phase I/II trials but have yet to establish themselves in Phase 3 clinical trials.

Conclusions

Although HER2-low BC is not a distinct clinical entity due to clinical behaviour being driven by hormone receptor status, the clinical trials confirming the efficacy of ADCs in this clinical scenario have prompted the adoption of this terminology in routine clinical practice. Treating patients based on the latest data and providing them with the opportunity to participate in clinical trials has significantly improved the prognosis for BC patients.

Keywords: HER2-low breast cancer, antibody-drug conjugates.

S11 – Oligometastatic breast cancer

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Oligometastatic breast cancer (OM BC) has retrospectively been identified as the disease with a different and more favorable natural history as compared to widespread metastatic BC. It seems that OM state does not simply represent disease identified slightly earlier in time but is instead associated with primary tumors with more limited capacity for metastatic progression. Indeed some studies have shown that OM state express a molecular signature that differs from widely metastaic disease but this needs to be validated. For the time being the most accepted definitoin of an OM disease is based on imaging and includes a maximun of 5 metastatic lesions that could all be potentially susceptible to ablative local treatment. High resolution imaging is mandatory, prefferably ^{18}F-FDG PET/CT, supplemented with liver-specific MRI and brain MRI. OM BC can present as synchronous or *de novo* OM BC, referring to stage IV disease presenting initially as OM, or as oligorecurrent BC where breast cancer relapses as OM after radical treatment of early-stage disease. OM BC represents about 20% of patients with metastatic BC. Retrospective reports and single arm prospective studies are consistent in suggesting favorable long-term outcome of OM BC receiving multimodality approach, including both locoregional and systemic treatment. The former includes local ablative approaches, mainly stereotactic ablative radiotherapy (SABR) or surgery. SABR has fewer side effects, is more suitable for multiple lesions treatment than surgery, and is the treatment modality with more supporting evidence. On the other hand, surgery allows the complete removal of the metastases and the acquisition of histological data. The phase II SABR-COMET trial was the first randomized trial in an OM setting to include BC patients. This study investigated whether addition of SABR on metastatic lesions to standard systemic therapy may improve outcome in patients with OM solid tumors, including 18 patients with BC. Up to 5 metastatic lesions were allowed and the primary tumor must have been removed. The 5-year OS rate was significantly better in the SABR arm (42.3%) compared to the control arm (17.7%). Specifically in OM BC the randomized phase II/III NRG-BR002 trial was conducted investigating the role of adding a metastasis-directed therapy to first line standard of care systemic therapy. 125 BC patients with up to 4 metastatic lesions and controlled primary tumor were randomized to SABR or surgery to metastatic lesions after up to 12 months of systemic therapy or systemic therapy

only. Unexpectedly, the trial failed to confirm PFS or OS benefit. Noteworthy, in this study the OS probability at 3 years was 70%, solidifying the indolent nature and relatively favorable long-term outcome in OM BC. Other randomized phase II/III trials evaluating local ablative approaches in combination with systemic therapy are ongoing. Hopefully they will provide us with information to whom and at what time should the ablative metastasis directed therapy be added and for how long should the systemic treatment be continued in the management OM BC to derive long term benefit. Some trials include translational research assessing the circulating tumor cells, cell- free DNA, and tumor tissue as potential prognostic and predictive biomarkers. Without definite conclusions from randomized trials the clinicians are left with case-to-case management of OM BC patients, relying on prognostic factors for selection of patients more likely to derive benefit from multimodality approach. Isolated sternal metastasis and con- tralateral axillary metastases are classified as OM but demonstrate good survival and should be treated with a curative approach. Other factors associated with favorable prognosis in OM BC are fewer metastatic sites, younger age, good performance status, non triple negative subtype, no CNS/liver involvement, and longer disease-free interval from primary treatment in case of oligorecurrent disease. Patients with OM BC should be discussed by a multidisciplinary team to carefully weigh the risk and benefits of aggressive multimodal treatment that should be reserved for highly selected patients after achieving response to standard first line systemic therapy.

Keywords: breast cancer, oligometastatic, multimodal treatment

S12 – Optimal management of a patient with advanced breast cancer in a visceral crisis

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Visceral crisis (VC) is an urgent situation in the management of a patient with advanced breast cancer (ABC). It is not solely the presence of visceral metastases, but is characterized by severe organ dysfunction assessed by signs and symptoms, laboratory findings and rapid disease progression. In 2019, ESMO-ESO guidelines for ABC5 introduced objective criteria; for hepatic VC a rapidly increasing bilirubin >1.5 x over upper normal limit (without Gilbert's syndrome or biliary obstruction) and for lung VC rapidly increasing dyspnea at rest which does not improve after pleural drainage. Management of VC should include the most effective therapy, not necessarily chemotherapy. Combination chemotherapy is reserved for patients with a rapid clinical progression, life-threatening visceral metastases or the need for rapid treatment of symptoms and/or disease control. The open possibility that chemotherapy is not the therapy of choice in all cases is based on findings of recently presented randomized open label phase II study (RIGHT CHOISE), conducted in HR+/HER2- subtype. Researchers compared progression-free survival (PFS) in patients with aggressive disease treated with combination chemotherapy or letrozole plus ribociclib. Two thirds of patients had symptomatic visceral disease. It revealed that patients treated with letrozole plus ribociclib compared to patients in combination chemotherapy arm have prolongation of median PFS for 1 year (24 vs 12.3 months, resp.) and longer time to treatment failure for 10 months (18.6 vs 8.5 months, resp.). We

present a treatment of a 51-years female with inflammatory HR+/HER2- breast cancer, treated with neoadjuvant systemic chemotherapy with sequential anthracyclines and taxanes, modified radical mastectomy and adjuvant radiotherapy. At regular check-up (after receiving 18 months of adjuvant endocrine therapy with tamoxifen) she developed distant skeletal and hepatic metastases. First treatment was urgent radiation therapy of spine due to critical stenosis at the level of TH11. Systemic treatment with letrozole plus ribociclib was chosen as the first treatment of extensive progression, including imminent visceral crisis.

Keywords: visceral crisis, breast cancer, chemotherapy, cyclin-dependent kinase 4/6 inhibitor, progression-free survival

S13 – Discussion on experience with chemo(immuno)therapy vs. mono-immunotherapy in relapsed/metastatic head and neck cancer

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Head and neck squamous cell carcinomas (HNSCCs) encompass a heterogeneous group of tumours. In less than 20% of patient's metastatic disease has been found at the time of diagnosis. Relapses affect about 10-15% of patients with early disease, but they are up to 4 times more frequent in locally advanced disease. Unfortunately, patients with HNSCC commonly present with locoregionally advanced disease. Relapsing SCCHN can be classified into locoregional recurrence only, locoregional recurrence with metastases, and metastases only. Previous treatment, duration of disease-free interval, programmed death-ligand 1 (PD-L1) expression, overall health status, tumour burden, disease pace and disease site have a significant impact on the choice of the first-line treatment for recurrent and/or metastatic disease. In majority of patient's further surgery and/or radiotherapy is not possible. From 2008 to 2019, the standard first-line treatment has been biochemotherapy according to the EXTREME trial combining the epidermal growth factor receptor inhibitor cetuximab with a platinum-doublet (cisplatin or carboplatin with 5-fluorouracil) in platinum-sensitive SCCHN patients. The EXTREME regimen significantly improved overall survival (OS) from 7.4 to 10.1 months, progression-free survival, and response rate in comparison with the platinum-doublet alone. However, a high rate of acute adverse events was observed in 82% of patients as well as the absence of significant benefit in patients with metastatic disease according to a subgroup analysis. Furthermore, 5-year OS was less than 5%.

The Keynote-048 trial compared pembrolizumab alone or with platinum-doublet (cisplatin or carboplatin with 5-fluorouracil) and EXTREME regimen in platinum-sensitive tumours. Immunochemotherapy significantly improved the 5-year median OS from 10.6 to 13.6 months and from 11.1 to 14.7 months in the combined positive score (CPS) ≥1 and CPS ≥20 subgroups, respectively. Pembrolizumab alone improved the 5-year median OS from 10.4 to 12.3 months and from 10.8 to 14.9 months in the CPS ≥1 and CPS ≥20 subgroups, respectively. Five-year OS ranged from 15.4% in patients with PD-L1 expression CPS ≥1 treated with pembrolizumab alone to 23.9% in those with CPS ≥ 20 treated with immunochemotherapy. In the PD-L1 negative subgroup accounting for 15% of the study population, EXTREME regimen proved its efficacy. In the low PD-L1 expression subgroup (CPS 1-19) pembrolizumab with chemotherapy was more efficient than the EXTREME regimen. Besides, pembrolizumab prolonged median duration of response by

more than 16 months, was substantially less toxic than EXTREME regimen and it was effective in the elderly subgroup. However, in comparison with EXTREME regimen both pembrolizumab and pembrolizumab with chemotherapy did not improve progression-free survival and objective response rate. Furthermore, the use of pembrolizumab was less effective in recurrent only than in metastatic disease with an increased risk of progression in more than one third of patients. Hyperprogression is described in about one quarter of patients receiving immune checkpoint inhibitors and it is more frequent in patients with locoregional recurrence relative to those with only metastatic disease. However, preclinical data revealed possibly restrained efficacy of immunotherapy in liver metastases via macrophage-mediated T cell elimination.

In deciding on the optimal treatment of patients with recurrent and/or metastatic head and neck cancer, an individualized approach within the framework of a multidisciplinary team is required.

Keywords: head and neck cancer, immunotherapy, recurrent disease, metastatic disease

S14 – Molecular markers in systemic therapy

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Precision oncology tends to make improvements in cancer diagnosis and treatment through collecting molecular information that support identification of molecular subtype for tumour classification, relevant predictive markers for treatment decisions according to specific tumour subtype, monitoring of response during cancer treatment, identification of markers of cancer therapy resistance and rapid identification of cancer recurrence. Tissue samples and immunohistochemistry are still gold standard to assess most molecular markers, but advances in molecular techniques put other molecular methods like digital droplet polymerase chain reaction (ddPCR), fluorescent *in situ* hybridisation (FISH), and next generation sequencing (NGS) under the spotlight. However, tissue biopsies do not overcome challenges and pitfalls of tumoral molecular heterogeneity, especially in some of the tumour sites like breast cancer (BC). BC is a highly heterogeneous disease with treatment strategies being challenged with high intratumoral and intertumorala complexity. Liquid biopsy (LB) has the potential to address this important issue through a non-invasive approach, allowing repeated sample collection during the course of the disease. LB involves analysis of circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), circulating tumor RNA (ctRNA), and tumor-derived extracellular vesicles (microvesicles, exosomes) and proteins. The importance of accurate identification of molecular markers in cancer diagnosis and treatment in the era of precision medicine is unquestionable, but its implementation is complicated. Based on the current evidence the European Society for Medical Oncology (ESMO) recommends the use of tumour multigene NGS in non-small cell lung cancer (NSCLC), cholangiocarcinoma, prostate and ovarian cancers and TMB testing in well- and moderately-differentiated neuroendocrine tumours (NETs), cervical, salivary, thyroid and vulvar cancers. The use of ctDNA and liquide biopsy is recommended in advanced cancers and select patients for targeted therapies, also in cases when rapid results are needed, and tissue is unavailable, as the ctDNA

assay genotyping is limited by false-negative results and lower sensitivity. Nevertheless, the Academic research centres should perform multigene NGS, in order to provide innovative treatments.

Keywords: molecular markers, precision medicine, cancer, liquid biopsy, next generation sequencing, ctDNA

S15 – The value of *early* end-points (MPR, pCR) in neoadjuvant trials

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Neoadjuvant systemic treatment options are increasingly being used in clinical trials for improving the outcome of early stage lung cancer. Overall survival (OS) is a traditional standard primary end-point of clinical trials assessing efficacy of neo-adjuvant treatment of lung cancer. The drawback of OS as primary endpoint of neoadjuvant clinical trials is a duration of a trial needed compared to trials using radiological or pathological measures as primary endpoint. Radiological measures have not proved reliability in predicting OS due to difficulties in differentiating histological features such as viable tumor and fibrosis. In lung cancer, previously has been established pathological criteria which are associated with improved OS. Namely, complete pathological response (CPR), defined as the absence of residual viable tumor, and major pathological response (MPR), defined as equal or less than 10% of residual viable tumor, are pathological criteria which are used as surrogate for OS in neoajuvant clinical trials in lung cancer.

Latest clinical trials show that CPR and MPR could be used as predictors of drug efficacy of immune check-point inhibitors in early stage lung cancer in neoadjuvant setting.

Keywords: early stage lung cancer, neoadjuvant systemic treatment, pathological measures; complete pathological response (CPR), major pathological response (MPR)

S16 – How to manage patients after CPI resistance?

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Immune checkpoint inhibitors (ICIs) are recommended as first-line treatment in almost all patients with non–small cell lung cancer (NSCLC) and have dramatically improved survival in patients with metastatic disease. However, almost all patients will experience disease progression at some point and require further therapeutic options.

The active substrate of immunotherapy is the patient's immune system and to date no single, widely scientifically accepted mechanism for resistance to anti–PD-(L)1 immunotherapy has been described. Most of the processes that may mediate immunotherapy resistance are primarily unexplored by large clinical

trials. Recent established molecular predictors of anti–PD-(L)1 response cannot predict which patient will develop resistance to ICI monotherapy or their combination with other therapies. Investigating tumor microenvironment subtypes could have potential applications for using this information as a broader cancer immunotherapeutic biomarker. Understanding the complexity of the microbiome and tumor metabolism can pave the way for understanding the mechanisms of malignant disease development and the formation of metastases and further modulation of antitumor therapies.

In practice, the second-line treatment strategy is largely influenced by the first-line treatment, although data to guide treatment selection are limited and based on historical cohorts or retrospective analyses. According to current guidelines, platinum-based doublet therapy is recommended as a subsequent systemic treatment option for patients with metastatic NSCLC after first-line therapy with single-agent ICIs, while for patients with metastatic NSCLC and disease progression after first-line therapy with a combination of ICIs and chemotherapy, subsequent systemic therapy options include docetaxel (± anti-angiogenic therapy), gemcitabine, albumin-bound paclitaxel, or pemetrexed (for non-squamous tumors), depending on which drug was not previously administered.

Conclussion

At progression after chemo-immunotherapy or ICI monotherapy, the standard treatment strategies are single-agent chemotherapy or combination with anti-angiogenic agents, which, however, all have modest efficacy and this is still an area of unmet need. The results of trials evaluating new drugs and new combinations need to be seen to find better alternative therapeutic strategies. Determining further treatment options for patients through randomized trials based on biomarkers after resistance to PD-(L)1 inhibitors is of utmost importance. In the future, personalized strategies may be required to predict and overcome immunotherapy resistance and improve patient survival and quality of life outcomes.

Keywors: NSCLC immunotherapy, mechanism of ICI resistance, post-PD-(L)1 therapy

S17 – Druggable genomic alterations in metastatic NSCLC and available drugs in our region

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Non-small cell lung cancer (NSCLC) is a heterogenous disease driven by a spectrum of molecular alterations, and this is why it has become probably the most dynamic field of cancer clinical research in past decade. The renaisssance has begun with establishing epidermal growth factor receptor (EGFR) activating mutations as a target for tyrosine kinase inhibitors (TKI), in 2004. Adenocarcinoma of the lung today represents the supstrate for practically all driven mutations that can be effectively inhibited by TKI. A very small percentage of activating mutations has been associated with the other non-squamous cell lung carcinomas, while the squamocellular carcinoma still presents as an orphan in terms of activated, druggable mutations. The mutations of EGFR and KRAS G12C are the most numerous mutations. EGFR is the most druggable one, affecting 10-15% of all advanced Caucasian NSCLC patients. Osimertinib, as an

representative of the third generation of TKI, revealed supreme median overall survival of 38.6 months, in the first-line treatment. This is very important breakthrough, in the light of fact that molecular and consequent clinical progression is inevitable in almost all patiens having genetic alterations in lung adenocarcinoma. Exon 20 insertion, an alteration of poor prognosis on standard EGFR TKI, now has two active drugs: amivantamab and monocertinib, both FDA approved. KRAS G12C mutation is one of the most frequent KRAS mutation in NSCLC, especially in current and former smokers (over 40%), which occurs among approximately 12–14% of NSCLC tumors, being until recently without active therapy. Sotorasib 2021. and adagrasib 2022. were FDA approved, for previously treated patients, proved to be particularly active in presence of co-occurring STK11 mutations. Of particular interest are genetic re-arrangements in anaplastic lymphoma kinase (ALK) gene (4-5% of all advanced lung adenocarcinoma). Having here three generation of ALK-inhibitors, an optimal treatment approach will require the use of pan-inhibitory ALK-TKI upfront to block on-target resistance and to have great CNS activity as well. The latest is of high importance, bearing in mind that 30-40% of ALK-positive patients will develop brain metastases. Less frequent alterations (1-2%) in genes such as ROS1, BRAF, HER2, RET, MET exon 14 and NTRK should also be assessed, if the next-generation sequencing (NGS) is being used for broader testing. With the increasing number of the next generation kinase inhibitors which are active against these alterations (crizotinib or lorlatinib for ROS1 rearrangement, dabrafenib + trametinib for BRAF mutations, trastuzumab-deruxcetan for HER2 mutations, capmatinib and tepotinib for exon14 skipping MET mutation, selpercatinib and pralsetinib for RET rearrangement, larotrectinib and entrectinib for NTRK and ROS1 alterations), more and more efficient targeted therapy has been brought to clinical practice for advanced non-squamous NSCLC. The availability of novel, targeted therapy for advanced/metastatic NSCLC in our region follows the heterogeneity of availability of other novel drugs in oncology in respective countries. The best situation is in Slovenia, following by Croatia, Montenegro, Serbia and Bosnia and Herzegovina. Better perception of great impact of new drugs in lung cancer on patient survival and mortality reduction will hopefully have a positive effect on stakeholder decision-making, particularly in currently non-EU countries.

Keywords: metastatic NSCLC, targeted therapy, tyrosine kinase inhibitors, next generation sequencing

S18 – The future of the systemic treatment of the upper GIT cancers

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For many years, fluoropyrimidines and platinum derivatives have been the key therapy in the treatment of upper gastrointestinal cancers, which was joined by trastuzumab in HER2+ advanced gastric cancer. Many studies have tried to intensify chemotherapy, so FLOT has become the most effective combination in the perioperative treatment of cancer of the gastroesophageal passage and stomach. The desire to improve efficiency has led to the search for new targets and the development of new drugs. Several studies have been conducted investigating immunotherapy in the treatment of upper gastrointestinal cancers. Therefore, immunotherapy with nivolumab proved to be effective in the adjunctive treatment of oesophageal and GEJ cancer. Both nivolumab and pembrolizumab in combination with chemotherapy

involving fluoropyrimidines and platinum derivatives are effective in suppressing non-resectable disease. The mentioned combinations lead to a prolongation of the time until the progression of the disease, as well as a prolongation of the overall survival in patients with a positive expression of PDL-1, described as CPS, which must be higher than 5% and 10%, respectively. Patients with HER2+ unresectable gastric cancer who have progressed after treatment with trastuzumab can be treated with trastuzumab deruxtecan in the second line to prolong overall survival. The search for new targets has led to the realization that in patients with advanced gastric cancer it may also be claudin. As a result of disturbed cell polarity associated with malignant transformation, epitopes of claudin (CLDN18.2) become exposed and available for the target binding of monoclonal antibodies, such as zolbetuximab. Only this, together with chemotherapy according to the EOX scheme, is in the first line, in patients with advanced gastric carcinoma, who are CLDN18.2 positive, effective and can void in an extended time until disease progression and also overall survival.

Keywords: gastric cancer, oesophageal cancer, immunotherapy, zolbetuximab, trastuzumab deruxtecan

S19 – Cancer of unknown primary: does primary still matter in the era of molecular profiling?

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Cancer of unknown primary (CUP) is defined as a carcinoma or undifferentiated neoplasm in which a standardised diagnostic work-up fails to identify the primary tumour responsible for metastatic seeding. It accounts for approximately 3-5% of all cancers. The incidence of CUP has been decreasing in recent years, probably due to improved diagnosis and identification of the primary tumour. The incidence increases with age and is higher in men than in women. Approximately 50% of CUP cases are well to moderately differentiated adenocarcinomas, 30% are poorly differentiated adenocarcinomas or undifferentiated carcinomas, 15% are squamous cell carcinomas and 5% are undifferentiated neoplasms.

Known risk factors include smoking, type 2 diabetes, autoimmune disease and family history. Smokers are at risk of developing CUP, and this risk correlates with the level of tobacco exposure: from 1.8-fold for smokers of 1-15 cigarettes/day to 4.1-fold for smokers of >25 cigarettes/day. Type 2 diabetes (1.8-fold) and autoimmune diseases are also associated with an increased risk of CUP, with relative risks of 3.5 for polymyositis/dermatomyositis, 1.8 for primary biliary cirrhosis and 1.7 for Addison's disease. High body mass index, waist circumference, low socioeconomic status and black ethnicity may be additional risk factors.

The probability of survival after diagnosis of CUP has remained at ~20% at 1 year and has not improved much over time. Approximately half of observed deaths occur within the first 3 months of diagnosis, so median survival is ~3 months. Survival is worse for adenocarcinoma and undifferentiated carcinoma than for squamous cell carcinoma (1-year survival of <20% and 36%, respectively). Older age is associated with worse survival. Patients with CUP limited to the lymph nodes have a better prognosis than those with extra-nodal disease.

After a thorough history, clinical examination and basic laboratory and imaging studies, pathology plays a key role in the diagnosis of CUP, so obtaining a quality tissue sample is crucial. Pathology usually

begins with staining for lineage-specific markers and screening for broad-spectrum keratins, which can confirm the diagnosis of carcinoma. The use of cytokeratin 7 and 20 can give an indication of the primary. The next step is to use more tissue-specific markers. However, in the majority of CUP cases, pathology will not provide a diagnosis with a high degree of certainty.

Traditionally, CUP has been divided into two subsets. The minority of cases (15%) can be considered a favourable subset. These are breast like, head and neck like, prostate like, bone like and renal like CUP. The similarity is based on a clinical and pathological picture, supplemented by immunochemistry (IHC). The new classification also includes oligometastatic CUP as a favourable subset. Treatment protocols should be equivalent to those used for putative primary disease. 85% of CUP patients are in the unfavourable subset. These can be summarised as having widespread disease with a high metastatic burden, usually visceral metastases. Treatment options are best supportive care (BSC) or empiric chemotherapy (ChT). Platinum- or taxane-based doublets are used as standard ChT. Triplet combinations have also been studied, but results show higher toxicity with no benefit in prolonging survival, so they are not recommended. Survival of patients with unfavourable CUP treated with platinum-based combination chemotherapy remains poor, with median overall survival (OS) of less than 10 months. The most common dilemma in the management of patients with CUP is whether and how to try to identify the primary tumour. One option is to speculate on the most likely tissue of origin by gene expression profiling. The other is to identify and target molecular aberrations. The first strategy is based on the assumption that the gene expression of the tumour resembles the pattern of the putative primary to some extent, and that we can therefore biologically assign an origin to the tumour. This theory was put to the test in the GEFCAPI 04 trial, which enrolled 243 patients. This was a phase III trial of empiric ChT with cisplatin and gemcitabine (control arm) or systemic treatment tailored by molecular gene expression analysis (experimental arm). The primary endpoint was progression-free survival (PFS). The most commonly recognised tissues of origin were pancreaticobiliary (19%), squamous cell carcinoma (SCC) (11%), renal (8%) and lung (8%). Of the 123 patients randomised to the experimental arm, the presumed tissue of origin could be assigned in 91 patients. Median PFS was 5.3 months in the control arm and 4.6 months in the experimental arm, the difference was not statistically significant (HR 0.95; 95%CI 0.72-1.25; p=0.7). The second strategy is to identify and target molecular aberrations using a next-generation sequencing (NGS) panel. The literature shows that 20-25% of CUP will have a tumour with an actionable molecular aberration. The theory is that targeting the driver molecular aberration in CUP is more important than the rest of the molecular ecosystem surrounding the tumour. An ongoing study, CUPISCO, is investigating the benefit of this approach in CUP patients. The trial will recruit a total of 790 patients. Patients will be randomised after 3 cycles of induction platinum-based ChT doublets. Responders will be randomised to the experimental arm (targeted therapy tailored to molecular profile) or to continue with standard ChT. Non-responders will go directly to molecularly targeted therapy. Results from this trial are expected in 2024. There are some new approaches to treating patients with CUP, one of which is treatment with immune checkpoint inhibitors (ICI). Pembrolizumab was the first ICI approved for agnostic treatment, based on the results of several studies that confirmed efficacy in microsatellite instability high (MSI-H)/mismatch repair deficient (MMRd) tumours (including patients with CUP), with a reported objective response rate (ORR) of around 40%. The efficacy of pembrolizumab was further investigated in the Keynote 158 study, which included patients with high tumour mutation burden (TMB-H). Based on the results of this study, the indication for agnostic treatment with pembrolizumab was expanded to include TMB-H tumours. The only published study to date that has tested the efficacy of ICIs in CUP patients is NivoCUP. This is a non-randomised phase 2 study of 56 patients, an unfavourable subset, 45 of whom were pre-treated. The primary endpoint was ORR, which

was reported in 22% of patients, with 2 patients achieving a complete response (CR). The results demonstrate a clear clinical benefit of nivolumab in patients with CUP, with benefits more evident in patients with known biomarkers of ICIs (PD-L1 expression, TMB and MSI status). Some patients responded well regardless of biomarker status, suggesting the need for further biomarker evaluation in this unique patient population. They support the potential of nivolumab to become an additional therapeutic option for CUP, a disease with limited treatment options. Based on the results of these studies, ICIs can be considered for MSI-H/MMRd, TMB-H or PD-L1 high CUP. ICIs may also be used in scenarios that suggest a primary cancer where ICIs are established as a treatment option.

Conclusion

CUP remains a difficult cancer to diagnose and treat. Special efforts should be made to identify patients with a favourable CUP subgroup, as patients in this subgroup can achieve long-term survival with appropriate treatment. The diagnostic workup should follow guidelines. It is important not to repeat diagnostic procedures, as more additional diagnostic tests are unlikely to increase the likelihood of identifying the primary site. Patients in the unfavourable subgroup must be informed about the advantages and disadvantages of empiric therapy. For many patients with widespread disease and poor condition, BSC may be the best treatment option. An honest discussion is therefore essential. Novel approaches are promising and represent a fundamental shift in the paradigm of cancer treatment from organ/tissue-specific to individual patient-focused treatment based on tumour-specific genomic alterations.

Keywords: cancer of unknown primary, molecular profiling, genomic analysis, therapeutic strategies, site-specific treatment.

S20 – Tailoring systemic therapy for medullary thyroid cancer

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Medullary thyroid cancer (MTC) is a rare neuroendocrine malignancy, originating from calcitonin producing parafolicullar C cells. Almost all familiar MTC (25% of all MTC) carry germline RET mutation. In sporadic MTC, over 60% of patients carry one of somatic RET mutations, most commonly M918T. Patients with progressive advanced/metastatic disease with multiple lesions have several options of systemic treatment. Multikinaze inhibitors vandetanib (targeting RET, VEGRF and EGFR pathways) and cabozantinib (targeting RET, VEGFR2 and MEK pathways) have been approved in randomized phase III trials (EXAM and ZETA, respectively). Both TKIs prolong progression-free survival compared to placebo. Overall survival benefit was not demonstrated. However, treatment-related side effects substantially affect quality of life of patients, desire dose reductions and treatment interruptions. Choice of treatment should be tailored to patients' and disease characteristics. Of note, based on significantly higher response rate in RET-mutated tumors compared to RET-nonmutated (52% vs 18%), vandetanib use is restricted to patients harboring RET mutation. Novel RET-specific TKIs selpercatinib and pralsetinib are approved in Europe in RET-mutant MTC patients after progression on the treatment with vandetanib and/or cabozantinib. In

open label cohort studies LIBRETO-001 (for selpercatinib) and ARROW (for pralsetinib), both RET inhibitors showed high response rate (over 60%), durable response and favorable toxicity profiles. In the USA RET inhibitors are approved already for the first line treatment of RET mutated MTC.

Keywords: medullary thyroid cancer, RET mutation, vandetanib, cabozantinib, selpercatinib, pralsetinib

S21 – The clinical importance of molecular characteristics in brain cancers

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In the past decade, with the progress of new targeted drugs and immunotherapy with immune checkpoint inhibitors, a breakthrough has been achieved even in solid cancers unresponsive to systemic treatment. Both targeted therapy with small molecule tyrosine kinase inhibitors and immunotherapy with immune checkpoint inhibitors in the form of monoclonal antibodies have led to an increase in survival for patients with metastatic melanoma from less than one year to sixty months. In the era of personalized systemic cancer treatment, biomarkers are an inevitable tool that can be used to predict the response to individual therapy.

The importance of molecular features in the systemic treatment of brain tumors

Next-generation sequencing (NGS) of tumor and inherited (germ) genomes is a DNA sequencing technology. With NGS, the entire human genome can be sequenced in a single day, in contrast to previous Sanger sequencing technology that was used to decipher the human genome and took more than a decade to provide a final draft. NGS has revolutionized and improved cancer treatment over the past two decades and is now crucial for evaluating therapeutic options in many solid and hematologic malignancies. With progress in the field of discovering the genetic background of tumors of the central nervous system (CNS), questions arise as to which genes are necessary for diagnosis, which are optional, but beneficial to have, and which are of no clinical importance. Brain tumors are clinically and molecularly extremely heterogeneous neoplasms. Due to the molecular heterogeneity of primary and recurrent tumors, the identification and validation of diagnostic, prognostic and potential predictive biomarkers is quite challenging. One of the most prominent molecular discoveries in the field of gliomas was the identification of mutations in genes IDH1/IDH2 in 2008, which changed the further classification of glial tumors. In 2016 in WHO classification there was a revision of grade II and III gliomas according to molecular features, and thus glioblastomas were divided into three groups according to the presence of IDH1,2 and/or 1p/19q codeletion. The 2021 WHO classification reduces the more than 15 entities of adult-type diffuse gliomas listed in the 2016 update to 3 types with better characterized biology and prognosis: astrocytoma, *IDH* mutant (WHO grades 2-4); oligodendroglioma, *IDH* mutant and 1p/19q codeleted (WHO grades 2 and 3); and glioblastoma, *IDH* wild type (WHO grade 4). The major changes include the restriction of the diagnosis of glioblastoma only to tumors that are *IDH* wild type; the reclassification of tumors previously diagnosed as *IDH*-mutated glioblastomas as astrocytomas, *IDH* mutated, grade 4; and the requirement for the presence

of *IDH* mutations for the classification of tumors as astrocytomas or oligodendrogliomas. Based on this, recommendations for systemic treatment and research with new drugs that are coming have also been adjusted. Most patients with glioblastoma are treated with a combined approach that includes adjuvant postoperative radiation and adjuvant chemotherapy after initial surgery. Even with maximum therapy, it has glioblastoma has a high recurrence rate and a poor overall survival of 1.5 to 2 years. The choice of appropriate systemic therapy for patients with glioblastoma and other infiltrative gliomas is always more dependent on adequate molecular characterization. For glioblastoma, tumor samples should be tested for methylation of the O6-methylguanine-DNA methyltransferase (MGMT) promoter and to isocitrate mutations dehydrogenase (IDH) type 1 or type 2. While the presence of an IDH1/2 mutation does not yet affect the first line treatment in regular clinical practice, however, results in a significantly improved prognosis and may affect eligibility to the clinical trial of new drugs in the first line. Furthermore, most IDH1/2-mutant astrocytomas stage 4 also shows methylation of the MGMT promoter, which is important for the choice of treatment as well as prognosis. MGMT promoter methylation in glioblastoma leads to gene silencing and loss of protein expression MGMT DNA repair predicts benefit of alkylating agent chemotherapy and predicts improved survival. BRAF mutation is present in 8% and some activity has already been recorded with BRAF inhibitors in monotherapy or in combination with MEK inhibitors, but most of the data comes from retrospective publications of individual oncology centers, and some from phase ½ studies or the largest study was of the Basket type. where 11 patients with anaplastic astrocytoma or glioblastoma were included. Response to BRAF with/without MEK inhibitors is around 10%. NTRK (NTRK1, NTRK2 or NTRK3) fusions are present in up to 3.1% of primary gliomas in adults. A study with the NTRK inhibitor larotrectinib, which included not only low-grade but also high-grade glioma in the Phase 2 Basket study, showed a 30% response to treatment, but the median overall survival was not reached at one year. In less than 20% of gliomas, the broken synthesis of MMR proteins is present, which leads to microsatellite instability and the resulting immunogenicity of the tumor, but mainly in lower-grade gliomas. Immunotherapy, or inhibitors of immune checkpoints – PD1 inhibitors, show an effectiveness of up to 10%, and the data comes mostly from the published experiences of individual oncology centers, and some from phase 1 and 2 studies.

Conclusion

Molecular diagnostics, as in all cancers, has also helped to identify groups in brain tumors that respond more to certain targeted therapies due to specific molecular properties, but progress is slow and major changes in systemic treatment will have to wait for larger studies. Regardless of everything, even now, based on the results of molecular characteristics in certain subgroups with the development of resistance to standard treatment, patients can also be treated with targeted therapy based on the multidisciplinary council evaluation, which plays an essential role in treatment decision making.

Keywords: brain tumors, molecular features, biomarkers

S22 – Immunotherapy in gynecologic oncology – new standard in metastatic endometrial and cervical cancer

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In the last decade immunotherapy already became a standard of care in various different solid tumors. In the treatment landscape of advanced gynecologic cancers immunotherapy is just starting to change our standard treatment approach. Recent advances in genomic characterization of gynecologic malignancies have helped in understanding of these tumors and planning the therapy but there is still need to answer which molecular or immunophenotypic markers can more accurate identify patients to benefit the most from immunotherapy. Advanced stage of endometrial cancer (EC) at the diagnosis is present in 10-15% of patients and is associated with poor prognosis. 5-year survival with advanced disease is around 18%. Also 20% of patients present with early disease will experience recurrence in a median of 3 years after diagnosis. Till now our patient have been treated with a golden standard chemotherapy doublet, cisplatin or carboplatin with paclitaxel. Response rate of this therapy range 40-60%, and the duration of the response was short. Until recently there was no standard second line, monochemotherapy with taxanes or anthracyclines was used. Advances in molecular understanding of EC have helped us to identify four different groups od EC. Group of mismatch repair deficient (MMRd)/microsatellite instability high (MSI-H) EC represent only 30% of all EC and are highly immunogenic with enhanced PD-L1 expression. These tumors have shown very good response on different immune checkpoint inhibitors (ICI) even in heavily pretreated patients. The efficacy as a monotherapy have shown dostarlimab, pembrolizumab and durvalumab. The majority of EC is MMR proficient or MSI stable (MSI-S) tumors and represent challenge and need for further studies. Study Keynote – 775 has demonstrated efficacy od pembrolizumab and levantinib combination in this subgroup of advanced EC. Toxicity profile is similar as seen in other solid tumors, a bit more adverse effects (AE) are seen in combination therapy with ICI and tyrosine kinase inhibitors (TKI), as levantinib, due to TKI AE. Although we have preventive and screening programs for cervical cancer, patients with recurrent, persistent or advanced cervical cancer have dismal prognosis as well. Until recently, these patients have been treated only with platinum-based chemotherapy and bevacizumab. However, ICI have opened a new possibility of effective treatment. PD-1 and PD-L1 are upregulated in cervical cancer and can be used as biomarker of immune response. Phase II study Keynote – 028 provided first evidence of clinical activity of pembrolizumab in advanced cervical cancer. This effect was confirmed in phase III.study Keynote – 158 where all patient that have complete or partial response had have PD-L1 >1%. Most commonly seen AE were hypothyroidism and fatigue. Clinical activity was proved also of the nivolumab (study CheckMate358). Response were seen in PD-L1 positive and negative group, although greater in PD-L1 positive group. Despite the clinical activity of ICI seeming to be superior to chemotherapy, this question was answered by the study phase III EMPOWER, where significand improvement of overall survival (OS) in the group treated cemiplimab, anti-PD-1 antibody, was shown over the group treated with chemotherapy of physician's choice. Concerning safety profile, 45% of patients with cemiplimab presented AE grade >3, mostly anemia. Currently ongoing studies FERMATA, Keynote-826, BEATcc are exploring synergistic effect of platinum based standard chemotherapy with or without bevacizumab in combination with ICI. The results of study Keynote -826 were presented in this year ASCO congress. Addition of pembrolizumab to chemotherapy with or without bevacizumab reduced risk of

death by 40% in PD-L1 >1%, 42% in group PD-L1 >10% and for 35% in all-comer population. The results of other two studies are still awaiting.

Immunotherapy opens a new effective treatment possibility in gynecologic cancers. Results of many ongoing studies are eagerly awaited with a hope of answers to many burning questions.

Keywords: immunotherapy, endometrial cancer, cervical cancer, pembrolizumab, advanced disease, standard therapy

S23 – Neoadjuvant/adjuvant immunotherapy in non-melanoma skin cancers

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Non-melanoma skin cancer is one of the most common cancers in the world. Basal cell carcinoma (BCC) accounts for 75%-80% of all skin cancers. BCC grows slowly and is often detected early. Most primary basal cell carcinomas are treated surgically or, in the case of superficial lesions, with non-surgical methods. The risk of recurrence is increased by tumour size, poorly defined margins of the lesion, aggressive histological subtype and previous recurrences. In extremely rare cases, BCC progresses to distant tissues (metastatic BCC). In case of multiple local recurrences or invasion of surrounding/distant structures, where surgery and/or radiation are not suitable, a multidisciplinary approach is essential for patients' treatment. The results of treatment with vismodegib and sonidegib show a significant reduction in the size of multiple lesions and the number of new lesions in patients with Gorlin syndrome. The most common side effects are muscle cramps, changes in taste, hair loss and fatigue. When targeted treatment is no longer effective, patients with advanced disease can undergo second line treatment using immunotherapy with checkpoint inhibitors such as, anti-PD-1 antibodies.

Squamous cell carcinoma (SCC) of the skin is a common cancer arising from the malignant proliferation of epidermal keratinocytes that has invaded the dermis or beyond. Most patients with cutaneous squamous cell carcinoma have an early form of the disease that can be successfully treated with surgery alone. A small percentage of patients have locoregionally advanced disease or disease with unfavourable histopathological features that can be treated with adjuvant radiotherapy and systemic therapy after surgery itself. However, surgical interventions in the advanced form of the disease are often mutilating and extensive. A multicentred, nonrandomized, phase 2 study was conducted to evaluate cemiplimab as neoadjuvant therapy in patients with stage II, III, or IV (M0) respectable cutaneous squamous cell carcinoma. Patients received up to four doses of cemiplimab preoperatively for curative intent. Primary endpoint was achievement of Neoadjuvant treatment with cemiplimab with pathologic complete response, which was observed response in a high percentage of patients with resectable cutaneous squamous cell carcinoma. In the systemic treatment of advanced disease, immunotherapy with checkpoint inhibitors – anti PD-1 antibodies Cemiplimab and Pembrolizumab is effective and standard of care.

Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine skin cancer with a poor prognosis, especially when it is in an advanced stage. Incidence is generally increasing, although incidence data show

differences between geographic areas. Risk factors include age, immunosuppression and exposure to ultraviolet radiation. A link between MCC and polyomavirus infection is known, although the exact mechanism leading to carcinogenesis is not yet fully understood. For localized disease, the treatment of choice is surgery (when possible), followed by adjuvant radiation or radiation combined with chemotherapy. For disseminated disease, immunotherapy with checkpoint inhibitors is standard of care for several years in first lines therapy, and chemotherapy in further lines if immunotherapy is not successful. First-line and second-line immunotherapy has good results with an acceptable safety profile of treatment, so this type of treatment has become standard and has replaced chemotherapy. The ADMEC-O trial is the first trial, testing the efficacy and safety of adjuvant immunotherapy in patients with completely resected MCC, compared with follow-up. The primary endpoint was DFS, and the secondary endpoints were overall survival (OS) and adverse events (AEs). DFS rates at 12 and 24 months favoured nivolumab treatment. Median OS has not yet been reached.

Keywords: non-melanoma skin cancers, BCC, SCC, Merckel carcinoma, neoadjuvant ICI

S24 – Neoadjuvant and/or adjuvant immunotherapy in malignant melanoma – the best approach

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Neoadjuvant immunotherapy has several advantages. It can induce stronger antitumor immune response as compared to adjuvant immunotherapy.

From analysis of OpACIN-neo and PRADO trial, authors concluded: Total lymph node dissection (TLND) can probably be omitted in patients with high-risk melanoma who achieve a major pathologic response to neoadjuvant IPI + NIVO without affecting survival outcomes. These patients are unlikely to derive further benefit from adjuvant systemic therapy use. Adjuvant systemic therapy improved survival outcomes for patients who achieved a pathologic nonresponse following neoadjuvant immune checkpoint inhibitor therapy. From S1801 trial we learned that, compared to the same treatment given entirely in the adjuvant setting, neoadjuvant pembrolizumab followed by adjuvant pembrolizumab improves event-free survival in resectable melanoma.

Unfortunately, despite our best efforts there will always be a group that do not get major benefit from neoadjuvant checkpoint inhibition, so I am not sure that we will ever move away completely from adjuvant treatment. The current randomized data support neoadjuvant plus adjuvant pembrolizumab and dropping adjuvant therapy may compromise outcome.

Keywords: Neoadjuvant/adjuvant immunotherapy, malignant melanoma, ICI

S25 – Immune-related adverse events: The true meaning for skin cancer patients

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Treatment with immune checkpoint inhibitors (ICIs) has shown to prolong overall survival and improve quality of life of patients with various types of cancer. The number of patients being treated with this type of immunotherapy is increasing rapidly. Immune checkpoint inhibitors can cause a special type of side effects called immune-related side effects (irAE). These are the result of excessive activation of the immune system. They can lead to serious and life-threatening complications, although most are mild to moderate. Any organ can be affected. Rapid recognition, appropriate treatment, and greater awareness among clinicians of various fields and patients and their relatives remain the key to their treatment. The American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), the Society for Immunotherapy of Cancer (SITC) and other organizations have developed detailed recommendations for the management of irAE, freely available on their websites. The guidelines provide clear instructions regarding possible differential diagnoses (e.g., infection, cancer progression, pulmonary embolism, etc.), the type of recommended immunosuppressive drugs and the duration of treatment. Effective management of irAE requires early recognition and appropriate treatment as soon as possible. Before deciding on further treatment, we determine the degree of adverse effect according to the CTCAE criteria. The drug of choice are corticosteroids, the dose and method of administration depend on the severity of irAE. If longer-term treatment with corticosteroids is planned, antimicrobial prophylaxis against pneumocystis and replacement of calcium and vitamin D are advised. In the case of irAE resistant to corticosteroids, other immunosuppressive drugs are used, such as infliximab, mycophenolate... For the successful management of more serious irAE, cooperation with subspecialists of other disciplines is necessary, such as gastroenterologists, pulmonologists, rheumatologists, cardiologists, dermatologists, and others. In the case of mild and moderate irAE grade 1 or 2, in most cases ICIs can be continued. In serious and life-threatening ones of grade 3 or 4, the treatment must be permanently interrupted. The use of ICIs is now a part of standard clinical practice. To achieve the optimal benefit of this treatment, timely recognition, and successful management of irAE is of utmost importance. IrAEs can remain unrecognized and untreated due to their diverse clinical picture. Greater awareness of irAE is needed at all levels of medical professions.

Keywords: immunotherapy, immune checkpoint inhibitors, immune-related side effects

S26 – Sex and gender differences in colon cancer

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Colorectal cancer (CRC) is the third most common cancer worldwide and the fourth leading cause of cancer death in the world**,** with mortality rates in males significantly higher than females. Apart from incidence and mortality sexual dimorphism influence clinicopathological features, as females are more frequently presenting right-sided tumors and BRAF mutations.

Toxicity associated with fluoropyrimidines, targeted therapies, and immunotherapies has been reported to be more extensive for females with CRC compared with the males. Tolerability to anticancer therapy might be related to pharmacokinetics of drugs. Recently several reports indicated sex-associated differences in pharmacokinetics of 5-fluorouracil with plasma clearance and dose have been found to be lower in females whereas plasma life and area under the plasma concentration time curve might be higher in females compared with males.

Those reports suggesting that current dosage of anticancer drugs which is based on body surface area, not taking into account sex differences related to body composition of females and males should be reconsidered. Finally, several reports suggested difference in efficacy of certain chemotherapeutical protocols related to sex, but more date from prospective clinical trials are needed. In the treatment of patients with CRC we have goal of personalizing treatments for each patient based mainly on molecular biomarkers. Introducing sex and gender into treatment decision might take as step further in offering effective, personalized treatment for all individuals. In that sense, interventional clinical trials focusing on sex-specific differences in efficacy and toxicity as a primary endpoint and the evaluation of specific dosing regimens according to sex should be conducted.

Keywords: Colorectal cancer, gender, sex

S27 – Integrating supportive & palliative care & geriatrics with oncology – clinical cases

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The main goal of supportive and palliative care is to ensure the quality of life of patients by alleviating the physical, psychological, sociological, and spiritual needs of patients and with support to their loved ones through all periods of the disease. The Multinational Association of Supportive Care in Cancer defines supportive care in cancer as "the prevention and management of the adverse effects of cancer and its treatment. This includes management of physical and psychological symptoms and side effects across the continuum of the cancer experience from diagnosis through treatment to post-treatment care. Enhancing rehabilitation, secondary cancer prevention, survivorship, and end-of-life care are integral to supportive care."Palliative care, according to the Center to Advance Palliative Care, is "specialized medical care for people living with serious illnesses. It is focused on providing patients with relief from the symptoms and stress of a serious illness—whatever the diagnosis. The goal is to improve quality of life for both the patient and the family. Palliative care is provided by a team of doctors, nurses, and other specialists who work with a patient's other doctors to provide an extra layer of support. Palliative care is appropriate at any age and at any stage in a serious illness, and can be provided together with curative treatment." Geriatrics is the medical specialty dedicated exclusively to providing high-quality, patient-centered care for older adults. Older adults have a unique set of issues and concerns which geriatric clinicians are trained to

focus upon. Illnesses, diseases, and medications may affect older people differently than younger adults, and older patients may have overlapping health problems that require multiple medications. Geriatricians prevent and manage illnesses and develop care plans that address the special health problems of older adults.

Case report – age and comorbidity in metastatic prostate cancer

Prostate cancer is the most common malignancy in the male population. Its incidence increases with advancing age an approximately 50% patients are older than 65 years when diagnosed. While aging is associated with increasing comorbidity, also standard hormonal treatment for prostate cancer can increase the risk for cardiovascular and other comorbidities (eg. diabetes, osteoporosis). In advanced prostate cancer patients are treated with hormonal treatment for several years and when developing castrate-resistant prostate cancer (CRPC) they are around 70 years old. In this age-group, according to observational studies, 75% of patient have at least one comorbidity and 30% having moderate or severe comorbidity. Acknowledgement of these facts and timely inclusion of patients into multidisciplinary management including geriatric and palliative care is of critical important for optimal treatment of patients. The presented case revolves around an 80-year-old patient with metastatic castrate-resistant prostate cancer. It presents authors view how to treat elderly, polymorbid patients in everyday practice and in doing so highlights the role of timely palliative and geriatric interventions to improve quality of life.

Conclusion

Treatment should be individualized based on the current condition and wishes of the patient. To ensure optimal care, early recognition of needs, timely inclusion of the treatment, and its integration into oncological interventions are important.

Keyword: supportive care, palliative care, geriatrics, integration

S28 – Optimal management of an older frail patient with ABC

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More than a half of breast cancer cases are diagnosed in women above the age of 60. As life expectancy is increasing and the therapeutic options evolve the number of elderly patients, living with breast cancer are expected to increase, too.

Even in adjuvant setting up to a quarter of elderly breast cancer patients are not treated according to the guidelines. The number is expected to be even higher in metastatic disease.

Undertreatment, most commonly due to unjustifiable fears of advanced age and associated comorbidities, is commonly practiced. On the other hand, overtreatment of unrecognised fragile elderly patients is often the cause of unnecessary harm.

Some kind of geriatric assessment should be performed at the beginning of the treatment, and it should be repeated as necessary, but mandatory every time a change of treatment course is planned or

when toxic side effects occur. As comprehensive geriatric assessment is time consuming and not available for all the elderly cancer patients, simplified tools for screening such as G8, VES-13 and mini-COG are used in everyday clinical practice. With these tools patients that benefit the most from geriatric examination and intervention are identified.

Most of chemotherapeutic agents, along with the targeted therapy and anti HER2 drugs can be safely given for elderly patients. However, dose adjustments and close monitoring of potential adverse events are needed. More aggressive and potentially toxic interventions can be replaced with safer but still effective therapies, such as the combination of CDK 4/6 inhibitors in combination with endocrine therapy, or even endocrine therapy alone in the fragile population.

Keywords: breast cancer, elderly, geriatric, systemic therapy

S29 – Management of oligometastatic and oligo-progressive disease in GU

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Metastatic prostate cancer has long been considered incurable and managed with systemic therapies alone. However, there is increasing evidence of an "oligometastatic" state where patients with low-volume metastatic disease may achieve sustained disease-free intervals as well as potentially improved overall survival (OS) with combinations of systemic and local therapy. The concept of oligometastatic disease was first described by Hellman and Weichselbaum who hypothesized that there may be an intermediate state between locally confined disease and fulminant metastatic disease. Although the definition of oligometastatic disease varies considerably in the literature, most definitions limit the maximum number of metastatic sites to between 3 to 5. The HORRAD and Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trials have established a survival benefit to prostate-directed RT in patients with low-volume metastatic disease. HORRAD was a phase III randomized trial investigating the addition of prostate-directed RT to lifelong androgen deprivation therapy (ADT) in men with newly diagnosed prostate cancer with bone metastases. The Systemic Treatment Options for Prostate Cancer (STOPCAP) meta-analysis of the 2 preceding trials reclassified STAMPEDE patients into low- or high-volume using the HORRAD definition of 4 or fewer bone lesions, and found a statistically significant survival benefit in low-volume patients, with RT improving the 3-year survival rate from 70% to 77%. Results of the phase II Stereotactic Ablative Radiotherapy Versus Standard of Care Palliative Treatment in Patients with Oligometastatic Cancers (SABR-COMET) trial support the use of concurrent MDT and systemic therapy. Patients with 1–5 metastatic lesions and a controlled primary tumor were randomized to receive standard-of-care treatment with or without SBRT to all oligometastatic sites. The results of SABR-COMET illustrate the potential survival benefits of integrating MDT into standard-of-care systemic therapy. The optimal choice of systemic therapy is also unknown, but likely includes the addition of a second agent to ADT. The Enzalutamide in First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer (ENZAMET) and TITAN trials found a survival benefit with the use of enzalutamide and apalutamide, respectively, for metastatic patients with either high-or low-volume metastatic disease. The STAMPEDE arm randomizing patients to ADT with or without abiraterone enrolled half nonmetastatic

patients; an OS benefit was seen with the addition of abiraterone for all patients, including those with nonmetastatic and low-volume metastatic disease. Data for docetaxel in limited volume disease has been mixed, with the STAMPEDE investigators finding benefit for both high- and low-volume patients, whereas the Androgen Ablation Therapy With or Without Chemotherapy in Treating Patients With Metastatic Prostate Cancer (CHAARTED) trial found a benefit for only those with high-volume disease. Accordingly, for optimal disease control, data suggests that systemic therapy and MDT, as well as treatment of the prostate, should be incorporated into the treatment of oligometastatic patients. However, the optimal ADT duration and sequencing of systemic and local therapy remains unknown. The ongoing Salvage Treatment of Oligorecurrent Nodal Prostate Cancer Metastases (STORM) trial seeks to provide insight into optimal management for these patients; men with oligorecurrent prostate cancer isolated to the pelvic lymph nodes will receive 6 months of ADT along with MDT, and are subsequently randomized to pelvic RT or not.

Conclusion

There is increasing evidence of an oligometastatic state, an intermediate between localized and polymetastatic disease, in which patients may experience prolonged survival with multimodality combinations of local and systemic therapy. Prostate cancer has become a flagship for the oligometastatic paradigm due to a relatively indolent disease course and early detection of metastatic disease using PSA screening and advanced imaging. Because oligometastatic prostate cancer encompasses a vast array of disease biology and clinical trajectories, the optimal management of oligometastatic disease remains unclear. Systemic therapy remains the cornerstone of treatment for patients with metastatic disease, but several studies demonstrate benefits to the integration of local therapy to the prostate and metastatic sites. Further study is needed to identify genomic and clinicopathologic classifiers to better select patients most likely to benefit from MDT.

Keywords: prostate, cancer, oligometastatic, oligo-progressive, metastatic, disease, therapy, radiotherapy, systemic, ADT, MDT, RT.

S30 – Pancreatic cancer-The future of the systemic treatment

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Pancreatic cancer is the third leading cause of cancer-related death in the United States and the fourth in Europe. Although some improvement in survival has recently been reported, pancreatic cancer is expected to become the second cause of cancer-related death by 2030. Approximately 15% of patients present with resectable or borderline resectable pancreatic cancer, with surgery followed by chemotherapy as the mainstay of treatment until recently. Adjuvant chemotherapy improves overall survival (OS) in patients with resected pancreatic cancer. However, about 50% of patients do not receive adjuvant chemotherapy because of early recurrence, surgical complications, or clinical deterioration. Neoadjuvant therapy may increase the proportion of patients that actually receive chemotherapy and thereby improve survival. Furthermore, neoadjuvant therapy may increase the microscopically margin-negative (R0) resection rate

and may identify patients with rapidly progressive disease who can be spared futile surgery. Many centers recommend neoadjuvant therapy for patients with borderline resectable pancreatic cancer on the basis of meta-analyses that include retrospective studies and small phase II trials. No large randomized controlled trials have been published yet to support this approach. The question remains ether neoadjuvant chemo or chemoradiotherapy improves OS compared with upfront surgery, both followed by adjuvant chemotherapy in patients with resectable and borderline resectable pancreatic cancer. Nowdays we have many questions about biomarkers based approches in PDAC and do we need NGS for all patients at the time of diagnosis on the other side do we have druggable targets in pancreatic cancer.

Keywords: pancreatic cancer, chemotherapy, neoadjuvant treatment, molecular alterations, germline testing

S31 – The importance of BRCA/HRD status in tailoring maintenance treatment in 1st line ovarian cancer

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Ovarian cancer (OC) has the highest mortality rate among gynecological malignancies and is associated with poor prognosis and low survival rate. Most patients with advanced OC experience relapse following the first line multimodal treatment. Relapsed OC is typically incurable, highlighting the need for effective first-line therapies that delay relapse, prolong survival and enhance the potential for cure. Homologous recombination deficiency (HRD) is present in approximately 50% of high-grade epithelial OC, of which ~20% are BRCA 1/2 mutations. BRCA testing alone does not identify all OC patients with HRD as many can have high genomic instability from alternative causes. HRD status is determined by presence of a BRCA and/or High Genomic Instability (GIS) Score. Ovarian cancers with HRD are particularly sensitive to PARP inhibitors. Research of front-line maintenance therapy started 20 years ago with the trial of mono paclitaxel. Later, the addition of bevacizumab to chemotherapy improved PFS and become the standard of care for advanced stages. The next therapy breakthrough was the introduction of olaparib for BRCA mutated OC and then other PARP inhibitors beyond BRCA mutations. SOLO-1, PAOLA-1, PRIMA and the most recent study ATHENA study in newly diagnosed high-grade epithelial OC have investigated front-line maintenance therapy with PARP inhibitors. SOLO1 trial included only patients with BRCA mutated tumors, while other studies included all comers. Those key clinical trials demonstrated a substantial PFS benefit (primary endpoint in all studies) from PARP inhibitor maintenance in first line. The greatest PFS benefit occurred in women with BRCA mutated tumors with consistent HR as impressive as 0.33 to 0.44. Also, a significant, but lesser benefit was noticed in women with HRD BRCA wild type, and even in those with HR proficient tumors. Why is HRD testing important for advanced ovarian cancer patients? Firstly, there are increasing 1L maintenance options for patients with advanced epithelial OC. Then, we can offer personalized 1L treatment options with biomarker testing to guide treatment decisions. Finally, we can gain information beyond BRCA status – who will benefit most from PARP inhibitors or PARP inhibitor combinations. International guidelines increasingly recognize the value of HRD testing to inform treatment decisions in OC. The clinical validity of determining the BRCA mutational status in relation to

benefit of using PARP inhibitors has already been proven, and determining the HRD status may inform magnitude of PARP inhibitor (olaparib, niraparib, rucaparib) benefit or use of olaparib + bevacizumab in 1L. 1st line maintenance studies have shown a statistically significant and clinically meaningful PFS improvement for patients with newly diagnosed advanced OC. The greatest benefit was observed in biomarker-positive population (patients with a BRCAm and/or those who are HDR-positive). OS analyses in SOLO-1 and PAOLA-1 have demonstrated that 1L olaparib maintenance with or without bevacizumab can improve long-term survival for biomarker-positive patients. First-line PARP inhibitor maintenance offers a realistic prospect of long-term survival, and potentially the possibility of cure for some patients with newly diagnosed advanced OC who are HRD-positive.

Keywords: 1L maintenance therapy in ovarian cancer, BRCA/HRD status, PARP inhibitors

S32 – Ocular melanoma

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Uveal melanoma, a rare and aggressive form of melanoma that arises in the uveal tract primarily metastasizes to the liver. There were limited systemic treatment options available for metastatic uveal melanoma, and the prognosis for patients with metastatic disease was generally poor. There is no universally standardized approach to the management of uveal melanoma. Chemotherapy and immunotherapy, have historically shown limited effectiveness in uveal melanoma. The reasons for this include the unique biology of uveal melanoma and the relative resistance of these tumors to conventional systemic therapies. Management in non-metastatic disease include surgery, laser therapy, photodynamic therapy and radiation therapy. Liver directed therapies like chemoembolization, radioembolization, regional isolation perfusion and immunoembolization are preferred options in case of "liver only disease". Effective therapy options for cutaneous melanoma like immunotherapy have limited efficacy in uveal melanoma. Pooled analysis for anti CTLA-4 inhibitors showed overall response rate (ORR) ~5–10%, median progression free survival (PFS) ~3 months and median overall survival (OS) ~6.5–10 months. Disappointing results for anti PD-1 inhibitors with ORR 3.6%, median PFS 2.6 months and median OS 7.6 months. Combined therapy, anti CTLA-4 plus anti PD-1 showed modest ORR 11.6-18%, median PFS 2.7-5.5 months and median OS 15-19.1 months. Tebentafusp, is a novel bispecific T-cell engager that redirects the immune system to target and kill gp100 expressing uveal melanoma cells. One-year OS with tebentafusp was 73% compared to 59% in control arm on single agent: Dacarbazine, Ipilimumab, or Pembrolizumab making this therapy a promising agent in uveal melanoma treatment. Uveal melanoma is still a rare disease with a clear unmet need in improving patient prognosis

Keywords: uveal melanoma, systemic treatment, immunotherapy, tebentafusp, targeted therapies

S33 – Beyond immunotherapy: new targets and new drugs in GU cancers

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Treatment landscape of metastatic renal cell carcinoma (mRCC) became extremely complex in the last 10 years, with some indications still not completely defined. There are no biomarkers available to have stronger criteria for some treatment decisions. Selecting second-line treatment after progression on an immune check point inhibitor (ICI)-based is a challenging task for clinicians. Although VEGFR-TKI or HIF-2α inhibition has demonstrated higher treatment response rates compared with rechallenging with immunotherapy, ongoing research suggests that individualized treatment selection based on clinical and treatment characteristics may be necessary. According to current guidelines, the available treatment options in the second-line treatment setting include VEGFR-TKIs, with or without readministration of ICI therapy. Some new drugs show activity, like belzutifan, with new mechanism of action and combination treatments are promising, too. Until recently, chemotherapy was the only treatment available for advanced or mUC. The treatment options for advanced urothelial cancer (UC) have been rapidly developing over the last few years. This development began with the approval of anti-FGFR (Fibroblast Growth Factor Response) and verious immune checkpoint inhibitors (ICIs), followed by the approval of enfortumab vedotin (EV) and antibody-drug conjugate (ADC) for the treatment of advanced urothelial carcinoma in 2019. Two ADCs – EV and sacituzumab govitecan, are approved following progression on platinum-containing chemotherapy and ICI. ADCs are emerging class of agents providing a unique mechanism of targeted drug delivery for a cytotoxic drug. Enfortumab-vedotin is a Nectin-4-targeted ADC, and improves overall survival in patients with advanced bladder cancer following platinum-based therapy and immunotherapy. Sacituzumab-govitecan is a Trop-2-targeted ADC, associated with a 27% response rate in patients with advanced bladder cancer following platinum-based therapy and immunotherapy. When selecting an antibody-drug conjugate to treat patients with bladder cancer, it is important to note the adverse event profile of each agent to optimize outcomes and safety for patients. EV-301 was a confirmatory phase 3, open-label, global study of enfortumab vedotin or investigator-chosen chemotherapy in patients with locally advanced UC or mUC. TROPHY-U-01 phase 2, cohort 1 and 2, showed ORR of 27% and 28%, respectively, with some complete responses. Targeted FGFR therapy with erdafitinib is also a treatment option in the second-line setting bus is reserved for patients with an FGFR2 or FGFR3 alterations and, to date, nas not been shown to result in an improvement in OS. In prostate cancer there are two directions of novel treatments – PARP inhibitors and Lu177-PSMA. Poly-ADP ribose polymerase inhibitors (PARPi) are an emerging therapeutic option for the treatment of prostate cancer. Their primary mechanism of action is *via* induction of synthetic lethality in cells with underlying deficiencies in homologous recombination repair (HRR). In men with metastatic castrate-resistant prostate cancer (mCRPC) and select HRR pathway alterations, PARPi treatment has been shown to induce objective tumor responses as well as improve progression free and overall survival. Presently, olaparib, rucaparib and niraparib are approved by EMA, some of them as monotherapy or in combinations with NARI. Ongoing research is focused on identifying which HRR alterations are best suited to predict response to PARPi so that these therapies can be most effectively utilized in the clinic. While resistance to PARPi remains a concern, combination therapies may represent a mechanism to overcome or delay resistance. The prevalence of germline or somatic alterations in DNA repair genes in patients with metastatic prostate cancer has been found to be as high as 20-30%. This includes *BRCA1/2*, as well as additional genes such as *ATM*, *FANCA*, *CHEK2*, *PALB2*, *CDK12*,

and *RAD51D*. Due to this high prevalence of mutations, current National Comprehensive Cancer Network (NCCN) guidelines recommend germline testing for homologous recombination repair genes in patients with metastatic prostate cancer. In patients for whom one of these mutations is identified, PARPi represent a potential therapeutic strategy in the management of metastatic prostate cancer.

Keywords: novel drugs, PARP inhibitors, target therapy

S34 – Adjuvant treatment in NSCLC – to whom and when?

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In the last decade, we have seen great progress in the treatment of lung cancer, which, with the introduction of targeted and immunotherapy, has become a potentially curable disease from an incurable disease with a low survival rate even in the early stages of the disease. Recent FDA approvals have changed the standard of care for patients with clinical stage I-III non–small cell lung cancer treated with surgical resection or definitive radiation therapy. Standard-of-care options for these patients now include the addition of an immune checkpoint inhibitor or targeted therapy. Modern therapies, which today are the standard of treatment with a relatively good toxic profile, have significantly extended the progression free survival and 5-y survival. During the presentation, the new results of the studies in which great advances were made in the treatment of NSCLC in the adjuvant setting will be emphasized, with special reference to the PACIFIC, IMPOWER 010, KEYNOTE 091 and ADAURA studies. Some of the results of studies in the perioperative/neoadjuvant setting will also be presented, considering that there are increasing dilemmas in the treatment approach, especially for borderline operable lung tumors. With the development of adjuvant and neoadjuvant treatment, new questions appeared, not only to whom to give adjuvant therapy, but a complete change of paradigm, which is increasingly moving in the direction of precision medicine. The optimal treatment sequence of adjuvant and/or neoadjuvant or post perioperative therapy remains an important unanswered question. It is necessary to recommend thoughtful discussions of each patient's case in a well attended tumor board that includes diagnostic specialists from pulmonology, radiology, nuclear medicine, and pathology. Several critical questions need further exploration, including the optimal regimen in the adjuvant setting and whether adjuvant therapy following neoadjuvant treatment will improve outcomes. Also, we need standardized predictive and prognostic biomarkers to guide the standard of care for neoadjuvant or adjuvant ICI or targeted selection. Greater PD-L1 expression before treatment initiation, serial circulating DNA for minimal residual disease monitoring and other factors are potential biomarkers of which we expect a clearer definition soon.

Keywords: Non–small cell lung cancer; Adjuvant immunotherapy; Adjuvant targeted therapy; Biomarkers.

S35 – Gastrointestinal stromal tumor (GIST)

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Gastrointestinal stromal tumors (GIST), though rare, is the most common mesenchymal tumors of the gastrointestinal tract. The most common sites of GISTs are stomach followed by small intestine. Until the discovery of KIT (or CD117) expression in GIST, the origin of GIST was proposed to be from interstitial cells of Cajal (ICCs) which are the pacemaker cells of gastrointestinal tract. The nature of GISTs became better understood with the identification of KIT expression and c-KIT mutations. Thereafter, platelet-derived growth factor receptor alpha (PDGFRA) mutations were recognized as oncogenic drivers as well, in the majority of GISTs. Although most GISTs have either mutation of KIT or PDGFRA kinase as driver mutations, approximately 10% of GISTs do not harbor these and are collectively grouped as KIT/PDGFRA-wild type (WT) GIST. They may have primary resistance to imatinib, first-line anti-tumor molecule, tyrosine-kinase inhibitor. A PDGFRA exon 18 D842V mutation has also intrinsic primary resistance. Targeted therapy is the mainstay of systemic treatment for GIST, but the treatment paradigm continues to evolve. Imatinib is still the „golden standard" of first-line treatment due to its durable efficacy and favorable safety. In phase I and II the respone rate edian OS of 57 months was shown regardless of 400 mg or 600 mg once daily. Later, the comparable efficacy in terms of response and 10-year OS between the doses (400 mg vs 800 mg), led to the use of 400 mg daily as the starda firt-line therapy. Exon 9 mutations harboring GISTs have better response on 800 mg than 400 mg, as demonstrated in a large meta-analysis (MetaGIST). Patients experienced progressive disease on imatinib are suggested to receive second-line sunitinib with a median progression free-surival (PFS) of about 6-9 months PFS. Regorafenib is currently established third-line therapy as the longer median PFS of approximately 4-5 months than the placebo arm. Ripretinib, a switch-control TKI by dual binding to both the switch pocket and the activation loop, locks the TKIs in an inactivated state. The phase III trial (INVICTUS) confirmed the role of ripretinib as the fourth-line treatment based on a median PFS of over 6 months compared to only 1 monthin the placebo arm. The preliminary results of the phase III INTRIGUE trial showed that ripretinib is not superior to sunitinib as a second-line TKI for patients with GIST in terms of PFS. The relative safety profile similar to imatinib provides heavily pretreated patients a feasible drug of choice. For patients further progressing, in some circumstances several targeted drugs may be used and participating in clinical trials is encouraged. Mutation analysis is relevant for evaluating the efficacy of approved TKI in patients with advanced GIST. Patients with exon 11 mutation appear to be sensitive to standard dose imatinib (400 mg daily), which is less effective for those with exon 9 mutations. After progression on imatinib treatment, secondary mutations commonly occured in KIT exon 13, 14 or 17. Secondary mutations in the activation loop of KIT gene were found in some patients after sunitinib failure. Sunitinib is more effective in KIT exon 13 and 14 mutation (ATP-binding pocket) but not exon 17-18 (activation loop). In contrast, regorafenib shows higher efficacy for supressing KIT exon 17 mutation but is less potent for the exon 13 mutations. The recent approved TKI, avapritinib, is undoubtedly showing the importance of molecular profiling. Patients with advanced GIST harboring PDGFRA exon 18 mutations, including D842V mutation, are indicated for the avapritinib use. Repritinib demonstrated potetn activity towards several primary and secondary KIT-mutations across the ATP-binding site (exon 13 and 14) and activation loop (exon 17 and 18). There are many experimental drugs developing for anti-tumor acitivity of GIST. For example, dasatinib showed acitivity in phase II single arme-trials for advanced GIST but less potent than regorafenib. Nilotinib in phase III trial failed to

show superiority to imatinib. Cabozantinib in EORTC 1317 phase II trial (CaboGIST), after failure of imatinib and sunitinib, showed median PFS of 6 months. A heat-shock protein (HSP90) inhibitor – TAS 116 has demonstrated activity in fourth-line therapy with a median PFS of 4.4 months. Antibody-drug conjugate (ADC), DS-6157 with antibody on G-protein coupled receptor 20, specifical for GIST cells, showed potency in early phase studies. To date, a few trials have been undergone to explore the immune response in GIST. Two published trials reported limited activity of anti-PD-1 blockade. Non-progression rate is 11.1% among 10 patients with advanced GIST receiving pembrolizumab. The role of anti-PD-1 blockade in advanced GIST remained unclear.

Keywords: GIST, imatinib, primary resistance, ripretinib, avapritinib

S36 – Hepatobiliary cancers – What a step forward!

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Liver cancer is the sixth most common cancer and third most common cause of cancer-related death worldwide. Hepatocellular carcinoma (HCC) is the most frequent liver cancer, comprises 80–90% of all liver cancers and has a dismal prognosis, especially when people are diagnosed at an advanced stage with poor performance status and decompensated liver cirrhosis. Approximately 22% of patients with unresectable HCC are alive at 3 years. HBV is highly associated with HCC in Asia and Africa, while HCV is highly associated with HCC in the west and Japan. Although anti-HCV treatment has had some success, HCV prevalence is increasing. While alcohol is a key risk factor for development of HCC in the west, non-alcoholic steatohepatitis (NASH) associated with obesity/diabetes is also an emerging risk factor for HCC. For many years the treatment of patients with advanced hepatocellular carcinoma was based on poorly effective chemotherapy, with no evidence of prolongation of OS in a series of studies. The first statistically significant prolongation of OS compared to placebo was demonstrated in the Sharp study, after which sorafenib became and remained the standard of treatment in the first line for a long time. IMbrave150 investigates a combination anti-VEGF bevacizumab + anti-PD-L1 atezolizumab, and HIMALAYA anti-CTLA-4 tremelimumab + anti-PD-L1 durvalumab. The trials resulted in similar landmark overall survival, significantly better than sorafenib, previous standard 1st line treatment. TKIs are still a treatment option for some patients in the first line (sorafenib and lenvatinib, which showed that it is not worse than sorafenib in a non-inferiority study), and certainly in the second line, as well as for cabozantinib and regorafenib. Although we are still waiting for reliable data on the effectiveness of TKIs after immunotherapy combinations. Billiary tract cancer (BTC) is a rare and aggressive heterogeneous cancer with poor prognosis, comprising intrahepatic cholangiocarcinoma, gallbladder cancer, extrahepatic cholangiocarcinoma and ampulla of Vater. For patients with unresectable or metastatic BTC, first-line SoC GemCis remained unchanged for over a decade and provides a median OS of <1 year. In the TOPAZ study durvalumab plus GemCis showed a statistically significant improvement in OS compared with placebo plus GemCis, with a long-term survival benefit, as well as improvements in prespecified secondary endpoints including PFS and ORR. The addition of durvalumab to GemCis demonstrated manageable safety, did not add to the toxicity that was observed with GemCis and showed no detriment in QoL versus placebo plus GemCis in

participants with advanced BTC. The survival benefit observed with the addition of durvalumab to Gem-Cis was consistent across all subgroups analysed in the TOPAZ-1 study, including in participants with clinically actionable alterations. Nearly 40% of patients with BTC harbour genetic alterations which are potential targets for precision medicine. Therefore, molecular analysis should be carried out before or during first-line therapy to evaluate options for second and higher lines of treatment. The most common clinically relevant mutations in IDH1 and IDH2 are present in ~10%-20% of patients with iCCA. Ivosidenib is an oral inhibitor of the mutant IDH1 enzyme and to date is the only targeted agent that has successfully completed a phase III trial in CCA. The ClarIDHy study showed that ivosidenib significantly improved PFS and OS. After phase 2 Fight-202 study showing clear survival benefit, pemigatinib was approved for the treatment of patients with locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy. In conclusion, the treatment landscape is continuously evolving to improve outcomes in patients with unresectable HCC and BCC, with recent advances observed with immunotherapy combinations.

Keywords: HCC, BCC, combination anti-VEGF bevacizumab and anti-PD-L1 atezolizumab, combination anti-CTLA-4 tremelimumab and anti-PD-L1 durvalumab, IDH1 mutation, Ivosidenib, FGFR2 fusion, pemigatinib