

ORAL PRESENTATIONS

BREAST CANCER

S1 - ROLE OF PATHOLOGIST IN MODERN ONCOLOGICAL TREATMENT

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The role of pathologists in cancer care is evolving to bring pathologists to the center of multidisciplinary collaborations, providing vital information to tumor boards about a patient's cancer diagnosis and treatment options. Developments in diagnostic technology and the rise of precision medicine mean pathologists are more involved in clinical decisions than ever.

More than ever before, pathologists are increasingly involved in the clinical management of patients.

Unlike in the past, diagnosis of tumors is made prior to their removal, owing to the new ability to acquire small tissue through modern imaging-guided technologies; this means that clinicians and pathologists alike have all the salient information up-front and can make more complex management decisions.

Range of tests which can be undertaken by pathologists on these very small samples has expanded. It includes the use of histochemical stains, immunohistochemical markers and molecular markers. This allows much more accurate prognostication and prediction of response to treatment than before. One of the best examples is the situation for patients presenting with advanced lung cancer: most patients can now have a small sample of tumor taken despite their frailty, which can allow foremost an accurate diagnosis of the type of tumor present, but also to assess the suitability of the patient for various available targeted therapies (EGFR mutation, ALK or ROS translocation, PD-L1 expression). The entire assessment can now be completed within a week and available for early discussion at tumor board meetings – a vital requirement for these very ill patients. Pathologists nowadays must integrate multiple different pieces of information derived from various tests, and correlate these with clinical information; thus, pathologists must now take an active role in clinical decision-making.

Information provided by pathological assessment is far more detailed and clinically guided than before. The information provided by pathologists is dynamically adapted based on the point of the patient's management and what is required at a given time in the patient's journey: the information which must be provided on a biopsy is different from that needed from a surgical specimen, which is in turn different from that needed on a biopsy of recurrent disease.

The first hurdle which pathologists must overcome is to become familiar with, and to be able to integrate the information derived from, the plethora of new and sophisticated techniques available which contribute to the depth of information accompanying the pathological diagnosis, including extensive sequencing and digital pathology. In achieving this, pathology departments must be more multidisciplinary than before: teams must consist both of medically-trained pathologists and of scientists from various backgrounds, including molecular biologist, geneticists and bioinformaticians.

The challenge is to ensure that those new technologies are nonetheless regarded as being complementary techniques to classical pathology, and are not considered a replacement on the basis of expertise in a single technology. Ultimately, it is the morphological diagnosis which has the biggest impact on predict-

ing prognosis and response to treatment in cancer, and technologies such as wider sequencing refine this. In the same vein, it remains absolutely necessary that the integration of data from all these sources be by a medically-trained pathologist, and translated into its clinical relevance, before being discussed with the clinical team at the tumor board meeting.

In general, pathologists will spend increasing amounts of time on each case in the future, and there will be a need for increasing specialization of individual pathologists. It is likely that, as the amount of information coming from increasingly large numbers of sources continues to increase, pathologists will be spending more and more time on each case, integrating this into a complete, clinically relevant report. Much of this will require the use of algorithmic analysis of the data to determine the best course of action for each individual patient. Developments in digital pathology will also allow more accurate and reproducible assessment of quantitative data.

Pathologists – equipped with both their pathological and clinical backgrounds – will have an increasingly important role to play in patient care, as long as laboratories remain well-resourced with both equipment and with staff.

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S2 - THE CURRENT APPROACH IN NEOADJUVANT SYSTEMIC TREATMENT OF BREAST CANCER PATIENTS

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About twenty years ago the neoadjuvant systemic treatment (NST) has become the golden standard and widely accepted therapy for the breast cancer patients with operable, early breast cancer.

It can downstage tumors allowing breast-conserving surgery, rather than mastectomy with results in long term outcomes that are comparable with adjuvant therapy. In addition to its impact on surgery, the neoadjuvant setting offers a valuable opportunity to monitor individual tumor response and, in the future, enable personalized treatment, enhance development of the new drugs and targeted therapy. The assessment of therapy response in neoadjuvant setting offers a relatively quick detection of patient subpopulations that benefit from an intervention and the main, central principle of the neoadjuvant studies is that the response to the NST is a surrogate of the long - term outcome of the treatment and the disease.

In the NST achieving the pathologic complete response (pCR) is associated with favorable disease-free and OS in early stage breast cancer. The correlation between pathologic response and long-term outcomes is strongest for patients with triple negative breast cancer and HER2 positive, and less for hormone-positive and lower grade disease. The presence and extent of residual invasive cancer after standard neoadjuvant therapy is a strong prognostic factor for risk of recurrence. In patients with residual cancer burden (RCB), NST permits evaluation of the effectiveness of systemic therapy, which can be used to guide and adjust adjuvant treatment recommendations (according to subtype), and identify patients who are candidates for clinical trials of novel agents in adjuvant setting.

Future neoadjuvant studies will evaluate the value of new biomarkers to define the patients with high risk breast cancer that do not achieve pCR or those who despite reaching pCR develop disease recurrence. Analysis of gene expression changes in patient-matched sequential samples collected before and on treatment logistically is more feasible and may be a promising way to consider the molecular changes that occur during treatment that are required for response. So, evolving technologies like NGS and gene expression profiles will improve our knowledge regarding the biology of the residual disease, the mechanisms behind treatment resistance, and potentially metastases.

Selection of the patients for NST is clear for patients with T4 tumors (locally advanced, inoperable disease including those with inflammatory breast cancer) and N2 or N3 regional nodal axillary disease. In patients with operable breast cancer who are clear candidates for adjuvant chemotherapy, NST may be considered if a patient desires breast-conserving surgery that is not possible due to breast-tumor size ratio, in patients with positive axillary nodes regardless of tumor size in the breast and in IHC aggressive subtypes (triple negative, HER2 positive and highly proliferative luminal B tumors) if tumors are larger than 2 cm independently of axillary status.

The decision on NST should be based on the predicted sensitivity to particular treatment types and predicted the benefit from their use. It usually incorporates chemotherapy, for HER2 positive disease in combination with anti-HER2 therapy and endocrine therapy for hormone-positive tumors.

The current approach is that the patients are managed by the coordinated multidisciplinary teams to decide the most appropriate neoadjuvant treatment plan and better stratify patients as well as the deter-

mination of eligibility for enrollment into clinical trials that incorporate novel therapeutics or predictive biomarkers.

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S3 - ADJUVANT THERAPY FOR BREAST CANCER TODAY

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Adjuvant systemic therapy is delivered after surgical treatment. It depends on individual risk of relapse and predicted sensitivity to treatment as well as benefit and toxicity of the therapy, comorbidity and collaboration between the health care team and patient.

The strongest prognostic factors in early breast cancer are expression of estrogen and progesterone receptor (ER/PR), HER2 and proliferation index, number of involved regional lymph nodes, tumor histology, size, grade and presence of peritumoral vascular invasion. Those parameters integrated into different scoring systems allow relatively accurate estimation of the probability of recurrence and death from breast cancer. Accordingly, clinicians can objectively estimate outcome with local treatment only and benefit expected from systemic adjuvant therapy.

Adjuvant systemic therapy should start optimally within 3–6 weeks after surgery. Significant decrease in systemic therapy efficacy occurs when it is administered more than 12 weeks after surgery.

ER/PR and HER2 are the only validated predictive factors allowing the selection of patients for endocrine therapies (ETs) and anti-HER2 therapy. High ER expression is usually associated with lesser absolute benefit of chemotherapy.

ET should be used in all luminal-like cancers. Indication for chemotherapy in this subgroup depends on individual risk of relapse considering tumor burden and characteristics of aggressiveness (high grade, high proliferation, positive vascular invasion) as well as sensitivity to ET and patient preferences. ET considers use of tamoxifen or aromatase inhibitor with or without ovarian function suppression depending on menopausal status and should last 5-10 years.

Few gene profiling tests which serve as decision making tools (Oncotype DX, MammaPrint, Prosigna, Endopredict) can be used to gain additional prognostic and predictive information of adjuvant chemotherapy benefit only in ER positive early breast cancer. They can help determine the individual's recurrence risk and predict benefit of chemotherapy in general.

The most of luminal A cancers do not require chemotherapy, except those with high disease burden.

Characteristics associated with lower endocrine sensitivity include low ER expression, lack of PR expression, high tumor grade and high proliferation.

Sensitivity to chemotherapy depends on intrinsic subtype, the highest is for HER2 positive (in combination with anti-HER2 therapy) and triple negative breast cancer (TNBC). Chemotherapy is recommended for the TNBC, HER2 positive high-risk luminal-like HER2 negative tumors. Standard adjuvant chemotherapy is based on anthracycline and taxane except for lower-risk patients. Non-anthracycline regimens are reserved for patients at risk for cardiac complications. Dose-dense protocols should be considered for highly proliferative tumors.

Adjuvant trastuzumab should be given for a year to all HER2-positive early breast cancer as it is highly effective and halves the recurrence and mortality risk. Dual blockade (trastuzumab/pertuzumab) can be considered in high risk patients. In cases of residual disease after neoadjuvant therapy, adjuvant trastuzumab can be replaced by adjuvant T-DM1. Neratinib can be considered in selected high risk patients not previously treated with dual blockade.

The final decision on adjuvant therapy should incorporate predictive treatment sequelae, patient's biological age, general health status, comorbidities and preferences.

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S4 - OPTIMAL TREATMENT OF AVANCED LUMINAL BREAST CANCER

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Hormone receptor (HR) positive breast cancer (BC), early and metastatic, is the most common subtype (up to 70% of the cases). Endocrine therapy (ET) is the mainstay of treatment of this type of BC in adjuvant and metastatic settings. ET alone is an effective option even in the presence of visceral metastases unless there is an extensive symptomatic visceral involvement or proof of endocrine resistance. ET consists of either: selective estrogen receptor modulator (SERM) (tamoxifen), selective estrogen receptor down regulator (SERD) (fulvestrant), aromatase inhibitors (AIs) (anastrozole, letrozole and exemestane) and progestin (megestrol acetate). Oophorectomy or administration of luteinizing hormone-releasing hormone (LHRH) agonists in combination with one of the above mentioned ET drugs is recommended for premenopausal women. Despite the fact that ET is the most effective treatment for HR+ mBC, vast majority of these patients will develop disease progression due to *de novo* or acquired ET resistance. Until recently, the only systemic treatment option for ET refractory disease was chemotherapy with its limitations regarding efficacy (less effectiveness than in ER- tumors) and toxicity. In order to overcome or delay the ET resistance, plenty of preclinical and clinical researches have been done. As a result, there are two main treatment options in the current clinical practice: inhibition of the mammalian target of rapamycin/PIK3CA (mTOR/PIK3CA) pathway by specific inhibitors (everolimus and alpelisib) and intervening in the cell cycle progression by targeting cyclin-dependent kinase 4/6 (CDK4/6). Three CDK4/6 inhibitors have been approved in metastatic HR +/HER2 - BC: palbociclib, ribociclib, and abemaciclib as first-line treatments in association with AIs (PALOMA-2, MONALEESA-2, and MONARCH-3) or as 2nd line therapies associated with fulvestrant (PALOMA-3, MONALEESA-3, and MONARCH-2). One trial addressed only premenopausal patients who received goserelin, and AI or tamoxifen combined with ribociclib obtained the same magnitude of benefit (MONALEESA-7). Introduction CDK4/6 inhibitors with AIs in the 1st line treatment resulted in a progression-free survival (PFS) gain of about 10 months, a consistent significant hazard ratio (HR) ranging between 0.55 and 0.57, and an improvement in overall response rate (ORR). Quality of life is maintained over all of the 1st -line trials and the side effects consisting mainly of hematological toxicity which are easily manageable. CDK4/6 inhibitors showed positive results beyond 1st -line settings when associated with fulvestrant: there was a consistent PFS gain of about 5 to 7 months and a consistent significant HR ranging from 0.50 to 0.55. Moreover, the first data concerning the overall survival (OS) were reported in the PALOMA-3 and MONALEESA trial. Nevertheless, there are some differences in the safety profile among the three CDK4/6 inhibitors: abemaciclib was associated with less grade 3 or 4 neutropenia (21% in the MONARCH-3 trial compared with 66% and 59% in the PALOMA-2 and MONALEESA-2 trials, respectively), more grade 3 or 4 diarrhea (9.5% in the MONARCH-3 trial compared with 1.4% and 1.2% in the PALOMA-2 and MONALEESA-2 trials, respectively) and with thromboembolic events (4% of patients). With ribociclib, a risk of QTc prolongation and liver toxicity has been reported. Abemaciclib showed promising single-agent activity, and possibly an activity against brain metastases knowing its ability to cross the blood-brain barrier.

Another potential mechanism of resistance to ET is the activation of the PI3K-AKT-mTOR pathway conducting to cell survival. In the pivotal BOLERO-2 phase III trial, it was demonstrated that everolimus (mTOR inhibitor) with exemestane prolonged the PFS and increased the ORR as compared with exemestane alone after progression on AIs: gain in PFS of about 4 months (HR:0.43, 95% CI(0.35-0.54); p<0.001).

Another drug, alpelisib, an alpha-selective PI3K pathway inhibitor, in combination with fulvestrant in PI3K-mutated luminal mBC tested in SOLAR 1 trial shown significant PFS gain (mPFS 5.7 vs 11 months, HR:0.65, $p < 0.00065$). SANDPIPER trial shown that combination of fulvestrant and taselelisib prolongs mPFS from 5.7 to 7.4 months (HR:0.70, $p = 0.0037$).

Despite the significant improvement in luminal metastatic BC treatment and treatment algorithm defined by current guidelines, many challenges remain. Most of the trials did not include pre-menopausal women, but most of the consensus recommend the same treatment as for post-menopausal women with ovarian suppression or ablation. Another issue is treatment of very young women (chemotherapy vs ET+CDK4/6) and older or fragile patients with (ET alone or combination with CDK4/6 or PI3KCA inhibitor). Does any patient with bone only disease required combined treatment or ET could be enough?

The correct sequencing of ET and targeted treatment association is still an unanswered issue. For instance, the mTOR inhibitor trials did not include patients pre-treated with CDK4/6 inhibitors and vice versa. Would the response to mTOR inhibitors be the same as it was before the era of CDK4/6 inhibitors? We still don't know is there any benefit on potential continuation of CDK4/6 inhibition beyond progression in advanced ER +HER2 – BC. Another hypothesis is testing in several ongoing trials: the combination of CDK4/6 inhibitors with different PI3K/mTOR inhibitors.

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S5 - OPTIMAL TREATMENT OPTIONS OF METASTATIC HER2 POSITIVE BREAST CANCER

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Breast cancer is heterogeneous disease, and HER2 positive breast cancers were initially connected with poor outcome. Anti-HER2 treatment substantially improved survival in early, as well as in advanced disease. Addition of trastuzumab to standard chemotherapy, the first anti-HER2 therapy, revolutionized breast cancer treatment and dramatically improved prognosis. Pertuzumab is another monoclonal antibody that binds to a different domain of HER2 receptor and prevents dimerisation of HER receptors, especially HER2/HER3. Its addition to taxane and trastuzumab in first-line therapy of metastatic HER2 positive breast cancer, improved progression free survival (PFS) and overall survival (OS) by almost 16 months, with median survival of almost 5 years. This combination is now established as preferred first-line regimen. Before pertuzumab small peroral tyrosine kinase inhibitor (TKI), lapatinib was in routine practice for advanced disease. Lapatinib is reversible inhibitor of HER1 and HER2 kinases. In combination with capecitabine, it showed improved PFS compared to capecitabine alone, but no efficacy was found on OS. Trastuzumab-emtansine (T-DM1) is an antibody-drug conjugate (ADC), comprised of trastuzumab and maytansine derivative, an antimetabolic agent. Conjugate is, after binding to HER2 receptor, internalized, degraded in the lysosomes, releasing active payload and resulting in tumor cell death. T-DM1 significantly improved PFS and OS in patients with advanced disease, previously treated with trastuzumab, when compared to combination of lapatinib and capecitabine. TDM-1 is now standard second-line treatment of metastatic HER2 positive breast cancer. There is no standard treatment in third or subsequent lines of therapy. Treatment options include lapatinib, capecitabine, combinations of trastuzumab with chemotherapy, dual anti-HER2 therapies, combination of HER2 and hormonal therapy in endocrine positive tumors. Unfortunately, vast majority of patients develop progressive disease, and high proportion, up to 50% of patients, develop brain metastases. A number of novel anti-HER2 treatments have been developed and studied.

Tyrosin-kinase inhibitors

Neratinib: pan-HER inhibitor, irreversibly binding to HER1, HER2, and HER4, approved as extended adjuvant therapy in early HER2 positive BC. In metastatic setting, several trials tested its efficacy. In NEfERT-T trial, combination of neratinib+paclitaxel was compared to trastuzumab+paclitaxel. It did not show superiority, but the incidence of brain metastases was significantly lower in neratinib arm, as well as significantly delayed. Another phase II trial TBCRC 022, with combination of neratinib and capecitabine showed reduction of CNS lesions of 49%. NALA, phase III study, compared neratinib+capecitabine with lapatinib+capecitabine in heavily pretreated patients. Combination with neratinib improved PFS, delayed the time to intervention for CNS disease and reduced risk of progression or death by 24%. At 12 months PFS was 29% for neratinib vs 15% for lapatinib arm.

Tucatinib: an oral TKI with high selectivity for kinase domain of HER2 receptor and minimal inhibition of EGFR. Its efficacy was demonstrated in HERCLIMB, phase II study. It included heavily pretreated patients, with or without brain metastases, that previously received trastuzumab, pertuzumab and TDM1. At 12 months PFS was 33% in tucatinib arm vs 12.3%. median duration of PFS was 7.8 months and 5.6 months and OS rate at 2 years was 44.9% in the tucatinib arm vs 26.6% in the placebo arm. Among the patients with brain metastases, PFS rate at 1 year was 24.9% in the tucatinib arm and 0% in placebo arm.

Pyrotinib: an irreversible pan-HER TKI that showed superior efficacy in combination with capecitabine, compared to lapatinib with capecitabine. In patients that received at least two previous lines of therapy, ORR was 78.5% in pyrotinib arm vs 57.1% in lapatinib arm, and median PFS of 18 months vs 7 months with lapatinib.

Antibody-drug conjugates (ADCs)

Antibody-drug conjugates: combination of monoclonal antibodies (MAbs) and potent cytotoxic drugs. Specific antibodies bind to receptor expressing tumor cells and deliver toxic agents more selectively causing death of tumor cells. The first in the class was T-DM1 and its efficacy led to development of various other anti-HER2 ADCs. Cleavable linker of newer ADCs, (opposite to non-cleavable linker in TDM1), mediates bystander killing effect of surrounding cancer cells via passive diffusion of cytotoxin into tumor microenvironment killing cells insensitive to antibody, but sensitive to cytotoxic drug linked to it.

Trastuzumab deruxtecan (DS-8201) is a conjugate of trastuzumab linked to a payload of topoisomerase 1 inhibitor exatecan. DS-8201 showed ORR of 54.5% in patients pretreated with TDM-1, trastuzumab and pertuzumab. DS-8201 also showed activity in low HER2 expressing tumors, with ORR of 50%. Trial DESTINY-Breast01, included patients with HER2 positive cancer that were previously treated with TDM-1 and trastuzumab, 66% also received pertuzumab. DS-8201 treatment showed ORR of 60.3%, with CR rate of 4.3%. Median PFS was 16.4 months. Serious side-effects were ILD in 9% and pneumonitis, fatal in 2.6% of patients.

SYD985: conjugate of trastuzumab linked to a duocarmycin payload (in prodrug form). After endocytosis, linker is cleaved and duocarmycin payload is released causing irreversible DNA alkylation in tumor cells. In breast cancer, study included patients with HER2+ and HER2-low breast cancer. Most HER2 positive patients received 3 and more prior regimens (80% T-DM1). SYD985 demonstrated ORR of 33% and a median PFS of 9.4 months. Efficacy was seen also in heavily pretreated HER2-low, HER+ and TNBC patients. The ORRs were 27% and 40%, respectively. A Phase III study (TULIP) is currently ongoing comparing SYD985 vs therapy of physician's choice.

HER2 antibodies

Margetuximab binds to the same epitope as trastuzumab, but significantly stronger to effector cells with more effect on antibody-dependent cell-mediated cytotoxicity (ADCC). Phase III SOPHIA trial, compared margetuximab plus chemotherapy with trastuzumab plus chemotherapy. Median OS was 26.1 months with margetuximab compared with 19.8 months treated with trastuzumab. Margetuximab significantly improved ORR 25.2% vs 13.7%, and CBR was 48.1% compared with 35.6% in trastuzumab arm. CR was observed in 1.2% of patients. The median PFS was 5.7 months versus 4.4 months the trastuzumab group. The risk of disease progression or death was decreased by 29%.

A novel class of antibodies are **bispecific antibodies**, targeting two different epitopes, either in same or in different receptors. MCLA-128 targets both HER2 and HER3, and in phase I/II showed clinical benefit in 6 heavily pretreated patients with median of 5 prior lines of therapy for metastatic disease. Two phase II studies are ongoing in combination with trastuzumab +/- chemotherapy and in combination with endocrine therapy in HR+ but HER2-low breast cancer. ZW25 binds to different epitopes of HER2 extracellular domains 2 and 4, with increased activity even in HER2 low expressing tumors.

Combinations with other agents

Since anti HER2 monoclonal antibodies mechanism of action include ADCC and adaptive immunity, many trials studied efficacy of combination of antiHER2 therapies and checkpoint inhibitors. Combination of pembrolizumab and trastuzumab in PANACEA study, phase Ib/II, demonstrated an ORR of 15.2% in

PD-L1 positive patients. In phase II trial, KATE2, combination of atezolizumab and T-DM1 did not improved PFS compared to T-DM1 alone, but efficacy was more profound in PD-L1 positive and stromal TIL+ subgroups.

Many studies showed synergistic action between CDK4/6 inhibitors and anti-HER2 therapy. Ongoing trials are evaluating role of CDK4/6 in HER2+ disease. The phase II monarchHER trial evaluated abemaciclib+ trastuzumab+fulvestrant in heavily pretreated patients with HR/HER2 positive breast cancer. The triplet had a median PFS of 8.3 compared to 5.7 months for trastuzumab plus chemotherapy and risk reduction for disease progression and death by 33%. PATINA study explores role of palbociclib in addition to trastuzumab, pertuzumab and AI, while SOLTI-1303PATRICIA trial evaluates combination of palbociclib, trastuzumab +/-letrozole in metastatic HER2+ patients. Many other trials combine anti HER2 therapies (TKIs, ADCs) with CD4/6 inhibitors and endocrine therapy.

In recent years data showed close relation of HER2 and PI3K/AKT/mTOR pathway. PI3K inhibition enhances HER2 signaling, so there was a rationale that the combination could overcome the resistance to HER2 therapy. Studies with mTOR inhibitor everolimus BOLERO-1 (combination with trastuzumab, paclitaxel) and BOLERO-3 (combination with trastuzumab and vinorelbine) did not show desired efficacy, although improved PFS was seen in patients with PIK3CA mutations. Alpelisib is α specific PI3K inhibitor evaluated in several trials with trastuzumab and T-DM1. Phase I study with TDM1 in heavily pretreated patients showed activity (ORR of 43%), even in T-DM1 resistant patients (ORR of 30%, CBR 60%).

Interesting therapy approach are HER2 targeting vaccines, since bulk of patients have HER2 low expression and do not benefit from HER2 therapy. *Nelipepimut-S* (NPS) is HER2 derived peptide, combined with GM-CSF, evaluated in phase II trials with trastuzumab in HER2 3+, HER2 1+ and 2+ tumors. Peptides are recognized as an antigen that stimulates the production cytotoxic T lymphocytes (CTLs), which destroy tumor cells expressing tHER2 antigen while GM—CSF boosts the number of immune cells. In study that included HER2+ and even TNBC patients had two arms. Patients received trastuzumab + GM-CSF +/- NPS. In NPS arm, DFS was slightly improved, 89.8% vs 83.8% respectively. At 36 months, the DFS rate was 86.7% with NPS and 80.8% without it. More profound benefit was seen in TNBC patients: 24-month DFS was 92.6% with NPS vs 70.2% without NPS.

As majority of patients experience disease progression, the need for new therapies is recognized. Many anti-HER2 agents have been, and are being developed; different combinations with CDK4/6 inhibitors, PI3K inhibitors, checkpoint inhibitors and vaccines are being explored - both approaches with promising results.

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S6 - THE OPTIMAL TREATMENT OF METASTATIC TRIPLE NEGATIVE BREAST CANCER

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Triple-negative breast cancer (TNBC) is defined by lack of expression of estrogen receptor, progesterone receptor and HER-2 amplification and accounts for approximately 15-20% of breast cancers. It is also a heterogeneous group of tumors which tend to have an aggressive phenotype with higher recurrence rates and lower survival rates. Metastatic TNBC is associated with poor prognosis and limited treatment options. Although chemotherapy has been the main treatment option for metastatic TNBC for a long time, this scenario has changed with the recent efficacy data on the polyadenosine diphosphate-ribose polymerase inhibitors (PARPis) for patients harboring a mutation in the *BRCA* genes (*BRCAmut*) and also with the results of immunotherapy agents in patients with PD-L1-positive tumors.

However, TNBC is known to be more immunogenic compared to other breast cancer subtypes, with tumor-infiltrating lymphocytes playing an important prognostic and predictive role. Response rates to single agent immune checkpoint blockade in unselected pretreated HER2-negative metastatic breast cancer (MBC) are low. However, they may be augmented when combined with chemotherapy. Immunotherapy agents in combination with systemic chemotherapy have been shown to alter the natural history of this devastating condition, particularly in patients whose tumors are positive for programmed cell death ligand 1 (PD-L1).

The safety and efficacy data from the phase III Impassion 130 trial have led to FDA and EMA approval of atezolizumab and nab-paclitaxel for patients with tumours tested positive for PD-L1 by the Ventana SP142 companion diagnostic immunohistochemical assay. It is an important advance for treatment of metastatic TNBC. However, ongoing investigations need to define better biomarkers of response, determine resistance mechanisms, and identify strategies to increase response rates. Chemotherapy-free combinations are also under the evaluation. Results presented on ESMO 2019 Congress from the phase I/II MEDIOLA trial supported the combination treatment of olaparib and durvalumab in the treatment of patients with germline *BRCA*-mutated metastatic breast cancer.

In patients without a *BRCA* mutation and with PD-L1-negative tumours, single-agent chemotherapy with taxanes (paclitaxel or docetaxel) as a first-line treatment is recommended. In patients with a high disease burden or who are symptomatic, combinations such as anthracyclines plus cyclophosphamide or platins with taxanes are valid options. While numerous studies investigating anti-vascular endothelial growth factor (VEGF) therapy suggest improved progression-free survival, studies to date have not demonstrated a survival benefit in the metastatic setting.

The androgen receptor (AR) has been identified as a possible predictive biomarker for antiandrogen therapy in ER- breast cancer. AR positivity has been associated with more favorable prognosis in TNBC. There are several studies that show AR is associated with lower Ki-67 proliferative marker, lower mitotic score, lower histologic grade and lower clinical stage. Biological insight into AR-positive breast cancer reveals that AR may cross-talk with several vital signaling pathways, including key molecules and receptors.

Despite recent treatment advances, metastatic TNBC remains aggressive disease with poor prognosis. The treatment of TNBC is constantly evolving, and the inclusion of patients in ongoing clinical trials

evaluating new targeted agents against cell surface antigens, immunotherapy agents and predictive biomarkers should be encouraged.

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S7 - A CASE REPORT OF LUMINAL BREAST CANCER

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This report describes the case of a 54-year-old female with breast cancer. In July 2016, she had noticed a mass in the right supraclavicular fossa. She was referred to our institution. Suspected primary tumor of the right breast with right supraclavicular, right retropectoral, right axillary, right parasternal and mediastinal lymph node metastases was revealed by positron-emission tomography (PET/CT). Pathological analysis of the extirpated supraclavicular lymph node revealed metastatic cancer. Estrogen receptors (ER) were positive in 100% of the tumor cells, progesterone receptors (PR) were positive in 20% of the tumor cells and human epidermal growth factor receptor 2 (HER2) status was negative. Ki-67 proliferation index was 25-30%. She was originally treated with endocrine therapy: letrozole (8/2016-8/2017); tamoxifen (8/2017-11/2017); ribociclib and exemestane (11/2017-6/2018). Then, in June 2018 patient presented with respiratory symptoms (cough and dyspnea), right shoulder and arm pain. There were palpable lymph nodes in the right supraclavicular fossa measuring about 4 centimeters in diameter on physical examination. Multi-slice computed tomography (MSCT) of the chest showed progression of the disease (conglomerate lymph node masses of the right axilla, right infraclavicular and right supraclavicular region). Patient underwent palliative three-dimensional conformal radiation therapy (3D CRT) of the right axillary and right supraclavicular lymph nodes in total dose (TD) of 25 Grays (Gy) in 5 fractions and after that started treatment with capecitabine chemotherapy (patient preference for oral chemotherapy). At that time patient also presented with pain of the right femur. A bone scintigraphy showed metastases in right occipital bone, sternum, right femur. Patient underwent palliative 3D CRT of the right femur (lesser trochanter and diaphysis) in TD 8 Gy/1 fraction. She was also treated with bisphosphonates. In November 2018, progression of the disease was detected on diagnostic workup (tumor infiltration of the superior and middle lobe in the right lung). Patient was treated with chemotherapy-weekly paclitaxel. Bronchoscopy with biopsy was also performed. Pathological analysis revealed metastatic breast cancer (ER 100%, PR 10%, HER2-negative). In April 2019, due to further progression of the disease in right lung, patient underwent palliative 3D CRT of the right lung mass (TD 20 Gy/5 fractions). In July 2019, patient achieved radiographic partial response. In August 2019, multiple small nodules of the right breast were detected by mammography and breast ultrasound. Core-biopsy was performed and pathological analysis revealed breast cancer (ER 100%, PR negative, HER2-positive; Ki-67 50-65%). Patient was treated with chemotherapy-gemcitabine and dual HER2-directed therapy (trastuzumab and pertuzumab). After 6 months of treatment, the patient achieved radiographic stable disease. It has been reported earlier that HER2-positive cancers may become negative following treatment with trastuzumab (1), but transformation of cancer status from HER2-negative to positive has not been extensively studied (2). A patient whose breast cancer changed from HER2-negative to positive, following treatment, was described in this case report. Re-biopsy therefore may be of necessity, during breast cancer treatment course, in order to re-assess the HER2 status. In this way the clinician is given the opportunity for HER2-directed therapy inclusion, for patients with transformation to HER2-positive cancer.

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SUPPORTIVE THERAPY

S8 - MANAGEMENT OF CANCER PAIN

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Cancer pain can be caused by the tumor itself, surgery, or is the result of chemotherapy or radiotherapy treatment. Neurological post-therapy impairments (due to radiation and chemotherapy) are significant causes of pain in cancer pain syndrome. These impairments often present up to 20% of total cancer pain. The most common clinical appearance of post-therapy complication is sensory and motor symmetrical polyneuropathy as a result of impaired axonal neurotransmitters transport and degeneration or segmental demyelination of axons. Besides peripheral painful neuropathies, asymmetrical focal or symmetrical distal poly-neuropathy, lesions in the central and autonomous nervous system are also possible. In accordance with these facts, appearance of symptoms like paresthesia, dyesthesia, numbness and burning together with attenuation or disappearance of reflexes are warnings of toxicity of applied cancer therapy. Considering pharmacotherapy, conventional analgesics are not effective. Because of that, neuropathic pain treatment is composed of four different groups of drugs (anticonvulsant, tricyclic antidepressant, opioid, drugs for topical use). It is advantageous to combine drugs with different mechanisms of action (rational polypragmasia).

Optimal pharmacologic management can achieve adequate pain control in 80-85% of patients. Exhausting, ineffective drug therapy often only increases the suffering of patients and significantly reduces the quality of life. The need for more invasive modalities should be infrequent. Invasive procedures to treat pain have their place in the algorithms for treatment that are presented as a conversion chart WHO for the treatment of cancer pain. Celiac plexus blockade is classically designed to treat very severe pain caused by cancer pancreas, gallbladder, liver, stomach, small intestine, omentum, mesentery and upward and lateral part of the colon. Neurolytic celiac plexus block leads to a long-acting improvement in 70-90% of patients with pancreatic cancer and other cancers in the abdomen. Superior hypogastric plexus block is used in patients who have pain in the pelvic viscera. Usually superior hypogastric neurolysis is used in a very strong visceral pelvic pain malignant origin. Patients with local invasion of cancer of the vagina, uterus, ovary, prostate and rectum that are associated with pelvic pain often have a significant reduction in pain after the blockade or neurolysis a superior hypogastric block. Block ganglion impar is indicated in cocigodinia, pain anorectal and perineal region due to malignant disease in the rectum, and after abdominal perineal resection of rectal cancer or pain as a result of radiation in this area. Intrathecal drug is reserved for patients with very severe pain that does not respond to conservative therapy.

Many patients with cancer suffer severe pain despite opioid peptide therapy or have unacceptable side effects due to the use of opioids. Intrathecal opioids significantly reduce pain in these patients, and the side effects are much less compared to other routes of administration of opioids. Continuous delivery of morphine and other opiates is possible to install percutaneous catheter intrathecal or epidural space.

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LUNG CANCER

S9 - OPTIMAL TREATMENT OF STAGE III NON-SMALL CELL LUNG CANCER

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The appropriate treatment of stage III non-small cell lung cancer (NSCLC) patients is a huge challenge in our everyday clinical practice due to patients' heterogeneity and the complexity of the available therapy modalities. Also, there is no clear consensus about the most efficient treatment for one part of such patients. In the light of that, a basic precondition for good results in the treatment of stage III NSCLC patients is a well organized multidisciplinary team.

Surgical treatment as a primary, initial treatment option is indicated in just a small number of those patients. The most efficient treatment for the majority of patients with good general condition is concurrent chemoradiotherapy (CRT). The median overall survival for them is of about 25 months. Once it was concluded that the concurrent CRT was the optimal therapeutical approach, a series of clinical studies followed, which throughout more than 10 years of research brought no further success in the treatment of stage III NSCLC patients. In some of those studies induction or consolidation chemotherapy was added to the concurrent CRT, while other studies investigated the efficacy of platinum-based chemotherapeutic protocols modifications in concomitance with radiotherapy (paclitaxel or pemetrexed applied instead of etoposide). Despite great expectations from the significant technological improvements in the radiotherapy field, with the increase of tumor dose from 60 to 74 Gy we did not obtain better efficiency, but just higher toxicity. Furthermore, we do not have any evidence that the overall survival improves with the surgical treatment after the chemo(radio)therapy. Finally, in phase III clinical study, when the patients who were treated with the concurrent CRT started to receive consolidation therapy with durvalumab or placebo, a long awaited progress was reached. The median progression-free survival increased significantly with durvalumab (5,6 months versus 16,8 months, HR 0,52, $p < 0,001$), just like the overall survival (HR = 0,68, 95% CI 0,53-0,87, $p = 0,00251$, median not reached with durvalumab versus 29,1 months with placebo).

It is important to mention that neoadjuvant immunotherapy shows very promising results. For example, in phase II trial neoadjuvant treatment with ipilimumab (one cycle) and nivolumab (three cycles) in 44% of patients with stage I-III (single N2) resectable NSCLC resulted with major pathological response (MPR, tumors with no more than 10% viable tumor cells). Even more impressive results are obtained with neoadjuvant chemoimmunotherapy. In phase II trial, 3 cycles of nivolumab, paclitaxel and carboplatin in patients with resectable stage III A (N2) NSCLC resulted with MPR in 83% of patients, 58% of patients had a complete pathologic response.

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S10 - TREATMENT OF EGFR MUTATED NSCLC

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EGFR mutations in lung carcinoma are a well established and studied molecular target for tyrosine kinase inhibitor therapy. There are three generations of EGFR inhibitors (EGFRi) available, two of which are used for first-line treatment: erlotinib, afatinib and gefitinib. All of them showed significantly better PFS compared to platinum- based chemotherapy (ChT) in their registrational studies, with no OS benefit due to a high crossover rate. (1-3) Subsequent real world data support these findings, without any preference between first and second generation EGFRi. The 3rd generation EGFRi, osimertinib, was first to show statistically significant benefit in PFS and OS compared to other EGFR TKIs (erlotinib and gefitinib) in the FLAURA study (mPFS 18.9 versus 10.2 months; HR 0.46, 95% CI 0.37–0.57), and the benefit was observed also in patients with CNS metastases (mPFS 15.2 vs 9.6 months, HR 0.47, 95% CI 0.30–0.74), which makes osimertinib now the preferred TKI in first-line setting. (4)

After progression on 1st and 2nd generation EGFRi, a newly acquired, exon 20 T790M mutation is responsible for TKI resistance in about 50% of cases. It can be detected by tissue rebiopsy or liquid biopsy, analyzing circulating tumor DNA. In the AURA3 study, osimertinib was compared to platinum- based ChT showing significant benefit in PFS (10.2 versus 4.4 months; HR 0.30, 95% CI 0.23–0.41). (5) If the resistance is acquired via other mechanisms, ChT remains standard of care to date, although other targeted therapies show promising results, but currently without EMA approval.

Treatment of ALK-rearranged NSCLC

ALK tyrosine kinase inhibitors (ALK TKIs) are recommended treatment options for ALK-rearranged NSCLC. Crizotinib, a first-generation ALK TKI showed superiority over platinum-based chemotherapy (ChT) in the first line setting. (6) Alectinib, a second-generation ALK TKI is a better treatment option than crizotinib or ChT based on ALEX and J-ALEX studies where it was shown that mPFS with alectinib was 34.8 (95% CI 17.7–NR), compared with 10.9 months (95% CI 9.1–12.9) with crizotinib. In patients with baseline CNS metastases, mPFS was 27.7 months for alectinib versus 7.4 months for crizotinib. The time to CNS progression was significantly longer with alectinib than with crizotinib. (7, 8) In patients with CNS involvement, front-line use of ALK TKIs is effective with the highest ORR seen with alectinib or ceritinib. Brigatinib was compared to crizotinib in ALTA-1L trial where HRs favoured brigatinib with mPFS at 12 months 67% for brigatinib and 43% for crizotinib (HR 0.49, P<.001). (12) Patients that are progressing on crizotinib should receive next-generation ALK TKIs, such as alectinib, ceritinib, or brigatinib (based on the data from ASCEND-5, ALUR and ALTA studies). (10-12) In patients previously treated with one or more second-generation ALK TKIs, a high proportion of patients responded to lorlatinib, a third-generation ALK TKI, a recommended after progression on first or second-generation ALK TKIs. (12)

Treatment of ROS1-rearranged NSCLC

Crizotinib, a first-generation ALK TKI that also inhibits ROS1 was evaluated in ROS1-rearranged NSCLC in few phase I and II studies, where crizotinib showed superior efficacy over platinum-based chemotherapy (ORR 72-80%, mPFS 9.1-19.2 months). (13) Ceritinib also showed superiority in patients with

ROS1-rearranged advanced NSCLC, especially in crizotinib-naive patients (ORR was 67%, with a disease control rate of 87%. The mPFS was 9.3 months for the entire cohort and reached 19.3 months for crizotinib-naive patients). (14) Brigatinib, lorlatinib, repotrectinib and entrectinib also have potential anti-ROS1 activity based on limited phase I and II studies. (12, 15, 16)

Treatment of NSCLC bearing other driver mutations

A B-RAF mutation, V600E is detected in 1-2% of lung adenocarcinomas. Both NCCN and ESMO recommend a BRAF/MEK inhibition therapy using dabrafenib in combination with trametinib as a first line treatment for these patients. (17)

Several other molecular targets have been detected in NSCLC, including HER2 or MET dysregulation via a number of possible mechanisms or RET or NTRK fusion, but targeting these pathways in NSCLC is currently not recommended

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S11 - CASE PRESENTATION: ALK-POSITIVE METASTATIC LUNG CANCER

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Lung cancer is the most common cause of cancer death in the world. ALK (Anaplastic Lymphoma Kinase) gene rearrangements is present about 5% of patient with non small cell lung cancer (NSCLC) (1). Crizotinib is ALK inhibitor which is in randomised phase 3 trials has shown superior progression-free survival (PFS, median 10.9 months) in patients with previously untreated advanced ALK-positive NSCLC (2). We present a case of ALK-positive metastatic lung cancer that after remarkably decreased disease maintained stable disease over 34 months with crizotinib.

In February 2017 a 50 year old female with smoking history 10 cigarettes per day for 20 years presented with cough and headache. Past medical history revealed hypertension. Chest CT detected right sided lung cancer with metastases to the right hilum, mediastinum and right supraclavicular lymph nodes, esophageal compression and minor pleural effusion right. Brain MRI showed multiple brain metastases. Pathology revealed adenocarcinoma by bronchoscopy and fine needle aspiration cytology of supraclavicular lymph nodes. Molecular testing was positive for ALK mutation and epidermal growth factor receptor (EGFR) mutation negative. The clinical stage was IVB according to the TNM classification. Patient treated with palliative whole brain radiotherapy to a dose of 30 Gy in 10 fractions. In April 2017, patient started treatment with oral crizotinib, at a dose of 250 mg twice daily. After 2 weeks of treatment complete remission of metastasis in right supraclavicular lymph nodes was verified by physical examination and forceful productive cough with expelling necrotic secretions. Follow-up chest CT and brain MRI imaging after a two month showed disease was decreased remarkably. Stable disease was confirmed after 2 months and maintained over 34 months after the starting treatment with crizotinib. Treatment-related adverse events were rash, visual disturbance, nausea, dysgeusia, peripheral edema and elevation in serum of lactate dehydrogenase (LDH) isoenzymes with aspartate transaminase (AST).

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S12 - METASTATIC LUNG CANCER TREATED WITH IMMUNOTHERAPYVIDE POPOVIĆ¹¹ *University Hospital Centre Split, Clinic for Pulmonary Diseases, Split, Croatia*

A 60-year-old patient, who had no previous illness or any chronic therapy, was treated for right-sided pleuropneumonia at the end of December 2018. He complained of coughing and sensation of stabbing in his right chest. He was treated with ciprofloxacin and then levofloxacin, but regression did not occur with antibiotic therapy. Thoracic MSCT verified centrally located expansive formation of the right upper pulmonary lobe infiltrating the lobar bronchus with consequent atelectasis, extensive mediastinal lymphadenopathy up to 2.2 cm (pretracheal), and right dorsobasal pleural effusion up to 4.5 cm. Cytologically, no malignant cells were found in the pleural effusion, and the finding suggested a lymphocytic type of effusion. Bronchoscopically taken sample was investigated pathohistologically and lung adenocarcinoma was diagnosed. He was presented on the multidisciplinary lung tumor team on January 30, 2019, and it was recommended to wait for the results of the EGFR testing and to start pembrolizumab treatment in case of negative findings and positive pleural effusion (malignant cells). No malignant cells were found cytologically in the repeated pleural effusion sample. In the meantime, he noticed that he could not close the right eye and had weakness in his right hand. On February 1, 2019, a brain MSCT was performed to describe: left frontal marginally imbedded annular secondary lesion 15 mm in diameter and right parasagittal parietal with a 13 mm diameter near falx, with a wider area of edema. He was presented again on the multidisciplinary lung tumor team on February 6, 2019, and was advised to begin pembrolizumab immunotherapy with a brain MRI for a possible gamma knife treatment of the brain metastases. After the brain MRI was done on March 25, 2019, he was treated with gamma knife (4 intracranial metastases) at KBC Zagreb (prescription doses 22-24 Gy to prescription isodoses 50-78%). On April 18, 2019, after the application of three cycles of pembrolizumab, he underwent the first control MSCT of the thorax and upper abdomen, which described a complete regression of pleural effusion, significant regression of lymphadenopathy with a few remaining minor lymph nodes, and suspected collocation within the upper right lobe consolidation. Based on this, he was presented again on the multidisciplinary team for lung tumors on April 24, 2019 and it was recommended to continue pembrolizumab immunotherapy. From June 3 to June 11, 2019, he was hospitalized for bilateral pulmonary embolism and has since been taking NOAK therapy. During hospitalization, he started taking therapy for iatrogenically provoked newly diagnosed diabetes mellitus. He was regularly presented on the multidisciplinary lung tumors team after every three cycles of pembrolizumab with the control MSCT of the thorax and upper abdomen which showed every time further regression of the primary tumor and mediastinal lymph nodes or a stationary finding in comparison with previous, and the team's recommendation was to continue immunotherapy with pembrolizumab. In addition, he had two control brain MRIs that showed good growth control of all treated meta changes and did not verify any new secondaryisms. He was last shown on the multidisciplinary team for lung tumors on February 19, 2020 with control MSCT of thorax and upper abdomen which was stationary and it was recommended to continue pembrolizumab immunotherapy. By February 27, 2020, he had received 16 cycles of pembrolizumab. He also feels subjectively fine and does not complain of significant dyspnoic problems. He tolerates effort quite well, didn't cough and was not febrile. He had no side effects of immunotherapy.

GASTROINTESTINAL TUMORS

S13 - OPTIMAL TREATMENT OF LOCOREGIONAL RECTAL CANCER

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Historically, the biggest problem in locally advanced rectal cancer is not distant recurrence. It is high rate of locoregional recurrence – up to 50%. First clinical trials tried to decrease this rate. As a result of clinical trials, in 1990 a consensus of using trimodality treatment (chemotherapy, radiotherapy and surgery) was reached. Using this approach local recurrence rate was decreased to 5-6%.

First trial of adjuvant radiotherapy in combination with fluoropyrimidines was Fisher et al from 1988. Local recurrence rate was decreased, but rate of distant recurrence remain the same.

In 2004, the results of big German trial on 832 patients was published, and in 2012 the results from the same trial after 11 years of follow up. This trial concluded that the local recurrence rate was significantly reduced in the preoperative group of patients (6% vs 13%; p=0.006), whilst toxicity was lower and the patients receiving neoadjuvant chemotherapy had better quality of life. However, no difference in overall survival rates have been observed.

The next question to answer was is there any difference in the terms of benefit in DFS, OS, and local control of disease, between SCRT (5 fractions of 5 Gy) and immediate surgery and LCRT (5 weeks of radiotherapy) and delayed surgery. The difference between these two modalities was in pathological complete response rate, but that was not surprising according to immediate surgery. This is important because of more often sphincter preserving in LCRT and delayed surgery group. At the other side there was no difference in local control, DFS and OS.

According to more often sphincter preserving in delayed surgery group big Stockholm III trial compared effects of SCRT with immediately and SCRT with delayed surgery. This trial showed that delayed surgery after SCRT has similar effects as immediately surgery after SCRT.

In 2017 we had results of study that compared SCRT and LCRT with adding of chemotherapy (fluoropyrimidins) and delayed surgery. This trial has confirmed that short course neoadjuvant chemoradiotherapy is safe and efficient treatment modality, and the results are comparable with standard long course neoadjuvant chemoradiotherapy.

At the other hand there are patients with pathological complete response after neoadjuvant therapy and that patients can maybe be candidates for „watch and wait“ approach, and this is subject of current clinical investigation. Also new trials are planning to explore the use of other radiosensitizing agents in neoadjuvant setting.

We have significant advancements in the management of locally advanced rectal cancer in last 30 years, resulting in improved local control rates, but risk of distant metastases remains an ongoing problem. We hope that new strategies in selecting patients for chemoradiotherapy or upfront chemotherapy should result in decreased morbidity for some patients.

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S14 - IMMUNOTHERAPY IN TREATMENT OF GASTROINTESTINAL TUMORS

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Introduction

The last decade we have witnessed great progress in understanding the immune response of tumors, spilling over into numerous studies of modern immunotherapy, primarily with anti PD1 monoclonal antibodies, in various malignancies with improved objective response rate (ORR), duration of response, progression-free survival (PFS) and overall survival (OS). This summary will outline the most important immunotherapy studies in gastrointestinal tumors.

Cancer of the esophagus and gastroesophageal junction

Based on a Phase III (TOGA) study and an improvement in overall survival (2.8 months gain in median OS, $p = 0.046$) over standard polychemotherapy, today's standard in the first line of treatment for advanced HER2 positive esophageal adenocarcinoma and esophagogastric junction (EGJ) is combination of cisplatin and fluoropyrimidine-based chemotherapy in combination with trastuzumab (1). The benefit was particularly observed in patients with HER expression of IHC3+ and IHC2+ and FISH positivity (4.2 months gain in median OS) (1). In the second line of treatment, in the same group of patients (regardless of HER2 status), considering first-line therapy and general patient status, ramucirumab monotherapy became the standard (REGARD study; 1.4 month gain in median OS versus placebo, $p = 0.047$) or in combination with paclitaxel (RAINBOW study; 2.3 months gain in median OS relative to paclitaxel alone, $p = 0.007$) (2,3).

Pembrolizumab, an anti PD1 monoclonal antibody, is the preferred treatment option in the second or later lines of MSI-H / dMMR tumors based on KEYNOTE-016 study with ORR of 71% and PFS rate of 67% at 20 weeks (4). Pembrolizumab is also a second-line therapeutic option for esophageal squamous cell carcinoma showing PD-L1 expression with CPS ≥ 10 (KEYNOTE-061, KEYNOTE-180 and 181) and third-line esophageal and EGJ adenocarcinoma with PD-L1 expression of CPS ≥ 1 (KEYNOTE-012) (5,6,7). First-line studies of pembrolizumab alone or in combination with cisplatin and 5-FU chemotherapy in patients with advanced EGJ cancer (KEYNOTE-059) are ongoing, as well as a study of the combination of pembrolizumab and cisplatin chemotherapy and 5-FU in patients with advanced adenocarcinoma, squamous cell carcinoma of the esophagus and adenocarcinoma of EGJ (KEYNOTE-590) (8,9).

Another anti-PD1 monoclonal antibody, nivolumab, in monotherapy or in combination with CTLA 4 antibody ipilimumab, showed activity in the treatment of advanced esophageal cancer and EGJ cancer, but has not yet become part of standard guidelines (CheckMate-032 study) and we need larger phase III trials (10). A phase III study, CheckMate 649, is ongoing, comparing nivolumab plus ipilimumab with nivolumab plus chemotherapy and chemotherapy alone in the first line of treatment. Due to the high incidence of high-grade toxicity in the nivolumab plus ipilimumab combination, enrollment in this study arm was terminated (11).

Avelumab, an anti PD-L1 monoclonal antibody, in a phase III study, Javelin Gastric 300, did not show better median PFS and OS compared with third-line chemotherapy (12). The Javelin Gastric 100 study is

ongoing, where avelumab is being tested as a maintenance therapy in monotherapy, in the first line of treatment (13). MSI-H/dMMR and PD-L1 status should be assessed in all esophageal and EGJ adenocarcinoma if metastatic disease is suspected.

Gastric cancer

For many years, the median OS of advanced or metastatic gastric cancer did not change and ranged from 9 to 11 months. With the combination of first-line cisplatin and fluoropyrimidine-based chemotherapy and trastuzumab, the median shifted to 11 months and in selected patients (high HER2 expression) to 16 months (1). Also, ramucirumab, in monotherapy or in combination with paclitaxel, has become the standard option in second-line treatment (2,3). In recent years we have witnessed the role of new immunotherapy (anti PD1 monoclonal antibodies) in the treatment of this group of patients. Pembrolizumab has gained an FDA-accelerated approval in 2017 for the treatment of patients with advanced and metastatic MSI-H or dMMR gastric cancer who have progressed to previous therapy or have no other treatment options (14). In 2017, the FDA also approved pembrolizumab for patients with advanced or metastatic gastric or EGJ cancer who progressed to prior cisplatin and fluoropyrimidine-based chemotherapy and HER2 immunotherapy. The approval was based on studies KEYNOTE-012 and KEYNOTE-059. KEYNOTE-016 is a Phase Ib study evaluating pembrolizumab in patients with PDL1 positive recurrent or metastatic gastric or EGJ adenocarcinoma. The ORR was 22 and 13%, respectively. The results of this study confirmed the results of the KEYNOTE-059 study with cohort I with 259 patients with gastric or EGJ adenocarcinoma who had progressed to previous chemotherapy. The ORR was 15% with 2% of patients with complete remission and a median duration of response of 16 months. A cohort 2 and 3 examining pembrolizumab in the first line of treatment as monotherapy or in combination with chemotherapy was included in the same study. Pre-eliminated data show promising results both in monotherapy and in combination as well as an acceptable toxicity profile (8,15). In a Phase III study, KEYNOTE-061, pembrolizumab was compared with paclitaxel in 395 patients with PD-L1 CPS ≥ 1 who had progressed to previous therapy. In this study pembrolizumab did not statistically significantly improve median OS of patients with paclitaxel (9.1 vs 8.3 months), but had a better toxicity profile and was better tolerated than paclitaxel (5). In addition to pembrolizumab, other checkpoint inhibitors (nivolumab, avelumab) have been studied in this group of patients and the results are presented in the section with esophageal and EGJ cancer, since studies with these drugs included patients with advanced or metastatic gastric cancer (10-13).

Colorectal cancer

For more than a decade, immunotherapy (bevacizumab, aflibercept, cetuximab, panitumumab, ramucirumab, trastuzumab) in combination with numerous chemotherapy protocols (based on irinotecan, oxaliplatin, and fluoropyrimidines) or in monotherapy, starting with first-line therapy and in subsequent-line treatment became standard of treatment for patients with advanced or metastatic colorectal cancer, which has led to a significant prolongation of life for this group of patients, with a median OS approaching 3 years, in the hands of good oncologists and institutions promoting excellence. Selection of the indicated immunotherapy is based on predictive biomarkers such as RAS, BRAF, HER2 and primary tumor site (right or left colon) (16).

New immunotherapy with checkpoint inhibitors also plays an important role in a subset of patients at this stage of the disease, and the administration of this agent is primarily based on MSI-H and dMMR status. The percentage of patients with stage IV colorectal cancer with MSI-H (dMMR) is 3-5% (17).

The activity of pembrolizumab was investigated in a phase II study involving 11 patients with dMMR and 21 patients with pMMR CRC with progressive metastatic disease. The ORR was 40% in the dMMR group and 0% in the pMMR. The PFS rate at week 20 was 78% in dMMR and 11% in pMMR. Median PFS and OS were not reached in the dMMR group while in the pMMR group it was 2.2 and 5 months, respectively. This study demonstrated that MSI is a predictive marker for the efficacy of pembrolizumab (18). Nivolumab is another checkpoint inhibitor that has been tested alone or in combination with ipilimumab in the treatment of metastatic CRC. In the CheckMate-142 multi-cohort study, 72 patients with dMMR CRC were enrolled. The ORR for these patients was 31% and the disease control rate at week 12 was 69%. Median duration of response not reached. The PFS and OS rates at 12 months were 50% and 73%, respectively, with grade 3 and 4 adverse events of 20% (19). In another cohort of patients in the same study, nivolumab was tested in combination with ipilimumab for 119 patients with dMMR. ORR was 55%, disease control rate at week 12 was 80%, and PFS and OS rate at month 12 was 71% and 85%, respectively. Grade 3 and 4 side effects have been reported in 32% of patients (20). Based on these studies, pembrolizumab, nivolumab or nivolumab in combination with ipilimumab have become the recommended therapeutic options in subsequent-line treatment in guidelines for the treatment of metastatic dMMR colon cancer.

Conclusion

Modern checkpoint inhibitor immunotherapy has become a standard treatment for patients with advanced and metastatic gastrointestinal tumors expressing MSI-H or dMMR or PDL1 positive tumors. Although checkpoint inhibitors are generally well tolerated, serious immune side effects are reported in 20-40% of patients, including skin, liver, kidney, gastrointestinal, lung, and endocrine toxicity, and it is very important for oncologists to know the potential toxicity of these drugs and patients should be aware and informed about possible occurrence of them.

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S15 - GASTROINTESTINAL NEUROENDOCRINE TUMORS

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Neuroendocrine tumors (NETs) represent a heterogeneous group of neoplasms that arise from cells in the diffuse neuroendocrine system. Although they can occur in multiple organs in the body, they are common in the gastrointestinal (GI) tract and pancreas, where they are thought to originate from enterochromaffin cells of the gut and islets of Langerhans cells in the pancreas. Although relatively rare, the incidence and prevalence of gastroenteropancreatic (GEP)-NETs (which is usual syntagme for all these tumors arising in GI system and pancreas) have been rising in most of the countries in the world.

Classification systems for GEP-NETs that are based on embryologic or anatomic origin, pathologic features, and clinical behavior have been developed and have been utilized to guide therapeutic strategies. Once a uniform disease, distinctions have been made among different subtypes of NETs, based on differentiation and grade. In 2010 World Health Organization (WHO) presented an update to the classification of digestive neuroendocrine neoplasms. The most prominent feature was more precise and clearly measure of grading definition. Since then, there has been growing recognition that the 2010 WHO-grade categories do not reflect the heterogeneous phenotype of neuroendocrine neoplasms (Ki-67 >20% or mitotic index >20/10 high power-fields). Thus, the recently updated 2019 WHO criteria for GEP-NETs includes categories of well-differentiated grade 1, grade 2, and grade 3 NETs and maintains categories of poorly differentiated grade 3 neuroendocrine carcinomas. Historically, GEP-NETs have been classified according to their site of origin in the embryologic gut and, therefore, divided into foregut, midgut, and hindgut tumors. Today, due to molecular profiling further characterization has been made explaining some of clinical and therapeutic phenotypes. Molecular profiling has uncovered distinctions between poorly differentiated NECs, NETs of the pancreas (pNETs) and those originating from other sites in the GI-tract. Poorly differentiated NECs harbor higher incidences of somatic mutations compared with the well-differentiated cohorts. In well-differentiated NETs, when the genome is mutated, variants are most commonly identified in *MEN1*, genes involving mechanistic (or mammalian) target of rapamycin (mTOR) pathway, *DAXX*, and *ATRX* for pNETs, and *CDKN1B* in small bowel NETs. In pNETs, the presence of variants in *DAXX* and *ATRX* not only function as biomolecular markers but also, due to associated chromosomal instability are correlated with more advanced tumor stage and metastasis, reduced relapse-free survival, and decreased tumor-associated survival.

Therapeutic response has been correlated with anatomic site of origin. Specifically, response rate to cytotoxic agents have been significantly better in pNETs compared with well-differentiated NETs arising elsewhere. NETs are characterized by their ability to secrete peptide hormones that can lead to symptoms related to hormone excess. NETs are classified as functional tumors if patients clinically experience symptoms due to hormone hypersecretion by tumor and by that, syndrome is dependent on the type of hormone produced. The best described is carcinoid syndrome with manifestations including diarrhea, flushing, and bronchospasm, related to secretion of serotonin and other vasoactive peptides. Carcinoid syndrome is most common in the setting of disseminated disease, particularly with liver involvement. Subtypes of pNETs secreting hormones, including gastrin, insulin, vasoactive intestinal peptide, and other peptide hormones, have been identified and are associated with unique clinical manifestations. Today, there are multiple options available for the management of patients with advanced, metastatic GEP-NETs, including surgical resection, liver-directed therapies for patients with metastases predominantly in the

liver, and systemic therapy. The goals of therapy are to improve symptoms related to hormone hypersecretion (in the case of functional tumors), slow disease progression and improve survival. Systemic therapy options include – somatostatin analogues (SSAs), radiolabeled SSAs, molecularly targeted agents including everolimus and sunitinib and cytotoxic chemotherapy. SSAs, both lanreotide and octreotide, are the oldest systemic treatment options. Their activity is based on existence of somatostatin receptors (sst-r) on the surface of tumor cells. They can control symptoms but also slow the tumor growth, which was proved through clinical trials phase III (PROMID, ELECT, CLARINET). The same biologic feature is the basis for another, recent treatment option – radiolabeled SSA. NETTER-1 trial was phase III trial of 177-Lu-DOTATATE for midgut metastatic NETs which showed median progression-free survival of 30 months and overall survival of 70 months. Another treatment option is vascular endothelial growth factor pathway (VEGF)-inhibitor (sunitinib, bevacizumab), and multiple clinical trials have evaluated the role of multi targeted tyrosine kinase inhibitors (TKIs) and monoclonal antibodies that target VEGF pathway. Rapamycin inhibitors (mTOR-inhibitors) have been evaluated in different trials (RADIANT-2, RADIANT-3, RADIANT-4), and it is evidence-based that in advanced nonfunctioning GI- and p-NETs as well as lung NETs, everolimus is superior to placebo regarding PFS (11 vs 3.9 months). Cytotoxic chemotherapies have been evaluated in advanced well-differentiated GEP-NETs. Activity was observed with alkylating agents, pNETs are more responsive than other tumors. Once, streptozocin-based therapy has been used but today temozolamide has more favorable administration schedule and toxicity profile. Efficacy was analyzed in both retrospective and prospective trials. Poorly differentiated, grad 3 NEC are commonly treated with platinum-based chemotherapy regimens using an approach that is similar to treatment of small cell lung carcinoma. Finally, immunotherapy-based treatments are currently under investigation in GEP-NETs. There is limited activity of single-agent therapy. KEYNOTE-158 trial with pembrolizumab showed response rate of 3,7% in different NETs originating in the lung, GI-tract, or pancreas.

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S16 - NOVEL TREATMENT OPTIONS FOR HEPATOCELLULAR CARCINOMA AND BILIARY TRACT CARCINOMA

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Hepatocellular carcinoma (HCC), as the most common primary liver cancer, is among leading causes of cancer-related death worldwide. It occurs mainly in the setting of chronic inflammatory liver diseases, thus making the treatment extremely complex. Forty percent of patients with HCC are diagnosed in advanced stage and are candidates for systemic treatment. The approval of multikinase inhibitor sorafenib in 2007 was followed by many unsuccessful phase III trials assessing novel targeted therapies and locoregional therapies, such as radioembolization, that did not fulfill the primary overall survival (OS) endpoints. From 2016 to 2018, five new drugs (lenvatinib in the first-line and regorafenib, cabozantinib, ramucirumab and immune checkpoint inhibitors (ICIs) in the second-line treatment) showed clinical efficacy and have been adopted by guidelines, but durable responses with monotherapy are rarely seen.

Liver, as the key immunologic organ, contains high proportion of various immune cell subtypes which play the role in HCC pathogenesis, making its phenotype immune evasive. Immune checkpoint inhibitors have shown modest efficacy as monotherapy in the first- and second-line treatment. Combination therapy for simultaneous inhibition of several immune checkpoints is currently being investigated. The CheckMate 040 trial (cohort 4) is investigating the combination of nivolumab and ipilimumab at various doses and dose intervals. The Arm A regimen (four cycles of nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg every 3 weeks, followed by a 240-mg flat dose of nivolumab every 2 weeks) showed superior ORR (32%) and survival benefit (median OS 22.8 months) over two other investigational arms. A phase III HIMALAYA trial is currently investigating the combination of durvalumab and tremelimumab against durvalumab or sorafenib alone, based on superior response rate versus durvalumab alone in the phase I trial. In recent years, combinations of ICIs and molecular agents targeting angiogenesis have shown great promise, based on the role of proangiogenic factors released by tumor cells and vascular endothelial cells in creating an immune-inhibitory microenvironment. Based on the improvement in ORR shown in a phase II study, first-line treatment with an anti-PD-L1 antibody atezolizumab in combination with bevacizumab was further investigated versus sorafenib in a phase III study (IMbrave150). The results were presented at ESMO Asia in 2019; median OS with the atezolizumab combination was not estimable (NE) compared to 13.2 months with sorafenib (HR 0.58; $p = 0.0006$). According to mRECIST criteria, the ORR was 33% versus 13% ($p < 0.0001$) in favor of combination. The authors concluded that atezolizumab plus bevacizumab has the potential to be a practice changing treatment in the first-line setting for patients with unresectable HCC. In a phase Ib study (Keynote- 524), lenvatinib in combination with pembrolizumab showed ORR of 53.3% which compared favorably with lenvatinib arm of registrational REFLECT trial (24.1%); disease control rate was 90.0%. The trial was expanded to the phase III (LEAP-002) in which this combination is being compared to lenvatinib alone. Many trials investigating combinations of immunotherapy and targeted agents (COSMIC- 312, SHR-1210-III-310, ORIENT-32) are ongoing, and it seems that more durable responses achieved by combining these agents may greatly change conventional treatment algorithms for HCC.

Patients with intermediate-stage HCC are at high risk for recurrence after locoregional treatment, and so far no adjuvant therapy has been proved effective. Recently published results of TACTICS trial showed PFS benefit of transarterial chemoembolization (TACE) plus sorafenib versus TACE alone (25.2 vs 13.5

months; $p=0.006$), but no difference in overall survival. The promising treatment strategy for early- and intermediate- stage HCC is the combination of locoregional therapies and ICIs. Radiofrequency ablation (RFA), TACE and radiotherapy can trigger the release of neoantigens and enhance the effects of immunotherapy (abscopal effect). Microsatellite lesions typically undetectable on imaging are the main cause of recurrence after curative therapy for HCC. When release of tumor antigen is induced by TACE or RFA, subsequent administration of an anti-PD-1 antibody may inhibit intrahepatic micrometastases. Several phase III trials investigating ICIs in the adjuvant treatment, alone or in combination with other strategies, such as antiangiogenic treatment or TACE (CheckMate 9DX, Keynote -937, EMERALD-2, EMERALD-1) are ongoing.

Biliary tract cancers (BTC) are poor prognosis malignancies with limited treatment options. Capecitabine remains the standard of care in the adjuvant setting. Several trials (ACTICCA-1, AdBTC-1, JCOG1202, ASCOT) are currently investigating whether there is added clinical benefit of intensification of chemotherapy, antiangiogenic treatment or immunotherapy in resected BTC. Treatment of advanced disease is still limited to first-line cisplatin and gemcitabine chemotherapy. Recent global efforts in genomic profiling and molecular subtyping of BTCs have uncovered a wealth of genomic aberrations which may carry prognostic significance and/or predict response to treatment, and several targeted agents (IDH inhibitors, FGFR inhibitors, BRAF inhibitors, anti-HER2 directed therapies, NTRK- fusion directed agents) have shown promising results in clinical trials. Based on the results of a basket trial, in 2017 FDA approved ICIs for patients with MSI/dMMR tumors (including BTC) after progression on standard treatment options. Given the promising responses to immunotherapy thus far, there is a strong rationale for testing the combined checkpoint inhibition and combining ICIs with chemotherapy, as well as the adoptive immunotherapy. The uptake of comprehensive genomic profiling for patients with BTCs and the expansion of basket trials to include these patients are growing. However, a deeper understanding of potential resistance mechanisms and the complex crosstalk between molecular pathways is growing and combination strategies targeting more than one pathway are being proposed. In order to benefit from tailored therapy, genomic testing for all patients with BTC should be considered and liquid biopsy may be the most convenient way to implement this.

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S17 - NEOADJUVANT / ADJUVANT TREATMENT OF GASTRIC CANCER

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Although there is a steady decline in gastric cancer (GC) incidence in the past few decades, it is still the fifth most frequently diagnosed cancer and the third leading cause of cancer death in the world. Survival is highly associated with the stage of the disease at diagnosis. Therefore, the optimisation of treatment of localised and loco-regional disease is of paramount importance.

As the recurrence rate after surgery is as high as 40-50% during the first 3 years, numerous studies have examined the optimal multimodal approach of the following strategies: postoperative chemotherapy (EORTC+ICCG, ACTS-GC, GIRC, CLASSIC, JACCRO GC-7), postoperative chemo-radiotherapy (SWOG/INT 0116, ARTIST), perioperative chemotherapy (MAGIC, FNCLL/FFCD, FLOT4-AIO), neoadjuvant chemotherapy (EORTC 40954), neoadjuvant chemo-radiotherapy (POET).

In Western countries according to the both, NCCN and ESMO guidelines, perioperative chemotherapy is recommended for patients with cT2 or greater non-metastatic disease. In MAGIC trial perioperative ECF (epirubicin, cisplatin, 5-fluorouracil) improved 5-years overall survival (OS) from 23% with surgery alone to 36%. Similarly, in FNCLL/FFCD trial perioperative CF (cisplatin, fluorouracil) improved 5-years survival from 19% with surgery alone to 34%. Most recently, FLOT4 trial compared ECF to FLOT (docetaxel, oxaliplatin, leucovorin, 5-fluorouracil) regimen in perioperative setting. After median follow-up of 43 months median OS of patients treated with FLOT was 50 months, and those treated with ECF 35 months ($p=0.012$). The estimated 3-years OS gain was 9%. Thus, FLOT became the new standard of care.

In patients with \geq pT2 or pN+ who have undergone surgery without preoperative chemotherapy postoperative chemo-radiotherapy is recommended in case of less than a D2 dissection or R+ margin. If D2 dissection was performed with R0 margins adjuvant chemotherapy is preferable. Although adjuvant chemo-radiotherapy improved 3-years OS in comparison with surgery alone ($p=0.005$) in the SWOG/INT 016 trial, the study was criticized frequently for inadequate lymphadenectomy in majority of included patients. In the ARTIST trial (only D2 dissection allowed) adjuvant chemo-radiotherapy improved 3-years disease-free survival (DFS) significantly ($p=0.04$) only in patients with positive lymph nodes but not in the whole cohort of patients. For patients treated with preoperative chemotherapy the addition of postoperative chemo-radiotherapy did not show any benefit in OS and DFS in comparison to perioperative chemotherapy in the CRITICS trial. Two trials, TOPGEAR and CRITICS-II, that are currently enrolling patients, investigate neoadjuvant chemo-radiotherapy.

Adjuvant chemotherapy resulted in improved OS and DFS in the CLASSIC and ACTS-GC studies performed in the Asian population but the applicability of the results of these studies to the Western population is somewhat uncertain. One meta-analysis confirmed a 6% absolute benefit for 5-fluorouracil-based chemotherapy compared with surgery alone, while a recent one concluded that adjuvant oxaliplatin-fluoropyrimidine was the most promising regimen after curative resection.

Two randomised, phase III trials compared perioperative and adjuvant chemotherapy in Asian population. In the PRODIGY trial neoadjuvant chemotherapy with docetaxel, oxaliplatin and S-1 followed by surgery and adjuvant S-1 improved 3-years progression-free survival (PFS) in comparison to surgery and adjuvant S-1 ($p=0.023$). The RESOLVE trial compared perioperative oxaliplatin and S-1 (SOX) with postoperative SOX or postoperative oxaliplatin and capecitabine (XELOX). Perioperative SOX improved 3-years

DFS compared with XELOX ($p=0.045$). Postoperative SOX was non-inferior to postoperative XELOX ($p=0.162$).

However, majority of previously mentioned trials investigated GC as one entity but in recent years we have become aware that GC is a very heterogeneous disease and that will influence the choice of treatment in the future. In post-hoc analysis of the MAGIC trial patients with high microsatellite instability had better survival when treated with surgery alone than chemotherapy. In the CLASSIC trial there was also no survival benefit of adjuvant chemotherapy in the high microsatellite instability group. Furthermore, there are several active clinical trials examining the role of immunotherapy in the perioperative and adjuvant treatment (Checkmate 577, KEYNOTE 585, ATTRACTION-05, VESTIGE) as well as the role of targeted therapy in the perioperative treatment of GC (PETRARCA, INNOVATION, RAMSES).

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GYNECOLOGICAL TUMORS

S18 - UPDATES ON CERVICAL CANCER TREATMENT

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Approximately 570 000 cases of cervical cancer and 311 000 deaths from the disease occurred in 2018. Cervical cancer was the fourth most common cancer in women.

Cervical cancer continues to be a major public health problem affecting middle-aged women, particularly in less-resourced countries. The global scale-up of HPV vaccination and HPV-based screening has potential to make cervical cancer a rare disease in the decades to come.

The implementation of primary and secondary prevention can make cervical cancer occurrence and death largely avoidable. Bivalent and quadrivalent HPV vaccines containing HPV16 and HPV18 antigens protect with high efficacy against infection and precancerous cervical lesions. Both types jointly cause 70–75% of all cervical cancers and 40–60% of its precursors.

By adding the two screening tests and the treatment of precancerous cervical lesions, cervical cancer cases will drop by 97% and 72 million cervical cancer cases will be averted over the next century. Furthermore, 62 million cervical cancer deaths will be averted.

Suggested therapy for FIGO 2018 stages IA to IB2 is surgical approach.

Therapy for FIGO 2018 stages IB3 to IVA consist of multimodality therapy concurrent chemoradiation (weekly cisplatin) comprising external-beam radiation therapy with systemic chemotherapy (CCRT) then intracavitary brachytherapy.

Immune checkpoint blockade with ipilimumab, combined with radiation therapy, is tolerable and effective in patients with node-positive, stage Ib2 to IVA cervical cancer, according to results of a prospective phase I study. In the phase I study, investigators evaluated sequential ipilimumab after chemoradiotherapy as a curative-intent treatment of patients with node-positive cervical cancer. Among patients who received at least 2 cycles of treatment, the 12-month OS rate was 90% and the PFS rate was 81%.

A new study, evaluating atezolizumab before and/or with chemoradiotherapy in this patient population has been launched to further evaluate the benefit of immune checkpoint blockade.

Phase II trial reported in the *Journal of Clinical Oncology*, da Costa et al found that neoadjuvant cisplatin/gemcitabine followed by standard chemoradiation therapy with cisplatin did not improve outcomes vs chemoradiation therapy alone in locally advanced cervical cancer. Outcomes were better with standard chemoradiation therapy alone.

Concurrent RT with platinum-based doublet chemotherapy significantly improved the OS and PFS both with more frequent grade 3 or 4 side effects in the polychemotherapy arm.

Study of Yavas on 109 patient showed that adjuvant chemotherapy (paclitaxel and carboplatin) after CRT in patients with LACC significantly improved both disease-free survival and overall survival (93.5% and 95.7% and 69.8% and 82.5 % for the CRT + chemotherapy and CRT groups) without increasing unmanageable toxicity. Future larger prospective trials are warranted to verify these findings.

Management of FIGO 2018 stages IVB and recurrent disease: From the GOG-0204 trial, paclitaxel plus cisplatin emerged as the palliative standard. The Japanese Clinical Oncology Group demonstrated significant noninferiority with substitution of carboplatin (area under the curve 5) for cisplatin in the phase III clinical trial JCOG0505 but noted that carboplatin was associated with shorter overall survival among cisplatin-naïve patients.

GOG-0240, a phase III open-label randomized study of chemotherapy doublets with and without bevacizumab every 21 days until progression. The triplet regimen is now standard of care.

Active Clinical Trials:

Evidence for activity of checkpoint inhibitors is accumulating.

KEYNOTE-158 phase II study of pembrolizumab in 77 pt demonstrated an objective response rate of 14.3%. FDA granted pembrolizumab as a second-line agent.

Investigators have launched the confirmatory, front-line, placebo-controlled phase III randomized KEYNOTE- 826 trial studying platinum-based chemotherapy plus optional bevacizumab with and without pembrolizumab, as well as the frontline phase III randomized BEATcc trial evaluating triplet therapy with cisplatin, paclitaxel, and bevacizumab with or without atezolizumab.

A second-line, phase III randomized trial, EMPOWER CERVICAL-1/GOG 3016, activated in 2017, is comparing the anti-PD-1 agent cemiplimab to physician's choice of chemotherapy.

Nivolumab was assessed in patients with recurrent or metastatic cervical cancer in the phase I/II CheckMate 358 trial. Patients received nivolumab 240 mg every 2 weeks the median duration of treatment was 5.6 months in the cervical cancer cohort. The ORR was 26.3% (95% CI, 9.1-51.2) in the cervical cancer arm. At a median follow-up of 19.2 months, the median duration of response (DOR) was not reached. The median PFS in the cervical cancer group was 5.1 months with a median OS of 21.9 months

CheckMate 358 is an ongoing phase I/II study of nivolumab and ipilimumab in patients with recurrent and metastatic cervical cancer. Results suggest clinical benefit from two regimens of Nivo + Ipi in pts with R/M cervical cancer regardless of PD-L1 status.

LN-145, a tumor-infiltrating lymphocyte (TIL) therapy, demonstrated promising response rates and an acceptable safety profile in patients with recurrent, metastatic, or persistent cervical cancer in the phase II study. Results presented at the 2019 ASCO for 27 patients reported an objective response rate of 44%. Of those who responded, 11% were complete responders and 33% were partial responders. Another 40% of patients had stable disease as their best response. It's worth mentioning that the follow-up for this study was very short; median follow-up was 7.4 months, and the median DOR had not reached.

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S19 - OPTIMAL TREATMENT OF ENDOMETRIAL CANCER

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Endometrial cancer is the most common gynecological cancer and primarily affects postmenopausal women. The incidence is rising due to increased obesity and aging of the population. In Croatia, endometrial cancer is the fourth most common cancer in woman with 717 new cases and 113 deaths in 2017. Surgery is the primary treatment in patients with endometrial cancer. Standard surgical procedure should involve hysterectomy with bilateral adnexectomy with or without lymphadenectomy. The role of lymphadenectomy in early stage of endometrial cancer is unclear.

Depending on findings from final pathological analysis of the uterus and other surgical specimens, patients can be stratified into risk categories. Adjuvant treatment is currently recommended based on a patient's individual risk (low-, intermediate- and high- risk) comprised of a combination of clinical finding (age) and pathological findings (FIGO stage, tumor type, grade and the presence of lymphovascular space invasion). Adjuvant radiotherapy can be delivered through vaginal brachytherapy (VBT) or external beam radiotherapy (EBRT) with or without VBT. The decision, which therapy approach should be done, depends on the clinical and pathological risk factors.

In patients with metastatic, recurrent or high grade disease, chemotherapy is recommended. The preferred chemotherapy regimen is paclitaxel/ carboplatin.

The extensive molecular-genetic characterization of endometrial cancer by the Cancer Genome Atlas Group (TCGA) is done and four different molecular subclasses were identified: POLE-mutant, MSI subclass, copy-number high and copy-number low subclass. In POLE-mutant endometrial cancer, an increased antitumor response by peritumoral and tumor-infiltrating CD8+ lymphocytes has been reported and patients in that group have an excellent prognosis with only occasional relapse, independent of receiving adjuvant treatment. Microsatellite unstable (MSI) subclass shows a similar increase in tumor-infiltrating lymphocytes, however, it is associated with negative prognostic factors such as higher histological grade, presence of LVSI, older age and advanced stage of disease (FIGO III/IV). Copy-number low subclass (non-specific molecular profile) are characterised by low mutational burden and it contains a heterogeneous of tumors. Copy-number high subclass (TP53 mutation positive) is associated with unfavorable overall and prognostic free survival. In this subgroup, amplification of the human epidermal growth factor receptor 2 (HER-2) and homologous recombination deficiency (HRd) are frequent.

It is assumed that in early stage patients with POLE subgroup and without other risk factors, adjuvant therapy could be omitted. In patients with MSI and copy-number low subclasses, vaginal brachytherapy should be recommended, and in patients with copy-number high subclass adjuvant treatment by EBRT is justified.

The ongoing PORTEC4a trial will determine value of integrating molecular parameters in adjuvant treatment.

Standard initial adjuvant therapy for advanced or recurrent endometrial cancer is paclitaxel plus carboplatin. Treatment options for advanced or recurrent disease after initial platinum-taxane therapy are being investigated.

Expression of estrogen and progesterone receptor are common in endometrial cancer and it is related to lower grade tumors. Targeting the endocrine receptors by hormonal therapy can provide durable response in patients with grade 1 metastatic endometrial cancer, especially with lung- or oligo-metastatic.

According to the KEYNOTE-028 study, in a subset of 24 patients with advanced endometrial cancer characterised with programmed death ligand 1 (PD-L1) positive tumors, pembrolizumab is associated with durable antitumor responses (3 partial response, 3 stable disease). In a phase 2 study of lenvatinib monotherapy in patients with advanced, previously treated endometrial cancer, 14% had an objective response and median PFI was 5.4 months.

In the KEYNOTE-146/Study 111 trial, the combination of pembrolizumab and lenvatinib is associated with good response (38.8%) in patients with previously treated metastatic endometrial cancer, and the median duration of response was not reached at the time of cut-off. According to this trial, FDA approved the combination of pembrolizumab and lenvatinib for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or mismatch repair deficient (dMMR), who have progression following prior systemic therapy and not candidates for curative surgery or radiation.

Some other trials evaluated the role of the molecular risk factors and if any of these molecular risk factors can be used for guide of the treatment. HER-2/neu amplification are frequently found in serous endometrial cancer. In a recent study, the combination of trastuzumab with carboplatin/paclitaxel in those patients resulted in a prolonged PFS of 13 months compared to 8 months in carboplatin/paclitaxel group (in patients undergoing primary treatment, the median PFS improved from 9.3 to 17.9 months).

Antiangiogenic therapy have some activity in endometrial cancer. Bevacizumab was shown to have a 13.5 % response rate in patients with persistent or recurrent endometrial cancer. In the GOG 86P trial, the addition of bevacizumab to first line paclitaxel/carboplatin chemotherapy did not improve PFS, but it increased OS. And the MITO END-2 trial failed to demonstrate a significant increase in PFS.

The PI3K-AKT-mTOR pathway is altered in over 80% endometrial cancers Promising results have been described for combined treatment with PI3K inhibition and endocrine therapy (the combination of everolimus and letrozole).

Some patients, especially in the TP53-mutated or serous-like subclass, have homologous recombination deficiency (HRd). In those patients, PARP inhibitors have been investigated.

Endometrial cancer is recognized as several biologically different cancers. Current practice is to decide which adjuvant therapy or therapies for advanced/recurrence disease select according to standard histopathological risk factors. However, with increasing knowledge of the molecular alterations of cancer, their prognostic value and possible therapeutic options, it is expected that the molecular characteristics will be taken into account prior deciding on the recommended therapy.

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S20 - METASTATIC RECURRENT ENDOMETRIAL CANCER: A CASE REPORT

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Case report: Endometrial cancer is the most common cancer of the female genital tract. Lung metastases from endometrial cancer are 20% more often than from any other gynecologic cancer. We report a case of a 73-year-old woman with endometrial cancer diagnosed at stage IIB according to the International Federation of Gynecology and Obstetrics (FIGO), 2008 classification of endometrial cancer. The patient underwent abdominal total hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy and omentectomy. Microscopically, it was good differentiated endometrial cancer which infiltrated more than half thickness of the uterine wall and cervical stroma. Estrogen and progesterone receptors were expressed in more than 70% of cancer cells. Left and right pelvic lymph nodes showed no evidence of malignancy in 15 examined nodes. Multidisciplinary team decision was to perform adjuvant radiotherapy to the pelvis. Adjuvant therapy recommendations for early-stage disease are based on high-risk prognostic factors predictive of increased risk of recurrence, including older age, histologic type, histologic grade, deep myometrial invasion, lymphovascular space invasion and involvement of lower uterine segment or cervix. Following this decision, 50Gy/25 fraction of pelvic external beam radiotherapy and 21Gy/3 fraction HDR Ir-192 brachyradiotherapy of vaginal cuff were administered. During regular clinical monitoring, in March 2017, the patient visited to a pulmonologist due to expectorated cough and weight loss. Morphologic evaluation with multi-slice computed tomography (MSCT) of chest showed multiple lung metastases. Lung biopsy was performed and pathological findings confirmed good differentiated, hormone positive metastasis from endometrial cancer. Hormonal therapy with megestrol-acetate (Megace 160 mg daily) was administered according to Multidisciplinary team decision. At the beginning of treatment patient's status was good and laboratory tests were within normal ranges. After two months of therapy patient had good quality of life, without therapy toxicity. The best response to hormonal therapy was partial response. Morphologic evaluation in November 2018 showed progression of disease due to the growth of existing metastases and occurrence of a new lung metastases. Patient was treated with 2nd line hormonal therapy, aromatase inhibitor (Letrozol 2,5 mg daily). Stable disease persisted until August 2019 when MSCT showed further disease progression in lung. Chemotherapy, TC protocol (paclitaxel and carboplatin) every three weeks were started. On the third day after the first cycle of chemotherapy the patient developed weakness and joint pain grade 3, dizziness, loss of appetite and uroinfection. Symptomatic-supportive treatment was given and general condition of patient recovered within a few days. Chemotherapy was continued in a reduced dose. Morphologic evaluation performed after five cycles of chemotherapy showed mild regression of disease. The treatment plan is to continue to administer chemotherapy until disease progression or unacceptable toxicity. Patient is still in good general condition. She developed chemotherapy-induced peripheral neuropathy grade 2 and alopecia. Treatment of metastatic endometrial cancer requires an individualized approach, based on patient's age, status, comorbidities, characteristics of tumor, previously administered therapy and the time from adjuvant treatment to disease progression.

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MELANOMA

S21 - RECENT ADVANCES IN TARGETED THERAPIES OF MELANOMA

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In the last decade, we are witnesses of head – spinning progress in melanoma therapy, providing prolonged clinical responses and benefit to melanoma patients, even cure.

Targeted therapies have become the standard of care in BRAF V600-positive metastatic melanoma, and, just recently, in the adjuvant treatment of high-risk BRAF V600-positive melanoma.

Furthermore, recent results of neoadjuvant trials show high efficacy, and numerous studies of targeted therapies in combination with immunotherapy, either concomitantly or sequentially, are ongoing, with encouraging initial results. Targeted therapy can be a therapeutic option only in BRAF V600 mutated disease, which is mutated in approximately 50% of melanoma patients.

Targeted therapy in melanoma nowadays comprises of dual inhibition of MAPK – signaling pathway, by inhibiting BRAF-protein and MEK-protein in patients with BRAF-mutated disease. A combination of the two inhibitors of the same pathway results in a better and prolonged response due to overcoming resistance to therapy.

The final results of coBRIM phase III trial at 5 years of follow-up showed that the combination regimen maintained an advantage in both overall survival (OS) and objective response rate (ORR) compared with vemurafenib alone.

Cobimetinib&vemurafenib improved OS and progression-free survival (PFS) by roughly 5 months compared with vemurafenib alone. The 5-years OS rates were 30.8% vs. 26.3%, respectively. The median OS was 22.5 months (95% CI, 20.3-28.8) with the combination compared with 17.4 months (95% CI, 14.5-19.8) for the monotherapy. The 5-year PFS rates were 14% versus 10%, respectively. The median PFS at 5 years was 12.6 months (95% CI, 9.5-14.8) with cobimetinib&vemurafenib versus 7.2 months (95% CI, 5.6-7.5) with vemurafenib alone.

The pooled extended-survival data from two trials (COMBI-d and COMBI-v) involving previously untreated patients who had received BRAF-inhibitor dabrafenib with MEK-inhibitor trametinib after the median duration of follow-up 22 months (range, 0 to 76) showed PFS rates 21% (95% confidence interval [CI], 17 to 24) at 4 years and 19% (95% CI, 15 to 22) at 5 years. The overall survival rates were 37% (95% CI, 33 to 42) at 4 years and 34% (95% CI, 30 to 38) at 5 years. In multivariate analysis, several baseline factors (e.g., performance status, age, sex, number of organ sites with metastasis, and LDH level) were significantly associated with both PFS and OS. Complete response occurred in 109 patients (19%) and was associated with an improved long-term outcome, with an overall survival rate of 71% (95% CI, 62 to 79) at 5 years.

Targeted therapies in melanoma are effective even in patients with brain metastases, as shown by the results of COMBI-MB clinical study, although the median duration of response was relatively short. A

recent meta-analysis from 2019 aimed to better clarify the activity and efficacy of combination targeted therapies (TT), monotargeted TT (monoTT), combination immunotherapy (CMI), monoimmunotherapy (MI), and combination with radiotherapy (CRI) in patients with melanoma brain metastases. A total of 15 trials were included in the meta-analysis, with 1132 patients analyzed. CMI demonstrated a statistically significant better OS compared with MI ($P = .03$, $P = .05$, and $P = .03$, respectively, at 6 months, 18 months, and 24 months) and combination TT ($P = .04$ and $P = .03$, respectively, at 18 months and 24 months). CMI demonstrated a statistically significant better PFS compared with combination TT ($P < .001$ at 12 months and 18 months), MI ($P = .02$, $P < .02$, and $P = .05$, respectively, at 6 months, 12 months, and 18 months), and mono TT ($P < .001$ at 6 months, 12 months, and 18 months). The intracranial ORR was higher with CMI compared with mono TT ($P < .001$) and MI ($P < .001$), whereas there was no difference between CMI and combination TT. The results suggested that CMI increases long-term PFS and OS compared with MI and combination TT. However, combination TT and CMI are associated with a similar intracranial response rate. The role of systemic therapy in combination with radiotherapy remains to be better elucidated.

Based on the results of COMBI-AD phase 3 clinical study, adjuvant targeted therapy of high-risk melanoma patients has become the standard of care of BRAF V600 – mutated disease. Longer follow-up confirms relapse-free survival benefit with adjuvant dabrafenib plus trametinib in patients with resected BRAF V600-mutant stage III melanoma. At median follow-up of 44 months (dabrafenib plus trametinib) and 42 months (placebo), 3- and 4-year RFS rates were 59% (95% CI, 55% to 64%) and 54% (95% CI, 49% to 59%) in the dabrafenib plus trametinib arm and 40% (95% CI, 35% to 45%) and 38% (95% CI, 34% to 44%) in the placebo arm, respectively (HR, 0.49; 95% CI, 0.40 to 0.59). Distant metastasis-free survival also favored dabrafenib plus trametinib (HR, 0.53; 95% CI, 0.42 to 0.67). The estimated cure rate was 54% (95% CI, 49% to 59%) in the dabrafenib plus trametinib arm compared with 37% (95% CI, 32% to 42%) in the placebo arm. Subgroup analysis of RFS demonstrated similar treatment benefits regardless of baseline factors, including disease stage, nodal metastatic burden, and ulceration.

The „hot topic“ in melanoma research in the last several years is neoadjuvant therapy. A number of neoadjuvant targeted and immunotherapy studies have been completed in melanoma to date and have yielded promising clinical activity. The recent pooled analysis from 2019, showed that in the neoadjuvant setting, IT and TT are active regimens in resectable clinical stage III melanoma patients and are associated with high pCR rate. The ability to achieve pCR correlates with improved RFS, however, more so in patients receiving immunotherapy. For patients with pCR after neoadjuvant therapy, 7% have recurred, 0/51 (0%) after IT, 7/17 (41%) after TT. For those without pCR, 34% have recurred, 18/82 (22%) after IT and 19/27 (70%) after TT. Twelve-month RFS was improved in those with pCR vs without pCR (95% vs 62%, $p < 0.001$), including in those with IT (100% vs 72%, $p < 0.001$) and TT (88% vs 43%, $p < 0.001$). Sixteen (9%) patients have died, including two who had a pCR, both from TT. Given these encouraging results, a number of studies with other molecularly targeted and immunotherapeutic agents and their combinations are ongoing in the neoadjuvant setting; long-term outcome data are eagerly awaited. Such studies also provide access to biospecimens before and during therapy, allowing for the conduct of biomarker and mechanistic studies that may have a significant impact in guiding adjuvant therapy choices and drug development.

Due to the potential of BRAF- and MEK- inhibitors for immunomodulation, and potential immunostimulation, i.e., synergy with immunotherapy, numerous clinical studies are ongoing, exploring the potential of combining targeted therapy with immunotherapy. Emerging evidence indicates that targeted therapy synergizes the function of immune cells and the immune microenvironment endorsing the rationale of combinatorial therapy. The potential molecular mechanisms included: (1) promotion of melanocyte differentia-

tion antigens expression; (2) agitation of T-cell infiltration into tumor microenvironment; and (3) abrogation of the immunosuppressive tumor microenvironment. Preclinical and clinical studies also proved the advantage of synergizing oncogene-targeted therapy and immunotherapy. However, the concomitant use of targeted therapy with immunotherapy has generated serious adverse events (AEs). It is also important to investigate proper sequencing of combination targeted therapy (BRAF&MEK inhibitors) with immune checkpoint inhibitors (anti-CTLA or anti-PD-1/PD-L1 antibody), due to the fact that patients treated with targeted therapy may display distinct immune-compatibility: either be more sensitive or be more tolerant. Apart from toxicity, proper sequencing and timing of therapies should be considered and accessed when the combinatorial regimens are designed. Specific biomarkers or predictors of response and AEs may be important to achieve personalized treatment. Although MEK-inhibitors can create favorable tumor microenvironment, they may impair the function of antigen-specific T-cells by inhibiting physiological MAPK pathway. Therefore, how to enhance synergy of combinatorial regimens through avoiding small molecular inhibitors induced T-cell toxicity is another challenge. In order to minimize the toxicity of combination targeted therapy with immunotherapy, novel drugs, and innovative combinatorial strategies need to be further explored. Better understanding the complex interference between targeted therapy and immunotherapy will be helpful in developing more effective agents and to design better combinatorial regimens.

It is highly desired to identify and characterize the biomarkers that predict response or adverse events with targeted or immunotherapeutic drugs. Initially, we need to determine which subpopulation of patients are likely to benefit from targeted therapy or immunotherapy, in other words, what biomarkers can be used to predict the effect of drugs before treatment.

In 2019, research in the melanoma field continued its rapid pace of advancement. In the last decade, researchers have made remarkable progress in clinical, translational and basic research, improving patients' outcomes, and later on, focusing on expanding our understanding of treatment resistance, of identifying new treatment targets, but also on improving melanoma detection and prevention. However, there are still some unmet needs in melanoma field (especially uveal melanoma, mucosal melanoma, patients with adverse prognostic factors---), and we eagerly await future headways.

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S22 - CUTANEOUS MELANOMA IMMUNOTHERAPY

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Effective immunotherapy in routine clinical application against human solid tumors started in the last decade. This immunotherapy is based on the so-called immune checkpoint blockade. This means that humanized monoclonal antibodies against inhibitory checkpoint cell membrane proteins (“inhibitory receptor molecules”) on CD8+ T cells or their ligands on antigen presenting cells (APC) or tumor cells block inhibitory signals and thus enable nonspecific T cell activation and clonal proliferation. In this way nonspecifically activated T cells recognize and eliminate autologous tumor cells in oncological patients. The curiosity of this approach is that these monoclonal antibodies are not directed against tumor cells but against molecules on (immune) cells which physiologically regulate T cell activity. The discovery and successful clinical application of such checkpoint inhibitors culminated in the award of the Nobel Prize in Physiology or Medicine in 2018. This anti-cancer immunotherapy approach was first applied in patients having metastatic melanoma. Later it was found that it can be successfully applied to patients having several other metastatic types of cancers, for example non-small cell lung cancer, kidney cancer and urothelial carcinoma. Remarkably, some 30 to 40% of treated patients have probably been cured, which was not the case before. The question of why in the case of certain types of cancers only a percentage of treated patients responds while in the case of many other types of cancer there is no effect whatsoever remains unanswered. This underscores the need to identify predictable parameters and mechanisms of primary and secondary resistance to immune checkpoint blockade. Some of the causes for this might lie in tumor micro-environment cell composition and even in gut microbiota composition (1-8). In view of the fact that for several years now immune checkpoint blockade has been standard therapy for patients having metastatic cutaneous melanoma as well as adjuvant therapy in patients with high-risk primary melanoma (stage IIB/C) or completely resected lymph node (LN) metastases (stage III) (9, 10) and that therapeutic responses are obtained only in part of the patients treated, the main focus of this topic is to present other possible immunotherapeutic approaches which could be exploited, such as autologous cellular therapy with adoptive T cell transfer raised in vitro and expanded with cytokine interleukin-2 (rIL-2) from tumor infiltrating lymphocytes (TILs) or with chimeric antigen receptor (CAR) T cell (11-14). The CAR is an artificial transmembrane receptor which has an antibody fragment that targets cell surface antigens on cancer cells, and an intracellular domain that activates the CD3 signalling pathway once antigen binding has occurred. Cytokine therapy with rIL-2 might also find a broader application due to the novel formulation of rIL-2 which is bound to polyethylene glycol (PEG) chains. This novel formulation of rIL-2 has a longer half-life and much better tolerability than rIL-2 (aldesleukin), which was previously used and approved for the treatment of metastatic renal cell carcinoma and metastatic melanoma and which had to be applied intravenously at a very high-dose levels, which resulted in significant and dose-limiting toxicities (2, 15). When considering immunotherapeutic approaches to melanoma, it seems that there are no registered clinical studies based on the use of antibody drug conjugates and on bispecific T cell engagers (BiTEs) (11-14). Oncolytic viruses (T-VEC, Imlygic) have also been approved as a form of local therapy for melanoma patients having unresectable cutaneous, subcutaneous, and nodal melanoma lesions. Clinical studies combining T-VEC therapy with other forms of therapy are also underway (16,17).

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S23 - IMMUNOTHERAPY SIDE EFFECTS AND HOW TO TREAT THEM

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Immunotherapy nowadays represent a new approach in standard of care in the treatment of metastatic melanoma. The survival of patients with metastatic melanoma is dramatically enlarged with immunotherapy. The positive results in adjuvant studies have recently been published too. The improvement in survival is also observed for other types of cancer, so number of patients treated with immunotherapy is increasing.

Immunotherapy in metastatic or unresectable melanoma include two immunomodulating approaches: anti-PD-1 drugs (nivolumab and pembrolizumab) and anti-CTLA-4 antibody (ipilimumab). The anti-PD-1 antibodies have a different toxicity profile to ipilimumab with fewer high grade events.

The side effects of checkpoint inhibitors are uniformly termed as immune-related adverse events (irAEs). These include endocrine, dermatologic, gastrointestinal (GI) toxicities, but all organs can be affected, though other inflammatory events are less common. All these adverse events have an autoimmune etiology and can appear at any time during the treatment and even one year after stopping the immunotherapy. IrAEs therefore need careful monitoring, follow-up and management. Several guidelines and algorithms have been developed and published for the management of irAEs. With appropriate treatment, applied on time, irAEs toxicities are usually reversible, but if they are not recognized early enough they can become severe and even life-threatening. Before treatment initiation with immunotherapy, patients should be informed about the potential AEs of immunotherapy and warned to report all cases directly to the treating team, physician or nurse.

Inhibitors of PD-1 interfere with normal mechanisms of immune tolerance while inhibiting tumor immune escape. The increase in immune activation caused by these inhibitors in normal tissues may be responsible for various types of significant irAEs, which include endocrine, skin, pulmonary, gastrointestinal, hepatic, renal, neurologic, cardiac, and hematologic autoimmune diseases. The meta analysis that included forty-six studies with 12,808 patients different cancer types treated with the PD-1 signaling inhibitors, showed the overall incidence of irAEs 26.82% (95% CI, 21.73–32.61; I², 92.80) in any grade and 6.10% (95% CI, 4.85–7.64; I², 52.00) in severe grade, respectively. The incidence of death due to irAEs was around 0.17%. The development of irAEs was unrelated to the dose of anti-PD-1 agents.

The optimal management of irAEs include the early recognition and the appropriately-timed use of immunosuppressive agents: steroids or anti-TNF- α , based on the severity of the event.

Hepatitis can occur in 5-10 % of patients treated with immunotherapy. All patients should have serum transaminases and bilirubin measured before every cycle of treatment. Hepatitis is usually asymptomatic and can be detected on routine blood monitoring. If hepatitis is suspected viral hepatitis and concomitant drug administration should be excluded. Liver biopsy can be considered in severe reactions. If grade 2 transaminase or total bilirubin elevation detected, immunotherapy should be withheld and transaminases and bilirubin measured twice weekly. If it last longer than 1–2 weeks corticosteroids at a dose of 1 mg/kg/day should be started. If no improvement occurs, or in case of grade 3 or 4 irAEs corticosteroid dose should be increased to 2 mg/kg/day and immunotherapy permanently discontinued. If there is no

response to corticosteroids within 2–3 days, mycophenolate mofetil should be added at 1000 mg twice daily. Third-line immunosuppressive therapy is not well defined, tacrolimus should be taken in considerations, and consultations with hepatologist can be helpful. Infliximab is not recommended for the treatment of immune-related hepatitis.

Gastrointestinal (GI) irAEs are associated with a high incidence of treatment-related grade 3 or 4 events with antiCTLA-4 antibody. GI irAEs that are commonly reported with anti-PD-1 treatment include colitis, diarrhea, and enteritis but just in 2-3% grade 3 or 4. The guidelines for managed GI irAe include close monitoring and prompt treatment of early symptoms. Non-inflammatory causes of symptoms, infection with different pathogens, should be ruled out. Colonoscopy and biopsy should be considered if the diagnosis is unclear or in the case of chronic grade 2 AEs. In the case of grade 3 or 4 AEs, systemic corticosteroids are required and corticosteroids also should be strongly considered if grade 2 AEs persist in spite of supportive care. Oral steroids starting at 1–2 mg/kg per day of prednisone can be used, but for patients requiring hospitalization or have significant comorbidities, intravenous methylprednisolone should be used for 1–2 days before an oral prednisone. If symptoms improve with steroid treatment, steroids should be continued until grade 1 or 0 toxicity is reached. In steroid-refractory cases, after 72 hours, the tumor necrosis factor- α (TNF- α) blocking agent infliximab (5 mg/kg once every 2 weeks) may be used. Treatment with infliximab can dramatically improve GI AEs, sometimes even within 24 hours, but this is not recommended in patients with GI perforation or sepsis.

Pulmonary ir AEs, including pneumonitis was reported in up to 3% of the patients. A lung specialist consultation could be helpful and chest X-rays and CT scans of the thorax are necessary for diagnosis. Bronchoscopy and lung biopsy should be considered for patients with changes in respiratory status, including symptoms of upper respiratory infection, cough, shortness of breath, or decrease in pulse oximetry below 90% on exertion. For patients with grade 2 mild-to-moderate symptoms or worsening of symptoms from baseline, treatment should be withhold and corticosteroids (1.0 mg/kg per day intravenous methylprednisolone) administered. If no improvement in symptoms observed after two weeks or if symptoms worsen, treatment for grade 3/4 severe events should be applied: discontinue treatment, hospitalize the patient with daily monitoring, and administer corticosteroids (2–4 mg/kg per day of intravenous methylprednisolone). If symptoms persist or worsen the use of non-corticosteroid immunosuppressive medication, such as infliximab should be considered.

Endocrine irAEs are generally of grade 1 and 2, but they can be difficult to diagnose. Incidence is approximately 6% for all grades, and 1% with grade 3/4. Nonspecific complaints, such as fatigue, nausea, amenorrhea, erectile dysfunction, hypotension, hyponatremia, hypoglycemia, and eosinophilia may reflect endocrine dysfunction. To identify endocrine dysfunction laboratory testing for thyroid-stimulating hormone, T4, adrenocorticotrophic hormone (ACTH), cortisol and testosterone in males should be done. If hypophysitis is suspected (patient with a headache or visual symptoms) a magnetic resonance imaging (MRI) scan of the brain should be done, with pituitary cuts and visual field testing. Treatment with immune checkpoint inhibition may continue once appropriate hormone replacement initiated, and patients monitored closely. If adrenal crisis is suspected based on severe dehydration, hypotension, stress-dose steroids should be administered, and delay or discontinuation of the treatment with anti-PD-1 therapy should be discussed.

The skin toxicities observed with anti-PD-1 agents include rash (14%), and pruritus (10%). Rash is typically focal with a maculopapular appearance occurring on the trunk, back, or extremities. All observed cases were low or moderate grade and successfully managed with topical steroids and anti-histamines for pruritus.

Conclusion: Immunotherapy had improved the survival of metastatic melanoma patients. IrAEs can develop at any time, usually in first weeks until three months, but the first onset has been documented even one year after discontinuation of the treatment. Patients should be informed of the potential AEs of immunotherapy before treatment initiation. Dose reductions of PD-1 antibodies and/or ipilimumab have not been utilized in any trial and are not recommended after resolution of toxicity. For some cases a members of the multidisciplinary team (endocrinologist, pulmonologist, gastroenterologist...) should be involved to address specific symptoms. In most cases, irAEs can be managed with treatment interruption and/or supportive care. If irAEs are not recognized early enough they can become severe and even life-threatening. With timely and appropriate treatment, irAEs toxicities are usually reversible.

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S24 - BRAF MUTANT METASTATIC MELANOMA: A CASE REPORT

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Case report: Skin melanoma accounts for 4% of all dermatological malignancies, but it is responsible for about 80% mortality of skin tumors. Approximately 50 % of melanomas harbour activating point mutations in the BRAF gene. Specific BRAF inhibitors, in combination with MEK inhibitors are the mainstays of treatment in patients with advanced locoregional inoperable and metastatic BRAF-mutant melanoma. A 69-year-old woman was presented with a stage IIIC cutaneous nodular melanoma on the lower left leg. Histological examination showed a 11 x 10 mm large lesion with tumor thickness of 4 mm, without ulceration (T4a), with large satellite nodules at 1mm distance from primary tumor and with present tumor infiltrating lymphocytes. Angiolymphatic invasion was described and a mitotic rate of 14/mm² was detected. Resection margin was 2,5 mm. Sentinel lymph node biopsy was positive (N1a). Postoperative positron emission tomography (PET)/computerized tomography (CT) scan showed an uptake in two inguinal lymph nodes but no evidence of distant metastasis (cM0). After left inguinal lymphadenectomy, metastases were found in two of the five examined lymph nodes. BRAF testing showed positive mutation in BRAF gene. Multidisciplinary team decision was intensive clinical follow up. Regular every 3 months clinical visits with abdominal and inguinal ultrasound and dermatological exam were performed. In March 2017 clinical exam showed enlarged palpable inguinal lymph nodes, with few dark subcutaneous nodules around the operation scar. Cytological analysis of inguinal lymph node confirmed melanoma metastasis. Morphologic evaluation showed dissemination of disease in iliac, femoral, inguinal lymph nodes and in multiple left leg subcutaneous nodules. Patient started 1st line treatment with BRAF and MEK inhibitors, dabrafenib and trametinib in June 2017. At the beginning of treatment patient was ECOG 0, laboratory tests were within normal ranges. Patient had no significant therapy toxicity. Ophthalmological and cardiological examinations were regularly done. Clinical examination after 2 cycles showed significant regression of subcutaneous lesions, and morphologic evaluation confirmed regression of disease. Further morphologic evaluation was performed every two cycles, with monthly clinical examination, and laboratory tests analysis. Stable disease persisted until February 2019, when metabolic and morphologic progression of one left inguinal lymph node occurred. Due to progression of disease, patient continued treatment with 2nd line therapy, immunotherapy with pembrolizumab. Continuous morphologic evaluation and clinical follow up showed significant regression of disease. In September 2018, because of pain and superficial bleeding of subcutaneous metastasis, patient received palliative radiotherapy. Patient received 19 cycles of pembrolizumab, without significant toxicity and impact on quality of life. In April 2019, patient developed symptomatic brain metastases. Palliative treatment was planned, but unfortunately, due to fast clinical deterioration, patient died in October 2019, 31 months after diagnosis of metastatic melanoma.

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S25 - STEREOTAXY

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While per se, stereotactic radiosurgery is not a new procedure, it has seen a new resurgence in recent years thanks to the advances in the technology and new understandings of the cancer.

While the first reports on stereotactic radiosurgery harken back to the mid-20th century and the concept of gamma knife, it became more widespread by the use of modified accelerators and later with the purpose build accelerators, the procedure has long been restricted to the use in central nervous system. Introduction of stereotactic body frame has enabled the radiation oncologists to begin with the treatment of lesions elsewhere in the body, which were further facilitated by cyber knife and image guided radiotherapy techniques. And while the intracranial lesions are still considered primary stereotactic targets, stereotactic body radiotherapy is used more and more often.

When started, most common indications for radiosurgery were brain metastases followed by arteriovenous malformations. Typically they were solitary lesions, treated by single fraction radiosurgery. Shift from Lexell type frame and localizers to removable masks, has enabled us to start treating patients with lesions requiring multiple fractions, so radiosurgery has in some cases evolved to stereotactic radiotherapy with up to 30 fractions, which by itself seems not to be an advance, but with the tighter margins, some benign diseases are being treated with far less side effects than previously. Simultaneously with the advances in central nervous system, stereotactic body radiotherapy started, it is now being used most widely in non-small cell lung cancer, liver tumours and spine, and new indications are emerging.

And as the basis for stereotaxy is polar coordinate system coupled with fixation and high precision delivery, things has changed somewhat. With the IGRT techniques, some authors claim that stereotactic radiotherapy is dead and prefer to use term high precision conformal radiotherapy, which in the case of central nervous system is practically synonymous, but is worth considering elsewhere, as the factors of inter and intra-fractional motions and changes are being introduced.

As to start with the endpoints, from the physical view, our aims are to optimise target dose and reduce normal tissue volumes and doses. We can achieve these endpoints by various means. Most commonly by using multiple small fields, we can also use multiple isocenters, multiple small beams, IMRT techniques, but also, we can start treating with hadron therapy. No method is superior to other in all aspects, while Cosi has shown that in case of treating skull base meningioma, Cyber knife was superior in shielding brain stem and the dose on optic nerve was higher. So every method has its proponents and adversaries but there is scarce evidence in favour of any method.

When considering stereotactic treatment, one should bear in mind, that although practical limitations for stereotactic treatment are quite lax, there are patients who don't benefit from it. Thus, the number of indexes have been proposed for use in these patients, from the most simple recursive partitioning analysis index to more elaborate and specific graded prognostic assessment indexes, which provide some insight on who would benefit the most from the treatment.

In Slovenia, program of radiosurgery started in year 2000, when we performed first radiosurgery in patient with solitary brain metastasis of renal adenocarcinoma. Sixteen years on, the patient was still doing well. The method was performed on in-house modified accelerator with cone collimators and using TPS we have been using at the time. The method faded out for some years and we haven't been treating

patients until 2006, when stereotactic radiosurgery programme commenced using Varian clinic 600 with micro-multi-leaf collimator and Brainscan/iPlan TPS. Since the start we treated up to 4 brain metastases on Saturdays, averaging 20 stereotactic radiosurgeries per year. In 2010, radiosurgery programme shifted to NovalisTx, we forgo use of frame in radiosurgery and nowadays patients are treated using stereotactic mask fixation, with the control of exactTrac using from 1 to 5 fractions. Stereotactic fractionated radiotherapy is used for treatment of meningeal tumours and schwannomas. In 2015 we also started the programme of stereotactic body radiotherapy, commencing with primary lung tumours and proceeding to liver, pancreas and spinal tumours. While all cranial stereotactic treatments are delivered on NovalisTx, extracranial treatments are also being performed on Elekta versa HD and Varian TrueBeam machine, which is now also being prepared for HyperArc treatment of brain lesions.

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UROGENITAL TUMORS

S26 - TESTICULAR CANCER – BETWEEN DE-ESCALATION AND HIGH-DOSE CHEMOTHERAPY WITH PERIPHERAL BLOOD STEM-CELL TRANSPLANTATION

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Testicular cancer (TC) is the most common cancer in young men with about one-third of all cases occurring in Europe. TC incidence rates increase in 21 out of 28 countries during the period 2010-2035. The TC incidence in 2010 and in 2035 in Croatia, age-standardized per 100 000 was 7.6 and would be 13.2. Cisplatin is the key drug in the treatment of the TC and life expectancy is higher than in other solid tumors. Many patients with good risk metastatic seminoma are over-treated with the standard chemotherapy BEP×3 or PEx4. We use FDG-PET in seminoma patients to evaluate residual masses that are after chemotherapy >3cm in size. FDG PET performed within the correct timeframe of 4 to 12 weeks after chemotherapy is a standard diagnostic tool for clinical decision-making in seminoma patients with postchemotherapy residual masses.

Based on the efficacy of FDG-PET in seminoma, the authors of the SEMITEP (NCT01887340) study hypothesized that PET scans could be used to de-escalate therapy in good-risk seminoma. At a median of 34 months of follow-up, there were no differences in PFS between patients who received four cycles of EP and those who received two cycles of EP + 1 cycle of carboplatin at AUC 7 and the latter was chosen for the de-escalation arm given in low-volume seminoma. The authors defined FDG-PET positivity by the presence of abnormal focal uptake. The primary study endpoint was the proportion of patients with negative early FDG-PET treated with de-escalating chemotherapy (CT). Secondary endpoints were PFS, OS, proportion of patients with negative early FDG-PET and the inter-rater reliability of early FDG-PET. 72% of patients enrolled on SEMITEP had a negative early FDG-PET. De-escalating therapy based on this finding appears to be safe and feasible at least during three years of follow-up. While toxicities were essentially similar, there was a decreased amount of neuropathy in the de-escalation group. Longer follow-up and multicenter phase III will be required to understand if PET-based de-escalation of therapy has an impact on patient survival.

20% to 30% of TC patients are either refractory or relapse following initial treatment and require salvage CT. The most effective salvage CT regimen is controversial. Options include: 1. standard dose CT combining cisplatin and ifosfamide with either etoposide, vinblastine or paclitaxel or 2. high-dose chemotherapy (HDCT) with peripheral blood stem-cell transplantation. The most commonly used HDCT regimens include either two or three courses of high dose carboplatin and etoposide followed by peripheral blood stem cell transplantation. HDCT can achieve better results, 63%, with 2-year PFS when given as the second line, and 49% as the third line therapy or later. There is ongoing international randomized multicenter phase III the “TIGER” trial comparing conventional-dose chemotherapy with TIP×4 vs TI-CE (pacli-

taxel, ifosfamide 2x) followed by HDCT with carboplatin and etoposide x3 as the first salvage treatment in relapsed or refractory germ cell tumors. This study will elucidate the usage of HDCT in regard to the TC risk group.

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S27 - HORMONAL THERAPY OF PROSTATE CANCER

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Androgen deprivation therapy of prostate cancer has been a cornerstone of disease treatment. The story began with Charles Brenton Huggins who established a method to measure the effect hormone changes have on prostatic function. He found out that castration or estrogen administration led to glandular atrophy. In 1941 the beneficial effect of androgen ablation on metastatic prostate cancer was realised when Huggins and Clarence Hodges treated patients by either castration or estrogen therapy. Huggins was the first to use a systemic approach to treat prostate cancer. Huggins was awarded the Nobel Prize in Physiology or Medicine in 1966. Nowadays story has somewhat changed meaning that androgen deprivation therapy (ADT) still is a method of choice but has to be combined with other therapy modalities such as radiotherapy, chemotherapy or novel hormonal agents. ADT alone is no longer a valid, evidence based, therapeutic approach except in isolated cases in which due to comorbidities or other medical conditions there is no possibility of combining other treatment methods. When ADT is combined with radiotherapy in patients with high risk prostate cancer a question of therapy duration has been raised. Previous praxis suggested that duration of the treatment should be 36 months. Nabid and colleagues have conducted a clinical trial evaluating a duration of ADT combined with radiotherapy in high risk prostate cancer patients and concluded that 18 months of ADT is not inferior to 36 months of ADT. Also 18 months of ADT concomitant with radiotherapy may in selected patients improve quality of life without compromising overall survival. This kind of treatment is an attractive alternative for patients not tolerating well ADT. With the emergence of recent trials, the treatment for hormone-sensitive metastatic prostate cancer (hsMPC) is changing from ADT alone to combination therapy – chemotherapy or novel androgen receptor blocking agents. Both, docetaxel chemotherapy and abiraterone in addition to ADT have been studied and had shown to improve outcomes. The Systemic Therapy in Advanced and Metastatic Prostate Cancer Evaluation of Drug Efficacy (STAMPEDE) and Chemo Hormonal Therapy versus Androgen Ablation Randomized Trial in Extensive Disease (CHAARTED) trials established docetaxel chemotherapy, in addition to the ADT, as the first-line therapy in metastatic prostate cancer. In the CHAARTED and the STAMPEDE (Arm C) trials, the hazard ratio (HR) for OS on adding six cycles of docetaxel to ADT was 0.61 and 0.78. Clinical studies LATITUDE and STAMPEDE trials (Arm G) have explored the role of abiraterone in combination with prednisolone in addition to ADT in newly diagnosed high-risk hsMPC cancer patients. The LATITUDE study included 1,199 patients who were randomized to receive either ADT plus abiraterone (1000 mg daily) plus prednisone (5 mg daily) (treatment arm – 597 patients) or ADT plus dual placebos (control arm – 602 patients). The study found that the treatment arm had an improvement in both the overall survival (OS - HR = 0.62; 95% CI = 0.51–0.76, $P < 0.0001$) and progression free survival (PFS - HR = 0.47; 95% CI = 0.39–0.55, $P < 0.0001$). The STAMPEDE (arm G) trial with very similar design as LATITUDE involved a total of 1,917 patients and showed an improvement of 37% in the OS (HR = 0.63; 95% CI = 0.52–0.76, $P < 0.001$). Another issue has been raised in disease defined as non-metastatic castration resistant prostate cancer (nmCRPC). This is a state in which a high velocity (PSA doubling time ≤ 10 months) PSA rise is noted in spite of castration level testosterone in serum and no metastatic disease with conventional imaging methods (CT scan, bone scintigraphy). This is a very serious and deadly disease which had no therapeutic options till recent. There are three possible clinical scenarios in the development of such disease. First is PSA rising during radiotherapy with ADT, second is salvage ADT after local treatment (surgery

and/or radiotherapy) and third PSA rise after ADT alone for localized disease (option which should not be done any more). Three clinical trials examined apalutamide (SPARTAN), enzalutamide (PROSPER) and darolutamide (ARAMIS) in high-risk M0 CRPC. All trials had similar design with 1200-1500 patients enrolled comparing active drug to placebo. Primary endpoint was defined as metastasis free survival and secondary endpoints were overall survival (OS), time to first skeletal related event, time to application of first chemotherapy and time to pain progression. All three clinical trials have met their primary endpoints showing metastasis free survival in the range of 36-40 months, and the results for overall survival are not yet available even though some interim analysis in ARAMIS trial show promising results. All this novelities in hormonal therapy of different stages of prostate cancer gives us hope to improve the number of completely cured prostate cancer patients. For those patients who cannot be completely cured, this new kind of treatment approach allows to have a significantly better life quality and a significant delay of metastatic disease spread and development and very probably possibility of having a longer time of overall survival.

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S28 - PROSTATE CANCER: WHAT'S NEW IN NON-HORMONAL SYSTEMIC TREATMENT

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Prostate cancer (PC) is one of the most common cancers in Western World and is second leading cause of cancer deaths in men behind lung cancer. Metastatic prostate cancer is an incurable disease with different behavior. The mainstay of systemic prostate cancer treatment is hormonal manipulation - chemical or surgical castration. But since 2014 addition of chemotherapy or new hormone agents to castration has prolonged survival in castration-sensitive prostate cancer (CSPC). Docetaxel is the only non-hormonal agent used in CSPC treatment with androgen deprivation therapy (ADT). Despite great advances in CSPC treatment many questions remained unresolved like drug and patient selection, optimum sequencing or combining, duration of therapy. Some data from the last ASCO-GU showed that gene expression profiling could help classify prostate cancer as luminal A, luminal B and basal subtype and predict benefit of adding docetaxel to ADT in luminal B subtype. In castration-resistant prostate cancer (CRPC) the treatment landscape is evolving, with new agents and strategies, and more optimal use of existing therapies under constant development. The main non-hormonal agent in CRPC is cabazitaxel and showed benefit in patients who had been previously treated with docetaxel and abiraterone or enzalutamide (CARD study). New data indicated importance of drug sequencing and support the use of earlier chemotherapy in the castration resistant state. The great efforts are still needed to properly select the most appropriate treatment for each single patient. Many prognostic and predictive biomarkers have been studied, none of which has an established validated role in daily clinical practice. However, better understanding of PC biology, a broader application of metastatic biopsies and liquid biopsy and molecular testing will help to achieve better treatment outcome. Recently, we have learned that approximately 12% of patients with mCRPC have germline DNA-repair pathway mutations, and 20-25% have somatic mutations and those patients could benefit from poly ADP-ribose polymerase (PARP) inhibitors or platinum chemotherapy. Based on early evidence from PARP-inhibitors studies, it seems that men with prostate cancers harboring mutations in BRCA1/2 will have the greatest response rates to PARP inhibitors. Whether or not men with other mutations in DNA-repair genes will have response remains to be seen. New data also showed that approximately 3-5% prostate cancers harbor mutations in mismatch-repair (MMR) genes and may benefit from pembrolizumab, FDA approved agent for all cancers with MMR deficiency or microsatellite instability (MSI)-high status. That is why some guidelines recommend germline and somatic genetic testing for all men with metastatic PC or mCRPC. Another emerging therapies in mCRPC are directed towards the prostate-specific membrane antigen (PSMA) as radionuclid therapy with beta-emitter lutetium-177 and chimeric antigen receptor (CAR) T-cells therapy with PSMA as target. We are eagerly awaiting results from many ongoing clinical trials about PARP-inhibitors, immunotherapy and many other new agents and various combinations in genomically-selected PC patients.

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S29 - NEWS IN PROSTATE CANCER RADIOTHERAPY

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The importance of clinical trials can be assessed by their impact on clinical guidelines for the treatment. In the recent period, the results of published radiotherapy studies are important for improving techniques and better defining radiation indications in the treatment of patients with prostate cancer.

In 2018, STAMPEDE A1 and HORRAD clinical trials were published to demonstrate the beneficial effect of prostate radiotherapy in primary metastatic prostate cancer. In the STAMPEDE A1 trial, the risk of death of locally irradiated patients with low-volume disease was reduced by 32%. In 2019, STOPCAP systematic review and meta-analysis of both studies showed significantly better biochemical disease control and survival without biochemical, clinical or radiographic progression in irradiated patients with primary metastatic prostate cancer. The greatest benefit was seen in patients with less than 5 bone metastases. Subsequent analysis of the STAMPEDE A1 trial showed a significant 38% reduction in mortality and a 43% reduction in the risk of disease recurrence in irradiated patients with less than 4 bone metastases. In 2019, prostate cancer radiotherapy in addition to androgen deprivation in patients with primary metastatic low-volume disease is recommended according to EAU guidelines.

It is important to highlight newly published clinical trials that tested radiation after prostatectomy. The results of the RADICALS-RT and RAVES studies were announced on the ESMO 2019 and ASTRO 2019 congresses. A prospective RADICALS-RT study included 1396 patients with adverse prognostic factors after radical prostatectomy. There was no significant difference in survival without biochemical progression between patients who received immediate adjuvant radiotherapy and patients who received early salvage radiotherapy. However, more adverse events have been reported with adjuvant radiotherapy. Over 60% of patients in the salvage group did not need further radiation. The smaller RAVES trial confirms the equal effectiveness of adjuvant and salvage radiotherapy in biochemical disease control. The ARTISTIC meta-analysis included both of these studies and the GETUG-AFU17 trial and confirmed the equal value of radiation immediately after prostatectomy (adjuvant radiotherapy) and delayed radiation (salvage radiotherapy) in the postoperative treatment of prostate cancer patients.

In the recent period we are faced with the widespread acceptance of ultra-hypofractionated radiotherapy (≥ 5 Gy) in primary treatment for prostate cancer. Systematic review of over 6000 patients treated by stereotactic body radiation therapy (SART or SBRT) showed a 7-year biochemical control of the disease in 93.7% of patients with adverse complications of grade ≥ 3 in only 3.1%. In 2019, the first results of two prospective randomized studies were published. The HYPO-RT-PC trial included 1200 patients, mainly intermediate-risk. SBRT was not inferior to conventional treatment in progression-free survival. Slightly more acute side effects were reported. The PACE-B trial included 874 patients and showed no difference in acute adverse events between ultra-hypofractionated radiotherapy and other radiation regimens. In 2019, the common guidelines of ASTRO, ASCO and AUA included SBRT into standard local treatment in low-risk patients, and, as a therapeutic option, in intermediate-risk patients with recommended additional systematic monitoring.

Published studies are changing or will soon change the way how radiotherapy is used in prostate cancer patients. Prostate radiotherapy is becoming a mandatory part of the treatment of primary metastatic low-volume disease. Adjuvant radiotherapy will be replaced by early salvage radiotherapy. Radio-

therapy in patients with local disease and low- and, partly, intermediate-risk will be ultra-hypofractionated and performed by stereotactic technique.

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S30 - NEOADJUVANT AND ADJUVANT TREATMENT OF BLADDER CANCER

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Bladder cancer is the tenth most common cancer worldwide, and it is about four times more common in male. Major histopathological type is urothelial cancer, caused predominantly by smoking, while in northern Africa due to other causal agent (infection with parasite *Shistosoma*) squamous cell cancer comprises approximately 75% of the cases. Vast majority of urothelial cancers arise in the bladder, then in renal pelvis and ureter. In 75% of cases it is diagnosed as non-muscle-invasive disease, meaning papillary non-invasive tumor (Ta), or only lamina propria invasive tumors (T1) or flat high-grade lesions (CIS), and in rest of the patients as a muscle-invasive disease and metastatic cancer.

In narrow sense neoadjuvant treatment is term reserved for chemotherapy applied in muscle-invasive localised bladder cancer before locoregional treatment, typically radical cystectomy. Although neoadjuvant chemotherapy has been proven to prolong overall survival, and it is recommended by various guidelines of oncological and urological societies, it is still largely underutilised. The main obstacle is probably lack of real multidisciplinary approach to these patients leading to assumptions that they are frail and not a good candidates for chemotherapy, and that this approach would lead to delay of curative intent surgery. As we now that only 50% of patients are alive 5 years after radical cystectomy it is clear that multimodal approach involving potent systemic therapy in order to decrease rate of distant metastases and prolong survival is needed. Recommended neoadjuvant chemotherapy protocols are cisplatin-gemcitabine (CG) combination and dose dense (dd) MVAC protocol (methotrexate, vinblastine, doxorubicin and cisplatin). There is a recent report on higher pathological complete response rate on dd MVAC in comparison with CG. Preliminary report of GETUG/AFU V05 VESPER randomized trial comparing these two protocols confirmed better pathological response of dd MVAC with higher acute toxicity. We are expecting outcomes of survival analysis in 2021.

Novel neoadjuvant therapy approaches are combining immunotherapy with chemotherapy or exploring immunotherapy alone (PURE-01, ABACUS, BLASST-1 trials). Major efforts are being made to find a predictive biomarker for response on neoadjuvant chemotherapy. The largest research is done in molecular profiling of urothelial cancer. By different assays several specific molecular subtypes of muscle-invasive bladder cancer have been identified. Investigations, that should be prospectively validated, suggest that basal and luminal tumors have equivalent response to neoadjuvant chemotherapy and that basal tumors may benefit the most from neoadjuvant chemotherapy.

The level of evidence for adjuvant chemotherapy is less strong, but it should be considered based on pathological findings on radical cystectomy, if neoadjuvant therapy has not been applied. Phase III IMvigor-010 clinical trial testing adjuvant atezolizumab versus observation after radical cystectomy failed to meet primary endpoint of disease-free survival for muscle-invasive urothelial cancer.

Adjuvant intravesical therapy with *Bacillus Calmette Guerin* (BCG) or chemotherapy is used to reduce recurrences or delay disease progression to higher stages or grades. Unfortunately, due to global shortage of BCG, alternative agents and therapies are urgently needed. In 2018, American Food and Drug Association (FDA) has approved pembrolizumab, anti PD-1 antibody for treatment of high risk BCG-unresponsive non-muscle-invasive bladder cancer with CIS.

In conclusion, bladder cancer has high global incidence and especially prevalence of patients with early stages of the disease. Goal is to treat carefully and vigorously non-muscle-invasive cancer to prevent its' invasion and further progression of the disease. Muscle-invasive bladder cancer is highly aggressive disease with only 50% survival on five years with radical cystectomy which prompts use of neoadjuvant, and sometimes adjuvant chemotherapy according to the best available evidence. We are still lacking proven predictive biomarkers for right patient selection for this approach. There are new agents and modalities on horizon, primarily immunotherapy that has, after proven benefit in metastatic setting, shown good results in early stages of the disease and is being tested in number of randomised clinical trials.

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S31 - NEW DEVELOPMENTS IN TREATMENT OF METASTATIC BLADDER CANCER

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There has been tremendous progress observed in metastatic setting of urothelial cancer, after many decades of stagnation. In last several years **five immune check-point inhibitors** have been approved for treatment of advanced or metastatic urothelial cancer after failure of prior platinum-based chemotherapy: atezolizumab, nivolumab, pembrolizumab, avelumab and durvalumab. In the first line setting, pembrolizumab and atezolizumab are approved for cisplatin-ineligible patients, however their use is restricted only to programmed death-ligand 1 (PD-L1) expressing tumors.

Role of anti-PD-1/PD-L1 antibodies in the first line treatment of metastatic disease will be defined by following ongoing large phase III trials: IMVigor130 (atezolizumab vs platinum-based chemotherapy + atezolizumab vs cisplatin + gemcitabine or carboplatin + gemcitabine), DANUBE (durvalumab vs durvalumab + tremelimumab vs cisplatin + gemcitabine or carboplatin + gemcitabine), KEYNOTE361 (pembrolizumab + cisplatin/gemcitabine or pembrolizumab + carboplatin/gemcitabine vs pembrolizumab vs cisplatin + gemcitabine or carboplatin + gemcitabine), CheckMate901 (nivolumab + ipilimumab vs nivolumab + cisplatin/gemcitabine vs cisplatin + gemcitabine or carboplatin + gemcitabine), and finally JAVELIN Bladder 100 (first line chemotherapy + avelumab switch maintenance vs observation). So far, interim PFS and OS analysis of IMVigor130 trial was reported on ESMO 2019. Atezolizumab combined with platinum-based chemotherapy showed PFS benefit and trend towards OS benefit, compared to chemotherapy arm. Importantly to note, atezolizumab alone arm fared not better than chemotherapy arm. Use of cisplatin was associated with improved OS in combinational arm.

Javelin Bladder 100 trial recently (January 6, 2020) reported that trial met its OS endpoint in the planned interim analysis, meaning that avelumab given as switch maintenance after standard cisplatin/gemcitabine chemotherapy significantly prolonged OS compared to observation.

Very recently, we witnessed another breakthrough in bladder cancer treatment. Concept of antibody-drug conjugates proved to be efficient in metastatic bladder cancer. **Enfortumab Vedotin (EV)** represents the first in class antibody-drug conjugate which specifically targets Nectin-4, transmembrane cell adhesion molecule highly expressed in urothelial cancer cells. EV-201 phase II study included 125 patients who failed prior platinum containing and immune checkpoint inhibitor therapy. Overall response rate was 44%, including 12% complete responses and 32% partial responses. Median duration of response was 7.6 months with manageable toxicity. Based on these results, on December 18, 2019, the Food and Drug Administration granted accelerated approval to enfortumab vedotin for patients with locally advanced or metastatic urothelial cancer who have previously received a PD-1 or PD-L1 inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

Next step in further development is testing **EV in combination with immunotherapy** (pembrolizumab).

At the 2020 ASCO GU meeting updated data were presented on a cohort of cisplatin-ineligible patients receiving first line enfortumab vedotin + pembrolizumab (EV-103 trial). The study included 45 patients. After a median follow-up period of 11.5 months, the confirmed investigator-assessed objective response

rate (ORR) was 73.3% (95% CI [58.1, 85.4]). A total of 15.6% of patients had a complete response, and the disease control rate was 93.3%. The responses appeared durable, with 55% ongoing at the time of data cutoff; 11 responses lasted beyond 10 months, and the median duration of response was not yet reached. The most common treatment-emergent adverse events associated with the regimen included fatigue (58%; 11% grade 3 or higher), alopecia (53%), and peripheral sensory neuropathy (53%; 4% grade 3 or higher).

Next antibody-drug conjugate showing activity in bladder cancer is **Sacituzumab Govitecan (SG)**, a Trop-2 directed antibody-drug conjugate linked to SN-38, a toxic payload that is the active metabolite of the chemotherapy drug irinotecan. TROPHY-U-01 trial was a phase 2 open-label study of SG on 100 patients with metastatic urothelial cancer who progressed on platinum-based chemotherapy or an immune checkpoint inhibitor therapy. Last updated data was presented at ESMO 2019. After a median follow-up of 4.1 months, 57% of patients continued on treatment. The ORR was 29% (10/35) with 6% of patients (2/35) achieving a complete response. Of the 10 patients who responded, 8 had ongoing response at the time of data collection. 74% of patients demonstrated a reduction in tumor burden by RECIST criteria. These data demonstrate that Sacituzumab Govitecan is a promising novel antibody-drug conjugate in the third-line setting following platinum-based chemotherapy and an immune checkpoint inhibitor therapy.

Next recently established breakthrough therapy for locally advanced or metastatic urothelial cancer is **erdafitinib**, a tyrosine kinase inhibitor of fibroblast growth factor receptor (FGFR1–4). Alterations in *FGFR* genes are common in urothelial carcinoma and may be associated with lower sensitivity to immune interventions. In phase 2 study, 99 patients with locally advanced and unresectable or metastatic urothelial carcinoma with prespecified *FGFR* alterations, who progressed during or after at least one course of chemotherapy or within 12 months after neoadjuvant or adjuvant chemotherapy received erdafitinib in either an intermittent or a continuous regimen. Overall response rate was 40% (3% with a complete response and 37% with a partial response). Among the 22 patients who had undergone previous immunotherapy, the confirmed response rate was 59%. The median duration of progression-free survival was 5.5 months, and the median duration of overall survival was 13.8 months.

Next step in drug development is **combination FGFR pathway inhibitors with immune checkpoint inhibitors**, the concept currently tested in ongoing phase I FORT-2 trial in patients with mRNA positive FGFR1/3 mutant metastatic urothelial cancer (rogaratanib+atezolizumab vs atezolizumab alone).

In conclusion, in last few years, a significant progress has been made in treatment of patients with metastatic bladder cancer, with advent of immune check-point inhibitors, targeted therapy, and antibody-drug conjugates. Combinational therapies are of special interest as they offer unique opportunity for disease control. Ongoing trials will define optimal regimen of systemic treatment.

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S32 - NEW DEVELOPMENTS AND UPDATE ON TREATMENT OF METASTATIC KIDNEY CANCER

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Kidney cancer treatment options continue to evolve and develop at rapid pace. Recently, on ASCO GU 2020 meeting, several important updates of key trials were presented. **The final analysis of CheckMate 025 study**, which established nivolumab as a standard 2nd-line therapy in patients that progressed on vascular endothelial growth factor (VEGF) targeted therapy was presented with over 5 years of follow-up. Final trial results showed that with long-term follow-up, nivolumab was associated with improved OS, with a median OS of 25.8 months versus 19 months, HR 0.73, $p < 0.0001$, when compared to everolimus. Progression-free survival was also improved with nivolumab (4.2 months versus 4.5 months, HR 0.84, $p = 0.03$). An overall response rate of 23% was observed with nivolumab, compared to 17% with everolimus ($p < 0.0001$) and nivolumab was also associated with prolonged duration of response (18.2 months). Nivolumab toxicity profile was similar to prior reports with no new signals of additional toxicity. Common adverse events with nivolumab included fatigue, diarrhea, pruritis and decreased appetite. Overall these data confirm the efficacy and safety of nivolumab in this setting as standard second line treatment.

Second important trial that was presented was a **phase I/II study of sitravatinib combined with nivolumab in patients with advanced clear cell renal cancer that progressed on prior anti-angiogenic therapy**. In patient who have been previously treated with a VEGF tyrosine kinase inhibitor (TKI), the checkpoint inhibitor nivolumab represents a standard 2nd-line strategy.

Sitravatinib is an orally-available small molecule, multi-targeted TKI. The hypothesis of this study was that sitravatinib could augment nivolumab responses. Nivolumab plus sitravatinib showed promising efficacy, with 15/38 (39%) achieving a confirmed objective response and 35/38 (92%) achieving clinical benefit (stable disease or partial response or completed response). At a median follow-up of 17.7 months, median overall survival had not been reached with 79% of patients alive. Median duration of treatment (10.3m) compared favorably to historical report of nivolumab alone (4.6 months). This early phase phase trial of sitravatinib, a multi-targeted oral TKI, in combination with nivolumab in pre-treated advanced clear-cell kidney cancer showed higher objective response rate and longer PFS than historically reported single-agent nivolumab in this setting.

Also, **CheckMate-214 trial** was updated on ASCO GU 2020 meeting, now with minimum follow-up of 42 months. The overall survival benefit for combination nivolumab/ipilimumab was maintained at a 42-month minimum follow-up (HR 0.66, 95% CI 0.55-0.90, $P < 0.0001$). The median overall survival for combination nivolumab/ipilimumab was 47 months versus 26.6 months in the sunitinib group. This overall survival benefit also held true in the secondary endpoint of intention to treat analysis, though with a slightly higher hazard ratio (HR 0.72, 95% CI 0.61-0.86, $P = 0.0002$). The exploratory analysis of the efficacy of combination nivolumab/ipilimumab in favorable-risk patients compared to sunitinib showed no overall survival benefit (HR 1.19, 95% CI 0.77-1.85, $P = 0.44$). As expected for good risk patients, the median overall survival was not reached in either group. Confirmed response rates were higher with combined immune checkpoint blockade relative to sunitinib in the intermediate/poor risk group, but not in the good risk group. The median duration response of combined checkpoint blockade has not been reached. Consistent

with the complete response data, there was a plateau in the PFS nivo/ipi curve at 34%. In post-hoc analysis, overall survival probability in patients who discontinued therapy appears similar to the patients who continued on therapy in the intention to treat analysis. **In summary, at 42 months of minimum follow-up (median 49 months), the overall survival and objective response rate seen with combined nivolumab and ipilimumab persisted as superior to sunitinib for intermediate/poor risk patients with metastatic renal cell cancer.** A post hoc analysis suggests that the overall survival benefit may persist in patients despite having to discontinue therapy due to adverse side effects. No specific benefit for this combination relative to TKI therapy was seen in the good risk population, though longer follow-up will be helpful for confirming this.

Recently updated ESMO guidelines now as first line treatment recommend pembrolizumab/axitinib combination as standard in good risk patients. Alternative options include sunitinib and pazopanib. In intermediate-risk and poor-risk patients two recommended regimens are pembrolizumab/axitinib and nivolumab/ipilimumab while alternatives include sunitinib, pazopanib and cabozantinib.

Currently, there is important work in progress related to biomarkers which could predict better response to immune checkpoint inhibitors as compared to VEGF-tarteded antiangiogenesis TKIs. Potentially, TKI could work better in tumors where the oncogenic driver is angiogenesis axis, while immune checkpoint inhibitors could work better in tumors with present immunosuppressive signature. Updates from Immotion151 trial (atezolizumab/bevacizumab versus sunitinib) biomarker analysis are expected in later 2020 (molecular gene expression signatures were correlated with clinical outcomes, prognostic risk groups, and tumor histology).

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S33 - RENAL CELL CARCINOMA – CASE REPORT

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The case aims to acknowledge long lasting benefit of different tyrosine kinase inhibitors (TKI) given in sequence and emphasizes the absence of cross-resistance and the need for continuous effective anti-tumor treatment after failure of immune checkpoint blockade.

The 58-year old patient was first referred to urology department in September 2005 due to accidental ultrasound confirmed mass in the right kidney. Initial staging showed no evidence of distal metastasis. Radical right nephrectomy was performed and pathology report confirmed clear cell renal carcinoma. He was followed until April 2008 when CT scan showed multiple, bilateral lung metastasis. He started treatment with sunitinib 50 mg 4/weeks schedule, later reduced to 37,5 mg due to the side effects. Control radiological assessment confirmed partial response but in March 2015 after nearly 7 years of sunitinib treatment there was radiological progression in the lungs and dose was due to be increased to 50 mg 2/weeks schedule. However, the treatment was not started because patient developed acute myocardial infarction and later when he recovered was operated because of cholangitis. After 6 months with no treatment he was retreated with sunitinib 50 mg and on the first evaluation there was 50% diameter regression of the lung metastasis and new soft tissue metastasis in the right shoulder but unfortunately sunitinib was discontinued due to cardiac toxicity. Patient was discussed on the multidisciplinary tumor board and started treatment with nivolumab 3mg/kg intravenously every 2 wk. After 3 months of treatment there was significant clinical progression in the lungs and new large painful bone metastasis in the right knee. The treatment with nivolumab was stopped, patient was discussed on the multidisciplinary tumor board and due to favorable toxicity profile treatment with pazopanib was recommended. In October 2016 he started with reduced dose of pazopanib 400 mg and 600 mg per day alternately and since there was no significant cardiac toxicity the dose was increased to 600 mg per day. At the first evaluation 3 months later there was significant reduction of the all sites of metastatic disease and he continued his treatment until August 2019 when there was radiologically confirmed progression in the lungs, shoulder and new large lytic lesion in the iliac bone. The bone metastasis was irradiated and in November 2019 a fourth line of systemic treatment was started with cabozantinib in reduced dose of 40 mg. The treatment is well tolerated and the first evaluation after 3 months showed radiological regression of all metastasis.

In the conclusion this case shows that renal cell carcinoma is heterogeneous disease with proportion of patients needing long-lasting and continuous treatment with TKI both before and after treatment with immunotherapy.

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